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 metaanalyses (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 ≥ 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 twotailed 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 test³⁷ 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. I. 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	Ja da d scale
Rubin et al. ²⁰ (BKE/THE-1) 2002 213 Bosenan Placebo 16 PlaH (70), APM (30) 5MM (3	Channick et al. ³¹	2001	32	Bosentan	Placebo	12	IPAH (84), APAH (16)	6MWD	4
Humbert er 1.2^{-6} (BREATHE-2) 2004 33 Epoprostenol + bosentan Epoprostenol + bosentan Epoprostenol + bacebo 16 RPH (10) TPR Gale er al. ²⁷ (BREATHE-2) 2006 54 Bosentan Pacebo 12 RPH (5), APH (19) SPC Gale er al. ²⁷ (BREATHE-3) 2008 192 Ambrisentan Pacebo 12 RPH (5), APH (10) SPC Gale er al. ²⁷ (ARIES-1) 2008 195 Bosentan* Pacebo* 24 RPH (5), APH (3) 6MV Gale er al. ²⁷ (AMBTION) 2015 300 Tadahili + ambrisentan Tadahili ambrisentan Tadahili + ambrisentan T	Rubin et al. ²⁹ (BREATHE-I)	2002	213	Bosentan	Placebo	16	IPAH (70), APAH (30)	6MWD	m
Galie et al. ¹² (BREATHE-3) 2006 54 Bosentan Placebo 12 PPAH (10) SPO Galie et al. ¹² (ARIES-1) 2008 201 Ambristeran Placebo 12 PPAH (63), APAH (37) 6MV Galie et al. ¹² (ARIES-1) 2008 192 Ambristeran Placebo 12 PPAH (63), APAH (37) 6MV Galie et al. ¹² (ARIT) 2013 742 Ambristeran Placebo 24 PPAH (63), APAH (37) 6MV Galie et al. ¹² (ERAPHIN) 2013 742 Macternan ⁶ Placebo 24 PAH (FPAH (56), APAH (47) Clini Galie et al. ¹² (EARPHIN) 2015 334 SIdenafil Tadalafil ambristertan+ 74* PAH/FPAH (55), APAH (37) 6MV Galie et al. ¹² (AMBTRO) 2015 304 Tadalafil ambristertan+ 74* PAH/FPAH (55), APAH (37) 6MV Galie et al. ¹² (SUFRO) 2017 205 Macternan ⁶ Flacebo 16 PAH/FPAH (65), APAH (37) 6MV Galie et al. ¹² (SUFRO) 2013 Macternan ⁶ Placebo <td>Humbert et al.²⁷ (BREATHE-2)</td> <td>2004</td> <td>33</td> <td>Epoprostenol + bosentan</td> <td>Epoprostenol + placebo</td> <td>16</td> <td>IPAH (82), APAH (18)</td> <td>TPR</td> <td>m</td>	Humbert et al. ²⁷ (BREATHE-2)	2004	33	Epoprostenol + bosentan	Epoprostenol + placebo	16	IPAH (82), APAH (18)	TPR	m
Galie et al. ³⁴ (ARIEs-1) 2008 201 Ambrisentan Placebo 12 IPAH (63), APAH (37) 6MM Galie et al. ³⁴ (ARIEs-2) 2008 192 Ambrisentan Placebo 12 IPAH (63), APAH (35) 6MM Galie et al. ³⁴ (SERAPHIN) 2013 182 Bosentar* Placebo* 24 IPAH (61), APAH (35) 6MM Galie et al. ³⁴ (SERAPHIN) 2013 142 Mathrisentan Tadahifi + ambrisentan Tadahifi + ambrisentan 74* IPAH (61), APAH (35) 6MM www Galie et al. ³⁴ (SERAPHIN) 2015 334 Sidenafi + bosentan Tadahifi/ambrisentan + 74* IPAH/IPAH (55), APAH (37) 6MM www Galie et al. ³⁶ (MPEN) 2015 334 Sidenafi + bosentan + placebo 165* IPAH/IPAH (55), APAH (37) 6MM www Galie et al. ³⁶ (MPEN) 2017 2015 304 Tadahifi + ambrisentan Sidenafi + placebo 165* IPAH (70) 6MM www Galie et al. ³⁶ (MPEN) 2015 2015 Tadahifi + ambrisentan Sidenafi + placebo 165*	Galiè et al. ²⁵ (BREATHE-5)	2006	54	Bosentan	Placebo	16	APAH (100)	SPO2&PVR	4
Galie et al. ²⁴ (ARIE-2) 208 192 Ambrisentan Placebo* 12 IPAH (61), APAH (33) 6MM Galie et al. ²⁴ (ARIE-2) 208 193 Bosentan* Placebo* 24 IPAH (61), APAH (33) 6MM Diddo et al. ¹⁴ (SERAPHIN) 2013 742 Mactentan* Placebo* 54 IPAH/FPAH (56), APAH (37) 6MM Galie et al. ¹⁴ (SERAPHIN) 2015 334 Sidenafil + ambrisentan Tadalafil + ambrisentan 74* IPAH/FPAH (56), APAH (37) 6MM Galie et al. ¹⁶ (MAESTRO) 2015 334 Sidenafil + placebo 165* IPAH (10) 6M 6MM Galie et al. ¹⁶ (MAESTRO) 2017 226 Mactentan* Placebo 165* IPAH (71) 6MM 6MM Galie et al. ¹⁶ (MAESTRO) 2017 226 Mactentan* Placebo 165 IPAH (74) 6MM 6MM Galie et al. ¹⁶ (MAESTRO) 2014 12 IPAH/FPAH (61), APAH (37) 6MM 6MM 6MM 6MM 6MM 6MM 6MM 6MM	Galiè et al. ²⁴ (ARIES-1)	2008	201	Ambrisentan	Placebo	12	IPAH (63), APAH (37)	6MWD	4
Galie et al. ²³ (ERLY) 2008 185 Bosentan* Placebo* 24 IPAH/FPAH (56), APAH (43) 6MM Puido et al. ¹⁴ (SERAPHIN) 2013 742 Macitentan* Placebo* 24 IPAH/FPAH (56), APAH (44) Clini Galie et al. ¹⁴ (SERAPHIN) 2013 500 Tadahfil + ambrisentan Tadahfil + ambrisentan 74* IPAH/FPAH (55), APAH (44) Clini Galie et al. ¹⁵ (AMBITION) 2015 334 Sidenafil + bosentan Indeabli Placebo 165* IPAH/FPAH (55), APAH (47) Clini McLaughin et al. ¹⁶ (MAESTRO) 2017 226 Mactentan* Placebo 165 IPAH/FPAH (55), APAH (37) MM Galie et al. ¹² (SUPER) 2017 226 Mactentan* Placebo 16 APAH (100) MM MM Sidenafil Placebo 16 APAH (100) MM MM </td <td>Galiè et al.²⁴ (ARIES-2)</td> <td>2008</td> <td>192</td> <td>Ambrisentan</td> <td>Placebo</td> <td>12</td> <td>IPAH (65), APAH (35)</td> <td>6MWD</td> <td>4</td>	Galiè et al. ²⁴ (ARIES-2)	2008	192	Ambrisentan	Placebo	12	IPAH (65), APAH (35)	6MWD	4
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Sitbon et al. ¹³ (GRIPHON) 2015 1156 Selexipag [*] Placebo [*] 67 [†] IPAH/FPAH (58), APAH (42) Clini 	Simonneau et al. ⁹	2012	43	ERA/PDE-51 + selexipag	ERA/PDE-51 + 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	m
×**								worsening	

APAH, associated pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; 6MWD, 6-min walk distance; VO₂, peak oxygen consumption; TPR, total pulmonary resistance; SPO₂, systemic pulse oximetry; PVR, pulmonary vascular resistance; ERA, endothelin receptor antagonist; PDE-5I, phosphodiesterase type 5 inhibitor.

		/0
D	RR (95% CI)	Weigh
Endothelin receptor antagonists		
Channick et al (2001)	0.08 (0.00, 1.39)	0.58
BREATHE-1 (2002)	0.31 (0.14, 0.68)	2.44
BREATHE-2 (2004)	3.65 (0.21, 65.05)	0.08
BREATHE-5 (2006)	0.46 (0.03, 6.92)	0.18
ARIES-1 (2008)	0.50 (0.17, 1.49)	1.03
ARIES-2 (2008)	0.22 (0.09, 0.54)	2.39
EARLY (2008)	0.23 (0.07, 0.77)	1.68
SERAPHIN (2013)	0.75 (0.63, 0.90)	19.82
AMBITION (2015)	0.64 (0.40, 1.03)	4.49
COMPASS-2 (2015)	0.83 (0.66, 1.05)	11.04
MAESTRO (2017)	2.95 (0.12, 71,60)	0.07
Subtotal (I-squared = 54.0%, p = 0.017)	0.68 (0.60, 0.77)	43.81
Phoenhodiastarasa tuna 5 inhibitors		
SUPER (2005)	0 48 (0 19 1 22)	1.35
PACES (2008)	0.33 (0.15, 0.70)	3 13
DHIDST (2000)	0.55 (0.13, 0.10)	2.67
EVALUATION (2011)	0.11 (0.01, 0.05)	0.71
Zhuang et al (2014)	0.38 (0.15 0.00)	1 75
	0.50 (0.15, 0.55)	5.56
AWIDITION (2015)	1.05 (0.34, 0.03)	0.20
	1.06 (0.22, 5.01)	0.30
Subtotal (I-squared = 0.0%, p = 0.592)	0.47 (0.36, 0.63)	15.54
Prostacyclin analogues		
ALPHABET (2002)	1.33 (0.31, 5.72)	0.39
Barst et al (2003)	0.62 (0.31, 1.27)	2.00
FREEDOM-C (2012)	0.67 (0.28, 1.61)	1.54
FREEDOM-M (2013)	0.73 (0.39, 1.35)	2.58
FREEDOM-C2 (2013)	1.07 (0.47, 2.45)	1.31
Subtotal (I-squared = 0.0%, p = 0.804)	0.78 (0.55, 1.11)	7.81
soluble guanylate cyclase stimulators		
PATENT-1 (2013)	0.25 (0.08, 0.74)	1.48
Subtotal (I-squared = .%, p = .)	0.25 (0.08, 0.74)	1.48
Prostacyclin receptor agonist		
Simonneau et al (2012)	0.15 (0.02, 1.50)	0.40
GRIPHON (2015) +	0.65 (0.55, 0.77)	30,97
Subtotal (I-squared = 35.0%, p = 0.215)	0.64 (0.55, 0.76)	31.37
Overall (I-squared = 36.4%, p = 0.034)	0.64 (0.58, 0.70)	100.00
01 1	100	
.01 1	100	

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.

		Proportion	of events (%)		Effect size		Homo	geneity
	Studies (n)	Treatment	Placebo	Total	RR (95% CI)	Р	²	Р
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 v	worsening							
All-cause mortality ^{5–9,13–31}	25	l 22/4027 (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 (<)	0.68	0.582	0.0	0.899
Treatment escalation ^{8,13–15,17,21,22,24,26,28,29}	12	33/2729	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

Study ID	RR (95% CI)	% Weight
Endothelin receptor antagonists		
BREATHE-1 (2002)	0.24 (0.02, 2.60)	2.26
BREATHE-2 (2004)	3.65 (0.21, 65.05)	0.55
ARIES-1 (2008)	0.50 (0.07, 3.47)	2.23
ARIES-2 (2008)	0.34 (0.06, 1.99)	3.32
EARLY (2008)	0.99 (0.06, 15.58)	0.84
SERAPHIN (2013)	0.94 (0.55, 1.60)	21.09
AMBITION (2015)	0.79 (0.25, 2.53)	5.14
COMPASS-2 (2015)	0.61 (0.29, 1.28)	14.34
MAESTRO (2017)	2.95 (0.12, 71.60)	0.42
Channick et al (2001)	(Excluded)	0.00
DREATHE-5 (2006)	(Excluded)	0.00
Subtotal (I-squared = 0.0%, p = 0.794)	0.79 (0.55, 1.13)	50.21
Phosphodiesterase type 5 inhibitors		1.05
SUPER (2005)	1.01 (0.11, 9.60)	1.25
PACES (2008)	0.07 (0.00, 1.13)	6.35
PHIRST (2009)	0.51 (0.05, 5.53)	1.34
EVALUATION (2011)	0.09 (0.00, 1.86)	2.85
Zhuang et al (2014)	0.36 (0.01, 8.55)	1.22
AMBITION (2015)	2.48 (0.49, 12.55)	1.68
	3.18 (0.13, 76.20)	0.41
Subtotal (I-squared = 27.5%, p = 0.216)	0.56 (0.27, 1.16)	15.09
Oral prostanoids		
AI PHABET (2002)	1 00 (0 06 15 65)	0.84
Barst et al (2003)	0.47 (0.04, 5.01)	1.73
EREEDOM-C (2012)	0.34 (0.01 8.22)	1.25
FREEDOM-M (2013)	0.81 (0.35, 1.90)	8.94
FREEDOM-C2 (2013)	1.46 (0.42, 5.08)	3.39
Subtotal (I-squared = 0.0%, p = 0.861)	0.88 (0.47, 1.66)	16.15
DATENT-1 (2013)	0 40 (0 08 1 94)	3 59
Subtotal (Leguared = % n =)	0.40 (0.08, 1.94)	3.59
. I	0.40 (0.00, 1.34)	3.55
Prostacyclin receptor agonist	1 50 /0 00 0 000	14.00
GRIPHON (2015)	1.58 (0.88, 2.82)	14.96
Simonneau et al (2012)	(Excluded)	0.00
Subtotal (I-squared = .%, p = .)	1.58 (0.88, 2.82)	14.96
Overall (I-squared = 0.0%, p = 0.624)	0.87 (0.68, 1.12)	100.00
.01 1 100	0	
Eavour Treatment Eavour Place	bo	

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-firstevent 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

Study ID	ES (95% CI)	% Weigh
Endothelin receptor antagonists		
Channick et al (2001)	76.00 (12.00, 139.00)	0.81
BREATHE-1 (2002)	44.00 (21.00, 67.00)	3.40
BREATHE-5 (2006)	53.10 (15.50, 90.70)	1.87
ARIES-1 (2008)	42.30 (23.90, 60.80)	4.11
ARIES-2 (2008)	45.90 (24.70, 67.20)	3.66
EARLY (2008)	19.10 (-3.60, 41.80)	3.44
SERAPHIN (2013)	19.50 (6.00, 33.10)	4.98
AMBITION (2015)	18.40 (4.10, 32.80)	4.83
COMPASS-2 (2015)	21 80 (5 90, 37 80)	4.54
(AESTRO (2017)	-4 70 (-22 80 13 50)	4 16
Subtotal (I-squared = 66.0% $p = 0.002$)	27 92 (16 80 39 04)	35 79
	21.02 (10.00, 00.04)	00.10
Phosphodiesterase type 5 inhibitors		
SUPER (2005)	46.90 (35.40, 58.40)	5.35
PACES (2008)	28.80 (13.90, 43.80)	4.72
PHIRST (2009)	22.30 (14.20, 30.40)	5.92
VALUATION (2011)	69.00 (41.00, 98.00)	2.70
/huang et al (2014)	- 36.10 (8.00, 64.20)	2.74
MBITION (2015)	30.50 (16.10, 44.50)	4.86
/izza et al (2017)	-2.40 (-25.60, 20.80)	3.37
Subtotal (I-squared = 77.5%, p = 0.000)	31.97 (19.53, 44.42)	29.65
Prostacyclin analogues		
	25 10 /1 20 42 20)	2 26
ALFHADET (2002)	25.10 (1.00, 40.00)	3.30
	34.00 (19.00, 49.00)	4./1
	11.00 (0.00, 22.00)	5.43
	26.00 (10.00, 41.00)	4.62
REEDOM-C2 (2013)	10.00 (-2.00, 22.00)	5.26
Subtotal (I-squared = 55.6%, p = 0.061)	19.88 (10.12, 29.64)	23.39
soluble guanylate cyclase stimulators		
PATENT-1 (2013)	36.00 (20.00, 52.00)	4.53
Subtotal (I-squared = .%, p = .)	36.00 (20.00, 52.00)	4.53
rostacyclin receptor agonist		
Simonneau et al (2012)	24.20 (-23.70, 72.20)	1.29
GRIPHON (2015)	12.00 (1.00, 24.00)	5.35
Subtotal (I-squared = 0.0%, p = 0.628)	12.66 (1.48, 23.85)	6.64
Overall (I-squared = 68.8%, p = 0.000)	26.62 (20.54, 32.71)	100.00
IOTE: Weights are from random effects analysis		
NOTE: Weights are from random effects analysis	1 100	

Favour Treatment Favour Placebo

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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