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[Intervention Review]

Prostacyclin for pulmonary hypertension in adults

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ABSTRACT

Background

Primary pulmonary hypertension (PPH) is progressive, resulting in right ventricular failure. Pulmonary hypertension can be idiopathic or associated with other conditions. Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation, and can be given orally, subcutaneously, intravenously or inhaled via a nebuliser.

Objectives

To determine the efficacy of prostacyclin or one of its analogues in idiopathic primary pulmonary hypertension.

Search methods

Electronic searches were carried out in CENTRAL, MEDLINE and EMBASE with pre-specified terms. Searches were current as of July 2006.

Selection criteria

Two reviewers selected randomised controlled trials (RCTs) involving adults with pulmonary hypertension for inclusion.

Data collection and analysis

Study quality was assessed and data extracted independently by two reviewers. Outcomes were analysed as continuous and dichotomous outcomes. We sub-grouped data where possible by aetiology of PH (PPH, PH secondary to connective tissue disorder or mixed populations).

Main results

Nine RCTs of mixed duration (3 days-52 weeks), recruiting 1175 participants were included (NYHA functional classes II-IV). **Intravenous prostacyclin versus usual care (four studies)** : There were significant improvements in exercise capacity of around 90 metres, cardiopulmonary haemodynamics and NYHA functional class over 3 days-12 weeks. Effects were consistent in primary and secondary pulmonary hypertension. **Oral prostacyclin versus placebo (two studies)** : Short-term data (3-6 months) indicated that there was a significant improvement in exercise capacity, but data from one study of 52 weeks reported no significant difference at 12 months. No significant differences were observed for any other outcome. **Subcutaneous treprostinil versus placebo (two studies, 8-12 weeks)**: One large study reported a significant median improvement in exercise capacity of around 16 metres. Cardiopulmonary haemodynamics and symptom scores favoured treprostinil. Infusion site pain and withdrawals due to adverse events were more frequent with treprostinil. **Inhaled prostacyclin versus placebo (one study, 12 weeks)**: There was a significant increase in exercise capacity of approximately 36 metres. Treatment led to better symptom scores and functional class status than with placebo. Subgroup analyses reported by individual studies showed a better exercise capacity in participants with PPH, than those participants with PH secondary to other diseases. Side effects and adverse events were common in the studies.

Authors' conclusions

There is evidence that intravenous prostacyclin in addition to conventional therapy at tolerable doses optimised by titration, can confer some short-term benefits (up to 12 weeks of treatment) in exercise capacity, NYHA functional class and cardiopulmonary haemodynamics. There is also some evidence that patients with more severe disease based upon NYHA functional class showed a greater response to treatment.

PLAIN LANGUAGE SUMMARY**Prostacyclin for pulmonary hypertension in adults**

Prostacyclin may benefit patients with pulmonary hypertension (raised blood pressure in the lungs) in the short term but studies longer in duration are required. Pulmonary hypertension occurs when blood is pumped through arteries in the lungs at an increased pressure. The condition can lead to heart failure and death. Once the diagnosis is made, life expectancy ranges from a few months to a few years. Most current treatments apart from lung transplantation do not improve survival. Over an 8-12 week period prostacyclin improved exercise capacity and some measures of blood flow when given intravenously or via injection to patients with pulmonary hypertension. However, with intravenous administration there can be serious side effects as the drug has to be given continuously via a pump into a catheter placed into a central vein. It is not clear how long the drug continues to confer benefit without serious side effects. Prostacyclin can also be given by mouth, under the skin or through an inhaler. These forms of administration may be safer than intravenous prostacyclin and there is evidence that these may be effective in the short term.

BACKGROUND

Pulmonary hypertension is a progressive and often fatal disease. Primary pulmonary hypertension (PPH) can be idiopathic or can be associated with collagen vascular diseases. It is common in scleroderma, especially in limited scleroderma (CREST) and in overlap syndromes. The pulmonary hypertension in connective tissue disorders can occur either directly or secondary to pulmonary fibrosis and right heart failure (Brundage 1990). Pulmonary vascular disease in the connective tissue diseases can also include pulmonary vasculitis, thromboembolism or pulmonary artery aneurysm (Wells 2000).

Pulmonary hypertension also occurs in autoimmune disorders such as systemic lupus erythematosus (SLE), polymyositis and dermatomyositis, and rarely in rheumatoid arthritis and Sjogrens syndrome. It can occur secondary to interstitial lung diseases, chronic obstructive lung disease, left ventricular failure, congenital heart disease and thromboembolic disease.

Pulmonary hypertension is characterised by progressive elevation of pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), leading to hypoxaemia (ventilation/perfusion mismatching), right ventricular failure and death. The pathogenesis of pulmonary hypertension is unknown but pulmonary vaso-constriction, in-situ thrombosis and endothelial injury may all be important (Rubin 1997). There is some evidence that there may be a lack of endogenous prostacyclin production in idiopathic primary pulmonary hypertension (Christman 1992; Loscalzo 1997).

Some studies suggest that primary pulmonary hypertension may occur in up to 33 % of patients with diffuse scleroderma and in 10-50% of those with the CREST syndrome, characterised by calcinosis, Raynaud's syndrome, oesophageal dysfunction, sclerodactyly and telangiectasia (Stupi 1986; Ungerer 1983). Pulmonary hypertension can be a leading cause of death in these patients (Salerni 1977). Histological evidence of pulmonary vasculopathy has been seen in 65 % of patients with CREST (Yousem 1990) although less than 10 % develop clinically overt pulmonary hypertension during life (Stupi 1986). These estimates depend on the diagnostic methods used. Limited scleroderma (CREST) is associated with anti centromere antibodies (ACA) in 60% of cases whereas diffuse scleroderma is associated with SCL 70 antibodies in 40% of cases. The main histological finding in scleroderma is concentric arteriolar fibrosis with ablation of the intima and media. In idiopathic primary pulmonary hypertension there are plexiform lesions and fibrinoid necrosis (Wells 2000). It has been argued that recurrent episodes of pulmonary vasospasm may occur in scleroderma (pulmonary Raynaud's phenomenon) resulting in irreversible changes to the pulmonary artery (Robin 1982; Furst 1981).

Once the diagnosis of primary pulmonary hypertension is established, life expectancy is greatly reduced. The median survival of patients with NYHA functional classes one and two is six years, two and a half years for NYHA functional class three and only six months for NYHA functional class four (D'Alonzo 1991). No conventional therapies have proven to be effective for pulmonary hypertension apart from transplantation although this is contraindicated in connective tissue diseases in most transplant programmes as there are complications due to multiple organ involvement.

Prostacyclin is a naturally occurring prostanoid produced from arachidonic acid by vascular endothelium that has vasodilating, antiplatelet aggregating and cytoprotective effects (Moncada 1976; Grant 1992). Epoprostenol is a preparation that can only be given intravenously. It has to be stored in the fridge, prepared daily in sterile conditions and can only be put into a central vein. As it has a short half-life, it has to be given continuously. Iloprost is a chemically stable derivative of prostacyclin with similar biologic properties but with a longer half -life of 13 minutes and can be given orally, as an infusion (either intravenously or subcutaneously) or in the nebulised form. It is pharmacologically equivalent to epoprostenol but as it is more stable, treatment at home is more practicable. Treprostinil is a stable prostacyclin analogue which has similar pharmacological actions to epoprostenol, but is chemically stable at room temperature and has a longer half life of three to four hours. It can therefore be given subcutaneously as a continuous infusion. Beraprost sodium is the first chemically stable and orally active prostacyclin analogue.

Prostacyclin (epoprostenol) and Iloprost have been shown in some studies that are not randomised controlled studies (RCTs) to be effective in improving cardiopulmonary variables with a reduction in the mean PAP and PVR and an improvement in CI. However, other studies have documented both serious adverse effects and lack of efficacy (Rubin 1990; Palmer 1988).

OBJECTIVES

The objectives of the review were to determine the benefit of prostacyclin or one of its analogues for the treatment of patients with primary pulmonary hypertension and its variant which occurs with collagen vascular diseases, especially systemic sclerosis or CREST syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised double- blind or single- blind, placebo - controlled, either parallel group or cross- over studies, were selected for inclusion in this review. The placebo group included patients receiving conventional treatment for pulmonary hypertension. Open, prospective trials and uncontrolled trials were not analysed but are discussed.

Types of participants

Adult subjects with a diagnosis of idiopathic primary pulmonary hypertension (with no obvious underlying cause) or pulmonary hypertension as part of a collagen vascular disease were included. The diagnosis of interstitial lung disease was based on clinical symptoms, imaging techniques (high resolution CT scanning), histology of lung specimens and results of bronchoalveolar lavage. The diagnosis of pulmonary hypertension was based on clinical symptoms (mainly breathlessness, but often very non specific) and the results of right heart catheterisation studies.

Types of interventions

The intervention in the actively treated group was prostacyclin or one of its analogues, such as Iloprost, epoprostenol, treprostinil or beraprost given intravenously, subcutaneously, nebulised or orally. The control group consisted of patients receiving conventional

treatment or placebo. Studies assessing the additive effects of prostacyclin will not be considered by this review.

Types of outcome measures

Primary outcomes

1. Exercise capacity (six minute walk)
2. NYHA functional class

Secondary outcomes

1. Cardiopulmonary haemodynamics- including mean pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), cardiac index (CI), cardiac output, systemic arterial oxygen saturation and systemic oxygen transport
2. Borg dyspnoea scores and dyspnoea-fatigue ratings
3. Signs and symptoms of pulmonary hypertension
4. Pulmonary function studies
5. Mortality
6. Adverse events

Search methods for identification of studies

Searches were current as of July 2006.

Electronic searches

The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE AND EMBASE were searched. The following strategy, was used in CENTRAL and MEDLINE, and adapted for use in EMBASE:

1. exp Lung Diseases, Interstitial/
2. sarcoidosis.mp.
3. (cryptogenic adj4 fibrosing adj4 alveolitis).mp.
4. pneumonitis.mp.
5. pulmonary fibrosis.mp.
6. (idiopathic adj4 pulmonary adj4 hemosiderosis).mp.
7. wegeners granulomatosis.mp.
8. exp Churg-strauss syndrome/
9. exp Crest syndrome/
10. or/1-9
11. exp Arthritis, rheumatoid/
12. exp Autoimmune diseases/
13. exp Connective tissue diseases/
14. scleroderma.mp.
15. or/11-14
16. (secondary adj4 pulmonary hypertension).mp.
17. 15 and 16
18. 17 or 10
19. exp Hypertension, Pulmonary/
20. (pulmonary adj5 hypertension).mp.
21. (pulmonary and hypertension).mp.
22. hypertension,pulmonary.mp.
23. or/19-22
24. 18 or 23
25. exp HEART CATHETERIZATION/
26. (catheterization adj heart).mp.
27. or/24-26
28. exp Vasodilator Agents/
29. exp VASODILATION/de
30. exp Epoprostenol/
31. exp ILOPROST/

32. (prostacyclin or epoprostenol or iloprost or beroprost or treprostinil or bosanten).mp.

33. or/28-32

34. 27 and 33

In MEDLINE and EMBASE this strategy was combined with an RCT filter, as outlined in the Airways Group Module.

Searching other resources

In addition to the electronic searches, handsearches of abstracts from meetings of the American and British Thoracic Societies, and the European Respiratory Society were conducted. Bibliographies of retrieved papers were checked to identify relevant cross-references. Drug companies were contacted for relevant trial data (published and unpublished).

Data collection and analysis

Selection of studies

All identified citations were reviewed to identify potentially relevant studies. Full text versions of the studies were assessed by two reviewers (NSP and TJL) to determine if they met the inclusion criteria. Differences were resolved by discussion. Those that met the inclusion criteria were assessed for study quality.

Data extraction and management

Data for trials were extracted independently by two reviewers and entered into the Cochrane Collaboration software program (Review Manager). Standard errors were converted to standard deviations. Authors and drug companies were contacted in an attempt to obtain missing and raw data.

Assessment of risk of bias in included studies

Cochrane approach to concealment of allocation:

- i. Grade A: adequate.
- ii. Grade B: unclear.
- iii. Grade C: clearly inadequate.

Additional assessments were performed using the Jadad five point scale (Jadad 1996):

- i. The study was described as randomised (yes: 1, no: 0)
- ii. Method of randomisation was described and was appropriate (yes: 1, no:-1)
- iii. The study was described as double blind (yes: 1, no: 0)
- iv. The method of blinding was described and was appropriate (yes: 1, no:-1)
- v. The was a description of withdrawals and drop outs (yes:1, no:0)
- vi Deduct 1 point if methods for randomisation or blinding were inappropriate.

Dealing with missing data

Unless otherwise stated, data have been used from published material. Data from unpublished sources were used where the published results were presented in a format unsuitable for MetaView. Study authors have been contacted for unpublished data. In the updated version of this review, separate data have been requested for mixed populations studied in the three additional clinical trials. No responses have been forthcoming for Galiè 2002; Olschewski 2002; Simonneau 2002, and so data are presented for their mixed populations.

Data synthesis

Results of the analyses for continuous outcomes were expressed as a weighted mean difference (WMD) together with 95% confidence interval (CI) or as a standardised mean difference (SMD) for related outcomes that cannot be aggregated into a common unit of measure. For dichotomous outcomes, odds ratio (OR) were used.

Subgroup analysis and investigation of heterogeneity

When significant heterogeneity was found and was not explained in terms of study quality, the following subgroup analyses were conducted where possible:

- i. Idiopathic primary pulmonary hypertension versus pulmonary hypertension due to collagen vascular diseases
- ii. Severity of ILD and pulmonary hypertension at baseline

Where significant heterogeneity was observed, Fixed Effects and Random Effects modelling were conducted and differences reported.

RESULTS

Description of studies

Results of the search

To date a total of 2077 titles and abstracts have been identified using the search strategy described above. Sixty-six studies have been retrieved based upon an examination of their titles or abstracts. Of these, a total of 72 unique studies have been retrieved. Sixty-three did not meet the entry criteria of the review (see [Characteristics of excluded studies](#)). Nine studies met the entry criteria of the review. We have made attempts to contact the authors for verification of methodological quality, randomisation procedure and additional information on outcome data. To date, four authors have responded with additional information.

Included studies

For details of the studies we have included, see [Characteristics of included studies](#).

Methods

The studies were all of a randomised, parallel group design.

Interventions

Three studies compared intravenous epoprostenol plus conventional therapy with conventional therapy alone ([Barst 1996](#); [Rubin 1990](#); [Badesch 2000](#)). One study compared intravenous iloprost with conventional therapy alone ([Thurm 1991](#)). Five studies assessed oral ([Galiè 2002](#); [Barst 2003](#)), inhaled ([Olschewski 2002](#)) and subcutaneous ([McLaughlin 2003](#); [Simonneau 2002](#)) analogues of prostacyclin compared active treatment with matching placebo. The dose of the drug was titrated up (limited by tolerability) in all studies with the exception of [Thurm 1991](#). One study lasted for 1 year ([Barst 2003](#)), five studies were of a 12 week duration ([Badesch 2000](#); [Barst 1996](#); [Galiè 2002](#); [Olschewski 2002](#); [Simonneau 2002](#)), two studies were eight weeks long ([McLaughlin 2003](#); [Rubin 1990](#)) and one lasted for three days ([Thurm 1991](#)).

Participants

[Badesch 2000](#); [Barst 1996](#); [McLaughlin 2003](#); [Rubin 1990](#) and [Thurm 1991](#) each recruited people with pulmonary hypertension

secondary to several aetiologies. [Badesch 2000](#) and [Thurm 1991](#) recruited participants with pulmonary hypertension secondary to scleroderma. [Barst 1996](#); [McLaughlin 2003](#) and [Rubin 1990](#) recruited participants with primary pulmonary hypertension. The remaining trials recruited mixed populations (patients with primary pulmonary hypertension and participants with pulmonary hypertension due to a variety of aetiologies, including connective tissue disorders and chronic thromboembolic diseases, see [Barst 2003](#); [Galiè 2002](#); [Simonneau 2002](#); [Olschewski 2002](#)). Baseline New York Heart Association (NYHA) classification of all included studies are summarised in [Table 1](#). [Barst 2003](#); [Galiè 2002](#) recruited participants with slightly less severe PH from NYHA classes II and III. All the other trials recruited patients predominantly from NYHA functional classes III and IV. Concomitant medication reported for each study in Characteristics of Included Studies included anticoagulants, calcium channel blockers, cardiac glycosides, supplemental oxygen therapy, diuretics and digoxin.

Outcomes

Exercise capacity was reported in all studies except [Thurm 1991](#) who measured lung function. Additional outcome measures were Borg dyspnoea score, cardiopulmonary haemodynamics, NYHA functional class, symptom scores, quality of life, mortality, tolerability and withdrawals. [Olschewski 2002](#) also reported on the number of participants achieving improvements in exercise capacity and NYHA functional class.

Risk of bias in included studies

The methodological quality of the studies was calculated by two independent reviewers using the Jadad score as specified before. The scores for the studies are as follows:

[Badesch 2000](#)=3 ; [Barst 1996](#)=3; [Galiè 2002](#)=4; [Olschewski 2002](#)=3; [Rubin 1990](#)=3; [Simonneau 2002](#)=4; [Thurm 1991](#)=3; [Barst 2003](#)=4; [McLaughlin 2003](#)=3.

Overall, the quality of the trials was adequate. The intravenous studies were conducted without a placebo control, hence their lower overall Jadad ratings. In such trials the blinding of participants and observers is impossible. These problems are discussed in more detail in the section on Methodological limitations. More recent trials using inhaled iloprost, oral beraprost and subcutaneous treprostinil were all placebo-controlled. In these studies the methodological quality was higher ([Galiè 2002](#); [Olschewski 2002](#); [Simonneau 2002](#); [McLaughlin 2003](#); [Barst 2003](#)), although limitations in reporting meant that no study obtained a Jadad score of 5. Side-effects and tolerability were well reported in the studies.

Effects of interventions

Results from this meta-analysis are reported by outcome. Subgroup analysis consisted of patients with either idiopathic primary pulmonary hypertension or pulmonary hypertension in the context of collagen vascular disease.

Intravenous prostacyclin versus usual care

[Badesch 2000](#); [Barst 1996](#); [Rubin 1990](#).

Primary outcomes

Exercise capacity

Barst 1996; Rubin 1990 and Badesch 2000 reported data for this outcome. Unpublished data were obtained for change scores in

exercise capacity for the Rubin 1990 study and incorporated into the meta-analysis. There was a significant difference in exercise capacity in favour of prostacyclin for the primary PAH subgroup (SMD: 0.69 [95% CI: 0.40, 0.97], Figure 1).

Figure 1. Forest plot of comparison: 1 Intravenous prostacyclin versus usual care, outcome: 1.1 Exercise capacity (metres walked in six minutes).

Unpublished data on exercise capacity were used from the Badesch 2000 study. The data obtained by the review authors and entered in to the meta-analysis were based upon the results of 44/55 in the control group and 50/56 in the epoprostenol group. Patients who had died during the study or who were unable to carry out the exercise test were assigned a value of 0 m walked.

A pooled analysis showed a significant treatment effect in favour of prostacyclin (SMD 0.69 [95% CI: 0.40, 0.97]). The effect size was very similar in all three trials. The pooled estimate represents a

difference in the six minute walk distance of around 90 metres in all three trials.

NYHA functional class

Participants with primary PAH treated with prostacyclin were more likely to improve NYHA functional status by at least one class compared with placebo (OR of 26.44[95% CI: 4.49,155.82]). Data pooled with studies analysis for all three studies gave an OR of 37.99 [95% CI: 8.43,171.22], Figure 2.

Figure 2. Forest plot of comparison: 1 Intravenous prostacyclin versus usual care, outcome: 1.7 Improvement in NYHA.

Secondary outcomes

Cardiopulmonary haemodynamics

Badesch 2000; Barst 1996 and Rubin 1990 measured several haemodynamic variables at the end of treatment with intravenous epoprostenol. The most relevant outcomes were mean pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR) and cardiac index (CI). Cardiac output was measured in Rubin 1990. Unpublished data were used for Rubin 1990. Patients in Badesch 2000 had slightly lower mean PAP and PVR values at baseline than the other two studies.

PAP

There was a significant reduction in PAP in the primary PAH subgroup in favour of epoprostenol of -6.82 mmHg (95% CI: -10.66, -2.98, Barst 1996; Rubin 1990). When pooled with data in patients with pulmonary hypertension due to scleroderma (Badesch 2000), there was a significant treatment effect in favour of prostacyclin of -6.30 mmHg (95% CI: -8.68, -3.92).

PVR

There was a significant decrease in PVR in favour of prostacyclin for subgroup of primary PAH of -4.97 mmHg/l/min (95% CI: -7.56, -2.38, Barst 1996; Rubin 1990). When pooled with data in patients with scleroderma associated PAH associated scleroderma (Badesch 2000) there was a significant treatment effect in favour of prostacyclin with a WMD of -5.32 mmHg/l/min (95% CI: -6.83, -3.82).

CI

The pooled analysis showed a significant treatment effect in favour of prostacyclin, with an improvement in cardiac index of 0.58 l/min/m² (95% CI: 0.38, 0.78). Although the studies assessed the effects of treatment in different populations, there was no heterogeneity between the Barst 1996 and Badesch 2000 (I square: 0%).

Cardiac output

Rubin 1990: Cardiac output increased by 0.52 l/min in the 10 patients treated with epoprostenol over an eight week period, compared to a 0.3 l/min increase in 11 patients on conventional therapy. An inter-group comparison calculated independently based upon unpublished data gave a non-significant result (P=0.655).

Mortality

Pooling mortality data from Rubin 1990 and Barst 1996 appeared to indicate that in the primary PAH studies prostacyclin reduced mortality compared with placebo (OR 0.11 (95% CI: 0.02, 0.62). A pooled analysis of the studies with Badesch 2000 generated an OR of 0.32 [95% CI: 0.13, 0.77]. However, we observed a high level of heterogeneity (I square = 41.4%), and with a Random Effects model there was no significant difference between prostacyclin and control groups (Odds ratio 0.32 [95% CI: 0.06, 1.58]).

Barst 1996 reported that eight patients who received conventional therapy died compared with no deaths the epoprostenol group died. No follow-up data were available on long term survival for this study. The eight patients who died had significantly lower exercise capacity at baseline than the 73 survivors (195±/-63 m versus 305 ±/-14 m, P < 0.03). No significant differences were found between the deceased and survivors on haemodynamic variables or short

term responses during dose titration. The difference between the eight deceased patients and the 73 survivors on a primary outcome measure at baseline, combined with their allocation to a placebo control group may be a confounding factor in the significant effect in this trial.

Causes of death in the three studies included respiratory failure, acute pulmonary oedema, right heart failure, arrhythmia, myocardial infarction, septic shock and one case of sudden death.

Systemic arterial oxygen saturation

There was no significant difference in the mean change in oxygen saturation (0.64 % [95% CI: -1.40, 2.69], Barst 1996; Badesch 2000).

Systemic oxygen transport

Rubin 1990: Systemic oxygen transport can be regarded as equivalent to oxygen saturation. Systemic oxygen transport improved by 77.12 ml/min in the treatment group, and by 13.18 ml/min in the conventional group. No between-group P values were reported in the published paper.

Quality of life & symptoms

Barst 1996: there was an improvement in some of the quality of life assessments. Scores were reported as median changes from baseline. Those receiving epoprostenol had significant improvement in all 4 parts of the Chronic Heart Failure Questionnaire (dyspnoea, fatigue, emotional function and mastery) and in some parts of the Nottingham Health Profile. Dyspnoea-Fatigue ratings also improved significantly in the treated group (P<0.01). There was no improvement in the control group in any of these assessments.

Badesch 2000: the Borg Dyspnoea scores and the Dyspnoea-fatigue ratings were presented as median changes from baseline in graphical format. There was an improvement in the epoprostenol group and a deterioration in the conventional therapy group. There was also an improvement in the severity of Raynaud's phenomenon (including pain, numbers of ulcers, arthritis) in the group treated with epoprostenol.

The data were not reported in a format suitable for MetaView, and no unpublished data were made available to the authors regarding these outcomes.

Side effects

Barst 1996 reported several minor complications related to the use of epoprostenol, including jaw pain, flushing, headaches, diarrhoea, nausea and vomiting. The more serious complications included four episodes of non-fatal catheter-related sepsis and one paradoxical embolus. There were 26 episodes of malfunctioning of the delivery system due to occlusion, perforations, pump malfunction and dislodgement of the catheter. During these periods the patients reported worsening symptoms. Four patients developed bleeding at the catheter site, seven developed irritation and infection at the catheter site and four developed pain at the catheter site.

Badesch 2000: epoprostenol caused jaw pain, nausea and anorexia. There was a 4% incidence of sepsis, cellulitis, haemorrhage and pneumothorax. Symptoms of syncope and pallor due to the

underlying disease occurred less commonly in patients receiving epoprostenol.

Rubin 1990: side effects included jaw pain (57%), diarrhoea (100%) and photosensitivity (36%). Other side effects were cutaneous flushing, dyspnoea during the heparin flush procedure which persisted for 15 to 30 minutes after re-establishing the prostacyclin infusion. Thrombophlebitis, ascites, pump malfunction and catheter replacements, under dosing of the infusion due to a problem with the syringe and paradoxical embolus were also reported.

We have not entered data in to RevMan for side-effects due to the absence of a placebo control.

Attrition

Barst 1996: 81 patients entered the study and completed the short-term dose-ranging phase. One patient developed a pneumothorax during the base-line cardiac catheterisation and was not enrolled in the study. Three patients had lung transplants during the study, one in the epoprostenol group and two in the conventional therapy group. Two patients receiving epoprostenol had to stop therapy, one due to side effects of jaw pain and diarrhoea and the other due to inability to manage the drug-delivery system. Eight patients died during the 12 week study period, all in the conventional therapy group.

Badesch 2000: No withdrawals or drop-outs were reported.

Rubin 1990: there were discrepancies in the numbers in the published data and the unpublished data subsequently supplied by GSK. In the paper, 24 patients were selected and 19 completed the study. It is reported that four patients died, three in the conventional therapy group and one in the epoprostenol group. One patient left the study due to adverse effects (pulmonary oedema). However, in the unpublished data it is reported that only one patient died in the conventional therapy group. Three patients had heart-lung transplants after 6, 14 and 18 months of treatment with epoprostenol and one patient had a single lung transplant after 10 months of treatment with epoprostenol. Four patients died subsequently.

Follow-up data

Rubin 1990: nine patients were followed up on active treatment for up to 18 months after the initial 8 week study period. This follow-up period was non-randomised with no blinding. The results showed that epoprostenol produced sustained haemodynamic and symptomatic improvement. However, frequent increases in the dose of epoprostenol were needed, with the mean dose having to be doubled every 6 - 12 months to achieve the same haemodynamic and symptomatic effects, indicating significant tachyphylaxis.

Intravenous Iloprost versus usual care

Thurm 1991

Primary outcomes

Exercise capacity

Data not reported.

NYHA functional class

Data not reported

Secondary outcomes

Lung function

Thurm 1991: the results showed that there was no significant improvement in DLCO and VC after infusion of Iloprost. Iloprost did not alter the abnormal postural DLCO response found in patients with scleroderma.

Side effects

Thurm 1991: no side effects were reported.

Attrition

Thurm 1991: all 14 patients completed the three day study.

Inhaled Iloprost versus placebo

Olschewski 2002

Primary outcomes

Exercise capacity

Continuous data for absolute change in exercise capacity were presented graphically. There was a significant difference between the two groups at 12 weeks of 36.4 metres ($P=0.004$). These data have been entered as generic inverse variance data with a SEM calculated from the published P value. Dichotomous data from the 6 minute walking test were reported as percentages of the sample. These have been entered but not analysed. Following treatment with iloprost 37.6% participants compared with 25.5% in the placebo group were reported as having achieved a 10% increase in distance walked in 6 minutes from baseline values ($P=0.06$). 42.6% (iloprost) versus 32.4% (placebo) had <10% increase to <10% decrease in distance walked, and 13.9% (iloprost) versus 25.5% (placebo) had a $\geq 10\%$ decrease in distance walked.

Data were also stratified by primary pulmonary hypertension and pulmonary hypertension due to other causes. There were non-significant differences between iloprost and placebo-treated participants with primary and secondary forms of pulmonary hypertension. 49.1% (iloprost) versus 30.9% (placebo) participants with PPH achieved a 10% increase in distance walked, 37.7% (iloprost) versus 20.0% (placebo) participants had between <10% increase to <10% decrease in distance walked and 5.7% (iloprost) versus 32.7% had $\geq 10\%$ decrease in distance walked. In pulmonary hypertension due to other causes 25% (iloprost) versus 19.1% (placebo) achieved a $\geq 10\%$ increase in distance walked, 47.9% (iloprost) versus 46.8% (placebo) had between <10% increase and <10% decrease in distance walked.

NYHA functional class

More patients had an improvement in the NYHA functional class on iloprost than on placebo: 1.0% achieved an improvement of 2 classes versus 0% in the placebo group. 23.8% improved by one class on iloprost versus 12.7% on placebo. 64.4% treated with iloprost and 65.7% on placebo had no change in functional class. Withdrawals were not included in the analysis.

Olschewski 2002 also reported a composite of improvement in exercise capacity and NYHA functional class. 16.8% in the iloprost group versus 4.9% in the placebo group achieved $\geq 10\%$ increase in distance walked together with an improvement in NYHA functional class ($P=0.007$). 20.8% with PPH treated with iloprost achieved this treatment goal, compared with 5.5% on placebo.

12.5% PH due to other causes in the iloprost group compared with 4.3% in the placebo group achieved the combined endpoint.

Secondary outcomes

Cardiopulmonary haemodynamics

These data were not stratified by disease aetiology. All were reported as change from baseline at 12 weeks:

Mean PAP decreased significantly after iloprost treatment by -4.6 ± 9.3 mm Hg from baseline values ($P < 0.001$). This compared with a decrease of -0.2 ± 6.9 mm Hg in the placebo-treated group (no P value reported).

PVR decreased in the treatment group by -239 ± 279 dyn/sec/cm⁵ ($P < 0.001$) versus an increase of $+96 \pm 322$ dyn/sec/cm⁵ ($P < 0.05$) in the placebo group.

Cardiac output: There were statistically significant changes in both groups. Following iloprost treatment, cardiac output increased by 0.55 ± 1.1 L/min ($P < 0.001$) versus a decrease of -0.19 ± 0.81 L/min ($P < 0.05$).

Mortality

A total of five patients died during the study: one with PPH from the iloprost group, and four from the placebo group (two with PPH), ($P = 0.37$).

Quality of life & symptoms

Quality of life was measured using the EuroQol scale. Data were reported for two constituent parts; a visual analogue scale and health state score. There was a significant difference on the visual analogue scale between the two groups: 52.8 ± 19.1 compared with 47.4 ± 21.1 after 12 weeks of treatment ($P = 0.026$). The health state score improved in the iloprost group from 0.49 ± 0.28 to 0.58 ± 0.27 , compared with unchanged scores in the placebo group (0.56 ± 0.29 and 0.59 ± 0.31 at baseline and 12 weeks respectively). All other measures on the EuroQol were reported as non-significant.

Mahler Dyspnoea scores improved in both groups, but the improvement was greater in the iloprost treated group compared with placebo ($+1.42 \pm 2.59$ versus $+0.30 \pm 2.45$, $P = 0.015$).

Clinical deterioration & attrition

See [Characteristics of included studies](#) for definition of clinical deterioration. 4.9% participants in the iloprost group and 8.8% in the placebo group suffered clinical deterioration according to the trialists prespecified criteria ($P = 0.41$). There were 4 withdrawals from the iloprost group compared with 14 from the placebo group. Reasons given included were death and clinical deterioration.

Side-effects

For a detailed summary of the safety profile of inhaled iloprost compared with placebo, please see [Table 2](#). Serious adverse events did not differ between the two groups (28 versus 25 participants from active and control groups, $P = 0.63$). Serious syncopal events occurred more frequently in the iloprost group (5 versus 0, $P = 0.03$). Flushing and jaw pain occurred more frequently in the iloprost group (27 versus 9, $P = 0.001$, and 12 versus 3, $P = 0.02$ respectively) but were not considered serious by the trialists.

Follow-up data

None reported.

Subcutaneous treprostinil versus placebo

[McLaughlin 2003](#); [Simonneau 2002](#)

Primary outcomes

Exercise capacity

There was a statistically significant improvement in median exercise capacity from baseline in the active group compared with the placebo group in [Simonneau 2002](#) (week 12: 10 metres (-24 to $+47$) in the treprostinil group versus 0 metres (-44 to $+32$) in the placebo-treated group, $P = 0.006$). No differences were detected between participants with primary and secondary pulmonary hypertension. [McLaughlin 2003](#) reported no significant difference in mean change from baseline scores between treprostinil and placebo.

NYHA functional class

Effect on NYHA functional class was not reported in either study.

Secondary outcomes

Cardiopulmonary haemodynamics

Data were available for [Simonneau 2002](#) and [McLaughlin 2003](#).

PAP

There was a significant difference in mean change from baseline in favour of treprostinil of -2.71 mmHg (95% CI -4.2 , -1.23). However there was considerable statistical heterogeneity between the two studies ($I^2 = 57.6\%$). With a Random Effects model the confidence intervals widened considerably and gave a non-significant difference of 1.44 mmHg (-5.98 , 3.10). The [McLaughlin 2003](#) study was considerably smaller than that of [Simonneau 2002](#). Rather than explain this difference in terms of the subgroup distinctions in the analysis, we feel that other contributory factors such as the different sample sizes in the trials may more adequately explain these apparently discrepant results. Further data sets in this analysis would help to confirm this interpretation.

PVR

There was a significant difference in change from baseline in favour of treprostinil of -4.73 units/m² (95% CI -6.31 , -3.15).

Cardiac Index

There was a significant difference in change from baseline in favour of treprostinil of 0.19 L/min/m² (95% CI 0.08 , 0.30).

Mortality

[Simonneau 2002](#) reported a total of 9 deaths in the treprostinil group and 10 in the placebo group during the study (seven from each group while receiving the study drug, two from the treprostinil group and three from the placebo group after withdrawal of the drug but before the end of the 12 week study period). No deaths were reported in [McLaughlin 2003](#).

Quality of life & symptoms

[Simonneau 2002](#) measured quality of life with the 'Minnesota Living with Heart Failure' questionnaire. No numerical values

were published for the scores of the respective treatment groups, although a significant difference was reported for the physical dimension score ($P=0.0064$). A non-significant difference was detected for the global dimension score ($P=0.17$).

[Simonneau 2002](#) and [McLaughlin 2003](#) measured symptoms with a 'Signs and Symptoms of Pulmonary Hypertension' composite score, a Dyspnoea Fatigue rating scale, and the Borg dyspnoea.

[Simonneau 2002](#) reported that following treatment with treprostinil, the composite score improved from 7.6 $\pm$ 0.5 at baseline to 8.5 $\pm$ 0.5 at week 12. The score for the placebo group altered from 7.5 $\pm$ 0.4 to 7.4 $\pm$ 0.2. The difference between the groups was statistically significant ($P<0.0001$).

[Simonneau 2002](#) reported that a significant difference in the Dyspnoea Fatigue Rating in favour of treprostinil of 0.9 ($P=0.0001$). Borg Dyspnoea Scores post-6 minute walking test improved in both groups with the treprostinil group improving from 4.3 $\pm$ 0.2 at baseline to 3.2 $\pm$ 0.2 at week 12. The placebo group score improved from 4.4 $\pm$ 0.2 to 4.2 $\pm$ 0.2 at week 12. The difference between the two groups was statistically significant ($P<0.0001$).

[McLaughlin 2003](#) reported non-significant differences in the Borg Dyspnoea Score and Dyspnoea Fatigue Rating.

Side effects/tolerability

We pooled data for two common adverse events. Infusion site pain was more common with treprostinil compared with placebo (OR 17.32 (95% CI 10.96, 27.39)). There was no significant difference in the instance of vomiting between the two groups (OR 1.05 (95% CI 0.5 to 2.21)). Whilst there was some degree of heterogeneity (I^2 37.1%), Random Effects modelling widened the confidence intervals around the non-significant result (OR 1.35 (95% CI 0.26 to 7.05)). [Simonneau 2002](#) reported that the mean dose of study drug was 9.3 ng/kg/min in the treprostinil group. Infusion system malfunctions occurred in 55 participants in the treprostinil group and 77 participants in the placebo group. Adverse events subsequent to these malfunctions occurred in four participants from each group. Three participants from the treprostinil group presented with gastrointestinal haemorrhage. There were reported significant differences between the two groups for number of participants suffering side-effects associated with the route of administration in the study (see [Table 3](#)). There were differences in favour of placebo in infusion site pain ($P<0.0001$), infusion site reaction ($P<0.0001$) but not in infusion site bleeding/bruising.

Furthermore treprostinil led to higher rates of diarrhoea ($P=0.009$), jaw pain ($P=0.001$), vasodilation ($P=0.01$) and oedema (21 versus 6, $P=0.002$). Adverse events with non-significant differences between the two groups were: headache, nausea, rash and dizziness. Intolerable infusion site pain led to withdrawals from the study (see below).

[McLaughlin 2003](#) reported significant differences between treprostinil and placebo for infusion site erythema/induration, and non-significant differences between treprostinil and placebo for hypotension, bradycardia, vasovagal, syncope and insomnia. For full details, please see [Table 4](#).

Clinical deterioration & attrition We pooled data on participants who withdrew due to drug-related adverse events. This was more likely to occur with treprostinil compared with placebo (OR 13.47 (95% CI 2.57 to 70.48)). [Simonneau 2002](#) reported that six participants in the treprostinil group and six from the placebo group suffered clinical deterioration leading to withdrawal from the study. No definition of deterioration was given. Five participants from the active treatment group and four from the placebo group were moved on to treatment with continuous intravenous epoprostenol.

Follow-up data

No follow-up data were reported.

Beraprost (oral prostacyclin analogue) versus placebo - titration studies

[Galiè 2002](#); [Barst 2003](#)

Primary outcomes

Exercise capacity

[Galiè 2002](#) reported a significant difference in favour of Beraprost of 25.1 m (95%CI: 1.8 to 48.3), $P=0.036$, with a greater improvement in participants with primary pulmonary hypertension (24.4 m in the beraprost group versus -22.8 m in the placebo group). In participants with pulmonary hypertension due to other causes, the mean change was 5.7 m on beraprost and 0.6 m on placebo (all values at 12 weeks). [Barst 2003](#) reported no significant difference in median change from baseline between the two groups at 12 months (23 metres, $P=0.18$)

Improvement in NYHA functional class

No significant difference (OR 1.43 (95% CI 0.71, 2.88), [Figure 3](#)).

Figure 3. Forest plot of comparison: 5 Oral beraprost versus placebo, outcome: 5.2 Improvement in functional class.

Secondary outcomes

Cardiopulmonary haemodynamics

Data on change from baseline in haemodynamics were available for both studies

PAP

No significant difference (-1.71 mmHg (95% CI -4.06, 0.63)).

PVR

No significant difference (-1.51 mmHg/L/min/m² (95% CI -3.2, 0.18)).

Cardiac Index

No significant difference (0.14 L/min/m² (95% CI -0.1, 0.38)).

Mortality

Data from the two studies did not indicate a significant difference in mortality (OR 0.97 (95% CI 0.19, 4.85)).

Quality of life/symptoms

Galiè 2002 and Barst 2003 reported data in different ways meaning that neither study could contribute to the same analysis.

Borg dyspnea score

Galiè 2002 reported an improvement in the beraprost group from 3.6 +/-2.4 to 3.0 +/-2.4 compared with a deterioration in the placebo group from 3.5 +/-2.4 to 3.9 +/-2.8. Mean difference adjusting for baseline values was -0.94 (95%CI: -1.63, -0.24), P = 0.009. In the

PPH subgroup of participants the mean difference after adjusting baseline values was -1.94 (95%CI: -2.63, -0.28), P = 0.013.

Barst 2003 reported no significant difference between treatment groups at any time point.

Side-effects

Barst 2003 reported no significant difference in quality of life. Side-effects/tolerability Galiè2002 split the reporting of data between weeks 1 to 6 (titration period) and weeks 7 to 12 (dose maintenance period), whereas Barst 2003 reported data for all participants at 52 weeks. We have pooled data from the weeks 1-6 with those of week 52 where available as from the reported data we could only calculate with certainty the number of participants suffering the adverse events from the first part of Galiè 2002:

Dizziness: OR 0.78 (95% CI 0.39 to 1.55)

Headache: OR 4.42 (95% CI 2.56 to 7.65)*

Jaw pain: OR 7.8 (95% CI 3.67 to 16.57)

Diarrhoea: OR 3.05 (95% CI 1.62 to 5.75)

Leg pain: OR 3.53 (95% CI 1.52 to 8.17)

*Denotes non-significant result when Random Effects modelling applied.

The moderate level of statistical heterogeneity on many of the outcomes relating to adverse effects could be explained by the longer period of titration in Barst 2003, leading to more frequent

adverse reactions. Nevertheless, it is noteworthy that differences in study duration did not lead to more heterogeneous findings. We might anticipate that dichotomised data from longer-term studies would provide higher event rates, due to the longer exposure to the study drug, than would data from studies of shorter duration. In this instance, such a variable may not be so important, as from weeks 7-12 in [Galiè 2002](#), many adverse events abated as drug dosage was maintained (see [Table 5](#)). Further studies would help to determine whether adverse events are common in the first few months of therapy or whether they persist and become increasingly prevalent as the drug is titrated with prolonged exposure. Disease-related adverse events occurred in both beraprost and placebo groups at similar rates. These events were less frequent in the maintenance period of therapy. Adverse events resulted in withdrawals from the study (see below).

Treatment failure/clinical deterioration & attrition

In spite of differing measurements of adverse events in [Galiè 2002](#) and [Barst 2003](#), there was low attrition in the studies attributable to poor drug tolerability, and no significant difference between beraprost and placebo in withdrawal due to adverse events (OR 3.55 (95% CI 0.84, 15.00)). The slight variation in the definition of treatment failure in the trials did not appear to affect the comparative instance of treatment failure between the studies, and there was no significant difference between beraprost and placebo when they were analysed overall (OR 0.85 (95% CI 0.33, 2.17)).

Follow-up

No follow-up data were reported.

DISCUSSION

We have reviewed evidence from nine randomised controlled trials, assessing the effects of prostacyclin administered as intravenous, inhaled, subcutaneous and oral preparations. The initial version of this review concluded that prostacyclin improved important markers of disease such as exercise capacity and functional class status. These conclusions were drawn from non-placebo controlled evidence of intravenous preparations of prostacyclin. It is of note that the positive findings reported for exercise capacity in placebo-controlled studies conducted subsequently to the original review are smaller. This may reflect important differences in the effect estimates derived from placebo and usual care control interventions in the studies. When given in any form, prostacyclin has been shown to improve cardiopulmonary haemodynamics. The impact on functional status is mixed, and may reflect varying potencies of the different drug delivery systems, as well as differences in baseline patient populations. In the absence of a proven effect on mortality, prostacyclin and other drugs assessed in clinical trials such as endothelin antagonists and phosphodiesterase inhibitors ([Liu 2004](#); [Kanthapillai 2004](#)) may offer only a stop gap until transplantation can be undertaken in this population.

We selected exercise capacity as the primary outcome for the review. When analysed as a continuous outcome (i.e. as average distance walked) only [Olschewski 2002](#) reported a significant difference in favour of inhaled iloprost. The significant pooled effect estimate previously reported in the review was derived from studies which did not have a placebo control. The effects of oral beraprost did not provide evidence of a consistent effect on exercise capacity. [Galiè 2002](#) showed an improvement in exercise capacity at 12 weeks

of 25.1 m with a greater improvement in those with primary pulmonary hypertension. When longer term data were recorded in [Barst 2003](#), the median difference in exercise capacity between beraprost and placebo only reached statistical significance in the first half of the study.

Improvements in functional capacity were observed for non-placebo controlled evidence pertaining to IV prostacyclin and to a large placebo-controlled trial of inhaled prostacyclin. Although intended to reflect a patient's ability to carry out physical activity, it is not widely regarded as an indicator of quality of life. Changes in functional class status could represent meaningful improvements to a patient's daily physical activity, but the absence of quality of life measurements in these studies precludes a more complete insight into the subjective improvements noticed by participants.

When compared with placebo, side-effects have been demonstrably more frequent with prostacyclin. Serious or life-threatening complications were rare in the RCTs reported. However, other studies ([Humbert 1998](#)) have suggested that there is an increased risk of sepsis and catheter-related thrombosis in patients with pulmonary hypertension in the context of connective tissue diseases. There may be an increased risk of acute pulmonary oedema due to pulmonary veno-occlusive disease in scleroderma ([Palmer 1988](#)). Additional information may be required to evaluate the benefit: risk ratio of long-term prostacyclin therapy in pulmonary hypertension associated with connective tissue diseases. The mechanisms which result in the development of idiopathic primary pulmonary hypertension and pulmonary hypertension in scleroderma are not clear. Pulmonary hypertension is a common complication of the scleroderma spectrum of diseases which includes diffuse scleroderma, limited scleroderma (the CREST syndrome) and the overlap syndrome. In the scleroderma spectrum of diseases, the antinuclear antibody (ANA) levels are elevated in 90-100 % of patients but do not correlate with the presence or severity of lung disease. SCL 70 is a predictor of interstitial lung disease and is found in 40% of patients with diffuse scleroderma. The presence of anti-centromere antibodies (ACA) is a predictor of pulmonary vascular disease and occurs in 60% of patients with CREST ([Stupi 1986](#); [Ungerer 1983](#)). In the [Badesch 2000](#) study, patients had either positive test for ACA or SCL 70 antibodies. However, no data were available as to which patients had which antibodies in order to do a sub-group analysis to see if these different groups responded differently to the prostacyclin infusion. The good haemodynamic and symptomatic response to prostacyclin in that study suggests that reversible vasospasm may be important in the development of pulmonary hypertension in patients with scleroderma.

In scleroderma, there is vasospasm of the pulmonary vasculature with structural changes in the walls of blood vessels. These patients have in the past been treated with agents such as captopril, nifedipine and prazosin with only limited success. Prostacyclin may act by vasodilating these vessels as well as by preventing platelet aggregation ([Menon 1998](#); [de la Mata 1994](#); [Humbert 1998](#)).

Patients with scleroderma may also have major morbidity due to Raynaud's phenomenon, with the development of digital ischaemia and ulceration. A Cochrane review of Iloprost and Cisaprost (prostacyclin analogues) in the treatment of Raynaud's phenomenon in scleroderma has shown that intravenous Iloprost was effective in decreasing the frequency and severity of attacks of

Raynaud's phenomenon and in preventing or healing digital ulcers. Oral iloprost was not as good and cisaprost had minimal or no efficacy when given orally (Pope 2001).

Thurm 1991 argue that patients with scleroderma have a fixed pulmonary vascular bed due to structural changes and have little reversible pulmonary vasospasm as iloprost infusion had no effect on diffusing capacity in the sitting or the supine position. There may be a reversible element early in the course of the disease, but progressively, with time, there are permanent, irreversible changes. In this study, most of the patients had diffuse scleroderma and so are more likely to develop pulmonary hypertension as a result of pulmonary fibrosis.

The acute vasodilator response to intravenous epoprostenol did not predict long-term response in these studies. This makes it less likely that long-term vasodilatation is the mechanism responsible for the haemodynamic improvements. There is some evidence that in scleroderma, an acute vasodilator response predicts a worse outcome (personal communication from Dr Carol Black). It is postulated that the beneficial effects of epoprostenol may be due to inhibition of platelet aggregation and thrombus formation in the vessels. The longer-term benefits may also be due to antiproliferative effects of prostacyclin, decreasing destructive remodeling processes in the pulmonary arterial tree. There is a lack of knowledge about the mechanism of action of epoprostenol and little published data on its metabolism during long-term infusion. There is no evidence that permanent regression of the pathological process occurs. It is also uncertain whether early, aggressive treatment prevents or retards progression of disease.

The limitations of the evidence assembled concern control treatments, blinding, the therapeutic dosage of prostacyclin and the patient populations recruited. Early studies using intravenous prostacyclin in general were affected by lack of blinding and lack of placebo control. It was considered unethical to insert intravenous indwelling catheters into patients in the control arm of all of the studies as these devices are associated with some risk. Therefore, patients receiving active treatment were immediately identifiable. However, in the Badesch 2000, all patients wore an ambulatory infusion pump and a hospital gown over their clothes so that the investigators assessing exercise capacity were blinded as to treatment group. However, this does not remove patient bias. The minor side effects of prostacyclin therapy are common and characteristic (jaw pain, diarrhoea, headache). It was also unacceptable to have seriously ill patients on no therapy. Therefore, the earlier studies were designed to compare conventional therapy plus prostacyclin with conventional therapy alone. The drugs given to patients receiving conventional therapy were not standardised and the doses of these were regulated by the clinicians as they felt appropriate. In at least one of the studies (Rubin 1990), there was a big difference in medical therapy between the patients in the conventional and in the treatment groups. All studies with the exception of Thurm 1991 had study protocols which titrated the study drug upwardly from the outset. The aim of this was to balance disease control with side effects. Given the short duration of the majority of studies, it is feasible that drug dose optimisation may not have been fully established in all participants, which may have been due to the side effect profile. The conflicting effects observed in the beraprost trials suggest that the initial benefit of this preparation of prostacyclin attenuates over time. This raises the possibility that in order to maintain short-term benefits, a

high dose of the drug needs to be given. Given the significant risk of unpleasant side effects associated with beraprost, such a treatment would require careful consideration. Current guidelines recommend endothelin receptor antagonists, and IV epoprostenol ahead of beraprost for long-term therapy in functional class III (ACCP 2004).

The more recent studies with other modes of delivery were able to use a placebo control. Therefore, blinding was possible and this reduces bias. However, these studies all included patients with diverse disease aetiologies and as subgroup analysis was not always provided, firm conclusions on the efficacy of the treatment in all forms of pulmonary hypertension is not possible. Certain trialists did make distinctions between the participants recruited to the studies. Subgroup analysis by the trialists in Simonneau 2002 indicated that greatest improvement was observed in more severely ill participants (NYHA functional Class 3). A dose-response relationship was also noted, with patients whose dose was titrated upwards, achieving a greater improvement in their 6 minute walk. There were no significant differences in response between patients with primary pulmonary hypertension and pulmonary hypertension secondary to other causes.

When the effects of beraprost are considered, it is noteworthy that the patients in these studies were not as compromised as those in the other studies. The lack of response in these patients could be explained by their [do you mean variation in severity]. There was no statistically significant improvement in NYHA functional class and cardio-pulmonary haemodynamics in either study. Patients with other forms of primary pulmonary hypertension did not show a statistically significant improvement. This included patients with congenital cardiac shunts, portal hypertension, collagen vascular diseases and HIV infection. It is not clear whether the patients with PPH were more compromised, and therefore showed a greater response. Several non-randomised studies have looked at nebulised prostacyclin in PPH and in pulmonary hypertension secondary to connective tissue disorders and have shown an improvement in exercise capacity, cardiopulmonary haemodynamic variables and symptoms (Hoepfer 2000; Stricker 1999; Olschewski 1996; Olschewski 1999; Olschewski 2000). There is some evidence that nebulised prostacyclin may produce a greater haemodynamic response than inhaled prostacyclin without a significant effect on systemic arterial pressure (Mikhail 1997; Olschewski 1999). The drug was well tolerated in this form except for mild coughing, headaches and jaw pain.

One small non-randomised study of only 18 patients has suggested that an ultrasonic device delivering inhaled iloprost may improve drug delivery and reduce delivery time compared to a jet nebulizer (Gessler 2001). Clearly, a randomised study with adequate numbers of patients will be necessary to clarify this. The safety profile of inhaled iloprost appears to be favourable compared to intravenous administration in the short-term.

Other non-randomised studies have shown that orally active prostacyclin analogues improved haemodynamic variables and NYHA functional class for up to 12 months of therapy (Okano 1996; Saadjian 1997; Vizza 2001). Flushing and headaches were the main side effects seen.

There is some evidence that a combination of inhaled iloprost with oral sildenafil (a selective phosphodiesterase-5 inhibitor) may have a synergistic effect, improving mean PAP and PVR (Wilkens 2001;

Ghofrani 2002) but larger randomised trials will be necessary before firm conclusions can be drawn.

There were no data available on the cost-effectiveness of treating patients with pulmonary hypertension with prostacyclin for several years. Higenbottam 1995; Higenbottam 1998 have suggested that the relative cost per index of quality of life may be similar for prostacyclin and heart-lung transplantation and that prostacyclin delayed the need for transplantation, though the procedure now performed is single lung transplantation.

Non-randomised long-term studies have consistently shown an improvement in symptoms, exercise capacity, NYHA functional class, cardiopulmonary haemodynamics and survival with intravenous prostacyclin in PPH (McLaughlin 1998; Barst 1994; Jones 1987; Shapiro 1997; Higenbottam 1987; Higenbottam 1993; Higenbottam 1998) and in pulmonary hypertension associated with SLE (Robbins 2000) and connective tissue diseases (Humbert 1998; Humbert 1999; McLaughlin 1998; Humbert 1998; Humbert 1999; de la Mata 1994; Menon 1998; Bartosik 1996).

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review has shown that prostacyclin can be effective in improving exercise capacity, cardiopulmonary haemodynamics, NYHA functional class and symptoms in patients with idiopathic primary pulmonary hypertension and with other forms of secondary pulmonary hypertension including that associated with scleroderma, provided a therapeutically effective dose of the drug can be administered without undue side-effects. Intravenous, subcutaneous, inhaled and oral analogues of prostacyclin were effective compared with control or placebo groups although to different extents. The majority of these studies were performed over a short period of time (eight - 12 weeks) and there are only a very limited amount of data currently available on survival or side effects over a longer period. Prognostic indicators were NYHA functional class, CI, PAP, PVR and mixed venous oxygen saturations (D'Alonzo 1991; Higenbottam 1995) and patient selection may be important when considering long-term treatment with intravenous prostacyclin. Although some of the side effects described are tolerated reasonably well by patients, potentially serious and life-threatening complications can occur, mainly related to the drug delivery system with intravenous administration. Subcutaneous treprostinil may therefore have an important role in treating patients with moderate symptoms who are not severe enough to require intravenous prostacyclin.

There is some evidence that increasing doses of the drug when given intravenously may be required with time to maintain the same effects i.e. tachyphylaxis (Rubin 1990). However, there is no guidance from the published randomised studies on the increases in the doses that may be required in the long-term and on the tolerability and side effects of such doses. There are few data on the cost effectiveness of this treatment in the long term and this may be an important factor, especially in the UK.

Prostacyclin is only one of several drugs now available for the treatment of pulmonary hypertension; endothelin receptor antagonists and selective phosphodiesterase-5 inhibitors have also been shown to be effective and combination of all of these will probably be the way to manage these patients.

Implications for research

There is a need for RCTs that follow patients for a much longer period of time so that the problems that may exist with tachyphylaxis can be assessed. There is also a need for information on side effects in the longer term. Studying groups of patients with scleroderma who have either ACA or SCL 70 antibodies and seeing if they respond differently to prostacyclin may be helpful in determining the mechanisms involved and in determining prognosis. Studies on patients with early and late disease may also be helpful in determining whether early treatment has a disease-modifying role although it may not be possible to do this for ethical reasons and because of the cost implications. Finally, trials combining prostacyclin analogues with other drugs are currently in progress, and these may clarify the role of this drug in patients with pulmonary hypertension.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Badesch 2000

Methods	Randomised open label controlled trial. Outcome assessor blinding: independent blinded observers assessed the primary efficacy measure which was exercise capacity. Withdrawals and drop outs were reported. Setting: 17 pulmonary hypertension referral centres.
Participants	N =111. 56 were allocated to receive epoprostenol and 55 to conventional therapy. All had scleroderma spectrum of disease. Age: >16 years. Gender: Epoprostenol (5M and 51F). Conventional therapy group (10M and 45F). Diagnosis: NYHA functional class. Exclusions: Thrombo-embolic disease/congenital heart disease. New therapies commenced in the last month or stopped within last week except anti-coagulant agents. Current prostacyclin therapy. Patients with interstitial lung disease of more than a mild degree were not included as they were thought to be less likely to show benefit.
Interventions	Epoprostenol via an indwelling central venous catheter and conventional treatment versus conventional treatment alone. Dosage was established according to signs and symptoms from an initial low dose. Trial for 12 weeks. Conventional therapy consisted of diuretics, calcium channel blockers and oral anti-coagulants. 94 out of the 111 patients were on oral anticoagulants.
Outcomes	Exercise capacity, cardiopulmonary haemodynamics, NYHA functional class and Borg dyspnoea scores.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation was conducted centrally according to a stratified randomised block design.
Allocation concealment?	Unclear risk	Information not specified

Barst 1996

Methods	Randomised, multi-centre open trial. Blinded observers assessed the subjective outcomes. Withdrawals and drop outs were reported.
Participants	Eligible: 81 patients with primary PAH. 41 received epoprostenol plus conventional therapy. 40 received conventional therapy alone. Average patient age was 40. In treatment group 10M and 31F, and in the conventional group 12M and 28F. Patients in NYHA III or IV despite optimal medical therapy were recruited.
Interventions	<p>Epoprostenol via a permanent central venous catheter, and conventional therapy, versus conventional therapy alone. Dosage was established after an initial 2ng per kg per min, and increased to optimum dosage. Trial duration 12 weeks.</p> <p>Conventional therapy consisted of anticoagulants, cardiac glycosides, supplemental oxygen therapy, diuretics and oral vasodilators</p>
Outcomes	Cardio-pulmonary Haemodynamics, exercise capacity and dyspnoea and dyspnoea fatigue ratings.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer generated randomisation with stratification according to severity.
Allocation concealment?	Unclear risk	Allocation concealment was not stated.

Barst 2003

Methods	Randomised, double-blind placebo controlled multi-centre trial. Methods of randomisation not reported (ITT population)
Participants	<p>116 participants with PAH according to WHO functional class II and III (Beraprost: 60; PLA: 56). Mean age: BER: 42 (SEM 2); PLA: 42 (SEM 2). Caucasian: BER: 73%; PLA: 75%; hispanic: BER: 10%; PLA: 13%; African origin: BER: 7%; PLA: 7%; M/F gender ratio (%): BER: 13/87; PLA: 16/84; PAH type: BER: primary: 78%, collagen vascular disease-related: 10%; congenital systemic to pulmonary shunts: 12%; PLA: primary: 70%; collagen vascular disease-related: 11%; congenital systemic to pulmonary shunts: 20%. WHO functional class: BER: II: 55%; III: 45%; PLA: II: 50%; III: 50%; Mean exercise capacity (6 min walk test): BER: 433 (SEM 11); PLA: 445 (SEM 10). Hemodynamics: mean RAP (mmHg): BER: 8.3 (SEM 0.7); PLA: 8.8 (SEM 0.6); mean PAP (mmHg): BER: 56 (SEM 2); PLA: 55 (SEM 2); PCWPM (mmHg): BER: 9 (SEM 0.4); PLA: 9 (SEM 0.5); CI (L/min/m²): BER: 2.7 (SEM 0.1); PLA: 2.4 (SEM 0.1); PVRI (U.m²): BER: 120 (SEM 2); PLA: 119 (SEM 2); SvO₂ (%): BER: 61 (SEM 2); PLA: 64 (SEM 2); HR (bpm): BER: 78 (SEM 1); PLA: 79 (SEM 2).</p> <p>Inclusion criteria: baseline peak VO₂ between 8 and 28ml/kg/min determined using upright cycle ergometer; resting mean PAP: $\geq$ 25mm Hg; resting PCWPM: $\leq$ 15 mmHg; PVR: $>$ 3 U.</p> <p>Exclusion criteria: initiation/halting PAH therapy one month prior to screening</p>
Interventions	<p>Beraprost versus matching placebo. 20ug beraprost 4xday. Dosage increased by 20ug 4xday until maximum dose was 200ug 4xday, based upon signs and symptoms of PAH. Dose was titrated upwards until acceptable safety profile breached. Study duration: 52 weeks.</p> <p>Participants were treated with usual therapy one of: anticoagulant therapy; vasodilators (other than prostacyclin or ERAs)</p>

Barst 2003 (Continued)

Outcomes	Exercise capacity; signs and symptoms; WHO functional class; haemodynamics; quality of life; safety & tolerability
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Notes	Sponsor terminated study early than per protocol (@9 months). Data recorded at end of study (12 months).
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Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised
Allocation concealment?	Unclear risk	Allocation concealment was not stated

Galiè 2002

Methods	Randomised, double-blind placebo-controlled multi-centre trial. Methods of randomisation not reported.
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Participants	130 participants with PAH defined by WHO criteria were enrolled (active treatment n=65, placebo n=65). Participants were recruited from NYHA functional class II and III. 50 were male. Mean age in the active treatment group was 45.8 +/-16.3 and was 45.1 +/-14.4 in the placebo group. Mean exercise capacity at baseline was 362 +/-94 in beraprost and 383 +/-93 in the control group. Borg dyspnoea score was 3.6 +/-2.4 in the active treatment group and 3.5 +/-2.4 in the placebo group. Right arterial pressure was 8 +/-5mm Hg and 9 +/-6 mm Hg in the placebo group. Mean PAP was 58 +/-21mm Hg in the active treatment group and 61 +/-15 in the placebo group. Cardiac Index: 2.4 L/min/m2 +/-0.7 (beraprost) 2.4 L/min/m2 +/-0.7 (placebo). PVR (U/m2): 22.7 +/-12.8 (beraprost) and 23.9 +/-10.8 (placebo). Inclusion criteria: Baseline exercise capacity between 50 and 500 metres in 6 minutes; mean PAP <25mm Hg; pulmonary capillary wedge pressure <15mm Hg. Exclusion criteria: Previous long-term treatment with prostacyclin within 1 month of trial.
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Interventions	Beraprost versus matching placebo. 20ug beraprost 4xday. Dosage increased by 20ug 4xday until maximum dose was 120ug 4xday. Dose was titrated upwards until acceptable safety profile breached. Study duration: 12 weeks.
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Treatment at inclusion: anticoagulants, diuretics, calcium channel blockers and digoxin.

Outcomes	Exercise capacity; Borg dyspnoea score; cardiopulmonary haemodynamics; NYHA functional class; mortality; safety.
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised
Allocation concealment?	Unclear risk	Allocation concealment was not stated.

McLaughlin 2003

Methods	Randomised, double-blind, placebo-controlled multi-centre trial. Method of randomisation not reported
Participants	<p>26 participants with primary PAH (PLA: 9; TREP: 17). Mean age: 37 (SEM 17, RANGE: 12-73); M/F (%): 19/81; NYHA III (%): 96; NYHA IV: 4. mean RAP (mmHg): PLA: 10 (SEM 1); TREP: 9 (SEM 1); mean PAP (mmHg): PLA: 64 (SEM 6); TREP: 59 (SEM 4); PCWpm (mmHg): PLA: 10 (SEM 1); TREP: 8 (SEM 1); CI (L/min/m²): PLA: 2.4 (SEM 0.2); TREP: 2.3 (SEM 0.2); MV sat (%): PLA: 61.7 (SEM 2.8); TREP: 62.1 (SEM 3); PVRI (Units/m²): PLA: 24.7 (SEM 3) L TREP: 24.8 (SEM 2.6); Exercise capacity: PLA: 384 (SEM 27); TREP: 373 (SEM 25); Borg: PLA: +2.4 (SEM 0.7); TREP: +3.2 (SEM 0.3)</p> <p>Inclusion criteria: Primary PAH based upon NIH criteria; ability to walk between 50 and 450 metres in 6 minute walk test; NYHA functional class III or IV despite conventional treatment; mean PAP >25 mmHg; PCWpm/left ventricular diastolic pressure <=15 mmHg; PVR >3 Wood units;</p>
Interventions	Subcutaneous treprostinil versus placebo. Dose initiated at 2.5-5ng/kg/min and adjusted upwards at increments of 2.5-5ng/kg/min every 24 hours based upon response to therapy, to a maximum dose of 20ng/kg/min. Participants received instruction from nurse on use of ambulatory infusion pump. Post-hospital discharge increase in dose could not be greater than 5ng/kg/min. Study duration: 8 weeks
Outcomes	Exercise capacity; pulmonary haemodynamics; safety and tolerability; symptoms
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Adequate sequence generation?	Unclear risk Described as randomised
Allocation concealment?	Unclear risk Allocation concealment was not stated.

Olschewski 2002

Methods	Randomised, double-blind placebo controlled multi-centre trial.
Participants	<p>203 participants with primary and secondary PAH. 101 received active treatment and 102 received placebo. Mean age: 51.2+/-13.2 (iloprost group), 52.8 +/-12.0 (placebo). 66 male participants. Primary pulmonary hypertension: 102, non-primary: 101 (51 in iloprost group, 51 in placebo group); NYHA III: 119, NYHA IV: 84; Mahler Dyspnoea Index: 4.14+/-1.8 (iloprost), 4.27+/-1.8 (placebo); 6 minute walk test: 332+/-93 (iloprost), 315+/-96 (placebo). MPAP: 52.8 +/-11.5 (iloprost), 53.8 +/-14.1 (placebo). Inclusion criteria: MPAP: >=30mm Hg; 50-500m on 6 minute walking test; NYHA class III/IV. Exclusion criteria: Patients taking investigational drugs; altered dose of calcium channel blockers in 6 weeks prior to study entry; pulmonary wedge artery pressure at rest of >15mm Hg; cardiac index at rest >1.5 to <4 L/min/m²; bleeding disorders; bilirubin level >3mg per decilitre; creatinine clearance <30ml/min; FVC <50%; FEV1 <mean normal value minus 2 standard deviations; clinical instability.</p>
Interventions	<p>Placebo or Inhaled iloprost delivered via nebuliser (10 ug/ml). Initial dose given: 2.5 ug delivered to participant and increased to maximum of 5.0ug depending on tolerability. Trial duration 12 weeks.</p> <p>52 participants in the active treatment group and 58 participants in the placebo group were on oral vasodilator therapy.</p>
Outcomes	Primary endpoint: Number of participants achieving >10% increase in distance walked compared with baseline values coupled with improvement in NYHA class; haemodynamic and gas exchange; Mahler dyspnoea index; quality of life; clinical deterioration and death; safety. Participants were deemed to have suffered clinical deterioration when they met two or more of the following criteria predefined by

Prostacyclin for pulmonary hypertension in adults (Review)

Olschewski 2002 (Continued)

the trialists: refractory systolic arterial hypotension (blood pressure <85mm Hg); worsening right ventricular failure (development of refractory edema or ascites); rapid progression of cardiogenic, hepatic, or renal failure; decrease of at least 30% in distance walked at 6 minutes and a decline in measures of haemodynamic function e.g. central venous pressure and mixed venous O2 saturation.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomisation was stratified according to disease etiology by an independent committee who were blinded to. Method of randomisation was not reported.
Allocation concealment?	Unclear risk	Allocation concealment was not specified

Rubin 1990

Methods	Randomised controlled trial. Withdrawals and drop outs were reported. Setting: 4 referral centres	
Participants	24 patients with primary PAH entered the study. 23 were randomised and 19 completed the study. 11 received prostacyclin and 12 received conventional treatment. Age range: 15-66. Prostacyclin group: 7 F and 4M. In conventional group: 9F and 3M. Exclusions: pulmonary hypertension due to thrombo-embolic disease. All patients had been on stable doses of medication for at least 2 weeks before the trial.	
Interventions	<p>Prostacyclin via permanent central venous catheter versus conventional treatment. Initial dosage of 1-2 ng per kg per min was increased to an optimal dose. Treatment was randomised for 8 weeks and then non-randomised for up to 18 months.</p> <p>Conventional therapy consisted of digoxin, diuretics, calcium antagonists and supplemental oxygen. All patients received anticoagulation. One patient in the conventional group appeared to receive no treatment, two were on digoxin, eight received diuretics, seven received calcium antagonists and one received methyldopa. In the treatment group, five patients were on a combination of digoxin and diuretics but five appeared not to be on diuretics or vasodilators.</p>	
Outcomes	Cardio-pulmonary haemodynamics. Exercise capacity.	

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Method of generating randomisation codes not specified
Allocation concealment?	Low risk	Randomisation was conducted by calling a central telephone number, and then opening next available sealed envelope.

Simonneau 2002

Methods	Randomised double-blind placebo controlled trial. Setting: 24 centres. Withdrawals and drop-outs were reported.	
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Prostacyclin for pulmonary hypertension in adults (Review)

Simonneau 2002 (Continued)

Participants	470 recruited (one placebo participant withdrew without receiving treatment) with primary and secondary PAH. 233 received active treatment and 236 received placebo. Age range: 44.6 +/-1.0 (active) 44.4 +/-0.9 (control). 87 male participants. 396 white participants, 21 black participants, 52 other. 6 minute walk test: 326 +/-5 (active), 327 +/-6 (control). Etiology; Primary pulmonary hypertension: 134(active), 136 (control). Connective tissue disease: 41 (active), 49 (control). Years since diagnosis: 4.3 +/-0.5 (active), 3.3 +/-0.5 (control).	
Interventions	<p>Subcutaneous administration of treprostinil (prostacyclin analogue) or placebo over 12 weeks. Dose was started at 1.25ng/kg/min and increased in order to improve symptoms and maintain acceptable side-effect profile. By week 12, maximum dose was 22.5 ng/kg/min. Study drugs were infused at abdominal wall.</p> <p>Treatment was in addition to conventional therapy, which could be: oral vasodilators, oral anticoagulants, diuretics, and/or digitalis.</p>	
Outcomes	Exercise Capacity, symptom scores, dyspnea-fatigue rating, mortality, lung transplantation, clinical deterioration, cardiopulmonary haemodynamics, quality of life, Borg dyspnea score, adverse events.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation was conducted with permuted block design. Participants stratified according to baseline exercise capacity and etiology of pulmonary hypertension.
Allocation concealment?	Unclear risk	Allocation concealment not specified

Thurm 1991

Methods	Randomised double-blind placebo controlled study. Withdrawals and drop-outs were reported	
Participants	14 patients were recruited. All patients had pulmonary hypertension, due to systemic sclerosis. 13 completed the study. 6 patients in the iloprost group and 7 in the placebo group. Age range: 35-72 (8 whites and 5 blacks). Mean age 55 in Iloprost group and 45 in placebo. Gender: 5F and 1M in iloprost group and in placebo group 5F and 2M.	
Interventions	IV iloprost or placebo, dose range (0.5 to 2ng per kg, per min). Trial duration 3 days. All other therapies were stopped.	
Outcomes	Lung function and changes in sitting and supine positions.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomisation was not specified.
Allocation concealment?	Unclear risk	Allocation concealment was not specified.

PAH: pulmonary arterial hypertension; PLA: placebo; RAP: right arterial pressure; PAP: pulmonary arterial pressure; PCWpm: mean capillary wedge pressure; CI: Cardiac index; PVRI: pulmonary vascular resistance index; VO2: oxygen consumption; ERAs: endothelin receptor antagonists. BER: beraprost; TREP: treprostinil; MV Sat: mixed venous saturation

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

Study	Reason for exclusion
Anonymous 2002	Correspondence.
Badesch 2002	Bosentan is not a prostacyclin analogue and so this randomised controlled trial could not be considered for inclusion.
Barst 1994	Open, multicenter, uncontrolled trial to evaluate the effects of long term intravenous infusion of prostacyclin on exercise capacity, haemodynamics and survival in patients with primary pulmonary hypertension.
Bartosik 1996	Study to determine the effects of intravenous iloprost on 8 patients with either diffuse or limited systemic sclerosis. Not a RCT.
Bendayan 2002	Review article.
Brenot 1995	Influence of long term continuous infusion of epoprostenol on survival in patients with primary pulmonary hypertension. Not a RCT.
Bresser 2004	Before and after study.
Budev 2004	Review article
Castelain 2001	This before and after study assessed exercise tolerance in primary pulmonary hypertension after 6 weeks.
Cea-Calvo 2003	Case series.
Chua 2005	Case report.
Cáneva 2002	Before and after study.
Dandel 2003	Retrospective analysis of prostacyclin as a stop gap to transplantation. Not a randomised comparison.
de la Mata 1994	Study to determine the effects of iloprost treatment in severe pulmonary hypertension secondary to systemic sclerosis and the primary antiphospholipid syndrome. Not a RCT.
Ewert 2001	Review article.
Galiè 2003	Review article
Gerlach 2002	Intra-operative study
Gessler 2001	This was a randomised trial which assessed the effectiveness of ultrasonic versus jet nebulisation of prostacyclin. This trial examines a question of delivery of prostacyclin which is outside the scope of the review.
Ghofrani 2002	This randomised controlled trial assessed the combination therapy of iloprost with oral sildenafil for pulmonary hypertension. The scope of this review is restricted to assessing the effectiveness of prostacyclin alone.

Study	Reason for exclusion
Ghofrani 2005	Case report.
Hache 2003	Pre-operative study
Halliglu 2003	Excluded as it was a paediatric study
Higenbottam 1998	To determine the effects of long-term intravenous epoprostenol in 98 patients with primary pulmonary hypertension and with pulmonary hypertension secondary to systemic disease and thromboembolic disease. Not a RCT.
Higenbottam 2001	Review article.
Highland 2003	Analysis of relative effects of different drugs in overview.
Hoeper 2000	Study to evaluate the effects of aerosolized iloprost on exercise capacity and haemodynamic variables over a one year period in patients with primary pulmonary hypertension. Not a RCT.
Hoeper 2002	Review article.
Humbert 1998	Study to determine the effects of epoprostenol given continuously on 12 patients with severe pulmonary hypertension secondary to SLE, systemic sclerosis, mixed CTD and primary Sjogren's syndrome. Not a RCT.
Humbert 2003	Randomised comparison of Bosentan (ERA) in addition to prostacyclin.
Jones 1987	Uncontrolled study of ten patients with severe pulmonary hypertension referred for heart lung transplantation. Continuous intravenous infusion of epoprostenol for 1-25 months was associated with subjective and clinical improvement. Not an RCT
Kramm 2002	Post-operative study.
Langer 2003	Intraoperative study.
Langleben 2002	Irrelevant comparison.
Leuchte 2002	Animal study.
McLaughlin 1998	Study to evaluate the effects of long-term therapy with intravenous epoprostenol in patients with advanced primary pulmonary hypertension. Not a RCT.
McLaughlin 2005	Assessment of prostacyclin as additive agent to standardised dose of bosentan.
Menon 1998	Measurement of pulmonary pressures and cardiac output in 7 patients with pulmonary hypertension before and during a systemic intravenous infusion of prostacyclin.
Mikhail 1997	A study to investigate the response to inhaled prostacyclin in patients with primary and secondary pulmonary hypertension and to compare its effects to those of intravenous prostacyclin and inhaled nitric oxides. Not a RCT.
Mikhail 2002	Review article.
Nagaya 2002	32 patients with pulmonary hypertension in NYHA class $\leq$ III were recruited for a before and after study of the long term effects of beraprost sodium. NYHA class improved following treatment. heart rate and blood pressure were unchanged.
Nagaya 2004	Study of the acute effects of prostacyclin.

Study	Reason for exclusion
Nakayama 2001	Before and after study.
Okano 1996	An observational study.
Olschewski 1996	Open uncontrolled trial. Nebulised prostacyclin in patients with idiopathic primary pulmonary hypertension and scleroderma.
Olschewski 1999	8 patients with lung fibrosis and pulmonary hypertension were given intravenous prostacyclin and inhaled prostacyclin and inhaled NO. Although treatment was administered in random order, the patient population suffered from both primary and secondary pulmonary hypertension. The diversity of the participants precluded combination with data from other studies, and the underlying causes were too varied to facilitate interpretation of data in the context of the clinical question posed by this review.
Olschewski 2000	An open, uncontrolled, multicenter study to assess the efficacy of inhaled iloprost in the treatment of pulmonary hypertension. Not a RCT.
Olschewski 2003	Randomised comparison of different methods of delivery of inhaled prostacyclin
Olschewski 2004	Review article.
Ono 2003	Before and after study.
Ono 2003a	Before and after study.
Opitz 2005	Non-randomised study
Robbins 2000	Case series of six patients with SLE and associated pulmonary hypertension receiving chronic treatment with epoprostenol.
Rubin 2005	Correspondence.
Saadjian 1997	This was a randomised double-blind controlled study on 23 male patients with pulmonary hypertension secondary to chronic obstructive lung disease (COLD). The average age of the patients was 62. All patients had poor lung function (FEV1 <70%) with mean PAP > 20 mmHg. Cicletanine has been shown to enhance the production of endogenous prostacyclin. In the short-term study, patients were allowed to rest for 30 minutes after the insertion of catheters and baseline measurements were made. They were given 50 mg of cicletanine or placebo orally and measurements made hourly for up to 3 hours. In the long-term study, 50 mg of cicletanine or placebo was administered orally on a daily basis with assessments at 3 and 12 months. Outcome measures were cardiopulmonary haemodynamics and oxygen saturation (PaO2). Adverse events were not reported. This study was excluded as it focused on secondary pulmonary hypertension and this review was concerned with primary pulmonary hypertension or pulmonary hypertension in scleroderma.
Scorza 2001	Randomised study examining the effects of iloprost in systemic sclerosis. Lung involvement was not listed as an inclusion criteria.
Shapiro 1997	Looking at the long term effects of continuous infusion of epoprostenol therapy on survival and pulmonary artery pressure in patients with primary pulmonary hypertension. Not randomized or controlled.
Stiebelhner 2003	Observational study.
Stricker 1999	Study to investigate the effects of acute administration of aerosolised prostacyclin or iloprost in 5 patients with severe pulmonary hypertension. not a RCT.

Study	Reason for exclusion
Tapson 2006	Non-randomised study.
Vizza 2001	Uncontrolled long-term study of the efficacy of beraprost in 13 patients with pulmonary hypertension.
Voswinckel 2006	Observational study.
Wilkens 2001	This combination therapy trial assessed prostacyclin and sildenafil and so was not within the scope of the review.
Yap 2003	Case study

DATA AND ANALYSES

Comparison 1. Intravenous prostacyclin versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exercise capacity (metres walked in six minutes)	3	196	Std. Mean Difference (IV, Fixed, 95% CI)	0.69 [0.40, 0.97]
1.1 Idiopathic primary pulmonary hypertension	2	102	Std. Mean Difference (IV, Fixed, 95% CI)	0.69 [0.29, 1.09]
1.2 Pulmonary hypertension in scleroderma	1	94	Std. Mean Difference (IV, Fixed, 95% CI)	0.68 [0.26, 1.10]
2 Improvement in NYHA	3	201	Odds Ratio (M-H, Fixed, 95% CI)	37.99 [8.43, 171.22]
2.1 Idiopathic primary pulmonary hypertension	2	90	Odds Ratio (M-H, Fixed, 95% CI)	26.44 [4.49, 155.81]
2.2 Pulmonary hypertension in scleroderma	1	111	Odds Ratio (M-H, Fixed, 95% CI)	67.23 [3.95, 1145.24]
3 Change in mean pulmonary artery pressure (mm Hg)	3	213	Mean Difference (IV, Fixed, 95% CI)	-6.30 [-8.68, -3.92]
3.1 Idiopathic primary pulmonary hypertension	2	102	Mean Difference (IV, Fixed, 95% CI)	-6.82 [-10.66, -2.98]
3.2 Pulmonary hypertension in scleroderma	1	111	Mean Difference (IV, Fixed, 95% CI)	-5.97 [-9.00, -2.94]
4 Change in pulmonary vascular resistance (mm Hg/l/min)	3	213	Mean Difference (IV, Fixed, 95% CI)	-5.32 [-6.83, -3.82]
4.1 Idiopathic primary pulmonary hypertension	2	102	Mean Difference (IV, Fixed, 95% CI)	-4.97 [-7.56, -2.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Pulmonary hypertension in scleroderma	1	111	Mean Difference (IV, Fixed, 95% CI)	-5.5 [-7.35, -3.65]
5 Change in cardiac index (l/min/m ²)	2	192	Mean Difference (IV, Fixed, 95% CI)	0.58 [0.38, 0.78]
5.1 Idiopathic primary pulmonary hypertension	1	81	Mean Difference (IV, Fixed, 95% CI)	0.5 [0.06, 0.94]
5.2 Pulmonary hypertension in scleroderma	1	111	Mean Difference (IV, Fixed, 95% CI)	0.6 [0.38, 0.82]
6 Change in cardiac output (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Mortality	3	215	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.06, 1.58]
7.1 Idiopathic primary pulmonary hypertension	2	104	Odds Ratio (M-H, Random, 95% CI)	0.14 [0.02, 0.90]
7.2 Pulmonary hypertension in scleroderma	1	111	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.20, 3.03]
8 Change in systemic arterial oxygen saturation (%)	2	192	Mean Difference (IV, Fixed, 95% CI)	0.64 [-1.40, 2.69]
8.1 Idiopathic primary pulmonary hypertension	1	81	Mean Difference (IV, Fixed, 95% CI)	2.60 [-1.56, 6.76]
8.2 Pulmonary hypertension in scleroderma	1	111	Mean Difference (IV, Fixed, 95% CI)	0.02 [-2.33, 2.37]
9 Change in systemic oxygen transport (ml/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Intravenous prostacyclin versus usual care, Outcome 1 Exercise capacity (metres walked in six minutes).

Analysis 1.2. Comparison 1 Intravenous prostacyclin versus usual care, Outcome 2 Improvement in NYHA.

Analysis 1.3. Comparison 1 Intravenous prostacyclin versus usual care, Outcome 3 Change in mean pulmonary artery pressure (mm Hg).

Analysis 1.4. Comparison 1 Intravenous prostacyclin versus usual care, Outcome 4 Change in pulmonary vascular resistance (mm Hg/l/min).

Analysis 1.5. Comparison 1 Intravenous prostacyclin versus usual care, Outcome 5 Change in cardiac index (l/min/m2).

Analysis 1.6. Comparison 1 Intravenous prostacyclin versus usual care, Outcome 6 Change in cardiac output (L/min).

Analysis 1.7. Comparison 1 Intravenous prostacyclin versus usual care, Outcome 7 Mortality.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Test for subgroup differences: Not applicable					
Favours treatment 0.001 0.1 1 10 1000 Favours control					

Analysis 1.8. Comparison 1 Intravenous prostacyclin versus usual care, Outcome 8 Change in systemic arterial oxygen saturation (%).

Study or subgroup	Treatment		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
1.8.1 Idiopathic primary pulmonary hypertension							
Barst 1996	41	2 (10.2)	40	-0.6 (8.9)		24.19%	2.6[-1.56,6.76]
Subtotal ***	41		40			24.19%	2.6[-1.56,6.76]
Heterogeneity: Tau ² =0; Chi ² =0, df=0(P<0.0001); I ² =100%							
Test for overall effect: Z=1.22(P=0.22)							
1.8.2 Pulmonary hypertension in scleroderma							
Badesch 2000	56	0.3 (7.9)	55	0.3 (4.3)		75.81%	0.02[-2.33,2.37]
Subtotal ***	56		55			75.81%	0.02[-2.33,2.37]
Heterogeneity: Not applicable							
Test for overall effect: Z=0.02(P=0.99)							
Total ***	97		95			100%	0.64[-1.4,2.69]
Heterogeneity: Tau ² =0; Chi ² =1.12, df=1(P=0.29); I ² =10.51%							
Test for overall effect: Z=0.62(P=0.54)							
Test for subgroup differences: Chi ² =1.12, df=1 (P=0.29), I ² =10.51%							
<div><div></div><div>Favours control</div><div>-10</div><div>-5</div><div>0</div><div>5</div><div>10</div><div>Favours treatment</div></div>							

Analysis 1.9. Comparison 1 Intravenous prostacyclin versus usual care, Outcome 9 Change in systemic oxygen transport (ml/min).

Study or subgroup	Treatment N Mean(SD)		Control N Mean(SD)		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Rubin 1990	10	77.1 (169.1)	11	13.2 (235)		63.94[-110.02,237.9]
Favours control -1000 -500 0 500 1000 Favours treatment						

Comparison 2. Introvenous iloprost versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DLco (ml/min/ml/Hg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Vital capacity (l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Intravenous iloprost versus usual care, Outcome 1 DLco (ml/min/ml/Hg).

Study or subgroup	Treatment		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Thurm 1991	6	11.1 (5.2)	7	12.7 (6)		-1.58[-7.67,4.51]
					Favours control	Favours treatment

Analysis 2.2. Comparison 2 Intravenous iloprost versus usual care, Outcome 2 Vital capacity (l).

Study or subgroup	Treatment		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Thurm 1991	6	2.3 (0.9)	7	2.8 (1.1)		-0.55[-1.63,0.53]
					Favours control	Favours treatment

Comparison 3. Inhaled iloprost versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exercise capacity: Participants achieving >10% increase	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Idiopathic primary pulmonary hypertension	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Pulmonary hypertension secondary to scleroderma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Mixed population studies	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Exercise capacity: Participants with < and >10% change	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Idiopathic primary pulmonary hypertension	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Pulmonary hypertension secondary to scleroderma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Mixed population studies	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Exercise capacity (change from baseline)	1		Metres (Fixed, 95% CI)	Totals not selected
3.1 Primary pulmonary hypertension	0		Metres (Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Pulmonary hypertension secondary to scleroderma	0		Metres (Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Mixed populations	1		Metres (Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 NYHA Functional class - participants with improvement	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Idiopathic primary pulmonary hypertension	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Pulmonary hypertension secondary to scleroderma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Mixed population studies	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 NYHA Functional class - participants with no improvement	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Idiopathic primary pulmonary hypertension	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Pulmonary hypertension secondary to scleroderma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Mixed population studies	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Mean PAP (change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Idiopathic primary pulmonary hypertension	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Pulmonary hypertension associated with scleroderma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Mixed population studies	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 PVR (change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Idiopathic primary pulmonary hypertension	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Pulmonary hypertension associated with scleroderma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Mixed population studies	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Cardiac output	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Idiopathic primary pulmonary hypertension	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Pulmonary hypertension associated with scleroderma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 Mixed population studies	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Dyspnoea score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Idiopathic primary pulmonary hypertension	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Pulmonary hypertension associated with scleroderma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Mixed population studies	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 Idiopathic primary pulmonary hypertension	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Pulmonary hypertension secondary to scleroderma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Mixed population studies	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Quality of life	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 Idiopathic primary pulmonary hypertension	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Pulmonary hypertension associated with scleroderma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Mixed population studies	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Clinical deterioration	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.1 Idiopathic primary pulmonary hypertension	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Pulmonary hypertension secondary to scleroderma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 Mixed population studies	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Adverse effects (all aetiologies - subgrouped by type of event)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.1 Syncope	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Serious adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

**Analysis 3.1. Comparison 3 Inhaled iloprost versus placebo,
Outcome 1 Exercise capacity: Participants achieving >10% increase.**

**Analysis 3.2. Comparison 3 Inhaled iloprost versus placebo,
Outcome 2 Exercise capacity: Participants with < and >10% change.**

Analysis 3.3. Comparison 3 Inhaled iloprost versus placebo, Outcome 3 Exercise capacity (change from baseline).

**Analysis 3.4. Comparison 3 Inhaled iloprost versus placebo,
Outcome 4 NYHA Functional class - participants with improvement.**

Analysis 3.5. Comparison 3 Inhaled iloprost versus placebo, Outcome 5 NYHA Functional class - participants with no improvement.

Analysis 3.6. Comparison 3 Inhaled iloprost versus placebo, Outcome 6 Mean PAP (change from baseline).

Analysis 3.7. Comparison 3 Inhaled iloprost versus placebo, Outcome 7 PVR (change from baseline).

Analysis 3.8. Comparison 3 Inhaled iloprost versus placebo, Outcome 8 Cardiac output.

Analysis 3.9. Comparison 3 Inhaled iloprost versus placebo, Outcome 9 Dyspnoea score.

Analysis 3.10. Comparison 3 Inhaled iloprost versus placebo, Outcome 10 Mortality.

Analysis 3.11. Comparison 3 Inhaled iloprost versus placebo, Outcome 11 Quality of life.

Analysis 3.12. Comparison 3 Inhaled iloprost versus placebo, Outcome 12 Clinical deterioration.

Analysis 3.13. Comparison 3 Inhaled iloprost versus placebo, Outcome 13 Adverse effects (all aetiologies - subgrouped by type of event).

Comparison 4. Subcutaneous treprostinil versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exercise capacity	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Primary pulmonary hypertension	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Pulmonary hypertension associated with scleroderma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Mixed population studies	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in exercise capacity (metres walked)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Primary pulmonary hypertension	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Pulmonary hypertension associated with scleroderma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Mixed population studies	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 NYHA functional class	0		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Idiopathic primary pulmonary hypertension	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Pulmonary hypertension secondary to scleroderma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Mixed population studies	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Change in Dyspnea score	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Primary pulmonary hypertension	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Pulmonary hypertension associated with scleroderma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Mixed population studies	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Mean PAP (change from baseline)	2	493	Mean Difference (IV, Fixed, 95% CI)	-2.71 [-4.20, -1.23]
5.1 Primary pulmonary hypertension	1	24	Mean Difference (IV, Fixed, 95% CI)	2.0 [-4.20, 8.20]
5.2 Pulmonary hypertension associated with scleroderma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Mixed population studies	1	469	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-4.53, -1.47]
6 PVR (change from baseline)	2	493	Mean Difference (IV, Fixed, 95% CI)	-4.73 [-6.31, -3.15]
6.1 Primary pulmonary hypertension	1	24	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-10.12, 0.12]
6.2 Pulmonary hypertension associated with scleroderma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Mixed population studies	1	469	Mean Difference (IV, Fixed, 95% CI)	-4.7 [-6.36, -3.04]
7 Cardiac index (change from baseline)	2	493	Mean Difference (IV, Fixed, 95% CI)	0.19 [0.08, 0.30]
7.1 Primary pulmonary hypertension	1	24	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.15, 0.95]
7.2 Pulmonary hypertension associated with scleroderma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Mixed population studies	1	469	Mean Difference (IV, Fixed, 95% CI)	0.18 [0.07, 0.29]
8 Mortality	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Idiopathic primary pulmonary hypertension	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Pulmonary hypertension secondary to scleroderma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 Mixed population studies	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Quality of life	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Idiopathic primary pulmonary hypertension	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Pulmonary hypertension associated with scleroderma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Mixed population studies	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Dyspnoea score	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 Primary pulmonary hypertension	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Pulmonary hypertension associated with scleroderma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Mixed population studies	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Withdrawals due to clinical deterioration	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.1 Idiopathic primary pulmonary hypertension	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Pulmonary hypertension secondary to scleroderma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Mixed population studies	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Withdrawals due to drug related adverse events	2	496	Odds Ratio (M-H, Fixed, 95% CI)	13.47 [2.57, 70.48]
12.1 Primary pulmonary hypertension	1	26	Odds Ratio (M-H, Fixed, 95% CI)	3.06 [0.13, 70.94]
12.2 Pulmonary hypertension secondary to scleroderma	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 Mixed population studies	1	470	Odds Ratio (M-H, Fixed, 95% CI)	19.76 [2.62, 149.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Side effects (all aetiologies - subgrouped by type of AE)	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Infusion site pain	2	495	Odds Ratio (M-H, Fixed, 95% CI)	17.32 [10.96, 27.39]
13.2 Vomiting	2	495	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.50, 2.21]

Analysis 4.1. Comparison 4 Subcutaneous treprostinil versus placebo, Outcome 1 Exercise capacity.

Study or subgroup	Treprostinil		Placebo		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
4.1.1 Primary pulmonary hypertension						
4.1.2 Pulmonary hypertension associated with scleroderma						
4.1.3 Mixed population studies						
Simonneau 2002	233	0 (0)	236	0 (0)		Not estimable
Favours treprostinil -10 -5 0 5 10 Favours placebo						

Analysis 4.2. Comparison 4 Subcutaneous treprostinil versus placebo, Outcome 2 Change in exercise capacity (metres walked).

Study or subgroup	Treprostinil		Placebo		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
4.2.1 Primary pulmonary hypertension						
McLaughlin 2003	15	37 (65.8)	9	-6 (84)		43[-21.2,107.2]
4.2.2 Pulmonary hypertension associated with scleroderma						
4.2.3 Mixed population studies						
Simonneau 2002	202	14.1 (66.8)	1	0 (0)		Not estimable
Favours placebo -100 -50 0 50 100 Favours treprostinil						

Analysis 4.4. Comparison 4 Subcutaneous treprostinil versus placebo, Outcome 4 Change in Dyspnea score.

Study or subgroup	Treatment		Control		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
4.4.1 Primary pulmonary hypertension						
McLaughlin 2003	15	0 (2.4)	9	1 (1.6)		-1[-2.58,0.58]
4.4.2 Pulmonary hypertension associated with scleroderma						
4.4.3 Mixed population studies						
Favours treprostinil -10 -5 0 5 10 Favours placebo						

Study or subgroup	Treatment		Control		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
Simonneau 2002	233	-1.1 (0)	236	-0.2 (0)		Not estimable
Favours treprostinil -10 -5 0 5 10 Favours placebo						

Analysis 4.5. Comparison 4 Subcutaneous treprostinil versus placebo, Outcome 5 Mean PAP (change from baseline).

Study or subgroup	Treprostinil		Placebo		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
4.5.1 Primary pulmonary hypertension							
McLaughlin 2003	15	0 (11.6)	9	-2 (3)		5.75%	2[-4.2,8.2]
Subtotal ***	15		9			5.75%	2[-4.2,8.2]
Heterogeneity: Not applicable							
Test for overall effect: Z=0.63(P=0.53)							
4.5.2 Pulmonary hypertension associated with scleroderma							
Subtotal ***	0		0				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
4.5.3 Mixed population studies							
Simonneau 2002	233	-2.3 (7.6)	236	0.7 (9.2)		94.25%	-3[-4.53,-1.47]
Subtotal ***	233		236			94.25%	-3[-4.53,-1.47]
Heterogeneity: Not applicable							
Test for overall effect: Z=3.84(P=0)							
Total ***	248		245			100%	-2.71[-4.2,-1.23]
Heterogeneity: Tau ² =0; Chi ² =2.36, df=1(P=0.12); I ² =57.55%							
Test for overall effect: Z=3.58(P=0)							
Test for subgroup differences: Chi ² =2.36, df=1 (P=0.12), I ² =57.55%							
					-10 -5 0 5 10		
					Favours treprostinil	Favours placebo	

Analysis 4.6. Comparison 4 Subcutaneous treprostinil versus placebo, Outcome 6 PVR (change from baseline).

Study or subgroup	Treprostinil		Placebo		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
4.6.1 Primary pulmonary hypertension							
McLaughlin 2003	15	-4.8 (6.2)	9	0.2 (6.2)		9.54%	-5[-10.12,0.12]
Subtotal ***	15		9			9.54%	-5[-10.12,0.12]
Heterogeneity: Not applicable							
Test for overall effect: Z=1.91(P=0.06)							
4.6.2 Pulmonary hypertension associated with scleroderma							
Subtotal ***	0		0				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
4.6.3 Mixed population studies							
Simonneau 2002	233	-3.5 (9.2)	236	1.2 (9.2)		90.46%	-4.7[-6.36,-3.04]
					-10 -5 0 5 10		
					Favours treprostinil	Favours placebo

Analysis 4.7. Comparison 4 Subcutaneous treprostnil versus placebo, Outcome 7 Cardiac index (change from baseline).

Analysis 4.8. Comparison 4 Subcutaneous treprostnil versus placebo, Outcome 8 Mortality.

Analysis 4.9. Comparison 4 Subcutaneous treprostinil versus placebo, Outcome 9 Quality of life.

Analysis 4.10. Comparison 4 Subcutaneous treprostinil versus placebo, Outcome 10 Dyspnoea score.

Analysis 4.11. Comparison 4 Subcutaneous treprostinil versus placebo, Outcome 11 Withdrawals due to clinical deterioration.

Analysis 4.12. Comparison 4 Subcutaneous treprostinil versus placebo, Outcome 12 Withdrawals due to drug related adverse events.

Analysis 4.13. Comparison 4 Subcutaneous treprostinil versus placebo, Outcome 13 Side effects (all aetiologies - subgrouped by type of AE).

Comparison 5. Oral beraprost versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exercise capacity (metres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Primary pulmonary hypertension	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Pulmonary hypertension associated with scleroderma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Mixed population studies	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Improvement in functional class	2	246	Odds Ratio (M-H, Fixed, 95% CI)	1.43 [0.71, 2.88]
2.1 Idiopathic primary pulmonary hypertension	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Pulmonary hypertension secondary to scleroderma	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Mixed population studies	2	246	Odds Ratio (M-H, Fixed, 95% CI)	1.43 [0.71, 2.88]
3 Mean PAP (change from baseline in mmHg)	2	196	Mean Difference (IV, Fixed, 95% CI)	-1.71 [-4.06, 0.63]
3.1 Primary pulmonary hypertension	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Pulmonary hypertension associated with scleroderma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Mixed population studies	2	196	Mean Difference (IV, Fixed, 95% CI)	-1.71 [-4.06, 0.63]
4 PVR (change from baseline in mmHg/L/min/m2)	2	191	Mean Difference (IV, Fixed, 95% CI)	-1.51 [-3.20, 0.18]
4.1 Idiopathic primary pulmonary hypertension	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Pulmonary hypertension associated with scleroderma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Mixed population studies	2	191	Mean Difference (IV, Fixed, 95% CI)	-1.51 [-3.20, 0.18]
5 Cardiac index	2	192	Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.10, 0.38]
5.1 Idiopathic primary pulmonary hypertension	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Pulmonary hypertension associated with scleroderma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 Mixed population studies	2	192	Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.10, 0.38]
6 Mortality	2	246	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.19, 4.85]
6.1 Idiopathic primary pulmonary hypertension	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Pulmonary hypertension secondary to scleroderma	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Mixed population studies	2	246	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.19, 4.85]
7 Quality of life	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Idiopathic primary pulmonary hypertension	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Pulmonary hypertension associated with scleroderma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Mixed population studies	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Dyspnoea score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Idiopathic primary pulmonary hypertension	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Pulmonary hypertension associated with scleroderma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 Mixed population studies	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Clinical deterioration	2	246	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.33, 2.17]
9.1 Idiopathic primary pulmonary hypertension	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Pulmonary hypertension secondary to scleroderma	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Mixed population studies	2	246	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.33, 2.17]
10 Withdrawals due to adverse events	2	246	Odds Ratio (M-H, Fixed, 95% CI)	3.55 [0.84, 15.00]
10.1 Idiopathic primary pulmonary hypertension	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Pulmonary hypertension secondary to scleroderma	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Mixed population studies	2	246	Odds Ratio (M-H, Fixed, 95% CI)	3.55 [0.84, 15.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Cardiac Index	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 Idiopathic primary pulmonary hypertension	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Pulmonary hypertension associated with scleroderma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Mixed population studies	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Exercise capacity (mean change from baseline)	1	132	Mean Difference (IV, Fixed, 95% CI)	16.25 [-5.04, 37.55]
12.1 Primary pulmonary hypertension	1	65	Mean Difference (IV, Fixed, 95% CI)	46.2 [5.32, 87.08]
12.2 Pulmonary hypertension associated with scleroderma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 Mixed population studies	1	67	Mean Difference (IV, Fixed, 95% CI)	5.10 [-19.85, 30.05]
13 Side-effects (all aetiologies subgrouped by type of event)	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Dizziness	2	246	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.39, 1.55]
13.2 Headache	2	246	Odds Ratio (M-H, Fixed, 95% CI)	4.42 [2.56, 7.65]
13.3 Jaw pain	2	246	Odds Ratio (M-H, Fixed, 95% CI)	7.80 [3.67, 16.57]
13.4 Diarrhoea	2	246	Odds Ratio (M-H, Fixed, 95% CI)	3.05 [1.62, 5.75]
13.5 Leg pain	2	246	Odds Ratio (M-H, Fixed, 95% CI)	3.53 [1.52, 8.17]
13.6 Syncope	2	246	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.08, 1.26]
13.7 Nausea	2	246	Odds Ratio (M-H, Fixed, 95% CI)	2.39 [1.28, 4.46]

Analysis 5.1. Comparison 5 Oral beraprost versus placebo, Outcome 1 Exercise capacity (metres).

Study or subgroup	Beraprost		Placebo		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI			
	N	Mean(SD)	N	Mean(SD)					
5.1.1 Primary pulmonary hypertension									
5.1.2 Pulmonary hypertension associated with scleroderma									
					Favours treatment	Favours control			
					-100	-50	0	50	100

Study or subgroup	Beraprost		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
5.1.3 Mixed population studies						
Galiè 2002	65	377 (113)	65	374 (121)		3[-37.25,43.25]
					Favours treatment	Favours control

Analysis 5.2. Comparison 5 Oral beraprost versus placebo, Outcome 2 Improvement in functional class.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
5.2.1 Idiopathic primary pulmonary hypertension					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
5.2.2 Pulmonary hypertension secondary to scleroderma					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
5.2.3 Mixed population studies					
Barst 2003	6/60	6/56		42.56%	0.93[0.28,3.06]
Galiè 2002	16/65	10/65		57.44%	1.8[0.75,4.33]
Subtotal (95% CI)	125	121		100%	1.43[0.71,2.88]
Total events: 22 (Treatment), 16 (Control)					
Heterogeneity: Tau²=0; Chi²=0.77, df=1(P=0.38); I²=0%					
Test for overall effect: Z=0.99(P=0.32)					
Total (95% CI)	125	121		100%	1.43[0.71,2.88]
Total events: 22 (Treatment), 16 (Control)					
Heterogeneity: Tau²=0; Chi²=0.77, df=1(P=0.38); I²=0%					
Test for overall effect: Z=0.99(P=0.32)					
Test for subgroup differences: Not applicable					
			Favours placebo		Favours beraprost

Analysis 5.3. Comparison 5 Oral beraprost versus placebo, Outcome 3 Mean PAP (change from baseline in mmHg).

Study or subgroup	Beraprost		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
5.3.1 Primary pulmonary hypertension							
Subtotal ***	0		0				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.3.2 Pulmonary hypertension associated with scleroderma							
Subtotal ***	0		0				Not estimable
Heterogeneity: Not applicable							
					Favours beraprost	Favours placebo

Analysis 5.4. Comparison 5 Oral beraprost versus placebo, Outcome 4 PVR (change from baseline in mmHg/L/min/m²).

Analysis 5.5. Comparison 5 Oral beraprost versus placebo, Outcome 5 Cardiac index.

Analysis 5.6. Comparison 5 Oral beraprost versus placebo, Outcome 6 Mortality.

Analysis 5.7. Comparison 5 Oral beraprost versus placebo, Outcome 7 Quality of life.

Analysis 5.8. Comparison 5 Oral beraprost versus placebo, Outcome 8 Dyspnoea score.

Analysis 5.9. Comparison 5 Oral beraprost versus placebo, Outcome 9 Clinical deterioration.

Analysis 5.10. Comparison 5 Oral beraprost versus placebo, Outcome 10 Withdrawals due to adverse events.

Analysis 5.11. Comparison 5 Oral beraprost versus placebo, Outcome 11 Cardiac Index.

Study or subgroup	Treatment		Control		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
5.11.1 Idiopathic primary pulmonary hypertension						
5.11.2 Pulmonary hypertension associated with scleroderma						
5.11.3 Mixed population studies						
Galiè 2002	65	0.2 (0.6)	65	0 (0.6)	+	0.2[-0.02,0.42]
					Favours treatment	Favours control

Analysis 5.12. Comparison 5 Oral beraprost versus placebo, Outcome 12 Exercise capacity (mean change from baseline).

Study or subgroup	Treatment		Control		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
5.12.1 Primary pulmonary hypertension							
Galiè 2002	35	23.4 (82.5)	30	-22.8 (85)		27.13%	46.2[5.32,87.08]
Subtotal ***	35		30			27.13%	46.2[5.32,87.08]
Heterogeneity: Not applicable							
Test for overall effect: Z=2.21(P=0.03)							
5.12.2 Pulmonary hypertension associated with scleroderma							
Subtotal ***	0		0				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.12.3 Mixed population studies							
Galiè 2002	30	5.7 (49.3)	37	0.6 (54.7)		72.87%	5.1[-19.85,30.05]
Subtotal ***	30		37			72.87%	5.1[-19.85,30.05]
Heterogeneity: Not applicable							
Test for overall effect: Z=0.4(P=0.69)							
Total ***	65		67			100%	16.25[-5.04,37.55]
Heterogeneity: Tau ² =0; Chi ² =2.83, df=1(P=0.09); I ² =64.65%							
Test for overall effect: Z=1.5(P=0.13)							
Test for subgroup differences: Chi ² =2.83, df=1 (P=0.09), I ² =64.65%							
					-10 -5 0 5 10		
					Favours placebo	Favours beraprost	

Analysis 5.13. Comparison 5 Oral beraprost versus placebo, Outcome 13 Side-effects (all aetiologies subgrouped by type of event).

Study or subgroup	Beraprost	Placebo	Odds Ratio		Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI			
5.13.1 Dizziness						
Barst 2003	14/60	17/56			74.5%	0.7[0.31,1.59]
Galiè 2002	5/65	5/65			25.5%	1[0.28,3.63]
Subtotal (95% CI)	125	121			100%	0.78[0.39,1.55]
			Favours beraprost	0.01 0.1 1 10 100	Favours placebo

ADDITIONAL TABLES

Table 1. NYHA functional class by study

Study ID	NYHA I (n)	NYHA II (n)	NYHA III (n)	NYHA IV (n)
Badesch 2000	0	5	87	19
Barst 1996	0	0	60	21
Rubin 1990	0	2	15	7
Thurm 1991	NA	NA	NA	NA
Simmoneau 2001	0	53	382	34
Olschewski 2002	0	0	119	84
Galiè 2002	0	64	66	0

Table 2. Safety profile - Olschewski 2002

Adverse event	Iloprost (n=101)	Placebo (n=102)	P value
Right ventricular failure + edema	4	10	0.16
Serious syncopal event	5	0	0.03
Increased cough	39	26	0.05
Headache	30	20	0.11
Flushing	27	9	0.001
Influenza-like syndrome	14	10	0.39
Peripheral edema	13	16	0.69
Nausea	13	8	0.26
Jaw pain	12	3	0.02
Hypotension	11	6	0.22
Diarrhea	9	11	0.81
Vertigo	7	11	0.46
Any syncope event	8	3	0.41

Table 3. Safety profile - Simonneau 2002

Event	Treprostinil (n=233)	Placebo (n=236)	p value
Infusion site reaction	196	62	<0.0001
Infusion site bleeding/bruising	79	102	ns
Headache	64	54	ns
Nausea	52	41	0.009
Rash	32	26	ns
Jaw pain	31	11	0.001
Vasodilation	25	11	0.01
Oedema	21	6	0.002
Dizziness	21	19	NS
Diarrhoea	58	36	0.009
Nausea	52	41	NS

Table 4. Safety profile - McLaughlin 2003

Side-effect	Treprostinil (n=17)	Placebo (n=9)	P value
Hypotension	4	0	NS
Vasovagal	0	2	NS
Bradycardia	0	2	NS
Syncope	1	3	NS
Insomnia	1	3	NS

Table 5. Safety profile - Galiè 2002

Event	B (wk 1-6)	B (wk 7-12)	PI (wk 1-6)	PI (wk 7-12)
Dizziness	5 (7.7)	0 (0.0)	5 (7.7)	2 (3.1)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Right heart failure	1 (1.5)	2 (3.1)	3 (4.6)	3 (4.6)
Headache	44 (67.7)	11 (16.9)	11 (16.9)	1 (1.5)

Table 5. Safety profile - Galiè 2002 *(Continued)*

Flushing	35 (53.8)	9 (13.8)	8 (12.3)	3 (4.6)
Jaw pain	18 (27.7)	3 (4.6)	1 (1.5)	0 (0.0)
Diarrhea	17 (26.2)	2 (3.1)	4 (6.2)	1 (1.5)
Leg pain	14 (21.5)	3 (4.6)	4 (6.2)	1 (1.5)
Nausea	13 (20.0)	4 (6.2)	3 (4.6)	2 (3.1)

WHAT'S NEW

Date	Event	Description
20 August 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 3, 2002

Date	Event	Description
5 July 2006	New search has been performed	Seven studies were retrieved from electronic literature searches which did not meet the entry criteria of the review.
3 February 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

SP wrote the protocol, EHW suggested changes. SP and TL reviewed the abstracts identified from electronic searches. SP and TL extracted and entered data. SP and TL conducted the meta-analysis. TL contacted the study investigators in order to obtain extra data. SP developed the discussion and conclusions with input from AW, and further input and approval from EHW.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- NHS Research and Development, UK.

External sources

- Garfield Weston Foundation, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [*therapeutic use]; Epoprostenol [*analogs & derivatives] [*therapeutic use]; Hypertension, Pulmonary [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans