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Combination Therapy in Pulmonary Arterial Hypertension: A Meta-Analysis

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Key Words
Combination therapy · Pulmonary arterial hypertension · Randomized controlled trial · Meta-analysis

Abstract
Objectives: It is unclear whether combination therapy is efficient and well tolerated in patients with pulmonary arterial hypertension (PAH). The objective was to analyze completed trials assessing the efficacy and safety of treating PAH with combination therapy. ***Methods:*** We performed a meta-analysis of all randomized controlled combination therapy trials that evaluated efficacy and safety in PAH patients. Trials were identified in the Cochrane Library, EMBASE and PubMed databases, reviews and reference lists of relevant papers. ***Results:*** Six trials with a total of 858 patients were included in the meta-analysis. Compared with the control group, combination therapy reduced clinical worsening [relative risk (RR) 0.48, 95% confidence interval (CI) 0.26–0.91, p = 0.023], increased the 6-min-walk distance significantly by 22.22 m, and reduced mean pulmonary arterial pressure, right atrial pressure and pulmonary vascular resistance. The incidence of serious adverse events was similar in the 2 groups (RR 1.17, 95% CI 0.40–3.42, p = 0.77). However, combination therapy did not influence mortality. ***Conclusions:*** Treatment of PAH with combination therapy improves multiple clinical and hemodynamic outcomes, but it has no effect on mortality. The long-term efficacy and safety of combination therapy in PAH requires further study based on large and rational-designed controlled clinical trials.

Introduction

Pulmonary arterial hypertension (PAH) is a chronic, devastating and progressive disease characterized by a pathological increase in pulmonary vascular resistance (PVR) that results in right ventricular dysfunction, limits exercise capacity and eventually leads to right-sided heart failure and premature death [1]. Although the pathogenesis of PAH remains unclear, at least three pathways are involved in its pathogenesis – the endothelin pathway, prostacyclin pathway and nitric oxide pathway [2, 3].

There is currently no cure for PAH, but 3 classes of drugs targeted at the three pathways have been developed and approved for the treatment of PAH: prostanoids, phosphodiesterase type 5 (PDE5) inhibitors and endothelin receptor antagonists (ERAs) [4]. These drugs alleviate symptoms and improve exercise capacity, hemodynamics and outcome. Despite these advances, PAH is still an incurable disease. Thus, those patients who do not sta-

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bilize on monotherapy and who do not have long-term improvements still need other treatment options [5].

Since the 3 classes of drugs act via separate pathways, concomitant use of 2 or 3 drugs may exert synergistic effects. Moreover, to date, no single drug has been shown to deliver completely satisfactory improvements in severely ill PAH patients. This makes combination therapy practical in theory. Combination therapy is an approach that uses a combination of drugs targeted at different pathways, and has the potential for additive or synergistic effects. The goal of this therapeutic strategy should be to increase efficacy while minimizing toxicity. It has been advocated for PAH, analogous to the strategies used in the treatment of systemic hypertension, heart failure and cancer. Potential combination therapy includes combining ERAs with prostanoids, ERAs with PDE5 inhibitors, prostanoids with PDE5 inhibitors and combining all 3 classes of drugs [6]. Combination therapy is indeed in common use in clinical practice and is now recommended in treatment guidelines. There are two types of combination therapy in current clinical practice, sequential add-on therapy and first-line combination treatment. However, the evidence to support these treatment options remains limited.

A number of randomized controlled trials (RCTs) of combination therapy in PAH have been published, the conclusions of which were inconsistent. The aim of this meta-analysis was to evaluate the efficacy and safety of combination therapy in PAH, and to lay the theoretical foundation for treatment.

Methods

Literature Search

We systematically searched PubMed, EMBASE, the Cochrane Library, previous reviews and reference lists from identified articles without language and time limitation. We used the following search terms: (PAH) AND (endothelin receptor antagonist OR prostanoids OR phosphodiesterase type 5 inhibitor OR bosentan OR ambrisentan OR sitaxsentan OR epoprostenol OR treprostinil OR iloprost OR sildenafil OR tadalafil).

Study Inclusion Criteria

The inclusion criteria were as follows: (1) RCTs that have been published (with or without a placebo group) on the treatment of PAH using combination therapy with 2 or 3 drugs, (2) evaluated adults with PAH who had had a follow-up of 8 weeks or more and (3) patients definitely diagnosed as having PAH (group 1 according to the clinical classification [7] of PAH). Acute studies that assess only hemodynamic variables were excluded.

Evaluation Indicators for Efficacy and Safety

All literature searches were independently reviewed by two professional co-workers (Y.B. and L.S.) to identify the trials which met the inclusion criteria. Differences were resolved by consensus. Evaluation indicators for efficacy included 6-min-walk distance (6MWD), clinical worsening, New York Heart Association (NYHA)/WHO functional class and hemodynamic parameters including mean pulmonary arterial pressure (mPAP), right atrial pressure (RAP), PVR and cardiac output. Serious adverse events that were considered to be related to the studied medication as indicated in the original articles were applied to evaluate the safety of drugs. The all-cause mortality was also assessed.

Quality Assessment

Studies were assessed for quality of randomization, blinding, reporting of withdrawals, generation of random numbers and concealment of allocation. The trials scored 1 point for each area addressed, therefore receiving a score between 0 and 5 (highest level of quality) [8].

Statistical Analysis

We calculated risk ratios (RR) for dichotomous data and weighted mean differences (WMD), with 95% confidence intervals (CI) for continuous data. A random-effects model (DerSimonian and Laird) was used [9]. The statistical heterogeneity of treatment effects between studies was formally tested with Cochran's test ($p < 0.1$). The I^2 statistic was also examined, and we considered $I^2 > 50\%$ to indicate significant heterogeneity between the trials [10]. Publication bias was assessed with funnel plots by Eggers' regression test [11]. Statistical analyses were performed with Stata software (version 9.0; Stata Corporation, College Station, Tex., USA) and REVMAN software (version 5.0; Cochrane Collaboration, Oxford, UK).

Results

Search Results and Characteristics

A total of 1,115 articles were identified by the combined search of PubMed, EMBASE, the Cochrane Library and a manual approach (searching previous studies cited in reviews and reference lists from identified articles) for RCTs, 7 of which satisfied the inclusion criteria [12–18]. In addition, since it is difficult to combine studies that included predominantly patients with idiopathic PAH with trials that enrolled only patients with Eisenmenger's syndrome, Iversen et al.'s study [17] was excluded from the final analysis. Thus, 6 trials were eventually included in the meta-analysis [12–16, 18] (fig. 1).

In the 6 trials, a total of 858 patients were enrolled, consisting of 495 patients in the combination treatment group and 363 patients in the control group. Table 1 shows the characteristics of the trials. Five RCTs presented results on combination therapy with 2 drugs. Among them, 3 RCTs assessed the effects of bosentan combined with prostanoids (iloprost) or PDE5 inhibitors (tadalafil), 2 RCTs assessed the effects of epoprostenol combined with bosentan or sildenafil; 1 RCT assessed the addition-

Table 1. RCT characteristics

Author	Date of publication	Official acronym	Subjects	Active drug	Comparator	Study period weeks	Etiology (%)	Primary endpoint	Design
Humbert et al. [12]	2004	BREATHE-2	33	epoprostenol + bosentan	epoprostenol + placebo	16	IPAH (82), APAH (18)	TPR	RCT
McLaughlin et al. [13]	2006	STEP	67	inhaled iloprost[1]	placebo[1]	12	IPAH (55), APAH (45)	6MWD	RCT
Hoeper et al. [14]	2006	COMBI	40	inhaled iloprost[1]	no placebo[1]	12	IPAH (100)	6MWD	RCT
Simonneau et al. [15]	2008	PACES	267	sildenafil[2]	placebo[2]	16	IPAH (79), APAH (21)	6MWD	RCT
Galie et al. [16]	2009	PHIRST	216	tadalafil[1]	placebo[1]	16	–	6MWD	RCT
McLaughlin et al. [18]	2010	TRIUMPH I	235	treprostinil[3]	placebo[3]	12	IPAH/FPAH (56), APAH (33), other (11)	6MWD	RCT

APAH = Associated with PAH; FPAH = familial PAH; IPAH = idiopathic PAH; TPR = total pulmonary resistance. [1] All patients were on background treatment with bosentan. [2] All patients were on background treatment with epoprostenol. [3] 70% of patients were on background treatment with bosentan; 30% of patients were on background treatment with sildenafil.

al effects of treprostinil, among which bosentan plus treprostinil or sildenafil plus treprostinil served as the treatment group, while bosentan plus placebo or sildenafil plus placebo served as the control group.

The average length of study durations was 14 weeks (range 12–16 weeks). In the 6 trials, the exclusive or predominant etiology was idiopathic and/or familial PAH.

In these RCTs, most of the participants were in NYHA/WHO functional class III. The primary endpoint was 6MWD in 5 studies and total pulmonary resistance in 1 study.

Data Quality

The quality scores of the trials varied from 2 to 5 (maximum score). All included trials were randomized, prospective and placebo controlled.

Efficacy Evaluation for PAH Medication

The 6MWD was the primary endpoint in 5 trials and the secondary endpoint in 1 trial. In 3 trials, the improvement in the 6MWD of patients in the combination therapy group was higher than that of the control group. One of 2 other trials showed that the 6MWD of patients in both the combination therapy and placebo groups was increased, but that the increase was lower in the combination therapy group. Another trial showed that the 6MWD of patients was decreased after combination medication, but that that of patients in the placebo group was increased.

Combination therapy significantly improved exercise capacity. The heterogeneity test showed no significant results ($I^2 = 10.6\%$; $p = 0.35$). We used the random effects model to assess the weighted mean improvement of exercise capacity. Compared to the placebo group, the combination therapy group significantly improved 6MWD by 22.22 m (WMD 22.22, 95% CI 13.58–30.86, $p < 0.0001$) (fig. 2a).

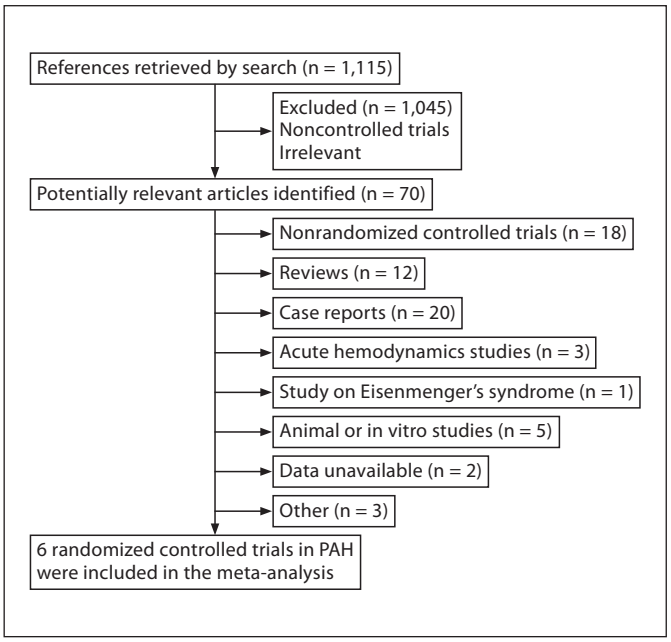

Fig. 1. Flow chart of the trial selection process, showing the number of citations retrieved by individual searches and the number of trials included.

NYHA/WHO Functional Class

Data for the NYHA/WHO functional class were available for 3 studies, benefits were not seen in functional class improvement (RR 1.29, 95% CI 0.37–4.5, $p = 0.7$) (fig. 2b).

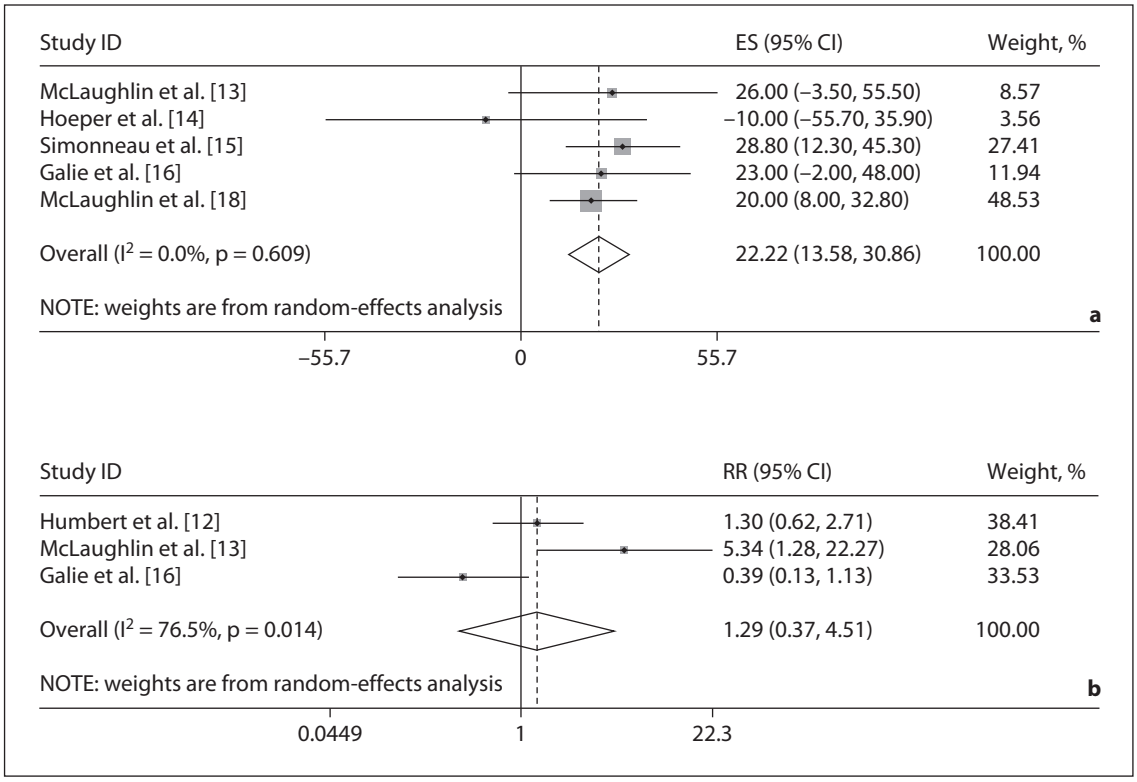

Fig. 2. a Random-effects meta-analysis of WMD (95% CI) of 6MWD with combination therapy compared to controls. Sizes of data markers indicate the weight of each study in the analysis. **b** Random-effects meta-analysis of RR (95% CI) of functional class improvement with combination therapy compared to controls. ES = Eisenmenger's syndrome.

Clinical Worsening

Clinical worsening refers to death, hospitalization, symptomatic deterioration, lack of improvement and the need for treatment escalation, e.g. additional drugs, the occurrence of interatrial fistulization or lung transplantation [19].

Among the 858 subjects in the 6 trials, 56 (6.5%) developed clinical worsening, consisting of 39 (10.7%) in the placebo group and 17 (3.4%) in the combination therapy group. The incidence of clinical worsening was statistically significantly lower in the combination therapy group than in the placebo group (RR 0.48, 95% CI 0.26–0.91, p = 0.023; fig. 3a).

Mortality

Mortality data were available for all 6 studies. Compared to the control group, combination therapy was not associated with a significant change in mortality (RR 0.44, 95% CI 0.04–4.65, p = 0.494; fig. 3b).

Hemodynamic Parameters

Data on mPAP and PVR were available for 3 studies, and on RAP and cardiac output for 2. Compared with the control group, the weighted mean reduction in RAP in the combination therapy group was –2.02 mm Hg (95% CI –3.35 to –0.68, p = 0.003; fig. 4a). Compared to the control group, the weighted mean reduction in mPAP and PVR in the combination therapy group was –5.56 mm Hg (95% CI –8.84 to –2.29, p = 0.001) and –194.35 mm Hg (95% CI –260.58 to –128.12, $p < 0.0001$; fig. 4b, c), respectively. There was no significant change in cardiac output in the combination therapy group compared to the control group (p = 0.31; fig. 4d). Only 1 trial [12] assessed the cardiac index, and we did not evaluate this parameter in our analysis.

Safety

All of the 6 trials evaluated the safety of combination therapy by assessing the serious adverse events. Specific

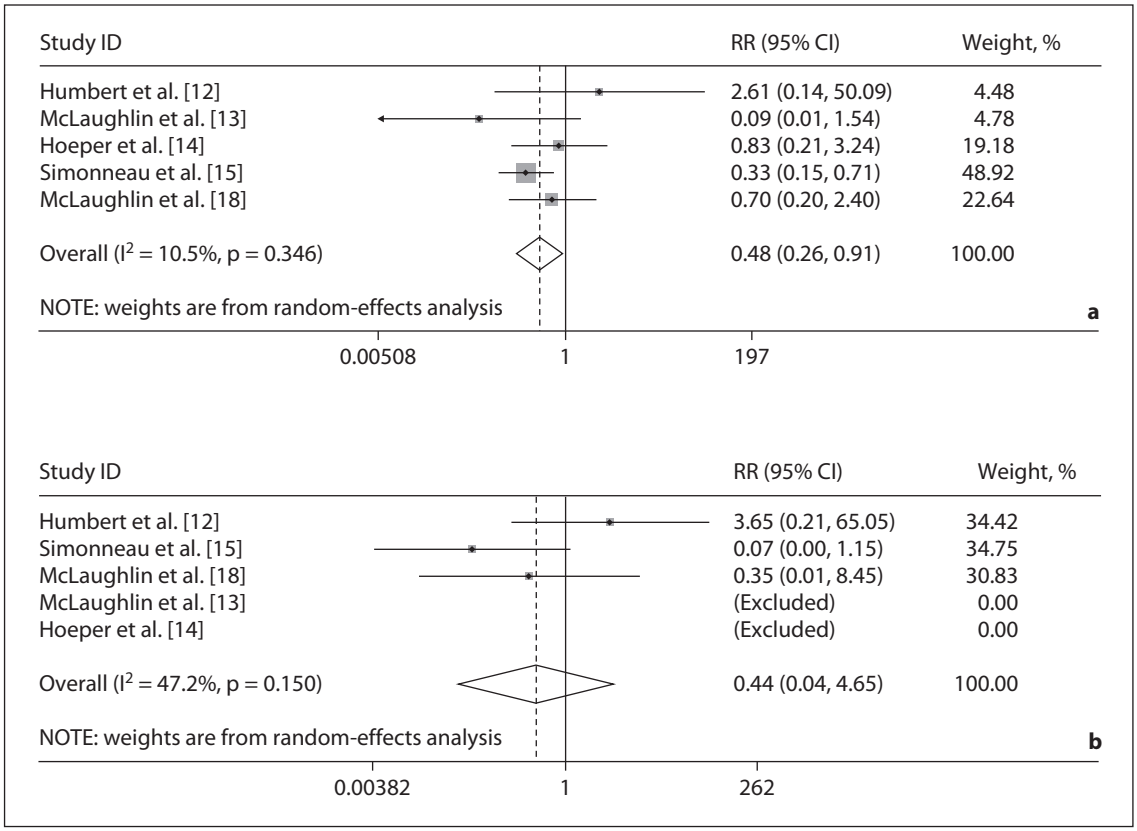

Fig. 3. a Random-effects meta-analysis of RR (95% CI) of clinical worsening with combination therapy compared to controls. **b** Random-effects meta-analysis of RR (95% CI) of mortality with combination therapy compared to controls.

data can be gained from 4 of the 6 trials [12–15]. In 1 of the 4 trials [14], no serious adverse events were found in the combination therapy group or in the control group. Among the 858 patients including those receiving combination therapy (n = 495) and control therapy (n = 363), 13 (1.5%) reported serious adverse events, consisting of 8 (1.6%) in the combination therapy group and 5 (1.4%) in the control group. The incidence of serious adverse events was similar in the combination group and in the control group, and the difference was not statistically significant (p = 0.77; fig. 5).

Publication Bias

For each comparison, a statistical analysis of funnel plots suggested no publication bias.

Discussion

This meta-analysis demonstrated that the combination therapy of PAH reduces the incidence of clinical worsening significantly and improves exercise capacity (measured by 6MWD) and hemodynamic status such as mPAP, RAP and PVR. There was no significant difference in the incidence of serious adverse events, showing that combination therapy is safe and well tolerated. Amelioration of the NYHA/WHO functional class and an improvement regarding mortality were not found in our study.

Potential combination therapy includes combining ERAs with prostanoids, ERAs with PDE5 inhibitors, prostanoids with PDE5 inhibitors and combining all 3 classes of drugs. The multipathways involved in the pathophysiology and variable pathoetiology of PAH make combination therapy an attractive, logical treatment option [20, 21] which is, in fact, in common use to-

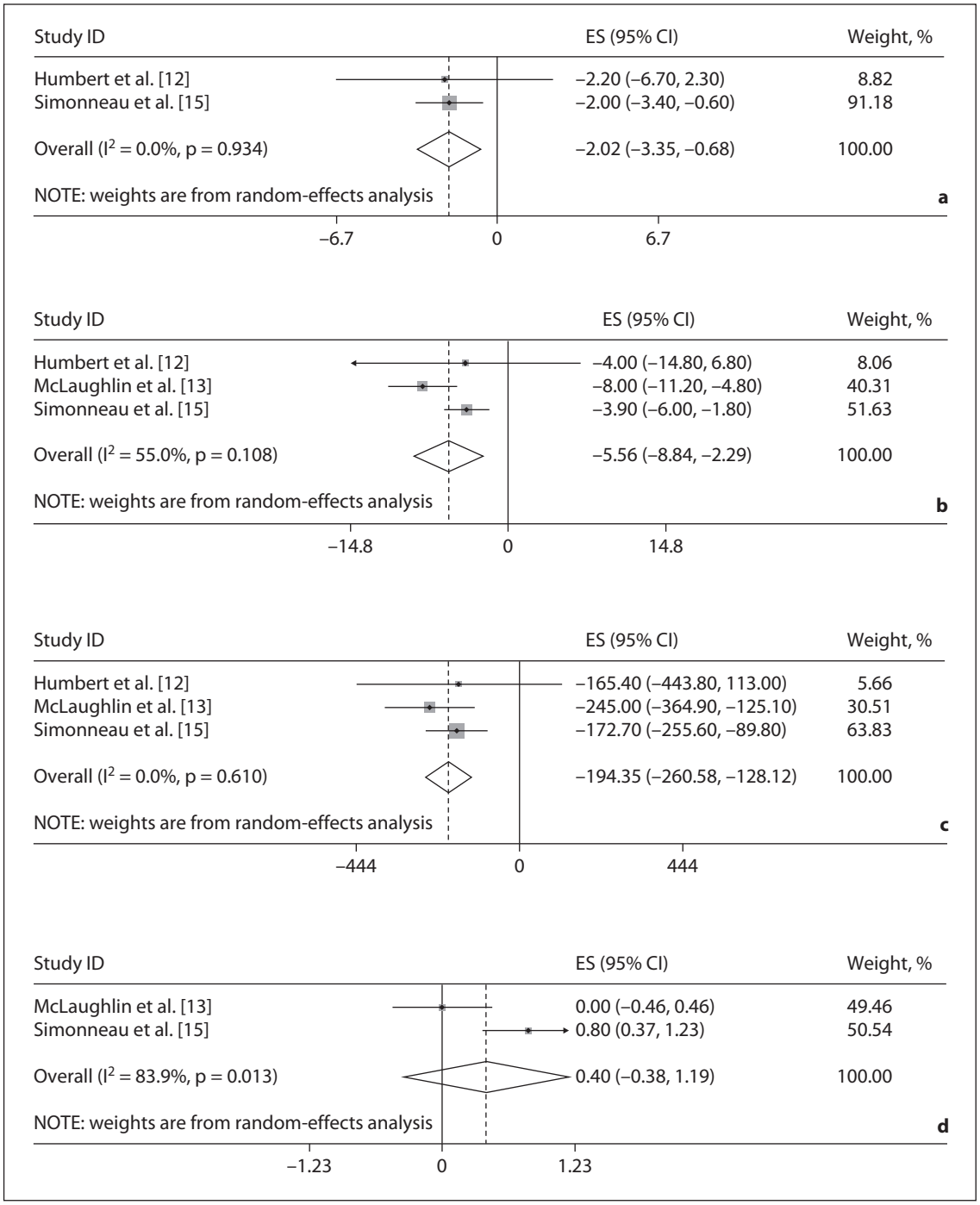

Fig. 4. a Random-effects meta-analysis of WMD (95% CI) of RAP with combination therapy compared to controls. **b** Random-effects meta-analysis of WMD (95% CI) of mPAP with combination therapy compared to controls. **c** Random-effects meta-analysis of WMD (95% CI) of PVR with combination therapy compared to controls. **d** Random-effects meta-analysis of WMD (95% CI) of cardiac output (CO) with combination therapy compared to controls. ES = Eisenmenger's syndrome.

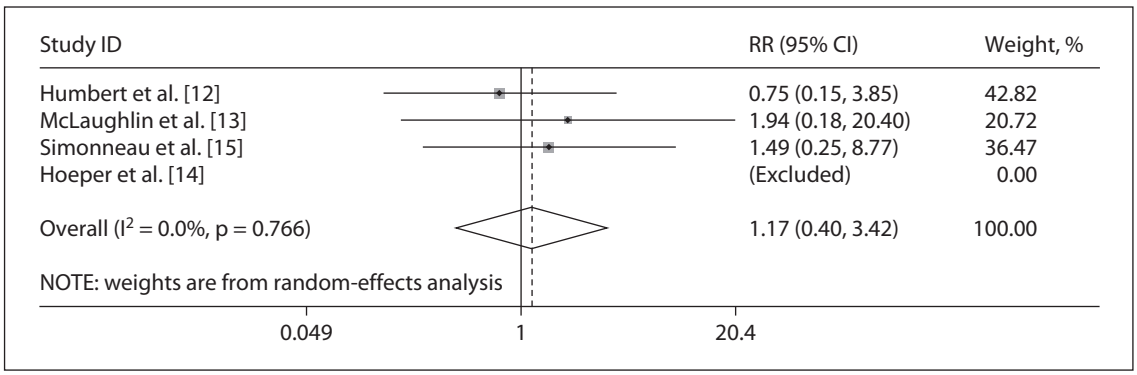

Fig. 5. Random-effects meta-analysis of RR (95% CI) of serious adverse events with combination therapy compared to controls.

day in clinical practice. As data from the REVEAL registry demonstrate, 45% of registered patients with PAH accepted treatment combining 2 or more drugs, and 9% accepted combination therapy with 3 or more drugs. The role of combination therapy has been explored, and the results are encouraging [22, 23]. However, the evidence supporting combination treatment is still poor, and there has not yet been any definite approval of combination therapy from the American College of Cardiology Foundation and the American Heart Association. To our knowledge, a meta-analysis of available RCTs focusing on combination therapy has not been published, and the favorable results observed in our meta-analysis supplied the basis of evidence-based medicine for the combination treatment of PAH for the first time, with both theoretical and clinical significance.

An important finding of this meta-analysis was the significant decrease in the incidence of clinical worsening in the combination therapy group. As a composite endpoint, clinical worsening has been used as a measurement of morbidity and mortality [24, 25]. It is superior to other endpoints in that it reflects the true clinical status and degree of disease progression in a patient population, and from previous study data its sensitivity for assessing combination therapy is promising. The results in this meta-analysis showed that 10.7% of patients in the control group and 3.4% of that in the combination therapy group developed clinical worsening; this suggests that although combination therapy can delay disease progression, PAH is still a progressive and incurable disease.

Our meta-analysis found that combination therapy significantly improved exercise capacity, measured by the 6MWD observed in 5 of 6 RCTs. The weighed mean improvement of 6MWD in the combination therapy group compared to the control group was 22.22 m, suggesting that combination treatment can improve the symptoms of patients with PAH. It is noteworthy that the placebo-corrected change in 6MWD in most of the RCTs is less than in many studies of monotherapy, which may be due to the short follow-up time of combination therapy or to the blunted response of patients to the further vasodilative effect of the add-on drugs.

This study observed statistically significant improvements in several hemodynamic parameters, including mPAP, RAP and PVR. The incidence of serious adverse events was similar in the combination treatment group and in the control group, with no significant difference between the two, suggesting that combination therapy of patients with PAH is safe and well tolerated. However, clinicians must still consider the risk of drug-drug interactions and the possible increased risk of additive toxicities. Close monitoring is necessary, although the drug interactions have so far not been found to be of clinical relevance.

As this meta-analysis showed, combination therapy resulted in a 56% nonsignificant improvement in all-cause mortality in the 858 patients. The previous two meta-analyses identified a reduction in all-cause mortality with pharmacotherapy of 43 and 39%, respectively [26, 27], both of which included more than 20 RCTs and 3,500 subjects. The reason for there being no benefit of combination therapy regarding mortality is unclear; it may be due to the small sample size of patients and studies or to the short duration of trials. But our run of results suggests that combination therapy may be a good clinical choice in improving symptoms and delaying disease progres-

sion, although not in improving prognosis (such as death). More large-scale studies should be designed to adequately shed light on this issue.

In addition to the commonly used endpoints mentioned above, N-terminal pro-brain natriuretic peptide (NT-proBNP) has been increasingly used as a biomarker for screening for PAH in high-risk patients [28]. Only 1 study in our meta-analysis assessed the level of NT-proBNP [18]. Due to NT-proBNP correlating with survival and other important endpoints [29, 30], more RCTs of PAH should confirm its role and include it as a secondary endpoint in the future.

Our study has several limitations. First, the majority of the included trials had a small sample size and a relatively short duration, making it difficult to assess the long-term effect of combination therapy. Second, because of the small number and differing design of the 6 studies, we did not perform a subgroup analysis to assess the effect of each class of combining strategies. Third, although several results of this study are positive, it is not clear whether a small increase of 6MWD (less than 30 m) and changes in only some hemodynamic parameters have an obvious clinical effect.

In conclusion, this meta-analysis suggests that combination therapy of patients with PAH is efficient in improving the symptoms and delaying disease progression, and is safe and well tolerated. Based on the current literature, the outlook of combination treatment is encouraging. However, most current studies are open, observational and have a relatively small number of enrolled patients. In future studies, large RCTs should be designed to adequately assess the efficacy and safety of combination therapy.

Acknowledgements

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Conflict of Interest

There were none to declare.

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