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Ruffolo AJ, Romano M, Ciapponi A

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[Intervention Review]

Prostanoids for critical limb ischaemia

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ABSTRACT

Background

Peripheral arterial occlusive disease (PAOD) is a common cause of morbidity and mortality due to cardiovascular diseases in the general population. While numerous treatments have been adopted for different disease stages, there is no option other than amputation for patients presenting with critical limb ischaemia (CLI), unsuitable for rescue or reconstructive intervention.

Objectives

To determine the effectiveness and safety of prostanoids in patients presenting with CLI.

Search methods

The Cochrane Peripheral Vascular Diseases Group searched their trials register (last searched October 2009) and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (last searched 2009, Issue 4) for publications describing randomised controlled trials (RCTs) of prostanoids for CLI. We ran additional searches in MEDLINE, EMBASE, LILACS, and SciSearch, and we also contacted pharmaceutical companies and experts, in order to identify unpublished data and trials still underway.

Selection criteria

Randomised controlled trials describing efficacy and safety of prostanoids compared with placebo or other pharmacological control treatments, in patients presenting with CLI, without chance of rescue or reconstructive intervention.

Data collection and analysis

Two authors independently selected trials, assessed trials for eligibility and methodological quality, and extracted data. Disagreements were resolved by consensus or by the third author.

Main results

We retrieved 532 citations which after the first screening resulted in 111 potential studies. Finally, after exclusion of studies of poor quality and a lack of sufficient information, 20 trials were included in the review.

Prostanoids seem to have efficacy regarding rest-pain relief (risk ratio (RR) 1.32, 95% confidence interval (CI) 1.10 to 1.57; P = 0.003), and ulcer healing (RR 1.54, 95% CI 1.22 to 1.96). Iloprost also shows favourable results regarding major amputations (RR 0.69, 95% CI 0.52 to 0.93). The more frequently reported adverse events when using prostanoids were headache, facial flushing, nausea, vomiting and diarrhoea.

Authors' conclusions

Despite some positive results regarding rest-pain relief, ulcer healing and amputations, there is no conclusive evidence based on this meta-analysis of the long-term effectiveness and safety of different prostanoids in patients with CLI. Further well-conducted, high quality randomised double-blinded trials should be performed.

PLAIN LANGUAGE SUMMARY

Prostanoids for treating people with severe peripheral arterial disease of the legs

People with severely narrowed arteries of the lower limbs may suffer rest pain, ulcers, or gangrene, and this problem is called critical limb ischaemia. There is no option other than amputation for patients who present with critical limb ischaemia and who are unsuitable for rescue or reconstructive intervention of the arteries. The question is whether specific drugs such as prostanoids reduce mortality and progression of the disease, including amputations, more than placebo or other treatments. This review of 20 trials did not find any conclusive evidence that prostanoids provided long-term benefit. Prostanoids seem to have efficacy regarding rest-pain relief and ulcer healing. Iloprost may also have favourable results regarding major amputations. The more frequently reported adverse events when using prostanoids were headache, facial flushing, nausea, vomiting and diarrhoea

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Prostanoids compared with placebo for critical limb ischaemia

Patient or population: patients with critical limb ischaemia
Settings:
Intervention: Prostanoids
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	Prostanoids				
Rest pain relief Questionnaires Follow-up: mean 21.4 weeks	**Study population**		**RR 1.32** (1.1 to 1.57)	1116 (9 studies)	⊕⊕◯◯ **low**[1,2]	
	271 per 1000	**358 per 1000** (298 to 425)				
	Medium risk population					
	243 per 1000	**321 per 1000** (267 to 382)				
Ulcer healing size of ulcer / granulation tissue at the base Follow-up: mean 17.5 weeks	**Study population**		**RR 1.54** (1.22 to 1.96)	1132 (8 studies)	⊕◯◯◯ **very low**[1,3,4]	
	322 per 1000	**496 per 1000** (393 to 631)				
	Medium risk population					
	244 per 1000	**376 per 1000** (298 to 478)				

Amputations (not defined if majors or totals) number of amputations[5] Follow-up: mean 23.11 weeks	**Study population**		**RR 0.89** (0.76 to 1.04)	1790 (9 studies)	⊕⊕◯◯ **low**[1,6]
	267 per 1000	**238 per 1000** (203 to 278)			
	Medium risk population				
	313 per 1000	**279 per 1000** (238 to 326)			
Mortality Follow-up: mean 32 weeks	**Study population**		**RR 1.07** (0.65 to 1.75)	1391 (5 studies)	⊕◯◯◯ **very low**[3,4,7]
	92 per 1000	**98 per 1000** (60 to 161)			
	Medium risk population				
	121 per 1000	**129 per 1000** (79 to 212)			
Adverse events (patients) Follow-up: mean 14.4 months	**Study population**		**RR 2.35** (1.99 to 2.78)	716 (8 studies)	⊕⊕◯◯ **low**[8,9]
	310 per 1000	**728 per 1000** (617 to 862)			
	Medium risk population				
	199 per 1000	**468 per 1000** (396 to 553)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Six trials with at least one inadequate criteria
[2] 95% confidence interval around the pooled or best estimate of effect includes both no effect and appreciable benefit or appreciable harm in 8 trials
[3] Unexplained heterogeneity of results
[4] 95% confidence interval around the pooled or best estimate of effect includes both no effect and appreciable benefit or appreciable harm in 5 trials
[5] Major amputations or total amputations (major + minor) depending on published results of each trial
[6] 95% confidence interval around the pooled or best estimate of effect includes both no effect and appreciable benefit or appreciable harm in 8 trials
[7] Four trials with at least one inadequate criteria
[8] Five trials with at least one inadequate criteria
[9] 95% confidence interval around the pooled or best estimate of effect includes both no effect and appreciable harm in 2 trials

BACKGROUND

Description of the condition

The term critical limb ischaemia (CLI) should be used for all chronic Ischaemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease. Unlike individuals with intermittent claudication (IC), patients with CLI have poor arterial blood flow to the lower limbs (resting perfusion) that is inadequate to sustain viability in the distal tissue bed. The European Working Group on CLI specifically defined this illness as the presence of ischaemic rest pain requiring analgesia for more than two weeks, or ulceration, or gangrene of the lower extremity with an ankle systolic blood pressure < 50 mm Hg and/or toe systolic pressure < 30 mm Hg (Anonymous 1991).

Peripheral arterial disease (PAD) affects approximately 20% of adults older than 55 years, and an estimated 27 million persons in North America and Europe (Hankey 2006). Critical limb ischaemia is the initial clinical presentation in only 1% to 2% of cases, whereas 40% to 50% of those affected begin with atypical leg pain, 10% to 35% with IC, and 20% to 50% are asymptomatic. After five years of progressive functional impairment, a further 1% to 2% of PAD cases will result in CLI and eventual amputation (Hirsch 2006).

Besides age, the most important clinical predictors for CLI progression are smoking and diabetes. The risk associated with smoking applies to all ages and increases with the number of cigarettes smoked. Major peripheral arterial disease deterioration occurs in those people with claudication who are heavy smokers (Cronenwett 1984; Jonason 1986). Diabetes appears to be more important for progression than for initial development of symptoms of PAD. People suffering with claudication and diabetes have a 35% risk of deterioration (McDaniel 1989), twice the risk of those with intermittent claudication but without diabetes (Jelnes 1986).

The prognosis for limb and patient survival is impaired in chronic CLI. Within a six-month period, 20% of patients die, 35% live but require amputation, and the remaining 45% live with no immediate need for amputation (Dormandy 2000).

Consistent with clinical predictors, CLI deteriorates to gangrene in 40% of diabetic patients compared with 9% of non-diabetic patients (Kannel 1994). The most important risk factors for amputation are those involved in the progression to CLI. Smoking is associated with a major amputation rate of 11% in patients with claudication (Juerguens 1960), and diabetes is associated with a 21% risk of amputation as compared with 3% in non-diabetic persons (Kannel 1994). Another important clinical predictor of amputation is an ankle brachial index (ABI) below 0.5 (Jelnes 1986).

The prognosis after amputation is even worse. According to the Second European Consensus Document on chronic critical limb ischaemia (Anonymous 1991), the peri-operative mortality is 5% to 10% for below-knee amputation, and 15% to 20% for above-knee amputation. Even when these patients survive, nearly 40% will die within two years of their major amputation. A second amputation is required in 30% of cases, and full mobility is achieved in only 50% of patients who have below-knee amputation and 25% of those who have above-knee amputation. Furthermore, it is well known that patients with peripheral arterial disease have an elevated risk of future myocardial infarction, stroke and vascular death, three-fold higher than patients with IC (Novo 2004). Psychological testing of such patients has typically disclosed quality-of-life indices similar to those of patients with cancer in critical or even terminal phases (Albers 1992). Therefore, due to its negative impact on quality of life, and the poor prognosis both in terms of limb and patient survival, CLI is a critical health issue.

Therapeutic options for CLI are limited to percutaneous transluminal angioplasty or surgical revascularization. Unfortunately, many patients with CLI are poor candidates for either procedure, because of co-morbidities or vascular anatomy (lack of conduit). These patients only have medical treatment as a therapeutic alternative, and amputation (when necessary) as the last chance to survive. An innovative treatment for CLI is therapeutic angiogenesis (Baumgartner 1998; Isner 1995; Isner 1996; Isner 1998), but studies are still at an initial stage, for example, Talisman Study (Talisman), Phase II Tact - Nagoya Study (Tact-Nagoya). In a recent study, signs of continuous muscle regeneration process have been seen in amputated ischaemic human limbs (Mackiewicz 2003). Hopefully these new therapies will lead to improved medical treatments for CLI.

Description of the intervention

Medical therapies for CLI that decrease pain, promote healing of skins lesions, and reduce the risk of amputation would be attractive alternatives. Several drugs have been used at this stage (for example, cilostazol, pentoxifylline, or naftidrofuryl) with no significant benefit. Prostanoids have been used for the treatment of PAD for more than two decades, due to some trials that recommended their use (Balzer 1991; Brock 1990; ICAI Group 1999; Norgren 1990; Trubestein 1989; Verstraete 1994). This family include the following drugs: prostaglandin E1 (also referred as PGE1 or alprostadil, in general intravenous/ intraarterial administration for 21 days); prostacyclin (also referred as PGI or epoprostenol, intravenous administration for four to seven days, intraarterial for 72 hours); iloprost (intravenous administration for 14 to 28 days/ oral for 28 days up to one year); lipoecaprost (intravenous administration for 50 days); and ciprostene (intravenous administration for seven days)

How the intervention might work

Prostanoids (prostaglandin E1, prostacyclin and iloprost) have been shown to have many pharmacologic actions that in theory could favourably alter the otherwise inexorable downhill course of CLI. These include the inhibition of activation, adhesion and aggregation of platelets, vasodilatation, vascular endothelial cytoprotection, inhibition of leucocyte activation, and antithrombotic and profibrinolitic activities (Balzer 1991; Brock 1990; ICAI Group 1999; Norgren 1990; Reiter 2003; Trubestein 1989).

Why it is important to do this review

A few meta-analyses (Creutzig 2004; Loosemore 1994) and reviews (Dormandy 1996) have been published, but they did not include all types of prostanoids and new ways of administration. Taking into account new approaches regarding this therapeutic option, it is very important to perform an updated systematic review, in order to find conclusive evidence about effectiveness and safety of the whole family of prostanoids in critical limb ischaemia.

OBJECTIVES

To determine the effectiveness and safety of prostanoids in patients with critical limb ischaemia.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

People irrespective of age or gender, presenting with critical limb ischaemia, without chance of rescue or reconstructive intervention.

Types of interventions

Prostaglandin E1 (PGE1, alprostadil), prostacyclin (PGI2 epoprostenol), iloprost, beraprost or cisaprost compared with placebo or other pharmacological control treatments (for example, pentoxifylline, cilostazol, naftidrofuryl, angiogenic therapy, or other prostanoids).

Types of outcome measures

Primary outcomes

- progression of disease: stabilization, major amputations (above / below knee), minor amputations (partial feet/fingers), total amputations (major plus minor);
- cardiovascular mortality/morbidity: myocardial infarction, stroke, arrhythmia (variation form the normal rhythm of the heart beat), sudden death;
- all-cause mortality;
- quality of life (measured according to a validated quality of life questionnaire).

Secondary outcomes

- evaluation of pain and/or use of analgesic drugs (measured according to a validated pain scale and a validated questionnaire, respectively)
- evolution of tissue lesions (healing/non-healing ulcers, according to surface area increase/decrease, and presence/absence of granulation tissue);
- ankle brachial index (ABI);
- adverse events of treatment.

Search methods for identification of studies

Electronic searches

The Cochrane Peripheral Vascular Diseases (PVD) Group searched their Specialised Register (last searched October 2009) and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (last searched 2009, Issue 4). See Appendix Appendix 1 for details of the search strategy used to search CENTRAL.

The PVD Group Specialised Register is maintained by the Trials Search Co-ordinator and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane PVD Group module in *The Cochrane Library.*

In addition, we ran searches in MEDLINE, EMBASE, LILACS, and SciSearch (1 January 1990 to 13 March 2009). For details of the search strategies we used to search MEDLINE *see* (Appendix 2) and EMBASE *see* (Appendix 3).

Searching other resources

We identified additional articles by reviewing reference lists of papers resulting from the electronic searches. We also contacted pharmaceutical companies (Bayer-Schering, Pfizer, Italfarmaco, Schwarz Pharma). There was no restriction on language of publication.

Data collection and analysis

Selection of studies

Selection of studies

Two review authors (AJR and MR) independently checked titles, abstracts, and keywords of all references retrieved. The full text of all studies considered potentially relevant were obtained and assessed independently by each author using a Study Eligibility Form. In case of disagreement between the two authors, this was resolved by consensus, or finally by the third author (AC).

Data extraction and management

Two authors (AJR and MR) collected all data from each included study using a Data Extraction Form, provided by the Cochrane PVD Group.
The following information was obtained:

1. publication type and source, including language of publication, year of publication, and method of retrieval of the report;
2. sources of support;
3. trial design, including method of generation and concealment of allocation sequences, and type of control intervention;
4. setting, including country, and level of care;
5. patients inclduing selection criteria used, number of withdrawals and drop-outs per group;
6. intervention, including dose, route of administration, and duration of treatment;
7. outcome measures included, modalities and schedule of assessments, adverse events and overall mortality and details of its causes;
8. analysis, including whether analysis was done according to the intention-to-treat principle;
9. results, including averages and variations of individual outcome assessments and different comparisons, test statistics and P-values for comparisons within and between groups.

Disagreements were resolved by consensus or by the third author (AC), if required. Primary authors were contacted by e-mail, in order to obtain additional information. All data were collected in original units, transformation for comparisons was not necessary.

Assessment of risk of bias in included studies

Two authors (AJR and MR) independently assessed the methodological quality of included studies, using the following criteria:

1. minimization of selection bias (randomisation method, allocation concealment and baseline equality);
2. minimization of performance bias (blinding of patients and of people administering the treatment);
3. minimization of attrition bias (losses to follow up, intention-to-treat analysis);
4. minimization of detection bias (blinding of outcome assessors/evaluators).

According to the fulfilment of these criteria (detailed in the PVD Group's form) each trial was classified in one of the following groups:

- A (Low risk of bias): all criteria met;
- B (Moderate risk of bias): $\geq$ 1 criteria partly met and $\leq$ 2 criteria inadequate;
- C (High risk of bias): $\geq$ 3 criteria inadequate.

We used the quality assessment to establish an inclusion threshold and to recommend improvement of quality in future trials. Trials classified as "C" (high risk of bias) were excluded.
We also used the Jadad scale. Trials classified Jadad 0 were also excluded (Jadad 1996). Disagreement between the two authors was resolved by consensus or finally by the third author (AC).

Measures of treatment effect

Even though there was an important clinical heterogeneity, we did perform an overall meta-analysis of prostanoids versus placebo. We also completed subgroup analysis of specific interventions (PGE1 versus ATP and versus placebo; iv iloprost and oral iloprost versus placebo), in accordance to clinical homogeneity (same prostanoid and route of administration).
All the reports were based on the intention-to-treat data from individual clinical trials.
Only dichotomous data could be obtained. They were analysed by the use of risk ratio (RR) with a confidence interval of 95%.

Dealing with missing data

In the event of missing data in the full reports, we planned to move the study to 'awaiting assessment' until further information could be obtained from the authors. However, in four cases (potentially relevant studies published as abstracts), authors did not have data, or did not reply, so finally their reports were excluded (Fonseca 1991; Menzoian 1995; Mingardi 1993; Schwarz 1995).

Assessment of heterogeneity

To test for statistical heterogeneity, although of limited power, the chi-square-test with a significance level set at P <0.1 and the I^2 test were used. For robustness of results, and in order to perform a conservative analysis, if I^2 was < 30, results were reported using

a fixed-effect model; if I^2 was between 30 and 50, results were reported using a random-effects model; and if I^2 was > 50, we did not allow meta-analysis.

Sensitivity analysis

Sensitivity analyses were performed to explore the quality of studies on the treatment effect size (quality threshold). Publication bias was also tested by performing a funnel plot for each comparison.

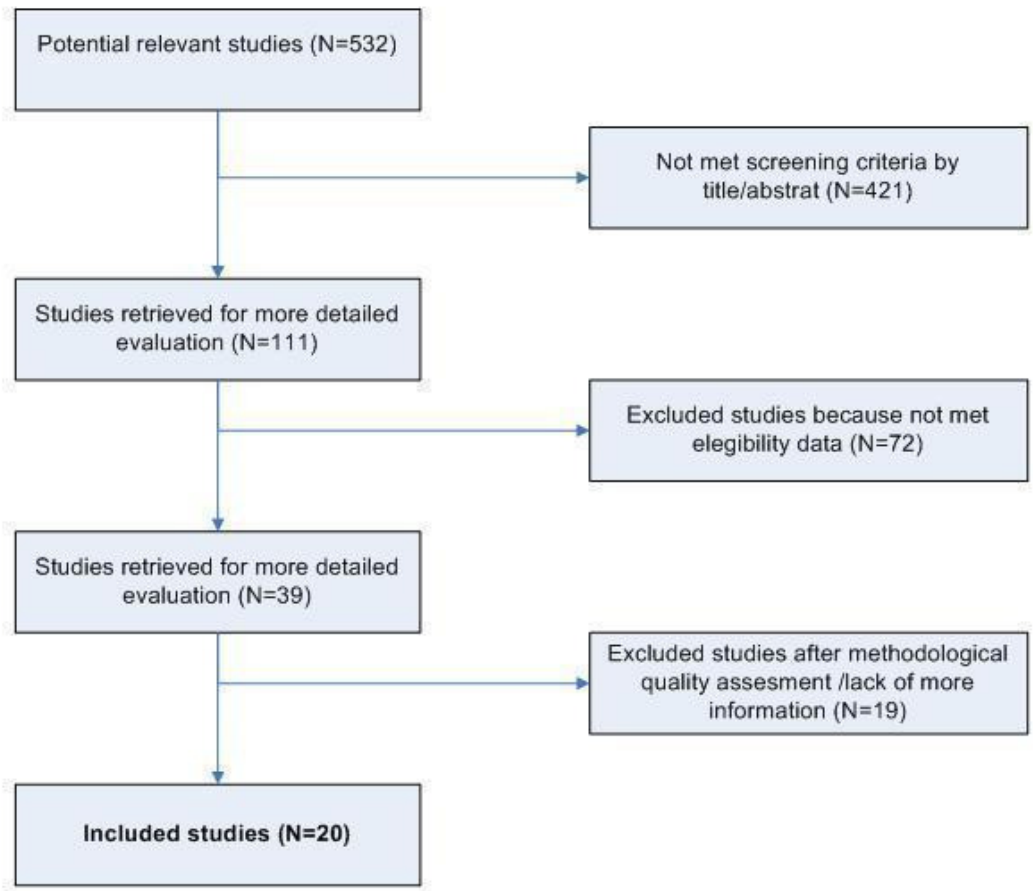
RESULTS

Description of studies

Results of the search

From the initial search, we obtained 532 citations (78 from the PVD Group, 90 from SciSearch, six from LILACS,193 from EMBASE, 80 from Pubmed, and 85 from pharmaceutical industry). After the first screening, we obtained 111 studies, including full text versions and the four abstracts previously mentioned (Fonseca 1991; Menzoian 1995; Mingardi 1993; Schwarz 1995). After we applied the Study Elegibility Form, only 39 of those were selected. Finally, in these 39 studies we performed methodological quality assessment, using the PVD Group's study assessment form and JADAD Scale, excluding 15 studies and the four abstracts (full text finally not available). (Figure 1).

Figure 1. Flow diagram of study selection.



To ensure the transparent and complete reporting of our review, we followed the PRISMA Statement for Reporting Systematic Reviews and Meta-Analysis of Studies that Evaluate Healthcare Interventions (PRISMA 2009).

Included studies

Details of the included studies are listed below and in the table 'Characteristics of included studies'.

In total, we included 20 trials in this review with a total of 2724 randomised participants. Four studies compared intravenous (iv) PGE1 with placebo (Diehm 1987; Diehm 1988; Stiegler 1992; Telles 1984); two studies (Böhme 1989; Trubestein 1987) compared intraarterial (IA) PGE1 with ATP (adenosine triphosphate). Five studies compared iv iloprost with placebo (Balzer 1991; Brock 1990; Dormandy 1991; Guilmot 1991; Norgren 1990); one study (Beischer 1998) compared low dose infusion of iloprost with a standard infusion; and another study compared iv iloprost with PGE1 (Schellong 2003). Oral iloprost was compared with placebo in two studies (Dormandy 2000a - Study A; Dormandy 2000b - Study B). Intravenous PGI2 was compared with placebo in two studies (Belch 1983; Hossmann 1983), and intraarterial PGI2 (21 SWG catheter inserted into the common femoral artery) was compared with naftidrofuryl in another one (Negus 1987). Finally, two other studies compared lipoecraprost (Brass 2006) and ciprostene (Linet 1991) with placebo, both using the iv route of administration.

Excluded studies

Details of the excluded studies are listed in the table ' Characteristics of excluded studies'.

We excluded 19 studies; the most frequent criteria for exclusion were subjects, treatment providers or outcomes assessors not blinded to assignment status, withdrawals $\geq$ 10% of the study population, no intention-to-treat analysis, care programmes not identical and Jadad Score of 0. Four out of the 19 studies were abstracts for which we were unable to obtain full text in spite of contacting the authors for further information (Fonseca 1991; Menzoian 1995; Mingardi 1993; Schwarz 1995).

Risk of bias in included studies

All of the included studies were classified as "B", which means moderate risk of bias ($\geq$ 1 criteria partly met and $\leq$ 2 criteria inadequate). There was no study classified as "A" (low risk of bias) (Figure 2 and Figure 3)

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

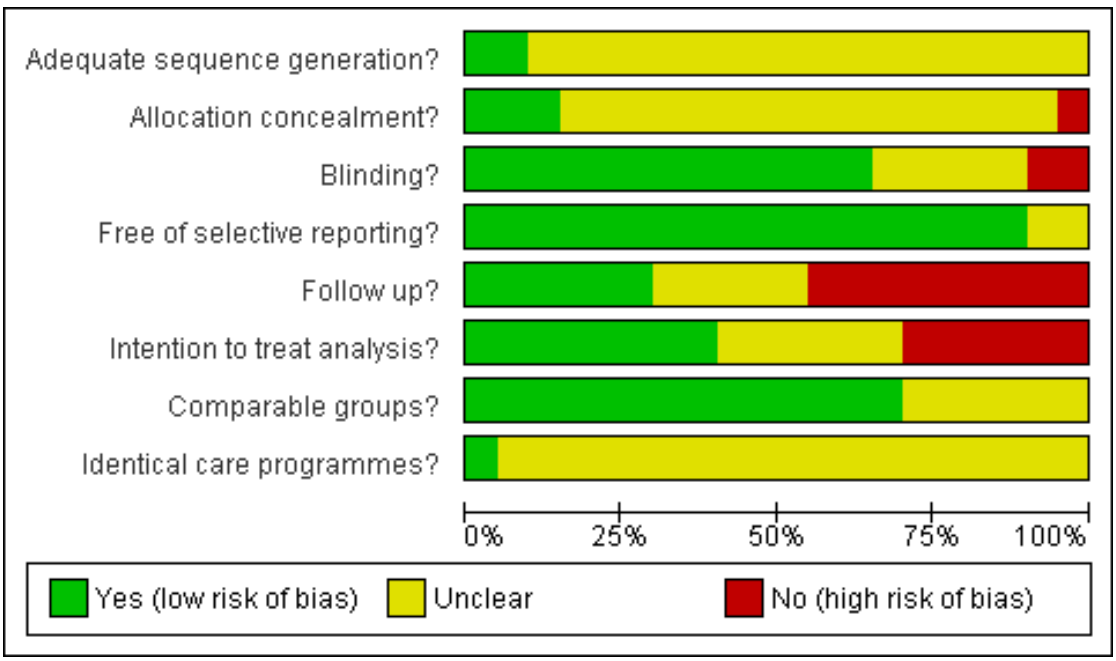
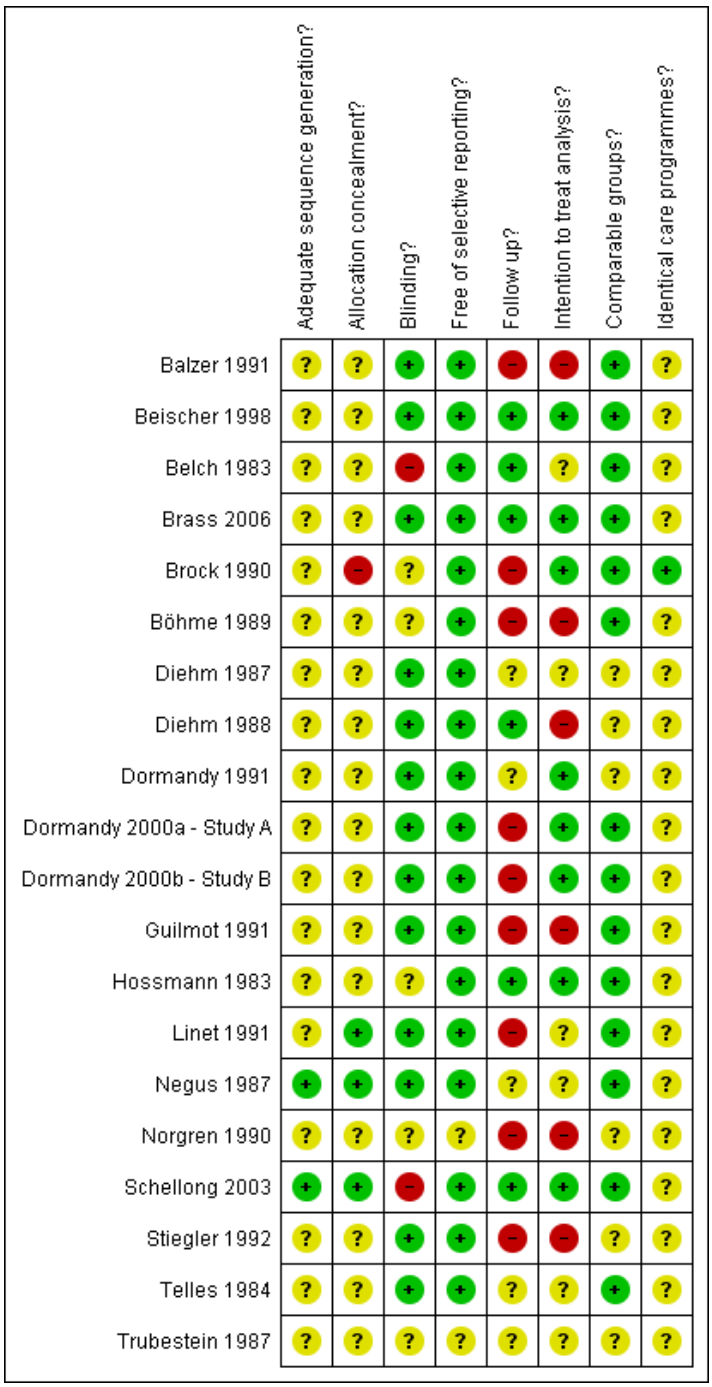


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** Prostanoids compared with placebo for critical limb ischaemia; **Summary of findings 2** PGE1 compared with placebo for critical limb ischaemia; **Summary of findings 3** Iloprost compared with placebo for critical limb ischaemia; **Summary of findings 4** Oral iloprost (high and low dose) versus placebo for critical limb ischaemia; **Summary of findings 5** PGE1 compared with ATP for critical limb ischaemia; **Summary of findings 6** Prostanoids compared with placebo (highest quality studies) for critical limb ischaemia

Prostanoids versus placebo (meta-analysis)

As we could obtain neither concrete definitions nor homogeneous definitions of some of the predefined outcomes, we dichotomised the following continuous results: evaluation of pain (pain relief if there was any improvement in a validated pain scale, no relief if pain was the same or worse); and evolution of tissue lesions (ulcer healing if there was any decrease in surface area and/or presence of granulation tissue, no healing if surface area was similar or bigger and/or absence of granulation tissue).

Although there was significant clinical heterogeneity (study designs, types of prostanoid and routes of administration differed significantly among the included studies), we completed a global meta-analysis of any type of prostanoid via any route versus placebo. The aim was to allow a meaningful meta-analysis of the same class of drug with the same expected "biochemical" action.

Thirteen studies were considered, showing that prostanoids were effective with regard to rest-pain relief (risk ratio (RR) 1.32, 95% confidence interval (CI) 1.10 to 1.57), and ulcer healing (RR 1.54, 95% CI 1.22 to 1.96). However, there was no statistically significant effect on amputations (RR 0.89, 95% CI 0.76 to 1.04) and mortality (RR 1.07, 95% CI 0.65 to 1.75). There was also a statistically significant increase in adverse events (RR 2.35, 95% CI 1.99 to 2.78). These results showed statistical homogeneity, although they should be considered with caution due to the moderate risk of bias.

As a sensitivity analysis, we excluded studies with a quality threshold of ≤ 1 criteria as inadequate, leaving eight studies in the analysis. The results (still under a moderate risk of bias) seemed to be robust. Results for rest-pain relief (RR 1.45, 95% CI 1.15 to 1.82), ulcer healing (RR 1.35, 95% CI 1.15 to 1.58) and adverse events (RR 2.38, 95% CI 1.91 to 2.96) remained statistically significant; results for amputations (RR 0.91, 95% CI 0.76 to 1.09) and mortality (RR 1.14, 95% CI 0.70 to 1.85) remained statistically non-significant.

Analysis of individual studies

Taking into account the moderate risk of bias and clinical heterogeneity in this global meta-analysis, we considered it appropriate to perform a subgroup analysis based on clinical homogeneity, thus considering each type of prostanoid and the respective route of administration separately. The following analyses were performed: iv PGE1 versus placebo; iv iloprost versus placebo; oral iloprost versus placebo; and iv PGE1 versus ATP.

Intravenous (iv) PGE1 versus placebo

The meta-analysis of this subgroup (Diehm 1987; Diehm 1988) showed non-statistically significant results regarding rest-pain relief (RR 1.52, 95% CI 0.69 to 3.34), and a reduction in analgesic consumption (RR 1.58, 95% CI 0.92 to 2.72). However, the number of adverse events was both clinically and statistically significantly increased in the PGE1 group (RR 5.81, 95% CI 1.62 to 20.86). The most frequent adverse events were flushing, headache, and redness of the infused vein.

Intravenous (iv) iloprost versus placebo

The meta-analysis of this subgroup (Balzer 1991; Dormandy 1991; Guilmot 1991) showed statistically significant results: rest-pain relief (RR 1.54, 95% CI 1.19 to 1.99); ulcer healing (RR 1.80, 95% CI 1.29 to 2.50); major amputations (RR 0.69, 95% CI 0.52 to 0.93); and adverse events (RR 2.05, 95% CI 1.68 to 2.49). However, total amputations showed statistically non-significant results (RR 0.79, 95% CI 0.60 to 1.03). The most frequent adverse events were headache, flushing, nausea and vomiting. Regarding ulcer healing, if we exclude one study (Brock 1990), in which all the patients were diabetics, the result is still robust (RR 1.55, 95% CI 1.13 to 2.14).

Oral iloprost (different doses) versus placebo

We completed a subgroup analysis regarding low dose (50 to 100 mg twice daily) and high dose (150 to 200 mg twice daily) of oral iloprost versus placebo (Dormandy 2000a - Study A; Dormandy 2000b - Study B). This analysis showed no statistically significant results in rest-pain relief (low dose RR 1.12, 95% CI 0.73 to 1.74; high dose RR 1.48, 95% CI 0.99 to 2.21); (ulcer healing (low dose RR 1.52, 95% CI 1.00 to 2.33; high dose RR 1.41, 95% CI 0.91 to 2.17); major amputations (low dose RR 0.86, 95% CI 0.65 to 1.12; high dose RR 0.84, 95% CI 0.64 to 1.11); and mortality (low dose RR 0.84, 95% CI 0.54 to 1.32; high dose RR 0.90, 95% CI 0.39 to 2.09)

Intraarterial (ia) PGE1 versus adenosine triphosphate (ATP)

The meta-analysis of this subgroup (Böhme 1989; Trubestein 1987) showed statistically significant results for ia PGE1: total amputations (RR 0.26, 95% CI 0.09 to 0.74) and adverse events (RR 2.78, 95% CI 1.41 to 5.48). The most frequent adverse events were erythema (abnormal redness of the skin), burning sensations, pain and swelling. Individual studies showed a better profile of PGE1 rather than ATP in rest-pain relief, analgesic consumption and ulcer healing, although the meta-analysis could not be completed due to differences in outcome definitions.

Analysis of individual studies

Unfortunately we could only describe the more important results of included studies in the remaining subgroups of prostanoids: ia PGE1 versus ATP; iv iloprost (low versus standard dose) (Böhme 1989; Trubestein 1987); iv PGI2 versus placebo (Belch 1983; Hossmann 1983); ia PGI2 versus naftidrofuryl (Negus 1987); iv lipoecraprost versus placebo (Brass 2006); and iv ciprostene versus placebo (Linet 1991). Meta-analyses of these subgroups were not possible, since we obtained only one acceptable study for each comparison, except for the subgroup iv PGI2 versus placebo in which even though we obtained two acceptable studies, they compared different outcomes (Belch 1983; Hossmann 1983).

Intravenous (iv) iloprost versus PGE1

In Schellong 2003 a better patient profile of iv PGE1 versus iloprost was described, regarding microcirculation and tolerability. Seven patients (19.4%) experienced mild adverse events during infusion of PGE1 compared with 11 patients (30.6%) during infusion of iloprost. The most frequent adverse events were flushing, pain at the infusion site, and headache.

Intravenous (iv) iloprost (low versus standard dose)

In Beischer 1998, no significant iv iloprost dose response was observed regarding ulcer healing or relief of rest pain. Rates of major amputations and death at the end of the follow-up period were not significantly different over the dose range. However, non-responders showed a considerably higher rate of major amputations compared with responders (39% versus 7%), and deaths at six months (20.5% versus 9.1%). Responders were defined by Beischer as patients with very good or good global efficacy, as judged by lesion healing and pain relief Side effects showed a statistically significant ($P < 0.001$) dose response, the most frequent included headache (37%), flushing (22%), and nausea (20%).

Intravenous (iv) PGI2 versus placebo

In Hossmann 1983, there was a favourable change (3.2 ± 0.7 cm) in a rest pain visual analogue score (VAS) on patients receiving iv PGI2, compared with no decrease of pain in placebo patients (statistical significance not reported). There was also a decrease of 50.7% of the area of necrosis in ulcers ($P < 0.05$), compared with a statistical non-significant reduction in the placebo arm. However, there was a change in systolic blood pressure (from 150.4 ± 4.8 mmHg to 142.8 ± 4.0 mmHg in the treatment group ($P < 0.05$). In Belch 1983, rest-pain relief was observed after six months in seven out of 15 patients receiving iv PGI2, versus only one out of 13 patients receiving placebo. However, 14 patients receiving iv PGI2 reported adverse events, compared with only one in the placebo group. The most frequent adverse events were facial flushing, headache, nausea and vomiting.

Intraarterial (ia) PGI2 versus naftidrofuryl

In Negus 1987, relief of pain for 24 hours after ia infusion was achieved in 11 of 14 patients receiving ia PGI2, and in nine of 15 patients receiving naftidrofuryl (statistical significance not reported). There was no significant difference in the long-term results between groups. Headache or flushing presented in five patients receiving PGI2.

Intravenous (iv) lipoecraprost versus placebo

In Brass 2006, at six months follow up, 16.2% of patients had major amputations and 10.1% had died in the iv lipoecraprost group, compared with 13% and 5.6% respectively, in the placebo group. In patients with ulcerations or gangrene at entry, 24.5% of the placebo group, and 23.2% of the lipoecraprost group were ulcer free at six months. Regarding rest pain, 24.3% of the placebo treated patients and 22.1% of the lipoecraprost were completely pain free at six months. The statistical significance of these data was not reported. Common side effects in the lipoecraprost group were headache, pain, and hypotension. The study was ended on a recommendation from the Data and Safety Monitoring Board.

Intravenous (iv) ciprostene versus placebo

In Linet 1991, the frequency of patients with at least one ulcer reduced in size by 50% or more at the end of follow up (four months) was 90% under iv ciprostene treatment, compared with 70% under placebo ($P = 0.015$). Regarding the number of ulcers reduced in size by 50% or more, at the end of follow up, ciprostene had a higher success rate compared with placebo (83% versus 62%, $P = 0.003$). In a subgroup analysis of diabetic patients, ciprostene had a statistically non-significant higher success rate than placebo. In both treatment groups, there was an immediate and significant decrease in rest pain, which continued during follow up. However, the proportion of ciprostene treated patients who required narcotics declined from 22% to 2% at four months, whereas in the placebo group the percentage increased from 14% to 15%. There was no difference in the ankle brachial index (ABI) between the two groups. Regarding side effects, more ciprostene treated

patients reported headache (P = 0.001) and nausea (P = 0.04) than placebo patients.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

PGE1 compared with placebo for critical limb ischaemia

Patient or population: patients with critical limb ischaemia
Settings:
Intervention: PGE1
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	PGE1				
Rest pain relief Questionnaires Follow-up: mean 3.5 weeks	**Study population**		**RR 1.52** (0.69 to 3.34)	69 (2 studies)	⊕○○○ **very low**[1,2]	
	152 per 1000	**231 per 1000** (105 to 508)				
	Medium risk population					
	243 per 1000	**369 per 1000** (168 to 812)				
Reduction in analgesics consumption Questionnaires Follow-up: mean 3.5 weeks	**Study population**		**RR 1.58** (0.92 to 2.72)	58 (2 studies)	⊕○○○ **very low**[3]	
	400 per 1000	**632 per 1000** (368 to 1000)				
	Medium risk population					
	410 per 1000	**648 per 1000** (377 to 1000)				

Adverse events (patients) Follow-up: mean 3.5 weeks	**Study population**		**RR 5.81** (1.62 to 20.86)	69 (2 studies)	⊕○○○ **very low**[1,2]
	61 per 1000	**354 per 1000** (99 to 1000)			
	Medium risk population				
	42 per 1000	**244 per 1000** (68 to 876)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] One trial with one inadequate criterion, and one trial with six criteria partly met
[2] 95% confidence interval around the pooled or best estimate of effect includes both no effect and appreciable benefit or appreciable harm in 2 trials
[3] No explanation was provided

Iloprost compared with placebo for critical limb ischaemia

Patient or population: patients with critical limb ischaemia
Settings:
Intervention: Iloprost
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	Iloprost				
Rest pain relief Questionnaires Follow-up: mean 14 weeks	**Study population**		**RR 1.54** (1.19 to 1.99)	318 (3 studies)	⊕⊕◯◯ **low**[1,2]	
	366 per 1000	**564 per 1000** (436 to 728)				
	Medium risk population					
	328 per 1000	**505 per 1000** (390 to 653)				
Ulcer healing size of ulcer / granulation tissue at the base Follow-up: mean 14.7 weeks	**Study population**		**RR 1.8** (1.29 to 2.5)	367 (3 studies)	⊕◯◯◯ **very low**[1,3,4]	
	283 per 1000	**509 per 1000** (365 to 707)				
	Medium risk population					
	254 per 1000	**457 per 1000** (328 to 635)				
Total Amputations Follow-up: mean 21.3 weeks	**Study population**		**RR 0.79** (0.6 to 1.03)	318 (3 studies)	⊕⊕◯◯ **low**[1,2]	

	463 per 1000	**366 per 1000** (278 to 477)			
	Medium risk population				
	465 per 1000	**367 per 1000** (279 to 479)			
Major amputations Follow-up: mean 21.3 weeks	**Study population**		**RR 0.69** (0.52 to 0.93)	318 (3 studies)	⊕⊕◯◯ **low**[1,2]
	443 per 1000	**306 per 1000** (230 to 412)			
	Medium risk population				
	442 per 1000	**305 per 1000** (230 to 411)			
Adverse events (patients) Follow-up: mean 21.3	**Study population**		**RR 2.05** (1.68 to 2.49)	378 (3 studies)	⊕⊕◯◯ **low**[1,2]
	406 per 1000	**832 per 1000** (682 to 1000)			
	Medium risk population				
	415 per 1000	**851 per 1000** (697 to 1000)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Two trials with at least one inadequate criterion

[2] 95% confidence interval around the pooled or best estimate of effect includes both no effect and appreciable benefit or appreciable harm in 2 trials

[3] Unexplained heterogeneity of results

[4] 95% confidence interval around the pooled or best estimate of effect includes both no effect and appreciable benefit in 1 trial

Oral iloprost (high and low dose) versus placebo for critical limb ischaemia

Patient or population: patients with critical limb ischaemia
Settings:
Intervention: Oral iloprost (high and low dose) versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Oral iloprost (high and low dose) versus placebo				
Rest pain relief (high and low dose) - Low dose iloprost (50-100 micro gr bid) Questionnaires Follow-up: mean 36 weeks[1]	**Study population**		**RR 1.12** (0.73 to 1.74)	224 (2 studies)	⊕⊕◯◯ **low**[2,3]	
	250 per 1000	**280 per 1000** (183 to 435)				
	Medium risk population					
	275 per 1000	**308 per 1000** (201 to 479)				
Rest pain relief (high and low dose) - High dose iloprost (150 - 200 micro gr bid) Questionnaires Follow-up: mean 36 weeks[1]	**Study population**		**RR 1.48** (0.99 to 2.21)	223 (2 studies)	⊕⊕◯◯ **low**[2,3]	
	250 per 1000	**370 per 1000** (248 to 553)				
	Medium risk population					
	275 per 1000	**407 per 1000** (272 to 608)				

Major Amputations (high and low dose) - Low dose iloprost (50-100 micro gr bid) Follow-up: mean 36 weeks[1]	**Study population**		**RR 0.86** (0.65 to 1.12)	537 (2 studies)	⊕⊕◯◯ **low**[2,3]
	301 per 1000	**259 per 1000** (196 to 337)			
	Medium risk population				
	309 per 1000	**266 per 1000** (201 to 346)			
Major Amputations (high and low dose) - High dose iloprost (150 - 200 micro gr bid) Follow-up: mean 36 weeks[1]	**Study population**		**RR 0.84** (0.64 to 1.11)	534 (2 studies)	⊕⊕◯◯ **low**[2,3]
	301 per 1000	**253 per 1000** (193 to 334)			
	Medium risk population				
	309 per 1000	**260 per 1000** (198 to 343)			
Mortality (high and low dose) - Low dose iloprost (50-100 micro gr bid) Follow-up: mean 36 weeks[1]	**Study population**		**RR 0.84** (0.54 to 1.32)	537 (2 studies)	⊕⊕◯◯ **low**[2,3]
	138 per 1000	**116 per 1000** (75 to 182)			
	Medium risk population				
	157 per 1000	**132 per 1000** (85 to 207)			
Mortality (high and low dose) - High dose iloprost (150 - 200 micro gr bid) Follow-up: mean 36 weeks	**Study population**		**RR 0.9** (0.39 to 2.09)	534 (2 studies)	⊕⊕◯◯ **low**[2,3]

	138 per 1000	**124 per 1000** (54 to 288)
	Medium risk population	
	157 per 1000	**141 per 1000** (61 to 328)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Long term follow up was 6 months in the first trial and 12 months in the second one
[2] Two trials with at least one inadequate criterion
[3] 95% confidence interval around the pooled or best estimate of effect includes both no effect and appreciable benefit or appreciable harm in 2 trials

PGE1 compared with ATP for critical limb ischaemia

Patient or population: patients with critical limb ischaemia
Settings:
Intervention: PGE1
Comparison: ATP

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ATP	PGE1				
Total Amputations Follow-up: mean 3 weeks	**Study population**		**RR 0.26** (0.09 to 0.74)	91 (2 studies)	⊕⊕◯◯ **low**[1,2]	
	310 per 1000	**81 per 1000** (28 to 229)				
	Medium risk population					
	298 per 1000	**77 per 1000** (27 to 221)				
Adverse event (patients) Follow-up: mean 3 weeks	**Study population**		**RR 2.78** (1.41 to 5.48)	91 (2 studies)	⊕⊕◯◯ **low**[1,2]	
	190 per 1000	**528 per 1000** (268 to 1000)				
	Medium risk population					
	178 per 1000	**495 per 1000** (251 to 975)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] One trial with two inadequate criteria, and one trial with eight criteria partly met
[2] 95% confidence interval around the pooled or best estimate of effect includes both no effect and appreciable benefit or appreciable harm in 1 trial

Prostanoids compared with placebo (highest quality studies) for critical limb ischaemia

Patient or population: patients with critical limb ischaemia
Settings:
Intervention: Prostanoids
Comparison: placebo (highest quality studies)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo (highest quality studies)	Prostanoids				
Rest pain relief Questionnaires Follow-up: mean 20.6 weeks	**Study population**		**RR 1.45** (1.15 to 1.82)	559 (5 studies)	⊕⊕◯◯ **low**[1,2]	
	297 per 1000	**431 per 1000** (342 to 541)				
	Medium risk population					
	308 per 1000	**447 per 1000** (354 to 561)				
Ulcer healing size of ulcer / granulation tissue at the base Follow-up: mean 23.2 weeks	**Study population**		**RR 1.35** (1.15 to 1.58)	843 (5 studies)	⊕⊕◯◯ **low**[1,3]	
	354 per 1000	**478 per 1000** (407 to 559)				
	Medium risk population					
	254 per 1000	**343 per 1000** (292 to 401)				

Amputations Follow-up: mean 27.3 weeks	**Study population**		**RR 0.91** (0.76 to 1.09)	1546 (6 studies)	⊕⊕◯◯ **low**[1,4]
	243 per 1000	**221 per 1000** (185 to 265)			
	Medium risk population				
	304 per 1000	**277 per 1000** (231 to 331)			
Mortality Follow-up: mean 34 weeks	**Study population**		**RR 1.14** (0.7 to 1.85)	1363 (4 studies)	⊕◯◯◯ **very low**[1,2,5]
	89 per 1000	**101 per 1000** (62 to 165)			
	Medium risk population				
	89 per 1000	**101 per 1000** (62 to 165)			
Adverse events (patients) Follow-up: mean 10.2 weeks	**Study population**		**RR 2.38** (1.91 to 2.96)	457 (5 studies)	⊕⊕◯◯ **low**[6,7]
	280 per 1000	**666 per 1000** (535 to 829)			
	Medium risk population				
	83 per 1000	**198 per 1000** (159 to 246)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Three trials with at least one inadequate criterion
[2] 95% confidence interval around the pooled or best estimate of effect includes both no effect and appreciable benefit or appreciable harm in 4 trials
[3] 95% confidence interval around the pooled or best estimate of effect includes both no effect and appreciable benefit or appreciable harm in 3 trials
[4] 95% confidence interval around the pooled or best estimate of effect includes both no effect and appreciable benefit or appreciable harm in 5 trials
[5] Unexplained heterogeneity of results
[6] Two trials with at least one inadequate criterion
[7] 95% confidence interval around the pooled or best estimate of effect includes both no effect and appreciable benefit or appreciable harm in 2 trials

DISCUSSION

We performed a systematic review obtaining 20 studies from 532 initial citations. From our global meta-analysis prostanoids were effective regarding rest-pain relief (RR 1.32, 95% CI 1.10 to 1.57), and ulcer healing (RR 1.54, 95% CI 1.22 to 1.96). However, they did not show a statistically significant effect regarding amputations and mortality. Adverse events were also statistically significant (RR 2.35, 95% CI 1.99 to 2.78). These results showed statistical homogeneity, though they should be considered with caution due to both clinical heterogeneity and moderate risk of bias.

After sensitivity analysis through quality threshold, there is still a moderate risk of bias but results seem to be robust: rest-pain relief, ulcer healing and adverse events remain statistically significant in contrast to amputations and mortality. Under this global comparison, amputations could not be counted as total amputations, or classified as major - minor, since not all the included studies clarified this issue. However, we tried to include all the available information in a generic outcome "amputations", to have at least a meaningful idea of this important result.

Regarding subgroup analysis, iv iloprost showed statistically significant results versus placebo for rest-pain relief (RR 1.54, 95% CI 1.19 to 1.99); ulcer healing (RR 1.80, 95% CI 1.29 to 2.50); and major amputations (RR 0.69, 95% CI 0.52 to 0.93) but also for adverse events (RR 2.05, 95% CI 1.68 to 2.49). In the same way, ia PGE1 showed statistically significant results versus ATP for total amputations (RR 0.26, 95% CI 0.09 to 0.74) and adverse events (RR 2.78, 95% CI 1.41 to 5.48) (Böhme 1989; Trubestein 1987). Curiously, when comparing iv PGE1 with placebo, results were statistically non-significant; only adverse events in PGE1 group were clinically and statistically significant, but showing a large confidence interval (RR 5.81, 95% CI 1.62 to 20.86). The remaining subgroup analysis of oral iloprost and its different doses did not show any statistically significant result.

As we could not complete a meta-analysis of the rest of the prostanoids, we present the results of individual studies.

Regarding publication bias, we did not detect important asymmetries from funnel plots of each of the meta-analysis performed. We present the funnel plots with more included studies (Figure 4; Figure 5; Figure 6; Figure 7).

Figure 4. Funnel plot of comparison: 1 Prostanoids vs placebo, outcome: 1.1 Rest pain relief.

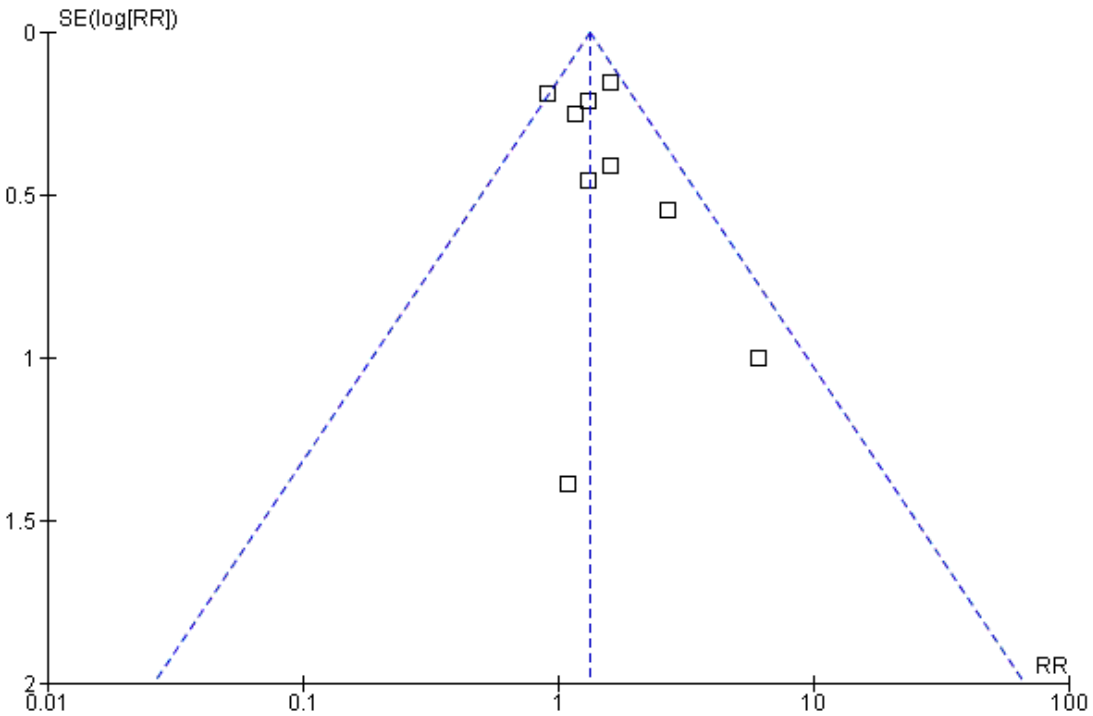


Figure 5. Funnel plot of comparison: 1 Prostanoids vs placebo, outcome: 1.2 Ulcer healing.

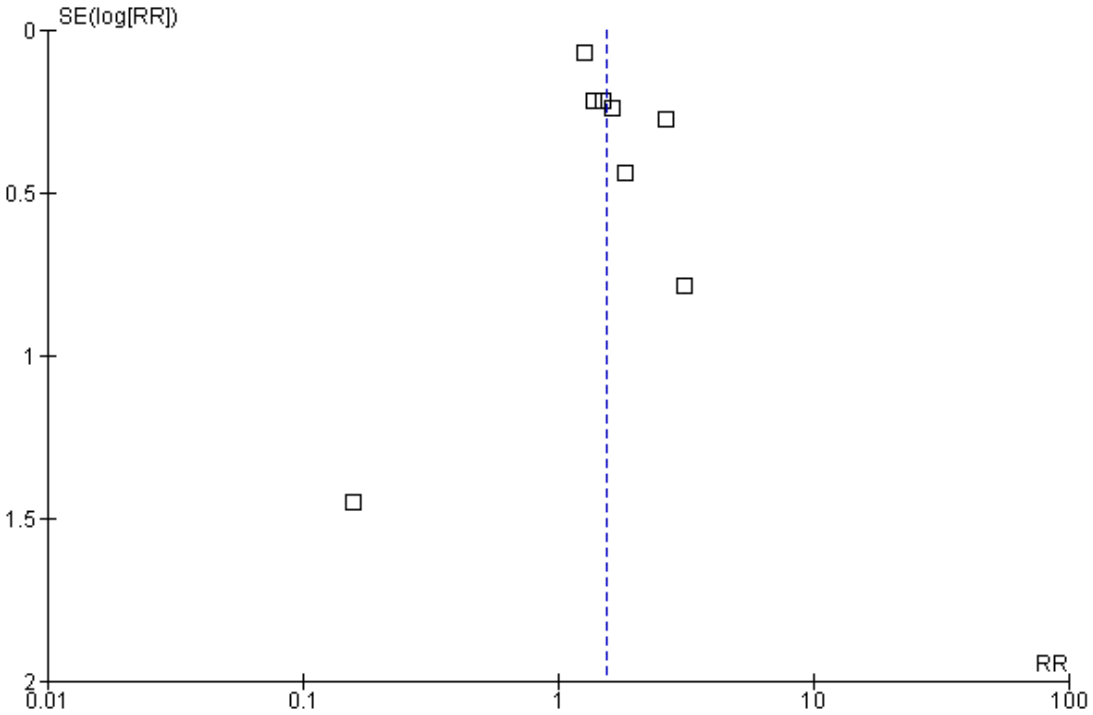


Figure 6. Funnel plot of comparison: 1 Prostanoids vs placebo, outcome: 1.3 Amputations.

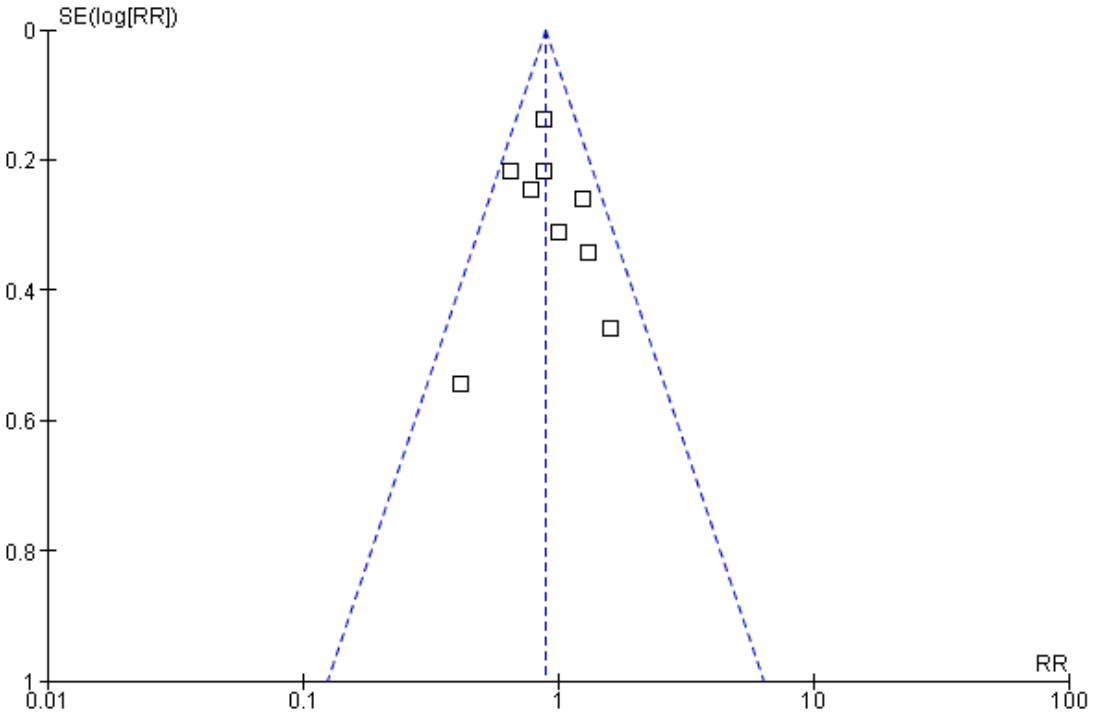
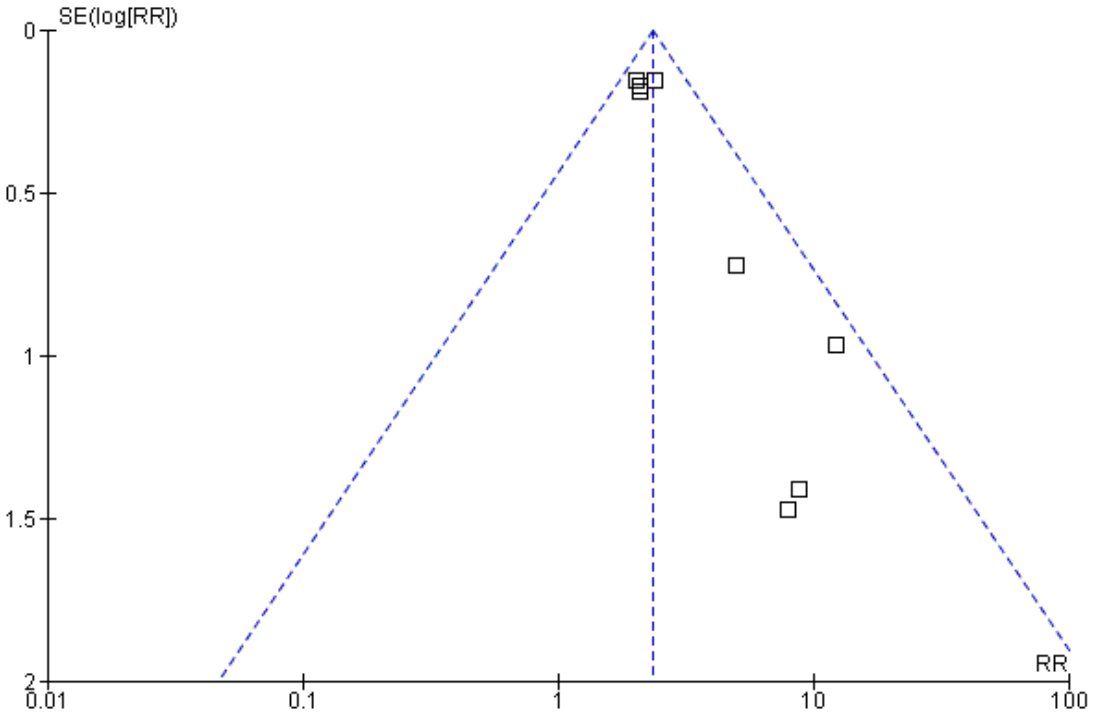


Figure 7. Funnel plot of comparison: 1 Prostanoids vs placebo, outcome: 1.5 Adverse events (patients).



Some published meta-analyses state the beneficial effects of iloprost (Loosemore 1994) and PGE1 (Creutzig 2004) in patients with CLI who are unsuitable for rescue or reconstructive intervention. Even though we analysed all the studies entered in both publications, after a strict methodological assessment, only a few of them were included in this review.

From a global perspective, prostanoids seem to have efficacy regarding rest-pain relief and ulcer healing, which is not relevant due to clinical heterogeneity. Iloprost shows favourable results not only in these outcomes but also in major amputations. Regarding adverse events when using prostanoids, the more frequently reported were headache, facial flushing, nausea, vomiting and diarrhoea.

In general, long term results (follow up > one year) were not available, so we could not obtain conclusions regarding any change in final disease prognosis after treatment with prostanoids.

It is also important to state that the included studies, although adjusting by a minimum threshold, presented poor methodological quality. All the studies could only be classified as "B" (moderate risk of bias), most of them presented unclear issues regarding methods section (see "Risk of bias tables"). Perhaps, one explanation of the general low quality (both in the included and excluded studies) could be that most of them were published a long time ago (between 15 and 30 years), when current concepts from evidence-based medicine were not so well established.

AUTHORS' CONCLUSIONS

Implications for practice

Despite some positive results regarding rest-pain relief, ulcer healing and amputations, there is no conclusive evidence based on a high quality meta-analysis of homogeneous randomised long term clinical trials, regarding efficacy and safety of different prostanoids in patients with CLI.

Implications for research

Further well-conducted randomised double blind trials, including a sufficient number of participants to provide statistically powerful information, should be performed. To analyse the long-term effects of prostanoids, a follow up longer than one year is recommended. Methodological issues on the published literature should be reviewed according to evidence-based medicine's perspective, in order to assure future high quality publications.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Balzer 1991

Methods	**Study design:** multicentre, randomised, double-blind, placebo-controlled trial
Participants	**Country:** Germany. **Number of study centres:** 13. **Setting:** hospital. **Number:** 113; experimental group 55; control group 58. **Age (median) years:** experimental group 69; control group 67. **Sex (M/F):** experimental group 33/22; control group 41/17. **Inclusion criteria:** nocturnal ischaemic pain at rest for at least 2 weeks, clinical signs advanced PAOD (stage III or IV) **Exclusion criteria:** "patients with trophic lesions" (no further details).
Interventions	**Experimental:** intravenous infusion of iloprost over 6 hours. **Control:** placebo. **Duration:** 14 days, follow up 4 weeks.
Outcomes	Rest-pain relief, use of analgesics, tolerability.
Notes	Stratification by diabetes mellitus. Source of funding: not stated. 11 patients withdrew from the study before completion; 102 patients included in the final analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"Patients were randomised within each centre"
Allocation concealment?	Unclear risk	"Patients were randomised within each centre"
Blinding? All outcomes	Low risk	The study is described as double blind
Free of selective reporting?	Low risk	Primary and secondary endpoints reported
Follow up?	High risk	Withdrawals > 10% of the study population; iloprost group 10, placebo 3
Intention to treat analysis?	High risk	Not performed
Comparable groups?	Low risk	Shown in Table 1
Identical care programmes?	Unclear risk	Not mentioned

Beischer 1998

Methods	**Study design:** multicentre, randomised, double-blind, dose-response study of 4 parallel dose groups
Participants	**Country:** Germany. **Number of study centres:** 32. **Setting:** hospital. **Number:** 302 entered; 299 ITT analysis. **Age (mean) years: (**25 µg) 72.6; (50 µg) 72.3; (75 µg) 73.3; (100 µg) 69.9. **Sex (M/F):** 53.5% / 46.5% **Inclusion criteria:** patients 40 years or older with stage IV PAOD confirmed by angiography; stable clinical condition for at least 2 weeks **Exclusion criteria:** patients suitable for reopening procedures or bypass surgery; sepsis or forefoot gangrene; osteomyelitis; major amputations (above the ankle) within the previous 4 weeks; sympathectomy within the last 3 months; bleeding disorders; unstable angina pectoris; congestive heart failure; MI or stroke within previous 6 week; type I diabetes; pregnant or breast feeding
Interventions	**Experimental:** intravenous infusion of iloprost 25, 50, 75 and 100 µg in 500 ml of saline or 5% glucose, over 6 hours daily **Duration:** 4 weeks; follow up 6 months
Outcomes	Death, major amputation, healing/number of trophic lesions, pain relief (VAS/ number of patients) , analgesics consumption, pulse rate, blood pressure, adverse events
Notes	Source of funding: Schering AG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	The study is described as double blind
Free of selective reporting?	Low risk	Primary and secondary endpoints reported
Follow up?	Low risk	3 patients excluded due to withdrawal of consent (1) and wrong diagnosis (2)
Intention to treat analysis?	Low risk	ITT analysis was performed over a population of 299 patients, from 302 entered
Comparable groups?	Low risk	Shown in Table 1
Identical care programmes?	Unclear risk	"During study treatment concomitant therapy with anti-inflammatory drugs, aspirin, oral anticoagulants, buflomedil, naftidrofuryl, bencyclan, pentoxifylline, or haemodilution was not

Beischer 1998 (*Continued*)

		allowed. Revascularization and sympathectomy during treatment phase were also not permitted. .."

Belch 1983

Methods	**Study design:** single-centre, randomised, double-blind, placebo-controlled trial
Participants	**Country:** UK. **Setting:** hospital. **Number:** 28; experimental group 15; control group 13. **Age years:** experimental group 67 ± 12; control group 69 ± 7. **Sex (M/F):** experimental group 9/6; control group 10/3. **Inclusion criteria:** ischaemic rest pain. **Exclusion criteria:** > 80 years of age, had diabetes, infection, or necrosis > $1cm^{2.}$
Interventions	**Experimental:** intravenous infusion of epoprostenol (prostacyclin - PGI2). **Control:** placebo. **Duration:** 4 days.
Outcomes	Rest-pain relief, analgesic consumption, side effects 24 days, 1 month, and 6 months post treatment, and mortality
Notes	Source of funding: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	High risk	Patients and assessing surgeon were blinded to treatment. Physician who administered all treatments was not blinded
Free of selective reporting?	Low risk	Primary and secondary endpoints reported
Follow up?	Low risk	Withdrawals < 10% of the study population
Intention to treat analysis?	Unclear risk	Not mentioned
Comparable groups?	Low risk	Shown in Table 1
Identical care programmes?	Unclear risk	Not mentioned

Brass 2006

Methods	**Study design:** multicentre, randomised, double-blind, placebo-controlled trial
Participants	**Country:** USA, UK, Japan. **Number of study centres:** 5. **Setting:** hospital. **Number:** 560 planned; 383 randomised; ITT population 379. **Age (mean) (range) years:** (ITT population) experimental group 69.7 (43.7 to 99.4); control group 69.7 (42.7 to 96.4) **Sex (M/F):** (ITT population) experimental group127/62; control group 130/60 **Inclusion criteria:** atherosclerotic CLI, aged > 40 years, without revascularization option, stratification by diabetic status **Exclusion criteria:** previous major amputation or if major amputation would be required; recent revascularization; receiving antihypertensive therapy; clinical evidence of sepsis; ESRD; recent MI
Interventions	**Experimental:** intravenous infusion of lipo-ecraprost (ecraprost 60 μg). **Control:** placebo. **Duration:** 8 weeks.
Outcomes	Major amputation/death at 180 days, all-cause mortality, cardiovascular adverse events, ulcer healing, rest-pain relief, other adverse events. Follow up at 6 and 12 months
Notes	Source of funding: Mitshubishi Pharma Corporation.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	The study is described as double blind
Free of selective reporting?	Low risk	Primary and secondary endpoints reported
Follow up?	Low risk	The study terminated early by recommendation of DSMB, after interim analysis: 383 randomised patients. At 6 months, withdrawals < 10% of the study population
Intention to treat analysis?	Low risk	ITT analysis from 379 patients who received at least one dose of study medication
Comparable groups?	Low risk	Shown in table 1
Identical care programmes?	Unclear risk	Not mentioned

Brock 1990

Methods	**Study design:** multicentre, randomised, placebo-controlled trial.
Participants	**Country:** Germany. **Number of study centres:** 11. **Setting:** hospital. **Number:** 109; experimental group 56; control group 53. **Age years:** < 40 to 80. **Sex (M/F):** 61/48. **Inclusion criteria:** diabetic patients with Ischaemic lesions **Exclusion criteria:** unstable diabetes; acute venous thrombosis or venous ulcers; indication for amputation; osteomyelitis, recent sympathectomy; unstable angina pectoris or MI
Interventions	**Experimental:** intravenous iloprost 2ng/kg/min over 6 hours/day. **Control:** placebo. **Duration:** 28 days.
Outcomes	Complete healing of tissue lesions, pain relief, analgesics consumption, tolerability
Notes	Source of funding: not stated. Diabetic patients.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	High risk	"Randomization according to the order of informed consent hand-over"
Blinding? All outcomes	Unclear risk	Not mentioned
Free of selective reporting?	Low risk	All outcomes reported
Follow up?	High risk	Withdrawals > 10 % of study population
Intention to treat analysis?	Low risk	ITT analysis was performed
Comparable groups?	Low risk	Shown in Table 1 and Table 2
Identical care programmes?	Low risk	Care programmes were identical

Böhme 1989

Methods	**Study design:** two-centre, randomised controlled trial.
Participants	**Country:** Germany, Switzerland. **Setting:** hospital. **Number:** 42 randomised; 34 analysed. **Age (mean) (range) years:** 69 (33 to 85). **Sex (M/F):** experimental group 11/7 ; control group 13/3. **Inclusion criteria:** PAOD stage III or IV. **Exclusion criteria:** not stated.
Interventions	**Experimental:** intraarterial infusion of prostaglandin E1 (PGE1) over 60 min **Control:** Adenosin Triphosphat (ATP). **Duration:** 23 days.
Outcomes	Rest-pain relief, healing of necrosis, adverse effects (infusion pain or irritation). Follow up 12 months
Notes	Source of funding: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Unclear risk	Not mentioned
Free of selective reporting?	Low risk	All stated outcomes reported
Follow up?	High risk	Withdrawals > 10 % of study population
Intention to treat analysis?	High risk	It is described that 34 of 42 randomised patients were analysed
Comparable groups?	Low risk	Shown in Table 2
Identical care programmes?	Unclear risk	Not mentioned

Diehm 1987

Methods	**Study design:** single-centre, randomised, double-blind, placebo-controlled trial
Participants	**Country:** Germany. **Setting:** hospital. **Number:** 23; experimental group 14; control group 9.

Diehm 1987 (*Continued*)

	Age (mean) years: experimental group 65.5; control group 65.0. **Sex (M/F):** experimental group 11/3; control group 5/4. **Inclusion criteria:** presenting rest pain due to PAOD, steady-state condition within the last 3 weeks; aged < 70 years; informed consent **Exclusion criteria:** possibility of vascular reconstruction; congestive heart failure; Mi within the previous 6 months; thrombocytosis > 4000,000/µl; liver or kidney disease; uncontrolled diabetes mellitus
Interventions	**Experimental:** intravenous infusion prostaglandin E1 (PGE1) 60 µg in 250 ml saline over 4 hours **Control:** placebo. **Duration:** 3 weeks.
Outcomes	Rest-pain relief, analgesic consumption, side effects at end of treatment (21 days) and after 4 weeks
Notes	Source of funding: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	The study is described as double blinded
Free of selective reporting?	Low risk	All outcomes reported
Follow up?	Unclear risk	Adequate during treatment period, unknown during follow-up period
Intention to treat analysis?	Unclear risk	Not mentioned
Comparable groups?	Unclear risk	Not mentioned
Identical care programmes?	Unclear risk	Not mentioned

Diehm 1988

Methods	**Study design:** single-centre, randomised, double-blind, placebo-controlled trial
Participants	**Country:** Germany. **Setting:** hospital. **Number:** 50; 46 evaluated; experimental group 22; control group 24. **Age (average) years:** experimental group 65; control group 66. **Sex (M/F):** experimental group 18/4; control group 16/8. **Inclusion criteria:** PAOD stage III, clinically in a steady state for 14 days prior to treatment start;

Diehm 1988 (*Continued*)

	< 70 years **Exclusion criteria:** blood vessel surgery; pregnancy; heart failure; MI within previous 6 months; thrombocytosis > 4000,000/µl; liver or kidney disease; uncontrolled diabetes mellitus
Interventions	**Experimental:** 3 ampoules of intravenous prostavasin (60 µg PGE1) during 4 hours **Control:** placebo. **Duration:** 3 weeks.
Outcomes	Rest-pain relief, analgesic consumption, side effects.
Notes	Source of funding: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	The study is described as double blinded
Free of selective reporting?	Low risk	All outcomes reported
Follow up?	Low risk	Withdrawals < 10% of the study population (4/50)
Intention to treat analysis?	High risk	4 excluded patients were not included in final analysis
Comparable groups?	Unclear risk	Not described
Identical care programmes?	Unclear risk	Not described

Dormandy 1991

Methods	**Study design:** multicentre, randomised, double-blind, placebo-controlled trial
Participants	**Country:** UK. **Number of study centres:** 14. **Setting:** hospital. **Number:** 151; experimental group 80; control group 71. **Age (mean ± SD) (range) years:** experimental group 73 ± 9.9 (33 to 89); control group 73 ± 9.7 (37 to 89) **Sex (M/F):** experimental group 52/28; control group 36/35. **Inclusion criteria:** patients with PAOD stage III or IV, unsuitable for surgical or catheter procedures **Exclusion criteria:** patients with inflammatory arteriopathies; venous ulcers; frank peripheral neu-

Dormandy 1991 (*Continued*)

	ropathy; or other serious concomitant disease
Interventions	**Experimental:** intravenous infusion of iloprost up to 2 ng/kg/min over 6 hours **Control:** placebo. **Duration:** 28 days (ulcer patients); 14 days (rest pain patients).
Outcomes	Ulcer healing, rest-pain relief, major amputation, death, side effects at the end of treatment at 6 months
Notes	Source of funding: Schering Healthcare Ltd.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	The study is described as double blind
Free of selective reporting?	Low risk	All outcomes reported
Follow up?	Unclear risk	Adequate during treatment period, inadequate during follow-up period
Intention to treat analysis?	Low risk	At 6 months, amputations and death rates were analysed on an ITT basis for all the patients where the information was available
Comparable groups?	Unclear risk	Diabetics: 49% in placebo group, 31% in iloprost group.
Identical care programmes?	Unclear risk	Not mentioned

Dormandy 2000a - Study A

Methods	**Study design:** multicentre, randomised, dose-ranging, double-blind, placebo-controlled trial
Participants	**Country:** France, Germany, Italy, Norway, Poland, Sweden, UK. **Number of centres:** 35 in 7 countries. **Setting:** hospital. **Number:** 178; experimental group (1) 58; experimental group (2) 58; control group 62 **Age (mean) years (M/F):** experimental group (1) 71/78; experimental group (2) 67/73; control group 69/ 73 **Sex (M/F):** experimental group (1) 34/24; experimental group (2) 42/16; control group 37/25 **Inclusion criteria:** trophic skin lesions (ulcers or gangrene) or rest pain due to severe arterial disease

Dormandy 2000a - Study A (*Continued*)

	Exclusion criteria: acute onset or rapid deterioration of the ischaemia; revascularisation procedure in previous 2 weeks; rapidly spreading cellulitis; regular treatment with antiplatelet other than aspirin; planned major amputation in next 2 weeks
Interventions	**Experimental:** oral iloprost; (1) low dose (100 µg twice daily); (2) high dose (200 µg twice daily) **Control:** placebo. **Duration:** 4 weeks.
Outcomes	Tolerability of doses, safety, death, major amputation, healing of trophic lesions, relief of rest pain at 6 months
Notes	Source of funding: Schering AG.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	The study is described as double blind
Free of selective reporting?	Low risk	All outcomes reported
Follow up?	High risk	Withdrawals > 10% of the study population
Intention to treat analysis?	Low risk	ITT analysis performed to analyse efficacy results at end of follow up
Comparable groups?	Low risk	Shown in Table 1a
Identical care programmes?	Unclear risk	"All patients received standard treatment for co-existing disease, pain relief, antibiotics if indicated and topical therapy for trophic lesions"

Dormandy 2000b - Study B

Methods	**Study design:** multicentre, randomised, double-blind, placebo-controlled trial
Participants	**Country:** Finland, France, Germany, Hungary, Italy, Norway, Poland, Portugal, Sweden, UK **Number of centres:** 37 in 10 countries. **Setting:** hospital. **Number:** 624; experimental group (1) 210; experimental group (2) 207; control group 207 **Age (mean) years (M/F):** experimental group (1) 66/74; experimental group (2) 65/74; control group 65/ 75 **Sex (M/F):** not listed.

Dormandy 2000b - Study B (*Continued*)

	Inclusion criteria: trophic skin lesions (ulcers or gangrene) or rest pain due to severe arterial disease **Exclusion criteria:** acute onset or rapid deterioration of the ischaemia; revascularization procedure in previous 2 weeks; rapidly spreading cellulitis; regular treatment with antiplatelet other than aspirin; planned major amputation in next 2 weeks
Interventions	**Experimental:** oral iloprost low dose (50 µg twice daily), iloprost high dose (150 µg twice daily) **Control:** placebo. **Duration:** 1 year.
Outcomes	Death, major amputation, healing of trophic lesions, rest-pain relief at 1 year
Notes	Source of funding: Schering AG.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	The study is described as double blind
Free of selective reporting?	Low risk	All outcomes reported
Follow up?	High risk	Withdrawals > 10% of the study population
Intention to treat analysis?	Low risk	ITT analysis performed to analyse efficacy results at end of follow up
Comparable groups?	Low risk	Shown in Table 1b
Identical care programmes?	Unclear risk	"All patients received standard treatment for co-existing disease, pain relief, antibiotics if indicated and topical therapy for trophic lesions"

Guilmot 1991

Methods	**Study design:** multicentre, randomised, placebo-controlled trial.
Participants	**Country:** France. **Number of study centres:** 13. **Setting:** hospital. **Number:** 128; experimental group 87; control group 41. **Age years:** experimental group 68 ± 11; control group 68 ± 12. **Sex (M/F):** experimental group 55/32; control group 30/11. **Inclusion criteria:** hospitalised patients with PAOD at a critical ischaemic stage with and without

Guilmot 1991 (*Continued*)

	diabetes mellitus;hospitalised men or postmenopausal women aged 40 to 85 years. Stratification by diabetes mellitus **Exclusion criteria:** patients suitable for reconstructive vascular surgery or likely to require amputation in the near future; inflammatory arteriopathy; venous ulcers
Interventions	**Experimental:** intravenous infusion of iloprost over 6 hours. **Control:** placebo. **Duration:** 21 days.
Outcomes	Healing and surface area of ulcers, rest-pain relief, amputation, quality of life, tolerability at days 21, 28, 60 and 120, side effects
Notes	Source of funding: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	The study is described as double blind
Free of selective reporting?	Low risk	All primary and secondary outcomes reported
Follow up?	High risk	Withdrawals > 10 % of study population
Intention to treat analysis?	High risk	Not performed
Comparable groups?	Low risk	Shown in Table 1
Identical care programmes?	Unclear risk	Not mentioned

Hossmann 1983

Methods	**Study design:** single centre, randomised, placebo-controlled trial.
Participants	**Country:** Germany. **Setting:** hospital. **Number:** 10. **Age years:** 33 to 77 years. **Sex (M/F):** 9/1. **Inclusion criteria:** PAOD stage III and IV. **Exclusion criteria:** not stated.

Hossmann 1983 (*Continued*)

Interventions	**Experimental:** intravenous infusion of prostacyclin PGI2 5 ng/kg/min. **Control:** placebo. **Duration:** 7 days (cross-over design, with 7 days between treatments).
Outcomes	Blood pressure, pain perception on a VAS.
Notes	Soure of funding: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Unclear risk	The study is not described as blind
Free of selective reporting?	Low risk	All outcomes reported
Follow up?	Low risk	Complete follow up for the 10 included patients
Intention to treat analysis?	Low risk	Not mentioned, but follow up was complete
Comparable groups?	Low risk	Cross-over design
Identical care programmes?	Unclear risk	Not mentioned

Linet 1991

Methods	**Study design:** multicentre, randomised, double-blind, placebo-controlled trial
Participants	**Country:** Australia, Austria, Belgium, Canada, Italy, France, Germany (2 centres), Mexico, Switzerland, UK (3 centres), USA (9 centres) **Number of study centres:** 22. **Setting:** hospital. **Number:** 211. **Age years:** experimental group 67.5 ± 1.36; control group 67.7 ± 1.31. **Sex (M/F):** 114/97. **Inclusion criteria:** aged > 18 years with atherosclerotic PVD manifested by Ischaemic ulcers of the lower extremities (for 3 weeks or longer); not at a stage requiring amputation **Exclusion criteria:** patients with infection/gangrene or exposed tendons or bones; CVD or MI within the previous 2 months; coagulation disorders; uncontrolled diabetes; hypertension; cancer; ARI; unstable angina

Linet 1991 (*Continued*)

Interventions	**Experimental:** intravenous infusion by mechanical pump of Ciprostene up to 120 ng/kg/min **Control:** placebo. **Duration:** 8 hours daily for 7 days.
Outcomes	Healing of ulcers, rest-pain relief, mortality, ABI, quality of life, amputation, adverse events, safety. Follow up of 4 months
Notes	Source of funding: Upjohn Company.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Low risk	Code of drug assignment supplied by sponsor. Pharmacist followed code supplied by sponsor
Blinding? All outcomes	Low risk	The study is described as double - blind. in an emergency the pharmacist (not blinded) was able to break the code for the investigator
Free of selective reporting?	Low risk	All outcomes reported
Follow up?	High risk	Withdrawals > 10 % of study population
Intention to treat analysis?	Unclear risk	Not mentioned
Comparable groups?	Low risk	Shown in Table 1. Hypertension history: 52% in ciprostene group, versus 35% in placebo group
Identical care programmes?	Unclear risk	Not mentioned

Negus 1987

Methods	**Study design:** single-centre, randomised, double-blind, controlled trial.
Participants	**Country:** UK. **Setting:** hospital. **Number:** 29; experimental group 14; control group 15. **Age years:** experimental group 70.3 ± 11.9; control group 68.3 ± 10.1. **Sex (M/F):** 18/11. **Inclusion criteria:** patients with Ischaemic rest pain requiring analgesics and atherosclerotic lower limb arteries unsuitable for reconstructive surgery **Exclusion criteria:** not stated.

Negus 1987 (*Continued*)

Interventions	**Experimental:** prostacyclin (PGI2, epoprostenol) 8 nano g/kg/min with 21 SWG catheter inserted into common femoral artery, constant infusion pump **Control:** Naftidrofuryl 0.02 mg/kg/min. **Duration:** 72 hours.
Outcomes	Relief of rest pain and analgesic consumption after treatment, digital or forefoot amputation or major amputation up to 4 years
Notes	Welcome Research Laboratories Ltd and Lipha Pharmaceuticals Ltd helped in purchasing equipment Source of financial assistance: SE Thames Regional Health Authority

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	"The choice of drug was by means of random numbers."
Allocation concealment?	Low risk	"those responsible for patient selection, proforma completion and subsequent evaluation having no knowledge of which agent was delivered"
Blinding? All outcomes	Low risk	"those responsible for patient selection, proforma completion and subsequent evaluation having no knowledge of which agent was delivered"
Free of selective reporting?	Low risk	All outcomes reported
Follow up?	Unclear risk	Not described
Intention to treat analysis?	Unclear risk	Not mentioned
Comparable groups?	Low risk	Shown in Table 1
Identical care programmes?	Unclear risk	Not mentioned

Norgren 1990

Methods	**Study design:** multicentre, randomised, double-blind, placebo-controlled trial
Participants	**Country:** Finland (2 study centres); Poland (1 study centre); Sweden (6 study centres) **Number of study centres:** 9. **Setting:** hospital. **Number:** 103; experimental group 50; control group 53.

	Age (mean) (range): 70 (41 to 85). **Sex (M/F):** 57/46. **Inclusion criteria:** patients with one or more Ischaemic ulcer of a measurable size, unsuitable for reconstructive surgery or interventional radiology. Patients stratified for centre and for diabetes **Exclusion criteria:** > 85 years.
Interventions	**Experimental:** intravenous infusion of Iloprost up to 2 ng/kg/min over 6 hours daily **Control:** placebo. **Duration:** 14 days.
Outcomes	Amputatipn, adverse events.
Notes	Source of funding: not stated. Follow up at 24 weeks not considered (high risk of bias).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Unclear risk	Not mentioned
Free of selective reporting?	Unclear risk	All outcomes reported
Follow up?	High risk	"Twenty five patients in the treatment group and 35 patients in the control group did not reach the end of the follow-up period" (n = 50 and 53, respectively)
Intention to treat analysis?	High risk	"As a result, data on clinical efficacy was limited to 46 of 50 patients in the iloprost group and to 52 of 53 patients in the placebo group"
Comparable groups?	Unclear risk	Ankle pressure: 44 + 34 mmHg in iloprost group, 57 + 33 mmHg in placebo group (P < 0.05). No more data regarding comparability
Identical care programmes?	Unclear risk	"Basic therapeutic measures were allowed and existing treatment was not changed during the investigation period. Drugs influencing platelet function and those known to interfere with prostaglandins were not given, though routine laboratory investigations regarding haematology, hepatic and renal function were performed"

Schellong 2003

Methods	**Study design:** multicentre, randomised, single-blind, controlled, cross-over trial
Participants	**Country:** Germany. **Number of study centres:** 5. **Setting:** hospital. **Number:** 36 **Age (mean ± SD) years:** 70.3 ± 12.2. **Sex (M/F):** 22/14. **Inclusion criteria:** patients with PAOD stage III or IV. **Exclusion criteria:** known diabetes mellitus; history of sensitivity to PGE1 or iloprost; decompensated heart failure; MI within previous 6 months; suspected pulmonary oedema; pregnancy or lactation; severe CHD; unstable angina pectoris
Interventions	**Experimental (1):** intravenous infusion of PGE1. **Experimental (2):** intravenous infusion of iloprost. **Duration:** 3 hours; 1 day of wash out between treatments.
Outcomes	Tolerability.
Notes	Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated random plan at blocks of four per study site
Allocation concealment?	Low risk	"Patients randomly assigned to consecutive therapy with the two prostaglandins using a computer generated random plan at blocks of four per study site"
Blinding? All outcomes	High risk	Patients were blinded. Treatment providers were not blind
Free of selective reporting?	Low risk	All outcomes reported
Follow up?	Low risk	All the patients completed the study (3 days)
Intention to treat analysis?	Low risk	"All the randomized patients (36) were included in the ITT analysis
Comparable groups?	Low risk	Cross-over study
Identical care programmes?	Unclear risk	Not mentioned

Stiegler 1992

Methods	**Study design:** single centre, double-blind, placebo-controlled trial.
Participants	**Country:** Germany. **Setting:** hospital. **Number:** 117 recruited; 73 completed the study; experimental group 36; control group 37 **Age (mean) (range) years:** 69 (44 to 86). **Sex (M/F):** 37/36 (completed). **Inclusion criteria:** arterial occlusive disease ("type II diabetic patients with ulcers in the forefoot area (for at least 14 days) on the basis of an arterial occlusive disease") **Exclusion criteria:** exclusion crieria was not stated in the full text.
Interventions	**Experimental:** 2 ampoules of 40 µg PGE1 in NaCl 250 ml **Control:** placebo. **Duration:** 3 to 4 weeks.
Outcomes	Ulcer sum-score, rest pain, amputation rate, tolerability
Notes	Source of funding: not stated 32 patients had to be excluded afterwards because they didn't meet inclusion - exclusion criteria; a further 12 patients did not complete the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	The study is described as double blind
Free of selective reporting?	Low risk	All outcomes reported
Follow up?	High risk	Withdrawals > 10% of study population
Intention to treat analysis?	High risk	Not performed
Comparable groups?	Unclear risk	Not mentioned
Identical care programmes?	Unclear risk	Not mentioned

Telles 1984

Methods	**Study design:** two-centre, randomised, placebo-controlled, double-blind trial
Participants	**Country:** UK. **Setting:** hospital. **Number:** 30. **Age (mean) (range) years:** 68.5 (40 to 84). **Sex (M/F):** 20/10. **Inclusion criteria:** patients presenting rest pain alone, Ischaemic ulceration or both, with reconstructive surgery not feasible **Exclusion criteria:** not stated.
Interventions	**Experimental:** intravenous infusion of prostaglandin E1 (PGE1) up to 10 ng/kg/min in 0.9% saline **Control:** placebo. **Duration:** over 72 hours.
Outcomes	Rest-pain relief, analgesic consumption, ulcer healing, ABI, amputation, blood pressure, heart rate, side effects. Follow up at 24 hours, 2 and 4 weeks
Notes	Source of funding: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	The study was described as double blind
Free of selective reporting?	Low risk	All outcomes reported
Follow up?	Unclear risk	Not described
Intention to treat analysis?	Unclear risk	Not mentioned
Comparable groups?	Low risk	Shown in Table 1
Identical care programmes?	Unclear risk	Not mentioned

Trubestein 1987

Methods	**Study design:** multicentre, randomised controlled trial.
Participants	**Country:** Germany. **Number of study centres:** 4. **Setting:** hospital. **Number:** 57; experimental group 31; control group 26. **Age (mean) years:** experimental group 68; control group 63. **Sex (M/F):** not stated. **Inclusion criteria:** patients with PAOD III and IV for at least 1 year, aged between 50 and 70 years **Exclusion criteria: "**manifested heart insufficiency and vascular surgery in the last 6 months"
Interventions	**Experimental:** intraarterial infusion of prostaglandin E1 (PGE1) 20 µg. **Control:** ATP 30 mg over 60 min daily in 50 ml saline solution. **Duration:** 3 weeks.
Outcomes	Rest pain, use of analgesics, healing or improvement of ulcers, amputation, adverse events
Notes	Source of funding: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Unclear risk	Not mentioned
Free of selective reporting?	Unclear risk	All outcomes reported
Follow up?	Unclear risk	Not mentioned
Intention to treat analysis?	Unclear risk	Not mentioned
Comparable groups?	Unclear risk	Not mentioned
Identical care programmes?	Unclear risk	Not mentioned

ABI: ankle brachial index
ARI: acute respiratory infection
CHD: coronary heart disease
CLI: critical limb ischaemia
ESRD: end stage renal disease
ITT: intention to treat
µg: microgram
MI: myocardial infarction

ng: nanogram
PAOD: peripheral arterial occlusive disease
PVD: peripheral vascular disease
VAS: visual anlogue score

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

Study	Reason for exclusion
Alstaedt 1993	Quality Score: C (subjects not blind to assignment status, treatment providers not blind to status, withdrawals > 10% of the study population).
Arosio 1998	Quality Score: C (subjects not blind to assignment status, treatment providers not blind to assignment status, outcome assessors not blind to assignment status)
Bandiera 1995	Quality Score: C (no intention-to-treat analysis, treatment providers not blind to assignment status, withdrawals > 10% of the study population).
Bertele 1999	Quality Score: C (subjects not blind to assignment status, treatment providers not blind to assignment status, care programmes were not identical)
Breuer 1995	Quality Score: C (subjects not blind to assignment status, treatment providers not blind to assignment status, outcome assessors not blind to assignment status)
Böhme 1994	Quality Score: C (no intention-to-treat analysis, subjects not blind to assignment status, treatment providers not blind to assignment status, withdrawals > 10% of the study population).
Ceriello 1998	Quality Score: C (subjects not blind to assignment status, treatment providers not blind to assignment status, outcome assessors not blind to assignment status)
Cronenwett 1986	Quality Score: C (treatment and control group not comparable at entry, subjects not blind to assignment status, treatment providers not blind to assignment status)
Di Paolo 2005	Quality Score: C (subjects not blind to assignment status, treatment providers not blind to assignment status, outcome assessors not blind to assignment status)
Diehm 1989	Quality Score: C (assigned treatment not adequately concealed prior to allocation, no intention-to-treat analysis, care programmes not identical)
Fonseca 1991	Abstract. Full text not available. Author does not have it. Sponsor did not answer
Guan 2003	Quality Score: C (no intention-to-treat analysis, subjects not blind to assignment status, treatment providers not blind to assignment status)
Heidrich 1991	Quality Score: C (no intention-to-treat analysis, subjects not blind to assignment status, treatment providers not blind to assignment status). Design: open - uncontrolled follow up

(*Continued*)

Karnik 1986	Quality Score: C (no intention-to-treat analysis, treatment providers not blind, withdrawals > 10% of the study population). Design: cross over to alternative in 6 cases of primary treatment failure
Menzoian 1995	Abstract. Full text not available. Author does not have a copy. Sponsor did not answer
Mingardi 1993	Abstract. Full text not available. Author did not answer. Sponsor does not have it
Petronella 2004	Quality Score: C (subjects not blind to assignment status, treatment providers not blind to assignment status, outcome assessors not blind to assignment status)
Schwarz 1995	Abstract. Full text not available.
Trübestein 1989	Quality Score: C (subjects not blind to assignment status, treatment providers not blind to assignment status, outcome assessors not blind to assignment status)

DATA AND ANALYSES

Comparison 1. Prostanoids vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rest-pain relief	9	1116	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.10, 1.57]
2 Ulcer healing	8	1132	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.22, 1.96]
3 Amputations (not defined if majors or totals)	9	1790	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.76, 1.04]
4 Mortality	5	1391	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.65, 1.75]
5 Adverse events (patients)	8	716	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [1.99, 2.78]

Comparison 2. PGE1 vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rest-pain relief	2	69	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.69, 3.34]
2 Reduction in analgesics consumption	2	58	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.92, 2.72]
3 Ulcer healing	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Total Amputations	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Adverse events (patients)	2	69	Risk Ratio (M-H, Fixed, 95% CI)	5.81 [1.62, 20.86]

Comparison 3. Iloprost vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rest-pain relief	3	318	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.19, 1.99]
2 Ulcer healing	3	367	Risk Ratio (M-H, Random, 95% CI)	1.80 [1.29, 2.50]
3 Total Amputations	3	318	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.60, 1.03]
4 Major amputations	3	318	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.52, 0.93]
5 Adverse events (patients)	3	378	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [1.68, 2.49]

Comparison 4. Oral iloprost (high and low dose) versus placebo.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rest-pain relief (all doses)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Ulcer healing (all doses)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Major Amputations (all doses)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Mortality (all doses)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5 Rest-pain relief (high and low dose)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Low dose iloprost (50-100 micro gr bid)	2	224	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.73, 1.74]
5.2 High dose iloprost (150 - 200 micro gr bid)	2	223	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.99, 2.21]
6 Ulcer healing (high and low dose)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Low dose iloprost (50-100 micro gr bid)	2	312	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.00, 2.33]
6.2 High dose iloprost (150 - 200 micro gr bid)	2	311	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.91, 2.17]
7 Major Amputations (high and low dose)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Low dose iloprost (50-100 micro gr bid)	2	537	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.65, 1.12]
7.2 High dose iloprost (150 - 200 micro gr bid)	2	534	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.64, 1.11]
8 Mortality (high and low dose)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Low dose iloprost (50-100 micro gr bid)	2	537	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.54, 1.32]
8.2 High dose iloprost (150 - 200 micro gr bid)	2	534	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.39, 2.09]

Comparison 5. PGE1 vs ATP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total Amputations	2	91	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.09, 0.74]
2 Adverse event (patients)	2	91	Risk Ratio (M-H, Fixed, 95% CI)	2.78 [1.41, 5.48]

Comparison 6. Prostanoids vs placebo (highest quality studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rest-pain relief	5	559	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [1.15, 1.82]
2 Ulcer healing	5	843	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.15, 1.58]
3 Amputations	6	1546	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.09]
4 Mortality	4	1363	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.70, 1.85]
5 Adverse events (patients)	5	457	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [1.91, 2.96]

Analysis 1.1. Comparison 1 Prostanoids vs placebo, Outcome 1 Rest-pain relief.

Review: Prostanoids for critical limb ischaemia

Comparison: 1 Prostanoids vs placebo

Outcome: 1 Rest-pain relief

Study or subgroup	Prostanoids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Balzer 1991	21/55	19/58		12.9 %	1.17 [0.71, 1.92]
Belch 1983	7/15	1/13		0.7 %	6.07 [0.86, 43.04]
Brass 2006	40/181	44/181		30.7 %	0.91 [0.62, 1.32]
Diehm 1987	10/14	4/9		3.4 %	1.61 [0.72, 3.58]
Diehm 1988	1/22	1/24		0.7 %	1.09 [0.07, 16.41]
Dormandy 1991	56/80	31/71		22.9 %	1.60 [1.19, 2.17]
Dormandy 2000a - Study A	16/40	4/13		4.2 %	1.30 [0.53, 3.20]
Dormandy 2000b - Study B	60/191	23/95		21.4 %	1.30 [0.86, 1.96]
Guilmot 1991	19/38	3/16		2.9 %	2.67 [0.92, 7.76]
Total (95% CI)	**636**	**480**		**100.0 %**	**1.32 [1.10, 1.57]**

Total events: 230 (Prostanoids), 130 (Placebo)

Heterogeneity: Chi^2 = 9.89, df = 8 (P = 0.27); I^2 =19%

Test for overall effect: Z = 3.01 (P = 0.0026)

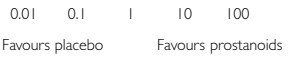
Analysis 1.2. Comparison 1 Prostanoids vs placebo, Outcome 2 Ulcer healing.

Review: Prostanoids for critical limb ischaemia

Comparison: 1 Prostanoids vs placebo

Outcome: 2 Ulcer healing

Study or subgroup	Prostanoids n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Brock 1990	31/50	12/51		12.5 %	2.64 [1.54, 4.52]
Dormandy 1991	33/80	18/71		14.6 %	1.63 [1.01, 2.62]
Dormandy 2000a - Study A	17/76	6/49		6.3 %	1.83 [0.77, 4.31]
Dormandy 2000b - Study B	61/225	22/112		16.3 %	1.38 [0.90, 2.12]
Guilmot 1991	47/78	15/37		16.3 %	1.49 [0.97, 2.28]
Linet 1991	95/106	74/105		31.0 %	1.27 [1.11, 1.46]
Stiegler 1992	6/36	2/37		2.3 %	3.08 [0.67, 14.28]
Telles 1984	0/9	3/10		0.7 %	0.16 [0.01, 2.68]
Total (95% CI)	**660**	**472**		**100.0 %**	**1.54 [1.22, 1.96]**
Total events: 290 (Prostanoids), 152 (Placebo)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 12.59, df = 7 (P = 0.08); I^2 =44%					
Test for overall effect: Z = 3.56 (P = 0.00037)					



Analysis 1.3. Comparison 1 Prostanoids vs placebo, Outcome 3 Amputations (not defined if majors or totals).

Review: Prostanoids for critical limb ischaemia

Comparison: 1 Prostanoids vs placebo

Outcome: 3 Amputations (not defined if majors or totals)

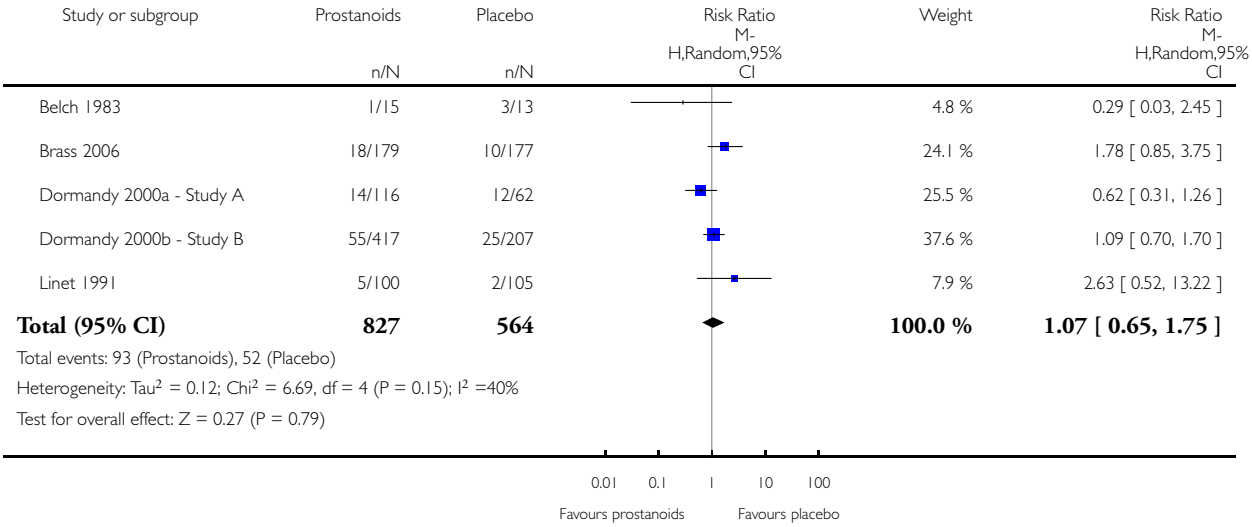
Study or subgroup	Prostanoids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Brass 2006	29/179	23/177		10.1 %	1.25 [0.75, 2.07]
Dormandy 1991	23/76	33/71		14.9 %	0.65 [0.43, 0.99]
Dormandy 2000a - Study A	29/116	20/62		11.3 %	0.78 [0.48, 1.25]
Dormandy 2000b - Study B	107/417	61/207		35.5 %	0.87 [0.67, 1.14]
Guilmot 1991	18/47	10/26		5.6 %	1.00 [0.54, 1.83]
Linet 1991	17/106	13/105		5.7 %	1.30 [0.66, 2.53]
Norgren 1990	20/46	26/52		10.6 %	0.87 [0.57, 1.33]
Stiegler 1992	4/36	10/37		4.3 %	0.41 [0.14, 1.19]
Telles 1984	7/14	5/16		2.0 %	1.60 [0.65, 3.92]
Total (95% CI)	**1037**	**753**		**100.0 %**	**0.89 [0.76, 1.04]**
Total events: 254 (Prostanoids), 201 (Placebo)					
Heterogeneity: Chi^2 = 9.17, df = 8 (P = 0.33); I^2 =13%					
Test for overall effect: Z = 1.43 (P = 0.15)					

Analysis 1.4. Comparison 1 Prostanoids vs placebo, Outcome 4 Mortality.

Review: Prostanoids for critical limb ischaemia

Comparison: 1 Prostanoids vs placebo

Outcome: 4 Mortality



Analysis 1.5. Comparison 1 Prostanoids vs placebo, Outcome 5 Adverse events (patients).

Review: Prostanoids for critical limb ischaemia

Comparison: 1 Prostanoids vs placebo

Outcome: 5 Adverse events (patients)

Study or subgroup	Prostanoids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Belch 1983	14/15	1/13		1.0 %	12.13 [1.84, 80.15]
Diehm 1987	6/14	0/9		0.5 %	8.67 [0.55, 137.33]
Diehm 1988	9/22	2/24		1.7 %	4.91 [1.19, 20.28]
Dormandy 1991	60/76	28/71		26.2 %	2.00 [1.47, 2.73]
Guilmot 1991	75/87	17/41		20.9 %	2.08 [1.43, 3.02]
Linet 1991	79/106	33/105		30.0 %	2.37 [1.75, 3.21]
Norgren 1990	43/50	22/53		19.3 %	2.07 [1.48, 2.91]
Telles 1984	3/14	0/16		0.4 %	7.93 [0.45, 141.43]
Total (95% CI)	**384**	**332**		**100.0 %**	**2.35 [1.99, 2.78]**

Total events: 289 (Prostanoids), 103 (Placebo)

Heterogeneity: $Chi^2 = 7.47$, df = 7 (P = 0.38); $I^2 = 6\%$

Test for overall effect: Z = 10.12 (P < 0.00001)

Test for subgroup differences: Not applicable

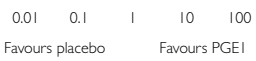
Analysis 2.1. Comparison 2 PGE1 vs placebo, Outcome 1 Rest-pain relief.

Review: Prostanoids for critical limb ischaemia

Comparison: 2 PGE1 vs placebo

Outcome: 1 Rest-pain relief

Study or subgroup	PGE1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Diehm 1987	10/14	4/9		83.6 %	1.61 [0.72, 3.58]
Diehm 1988	1/22	1/24		16.4 %	1.09 [0.07, 16.41]
Total (95% CI)	**36**	**33**		**100.0 %**	**1.52 [0.69, 3.34]**
Total events: 11 (PGE1), 5 (Placebo)					
Heterogeneity: Chi^2 = 0.08, df = 1 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 1.05 (P = 0.29)					



Analysis 2.2. Comparison 2 PGE1 vs placebo, Outcome 2 Reduction in analgesics consumption.

Review: Prostanoids for critical limb ischaemia

Comparison: 2 PGE1 vs placebo

Outcome: 2 Reduction in analgesics consumption

Study or subgroup	PGE1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Diehm 1987	9/14	4/9		42.8 %	1.45 [0.63, 3.31]
Diehm 1988	12/19	6/16		57.2 %	1.68 [0.82, 3.46]
Total (95% CI)	**33**	**25**		**100.0 %**	**1.58 [0.92, 2.72]**
Total events: 21 (PGE1), 10 (Placebo)					
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 1.66 (P = 0.098)					

Analysis 2.3. Comparison 2 PGE1 vs placebo, Outcome 3 Ulcer healing.

Review: Prostanoids for critical limb ischaemia

Comparison: 2 PGE1 vs placebo

Outcome: 3 Ulcer healing

Study or subgroup	PGE1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Stiegler 1992	6/36	2/37			3.08 [0.67, 14.28]
Telles 1984	0/9	3/10			0.16 [0.01, 2.68]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 6 (PGE1), 5 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P<0.00001); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.0 (P < 0.00001)					

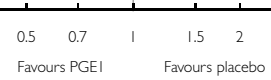
Analysis 2.4. Comparison 2 PGE1 vs placebo, Outcome 4 Total Amputations.

Review: Prostanoids for critical limb ischaemia

Comparison: 2 PGE1 vs placebo

Outcome: 4 Total Amputations

Study or subgroup	PGE1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Stiegler 1992	4/36	10/37			0.41 [0.14, 1.19]
Telles 1984	7/14	5/16			1.60 [0.65, 3.92]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 11 (PGE1), 15 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P<0.00001); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.0 (P < 0.00001)					

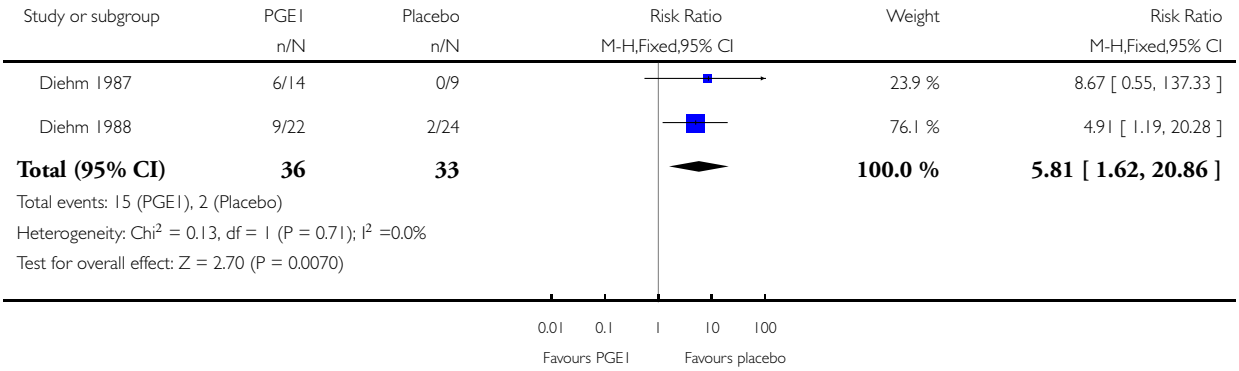


Analysis 2.5. Comparison 2 PGE1 vs placebo, Outcome 5 Adverse events (patients).

Review: Prostanoids for critical limb ischaemia

Comparison: 2 PGE1 vs placebo

Outcome: 5 Adverse events (patients)

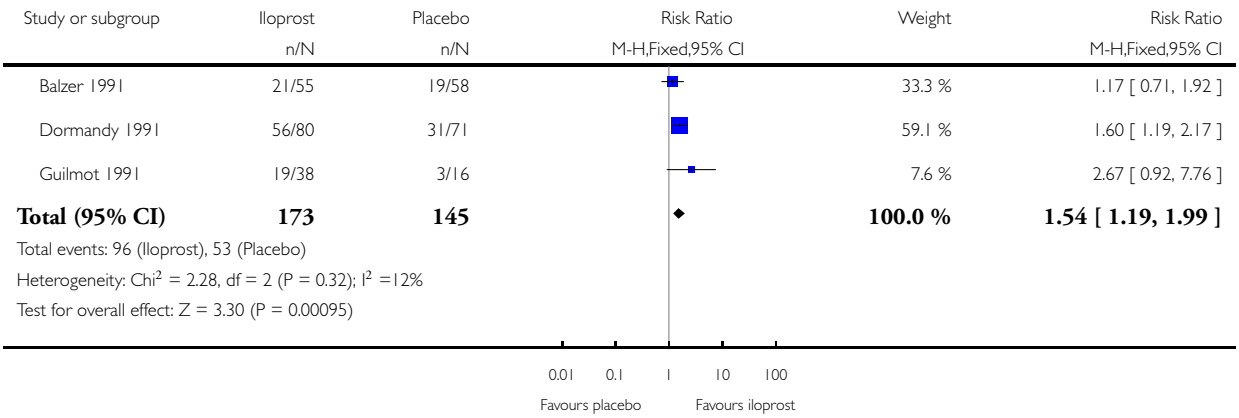


Analysis 3.1. Comparison 3 Iloprost vs placebo, Outcome 1 Rest-pain relief.

Review: Prostanoids for critical limb ischaemia

Comparison: 3 Iloprost vs placebo

Outcome: 1 Rest-pain relief

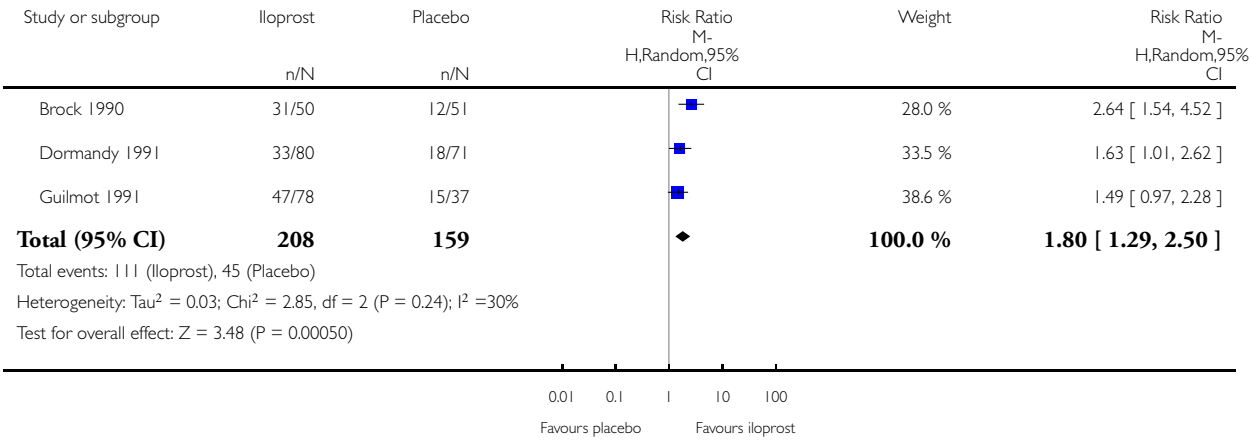


Analysis 3.2. Comparison 3 Iloprost vs placebo, Outcome 2 Ulcer healing.

Review: Prostanoids for critical limb ischaemia

Comparison: 3 Iloprost vs placebo

Outcome: 2 Ulcer healing

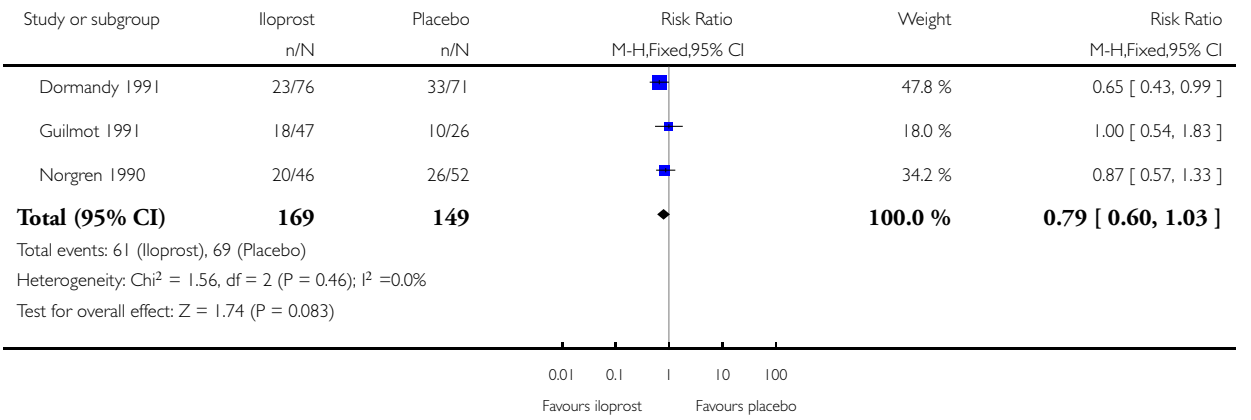


Analysis 3.3. Comparison 3 Iloprost vs placebo, Outcome 3 Total Amputations.

Review: Prostanoids for critical limb ischaemia

Comparison: 3 Iloprost vs placebo

Outcome: 3 Total Amputations

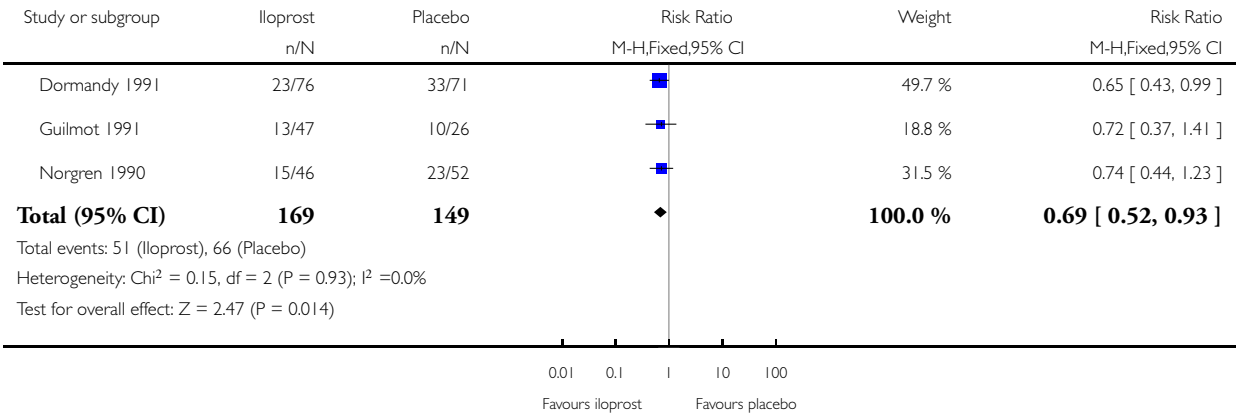


Analysis 3.4. Comparison 3 Iloprost vs placebo, Outcome 4 Major amputations.

Review: Prostanoids for critical limb ischaemia

Comparison: 3 Iloprost vs placebo

Outcome: 4 Major amputations



Analysis 3.5. Comparison 3 Iloprost vs placebo, Outcome 5 Adverse events (patients).

Review: Prostanoids for critical limb ischaemia

Comparison: 3 Iloprost vs placebo

Outcome: 5 Adverse events (patients)

Study or subgroup	Iloprost n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dormandy 1991	60/76	28/71		39.4 %	2.00 [1.47, 2.73]
Guilmot 1991	75/87	17/41		31.5 %	2.08 [1.43, 3.02]
Norgren 1990	43/50	22/53		29.1 %	2.07 [1.48, 2.91]
Total (95% CI)	**213**	**165**		**100.0 %**	**2.05 [1.68, 2.49]**
Total events: 178 (Iloprost), 67 (Placebo)					
Heterogeneity: Chi^2 = 0.03, df = 2 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 7.15 (P < 0.00001)					

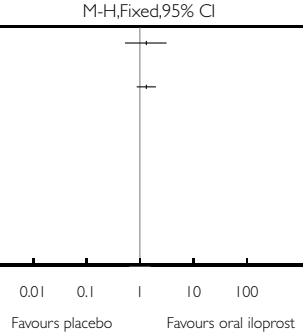
Analysis 4.1. Comparison 4 Oral iloprost (high and low dose) versus placebo., Outcome 1 Rest-pain relief (all doses).

Review: Prostanoids for critical limb ischaemia

Comparison: 4 Oral iloprost (high and low dose) versus placebo.

Outcome: 1 Rest-pain relief (all doses)

Study or subgroup	Oral Iloprost n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dormandy 2000a - Study A	16/40	4/13			1.30 [0.53, 3.20]
Dormandy 2000b - Study B	60/191	23/95			1.30 [0.86, 1.96]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 76 (Oral Iloprost), 27 (Placebo)					
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P < 0.00001)					



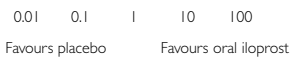
Analysis 4.2. Comparison 4 Oral iloprost (high and low dose) versus placebo., Outcome 2 Ulcer healing (all doses).

Review: Prostanoids for critical limb ischaemia

Comparison: 4 Oral iloprost (high and low dose) versus placebo.

Outcome: 2 Ulcer healing (all doses)

Study or subgroup	Oral Iloprost n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dormandy 2000a - Study A	17/76	6/49			1.83 [0.77, 4.31]
Dormandy 2000b - Study B	61/225	22/112			1.38 [0.90, 2.12]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 78 (Oral Iloprost), 28 (Placebo)					
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P < 0.00001)					



Analysis 4.3. Comparison 4 Oral iloprost (high and low dose) versus placebo., Outcome 3 Major Amputations (all doses).

Review: Prostanoids for critical limb ischaemia

Comparison: 4 Oral iloprost (high and low dose) versus placebo.

Outcome: 3 Major Amputations (all doses)

Study or subgroup	Oral Iloprost n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dormandy 2000a - Study A	29/116	20/62			0.78 [0.48, 1.25]
Dormandy 2000b - Study B	107/417	61/207			0.87 [0.67, 1.14]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 136 (Oral Iloprost), 81 (Placebo)					
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P < 0.00001)					

Analysis 4.4. Comparison 4 Oral iloprost (high and low dose) versus placebo., Outcome 4 Mortality (all doses).

Review: Prostanoids for critical limb ischaemia

Comparison: 4 Oral iloprost (high and low dose) versus placebo.

Outcome: 4 Mortality (all doses)

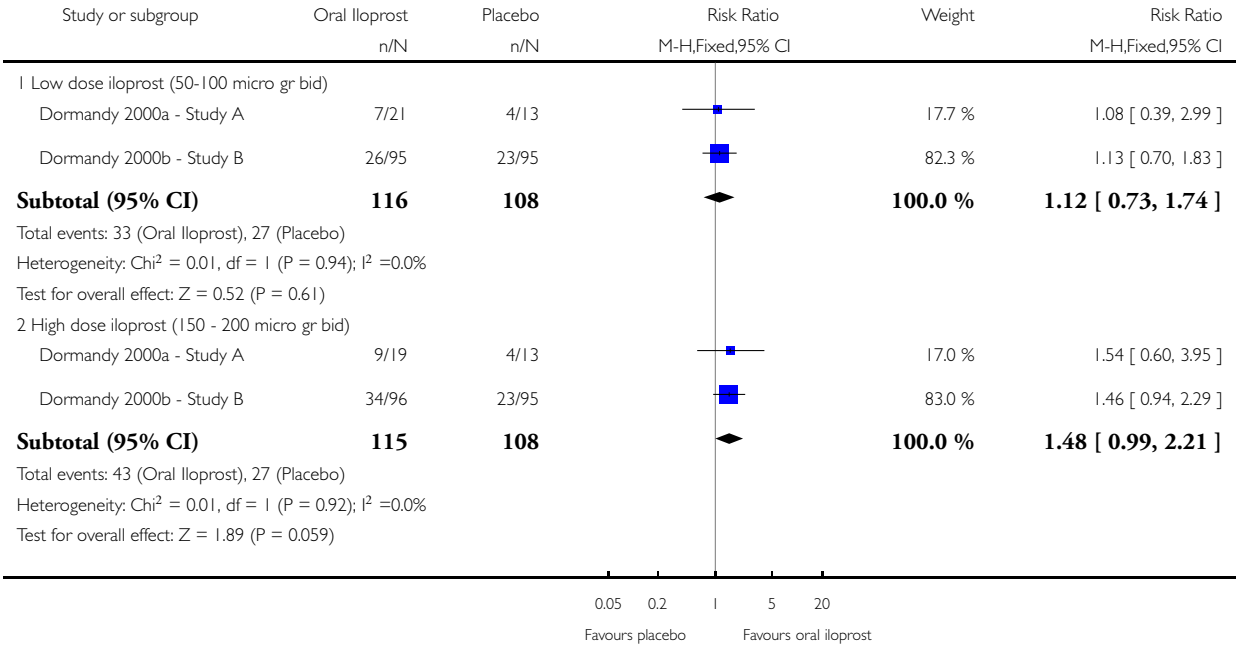
Study or subgroup	Oral Iloprost n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dormandy 2000a - Study A	14/116	12/62			0.62 [0.31, 1.26]
Dormandy 2000b - Study B	55/417	25/207			1.09 [0.70, 1.70]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 69 (Oral Iloprost), 37 (Placebo)					
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P < 0.00001)					

Analysis 4.5. Comparison 4 Oral iloprost (high and low dose) versus placebo., Outcome 5 Rest-pain relief (high and low dose).

Review: Prostanoids for critical limb ischaemia

Comparison: 4 Oral iloprost (high and low dose) versus placebo.

Outcome: 5 Rest-pain relief (high and low dose)

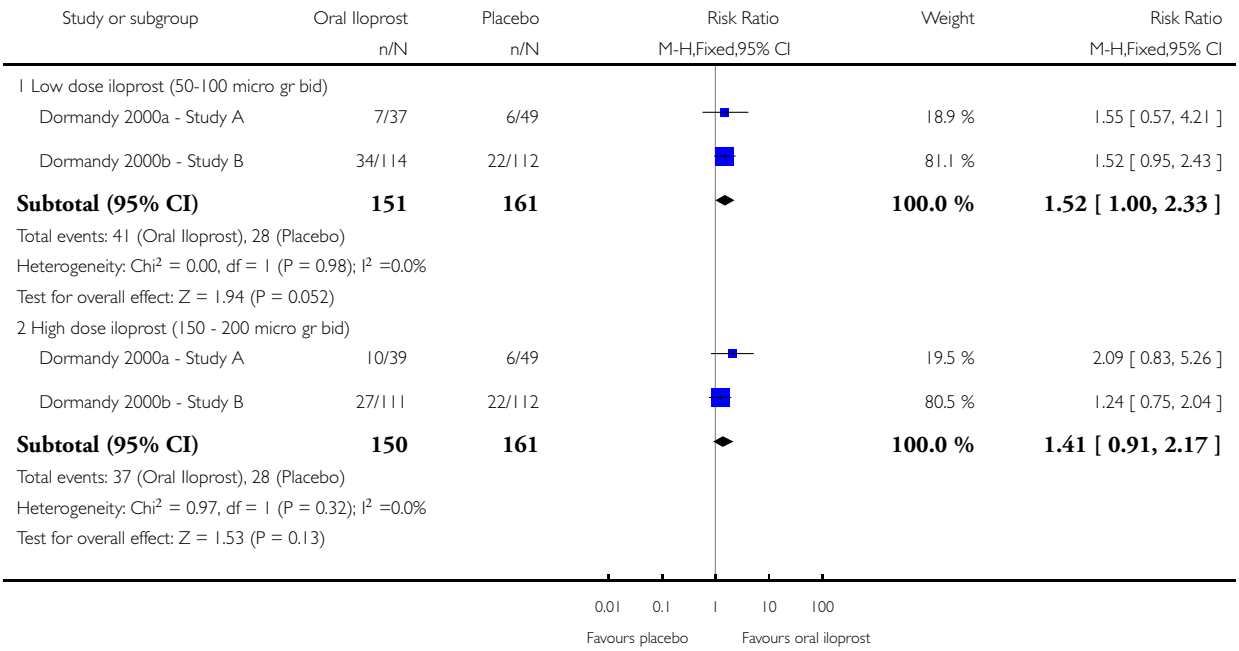


Analysis 4.6. Comparison 4 Oral iloprost (high and low dose) versus placebo., Outcome 6 Ulcer healing (high and low dose).

Review: Prostanoids for critical limb ischaemia

Comparison: 4 Oral iloprost (high and low dose) versus placebo.

Outcome: 6 Ulcer healing (high and low dose)

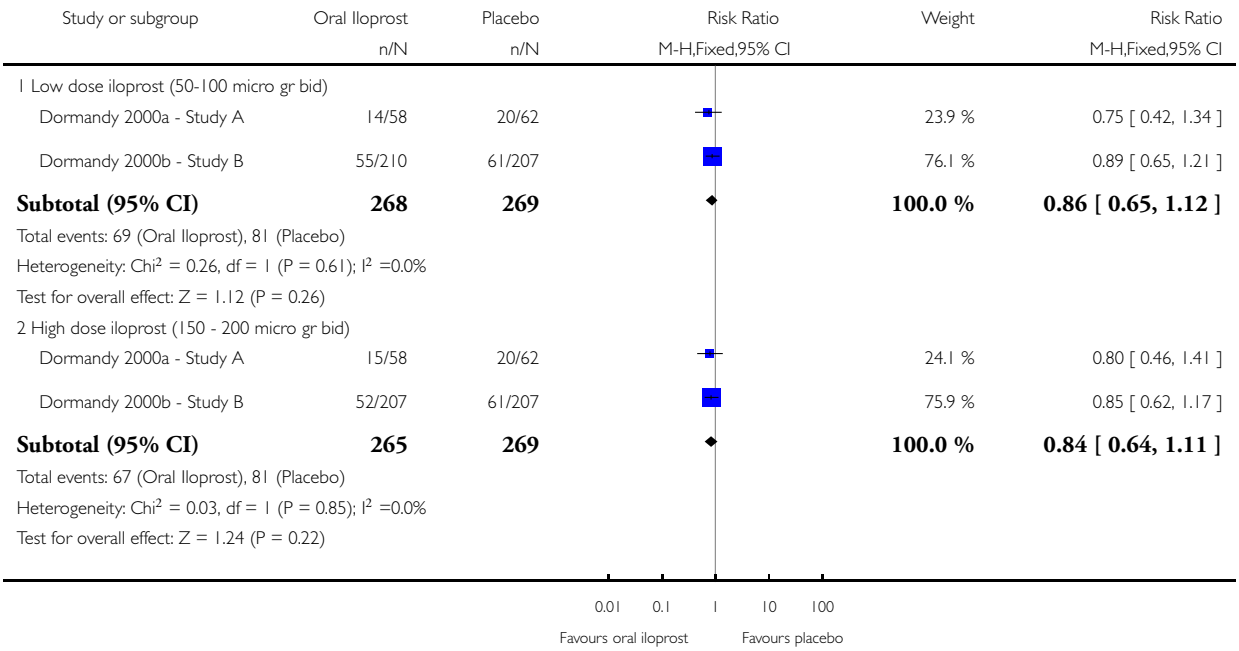


Analysis 4.7. Comparison 4 Oral iloprost (high and low dose) versus placebo., Outcome 7 Major Amputations (high and low dose).

Review: Prostanoids for critical limb ischaemia

Comparison: 4 Oral iloprost (high and low dose) versus placebo.

Outcome: 7 Major Amputations (high and low dose)



Analysis 4.8. Comparison 4 Oral iloprost (high and low dose) versus placebo., Outcome 8 Mortality (high and low dose).

Review: Prostanoids for critical limb ischaemia

Comparison: 4 Oral iloprost (high and low dose) versus placebo.

Outcome: 8 Mortality (high and low dose)

Study or subgroup	Oral Iloprost n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low dose iloprost (50-100 micro gr bid)					
Dormandy 2000a - Study A	8/58	12/62		29.7 %	0.71 [0.31, 1.62]
Dormandy 2000b - Study B	23/210	25/207		70.3 %	0.91 [0.53, 1.54]
Subtotal (95% CI)	**268**	**269**		**100.0 %**	**0.84 [0.54, 1.32]**
Total events: 31 (Oral Iloprost), 37 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.23$, df = 1 (P = 0.63); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.74 (P = 0.46)					
2 High dose iloprost (150 - 200 micro gr bid)					
Dormandy 2000a - Study A	6/58	12/62		39.8 %	0.53 [0.21, 1.33]
Dormandy 2000b - Study B	32/207	25/207		60.2 %	1.28 [0.79, 2.08]
Subtotal (95% CI)	**265**	**269**		**100.0 %**	**0.90 [0.39, 2.09]**
Total events: 38 (Oral Iloprost), 37 (Placebo)					
Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 2.74$, df = 1 (P = 0.10); $I^2 = 64\%$					
Test for overall effect: Z = 0.24 (P = 0.81)					

Analysis 5.1. Comparison 5 PGE1 vs ATP, Outcome 1 Total Amputations.

Review: Prostanoids for critical limb ischaemia

Comparison: 5 PGE1 vs ATP

Outcome: 1 Total Amputations

Study or subgroup	PGE1 n/N	ATP n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Böhme 1989	1/18	4/16		30.2 %	0.22 [0.03, 1.79]
Trubestein 1987	3/31	9/26		69.8 %	0.28 [0.08, 0.93]
Total (95% CI)	**49**	**42**		**100.0 %**	**0.26 [0.09, 0.74]**
Total events: 4 (PGE1), 13 (ATP)					
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² =0.0%					
Test for overall effect: Z = 2.52 (P = 0.012)					

Analysis 5.2. Comparison 5 PGE1 vs ATP, Outcome 2 Adverse event (patients).

Review: Prostanoids for critical limb ischaemia

Comparison: 5 PGE1 vs ATP

Outcome: 2 Adverse event (patients)

Study or subgroup	PGE1 n/N	ATP n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Böhme 1989	11/18	2/16		24.5 %	4.89 [1.27, 18.82]
Trubestein 1987	15/31	6/26		75.5 %	2.10 [0.95, 4.62]
Total (95% CI)	**49**	**42**		**100.0 %**	**2.78 [1.41, 5.48]**
Total events: 26 (PGE1), 8 (ATP)					
Heterogeneity: Chi² = 1.16, df = 1 (P = 0.28); I² =14%					
Test for overall effect: Z = 2.95 (P = 0.0031)					

Analysis 6.1. Comparison 6 Prostanoids vs placebo (highest quality studies), Outcome 1 Rest-pain relief.

Review: Prostanoids for critical limb ischaemia

Comparison: 6 Prostanoids vs placebo (highest quality studies)

Outcome: 1 Rest-pain relief

Study or subgroup	Prostanoids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Diehm 1987	10/14	4/9		6.5 %	1.61 [0.72, 3.58]
Diehm 1988	1/22	1/24		1.3 %	1.09 [0.07, 16.41]
Dormandy 1991	56/80	31/71		43.5 %	1.60 [1.19, 2.17]
Dormandy 2000a - Study A	16/40	4/13		8.0 %	1.30 [0.53, 3.20]
Dormandy 2000b - Study B	60/191	23/95		40.7 %	1.30 [0.86, 1.96]
Total (95% CI)	**347**	**212**		**100.0 %**	**1.45 [1.15, 1.82]**
Total events: 143 (Prostanoids), 63 (Placebo)					
Heterogeneity: Chi^2 = 0.87, df = 4 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 3.16 (P = 0.0016)					

Analysis 6.2. Comparison 6 Prostanoids vs placebo (highest quality studies), Outcome 2 Ulcer healing.

Review: Prostanoids for critical limb ischaemia

Comparison: 6 Prostanoids vs placebo (highest quality studies)

Outcome: 2 Ulcer healing

Study or subgroup	Prostanoids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dormandy 1991	33/80	18/71		14.3 %	1.63 [1.01, 2.62]
Dormandy 2000a - Study A	17/76	6/49		5.5 %	1.83 [0.77, 4.31]
Dormandy 2000b - Study B	61/225	22/112		22.0 %	1.38 [0.90, 2.12]
Linet 1991	95/106	74/105		55.7 %	1.27 [1.11, 1.46]
Telles 1984	0/9	3/10		2.5 %	0.16 [0.01, 2.68]
Total (95% CI)	**496**	**347**		**100.0 %**	**1.35 [1.15, 1.58]**
Total events: 206 (Prostanoids), 123 (Placebo)					
Heterogeneity: Chi^2 = 3.97, df = 4 (P = 0.41); I^2 =0.0%					
Test for overall effect: Z = 3.78 (P = 0.00016)					

Analysis 6.3. Comparison 6 Prostanoids vs placebo (highest quality studies), Outcome 3 Amputations.

Review: Prostanoids for critical limb ischaemia

Comparison: 6 Prostanoids vs placebo (highest quality studies)

Outcome: 3 Amputations

Study or subgroup	Prostanoids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Brass 2006	29/179	23/177		12.7 %	1.25 [0.75, 2.07]
Dormandy 1991	23/76	33/71		18.7 %	0.65 [0.43, 0.99]
Dormandy 2000a - Study A	29/116	20/62		14.3 %	0.78 [0.48, 1.25]
Dormandy 2000b - Study B	107/417	61/207		44.7 %	0.87 [0.67, 1.14]
Linet 1991	17/106	13/105		7.2 %	1.30 [0.66, 2.53]
Telles 1984	7/14	5/16		2.6 %	1.60 [0.65, 3.92]
Total (95% CI)	**908**	**638**		**100.0 %**	**0.91 [0.76, 1.09]**
Total events: 212 (Prostanoids), 155 (Placebo)					
Heterogeneity: Chi^2 = 7.03, df = 5 (P = 0.22); I^2 =29%					
Test for overall effect: Z = 1.01 (P = 0.31)					

Analysis 6.4. Comparison 6 Prostanoids vs placebo (highest quality studies), Outcome 4 Mortality.

Review: Prostanoids for critical limb ischaemia

Comparison: 6 Prostanoids vs placebo (highest quality studies)

Outcome: 4 Mortality

Study or subgroup	Prostanoids n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Brass 2006	18/179	10/177		25.1 %	1.78 [0.85, 3.75]
Dormandy 2000a - Study A	14/116	12/62		26.6 %	0.62 [0.31, 1.26]
Dormandy 2000b - Study B	55/417	25/207		40.4 %	1.09 [0.70, 1.70]
Linet 1991	5/100	2/105		7.9 %	2.63 [0.52, 13.22]
Total (95% CI)	**812**	**551**		**100.0 %**	**1.14 [0.70, 1.85]**
Total events: 92 (Prostanoids), 49 (Placebo)					
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 5.22$, df = 3 (P = 0.16); $I^2 = 43\%$					
Test for overall effect: Z = 0.53 (P = 0.60)					

Analysis 6.5. Comparison 6 Prostanoids vs placebo (highest quality studies), Outcome 5 Adverse events (patients).

Review: Prostanoids for critical limb ischaemia

Comparison: 6 Prostanoids vs placebo (highest quality studies)

Outcome: 5 Adverse events (patients)

Study or subgroup	Prostanoids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Diehm 1987	6/14	0/9		0.9 %	8.67 [0.55, 137.33]
Diehm 1988	9/22	2/24		2.9 %	4.91 [1.19, 20.28]
Dormandy 1991	60/76	28/71		44.5 %	2.00 [1.47, 2.73]
Linet 1991	79/106	33/105		50.9 %	2.37 [1.75, 3.21]
Telles 1984	3/14	0/16		0.7 %	7.93 [0.45, 141.43]
Total (95% CI)	**232**	**225**		**100.0 %**	**2.38 [1.91, 2.96]**

Total events: 157 (Prostanoids), 63 (Placebo)

Heterogeneity: Chi^2 = 3.70, df = 4 (P = 0.45); I^2 =0.0%

Test for overall effect: Z = 7.81 (P < 0.00001)

Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. CENTRAL

#1 MeSH descriptor Arterial Occlusive Diseases explode all trees
#2 MeSH descriptor Ischemia, this term only
#3 (peripheral near (arter* or vasc*)) or atherosclerosis or arteriosclerosis or PVD or PAOD or PAD
#4 critical near limb
#5 (isch* or CLI)
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Prostaglandins explode all trees
#8 (prostagland* or prostanoid* or prostacyclin)
#9 (PGE* or PGI*)
#10 (AS-013) or iloprost or ventavis or liprostin or alprostadil or taprostene or beraprost* or TTC-909 or clinprost or misoprostol or cicaprost or cisaprost or Epoprostenol or ciprostene or prostavasin or lipoecraprost or lipo-ecraprost
#11 (#7 OR #8 OR #9 OR #10)
#12 (#6 AND #11)

Appendix 2. MEDLINE (Ovid) search strategy

1. exp Peripheral Vascular Diseases/
2. (vascular adj4 disease).ti,ab.
3. ((leg or limb) adj4 isc?emia).ti,ab.
4. Ischemia/dt [Drug Therapy]
5. or/1-4
6. exp Prostaglandins/tu [Therapeutic Use]
7. Alprostadil/tu [Therapeutic Use]
8. PGE.ti,ab.
9. PGI.ti,ab.
10. Epoprostenol/tu [Therapeutic Use]
11. Iloprost/tu [Therapeutic Use]
12. alprostadil.ti,ab.
13. epoprostenol.ti,ab.
14. iloprost.ti,ab.
15. beraprost.ti,ab.
16. cisaprost.ti,ab.
17. or/6-16
18. 5 and 17

Appendix 3. EMBASE search strategy

1. Peripheral Vascular Disease/dt [Drug Therapy]
2. (vascular adj4 disease).ti,ab.
3. ((leg or limb) adj4 isc?emia).ti,ab.
4. ISCHEMIA/dt [Drug Therapy]
5. or/1-4
6. Prostaglandin/
7. Prostaglandin E1/
8. alprostadil.ti,ab.
9. (PGE or PGI).ti,ab.
10. Prostacyclin/
11. epoprostenol.ti,ab.
12. ILOPROST/
13. iloprost.ti,ab.
14. BERAPROST/
15. beraprost.ti,ab.
16. cisaprost/
17. cisaprost.ti,ab.
18. or/6-17
19. 5 and 18

WHAT'S NEW

Last assessed as up-to-date: 28 October 2009.

Date	Event	Description
16 February 2010	Amended	CENTRAL search strategy amended.

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 1, 2010

Date	Event	Description
29 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

AJ Ruffolo: conceived and designed the protocol and wrote the text of the protocol. He is the guarantor for the review, and he selected studies, assessed methodological quality of selected studies, extracted data and wrote the text of the review.

M Romano: collaborated in the design of the protocol. She selected studies, assessed methodological quality of selected studies, and extracted data.

A Ciapponi: gave general supervision of the protocol. He resolved any disagreements regarding selection of studies, assessment of study quality and data extraction.

DECLARATIONS OF INTEREST

Dr Antonio Ruffolo is employed by Boehringer Ingelheim, Germany. Boehringer Ingelheim is currently not working in the field of this review and does not have any product related to this review either in clinical development or marketed. Dr Ruffolo is not receiving any kind of support from Boehringer Ingelheim to complete the review. His interest is purely personal and stems from work undertaken in the Peripheral Vascular Surgery Division at Hospital Militar Central (Buenos Aires, Argentina) before he entered the pharmaceutical industry in 2006.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Although approved protocol defined moderate risk of bias when at least one criterion is partly met and no criteria are inadequate, the editors of the PVD Group proposed a substantial change in this definition, allowing under this category studies with up to two inadequate criteria. The aim of this change was to include more randomised trials and to enable sensitivity analyses according to risk of bias.

Software used in the protocol was Revman 4.2, which was updated to Revman 5.0 for the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Alprostadil [therapeutic use]; Amputation; Epoprostenol [therapeutic use]; Iloprost [therapeutic use]; Ischemia [*drug therapy]; Leg [*blood supply; surgery]; Leg Ulcer [drug therapy]; Peripheral Vascular Diseases [*drug therapy]; Prostaglandins [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic; Vasodilator Agents [therapeutic use]

MeSH check words

Humans