Raynaud's phenomenon (primary)

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ABSTRACT

INTRODUCTION: Raynaud's phenomenon is an episodic, reversible vasospasm of the peripheral arteries (usually digital). It causes pallor, followed by cyanosis and/or redness, often with pain and, at times, paraesthesia. On rare occasions, it can lead to ulceration of the fingers and toes (and, in some cases, of the ears or nose). This review focuses on primary (idiopathic) Raynaud's phenomenon, occurring in the absence of an underlying disease. The prevalence of primary Raynaud's phenomenon varies by sex, country, and exposure to workplace vibration. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of drug treatments for primary Raynaud's phenomenon? We searched: Medline, Embase, The Cochrane Library, and other important databases up to August 2013 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 9 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: amlodipine, diltiazem, nicardipine, and nifedipine.

QUESTIONS

INTERVENTIONS

TREATMENTS

Trade off between benefits and harms

Unknown effectiveness

Covered elsewhere in Clinical Evidence

Raynaud's phenomenon (secondary)

Key points

- Raynaud's phenomenon is an episodic, reversible vasospasm of the peripheral arteries (usually digital). It causes pallor, followed by cyanosis and/or redness, often with pain and, at times, paraesthesia. On rare occasions, it can lead to ulceration of the fingers and toes (and, in some cases, of the ears or nose). This review focuses on primary (idiopathic) Raynaud's phenomenon occurring in the absence of an underlying disease.

  Prevalence, which varies by sex and country, is around 3% to 5% in most population studies, 80% to 90% of which is primary Raynaud's phenomenon; it is slightly higher in women than in men.

  Attacks may last from several minutes to a few hours, and long-term sufferers of initially idiopathic Raynaud's phenomenon can later go on to display features of underlying disorders such as systemic sclerosis.
- Nifedipine seems to reduce the frequency and severity of Raynaud's attacks, although it is associated with high rates of adverse effects such as tachycardia, headache, and flushing.
- We found no evidence of sufficient quality to judge the effectiveness of amlodipine or diltiazem in treating primary Raynaud's phenomenon.
- Nicardipine may successfully treat primary Raynaud's phenomenon, but we found no studies large enough to enable us to draw firm conclusions.

Clinical context

GENERAL BACKGROUND

Raynaud's phenomenon (RP) occurs in 3 to 5% of the population. It is reversible vasospasm of arteries; especially of the digits with pallor and either redness and/or cyanosis RP is divided into primary (no associated underlying cause, i.e. idiopathic, also known as Raynaud's disease) or secondary RP (associated with an underlying cause such as connective tissue disease). Primary RP often does not need treatment with medication but keeping warm and smoking cessation are recommended despite lack of RCT data. If these measures do not work, drug therapy, such as calcium channel blockers, is considered.

FOCUS OF THE REVIEW

Calcium channel blockers (mostly of the dihydropyridine type: nifedipine, nicardipine, amlodipine, and less often diltiazem) on an as-needed basis are the mainstay of medical management for primary RP. Other vasodilator classes are rarely used in primary RP. Decision-making regarding which calcium channel blocker to prescribe depends on

need for a medication and tolerability and efficacy, where nifedipine is usually the first-line drug treatment. This review looks at the evidence for calcium channel blockers in primary RP.

COMMENTS ON EVIDENCE

Within the calcium channel blockers group, nifedipine has the largest body of evidence to support its efficacy. The benefit of RP treatment are greater in primary RP (idiopathic) compared to secondary RP as the latter is more difficult to treat due to blood vessel abnormalities that may not be reversible superimposed on vasospasm.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, May 2010, to August 2013. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the review, please see the Methods section. Searching of electronic databases retrieved 18 studies. After de-duplication and removal of conference abstracts, 6 records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of all 6 studies so none were added at this update.

ADDITIONAL INFORMATION

Topical nitrates may be used to treat primary RP, especially if there are side effects related to calcium channel blocker use such as symptomatic hypotension. Topical nitrates are applied to the web spaces between fingers (as prevention or treatment) in a small amount in order to avoid side effects such as hypotension, flushing and headaches. If RP has complications such as digital ulcers or severe ischemia, then secondary causes of RP should be sought. In these rare cases, data from secondary RP trials may be considered although not tested in primary RP such as phosphodiesterase 5 inhibitors and intravenous prostacyclin (iloprost).

DEFINITION

Raynaud's phenomenon is an episodic, reversible vasospasm of the peripheral arteries (usually digital). It causes pallor, followed by cyanosis and/or erythema, which can cause pain and, at times, paraesthesia. On rare occasions, it can lead to ulceration of the fingers and toes (and, in some cases, of the ears or nose). Primary or idiopathic Raynaud's phenomenon (Raynaud's disease) occurs without an underlying disease. Secondary Raynaud's phenomenon (Raynaud's syndrome) occurs in association with an underlying disease — usually connective tissue disorders, such as systemic sclerosis (SSc; scleroderma), systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, or polymyositis. This review excludes secondary Raynaud's phenomenon. **Diagnosis:** The diagnosis of Raynaud's phenomenon is by a history of clearly demarcated pallor of digit(s), followed by at least one other colour change (cyanosis, erythema), which is usually precipitated by cold. A good history, physical examination, and laboratory results can help rule out secondary Raynaud's phenomenon. Review of symptoms or signs for connective tissue disease should be done. Laboratory testing may include full blood count (FBC), ESR, and ANA with pattern if connective tissue diseases are suspected. Magnification of the nail-beds to observe abnormal capillaries is also important in order to rule out Raynaud's phenomenon associated with connective tissue diseases.

INCIDENCE/ PREVALENCE

The prevalence of primary Raynaud's phenomenon varies by sex, country, and workplace exposure to vibration. One large US cohort study (4182 people) found symptoms in 9.6% of women and 8.1% of men, of whom 81% had primary Raynaud's phenomenon. [1] Smaller cohort studies in Spain have estimated the prevalence of Raynaud's phenomenon to be 3.7% to 4.0%, of which 90% is primary Raynaud's phenomenon. [2] [3] One study in Japan (332 men, 731 women) found symptoms of primary Raynaud's phenomenon in 3.4% of women and 3.0% of men. [4] A study of 12,907 people in the UK reported that 4.6% of people had demarcated finger blanching with cold exposure. [5]

AETIOLOGY/ RISK FACTORS

The cause of primary Raynaud's phenomenon is unknown. [6] There is evidence for genetic predisposition, [7] [8] usually in those with early-onset Raynaud's phenomenon (aged under 40 years). [9] One prospective observational study (424 people with Raynaud's phenomenon) found that 73% of sufferers first developed symptoms before the age of 40 years. [9] Women are at higher risk than men (OR 3.0, 95% CI 1.2 to 7.8, in one US case control study of 235 people). [10] The other known risk factor is occupational exposure to vibration from tools (symptoms developed in about 8% with exposure *v* 2.7% with no exposure in 2 cohorts from Japan). [11] [12] People who are obese may be at lower risk. [10] Exposure to cold or heightened emotion can worsen symptoms.

PROGNOSIS

Attacks may last from several minutes to a few hours. One systematic review (search date 1996, 10 prospective observational studies, 639 people with primary Raynaud's phenomenon) found that 13% of long-term sufferers later manifested an underlying disorder, such as systemic sclerosis. [13] In a large cohort of patients diagnosed with Raynaud's phenomenon without a known connective tissue disease who were seen in a specialist rheumatology clinic, 13% developed systemic sclerosis

over time. Those who progressed to systemic sclerosis had both abnormal dilated capillaries at the nail folds and systemic-sclerosis-specific antibodies. [14] Complications of Raynaud's phenomenon, such as digital ulceration or severe ischaemia, may indicate a secondary cause. In general, complications of primary Raynaud's phenomenon do not occur. However, some patients without a known underlying cause have complications. They may over time manifest as secondary Raynaud's phenomenon but are not yet able to be diagnosed. For instance, a small proportion (1%–2%) of people with primary Raynaud's phenomenon may transition to secondary Raynaud's phenomenon annually. [15] The latter are likely the patients who have complications of Raynaud's phenomenon.

AIMS OF INTERVENTION To reduce the number and severity of attacks; to prevent tissue damage; to minimise adverse effects of treatment.

OUTCOMES **Raynaud's attacks**: including frequency, severity, impact, and duration of symptoms (as assessed by patient diary); severity assessed by visual analogue scales, Likert scales, or the Raynaud's Condition Score; [16] and **digital ulceration**, including rates, size, and healing. **Adverse effects** of treatment.

METHODS *Clinical Evidence* search and appraisal August 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to August 2013, Embase 1980 to August 2013, and The Cochrane Database of Systematic Reviews 2013, issue 2 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against pre-defined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against pre-defined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single-blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required for included studies. We searched for any RCTs comparing included options in the review versus placebo, or versus each other, in people with primary Raynaud's. Many RCTs included people with both primary and secondary Raynaud's phenomenon. We excluded RCTs in which less than 50% of people had primary Raynaud's phenomenon or where the type of Raynaud's was unclear. We also excluded RCTs in which attacks were experimentally induced (e.g., by dipping the hands in cold water) or those that did not assess clinical outcomes. Some RCTs compared changes in symptoms from baseline within each treatment group, rather than directly comparing outcomes between treatment groups. These have been described in the comment sections. We included systematic reviews of RCTs and RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 11). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of drug treatments for primary Raynaud's phenomenon?

OPTION NIFEDIPINE

- For GRADE evaluation of interventions for Raynaud's phenomenon (primary), see table, p 11 .
- Nifedipine seems to reduce the frequency and severity of Raynaud's attacks, although it is associated with high rates of adverse effects, such as tachycardia, headache, and flushing.

Benefits and harms

Nifedipine versus placebo:

We found one systematic review (search date 2003; 12 RCTs [11 RCTs of crossover design]). [17] Most RCTs identified by the review also included people with a diagnosis other than primary Raynaud's phenomenon. In such cases, the review included the RCT if a subset of people with primary Raynaud's phenomenon could be identified separately and their outcome assessed independently, or if >75% of people had primary Raynaud's. The review noted various methodological limitations of the identified RCTs; see Further information on studies for full details. The review also described the effects of calcium-channel blockers as a class; see Further information on studies for results.

Raynaud's attacks

Compared with placebo Nifedipine may reduce the frequency and severity of Raynaud's attacks in people with primary Raynaud's phenomenon (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of Raynaud's attacks					
[17] Systematic review	Number of people in analysis not reported 10 RCTs in this analysis	**Frequency of ischaemic attacks** with nifedipine with placebo Absolute results not reported	WMD –6.05, 95% CI –11.19 to –0.19 P = 0.04 Potential for bias in meta-analysis; see Further information on studies for full details	○○○	nifedipine
Severity of Raynaud's attacks					
[17] Systematic review	Number of people in analysis not reported 5 RCTs in this analysis	**Severity of ischaemic attacks (measured on a 10-cm visual analogue scale)** with nifedipine with placebo Absolute results not reported	WMD –1.81 95% CI –3.08 to –0.54 P = 0.005 Potential for bias in meta-analysis; see Further information on studies for full details	○○○	nifedipine
[17] Systematic review	Number of people in analysis not reported 5 RCTs in this analysis	**Improvement in ischaemic attacks (measured on a 5-point scale; no further definition of the scale reported)** with nifedipine with placebo Absolute results not reported	WMD –1.11 95% CI –1.38 to –0.85 P = 0.005 Potential for bias in meta-analysis; see Further information on studies for full details	○○○	nifedipine

Digital ulceration

No data from the following reference on this outcome. [17]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] RCT **Crossover design**	22 people In review [17]	**Adverse effects (not further detailed)** 10/22 (45%) with nifedipine 10 mg	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial		16/22 (72%) with nifedipine 20 mg 6/22 (27%) with placebo			
[19] RCT **Crossover design**	26 people In review [17]	**Adverse effect** 16/21 (76%) with nifedipine Not reported with placebo			
[20] RCT	Number of people not reported In review [17]	**Oedema** 24% with nifedipine 0% with placebo	P = 0.01	○○○	placebo
[20] RCT	Number of people not reported In review [17]	**Flushing** 8% with nifedipine 0% with placebo	P = 0.01	○○○	placebo
[20] RCT	Total number of people not reported In review [17]	**Tachycardia** 2 people with nifedipine 0 people with placebo	Significance not assessed		
[21] RCT	39 people In review [17]	**Overall adverse effects** with nifedipine with placebo Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[21] RCT	39 people In review [17]	**Palpitations** 7/18 (39%) with nifedipine 1/18 (6%) with placebo	P <0.05	○○○	placebo
[22] RCT **Crossover design**	23 people In review [17]	**Adverse effects (post-crossover results)** 14/23 (61%) with nifedipine 2/23 (9%) with placebo Adverse effects included headaches, flushing, and ankle swelling	P = 0.05	○○○	placebo
[23] RCT **Crossover design**	34 people In review [17]	**Adverse effects (post-crossover results) , 12 weeks** 26/34 (76%) with nifedipine 5/34 (15%) with placebo Adverse effects included flushing, headache, and oedema	Significance not assessed		

Further information on studies

[17] **Methodological limitations of the identified RCTs** Most RCTs were small; the number of people included in each RCT with primary Raynaud's phenomenon ranged from three to 130 people (8 RCTs included 21 people or fewer with primary Raynaud's). The review noted that most RCTs included people with or without primary Raynaud's phenomenon, so the meta-analysis could be regarded as a subset analysis of the original RCTs, which could be biased if randomisation was not stratified in people with primary Raynaud's. It also noted that most RCTs of crossover design did not report pre-crossover results. Results after crossover may not allow for confounding factors, such as inadequate washout and the naturally variable course of Raynaud's phenomenon.

The review included RCTs with a withdrawal rate of up to 35%. It noted that many of the included RCTs were of short duration (median 2 weeks, range 1−10 weeks) and used relatively low doses of nifedipine. **Effects of calcium-channel blockers as a class** The review also compared calcium-channel blockers as a group versus placebo. The meta-analysis included 12 RCTs of nifedipine, two RCTs of nisoldipine, two RCTs of nicardipine, and one RCT of diltiazem. It found that calcium-channel blockers as a group significantly reduced the frequency and the severity of attacks compared with placebo (frequency of ischaemic attacks: 17 RCTs; WMD –2.08, 95% CI –3.90 to –1.70; severity [measured on a 10-cm visual analogue scale]: 8 RCTs; WMD –1.39, 95% CI –2.20 to –0.58). However, most of the RCTs included in this analysis involved nifedipine.

Comment:

Complications of Raynaud's phenomenon, such as digital ulceration or severe ischaemia, may indicate a secondary cause. In general, complications of primary Raynaud's phenomenon do not occur. However, some patients without a known underlying cause have complications. They may over time manifest as secondary Raynaud's phenomenon but are not yet able to be diagnosed. For instance, a small proportion (1%–2%) of people with primary Raynaud's phenomenon may transition to secondary Raynaud's phenomenon annually. [15] The latter are likely the patients who have complications of Raynaud's phenomenon.

Clinical guide:
The evidence suggests that nifedipine gives some benefit in reducing the frequency, severity, and number of primary Raynaud's attacks.

OPTION NICARDIPINE

- For GRADE evaluation of interventions for Raynaud's phenomenon (primary), see table, p 11 .
- Nicardipine may successfully treat primary Raynaud's phenomenon, but we found no studies large enough to enable us to draw conclusions.

Benefits and harms

Nicardipine versus placebo:

We found two RCTs. [24] [25]

Raynaud's attacks

Compared with placebo We don't know whether nicardipine is more effective at reducing the frequency, duration, or severity of ischaemic attacks at 6 to 8 weeks in people with primary Raynaud's phenomenon (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of Raynaud's attacks					
[24] RCT **Crossover design**	69 people with primary Raynaud's phenomenon	**Frequency of ischaemic attacks (post-crossover results) , 8 weeks** 4.9 attacks/week with nicardipine 5.8 attacks/week with placebo	Mean difference: 0.9 95% CI 0 to 2.2 P = 0.02 Data reported are post-crossover results and should be interpreted with caution; see Further information on studies for full details	○○○	nicardipine
[25] RCT **Crossover design**	25 people (16 with primary Raynaud's phenomenon and 9 people with secondary Raynaud's phenomenon)	**Mean frequency of ischaemic attacks (post-crossover results) , 6 weeks** 4.4 attacks/day with nicardipine (30 mg twice-daily) 4.4 attacks/day with placebo Analysis of 16 people with primary Raynaud's phenomenon	Reported as not significant P value not reported The RCT is likely to have been too small to detect a clinically important difference in outcomes Data reported are post-crossover results and should be interpreted with caution; see Further information on studies for full details	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Severity of Raynaud's attacks					
[24] RCT **Crossover design**	69 people with primary Raynaud's phenomenon	**Overall disability (mean score post-crossover; measured on a 10-cm visual analogue scale, where 0 represented no disability) , 8 weeks** 2.6 with nicardipine 3.3 with placebo	P = 0.018 Data reported are post-crossover results and should be interpreted with caution; see Further information on studies for full details	○○○	nicardipine
[24] RCT **Crossover design**	69 people with primary Raynaud's phenomenon	**Severity of ischaemic attacks (post-crossover results; measured on a scale of 1–4, where 1 represented mild and 4 highly severe) , 8 weeks** 1.36 with nicardipine 1.55 with placebo	Mean difference: 0.2 95% CI 0 to 0.4 P value reported as not significant Data reported are post-crossover results and should be interpreted with caution; see Further information on studies for full details	⟷	Not significant
[25] RCT **Crossover design**	25 people (16 with primary Raynaud's phenomenon and 9 people with secondary Raynaud's phenomenon)	**Mean severity of ischaemic attack (post-crossover results; measured on a 10-point scale, where 0 represented no pain) , 6 weeks** 3.5 with nicardipine (30 mg twice-daily) 3.7 with placebo Analysis of 16 people with primary Raynaud's phenomenon	Reported as not significant P value not reported The RCT is likely to have been too small to detect a clinically important difference in outcomes Data reported are post-crossover results and should be interpreted with caution; see Further information on studies for full details	⟷	Not significant
[25] RCT **Crossover design**	25 people (16 with primary Raynaud's phenomenon and 9 people with secondary Raynaud's phenomenon)	**Mean duration of ischaemic attack (post-crossover results) , 6 weeks** 13 minutes with nicardipine (30 mg twice-daily) 11 minutes with placebo Analysis of 16 people with primary Raynaud's phenomenon	Reported as not significant P value not reported The RCT is likely to have been too small to detect a clinically important difference in outcomes Data reported are post-crossover results and should be interpreted with caution; see Further information on studies for full details	⟷	Not significant

Digital ulceration

No data from the following reference on this outcome. [24] [25]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[24] RCT **Crossover design**	69 people with primary Raynaud's phenomenon	**Withdrawals due to adverse effects** 5/69 (7%) with nicardipine 2/69 (3%) with placebo	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[25] RCT **Crossover design**	25 people (16 with primary Raynaud's phenomenon and 9 people with secondary Raynaud's phenomenon)	**Withdrawals due to adverse effects** 2/16 (13%) with nicardipine 1/16 (6%) with placebo Adverse effects included flushing, headache, and palpitations Analysis of 16 people with primary Raynaud's phenomenon	Significance not assessed The RCT is likely to have been too small to detect a clinically important difference in outcomes		

Further information on studies

[24] [25] The results of the crossover trials should be viewed with caution, as no pre-crossover results were available and results may not allow for confounding factors such as inadequate washout and the naturally variable course of Raynaud's phenomenon.

Comment: Complications of Raynaud's phenomenon, such as digital ulceration or severe ischaemia, may indicate a secondary cause. In general, complications of primary Raynaud's phenomenon do not occur. However, some patients without a known underlying cause have complications. They may over time manifest as secondary Raynaud's phenomenon but are not yet able to be diagnosed. For instance, a small proportion (1%–2%) of people with primary Raynaud's phenomenon may transition to secondary Raynaud's phenomenon annually. [15] The latter are likely the patients who have complications of Raynaud's phenomenon.

Clinical guide:
Nicardipine may successfully treat primary Raynaud's phenomenon but the studies we found had too few participants with primary Raynaud's phenomenon to enable us to draw conclusions. However, in clinical practice, dihydropyridine-type calcium-channel blockers may have similar effects to nifedipine on Raynaud's phenomenon.

OPTION AMLODIPINE

- For GRADE evaluation of interventions for Raynaud's phenomenon (primary), see table, p 11 .
- We found no evidence of sufficient quality to judge the effectiveness of amlodipine in treating primary Raynaud's phenomenon.

Benefits and harms

Amlodipine versus placebo:

We found no RCTs that reported between-group comparisons of amlodipine versus placebo (see comment).

Further information on studies

Comment: We found one RCT that presented within-group comparisons of changes in outcomes from baseline (24 people, 15 with primary Raynaud's phenomenon, crossover design, outcomes assessed after crossover). [26] It found that amlodipine significantly reduced the number of acute attacks per week from baseline at 7 weeks (from 11.8 attacks/week at baseline to 8.6 attacks/week after treatment; P <0.001) and reduced the severity of attacks from baseline (from a discomfort score of 7.8 at

baseline to 5.1 after treatment). However, the RCT did not assess the significance of the difference in frequency and severity of attacks between groups. It found that amlodipine was associated with ankle oedema (55% of people taking amlodipine *v* 0% of people taking placebo), flushing, and headaches compared with placebo (10%–20% with amlodipine *v* 0% with placebo). [26] The RCT included people with secondary Raynaud's phenomenon, so results may not be applicable in people with primary Raynaud's phenomenon.

Complications of Raynaud's phenomenon, such as digital ulceration or severe ischaemia, may indicate a secondary cause. In general, complications of primary Raynaud's phenomenon do not occur. However, some patients without a known underlying cause have complications. They may over time manifest as secondary Raynaud's phenomenon but are not yet able to be diagnosed. For instance, a small proportion (1%–2%) of people with primary Raynaud's phenomenon may transition to secondary Raynaud's phenomenon annually. [15] The latter are likely the patients who have complications of Raynaud's phenomenon.

Clinical guide:
We cannot generalise the benefits of dihydropyridine calcium-channel blockers such as nifedipine to amlodipine, as it has not been primarily studied in RCTs in the treatment of primary Raynaud's phenomenon.

OPTION DILTIAZEM

- For GRADE evaluation of interventions for Raynaud's phenomenon (primary), see table, p 11 .
- We found no evidence of sufficient quality to judge the effectiveness of diltiazem in treating primary Raynaud's phenomenon.

Benefits and harms

Diltiazem versus placebo:

We found no RCTs that met *Clinical Evidence* inclusion criteria (see comment).

Further information on studies

Comment:

One crossover RCT (30 people, 19 with primary Raynaud's phenomenon, outcomes assessed after crossover) found that diltiazem significantly reduced the number and duration of attacks over 8 weeks compared with placebo (mean reduction in attacks from baseline: 22.9/month with diltiazem *v* 4.6/month with placebo; P = 0.01; mean reduction in duration from baseline: 444 minutes/month with diltiazem *v* 160 minutes/month with placebo; P <0.01). [27] The results of this RCT should be interpreted with caution as it reported comparisons from baseline, thus removing the benefits of randomisation, and analysis was not by intention-to-treat (8/30 [27%] people withdrew from the trial). Two people withdrew from the trial because of adverse effects (rash or headache) while taking diltiazem. The RCT included people with secondary Raynaud's phenomenon, so results may not be fully applicable in people with primary Raynaud's phenomenon.

Complications of Raynaud's phenomenon, such as digital ulceration or severe ischaemia, may indicate a secondary cause. In general, complications of primary Raynaud's phenomenon do not occur. However, some patients without a known underlying cause have complications. They may over time manifest as secondary Raynaud's phenomenon but are not yet able to be diagnosed. For instance, a small proportion (1%–2%) of people with primary Raynaud's phenomenon may transition to secondary Raynaud's phenomenon annually. [15] The latter are likely the patients who have complications of Raynaud's phenomenon.

GLOSSARY

Very low-quality evidence Any estimate of effect is very uncertain.

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Disclaimer

GRADE **Evaluation of interventions for Raynaud's phenomenon (primary).**

Important outcomes			Digital ulceration, Raynaud's attacks						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of drug treatments for primary Raynaud's phenomenon?									
12 (unclear) [17]	Raynaud's attacks	Nifedipine versus placebo	4	–3	0	–1	0	Very low	Quality points deducted for incomplete reporting of results, poor crossover methodology, and poor follow-up. Directness point deducted for RCTs that included people with other conditions
2 (94) [24] [25]	Raynaud's attacks	Nicardipine versus placebo	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and poor crossover methodology. Directness point deducted for broad inclusion criteria

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.