Systematic literature review to inform the Portuguese recommendations for the management of Raynaud's phenomenon and digital ulcers in systemic sclerosis and other connective tissue diseases.

Costa E[1]*, Cunha-Santos F[2]*, Dourado E[3,4]*, Oliveira D[5,6]*, Falzon L[7] Romão VC[8,9], Duarte AC[10], Cordeiro A[10], Santiago T[11,12], Sepriano A[13,14]

* These authors contributed equally to this work.

[1] Rheumatology Department, Hospital de Braga, Braga, Portugal.
[2] Rheumatology Department, Unidade Local de Saúde da Guarda, Guarda, Portugal.
[3] Rheumatology Department, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal.
[4] Aveiro Rheumatology Research Centre, Egas Moniz Health Alliance.
[5] Rheumatology Department, Centro Hospitalar Universitário de São João, Porto, Portugal.
[6] Center for Health Technology and Services Research (CINTESIS), Faculdade de Medicina da Universidade do Porto, Porto, Portugal.
[7] Health Economics and Decision Science, School of Medicine and Population Health, University of Sheffield, Sheffield, United Kingdom.
[8] Rheumatology Department, Centro Hospitalar Universitário Lisboa Norte, Centro Académico de Medicina de Lisboa, Lisbon, Portugal.
[9] Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Centro Académico de Medicina de Lisboa, Lisbon, Portugal.
[10] Rheumatology Department, Hospital Garcia de Orta, Almada, Portugal.
[11] Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.
[12] Faculty of Medicine, University of Coimbra, Coimbra, Portugal.
[13] NOVA Medical School, Universidade Nova de Lisboa, Lisbon, Portugal.
[14] Rheumatology Department, Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal.

Correspondence to
Emanuel Costa
E-mail: emanuel.costa@hb.min-saude.pt
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Abstract

Objective: To perform a systematic literature review (SLR) aimed at evaluating the efficacy and safety of pharmacological and non-pharmacological treatments for Raynaud's phenomenon (RP) and digital ulcers (DU) in patients with systemic sclerosis (SSc) and other connective tissue diseases (CTD), in order to inform the Portuguese recommendations for managing RP and DU in these patients.

Methods: A SLR was conducted until May 2022 to identify studies assessing the efficacy and safety of pharmacological and non-pharmacological interventions for RP and DU in SSc and other CTD. Eligible study designs included randomized controlled trials (RCTs), controlled clinical trials, and their extensions for assessing efficacy and safety of interventions. Observational studies with a comparator were included for evaluating the efficacy and safety of non-pharmacological interventions and safety of pharmacological interventions. The risk of bias of each study was assessed using standard tools.

Results: Out of 71 publications meeting the inclusion criteria, 59 evaluated pharmacological and 12 non-pharmacological interventions. We found moderate quality evidence supporting the efficacy of calcium channel blockers, phosphodiesterase-5 inhibitors, and intravenous prostacyclin analogues in reducing RP frequency, severity, and duration. Intravenous iloprost had a small to moderate effect size in improving DU healing. Phosphodiesterase-5 inhibitors were effective in reducing total DU count, new DU occurrence, and enhancing DU healing. Bosentan effectively prevented new DU in SSc patients. No new safety concerns were associated with these treatments. The studies on non-pharmacological interventions were, in general, of low quality, and had a small sample size. Warming measures decreased frequency and duration of RP attacks; laser therapy improved RP-related outcomes; local oxygen-ozone therapy improved RP outcomes as an add-on therapy; bone marrow mononuclear cell implantation improved DU-associated pain; periarterial sympathectomy and vascular bypass reduced DU number and finger amputation risk.

Conclusion: The available evidence supports the efficacy and safety of pharmacological interventions, namely nifedipine, sildenafil, iloprost, and bosentan in treating RP and DU in patients with SSc and other CTD. Scarce and low-quality evidence does support the use of some non-pharmacological interventions but with only a modest effect size. This SLR underscores the limited availability of high-quality evidence for determining the optimal treatment of RP and/or DUs, emphasising the need for further studies to evaluate efficacy and safety aspects.

Keywords: Digital Ulcers; Connective Tissue Diseases; Raynaud Phenomenon; Scleroderma and related disorders; Systematic Literature Review

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Key-messages:

- Calcium channel blockers and phosphodiesterase-5 inhibitors reduce RP frequency, severity, and duration.
- Intravenous iloprost and phosphodiesterase-5 inhibitors improve DU healing; bosentan and phosphodiesterase-5 inhibitors prevent new DU.
- The beneficial effect of non-pharmacological interventions is only modest, with very low to low-quality evidence.

Introduction

Raynaud's phenomenon (RP) is characterised by pallor followed by cyanosis and redness of an extremity, caused by transient and reversible episodes of localised tissue hypoperfusion. This condition can occur as a primary phenomenon (idiopathic) or be secondary to a wide range of underlying causes, including connective tissue diseases (CTD). Proper investigation is warranted to rule out secondary causes and institute appropriate management.[1–5]

RP is a cardinal feature of systemic sclerosis (SSc), occurring in up to 95% of patients, usually very early in the course of the disease.[6,7] RP severity ranges from mildly symptomatic discolouration of the fingers to severe pain due to ischaemia, which may become irreversible, leading to digital ulcers (DUs) or gangrene. However, only limited data support an association between the severity of RP-associated symptoms and the presence of DUs.[8] Approximately 50% of patients with SSc will develop DU at some stage during the disease course.[9] This manifestation of peripheral microvascular injury is associated with significant morbidity, functional disability, and even increased mortality.[10,11]

Over the past forty years, various pharmacological and non-pharmacological interventions were explored to manage RP and DUs. Despite that, treatment of RP is often not fully effective,[12] and consequently approximately one-third of patients with SSc have refractory DUs.[13]

The European Alliance of Associations for Rheumatology (EULAR) recommendations for the treatment of SSc[14] were updated in 2017. They are the most accepted evidence- and consensus-based guidelines in which the treatment of RP and DUs has been addressed. However, they were informed by a SLR completed in 2014, the results of which were not published. Additionally, these recommendations revealed a wide range of agreement between worldwide experts, ranging from

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4.6 to 8.7 (1-10 scale).[15] This suggests that there is controversy in some areas, potentially due to lack of evidence on efficacy and safety of available treatment options.

In 2019, the European Reference Network (ERN) on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ReCONNET) conducted a systematic literature review (SLR) on published guidelines for managing several SSc disease domains.[16] Only five clinical practice recommendations on the "treatment" domain were identified.[14,17–20] From these five recommendations, only three addressed RP and DU treatment. Since this SLR, Hachulla *et al*. published in 2021 the "French recommendations for the management of SSc", which did not include a systematic review of the evidence.[21]

The EULAR[14] and the 2016 British Society for Rheumatology[22] guidelines only provide specific first-line treatment recommendations. Treatment algorithms for RP and DU were later developed, often adding treatment rather than switching.[23]

We herein present the results of a SLR on the efficacy and safety of pharmacological and non-pharmacological interventions in patients with RP and DUs associated with CTDs. This SLR was aimed at supporting the development of the first recommendations for the management of RP and DUs in SSc and other CTDs of the Portuguese Society of Rheumatology (SPR).

Methods

This SLR was conducted according to the methodology of EULAR Standardized Operating Procedures (SOP),[24] the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[25] and the Cochrane Handbook for Systematic Reviews of Interventions[26].

The task force responsible for the Portuguese recommendations for the management of RP and DUs in SSc and other CTD outlined the scope of the literature search according to the Population, Intervention, Comparator, Outcomes (PICO) format and defined the studies eligibility criteria.[26,27] The detailed PICOs – one for pharmacological treatments and the other for non-pharmacological treatments – are provide in Supplementary Material Section I-A.

The search was performed by a professional librarian (LF) in PubMed, EMBASE, Cochrane Central, clinicaltrials.gov and WHO-ICTRP without language restrictions from their inception until May 2022. Additionally, conference abstracts of the EULAR and American College of Rheumatology (ACR) annual conferences were screened from 2019 until 2021. Details on complete search strategies are provided in Supplementary Material Section I-B. The SLR focused on the efficacy and safety of both pharmacological and non-pharmacological therapeutic interventions for patients aged 18 years or

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older with secondary RP or DU associated with an CTD, including antiphospholipid syndrome, idiopathic inflammatory myopathies, mixed CTD, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, SSc, undifferentiated CTD, and overlap syndromes. The outcome measures for the efficacy assessment included: (i) the mean daily frequency of RP attacks, (ii) the mean severity of RP attacks measured using Raynaud's Condition Score (RCS), visual analogue scale (VAS), or any other severity score, (iii) the mean duration of each RP attack, (iv) the percentage of DUs with improvement/healing, (v) the number of new DUs, and (vi) the intensity of RP/DUs associated pain (measured through VAS). Additional outcomes that were considered/included: (i) the time to improvement/healing of the DUs, (ii) the patient's global assessment (VAS), and (iii) disability scores (e.g., The Health Assessment Questionnaire - HAQ). The safety outcomes were the number of withdrawals due to adverse events (AEs); the number of serious adverse events (SAEs), deaths or hospitalizations; the total number of AEs; and the occurrence of infections. The comparator was the same pharmacological/non-pharmacological treatment in different doses or regimens, another pharmacological/non-pharmacological treatment, the combination of pharmacological and non-pharmacological interventions, or a placebo.

The SLR focused on randomised clinical trials (RCTs), controlled clinical trials (CCTs), open-label extensions and long-term extensions for assessing the efficacy and safety of pharmacological and non-pharmacological interventions. Studies evaluating pharmacological interventions were only eligible if they included a comparator group. Cohort studies/registries with a comparator were considered for assessing the safety of both pharmacological and non-pharmacological interventions and the efficacy non-pharmacological interventions. Studies including patients with primary and secondary RP were only considered if data were reported separately for those with secondary RP or DUs. If an SLR was retrieved, it was used to identify additional references.

Selection of studies

First, reviewers screened titles and abstracts in duplicate and blinded manner (pharmacological search: EC and DO; non-pharmacological search: ED and FCS) according to a predefined list of selection criteria. After unblinding, conflicts and doubts regarding eligibility were discussed between the two reviewers until a consensus was reached. After consensus was reached for all studies, the full texts of the selected papers were again blindly and independently screened by the aforementioned reviewers and disagreements were discussed until a consensus was reached after

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a new unblinding. A third reviewer (AS) was involved whenever necessary in both phases. PRISMA flow diagrams can be found in Supplementary Figure S1 and S2.

Data extraction and quality assessment

Data extraction and quality assessment were performed independently by the same two reviewers. Disagreements were resolved through the aforementioned methods.

Information on study design, patient characteristics, interventions, comparators, and outcomes (descriptive statistics and association measures) were extracted from the included papers using a predefined data extraction sheet.

The risk of bias (RoB) of each study was assessed independently by two reviewers according to the Cochrane Handbook for Systematic Reviews.[28] For RCTs, Version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2)[29] was used and reported as low, unclear or high. For non-randomised studies, the Risk-of-Bias In Non-Randomised Studies - of Interventions (ROBINS-I)[30] was used, and reported as low, moderate, serious or critical risk of bias. The visual assessment of RoB through traffic light plots of the domain-level judgements for each individual result and weighted bar plots of the distribution of RoB judgements within each bias domain was performed with *robvis* (visualisation tool)[31] – Supplementary Material Section II.

Statistical analyses

The data were summarised descriptively, and the following effect size (ES) measures were either extracted or calculated: i) binary outcomes: odds ratio (OR) and risk ratio (RR); continuous outcomes: standardised mean difference (SMD) and Cohen's d (Box I). In case an ES measure was not possible to calculate due to missing data, the percentage of the patients with the outcome at follow-up (for binary outcomes) or the delta (Δ) between follow-up (FU) and baseline (BL) (for continuous outcomes) in each group was reported.

The interpretation of SMD and Cohen's *d* was the same: values ranging from 0.2 to 0.5 are considered a small ES; 0.5-0.8 a medium ES; >0.8 a large ES.[32,33]

Data pooling was not performed due to high heterogeneity across studies[34].

Results

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Pharmacological Interventions

Study characteristics

The literature search for pharmacological interventions yielded 5618 references. After deduplication, 3883 remained for title and abstract screening, of which 233 were selected for full article review and 59 were finally included (Supplementary Figure S1 and S2).

Of the total 59 studies[35–92], 58 were RCTs (36 were parallel, 22 were crossover) and one was a CCT. The studies were published between 1983 and 2019 and evaluated 21 interventions. Fifty-one were placebo-controlled trials, six were head-to-head trials and two compared the same intervention at different posology. Study sample sizes ranged from 8 to 308 patients. Overall, 4025 patients were included, among whom 3829 (95.1%) had secondary RP. The main characteristics of included studies are presented in Supplementary Tables S1,2.

The RoB was considered low in 19 (32.2%), unclear in 31 (52.5%) and high in seven (11.9%) studies (Supplementary Figures S3-S8 and Table S1). Two of the included RCT were only available as conference abstracts and were therefore not assessed for RoB due to limited information and were classified as unknown RoB.

A detailed report of all the efficacy and safety data can be consulted in Supplementary Material Section III.

Calcium channel blockers

Calcium channel blockers inhibit the entry of calcium ions into cardiac and smooth muscle cells, leading to vasodilation in the blood vessels and decreased cardiac workload.

Seven studies (six crossover RCTs at unclear RoB and one parallel single-blinded study at high RoB) assessed the efficacy and/or safety of calcium channel blockers (CCBs) in 164 patients with secondary RP (Table I and Supplementary Table S3,4).[35–41]

Nifedipine, a dihydropyridine-class calcium antagonist, reduces the frequency[35,36,39,40] (four studies, small to medium ES – SMD 0.37-0.50) and severity[36,39,40] (three studies, small to medium ES – SMD 0.35-0.51) of RP. One study evaluated the duration of RP-attacks[38], and reported a 37% reduction in the duration of attacks with a medium ES (SMD 0.51). The efficacy of non-dihydropyridine class calcium antagonists (i.e., diltiazem) was evaluated in only one crossover RCT[37], which showed no benefits compared to placebo. One study[41], at high RoB has shown the efficacy of diltiazem gel compared with placebo in reducing the diameter of DU but with a small ES (SMD 0.42). None of the included studies evaluated the efficacy of extended-release nifedipine.

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Thirty-nine patients in the intervention group versus 15 patients in the placebo group experienced AEs (RR 2.59). Headaches and nausea were the most frequent AEs ($p<0.01$ vs placebo in one study). No SAEs were reported.

Phosphodiesterase-5 Inhibitors

PDE5 inhibitors work by blocking the enzymatic action of phosphodiesterase-5, which leads to increased levels of cyclic guanosine monophosphate (cGMP), promoting vasodilation in the smooth muscle and enhancing blood flow.

Nine studies[42–50] (two parallel RCTs at low RoB, one parallel RCT, and six crossover RCTs at unclear RoB) were included to assess the efficacy and safety of phosphodiesterase-5 inhibitors (PDE5i) such as sildenafil, tadalafil, vardenafil, and udenafil in 352 patients with secondary RP. Regarding DUs, four studies evaluated the efficacy of PDE5i.[42,44,46,49] (Table 2 and Supplementary Table S5,6)

The studies consistently demonstrated that PDE5i reduced the frequency [43,46,49] (three studies, small ES – SMD 0.28-0.40), severity[45,46,49] (three studies, small ES – SMD 0.25-0.43), and duration[44,46,49] (three studies, small ES – SMD 0.34-0.46) of RP attacks. ES measures consistently favoured PDE5i compared to placebo for RP outcomes.

The Sildenafil Effect on Digital Ulcer Healing in Scleroderma (SEDUCE) trial (low RoB) [42] showed a numerical reduction in the time to DU healing with sildenafil, although not statistically significant. However, there was a significant reduction in the number of DUs per patient at 8 and 12 weeks compared to placebo. Two additional studies also demonstrated the positive effects of PDE5i compared to placebo in terms of increasing the proportion of patients showing improvement or healing of DUs and reducing the occurrence of new DUs. Two additional studies[44,49] also demonstrated the positive effects of PDE5i compared to placebo in terms of improving ulcer healing and reducing the occurrence of new DUs. In a multicentre RCT (unclear RoB),[49] tadalafil as an add-on therapy to vasodilators significantly improved DU healing (RR 4.35; $p<0.01$) and was associated with a significantly lower risk of new DU (RR 0.1; $p<0.01$) compared to placebo.

AEs were more frequent in the PDE5i group than the placebo group (213 vs 81) with a RR of 2.81. Vasomotor reactions/flushing ($p<0.01$ in three studies) and headaches ($p<0.01$ in 1 study) were the most common AEs. Nine SAEs and 32 withdrawals were recorded in PDE5i treated patients across the studies.

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Prostacyclin analogues

Prostacyclin analogues mimic the actions of endogenous prostacyclin by activating its receptor, (prostacyclin receptor), leading to increased levels of cyclic adenosine monophosphate (cAMP) and subsequent vasodilation, inhibition of platelet aggregation, and attenuation of smooth muscle cell proliferation, thereby improving blood flow.

Twelve RCTs[51–62] (four studies with low risk of bias and eight with unclear risk of bias) involving 1002 patients were included to evaluate the efficacy and safety of prostacyclin analogues. Four RCTs compared oral prostacyclin analogues to placebo, four RCTs compared intravenous (IV) prostacyclin analogues to placebo, and four RCTs were head-to-head comparisons. The summarised data are presented in Table 3 and Supplementary Table S7,8.

The efficacy and safety of IV prostacyclin analogues, specifically iloprost, were assessed in eight RCTs (four placebo-controlled and four head-to-head comparisons). The data showed that IV iloprosthad a small ES (SMD 0.18-0.41) in reducing the frequency (one study at low RoB, and one study at unclear RoB) and severity (one study at low RoB, and one study at unclear RoB) of RP attacks compared to placebo. Two RCTs comparing IV iloprost to nifedipine did not find significant differences in RP attack frequency or duration,[60,61] however iloprost showed slight superiority in improving RP attack severity (small ES – SMD 0.31). [61] One RCT compared low dose (0.5 ng/kg/min) to high dose (2 ng/kg/min) IV iloprost and found no significant differences in RP attack outcomes.[58]

Two RCTs demonstrated that IV iloprost was effective in healing DUs in patients with SSc, with a reduction in the number of DUs compared to placebo in one RCT (RR 2.65),[56] and improvement in DU healing in another RCT.[55] In addition, one RCT comparing IV iloprost with oral nifedipine suggested the superiority of iloprost in reducing the total number of DUs (SMD – 0.50).[60]

No studies assessing the efficacy and safety of iloprost infusion through an elastomeric pump met the inclusion criteria.

Oral prostacyclin analogues did not show benefits in RP or DU treatment outcomes based on the four included RCTs.[51–54]

Most RCTs had low reporting of safety outcomes. AEs were more frequent in the prostacyclin analogues group (RR 2.74). The most common AEs were headache and nausea ($p<0.05$, three studies). Several studies reported that most AEs were mild to moderate and could be improved by reducing the infusion rate.

Endothelin receptor antagonists

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Endothelin receptor antagonists block the binding of endothelin, a potent vasoconstrictor, to its receptors (ETA and ETB), preventing the vasoconstrictive effects and subsequent smooth muscle cell proliferation.

Five studies (all parallel RCTs at low RoB) assessed the efficacy and/or safety of endothelin receptor antagonists (ERA) in 881 patients with secondary RP (Table 4 and Supplementary Table S9-12).[63–66] Only one RCT evaluated the efficacy of bosentan on RP-attacks outcomes and the results did not show any benefit in reducing the frequency, severity or duration.[66]

Two RCTs at low RoB have shown the efficacy of bosentan in reducing the number of new DUs in patients with SSc. The RAPIDS-1 and RAPIDS-2[63,65] studies included 310 SSc patients with a history of or having at least one active DU at baseline. Oral bosentan significantly reduced the number of new DUs in both trials but with small ES (SMD: 0.25; p=0.04). The reduction in the proportion of patients with DU was not statistically significant in any of the RAPIDS trials, suggesting that bosentan did not affect DU healing. Two double-blinded RCTs at low RoB (DUAL-1 and DUAL-2)[64] did not find a significant difference between macitentan, a selective antagonist of endothelin-1 receptor, and placebo in the prevention of new DUs over 16 weeks in patients with SSc with active DUs at baseline. The two major concerns related to using of bosentan and other ERA are: potential liver injury and teratogenicity. AEs and SAEs were more common in the ERA than in the placebo group (RR 1.88 and RR 1.34, respectively). The most frequent AEs were headache and liver function tests abnormalities.

Other pharmacological interventions

Topical nitrates function by releasing nitric oxide, which in turn activates guanylate cyclase in smooth muscle cells, leading to an increase in cGMP and consequently vasodilation in the blood vessels, improving blood flow.

The efficacy of glyceryl trinitrate transdermal patches on RP-attacks outcomes was assessed in only one crossover RCT, at unclear RoB, with 21 secondary RP patients[67] (Supplementary Table S13,14). The authors reported a statistically significant difference between glyceryl trinitrate patches and placebo in reducing the frequency (p=0.04) and severity (p=0.03) of RP. Headache was the most frequent AE in the intervention group and occurred more commonly than in the control group (p<0.01).

A small crossover RCT, at unclear RoB, showed, in a post-hoc analysis, that fluoxetine, a selective serotonin reuptake inhibitor, was more effective than nifedipine in reducing the severity and

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comparable in reducing the frequency of RP attacks in SSc patients. Fluoxetine was better tolerated than nifedipine.[70]

As demonstrated in two parallel placebo-controlled RCTs at low and unknown risk of bias, the addiction of atorvastatin (40mg/day) to standard vasodilator therapy reduced the RP severity (SMD 0.23 and 0.22).[71,72] Additionally, one of these studies reported a significant reduction in the number, severity, and pain associated with DUs with atorvastatin, and no AEs were reported.

ACE inhibitors (quinapril) and angiotensin receptor blockers (losartan) showed no benefit in RP outcomes, according to two parallel RCTs at low RoB.[68,69]

A single RCT at unclear RoB demonstrated that regional grafting of autologous adipose tissue, recognized for containing pluripotent cells (adipose-derived stromal cells) and a stromal/vascular fraction, improved the healing of DU (RR: 11.94; p< 0.01) and a reduced DU pain intensity (p<0.01) compared to a sham procedure.[91]

Two small parallel RCTs (low RoB and high Ro B) evaluated the effectiveness of botulinum toxin injections in interdigital web spaces.[89,90] These studies yielded conflicting results regarding the outcomes of RP and did not demonstrate any benefits in reducing the risk of new DUs or improving DU healing. The most frequently reported AE was temporary muscle weakness.

Several other phamachological interventions, including aminaphtone[73,74], N-Acetylcysteine[75], Vitamin E gel[76], nitroglycerin gel[92], cyclophosphamide[77], ketanserin (5HT2 antagonist)[78–80], prazosin (alpha-adrenergic blocker)[81,82], stanozolol[83], cilostazol (phosphodiesterase III inhibitor)[84], riociguat[85,86], dimethyl sulfoxide[87] and selexipag (prostacyclin receptor agonist)[88] did not reveal clinically meaningful benefits in the treatment or prevention of RP and DUs. (Supplementary Tables S15-46).

No study evaluating the efficacy of pentoxifylline or acetylsalicylic acid fulfilled the inclusion criteria of this SLR.

Non-pharmacological Interventions

Study characteristics

The literature search for non-pharmacological interventions yielded 7040 references. After deduplication, 2774 remained for the title and abstract screening, of which 157 were selected for full article review, and 12 were included.

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Out of the 12 studies[93–104], four were RCTs, two were CCTs, three were prospective cohort studies and three were retrospective cohort studies. Overall, 415 patients with secondary RP and/or DUs were included. The main characteristics of included studies are presented in Table 5 and Supplementary material section IV, Table S47.

The RoB was considered low in one (25%), unclear in one (25%) and high in two (50%) RCTs. For the non-randomised studies, the RoB was considered moderate in three (37,5%), serious in two (25%) and critical in three (37,5%). Individual RoB assessments are shown in Supplementary Material Section II-A.

The complete data of each study can be accessed in Supplementary Tables S48-58.

Warming measures

One crossover CCT, at critical RoB, evaluated the efficacy of hand-warming measures. Twelve patients with SSc were exposed to hand warming in water for five minutes every four hours on alternate weeks. A decrease in RP-attacks frequency ($p<0.01$) and duration ($p<0.05$) was reported by comparing the period with and without hand warming.[94] A crossover RCT, at high RoB, addressed the efficacy of proximal heating in RP outcomes in 14 patients with SSc. In this study, heating the neck (ΔFU–BL:-0.9; p=0.02) or elbows (ΔFU–BL:-0.6; p=0.04), but not wrists, relieved the severity of RP[99]. More than half of patients (64%) experienced AEs (mostly mild burns). There was no benefit in RP-attacks outcomes (frequency, duration, severity) of silver fibre gloves over normal gloves in a crossover RCT at unclear RoB.[100]

Laser therapy

One prospective observational study (with no comparator), at moderate RoB, evaluated the efficacy of Multiwave Locked System laser therapy regarding RP outcomes in 40 patients with RP secondary to CTD[96]. In this study, Multiwave Locked System laser therapy reduced the number of RP-attacks per week (ΔFU–BL: -5.0, $p<0.01$), associated pain measured through VAS (ΔFU–BL: -1.5, $p<0.01$), and mean duration (ΔFU–BL: -5.0 minutes, $p<0.01$). Another prospective single-arm observational study, at moderate RoB, assessed the efficacy of low-level laser therapy in RP outcomes in 29 patients[97] and reported significant improvement of RP severity measured through VAS (ΔFU–BL: -6.0, $p<0.01$).

Sympathectomy

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One retrospective cohort study (critical RoB) has shown that periarterial sympathectomy was more effective at reducing the number of DUs (RR: 6.00; p<0.01) and finger amputation risk (RR: 0.47; p=0.03) in patients with CTD-associated DUs than in patients with atherosclerosis-associated DUs.[103] Another retrospective cohort study (serious RoB) showed that concomitant vascular bypass plus periarterial sympathectomy performed better than periarterial sympathectomy alone in complete and durable healing of DUs (RR 3.80; p=0.03).[104] On the contrary, a retrospective cohort study at serious RoB, showed no benefit from endoscopic thoracic sympathectomy in improving the frequency, severity or recurrence of RP in patients with CTD. In addition, reflex sweating was a frequent resulting AE (85.7%).[102]

Other interventions

The efficacy of local oxygen-ozone therapy on RP and DUs outcomes in SSc-patients was evaluated in one small (n=25) RCT at low RoB. During each session, participants received an oxygen-ozone mixture with a specific ozone concentration (1-2 weekly administrations for 30 mins) administered through a specialized bag using an ozone generator device.

In this study, adding local oxygen-ozone therapy to standard medical care was superior to standard medical therapy alone in reduction of RP frequency (ΔFU–BL: -1.5 attacks per day; p<0.01), and duration (ΔFU–BL: -9.2 minutes; p=0.03), and in reducing the DU-associated pain severity (ΔFU–BL: -2.5 in VAS; p<0.01).[98]

One prospective observational study (moderate RoB) evaluating bone marrow mononuclear cell implantation in SSc patients with high-grade ischaemic DUs reported improvement of DU-associated pain (SMD: 0.34; p<0.01).[101]

Hand physical therapy did not show improvement of disability and pain associated with RP and DUs in SSc patients (one study at critical RoB),[93] and ischemic preconditioning did not improve RP outcome measures in CTD patients (one study at high RoB).[95]

Discussion

The management of RP and DUs associated with CTDs remain a challenge in our daily practice. Although numerous therapeutic approaches were tested over the years, this SLR shows that, with some exceptions (CCB, PDE5i, prostacyclin analogues and ERA), there is only limited evidence supporting their efficacy. Our results are generally in line with current treatment

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recommendations.[14] However, they also highlight the fragility of the scientific evidence supporting them and challenge the clinical relevance of some therapeutic options.

A major challenge in investigating new therapies is the difficulty in designing high-quality RCTs with a representative number of patients capable of elucidating the true effect of the compared interventions. Although RCTs are the ideal way to assess treatment efficacy, they are onerous, time-consuming, and particularly complex in rare and heterogeneous diseases such as CTDs. We believe these are some of the reasons behind the paucity of RCTs for this indication. This is especially true for non-pharmacological treatments. Additionally, several RCTs had a crossover design, which hinders a proper interpretation because of the possibility of a carry-over effect and the lack of comparability of results against those from parallel RCTs.

Moreover, there is a lack of agreement among rheumatologists regarding what constitutes a DU (its definition, progression and healing) in patient with CTD. Consequently, different outcomes were used across RCTs which limits across-study comparisons. In fact, there is no currently validated diagnostic technique with the ability to assess DU, predict its future occurrence, and evaluate the effect of treatment in patients with CTD. Recently, promising new diagnostic and monitoring methods have been proposed to assess and monitor vascular disease over time which might lead to better outcome assessment in these patients [105-106].

RCTs with low to moderate quality of evidence showed that CCBs (specifically the dihydropyridine class) reduce the frequency and severity of RP with small ES. These results support the efficacy of CCBs and align with previous meta-analyses[107–109], despite the heterogeneity and the small magitude of the ES reported. Furthermore, none of the included studies evaluated the efficacy of extended-release formulations.

Moderate-quality evidence supports that PDE5i's reduce RP attacks' frequency, severity and duration with small ES estimates. These results are in line with a previous meta-analysis[110]. The level of evidence was stronger for PDE5i than for CCBs, which had slightly fewer AEs than the former (RR 2.59 vs 2.81, respectively). Moderate-to-high-quality RCTs showed that PDE5i reduced the total number of existing and new DUs and improved DU healing with small-to-medium ES. This therapeutic class was frequently chosen by SSc experts in the treatment and prevention of DU after the failure of first-line therapies.[111]

IV prostacyclin analogues reduce the frequency and severity of RP attacks, improve DU healing, and reduce the number of DUs compared to placebo. Additionally, IV iloprost reduce the RP attack severity and the total number of DU compared with oral nifedipine. Accordingly, EULAR

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recommendations for the treatment of SSc[14] recommend IV iloprost for healing DUs in patients with SSc. However, this SLR highlights the overall small ES of prostacyclin analogues in RP attack outcomes. Of note, low dose (0.5 ng/kg/min) and high dose (2 ng/kg/min) IV iloprost do not seem to significantly differ in improving RP attack outcomes.

The effect of bosentan on DUs prevention and healing was evaluated in two high-quality RCTs,[63,65] including 310 patients with SSc with a history of or having at least one active DU at baseline. Bosentan significantly reduced the number of new DUs in both trials with small ESs.

The only non-pharmacological intervention evaluated by an RCT at low RoB was local oxygen-ozone therapy. Local oxygen-ozone therapy was superior to standard medical therapy alone in reducing RP frequency and duration and the severity of DU-associated pain, which suggests a role for this technique in patients with refractory DUs. Although this is a promising high-quality study, the small sample size (n=25) warrants that replication of these findings is needed before firm conclusions can be made on the efficacy of local oxygen-ozone therapy.

Two small crossover trials at high and critical RoB evaluated the efficacy of proximal heating and hand-warming measures. Hand warming, commonly prescribed in real-world scenarios, decreased RP attacks frequency and duration. Even though heating the neck or elbows relieved the severity of RP, more than half of patients experienced AEs, which limits the clinical application of this method. There was no benefit in RP attack outcomes using hand physical therapy, ischemic preconditioning, or silver fibre gloves (compared to regular gloves).

The remaining non-pharmacological interventions were only evaluated by non-randomised studies. In non-randomised studies, several patient characteristics may influence treatment effects. These characteristics are difficult to identify in the context of a rare condition, especially in secondary RP, considering the large within-patient and between-patient variability of the RP experience. A retrospective cohort study at serious RoB suggested that concomitant vascular bypass plus periarterial sympathectomy performed better than periarterial sympathectomy alone in complete and durable healing of DUs, and a prospective observational study at moderate RoB suggested bone marrow mononuclear cell implantation in SSc patients with high-grade ischaemic DUs improved DU-associated pain.

For all included studies, the outcome measures, evaluation time points, study design, and analytical methods were heterogeneous across the included studies, hampering the pooling of data. The reported ES varied widely for some outcomes, which may indicate publication bias. Therefore, the ES reported here should be interpreted with caution. There was also a small number of trials for

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many interventions, and the available evidence might be insufficient to draw firm conclusions for several of these. In addition to the limitations in the evidence, this SLR has some limitations itself. Although an extensive literature search has been performed, we chose to report ES to compare results over different outcomes and scoring methods. However, ES measures were not extractable for all studies, which limits, to some extent, the interpretation of the results.

Finally, most studies did not evaluate safety systematically. To overcome the paucity of safety data, we assessed safety outcomes by drug class rather than individual drugs. In general, there were no new safety issues identified for the main pharmacological classes. Headache was the most frequently reported AE in the BCC, PDE5i, prostacyclin analogues, and ERA classes and serious events were uncommon. Notably, in the prostacyclin analogues group, most AE were mild to moderate and improved by reducing the infusion rate. However, longitudinal observational studies are essential to best detect any safety signals not found by RCTs.

In conclusion, this SLR summarizes the scientific evidence on essentially all the relevant pharmacological and non-pharmacological treatments for RP and DU associated with CTDs, and is, to the best of our knowledge, one of the most comprehensive yet produced. Although numerous interventions have been used over the years to manage secondary RP and/or DUs in clinical practice, our SLR emphasizes the scarcity of (high-quality) evidence supporting the effectiveness of some of these therapeutic options. There is, therefore, an urgent need to further evaluate the existing therapeutic options and to develop new pharmacological and non-pharmacological therapeutic strategies for secondary RP and DUs. The results of this SLR informed a Task Force responsible for developing the first Portuguese recommendations for the management of RP and DUs in patients with SSc and other CTDs aiming at improving the healthcare of these patients.

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Tables and Figures

$$SMD = \sqrt{\frac{SD_t^2.(n_t-1)+SD_c^2.(n_c-1)}{n_t+n_c-2}}$$

$$\text{Cohen's d} = \frac{M_a-M_b}{SD_b}$$

Box I: Standard Mean Deviation and Cohen's d formulas. c: control; Ma: Mean after the intervention; Mb: Mean baseline; t: treatment; SD: Standard deviation; SDb: Standard deviation baseline.

Table I- Efficacy outcomes of pharmacological interventions – Calcium channel blockers

Study ID	Study design	Population	Intervention	N	Outcome	Mean (SD) FU	P-value	SMD	RoB
Kahan et al. 1985a[35]	RCT crossover	Idiopathic 12 SSc 10 SLE 5 RA 3	Nifedipine 60mg id Placebo	18	RP frequency *	10.4 (15.1) 28.1 (4.9)	**<0.01** REF	0.40	Unclear
Kahan et al. 1985b[36]	RCT crossover	SSc 7 SLE 2 RA 1 Idiopathic 5	Nifedipine 60mg id Prazosin 3mg id Placebo	10	RP frequency *	7.7 (7.8) 18.5 (10.2) 18.1 (6.6)	**<0.01** NS REF	0.50	Unclear
					RP severity-VAS	2.9 (2.6) 5.9 (2.3) 6.2 (1.5)	**<0.01** NS REF	0.51	
Kahan et al. 1985c[37]	RCT crossover	SSc 7 SLE 1 RA 2 Idiopathic 6	Diltiazem 120mg tid Placebo	10	RP frequency *	15.1 (9.9) 20.4 (4.9)	NS REF	0.46	Unclear
					RP severity-VAS*	5.1 (3.2) 6.6 (1.3)	NS REF	0.45	
Kahan et al. 1987[40]	RCT crossover	SSc 15 RA 2 Idiopathic 3	Nicardipine 60mg id Placebo	17	RP frequency *	23.1 (17.0) 29.6 (13.6)	**<0.05** REF	0.37	Unclear
					RP Severity-VAS*	1.8 (0.7) 2.2 (0.4)	**<0.05** REF	0.35	
Rodeheffer et al. 1983[39]	RCT crossover	SSc 9 Idiopathic 6	Nifedipine 30-60mg id Placebo	9	RP frequency *	13.1 (5.1) 15.0 (4.2)	**0.02** REF	0.48	Unclear
					VAS improvement*	NR NR	**0.02** REF	NC	
Thomas et al. 1987[38]	RCT crossover	SSc 10	Nifedipine 30-60mg id Placebo	10	Duration attacks*	18.7 (4.5) 29.7 (9.6)	**0.02** REF	0.51	Unclear
					RP frequency	1.3 (0.5) 1.6 (0.5)	NS REF	0.47	
					New DU	9U in 3Pts 18U in 6Pts	NS REF	NC	

Detailed results are shown in Supplementary Tables S3,4.
DU: Digital ulcer; FU: Follow-up; NC: Not possible to calculate; NR: Not reported; NS: Non significative; RA: Rheumatoid arthritis; RCS: Raynaud Condition Score; RCT: Randomised controlled trial; REF: Reference RP: Raynaud phenomenon; SLE: Systemic Lupus Erythematous; SMD: Standardised mean difference; SSc: Systemic sclerosis; VAS: Visual analogue scale. * Primary outcome.

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Table II- Efficacy outcomes of pharmacological interventions – Phosphodiesterase-5 inhibitors

Study ID	Study design	Population	Intervention	N	Outcome	Mean (SD) FU	p-value	SMD	RoB
Hachulla et al. 2014[42]	RCT parallel	SSc 83	Sildenafil 20mg tid Placebo	42 41	Time to DU healing*	NR NR	0.25 REF	HR 1.27 (0.85-1.89)	Low
					Number DU	0.9 (1.6) 1.5 (2.7)	**0.01** REF	OR 0.57 (0.37- 0.88)	
					Healing rate	NR NR	**0.03** REF	OR 1.78 (1.06-2.97)	
					New DU	8/42 15/41	0.10 REF	OR 0.42 (0.15-1.17)	
Herrick et al. 2011[43]	RCT parallel	SSc 57	Sildenafil 200mg id Placebo	30 27	% Change in RP frequency*	-44% -18.1%	**0.03** REF	NC	Low
					RCS	2.8 (2.04) 2.6 (2.35)	NS REF	0.18	
					RP duration	15.0 18.4	NS REF	NC	
					RP-VAS pain	2.5 2.2	NS REF	NC	
Andrigueti et al. 2017[44]	RCT parallel	SSc 41	Sildenafil 100mg id Placebo	21 20	RP Duration	11.8 (21) 21.9 (22.6)	**0.04** REF	0.34	Unclear
					RP frequency	1.1 (2.5) 1.0 (3.0)	NS REF	0.33	
					RP severity-VAS	6.0 (8.25) 3.0 (9.0)	NS REF	0.31	
					RCS	1.3 (3.2) 1.1 (5.6)	NS REF	0.33	
					DU healing	4 Pts with DU at base line (3I vs 1P). FU: 0 in I and 1 in P			
Caglayanet al. 2012[45]	RCT crossover	SScD 13 SScL 25 MCTD 9 Idiopathic 6	Vardenafil 10mg bid Placebo	47	RCS Mean reduction*	-0.69 (0.68) 0.28 (2.29)	**0.04** REF	0.25	Unclear
Fries et al. 2005[46]	RCT crossover	SSc 14 MCTD 2 Idiopathic2	Sildenafil 50mg bid Placebo	16	RP frequency	35 (14) 52 (18)	**0.01** REF	0.38	Unclear
					RP duration*	581±133 1046±245	**0.01** REF	0.46	
					RCS daily mean	2.2±0.4 3.0±0.5	**0.04** REF	0.33	
Roustit et al. 2018[47]	RCT multiple crossover N-of-1 (blocks)	Idiopathic: 26 Secondary: 12	Sildenafil 40mg (max bid) Sildenafil 80mg (max bid) Placebo	12	RCS change*	-0.14 (0.19) -0.05 (0.16) NR	NS NS REF	HR 0.92 (0.81-1.04) HR 0.97 (0.88-1.1)	Unclear
Schiopu et al. 2009[48]	RCT crossover	SSc 45	Tadalafil 20mg id Placebo	23 22	RCS change*	2.43 (2.01) 2.53 (2.22)	NS REF	0.24	Unclear
Shenoy et al. 2010[49]	RCT crossover	SSc 24 MCTD 1	Tadalafil 20mg alternate days Placebo	25	RCS*	3.86 (0.46) 5.20 (0.53)	**0.01** REF	0.43	Unclear
					RP duration*	33.81 (7.89) 54.89 (11.33)	**0.02** REF	0.36	
					RP frequency*	2.29 (0.29) 3.37 (0.38)	**<0.01** REF	0.40	
					New DU	1/24 13/25	**<0.01** REF	RR 0.1	
					DU healing	24/24 3/13	**<0.01** REF	RR 4.35	
Young Lee et al. 2014[50]	RCT crossover	SSc 20 MCTD 3 SSj 3	Udenafil 100 mg id Amlodipine 10 mg id	26	RP frequency *	0.5 (0.9) 0.5 (1.4)	NS REF	0.28	Unclear

Detailed results are shown in Supplementary Tables S5,6.
DU: Digital ulcer; FU: Follow-up; MCTD: Mixed connective tissue disease; NC: Not possible to calculate; NR: Not reported; NS: Non significative; RA: Rheumatoid arthritis; RCS: Raynaud condition score; RCT: Randomized controlled trial; REF: Reference RP: Raynaud phenomenon; SSj: Sjögren's syndrome; SLE: Systemic Lupus Erythematous; SMD: Standardised mean difference; SSc: Systemic sclerosis; VAS: Visual analogue scale. * Primary outcome.

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Table III - Efficacy outcomes of pharmacological interventions – Prostacyclin analogues

Study ID	Study design	Population	Intervention	N	Outcome	Mean (SD) FU	P value	SMD	RoB
IV Prostacyclin analogues vs placebo									
Wigley et al. 1994[55]	RCT parallel	SSc 131	Iloprost Placebo	64 67	% Improvement RP frequency*	39.1 22.2	**<0.001** REF	0.18	Low
					% Improvement RP severity (VAS)*	34.8 19.7	**<0.001** REF	0.18	
					% DU improvement*	25.7 18.8	NS	NC	
McHugh et al. 1988[62]	RCT crossover	SSc 26 MCTD 3	Iloprost Placebo	29 29	% Change RP duration	-9 26	NS	NC	Unclear
					% Change RP severity	-20 -1	**0.01** REF		
					% Change RP VAS pain	-16 -11	NS		
Wigley et al. 1992[56]	RCT parallel	SSc 35	Iloprost Placebo	18 17	Complete DU healing*	7/18 4/17	**0.02** REF	RR 2.65	Unclear
					RP frequency*	NR NR	NS	NC	
					RP duration*	32.7 (53.3) 80.4 (208.0)	NS	0.35	
					RP severity*	0.82 (0.97) 0.61 (0.49)	NS	0.35	
Yardumian et al. 1988[57]	RCT crossover	SSc 10 MCTD 2	Iloprost Placebo	12 12	Change RP frequency *	3.7 (3.2) 4.5 (3.7)	**<0.01** REF	0.41	Unclear
IV Prostacyclin analogues Head-to-Head									
Torley et al. 1991[58]	RCT parallel	SSc 43 DM 1 MCTD 5 RA 1 SSj 1 UCTD 4	IV Iloprost 0.5 ng/kg/min IV Iloprost 2 ng/kg/min	27 28	% Change RP frequency*	-37 -28	NS	NC	Low
					% Change RP duration*	-46 -20	NS	NC	
					% Change RP severity*	-23 -10	NS	NC	
Kawald et al. 2008[59]	RCT parallel, open label	SSc 50	IV Iloprost 2 ng/kg/min IV Iloprost 0.5 ng/kg/min	25 25	% Change number DU	76.2 61.0	NS	NC	Unclear
					% Change attacks per week	46 42	NS	NC	
					DU healing	15/63 25/64	NS	RR 1.62	
Rademaker et al. 1989[60]	RCT parallel	SSc 23	IV iloprost 2 ng/kg/min Nifedipine 60 id	12 11	% Change RP frequency*	-55.4 -41.5	NS	NC	Unclear
					% Change RP duration*	-46.8 -44.7	NS	NC	
					% Change RP severity*	-34.6 -31.5	NS	NC	
					DU number*	0.6±0.3 1.4±0.5	**0.04** REF	0.50	
Scorza et al. 2001[61]	RCT parallel	SSc 46	IV iloprost 2 ng/kg/min Nifedipine 40 mg id	29 17	RP severity (RCS)*	1.22±0.13 1.33±0.22	**<0.05** REF	0.31	Unclear

Detailed results are shown in Supplementary Tables S7,8.
DM: Dermatomyositis; DU: Digital ulcer; FU: Follow-up; MCTD: Mixed connective tissue disease; NC: Not possible to calculate; NR: Not reported; NS: Non significative; RA: Rheumatoid arthritis; RCS: Raynaud condition score; RCT: Randomized controlled trial; REF: Reference RP: Raynaud phenomenon; SSj: Sjögren's syndrome; SLE: Systemic Lupus Erythematous; SMD: Standardised mean difference; SSc: Systemic sclerosis; UCTD: Undifferentiated connective tissue disease; VAS: Visual analogue scale. * Primary outcome.

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Table IV - Efficacy outcomes of pharmacological interventions – Endothelin receptor antagonists

Study ID	Study design	Population	Intervention	N	Outcome	Mean (SD) FU	p-value	SMD	RoB
Cerinic et al. 2011[63]	RCT parallel	SSc 188	Bosentan Placebo	98 90	New DU*	1.9 (0.2) 2.7 (0.3)	**0.04** REF	0.22	Low
					DU healing	35/95 35/89	0.76 REF	HR 0.94	
Korn et al. 2004[65]	RCT parallel	SSc 122	Bosentan Placebo	79 43	New DU*	1.4 2.7	**<0.01** REF	RR 0.96	Low
					Time to DU healing	NR NR	NS REF	NC	
Nguyen et al. 2010[66]	RCT parallel	SSc 17	Bosentan Placebo	9 8	% Change RP severity (RCS)*	-31 (40) -36 (35)	NS REF	NC	Low
					% Change VAS pain*	253 (346) -53 (47)	**0.01** REF	0.52	
					% Change RP frequency*	-30 (31) -57 (29)	NS REF	NC	
					% Change RP duration*	-26 (13) -44 (24)	NS REF	NC	
Khanna et al. 2016[64]	RCT parallel	SSc 289	Macitentan 3 mg Macitentan 10 mg Placebo	95 97 97	New DU*	0.94 (0.35) 1.08 (0.33) 0.85 (0.23)	0.7 0.36 REF	0.15 0.15	Low
Khanna et al. 2016[64]	RCT parallel	SSc 265	Macitentan 3 mg Macitentan 10 mg Placebo	88 88 89	New DU*	1.44 (0.40) 1.46 (0.43) 1.29 (0.42)	0.43 0.41 REF	0.15 0.15	Low

Detailed results are shown in Supplementary Tables S9-12.
DU: Digital ulcer; FU: Follow-up; NC: Not possible to calculate; NR: Not reported; NS: Non significative; RCS: Raynaud condition score; RCT: Randomized controlled trial; REF: Reference RP: Raynaud phenomenon; SMD: Standardised mean difference; SSc: Systemic sclerosis; VAS: Visual analogue scale. * Primary outcome.

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Table V - Efficacy outcomes of non-pharmacological interventions.

Study ID	Study design	Population	Intervention	N	Outcome	Mean BL	Mean FU	Δ FU–BL Mean	Δ FU–BL p-value	Δ FU–BL Cohen D	Δ I–C	I vs C SMD (95% CI)	I vs C p-value	RoB
Horvath et al. 2016[93]	CCT	SSc	Hand physical therapy	31	RP pain VAS	3.72	2.55	-1.17	0.05	-0.42	-1.22	-0.38 (-0.92; 0.18)	0.21	Critical
			No intervention	22		3.58	3.47	-0.05	0.49	0.02				
Goodfield et al. 1988[94]	Crossover CCT	SSc	Hand warming 5min every 4h	12	Frequency RP attacks/week	NR	11.8	NC	NC	NC	NC	NC	<0.01	Critical
			Same patients, alternate weeks, no HW	12		NR	14.4	NC	NC	NC				
Neferu et al. 2017[95]	Crossover CCT	CTD	Ischemic preconditioning	8	Frequency RP attacks/week	14.6	14.8	+0.2	NR	NC	-0.5	NC	0.84	High
			Low pressure inflations	10		18.7	19.4	+0.7	NR	NC				
Kuryliszyn-Moskal et al. 2013[96]	Prospective observational	CTD	MLS laser in secondary RP	40	Frequency RP attacks/week	20.0	15.0	-5.0	<0.001	NC	NC	NC	NR	Moderate
			MLS laser in primary RP	38		6.0	5.0	-1.0	<0.001	NC				
Al-Awami et al. 2001[97]	Prospective observational	CTD	Low level laser in secondary RP	29	RP severity VAS	8.0	2.0	-6.0	<0.001	NC	NC	NC	1.0	Moderate
			Low level laser in primary RP	11		8.0	1.0	-7.0	<0.001	NC				
Kaymaz et al. 2021[98]	RCT	SSc with DU	Local oxygen-ozone + MT	13	Frequency RP attacks/day	3.5	2.0	-1.5	<0.01	NC	-1.3	NC	<0.01	Low
			Medical therapy	12		4.0	3.8	-0.2	0.26	NC				
Shima et al. 2022[99]	Crossover RCT	SSc	Proximal heat stress neck	14	RP severity VAS	3.8	2.9	-0.9	0.02	NC	NC	NC	NC	High
			Proximal heat stress elbow	14		3.5	2.9	-0.6	0.04	NC				
			Proximal heat stress wrist	14		2.9	3.0	+0.1	0.86	NC				
Liem et al. 2022[100]	Crossover RCT	SSc	Silver fibre gloves	75	RCS	6.4	3.9	-2.5	NR	NC	0	-0.1 (-0.2; 0.1)	0.7	Unclear
			Normal gloves	75		6.4	3.9	-2.5	NR	NC				
Takagi et al. 2014[101]	Prospective observational	SSc with DU	BMMC implantation in SSc pts	11	DU pain VAS	9.3	1.1	-8.2	<0.01	NC	-2.1	-0.34 (-0.81; 0.15)	NR	Moderate
			BMMC implantation in arteriosclerosis obliterans pts	29		7.7	1.6	-6.1	<0.01	NC				
Matsumoto et al. 2002[102]	Retrospective cohort	CTD	ETS in CTD-RP pts	8	Long-term reduced RP frequency and severity, %	-	75	NC	NC	NC	NC	0.9 (0.4; 1.7)	NC	Serious
			ETS in non-CTD-RP pts	20		-	95	NC	NC	NC				
Hartzell et al. 2009[103]	Retrospective cohort	CTD with DU	PS in CTD-DUs pts	20 pts 42 fingers	Reduction in number of DUs, % of pts	-	75	NC	NC	NC	NC	6.0 (0.9; 38.2)	<0.01	Critical
			PS in atherosclerosis-DUs pts	8 pts 17 fingers		-	13	NC	NC	NC				
Shammas et al. 2017[104]	Retrospective cohort	CTD with DU	PS+VB	9 pts 9 hands	Complete and durable DU healing, % of hands	-	56	NC	NC	NC	NC	3.8 (1.3; 11.0)	0.03	Serious
			PS alone	18 pts 27 hands		-	15	NC	NC	NC				

Detailed results are shown in Supplementary Tables S48-58.
BL: Baseline; BMMC: Bone marrow mononuclear cells; C: Control; CCT: Controlled clinical trial; CTD: Connective tissue diseases; DU: Digital ulcer; ETS: Endoscopic thoracic sympathectomy; FU: Follow-up; I: Intervention; MLS: Multiwave Locked System; MT: Medical therapy; NC: Not possible to calculate; NR: Not reported; PS: Periarterial sympathectomy; Pts: patients; RCS: Raynaud condition score; RP: Raynaud phenomenon; RCT: Randomized controlled trial; SMD: Standardised mean difference; SSc: Systemic sclerosis; VAS: Visual analogue scale

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Intervention	Outcome							
	RCS	RP severity	RP duration	RP frequency	DU healing	DU number	DU prevention	LoE*
Pharmacological interventions								
CCB								1a†
PDE5i								1a
Prostacyclin analogues								1a
Endothelin receptor antagonists								1b‡
Nitroglycerin								1a
ACEi/ARB								1b
Atorvastatin								1b
SSRI								2b
Botulinum toxin								1b
Regional grafting of adipose tissue								2b
Aminaphtone								2b
Selexipag								1b
Vitamin E gel								2b
Riociguat								1b
Prazosin								2b
Dimethyl sulfoxide								2b
N-acetylcysteine								1b
Cyclophosphamide								1b
Ketanserin								1a
Stanozolol								2b
Cilostazol								1b
Non-pharmacological interventions								
Hand warming for 5min every 4h								4
Heating neck or elbows								2b
Low level laser therapy								4
Multiwave Locked System laser therapy								4
Periarterial sympathectomy								4
Concomitant vascular bypass								4
Endoscopic thoracic sympathectomy								4
Local oxygen-ozone therapy								1b
Hand physical therapy								4
Ischemic preconditioning								2b
Silver fiber gloves								2b

	Effective		Not effective
	Limited/conflicting evidence		Not evaluated/reported

Figure 1- Efficacy of different interventions for the treatment of Raynaud phenomenon and digital ulcers in patients with systemic sclerosis and other connective tissue diseases.

ACEi/ARB: angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers; CCB: calcium channel blockers; DU: digital ulcer; LoE: level of evidence; PDE5i: phosphodiesterase-5 inhibitors; RCS: Raynaud Condition Score; RP: Raynaud phenomenon; SSRI: selective serotonin reuptake inhibitors.

*Oxford Centre for Evidence-Based Medicine. The Oxford 2009 levels of evidencehttps://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-forevidence-based-medicine-levels-of-evidence-march-2009.

†Supportive data only for dihydropyridine subclass.

‡Supportive data only for bosentan.

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40. Table S30 – Vitamin E gel – Safety 44
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43. Table S33 – Alpha adrenergic blockers – Efficacy 45
44. Table S34 – Alpha adrenergic blockers – Safety 46
45. Table S35 – Dimethyl sulfoxide – Efficacy 46
46. Table S36 – Dimethyl sulfoxide – Safety 46
47. Table S37 – N-acetylcysteine – Efficacy 47
48. Table S38 – N-acetylcysteine – Safety 47
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A- PICOs, databases and inclusion/exclusion criteria

1. Databases

- Pubmed, EMBASE, Cochrane Central, clinicaltrials.gov, WHO-ICTRP
- From 1-1-1966 to 13-05-2022
- Search of published abstracts in the online abstract libraries of the EULAR and the ACR annual meetings for the years 2019 and 2021 (for efficacy evaluation only)

2. PICOs

2.1. Non-pharmacological treatment: efficacy and safety

Patients	**Inclusion criteria** - Patients with secondary Raynaud´s associated with an autoimmune rheumatic connective tissue disease, including: > Systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, idiopathic inflammatory myopathies, Sjögren's syndrome, antiphospholipid syndrome, undifferentiated connective tissue disease, overlap syndromes > Patients aged 18 years or over.
Intervention	All non-pharmacological treatments including: - General lifestyle measures/education - Local wound care - Digital (palmar) sympathectomy - Surgery (surgical debridement, amputation) - Exercise - Physiotherapy (including biofeedback, deep oscillation, transcutaneous electrical nerve stimulation) - Acupuncture - Hyperbaric chamber - Self-help groups - **Others treatments** (eg, ascorbic acid, primrose oil, vitamin E, vitamin C, vitamin E, gamolenic acid, gingko biloba, omega-3 essential fatty acids) All regimens and duration.
Comparison	Other non-pharmacological treatments, pharmacological treatments in different dose or regimens, any combination therapy, none (if population-based incidence rates are reported – for safety).
Outcomes	**Efficacy:** - Mean daily frequency of RP attacks; - Mean severity of RP attacks measured using the Raynaud's Condition Score (RCS), a visual analogue scale, or any other severity score; - Mean duration of each attack. - Frequency, severity and duration of RP attacks

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	- DUs with improvement/healing - New DUs - Time to improvement/healing of the DUs - Raynaud´s/DUs pain (visual analogical scale day and night) - Patient's global assessment (VAS) - Disability (eg, HAQ) - Raynaud condition score - Quality of life (eg, EQ5D, SF-36) **Safety (short term and long term):** Withdrawals due to AEs, Number of serious adverse events (AE), deaths or hospitalization, number of AEs, any infection.

2.2. Pharmacological treatment: efficacy and safety

Patients	**Inclusion criteria** - Patients with secondary Raynaud´s associated with an autoimmune rheumatic connective tissue disease, including: > Systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, idiopathic inflammatory myopathies, Sjögren's syndrome, antiphospholipid syndrome, undifferentiated connective tissue disease, overlap syndromes > Patients aged 18 years or over.
Intervention	All pharmacological treatment including: - **calcium channel blockers** (eg, nifedipine, amlodipine, diltiazem) - **angiotensin II receptor blockers** (eg, losartan) - **selective serotonin reuptake inhibitors** (eg, fluoxetine) - **alpha blockers** (eg, prazosin) **- angiotensin-converting enzyme inhibitors** (eg, lisinopril, captopril, enalapril, quinapril) **- prostacyclin analogues** (eg, iloprost, epoprostenol, treprostinil, alprostadil) - **endothelin receptor antagonists** (eg, bosentan, macitentan) - **phosphodiesterase type 5 inhibitors** (eg, sildenafil, tadalafil, vardenafil) - **antithrombotic therapy** (eg, aspirin, dipyridamole, clopidogrel, heparin, vitamin K antagonist and non-vitamin K antagonist oral anticoagulants) - **topical nitrate** (eg, nitroglycerin) - **statins** (eg, atorvastatin) - i**mmunosuppressants** (eg, glucocorticoids, methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, rituximab, tocilizumab, abatacept) - **Local/regional block** - **Botulinum toxin** - **Others treatments** (eg, pentoxifylline, aminaphtone, N-Acetylcysteine) All formulations, regimens and duration.

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Comparison	Same pharmacological treatment in different dose or regimes, another pharmacological treatment, combination of pharmacological treatment with additional treatment, placebo, and none (if population-based incidence rates are reported – for safety)
Outcomes	**Efficacy:** - Mean daily frequency of RP attacks; - Mean severity of RP attacks measured using the Raynaud's Condition Score (RCS), a visual analogue scale, or any other severity score; - Mean duration of each attack. - Frequency, severity and duration of RP attacks - DUs with improvement/healing - New DUs - Time to improvement/healing of the DUs - Raynaud´s/DUs pain pain (visual analogical scale day and night) - Patient's global assessment (VAS) - Disability (eg, HAQ) - Raynaud condition score **Safety (short term and long term):** Withdrawals due to AEs, Number of serious adverse events (AE), deaths or hospitalization, number of AEs, any infection.

3. Inclusion / exclusion criteria (eligible study types)

3.1. Study type

- Published ≥1966
- SLRs/meta-analyses to identify references from original studies (SLRs/meta-analysis/indirect comparisons will not be included; exception: Cochrane reviews; if a Cochrane review is identified, it will be used and the original studies from then onwards will be used).
- Randomized clinical trials (RCTs) / controlled clinical trials (CCTs) / open-label extensions / long-term extensions (both for efficacy and safety).
- Cohort-studies/registries but only when a comparator is available, as descriptions of safety events without a comparator group do not allow for a proper interpretation. Non-randomized studies will also be used to assess efficacy for non-pharmacological therapies.
- - Studies that included patients with primary or secondary Raynaud's phenomenon will be eligible if outcome data is reported separately for those with secondary Raynaud's phenomenon.
- No language restriction.

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B- Search strategy

62. Search Strategies for Non-Pharmacological Treatment

MEDLINE (Ovid) and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
Searched 1946 to May 20, 2021 and updated 2021 to May 13, 2022

1 exp Raynaud Disease/
2 (raynaud$ or CREST).tw.
3 ((digit$ or finger$ or toe$) and ulcer$).tw.
4 or/1-3
5 secondary.tw.
6 Connective Tissue Diseases/
7 exp Scleroderma, Systemic/
8 (systemic adj (Scleroderma or Sclerosis)).tw.
9 exp arthritis, rheumatoid/
10 ((rheumatoid or reumatoid or rheumat$ or reumat$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.
11 (felty$ adj2 syndrome).tw.
12 (caplan$ adj2 syndrome).tw.
13 exp Lupus Erythematosus, Systemic/
14 (lupus or sle).tw.
15 connective tissue disease$.tw.
16 exp Myositis/
17 idiopathic inflammatory myopath$.tw.
18 sjogren$.tw.
19 ((anti phospholipid or antiphospholipid or anitbody or hughes or overlap) adj syndrome$).tw.
20 or/5-19
21 th.xs.
22 and/4,20-21
23 ("review" or "review academic" or "review tutorial").pt.
24 (medline or medlars or embase or pubmed).tw,sh.
25 (scisearch or psychinfo or psycinfo).tw,sh.
26 (psychlit or psyclit).tw,sh.
27 cinahl.tw,sh.
28 ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
29 (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
30 (pooling or pooled or mantel haenszel).tw,sh.
31 (retraction of publication or retracted publication).pt.
32 (peto or dersimonian or der simonian or fixed effect).tw,sh.
33 or/24-32
34 23 and 33
35 meta-analysis.pt.
36 meta-analysis.sh.
37 (meta-analys$ or meta analys$ or metaanalys$).tw,sh.
38 (systematic$ adj5 review$).tw,sh.
39 (systematic$ adj5 overview$).tw,sh.

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40 (quantitativ$ adj5 review$).tw,sh.
41 (quantitativ$ adj5 overview$).tw,sh.
42 (quantitativ$ adj5 synthesis$).tw,sh.
43 (methodologic$ adj5 review$).tw,sh.
44 (methodologic$ adj5 overview$).tw,sh.
45 (integrative research review$ or research integration).tw.
46 randomized controlled trial.pt.
47 controlled clinical trial.pt.
48 randomized.ab.
49 placebo.ab.
50 drug therapy.fs.
51 randomly.ab.
52 trial.ab.
53 groups.ab.
54 Epidemiologic studies/
55 exp case control studies/
56 exp cohort studies/
57 Case control.tw.
58 (cohort adj (study or studies)).tw.
59 Cohort analy$.tw.
60 (Follow up adj (study or studies)).tw.
61 observational study.pt.
62 (observational adj (study or studies)).tw.
63 Longitudinal.tw.
64 Retrospective.tw.
65 Cross sectional.tw.
66 Cross-sectional studies/
67 or/34-66
68 and/4,20,67
69 22 or 68

Embase (Embase.com)
Searched 1980 to 21 May 2021 and updated 2021 to May 16, 2022
#43. #4 AND #20 AND #41 AND ([article]/lim OR [article in press]/lim OR [review]/lim)
#42. #4 AND #20 AND #41
#41. #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
#40. observational:ab,ti OR prospective*:ab,ti OR longitudinal*:ab,ti OR cohort*:ab,ti OR 'cross sectional':ab,ti
#39. 'cross-sectional study'/de
#38. 'cohort analysis'/de
#37. 'prospective study'/de
#36. 'longitudinal study'/de
#35. 'observational study'/de
#34. 'crossover procedure'/de
#33. 'single-blind procedure'
#32. crossover*:ab,ti OR 'cross over*':ab,ti
#31. placebo*:ab,ti

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#30. (doubl* NEAR/2 blind*):ab,ti
#29. allocat*:ab,ti
#28. trial:ti
#27. 'randomized controlled trial'/exp
#26. random*:ab,ti
#25. intervention*:ti
#24. 'meta analysis'/exp
#23. 'systematic review':ab,ti
#22. 'systematic review'/de
#21. medline:ab,ti
#20. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#19. (('anti phospholipid' OR antiphospholipid OR anitbody OR hughes OR overlap) NEAR/2 syndrome*):ab,ti
#18. sjogren*:ab,ti
#17. 'idiopathic inflammatory myopathy':ab,ti OR 'idiopathic inflammatory myopathies':ab,ti
#16. 'myositis'/exp
#15. 'connective tissue disease':ab,ti OR 'connective tissue diseases':ab,ti
#14. lupus:ab,ti OR sle:ab,ti
#13. 'systemic lupus erythematosus'/exp
#12. (caplan* NEAR/2 syndrome):ab,ti
#11. (felty* NEAR/2 syndrome):ab,ti
#10. ((rheumatoid OR reumatoid OR rheumat* OR reumat*) NEAR/3 (arthrit* OR artrit* OR diseas* OR condition* OR nodule*)):ab,ti
#9. 'rheumatoid arthritis'/exp
#8. (systemic NEAR/2 (scleroderma OR sclerosis)):ab,ti
#7. 'systemic sclerosis'/exp
#6. 'connective tissue disease'/exp
#5. secondary:ab,ti
#4. #1 OR #2 OR #3
#3. (digit*:ab,ti OR finger*:ab,ti OR toe*:ab,ti) AND ulcer*:ab,ti
#2. raynaud*:ab,ti OR crest:ab,ti
#1. 'secondary raynaud phenomenon'/exp

ACR and EULAR Conference abstracts (Embase)
#56. #72 AND #75 AND (2021:py OR 2022:py)
#45. #73 OR #74
#44. eular:nc
#43. 'american college of rheumatology':nc
#42. #4 AND #20 AND #41
#41. #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
#40. observational:ab,ti OR prospective*:ab,ti OR longitudinal*:ab,ti OR cohort*:ab,ti OR 'cross sectional':ab,ti
#39. 'cross-sectional study'/de
#38. 'cohort analysis'/de
#37. 'prospective study'/de
#36. 'longitudinal study'/de

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#35. 'observational study'/de
#34. 'crossover procedure'/de
#33. 'single-blind procedure'
#32. crossover*:ab,ti OR 'cross over*':ab,ti
#31. placebo*:ab,ti
#30. (doubl* NEAR/2 blind*):ab,ti
#29. allocat*:ab,ti
#28. trial:ti
#27. 'randomized controlled trial'/exp
#26. random*:ab,ti
#25. intervention*.ti
#24. 'meta analysis'/exp
#23. 'systematic review':ab,ti
#22. 'systematic review'/de
#21. medline:ab,ti
#20. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#19. (('anti phospholipid' OR antiphospholipid OR anitbody OR hughes OR overlap) NEAR/2 syndrome*):ab,ti
#18. sjogren*:ab,ti
#17. 'idiopathic inflammatory myopathy':ab,ti OR 'idiopathic inflammatory myopathies':ab,ti
#16. 'myositis'/exp
#15. 'connective tissue disease':ab,ti OR 'connective tissue diseases':ab,ti
#14. lupus:ab,ti OR sle:ab,ti
#13. 'systemic lupus erythematosus'/exp
#12. (caplan* NEAR/2 syndrome):ab,ti
#11. (felty* NEAR/2 syndrome):ab,ti
#10. ((rheumatoid OR reumatoid OR rheumat* OR reumat*) NEAR/3 (arthrit* OR artrit* OR diseas* OR condition* OR nodule*)):ab,ti
#9. 'rheumatoid arthritis'/exp
#8. (systemic NEAR/2 (scleroderma OR sclerosis)):ab,ti
#7. 'systemic sclerosis'/exp
#6. 'connective tissue disease'/exp
#5. secondary:ab,ti
#4. #1 OR #2 OR #3
#3. (digit*:ab,ti OR finger*:ab,ti OR toe*:ab,ti) AND ulcer*:ab,ti
#2. raynaud*:ab,ti OR crest:ab,ti
#1. 'secondary raynaud phenomenon'/exp

The Cochrane Library
Searched May 23, 2021 and updated 2021 to May 12, 2022
#1 MeSH descriptor: [Raynaud Disease] explode all trees
#2 (raynaud* or CREST):ti,ab
#3 ((digit* OR finger* OR toe*) and ulcer*):ti,ab
#4 #1 OR #2 OR #3
#5 secondary:ti,ab
#6 MeSH descriptor: [Connective Tissue Diseases] this term only
#7 MeSH descriptor: [Scleroderma, Systemic] explode all trees

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#8 (systemic NEXT (Scleroderma OR Sclerosis)):Ti,ab
#9 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
#10 ((rheumatoid or reumatoid or rheumat* or reumat*) NEAR/3 (arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab
#11 (felty* NEAR/2 syndrome):ti,ab
#12 (caplan* NEAR/2 syndrome):ti,ab
#13 MeSH descriptor: [Lupus Erythematosus, Systemic] explode all trees
#14 (lupus OR sle):ti,ab
#15 "connective tissue disease*":ti,ab
#16 MeSH descriptor: [Myositis] explode all trees
#17 "idiopathic inflammatory myopathy":ti,ab OR "idiopathic inflammatory myopathies":ti,ab
#18 sjogren*:ti,ab
#19 (("anti phospholipid" OR antiphospholipid OR anitbody OR hughes OR overlap) NEXT syndrome*):Ti,ab
#20 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21 #4 AND #20

Epistemonikos
Searched May 23, 2021 and updated 2021 to May 12, 2022
(title:(raynaud*) OR abstract:(raynaud*))

ClinicalTrials.gov
Searched May 23, 2021 and updated 2021 to May 12, 2022
Raynaud Disease in Condition OR Raynaud Phenomenon in Condition or Raynaud Syndrome in Condition OR Digital Ulcer in Condition

WHO-ICTRP
Not accessible at the time of searching in 2021, but all years searched on May 12, 2022
Raynaud OR Raynauds in Condition

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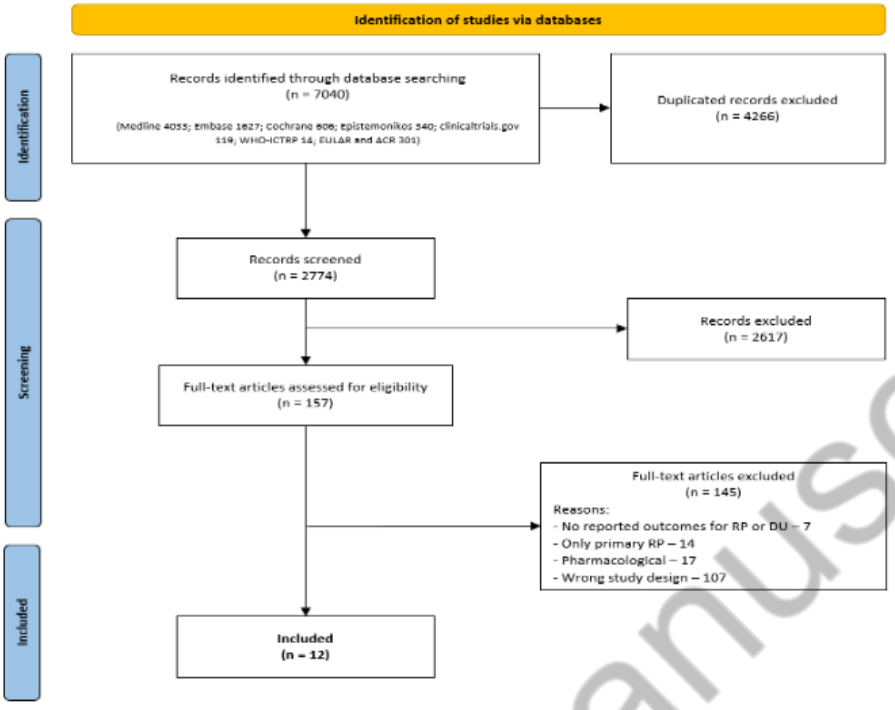

Figure S1- Flow diagram of search and selection of papers for non-pharmacological systematic review. DU, digital ulcers; RP, Raynaud phenomenon.

63. Search Strategies for Pharmacological Treatment

MEDLINE (Ovid) and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations.
Searched 1946 to May 20, 2021 and updated 2021 to May 11, 2022

1 exp Raynaud Disease/
2 (raynaud$ or CREST).tw.
3 ((digit$ or finger$ or toe$) and ulcer$).tw.
4 or/1-3
5 secondary.tw.
6 Connective Tissue Diseases/
7 exp Scleroderma, Systemic/
8 (systemic adj (Scleroderma or Sclerosis)).tw.
9 exp arthritis, rheumatoid/
10 ((rheumatoid or reumatoid or rheumat$ or reumat$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.
11 (felty$ adj2 syndrome).tw.
12 (caplan$ adj2 syndrome).tw.
13 exp Lupus Erythematosus, Systemic/
14 (lupus or sle).tw.
15 connective tissue disease$.tw.
16 exp Myositis/

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17 idiopathic inflammatory myopath$.tw.
18 sjogren$.tw.
19 ((anti phospholipid or antiphospholipid or anitbody or hughes or overlap) adj syndrome$).tw.
20 or/5-19
21 exp drug therapy/
22 dt.fs.
23 pharmacologic.tw.
24 exp Calcium Channel Blockers/
25 calcium channel blocker$.tw.
26 exp Angiotensin Receptor Antagonists/
27 (Angiotensin adj2 Receptor).tw.
28 exp Serotonin Uptake Inhibitors/
29 SSRI$.tw.
30 exp Adrenergic alpha-Antagonists/
31 alpha blocker$.tw.
32 exp Angiotensin-Converting Enzyme Inhibitors/
33 angiotensin-converting enzyme inhibitor$.tw.
34 exp Prostaglandins/
35 (prostaglandin$ or prostacyclin analogue$).tw.
36 Endothelin Receptor Antagonists/
37 endothelin receptor antagonist$.tw.
38 Phosphodiesterase 5 Inhibitors/
39 phosphodiesterase type 5 inhibitor$.tw.
40 exp Fibrinolytic Agents/
41 exp Antifibrinolytic Agents/
42 (Fibrinolytic$ or Antifibrinolytic$).tw.
43 Aspirin/
44 aspirin.tw.
45 Dipyridamole/
46 Clopidogrel/
47 Dipyridamole.tw.
48 clopidogrel.tw.
49 Heparin/
50 heparin.tw.
51 exp Anticoagulants/
52 anticoagulant$.tw.
53 (vitamin K antagonist or non-vitamin K antagonist).tw.
54 topical nitrate$.tw.
55 nitroglycerin.tw.
56 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
57 (Hydroxymethylglutaryl-CoA Reductase Inhibitor$ or hydroxymethylglutaryl coenzyme a reductase inhibitor$).tw.
58 statin$.tw.
59 exp Immunosuppressive Agents/
60 immunosuppressive$.tw.
61 exp Glucocorticoids/
62 glucocorticoid$.tw.
63 Methotrexate/

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64 (methotrexate or mycophenolate mofetil or azathioprine or cyclophosphamide or rituximab or tocilizumab or abatacept).tw.
65 exp Nerve Block/
66 ((local or regional) adj block).tw.
67 exp Botulinum Toxins/
68 Botulinum toxin.tw.
69 (pentoxifylline or aminaftone or N-Acetylcysteine).tw.
70 or/21-69
71 and/4,20,70
72 exp animals/ not humans.sh.
73 71 not 72

Embase (Embase.com)
Searched 1980 to May 20, 2021 and updated 2021 to May 11, 2022
#76. #72 AND #75 AND (2019:py OR 2020:py)
#75. #73 OR #74
#74. eular:nc
#73. 'american college of rheumatology':nc
#72. #4 AND #20 AND #71
#71. #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70
#70. pentoxifylline:ab,ti OR aminaftone:ab,ti OR 'n acetylcysteine':ab,ti
#69. 'botulinum toxin':ab,ti
#68. 'botulinum toxin'/de
#67. ((local OR regional) NEAR/2 block):ab,ti
#66. 'nerve block'/exp
#65. (methotrexate:ab,ti OR mycophenolate:ab,ti) OR mofetil:ab,ti OR azathioprine:ab,ti OR cyclophosphamide:ab,ti OR rituximab:ab,ti OR tocilizumab:ab,ti OR abatacept:ab,ti
#64. 'methotrexate'/de
#63. glucocorticoid*:ab,ti
#62. 'glucocorticoid'/exp
#61. immunosuppressive*:ab,ti
#60. 'immunosuppressive agent'/exp
#59. statin*:ab,ti
#58. 'hydroxymethylglutaryl coenzyme a reductase inhibitor':ab,ti OR 'hydroxymethylglutaryl coenzyme a reductase inhibitors':ab,ti OR 'hydroxymethylglutaryl-coa reductase inhibitor':ab,ti OR 'hydroxymethylglutaryl-coa reductase inhibitors':ab,ti
#57. 'hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp
#56. nitroglycerin:ab,ti
#55. 'glyceryl trinitrate'/de
#54. 'topical nitrate':ab,ti OR 'topical nitrates':ab,ti
#53. 'vitamin k antagonist':ab,ti OR 'non-vitamin k antagonist':ab,ti
#52. anticoagulant*:ab,ti
#51. 'anticoagulant agent'/exp
#50. heparin:ab,ti
#49. 'heparin'/de

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#48. clopidogrel:ab,ti
#47. 'clopidogrel'/de
#46. dipyridamole:ab,ti
#45. 'dipyridamole'/de
#44. aspirin:ab,ti
#43. 'acetylsalicylic acid'/de
#42. fibrinolytic*:ab,ti OR antifibronilytic*:ab,ti
#41. 'fibrinolytic agent'/exp
#40. 'antifibrinolytic agent'/exp
#39. ((phosphodiesterase NEAR/2 '5 inhibitor'):ab,ti) OR ((phosphodiesterase NEAR/2 '5 inhibitors'):ab,ti)
#38. 'phosphodiesterase v inhibitor'/exp
#37. 'endothelin receptor antagonist':ab,ti OR 'endothelin receptor antagonists':ab,ti
#36. 'endothelin receptor antagonist'/exp
#35. prostaglandin*:ab,ti OR 'prostacyclin analogue':ab,ti OR 'prostacyclin analogues':ab,ti
#34. 'prostaglandin'/exp
#33. 'angiotensin-converting enzyme inhibitor':ab,ti OR 'angiotensin-converting enzyme inhibitors':ab,ti
#32. 'dipeptidyl carboxypeptidase inhibitor'/exp
#31. 'alpha blocker':ab,ti OR 'alpha blockers':ab,ti
#30. 'alpha adrenergic receptor blocking agent'/exp
#29. ssri*:ab,ti
#28. 'serotonin uptake inhibitor'/exp
#27. (angiotensin NEAR/2 receptor*):ab,ti
#26. 'angiotensin receptor antagonist'/exp
#25. 'calcium channel blocker':ab,ti OR 'calcium channel blockers':ab,ti
#24. 'calcium channel blocking agent'/exp
#23. pharmacologic:ab,ti
#22. 'drug therapy'/lnk
#21. 'drug therapy'/exp
#20. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#19. (('anti phospholipid' OR antiphospholipid OR anitbody OR hughes OR overlap) NEAR/2 syndrome*):ab,ti
#18. sjogren*:ab,ti
#17. 'idiopathic inflammatory myopathy':ab,ti OR 'idiopathic inflammatory myopathies':ab,ti
#16. 'myositis'/exp
#15. 'connective tissue disease':ab,ti OR 'connective tissue diseases':ab,ti
#14. lupus:ab,ti OR sle:ab,ti
#13. 'systemic lupus erythematosus'/exp
#12. (caplan* NEAR/2 syndrome):ab,ti
#11. (felty* NEAR/2 syndrome):ab,ti
#10. ((rheumatoid OR reumatoid OR rheumat* OR reumat*) NEAR/3 (arthrit* OR artrit* OR diseas* OR condition* OR nodule*)):ab,ti
#9. 'rheumatoid arthritis'/exp
#8. (systemic NEAR/2 (scleroderma OR sclerosis)):ab,ti
#7. 'systemic sclerosis'/exp
#6. 'connective tissue disease'/exp

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#5. secondary:ab,ti
#4. #1 OR #2 OR #3
#3. (digit*:ab,ti OR finger*:ab,ti OR toe*:ab,ti) AND ulcer*:ab,ti
#2. raynaud*:ab,ti OR crest:ab,ti
#1. 'secondary raynaud phenomenon'/exp

ACR and EULAR Conference abstracts (Embase)
#73. #4 AND #20 AND #71 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [humans]/lim
#72. #4 AND #20 AND #71
#71. #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70
#70. pentoxifylline:ab,ti OR aminaftone:ab,ti OR 'n acetylcysteine':ab,ti
#69. 'botulinum toxin':ab,ti
#68. 'botulinum toxin'/de
#67. ((local OR regional) NEAR/2 block):ab,ti
#66. 'nerve block'/exp
#65. (methotrexate:ab,ti OR mycophenolate:ab,ti) AND mofetil:ab,ti OR azathioprine:ab,ti OR cyclophosphamide:ab,ti OR rituximab:ab,ti OR tocilizumab:ab,ti OR abatacept:ab,ti
#64. 'methotrexate'/de
#63. glucocorticoid*:ab,ti
#62. 'glucocorticoid'/exp
#61. immunosuppressive*:ab,ti
#60. 'immunosuppressive agent'/exp
#59. statin*:ab,ti
#58. 'hydroxymethylglutaryl coenzyme a reductase inhibitor':ab,ti OR 'hydroxymethylglutaryl coenzyme a reductase inhibitors':ab,ti OR 'hydroxymethylglutaryl-coa reductase inhibitor':ab,ti OR 'hydroxymethylglutaryl-coa reductase inhibitors':ab,ti
#57. 'hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp
#56. nitroglycerin:ab,ti
#55. 'glyceryl trinitrate'/de
#54. 'topical nitrate':ab,ti OR 'topical nitrates':ab,ti
#53. 'vitamin k antagonist':ab,ti OR 'non-vitamin k antagonist':ab,ti
#52. anticoagulant*:ab,ti
#51. 'anticoagulant agent'/exp
#50. heparin:ab,ti
#49. 'heparin'/de
#48. clopidogrel:ab,ti
#47. 'clopidogrel'/de
#46. dipyridamole:ab,ti
#45. 'dipyridamole'/de
#44. aspirin:ab,ti
#43. 'acetylsalicylic acid'/de
#42. fibrinolytic*:ab,ti OR antifibronilytic*:ab,ti
#41. 'fibrinolytic agent'/exp
#40. 'antifibrinolytic agent'/exp

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#39. ((phosphodiesterase NEAR/2 '5 inhibitor'):ab,ti) OR ((phosphodiesterase NEAR/2 '5 inhibitors'):ab,ti)
#38. 'phosphodiesterase v inhibitor'/exp
#37. 'endothelin receptor antagonist':ab,ti OR 'endothelin receptor antagonists':ab,ti
#36. 'endothelin receptor antagonist'/exp
#35. prostaglandin*:ab,ti OR 'prostacyclin analogue':ab,ti OR 'prostacyclin analogues':ab,ti
#34. 'prostaglandin'/exp
#33. 'angiotensin-converting enzyme inhibitor':ab,ti OR 'angiotensin-converting enzyme inhibitors':ab,ti
#32. 'dipeptidyl carboxypeptidase inhibitor'/exp
#31. 'alpha blocker':ab,ti OR 'alpha blockers':ab,ti
#30. 'alpha adrenergic receptor blocking agent'/exp
#29. ssri*:ab,ti
#28. 'serotonin uptake inhibitor'/exp
#27. (angiotensin NEAR/2 receptor*):ab,ti
#26. 'angiotensin receptor antagonist'/exp
#25. 'calcium channel blocker':ab,ti OR 'calcium channel blockers':ab,ti
#24. 'calcium channel blocking agent'/exp
#23. pharmacologic:ab,ti
#22. 'drug therapy'/lnk
#21. 'drug therapy'/exp
#20. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#19. (('anti phospholipid' OR antiphospholipid OR anitbody OR hughes OR overlap) NEAR/2 syndrome*):ab,ti
#18. sjogren*:ab,ti
#17. 'idiopathic inflammatory myopathy':ab,ti OR 'idiopathic inflammatory myopathies':ab,ti
#16. 'myositis'/exp
#15. 'connective tissue disease':ab,ti OR 'connective tissue diseases':ab,ti
#14. lupus:ab,ti OR sle:ab,ti
#13. 'systemic lupus erythematosus'/exp
#12. (caplan* NEAR/2 syndrome):ab,ti
#11. (felty* NEAR/2 syndrome):ab,ti
#10. ((rheumatoid OR reumatoid OR rheumat* OR reumat*) NEAR/3 (arthrit* OR artrit* OR diseas* OR condition* OR nodule*)):ab,ti
#9. 'rheumatoid arthritis'/exp
#8. (systemic NEAR/2 (scleroderma OR sclerosis)):ab,ti
#7. 'systemic sclerosis'/exp
#6. 'connective tissue disease'/exp
#5. secondary:ab,ti
#4. #1 OR #2 OR #3
#3. (digit*:ab,ti OR finger*:ab,ti OR toe*:ab,ti) AND ulcer*:ab,ti
#2. raynaud*:ab,ti OR crest:ab,ti
#1. 'secondary raynaud phenomenon'/exp

The Cochrane Library
Searched May 23, 2021 and updated 2021 to May 12, 2022
#1 MeSH descriptor: [Raynaud Disease] explode all trees

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#2 (raynaud* or CREST):ti,ab
#3 ((digit* OR finger* OR toe*) and ulcer*):ti,ab
#4 #1 OR #2 OR #3
#5 secondary:ti,ab
#6 MeSH descriptor: [Connective Tissue Diseases] this term only
#7 MeSH descriptor: [Scleroderma, Systemic] explode all trees
#8 (systemic NEXT (Scleroderma OR Sclerosis)):Ti,ab
#9 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
#10 ((rheumatoid or reumatoid or rheumat* or reumat*) NEAR/3 (arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab
#11 (felty* NEAR/2 syndrome):ti,ab
#12 (caplan* NEAR/2 syndrome):ti,ab
#13 MeSH descriptor: [Lupus Erythematosus, Systemic] explode all trees
#14 (lupus OR sle):ti,ab
#15 "connective tissue disease*":ti,ab
#16 MeSH descriptor: [Myositis] explode all trees
#17 "idiopathic inflammatory myopathy":ti,ab OR "idiopathic inflammatory myopathies":ti,ab
#18 sjogren*:ti,ab
#19 (("anti phospholipid" OR antiphospholipid OR anitbody OR hughes OR overlap) NEXT syndrome*):Ti,ab
#20 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21 #4 AND #20

Epistemonikos
Searched May 23, 2021 and updated 2021 to May 12, 2022
(title:(raynaud*) OR abstract:(raynaud*))

ClinicalTrials.gov
Searched May 23, 2021 and updated 2021 to May 21, 2022
Raynaud Disease in Condition

WHO-ICTRP
Not accessible at the time of searching in 2021, but all years searched on May 12, 2022
Raynaud OR Raynauds in Conditio

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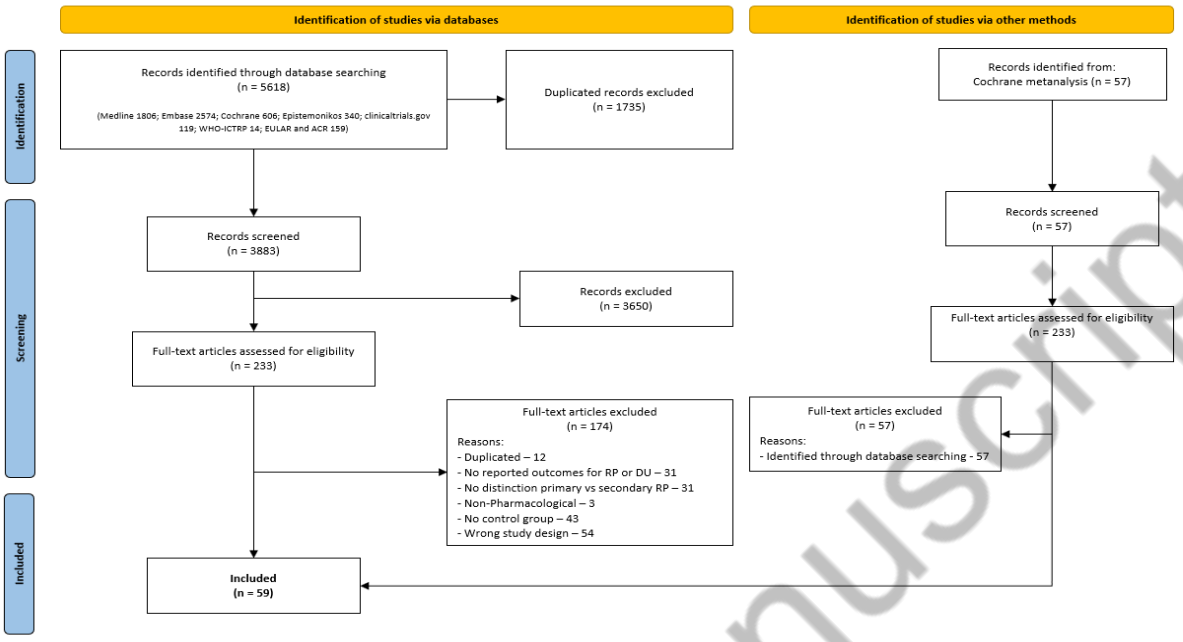

Figure S2- Flow diagram of search and selection of papers for pharmacological systematic review. DU, digital ulcers; RP, Raynaud phenomenon.

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A- Non-pharmacological RoB assessment of included studies.

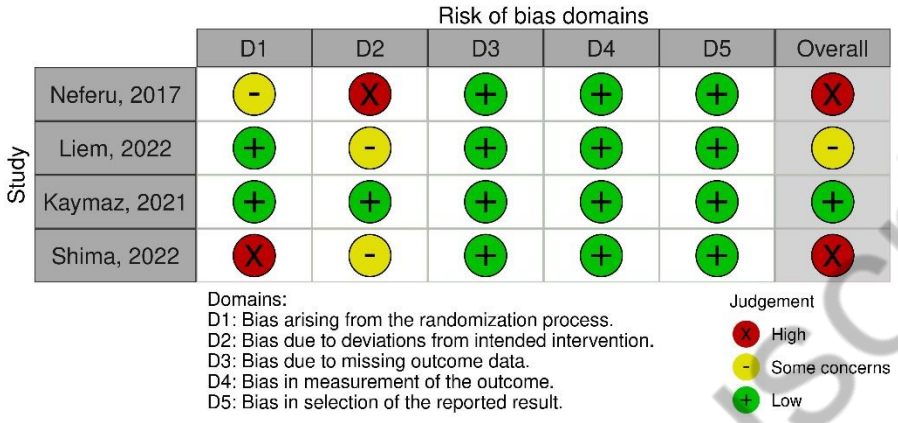

Figure S3: RoB traffic light plot of randomized clinical trials included in non-pharmacological SLR.

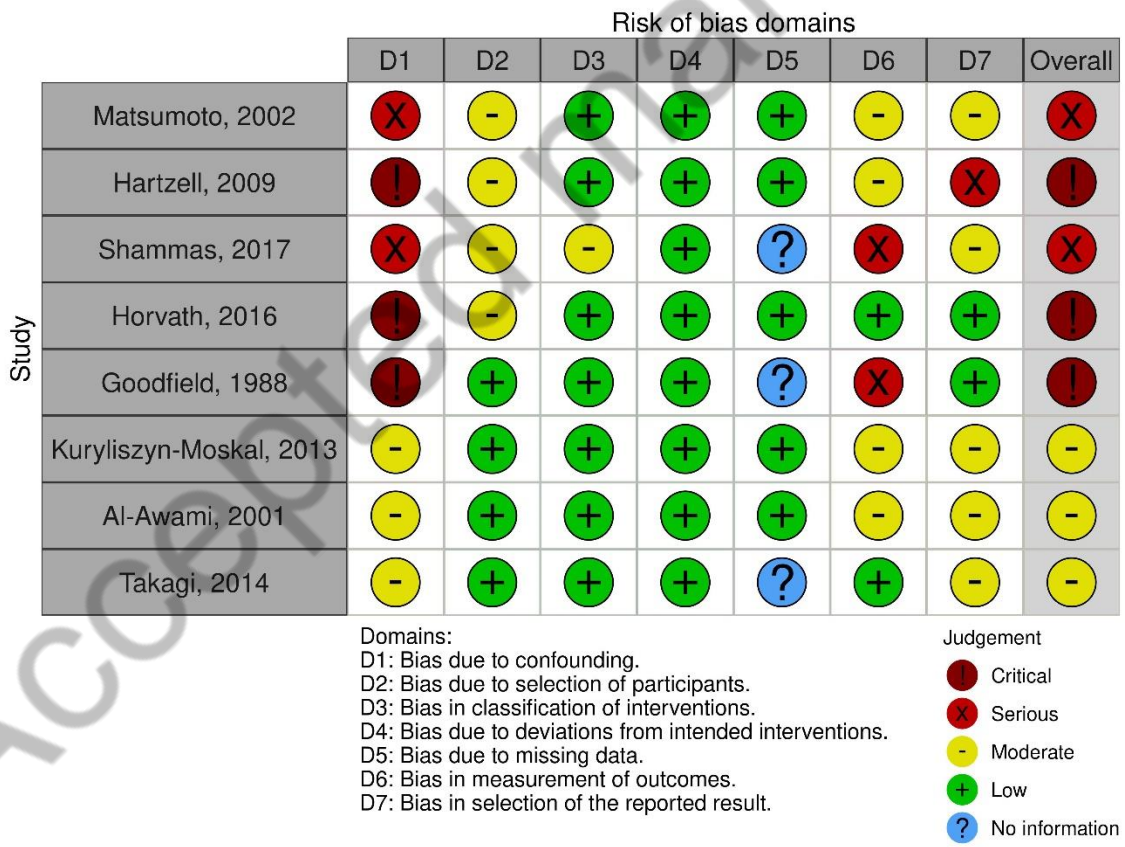

Figure S4: RoB traffic light plot of non-randomized studies included in non-pharmacological SLR.

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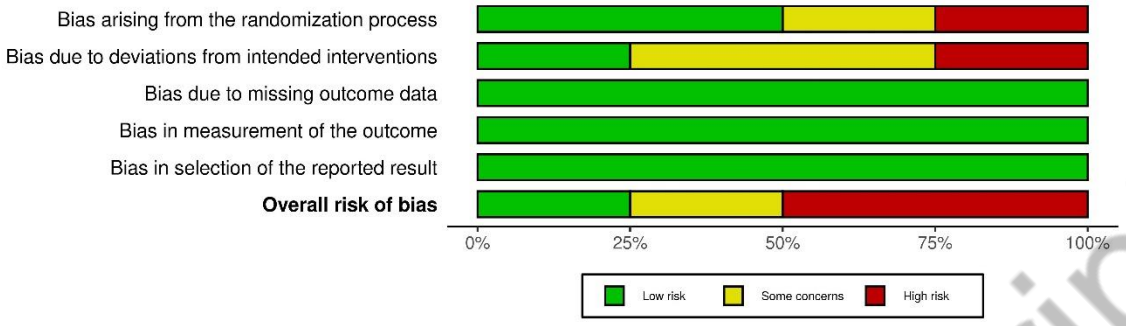

Figure S5: RoB weighted bar plot of randomized clinical trials included in non-pharmacological SLR.

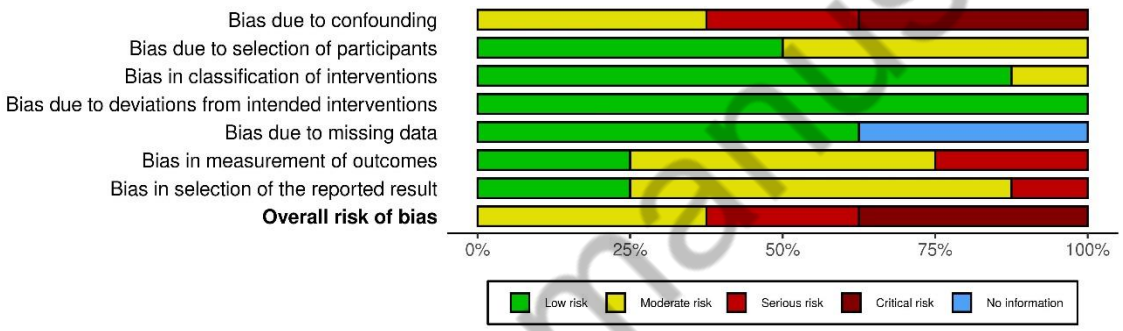

Figure S6: RoB weighted bar plot of non-randomized studies included in non-pharmacological SLR

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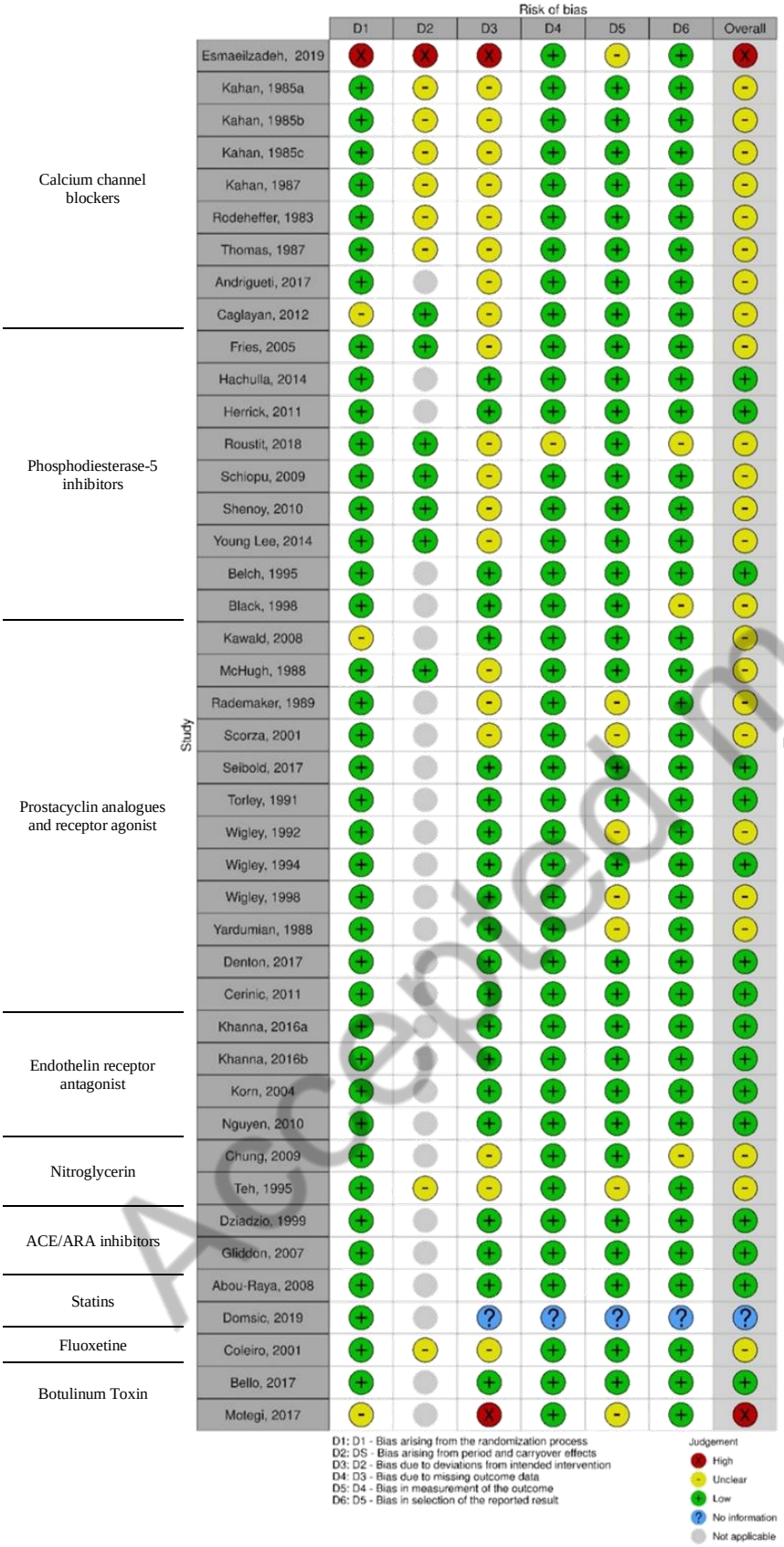
B- Pharmacological RoB assessment of included studies.



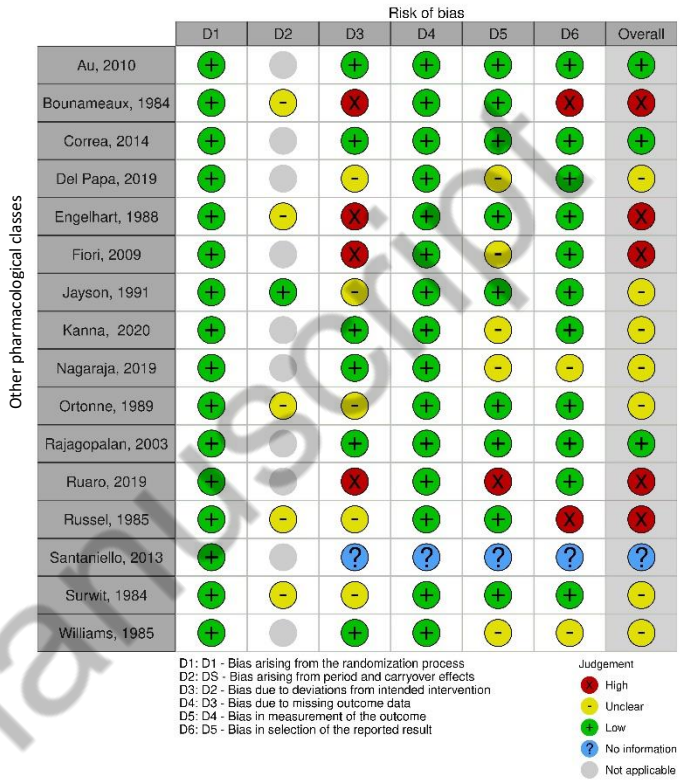


Figure S7: RoB traffic light plot of randomized clinical trials included in pharmacological SLR.

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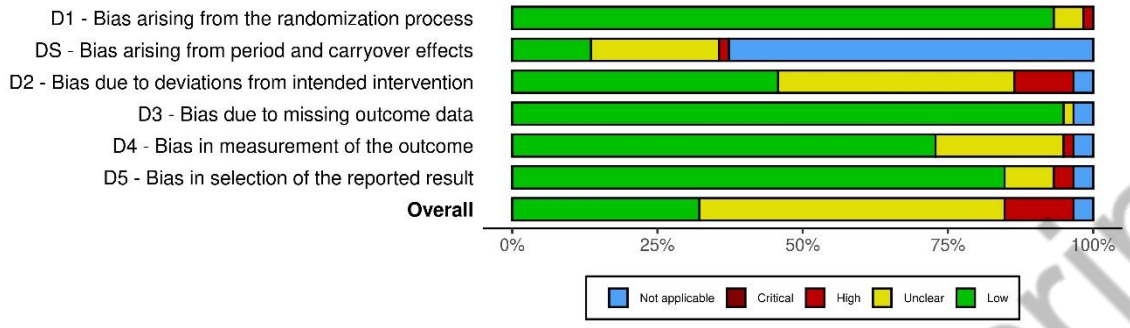

Figure S8: RoB weighted bar plot of studies included in pharmacological SLR.

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Table S1 – Global overview of included studies.

Intervention	Studies, n	Secondary RP Pts, n(%)	Low RoB, n(%)	Unclear RoB, n(%)	High Rob, n(%)
Calcium Channel Blockers	7	164 (84%)	0 (0%)	6 (86%)	1 (14%)
Phosphodiesterase-5 Inhibitors	9	352 (90%)	1 (11%)	8 (89%)	0 (0%)
Prostacyclin Analogues	12	1002 (100%)	4 (33%)	8 (67%)	0 (0%)
Endothelin receptor antagonist	5	890 (100%)	5 (100%)	0 (0%)	0 (0%)
Nitroglycerin	2	194 (81%)	0 (0%)	2 (100%)	0 (0%)
Angiotensin-converting-enzyme inhibitors/Angiotensin receptor blockers	2	237 (90%)	2 (100%)	0 (0%)	0 (0%)
Statins	2	107 (100%)	2 (100%)	0 (0%)	0 (0%)
Selective serotonin reuptake inhibitors	1	27 (51%)	0 (0%)	1 (100%)	0 (0%)
Aminaphtone	2	96 (82%)	0 (0%)	0 (0%)	2 (100%)
Cyclophosphamide	1	158 (100%)	1 (100%)	0 (0%)	0 (0%)
5HT2 antagonists (Ketanserin)	3	42 (100%)	0 (0%)	0 (0%)	3 (100%)
Prostacyclin receptor agonist (Selexipag)	1	74 (100%)	1 (100%)	0 (0%)	0 (0%)
Alpha adrenergic blockers (Prazosin)	2	26 (65%)	0 (0%)	1 (50%)	1 (50%)
N-acetylcysteine	1	42 (100%)	1 (100%)	0 (0%)	0 (0%)
Stanozolol	1	24 (100%)	0 (0%)	1 (100%)	0 (0%)
Phosphodiesterase III inhibitor (Cilostazol)	1	21 (53%)	1 (100%)	0 (0%)	0 (0%)
Riociguat	2	139 (100%)	0 (0%)	2 (100%)	0 (0%)
Dimethyl sulfoxide	1	84 (100%)	0 (0%)	1 (100%)	0 (0%)
Vitamin E gel	1	27 (100%)	0 (0%)	0 (0%)	1 (100%)
Botulinum Toxin	2	85 (100%)	1 (50%)	0 (0%)	1 (50%)
Regional grafting of autologous adipose tissue	1	38 (100%)	0 (0%)	1 (100%)	0 (0%)
TOTAL	59	3829 (95%)	19 (32%)	31 (53%)	9 (15%)

S1: Pts: patients; RP: Raynaud phenomenon.

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Table S2 – Summary of articles included in pharmacological SLR.

Study	Year of publication	Type of study	Population	Intervention	Control	Patients at FU/BL	N Secondary Raynaud	N sRP treated	RoB
Calcium Channel Blockers									
Esmaeilzadeh et al., Rheumatology Research	2019	RCT parallel Single blind	Secondary RP (SSc)	Diltiazem gel	Nitroglycerin ointment	53/90	90	60	High
Kahan et al., International Journal of Angiology	1985	RCT cross-over	Primary and secondary RP	Nifedipine	Placebo	30/30	18	18	Unclear
Kahan et al., European Heart Journal	1985	RCT cross-over	Primary and secondary RP	Nifedipine	Placebo	15/15	10	10	Unclear
Kahan et al., Annals of the Rheumatic Diseases	1985	RCT cross-over	Primary and secondary RP	Diltiazem	Placebo	16/16	10	10	Unclear
Kahan et al., Angiology	1987	RCT cross-over	Primary and secondary RP	Nicardipine	Placebo	20/20	17	17	Unclear
Rodeheffer et al., NEJM	1983	RCT cross-over	Primary and secondary RP	Nicardipine	Placebo	15/15	9	9	Unclear
Thomas et al., British Journal of Dermatology	1987	RCT cross-over	Secondary RP (SSc)	Nifedipine	Placebo	9/10	10	10	Unclear
Phosphodiesterase-5 Inhibitors									
Andrigueti et al., Clinical and Experimental Rheumatology	2017	RCT parallel	Secondary RP (SSc)	Sildenafil	Placebo	41/41	41	21	Unclear
Caglayan et al., Arch Intern Med	2012	RCT cross-over	Primary and secondary RP	Vardenafil	Placebo	50/53	47	41	Unclear
Fries et al., Circulation	2005	RCT cross-over	Primary and secondary RP	Sildenafil	Placebo	18/20	16	16	Unclear
Hachulla et al., Annals of the Rheumatic Diseases	2014	RCT parallel	Secondary RP (SSc)	Sildenafil	Placebo	70/83	83	42	Low
Herrick et al., Arthritis & Rheumatism	2011	RCT parallel	Secondary RP (SSc)	Sildenafil	Placebo	51/57	57	30	Low
Roustit et al., Annals of Internal Medicine	2018	RCT, multiple cross-over N-of-1	Primary and secondary RP	Sildenafil	Placebo	38/41	12	12	Unclear
Schiopu et al., The Journal of Rheumatology	2009	RCT cross-over	Secondary RP (SSc)	Tadalafil	Placebo	39/45	45	45	Unclear
Shenoy et al., Rheumatology	2010	RCT cross-over	Secondary RP	Tadalafil	Placebo	24/25	25	25	Unclear
Young Lee et al., Rheumatology	2014	RCT cross-over	Secondary RP	Udenafil	Amlodipine	26/26	26	26	Unclear

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Continued

Prostacyclin Analogues									
Belch et al., Annals of the Rheumatic Diseases	1995	RCT parallel	Secondary RP (SSc)	Iloprost	Placebo	59/63	63	32	Low
Black et al., British journal of rheumatology	1998	RCT parallel	Secondary RP (SSc)	Iloprost	Placebo	72/103	103	68	Unclear
Kawald et al., The Journal of Rheumatology	2008	RCT parallel	Secondary RP (SSc)	Iloprost	Iloprost	50/50	50	25	Unclear
McHugh et al., Annals of the Rheumatic Diseases	1988	RCT cross-over	Secondary RP	Iloprost	Placebo	26/29	29	29	Unclear
Rademaker et al., BMJ	1989	RCT parallel	Secondary RP (SSc)	Iloprost	Nifedipine	16/23	23	12	Unclear
Scorza et al., Clinical and Experimental Rheumatology	2001	RCT parallel	Secondary RP (SSc)	Iloprost	Nifedipine	35/46	46	29	Unclear
Seibold et al., Journal of Scleroderma and Related Disorders	2017	RCT parallel	Secondary RP (SSc)	Treprostinil	Placebo	124/147	147	71	Low
Torley et al., Annals of the Rheumatic Diseases	1991	RCT parallel	Secondary RP	Iloprost	Iloprost	51/55	55	55	Low
Wigley et al., The Journal of Rheumatology	1992	RCT parallel	Secondary RP (SSc)	Iloprost	Placebo	33/35	35	18	Unclear
Wigley et al., Ann Intern Med	1994	RCT parallel	Secondary RP (SSc)	Iloprost	Placebo	114/131	131	64	Low
Wigley et al., Arthritis and Rheumatism	1998	RCT parallel	Secondary RP (SSc)	Iloprost	Placebo	287/308	308	157	Unclear
Yardumian et al., British Journal of Rheumatology	1988	RCT cross-over	Secondary RP	Iloprost	Placebo	12/12	12	12	Unclear
Endothelin receptor antagonist									
Cerinic, et al., Ann Rheum Dis	2011	RCT parallel	Secondary RP (SSc)	Bosentan	Placebo	148/188	188	98	Unclear
Khanna, et al., DUAL1, Jamma	2016	RCT parallel	Secondary RP (SSc)	Macitentan	Placebo	223/289	289	192	Low
Khanna, et al., DUAL2, Jamma	2016	RCT parallel	Secondary RP (SSc)	Macitentan	Placebo	216/265	265	176	Low
Korn, et al., Arthritis and Rheumatism	2004	RCT parallel	Secondary RP (SSc)	Bosentan	Placebo	103/122	122	79	Low
Nguyen, et al., Rheumatology	2010	RCT parallel	Secondary RP (SSc)	Bosentan	Placebo	17/17	17	9	Low

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Continued									
Angiotensin-converting-enzyme inhibitors/Angiotensin receptor blockers									
Dziadzio et al., Arthritis and Rheumatism	1999	RCT parallel	Primary and secondary RP	Losartan	Nifedipine	48/52	27	14	Low
Gliddon et al., Arthritis and Rheumatism	2009	RCT parallel	Secondary RP (SSc)	Quinapril	Placebo	188/213	210	105	Low
Statins									
Abou-Raya et al., The Journal of Rheumatology	2008	RCT parallel	Secondary RP (SSc)	Atorvastatin	Placebo	84/84	84	56	Low
Domsic et al., Arthritis Rheumatol	2019	RCT parallel	Secondary RP (SSc)	Atorvastatin	Placebo	23/24	24	14	Unknown
Selective serotonin reuptake inhibitors									
Coleiro et al., Rheumatology	2001	RCT Cross-over	Primary and secondary RP	Fluoxetine	Nifedipine	49/53	27	27	High
Aminaphtone									
Ruaro et al., Frontiers in Pharmacology	2019	Controlled trial open label	Primary and secondary RP	Aminaphtone	Standard treatment	90/92	71	35	High
Santaniello et al., ACR annual meeting AB706	2013	RCT parallel	Secondary RP (SSc)	Aminaphtone	Placebo	25/25	25	13	High
Cyclophosphamide									
Au et al., Arthritis Care & Research	2010	RCT parallel	Secondary RP (SSc)	Cyc	Placebo	132/158	158	79	Low
Nitroglycerin									
Chung, et al., Arthritis and rheumatism	2009	RCT parallel	Primary and secondary RP	Nitroglycerine gel	Placebo	212/219	173	109	Unclear
Teh, et al., British Journal of Rheumatology	1995	RCT cross-over	Secondary RP (SSc)	Glycerine trinitrate patches	Placebo	15/21	21	21	Unclear
5HT2 antagonist									
Bounameaux, et al., Journal of cardiovascular pharmacology	1984	RCT cross-over	Secondary RP	Ketanserin	Placebo	8/9	9	9	High
Engelhart et al., British Journal of Dermatology	1988	RCT cross-over	Secondary RP (SSc)	Ketanserin	Placebo	9/9	9	9	High
Ortonne, et al., British Journal of Dermatology	1989	RCT parallel	Secondary RP (SSc)	Ketanserin	Placebo	24/24	24	14	High
Prostacyclin receptor agonist									

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Denton et al., Arthritis and Rheumatology	2017	RCT parallel	Secondary RP (SSc)	Selexipag	Placebo	64/74	74	38	Low
Continued									
Alpha adrenergic blockers									
Surwit et al., Arch Dermatology	1984	RCT cross-over	Secondary RP (SSc)	Prazosin	Placebo	19/20	20	11	Unclear
Russel et al., Journal of Rheumatology	1985	RCT cross-over	Primary and secondary RP	Prazosin	Placebo	19/20	6	6	High
N-Acetylcysteine									
Correa et al., Revista Brasileira de Reumatologia	2014	RCT parallel	Secondary RP (SSc)	N-Acetylcysteine	Placebo	42/42	42	21	Low
Stanozolol									
Jayson et al., Annal of rheumatic diseases	1991	RCT cross-over	Secondary RP (SSc)	Stanozolol	Placebo	17/24	24	24	Unclear
Phosphodiesterase III inhibitor									
Rajagopalan et al., The American Journal of Cardiology	2003	RCT parallel	Primary and secondary RP	Cilostazol	Placebo	35/40	21	11	Low
Riociguat									
Nagaraja, et al., Arthritis Research & Therapy	2019	RCT parallel	Secondary RP (SSc)	Riociguat	Placebo	15/18	18	9	Unclear
Kanna, et al., Ann Rheum Dis	2020	RCT parallel	Secondary RP (SSc)	Riociguat	Placebo	88/121	121	60	Unclear
Dimethyl sulfoxide									
Williams, et al., Arthritis and Rheumatism	1985	RCT parallel	Secondary RP (SSc)	Dimethyl sulfoxide	Placebo	55/84	84	53	Unclear
Vitamin E gel									
Fiori, et al., Clin Exp Rheumatol	2009	RCT parallel	Secondary RP (SSc)	Vitamin E gel	Placebo	27/27	27	15	High
Botulinum Toxin									
Motegi, et al., Acta Derm Venere	2017	RCT parallel	Secondary RP (SSc)	Botulinum Toxin	Placebo	45/45	45	37	High
Bello, et al., Arthritis and Rheumatology	2017	RCT parallel	Secondary RP (SSc)	Botulinum Toxin	Placebo	40/40	40	20	Low
Regional grafting of autologous adipose tissue									
Del Papa, et al., Arthritis Research & Therapy	2019	RCT cross-over	Secondary RP (SSc)	Regional grafting adipose tissue	Sham procedure	38/38	38	25	Unclear

BL: Baseline; FU: Follow-up; RP: Raynaud phenomenon; RCT: Randomized controlled trial; SSc: Systemic sclerosis.

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Table S3 – Calcium channel blockers – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Esmaeilzadeh 2019, Rheumatology Research	Single blind RCT	SSc: 90	Diltiazem gel (2%) Nitroglycerin ointment 2% Placebo	18 16 17	8 weeks	Diameter of ulcers DU reduction	1,41±0,23 1,16±0,21 1,89±0,21	**p<0.01** **p=0.03** **REF***	0,42 0,54	High
Kahan 1985a, International Journal of Angiology	RCT cross-over	Idiopathic: 12 SSc: 10 SLE: 5; RA: 3	Nifedipine 60mg daily 1w Placebo 1w	18 18	2 weeks	Attacks per week	10,4±15,1 28,1±4,9	**p<0.01** REF	0,40	Unclear
Kahan, 1985b European Heart Journal	RCT cross-over	SSc: 7 SLE: 2; RA: 1; Idiopathic: 5	Nifedipine 60mg daily 1w Prazosin 3mg daily 1w Placebo 1w+1w	10 10 10	4 weeks	Attacks per week	7,7±7,8 18,5±10,2 18,1±6,6	**p<0.01** NS REF#	0.50	Unclear
						VAS Severity	2,9±2,6 5,9+2,3 6,2+1,5	**p<0.01** NS REF#	0,60	
Kahan, 1985c Annals of the Rheumatic Diseases	RCT cross-over	SSc: 7 SLE: 1 RA: 2 Idiopathic: 6	Diltiazem 120mg 3x/daily 2w Placebo 2w	10 10	5 weeks	Attacks per 2 weeks	15,1±9,9 20,4±4,9	NS REF	0.46	Unclear
						VAS Severity	5,1±3,2 6,6±1,3	NS REF	0,45	
Kahan, 1987 Angiology	RCT cross-over	SSc: 15 RA:2 Idiopathic: 3	Nicardipine, 60mg daily 2w Placebo 2w	17 17	5 weeks	Attacks per 2 weeks	23,1±17,0 29,6±13,6	**p<0.05** REF	0.37	Unclear
						VAS Severity	1,8±0,7 2,2±0,4	**p<0.05** REF	0.36	
Rodeheffer, 1983 NEJM	RCT cross-over	SSc:9; Idiopathic:6	Nifedipine 30-60mg daily 2w Placebo 2w	9 9	5 weeks	Attacks per 2 weeks	13,1±5,1 15,0±4,2	**p=0.02** REF	0,48	Unclear
						VAS improvement	NR NR	**p=0,02** REF	NC	
Thomas, 1987 British Journal of Dermatology	RCT cross-over	SSc: 10	Nifedipine 30-60mg daily 6w Placebo 6w	10 10	14 weeks	Duration attacks	18,7±4,5 29,7±9,6	**p=0.02** REF	0,51	Unclear
						Attacks per day	1,3±0,5 1,6±0,5	NS REF	0,47	
						Number new ulcers	9U in 3Pts 18U in 6Pts	NS REF	NC	

DU: Digital ulcer; FU: Follow-up; NC: Not possible to calculate; RA: Rheumatoid arthritis; RCT: Randomised controlled trial; REF: Reference RP: Raynaud phenomenon; SLE: Systemic Lupus Erythematous; SMD: Standardised mean difference; SSc: Systemic sclerosis; VAS: Visual analogue scale.

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Table S4 – Calcium channel blockers – Safety.

Study ID	Type of study	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Esmaeilzadeh 2019, Rheumatology Research	Single blind RCT	Diltiazem gel (2%) Nitroglycerin ointment 2% Placebo	6 nitroglycerine 9 diltiazem 6 placebo	NR	21	Headache (6,6%); nausea, vomiting, ulcer pain Chest pain, headache (20%); pain (23,3%) Nausea, vomiting
Kahan 1985a, International Journal of Angiology	RCT	Nifedipine 60mg daily Placebo	9 3	NR	NR	NR
Kahan, 1985b, European Heart Journal	RCT, cross-over	Nifedipine 60mg daily Prazosin 3mg daily Placebo	6 3 2	NR NR NR	0	Headache, flushing, dizziness, nausea, ankle oedema Dizziness, headache and nausea Dizziness
Kahan, 1985c, Annals of the Rheumatic Diseases	RCT, cross-over	Diltiazem 120mg 3x/daily Placebo	6 2	0	0	Headache (2), flushing (2), dizziness (1), nausea (2), and ankle oedema (1) Headache (1), nausea (1)
Kahan, 1987 Angiology	RCT, cross-over	Nicardipine, 60mg daily Placebo	7 2	0	0	Headache, flushing, palpitations, nausea, and ankle swelling Headache
Rodeheffer, 1983 NEJM	RCT, cross-over	Nifedipine 30-60mg daily Placebo	NR	NR	NR	Headaches - 80% nifedipine patients vs 20% placebo patients. **p=0.003**
Thomas, 1987 British Journal of Dermatology	RCT, cross-over	Nifedipine 30mg daily Placebo	2	NR	1 Due AE: 0	1 nausea 1 headaches

NR: Not reported; RCT: Randomised controlled trial; AE: Adverse events.

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Table S5 – Phosphodiesterase-5 inhibitors – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Andrigueti, 2017 Clinical and Experimental Rheumatology	RCT, parallel	SSc: 41	Sildenafil 100mg daily Placebo	21 20	8 weeks	RP Duration	11,8±21 21,9±22,6	**p<0.04** REF	0,34	Unclear
						Attacks per day	1,1±2,5 1,0±3,0	NS REF	-0,33	
						VAS Severity	6,0±8,25 3,0±9,0	NS REF	-0,31	
						RCS	1,3±3,2 1,1±5,6	NS REF	-0,33	
						DU healing	4 Pts with DU at base line (3I vs 1P). FU: 0 in I and 1 in P. RR 0,35			
Caglayan, 2012 Arch Intern Med	RCT cross-over	SScD: 13 SScL: 25 MCTD: 9 Idiopathic: 6	Vardenafil 10mg twice 2w Placebo 2w	47 47	6 weeks	RCS Mean reduction	-0,36±1,11 **-0,69±0,68** 0,28±2,29 REF --	NS **p=0,04** NS REF --	-- 0,25 -- -- --	Unclear
Fries, 2005 Circulation	RCT cross-over	SSc: 14 MCTD: 2 Idiopathic:2	Sildenafil 50mg twice 4w Placebo 4w	16 16	10 weeks	Attacks in 4 weeks	35±14 52±18	**p<0.01** REF	0,38	Unclear
						Duration in 4 weeks	581±133 1046±245	**p<0.01** REF	0,46	
						RCS daily mean	2.2±0,4 3,0±0,5	**p=0,04** **REF**	0,33	
Hachulla, 2014 Annals of the Rheumatic Diseases	RCT, parallel	SSc: 83	Sildenafil 20mg three/day Placebo	42 41	12 weeks	DU healing ITT	NR NR	p=0,25 REF	HR 1,27 (0.85-1.89)	Low
						DU healing Per protocol	NR NR	p=0,10 REF	HR 1,27 (0.93-2,19)	
						Number DU at 8w ITT	1,2±1,6 1,8±2,4	**p=0,04** REF	OR 0,69 (0,47- 0,99)	
						Number DU at 8w Per protocol	NR NR	**p=0,03** REF	OR 0,64 (0,43- 0,94)	
						Number DU at 12w ITT	0,9±1,6 1,5±2,7	**p=0,01** REF	OR 0,57 (0,37- 0,88)	

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						Number DU at 12w Per protocol	NR NR	**p<0,01** REF	OR 0,47 (0,29- 0,76)	
						Healing rate at 8w ITT	NR NR	**p<0,01** REF	OR 1.82 (1.15-2.88)	
						Healing rate at 12w ITT	NR NR	**p=0,03** REF	OR 1.78 (1.06-2.97)	
						Complete heal DUs 12w ITT	26/42 23/41	p=0.45 REF	OR 1.50 (0.52-4.37)	
						Complete heal DUs 12w Per protocol	NR NR	**p<0,01** REF	OR 2.62 (1.50-4.56)	
						New DU between 4w-12w ITT	8/42 15/41	p=0,10 REF	OR 0.42 (0.15-1.17)	
						New DU between 4w-12w Per protocol	6/32 14/36	p=0,07 REF	OR 0.36 (0.12-1.10)	
						VAS Pain	26.0±22.6 34.6±30.7	NS REF	0.22	
						Raynaud severity	35.0±30.7 35.7±29.4	NS REF	0.21	
						HAQ	0.8±0.8 1.1±0.9	NS REF	0,21	
						Cochin hand function score	22.5±19.9 27.2±18.7	NS REF	0,22	
Herrick, 2011 Arthritis & Rheumatism	RCT, parallel	SSc: 57	Sildenafil 200mg/day Placebo	30 27	4 weeks	% change in RP attacks per week	-44% -18,1%	**p=0,03** **REF**	NC	Low
						RCS	2.8±2.04 2.6±2.35	NS REF	0,18	
						RP duration	15.0 18.4	NS REF	NC	
						VAS pain RP	2.5 2.2	NS REF	NC	
Roustit, 2018 Annals of Internal Medicine	RCT, multiple cross-over N-of-1	Primary: 26 Secondary: 12	Sildenafil 40mg (max twice daily) Sildenafil 80mg (max twice daily) Placebo	12 12 12	4 weeks	RCS change	-0.14±0,19 -0,05±0,16 NR	NS NS REF	HR 0,92 (0,81-1,04) HR 0,97 (0,88-1,1)	Unclear
						RP duration change	-0.4,4±4,8 -3,9±4,4 NR	NS NS REF	HR 0,9 (0,70-1,00) HR 0,91 (0,81-1,02)	
						RP attacks/day	-0.10±0,15 -0.10±0,15	NS NS	HR 0,91 (0,8-1,04)	

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							NR	REF	HR 0,93 (0,83-1,04)	
Schiopu, 2009 The Journal of Rheumatology	RCT, cross-over	SSc: 45	Tadalafil 20mg daily 4w Placebo 4w	39 39	4 weeks	RCS	2.43 ± 2.01 2.53 ± 2.22	NS REF	0,24	Unclear
						RP duration	40,61±63,81 47,0±77,60	NS REF	0,23	
						Attacks per day	2.08 ± 1.72 2.1 ± 1.78	NS REF	0,24	
Shenoy, 2010 Rheumatology	RCT, cross-over	SSc: 24 MCTD:1	Tadalafil 20mg on alternate days 6w Placebo 6w	25 25	6 weeks	RCS	3,86±0,46 5,20±0,53	**p<0,01** **REF**	0,43	Unclear
						RP duration	33,81±7,89 54,89±11,33	**p=0,02** **REF**	0,36	
						Attacks per day	2,29±0,29 3,37±0,38	**p<0,01** **REF**	0,40	
						New DU	1/24 13/25	**p<0,01** **REF**	RR 0,1	
						DU healing	24/24 3/13	**p<0,01** **REF**	RR 4,35	
Young Lee, 2014 Rheumatology	RCT, cross-over	SSc: 20 MCTD: 3 SSj: 3	Udenafil 100 mg/day Amlodipine 10 mg/day	26 26	4 weeks	Attacks per day improvement	0,5±0,9 0,5±1,4	NS REF	0,28	Unclear

DU: Digital ulcer; FU: Follow-up; HAQ: Health Assessment Questionnaire Disability Index; HR: Hazard ratio; ITT: Intention-to-treat; MCTD: Mixed connective tissue disease; NR: Not reported; NS: Non significative; OR: Odds Ratio; Pts: patients; RCS: Raynaud condition score; RCT: Randomized controlled trial; REF: Reference RP: Raynaud phenomenon; SSj: Sjögren's syndrome; SLE: Systemic Lupus Erythematous; SMD: Standardised mean difference; SSc: Systemic sclerosis; SScD: Dlfuse Systemic sclerosis; SScL: Limited Systemic sclerosis; VAS: Visual analogue scale.

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Table S6 – Phosphodiesterase-5 inhibitors – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Andrigueti, 2017 Clinical and Experimental Rheumatology	Sildenafil 100mg daily Placebo	13 1	0	0	7vs1 (33%vs5%) Headache p=0.022 4 (19%) Flushing, only in sildenafil 2 (9%) nausea, only in sildenafil
Caglayan, 2012 Arch Intern Med	Vardenafil 10 mg twice a day Placebo	52 16	3 Due to treatment: 0	2	Flush symptoms (12 vs 2; P = .01) Headache (14 vs 7; P = .19) Dyspepsia (7 vs 1; P = .07) Dizziness (9 vs 2; P = .07) Nasal stuffiness (7 vs 1; P = .07) Visual abnormalities (4 vs 3; P =0.99)
Fries, 2005 Circulation	Sildenafil 50mg twice daily Placebo	10 0	0	3	1 swelling of the nasal mucosa 3 headaches 3 facial sensations of heat 2 nauseas 1 dizziness
Hachulla, 2014 Annals of the Rheumatic Diseases	Sildenafil 20mg three/day Placebo	NR	5 3	14 (8 SAE)	Adverse events led to study discontinuation for five patients in the sildenafil group (drowsiness, syncope, headache, facial oedema, rash: n =1 each) and three in the placebo group (leg oedema, headache and vomiting, dizziness: n=1 each).
Herrick, 2011 Arthritis & Rheumatism	Sildenafil 200mg/day Placebo	43 17	0 0	4, due sildenafil 1 Allergic reaction 1 Headache and myalgia 1Chest pain with 1 Palpitations	The most frequent adverse events were headache and dyspepsia. Dyspepsia sildenafil (9) placebo (5) Headache sildenafil (15) placebo (8)
Roustit, 2018 Annals of Internal Medicine	Sildenafil 40mg Sildenafil 80 mg Placebo	29 (71%) 28 (68%) 12 (29%)	1, Deep vein thrombosis not related to treatment	3 (SAE, pregnancy, hypotension)	The most common adverse events associated with sildenafil were headache and flush (p<0,01) Spontaneous erection 3 Hypotension 1
Schiopu, 2009 The Journal of Rheumatology	Tadalafil 20mg daily Placebo	NR	0	6	Headache, back pain, fluid retention, and vasomotor changes - similar to placebo
Shenoy, 2010 Rheumatology	Tadalafil 20mg daily Placebo	38 25	0	1, due to an erection	Patients while on tadalafil reported heaviness of eyelids and nasal stuffiness more commonly than when on placebo
Young Lee, 2014	Udenafil 100 mg/day Amlodipine 10 mg/day	NR	0	2, due to AE (generalized myalgia, facial swelling)	The most common adverse reaction to udenafil was facial flushing (50.0%), followed by facial oedema (38.5%) and generalized oedema (23.1%). With amlodipine, facial flushing was observed in 30.8% of patients, while facial oedema and generalized oedema were present in 15.4% of the patients. Similar adverse effect profiles

AE: adverse events; NR: Not reported; SAE: severe adverse events.

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Table S7 – Prostacyclin analogues – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Belch, 1995 Annals of the Rheumatic Diseases	RCT, parallel	SSc:63	PO iloprost 50-150ug twice/day 10 days Placebo	32 31	10 and 24 days	Change RP duration 10 days	-40±17 -24±20	NS REF	0,26	Low
						Change RP duration 24 days	-25±28 -25±20	NS REF	0,25	
						Change VAS pain 10 days	1±26 -23±27	NS REF	0,26	
						Change VAS pain 24 days	-27±26 -7±16	NS REF	0,26	
						Change severity 10 days	-6±6 -1±7	NS REF	0,27	
						Change severity 24 days	-9±9 0±9	NS REF	0,27	
Black, 1998 British journal of rheumatology	RCT, parallel	SSc: 103	PO iloprost 50ng twice/day PO iloprost 100ng twice/day Placebo	33 35 35	6 and 12 weeks	% Change RP duration 6w	-40±41 -35±44 10±125	**p=0,03**	0,26	Unclear
						% Change RP duration 12w	-60±27 -60±29 -9±79	**p<0,01**	0,28	
						% Change attacks per day 6w	-31±36 -34±40 -13±58	NS REF	0,24	
						% Change attacks per day 12w	-46±29 -50±32 -15±66	NS REF	0,25	
						% Change RCS 6w	-29±39 -47±39 -14±47	NS REF	0,25	
						% Change RCS 12w	-38±38 -60±34 -12±44	**p<0,01** **REF**	0,30	
Kawald, 2008 The Journal of Rheumatology	RCT, Parallel, open label	SSc: 50	IV Iloprost 2.0 ng/kg/min, 6 hours daily, 21 days IV Iloprost 0.5 ng/kg/min, 6 hours daily, 21 days	25 25	4 weeks	% Change number DU	76,2 61,0	NS* REF	NC	Unclear
						% Change attacks per week	46 42	NS* REF	NC	
						DU healing	15/63 25/64	NS* REF	RR 1,62	

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Rademaker, 1989 BMJ	RCT, parallel	SSc: 23	IV iloprost 2 ng/kg/min for 8 hours on 3 consecutive days with a further single infusion at week 8 Nifedipine 60mg/daily	12 11	16 weeks	% Change RP attacks	-55,4 -41,5	NS REF	NC	Unclear
						% Change RP duration	-46,8 -44,7	NS REF	NC	
						% Change RP severity	-34,6 -31,5	NS REF	NC	
						DU number	0,6±0,3 1,4±0,5	**p=0,04** **REF**	0,50	
Scorza, 2001 Clinical and Experimental Rheumatology	RCT, parallel	SSc: 46	IV iloprost 2 ng/kg/min on 5 consecutive days, 8 hours a day and subsequently 1 day every 6 weeks Nifedipine 40mg/daily	29 17	12 months	RCS	1,22±0,13 1,33±0,22	**p<0,05** **REF**	0,31	Unclear
Seibold, 2017 Journal of Scleroderma and Related Disorders	RCT, parallel	SSc: 147	PO treprostinil twice/day (0.5mg-16mg/day) Placebo	71 76	20 weeks	Reduction net ulcer burden	-0.43 ± 1.83 -0.10 ± 1.81	NS REF	0,17	Low
						New DU	22 (29%) 24 (34%)	NS REF	RR 0,85	
						DU number	NR NR	NS REF	NC	
						DU time to healing	96.7 ± 39.7 90.2 ± 35.6	NS REF	0,18	
						DU healing %	62 61	NS REF	RR 1,02	
						VAS pain DU	NR NR	NS REF	NC	
Torley, 1991 Annals of the Rheumatic Diseases	RCT, parallel	SSc: 43 DM: 1 MCTD: 5 RA: 1 SSj: 1 UCTD: 4	IV Iloprost 0-5 ng/kg/min, 6 hours for 3 days IV Iloprost 2 ng/kg/min,6 hours for 3 days	27 28	8 weeks	% Change RP attacks	-37 -28	NS REF	NC	Low
						% Change RP duration	-46 -20	NS REF	NC	
						% Change RP severity	-23 -10	NS REF	NC	
Wigley, 1992 The Journal of Rheumatology	RCT, parallel	SSc:35	IV Iloprost 0.5-2.0 ng/kg/min, six hours for 5 days Placebo	18 17	10 weeks	Complete DU healing	7/18 4/17	**p=0,02** **REF**	RR 2,65	Unclear
						RP frequency	NR NR	NS REF	NC	
						RP duration	32,7±53,3 80,4±208,0	NS REF	0,35	
						RP severity	0,82±0,97 0,61±0,49		0,35	

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Wigley, 1994 Ann Intern Med	RCT, parallel	SSc: 131	IV Iloprost 0.5-2.0 ng/kg/min, six hours for 5 days Placebo	64 67	9 weeks	% Improvement RP attacks frequency	39,1 22,2	**p<0,01** **REF**	0,18	Low
						% Improvement severity (VAS)	34,8 19,7	**p<0,01** **REF**	0,18	
						% DU improvement	25,7 18,8	NS REF	NC	
						HAQ DU	0.92 ± 0.65 0.80 ± 0.67	**p<0,01** **REF**	0,24	
Wigley, 1998 Arthritis and Rheumatism	RCT, parallel	SSc: 308	PO iloprost 50ng twice a day Placebo	157 151	6 weeks	RP duration	-24.32 -34.34	NS REF	0,11	Unclear
						RP daily frequency	-1.02 -0.83	NS REF	0,11	
						RCS reduction	-1.32 -1.00	NS REF	0,11	
Yardumian, 1988 British Journal of Rheumatology	RCT, cross-over	SSc:10 MCTD:2	IV iloprost 1-3ng/kg/min, 5h for 3 days Placebo	12 12	6 weeks	Change RP frequency	3,7± 3,2 4,5± 3,7	**p<0,01** **REF**	0,41	Unclear
McHugh, 1988 Annals of the Rheumatic Diseases	RCT, cross-over	SSc: 26 MCTD: 3	IV Iloprost 2.0 ng/kg/min, 3-6h, for 3 days, 6 weeks interval Placebo	29 29	2-6 weeks	% Change RP attacks	-30 -2	**p=0,04** **REF**	NC	Unclear
						% Change RP duration	-9 +26	NS REF	NC	
						% Change RP severity	-20 -1	**p=0,01** **REF**	NC	
						% Change RP VAS pain	-16 -11	NS REF	NC	

DM: Dermatomyositis; DU: Digital ulcer; FU: Follow-up; HAQ: Health Assessment Questionnaire Disability Index; MCTD: Mixed connective tissue disease; NC: Not possible to calculate; NR: Not reported; NS: Non significative; OR: Odds Ratio; Pts: patients; RA: Rheumatoid arthritis; RCS: Raynaud condition score; RCT: Randomized controlled trial; REF: Reference RP: Raynaud phenomenon; SSj: Sjögren's syndrome; SLE: Systemic Lupus Erythematous; SMD: Standardised mean difference; SSc: Systemic sclerosis; UCTD: Undifferentiated connective tissue disease; VAS: Visual analogue scale.

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Table S8 – Prostacyclin analogues – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Belch, 1995 Annals of the Rheumatic Diseases	PO iloprost 50-150ug twice/day 10 days Placebo	31 (97%) 19 (61%) p<0,01	0	3 1	NR 50% were classified as mild, 32% as moderate, and 18% severe
Black, 1998 British journal of rheumatology	PO iloprost 50ng twice/day PO iloprost 100ng twice/day Placebo	28 (85%) 34 (97%) 28 (80%) p=0.08	2	10 18 3 (29 due AE)	Headache, flushing, nausea, trismus p<0,05
Kawald, 2008 The Journal of Rheumatology	IV Iloprost 2.0 ng/kg/min, 6 hours daily, 21 days IV Iloprost 0.5 ng/kg/min, 6 hours daily, 21 days	21 14	NR	0 0	Flushing (high-dose 48%, low-dose 40%) Headache (high-dose 24%, low-dose 12%) Nausea or vomiting (high-dose 12%, low-dose 4%)
McHugh, 1988 Annals of the Rheumatic Diseases	IV Iloprost 2.0 ng/kg/min, 3-6h, for 3 days, 6 weeks interval Placebo	50 NR	NR	6, not related with treatment	Side effects were common, with headache (18/26), facial flushing (6/26), nausea (14/26), vomiting (7/26), and diarrhoea (5/26) occurring in all but three of 26 patients Only 13/26 tolerated a dosage of Iloprost of 2-0 ng/kg/min.
Rademaker, 1989 BMJ	IV iloprost 2 ng/kg/min for eight hours on three consecutive days with a further single infusion at week 8 Vs Nifedipine 60mg/day	NR	NR	2 4 (3 due AE)	Headache, nausea, and vomiting occurred in more than half the patients during the infusion of iloprost but passed off rapidly afterwards.
Scorza, 2001 Clinical and Experimental Rheumatology	IV iloprost 2 ng/kg/min on 5 consecutive days, 8 hours a day and subsequently 1 day every 6 weeks Nifedipine 40mg/daily	NR	0	6 (not related to treatment) 5 (intolerance)	Iloprost: hypotension, nausea, vomiting, jaw pain. Nifedipine: headache, hypotension
Seibold, 2017 Journal of Scleroderma and Related Disorders	PO treprostinil twice/day (0.5mg-16mg/day) Placebo	71 (100%) 74 (97%)	9 patients, 22 events. 4 patients, 5 events. Six events in the active treatment group were considered probably or possibly attributable to study drug.	19	headache 73%vs37%, nausea 56%vs 14%, diarrhoea 52%vs16%, flushing 24%vs 3%, pain in jaw 23%vs5% and vomiting 17%vs1%
Torley, 1991 Annals of the Rheumatic Diseases	IV Iloprost 0-5 ng/kg/min, 6 hours for 3 days IV Iloprost 2 ng/kg/min,6 hours for 3 days	30 (9 low dose, 21 in standard dose) (p<0001)	0	4 0	Headache, flushing, nausea, diarrhoea, abdominal cramps, dizziness

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Wigley, 1992 The Journal of Rheumatology	IV Iloprost 0.5-2.0 ng/kg/min, six hours for 5 days Placebo	105 (74 iloprost, placebo 31)	8 2	2	Headache, nausea, jaw pain, flushing, vomiting p<0.001
Wigley, 1994 Ann Intern Med	IV Iloprost 0.5-2.0 ng/kg/min, six hours for 5 days Placebo	92% iloprost vs 57% placebo (p<0.001)	NR	8 9	Headache, flushing, nausea, jaw pain, diarrhoea, vomiting, reaction at injection site p< 0.001 Myalgia p=0,03
Wigley, 1998 Arthritis and Rheumatism	PO iloprost 50ng twice a day Placebo	95..5% 91.9%	10 3 None of the serious adverse events were considered to be secondary to iloprost	14 7	headache, vasodilation, abdominal pain, and nausea (p<0.05)
Yardumian, 1988	IV iloprost 1-3ng/kg/min, 5h for 3 days Placebo	NR	NR	NR	Facial flushing and frontal headache

AE: adverse events; NR: Not reported; SAE: severe adverse events.

Table S9 – Endothelin receptor antagonist: bosentan – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Korn, et al, 2004 ARTHRITIS & RHEUMATISM	RCT, parallel	SSc: 122	PO Bosentan, 62.5 mg twice daily for 4 weeks> 125 mg twice daily 12 weeks Placebo	79 43	16 weeks	New DU	45/78 26/43	p=0.083 REF	RR=0,96	Low
						Time to healing	NR NR	NS REF	NC	
Nguyen, et al, 2010 Rheumatology	RCT, parallel	SSc: 17	PO Bosentan, 62.5 mg twice daily for 4 weeks> 125 mg twice daily 12 weeks Placebo	9 8	16 weeks	% Change RP severity (RCS)	-31 (40) -36(35)	NS REF	NC	Low
						% Change RP-VAS pain 20w	**253(346)** -53(47)	**p=0.01** REF	NC	
						% Change RP- frequency	-30 (31) -57 (29)	NS REF	NC	
						% Change RP-duration	-26 (13) -44(24)	NS REF	NC	
Cerinic, et al, 2011 Ann Rheum Dis	RCT, parallel	SSc: 188	PO Bosentan, 62.5 mg twice daily for 4 weeks> 125 mg twice daily 20 weeks	98 90	24 weeks	New DU	1.9 (0.2) 2.7 (0.3)	**p=0.04** **REF**	0.25	Low

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Placebo	Du healing	35/95 35/89	p=0.76 REF	HR= 0,94	

DU: Digital ulcer; FU: Follow-up; NC: Not possible to calculate; NR: Not reported; NS: Non significative; RCS: Raynaud condition score; RCT: Randomized controlled trial; REF: Reference; RP: Raynaud phenomenon; RR: Risk ratio; SMD: Standardised mean difference; SSc: Systemic sclerosis; VAS: Visual analogue scale.

Table S10 – Endothelin receptor antagonist: bosentan – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Korn, et al, 2004 ARTHRITIS & RHEUMATISM	PO Bosentan, 62.5 mg twice daily for 4 weeks> 125 mg twice daily 12 weeks Placebo	153 77	4 Ventricular tachycardia Palpitations, Dyspnea High-altitude sickness, acute, Vomiting Esophagitis, digital ischemia	4	Headache NOS, Liver function tests NOS abnormal Upper respiratory tract infection NOS, Vomiting NOS Diarrhoea NOS, Infected skin ulcer Arthralgia, Pain in limb Fatigue, Nasopharyngitis, oedema lower limb Flushing, Constipation Esophageal reflux aggravated
Nguyen, et al, 2010 Rheumatology	PO Bosentan, 62.5 mg twice daily for 4 weeks> 125 mg twice daily 12 weeks Placebo	NR	0	1 (treatment-related peripheral oedema)	Peripheral oedema
Cerinic, et al, 2011 Ann Rheum Dis	PO Bosentan, 62.5 mg twice daily for 4 weeks> 125 mg twice daily 20 weeks Placebo	83 76	9 7	22 (9 due AE) 16 (7 due AE)	Peripheral oedema; Elevated aminotransferases; Arthralgia; Headache; Infected skin ulcer Upper respiratory tract infection; diarrhoea; Pain in extremity; Nausea Skin ulcer/disease progression; Urinary tract infection Dermatitis

AE: adverse events; NOS: not otherwise specified; NR: Not reported; SAE: severe adverse events.

Table S11 – Endothelin receptor antagonist: macitentan – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Khanna, et al DUAL1, 2016 Jamma	RCT, parallel	SSc: 289	PO 3 mg Macitentan, once daily PO 10 mg Macitentan, once daily Placebo	95 97 97	16 weeks	New DU	0.94 (0.35) 1.08 (0.33) 0.85 (0.23)	p=0.7 p=0.36 REF	0.15 0.15	Low
Khanna, et al DUAL2, 2016 Jamma	RCT, parallel	SSc: 265	PO 3 mg Macitentan, once daily PO 10 mg Macitentan, once daily Placebo	88 88 89	16 weeks	New DU	1.44 (0.4) 1.46 (0.43) 1.29 (0.42)	p=0.43 p=0.41 REF	0.15 0.15	Low

DU: Digital ulcer; FU: Follow-up; RCT: Randomized controlled trial; REF: Reference; SMD: Standardised mean difference.

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Table S12 – Endothelin receptor antagonist: macitentan – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Khanna, et al DUAL1, 2016 Jamma	PO 3 mg Macitentan, once daily PO 10 mg Macitentan, once daily Placebo	205 219 210	17 14 13	32 (12 due AE) 28 (14 due AE) 23 (10 due AE)	Adverse events more frequently associated with macitentan than with placebo were headache, peripheral oedema, skin ulcer, anemia, upper respiratory tract infection, diarrhoea, and nasopharyngitis.
Khanna, et al DUAL2, 2016 Jamma	PO 3 mg Macitentan, once daily PO 10 mg Macitentan, once daily Placebo	73 75 69	10 21 13	88 (8 due AE) 87 (15 due AE) 89 (13 due AE)	

AE: adverse events; SAE: severe adverse events.

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Table S13 – Topical nitrate – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Chung, et al, 2009 Arthritis and rheumatism	RCT	Secondary: 150 Primary: 69	MQX-503, nitroglycerin gel Placebo	111 108	4 weeks	RCS change	0.48 0,04	**p=0,02** **REF**	0,37	Unclear
						New DU	NR NR	**NS** **REF**	NC	
						Number RP attacks	-0,73 -0,54	NS REF	NC	
						RP duration	NR NR	**NS** **REF**	NC	
Teh, et al, 1995 British Journal of Rheumatology	RCT Cross-over	Secondary: 21 Primary: 21	Sustained-release glyceryl trinitrate (GTN) patches Placebo	21 21	2 weeks	RP frequency	NR NR	**p<0,04** **REF**	NC	Unclear
						RP severity	NR NR	**p=0,03** **REF**	NC	
						VAS pain	NR NR	**p=0,04**	NC	

DU: Digital ulcer; FU: Follow-up; NC: Not possible to calculate; NR: Not reported; NS: Non significative; RCS: Raynaud condition score; RCT: Randomized controlled trial; REF: Reference; RP: Raynaud phenomenon; SMD: Standardised mean difference; VAS: Visual analogue scale.

Table S14 – Topical nitrate – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Chung, et al, 2009 Arthritis and rheumatism	MQX-503, nitroglycerin gel Placebo	79 71	3	7	Headache, upper respiratory infection, dizziness, nausea, seasonal allergy, sinusitis, arthralgia, gastroesophageal reflux, skin ulcer, pruritus, skin irritation, fatigue, nasopahyngitis, paresthesia, dry skin, hypokalemia
Teh, et al, 1995 British Journal of Rheumatology	Sustained-release glyceryl trinitrate patches Placebo	5	2	5	6 Headaches p=0.001 (vs placebo)

SAE: severe adverse events.

Table S15 – Selective serotonin reuptake inhibitors (SSRIs) – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB

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Coleiro, et al, Rheumatology 2001	RCT Cross-over	Primary RP: 26 Secondary RP: 27	PO Fluoxetine 20 mg, daily PO Nifedipine 40 mg, daily	27 27	6 weeks	RP frequency	NR NR	NS REF	NC	High

FU: Follow-up; NC: Not possible to calculate; NR: Not reported; NS: Non significative; RCT: Randomized controlled trial; REF: Reference; RP: Raynaud phenomenon; SMD: Standardised mean difference.

Table S16 – Selective serotonin reuptake inhibitors (SSRIs) – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Coleiro, et al, Rheumatology 2001	PO Fluoxetine 20 mg, daily PO Nifedipine 40 mg, daily	31 35	NR	4 Headaches, nauseas and palpitations, apathy, lethargy, impaired concentration	Headaches, nauseas and palpitations, apathy, lethargy, facial flushing, lower limb swelling

NR: Not reported; SAE: severe adverse events.

Table S17 – Statins – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Abou-Raya, et al, 2008 The Journal of Rheumatology	RCT, parallel	SSc: 84	PO Atorvastatin 40 mg/day Placebo	56 28	4 months	DU number	2.4 (0.9) 3.9 (1,3)	**p=0.001** **REF**	0.24	Low
						DU severity VAS	4,9 (4,1) 5,7 (3,4)	**p<0.01** **REF**	-0,23	
						DU pain VAS	4,7 (2,7) 5,8 (4,6)	**p<0.01** **REF**	-0,23	
						RP severity VAS	4,9 (3,5) 5,7 (3,8)	**p<0.01** **REF**	-0,23	
Domsic, et al, 2019 Arthritis Rheumatol	RCT, parallel	SSc: 24	PO Atorvastatin 40 mg/day Placebo	10 14	16 weeks	Median Change RCS	-2.0 (-2.0 ,0) 0.0 (-1.0, 1.0)	p=0.12 REF	0.22	Unknown
						Median Change RP VAS	0.5 (-1.5, 6.0) 0.0 (-1.0, 1.5)	p=0.38 REF	NC	
						Improvement reactive hyperemia index (RHI)	6/10 4/14	p=0.32 REF	RR=2,06	

DU: Digital ulcer; FU: Follow-up; NC: Not possible to calculate; NS: Non significative; RCS: Raynaud condition score; RCT: Randomized controlled trial; REF: Reference; RP: Raynaud phenomenon; RR: Risk ratio; SMD: Standardised mean difference; SSc: Systemic sclerosis; VAS: Visual analogue scale.

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Table S18 – Statins – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Abou-Raya, et al, 2008 The Journal of Rheumatology	PO Atorvastatin 40 mg/day Placebo	NR	0	0	-
Domsic, et al, 2019 Arthritis Rheumatol	PO Atorvastatin 40 mg/day Placebo	NR	NR	NR	-

NR: Not reported; SAE: severe adverse events.

Table S19 – Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Dziadzio, et al, 1999 ARTHRITIS & RHEUMATISM	RCT, parallel	SSc: 27 Primary RP: 25	PO Losartan 50mg once daily PO Nifedipine 40mg twice a day.	26 26	15 weeks	RP frequency	2.62 (2. 56) 4.17 (2.73)	p=0.091 REF	NC	Low
						RP severity	3.77 (2.40) 4.12 (2.55)	p=0.064 REF	NC	
Gliddon, et al, 2007 ARTHRITIS & RHEUMATISM	RCT, parallel	SSc: 210	PO Quinapril 20 mg until 80 mg/day Placebo	104 106	Every 3 months	New DU	Treatment effect mean (95% CI)= -0.08 (-0.23,0.06)			Low

DU: Digital ulcer; FU: Follow-up; NC: Not possible to calculate; RCT: Randomized controlled trial; REF: Reference; RP: Raynaud phenomenon; SMD: Standardised mean difference; SSc: Systemic sclerosis.

Table S20 – Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Dziadzio, et al, 1999 ARTHRITIS & RHEUMATISM	PO Losartan 50mg once daily PO Nifedipine 40mg twice a day.	10/26 (39%) 3/26 (12%)	4 (15%)	NR	10 of 26 (39%) versus 3/26 (12%), p<0.005 Headache, flushing, nausea and ankle swelling

NR: Not reported; SAE: severe adverse events.

Table S21 – Botulinum Toxin – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB

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Motegi, et al, 2017)Acta Derm Venere	RCT, parallel single blinded	SSc: 45	Botulinum toxin 250U Botulinum toxin 1000U Botulinum toxin 2000U Placebo	9 10 18 8	16 weeks	RCS	NR NR NR NR	**p<0.01** **p<0.01** **p<0.01** **REF**	NC	High
						DU healing	- 3/10 3/13 0/8	NR NR NR REF	NC	
						VAS pain	NR NR NR NR	**NS** **p<0.01** **p<0.01** **REF**	NC	
Bello, et al, 2017 ARTHRITIS & RHEUMATOLOGY	RCT, parallel	SSc: 40	Botulinum toxin 50U Placebo	20 20	16 weeks	VAS pain	NR NR	**NS** **REF**	NC	Low
						RCS decrease	0,18(0,05) 0,14(0,04)	**NS** **REF**	NC	
						New DU risk	REF 16,67%	**REF** **NS**	RR=1,17	

DU: Digital ulcer; FU: Follow-up; NC: Not possible to calculate; NR: Not reported; NS: Non significative; RCS: Raynaud condition score; RCT: Randomized controlled trial; REF: Reference; RP: Raynaud phenomenon; RR: Risk ratio; SMD: Standardised mean difference; SSc: Systemic sclerosis; VAS: Visual analogue scale.

Table S22 – Botulinum Toxin – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Motegi, et al, 2017)Acta Derm Venere	Botulinum toxin 250U Botulinum toxin 1000U Botulinum toxin 2000U Placebo	3	0	0	Muscle weakness
Bello, et al, 2017 ARTHRITIS & RHEUMATOLOGY	Botulinum toxin Placebo	2	0	0	Muscle weakness

SAE: severe adverse events.

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Table S23 – Regional grafting of autologous adipose tissue – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Del Papa, et al, Arthritis Research & Therapy 2019	RCT, parallel	SSc: 38	Regional grafting of autologous adipose tissue Sham procedure as a placebo	25 13	8 weeks	DU healing	23/25 1/13	**p<0.001** REF	RR= 11,94	Unclear
						VAS Pain reduction 50%	21/25 0/13	**p<0.001** REF	NC	

DU: Digital ulcer; FU: Follow-up; NC: Not possible to calculate; RCT: Randomized controlled trial; REF: Reference; RR: Risk ratio; SMD: Standardised mean difference; SSc: Systemic sclerosis; VAS: Visual analogue scale.

Table S24 – Regional grafting of autologous adipose tissue – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Del Papa, et al, Arthritis Research & Therapy 2019	Regional grafting of autologous adipose tissue Sham procedure as a placebo	0	0	0	0

SAE: severe adverse events.

Table S25 – Aminaphtone – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Ruaro, 2019 Frontiers in Pharmacology	Controlled trial, open label	Secondary: 71 Primary: 21	Aminaftone 75 mg twice daily Control group	46 46	24 weeks	Attacks per day	1.24±0.74 1.33±0.67	NS REF	0,22	High
						RP duration	5.2±2.5 6.04±3.44	NS REF	0,23	
						RCS	3.5±0.9 3.62±1.03	NS REF	0,22	
Santaniello, 2013 ACR annual meeting AB706	RCT, parallel	SSc: 25	Aminaftone 75mg 3 times daily Placebo	13 12	12 weeks	% change attacks per day	-67,9% - 44,2%	p=0,06 REF	NC	High
						RP severity	NR NR	NS REF	NC	
						RP duration	NR NR	NS REF	NC	

FU: Follow-up; NC: Not possible to calculate; NR: Not reported; NS: Non significative; RCS: Raynaud condition score; RCT: Randomized controlled trial; REF: Reference; RP: Raynaud phenomenon; SMD: Standardised mean difference; SSc: Systemic sclerosis.

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Table S26 – Aminaphtone – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Ruaro, 2019 Frontiers in Pharmacology	AMN 75 mg twice daily Control group	NR	0 0	2 0	Headache
Santaniello, 2013 ACR annual meeting AB706	AMN 75mg 3 times daily Placebo	NR	NR	NR	NR

AMN: aminaphtone; NR: Not reported; SAE: severe adverse events.

Table S27 – Prostacyclin receptor agonist – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Denton, 2017 Arthritis and Rheumatology	RCT, parallel	SSc: 74	Selexipag up to 1600µg twice daily Placebo	38 36	8 weeks	Attacks per week	22.4±5.9 21.5±13.5	NS REF	0,26	Low
						RP duration	2.7±17.0 4.6±26.5	NS REF	0,32	
						RCS	NR NR	NS REF	NC	

FU: Follow-up; NC: Not possible to calculate; NR: Not reported; NS: Non significative; RCS: Raynaud condition score; RCT: Randomized controlled trial; REF: Reference; RP: Raynaud phenomenon; SMD: Standardised mean difference; SSc: Systemic sclerosis.

Table S28 – Prostacyclin receptor agonist – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Denton, 2017 Arthritis and Rheumatology	Selexipag Placebo	100% 86,8%	4 2	6 2	Headache, nausea, diarrhoea, dizziness, jaw pain

SAE: severe adverse events.

Table S29 – Vitamin E gel – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Fiori, et al, 2009 Clin Exp Rheumatol	RCT, parallel	SSc: 27	Vitamin E gel+ Standard DU care protocol Standard DU care protocol	15 12	12 weeks	DU number	3.46 (2.35)	NS REF	0,39	High
						DU diameter	1.1 (0.4)	NS	0,39	

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	(Twice a week)			REF	
		DU time to healing	13.2 (2.72)	**p<0.001** **REF**	0,50

DU: Digital ulcer; FU: Follow-up; NS: Non significative; RCT: Randomized controlled trial; REF: Reference; SMD: Standardised mean difference; SSc: Systemic sclerosis.

Table S30 – Vitamin E gel – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Fiori, et al, 2009 Clin Exp Rheumatol	Vitamin E gel+ Standard DU care protocol Standard DU care protocol (Twice a week)	0	-	-	-

DU: Digital Ulcers; SAE: severe adverse events.

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Table S31 – Riociguat – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Nagaraja, et al, 2019 Arthritis Research & Therapy	RCT, parallel	SSc: 17	PO Riociguat 2.5 mg, 3 times daily Placebo	9 8	16 weeks	RP frequency	-1.24 -0.96	p=0.57 REF	Treatment Difference (CI 95%)= -0,28 (-1.36; 0.79)	Unclear
						RCS	-1.15 -0.82	p=0.76 REF	Treatment Difference (CI 95%)=-0.33 (2.60;0.79)	
						RP duration	-44.8 150.3	p=0.40 REF	Treatment Difference (CI 95%)=-– 195.1 (–683.7 to 293.5)	
						Net Ulcer burden	-1.22 -0.98	p=0.70 REF	Treatment Difference (CI 95%)=-0.24(-1.46;0.99)	
Kanna, et al, 2020 Ann Rheum Dis	RCT, parallel	SSc: 121	PO Riociguat adjusted every 2 weeks from 0.5 mg to 2.5 mg three times daily Placebo	60 61	52 weeks	RCS improvement >50% (14 weeks)	19/46 13/50	NS REF	RR=1.58	Unclear
						New DU	5/60 12/61	NS REF	RR=0.47	
						Reductions in net ulcer burden	-0.09 (0.50) -0.08 (1.47)	p=0.44 REF	0.50	

DU: Digital ulcer; FU: Follow-up; NS: Non significative; RCS: Raynaud condition score; RCT: Randomized controlled trial; REF: Reference; RP: Raynaud phenomenon; SMD: Standardised mean difference; SSc: Systemic sclerosis.

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Table S32 – Riociguat – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Nagaraja, et al, 2019 Arthritis Research & Therapy	PO Riociguat 2.5 mg, 3 times daily Placebo	21	3	0	Cardiac disorders; Gastrointestinal disorders General disorders Hepatobiliary disorders Infections and infestations Injury, poisoning, and procedural Complications; Metabolism and nutrition disorders Musculoskeletal and connective tissue disorders Nervous system disorders Renal and urinary disorders Respiratory, thoracic and mediastinal disorders Surgical and medical procedures Vascular disorders
Kanna, et al, 2020 Ann Rheum Dis	PO Riociguat adjusted every 2 weeks from 0.5 mg to 2.5 mg three times daily Placebo	58	9	11	Gastrointestinal events (eg, gastro- oesophageal reflux disease, diarrhoea or nausea) or nervous system disorders (eg, dizziness, headache) Symptomatic hypotension Dizziness Respiratory, thoracic and mediastinal AE

SAE: severe adverse events.

Table S33 – Alpha adrenergic blockers – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Surwit, 1984 Arch Dermatology	RCT, cross-over	SSc: 20	Prazosin 1mg 3 times daily Placebo	11 9	8 weeks	Attacks per week	1.24±0.74 1,59±0,5	**p<0,03** **REF**	0,46	Unclear
						RP severity VAS	NR NR	NS REF	NC	
Russel, 1985 Journal of Rheumatology	RCT, cross-over	Primary: 14 Secondary: 6	Prazosin 1mg 3 times daily Placebo	13 12	6 weeks	Improvement VAS >2%	NR NR	NS REF	NC	High

FU: Follow-up; NC: Not possible to calculate; NR: Not reported; NS: Non significative; RCS: Raynaud condition score; RCT: Randomized controlled trial; REF: Reference; RP: Raynaud phenomenon; SMD: Standardised mean difference; SSc: Systemic sclerosis; VAS: Visual analogue scale.

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Table S34 – Alpha adrenergic blockers – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Surwit, 1984 Arch Dermatology	Prazosin 1mg 3 times daily Placebo	3	0 0	1 0	Headaches, hypotension, dizziness
Wollersheirn, 1986 Clin Pharmacol Ther	Prazosin 1mg 3 times daily Placebo	NR	NR	NR	NR

NR: Not reported; SAE: severe adverse events.

Table S35 – Dimethyl sulfoxide – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Williams, et al,1985 Arthritis and Rheumatism	RCT, parallel	SSc: 84	Topical Dimethyl sulfoxide 2% Topical Dimethyl sulfoxide 70% Topical normal saline (thrice-daily soaking)	25 28 31	12 weeks	Median Change VAS pain global	6 (-91-86) 20 (-16-77) -1 (-48-80)	NS REF	NC	Unclear
						Median Change DU- total number	1(-6-5) 1 (-2-4) 0 (-7-7)	NS REF	NC	
						Median Change DU-total surface area	18 (-307-70) 15 (0-130) 15 (-36-107)	NS REF	NC	
						Median Change DU-average surface area	3 (-71-70) 4 (-8-130) 4 (-57-34)	NS REF	NC	
						Median Change- number of inflamed ulcers	0 (- 1-2) 0 (- 1-1) 0 (-1-2)	NS REF	NC	
						Median Change-number of infected ulcers	0 (-4-2) 0 (0-1) 0 (- 2-2)	NS REF	NC	

DU: Digital ulcer; FU: Follow-up; NC: Not possible to calculate; NR: Not reported; NS: Non significative; RCS: Raynaud condition score; RCT: Randomized controlled trial; REF: Reference; SMD: Standardised mean difference; SSc: Systemic sclerosis; VAS: Visual analogue scale.

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Table S36 – Dimethyl sulfoxide – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Williams, et al,1985 Arthritis and Rheumatism	Topical Dimethyl sulfoxide 2% Topical Dimethyl sulfoxide 70% Topical normal saline (thrice-daily soaking)	NR	NR	9 patients (1- DMSO2%; 8-DMSO70%) » severe skin reactions	Skin reactions Distinctive odour to their breath

DMSO: Dimethyl sulfoxide; NR: Not reported; SAE: severe adverse events.

Table S37 – N-acetylcysteine – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Correa et al, 2014 Revista Brasileira de Reumatologia	RCT, parallel	SSc: 42	N-acetylcysteine-oral Placebo	21 21	4 weeks	RP frequency	7,2 ± 4,5 10 ± 8,4	NS REF	NC	Low
						RP severity	5,7 ± 2,6 6,8 ± 2,1	NS REF	NC	

FU: Follow-up; NC: Not possible to calculate; NS: Non significative; RCT: Randomized controlled trial; REF: Reference; RP: Raynaud phenomenon; SMD: Standardised mean difference; SSc: Systemic sclerosis.

Table S38 – N-acetylcysteine – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Correa et al, 2014 Revista Brasileira de Reumatologia	N-acetylcysteine oral Placebo	2	0	0	Epigastric pain and increased menstrual flow

SAE: severe adverse events.

Table S39 – Cyclophosphamide – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD)	P-value	SMD	RoB
Au et al, 2010 Arthritis Care & Research	RCT, parallel	SSc: 158	PO CYC initiated at 1 mg/kg/day by mouth (to the nearest 25 mg) and increased every month by 1 capsule until a maximum dosage of 2 mg/kg/ day Placebo	79 79	56 weeks	DU number	9 (13) 11 (17.5)	0.23 REF	0.17	Low

DU: Digital ulcer; FU: Follow-up; RCT: Randomized controlled trial; REF: Reference; SMD: Standardised mean difference; SSc: Systemic sclerosis.

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Table S40 – Cyclophosphamide – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Au et al, 2010 Arthritis Care & Research	PO CYC initiated at 1 mg/kg/day by mouth (to the nearest 25 mg) and increased every month by 1 capsule until a maximum dosage of 2 mg/kg/ day Placebo	17% 11%	20% 16%	NR	Hematuria, leukopenia, neutropenia, anemia and pneumonia p<0.05 (vs placebo: leukopenia and neutropenia)

CYC: cyclophosphamide; NR: Not reported; SAE: severe adverse events.

Table S41 – 5HT2 antagonist: Ketanserin – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD)	P-value	SMD	RoB
Bounameaux, et al,1984 Journal of cardiovascular pharmacology	RCT Cross-over	Secondary: 12	Ketanserin Placebo	**9** **9**	16 weeks	RP frequency	1.6 (0.5) 1,3(0,5)	NS REF	NC	High
Engelhart et al., 1988 British Journal of Dermatology	RCT Cross-over	SSc: 9	Ketanserin Placebo	**9** **9**	6 weeks	RP frequency	NR NR	NS REF	NC	High
Ortonne, et al,1989 British Journal of Dermatology	RCT Cross-over	SSc: 24	Ketanserin Placebo	14 10	24 weeks	RP frequency	73,4(46,7) 61,2(18,0)	NS REF	NC	Unclear
						RP severity	46,7(22,3) 55,7(20,1)	NS REF	NC	
						RP duration	40,7(18,1) 46,3(26,3)	NS REF	NC	

FU: Follow-up; NC: Not possible to calculate; NR: Not reported; NS: Non significative; RCT: Randomized controlled trial; REF: Reference; RP: Raynaud phenomenon; SMD: Standardised mean difference; SSc: Systemic sclerosis.

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Table S42 – 5HT2 antagonist: Ketanserin – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Bounameaux, et al,1984 Journal of cardiovascular pharmacology	Ketanserin Placebo	NR	NR	NR	NR
Engelhart et al., 1988 British Journal of Dermatology	Ketanserin Placebo	9	NR	NR	Weight gain, tired, dizzy, vomiting, diarrhoea, colder hands, weight gain, burning skin, leg and fingers oedema, dry skin with fissures, dry mouth, flaccid leg muscles.
Ortonne, et al,1989 British Journal of Dermatology	Ketanserin Placebo	28	NR	NR	Drowsiness was the most common) No substantial differences in the frequency or severity of adverse events in the two groups

NR: Not reported; SAE: severe adverse events.

Table S43 – Stanozolol – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Jayson et al, 1991 Annal of rheumatic diseases	RCT Cross-over	SSc: 24 Primary: 21	Stanozolol Placebo	24 24	24 weeks	RP frequency	NR NR	NS REF	NC	Unclear
						RP severity	NR NR	NS REF	NC	

FU: Follow-up; NC: Not possible to calculate; NR: Not reported; NS: Non significative; RCT: Randomized controlled trial; REF: Reference; RP: Raynaud phenomenon; SMD: Standardised mean difference; SSc: Systemic sclerosis.

Table S44 – Stanozolol – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Jayson et al, 1991 Annal of rheumatic diseases	Stanozolol Placebo	15	1 (died)	6 1	Cramps and weight gain p>0.05 (vs placebo)

SAE: severe adverse events.

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Table S45 – Phosphodiesterase III inhibitor – Efficacy.

Study ID	Type of study	Population	Intervention	N	Time-point	Primary outcome	Mean (SD) at FU	P-value	SMD	RoB
Rajagopalan, 2003 The American Journal of Cardiology	RCT, parallel	Secondary: 21 Primary: 19	Cilostazol 100 mg twice daily Placebo	20 20	6 weeks	Attacks per week	46±51 45±27	NS REF	0,31	Low
						VAS severity	3,0±2,5 2,6±1,0	NS REF	0,30	

FU: Follow-up; NS: Non significative; RCT: Randomized controlled trial; REF: Reference; SMD: Standardised mean difference; VAS: Visual analogue scale.

Table S46 – Phosphodiesterase III inhibitor – Safety.

Study ID	Intervention	Number of adverse events	SAE	Withdrawals	All adverse events
Rajagopalan, 2003 The American Journal of Cardiology	Cilostazol 100 mg twice daily Placebo	NR	0 0	3 (Due AE) 2	35% cilostazol headaches vs 0% placebo

AE: adverse events; NR: Not reported; SAE: severe adverse events.

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Table S47 – Summary of articles included in non-pharmacological SLR.

Intervention	Study	Type of study	RP type	Patients at FU/total	Age
Hand physical therapy	Horvath et al.	Controlled clinical trial	SSc	50/53	18-75
Hand warming in water	Goodfield et al.	Controlled clinical trial	SSc	12/12	NR
Ischemic preconditioning	Neferu et al.	RCT	CTD	18/21	mean 60.8 (9.4)
Laser therapy	Kuryliszyn-Moskal et al.	Prospective observational	CTD	40/40	26-66
	Al-Awami et al.	Prospective observational	CTD	40/40	33-69
Local oxygen-ozone therapy	Kaymaz et al.	RCT	SSc	25/25	median 38
Proximal heat stress	Shima et al.	RCT	SSc	14/16	20-80
Silver fibre gloves	Liem et al.	RCT	SSc	75/85	mean 60 (12)
Bone marrow mononuclear cell implantation into the ischaemic limb	Takagi et al.	Prospective observational	SSc	40/40	mean 65.1 (8.2)
Endoscopic thoracic sympathectomy	Matsumoto et al.	Retrospective cohort	CTD	23/28	26-73
Periarterial sympathectomy (targeted to the areas of ulceration)	Hartzell et al.	Retrospective cohort	CTD	28/28	24-79
Periarterial sympathectomy of the hand + vascular bypass	Shammas et al.	Retrospective cohort	CTD	27/27	16-78

CTD: Connective tissue disease; FU: Follow-up; NR: not reported; RCT: Randomised controlled trial RP: Raynaud phenomenon; SSc: Systemic sclerosis.

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Table S48 – Hand physical therapy – Efficacy.

Study	Intervention	Mean BL	Mean FU	Δ FU – BL Mean	Δ FU - BL P-value	Δ FU - BL Cohen D	Δ I vs Δ C	I vs C SMD (95% CI)	I vs C P-value
Study ID: Horvath 2016, C&ER (Critical RoB) Study design: controlled clinical trial Population: RP secondary to SSc (age 18-75 years) Intervention: hand physical therapy in SSc pts (N=31) Control: SSc patients with no intervention (N=22) Follow-up: 24 weeks	**VAS Pain due to Raynaud (0-10)**								
	Hand PT	3.72	2.55	-1.17	0.05	-0.42	-1.22	-0.38 (-0.92; 0.18)	0.21
	Control	3.58	3.47	-0.05	0.49	0.02			
	VAS Pain due to DU (0-10)								
	Hand PT	1.86	0.89	-0.97	0.08	-0.31	-1.47	-0.37 (-0.91; 0.19)	0.11
	Control	1.49	1.89	+0.50	0.86	0.19			
	HAQ-DI (0-3)								
	Hand PT	1.13	0.75	-0.38	0.02	NC	-0.38	NC	0.22
	Control	0.88	0.88	+0.0	0.44	NC			

BL: Baseline; C: Control group; DU: Digital ulcer; FU: Follow-up; HAQ-DI: Health Assessment Questionnaire-Disability Index; I: Intervention group; NC: Not possible to calculate; Pts: Patients; PT: Physical therapy; RP: Raynaud phenomenon; SSc: Systemic sclerosis; VAS: Visual analogue scale.

Table S49 – Hand warming in water – Efficacy.

Study	Intervention	Mean BL	Mean FU	Δ FU – BL Mean	Δ FU - BL P-value	Δ FU - BL Cohen D	Δ I vs Δ C	I vs C SMD	I vs C P-value
Study ID: Goodfield 1988, BJ Derm (Critical RoB) Study design: crossover controlled clinical trial Population: RP secondary to SSc Intervention: Hand warming 5 mins every 4h (N=12) Control: Same pts, alternate weeks, no HW (N=12) Follow-up: 6 weeks	**Frequency of Raynaud attacks (times/week)**								
	HW weeks	NR	11.8	NC	NC	NC	NC	NC	**<0.01**
	Control weeks	NR	14.4	NC	NC	NC	NC	NC	
	Duration of Raynaud attacks (minutes)								
	HW weeks	NR	26.0	NC	NC	NC	NC	NC	**<0.05**
	Control weeks	NR	30.0	NC	NC	NC	NC	NC	

BL: Baseline; C: Control group; FU: Follow-up; HW: Hand warming; I: Intervention group; NC: Not possible to calculate; NR: Not reported; Pts: Patients; RP: Raynaud phenomenon; SSc: Systemic sclerosis.

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Table S50 – Ischemic preconditioning – Efficacy.

Study	Intervention	Mean BL	Mean FU	Δ FU – BL Mean	Δ FU - BL P-value	Δ FU - BL Cohen D	Δ I vs Δ C	I vs C SMD	I vs C P-value
Study ID: Neferu 2017, J Scl&RD (High RoB) Study design: crossover RCT Population: RP secondary to CTD (mean age 60.8±9.4) Intervention: Ischemic preconditioning (N=8) Control: Low pressure inflations (N=10) Follow-up: 8 weeks	**Frequency of Raynaud's attacks (attacks/week)**								
	IP	14.6	14.8	+0.2	NR	NC	-0.5	NC	0.84
	Control	18.7	19.4	+0.7	NR	NC			
	Duration of Raynaud's attacks (mean minutes/week)								
	IP	472.6	316.5	-156.1	NR	NC	-181.0	NC	0.65
	Control	812.6	837.5	+24.9	NR	NC			
	VAS of Raynaud's attacks severity (0-10)								
	IP	2.7	0.4	-2.3	NR	NC	-3,4	NC	0.89
	Control	3.0	4.1	+1.1	NR	NC			
	HAQ-DI (0-3)								
	IP	0.9	2.1	+1.2	NR	NC	+1.3	NC	0.10
	Control	0.9	0.8	-0.1	NR	NC			

BL: Baseline; C: Control group; FU: Follow-up; HAQ-DI: Health Assessment Questionnaire-Disability Index; I: Intervention group; IP: Ischemic preconditioning; NC: Not possible to calculate; NR: Not reported; RCT: Randomized controlled trial; RP: Raynaud phenomenon; RP: Raynaud phenomenon; VAS: Visual analogue scale.

Table S51 – Laser therapy – Efficacy.

Study	Intervention	Mean BL	Mean FU	Δ FU – BL Mean	Δ FU - BL P-value	Δ FU - BL Cohen D	Δ I vs Δ C	I vs C SMD	I vs C P-value
Study ID: Kuryliszyn-Moskal 2013, CR (Moderate RoB) Study design: prospective observational study Population: RP secondary to CTD (age 26-66 yo) Intervention: MLS laser in secondary RP (N=40) Control: MLS laser in primary RP (N=38) Follow-up: 3 weeks	**Frequency of Raynaud's attacks (attacks/week)**								
	Secondary RP	20.0	15.0	-5.0	**<0.001**	NC	-4.0	NC	NR
	Primary RP	6.0	5.0	-1.0	**<0.001**	NC			
	Duration of Raynaud's attacks (in minutes)								
	Secondary RP	15.0	10.0	-5.0	**<0.001**	NC	-2.5	NC	NR
	Primary RP	15.0	12.5	-2.5	**<0.001**	NC			

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VAS of Raynaud's attacks severity (0-10)								
Secondary RP	4.6	3.1	-1.5	**<0.001**	NC	-1.0	NC	NR
Primary RP	1.9	1.5	-0.5	**<0.001**	NC			

Study	Intervention	Mean BL	Mean FU	Δ FU – BL Mean	Δ FU - BL P-value	Δ FU - BL Cohen D	Δ I vs Δ C	I vs C SMD	I vs C P-value
Study ID: Al-Awami 2001, Vasa (Moderate RoB) Study design: prospective observational study Population: RP secondary to CTD (age 33-69 yo) Intervention: Low level laser in secondary RP (N=29) Control: Low level laser in primary RP (N=11) Follow-up: 3 months	**VAS of Raynaud's attacks severity (0-10)**								
	Secondary RP	8.0	2.0	-6.0	**<0.001**	NC	+1.0	NC	1.0
	Primary RP	8.0	1.0	-7.0	**<0.001**	NC			

BL: Baseline; C: Control group; CTD: Connective tissue disease; FU: Follow-up; I: Intervention group; MLS: Multiwave locked system; NC: Not possible to calculate; NR: Not reported; RP: Raynaud phenomenon; VAS: Visual analogue scale.

Table S52 – Local oxygen-ozone therapy – Efficacy.

Study	Intervention	Mean BL	Mean FU	Δ FU – BL Mean	Δ FU - BL P-value	Δ FU - BL Cohen D	Δ I vs Δ C	I vs C SMD	I vs C P-value
Study ID: Kaymaz 2021, Mod Rh (Low RoB) Study design: RCT Population: RP secondary to SSc (median age 38yo), with DU Intervention: Local oxygen-ozone therapy + MT (N=13) Control: MT only (N=12) Follow-up: 4 weeks	**Frequency of Raynaud's attacks (attacks/day)**								
	Oxygen-ozone	3.5	2.0	-1.5	**<0.01**	NC	-1.3	NC	**<0.01**
	Control	4.0	3.8	-0.2	0.26	NC			
	Duration of Raynaud's attacks (mean minutes/attack)								
	Oxygen-ozone	11.0	1.8	-9.2	**<0.01**	NC	-3.2	NC	**0.03**
	Control	10.0	4.0	-6.0	0.04	NC			
	VAS of DU pain (0-10)								
	Oxygen-ozone	6.5	4.0	-2.5	**<0.01**	NC	-2.0	NC	**<0.01**
	Control	7.5	7.0	-0.5	0.03	NC			
	HAQ (0-3)								
	Oxygen-ozone	1.5	1.0	-0.5	**0.02**	NC	-1.0	NC	**0.02**

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	Control	1.0	1.5	+0.5	0.84	NC			

BL: Baseline; C: Control group; DU: Digital Ulcers; FU: Follow-up; HAQ-DI: Health Assessment Questionnaire; I: Intervention group; MT: Medical Therapy; NC: Not possible to calculate; NR: Not reported; RP: Raynaud phenomenon; VAS: Visual analogue scale.

Table S53 – Proximal heat stress – Efficacy.

Study	Intervention	Mean BL	Mean FU	Δ FU – BL Mean	Δ FU - BL P-value	Δ FU - BL Cohen D	Δ I vs Δ C	I vs C SMD	I vs C P-value
Study ID: Shima 2022, Mod Rh (High RoB) Study design: crossover RCT Population: RP secondary to SSc (age 20-80 yo) Intervention (1): Proximal heat stress neck (N=14) Intervention (2): Proximal heat stress elbow (N=14) Intervention (3): Proximal heat stress wrist (N=14) Follow-up: 6 weeks	**Median VAS of Raynaud's attacks severity (0-10)**								
	Neck	3.8	2.9	-0.9	**0.02**	NC	NC	NC	NC
	Elbow	3.5	2.9	-0.6	**0.04**	NC	NC	NC	NC
	Wrist	2.9	3.0	+0.1	0.86	NC	NC	NC	NC

BL: Baseline; C: Control group; FU: Follow-up; I: Intervention group; NC: Not possible to calculate; RCT: Randomized controlled trial; RP: Raynaud phenomenon; RP: Raynaud phenomenon; VAS: Visual analogue scale.

Table S54 – Silver fibre gloves – Efficacy.

Study	Intervention	Mean BL	Mean FU	Δ FU – BL Mean	Δ FU - BL P-value	Δ FU - BL Cohen D	Δ I vs Δ C	I vs C β (95% CI)	I vs C P-value
Study ID: Liem 2022, Mod Rh (Unclear RoB) Study design: crossover RCT Population: RP secondary to SSc (mean age 60±12yo) Intervention: Silver fibre gloves (N=75) Control: Normal gloves (N=75) Follow-up: 12 weeks	**Raynaud condition score (0-100)**								
	SFG	6.4	3.9	-2.5	NR	NC	0	-0.1 (-0.2; 0.1)	0.7
	Control	6.4	3.9	-2.5	NR	NC			
	Frequency of Raynaud's attacks (attacks/day)								
	SFG	NR	NR	NR	NR	NC	NR	0.5 (-0.3; 1.2)	NS
	Control	NR	NR	NR	NR	NC			
	Duration of Raynaud's attacks (mean minutes/attack)								
	SFG	NR	NR	NR	NR	NC	NR	-39.8 (-115.7; 36.1)	NS
	Control	NR	NR	NR	NR	NC			
	HAQ-DI (0-3)								
	SFG	NR	NR	NR	NR	NC	NR	-0.04 (-0.05; -0.03)	NCS
	Control	NR	NR	NR	NR	NC			

BL: Baseline; C: Control group; FU: Follow-up; I: Intervention group; HAQ-DI: Health Assessment Questionnaire-Disability Index; NC: Not possible to calculate; NR: Not reported; NS: Non significative; RCT: Randomized controlled trial; RP: Raynaud phenomenon; SFG: Silver fibre gloves; VAS: Visual analogue scale.

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Table S55 – Bone marrow mononuclear cell implantation into the ischaemic limb – Efficacy.

Study	Intervention	Mean BL	Mean FU	Δ FU – BL Mean	Δ FU - BL P-value	Δ FU - BL Cohen D	Δ I vs Δ C	I vs C SMD (95% CI)	I vs C P-value
Study ID: Takagi 2014, Rheumatology (Moderate RoB) Study design: prospective observational study Population: RP secondary to SSc (mean age 65.1±8.2), with DU Intervention: BMMC implantation in SSc pts (N=11) Control: BMMC implantation in arteriosclerosis obliterans pts (N=29) Follow-up: 4 weeks (VAS), 2 years (limb amputation)	**VAS Pain due to DU (0-10)**								
	SSc	9.3	1.1	-8.2	**<0.01**	NC	-2.1	-0.34 (-0.81; 0.15)	NR
	AO	7.7	1.6	-6.1	<0.01	NC			

AO: arteriosclerosis obliterans; BL: Baseline; BMMC: Bone marrow mononuclear cell implantation; C: Control group; DU: Digital Ulcers; FU: Follow-up; I: Intervention group; NC: Not possible to calculate; NR: Not reported; Pts: Patients; RP: Raynaud phenomenon; SSc; Systemic Sclerosis; VAS: Visual analogue scale.

Table S56 – Endoscopic thoracic sympathectomy – Efficacy.

Study	Intervention	BL	FU	Δ FU – BL Mean	Δ FU - BL P-value	Δ FU - BL Cohen D	Δ I vs Δ C	I vs C RR (95% CI)	I vs C P-value
Study ID: Matsumoto 2002, J Vas Surg (Serious RoB) Study design: retrospective cohort Population: RP secondary to CTD (age 26-73 years) Intervention: ETS in CTD-RP pts (N=8) Control: ETS in non-CTD-RP pts (N=20) Follow-up: 12-91 months	**Immediate improvement of RP frequency and severity (%)**								
	CTD-RP	-	88	NC	NC	NC	NC	0.9 (0.5; 1.8)	NC
	Non-CTD-RP	-	95	NC	NC	NC			
	RP recurrence at 3 months (%)								
	CTD-RP	-	13	NC	NC	NC	NC	2.3 (0.2; 33.3)	NC
	Non-CTD-RP	-	0	NC	NC	NC			
	RP recurrence at 12 months (%)								
	CTD-RP	-	13	NC	NC	NC	NC	0.3 (0.0; 2.1)	NC
	Non-CTD-RP	-	55	NC	NC	NC			
	Long-term reduced RP frequency and severity (% at median 63 months)								
	CTD-RP	-	75	NC	NC	NC	NC	0.9 (0.4; 1.7)	NC
	Non-CTD-RP	-	95	NC	NC	NC			

BL: Baseline; CTD: Connective tissue disease; C: Control group; ETS: Endoscopic thoracic sympathectomy; FU: Follow-up; I: Intervention group; NC: Not possible to calculate; Pts: Patients; RP: Raynaud phenomenon VAS: Visual analogue scale.

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Table S57 – Periarterial sympathectomy – Efficacy.

Study	Intervention	BL	FU	Δ FU – BL Mean	Δ FU – BL P-value	Δ FU – BL Cohen D	Δ I vs Δ C	I vs C RR (95% CI)	I vs C P-value
Study ID: Hartzell 2009, J Hand Surg (Critical RoB) Study design: retrospective cohort Population: RP secondary to CTD (age 24-79), with DU Intervention: PS in pts with CTD-DUs (N=20 pts, 42 fingers) Control: PS in pts with atherosclerosis-DUs (N=8 pts, 17 fingers) Follow-up: minimum 23 months, average 96 months	**Reduction in the number of DUs (% of pts)**								
	CTD	-	75	NC	NC	NC	NC	6.00 (0.94; 38.19)	<0.01
	Atherosclerosis	-	13	NC	NC	NC			
	Finger amputation (% of fingers with DUs)								
	CTD	-	26	NC	NC	NC	NC	0.47 (0.22; 0.96)	0.03
	Atherosclerosis	-	59	NC	NC	NC			
	Non-CTD-RP	-	95	NC	NC	NC			

BL: Baseline; CTD: Connective tissue disease; C: Control group; DU: Digital Ulcers; FU: Follow-up; I: Intervention group; NC: Not possible to calculate; Pts: Patients; RP: Raynaud phenomenon.

Table S58 – Periarterial sympathectomy of the hand + vascular bypass – Efficacy.

Study	Intervention	BL	FU	Δ FU – BL Mean	Δ FU - BL P-value	Δ FU - BL Cohen D	Δ I vs Δ C	I vs C RR (95% CI)	I vs C P-value
Study ID: Shammas 2017, J Hand Surg (Serious RoB) Study design: retrospective cohort Population: RP secondary to CTD (age 16-78), with DU Intervention: PS+VB (N=9 pts, 9 hands) Control: PS alone (N=18 pts, 27 hands) Follow-up: median 2.8 years (7 months to 7 years) in the PS group; 1.8 years (range 4 months to 7 years) in the PS+VB group	**Complete and durable healing of DUs (% of hands)**								
	PS+VB	-	56	NC	NC	NC	NC	3.8 (1.3; 11.0)	**0.03**
	PS	-	15	NC	NC	NC			
	Mean duration of each active ulcer until healing (days)								
	PS+VB	-	69	NC	NC	NC	NC	NC	0.40
	PS	-	70	NC	NC	NC			
	Finger amputation (% of hands with DUs that had at least 1 finger amputation)								
	PS+VB	-	22	NC	NC	NC	NC	0.4 (0.1; 1.5)	0.25
	PS	-	52	NC	NC	NC			

BL: Baseline; CTD: Connective tissue disease; C: Control group; DU: Digital Ulcers; FU: Follow-up; I: Intervention group; NC: Not possible to calculate; PS: Periarterial sympathectomy of the hand; Pts: Patients; RP: Raynaud phenomenon; VB: vascular bypass.

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Table S58 – Non-pharmacological – Safety.

Intervention	All adverse events	SAE
Hand physical therapy	Mild hypertension (similar vs controls), 2 infections	0
Hand warming in water	NR	NR
Ischemic preconditioning	NR numerically (uncommon, not diff from sham)	NR
Laser therapy (MLS laser therapy)	NR	NR
Laser therapy (low level laser)	0	0
Local oxygen-ozone therapy	NR	NR
Proximal heat stress	9 (64%), mostly mild burns	0
Silver fiber gloves	6 (7%; 2 treatment vs 4 controls)	0
Periarterial sympathectomy (PS)	2 flexion cont. (1 each group), 1 wound heal comp.	NR
PS + vascular bypass	26% infection, 11% inc./delayed wound heal	NR
Thoracic sympathectomy	Reflex sweating in 85.7%	0
Mononuclear cell implantation	NR	NR

MLS: Multiwave Locked System; NR: Not reported; PS: Periarterial sympathectomy; SAE: severe adverse event

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