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Prostacyclin for pulmonary arterial hypertension (Review)

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[Intervention Review]

Prostacyclin for pulmonary arterial hypertension

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ABSTRACT

Background

Pulmonary arterial hypertension (PAH) is characterised by pulmonary vascular changes, leads to elevated pulmonary artery pressures, dyspnoea, a reduction in exercise tolerance, right heart failure, and ultimately death.

Prostacyclin analogue drugs mimic endogenous prostacyclin which leads to vasodilation, inhibition of platelet aggregation, and reversal of vascular remodelling. Prostacyclin's short half-life theoretically enhances selectivity for the pulmonary vascular bed by direct (via central venous catheter) administration. Initial continuous infusion prostacyclins were efficacious, but use of intravenous access increases the risk of adverse events. Newer and safer subcutaneous, oral and inhaled preparations are now available, though possibly less potent.

Selexipag is an oral selective prostacyclin receptor (IP receptor) agonist that works similarly to prostacyclin, potentially more stable, with less complex administration and titration.

Objectives

To determine the efficacy and safety of prostacyclin, prostacyclin analogues or prostacyclin receptor agonists for PAH in adults and children.

Search methods

We performed searches on CENTRAL, MEDLINE, and Embase up to 16 September 2018. We handsearched review articles, clinical trial registries, and reference lists of retrieved articles.

Selection criteria

We included any randomised controlled trials (RCTs) which compared prostacyclin, prostacyclin analogues or prostacyclin receptor agonists to control (placebo, any other treatment or usual care) for at least six weeks.

Data collection and analysis

We used standard methods specified by Cochrane. Primary outcomes included change in World Health Organization (WHO) functional class, six-minute walk distance (6MWD), and mortality.

Main results

Seventeen trials with 3765 mostly adult participants were included; median trial duration was 12 weeks. Fifteen trials used prostacyclin analogues: intravenous (N = 4); subcutaneous (N = 1); oral (N = 5); inhaled (N = 5); two used oral prostacyclin receptor agonists. Three intravenous and two inhaled trials were open-label.

Participants using prostacyclin had 2.39 times greater odds of improving by at least one WHO functional class (95% confidence interval (CI) 1.72 to 3.32; 24 per 100 (95% CI 18.5 to 30.4) with prostacyclin compared to 12 per 100 with control; 8 trials, 1066 participants; moderate-certainty evidence). Improvement occurred with intravenous (odds ratio (OR) 14.96, 95% CI 4.76 to 47.04), and inhaled (OR 2.94, 95% CI 1.53 to 5.66), but not with oral preparations. Participants using prostacyclin increased their 6MWD by 19.50 metres (95% CI 14.82 to 24.19; 13 trials, 2283 participants; low-certainty evidence), which was clinically significant with intravenous (mean difference (MD) 91.76 metres; 95% CI 58.97 to 124.55), but not with non-intravenous preparations (subcutaneous: MD 16.00 metres, 95% CI 7.38 to 24.62; oral: MD 14.76 metres, 95% CI 7.81 to 21.70; inhaled: MD 26.97 metres, 95% CI 17.21 to 36.73). Mortality was reduced in the intravenous (OR 0.29, 95% CI 0.12 to 0.69; risk of death 6 per 100 (95% CI 2.38 to 12.31) with prostacyclin compared to 17 per 100 with control; 4 trials, 255 participants), but not in the non-intravenous studies (OR 0.82, 95% CI 0.48 to 1.40; risk of death 21 per 1000 (95% CI 12.00 to 34.20) with prostacyclin compared to 25 per 1000 with control; moderate-certainty evidence; 12 trials, 2299 participants). We reduced the certainty of evidence due to few studies per subgroup and use of open-label trials.

Prostacyclins improved cardiopulmonary haemodynamics (reduction in mean pulmonary artery pressure by 3.60 mmHg (95% CI -4.73 to -2.48); pulmonary vascular resistance by 2.81 WU (95% CI -3.80 to -1.82); right atrial pressure by 1.90 mmHg (95% CI -2.58 to -1.22), and increase in cardiac index by 0.31 L/min/m^2 (95% CI 0.23 to 0.38); low-certainty evidence), improved dyspnoea (low-certainty evidence, and improved quality of life (moderate-certainty evidence), when compared to control. When only subcutaneous/inhaled trials were included the effect was still significant, but the magnitude was smaller. There was no difference across oral trials.

Adverse events were increased in all prostacyclin preparations, including vasodilation (OR 5.03, 95% CI 3.84 to 6.58), headache (OR 3.16, 95% CI 2.62 to 3.80), jaw pain (OR 5.25, 95% CI 3.96 to 6.98), diarrhoea (OR 2.81, 95% CI 2.29 to 3.46), nausea/vomiting (OR 2.39, 95% CI 1.98 to 2.88), myalgias (OR 2.75, 95% CI 1.65 to 4.58), upper respiratory tract events (OR 1.61, 95% CI 1.22 to 2.13), extremity pain (OR 3.36, 95% CI 2.32 to 4.85), and infusion site reactions (OR 14.41, 95% CI 9.16 to 22.66). In the intravenous trials, there was a 12%-25% risk of serious non-fatal events including sepsis, haemorrhage, pneumothorax and pulmonary embolism.

Two trials (1199 participants) compared oral selexipag to placebo; no trials compared selexipag with prostacyclin. There was a small 12.62 metre improvement in 6MWD (95% CI 1.90 to 23.34; high-certainty evidence), and weak evidence for haemodynamics. The effect was uncertain for WHO functional class. The risk of death with selexipag was five per 100 compared to three per 100 with placebo, though the CI crossed zero so the true effect is uncertain (risk difference (RD) 0.02 (95% CI -0.00 to 0.04). There was less clinical worsening with selexipag (OR 0.47, 95% CI 0.37 to 0.60), though more side effects, including vasodilation (OR 2.67, 95% CI 1.72 to 4.17), headache (OR 3.91, 95% CI 3.07 to 4.98), jaw pain (OR 5.33, 95% CI 3.64 to 7.81), diarrhoea (OR 3.11, 95% CI 2.39 to 4.05), nausea/vomiting (OR 2.92, 95% CI 2.29 to 3.73), pain in the extremities (OR 2.44, 95% CI 1.69 to 3.52), and myalgias (OR 3.05, 95% CI 2.02 to 4.58).

Authors' conclusions

This review demonstrates clinical and statistical benefit for intravenous prostacyclin (compared to control) with improved functional class, 6MWD, mortality, symptoms scores, and cardiopulmonary haemodynamics, but at a cost of adverse events. This may be due to a true effect, or may be overestimated due to the inclusion of small, short or open-label studies. There was a statistical and small clinical benefit in function and haemodynamics for inhaled prostacyclin, but the effect is uncertain for mortality. The effect of oral prostacyclins are less certain. Selexipag demonstrated less clinical worsening without discernable impact on survival, increased adverse events; and the effect on other outcomes is less certain. Real-world registry data may provide further information about clinical effect.

PLAIN LANGUAGE SUMMARY

Prostacyclin in pulmonary arterial hypertension

Review question

We wanted to review whether a group of drugs called prostacyclin analogues help people with pulmonary hypertension. Cochrane researchers collected and analysed all relevant studies to answer this question.

Why this review is important

Pulmonary hypertension can cause breathlessness, reduced exercise tolerance, reduced quality of life, hospitalisations, and early death. Prostacyclin analogues may improve blood circulation in the right heart and lungs. We wanted to make sure if these drugs are being used, there is evidence of benefit and little or no harm.

Main findings

We found and included 17 trials with 3765 people. Most of the studies were 12 weeks long. Some trials were as long as 52 weeks. Most trials involved adults. People who were given prostacyclin analogues were compared to people who were not given prostacyclin. People in four trials were given the drugs by a continuous drip (24 hours/day) into a vein (intravenous) and in one trial through continuous injection under the skin (subcutaneous). In five trials people inhaled the drugs through a nebuliser and in five trials they took tablets (oral). People in two studies took selexipag tablets. Selexipag is an agonist of the prostacyclin receptor and the trials in selexipag were analysed separately.

People who were given prostacyclins via intravenous drip showed improved survival (a lower chance of dying). They could also walk on average 92 metres further in six minutes than people not given the prostacyclin drip. They were also more likely to improve their functional class (what you can and cannot do on a daily basis). People with intravenous prostacyclins had better heart function on average than those who had no treatment.

Overall, the results were less clear for people given oral, inhaled or subcutaneous prostacyclins. It was not clear whether giving the drug in these ways led to improved survival. People who took inhaled (nebuliser) prostacyclins improved their functional class, walked on average 27 metres further in six minutes, and had better heart function. There was also some evidence that subcutaneous prostacyclins improved heart function. It was not clear if taking tablets improved functional class or heart function. People receiving this treatment only walked 15 metres further in six minutes than those not receiving prostacyclin tablets.

Whilst this review found evidence was best for prostacyclin via continuous drip, it may be inconvenient, and might increase risks such as intravenous line-related infections. Furthermore almost all people taking recommended doses in any form have important drug-related side effects (including flushing, headache, jaw pain, diarrhoea, pain in their extremities, upper respiratory tract side effects, nausea and vomiting).

People taking selexipag had less clinical worsening, and a small 13-metre difference in their six-minute walk test compared to people taking placebo. People who used selexipag were also more likely to have side effects including flushing, jaw pain, diarrhoea, nausea/vomiting, and pain in the muscles/extremities.

Limitations

There is moderate-certainty evidence that prostacyclin helps people compared to those who do not use it. The benefit is best for those who receive the drug via a continuous drip, but the risks are higher. Also, on average, the studies only lasted three months (some up to 1 year), and this may not be enough time to see benefit or risks.

This review only looked at those with a diagnosis of pulmonary arterial hypertension, not those with pulmonary hypertension associated with left heart disease, lung disease, or pulmonary hypertension due to blood clots.

This review is current to September 2018.

Summary of findings for the main comparison. Prostacyclin compared to control for pulmonary arterial hypertension

Prostacyclin compared to control for pulmonary arterial hypertension

Patient or population: pulmonary arterial hypertension
Setting: outpatients
Intervention: prostacyclin
Comparison: control (placebo or usual care)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with control	Risk with prostacyclin				
Improvement in WHO functional class Mean follow-up 16 weeks	Study population 116 per 1000	239 per 1000 (185 to 304)	OR 2.39 (1.72 to 3.32)	1066 (8 RCTs)	⊕⊕⊕⊖ Moderate[1]	
6MWD Mean follow-up 15 weeks	The mean 6MWD was 257 m*	MD 19.50 m higher (14.82 higher to 24.19 higher)	-	2283 (13 RCTs)	⊕⊕⊖⊖ Low[1,2]	6MWD in PAH MCID is 41 m
Mortality Mean follow-up 15 weeks	Study population 39 per 1000	24 per 1000 (15 to 37)	OR 0.60 (0.38 to 0.94)	2554 (15 RCTs)	⊕⊕⊕⊖ Moderate[1]	
mPAP (the higher the mPAP, the worse the pulmonary hypertension) Mean follow-up 11 weeks	The mPAP ranged from 56 to 66 mmHg#	MD 3.60 mmHg lower (4.73 lower to 2.48 lower)	-	1132 (8 RCTs)	⊕⊕⊖⊖ Low[1,2]	
PVR (the higher the PVR, the worse the pulmonary hypertension) Mean follow-up 11 weeks	The mean PVR ranged from 26 to 29 units/m^2#	MD 2.81 WU lower (3.80 lower to 1.82 lower)	-	658 (7 RCTs)	⊕⊕⊕⊖ Moderate[1]	

Cardiac index (the lower the cardiac index, the worse the pulmonary hypertension) Mean follow-up 11 weeks	The mean cardiac Index ranged from 2 to 2.4 L/min/m$^{2\#}$	MD 0.31 L/min/m 2 higher (0.23 higher to 0.38 higher)	-	868 (6 RCTs)	⊕⊕⊖⊖ Low[1,2]	
RAP (the lower the RAP, the worse the pulmonary hypertension) Mean follow-up 11 weeks	The mean RAP ranged from 8 to 13 mmHg$^{\#}$	MD 1.90 mmHg lower (2.58 lower to 1.22 lower)	-	1060 (6 RCTs)	⊕⊕⊕⊖ Moderate[1]	The higher the RAP, the worse the pulmonary hypertension
Dyspnoea (lower scores indicates more severe breathlessness) Mean follow-up 17 weeks	-	SMD 0.21 lower (0.32 lower to 0.11 lower)	-	1521 (8 RCTs)	⊕⊕⊖⊖ Low[1,2]	Using an illustrative SD, this converts to a difference of 0.64 units on the Borg scale. MCID in PAH is 0.9 units
Quality of life Mean follow-up 12 weeks	-	SMD 0.28 better (0.04 better to 0.42 better)	-	271 (3 RCTs)	⊕⊕⊕⊖ Moderate[1]	
Headache^{+} Mean follow-up 12 weeks	277 per 1000	529 per 1000 (95% CI 501 to 593)	3.16 (2.62 to 3.80)	2351 (12 RCTs)	⊕⊕⊕⊖ Moderate[2]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

6MWD: six-minute walk distance; **CI:** confidence interval; **MCID:** minimum clinically important difference; **MD:** mean difference; **OR:** odds ratio; **PAH:** pulmonary arterial hypertension; **mPAP:** mean pulmonary arterial pressure; **PVR:** pulmonary vascular resistance; **RAP:** right atrial pressure; **RCT:** randomised controlled trials; **SD:** standard deviation; **SMD:** standardised mean difference; **WHO:** World Health Organization

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

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

[1]Downgraded due to the risk of bias with open-label studies.
[2]Downgraded due to imprecision owing to significantly high heterogeneity, although the direction of effect is consistent.
*based on only one study which published placebo data; all other studies reported a mean difference between groups.
#based on baseline data; all other studies reported a mean difference between groups.
+This was chosen as the most commonly experienced adverse event.

Summary of findings 2. Selexipag compared to placebo for pulmonary arterial hypertension

Selexipag compared to placebo for pulmonary arterial hypertension

Patient or population: pulmonary arterial hypertension
Setting: outpatients
Intervention: selexipag
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with placebo	Risk with selexipag				
Improvement in WHO functional class Mean follow-up 17 weeks	Study population 100 per 1000	152 per 1000 (19 to 635)	OR 1.61 (0.17 to 15.63)	43 (1 RCT)	⊕⊕⊕⊖ Moderate[1]	
6MWD Mean follow-up 40 weeks	The mean 6MWD ranged from 348 to 396 m	MD 12.62 m higher (1.90 higher to 23.34 higher)	-	1199 (2 RCTs)	⊕⊕⊕⊕ High	6MWD in PAH MCID is 41 m
Mortality Mean follow-up 40 weeks	Study population 30 per 1000	48 per 1000 (27 to 84)	**Risk difference** 0.02 (-0.00 to 0.04)	1199 (2 RCTs)	⊕⊕⊕⊖ Moderate[1]	
mPAP the higher the mPAP, the worse the pulmonary hypertension) Mean follow-up 17 weeks	The mPAP was 60 mmHg	MD 7.4 mmHg lower (15.9 lower to 1.1 higher)	-	43 (1 RCT)	⊕⊕⊕⊖ Moderate[2]	
PVR	The mean PVR was 1687 dyn/sec/m^2	MD 33 dyn/sec/m^2 lower (47 lower to 19 lower)	-	43 (1 RCT)	⊕⊕⊕⊖ Moderate[2]	

(the higher the PVR, the worse the pulmonary hypertension) Mean follow-up 17 weeks						
Cardiac index (the lower the cardiac index, the worse the pulmonary hypertension) Mean follow-up 17 weeks	The mean cardiac index was 2.3 L/min/m^2	MD 0.5 L/min/m^2 higher (0.13 higher to 0.87 higher)	-	43 (1 RCT)	⊕⊕⊕⊖ Moderate[2]	
RAP (the lower the RAP, the worse the pulmonary hypertension) Mean follow-up 17 weeks	The mean RAP was 8.3 mmHg	MD 3.2 mmHg higher (0.8 higher to 5.6 higher)	-	43 (1 RCT)	⊕⊕⊕⊖ Moderate[2]	
Dyspnoea (lower scores indicates more severe breathlessness) Mean follow-up 17 weeks	-	MD 0.1 lower (1.4 lower to 1.2 higher)	-	43 (1 RCT)	⊕⊕⊕⊖ Moderate[1]	MCID in PAH is 0.9 units
Headache[+] Mean follow-up 40 weeks	Study population 325 per 1000	 653 per 1000	3.91 (3.07 to 4.98)	1199 (2 RCTs)	⊕⊕⊕⊕ High	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

6MWD: six-minute walk distance; **CI:** confidence interval; **MCID:** minimum clinically important difference; **MD:** mean difference; **OR:** odds ratio; **PAH:** pulmonary arterial hypertension; **mPAP:** mean pulmonary arterial pressure; **PVR:** pulmonary vascular resistance; **RAP:** right atrial pressure; **RCT:** randomised controlled trials; **RR: r**isk ratio; **SD:** standard deviation; **WHO:** World Health Organization

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

[1]Downgraded due to imprecision with confidence intervals including no difference.
[2]Downgraded due to imprecision owing to small participant numbers in one trial.
[+]This was chosen as the most commonly experienced adverse event.

BACKGROUND

Description of the condition

Pulmonary hypertension is defined as a mean pulmonary arterial pressure (mPAP) exceeding 25 mmHg measured by right heart catheterisation (Galiè 2016). More than 50 diseases across five main categories (World Health Organization (WHO) type 1 to 5) are reported as potential aetiologies (Simonneau 2013). Many cause progressive disease, with associated right ventricular strain, hypertrophy, remodelling within the pulmonary vasculature and premature death. In the later stages of the disease, cardiopulmonary dysfunction leads to burdensome symptoms, such as exercise intolerance, syncope, oedema and breathlessness. The development of several specific therapies for WHO Group 1 pulmonary arterial hypertension (PAH) has led to heightened interest in the condition. Unfortunately, most people presenting with PAH have progressed to advanced disease at the time of specialist referral (Humbert 2006; Thenappan 2007); and the true prevalence of pulmonary hypertension is likely under-recognised (Galiè 2016). Modern therapies have reduced morbidity and improved survival (Thenappan 2007); however the risks and side effects warrant their careful selection. Prostaglandins have an unusual spectrum of side effects and almost all patients on an effective dose will have significant prostaglandin-related side effects.

The WHO classification system for pulmonary hypertension is widely used, grouping disorders based on underlying mechanisms (Simonneau 2013). This provides a framework for treatment, as pathophysiology varies greatly between groups. Group 1 comprises PAH, formerly termed "primary pulmonary hypertension", which refers to precapillary flow obstruction, independent of venous thromboembolism or hypoxaemic lung disease (Badesch 2009). PAH is a rare disease, with an estimated prevalence of 10 to 52 cases per million (Ling 2012; Peacock 2007).

The gold standard diagnostic tool in pulmonary hypertension is right heart catheterisation, which determines a diagnosis of pulmonary hypertension, and further characterises the aetiology according to the WHO classification (Galiè 2016). PAH is determined as pulmonary hypertension (mean pulmonary arterial pressure (mPAP) equal to or higher than 25 mmHg) with a normal back pressure from the heart (a pulmonary arterial wedge pressure equal to or less than 15 mmHg) and a pulmonary vascular resistance (PVR) more than 3 Wood units measured during right heart catheterisation. A pulmonary arterial wedge pressure higher than 15 mmHg indicates contributing left heart dysfunction. Other baseline evaluation includes high-resolution computed tomography (HRCT) and ventilation–perfusion (VQ) scanning to rule out other causes (non-WHO Group 1); and exercise testing such as six-minute walk distance (6MWD) (Galiè 2016) for baseline evaluation and prognostication.

Beyond confirmation of the diagnosis, right heart catheterisation and other baseline tests assist to stratify risk of progression which assists in directing treatment. Goals of therapy are relief of symptoms, improved exercise capacity, improved quality of life, arresting progression and reducing mortality. People with PAH often respond to disease-specific modifying therapies, including calcium channel blockers, prostacyclin analogues, endothelin receptor antagonists and phosphodiesterase-5 inhibitors. In contrast, indications for advanced therapies in other groups of pulmonary hypertension are less clear cut and treatment of underlying conditions is first line (Galiè 2016).

Description of the intervention

Prostacyclin is endogenously synthesised by endothelial cells using the cyclo-oxygenase arachidonic pathway. Prostacyclin exerts vasodilatory, antithrombotic and antiproliferative effects that are essential for endothelial function (Mitchell 2014). The principal target of prostacyclin is the IP G protein-coupled receptor in the smooth muscle of arterioles. Its activation triggers intracellular cyclic adenosine monophosphate formation, activating protein kinase A, which mediates vasodilation of the pulmonary arteries, inhibition of platelet aggregation, and relaxation of the smooth muscle (Humbert 2015). Disequilibrium between vasodilating mediators, such as a reduction in the normal release of prostacyclin, and increased release of vasoconstricting mediators, such as thromboxane A2, plays a causative role in PAH (Christman 1992; Sitbon 2016). Currently there are three prostacyclin analogues available - epoprostenol, iloprost and treprostinil. Selexipag is a selective IP prostacyclin receptor agonist that is structurally distinct from prostacyclin. It is rapidly hydrolysed to a long-acting metabolite that binds to IP receptors, resulting in the same actions as prostacyclin - vasodilation, inhibition of platelet aggregation, and anti-inflammatory effects (Noel 2017).

How the intervention might work

Epoprostenol directly vasodilates the pulmonary and systemic arterial vasculature, and has been demonstrated in previous trials to reduce ventricular afterload, pulmonary vascular resistance (PVR) and platelet aggregation, and to increase cardiac output (Sitbon 2016).

The key attributes of synthetic prostacyclin agents are prostacyclin's short half-life at room temperature (minutes) and that it mainly only exerts local effects (Mitchell 2014). The first synthetic agent (epoprostenol) demonstrated significant efficacy as a therapeutic agent in the improvement of haemodynamic parameters, exercise capacity, and mortality (Barst 1996). However it is not without drawbacks. Its short half-life requires continuous intravenous infusion, via a central venous catheter and continuous pump, requiring central line placement, and potentially introducing the risk of central line-associated blood stream infection (Kallen 2008). Initial preparations were required to be refrigerated or kept on ice; however newer preparations have a more stable half-life of 24 hours (Sitbon 2012).

Iloprost is a prostacyclin analogue that is most frequently used via inhalation. It has a slightly longer half-life of 20 to 30 minutes, but still requires 5 to 10 inhalation doses throughout the day. Treprostinil has a much more stable half-life of four hours, and can be administrated at much lower infusion rates via a subcutaneous or intravenous pump (Tapson 2006). However, treprostinil is metabolised by cytochrome P450 (CYP)2C8 in the liver and its metabolites are renally excreted, so clearance may be affected by hepatic impairment. Cumulative effects of treprostinil can occur if used with antihypertensives or anticoagulants (Simonneau 2002).

Beraprost is also available as an orally active prostacyclin analogue, theorised to maintain a stable structure due to its cyclopenta benzofuranyl skeleton. It acts by binding to prostacyclin membrane

receptors to inhibit the release of calcium, leading to relaxation of smooth muscle cells and vasodilation, and inhibiting platelet aggregation. Given three times a day, it has previously exhibited improved outcomes in those with intermittent claudication due to peripheral arterial disease (Melian 2002).

For all prostacyclin agents, dose titration is individualised according to the individual patient. A characteristic pattern of adverse effects, particularly systemic hypotension, but also including flushing, diarrhoea, and muscle pains (Barst 1996; Sitbon 2016), may limit dose escalation. Indeed the dose is often up-titrated until side effects are evident. This makes patient and investigator concealment (blinding) somewhat problematic in clinical trials. The method of delivery and the drug itself are expensive. Furthermore, therapy must be continuous, as abrupt withdrawal may precipitate rebound pulmonary hypertension, which can be fatal.

Selexipag is an oral selective prostacyclin receptor (IP receptor) agonist that works similarly to prostacyclin. It is postulated that the density of prostacyclin receptors varies between patients, therefore requiring complex personally tailored dosing of prostacyclin analogues, however, clinical trials in selexipag indicates patients respond similarly to the low-, medium- and high-dose regiments, therefore it offers a potentially more stable drug, with less complex administration and titration (GRIPHON).

Why it is important to do this review

Evidence in the literature suggests that prostacyclin analogues are efficacious in the treatment of PAH; however the treatment may come with considerable risks and side effects. The purpose of this review is to summarise the available published data regarding the relative efficacy and safety of prostacyclin analogues, in particular on haemodynamic response, and on participant-centred outcomes, such as exercise tolerance, adverse effects, and quality of life.

Unfortunately, patients with PAH usually have advanced disease at presentation. Early diagnosis and management of this progressive condition offers a greater scope to delay or prevent onset of end-stage symptoms. Recognising the presence of pulmonary hypertension as well as the underlying cause allows early initiation of appropriate treatment and potentially avoidance of end-stage disease states.

OBJECTIVES

To determine the efficacy and safety of prostacyclin, prostacyclin analogues or prostacyclin receptor agonists, compared to placebo or any other treatment, for pulmonary arterial hypertension (PAH) in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

We included any randomised controlled trials (RCTs) which compared prostacyclin or analogues to control (placebo, any other treatment or usual care) for at least six weeks. We defined 'randomised' as studies which are described by the author as 'randomised' anywhere in the manuscript. All defined trials, published or unpublished, in any language, were potentially eligible for inclusion.

Types of participants

We included any individual with a diagnosis of World Health Organization (WHO) Group 1 pulmonary hypertension, referred to as pulmonary arterial hypertension (PAH), as per the present definition of a mean pulmonary arterial pressure (mPAP) higher than 25 mmHg by right heart catheterisation (Galiè 2016). We did not include other WHO diagnostic groups (2 to 5) of pulmonary hypertension. We planned to specify subgroups of adults older than 18 years and a paediatric population younger than 18 years, however, no trials reported separate outcome data or individual patient data to make these subgroup comparisons.

Types of interventions

We included studies comparing any type of prostacyclin treatment by any route of administration with placebo or any other treatment for at least six weeks. This included, but was not limited to, prostaglandins, epoprostenol, iloprost, beraprost, treprostinil, prostacyclin receptor agonist and selexipag, via the intravenous, subcutaneous, inhaled, and oral route. We separated comparisons into prostacyclin versus control and selexipag versus control. We included studies with co-interventions, provided they were not part of the randomised treatment, by any route of administration, with placebo or any other treatment used for pulmonary hypertension. Where multiple doses were used, we planned to perform subgroup analyses by dose, however, in the included studies, doses were titrated per individual participant. Where studies were too heterogeneous for meta-analyses, or where only descriptive data were available, we described them in narrative form.

Types of outcome measures

Primary outcomes

1. Change in WHO or New York Heart Association (NYHA) functional class (Badesch 2009)
2. Six-minute walk distance (6MWD) test (Badesch 2009)
3. Mortality

Secondary outcomes

1. Cardiopulmonary haemodynamics: including mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), cardiac index, cardiac output, systemic arterial oxygen saturation and systemic oxygen transport
2. Exercise capacity tests other than 6MWD test
3. Symptom scales: Borg dyspnoea score (Badesch 2009), dyspnoea-fatigue ratings (Badesch 2009)
4. Quality of life
5. Clinical worsening
6. Adverse events
7. Cost analysis

Reporting of one or more outcomes was not a criterion for inclusion of a study in the review. We only included trials which have treated participants for at least six weeks. We did not find any studies which reported multiple time points, nor did we find any studies which reported post-intervention follow-up separate to the initial trial results. We are aware that some included trials may use composite

outcomes. Where these were presented, we re-analysed data to report only outcomes specified above.

Search methods for identification of studies

Electronic searches

We identified studies from searches of the following databases up to 16 September 2018.

1. Cochrane Airways Register of Trials through the Cochrane Register of Studies (CRS Web).
2. Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies (CRS Web).
3. MEDLINE Ovid SP 1946 to 16 September 2018.
4. Embase Ovid SP 1974 to 16 September 2018.

In addition, we searched the CENTRAL database in the Cochrane Library for conference abstracts and grey literature. The database search strategies are listed in Appendix 1. We did not apply any restrictions for language, date or type of publication.

We also searched the following trials registries for additional trials for inclusion and for additional data for included trials.

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.ClinicalTrials.gov).
2. World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch).

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We handsearched reference lists of included studies, relevant chapters and review articles. We used Google to search for grey literature and conference abstracts. We planned to translate any relevant article into English for potential inclusion, however we did not identify any other language papers. Where data were missing, we checked on trial registries and attempted to contact the trial investigators. We searched for errata or retractions from included studies published in full text on PubMed and reported the date this was done within the review.

Data collection and analysis

Selection of studies

Two independent review authors (HB, HLY) independently screened all abstracts to determine if they met the accepted inclusion criteria using Covidence. We obtained full-text publications for those papers which definitely or may meet inclusion criteria. Two independent review authors (HB, HLY) then reviewed all full-text articles to determine eligibility, and recorded reasons for any that are ineligible. We resolved any concerns or disagreement through discussion with other review authors (AB, TW, MH). We included a PRISMA study flow diagram in the full review to document the screening process and included a 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

Two review authors (HB and HLY) independently extracted data from included studies, and where appropriate, pooled data in Cochrane's statistical software Review Manager 5 (RevMan 5) (Review Manager 2014), for further analysis. Following, both review authors met to check consistency of data entered into RevMan 5 prior to meta-analyses being performed. The Cochrane Airways group methodologist (Christopher Cates) assisted with generic inverse variance analysis. We planned to resolve disagreements by consensus or by involving a third review author (AB). We used a data collection form which was piloted for inclusion in the review, containing the following data.

- Methods: study design, duration, study setting, date of study
- Participants: number, mean age and age range, gender, inclusion and exclusion criteria, and differences in baseline characteristics
- Intervention: type of prostacyclin analogue, dose, mode of administration, control drug, co-interventions and exclusions
- Outcomes: primary and secondary outcomes as specified, type of scale used, time points collected
- 'Risk of bias' summary
- Other: funding for trial, any conflicts of interest for trial authors

Assessment of risk of bias in included studies

Two independent authors (HB, HLY) assessed the included studies for risk of bias using Cochrane's tool for assessment of risk of bias according to the following domains (Higgins 2011).

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other bias

We judged each potential source of bias as low, unclear risk (insufficient information to form a judgement), or high risk, and provided justification with evidence from each trial in the 'Risk of bias' table. When considering treatment effects, we took into account the risk of bias for the studies that contribute to that outcome. We provided a quote from the study report together with justification for our judgement in the 'Risk of bias' table.

Assessment of bias in conducting the systematic review

We conducted the review according to our previously published protocol and justified any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

Where possible, we pooled and presented results from dichotomous data as odds ratios (ORs). Where zero totals were obtained, we presented these data as risk differences (RDs). Where possible, we presented results from continuous variables using a fixed-effect model and calculated the mean differences (MDs) or standardised mean differences (SMDs) where scales are combined, with the 95% confidence intervals (95% CIs). If data from rating scales are combined in a meta-analysis, we ensured that they are entered with a consistent direction of effect (e.g. lower scores always indicate improvement). Where both change from baseline and endpoint scores were available for continuous data, we used change from baseline scores where possible. We only combined data reported at different time points if this is clinically

appropriate. We described skewed data narratively (e.g. as medians and interquartile ranges for each group).

We used intention-to-treat or 'full analysis set' analyses where they are reported (i.e. those where data have been imputed for participants who were randomly assigned but did not complete the study) instead of 'completer' or 'per-protocol' analyses.

Unit of analysis issues

For dichotomous outcomes, we used participants, rather than events, as the unit of analysis (i.e. number of children admitted to hospital, rather than number of admissions per child). However, where rate ratios are reported in a study, we analysed them on this basis. No cluster-randomised trials were included, however if cluster-randomised trials are included in future versions of the review, we will only use data which has been, or can be, adjusted to account for the clustering.

Dealing with missing data

We contacted investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. Han 2017 to obtain individual data). Where this was not possible, and the missing data are thought to introduce serious bias, we took this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

For pooled analyses, we quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across trials due to heterogeneity rather than sampling error. Significant statistical heterogeneity was considered to be present if the I^2 is greater than 50%. Where significant heterogeneity was identified, we planned to explore possible causes using prespecified subgroup analyses.

Assessment of reporting biases

We were unable to pool more than 10 studies using the same intervention, so we did not explore further possible small-study and publication biases as stated a priori.

Data synthesis

We performed pooled quantitative meta-analysis where trials were considered clinically homogenous. We used a fixed-effect model to synthesise and report mean difference (MD) and 95% CIs. We synthesised and report dichotomous and continuous data separately for each outcome.

Where there was substantial heterogeneity (> 50%), we also reported outcomes in the text, including the direction and size of the effect along with the strength of the evidence (risk of bias).

'Summary of findings' table

We created a 'Summary of findings' table using the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* along with GRADEPro GDT software (GRADEpro GDT; Higgins 2011). The outcomes included:

- WHO functional class status;
- mortality;
- change in haemodynamics;
- 6MWD;
- dyspnoea;
- quality of life;
- adverse events.

We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We justified all decisions to downgrade the quality of studies using footnotes and made comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses comparing the different routes of administration, and presented these results under each outcome. We planned to compare different prostacyclin analogues, but assessed there were too few studies (one to two per type) to draw meaningful comparisons. We planned to compare children versus adults, but separate data were not available. We planned to compare the effect of WHO functional class at baseline, however almost all trials included functional class III/IV.

Sensitivity analysis

We included a fixed-effect versus random-effect sensitivity analysis in a tabular format.

We included open-label versus blinded trials sensitivity analysis under each per-protocol specified outcomes (functional class, 6MWD, mortality, and cardiopulmonary haemodynamics).

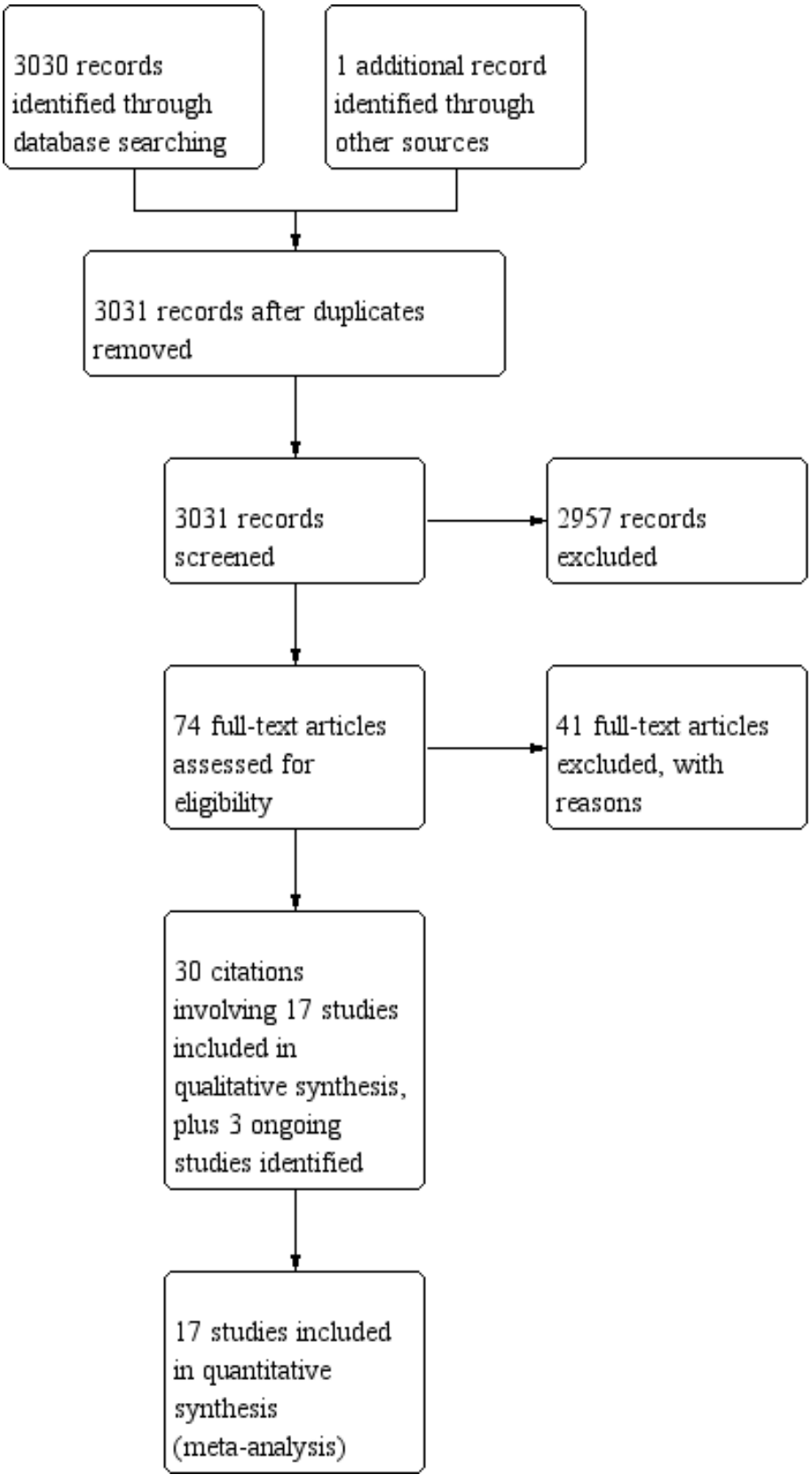
RESULTS

Description of studies

Results of the search

We identified 3031 citations in the initial search as described in the methods, and after two review authors (HB and HLY) independently screened abstracts, we selected 74 articles for full-text review. After further assessment, we included 17 trials with 3765 participants in the final meta-analysis, which included 30 separate citations (see Figure 1). We also noted three ongoing studies (see Characteristics of ongoing studies). The search was run on 16 September 2018.

Figure 1. Study flow diagram



Included studies

We included 17 trials with 3765 participants in the final meta-analysis (see Characteristics of included studies; Table 1). All included studies were randomised, parallel-group trials involving people with World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH) (confirmed on right heart catheterisation). Five studies were open-label (Badesch 2000; Barst 1996; Han 2017; Olschewski 2010; Rubin 1990), where participants were randomised to prostacyclin or conventional treatment.

Fifteen trials compared a prostacyclin analogue with placebo/conventional treatment, and two trials compared selexipag (an oral selective IP prostacyclin receptor agonist) to placebo (GRIPHON; Simonneau 2012).

In those trials which studied prostacyclin, three used intravenous epoprostenol (Badesch 2000; Barst 1996; Rubin 1990), and one used intravenous treprostinil (TRUST). All of these studies recruited mostly or exclusively NYHA functional class III and IV. Three studies were open-label (Badesch 2000; Barst 1996; Rubin 1990), and one was placebo-controlled (TRUST). Badesch 2000 recruited people with scleroderma-associated PAH, and all other trials recruited people with Group 1 PAH.

One trial used subcutaneous treprostinil compared to placebo (Simonneau 2002). Most (80%) participants were functional class III, and 10% were functional class II and 10% functional class IV.

Five trials used oral prostacyclin compared to placebo, including treprostinil (FREEDOM-C; FREEDOM-C2; FREEDOM-M), and beraprost (ALPHABET; Barst 2003). In the FREEDOM studies, the participants were mostly functional class III, but in Barst 2003 50% were functional class II and 50% functional class III.

Five trials used inhaled preparations, including iloprost (AIR; Han 2017; McLaughlin 2006; Olschewski 2010), and treprostinil (TRIUMPH). Participants were all functional class III/IV.

Prostacyclin in any form is usually up-titrated in a dose-dependent manner, initially limited by side effects, but as the patient develops tolerance the dose is able to be increased. In most studies, both the intervention and control group were given opportunity to up-titrate, and final doses in each group were provided.

Some trials enrolled participants already on PAH-specific disease modifying therapy (PDE-5 inhibitor or ERA) (AIR; FREEDOM-C; FREEDOM-C2; McLaughlin 2006; Simonneau 2002; Simonneau 2012; TRIUMPH), but some trials specifically excluded these participants and studied prostacyclin as initial therapy (FREEDOM-M; GRIPHON).

Trial duration was a mean of 19 weeks (median 12 weeks), and most included an initial titration phase, prior to commencement.

Excluded studies

We excluded 41 studies for the following reasons: wrong study design (n = 24); wrong participant population (n = 2); duration of study did not meet prespecified criteria (n = 6); study was withdrawn before participants were enrolled (n = 4); wrong intervention (compared different doses or delivery devices) (n = 5); see Characteristics of excluded studies.

Risk of bias in included studies

We assessed risk of bias in the included studies using the Cochrane 'Risk of bias' assessment tool (Higgins 2011), including the domains of allocation, blinding, incomplete outcome data, and selective reporting. Please see Figure 2 and Figure 3 for a summary of the 'Risk of bias' findings.

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

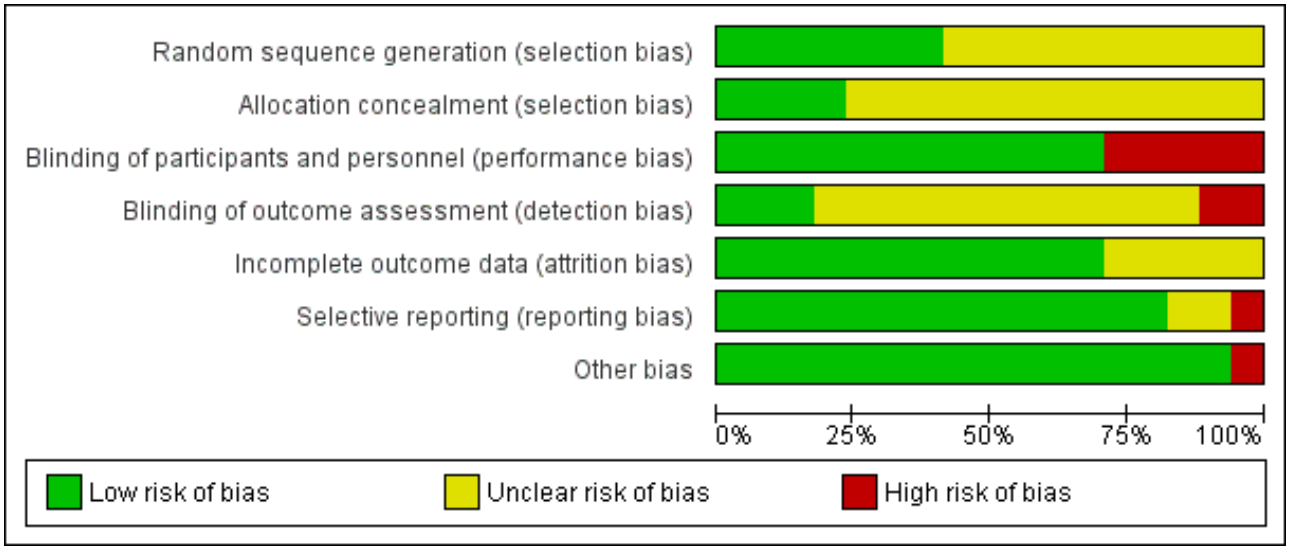
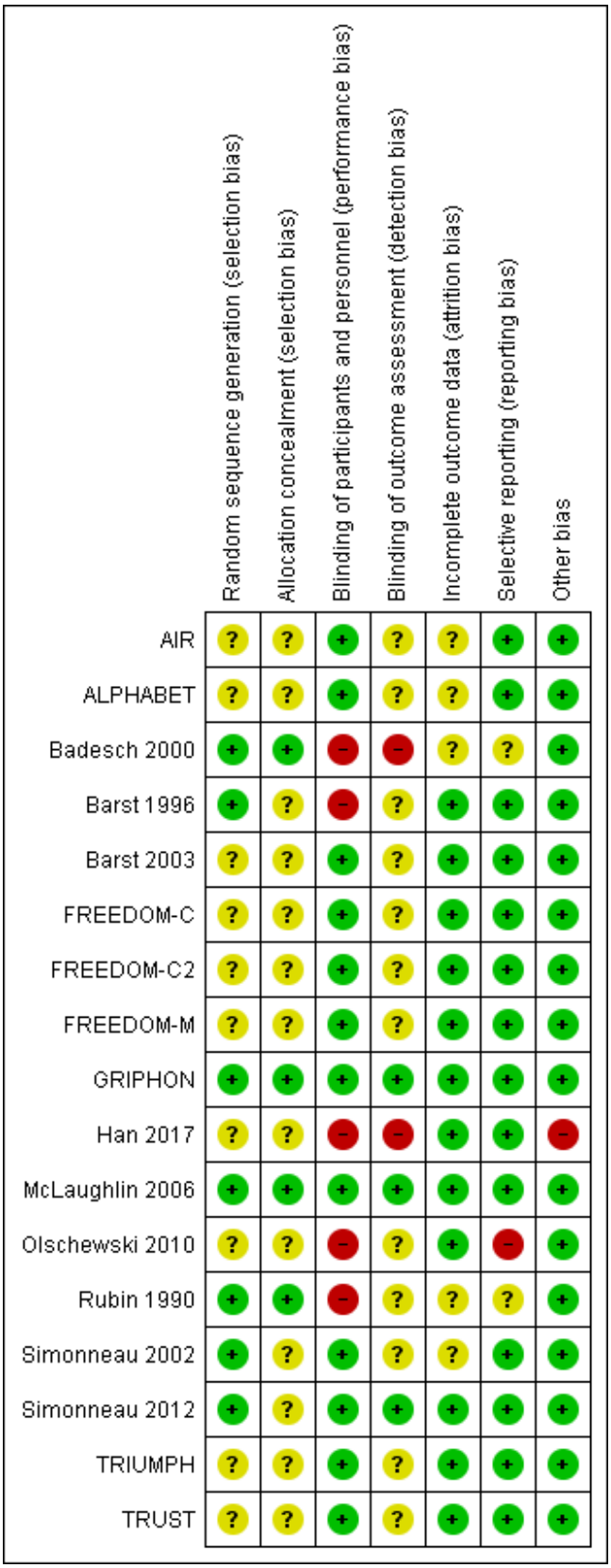


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Although all studies were reported as randomised, few studies reported methods of randomisation or allocation concealment. Badesch 2000, GRIPHON, McLaughlin 2006 and Rubin 1990 clearly reported both domains, and Barst 1996, Simonneau 2002 and Simonneau 2012 clearly reported methods of randomisation and we judged them to be at low risk of bias. All other studies were probably randomised appropriately, but methods were not clearly stated.

Blinding

Twelve studies were placebo-controlled (judged to be at low risk of bias) and five studies were open-label (Badesch 2000; Barst 1996; Han 2017; Olschewski 2010; Rubin 1990), with participants randomised to an intervention group or conventional treatment. We judged the latter to be at high risk of bias.

In those with a placebo arm, saline infusions or inhalational preparations were utilised. In TRUST, a central venous catheter was placed in participants from both arms of the study. Given this was an up-titration study, most studies (except FREEDOM-M and TRUST), reported the final cumulative prostacyclin and equivalent placebo doses, as a method to confirm blinding. We noted in FREEDOM-C, FREEDOM-C2 and Simonneau 2002, the placebo dose was twice as high as the prostacyclin cumulative dose.

Blinding of outcome assessment was only explicitly reported in three studies (GRIPHON; McLaughlin 2006; Simonneau 2012), which we judged to be at low risk of bias. Simonneau 2002 explicitly reported blinding for six-minute walk distance (6MWD) only. Outcome assessment for other placebo-controlled studies were probably blinded, but methods were not clearly stated, and so we assigned these studies an unclear risk in this domain.

Incomplete outcome data

AIR, ALPHABET, Badesch 2000, Rubin 1990, and Simonneau 2002 did not report dropouts or withdrawals, so we judged these to be at unclear risk of bias. The remaining studies were at low risk of bias.

Selective reporting

Rubin 1990 reported data as post-treatment scores but reported confidence intervals (CIs) for the mean difference (MD). Badesch 2000 did not report CIs or error bars for some reported outcomes. Olschewski 2010 randomised participants to inhaled prostacyclin or conventional treatment for three months, at which point all participants were on prostacyclin, and then reported results at the end of two years. We assessed selective reporting bias as low risk for all other studies.

Other potential sources of bias

We assessed Han 2017 as a high risk of bias as analysis reported as standard deviation (SD) were re-analysed using individual patient data as standard error. It is unclear if there are other methodological issues with this paper. No other issues were identified for the remaining studies.

Effects of interventions

See: **Summary of findings for the main comparison** Prostacyclin compared to control for pulmonary arterial hypertension; **Summary of findings 2** Selexipag compared to placebo for pulmonary arterial hypertension

Prostacyclin versus control

Change in World Health Organization (WHO) functional class

Those who were using prostacyclin were more likely to improve their WHO functional class (239 per 1000) compared to those who did not (116 per 1000); (odds ratio (OR) 2.39, 95% confidence interval (CI) 1.72 to 3.32; P < 0.00001; 8 trials, 1066 participants; Analysis 1.1). Using the Chi^2 test for subgroup differences, there was a significant difference between route of administration (P = 0.0003), with the greatest effect seen in the intravenous prostacyclin arm.

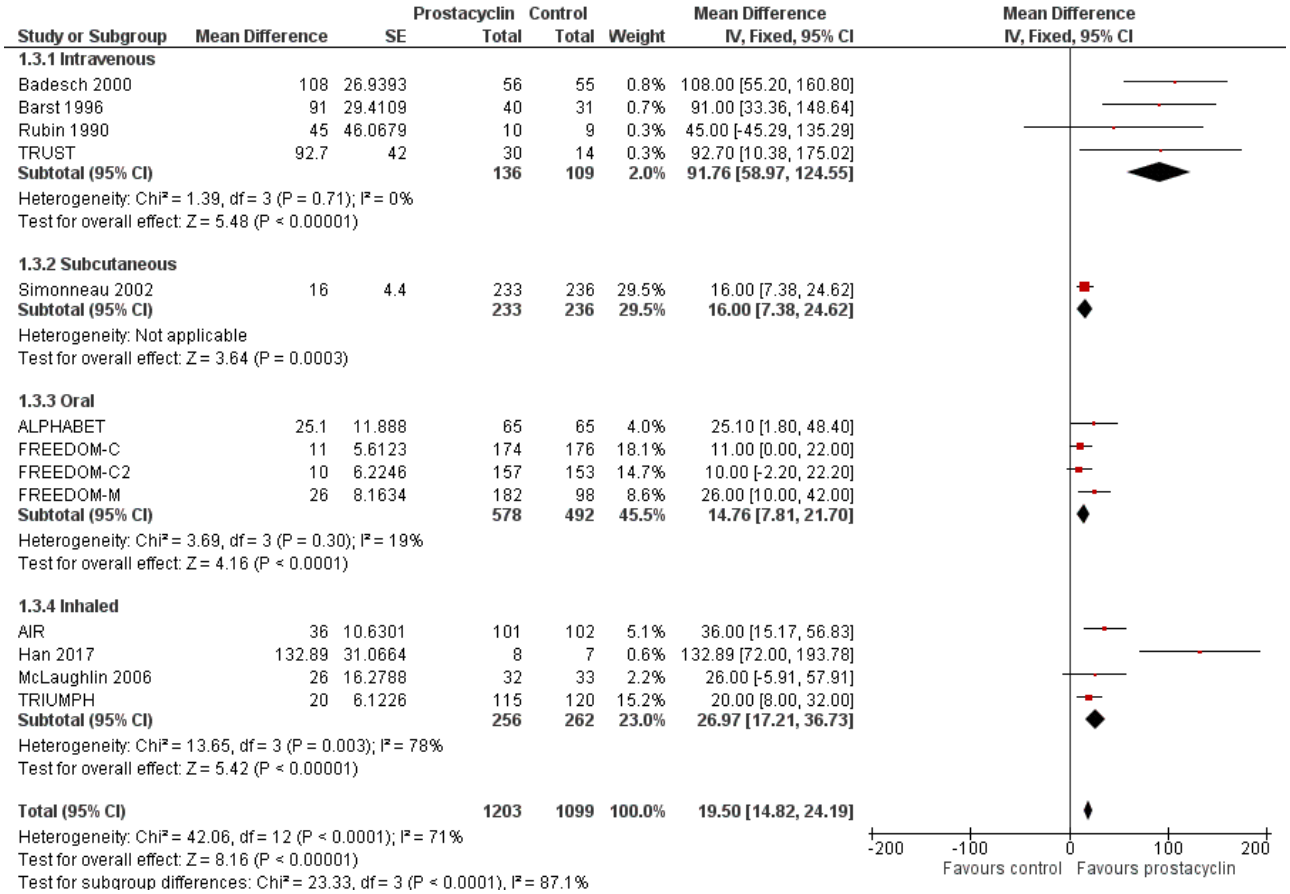
When excluding open-label trials, there was still a significant difference, though the effect size was smaller: OR 2.39 (95% CI 1.72 to 3.32) for all trials compared to OR 1.77 (95% CI 1.24 to 2.52) when open-label trials were excluded, and there was no significant difference between fixed- and random-effects (see Table 2; Table 3). A post hoc sensitivity analysis was carried out whereby the TRUST trial was excluded due to its premature termination following safety concerns. The removal of this study had a minimal impact on the pooled effect estimates.

There was no difference in the proportion of those worsening across the two arms (OR 0.88, 95% CI 0.57 to 1.37; P = 0.7; 5 trials, 805 participants; Analysis 1.2), and no difference across subgroups.

Six-minute walk distance (6MWD)

There was a small, statistically significant improvement in 6MWD (mean difference (MD) 19.50 metres, 95% CI 14.82 to 24.19; P < 0.00001; 13 trials, 2283 participants; Analysis 1.3; Figure 4), though it did not meet the minimum clinically important threshold of 41 metres (Khair 2016). Although all modes of administration produced a significant improvement, there was a statistically significant difference across subgroups (P < 0.0001), with the greatest effect seen in the intravenous trials: MD 91.76 metres compared to 16.00 metres in the subcutaneous trial, 14.76 metres in the oral trials, and 26.97 metres in the inhaled trials.

Figure 4. Forest plot of comparison: 1 Prostacyclin versus control, outcome: 1.3 6MWD.

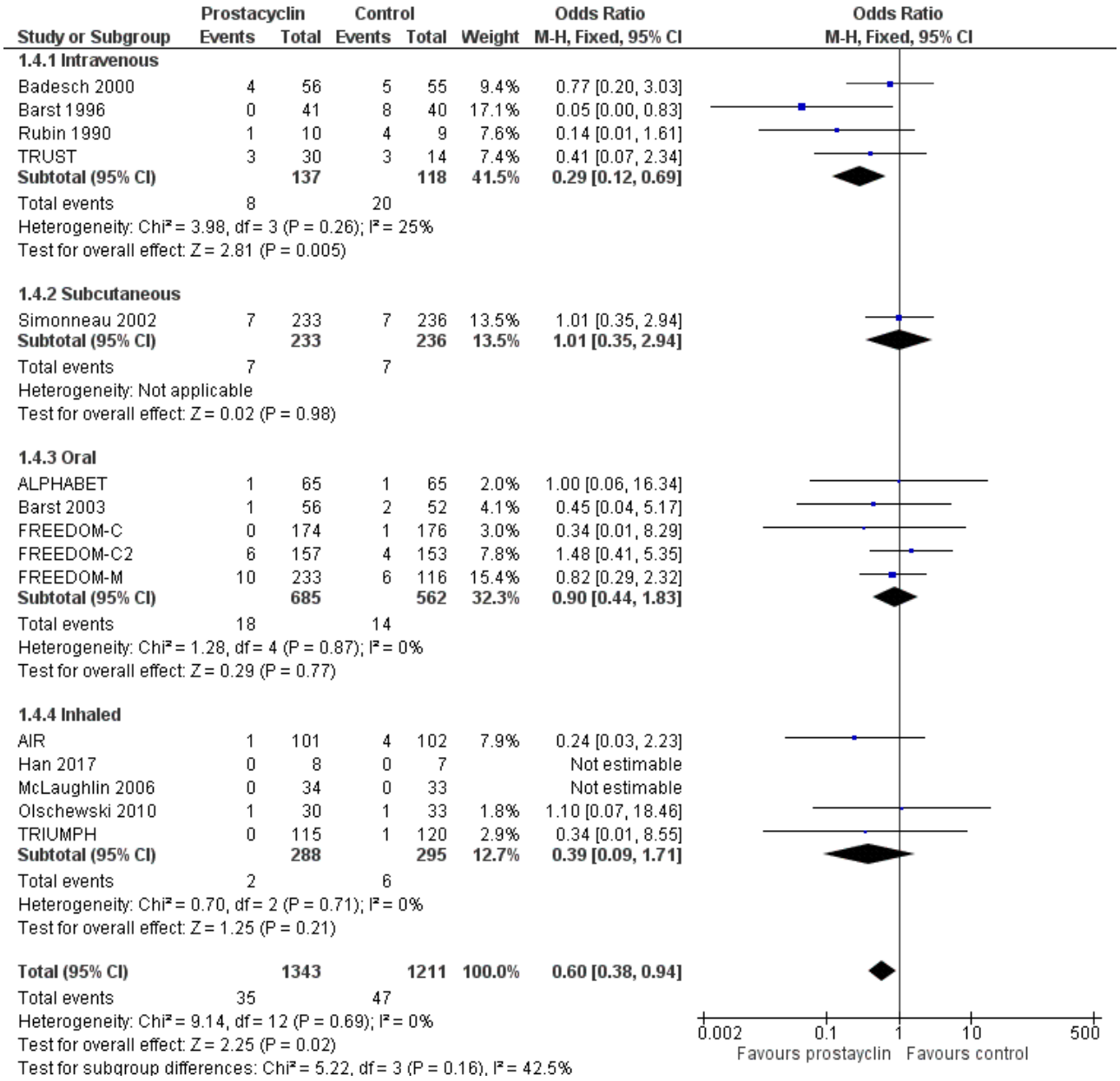


When excluding open-label trials, there was still a significant difference, though the effect size was slightly smaller (MD 19.50 metres, 95% CI 14.82 to 24.19) for all trials compared to MD 17.55 metres (95% CI 12.82 to 22.29) when open-label trials were excluded, and there was no significant difference between fixed- and random-effects (see Table 2; Table 3). Exclusion of the TRUST trial had a minimal impact on the pooled effect estimates.

Mortality

There was a significant difference in mortality overall (OR 0.60, 95% CI 0.38 to 0.94; P = 0.02; 15 trials, 2554 participants; Analysis 1.4; Figure 5), whereby the risk of death over 12 weeks was two per 100 participants in the prostacyclin group compared to four per 100 in the control group (95% CI 1.50 to 4.12). This effect was largely due to the intravenous trials, and when the intravenous trials were excluded, this effect was lost (OR 0.82, 95% CI 0.48 to 1.40; P = 0.46). However, most studies were only approximately 12 weeks duration and most were not powered to assess mortality.

Figure 5. Forest plot of comparison: 1 Prostacyclin versus control, outcome: 1.4 Mortality.



When intravenous trials are analysed separately, the risk of death was 17 per 100 in the control group, compared to six (95% CI 2.38 to 12.31) per 100 for the prostacyclin group. There is, however, higher baseline mortality in these trials compared to the other included studies.

There was no significant difference between fixed- and random-effects (see Table 2). When open-label studies were excluded (which were almost all intravenous studies), the effect on mortality was lost (OR 0.76, 95% CI 0.45 to 1.29; P = 0.32) (see Table 3). However, it is less likely that the outcome of mortality would be affected by the degree of blinding of the studies. This was a post hoc sensitivity analysis whereby the TRUST trial was excluded due to its premature termination following safety concerns. The removal of this study had a minimal impact on the pooled effect estimates of mortality.

Cardiopulmonary haemodynamics

Only eight trials assessed change in haemodynamic parameters over the trial duration (AIR; ALPHABET; Badesch 2000; Barst 1996; Barst 2003; Han 2017; McLaughlin 2006; Simonneau 2002).

There was a significant improvement in mean pulmonary arterial pressure (mPAP) (MD -3.60 mmHg, 95% CI -4.73 to -2.48; P < 0.00001; Analysis 1.5); pulmonary vascular resistance (PVR) (MD -2.81 WU, 95% CI -3.80 to -1.82; P < 0.00001; Analysis 1.6), (Simonneau 2002 measured PVR as a geometric mean, so was not included in the meta-analysis, but demonstrated a similar effect, whereby the change from baseline for treprostinil was -3.5 WU, standard error (SE) 0.6, and change from baseline for control was 1.2 WU, SE 0.06, P = 0.0001); cardiac index (MD 0.31 L/min/m^2, 95% CI 0.23 to 0.38; P < 0.00001; Analysis 1.7); cardiac output (MD 0.57 L/min, 95% CI 0.32

to 0.81; P < 0.00001; Analysis 1.8); and right atrial pressure (RAP) (MD -1.90 mmHg, 95% CI -2.58 to -1.22; P < 0.00001; Analysis 1.9). There was a significant difference across route of administration subgroups for mPAP (P = 0.006), cardiac index (P < 0.0001), and cardiac output (P < 0.0001), however some of these differences may be accounted for by other differences between studies rather than route of administration.

Comparing fixed-effect to random-effects, there was a difference in PVR and cardiac index (see Table 2). There was also substantial heterogeneity in these outcomes, suggesting that small-study effects may be influencing the overall effect size. When open-label studies were excluded, the effects were still significant (see Table 3).

Although no minimum clinically relevant data currently exists for pulmonary haemodynamics, the clinical impact may be contextualised by applying these MDs to the risk stratification data, which correlates with mortality. A RAP < 8 mm Hg is classified as low risk, and > 14 mmHg as high risk. The overall reduction in RAP in all prostacyclin preparations was -1.90 mmHg (95% CI -2.58 to -1.22), and the intravenous preparations demonstrated a reduction in RAP of -2.41 (95% CI -4.10 to -0.72) compared to control. A cardiac index > 2.5 L/min/m^2 is classified as low risk and < 2.0 L/min/m^2 as high risk. Overall all prostacyclin preparations improved cardiac index by 0.31 L/min/m^2 (95% CI 0.23 to 0.38) and intravenous preparations by 0.57 L/min/m^2 (95% CI 0.40 to 0.74).

Exercise capacity tests

Only Barst 2003 reported additional exercise capacity tests. Using cardiopulmonary exercise testing and measuring peak VO_2 with cycle ergometry, there was a trend towards improvement in favour of beraprost (Hodges Lehmann estimate MD between groups at 12 months of 66 mL/min), though this did not reach statistical significance.

Symptom scales including dyspnoea and fatigue

Five studies (ALPHABET; FREEDOM-C2; FREEDOM-M; McLaughlin 2006; TRUST) assessed dyspnoea using the Borg dyspnoea scale, AIR used the Mahler Transition Dyspnoea Index, and Barst 1996 and Simonneau 2002 used the Dyspnoea Fatigue Rating. For all scales lower scores indicate more severe breathlessness (Badesch 2009). These results were pooled in a standardised mean difference (SMD) to account for the different scales used, and the direction of effect was imputed to be consistent across scales. There was a significant improvement in dyspnoea (SMD -0.21, 95% CI -0.32 to -0.11; P < 0.00001; Analysis 1.10). Significant heterogeneity was noted (I^2 = 72%; P = 0.0007). Using the calculated SD from the largest study (Simonneau 2002), an illustrative Borg score of -0.64 was determined. This is less than the minimum clinically important difference of 0.9 (Khair 2016).

When open-labelled studies were excluded, there was still a significant difference (SMD -0.18, 95% CI -0.29 to -0.08; P = 0.0007; 7 trials, 1449 participants).

Badesch 2000 provided dyspnoea data using the Borg dyspnoea scale and Dyspnoea Fatigue Rating, but did not provide CIs, so we were unable to combine these data into the meta-analysis. The post-treatment score for Borg at 12 weeks was 1 in the conventional group and -2 in the epoprostenol group, and the post-treatment score for Dyspnoea Fatigue Rating at 12 weeks was -1 in the conventional group and 1 in the epoprostenol group (lower scores indicate more breathlessness in both scales).

Quality of life

Three studies provided quality of life data suitable for meta-analyses: Barst 1996 using the Chronic Heart Failure Questionnaire (Mastery) (Guyatt 1989) (lower scores indicate worse quality of life), FREEDOM-C2 used the Cambridge Pulmonary Hypertension Outcome Review (McKenna 2006) (lower scores indicate better quality of life), and Han 2017 used the Minnesota Living with Heart Failure Questionnaire (Cenedese 2006) (lower scores indicate better quality of life). These results were pooled in a SMD to account for the different scales used, and the direction of effect was imputed to be consistent across scales. When data were pooled, there was a significant difference in quality of life scores (SMD 0.28, 95% CI 0.04 to 0.52; P = 0.02; Analysis 1.11). There was significant heterogeneity across trials (I^2 = 72%; P = 0.03). When open-labelled studies were excluded, results were no longer significant (MD 0.07, 95% CI -0.22 to 0.36; P = 0.65), however this only included one trial with 187 participants.

A further three studies provided descriptive data. Barst 2003 (using the Minnesota Living with Heart Failure Questionnaire) reported beraprost did not result in significant improvement relative to control in global, physical, or emotional indices of quality of life. TRIUMPH (using the Minnesota Living with Heart Failure Questionnaire) reported a between-treatment median difference of 4 in the global score (P = 0.027) and 2 in the physical score (P = 0.037), for participants receiving inhaled treprostinil. Simonneau 2002 (also using the Minnesota Living with Heart Failure Questionnaire reported that participants treated with treprostinil experienced a significant improvement in their physical dimension score at Week 12 (P = 0.0064) with a trend toward improvement in the global dimension score (P = 0.17) as compared with the control group.

Clinical worsening

There was a significant difference in clinical worsening favouring prostacyclins (OR 0.67, 95% CI 0.48 to 0.92; P = 0.001; 12 trials, 2238 participants; Analysis 1.12). In the control group, seven out of 100 participants experienced clinical worsening, compared to five participants (95% CI 4.50 to 8.27) in the prostacyclin group. The definition of clinical worsening varied across studies (see Characteristics of included studies), but this did not affect heterogeneity of results.

Adverse events

There was an increased risk of adverse events in the prostacyclin group including vasodilation (OR 5.03, 95% CI 3.84 to 6.58; P < 0.00001; 11 trials, 2277 participants; Analysis 1.15), headache (OR 3.16, 95% CI 2.62 to 3.80; P < 0.00001; 12 trials, 2351 participants; Analysis 1.16), jaw pain (OR 5.25, 95% CI 3.96 to 6.98; P < 0.00001; 10 trials, 2149 participants; Analysis 1.17), diarrhoea (OR 2.81, 95% CI 2.29 to 3.46; P < 0.00001; 10 trials, 2317 participants; Analysis 1.18), nausea or vomiting (OR 2.39, 95% CI 1.98 to 2.88; P < 0.00001; 11 trials, 2399 participants; Analysis 1.20), pain in the extremities (OR 3.36, 95% CI 2.32 to 4.85; P < 0.00001; 6 trials, 1236 participants; Analysis 1.22), myalgias (OR 2.75, 95% CI 1.65 to 4.58; P = 0.00001; 3 trials, 1009 participants; Analysis 1.23), upper respiratory tract events (OR 1.61, 95% CI 1.22 to 2.13; P = 0.0009; 7 trials, 1038 participants; Analysis 1.24), and infusion site reactions (OR 14.41,

95% CI 9.16 to 22.66; P < 0.00001; 2 trials, 580 participants; Analysis 1.26).

There was no significant difference in the incidence of syncope (OR 0.77, 95% CI 0.42 to 1.42; P = 0.41; 4 trials, 560 participants; Analysis 1.13), dizziness (OR 1.09, 95% CI 0.84 to 1.42; P = 0.52; 7 trials, 1939 participants; Analysis 1.14), leg pain (OR 2.96, 95% CI 1.02 to 8.62; P = 0.05; 2 trials, 246 participants; Analysis 1.19), abdominal pain (OR 1.35, 95% CI 0.75 to 2.42; P = 0.32; 2 trials, 465 participants; Analysis 1.21), or peripheral oedema (OR 1.46, 95% CI 0.98 to 2.17; P = 0.06; 6 trials, 1228 participants; Analysis 1.25); see Table 4 for all adverse events and their corresponding risks.

In the intravenous studies, three of four trials adequately reported line-related side effects. There was a 12% to 25% risk of serious non-fatal events attributed to the catheter, including sepsis, haemorrhage, pneumothorax and pulmonary embolism (Barst 1996: 5/41; Badesch 2000: 8/56; TRUST: 11/44; Rubin 1990: not reported), and two participants in TRUST died due to catheter-related events on control in the double-blind phase. Pump failure resulting in a temporary discontinuation in drug delivery occurred on five occasions (total 10 participants) in Rubin 1990 and on 26 occasions (total 41 participants) in Barst 1996. (Badesch 2000 and TRUST not reported).

Cost analysis

No trials reported cost analysis.

Selexipag versus placebo

Two studies (1199 participants) compared selexipag (a selective IP prostacyclin receptor antagonist) with placebo (GRIPHON; Simonneau 2012).

Change in WHO functional class

There was no significant difference in the number of participants who improved (OR 1.61, 95% CI 0.17 to 15.63; P = 0.68; 1 trial, 43 participants; Analysis 2.1), but the CI is wide. One per 100 participants in the placebo group had an improvement compared to 15 per 100 (95% CI 1.90 to 63.50) participants in the selexipag group.

There was a benefit of selexipag compared to placebo for worsening in WHO functional class (OR 0.79, 95% CI 0.60 to 1.04; P = 0.09; 2 trials, 1199 participants; Analysis 2.2), but the CI includes no difference. Twenty-one participants per 100 in the prostacyclin group experienced worsening in WHO functional status compared to 25 per 100 (95% CI 17.48 to 26.13) in the placebo group.

Six-minute walk distance (6MWD)

There was a small significant improvement in 6MWD (MD 12.62 metres, 95% CI 1.90 to 23.34; P = 0.02; 2 trials, 1199 participants; Analysis 2.3), though it did not meet the minimum clinically important threshold of 41 metres (Khair 2016).

Mortality

There was no statistically significant difference in mortality (risk difference (RD) 0.02 (95% CI -0.00 to 0.04); P = 0.13; 2 trials, 1159 participants; Analysis 2.4). Risk of death was increased as five per 100 participants in the selexipag group died compared to three per 100 participants in the placebo group, though the CI crossed zero, so the true effect is uncertain.

Cardiopulmonary haemodynamics

Only one trial assessed change in haemodynamic parameters (Simonneau 2012; 43 participants), and found an improvement in PVR (MD -33.00 dyn/s/cm^{-5}, 95% CI -47.00 to -19.00; P < 0.00001; Analysis 2.6), cardiac index (MD 0.50 L/min/m^2, 95% CI 0.13 to 0.87; P = 0.008; Analysis 2.7), and RAP (MD 3.20 mmHg, 95% CI 0.80 to 5.60; P = 0.009; Analysis 2.8), but no significant difference in mPAP (MD -7.40 mmHg, 95% CI -15.90 to 1.10; Analysis 2.5).

Exercise capacity tests

Neither study assessed exercise capacity tests.

Symptom scales including dyspnoea and fatigue

There was no significant difference in dyspnoea, as assessed with the Borg dyspnoea scale (MD -0.10, 95% CI -1.40 to 1.20; P = 0.88; 1 trial, 43 participants; Analysis 2.9) (lower scores indicate better control of dyspnoea; minimum clinically important difference in PAH is 0.9 units).

Quality of life

Neither study assessed quality of life.

Clinical worsening

Both studies (1199 participants) assessed clinical worsening. There was a significant difference in clinical worsening (OR 0.47, 95% CI 0.37 to 0.60; P < 0.00001; Analysis 2.10), favouring selexipag. In the placebo group, 38 out of 100 people experienced clinical worsening compared to 22 (95% CI 18 to 27) in the selexipag group.

Adverse events

There was a significant increase in incidence of headache (OR 3.91, 95% CI 3.07 to 4.98; P < 0.00001; Analysis 2.12), vasodilation (OR 2.67, 95% CI 1.72 to 4.17; P < 0.0001; Analysis 2.13), jaw pain (OR 5.33, 95% CI 3.64 to 7.81; P < 0.00001; Analysis 2.14), diarrhoea (OR 3.11, 95% CI 2.39 to 4.05; P < 0.00001; Analysis 2.15), nausea and vomiting (OR 2.92, 95% CI 2.29 to 3.73; P < 0.00001; Analysis 2.16), pain in extremities (OR 2.44, 95% CI 1.69 to 3.52; P < 0.00001; Analysis 2.17), or myalgias (OR 3.05, 95% CI 2.02 to 4.58; P < 0.00001; Analysis 2.18). There was no difference in dizziness (OR 1.04, 95% CI 0.76 to 1.44; P = 0.79; Analysis 2.11), or upper respiratory tract infections (OR 0.99, 95% CI 0.78 to 1.26; P = 0.96; Analysis 2.19), see Table 5 for all adverse events and their corresponding risks.

Cost analysis

No studies assessed cost analysis.

DISCUSSION

Summary of main results

This review demonstrates clinical and statistical benefit for the use of intravenous prostacyclin compared to control in terms of improved functional class, six-minute walk distance (6MWD), mortality, symptoms scores, and cardiopulmonary haemodynamics, but at a cost of increased risk of adverse events.

This review also demonstrates a statistical and small benefit for inhaled prostacyclin compared to placebo in terms of improvement in functional class, symptoms scores, and cardiopulmonary haemodynamics, a statistical benefit for 6MWD,

but the effect is uncertain for mortality. The use of oral prostacyclin did not demonstrate a statistical or clinical benefit for improvement in functional class, symptoms scores, cardiopulmonary haemodynamics, or mortality.

In these trials, there was only demonstrably significant mortality benefit using intravenous preparations; but not in subcutaneous, oral or inhaled preparations. This may be due to a true effect, or the inclusion of unblinded trials using intravenous preparations that may have over estimated the result, the low participant numbers, and relatively short trial duration.

Selexipag is a selective IP prostacyclin receptor agonist that works similarly to prostacyclin, offering a potentially more stable drug, with oral administration and titration, with potentially similar efficacy. We assessed two trials comparing selexipag to placebo; no trials compared selexipag with prostacyclin. When compared to placebo in large, long-term trials, selexipag had less clinical worsening, but increased adverse events; the effect on other clinical outcomes is less certain. The rate of death was increased in the selexipag group, though the confidence interval crossed zero, so the true effect is uncertain.

Overall completeness and applicability of evidence

In the included trials comparing prostacyclin with control, there was demonstrable mortality benefit using intravenous preparations; but not in subcutaneous, oral or inhaled preparations. The certainty of evidence for mortality benefit was reduced as three out of four of these included trials were open-label. It is unclear in other studies if using non-intravenous preparations did not confer a mortality benefit due to their short (median 12 weeks) duration, or that they were under-powered to detect a mortality difference, or if this is a true signal of no benefit.

When prostacyclin was first developed for PAH, it was delivered intravenously due to the short half-life and potent local effects of the drug. Given the risks of rebound effects if the continuous infusion was suddenly stopped, the drug was administered by a central venous catheter - a direct and reliable access. Invasive central catheter placement is associated with increased risk of adverse events, including infection, bleeding, and damage to surrounding structures. Of concern, these included studies demonstrated a 12% to 25% risk of non-fatal serious line-related events and two line-related deaths. Although efficacious, the decision to commence intravenous prostacyclin must be weighed against the increased risk of serious side effects. The heterogeneity of line-related events between these included trials likely reflects real-world heterogeneity between clinical centres, and catheter placement should only be considered in experienced centres.

The decision to commence continuous intravenous therapy should also be weighed by the patient's ability to reliably control the pump device; several participants in these studies were not randomised because of their inability to work the device. Particular consideration should be given to people with connective tissue disease-related PAH, who may have reduced dexterity.

In recent years, research has been undertaken to develop a safer, more convenient preparation of prostacyclin - including via the inhaled, subcutaneous and oral routes. One subcutaneous trial (Simonneau 2002), five oral trials (ALPHABET; Barst 2003; FREEDOM-C; FREEDOM-C2; FREEDOM-M), and four inhaled trials (AIR; Han 2017; McLaughlin 2006; TRIUMPH), were included in this review. Subgroup analyses suggest that these preparations did not result in the same mortality benefit as intravenous preparations and the overall effect on 6MWD and improvement in World Health Organization (WHO) functional class was less, though it still provided some benefit. However, these trials were not powered for mortality and median duration was only 12 weeks. No randomised controlled trials (RCTs) have compared different preparations head to head. One small study compared inhaled to continuous infusion prostacyclin in 16 participants for 12 weeks (and 4 participants up to 1 year) (Pepke-Zaba 2000). They reported no difference in effect between groups, though data were limited. Another retrospective study reported the safe transition from intravenous or subcutaneous to inhaled treprostinil, with no immediate significant change in function (Enderby 2014).

Certainty of the evidence

We included several open-label studies, which reduced the certainty of the evidence. When these studies were excluded, the differences were still significant, and the direction of effect was still the same, but the magnitude of the effect was smaller. Using subgroup analyses to draw these conclusions, however, relies on a smaller sample size which reduced confidence in these conclusions.

We found the evidence for 6MWD, some haemodynamics, and quality of life scores to be of moderate or low certainty due to imprecision of results from significant heterogeneity. We found that the Chi^2 test for subgroup difference was also significant, indicating that this heterogeneity is in part explained by the difference between the different drugs used.

Although there was statistical significance in the difference in 6MWD with the use of prostacyclins, the overall effect did not meet the minimum clinically important threshold of 41 metres. In addition, although there was a statistically significant difference in the level of dyspnoea reduction, the illustrative Borg score did not meet the clinically important threshold of 0.9 units.

Potential biases in the review process

We conducted this review in accordance with established Cochrane standards. Two review authors independently screened search results and resolved discrepancies by discussion and consensus. We did not restrict the literature search by language. Publication bias is possible, whereby failure to identify unpublished negative trials could have led to an overestimation of effect.

Agreements and disagreements with other studies or reviews

The data from this review are limited by the short follow-up duration. At least two further real-world long-term registry studies have assessed the longer-term use of intravenous epoprostenol in PAH patients (McLaughlin 2002; Sitbon 2002). McLaughlin 2002 followed patients for at least three years, and found observed survival with epoprostenol therapy at one, two, and three years was 87.8%, 76.3%, and 62.8% respectively. Sitbon 2002 followed patients for five years and observed an overall survival rate at one, two, three, and five years of 85%, 70%, 63%, and 55%, respectively. These data are compared to historical cohort data with no therapy, where the expected survival was 58.9%, 46.3%, and 35.4% at one, two, and three years, respectively (D'Alonzo

1991). Our data for intravenous-only studies (duration of 12 weeks only) found a survival rate of 94% for intravenous epoprostenol at 12 weeks compared to an 83% survival rate without intravenous epoprostenol. While there are limitations to observational registry data, it supports the findings in this review that intravenous prostacyclin analogues do suggest a mortality benefit.

The European Society of Cardiology (ESC) guidelines (Galiè 2016), and further registry studies (McLaughlin 2002; Sitbon 2002), have derived and validated clinical and investigational parameters to stratify risk of mortality in PAH patients. They found that WHO functional class, 6MWD, and pro-brain natriuretic peptide (BNP), as well as cardiopulmonary parameters including right atrial pressure (RAP) and cardiac index, were the most reliable predictors of survival. Whilst this review had short duration of follow-up, which limits the conclusions regarding overall mortality, it did find that use of prostacyclin significantly improved WHO functional class, 6MWD, RAP, and cardiac index. These effects were largest using intravenous prostacyclin, but changes were also present across other preparations.

AUTHORS' CONCLUSIONS

Implications for practice

This review demonstrates clinical and statistical benefit for the use of prostacyclin compared to control in terms of improved functional class, six-minute walk distance (6MWD), mortality, symptoms scores, and cardiopulmonary haemodynamics, (low- to moderate-certainty evidence) but at a cost of increased risk of adverse events. There is a statistical benefit for the use of 6MWD, haemodynamics, and avoidance of clinical worsening using selexipag, however the clinical significance remains uncertain.

Implications for research

In these trials, there was only mortality benefit using intravenous preparations; but not in subcutaneous, oral or inhaled preparations. This may be due to a true effect, however this effect may be overestimated due to the inclusion of small, short or open-label studies. Larger trials or real-world registry data examining the use of non-intravenous preparations may provide further information about long-term effect.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

AIR

Methods	Randomised, blinded, parallel-group placebo-controlled trial
Participants	People with Group 1 PAH (including primary or idiopathic), drug-induced, or scleroderma-associated PAH The inclusion criteria were a mean PAH greater than 30 mm Hg, 6MWD 50 metres to 500 metres, and a NYHA functional class of III or IV despite the use of standard conventional therapy (anticoagulants, diuretics, digitalis, calcium channel blockers, and supplemental oxygen). People who were taking investigational drugs, prostanoids, or beta blockers were excluded. Approximately 50% in each group were taking oral vasodilator therapy. n = 203
Interventions	Inhaled iloprost at 2.5 µg to 5 µg per inhalation (90% of participants used 5 µg) six or nine times daily, with an overnight break (n = 101) compared to placebo using the same inhalation device with saline (n = 102)
Outcomes	Change in WHO functional class, 6MWD, mortality, haemodynamic parameters, Mahler Transition Dyspnoea Index, clinical worsening (not explicitly stated), adverse events Outcomes were measured at 12 weeks
Notes	Industry sponsored
Risk of bias	

AIR *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The paper states that participants were randomly assigned after stratification according to NYHA functional class (III or IV) and type of pulmonary hypertension (primary or non-primary) by an independent committee whose members were unaware of patients' identities. Random sequence generation was probably done, however, methods of random sequence generation were not provided.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The same inhaler device was used in the intervention and placebo group.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated whether the outcome assessors were blinded or who performed outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts or non-completers were not reported. The study included data on participants who prematurely discontinued the study using a last-observation-carried-forward analysis for the 6MWD test. Participants who died were assigned a value of 0 metres.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other bias unlikely

ALPHABET

Methods	Randomised, blinded, parallel-group placebo-controlled trial
Participants	Males or females over 8 years of age with PAH in NYHA functional classes II and III, including primary pulmonary hypertension, pulmonary hypertension associated with collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension and HIV infection; a baseline 6MWD between 50 metres and 500 metres, a mPAP > 25 mmHg and a pulmonary capillary wedge pressure < 15 mmHg were required for inclusion. Participants were excluded if they had received long-term treatment with other prostacyclin analogues within one month of enrolment. Additional therapies including anticoagulants, diuretics, and calcium channel blockers were included; use of PDE-5 inhibitors or ERAs were not reported. n = 130
Interventions	Oral beraprost sodium (n = 65) compared to placebo (n = 65) In the first six weeks participants were up-titrated with 20 µg or matching placebo four times a day for the first week, and the dose was increased by 20 µg or matching placebo four times a day each week. The maximal dose allowed in the study was 120 µg four times a day at week 6. At the end of 12 weeks, mean dose of drug was 80 $\pm$ 35 µg four times a day (median 80 µg four times a day) in the beraprost sodium group, and the hypothetical dose in the placebo group was 111 $\pm$ 22µg four times a day.

ALPHABET *(Continued)*

Outcomes	Change in WHO functional class, 6MWD, Borg dyspnoea score, clinical worsening (hospitalisation for worsening of symptoms related to pulmonary hypertension), haemodynamics, adverse events Outcomes were measured at 6 and 12 weeks
Notes	Industry funded: Sanofi-Adventis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as randomised, and probably done, but no methods of randomisation were detailed
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled. Given this was an up-titration study, number of doses between intervention and placebo were outlined.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	States how missing data were dealt with, but does not state how many participants were affected. In the event that no data were available at week 12 for the primary or secondary efficacy variable, the week 6 values or, if lacking, the baseline values were carried forward and used as values at week 12 (last observation carried forward). Two additional methods for missing data imputation were prospectively planned for the primary efficacy variable to ensure robustness of the results: the "left censored data" and "worst quartile" methods.
Selective reporting (reporting bias)	Low risk	Outcomes were reported
Other bias	Low risk	Other bias unlikely

Badesch 2000

Methods	Randomised, parallel-group open-label trial
Participants	People with pulmonary hypertension secondary to the scleroderma spectrum of disease. 69% in each group were on oral vasodilator therapy n = 111
Interventions	Intravenous epoprostenol plus usual treatment compared to usual treatment only Mean final dosing not given
Outcomes	6MWD, NHYA functional class, Borg dyspnoea score, Dyspnoea Fatigue Rating, cardiopulmonary haemodynamics, adverse events, mortality Outcomes measured at 6 and 12 weeks

Badesch 2000 *(Continued)*

Notes	Industry funded: "The funding source for the study, Glaxo Wellcome, Inc. assisted in the collection, gathering, and analysis of data and was aware of the decision to submit the paper for publication".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Investigators contacted a central randomisation centre to obtain treatment assignment, which was based on a stratified randomised block design. Assignments were stratified on the basis of vasodilator use at baseline (yes or no) and exercise capacity at baseline (50 metres to < 200 metres or ≥ 200 metres) and were randomised within blocks.
Allocation concealment (selection bias)	Low risk	Investigators contacted a central randomisation centre to obtain treatment assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Investigators were not blinded to treatment group assignment; however, independent blinded observers assessed the primary efficacy measure, exercise capacity.
Blinding of outcome assessment (detection bias) All outcomes	High risk	For outcomes of 6MWD, assessors were blinded. For mortality, this would not have had an impact on the interpretation of results. However for other outcomes, assessors were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals and cross-overs not reported
Selective reporting (reporting bias)	Unclear risk	Confidence intervals or error bars not reported for some outcomes
Other bias	Low risk	Other bias unlikely

Barst 1996

Methods	Randomised, parallel-group, open-label trial
Participants	Primary pulmonary hypertension who were NHYA III or IV despite optimal treatment (which included anticoagulants, oral vasodilators (68% in each group), diuretic agents, cardiac glycosides, and supplemental oxygen n = 81
Interventions	Intravenous epoprostenol (flolan) versus conventional therapy mean max dose of epoprostenol was 9.2 ± 0.5 ng/kg/min
Outcomes	6MWD, cardiopulmonary haemodynamics, Chronic Heart Failure Questionnaire, Dyspnoea Fatigue Rating, clinical worsening (transplantation), adverse events, mortality Outcomes measured at 12 weeks
Notes	Partly industry funded and partly publicly funded - "Supported in part by Burroughs Wellcome, Research Triangle Park, N.C. Dr.Rubin is the recipient of an academic award in vascular disease from the

Barst 1996 *(Continued)*

	National Heart, Lung, and Blood Institute. Dr. Badesch is the recipient of a clinical investigator award from the National Institutes of Health".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated, adaptive randomisation was performed, with stratification according to the functional class, study centre, and baseline vasodilator use
Allocation concealment (selection bias)	Unclear risk	Not clear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts reported
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	Other bias unlikely

Barst 2003

Methods	Randomised, blinded, parallel-group placebo-controlled trial
Participants	Males or females over eight years of age with PAH in WHO functional classes II or III, including primary pulmonary hypertension, and PAH related to collagen vascular diseases or congenital systemic-to-pulmonary shunts, despite treatment with anticoagulant drugs, vasodilators (other than prostanoids or endothelin receptor antagonists), diuretics, cardiac glycosides, or supplemental oxygen. The inclusion criteria were a baseline peak oxygen consumption (VO^2) during exercise between 8 mL/kg/min and 28 mL/kg/min determined during upright cycle ergometry (actual range for inclusion varied based on age and gender), a resting mPAP ≥ 25 mmHg, with mean pulmonary capillary wedge pressure of ≤ 15 mmHg and PVR > 3U. People were excluded if they had started or stopped any PAH therapy within one month before screening. n = 116
Interventions	Oral beraprost (n = 60) versus placebo (n = 56) People received 20 µg of beraprost sodium or matching placebo four times daily with meals for the first two weeks, and the dose was increased by 20 µg or matching placebo four times daily with meals every two weeks, based on increasing signs, symptoms, and tolerability. The maximal dose allowed in the study was 200 µg four times daily. At the end of 3, 6, 9, and 12 months, the mean dose of drug was 71 ± 3 µg (n = 60), 92 ± 4 µg (n = 57), 98 ± 6 µg (n = 49), and 107 ± 7 µg (n = 8), respectively, four times daily in the beraprost group, and 83 ± 4 µg

Barst 2003 *(Continued)*

	(n = 53), 104 ± 4μg (n = 47), 117 ± 4 μg (n = 43), and 122 ± 6 μg (n = 31), respectively, four times daily in the placebo group.
Outcomes	Change in WHO functional class, 6MWD, mortality, clinical worsening (described as disease progression), quality of life (though data not shown), adverse events Outcomes were evaluated at baseline and after 3, 6, 9, and 12 months of treatment with study drug
Notes	Industry funded: "This study was supported by United Therapeutics Corporation, Research Triangle Park, North Carolina"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States randomised, and probably done, but methods not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled and as this was an up-titration study, number of doses between intervention and placebo were outlined.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clearly reported: the study was prematurely terminated by the sponsor to accelerate assessment of the study results. Fifty-six participants (93%) on beraprost and 52 participants (93%) on placebo were included in the 12-month evaluation; and 116 participants (100%) were included in the 9-month evaluation per protocol.
Selective reporting (reporting bias)	Low risk	Outcomes were reported
Other bias	Low risk	Other bias unlikely

FREEDOM-C

Methods	Randomised, blinded, parallel-group placebo-controlled trial
Participants	People 12 to 70 years of age with symptomatic idiopathic PAH (including PAH associated with anorexigen/toxin use); familial PAH; or PAH associated with congenital heart disease (repaired congenital systemic-to-pulmonary shunts for 5 years), connective tissue disease, or HIV infection. The diagnosis of PAH required a mPAP ≤ 25 mmHg, pulmonary capillary wedge pressure or left ventricular end-diastolic pressure ≤ 15 mmHg, PVR > 3 Wood units, and absence of unrepaired congenital heart disease, with a baseline 6MWD of 100 metres to 450 metres. All participants were required to be on an approved PDE-5 inhibitor or ERA therapy, or combination thereof, for 90 days and at a stable dose for 30 days before study entry. n = 349

FREEDOM-C *(Continued)*

Interventions	Oral treprostinil or placebo twice daily in combination with a PDE-5 inhibitor and/or an ERA. At study initiation, participants were administered a 1 mg twice daily starting dose, with increases in 1 mg increments. Additional tablet doses of 0.5 mg and 0.25 mg were made available to participants at sequentially later times in the study. Participants for whom all doses were available received oral treprostinil at 0.5 mg twice daily and, if clinically tolerated, received dose increases by 0.5 mg increments every 3 days. Doses were increased up to a maximum of 16 mg twice daily over the 16 weeks, depending on adverse events and symptoms and signs of PAH, at the end of 16 weeks. At week 16, the mean dose of UT-15C was 3.1 mg (SD 1.9), and the mean dose of placebo was 6.1 mg (SD 3.6).
Outcomes	6MWD, time to clinical worsening (death; transplantation or atrial septostomy; or clinical deterioration, defined as hospitalisation related to PAH, 20% decrease in 6MWD from baseline and a decrease in WHO functional class, or initiation of a new PAH therapy), Borg dyspnoea score, and Dyspnoea Fatigue Rating, adverse events Outcomes were measured at 16 weeks
Notes	Some raw data for outcomes were obtained on the NCT clinical trials registry Industry funded: "This study was funded by United Therapeutics Corporation"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated randomised, and probably done, but methods not reported. Blocked and stratified by background therapy (PDE-5 inhibitor alone, ERA alone, or PDE-5 inhibitor 1 ERA) and baseline 6MWD (< 350 metres and > 350 metres)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled, and as this was an up-titration study, numbers of tablets across the intervention and placebo groups were reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts, withdrawals, and cross-over participants were reported with reasons supplied
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other bias unlikely

FREEDOM-C2

Methods	Randomised, blinded, parallel-group placebo-controlled trial

FREEDOM-C2 *(Continued)*

Participants	People aged 18 to 75 years with idiopathic PAH (including PAH associated with appetite suppressant or toxin use), familial PAH, or PAH associated with congenital heart disease (repaired congenital systemic-to-pulmonary shunts for 5 years); connective tissue disease; or HIV. Diagnosis of PAH required a mPAP of ≤ 25 mmHg, pulmonary capillary wedge pressure or left ventricular end diastolic pressure of ≤ 15 mmHg, PVR of > 3 Wood units, and the absence of unrepaired congenital heart disease. Participants were required to have received ERA or PDE-5 inhibitor therapy for 90 days with a stable dose for 30 days before baseline and throughout the duration of the study. Baseline 6MWD was required to be between 150 metres and 425 metres. n = 310
Interventions	Oral treprostinil or placebo twice daily in combination with a PDE-5 inhibitor and/or an ERA. The study drug was initiated at 0.25 mg twice daily (every 12 ± 1 h), with dose escalation of an additional 0.25 mg twice daily every 3 days if clinically indicated. After the first 4 weeks, dose escalations could include increments of either 0.25 mg or 0.5 mg twice daily every 3 days. Mean treprostinil dose at 16 weeks: 3.1 ± 1.9 mg twice daily (range: 0.25 mg to 10.5 mg) compared with placebo dose: 6.1 ± 3.6 mg twice daily (range: 0.25 mg to 16.0 mg)
Outcomes	6MWD, Borg dyspnoea score, NT-proBNP level, WHO functional classification, Cambridge Pulmonary Hypertension Outcome Review, Clinical worsening defined as death, transplantation, or atrial septostomy; hospitalisation as a result of right-side heart failure; a decrease in 6MWD of 20% from baseline (or too ill to walk) and the addition of an inhaled prostacyclin, ERA, or PDE-5 inhibitor; or initiation of parenteral prostacyclin therapy for the treatment of PAH, adverse events Outcomes were measured at 16 weeks
Notes	This is a different cohort of participants from the FREEDOM-M study, which examined monotherapy, and the FREEDOM C-2 study, which uses treprostinil on a background of combination PDE5-inhibitor and ERA, but due to the high dropout rate for side effects starting at 1 mg twice daily, this FREEDOM C-2 study was created to commence treprostinil at 0.25 mg twice daily. Inudstry funded: "This study was funded by United Therapeutics Corporation"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated randomised, and probably done, but methods not reported. Blocked and stratified by background therapy (PDE-5 inhibitor alone, ERA alone, or PDE-5 inhibitor 1 and ERA) and baseline 6MWD (< 350 metres and > 350 metres)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled, and as this was an up-titration study, numbers of tablets across the intervention and placebo groups were reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts, withdrawals, and cross-over participants were reported with reasons supplied

FREEDOM-C2 *(Continued)*

Selective reporting (reporting bias)	Low risk	It was stated that no secondary outcomes were significant, and no further data given, however these were reported on the clinical trials registry
Other bias	Low risk	Other bias unlikely

FREEDOM-M

Methods	Randomised, blinded, parallel-group placebo-controlled trial
Participants	People aged 12 to 75 years of age with idiopathic or hereditary PAH (including PAH associated with appetite suppressant/toxin use), PAH associated with repaired congenital systemic-to-pulmonary shunts (repaired ≥ 5 years), or PAH associated with collagen vascular disease or HIV. Participants were ineligible if they had received ERA, PDE-5I, or prostacyclin therapy within 30 days of baseline or if they had evidence of significant left-sided heart disease or parenchymal lung disease. Baseline 6MWD was required to be between 100 metres and 450 metres. Participants were required to be optimally treated with conventional PAH therapies (e.g. anticoagulants, oral vasodilators, oxygen, digoxin) n = 349
Interventions	Oral trepostinil compared to placebo Study drug was originally initiated at 1.0 mg twice daily; however, on the basis of tolerability issues identified in the FREEDOM-C study, the study protocol was later amended to lower the starting dose to 0.5 mg twice daily and eventually 0.25 mg twice daily. Study drug was administered every 12 ± 2 hours with dose escalation of an additional 0.25 mg to 0.5 mg twice daily every 3 days and a maximum possible dose of 12 mg twice daily.
Outcomes	6MWD, Borg dyspnoea score, clinical worsening, Dyspnoea Fatigue Rating, WHO functional class, and symptoms of PAH. Clinical worsening was defined as one of the following: cardiovascular death, transplantation, atrial septostomy, or clinical deterioration. Clinical deterioration was defined as the initiation of new, approved PAH-specific therapy (ERA, PDE-5I, or prostacyclin) plus either hospitalisation for decompensated PAH or a ≥ 20% decrease in 6MWD from baseline combined with worsening WHO functional class Outcomes were reported at 12 weeks
Notes	This studies a different cohort of participants than FREEDOM C or FREEDOM C-2, which examined oral treprostinil with combination therapy Data were presented according to intention-to-treat and modified intention-to-treat. The primary analysis population or mean ITT population was the population of patients with access to the 0.25 mg strength tablet at the time of randomisation. The ITT population (as well as the safety population) was defined as all randomised participants. Industry based: "This study was funded by United Therapeutics Corporation"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated randomised, and probably done, but methods not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not reported

FREEDOM-M *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled. Reported the average dose for treprostinil but not for placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts, withdrawals, and cross-over participants were reported with reasons supplied
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other bias unlikely

GRIPHON

Methods	Randomised, double-blinded, parallel-group placebo-controlled trial, event driven
Participants	Participants aged 18 to 75 years of age who had idiopathic or inheritable PAH or PAH associated with HIV infection, drug use or toxin exposure, connective tissue disease, or repaired congenital systemic-to-pulmonary shunts. Confirmation of the diagnosis by means of right heart catheterisation was required before screening. Participants were required to have a PVR of at least 5 Wood units (400 dyn·sec/cm^{-5}) (which is higher than the usual stated criteria) and a 6MWD of 50 metres to 450 metres. Participants who were not receiving treatment for PAH and those who were receiving an ERA, a PDE-5 inhibitor, or both at a dose that had been stable for at least 3 months were eligible for enrolment; participants who were receiving prostacyclin analogues were not eligible n = 1156
Interventions	Oral selexipag versus placebo During the 12-week dose adjustment phase, selexipag was initiated at a dose of 200 µg twice daily and was increased weekly in twice-daily increments of 200 µg until unmanageable adverse effects associated with prostacyclin use, such as headache or jaw pain, developed. The dose was then decreased by 200 µg in both daily doses, and this reduced dose was considered to be the maximum tolerated dose for that participant. The maximum dose allowed was 1600 µg twice daily.
Outcomes	The primary endpoint in a time-to-event analysis was a composite of death or a complication related to PAH, whichever occurred first, up to the end of the treatment period. Complications related to PAH were disease progression or worsening of PAH that resulted in hospitalisation, initiation of parenteral prostanoid therapy or long-term oxygen therapy, or the need for lung transplantation or balloon atrial septostomy as judged by the physician. Disease progression was defined as a decrease from baseline of at least 15% in the 6MWD (confirmed by means of a second test on a different day) accompanied by a worsening in WHO functional class (for those with WHO functional class II or III at baseline) or the need for additional treatment of PAH (for the patients with WHO functional class III or IV at baseline). Median time-to-event was 63 weeks Separate outcomes including 6MWD, mortality, absence of worsening in WHO functional class, and adverse events were also included
Notes	A very detailed protocol was supplied in the supplementary appendix Industry funded: "Funded by Actelion Pharmaceuticals"

GRIPHON *(Continued)*

	ClinicalTrials.gov number: NCT01106014

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation and drug packaging was performed by an independent company. Patients were randomised to one of the treatment groups using a centralised randomisation system via the Interactive Web/Voice Response System (IWRS/IVRS).
Allocation concealment (selection bias)	Low risk	Allocation was performed by an independent company, with placebo-controlled drug packaging, so selection bias was unlikely
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled, states participants and investigators were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo-controlled, states participants and investigators were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts, withdrawals, and cross-over participants were reported with reasons supplied
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported, and the protocol was supplied in a supplementary appendix
Other bias	Low risk	Other bias unlikely

Han 2017

Methods	Randomised, multicentre, open-label controlled trial
Participants	Participants were between 15 and 80 years old, had WHO functional class III or IV with symptoms of PAH, and had been diagnosed with idiopathic PAH or chronic thromboembolism pulmonary hypertension, according to criteria in current guidelines. For each participant, mPAP was required to be ≥ 25 mmHg, and the pulmonary capillary wedge pressure was required to be ≤ 15 mmHg. Participants had not received previous treatment with an approved therapy for PAH before enrolment. Participants with acute pulmonary thromboembolism, left-sided heart disease, pulmonary disease with FEV 1/FVC < 50% predicted or total lung capacity < 60%, renal insufficiency, chronic liver disease, or portal hypertension were excluded from the study. N = 27 total, with 14 included in our analysis
Interventions	Combination inhaled iloprost with bosentan, versus iloprost alone, versus bosentan alone, in three randomised arms Iloprost was administered at increasing doses to a target of 10 µg 4 to 6 times/day
Outcomes	The primary endpoint was change in peak 6MWD that were defined as within 10 to 60 min after iloprost inhalation at week 6 and 3 months

Han 2017 *(Continued)*

	Prespecified secondary efficacy endpoints included changes in haemodynamic variables that were measured by right heart catheterisation from baseline to 3 months after the initiation of treatment. Secondary efficacy endpoints also included changes in NT-proBNP levels, WHO functional class, and Minnesota Living with Heart Failure Questionnaire scores from baseline to 6 weeks and 3 months after the initiation of treatment. Safety assessments included laboratory measurements and evaluation of adverse events
Notes	Data from combined bosentan and iloprost versus bosentan alone were used (N = 14). Individual patient data was kindly sent by authors and re-analysed. Where SD was reported, it was likely actually standard error according to reanalysis and so was imputed into the meta-analysis as such. This work was supported by National Natural Science Foundation Grants. The study drugs were provided by Actelion Pharmaceuticals Ltd (Allschwil, Switzerland) (bosentan) and Bayer (Leverkusen, Germany) (iloprost).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as randomised, but methods of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals reported
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	High risk	Incorrectly reported as SD, not standard error, however individual patient data was provided for reanalysis

McLaughlin 2006

Methods	Randomised, double-blinded, parallel-group placebo-controlled trial
Participants	People aged 10 to 80 years with symptomatic PAH receiving bosentan for 4 months or more, with a 6MWD of 100 metres to 425 metres, resting mPAP greater than 25 mmHg, pulmonary capillary wedge pressure less than 15 mmHg, and PVR of 240 dyn·s/cm^{-5} or greater n = 67

McLaughlin 2006 *(Continued)*

Interventions	Either iloprost inhalation (5 µg) or placebo inhaled six to nine times daily while awake using the Prodose AAD device, with existing therapy with oral bosentan (125 mg twice daily). The mean number of study drug inhalations per day was 5.6 in the iloprost group and 5.7 in the placebo group. The mean total daily dose of study drug was 26.8 µg (range: 2.5 to 32.4 µg) in the iloprost group and 27.8 µg (range: 11.6 to 33.3µg) in the placebo group
Outcomes	6MWD, performed pre-inhalation at baseline, post-inhalation at weeks 4 and 8, and at both time points at Week 12, with the two tests separated by at least 2 h and the temporal sequence randomised (i.e. whether pre- or post-inhalation). NYHA functional class and post-inhalation Borg dyspnoea score were also assessed at baseline and Weeks 4, 8, and 12. Haemodynamic parameters were measured by right-heart catheterisation at baseline and week 12, both pre- and post-inhalation (15 min). Clinical worsening (described as clinical deterioration)
Notes	Industry funded: "Supported by CoTherix, Inc. (South San Francisco, CA)"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was communicated to sites using a blinded interactive voice response system, and was stratified and blocked according to etiology: idiopathic PAH or associated PAH; i.e. collagen vascular disease, repaired congenital heart disease, HIV infection, or anorexigen use)
Allocation concealment (selection bias)	Low risk	Randomisation was performed outside the site and drug labelling was placebo-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled, and as this was an up-titration study, numbers of tablets across the intervention and placebo groups were reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reported as blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts, withdrawals, and cross-over participants were reported with reasons supplied
Selective reporting (reporting bias)	Low risk	Prespecified outcomes and their measurements with respect to timing of inhalation were reported
Other bias	Low risk	Other bias unlikely

Olschewski 2010

Methods	Randomised, parallel-group, open-label study
Participants	People aged from 18 to 70 years with idiopathic or familial PAH, previously classified as primary pulmonary hypertension (idiopathic PAH group), or other forms of pulmonary hypertension, previously classified as secondary pulmonary hypertension, with a mPAP at rest of 40 mmHg. People on PDE-5 inhibitors or ERAs were excluded This was a separately recruited group to the AIR study.

Olschewski 2010 *(Continued)*

	n = 63
Interventions	Inhaled iloprost 4 µg, 6 to 9 times daily, compared to conventional treatment The mean inhaled daily dose of iloprost divided into 6 to 9 doses was 25 µg at month 1 and 29 µg at year 2
Outcomes	Adverse events, mortality
Notes	The trial included three months with one group randomised to epoprostenol and one group randomised to conventional treatment; following, all participants were treated with epoprostenol. Outcomes were reported at the end of the study (at two years) so this data could not be used in the meta-analysis. Adverse events could be extracted Industry funded: "This study was sponsored by Schering AG, Berlin, Germany" ClinicalTrials.gov Identifier: NCT00414687

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States "randomised" but no details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No suggestion that outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts reported
Selective reporting (reporting bias)	High risk	Only outcomes at 2 years were reported
Other bias	Low risk	Other bias unlikely

Rubin 1990

Methods	Randomised, parallel-group open-label trial
Participants	Primary pulmonary hypertension, no vasodilators (unresponsive or unable to tolerate) n = 19
Interventions	Intravenous epoprostenol (flolan) compared to conventional therapy

Rubin 1990 *(Continued)*

Outcomes	Cardiopulmonary haemodynamics, 6MWD, adverse events, mortality Outcomes measured at 8 weeks
Notes	Funding source not stated but it is noted several of the authors are employed by Burroughs Wellcome Company.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned after the dose-ranging study by calling a central telephone number. At that time the next available sequentially numbered sealed envelope for that patient's status was opened, and the patient allocated to conventional therapy or prostacyclin
Allocation concealment (selection bias)	Low risk	Sequentially sealed envelopes used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not dropouts reported
Selective reporting (reporting bias)	Unclear risk	Data not interpretable (presented as mean baseline and mean post-treatment scores, with the confidence intervals of the mean differences)
Other bias	Low risk	Other bias unlikely

Simonneau 2002

Methods	Randomised, double-blinded, parallel-group placebo-controlled trial
Participants	Inclusion criteria • Primary pulmonary hypertension or pulmonary hypertension associated with connective tissue diseases or associated with congenital systemic-to-pulmonary shunts • Age between 8 and 75 years • NYHA functional class II, III, or IV • Significant pulmonary hypertension defined by • mPAP > 25 mmHg at rest • Mean pulmonary capillary wedge pressure < 15 mmHg • PVR > 3 mmHg/L/min • Ventilation perfusion lung scan or pulmonary angiography not indicative of thromboembolic disease Exclusion criteria

Simonneau 2002 *(Continued)*

- Significant parenchymal pulmonary disease as evidenced by pulmonary function tests or high resolution CT scan
- Porto pulmonary hypertension or HIV-associated pulmonary hypertension
- Uncontrolled sleep apnoea
- History of left-side heart disease
- Other diseases associated with pulmonary hypertension (e.g. sickle cell anaemia, schistosomiasis)
- Baseline exercise capacity of less than 50 metres or greater than 450 metres walked in 6 min
- Any new type of chronic therapy for pulmonary hypertension added within the last month
- Any pulmonary hypertension medication discontinued within the last week except anticoagulants
- Any use of prostaglandin derivatives within the past 30 d

n = 470

Interventions	Continuous subcutaneous infusion of treprostinil plus conventional therapy versus continuous infusion of placebo (vehicle solution without treprostinil) plus conventional therapy. Conventional therapy could include oral vasodilators, oral anticoagulants, diuretics, and/or digitalis. Chronic study drug infusion was initiated at the dose of 1.25 ng/kg/min. During the 12-week study, doses were increased to a maximum dose at which pulmonary hypertension signs and symptoms were improved while achieving an acceptable side effect profile. At week 12, the maximum allowable dose was 22.5 ng/kg/min. By the end of the 12-week study period, the mean dose of the study drug received was 9.3 ng/kg/min versus 19.1 ng/kg/min in the placebo group (P < 0.001).
Outcomes	6MWD, signs or symptoms of PAH, lung transplantation, mortality, Dyspnoea Fatigue Rating, cardiopulmonary haemodynamics measured by right heart catheterisation, global, physical, and emotional quality of life using the Minnesota Living with Heart Failure Questionnaire, adverse events Outcomes were assessed at week 6 and 12
Notes	Industry funded: "This study was supported by United Therapeutics Corporation, Research Triangle Park, North Carolina"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was based on a permuted block design stratified on the basis of baseline exercise capacity and etiology of PAH.
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled. As this was an up-titration study, doses for both groups were reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was reported that for the 6MWD test was administered by a “blinded” tester not involved in the participant’s daily care and unaware of the participant’s treatment assignment, however other outcomes were not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts and withdrawals were not reported

Simonneau 2002 *(Continued)*

Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other bias unlikely

Simonneau 2012

Methods	Randomised, double-blinded, parallel-group placebo-controlled trial
Participants	Male or female adults (over 18 years) with symptomatic PAH of idiopathic or hereditary origin, associated with connective tissue diseases (PAH-connective tissue disease), corrected congenital heart disease (congenital systemic-to-pulmonary shunts surgically repaired > 5 yrs previously), or anorexigen use. Background targeted treatment with ERAs and/or PDE-5 inhibitors was mandatory and participants had to have been on stable doses for > 12 weeks before screening. Participants were required to have a baseline PVR of > 400 dyn.s/cm^{-5}, and two 6MWD tests of 150 metres to 500 metres inclusive and within 15% of each other. Participants were excluded if they had clinically unstable right heart failure within the last 3 months (WHO functional class IV), had received or were scheduled to receive long-term epoprostenol within 3 months of screening, had a ventilation perfusion lung scan or pulmonary angiography indicative of thromboembolic disease, had evidence of left-sided heart disease, or had received any investigational drug within 30 days of screening. n = 43
Interventions	Selexipag 200 mg twice daily or matching placebo on day 1, then up-titrated to 400 mg twice daily on day 3, to 600 mg twice daily on day 7, and to 800 mg twice daily on day 21 according to side effects. Final dosage was required to be stable for > 4 weeks prior to evaluation at week 17. Participants on selexipag received treatment for a mean of 143.3 (SD 28.6) days (median 149.0 days; range 17 to 176 days), compared with 135.1 (SD 27.4) days (median 146.0 days; range 61 to 152 days) for participants on placebo. Among selexipag-treated participants, 14 (42.4%) were on a final dosage of 800 mg twice daily, seven (21.2%) were on 600 mg twice daily, six (18.2%) were on 400 mg twice daily and four (12.1%) were on 200 mg twice daily.
Outcomes	Haemodynamic parameters measured on right heart catheterisation, 6MWD, aggravation of PAH (defined as death, transplantation, hospitalisation due to worsening PAH, or aggravation of PAH symptoms, i.e. a > 10% deterioration in 6MWD or the need for additional PAH-specific therapies), Borg dyspnoea score, WHO functional class, and NT-proBNP concentration Outcomes were measured at week 17
Notes	Industry funded: by Actelion Pharmaceuticals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation schedule 3:1 (selexipag:placebo) was computer generated by Penn Pharmaceutical Services Ltd
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled. As this was an up-titration study, doses and duration for both groups were reported

Simonneau 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "As the study was blinded, investigators assessed the relationship between adverse events and study treatment before the treatment code was broken. After week 17 data were fixed and locked, participants eligible to enter the open-label extension were not blinded. For participants who discontinued prematurely or otherwise did not enter the open-label extension, study treatment remained blinded until all week 17 data were cleaned and reconciled"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were reported
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other bias unlikely

TRIUMPH

Methods	Randomised, blinded, parallel-group placebo-controlled trial
Participants	Adults aged 18 and 75 years with a confirmed diagnosis of idiopathic or familial PAH or PAH associated with collagen vascular disease, HIV infection, or anorexigen use. Participants were NYHA functional class III or IV severity with a baseline 6MWD between 200 metres and 450 metres and were receiving bosentan 125 mg daily or any prescribed dose of sildenafil, 20 mg three times daily, for at least 3 months before study entry. n=235
Interventions	Inhaled treprostinil sodium or placebo 4 times daily in combination with bosentan or sildenafil. At the discretion of the study investigator, participants initiated therapy at 3 breaths (18 µg)/inhalation. If clinically tolerated, the dosing was to be increased over the first 2 weeks to reach a maximum of 9 breaths (54 µg) at each of the 4 daily doses. The mean dose of study drug was 50 ±10µg in the inhaled treprostinil group and 52 ±7µg in the inhaled placebo group.
Outcomes	NYHA functional classification, 6MWD, Borg dyspnoea score (immediately after 6MWD) Minnesota Living with Heart Failure Questionnaire, NT-pro BNP, adverse events, time to clinical worsening (defined as death, transplantation, hospital stay due to worsening PAH, or initiation of additional approved PAH-specific therapy) Outcomes reported at 12 weeks
Notes	Industry funded: "This research was funded by United Therapeutics Corporation"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Called a randomised trial, but methods not stated
Allocation concealment (selection bias)	Unclear risk	Not stated

TRIUMPH *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled, as this was an up-titration study, final doses in the intervention and placebo group were reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals reported
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Low risk	Other bias unlikely

TRUST

Methods	Randomised, blinded, parallel-group placebo-controlled trial
Participants	Adults aged 16 to 75 years with idiopathic PAH (sporadic or familial) or PAH associated with HIV or collagen vascular disease. Other entry criteria included: mPAP > 35 mm Hg; pulmonary capillary wedge pressure < 16 mmHg; PVR 5 mm Hg/litre/min; stable NYHA Functional Class III or IV symptoms on adjunctive therapies (anticoagulants, diuretics, digoxin, oxygen, vasodilators (27%)); and screening 6MWD of 50 to 325 meters. n = 44 Enrollment was closed after 45 of the planned 126 patients were randomised because of safety considerations, mostly in the treatment arm
Interventions	Intravenous treprostinil compared to placebo Treprostinil (1 mg/mL) or placebo was provided in blind-labelled, multiple entry vials for infusion after dilution in sterile saline via and ambulatory pump (CADD pump). The initial study drug dose was 4 ng/kg/min treprostinil or an equivalent volume of diluted placebo; the range of doses at week 1 was 8 to 14 ng/kg/min (actively treated) and 6 to 10 ng/kg/ min (placebo treated). After the first week, dose increases up to 8 ng/kg/min weekly (or placebo equivalent) were allowed to a maximum of 100 ng/kg/min.
Outcomes	6MWD, Borg dyspnoea score, Dysponea Fatigue Rating, clinical worsening (death, lung transplant, hospitalisation, unblinding for rescue or too-ill-to-walk), change in NYHA functional class, adverse events, cytokine growth factors
Notes	Industry funded: "United Therapeutics Corp. Research Triangle Park, NC"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Methods of randomisation not stated

TRUST *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants had central venous catheters placed, and placebo matched infusions were given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specifically stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were reported
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other bias unlikely

Abbreviations
6MWD: six-minute walk distance; CT: computed tomography; ITT: intention-to-treat analysis; ERA: endothelin receptor antagonist; HIV: human immunodeficiency virus; mITT: modified intention-to-treat analysis; mPAP: mean pulmonary arterial pressure; n: number of participants; NCT: National Clinical Trials; NT-proBNP: plasma N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; SD: standard deviation; WHO: World Health Organization; PDE-5 inhibitor: phosphodiesterase-5 inhibitor; SD: standard deviation

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

Study	Reason for exclusion
Bruderer 2014	Wrong patient population (includes healthy participants), and does not meet minimum required trial duration
Herald 2006	Wrong study design - letter to the editor with no new data
Higenbottam 1996	Wrong study design - letter to the editor with no new data
Higenbottam 1998	Wrong patient population
Jing 2013	Wrong study design - not clearly a randomised controlled trial
Klings 2000	Wrong study design - letter to the editor with no new data
Kumar 2013	Wrong study design - does not compare to a control/placebo group
Kunieda 2013	Wrong study design - not randomised
Leuchte 2003	Wrong study design - case report
Matthes 2001	Wrong study design - review
NCT00709098 2008	Wrong study design - does not compare to a placebo/other intervention group

Study	Reason for exclusion
NCT00709956 2008	Wrong timeframe - too short
NCT00760916 2008	Study was withdrawn before participants were enrolled
NCT00993408 2009	Single test dose study
NCT01094067 2010	Single test dose study
NCT01105091 2010	Wrong timeframe - only 28 days
NCT01302444 2011	Wrong intervention - all participants were on prostacyclin and study compared tadalafil to no tadalafil
NCT01393795 2011	Wrong intervention - does not compare prostacyclin drug
NCT01557647 2012	Study was withdrawn before participants were enrolled - no reasons were given
NCT01598441 2012	Wrong timeframe - only two days duration
NCT02032836 2014	Wrong intervention - compared different delivery devices
NCT02482402 2014	Study was withdrawn due to lack of recruitment
NCT02893995 2016	Wrong study design - compared different rates of the same drug
NCT02999906 2016	Study was withdrawn before enrolment due to "business reasons"
Olschewski 1998	Wrong study design - not clearly a randomised controlled trial and trial duration of only four weeks
Pepke-Zaba 2000	Wrong intervention - compares different forms of prostacyclin
Preston 2015	Wrong intervention
Robbins 2000	Wrong study design - not a randomised controlled trial
Rubenfire 2007	Wrong study design - only 14 days duration
Rubin 2005	Wrong study design - case report
Saba 2001	Wrong study design - letter to the editor with no new data
Saggar 2013	Wrong study design - does not compare to an intervention/placebo arm, only conventional treatment
Shah 2010	Wrong study design - no long-term follow-up
Voswinckel 2006	Wrong study design - no long-term follow-up
Voswinckel 2006a	Wrong study design - letter to the editor with no new data
Wade 2007	Wrong study design - not clearly a randomised controlled trial
White 2013	Wrong study design - not a randomised controlled trial
White 2013a	Wrong study design - not a randomised controlled trial

Study	Reason for exclusion
Wilkens 2001	Wrong study design - not a randomised controlled trial
Wilkens 2001a	Wrong timeframe - short-term duration
Zamanian 2013	Wrong study design - observational study

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

NCT 2013

Trial name or title	Beraprost-314d Added-on to Tyvaso® (BEAT)
Methods	Randomised controlled trial
Participants	Participants with pulmonary arterial hypertension
Interventions	BPS-314d-MR (beraprost sodium) when added-on to inhaled treprostinil (Tyvaso®) compared to placebo
Outcomes	Primary outcome: time to clinical worsening Secondary outcomes: 6-minute walk distance, Borg dyspnoea score, WHO functional class, NT-pro-BNP levels Outcome measures will be assessed at 12 and 144 weeks
Starting date	July 26, 2013
Contact information	Lung Biotechnology PBC
Notes	clinicaltrials.gov/show/NCT01908699

NCT 2015

Trial name or title	The efficacy and safety of initial triple versus initial dual oral combination therapy in patients with newly diagnosed pulmonary arterial hypertension (TRITON)
Methods	Randomised controlled trial
Participants	Newly diagnosed pulmonary arterial hypertension
Interventions	Triple oral combination treatment (macitentan, tadalafil, and selexipag) compared to dual oral combination treatment (macitentan, tadalafil, and placebo)
Outcomes	Pulmonary vascular resistance (no other outcomes listed) at 26 weeks
Starting date	September 23, 2015
Contact information	loic.perchenet@actelion.com
Notes	clinicaltrials.gov/show/NCT02558231

TRACE 2018

Trial name or title	TRACE 2018
Methods	Multicentre, double-blind, randomised, exploratory Phase 4 study
Participants	Eligible PAH patients are 18-75 years, in World Health Organization functional class (WHO FC) II or III, with a 6-minute walk distance (6MWD) >= 100 m, and on stable treatment with an endothelin receptor antagonist alone or in combination with a phosphodiesterase-5 inhibitor or soluble guanylate cyclase stimulator
Interventions	Randomises (1:1) 100 patients to receive selexipag or placebo for 24 weeks
Outcomes	Primary outcomes: daily life physical activity (DLPA), measured by the wrist-worn accelerometer ActiGraph GT9X Link, day and night during a 14 day baseline period and throughout the 24-week treatment period. Daily data upload on a provided smartphone allows wear-time monitoring. The PAH-SYMPACT questionnaire is the first PAH-specific PRO instrument developed and validated according to the FDA guidance The primary endpoint is change from baseline to week 24 in actigraphy-assessed DLPA, as measured by: daily time spent in non-sedentary activity, total DLPA per day, total sleep time, wake time after sleep onset, number of awakenings and sleep efficiency. Secondary endpoints include change in score from baseline in cardiovascular symptoms, cardiopulmonary symptoms, physical impact and cognitive/emotional impact domains of PAH-SYMPACT, change in WHO FC, 6MWD, Borg dyspnoea score and NT-proBNP. Safety and tolerability of selexipag are monitored.
Starting date	Not stated
Contact information	I Preston, Tufts Medical Centre, Boston, MA, USA
Notes	adisinsight.springer.com/trials/700282735

DATA AND ANALYSES

Comparison 1. Prostacyclin versus control

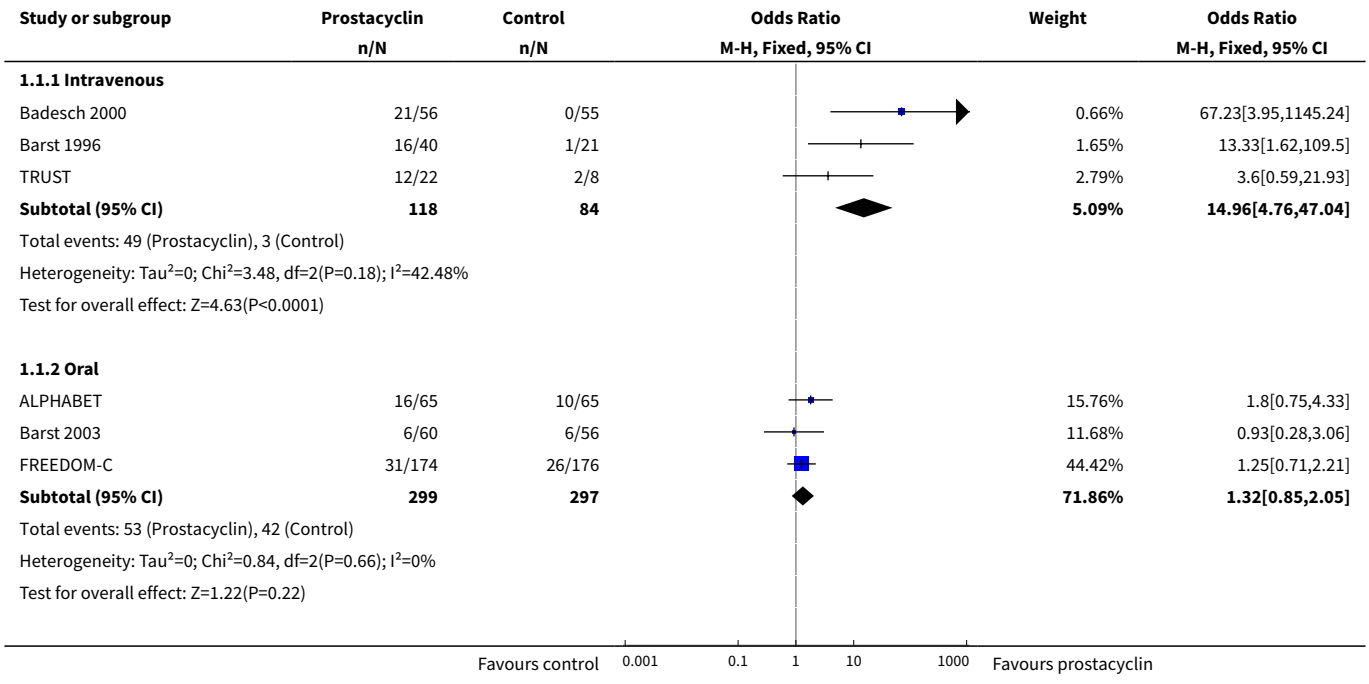
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in WHO functional class	8	1066	Odds Ratio (M-H, Fixed, 95% CI)	2.39 [1.72, 3.32]
1.1 Intravenous	3	202	Odds Ratio (M-H, Fixed, 95% CI)	14.96 [4.76, 47.04]
1.2 Oral	3	596	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.85, 2.05]
1.3 Inhaled	2	268	Odds Ratio (M-H, Fixed, 95% CI)	2.94 [1.53, 5.66]
2 Worsening of WHO functional class	5	805	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.57, 1.37]
2.1 Intravenous	1	71	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.29, 6.07]

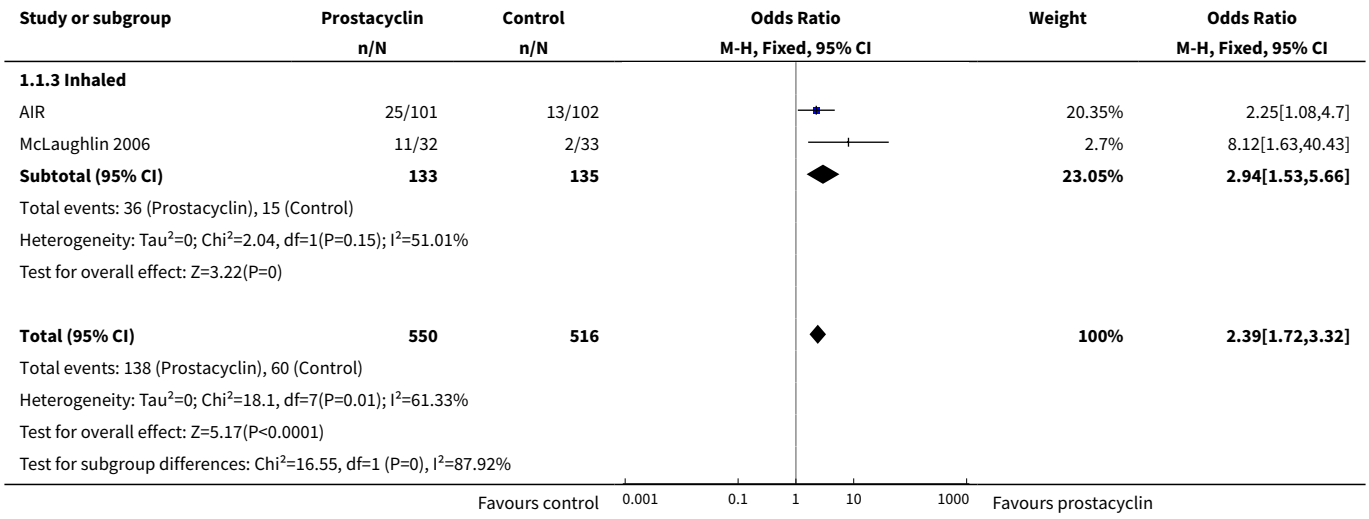
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.2 Oral	2	466	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.54, 1.51]
2.3 Inhaled	2	268	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.24, 1.89]
3 6MWD	13	2302	Mean Difference (Fixed, 95% CI)	19.50 [14.82, 24.19]
3.1 Intravenous	4	245	Mean Difference (Fixed, 95% CI)	91.76 [58.97, 124.55]
3.2 Subcutaneous	1	469	Mean Difference (Fixed, 95% CI)	16.0 [7.38, 24.62]
3.3 Oral	4	1070	Mean Difference (Fixed, 95% CI)	14.76 [7.81, 21.70]
3.4 Inhaled	4	518	Mean Difference (Fixed, 95% CI)	26.97 [17.21, 36.73]
4 Mortality	15	2554	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.38, 0.94]
4.1 Intravenous	4	255	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.12, 0.69]
4.2 Subcutaneous	1	469	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.35, 2.94]
4.3 Oral	5	1247	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.44, 1.83]
4.4 Inhaled	5	583	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.09, 1.71]
5 mPAP	8	1132	Mean Difference (Fixed, 95% CI)	-3.60 [-4.73, -2.48]
5.1 Intravenous	2	192	Mean Difference (Fixed, 95% CI)	-6.23 [-8.64, -3.83]
5.2 Subcutaneous	1	469	Mean Difference (Fixed, 95% CI)	-0.7 [-3.19, 1.79]
5.3 Oral	2	196	Mean Difference (Fixed, 95% CI)	-1.71 [-4.06, 0.63]
5.4 Inhaled	3	275	Mean Difference (Fixed, 95% CI)	-4.88 [-6.77, -2.99]
6 PVR	7	658	Mean Difference (Fixed, 95% CI)	-2.81 [-3.80, -1.82]
6.1 Intravenous	2	192	Mean Difference (Fixed, 95% CI)	-5.31 [-6.83, -3.80]
6.2 Oral	2	191	Mean Difference (Fixed, 95% CI)	-1.51 [-3.20, 0.18]
6.3 Inhaled	3	275	Mean Difference (Fixed, 95% CI)	-0.10 [-2.16, 1.96]
7 Cardiac index	6	868	Mean Difference (Fixed, 95% CI)	0.31 [0.23, 0.38]
7.1 Intravenous	2	192	Mean Difference (Fixed, 95% CI)	0.57 [0.40, 0.74]
7.2 Subcutaneous	1	469	Mean Difference (Fixed, 95% CI)	0.18 [0.07, 0.29]
7.3 Oral	2	192	Mean Difference (Fixed, 95% CI)	0.16 [-0.04, 0.36]
7.4 Inhaled	1	15	Mean Difference (Fixed, 95% CI)	0.48 [0.30, 0.66]
8 Cardiac output	2	260	Mean Difference (Fixed, 95% CI)	0.57 [0.32, 0.81]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
8.1 Inhaled	2	260	Mean Difference (Fixed, 95% CI)	0.57 [0.32, 0.81]
9 RAP	6	1060	Mean Difference (Fixed, 95% CI)	-1.90 [-2.58, -1.22]
9.1 Intravenous	2	192	Mean Difference (Fixed, 95% CI)	-2.41 [-4.10, -0.72]
9.2 Subcutaneous	1	469	Mean Difference (Fixed, 95% CI)	-1.90 [-3.01, -0.79]
9.3 Oral	2	196	Mean Difference (Fixed, 95% CI)	-1.0 [-2.60, 0.60]
9.4 Inhaled	1	203	Mean Difference (Fixed, 95% CI)	-2.2 [-3.49, -0.91]
10 Dyspnoea	8	1521	Std. Mean Difference (Fixed, 95% CI)	-0.21 [-0.32, -0.11]
10.1 Intravenous	2	116	Std. Mean Difference (Fixed, 95% CI)	-0.92 [-1.31, -0.52]
10.2 Subcutaneous	1	469	Std. Mean Difference (Fixed, 95% CI)	-0.33 [-0.51, -0.14]
10.3 Oral	3	668	Std. Mean Difference (Fixed, 95% CI)	-0.09 [-0.25, 0.06]
10.4 Inhaled	2	268	Std. Mean Difference (Fixed, 95% CI)	-0.05 [-0.29, 0.19]
11 Quality of life	3	271	Std. Mean Difference (Fixed, 95% CI)	0.28 [0.04, 0.52]
11.1 Intravenous	1	69	Std. Mean Difference (Fixed, 95% CI)	0.78 [0.29, 1.28]
11.2 Oral	1	187	Std. Mean Difference (Fixed, 95% CI)	0.07 [-0.22, 0.36]
11.3 Inhaled	1	15	Std. Mean Difference (Fixed, 95% CI)	0.88 [-0.20, 1.95]
12 Clincal worsening	12	2238	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.48, 0.92]
12.1 Intravenous	2	125	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.10, 1.01]
12.2 Subcutaneous	1	469	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.38, 1.73]
12.3 Oral	5	1126	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.53, 1.25]
12.4 Inhaled	4	518	Odds Ratio (M-H, Fixed, 95% CI)	0.42 [0.20, 0.89]
13 Adverse events - syncope	4	560	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.42, 1.42]
14 Adverse events - dizziness	10	1939	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.84, 1.42]
15 Adverse events - va-sodilation	11	2277	Odds Ratio (M-H, Fixed, 95% CI)	5.03 [3.84, 6.58]
16 Adverse events - headache	12	2351	Odds Ratio (M-H, Fixed, 95% CI)	3.16 [2.62, 3.80]
17 Adverse events - jaw pain	10	2149	Odds Ratio (M-H, Fixed, 95% CI)	5.25 [3.96, 6.98]

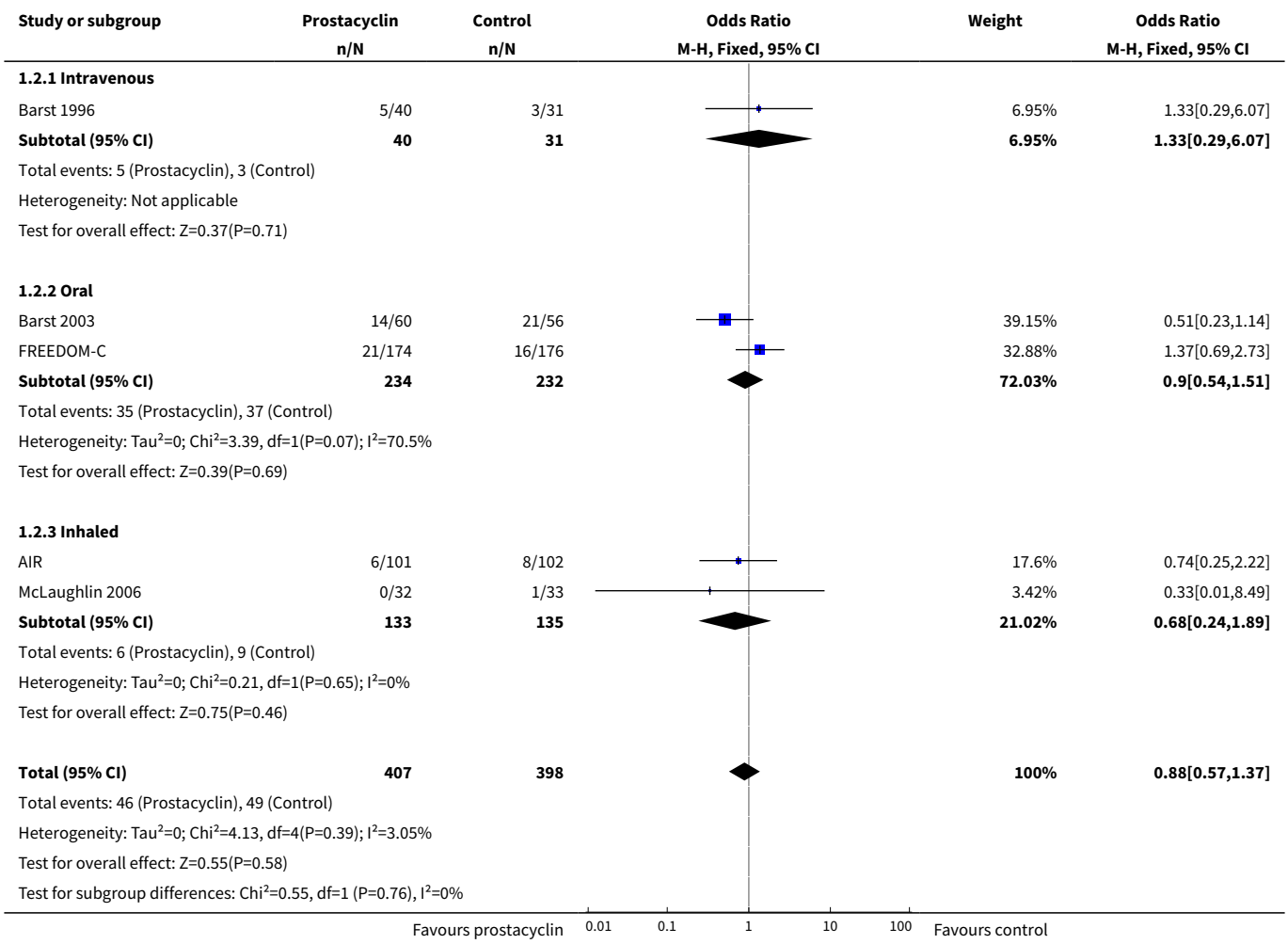
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
18 Adverse events - di-arrhoea	10	2317	Odds Ratio (M-H, Fixed, 95% CI)	2.81 [2.29, 3.46]
19 Adverse events - leg pain	2	246	Odds Ratio (M-H, Fixed, 95% CI)	2.96 [1.02, 8.62]
20 Adverse events - nausea and vomiting	12	2399	Odds Ratio (M-H, Fixed, 95% CI)	2.39 [1.98, 2.88]
21 Adverse events - abdominal pain	2	465	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.75, 2.42]
22 Adverse events - pain in extremity	6	1236	Odds Ratio (M-H, Fixed, 95% CI)	3.36 [2.32, 4.85]
23 Adverse events - myalgia	3	1009	Odds Ratio (M-H, Fixed, 95% CI)	2.75 [1.65, 4.58]
24 Adverse events - upper respiratory tract events	7	1038	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [1.22, 2.13]
25 Adverse events - peripheral oedema	6	1228	Odds Ratio (M-H, Fixed, 95% CI)	1.46 [0.98, 2.17]
26 Adverse events - in-fusion site reaction	2	580	Odds Ratio (M-H, Fixed, 95% CI)	14.41 [9.16, 22.66]

Analysis 1.1. Comparison 1 Prostacyclin versus control, Outcome 1 Improvement in WHO functional class.



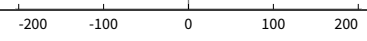


Analysis 1.2. Comparison 1 Prostacyclin versus control, Outcome 2 Worsening of WHO functional class.



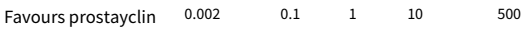
Analysis 1.3. Comparison 1 Prostacyclin versus control, Outcome 3 6MWD.

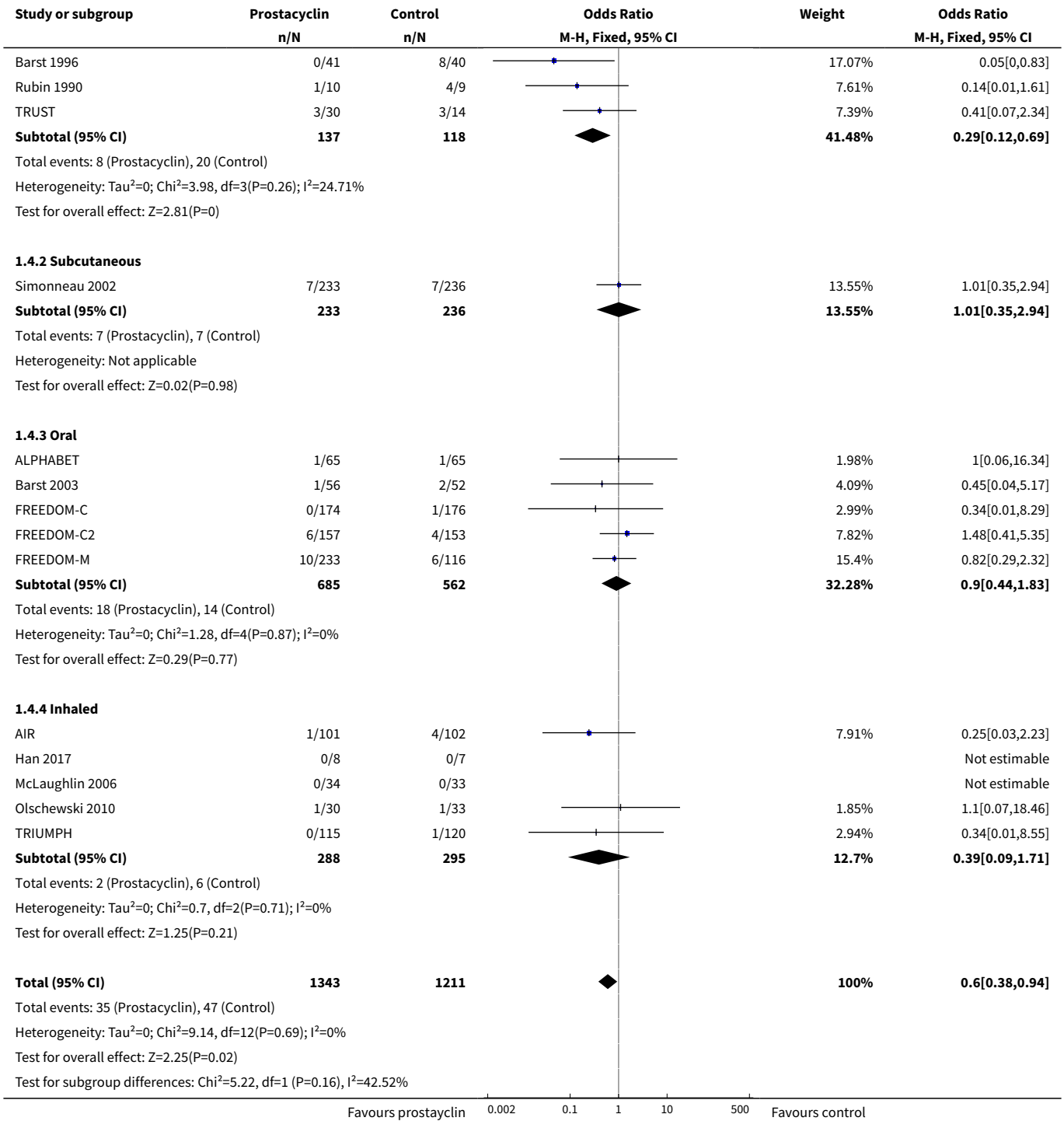
Study or subgroup	Prostacyclin N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 Intravenous						
Badesch 2000	56	55	108 (26.939)		0.79%	108[55.2,160.8]
Barst 1996	40	31	91 (29.411)		0.66%	91[33.36,148.64]
Rubin 1990	10	9	45 (46.068)		0.27%	45[-45.29,135.29]
TRUST	30	14	92.7 (42)		0.32%	92.7[10.38,175.02]
Subtotal (95% CI)					**2.04%**	**91.76[58.97,124.55]**
Heterogeneity: Tau²=0; Chi²=1.39, df=3(P=0.71); I²=0%						
Test for overall effect: Z=5.48(P<0.0001)						
1.3.2 Subcutaneous						
Simonneau 2002	233	236	16 (4.4)		29.48%	16[7.38,24.62]
Subtotal (95% CI)					**29.48%**	**16[7.38,24.62]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.64(P=0)						
1.3.3 Oral						
ALPHABET	65	65	25.1 (11.888)		4.04%	25.1[1.8,48.4]
FREEDOM-C	174	176	11 (5.612)		18.12%	11[0,22]
FREEDOM-C2	157	153	10 (6.225)		14.73%	10[-2.2,22.2]
FREEDOM-M	182	98	26 (8.163)		8.56%	26[10,42]
Subtotal (95% CI)					**45.46%**	**14.76[7.81,21.7]**
Heterogeneity: Tau²=0; Chi²=3.69, df=3(P=0.3); I²=18.61%						
Test for overall effect: Z=4.16(P<0.0001)						
1.3.4 Inhaled						
AIR	101	102	36 (10.63)		5.05%	36[15.17,56.83]
Han 2017	8	7	132.9 (31.066)		0.59%	132.89[72,193.78]
McLaughlin 2006	32	33	26 (16.279)		2.15%	26[-5.91,57.91]
TRIUMPH	115	120	20 (6.123)		15.23%	20[8,32]
Subtotal (95% CI)					**23.02%**	**26.97[17.21,36.73]**
Heterogeneity: Tau²=0; Chi²=13.65, df=3(P=0); I²=78.01%						
Test for overall effect: Z=5.42(P<0.0001)						
Total (95% CI)					**100%**	**19.5[14.82,24.19]**
Heterogeneity: Tau²=0; Chi²=42.06, df=12(P<0.0001); I²=71.47%						
Test for overall effect: Z=8.16(P<0.0001)						
Test for subgroup differences: Chi²=23.33, df=1 (P<0.0001), I²=87.14%						



Analysis 1.4. Comparison 1 Prostacyclin versus control, Outcome 4 Mortality.

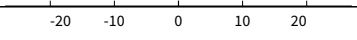
Study or subgroup	Prostacyclin n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.1 Intravenous					
Badesch 2000	4/56	5/55		9.41%	0.77[0.2,3.03]





Analysis 1.5. Comparison 1 Prostacyclin versus control, Outcome 5 mPAP.

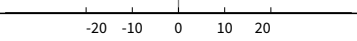
Study or subgroup	Prostacyclin N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 Intravenous						
Badesch 2000	56	55	-6 (1.536)		13.87%	-5.97[-8.98,-2.96]
Barst 1996	41	40	-6.7 (2.041)		7.85%	-6.7[-10.7,-2.7]
Subtotal (95% CI)					**21.72%**	**-6.23[-8.64,-3.83]**
Heterogeneity: Tau^2=0; Chi^2=0.08, df=1(P=0.78); I^2=0%						
Test for overall effect: Z=5.08(P<0.0001)						
1.5.2 Subcutaneous						
Simonneau 2002	233	236	-0.7 (1.273)		20.18%	-0.7[-3.19,1.79]
Subtotal (95% CI)					**20.18%**	**-0.7[-3.19,1.79]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.55(P=0.58)						
1.5.3 Oral						
ALPHABET	65	65	-2 (1.414)		16.35%	-2[-4.77,0.77]
Barst 2003	38	28	-1 (2.236)		6.54%	-1[-5.38,3.38]
Subtotal (95% CI)					**22.89%**	**-1.71[-4.06,0.63]**
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.71); I^2=0%						
Test for overall effect: Z=1.43(P=0.15)						
1.5.4 Inhaled						
AIR	101	102	-4.4 (1.15)		24.71%	-4.4[-6.65,-2.15]
Han 2017	8	7	-16.9 (4.482)		1.63%	-16.9[-25.68,-8.12]
McLaughlin 2006	29	28	-4 (1.92)		8.87%	-4[-7.76,-0.24]
Subtotal (95% CI)					**35.21%**	**-4.88[-6.77,-2.99]**
Heterogeneity: Tau^2=0; Chi^2=7.58, df=2(P=0.02); I^2=73.6%						
Test for overall effect: Z=5.06(P<0.0001)						
Total (95% CI)					**100%**	**-3.6[-4.73,-2.48]**
Heterogeneity: Tau^2=0; Chi^2=21.84, df=7(P=0); I^2=67.95%						
Test for overall effect: Z=6.3(P<0.0001)						
Test for subgroup differences: Chi^2=14.04, df=1 (P=0), I^2=78.64%						



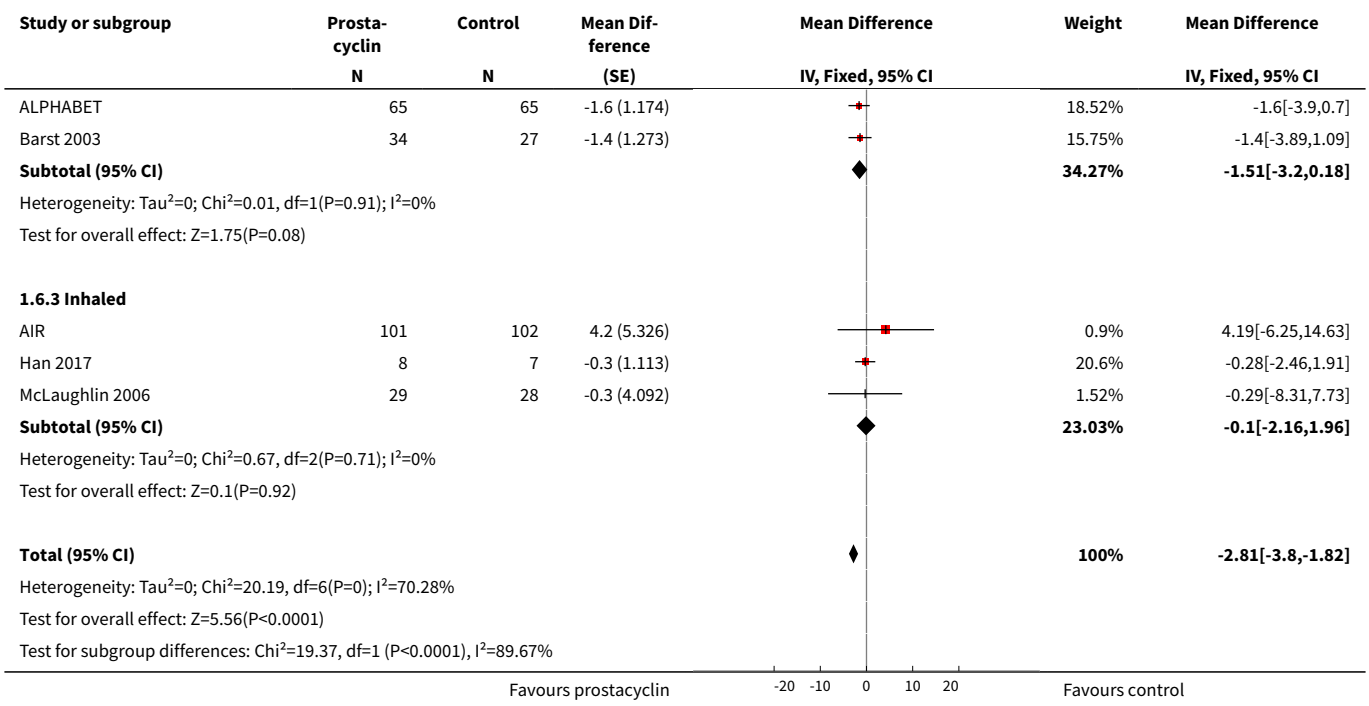
Favours prostacyclin — Favours control

Analysis 1.6. Comparison 1 Prostacyclin versus control, Outcome 6 PVR.

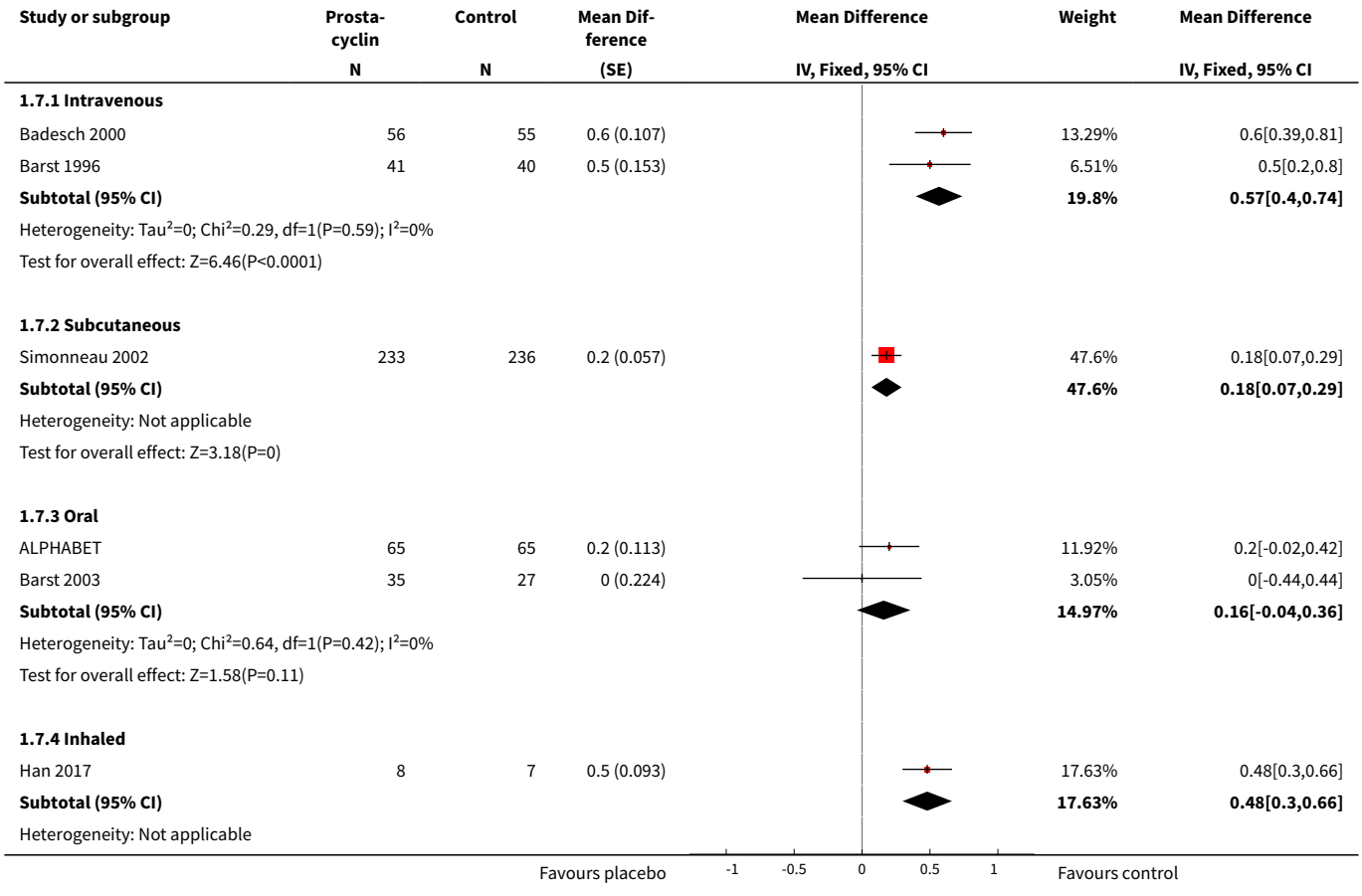
Study or subgroup	Prostacyclin N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 Intravenous						
Badesch 2000	56	55	-5.5 (0.934)		29.26%	-5.5[-7.33,-3.67]
Barst 1996	41	40	-4.9 (1.378)		13.44%	-4.9[-7.6,-2.2]
Subtotal (95% CI)					**42.71%**	**-5.31[-6.83,-3.8]**
Heterogeneity: Tau^2=0; Chi^2=0.13, df=1(P=0.72); I^2=0%						
Test for overall effect: Z=6.87(P<0.0001)						
1.6.2 Oral						

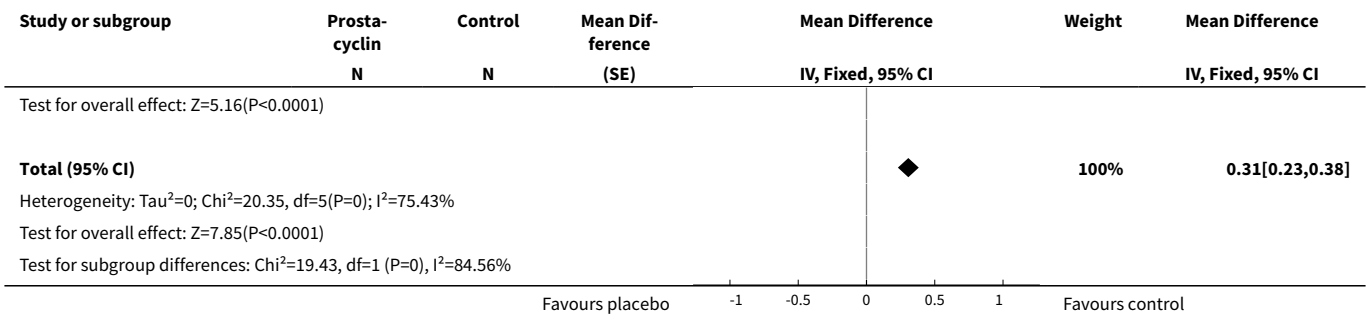


Favours prostacyclin — Favours control

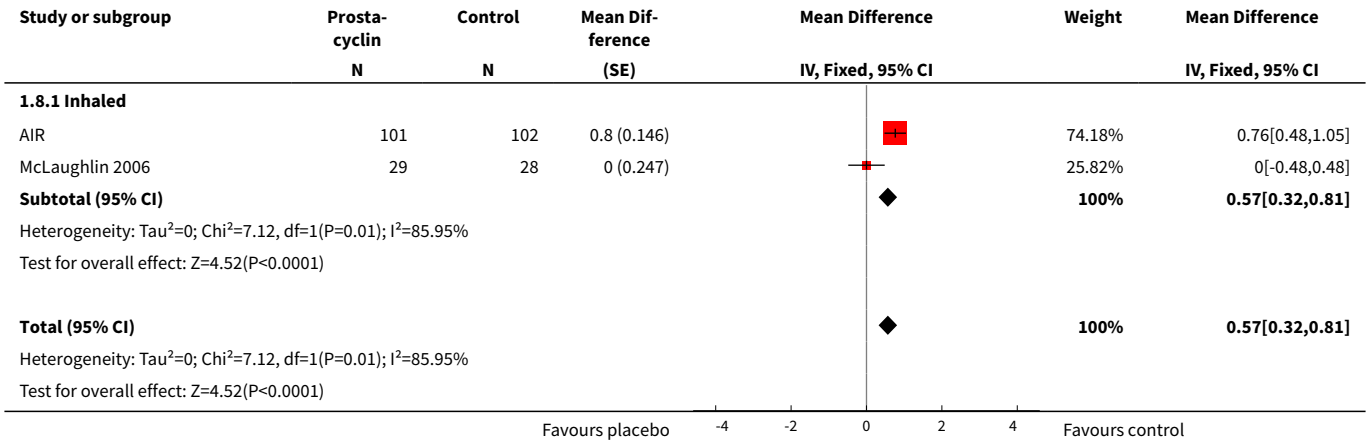


Analysis 1.7. Comparison 1 Prostacyclin versus control, Outcome 7 Cardiac index.

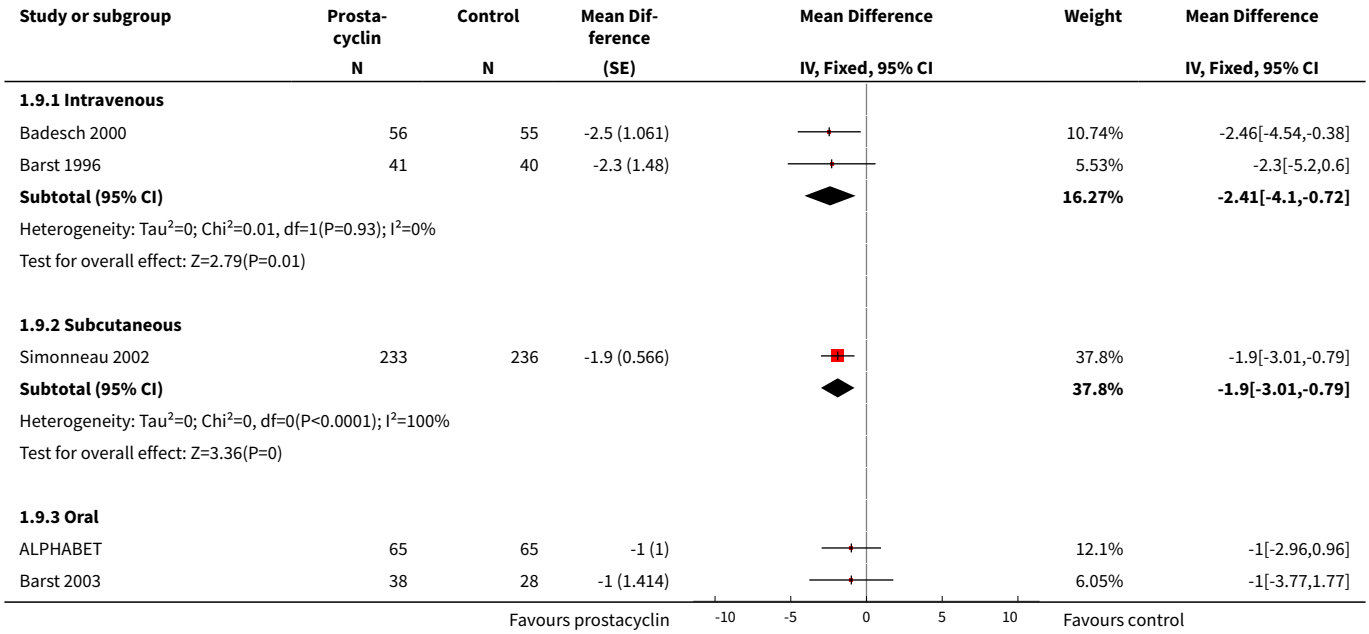


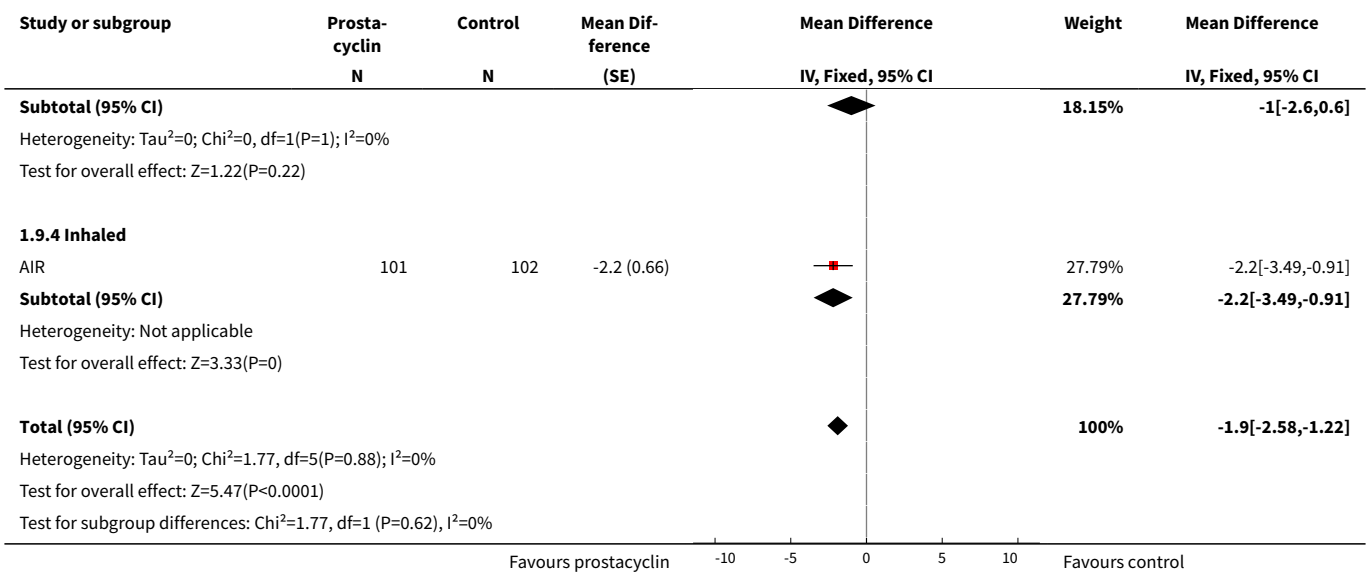


Analysis 1.8. Comparison 1 Prostacyclin versus control, Outcome 8 Cardiac output.

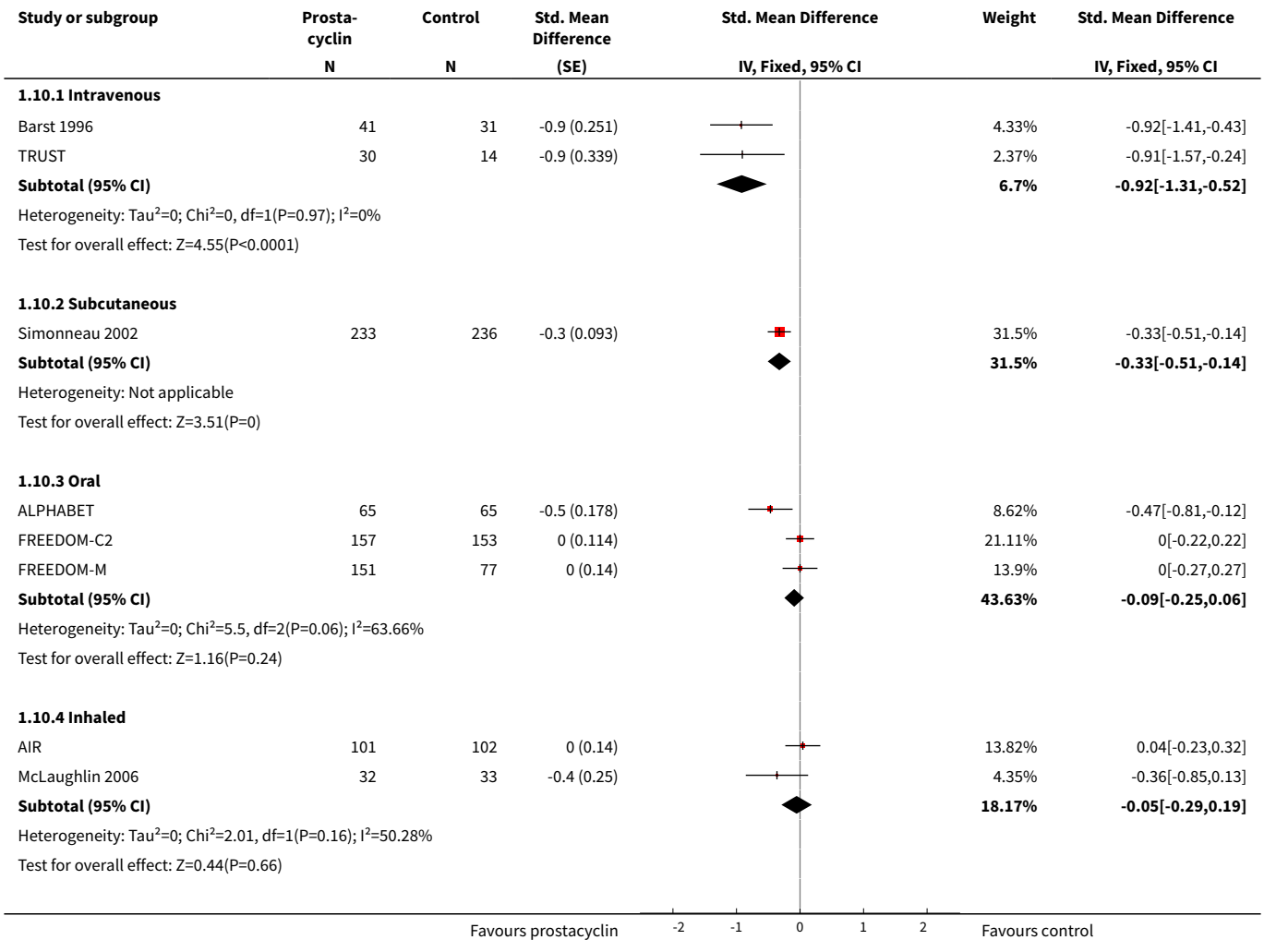


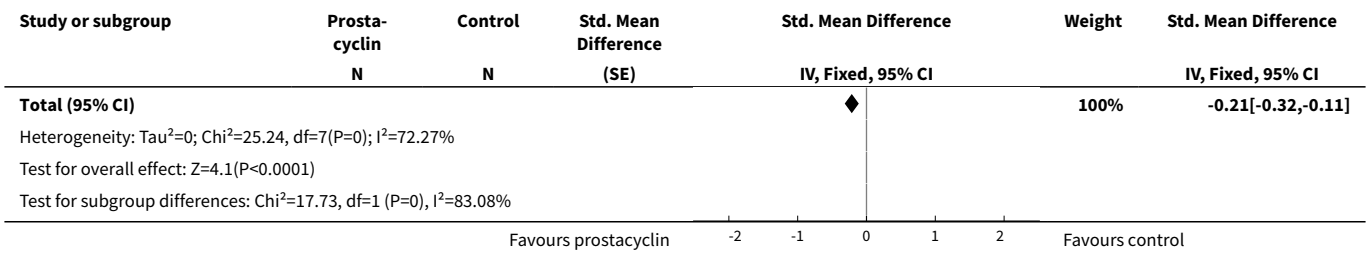
Analysis 1.9. Comparison 1 Prostacyclin versus control, Outcome 9 RAP.



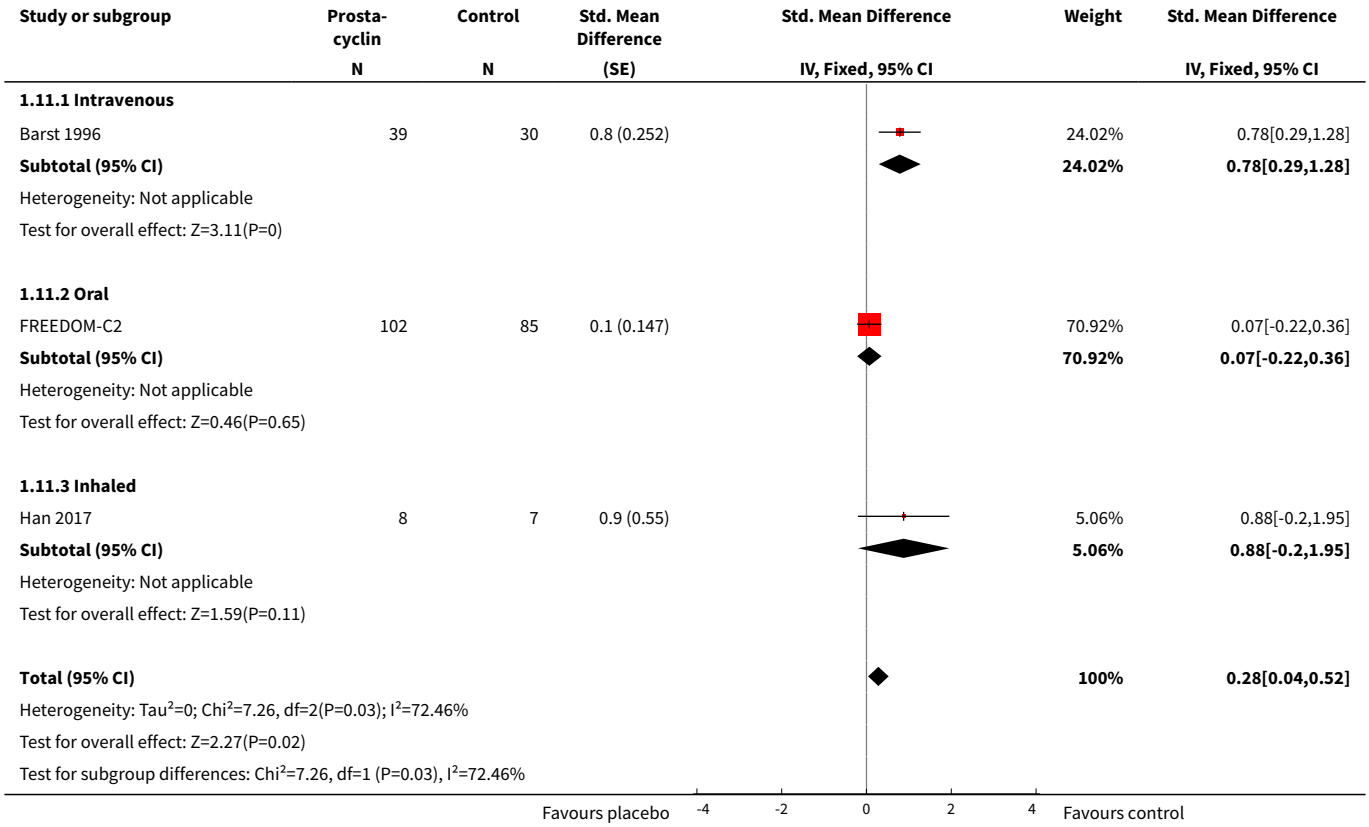


Analysis 1.10. Comparison 1 Prostacyclin versus control, Outcome 10 Dyspnoea.

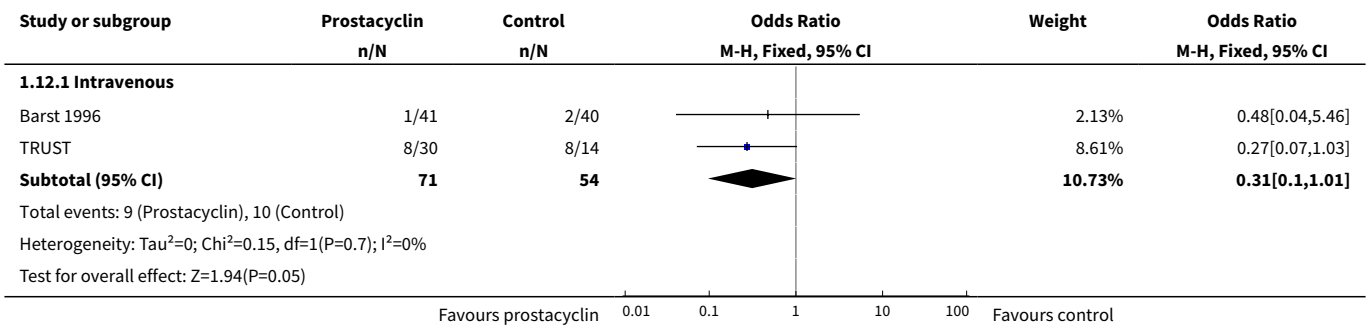


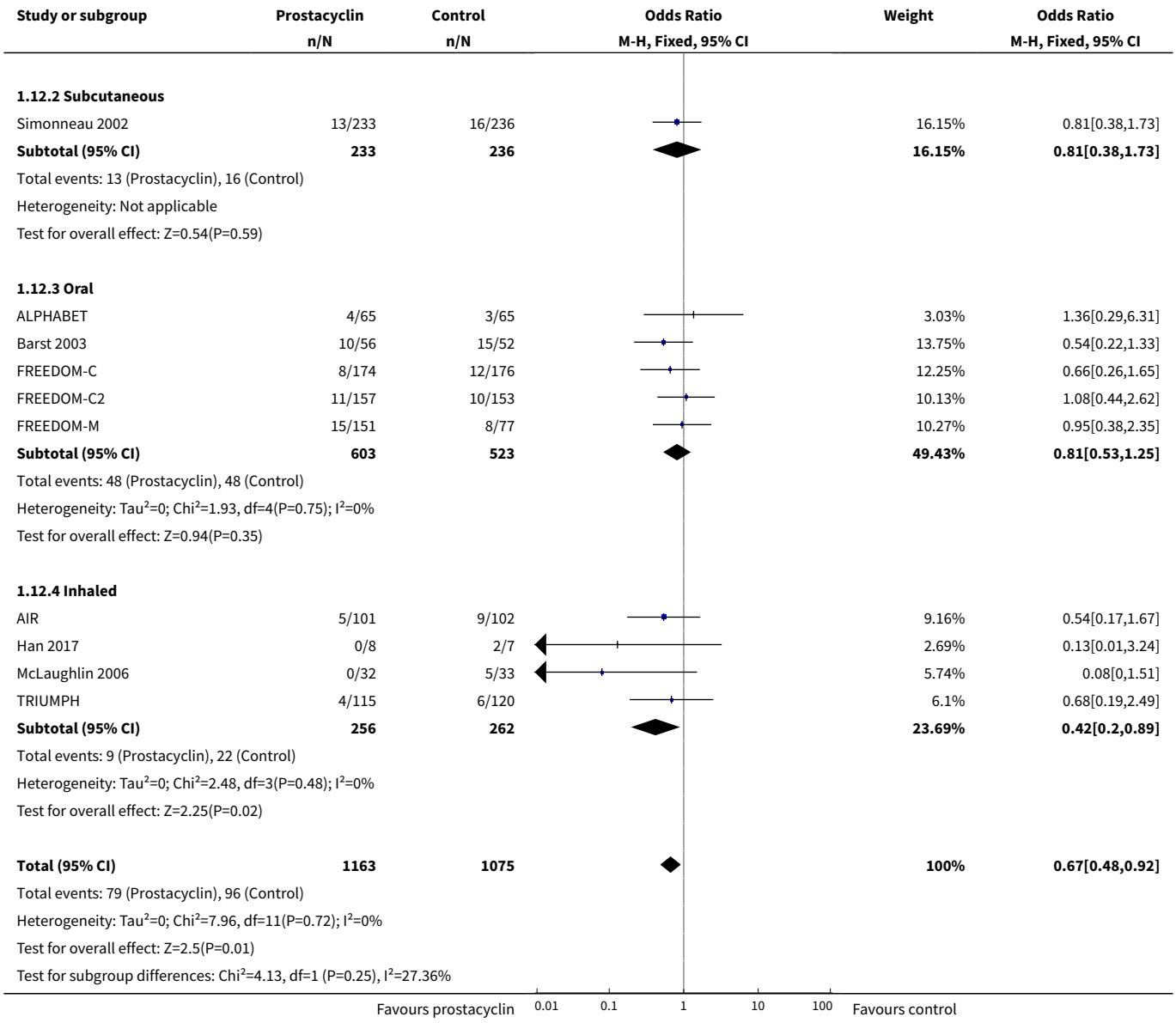


Analysis 1.11. Comparison 1 Prostacyclin versus control, Outcome 11 Quality of life.

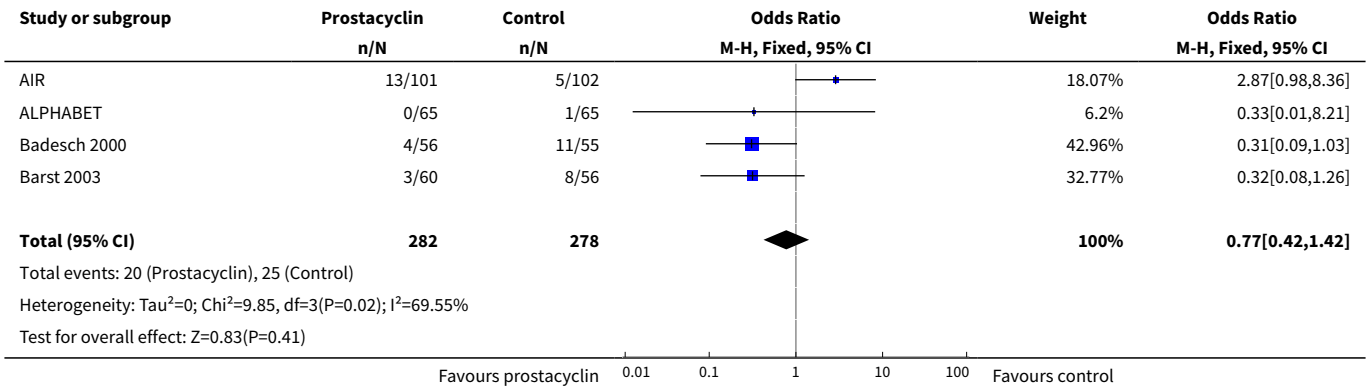


Analysis 1.12. Comparison 1 Prostacyclin versus control, Outcome 12 Clincal worsening.





Analysis 1.13. Comparison 1 Prostacyclin versus control, Outcome 13 Adverse events - syncope.



Analysis 1.14. Comparison 1 Prostacyclin versus control, Outcome 14 Adverse events - dizziness.

Study or subgroup	Prostacyclin n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
AIR	7/101	11/102		9.8%	0.62[0.23,1.66]
ALPHABET	0/65	2/65		2.39%	0.19[0.01,4.12]
Barst 2003	14/60	17/56		12.97%	0.7[0.31,1.59]
FREEDOM-C	30/174	28/176		22.16%	1.1[0.63,1.94]
FREEDOM-C2	30/157	15/153		11.82%	2.17[1.12,4.23]
Han 2017	1/8	0/7		0.42%	3[0.1,86.09]
McLaughlin 2006	5/35	8/32		6.89%	0.5[0.14,1.73]
Simonneau 2002	21/233	19/236		16.52%	1.13[0.59,2.16]
TRIUMPH	20/115	18/120		14%	1.19[0.6,2.39]
TRUST	7/30	3/14		3.02%	1.12[0.24,5.16]
Total (95% CI)	**978**	**961**		**100%**	**1.09[0.84,1.42]**
Total events: 135 (Prostacyclin), 121 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.7, df=9(P=0.38); I^2=7.23%					
Test for overall effect: Z=0.64(P=0.52)					

Analysis 1.15. Comparison 1 Prostacyclin versus control, Outcome 15 Adverse events - vasodilation.

Study or subgroup	Prostacyclin n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
AIR	27/101	9/102		12.04%	3.77[1.67,8.51]
ALPHABET	9/65	3/65		4.74%	3.32[0.86,12.89]
Barst 2003	34/60	15/56		12.34%	3.57[1.64,7.81]
FREEDOM-C	85/174	27/176		25.2%	5.27[3.18,8.75]
FREEDOM-C2	55/127	16/153		15.1%	6.54[3.5,12.23]
FREEDOM-M	50/233	9/116		17.32%	3.25[1.54,6.87]
Han 2017	2/8	0/7		0.7%	5.77[0.23,143.37]
McLaughlin 2006	9/35	3/32		4.27%	3.35[0.82,13.7]
Olschewski 2010	8/30	4/33		5.13%	2.64[0.7,9.89]
Simonneau 2002	25/233	1/236		1.63%	28.25[3.79,210.27]
TRIUMPH	17/115	1/120		1.53%	20.64[2.7,157.87]
Total (95% CI)	**1181**	**1096**		**100%**	**5.03[3.84,6.58]**
Total events: 321 (Prostacyclin), 88 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.52, df=10(P=0.48); I^2=0%					
Test for overall effect: Z=11.77(P<0.0001)					

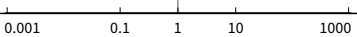
Analysis 1.16. Comparison 1 Prostacyclin versus control, Outcome 16 Adverse events - headache.

Study or subgroup	Prostacyclin n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
AIR	30/101	20/102		10.97%	1.73[0.91,3.31]
ALPHABET	11/65	1/65		0.65%	13.04[1.63,104.24]
Barst 2003	44/60	32/56		6.92%	2.06[0.95,4.5]
FREEDOM-C	150/174	65/176		6.99%	10.67[6.29,18.11]
FREEDOM-C2	112/157	61/153		13.89%	3.75[2.34,6.03]
FREEDOM-M	160/233	36/116		11.81%	4.87[3.01,7.88]
Han 2017	1/8	0/7		0.35%	3[0.1,86.09]
McLaughlin 2006	19/35	7/32		2.62%	4.24[1.45,12.36]
Olschewski 2010	4/30	3/33		1.94%	1.54[0.31,7.52]
Simonneau 2002	64/233	54/236		30.52%	1.28[0.84,1.94]
TRIUMPH	47/115	27/120		12.26%	2.38[1.35,4.2]
TRUST	15/30	2/14		1.07%	6[1.14,31.53]
Total (95% CI)	**1241**	**1110**		**100%**	**3.16[2.62,3.8]**
Total events: 657 (Prostacyclin), 308 (Control)					
Heterogeneity: Tau^2=0; Chi^2=50.87, df=11(P<0.0001); I^2=78.38%					
Test for overall effect: Z=12.12(P<0.0001)					

Favours prostacyclin — Favours control

Analysis 1.17. Comparison 1 Prostacyclin versus control, Outcome 17 Adverse events - jaw pain.

Study or subgroup	Prostacyclin n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
AIR	12/101	3/102		5.43%	4.45[1.22,16.28]
ALPHABET	2/65	0/65		0.99%	5.16[0.24,109.55]
Badesch 2000	42/56	0/55		0.26%	325.34[18.87,5609.65]
Barst 2003	34/60	11/56		10.18%	5.35[2.32,12.32]
FREEDOM-C	74/174	21/176		24.78%	5.46[3.16,9.43]
FREEDOM-C2	39/157	10/153		15.72%	4.73[2.26,9.87]
FREEDOM-M	59/233	8/116		16.47%	4.58[2.11,9.95]
McLaughlin 2006	10/35	3/32		4.62%	3.87[0.96,15.63]
Simonneau 2002	21/233	11/236		20.53%	2.03[0.95,4.3]
TRUST	8/30	0/14		1.01%	10.96[0.59,204.67]
Total (95% CI)	**1144**	**1005**		**100%**	**5.25[3.96,6.98]**
Total events: 301 (Prostacyclin), 67 (Control)					
Heterogeneity: Tau^2=0; Chi^2=14.93, df=9(P=0.09); I^2=39.71%					
Test for overall effect: Z=11.45(P<0.0001)					

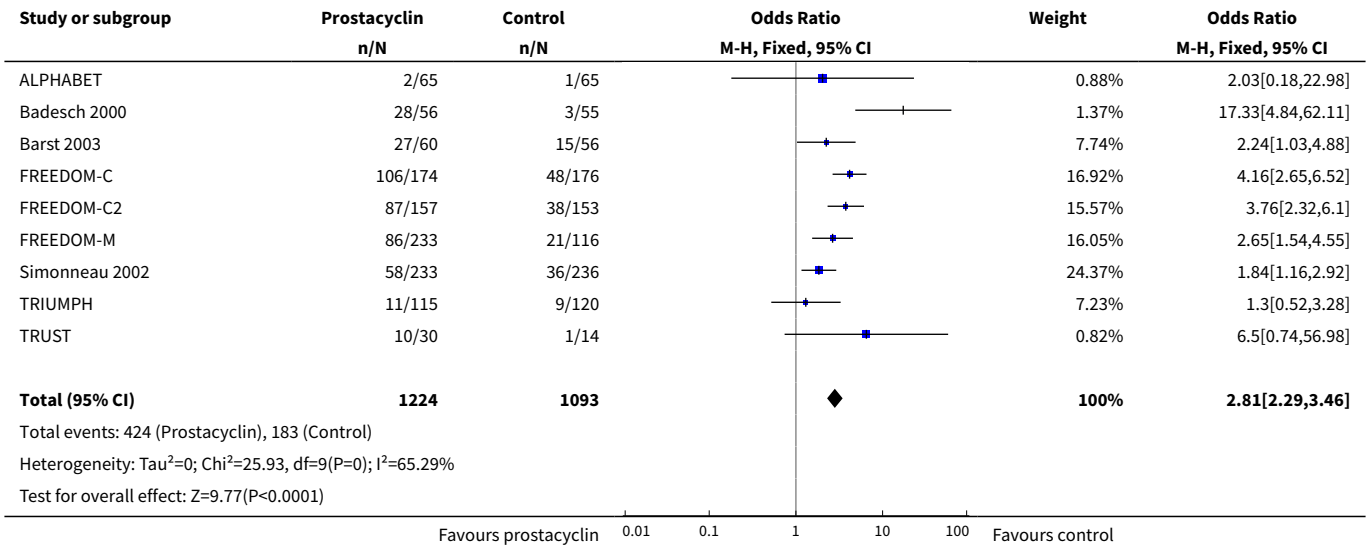


Favours prostacyclin — Favours control

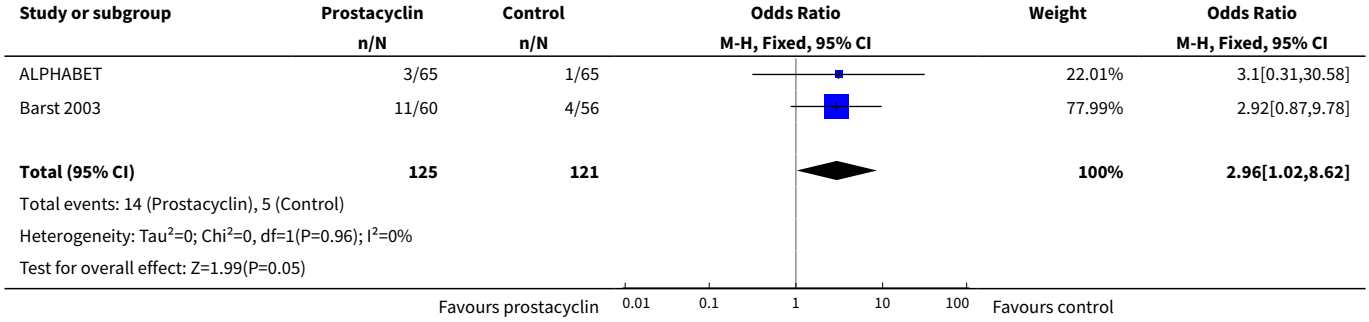
Analysis 1.18. Comparison 1 Prostacyclin versus control, Outcome 18 Adverse events - diarrhoea.

Study or subgroup	Prostacyclin n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
AIR	9/101	11/102		9.04%	0.81[0.32,2.05]

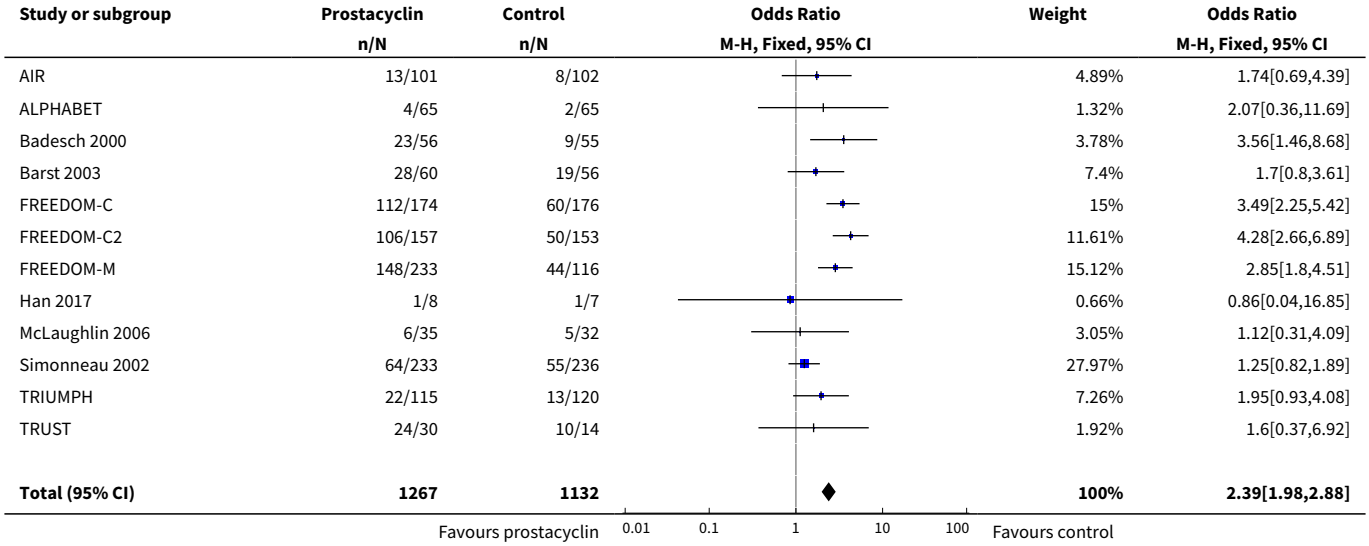
Favours prostacyclin — Favours control

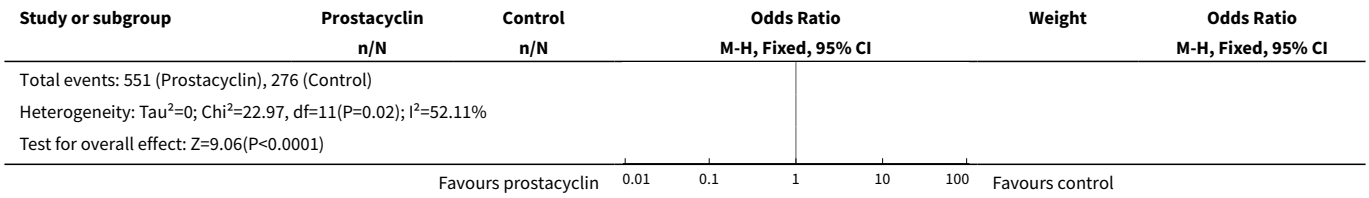


Analysis 1.19. Comparison 1 Prostacyclin versus control, Outcome 19 Adverse events - leg pain.

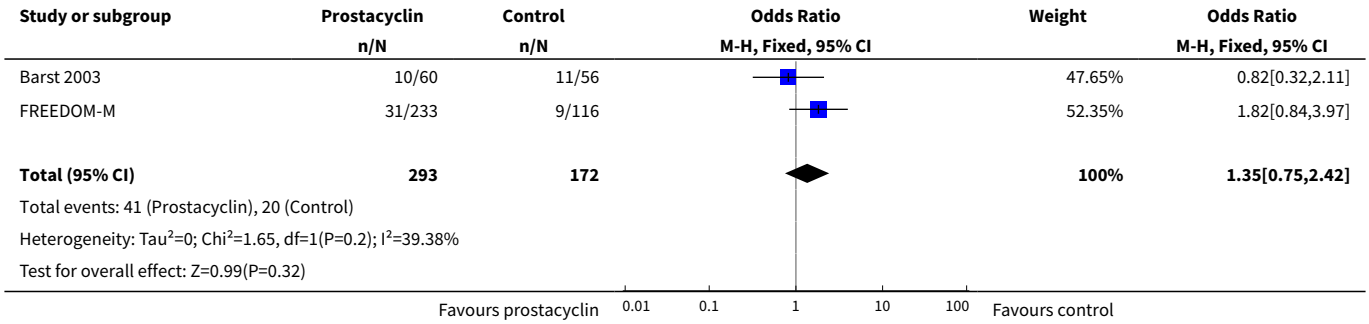


Analysis 1.20. Comparison 1 Prostacyclin versus control, Outcome 20 Adverse events - nausea and vomiting.

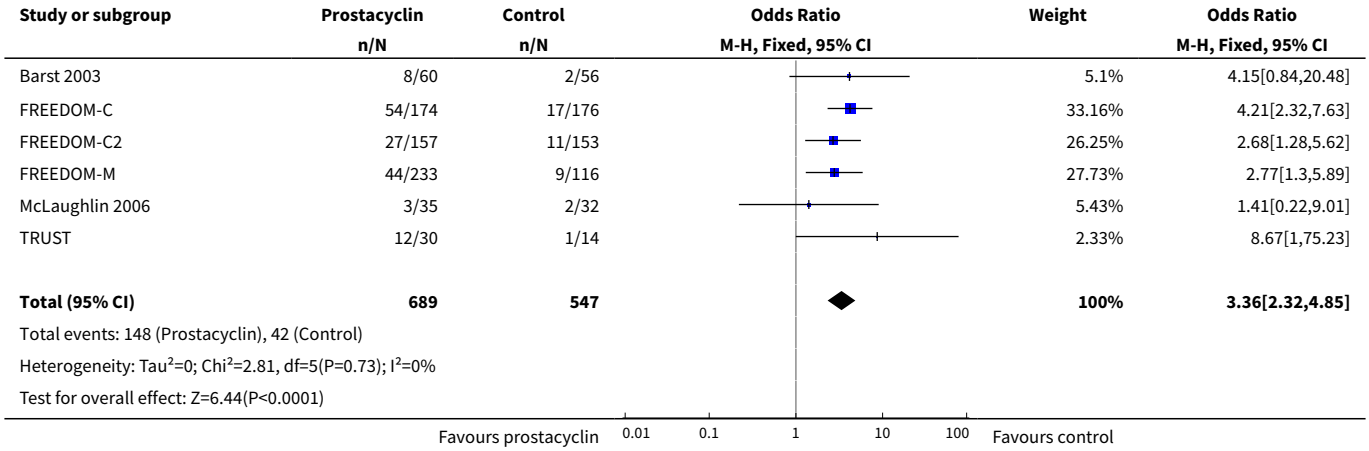




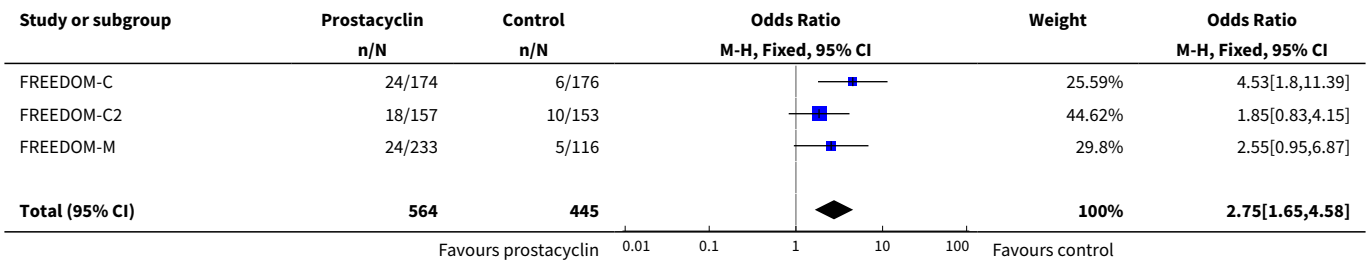
Analysis 1.21. Comparison 1 Prostacyclin versus control, Outcome 21 Adverse events - abdominal pain.



Analysis 1.22. Comparison 1 Prostacyclin versus control, Outcome 22 Adverse events - pain in extremity.



Analysis 1.23. Comparison 1 Prostacyclin versus control, Outcome 23 Adverse events - myalgia.



Study or subgroup	Prostacyclin n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Total events: 66 (Prostacyclin), 21 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.07, df=2(P=0.35); I^2=3.56%					
Test for overall effect: Z=3.86(P=0)					

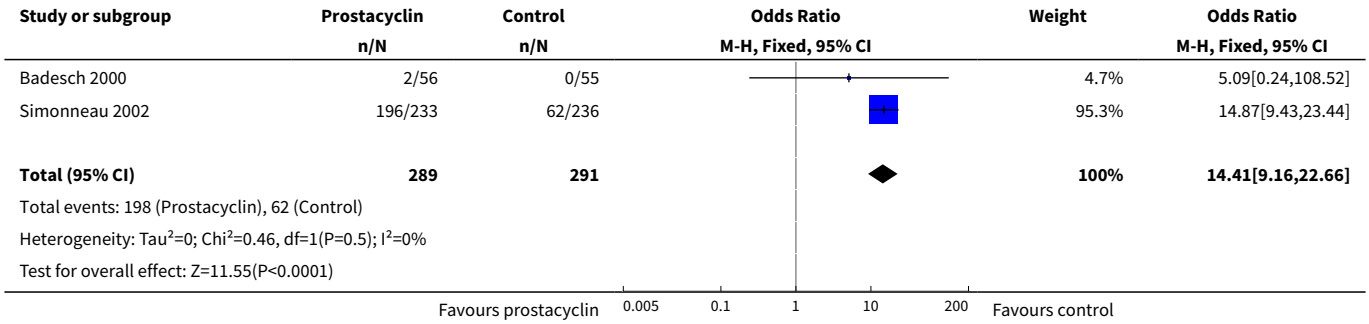
Analysis 1.24. Comparison 1 Prostacyclin versus control, Outcome 24 Adverse events - upper respiratory tract events.

Study or subgroup	Prostacyclin n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
AIR	53/101	36/102		22.03%	2.02[1.15,3.56]
Barst 2003	18/60	27/56		25.3%	0.46[0.21,0.99]
FREEDOM-C2	17/157	13/153		15.2%	1.31[0.61,2.79]
McLaughlin 2006	15/35	10/32		7.73%	1.65[0.6,4.5]
Olschewski 2010	8/30	6/33		5.42%	1.64[0.49,5.43]
TRIUMPH	62/115	35/120		20.43%	2.84[1.66,4.87]
TRUST	8/30	3/14		3.88%	1.33[0.29,6.04]
Total (95% CI)	**528**	**510**		**100%**	**1.61[1.22,2.13]**
Total events: 181 (Prostacyclin), 130 (Control)					
Heterogeneity: Tau^2=0; Chi^2=15.66, df=6(P=0.02); I^2=61.68%					
Test for overall effect: Z=3.32(P=0)					

Analysis 1.25. Comparison 1 Prostacyclin versus control, Outcome 25 Adverse events - peripheral oedema.

Study or subgroup	Prostacyclin n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
AIR	13/101	16/102		33.98%	0.79[0.36,1.75]
Barst 2003	8/60	5/56		10.98%	1.57[0.48,5.12]
FREEDOM-C2	17/157	10/153		22.13%	1.74[0.77,3.92]
McLaughlin 2006	3/35	3/32		7.02%	0.91[0.17,4.85]
Olschewski 2010	3/30	6/33		12.6%	0.5[0.11,2.21]
Simonneau 2002	21/233	6/236		13.29%	3.8[1.5,9.59]
Total (95% CI)	**616**	**612**		**100%**	**1.46[0.98,2.17]**
Total events: 65 (Prostacyclin), 46 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.87, df=5(P=0.11); I^2=43.64%					
Test for overall effect: Z=1.86(P=0.06)					

Analysis 1.26. Comparison 1 Prostacyclin versus control, Outcome 26 Adverse events - infusion site reaction.

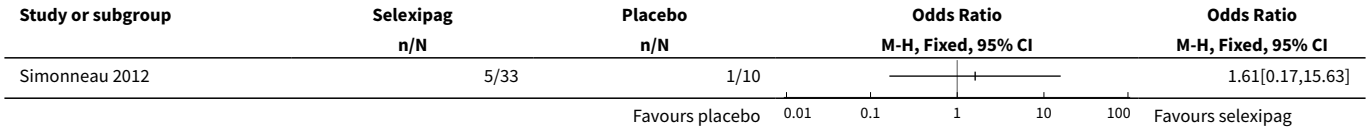


Comparison 2. Selexipag versus placebo

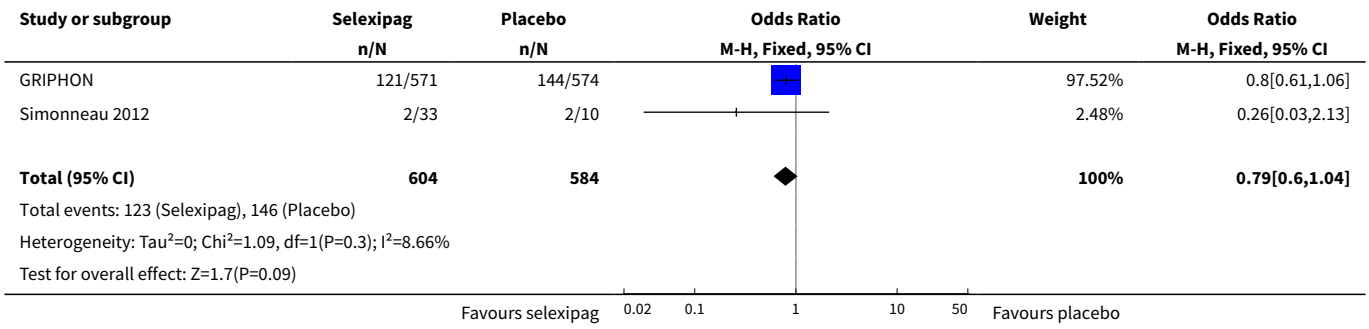
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in WHO FC	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Worsening in WHO FC	2	1188	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.60, 1.04]
3 6MWD	2	1199	Mean Difference (Fixed, 95% CI)	12.62 [1.90, 23.34]
4 Mortality	2	1199	Risk Difference (M-H, Fixed, 95% CI)	0.02 [-0.00, 0.04]
5 mPAP	1		Mean Difference (Fixed, 95% CI)	Totals not selected
6 PVR	1		Mean Difference (Fixed, 95% CI)	Totals not selected
7 Cardiac index	1		Mean Difference (Fixed, 95% CI)	Totals not selected
8 RAP	1		Mean Difference (Fixed, 95% CI)	Totals not selected
9 Dyspnoea	1	43	Mean Difference (Fixed, 95% CI)	-0.1 [-1.40, 1.20]
10 Clinical worsening	2	1199	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.37, 0.60]
11 Adverse events- dizziness	2	1195	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.76, 1.44]
12 Adverse events - headache	2	1195	Odds Ratio (M-H, Fixed, 95% CI)	3.91 [3.07, 4.98]
13 Adverse events - vasodilation	2	1195	Odds Ratio (M-H, Fixed, 95% CI)	2.67 [1.72, 4.17]
14 Adverse events - jaw pain	2	1195	Odds Ratio (M-H, Fixed, 95% CI)	5.33 [3.64, 7.81]
15 Adverse events - diarrhoea	2	1195	Odds Ratio (M-H, Fixed, 95% CI)	3.11 [2.39, 4.05]
16 Adverse events - nausea or vomiting	2	1195	Odds Ratio (M-H, Fixed, 95% CI)	2.92 [2.29, 3.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17 Adverse events - pain in extremity	2	1195	Odds Ratio (M-H, Fixed, 95% CI)	2.44 [1.69, 3.52]
18 Adverse events - myalgias	2	1195	Odds Ratio (M-H, Fixed, 95% CI)	3.05 [2.02, 4.58]
19 Adverse events - upper respiratory tract infection	2	1195	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.78, 1.26]

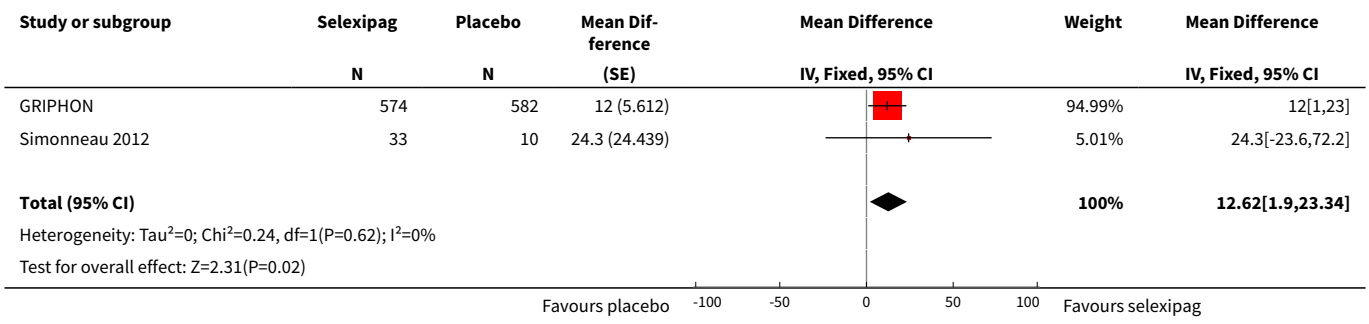
Analysis 2.1. Comparison 2 Selexipag versus placebo, Outcome 1 Improvement in WHO FC.



Analysis 2.2. Comparison 2 Selexipag versus placebo, Outcome 2 Worsening in WHO FC.



Analysis 2.3. Comparison 2 Selexipag versus placebo, Outcome 3 6MWD.

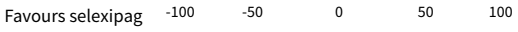


Analysis 2.4. Comparison 2 Selexipag versus placebo, Outcome 4 Mortality.

Study or subgroup	Selexipag n/N	Placebo n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
GRIPHON	28/574	18/582		97.41%	0.02[-0,0.04]
Simonneau 2012	0/33	0/10		2.59%	0[-0.13,0.13]
Total (95% CI)	**607**	**592**		**100%**	**0.02[-0,0.04]**
Total events: 28 (Selexipag), 18 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.79); I^2=0%					
Test for overall effect: Z=1.53(P=0.13)					

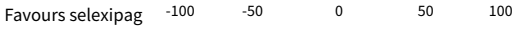
Analysis 2.5. Comparison 2 Selexipag versus placebo, Outcome 5 mPAP.

Study or subgroup	Selexipag N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Simonneau 2012	33	10	-7.4 (4.337)		-7.4[-15.9,1.1]



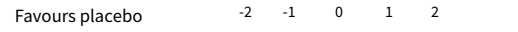
Analysis 2.6. Comparison 2 Selexipag versus placebo, Outcome 6 PVR.

Study or subgroup	Selexipag N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Simonneau 2012	33	10	-33 (7.143)		-33[-47,-19]



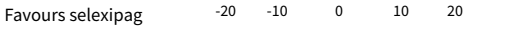
Analysis 2.7. Comparison 2 Selexipag versus placebo, Outcome 7 Cardiac index.

Study or subgroup	Selexipag N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Simonneau 2012	33	10	0.5 (0.189)		0.5[0.13,0.87]



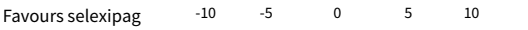
Analysis 2.8. Comparison 2 Selexipag versus placebo, Outcome 8 RAP.

Study or subgroup	Selexipag N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Simonneau 2012	33	10	3.2 (1.225)		3.2[0.8,5.6]



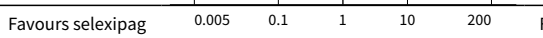
Analysis 2.9. Comparison 2 Selexipag versus placebo, Outcome 9 Dyspnoea.

Study or subgroup	Selexipag N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Simonneau 2012	33	10	-0.1 (0.663)		100%	-0.1[-1.4,1.2]
Total (95% CI)					**100%**	**-0.1[-1.4,1.2]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.15(P=0.88)						



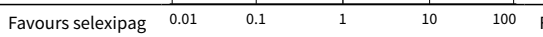
Analysis 2.10. Comparison 2 Selexipag versus placebo, Outcome 10 Clinical worsening.

Study or subgroup	Selexipag n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
GRIPHON	145/574	242/582		98.37%	0.47[0.37,0.61]
Simonneau 2012	1/33	2/10		1.63%	0.13[0.01,1.56]
Total (95% CI)	**607**	**592**		**100%**	**0.47[0.37,0.6]**
Total events: 146 (Selexipag), 244 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.07, df=1(P=0.3); I^2=6.12%					
Test for overall effect: Z=5.96(P<0.0001)					



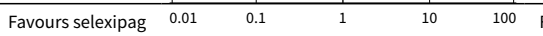
Analysis 2.11. Comparison 2 Selexipag versus placebo, Outcome 11 Adverse events- dizziness.

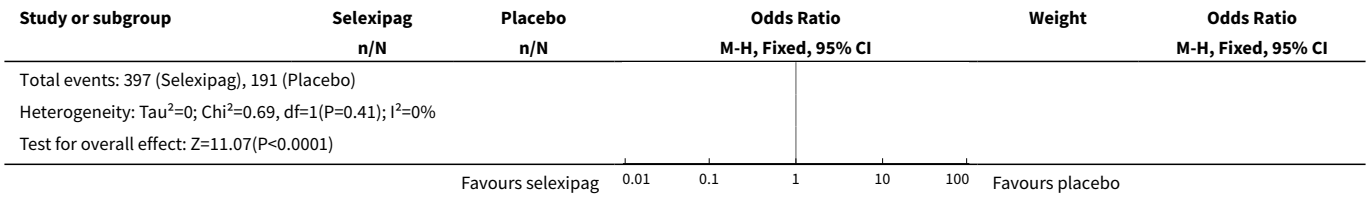
Study or subgroup	Selexipag n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
GRIPHON	86/575	85/577		99.13%	1.02[0.74,1.41]
Simonneau 2012	5/33	0/10		0.87%	4.05[0.21,79.81]
Total (95% CI)	**608**	**587**		**100%**	**1.04[0.76,1.44]**
Total events: 91 (Selexipag), 85 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.82, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=0.26(P=0.79)					



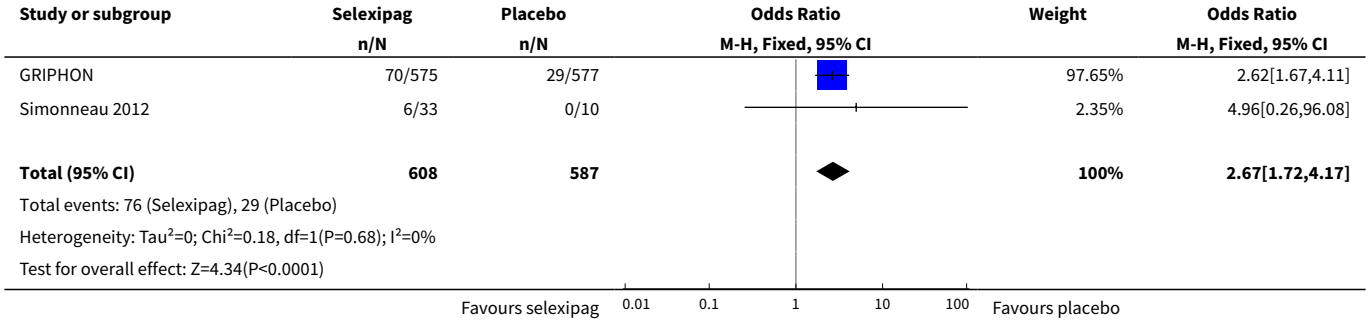
Analysis 2.12. Comparison 2 Selexipag versus placebo, Outcome 12 Adverse events - headache.

Study or subgroup	Selexipag n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
GRIPHON	375/575	189/577		98.46%	3.85[3.01,4.91]
Simonneau 2012	22/33	2/10		1.54%	8[1.45,44.24]
Total (95% CI)	**608**	**587**		**100%**	**3.91[3.07,4.98]**

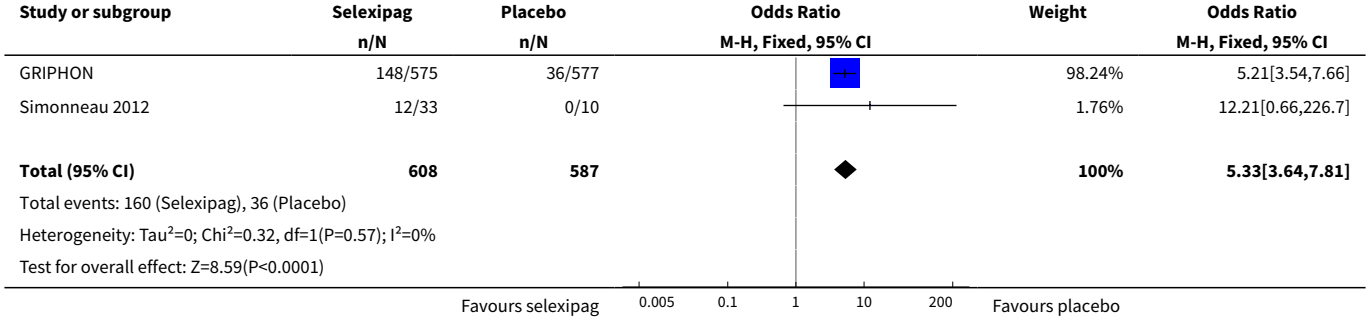




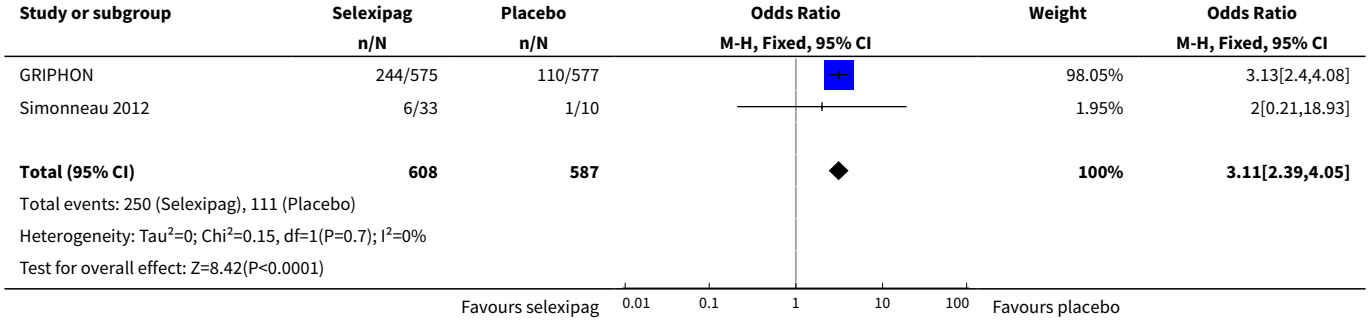
Analysis 2.13. Comparison 2 Selexipag versus placebo, Outcome 13 Adverse events - vasodilation.



Analysis 2.14. Comparison 2 Selexipag versus placebo, Outcome 14 Adverse events - jaw pain.



Analysis 2.15. Comparison 2 Selexipag versus placebo, Outcome 15 Adverse events - diarrhoea.



Analysis 2.16. Comparison 2 Selexipag versus placebo, Outcome 16 Adverse events - nausea or vomiting.

Study or subgroup	Selexipag n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
GRIPHON	297/575	156/577		99.28%	2.88[2.25,3.69]
Simonneau 2012	9/33	0/10		0.72%	8.14[0.43,153.15]
Total (95% CI)	**608**	**587**		**100%**	**2.92[2.29,3.73]**
Total events: 306 (Selexipag), 156 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.48, df=1(P=0.49); I^2=0%					
Test for overall effect: Z=8.58(P<0.0001)					

Analysis 2.17. Comparison 2 Selexipag versus placebo, Outcome 17 Adverse events - pain in extremity.

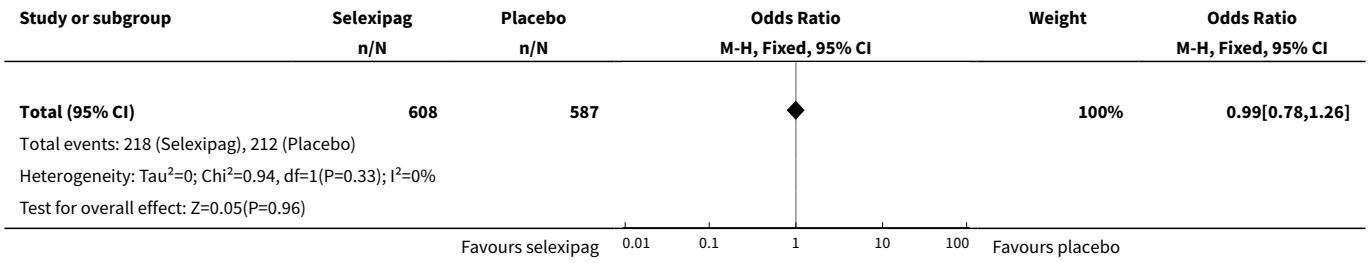
Study or subgroup	Selexipag n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
GRIPHON	97/575	46/577		98.65%	2.34[1.61,3.4]
Simonneau 2012	10/33	0/10		1.35%	9.38[0.5,175.52]
Total (95% CI)	**608**	**587**		**100%**	**2.44[1.69,3.52]**
Total events: 107 (Selexipag), 46 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.86, df=1(P=0.35); I^2=0%					
Test for overall effect: Z=4.75(P<0.0001)					

Analysis 2.18. Comparison 2 Selexipag versus placebo, Outcome 18 Adverse events - myalgias.

Study or subgroup	Selexipag n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
GRIPHON	92/575	34/577		97.75%	3.04[2.01,4.59]
Simonneau 2012	4/33	0/10		2.25%	3.2[0.16,64.69]
Total (95% CI)	**608**	**587**		**100%**	**3.05[2.02,4.58]**
Total events: 96 (Selexipag), 34 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.97); I^2=0%					
Test for overall effect: Z=5.34(P<0.0001)					

Analysis 2.19. Comparison 2 Selexipag versus placebo, Outcome 19 Adverse events - upper respiratory tract infection.

Study or subgroup	Selexipag n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
GRIPHON	206/575	210/577		98.57%	0.98[0.77,1.24]
Simonneau 2012	12/33	2/10		1.43%	2.29[0.42,12.56]



ADDITIONAL TABLES

Table 1. Summary of study characteristics

Study	N	Intervention	Comparator	Blinded	Duration
AIR	203	Inhaled iloprost	Placebo	Blinded	12 weeks
ALPHABET	130	Oral beraprost	Placebo	Blinded	12 weeks
Badesch 2000	111	Intravenous epoprostenol	Usual treatment	Open-label	12 weeks
Barst 1996	81	Intravenous epoprostenol	Conventional treatment	Open-label	12 weeks
Barst 2003	116	Oral beraprost	Placebo	Blinded	12 months
FREEDOM-C	349	Oral treprostinil	Placebo	Blinded	16 weeks
FREEDOM-C2	310	Oral treprostinil	Placebo	Blinded	16 weeks
FREEDOM-M	349	Oral treprostinil	Placebo	Blinded	12 weeks
GRIPHON	1156	Selexipag	Placebo	Blinded	Median 63 weeks
Han 2017	27	Inhaled iloprost	Other treatment*	Open-label	12 weeks
McLaughlin 2006	67	Inhaled iloprost	Placebo	Blinded	12 weeks
Olschewski 2010	63	Inhaled iloprost	Placebo	Open-label	2 years
Rubin 1990	19	Intravenous epoprostenol	Conventional treatment	Open-label	8 weeks
Simonneau 2002	470	Subcutaneous treprostinil	Placebo	Blinded	12 weeks
Simonneau 2012	43	Selexipag	Placebo	Blinded	17 weeks
TRIUMPH	235	Inhaled treprostinil	Placebo	Blinded	12 weeks
TRUST	44	Intravenous treprostinil	Placebo	Blinded	12 weeks

N = number of participants
*Inhaled iloprost + bosentan versus inhaled iloprost alone versus bosentan alone

Table 2. Sensitivity analysis: fixed- versus random-effects

Outcome	Number of studies	Effect measure	Fixed-effect size (95% CI)	Random-effect size (95% CI)
Functional class - improvement	8	OR	2.39 (1.72 to 3.32)	2.66 (1.37 to 5.19)
Functional class - worsening	5	OR	0.88 (0.57 to 1.37)	0.88 (0.56 to 1.40)
Six-minute walk distance	13	MD	19.50 (14.82 to 24.19)*	29.55 (18.63 to 40.48)*
Mortality	15	OR	0.60 (0.38 to 0.94)	0.68 (0.42 to 1.10)
mPAP	8	MD	-3.60 (-4.73 to -2.48)*	-4.10 (-6.22 to -1.99)*
PVR	7	MD	-2.81 (-3.80 to -1.82)*	-2.40 (-4.44 to -0.35)*
Cardiac index	6	MD	0.31 (0.23 to 0.38)*	0.34 (0.17 to 0.52)*
Cardiac output	2	MD	0.57 (0.32 to 0.81)	0.41 (-0.34 to 1.15)
RAP	6	MD	-1.90 (-2.58 to -1.22)	-1.90 (-2.58 to -1.22)
Dyspnoea	8	SMD	-0.21 (-0.32 to -0.11)*	-0.29 (-0.50 to -0.08)*
Quality of life	3	SMD	0.28 (0.04 to 0.52)*	0.48 (-0.11 to 1.08)*

*High heterogeneity
Abbreviations: MD - mean difference; SMD - standardised mean difference; CI - confidence interval; mPAP - mean pulmonary arterial pressure; PVR - pulmonary vascular resistance; RAP - right atrial pressure

Table 3. Sensitivity analysis: blinded versus open-label studies

Outcome	All studies effect size (95% CI)	Blinded studies only effect size (95% CI)
Functional class - improvement	2.39 (1.72 to 3.32)+	1.77 (1.24 to 2.52)+
Functional class - worsening	0.88 (0.57 to 1.37)	0.85 (0.54 to 1.35)
Six-minute walk test distance	19.50 (14.82 to 24.19)+	17.55 (12.82 to 22.29)+
Mortality	0.60 (0.38 to 0.94)+	0.76 (0.45 to 1.29)*
PAP	-3.60 (-4.73 to -2.48)+	-2.58 (-3.86 to -1.30)+
PVR	-2.81 (-3.80 to -1.82)+	-1.32 (-2.95 to 0.32)*
Cardiac index	0.31 (0.23 to 0.38)+	0.18 (0.08 to 0.27)+

Table 3. Sensitivity analysis: blinded versus open-label studies *(Continued)*

Cardiac output	0.57 (0.32 to 0.81)+	0.57 (0.32 to 0.81)+
RAP	-1.90 (-2.58 to -1.22)+	-1.80 (-2.55 to -1.06)+
Dyspnoea	-0.21 (-0.32 to -0.11)+	-0.18 (-0.29 to -0.08)+
Quality of life	0.28 (0.04 to 0.52)+	0.07 (-0.22 to 0.36)*

+Statistically significant; *no longer statistically significant
Abbreviations: CI - confidence interval; PAP - pulmonary arterial pressure; PVR - pulmonary vascular resistance; RAP - right atrial pressure

Table 4. Prostacyclin versus control: adverse events

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)
	Risk with placebo	Risk with selexipag		
Syncope	90 per 1000	71 per 1000 (40 to 123)	OR 0.77 (0.42 to 1.42)	560 (4)
Dizziness	126 per 1000	136 per 1000 (108 to 170)	OR 1.09 (0.84 to 1.42)	1939 (10)
Vasodilation	80 per 1000	305 per 1000 (251 to 365)	OR 5.03 (3.84 to 6.58)	2277 (11)
Headache	227 per 1000	548 per 1000 (502 to 593)	OR 3.16 (2.62 to 3.80)	2351 (12)
Jaw pain	67 per 1000	273 per 1000 (220 to 333)	OR 5.25 (3.96 to 6.98)	2149 (10)
Diarrhoea	167 per 1000	361 per 1000 (315 to 410)	OR 2.81 (2.29 to 3.46)	2317 (10)
Leg pain	41 per 1000	113 per 1000 (42 to 271)	OR 2.96 (1.02 to 8.62)	246 (2)
Nausea and vomiting	244 per 1000	435 per 1000 (390 to 481)	OR 2.39 (1.98 to 2.88)	2399 (12)
Abdominal pain	116 per 1000	151 per 1000 (90 to 242)	OR 1.35 (0.75 to 2.42)	465 (2)
Pain in extremities	77 per 1000	218 per 1000 (162 to 287)	OR 3.36 (2.32 to 4.85)	1236 (6)

Table 4. Prostacyclin versus control: adverse events *(Continued)*

Myalgia	47 per 1000	120 per 1000 (76 to 185)	OR 2.75 (1.65 to 4.58)	1009 (3)
Upper respiratory tract events	255 per 1000	355 per 1000 (294 to 422)	OR 1.61 (1.22 to 2.13)	1038 (7)
Peripheral oedema	75 per 1000	106 per 1000 (74 to 150)	OR 1.46 (0.98 to 2.17)	1228 (6)
Infusion site reactions	213 per 1000	796 per 1000 (713 to 860)	OR 14.41 (9.16 to 22.66)	580 (2)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio

Table 5. Selexipag versus placebo: adverse events

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)
	Risk with placebo	Risk with selexipag		
Dizziness	145 per 1000	150 per 1000 (114 to 196)	OR 1.04 (0.76 to 1.44)	1195 (2)
Headache	325 per 1000	653 per 1000 (597 to 706)	OR 3.91 (3.07 to 4.98)	1195 (2)
Vasodilation	49 per 1000	122 per 1000 (82 to 178)	OR 2.67 (1.72 to 4.17)	1195 (2)
Jaw pain	61 per 1000	258 per 1000 (192 to 338)	OR 5.33 (3.64 to 7.81)	1195 (2)
Diarrhoea	189 per 1000	420 per 1000 (358 to 486)	OR 3.11 (2.39 to 4.05)	1195 (2)
Nausea or vomiting	266 per 1000	514 per 1000 (453 to 574)	OR 2.92 (2.29 to 3.73)	1195 (2)
Pain in extremity	78 per 1000	172 per 1000 (126 to 230)	OR 2.44 (1.69 to 3.52)	1195 (2)
Myalgias	58 per 1000	158 per 1000 (110 to 220)	OR 3.05 (2.02 to 4.58)	1195 (2)
Upper respiratory tract infection	361 per 1000	359 per 1000 (306 to 416)	OR 0.99 (0.78 to 1.26)	1195 (2)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio

APPENDICES

Appendix 1. MEDLINE search strategy

CENTRAL & Cochrane Airways Trials Register

#1 MESH DESCRIPTOR Hypertension, Pulmonary EXPLODE ALL

#2 MESH DESCRIPTOR Pulmonary Heart Disease EXPLODE ALL

#3 pulmonary* NEAR2 hypertensi*:ti,ab,kw

#4 #1 OR #2 OR #3

#5 MESH DESCRIPTOR Epoprostenol

#6 MESH DESCRIPTOR Iloprost

#7 epoprostenol OR iloprost OR beraprost OR treprostinil OR selexipag OR prostacyclin*

#8 #5 OR #6 OR #7

#9 #8 AND #4

MEDLINE (Ovid)

1. exp Hypertension, Pulmonary/

2. Pulmonary Heart Disease/

3. (pulmonary adj2 hypertensi$).tw.

4. or/1-3

5. Epoprostenol/

6. Iloprost/

7. epoprostenol.tw.

8. iloprost.tw.

9. beraprost.tw.

10. treprostinil.tw.

11. selexipag.tw.

12. prostacyclin*.tw.

13. or/5-12

14. 4 and 13

15. (controlled clinical trial or randomised controlled trial).pt.

16. (randomised or randomised).ab,ti.

17. placebo.ab,ti.

18. dt.fs.

19. randomly.ab,ti.

20. trial.ab,ti

21. groups.ab,ti.

22. or/15-21

23. Animals/

24. Humans/

25. 23 not (23 and 24)

26. 22 not 25

27. 14 and 26

Embase (Ovid)

1. pulmonary hypertension/

2. (pulmonary$ adj2 hypertensi$).ti,ab.

3. 1 or 2

4. prostacyclin/

5. iloprost/

6. beraprost/

7. uniprost/

8. bosentan/

9. prostacyclin.ti,ab.

10. iloprost.ti,ab.

11. beraprost.ti,ab.

12. treprostinil.ti,ab.

13. epoprostenol.ti,ab.

14. selexipag.ti,ab.

15. or/4-14

16. 3 and 15

17. Randomized Controlled Trial/

18. randomisation/

19. controlled clinical trial/

20. Double Blind Procedure/

21. Single Blind Procedure/

22. Crossover Procedure/

23. (clinica$ adj3 trial$).tw.

24. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).tw.

25. exp Placebo/

26. placebo$.ti,ab.

27. random$.ti,ab.

28. ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).tw.

29. (crossover$ or cross-over$).ti,ab.

30. or/17-29

31. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/

32. human/ or normal human/ or human cell/

33. 31 and 32

34. 31 not 33

35. 30 not 34

36. 16 and 35

ClinicalTrials.gov

Field	Search terms
Study type:	Interventional
Condition:	pulmonary hypertension
Interventions:	prostacylin OR epoprostenol OR iloprost OR beraprost OR treprostinil OR selexipag

CONTRIBUTIONS OF AUTHORS

HB and TF drafted the protocol, and AB and TW provided comments and changes. HB and HLY screened abstracts and TW and AB provided a third opinion where required. HB and HLY extracted data. HB drafted the review and HLY, AB, MH, and TW provided revisions and comments.

Contributions of editorial team

Rebecca Fortescue (Co-ordinating Editor, Contact Editor): edited the review; advised on methodology, interpretation and content; approved the final review prior to publication.
Chris Cates (Co-ordinating Editor) checked the data entry prior to the full write up of the review.
Emma Dennett (Managing Editor): co-ordinated the editorial process; advised on interpretation and content; edited the review.
Emma Jackson (Assistant Managing Editor): conducted peer review, and edited the Plain Language Summary and reference sections of the protocol and the review.
Elizabeth Stovold (Information Specialist): designed the search strategy, ran the searches and edited the search methods section.

DECLARATIONS OF INTEREST

HB: has previously been awarded a travel scholarship that was determined by an independent abstract committee, funded by GSK. GSK had no involvement in the determination of recipients. The Cochrane funding arbiter was consulted and agreed it did not represent a conflict of interest as GSK had no role in the allocation of the travel scholarship.

HLY: none known

TF: none known

AB: none known

MH: has relationships with drug companies in the field of pulmonary hypertension including Actelion, Arena, Bayer, Eiger, GSK, and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards. MH has relationships with drug companies in the field of severe asthma outside the submitted work. These companies are Astrazeneca, GSK, MSD, Novartis, Roche/Genentech, Sanofi/Regereron, and Teva. In addition to being investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards.

TW: is a paid member of scientific advisory boards for Actelion Australia, GSK Australia and Bayer Australia. He has received travel support, consultancy payments and research/education grants from Actelion Australia.

SOURCES OF SUPPORT

Internal sources

- The authors declare that no such funding was received for this systematic review, Other.

External sources

- The authors declare that no such funding was received for this systematic review, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not explicitly state we would present dichotomous data with zero totals as risk difference (RD).

In the protocol, we intended to assess changes in New York Heart Association (NYHA) functional class, however, the nomenclature for pulmonary arterial hypertension (PAH) patients is now World Health Organization (WHO) functional class. It should be noted however, that the NHYA and WHO classification system both classify patients in the same way.

Although we did not specify that we would include adverse events in the 'Summary of findings' table in the protocol, we added them to the review as they are clinically relevant and to comply with Cochrane standards.

We initially planned to only include single- or double-blinded trials, however given the importance of unblinded trials, we included these in the final meta-analysis and described similarities and differences between them.

We initially stated in our Objectives that we would assess the efficacy of prostacyclin, however as it was noted in peer review, our a priori outcomes also included safety, therefore we amended our objectives to include assessment of efficacy and safety.

We added 'clinical worsening' as an outcome.

Following peer review, we performed a post hoc sensitivity analysis on all relevant outcomes, whereby we excluded the TRUST trial due to its premature termination following safety concerns.

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [*therapeutic use]; Dyspnea [drug therapy]; Epoprostenol [*therapeutic use]; Exercise Tolerance; Hypertension, Pulmonary [*drug therapy]; Quality of Life

MeSH check words

Humans