

Targeted drugs for pulmonary arterial hypertension: a network meta-analysis of 32 randomized clinical trials

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Background: Pulmonary arterial hypertension (PAH) is a devastating disease and ultimately leads to right heart failure and premature death. A total of four classical targeted drugs, prostanoids, endothelin receptor antagonists (ERAs), phosphodiesterase 5 inhibitors (PDE-5Is), and soluble guanylate cyclase stimulator (sGCS), have been proved to improve exercise capacity and hemodynamics compared to placebo; however, direct head-to-head comparisons of these drugs are lacking. This network meta-analysis was conducted to comprehensively compare the efficacy of these targeted drugs for PAH.

Methods: Medline, the Cochrane Library, and other Internet sources were searched for randomized clinical trials exploring the efficacy of targeted drugs for patients with PAH. The primary effective end point of this network meta-analysis was a 6-minute walk distance (6MWD).

Results: Thirty-two eligible trials including 6,758 patients were identified. There was a statistically significant improvement in 6MWD, mean pulmonary arterial pressure, pulmonary vascular resistance, and clinical worsening events associated with each of the four targeted drugs compared with placebo. Combination therapy improved 6MWD by 20.94 m (95% confidence interval [CI]: 6.94, 34.94; $P=0.003$) vs prostanoids, and 16.94 m (95% CI: 4.41, 29.47; $P=0.008$) vs ERAs. PDE-5Is improved 6MWD by 17.28 m (95% CI: 1.91, 32.65; $P=0.028$) vs prostanoids, with a similar result with combination therapy. In addition, combination therapy reduced mean pulmonary artery pressure by 3.97 mmHg (95% CI: -6.06, -1.88; $P<0.001$) vs prostanoids, 8.24 mmHg (95% CI: -10.71, -5.76; $P<0.001$) vs ERAs, 3.38 mmHg (95% CI: -6.30, -0.47; $P=0.023$) vs PDE-5Is, and 3.94 mmHg (95% CI: -6.99, -0.88; $P=0.012$) vs sGCS. There were no significant differences in all-cause mortality and severe adverse events between prostanoids, ERAs, PDE-5Is, sGCS, combination therapy, and placebo.

Conclusion: All targeted drugs for PAH are associated with improved clinical outcomes, especially combination therapy. However, all these drugs seem to show less favorable effects on survival in the short-term follow-up, suggesting further clinical trials are required.

Keywords: pulmonary arterial hypertension, targeted drugs, 6-minute walk distance, prostanoids, network meta-analysis

Introduction

Pulmonary arterial hypertension (PAH) is a life-threatening disease associated with elevated pulmonary vascular resistance (PVR), ultimately leading to right heart failure and premature death.¹ Recent data from the National Institutes of Health in the United States² showed that the five-year survival rate from the time of a diagnostic right-sided heart catheterization was only 57%,³ and the treatments for PAH were very limited and expensive. Apart from the use of support measures (such as long-term

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oxygen therapy, diuretics, oral anticoagulants, and digoxin), targeted therapies including prostanoids, endothelin receptor antagonists (ERAs), phosphodiesterase 5 inhibitors (PDE-5Is), and soluble guanylate cyclase stimulator (sGCS) are also recommended by current guidelines and expert consensus.^{1,4,5} These targeted drugs have been proven to alleviate symptoms and to improve exercise capacity and hemodynamics compared to placebo by several randomized controlled clinical trials (RCTs)^{6–11} and meta-analyses.^{12–14} However, direct head-to-head comparisons are lacking, and traditional meta-analysis methods do not allow adequate assessment of the comparative effectiveness of all therapies. Therefore, we performed this network meta-analysis of all relevant randomized clinical trials to comprehensively compare the efficacy of targeted drugs for PAH treatment.

Methods

Literature search

Literature comparing targeted drugs for patients with PAH was acquired through searching Medline, EMBASE, and Cochrane Controlled Trials Registry data from January 1990 to December 2015. In order to search and include all relevant studies, we used combinations of various key words, including: pulmonary arterial hypertension, pulmonary hypertension, prostanoids, prostacyclin analogues, ERAs, PDE-5Is, sGCS, epoprostenol, iloprost, beroprost, treprostinil, bosentan, ambrisentan, macitentan, sildenafil, tadalafil, vardenafil, riociguat, and clinical trial. References from reviews and selected articles were further screened.

Inclusion and exclusion criteria

The inclusion criteria were: 1) the study was a RCT; 2) the sample population was definitely diagnosed as PAH according to current guidelines; 3) at least one of the prostanoids (epoprostenol, iloprost, beroprost, and treprostinil), ERAs (bosentan, ambrisentan, and macitentan), PDE-5Is (sildenafil, tadalafil, and vardenafil), sGCS (riociguat), and combination therapy were used, regardless of drug dosage forms; and 4) there was at least 8 weeks clinical follow-up. The following were excluded: 1) non-English language studies; 2) studies with duplicate publication, or different studies from the same sample origin; 3) crossover, 2x2 factorial, and pediatric studies; and 4) studies of sitaxsentan as it has been withdrawn from the market due to severe liver toxicity.

Data extraction and quality assessment

All relevant articles were independently reviewed by two investigators (GXF and ZJJ) to assess the eligibility of the article and abstract with standardized data abstraction forms,

and disagreement was resolved by a third investigator (JXM). The following data were extracted from each included study: study's name, first author, publication date, baseline demographics, and clinical outcomes at follow-up. The quality of the retrieved studies was assessed by Jadad score.¹⁵

Study end points

The primary effective end point of this network meta-analysis was a 6-minute walk distance (6MWD). The secondary end points included mean pulmonary arterial pressure (mPAP), PVR, all-cause mortality, and clinical worsening events. The definitions of clinical worsening events were slightly different across studies, and we used the trial-specific definitions for each study. The safety end point was severe adverse events (SAEs), mainly including PAH-related adverse events and treatment-related adverse events.

Statistical analysis

This network meta-analysis was conducted with Stata software 14.0 (StataCorp, College Station, TX, USA) using the network family of commands.^{16–19} The network meta-analysis was performed to obtain estimates for outcomes of primary and secondary end points, presented as odds ratios (OR) for dichotomous variables or weighted mean differences (WMD) for continuous variables with 95% confidence intervals (CIs). The plot of a network of drugs was a visual representation of the evidence base and offered a concise description of its characteristics. It consisted of nodes representing the drugs being compared and edges representing the available direct comparisons (comparisons evaluated in at least one study) between pairs of drugs.¹⁶ The common heterogeneity was explored in every network by comparing the magnitude of the τ value for the network with an empirical distribution of heterogeneity variances specific to the types of outcome and treatments. An inconsistency model was used only when the P -value of χ^2 test was more than 0.05. Otherwise, a consistency model was performed.^{17,19} A node-splitting method was also used, separating evidence for a particular comparison into direct and indirect evidence, excluding one direct comparison at a time, and estimating the indirect treatment effect for the excluded comparison.¹⁸ All P -values were two-tailed with the statistical significance set at <0.05 .

Results

Eligible studies and patient characteristics

Thirty-two eligible studies^{2,6–11,20–44} including a total of 6,758 patients, were identified in the present network meta-analysis (Figure S1). The quality of each study was good according to the Jadad score.

The baseline characteristics are summarized in Table S1. Four important classes of drugs for PAH (prostanoids, ERAs, PDE-5Is, and sGCS) and combination therapy were compared with placebo and with each other. Networks of eligible comparisons for the primary outcomes (6MWD) are presented in Figure 1. Most enrolled patients were female and in the New York Heart Association/World Health Organization (NYHA/WHO) Functional Class II/III. The predominant etiology was idiopathic and/or familial PAH, and the median period of study follow-up was 16 weeks (range from 8 to 115 weeks).

6MWD

A 6MWD was reported in 32 RCTs. As shown in Figure 2A, there was a statistically significant improvement in 6MWD associated with each of the four drug classes compared with placebo, with a consistency model used ($\tau=8.72$, $\chi^2=7.79$, $P=0.455$). Prostanoids, ERAs, and sGCS showed a comparable 6MWD for PAH patients. Compared with prostanoids, PDE-5Is improved 6MWD by 17.28 m (95% CI: 1.91, 32.65; $P=0.028$), meanwhile combination therapy improved it by 20.94 m (95% CI: 6.94, 34.94; $P=0.003$). Furthermore, combination therapy was superior to ERAs for improving 6MWD by 16.94 m (95% CI: 4.41, 29.47; $P=0.008$).

In 22 studies, oral targeted drugs including oral prostanoids, oral ERAs, oral PDE-5Is, sGCS, and combination therapy were also associated with a more improved 6MWD than placebo, with a consistency model used ($\tau=7.37$, $\chi^2=11.2$, $P=0.130$; Figure 2B). Compared with oral prostanoids, oral PDE-5Is and combination therapy improved 6MWD by

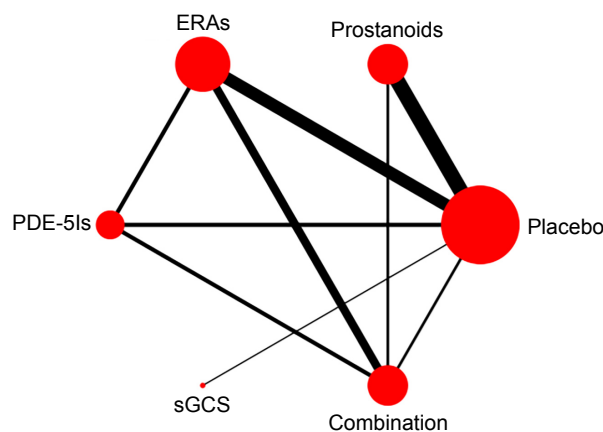


Figure 1 Network of available drugs for PAH.

Note: The size of nodes is proportional to the number of individuals randomized to each treatment, and the thickness of lines to the number of direct comparisons in trials.

Abbreviations: ERAs, endothelin receptor antagonists; PAH, pulmonary arterial hypertension; PDE-5Is, phosphodiesterase 5 inhibitors; sGCS, soluble guanylate cyclase stimulator.

27.53 m (95% CI: 9.29, 45.77; $P=0.003$) and 30.62 (95% CI: 10.99, 50.25; $P=0.002$), respectively.

Mean pulmonary artery pressure and pulmonary vascular resistance

There were significant reduced mPAP found in prostanoids, ERAs, PDE-5Is, sGCS, and combination therapy (17 studies, Figure 3A), with an inconsistency model used ($\tau=0.27$, $\chi^2=8.65$, $P=0.003$). ERAs increased mPAP by 4.27 mmHg (95% CI: 1.03, 7.51; $P=0.010$) than prostanoids, while PDE-5Is had a similar mPAP change compared with prostanoids, ERAs, and sGCS. In addition, combination therapy reduced mPAP by 3.97 mmHg (95% CI: -6.06, -1.88; $P<0.001$) vs prostanoids, 8.24 mmHg (95% CI: -10.71, -5.76; $P<0.001$) vs ERAs, 3.38 mmHg (95% CI: -6.30, -0.47; $P=0.023$) vs PDE-5Is, and 3.94 mmHg (95% CI: -6.99, -0.88; $P=0.012$) vs sGCS.

As shown in Figure 3B ($n=11$ studies), oral targeted drugs could decrease mPAP significantly more than placebo, with no significant heterogeneity found ($\tau=0$). Of note, oral prostanoids, oral ERAs, oral PDE-5Is, and sGCS had approximately comparable mPAP changes with each other. Combination therapy was associated with reduced mPAP by 11.45 mmHg (95% CI: -15.37, -7.53; $P<0.001$) vs prostanoids, 8.24 mmHg (95% CI: -10.69, -5.79; $P<0.001$) vs ERAs, 10.03 mmHg (95% CI: -14.10, -5.95; $P<0.001$) vs PDE-5Is, and 10.57 mmHg (95% CI: -14.71, -6.42; $P<0.001$) vs sGCS.

In 16 studies, targeted drugs including prostanoids, ERAs, PDE-5Is, sGCS, and combination therapy were associated with more reduced PVR than placebo, with a consistency model used, regardless of the forms of drug administration ($\tau=1.71$, $\chi^2=0.36$, $P=0.550$; Figure 3C; $\tau=1.01$, $\chi^2=3.17$, $P=0.075$; Figure 3D). Moreover, the mean values of the reduction in PVR were ~14.7%, 9.8%, 19.2%, 28.2%, and 22.4% for prostanoids, ERAs, PDE-5Is, sGCS, and combination therapy respectively (~ mean 17.5% for single targeted drug), while the values of PVR were increased by 3.4% in terms of placebo. However, prostanoids, ERAs, PDE-5Is, sGCS, and combination therapy were comparable in reduced PVR with each other.

All-cause mortality

All-cause mortality was reported in 24 studies. There were no significant differences in all-cause mortality between prostanoids, ERAs, PDE-5Is, sGCS, combination therapy, and placebo (odds ratio [OR]: 0.59, 95% CI: 0.34, 1.03; $P=0.063$ for prostanoids; OR: 0.65, 95% CI: 0.29, 1.46; $P=0.295$ for ERAs; OR: 0.60, 95% CI: 0.18, 1.97; $P=0.397$ for PDE-5Is; OR: 0.39, 95% CI: 0.07, 2.08; $P=0.271$ for sGCS; OR: 0.54, 95% CI: 0.17, 1.74; $P=0.301$ for combination therapy;

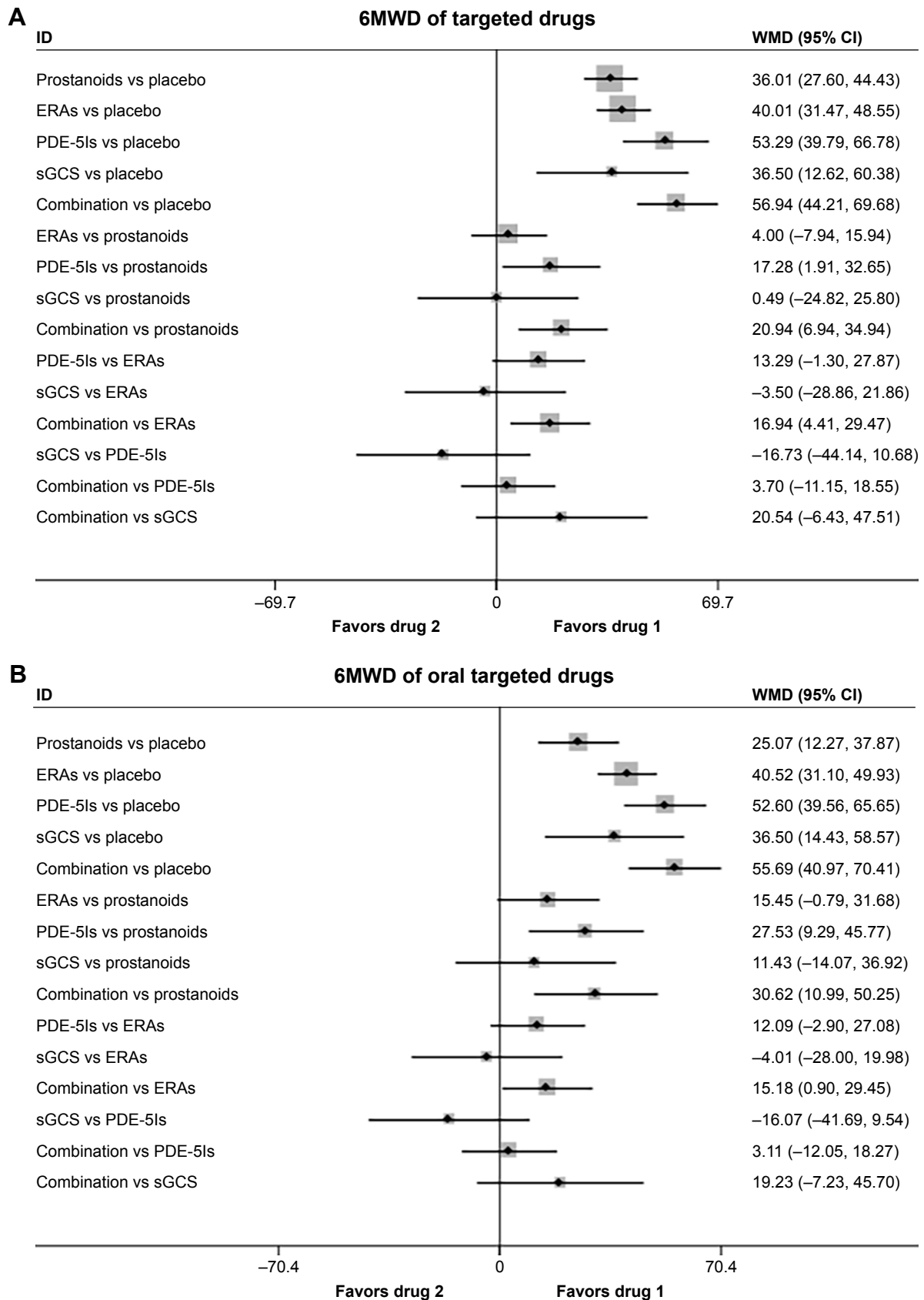


Figure 2 Pooled WMD and 95% CIs determined by network meta-analysis for 6MWD of targeted drugs (A) or oral targeted drugs (B) for PAH. **Abbreviations:** 6MWD, 6-minute walk distance; CI, confidence interval; ERAs, endothelin receptor antagonists; PAH, pulmonary arterial hypertension; PDE-5Is, phosphodiesterase 5 inhibitors; sGCS, soluble guanylate cyclase stimulator; WMD, weighted mean difference.

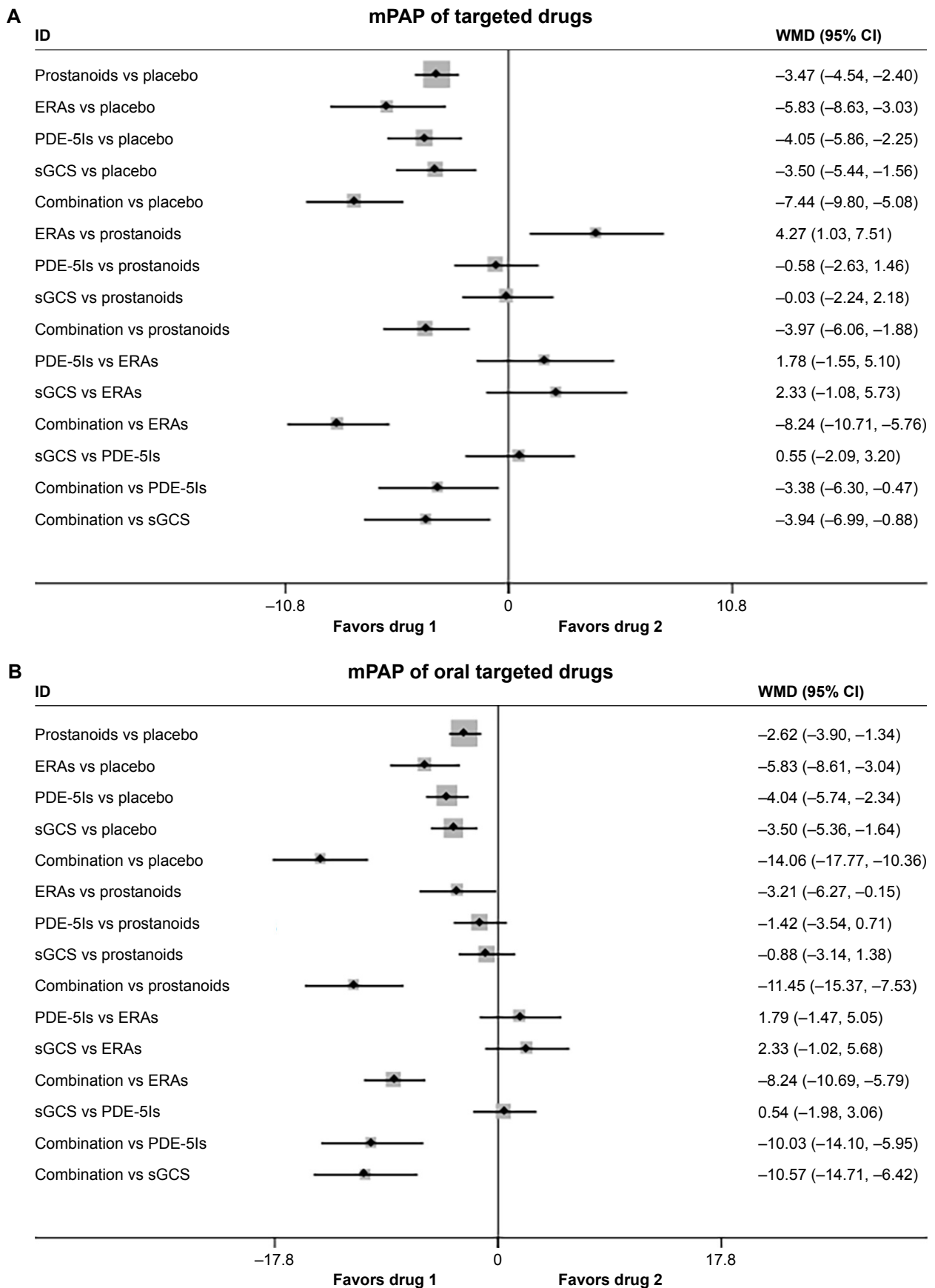


Figure 3 (Continued)

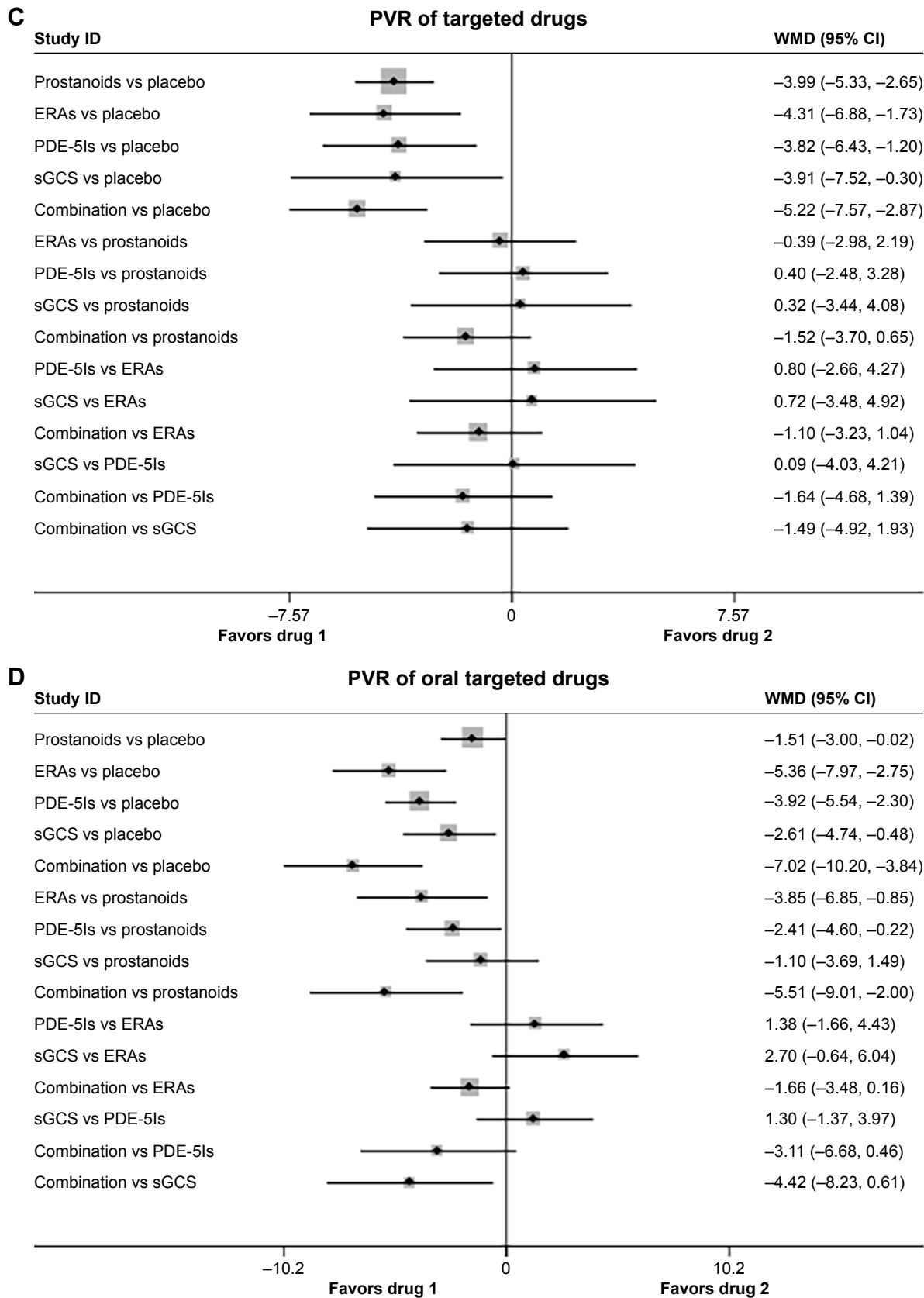


Figure 3 Pooled WMD and 95% CIs determined by network meta-analysis for mean pulmonary artery pressure of targeted drugs (A) or oral targeted drugs (B) for PAH. Pooled WMD and 95% CIs determined by network meta-analysis for pulmonary vascular resistance of targeted drugs (C) or oral targeted drugs (D) for PAH. **Abbreviations:** CI, confidence interval; ERAs, endothelin receptor antagonists; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PDE-5Is, phosphodiesterase 5 inhibitors; PVR, pulmonary vascular resistance; sGCS, soluble guanylate cyclase stimulator; WMD, weighted mean difference.

respectively; Figure 4A), with a consistency model used ($\tau=0.21$, $\chi^2=4.69$, $P=0.320$).

Among the 15 studies, oral prostanoids, oral ERAs, oral PDE-5Is, sGCS, and combination therapy could not decrease all-cause mortality more than placebo (OR: 0.76, 95% CI: 0.33, 1.77; $P=0.528$ for oral prostanoids; OR: 0.70, 95% CI: 0.30, 1.64; $P=0.415$ for oral ERAs; OR: 0.86, 95% CI: 0.23, 3.23; $P=0.824$ for oral PDE-5Is; OR: 0.39, 95% CI: 0.08, 2.01; $P=0.262$ for sGCS; OR: 0.87, 95% CI: 0.22, 3.38; $P=0.840$ for combination therapy, respectively; Figure 4B), with a consistency model used ($\tau=0.14$, $\chi^2=3.06$, $P=0.383$).

Clinical worsening events

In 22 studies, there were significantly lower rates of clinical worsening events in prostanoids, ERAs, PDE-5Is, sGCS, and combination therapy than in placebo (Figure 5A), with a consistency model used ($\tau=0.30$, $\chi^2=8.09$, $P=0.325$). However, prostanoids, ERAs, PDE-5Is, sGCS, and combination therapy were comparable in clinical worsening events with each other.

Oral ERAs, oral PDE-5Is, sGCS, and combination therapy were associated with reduced clinical worsening events than placebo, while oral prostanoids had similar events with placebo (18 studies, Figure 5B), with a consistency

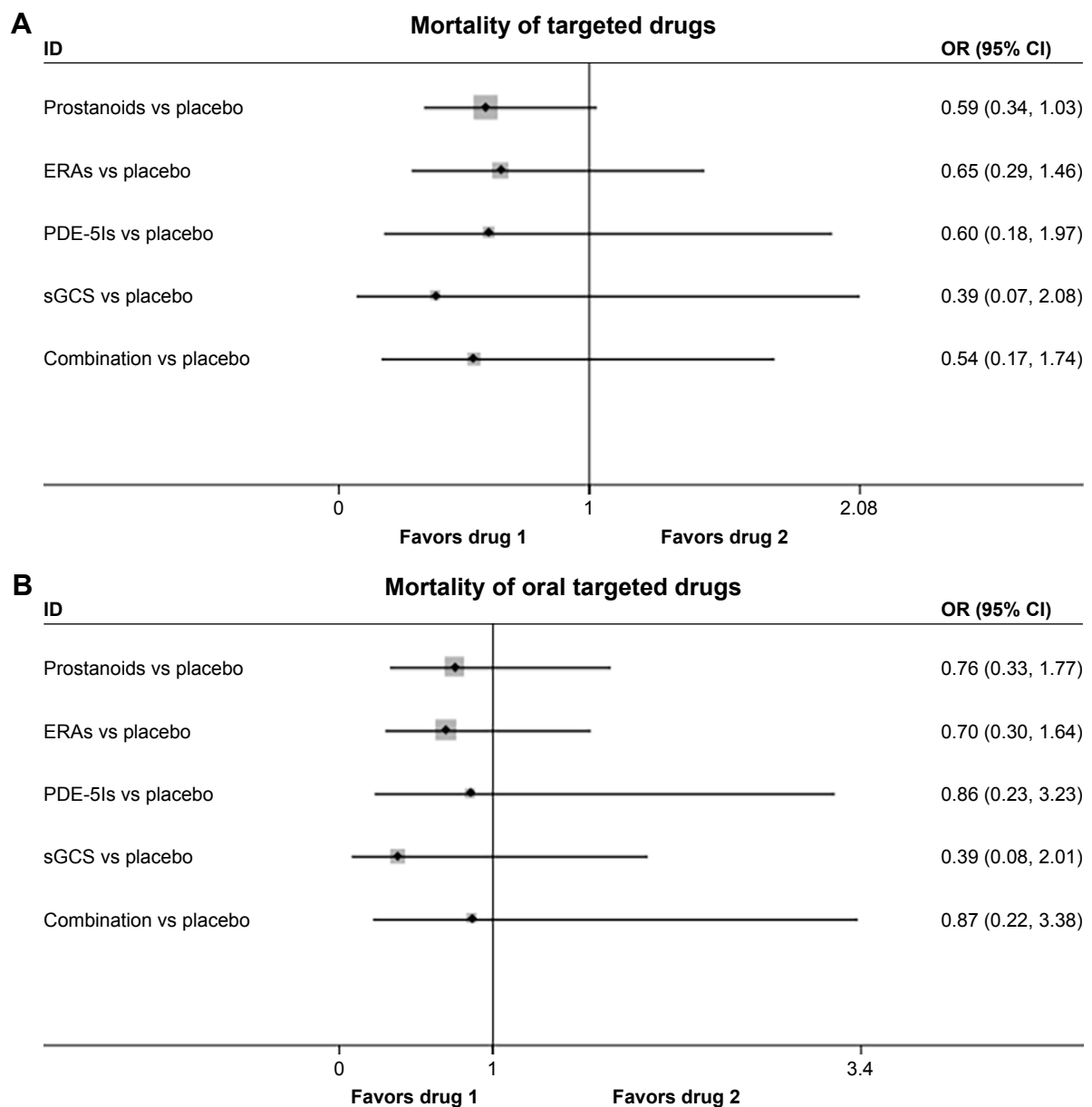


Figure 4 Pooled OR and 95% CIs determined by network meta-analysis for all-cause mortality of targeted drugs (A) or oral targeted drugs (B) for PAH.

Abbreviations: CI, confidence interval; ERAs, endothelin receptor antagonists; OR, odds ratio; PAH, pulmonary arterial hypertension; PDE-5Is, phosphodiesterase 5 inhibitors; sGCS, soluble guanylate cyclase stimulator.

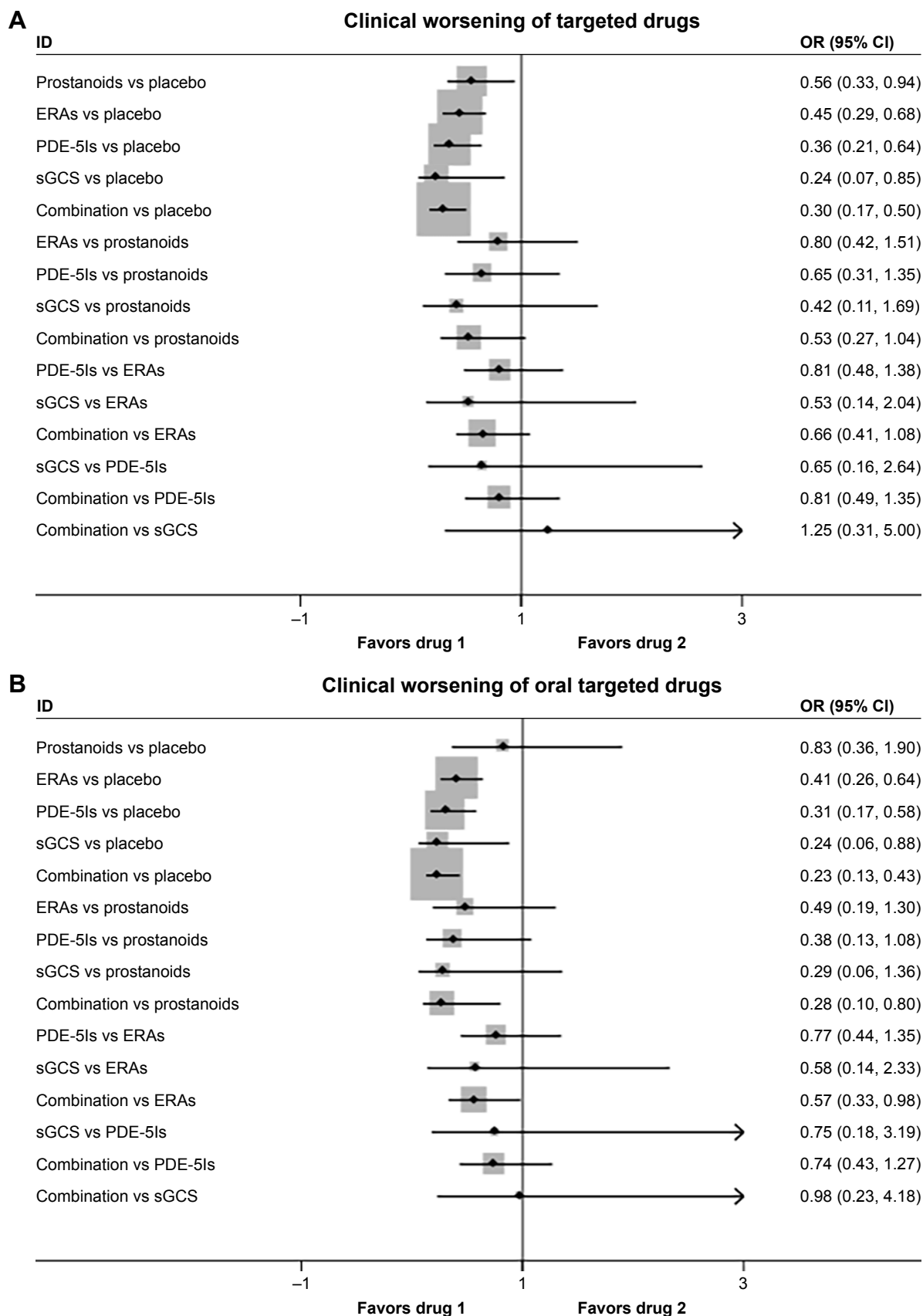


Figure 5 Pooled OR and 95% CIs determined by network meta-analysis for clinical worsening events of targeted drugs (A) or oral targeted drugs (B) for PAH.

Abbreviations: CI, confidence interval; ERAs, endothelin receptor antagonists; OR, odds ratio; PAH, pulmonary arterial hypertension; PDE-5Is, phosphodiesterase 5 inhibitors; sGCS, soluble guanylate cyclase stimulator.

model used ($\tau=0.33$, $\chi^2=4.87$, $P=0.561$). Oral prostanoids, oral ERAs, oral PDE-5Is, and sGCS were comparable with each other. Moreover, combination therapy improved clinical worsening events more than oral prostanoids (OR: 0.28, 95% CI: 0.10, 0.80; $P=0.017$) and oral ERAs (OR: 0.57, 95% CI: 0.33, 0.98; $P=0.044$).

SAEs

A total of 19 studies evaluated the safety of targeted drugs by assessing the SAEs. The incidences of SAEs were similar, and the differences were not statistically significant between

targeted drugs and placebo, with a consistency model used, regardless of the forms of drug administration ($\tau=0.07$, $\chi^2=1.29$, $P=0.863$; Figure 6A; $\tau=0$, $\chi^2=0.63$, $P=0.889$; Figure 6B).

Discussion

To the best of our best knowledge, this was the first network meta-analysis comparing the efficacy of different targeted drugs of PAH. The major findings of the present meta-analysis were as follows: 1) prostanoids, ERAs, PDE-5Is, sGCS, and combination therapy could improve 6MWD,

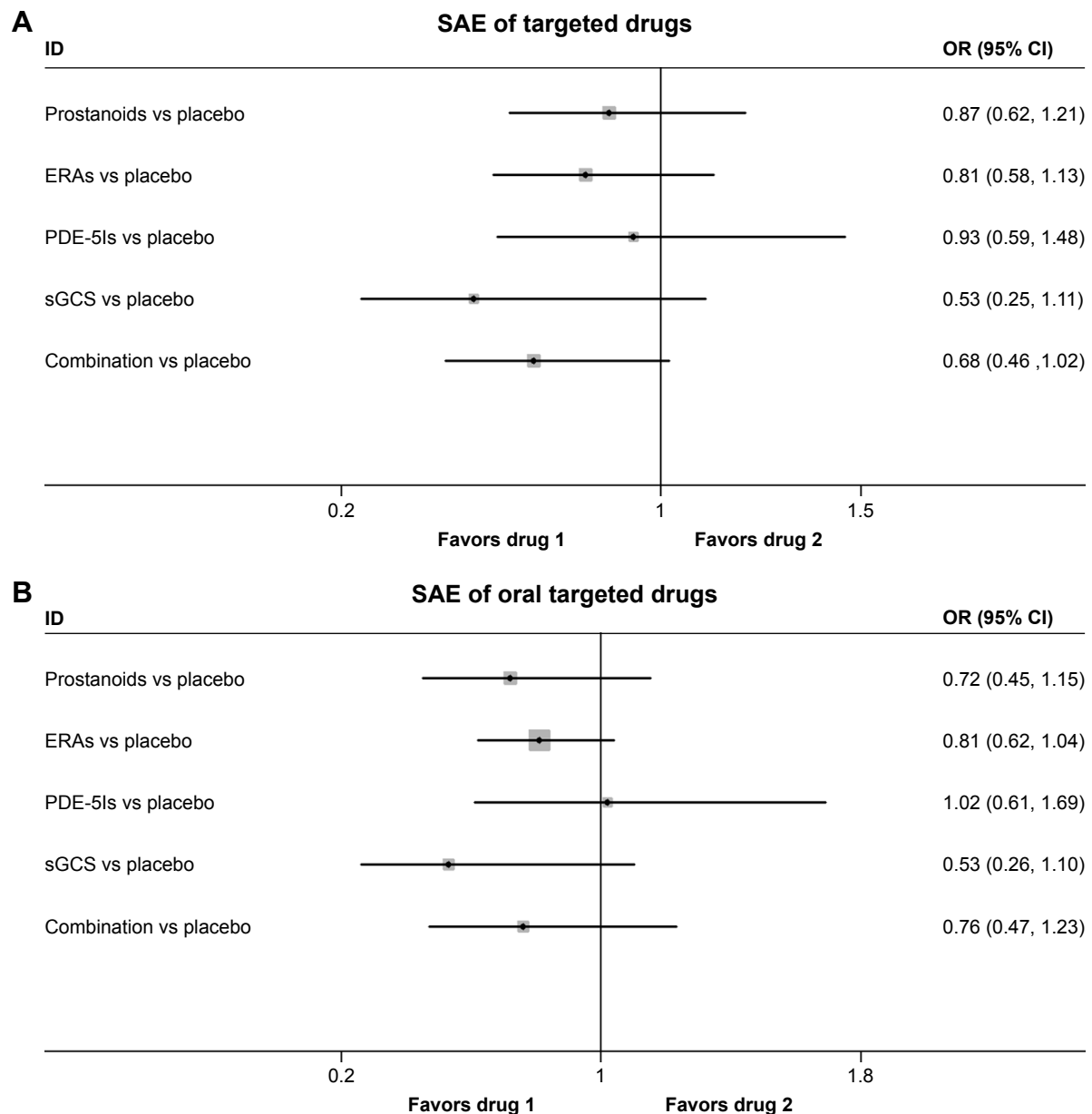


Figure 6 Pooled OR and 95% CIs determined by network meta-analysis for SAEs of targeted drugs (A) or oral targeted drugs (B) for PAH.

Abbreviations: CI, confidence interval; ERAs, endothelin receptor antagonists; OR, odds ratio; PAH, pulmonary arterial hypertension; PDE-5Is, phosphodiesterase 5 inhibitors; SAE, serious adverse event; sGCS, soluble guanylate cyclase stimulator.

mPAP, PVR, and clinical worsening events for patients with PAH, regardless of drug dosage forms; 2) nonoral targeted drugs for PAH patients, including intravenous, inhaled, and subcutaneous forms, were superior to their oral forms; 3) none of the targeted drugs could significantly reduce the risk of all-cause mortality of PAH patients; 4) PDE-5Is might be more superior to prostanoids in increasing 6MWD (primary end point), with a similar result with combination therapy; and 5) PAH patients might benefit mostly from the combination therapy and modestly from prostanoids.

PAH is a hemodynamic and pathophysiologic state, characterized by a progressive increase in pulmonary vascular resistance and loss of pulmonary arterial compliance, which is associated with dyspnea, decreased exercise tolerance, and right heart failure.¹ According to the classification of WHO, PAH could be idiopathic, heritable, or associated with connective tissue disease, congenital heart disease, portal hypertension, and others.⁴⁵ The pathophysiology of PAH is complex, but it involves vasoconstriction and/or vasodilation imbalance, thrombosis, cell proliferation, and remodeling of the pulmonary arterial walls, particularly the molecular mechanisms of endothelial dysfunction factors including nitric oxide, prostacyclin, and endothelin.⁴⁶ Treatment options for PAH have developed rapidly, due to the increasing knowledge of the pathophysiology of this disease, mainly including supportive therapy, psychosocial support, and targeted drug therapy. Classical compounds of targeted drugs cover prostacyclin analogs, ERAs, PDE-5Is, and sGCS. The importance of distinguishing PAH from the other types of pulmonary hypertension is that these specific drugs target the molecular pathways of PAH, which might not be effective in the other forms of pulmonary hypertension. For this reason, these targeted drugs in treating non-PAH pulmonary hypertension are not supported,⁴⁷ except for riociguat (sGCS), which is also approved for patients with chronic thromboembolic pulmonary hypertension. Furthermore, many RCTs^{9-11,31} and meta-analyses¹²⁻¹⁴ have demonstrated that these four types of targeted drugs has been shown to improve hemodynamics, exercise capacity, and possible survival. However, which drug or therapy regimen could provide the best efficacy for PAH patients in these four targeted drugs and their combination therapies remains unanswered. So far, direct head-to-head comparisons of targeted drugs are lacking, and traditional meta-analyses do not allow adequate assessment of the comparative effectiveness of all therapy regimens. Therefore, a comprehensive network meta-analysis enrolling as many relevant studies as possible is warranted to guide clinical practice in the real world.

In the present network meta-analysis, we confirmed that all targeted drugs could improve 6MWD and hemodynamics compared to placebo, in accordance with previous studies,^{13,14} but there was no significant decreased risk of mortality found in these active treatments. Similarly, the meta-analysis by Zhang et al¹⁴ and Lajoie et al⁴⁸ concluded that oral targeted drugs, and even combination therapy, were associated with no sufficient efficacy on survival in the short-term follow-up. Although another meta-analysis by Galiè et al⁴⁹ showed significant reduction in mortality in PAH patients with the targeted drugs, only one study by Brast et al with epoprostenol²¹ provided favorable data in the total of 23 RCTs analyzed. Of note, none of the current studies of targeted drugs were designed to evaluate the mortality of PAH, and most studies showed no survival benefit, which might due to the small sample size and relative short duration. In addition, all studies included safety margins for patients on placebo, who were allowed to switch to active drug or other medications in case of deterioration. Future clinical trials, setting mortality as the primary end point with enough power, should be designed to clarify the real survival value of targeted drugs. Furthermore, we found that combination therapy improved 6MWD and reduced the risk of clinical worsening in PAH patients compared with monotherapy, especially prostanoids. The results were also consistent with previous studies.^{50,51} Overall, we concluded that monotargeted drugs and their combination regimens could improve multiple clinical and hemodynamic outcomes, but they might have no effect on mortality.

Several questions remain unanswered. First, we found none of clinical trials assessing mortality as a primary end point. Surrogate end points, including 6MWD, hemodynamics, and clinical worsening events, have played a critical role in PAH clinical trials because of disease rarity, small population, participant burden, cost, and short follow-up time.⁵² However, it is still unclear whether these surrogate end points could represent the true response to targeted drugs for PAH patients. Second, many agents approved for PAH are always delivered in pill form, for stability and a convenient administration route. Although oral targeted drugs have an important position in the PAH management, they have several limitations and drawbacks, especially in patients in WHO IV category and with severe right heart failure. According to our study, non-oral-targeted drugs, including intravenous, inhaled, and subcutaneous drugs, have improved efficacy compared to oral forms. Third, numerous RCTs and meta-analyses have suggested that sequential combination therapy is effective, meanwhile the recent AMBITION (Ambrisentan and Tadalafil in Patients with Pulmonary

Arterial Hypertension) study showed upfront treatment with tadalafil and ambrisentan was superior to monotherapy.³⁰ Nevertheless, it is still unclear whether upfront combination therapy improves clinical outcomes compared with sequential add-on therapy in cases of unsatisfactory response to initial monotherapy, which is recommended by the guidelines.^{1,5} In addition, various treatment options, apart from targeted drugs, are also available for PAH, including atrial septostomy, pulmonary transplantation, and pulmonary artery denervation (PADN). PADN from single-center studies has been demonstrated to be safe and effective in improving 6MWD and hemodynamics and in reducing PAH-related events and death throughout the 1-year follow-up.^{53,54} Further multicenter RCTs are required to confirm the efficacy of PADN and to explore whether PADN could replace the targeted drugs, given the expensive fee and unclear long-term effect.

Limitations

There are several limitations in the present study. First, different studies used different clinical worsening events definition, which might be an important source of bias. Second, lack of other potential confounding factors, such as etiology of PAH, WHO function, background treatment, and withdrawal due to adverse effects, did not allow us to investigate the detailed impact of targeted drugs on clinical end points and the underlying mechanisms. Third, there was no publication bias evaluation in the present study, which did not affect the interpretation of the results. Fourth, the study about selexipag, a novel prostacyclin receptor agonist, was excluded in present meta-analysis, just because the publication date of GRIPHON study⁵⁵ was later than the predetermined time period in our protocol. Furthermore, there was not enough data about PAH-related SAEs and treatment-related SAEs in most of the enrolled studies. As a result, we could not evaluate the SAEs caused by targeted drugs. Finally, the follow-up period in all enrolled studies was relatively different for comparison of targeted drugs.

Conclusion

In conclusion, this network meta-analysis suggests that all targeted drugs for PAH are associated with improved clinical outcomes, especially combination therapy. However, all these drugs seem to show less favorable effects on survival in the short-term follow-up, suggesting further clinical trials are required.

Acknowledgment

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Author contributions

CSL had the original idea and designed the study. GXF and ZJJ performed the systematic literature search, study identification, data extraction, and quality assessment. JXM and GZ undertook the statistical analysis. WZM, LB, and MWX drafted the article. All authors revised and approved the final report. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

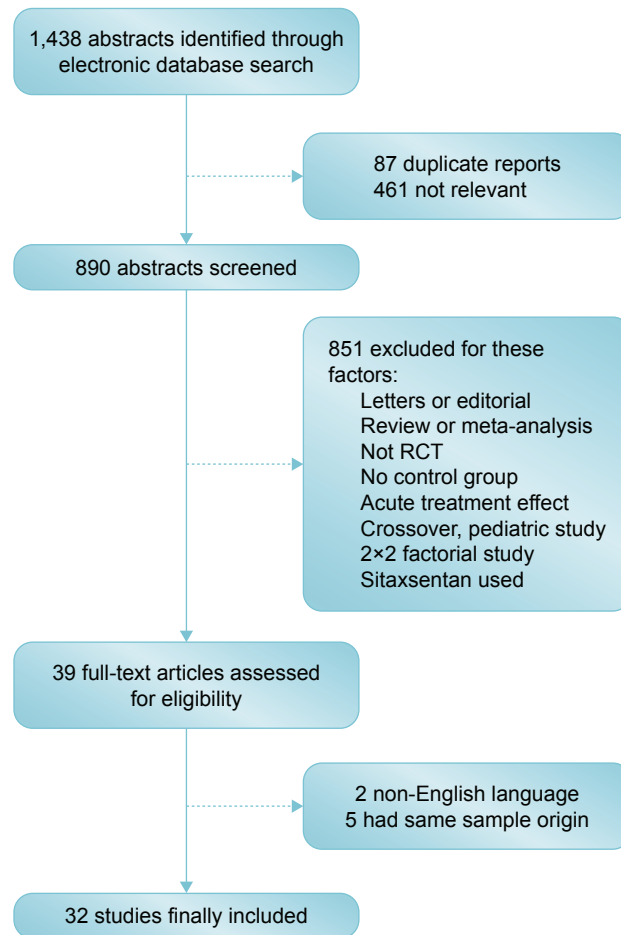


Figure S1 Study selection flow chart.

Abbreviation: RCT, randomized controlled trial.

Table S1 General characteristics of the included studies

Reference/study acronym, year	Treatment (n)	Control (n)	Age (mean age)	Female (%)	Etiology (%)	Period (wk)	Active drug	Comparator	Primary end point	Jadad score
Rubin et al. ¹ 1990	11	12	36	70	IPAH (100)	8	Epoprostenol (IV)	Conventional therapy	TPR	2
AIR. ² 2002	101	102	52	67.5	IPAH (50), APAH (22), CTEPH (28)	12	Iloprost (INH)	Placebo	6MWD, NYHA	4
ALPHABET. ³ 2002	65	65	45	61.5	IPAH (48), APAH (52)	12	Beraprost (PO)	Placebo	6MWD	3
ARIES I. ⁴ 2008	67	67	51	85.8	IPAH (63), APAH (37)	12	Ambrisentan (PO)	Placebo	6MWD	3
ARIES I. ⁴ 2008	68	67	49	83.6	IPAH (63), APAH (37)	12	Ambrisentan (PO)	Placebo	6MWD	3
ARIES2. ⁴ 2008	64	65	51	71.3	IPAH (65), APAH (35)	12	Ambrisentan (PO)	Placebo	6MWD	3
ARIES2. ⁴ 2008	63	65	51	74.2	IPAH (65), APAH (35)	12	Ambrisentan (PO)	Placebo	6MWD	3
Badesch et al. ⁵ 2000	56	55	55	91	APAH (100)	12	Epoprostenol (IV)	Conventional therapy	6MWD	2
Barst et al. ⁶ 1996	41	40	40	72.8	IPAH (100)	12	Epoprostenol (IV)	Conventional therapy	6MWD	2
Barst et al. ⁷ 2003	60	56	42	85.6	IPAH (74), APAH (26)	48	Beraprost (PO)	Placebo	Disease progression	3
BREATHE-1. ⁸ 2002	144	69	48	78.9	IPAH (70), APAH (30)	16	Bosentan (PO)	Placebo	6MWD	3
BREATHE-2. ⁹ 2004	22	11	46	69.7	IPAH (82), APAH (18)	16	Bosentan (PO) + epoprostenol (IV)	Epoprostenol (IV)	TPR	3
BREATHE-5. ¹⁰ 2006	37	17	39	61.1	APAH (100)	16	Bosentan (PO)	Placebo	SpO ₂ , PVR	3
Channick et al. ¹¹ 2001	21	11	51	87.5	IPAH (84), APAH (16)	12	Bosentan (PO)	Placebo	6MWD	4
EARLY. ¹² 2008	93	92	45	69.7	IPAH (61), APAH (39)	24	Bosentan (PO)	Placebo	PVR, 6MWD	4
EVALUATION. ¹³ 2011	44	22	31	82.8	IPAH (61), APAH (39)	12	Vardenafil (PO)	Placebo	6MWD	4
FREEDOM-C. ¹⁴ 2012	174	176	51	87.3	IPAH/FPAH (66), APAH (34)	16	Treprostinil (PO)	Placebo	6MWD	3
FREEDOM-C2. ¹⁵ 2013	157	153	51	77.7	IPAH/FPAH (65), APAH (35)	16	Treprostinil (PO)	Placebo	6MWD	3
FREEDOM-M. ¹⁶ 2013	233	116	41	75.1	IPAH/FPAH (74), APAH (26)	12	Treprostinil (PO)	Placebo	6MWD	3
COMBI. ¹⁷ 2006	19	21	52	77.5	IPAH (100)	12	Iloprost (INH) + bosentan (PO)	Bosentan (PO)	6MWD	3
McLaughlin et al. ¹⁸ 2003	17	9	37	81	IPAH (100)	8	Treprostinil (SC)	Placebo	6MWD	2
STEP. ¹⁹ 2006	34	33	50	79	IPAH (55), APAH (45)	12	Iloprost (INH) + bosentan (PO)	Bosentan (PO)	6MWD	4
PATENT-1. ²⁰ 2013	254	126	51	79	IPAH (61), FPAH (2), APAH (37)	12	Riociguat (PO)	Placebo	6MWD	3
PATENT-1. ²⁰ 2013	63	126	51	79	IPAH (61), FPAH (2), APAH (37)	12	Riociguat (PO)	Placebo	6MWD	3
PHIRST-1. ²¹ 2011	45	45	51	79	IPAH (62), APAH (38)	16	Tadalafil (PO) + bosentan (PO)	Bosentan (PO)	6MWD	3
PHIRST-1. ²¹ 2011	42	45	51	78	IPAH (61), APAH (39)	16	Tadalafil (PO) + bosentan (PO)	Bosentan (PO)	6MWD	3
PHIRST-1. ²¹ 2011	37	37	58	76	IPAH (64), APAH (36)	16	Tadalafil (PO)	Placebo	6MWD	3
PHIRST-1. ²¹ 2011	37	37	57	76	IPAH (64), APAH (36)	16	Tadalafil (PO)	Placebo	6MWD	3
SERAPH. ²² 2005	15	12	43	81	IPAH (88), APAH (12)	16	Sildenafil (PO)	Bosentan (PO)	RVM	4
SERAPHIN. ²³ 2013	250	250	46	75	IPAH (55), FPAH (2), APAH (43)	115	Macitentan (PO)	Placebo	TTCW	3
SERAPHIN. ²³ 2013	242	250	46	77	IPAH (53), FPAH (1), APAH (46)	115	Macitentan (PO)	Placebo	TTCW	3
SIMONNEAU. ²⁴ 2002	233	236	44	81	IPAH (58), APAH (42)	12	Treprostinil (SC)	Placebo	6MWD	4
PACES. ²⁵ 2008	133	134	48	80	IPAH (79), APAH (21)	16	Sildenafil (PO) + epoprostenol (IV)	Epoprostenol (IV)	6MWD	4
SUPER. ²⁶ 2005	69	70	48	76	IPAH (62), APAH (38)	12	Sildenafil (PO)	Placebo	6MWD	4
SUPER. ²⁶ 2005	67	70	50	76	IPAH (62), APAH (38)	12	Sildenafil (PO)	Placebo	6MWD	4
SUPER. ²⁶ 2005	71	70	48	80	IPAH (63), APAH (37)	12	Sildenafil (PO)	Placebo	6MWD	4
TRIUMPH. ²⁷ 2010	115	120	53	81	IPAH/FPAH (56), APAH (44)	12	Treprostinil (INH)	Placebo	6MWD	3
TRUST. ²⁸ 2010	30	14	32	61	IPAH/FPAH (95), APAH (5)	12	Treprostinil (IV)	Placebo	6MWD	3
AMBITION. ²⁹ 2015	253	126	54	76	IPAH (53), FPAH (3), APAH (44)	24	Ambrisentan (PO) + tadalafil (PO)	Ambrisentan (PO)	Clinical failure	4
AMBITION. ²⁹ 2015	253	121	55	77	IPAH (52), FPAH (3), APAH (45)	24	Ambrisentan (PO) + tadalafil (PO)	Tadalafil (PO)	Clinical failure	4
Zhuang et al. ³⁰ 2014	60	64	51	79	IPAH (63), APAH (37)	16	Tadalafil (PO) + ambrisentan (PO)	Ambrisentan (PO)	6MWD	3
PATENT PLUS. ³¹ 2015	12	6	59	67	IPAH (50), APAH (50)	12	Riociguat (PO) + sildenafil (PO)	Sildenafil (PO)	Supine SBP	4
COMPASS-2. ³² 2015	159	175	54	76	IPAH (64), FPAH (2), APAH (34)	16	Bosentan (PO) + sildenafil (PO)	Sildenafil (PO)	TTCW	3

Abbreviations: 6MWD, 6-minute walk distance; APAH, acquired pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; FPAH, familial pulmonary arterial hypertension; INH, inhaled; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; PO, per os [orally]; SC, subcutaneous; TTCW, time to clinical worsening.

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