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Results from the international collaborative systematic literature review informing the 2023 EULAR recommendations for the treatment of systemic sclerosis

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ABSTRACT

Background The EULAR recommendations for the treatment of systemic sclerosis (SSc) were updated in 2017, informed by a systematic literature review (SLR) completed in 2014.

Objectives The aim of this new SLR was to provide the most up-to-date literature to underpin contemporary EULAR recommendations for the management of SSc.

Methods 30 searches for 30 interventions (including several outcomes/clinical questions), and 1 dedicated search (with several interventions) for calcinosis were prioritised by the task force. Three types of questions were defined: type I questions, unchanged as compared with the previous recommendations; type II questions exploring interventions already mentioned in the previous recommendations but with new outcomes; type III questions for new interventions.

Results 14 490 abstracts were retrieved from the databases on 31 March 2022 and 2021 abstracts were retrieved on 11 October 2022. 483 new full texts were evaluated and 172 new articles were included for the first search and 9 for the second search. The majority of the questions covered by this SLR explored new interventions (40% of type III questions) or new outcomes (26% of type II questions). New interventions included targeted therapies such as abatacept, Janus kinase inhibitors or nintedanib, and updated questions incorporated the results from key game-changing randomised controlled trials including trials on tocilizumab, mycophenolate or rituximab in SSc-interstitial lung disease.

Conclusions This SLR provides and summarises the highest level of evidence for the new EULAR recommendations for the treatment of SSc, providing an unprecedented comprehensive overview of recent knowledge on SSc treatments and participating in defining the future research agenda.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In 2017, the European Scleroderma Trials and Research, under the aegis of the EULAR, proposed a revised set of recommendations for the treatment of systemic sclerosis (SSc).
⇒ These recommendations were based on a systematic literature review (SLR) that concluded in 2014.
⇒ An update was necessary to inform future recommendations.

WHAT THIS STUDY ADDS

⇒ This SLR provides and summarises the highest level of evidence to address questions prioritised for the new EULAR recommendations for the treatment of SSc.
⇒ It offers a comprehensive overview of the evidence on SSc treatments and contributes to defining the research agenda for SSc management.
⇒ The 2023 SLR includes targeted therapies (eg, abatacept, Janus kinase inhibitors and nintedanib) and incorporates results from key, game-changing trials on tocilizumab, mycophenolate and rituximab.
⇒ Additionally, this SLR manuscript presents the most updated and highest level of evidence on interventions and outcomes not ultimately included in the final version of the recommendations but still potentially useful for clinicians.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This SLR provided the new EULAR SSc treatment recommendations task force with the available evidence published since 2014, informing the development of updated treatment guidelines.

INTRODUCTION

Systemic sclerosis (SSc) is a rare and heterogeneous systemic autoimmune disease characterised by a triad of pathogenic factors that includes (i) vasculopathy, (ii) inflammation and autoimmunity and (iii) fibrosis characterised by collagen deposit in the skin and internal organs such as lungs or myocardium.[1] Three main subsets of SSc are described based on the extent of skin fibrosis[2 3]: diffuse cutaneous SSc (dcSSc) with distal and proximal skin involvement, limited cutaneous SSc (lcSSc) characterised by distal skin fibrosis and SSc sine scleroderma, defined by the absence of skin fibrosis despite SSc-related features. To date, SSc is the rheumatic disease with

Table 1 List of the 31 searches/questions and related outcomes prioritised by the task force, and number of publications* related to these searches

Questions/Searches	No. of total articles selected per question (in 2014)	No. of total articles selected per question (March 2022 update)	No. of total articles selected per question (November 2022 update)	Outcomes/Manifestations of interest (highest available level of evidence)
Total	**N=171**	**N=172**	**N=9**	
Type I questions: unchanged as compared with the previous set of recommendations	**67**	**35**	**0**	
Methotrexate	**6**	**1**	**0**	1. Skin fibrosis (1b) 2. MSK (2b) 3. ILD (2b)
HSCT	**17**	**5**	**0**	1. Survival (1a) 2. Event-free survival (1a) 3. Skin fibrosis (1a) 4. ILD (1a) 5. PRO (1a)
Calcium channel blockers	**4**	**0**	**0**	1. RP (1a)
Angiotensin receptor antagonists	**2**	**0**	**0**	1. Prevention of SRC (5) 2. Improvement of SRC (5)
Prostacyclins	**8**	**7**	**0**	1. RP (1a) 2. DU (1a) 3. PAH (1a)
Selective PDE-5 inhibitors	**16**	**7**	**0**	1. RP (1a) 2. DU (1a) 3. PAH (1a) 4. Erectile dysfunction (3)
Antiplatelet agents	**1**	**2**	**0**	DU (2b)
Proton pump inhibitors	**7**	**6**	**0**	Oesophageal involvement (3)
Prokinetic agents	**2**	**3**	**0**	GI involvement (1b)
Riociguat	**1**	**1**	**0**	PAH (1b)
Local wound care	**3**	**3**	**0**	DU (2a)
Type II questions: intervention already mentioned but including new outcome(s)†	**104**	**65**	**5**	
Corticosteroids	**17**	**12**	**2**	1. ILD (2b) 2. SRC (3) 3. Heart involvement† (3) 4. MSK† (3)
Cyclophosphamide	**26**	**7**	**1**	1. ILD (1a) 2. Skin fibrosis (1b) 3. Other organ involvement including heart involvement† (3) 4. Survival† (2b)
Mycophenolate mofetil	**12**	**8**	**0**	1. ILD (1a) 2. Skin fibrosis (1b) 3. Heart involvement† (1b) 4. Survival† (1b) 5. Combination with nintedanib on ILD† (1b)
Anti-CD20 therapy (rituximab)	**11**	**14**	**2**	1. Skin fibrosis (1a) 2. ILD (1a) 3. Heart involvement/PAH† (1b) 4. MSK† (2b)
Tocilizumab	**1**	**5**	**0**	1. Skin fibrosis (1b) 2. ILD (1b) 3. MSK (1b) 4. Heart involvement† (1b)
ACE inhibitors	**5**	**3**	**0**	1. Prevention of SRC (3) 2. Improvement of SRC (3) 3. Worsening of SRC† (3)

Continued

Table 1 Continued

Questions/Searches	No. of total articles selected per question (in 2014)	No. of total articles selected per question (March 2022 update)	No. of total articles selected per question (November 2022 update)	Outcomes/Manifestations of interest (highest available level of evidence)
Endothelin receptor antagonists	**30**	**12**	**0**	1. RP (2b) 2. DU (1a) 3. PAH (1a) 4. Heart involvement† (5) 5. Combination with PDE-5i for DU† (1b) 6. Prevention of SRC† (2b)
Antibiotics	**2**	**4**	**0**	1. SIBO (2b) 2. DU† (4)
Type III questions: interventions not mentioned in the previous recommendations	**NA**	**72**	**4**	
Anticoagulants	–	**8**	**0**	1. DU (2b) 2. PAH (2a)
Selexipag	–	**1**	**0**	1. PAH (1b)
Abatacept	–	**4**	**0**	1. Skin fibrosis (1b) 2. ILD (1b) 3. MSK (1b) 4. Heart involvement (5)
Physical therapy	–	**22**	**1**	1. Hand function (1a) 2. QoL (1a) 3. ILD (2b)
Hyperbaric chamber	–	**0**	**0**	DU (5)
Nutritional support	–	**7**	**0**	QoL (2a)
Botox	–	**3**	**1**	DU (1b)
Intravenous immunoglobulin	–	**5**	**0**	1. Skin fibrosis (1b) 1. GI involvement (2b) 2. Heart involvement (2b)
JAK inhibitors	–	**2**	**0**	1. Skin fibrosis (2a) 2. MSK (2a) 3. ILD (2a) 4. Heart involvement (5)
Pentoxyphilline	–	**0**	**0**	1. RP (5) 2. DU (5)
Nintedanib	–	**8**	**2**	1. ILD (1b) 2. PRO (1b) 3. QoL (1b) 4. Other manifestations (1b)
Any therapeutic approach for calcinosis	–	**12**	**0**	Any calcinosis-related outcomes, including calcinosis-related pain (visual analogue scale), calcinosis-related DUs, assessment of local inflammation, radiographic assessment, disability (4)

*Several publications could be derived from a same single RCT, with new outcomes explored/reported depending on the publication.
†New outcome as compared with the 2017 set of recommendations.
DU, digital ulcers; GI, gastrointestinal; HSCT, haematopoietic stem cell transplantation ; ILD, interstitial lung disease; JAK, Janus kinase; MSK, musculoskeletal manifestations; NA, not appropriate; PAH, pulmonary arterial hypertension; PDE-5i, phosphodiesterase type 5 inhibitors; PRO, patient-reported outcomes; QoL, quality of life; RCT, randomised controlled trial; RP, Raynaud's phenomenon; SIBO, small intestinal bacterial overgrowth; SLR, systematic literature review; SRC, scleroderma renal crisis .

the highest individual mortality rate.[1] The main causes of death are SSc-interstitial lung disease (SSc-ILD) and SSc-related heart involvement.[4] Considering the complexity of the disease and the need for early intervention to limit the onset and/or progression of life-threatening manifestations,[5] there is an important need for treatment recommendations.[6 7]

The European Scleroderma Trials and Research (EUSTAR) under the aegis of EULAR proposed a first set of recommendations in 2009 that were updated by a new publication in 2017 based on a dual combination of expert opinion and evidence from the literature.[6 7] The 2017 recommendations were based on a systematic literature review (SLR) that ended up in 2014.[6] Since then, there has been an unprecedented wave of phase II and phase III randomised controlled trials (RCTs) that have led to significant progress in the understanding and management of SSc.[8] Based on these RCTs, new drugs have been approved by regulatory agencies including nintedanib, a tyrosine kinase inhibitor with antifibrotic properties approved in the treatment of SSc-ILD in the USA, Europe and Japan[9]; tocilizumab, a humanised monoclonal antibody targeting the IL-6 receptor and approved in the USA for the treatment of SSc-ILD[10 11] and rituximab, a chimeric monoclonal antibody targeting CD20 and approved in Japan.[12–14] All these new approvals since the 2017 EULAR recommendations for the treatment of SSc stress the need for an update of these recommendations. Most of these RCTs focused on SSc-related skin involvement and ILD, with a majority of trials designed for dcSSc, but comprehensive updated guidelines for the management of other key SSc-related

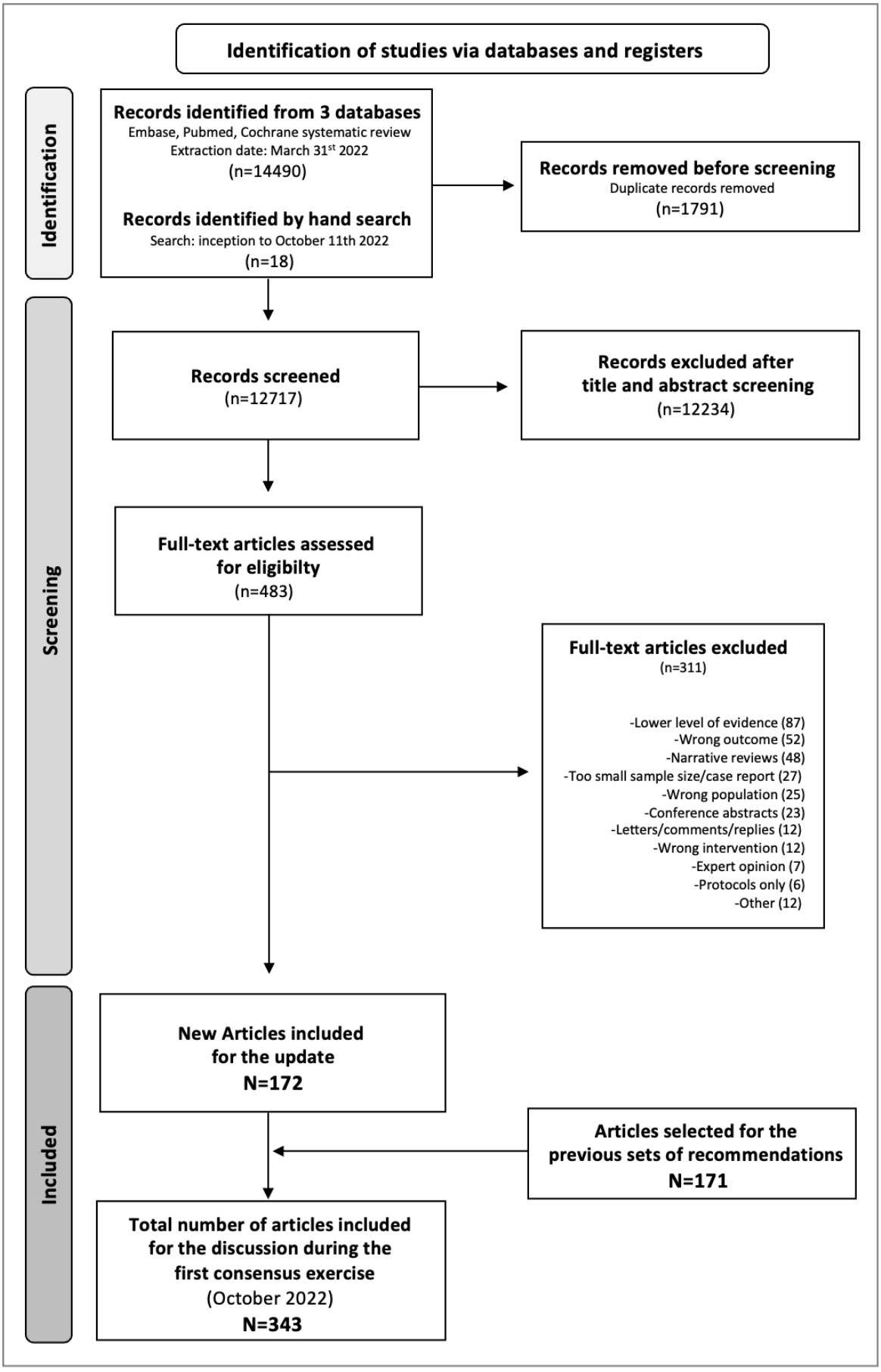

Figure 1 Flowchart for the first search. Computed search (31 March 2022) and hand search (11 October 2022).

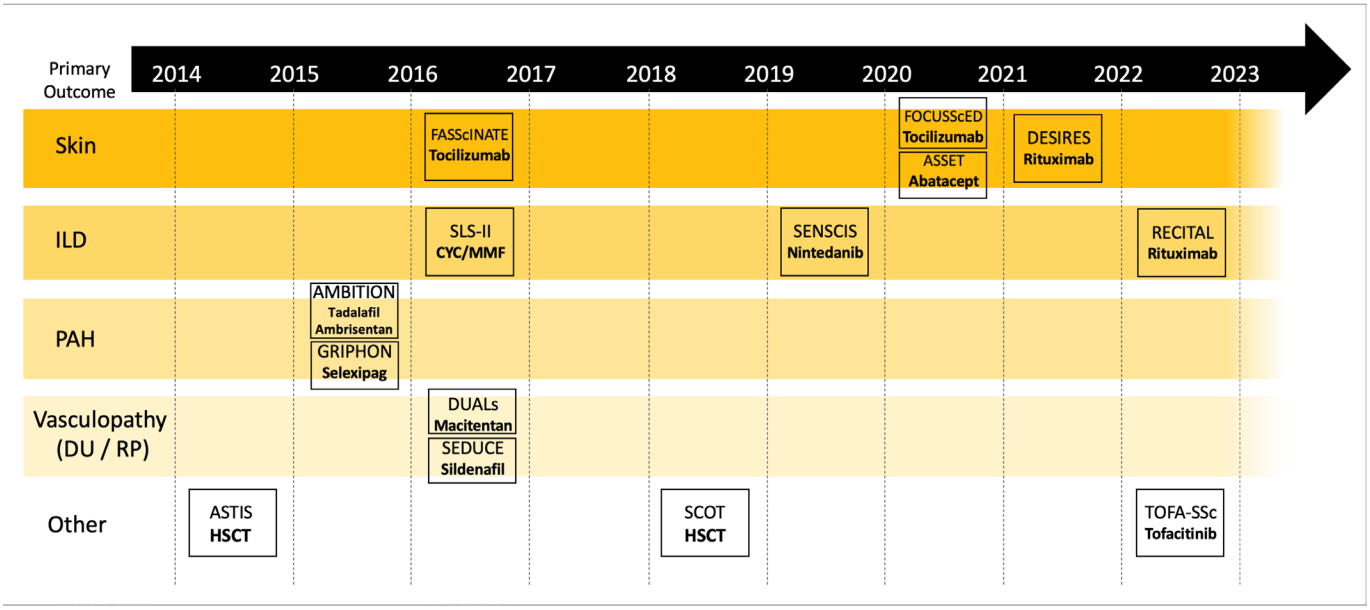

Figure 2 High-quality randomised controlled trials (JADAD=5) included in this systematic literature review, published since the previous set of recommendations and sorted by publication date and primary outcome. CYC, cyclophosphamide; DU, digital ulcers; HSCT, haematopoietic stem cell transplantation; ILD, interstitial lung disease; MMF, mycophenolate mofetil; PAH, pulmonary arterial hypertension; RP, Raynaud's phenomenon; SSc, systemic sclerosis; TOFA, tofacitinib.

manifestations in all patients with SSc, including lcSSc and sine scleroderma, are still needed.[15] Such updated recommendations are meant to involve statements regarding key major manifestations, included rare although severe SSc-related complications such as scleroderma renal crisis (SRC).[16]

To that end, an SLR is needed to summarise the main available date, inform the discussions and to help define the level of evidence and strength of recommendations. Considering the high number of SSc-related clinical manifestations, and the high number of related outcomes, an SLR providing the most up-to-date content of the literature for the recommendations of SSc is a challenge, making this disease specific among all rheumatic diseases and other sets of EULAR recommendations. The objective of the proposed SLR was to provide a critical review of the updated evidence on SSc treatment to address the questions prioritised by an international task force. The results from this SLR informed the next steps that defined the 2023 EULAR recommendations for the treatment of SSc. The current manuscript provides the methodology, detailed protocol and key results of this SLR.

METHODS

Protocol

This SLR was based on an updated version of protocols used for the 2009 and 2017 SSc recommendations as published previously.[6 7] Task force members for this SLR included a methodologist (PGC), a librarian (JE), five reviewers for abstract screening, data extraction and summaries of available evidence (AL, TS, JČ, EB; AL also supervised all others) and the two leaders of the recommendations task force (FdG and YAS). The SLR protocol was not declared prior to the beginning of the search considering that (a) this SLR was time-sensitive to be able to deliver the recommendations on time and to remain updated, (b) the SLR protocols from the prior recommendations were already published and approved, (c) this was an update of the previous SLR and not a new SLR started from scratch. This report follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline for the report of SLR.

Question selection and categorisation

The questions and intervention of interest were selected through an online survey followed by an online consensus meeting. Only questions with 80% of agreement during the consensus meeting were included in the SLR. This approach is further detailed in the recommendation article. Unless specified, questions were focused on a specific intervention, and several subitems were defined if several outcomes per intervention were to be explored. Sixty-seven clinical questions addressing 30 different interventions were explored (table 1). Each question was considered separately with 30 SLRs for the 30 interventions (including several outcomes), and 1 dedicated SLR (with several interventions) for calcinosis (31 searches in total). Calcinosis was explored through a dedicated SLR, considering that (a) this outcome was mentioned as a priority by patient representative during the first consensus meeting and (b) a systematic search for all available interventions for calcinosis was needed to fully cover this outcome, which appeared to be neglected so far.

Three categories of questions were defined prior the beginning of the SLR:

- Type I questions: questions that were unchanged as compared with the previous set of recommendations, that is, same interventions and same outcome(s) of interest.
- Type II questions: questions exploring the efficacy/effectiveness of an intervention already mentioned in the previous set of recommendations but with new outcome(s) added for this update of the recommendations.
- Type III questions: new interventions not mentioned in the previous set of recommendations.

Searching strategy

- Databases: Embase, PubMed and Cochrane Systematic Reviews.

Table 2 Main conclusions for type I questions based on the highest available level of evidence used as starting points for the discussions during the consensus exercise

Questions/Searches	Summaries provided for the consensus exercise: the summaries served as starting points for the discussions during the consensus exercise. Detailed data from pivotal trials were also provided. These summaries are not recommendations themselves. They were extensively discussed during the consensus exercise to aid in shaping the final recommendations.
Type I questions	**Questions that were unchanged as compared with the previous set of recommendations, that is, same interventions and same outcome(s) of interest.**
Methotrexate	***Skin***: there is no new RCT investigating MTX therapy for skin involvement in SSc since the last set of recommendations. A large European prospective observational cohort (ESOS study[1]*) including 326 patients with early dcSSc (within 3 years of onset) compared the efficacy of four treatment protocols: 20–25 mg weekly MTX (n=65), up to 1 g two times per day MMF (n=118), CYC (n=87) and no immunosuppression. The authors found a modest improvement in the mRSS across all groups at 12 months, with no significant difference between treatments: −4.0 units (−5.2 to −2.7) for MTX, −4.1 (−5.3 to −2.7) for MMF, −3.3 (−4.9 to −1.7) for CYC and −2.2 (−4.0 to −0.3) for no immunosuppressant (p value for between-group differences=0.346). The improvement in mRSS was the smallest in the no-immunosuppressant group, which also experienced the highest mortality. In a subsequent open- label, single-centre, RCT (only published as an abstract at the time of SLR), two doses of MTX (15 mg vs 25 mg weekly) were tested in 18 early diffuse patients, for 24 weeks. Both doses of MTX had positive effects on improvement of mRSS, slightly favouring the 25 mg MTX group compared with 15 mg MTX group, p<0.56. Since the authors of this trial have only published the data as an abstract, we can expect the full-text paper to offer more detailed insights on this topic. ***MSK***: there are no new studies investigating MTX for MSK involvement of higher quality than those used for the last set of recommendations. ***ILD***: there are no new studies investigating MTX for ILD involvement of higher quality than those used for the last set of recommendations.
HSCT	***Survival***: since the last recommendations, one high-quality RCT—'SCOT'—was published.[2]* In this trial, safety and efficacy were compared between myeloablative HSCT (n=36) and conventional therapy (CYC, n=36) in patients with SSc with organ involvement (pulmonary, renal and/or high mRSS) from 14 centres within 4,5 years. Using PPP analysis, the rate of OS at 54th month and rates of EFS assessed either at 54 months or 72 months, were significantly higher in group treated with HCTS (p=0.02,p=0.02, p=0.03, respectively). Both analyses (ITT and PPP) showed that the treatment groups began to separate in favour of the transplantation group at approximately 2 years. No transplant recipient died within a year after the transplantation. Nearly 30% died due to myelodysplastic syndrome. The frequency of severe adverse events and adverse events ≥grade 3 was higher in the transplant group. Data from long-term follow-up of the ASTIS cohort[3]* supported evidence of better survival in transplanting group even after 60 months (OS, HR 0.32 (95% CI 0.08 to 1.24, EFS HR 0.42, 95% CI 0.17 to 1.07). Recently, a meta-analysis (3 RCTs and 1 retrospective case-control study) confirmed that AHSCT reduces the risk of all-cause mortality in SSc compared with standard treatment.[4 5*] Nonetheless, the risk of treatment-related mortality was remarkably higher after transplantation (RR 0.5 (95% CI 0.33 to 0.75)) as compared with CYC (RR 9.00 (95% CI 1.57 to 51.69)). ***Skin***: although both assessed groups in SCOT study did not differ on mRSS at baseline, treatment with myeloablative HSCT showed significant improvement of skin fibrosis over 4.5 years (absolute improvement −27%, 95% CI −47% to 6%). Long-term analysis of ASTIS study also pointed towards beneficial effect of non-myeloablative HSCT on the skin at either group level or compared with conventional modality.[6]* Finally, joint analysis of two RCTs (ASSIST[7*] and ASTIS[3*]) confirmed that AHSCT contribute to significant skin improvement (MD 10.62 (95% CI −14.21 to −7.03)), which was supported by the conclusions of a systematic review including three RCTS, which highlighted that 'all three trials showed improvement in mRSS favouring the HSCT groups'.[4 5*] ***ILD***: new evidence from 2014 of the HSCT efficacy in SSc-ILD derives from SCOT, long-term analysis of ASTIS study and meta-analysis of two RCTs (ASSIST and ASTIS).[5*] In all studies, treatment effect was evaluated by changes in pulmonary functional tests. In SCOT, the majority of patients in the HSCT group had increased/unchanged FVC% or DLCO% (75%, 69%, respectively). On the contrary, CYC-treated cases showed a worsening of FVC% in 54% and DLCO% in 67%. Furthermore, although improvement of both FVC% and DLCO% was observed in HSCT group compared with CYC after 5 years in the ASTIS trial, the results were not significantly different. When analysing results from both ASSIST and ASTIS trials, which included a total of 75 patients, HSCT had significant beneficial impact on both FVC% and TLC%. None of the above-mentioned studies examined a change in either HRCT or CRP levels. However, data from a Japanese study showed that 14% of subjects had ILD-HRCT progression after non-myeloablative HSCT. ***PRO/QoL***: as a secondary outcome, the effect of HSCTs on PRO was assessed in all analysed studies. The evidence of the beneficial impact of HSCT treatment on functional disability derives from SCOT trial, ASIST long-term analysis (p=0.05) and review of three RCTs.[4 5*] Considering the health-related QoL assessed by SF-36, only physical component benefits from HSCT in both SCOT study and joint analysis from ASSIST and ASTIS trials (MD 6.99 (95% CI 2.79 to 11.18)). New evidence added to this question since the last recommendations does not impact the conclusions of the previous set of recommendations.
CCB	***RP***: there are no new studies of higher quality than those used in the last set of recommendations investigating CCBs for the treatment of RP.
Angiotensin receptor antagonists	***SRC***: no new trials have been published from 2014 to 2022 on the prevention or improvement of SRC using angiotensin receptor antagonists. Expert opinion will be crucial in formulating recommendations, and the 2017 statement could remain unchanged, as no new data with a higher level of evidence has been available since then.

Continued

Table 2 Continued

Questions/Searches	Summaries provided for the consensus exercise: the summaries served as starting points for the discussions during the consensus exercise. Detailed data from pivotal trials were also provided. These summaries are not recommendations themselves. They were extensively discussed during the consensus exercise to aid in shaping the final recommendations.
Prostacyclins	***RP/DU***: intravenous iloprost efficacy has been suggested for DU healing and prevention in two retrospective cohort studies.[8 9*] Results from one SLR and consensus expert suggested the effectiveness of iloprost in RP secondary to SSc and in healing of DU but head-to-head trials assessing dose titration and regimes are still needed.[10*] An RCT failed to demonstrate the efficacy of oral treprostinil in DU healing and prevention.[11*] Results from two registered RCTs, one on the efficacy of oral treprostinil in patients with symptomatic primary or secondary RP resistant to vasodilatory therapy (NCT02583789), the other about the rheopheresis for RP and DU (the RHEACT trial) are still awaited. Overall, no studies with a higher level of evidence than those cited in the previous set of recommendations have been published regarding iloprost and DU healing/RP. ***PAH***: from a small meta-analysis (with small number of RCTs enrolled) oral prostaglandins could improve exercise capacities, haemodynamics parameters (PVR, PAP) in patients with SSc-PAH.[12*] In a long-term follow-up retrospective study (7.6±2.5 years), patients with SSc on intravenous prostanoids had a stabilisation or improvement of cardiopulmonary function (sPAP; TAPSE and pBNP from baseline), although these analyses were not performed in patients with SSc with a definite PAH. The estimated 5-year survival in patients with SSc-PAH on intravenous prostanoids remained poor (estimated survival at 5 years of 18%).[8*] Given that no new studies with a higher level of evidence have been retrieved since 2014, the conclusions of the previous set of recommendations could remain unchanged.
Selective PDE-5i	***RP/DU***: the new evidence on the efficacy of selective PDE-5i on SSc-related vasculopathy (DU) since the 2014 SLR comes from the SEDUCE study.[13*] This RCT evaluated the beneficial effect of sildenafil (n=42) compared with placebo (n=41) in patients with SSc with active DU (n=83) on digital vasculopathy. Although the time to healing (the primary end point) was shorter in sildenafil group (20 mg three times per day), statistical significant difference was not reached (aHR 1.27 (95% CI 0.85 to 1.89)). Therefore, this trial is considered a negative trial. However, data from a subgroup analysis of ITT population who were on ERA (bosentan) at the time of the randomisation (PDE-5i 15+ERA13), pointed towards the potentially beneficial effects of combination therapy (ERA+PDE-5i) on DU healing in an unadjusted model (HR 1.75 (95% CI 0.94 to 3.26) p=0.08, aHR p=0.41). Nevertheless, the number of DU was significantly reduced by 31% at W8 (OR 0.69 (95% CI 0.47 to 0.99)) and 43% at W12 (OR 0.57 (95% CI 0.37 to 0.88)) in the sildenafil group, reflecting a higher healing rate in the sildenafil group at W8 OR 1.82 (95% CI 1.15 to 2.88) and W12 OR 1.78 (95% CI 1.06 to 2.97). Moreover, the results of this RCT could suggest that sildenafil might be preventive for new DU onset in SSc (OR 0.42 (95% CI 0.15 to 1.17), p=0.10). Regarding PRO (including RP), pain, hand disability and the severity of RP decreased over time without difference between groups. ***PAH***: two post hoc analyses of RCTs (AMBITION),[14 15*] one prospective controlled single-arm study (ATPAHSO),[16*] two retrospective cohort studies (RESCLE[17*] and PHAROS registry[18*]) and one meta-analysis[12*] (cohort and RCTs data) were retrieved in the literature since 2014 regarding the effects of PDE-5i on PAH in SSc. All studies had specific analyses focusing on SSc-PAH and the primary outcome was related to PAH. Data with a high level of evidence pointed towards the beneficial effects of upfront combination therapy (ambrisentan+tadalafil) over monotherapy on SSc-PAH, especially in patients with lcSSc. Combination therapy was generally well tolerated. ***Erectile dysfunction***: although erectile dysfunction significantly impacts health-related QoL in patients with SSc, no studies have assessed the efficacy of PDE-5i on SSc-related erectile dysfunction since 2014.
Antiplatelet agents	***DU***: no new RCTs investigating antiplatelet therapy for DUs have been published since the last set of recommendations. Only new data from cohort studies are available, which provide lower-level evidence compared with what was used for the previous recommendations. One cohort study from the EUSTAR group suggested a protective role of platelets inhibitors, but the type of platelet inhibitor was not explored/mentioned (aspirin or clopidogrel) and it was not a controlled study.[19*] On the contrary, one open-label 'quasi-experimental' study with small sample size (n=13 patients analysed) exploring the impact of clopidogrel on endothelial dysfunction and vascular outcomes, was withdrawn because of the onset of new DUs in three patients (23% of the patients).[20*] Due to lack of evidence and conflicting results regarding the role of antiplatelet therapy for digital ulcers in patients with SSc, expert opinion will be of key importance for formulation of recommendation.
Proton pump inhibitors	***Oesophageal involvement***: the systematic literature review found no new studies specifically demonstrating the beneficial effects of PPIs on oesophageal involvement in patients with SSc. The beneficial effects of PPIs on oesophageal involvement specifically in patients with SSc remains controversial: two cohort studies reported that despite PPI treatment, patients with SSc still had esophagitis and/or gastritis confirmed by endoscopy and abnormal oesophageal acid exposure confirmed by impedance-pH study, respectively.[21 22*] In an RCT, among 148 patients with SSc, 88 reported GERD symptoms (evaluated with GERD questionnaire) that partially responded to high dose of PPIs (prevalence estimate around 53.9% (95% CI 47.4 to 60.3).[23*] It is noteworthy that none of these studies specifically assessed the efficacy of PPIs in SSc. However, the impact of PPIs on reflux is well established in studies involving populations other than patients with SSc.
Prokinetic agents	***GI involvement***: in one RCT including patients with SSc with GERD with partial response to PPIs (n=88), domperidone and alginic acid showed improvement of severity and frequency of symptoms and beneficial impact on QoL after 4 weeks of treatment with both drugs; however, 17% of the patients did not respond to this combination therapy.[23*] The effects of buspirone, an oral 5-HT1A receptor agonist, on patients with SSc with oesophageal involvement despite PPI use were evaluated in a an open-label trial. Oesophageal involvement and GI symptoms were assessed by high-resolution manometry, CT chest and visual analogue scale, respectively.[24*] Buspirone increased the lower oesophageal sphincter resting pressure and decreased scores for heartburn and regurgitation at 4 weeks compared with baseline. In a crossover 2×2 study, prucalopride, a 5-HT4 receptor agonist, was significantly associated with an improvement of colonic function, assessed as intestinal evacuations, UCLA GIT 2.0 constipation and augmented orofecal transit time, in patients with SSc with mild-to-severe symptoms of constipation (n=40).[25*] Furthermore, prucalopride was associated with reduction in the subjective severity of GERD (Likert scale, UCLA GIT 2.0 subscale). Seven subjects withdrew from the treatment due to side effects.
Riociguat	***PAH***: based on prospective planned analyses of an RCT (patent 1 and patient 2 studies) assessing efficacy and safety of riociguat in subgroup of patients with PAH-associated CTD,[26*] riociguat was well tolerated, showed efficacy in SSc-PAH and was associated with sustained improvements at 2 years. Riociguat may also prevent deterioration of PAH in patients with SSc.

Continued

Table 2 Continued

Questions/Searches	Summaries provided for the consensus exercise: the summaries served as starting points for the discussions during the consensus exercise. Detailed data from pivotal trials were also provided. These summaries are not recommendations themselves. They were extensively discussed during the consensus exercise to aid in shaping the final recommendations.
Local wound care	***DU***: literature research revealed only two RCTs investigating local wound therapy for DUs in SSc.[27 28*] One high-quality but small RCT about grafting with autologous adipose tissue was effective on DU healing after 8 weeks, patients in the treatment group reported a significant reduction in pain and a partial restoration of the capillary bed in the treated digits.[27*] Twelve patients in the control group required rescue adipose tissue grafting, with DU healing achieved after 8 weeks in all of them. Another small RCT about oxygen-ozone therapy showed efficacy on ulcer healing and reduction of pain VAS score in the oxygen-ozone group.[28*] However, the follow-up period in that study was only of 20 days. Blinded and placebo-controlled studies are needed. Results from trials on the efficacy of adipose-derived stromal cell injection (Subcutaneous Injections of Autologous Adipose Stem Cells to Heal Digital Ulcers in Patients with Scleroderma) and on the safety and efficacy of mesenchymal stromal cells for DUs (a randomised placebo-controlled double-blind trial to assess the safety of intramuscular administration of allogeneic mesenchymal stromal cells for digital ulcers in systemic sclerosis: the MANUS) are awaited. No other high-level evidence for the efficacy of local wound healing methods was found. Due to the very limited evidence available, expert opinion will be crucial for formulating recommendations.

*The references cited in this table are provided in the supplementary materials and do not refer to the reference list included in the main text.
aHR, adjusted HR; AHSCT, Autologous Hematopoietic Stem Cell Transplantation; AMBITION, Ambrisentan and Tadalafil Combination Therapy in Subjects With Pulmonary Arterial Hypertension (PAH); ASC, Adipocytes derived Stromal Cells; ASSIST, American Scleroderma Stem Cell versus Immune Suppression Trial; ASTIS, Autologous Stem Cell Transplantation International Scleroderma; CCB, calcium channel blocker; CRP, C reactive protein; CTD, connective tissue disease; CYC, cyclophosphamide; DLCO, diffusing capacity of the lungs for carbon monoxide; DU, digital ulcer; EFS, event-free survival; ERA, endothelin receptor antagonist; ESOS, European Scleroderma Observational Study; EUSTAR, European Scleroderma Trials and Research; FVC, forced vital capacity; GERD, gastro-oesophageal reflux disease; GI, gastrointestinal; GIT, gastrointestinal tract; HSCT, haematopoietic stem cell transplantation; 5-HT4, 5-hydroxytryptamine receptor 4; 5-HT1A, 5-hydroxytryptamine receptor 1A; ILD, interstitial lung disease; ITT, intention to treat; IVIG, intravenous immunoglobulin; lcSSc, limited cutaneous systemic sclerosis; MD, mean difference; MMF, mycophenolate mofetil; mRSS, modified Rodnan skin score; MSK, musculoskeletal manifestation; MTX, methotrexate; OS, overall survival; PAH, pulmonary arterial hypertension; pBNP, Pro-brain Natriuretic Peptide; PDE-5i, phosphodiesterase type 5 inhibitors; PHAROS, severe Pulmonary Hypertension mAnagement acROSs Europe; PPI, proton pump inhibitor; PPP, per-protocol population; PRO, patient-reported outcomes; PVR, pulmonary vascular resistance; QoL, quality of life; RCT, randomised controlled trial; RESCLE, Spanish Scleroderma Registry; RHEACT, A randomised controlled prospective single-center feasibility study of Rheopheresis for Raynaud's syndrome and Digital Ulcers in Systemic Sclerosis.; RP, Raynaud's phenomenon; RR, relative risk; RTX, rituximab; SCOT, Scleroderma Cyclophosphamide Or Transplantation; SEDUCE, Sildenafil Effect on Digital Ulcer Healing in sClerodErma; SF-36, 36-item Short Form Health Survey; SIBO, small intestinal bacterial overgrowth; SLR, systematic literature review; sPAP, Systolic Pulmonary Arterial Pressure; SRC, scleroderma renal crisis; SSc, systemic sclerosis; TAPSE, Tricuspid Annular Plane Systolic Excursion; TCZ, tocilizumab; TLC, total lung capacity; UCLA, University of California, Los Angeles; W, week.

- Search terms:
  - For type I and II questions: search terms from the previous set of recommendations were kept unchanged.
  - For type III questions: new search terms were designed with the help of a dedicated librarian after discussion with the SLR task force.
  - Search terms for all questions can be requested from the corresponding author.
- Population of interest:
  - The PICOS strategy was used to defined the population and outcome of interest (online supplemental table 1).
- Publication dates and time period:
  - Two rounds of SLR were performed to ensure the most up-to-date level of evidence, using the same approach for both rounds. Between the two rounds, reviewers also performed regular manual searches before the consensus meeting (October 2022) to ensure a real-time update of the level of evidence before the consensus meeting.

→First round:

- for type I and type II questions: new articles published from 1 October 2014 to 31 March 2022.
- For type III questions: from inception of the databases to 31 March 2022.

→ Second round:

- for types I, II and III questions, all new articles published from 1 April 2022 to 30 November 2022, with same or higher level of evidence were included.

Eligibility criteria

Online supplemental table 2 provides the inclusion and exclusion criteria.

Level of evidence and grade of recommendation

Level of evidence and grade of recommendation were based on the Centre for Evidence-Based Medicine (CEBM) classification (OCEBM levels of evidence, University of Oxford: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence).

Abstract screening for full-text review

Abstract screening was performed using Rayyan software. In case of any doubt, abstracts were discussed among the team and were included rather than excluded for full-text evaluation to ensure comprehensiveness.

Full-text evaluation

For all abstracts selected, full-text evaluation was performed to refined inclusion and exclusion criteria adapted to each question and to define the highest level of evidence required for final inclusion in the data extraction step (table 1).

For each question type, the selection strategy was further refined as follows based on full-text evaluation:

- For type I questions: selection of studies only with a same or higher level of evidence.
- For type II questions: selection of studies only with a same or higher level of evidence, article selected from the previous set of recommendation were kept for data extraction to include new outcomes that had not been explored in the previous set of recommendations.
- For type III questions: selection of studies with the highest level of evidence since inception of the databases.

Data extraction

Data extraction template was defined prior to the beginning of the SLR based on the existing protocols from the previous sets of recommendations.[6]

10% of all articles from each reviewer (ie, from 6 to 12 articles per reviewer) were assessed by a second reviewer to ensure consistency and reliability of data extraction. In case

Table 3 Main conclusions for type II questions based on the highest available level of evidence used as starting points for the discussions during the consensus exercise

Questions/Searches	Summaries provided for the consensus exercise: the summaries served as starting points for the discussions during the consensus exercise. Detailed data from pivotal trials were also provided. These summaries are not recommendations themselves. They were extensively discussed during the consensus exercise to aid in shaping the final recommendations.
Type II questions	**Questions exploring the efficacy/effectiveness of an intervention already mentioned in the previous set of recommendations but with new outcome(s) added for this update of the recommendations.**
Corticosteroids	***ILD:*** a post hoc analysis from the SENSCIS trial focusing on steroids use showed numerically higher rate of FVC% decline in steroid group versus non-steroid group in the placebo arm. Another study evaluating efficacy of intravenous CYC with GC (steroid group, n=9) and without GC (n=10), showed no significant difference in FVC decline (p=0.79) and DLCO (p=0.93) from baseline to 12 months. Most of the retrieved studies were not adequately designed to evaluate the specific effects of steroids on ILD progression, and the effects observed were inconsistent across studies.[29*] Expert opinion will be crucial in formulating recommendations. ***SRC***: available evidence regarding safety of steroids and the occurrence of SRC was heterogenous. Since 2014, six additional studies have indicated an association between steroids and SRC, but the HRs or ORs varied among these studies. One EUSTAR study (n=7546 patients with SSc without SRC vs n=105 patients with SSc with SRC), showed no differences on history of high-dose steroid use in the SRC (3%) group versus non-SRC (2.6%) group (p=0.6).[30*] The effects of corticosteroid pulses, administered with rituximab (intravenous 100 mg before each infusion), on kidney function were retrospectively evaluated in an observational study involving 34 patients with SSc.[31*] After 3.4 years of follow-up, none of the patients developed SRC. ***Heart involvement***: in one observational study including 12 patients with SSc with MRI findings compatible with myocarditis and treated with 0.5 mg/kg steroid to be tapered after 2 weeks over 24 weeks, 66% (8 patients) showed MRI improvement by week 24, however on long term follow-up, 4 patients died (3 cardiac complications; 1 SRC).[32*] In a second study including 32 patients with SSc with no evidence of myocardial involvement, resting radionuclide ventriculography with 99mTc was performed before and 20 days after the administration of prednisolone, 20 mg/day, showing significant improvement in the baseline LVEF (mean 18%, p=0.0001) in the SSc group; this improvement was greater in patients with dcSSc than in those with lcSSc (27% vs 10%, p=0.02). Improvement in LVEF was also observed in the 6 patients who initially had impaired LVEF.[33*] Given the lack of evidence on the impact of steroids on myocardial involvement, expert opinion will be crucial in formulating recommendations. ***MSK***: no studies on steroid use investigated MSK outcomes in patients with SSc.
CYC	***ILD***: new data from the literature (RCTs, observational studies, meta-analyses) since the previous recommendations overall support the efficacy of CYC to preserve and/or improve lung function in SSc-ILD.34,35 The previous set of recommendations was based on two RCTs supporting the efficacy of CYC on SSc-ILD.[36,37*] Since then, one RCT has confirmed the trajectory of lung function (FVC) with CYC, although the control group was on MMF and not on placebo, precluding firm conclusions regarding efficacy CYC itself.[34*] There was no difference in terms of efficacy between MMF and CYC in SLS-II. An open-label RCT comparing intravenous CYC and RTX suggested the superiority of RTX versus CYC on lung function in SSc-ILD, although the number of patients was limited in each arm.[35] Considering the adverse events associated with CYC, expert opinion will be of key importance regarding the place of CYC as first-line therapy in SSc-ILD. The statement from 2017 remains adapted in 2022, although the safety of CYC as compared with other drugs (MMF, RTX, TCZ) should be taken into account for the final statement in the upcoming recommendations. ***Skin***: extrapolation from SLS-I and SLS-II suggest some efficacy of CYC on skin involvement in SSc, but there is still a lack of RCT evaluating CYC and using mRSS as the primary outcome.[38*] ***Heart involvement***: only a small prospective study showed no increase in any of the 9 scores of the Medsger *et al* organ/system severity scale and no change in the European Scleroderma Study Group activity index after CYC.[39*] Other evidence from the literature is scarce and rely on case reports that do not reach the level of evidence for this SLR. Considering the lack of evidence on the impact on CYC on heart involvement (and other visceral manifestation), expert opinion will be of key importance for formulation of recommendation. ***Survival***: in a long-term prospective, open, randomised controlled study on 18 consecutive patients with SSc-ILD, the 5-year Kaplan-Meier survival risk assessment did not show any differences between the two groups (CYC intravenous monthly infusions of 1 g/m^2/dose during 12 months vs CYC similar dosage+prednisone 60 mg/day during 1 month, then decrease) (p=1.00).[40*] In another retrospective analysis the 5-year and 10-year survival rates were not different between the non-treatment and treatment groups. Indeed, the probability of survival (Kaplan-Meier method) was 86.0% and 76.0% in the non-treatment group and 85.7% and 81.0% in the treatment group, respectively (p=0.984 and 0.578). In the treatment group, the probability of survival at 5 and 10 years was 85.7% and 78.6%, respectively, for recipients of glucocorticoid monotherapy and 85.7% and 85.7%, respectively, for patients given immunosuppressive agents (p=0.950 and 0.656).[41*] In the ESOS cohort, on early diffuse cutaneous SSc, there was no significant difference regarding survival between the four treatment arms (MTX, MMF, CYC and azathioprine) at 12 and 24 months.[1*] A meta-analysis included data from seven RCTs (for a total of 855 patients) also reported the number of deaths at the longest available follow-up.[42*] In the context of a very low number of events, the number of deaths was not significantly different between treatments (including data on CYC, CYC and prednisone, CYC and azathioprine) and placebo. Considering all these studies and their limitations, there is still a lack of high-level studies evaluating the impact of CYC on survival in SSc.

Continued

Table 3 Continued

Questions/Searches	Summaries provided for the consensus exercise: the summaries served as starting points for the discussions during the consensus exercise. Detailed data from pivotal trials were also provided. These summaries are not recommendations themselves. They were extensively discussed during the consensus exercise to aid in shaping the final recommendations.
MMF	**ILD**: the evidence for the efficacy of MMF is primarily based on the results of the SLS-II study, which found that 2 years of MMF improved FVC% to a degree comparable to that achieved with 1 year of CYC.[34*] Subsequently, a joint analysis of results from the SLS-I and SLS-II trials reported significant improvements with MMF in both the FVC percentage of predicted and the DLCO percentage of predicted, compared with placebo.[36*] ***Skin***: data from the literature support the use of MMF in SSc considering the data from SLS-II and post hoc analyses from the SLS-I and SLS-II.[38*] However, in both of the previously mentioned studies, the effect of therapy on mRSS was assessed as a secondary outcome. ***Heart involvement***: evidence is scarce and primarily comes from case reports, which were not included for data extraction. The limitations inherent in the observational design of these studies impede drawing definitive conclusions. ***Survival***: in a systematic review (of non-randomised studies) focusing on safety and effectiveness of MMF in SSc, the MMF monotherapy group had significantly better survival than other treatment groups.[43*] This result was mainly based on a previous study who reported a 5-year survival of 91.7% in MMF-treated patients compared with 77.8% in the control group (p=0.01).[44*]
Anti-CD20 therapy (rituximab)	***Skin***: data from the literature support the use of RTX for skin involvement in SSc considering that the primary end point was met in a small high-quality RCT (DESIRES trial) with mRSS as primary end point. The absolute change in mRSS 24 weeks after initiation of study treatment was lower in the RTX group than in the placebo group (−6.30 in the RTX group vs 2.14 in the placebo group; difference −8.44 (95% CI −11.00 to −5.88); p<0·0001).[45*] *ILD*: data from the literature support the use of RTX for the treatment of SSc-ILD, although this statement is based on extrapolation of secondary end points from the DESIRES trial.[45*] An RCT (RECITAL trial) assessing the efficacy of RTX versus CYC for patients with CTD-ILD, including SSc-ILD was recently completed, supporting the use of RTX in this indication.[46*] ***Heart involvement***: evidence of efficacy and safety of RTX in SSc-associated PAH derives from a proof-of-concept, prospective, double-blind, multicentre, phase II randomised clinical trial of patients with SSc-PAH (RESTORE substudy).[47*] The primary efficacy end point, 6 min walk distance, favoured RTX but did not reach statistical significance (p=0.12). However, data at week 48 showed a significant benefit for RTX (p=0.03). RTX treatment appeared to be safe and well tolerated. Apart from this trial, given the lack of evidence on the impact of RTX on cardiac outcomes, such as scleroderma-associated PAH and primary cardiac involvement, expert opinion will be crucial in formulating recommendations. ***MSK***: evidence is scarce and derives mostly from three open-label studies.[48–50*] Overall, data suggested effectiveness of RTX on MSK involvement, particularly in arthritis. However, the limitations inherent in the observational design of these studies hindered the ability to draw definitive conclusions. Given the lack of evidence on the impact of RTX on joint involvement, expert opinion will be crucial for formulating recommendations.
TCZ	***Skin***: in two high-quality RCTs (phase II FaSScinate and phase III focuSSced trials), the primary outcome regarding skin involvement (evolution of mRSS at week 48) was not met despite a numerical trend favouring TCZ (mRSS (48 weeks): difference in means (95% CI): −3.55 (−7.23 to 0.12), p=0.0579 favouring TCZ in the phase II trial, mRSS (48 weeks) adjusted difference in LSM −1.7 (95% CI −3.8 to 0.3), p=0.10 favouring TCZ in the phase III trial).[51,52*] Based on these results, data from the literature do not support the use of TCZ as first-line therapy for skin involvement in dcSSc. Nonetheless, considering this numerical trend in both trials, expert opinion will play a key role in shaping recommendations. As only patients with dcSSc were included in these trials, there is a lack of evidence regarding the impact of TCZ on skin involvement in lcSSc. ***ILD***: in both RCTs (FaSScinate and focuSSced trials),[51,52*] FVC declined assessed as secondary outcome was reduced with TCZ in comparison with placebo, supporting the use of TCZ to limit FVC decline in patients with early dcSSc with SSc-ILD (phase II trial: TCZ −117 mL vs placebo −237 mL; 120 mL, 95% CI −23 to 262; p=0.0990 at week 48 but fewer patients in the TCZ group than in the placebo group had worsening of % pred FVC at 24 weeks (p=0.009) or at 48 weeks (p=0.037)). Phase III trial: in patients with SSc-ILD at baseline, the LSM of FVC (% pred) change from baseline was −6.4 in the placebo group and 0.1 in the TCZ with LSM difference between treatment groups of 6.5 (95% CI 3.4 to 9.5), p<0.0001 at week 48). TCZ had no impact on respiratory-related PROs (St George's Respiratory Questionnaire). Based on the results of FVC decline in both trials, data from the literature support the use of TCZ for the treatment of SSc-ILD in early dcSSc, although this statement is based on extrapolation of secondary end point of two negative trials regarding their primary end point. There are no data of sufficient level of evidence in the literature to support the use of TCZ on SSc-ILD in patients with lcSSc based on the available literature. ***MSK***: data from the phase II trial suggested the efficacy of TCZ on tender join count (both in the double-blind period and in the OL period) but tender joint count 28 was only a secondary outcome and there was only a small proportion of patients with joint involvement in this study. Data on joint involvement were not reported in the publication of the phase III trial.[51,52*] Considering the lack of evidence on the impact of TCZ on joint involvement in the literature, expert opinion will play a key role in shaping recommendations. ***Heart involvement***: in the available RCTs, heart involvement was not explored as an efficacy end point. Although data on adverse events suggest a potential positive impact of TCZ on cardiac adverse events, these were not predefined outcomes for efficacy assessment, so no definitive conclusions can be drawn from these results.[51,52*] Other data in the literature regarding heart involvement and TCZ are case reports/series of fewer than five patients that did not reach the level of quality to be included in this review. Given the lack of evidence on the impact of TCZ on heart involvement, expert opinion will be crucial in formulating recommendations.

Continued

Table 3 Continued

Questions/Searches	Summaries provided for the consensus exercise: the summaries served as starting points for the discussions during the consensus exercise. Detailed data from pivotal trials were also provided. These summaries are not recommendations themselves. They were extensively discussed during the consensus exercise to aid in shaping the final recommendations.
ACE-i	***SRC prevention***: since 2014, the literature search has not identified any new studies with a higher level of evidence regarding the prevention of SRC. Although the selected studies suggest that ACE-i may increase the risk of SRC, it is important to note that these studies are of relatively low quality (primarily longitudinal studies, with no RCTs) and lack data on factors such as the duration and dosage of ACE-i therapy, the degree of proteinuria and other potential confounders. Therefore, expert opinion will be crucial in formulating recommendations. ***Improvement of SRC***: since the last recommendations, one meta-analysis of cohort studies analysed whether the ACE-i could improve the prognosis of SRC in SSc.[53*] Included studies were considered of good quality, which was assessed by the Newcastle-Ottawa Scale including scores for the selection, comparability and outcome. Joint analyses revealed that patients with prior exposure to ACE-i were at statistically higher risk of poor prognosis (long-term dialysis/renal transplantation and death). On the other hand, although the SRC mortality rate was higher in the cohort exposed to ACE-i, this result was not statistically significant. There is still a lack of RCT regarding the efficacy of ACE-i on the improvement of SRC-related outcomes. Prior exposure to ACE-i might be related to SRC poor prognosis. Considering all points mentioned above, expert opinion will be crucial in formulating recommendations.
ERAs	***RP***: large RCTs with primary end points related to RP are lacking. Uncontrolled studies have shown a preference for treatment with an ERA, primarily bosentan, for RP. However, the only available evidence from an RCT and a nifedipine-controlled study indicates no statistically significant effect.[54,55*] Given all the points mentioned above, expert opinion is crucial for formulating recommendations. ***DU***: there is no new higher evidence for the use of bosentan than what was specified in the previous set of recommendations: bosentan has confirmed efficacy in two high-quality RCTs to reduce the number of new DUs in patients with SSc.[56,57*] Regarding macitentan, data from the literature (including two large RCTs) do not support the use of macitentan to prevent DU onset.[58*] ***PAH***: data with a high level of evidence pointed towards the beneficial effect of upfront combination therapy (ambrisentan+tadalafil) over monotherapy on PAH in patients with SSc, especially in patients with lcSSc, highlighting that combination therapy was generally well tolerated.[14*] Data from retrospective studies on the efficacy of ERA monotherapy are conflicting. Given the findings from previous literature searches and the current evidence, expert opinion will be crucial for formulating recommendations. ***Heart***: literature review has not revealed any study specifically assessing ERA's effect on SSc-related cardiomyopathy. ***Combination with PDE-5i for DU***: although the combination of bosentan and sildenafil has been evaluated in RP and other microvascular parameters, based on our literature search, its impact on DU has not been evaluated as a primary end point. Data from a subgroup analysis of ITT population from the SEDUCE study[13*] focusing on patients in ERA (bosentan) at the time of the randomisation (PDE-5i 15+ERA 13), pointed towards the potentially beneficial effect of combination therapy (ERA+PDE-5i) on the time to healing of DUs in unadjusted model (HR 1.75 (95% CI 0.94 to 3.26), p=0.08, aHR p=0.41). ***Prevention of SRC***: data from a retrospective longitudinal study,[17*] which assessed the incidence rate of SRC among patients with SSc with a history of DUs, suggested that specific treatment, with the dominant frequency of ERA Mono (74%, mainly bosentan), could be potentially beneficial for SRC in comparison with non-treatment, but results did not reach statistical significance level (HR 0.7 (95% CI –2.2 to 3.7), p=0.620)). Treated patients had an incidence rate of 2.7 (1.3–4.9) per 1000 patient-years for SRC compared with 3.4 (1.6–6.5) per 1000 patient-years in untreated patients. So far, there are no good-quality data to support the beneficial effect of ERA on SRC in SSc. Considering this lack of evidence, expert opinion will be of key importance for the formulation of the recommendation.
Antibiotics	***SIBO***: from a meta-analysis (of non-RCT studies) conducted to assess the prevalence of SIBO in scleroderma (n=700 patients with SSc), antibiotic showed effectiveness to eradicate SIBO.[59*] Another systematic review came to the same conclusions about antibiotics but the best result to eradicate SIBO was obtained only in five patients after octreotide treatment.[60*] In addition, in a small open-label trial, the comparison of treatment with probiotics, antibiotics or a combination of both in the management of GI symptoms was evaluated in 40 patients with SSc with SIBO.[61*] At the end of the 2-month period, SIBO was eradicated in 55% of the combination therapy group, 33% of the probiotic group and 25% of the antibiotic treatment group. In addition, the probiotic group and combination therapy groups had decreased diarrhoea, abdominal pain and gas, bloating and flatulence. Results from these studies published since 2014 have no impact on the statement from the previous set of recommendations. ***DU:*** in a meta-analysis conducted to assess the prevalence of SIBO in scleroderma, the only data that had emerged regarding DUs was the absence of significant differences between SSc with and without SIBO in digital ulcer with an OR of 1.57 (95% CI 0.54 to 4.53, p=0.41).[59*] In a retrospective study conducted to describe microbiological findings on digital ulcers,[62*] 100% of the germs isolated in infected DUs responded to systemic antibiotics therapy except for methicillin-resistant *Staphylococcus aureus*, which required a more aggressive and long-lasting antibiotic combination therapy, in addition to mechanical procedures. Given the lack of high-quality studies on the impact of antibiotics on DUs, expert opinion will be crucial for formulating recommendations.

Continued

Table 3 Continued

Questions/Searches	Summaries provided for the consensus exercise: the summaries served as starting points for the discussions during the consensus exercise. Detailed data from pivotal trials were also provided. These summaries are not recommendations themselves. They were extensively discussed during the consensus exercise to aid in shaping the final recommendations.

*The references cited in this table are provided in the supplementary materials and do not refer to the reference list included in the main text.
ACE-i, ACE-inhibitors; CTD, connective tissue disease; CYC, cyclophosphamide; dcSSc, diffuse SSc; DLCO, diffusing capacity of the lungs for carbon monoxide; DU, digital ulcer; ERA, endothelin receptor antagonist; ESOS, European Scleroderma Observational Study; EUSTAR, European Scleroderma Trials and Research; EUSTAR, European Scleroderma Trials and Research; FVC, forced vital capacity; GC, glucosteroids; GI, gastrointestinal; ILD, interstitial lung disease; lcSSc, limited cutaneous SSc; LSM, Least Squares Mean; LVEF, left ventricular ejection fraction; MMF, mycophenolate mofetil; mRSS, modified Rodnan skin score; MSK, musculoskeletal manifestations; MTX, methotrexate; OL, Open label; PAH, pulmonary arterial hypertension; PDE-5i, phosphodiesterase type 5 inhibitors; % pred, per cent predicted; RCT, randomised controlled trial; RECITAL, Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK; RP, Raynaud's phenomenon; RTX, rituximab; SEDUCE, Sildenafil Effect on Digital Ulcer Healing in sClerodErmareply Reply; SENSCIS, Study of Efficacy and Safety of Nintedanib in Systemic Sclerosis; SIBO, small intestinal bacterial overgrowth; SLS, Scleroderma Lung Study; SRC, scleroderma renal crisis; SSc, systemic sclerosis; TCZ, tocilizumab.

of discrepancy, data extraction from the considered study was discussed with senior task leader to reach consensus.

- For type I questions: data extraction from the previous set of recommendations was kept unchanged, new articles were added to the data extraction file and level of evidence was updated accordingly.
- For type II questions: results from the new outcomes were collected from articles including in the previous set of recommendations, data extraction was kept unchanged for outcomes already retrieved in the previous set of recommendations. New articles were added to the data extraction file, results from previous and new outcomes were collected, the level of evidence was updated accordingly.
- For type III questions: data from articles according to the defined template were retrieve and level of evidence was defined based on the available studies.

Level of evidence for each question was discussed within the team and with a methodologist to collectively define the final level of evidence, informing the strength of the upcoming recommendation statements.

Quality appraisal

The articles fulfilling the inclusion criteria for data extraction with the highest level of evidence for each search underwent quality appraisal using the JADAD scale.[6] A scale such as the Cochrane 'Risk of Bias' tool could have been preferred but as this was an update of the previous set of recommendations, we used the same scale as used previously.[6] For each study, quality appraisal from 0 to 5 was collected in the data extraction table, together with the extracted data for each outcome of interest.

Continued update of the level of evidence and second round of SLR

SLR task leaders and experts ensured that new studies fulfilling the inclusion criteria and with the adapted level of evidence published since 31 March 2022 were included and discussed during subsequent face-to-face meetings throughout the process to maintain an updated level of evidence on all questions. A new systematic search for all questions was performed in all three databases in December 2022, and all abstracts published from 31 March 2022 to 1 December 2022 were included, and screened following the same approach as for the first round of SLR.

RESULTS

Questions included in the SLR

The list of 31 questions is provided in table 1 and online supplemental table 3. As compared with the previous set of recommendations, some interventions were suppressed as they were not selected during the consensus exercise: azathioprine, fluoxetine, non-steroid anti-inflammatory drugs, statins, tumour necrosis factor-α inhibitors, lymph drainage.

On the contrary, 11 new interventions were explored, including 4 new targeted therapies: selexipag, abatacept, Janus kinase (JAK) inhibitors and nintedanib. Regarding newly explored outcomes, emphasis was made on survival, musculoskeletal manifestations (MSK) and heart involvement, as compared with the previous set of recommendations.

Included studies

Figure 1 and online supplemental figure 1 provide the overall flowcharts for first and second searches. 172 and 9 articles were included for data extraction based on first and second search, respectively. These 181 (172+9) selected articles published since 2014 included 76 RCTs (41.9%) and 24 SLR or meta-analyses (13,3%) (online supplemental table 3). 171 articles from the previous set of recommendations were included and updated in case of missing outcomes. These 171 articles from the previous recommendations included 35 RCTs (20.5%) and 22 SLR or meta-analyses (12.9%). In total, 352 articles were included and extracted to define the level of evidence and support the discussions on the final statements for this updated set of recommendations.

Regarding the level of evidence, all following outcomes reached a level 1 (1a, 1b or 1c) of evidence: skin fibrosis, survival, ILD, patient-reported outcomes (PRO), Raynaud's phenomenon (RP), digital ulcers (DU), pulmonary arterial hypertension (PAH), heart involvement, MSK, quality of life (QoL) and hand function. Despite available RCTs (level of evidence 1b), some outcomes such as heart involvement or MSK were not the primary outcome measures in these trials, and were only secondary/exploratory outcomes from negative RCTs (ie, unmet primary objective) leading to a strength of recommendations of at best B (ie, extrapolation of results from level 1 studies). The highest level of evidence was 2a for small intestinal bacterial overgrowth, 2b for gastrointestinal (GI) (including gastro-oesophageal reflux disease), 2b for SRC, 3b for erectile dysfunction, 4 for calcinosis-related outcomes, with various levels of evidence depending on the interventions (table 1).

This updated SLR included a substantial number of RCTs with JADAD score of 5 (ie, high-quality RCTs) as compared with the previous set of recommendations (14 RCTs, figure 2). The outcome with the highest number of RCTs was skin, used as primary outcome in four high-quality RCTs published since 2014,[10–12 17 18] all dedicated to dcSSc, followed by ILD (three high-quality RCTs) and PAH (two high-quality RCTs).[9 14 19–22] ILD and PAH trials included patients with SSc (lcSSc and dcSSc)

and patients with connective tissue disease (CTD)-ILD and CTD-associated PAH or idiopathic PAH. Although DU was the primary end point in two trials published in 2016 (both negative on their primary objective), no new trials were published since 2016.[23 24] On the contrary, the majority of high-quality RCTs exploring the impact of active therapy on skin were published in the past 3 years (2020–2023) and they were also negative for their primary outcome measure (modified Rodnan skin score (mRSS)) excepted the Study of the Efficacy and Safety of Rituximab in Participants With Systemic Sclerosis (DESIRES) trial assessing the efficacy of rituximab on mRSS.[10–12 17 18]

Conclusions from data extraction

For all interventions, the SLR team provided a brief final conclusion including the main results from the studies with the highest level of evidence for each outcome, and a proposal on the strength of the recommendations. All conclusions were provided by the reviewer in charge of the considered intervention and then revised by another reviewer (AL). In case of discrepancies on the level of evidence/grade of recommendations, the final decision was collectively made with all task force leaders, including the methodologist (PGC). All 31 summaries are provided in tables 2–4 for types I, II and III questions, respectively. The list of the 90 main references used to write these summaries are included as online supplemental materials. These brief conclusions were not used as statements for the recommendations per se but were used as discussion starting points during the consensus meetings. Each time it was needed, the data extraction tables of the studies were presented during the consensus exercise to further support the discussion and explore details that were not covered by the summaries. Final statements for the recommendations were based on the outcomes of interest. Interventions were included for each outcome as deemed appropriate by the task force members, including international experts and patient representatives. The summaries from tables 2–4 include the most updated and highest level of evidence for all 30 interventions (and calcinosis), with associated references, including for interventions and/or outcomes that were not ultimately retained in the final version of the recommendations.

DISCUSSION

The main objective of this SLR was to inform the task force on the highest level of evidence available for the 31 searches prioritised in this new update of the EULAR/EUSTAR recommendations for the treatment of SSc. The main results of the SLR (tables 2–4) were used as discussion starting points for the consensus meeting that defined the final statement for each outcome/organ involvement of interest in the updated recommendations. This approach ensured that these recommendations were based on updated results from the literature, incorporated expert opinion—especially when the level of evidence was low—and included the perspectives of patient representatives.

This SLR was stratified by research questions prioritised during an online Delphi exercise, and 30 interventions were explored. A specific search was also conducted for calcinosis, considering the potential range of interventions for this specific outcome, which was identified among the priorities by patient partners from the task force. Seven interventions from the previous recommendations were suppressed through the Delphi exercise and 11 new interventions were explored, including targeted therapies.[6] A total of 352 articles were analysed and used to inform the consensus meeting. This high number of articles reflects the challenge represented by SSc as compared with other rheumatic diseases, considering the numerous SSc-related clinical manifestations and organ damage, the lack of RCTs for rare although severe manifestations (such as SRC) and the small sample size of some RCTs. For interventions already explored in the previous recommendation but with new outcomes to analyse, all new studies published since October 2014 were included, with data extraction of outcomes included from the previous set of recommendations,[6] and new outcomes selected for this new set of recommendations. For such new outcomes, in studies published prior to October 2014, data extraction was only performed on full texts included in the previous set of recommendations. This means that studies only focusing on new outcomes and published before October 2014 were not included and this could be considered as a limitation. Due to the high number of SSc-relates outcomes, the subsequent high number of articles, and the time period covered (almost 10 years), completing this SLR on time while ensuring the most updated evidence available was also challenging, and two searches were conducted for all questions to ensure that no new articles would have been missed during the process (table 1). Considering this time-sensitive issue, only 10% of all articles from each reviewer benefited from a double data extraction. This could be considered a limitation of our approach; however, given the number of retrieved articles, this 10% threshold included 6–12 articles per reviewer, which was deemed sufficient to identify discrepancies in data extraction that would need to be discussed. No major discrepancies were identified based on this double extraction of 10% of the articles. Moreover, AL reviewed all the summaries and ensured that all data included in the 31 summaries were properly extracted. YA and FdG also reviewed the content and the articles reported in these summaries prior to the consensus meeting and for the preparation of the final manuscript of the recommendations.

Since this SLR was based on the 31 research questions prioritised by the task force, some SSc-related RCTs were not included, such as the trial on rituximab on SSc-PAH or riociguat on skin involvement,[25 26] since these outcomes had not been selected through the Delphi exercise for these interventions. This SLR highlights the high number of high-quality RCT published in SSc since the last update, with >14 new RCTs covering important manifestations of the disease such as skin involvement, ILD, vasculopathy or overall survival as primary end points. Although these RCTs reported on their primary end points, secondary and exploratory end points should not be neglected, as some recent approvals by regulatory agencies were based on secondary outcomes despite negative results on the primary objective.[8] This is the case for tocilizumab for the treatment of SSc-ILD, since the impact on mRSS in focuSSced and FaSScinate was negative in these trials, but with positive results on SSc-ILD-related outcomes.[10 11 18]

This SLR highlights the recent interest in fibrotic manifestations of the disease, including skin fibrosis. Due to this recent emphasis on fibrotic manifestations, these skin-driven RCTs focused on patients with early dcSSc, making lcSSc a neglected subset considering its high prevalence and its impact on QoL.[15 27] RCTs focusing on key domains of the disease, such as GI, calcinosis or SRC are still missing resulting in lower levels of evidence for these important manifestations of the disease. Efforts are needed to improve the development of adapted outcome measures for these manifestations and for lcSSc to foster the design of RCTs focusing on these populations.[27] This is an important issue since some of these domains are nonetheless considered bothersome from the patients' perspective.[28] The results from this SLR reflected the primary interests of researchers rather than

Table 4 Main conclusions for type I questions based on the highest available level of evidence used as starting points for the discussions during the consensus exercise

Questions/Searches	Summaries provided for the consensus exercise: the summaries served as starting points for the discussions during the consensus exercise. Detailed data from pivotal trials were also provided. These summaries are not recommendations themselves. They were extensively discussed during the consensus exercise to aid in shaping the final recommendations.
Type III questions	**New interventions, not mentioned in the previous set of recommendations.**
AC	***DU***: only one prospective open-label pilot study and one retrospective cohort single-centre study have reported data regarding the effect of AC on DUs, which were not the primary outcome in any of these studies. LMWH led to a significant improvement in the primary outcome—RP severity assessed by the VAS—after 24 weeks compared with the conventional therapy group. Although there was a tendency for the number of DUs to decrease in those treated with LMWH, the difference was not statistically significant.[63*] Of note, SSc cases were mostly presented in LMWH-treated cohort (75%), while the control group counted 64% of patients with primary RP, who have not been treated with an injectable placebo. Another study with a rather low number of patients with SSc (n=15) reported that at least 4 months of AC treatment had a significant beneficial impact on severity of pain and the number of ischaemic ulcers. In both studies, ACs were generally well tolerated without major bleeding events.[64*] Overall, rather low evidence level of studies, small cohorts, inappropriate control group (selection bias)/lack of control group, absence of adapted placebo, short follow-up period, missing information regarding dosage/type of AC, type of DUs and confounders should be considered when reaching a conclusion regarding AC and DUs. ***PAH***: evidence of safety and efficacy of ACs for PAH in SSc derives from five cohort studies and one meta-analysis of cohort studies.[65–68*] Most of the studies enrolled cases with incident PAH and confirmed SSc. Their primary outcome was an assessment of survival, including predictors of mortality related to AC, over approximately 3 years of follow-up. Warfarin was the most frequently used AC. Patients naïve to AC therapy served as controls. A sample size of SSc PAH cohort exposed to AC varied from 27 to 104 cases. Regarding survival, two prospective cohort studies reported beneficial effects of warfarin in patients with CTD PAH.[66,67*] On the contrary, all other studies demonstrated a low probability of a survival benefit with AC. Data from the REVEAL study pointed out towards harmful effects of warfarin regardless of discontinuation time and disease severity (current users HR 1.57; 95% CI 1.04 to 2.36; p=0.031, past users a HR 1.49; 95% CI 1.01 to 2.20; p=0.046).[68*] Recently, sensitive analysis specific to SSc PAH from the available meta-analysis confirmed a significant increase in mortality with ACs (HR 1.58, 95% CI 1.08 to 2.31, p=0.02).[65*]
Selexipag	***PAH***: in one high-quality RCT including 1156 patients of different causes,[69*] selexipag was well-tolerated in the PAH-SSc subgroup (n=170 patients with SSc, 77 on treatment vs 93 on placebo) and showed a risk reduction of 44% (HR 0.56; 95% CI 0.34 to 0.91) favouring selexipag as compared with placebo for the primary composite end point of morbidity/mortality in patients with PAH-SSc.[70*] These results support a clinical benefit of selexipag treatment in patients with SSc-PAH either on no treatment or on stable doses of PDE-5i, ERAs or both.
Abatacept	***Skin/ILD/MSK/heart***: the highest level of evidence for efficacy and safety of abatacept derived from one phase II RCT, the ASSET trial,[71*] and its open-label extension trial.[72*] In ASSET, abatacept was associated with numerical, but not statistically significant skin improvement, over the 18-month period, in patients with early diffuse SSc (disease duration ≤36 months). Abatacept showed beneficial trends in FVC (FVC% predicted) and joint/swollen count when compared with placebo. A clinically relevant improvement in disability (HAQ-DI) and in ACR-CRISS was also found. A phase III trial is required to definitively draw proper conclusions about safety and efficacy of abatacept in this population.
Physical therapy	***Hand function***: therapeutic exercises (stretching, active exercises, massages, manual lymph drainage and biofeedback) improved the functionality, reduced pain in the hands and wrists, increased range of motion in the majority of RCTs from a systematic literature review including 15 RCTs and 1 quasi-experimental study,[73*] with durations ranging from 2 weeks to 3 months, and follow-up periods of up to 12 months. However, loss of achieved benefits in most outcomes during the follow-up period, up to 12 months (n=6),emphasising the need of continuous and regular supervised physical therapy modalities. Most of these RCTs were nonetheless of small sample size with JADAD score <5. Considering the various interventions, outcome measures and the lack of large RCTs, expert opinion will be of key importance for the wording of the recommendations. ***QoL:*** therapeutic exercises (stretching, active exercises, massages, manual lymph drainage) improved the QoL in patients with SSc in 13 RCTs improvement with durations ranging from 2 weeks to 3 months,[73*] and follow-up periods up to 12 months. However, loss of achieved benefits in most outcomes during the follow-up period, up to 12 months (n=5 RCTs) emphasises the need for continuous and regular supervised physical therapy. Considering the various interventions, outcome measures and the lack of large RCTs, expert opinion will be of key importance for the wording of the recommendations. ***ILD***: supervised exercise (aerobic, resistance and breathing exercise) resulted in significant change in pulmonary VAS in 2 RCTs, however, improvement did not persist at 6 months (p<0.43) in one study.[73*] One prospective study assessing a pulmonary rehabilitation programme (8 weeks, 5 sessions per week) showed marked improvement in all aspects of St George's Respiratory Questionnaire.[74*] However, no long-term evaluation was reported. Considering the various interventions, outcome measures and the lack of large RCTs, expert opinion will be of key importance for the wording of the recommendations.
Hyperbaric chamber	***DU***: none of the evidence from the literature meets the minimal quality threshold for these recommendations, as only case series involving fewer than five patients reported data on the effect of hyperbaric chamber on DUs in SSc.
Nutritional support	***QoL***: data on the impact of nutritional support on QoL in patients with SSc are scarce. One RCT with a small sample size found no effect of probiotics on the SF-36, HAQ-DI or the social and emotional components of the UCLA SCTC GIT assessment scale.[75*] Home parenteral nutrition has been evaluated in small observational studies with conflicting results. Individualised nutritional counselling had no impact on QoL in two observational studies of small sample size.[76,77*] Considering the lack of consistent results, expert opinion will be of key importance for the wording of the recommendations.
Botox	***DU***: two RCTs[78,79*] and one uncontrolled trial[80*] were retrieved in the literature regarding the effects of botulinum toxin on vascular manifestations in the hand of patients with SSc. None of these trials had DU as their primary outcome. One RCT with RP as primary outcome, was negative for its primary outcome and the prevalence of DU at baseline and during follow-up was too low to assess the efficacy of botulinum toxin on DU healing/onset.[79*] Another RCT using finger blood flow as primary outcome, showed no significant effect on DU healing, although the RR of developing new ulcers was higher in hands allocated to placebo treatment than in hands allocated to Botox-A, without reaching statistical significance.[78*] Another trial with RP severity as primary end point, but with no placebo procedure in the controlled arm (only no treatment), showed that the numbers of DU at 4–16 weeks was lower in the two treatment arms with higher dosages, and that no new DU occurred in the two treatments arms with the higher dosages.[80*] Overall, based on secondary outcomes of small RCTs or low-quality RCTs, botulinum toxin showed numerical effects towards a lower risk of DU during follow-up but RCTs based on DU as primary outcome are needed to confirm these results.

Continued

Table 4 Continued

Questions/Searches	Summaries provided for the consensus exercise: the summaries served as starting points for the discussions during the consensus exercise. Detailed data from pivotal trials were also provided. These summaries are not recommendations themselves. They were extensively discussed during the consensus exercise to aid in shaping the final recommendations.
IVIG	***Skin***: an RCT studied the effects of IVIG in a population of patients with active dcSSc (n=63) found that the change in mRSS reached statistical significance only when a second IVIG cycle was administered (mRSS decreased −1.4±1.0 to −5.7±1.0 at 32 weeks, and 60 weeks in the IVIG→IVIG (GG) group; from −1.3±1.0 to −5.0±1.0 at 32 weeks in the placebo→IVIG (PG) group) (p=0.0040).[81*] ***GI and MSK***: IVIG (>1 g/kg/cycle) showed some beneficial effects on musculoskeletal involvement, systemic inflammation, digestive tract symptoms and with corticosteroid-sparing effects in an observational cohort of patients with early diagnosed (4.1±5.2 years before) SSc (n=46) with both diffuse (59%) and limited cutaneous involvement.[82*] In this study, most patients had an overlap syndrome with idiopathic inflammatory myopathies (85%) and the main indication for IVIG were muscle (80%) and digestive tract involvements (11%). In another observational study on 15 SSc with overlap polymyositis, treatment with IVIG (2 g/kg/month) showed some improvement on GI symptoms, evaluated through questionnaires.[83*] A significant reduction in GERD frequency and intensity mean scores (p=0.006 and p=0.013, respectively), and of the GIT 2.0 score (from 1.07 (SD 0.67) to 0.60 (0.46), p=0.002) was reported. Regarding MSK involvement, they described a reduction of Medical Research Council sum score and CPK levels were reduced (p=0.001 and p=0.025, respectively). This beneficial effect was also confirmed for mRSS (from 21.5 (SD 13.8) to 10 (10.6), p=0.005). In a small open-label study, IVIG (2 g/kg/4 days/month for six consecutive courses) seems to improve join involvement in SSc (n=7) with severe and refractory joint involvement which did not respond to previous therapy with methotrexate and CYC.[84*] After 6 months, reduction of the number of swollen joint pain (p=0.001) and tender joint pain (p=0.001) (VAS p=0.05) and RI (p=0.005) was achieved as well as improvement of hand function (p=0.05) and HAQ (p=0.05), except in one patient with erosive arthritis.
JAK inhibitors	Level of evidence in the literature for the use of JAK inhibitors in patients with SSc is low, with only one SLR, which is based on case reports, case series or open-label studies[85*] and one phase I/II RCT with small sample size.[86*] The only two JAK inhibitors with available data are tofacitinib and baricitinib. ***Skin***: a majority of patients who received JAK inhibitors showed improvement of mRSS, but with no significant difference versus placebo in one RCT of small sample size. There was a numerical trend favouring tofacitinib.[86,87*] ***MSK***: HAQ-DI tend to improve in the tofacitinib arm (p=0.3 in the double-blind phase, p=0.07 at the end of the open-label extension) and all patients reported in the SLR and receiving a JAK inhibitor for articular involvement experienced articular response, although the absence of controls precluded firm conclusions.[86] *Internal organ involvement*: the main available data were about ILD. In the tofacitinib RCT, there was no difference in terms of FVC% predicted at the end of the double-blind section, and a numerical trend favouring placebo.[86] In the SLR, 97% of the patients did not experience ILD progression.[85*]
Pentoxyphilline	***RP/DU***: none of the evidence from the literature meets the minimal quality threshold for these recommendations, as only case series involving fewer than five patients have reported data on the effect of pentoxifylline on RP and DUs in SSc. Given the widespread use of pentoxifylline in some countries and the lack of robust evidence regarding its effects on RP and DUs in SSc, expert opinion is crucial for formulating recommendations.
Nintedanib	***ILD***: in SENSCIS study,[88*] a large and multinational trial, the primary end point regarding SSc-ILD (annual rate of decline in FVC) was met at week 52. The nintedanib group showed a lower annual rate of decline in FVC (−52.4±13.8 mL/year) than the placebo group (−93.3±13.5 mL/year). The difference was 41.0 mL/year (95% CI 2.9 to 79.0; p=0.04), with a relative rate of reduction in FVC of 44%. Moreover, in the nintedanib arm, patients who were taking MMF at baseline presented a minor rate of change in FVC (−40.2 mL) than naïve patients (−63.9 mL). Data from the literature support the use of nintedanib for the treatment of SSc-ILD in SSc, considering that the primary end point was met in one large and international RCT. The phase III INBUILD basket trial on 170 patients with progressive ILD (including 39 patients with SSc-ILD) also confirmed the beneficial impact of nintedanib on FVC, since the rate of decline in FVC over 52 weeks was −75.9 mL/year with nintedanib vs −178.6 mL/year with placebo (difference 102.7 mL/year (95% CI 23.2, 182.2); nominal p=0.012).[89*] ***Combination therapy with MMF for ILD***: data from the literature suggest a potential clinical benefit of combination of MMF and nintedanib for SSc-ILD considering the lower numerical annual rate of decrease in FVC and consistently lower proportions of patients with categorical decreases in FVC in the MMF group versus non-MMF group.[90*] Thus, expert opinion will be of key importance for formulation of recommendation. ***PRO/QoL***: no significant absolute change for PRO (assessed as secondary end points), including St George's Respiratory Questionnaire, HAQ-DI and Functional Assessment of Chronic Illness Therapy-Dyspnoea score, was found, at week 52.[88*] In SENCIS-ON, the mean scores on the UCLA SCTC GIT instrument in both the continued nintedanib and initiated nintedanib groups suggested that most patients had no or mild GI symptoms at the start of the trial. However, a small worsening in mean UCLA SCTC GIT instrument total score was observed over 52 weeks. ***Other manifestations***: in the SENSCIS trial,[90*] the absolute change in mRSS from baseline to week 52 was assessed as a secondary end point; and did not differ significantly between the trial groups with differences of: −0.21 (95% CI −0.94 to 0.53), p=0.58. Also, there was no difference between nintedanib and placebo in digital ulcer burden (ie, in the number of fingers with ulcers of vascular origin distal to the proximal interphalangeal joints). Data from the literature do not support the use of nintedanib for skin involvement or DUs in SSc, considering that these secondary end points were not met in one international RCT.
Any therapeutic approach for calcinosis	***Any calcinosis-related outcome***: there is limited evidence to guide clinicians on the treatment of SSc-related calcinosis. The safety and efficacy of diltiazem, rituximab, minocycline and treprostinil for calcinosis in SSc are primarily based on case reports and small retrospective case series. Regarding topical or non-pharmacological treatments for SSc-related calcinosis, studies have been published on carbon dioxide laser therapy, surgical debulking and topical sodium thiosulfate. However, these studies have several limitations, including retrospective design, small sample sizes, lack of control groups, absence of standardised methods for assessing clinical and imaging responses, limited follow-up and lack of PROs. These limitations impede drawing reliable conclusions about the efficacy and safety of each treatment for SSc-related calcinosis.

Continued

Table 4 Continued

Questions/Searches	Summaries provided for the consensus exercise: the summaries served as starting points for the discussions during the consensus exercise. Detailed data from pivotal trials were also provided. These summaries are not recommendations themselves. They were extensively discussed during the consensus exercise to aid in shaping the final recommendations.

*The references cited in this table are provided in the supplementary materials and do not refer to the reference list included in the main text.
AC, anticoagulants; ACR-CRISS, American College of Rheumatology's Scleroderma Clinical Trials Consortium and the CRIteria for the Improvement of SSc; aHR, adjusted HR; ASSET, Safety and efficacy of abatacept in early diffuse cutaneous systemic sclerosis (ASSET); CPK, Creatine Phosphokinase (a blood test used to measure muscle damage); CTD, connective tissue disease; dcSSc, diffuse cutaneous SSc; DU, digital ulcer; ERA, endothelin receptor antagonist; FVC, forced vital capacity; GERD, gastro-oesophageal reflux disease; GI, gastrointestinal; GIT, gastrointestinal tract; HAQ-DI, Health Assessment Questionnaire-Disability Index; ILD, interstitial lung disease; INBUILD, Efficacy and Safety of Nintedanib in Patients With Progressive Fibrosing Interstitial Lung Disease; IVIG, intravenous immunoglobulin; JAK, Janus kinase; LMWH, low molecular weight heparin; MMF, mycophenolate mofetil; MSK, musculoskeletal manifestations; PAH, pulmonary arterial hypertension; PDE-5i, phosphodiesterase type 5 inhibitors; PRO, patient-reported outcome; QoL, quality of life; RCT, randomised controlled trial; REVEAL, Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; RI, Ritchie Index; RP, Raynaud's phenomenon; RR, relative risk; SCTC, Scleroderma Clinical Trial Consortium; SENCIS-ON, Study of Efficacy and Safety of Nintedanib in Systemic Sclerosis – Open Label extension; SF-36, 36-item Short Form Health Survey; SLR, systematic literature review; SSc, systemic sclerosis; UCLA, University of California, Los Angeles; VAS, visual analogue scale.

those of patients, although the patient perspective is of growing interest in the management of rare diseases with multiple organ involvement such as SSc. Thus including the patient perspectives during the discussion that defined the final statements of the recommendations was a major point to consider, stressing that recommendations could not be only guided by the SLR. Expert opinion was also needed to deliver a clear message to physicians for the management of important domains or subpopulations that still lack available RCTs. To that end, observational studies for a complex and rare disease like SSc are of upmost importance to support expert opinions. International longitudinal cohorts, such as the EUSTAR database, offer a unique opportunity to guide expert opinion, especially for rare but severe manifestations.[4 29–32]

This SLR has some limitations. SLR protocol was not specifically published before starting the literature search and SLR was not referenced, but it was an update, with time-sensitive issues, and protocols from the previous set of recommendations were already published, without major deviation from these protocols.[6 7] Abstract screening was performed by only one reviewer, but this was explained by the high number of abstracts to be screened (12 717 for the first search and 2021 for the second search). We may have failed in identifying some studies published before October 2014 with interventions of interest already included in the previous set of recommendations but with new outcomes selected for this update. Live discussion with experts in the field has limited this selection bias, and new studies published after October 2014 were included for these new outcomes. ACR/EULAR 2013 classification criteria could not be retrospectively applied in all studies published prior to 2013.[33]

This SRL also has several strengths. Each step was supervised by a dedicated methodologist. Three databases were searched, and search terms were designed by a dedicated librarian, informed by the task force leaders. This SLR was based on a comprehensive literature search despite the complexity of the task considering the high number of interventions, the high number of outcomes and the lack of RCTs leading to the analysis of observational studies as well. This SLR also took into account the previous set of recommendations, and updated previous data extraction with new outcomes as deemed appropriate by the Delphi exercise, reflecting the evolution of knowledge and practice. This SLR was performed by an international team of reviewers supervised by international experts in the field. Data extraction was supervised by the same researcher (AL), ensuring the consistency of the approach and methods. Two rounds of SLR ensured a most up-to-date screening of the literature.

Based on a robust methodology, as per EULAR guidelines, this SLR provides and summarises the highest level of evidence to address questions prioritised in the update of EULAR recommendations for the treatment of SSc, providing an unprecedented comprehensive overview of recent knowledge on SSc treatments and participating in defining the future research agenda for SSc management. This SLR manuscript also provides the most updated and highest level of evidence on interventions and/or outcomes that were not ultimately included in the final version of the recommendations. However, evidence on these outcomes and interventions may still be relevant for clinicians seeking guidance and references, making this SLR an essential complement to the statements provided in the recommendations manuscript.

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Results from the international collaborative systematic literature review informing the 2023 EULAR recommendations for the treatment of Systemic sclerosis

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Supplementary Materials :

List of reference for Table 2,
3 supplementary Tables,
1 Supplementary Figure.

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Supplementary Table 1: PICOS (Population, Intervention, Comparator, Outcomes, Studies) strategy

PICOS Item	Definition
Population	Patients included in the study had to be adults with definite SSc, according to the ACR classification criteria, or as classified according to subtype as defined by LeRoy et al., or according to the ACR-EULAR classification criteria. Studies including patients with other diagnoses, such as RP or PAH, were only included if subgroup analysis of SSc patients was provided and the subgroups were larger than n=5
Intervention	One of the 30 interventions selected by the task force. For calcinosis any intervention was included.
Comparator	The following comparator were accepted : standard of care, placebo, no intervention, same patient as comparator for before/after studies.
Outcomes	One or several outcomes were included according to the list of outcome prioritized by the task force for each intervention, candidate outcomes included : Survival, Event-free survival, Skin fibrosis, ILD, RP, PAH, DU, MSK, PRO, QoL, GI, Erectile dysfunction, SIBO, Calcinosis-related outcomes, Hand function, Hear involvement, Prevention, improvement, worsening of SRC.
Studies	Studies were selected following the inclusion and exclusion criteria presented in Table 3.

DU: digital ulcers; GI : Gastro-interstinal ; ILD : interstitial Lung Disease; MSK: musculoskeletal manifestations ; PAH: Pulmonary Arterial Hypertension; PRO : Patient reported outcomes ; QoL : Quality of Life ; RP : Raynaud's Phenomenon ; SIBO: Small intestinal Bacterial overgrowth ; SRC: Scleroderma Renal Crisis

Supplementary Table 2: Inclusion and exclusion criteria for data extraction.

Inclusion criteria	Exclusion criteria
Meta-analysis of randomized controlled trials (RCTs), systematic reviews, RCTs, controlled trials, case-control study, uncontrolled trial/cohort study/case series were included. For each search/question only the studies with the highest level of evidence were included for data extraction	Cross sectional studies, case reports and case series with less than five patients with SSc were excluded, Conference abstract, narrative reviews were excluded, Protocols of published an unpublished studies were excluded, protocol of awaited publications were excluded but kept for the records for hand search and updated search. For each search/question, based on the level of evidence, studies with lower lever of evidence were excluded.

Supplementary Table 3: list of the 31 searches/questions and related outcomes prioritized by the task force, and numbers of publications[#] related to these searches.

Questions/Searches	Nb of total articles selected per question (in 2014)	*Meta-analysis or SLR[s] of RCTs n(%)*	*RCTs n(%)*	*Case-control studies n(%)*	*Observational studies (including cohort studies) n(%)*	Nb of total articles selected per question (March 2022 update)	*Meta-analysis or SLR[s] of RCTs n(%)*	*RCTs n(%)*	*Case-control studies n(%)*	*Observational studies (including cohort studies) n(%)*	Nb of total articles selected per question (November 2022 update)	*Meta-analysis or SLR[s] of RCTs n(%)*	*RCTs n(%)*	*Case-control studies n(%)*	*Observational studies (including cohort studies) n(%)*	Outcomes/ Manifestations of interest (Highest available level of evidence)
Total	**N=171**	**22 (12.9)**	**35 (20.5)**	**12 (7)**	**102 (59.6)**	**N=172**	**24 (14)**	**70 (40.7)**	**8 (4.7)**	**70 (40.7)**	**N=9**	**0**	**6 (66.7)**	**1 (11.1)**	**2 (22.2)**	
Type I questions : unchanged as compared to the previous set of recommendations	**67**	**9 (13.4)**	**18 (26.9)**	**1 (1.5)**	**39 (58.2)**	**35**	**5 (14.3)**	**11 (31.4)**	**1 (2.9)**	**18 (51.4)**	**0**	**0**	**0**	**0**	**0**	
1. Methotrexate	**6**	1 (16.7)	2 (33.3)	0 (0)	3 (50)	**1**	0	0	0	1 (100)	**0**	0	0	0	0	1. Skin fibrosis (1b) 2. MSK (2b) 3. ILD (2b)
2. HSCT	**17**	0	2 (11.8)	0	15 (88.2)	**5**	2 (40)	1 (20)	0	2 (40)	**0**	0	0	0	0	1. Survival (1a) 2. Event-free survival (1a) 3. Skin fibrosis (1a) 4. ILD (1a) 5. PRO (1a)
3. Calcium channel blockers	**4**	2 (50)	2 (50)	0	0	**0**	0	0	0	0	**0**	0	0	0	0	1.RP (1a)
4. Angiotensin receptor antagonists	**2**	0	0	0	2 (100)	**0**	0	0	0	0	**0**	0	0	0	0	1. Prevention of SRC (5) 2. Improvement of SRC (5)
5. Prostacyclins	**8**	1 (12.5)	2 (25)	1 (12.5)	4 (50)	**7**	1 (14.3)	3 (42.9)	0	3 (42.9)	**0**	0	0	0	0	1. RP (1a) 2. DU (1a) 3. PAH (1a)
6. Selective PDE-5 inhibitors	**16**	5 (31.3)	6 (37.5)	0	5 (31.3)	**7**	1 (14.3)	3 (42.9)	0	3 (42.9)	**0**	0	0	0	0	1. RP (1a) 2. DU (1a)

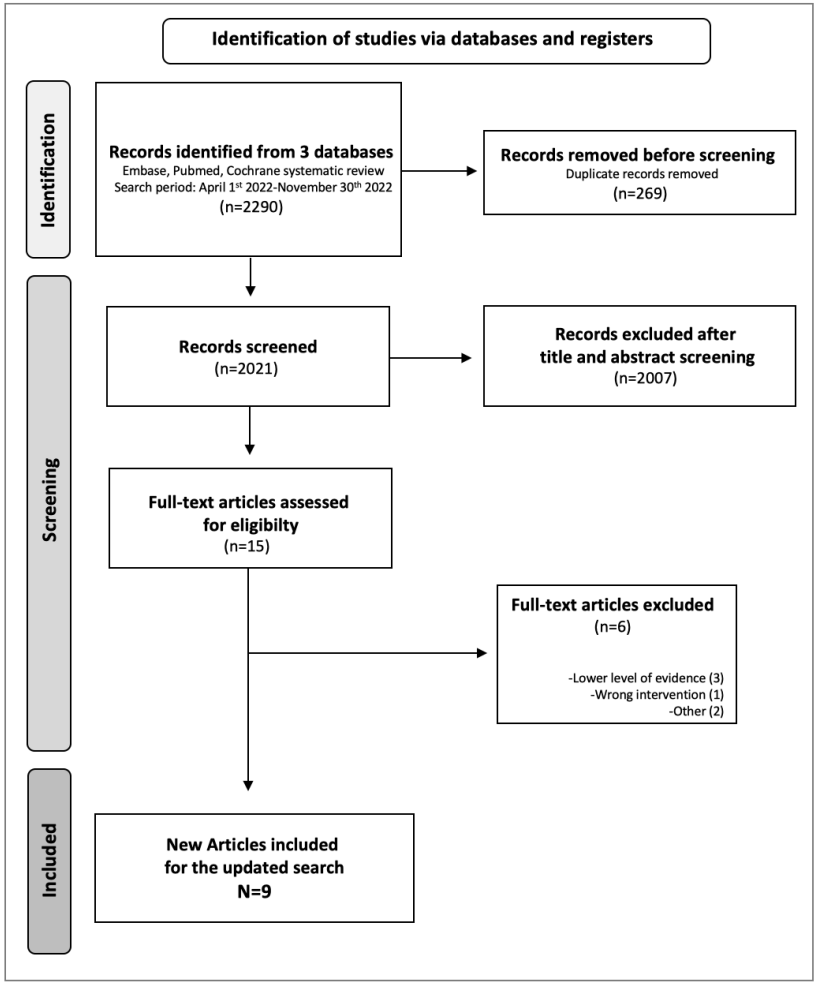
															3. PAH (1a) 4.Erectile dysfunction (3)
7. Anti-platelet Agents	**1**	0	1 (100)	0	0	**2**	0	0	0	2 (100)	**0**	0	0	0	0	1. DU (2b)
8. Proton Pump inhibitors	**7**	0	0	0	7 (100)	**6**	0	1 (16.7)	1 (16.7)	4 (66.7)	**0**	0	0	0	0	1. Esophageal involvement (3)
9. Prokinetic agents	**2**	0	1 (50)	0	1 (50)	**3**	0	2 (66.7)	0	1 (33.3)	**0**	0	0	0	0	1. GI involvement (1b)
10. Riociguat	**1**	0	1 (100)	0	0	**1**	0	1 (100)	0	0	**0**	0	0	0	0	1. PAH (1b)
11. Local Wound Care	**3**	0	1 (33.3)	0	2 (66.7)	**3**	1 (33.3)	2 (66.7)	0	0	**0**	0	0	0	0	1. DU (2a)
Type II questions : intervention already mentioned but including new outcome(s)*	**104**	**13 (12.5)**	**17 (16.3)**	**11 (10.6)**	**63 (60.6)**	**65**	**14 (21.5)**	**24 (36.9)**	**7 (10.8)**	**20 (30.8)**	**5**	**0**	**4 (80)**	**0**	**1 (20)**	
1. Corticosteroids	**17**	3 (17.6)	1 (5.9)	3 (17.6)	10 (58.8)	**12**	0	0	5 (41.7)	7 (58.3)	**2**	0	1 (50)	0	1 (50)	1. ILD (2b) 2. SRC (3) 3. Heart involvement* (3) 4. MSK* (3)
2. Cyclophosphamide	**26**	5 (19.2)	8 (30.8)	2 (7.7)	11 (42.3)	**7**	1 (14.3)	3 (42.9)	0	3 (42.9)	**1**	0	1 (100)	0	0	1. ILD (1a) 2. Skin Fibrosis (1b) 3. Other organ involvement including heart involvement* (3) 4. Survival* (2b)
3. Mycophenolate mofetil	**12**	1 (8.3)	0	3 (25)	8 (66.7)	**8**	2 (25)	6 (75)	0	0	**0**	0	0	0	0	1. ILD (1a) 2. Skin fibrosis (1b) 3. Heart involvement* (1b) 4. Survival* (1b) 5. Combination with Nintedanib on ILD* (1b)
4. Anti-CD20 therapy (Rituximab)	**11**	1 (9.1)	2 (18.2)	0	8 (72.7)	**14**	7 (50)	5 (35.7)	0	2 (14.3)	**2**	0	2 (100)	0	0	1. Skin fibrosis (1a) 2. ILD (1a)

															3. Heart involvement/PAH* (1b) 4. MSK* (2b)
5. Tocilizumab	**1**	0	0	0	1 (100)	**5**	0	5 (100)	0	0	**0**	0	0	0	0	1. Skin fibrosis (1b) 2. ILD (1b) 3. MSK (1b) 4.Heart involvement* (1b)
6. ACE-inhibitors	**5**	0	1 (20)	1 (20)	3 (60)	**3**	1 (33.3)	0	0	2 (66.7)	**0**	0	0	0	0	1. Prevention of SRC (3) 2. Improvement of SRC (3) 3. Worsening of SRC* (3)
7. Endothelin receptor antagonists	**30**	3 (10)	5 (16.7)	2 (6.7)	20 (66.7)	**12**	1 (8.3)	5 (41.7)	1 (8.3)	5 (41.7)	**0**	0	0	0	0	1. RP (2b) 2. DU (1a) 3. PAH (1a) 4. Heart involvement* (5) 5. Combination with PDE-5i for DU* (1b) 6. Prevention of SRC* (2b)
8. Antibiotics	**2**	0	0	0	2 (100)	**4**	2 (50)	0	1 (25)	1 (25)	**0**	0	0	0	0	1. SIBO (2b) 2. DU* (4)
Type III questions : interventions not mentioned in the previous recommendations.	**NA**	**-**	**-**	**-**	**-**	**72**	**5 (6.9)**	**35 (48.6)**	**0**	**32 (44.4)**	**4**	**0**	**2 (50)**	**1 (25)**	**1 (25)**	
1. Anti-coagulants	**-**	-	-	-	-	**8**	1 (12.5)	0	0	7 (87.5)	**0**	0	0	0	0	1.DU (2b) 2.PAH (2a)
2. Selexipag	**-**	-	-	-	-	**1**	0	1 (100)	0	0	**0**	0	0	0	0	1.PAH (1b)
3. Abatacept	**-**	-	-	-	-	**4**	0	2 (50)	0	2 (50)	**0**	0	0	0	0	1. Skin fibrosis (1b) 2. ILD (1b) 3. MSK (1b) 4. Heart involvement (5)
4. Physical Therapy	**-**	-	-	-	-	**22**	1 (4.5)	19 (86.4)	0	2 (9.1)	**1**	0	0	0	1 (100)	1. Hand function (1a) 2. QoL (1a)

																3. ILD (2b)
5. Hyperbaric Chamber	-	-	-	-	-	**0**	0	0	0	0	**0**	0	0	0	0	1. DU (5)
6. Nutritional Support	-	-	-	-	-	**7**	1 (14.3)	1 (14.3)	0	5 (71.4)	**0**	0	0	0	0	1. QoL (2a)
7. Botox	-	-	-	-	-	**3**	0	2 (66.7)	0	1 (33.3)	**1**	0	0	1 (100)	0	1. DU (1b)
8. Intravenous Immunoglobulin	-	-	-	-	-	**5**	1 (20)	1 (20)	0	3 (60)	**0**	0	0	0	0	1.Skin fibrosis (1b) 2. GI involvement (2b) 3. Heart involvement (2b)
9. JAK Inhibitors	-	-	-	-	-	**2**	1 (50)	1 (50)	0	0	**0**	0	0	0	0	1. Skin fibrosis (2a) 2. MSK (2a) 3. ILD (2a) 4. Heart Involvement (5)
10. Pentoxyphilline	-	-	-	-	-	**0**	0	0	0	0	**0**	0	0	0	0	1. RP (5) 2. DU (5)
11. Nintedanib	-	-	-	-	-	**8**	0	8 (100)	0	0	**2**	0	2 (100)	0	0	1. ILD (1b) 2. PRO (1b) 3. QoL (1b) 4. Other manifestations (1b)
12. Any therapeutic approach for Calcinosis	-	-	-	-	-	**12**	0	0	0	12 (100)	**0**	0	0	0	0	1. Any calcinosis-related outcomes, including calcinosis-related pain (visual analog scale), calcinosis-related DUs, assessment of local inflammation, radiographic assessment, disability (4)

*ACE : Angiotensin Conversion Enzyme DU: digital ulcers; GI : Gastro-interstinal ; HSCT: Haematopoietic stem cell transplantation ; ILD : interstitial Lung Disease; MSK: musculoskeletal manifestations ; PAH: Pulmonary Arterial Hypertension ; PDE-5: Phospho-di-Esterase; PRO : Patient reported outcomes ; QoL : Quality of Life ; RP : Raynaud's Phenomenon ; SIBO: Small intestinal Bacterial overgrowth ; SRC: Scleroderma Renal Crisis * New outcome as compared to the 2017 set of recommendations NA: not appropriate*

#several publications could be derived from a same single RCT, with new outcomes explored/reported depending on the publication. $including SLR of observational studies



Supplementary Figure 1: Flow chart for the updated search (computed search April 1st 2022 to November 30th 2022)