BMJ open

Pulmonary arterial hypertension associated with connective tissue disease: meta-analysis of clinical trials

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003113
Article Type:	Research
Date Submitted by the Author:	24-Apr-2013
Complete List of Authors:	Kuwana, Masataka; Keio University School of Medicine, Department of Internal Medicine, Division of Rheumatology Watanabe, Hiroshi; Hamamatsu University School of Medicine, Department of Clinical Pharmacology and Therapeutics Matsuoka, Nobushige; Pfizer, Division of Clinical Statistics Sugiyama, Naonobu; Pfizer, Division of Medical Affairs
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Cardiovascular medicine, Evidence based practice, Medical management, Pharmacology and therapeutics, Respiratory medicine
Keywords:	Hypertension < CARDIOLOGY, Cardiology < INTERNAL MEDICINE, Dermatology < INTERNAL MEDICINE, Rheumatology < INTERNAL MEDICINE, Vascular medicine < INTERNAL MEDICINE, THORACIC MEDICINE

Pulmonary arterial hypertension associated with connective tissue disease: meta-analysis of clinical trials

Masataka Kuwana,[1] Hiroshi Watanabe,[2] Nobushige Matsuoka,[3] Naonobu Sugiyama[4]

[1]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

[2]Department of Clinical Pharmacology and Therapeutics, Hamamatsu University School of Medicine, Shizuoka, Japan

[3]Division of Clinical Statistics, Pfizer Japan Inc.

[4]Division of Medical Affairs, Pfizer Japan Inc.

Correspondence to Masataka Kuwana

Department of Internal Medicine, Division of Rheumatology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.

TEL: 81-3-3350-3567; FAX: 81-3-3350-3567

E-mail: kuwanam@z5.keio.jp

Running head: Pulmonary arterial hypertension associated with connective tissue disease

Abstract

Objectives: Few studies have focused on pulmonary arterial hypertension (PAH) associated with connective tissue diseases (CTDs). The optimal treatment for CTD-PAH has yet to be established. **Design:** Meta-analysis of data from evaluations of treatment for PAH generally (19 studies) and CTD-PAH specifically (9 studies) to compare the effects of pulmonary vasodilative PAH agents. MEDLINE, EMBASE, and BIOSIS were searched. English-language full-text articles published between January 1990 and August 2012 were eligible. **Setting:** International. **Participants:** Patients with PAH generally (*n*=3073) and CTD-PAH specifically (*n*=678). **Primary outcome measure:** Exercise capacity (6-minute walk distance, 6MWD). **Results:** Patients with PAH (all forms) had mean age 32–55 years (women, 61–87%); CTD-PAH patients had mean age 45–55 years (women, 74–95%). Mean change in 6MWD from baseline (95%CI) for the active treatment group versus the control group in all PAH patients was 34.6 m (27.4, 41.9 m). Mean differences from the results for patients receiving placebo by subgroup of patients receiving phosphodiesterase (PDE)-5 inhibitors, endothelin receptor antagonists (ERAs), and prostacyclin (PGI_2) analogues were 22.4–45.5 m, 39.5–44.2 m, and 12.4–64.9 m, respectively. Mean difference between changes in 6MWD in CTD-PAH patients was 34.2 m (23.3, 45.0 m). Mean differences by subgroup of patients receiving PDE-5 inhibitors, ERAs, and PGI_2 analogues in CTD-PAH patients were 37.0–47.1 m, 14.1–21.7 m, and 21.0–108.0 m, respectively. ERAs were less effective in CTD-PAH patients than all form-PAH patients: 14.1 m (–4.4, 32.6 m) versus 39.5 m (19.5, 59.6 m) for bosentan, and 21.7 m (2.2, 41.3 m) versus 44.2 m (30.2, 58.2 m) for ambrisentan. **Conclusions:** All 3 types of PAH agent are effective. However, ERAs may be a less effective

choice against CTD-PAH; further studies are needed. Limitations include the limited number of studies for some agents and for CTD-PAH patients.

Article summary

Article focus

- Pulmonary arterial hypertension (PAH) is a progressive disease characterised by abnormally high blood pressure in the pulmonary arteries.
- Patients with PAH associated with connective tissue diseases (CTDs) such as systemic sclerosis (SSc) have a particularly poor prognosis.
- Few studies have focused on patients with CTD-PAH, so the optimal treatment for these patients is unclear.

Key messages

- The effects of the phosphodiesterase-5 inhibitors sildenafil and tadalafil, and the prostacyclin analogue epoprostenol, are consistent in patients with CTD-PAH and in those with PAH generally.
- The endothelin receptor antagonists bosentan and ambrisentan may be less effective in patients with CTD-PAH than in those with PAH generally.

Strengths and limitations of this study

- The meta-analysis used all currently available data from clinical studies on treatment for PAH.
- Few studies were identified for some PAH agents and for CTD-PAH patients.
- Study designs and patient background characteristics, including the percentages of patients with SSc-PAH, were inconsistent between studies.

Introduction

Pulmonary hypertension is a heterogeneous condition with sustained elevation of pressure in the pulmonary arteries, and is defined as mean pulmonary artery pressure ≥ 25 mmHg at rest.[1] The most recent and widely accepted clinical classification of pulmonary hypertension is that proposed at the Fourth World Symposium on Pulmonary Hypertension at Dana Point in 2008.[2] It classifies pulmonary hypertension into 5 groups. Group 1 comprises pulmonary arterial hypertension (PAH), which includes idiopathic PAH, heritable PAH, drug- and toxin-induced PAH, PAH associated with various diseases, and persistent pulmonary hypertension of the newborn. Group 2 comprises pulmonary hypertension owing to left heart disease; group 3, pulmonary hypertension owing to lung diseases and/or hypoxia; group 4, chronic thromboembolic pulmonary hypertension; and group 5, pulmonary hypertension of unknown cause. In this classification of pulmonary hypertension, PAH is recognised as having an extremely poor prognosis and requires specific medical treatment.

Connective tissue disease (CTD) is the most common condition associated with PAH. Recent cohort studies have shown that most patients with PAH associated with CTD have systemic sclerosis (SSc).[3 4] In fact, the prevalence of PAH in patients with SSc is reported to be 7–12%.[5 6] Patients with SSc-PAH have poor prognosis compared with patients with idiopathic PAH.[7] Therefore, early and appropriate diagnosis and selection of the optimal treatment regimen are important for SSc-PAH, to improve the hemodynamics, exercise capacity, and eventually survival of patients.

The optimal treatment for PAH has not been established. However, there has been major progress in medical treatment for PAH in recent years. Several new agents with different

mechanisms have been introduced, including phosphodiesterase (PDE)-5 inhibitors (e.g. oral sildenafil and tadalafil), endothelin receptor antagonists (ERAs) (e.g. oral bosentan and ambrisentan), and prostacyclin (PGI_2) analogues (e.g. continuous intravenous epoprostenol). The introduction of these new agents is expected to contribute to the improvement of exercise capacity, subjective symptoms, and quality of life, as well as the short- and long-term survival of patients.

Although the efficacy and safety of these new agents have been shown in small- or medium-scale randomised controlled trials (RCTs) and open-label trials, evidence from large-scale comparative studies of these agents remains insufficient because PAH is a rare disease. Therefore, to compare the new agents and establish a therapeutic strategy for PAH, several systematic reviews and meta-analyses of available clinical study results have been done.[8–13] However, most of these analyses include studies on all forms of PAH, and studies that focus on CTD-PAH are limited. In fact, our literature search showed only one such report: a meta-analysis by Avouac *et al.*,[8] which investigated the efficacy of oral PAH agents mainly in patients with SSc.

Therefore, in this meta-analysis of studies designed as RCTs and open-label, single-arm trials, we aimed to evaluate the effect of each PAH agent on exercise capacity in patients with CTD-PAH compared with patients with all forms of PAH. We chose 6-minute walk distance (6MWD) as an endpoint because it was used as a primary endpoint in most previous randomised studies of PAH agents.[14]

Methods

Eligibility criteria

To evaluate the effects of 3 typical types of PAH agent, we included RCTs in which the following PAH agents were administered to patients with all forms of PAH.

- PDE-5 inhibitors: sildenafil and tadalafil
- ERAs: bosentan and ambrisentan
- PGI_2 analogues: epoprostenol, beraprost, iloprost, and treprostinil.

Because the number of RCTs in patients with CTD-PAH is limited, we also included open-label, single-arm trials evaluating the effects of PAH agents in patients with CTD-PAH. Non-interventional studies (e.g. case reports and observational studies) were excluded. Studies in which results for 6MWD were not reported were also excluded.

Search strategy

We searched MEDLINE, EMBASE, and BIOSIS for English-language full-text articles published between January 1990 and August 2012, using the key terms ‘pulmonary arterial hypertension’, ‘6 minute walk’, and the names of individual drugs. In addition to these key terms, we used the term ‘randomised controlled trial’ or ‘RCT’ to identify RCTs evaluating all forms of PAH, and ‘connective tissue disease’ or ‘CTD’ to identify studies evaluating CTD-PAH. The last search was run on 5 December 2012. Additional studies were identified through manual searching.

Primary endpoint

The primary outcome measure was the difference in mean change from baseline in 6MWD between groups. However, for single-arm studies, the mean change from baseline was used as

the primary outcome measure.

Data collection

Relevant data were extracted and reviewed by NM and NS. Data on study characteristics (year and design), variables including PAH agents used, total patient numbers and the percentage of CTD-PAH patients, and outcomes were extracted.

Risk of bias

To determine the validity of the included studies, we assessed the risk of bias for each study in terms of random sequence generation, allocation concealment, blinding, and other sources of bias, as recommended by the Cochrane Collaboration. Each domain was judged to have high, low, or unclear risk of bias. We did not detect clear publication bias, because the number of included studies was small.

Statistical analysis

We pooled outcomes using a random effects model by each PAH agent for all forms of PAH and CTD-PAH. Heterogeneity was assessed using the I^2 statistic, which describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error (chance).

Results

Selection of studies

A total of 196 articles were identified for evaluation of treatments for all forms of PAH. Of these, 19 articles (reporting data from 3073 patients) met the eligibility criteria for evaluations of treatments for all forms of PAH (3 articles for sildenafil,[15–17] 1 article for tadalafil,[18] 4 articles for bosentan,[19–22] 1 article for ambrisentan,[23] 3 articles for epoprostenol,[24–26] 1 article for beraprost,[27] 2 articles for iloprost,[28 29] and 4 articles for treprostinil[30–33]) (figure 1a). The main reasons for exclusion were that the article was a review and that the article reported the results of a study that involved patients other than those with PAH.

For evaluation of treatments for CTD-PAH, a total of 269 articles were identified. Of these, 9 articles (reporting data from 678 patients) met the eligibility criteria for evaluations of treatments for CTD-PAH (1 article for sildenafil,[34] 1 article for tadalafil,[18] 2 articles for bosentan,[35 36] 2 articles for ambrisentan,[37 38] 1 article for epoprostenol,[26] 1 article for beraprost,[39] and 1 article for treprostinil[40] (figure 1b). The main reasons for exclusion were that the article was a review and that the article reported the results of a study that involved patients other than those with CTD-PAH.

Characteristics and overview of the included studies

Of the 19 studies on treatments for all forms of PAH included in this analysis (table 1), 15 were randomised, placebo-controlled, double-blind studies;[15–23 27 28 30–33] 3 were randomised, open-label studies comparing with conventional treatment;[24–26] and 1 was a randomised, open-label study evaluating the effects of iloprost when added to bosentan.[29] The observation period was either 12 or 16 weeks in most of the studies, with some exceptions (1 study each with 6- and 24-week observation periods,[16 22] and 2 studies with an 8-week observation

period[24 31]). Of the placebo-controlled randomised comparative studies, 1 study of sildenafil was done in patients previously treated with epoprostenol;[17] 2 studies of iloprost, in patients previously treated with bosentan;[28 29] and 1 study of treprostinil, in patients previously treated with bosentan or sildenafil.[32]

Of the 9 studies on treatments for CTD-PAH included in this analysis (table 2), 5 were placebo-controlled, double-blind studies,[18 34 35 37 40] 1 was a randomised, open-label study comparing with conventional treatment,[26] and 3 were open-label, single-arm studies.[36 38 39] The observation period in these studies was 8–28 weeks. One study each evaluating bosentan[36] and epoprostenol[26] included only SSc-PAH patients.

Background of all PAH patients

The background of all PAH patients, based on data from the 19 studies, can be summarised as follows (full data in supplementary table 1). Mean age was 32–55 years, and the percentage of women was 61–87%. In the studies of sildenafil,[15–17] tadalafil,[18] ambrisentan,[23] and beraprost,[27] most patients were classified according to World Health Organisation functional class (WHO-FC) as in WHO-FC II or III, with 1 study including only patients in WHO-FC II.[22] In contrast, in the studies of epoprostenol,[24–26] the percentage of patients in WHO-FC IV was higher than that in studies of other agents. In the studies of iloprost, most patients were in WHO-FC III.[28 29] In the studies of treprostinil, most patients were in WHO-FC III in 3 studies[30 32 33] and in WHO-FC II in 1 study.[31] Baseline 6MWD was 226.6–434.5 m, and it was lower in the 3 studies of epoprostenol (226.6, 294.3, and 255.9 m)[24–26] compared with in studies on other agents. Therefore patients with more severe disease were included in the studies of epoprostenol than in other studies. One study of

bosentan included only patients with Eisenmenger syndrome.[21]

Background of the subgroup of CTD-PAH patients

The background of patients with CTD-PAH, using data from 9 studies, can be summarised as follows (full data in supplementary table 2). Mean age was 45–55 years, and the percentage of women was 74–95%. In 1 study of tadalafil, there was no information on baseline 6MWD or WHO-FC.[18] As for the distribution of patients according to WHO-FC, a study of beraprost included more patients in WHO-FC II,[39] and a study of epoprostenol included more patients in WHO-FC IV,[26] compared with studies of other agents.

In 5 studies in which information on underlying CTDs was available, SSc-PAH patients accounted for 45–100% of all patients included. Their mean age was 51–55 years, and the percentage of women was 74–90%.

In studies of bosentan[36] and epoprostenol[26] that included only SSc-PAH patients, baseline 6MWD was < 300 m, which was lower than that in studies of other agents. Therefore the study of beraprost included more patients with relatively mild PAH, whereas the study of epoprostenol included more patients with more severe disease.

Results of 6MWD

We pooled the data, including those for non-approved doses, to evaluate the effect of each PAH agent on exercise capacity in patients with CTD-PAH compared with in patients with all forms of PAH.

6MWD in All PAH patients

The mean differences between changes in 6MWD compared with the control group are shown in figure 2 by each agent. Briefly, the mean difference between changes in 6MWD (95%CI) was 45.5 m (32.9, 58.1 m) for sildenafil, 22.4 m (14.0, 30.9 m) for tadalafil, 39.5 m (19.5, 59.6 m) for bosentan, 44.2 m (30.2, 58.2 m) for ambrisentan, 64.9 m (20.4, 109.4 m) for epoprostenol, 25.1 m (1.9, 48.4 m) for beraprost, 12.4 m (–21.9, 46.6 m) for iloprost, and 17.3 m (6.1, 28.4 m) for treprostinil. Numerical improvement in 6MWD was obtained in patients using each agent compared with those using the control agent. Mean difference between changes in 6MWD from the control group was 12.4–64.9 m, and the total mean difference (95%CI) combining data for all agents was 34.6 m (27.4, 41.9 m). Mean difference from the effects of placebo by subgroup of patients receiving PDE-5 inhibitors, ERAs, and PGI_2 analogues were 22.4–45.5 m, 39.5–44.2 m, and 12.4–64.9 m, respectively.

6MWD in a subgroup of CTD-PAH patients

In the subgroup of CTD-PAH patients, the mean differences between changes in 6MWD compared with the control group are shown in figure 3 by each agent. For single-arm studies, the mean changes from baseline are shown. Briefly, the mean difference between changes in 6MWD (95%CI) was 47.1 m (27.9, 66.3 m) for sildenafil, 37.0 m (19.0, 55.0 m) for tadalafil, 14.1 m (–4.4, 32.6 m) for bosentan, 21.7 m (2.2, 41.3 m) for ambrisentan, 108.0 m (45.6, 170.4 m) for epoprostenol, 58.5 m (21.4, 95.6 m) for beraprost, and 21.0 m (–6.9, 48.9 m) for treprostinil. Numerical improvement in 6MWD was obtained in patients using all agents compared with those using the control agent. The mean difference between changes in 6MWD (95%CI) in patients with CTD-PAH was 34.2 m (23.3, 45.0 m). The mean differences by subgroup of patients receiving PDE-5 inhibitors, ERAs, and PGI_2 analogues

were 37.0–47.1 m, 14.1–21.7 m, and 21.0–108.0 m, respectively.

Difference in exercise capacity between all PAH patients and CTD-PAH patients

When the mean differences between changes in 6MWD were compared between all PAH patients and each subgroup of CTD-PAH patients, no difference in exercise capacity was found between the patient groups for PDE-5 inhibitors (sildenafil and tadalafil). In contrast, for ERAs (bosentan and ambrisentan), the mean values in CTD-PAH patients (bosentan, 14.1 m; ambrisentan, 21.7 m) were lower than the lower limit of 95%CI of the mean values in all PAH patients (bosentan, 19.5, 59.6 m; ambrisentan, 30.2, 58.2 m), suggesting that effects on exercise capacity may vary between patient groups. For PGI_2 (epoprostenol, beraprost, and treprostinil), no obvious trends were found between patient groups.

Risk of bias

We rated risk of bias for each study (full data in supplementary table 3). In studies for all forms of PAH, none were at high risk of bias for random sequence generation or allocation concealment; however, the method of randomisation and allocation concealment were unclear (i.e. not reported) for 11 studies and 9 studies, respectively. Four studies were at high risk of bias for blinding because they were open-label studies. Three studies were at high risk for another source of bias (imbalance in missing data between groups,[17] imbalance in baseline 6MWD,[25] and early termination based on futility analysis[29]).

Of studies for CTD-PAH, 3 studies were at high risk of bias with respect to all domains because they were open-label, single-arm studies.[36 38 39] One study was at high risk of bias resulting from imbalance in baseline characteristics.[35] The remaining studies were judged to

be not of high risk of bias in any of the domains.

Discussion

A finding of the present meta-analysis of 19 studies is that in combined patients with all forms of PAH, all agents increase 6MWD compared with the control group.[15–33] Likewise, the meta-analysis of 9 studies on CTD-PAH patients also showed an increase in 6MWD by all agents.[18 26 34–40] The finding that all agents increase 6MWD in all PAH patients is consistent with the results of the 5 previous systematic reviews and meta-analyses that evaluated the 3 types of agent (PDE-5 inhibitors, ERAs, and PGI_2 analogues).[9–13] To date, reports of meta-analyses that included patients with CTD-PAH including SSc-PAH are limited to 1 study that evaluated 3 oral agents (sildenafil, bosentan, and sitaxsentan) alone.[8] The findings of this meta-analysis are important because patients with all PAH as well as a subgroup of CTD-PAH patients were included, and the effects of 3 types of agent, including intravenous preparations, were thoroughly evaluated. Our meta-analysis shows similar trends to the findings of Avouac *et al*.[8]

When the mean differences between changes in 6MWD were compared between all PAH patients and CTD-PAH patients, the effects of ERAs (bosentan and ambrisentan) on exercise tolerance may be less in CTD-PAH patients, whereas no difference in exercise capacity was found between patient groups for PDE-5 inhibitors and PGI_2 analogues. This result should be interpreted cautiously because recent data from registries have shown that 6MWD is significantly lower in patients with CTD-PAH than in those with idiopathic PAH,[4 41] and a systematic review has shown that 6MWD may be only partially valid in patients with

SSc-PAH. [42]

This analysis has several limitations. First, we could identify only a limited number of studies for some agents (1 study each for tadalafil, ambrisentan, and beraprost), and studies that included a subgroup of patients with CTD-PAH including SSc-PAH were scarce. Second, ideally data for patients with CTD-PAH should be compared with those for patients with other forms of PAH. However, there were insufficient data for forms of PAH other than CTD-PAH, so this analysis compared data for all PAH and CTD-PAH. Third, the study designs varied: some studies that included CTD-PAH patients were done in an open-label or single-arm, open-label manner, some having a short observation period (12 or 16 weeks) or using combination therapy. Of note, in studies of combination therapy, changes in 6MWD are expected to be smaller, because patients are already receiving PAH therapy at the start of the study. Patient background characteristics were also inconsistent between studies: patients were in various WHO FC classes and had various baseline 6MWD values, which can influence the effects of each agent, and some articles reported no such information. Moreover, the percentage of SSc-PAH patients in the study population also varied, which is a study limitation because there is a difference in treatment response between SSc and non-SSc patients, and patients with SSc-PAH have poor prognosis compared with patients with other CTD-PAH.[4 7] In this meta-analysis, the percentages of SSc-PAH patients were as follows: for sildenafil, 45% in the study by Badesch *et al.*;[34] for bosentan, 79% in the study by Denton *et al.*;[35] and 100% in the study by Launay *et al.*;[36] and for epoprostenol, 100% in the study by Badesch *et al.*[26] The percentage was unknown in the study of tadalafil by Galiè *et al.*;[18] in those of ambrisentan by Badesch *et al.*;[37 38] and in that of beraprost by Kunieda et al.[39] Patients with SSc-PAH were more frequently enrolled in studies for bosentan[35 36] than in the

sildenafil study.[34] A fourth limitation of our study was the inclusion of data for non-approved, possibly subtherapeutic doses, which may have reduced the effects of the PAH agents in some studies. Finally, there may be publication bias, so negative results are likely to be unpublished.[43]

Furthermore, the present analysis is intended to compare changes in 6MWD over a short period of time, therefore whether the results are associated with patient survival remains unclear. However, 6MWD is effective as an indicator of the severity of PAH.[44] Moreover, an ongoing large-scale registry, the US Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL), which aims to clarify the characteristics and prognosis of PAH patients and the latest treatment for PAH, has shown that 6MWD is an independent predictor that is significantly associated with 1-year survival.[45] Several other studies have also confirmed its role as an independent predictor of prognosis.[46–50] In addition, investigators who did a placebo-controlled randomised trial of the PDE-5 inhibitor sildenafil have recently identified the minimum clinically meaningful changes in 6MWD, and concluded that it would be a useful indicator to determine the efficacy of other PAH agents.[51]

However, pharmacological treatment for PAH is shifting from monotherapy to combination therapy, and it is expected that clinical studies investigating the efficacy of combination therapy will increase. Therefore, it will be increasingly difficult to do a meta-analysis that includes all the new studies to detect differences between PAH agents. The present analysis is meaningful because it included all available clinical study results to date, and we hope that it contributes to the improvement of the treatment for PAH.

In conclusion, the present meta-analysis of studies that included CTD-PAH patients showed an increase in 6MWD by all agents, that is, PDE-5 inhibitors, ERAs, and PGI_2

analogues. Comparison of the mean differences between changes in 6MWD suggest that, for bosentan and ambrisentan, the effects on exercise tolerance may differ depending on patient group, whereas the PDE-5 inhibitors sildenafil and tadalafil and the PGI_2 analogue epoprostenol show consistent effects regardless of the presence or absence of CTD. Further studies are needed to clarify the clinical implications of these findings.

Competing interests

MK has received research funding from Actelion Pharmaceuticals, GlaxoSmithKline, Novartis and Pfizer, and lecture fees from Actelion Pharmaceuticals, Pfizer, GlaxoSmithKline, Nippon Shinyaku, Mitsubishi Tanabe Pharma and Takeda Pharmaceuticals. WH has received research funding from the Ministry of Health, Labour and Welfare of Japan, Teika Seiyaku, Takeda Pharmaceuticals, Mochida, Pfizer, Asteras and Daiichi Sankyo, and lecture fees from Pfizer, Acterion, Novartis, Daiich Sankyo, GlaxoSmithKline and Nihon Shinyaku. NM and NS are employees of Pfizer Japan Inc.

Contributors

N. Matsuoka, a statistician employed by Pfizer Japan, collected the data and did the statistical analyses described in this article.

Dr N. Sugiyama, a rheumatologist employed by Pfizer Japan, reviewed the collection and analyses of the data. He helped conceive and design the meta-analysis, interpret the results, and revise the manuscript.

Dr M. Kuwana is directly responsible for the manuscript. He reviewed the data analyses and drafted the manuscript, providing important intellectual content from the perspective of a CTD-PAH specialist.

Dr H. Watanabe revised the manuscript critically for important intellectual content from the perspective of a PAH specialist.

Data sharing

No additional data available.

Funding

None

References

1. Badesch DB, Champion HC, Sanchez MA, *et al*. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;54:S55–66.
2. Simonneau G, Robbins IM, Beghetti M, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;54:S43–54.
3. Condliffe R, Kiely DG, Peacock AJ, *et al.* Connective tissue disease-associated pulmonary hypertension in the modern treatment era. *Am J Respir Crit Care Med* 2009;179:151–7.
4. Chung L, Liu J, Parsons L, *et al.* Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. *Chest* 2010;138:1383–94.
5. Hachulla E, Gressin V, Guilevin L, *et al.* Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum* 2005;52:3792–800.
6. Mukerjee D, St George D, Coleiro B, *et al.* Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis* 2003;62:1088–93.
7. Kawut SM, Taichman DB, Archer-Chicko CL, *et al.* Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. *Chest* 2003;123:344–50.
8. Avouac J, Wipff J, Kahan A, *et al.* Effects of oral treatments on exercise capacity in systemic sclerosis related pulmonary arterial hypertension: a meta-analysis of

randomised controlled trials. *Ann Rheum Dis* 2008;67:808–14.

9. Galiè N, Manes A, Negro L, *et al.* A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. *Eur Heart J* 2009;30:394–403.
10. Galiè N, Palazzini M, Manes A. Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analyses. *Eur Heart J* 2010;31:2080–6.
11. Macchia A, Marchioli R, Tognoni G., *et al.* Systematic review of trials using vasodilators in pulmonary arterial hypertension: why a new approach is needed. *Am Heart J* 2010;159:245–57.
12. He B, Zhang F, Li X, *et al.* Meta-analysis of randomized controlled trials on treatment of pulmonary arterial hypertension. *Circ J* 2010;74:1458–64.
13. Ryerson CJ, Nayar S, Swiston JR, *et al.* Pharmacotherapy in pulmonary arterial hypertension: a systematic review and meta-analysis. *Respir Res* 2010;11:12.
14. McLaughlin VV, Badesch DB, Delcroix M, *et al.* End points and clinical trial design in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;54:S97–107.
15. Galiè N, Ghofrani HA, Torbicki A, *et al.* Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005;353:2148–57.
16. Singh TP, Rohit M, Grover A, *et al.* A randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe pulmonary artery hypertension. *Am Heart J* 2006;151:851.e1–5.
17. Simonneau G, Rubin LJ, Galiè N, *et al.* Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008;149:521–30.
18. Galiè N, Brundage BH, Ghofrani HA, *et al.* Tadalafil therapy for pulmonary arterial

hypertension. *Circulation* 2009;119:2894–903.

19. Channick RN, Simonneau G, Sitbon O, *et al.* Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001;358:1119–23.
20. Rubin LJ, Badesch DB, Barst RJ, *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896–903.
21. Galiè N, Beghetti M, Gatzoulis MA, *et al.* Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation* 2006;114:48–54.
22. Galiè N, Rubin LJ, Hoeper M, *et al.* Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008;371:2093–100.
23. Galiè N, Olschewski H, Oudiz RJ, *et al.* Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation* 2008;117:3010–9.
24. Rubin LJ, Mendoza J, Hood M, *et al.* Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. *Ann Intern Med* 1990;112:485–91.
25. Barst RJ, Rubin LJ, Long WA, *et al.* A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996;334:296–302.

26. Badesch DB, Tapson VF, McGoon MD, *et al.* Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000;132:425–34.
27. Galiè N, Humbert M, Vachiéry JL, *et al.* Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2002;39:1496–502.
28. McLaughlin VV, Oudiz RJ, Frost A, *et al.* Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006;174:1257–63.
29. Hoeper MM, Leuchte H, Halank M, *et al.* Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2006;28:691–4.
30. Simonneau G, Barst RJ, Galiè N, *et al.* Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002;165:800–4.
31. McLaughlin VV, Gaine SP, Barst RJ, *et al.* Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension. *J Cardiovasc Pharmacol* 2003;41:293–9.
32. McLaughlin VV, Benza RL, Rubin LJ, *et al.* Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2010;55:1915–22.
33. Hiremath J, Thanikachalam S, Parikh K, *et al.* Exercise improvement and plasma biomarker changes with intravenous treprostinil therapy for pulmonary arterial hypertension: a placebo-controlled trial. *J Heart Lung Transplant* 2010;29:137–49.
34. Badesch DB, Hill NS, Burgess G, *et al.* Sildenafil for pulmonary arterial hypertension

associated with connective tissue disease. *J Rheumatol* 2007;34:2417–22.

35. Denton CP, Humbert M, Rubin L, *et al.* Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions. *Ann Rheum Dis* 2006;65:1336–40.
36. Launay D, Sitbon O, Le Pavec J, *et al.* Long-term outcome of systemic sclerosis–associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by the addition of prostanoids or sildenafil. *Rheumatology* 2010;49:490–500.
37. Badesch DB. Ambrisentan therapy for pulmonary arterial hypertension: a comparison by PAH etiology. *Chest* 2007;slide presentations:488S.
38. Badesch DB, Feldman J, Keogh A, *et al.* ARIES-3: ambrisentan therapy in a diverse population of patients with pulmonary hypertension. *Cardiovasc Ther* 2012;30:93–9.
39. Kunieda T, Nakanishi N, Matsubara H, *et al.* Effects of long-acting beraprost sodium (TRK-100STP) in Japanese patients with pulmonary arterial hypertension. *Int Heart J* 2009;50:513–29.
40. Oudiz R, Schilz RJ, Barst RJ, *et al.* Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. *Chest* 2004;126:420–7.
41. Clements PJ, Tan M, McLaughlin VV, *et al.* The pulmonary arterial hypertension quality enhancement research initiative: comparison of patients with idiopathic PAH to patients with systemic sclerosis-associated PAH. *Ann Rheum Dis* 2012;71:249–52.
42. Avouac J, Kowal-Bielecka O, Pittrow D, et al.; EPOSS Group. Validation of the 6 min walk test according to the OMERACT filter: a systematic literature review by the EPOSS-OMERACT group. Ann Rheum Dis 2010; 69:1360–1363.

43. Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey. *BMJ* 2012;344:d7762.

44. Naeije R. The 6-min walk distance in pulmonary arterial hypertension: "Je t'aime, moi non plus". *Chest* 2010;137:1258–60.

45. Benza RL, Miller DP, Gomberg-Maitland M, *et al.* Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010;122:164–72.

46. Miyamoto S, Nagaya N, Satoh T, *et al.* Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000;161:487–92.

47. Sitbon O, Humbert M, Nunes H, *et al.* Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002;40:780–8.

48. Groepenhoff H, Vonk-Noordegraaf A, Boonstra A, *et al.* Exercise testing to estimate survival in pulmonary hypertension. *Med Sci Sports Exerc* 2008;40:1725–32.

49. Humbert M, Sitbon O, Chaouat A, *et al.* Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010;122:156–63.

50. Humbert M, Sitbon O, Yaïci A, *et al.* Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010;36:549–55.

51. Gilbert C, Brown MC, Cappelleri JC, *et al.* Estimating a minimally important difference

in pulmonary arterial hypertension following treatment with sildenafil. *Chest* 2009;135:137–42.

Figure legends

Figure 1 Flow diagram summarising selection of studies evaluating treatments for patients with (**a**) all forms of pulmonary arterial hypertension (PAH) and (**b**) connective tissue disease-PAH. RCT, randomised controlled trial.

Figure 2 Effects of individual pulmonary arterial hypertension (PAH) agents on 6-minute walk distance (6MWD) in patients with any form of PAH. ERA, endothelin receptor antagonist; PDE, phosphodiesterase; PGI_2, prostacyclin.

Figure 3 Effects of individual pulmonary arterial hypertension (PAH) agents on 6-minute walk distance (6MWD) in patients with PAH associated with connective tissue disease. ERA, endothelin receptor antagonist; PDE, phosphodiesterase; PGI_2, prostacyclin. For single-arm studies, the mean changes from baseline are shown.

Table 1 Summary of included studies evaluating treatment with PAH agents in patients with all forms of PAH

Source (official acronym)	PAH agent	No. of patients	No. (%) of CTD-PAH patients	Study design	Intervention	Control	Period (weeks)	Results for CTD-PAH
Galiè *et al.* (2005)[15] (SUPER-1)	Sildenafil	278	84 (30)	RCT, DB	20 mg × 3/day, 40 mg × 3/day, 80 mg × 3/day	Placebo	12	Available in Badesch *et al.* (2007)[34]
Singh *et al.* (2006)[16]	Sildenafil	20	0	RCT, DB	25 mg on first day, then if no hypotension, 100 mg × 3/day	Placebo	6	None
Simonneau *et al.* (2008)[17] (PACES)	Sildenafil	267	55 (21)	RCT, DB	20 mg × 3/day, titrated to 40 mg and 80 mg × 3/day, as tolerated, at 4-week intervals on background treatment with epoprostenol	Placebo on background treatment with epoprostenol	16	None
Galiè *et al.* (2009)[18] (PHIRST)	Tadalafil	405	95 (24)	RCT, DB	2.5 mg, 10 mg, 20 mg, 40 mg	Placebo	16	Available in this article
Channick *et al.* (2001)[19]	Bosentan	32	5 (16)	RCT, DB	62.5 mg × 2/day for 4 weeks, then 125 mg × 2/day	Placebo	12	Available in Denton *et al.* (2006)[35]
Rubin *et al.* (2002)[20] (BREATHE-1)	Bosentan	213	63 (30)	RCT, DB	62.5 mg × 2/day for 4 weeks, then 125 mg or 250 mg × 2/day	Placebo	16	Available in Denton *et al.* (2006)[35]
Galiè *et al.* (2006)[21]	Bosentan	54	0	RCT, DB	62.5 mg × 2/day for	Placebo	16	None

Source (official acronym)	PAH agent	No. of patients	No. (%) of CTD-PAH patients	Study design	Intervention	Control	Period (weeks)	Results for CTD-PAH
(BREATHE-5)					4 weeks, then 125 mg × 2/day			
Galiè *et al.* (2008)[22] (EARLY)	Bosentan	185	33 (18)	RCT, DB	62.5 mg × 2/day for 4 weeks, then 125 mg × 2/day	Placebo	24	None
Galiè *et al.* (2008)[23] (ARIES)	Ambrisentan	393	124 (32)	RCT, DB	2.5 mg, 5 mg, 10 mg	Placebo	12	Available in Badesch (2007)[37]
Rubin *et al.* (1990)[24]	Epoprostenol	23	0	RCT, open-label	Initial dosage of 1–2 ng/kg/min, then titrated to an optimal dose	Conventional therapy	8	None
Barst *et al.* (1996)[25]	Epoprostenol	81	0	RCT, open-label	Initial dosage of 2 ng/kg/min, then titrated to optimal dosage	Conventional therapy	12	None
Badesch *et al.* (2000)[26]	Epoprostenol	111	111 (100)	RCT, open-label	Dosage established according to signs and symptoms from an initial low dose	Conventional therapy	12	Available in this article
Galiè *et al.* (2002)[27] (ALPHABET)	Beraprost	130	13 (10)	RCT, DB	20 mg × 4/day for first week, then titrated to 120 mg ×	Placebo	12	None

Source (official acronym)	PAH agent	No. of patients	No. (%) of CTD-PAH patients	Study design	Intervention	Control	Period (weeks)	Results for CTD-PAH
					4/day			
McLaughlin *et al.* (2006)[28] (STEP)	Inhaled iloprost	67	NR	RCT, DB	5 mg on background treatment with bosentan (125 mg × 2/day)	Placebo on background treatment with bosentan (125 mg × 2/day)	12	None
Hoeper *et al.* (2006)[29] (COMBI)	Inhaled iloprost	40	0	RCT, open-label	5 mg on background treatment with bosentan (125 mg × 2/day)	Placebo on background treatment with bosentan (125 mg × 2/day)	12	None
Simonneau *et al.* (2002)[30]	Treprostinil	469	90 (19)	RCT, DB	Initial dosage of 1.25 ng/kg/min, then titrated to maximum dosage of 22.5 ng/kg/min	Placebo	12	None
McLaughlin *et al.* (2003)[31]	Treprostinil	26	0	RCT, DB	Initial dosage of 2.5 or 5.0 ng/kg/min, then titrated to maximum dosage of 20 ng/kg/min	Placebo	8	Available in Oudiz *et al.* (2004)[40]
McLaughlin *et al.*	Treprostinil	235	0	RCT, DB	Initiated at 3 breaths	Placebo	12	None

Source (official acronym)	PAH agent	No. of patients	No. (%) of CTD-PAH patients	Study design	Intervention	Control	Period (weeks)	Results for CTD-PAH
(2010)[32]					(18 mg)/inhalation, then titrated to maximum dosage of 9 breaths (54 mg) at each of the 4 daily doses			
Hiremath *et al.* (2010)[33]	Treprostinil	44	2 (5)	RCT, DB	Initial dose of 4 ng/kg/min, then titrated to maximum dose of 100 ng/kg/min	Placebo	12	None

CTD, connective tissue disease; DB, double-blind; NR, not reported; PAH, pulmonary arterial hypertension; RCT, randomised controlled trial.

Table 2 Summary of included studies evaluating treatment with PAH agents in patients with CTD-PAH

Source (official acronym)	PAH agent	No. of CTD-PAH patients	No. (%) of SSc-PAH patients	Study design	Intervention	Control	Period (weeks)
Badesch *et al.* (2007)[34] (SUPER-1)	Sildenafil	84	38 (45)	RCT, DB	20 mg × 3/day, 40 mg × 3/day, 80 mg × 3/day	Placebo	12
Galiè *et al.* (2009)[18] (PHIRST)	Tadalafil	95	NR	RCT, DB	2.5 mg, 10 mg, 20 mg, 40 mg	Placebo	16
Denton *et al.* (2006)[35]	Bosentan	66	52 (79)	RCT, DB	62.5 mg × 2/day for 4 weeks, then 125 or 250 mg × 2/day	Placebo	12 or 16
Launay *et al.* (2010)[36]	Bosentan	49	49 (100)	Single-arm, open-label	62.5 mg × 2/day for 4 weeks, then 125 or 250 mg × 2/day	None	28
Badesch (2007)[37] (ARIES)	Ambrisentan	124	NR	RCT, DB	2.5 mg, 5 mg, 10 mg	Placebo	12
Badesch *et al.* (2012)[38] (ARIES-3)	Ambrisentan	40	NR	Single-arm, open-label	5 mg	None	24
Badesch *et al.* (2000)[26]	Epoprostenol	111	111 (100)	RCT, open-label	Dosage established according to signs and symptoms from initial low dose	Conventional therapy	12
Kunieda *et al.* (2009)[39]	Beraprost	19	NR	Single-arm, open-label	Initial dose of 120 mg/day, then titrated to maximum dose of 360 mg/day	None	12
Oudiz *et al.* (2004)[40]	Treprostinil	90	45 (50)	RCT, DB	Initial dosage of 2.5 or 5.0 ng/kg/min, then titrated to	Placebo	8

Source (official acronym)	PAH agent	No. of CTD-PAH patients	No. (%) of SSc-PAH patients	Study design	Intervention	Control	Period (weeks)
					maximum dosage of 20 ng/kg/min		

CTD, connective tissue disease; DB, double-blind; NR, not reported; PAH, pulmonary arterial hypertension; RCT, randomised controlled trial; SSc, systemic sclerosis.

Figure 1a

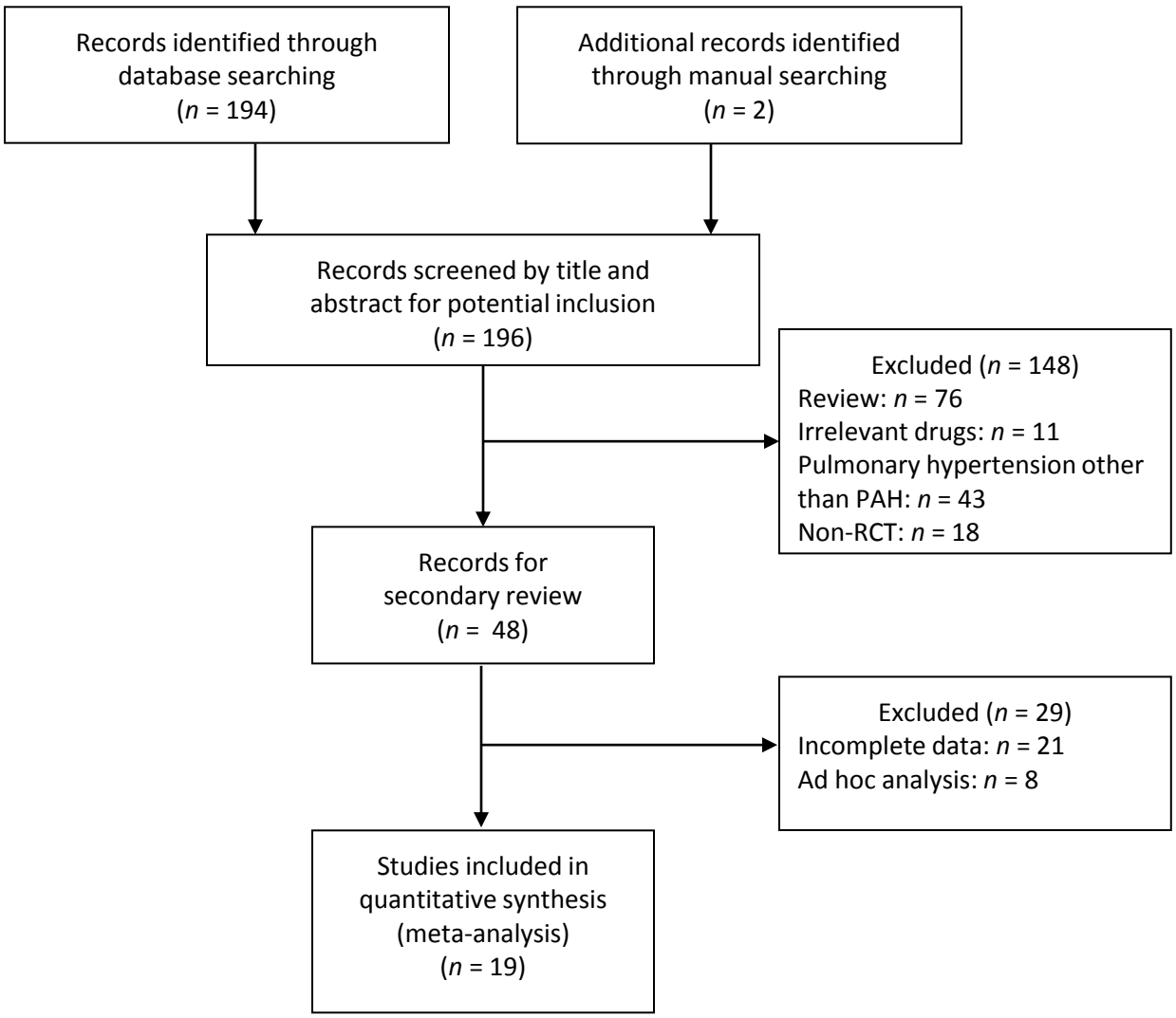

Records identified through database searching (n = 194)
Additional records identified through manual searching (n = 2)
Records screened by title and abstract for potential inclusion (n = 196)
Excluded (n = 148)
Review: n = 76
Irrelevant drugs: n = 11
Pulmonary hypertension other than PAH: n = 43
Non-RCT: n = 18
Records for secondary review (n = 48)
Excluded (n = 29)
Incomplete data: n = 21
Ad hoc analysis: n = 8
Studies included in quantitative synthesis (meta-analysis) (n = 19)

Figure 1b

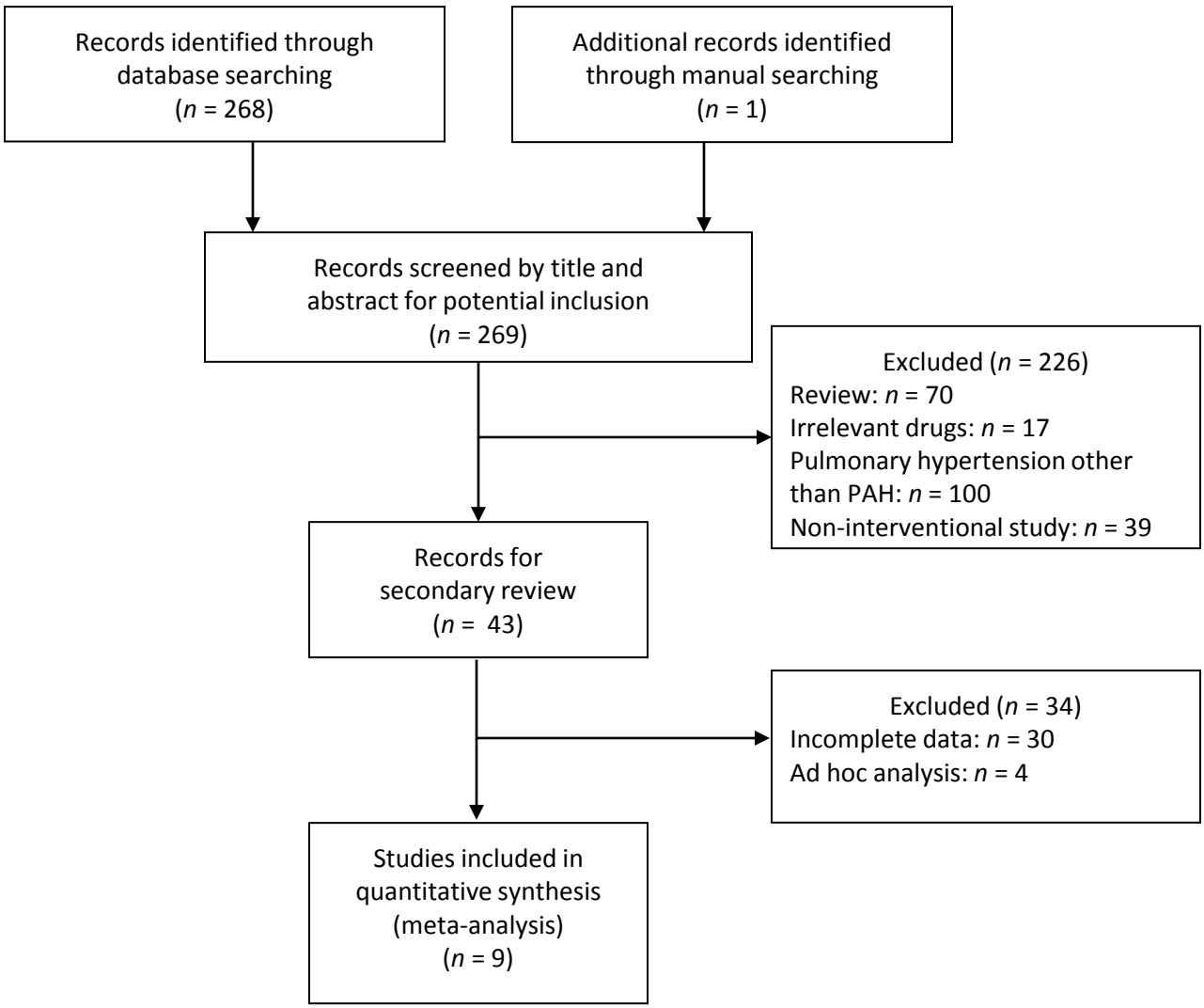

Records identified through database searching (n = 268)
Additional records identified through manual searching (n = 1)
Records screened by title and abstract for potential inclusion (n = 269)
Excluded (n = 226)
Review: n = 70
Irrelevant drugs: n = 17
Pulmonary hypertension other than PAH: n = 100
Non-interventional study: n = 39
Records for secondary review (n = 43)
Excluded (n = 34)
Incomplete data: n = 30
Ad hoc analysis: n = 4
Studies included in quantitative synthesis (meta-analysis) (n = 9)

Figure 2

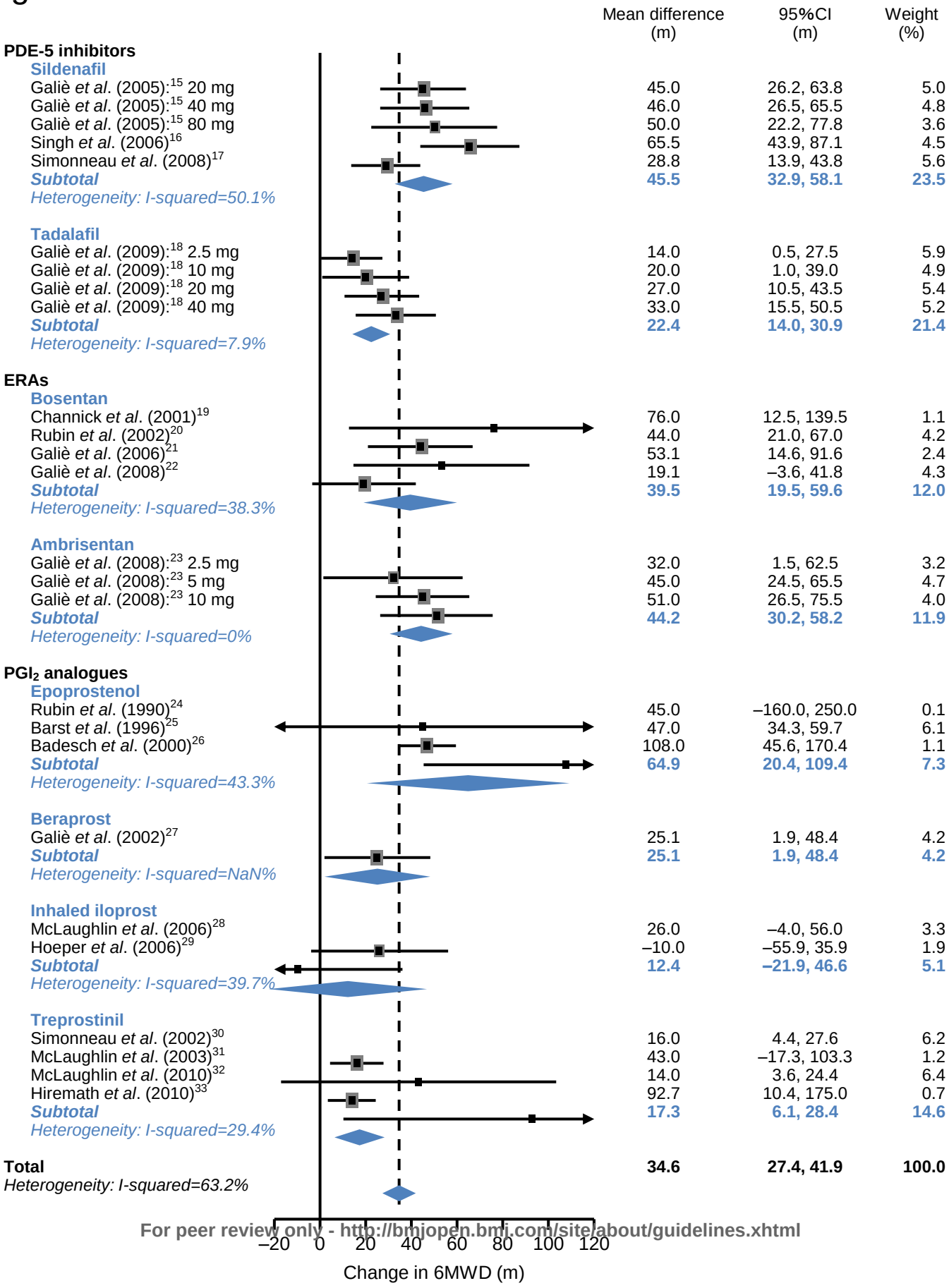
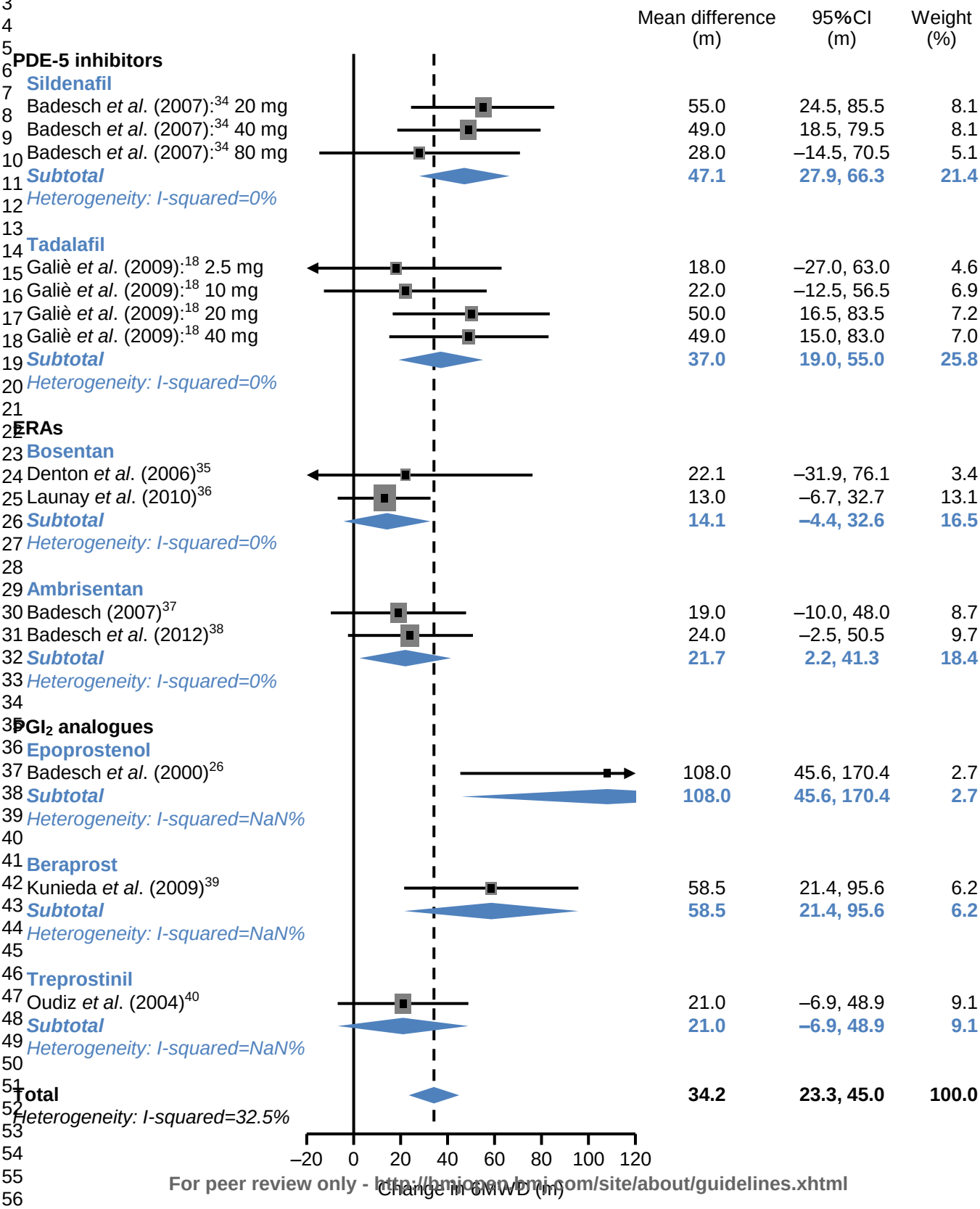


Figure 3



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8–9 and Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9–10 and Tables 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13 and Suppl. table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11–13, Figs 2 and 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11–13, Figs 2 and 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13 and Suppl. table 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15–16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplementary table 1 Baseline characteristics of patients with all forms of PAH

Source	PAH agent	Female, *n* (%)	Mean age (years)	Mean weight (kg)	WHO functional class, *n* (%)				Mean baseline 6MWD (m)	Mean PAP (mmHg)
					I	II	III	IV		
Galiè *et al* (2005)[15]	Sildenafil	209 (76)	49	72.7	1 (1)	107 (39)	160 (58)	9 (3)	343.7	52.8
Singh *et al.* (2006)[16]	Sildenafil	15 (75)	NR	NR	0	8 (40)	11 (55)	1 (5)	262.0	95.4
Simonneau *et al.* (2008)[17]	Sildenafil	213 (80)	48	71.4	3 (1)	68 (26)	175 (66)	16 (6)	345.3	51.7
Galiè *et al.* (2009)[18]	Tadalafil	317 (78)	54	75.4	4 (1)	130 (32)	264 (65)	7 (2)	343.6	53.2
Channick *et al.* (2001)[19]	Bosentan	28 (85)	51	86.3	0	0	32 (100)	0	358.3	54.7
Rubin *et al.* (2002)[20]	Bosentan	168 (79)	48	71.9	0	0	195 (92)	18 (9)	334.5	54.4
Galiè *et al.* (2006)[21]	Bosentan	33 (61)	39	63.7	0	0	54 (100)	0	342.8	76.0
Galiè *et al.* (2008)[22]	Bosentan	129 (70)	45	68.1	0	185 (100)	0	0	434.5	52.4
Galiè (2008)[23]	Ambrisentan	311 (79)	51	72.1	8 (2)	151 (38)	216 (55)	18 (5)	344.6	49.2
Rubin *et al.* (1990)[24]	Epoprostenol	16 (70)	36	NR	0	2 (9)	15 (65)	6 (26)	226.6	60.3
Barst *et al.* (1996)[25]	Epoprostenol	59 (73)	40	NR	0	0	60 (74)	21 (26)	294.3	60.0
Badesch *et al.* (2000)[26]	Epoprostenol	96 (87)	55	NR	0	5 (5)	87 (78)	19 (17)	255.9	50.0
Galiè *et al.* (2002)[27]	Beraprost	80 (62)	46	NR	0	64 (49)	66 (51)	0	372.5	59.5
McLaughlin *et al.* (2006)[28]	Inhaled iloprost	53 (79)	50	NR	0	1 (2)	63 (94)	3 (5)	335	52

Hoeper *et al.* (2006)[29]	Inhaled iloprost	31 (78)	52	NR	0	0	40 (100)	0	306.0	56.6
Simonneau (2002)[30]	Treprostinil	382 (81)	45	NR	0	53 (11)	382 (81)	34 (7)	326.5	61.0
McLaughlin *et al.* (2003)[31]	Treprostinil	21 (81)	37	NR	0	25 (96)	1 (4)	0	376.8	60.7
McLaughlin *et al.* (2010)[32]	Treprostinil	191 (81)	54	NR	0	0	230 (98)	5 (2)	348.6	NR
Hiremath *et al.* (2010)[33]	Treprostinil	27 (61)	32	47	0	0	42 (95)	2 (5)	250.4	65

NR, not reported, PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; 6MWD, 6-minute walk distance; WHO, World Health Organisation.

Supplementary table 2 Baseline characteristics of patients with CTD-PAH

Study	PAH agent	Female, *n* (%)	Mean age (years)	Mean weight (kg)	WHO functional class, *n* (%)				Mean baseline 6MWD (m)	Mean PAP (mmHg)
					I	II	III	IV		
Badesch *et al.* (2007)[34]	Sildenafil	70 (83)	53	NR	0	32 (38)	51 (61)	1 (1)	342	47
Galiè *et al.* (2009)[18]	Tadalafil	NR	NR	NR	NR	NR	NR	NR	NR	NR
Denton *et al.* (2006)[35]	Bosentan	55 (83)	55	NR	0	0	63 (96)	3 (5)	328.3	46.4
Launay *et al.* (2010)[36]	Bosentan	36 (74)	NR	NR	0	6 (12)	38 (78)	5 (10)	268	46
Badesch (2007)[37]	Ambrisentan	NR	NR	NR	NR	NR	NR	NR	335	NR
Badesch *et al.* (2012)[38]	Ambrisentan	36 (90)	55	NR	0	12 (30)	27 (68)	1 (3)	324	45
Badesch *et al.* (2000)[26]	Epoprostenol	96 (87)	55	NR	0	5 (5)	87 (78)	19 (17)	255.9	50.0
Kunieda *et al.* (2009)[39]	Beraprost	18 (95)	45	47.6	3 (16)	12 (63)	4 (21)	0	367.9	39.2
Oudiz *et al.* (2004)[40]	Treprostinil	81 (90)	51	NR	0	9 (10)	67 (74)	14 (16)	288.7	NR

CTD, connective tissue disease; NR, not reported; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; 6MWD, 6-minute walk distance; WHO, World Health Organisation.

Supplementary table 3 Risk of bias

Source	PAH agent	Random sequence generation	Allocation concealment	Blinding	Other source(s) of bias
All forms of PAH					
Galiè *et al* (2005)[15]	Sildenafil	Unclear	Low	Low	Low
Singh *et al.* (2006)[16]	Sildenafil	Unclear	Low	Low	Low
Simonneau *et al.* (2008)[17]	Sildenafil	Low	Low	Low	High
Galiè *et al.* (2009)[18]	Tadalafil	Unclear	Unclear	Low	Low
Channick *et al.* (2001)[19]	Bosentan	Low	Low	Low	Low
Rubin *et al.* (2002)[20]	Bosentan	Unclear	Unclear	Low	Low
Galiè *et al.* (2006)[21]	Bosentan	Unclear	Low	Low	Low
Galiè *et al.* (2008)[22]	Bosentan	Low	Low	Low	Low
Galiè (2008)[23]	Ambrisentan	Unclear	Low	Low	Low
Rubin *et al.* (1990)[24]	Epoprostenol	Unclear	Low	High	Unclear
Barst *et al.* (1996)[25]	Epoprostenol	Low	Unclear	High	High
Badesch *et al.* (2000)[26]	Epoprostenol	Low	Unclear	High	Low
Galiè *et al.* (2002)[27]	Beraprost	Unclear	Unclear	Low	Low
McLaughlin *et al.* (2006)[28]	Inhaled iloprost	Low	Low	Low	Low
Hoeper *et al.* (2006)[29]	Inhaled iloprost	Low	Low	High	High
Simonneau (2002)[30]	Treprostinil	Low	Unclear	Low	Low
McLaughlin *et al.* (2003)[31]	Treprostinil	Unclear	Unclear	Low	Low
McLaughlin *et al.* (2010)[32]	Treprostinil	Unclear	Unclear	Low	Low
Hiremath *et al.* (2010)[33]	Treprostinil	Unclear	Unclear	Low	Low
CTD-PAH					
Badesch *et al.* (2007)[34]	Sildenafil	Unclear	Low	Low	Low
Galiè *et al.* (2009)[18]	Tadalafil	Unclear	Unclear	Low	Low
Denton *et al.* (2006)[35]	Bosentan	Unclear	Unclear	Low	High
Launay *et al.* (2010)[36]	Bosentan	High	High	High	High

Source	PAH agent	Random sequence generation	Allocation concealment	Blinding	Other source(s) of bias
Badesch (2007)[37]	Ambrisentan	Unclear	Low	Low	Unclear
Badesch *et al.* (2012)[38]	Ambrisentan	High	High	High	High
Badesch *et al.* (2000)[26]	Epoprostenol	Low	Unclear	No	Low
Kunieda *et al.* (2009)[39]	Beraprost	High	High	High	High
Oudiz *et al.* (2004)[40]	Treprostinil	Unclear	Unclear	Low	Low

CTD, connective tissue disease; PAH, pulmonary arterial hypertension.

BMJ open

Pulmonary arterial hypertension associated with connective tissue disease: meta-analysis of clinical trials

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003113.R1
Article Type:	Research
Date Submitted by the Author:	10-Jun-2013
Complete List of Authors:	Kuwana, Masataka; Keio University School of Medicine, Department of Internal Medicine, Division of Rheumatology Watanabe, Hiroshi; Hamamatsu University School of Medicine, Department of Clinical Pharmacology and Therapeutics Matsuoka, Nobushige; Pfizer, Division of Clinical Statistics Sugiyama, Naonobu; Pfizer, Division of Medical Affairs
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Cardiovascular medicine, Evidence based practice, Medical management, Pharmacology and therapeutics, Respiratory medicine
Keywords:	Hypertension < CARDIOLOGY, Cardiology < INTERNAL MEDICINE, Dermatology < INTERNAL MEDICINE, Rheumatology < INTERNAL MEDICINE, Vascular medicine < INTERNAL MEDICINE, THORACIC MEDICINE

Pulmonary arterial hypertension associated with connective tissue disease: meta-analysis of clinical trials

Masataka Kuwana,[1] Hiroshi Watanabe,[2] Nobushige Matsuoka,[3] Naonobu Sugiyama[4]

[1]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

[2]Department of Clinical Pharmacology and Therapeutics, Hamamatsu University School of Medicine, Shizuoka, Japan

[3]Division of Clinical Statistics, Pfizer Japan Inc.

[4]Division of Medical Affairs, Pfizer Japan Inc.

Correspondence to Masataka Kuwana

Department of Internal Medicine, Division of Rheumatology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.

TEL: 81-3-3350-3567; FAX: 81-3-3350-3567

E-mail: kuwanam@z5.keio.jp

Running head: Pulmonary arterial hypertension associated with connective tissue disease

Abstract

Objectives: Few studies have focused on pulmonary arterial hypertension (PAH) associated with connective tissue diseases (CTDs). The optimal treatment for CTD-PAH has yet to be established. **Design:** Meta-analysis of data from evaluations of treatment for PAH generally (19 studies) and CTD-PAH specifically (9 studies) to compare the effects of pulmonary vasodilative PAH agents. MEDLINE, EMBASE, and BIOSIS were searched. English-language full-text articles published between January 1990 and August 2012 were eligible. **Setting:** International. **Participants:** Patients with PAH generally (*n*=3073) and CTD-PAH specifically (*n*=678). **Primary outcome measure:** Exercise capacity (6-minute walk distance, 6MWD). **Results:** Patients with PAH (all forms) had mean age 32–55 years (women, 61–87%); CTD-PAH patients had mean age 45–55 years (women, 74–95%). Overall estimate of mean change in 6MWD from baseline (95%CI) for the active treatment group versus the control group in all PAH patients was 34.6 m (27.4 to 41.9 m). Pooled mean differences from the results for patients receiving placebo by subgroup of patients receiving phosphodiesterase (PDE)-5 inhibitors, endothelin receptor antagonists (ERAs), and prostacyclin (PGI_2) analogues were 22.4–45.5 m, 39.5–44.2 m, and 12.4–64.9 m, respectively. Overall estimate of mean difference between changes in 6MWD in CTD-PAH patients was 34.2 m (23.3 to 45.0 m). Pooled mean differences by subgroup of patients receiving PDE-5 inhibitors, ERAs, and PGI_2 analogues in CTD-PAH patients were 37.0–47.1 m, 14.1–21.7 m, and 21.0–108.0 m, respectively. ERAs were less effective in CTD-PAH patients than all-form PAH patients: 14.1 m (–4.4 to 32.6 m) versus 39.5 m (19.5 to 59.6 m) for bosentan, and 21.7 m (2.2 to 41.3 m) versus 44.2 m (30.2 to 58.2 m) for ambrisentan. **Conclusions:** All 3

types of PAH agent are effective. However, ERAs may be a less effective choice against CTD-PAH; further studies are needed. Limitations include the limited number of studies for some agents and for CTD-PAH patients.

Article summary

Article focus

- Pulmonary arterial hypertension (PAH) is a progressive disease characterised by abnormally high blood pressure in the pulmonary arteries.
- Patients with PAH associated with connective tissue diseases (CTDs) such as systemic sclerosis (SSc) have a particularly poor prognosis.
- Few studies have focused on patients with CTD-PAH, so the optimal treatment for these patients is unclear.

Key messages

- The effects of the phosphodiesterase-5 inhibitors sildenafil and tadalafil, and the prostacyclin analogue epoprostenol, are consistent in patients with CTD-PAH and in those with PAH generally.
- The endothelin receptor antagonists bosentan and ambrisentan may be less effective in patients with CTD-PAH than in those with PAH generally.

Strengths and limitations of this study

- The meta-analysis used all currently available data from clinical studies on treatment for PAH.
- Few studies were identified for some PAH agents and for CTD-PAH patients.
- Study designs and patient background characteristics, including the percentages of patients with SSc-PAH, were inconsistent between studies.

Introduction

Pulmonary hypertension is a heterogeneous condition with sustained elevation of pressure in the pulmonary arteries, and is defined as mean pulmonary artery pressure ≥ 25 mmHg at rest.[1] The most recent and widely accepted clinical classification of pulmonary hypertension is that proposed at the Fourth World Symposium on Pulmonary Hypertension at Dana Point in 2008.[2] It classifies pulmonary hypertension into 5 groups. Group 1 comprises pulmonary arterial hypertension (PAH), which includes idiopathic PAH, heritable PAH, drug- and toxin-induced PAH, PAH associated with various diseases, and persistent pulmonary hypertension of the newborn. Group 2 comprises pulmonary hypertension owing to left heart disease; group 3, pulmonary hypertension owing to lung diseases and/or hypoxia; group 4, chronic thromboembolic pulmonary hypertension; and group 5, pulmonary hypertension of unknown cause. In this classification of pulmonary hypertension, PAH is recognised as having an extremely poor prognosis and requires specific medical treatment.

Connective tissue disease (CTD) is the most common condition associated with PAH. Recent cohort studies have shown that most patients with PAH associated with CTD have systemic sclerosis (SSc).[3 4] In fact, the prevalence of PAH in patients with SSc is reported to be 7–12%.[5 6] Patients with SSc-PAH have poor prognosis compared with patients with idiopathic PAH.[7] Therefore, early and appropriate diagnosis and selection of the optimal treatment regimen are important for SSc-PAH, to improve the hemodynamics, exercise capacity, and eventually survival of patients.

The optimal treatment for PAH has not been established. However, there has been major progress in medical treatment for PAH in recent years. Several new agents with different

mechanisms have been introduced, including phosphodiesterase (PDE)-5 inhibitors (e.g. oral sildenafil and tadalafil), endothelin receptor antagonists (ERAs) (e.g. oral bosentan and ambrisentan), and prostacyclin (PGI_2) analogues (e.g. continuous intravenous epoprostenol). The introduction of these new agents is expected to contribute to the improvement of exercise capacity, subjective symptoms, and quality of life, as well as the short- and long-term survival of patients.

Although the efficacy and safety of these new agents have been shown in small- or medium-scale randomised controlled trials (RCTs) and open-label trials, evidence from large-scale comparative studies of these agents remains insufficient because PAH is a rare disease. Therefore, to compare the new agents and establish a therapeutic strategy for PAH, several systematic reviews and meta-analyses of available clinical study results have been done.[8–13] However, most of these analyses include studies on all forms of PAH, and studies that focus on CTD-PAH are limited. In fact, our literature search showed only one such report: a meta-analysis by Avouac *et al.*,[8] which investigated the efficacy of oral PAH agents mainly in patients with SSc.

Therefore, in this meta-analysis of studies designed as RCTs and open-label, single-arm trials, we aimed to evaluate the effect of each PAH agent on exercise capacity in patients with CTD-PAH compared with patients with all forms of PAH. We chose 6-minute walk distance (6MWD) as an endpoint because it was used as a primary endpoint in most previous randomised studies of PAH agents.[14]

Methods

Eligibility criteria

To evaluate the effects of 3 typical types of PAH agent, we included RCTs in which the following PAH agents were administered to patients with all forms of PAH.

- PDE-5 inhibitors: sildenafil and tadalafil
- ERAs: bosentan and ambrisentan
- PGI_2 analogues: epoprostenol, beraprost, iloprost, and treprostinil.

Because the number of RCTs in patients with CTD-PAH is limited, we also included open-label, single-arm trials evaluating the effects of PAH agents in patients with CTD-PAH.

We excluded reviews and non-interventional studies (e.g. case reports and observational studies as opposed to RCTs). We included only principal studies and excluded ad hoc analyses. Studies in which results for 6MWD were not reported were also excluded, as were studies on pulmonary hypertension other than PAH.

Search strategy

We searched MEDLINE, EMBASE, and BIOSIS for English-language full-text articles published between January 1990 and August 2012, using the key terms ‘pulmonary arterial hypertension’, ‘6 minute walk’, and the names of individual drugs. In addition to these key terms, we used the term ‘randomised controlled trial’ or ‘RCT’ to identify RCTs evaluating all forms of PAH, and ‘connective tissue disease’ or ‘CTD’ to identify studies evaluating CTD-PAH. The last search was run on 5 December 2012. Additional studies were identified through manual searching.

Primary endpoint

The primary outcome measure was the difference in mean change from baseline in 6MWD between groups. However, for single-arm studies, the mean change from baseline was used as the primary outcome measure.

Data collection

Relevant data were extracted and reviewed by NM and NS. Data on study characteristics (year and design), variables including PAH agents used, total patient numbers and the percentage of CTD-PAH patients, and outcomes (mean difference, m and 95%CI, m or standard error) were extracted.

Risk of bias

To determine the validity of the included studies, we assessed the risk of bias for each study in terms of random sequence generation, allocation concealment, blinding, and other sources of bias, as recommended by the Cochrane Collaboration. Each domain was judged to have high, low, or unclear risk of bias. We did not detect clear publication bias, because the number of included studies was small.

Statistical analysis

We pooled outcomes by each PAH agent for all forms of PAH and for CTD-PAH. We used a random effects model based on the DerSimonian−Laird method because of known clinical and methodological heterogeneity (e.g. the various doses of each PAH agent). I^2 values were calculated as a measure of heterogeneity. The I^2 statistic, which describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error (chance),

and we considered $I^2 > 75\%$ as representing considerable heterogeneity.

Results

Selection of studies

A total of 196 articles were identified for evaluation of treatments for all forms of PAH. Of these, 19 articles (reporting data from 3073 patients) met the eligibility criteria for evaluations of treatments for all forms of PAH (3 articles for sildenafil,[15–17] 1 article for tadalafil,[18] 4 articles for bosentan,[19–22] 1 article for ambrisentan,[23] 3 articles for epoprostenol,[24–26] 1 article for beraprost,[27] 2 articles for iloprost,[28 29] and 4 articles for treprostinil[30–33]) (figure 1a). The main reasons for exclusion were that the article was a review and that the article reported the results of a study that involved patients other than those with PAH.

For evaluation of treatments for CTD-PAH, a total of 269 articles were identified. Of these, 9 articles (reporting data from 678 patients) met the eligibility criteria for evaluations of treatments for CTD-PAH (1 article for sildenafil,[34] 1 article for tadalafil,[18] 2 articles for bosentan,[35 36] 2 articles for ambrisentan,[37 38] 1 article for epoprostenol,[26] 1 article for beraprost,[39] and 1 article for treprostinil[40] (figure 1b). The main reasons for exclusion were that the article was a review and that the article reported the results of a study that involved patients other than those with CTD-PAH.

Characteristics and overview of the included studies

Of the 19 studies on treatments for all forms of PAH included in this analysis (table 1), 15

were randomised, placebo-controlled, double-blind studies;[15–23 27 28 30–33] 3 were randomised, open-label studies comparing with conventional treatment;[24–26] and 1 was a randomised, open-label study evaluating the effects of iloprost when added to bosentan.[29] The observation period was either 12 or 16 weeks in most of the studies, with some exceptions (1 study each with 6- and 24-week observation periods,[16 22] and 2 studies with an 8-week observation period[24 31]). Of the placebo-controlled randomised comparative studies, 1 study of sildenafil was done in patients previously treated with epoprostenol;[17] 2 studies of iloprost, in patients previously treated with bosentan;[28 29] and 1 study of treprostinil, in patients previously treated with bosentan or sildenafil.[32]

Of the 9 studies on treatments for CTD-PAH included in this analysis (table 2), 5 were placebo-controlled, double-blind studies,[18 34 35 37 40] 1 was a randomised, open-label study comparing with conventional treatment,[26] and 3 were open-label, single-arm studies.[36 38 39] The observation period in these studies was 8–28 weeks. One study each evaluating bosentan[36] and epoprostenol[26] included only SSc-PAH patients.

Background of all PAH patients

The background of all PAH patients, based on data from the 19 studies, can be summarised as follows (full data in supplementary table 1). Mean age was 32–55 years, and the percentage of women was 61–87%. In the studies of sildenafil,[15–17] tadalafil,[18] ambrisentan,[23] and beraprost,[27] most patients were classified according to World Health Organisation functional class (WHO-FC) as in WHO-FC II or III, with 1 study including only patients in WHO-FC II.[22] In contrast, in the studies of epoprostenol,[24–26] the percentage of patients in WHO-FC IV was higher than that in studies of other agents. In the studies of iloprost, most

patients were in WHO-FC III.[28 29] In the studies of treprostinil, most patients were in WHO-FC III in 3 studies[30 32 33] and in WHO-FC II in 1 study.[31] Baseline 6MWD was 226.6–434.5 m, and it was lower in the 3 studies of epoprostenol (226.6, 294.3, and 255.9 m)[24–26] compared with in studies on other agents. Therefore patients with more severe disease were included in the studies of epoprostenol than in other studies. One study of bosentan included only patients with Eisenmenger syndrome.[21]

Background of the subgroup of CTD-PAH patients

The background of patients with CTD-PAH, using data from 9 studies, can be summarised as follows (full data in supplementary table 2). Mean age was 45–55 years, and the percentage of women was 74–95%. In 1 study of tadalafil, there was no information on baseline 6MWD or WHO-FC.[18] As for the distribution of patients according to WHO-FC, a study of beraprost included more patients in WHO-FC II,[39] and a study of epoprostenol included more patients in WHO-FC IV,[26] compared with studies of other agents.

In 5 studies in which information on underlying CTDs was available, SSc-PAH patients accounted for 45–100% of all patients included. Their mean age was 51–55 years, and the percentage of women was 74–90%.

In studies of bosentan[36] and epoprostenol[26] that included only SSc-PAH patients, baseline 6MWD was < 300 m, which was lower than that in studies of other agents. Therefore the study of beraprost included more patients with relatively mild PAH, whereas the study of epoprostenol included more patients with more severe disease.

Results of 6MWD

The actual values of the outcomes for each study are presented on the right sides of figures 2 and 3. We pooled the data, including those for non-approved doses, to evaluate the effect of each PAH agent on exercise capacity in patients with CTD-PAH compared with in patients with all forms of PAH.

6MWD in All PAH patients

The mean differences between changes in 6MWD compared with the control group are shown in figure 2 by each agent. With a random effects model, the pooled mean difference between changes in 6MWD was 45.5 m (95% confidence interval (CI) 32.9 to 58.1 m, I^2=50.1%) for sildenafil, 22.4 m (95%CI 14.0 to 30.9 m, I^2=7.9%) for tadalafil, 39.5 m (95%CI 19.5 to 59.6 m, I^2=38.3%) for bosentan, 44.2 m (95%CI 30.2 to 58.2 m, I^2=0%) for ambrisentan, 64.9 m (95%CI 20.4 to 109.4 m, I^2=43.3%) for epoprostenol, 25.1 m (95%CI 1.9 to 48.4 m, I^2= not applicable [NA]) for beraprost, 12.4 m (95%CI –21.9 to 46.6 m, I^2=39.7%) for iloprost, and 17.3 m (95%CI 6.1 to 28.4 m, I^2=29.4%) for treprostinil. Numerical improvement in 6MWD was obtained in patients using each agent compared with those using the control agent. The pooled mean difference between changes in 6MWD from the control group ranged from 12.4 to64.9 m, and the overall estimate of mean difference was 34.6 m (95%CI 27.4 to 41.9 m, I^2=63.2%). The ranges of mean difference from the effects of placebo by subgroup of patients receiving PDE-5 inhibitors, ERAs, and PGI_2 analogues were 22.4–45.5 m, 39.5–44.2 m, and 12.4–64.9 m, respectively. Considerable heterogeneity was not observed.

6MWD in a subgroup of CTD-PAH patients

In the subgroup of CTD-PAH patients, the mean differences between changes in 6MWD compared with the control group are shown in figure 3 by each agent. For single-arm studies, the mean changes from baseline are shown. With a random effects model, the pooled mean difference between changes in 6MWD was 47.1 m (95%CI 27.9 to 66.3 m, I^2=0%) for sildenafil, 37.0 m (95%CI 19.0 to 55.0 m, I^2=0%) for tadalafil, 14.1 m (95%CI –4.4 to 32.6 m, I^2=0%) for bosentan, 21.7 m (95%CI 2.2 to 41.3 m, I^2=0%) for ambrisentan, 108.0 m (95%CI 45.6 to 170.4 m, I^2=NA) for epoprostenol, 58.5 m (95%CI 21.4 to 95.6 m, I^2=NA) for beraprost, and 21.0 m (95%CI –6.9 to 48.9 m, I^2=NA) for treprostinil. Numerical improvement in 6MWD was obtained in patients using all agents compared with those using the control agent. The overall estimate of mean difference between changes in 6MWD in patients with CTD-PAH was 34.2 m (95%CI 23.3 to 45.0 m, I^2=32.5%). The ranges of mean differences by subgroup of patients receiving PDE-5 inhibitors, ERAs, and PGI_2 analogues were 37.0–47.1 m, 14.1–21.7 m, and 21.0–108.0 m, respectively. Considerable heterogeneity was not observed.

We did an additional sensitivity analysis excluding open-label single-arm studies for CTD-PAH patients only (supplementary figure). The overall estimate of mean difference between changes in 6MWD in patients with CTD-PAH was 37.2 m (95%CI 25.0 to 49.3 m, I^2=20.5%) and the ranges of mean differences by subgroup of patients receiving PDE-5 inhibitors, ERAs, and PGI_2 analogues were 37.0−47.1 m, 19.0−22.1 m, and 21.0−108.0 m, respectively.

Difference in exercise capacity between all PAH patients and CTD-PAH patients

When the pooled mean differences between changes in 6MWD were compared between all

PAH patients and each subgroup of CTD-PAH patients, no difference in exercise capacity was found between the patient groups for PDE-5 inhibitors (sildenafil and tadalafil). In contrast, for ERAs (bosentan and ambrisentan), the pooled mean values in CTD-PAH patients (bosentan, 14.1 m; ambrisentan, 21.7 m) were lower than the lower limit of 95%CI of the mean values in all PAH patients (bosentan 19.5 to 59.6 m; ambrisentan 30.2 to 58.2 m), suggesting that effects on exercise capacity may vary between patient groups. For PGI_2 (epoprostenol, beraprost, and treprostinil), no obvious trends were found between patient groups.

Risk of bias

We rated risk of bias for each study (full data in supplementary table 3). In studies for all forms of PAH, none were at high risk of bias for random sequence generation or allocation concealment; however, the method of randomisation and allocation concealment were unclear (i.e. not reported) for 11 studies and 9 studies, respectively. Four studies were at high risk of bias for blinding because they were open-label studies. Three studies were at high risk for another source of bias (imbalance in missing data between groups,[17] imbalance in baseline 6MWD,[25] and early termination based on futility analysis[29]).

Of studies for CTD-PAH, 3 studies were at high risk of bias with respect to all domains because they were open-label, single-arm studies.[36 38 39] One study was at high risk of bias resulting from imbalance in baseline characteristics.[35] The remaining studies were judged to be not of high risk of bias in any of the domains.

Discussion

A finding of the present meta-analysis of 19 studies is that in combined patients with all forms of PAH, all agents increase 6MWD compared with the control group.[15–33] Likewise, the meta-analysis of 9 studies on CTD-PAH patients also showed an increase in 6MWD by all agents.[18 26 34–40] The finding that all agents increase 6MWD in all PAH patients is consistent with the results of the 5 previous systematic reviews and meta-analyses that evaluated the 3 types of agent (PDE-5 inhibitors, ERAs, and PGI_2 analogues).[9–13] To date, reports of meta-analyses that included patients with CTD-PAH including SSc-PAH are limited to 1 study that evaluated 3 oral agents (sildenafil, bosentan, and sitaxsentan) alone.[8] The findings of this meta-analysis are important because patients with all PAH as well as a subgroup of CTD-PAH patients were included, and the effects of 3 types of agent, including intravenous preparations, were thoroughly evaluated. Our meta-analysis shows similar trends to the findings of Avouac *et al*.[8]

When the mean differences between changes in 6MWD were compared between all PAH patients and CTD-PAH patients, the effects of ERAs (bosentan and ambrisentan) on exercise tolerance may be less in CTD-PAH patients, whereas no difference in exercise capacity was found between patient groups for PDE-5 inhibitors and PGI_2 analogues. This result should be interpreted cautiously because recent data from registries have shown that 6MWD is significantly lower in patients with CTD-PAH than in those with idiopathic PAH,[4 41] and a systematic review has shown that 6MWD may be only partially valid in patients with SSc-PAH. [42]

This analysis has several limitations. First, we could identify only a limited number of studies for some agents (1 study each for tadalafil, ambrisentan, and beraprost), and studies

that included a subgroup of patients with CTD-PAH including SSc-PAH were scarce. Second, ideally data for patients with CTD-PAH should be compared with those for patients with other forms of PAH. However, there were insufficient data for forms of PAH other than CTD-PAH, so this analysis compared data for all PAH and CTD-PAH. Third, the study designs varied: some studies that included CTD-PAH patients were done in an open-label or single-arm, open-label manner, some having a short observation period (12 or 16 weeks) or using combination therapy. Of note, in studies of combination therapy, changes in 6MWD are expected to be smaller, because patients are already receiving PAH therapy at the start of the study. Patient background characteristics were also inconsistent between studies: patients were in various WHO FC classes and had various baseline 6MWD values, which can influence the effects of each agent, and some articles reported no such information. Moreover, the percentage of SSc-PAH patients in the study population also varied, which is a study limitation because there is a difference in treatment response between SSc and non-SSc patients, and patients with SSc-PAH have poor prognosis compared with patients with other CTD-PAH.[4 7] In this meta-analysis, the percentages of SSc-PAH patients were as follows: for sildenafil, 45% in the study by Badesch *et al.*;[34] for bosentan, 79% in the study by Denton *et al.*;[35] and 100% in the study by Launay *et al.*;[36] and for epoprostenol, 100% in the study by Badesch *et al.*[26] The percentage was unknown in the study of tadalafil by Galiè *et al.*;[18] in those of ambrisentan by Badesch *et al.*;[37 38] and in that of beraprost by Kunieda et al.[39] Patients with SSc-PAH were more frequently enrolled in studies for bosentan[35 36] than in the sildenafil study.[34]

It would have been interesting to do a sensitivity analysis with the data from SSc-PAH patients only, but this is not possible for the following reasons. There are only two articles

(Launay *et al*., 2010[36] and Badesch *et al*., 2000[26]) from which data for the subpopulation of SSc-PAH patients can be extracted. Another limitation of our study was the inclusion of data for non-approved, possibly subtherapeutic doses, which may have reduced the effects of the PAH agents in some studies. Finally, there may be publication bias, so negative results are likely to be unpublished.[43]

Furthermore, the present analysis is intended to compare changes in 6MWD over a short period of time, therefore whether the results are associated with patient survival remains unclear. However, 6MWD is effective as an indicator of the severity of PAH.[44] Moreover, an ongoing large-scale registry, the US Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL), which aims to clarify the characteristics and prognosis of PAH patients and the latest treatment for PAH, has shown that 6MWD is an independent predictor that is significantly associated with 1-year survival.[45] Several other studies have also confirmed its role as an independent predictor of prognosis.[46–50] In addition, investigators who did a placebo-controlled randomised trial of the PDE-5 inhibitor sildenafil have recently identified the minimum clinically meaningful changes in 6MWD, and concluded that it would be a useful indicator to determine the efficacy of other PAH agents.[51]

However, pharmacological treatment for PAH is shifting from monotherapy to combination therapy, and it is expected that clinical studies investigating the efficacy of combination therapy will increase. Therefore, it will be increasingly difficult to do a meta-analysis that includes all the new studies to detect differences between PAH agents. The present analysis is meaningful because it included all available clinical study results to date, and we hope that it contributes to the improvement of the treatment for PAH.

In conclusion, the present meta-analysis of studies that included CTD-PAH patients

showed an increase in 6MWD by all agents, that is, PDE-5 inhibitors, ERAs, and PGI_2 analogues. Comparison of the mean differences between changes in 6MWD suggest that, for bosentan and ambrisentan, the effects on exercise tolerance may differ depending on patient group, whereas the PDE-5 inhibitors sildenafil and tadalafil and the PGI_2 analogue epoprostenol show consistent effects regardless of the presence or absence of CTD. Further studies are needed to clarify the clinical implications of these findings.

Competing interests

MK has received research funding from Actelion Pharmaceuticals, GlaxoSmithKline, Novartis and Pfizer, and lecture fees from Actelion Pharmaceuticals, Pfizer, GlaxoSmithKline, Nippon Shinyaku, Mitsubishi Tanabe Pharma and Takeda Pharmaceuticals. WH has received research funding from the Ministry of Health, Labour and Welfare of Japan, Teika Seiyaku, Takeda Pharmaceuticals, Mochida, Pfizer, Asteras and Daiichi Sankyo, and lecture fees from Pfizer, Acterion, Novartis, Daiich Sankyo, GlaxoSmithKline and Nihon Shinyaku. NM and NS are employees of Pfizer Japan Inc.

Contributors

N. Matsuoka, a statistician employed by Pfizer Japan, collected the data and did the statistical analyses described in this article.

Dr N. Sugiyama, a rheumatologist employed by Pfizer Japan, reviewed the collection and analyses of the data. He helped conceive and design the meta-analysis, interpret the results,

and revise the manuscript.

Dr M. Kuwana is directly responsible for the manuscript. He reviewed the data analyses and drafted the manuscript, providing important intellectual content from the perspective of a CTD-PAH specialist.

Dr H. Watanabe revised the manuscript critically for important intellectual content from the perspective of a PAH specialist.

References

1. Badesch DB, Champion HC, Sanchez MA, *et al*. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;54:S55–66.
2. Simonneau G, Robbins IM, Beghetti M, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;54:S43–54.
3. Condliffe R, Kiely DG, Peacock AJ, *et al.* Connective tissue disease-associated pulmonary hypertension in the modern treatment era. *Am J Respir Crit Care Med* 2009;179:151–7.
4. Chung L, Liu J, Parsons L, *et al.* Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. *Chest* 2010;138:1383–94.
5. Hachulla E, Gressin V, Guilevin L, *et al.* Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum* 2005;52:3792–800.
6. Mukerjee D, St George D, Coleiro B, *et al.* Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis* 2003;62:1088–93.
7. Kawut SM, Taichman DB, Archer-Chicko CL, *et al.* Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. *Chest* 2003;123:344–50.
8. Avouac J, Wipff J, Kahan A, *et al.* Effects of oral treatments on exercise capacity in systemic sclerosis related pulmonary arterial hypertension: a meta-analysis of

randomised controlled trials. *Ann Rheum Dis* 2008;67:808–14.

9. Galiè N, Manes A, Negro L, *et al.* A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. *Eur Heart J* 2009;30:394–403.
10. Galiè N, Palazzini M, Manes A. Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analyses. *Eur Heart J* 2010;31:2080–6.
11. Macchia A, Marchioli R, Tognoni G., *et al.* Systematic review of trials using vasodilators in pulmonary arterial hypertension: why a new approach is needed. *Am Heart J* 2010;159:245–57.
12. He B, Zhang F, Li X, *et al.* Meta-analysis of randomized controlled trials on treatment of pulmonary arterial hypertension. *Circ J* 2010;74:1458–64.
13. Ryerson CJ, Nayar S, Swiston JR, *et al.* Pharmacotherapy in pulmonary arterial hypertension: a systematic review and meta-analysis. *Respir Res* 2010;11:12.
14. McLaughlin VV, Badesch DB, Delcroix M, *et al.* End points and clinical trial design in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;54:S97–107.
15. Galiè N, Ghofrani HA, Torbicki A, *et al.* Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005;353:2148–57.
16. Singh TP, Rohit M, Grover A, *et al.* A randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe pulmonary artery hypertension. *Am Heart J* 2006;151:851.e1–5.
17. Simonneau G, Rubin LJ, Galiè N, *et al.* Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008;149:521–30.
18. Galiè N, Brundage BH, Ghofrani HA, *et al.* Tadalafil therapy for pulmonary arterial

hypertension. *Circulation* 2009;119:2894–903.

19. Channick RN, Simonneau G, Sitbon O, *et al.* Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001;358:1119–23.
20. Rubin LJ, Badesch DB, Barst RJ, *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896–903.
21. Galiè N, Beghetti M, Gatzoulis MA, *et al.* Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation* 2006;114:48–54.
22. Galiè N, Rubin LJ, Hoeper M, *et al.* Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008;371:2093–100.
23. Galiè N, Olschewski H, Oudiz RJ, *et al.* Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation* 2008;117:3010–9.
24. Rubin LJ, Mendoza J, Hood M, *et al.* Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. *Ann Intern Med* 1990;112:485–91.
25. Barst RJ, Rubin LJ, Long WA, *et al.* A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996;334:296–302.

26. Badesch DB, Tapson VF, McGoon MD, *et al.* Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000;132:425–34.
27. Galiè N, Humbert M, Vachiéry JL, *et al.* Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2002;39:1496–502.
28. McLaughlin VV, Oudiz RJ, Frost A, *et al.* Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006;174:1257–63.
29. Hoeper MM, Leuchte H, Halank M, *et al.* Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2006;28:691–4.
30. Simonneau G, Barst RJ, Galiè N, *et al.* Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002;165:800–4.
31. McLaughlin VV, Gaine SP, Barst RJ, *et al.* Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension. *J Cardiovasc Pharmacol* 2003;41:293–9.
32. McLaughlin VV, Benza RL, Rubin LJ, *et al.* Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2010;55:1915–22.
33. Hiremath J, Thanikachalam S, Parikh K, *et al.* Exercise improvement and plasma biomarker changes with intravenous treprostinil therapy for pulmonary arterial hypertension: a placebo-controlled trial. *J Heart Lung Transplant* 2010;29:137–49.
34. Badesch DB, Hill NS, Burgess G, *et al.* Sildenafil for pulmonary arterial hypertension

associated with connective tissue disease. *J Rheumatol* 2007;34:2417–22.

35. Denton CP, Humbert M, Rubin L, *et al.* Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions. *Ann Rheum Dis* 2006;65:1336–40.
36. Launay D, Sitbon O, Le Pavec J, *et al.* Long-term outcome of systemic sclerosis–associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by the addition of prostanoids or sildenafil. *Rheumatology* 2010;49:490–500.
37. Badesch DB. Ambrisentan therapy for pulmonary arterial hypertension: a comparison by PAH etiology. *Chest* 2007;slide presentations:488S.
38. Badesch DB, Feldman J, Keogh A, *et al.* ARIES-3: ambrisentan therapy in a diverse population of patients with pulmonary hypertension. *Cardiovasc Ther* 2012;30:93–9.
39. Kunieda T, Nakanishi N, Matsubara H, *et al.* Effects of long-acting beraprost sodium (TRK-100STP) in Japanese patients with pulmonary arterial hypertension. *Int Heart J* 2009;50:513–29.
40. Oudiz R, Schilz RJ, Barst RJ, *et al.* Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. *Chest* 2004;126:420–7.
41. Clements PJ, Tan M, McLaughlin VV, *et al.* The pulmonary arterial hypertension quality enhancement research initiative: comparison of patients with idiopathic PAH to patients with systemic sclerosis-associated PAH. *Ann Rheum Dis* 2012;71:249–52.
42. Avouac J, Kowal-Bielecka O, Pittrow D, et al.; EPOSS Group. Validation of the 6 min walk test according to the OMERACT filter: a systematic literature review by the EPOSS-OMERACT group. Ann Rheum Dis 2010; 69:1360–1363.

43. Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey. *BMJ* 2012;344:d7762.

44. Naeije R. The 6-min walk distance in pulmonary arterial hypertension: "Je t'aime, moi non plus". *Chest* 2010;137:1258–60.

45. Benza RL, Miller DP, Gomberg-Maitland M, *et al.* Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010;122:164–72.

46. Miyamoto S, Nagaya N, Satoh T, *et al.* Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000;161:487–92.

47. Sitbon O, Humbert M, Nunes H, *et al.* Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002;40:780–8.

48. Groepenhoff H, Vonk-Noordegraaf A, Boonstra A, *et al.* Exercise testing to estimate survival in pulmonary hypertension. *Med Sci Sports Exerc* 2008;40:1725–32.

49. Humbert M, Sitbon O, Chaouat A, *et al.* Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010;122:156–63.

50. Humbert M, Sitbon O, Yaïci A, *et al.* Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010;36:549–55.

51. Gilbert C, Brown MC, Cappelleri JC, *et al.* Estimating a minimally important difference

in pulmonary arterial hypertension following treatment with sildenafil. *Chest* 2009;135:137–42.

Figure legends

Figure 1 Flow diagram summarising selection of studies evaluating treatments for patients with (**a**) all forms of pulmonary arterial hypertension (PAH) and (**b**) connective tissue disease-PAH. RCT, randomised controlled trial.

Figure 2 Effects of individual pulmonary arterial hypertension (PAH) agents on 6-minute walk distance (6MWD) in patients with any form of PAH. ERA, endothelin receptor antagonist; PDE, phosphodiesterase; PGI_2, prostacyclin; NA, not applicable.

Figure 3 Effects of individual pulmonary arterial hypertension (PAH) agents on 6-minute walk distance (6MWD) in patients with PAH associated with connective tissue disease. ERA, endothelin receptor antagonist; PDE, phosphodiesterase; PGI_2, prostacyclin; NA, not applicable. For single-arm studies, the mean changes from baseline are shown.

Pulmonary arterial hypertension associated with connective tissue disease: meta-analysis of clinical trials

Masataka Kuwana,[1] Hiroshi Watanabe,[2] Nobushige Matsuoka,[3] Naonobu Sugiyama[4]

[1]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

[2]Department of Clinical Pharmacology and Therapeutics, Hamamatsu University School of Medicine, Shizuoka, Japan

[3]Division of Clinical Statistics, Pfizer Japan Inc.

[4]Division of Medical Affairs, Pfizer Japan Inc.

Correspondence to Masataka Kuwana

Department of Internal Medicine, Division of Rheumatology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.

TEL: 81-3-3350-3567; FAX: 81-3-3350-3567

E-mail: kuwanam@z5.keio.jp

Running head: Pulmonary arterial hypertension associated with connective tissue disease

Abstract

Objectives: Few studies have focused on pulmonary arterial hypertension (PAH) associated with connective tissue diseases (CTDs). The optimal treatment for CTD-PAH has yet to be established. **Design:** Meta-analysis of data from evaluations of treatment for PAH generally (19 studies) and CTD-PAH specifically (9 studies) to compare the effects of pulmonary vasodilative PAH agents. MEDLINE, EMBASE, and BIOSIS were searched. English-language full-text articles published between January 1990 and August 2012 were eligible. **Setting:** International. **Participants:** Patients with PAH generally (*n*=3073) and CTD-PAH specifically (*n*=678). **Primary outcome measure:** Exercise capacity (6-minute walk distance, 6MWD). **Results:** Patients with PAH (all forms) had mean age 32–55 years (women, 61–87%); CTD-PAH patients had mean age 45–55 years (women, 74–95%). Overall estimate of m~~M~~ean change in 6MWD from baseline (95%CI) for the active treatment group versus the control group in all PAH patients was 34.6 m (27.4 to~~,~~ 41.9 m). Pooled ~~Mean~~ mean differences from the results for patients receiving placebo by subgroup of patients receiving phosphodiesterase (PDE)-5 inhibitors, endothelin receptor antagonists (ERAs), and prostacyclin (PGI_2) analogues were 22.4–45.5 m, 39.5–44.2 m, and 12.4–64.9 m, respectively. Overall estimate of ~~M~~mean difference between changes in 6MWD in CTD-PAH patients was 34.2 m (23.3~~,~~ to 45.0 m). Pooled ~~Mean~~ mean differences by subgroup of patients receiving PDE-5 inhibitors, ERAs, and PGI_2 analogues in CTD-PAH patients were 37.0–47.1 m, 14.1–21.7 m, and 21.0–108.0 m, respectively. ERAs were less effective in CTD-PAH patients than all--form -PAH patients: 14.1 m (–4.4 to~~,~~ 32.6 m) versus 39.5 m (19.5 to~~,~~ 59.6 m) for bosentan, and 21.7 m (2.2 to~~,~~ 41.3 m) versus 44.2 m (30.2 to~~,~~ 58.2 m)

for ambrisentan. **Conclusions:** All 3 types of PAH agent are effective. However, ERAs may be a less effective choice against CTD-PAH; further studies are needed. Limitations include the limited number of studies for some agents and for CTD-PAH patients.

Article summary

Article focus

- Pulmonary arterial hypertension (PAH) is a progressive disease characterised by abnormally high blood pressure in the pulmonary arteries.
- Patients with PAH associated with connective tissue diseases (CTDs) such as systemic sclerosis (SSc) have a particularly poor prognosis.
- Few studies have focused on patients with CTD-PAH, so the optimal treatment for these patients is unclear.

Key messages

- The effects of the phosphodiesterase-5 inhibitors sildenafil and tadalafil, and the prostacyclin analogue epoprostenol, are consistent in patients with CTD-PAH and in those with PAH generally.
- The endothelin receptor antagonists bosentan and ambrisentan may be less effective in patients with CTD-PAH than in those with PAH generally.

Strengths and limitations of this study

- The meta-analysis used all currently available data from clinical studies on treatment for PAH.
- Few studies were identified for some PAH agents and for CTD-PAH patients.
- Study designs and patient background characteristics, including the percentages of patients with SSc-PAH, were inconsistent between studies.

Introduction

Pulmonary hypertension is a heterogeneous condition with sustained elevation of pressure in the pulmonary arteries, and is defined as mean pulmonary artery pressure ≥ 25 mmHg at rest.[1] The most recent and widely accepted clinical classification of pulmonary hypertension is that proposed at the Fourth World Symposium on Pulmonary Hypertension at Dana Point in 2008.[2] It classifies pulmonary hypertension into 5 groups. Group 1 comprises pulmonary arterial hypertension (PAH), which includes idiopathic PAH, heritable PAH, drug- and toxin-induced PAH, PAH associated with various diseases, and persistent pulmonary hypertension of the newborn. Group 2 comprises pulmonary hypertension owing to left heart disease; group 3, pulmonary hypertension owing to lung diseases and/or hypoxia; group 4, chronic thromboembolic pulmonary hypertension; and group 5, pulmonary hypertension of unknown cause. In this classification of pulmonary hypertension, PAH is recognised as having an extremely poor prognosis and requires specific medical treatment.

Connective tissue disease (CTD) is the most common condition associated with PAH. Recent cohort studies have shown that most patients with PAH associated with CTD have systemic sclerosis (SSc).[3 4] In fact, the prevalence of PAH in patients with SSc is reported to be 7–12%.[5 6] Patients with SSc-PAH have poor prognosis compared with patients with idiopathic PAH.[7] Therefore, early and appropriate diagnosis and selection of the optimal treatment regimen are important for SSc-PAH, to improve the hemodynamics, exercise capacity, and eventually survival of patients.

The optimal treatment for PAH has not been established. However, there has been major progress in medical treatment for PAH in recent years. Several new agents with different

mechanisms have been introduced, including phosphodiesterase (PDE)-5 inhibitors (e.g. oral sildenafil and tadalafil), endothelin receptor antagonists (ERAs) (e.g. oral bosentan and ambrisentan), and prostacyclin (PGI_2) analogues (e.g. continuous intravenous epoprostenol). The introduction of these new agents is expected to contribute to the improvement of exercise capacity, subjective symptoms, and quality of life, as well as the short- and long-term survival of patients.

Although the efficacy and safety of these new agents have been shown in small- or medium-scale randomised controlled trials (RCTs) and open-label trials, evidence from large-scale comparative studies of these agents remains insufficient because PAH is a rare disease. Therefore, to compare the new agents and establish a therapeutic strategy for PAH, several systematic reviews and meta-analyses of available clinical study results have been done.[8–13] However, most of these analyses include studies on all forms of PAH, and studies that focus on CTD-PAH are limited. In fact, our literature search showed only one such report: a meta-analysis by Avouac *et al.*,[8] which investigated the efficacy of oral PAH agents mainly in patients with SSc.

Therefore, in this meta-analysis of studies designed as RCTs and open-label, single-arm trials, we aimed to evaluate the effect of each PAH agent on exercise capacity in patients with CTD-PAH compared with patients with all forms of PAH. We chose 6-minute walk distance (6MWD) as an endpoint because it was used as a primary endpoint in most previous randomised studies of PAH agents.[14]

Methods

Eligibility criteria

To evaluate the effects of 3 typical types of PAH agent, we included RCTs in which the following PAH agents were administered to patients with all forms of PAH.

- PDE-5 inhibitors: sildenafil and tadalafil
- ERAs: bosentan and ambrisentan
- PGI_2 analogues: epoprostenol, beraprost, iloprost, and treprostinil.

Because the number of RCTs in patients with CTD-PAH is limited, we also included open-label, single-arm trials evaluating the effects of PAH agents in patients with CTD-PAH. We excluded reviews and non-interventional studies (e.g. case reports and observational studies as opposed to RCTs) ~~were excluded~~. We included only principal studies and excluded ad hoc analyses. Studies in which results for 6MWD were not reported were also excluded, as were studies on pulmonary hypertension other than PAH.

Search strategy

We searched MEDLINE, EMBASE, and BIOSIS for English-language full-text articles published between January 1990 and August 2012, using the key terms 'pulmonary arterial hypertension', '6 minute walk', and the names of individual drugs. In addition to these key terms, we used the term 'randomised controlled trial' or 'RCT' to identify RCTs evaluating all forms of PAH, and 'connective tissue disease' or 'CTD' to identify studies evaluating CTD-PAH. The last search was run on 5 December 2012. Additional studies were identified through manual searching.

Primary endpoint

The primary outcome measure was the difference in mean change from baseline in 6MWD between groups. However, for single-arm studies, the mean change from baseline was used as the primary outcome measure.

Data collection

Relevant data were extracted and reviewed by NM and NS. Data on study characteristics (year and design), variables including PAH agents used, total patient numbers and the percentage of CTD-PAH patients, and outcomes (mean difference, m and 95%CI, m or standard error) were extracted.

Risk of bias

To determine the validity of the included studies, we assessed the risk of bias for each study in terms of random sequence generation, allocation concealment, blinding, and other sources of bias, as recommended by the Cochrane Collaboration. Each domain was judged to have high, low, or unclear risk of bias. We did not detect clear publication bias, because the number of included studies was small.

Statistical analysis

~~We pooled outcomes using a random effects model by each PAH agent for all forms of PAH and CTD-PAH.~~We pooled outcomes by each PAH agent for all forms of PAH and for CTD-PAH. We used a random effects model based on the DerSimonian−Laird method because of known clinical and methodological heterogeneity (e.g. the various doses of each PAH agent). I^2 values were calculated as a measure of heterogeneity. ~~Heterogeneity was~~

assessed using tThe I^2 statistic, which describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error (chance), and we considered $I^2 \geq 75\%$ as representing considerable heterogeneity.

Results

Selection of studies

A total of 196 articles were identified for evaluation of treatments for all forms of PAH. Of these, 19 articles (reporting data from 3073 patients) met the eligibility criteria for evaluations of treatments for all forms of PAH (3 articles for sildenafil,[15–17] 1 article for tadalafil,[18] 4 articles for bosentan,[19–22] 1 article for ambrisentan,[23] 3 articles for epoprostenol,[24–26] 1 article for beraprost,[27] 2 articles for iloprost,[28 29] and 4 articles for treprostinil[30–33]) (figure 1a). The main reasons for exclusion were that the article was a review and that the article reported the results of a study that involved patients other than those with PAH.

For evaluation of treatments for CTD-PAH, a total of 269 articles were identified. Of these, 9 articles (reporting data from 678 patients) met the eligibility criteria for evaluations of treatments for CTD-PAH (1 article for sildenafil,[34] 1 article for tadalafil,[18] 2 articles for bosentan,[35 36] 2 articles for ambrisentan,[37 38] 1 article for epoprostenol,[26] 1 article for beraprost,[39] and 1 article for treprostinil[40] (figure 1b). The main reasons for exclusion were that the article was a review and that the article reported the results of a study that involved patients other than those with CTD-PAH.

Characteristics and overview of the included studies

Of the 19 studies on treatments for all forms of PAH included in this analysis (table 1), 15 were randomised, placebo-controlled, double-blind studies;[15–23 27 28 30–33] 3 were randomised, open-label studies comparing with conventional treatment;[24–26] and 1 was a randomised, open-label study evaluating the effects of iloprost when added to bosentan.[29] The observation period was either 12 or 16 weeks in most of the studies, with some exceptions (1 study each with 6- and 24-week observation periods,[16 22] and 2 studies with an 8-week observation period[24 31]). Of the placebo-controlled randomised comparative studies, 1 study of sildenafil was done in patients previously treated with epoprostenol;[17] 2 studies of iloprost, in patients previously treated with bosentan;[28 29] and 1 study of treprostinil, in patients previously treated with bosentan or sildenafil.[32]

Of the 9 studies on treatments for CTD-PAH included in this analysis (table 2), 5 were placebo-controlled, double-blind studies,[18 34 35 37 40] 1 was a randomised, open-label study comparing with conventional treatment,[26] and 3 were open-label, single-arm studies.[36 38 39] The observation period in these studies was 8–28 weeks. One study each evaluating bosentan[36] and epoprostenol[26] included only SSc-PAH patients.

Background of all PAH patients

The background of all PAH patients, based on data from the 19 studies, can be summarised as follows (full data in supplementary table 1). Mean age was 32–55 years, and the percentage of women was 61–87%. In the studies of sildenafil,[15–17] tadalafil,[18] ambrisentan,[23] and beraprost,[27] most patients were classified according to World Health Organisation functional class (WHO-FC) as in WHO-FC II or III, with 1 study including only patients in

WHO-FC II.[22] In contrast, in the studies of epoprostenol,[24–26] the percentage of patients in WHO-FC IV was higher than that in studies of other agents. In the studies of iloprost, most patients were in WHO-FC III.[28 29] In the studies of treprostinil, most patients were in WHO-FC III in 3 studies[30 32 33] and in WHO-FC II in 1 study.[31] Baseline 6MWD was 226.6–434.5 m, and it was lower in the 3 studies of epoprostenol (226.6, 294.3, and 255.9 m)[24–26] compared with in studies on other agents. Therefore patients with more severe disease were included in the studies of epoprostenol than in other studies. One study of bosentan included only patients with Eisenmenger syndrome.[21]

Background of the subgroup of CTD-PAH patients

The background of patients with CTD-PAH, using data from 9 studies, can be summarised as follows (full data in supplementary table 2). Mean age was 45–55 years, and the percentage of women was 74–95%. In 1 study of tadalafil, there was no information on baseline 6MWD or WHO-FC.[18] As for the distribution of patients according to WHO-FC, a study of beraprost included more patients in WHO-FC II,[39] and a study of epoprostenol included more patients in WHO-FC IV,[26] compared with studies of other agents.

In 5 studies in which information on underlying CTDs was available, SSc-PAH patients accounted for 45–100% of all patients included. Their mean age was 51–55 years, and the percentage of women was 74–90%.

In studies of bosentan[36] and epoprostenol[26] that included only SSc-PAH patients, baseline 6MWD was < 300 m, which was lower than that in studies of other agents. Therefore the study of beraprost included more patients with relatively mild PAH, whereas the study of epoprostenol included more patients with more severe disease.

Results of 6MWD

The actual values of the outcomes for each study are presented on the right sides of figures 2 and 3. We pooled the data, including those for non-approved doses, to evaluate the effect of each PAH agent on exercise capacity in patients with CTD-PAH compared with in patients with all forms of PAH.

6MWD in All PAH patients

The mean differences between changes in 6MWD compared with the control group are shown in figure 2 by each agent. ~~Briefly~~With a random effects model, the pooled mean difference between changes in 6MWD ~~(95%CI)~~ was 45.5 m (95% confidence interval (CI) 32.9~~,~~ to 58.1 m, I^2=50.1%) for sildenafil, 22.4 m (95%CI 14.0~~,~~ to 30.9 m, I^2=7.9%) for tadalafil, 39.5 m (95%CI 19.5 to~~,~~ 59.6 m, I^2=38.3%) for bosentan, 44.2 m (95%CI 30.2 to~~,~~ 58.2 m, I^2=0%) for ambrisentan, 64.9 m (95%CI 20.4 to~~,~~ 109.4 m, I^2=43.3%) for epoprostenol, 25.1 m (95%CI 1.9~~,~~ to 48.4 m, I^2= not applicable [NA]) for beraprost, 12.4 m (95%CI –21.9 to~~,~~ 46.6 m, I^2=39.7%) for iloprost, and 17.3 m (95%CI 6.1~~,~~ to 28.4 m, I^2=29.4%) for treprostinil. Numerical improvement in 6MWD was obtained in patients using each agent compared with those using the control agent. The pooled ~~Mean~~ mean difference between changes in 6MWD from the control group ~~was~~ ranged from 12.4 to~~–~~64.9 m, and the overall estimate of ~~total~~ mean difference ~~(95%CI) combining data for all agents~~ was 34.6 m (95%CI 27.4 to~~,~~ 41.9 m, I^2=63.2%). The ranges of ~~Mean~~ mean difference from the effects of placebo by subgroup of patients receiving PDE-5 inhibitors, ERAs, and PGI_2 analogues were 22.4–45.5 m, 39.5–44.2 m, and 12.4–64.9 m, respectively. Considerable heterogeneity was

not observed.

6MWD in a subgroup of CTD-PAH patients

In the subgroup of CTD-PAH patients, the mean differences between changes in 6MWD compared with the control group are shown in figure 3 by each agent. For single-arm studies, the mean changes from baseline are shown. With a random effects model~~Briefly~~, the pooled mean difference between changes in 6MWD ~~(95%CI)~~was 47.1 m (95%CI 27.9 to~~,~~ 66.3 m, I^2=0%) for sildenafil, 37.0 m (95%CI 19.0 to~~,~~ 55.0 m, I^2=0%) for tadalafil, 14.1 m (95%CI –4.4 to~~,~~ 32.6 m, I^2=0%) for bosentan, 21.7 m (95%CI 2.2 to~~,~~ 41.3 m, I^2=0%) for ambrisentan, 108.0 m (95%CI 45.6 to~~,~~ 170.4 m, I^2=NA) for epoprostenol, 58.5 m (95%CI 21.4 to~~,~~ 95.6 m, I^2=NA) for beraprost, and 21.0 m (95%CI –6.9 to~~,~~ 48.9 m, I^2=NA) for treprostinil. Numerical improvement in 6MWD was obtained in patients using all agents compared with those using the control agent. The overall estimate of mean difference between changes in 6MWD ~~(95%CI)~~in patients with CTD-PAH was 34.2 m (95%CI 23.3 to~~,~~ 45.0 m, I^2=32.5%). The ranges of mean differences by subgroup of patients receiving PDE-5 inhibitors, ERAs, and PGI_2 analogues ~~–~~were 37.0–47.1 m, 14.1–21.7 m, and 21.0–108.0 m, respectively. Considerable heterogeneity was not observed.

We did an additional sensitivity analysis excluding open-label single-arm studies for CTD-PAH patients only (supplementary figure). The overall estimate of mean difference between changes in 6MWD in patients with CTD-PAH was 37.2 m (95%CI 25.0 to 49.3 m, I^2=20.5%) and the ranges of mean differences by subgroup of patients receiving PDE-5 inhibitors, ERAs, and PGI_2 analogues were 37.0−47.1 m, 19.0−22.1 m, and 21.0−108.0 m, respectively.

Difference in exercise capacity between all PAH patients and CTD-PAH patients

When the pooled mean differences between changes in 6MWD were compared between all PAH patients and each subgroup of CTD-PAH patients, no difference in exercise capacity was found between the patient groups for PDE-5 inhibitors (sildenafil and tadalafil). In contrast, for ERAs (bosentan and ambrisentan), the pooled mean values in CTD-PAH patients (bosentan, 14.1 m; ambrisentan, 21.7 m) were lower than the lower limit of 95%CI of the mean values in all PAH patients (bosentan, 19.5 to, 59.6 m; ambrisentan, 30.2 to, 58.2 m), suggesting that effects on exercise capacity may vary between patient groups. For PGI_2 (epoprostenol, beraprost, and treprostinil), no obvious trends were found between patient groups.

Risk of bias

We rated risk of bias for each study (full data in supplementary table 3). In studies for all forms of PAH, none were at high risk of bias for random sequence generation or allocation concealment; however, the method of randomisation and allocation concealment were unclear (i.e. not reported) for 11 studies and 9 studies, respectively. Four studies were at high risk of bias for blinding because they were open-label studies. Three studies were at high risk for another source of bias (imbalance in missing data between groups,[17] imbalance in baseline 6MWD,[25] and early termination based on futility analysis[29]).

Of studies for CTD-PAH, 3 studies were at high risk of bias with respect to all domains because they were open-label, single-arm studies.[36 38 39] One study was at high risk of bias resulting from imbalance in baseline characteristics.[35] The remaining studies were judged to

be not of high risk of bias in any of the domains.

Discussion

A finding of the present meta-analysis of 19 studies is that in combined patients with all forms of PAH, all agents increase 6MWD compared with the control group.[15–33] Likewise, the meta-analysis of 9 studies on CTD-PAH patients also showed an increase in 6MWD by all agents.[18 26 34–40] The finding that all agents increase 6MWD in all PAH patients is consistent with the results of the 5 previous systematic reviews and meta-analyses that evaluated the 3 types of agent (PDE-5 inhibitors, ERAs, and PGI_2 analogues).[9–13] To date, reports of meta-analyses that included patients with CTD-PAH including SSc-PAH are limited to 1 study that evaluated 3 oral agents (sildenafil, bosentan, and sitaxsentan) alone.[8] The findings of this meta-analysis are important because patients with all PAH as well as a subgroup of CTD-PAH patients were included, and the effects of 3 types of agent, including intravenous preparations, were thoroughly evaluated. Our meta-analysis shows similar trends to the findings of Avouac *et al*.[8]

When the mean differences between changes in 6MWD were compared between all PAH patients and CTD-PAH patients, the effects of ERAs (bosentan and ambrisentan) on exercise tolerance may be less in CTD-PAH patients, whereas no difference in exercise capacity was found between patient groups for PDE-5 inhibitors and PGI_2 analogues. This result should be interpreted cautiously because recent data from registries have shown that 6MWD is significantly lower in patients with CTD-PAH than in those with idiopathic PAH,[4 41] and a systematic review has shown that 6MWD may be only partially valid in patients with

SSc-PAH. [42]

This analysis has several limitations. First, we could identify only a limited number of studies for some agents (1 study each for tadalafil, ambrisentan, and beraprost), and studies that included a subgroup of patients with CTD-PAH including SSc-PAH were scarce. Second, ideally data for patients with CTD-PAH should be compared with those for patients with other forms of PAH. However, there were insufficient data for forms of PAH other than CTD-PAH, so this analysis compared data for all PAH and CTD-PAH. Third, the study designs varied: some studies that included CTD-PAH patients were done in an open-label or single-arm, open-label manner, some having a short observation period (12 or 16 weeks) or using combination therapy. Of note, in studies of combination therapy, changes in 6MWD are expected to be smaller, because patients are already receiving PAH therapy at the start of the study. Patient background characteristics were also inconsistent between studies: patients were in various WHO FC classes and had various baseline 6MWD values, which can influence the effects of each agent, and some articles reported no such information. Moreover, the percentage of SSc-PAH patients in the study population also varied, which is a study limitation because there is a difference in treatment response between SSc and non-SSc patients, and patients with SSc-PAH have poor prognosis compared with patients with other CTD-PAH.[4 7] In this meta-analysis, the percentages of SSc-PAH patients were as follows: for sildenafil, 45% in the study by Badesch *et al.*;[34] for bosentan, 79% in the study by Denton *et al.*;[35] and 100% in the study by Launay *et al.*;[36] and for epoprostenol, 100% in the study by Badesch *et al.*[26] The percentage was unknown in the study of tadalafil by Galiè *et al.*;[18] in those of ambrisentan by Badesch *et al.*;[37 38] and in that of beraprost by Kunieda et al.[39] Patients with SSc-PAH were more frequently enrolled in studies for bosentan[35 36] than in the

sildenafil study.[34]

It would have been interesting to do a sensitivity analysis with the data from SSc-PAH patients only, but this is not possible for the following reasons. There are only two articles (Launay *et al*., 2010[36] and Badesch *et al*., 2000[26]) from which data for the subpopulation of SSc-PAH patients can be extracted. ~~A fourth~~Another limitation of our study was the inclusion of data for non-approved, possibly subtherapeutic doses, which may have reduced the effects of the PAH agents in some studies. Finally, there may be publication bias, so negative results are likely to be unpublished.[43]

Furthermore, the present analysis is intended to compare changes in 6MWD over a short period of time, therefore whether the results are associated with patient survival remains unclear. However, 6MWD is effective as an indicator of the severity of PAH.[44] Moreover, an ongoing large-scale registry, the US Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL), which aims to clarify the characteristics and prognosis of PAH patients and the latest treatment for PAH, has shown that 6MWD is an independent predictor that is significantly associated with 1-year survival.[45] Several other studies have also confirmed its role as an independent predictor of prognosis.[46–50] In addition, investigators who did a placebo-controlled randomised trial of the PDE-5 inhibitor sildenafil have recently identified the minimum clinically meaningful changes in 6MWD, and concluded that it would be a useful indicator to determine the efficacy of other PAH agents.[51]

However, pharmacological treatment for PAH is shifting from monotherapy to combination therapy, and it is expected that clinical studies investigating the efficacy of combination therapy will increase. Therefore, it will be increasingly difficult to do a meta-analysis that includes all the new studies to detect differences between PAH agents. The

present analysis is meaningful because it included all available clinical study results to date, and we hope that it contributes to the improvement of the treatment for PAH.

In conclusion, the present meta-analysis of studies that included CTD-PAH patients showed an increase in 6MWD by all agents, that is, PDE-5 inhibitors, ERAs, and PGI_2 analogues. Comparison of the mean differences between changes in 6MWD suggest that, for bosentan and ambrisentan, the effects on exercise tolerance may differ depending on patient group, whereas the PDE-5 inhibitors sildenafil and tadalafil and the PGI_2 analogue epoprostenol show consistent effects regardless of the presence or absence of CTD. Further studies are needed to clarify the clinical implications of these findings.

Competing interests

MK has received research funding from Actelion Pharmaceuticals, GlaxoSmithKline, Novartis and Pfizer, and lecture fees from Actelion Pharmaceuticals, Pfizer, GlaxoSmithKline, Nippon Shinyaku, Mitsubishi Tanabe Pharma and Takeda Pharmaceuticals. WH has received research funding from the Ministry of Health, Labour and Welfare of Japan, Teika Seiyaku, Takeda Pharmaceuticals, Mochida, Pfizer, Asteras and Daiichi Sankyo, and lecture fees from Pfizer, Acterion, Novartis, Daiich Sankyo, GlaxoSmithKline and Nihon Shinyaku. NM and NS are employees of Pfizer Japan Inc.

Contributors

N. Matsuoka, a statistician employed by Pfizer Japan, collected the data and did the statistical

analyses described in this article.

Dr N. Sugiyama, a rheumatologist employed by Pfizer Japan, reviewed the collection and analyses of the data. He helped conceive and design the meta-analysis, interpret the results, and revise the manuscript.

Dr M. Kuwana is directly responsible for the manuscript. He reviewed the data analyses and drafted the manuscript, providing important intellectual content from the perspective of a CTD-PAH specialist.

Dr H. Watanabe revised the manuscript critically for important intellectual content from the perspective of a PAH specialist.

References

1. Badesch DB, Champion HC, Sanchez MA, *et al*. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;54:S55–66.
2. Simonneau G, Robbins IM, Beghetti M, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;54:S43–54.
3. Condliffe R, Kiely DG, Peacock AJ, *et al.* Connective tissue disease-associated pulmonary hypertension in the modern treatment era. *Am J Respir Crit Care Med* 2009;179:151–7.
4. Chung L, Liu J, Parsons L, *et al.* Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. *Chest* 2010;138:1383–94.
5. Hachulla E, Gressin V, Guilevin L, *et al.* Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum* 2005;52:3792–800.
6. Mukerjee D, St George D, Coleiro B, *et al.* Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis* 2003;62:1088–93.
7. Kawut SM, Taichman DB, Archer-Chicko CL, *et al.* Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. *Chest* 2003;123:344–50.
8. Avouac J, Wipff J, Kahan A, *et al.* Effects of oral treatments on exercise capacity in systemic sclerosis related pulmonary arterial hypertension: a meta-analysis of

randomised controlled trials. *Ann Rheum Dis* 2008;67:808–14.

9. Galiè N, Manes A, Negro L, *et al.* A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. *Eur Heart J* 2009;30:394–403.
10. Galiè N, Palazzini M, Manes A. Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analyses. *Eur Heart J* 2010;31:2080–6.
11. Macchia A, Marchioli R, Tognoni G., *et al.* Systematic review of trials using vasodilators in pulmonary arterial hypertension: why a new approach is needed. *Am Heart J* 2010;159:245–57.
12. He B, Zhang F, Li X, *et al.* Meta-analysis of randomized controlled trials on treatment of pulmonary arterial hypertension. *Circ J* 2010;74:1458–64.
13. Ryerson CJ, Nayar S, Swiston JR, *et al.* Pharmacotherapy in pulmonary arterial hypertension: a systematic review and meta-analysis. *Respir Res* 2010;11:12.
14. McLaughlin VV, Badesch DB, Delcroix M, *et al.* End points and clinical trial design in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;54:S97–107.
15. Galiè N, Ghofrani HA, Torbicki A, *et al.* Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005;353:2148–57.
16. Singh TP, Rohit M, Grover A, *et al.* A randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe pulmonary artery hypertension. *Am Heart J* 2006;151:851.e1–5.
17. Simonneau G, Rubin LJ, Galiè N, *et al.* Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008;149:521–30.
18. Galiè N, Brundage BH, Ghofrani HA, *et al.* Tadalafil therapy for pulmonary arterial

hypertension. *Circulation* 2009;119:2894–903.

19. Channick RN, Simonneau G, Sitbon O, *et al.* Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001;358:1119–23.
20. Rubin LJ, Badesch DB, Barst RJ, *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896–903.
21. Galiè N, Beghetti M, Gatzoulis MA, *et al.* Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation* 2006;114:48–54.
22. Galiè N, Rubin LJ, Hoeper M, *et al.* Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008;371:2093–100.
23. Galiè N, Olschewski H, Oudiz RJ, *et al.* Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation* 2008;117:3010–9.
24. Rubin LJ, Mendoza J, Hood M, *et al.* Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. *Ann Intern Med* 1990;112:485–91.
25. Barst RJ, Rubin LJ, Long WA, *et al.* A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996;334:296–302.

26. Badesch DB, Tapson VF, McGoon MD, *et al.* Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000;132:425–34.
27. Galiè N, Humbert M, Vachiéry JL, *et al.* Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2002;39:1496–502.
28. McLaughlin VV, Oudiz RJ, Frost A, *et al.* Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006;174:1257–63.
29. Hoeper MM, Leuchte H, Halank M, *et al.* Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2006;28:691–4.
30. Simonneau G, Barst RJ, Galiè N, *et al.* Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002;165:800–4.
31. McLaughlin VV, Gaine SP, Barst RJ, *et al.* Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension. *J Cardiovasc Pharmacol* 2003;41:293–9.
32. McLaughlin VV, Benza RL, Rubin LJ, *et al.* Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2010;55:1915–22.
33. Hiremath J, Thanikachalam S, Parikh K, *et al.* Exercise improvement and plasma biomarker changes with intravenous treprostinil therapy for pulmonary arterial hypertension: a placebo-controlled trial. *J Heart Lung Transplant* 2010;29:137–49.
34. Badesch DB, Hill NS, Burgess G, *et al.* Sildenafil for pulmonary arterial hypertension

associated with connective tissue disease. *J Rheumatol* 2007;34:2417–22.

35. Denton CP, Humbert M, Rubin L, *et al.* Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions. *Ann Rheum Dis* 2006;65:1336–40.
36. Launay D, Sitbon O, Le Pavec J, *et al.* Long-term outcome of systemic sclerosis–associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by the addition of prostanoids or sildenafil. *Rheumatology* 2010;49:490–500.
37. Badesch DB. Ambrisentan therapy for pulmonary arterial hypertension: a comparison by PAH etiology. *Chest* 2007;slide presentations:488S.
38. Badesch DB, Feldman J, Keogh A, *et al.* ARIES-3: ambrisentan therapy in a diverse population of patients with pulmonary hypertension. *Cardiovasc Ther* 2012;30:93–9.
39. Kunieda T, Nakanishi N, Matsubara H, *et al.* Effects of long-acting beraprost sodium (TRK-100STP) in Japanese patients with pulmonary arterial hypertension. *Int Heart J* 2009;50:513–29.
40. Oudiz R, Schilz RJ, Barst RJ, *et al.* Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. *Chest* 2004;126:420–7.
41. Clements PJ, Tan M, McLaughlin VV, *et al.* The pulmonary arterial hypertension quality enhancement research initiative: comparison of patients with idiopathic PAH to patients with systemic sclerosis-associated PAH. *Ann Rheum Dis* 2012;71:249–52.
42. Avouac J, Kowal-Bielecka O, Pittrow D, et al.; EPOSS Group. Validation of the 6 min walk test according to the OMERACT filter: a systematic literature review by the EPOSS-OMERACT group. Ann Rheum Dis 2010; 69:1360–1363.

43. Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey. *BMJ* 2012;344:d7762.

44. Naeije R. The 6-min walk distance in pulmonary arterial hypertension: "Je t'aime, moi non plus". *Chest* 2010;137:1258–60.

45. Benza RL, Miller DP, Gomberg-Maitland M, *et al.* Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010;122:164–72.

46. Miyamoto S, Nagaya N, Satoh T, *et al.* Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000;161:487–92.

47. Sitbon O, Humbert M, Nunes H, *et al.* Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002;40:780–8.

48. Groepenhoff H, Vonk-Noordegraaf A, Boonstra A, *et al.* Exercise testing to estimate survival in pulmonary hypertension. *Med Sci Sports Exerc* 2008;40:1725–32.

49. Humbert M, Sitbon O, Chaouat A, *et al.* Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010;122:156–63.

50. Humbert M, Sitbon O, Yaïci A, *et al.* Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010;36:549–55.

51. Gilbert C, Brown MC, Cappelleri JC, *et al.* Estimating a minimally important difference

in pulmonary arterial hypertension following treatment with sildenafil. *Chest* 2009;135:137–42.

Figure legends

Figure 1 Flow diagram summarising selection of studies evaluating treatments for patients with (**a**) all forms of pulmonary arterial hypertension (PAH) and (**b**) connective tissue disease-PAH. RCT, randomised controlled trial.

Figure 2 Effects of individual pulmonary arterial hypertension (PAH) agents on 6-minute walk distance (6MWD) in patients with any form of PAH. ERA, endothelin receptor antagonist; PDE, phosphodiesterase; PGI_2, prostacyclin; NA, not applicable.

Figure 3 Effects of individual pulmonary arterial hypertension (PAH) agents on 6-minute walk distance (6MWD) in patients with PAH associated with connective tissue disease. ERA, endothelin receptor antagonist; PDE, phosphodiesterase; PGI_2, prostacyclin; NA, not applicable. For single-arm studies, the mean changes from baseline are shown.

Table 1 Summary of included studies evaluating treatment with PAH agents in patients with all forms of PAH

Source (official acronym)	PAH agent	No. of patients	No. (%) of CTD-PAH patients	Study design	Intervention	Control	Period (weeks)	Results for CTD-PAH
Galiè *et al.* (2005)[15] (SUPER-1)	Sildenafil	278	84 (30)	RCT, DB	20 mg × 3/day, 40 mg × 3/day, 80 mg × 3/day	Placebo	12	Available in Badesch *et al.* (2007)[34]
Singh *et al.* (2006)[16]	Sildenafil	20	0	RCT, DB	25 mg on first day, then if no hypotension, 100 mg × 3/day	Placebo	6	None
Simonneau *et al.* (2008)[17] (PACES)	Sildenafil	267	55 (21)	RCT, DB	20 mg × 3/day, titrated to 40 mg and 80 mg × 3/day, as tolerated, at 4-week intervals on background treatment with epoprostenol	Placebo on background treatment with epoprostenol	16	None
Galiè *et al.* (2009)[18] (PHIRST)	Tadalafil	405	95 (24)	RCT, DB	2.5 mg, 10 mg, 20 mg, 40 mg	Placebo	16	Available in this article
Channick *et al.* (2001)[19]	Bosentan	32	5 (16)	RCT, DB	62.5 mg × 2/day for 4 weeks, then 125 mg × 2/day	Placebo	12	Available in Denton *et al.* (2006)[35]
Rubin *et al.* (2002)[20] (BREATHE-1)	Bosentan	213	63 (30)	RCT, DB	62.5 mg × 2/day for 4 weeks, then 125 mg or 250 mg × 2/day	Placebo	16	Available in Denton *et al.* (2006)[35]
Galiè *et al.* (2006)[21]	Bosentan	54	0	RCT, DB	62.5 mg × 2/day for	Placebo	16	None

Source (official acronym)	PAH agent	No. of patients	No. (%) of CTD-PAH patients	Study design	Intervention	Control	Period (weeks)	Results for CTD-PAH
(BREATHE-5)					4 weeks, then 125 mg × 2/day			
Galiè *et al.* (2008)[22] (EARLY)	Bosentan	185	33 (18)	RCT, DB	62.5 mg × 2/day for 4 weeks, then 125 mg × 2/day	Placebo	24	None
Galiè *et al.* (2008)[23] (ARIES)	Ambrisentan	393	124 (32)	RCT, DB	2.5 mg, 5 mg, 10 mg	Placebo	12	Available in Badesch (2007)[37]
Rubin *et al.* (1990)[24]	Epoprostenol	23	0	RCT, open-label	Initial dosage of 1–2 ng/kg/min, then titrated to an optimal dose	Conventional therapy	8	None
Barst *et al.* (1996)[25]	Epoprostenol	81	0	RCT, open-label	Initial dosage of 2 ng/kg/min, then titrated to optimal dosage	Conventional therapy	12	None
Badesch *et al.* (2000)[26]	Epoprostenol	111	111 (100)	RCT, open-label	Dosage established according to signs and symptoms from an initial low dose	Conventional therapy	12	Available in this article
Galiè *et al.* (2002)[27] (ALPHABET)	Beraprost	130	13 (10)	RCT, DB	20 mg × 4/day for first week, then titrated to 120 mg ×	Placebo	12	None

Source (official acronym)	PAH agent	No. of patients	No. (%) of CTD-PAH patients	Study design	Intervention	Control	Period (weeks)	Results for CTD-PAH
					4/day			
McLaughlin *et al.* (2006)[28] (STEP)	Inhaled iloprost	67	NR	RCT, DB	5 mg on background treatment with bosentan (125 mg × 2/day)	Placebo on background treatment with bosentan (125 mg × 2/day)	12	None
Hoeper *et al.* (2006)[29] (COMBI)	Inhaled iloprost	40	0	RCT, open-label	5 mg on background treatment with bosentan (125 mg × 2/day)	Placebo on background treatment with bosentan (125 mg × 2/day)	12	None
Simonneau *et al.* (2002)[30]	Treprostinil	469	90 (19)	RCT, DB	Initial dosage of 1.25 ng/kg/min, then titrated to maximum dosage of 22.5 ng/kg/min	Placebo	12	None
McLaughlin *et al.* (2003)[31]	Treprostinil	26	0	RCT, DB	Initial dosage of 2.5 or 5.0 ng/kg/min, then titrated to maximum dosage of 20 ng/kg/min	Placebo	8	Available in Oudiz *et al.* (2004)[40]
McLaughlin *et al.*	Treprostinil	235	0	RCT, DB	Initiated at 3 breaths	Placebo	12	None

Source (official acronym)	PAH agent	No. of patients	No. (%) of CTD-PAH patients	Study design	Intervention	Control	Period (weeks)	Results for CTD-PAH
(2010)[32]					(18 mg)/inhalation, then titrated to maximum dosage of 9 breaths (54 mg) at each of the 4 daily doses			
Hiremath *et al.* (2010)[33]	Treprostinil	44	2 (5)	RCT, DB	Initial dose of 4 ng/kg/min, then titrated to maximum dose of 100 ng/kg/min	Placebo	12	None

CTD, connective tissue disease; DB, double-blind; NR, not reported; PAH, pulmonary arterial hypertension; RCT, randomised controlled trial.

Table 2 Summary of included studies evaluating treatment with PAH agents in patients with CTD-PAH

Source (official acronym)	PAH agent	No. of CTD-PAH patients	No. (%) of SSc-PAH patients	Study design	Intervention	Control	Period (weeks)
Badesch *et al.* (2007)[34] (SUPER-1)	Sildenafil	84	38 (45)	RCT, DB	20 mg × 3/day, 40 mg × 3/day, 80 mg × 3/day	Placebo	12
Galiè *et al.* (2009)[18] (PHIRST)	Tadalafil	95	NR	RCT, DB	2.5 mg, 10 mg, 20 mg, 40 mg	Placebo	16
Denton *et al.* (2006)[35]	Bosentan	66	52 (79)	RCT, DB	62.5 mg × 2/day for 4 weeks, then 125 or 250 mg × 2/day	Placebo	12 or 16
Launay *et al.* (2010)[36]	Bosentan	49	49 (100)	Single-arm, open-label	62.5 mg × 2/day for 4 weeks, then 125 or 250 mg × 2/day	None	28
Badesch (2007)[37] (ARIES)	Ambrisentan	124	NR	RCT, DB	2.5 mg, 5 mg, 10 mg	Placebo	12
Badesch *et al.* (2012)[38] (ARIES-3)	Ambrisentan	40	NR	Single-arm, open-label	5 mg	None	24
Badesch *et al.* (2000)[26]	Epoprostenol	111	111 (100)	RCT, open-label	Dosage established according to signs and symptoms from initial low dose	Conventional therapy	12
Kunieda *et al.* (2009)[39]	Beraprost	19	NR	Single-arm, open-label	Initial dose of 120 mg/day, then titrated to maximum dose of 360 mg/day	None	12
Oudiz *et al.* (2004)[40]	Treprostinil	90	45 (50)	RCT, DB	Initial dosage of 2.5 or 5.0 ng/kg/min, then titrated to	Placebo	8

Source (official acronym)	PAH agent	No. of CTD-PAH patients	No. (%) of SSc-PAH patients	Study design	Intervention	Control	Period (weeks)
					maximum dosage of 20 ng/kg/min		

CTD, connective tissue disease; DB, double-blind; NR, not reported; PAH, pulmonary arterial hypertension; RCT, randomised controlled trial; SSc, systemic sclerosis.

Figure 1a

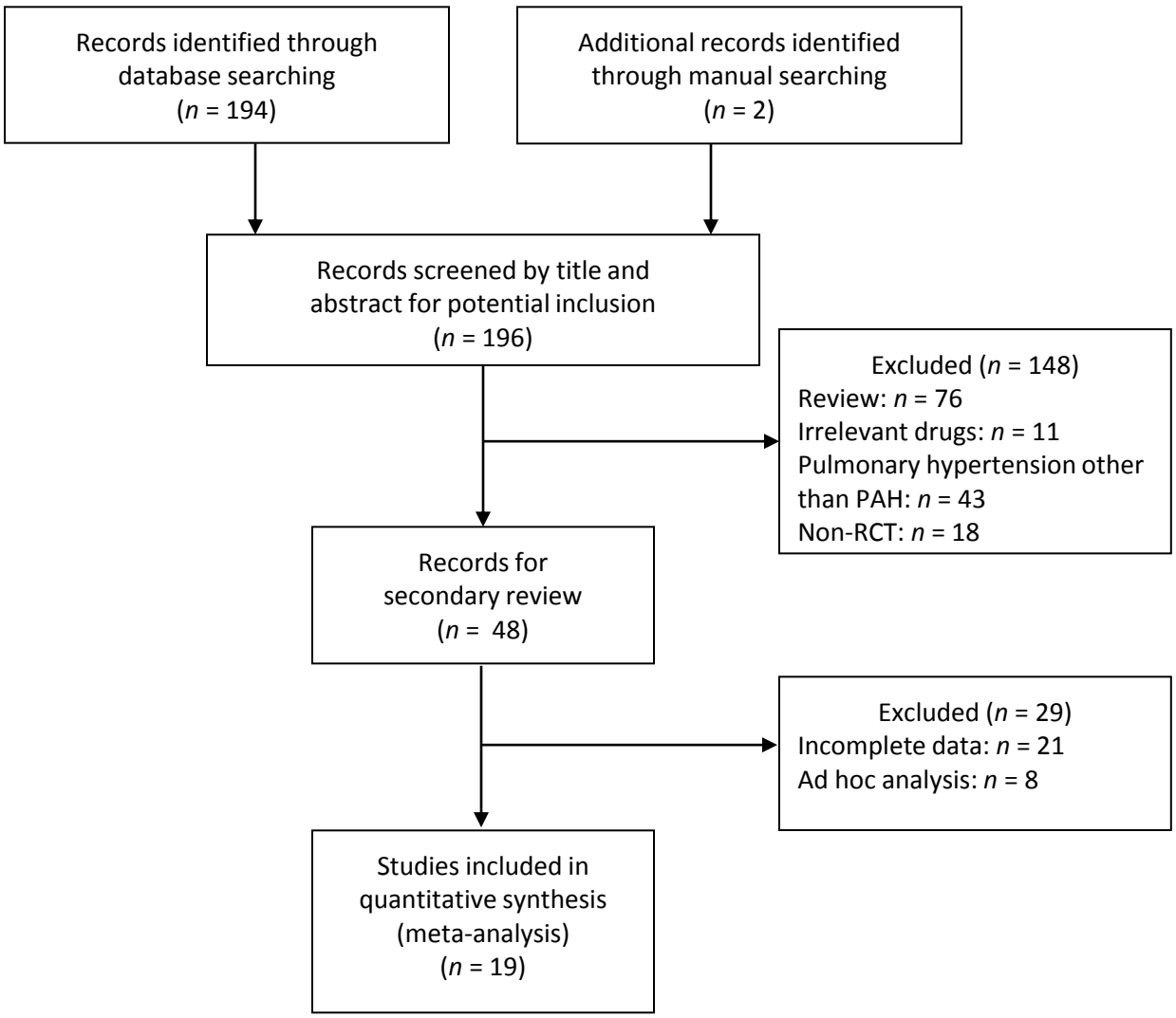

Records identified through database searching (n = 194)
Additional records identified through manual searching (n = 2)
Records screened by title and abstract for potential inclusion (n = 196)
Excluded (n = 148)
Review: n = 76
Irrelevant drugs: n = 11
Pulmonary hypertension other than PAH: n = 43
Non-RCT: n = 18
Records for secondary review (n = 48)
Excluded (n = 29)
Incomplete data: n = 21
Ad hoc analysis: n = 8
Studies included in quantitative synthesis (meta-analysis) (n = 19)

Figure 1b

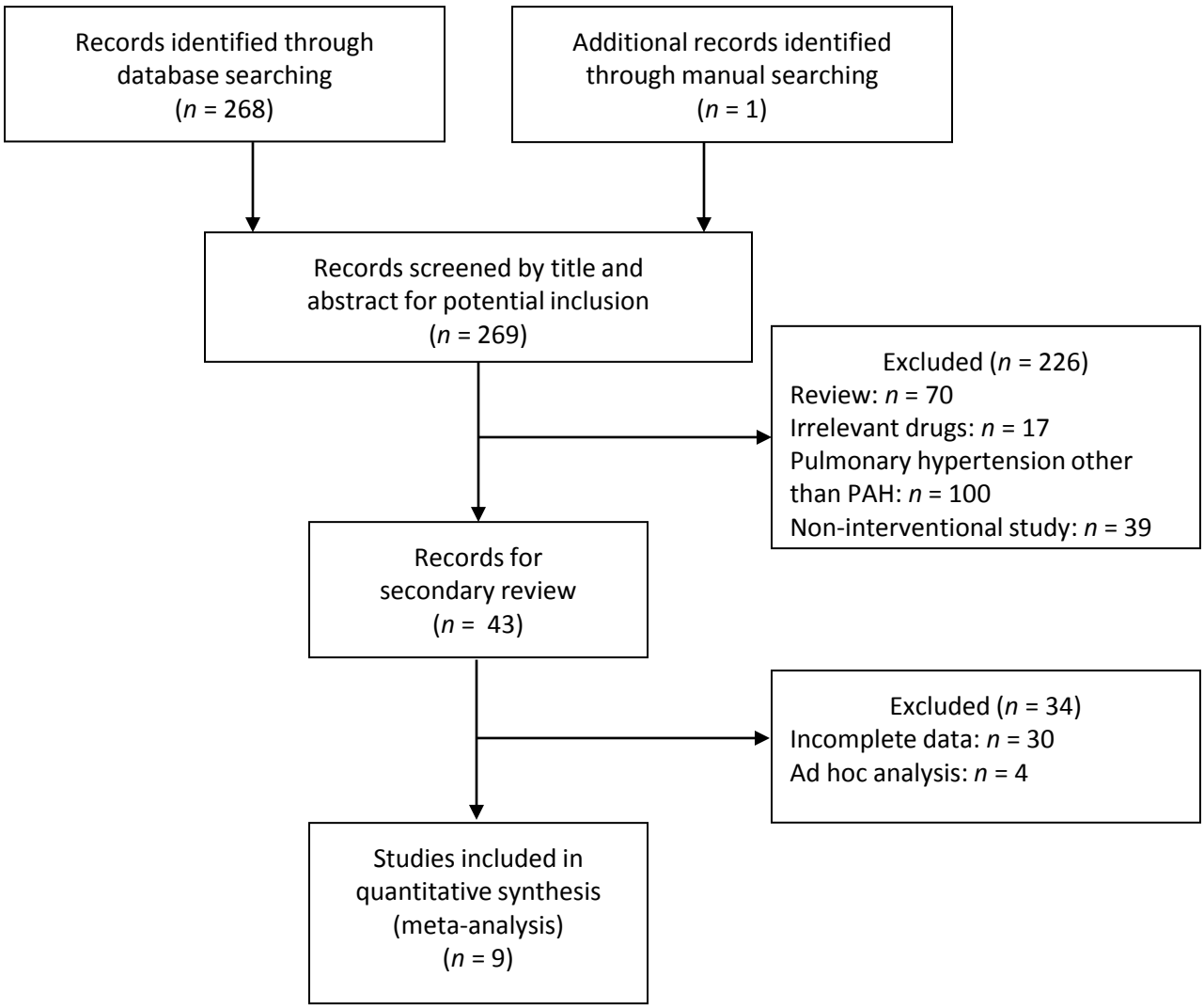

Records identified through database searching (n = 268)
Additional records identified through manual searching (n = 1)
Records screened by title and abstract for potential inclusion (n = 269)
Excluded (n = 226)
Review: n = 70
Irrelevant drugs: n = 17
Pulmonary hypertension other than PAH: n = 100
Non-interventional study: n = 39
Records for secondary review (n = 43)
Excluded (n = 34)
Incomplete data: n = 30
Ad hoc analysis: n = 4
Studies included in quantitative synthesis (meta-analysis) (n = 9)

Figure 2

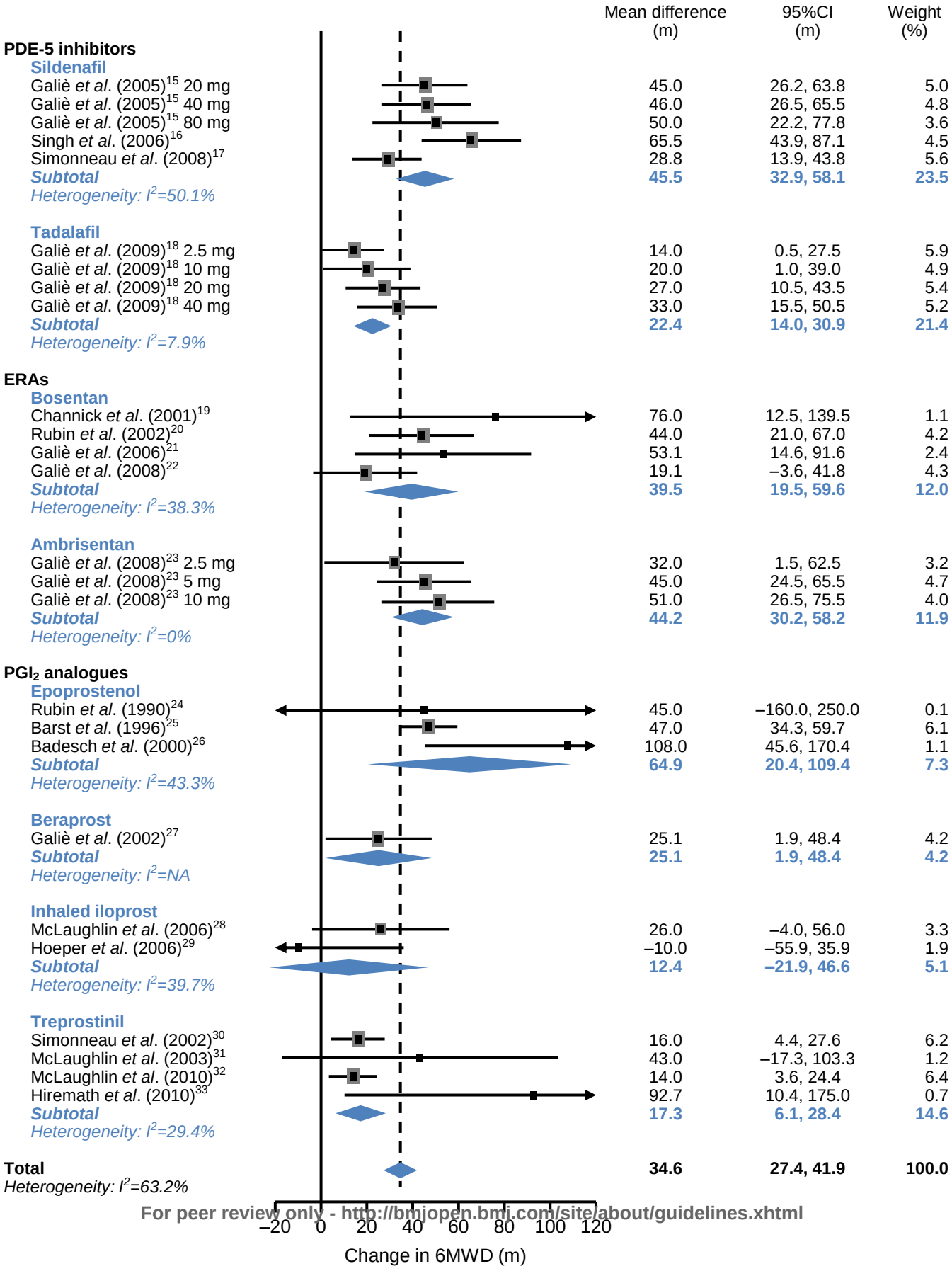
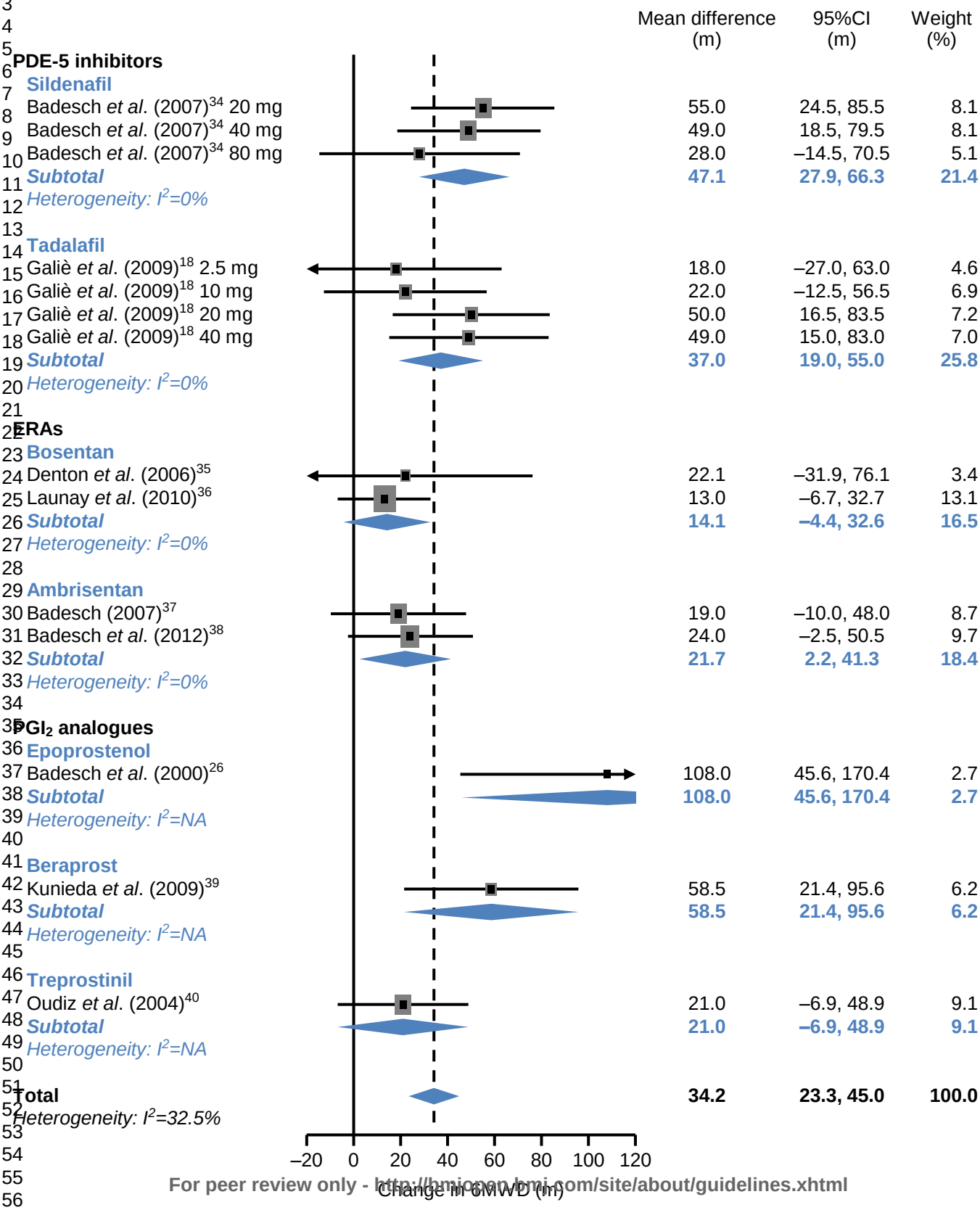


Figure 3



Supplementary table 1 Baseline characteristics of patients with all forms of PAH

Source	PAH agent	Female, *n* (%)	Mean age (years)	Mean weight (kg)	WHO functional class, *n* (%)				Mean baseline 6MWD (m)	Mean PAP (mmHg)
					I	II	III	IV		
Galiè *et al* (2005)[15]	Sildenafil	209 (76)	49	72.7	1 (1)	107 (39)	160 (58)	9 (3)	343.7	52.8
Singh *et al.* (2006)[16]	Sildenafil	15 (75)	NR	NR	0	8 (40)	11 (55)	1 (5)	262.0	95.4
Simonneau *et al.* (2008)[17]	Sildenafil	213 (80)	48	71.4	3 (1)	68 (26)	175 (66)	16 (6)	345.3	51.7
Galiè *et al.* (2009)[18]	Tadalafil	317 (78)	54	75.4	4 (1)	130 (32)	264 (65)	7 (2)	343.6	53.2
Channick *et al.* (2001)[19]	Bosentan	28 (85)	51	86.3	0	0	32 (100)	0	358.3	54.7
Rubin *et al.* (2002)[20]	Bosentan	168 (79)	48	71.9	0	0	195 (92)	18 (9)	334.5	54.4
Galiè *et al.* (2006)[21]	Bosentan	33 (61)	39	63.7	0	0	54 (100)	0	342.8	76.0
Galiè *et al.* (2008)[22]	Bosentan	129 (70)	45	68.1	0	185 (100)	0	0	434.5	52.4
Galiè (2008)[23]	Ambrisentan	311 (79)	51	72.1	8 (2)	151 (38)	216 (55)	18 (5)	344.6	49.2
Rubin *et al.* (1990)[24]	Epoprostenol	16 (70)	36	NR	0	2 (9)	15 (65)	6 (26)	226.6	60.3
Barst *et al.* (1996)[25]	Epoprostenol	59 (73)	40	NR	0	0	60 (74)	21 (26)	294.3	60.0
Badesch *et al.* (2000)[26]	Epoprostenol	96 (87)	55	NR	0	5 (5)	87 (78)	19 (17)	255.9	50.0
Galiè *et al.* (2002)[27]	Beraprost	80 (62)	46	NR	0	64 (49)	66 (51)	0	372.5	59.5
McLaughlin *et al.* (2006)[28]	Inhaled iloprost	53 (79)	50	NR	0	1 (2)	63 (94)	3 (5)	335	52

Hoeper *et al.* (2006)[29]	Inhaled iloprost	31 (78)	52	NR	0	0	40 (100)	0	306.0	56.6
Simonneau (2002)[30]	Treprostinil	382 (81)	45	NR	0	53 (11)	382 (81)	34 (7)	326.5	61.0
McLaughlin *et al.* (2003)[31]	Treprostinil	21 (81)	37	NR	0	25 (96)	1 (4)	0	376.8	60.7
McLaughlin *et al.* (2010)[32]	Treprostinil	191 (81)	54	NR	0	0	230 (98)	5 (2)	348.6	NR
Hiremath *et al.* (2010)[33]	Treprostinil	27 (61)	32	47	0	0	42 (95)	2 (5)	250.4	65

NR, not reported, PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; 6MWD, 6-minute walk distance; WHO, World Health Organisation.

Supplementary table 2 Baseline characteristics of patients with CTD-PAH

Study	PAH agent	Female, *n* (%)	Mean age (years)	Mean weight (kg)	WHO functional class, *n* (%)				Mean baseline 6MWD (m)	Mean PAP (mmHg)
					I	II	III	IV		
Badesch *et al.* (2007)[34]	Sildenafil	70 (83)	53	NR	0	32 (38)	51 (61)	1 (1)	342	47
Galiè *et al.* (2009)[18]	Tadalafil	NR	NR	NR	NR	NR	NR	NR	NR	NR
Denton *et al.* (2006)[35]	Bosentan	55 (83)	55	NR	0	0	63 (96)	3 (5)	328.3	46.4
Launay *et al.* (2010)[36]	Bosentan	36 (74)	NR	NR	0	6 (12)	38 (78)	5 (10)	268	46
Badesch (2007)[37]	Ambrisentan	NR	NR	NR	NR	NR	NR	NR	335	NR
Badesch *et al.* (2012)[38]	Ambrisentan	36 (90)	55	NR	0	12 (30)	27 (68)	1 (3)	324	45
Badesch *et al.* (2000)[26]	Epoprostenol	96 (87)	55	NR	0	5 (5)	87 (78)	19 (17)	255.9	50.0
Kunieda *et al.* (2009)[39]	Beraprost	18 (95)	45	47.6	3 (16)	12 (63)	4 (21)	0	367.9	39.2
Oudiz *et al.* (2004)[40]	Treprostinil	81 (90)	51	NR	0	9 (10)	67 (74)	14 (16)	288.7	NR

CTD, connective tissue disease; NR, not reported; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; 6MWD, 6-minute walk distance; WHO, World Health Organisation.

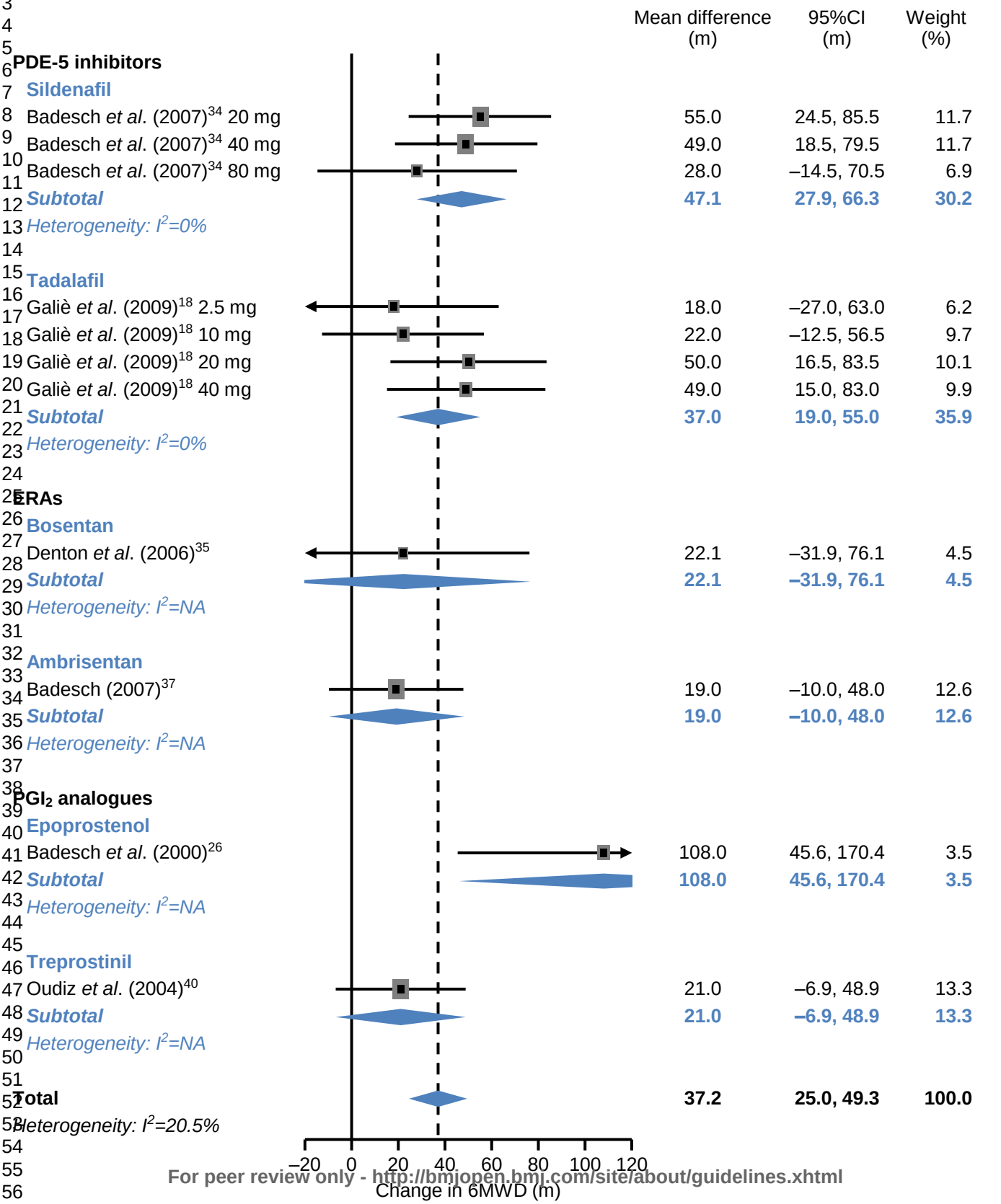
Supplementary table 3 Risk of bias

Source	PAH agent	Random sequence generation	Allocation concealment	Blinding	Other source(s) of bias
All forms of PAH					
Galiè *et al* (2005)[15]	Sildenafil	Unclear	Low	Low	Low
Singh *et al.* (2006)[16]	Sildenafil	Unclear	Low	Low	Low
Simonneau *et al.* (2008)[17]	Sildenafil	Low	Low	Low	High
Galiè *et al.* (2009)[18]	Tadalafil	Unclear	Unclear	Low	Low
Channick *et al.* (2001)[19]	Bosentan	Low	Low	Low	Low
Rubin *et al.* (2002)[20]	Bosentan	Unclear	Unclear	Low	Low
Galiè *et al.* (2006)[21]	Bosentan	Unclear	Low	Low	Low
Galiè *et al.* (2008)[22]	Bosentan	Low	Low	Low	Low
Galiè (2008)[23]	Ambrisentan	Unclear	Low	Low	Low
Rubin *et al.* (1990)[24]	Epoprostenol	Unclear	Low	High	Unclear
Barst *et al.* (1996)[25]	Epoprostenol	Low	Unclear	High	High
Badesch *et al.* (2000)[26]	Epoprostenol	Low	Unclear	High	Low
Galiè *et al.* (2002)[27]	Beraprost	Unclear	Unclear	Low	Low
McLaughlin *et al.* (2006)[28]	Inhaled iloprost	Low	Low	Low	Low
Hoeper *et al.* (2006)[29]	Inhaled iloprost	Low	Low	High	High
Simonneau (2002)[30]	Treprostinil	Low	Unclear	Low	Low
McLaughlin *et al.* (2003)[31]	Treprostinil	Unclear	Unclear	Low	Low
McLaughlin *et al.* (2010)[32]	Treprostinil	Unclear	Unclear	Low	Low
Hiremath *et al.* (2010)[33]	Treprostinil	Unclear	Unclear	Low	Low
CTD-PAH					
Badesch *et al.* (2007)[34]	Sildenafil	Unclear	Low	Low	Low
Galiè *et al.* (2009)[18]	Tadalafil	Unclear	Unclear	Low	Low
Denton *et al.* (2006)[35]	Bosentan	Unclear	Unclear	Low	High
Launay *et al.* (2010)[36]	Bosentan	High	High	High	High

Source	PAH agent	Random sequence generation	Allocation concealment	Blinding	Other source(s) of bias
Badesch (2007)[37]	Ambrisentan	Unclear	Low	Low	Unclear
Badesch *et al.* (2012)[38]	Ambrisentan	High	High	High	High
Badesch *et al.* (2000)[26]	Epoprostenol	Low	Unclear	No	Low
Kunieda *et al.* (2009)[39]	Beraprost	High	High	High	High
Oudiz *et al.* (2004)[40]	Treprostinil	Unclear	Unclear	Low	Low

CTD, connective tissue disease; PAH, pulmonary arterial hypertension.

Supplementary figure



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8–9 and Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9–10 and Tables 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13 and Suppl. table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11–13, Figs 2 and 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11–13, Figs 2 and 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13 and Suppl. table 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15–16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097