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Su KYC, Sharma M, Kim HJ, Kaganov E, Hughes I, Abdeen MH, Ng JHK

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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 15
OBJECTIVES 16
METHODS 16
RESULTS 19
Figure 1. 20
Figure 2. 23
Figure 3. 24
DISCUSSION 30
AUTHORS' CONCLUSIONS 34
ACKNOWLEDGEMENTS 34
REFERENCES 35
CHARACTERISTICS OF STUDIES 41
DATA AND ANALYSES 62
Analysis 1.1. Comparison 1: ACE inhibitor versus placebo, Outcome 1: Frequency of attacks per week 63
Analysis 1.2. Comparison 1: ACE inhibitor versus placebo, Outcome 2: Severity of symptoms 64
Analysis 1.3. Comparison 1: ACE inhibitor versus placebo, Outcome 3: Duration of attacks 64
Analysis 1.4. Comparison 1: ACE inhibitor versus placebo, Outcome 4: Capillaroscopic flow/skin perfusion by ultrasound 65
Analysis 1.5. Comparison 1: ACE inhibitor versus placebo, Outcome 5: Subjective assessment of improvement (10-cm visual analogue scale) 65
Analysis 1.6. Comparison 1: ACE inhibitor versus placebo, Outcome 6: Adverse events 66
Analysis 2.1. Comparison 2: Alpha blockers versus placebo, Outcome 1: Frequency of attacks - buflomedil 66
Analysis 2.2. Comparison 2: Alpha blockers versus placebo, Outcome 2: Severity of symptoms - buflomedil 67
Analysis 2.3. Comparison 2: Alpha blockers versus placebo, Outcome 3: Adverse events - buflomedil 67
Analysis 3.1. Comparison 3: Beraprost versus placebo, Outcome 1: Frequency of attacks per week 67
Analysis 3.2. Comparison 3: Beraprost versus placebo, Outcome 2: Severity of attacks (1 to 4 scale) 68
Analysis 3.3. Comparison 3: Beraprost versus placebo, Outcome 3: Disability (100-mm visual analogue scale) 68
Analysis 3.4. Comparison 3: Beraprost versus placebo, Outcome 4: Adverse events 68
Analysis 4.1. Comparison 4: Dazoxiben versus placebo, Outcome 1: Frequency of attacks per week 69
Analysis 5.1. Comparison 5: Ketanserin versus placebo, Outcome 1: Frequency of attacks per week 69
Analysis 5.2. Comparison 5: Ketanserin versus placebo, Outcome 2: Severity score (frequency of attacks/d × duration of attacks) 70
Analysis 5.3. Comparison 5: Ketanserin versus placebo, Outcome 3: Duration of attacks per day (minutes) 70
Analysis 5.4. Comparison 5: Ketanserin versus placebo, Outcome 4: Capillaroscopic flow/skin perfusion by ultrasound 70
Analysis 5.5. Comparison 5: Ketanserin versus placebo, Outcome 5: Adverse events 70
Analysis 6.1. Comparison 6: Nitrate/nitrate derivatives versus placebo, Outcome 1: Frequency of attacks 71
Analysis 6.2. Comparison 6: Nitrate/nitrate derivatives versus placebo, Outcome 2: Severity of symptoms 71
Analysis 6.3. Comparison 6: Nitrate/nitrate derivatives versus placebo, Outcome 3: Capillaroscopic flow/skin perfusion by ultrasound 72
Analysis 6.4. Comparison 6: Nitrate/nitrate derivatives versus placebo, Outcome 4: Raynaud Condition Score 72
Analysis 7.1. Comparison 7: Phosphodiesterase inhibitors versus placebo, Outcome 1: Frequency of attacks per week 73
Analysis 7.2. Comparison 7: Phosphodiesterase inhibitors versus placebo, Outcome 2: Severity of symptoms 74
Analysis 7.3. Comparison 7: Phosphodiesterase inhibitors versus placebo, Outcome 3: Duration of attacks 74
Analysis 7.4. Comparison 7: Phosphodiesterase inhibitors versus placebo, Outcome 4: Capillaroscopic flow/skin perfusion by ultrasound 74
Analysis 7.5. Comparison 7: Phosphodiesterase inhibitors versus placebo, Outcome 5: Adverse events 75
Analysis 7.6. Comparison 7: Phosphodiesterase inhibitors versus placebo, Outcome 6: Raynaud Condition Score 75
ADDITIONAL TABLES 75
APPENDICES 78

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WHAT'S NEW 90
HISTORY 90
CONTRIBUTIONS OF AUTHORS 91
DECLARATIONS OF INTEREST 91
SOURCES OF SUPPORT 91
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 91
INDEX TERMS 91

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[Intervention Review]

Vasodilators for primary Raynaud's phenomenon

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ABSTRACT

Background

Numerous agents have been suggested for the symptomatic treatment of primary Raynaud's phenomenon. Apart from calcium channel blockers, which are considered to be the drugs of choice, evidence of the effects of alternative pharmacological treatments is limited. This is an update of a review first published in 2008.

Objectives

To assess the effects of drugs with vasodilator effects on primary Raynaud's phenomenon as determined by frequency, severity, and duration of vasospastic attacks; quality of life; adverse events; and Raynauds Condition Score.

Search methods

The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase, and CINAHL databases, and the World Health Organization International Clinical Trials Registry Platform and the ClinicalTrials.gov trial register to November 16, 2020.

Selection criteria

We included randomized controlled trials evaluating effects of oral, intravenous, and topical formulations of any drug with vasodilator effects on subjective symptoms, severity scores, and radiological outcomes in primary Raynaud's phenomenon. Treatment with calcium channel blockers was not assessed in this review, nor were these agents compared.

Data collection and analysis

Two review authors independently selected studies for inclusion, assessed studies using the Cochrane "Risk of bias" tool, and extracted study data. Outcomes of interest included frequency, severity, and duration of attacks; quality of life (QoL); adverse events (AEs); and the Raynaud Condition Score (RCS). We assessed the certainty of the evidence using GRADE.

Main results

We identified seven new studies for this update. In total, we included 15 studies involving 635 participants. These studies compared different vasodilators to placebo. Individual studies used different methods and measures to report different outcomes.

Angiotensin-converting enzyme (ACE) inhibitors

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Combining data from three studies revealed a possible small increase in the frequency of attacks per week after treatment (captopril or enalapril) compared to placebo (mean difference [MD] 0.79, 95% confidence interval [CI] 0.43 to 1.17; low-certainty evidence). There was no evidence of a difference between groups in severity of attacks (MD -0.17, 95% CI -4.66 to 4.31; 34 participants, 2 studies; low-certainty evidence); duration of attacks (MD 0.54, 95% CI -2.42 to 1.34; 14 participants, 1 study; low-certainty evidence); or AEs (risk ratio [RR] 1.35, 95% CI 0.67 to 2.73; 46 participants, 3 studies; low-certainty evidence). QoL and RCS were not reported.

Alpha blockers

Two studies used alpha blockers (buflomedil or moxisylyte). We were unable to combine data due to the way results were presented. Buflomedil probably reduced the frequency of attacks compared to placebo (MD -8.82, 95% CI -11.04 to -6.60; 31 participants, 1 study; moderate-certainty evidence) and may improve severity scores (MD -0.41, 95% CI -0.62 to -0.30; moderate-certainty evidence). With moxisylyte, investigators reported fewer attacks ($P < 0.02$), less severe symptoms ($P < 0.01$), and shorter duration of attacks, but the clinical relevance of these results is unclear. No evidence of a difference in AEs between buflomedil and placebo groups was noted (RR 1.41, 95% CI 0.27 to 7.28; 31 participants, 1 study; moderate-certainty evidence). More AEs were observed in participants in the moxisylyte group than in the placebo group.

Prostaglandin/prostacyclin analogues

One study compared beraprost versus placebo. There was no evidence of benefit for frequency (MD 2.00, 95% CI -0.35 to 4.35; 118 participants, low-certainty evidence) or severity (MD -0.06, 95% CI -0.34 to 0.22; 118 participants, low-certainty evidence) of attacks. Overall, more AEs were noted in the beraprost group (RR 1.59, 95% CI 1.05 to 2.42; 125 participants; low-certainty evidence). This study did not report on duration of attacks, QoL, or RCS.

Thromboxane synthase inhibitors

One study compared a thromboxane synthase inhibitor (dazoxiben) versus placebo. There was no evidence of benefit for frequency of attacks (MD 0.8, 95% CI -1.81 to 3.41; 6 participants; very low-certainty evidence). Adverse events were not reported in subgroup analyses of participants with primary Raynaud's phenomenon, and the study did not report on duration of attacks, severity of symptoms, QoL, or RCS.

Selective serotonin reuptake inhibitors

One study compared ketanserin with placebo. There may be a slight reduction in the number of attacks per week with ketanserin compared to placebo (MD -14.0, 95% CI -27.72 to -0.28; 41 participants; very low-certainty evidence) and reduced severity score (MD -133.00, 95% CI -162.40 to -103.60; 41 participants; very low-certainty evidence). There was no evidence that ketanserin reduced the duration of attacks (MD -4.00, 95% CI -14.82 to 6.82; 41 participants; very low-certainty evidence), or that AEs were increased in either group (RR 1.54, 95% CI 0.89 to 2.65; 41 participants; very low-certainty evidence). This study did not report on QoL or RCS.

Nitrate/nitrate derivatives

Four studies compared topical treatments of nitroglycerin or glyceryl trinitrate versus placebo, each reporting on limited outcomes. Meta-analysis demonstrated no evidence of effect on frequency of attacks per week (MD -1.57, 95% CI -4.31 to 1.17; 86 participants, 2 studies; very low-certainty evidence). We were unable to pool any data for the remaining outcomes.

Phosphodiesterase inhibitors

Three studies compared phosphodiesterase inhibitors (vardenafil, cilostazol or PF-00489791) to an equivalent placebo. Results showed no evidence of a difference in frequency of attacks (standardized MD [SMD] -0.05, 95% CI -6.71 to 6.61; 111 participants, 2 studies; low-certainty evidence), severity of attacks (MD -0.03, 95% CI -1.04 to 0.97; 111 participants, 2 studies; very low-certainty evidence), duration of attacks (MD -1.60, 95% CI -7.51 to 4.31; 73 participants, 1 study; low-certainty evidence), or RCS (SMD -0.8, 95% CI -1.74 to 0.13; 79 participants, 2 studies; low-certainty evidence). Study authors reported that 35% of participants on cilostazol complained of headaches, which were not reported in the placebo group. PF-00489791 caused 34 of 54 participants to experience AEs versus 43 of 102 participants receiving placebo (RR 1.49). Headache was most common, affecting 14 participants (PF-00489791) versus nine participants (placebo).

Authors' conclusions

The included studies investigated several different vasodilators (topical and oral) for treatment of primary Raynaud's phenomenon. Small sample sizes, limited data, and variability in outcome reporting yielded evidence of very low to moderate certainty. Evidence is insufficient to support the use of vasodilators and suggests that vasodilator use may even worsen disease.

PLAIN LANGUAGE SUMMARY

Vasodilator drugs to reduce the symptoms of primary Raynaud's phenomenon

Background

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Raynaud's phenomenon (RP) is a condition affecting the small blood vessels in the extremities, usually in the fingers but also in the toes and other body parts. It is caused by temporary narrowing of the blood vessels, which leads to color changes with associated numbness, tingling, and pain. Various triggers for this condition are known, such as stress, cold, and use of vibrational hand tools. Conservative measures to control this condition include stopping smoking and maintaining both peripheral and ambient warmth. Medications that dilate the blood vessels such as calcium channel blockers (CCBs) may be used but can have side effects. This review aims to investigate the effectiveness and safety of drugs that dilate the blood vessels other than CCBs.

Study characteristics and key results

We found seven new studies for this update, bringing the total to 15 (search was good to November 16, 2020). This update now includes other routes of administration such as through the veins (intravenous) and the skin (topical), in contrast to previous reviews, which focused on oral forms of treatment. The studies were published between 1989 and 2013 and involved a total of 635 participants randomly assigned to receive treatment or placebo control. Many studies did not describe various aspects of study methods such as randomization, allocation concealment, and blinding. Treatment duration varied between two weeks and six months.
Angiotensin-converting enzyme (ACE) inhibitors as a drug class, specifically enalapril and captopril in this review, in general increased the frequency of Raynaud's attacks per week but did not affect the severity of the attacks. Enalapril worsened subjective assessment of improvement, and captopril did not improve subjective outcomes or digital blood flow. Buflomedil showed a small reduction in the frequency and severity of attacks with increased side effects. Beraprost and dazoxiben did not demonstrate any change in frequency or severity of attacks nor in disability score and were associated with increased side effects. Ketanserin did not demonstrate improvement in frequency or duration of attacks nor in digital blood flow but did demonstrate improvement in severity scoring of RP. In a small study, moxisylyte was shown to reduce the frequency and severity of attacks to a small degree but with increased side effects. Topical glyceryl trinitrate did not show any effect on reducing the frequency of attacks per week. One study reported subjective improvement in Raynaud Condition Score (RCS). One small study reported improvements in frequency and severity of attacks as subjective changes. Headaches were the most significant and common side effect of treatment. Phosphodiesterase inhibitors did not cause a reduction in frequency, severity, or duration of attacks and did not improve RCS. One study reported in favor of vardenafil alone to reduce RCS but found that the effect is likely small. One study reported that cilostazol increased the frequency and severity of attacks; more research is needed to confirm this finding. Risk of headache as a side effect of treatment was increased with cilostazol use. PF-00489791 at a dose of 20 mg was found to slightly improve all subjective outcome measures and RCS.

Reliability of the evidence

We have very low to moderate confidence in these results, so we cannot make any firm conclusions about the benefit of these drugs for improving symptoms of primary RP. We cannot be confident because of the small numbers of participants involved in studies, issues with how studies were designed, and differences in how they measured whether or not treatments were effective. Therefore, the clinical importance of these results is difficult to assess, especially when placebo response is high. It is also pertinent that the results for each drug class and for individual drugs within each drug class must be interpreted in the context that they may have varying pharmacologic effects in addition to vasodilation. This must be taken into consideration when any conclusions are made about the overall effects of each drug class and/or individual drug.

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SUMMARY OF FINDINGS

Summary of findings 1. Angiotensin-converting enzyme inhibitors compared to placebo for primary Raynaud's phenomenon

ACE inhibitors compared to placebo for treatment of primary Raynaud's phenomenon

Patient or population: primary Raynaud's phenomenon
Setting: outpatient clinic[a]
Intervention: ACE inhibitor[b]
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with ACE inhibitor				
Frequency of attacks (per week) (4 to 6-week follow-up)		MD 0.79 higher (0.43 higher to 1.16 higher)	-	44 (3 RCTs)	⊕⊕⊝⊝ LOW[c,d]	There may be increased frequency of attacks with treatment
Severity of attacks (mild, moderate, and severe. then converted to numeric representation) (4 to 6-week follow-up)		MD 0.17 lower (4.66 lower to 4.31 higher)	-	34 (2 RCTs)	⊕⊕⊝⊝ LOW[c,e]	No evidence of a difference
Duration of attacks (minutes) (4 to 6-week follow-up)		MD 0.54 higher (1.34 lower to 2.42 higher)	-	14 (1 RCT)	⊕⊕⊝⊝ LOW[c,e]	No evidence of a difference
QoL	See comment		-	-	-	This outcome was not reported by any study
Adverse events (4 to 6-week follow-up)	182 per 1000	245 per 1000 (122 to 496)	RR 1.35 (95% CI 0.67 to 2.73)	46 (3 RCTs)	⊕⊕⊝⊝ LOW[c,d]	No evidence of a difference
RCS	See comment		-	-	-	This outcome was not reported by any study

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*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ACE: angiotensin-converting enzyme; CI: confidence interval; MD: mean difference; QoL: quality of life; RCS: Raynaud Condition Score; RCT: randomized controlled trial; RR: risk ratio,

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Outpatient clinic - Madsen 1984 and Challenor 1991 did not specify.
[b]Studies included in this comparison investigated the drugs captopril (in Madsen 1984 and Rustin 1987) and enalapril (Challenor 1991).
[c]We downgraded by one step due to concerns over risk of bias (selection and performance bias).
[d]We downgraded by one step due to inconsistency (heterogeneity) between studies.
[e]We downgraded by one step due to imprecision.

Summary of findings 2. Alpha blockers compared to placebo for primary Raynaud's phenomenon

Alpha blockers compared to placebo for primary Raynaud's phenomenon

Patient or population: primary Raynaud's phenomenon
Setting: GP practice/outpatient clinic
Intervention: alpha blockers[a]
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with alpha blocker				
Frequency of attacks (4 weeks' to 180 days' follow-up)	Moxisylyte		-	33 (1 RCT)	-	19 participants had fewer attacks during the moxisylyte period and 10 during the placebo period. Four participants had an equal number of attacks in each period
	See comment					
	Buflomedil		-	31 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	Frequency of attacks per week may be reduced with buflomedil treatment
		MD 8.82 lower				

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		(11.04 lower to 6.6 lower)				
Severity of attacks (Dichotomous outcome over 4 weeks' to 180 days' follow-up)	Moxisylyte		-	25 (1 RCT)	-	Of 25 participants, 7 reported more severe attacks during the moxisylyte period and 18 participants reported more severe attacks during the placebo period
	See comment					
	Buflomedil		-	31 (1 RCT)	⊕⊕⊝⊝ MODERATE[b]	Severity of attacks may be slightly reduced
		MD 0.41 lower (0.52 lower to 0.3 lower)				
Duration of attacks (4 weeks)	Moxisylyte		-	33 (1 RCT)	-	Fifteen participants recorded shorter total duration of attacks while on moxisylyte, and 9 had shorter duration of attacks on placebo
	See comment					
	Buflomedil		-	-	-	This outcome was not reported
	See comment					
QoL	See comment		-	-	-	This outcome was not reported
Adverse events (4 weeks' to 180 days' follow-up)	Moxisylyte		-	33 (1 RCT)	-	Total of 13 participants during the moxisylyte phase and 3 during the placebo phase reported adverse events
	See comment					
	Buflomedil		RR 1.41 (0.27 to 7.28)	31 (1 RCT)	⊕⊕⊕⊝ MODERATE[b]	No evidence of a difference in adverse events was seen between buflomedil and placebo groups
	133 per 1000	188 per 1000 (36 to 971)				
RCS	See comment		-	-	-	This outcome was not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; GP: general practitioner; MD: mean difference; QoL: quality of life; RCS: Raynaud Condition Score; RCT: randomized controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

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Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Buflomedil (in Le Quentrec 1991) and moxisylyte (thymoxamine; in Jaffe 1980).
[b]We downgraded by one step due to concerns over risk of bias and imprecision (small number of participants and only one study included).

Summary of findings 3. Prostagladin/prostacyclin analogues compared to placebo for primary Raynaud's phenomenon

Beraprost compared to placebo for primary Raynaud's phenomenon

Patient or population: primary Raynaud's phenomenon
Setting: outpatient clinic
Intervention: beraprost
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with beraprost				
Frequency of attacks per week (6 weeks' follow- up)		MD 2 higher (0.35 lower to 4.35 higher)	-	118 (1 RCT)	⊕⊕⊝⊝ LOW[a,b]	No evidence of a difference
Severity of attacks (1 to 4 scale, 6 weeks' follow-up)		MD 0.06 lower (0.34 lower to 0.22 higher)	-	118 (1 RCT)	⊕⊕⊝⊝ LOW[a,b]	No evidence of a difference
Duration of attacks	See comment		-	-	-	This outcome was not reported
QoL	See comment		-	-	-	This outcome was not reported
Adverse events (6 weeks' follow-up)	Study population 339 per 1000	539 per 1000 (356 to 820)	RR 1.59 (1.05 to 2.42)	125 (1 RCT)	⊕⊕⊝⊝ LOW[a,b]	There may be more adverse events in the beraprost group
RCS	See comment					This outcome was not reported

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; MD: mean difference; QoL: quality of life; RCS: Raynaud Condition Score; RCT: randomized controlled trial; RR: risk ratio.

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GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]We downgraded by one step due to inconsistency.
[b]We downgraded by one step due to imprecision (small number of participants and one study).

Summary of findings 4. Thromboxane synthase inhibitors compared to placebo for primary Raynaud's phenomenon

Dazoxiben compared to placebo for primary Raynaud's phenomenon

Patient or population: primary Raynaud's phenomenon
Setting: outpatient clinic
Intervention: dazoxiben
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with dazoxiben				
Frequency of attacks Per week (over 2 weeks)		MD 0.8 higher (1.81 lower to 3.41 higher)	-	6 (1 RCT)	⊕⊝⊝⊝ VERY LOW[a]	There was no evidence of an effect of dazoxiben compared with placebo
Severity of attacks	See comment		-	-	-	This outcome was not reported
Duration of attacks	See comment		-	-	-	This outcome was not reported
QoL	See comment		-	-	-	This outcome was not reported
Adverse events	See comment		-	-	-	Unclear how many participants had primary Raynaud's phenomenon among 5 participants who had adverse events

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RCS	See comment	-	-	-	This outcome was not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; MD: mean difference; QoL: quality of life; RCS: Raynaud Condition Score; RCT: randomized controlled trial.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]We downgraded by three steps due to risk of bias concerns (selection and performance bias), inconsistency of result, and imprecision (small number of participants with primary Raynaud's phenomenon).

Summary of findings 5. Selective serotonin reuptake inhibitors compared to placebo for primary Raynaud's phenomenon

Ketanserin compared to placebo for primary Raynaud's phenomenon

Patient or population: primary Raynaud's phenomenon
Setting: outpatient clinic
Intervention: ketanserin
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with ketanserin				
Frequency of attacks Per week (over 4 weeks)		MD 14 lower (27.72 lower to 0.28 lower)	-	41 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a]	There may be a slight reduction in the number of attacks per week in the ketanserin group compared to the placebo group
Severity of attacks (frequency of attacks/d × duration of attacks, over 4 weeks)		MD 133 lower (162.4 lower to 103.6 lower)	-	41 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a]	Severity score may be slightly reduced after ketanserin compared to placebo
Duration of attacks		MD 4 lower	-	41 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a]	No evidence of a difference in duration of attacks

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Per day (minutes, over 4 weeks)		(14.82 lower to 6.82 higher)				
QoL	See comment		-	-	-	This outcome was not reported
Adverse events (over 4 weeks)	Study population		RR 1.54 (0.89 to 2.66)	41 (1 RCT)	⊕⊝⊝⊝ VERY LOW[a]	Headache, dry mouth. and dizziness were reported more frequently in the treatment group
	317 per 1000	488 per 1000 (282 to 843)				
RCS	See comment		-	-	-	This outcome was not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; MD: mean difference; QoL: quality of life; RCS: Raynaud Condition Score; RCT: randomized controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]We downgraded by three steps due to risk of bias concerns (selection and performance bias), imprecision (small number of participants), and inconsistency (wide confidence intervals).

Summary of findings 6. Nitrate/nitrate derivatives compared to placebo for primary Raynaud's phenomenon

Nitroglycerin or glyceryl trinitrate (GTN) compared to placebo for primary Raynaud's phenomenon

Patient or population: primary Raynaud's phenomenon
Setting: outpatient clinic[a]
Intervention: GTN or Nitroderm
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with GTN				
Frequency of attacks	Continuous data		-	86	⊕⊝⊝⊝ VERY LOW[b,c,d]	No evidence of a difference

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(1 or 4 weeks' follow-up)		MD 1.57 lower (4.31 lower to 1.17 higher)		(2 RCTs)		
	Dichotomous data		-	14 (1 RCT)	-	Six participants reported response to Nitroderm compared to 1 in the placebo group
	See comment					
Severity of attacks (1 week follow-up)	Continuous data		-	17 (1 RCT)	⊕⊝⊝⊝ VERY LOW[b,c,e]	Severity may be reduced but the clinical relevance of this is unclear
		MD 4.25 lower (5.71 lower to 2.79 lower)				
	Dichotomous data		-	14 (1 RCT)	-	Five participants reported a positive result compared to 1 in the placebo group
	See comment					
Duration of attacks (2 or 4 weeks' follow-up)	See comment		-	77 (2 RCTs)	-	Sovijarvi 1984 reported lack of differences in duration of attacks between GTN and placebo groups (no data provided) Chung 2009 reported no significant decrease in duration of attacks
QoL	See comment		-	-	-	No studies reported on this outcome
Adverse events (3 weeks' follow-up)	See comment		-	8 (1 RCT)	-	All 8 participants reported headaches with nitroglycerin
RCS (4 weeks' follow-up)		MD 0.36 lower (0.98 lower to 0.26 higher)	-	69 (1 RCT)	⊕⊕⊝⊝ LOW[c,e]	No evidence of a difference following GTN treatment

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; GTN: glyceryl trinitrate; MD: mean difference; QoL: quality of life; RCS: Raynaud Condition Score; RCT: randomized controlled trial.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

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Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Studies were conducted in outpatient settings, except for Sovijarvi 1984 (laboratory room).
[b]We downgraded by one step, as Teh 1995 was at risk of performance bias due to unclear blinding. The other studies (not used in analysis) did not report numeric values and are at high risk of attrition bias. Inconsistent reporting methods were used throughout the study and risk of reporting bias is high.
[c]We downgraded by one step for inconsistency (wide confidence intervals).
[d]We downgraded by one step due to imprecision (small numbers).
[e]We downgraded by one step due to a small number of participants and only one included study.

Summary of findings 7. Phosphodiesterase inhibitors compared to placebo for primary Raynaud's phenomenon

Phosphodiesterase inhibitors compared to placebo for primary Raynaud's phenomenon

Patient or population: primary Raynaud's phenomenon
Setting: outpatient clinic
Intervention: phosphodiesterase inhibitors[a]
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with phosphodiesterase inhibitors				
Frequency of attacks (per week) (4 and 6 weeks' follow-up)		SMD 0.05 lower (6.71 lower to 6.61 higher)	-	111 (2 RCTs)	⊕⊕⊝⊝ LOW[b,c]	No evidence of a difference but studies showed conflicting results
Severity of attacks (Likert scale 1 to 9 or 11 points; 4 and 6 weeks' follow-up)		SMD 0.03 lower (1.04 lower to 0.97 higher)	-	111 (2 RCTs)	⊕⊝⊝⊝ VERY LOW[b,c,d]	No evidence of a difference but studies showed conflicting results

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Duration of attacks (4 weeks' follow-up)		MD 1.60 lower (7.51 lower to 4.31 higher)	-	73 (1 RCT)	⊕⊕⊝⊝ LOW[b,c]	No evidence of a difference
QoL	See comment		-	-	-	This outcome was not reported
Adverse events	See comment		-	138 (3 RCTs)	-	35% of participants on cilostazol complained of headaches. Two participants on cilostazol complained of palpitations These were not reported in the placebo group No specific adverse events were reported in the vardenafil group compared to the placebo group 34/54 participants experienced adverse events in the PF-00489791 treatment group compared with 43/102 participants in the placebo group. Headache was the most commonly reported adverse event, affecting 14 participants in the PF-00489791 group and 9 participants in the placebo group
RCS (6 weeks' follow-up)		SMD 0.80 lower (1.74 lower to 0.13 higher)	-	79 (2 RCTs)	⊕⊕⊝⊝ LOW[b,c]	No evidence of a difference

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; MD: mean difference; QoL: quality of life; RCS: Raynaud Condition Score; RCT: randomized controlled trial; SMD: standardized mean difference.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Studies investigated cilostazol (Rajagopalan 2003); vardenafil (Caglayan 2012); and PF-00489791 (NCT01090492).
[b]We downgraded by one step due to risk of bias concerns (unclear blinding placing studies at risk of allocation/performance bias). One study - NCT01090492 - did not report incomplete outcome data and was at risk of attrition bias. Rajagopalan 2003 failed to define the numbers of participants in control and intervention groups when reporting outcomes.
[c]We downgraded by one step due to imprecision.

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[d]We downgraded by one step due to inconsistency (high heterogeneity).

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BACKGROUND

Description of the condition

The phenomenon of episodic digital ischemia provoked by cold, cyanosis, and emotion was first described by Maurice Raynaud in 1862 (Belch 1990). At average onset of 40 years of age (Pope 2011), this common condition is estimated to have a prevalence of 1.6% to 7.2% in the general population, more likely affecting women at 2.1% to 15.8%, compared to 0.8% to 6.5% among men (Garner 2015).

Raynaud's phenomenon (RP) is classically characterized by "triphasic" color change, reflecting the vasospastic nature of the condition. Observed changes often take place in three distinct phases (Hughes 2016). The first phase, reflective of vasospasm/constriction of the small arteries of the distal digits, leads to the well-circumscribed pallor of the fingers. The second phase is caused by cyanosis, which quickly resolves and followed by the final phase involving hyperemia, characterized by restoration of blood flow (Bakst 2008).

Raynaud's phenomenon is divided into primary, also known as idiopathic disease, and secondary, which is associated with various disease states. It usually occurs in the presence of triggers such as stress or cold and in occupations that utilize heavy or vibrational machinery. Raynaud's phenomenon commonly affects the fingers and toes but has been observed to affect other areas such as ears, nose, and even nipples (Maverakis 2014; Prodigy 2006). Common rheumatologic conditions that can predispose include systemic sclerosis, systemic lupus erythematosus, and vasculitides. Certain medications, including beta blockers, ergot alkaloids, and chemotherapeutics such as cisplatin and bleomycin, can also act as triggers (Wigley 2016).

The exact pathophysiology of RP is not completely understood but is postulated to involve a complex interplay of factors that impair vasoconstriction and vasodilatation, as well as intravascular factors. Vasoconstriction is thought to be mediated by alpha-2 adrenergic effects and to be more sensitive in the distal vascular beds and more responsive to a cold stimulus (Cooke 2005). Vasoconstriction is also increased among patients with systemic sclerosis. Vasodilatory effects are thought to be related to calcitonin gene-related peptide, but many other factors such as substance P, neurokinin A, and vasoactive intestinal peptide are thought to be implicated. It has been observed that RP can be exacerbated by conditions that affect the viscosity of blood vessels; suggested intravascular factors include platelet activation and oxidative stress. Finally, genetic and hormonal factors, in addition to neural abnormalities of vessels, have been implicated in the pathogenesis (Prete 2014).

The approach to diagnosis of RP has been updated since publication of the previous review, and agreement on these changes was reached by an international consensus panel in 2013 (Maverakis 2014). The new diagnostic criteria require a patient to be diagnosed with RP in three steps, yielding a disease score. The condition is then classified into primary disease based on a normal capillaroscopy, a physical examination negative for findings to suggest a secondary cause, the absence of a history of connective tissue disease, and a negative or low-titer antinuclear antibody (such as 1:40) by indirect immunofluorescence. Notably, a negative erythrocyte sedimentation rate is no longer required (Maverakis 2014).

Description of the intervention

Symptomatic treatment for primary RP consists of conservative measures such as avoiding exposure to cold and using protective clothing. Smoking and other behaviors that may contribute to symptoms including use of drugs or vibratory tools should be avoided. In comparison to those with secondary RP, in which trophic changes, painful ulcers, and gangrene may develop, requiring more invasive measures, most patients with primary RP can control their symptoms by using conservative measures (Block 2001). If attacks persist despite adequate conservative measures, use of a calcium channel blocker (CCB) is recommended as first-line treatment (Pope 2011; Prodigy 2006). Treatment with CCBs is not discussed in this review, as it is addressed in another Cochrane systematic review (Ennis 2016). Several side effects have been reported with use of CCBs, and a range of other drugs have been used in multiple studies owing to their vasodilatory action. A list of drugs with vasodilatory effects is included in Table 1 (AMH 2018). Medications used primarily for conditions such as hypertension, depression, ischemic heart disease, secondary RP, and erectile dysfunction are also used in treating primary RP, with only limited data available regarding their effectiveness. These include the alpha blockers buflomedil and moxisylyte (thymoxamine), the thromboxane synthase inhibitor dazoxiben, and PF-00489791, a phosphodiesterase Inhibitor that has been used only in early trial stages.

How the intervention might work

The pathophysiology of RP involves intermittent vasodilation and vasoconstriction, resulting in episodic digital ischemia. It is therefore the action of vasodilatory agents such as CCBs that provides at least moderate effectiveness in this condition (Smith 1985). Other interventions with vasodilatory properties have not yet been fully validated and include oral, topical, and intravenous medications that may be administered locally to affected digits and/or systemically. These include angiotensin-converting enzyme (ACE) inhibitors, nitrates, alpha blockers, phosphodiesterase inhibitors, prostacyclins, and selective serotonin receptor inhibitors (SSRIs). These interventions have worked with other vasospastic conditions including coronary artery vasospasm and cerebral artery vasospasm and in related conditions such as erectile dysfunction and pulmonary arterial hypertension. For example, ACE inhibitors and angiotensin receptor blockers (ARBs) are widely used for high blood pressure, nitrates are used in acute myocardial infarction to dilate coronary vessels, and prostacyclins and phosphodiesterase-5 inhibitors may be used in primary pulmonary hypertension (Duarte 2013).

Antithrombotic treatments have been used in severe disease, especially in secondary RP as the result of frequent complications such as severe ischemia leading to digital amputation, but less often in primary RP. Regulation of vascular tone involves many factors and defects in the complex interaction between smooth muscle and endothelium, and innervation of vessels contributes to primary RP. This leads to abnormal autoregulation of the small blood vessels causing vasoconstriction and is thought to be the primary defect in primary RP. The underlying molecular process is poorly understood but has been postulated to be caused by a combination of vasoconstrictive mediators,

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exaggerated vasoconstrictive responses, and blunted vasodilatory responses (Block 2001). Angiotensin-II, a vasoconstrictor once bound to angiotensin-II receptors on vascular smooth muscle, can be inhibited by ACE inhibitors or by angiotensin-II receptor antagonists. The sympathetic nervous system releases catecholamine, which binds to alpha receptors, resulting in vasoconstriction of peripheral vessels that would be blocked by alpha blockers. Alpha blockers produce their effects by blocking alpha receptors that constrict vessels mediated by catecholamines. Serotonin released by platelets contributes to vasospasm in scleroderma-related RP, leading to the postulated effects of serotonergic S2 receptor antagonists and serotonin-converting enzyme inhibitors as vasodilators. Nitrate and its derivatives produce vasodilatory effects through donation of nitric oxide, which results in relaxation of vascular smooth muscle. Phosphodiesterase inhibitors exert their vasodilator effects through vascular smooth muscle relaxation resulting from increased levels of molecular second messengers - monophosphate nucleotides. Prostacyclin, a prostaglandin member of the eicosanoid family, exerts vasodilator effects through smooth muscle relaxation by a similar mechanism as phosphodiesterase inhibitors, hence the theory of prostacyclin analogues. Thromboxane is another member of the eicosanoid family, but opposite to prostacyclin, it has a vasoconstrictive effect on vessels, leading to the theory of thromboxane synthase inhibitors.

Why it is important to do this review

Currently, limited treatment options are available for people with primary RP. Calcium channel blockers, the most commonly used class of drugs, have potential side effects including headache, postural hypotension, peripheral oedema, and constipation (Abernethy 1999). Furthermore, most studies have examined RP in the context of secondary conditions; therefore different treatments may have differing levels of effectiveness in primary compared to secondary RP.

This is the second update of the review first published in 2008 (Vinjar 2008). For this update, we have expanded the scope of the review to include any treatments given by any administration route including topical and intravenous vasodilators. We present all current evidence for vasodilatory drugs for treatment of primary RP, with the aim of guiding decision-making among healthcare professionals and patients alike.

OBJECTIVES

To assess the effects of drugs with vasodilator effects on primary Raynaud's phenomenon as determined by frequency, severity, and duration of vasospastic attacks; quality of life; adverse events; and Raynaud Condition Score.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized controlled trials (RCTs) comparing a drug with vasodilator effects versus placebo for treatment of primary Raynaud's phenomenon (RP). We considered any method of randomization, and we included both parallel and cross-over studies. We applied no language restrictions. Treatment with calcium channel blockers (CCBs) is addressed in another Cochrane systematic review (Ennis 2016).

Types of participants

We included trials involving participants with primary RP. We included trials with a mixture of primary and secondary RP if participants with primary RP could be identified and if data for this subgroup could be extracted. Study authors' definition of primary RP was accepted, unless details in the description of clinical characteristics of participants with primary RP did not comply with current diagnostic criteria or were deemed to be indicative of secondary RP or an alternative disease process.

Types of interventions

We included trials comparing oral, topical, or intravenous administration of any drug with vasodilator effects versus placebo or other drugs, including drugs registered for treatment of cardiovascular disease and genitourinary disease (Chapters 7 and 13 of the Australian Medicines Handbook [AMH] - AMH 2018 - and as Class C of the Anatomical Therapeutical Classification [ATC] system - ATC classification).

Medications that were not defined as having vasodilatory properties, as contraindicated, or as recommended to be used with caution in patients with pre-existing peripheral vascular disease or impaired circulation were excluded. This included all types of beta blockers and oxerutins. Other drugs with vasodilatory effects or with both vasodilatory and calcium channel blocking-actions that have been suggested for treatment of RP but are primarily used for non-cardiovascular diseases were included. See Table 1 for details of drugs with vasodilatory effects. We excluded all studies providing treatment with, or comparison with, calcium channel blockers or alternative (complementary) medicine or non-pharmacologic modalities. We also excluded studies that failed to evaluate all required outcomes.

Owing to daily and seasonal variation in the frequency and duration of attacks, we excluded trials providing treatments administered only once (single-dose trials) or over a period shorter than one week.

Types of outcome measures

Primary outcomes

- Frequency of attacks
- Severity of attacks or severity of symptoms during attacks measured on validated scales (e.g. pain and numbness on visual analogue scales or Likert scales; cold sensitivity as Cold Intolerance Severity Score [CISS])
- Duration of attacks
- Quality of life scores (measured by Health Assessment Questionnaires [HAQs], Short Form-36 [SF-36], or QuickDASH Outcome Measure)
- Adverse events (including withdrawals)

Secondary outcomes

- Raynaud Condition Score
- Capillaroscopic flow/skin perfusion (measured by Doppler ultrasound or laser Doppler ultrasound imaging)

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Search methods for identification of studies

We applied no language restrictions.

Electronic searches

The Cochrane Vascular Information Specialist first searched the following databases for relevant trials (July 31, 2014).

- Cochrane Vascular Specialised Register (July 31, 2014).
- Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 6), in the Cochrane Library, via the Cochrane Register of Studies Online.

See Appendix 1 for details of the search strategy used to search CENTRAL.

The Information Specialist also searched the following trial registries for details of ongoing and unpublished studies, using the term "raynaud" (July 31, 2014).

- ClinicalTrials.gov (clinicaltrials.gov).
- World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch).

The Cochrane Vascular Information Specialist subsequently conducted systematic searches of the following databases for RCTs and controlled clinical trials without language, publication year, or publication status restrictions.

- Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web, searched on November 16, 2020).
- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, via Cochrane Register of Studies Online (CRSO 2020, issue 10).
- MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE) (searched from July 31, 2014, to November 16, 2020).
- Embase Ovid (searched from July 31, 2014, to November 16, 2020).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) Ebsco (searched from July 31, 2014, to November 16, 2020).
- Allied and Complementary Medicine Database (AMED) Ovid (searched from July 31, 2014, to November 16, 2020).

The Information Specialist modelled search strategies for other databases on the search strategy designed for CENTRAL. When appropriate, these strategies were combined with adaptations of the highly sensitive search strategy designed by Cochrane for identifying RCTs and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 6; Lefebvre 2011). Search strategies for major databases are provided in Appendix 2.

The Information Specialist searched the following trials registries on November 16, 2020.

- World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch).
- ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

We did not check other resources.

Data collection and analysis

Selection of studies

All members of the review team identified trials for possible inclusion and independently reviewed abstracts and full-text articles as appropriate. Abstracts were translated for the screening process and were included in the full-text reviews if they appeared to fulfill selection criteria, or if they did not provide enough information to allow a decision regarding exclusion. We obtained full-text articles and translated them as necessary via the Cochrane Task Exchange website (taskexchange.cochrane.org) or with the assistance of personal contacts who were native speakers. Translators were advised to follow inclusion criteria and to specify reasons for exclusion. If there was any uncertainty regarding the study, a full, direct translation would be requested, after which a member of the review team would review the article for inclusion. Two members of the team (KS and HA) contacted study authors for additional information to be used for inclusion or exclusion of studies. Two pharmaceutical companies and two study authors were contacted for additional information. All disagreements regarding article selection were discussed and were resolved between members, and if consensus could not be reached, KS or JN would review and make a final decision.

Data extraction and management

Each study was independently reviewed by two members of the review team (KS, MS, HA, JK). Data from included studies were extracted and recorded using Covidence (covidence.org), as recommended by Cochrane. Recorded data included sponsorship source, country where the study took place, type of setting (inpatient versus outpatient, hospital versus research center), author contact details, design of the study (randomization, blinding, and cross-over versus parallel), baseline population characteristics, inclusion and exclusion criteria, types of interventions including dosing and route of administration, and finally, outcome measures of the study. We decided prior to data extraction that in the event that studies reported results at two different doses, results on the higher dose should be used in meta-analyses. It is an assumption of meta-analysis that studies are independent, that is, two or more results from a single study cannot be included in a meta-analysis. We chose the result associated with the higher dose, assuming a dose-effect relationship, as we are interested in identifying evidence of any effect.

Assessment of risk of bias in included studies

Two members of the author review team independently assessed the methodological quality of included trials (KS, MS, HA, EK, JK), using Cochrane's "Risk of bias" tool (Higgins 2011), and we recorded our judgements in Covidence. Domains assessed included sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and any other sources of bias that the review team believed could affect the quality of a study. We judged each domain as being at low high or unclear risk of bias. We resolved disagreements through discussion.

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Measures of treatment effect

We performed statistical analysis according to the statistical guidelines provided to review authors by Cochrane Vascular and described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We carried out statistical analyses using the Web-based Review Manager software (RevMan Web 2019).

For continuous data, we extracted mean differences (MDs) and their standard errors (SEs). SE incorporates both standard deviation (SD) and the number of subjects for the mean of the differences or the difference of the means and is the parameter that when estimated enables results from both parallel and cross-over trials to be pooled. This is the main reason that we used SE over SD throughout the study. If different scales were used to measure effects, we planned to use standardized mean differences (SMDs) with 95% CIs when it was possible to meta-analyze data from studies.

Frequency of attacks was reported variably and was converted to attacks per week when possible. Most studies reported mean and SD of frequency of attacks, and we converted these to MD (drug to placebo) and SE.

Duration of attacks was recorded in minutes. Most studies reported mean and SD of duration of attacks, and we converted these to MD (drug to placebo) and SE. Severity of attacks was assessed by a variety of methods. In each case, results were converted to MD (drug to placebo) and SE. Vayssairat 1996 utilised a severity measure on a 1 to 4 scale, and study authors did not state whether this was a categorical or a continuous measure but reported mean and SD; therefore we continued this reporting method. We used MD to report quality of life (QoL). As different VAS scales were used, we calculated SMD with 95% CI. We measured adverse events as risk ratios (RRs) with 95% CIs. Raynaud Condition Score was presented either out of 10 or out of 100. We converted all to a score out of 10 and then to MD (drug to placebo) and SE. Capillaroscopic flow/skin perfusion was reported by a range of measurement techniques for blood flow in the skin, and we calculated MD and SE between groups with 95% CI.

Four studies were parallel trials for which results were easily converted to the MD (SE) format (Chung 2009; Le Quentrec 1991; Rajagopalan 2003; Vayssairat 1996). Rustin 1987 provided results from a cross-over trial already in the appropriate format (and corrected for period effect). Six studies were cross-over trials that presented results so that it was possible to calculate the mean of the individual difference and SE (Caglayan 2012; Challenor 1991; Ettinger 1984; Madsen 1984; NCT01090492; Teh 1995). Van de Wal 1987 and Sovijarvi 1984 provided only group means for their cross-over studies, thus preventing an accurate estimate of SE. In these cases, we used individual correlation between placebo and drug responses to estimate SE. We chose a conservative value of 0.5, as this was smaller than the correlations observed in the other studies (0.8 to 0.95) and provided the study with equivalent power to a parallel study with twice the number of participants. No changes from baseline values were included in the analyses. Two cross-over studies presented dichotomous data that were reported narratively, as it was not possible to present these data accurately in an analysis format (Jaffe 1980; Nahir 1986).

Unit of analysis issues

All studies used the individual participant as the unit of analysis. All cross-over studies were assessed to determine whether the washout period between study arms was sufficient to ensure no carrying over of effect between the first and second periods. Five studies did not include washout periods (Jaffe 1980; Madsen 1984; Rustin 1987; Sovijarvi 1984; Teh 1995). The medications used in these studies were oral captopril, topical glyceryl trinitrate, and moxisylyte, which have a half-life ($t_{1/2}$) of two hours, six minutes, and two hours, respectively. Even in the absence of the washout period, elimination time was less than or equal to 10 hours (based on five half lives, or the time for a medication to reach majority elimination (Ito 2011)), the drug effect dissipated by the next day. Challenor 1991 had three days of drug titration to minimize the side effect of enalapril, which has a $t_{1/2}$ of 11 hours. It is safe to conclude that the drug effect was eliminated after or during the titration period (more than five $t_{1/2}$). Van de Wal 1987 and NCT01090492 indicated two-week washout periods, which was longer than the five $t_{1/2}$ of ketanserin and PF-00489791, respectively. Nahir 1986, Caglayan 2012, and Ettinger 1984 included one-week washout periods, which were longer than the five $t_{1/2}$ of glyceryl trinitrate. No analyses for cross-over trials were carried out using results from only the first treatment period.

Two trials measured outcomes on more than one occasion (Le Quentrec 1991; Vayssairat 1996). Le Quentrec 1991 measured outcomes at two, four, and six months, using the same dose during the whole treatment period. Differences in outcomes between four and six months were minor. We used the six-month outcomes in this review. Vayssairat 1996 measured outcomes after phase 2, 20 µg three times daily, and phase 3, 40 µg three times daily. We used the latter outcomes in this review under the assumption of a dose-response relationship.

We used the generic inverse variance (GIV) option in RevMan Web 2019 so that results from cross-over trials could be combined with results from parallel trials. Standard errors (SEs) had to be estimated from the cross-over trials and could then be entered along with main effects (as mean differences) using the GIV option and combined with SEs and MDs from parallel studies. No information was provided for active and placebo groups individually, nor for numbers in each treatment group, as these do not make sense specifically in the context of cross-over trials.

Dealing with missing data

One member of the review team (KS or HA) contacted study authors or trial coordinators (one was a pharmaceutical company) for additional information when data were believed to be missing (Caglayan 2012; Chung 2009; NCT01090492; Rajagopalan 2003; Vayssairat 1996). Chung 2009 included an intention-to-treat discussion that included all randomized participants who had applied at least one dose of the study drug and had recorded data in their electronic diaries. These investigators utilized only observed data and performed no imputation. Caglayan 2012 performed an intention-to-treat analysis. Additional information for Vayssairat 1996 clarified that intention-to-treat analyses had been carried out. For all other trials with exclusions, withdrawals, or losses to follow up, no intention-to-treat analysis was discussed or presented (Nahir 1986; NCT01090492; Rajagopalan 2003; Sovijarvi 1984; Teh 1995). In these, calculations of results for the cross-over trials had been based on participants who completed both treatment arms.

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No data were re-analyzed according to the principles of intention-to-treat.

Assessment of heterogeneity

We used RevMan Web for meta-analysis (RevMan Web 2019), and the heterogeneity statistics presented consist of Chi^2 and P value for Cochrane's heterogeneity statistic Q, along with I^2, yielding a percentage of total variation across studies due to heterogeneity above what is expected by chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. Analyses with $I^2 > 50\%$ and $P(Q) < 0.05$ were performed with a random-effects model (traditional Der Simonian and Laird method) (DerSimonian 1986). A random-effects model was also used if there was empirical evidence for heterogeneity; otherwise a fixed-effect model was used. Tau^2, the estimated variance of effect under a random-effects analysis, was also presented in this instance.

Assessment of reporting biases

We were not able to construct a funnel plot to assess the possibility of publication bias because of lack of comparable studies.

Data synthesis

We carried out meta-analyses using RevMan Web and guidelines provided by Cochrane Vascular (RevMan Web 2019). We performed statistical analysis according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). As both parallel and cross-over trials were included in this meta-analysis, we used the methods described in Curtain 2002 and Elbourne 2002 to appropriately combine results from all eligible studies. We carried out meta-analyses using MD (and SE) between treatment and control post-intervention values. In the case of parallel trials, this was the difference in the means of treatment and placebo groups. For cross-over trials, this was the mean of the differences for each individual between treatment and placebo phases. We performed meta-analyses using weighted mean differences (MDs) when the unit of measure was the same or was very similar (e.g. frequency of attacks), or using SMDs where there was heterogeneity in measurement methods (e.g. severity or capillaroscopic flow/skin perfusion). We presented results for drugs separately because of lack of pharmacological similarity.

Subgroup analysis and investigation of heterogeneity

We were unable to perform subgroup analyses involving gender, age, and duration of attacks due to insufficient data regarding separate participant groups amongst the included studies. We were unable to determine numbers needed to treat due to limited results. Potential analyses that could prove useful in establishing treatment efficacy in the future, should new studies be included, involve gender, age, and duration of attack subgroups. We were, however, able to group and present the data across all included studies by pharmacological class. This allowed for comparisons and assessments of qualitative and quantitative interactions between different classes of vasodilators. Pre-existing subgroup analyses from individual studies were included and discussed if relevant to the outcomes of this meta-analysis.

Sensitivity analysis

Challenor 1991 received very high weight for frequency of attacks compared to the other studies because of a remarkably small reported SD of frequency of attacks for both groups. Because of this, we performed a sensitivity analysis excluding the enalapril trial from the meta-analysis. Due to the limited number of available studies for each comparison, we were unable to carry out any further sensitivity analyses.

Summary of findings and assessment of the certainty of the evidence

We created "Summary of findings" tables according to Higgins 2011 and used the GRADE method to present the most important findings of this systematic review (Atkins 2004). We used GRADEproGDT software to assist in preparation of "Summary of findings" tables (GRADEpro GDT 2015). We included the six outcomes of greatest clinical relevance to patients and healthcare professionals: frequency of attacks, duration of attacks, severity of attacks, QoL, adverse events, and RCS. We created one table for each drug type: ACE inhibitor compared to placebo for primary Raynaud's phenomenon (Summary of findings 1); alpha blockers compared to placebo for primary Raynaud's phenomenon (Summary of findings 2); prostaglandin/prostacyclin analogues compared to placebo for primary Raynaud's phenomenon (Summary of findings 3); thromboxane synthase inhibitors compared to placebo for primary Raynaud's phenomenon (Summary of findings 4); selective serotonin reuptake inhibitors compared to placebo for primary Raynaud's phenomenon (Summary of findings 5); nitrate/nitrate derivatives compared to placebo for primary Raynaud's phenomenon (Summary of findings 6); and phosphodiesterase inhibitors compared to placebo for primary Raynaud's phenomenon (Summary of findings 7); The certainty of evidence for each outcome was determined by the GRADE approach, which considers overall risk of bias of included studies, directness of evidence, inconsistency within results, precision of estimates, and risk of publication bias (Atkins 2004).

RESULTS

Description of studies

See Figure 1.

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Figure 1. Study flow diagram.

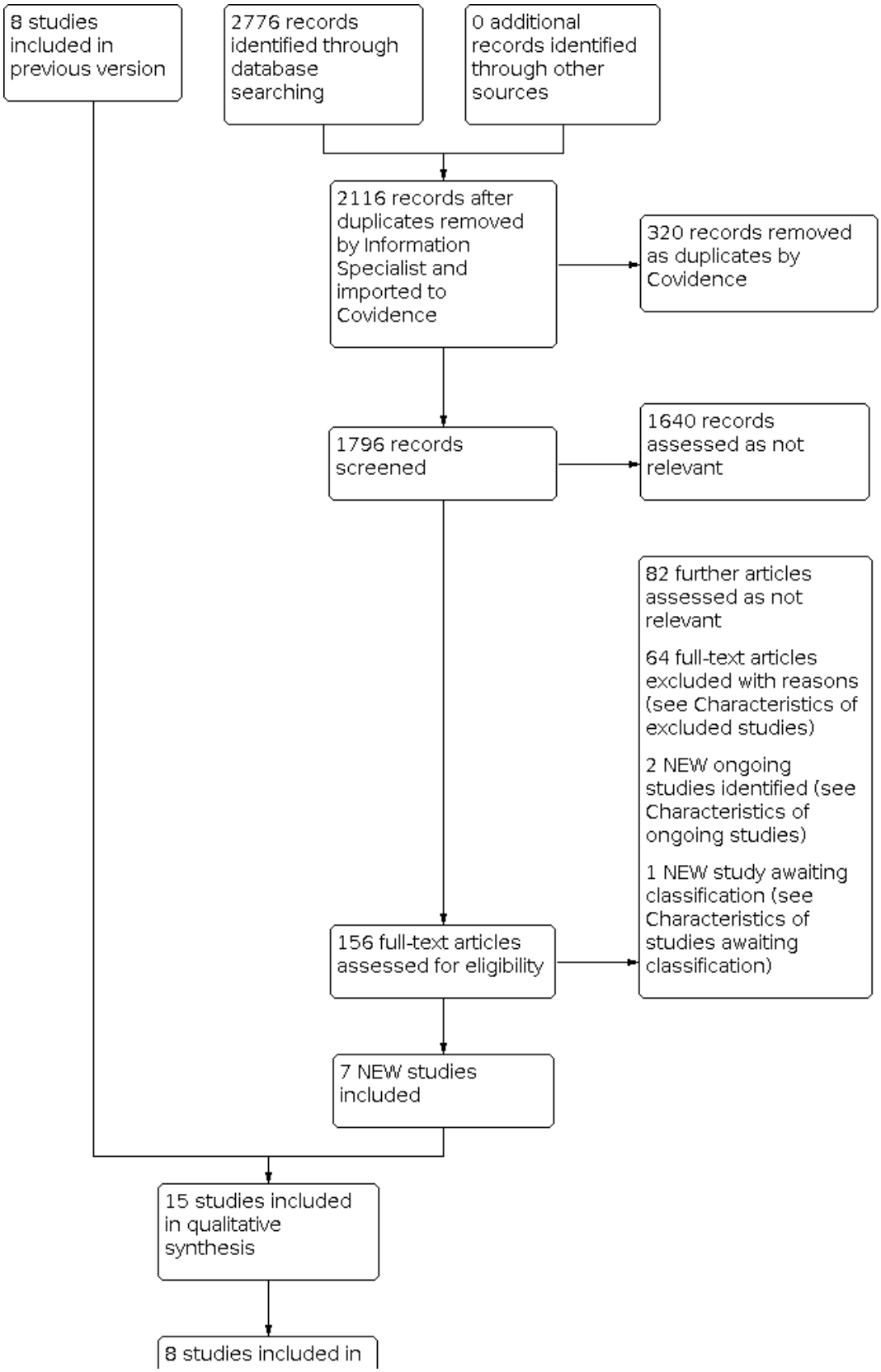

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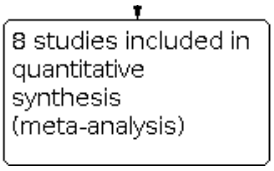
Figure 1. (Continued)



Results of the search

We identified seven new studies for this update (Caglayan 2012; Chung 2009; Nahir 1986; NCT01090492; Rajagopalan 2003; Sovijarvi 1984; Teh 1995); excluded 22 new studies (Allegra 1983; Arcas Meca 1972; Barry 2000; Belch 1985; Bellucci 1987; Belluci 1990; Brotzu 1989; Clement 1980; Diehm 1983; Fischer 1985; JaniniDa 1988; Jenkins 2013; Kingma 1995; Kirichenko 1991; Lee 2014; McFadyen 1973; Mirza 2019; NCT00419419; NCT0048776; Roustit 2017; Strozzi 1982; Surwit 1982); identified two ongoing studies (EUCTR2005-000295-41-DE; NCT02583789), and assessed one study as awaiting classification (Sakaguchi 1990).

Included studies

See the Characteristics of included studies table.

We identified seven new studies for this update (Caglayan 2012; Chung 2009; Nahir 1986; NCT01090492; Rajagopalan 2003; Sovijarvi 1984; Teh 1995). Two studies were published and made available since the last update (Caglayan 2012; NCT01090492), and four were added due to the change in our study selection criteria to expand from oral vasodilators to any vasodilator (Chung 2009; Nahir 1986, Sovijarvi 1984; Teh 1995). The final additional study was excluded by the previous review authors on the basis of not reporting numbers of participants in treatment and control groups (Rajagopalan 2003). This brings the total to 15 included studies with 635 participants (Caglayan 2012; Challenor 1991; Chung 2009; Ettinger 1984; Jaffe 1980; Le Quentrec 1991; Madsen 1984; Nahir 1986; NCT01090492; Rajagopalan 2003; Rustin 1987; Sovijarvi 1984; Teh 1995; Van de Wal 1987; Vayssairat 1996). The largest included study was Chung 2009, which included 140 participants. The remainder of the studies involved numbers of participants ranging from 6 in Ettinger 1984 to 125 in Vayssairat 1996.

Of the seven new studies included in this update, one was referenced as an ongoing study (NCT01090492), and four investigated topical formulations and therefore were not within the scope of the previous review (Chung 2009; Nahir 1986; Sovijarvi 1984; Teh 1995). One was published in August of 2012 after publication of the previous version of the review (Caglayan 2012). The remaining study was excluded by the previous review authors on the basis of not reporting numbers of participants in treatment and control groups (Rajagopalan 2003). Inclusion in this review was allowed, as we were able to calculate the number of participants in each group based on means and standard deviations provided in the original study.

Variation in the included studies was notable in terms of included participant characteristics and outcome measures. A consensus definition for primary RP was established only in 2014 (Maverakis 2014), with four different criteria described before this (Maverakis 2014). Additionally, there were distinct differences in terms of important baseline demographics such as gender, smoking, and weather and setting of the study; furthermore, baseline disease severity demonstrated variation based on various outcome measures.

The included studies were published between 1989 and 2013. A total of 11 medications with vasodilating effects were represented. The included studies used oral and non-oral routes of administration and topical therapy. We excluded studies that mentioned intravenous vasodilators, as we excluded trials with treatments administered only once.

Participants

Five studies included participants with both primary and secondary Raynaud's phenomenon (RP) (Caglayan 2012; Chung 2009; Nahir 1986; NCT01090492; Rajagopalan 2003). Jaffe 1980 included a combination of primary RP and chilblains but separately presented results for each group and therefore was included. All remaining studies included only patients with primary RP (Challenor 1991; Ettinger 1984; Jaffe 1980; Le Quentrec 1991; Madsen 1984; Rustin 1987; Sovijarvi 1984; Teh 1995; Van de Wal 1987; Vayssairat 1996).

All studies defined primary and secondary RP using varying definitions. Nahir 1986 did not discuss its definition of primary RP. Le Quentrec 1991 defined primary disease as diagnosed by "classical criteria," with no references to define this. Challenor 1991 defined primary RP using the Blunt and Porter 1981 definition. Caglayan 2012 included a link for inclusion and exclusion criteria, but at the time of writing this review, the link was defunct. Heterogeneity was significant in the definition of secondary RP, with the general theme being the absence of any biochemical, serological, or clinical findings including digital ulceration.

The baseline frequency of attacks was similar to that in previous reviews, at 7 to 21 per week in all trials except Van de Wal 1987, which reported a mean of 91 attacks per week. It is unlikely that this is an error in reporting. Overall duration of disease was between 1 and 50 years, with an approximate median of 15 to 20 years. Ten of 41 participants in this trial had previously undergone thoracic sympathectomy, reflecting severe disease.

One study included only female participants (Rustin 1987); others included more female than male participants, reflecting the prevalence of RP in the population. Median age of participants was generally consistent, at between 20 and 40 years, with an overall range of 21 to 74 years.

The studies took place in different settings, including a laboratory setting for Sovijarvi 1984; a general practice for Jaffe 1980; and specialist outpatient clinics for seven studies (Caglayan 2012; Chung 2009; Ettinger 1984; Le Quentrec 1991; Rajagopalan 2003; Rustin 1987; Vayssairat 1996). Two multicenter studies included a combination of universities and hospital clinical settings (NCT01090492; Vayssairat 1996). The setting was not described in five trials (Challenor 1991; Madsen 1984; Nahir 1986; Teh 1995; Van de Wal 1987).

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All trials were conducted during the winter, and one was conducted from winter to early spring (Chung 2009). The prevalence of smoking was reported by most study authors and varied between 5% and 53%. Two studies included active smoking as an exclusion criterion (NCT01090492; Rajagopalan 2003). Studies differed in their details and descriptions of exclusion criteria.

Interventions

See additional Table 2 and Table 3.

Among the studies, seven classes of drugs that cause vasodilation were represented: ACE inhibitors, selective serotonin reuptake inhibitors, nitrates/nitrate derivatives, phosphodiesterase-5 inhibitors, prostacyclin/prostanoids, alpha blockers, and thromboxane synthase inhibitors. Table 1 presents classifications of drugs with vasodilator effects from the Australian Medicines Handbook. Thromboxane synthase inhibitors were included in this study, although they are not included in Table 1 . Two trials involved captopril (Madsen 1984; Rustin 1987), and four involved glyceryl trinitrate (GTN) (Chung 2009; Nahir 1986; Sovijarvi 1984; Teh 1995), one of which involved MQX-503, a novel vehicle for delivery (Chung 2009). The rest were single trials on each of the following: beraprost (Vayssairat 1996), buflomedil (Le Quentrec 1991), cilostazol (Rajagopalan 2003), dazoxiben (Ettinger 1984), enalapril (Challenor 1991), ketanserin (Van de Wal 1987), PF-00489791 (NCT01090492), moxisylyte (Jaffe 1980), and vardenafil (Caglayan 2012).

Twelve studies compared the drug with a single placebo (Caglayan 2012; Challenor 1991; Chung 2009; Jaffe 1980; Le Quentrec 1991; Madsen 1984; Nahir 1986; NCT01090492; Rajagopalan 2003; Rustin 1987; Van de Wal 1987; Vayssairat 1996). Sovijarvi 1984 compared GTN against two sets of placebo. Ettinger 1984 compared dazoxiben and a calcium channel blocker as single and combined agents against placebo. Calcium channel blocker data have been excluded from this review. Five studies tested topical agents (Chung 2009; NCT01090492; Nahir 1986; Sovijarvi 1984; Teh 1995), and the remaining 10 assessed oral medications (Caglayan 2012; Challenor 1991; Ettinger 1984; Jaffe 1980; Le Quentrec 1991; Madsen 1984; Rajagopalan 2003; Rustin 1987; Van de Wal 1987; Vayssairat 1996)

Length of studies

Lengths of treatment in studies varied from weeks to months, with the longest lasting six months (Le Quentrec 1991). Teh 1995 and Sovijarvi 1984 had a one-week run-in period before the start of the study, Van de Wal 1987 had a run-in period of four weeks. Four studies had two-week run-in periods (Chung 2009; Ettinger 1984; Rustin 1987; Vayssairat 1996). Four studies had no run-in period (Challenor 1991; Jaffe 1980; Le Quentrec 1991; Madsen 1984). For some cross-over studies, one-week washout periods were utilized (Caglayan 2012; Ettinger 1984; Nahir 1986). All studies were double-blind during the active treatment phase, except Chung 2009, which was triple-blinded according to obtained trial data. Caglayan 2012 had an extra four-week follow-up period, Chung 2009 had a one-week follow-up, and Van de Wal 1987 had a 12-week long-term follow-up.

Outcomes

Subjective measurements were reported by all studies except Sovijarvi 1984. These measures included documentation by participants regarding frequency of attack in Madsen 1984 and dual reporting of frequency and severity in other studies (Challenor 1991; Jaffe 1980; Le Quentrec 1991; Nahir 1986; Rajagopalan 2003; Teh 1995; Vayssairat 1996). Visual analogue scale (VAS) scores were also reported (Challenor 1991), as was the Raynaud Condition Score (RCS) (Caglayan 2012; Chung 2009). Despite measuring the same outcomes, scales used between different studies varied substantially. Number of attacks was measured as episodes per day (Challenor 1991; Le Quentrec 1991), as daily mean (Madsen 1984), as the mean of attacks at completion of the study (Rajagopalan 2003), or simply as dichotomous outcomes (Jaffe 1980; Nahir 1986). Severity of attacks lacked any standardization between chosen numerical scales (Challenor 1991; Le Quentrec 1991; Rajagopalan 2003; Teh 1995, Vayssairat 1996), or dichotomous outcomes were reported (Nahir 1986). Duration of attacks was measured by Chung 2009 Jaffe 1980 NCT01090492 Rustin 1987, and Van de Wal 1987. Teh 1995 was the only study that provided a quality of life score.

Objective measures used included Doppler evaluation/capillaroscopy rheographic evaluation of blood flow (Sovijarvi 1984). Rajagopalan 2003 and Rustin 1987 used laser Doppler flowmetry to measure blood flow. Rustin 1987 used digit II and expressed the result in volts, Rajagopalan 2003 used digit III and expressed flow as the peak perfusion ratio. Sovijarvi 1984 and Van de Wal 1987 measured digital systolic blood pressure (mmHg) by venous occlusion plethysmography of digit II. Van de Wal 1987 also used digit IV (we report results for digit II). Adverse events were recorded in all trials.

Excluded studies

We excluded 22 new studies for this update (Allegra 1983; Arcas Meca 1972; Barry 2000; Belch 1985; Bellucci 1987; Belluci 1990; Brotzu 1989; Clement 1980; Diehm 1983; Fischer 1985; JaniniDa 1988; Jenkins 2013; Kingma 1995; Kirichenko 1991; Lee 2014; McFadyen 1973; Mirza 2019; NCT00419419; NCT0048776; Roustit 2017; Strozzi 1982; Surwit 1982). In total, we excluded 59 full-text studies. See Characteristics of excluded studies.

Six studies were excluded because participants did not meet the inclusion criteria, mainly due to a prior diagnosis of secondary Raynaud's phenomenon (Belch 1995; Kirichenko 1991; Lee 2014; Marasini 2004; Surwit 1982; Torley 1990). One study was excluded as the population group was not clearly defined (Clement 1986). Five studies were excluded as a single dose of medication was administered only once (Courbier 1981; McFadyen 1973; Mohrland 1985; Tucker 1999; Wesseling 1981). Two studies were excluded for use of a single dose of treatment (Seibold 1986; Shawket 1991). Five studies described intervention or medications that was not within the scope of this review, such as use of calcium channel blockers, and were excluded (Allegra 1983; Brotzu 1989; Dumoulin 1981; Dziadzio 1999b; Sunderland 1988). Many of the studies that were excluded included fewer than 10 participants with primary Raynaud's phenomenon. Moreover, multiple studies also had more than one reason for exclusion.

Thirty-two studies were excluded because we were unable to extract the data specific for primary Raynaud's participants (Arcas Meca 1972; Arosio 1989; Bali 2011; Barry 2000; Belch 1983; Belch 1985; Bellucci 1987; Clement 1980; Coffman 1989; Coleiro 2001b; Courbier 1981; Davinroy 1993; Diehm 1983; Fischer 1985; Friedman 2007; JaniniDa 1988; Jenkins 2013; Kahan 1985; Kingma 1995; Kyle 1992; Longstaff 1985; Luderer 1984; Marasini 1988; Maurel 1995; Mirza 2019; NCT00419419; Nilsen 1979; Roustit 2017; Russell 1985;

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Strozzi 1982; Tooke 1990; Wollersheim 1986). This was mainly due to presentation of combined results for all participants and we were not able to clearly differentiate between participants with primary and secondary Raynaud's phenomenon. Grigg 1989a was excluded for including an outcome measurement that was not within the defined primary or secondary outcomes.

In the previous version of the review, Cleophas 1984 was excluded because some participants with primary Raynaud's tested positive for anti-nuclear antibodies (ANAs). We revised the reason for exclusion for Cleophas 1984 to the use of a beta blocker as a comparator, lack of a placebo group, and no subgroup analysis.

The following classes of drugs or single drugs were not represented in the included studies as the study design did not meet inclusion criteria: angiotensin-II receptor antagonists, antihistamines, botulinum toxin, bradilan, CL115,347 (Cyanamid International), debrisoquine, guanethidine, pentoxifylline, reserpine, and suloctidil (see additional Table 2 and Table 3). Some medications are not mentioned in Table 1, as this is not an exhaustive list of medications with any vasodilatory effect. This was done to ensure that the results discussed and analyzed were specific to vasodilators.

Two new ongoing studies were identified for this update (EUCTR2005-000295-41-DE; NCT02583789; see Ongoing studies). One study was assessed as awaiting classification (Sakaguchi 1990; see Studies awaiting classification).

Risk of bias in included studies

See Figure 2 and Figure 3 for details on risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

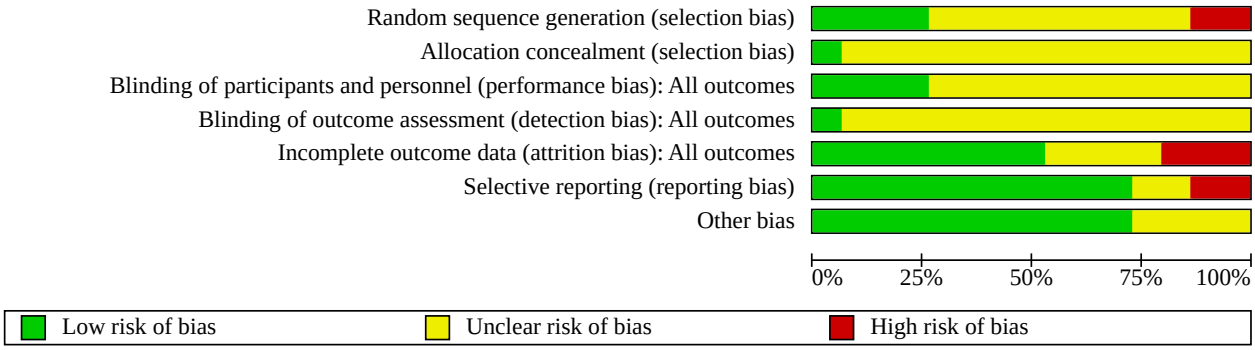

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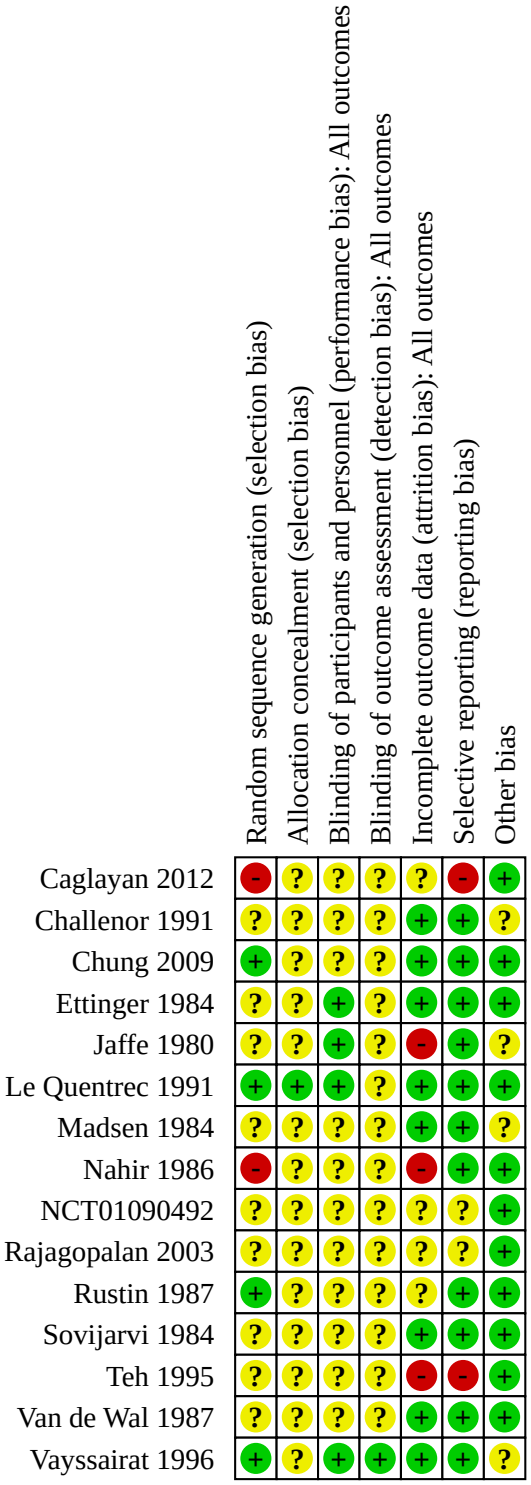
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

Four of the 15 studies included in this review reported their random sequence generation methods appropriately and were found to have low risk (Chung 2009; Le Quentrec 1991; Rustin 1987; Vayssairat 1996). One study utilized a random number system (Rustin 1987), and three used a randomization table (Chung 2009; Le Quentrec 1991; Vayssairat 1996). The remainder of the studies had unclear risk of bias regarding how their sequences were generated, as they failed to disclose their methods of randomization. The supplementary data supplied by Caglayan 2012 described a form of constrained randomization utilizing permuted blocks of lengths four and six that were computer-generated, sex-stratified and in pseudo-random sequence; given the binary nature of the stratification, this study was deemed to be at high risk of bias. With regard to allocation concealment; one of the 15 studies clearly and adequately described its methods and was deemed to be at low risk of bias (Le Quentrec 1991). Chung 2009 did not publish its study methods but instead included them publicly online in NCT00266669 2005 risk of bias was assessed based on this information. Nahir 1986 included a purely female population, resulting in high risk of bias. For the remainder of the included studies, no information was stated or could be elicited regarding how allocation was concealed. This lack of disclosure led to the remainder of studies holding unclear risk with regard to bias.

Blinding

Performance bias

Regarding blinding of participants and personnel, four studies were deemed to have low risk of bias because they were blinded with identical or matching placebo (Ettinger 1984; Jaffe 1980; Le Quentrec 1991; Vayssairat 1996). Other studies failed to specify how double-blinding was achieved, risking interviewer bias (Challenor 1991; Chung 2009; Caglayan 2012; Madsen 1984; NCT01090492; Nahir 1986; Rajagopalan 2003; Rustin 1987; Sovijarvi 1984; Teh 1995; Van de Wal 1987), resulting in a risk rating of "unclear." Madsen 1984 further failed to mention the frequency of evaluation with its interviewers.

Detection bias

One study appropriately identified the measures through which their outcome assessment remained blinded (Vayssairat 1996). The remaining studies were deemed to have unclear risk for the following reasons. Self-reported outcome measures performed by the participants of six studies were used to collate data (Chung 2009; Ettinger 1984; Jaffe 1980; Nahir 1986; Vayssairat 1996; Teh 1995). Self-reporting carries unavoidable bias given its subjective nature. Some studies attempted to control this risk of bias by asking participants to record quantitative measures such as number of attacks and by setting the precedent for these recordings to occur daily (Challenor 1991; Madsen 1984; Rustin 1987). However, it cannot be clarified whether all participants accurately recorded the number of attacks regularly, without consideration of other influencing variables that may have compounded on their compliance with instructions. Similarly, it was found that within Jaffe 1980, many participants were unable to quantify the severity of their symptoms appropriately and accurately.

Most of the included studies failed to disclose, if mentioned, how outcomes and statisticians were blinded, especially with respect to studies that utilized physical examination at the screening and completion phases of treatment (Caglayan 2012; Challenor 1991; Madsen 1984; NCT01090492; Rajagopalan 2003; Rustin 1987; Sovijarvi 1984; Teh 1995; Van de Wal 1987). Consequently, we were unable to confidently assess the level of bias they presented - leaving this as unclear. Ettinger 1984 Jaffe 1980 Le Quentrec 1991, and Nahir 1986 did not indicate that their assessors were blinded, and so were assessed as unclear.

Incomplete outcome data

Eight included studies were at low risk of attrition bias, with all participants accounted for in the results and the significance of dropouts addressed (Challenor 1991; Chung 2009; Ettinger 1984; Le Quentrec 1991; Madsen 1984; Sovijarvi 1984; Van de Wal 1987; Vayssairat 1996). Two studies showed unclear risk of bias (Rajagopalan 2003; Rustin 1987), with unclear significance of dropouts for data projection and unclear formulation of results. Caglayan 2012 did not present dropout rate, although serious adverse events were noted, which suggested unclear risk of bias. NCT01090492 did not specify any incomplete outcome data within the online published study, also resulting in unclear attrition bias. The risk of attrition bias was considered high in Jaffe 1980, as five participants were excluded from the analysis for objectively atypical reasons - two for not having experienced attacks of Raynaud's phenomenon during the trial, and a further three for experiencing adverse events whilst on placebo. Teh 1995 failed to provide discrete numerical values within its results section, resulting in analytical inadequacies throughout the presented data. Of 21 participants, two were excluded following incomplete data collection, and two others following unspecified adverse events related to the GTN. Although participant withdrawals were discussed, these participants were not included in the statistical analysis, and there was no discussion regarding the impact the withdrawals may have had on study data. We judged this study to be at high risk of bias. Nahir 1986 also had high risk of attrition bias, as there were three withdrawals from a comparatively small study size. Two participants withdrew from the treatment group due to headaches/dizziness, and one participant with recurrent dermatitis withdrew from an unspecified group.

Selective reporting

Eleven studies accounted for all pre-specified outcome measures in their results, resulting in assignment of low risk of selective reporting bias (Challenor 1991; Chung 2009; Ettinger 1984; Jaffe 1980; Le Quentrec 1991; Madsen 1984; Nahir 1986; Rustin 1987; Sovijarvi 1984; Van de Wal 1987; Vayssairat 1996). NCT01090492 and Rajagopalan 2003 presented unclear risk with regard to reporting bias, as they failed to specify details regarding participant dropout and completion of data collection. Furthermore, Rajagopalan 2003 failed to define the number of participants in the control and intervention groups when reporting outcomes. However, based on means and standard deviations, we calculated the number of participants in each group and thus included this study in the meta-analysis. Caglayan 2012 was deemed at high risk of subgroup analysis for performance of analysis only for its RCS group and not for the digital blood flow subsection. The website used to present study inclusion criteria was unavailable for checking the variable and invariable characteristics of participants against the final data. Teh 1995 was also deemed at high risk of reporting bias, as the means by which outcomes were reported varied throughout the results, thus allowing for bias through data reporting. Furthermore, participants were excluded from aspects of results formulation

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if their diary entries were considered "poor." Le Quentrec 1991 was rated as low risk, as all pre-specified outcome measures were accounted for in the results, despite lack of clarification of criteria.

Other potential sources of bias

Eleven studies were at low risk of other potential sources of bias (Caglayan 2012; Chung 2009; Ettinger 1984; Le Quentrec 1991; Nahir 1986; NCT01090492; Rajagopalan 2003; Rustin 1987; Sovijarvi 1984; Teh 1995; Van de Wal 1987). Three studies were assessed as being at unclear risk of other bias because they were cross-over studies, and although it is unlikely that the drugs had carry-over effects, information detailing effects or how appropriate washout times were achieved was lacking (Challenor 1991; Jaffe 1980; Madsen 1984). Vayssairat 1996 was assessed as being at unclear risk, as study groups did not meet the size calculation.

Effects of interventions

See: **Summary of findings 1** Angiotensin-converting enzyme inhibitors compared to placebo for primary Raynaud's phenomenon; **Summary of findings 2** Alpha blockers compared to placebo for primary Raynaud's phenomenon; **Summary of findings 3** Prostagladin/prostacyclin analogues compared to placebo for primary Raynaud's phenomenon; **Summary of findings 4** Thromboxane synthase inhibitors compared to placebo for primary Raynaud's phenomenon; **Summary of findings 5** Selective serotonin reuptake inhibitors compared to placebo for primary Raynaud's phenomenon; **Summary of findings 6** Nitrate/nitrate derivatives compared to placebo for primary Raynaud's phenomenon; **Summary of findings 7** Phosphodiesterase inhibitors compared to placebo for primary Raynaud's phenomenon

The 15 included studies reported on 11 different vasodilators, using oral, non-oral, and topical administration. We were not always able to carry out meta-analysis due to limited data or to clinical and methodological differences. We have presented the results by drug class and by drug separately below.

Angiotensin-converting enzyme (ACE) inhibitors

(Captopril [ATC code C09AA01] and enalapril [ATC code C09AA02], ACE inhibitors, plain)

Three cross-over studies including two studies comparing captopril 25 mg three times daily - Madsen 1984; Rustin 1987 - and enalapril 20 mg once daily - Challenor 1991 - with placebo were included. All of the 46 included participants had primary Raynaud's phenomenon (RP). The duration for all captopril trials was two periods of six weeks and for the enalapril trial two periods of four weeks. See Summary of findings 1.

Frequency of attacks

For the meta-analysis of the ACE inhibitors captopril and enalapril, frequency of attacks may be increased with treatment (mean difference [MD] 0.79, 95% confidence interval [CI] 0.43 to 1.16; 44 participants, 3 studies; low-certainty evidence; see Analysis 1.1).

Subgroup analysis revealed no clear differences in frequency of attacks between captopril and placebo groups (MD 0.72, 95% CI -1.73 to 3.16; 2 studies; low-certainty evidence). Enalapril alone was associated with a small increase in the frequency of attacks per week (Challenor 1991). The difference in the mean number of attacks per week was 0.80 (95% CI 0.43 to 1.17; 20 participants, 1 study; low-certainty evidence; see Analysis 1.1), favouring placebo. Thirteen of 20 participants experienced more attacks on enalapril than on placebo. No differences between subgroups was detected by the subgroup test (P = 0.94). A random-effects model was used because captopril and enalapril belong to the same class of drugs but have different pharmacological properties, and the duration of treatment periods was unequal (DerSimonian 1986). Although there was similarity among participants in the two captopril trials, as well as in dose, length of treatment, and lack of a washout period, heterogeneity was high (Madsen 1984; Rustin 1987).

Severity of attacks

Challenor 1991 and Rustin 1987 reported on severity. No evidence suggested a difference in the severity of attacks between ACE inhibitors and placebo (MD -0.17, 95% CI -4.66 to 4.31; 34 participants, 2 studies; low-certainty evidence; see Analysis 1.2). No differences between subgroups were detected with the subgroup test (P = 0.69).

Duration of attacks

Only Rustin 1987 reported on this; captopril did not appear to make any clear difference in duration of attacks (MD 0.54, 95% CI -1.34 to 2.42; 14 participants, 1 study; low-certainty evidence; see Analysis 1.3). Rustin 1987 did not stipulate units of attack duration, but "minutes" seemed most likely and was assumed.

Capillaroscopic flow/skin perfusion

Only Rustin 1987 reported on this, describing no clear changes in capillaroscopic flow following treatment (MD 0.19, 95% CI -0.05 to 0.42; 13 participants, 1 study; low-certainty evidence; see Analysis 1.4). These findings were imprecise.

Subjective assessment of improvement

Only Challenor 1991 reported on this outcome. When enalapril treatment was compared with placebo, an increased subjective assessment of improvement may be detected in the placebo group (10-cm visual analogue scale) (MD 1.10, 95% CI 0.32 to 1.88; 1 study; low-certainty evidence; see Analysis 1.5).

Adverse events

One individual from the Rustin 1987 trial, which featured captopril, withdrew due to pregnancy, and one participant withdrew from the Challenor 1991 trial, which involved enalapril. The withdrawal in the enalapril study was done for personal reasons and was deemed unrelated to treatment by study authors. No side effects were reported in the Rustin 1987 trial. Madsen 1984 reported one participant with nausea the first week and one with pain in the calf muscle during the whole intervention period in the captopril group, and no side effects in the placebo group. In the Challenor 1991 trial, nine participants receiving enalapril and eight participants receiving placebo reported side effects. Dizziness was most commonly reported, but all side effects were transient. Pooling of data revealed no clear evidence of a difference in adverse events between treatment and placebo groups (risk ratio [RR] 1.35, 95% CI 0.67 to 2.73; 46 participants, 3 studies; low-certainty evidence; see Analysis 1.6). No differences between subgroups were detected with the subgroup test (P = 0.33).

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Raynaud Condition Score

No study reported on the Raynaud Condition Score.

Alpha blockers

(Buflomedil [ATC code C04AX20] and moxisylyte [thymoxamine] [ATC code C04AX10])

Two studies used alpha blockers. One study included in this update investigated buflomedil (Le Quentrec 1991). It involved 31 participants with primary RP and compared buflomedil 300 mg twice daily with placebo in a parallel study design. We used outcomes measured at six months; this study reported outcomes also at two months and at four months. The second study compared moxisylyte 40 mg four times daily with placebo (Jaffe 1980). This study initially included 41 participants, all with primary RP, and 33 individuals completed the study. Participants did not complete the study for various reasons. This study had a cross-over design; each treatment period lasted two weeks. See Summary of findings 2.

Frequency of attacks

We were not able to combine the data in a meta-analysis, as data were presented as number of attacks (dichotomous) in Jaffe 1980 and as difference in frequency in Le Quentrec 1991 (continuous).

In Le Quentrec 1991, the frequency of attacks per week was probably reduced with buflomedil treatment (MD -8.82, 95% CI -11.04 to -6.60; 31 participants, 1 study; moderate-certainty evidence; see Analysis 2.1). Baseline frequency was 24 attacks per week in both intervention groups.

In Jaffe 1980, 33 participants with primary RP completed both treatment arms for the outcome "frequency of attacks." Nineteen participants had fewer attacks during the moxisylyte period, and 10 during the placebo period. Four participants had an equal number of attacks in each period. More participants on moxisylyte experienced less frequent attacks (P < 0.02; Wilcoxon matched pair signed rank test), as reported by study authors.

Severity of attacks

Both studies reported on severity of attacks, but we were unable to carry out a meta-analysis, as they used different methods to present the data.

Le Quentrec 1991 results indicate that the severity of attacks was slightly reduced with buflomedil treatment (MD -0.41, 95% CI -0.52 to -0.30; 31 participants, 1 study; moderate-certainty evidence; see Analysis 2.2).

In Jaffe 1980, only 25 participants were able to quantify the severity of the attacks - study authors reported that not all participants were able to quantify the severity of attacks in a meaningful way. Out of these 25 participants, 7 participants reported more severe attacks during the moxisylyte period and 18 reported more severe attacks during the placebo period. More participants had more severe attacks during placebo treatment (P < 0.01), as reported by study authors. The remaining participants were unchanged or had less severe attacks.

Duration of attacks

Only Jaffe 1980 reported on duration of attacks. Fifteen participants recorded shorter total duration of attacks while on moxisylyte, and nine had shorter duration of attacks while on placebo (P > 0.01), as reported by study authors.

Adverse events

Le Quentrec 1991 reported no withdrawals from the trial. No evidence of a difference in adverse events was noted between the buflomedil and placebo groups (RR 1.41, 95% CI 0.27 to 7.28; 31 participants, 1 study; moderate-certainty evidence; see Analysis 2.3). Two side effects were reported in the placebo group (gastric upset) and three in the buflomedil group (gastric burning, vertigo, hot flush). Study authors reported that side effects disappeared spontaneously with neither modification nor withdrawal of treatment.

In Jaffe 1980, one participant was withdrawn from the treatment phase because of an embolus deemed by trial authors not to be drug related, and three participants were withdrawn from the placebo phase because of side effects. A total of 13 participants during the moxisylyte phase and three during the placebo phase reported adverse events. Adverse events may be more frequent in the moxisylyte group (Analysis 2.3). Dyspepsia, heartburn, flushing, and changes in taste were reported by two or more participants in the treatment group and by none in the placebo group. No differences between subgroups were detected with the subgroup test (P = 0.28), as reported by study authors.

Neither study reported on the remaining outcomes of interest (quality of life scores, Raynaud Condition Score, or capillaroscopic flow/skin perfusion).

Prostaglandin/prostacyclin analogues

(Beraprost [ATC code B01AC19]; platelet aggregation inhibitors excluding heparin; prostacyclin analogue)

One study investigated the use of prostacyclin analogues (Vayssairat 1996). This study included 125 participants with primary RP in a parallel design and compared beraprost 40 µg three times daily with placebo. We used the phase 3 results as reported by trial authors. See Summary of findings 3.

Frequency of attacks

Vayssairat 1996 found that the reduction of attacks from baseline was 44% in the placebo group and 37% in the beraprost group. There was no clear difference in the number of attacks per week in the beraprost group compared to the placebo group compared to the baseline values of 11 to 12 attacks per week (MD 2.0, 95% CI -0.35 to 4.35; 118 participants, 1 study; low-certainty evidence; see Analysis 3.1).

Severity of attacks

Neither severity of attacks (measured on a 1 to 4-point scale) nor disability score (measured on a 100-mm visual analogue scale) was found to be clearly different between the beraprost group and the placebo group (MD -0.06, 95% CI -0.34 to 0.22; 118 participants, 1 study; low-certainty evidence; see Analysis 3.2; and MD 3.00, 95% CI -7.48 to 13.48; 118 participants, 1 study; see Analysis 3.3, respectively). Both results had a wide confidence interval, reflecting poor precision.

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Adverse events

In total, 16 participants withdrew from the study - nine from the beraprost group and seven from the placebo group. Of these withdrawals, four from the beraprost group and three from the placebo group were reported to be due to side effects. Overall, more side effects were noted in the beraprost group (34/63) compared to the placebo group (21/62) (RR 1.59, 95% CI 1.05 to 2.42; 125 participants, 1 study; low-certainty evidence; see Analysis 3.4). Headache was reported by 16 of 63 in the treatment group and by 1 of 62 in the placebo group. Two participants in each group were noted to have elevation in liver transaminases.

This study did not report on the remaining outcomes of interest (duration of attacks, quality of life scores, Raynaud Condition Score, or capillaroscopic flow/skin perfusion).

Thromboxane synthase inhibitors

(Dazoxiben, thromboxane synthase inhibitor [no ATC code])

One included study used the thromboxane synthase inhibitor dazoxiben in a cross-over design involving 25 participants, six of whom had primary RP (Ettinger 1984). This trial compared dazoxiben 100 mg four times daily with nifedipine or placebo. Data from the nifedipine arm were not included. One participant with primary RP was withdrawn due to poor compliance. See Summary of findings 4.

Frequency of attacks

Results show no evidence of an effect of dazoxiben compared with placebo. The mean frequency of attacks per week during intervention was 12.0 ± 6.02 (SD) in the dazoxiben group and 11.2 ± 8.11 (SD) in the placebo group (MD 0.80, 95% CI -1.81 to 3.41; 6 participants, 1 study; very low-certainty evidence; see Analysis 4.1).

Adverse events

Adverse events were not reported in the subgroup analysis of participants with primary RP. This study did not report on the remaining outcomes of interest (duration of attacks, severity of attacks; quality of life scores, Raynaud Condition Score, or capillaroscopic flow/skin perfusion).

Selective serotonin reuptake inhibitors

(Ketanserin [ATC code C02KD01], other antihypertensives, serotonin antagonists)

One included study used ketanserin (Van de Wal 1987). This was a cross-over trial comparing ketanserin 40 mg twice daily with placebo. In all, 41 participants with primary RP were included, and each treatment period duration was four weeks. See Summary of findings 5.

Frequency of attacks

Baseline average frequency of attacks was reported to be 12 times a day. The average frequency of attacks observed with ketanserin treatment was 56 times per week versus 70 times per week in the placebo group, with SE of 7. There may be a slight reduction in the number of attacks per week in the ketanserin group compared to the placebo group (MD -14.0, 95% CI -27.72 to -0.28; 41 participants, 1 study; very low-certainty evidence; see Analysis 5.1).

Severity score and subjective assessment

Severity scores were calculated by multiplying the average frequency per day by the average duration of attacks. The severity score may be reduced after ketanserin treatment compared to placebo (MD -133.00, 95% CI -162.40 to -103.60; 41 participants, 1 study; very low-certainty evidence; see Analysis 5.2). A subjective assessment was also performed, with 24 participants reporting improvement in symptoms after ketanserin treatment and 14 after placebo. Later in the treatment program, 29 participants reported general improvement, and 22 of these individuals reported further improvement at the end of long-term treatment with ketanserin.

Duration of attacks

There was no clear difference in the duration of attacks following ketanserin or placebo use (MD -4.00, 95% CI -14.82 to 6.82; 41 participants, 1 study; very low-certainty evidence; see Analysis 5.3). Symptoms lasted approximately 50 minutes. Following treatment, the duration of these attacks lasted on average 28 minutes with both ketanserin and placebo, and both groups had an SE of six.

Capillaroscopic flow/skin perfusion

There was no clear difference between groups in digital blood flow of the second finger with treatment of 3 mmHg (MD 3.00, 95% CI -3.93 to 9.93; 41 participants, 1 study; very low-certainty evidence; see Analysis 5.4).

Adverse events

Two participants withdrew from the study: one for causes unspecified, the other for non-medical reasons. Twenty participants in the ketanserin group and 13 in the placebo group reported adverse events (RR 1.54, 95% CI 0.89 to 2.66; 41 participants, 1 study; very low-certainty evidence; see Analysis 5.5). Headache, dry mouth, and dizziness were reported more frequently in the treatment group. This study did not report on the remaining outcomes of interest (QoL score and Raynaud Condition Score).

Nitrate/nitrate derivatives

(Organic nitrates [ATC code C01DA02])

Four studies used topical treatments of nitroglycerin or glyceryl trinitrate (GTN) (Chung 2009; Nahir 1986; Sovijarvi 1984; Teh 1995). Chung 2009 conducted a two-week single-blind run-in followed by a four-week double-blind treatment phase. This study was a randomized, parallel, vehicle-controlled trial. The active agent was topical 0.9% nitroglycerin in the novel vehicle called MQX-503. Participants with primary RP included 32 of 111 in the treatment group and 37 of 108 in the placebo group. Participants were given electronic diaries to record frequency, duration, and severity of attacks and adverse experiences. They completed health assessment questionnaires (HAQs) and physicians completed global assessment questionnaires (GAQs) at each visit. Nahir 1986 studied 18 participants, seven with primary RP, with a double-blind cross-over design comparing Nitroderm TTS 5 mg against placebo. Participants kept a daily record of frequency and severity of attacks. Results were reported dichotomously as positive or negative responses. Sovijarvi 1984 conducted a trial on eight participants using 12.5 mg nitroglycerin versus placebo in a double-blind cross-over design. This study had a one-week single-blind run-in period and continued as a randomized double-blind cross-over for two weeks. Participants kept daily diary records of frequency, severity,

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and duration of attacks. During the four visits of the trial, digital blood pressure responses to different temperatures were recorded. Teh 1995 recruited 42 participants including 21 with primary RP. Seventeen participants completed the trial; according to study authors, two individuals were excluded due to incomplete data of subjective assessment and two withdrew during the GTN treatment period due to side effects such as headache and nausea. After a one-week washout period, participants were randomized to GTN 0.2 mg/hr or placebo patches for seven days. Outcomes recorded were frequency and severity of attacks. VAS was recorded at baseline and at the end of treatment. Severity of attacks was numerically scored from 0 to 3 (nil to severe). All participants had thermography recording post patches at room temperature and post cold challenge.

It was not possible to combine all data, as not all studies reported on the same outcomes, and when they did, types of data were limited. None of the studies reported quality of life scores for participants with primary Raynaud's phenomenon. See Summary of findings 6.

Frequency of attacks

We were able to combine two studies in a meta-analysis of frequency of attacks (Chung 2009; Teh 1995). We noted no clear overall difference in frequency between treatment and placebo groups (MD -1.57, 95% CI -4.31 to 1.17; 86 participants, 2 studies; very low-certainty evidence; see Analysis 6.1).

In Nahir 1986, six participants reported response to Nitroderm compared to one in the placebo group.

Sovijarvi 1984 authors reported lack of differences between GTN and placebo treatments in the frequency of RP attacks without providing data.

Severity of attacks

In Teh 1995, overall severity of attacks (numbness, pain, and colour change) was reduced in the treatment group (MD -4.25, 95% CI -5.71 to -2.79; 17 participants, 1 study; very low-certainty evidence; see Analysis 6.2), but the clinical relevance of this result is not clear, as there is no severity correlation for these numbers. VAS scoring was no different between groups.

In Nahir 1986, decreased severity on VAS by 2 cm was reported as a positive. Five participants reported a positive result compared to one in the placebo group.

Chung 2009 reported both participant- and physician-reported that VAS scores at the target week were similar to baseline but did not report the recorded data within the article.

Sovijarvi 1984 did not report on severity of attacks.

Duration of attacks

Both Chung 2009 and Sovijarvi 1984 reported this outcome. Sovijarvi 1984 authors reported lack of differences between GTN and placebo treatments in duration of RP symptoms without providing data. Chung 2009 reported no significant difference (P > 0.2) in the duration of attacks at baseline (28.8 ± 12.9 minutes, intervention; 29.8 ± 13.6 minutes, placebo), with no significant decrease in the duration of attacks.

Capillaroscopic flow/skin perfusion

In Sovijarvi 1984, digital blood pressure analysis did not reveal any clear effect compared to placebo (MD 15.60, 95% CI -2.54 to 33.74; 8 participants, 1 study; see Analysis 6.3).

Teh 1995 reported no statistical differences in thermography results; however, no numerical data were provided by study authors to corroborate this statement.

Adverse events

In Chung 2009 and Nahir 1986, the numbers of adverse events were not reported separately for participants with primary Raynaud's phenomenon.

In Sovijarvi 1984, all eight participants reported headaches with nitroglycerin; four graded symptoms as severe.

In Teh 1995, two out of 21 participants with primary RP withdrew due to adverse events.

Raynaud Condition Score

Whilst Chung 2009 included participants with both primary and secondary RP, a subgroup analysis of the Raynaud Condition Score among those with primary RP was performed by study authors. This did not show clear evidence of a difference following GTN treatment (MD -0.36, 95% CI -0.98 to 0.26; 69 participants, 1 study; low-certainty evidence; see Analysis 6.4).

None of the studies reported on quality of life.

Phosphodiesterase inhibitors

(Cilostazol [ATC Code B01AC23], platelet aggregation inhibitors excluding heparin; vardenafil [ATC Code G04BE09], drugs used in erectile dysfunction; PF-00489791, used only in trials).

Three studies assessed the efficacy of phosphodiesterase inhibitors for improving symptoms of individuals with RP (Caglayan 2012; NCT01090492; Rajagopalan 2003). These compared vardenafil (Caglayan 2012), cilostazol (Rajagopalan 2003), and PF-00489791 (NCT01090492), with an equivalent placebo. Two studies were cross-over trials (Caglayan 2012; NCT01090492), and one used a parallel design (Rajagopalan 2003). In all studies, there was a mixture of primary and secondary RP. Caglayan 2012 was a two-period cross-over study conducted for six weeks to assess 10 mg vardenafil twice daily versus placebo. Treatments were switched following a one-week washout phase and a follow-up phase up to four weeks after last drug intake. Of 53 participants included in the study, six had primary RP. In Rajagopalan 2003, individuals were randomized to cilostazol 100 mg twice daily for six weeks or placebo in a double-blind format. Forty participants completed the study - 19 with primary RP. Initially, 45 individuals were screened, and two participants withdrew due to pregnancy and severe respiratory disease. Three participants who were randomly assigned to cilostazol withdrew before completion due to severe headaches. NCT01090492 measured the effects of the phosphodiesterase inhibitor, PF-00489791 versus placebo. This study included 243 participants with primary or secondary RP. A total of 113 participants fulfilled the criteria for primary RP. Either 4 mg or 20 mg of PF-00489791 was provided once daily for the first four-week cross-over period followed by placebo once daily for the second four-week cross-over period. A washout period of two

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weeks occurred between intervention periods, during which two placebo tablets matched to PF-00489791 were given orally once daily. We report outcomes for the 20-mg dose. See Summary of findings 7.

Frequency of attacks

Two studies reported on this outcome, with different effects. We combined the data in a meta-analysis (NCT01090492; Rajagopalan 2003). Overall, there was no clear reduction in the number of attacks per week (standardized mean difference [SMD] -0.05, 95% CI -6.71 to 6.61; 111 participants, 2 studies; low-certainty evidence; see Analysis 7.1). A random-effects analysis was used due to the different measures utilized in these studies and due to the high degree of heterogeneity (95%).

In Rajagopalan 2003, compared to placebo, cilostazol showed an increase in the frequency of attacks per week (MD 3.50, 95% CI 0.64 to 6.36; 38 participants; see Analysis 7.1). In NCT01090492, 20 mg PF-00489791 resulted in a reduction in the frequency of Raynaud attacks compared to placebo (MD -3.30, 95% CI -3.92 to -2.68; 73 participants; see Analysis 7.1).

Severity of attacks

Two studies reported on this outcome and showed inconsistent results (NCT01090492; Rajagopalan 2003). We combined the data in a meta-analysis (NCT01090492; Rajagopalan 2003). There was no clear reduction in the severity of attacks per week (SMD -0.03, 95% CI -1.04 to 0.97; 111 participants, 2 studies; very low-certainty evidence; see Analysis 7.2). A difference was detected by the subgroup test for differences (P < 0.00001). A random-effects analysis was used due to the different measures utilized in these studies and due to the high degree of heterogeneity (96%).

In Rajagopalan 2003, compared to placebo, cilostazol was found to cause an increase in attack severity, measured on a 1 to 9-point scale per attack (SMD 0.50, 95% CI 0.09 to 0.91). In NCT01090492, severity scores as measured on an 11-point Likert scale were reduced in the treatment group (SMD -0.53, 95% CI -0.63 to -0.43).

Duration of attacks

Only NCT01090492 reported on duration of attacks and detected no clear differences (MD -1.60, 95% CI -7.51 to 4.31; 73 participants, 1 study; low-certainty evidence; see Analysis 7.3).

Capillaroscopic flow/skin perfusion

In Rajagopalan 2003, no clear changes in nitroglycerin-mediated dilation or microvascular flow indexes were detected between the two groups (MD 18.00, 95% CI -7.34 to 43.34; 38 participants, 1 study; low-certainty evidence; see Analysis 7.4).

Adverse events

In Caglayan 2012, the most common side effects included flushing, headache, dyspepsia, and dizziness among others. These were reported to be not specific to either group. Serious adverse events occurred in one individual receiving vardenafil; this was not related to the drug and resolved.

In Rajagopalan 2003, study authors reported that among those who completed the study, 35% of those on cilostazol complained of headaches; this was not reported in the placebo group. Two participants in the treatment group also complained of palpitations. Among both treatment and control groups, 10% reported gastrointestinal side effects such as diarrhea and nausea.

NCT01090492 reported that 34 out of 54 participants in the 20-mg treatment group and 43 out of 102 participants in the placebo group experienced adverse events, resulting in an RR of 1.49 (Analysis 7.5). Headache was the most commonly reported side effect, affecting 14 participants in the 20-mg treatment group and 9 in the placebo group.

Raynaud Condition Score

Two studies reported on RCS (Caglayan 2012; NCT01090492). A meta-analysis revealed no clear reduction (SMD -0.80, 95% CI -1.74 to 0.13; 79 participants, 2 studies; low-certainty evidence; see Analysis 7.6). A random-effects analysis was used due to the different measures used in these studies and due to the high degree of heterogeneity (52%). Testing for subgroup differences was performed (P = 0.15).

Caglayan 2012 reported subgroup data for primary RP. Among six individuals with primary RP, a small reduction in RCS was noted (MD -1.61, 95% CI -3.09 to -0.13; 6 participants). Study authors reported a long-term benefit of vardenafil, evidenced by lower RCS during the washout phase and in the second phase of the study among individuals who were initially assigned to vardenafil.

In NCT01090492, 20 mg PF-00489791 shows improved RCS (MD -0.52; 95% CI -0.60 to -0.44; 73 participants).

None of the studies reported on quality of life.

DISCUSSION

Summary of main results

This review summarizes the latest evidence for treatment of primary Raynaud's phenomenon (RP) using drugs with vasodilator effects excluding calcium channel blockers. Seven new studies were identified for this update. In total, 15 studies with 635 participants were included. The studies involved ten drugs from eight drug classes: angiotensin-converting enzyme (ACE) inhibitors, 5-HT2 receptor antagonists, nitrates/nitrate derivatives, phosphodiesterase inhibitors, prostacyclin analogues, alpha blockers, and thromboxane synthase inhibitors - all compared to placebo. Of the seven new studies, four investigated the use of glyceryl trinitrate (GTN) and three investigated the use of phosphodiesterase inhibitors. This update also aimed to include intravenous and topical formulations.

Angiotensin-converting enzyme (ACE) inhibitors

Three studies investigated the use of ACE inhibitors (Challenor 1991; Madsen 1984; Rustin 1987); these studies demonstrated that there may be a small increase in the frequency of attacks with treatment. They provided no evidence of a difference in severity of attacks, duration of attacks, or adverse events. Quality of life (QoL) and Raynaud Condition Score (RCS) were not reported. As Challenor 1991 was heavily weighted (95.6%) in the analysis, the overall result was similar to the result in Challenor 1991, despite heterogeneous outcomes in Madsen 1984 and Rustin 1987. See Summary of findings 1.

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Captopril alone did not improve frequency of attacks, severity of attacks, or duration of attacks, nor did it improve digital blood flow (Madsen 1984; Rustin 1987).

Enalapril alone is associated with a small increase in the frequency of attacks per week and worsening of subjective assessment of improvement on a 10-point scale (no clear difference in severity rating of attacks was noted) (Challenor 1991).

Alpha blockers

Two studies used alpha blockers. One study investigated buflomedil (Le Quentrec 1991), and one moxisylyte (Jaffe 1980). We were not able to combine the data in a meta-analysis because of how the results were presented. Buflomedil probably reduced the frequency of attacks per week compared to placebo. This effect was small but precise. Results showed a small improvement in severity scores between buflomedil and placebo (Le Quentrec 1991).

An effect in favor of moxisylyte compared with placebo was reported by study authors, along with numbers of participants experiencing fewer attacks ($P < 0.02$), less severe symptoms ($P < 0.01$), and attacks of shorter duration (). The study comprised a small number of participants, and the magnitude of the effect was not clear.

No evidence shows a difference in adverse events between buflomedil and placebo groups. More side effects were observed among participants in the moxisylyte group compared to the placebo group. See Summary of findings 2.

Prostaglandin/prostacyclin analogues

One study investigated the use of prostacyclin analogues, comparing beraprost with placebo (Vayssairat 1996). Results show no evidence of benefit of beraprost compared with placebo for frequency of attacks, severity of attacks, nor disability score (Vayssairat 1996). Overall, more side effects were noted in the beraprost group (34/64) compared to the placebo group (21/62). This study did not report on duration of attacks, quality of life (QoL), or Raynaud Condition Score (RCS). See Summary of findings 3.

Thromboxane synthase inhibitors

One included study compared the thromboxane synthase inhibitor dazoxiben versus placebo (Ettinger 1984). Results show no evidence of beneficial effects of dazoxiben compared with placebo for frequency of attacks. Adverse events were not reported in the subgroup analysis of participants with primary RP, and the study did not report on duration of attacks, severity of attacks, QoL, or RCS. See Summary of findings 4.

Selective serotonin reuptake inhibitors

One included study compared ketanserin with placebo (Van de Wal 1987). There may be a slight reduction in the number of attacks per week with ketanserin compared to placebo. Similarly, the severity score may be slightly reduced after ketanserin treatment. No evidence suggests that ketanserin reduced the duration of attacks, or that adverse events were increased in either group. This study did not report on QoL or on RCS. See Summary of findings 5.

Nitrate/nitrate derivatives

Four studies compared topical treatment of nitroglycerin or glyceryl trinitrate (GTN) versus placebo (Chung 2009; Nahir 1986; Sovijarvi 1984; Teh 1995). The meta-analysis for topical GTN showed no evidence of reduced frequency of attacks per week in two highly heterogeneous studies. Nahir 1986 utilized dichotomous outcomes to demonstrate an effect on reduction in frequency of attacks with topical GTN. However, the clinical implication was difficult to judge due to the small sample size of the study and lack of qualitative data. Sovijarvi 1984 reported lack of differences between GTN and placebo in the frequency of RP attacks without providing data. Three studies reported on severity of attacks. In Teh 1995, overall severity of attacks (numbness, pain, and color change) was reduced in the treatment group, but the clinical relevance of this result is not clear. In Nahir 1986, five participants from the GTN group reported a positive result compared to one in the placebo group. Chung 2009 recorded severity of attacks reported by both physicians and patients on a 0 to 100 scale; no significant difference was noted in either group, and no numeric data were reported. Sovijarvi 1984 reported on duration of attacks but observed lack of differences between GTN and placebo (no data provided). Chung 2009 reported no significant differences between groups in the duration of attacks. Chung 2009 reported RCS but did not show evidence of a difference. None of the studies reported on QoL. See Summary of findings 6.

Phosphodiesterase inhibitors

Three studies assessed the efficacy of phosphodiesterase inhibitors for improving symptoms among individuals with RP (Caglayan 2012; NCT01090492; Rajagopalan 2003). These studies compared vardenafil (Caglayan 2012), cilostazol (Rajagopalan 2003), and PF-00489791 (NCT01090492), with an equivalent placebo. Meta-analysis showed no evidence of a difference between treatment and placebo in terms of frequency of attacks or severity of attacks (NCT01090492; Rajagopalan 2003). Only NCT01090492 reported on duration of attacks; no clear difference was detected. Rajagopalan 2003 authors reported that 35% of participants on cilostazol complained of headaches, and this was not reported in the placebo group. In NCT01090492, 34 of 54 participants in the treatment arm experienced adverse events, as did 43 of 102 participants in the placebo arm. Headache was the most common adverse event among 14 participants in the treatment arm and among 9 participants in the placebo arm. There was no clear reduction in RCS (Caglayan 2012; NCT01090492). None of the studies reported on QoL See Summary of findings 7.

The following classes of drugs, or single drugs with vasodilator effects, were not represented in the included studies: neprilysin inhibitors, angiotensin-II receptor antagonists, potassium channel activators, reflex sympathetic stimulators, endothelin antagonists, naftidrofuryl, and antihistamines.

Overall completeness and applicability of evidence

It is difficult to quantify the clinical effects of various treatments. Chung 2009 and Vayssairat 1996 performed sample size calculations; Chung 2009 aimed to find at least a 20% difference in the proportion of participants with 30% improvement in RCS. Vayssairat 1996 was powered to detect a 50% difference in the number of attacks, irrespective of placebo effect, which would be a clinically meaningful outcome for patients with RP. Study authors acknowledged the absence of a defined minimally detectable clinical difference for RCS.

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As mentioned in the Included studies section, significant changes have been made to the definition of primary RP over the last 30 years; this, in part, may affect the observed heterogeneity of outcomes. As consensus on criteria was reached as of 2014, this is less likely to be an issue with new studies. Variation in demographics such as gender and smoking and disease severity at baseline may also play a role in heterogeneity of outcomes. The consistency of winter months selected for the study season was reasonable, but as temperature may differ in different parts of the world or even among study settings, reporting of average temperatures within settings may aid in standardization of investigation of primary RP and may further reduce heterogeneity and bias. Of note, only one of the included studies provided a breakdown of the demographics of study participants; educational level, occupation, and other socio-demographic factors were not discussed in all studies.

Early results are promising, especially in large cohort, multicenter trials (NCT01090492), for certain agents such as topical glyceryl trinitrate and phosphodiesterase inhibitors. The review highlights various agents that have been studied, but there is a paucity of data to suggest a clinically meaningful outcome with these therapies.

Although Nahir 1986 included a female population only, we believe that the broad range of patient demographics in other studies allows for general applicability, thus providing external validity. We acknowledge additional difficulties in that RP diagnostic criteria have changed several times over the years. A predominantly outpatient setting during winter was appropriate for studying RP with these study designs.

Although it was the intention of review authors to incorporate the degree of sonographic or capillaroscopic findings as a demonstration of the effects of therapy, too few trials were included for performance of a meta-analysis.

As mentioned in previous reviews, there were difficulties in interpretation and analysis due to lack of simplistic mean and standard deviation and/or standard error format, or lack of reported data, which rendered it difficult to calculate outcomes for meta-analysis despite review authors' intentions.

Quality of the evidence

Some reviews reported outcome measures associated with significant P values, indicating that the effect seen was unlikely due to chance. Despite P values, the magnitude of effects was generally small. In addition, imprecision along with evidence of very low to moderate certainty makes it difficult to draw definitive conclusions regarding treatment outcomes.

Although meta-analyses for phosphodiesterase inhibitors, ACE inhibitors, and glyceryl trinitrate were performed, we acknowledge that the outcomes were non-specific in nature, and further study of individual drugs in this class is needed, as evidenced by differences in outcomes (e.g. cilostazol versus PF-00489791). We also note that there is inherent heterogeneity when meta-analyses of drug classes are performed, as the pharmacokinetics and the pharmacodynamics of an agent can be significantly different and may be impacted by study design, leading to differences in outcomes. Additionally, topical drug delivery shows heterogeneity, as delivery vehicle, patch design, concentration of agent, and duration and method of application would impact differences in effects between studies. Most studies - 11 out of 15 - used a cross-over design, which provides some advantages for studies with small sample sizes and a parallel design. As participants are involved in both control and treatment groups, a larger pool of data can be analyzed, increasing the power of study outcomes. Results are more precise, as interventions are evaluated among the same participants, which reduces the effects of demographic factors. In this review, however, data had to be presented as though studies used a parallel design due to inadequately reported results. This subsequently led to loss of power and precision from what was intended as originally designed. Some studies did not have any washout periods between carry-over periods (Jaffe 1980; Madsen 1984; Rustin 1987; Sovijarvi 1984; Teh 1995). However, elimination times were less than the period between last treatment and first dose given after carry-over. Remaining studies with a cross-over design had adequate washout periods, which exceeded elimination times of treatment (Caglayan 2012; Challenor 1991; Ettinger 1984; Nahir 1986; NCT01090492; Van de Wal 1987).

Jaffe 1980 and Nahir 1986 reported dichotomous outcomes that were difficult to clinically quantify given the lack of standardization. Examples of these include "patients experienced shorter attacks" and "patients experienced more severe attacks." Therefore, clinical importance was not assessed.

All studies reported subjective outcomes of Raynaud's phenomenon, which were the main defined outcomes. Primary RP rarely causes permanent tissue damage. Hence, the aim of treatment has been prophylactic and symptomatic control. Only three studies - Caglayan 2012; Chung 2009; NCT01090492 - reported a validated outcome measure - the Raynaud Condition Score, which has been used as the primary outcome measure for clinical trials for RP since the early 2000s (Merkel 2002). Apart from this, there was considerable variation in types of severity measurements that did not include the same scales. Variability in reporting of subjective measures made comparison of results among studies difficult or impossible. One of the secondary outcomes in this review was capillaroscopic flow/skin perfusion by ultrasound scan, which was reported in four studies (Rajagopalan 2003; Rustin 1987; Sovijarvi 1984; Van de Wal 1987). This may be a surrogate measure representing the severity of disease activity. However, the clinical correlation is unclear, as variability in measurements made it impossible to compare data and assess clinical importance.

The certainty of evidence for outcomes lies between very low and low for the reasons described above, except for outcomes reported in Le Quentrec 1991, for which evidence was of moderate certainty. A number of outcomes relied on data from one or two studies, and so evidence was downgraded due to small numbers of participants, imprecision, and bias concerns. Heterogeneity among methodological reasons and inconsistency in the direction of effect also led to downgrading of the evidence.

Although overall sample size was increased from that in previous version of the review, lack of comparable outcomes and bias concerning imprecision and heterogeneity among the same classes of medications resulted in low-certainty evidence. Overall, It is not possible to assess the clinical implications of effects of various treatments for this reason. There were suggestions that treatment may provide some benefit for subjective measures of RP; however, the magnitude of effect observed was small, and thus clinical relevance is not clear.

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Potential biases in the review process

A systematic approach to the search for studies for inclusion in this Cochrane Review was intended to reduce bias; this included defining inclusion and exclusion criteria and limiting study design to randomized controlled trials (RCTs). Including only studies that compared vasodilating drugs with placebo enhanced efficacy as reported in the results and provided a baseline for all treatment comparisons. Furthermore, the randomization aspect generally favors lower risk of bias compared to other study designs and minimizes confounding factors. However, when only RCTs are included, generalizing results to the general population becomes more difficult for a condition that can be affected by many individual and environmental factors; therefore the data may not represent individual outcomes.

Within the method itself, both cross-over and parallel studies were included. Each design has its advantages, with cross-over allowing evaluation of interventions in the same group of participants, reducing long-term participant response bias. Parallel studies generally utilize a larger, and consequently more diverse, participant pool. However, it is noted that due to different aspects of study design used by respective researchers, such as washout time frames and carry-over, bias in the review process may have been introduced when these studies were compared against one another, and when data were presented in a way that allows best comparison between parallel and cross-over studies.

Many studies were described as using "double-blinding" through utilization of identical placebo without elaboration of the manner in which blinding was applied. This contravenes the CONSORT 2010 statement regarding double blinding terminology and the recommendation for explicit distinction of blinded parties (i.e. assessors, participants, or investigators). We therefore deemed these studies to be at unclear risk of bias.

For the purposes of this review, only data from participants with primary RP were included. Combined data from participants with primary and secondary RP were not included in this review. Although this does discriminate findings against the broader group of individuals who may also have secondary RP, the results are more accurate for the group of individuals who experienced attacks according to current diagnostic criteria. Consequently, there were fewer independent rheumatologic pathologic variables that could have impacted participant response to treatment than would likely occur in secondary RP, by definition. Similarly, through inclusion of only vasodilatory medications without calcium channel blocker properties and by exclusion of alternative medicines and non-pharmacologic modalities, a more thorough analysis of efficacy among treatment groups could be performed. However, it is appreciated that again, the results are not inclusive of or applicable to patients on multiple therapies or receiving different therapies in the community setting. Some studies include both primary and secondary RP.

Through inclusion only of trials that lasted longer than one week, bias masked by duration was controlled. The specific time frame of trials allowed for processing of more longitudinal data and enabled assessment of whether therapy was effective in altering outcome measures over the long term - a feature more classically applied to clinical methods of treatment.

Despite inclusion of alternative routes of administration, thus increasing the sample size from the previous review of 290 participants in eight included studies to 635 participants in 15 studies, the final number of included studies was comparably limited. The review suffered from two primary limitations: first, the multitude of single studies on different drugs, and second, the high variability in study design and outcome measures. It may be argued that through use of specific inclusion and exclusion criteria, there was selection bias with potential for outcome bias during analysis of results, and that the quality of other excluded studies may have been methodologically superior. There is no way to ensure that certain studies were not missed with the search terminologies used. Although the approach taken was to narrow down studies, it is appreciated that certain studies that were ultimately testing the same outcomes in the included patient population but were published using different vocabulary may have been missed. By not restricting published language or study origin, cultural bias was reduced, and this increased external validity for multicultural general populations. As discussed above, however, allowing inclusion of specific studies that treated only one population sample, for example, women, may have introduced risk of overall application of results for the general community.

Most outcome measures assessed were subjective in nature. Given that primary RP, outside of its attacks, is not commonly known to present with pathologic features or damage, and that attacks are experienced by affected patients, the measures presented are appropriate in measuring any response to treatment. Possible risk of bias from subjective (i.e. self-reported) outcomes has been taken into consideration. More recent studies use more objective measures, such as capillaroscopic flow/skin perfusion measurements, which were not used in older studies; it is only in recent times that level of blood flow or amount of vasoconstriction is postulated to directly correlate with symptom and subjective attack experience (Wilkinson 2018). This reduces the comparability of findings.

Not limiting year of publication allows for consideration of an increased number of studies fitting the inclusion criteria. However, this introduces several inherent risks. First, in current practice, during application for approval to proceed with trials and studies, a strict and widely used code of ethics and principles must be approved before a study can occur. As 32 years has passed between oldest and newest publications - Jaffe 1980 and Caglayan 2012 - it is probable that quality of methods and ethical limitations may vary between trials of the 1980s and studies of the 2010s. Although this cannot be proved or quantified due to lack of available trial information and details regarding approval methods, it suggests that there is risk of bias with regard to external validity.

Agreements and disagreements with other studies or reviews

The results of this review do not provide evidence in favor of vasodilator use - oral or topical - for treatment of primary RP. This is consistent with reports from other reviews on treatment of primary RP (Distler 2006; Pope 2011).

Distler 2006 included four studies looking at effects of vasodilators apart from calcium channel blockers (CCBs) on primary RP, which were included in our review (Caglayan 2012; Challenor 1991; Rustin 1987; Vayssairat 1996). The Distler review included studies on secondary RP, as well as use of CCBs. Defined outcomes were

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different, and changes in fingertip ulcers and peripheral circulation were described. Pope 2011 included a total of 20 studies on effects of drugs for primary RP. Fifteen studies compared CCBs versus placebo, and two studies looked at the effect of Inositol nicotinate, which is not a vasodilator. Among the remaining three studies, two were excluded from our review as it is not possible to distinguish participants with primary and secondary RP (Davinroy 1993; Wollersheim 1986b). Data on moxisylyte versus placebo were included in Pope 2011, for which the author agrees that evidence is of very low quality based on the GRADE system.

Our review included RCTs looking at effects of different vasodilators on primary RP excluding CCBs. We excluded a large number of studies because it is not possible to differentiate participants with primary and secondary RP. We excluded participants with secondary RP because of differences in pathophysiology and clinical complications associated with primary and secondary RP. Primary RP rarely leads to permanent tissue damage, whereas secondary RP is associated with abnormalities in vascular structure that may be irreversible and can lead to digital ulceration (Herrick 2005). Defined outcomes were mainly subjective for this reason. This review performed a GRADE evaluation of the certainty of evidence for interventions.

AUTHORS' CONCLUSIONS

Implications for practice

The included studies investigated several different vasodilators (topical and oral) for treatment of primary RP. Small sample sizes, limited data, and variability in outcome reporting resulted in evidence of very low to moderate certainty. These results provide insufficient evidence to support the use of vasodilators, which may worsen disease. Differing routes of administration and pharmacologic properties of treatments as well as side effects should be taken into account when optimal therapy is selected for primary RP.

Implications for research

Based on the results of this review, a more robust and consistent research design is required for treatment of primary RP. Studies of longer treatment duration, with sufficient power to define a significant treatment effect, are needed, with sufficient follow-up to identify significant adverse events. Standardization of outcome reporting, such as through use of the Raynaud Condition Score, and clinically important effects need to be defined.

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* Indicates the major publication for the study

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Caglayan 2012

Study characteristics	
Methods	Study design: double-blind randomized placebo-controlled 2-period cross-over study for 6 weeks Method of randomization: computer generated Concealment of allocation: unknown Exclusions post randomization Losses to follow up: unknown
Participants	Country: Germany Setting: outpatient clinics of the Departments of Dermatology and Angiology at the University Hospital Cologne, from January 2006 through August 2009 No.: 53 Individuals with primary and secondary RP; 47 individuals with secondary RP (primarily due to SS) and 6 with primary RP Age: unavailable Sex: 42 female, 11 male Other: N/A Inclusion criteria: unavailable Exclusion criteria: unavailable
Interventions	Treatment: vardenafil (10 mg twice daily) Control: placebo Duration: 6 weeks Wash-out period: treatments were switched after a 1-week washout phase Patients were followed up to 4 weeks after the last drug intake All vasoactive agents were discontinued at least 1 week before study entry
Outcomes	Raynaud Condition Questionnaire Digital blood flow - measured by laser Doppler perfusion imager
Notes	Adverse events were notably more prevalent with vardenafil treatment (e.g. flushes, headache, dizziness) - unknown whether in PRP or SRP Caglayan 2012 was contacted but no response was received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	In supplementary data provided, randomization was achieved by permuted blocks of lengths 4 and 6 that were computer generated, sex stratified, and pseudo-random sequenced
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment method performed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Method of blinding of participants not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment mentioned

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Caglayan 2012 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Although serious adverse events were noted, no discussion regarding whether this caused dropout. Dropout rate as a whole not specified
Selective reporting (reporting bias)	High risk	Subgroup analysis done only for RCS, not for digital blood flow
Other bias	Low risk	No reasons to suspect other bias

Challenor 1991

Study characteristics	
Methods	Study design: randomized double-blind placebo-controlled cross-over trial Method of randomization: not stated Concealment of allocation: not stated Exclusions post randomization: 1 Losses to follow-up: none
Participants	Country: UK Setting: not stated; winter season No.: 21/21 primary RP Age: mean 38.6 years (range 21 to 59 years) Sex: females 19; males 2 Other: 14% smokers Inclusion criteria: primary RP Exclusion criteria: secondary RP (history, examination, and appropriate blood tests)
Interventions	Treatment: enalapril 20 mg once daily Control: matching placebo Duration: 2 × 4 weeks (including 3-day dose titration first week) Washout period: none
Outcomes	Frequency of attacks Duration of attacks Severity of attacks (1: mild, 2: moderate, 3: severe) Subjective assessment of improvement: 5-point rating scale and 10-cm VAS Skin temperature at rest and after cold challenge: cooled water bath 15 degrees 5 minutes Adverse events Enalapril at concentration 2 and 4 hours after last dose
Notes	No power calculation Support: pharmaceutical company

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description of sequence generation methods beyond stating randomized
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment methods

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Challenor 1991 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No method of blinding mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant reported to have dropped out for personal reasons; no other dropouts
Selective reporting (reporting bias)	Low risk	All study outcomes reported
Other bias	Unclear risk	Cross-over design, although study authors reported no evidence of effects of order nor treat-order interactions

Chung 2009

Study characteristics	
Methods	Study design: randomized placebo-controlled study; 2-week single-blind run-in period; 4-week double-blind treatment phase Method of randomization: randomization table developed for MediQuest by Quantitative Applications Consultants Concealment of allocation: unknown Exclusions post randomization: unknown Losses to follow-up: 94% completed the study
Participants	Country: USA and Canada Setting: clinical centers No.: 219 individuals with primary or secondary RP (69 with primary RP and 150 with secondary RP) Age: mean 46 years Sex: majority reported to be female Other: 108 randomly assigned to receive placebo, and 111 assigned to receive MQX-503 Inclusion criteria: 18 to 70 years of age, male and female Exclusion criteria: using any form of nitrate therapy or medication that interacts with nitroglycerin, any allergies to nitrate therapy along with history of headaches, MIs, other cardiac conditions
Interventions	Treatment: 0.9% MQX-503 gel Control: placebo Duration: 4 weeks Washout period: unknown
Outcomes	Change in RCS Frequency of RP events Duration of RP events Severity of attacks on VAS
Notes	Safety - at least 1 adverse event reported by 71% of participants receiving MQX-503 and by 71 (66%) of participants receiving placebo

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Chung 2009 *(Continued)*

7 participants discontinued the trial - 2 due to unsatisfactory response, 3 due to adverse events, 2 due to unacceptable concomitant medication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	From trial protocol (NCT00266669): "all patients were randomly assigned to one of two groups using a randomization table developed for MediQuest by Quantitative Applications Consultants. The type of gel (MQX-503 or vehicle) provided to the patients in each group during the active-treatment vs. vehicle phase of the study was defined by random group assignment. Appendix 16.1.7 exhibits a detailed description of the randomization method and the randomization table used in the study"
Allocation concealment (selection bias)	Unclear risk	Unclear how allocation concealment was performed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	From trial protocol (NCT00266669): "patients were blinded as to treatment assignment. The vehicle gel was indistinguishable from the active-treatment gel in smell, feel, and consistency, and the study drug pouches were identical and not labelled in a manner that would compromise the blind. Patient codes were held by and only available to the Clinical Supplies Coordinator. The blind was broken only after completion of data analysis. The blind would have been broken if a patient experienced a severe adverse event that could possibly be related to the study drug dose. If such an event occurred, the investigator was instructed to call MediQuest's Clinical Supplies Coordinator. No such event occurred. Prior and Concomitant Therapy"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Mostly self-reported outcome measures; at risk of recall bias if participants are putting in entries retrospectively. No specific mention of blinding of outcome assessors, especially with respect to physical examination of patients at screening and completion of the treatment phase; at risk of observer bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 participants (2 treatment arm and 5 placebo arm) noted to have discontinued from the study; remainder with reported outcomes. Mentioned that 94% of randomized cohort completed the study without major protocol violation; no further elaboration regarding how this was accounted for
Selective reporting (reporting bias)	Low risk	Selective outcome reporting unlikely; all outcomes accounted for
Other bias	Low risk	No reasons to suspect other bias

Ettinger 1984

Study characteristics

Methods	Study design: randomized double-blind placebo controlled cross-over trial Method of randomization: "randomly assigned" Concealment of allocation: not stated Exclusions post randomization: 1 inadequate compliance (in primary RP group) Losses to follow-up: none (in primary RP group)
Participants	Country: USA Setting: hospital; winter season No.: 6/25 primary RP

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Ettinger 1984 *(Continued)*

	Age: mean 33.8 years (range 22 to 55 years) Sex: females 5; males 1 Inclusion criteria: primary or secondary RP; at least 1 attack per day; age > 18 and < 65 years Exclusion criteria: serious renal, cardiac, hepatic, pulmonary, hematologic, or metabolic disease; concomitant treatment with aspirin, NSAIDs, dipyridamole, sulfinpyrazone, vasodilators, or drugs that interfere with sympathetic nervous system function
Interventions	Treatment: dazoxiben 100 mg 4 times daily or nifedipine 20 mg 3 times daily Control: placebo same doses; all took 7 capsules a day; drugs + placebo Duration: 10 weeks: 2 weeks placebo run-in period, 3 × 2 weeks of 1 of 6 possible sequences of 3 combinations of placebo, dazoxiben, and nifedipine Washout: 1 week in between 2-week periods
Outcomes	Frequency of attacks No subgroup data for other outcomes
Notes	No power calculation Support: pharmaceutical company Dazoxiben: experimental drug, unregistered Data from nifedipine arm not used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomized to 1 of 6 permutations of possible sequences of treatment; not enough information to determine adequate randomization
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double-blind, using placebo controls; single-blind (staff) placebo washout periods
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All dropouts reported; 3 dropouts in run-in phase and 3 in nifedipine arm due to orthostatic hypertension
Selective reporting (reporting bias)	Low risk	All specified outcomes reported on. However, in Figure 1, says "Physical Exam and Biochemical Profile" were taken at all change-over periods within the study; this is not described in the results, although it is not specified as an outcome either
Other bias	Low risk	Cross-over study; however adequate washout period between treatments

Jaffe 1980

Study characteristics

Methods	Study design: randomized double-blind placebo-controlled cross-over trial Method of randomization: "random procedure"

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Jaffe 1980 *(Continued)*

	Concealment of allocation: not stated Exclusions post randomization: 2 excluded because of no attacks in trial period (1 moxisylyte, 1 placebo) Losses to follow-up: total 8 (19%) lost to follow-up for frequency data; accessible data for 25 vs 26 participants (37% lost to follow-up) for severity and duration of attacks data
Participants	Country: UK Setting: general practice, multicenter; winter season No.: 41/41 primary RP (+33 chilblains, separate description and results) Age: median 41 years (range 17 to 73 years) Sex: females 27; males 14 Other: 34% smokers Inclusion criteria: primary RP Exclusion criteria: age < 18 or > 75 years, recent myocardial infarction, angina pectoris, diabetes, hypertension requiring drug treatment, pregnancy, tricyclic antidepressant medication, vasodilator therapy within 2 weeks of admission to trial
Interventions	Treatment: moxisylyte (thymoxamine) 40 mg 4 times daily Control: matching placebo 1 four times daily Duration: 2 × 2 weeks Washout period: none
Outcomes	Frequency of attacks Duration of attacks. Severity of attacks on 3-point scale (1: slight, 2: moderate, 3: severe). Severity score = frequency × severity grade Adverse events
Notes	No power calculation Support: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"…allocation to the initial medication being determined by a random procedure"; insufficient information
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double-blind, using matching placebo controls
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	All participants were accounted for, but 5 were excluded from the analysis: 2 for not experiencing attacks and 3 for experiencing side effects while on placebo
Selective reporting (reporting bias)	Low risk	All study outcomes reported

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Jaffe 1980 *(Continued)*

Other bias	Unclear risk	Cross-over study design with no analysis of carry-over effect, which could introduce bias

Le Quentrec 1991

Study characteristics	
Methods	Study design: randomized double-blind placebo-controlled parallel trial Method of randomization: randomization table Concealment of allocation: distribution by randomization table undertaken by manufacturer of strictly identical treatment packs. Code broken at end of trial Exclusions post randomization: none Losses to follow-up: none
Participants	Country: France Setting: specialist outpatient clinic; 2 autumn and winter seasons No.: 31/31 primary RP Age: mean 39.3 years (range 22 to 67 years) Sex: females 28; males 3 Other: 27% smokers. Concomitant disease: 2 diabetes, 2 arterial disease Inclusion criteria: severe idiopathic RP; at least 1 attack related to cold exposure per day within the past 2 years, according to clinical examination, blood tests, and bilateral nailfold capillaroscopy Exclusion criteria: unilateral RP secondary to thoracic outlet or locoregional pathologic disturbances; bilateral cases secondary to collagen disease or scleroderma; treated with a vasoactive or platelet aggregant drug less than 2 weeks before the trial; pregnant and breast-feeding women
Interventions	Treatment: buflomedil 300 mg twice daily Control: placebo identical Duration: 6 months
Outcomes	Mean number of attacks per day Severity of attacks (4-point score: 0: none, 1: slight, 2: moderate, 3: severe) Adverse events Efficacy confirmed by capillaroscopic criteria
Notes	No power calculation Support: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Used a randomization table
Allocation concealment (selection bias)	Low risk	Randomization and treatment preparation performed by treatment manufacturer
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double-blind; "All treatment packs were strictly identical in appearance and distribution by randomization table was undertaken by the manufacturer"; randomization code not broken until end of study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of blinding of outcome assessors

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Le Quentrec 1991 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants who entered the study completed the study at 6 months
Selective reporting (reporting bias)	Low risk	For capillaroscopic criteria, morphology and aspects of background were not reported
Other bias	Low risk	No indication of other bias

Madsen 1984

Study characteristics	
Methods	Study design: randomized double-blind placebo-controlled cross-over trial Method of randomization: not stated Concealment of allocation: not stated Exclusions post randomization: none Losses to follow-up: none
Participants	Country: Denmark Setting: not stated; winter season No.: 10/10 primary RP Age: median 44 years (range 27 to 71 years) Sex: females 8; males 2 Inclusion criteria: primary RP; screened for underlying disease Exclusion criteria: secondary RP according to described criteria; hypertension BP > 150/90
Interventions	Treatment: captopril 25 mg 3 times daily Control: placebo 1 three times daily Duration: 2 × 6 weeks Washout period: none
Outcomes	Number of daily attacks Accompanying numbness or pain Improvement on 3-point scale: improved, unchanged, worse Adverse events
Notes	No power calculation Support: pharmaceutical company

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description of sequence generation methods
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study described as double-blind but no further explanation of blinding methods

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Madsen 1984 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 10 participants completed the study
Selective reporting (reporting bias)	Low risk	All study outcomes reported
Other bias	Unclear risk	Cross-over study; study authors did not evaluate carry-over of treatment effects and therefore could be of concern

Nahir 1986

Study characteristics	
Methods	Study design: randomized double-blind cross-over trial Method of randomization: unknown Concealment of allocation: unknown Exclusions post randomization: unknown Losses to follow-up: unknown
Participants	Country: Israel Setting: December through to Feburary No.: 18 participants (7 primary RP, 5 SS, 3 CREST, 3 SLE) Age: unknown Sex: all females Other: non-smokers Inclusion criteria: unavailable Exclusion criteria: beta blocker use; CCB use; any medication that may influence RP; smokers
Interventions	Treatment: Nitroderm TTS 5 mg adhesive tape Control: placebo Duration: 2 weeks of treatment per treatment period Washout period: 1 week between 2 cross-over periods
Outcomes	Number and severity of RP attacks and precipitating factor BP, pulse, serum BUN, electrolytes, creatinine, LFTs, CBC
Notes	Safety - 2 participant withdrawals due to headache and 1 due to recurrent local dermatitis, unclear from which group Review authors were unable to contact study authors to obtain missing information

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Only female participants included
Allocation concealment (selection bias)	Unclear risk	No discussion on allocation concealment

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Nahir 1986 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind method with no further elaboration; participants were also reviewed weekly, which is a potential source of researcher bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding was performed, but outcome assessment is not likely to be affected, given outcome assessment was via patient diary
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participant withdrawals due to headache and 1 due to recurrent local dermatitis; not clear which group they were from, and given small numbers, study is at risk of bias
Selective reporting (reporting bias)	Low risk	All outcome measures reported
Other bias	Low risk	No reason to suspect other bias

NCT01090492

Study characteristics	
Methods	Study design: randomized controlled trial; 2-period cross-over study for 4 weeks Method of randomization: unavailable Concealment of allocation: unavailable Exclusions post randomization: unavailable Losses to follow-up: unavailable
Participants	Country: USA, Canada, Columbia, Czechia, Germany, Hungary, Korea, Mexico, Poland, Spain, Sweden Setting: medical centers No.: 243 participants (113 with primary RP) Age: 18 to 65 years Sex: males and females Other: n/a Inclusion criteria: active RP; stable disease; medication requirements over previous 2 months; if secondary RP, diagnosis of scleroderma by ACR criteria or by presence of > 3/5 features of CREST syndrome Exclusion criteria: uncontrolled hypertension; DM; angina or using oral nitrates; smoking within 3 months or smoking cessation using nicotine products; currently taking sildenafil, tadalafil, or vardenafil; ulnar arterial occlusive disease as shown by a modified Allen test; pregnant or breast-feeding or considering pregnancy in next 4 months; participation in trial for investigational drug within 30 days
Interventions	Treatment: PF-00489791 4 mg and 20 mg Control: placebo Duration: 4-week cross-over period, then cross-over for second 4-week cross-over period Washout period: a washout period of 2 weeks was maintained between interventions
Outcomes	RCS Frequency in the number of Raynaud's attacks over the span of 4 weeks (number reported over 7-day period before each week from patient diary, respectively) Mean duration of Raynaud's attacks for a time period Rating of pain experienced in the past 24 hours on an 11-point Likert scale (0 = no Raynaud's pain, 10 = worst possible pain) Measurement of ulcers (presence assessed at baseline, post baseline was measured and scored) Plasma concentration of PF-00489791 and its metabolites
Notes	NCT01090492 responded to review authors' request but did not provide additional information

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NCT01090492 *(Continued)*

	We report outcomes for 20-mg dose only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified in the study; published online
Allocation concealment (selection bias)	Unclear risk	Not specified in the study; published online
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified in the study; published online
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified in the study; published online
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified in the study; published online
Selective reporting (reporting bias)	Unclear risk	Not specified in the study; published online
Other bias	Low risk	Not specified in the study; published online

Rajagopalan 2003

Study characteristics

Methods	Study design: randomized double-blind controlled trial Method of randomization: unknown Concealment of allocation: unknown Exclusions post randomization: unknown Losses to follow-up: 3 participants in the cilostazol arm withdrew before study completion
Participants	Country: USA Setting: rheumatology outpatient clinic; over 2 winters No.: 40 participants (19 with primary RP, 21 with secondary RP) Age: mean 47 years Sex: male and female Other: post-menopausal females and smokers excluded Inclusion criteria: primary and secondary RP; women of childbearing age on effective birth control method (on OCP > 4 months) Exclusion criteria: RS secondary to causes other than CT disease; CHF; blood pressure > 160/100 mmHg; cholesterol 220 mg/dL; diabetes (fasting glucose 100 mg/dL, or hemoglobin A1C 8); creatinine 2.5 mg/dL; hepatic failure; current smoker; taking 2 antihypertensive drugs, lipid-lowering therapy, CYP3A4 inhibitors, or had recently initiated an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; pregnant, breast-feeding, or postmenopausal; active cardiac, central nervous system, or pulmonary disease
Interventions	Treatment: cilostazol 100 mg Control: placebo

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Rajagopalan 2003 *(Continued)*

	Duration: 6 weeks Washout period: n/a
Outcomes	Standard questionnaire (severity and frequency of RP attacks) Brachial artery vasoreactivity Laser Doppler fluxmetry CPT
Notes	Review authors were unable to contact study authors to obtain missing information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinding but which party not stated. Identical placebo used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specifics regarding blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details provided
Selective reporting (reporting bias)	Unclear risk	Insufficient details provided; study authors failed to define numbers of participants in control and intervention groups when reporting outcomes and failed to specify details regarding participant dropout and completion of data collection
Other bias	Low risk	Insufficient details provided

Rustin 1987

Study characteristics

Methods	Study design: randomized double-blind placebo-controlled cross-over trial Method of randomization: "random number system" Concealment of allocation: not stated Exclusions post randomization: 1 - pregnant Losses to follow-up: none for subjective data, 1 for objective data
Participants	Country: UK Setting: specialist outpatient clinic; winter season No.: 15/15 primary RP Age: mean 35 years (range 21 to 52 years) Sex: females 15, males 0 Other: 26% smokers

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Rustin 1987 *(Continued)*

	Inclusion criteria: primary RP according to diagnostic criteria with negative ANA, chest and hand radiographs, lung function tests, and nailfold capillaroscopy; no features of connective tissue disease on general examination or occupational cause for RP Exclusion criteria: hypertension, ischemic heart disease, abnormal full blood count, impaired renal or hepatic function
Interventions	Treatment: captopril 25 mg 3 times daily Control: placebo 3 times daily Duration: 2-week placebo run-in, 2 × 6 weeks intervention Washout period: none
Outcomes	Frequency of attacks Duration of attacks Severity of attacks (mild, moderate, severe) Pain of attacks (no scale) Cold test 1 minute 20 degrees Digital blood flow by laser Doppler flowmetry and photoplethysmography Adverse events
Notes	No power calculation Support: pharmaceutical company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"… divided using a random number system into two groups"
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study described as double-blind but no further explanation of blinding methods
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Selective reporting (reporting bias)	Low risk	All study outcomes reported on
Other bias	Low risk	Cross-over design- although authors reported no evidence of treatment period interactions

Sovijarvi 1984

Study characteristics

Methods	Study design: randomized double-blind cross-over trial Method of randomization: unknown

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Sovijarvi 1984 *(Continued)*

	Concealment of allocation: unknown Exclusions post randomization: unknown Losses to follow-up: none
Participants	Country: Finland Setting: Departments of Clinical Physiology and Internal Medicine No.: 8 (7 with primary RP, 1 with positive antinuclear antibodies) Age: mean 44 years Sex: 2 males, 6 females Other: None Inclusion criteria: unknown Exclusion criteria: unknown
Interventions	Treatment: 12.5 mg nitroglycerin Control: placebo Duration: 3 weeks (1-week single-blind run-in phase with placebo followed by 2-week trial phase with cross-over at end of week) Washout period: none
Outcomes	Recording of daily number and duration of attacks Arterial BP of upper arm; HR; digital BP changes after cold provocation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not stated
Allocation concealment (selection bias)	Unclear risk	No discussion regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind study, but no discussion regarding who was blinded; Identical placebo used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No discussion regarding blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts; all outcomes reported
Selective reporting (reporting bias)	Low risk	All aspects commented on
Other bias	Low risk	Unclear

Teh 1995

Study characteristics

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Teh 1995 *(Continued)*

Methods	Study design: randomized double-blind cross-over study Method of randomization: unknown Concealment of allocation: unknown Exclusions post randomization: 2 primary RP participants excluded due to incomplete data Losses to follow-up: 8 withdrawals before completion of study (2 primary RP due to adverse events related to GTN)
Participants	Country: UK Setting: winter months (November to February) No.: 42 participants (21 primary RP, 21 secondary RP); 17 primary RP completed the study Age: mean 39.4 years Sex: in primary RP, 15 women and 6 men Other: mean duration of RP attack 86.6 months Inclusion criteria: over 16 years of age Exclusion criteria: vasoactive medication for any indication; previous intolerance to nitrates; critical digital ischemia
Interventions	Treatment: GTN patches (0.2 mg/hr) for 7 days Control: placebo patch for 7 days Duration: 2 weeks Washout period: none
Outcomes	Frequency and severity of RP attacks Infrared thermography
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind method stated; identical placebo used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessors specified; potential recall bias from self-reporting arms of the study, which was not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	Mean and discrete numeric results not broken down and presented; P value and confidence interval only given; dropouts accounted for but not part of statistical analysis
Selective reporting (reporting bias)	High risk	Means by which outcomes were reported varied between protocol and study report
Other bias	Low risk	No reason to suspect other bias

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Van de Wal 1987

Study characteristics	
Methods	Study design: randomized double-blind placebo-controlled cross-over trial Method of randomization: "assigned at random" Concealment of allocation: not stated Exclusions post randomization: none Losses to follow-up: 1
Participants	Country: The Netherlands Setting: not stated; 2 winter seasons No.: 41/41 primary RP Age: mean 46 years (range 15 to 74 years) Sex: females 26; males 15 Other: 51% smokers; 10 participants underwent thoracic sympathectomy at least 2 years before the study Inclusion criteria: primary RP as defined by criteria: recurrent ischemic attacks, no evidence of arterial obstruction, no evidence of underlying abnormalities, extensive blood and serologic examination to exclude secondary RP Exclusion criteria: secondary RP as described by criteria for primary RP; no other vasoactive drugs in trial period
Interventions	Treatment: ketanserin 40 mg twice daily (20 mg twice daily first 2 weeks) Control: placebo Duration: 4-week run-in with placebo, 2 × 6-week intervention Washout period: none
Outcomes	Frequency of attacks Duration of attacks Cold sensation, numbness, paresthesia, pain Severity score (frequency of attacks/d × duration of attacks) Adverse events Non-invasive vascular measurements: digital skin temperature, digital systolic blood pressure, Doppler spectral analysis Cold test ice water 2 minutes
Notes	No power calculation Support: pharmaceutical company

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"… assigned at random"; insufficient detail to determine adequate random sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study described as double-blind but no further explanation of blinding methods
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of blinding of outcome assessors
Incomplete outcome data (attrition bias)	Low risk	Dropouts were few and were thoroughly described

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Van de Wal 1987 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	All study outcomes reported
Other bias	Low risk	Cross-over design - although study authors reported no evidence of carry-over

Vayssairat 1996

Study characteristics	
Methods	Study design: randomized double-blind placebo-controlled parallel trial Method of randomization: random numbers table prepared by pharmaceutical company; individual randomization envelopes left at each center Concealment of allocation: centers unaware of randomization code Exclusions post randomization: none (7 pre-randomization) Losses to follow-up: 16 (9 in beraprost group, 7 in placebo group)
Participants	Country: France Setting: multicenter; specialist outpatient clinic No.: 125/125 primary RP (118 after randomization) Age (mean ± SD): beraprost group 40 ± 12 years, placebo group 37 ± 11 years Sex: females 96, males 29 Inclusion criteria: primary RP defined by criteria: duration > 2 years, no underlying disease, no past or present digital tip necrosis, normal pulses, normal nailfold capillary microscopy, no positive ANA Exclusion criteria: age < 18 or > 65 years, pregnant, secondary RP, < 5 attacks of RP per week, associated acute or chronic disease, any drug treatment except paracetamol and contraceptive pills
Interventions	Treatment: phase II: beraprost sodium 20 µg 3 times daily; phase III: beraprost sodium 40 µg 3 times daily Control: placebo Duration: phase I: 2-week run-in, no treatment; phase II: 3 weeks; phase III: 3 weeks
Outcomes	Number of attacks Severity of attacks (graded 1 to 4) Overall disability: VAS scale 100 mm Adverse events Cold test (13 degrees, 5 minutes) and hemodynamic data Blood tests
Notes	Includes sample size calculation Support: pharmaceutical company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was based on a random number table and was done in blocks of 2 to have patients with similar outdoor environmental temperatures in the placebo and beraprost groups"
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment methods
Blinding of participants and personnel (performance bias)	Low risk	Study described as double-blind in addition to blinding of statisticians; identical placebo control used

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Vayssairat 1996 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Results validated blindly; statisticians blinded as well
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts were reported and were similar between treatment groups
Selective reporting (reporting bias)	Low risk	All study outcomes reported
Other bias	Unclear risk	Sample size calculation determined 80 participants per group would be needed to reach specified power, but only 59 per group were analyzed

ACR: urine albumin-to-creatinine ratio.
ANA: antinuclear antibodies.
BP: blood pressure.
BUN: blood urea nitrogen.
CBC: complete blood count.
CCB: calcium channel blocker.
CHF: chronic heart failure.
CPT: cold pressor testing.
CREST: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia.
CT: computed tomography.
DM: diabetes mellitus.
GTN: glyceryl trinitrate.
HR: heart rate.
LFTs: liver function tests.
NSAIDs: non-steroidal anti-inflammatory drugs.
OCP: oral contraceptive pill.
RCS: Raynaud Condition Score.
RP: Raynaud's phenomenon.
SLE: systemic lupus erythematosus.
SS: systemic sclerosis.
VAS: visual analogue scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Allegra 1983	Wrong intervention; use of a selective calcium channel blocker
Arcas Meca 1972	Results could not be extracted/interpreted; data for secondary and primary RP not separated and therefore could not be analyzed
Arnot 1978	Results could not be extracted/interpreted; data for secondary and primary RP not separated and therefore could not be analyzed
Arosio 1989	Results presented combined for all participants; no subgroup analysis possible
Bali 2011	Results could not be extracted/interpreted; data for secondary and primary RP not separated and therefore could not be analyzed
Barry 2000	Results could not be extracted/interpreted; data for secondary and primary RP not separated and therefore could not be analyzed

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Study	Reason for exclusion
Belch 1983	Results could not be extracted/interpreted; data for secondary and primary RP not separated and therefore could not be analyzed
Belch 1985	Results could not be extracted/interpreted; data for secondary and primary RP not separated and therefore could not be analyzed
Belch 1995	All participants have scleroderma
Bellucci 1987	Results could not be extracted/interpreted; data for secondary and primary RP not separated and therefore could not be analyzed
Belluci 1990	Wrong (subjective) outcomes
Brotzu 1989	Patients given both beta blocker and calcium channel blocker
Clement 1980	Results could not be extracted/interpreted; unable to differentiate between acrocyanosis patients and those with RP
Clement 1986	Wrong patient population
Cleophas 1984	Does not clearly differentiate between primary and secondary; used beta blockers
Coffman 1989	Results presented combined for all participants (primary and secondary RP); no subgroup analysis possible
Coleiro 2001	Results presented combined for all participants; no subgroup analysis possible
Courbier 1981	Results could not be extracted/interpreted; data for secondary and primary RP not separated and therefore could not be analyzed; single dose
Davinroy 1993	Results could not be extracted/interpreted, as they were presented combined for primary and secondary Raynaud's patients
Diehm 1983	Results could not be extracted/interpreted; data for secondary and primary RP not separated and therefore could not be analyzed; randomization not clear
Dumoulin 1981	Wrong medication; suloctidil appeared to be a calcium channel blocker
Dziadzio 1999	Comparison with calcium channel blocker
Fischer 1985	Wrong outcomes; cannot differentiate between primary and secondary RP
Friedman 2007	Results could not be extracted/interpreted; unable to differentiate between primary and secondary RP
Grigg 1989	Wrong outcomes; subjective outcome measure; outcome measured in question is more a provocation and response test than an outcome of interest
JaniniDa 1988	Wrong intervention; unable to differentiate between primary and secondary RP
Jenkins 2013	Wrong patient population; not specified whether individuals had primary or secondary RP
Kahan 1985	Results for primary RP patients could not be extracted/interpreted
Kingma 1995	Results for primary RP could not be extracted/interpreted; outcome results for the 2 primary Raynaud's patients could not be extracted

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Study	Reason for exclusion
Kirichenko 1991	Wrong patient population; individuals have secondary RP
Kyle 1992	Wrong outcomes; cannot differentiate between primary and secondary RP
Lee 2014	Wrong patient population; individuals have secondary RP
Longstaff 1985	Results presented combined for all participants; could not differentiate between primary and secondary RP
Luderer 1984	Results could not be extracted/interpreted; unable to differentiate between primary and secondary RP
Marasini 1988	Results could not be extracted/interpreted; unable to differentiate between primary and secondary RP; wrong outcomes
Marasini 2004	All participants with secondary RP
Maurel 1995	Results could not be extracted/interpreted; unable to differentiate between primary and secondary RP; no outcomes for frequency or severity of attacks
McFadyen 1973	Single-dose trial
Mirza 2019	Unable to differentiate between primary and secondary RP
Mohrland 1985	Single-dose trial
NCT00048763	All participants had secondary RP. Pharmaceutical company was contacted by previous review authors and the following information received: "for each study approximately 51 subjects were planned. For study 21-02-335 (primary RP) 27 subjects were enrolled and one subject completed all periods"; "The study was discontinued early due to prolongation of QTc intervals on ECGs (later attributed to technical problems with the ECG machines). the quantity of data collected was too small to evaluate efficacy and pharmacokinetics properly" Entry at www.clinicaltrials.gov only
NCT00419419	Results could not be extracted/interpreted; cannot differentiate between primary and secondary RP
NCT0048776	All participants had primary RP. Results never published. Pharmaceutical company contacted for further information: "for each study approximately 51 subjects were planned. For study 21-02-335 (primary RP) 27 subjects were enrolled and one subject completed all periods"; "The study was discontinued early due to prolongation of QTc intervals on ECGs (later attributed to technical problems with ECG machines). The quantity of the data collected was too small to evaluate efficacy and pharmacokinetics properly" Entry at www.clinicaltrials.gov only
NCT01233999	Use of botulinum toxin. All participants had primary RP. Results never published and quantity of data was small. Medication was not oral but was injected. Pharmaceutical company contacted for further information by previous authors and was excluded
Nielsen 1983	Study includes multiple increasing doses for some participants; unclear length of treatment for each participant and dose
Nilsen 1979	Results could not be extracted/interpreted; cannot differentiate between primary and secondary RP

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Study	Reason for exclusion
Roustit 2017	Cannot differentiate between primary and secondary RP; wrong outcomes
Russell 1985	Results presented combined for all participants; could not extract data specific for primary RP
Seibold 1986	Single dose of treatment used
Shawket 1991	Single dose of treatment given
Shcherbakov 1992	Results presented combined for all participants; unable to extract data specific for primary RP; unclear reporting of outcomes and nil quantifiable data
Strozzi 1982	Results could not be extracted/interpreted; unclear if any participants have primary RP
Sunderland 1988	Wrong intervention (Hexopal)
Surwit 1982	Wrong patient population; all individuals have secondary RP
Tooke 1990	Results could not be extracted/interpreted; cannot differentiate between primary and secondary RP; 2 different articles on the same study
Torley 1990	All participants have secondary RP
Tucker 1999	Single dose
Wesseling 1981	Single-dose study, no results for subgroups
Wollersheim 1986	Results could not be extracted/interpreted; some mention of comparison of primary with secondary Raynaud's but not with placebo; could not differentiate primary vs secondary RP results

RP: Raynaud's phenomenon.

Characteristics of studies awaiting classification *[ordered by study ID]*

Sakaguchi 1990

Methods	Double-blind placebo-controlled
Participants	Raynaud's phenomenon and Raynaud's syndrome
Interventions	Beraprost
Outcomes	-
Notes	Awaiting translation to determine eligibility

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2005-000295-41-DE

Study name	Double-blind,placebo-controlled cross-over study for evaluation of the efficacy of the PDE-5-inhibitor vardenafil on the peripheral perfusion and the clinical symptomatology of patients with Raynaud's disease

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EUCTR2005-000295-41-DE *(Continued)*

Methods	Double-blind placebo-controlled cross-over study
Participants	60 (planned) participants with diagnosis of Raynaud's disease (primary and secondary) for > 1 year; age between 18 and 65 years
Interventions	Vardenafil
Outcomes	Study in progress
Starting date	December 20, 2005
Contact information	Not stated
Notes	Sponsored by Universität zu Köln, Germany

NCT02583789

Study name	Assess efficacy of oral treprostinil in patients with symptomatic primary or secondary RP
Methods	Double-blinded placebo-controlled cross-over study
Participants	20 participants with primary or secondary RP
Interventions	Treprostinil
Outcomes	Study in progress
Starting date	May 2016
Contact information	Laurie Lawler, RN
Notes	

PDE-5: phosphodiesterase-5.
RP: Raynaud's phenomenon.

DATA AND ANALYSES

Comparison 1. ACE inhibitor versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Frequency of attacks per week	3		Mean Difference (IV, Random, 95% CI)	0.79 [0.43, 1.16]
1.1.1 Captopril	2		Mean Difference (IV, Random, 95% CI)	0.72 [-1.73, 3.16]
1.1.2 Enalapril	1		Mean Difference (IV, Random, 95% CI)	0.80 [0.43, 1.17]
1.2 Severity of symptoms	2		Mean Difference (IV, Random, 95% CI)	-0.17 [-4.66, 4.31]

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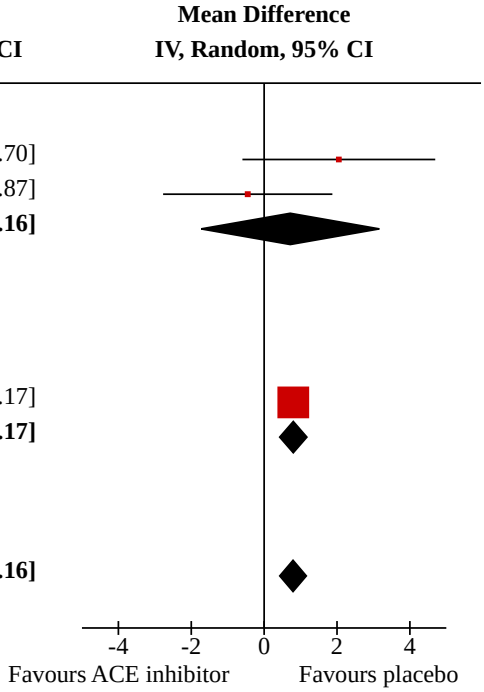
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.1 Captopril	1		Mean Difference (IV, Random, 95% CI)	-1.30 [-7.18, 4.58]
1.2.2 Enalapril	1		Mean Difference (IV, Random, 95% CI)	1.40 [-5.55, 8.35]
1.3 Duration of attacks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3.1 Captopril	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4 Capillaroscopic flow/ skin perfusion by ultrasound	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4.1 Captopril	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5 Subjective assessment of improvement (10-cm visual analogue scale)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5.1 Enalapril	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6 Adverse events	3	88	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.67, 2.73]
1.6.1 Captopril	2	48	Risk Ratio (M-H, Fixed, 95% CI)	5.00 [0.27, 92.62]
1.6.2 Enalapril	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.55, 2.32]

Analysis 1.1. Comparison 1: ACE inhibitor versus placebo, Outcome 1: Frequency of attacks per week

Study or Subgroup	MD	SE	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Captopril				
Madsen 1984	2.05	1.35	1.9%	2.05 [-0.60 , 4.70]
Rustin 1987	-0.45	1.185	2.5%	-0.45 [-2.77 , 1.87]
Subtotal (95% CI)			**4.4%**	**0.72 [-1.73 , 3.16]**
Heterogeneity: Tau² = 1.51; Chi² = 1.94, df = 1 (P = 0.16); I² = 48%				
Test for overall effect: Z = 0.57 (P = 0.57)				
1.1.2 Enalapril				
Challenor 1991	0.8	0.19	95.6%	0.80 [0.43 , 1.17]
Subtotal (95% CI)			**95.6%**	**0.80 [0.43 , 1.17]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 4.21 (P < 0.0001)				
Total (95% CI)			**100.0%**	**0.79 [0.43 , 1.16]**
Heterogeneity: Tau² = 0.00; Chi² = 1.97, df = 2 (P = 0.37); I² = 0%				
Test for overall effect: Z = 4.27 (P < 0.0001)				
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%				



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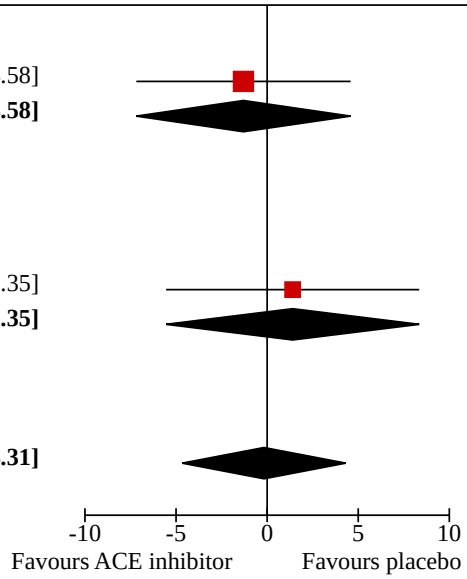
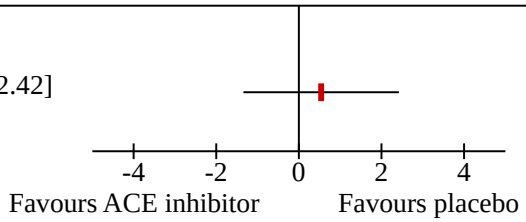
Analysis 1.2. Comparison 1: ACE inhibitor versus placebo, Outcome 2: Severity of symptoms

Study or Subgroup	MD	SE	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Captopril				
Rustin 1987	-1.3	3	58.3%	-1.30 [-7.18 , 4.58]
Subtotal (95% CI)			**58.3%**	**-1.30 [-7.18 , 4.58]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.43 (P = 0.66)				
1.2.2 Enalapril				
Challenor 1991	1.4	3.544	41.7%	1.40 [-5.55 , 8.35]
Subtotal (95% CI)			**41.7%**	**1.40 [-5.55 , 8.35]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.40 (P = 0.69)				
Total (95% CI)			**100.0%**	**-0.17 [-4.66 , 4.31]**
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%				
Test for overall effect: Z = 0.08 (P = 0.94)				
Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%				



Analysis 1.3. Comparison 1: ACE inhibitor versus placebo, Outcome 3: Duration of attacks

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
1.3.1 Captopril			
Rustin 1987 (1)	0.54	0.96	0.54 [-1.34 , 2.42]



Footnotes

(1) Assumed attacks measured in minutes

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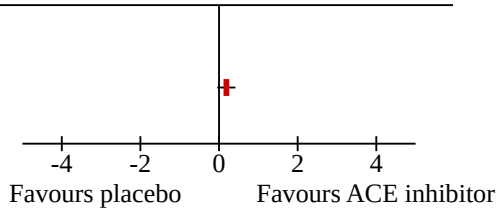
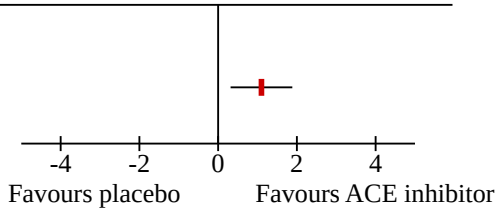
Analysis 1.4. Comparison 1: ACE inhibitor versus placebo, Outcome 4: Capillaroscopic flow/skin perfusion by ultrasound

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
1.4.1 Captopril			
Rustin 1987	0.186	0.118	0.19 [-0.05 , 0.42]



Analysis 1.5. Comparison 1: ACE inhibitor versus placebo, Outcome 5: Subjective assessment of improvement (10-cm visual analogue scale)

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
1.5.1 Enalapril			
Challenor 1991	1.1	0.4	1.10 [0.32 , 1.88]



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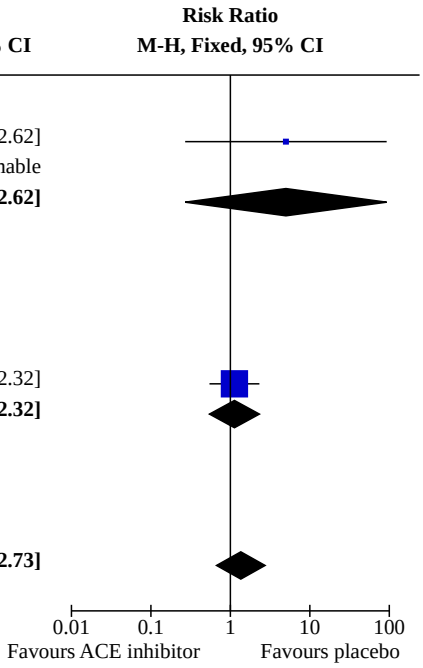
Analysis 1.6. Comparison 1: ACE inhibitor versus placebo, Outcome 6: Adverse events

Study or Subgroup	ACE inhibitor Events	ACE inhibitor Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Captopril						
Madsen 1984	2	10	0	10	5.9%	5.00 [0.27 , 92.62]
Rustin 1987	0	14	0	14		Not estimable
Subtotal (95% CI)		**24**		**24**	**5.9%**	**5.00 [0.27 , 92.62]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
1.6.2 Enalapril						
Challenor 1991 (1)	9	20	8	20	94.1%	1.13 [0.55 , 2.32]
Subtotal (95% CI)		**20**		**20**	**94.1%**	**1.13 [0.55 , 2.32]**
Total events:	9		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
Total (95% CI)		**44**		**44**	**100.0%**	**1.35 [0.67 , 2.73]**
Total events:	11		8			
Heterogeneity: Chi² = 1.02, df = 1 (P = 0.31); I² = 2%						
Test for overall effect: Z = 0.84 (P = 0.40)						
Test for subgroup differences: Chi² = 0.95, df = 1 (P = 0.33), I² = 0%						



Footnotes

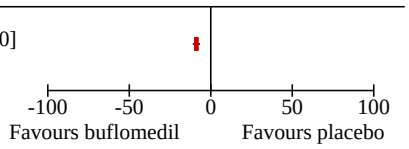
(1) Dizziness most common side effect

Comparison 2. Alpha blockers versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Frequency of attacks - buflomedil	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.2 Severity of symptoms - buflomedil	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.3 Adverse events - buflomedil	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Alpha blockers versus placebo, Outcome 1: Frequency of attacks - buflomedil

Study or Subgroup	MD	SE	Experimental Total	Control Total	Mean Difference IV, Fixed, 95% CI
Le Quentrec 1991 (1)	-8.82	1.132	16	15	-8.82 [-11.04 , -6.60]



Footnotes

(1) Frequency of events per week

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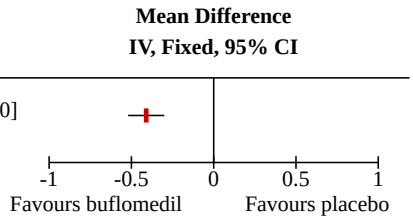
Analysis 2.2. Comparison 2: Alpha blockers versus placebo, Outcome 2: Severity of symptoms - buflomedil

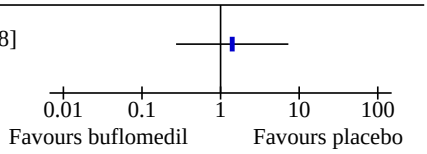
Study or Subgroup	MD	SE	Experimental Total	Control Total	Mean Difference IV, Fixed, 95% CI
Le Quentrec 1991 (1)	-0.41	0.056	16	15	-0.41 [-0.52 , -0.30]



Footnotes
(1) 1: mild; 2: moderate; 3: severe

Analysis 2.3. Comparison 2: Alpha blockers versus placebo, Outcome 3: Adverse events - buflomedil

Study or Subgroup	alpha blocker Events	alpha blocker Total	placebo Events	placebo Total	Risk Ratio M-H, Fixed, 95% CI
Le Quentrec 1991	3	16	2	15	1.41 [0.27 , 7.28]

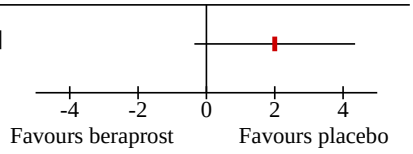


Comparison 3. Beraprost versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Frequency of attacks per week	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.2 Severity of attacks (1 to 4 scale)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.3 Disability (100-mm visual analogue scale)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: Beraprost versus placebo, Outcome 1: Frequency of attacks per week

Study or Subgroup	MD	SE	Beraprost Total	Placebo Total	Mean Difference IV, Fixed, 95% CI
Vayssairat 1996	2	1.2	59	59	2.00 [-0.35 , 4.35]



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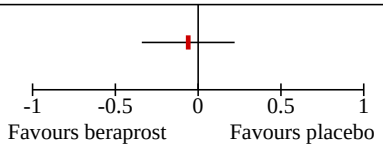
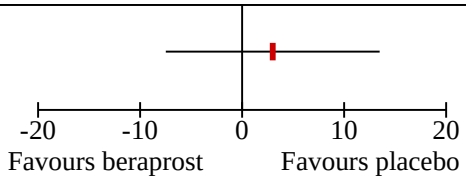
Analysis 3.2. Comparison 3: Beraprost versus placebo, Outcome 2: Severity of attacks (1 to 4 scale)

Study or Subgroup	MD	SE	Experimental Total	Control Total	Mean Difference IV, Fixed, 95% CI
Vayssairat 1996	-0.06	0.143	59	59	-0.06 [-0.34 , 0.22]



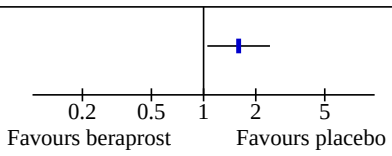
Analysis 3.3. Comparison 3: Beraprost versus placebo, Outcome 3: Disability (100-mm visual analogue scale)

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
Vayssairat 1996	3	5.348	3.00 [-7.48 , 13.48]



Analysis 3.4. Comparison 3: Beraprost versus placebo, Outcome 4: Adverse events

Study or Subgroup	Beraprost Events	Beraprost Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Vayssairat 1996 (1)	34	63	21	62	1.59 [1.05 , 2.42]



Footnotes

(1) The incidence of headache was higher in Beraprost group (16 vs 1)

Comparison 4. Dazoxiben versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Frequency of attacks per week	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

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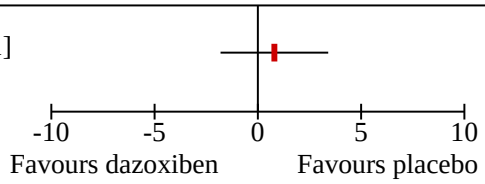
Analysis 4.1. Comparison 4: Dazoxiben versus placebo, Outcome 1: Frequency of attacks per week

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
Ettinger 1984	0.8	1.33	0.80 [-1.81 , 3.41]

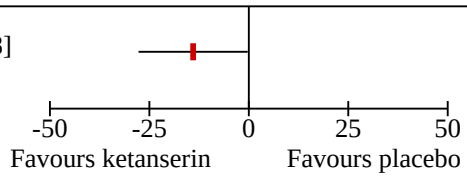


Comparison 5. Ketanserin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Frequency of attacks per week	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.2 Severity score (frequency of attacks/d × duration of attacks)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.3 Duration of attacks per day (minutes)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.4 Capillaroscopic flow/skin perfusion by ultrasound	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.5 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5: Ketanserin versus placebo, Outcome 1: Frequency of attacks per week

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
Van de Wal 1987	-14	7	-14.00 [-27.72 , -0.28]



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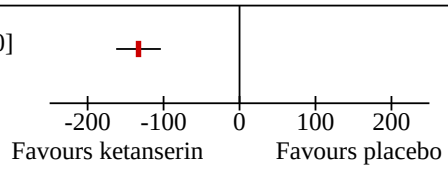
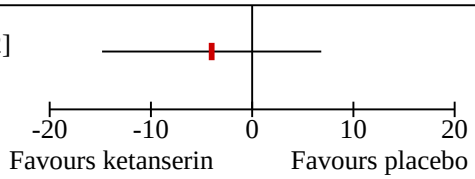
Analysis 5.2. Comparison 5: Ketanserin versus placebo, Outcome 2: Severity score (frequency of attacks/d × duration of attacks)

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
Van de Wal 1987	-133	15	-133.00 [-162.40 , -103.60]



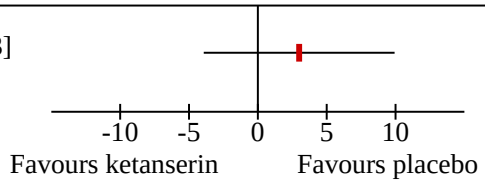
Analysis 5.3. Comparison 5: Ketanserin versus placebo, Outcome 3: Duration of attacks per day (minutes)

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
Van de Wal 1987	-4	5.523	-4.00 [-14.82 , 6.82]



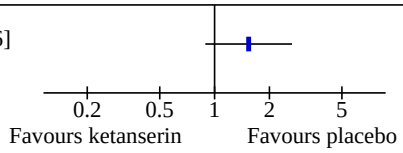
Analysis 5.4. Comparison 5: Ketanserin versus placebo, Outcome 4: Capillaroscopic flow/skin perfusion by ultrasound

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
Van de Wal 1987	3	3.536	3.00 [-3.93 , 9.93]



Analysis 5.5. Comparison 5: Ketanserin versus placebo, Outcome 5: Adverse events

Study or Subgroup	Ketanserin Events	Ketanserin Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Van de Wal 1987	20	41	13	41	1.54 [0.89 , 2.66]



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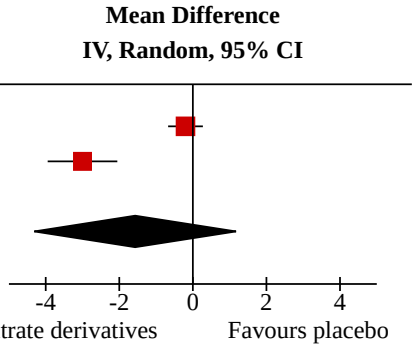
Comparison 6. Nitrate/nitrate derivatives versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Frequency of attacks	2		Mean Difference (IV, Random, 95% CI)	-1.57 [-4.31, 1.17]
6.2 Severity of symptoms	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.3 Capillaroscopic flow/skin perfusion by ultrasound	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.4 Raynaud Condition Score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6: Nitrate/nitrate derivatives versus placebo, Outcome 1: Frequency of attacks

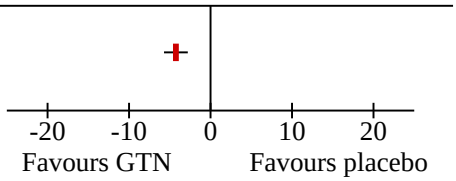
Study or Subgroup	MD	SE	Weight	Mean Difference IV, Random, 95% CI
Chung 2009	-0.2	0.241	51.1%	-0.20 [-0.67 , 0.27]
Teh 1995	-3	0.483	48.9%	-3.00 [-3.95 , -2.05]
Total (95% CI)			**100.0%**	**-1.57 [-4.31 , 1.17]**

Heterogeneity: Tau² = 3.77; Chi² = 26.91, df = 1 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Nitrate/nitrate derivatives versus placebo, Outcome 2: Severity of symptoms

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
Teh 1995	-4.25	0.744	-4.25 [-5.71 , -2.79]



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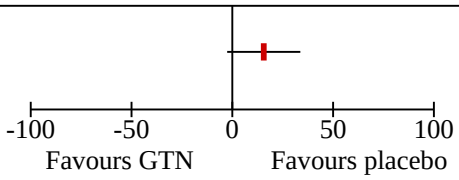
Analysis 6.3. Comparison 6: Nitrate/nitrate derivatives versus placebo, Outcome 3: Capillaroscopic flow/skin perfusion by ultrasound

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
Sovijarvi 1984 (1)	15.6	9.257	15.60 [-2.54 , 33.74]

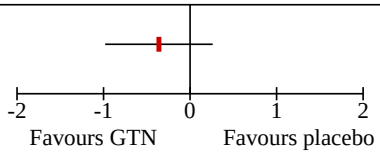


Footnotes

(1) Digital blood pressure in mmHg

Analysis 6.4. Comparison 6: Nitrate/nitrate derivatives versus placebo, Outcome 4: Raynaud Condition Score

Study or Subgroup	MD	SE	GTN Total	Placebo Total	Mean Difference IV, Fixed, 95% CI
Chung 2009	-0.36	0.317	32	37	-0.36 [-0.98 , 0.26]



Comparison 7. Phosphodiesterase inhibitors versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Frequency of attacks per week	2		Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-6.71, 6.61]
7.1.1 Cilostazol	1		Std. Mean Difference (IV, Random, 95% CI)	3.50 [0.64, 6.36]
7.1.2 PF-00489791	1		Std. Mean Difference (IV, Random, 95% CI)	-3.30 [-3.92, -2.68]
7.2 Severity of symptoms	2		Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-1.04, 0.97]
7.2.1 Cilostazol	1		Std. Mean Difference (IV, Random, 95% CI)	0.50 [0.09, 0.91]
7.2.2 PF-00489791	1		Std. Mean Difference (IV, Random, 95% CI)	-0.53 [-0.63, -0.43]
7.3 Duration of attacks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.4 Capillaroscopic flow/skin perfusion by ultrasound	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

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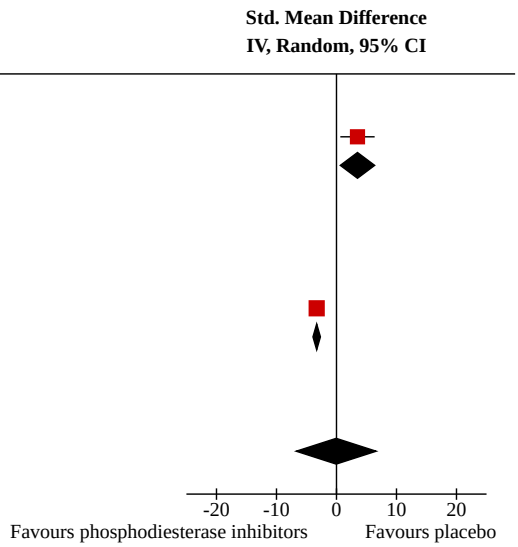
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.5 Adverse events	1	156	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.10, 2.03]
7.6 Raynaud Condition Score	2		Std. Mean Difference (IV, Random, 95% CI)	-0.80 [-1.74, 0.13]
7.6.1 Vardenafil	1		Std. Mean Difference (IV, Random, 95% CI)	-1.61 [-3.09, -0.13]
7.6.2 PF-00489791	1		Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.60, -0.44]

Analysis 7.1. Comparison 7: Phosphodiesterase inhibitors versus placebo, Outcome 1: Frequency of attacks per week

Study or Subgroup	SMD	SE	Weight	Std. Mean Difference IV, Random, 95% CI
7.1.1 Cilostazol				
Rajagopalan 2003	3.5	1.459	47.8%	3.50 [0.64 , 6.36]
Subtotal (95% CI)			**47.8%**	**3.50 [0.64 , 6.36]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.40 (P = 0.02)				
7.1.2 PF-00489791				
NCT01090492	-3.3	0.315	52.2%	-3.30 [-3.92 , -2.68]
Subtotal (95% CI)			**52.2%**	**-3.30 [-3.92 , -2.68]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 10.48 (P < 0.00001)				
Total (95% CI)			**100.0%**	**-0.05 [-6.71 , 6.61]**
Heterogeneity: Tau² = 22.01; Chi² = 20.75, df = 1 (P < 0.00001); I² = 95%				
Test for overall effect: Z = 0.01 (P = 0.99)				
Test for subgroup differences: Chi² = 20.75, df = 1 (P < 0.00001), I² = 95.2%				



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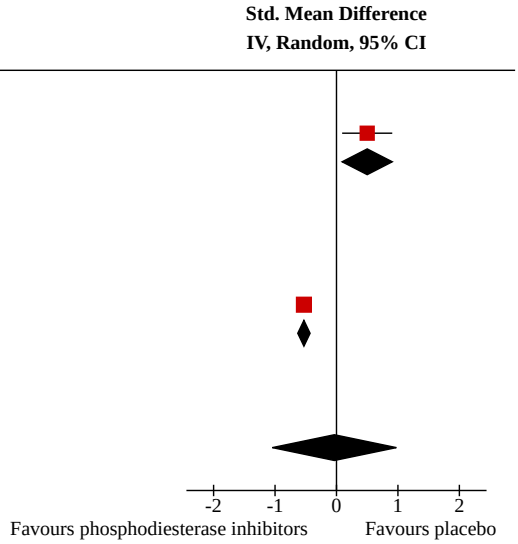
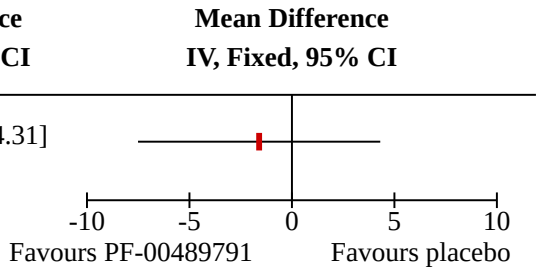
Analysis 7.2. Comparison 7: Phosphodiesterase inhibitors versus placebo, Outcome 2: Severity of symptoms

Study or Subgroup	SMD	SE	Weight	Std. Mean Difference IV, Random, 95% CI
7.2.1 Cilostazol				
Rajagopalan 2003	0.5	0.208	48.1%	0.50 [0.09 , 0.91]
Subtotal (95% CI)			**48.1%**	**0.50 [0.09 , 0.91]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.40 (P = 0.02)				
7.2.2 PF-00489791				
NCT01090492	-0.53	0.051	51.9%	-0.53 [-0.63 , -0.43]
Subtotal (95% CI)			**51.9%**	**-0.53 [-0.63 , -0.43]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 10.39 (P < 0.00001)				
Total (95% CI)			**100.0%**	**-0.03 [-1.04 , 0.97]**
Heterogeneity: Tau² = 0.51; Chi² = 23.13, df = 1 (P < 0.00001); I² = 96%				
Test for overall effect: Z = 0.07 (P = 0.95)				
Test for subgroup differences: Chi² = 23.13, df = 1 (P < 0.00001), I² = 95.7%				



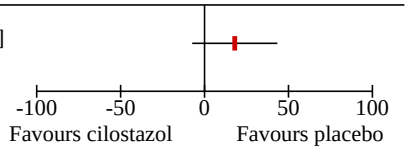
Analysis 7.3. Comparison 7: Phosphodiesterase inhibitors versus placebo, Outcome 3: Duration of attacks

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
NCT01090492	-1.6	3.015	-1.60 [-7.51 , 4.31]



Analysis 7.4. Comparison 7: Phosphodiesterase inhibitors versus placebo, Outcome 4: Capillaroscopic flow/skin perfusion by ultrasound

Study or Subgroup	MD	SE	Cilostazol Total	Placebo Total	Mean Difference IV, Fixed, 95% CI
Rajagopalan 2003	18	12.93	19	19	18.00 [-7.34 , 43.34]



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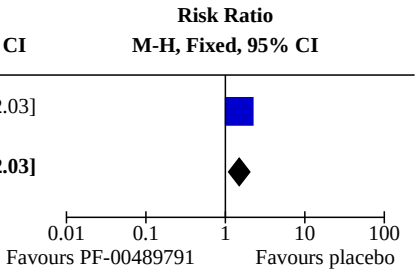
Analysis 7.5. Comparison 7: Phosphodiesterase inhibitors versus placebo, Outcome 5: Adverse events

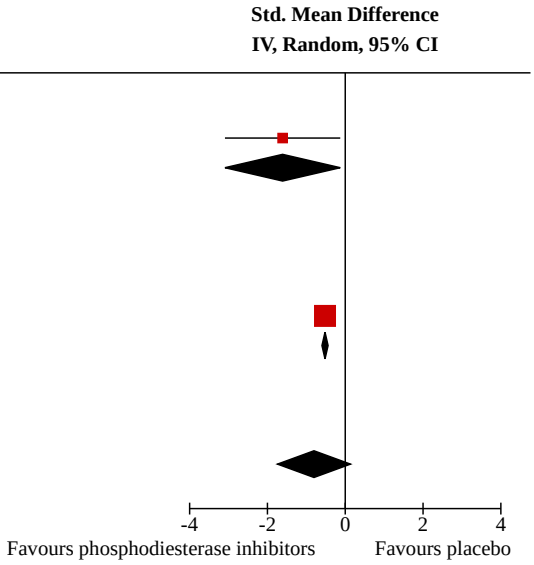
Study or Subgroup	PF-00489791 Events	PF-00489791 Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NCT01090492	34	54	43	102	100.0%	1.49 [1.10 , 2.03]
Total (95% CI)		**54**		**102**	**100.0%**	**1.49 [1.10 , 2.03]**
Total events:	34		43			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.57 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 7.6. Comparison 7: Phosphodiesterase inhibitors versus placebo, Outcome 6: Raynaud Condition Score

Study or Subgroup	SMD	SE	Weight	Std. Mean Difference IV, Random, 95% CI
7.6.1 Vardenafil				
Caglayan 2012	-1.61	0.756	26.0%	-1.61 [-3.09 , -0.13]
Subtotal (95% CI)			**26.0%**	**-1.61 [-3.09 , -0.13]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.13 (P = 0.03)				
7.6.2 PF-00489791				
NCT01090492	-0.52	0.04	74.0%	-0.52 [-0.60 , -0.44]
Subtotal (95% CI)			**74.0%**	**-0.52 [-0.60 , -0.44]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 13.00 (P < 0.00001)				
Total (95% CI)			**100.0%**	**-0.80 [-1.74 , 0.13]**
Heterogeneity: Tau² = 0.31; Chi² = 2.07, df = 1 (P = 0.15); I² = 52%				
Test for overall effect: Z = 1.68 (P = 0.09)				
Test for subgroup differences: Chi² = 2.07, df = 1 (P = 0.15), I² = 51.8%				



ADDITIONAL TABLES

Table 1. Classification of drugs with vasodilator effects, from Australian Medicines Handbook

Pharmacologic class	ATC code	Generic name
Phosphodiesterase-3 inhibitor	C01CE02, B01AC23	Milrinone, cilostazol
Neprilysin inhibitor	C09DX04	Sacubitril
Nitrate/nitrate derivative	C01D, C08EX02, C02D-D01	Glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate, nicorandil, sodium nitroprusside
Angiotensin-converting enzyme (ACE) inhibitor	C09A	Captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril
Angiotensin-II receptor antagonist	C09C	Candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Selective alpha-blocker	C02CA, C02AC	Prazosin, terazosin, moxonidine, tamsulosin, alfuzosin

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Table 1. Classification of drugs with vasodilator effects, from Australian Medicines Handbook *(Continued)*

Potassium channel activator	C02DA	Diazoxide
Reflex sympathetic stimulator	C02D	Hydralazine, minoxidil
Prostacyclin/prostanoid	B01AC, G04BE01	Epoprostenol, iloprost, treprostinil, alprostadil, beraprost
Endothelin antagonist	C02KX	Ambrisentan, bosentan, macitentan, rociguat
Phosphodiesterase-5 inhibitor	G04BE	Sildenafil, tadalafil, vardenafil
Selective serotonin reuptake inhibitor	N06AB, C02KD01	Citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, ketanserin
Peripheral vasodilator, mechanism not well defined	C04AD	Pentoxifylline, perhexiline

AMH: Australian Medicines Handbook.
ATC: Anatomical Therapeutic Chemical Classification.

Table 2. Included and excluded trials presented by AMH chapter and ATC code

AMH Chapter	Class	ATC Code	Trials
Cardiovascular drugs	Vasodilators, antihypertensive drugs, and prostacyclin analogues	C02D, B01A	Included: Rajagopalan 2003; Vayssairat 1996 Excluded: Bali 2011; Belch 1983; Belch 1995; Belluci 1990; Kingma 1995; Kirichenko 1991; Kyle 1992; Marasini 2004; Mohrland 1985; NCT00048763; Shawket 1991; Torley 1990 Ongoing: NCT02583789 Awaiting classification: Sakaguchi 1990
Cardiovascular drugs	Phosphodiesterase type 5 inhibitors	G04BE	Included: Caglayan 2012; NCT01090492 Excluded: Friedman 2007; Kahan 1985; Lee 2014 [a]; Mirza 2019; Roustit 2017 Ongoing: EUCTR2005-000295-41-DE
Cardiovascular drugs/endocrine drugs	Alpha adrenoreceptor-blocking drugs	C02C	Included: none Excluded: Clement 1980; Clement 1986; Cleophas 1984; Grigg 1989; Nielsen 1983; Russell 1985; Surwit 1982; Wollersheim 1986
Unlisted	Serotonin antagonists (Ketanserin)	C02KD	Included: Van de Wal 1987 Excluded: Arosio 1989 [b]; Bellucci 1987; Coffman 1989; Longstaff 1985; Marasini 1988; Seibold 1986; Tooke 1990
Cardiovascular drugs	Angiotensin-converting enzyme inhibitors	C09A	Included: Challenor 1991; Madsen 1984; Excluded: JaniniDa 1988; Shcherbakov 1992
Cardiovascular drugs	Angiotensin-II receptor antagonists	C09C	Included: none Excluded: Barry 2000; Dziadzio 1999
Cardiovascular drugs	Nitrates	C01D	Included: Chung 2009; Nahir 1986; Teh 1995 Excluded: Diehm 1983; Fischer 1985; Tucker 1999

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Table 2. Included and excluded trials presented by AMH chapter and ATC code *(Continued)*

Unlisted	Peripheral vasodilators and related drugs	C04A	Included: Jaffe 1980; Le Quentrec 1991 Excluded: Courbier 1981; Davinroy 1993; Maurel 1995; Nilsen 1979; Sunderland 1988; Wesseling 1981
Psychotropic drugs	Selective serotonin reuptake inhibitors	N06A B	Included: none Excluded: Coleiro 2001
Allergy and anaphylaxis	Antihistamines	N07CA	Included: none Excluded: none
	Other (including Bradilan, Dazoxiben, UK-38, 485 (dazmegrel))		Included: Ettinger 1984 Excluded: Arcas Meca 1972; Arnot 1978; Arosio 1989 [b]; Belch 1985; Dumoulin 1981; Jenkins 2013; Luderer 1984; McFadyen 1973; NCT01233999; Strozzi 1982 [c]

AMH: Australian Medicines Handbook.
ATC: Anatomical Therapeutical Classification.
[a]Comparison between udenafil and amlodipine.
[b]This study mentions ketanserin and pentoxifylline.
[c]This study mentions alpha-methyldopa, guanethidine, and debrisoquine.

Table 3. Identified drugs presented by AMH chapter and ATC codes

AMH	Class	ATC code	Drug name
Cardiovascular drugs	Vasodilators, antihypertensive drugs including prostacyclin analogues	C02D, B01A	Included: beraprost sodium, cilostazol Excluded: alprostadil, cilostazol, epoprostenol, iloprost, prostacyclin, prostaglandin E1, treprostinil (prostacyclin PGI2 analogue) Ongoing: beraprost
Cardiovascular drugs	Phosphodiesterase inhibitors/phosphodiesterase type 5 inhibitors	G04BE	Included: vardenafil Excluded: PF-00489791, sildenafil, tadalafil, udenafil, vardenafil Ongoing: vardenafil
Cardiovascular drugs/endocrine drugs	Alpha adrenoreceptor-blocking drugs	C02C	Included: thymoxamine Excluded: indoramin, prazosin, phenoxybenzamine, thymoxamine
Cardiovascular drugs	Angiotensin-converting enzyme inhibitors	C09A	Included: captopril, enalapril Excluded: captopril, enalapril
Cardiovascular drugs	Angiotensin-II receptor antagonists	C09C	Included: none Excluded: losartan
Cardiovascular drugs	Nitrates	C01D	Included: nitroglycerin/glyceryl trinitrate Excluded: glyceryl trinitrate/nitroglycerin/sodium nitrate, isosorbide dinitrate
Unlisted	Peripheral vasodilators and related drugs	C04A	Included: buflomedil, thymoxamine Excluded: buflomedil, inositol nicotinate, isoxsuprine, naftidrofuryl

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Table 3. Identified drugs presented by AMH chapter and ATC codes *(Continued)*

Psychotropic drugs	Selective serotonin re-uptake inhibitors	N06AB	Included: ketanserin Excluded: fluoxetine, ketanserin
Allergy and anaphy-laxis	Antihistamines	N07CA	Included: none Excluded: none
	Others		Included: dazoxiben Excluded: alpha-methyldopa, botulinum toxin, bradilan, CL115,347 (Cyanamid International), dazoxiben, debriso-quine, guanethidine, pentoxifylline, reserpine, suloctidil

AMH: Australian Medicines Handbook.
ATC: Anatomical Therapeutical Classification.

APPENDICES

Appendix 1. CENTRAL search strategy July 2014

#1	MESH DESCRIPTOR Raynaud Disease EXPLODE ALL TREES	264
#2	raynaud:TI,AB,KY	461
#3	#1 OR #2	462
#4	MESH DESCRIPTOR Vasodilator Agents EXPLODE ALL TREES	3259
#5	MESH DESCRIPTOR Vasodilation	1689
#6	(bosentan or hydralazine or iloprost or alprostadil or beraprost or silde-nafil):TI,AB,KY	2366
#7	MESH DESCRIPTOR Antihypertensive Agents EXPLODE ALL TREES	6201
#8	MESH DESCRIPTOR Adrenergic alpha-Antagonists EXPLODE ALL TREES	1015
#9	(Doxazosin or thymoxamine or indoramin or prazosin or terazosin or ura-pidil):TI,AB,KY	1554
#10	(alpha near2 (antag* or inhib* or block*)):TI,AB,KY	2914
#11	MESH DESCRIPTOR Serotonin Antagonists EXPLODE ALL TREES	935
#12	Ketanserin:TI,AB,KY	423
#13	(serotonin near2 (antag* or inhib* or block*)):TI,AB,KY	4332
#14	MESH DESCRIPTOR Angiotensin-Converting Enzyme Inhibitors EXPLODE ALL TREES	3451
#15	(angiotensin near2 (antag* or inhib* or block*)):TI,AB,KY	6729
#16	(ace near2 (antag* or inhib* or block*)):TI,AB,KY	2662

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(Continued)

#17	(captopril or cilazapril or enalapril maleate or fosinopril sodium or imidapril or lisinopril or moexipril or perindopril or quinalapril or ramipril or trandolapril):TI,AB,KY	4905
#18	(candesartan cilexitil or eprosartan or losartan or olmesartan or medoxomil or telmisartan or valsartan):TI,AB,KY	3091
#19	MESH DESCRIPTOR Nitrates EXPLODE ALL TREES	650
#20	(Glyceryl trinitrate or isosorbide dinitrate or isosorbide mononitrate):TI,AB,KY	2043
#21	(Cilostazol or inositol nicotinate or moxisylyte or naftidrofuryl or pentoxif*):TI,AB,KY	1347
#22	MESH DESCRIPTOR Serotonin Uptake Inhibitors EXPLODE ALL TREES	2071
#23	(Citalopram or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline):TI,AB,KY	6762
#24	MESH DESCRIPTOR Histamine Antagonists EXPLODE ALL TREES	2480
#25	(histamine near2 (antag* or inhib* or block*)):TI,AB,KY	3020
#26	Cinnarizine:TI,AB,KY	170
#27	MESH DESCRIPTOR Phosphodiesterase 5 Inhibitors EXPLODE ALL TREES	157
#28	(phosphodiesterase near2 (antag* or inhib* or block*)):TI,AB,KY	1197
#29	(Sildenafil or tadalafil or vardenafil):TI,AB,KY	1101
#30	#4 OR #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 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	39602
#31	#3 AND #30	160

Appendix 2. Database searches November 2020

Source	Search strategy	Hits retrieved
VASCULAR REGISTER IN CRSW	#1 Raynaud* AND INREGISTER	25.10.18: 0
	#2 Vasodila* AND INREGISTER	02.12.19: 10
	#3 #1 AND #2	16.11.20: 8
CENTRAL via CRSO	#1 MESH DESCRIPTOR Raynaud Disease EXPLODE ALL TREES 321	25.10.18: 441
	#2 raynaud*:TI,AB,KY 659	02.12.19: 108
	#3 #1 OR #2 661	16.11.20: 110
	#4 MESH DESCRIPTOR Vasodilator Agents EXPLODE ALL TREES 24070	

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(Continued)

#5 MESH DESCRIPTOR VASODILATION EXPLODE ALL TREES 2022

#6 (bosentan or hydralazine or iloprost or alprostadil or beraprost or sildenafil):TI,AB,KY 3501

#7 MESH DESCRIPTOR Antihypertensive Agents EXPLODE ALL TREES 25663

#8 MESH DESCRIPTOR Adrenergic alpha-Antagonists EXPLODE ALL TREES 3341

#9 (Doxazosin or thymoxamine or indoramin or prazosin or terazosin or urapidil):TI,AB,KY 1914

#10 (alpha adj2 (antag* or inhib* or block*)):TI,AB,KY 4147

#11 MESH DESCRIPTOR Serotonin Antagonists EXPLODE ALL TREES 5540

#12 Ketanserin:TI,AB,KY 455

#13 (serotonin adj2 (antag* or inhib* or block*)):TI,AB,KY 5955

#14 MESH DESCRIPTOR Angiotensin-Converting Enzyme Inhibitors EXPLODE ALL TREES 6029

#15 (angiotensin adj2 (antag* or inhib* or block*)):TI,AB,KY 9290

#16 (ace adj2 (antag* or inhib* or block*)):TI,AB,KY 3277

#17 (captopril or cilazapril or enalapril maleate or fosinopril sodium or imidapril or lisinopril or moexipril or perindopril or quinalapril or ramipril or trandolapril):TI,AB,KY 5957

#18 (candesartan cilexitil or eprosartan or losartan or olmesartan or medoxomil or telmisartan or valsartan):TI,AB,KY 4860

#19 MESH DESCRIPTOR NITRATES EXPLODE ALL TREES 888

#20 (Glyceryl trinitrate or isosorbide dinitrate or isosorbide mononitrate):TI,AB,KY 2978

#21 MESH DESCRIPTOR Serotonin Uptake Inhibitors EXPLODE ALL TREES 5973

#22 (Citalopram or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline):TI,AB,KY 9177

#23 (Cilostazol or inositol nicotinate or moxisylyte or naftidrofuryl or pentoxif*):TI,AB,KY 1924

#24 MESH DESCRIPTOR Histamine Antagonists EXPLODE ALL TREES 7616

#25 (histamine adj2 (antag* or inhib* or block*)):TI,AB,KY 3494

#26 MESH DESCRIPTOR Phosphodiesterase 5 Inhibitors EXPLODE ALL TREES 1332

#27 Cinnarizine:TI,AB,KY 192

#28 (phosphodiesterase adj2 (antag* or inhib* or block*)):TI,AB,KY 2065

#29 (Sildenafil or tadalafil or vardenafil):TI,AB,KY 2238

#30 #4 OR #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 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 81511

#31 #3 AND #30 316

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(Continued)

	#32 01/01/2014 TO 24/10/2018:CD 570405 #33 #31 AND #32 77 #34 alfuzosin:TI,AB,KY 212 #35 Ambrisentan:TI,AB,KY 126 #36 Dapoxetine:TI,AB,KY 71 #37 Diazoxide:TI,AB,KY 96 #38 Epoprostenol:TI,AB,KY 569 #39 Irbesartan:TI,AB,KY 712 #40 Lisiniopril:TI,AB,KY 0 #41 Macitentan:TI,AB,KY 114 #42 Milrinone:TI,AB,KY 308 #43 minoxidil:TI,AB,KY 305 #44 Moxonidine:TI,AB,KY 118 #45 nicorandil:TI,AB,KY 296 #46 Pentoxifylline:TI,AB,KY 1022 #47 perhexiline:TI,AB,KY 85 #48 quinapril:TI,AB,KY 329 #49 rociguat:TI,AB,KY 1 #50 Sacubitril:TI,AB,KY 181 #51 Tamsulosin:TI,AB,KY 953 #52 Treprostinil:TI,AB,KY 147 #53 MESH DESCRIPTOR Sildenafil Citrate EXPLODE ALL TREES 814 #54 #4 OR #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 OR #20 OR #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 631433 #55 #3 AND #54 441	
Clinicaltrials.gov	Raynaud OR Raynaud's OR Raynaud OR Raynaud disease | Vasodilator OR Antihypertensive OR Adrenergic alpha-Antagonists OR Serotonin Antagonists OR Angiotensin-Converting Enzyme Inhibitors	25.10.18: 32 02.12.19: 6 16.11.20: 4
ICTRP Search Portal	Raynaud OR Raynaud's OR Raynaud OR Raynaud disease | Vasodilator OR Antihypertensive OR Adrenergic alpha-Antagonists OR Serotonin Antagonists OR Angiotensin-Converting Enzyme Inhibitors	25.10.18: 1 02.12.19: 0 16.11.20: 0
MEDLINE (Ovid MEDLINE® Epub Ahead	1 exp Raynaud Disease/ 6570	25.10.18: 998

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(Continued)

of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present	2 raynaud*.ti,ab. 6731	02.12.19: 27
	3 1 or 2 9177	16.11.20: 38
	4 exp Vasodilator Agents/ 410533	
	5 exp VASODILATION/ 30789	
	6 (bosentan or hydralazine or iloprost or alprostadil or beraprost or sildenafil).ti,ab. 14949	
	7 exp Antihypertensive Agents/ 245458	
	8 exp Adrenergic alpha-Antagonists/ 48892	
	9 (Doxazosin or thymoxamine or indoramin or prazosin or terazosin or urapidil).ti,ab. 13131	
	10 (alpha adj2 (antag* or inhib* or block*)).ti,ab. 45486	
	11 exp Serotonin Antagonists/ 49630	
	12 Ketanserin.ti,ab. 4504	
	13 (serotonin adj2 (antag* or inhib* or block*)).ti,ab. 18486	
	14 exp Angiotensin-Converting Enzyme Inhibitors/ 41972	
	15 (angiotensin adj2 (antag* or inhib* or block*)).ti,ab. 17998	
	16 (ace adj2 (antag* or inhib* or block*)).ti,ab. 18999	
	17 (captopril or cilazapril or enalapril maleate or fosinopril sodium or imidapril or lisinopril or moexipril or perindopril or quinalapril or ramipril or trandolapril).ti,ab. 18313	
	18 (candesartan cilexitil or eprosartan or losartan or olmesartan or medoxomil or telmisartan or valsartan).ti,ab. 13883	
	19 exp NITRATES/ 31814	
	20 (Glyceryl trinitrate or isosorbide dinitrate or isosorbide mononitrate).ti,ab. 4954	
	21 exp Serotonin Uptake Inhibitors/ 35285	
	22 (Citalopram or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline).ti,ab. 23972	
	23 (Cilostazol or inositol nicotinate or moxisylyte or naftidrofuryl or pentoxif*).ti,ab. 6239	
	24 exp Histamine Antagonists/ 60158	
	25 (histamine adj2 (antag* or inhib* or block*)).ti,ab. 6448	
	26 Cinnarizine.ti,ab. 722	
	27 exp Phosphodiesterase 5 Inhibitors/ 7473	
	28 (phosphodiesterase adj2 (antag* or inhib* or block*)).ti,ab. 11497	
	29 (tadalafil or vardenafil).ti,ab. 2233	
	30 "sodium nitroprusside".ti,ab. 13131	
	31 alfuzosin.ti,ab. 492	

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(Continued)

32 Ambrisentan.ti,ab. 301

33 Dapoxetine.ti,ab. 194

34 Diazoxide.ti,ab. 3210

35 Epoprostenol.ti,ab. 968

36 Irbesartan.ti,ab. 1538

37 Lisiniopril.ti,ab. 0

38 Macitentan.ti,ab. 195

39 Milrinone.ti,ab. 1806

40 minoxidil.ti,ab. 1686

41 Moxonidine.ti,ab. 567

42 nicorandil.ti,ab. 1504

43 Pentoxifylline.ti,ab. 4194

44 perhexiline.ti,ab. 525

45 quinapril.ti,ab. 737

46 rociguat.ti,ab. 0

47 Sacubitril.ti,ab. 377

48 Tamsulosin.ti,ab. 1571

49 Treprostinil.ti,ab. 435

50 exp Sildenafil Citrate/ 5048

51 or/4-50 824362

52 3 and 51 1379

53 randomized controlled trial.pt. 470112

54 controlled clinical trial.pt. 92712

55 randomized.ab. 424838

56 placebo.ab. 192687

57 drug therapy.fs. 2056037

58 randomly.ab. 299399

59 trial.ab. 442674

60 groups.ab. 1845353

61 or/53-60 4304625

62 exp animals/ not humans.sh. 4507542

63 61 not 62 3721383

64 52 and 63 998

65 from 64 keep 1-998 998

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(Continued)

Embase	1 exp Raynaud phenomenon/ 12099	25.10.18: 734
	2 raynaud*.ti,ab. 9660	02.12.19: 92
	3 1 or 2 14444	16.11.20: 110
	4 exp vasodilator agent/ 574060	
	5 exp vasodilatation/ 77616	
	6 (bosentan or hydralazine or iloprost or alprostadil or beraprost or sildenafil).ti,ab. 21226	
	7 exp antihypertensive agent/ 641044	
	8 exp alpha adrenergic receptor blocking agent/ 276545	
	9 (Doxazosin or thymoxamine or indoramin or prazosin or terazosin or urapidil).ti,ab. 15269	
	10 (alpha adj2 (antag* or inhib* or block*)).ti,ab. 48448	
	11 exp serotonin antagonist/ 204382	
	12 Ketanserin.ti,ab. 4884	
	13 (serotonin adj2 (antag* or inhib* or block*)).ti,ab. 24182	
	14 exp dipeptidyl carboxypeptidase inhibitor/ 163741	
	15 (angiotensin adj2 (antag* or inhib* or block*)).ti,ab. 24884	
	16 (ace adj2 (antag* or inhib* or block*)).ti,ab. 28775	
	17 (captopril or cilazapril or enalapril maleate or fosinopril sodium or imidapril or lisinopril or moexipril or perindopril or quinalapril or ramipril or trandolapril).ti,ab. 24871	
	18 (candesartan cilexitil or eprosartan or losartan or olmesartan or medoxomil or telmisartan or valsartan).ti,ab. 20929	
	19 (Glyceryl trinitrate or isosorbide dinitrate or isosorbide mononitrate).ti,ab. 6441	
	20 exp serotonin uptake inhibitor/ 235187	
	21 (Citalopram or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline).ti,ab. 33080	
	22 (Cilostazol or inositol nicotinate or moxisylyte or naftidrofuryl or pentoxif*).ti,ab. 8555	
	23 exp antihistaminic agent/ 222975	
	24 (histamine adj2 (antag* or inhib* or block*)).ti,ab. 7617	
	25 Cinnarizine.ti,ab. 877	
	26 exp phosphodiesterase V inhibitor/ 27049	
	27 (phosphodiesterase adj2 (antag* or inhib* or block*)).ti,ab. 14510	
	28 (Sildenafil or tadalafil or vardenafil).ti,ab. 11928	
	29 alfuzosin.ti,ab. 692	

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(Continued)

30 Ambrisentan.ti,ab. 652

31 Dapoxetine.ti,ab. 338

32 Diazoxide.ti,ab. 3983

33 Epoprostenol.ti,ab. 1576

34 Irbesartan.ti,ab. 2371

35 Lisiniopril.ti,ab. 1

36 Macitentan.ti,ab. 442

37 Milrinone.ti,ab. 2608

38 minoxidil.ti,ab. 2275

39 Moxonidine.ti,ab. 819

40 nicorandil.ti,ab. 2132

41 Pentoxifylline.ti,ab. 5322

42 perhexiline.ti,ab. 640

43 quinapril.ti,ab. 951

44 rociguat.ti,ab. 1

45 Sacubitril.ti,ab. 675

46 Tamsulosin.ti,ab. 2561

47 Treprostinil.ti,ab. 908

48 exp sildenafil/ 19943

49 or/4-48 1519000

50 3 and 49 3805

51 randomized controlled trial/ 518986

52 controlled clinical trial/ 458184

53 random$.ti,ab. 1341813

54 randomization/ 79825

55 intermethod comparison/ 239695

56 placebo.ti,ab. 277614

57 (compare or compared or comparison).ti. 462043

58 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 1809772

59 (open adj label).ti,ab. 66600

60 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 211128

61 double blind procedure/ 154280

62 parallel group$1.ti,ab. 22355

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(Continued)

	63 (crossover or cross over).ti,ab. 94501	
	64 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 289979	
	65 (assigned or allocated).ti,ab. 340890	
	66 (controlled adj7 (study or design or trial)).ti,ab. 302232	
	67 (volunteer or volunteers).ti,ab. 227096	
	68 trial.ti. 254058	
	69 or/51-68 4110857	
	70 50 and 69 734	
CINAHL	S65 S51 AND S64 37	25.10.18: 37
	S64 S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 295,017	02.12.19: 12
	S63 MH "Random Assignment" 39,643	16.11.20: 8
	S62 MH "Single-Blind Studies" or MH "Double-Blind Studies" or MH "Triple-Blind Studies" 33,125	
	S61 MH "Crossover Design" 11,347	
	S60 MH "Factorial Design" 925	
	S59 MH "Placebos" 8,410	
	S58 MH "Clinical Trials" 93,441	
	S57 TX "multi-centre study" OR "multi-center study" OR "multicentre study" OR "multicenter study" OR "multi-site study" 4,609	
	S56 TX crossover OR "cross-over" 14,777	
	S55 AB placebo* 28,886	
	S54 TX random* 223,391	
	S53 TX "latin square"TX trial* 2	
	S52 TX "latin square" 145	
	S51 S3 AND S50 124	
	S50 S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 45,975	
	S49 (MH "Sildenafil") 942	
	S48 TX Treprostinil 103	
	S47 TX Tamsulosin 224	
	S46 TX Sacubitril 90	
	S45 TX rociguat 0	
	S44 TX quinapril 41	

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(Continued)

S43 TX perhexiline 8

S42 TX Pentoxifylline 357

S41 TX nicorandil 93

S40 TX Moxonidine 25

S39 TX minoxidil 133

S38 TX Milrinone 194

S37 TX Macitentan 37

S36 TX Lisiniopril 0

S35 TX Irbesartan 285

S34 TX Epoprostenol 546

S33 TX Diazoxide 127

S32 TX Dapoxetine 23

S31 TX Ambrisentan 55

S30 TX alfuzosin 41

S29 TX Sildenafil or tadalafil or vardenafil 1,476

S28 TX phosphodiesterase n2 (antag* or inhib* or block*) 1,126

S27 (MH "Phosphodiesterase Inhibitors+") 1,902

S26 TX Cinnarizine 16

S25 TX histamine n2 (antag* or inhib* or block*) 2,709

S24 (MH "Histamine Antagonists+") 3,729

S23 TX Cilostazol or inositol nicotinate or moxisylyte or naftidrofuryl or pentoxif* 566

S22 TX Citalopram or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline 3,567

S21 (MH "Serotonin Uptake Inhibitors+") 6,734

S20 TX Glyceryl trinitrate or isosorbide dinitrate or isosorbide mononitrate 429

S19 (MH "Nitrates+") 953

S18 TX candesartan cilexitil or eprosartan or losartan or olmesartan or medoxomil or telmisartan or valsartan 1,765

S17 TX captopril or cilazapril or enalapril maleate or fosinopril sodium or imidapril or lisinopril or moexipril or perindopril or quinalapril or ramipril or trandolapril 1,524

S16 TX ace n2 (antag* or inhib* or block*) 1,895

S15 TX angiotensin n2 (antag* or inhib* or block*) 7,337

S14 (MH "Angiotensin-Converting Enzyme Inhibitors+") 5,700

S13 TX serotonin n2 (antag* or inhib* or block*) 5,440

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(Continued)

	S12 TX Ketanserin 48	
	S11 (MH "Serotonin Antagonists+") 1,228	
	S10 TX alpha n2 (antag* or inhib* or block*) 1,881	
	S9 TX Doxazosin or thymoxamine or indoramin or prazosin or terazosin or urapidil 401	
	S8 (MH "Adrenergic Alpha-Antagonists+") 1,086	
	S7 (MH "Antihypertensive Agents+") 17,437	
	S6 TX bosentan or hydralazine or iloprost or alprostadil or beraprost or sildenafil 2,107	
	S5 (MH "Vasodilation") 1,947	
	S4 (MH "Vasodilator Agents+") 10,431	
	S3 S1 OR S2 786	
	S2 TX raynaud* 754	
	S1 (MH "Raynaud's Disease+") 525	
AMED	1 exp Raynauds disease/ 19	25.10.18: 0
	2 raynaud*.ti,ab. 49	02.12.19: 0
	3 1 or 2 52	16.11.20: 0
	4 exp Vasodilator agents/ 109	
	5 exp Vasodilation/ 85	
	6 (bosentan or hydralazine or iloprost or alprostadil or beraprost or sildenafil).ti,ab. 31	
	7 exp Antihypertensive agents/ 225	
	8 (Doxazosin or thymoxamine or indoramin or prazosin or terazosin or urapidil).ti,ab. 33	
	9 (alpha adj2 (antag* or inhib* or block*)).ti,ab. 240	
	10 Ketanserin.ti,ab. 8	
	11 (serotonin adj2 (antag* or inhib* or block*)).ti,ab. 112	
	12 (angiotensin adj2 (antag* or inhib* or block*)).ti,ab. 43	
	13 (ace adj2 (antag* or inhib* or block*)).ti,ab. 57	
	14 (captopril or cilazapril or enalapril maleate or fosinopril sodium or imidapril or lisinopril or moexipril or perindopril or quinalapril or ramipril or trandolapril).ti,ab. 39	
	15 (candesartan cilexitil or eprosartan or losartan or olmesartan or medoxomil or telmisartan or valsartan).ti,ab. 17	
	16 (Glyceryl trinitrate or isosorbide dinitrate or isosorbide mononitrate).ti,ab. 12	
	17 (Citalopram or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline).ti,ab. 139	

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18 (Cilostazol or inositol nicotinate or moxisylyte or naftidrofuryl or pentoxif*).ti,ab. 14

19 exp Histamine antagonists/ 24

20 (histamine adj2 (antag* or inhib* or block*)).ti,ab. 77

21 Cinnarizine.ti,ab. 1

22 (Sildenafil or tadalafil or vardenafil).ti,ab. 23

23 alfuzosin.ti,ab. 0

24 Ambrisentan.ti,ab. 0

25 Dapoxetine.ti,ab. 0

26 Diazoxide.ti,ab. 4

27 Epoprostenol.ti,ab. 4

28 Irbesartan.ti,ab. 4

29 Lisiniopril.ti,ab. 0

30 Macitentan.ti,ab. 0

31 Milrinone.ti,ab. 3

32 minoxidil.ti,ab. 5

33 Moxonidine.ti,ab. 0

34 nicorandil.ti,ab. 0

35 Pentoxifylline.ti,ab. 12

36 perhexiline.ti,ab. 0

37 quinapril.ti,ab. 0

38 rociguat.ti,ab. 0

39 Sacubitril.ti,ab. 0

40 Tamsulosin.ti,ab. 3

41 Treprostinil.ti,ab. 1

42 or/4-41 1117

43 3 and 42 1

44 exp CLINICAL TRIALS/ 3847

45 RANDOM ALLOCATION/ 318

46 DOUBLE BLIND METHOD/ 676

47 Clinical trial.pt. 1214

48 (clinic* adj trial*).tw. 5511

49 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. 2906

50 PLACEBOS/ 595

51 placebo*.tw. 3181

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(Continued)

52 random*.tw. 18096

53 PROSPECTIVE STUDIES/ 1146

54 or/44-53 23190

55 43 and 54 0

WHAT'S NEW

Date	Event	Description
16 November 2020	New search has been performed	Scope of the review has expanded from oral vasodilators to include all vasodilators. Searches were run, 7 new studies were included, 22 new studies were excluded, and 2 new ongoing studies have been identified
16 November 2020	New citation required but conclusions have not changed	New author team has taken over the review. Scope of the review has expanded from oral vasodilators to include all vasodilators. Searches were run, 7 new studies were included, 22 new studies were excluded, and 2 new ongoing studies have been identified. Review has been updated according to current Cochrane reporting standards, and "Summary of findings" tables have been added. No changes were made to conclusions

HISTORY

Protocol first published: Issue 3, 2007
Review first published: Issue 2, 2008

Date	Event	Description
15 May 2012	New citation required but conclusions have not changed	Review updated. New author (JM) joined and one author (BV) stepped down from the review team. Eleven additional studies excluded and one ongoing study added. Conclusions not changed.
15 May 2012	New search has been performed	Review updated, searches updated. For this update we identified an additional 15 articles for possible inclusion. Eleven were excluded and one was a second reference to a previously excluded study. We found one ongoing study and two articles were deemed not relevant.
30 April 2008	Amended	Converted to new review format.
18 December 2007	New citation required and conclusions have changed	Substantive amendment

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CONTRIBUTIONS OF AUTHORS

KYS: screening of studies for inclusion, review of full texts and extraction of data from studies, contact for and coordination of translation of non-English studies, evaluation of included studies for risk of bias, performance of statistical analysis, creation of summary of findings tables, and updates to and finalization of the text of the review.
MS: screening of studies for inclusion, review of full texts and extraction of data from studies, evaluation of included studies for risk of bias including tables, updates to and finalization of the text of the review.
HK: screening of studies for inclusion, review of full texts and extraction of data from studies, performance of statistical analysis and creation of results tables, updates to and finalization of the text of the review.
EK: screening of studies for inclusion, review of full texts, updates to and finalization of the text of the review.
IH: analysis and interpretation of study articles, providing advice regarding discussion points for statistical components of the review.
MHA: consideration of trials for inclusion, updates to risk of bias and finalization of the text of the review.
JHKN: consideration of trials for inclusion, evaluation of included studies for risk of bias, and finalization of the text of the review.

DECLARATIONS OF INTEREST

KYS: none known.
MS: none known.
HK: none known.
EK: none known.
IH: has declared affiliation to Gold Coast Health through guidelines for treatment of rheumatoid-type diseases.
MHA: none known
JHKN: declares that her Institution received funds for clinical trials (Abbvie, Pfizer, MSD, Roche, and Paradigm). None of these trials are related to Raynaud's phenomenon.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- Chief Scientist Office, Scottish Government Health Directorates, Scottish Government, UK

  The Cochrane Vascular editorial base is supported by the Chief Scientist Office.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title was changed from “Oral vasodilators for primary Raynaud’s phenomenon” to “Vasodilators for primary Raynaud’s phenomenon.” This was done to clarify the change in scope by which inclusion criteria now include any drug with vasodilatory action with non-oral formulations (including topical and intravenous). We reordered outcomes and added two new outcome measures (Raynaud Condition Score and capillaroscopic flow/skin perfusion), to reflect current clinical relevance. We reviewed all studies excluded in the previous version and re-assessed some as irrelevant during the title and abstract screening process. We removed these studies, as they were not randomized controlled trials, they included only participants with secondary RP, they used only a single medication dose, or treatment lacked vasodilatory actions. We assessed risk of bias using the Cochrane "Risk of bias" tool, and we assessed the certainty of evidence using GRADE.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Randomized Controlled Trials as Topic; Raynaud Disease [*drug therapy]; Vasodilator Agents [*administration & dosage]

MeSH check words

Humans

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