Research Article

Pulmonary Circulation

Efficacy and safety of oral targeted therapies in pulmonary arterial hypertension: a meta-analysis of randomized clinical trials

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Abstract

Oral targeted therapies play an important role in the treatment of pulmonary arterial hypertension (PAH). Several new oral agents have emerged for PAH in recent years. However, whether they provide a survival advantage is still not clear. This meta-analysis aimed to assess the efficacy and safety of oral targeted therapies, especially on predefined clinical worsening events. Trials were searched in the Cochrane Library, EMBASE, and PUBMED databases through June 2018. We calculated risk ratios for dichotomous data and weighted mean differences with 95% confidence intervals (CI) for continuous data. Twenty-five trials with a total of 6847 participants were included in the meta-analysis. Oral targeted therapies were associated with significant risk reduction in clinical worsening compared with placebo (relative risk [RR] 0.64; 95% CI = 0.58–0.70; $P < 0.001$). This reduction in risk was driven by reduction in non-fatal endpoints, including PAH-related admissions to hospital (RR = 0.66; 95% CI = 0.56–0.76; $P < 0.001$), treatment escalation (RR = 0.43; 95% CI = 0.28–0.66; $P < 0.001$), and symptomatic progression (RR = 0.55; 95% CI = 0.48–0.64; $P < 0.001$), but not by reduction of mortality (RR = 0.87; 95% CI = 0.68–1.12; $P = 0.215$). Oral targeted therapies were also associated with improvement in 6-min walk distance (26.62 m; 95% CI = 20.54–32.71; $P < 0.001$) and World Health Organization functional class (RR = 1.36; 95% CI = 1.20–1.54; $P < 0.001$). The results of this meta-analysis showed the benefits of oral treatments on clinical worsening events in PAH. However, these oral agents did not show any survival benefit in the short-term follow-up.

Keywords

pulmonary arterial hypertension, meta-analysis, randomized controlled trials

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Introduction

Pulmonary arterial hypertension (PAH) is a devastating, progressive disease, manifested as a progressive increase in pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP) which ultimately leads to limited exercise capacity, right heart failure, and eventually death.[1] In the past 20 years, several specific drugs targeting endothelial dysfunction have emerged in the era of PAH treatment. Although the survival rate has greatly improved compared with that in national registry study in 1991,[2] the prognosis is still poor.[3] Current approved PAH-specific therapies include five pharmacological classes of drugs: prostacyclin analogues; endothelial receptor antagonists (ERAs); phosphodiesterase type 5 inhibitors (PDE-5Is); soluble guanylate cyclase stimulators (sGCs); and a selective prostacyclin receptor agonist.[1]

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Previous clinical trials have confirmed the efficiency of oral agents in alleviating the symptoms of PAH and improving the exercise capacity and hemodynamics.[4] Combination therapy with two oral agents could further improve exercise capacity, functional class (FC), and hemodynamic status compared with monotherapy.[5–9] However, because of the limited improvement of exercise capacity by medication, short duration, and the small size of the individual studies, whether these oral agents have a survival benefit is still controversial.[10] Meta-analyses have suggested that oral pulmonary vasodilators are beneficial in decreasing clinical worsening and increasing 6-min walk distance (6MWD), but do not show any survival benefits.[11,12] However, there have been several new oral agents available for PAH treatment in recent years, including riociguat, macitentan, and selexipag. These new oral agents have demonstrated significant benefits in the treatment of PAH.[13–15] Therefore, in the era of many new oral agents, a new meta-analysis focusing on survival advantage is still needed in this area.

In the present study, we performed a new meta-analysis on PAH therapy with all oral targeted drugs,[5–9,13–31] including data from six recently published randomized controlled trials (RCTs),[5–8,13,16] with the aim of determining whether the benefits of oral targeted therapies on exercise capacity and hemodynamics are translated into improvement of clinical outcomes, particularly overall mortality and morbidity.

Methods

This meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[32]

Protocol and registration

The study protocol was not published online.

Eligibility and exclusion criteria

The inclusion criteria were as follows: (1) randomized double-blind placebo-controlled trials; (2) patients definitely diagnosed as PAH according to the guideline;[1] (3) any study on oral targeted therapies including oral prostanoids, ERAs, PDE-5Is, prostacyclin receptor agonists, and sGCS; (4) adult PAH patients who had a follow-up of $\geq$8 weeks; (5) they reported one of the primary and secondary outcomes of interest. The exclusion criteria were as follows: (1) any study on intravenous, inhaled, or subcutaneous targeted therapies; (2) PAH diagnosed by echocardiography; (3) studies of newborns or children with PAH; and (4) acute hemodynamic studies. In addition, as sitaxsentan was withdrawn from the market due to liver toxicity, studies of sitaxsentan were excluded.

Information source and search

We systematically searched PubMed, EMBASE, the Cochrane Library, previous reviews, and reference lists from identified articles with the strategy of using the term "pulmonary hypertension" through to June 2018. In MEDLINE and EMBASE, this strategy was combined with an RCT filter. No language restriction was applied. We included studies published in abstract form if sufficient information was available to assess methodologic quality. When the same population was reported in several publications, we retained only the most informative article or complete study to avoid duplication of information.

Study selection

All literature searches were independently reviewed by two reviewers (YGZ and HM) to identify relevant trials that met the inclusion criteria. Disparities were resolved by discussion. The concordance analyses suggested high concordance between the two reviewers (Kappa = 0.83; $P < 0.05$). The selected articles were further examined to determine if they contained relevant information.

Data collection process and data items

We applied a predefined standardized form from the Cochrane Handbook to this process. Each reviewer extracted the data from included studies independently. Discrepancies were resolved by discussion between the two reviewers. If consensus could not be achieved, a third independent reviewer would be involved in the decision. In event-driven studies, we extracted data on the first event only. For incompletely presented data, we contacted the study investigators to request the data.

Quality assessment

Quality assessment of each study was assessed using the Jadad scale,[33] which graded studies according to the random assignment, double blinding, and the flow of patients. The studies with low Jadad scores were excluded (Jadad scale < 3).

Summary measures

Clinical worsening is a composite endpoint generally defined as a combination of death, admission to hospital, lung transplantation, treatment escalation including initiation of prostaglandins, and symptomatic progression.[12,34] The primary aim of our analysis was to assess whether oral targeted therapies reduced the risk of clinical worsening in PAH. Whenever possible, we also assessed if this outcome was homogeneous among subgroups of PAH-specific therapy classes. The additional secondary parameters included all-cause mortality, lung transplantation, admission to

hospital, treatment escalation, World Health Organization (WHO) FC improvement, symptomatic progression, as well as exercise capacity (6MWD). Treatment discontinuation was used to assess the safety of drugs.

Synthesis of results and bias analysis

We calculated relative risks (RR) for dichotomous data and weighted mean differences (WMD), with 95% confidence intervals (CI) for continuous data. All tests were two-tailed and a P value < 0.05 was deemed statistically significant. For the multi-armed trial (AMBITION), we split the data between two treatment-control comparisons by splitting the control group and halving the sample sizes. In those multi-dose trials including BREATHE-1, SUPUR-1, PHIRST, ARIES, PATENT-1, and SERAPHIN, we combined all active arms into one and compared it with the control group. For exercise capacity (as assessed by 6MWD), we computed the effect size of the tested drugs by using the WMD, which was calculated after subtracting from baseline the end-study values in treated and control groups. In studies reporting the median and quartiles, mean and standard deviation (SD) were estimated from median and quartiles.[35] When only baseline/end of study data were presented, mean changes as well as their associated SD were calculated according to the formula described in the Cochrane Handbook.[36]

The Cochran Q test and I-squared were used to assess the magnitude of effect size heterogeneity. Study-level heterogeneity was considered to exist if the I-squared was > 50%. When the research effect size was homogeneous, the data were analyzed using a fixed effect model (Mantel–Haenszel method), otherwise the random effect model (DerSimonian–Laird method) for combined effect size was applied for estimation. Publication bias was assessed with funnel plots by Eggers' regression test[37] and Begg's rank correlation test.[38] If publication bias was indicated, we further conducted a trim and fill analysis.[39] All analyses were performed using Stata 12.0 (Stata Corporation, College Station, TX, USA).

Results

Study selection

A total of 5929 studies were identified using the aforementioned search methods, among which 24 articles met the inclusion criteria (Fig. 1).[5–9,13–31] As ARIES-1 and ARIES-2 were reported in one article, 25 RCTs were included.[24] Among them, 11 assessed the effects of ERAs, seven assessed the effects of PDE-5Is, five assessed the effects of prostacyclin analogues, two assessed the effects of prostacyclin receptor agonists, and one assessed the effects of sGCs. The AMBITION study investigated both the effects

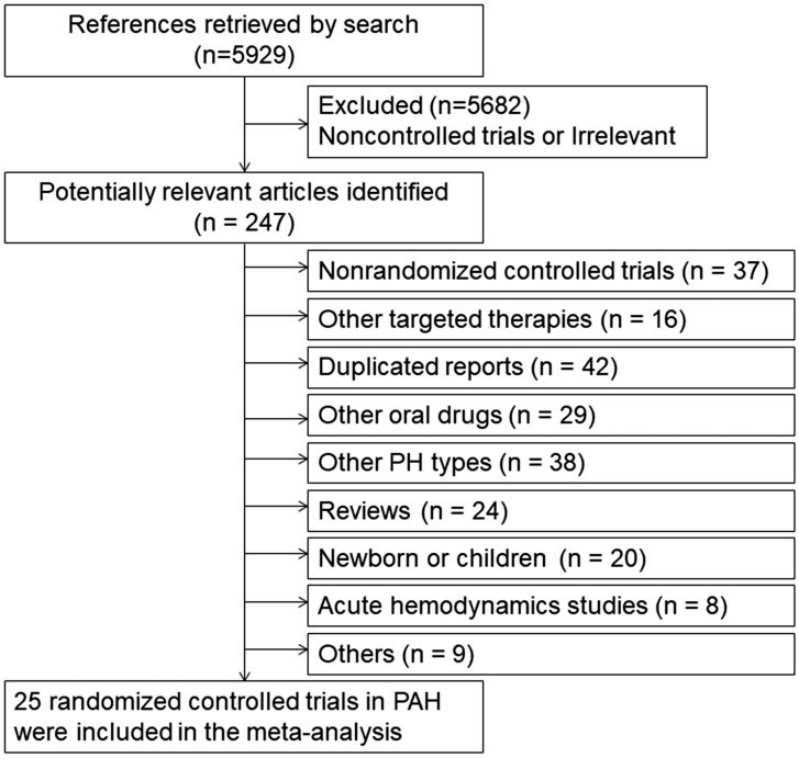

Fig. 1. Flowchart of study selection.

of ambrisentan or tadalafil as add-on therapy, while compared with monotherapy.[7] The PATENT-PLUS study was not included in this meta-analysis, as combination of riociguat and sildenafil was not recommended in the guideline.[40] In addition, Iversen's study was excluded because of its cross-over design and low Jadad scale (Jadad scale = 2).[41]

Study characteristics

The characteristics of included trials were summarized in Table 1. A total of 6847 patients were enrolled in the 25 RCTs, with 4027 patients in the oral targeted treatment group and 2820 patients in the placebo group. The duration of the different trials was in the range of 12–165 weeks (median = 16 weeks). Of these 25 studies, five were the long-term and event-driven trials using a composite primary endpoint of morbidity and mortality.[6,7,13,14,28] In 23 trials, the predominant etiology was idiopathic and/or familial PAH. Two trials included exclusively patients with Eisenmenger's syndrome.[16,25] Most of the participants were in New York Heart Association (NYHA)/WHO FC II/III; only one study included exclusively NYHA/WHO FC II patients.[23] The 6MWD alone or in combination was the primary endpoint in 17 trials; additional primary endpoints included clinical worsening in five trials [6,7,13,14,28] and PVR in three trials.[9,25,27]

Pooled analysis of clinical worsening

Clinical worsening, assessed in 20 studies, was the primary outcome in five studies[6,7,13,14,28] and the secondary outcome in 15 studies (Supplementary Table 1).[5,8,9,15–24,26,29] In the other five trials that did not report this endpoint as defined, we extracted the data according to the definition.[16,25,27,30,31] If the study did not report all the relevant endpoints of clinical worsening, we combined the reported endpoints together as clinical worsening.

Clinical worsening occurred in 18.9% (1293/6847) participants: 14.6% (587/4027) in the oral targeted treatment group and 25.0% (706/2820) in the placebo group (Fig. 2, Table 2). The cumulative RR estimate of clinical worsening was a significant reduction of 36% (RR = 0.64; 95% CI = 0.58–0.70; $P < 0.001$). The overall heterogeneity suggested moderate heterogeneity ($I^2 = 36.4\%$; $P = 0.034$) and data were assessed by a fixed effects model. Similar results were noted if we used a random effects model (RR = 0.59; 95% CI = 0.51–0.70) or excluded five studies which did not report clinical worsening (RR = 0.64; 95% CI = 0.58–0.70). Furthermore, subgroup analyses according to the drug classes suggested that ERAs, PDE-5Is, sGCs, and prostacyclin receptor agonists produced beneficial effects on reducing clinical worsening. However, oral prostanoids only showed a trend toward reducing clinical worsening but did not have statistical significance (Fig. 2).

With regard to publication bias, Begg's rank correlation test indicated no publication bias ($P = 0.440$), but Egger's linear regression test indicated possible publication bias for the association ($P = 0.011$) (Fig. 3). However, when we excluded the four studies with the logRR far from the middle line in the funnel plot, this resulted in a similar RR for clinical worsening (RR = 0.66; 95% = CI 0.60–0.72; $P < 0.001$).

Other outcomes

A meta-analysis of other outcomes was summarized in Table 2. Overall mortality (Fig. 4) in the 25 trials was 3.27% (224/6847 patients). Mortality in the treatment group and placebo group was 3.03% (122/4027 patients) and 3.62% (102/2820 patients), respectively. Oral targeted therapies were not associated with reduced all-cause mortality (RR = 0.87; 95% CI = 0.68–1.12; $P = 0.215$) and no heterogeneity ($I^2 = 0.0\%$; $P = 0.624$) was apparent among studies (Table 2). Moreover, oral targeted treatment significantly improved exercise capacity assessed by 6MWD. The weighted mean improvement of 6MWD assessed by the random effects model in patients allocated to experimental treatments was 26.62 m (range = −4.7–76 m; 95% CI = 20.54–32.71; $P < 0.001$) (Fig. 5).

Monotherapy versus combination therapy sub-analysis

Of the 25 trials, ten assessed the effects of PAH-specific monotherapy,[18,20,24–26,28–31] nine assessed the effects of combination therapy,[5–9,17,19,22,27] and the other six included both treatment-naïve and background vasodilator-treated patients.[13–16,21,23] A meta-analysis of ten studies with only treatment-naïve patients revealed that monotherapy was associated with a significant reduction in clinical worsening (RR = 0.46; 95% CI = 0.34–0.62; $P < 0.001$). It was associated with a non-significant reduction in mortality (RR = 0.56; 95% CI = 0.32–1.00; $P = 0.051$), but significantly reduced PAH-related admissions to hospital (RR = 0.46; 95% CI = 0.30–0.73; $P = 0.001$) and symptomatic progression (RR = 0.31; 95% CI = 0.17–0.55; $P < 0.001$), improved WHO FC (RR = 1.68; 95% CI = 1.32–2.14; $P < 0.001$), and increased the 6MWD by 41.1 m. Moreover, monotherapy did not significantly increase the incidence of treatment discontinuation (RR = 1.59; 95% CI = 0.94–2.69; $P = 0.082$).

Regarding the nine trials with only background vasodilator-treated patients, a total of 2062 patients were enrolled to evaluate combination therapy versus monotherapy. A meta-analysis of these nine studies revealed that combined therapy did not show any benefit in reducing mortality (RR = 0.77; 95% CI = 0.49–1.22; $P = 0.268$) and improving WHO FC (RR = 1.17; 95% CI = 0.98–1.39; $P = 0.075$), but it reduced clinical worsening (RR = 0.67; 95% CI = 0.57–0.80; $P < 0.001$), treatment escalation (RR = 0.14; 95% CI = 0.04–0.47; $P = 0.001$), symptomatic progression (RR = 0.64; 95% CI = 0.49–0.83; $P < 0.001$), and increased the 6MWD by 18.7 m. Combination therapy was associated

Table 1. Randomized controlled trial characteristics.

First author (official acronym)	Publication year	Participants (n)	Active drug	Comparator	Study period (weeks)	Etiology (%)	Primary endpoint	Jadad scale
Channick et al.[31]	2001	32	Bosentan	Placebo	12	IPAH (84), APAH (16)	6MWD	4
Rubin et al.[29] (BREATHE-1)	2002	213	Bosentan	Placebo	16	IPAH (70), APAH (30)	6MWD	3
Humbert et al.[27] (BREATHE-2)	2004	33	Epoprostenol + bosentan	Epoprostenol + placebo	16	IPAH (82), APAH (18)	TPR	3
Galiè et al.[25] (BREATHE-5)	2006	54	Bosentan	Placebo	16	APAH (100)	SPO2&PVR	4
Galiè et al.[24] (ARIES-1)	2008	201	Ambrisentan	Placebo	12	IPAH (63), APAH (37)	6MWD	4
Galiè et al.[24] (ARIES-2)	2008	192	Ambrisentan	Placebo	12	IPAH (65), APAH (35)	6MWD	4
Galiè et al.[23] (EARLY)	2008	185	Bosentan*	Placebo*	24	IPAH (61), APAH (39)	6MWD&PVR	5
Pulido et al.[14] (SERAPHIN)	2013	742	Macitentan*	Placebo*	96*	IPAH/FPAH (56), APAH (44)	Clinical worsening	3
Galiè et al.[7] (AMBITION)	2015	500	Tadalafil + ambrisentan	Tadalafil/ambrisentan+ placebo	74*	IPAH/FPAH (56), APAH (44)	Clinical worsening	5
McLaughlin et al.[6] (COMPASS-2)	2015	334	Sidenafil + bosentan	Sidenafil + placebo	165*	IPAH/FPAH (65), APAH (35)	Clinical worsening	3
Galie et al.[16] (MAESTRO)	2017	226	Macitentan*	Placebo*	16	APAH (100)	6MWD	3
Galiè et al.[26] (SUPER)	2005	277	Sildenafil	Placebo	12	IPAH (63), APAH (37)	6MWD	4
Simonneau et al.[22] (PACES)	2008	265	Epoprostenol + sidenafil	Epoprostenol + placebo	16	IPAH (79), APAH (21)	6MWD	4
Galiè et al.[21] (PHIRST)	2009	405	Tadalafil*	Placebo*	16	IPAH/FPAH (61), APAH (39)	6MWD	3
Jing et al.[20] (EVALUATION)	2011	64	Vardenafil	Placebo	12	IPAH (61), APAH (39)	6MWD	4
Zhuang et al.[8]	2014	124	Ambrisentan + tadalafil	Ambrisentan + placebo	16	IPAH (63), APAH (37)	6MWD	3
Vizza et al.[5]	2017	103	Bosentan + sidenafil	Bosentan + placebo	12	IPAH/FPAH (65), APAH (35)	6MWD	3
Galie et al.[30] (ALPHABET)	2002	130	Beraprost	Placebo	12	IPAH (48), APAH (52)	6MWD	3
Barst et al.[28]	2003	116	Beraprost	Placebo	36	IPAH (74), APAH (26)	Clinical worsening	3
Tapson et al.[19] (FREEDOM-C)	2012	350	ERA/PDE-5I + treprostinil	ERA/PDE-5I + placebo	16	IPAH/FPAH (66), APAH (34)	6MWD	3
Jing et al.[18] (FREEDOM-M)	2013	349	Treprostinil	Placebo	12	IPAH/FPAH (74), APAH (26)	6MWD	3
Tapson et al.[17] (FREEDOM-C2)	2013	310	ERA/PDE-5I + treprostinil	ERA/PDE-5I + placebo	16	IPAH/FPAH (65), APAH (35)	6MWD	3
Ghofrani et al.[15] (PATENT-1)	2013	443	Riociguat*	Placebo*	12	IPAH/FPAH (63), APAH (37)	6MWD	3
Simonneau et al.[9]	2012	43	ERA/PDE-5I + selexipag	ERA/PDE-5I + placebo	17	IPAH/FPAH (78), APAH (22)	PVR	5
Sitbon et al.[13] (GRIPHON)	2015	1156	Selexipag*	Placebo*	67†	IPAH/FPAH (58), APAH (42)	Clinical worsening	3

*These six studies included both treatment-naïve and background vasodilator-treated patients.

†The periods indicate the mean duration between the treatment group and the placebo group.

APAH, associated pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; 6MWD, 6-min walk distance; VO_2, peak oxygen consumption; TPR, total pulmonary resistance; SPO_2, systemic pulse oximetry; PVR, pulmonary vascular resistance; ERA, endothelin receptor antagonist; PDE-5I, phosphodiesterase type 5 inhibitor.

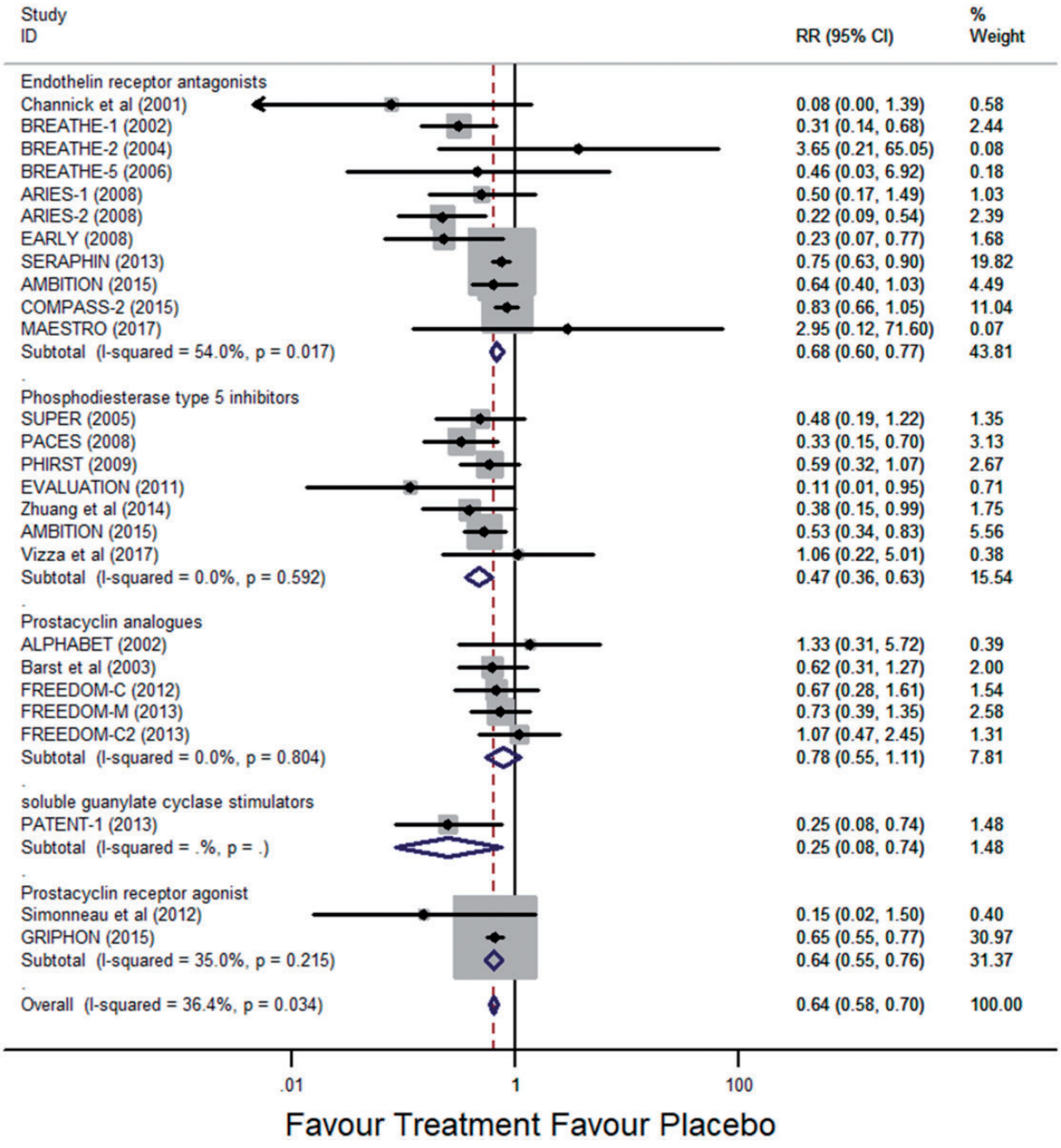

Fig. 2. Reduction of clinical worsening in oral targeted treatment groups compared with the placebo groups. Data were analyzed with the fixed effects model.
RR, relative risk.

with a significant increase in the incidence of withdrawal due to adverse effects (RR = 1.60; 95% CI = 1.23–2.07; $P < 0.001$).

Discussion

This meta-analysis compared the clinical outcomes of oral targeted treatments versus placebo in a large population of patients with PAH between 2001 and 2018. In this study, we included five classes of oral drugs which were available for PAH treatment in recent years. The results demonstrated that oral targeted therapies significantly reduced the incidence of clinical worsening but showed no positive efficacy on survival. Compared with placebo, oral agents also reduced the incidence of PAH-related admissions to hospital, treatment escalation, symptomatic progression, and improved exercise capacity (measured by 6MWD and WHO FC improvement). However, oral targeted therapies were associated with a higher incidence of withdrawal due to adverse effects.

Table 2. Primary and secondary outcomes.

	Studies (n)	Proportion of events (%)			Effect size		Homogeneity	
		Treatment	Placebo	Total	RR (95% CI)	*P*	I^2	*P*
Primary outcome								
Clinical worsening[5–9,13–31]	25	587/4027 (14.6)	706/2820 (25.0)	1293/6847 (18.9)	0.64 (0.58–0.70)	<0.001	36.4	0.034
Secondary outcomes as first event of clinical worsening								
All-cause mortality [5–9,13–31]	25	122/4027 (3.0)	102/2820 (3.6)	224/6847 (3.3)	0.87 (0.68–1.12)	0.292	0.0	0.62
Admission to hospital[5–8,13–15,18–24,26,29,30]	18	270/3566 (7.6)	300/2427 (12.4)	570/5993 (9.5)	0.66 (0.56–0.76)	<0.001	31.6	0.093
Lung transplantation[6,13,14,18,19,22,31]	7	3/1787 (<1)	4/1441 (<1)	7/3228 (<1)	0.68 (0.17–2.66)	0.582	0.0	0.899
Treatment escalation[8,13–15,17,21,22,24,26,28,29]	12	33/2729 (1.2)	55/1715 (3.2)	88/4444 (2.0)	0.43 (0.28–0.66)	<0.001	14.7	0.304
Symptomatic progression[5–9,13–15,17–19,21,23–25,28,30,31]	19	285/3441 (8.3)	364/2411 (15.1)	649/5852 (11.1)	0.55 (0.48–0.64)	<0.001	18.0	0.230
Other secondary outcomes								
All-cause mortality[5–9,13–31]*	25	264/4027 (6.2)	240/2820 (8.5)	504/6847 (7.4)	0.88 (0.75–1.04)	0.125	0.0	0.850
FC improvement[5–9,14–16,19,20,23–31]	20	636/2598 (24.5)	312/1752 (17.8)	948/4350 (21.8)	1.36 (1.20–1.54)	<0.001	20.7	0.193
FC worsening[5–9,13,15,19–21,23–25,28,29,31]	17	253/2599 (9.7)	304/1898 (16.0)	557/4497 (12.4)	0.53 (0.40–0.72)	<0.001	51.4	0.006
Treatment discontinuation[5–9,13–31]	25	374/4027 (9.3)	198/2820 (7.0)	572/6847 (8.4)	1.42 (1.20–1.66)	0.000	47.3	0.007

*All deaths, including those as first event of clinical worsening and those after censoring for another event.
RR, rate ratio; CI, confidence interval; PAH, pulmonary arterial hypertension; FC, functional class.

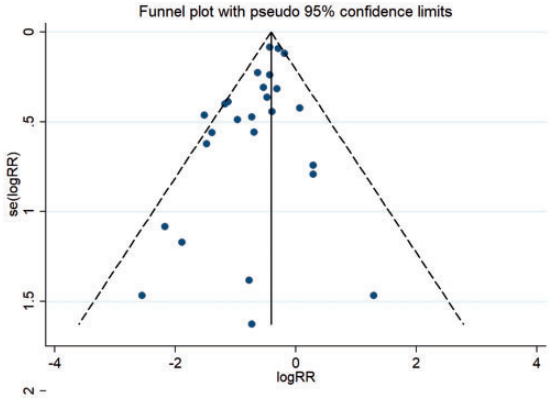

Fig. 3. Publication bias of the meta-analysis. Studies were plotted with RRs along the horizontal axis and SE of the RR along the vertical axis. RR, risk ratio; SE, standard error.

Clinical worsening is a composite endpoint, which can truly reflect the clinical status and degree of disease progression. It has been used as the primary endpoint of morbidity and mortality in several recently published studies.[6,7,13,14] We noted a reduction in the overall risk of clinical worsening of 36% for patients assigned to oral targeted treatment when compared with patients assigned to placebo. Subgroup analyses suggested that ERAs, PDE-5Is, sGCs, and IP receptor agonists produced beneficial effects on reducing clinical worsening, while oral prostanoids only showed a trend. Oral prostanoids had limited clinical benefit observed in the RCTs and were weakly recommended in the guideline.[1] In the analysis excluding oral prostanoids, the cumulative RR estimate of clinical worsening was a reduction of 38%. Zhang et al.[11] found that the use of oral drugs was associated with a 45% reduction in clinical worsening events. He et al.[42] also concluded that clinical worsening was reduced by 67% in patients who received inhaled iloprost, oral bosentan, and sildenafil. Therefore, our study was consistent with these previous studies about the impact of oral drugs on clinical worsening.

Conversely, oral targeted treatment was not associated with significant reductions in deaths and transplantation occurring as first events. This result was also consistent with a previous study by Zhang et al;[11] however, in a meta-analysis of 35 RCTs by Liu et al.,[43] active treatments were associated with a 29% reduction in mortality ($P = 0.004$). This former analysis of active treatment strategies included both oral agents and those non-oral agents, including epoprostenol, iloprost, and treprostinil. Of all

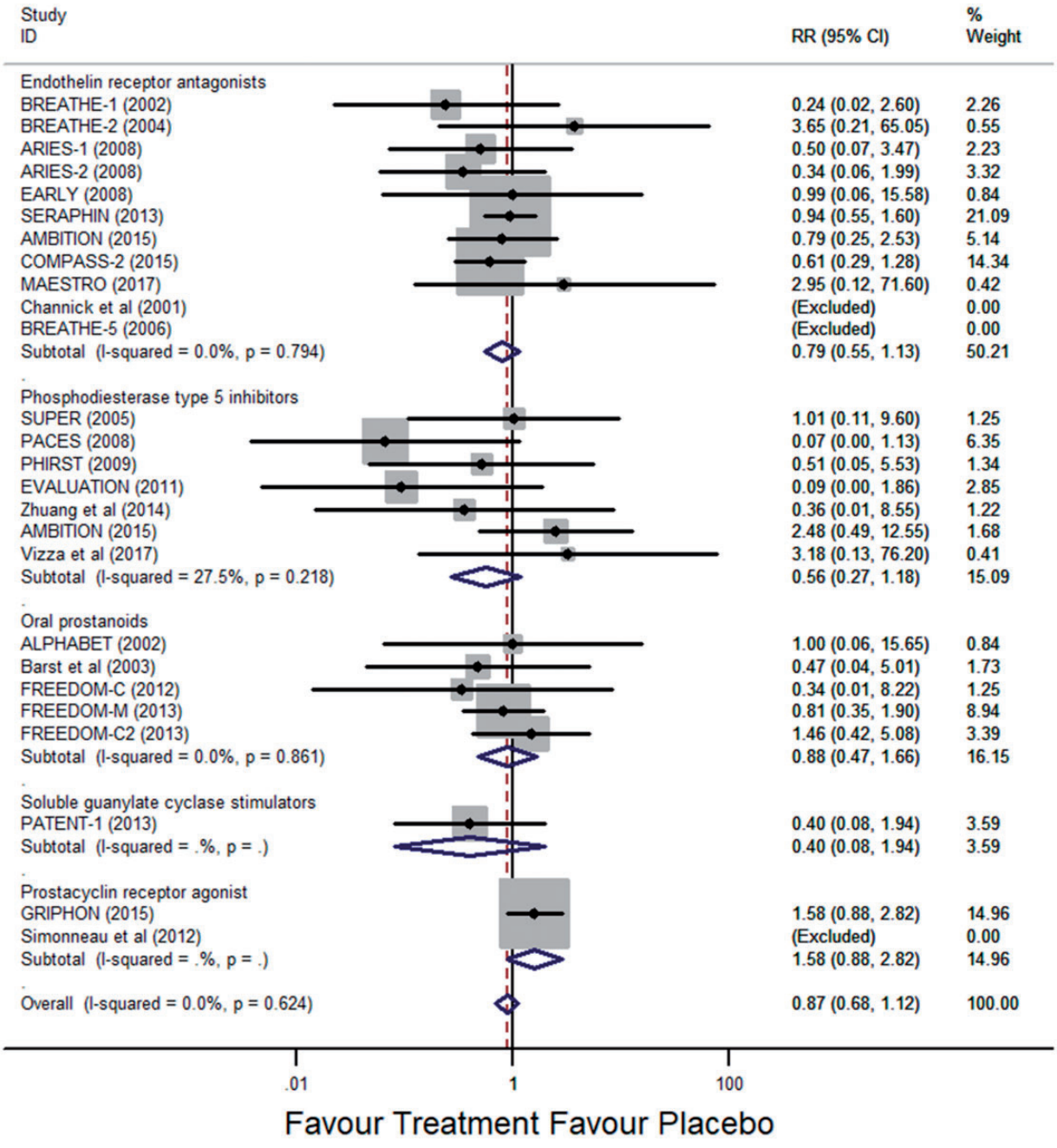

Fig. 4. Cumulative RR estimate of all-cause mortality in oral targeted treatment groups compared with control groups. Data were analyzed with the fixed effect model.
RR, relative risk.

these trials that provided mortality data, only the PPHSG trial of epoprostenol showed significantly mortality reduction in the active treatment group than in the placebo group (RR = 0.06; 95% CI = 0.00–0.96).[44] In this study, we included five long-term trials which used clinical worsening as the primary outcome. Indeed, the analysis of death as first events was limited by informative censoring by other components of the definition of clinical worsening.[45] Death as a first event was uncommon in PAH and it most commonly occurred subsequent to symptomatic progression or admission to hospital. Therefore, the use of a time-to-first-event outcome might have underestimated the beneficial effects of oral agents on mortality. If we took all deaths into account, including both those as first event and those after censoring for another event, oral targeted therapy was associated with a non-significant trend for reduced all-cause mortality.

Combination therapy is a new trend in the treatment of PAH and it can be applied sequentially or initially (upfront). Combining two or more agents from different classes has

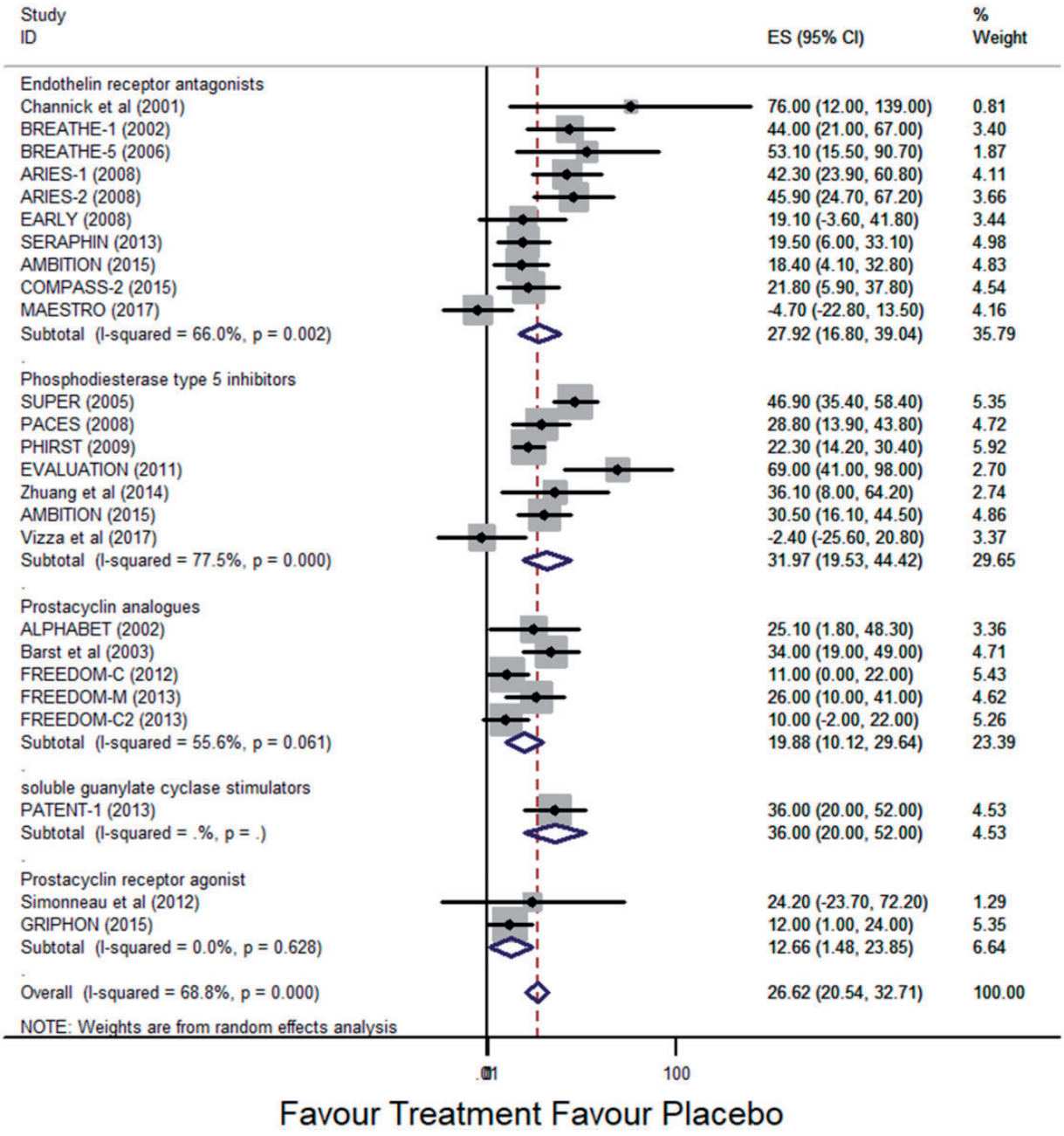

Fig. 5. Weighted mean improvement of 6MWD in patients allocated to oral targeted therapies compared with control groups. ES, estimate.

theoretical appeal, since modulation of several pathways by combining drugs may improve patient outcomes without increasing drug toxicity. In the new guideline of PAH, combination therapy was recommended as evidence Grade IB.[1] In the previous meta-analysis of 2011, combination therapy was only associated with moderate improvements in 6MWD without evidence of reduction in mortality or other clinical worsening events.[46] However, several new studies focusing on combination therapy have been published in recent years.[5–8] These trials have event-driven protocols that require increased patient recruitment and longer study duration. In our study, we included these recently published studies and found that combination therapy was associated with a significant reduction in clinical worsening but had non-significant effects on mortality. These results were consistent with several recently published meta-analyses, which also suggested that combination therapy significantly reduced the risk of a combined clinical worsening events by approximately 35%.[34,45] These findings confirmed the efficiency of combination therapy on clinical outcomes. However, regarding combination therapy, there were still several questions that need to be answered.

First, drug–drug interactions differ among different classes of drugs and it remains unknown which therapeutic classes are most effective in combination. Second, both upfront and sequential combination therapies are recommended in the guideline and it remains controversial which treatment route is more effective in clinic practice. In addition, owning to the short duration and study design, the benefits of combination therapy on mortality remain inconclusive.

Several potential limitations should be taken into consideration when interpreting the present results. First, it was not possible to obtain individual patient-level data from the RCTs, which may have weakened the accuracy of our analysis. Second, the majority of the included trials had a small sample size and relatively short duration, making it difficult to assess the long-term effects. Third, clinical worsening was defined differently in different studies and only some of the trials reported some secondary outcome parameters, possibly leading to reporting bias. Fourth, we did not register our review protocol in the PROSPERO online registry and this may be associated with a perceived risk for publication and reporting bias. Furthermore, the time between the publication of the first and the last trial was prolonged (about 17 years) and considerable progress has been made in treatments and medical care. Finally, as the funnel plot is asymmetry (Egger test, $P = 0.011$; Fig. 3), publication bias in favor of the publication of positive studies also cannot be excluded.

Conclusions

Our meta-analysis suggested that oral targeted therapies significantly reduced the risk of clinical worsening but had less favorable effects on survival in the short-term follow-up. Oral treatment also reduced the risk for admission to hospital, treatment escalation, and symptomatic progression, and resulted in improved patient functional status. These observations support the use of oral targeted therapies in the treatment of PAH.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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References

1. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2016; 37: 67–119.
2. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991; 115: 343–349.
3. Benza RL, Miller DP, Barst RJ, et al. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. *Chest* 2012; 142: 448–456.
4. O'Callaghan DS, Savale L, Montani D, et al. Treatment of pulmonary arterial hypertension with targeted therapies. *Nat Rev Cardiol* 2011; 8: 526–538.
5. Vizza CD, Jansa P, Teal S, et al. Sildenafil dosed concomitantly with bosentan for adult pulmonary arterial hypertension in a randomized controlled trial. *BMC Cardiovasc Disord* 2017; 17: 239.
6. McLaughlin V, Channick RN, Ghofrani HA, et al. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. *Eur Respir J* 2015; 46: 405–413.
7. Galiè N, Barberà JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015; 373: 834–844.
8. Zhuang Y, Jiang B, Gao H, et al. Randomized study of adding tadalafil to existing ambrisentan in pulmonary arterial hypertension. *Hypertens Res* 2014; 37: 507–512.
9. Simonneau G, Torbicki A, Hoeper MM, et al. Selexipag: An oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. *Eur Respir J* 2012; 40: 874–880.
10. Galie 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.
11. Zhang HD, Zhang R, Jiang X, et al. Effects of oral treatments on clinical outcomes in pulmonary arterial hypertension: A systematic review and meta-analysis. *Am Heart J* 2015; 170: 96–103.
12. Zheng YG, Ma H, Hu EC, et al. Oral targeted therapies in the treatment of pulmonary arterial hypertension: A meta-analysis of clinical trials. *Pulm Pharmacol Ther* 2014; 29: 241–249.
13. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2015; 373: 2522–2533.
14. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013; 369: 809–818.
15. Ghofrani HA, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2013; 369: 330–340.
16. Galie N, Landzberg M, Beghetti M, et al. Evaluation of macitentan in patients with Eisenmenger syndrome: results from the randomised controlled MAESTRO study. *ESC Congress* 2017; 38: 1162–1163.
17. Tapson VF, Jing ZC, Xu KF, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (The FREEDOM-C2 Study): A randomized controlled trial. *Chest* 2013; 144: 952–958.
18. Jing ZC, Parikh K, Pulido T, et al. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized, controlled trial. *Circulation* 2013; 127: 624–633.
19. Tapson VF, Torres F, Kermeen F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): a randomized controlled trial. *Chest* 2012; 142: 1383–1390.

20. Jing ZC, Yu ZX, Shen JY, et al. Vardenafil in pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled study. *Am J Respir Crit Care Med* 2011; 183: 1723–1729.
21. Galiè N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 2009; 119: 2894–2903.
22. 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: 521–530.
23. Galie N, Rubin L, 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: 2093–2100.
24. 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: 3010–3019.
25. 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.
26. Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005; 353: 2148–2157.
27. Humbert M, Barst RJ, Robbins IM, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004; 24: 353–359.
28. Barst RJ, McGoon M, McLaughlin V, et al. Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2003; 41: 2119–2125.
29. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; 346: 896–903.
30. Galie N, Humbert M, Vachiery 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: 1496–1502.
31. 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: 1119–1123.
32. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; 339: b2700.
33. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1–12.
34. Fox BD, Shtraichman O, Langleben D, et al. Combination therapy for pulmonary arterial hypertension: a systematic review and meta-analysis. *Can J Cardiol* 2016; 32: 1520–1530.
35. Greenland S. Quantitative methods in the review of epidemiologic literature. *Epidemiol Rev* 1987; 9: 1–30.
36. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. Oxford: The Cochrane Collaboration, 2011. Available at: http://handbook.cochrane.org.
37. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
38. Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088–1101.
39. Duval S and Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; 56: 455–463.
40. Galiè N, Müller K, Scalise AV, et al. PATENT PLUS: A blinded, randomised and extension study of riociguat plus sildenafil in pulmonary arterial hypertension. *Eur Respir J* 2015; 45: 1314–1322.
41. Iversen K, Jensen AS, Jensen TV, et al. Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial. *Eur Heart J* 2010; 31: 1124–1131.
42. He B, Zhang F, Li X, et al. Meta-analysis of randomized controlled trials on treatment of pulmonary arterial hypertension. *Circ J* 2010; 74: 1458–1464.
43. Liu HL, Chen XY, Li JR, et al. Efficacy and safety of PAH-specific therapy in pulmonary arterial hypertension: a meta-analysis of randomized clinical trials. *Chest* 2016; 150: 353–366.
44. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996; 334: 296–301.
45. Lajoie AC, Lauzière G, Lega JC, et al. Combination therapy versus monotherapy for pulmonary arterial hypertension: A meta-analysis. *Lancet Respir Med* 2016; 4: 291–305.
46. Fox BD, Shimony A and Langleben D. Meta-analysis of monotherapy versus combination therapy for pulmonary arterial hypertension. *Am J Cardiol* 2011; 108: 1177–1182.