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[Intervention Review]

Endothelin receptor antagonists for pulmonary arterial hypertension

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ABSTRACT

Background

Pulmonary arterial hypertension is a devastating disease, which leads to right heart failure and premature death. Recent evidence suggests that endothelin receptor antagonists may be promising drugs in the treatment of pulmonary arterial hypertension.

Objectives

To evaluate the efficacy of endothelin receptor antagonists in pulmonary arterial hypertension.

Search methods

We searched CENTRAL (Cochrane Central Register of Controlled Trials), MEDLINE, EMBASE, and the reference section of retrieved articles. Searches are current as of January 2012.

Selection criteria

We included randomised trials (RCTs) and quasi-randomised trials involving patients with pulmonary arterial hypertension.

Data collection and analysis

Five review authors independently selected studies, assessed study quality and extracted data.

Main results

We included 12 randomised controlled trials involving 1471 patients. All the trials were of relatively short duration (12 weeks to six months). After treatment, patients treated with endothelin receptor antagonists could walk on average 33.71 metres (95% confidence interval (CI) 24.90 to 42.52 metres) further than those treated with placebo in a six-minute walk test. Endothelin receptor antagonists improved more patients' World Health Organization/New York Heart Association (WHO/NYHA) functional class status than placebo (odds ratio (OR) 1.60; 95% CI 1.20 to 2.14), and reduced the odds of functional class deterioration compared with placebo (OR 0.26; 95% CI 0.16 to 0.42). There was a reduction in mortality that did not reach statistical significance on endothelin receptor antagonists (OR 0.57; 95% CI 0.26 to 1.24), and limited data suggest that endothelin receptor antagonists improve the Borg dyspnoea score and cardiopulmonary haemodynamics in symptomatic patients. Hepatic toxicity was not common, and endothelin receptor antagonists were well tolerated in this population. However, several cases of irreversible liver failure caused by sitaxsentan have been reported that led to license holder for sitaxsentan to withdraw the product from all markets worldwide.

Authors' conclusions

Endothelin receptor antagonists can increase exercise capacity, improve WHO/NYHA functional class, prevent WHO/NYHA functional class deterioration, reduce dyspnoea and improve cardiopulmonary haemodynamic variables in patients with pulmonary arterial hypertension with WHO/NYHA functional class II and III. However, there was only a trend towards endothelin receptor antagonists reducing mortality in patients with pulmonary arterial hypertension. Efficacy data are strongest in those with idiopathic pulmonary hypertension. The irreversible liver failure caused by sitaxsentan and its withdrawal from global markets emphasise the importance of hepatic monitoring in patients treated with endothelin receptor antagonists.

PLAIN LANGUAGE SUMMARY

Endothelin receptor antagonists for pulmonary arterial hypertension

Pulmonary hypertension is an increase in blood pressure in the pulmonary artery, pulmonary vein, or pulmonary capillaries, together known as the lung vasculature, leading to shortness of breath, dizziness, fainting, and other symptoms, all of which are exacerbated by exertion. The World Health Organization (WHO) has reclassified pulmonary hypertension into five groups based on their mechanisms rather than associated conditions. We have focused on pulmonary arterial hypertension (PAH) only in this review. Pulmonary arterial hypertension is a devastating disease characterised by an increase in pulmonary vascular resistance which leads to right ventricular failure and ultimately death.

Traditional therapies for pulmonary arterial hypertension include prostacyclin and its analogues, calcium channel blockers, nitric oxide (NO), and important adjunctive therapies, such as anticoagulants and oxygen. Endothelin receptor antagonists have recently been proposed as an alternative to these traditional therapies. This review includes twelve trials on 1471 participants. Endothelin receptor antagonists can improve exercise capacity, symptoms, and cardiopulmonary haemodynamic variables in people with symptomatic pulmonary arterial hypertension over a period of three to six months treatment. There is uncertainty as to whether endothelin receptor antagonists reduce mortality in this population. The most severe potential side effect was hepatic toxicity which was not common in these short-term trials.

BACKGROUND

Description of the condition

Pulmonary arterial hypertension (PAH) is a rare disease of the distal pulmonary arteries that is characterised by vasoconstriction, vascular proliferation, obstructive remodelling of the pulmonary vessel wall, inflammation and thrombosis, which lead to a progressive increase in pulmonary vascular resistance and, ultimately, right ventricular failure and death (Archer 2010; Galiè 2009a). Classically, pulmonary veins are unaffected. PAH includes five subcategories (Galiè 2009a; NHLBI 2011): (1) Idiopathic PAH; (2) Heritable PAH; (3) drug- and toxin-induced PAH; (4) Associated with PAH (APAH) including connective tissue diseases, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, chronic haemolytic anaemia; (5) Persistent pulmonary hypertension of the newborn.

The pathogenesis of PAH involves multiple mechanisms. However, endothelial dysfunction characterised by over-expression of vasoconstrictors and downexpression of vasoactive mediators plays a key role in PAH. Reduced production of vasoactive mediators such as nitric oxide (NO) and prostacyclin, along with over-expression of vasoconstrictors such as endothelin-1 (ET-1) and thromboxane A₂, increase pulmonary vascular tone and promote pulmonary vascular remodelling. Therefore, the substances targeting these mechanisms represent logical therapeutic strategies (Archer 2010; Galiè 2009a; Liu 2006a).

Description of the intervention

Endothelin receptor antagonists (ERAs) are a class of potent vasodilators and antimitotic substances, which could specifically dilate and remodel the pulmonary arterial system, and which have recently been proposed as an alternative to traditional therapies. Two separate receptors for ET have been identified: endothelin type A (ET-A) receptors, which are most commonly found on vascular smooth muscle cells, and which induce vasoconstriction by increasing intracellular calcium; and endothelin type B (ET-B) receptors located on endothelial cells, which stimulate the release of vasodilating agents such as NO and prostacyclin. However, ET-B receptors also appear on vascular smooth muscle cells where they stimulate vasoconstriction. Theoretically, either selective blocking of ET-A receptors alone or non-selective blocking of both ET-A and ET-B receptors together could dilate local vessels.

How the intervention might work

Research evidence suggests that endothelin is overexpressed in the lungs of patients with PAH (Gaiad 1993) and elevated plasma endothelin concentrations are correlated with poorer prognosis (Rubens 2001). Furthermore, an overproduction of endothelin may also lead to pulmonary vascular remodelling in PAH (Kim 2000; Mansoor 1995; Wort 2001). Recently a number of RCTs have been published (ARIES-1; ARIES-2; BREATHE-1; BREATHE-2; STRIDE-1; STRIDE-2) suggesting that ERAs could increase exercise capacity and improve patients' functional class and symptoms.

Why it is important to do this review

Currently, treatment options for PAH include prostacyclin and its analogues, calcium channel blockers, NO, and important adjunctive therapies, including anticoagulants and oxygen (Liu 2006a). Over the past decades, the prognosis of patients with

PAH has greatly improved with the use of combinations of these treatments. However, all of these treatments have some limitations. Vasodilators, especially calcium channel blockers, are only effective in a small proportion of patients (Reeves 1986; Sitbon 1998). Prostacyclin has been delivered via continuous intravenous infusion, which may lead to severe side effects such as catheter infection, catheter thrombosis, and paradoxical embolism (Badesch 2000). Furthermore, pump or catheter malfunction may result in life-threatening loss of haemodynamic effects. Recent clinical data showed that analogues of prostacyclin are effective in patients with PAH at least for the short term (12 weeks), and have few severe side effects (Paramothayan 2005) but long-term effects remain to be confirmed. Inhaled NO can improve exercise capacity in patients with PAH (Hasuda 2000) but this treatment requires a continuous inhalation device and is therefore impractical. Phosphodiesterase-5 inhibitors (PDEI, for example, sildenafil) are a promising new group of drugs, and results of a randomised controlled trial (RCT) confirmed its short term (12 weeks) efficacy in PAH (Galiè 2005a), yet its long-term efficacy remains to be confirmed. ERAs are the most promising new drug class for treatment of PAH.

OBJECTIVES

To assess the efficacy of endothelin receptor antagonists (ERAs) in the treatment of patients with PAH.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised trials (RCTs) or quasi-randomised clinical trials.

Types of participants

We included trials involving adults and children (≥12 years) with PAH who required medical treatment for their condition and who were anticoagulated. We included diagnoses of PAH based on clinical symptoms with a combination of pulmonary and cardiac imaging and, ideally, the results of right-heart catheterisation. We included studies with patients with PAH secondary to other diseases if there were available data assessing the outcomes specific to the PAH component of their syndrome.

Types of interventions

We considered trials in which an ERA was taken alone or in combination against any comparator, in patients who were also anticoagulated.

Types of outcome measures

Primary outcomes

1. Exercise capacity (as measured by a six-minute walk test (6MWD)).
2. World Health Organization (WHO) functional class or New York Heart Association (NYHA) functional class (WHO/NYHA).
3. Borg dyspnoea scores and dyspnoea-fatigue ratings.
4. Mortality.

Secondary outcomes

1. Cardiopulmonary haemodynamics including mean pulmonary artery pressure (PAP); pulmonary vascular resistance (PVR), cardiac index (CI), cardiac output (CO), systemic arterial oxygen saturation and systemic oxygen transport.
2. Pulmonary function tests.
3. Adverse events (for example, hepatic toxicity).

Search methods for identification of studies

Electronic searches

Literature searches were undertaken by Cochrane Airway Group Trials Search Coordinator using the following sources: the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2011, Issue 4), which contains the Cochrane Airways Group Register of trials, MEDLINE (from 1966 to January 2012), and EMBASE (from 1980 to January 2012). No language restrictions were applied. The database search strategies can be found in [Appendix 1](#).

Searching other resources

We handsearched the reference lists of retrieved articles for additional trials. We also searched documents released from US Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Data collection and analysis

We minimised bias in the review process by performing a systematic search, piloting data extraction forms, extracting data in duplicate.

Selection of studies

Five review authors independently selected trials for inclusion in the review. We resolved differences by discussion.

Assessment of risk of bias in included studies

We independently assessed the methodological quality of included trials against the following criteria.

1. Was the study described as randomised?
2. Was the allocation concealment adequate?
3. Were the participants blinded?
4. Was there blinded outcome assessment?
5. Was there a description of withdrawals and drop-outs?
6. Were the results analysed according to intention-to-treat?

Measures of treatment effect

We treated short ordinal scales (e.g. WHO functional class, NYHA class) as dichotomous measures (we arranged the data into two categories: improvement or deterioration in class). We analysed linear scales (e.g. Borg dyspnoea scores) as continuous data.

Dealing with missing data

For missing data on prespecified primary outcomes, we contacted the study investigators to request the data. If the data were not available we performed sensitivity analyses to assess how sensitive results were to reasonable changes in the assumptions that we made.

Assessment of heterogeneity

We compared the χ^2 statistic with its degrees of freedom to identify heterogeneity. If the statistic was bigger than its degrees of freedom and $I^2 > 30\%$, we took this as evidence of heterogeneity.

Assessment of reporting biases

Standard funnel plots for the primary outcome i.e. 6MWD were conducted to investigate the potential for publication bias influencing the analysis. Funnel plots for the ERAs compared with placebo trials (outcome: change from baseline in 6MWD) are qualitatively symmetrical, and do not suggest the presence of publication bias.

Data synthesis

In the absence of significant heterogeneity, we combined results using a mean difference (MD) for continuous data, and Odds Ratio (OR) for dichotomous data. If there was significant heterogeneity (i.e. the ratio of χ^2 statistic and its degrees of freedom was bigger than 1.0, and the $I^2 > 30\%$), we used the random-effects model to assess treatment effect.

A number of articles reported studies where more than one eligible treatment arm was included. For these studies we split the data between two treatment-control comparisons by splitting the control group and halving the sample sizes. For example, [STRIDE-1](#) was a triple-arm clinical study which did not provide combined 'sitaxsentan' data versus placebo on secondary outcomes, such as mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR) and confidence intervals (CIs). We divided the data down into two trials: [STRIDE-1 \(100mg\)](#) using sitaxsentan 100 mg daily and [STRIDE-1 \(300mg\)](#) using sitaxsentan 300 mg daily; data for placebo participants were entered with the number of participants in each of the placebo 'groups' halved. Thus, the total numbers in the meta-analysis added up to the original size of the group. The same method was used in [STRIDE-2](#) and [STRIDE-4](#): See the table [Characteristics of included studies](#). [STRIDE-2](#) compared sitaxsentan with both a placebo arm and an open-label bosentan arm. For this study, we used the data from patients treated with bosentan and placebo for reference in the notes, and we did not pool the data with those of other studies.

Subgroup analysis and investigation of heterogeneity

1. Non-selective ERA (antagonising both ET-A and ET-B) versus selective ERA (antagonising ET-A) only.
2. Patients with idiopathic PAH versus patients with PAH related to other conditions.

Sensitivity analysis

When there was a significant difference in the characteristics of participants, intervention, comparator or outcome, we conducted a sensitivity analysis to assess how the results were affected by reasonable changes to the assumptions that were made.

RESULTS

Description of studies

Results of the search

The literature search identified 2202 titles and abstracts. Of these, we eventually identified 12 RCTs ([ARIES-1](#); [ARIES-2](#);

BREATHE-1; BREATHE-2; BREATHE-5; Channick 2001; EARLY; STRIDE-1; STRIDE-2; STRIDE-4; SERAPH; ASSET-1) for inclusion in this version. We divided three trials based on the doses given (STRIDE-1; STRIDE-2; STRIDE-4) see [Data synthesis](#) for details. A flow diagram ([Figure 1](#)) summarises the process of identifying studies eligible for inclusion in the analysis. We obtained full-text versions of these 12 studies from published papers or from the FDA and European EMEA websites. [Galiè 2003](#) reported

data from a subset of participants from the [BREATHE-1](#) study ([BREATHE-1](#)). Studies referenced in multiple sources were assessed for completeness of study details. When there was a discrepancy in the data between published journal papers and documents from FDA and EMEA, then the data from FDA or EMEA were used. We identified one abstract that is potentially eligible ([Palazzini 2010](#)), but since we did not have further information, we added details of the study into [Characteristics of studies awaiting classification](#).

Figure 1. Study flow diagram.

Figure 1. (Continued)

Included studies

Methods

Eleven studies were randomised and placebo-controlled ([ARIES-1](#); [ARIES-2](#); [BREATHE-1](#); [BREATHE-2](#); [BREATHE-5](#); [Channick 2001](#); [EARLY](#); [STRIDE-1](#); [STRIDE-2](#); [STRIDE-4](#); [ASSET-1](#)). One study was a randomised head-to-head study of bosentan (an ERA) and sildenafil (a phosphodiesterase-5 inhibitors (PDEI)) ([SERAPH](#)). A full description of each study with clinical characteristics at baseline, inclusion/exclusion criteria, methods of randomisation and outcomes is provided in the table of [Characteristics of included studies](#).

Interventions

Six trials compared a non-selective ERA (bosentan) against placebo ([BREATHE-1](#); [BREATHE-2](#); [BREATHE-5](#); [Channick 2001](#); [EARLY](#); [ASSET-1](#)). Five trials compared selective ERAs (sitaxsentan or ambrisentan) against placebo ([ARIES-1](#); [ARIES-2](#); [STRIDE-1](#); [STRIDE-2](#); [STRIDE-4](#)). [BREATHE-2](#) compared bosentan combined with intravenous prostacyclin against intravenous prostacyclin in combination with placebo. [SERAPH](#) compared bosentan against sildenafil.

Participants

Ten trials recruited patients with idiopathic PAH and PAH secondary to collagen vascular disease and congenital heart disease ([ARIES-1](#); [ARIES-2](#); [BREATHE-1](#); [BREATHE-2](#); [Channick 2001](#); [EARLY](#); [STRIDE-1](#); [STRIDE-2](#); [STRIDE-4](#); [SERAPH](#)). [BREATHE-5](#) recruited patients with PAH secondary to congenital heart disease (i.e. Eisenmenger's

syndrome). [ASSET-1](#) recruited patients with PAH secondary to sickle cell disease.

Outcomes

Six trials used the six-minute walk distance (6MWD) as the primary outcome measure ([ARIES-1](#); [ARIES-2](#); [BREATHE-1](#); [Channick 2001](#); [STRIDE-2](#); [STRIDE-4](#)) while one trial used change from baseline in SpO₂ and pulmonary vascular resistance (PVR) as primary outcome ([BREATHE-5](#)). [STRIDE-1](#) used peak exercise VO₂ as its primary outcome. [EARLY](#) used PVR as primary outcome. [ASSET-1](#) used change from baseline in PVR as the primary outcome. The primary efficacy parameter in [BREATHE-2](#) was the change from baseline to week 16 in total pulmonary resistance (TPR). [SERAPH](#) used change in right ventricle mass from baseline as its primary endpoint. Additional outcome measures used in studies were WHO or NYHA functional class status, Borg dyspnoea score, cardiopulmonary haemodynamics, drug safety and tolerability. Details can be found in table of [Characteristics of included studies](#).

Excluded studies

Fifty four studies were excluded, with reasons given in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

All but one trial ([SERAPH](#)) were reported as international, multicentre, double-blind, randomised, placebo-controlled trials. [SERAPH](#) is a single-centre, double-blind, randomised, placebo-controlled trial. Randomisation in all trials was conducted centrally according to computer-generated random number programmes.

Allocation concealment in all trials is judged to be adequate. All trials described drop-outs and withdrawals. All but two trials ([EARLY](#) and [ASSET-1](#)) were analysed statistically with an intention-

to-treat analysis. A full description of the risk of bias in the included studies can be found in the table of [Characteristics of included studies](#) and a summary of the risks of bias is shown in [Figure 2](#).

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
ARIES-1	+	+	?	+	+	?
ARIES-2	+	+	?	+	+	?
ASSET-1	+	+	?	-	-	?
BREATHE-1	+	+	?	+	?	?
BREATHE-2	+	+	?	+	?	?
BREATHE-5	+	+	+	+	?	?
Channick 2001	+	+	?	+	?	?
EARLY	+	+	+	+	+	?
Galiè 2003	+	+	?	+	?	?
SERAPH	+	+	?	+	?	?
STRIDE-1	+	+	?	+	?	?
STRIDE-1 (100mg)	+	+	?	+	?	?

Figure 2. (Continued)

STRIDE-1 (100mg)	+	+	?	+	?	?
STRIDE-1 (300mg)	+	+	?	+	?	?
STRIDE-2	+	+	?	+	?	?
STRIDE-2 (100mg)	+	+	?	+	?	?
STRIDE-2 (50mg)	+	+	?	+	?	?
STRIDE-4	+	+	?	+	?	?
STRIDE-4 (100mg)	+	+	?	+	?	?
STRIDE-4 (50mg)	+	+	?	+	?	?

Allocation

All of the trials included in the review used computer-generated random numbers and we judged allocation concealment to be adequate.

Blinding

Only [EARLY](#) and [BREATHE-5](#) reported detailed descriptions of how treating clinicians, participants and assessors were blinded sufficient that we could judge them to be at low risk of bias. Other trials were stated to be double blind, but, as no further information was available we judged them to be at unclear risk of bias.

Selective reporting

All studies had low risk of attrition bias apart from [ASSET-1](#) which had a large number of drop-outs. Only [ARIES-1](#); [ARIES-2](#); and [EARLY](#) reported their prespecified primary outcomes according to pre-published protocols in ClinicalTrials.gov and are therefore at low risk of selective reporting bias. We did not have access to the other studies' protocols. All but two trials ([EARLY](#); [ASSET-1](#)) performed statistical analysis based on intention-to-treat. However, participants lost to follow-up in the [EARLY](#) trial made up only a small proportion of the whole population, indicating a low risk of bias from incomplete outcome data. [ASSET-1](#) did not report an intention-to-treat analysis and therefore we judged this trial to be at high risk of selective reporting bias. The remaining trials were unclear.

Other potential sources of bias

[ASSET-1](#) stopped early and only enrolled 14 participants, and the data were not analysed for efficacy.

Effects of interventions

Only outcomes specified in the protocol were included in the meta-analysis. Unless otherwise stated, data used in the review were from published material or documents released from the FDA and EMEA.

ERAs versus placebo

Primary outcomes

Exercise capacity

Ten trials on 1356 participants ([ARIES-1](#); [ARIES-2](#); [BREATHE-1](#); [BREATHE-2](#); [BREATHE-5](#); [Channick 2001](#); [EARLY](#); [STRIDE-1](#); [STRIDE-2](#); [STRIDE-4](#)) assessed change from baseline in six-minute walk test (6MWD). The pooled data showed that patients treated with ERAs could walk 33.7 metres (mean difference (MD) 33.71; 95% confidence interval (CI) 24.90 to 42.52, 9 trials, 1323 participants, [Analysis 1.1](#)) further than those treated with placebo. No significant heterogeneity was observed between the trials.

The pooled data showed that the placebo-corrected therapeutic effect of the non-selective ERA bosentan on 6MWD was (MD 34.82 metres; 95% CI 19.25 to 50.40), and the selective ERAs was (MD 33.19; 95% CI 22.51 to 43.87).

[BREATHE-2](#) did not provide sufficient information for us to use data from the exercise capacity test. The published results showed that there was a remarkable increase in the 6MWD in both treatment groups (68 metres [median] in the bosentan/prostacyclin group versus 74 metres [median] in the placebo/prostacyclin group). However, no statistical difference was observed between the two groups in the 6MWD test.

WHO or NYHA functional class

Ten trials on 1301 ([ARIES-1](#); [ARIES-2](#); [BREATHE-1](#); [BREATHE-2](#); [BREATHE-5](#); [Channick 2001](#); [EARLY](#); [STRIDE-1](#); [STRIDE-2](#) and

STRIDE-4 reported the detailed numbers of patient with improved or deteriorated WHO/NYHA functional class.

ERAs improved more patients' functional class than placebo (odds ratio (OR) 1.60; 95% CI 1.20 to 2.14; [Analysis 1.2](#)), and lowered the odds of functional class deterioration in patients given ERAs (OR 0.26; 95% CI 0.16 to 0.42; [Analysis 1.3](#)).

For patients treated with the non-selective ERA bosentan, 101/310 patients improved their functional class versus 34/199 in placebo group (OR 1.92; 95% CI 1.20 to 3.06; [Analysis 1.2](#)) favouring bosentan; and for selective ERAs (sitaxsentan and ambrisentan) 124/504 patients improved their functional class versus 51/288 in the placebo group (OR 1.43; 95% CI 0.99 to 2.07), favouring selective ERAs, although not reaching statistical significance ([Analysis 1.2](#)).

Both non-selective ERA bosentan and selective ERAs (ambrisentan and sitaxsentan) significantly lowered the occurrence of WHO/NYHA function deterioration in patients with PAH (OR 0.31; 95% CI 0.13 to 0.72 for bosentan, and OR 0.24; 95% CI 0.14 to 0.42 for selective ERAs; [Analysis 1.3](#)).

Borg dyspnoea score

Five trials on 731 participants reported Borg dyspnoea scores ([Channick 2001](#); [BREATHE-1](#); [STRIDE-2](#); [ARIES-1](#); [ARIES-2](#)). There was heterogeneity in the selective ERA trials that cannot be explained in terms of clinical characteristics and methodological quality, so we pooled the data using a random-effects model. Overall Borg dyspnoea scores were lower with ERA by 0.64 units (95% CI -0.96 to -0.32) than placebo ([Analysis 1.4](#)).

Patients treated with the non-selective ERA bosentan had a Borg dyspnoea score lower than those treated with placebo (MD -0.67; 95% CI -1.24 to -0.11); as did patients treated with selective ERAs (MD -0.63; 95% CI -1.11 to -0.14; [Analysis 1.4](#)).

Mortality

Twenty-two deaths were recorded in eight trials on 1201 participants ([ARIES-1](#); [ARIES-2](#); [BREATHE-1](#); [BREATHE-2](#); [EARLY](#); [STRIDE-1](#); [STRIDE-2](#); [ASSET-1](#)), with 11 on active treatment and 11 on placebo. There was a non-significant trend towards ERAs lowering the mortality in patients with PAH (OR 0.57; 95% CI 0.26 to 1.24).

Subgroup analysis from the pooled data showed that selective ERAs did significantly lower the mortality in patients with PAH (OR 0.28; 95% CI 0.09 to 0.83), whereas there was no significant difference between the non-selective ERA bosentan and placebo (OR 1.34; 95% CI 0.39 to 4.55).

To compare the treatment effects of subgroups (selective ERAs versus non-selective ERA bosentan) on mortality, we calculated the interaction between the two subgroups using a method previously described by [Altman 2003](#). The estimated interaction effect is a Relative Odds Ratio 0.21 (95% CI 0.04 to 1.10), indicating that there is no clear evidence of a different treatment effect between non-selective ERA bosentan and selective ERAs on mortality.

Secondary outcomes

Cardiopulmonary haemodynamics

Six studies ([STRIDE-1](#); [Channick 2001](#); [BREATHE-1](#); [BREATHE-2](#); [BREATHE-5](#); [EARLY](#)) measured up to three haemodynamics

variables: mean pulmonary artery pressure (PAP), pulmonary vascular resistance (mPVR), and cardiac index (CI). Haemodynamic variables in [Channick 2001](#), [STRIDE-1](#); [BREATHE-2](#) and [EARLY](#) were measured by right-heart catheterisation compared with those in [BREATHE-1](#) which used an echocardiological method. The data from [BREATHE-1](#) were reported as a subgroup analysis in [Galiè 2003](#).

Mean pulmonary artery pressure (mPAP)

Five studies on 430 participants assessed mPAP ([STRIDE-1](#); [Channick 2001](#); [BREATHE-2](#); [BREATHE-5](#); [EARLY](#)). Pooled data from [STRIDE-1](#); [Channick 2001](#); [BREATHE-5](#) and [EARLY](#) showed that ERAs lowered mPAP by 4.82 mmHg (95% CI -6.73 to -2.90 mmHg; [Analysis 1.6](#)) more than placebo.

The non-selective ERA (bosentan) lowered mPAP by 5.83 mmHg (95% CI -8.62 to -3.05 mmHg; [Analysis 1.6](#)) more than placebo, whereas the selective ERA (sitaxsentan) lowered mPAP 3.90 mmHg (95% CI -6.54 to -1.25 mmHg; [Analysis 1.6](#)) more than placebo.

[BREATHE-2](#) did not report data for change from baseline in mPAP, but reported data in the form of an end of treatment score: mean $\pm$ standard error (SE) was 59.2 $\pm$ 3.2 mm Hg in the placebo group and 52.5 $\pm$ 2.4 mmHg in the bosentan group which was not statistically significant ($P = 0.3$).

Pulmonary vascular resistance

Five studies on 490 participants reported PVR data, and all of them showed that ERA significantly improved PVR compared with placebo ([STRIDE-1](#); [Channick 2001](#); [BREATHE-2](#); [BREATHE-5](#); [EARLY](#)). [BREATHE-2](#) did not report data on PVR as change from baseline, but reported an end of treatment score, as mean $\pm$ SE (1050 $\pm$ 154 dyn/s/cm⁵ in the placebo group, and 947 $\pm$ 104 dyn/s/cm⁵ in the bosentan group), with no significant difference between the two groups ($P = 0.3$) at week 16.

There was significant heterogeneity observed between the studies, so we pooled them using random-effects modelling. Data from three trials ([Channick 2001](#); [STRIDE-1](#); [BREATHE-5](#); [EARLY](#)) showed that ERAs could significantly reduce PVR by 270.17 dyn/s/cm⁵ (95% CI -343.61 to -196.72 dyn/s/cm⁵; [Analysis 1.7](#)) more than placebo.

Cardiac index

Five studies on 457 participants reported cardiac index data ([BREATHE-1](#); [STRIDE-1](#); [Channick 2001](#); [BREATHE-2](#); [EARLY](#)). There was significant heterogeneity observed between the studies, so we pooled them using a random-effects model. The pooled data from [BREATHE-1](#); [Channick 2001](#); [STRIDE-1](#); and [EARLY](#) showed that ERAs could significantly increase cardiac index compared with placebo (MD 0.44 L/min/m²; 95% CI 0.22 to 0.65; [Analysis 1.8](#)). The placebo-corrected therapeutic effect of the non-selective ERA (bosentan) on CI was (MD 0.52 L/min/m²; 95% CI 0.11 to 0.93), whereas, for the selective ERA (sitaxsentan) it was (MD 0.35 L/min/m²; 95% CI 0.18 to 0.52).

Adverse events

Seven trials on 879 participants reported hepatic toxicity in detail ([BREATHE-1](#); [BREATHE-2](#); [BREATHE-5](#); [Channick 2001](#); [EARLY](#); [STRIDE-1](#); [STRIDE-2](#)). There was heterogeneity between the studies, so the data were pooled using a random-effects model. Overall, 54/618 participants receiving ERA had hepatic toxicity events

compared with 14/382 participants given placebo, which was not significantly different (OR 1.94; 95% CI 0.67 to 5.65) though the direction of the effect favoured placebo.

[ARIES-1](#) and [ARIES-2](#) reported reassuring combined data for hepatic toxicity. None of the 261 patients receiving ambrisentan developed serum aminotransferase concentrations greater than three times the upper limit of normal compared with three patients (2.3%) displaying elevated levels in the placebo groups.

Subgroup analysis

The subgroup analysis of non-selective ERAs versus selective ERAs is described above for mortality. We could not perform a subgroup analysis comparing participants with idiopathic PAH versus participants with PAH related to other conditions due to a lack of sufficient information. However, [Denton 2006](#) reported the combined data from two trials ([Channick 2001](#); [BREATHE-1](#)) comparing bosentan for PAH secondary to connective tissue disease (PAH-CTD). There was no significant difference between the bosentan and placebo groups.

[Seibold 2005](#) reported the combined data of sitaxsentan from [STRIDE-1](#); [STRIDE-2](#) and [STRIDE-4](#) for PAH-CTD, which included sitaxsentan at 50 mg, 100 mg and 300 mg once daily; 110/512 patients had PAH-CTD including 63 with systemic sclerosis (SSc), 22 with overlap/mixed connective tissue disease and 25 with systemic lupus erythematosus. The data showed that the change from baseline in 6MWD was -16 ± 15.0 metres (mean $\pm$ SE) for placebo (N = 28), -2 ± 13.4 metres for sitaxsentan 50 mg daily (N = 26), 21 ± 10.4 metres for sitaxsentan 100 mg daily (N = 39), and 2 ± 14.1 metres for sitaxsentan 300 mg daily (N = 17). Only patients treated with 100 mg daily (the authorised dose by EMEA) significantly improved with 6MWD, which was comparable to those patients with idiopathic PAH treated with sitaxsentan.

[Badesch 2007](#) reported the pooled data about ambrisentan therapy in the treatment of idiopathic PAH (n = 251) and PAH-CTD (n = 124). At week 12, the placebo-adjusted increase in 6MWD was 58 metres (95% CI: 36 to 79) in patients with idiopathic PAH and 19 metres (95% CI: -10 to 48) in patients with PAH-CTD; the placebo-adjusted decrease in Borg dyspnoea score was -0.8 (95% CI: -1.4 to -0.19) in the idiopathic PAH group and -1.0 (95% CI: -1.7 to -0.18) in the PAH-CTD group. WHO functional class deterioration was 2.4% in patients with idiopathic PAH and 3.7% in patients with PAH-CTD in ambrisentan group, compared with 16.5% in patients with idiopathic PAH and 20.9% in patients with PAH-CTD in placebo group.

The [ASSET-1](#) study stopped early due to slow site initiation and enrolment. Only 14 patients with PAH secondary to sickle cell disease were enrolled in the study, and the data were not analysed for efficacy. The changes in 6MWD, PVR and mPAP are summarised in additional tables ([Table 1](#)). At the end of study, there was a greater increase in median 6MWD in placebo versus bosentan group compared with baseline. A decrease in PVR and mPAP was observed in both placebo and bosentan groups.

ERAs versus sildenafil

Primary outcomes

Exercise capacity

[SERAPH](#) reported that mean 6MWD increased on both treatments compared with baseline. There was no difference between the treatment groups when analysed by intention-to-treat. However, detailed data were not available. There was no significant difference in exercise capacity between patients treated with sildenafil and those treated with bosentan (MD 55 m; 95% CI 2 to 108; [Analysis 2.1](#)).

Secondary outcomes

Borg dyspnoea score

There was no significant difference between the two groups ([Analysis 2.2](#)).

Mortality

There was only one death and that was in the sildenafil group at week 14.

Cardiac index (comparison 02.04)

There was no difference between treatments in this outcome (95% CI -0.14 to 0.14; [Analysis 2.4](#)).

DISCUSSION

Twelve trials on 1471 participants are included in this review ([ARIES-1](#); [ARIES-2](#); [BREATHE-1](#); [BREATHE-2](#); [BREATHE-5](#); [Channick 2001](#); [EARLY](#); [STRIDE-1](#); [STRIDE-2](#); [STRIDE-4](#); [SERAPH](#); [ASSET-1](#)).

Clinical efficacy

Endothelin receptor antagonists (ERAs) can increase 6MWD, improve WHO/NYHA functional class, prevent WHO/NYHA functional class deterioration, lower the Borg dyspnoea score and improve cardiopulmonary haemodynamic measures in the relatively short term of three to six months therapy in patients with pulmonary arterial hypertension (PAH).

PAH has a high mortality rate. Only anticoagulation has shown some survival benefit in patients with idiopathic PAH in observational studies ([Fuster 1984](#); [Rich 1992](#)). Transplantation remains the preferred therapy with a major reduction in mortality. Currently, the evidence that ERAs have an impact on the risk of death is limited by the short duration of the studies and infrequent occurrence of this event in some trials ([Channick 2001](#); [BREATHE-5](#) and [STRIDE-4](#)). There is insufficient certainty around the observed result to exclude either a reduction in mortality or no difference.

Furthermore, the six-minute walk test (6MWT), as well as being a reliable tool for the assessment of exercise capacity in patients with PAH is also an independent predictor of mortality ([Miyamoto 2000](#); [Sitbon 2002](#)). [Barst 1996](#) showed that a treatment-related improvement of 47 metres in the 6MWT was associated with improved survival in patients with idiopathic PAH treated with prostacyclin. There was a similar improvement in exercise with ERAs. [McLaughlin 2005](#) reported long-term observational survival data from the extension studies of [Channick 2001](#) and [BREATHE-1](#) which further confirmed this observation; Kaplan-Meier survival estimates in the patients with idiopathic PAH given bosentan

were 96% at 12 months and 89% at 24 months, compared to the predicted survivals of 69% and 57%, respectively. [Chen 2008](#) reported that the estimated three-year survival in patients with PAH with WHO/NYHA function class III was 87% (95% CI, 81 to 91) for bosentan versus 75% (95% CI, 71 to 79) for prostacyclin.

The exact mechanism of action of ERAs on the pulmonary vascular bed remains unclear. Vasodilatation is likely to be just a part of the mechanism since usually 70% to 80% of patients with idiopathic PAH do not respond acutely to vasodilators ([Rich 1992](#); [Sitbon 1998](#)). Endothelin is likely to be involved in pulmonary vasoconstriction, inflammation, cellular proliferation and fibrosis, i.e. vascular remodelling ([Filep 1995](#); [Gater 1996](#); [Katwa 1993](#)). Recent research has illustrated that bosentan has the capacity to blunt the vascular remodelling normally associated with PAH ([Kim 2000](#)). If ERAs could prevent remodelling in patients, they might substantially improve the long-term survival in those with mild symptoms (WHO class II or I), but this needs to be confirmed by long-term follow-up studies.

The head-to-head study conducted by [SERAPH](#) did not show that there was a significant difference between bosentan and sildenafil but because of the small sample size in this study, the results should be interpreted with caution.

Combination therapy is an attractive option to treat the multiple pathophysiological mechanisms in PAH. Combination therapy might be pursued by the simultaneous initiation of two (or more) treatments or by the addition of a second (or third) treatment to a previous therapy that is considered insufficient. Which strategy is the best choice is currently unknown as few data are available. The [BREATHE-2](#) trials with small sample sizes explored the efficacy and safety of combination therapy (bosentan in combination with intravenous prostacyclin), and showed a trend without statistical significance toward haemodynamic and clinical improvement of this combination in patients with PAH. Clearly there is an interaction between bosentan and prostacyclin in the [BREATHE-2](#) trial. However, in light of predefined subgroups in the protocol, [BREATHE-2](#) trial was included in the meta-analysis of ERAs versus placebo. Nevertheless, excluding [BREATHE-2](#) from the meta-analysis made little difference to the results.

Subgroup analysis

Both a non-selective ERA and selective ERA can dilate constricted pulmonary pre-capillary arterioles and improve exercise capacity and symptoms. Determining the relative benefit of these agents requires head-to-head comparisons. A post-hoc analysis of the [STRIDE-2](#) trial that was neither designed nor powered to detect non-inferiority or equivalence showed the mean difference in the 18-week change from baseline between sitaxsentan and bosentan was 1.9 metres (95% CI -22.7 to 26.5; $P = 0.9$).

Efficacy data for ERAs in PAH secondary to other conditions (i.e. not idiopathic PAH) are still limited. The role of ERAs in this setting still needs to be confirmed in future studies.

Safety and tolerability

One major concern about ERAs is hepatotoxicity and its capacity to cause substantial damage to the liver. This review did not show a high occurrence of hepatic toxicity when using lower dose of bosentan (125 mg or 250 mg twice daily). This safety profile is consistent with results of European post-marketing surveillance of

bosentan in pulmonary hypertension ([Humbert 2007](#)). However, there were three reported cases of irreversible liver failure induced by sitaxsentan, one from the UK (in 2009) and two cases from clinical trials in India and the Ukraine (in 2010). The reported fatal hepatic toxicity in association with sitaxsentan was idiosyncratic, was unlikely to be detected by monthly monitoring, and was irreversible when sitaxsentan was discontinued. Thus, sitaxsentan has been withdrawn from the market voluntarily by its license holder. These cases emphasise the importance of dosing and hepatic monitoring in patients with PAH.

Sitaxsentan inhibits the CYP2C9 P450 cytochrome enzyme, the principal hepatic enzyme involved in warfarin metabolism. In patients using warfarin or warfarin analogues, the incidence of bleeding was higher on sitaxsentan. However, it became less common with reduction in the warfarin dose at sitaxsentan initiation ([STRIDE-2](#)).

Summary of main results

The pooled data showed that ERAs can increase exercise capacity, improve WHO/NYHA functional class, prevent WHO/NYHA functional class deterioration, decrease Borg dyspnoea scores and improve cardiopulmonary haemodynamic variables in patients with PAH, with most evidence coming from studies in patients with the idiopathic form of the disease. The direction of effect on mortality favours ERAs over placebo although there is insufficient certainty around the observed result to exclude no difference.

Overall completeness and applicability of evidence

All trials identified in the present review addressed the main objectives of our review (i.e. 6MWD, WHO/NYHA functional class and mortality). All relevant types of participants, interventions and outcomes have been investigated. The evidence we collected is highly relevant to the review questions. The pooled evidence shows that ERAs have significant therapeutic effects on PAH especially for patients with idiopathic PAH.

Quality of the evidence

All the data included in the meta-analysis were from randomised placebo-controlled clinical trials and the participants, treating clinicians and assessors were blinded. All but one trial ([EARLY](#)), performed analyses based on intention-to-treat for their pre-specified primary outcomes. On this basis we consider the quality of the evidence to be high. Overall, the results of the studies included in the review are consistent confirming the internal validity of the results of the review.

Agreements and disagreements with other studies or reviews

Our results are consistent with recent overviews. Our review is more current than these overviews and provides more robust data which further confirm the clinical efficacy of ERAs in patients with PAH.

AUTHORS' CONCLUSIONS

Implications for practice

Endothelin receptor antagonists (ERAs) can increase exercise capacity, improve WHO/NYHA functional class, prevent deterioration in WHO/NYHA functional class, reduce dyspnoea scores and improve cardiopulmonary haemodynamic variables in

patients with pulmonary arterial hypertension (PAH) with WHO/NYHA functional class II and III. However, there was only a trend towards ERAs reducing mortality in patients with PAH. Efficacy data are strongest in those with the idiopathic form of the disease. The irreversible liver failure caused by sitaxsentan and its withdrawal from global markets emphasise the importance of hepatic monitoring in patients treated with ERAs.

Implications for research

This review shows that the question of the effects of ERAs on PAH should now be regarded as partially answered. Further randomised trials to address the remaining uncertainty about the effects of

ERAs on PAH associated with connective tissue disease are still needed. ERAs' effect on mortality remains uncertain and long-term observational studies are warranted.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

ARIES-1

Methods	Multicentre randomised placebo-controlled, parallel, double-blind trial. Randomisation was conducted centrally according to a computer-generated random number. Allocation concealment was adequate. Dropouts and withdrawals were described. Intention-to-treat analysis was conducted. Study duration is 12 weeks.
Participants	<p>Total n = 201 (67 in placebo group, 67 in ambrisentan 5 mg group, 67 in ambrisentan 10 mg group). Women (59 in placebo group, 56 in ambrisentan 5 mg group, 53 in ambrisentan 10 mg group). Age (48 ± 16 in placebo group, 53 ± 14 in ambrisentan 5 mg group, 49 ± 16 in ambrisentan 10 mg group). Idiopathic PAH (43 in placebo group, 42 in sitaxsentan 5 mg group, 41 in sitaxsentan 10 mg group).</p> <p>PAH secondary to connective tissue disease (21 in placebo group, 19 in ambrisentan 5 mg group, 22 in ambrisentan 10 mg group).</p> <p>PAH secondary to HIV (2 in placebo group, 3 in ambrisentan 5 mg group, 2 in ambrisentan 10 mg group).</p> <p>PAH secondary to anorexigen use (1 in placebo group, 2 in ambrisentan 5 mg group, 2 in ambrisentan 10 mg group).</p> <p>WHO functional class I (2 in placebo group, 1 in ambrisentan 5 mg group, 2 in ambrisentan 10 mg group).</p> <p>WHO functional class II (23 in placebo group, 20 in ambrisentan 5 mg group, 22 in ambrisentan 10 mg group).</p> <p>WHO functional class III (41 in placebo group, 40 in ambrisentan 5 mg group, 36 in ambrisentan 10 mg group).</p> <p>WHO functional class IV (1 in placebo group, 6 in ambrisentan 5 mg group, 7 in ambrisentan 10 mg group).</p> <p>6MWD was 342 ± 73 m placebo group, 340 ± 77 m in ambrisentan 5 mg group, 341 ± 78 m in ambrisentan 10 mg group.</p>
Interventions	Patients were randomised to receive placebo or ambrisentan 5 or 10 mg PO daily for 12 weeks.
Outcomes	Primary outcomes: Change from baseline in 6MWD.

ARIES-1 (Continued)

Secondary outcomes: Change from baseline in WHO functional class (FC), Borg dyspnoea index and time to clinical worsening, plasma BNP and SF-36 health survey physical functioning scale.

Notes The combined data of [ARIES-1](#) and [ARIES-2](#) showed that 21 patients discontinued in the placebo group in [ARIES-1](#) and [ARIES-2](#), 6 patients in ambrisentan 2.5 mg group, 9 patients in ambrisentan 5 mg group, and 5 patients in ambrisentan 10 mg group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A central randomisation scheme stratified by PAH cause (idiopathic versus other PAH causes) was used to assign patients."
Allocation concealment (selection bias)	Low risk	See above. Assumed done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>"For safety reasons, patients who met 2 early escape criteria after a minimum of 4 weeks of treatment could discontinue the study prematurely. Early escape criteria were (1) 20% decrease in the 6-minute walk distance, (2) an increase in World Health Organization (WHO) functional class, (3) a worsening right ventricular failure (as indicated by increased jugular venous pressure, new/worsening hepatomegaly, ascites, or peripheral edema), (4) progressing hepatic or renal failure, and (5) systolic blood pressure 85 mm Hg. All requests for early escape were adjudicated in a blinded fashion by the ARIES Steering Committee, and all study assessments were collected before unblinding of treatment."</p> <p>"All patients who received at least 1 dose of study drug were analyzed for efficacy (intention to treat). Missing data at week 12 were imputed by use of the last observation carried forward with 1 exception: If a patient discontinued the study because of clinical worsening and did not have a premature discontinuation visit, a 6-minute walk distance of 0 m, a WHO functional class of IV, and a Borg dyspnoea score of 10 were imputed."</p> <p>"All randomised patients received at least 1 dose of study drug, except for 1 patient in the 10-mg group of ARIES-1"</p>
Selective reporting (reporting bias)	Low risk	They reported the prespecified primary outcome. ClinicalTrials.gov Identifier: NCT00091598
Other bias	Unclear risk	None identified

ARIES-2

Methods Multicentre randomised placebo-controlled, parallel, double-blind trial. Randomisation was conducted centrally according to a computer-generated random number. Allocation concealment was adequate. Dropouts and withdrawals were described. Intention-to-treat analysis was conducted. Study duration is 12 weeks.

Participants Total n = 192 (65 in placebo group, 64 in ambrisentan 2.5 mg group, 63 in ambrisentan 5 mg group). Women (44 in placebo group, 48 in ambrisentan 2.5 mg group, 51 in ambrisentan 5 mg group). Age (51 ± 14 in placebo group, 52 ± 15 in ambrisentan 2.5 mg group, 50 ± 16 in ambrisentan 5 mg group).

ARIES-2 (Continued)

Idiopathic PAH (42 in placebo group, 42 in ambrisentan 2.5 mg group, 41 in ambrisentan 5 mg group).
PAH secondary to connective tissue disease (22 in placebo group, 19 in ambrisentan 2.5 mg group, 21 in ambrisentan 5 mg group).

PAH secondary to HIV (1 in placebo group, 2 in ambrisentan 2.5 mg group, 1 in ambrisentan 5 mg group).

PAH secondary to anorexigen use (0 in placebo group, 1 in ambrisentan 2.5 mg group, 0 in ambrisentan 5 mg group).

WHO functional class I (2 in placebo group, 0 in ambrisentan 2.5 mg group, 1 in ambrisentan 5 mg group).

WHO functional class II (24 in placebo group, 34 in ambrisentan 2.5 mg group, 28 in ambrisentan 5 mg group).

NYHA functional class III (37 in placebo group, 29 in ambrisentan 2.5 mg group, 33 in ambrisentan 5 mg group).

WHO functional class IV (2 in placebo group, 1 in ambrisentan 2.5 mg group, 1 in ambrisentan 5 mg group).

6MWD was 343 ± 86 m in placebo group, 347 ± 84 m in ambrisentan 2.5 mg group, 355 ± 84 m in ambrisentan 5 mg group.

Interventions	Patients were randomised to receive placebo or ambrisentan 2.5 or 5 mg daily for 12 weeks.
Outcomes	Primary outcomes: Change from baseline in 6MWD. Secondary outcomes: Change from baseline in WHO FC, Borg dyspnoea index and time to clinical worsening, plasma BNP and SF-36 health survey physical functioning scale.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A central randomisation scheme stratified by PAH cause (idiopathic versus other PAH causes) was used to assign patients."
Allocation concealment (selection bias)	Low risk	See above. Assumed done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"For safety reasons, patients who met 2 early escape criteria after a minimum of 4 weeks of treatment could discontinue the study prematurely. Early escape criteria were (1) 20% decrease in the 6-minute walk distance, (2) an increase in World Health Organization (WHO) functional class, ¹³ (3) a worsening right ventricular failure (as indicated by increased jugular venous pressure, new/worsening hepatomegaly, ascites, or peripheral edema), (4) progressing hepatic or renal failure, and (5) systolic blood pressure 85 mm Hg. All requests for early escape were adjudicated in a blinded fashion by the ARIES Steering Committee, and all study assessments were collected before unblinding of treatment." "All patients who received at least 1 dose of study drug were analyzed for efficacy (intention to treat). Missing data at week 12 were imputed by use of the last observation carried forward with 1 exception: If a patient discontinued the study because of clinical worsening and did not have a premature discontinuation visit, a 6-minute walk distance of 0 m, a WHO functional class of IV, and a Borg dyspnoea score of 10 were imputed."

ARIES-2 (Continued)

Selective reporting (reporting bias)	Low risk	They reported the prespecified primary outcome. ClinicalTrials.gov Identifier: NCT00091598
Other bias	Unclear risk	None identified

ASSET-1

Methods	Multicentre randomised placebo-controlled, parallel, double-blind trial. Randomisation was according to a computer-generated random number. Allocation concealment was adequate. However, enrolment into the trial was stopped early due to slow enrolment. Dropouts and withdrawals were described. Four patients were discontinued from the study (2 on bosentan and 2 on placebo). Intention-to-treat was not performed. Study duration is 16 weeks.	
Participants	Total n = 14 (6 in placebo group; 8 in bosentan group). Women (10). Mean age in ASSET-1 was 40 (Interquartile range, 34 to 53). All patients were PAH secondary Sickle Cell Disease. 6MWD in ASSET-1 at baseline was 353 m (Interquartile range, 295 to 390).	
Interventions	Intervention group: 62.5 mg bosentan twice daily for the first 4 weeks followed by the target dose (125 mg or 250 mg twice daily) for 12 weeks. Control group: placebo.	
Outcomes	Primary outcomes: Change from baseline in PVR at week 16. Secondary outcomes: change in 6MWD, and safety of bosentan.	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised allocation by pharmacy-controlled randomisation.
Allocation concealment (selection bias)	Low risk	See above. Assumed done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	High risk	"Fourteen patients were randomised before enrolment was stopped due to slow site initiation and enrolment. Enrolled patients remained on study medication, i.e. placebo or bosentan, until their study participation was completed." Intention-to-treat was not performed. The data were also not analysed for efficacy
Selective reporting (reporting bias)	High risk	The original primary outcome is change in 6MWD. ClinicalTrials.gov identifier: NCT00310830
Other bias	Unclear risk	Trial stopped early.

BREATHE-1

Methods	<p>Multicentre randomised placebo-controlled, parallel, double-blind trial. Randomisation was conducted according to a computer-generated random number. Allocation concealment was adequate. Dropouts and withdrawals were described. Intention-to-treat was performed.</p> <p>Study duration is 16 weeks.</p>
Participants	<p>Total n = 213 (69 in placebo group; 144 in bosentan group).</p> <p>Women (54 in placebo group; 114 in bosentan group). Age (47.2 ± 16.2 in placebo group; 48.7 ± 15.8 in bosentan group).</p> <p>Idiopathic PAH (48 in placebo group; 102 in bosentan group). PAH secondary to collagen vascular disease (21 in placebo group; 42 in bosentan group).</p> <p>WHO functional class III (65 in placebo group; 130 in bosentan group).</p> <p>WHO functional class IV (4 in placebo group; 14 in bosentan group).</p> <p>6MWD in placebo group was 344 ± 76m and 330 ± 74m in bosentan group.</p>
Interventions	<p>Intervention group: 62.5 mg bosentan twice daily for the first 4 weeks followed by the target dose (125 mg or 250 mg twice daily) for 12 weeks.</p> <p>Control group: placebo.</p>
Outcomes	<p>Primary outcomes: Change from baseline in 6MWD.</p> <p>Secondary outcomes: Borg dyspnoea index; WHO functional class.</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised allocation by pharmacy-controlled randomisation.
Allocation concealment (selection bias)	Low risk	See above. Assumed done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Any data missing at the week 16 assessment were derived by using predefined replacement rules with the purpose of minimizing bias. For patients who discontinued the study medication because of clinical worsening, the values recorded at the time of discontinuation was used; patients for whom no value was recorded (including patients who died) were assigned the worst possible value (0 m). For all other patients without a week 16 assessment, the last six-minute walking distance, score on the Borg dyspnoea index, and WHO functional class were used as week 16 values."
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol.
Other bias	Unclear risk	None identified

BREATHE-2

Methods	Multicentre randomised placebo-controlled, parallel, double-blind trial. Randomisation was conducted according to a computer-generated random number. Allocation concealment was adequate. Dropouts and withdrawals were described (Each group had one premature discontinuation due to an adverse event. One patient in intervention group discontinued due to clinical worsening and 2 patients in intervention group died.) Intention-to-treat was performed. Study duration is 16 weeks.
Participants	Total n = 33 (11 in placebo group; 22 in intervention group). Total 28 completed (10 in placebo group; 18 in intervention group). Women (6 in placebo group; 17 in intervention group). Age (47 ± 19 in placebo group; 45 ± 17 in intervention group). Idiopathic PAH (10 in placebo group, 17 in intervention group). PAH secondary to scleroderma (1 in placebo group; 4 in intervention group). PAH secondary to systemic lupus erythematosus (0 in placebo group; 1 in intervention group). NYHA functional class III (8 in placebo group; 17 in intervention group). NYHA functional class IV (3 in placebo group, 5 in intervention group).
Interventions	33 patients with PAH started prostacyclin treatment (2 ng/kg/min starting dose, up to 14 ± 2 ng/kg/min at week 16) and were randomised for 16 weeks in a 2:1 ratio to bosentan (62.5 mg twice daily for 4 weeks then 125 mg twice daily) or placebo.
Outcomes	Primary outcomes: Change from baseline to week 16 in TPR. Secondary outcomes: Change in CI, PVR, mPAP, and mean right atrial pressure (mRAP), 6MWD, NYHA functional class and dyspnoea-fatigue rating.
Notes	The standard deviations of change from baseline in 6MWD were estimated from figures.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised allocation by pharmacy-controlled randomisation.
Allocation concealment (selection bias)	Low risk	See above. Assumed done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The two bosentan patients who died and the two patients (one bosentan and one placebo) who were withdrawn were assigned the worst value observed at the 16 week time point or at withdrawal in all patients belonging to the same analysis population." "Two patients on bosentan/epoprostenol therapy were assigned a 0-m walk distance and a 0-dyspnoea-fatigue rating at week 16. Two patients (one on placebo/epoprostenol and one on bosentan/epoprostenol) were too impaired to walk and two patients on bosentan/epoprostenol did not perform the assessment. These patients were not included in the analysis."
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol.
Other bias	Unclear risk	None identified

BREATHE-5

Methods	Randomisation was controlled by study medication packaging (Almedica HPS AG, Reinach, Switzerland). Patients were randomised in a consecutive order, starting with the lowest provided medication number. The investigators, patients, monitors, and sponsor personnel remained blinded to the treatment until closure of the clinical database. Dropouts and withdrawals were described (Both group had two premature discontinuations due to adverse events). Intention-to-treat was performed. Study duration is 16 weeks.
Participants	Total n = 54 (17 in placebo group; 37 in intervention group). Women (10 in placebo group; 23 in intervention group). Age (44.2 ± 8.5 in placebo group; 37.2 ± 12.0 in intervention group). All patients were with Eisenmenger Syndrome. All patients were in WHO functional class III. 6MWD was 366 ± 68 m in placebo group and 332 ± 83 m in bosentan group.
Interventions	Intervention group: 62.5 mg bosentan twice daily for the first 4 weeks followed by the target dose (125 mg twice daily) for 12 weeks. Patients who did not tolerate the target dose of 125 mg twice daily could be down titrated to the starting dose (62.5 mg twice daily). Control group: placebo.
Outcomes	Primary outcomes: Change from baseline in SpO ₂ and iPVR. Secondary outcomes: Change from baseline in 6MWD, WHO FC, CI, PVR, mPAP, and mRAP.
Notes	Standard deviations were estimated from standard errors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was controlled by study medication packaging (Almedica HPS AG, Reinach, Switzerland)."
Allocation concealment (selection bias)	Low risk	"The investigators, patients, monitors, and sponsor personnel remained blinded to the treatment until closure of the clinical database."
Blinding (performance bias and detection bias) All outcomes	Low risk	"The investigators, patients, monitors, and sponsor personnel remained blinded to the treatment until closure of the clinical database."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Because of the study design characteristics, the primary analysis population was the per-protocol population, and a robustness analysis using the all-randomized population was to be performed on the second primary end point."
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol.
Other bias	Unclear risk	None identified

Channick 2001

Methods	Multicentre randomised parallel trial comparing bosentan with placebo for 12 weeks. Randomisation was computer generated with a block size of three. Allocation concealment adequate. Dropouts and withdrawals were described. Intention-to-treat analysis was conducted. Study duration is 12 weeks.
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Channick 2001 (Continued)

Participants	<p>Total n = 32 (30 completed protocol; 21 in bosentan group; 11 in placebo group).</p> <p>Women (11 in placebo group, 17 in bosentan group).</p> <p>Age (47.4 ± 14.0 in placebo group; 52.2 ± 12.2 in bosentan group).</p> <p>Idiopathic PAH (10 in placebo group, 17 in bosentan group). PAH secondary to scleroderma (1 in placebo group, 4 in bosentan group).</p> <p>All participants were in WHO functional class III.</p> <p>6MWD was 355 ± 82 m in placebo group, and 360 ± 86 m in bosentan group.</p>
Interventions	Intervention group: 62.5 mg bosentan twice daily for the first 4 weeks followed by the target dose (125 mg twice daily). Control group: placebo.
Outcomes	<p>Primary outcomes: 6MWD.</p> <p>Secondary outcomes: Cardiopulmonary haemodynamics (CI, PVR, mPAP, and mRAP), WHO functional class .</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was computer generated using Drug Labelling System with a block size of three."
Allocation concealment (selection bias)	Low risk	See above. Assumed done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"With the exception of the a priori planned analysis on the 6-min walk test, which was confirmatory, all other analyses were exploratory by their nature. Statistical analyses were done on an intention-to treat basis."
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol.
Other bias	Unclear risk	None identified

EARLY

Methods	<p>Multicentre randomised placebo-controlled, parallel, double-blind trial. Randomisation was conducted centrally according to centralised integrated voice recognition system. Allocation concealment adequate. Treating study personnel, participants and assessors were all blinded.</p> <p>Dropouts and withdrawals were described (In placebo group, 12 patients discontinued. Of these, 9 due to adverse events; 1 withdrew consent; 2 protocol violations. In bosentan group, 10 patients discontinued. Of these, 9 due to adverse events; 1 withdrew consent).</p> <p>Intention-to-treat was not performed.</p>
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EARLY (Continued)

Study duration is 6 months.

Participants	<p>Total n = 185 (92 in placebo group; 93 in intervention group). Women (71 in placebo group; 58 in intervention group). Age (44.2 ± 16.5 in placebo group; 45.2 ± 17.9 in intervention group). Idiopathic PAH (58 in placebo group, 54 in bosentan group). PAH secondary to connective tissue disease (15 in placebo group; 18 in bosentan group). PAH secondary to HIV (2 in placebo group; 5 in bosentan group).</p> <p>All patients were in WHO functional class II.</p> <p>6MWD was 431 ± 91 m in placebo group and 438 ± 86 m in bosentan group.</p>
Interventions	<p>Participants either treated with bosentan at an initial dose of 62.5 mg twice daily, up-titrating to 125 mg twice daily after 4 weeks, or remaining at 62.5 mg twice daily if bodyweight <40 kg, or placebo for a 6-month double-blind treatment period.</p>
Outcomes	<p>Primary outcomes: PVR and change from baseline in 6MWD.</p> <p>Secondary outcomes: time to clinical worsening, change from baseline to month 6 in WHO FC, Borg dyspnoea index, mPAP, CI, RAP, and mixed venous oxygen saturation.</p>
Notes	<p>Standard deviations were estimated from confidence intervals.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned in a one to one ratio to receive either bosentan using a centralised integrated voice recognition system."
Allocation concealment (selection bias)	Low risk	"This system assigned a unique randomisation number to each patient and designated the correct blinded study medication to be dispensed, both at the start of study treatment and at each scheduled visit. This code was accessible only to authorised individuals who were not involved in the conduct or analysis of the study, until the time of unblinding."
Blinding (performance bias and detection bias) All outcomes	Low risk	"This system assigned a unique randomisation number to each patient and designated the correct blinded study medication to be dispensed, both at the start of study treatment and at each scheduled visit. This code was accessible only to authorised individuals who were not involved in the conduct or analysis of the study, until the time of unblinding."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The main analysis on the primary endpoints was to be done on the all-randomised analysis set, which included all randomised patients. Analyses of pulmonary vascular resistance and 6-min walk distance included all randomised patients who had a valid baseline assessment and an assessment or an imputed value for month 6. Missing values at month 6 of primary and secondary endpoints were replaced with the last observation carried forward or, in case of clinical worsening, the worst substitution rule. For pulmonary vascular resistance, the worst value was calculated with either the highest absolute value observed in all patients or by applying the highest absolute increase observed to baseline, whichever was higher. For 6-min walk distance the worst value was calculated by applying the greatest percentage decrease observed to baseline, in the case of clinical worsening or with 0 m if death occurred. Patients who did not worsen and did not have a valid on-treatment value were excluded from the relevant analysis."

EARLY (Continued)

Selective reporting (reporting bias)	Low risk	They reported the prespecified primary outcome. ClinicalTrials.gov Identifier: NCT00091715.
Other bias	Unclear risk	None identified

Galiè 2003

Methods	This trial report is on a subset of patients from the BREATHE-1 study
Participants	Total n = 85 (81 completed study; 26 in placebo group; 55 in bosentan group). Men (5 in placebo group; 8 in bosentan group). Women (24 in placebo group; 48 in bosentan group). Age (44.9 ± 19.2 in placebo group; 45.1 ± 16.2 in bosentan group). PAH secondary to scleroderma (4 in placebo group; 7 in bosentan group). Other (2 in placebo group; 1 in bosentan group). WHO functional class III (28 in placebo group; 49 in bosentan group). WHO functional class IV (1 in placebo group; 7 in bosentan group).
Interventions	Same as BREATHE-1 .
Outcomes	Cardiac index.
Notes	This is a subgroup analysis of BREATHE-1 study. The study reports data from 13/27 study centres who volunteered to participate in an echocardiography sub-study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See BREATHE-1 .
Allocation concealment (selection bias)	Low risk	See BREATHE-1 .
Blinding (performance bias and detection bias) All outcomes	Unclear risk	See BREATHE-1 .
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Statistical analyses were based on the intent to treat population (full analysis set)"
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol.
Other bias	Unclear risk	None identified

SERAPH

Methods	Single-centre randomised head to head double-blind trial.
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Endothelin receptor antagonists for pulmonary arterial hypertension (Review)

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SERAPH (Continued)

Randomisation was conducted according to a computer-generated random list.
Allocation concealment was adequate.
Dropouts and withdrawals were described (25 patients completed the study, one patient in sildenafil died at week 14.)
Intention-to-treat analysis was conducted.
Study duration is 16 weeks.

Participants	Total n = 26 (14 in sildenafil group, 12 in bosentan group). Total 25 completed (13 in sildenafil group, 12 in bosentan group). Women (11 in sildenafil group; 10 in bosentan group). Men (3 in placebo group; 2 in sitaxsentan group). Age (44.4 with range from 28 to 62 in sildenafil group; 41.1 with range from 27 to 55 in bosentan group). Idiopathic PAH (12 in sildenafil group, 11 in bosentan group). PAH secondary to scleroderma (1 in placebo group; 1 in intervention group). PAH secondary to systemic lupus erythematosus (1 in placebo group; 0 in intervention group).
Interventions	Intervention group: bosentan (62.5 mg twice daily for first four weeks, then up-titrated to 125 mg twice daily). Control group: sildenafil (50 mg twice daily during the first four weeks, then up-titrated to 50 mg three times daily).
Outcomes	Primary outcome: change in right ventricle mass from baseline. Secondary outcomes: Change from baseline in 6MWD, CI, Borg dyspnoea index, quality of life, and plasma B-type natriuretic peptide level from baseline.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The medication was blinded in identical-looking gelatin capsules and randomised using a computer generated random list by the Hammersmith Hospital pharmacy."
Allocation concealment (selection bias)	Low risk	"The medication was blinded in identical-looking gelatin capsules and randomised using a computer generated random list by the Hammersmith Hospital pharmacy."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Statistical analysis was performed by intention to treat (where missing values were replaced with 0 m for the 6-minute walk and the last measurement carried forward for other observations) and on data from all patients who completed the protocol."
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol.
Other bias	Unclear risk	None identified

STRIDE-1

Methods	Randomisation was performed centrally and stratified by centre in blocks according to a computer-generated random number table. Dropouts and withdrawals were described (In placebo group, 5 pa-
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STRIDE-1 (Continued)

tients discontinued. Of these, 4 due to adverse events; 1 was lost to follow-up. In the sitaxsentan 300 mg group, 7 patients discontinued due to adverse events; No patients discontinued in the sitaxsentan 100 mg group.).
Intention-to-treat analysis was conducted. Study duration is 12 weeks.

Participants	<p>Total n = 178 (60 in placebo group, 55 in the sitaxsentan 100 mg group, 63 in the sitaxsentan 300 mg group).</p> <p>Women (47 in placebo group, 47 in the sitaxsentan 100 mg group, 47 in the sitaxsentan 300 mg group).</p> <p>Age (48 ± 14 in placebo group, 45 ± 14 in sitaxsentan 100 mg group, 44 ± 12 in sitaxsentan 300 mg group).</p> <p>Idiopathic PAH (37 in placebo group, 23 in sitaxsentan 100 mg group, 34 in sitaxsentan 300 mg group).</p> <p>PAH secondary to connective tissue disease (9 in placebo group, 16 in sitaxsentan 100 mg group, 17 in sitaxsentan 300 mg group).</p> <p>PAH secondary to congenital heart disease (14 in placebo group, 16 in sitaxsentan 100 mg group, 12 in sitaxsentan 300 mg group).</p> <p>NYHA functional class II (22 in placebo group, 16 in sitaxsentan 100 mg group, 21 in sitaxsentan 300 mg group).</p> <p>NYHA functional class III (36 in placebo group, 39 in sitaxsentan 100 mg group, 42 in sitaxsentan 300 mg group).</p> <p>NYHA functional class IV (2 in placebo group, 0 in sitaxsentan 100 mg group, 0 in sitaxsentan 300 mg group).</p> <p>6MWD was 413 ± 105 m in placebo group, 394 ± 114 m in sitaxsentan 100 mg group, 387 ± 110 m in sitaxsentan 300 mg group.</p>
Interventions	<p>Intervention group: 100 mg once daily or 300 mg once daily.</p> <p>Control group: placebo</p>
Outcomes	<p>Primary outcomes: Peak oxygen consumption (Peak O₂).</p> <p>Secondary outcomes: Exercise capacity (6MWD), NYHA functional class, PAP, CI, and PVR.</p>
Notes	<p>STRIDE-1 trial compared two doses of sitaxsentan with placebo, the combined sitaxsentan data were not available, we therefore broke up the placebo group into two parts (STRIDE-1 (100mg) study and STRIDE-1 (300mg) study), so that the total numbers added up to the original size of the group.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed centrally and stratified by center in blocks according to a computer-generated random number table."
Allocation concealment (selection bias)	Low risk	See above. Assumed done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>"The efficacy analysis was prospectively defined and conducted according to the intent-to-treat principle, consisting of analysis of all patients who received any dose of study drug and according to the group randomised."</p> <p>"Based on prespecified rules, missing values were replaced using the last observation carried forward data imputation method. If no postbaseline value was available, the baseline value was carried forward."</p>

STRIDE-1 (Continued)

Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol.
Other bias	Unclear risk	None identified

STRIDE-1 (100mg)

Methods	Multicentre randomised placebo-controlled, parallel, double-blind trial. Randomisation was conducted centrally according to a computer-generated random number. Allocation concealment adequate. Dropouts and withdrawals were described (In placebo group, 5 patients discontinued. Of these, 4 due to adverse events; 1 was lost to follow up. In sitaxsentan 300mg group, 7 patients discontinued due to adverse events; No patients discontinued in sitaxsentan 100mg group.). Intention-to-treat analysis was conducted. Study duration is 12 weeks.	
Participants	Total n = 178 (60 in placebo group, 55 in sitaxsentan 100 mg group, 63 in sitaxsentan 300 mg group). Women (47 in placebo group, 47 in sitaxsentan 100 mg group, 47 in sitaxsentan 300 mg group). Age (48 ± 14 in placebo group, 45 ± 14 in sitaxsentan 100 mg group, 44 ± 12 in sitaxsentan 300 mg group). Idiopathic PAH (37 in placebo group, 23 in sitaxsentan 100 mg group, 34 in sitaxsentan 300 mg group). PAH secondary to connective tissue disease (9 in placebo group, 16 in sitaxsentan 100 mg group, 17 in sitaxsentan 300 mg group). PAH secondary to congenital heart disease (14 in placebo group, 16 in sitaxsentan 100 mg group, 12 in sitaxsentan 300 mg group). NYHA functional class II (22 in placebo group, 16 in sitaxsentan 100 mg group, 21 in sitaxsentan 300 mg group). NYHA functional class III (36 in placebo group, 39 in sitaxsentan 100 mg group, 42 in sitaxsentan 300 mg group). NYHA functional class IV (2 in placebo group, 0 in sitaxsentan 100 mg group, 0 in sitaxsentan 300 mg group). 6MWD was 413 ± 105 m in placebo group, 394 ± 114 m in sitaxsentan 100 mg group, 387 ± 110 m in sitaxsentan 300 mg group.	
Interventions	Intervention group: 100 mg once daily or 300 mg once daily. Control group: placebo	
Outcomes	Primary outcomes: Peak oxygen consumption (Peak O ₂). Secondary outcomes: Exercise capacity (six minute walk distance), NYHA functional class, PAP, CI, and PVR.	
Notes	STRIDE-1 trial compared two doses of sitaxsentan with placebo, the combined sitaxsentan data were not available, we therefore broke up the placebo group into two parts (STRIDE-1 (100mg) study and STRIDE-1 (300mg) study), so that the total numbers added up to the original size of the group.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed centrally and stratified by center in blocks according to a computer-generated random number table."
Allocation concealment (selection bias)	Low risk	See above. Assumed done.

STRIDE-1 (100mg) (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The efficacy analysis was prospectively defined and conducted according to the intent-to-treat principle, consisting of analysis of all patients who received any dose of study drug and according to the group randomised." "Based on prespecified rules, missing values were replaced using the last observation carried forward data imputation method. If no post baseline value was available, the baseline value was carried forward."
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol.
Other bias	Unclear risk	None identified

STRIDE-1 (300mg)

Methods	Multicentre randomised placebo-controlled, parallel, double-blind trial. Randomisation was conducted centrally according to a computer-generated random number. Allocation concealment adequate. Dropouts and withdrawals were described (In placebo group, 5 patients discontinued. Of these, 4 due to adverse events; 1 was lost to follow up. In sitaxsentan 300mg group, 7 patients discontinued due to adverse events; No patients discontinued in sitaxsentan 100 mg group.). Intention-to-treat analysis was conducted. Study duration is 12 weeks.	
Participants	Total n = 178 (60 in placebo group, 55 in sitaxsentan 100 mg group, 63 in sitaxsentan 300 mg group). Women (47 in placebo group, 47 in sitaxsentan 100 mg group, 47 in sitaxsentan 300 mg group). Age (48 ± 14 in placebo group, 45 ± 14 in sitaxsentan 100 mg group, 44 ± 12 in sitaxsentan 300 mg group). Idiopathic PAH (37 in placebo group, 23 in sitaxsentan 100 mg group, 34 in sitaxsentan 300 mg group). PAH secondary to connective tissue disease (9 in placebo group, 16 in sitaxsentan 100 mg group, 17 in sitaxsentan 300 mg group). PAH secondary to congenital heart disease (14 in placebo group, 16 in sitaxsentan 100 mg group, 12 in sitaxsentan 300 mg group). NYHA functional class II (22 in placebo group, 16 in sitaxsentan 100 mg group, 21 in sitaxsentan 300 mg group). NYHA functional class III (36 in placebo group, 39 in sitaxsentan 100 mg group, 42 in sitaxsentan 300 mg group). NYHA functional class IV (2 in placebo group, 0 in sitaxsentan 100 mg group, 0 in sitaxsentan 300 mg group). 6MWD was 413 ± 105 m in placebo group, 394 ± 114 m in sitaxsentan 100 mg group, 387 ± 110 m in sitaxsentan 300 mg group.	
Interventions	Intervention group: 100 mg once daily or 300 mg once daily. Control group: placebo	
Outcomes	Primary outcomes: Peak oxygen consumption (Peak O ₂). Secondary outcomes: Exercise capacity (six minute walk distance), NYHA functional class, PAP, CI, and PVR.	
Notes	STRIDE-1 trial compared two doses of sitaxsentan with placebo, the combined sitaxsentan data were not available, we therefore broke up the placebo group into two parts (STRIDE-1 (100mg) study and STRIDE-1 (300mg) study), so that the total numbers added up to the original size of the group.	

STRIDE-1 (300mg) (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed centrally and stratified by center in blocks according to a computer-generated random number table."
Allocation concealment (selection bias)	Low risk	See above. Assumed done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The efficacy analysis was prospectively defined and conducted according to the intent-to-treat principle, consisting of analysis of all patients who received any dose of study drug and according to the group randomised." "Based on prespecified rules, missing values were replaced using the last observation carried forward data imputation method. If no post baseline value was available, the baseline value was carried forward."
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol.
Other bias	Unclear risk	None identified

STRIDE-2

Methods	Multicentre randomised placebo-controlled, parallel, double-blind trial. Randomisation was conducted centrally according to a computer-generated random number. Allocation concealment adequate. Dropouts and withdrawals were described (In placebo group, 11 patients discontinued. In the sitaxsentan 50 mg group, 8 patients discontinued the study; In the sitaxsentan 100 mg group, 4 patients discontinued the study; In the open-label bosentan group, 8 patients discontinued the study.). Intention-to-treat analysis was conducted. Study duration is 18 weeks.
Participants	Total n = 245 (62 in placebo group, 62 in sitaxsentan, 61 mg group, 60 in sitaxsentan 100 mg group, and 60 in bosentan group). Women (47 in placebo group, 53 in sitaxsentan 50 mg group, 43 in sitaxsentan 100 mg group, and 47 in bosentan group). Age (53 ± 15 in placebo group, 57 ± 13 in sitaxsentan 50 mg group, 55 ± 14 in sitaxsentan 100 mg group, and 49 ± 16 in bosentan). Idiopathic PAH (37 in placebo group, 34 in sitaxsentan 50 mg group, 39 in sitaxsentan 100 mg group, and 34 in bosentan group). PAH secondary to connective tissue disease (17 in placebo group, 19 in sitaxsentan 50 mg group, 18 in sitaxsentan 100 mg group, and 20 in bosentan group). PAH secondary to congenital heart disease (7 in placebo group, 9 in sitaxsentan 50 mg group, 4 in sitaxsentan 100 mg group, and 6 in bosentan group). WHO functional class II (23 in placebo group, 21 in sitaxsentan 50 mg group, 26 in sitaxsentan 100 mg group, and 22 in bosentan group). WHO functional class III (35 in placebo group, 38 in sitaxsentan 50 mg group, 34 in sitaxsentan 100 mg group, and 37 in bosentan group). WHO functional class IV (4 in placebo group, 3 in sitaxsentan 50 mg group, 1 in sitaxsentan 100 mg group, and 1 in bosentan group).

STRIDE-2 (Continued)

6MWD was 321 ± 85 m in placebo group, 328 ± 80 m in sitaxsentan 50 mg group, 360 ± 72 m in sitaxsentan 100 mg group, and 337 ± 80 m in bosentan group.

Interventions	Patients were randomised to receive placebo, sitaxsentan 50 mg, or sitaxsentan 100 mg orally once daily, or open-label bosentan for 18 weeks.
Outcomes	Primary outcomes: Change from baseline in 6MWD. Secondary outcomes: Change from baseline in WHO FC, Borg dyspnoea index and time to clinical worsening.
Notes	STRIDE-2 trial compared sitaxsentan with both a placebo arm and an open-label bosentan arm, therefore we list the data of patients treated with bosentan and placebo for reference. However, the data were not pooled with other data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed centrally according to a computer-generated random number table. Randomization was 1:1:1:1."
Allocation concealment (selection bias)	Low risk	See above. Assumed done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All efficacy analyses were conducted on the intent-to treat (ITT) population, which was defined as all randomised patients who took any dose of study drug and performed at least one valid post-baseline 6MW test." "All missing values were imputed using the last observation carried forward method. If the patient was unable to perform the 6MWD test because of clinical worsening or death, the 6MWD distance was assigned a value of 0 m with a Borg dyspnoea score of 10 for the visit."
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol.
Other bias	Unclear risk	None identified

STRIDE-2 (100mg)

Methods	Randomisation was performed centrally according to a computer-generated random number table with 1:1:1:1. Allocation concealment adequate Dropouts and withdrawals were described (In placebo group, 11 patients discontinued. In sitaxsentan 50 mg group, 8 patients discontinued the study; In sitaxsentan 100 mg group, 4 patients discontinued the study; In the open-label bosentan group, 8 patients discontinued the study.). Intention-to-treat analysis was conducted. Study duration is 18 weeks.
Participants	Total n = 245 (62 in placebo group, 62 in sitaxsentan, 61 mg group, 60 in sitaxsentan 100 mg group, and 60 in bosentan group). Women (47 in placebo group, 53 in sitaxsentan 50 mg group, 43 in sitaxsentan 100 mg group, and 47 in bosentan group).

STRIDE-2 (100mg) (Continued)

Age (53 ± 15 in placebo group, 57 ± 13 in sitaxsentan 50 mg group, 55 ± 14 in sitaxsentan 100 mg group, and 49 ± 16 in bosentan).

Idiopathic PAH (37 in placebo group, 34 in sitaxsentan 50 mg group, 39 in sitaxsentan 100 mg group, and 34 in bosentan group).

PAH secondary to connective tissue disease (17 in placebo group, 19 in sitaxsentan 50 mg group, 18 in sitaxsentan 100 mg group, and 20 in bosentan group).

PAH secondary to congenital heart disease (7 in placebo group, 9 in sitaxsentan 50 mg group, 4 in sitaxsentan 100 mg group, and 6 in bosentan group).

WHO functional class II (23 in placebo group, 21 in sitaxsentan 50 mg group, 26 in sitaxsentan 100 mg group, and 22 in bosentan group).

WHO functional class III (35 in placebo group, 38 in sitaxsentan 50 mg group, 34 in sitaxsentan 100 mg group, and 37 in bosentan group).

WHO functional class IV (4 in placebo group, 3 in sitaxsentan 50 mg group, 1 in sitaxsentan 100 mg group, and 1 in bosentan group).

6MWD was 321 ± 85 m in placebo group, 328 ± 80 m in sitaxsentan 50 mg group, 360 ± 72 m in sitaxsentan 100 mg group, and 337 ± 80 m in bosentan group.

Interventions	Patients were randomised to receive placebo, sitaxsentan 50 mg, or sitaxsentan 100 mg orally once daily, or open-label bosentan for 18 weeks.
Outcomes	Primary outcomes: Change from baseline in 6MWD. Secondary outcomes: Change from baseline in WHO FC, Borg dyspnoea index and time to clinical worsening.
Notes	STRIDE-2 trial compared sitaxsentan with both a placebo arm and an open-label bosentan arm, therefore we list the data of patients treated with bosentan and placebo for reference. However, the data were not pooled with other data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed centrally according to a computer-generated random number table. Randomization was 1:1:1:1."
Allocation concealment (selection bias)	Low risk	See above. Assumed done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All efficacy analyses were conducted on the intent-to treat (ITT) population, which was defined as all randomised patients who took any dose of study drug and performed at least one valid post-baseline 6MW test." "All missing values were imputed using the last observation carried forward method. If the patient was unable to perform the 6MWD test because of clinical worsening or death, the 6MWD distance was assigned a value of 0 m with a Borg dyspnoea score of 10 for the visit."
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol.
Other bias	Unclear risk	None identified

STRIDE-2 (50mg)

Methods	Multicentre randomised placebo-controlled, parallel, double-blind trial. Randomisation was conducted centrally according to a computer-generated random number. Allocation concealment adequate. Dropouts and withdrawals were described (In placebo group, 11 patients discontinued. In the sitaxsentan 50 mg group, 8 patients discontinued the study; In sitaxsentan 100 mg group, 4 patients discontinued the study; In the open-label bosentan group, 8 patients discontinued the study.). Intention-to-treat analysis was conducted. Study duration is 18 weeks.
Participants	<p>Total n = 190 (62 in placebo group, 62 in sitaxsentan, 61 mg group, 60 in sitaxsentan 100 mg group, and 47 in bosentan group).</p> <p>Women (47 in placebo group, 53 in sitaxsentan 50 mg group, 43 in sitaxsentan 100 mg group, and 47 in bosentan group).</p> <p>Age (53 ± 15 in placebo group, 57 ± 13 in sitaxsentan 50 mg group, 55 ± 14 in sitaxsentan 100 mg group, and 49 ± 16 in bosentan).</p> <p>Idiopathic PAH (37 in placebo group, 34 in sitaxsentan 50 mg group, 39 in sitaxsentan 100 mg group, and 34 in bosentan group).</p> <p>PAH secondary to connective tissue disease (17 in placebo group, 19 in sitaxsentan 50 mg group, 18 in sitaxsentan 100 mg group, and 20 in bosentan group).</p> <p>PAH secondary to congenital heart disease (7 in placebo group, 9 in sitaxsentan 50 mg group, 4 in sitaxsentan 100 mg group, and 6 in bosentan group).</p> <p>WHO functional class II (23 in placebo group, 21 in sitaxsentan 50 mg group, 26 in sitaxsentan 100 mg group, and 22 in bosentan group).</p> <p>WHO functional class III (35 in placebo group, 38 in sitaxsentan 50 mg group, 34 in sitaxsentan 100 mg group, and 37 in bosentan group).</p> <p>WHO functional class IV (4 in placebo group, 3 in sitaxsentan 50 mg group, 1 in sitaxsentan 100 mg group, and 1 in bosentan group).</p> <p>6MWD was 321 ± 85 m in placebo group, 328 ± 80 m in sitaxsentan 50 mg group, 360 ± 72 m in sitaxsentan 100 mg group, and 337 ± 80 m in bosentan group.</p>
Interventions	Patients were randomised to receive placebo, sitaxsentan 50 mg, or sitaxsentan 100 mg orally once daily, or open-label bosentan for 18 weeks.
Outcomes	<p>Primary outcomes: Change from baseline in 6MWD.</p> <p>Secondary outcomes: Change from baseline in WHO FC, Borg dyspnoea index and time to clinical worsening.</p>
Notes	STRIDE-2 trial compared sitaxsentan with both a placebo arm and an open-label bosentan arm, therefore we list the data of patients treated with bosentan and placebo for reference. However, the data were not pooled with other data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed centrally according to a computer-generated random number table. Randomization was 1:1:1:1."
Allocation concealment (selection bias)	Low risk	See above. Assumed done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All efficacy analyses were conducted on the intent-to treat (ITT) population, which was defined as all randomised patients who took any dose of study drug and performed at least one valid post-baseline 6MW test."

STRIDE-2 (50mg) (Continued)

"All missing values were imputed using the last observation carried forward method. If the patient was unable to perform the 6MWD test because of clinical worsening or death, the 6MWD distance was assigned a value of 0 m with a Borg dyspnoea score of 10 for the visit."

Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol.
Other bias	Unclear risk	None identified

STRIDE-4

Methods	Multicentre randomised placebo-controlled, parallel, double-blind trial. Randomisation was conducted centrally according to a computer-generated random number. Allocation concealment adequate. Dropouts and withdrawals were described (In placebo group, 4 patients discontinued. In sitaxsentan 50 mg group, 4 patients discontinued the study; In sitaxsentan 100 mg group, 3 patients discontinued the study.). Intention-to-treat analysis was conducted. Study duration is 18 weeks.	
Participants	Total n = 98 (34 in placebo group, 32 in sitaxsentan 50 mg group, 32 in sitaxsentan 100 mg group). Gender (Nil). Age (Nil). Idiopathic PAH (65% in placebo group, 80% in sitaxsentan 50 mg group, 69% in sitaxsentan 100 mg group). PAH secondary to connective tissue disease (9% in placebo group, 22% in sitaxsentan 50 mg group, 16% in sitaxsentan 100 mg group). PAH secondary to congenital heart disease (26% in placebo group, 6% in sitaxsentan 50 mg group, 16% in sitaxsentan 100 mg group). WHO functional class II (56% in placebo group, 72% in sitaxsentan 50 mg group, 56% in sitaxsentan 100 mg group). WHO functional class III (41% in placebo group, 28% in sitaxsentan 50 mg group, 44% in sitaxsentan 100 mg group). WHO functional class IV (3% in placebo group, 0% in sitaxsentan 50 mg group, 0% in sitaxsentan 100 mg group). 6MWD was 341.6 ± 82 m in placebo group, 355.3 ± 73m in sitaxsentan 50 mg group, 342.8 ± 83 m in sitaxsentan 100 mg group.	
Interventions	Patients were randomised to receive placebo, sitaxsentan 50 mg, or sitaxsentan 100 mg orally once daily for 18 weeks.	
Outcomes	Primary outcomes: Change from baseline in 6MWD. Secondary outcomes: Change from baseline in WHO FC, Borg dyspnoea index and time to clinical worsening.	
Notes	STRIDE-4 trial compared two doses of sitaxsentan with placebo, the combined sitaxsentan data were not available, we therefore broke up the placebo group into two parts (STRIDE-4 (50mg) study and STRIDE-4 (100mg) study), so that the total numbers added up to the original size of the group.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised allocation by pharmacy-controlled randomisation.

STRIDE-4 (Continued)

Allocation concealment (selection bias)	Low risk	See above. Assumed done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All efficacy analyses were performed using the intent-to-treat population, defined as all randomised patients who received 1 dose of study drug. All missing values were imputed using the last observation carried forward (LOCF) method."
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol.
Other bias	Unclear risk	None identified

STRIDE-4 (100mg)

Methods	Multicentre randomised placebo-controlled, parallel, double-blind trial. Randomisation was conducted centrally according to a computer-generated random number. Allocation concealment adequate. Dropouts and withdrawals were described (In placebo group, 4 patients discontinued. In sitaxsentan 50 mg group, 4 patients discontinued the study; In sitaxsentan 100 mg group, 3 patients discontinued the study.). Intention-to-treat analysis was conducted. Study duration is 18 weeks.
Participants	Total n = 98 (34 in placebo group, 32 in sitaxsentan 50 mg group, 32 in sitaxsentan 100 mg group). Gender (Nil). Age (Nil). Idiopathic PAH (65% in placebo group, 80% in sitaxsentan 50 mg group, 69% in sitaxsentan 100 mg group). PAH secondary to connective tissue disease (9% in placebo group, 22% in sitaxsentan 50 mg group, 16% in sitaxsentan 100 mg group). PAH secondary to congenital heart disease (26% in placebo group, 6% in sitaxsentan 50 mg group, 16% in sitaxsentan 100 mg group). WHO functional class II (56% in placebo group, 72% in sitaxsentan 50 mg group, 56% in sitaxsentan 100 mg group). WHO functional class III (41% in placebo group, 28% in sitaxsentan 50 mg group, 44% in sitaxsentan 100 mg group). WHO functional class IV (3% in placebo group, 0% in sitaxsentan 50 mg group, 0% in sitaxsentan 100 mg group). 6MWD was 341.6 ± 82 m in placebo group, 355.3 ± 73m in sitaxsentan 50 mg group, 342.8 ± 83 m in sitaxsentan 100 mg group.
Interventions	Patients were randomised to receive placebo, sitaxsentan 50 mg, or sitaxsentan 100 mg orally once daily for 18 weeks.
Outcomes	Primary outcomes: Change from baseline in 6MWD. Secondary outcomes: Change from baseline in WHO FC, Borg dyspnoea index and time to clinical worsening.
Notes	STRIDE-4 trial compared two doses of sitaxsentan with placebo, the combined sitaxsentan data were not available, we therefore broke up the placebo group into two parts (STRIDE-4 (50mg) study and STRIDE-4 (100mg) study), so that the total numbers added up to the original size of the group.

STRIDE-4 (100mg) (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised allocation by pharmacy-controlled randomisation.
Allocation concealment (selection bias)	Low risk	See above. Assumed done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All efficacy analyses were performed using the intent-to-treat population, defined as all randomised patients who received 1 dose of study drug. All missing values were imputed using the last observation carried forward (LOCF) method."
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol.
Other bias	Unclear risk	None identified

STRIDE-4 (50mg)

Methods	Multicentre randomised placebo-controlled, parallel, double-blind trial. Randomisation was conducted centrally according to a computer-generated random number. Allocation concealment adequate. Dropouts and withdrawals were described (In placebo group, 4 patients discontinued. In the sitaxsentan 50 mg group, 4 patients discontinued the study; In the sitaxsentan 100 mg group, 3 patients discontinued the study.). Intention-to-treat analysis was conducted. Study duration is 18 weeks.
Participants	Total n = 98 (34 in placebo group, 32 in sitaxsentan 50 mg group, 32 in sitaxsentan 100 mg group). Gender (Nil). Age (Nil). Idiopathic PAH (65% in placebo group, 80% in sitaxsentan 50 mg group, 69% in sitaxsentan 100 mg group). PAH secondary to connective tissue disease (9% in placebo group, 22% in sitaxsentan 50 mg group, 16% in sitaxsentan 100 mg group). PAH secondary to congenital heart disease (26% in placebo group, 6% in sitaxsentan 50 mg group, 16% in sitaxsentan 100 mg group). WHO functional class II (56% in placebo group, 72% in sitaxsentan 50 mg group, 56% in sitaxsentan 100 mg group). WHO functional class III (41% in placebo group, 28% in sitaxsentan 50 mg group, 44% in sitaxsentan 100 mg group). WHO functional class IV (3% in placebo group, 0% in sitaxsentan 50 mg group, 0% in sitaxsentan 100 mg group). 6MWD was 341.6 ± 82 m in placebo group, 355.3 ± 73m in sitaxsentan 50 mg group, 342.8 ± 83 m in sitaxsentan 100 mg group.
Interventions	Patients were randomised to receive placebo, sitaxsentan 50 mg, or sitaxsentan 100 mg orally once daily for 18 weeks.
Outcomes	Primary outcomes: Change from baseline in 6MWD.

STRIDE-4 (50mg) (Continued)

Secondary outcomes: Change from baseline in WHO FC, Borg dyspnoea index and time to clinical worsening.

Notes **STRIDE-4** trial compared two doses of sitaxsentan with placebo, the combined sitaxsentan data were not available, we therefore broke up the placebo group into two parts (**STRIDE-4 (50mg)** study and **STRIDE-4 (100mg)** study), so that the total numbers added up to the original size of the group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised allocation by pharmacy-controlled randomisation.
Allocation concealment (selection bias)	Low risk	See above. Assumed done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated double blind. No further information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All efficacy analyses were performed using the intent-to-treat population, defined as all randomised patients who received 1 dose of study drug. All missing values were imputed using the last observation carried forward (LOCF) method."
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol.
Other bias	Unclear risk	None identified

BNP: B-type natriuretic peptide

CI: cardiac index

FC: functional class

m: metre

6MWD: six-minute walk test

mPAP: mean pulmonary artery pressure

mRAP: mean right atrial pressure

PAH: pulmonary arterial hypertension

PAH-CTD: pulmonary arterial hypertension secondary to connective tissue disease

PAP: pulmonary artery pressure

PO: oral

PVR: pulmonary vascular resistance

SF36: short form 36 health survey

SSC: systemic sclerosis

TPR: total pulmonary resistance

Characteristics of excluded studies [author-defined order]

Study	Reason for exclusion
Benza 2007	Patients were not randomised to an ERA.
BUILD-2	Patients did not have PAH.
Burgess 2008	Patients did not have PAH.

Study	Reason for exclusion
Coyne 2005	Patients did not have PAH.
Galiè 2005b	Patients were not randomised to an ERA.
Givertz 2000	Patients did not have PAH.
Gomberg-Maitland 2005	Patients were not randomised to an ERA.
Hoepfer 2006	Patients were not randomised to an ERA.
Kalra 2002	Patients did not have PAH.
Kaluski 2008a	Patients did not have PAH.
King 2008	Patients did not have PAH.
Kiowski 1995	Patients were not randomised to an ERA.
Korn 2004	Patients did not have PAH.
McLaughlin 2003	Patients were not randomised to an ERA.
McLaughlin 2006	Patients were not randomised to an ERA.
Mereles 2006	Patients were not randomised to an ERA.
Modesti 2006	Patients did not have PAH.
RAPID-1	Patients did not have PAH.
Robbins 2006	Patients were not randomised to an ERA.
Galiè 2009c	Long term follow-up data of RCT using sitaxsentan.
McLaughlin 2010	Patients were not randomised to an ERA.
Iversen 2010	Patients were not randomised to an ERA.
Galiè 2010	Patients were not randomised to an ERA.
Lee 2009	Patients were not randomised to an ERA.
Simonneau 2010	Patients were not randomised to an ERA.
Ghofrani 2010	Patients were not randomised to an ERA.
Oudiz 2009	Long term follow-up data of RCT using sitaxsentan.
Oudiz 2007	Long term follow-up data of RCT using sitaxsentan.
Worthington 2010	Patients were not randomised to an ERA.
Galiè 2009b	Patients were not randomised to an ERA.
Bose 2009	Patients did not have PAH.

Study	Reason for exclusion
Faoro 2009a	Patients did not have PAH.
Faoro 2009b	Patients did not have PAH.
Frey 2008	Patients did not have PAH.
Gotzkowsky 2010	Patients did not have PAH.
Huez 2009	Patients did not have PAH.
Jais 2008	Patients did not have PAH.
Kaluski 2008b	Patients did not have PAH.
Naeije 2010	Patients did not have PAH.
Nakahara 2010	Patients did not have PAH.
Reesink 2010	Patients did not have PAH.
Seheult 2009	Patients did not have PAH.
Seibold 2010	Patients did not have PAH.
Spence 2008	Patients did not have PAH.
Spence 2009	Patients did not have PAH.
Stavros 2010	Patients did not have PAH.
Stolz 2008	Patients did not have PAH.
Wrishko 2008	Patients did not have PAH.
Dhaun 2011	Patients did not have PAH.
Denault 2010	Patients did not have PAH.
Gillies 2011	Patients did not have PAH.
Kefford 2010	Patients did not have PAH.
Barst 2011	Patients were not randomised to an ERA.
Shenoy 2011	Patients did not have PAH.
ASSET-2	Patients did not have PAH.

ERA: endothelin receptor antagonists

PAH: pulmonary arterial hypertension

RCT: randomised controlled trial

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

Palazzini 2010

Methods	Randomisation method was not clear.
Participants	<p>Total n = 144.</p> <p>Seventy patients were randomised to the bosentan group [mean age 56 ± 16; 25% idiopathic PAH (IPAH), 16% PAH associated with congenital heart disease (CHD-PAH), 11% PAH associated with connective tissue disease (CTDPAH), 10% PAH associated with portal-hypertension (PO-PAH), 7% PAH associated with HIV (HIV-PAH) and 31% CTEPH]</p> <p>Seventy-seven patients were randomised to the sildenafil group (mean age 55 ± 18; 31% IPAH, 12% CHD-PAH, 16% CTD-PAH, 8% PO-PAH, 4% HIVPAH and 29% CTEPH)</p> <p>Total 126 completed (69 in sildenafil group, 57 in bosentan group).</p>
Interventions	Patients were randomised to receive either bosentan or sildenafil.
Outcomes	Outcome data were RAP, mPAP, CI, PVR, MVO ₂ and, 6MWD.
Notes	

mPAP: Mean pulmonary artery pressure
MVO₂: mixed venous oxygen saturation
6MWD: six-minute walk test
PAH: pulmonary arterial hypertension
PVR: pulmonary vascular resistance
RAP: right atrial pressure

DATA AND ANALYSES

Comparison 1. Endothelin receptor antagonists versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline in six-minute walk	11	1323	Mean Difference (IV, Fixed, 95% CI)	33.71 [24.90, 42.52]
1.1 Non-selective ERA	4	476	Mean Difference (IV, Fixed, 95% CI)	34.82 [19.25, 50.40]
1.2 Selective ERA	7	847	Mean Difference (IV, Fixed, 95% CI)	33.19 [22.51, 43.87]
2 Proportion of patients with improved functional class	10	1301	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [1.20, 2.14]
2.1 Non-selective ERAs	5	509	Odds Ratio (M-H, Fixed, 95% CI)	1.92 [1.20, 3.06]
2.2 Selective ERAs	5	792	Odds Ratio (M-H, Fixed, 95% CI)	1.43 [0.99, 2.07]
3 Proportion of patients with deteriorated functional class	9	1330	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.16, 0.42]
3.1 Non-selective ERA	4	476	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.13, 0.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Selective ERAs	5	854	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.14, 0.42]
4 Change from baseline in Borg dyspnoea index	5	731	Mean Difference (IV, Random, 95% CI)	-0.64 [-0.96, -0.32]
4.1 Non-selective ERAs	2	215	Mean Difference (IV, Random, 95% CI)	-0.67 [-1.24, -0.11]
4.2 Selective ERAs	3	516	Mean Difference (IV, Random, 95% CI)	-0.63 [-1.11, -0.14]
5 Mortality	8	1201	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.26, 1.24]
5.1 Non-selective ERAs	4	445	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [0.39, 4.55]
5.2 Selective ERAs	4	756	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.09, 0.83]
6 Change from baseline in mean pulmonary artery pressure	5	430	Mean Difference (IV, Fixed, 95% CI)	-4.82 [-6.73, -2.90]
6.1 Non-selective ERAs	3	252	Mean Difference (IV, Fixed, 95% CI)	-5.83 [-8.62, -3.05]
6.2 Selective ERAs	2	178	Mean Difference (IV, Fixed, 95% CI)	-3.90 [-6.54, -1.25]
7 Change from baseline in pulmonary vascular resistance	5	490	Mean Difference (IV, Random, 95% CI)	-270.17 [-343.61, -196.72]
7.1 Non-selective ERAs	3	252	Mean Difference (IV, Random, 95% CI)	-325.19 [-502.08, -148.31]
7.2 Selective ERAs	2	238	Mean Difference (IV, Random, 95% CI)	-249.37 [-330.22, -168.51]
8 Change from baseline in cardiac Index	5	457	Mean Difference (IV, Random, 95% CI)	0.44 [0.22, 0.65]
8.1 Non-selective ERAs	3	279	Mean Difference (IV, Random, 95% CI)	0.52 [0.11, 0.93]
8.2 Selective ERAs	2	178	Mean Difference (IV, Random, 95% CI)	0.35 [0.18, 0.52]
9 Hepatic toxicity	7	879	Odds Ratio (M-H, Random, 95% CI)	1.94 [0.67, 5.65]
9.1 Non-selective ERAs	5	517	Odds Ratio (M-H, Random, 95% CI)	3.12 [0.76, 12.82]
9.2 Selective ERAs	2	362	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.31, 2.51]

Analysis 1.1. Comparison 1 Endothelin receptor antagonists versus placebo, Outcome 1 Change from baseline in six-minute walk.

Analysis 1.2. Comparison 1 Endothelin receptor antagonists versus placebo, Outcome 2 Proportion of patients with improved functional class.

Analysis 1.3. Comparison 1 Endothelin receptor antagonists versus placebo, Outcome 3 Proportion of patients with deteriorated functional class.

Analysis 1.4. Comparison 1 Endothelin receptor antagonists versus placebo, Outcome 4 Change from baseline in Borg dyspnoea index.

Analysis 1.5. Comparison 1 Endothelin receptor antagonists versus placebo, Outcome 5 Mortality.

Analysis 1.6. Comparison 1 Endothelin receptor antagonists versus placebo, Outcome 6 Change from baseline in mean pulmonary artery pressure.

Analysis 1.7. Comparison 1 Endothelin receptor antagonists versus placebo, Outcome 7 Change from baseline in pulmonary vascular resistance.

Analysis 1.8. Comparison 1 Endothelin receptor antagonists versus placebo, Outcome 8 Change from baseline in cardiac Index.

Analysis 1.9. Comparison 1 Endothelin receptor antagonists versus placebo, Outcome 9 Hepatic toxicity.

Comparison 2. Endothelin receptor antagonists versus sildenafil

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Six-minute walk	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Symptoms	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Cardiac Index	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Endothelin receptor antagonists versus sildenafil, Outcome 1 Six-minute walk.

Study or subgroup	N	ERAs Mean(SD)	N	Sildenafil Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
SERAPH	12	59 (53)	13	114 (84.6)		-55[-109.92,-0.08]

Favours sildenafil -100 -50 0 50 100 Favours ERAs

Analysis 2.2. Comparison 2 Endothelin receptor antagonists versus sildenafil, Outcome 2 Symptoms.

Study or subgroup	ERAs		Sildenafil		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
SERAPH	12	0.2 (2.7)	13	-1.5 (2.8)		1.7[-0.42,3.82]
					Favours ERAs	Favours sildenafil

Analysis 2.3. Comparison 2 Endothelin receptor antagonists versus sildenafil, Outcome 3 Mortality.

Study or subgroup	ERAs		Sildenafil		Odds Ratio	Odds Ratio
	n/N		n/N		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
SERAPH	0/12		1/14			0.36[0.01,9.68]
					Favours bosentan	Favours sildenafil

Analysis 2.4. Comparison 2 Endothelin receptor antagonists versus sildenafil, Outcome 4 Cardiac Index.

Study or subgroup	ERAs		Sildenafil		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
SERAPH	12	0.3 (0.2)	13	0.3 (0.2)		0[-0.14,0.14]
					Favours ERAs	Favours sildenafil

ADDITIONAL TABLES

Table 1. Data of ASSET-1 study

	Bosentan		Placebo	
	n	Median difference (Interquartile range [IQR])	n	Median difference (IQR)
Characteristic				
6MWD (m)	6	-9 (-18 to -5)	7	38 (3 to 52)
PVR, (dyn/sec/cm ⁻⁵)	5	-90 (-111 to -41)	4	-60 (-98 to 8)
mPAP (mm Hg)	5	-6 (-6 to -5)	4	-4 (-8 to 1)

IQR: interquartile range
6MWD: six-minute walk test
PVR: pulmonary vascular resistance

APPENDICES

Appendix 1. Database search strategies

CENTRAL

#1 MeSH descriptor Receptors, Endothelin explode all trees
#2 endothelin* near receptor*

#3 endothelium* near receptor*
#4 bosentan or tracleer or sitaxsentan
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Hypertension, Pulmonary, this term only
#7 MeSH descriptor Pulmonary Heart Disease explode all trees
#8 pulmonar* near hypertensi*
#9 (#6 OR #7 OR #8)
#10 (#5 AND #9)

MEDLINE**Topic search**

1. exp Receptors, Endothelin/
2. (endothelin\$ adj5 receptor\$).mp.
3. (endothelium\$ adj5 receptor\$).mp.
4. (bosentan or tracleer or sitaxsentan or ambrisentan).mp.
5. 1 or 2 or 3 or 4
6. exp Hypertension, Pulmonary/
7. exp Pulmonary Heart Disease/
8. (pulmonar\$ adj5 hypertensi\$).mp.
9. 6 or 7 or 8
10. 5 and 9

RCT filter

1. (clinical trial or controlled clinical trial or randomised controlled trial).pt.
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

EMBASE**Topic search**

1. exp Endothelin Receptor/
2. (endothelin\$ adj5 receptor\$).mp.
3. (endothelium\$ adj5 receptor\$).mp.

4. (bosentan or tracleer or sitaxsentan or ambrisentan).mp.

5. 1 or 2 or 3 or 4

6. exp Pulmonary Hypertension/

7. exp Cor Pulmonale/

8. (pulmonar\$ adj5 hypertensi\$).mp.

9. 6 or 7 or 8

10. 5 and 9

RCT filter

1. Randomized Controlled Trial/

2. randomisation/

3. Controlled Study/

4. Clinical Trial/

5. controlled clinical trial/

6. Double Blind Procedure/

7. Single Blind Procedure/

8. Crossover Procedure/

9. or/1-8

10. (clinica\$ adj3 trial\$).mp.

11. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (mask\$ or blind\$ or method\$)).mp.

12. exp Placebo/

13. placebo\$.mp.

14. random\$.mp.

15. ((control\$ or prospectiv\$) adj3 (trial\$ or method\$ or stud\$)).mp.

16. (crossover\$ or cross-over\$).mp.

17. or/10-16

18. 9 or 17

19. exp ANIMAL/

20. Nonhuman/

21. Human/

22. 19 or 20

23. 22 not 21

24. 18 not 23

WHAT'S NEW

Date	Event	Description
12 January 2012	New citation required and conclusions have changed	Since the original review was published, one of the included drugs, sitaxsentan, has been withdrawn and this has been noted in the review. The review has been edited for style and the plain language summary revised.
12 January 2012	New search has been performed	New literature search run, no new studies added. However, one prematurely discontinued study was found and the study data were added to characteristics of included studies (ASSET-1), we also found an abstract that appeared to be included and added this to studies awaiting classification (Palazzini 2010).

HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 1, 2005

Date	Event	Description
4 December 2008	New citation required and conclusions have changed	Substantive amendment. Five new studies have been added and the results and conclusions have been updated.
29 February 2008	New search has been performed	Literature search re-run
3 May 2006	New citation required and conclusions have changed	This review has been updated with an additional two studies (Humbert 2004; Wilkins 2005). The additional data narrowed the confidence interval around the significant increase in the risk of improved functional class status in favour of ERAs.

CONTRIBUTIONS OF AUTHORS

CL: Protocol initiation, study assessment, data extraction and entry, interpretation and write-up. Overall responsibility for maintaining the review.

JC: Protocol development, study assessment, data extraction, interpretation and write-up.

GY: study assessment, data extraction, interpretation and write-up.

DB: study assessment, interpretation and write-up.

LK: study assessment, interpretation and write-up.

EHW: revision and editing of the review.

DECLARATIONS OF INTEREST

This systematic review was supported by a grant from WHO while CL in residence at the Australasian Cochrane Centre. Dr Chao Liu participated in training from the Australasian Cochrane Centre (including the Cochrane Review Completion Program) while in Australia.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- World Health Organization (WHO), Not specified.

WHO sponsored Dr Chao Liu to receive evidence-based practice training at Monash University in Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review was written fully in accord with the protocol.

INDEX TERMS**Medical Subject Headings (MeSH)**

*Endothelin Receptor Antagonists; Antihypertensive Agents [*therapeutic use]; Hypertension, Pulmonary [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans