African Journal of Pharmacy and Pharmacology Vol. 5(20), pp. 2199-2208, 29 November, 2011
Available online at http://www.academicjournals.org/AJPP
DOI: 10.5897/AJPP11.188
ISSN 1996-0816 ©2011 Academic Journals

Full Length Research Paper

Efficacy and safety of prostacyclins therapy in pulmonary arterial hypertension: A meta-analysis

Xi-Qian Xing[1#], Bei Han[2#], Xu-Wei Wu[1], Yi Xiao[1] and Shang-Jie Wu[2]*

[1]First Department of Respiratory Medicine, Yan'An Hospital Affilliated to Kunming Medical College, Kunming, Yunnan, P.R. China.
[2]Department of Respiratory Medicine, the Second Xiangya Hospital, Central South University, Changsha, Hunan, P.R. China.

Accepted 4 May, 2011

Prastacyclins have played a prominent role in the treatment of pulmonary arterial hypertension (PAH). To evaluate the efficacy and safety of prostacyclins therapy in PAH, a search was performed in PubMed, OVID and EMBASE to identify relevant articles randomized controlled trials and a meta-analysis was conducted. Ten documents (including 1261 patients) accorded to the demand of enrollment. Compared with placebo treatment, prostacyclins can improve exercise capacity, cardiac function and clinical symptoms, decrease mean pulmonary arterial pressure and pulmonary vascular resistance, and may not be able to reduce the mortality of severe PAH patients in short-term. Generally, PAH patients can tolerate headache, injection site pain and other side effects.

Key words: Prostacyclin, pulmonary arterial hypertension, meta-analysis.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a debilitating chronic disorder of the pulmonary vasculature characterized by elevated mean pulmonary arterial pressure and pulmonary vascular resistance, right-sided heart failure and early mortality (Benedict et al., 2007). True incidence of PAH is unknown, but it is calculated that one to two new cases of primary PAH per million inhabitants in the general population (Nauser and Stites, 2001; Widlitz and Barst, 2003). Mortality associated with PAH is extremely elevated. Once diagnosis has been confirmed mean survival among adults is 2.8 years (D'Alonzo et al., 1991). Early diagnosis and treatment will improve the quality of life of patients with PAH. Prastacyclins have played a prominent role in the treatment of PAH. They are potent vasodilators in both the pulmonary and systemic circulations and inhibitors of platelet aggregation, and can (treprostinil), orally (beraprost) and inhaled (iloprost).In be given intravenously (epoprostenol), subcutaneously this study, in order to gather reliable evidence, we present the data of a meta-analysis on randomized controlled trials (RCTs) with prostacyclins performed exclusively in PAH patients published from January 1994 to January 2010.

*Corresponding author. E-mail: shangjie_wu@yahoo.com. Tel: +86 731 8536 2066. Fax: +86 731 8417 6669.

[#] These authors contributed equally to this work and are joint-first authors.

PATIENTS AND METHODS

Search strategy

A search was performed in PubMed, OVID and Embase (all from January 1994 to 2010) to identify relevant articles RCTs about the efficacy and safety of prostacyclins therapy in PAH patients, using the terms 'pulmonary hypertension', 'pulmonary arterial hypertension', 'prostacyclin' limited with human and randomized controlled trial. Each study was used as a unit for statistical analysis.

Inclusion criteria

These include: (1) Randomized controlled trials; (2) Participants were adult patients with PAH, including idiopathic PAH, familial PAH, as well as connective tissue disease, pulmonary shunt, portal hypertension, HIV infection and thyroid disease; (3) Conventional

therapy or placebo-control study; (4) the participants were assessed at least an indicator of the following: 6 min walk distance (6 MWD), Borg dyspnea score, cardiac index, mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR), mortality, clinical deterioration and adverse effects.

Exclusion criteria

Once meeting one of the following criteria it was excluded from the study: (1) Open, prospective trials and uncontrolled trials; (2) Participants accepted prostacyclin therapy in perioperative period; (3) Children with PAH; (4) The repeated information of the same study population or duplicate publication.

Study quality and data extraction

The quality of the study and the extracted data were assessed independently by two reviewers. When we could not reach a consensus, we addressed the relevant experts for theirs opinion. Assessments of the quality of studies selected for inclusion were based on the Jadad scale (Jadad et al., 1996). The principal information obtained included: first author, quality score, therapy program, the number of cases and valuable patients, average age, sex ratio, type of PAH, basic mPAP, the variance of 6 MWD, Borg dyspnea score, cardiac index, mPAP and PVR, mortality, clinical deterioration and the incidence of adverse effects.

Data analysis

Data analyses were performed using Review Manager 5.0.17 supplied by the Cochrane collaboration. Outcomes were analysed as continuous and dichotomous outcomes, and the relative risk (RR), weighted mean difference (WMD) and their 95% confidence interval (95% CI) were calculated respectively. The variability of the selected studies was evaluated through a heterogeneity test using models with fixed effects when the test was statistically non-significant ($P \geq 0.05$) and random effects when the test was statistically significant ($P < 0.05$). In order to avoid the non-reliable results caused by low quality of the trials, sensitivity analyses were performed by excluding the trials of low score. Finally, we have analyzed publication bias by mapping funnel plot. All statistical tests for efficacy variables were two-tailed, with an alpha level of 0.05.

RESULTS

Characteristics of the studies

We select 10 RCTs (Badesch et al., 2000; Barst et al., 1996, 2003; Galie et al., 2002; Hoeper et al., 2006; McLaughlin et al., 2003, 2006; Olschewski et al., 2002; Rubenfire et al., 2007; Simonneau et al., 2002) meeting the inclusion criteria finally. Table 1 shows the 10 RCTs characteristics recruiting 1261 patients with pulmonary arterial hypertension that have been conducted over a 16-year period. The length of the study periods was from 8 up to 12 weeks.

Six-minute walk distance

Investigational treatments significantly improved exercise capacity as assessed by the 6 MWD. The overall heterogeneity test provided statistically non-significant results ($P = 0.77$). The evaluated mean improvement of exercise capacity assessed by the fix effect model in patients allocated to active treatments in the 7 RCTs (70%) reporting this index (Figure 1) was 28.81 m (95% CI 16.50, 41.13, $P < 0.00001$).

Borg dyspnea score

In the 7 RCTs reporting that contained Borg dyspnea score data, investigational treatments significantly improved exercise capacity as assessed by the Borg dyspnea score. The overall heterogeneity test of 6 RCTs (60%) provided statistically non-significant results ($P = 0.55$). The weighted mean improvement of exercise capacity assessed by the fix effect model in patients allocated to active treatments was -0.69 (95% CI -1.00, -0.37, $P < 0.0001$) (Figure 2). One RCT showed that the mean of Borg dyspnea score in patients allocated to active treatments decreased by 2.0, and that of the patients treated with placebo increased by 1.0.

Haemodynamic parameter

Investigational treatments significantly improved haemodynamic parameters as assessed by cardiac index, mean pulmonary arterial pressure and pulmonary vascular resistance. The weighted mean increase in cardiac index in patients allocated to active treatments in the 8 RCTs (80%) reporting this parameter (Figure 3) was 0.30 0.30 L/min/m^2 (95% CI 0.18, 0.43, $P < 0.00001$). The weighted mean reduction of PmAP in patients allocated to active treatments in the 7 RCTs (70%) reporting this parameter (Figure 4) was -4.31 mmHg (95% CI -6.13, -2.50, $P < 0.00001$). The weighted mean reduction in pulmonary vascular resistance in patients allocated to active treatments in the 7 RCTs (70%) reporting this parameter (Figure 5) was -4.07 mmHg (95% CI -4.71, -3.42, $P < 0.00001$). Statistical tests indicated the existence of heterogeneous study results for the first two haemodynamic parameters ($P = 0.009$ and 0.01) and those data were assessed by the random effect model.

Heterogeneity test of the third parameter provided statistically non-significant results ($P = 0.14$), so the third parameter was assessed by the fix effect model.

Clinical deterioration and mortality

The criteria of clinical deterioration were: PAH patients met two or more of the following criteria: refractory systolic arterial hypotension (blood pressure, less than 85 mmHg); worsening right ventricular failure; rapidly progressing cardiogenic, hepatic or renal failure; a decrease of at least 30% in the distance walked in 6 min; and a decline in measures of hemodynamic function such

Table 1. Characteristics of the 10 studies included in the meta-analysis.

First author	Quality score	Therapy program	Number of patients	Number of valuable patients	Average age	Male/female	Basic mPAP (mmHg)
Badesch (2000)	3	Epoprostenol (2.2-11.2 ng/kg/min) + conventional therapy and conventional therapy, 12 weeks.	111	111	55	15/96	50
Barst (1996)	3	Epoprostenol (4-9.2 ng/kg/min) + conventional therapy and conventional therapy, 12 weeks.	81	81	40	22/59	60
McLaughlin (2003)	4	Treprostinil (2.5-20 ng/kg/min) and placebo, 8 weeks.	26	24	37	5/21	61.5
Rubenfire (2007)	2	Treprostinil (22.3-32.2 ng/kg/min) and placebo, 8 weeks.	22	22	44	3/19	Unknown *
Simonneau (2002)	5	Treprostinil (1.25-22.5 ng/kg/min) and placebo, 12 weeks.	470	469	44	87/382	61
Barst (2003)	4	Beraprost (20-200 ug, QID) and placebo, 12 months.	116	116	42	17/99	55.5
Galie (2002)	4	Beraprost (20-120 ug, QID) and placebo, 12 weeks.	130	130	45	50/80	59.5
Hoeper (2006)	3	Iloprost (5 ug per inhalation, 6 times per day) and placebo, 12 weeks.	40	40	52	9/31	56.5
McLaughlin (2006)	3	Iloprost (5 ug per inhalation 6 times per day) and placebo, 12 weeks.	67	65	50	14/53	52
Olschewski (2002)	4	Iloprost (2.5-5 ug per inhalation, 6-9 times per day) and placebo, 12 weeks.	203	203	52	66/137	53

* showed no basic mPAP, but its WHO functional class of PAH is II～III.

such as central venous pressure and mixed venous oxygen saturation. Investigational treatments significantly released clinical deterioration (Figure 6). The overall heterogeneity test provided statistically non-significant results (P = 0.23). The total RR of this parameter in patients allocated to active treatments in the 10 RCTs assessed by the fix effect model was 0.50 (95% CI 0.33, 0.76, P = 0.001). In the 10 RCTs reporting all-cause mortality, investigational treatments did not decrease mortality (Figure 7). The overall heterogeneity test of 10 RCTs provided statistically non-significant results (P = 0.29).

The total RR of patients allocated to active treatments assessed by the fix effect model was 0.53 (95% CI 0.28, 1.01, P = 0.05).

Adverse effects

In the 7 RCTs (70%) reporting the most prominent

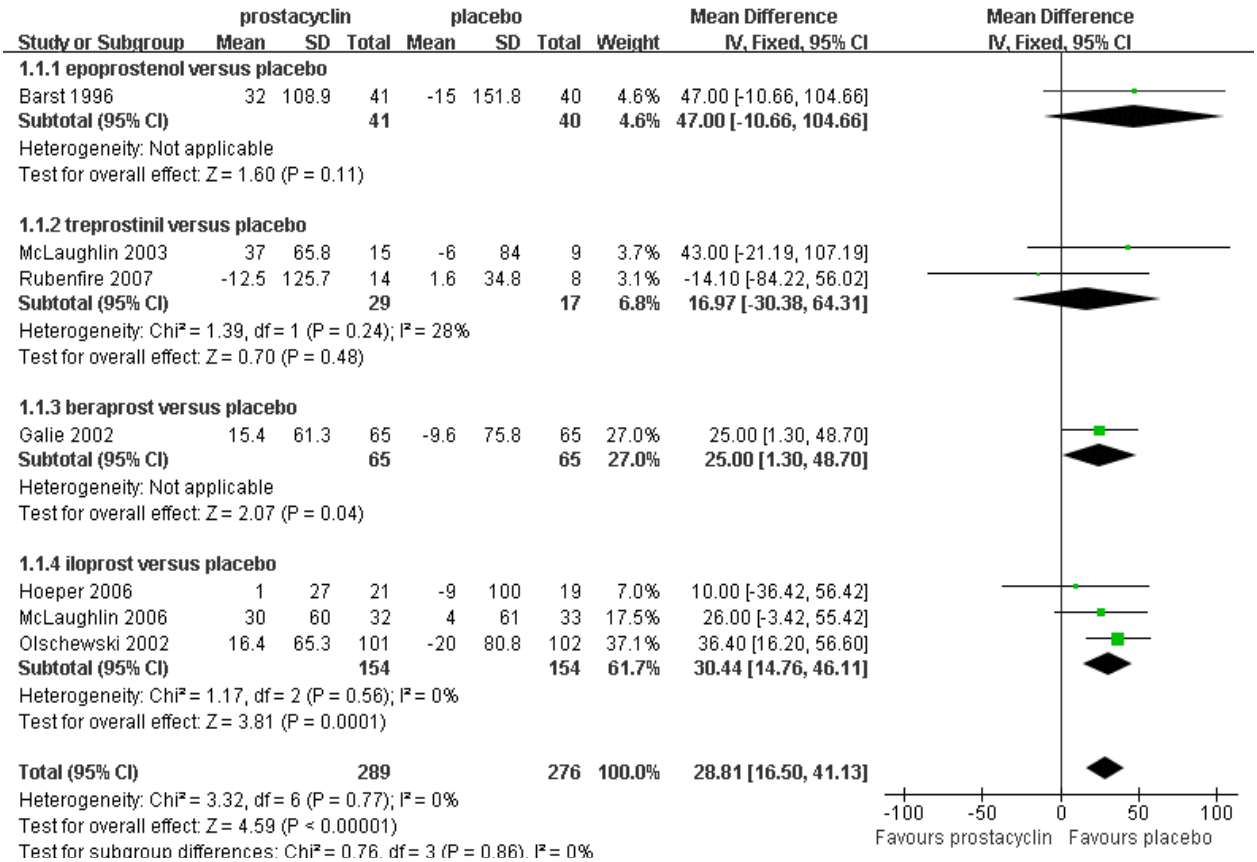

Figure 1. Meta-analysis of 6 min walk distance. CI = confidence interval.

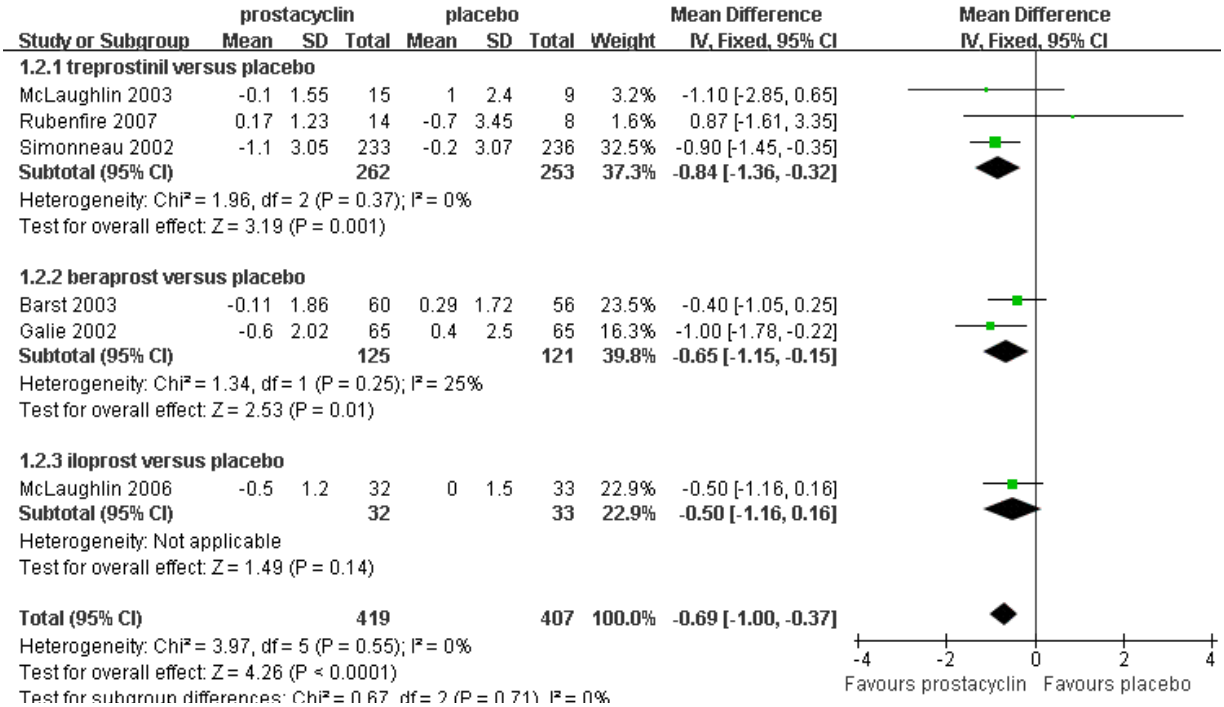

Figure 2. Meta-analysis of Borg dyspnea score. CI, confidence interval.

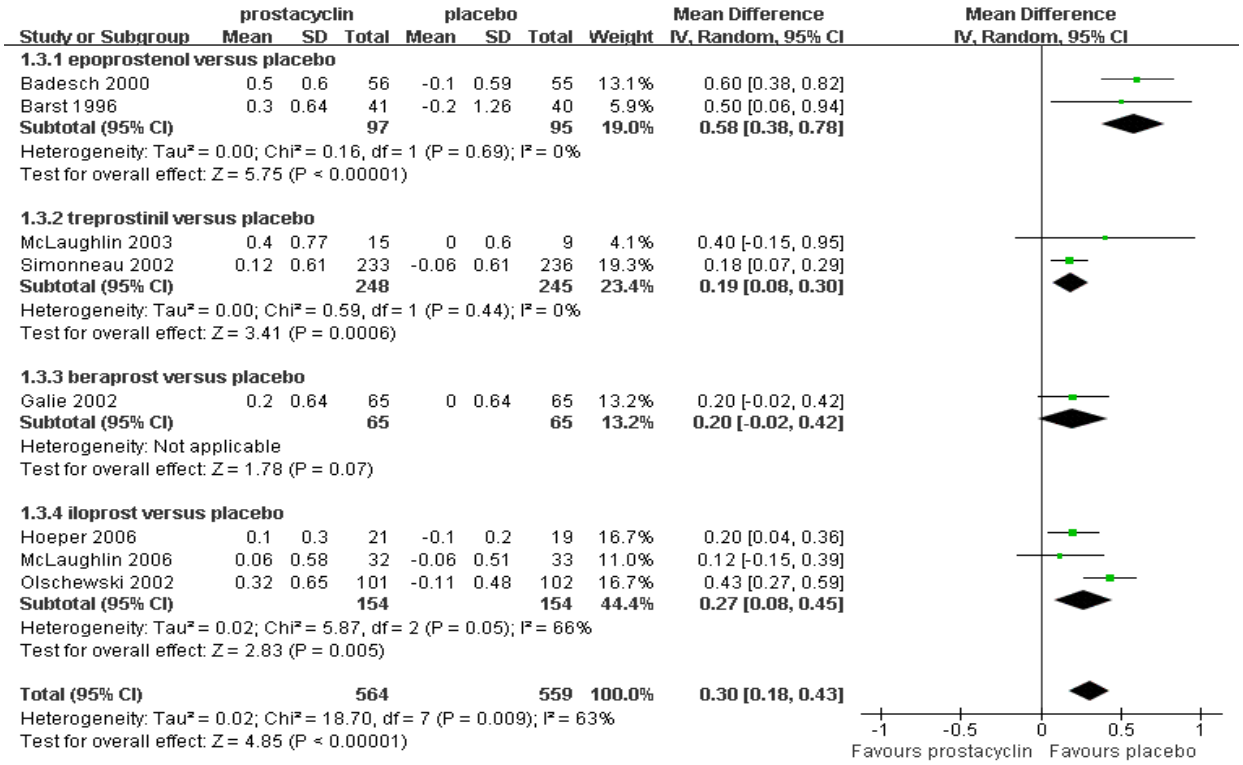

Figure 3. Meta-analysis of cardiac index. CI, confidence interval.

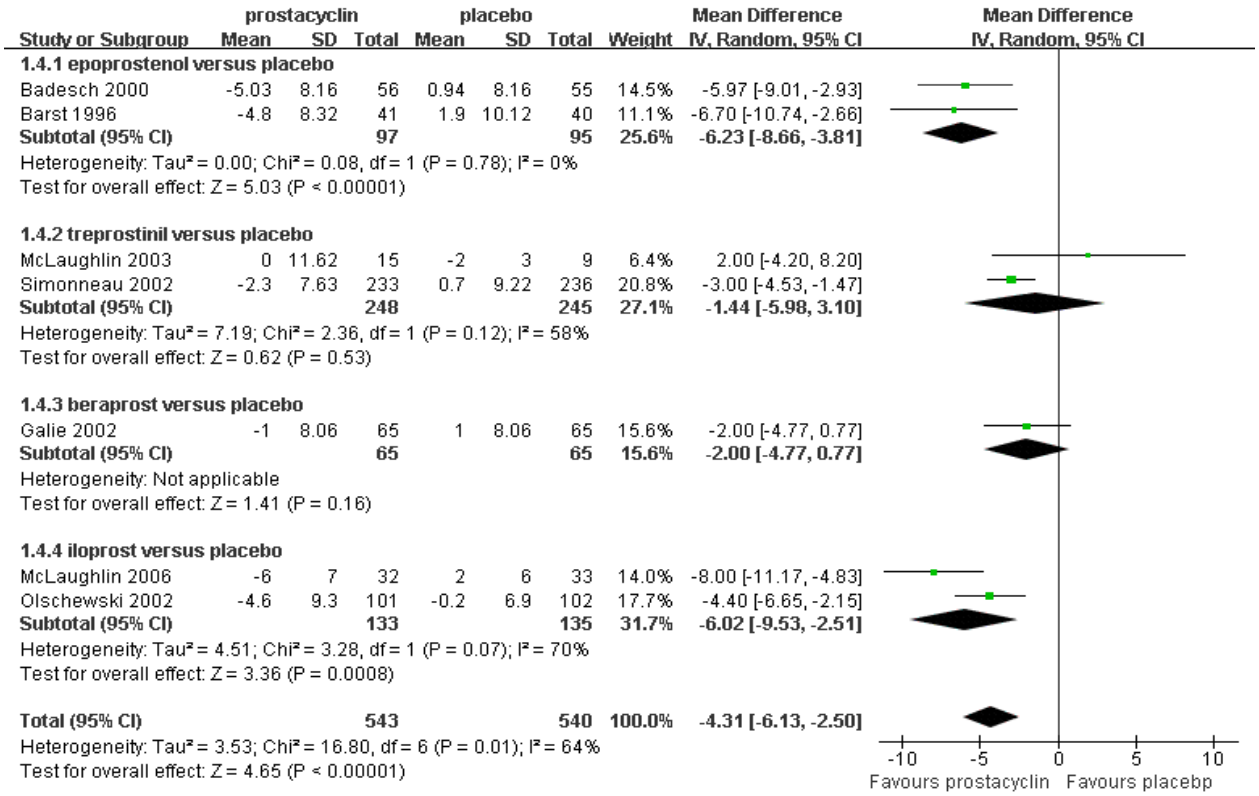

Figure 4. Meta-analysis of mean pulmonary arterial pressure. CI = confidence interval.

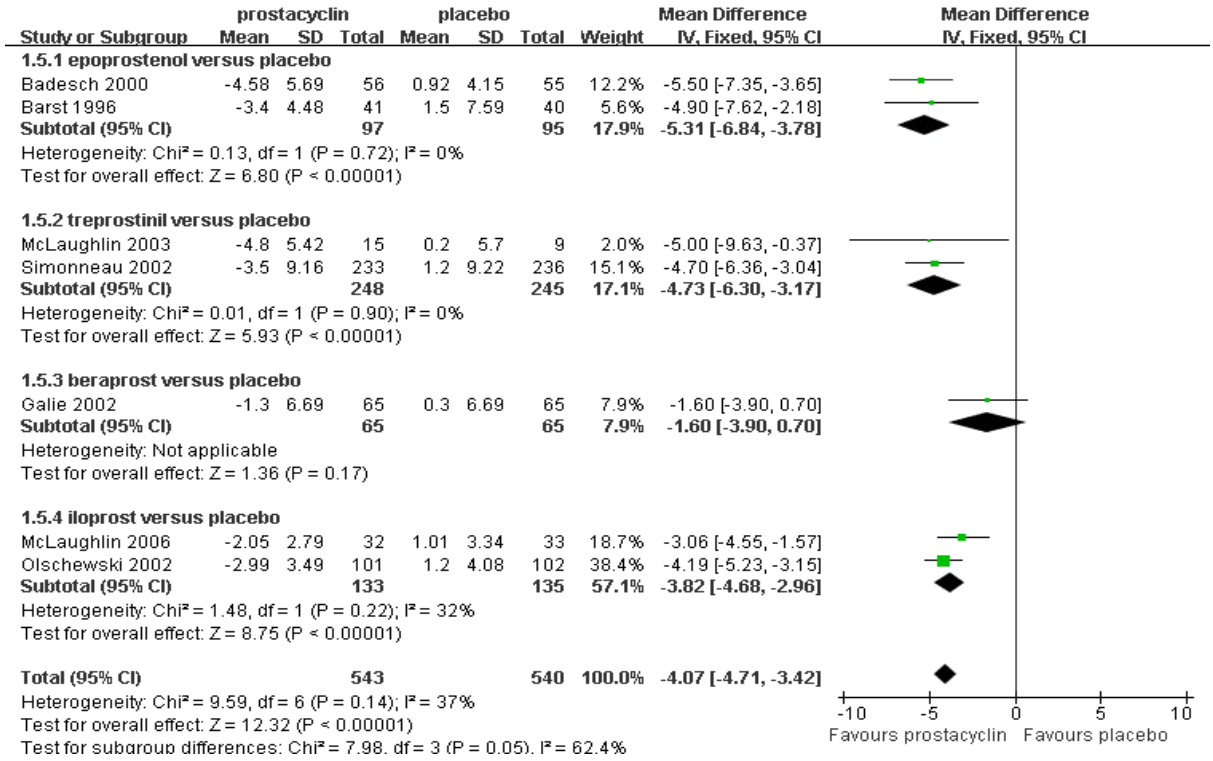

Figure 5. Meta-analysis of pulmonary vascular resistance. CI = confidence interval.

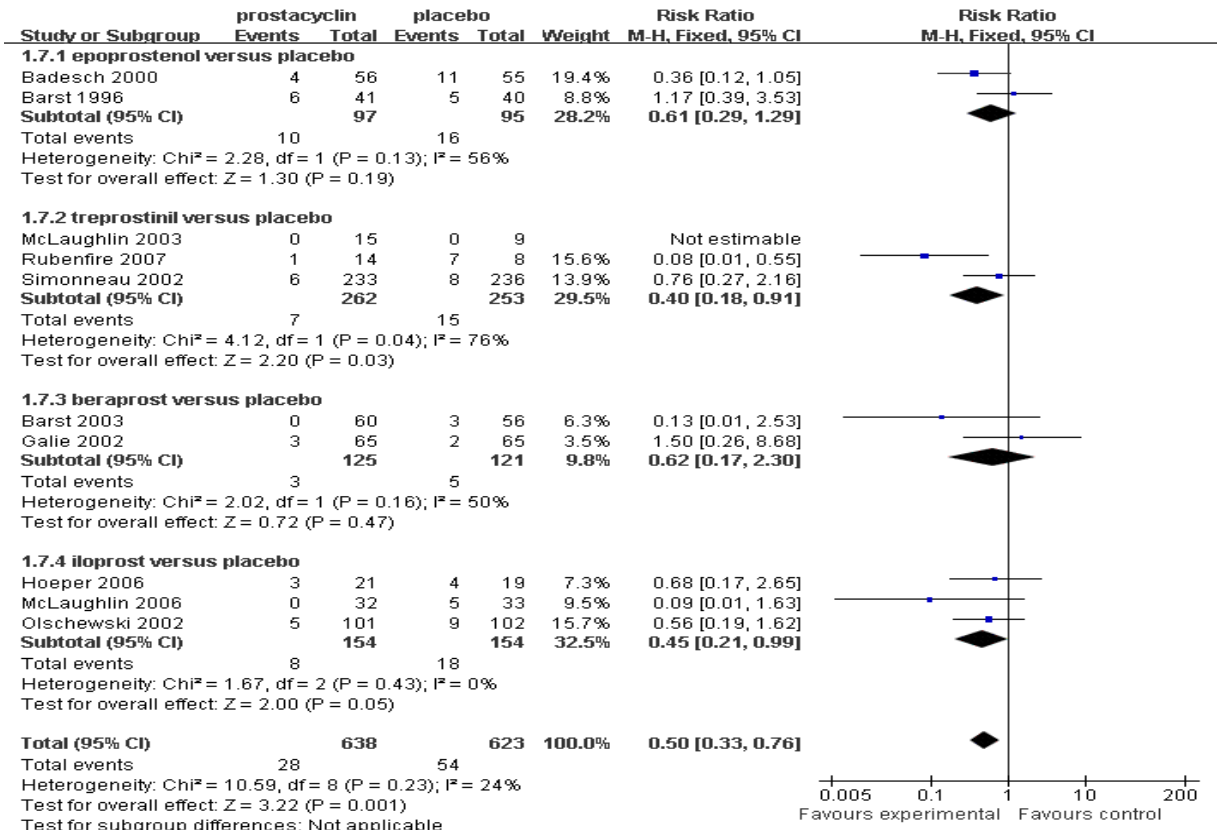

Figure 6. Meta-analysis of clinical deterioration. CI = confidence interval.

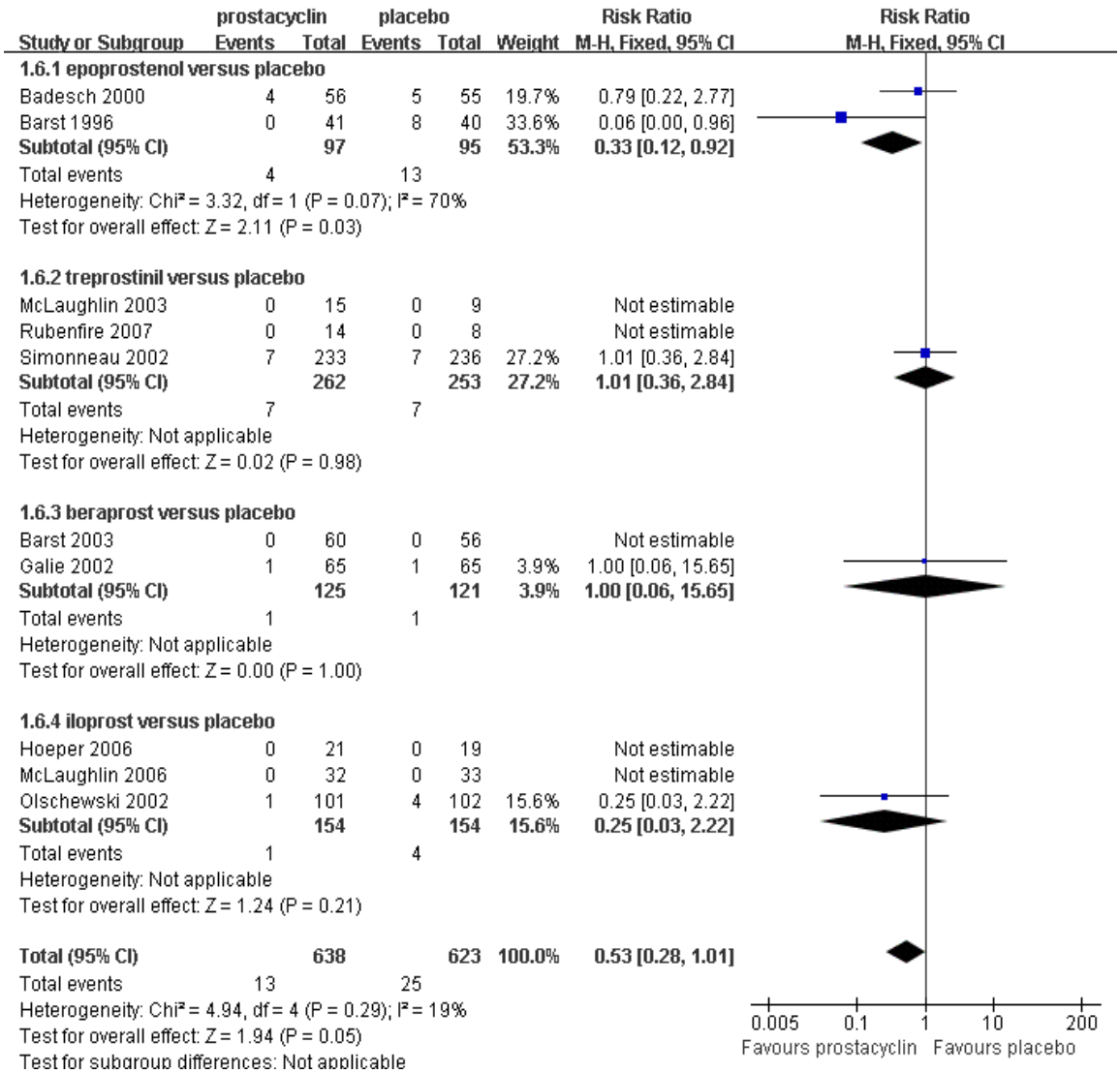

Figure 7. Meta-analysis of mortality. CI = confidence interval.

aversive effect was headache; investigational treatments increased the incidence of headache (Figure 8). The overall heterogeneity test of 7 RCTs provided statistically significant level of difference (P = 0.06). The total RR of patients allocated to active treatments assessed by the fix effect model was 1.33 (95% CI 1.12, 1.59, P = 0.002).

Sensitivity analysis and publication bias

Because the meta-analysis included a RCT (Rubenfire et al., 2007) of low score, sensitivity analyses were performed by excluding the trial of low score. The results showed as follows (Table 2). We mapped funnel plot (Figure 9) analyses publication bias. The funnel plot was symmetrical with naked-eye, so there was no publication bias in the meta-analysis.

DISCUSSION

A metabolite of arachidonic acid, prostacyclin is endogenously produced by vascular endothelium. It is a potent vasodilator in both the pulmonary and systemic circulations, and has anti-platelet aggregatory activity. The use of prostacyclins for PAH treatment is based upon the imbalance between the activities of thromboxane A2 and prostacyclin metabolites (Widlitz and Barst, 2003). Prostacyclins induce relaxation of the respiratory vascular musculature, stimulating production of cyclic adenosine monophosphate (cAMP), and inhibit respiratory muscle cell growth and platelet aggregation (Humbert et al., 2004).

In this meta-analysis, we evaluated the short-term efficacy and adverse effects, focusing on the evaluation of exercise capacity, hemodynamic changes, clinical

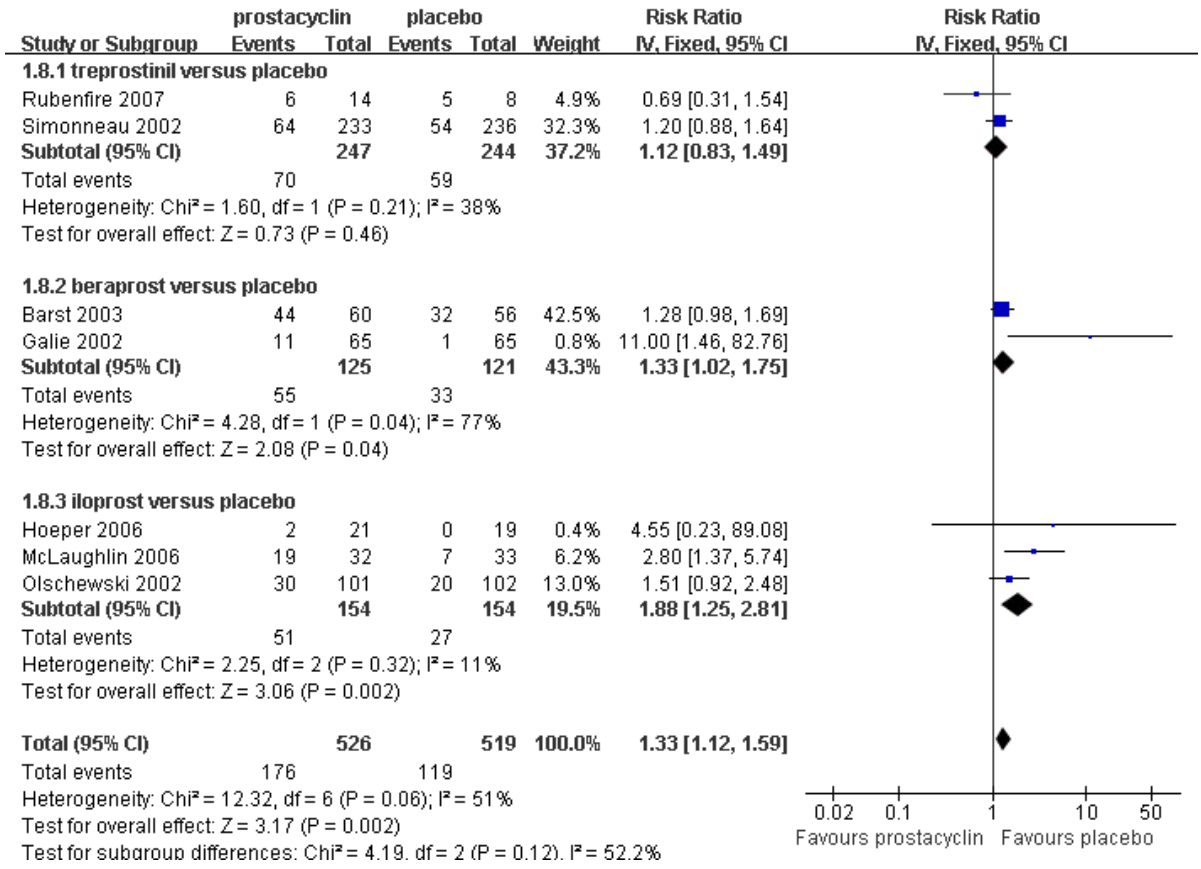

Figure 8. Meta-analysis of the incidence of headache. CI = confidence interval.

Table 2. Sensitivity analysis.

Index	RR/WMD (95% CI)	RR_S/WMD_S (95% CI)
6-min walk distance	28.81 (16.50, 41.13)	30.18 (17.67, 42.69)
Borg dyspnea score	-0.69 (-1.00, -0.32)	-0.71 (-1.03, -0.39)
Mortality	0.53 (0.28, 1.01)	0.53 (0.28, 1.01)
Clinical deterioration	0.50 (0.33, 0.76)	0.58 (0.37, 0.90)
Incidence of headache	1.33 (1.12, 1.59)	1.38 (1.15, 1.66)

RR, Relative risk; WMD, weighted mean difference; CI, confidence interval.

deterioration, mortality and headache. The meta-analysis has confirmed the improvement of exercise capacity and cardiac function as assessed by 6 MWD, Borg dyspnes score and cardiac index, but the results did not correspond with the report of Paramothayan et al. (2005) exactly. Such difference between general analysis and subgroup analysis may be caused by the new RCTs publicshed in recent years. These results were not surprising as the 6 MWD and Borg dyspnea score has been represented as the primary endpoint for the majority of the RCTs and both patients sample size and statistical power were calculated according to the predicted change of these parameters. The weighted average improvement was about 28.81 m when compared with placebo treatment. In addition, statistically significant improvement in the haemodynamic data, including cardiac index, mean pulmonary arterial pressure and pulmonary vascular resistance were observed.

The decrease of the mean pulmonary arterial pressure and pulmonary vascular resistance provide more direct evidence for the effectiveness of the prostacyclins treatment in PAH. The results of this meta-analysis on RCTs performed in PAH patients show that the mortality in the control groups may be high. Because 95% CI of the

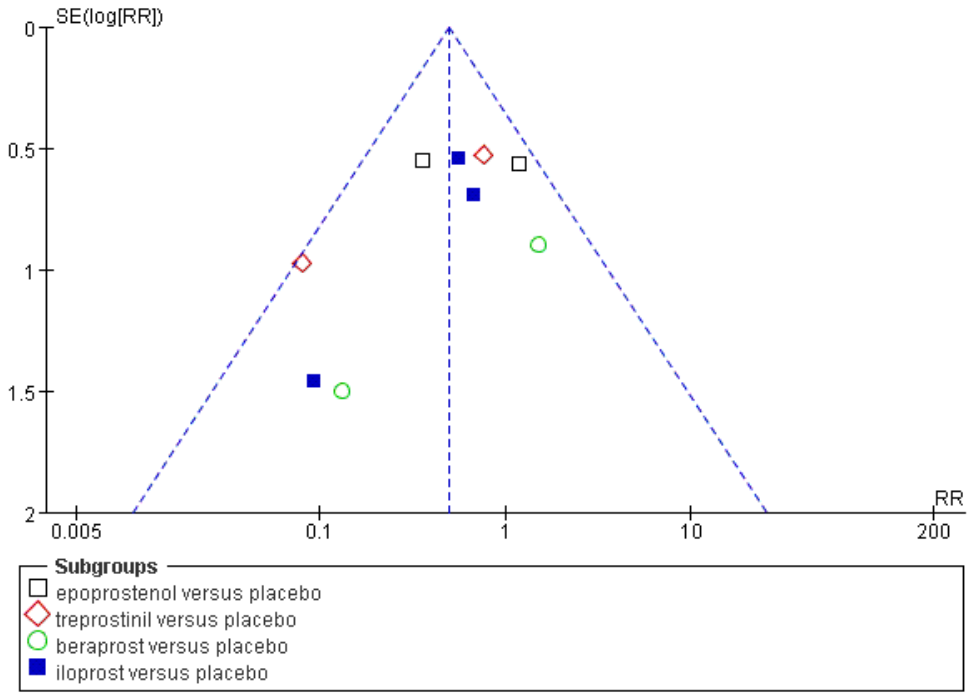

Figure 9. Publication bias according to the index of clinical deterioration.

mortality included 1 and intersect of the horizontal and the vertical lines were invalid, the two groups of patients with short-term mortality show no significant difference. Studies have reported that the actual survival rate in PAH patients improved obviously by the application of prostacyclin drug treatment (Barst et al., 2006; Opitz et al., 2005). Because the clinical symptoms and exercise capacity of patients improved and the clinical deterioration released significantly, this pointed that mortality may not be suitable for the evaluation of short-term effect in PAH patients with prostacyclin treatment. In addition, the risk of headache with application of prostacyclin increased, especially with beraprost in subgroup analysis. The limitations of this meta-analysis include the prolonged period of time between the publication of the first and the last RCT (about 16 years), the difference duration of the trials, the lack of blindness in some studies (Badesch et al., 2000; Barst et al., 1996; Hoeper et al., 2006; McLaughlin et al., 2006), the pooling of multiple active treatment arms (potential alteration of the trial structure), the report of secondary outcome parameters only in part of the RCTs (possible reporting bias), and potential heterogeneity in the conduct of the trials and in the definition of hospitalization for PAH in different RCTs (no individual patients data were reviewed).

A publication bias, favoring the publication of positive studies, also can not be excluded. The funnel plot analysis (plots of effects estimates against standard error of the estimate) did not show asymmetry (Figure 9) and a possible publication bias should not have influenced substantially the results of this meta-analysis. In conclusion, the results of this meta-analysis point out that improvement of exercise capacity, cardiac function and haemodynamics were observed in the patients treated with targeted therapies approved for PAH. Clinical deterioration released obviously in the groups of RCTs reporting these data and mortality may not be reduced in short-term. Generally patients can tolerate headache and other side effects of this treatment. There is also a need for more information on side effects in the longer term. Additional efforts are required to explore new strategies including RCTs with initial with new designs including morbidity and mortality endpoints and prolonged observation periods. Finally, trials combining prostacyclin analogues with other drugs are currently in progress, and these data may clarify the therapeutic effectives of this drug in treatment of the pulmonary hypertensive patients.

ACKNOWLEDGEMENTS

This study was supported by National Natural Science Foundation of China (81100037); Applied Basic Research Programs of Yunnan Province (2011FB154); Foundation of Yunnan Educational Committee (2010C091); the Graduate degree Education Innovation Foundation of Central South University (2011JG31).

REFERENCES

Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley

FM, Rich S, Barst RJ, Barrett PS, Kral KM, Jobsis MM, Loyd JE, Murali S, Frost A, Girgis R, Bourge RC, Ralph DD, Elliott CG, Hill NS, Langleben D, Schilz RJ, McLaughlin VV, Robbins IM, Groves BM, Shapiro S, Medsger TA Jr (2000). Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann. Intern. Med., 132(6): 425-434.

Barst RJ, Galie N, Naeije R, Simonneau G, Jeffs R, Arneson C, Rubin LJ (2006). Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. Eur. Respir. J., 28(6): 1195-1203.

Barst RJ, McGoon M, McLaughlin V, Tapson V, Rich S, Rubin L, Wasserman K, Oudiz R, Shapiro S, Robbins IM, Channick R, Badesch D, Rayburn BK, Flinchbaugh R, Sigman J, Arneson C, Jeffs R (2003). Beraprost therapy for pulmonary arterial hypertension. J. Am. Coll. Cardiol., 41(12): 2119-2125.

Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, Koerner SK, Langleben D, Keller CA, Murali S, Uretsky BF, Clayton LM, Jöbsis MM, Blackburn SD, Shortino D, Crow JW (1996). A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N. Engl. J. Med., 334(5): 296-302.

Benedict N, Seybert A, Mathier MA (2007). Evidence-based pharmacologic management of pulmonary arterial hypertension. Clin. Therapeut., 29(10): 2134-2153.

D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, Levy PS, Pietra GG, Reid LM, Reeves JT, Rich S, Vreim CE, Williams GW, Wu M (1991). Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann. Intern. Med., 115(5): 343-349.

Galie N, Humbert M, Vachiery JL, Vizza CD, Kneussl M, Manes A, Sitbon O, Torbicki A, Delcroix M, Naeije R, Hoeper M, Chaouat A, Morand S, Besse B, Simonneau G (2002). Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. J. Am. Coll. Cardiol., 39(9): 1496-1502.

Hoeper MM, Leuchte H, Halank M, Wilkens H, Meyer FJ, Seyfarth HJ, Wensel R, Ripken F, Bremer H, Kluge S, Hoeffken G, and Behr J (2006). Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. Eur. Respir. J., 28(4): 691-694.

Humbert M, Sitbon O, Simonneau G (2004). Treatment of pulmonary arterial hypertension. N. Engl. J. Med., 351(14): 1425-1436.

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, and McQuay HJ (1996). Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control. Clin. Trials., 17(1): 1-12.

McLaughlin VV, Gaine SP, Barst RJ, Oudiz RJ, Bourge RC, Frost A, Robbins IM, Tapson VF, McGoon MD, Badesch DB, Sigman J, Roscigno R, Blackburn SD, Arneson C, Rubin LJ, and Rich S (2003). Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension. J. Cardiovasc. Pharmacol., 41(2): 293-299.

McLaughlin VV, Oudiz RJ, Frost A, Tapson VF, Murali S, Channick RN, Badesch DB, Barst RJ, Hsu HH, Rubin LJ (2006). Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am. J. Respir. Crit. Care. Med., 174(11): 1257-1263.

Nauser TD, Stites SW (2001). Diagnosis and treatment of pulmonary hypertension. Am. Fam. Physician., 63(9): 1789-1798.

Olschewski H, Simonneau G, Galie N, Higenbottam T, Naeije R, Rubin LJ, Nikkho S, Speich R, Hoeper MM, Behr J, Winkler J, Sitbon O,Popov W, Ghofrani HA, Manes A, Kiely DG, Ewert R, Meyer A, Corris PA, Delcroix M, Gomez-Sanchez M, Siedentop H, Seeger W (2002). Inhaled iloprost for severe pulmonary hypertension. N. Engl. J. Med., 347(5): 322-329.

Opitz CF, Wensel R, Winkler J, Halank M, Bruch L, Kleber FX, Hoffken G, Anker SD, Negassa A, Felix SB, Hetzer R, Ewert R (2005). Clinical efficacy and survival with first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension. Eur. Heart. J., 26(18): 1895-1902.

Paramothayan NS, Lasserson TJ, Wells AU, Walters EH (2005). Prostacyclin for pulmonary hypertension in adults. Cochrane. Database. Syst. Rev., 2003(2): CD002994.

Rubenfire M, McLaughlin VV, Allen RP, Elliott G, Park MH, Wade M, Schilz R (2007). Transition from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension: a controlled trial. Chest, 132(3): 757-763.

Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, Keogh A, Oudiz R, Frost A, Blackburn SD, Crow JW, Rubin LJ (2002). Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am. J. Respir. Crit. Care. Med., 165(6): 800-804.

Widlitz A, Barst RJ (2003). Pulmonary arterial hypertension in children. Eur. Respir. J., 21(1): 155-176.