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Original article

Prostacyclin and its analogues in pulmonary artery hypertension: a meta-analysis

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Abstract

Objective:
Individual studies examining the effects of prostacyclin and its analogues on pulmonary artery hypertension (PAH) have reported controversial results. This study aims to evaluate the efficacy of these agents for PAH by a meta-analysis based on randomized controlled trials (RCTs).

Research design and methods:
We systematically searched Pubmed, MEDLINE, EMBASE, ISI Web of Science, and the Cochrane Library through April 2012. All published RCTs reporting the effects of treatment with prostacyclin or its analogues in PAH were included. Summary statistics were calculated using a random effects model.

Results:
A total of 14 RCTs with 1606 participants were analyzed. Overall, prostacyclin and its analogues increased 6-minute walk distance (6-MWD) (weighted mean differences [WMD] = 18.78 meters, 95% confidence interval [CI]: 11.21 to 26.35; $p < 0.01$) and improved NYHA functional class status (odds ratios [OR] = 3.98, 95% CI: 1.70 to 9.34; $p = 0.001$) compared with the control. Moreover, these agents led to statistically significant reductions in mean pulmonary artery pressure (mPAP) (WMD = −4.63 mmHg, 95% CI: −6.81 to −2.44; $p < 0.01$) and pulmonary vascular resistance (PVR) (standardized mean difference [SMD] = −0.69, 95% CI: −0.96 to −0.43; $p < 0.01$). Notably, there were distinct effects on these endpoints observed in pooled subgroup analyses based on agent class (all p for interaction < 0.01). In addition, PAH-specific therapy appeared to have superiority over the control in reducing the incidence of all-cause death (OR = 0.49, 95% CI: 0.26 to 0.94; $p = 0.03$). However, there existed a substantial publication bias, which appeared to markedly impact the overall result of 6-MWD.

Conclusions:
PAH-specific treatment with prostacyclin and its analogues significantly improved exercise capacity, cardiopulmonary hemodynamics, and lowered all-cause mortality in patients with PAH.

Introduction

Pulmonary arterial hypertension (PAH), a progressive and devastating disease of unknown etiology, is characterized by elevation of pulmonary artery pressure and pulmonary vascular resistance (PVR) that ultimately results in right ventricular failure and high mortality[1]. Once the diagnosis is established, the estimated median survival is less than 3 years and the 1 year survival rate is 68% in the absence of modern pharmacotherapy[2,3]. PAH is closely associated with reduced pulmonary levels of prostacyclin (epoprostenol) as a result of underexpression of endothelial prostacyclin synthase[4]. Subsequent pulmonary vasoconstriction, in-situ thrombosis, and endothelial dysfunction have been recognized as major pathogenic components of PAH[5]. Thus, prostacyclin pathway plays an important role in promoting the pathogenesis of PAH[6]. Therapies for PAH targeting

the prostacyclin pathway (e.g. prostacyclin or its analogues) are believed to be efficacious by reversing or diminishing vasoconstriction, and by exerting antithrombotic and cytoprotective effects[7–9]. Currently, prostacyclin and its analogues (iloprost, treprostinil, and beraprost) have been widely used in the clinical management of PAH patients on the basis of the promotion of the prostacyclin pathway. Previous meta-analyses have demonstrated the benefits of these agents in improving the efficacy endpoints of exercise tolerance, New York Heart Association (NYHA) functional class status, and pulmonary hemodynamics[10–12]. However, limited study size and the lack of the latest trials included in them might weaken the robustness of their conclusions. In addition, it is notable that these agents have disparate binding affinities for the various prostaglandin receptors and different G-protein-coupled receptor interactions[13]. The question whether the pharmacological differences among prostacyclin and its analogues result in varying clinical efficacy and safety remains uncertain. The issue was not involved in the previous meta-analyses[10–12]. We therefore systematically reviewed all randomized controlled trials (RCTs) comparing prostacyclin or its analogues to placebo or control comparator, and performed a meta-analysis of the available data from RCTs to evaluate the effect of PAH-specific treatment with prostacyclin and its analogues.

Methods

Selection criteria

For inclusion, studies comparing prostacyclin and its analogues (e.g. iloprost, treprostinil, or beraprost) with placebo or conventional medical treatment in patients with PAH regardless of etiology had to have a randomized design and report efficacy or safety endpoints (e.g. 6-minute walk distance [6-MWD], NYHA functional class, mean pulmonary artery pressure [mPAP], PVR, or all-cause mortality). Also studies of adding prostacyclin/its analogues or placebo to stable monotherapy with other PAH-specific drugs (e.g. bosentan, sildenafil) were included in the meta-analysis. Trials were excluded if they directly compared prostacyclin or its analogues with other PAH-specific therapies.

Study identification

A systematic search was conducted for eligible studies. The databases searched included Pubmed, MEDLINE, ISI Web of Science, EMBASE, and the Cochrane Library (through April 2012). Complex search strategies were formulated using the following MESH terms and text words: 'epoprostenol', 'prostacyclin', 'iloprost', 'treprostinil', 'beraprost', 'pulmonary hypertension', 'pulmonary artery hypertension'. Searches were restricted to English-language literature and were first screened by two independent reviewers (W.Z., Y.C.) who looked at titles of papers and the available abstracts. The full text of each article selected was then retrieved and independently assessed by each of the two reviewers for inclusion according to the above prespecified selection criteria. In addition, reference lists of all eligible articles and previous systematic reviews were hand-searched for other relevant papers.

Data extraction

Two investigators (W.Z., Y.C.) independently assessed trial eligibility and quality. Disagreements were resolved by consensus. The quality of included trials was evaluated with the previously validated 5 point Jadad scale on the basis of the following quality criteria: sequence generation of the allocation; concealment of allocation; blinding of participants, personnel, and outcome assessors; use of intention to treat analysis; description of withdrawals and dropouts[14]. A standardized form was used to extract data including characteristics of the study, participant characteristics, treatment strategies, and follow-up duration from the eligible trials. Information on efficacy and safety endpoints was also recorded.

Data aggregation

We pooled treatment effects and calculated weighted mean differences (WMD) or odds ratios (ORs) with 95% confidence intervals (CIs) using random-effects models. Alternatively, standardized mean difference (SMD) was used to investigate the combined results when the individual results were measured with different scales. We tested for heterogeneity with the Cochran Q-test and measured inconsistency (I^2; the percentage of total variance across studies that is due to heterogeneity rather than chance) of treatment effects across trials. Data stratified according to the clinical factors potentially affecting the progression and prognosis of PAH were analyzed by meta-regression methods. Sensitivity analyses were conducted to examine the robustness of the effect by omitting each trial one at a time from analysis, and by deleting trials with observation duration shorter than 24 hours or low Jadad score (<3), and thereafter computing meta-analysis estimates for the remaining studies. Publication bias was quantitatively assessed using the Begg adjusted-rank correlation test[15] and Egger regression asymmetry test[16] based on the changes in 6-MWD, mPAP, and all-cause mortality. If publication bias was found, the 'trim and fill' method was used to correct it and to find the corresponding influence on the combined results[17]. Publication bias analyses and meta-regression analyses were conducted with STATA 10.0 software (Stata Corp., College Station, TX, USA).

The pooled analyses were performed with the RevMan 5.1 software (The Cochrane Collaboration, Copenhagen, Denmark). Results were considered statistically significant at $p < 0.05$.

Results

From the primary electronic databases, we identified a total of 873 articles. No additional citations were identified from reference review (Figure 1). Using the prespecified inclusion criteria, the reviewers identified 28 trials for full review. Upon full text review, 14 relevant studies were included in the meta-analysis[18–31].

Study design and baseline characteristics for each of the qualifying trials are shown in Table 1. The meta-analysis included a total of 1606 participants in the 14 eligible trials: 235 patients in four prostacyclin-treatment trials (one for inhaled delivery and three for intravenous delivery)[18–21]; 395 in five iloprost-treatment trials (all for inhaled delivery)[22–26]; 730 in three treprostinil-treatment trials (one for inhaled delivery and two for subcutaneous delivery)[27–29]; 246 in two beraprost-treatment trials (both for oral delivery)[30,31]. Among them 803 were randomly allocated to receive prostacyclin or its analogues and 803 to the control group. Of the 14 enrolled trials, eight compared prostacyclin or its analogues with placebo[18,20,23,25,27,29–31], three compared these agents with conventional therapy alone[19,21,26], and the other three compared prostacyclin or its analogues plus other PAH-specific treatment (bosentan, sildenafil, or both) with the latter alone[22,24,28]. The mean follow-up duration ranged from 25 minutes to 2 years. The majority of patients in the analysis maintained poor cardiopulmonary function, predominantly with NYHA functional class III or IV, and only two studies enrolled PAH patients in NYHA class II or III[30,31]. There consistently exists moderately increased mPAP ranging from 40 mmHg to 61 mmHg, and moderately decreased exercise tolerance (mean baseline 6-MWD: 225 m to 439 m). The level of evidence for each article was graded with a score of 2 to 5 according to the Jadad quality score (Table 1).

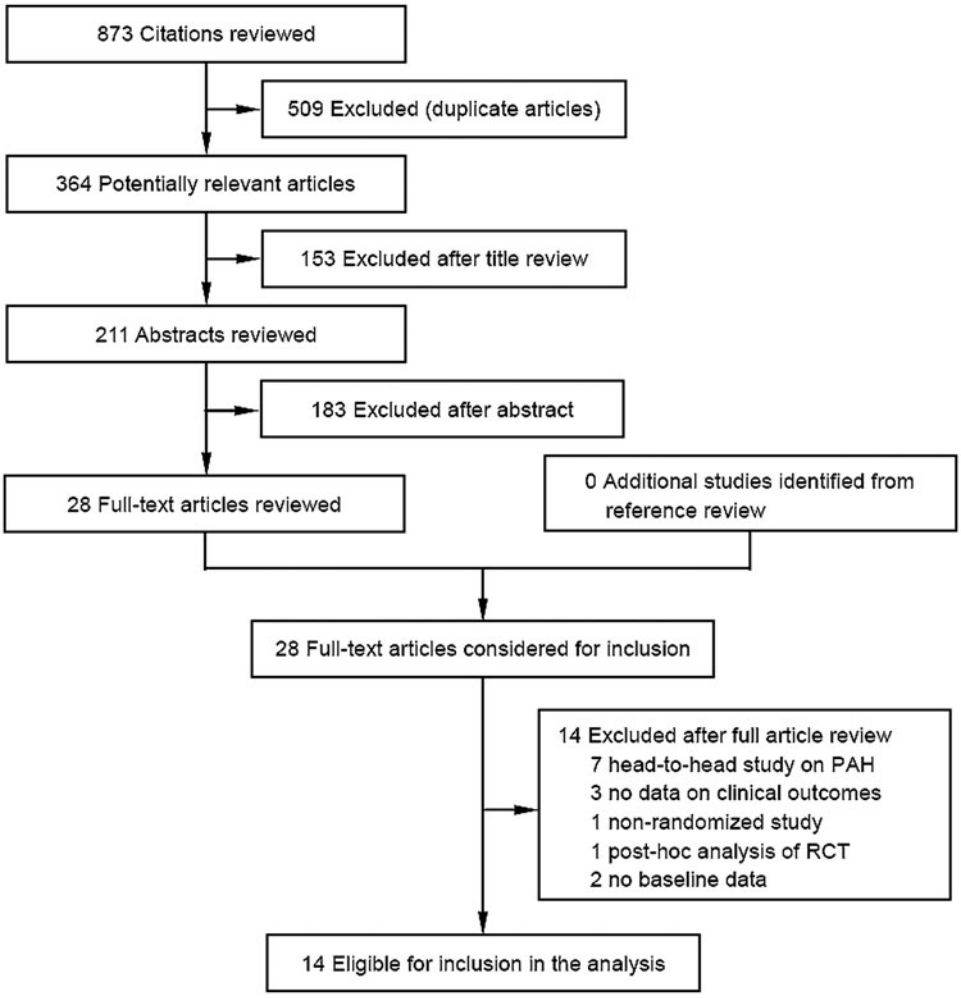

Figure 1. Flowchart of selection of studies for inclusion in meta-analysis. RCTs = randomized controlled trials; PAH = pulmonary arterial hypertension.

Table 1. Baseline characteristics of randomized controlled trials included in the meta-analysis.

Study	No. enrolled	Etiology of PAH	Mean age	Female, %	Mean pulmonary artery pressure (mmHg)	NYHA II/III/IV (%)	Baseline 6-MWD (m)	Drug delivery	Active intervention	Control	Follow-up duration	Jadad score
Badesch[18]	111	Scleroderma	55.1	86.5	50	4.5/78.4/17.1	255	Continuous intravenous	Prostacyclin 11.2 ng/kg/min	Placebo	12 w	4
Barst[19]	81	IPAH	40	72.8	60	0/72.8/27.2	294	Continuous intravenous	Prostacyclin begin with 2 ng/kg/min	Conventional therapy	12 w	4
Hache[20]	20	cardiac surgery with cardiopulmonary bypass	61.5	55.0	40	NA	NA	Inhaled	Prostacyclin 60 ug per day	Placebo	25 min	3
Rubin[21]	23	IPAH	36.2	69.6	60.4	8.7/65.2/26.1	225	Continuous intravenous	Prostacyclin begin with 1–2 ng/kg/min	Conventional therapy	2 m	3
Hoeper[22]	40	IPAH	52	77.5	56.5	0/100/0	306	Inhaled	Iloprost 5 ug q.4.h + bosentan 125 mg b.i.d.	Bosentan	12 w	3
Kramm[23]	22	pulmonary endarterectomy	55	36.4	46	18.2/50/31.8	NA	Inhaled	Iloprost 25 ug per day	Placebo	2 h	4
McLaughlin[24]	67	IPAH/APAH	50	79	52	1.5/94/4.5	335	Inhaled	Iloprost 5 ug per day + bosentan 125 mg b.i.d	Bosentan	12 w	5
Olschewski[25]	203	IPAH/APAH	52.0	67.5	53.3	0/58.6/41.4	323	Inhaled	Iloprost 5 ug, q.4.h	Placebo	12 w	3
Olschewski[26]	63	IPAH/APAH	45.5	69.8	55.6	33.3/47.6/19	341	Inhaled	Iloprost 4 ug, q.4.h	Conventional therapy	2 y	2
McLaughlin[27]	26	IPAH	37	81	57.3	0/96/4	377	Subcutaneous	Treprostinil 13 ng/min/kg	Placebo	8 w	4
McLaughlin[28]	235	IPAH/APAH	53.5	81.3	NA	0/97.9/2.1	349	Inhaled	Treprostinil 54 ug per day + bosentan or sildenafil	Bosentan or sildenafil	12 w	5
Simonneau[29]	469	IPAH/APAH	44.5	81.4	61.0	11.3/81.4/7.3	327	Subcutaneous	Treprostinil 22.5 ng/kg/min	Placebo	12 w	5
Barst[30]	116	IPAH/APAH	42	85.5	55.5	52.5/47.5/0	439	Oral	Beraprost 120 ug q.6.h	Placebo	9 m	4
Galie[31]	130	IPAH/APAH	45.5	61.5	59.5	49.2/50.8/0	373	Oral	Beraprost 80 ug q.6.h	Placebo	12 w	4

APAH = acquired pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; NA = not available; NYHA = New York Heart Association; PAH = pulmonary artery hypertension; 6-MWD = six-minute walk distance.

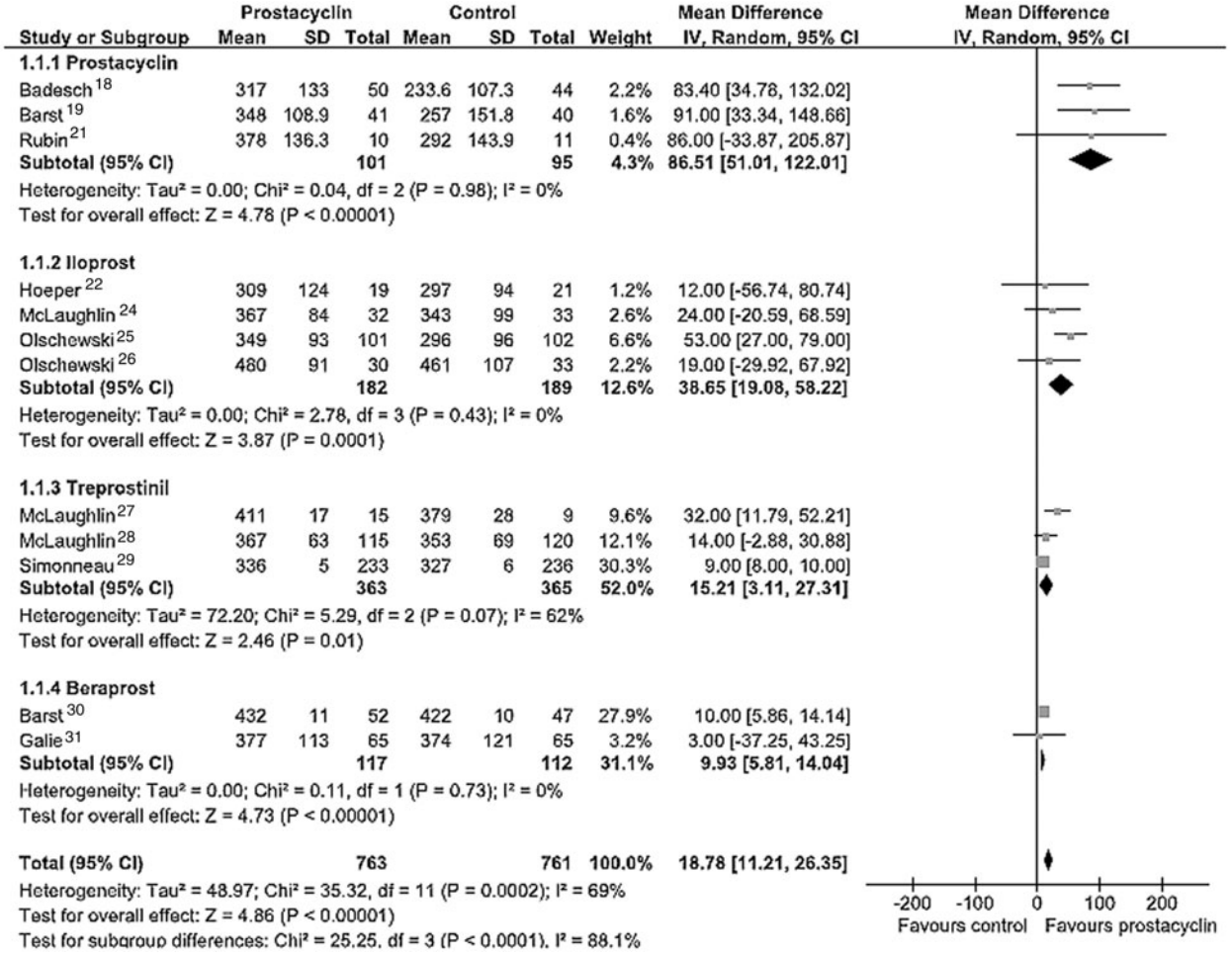

Figure 2. Forest plot of weighted mean differences for 6-minute walk distance in patients treated with prostacyclin or its analogues compared with the control. The size of the square is proportional to the weight of the individual studies. CI = confidence interval; SD = standard deviation.

Overall, PAH-specific treatment with prostacyclin and its analogues brought an absolute increase in 6-MWD from the baseline compared with the control (WMD = 18.78 m, 95% CI: 11.21 to 26.35; $p < 0.01$; $I^2 = 69\%$, Figure 2). Similarly, the benefit was also observed when separately considering PAH-specific agent class (intravenous prostacyclin: WMD = 86.51 m, 95% CI: 51.01 to 122.01; $p < 0.01$; inhaled iloprost: WMD = 38.65 m, 95% CI: 19.08 to 58.22; $p < 0.01$; subcutaneous or inhaled treprostinil: WMD = 15.21 m, 95% CI: 3.11 to 27.31; $p = 0.01$; oral beraprost: WMD = 9.93 m, 95% CI: 5.81 to 14.04; $p < 0.01$, Figure 2). However, the subgroup analysis of treprostinil on the basis of the route of drug administration did not show a benefit regardless of subcutaneous or inhaled delivery (Table 2). In addition, it was notable that there were statistically significant differences among these agents in increasing 6-MWD (p for interaction <0.01). Meanwhile, PAH-specific treatment with prostacyclin and its analogues showed a beneficial effect on improvement in NYHA functional class (OR = 3.98, 95% CI: 1.70 to 9.34; $p = 0.001$; Figure 3). Except for no significant differences being shown in the oral beraprost subgroup, both intravenous prostacyclin and inhaled iloprost delivery significantly improved cardiac functional class (prostacyclin: OR = 35.29, 95% CI: 7.97 to 156.16; $p < 0.001$; iloprost: OR = 2.69, 95% CI: 1.35 to 5.34; $p = 0.005$), with statistically significant differences among the three agents (p for interaction <0.01). The inconsistency in treatment effects ($I^2 = 65\%$) was explicable by the class of target drugs (all p for subgroup heterogeneity test >0.05; Figure 3).

With respect to the variances in pulmonary hemodynamics, overall results revealed that prostacyclin and its analogues led to statistically significant reductions in mPAP (WMD = −4.63 mmHg, 95% CI: −6.81 to −2.44; $p < 0.01$; $I^2 = 83\%$; Figure 4) and PVR (SMD = −0.69, 95% CI: −0.96 to −0.43; $p < 0.01$; $I^2 = 72\%$; Figure 5). Meanwhile, the favorable effects on the two endpoints

Table 2. Subgroup analyses based on the route of drug administration.

Subgroup	6-MWD			mPAP			Mortality		
	No. of studies	WMD (95% CI)	*p* value	No. of studies	WMD (95% CI)	*p* value	No. of studies	OR (95% CI)	*p* value
Intravenous prostacyclin	3	86.51 [51.01, 122.01]	<0.001	3	−6.30 [−8.68, −3.92]	<0.001	3	0.32 [0.06, 1.58]	0.16
Inhaled prostacyclin	–	–	–	1	10.10 [−4.60, 24.80]	0.18	–	–	–
Inhaled iloprost	4	38.65 [19.08, 58.22]	<0.001	4	−7.31 [−9.95, −4.68]	<0.001	5	0.41 [0.14, 1.17]	0.10
Inhaled treprostinil	1	14.00 [−2.88, 30.88]	0.10	–	–	–	1	0.34 [0.01, 8.55]	0.52
Subcutaneous treprostinil	2	18.19 [−3.89, 40.27]	0.11	2	−1.44 [−5.98, 3.10]	0.53	2	0.74 [0.10, 5.49]	0.77
Oral beraprost	2	9.93 [5.81, 14.04]	<0.001	2	−1.71 [−4.06, 0.63]	0.15	2	0.97 [0.17, 5.37]	0.97

6-MWD = six-minute walk distance; CI = confidence interval; mPAP = mean pulmonary artery pressure; OR = odds ratio; WMD = weighted mean difference.

were shown in prostacyclin- and iloprost-treatment subgroups, whereas the benefit was found only in decreasing PVR in the treprostinil subgroup. In contrast, there was no significant difference in either endpoint between PAH-specific therapy and the control in the beraprost subgroup (Figures 4 and 5). The statistically significant differences in attenuating mPAP and PVR were found among these agents (mPAP: p for interaction = 0.009; PVR: p for interaction = 0.04). Notably, intravenous prostacyclin delivery appeared to significantly decrease mPAP in subjects with PAH, whereas inhaled administration did not show the benefit (Table 2).

Moreover, the administration of prostacyclin and its analogues pronouncedly reduced the incidence of all-cause death compared with the control (OR = 0.49, 95% CI: 0.26 to 0.94; $p = 0.03$; $I^2 = 0\%$; Figure 6). However, the findings of pooled subgroup analyses based on drug class did not show the benefit of the individual agents (intravenous prostacyclin: OR = 0.32, 95% CI: 0.06 to 1.58; $p = 0.16$; inhaled iloprost: OR = 0.41, 95% CI: 0.14 to 1.17; $p = 0.01$; subcutaneous or inhaled treprostinil: OR = 0.60, 95% CI: 0.11 to 3.27; $p = 0.55$; oral beraprost: OR = 0.97, 95% CI: 0.17, 5.37; $p = 0.97$; Figure 6). Similarly, the different route of treprostinil administration did not result in a significant difference in therapy effect (Table 2). Of note, when the study by Barst *et al.*[19] was omitted from the analysis the statistical difference in overall estimate vanished (OR = 0.56, 95% CI: 0.29 to 1.08; $p = 0.08$; $I^2 = 0\%$).

Except for the above process, omission of each trial one at a time from the analysis, or deleting the studies with shorter-term observation[20,23] or lower Jadad score[26] did not have any relevant influence on the overall results of the analysis, which further confirmed in direction and magnitude all the results in the present study.

In addition, meta-regression analysis demonstrated that clinical factors, such as age, gender percentage, baseline NYHA functional class, baseline mPAP, baseline 6-MWD, etiology, type of control, and follow-up duration, had no influence on the overall results in the meta-analysis (all $p > 0.10$). Notably, publication bias was found in Egger's test for the 6-MWD (Egger's test: $p = 0.006$; Begg's test: $p = 0.37$). After conducting the 'trim and fill' method to correct the potential publication bias, an overall estimate was changed from the primary overall results (logOR = 0.06, 95% CI: 0.004 to 0.923; $p = 0.04$). It suggested that there might be a significant impact of publication bias on the pooling result on 6-WMD. In addition, neither Egger's test nor Begg's test based on the data on mPAP and all-cause mortality showed statistical significance (Egger's test: $p = 0.68$, 0.22, respectively; Begg's test: $p = 0.59$, 0.95, respectively).

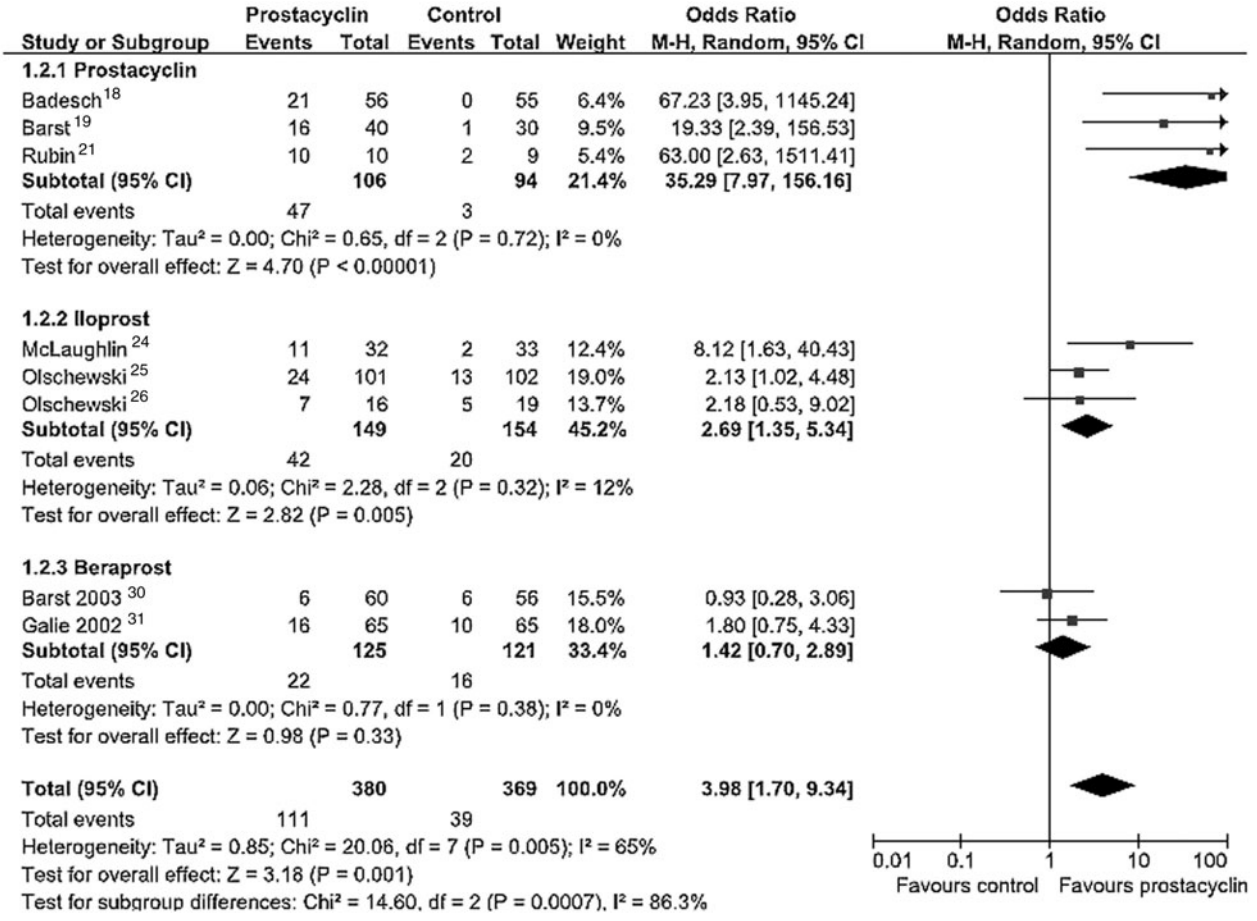

Figure 3. Forest plot of odds ratios for NYHA functional class status in patients treated with prostacyclin or its analogues compared with the control. CI = confidence interval.

Discussion

The study revealed that compared with the control PAH-specific treatment with prostacyclin and its analogues significantly increased 6-MWD and lowered NYHA functional class as well as reducing mPAP and PVR in patients with PAH regardless of etiology. Moreover, there were significant differences in improving these efficacy endpoints among prostacyclin and its analogues with distinct access of delivery. Intravenous prostacyclin delivery seemed likely to be associated with the reduced mPAP. However, inhaled administration did not show a beneficial effect. Also these agents showed superiority over the control in reducing all-cause mortality in PAH patients.

The 6-minute walk test and NYHA functional classification have served as the primary efficacy measure in the majority of clinical studies on PAH-specific therapies, either singly or as part of a composite endpoint[32,33]. Although prostacyclin, the first prostaglandin receptor agonist approved by The U.S. Food and Drug Administration[1], had been verified effective in improving 6-MWD and NYHA functional class in patients with PAH, the issue of whether its analogs characterized by more stable physical property and convenient administration exert a more beneficial effect remains unclear. Previous meta-analyses did not investigate the intra-drug class differences in efficacy endpoints among these agents[10,11]. In the present study, the beneficial effects of prostacyclin and it analogs on exercise tolerance and cardiac functional class status were confirmed based on the latest available clinical evidence. Moreover, we did not find a superiority in prostacyclin analogues over prostacyclin, and prostacyclin seemed likely to be more favorable in improving 6-MWD and NYHA functional class than its analogues.

Similarly, the benefit of prostacyclin and its analogues in improving pulmonary hemodynamic circulation was shown in the present study. The distinct effect of different agents was also found. Intravenous prostacyclin and inhaled iloprost showed a benefit in improving pulmonary hemodynamics compared with the control. There was no

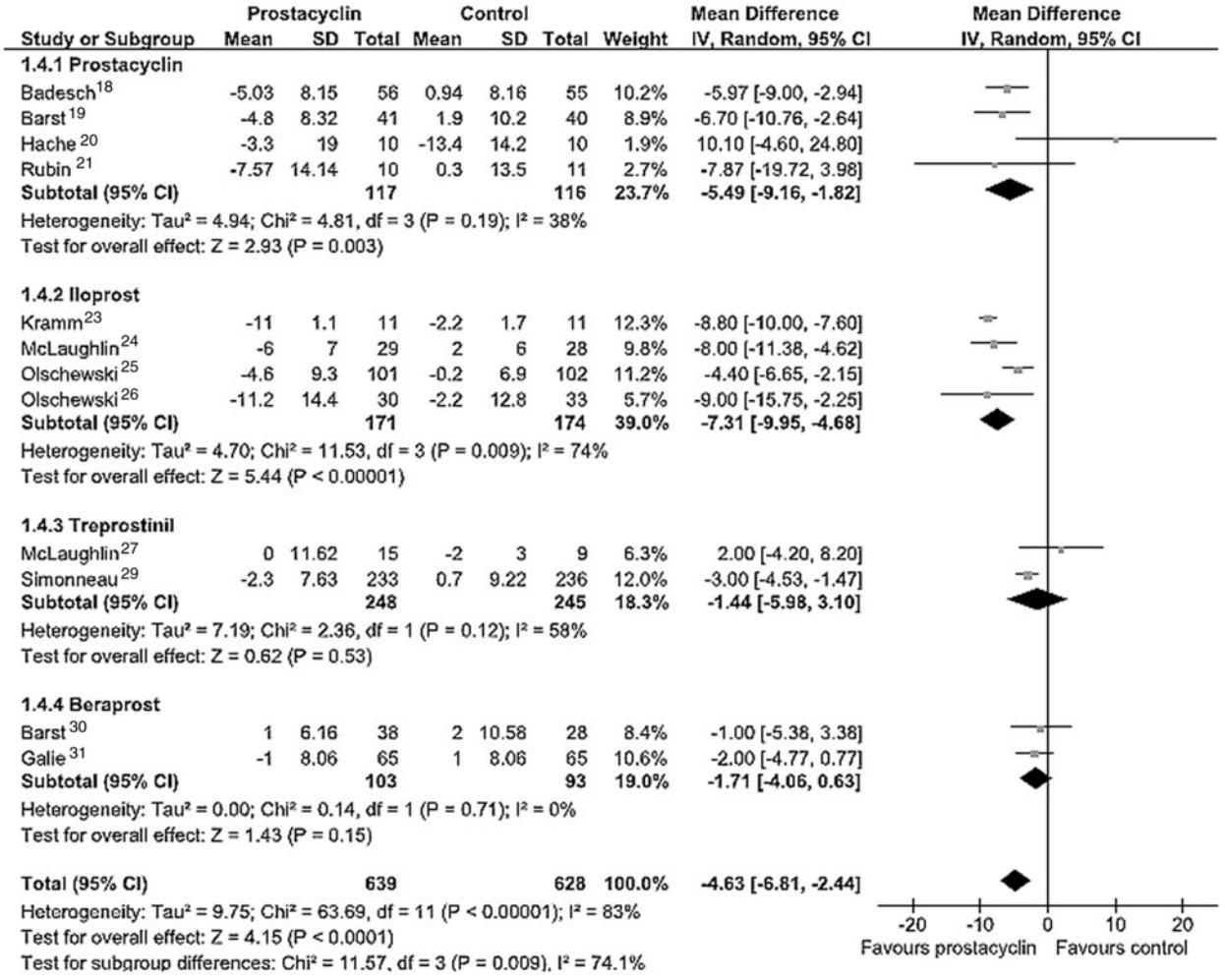

Figure 4. Forest plot of weight mean differences for mean pulmonary arterial pressure in patients treated with prostacyclin or its analogues compared with the control. CI = confidence interval; SD = standard deviation.

significant benefit shown in the oral beraprost treatment subgroup. The baseline characteristics of subjects in the two enrolled small-scale studies[30,31] might partially explain the disappointing findings. Of 14 studies enrolled in the present meta-analysis, only the two studies involving oral beraprost treatment enrolled PAH subjects with relatively mild (NYHA class II to III) symptoms, whereas other studies consistently selected PAH cases with predominantly more severe (class III to IV) symptoms. It might be difficult for PAH patients with the lower NYHA functional class to significantly improve quality of life following oral beraprost treatment. Moreover, oral delivery access might suffer from first pass effect so that the dose reaching the lungs has been lower than other accesses. It might be the other reason for the neutral result in the oral beraprost subgroup. Nevertheless, the benefits of oral beraprost cannot be denied based on the pooled subgroup analysis. We therefore need to further identify the specific patients who could achieve benefit from PAH-specific therapy.

The question whether the favorable effects on cardiopulmonary function and dynamics eventually translated into a clinically significant benefit was under investigation. Some data have demonstrated that increased exercise capacity and cardiopulmonary dynamics were strong independent predictors of reduced morbidity and mortality[34–36]. However, others provided an opposite result[37,38]. In the meta-analysis based on the available latest RCTs, the overall estimates demonstrated the prognostic value of prostacyclin and its analogues in reducing the risk of death in patients with PAH. Although the benefit vanished in a statistically rigorous analysis that omitted the study by Barst *et al.*[19] from the meta-analysis, we still observed a tendency toward reduction in all-cause mortality as a result of PAH-specific therapy. In addition, the clinical benefit was not detected in the subgroup analyses according to

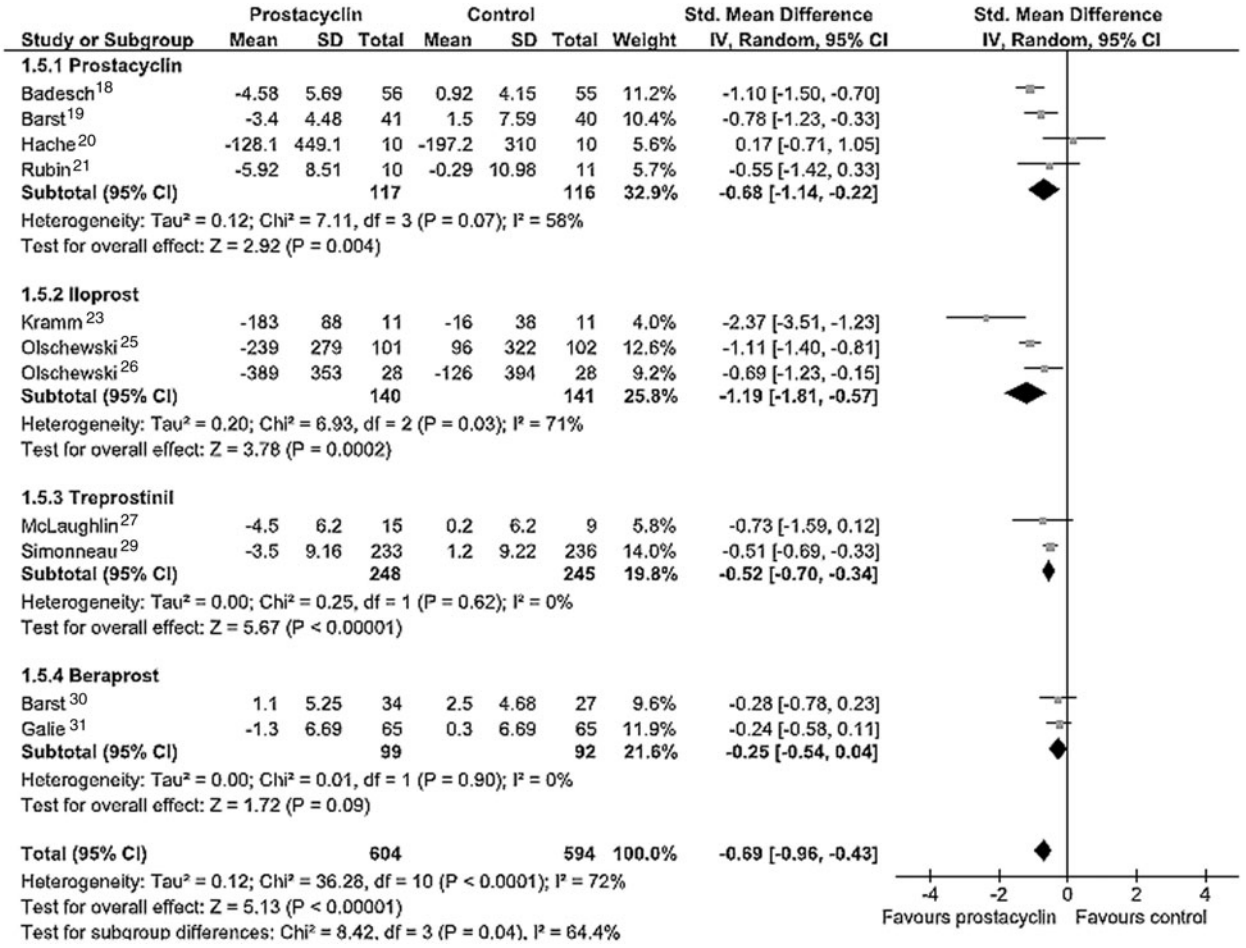

Figure 5. Forest plot of standardized mean difference for pulmonary vascular resistance in patients treated with prostacyclin or its analogues compared with the control. CI = confidence interval; SD = standard deviation.

drug class. When the individual trials in each subgroup were pooled, prostacyclin and its analogs did not significantly increase survival rate in PAH patients compared with the control. Notably, follow-up duration in the majority of the enrolled trials ranged from 8 weeks to 12 weeks. It seemed to be too short to find the prognostic benefit as a result of prostacyclin and its analogues. That is to say, the occurrence of treatment-related benefit in clinical outcome might appear later than functional improvement.

The findings of the meta-analysis were generated based on appropriate meta-analytic techniques with random-effects models. Sensitivity analysis further confirmed the reliability and stability of the main results in this study. Obviously, these yielded methodological support to the robustness of our overall analysis. A major limitation of our study was that there existed a substantial publication bias which might influence the overall results when the efficacy endpoint of 6-WMD was analyzed. Nevertheless, we performed the 'trim and fill' analysis to correct and evaluate the impact on the overall result. Moreover, the biases were not found in the analyses of other endpoints. Due to the limited study numbers, the current meta-analysis did not further investigate the dose-dependent effect of prostacyclin and its analogues.

Conclusion

Based on the available data from RCTs, our meta-analysis demonstrated substantial benefits from prostacyclin and its analogs, indicating that these agents significantly improved exercise capacity, cardiopulmonary hemodynamics, and lowered all-cause mortality in patients with PAH regardless of cause. The distinct agents and different delivery access might have the different effect on improving efficacy endpoints of PAH subjects. These observations supported the concept of therapies for PAH targeting the prostacyclin pathway as a promising treatment option for PAH.

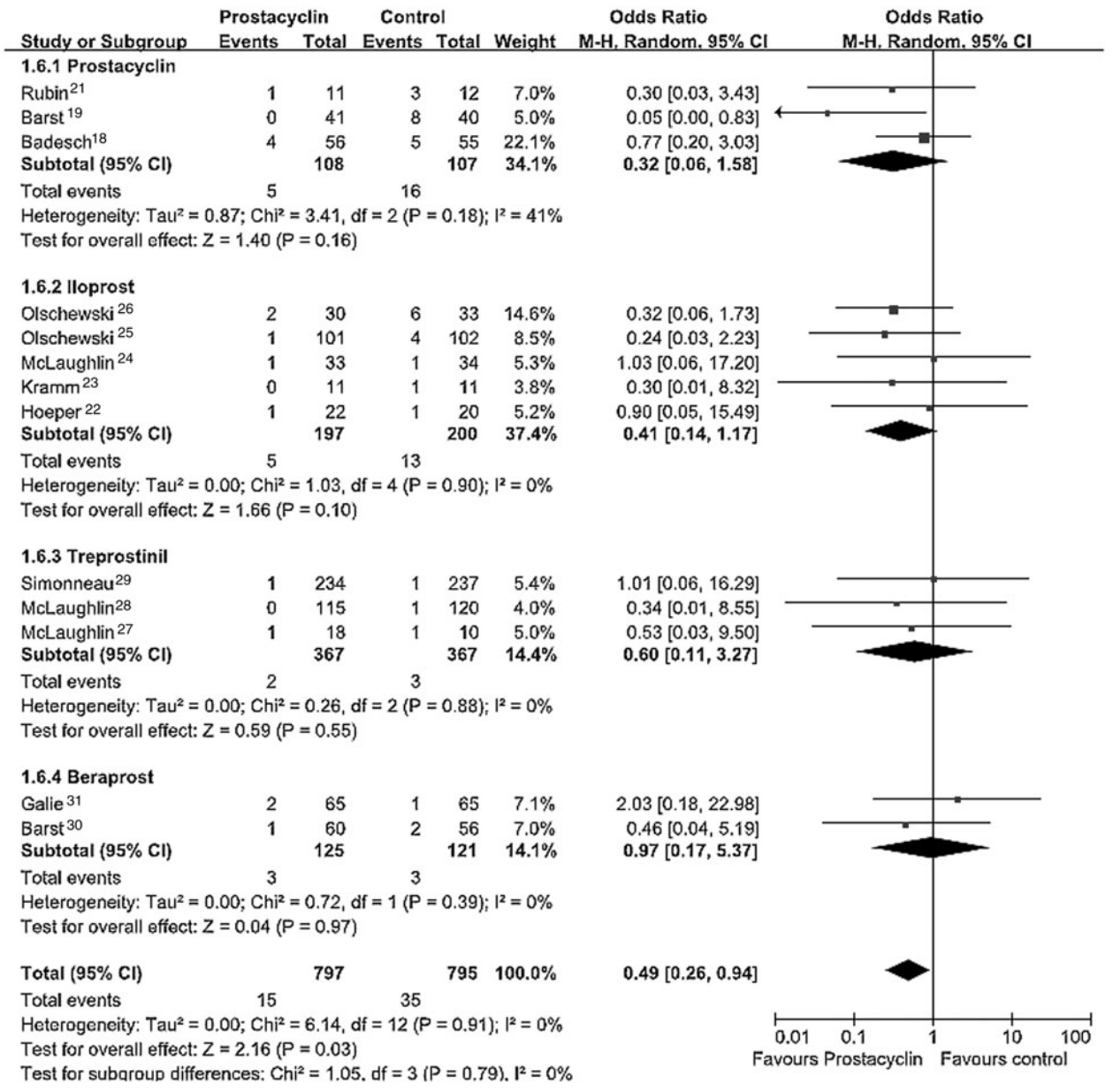

Figure 6. Forest plot of odds ratios for all-cause mortality in patients treated with prostacyclin or its analogues compared with the control. CI = confidence interval.

Transparency

Declaration of funding

This work was not funded by an industry sponsor.

Declaration of financial/other relationships

T.L., W.Z., Y.C., N.G., S.M. and X.L. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

T.L. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The study concept and design was carried out by T.L. Data collection was carried out by W.Z. and Y.C. Data analysis/interpretation was carried out by T.L., N.G. and S.M. T.L., W.Z. and Y.C. drafted the article. S.M. and X.L. carried out critical revision of the article. All authors approved the submitted and final versions.

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