Supplementary methods

I. Selection process of clinical questions and identification of key words

The expert committee held all meetings online. During the first meeting the scope, main items of the recommendations and the methodology were defined. They agreed to identify the clinical questions and vote at the next meeting. On 20 December 2020, a great deal of agreement was reached on the clinical questions seen in Table S1 and the literature review step was started. Then, appropriate key phrases pointing to each question were identified for the literature review (Supplementary Table S2).

Supplementary Table S1. Clinical questions for systematic literature research during the first second meeting.

I.	Definition and classification of ulcers in systemic sclerosis 1.What is the definition of systemic sclerosis associated skin ulcer? 2.How can the systemic sclerosis-associated skin ulcers be classified by aetiology? 3.How can the systemic sclerosis-associated digital ulcers be classified by aetiology? 4.How can the systemic sclerosis-associated digital ulcers be classified according to clinical course?
II.	Risk factors and poor prognostic factors for the development of digital ulcers 1.What are the risk factors for the development of systemic sclerosis-associated digital ulcers? 2.What are the poor prognostic factors for systemic sclerosis-associated digital ulcers?
III.	Non-drug methods for the prevention and treatment of digital ulcers 1.What are the non-drug methods for the prevention and treatment of systemic sclerosis-associated digital ulcers?
IV.	Calcium channel blockers 1. Should calcium channel blockers be used in systemic sclerosis-associated digital ulcers?
V.	Prostacyclin analogues 1. Should prostacyclin analogues be used in systemic sclerosis-associated digital ulcers?
VI.	PDE-5 inhibitors 1. Should PDE-5 inhibitors be used in systemic sclerosis-associated digital ulcers?
VII.	Endothelin receptor antagonists 1. Should endothelin receptor antagonists be used in systemic sclerosis-associated digital ulcers?
VIII.	Anti-platelet and anticoagulant drugs 1. Should anti-platelet drugs be used in systemic sclerosis-associated digital ulcers?
IX.	Statins 1. Should statins be used in systemic sclerosis-associated digital ulcers?
X.	ACEI and ARBs 1. Should ACEI and ARBs be used in systemic sclerosis-associated digital ulcers?
XI.	Antibiotics 1.What are the situations when antibiotics should be used in the treatment of systemic sclerosis-associated digital ulcers?
XII.	Botulinum toxin 1. Should botulinum toxin be used in systemic sclerosis-associated digital ulcers?
XIII.	Cellular therapies 1. Should cellular therapies be used in systemic sclerosis-associated digital ulcers?
XIV.	Digital sympathectomy 1. Should digital sympathectomy be used in systemic sclerosis-associated digital ulcers?
XV.	Surgical methods 1. Should surgical methods be used in systemic sclerosis-associated digital ulcers?
XVI.	Wound care 1.What are the recommendations for wound care in systemic sclerosis-associated digital ulcers?
XVII.	Pain control 1.How should pain control be provided in systemic sclerosis-associated digital ulcers?
XVIII.	Complications/conditions associated with pharmacological treatments 1.What complications/conditions should be considered when using pharmacological treatments in systemic sclerosis-associated digital ulcers?

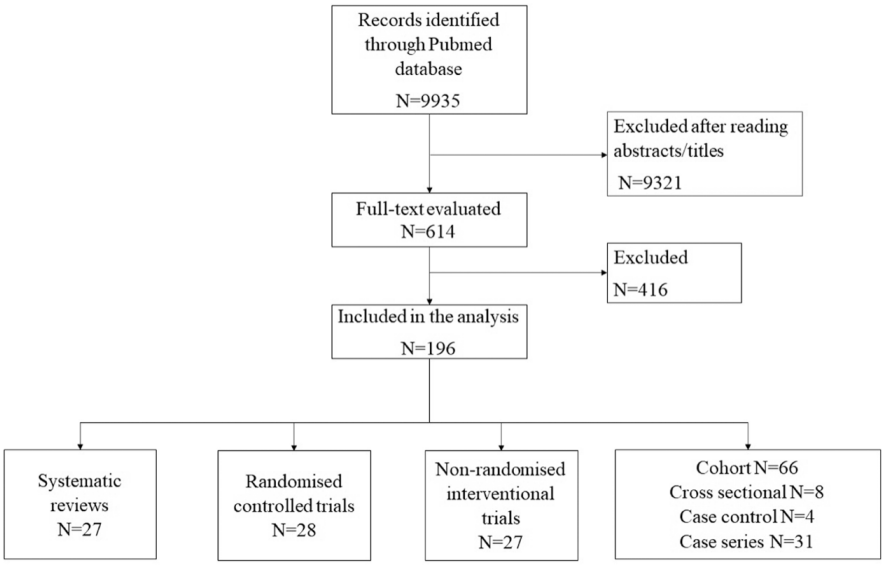
Supplementary Table S2. Combination of keywords, used for each question, to perform the systematic literature search.

Definition of systemic sclerosis-associated skin ulcer	"(systemic sclerosis or scleroderma) AND digital ulcer definition"
Classification of systemic sclerosis-associated skin ulcers by aetiology	"(systemic sclerosis or scleroderma) AND digital ulcer definition"
Classification of systemic sclerosis-associated digital ulcers by aetiology	"(systemic sclerosis or scleroderma) AND digital ulcer definition"
Classification of systemic sclerosis-associated digital ulcers according to clinical course	"(systemic sclerosis or scleroderma) AND digital ulcer definition"
Risk factors	"(systemic sclerosis or scleroderma) AND digital ulcer risk factors"
Poor prognostic factors	"(systemic sclerosis or scleroderma) AND (poor prognostic factors AND digital ulcer)"
Non-drug methods for the prevention and treatment	"(systemic sclerosis OR scleroderma) AND (prevention AND treatment AND digital ulcers)"
Calcium channel blockers	"(systemic sclerosis OR scleroderma) AND (calcium channel blockers OR Nifedipine OR Amlodipine OR Felodipine OR Isradipine OR Nicardipine OR Verapamil OR Diltiazem)"
Prostacyclin analogues	"(Systemic Sclerosis OR Scleroderma) AND (Iloprost OR Beraprost OR Treprostenil OR Cisaprost OR Epoprostenol)"
PDE-5 inhibitors	"(Systemic Sclerosis OR Scleroderma) AND (Sildenafil OR Tadalafil OR Verdenafil)"
Endothelin receptor antagonists	"(Systemic Sclerosis OR Scleroderma) AND (Bosentan OR Macitentan OR Ambrisentan)"
Anti-platelet/anti-coagulant drugs	"(systemic sclerosis OR scleroderma) AND (Acetylsalicylic acid OR Warfarin OR Bemiparin OR Certoparin OR Dalteparin OR Parnaparin OR Enoxaparin OR Tinzaparin OR Reviparin OR Dipyridamole OR Cilostazol)"
Statins	"(Systemic Sclerosis OR Scleroderma) AND Atorvastatin OR Cerivastatin OR Fluvastatin OR Lovastatin OR Mevastatin OR Pitavastatin OR Pravastatin OR Simvastatin)"
ACE inhibitors/angiotensin receptor antagonists	"(systemic sclerosis OR scleroderma) AND (Perindopril OR Captopril OR Enalapril OR Lisinopril OR Ramipril OR Quinapril OR Benazepril OR Cilazapril OR Trandolapril OR Valsartan OR Telmisartan OR Losartan OR Irbesartan OR Olmesartan OR Candesartan)"
Antibiotics	"(systemic sclerosis OR scleroderma) AND (antibiotics AND digital ulcers)"
Botulinum toxin	"(systemic sclerosis OR scleroderma) AND botulinum"
Cellular therapies	"(Systemic Sclerosis OR Scleroderma) AND cellular therapies"
Digital sympathectomy	"(Systemic Sclerosis OR Scleroderma) AND digital sympathectomy"
Surgical methods	"(systemic sclerosis OR scleroderma) AND (digital ulcer AND surgical treatment)"
Wound Care	"(systemic sclerosis OR scleroderma) AND (wound care OR wound management OR wound bed preparation OR debridement OR wound dressing OR dressing OR occlusive dressing OR moist wound healing OR topical agent)"
Pain control	"(systemic sclerosis OR scleroderma) AND pain control"
Complications/conditions associated with pharmacological treatments	"(systemic sclerosis OR scleroderma) AND (digital ulcer AND complication AND pharmacological treatments)"
Other treatments	"(Systemic Sclerosis OR Scleroderma) AND Pentoxifyllin"

II. Results of systematic literature review

Our search of the PubMed database from inception to December 2021 retrieved 9935 citations and 9321 were excluded after evaluating the titles and abstracts. Out of 614 full texts 196 were selected for data extraction (Figure S1). Studies with a design of randomized controlled trials (RCTs), meta-analysis of randomized controlled trials (RCTs), systematic reviews, case control studies, uncontrolled trials, cohorts, case reports and case series with more than five patients were included. SSc was defined according to the ACR or ACR/EULAR classification criteria, and classified into subtype as defined by Leroy et al (1)(2)(3). Studies concerning patients with Raynaud's phenomenon or pulmonary arterial hypertension (PAH), were only included if they were studying a treatment addressed in the clinical questions.

Definition of the skin ulcers, classification of the skin and DUs by aetiology as well as the classification of systemic sclerosis-associated DUs according to the course are provided in Table S3. To define the clinical conditions more clearly where the combination treatment may be effective, the committee decided to use two new definitions including severe and refractory DUs. Severe ulcer: acute onset, symptomatic new DUs that progress significantly in days. Refractory ulcer: DUs that progress despite adequate treatment.



Supplementary Fig. S1. Flow chart of study selection for data analysis.

Supplementary Table S3. Recommendations regarding definitions of DU associated with SSc.

Systemic sclerosis associated skin ulcer (4)	**Skin ulcer** is the loss of epidermal covering due to a break in the basement membrane which separates dermis from epidermis, and is sometimes accompanied by a loss of tissue that extends deeper underlying structures (*e.g.*, muscle, ligament, fat, bone) **Active skin ulcer:** ulcer with a depth and clearly visible base, with de-epithelialized areas anywhere at the base of the ulcer, including areas where epithelialization has begun. **Healed skin ulcer:** Ulcer with complete epithelialization has been achieved
Classification of systemic sclerosis-associated skin ulcers by aetiology (5)	**Digital ulcer (DU):** ulcer localized on the tips of the fingers, or near the nails **Skin ulcers on bony prominence:** ulcer on proximal interphalangeal, metacarpophalangeal and elbow joint contractures **Calcinosis-related skin ulcer:** ulcer localized over subcutaneous calcinosis **Lower extremity skin ulcer:** skin ulcer localized between the knees and feet/ankles **Skin ulcer with gangrene:** ulcer presenting with gangrene and requiring differential diagnosis for critical ischemic lesions
Classification of systemic sclerosis-associated DUs by aetiology (6)	**DU caused by digital pitting scar:** ulcer that develops on the ground of a hyperkeratotic lesion ("pitting" scar) **Pure ischemic DU:** ulcer of microvascular ischemic nature, **DU caused by calcinosis:** ulcer with calcinosis on the base when the lesion is removed, **DU caused by gangrene:** complicated DU derived from gangrene which tends to extend into deep tissues or bone, and usually with inflammation
Classification of systemic sclerosis-associated DUs according to the course (7)	**Episodic DU (rarely recurring):** ≥1 DU and/or new DU detected at only one follow-up visit and absence of DU at the remaining follow-up visits, **Recurrent DU (frequently recurring):** DU and/or new DU detected at ≥2 or more follow-up visits, no DU at least one follow-up visit, **Chronic DU:** ≥1 DUs and/or new DU detected at all follow-up visits

III.Overarching principles

A. Risk factors for the development of DUs in patients with SSc; first 5 years of disease or long disease duration, diffuse disease type, joint contracture, high modified Rodnan score, anti-Scl-70 positivity, late pattern findings on capillaroscopy, and male gender.

Although there are many studies on DUs in SSc patients, there is not a single systematic study examining possible risk factors together. Also, most studies to date are retrospective cohorts or cross-sectional studies. DUs have been reported to occur within 1 year of the first symptom in 43% of patients and within 5 years of the first symptom in 73% of patients (8). The risk of developing DU is higher in patients of the male gender, disease onset before 30 years of age, long disease duration, joint contracture, high modified Rodnan score, anti-Scl70 positivity, disease type with extensive skin involvement, and late pattern findings on nail fold capillaroscopy (9) (10) (11) (12) (13) (14) (15) (16) (17) (18) (19) (20) (21) (22). High levels of endoglin and biomarkers like ET-1 and IL-6 and low VEGF were found to be risk factors (10) (23) (24).

B. Poor prognostic factors for DUs in systemic sclerosis are; previous gangrene, smoking, ≥3 DUs, a history of upper extremity sympathectomy, and smoking.

Having a previous history of DU increases the risk of developing new DU. Despite vasodilator therapy, it was observed that 66% of the patients with DU episodes had more than 1 DU episode, and 50% had 2 or more DU episodes. About half of patients with DU require hospitalization for ulcer treatment and 7% require surgical amputation (8). Gangrene was reported in 9% of the EUSTAR cohort. Having a history of DU increases the risk of gangrene 38.4 times (95% CI 9.16- 160.73) (25). In a prospective observational study, previous gangrene, smoking, ≥3 DUs, and previous upper extremity sympathectomy were identified as independent risk factors for the development of gangrene (26). The use of IV vasodilator (OR 3.8, CI:1.1-12.9), digital debridement (OR 4.5, CI: 1.1-18.3), digital amputation (OR 3.4, CI:0.8-15) was found to be higher in active smokers than non-smokers (27).

C. Liver function tests and haemoglobin monitoring should be performed during bosentan use. Bosentan is contraindicated in pregnancy. Data on the use of PDE5is and prostaglandin analogs in pregnancy are limited from experience in PAH patients. Non-arteritic anterior ischaemic optic neuropathy is a contraindication for PDE5is. Drug interactions should be considered during the use of bosentan / PDE5is. Bosentan, PDE5is and iloprost should be used with caution in patients with renal and/or hepatic impairment and pulmonary hypertension.

Frequently reversible and dose-related increases in liver aminotransferase levels can occur with bosentan. Therefore, bosentan should be avoided as much as possible in patients with moderate to severe hepatic impairment. However, it should be known that bosentan causes reversible, dose-dependent and asymptomatic aminotransferase elevation (28). Decreased hemoglobin levels and anaemia may develop during bosentan treatment. Frequent monitoring of haemoglobin concentrations is recommended at the start of treatment and every 3 months thereafter (29). Pregnancy is contraindicated during bosentan therapy. Bosentan is considered teratogenic. Therefore, pregnancy should be excluded before starting treatment and avoided during treatment. Stimulation of CYP2C9 and CYP3A4 by bosentan reduces the efficacy of estrogenic contraception (30). Drug interactions should be considered during the use of bosentan. Drugs (such as ketoconazole, cyclosporine, simvastatin, and warfarin) that are metabolized similarly to endothelin receptor antagonists (ERAs) may interact because they affect CYP enzymes (31)(32).

Phosphodiesterase 5 inhibitors (PDE-5is) should be used with caution in patients with renal and hepatic impairment. The metabolites of PDE5is are mostly excreted via the intestines and little is excreted by the kidneys. Therefore, the use of PDE5is in renal failure does not pose a significant obstacle as in liver failure (33). PDE-5 inhibitors are well tolerated in mild to moderate renal impairment. However, in patients with GFR <30 ml/min, it is appropriate to start the treatment with low doses and increase it as tolerated. Patients using PDE5is may have elevated liver enzymes that do not require discontinuation of the drug. Although PDE5is are well tolerated in mild hepatic impairment, they are considered contraindicated in severe hepatic impairment and chronic hepatic failure due to insufficient evidence (34). Despite limited evidence derived from patients with pulmonary arterial hypertension, PDE-5is, and inhaled/i.v./subcutaneous (s.c.) prostacyclin analogues may be used during pregnancy (35). PDE5is does not affect sperm quality and count. Therefore, the use of PDE5is in male patients is not an obstacle (36). Non-arteritic anterior ischemic optic neuropathy is a contraindication for PDE5is. In case of sudden visual impairment, the drug should be discontinued immediately(37). Drug interactions should be considered in patients receiving treatments such as nitrates and alpha-blockers. Hypotension as a result of vasodilation with PDE5is may aggravate palpitations. Antiviral drugs such as cimetidine, ketoconazole, erythromycin and ritonavir, which affect the activity of the CYP3A4 enzyme, may decrease the clearance of PDE5is and increase their side effects (38).

Iloprost should be used with caution in patients with renal and hepatic impairment. In mild renal and hepatic impairment, no dose adjustment is necessary except in chronic renal failure requiring dialysis. If the use of the drug is necessary, dose titration should be considered (39)(40). Iloprost does not affect female or male fertility. It has been reported that iloprost may cause uterine contractions and malformations with local effects on placental blood flow (41).

D. In SSc patients with the group I pulmonary hypertension (PH); oral PDE5is may be preferred for the treatment of active DUs. Oral PDE5is and bosentan treatments may be preferred to prevent the development of new ulcers. IV infusions of iloprost may be used for the treatment of active DUs in patients not taking any other drugs that affect the prostaglandin pathway. In the presence of PH due to left heart failure (Group II PH); PDE5is may be preferred for the treatment of active DUs and prevention of DU development. In the presence of pulmonary hypertension (Group III PH) associated with interstitial lung disease (ILD); oral PDE5is may be preferred for active DU treatment and new ulcer development. If necessary, IV iloprost may be used to treat active DUs. Considering the data from the patients with idiopathic pulmonary fibrosis, ERAs and soluble guanylate cyclase (sGC) stimulators should be used with caution in these patients.

Although there are not enough studies in patients with PAH and DU together, intravenous iloprost and oral PDE-5is be effective in ulcer healing (42). PDE5is may be preferred to prevent new ulcer development (43). Bosentan, which has been shown to be effective in the development of new DUs, may be included in the treatment to pre-

vent the formation of new ulcers.(44). Pulmonary vasodilators are not recommended for the treatment of left heart-associated pulmonary hypertension (group II PH). Since there is evidence that PDE5is can improve exercise capacity and hemodynamic parameters in patients with hearth failure with preserved ejection fraction (HFpEF) and combine pre-post capillary PH, they may be used both in the treatment and prevention of DUs (45)(46). Although the benefit of PAH-specific therapy in group III PH has not been proven, there is little data to suggest that some of these drugs may not worsen hypoxemia (47). If necessary, intravenous iloprost and PDE5is may be used to heal active DUs and prevent new ulcers. In the light of current data in patients with PH associated with idiopathic pulmonary fibrosis, it has been shown that endothelin receptor antagonists (ambrisentan) and riociguat worsen lu ng disease and should be used with caution for recovery and/or prevention of DUs (48)(49). Sildenafil is the most frequently mentioned PDE5is agent in patients with both group II and group III PH (50).

Supplementary Table S4. Overarching principles regarding the risk factors, poor prognostic factors, prevention of DU, possible adverse effects of medical treatments and special recommendations for patients with DUs accompanied by ILD or PH.

		Level of evidence	External voting	Strength of recommendation
Overarching principles	High risk factors for the development of DUs in patients with SSc are; first 5 years of disease or long disease duration, diffuse disease subtype, joint contracture, high modified Rodnan score, anti-Scl-70 positivity, late pattern findings on capillaroscopy, and male gender.	NA	8.56	NA
	Poor prognostic factors for DUs in SSc are; previous gangrene, smoking, ≥3 DUs and a history of upper extremity sympathectomy.	NA	8.74	NA
	Drug interactions should be considered during the use of bosentan/ phosphodiesterase 5 inhibitors (PDE5is). Bosentan, PDE5is and iloprost should be used with caution in patients with renal and/or hepatic impairment. Liver function tests and haemoglobin monitoring should be performed during bosentan use. Bosentan is contraindicated in pregnancy. Bosentan may reduce the efficacy of estrogenic contraception by induction of CYP2C9 and CYP3A4. Data on the use of PDE5is and prostaglandin analogues in pregnancy are limited from experience in patients with pulmonary arterial hypertension (PAH). Non-arteritic anterior ischaemic optic neuropathy is a contraindication for PDE5is.	NA	9.49	NA
	In SSc patients with the group I pulmonary hypertension (PH); oral PDE5is may be preferred for the treatment of active DUs. Oral PDE5is and bosentan treatments may be preferred to prevent the development of new ulcers. IV infusions of iloprost may be used for the treatment of active DUs in patients not taking any other drugs that affect the prostaglandin pathway. In the presence of PH due to left heart failure (Group II PH); PDE5is may be preferred for the treatment of active DUs and prevention of DU development. In the presence of pulmonary hypertension (Group III PH) associated with interstitial lung disease (ILD); oral PDE5is may be preferred for active DU t reatment and new ulcer development. If necessary, IV iloprost may be used to treat active DUs. Considering the data from the patients with idiopathic pulmonary fibrosis, ERAs and soluble guanylate cyclase (sGC) stimulators should be used with caution in these patients.	NA	9.49	NA

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