A meta-analysis of the safety and efficacy of bosentan therapy combined with prostacyclin analogues or phosphodiesterase type-5 inhibitors for pulmonary arterial hypertension

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Abstract. Bosentan is an effective drug for the treatment of pulmonary arterial hypertension (PAH). The aim of the present meta-analysis was to examine the evidence concerning the efficacy and safety of bosentan therapy combined with prostacyclin analogues or phosphodiesterase type 5 (PDE-5) inhibitors for treating PAH. Eligible published studies were collected from Embase, PubMed, The Cochrane Library and the www.clinicaltrials.gov website. Heterogeneity was assessed using the Cochran Q-statistic test. Results were presented as risk ratios or mean differences with 95% confidence intervals (CI). A total of five studies, comprising 310 patients were included for analysis. No significant improvements in six-minute walk distance (6MWD; mean difference, 16.43 m), clinical worsening (risk ratio, 0.54) and the World Health Organization functional classification (class I: risk ratio, 1.17; class II: risk ratio, 1.18) were observed in patients treated with bosentan in combination with prostacyclin analogues or PDE-5 inhibitors. However, a significant reduction in the mean pulmonary artery pressure (mPAP; 95% CI: -17.06, -6.83; P<0.0001) following bosentan combination therapy was observed. Comparisons of adverse event rates in the bosentan combination therapy (55.6%) and monotherapy (51.8%) suggested that there is no reduction in adverse events (risk ratio, 1.10). The results indicated that bosentan combined with prostacyclin analogues or PDE-5 inhibitors may not improve 6MWD, cardiac function, clinical worsening and adverse events. However, bosentan combined with prostacyclin analogues or PDE-5 inhibitor therapy was able to significantly reduce mPAP compared with the effect of bosentan monotherapy.

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease associated with a massive increase in pulmonary vascular resistance and pulmonary artery pressure (PAP). PAH is a rare disease with an incidence of approximately 2.4-7.6 cases per million (1), which may lead to fatal right heart failure in the absence of appropriate treatment. The pathogenesis of PAH has not been fully elucidated; however, dysfunction of three metabolic/physiological pathways, including the endothelin pathway, the prostacyclin pathway and the nitric oxide pathway, have been attributed to the pathogenesis of PAH (2,3). Targeting of these pathways had been rationally exploited for the discovery of chemotherapeutics against PAH. For example, prostacyclin analogues, phosphodiesterase type 5 (PDE-5) inhibitors and endothelin receptor antagonists (ERAs) are drugs that are commonly used for the treatment of PAH (4). These drugs relieve symptoms, raise exercise capacity and improve hemodynamics. However, the efficacies of these commonly used drugs in delaying the progression of the disease are limited. Owing to these limitations, the current treatment options for PAH are not satisfactory. Combination therapies exist, where two or three drugs aimed at different pathways, such as ERAs, prostacyclin analogues and PDE-5 inhibitors are simultaneously used (5). Previous studies had indicated that combination therapy significantly improved activity tolerance, hemodynamic parameters, clinical deterioration time and quality of life for patients with PAH (6-8). Results from a previous meta-analysis suggest that combination therapies only offered a modest increase in exercise ability (9). The evidence to support these treatment options is limited. Bosentan, an ERA, serves a crucial role in proliferation inhibition, improvement of endothelial function and expansion of pulmonary vessels (10). ERA treatment significantly improved the activity tolerance and exercise capacity of PAH

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patients as well as prolonging the survival time (11); however, PAH remains a progressive disease with a high mortality rate (12-15). The mortality rate of pulmonary hypertension in the United States was about 4.5-12.3/10 million in 2015 (16). In order to achieve long-term efficacy, combined therapy has been widely used in clinical practice. However, only a few randomized controlled trials are available regarding the efficacy and safety of combining bosentan with prostacyclin analogues or PDE-5 inhibitors, and there is limited evidence to support the superior effects of bosentan combination therapy over monotherapy (17). The present meta-analysis focused on providing an improved analysis of bosentan combination for PAH treatment, and laying a theoretical foundation for the development of other treatment strategies in the future. Bosentan was the first oral PAH targeted drug in 2002 (18). Subsequently, a number of multi-center, randomized controlled clinical trials have been published to confirm its efficacy in controlling pulmonary hypertension (19,20). Bosentan was approved in China for the treatment of PAH in 2006 and was permitted for use as class I drug in 2015, according to European Society of Cardiology-European Respiratory Society Guidelines on Pulmonary Hypertension (21). The evidence-based medicine of bosentan combined with prostacyclin analogues or PDE-5 inhibitors is lacking. Therefore, it is necessary to conduct meta-analyses of randomized controlled trials to evaluate the effects of bosentan combined with prostacyclin analogues or PDE-5 inhibitors for the treatment of PAH. The present meta-analysis may provide evidence of the efficacy and safety of bosentan therapy combined with prostacyclin analogues or PDE-5 inhibitors.

Materials and methods

Study inclusion and exclusion criteria. The following criteria was used for selecting previous studies to analyse: i) Only randomized controlled trials (RCT) that combined bosentan with prostacyclin analogues or PDE-5 inhibitors for the treatment of PAH were included; ii) studies in which the control group was treated with bosentan or placebo were included (bosentan monotherapy), and follow-up time in the study was ≥12 weeks.; iii) studies of the bosentan treatment within 3 months prior to randomization were included. Efficacy indicator of primary endpoint was indicated as six-minute walk distance (6MWD), and adverse events were examined to evaluate safety.

Literature search. RCT of bosentan combination therapy vs. bosentan monotherapy for treatment of PAH were searched from PubMed (www.ncbi. nlm.nih.gov/pubmed), Embase (www.embase.com), and the Cochrane library (www.cochrane library. com). The following keywords were used for searching the relevant trial studies included in this meta-analysis: 'Phosphodiesterase type 5 inhibitor' or 'PDE-5 inhibitor' or 'sildenafil' or 'tadalafil' or 'vardenafil' or 'prostacyclin analogs' or 'epoprostenol' or 'iloprost' or 'treprostinil' paired with 'pulmonary arterial hypertension' or 'PAH' and 'bosentan'.

Quality assessment. The selected studies were also assessed for the quality of trials using the Cochrane Collaboration

recommended tool for assessing risk of bias (22). This tool included the domains of selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other sources of bias. The 'risk of bias' assessment tool was used to further review bias among individual studies (22).

Statistical analysis. Results are represented as risk ratios for dichotomous data and mean differences for continuous data with 95% confidence intervals (CI). Statistical heterogeneity across studies was tested using Cochran's Q test. The fixed effects model was selected for analysis when no significant heterogeneity between the studies was found (P>0.10; I^2 ≤50%). Alternatively, the random effects model was used in case heterogeneity among studies. The RevMan software package (version 5.2; Cochrane) was used for all statistical analyses.

Results

Study characteristics. In the present meta-analysis, one RCT (PHIRST-1: Tadalafil in the Treatment of Pulmonary Arterial Hypertension) was reported twice (23,24). The trials consisted of patients with congenital heart disease-associated PAH (25) and Eisenmenger's syndrome (26). The subjects of six studies were treated with ERA or PDE-5 inhibitor as background treatment (27-32); therefore, these were excluded from the analysis. Overall, a total of 310 subjects in 5 RCTs were included in this analysis (Fig. 1 and Table I).

Data quality. The quality of the five studies was assessed and the risk of bias was estimated by Cochrane Collaboration's tool. The results were shown in Fig. 2. The majority of the included studies had a low risk of bias according to the following criteria: Selection bias, performance bias, detection bias, attrition bias, reporting bias and other sources of bias.

Meta-analysis results. 6MWD was used as an indicator of exercise ability in all the five trials included in the present study. Compared with bosentan monotherapy, four of the five studies in bosentan combination therapy reported a significant improvement in walking distance (Fig. 3). The mean difference of 6MWD in bosentan combination therapy was 16.43 m (95% CI: -4.91, 37.76), but there was no statistical significance between bosentan combination and bosentan monotherapy (P=0.13). No significant heterogeneity (I^2=0%; P=0.81) was detected in bosentan combination therapy compared with bosentan monotherapy.

Cardiac functional improvement was also one of the efficacy indicators of this meta-analysis. The New York Heart Association (NYHA) and the World Health Organization (WHO) functional classification systems were used to identify functional impairment in PAH. McLaughlin *et al* (33) and Hoeper *et al* (34) performed their studies using the NYHA functional classification, the remaining three studies were performed using the WHO functional classification (23,35,36). After meta-analysis, the result showed that there was significant heterogeneity (I^2 =73%; P=0.02) in WHO functional class

Table I. Study characteristics.

Author, year	Study	n	Sex (male/female)	MT	CT	Follow-up (weeks)	Primary endpoint	(Refs.)
McLaughlin et al, 2006	STEP	67	14/53	Placebo + bosentan	Bosentan + Iloprost (5 ug)	12	6MWD	(33)
Hoeper et al, 2006	COMBI	40	9/31	Bosentan	Bosentan + Iloprost (5 ug)	12	6MWD	(34)
Barst et al, 2011	PHIRST	87	19/68	Placebo + bosentan	Bosentan + tadafil (40 mg)	16	6MWD	(23)
Han et al, 2017	BIPH	15	5/10	Bosentan	Bosentan + Iloprost (10 ug)	12	6MWD	(35)
Vizza et al, 2017		103	25/79	Bosentan	Bosentan + Sildenafil (20 mg)	12	6MWD	(36)

6MWD, 6-min walk distance; BIPH, bosentan with iloprost in the treatment of pulmonary hypertension patients; COMBI, combination therapy of bosentan and aerosolised iloprost in idiopathic pulmonary arterial hypertension; CT, bosentan combination therapy; MT, bosentan monotherapy; PHIRST, pulmonary arterial hypertension and response to tadalafil; STEP, safety and pilot efficacy trial in combination with bosentan for evaluation in pulmonary arterial hypertension.
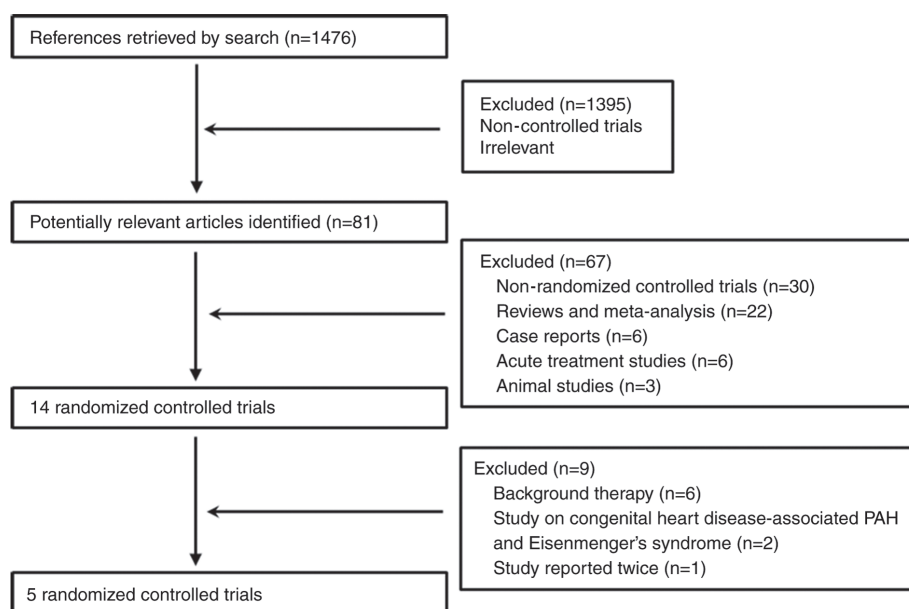

Figure 1. Flow diagram for the studies included in the meta-analysis concerning the therapy effect of bosentan combined with either prostacyclin analogues or phosphodiesterase type 5 inhibitors in PAH. PAH, pulmonary arterial hypertension.

improvement I between bosentan combination therapy and bosentan monotherapy (Fig. 4). The random effects model was used for the analysis. Functional class improvement I from baseline to endpoint of study was indicated to be 18% (18/100) in bosentan combination therapy and 17% (18/105) in bosentan monotherapy (Fig. 4A). The WHO functional class improvement II from baseline to endpoint of study was 4% (4/100) in bosentan combination therapy and 2.9% (3/105) in bosentan monotherapy, without significant heterogeneity ($I^2=0\%$; P=0.44) (Fig. 4B). Therefore, functional class improvements I and II exhibited no significant difference between the bosentan combination and monotherapy groups (P>0.05).

Two of the five trial studies reported the effects of bosentan combination therapy on mean PAP (mPAP; Fig. 5) (33,35).

The difference of mPAP demonstrated an average of only 11.95 mmHg (95% CI: -17.06, -6.83; P<0.00001) between bosentan combination therapy and monotherapy, and there was no heterogeneity between the groups ($I^2=6\%$; P=0.30). These data suggested that combination therapy may significantly reduce mPAP.

One study did not include any data of clinical worsening (35) The clinical worsening rate in combination therapy was 5.5% (8/145) compared with that of monotherapy of 10.5% (16/152). The heterogeneity between the groups was found to be non-significant ($I^2=13\%$; P=0.33). Clinical worsening incidence in the combination therapy was below that of monotherapy (risk ratio, 0.54; 95% CI: 0.25, 1.20), but without statistical significance (P=0.13; Fig. 6).
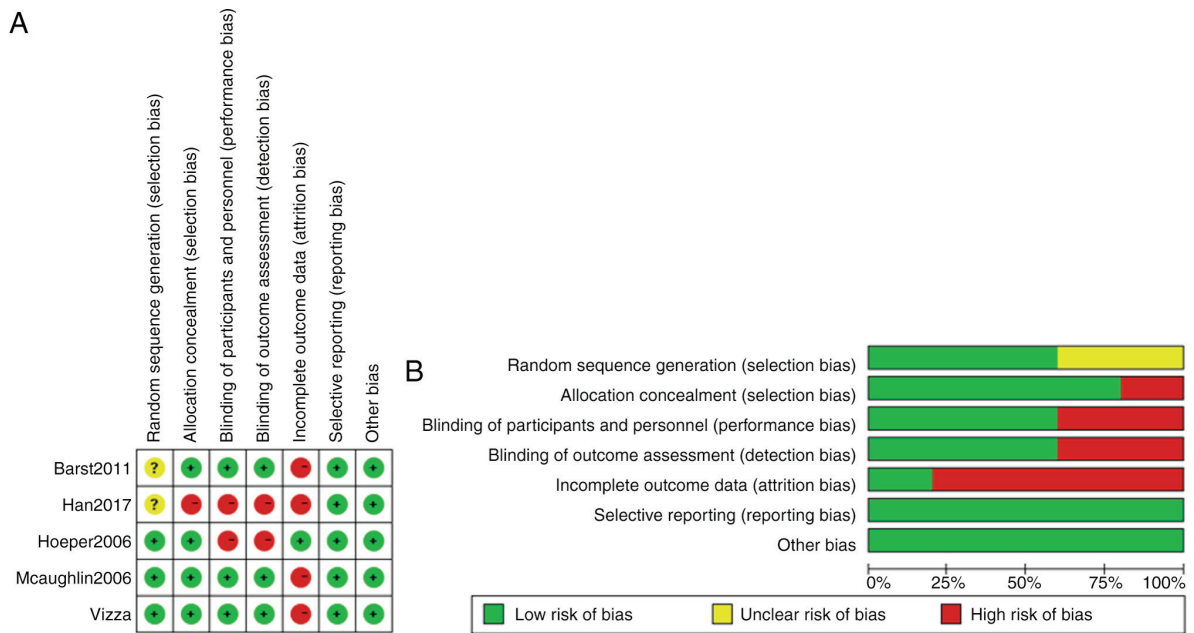
Figure 2. Risk of bias summary. (A) Risk of bias for each included RCT, representing low risk of bias (+), high risk of bias (-), and unclear risk of bias (?). (B) Bar chart comparing percentage risk of bias for each included RCT. Green, low risk of bias high; red, risk of bias; yellow, unclear risk of bias. RCT, randomized controlled trial.
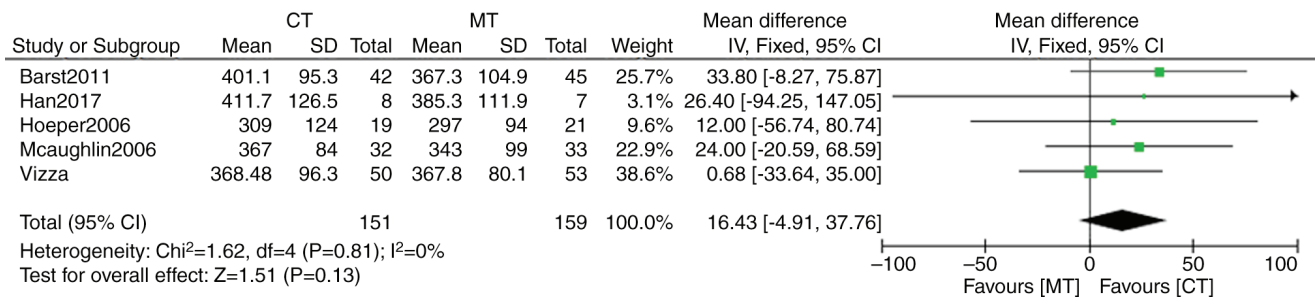

Figure 3. Effect of bosentan combined with prostacyclin analogues or phosphodiesterase type 5 inhibitors vs. bosentan monotherapy on 6MWD. There was no significant heterogeneity (I2=0%; P=0.81) The mean difference of 6MWD was not significant between bosentan combination and bosentan monotherapy (P=0.13). 6MWD, six-minute walking distance; CI, confidence intervals; CT, combination therapy; IV, inverse variance; MT, monotherapy.

Figure 4. Effect of bosentan combined with prostacyclin analogues or phosphodiesterase type 5 inhibitors vs. bosentan monotherapy on WHO functional class improvement. (A) WHO functional class improvement I and (B) WHO functional class improvement II. Functional class improvement I and II from baseline to endpoint of study were not significantly different in bosentan monotherapy and bosentan combination therapy (P>0.05). CI, confidence intervals; CT, combination therapy; M-H, Mantel-Haenszel; MT, monotherapy; WHO, World Health Organization.

Study or Subgroup	CT Mean	SD	Total	MT Mean	SD	Total	Weight	Mean difference IV, Fixed, 95% CI	Mean difference IV, Fixed, 95% CI
Han2017	37.6	8.3	8	52	5.2	7	54.5%	−14.40 [−21.32, −7.48]	
Mcaughlin2006	46	13	29	55	16	28	45.5%	−9.00 [−16.58, −1.42]	
Total (95% CI)			37			35	100.0%	−11.95 [−17.06, −6.83]	

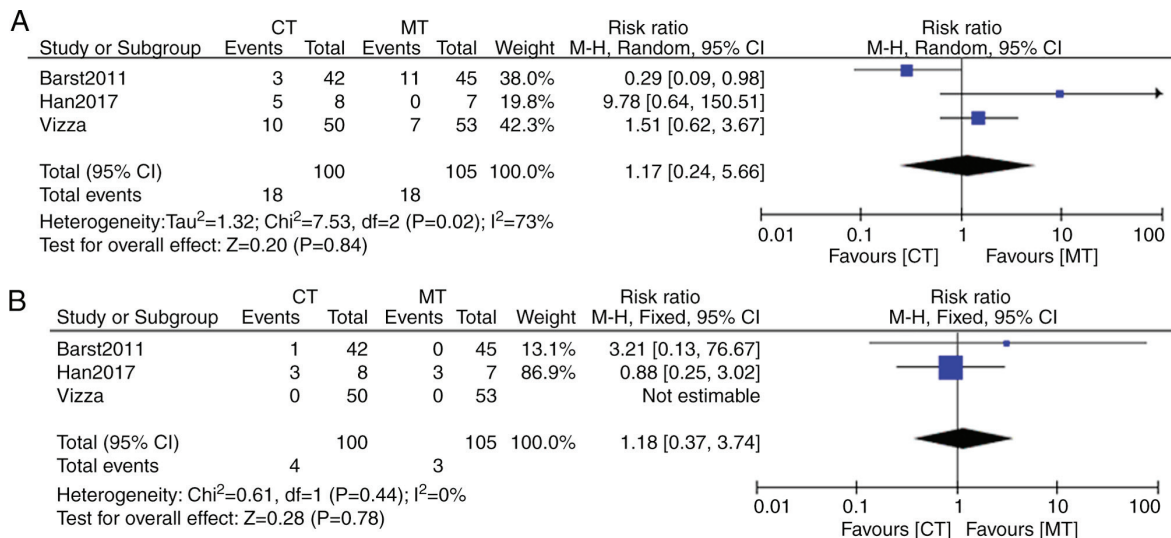Heterogeneity: Chi²=1.06, df=1 (P=0.30); I²=6%
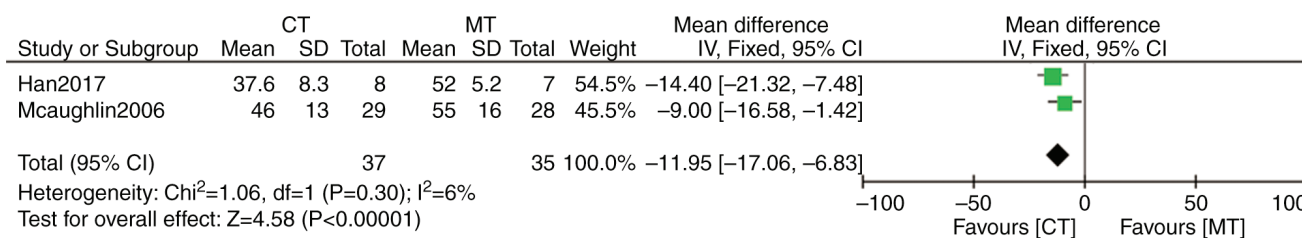Test for overall effect: Z=4.58 (P<0.00001)

Figure 5. Effect of bosentan combined with prostacyclin analogues or phosphodiesterase type 5 inhibitors vs. bosentan monotherapy on mean pulmonary artery pressure. Compared with bosentan monotherapy, combination therapy may significantly reduce mPAP (P<0.05). CI, confidence intervals; CT, combination therapy; IV, inverse variance; MT, monotherapy; SD, standard deviation; mPAP, mean pulmonary artery pressure.

Study or Subgroup	CT Events	Total	MT Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI	Risk ratio M-H, Fixed, 95% CI
Barst2011	2	42	5	45	29.9%	0.43 [0.09, 2.09]	
Hoeper2006	3	19	4	21	23.5%	0.83 [0.21, 3.24]	
Mcaughlin2006	0	34	5	33	34.6%	0.09 [0.01, 1.54]	
Vizza	3	50	2	53	12.0%	1.59 [0.28, 9.12]	
Total (95% CI)		145		152	100.0%	0.54 [0.25, 1.20]	
Total events	8		16				

Heterogeneity: Chi²=3.46; df=3 (P=0.33); I²=13%
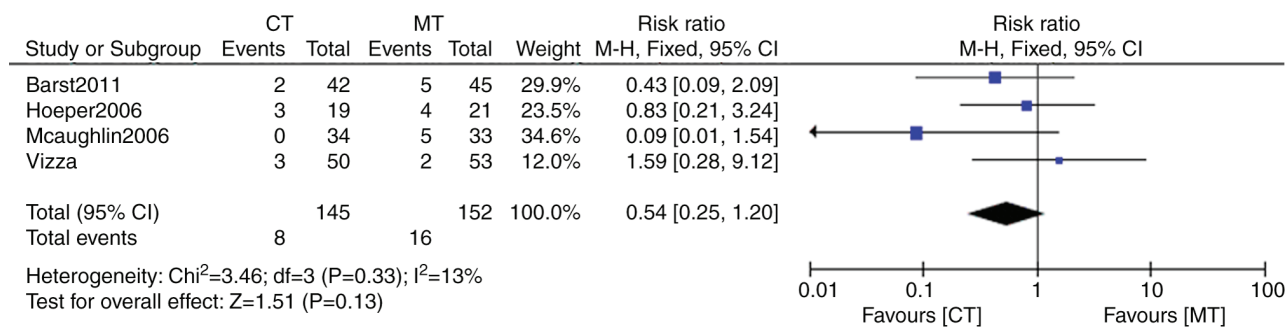Test for overall effect: Z=1.51 (P=0.13)

Figure 6. Effect of bosentan combined with prostacyclin analogues or phosphodiesterase type 5 inhibitors vs. bosentan monotherapy on clinical worsening. The heterogeneity between the groups was found to be non-significant. Clinical worsening incidence in the combination therapy was below that of monotherapy, but without statistical significance (P>0.05). CI, confidence intervals; CT, combination therapy; M-H, Mantel-Haenszel; MT, monotherapy.

Study or Subgroup	CT Mean	Total	MT Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI	Risk ratio M-H, Fixed, 95% CI
Barst2011	39	42	38	45	52.7%	1.10 [0.95, 1.28]	
Han2017	7	8	5	7	7.7%	1.23 [0.72, 2.10]	
Mcaughlin2006	7	35	5	32	7.5%	1.28 [0.45, 3.63]	
Vizza	22	50	23	53	32.1	1.01 [0.65, 1.57]	
Total (95% CI)		135		137	100.0%	1.10 [0.91, 1.32]	
Total events	75		71				

Heterogeneity: Chi²=0.37, df=3 (P=0.95); I²=0%
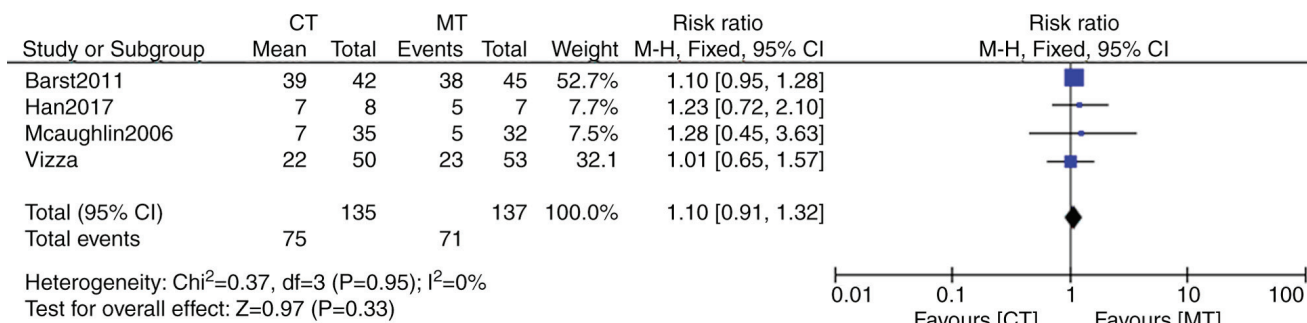Test for overall effect: Z=0.97 (P=0.33)

Figure 7. Effect of bosentan combined with prostacyclin analogues or phosphodiesterase type 5 inhibitors vs. bosentan monotherapy on adverse events. The incidence of adverse events was not significantly different between the bosentan combination therapy and the monotherapy groups (P>0.05). CI, confidence intervals; CT, combination therapy; M-H, Mantel-Haenszel; MT, monotherapy.

All of the five trials described adverse events, but in one study, detailed data on adverse events was not provided (23). These adverse events mainly included headaches, coughing, flushing, chest pains, nausea, dizziness and diarrhea. A total of 71 events (51.8%; n=137) were reported in the monotherapy group, whereas 75 adverse events (55.6%, n=135) were reported in the combination therapy group (Fig. 7). The risk ratio of adverse events between combination and monotherapy was 1.1 (95% CI: 0.91, 1.32). However, the difference between the groups was not statistically significant (P=0.33). Thus, the incidence of adverse events was not significantly different between the bosentan combination therapy and the monotherapy groups.

Discussion

For the present meta-analysis, rigorous selection criteria were applied. Studies of the bosentan treatment within 3 months prior to randomization, and studies in which the control group was treated with bosentan or placebo were included. These criteria resulted in only five studies that were included in this analysis, which comprised a total of 310 subjects. The present meta-analysis referred to the outcomes of previous studies of combination therapy, and also formed the basis on the safety and efficacy of combining bosentan with prostacyclin analogues or PDE-5 inhibitors.

The results from the present meta-analysis demonstrated that bosentan combined with prostacyclin analogues or PDE-5 inhibitors was superior to the bosentan monotherapy in reducing mPAP by 11.95 mmHg. However, compared with bosentan monotherapy, bosentan combined with prostacyclin analogues or PDE-5 inhibitors did not improve exercise capacity, cardiac function or clinical worsening in PAH. Notably 5.5% of the patients in the combination therapy developed clinical worsening compared with 10.5% in monotherapy. The clinical worsening rate was significantly

reduced in the bosentan combination therapy group although the curative effect of treatment was not significant. These data indicated that although bosentan therapy relieved the patient of the symptoms and clinical worsening, it still failed to prevent and slow the progression of PAH. The incidence of adverse events in bosentan combination therapy was similar to that of monotherapy, which suggested that bosentan combination therapy was safe for PAH patients.

Drug interaction is a problem that cannot be ignored in combination drug therapies (37). Although the combination of bosentan with sildenafil or tadalafil could lead to a decrease in plasma concentration of sildenafil and tadalafil, bosentan concentration was increased by inducing cytochrome P450 3A4 isoenzyme. However, the clinical significance of this interaction has not been well established. Currently, there is no evidence that interactions between bosentan and sildenafil decrease drug safety.

Since the treatment regimens among the five studies were different, the effect of bosentan combination therapy could not be harmonized. In some studies, treatment with prostacyclin analogues or PDE-5 inhibitors was initiated prior to treatment with bosentan, whereas in other studies patients were treated with bosentan for some time and then given prostacyclin analogues or PDE-5 inhibitors (27-32). It was difficult to determine which combination therapy regimen was most effective, and current published guidelines do not offer a specific recommended regimen. As the current findings may be limited by the relatively short duration (12 weeks) of the trials, it was not possible to determine the long-term efficacy and safety of bosentan combination therapy. Therefore, the true clinical features and progression of the disease in patients could not be determined. Given the limited number of studies included in the present analysis, the results should be confirmed through future research. A larger randomized controlled trial should be designed for future studies to adequately assess the efficacy and safety of bosentan combination therapy.

In conclusion, results from the present meta-analysis suggested that bosentan combined with prostacyclin analogues or PDE-5 inhibitors do not impart additional advantages for the improvement of the 6MWD, cardiac function, clinical worsening, and incidence of adverse events. However, bosentan combined with prostacyclin analogues or PDE-5 inhibitors may significantly reduce mPAP compared with bosentan monotherapy.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from PubMed, Embase, the Cochrane Library and the www.clinicaltrials.gov website.

Authors' contributions

ZCD, ZQL and DXL contributed to study conception and design; drafted the submitted article, revised it critically for important intellectual content. ZCD and BL independently appraised study quality of the included trials and contributed to the analysis and interpretation of data. RLG contributed to study conception and design. ZCD and BT contributed to acquisition, analysis, and interpretation of data. ZCD and SL contributed to the literature search, acquisition of data, and drafted the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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