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HEMODYNAMICS, EXERCISE CAPACITY AND CLINICAL EVENTS IN PULMONARY ARTERIAL HYPERTENSION

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ABSTRACT

Purpose of this study was to clarify whether changes in cardiopulmonary hemodynamics induced by pharmacologic therapy correlate with exercise capacity and clinical events in patients with pulmonary arterial hypertension.

Sixteen randomized trials including 2,353 patients, followed up for 16.4±10.6 weeks, measuring cardiopulmonary hemodynamics by right heart catheterization and reporting clinical events were included. Meta-analysis and meta-regression analysis were performed to assess the effects of treatments on clinical events and the relationship between hemodynamic (pulmonary artery pressure, pulmonary vascular resistance, cardiac index and right atrial pressure) changes and clinical events.

Treatments significantly reduced all-cause death (odds ratio [OR]:0.5; 95% confidence interval [IC]:0.3 to 0.7; $p<0.01$), hospitalization for pulmonary arterial hypertension (OR:0.4; IC:0.2 to 0.7; $p<0.01$), initiation of rescue therapy (OR:0.3; IC:0.2 to 0.6; $p<0.01$) and the composite outcome (OR:0.3; IC:0.3 to 0.5; $p<0.01$). No relationship was found between changes of hemodynamic parameters and clinical events, whereas changes of cardiac index and pulmonary vascular resistance significantly correlated with changes of 6 minute walking distance ($r=0.64$, $p=0.03$; $r=-0.55$; $p=0.04$ respectively).

In patients with pulmonary arterial hypertension, improvements of cardiopulmonary hemodynamics, observed in randomized clinical trials, correlate with exercise capacity changes but do not predict clinical events in a short-term follow up.

Key words cardiopulmonary hemodynamic; exercise tolerance; right heart catheterization; six minute walking distance

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a chronic syndrome characterized by progressive deterioration of cardiopulmonary hemodynamics and right ventricular function, leading to impaired exercise capacity and premature death [1].

Right heart catheterization (RHC) is recommended by guidelines to measure cardiopulmonary hemodynamic parameters with the purpose of diagnosing PAH, defining its etiology, guiding therapeutic management and obtaining prognostic information [2,3]. Yet, although the role of cardiopulmonary hemodynamic parameters is well recognized for the initial diagnostic workup, it is still uncertain whether changes of hemodynamics parameters reflect variations in the exercise capacity and in the incidence of subsequent clinical events in patients with PAH. In fact, although changes of cardiopulmonary hemodynamic parameters represented the primary end-point [4-8] or were reported in several PAH randomized clinical trials [9-19], it has been not extensively investigated whether improvement of hemodynamic parameters correlates with improved exercise capacity. More importantly, the relationship of hemodynamic changes with major clinical events has never been assessed from randomized studies. Yet, these information are important for management of PAH patients to ultimately improve patient care.

Therefore, the aim of this meta-analysis was to investigate the relationship between changes of cardiopulmonary hemodynamic parameters induced by pharmacological therapies and exercise capacity and clinical events in PAH patients enrolled in randomized clinical trials.

MATERIALS AND METHODS

Data Sources and Searches. The study was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [20,21].

The MEDLINE, Cochrane database, ISI Web of Science and SCOPUS database were searched for articles published in all languages until November 2011.

Study Selection. Inclusion criteria were as follows: evaluation of cardiopulmonary hemodynamic by RHC at baseline and at end of follow-up; report of clinical events (all-cause death, hospitalization for PAH and/or lung or heart-lung transplantation, initiation of PAH rescue therapy); comparison of active drug treatment versus placebo or of different doses of active drugs; randomized protocol design. Studies were identified using the major medical subject headings "pulmonary arterial hypertension", "randomized", "hemodynamics". Hospitalization was defined as end-point when it lasted at least 24 hours and was determined by worsening of PAH clinical status. Rescue therapy was defined as interruption of blindness status of patients enrolled in clinical trials due to worsening clinical status.

Data Extraction and Quality Assessment. Two reviewers independently screened articles according to fulfillment of inclusion criteria. Baseline characteristics, hemodynamic values (pulmonary artery pressure [PAP], pulmonary vascular resistance [PVR], right atrial pressure [RAP] and cardiac index [CI]) at baseline and end of follow-up, and clinical events were abstracted. A composite outcome including the above events was calculated and the assessment of the relationship between cardiopulmonary hemodynamic changes and composite outcome represented the first objective of the study. Additionally, the relationship between changes of hemodynamic parameters and changes of 6 minute walking distance (6MWD) was also investigated. The quality of the trials was evaluated by Detsky method [22] whereas publication bias was assessed using Macaskill's modified test [23].

Of 14,906 articles identified by the initial search, 16 randomized trials including 2,353 patients were included in the study (Figure 1). In 13 of these trials, including 1,310 patients [4-8,10,12-17,19], changes of 6MWD were also reported.

Data Synthesis and Analysis. Weighted random-effects meta-regression analysis was performed with the metareg command [24](STATA version 11.0, StataCorps, College Station, Texas) to test the relationship between cardiopulmonary hemodynamic changes from baseline to end of follow-up and clinical events, as previously reported [25]. For this analysis, the achieved differences between cardiopulmonary hemodynamic changes in active treatment and control groups were considered (ΔPAP, ΔPVR, ΔRAP, ΔCI). For all meta-regression analyses, a random-effects model was used. Tau^2 and the restricted maximum likelihood (REML) methods, were employed to explain residual heterogeneity not explained by potential effect modifiers [26]. To further explore the influence of the degree of hemodynamic changes on the relationship with clinical events, for each hemodynamic parameter, studies were divided in tertiles with the first tertile including trials with the least favorable changes and the upper tertile including studies with the most favorable changes. Then, meta-regression was repeated, for each parameter, only for most favorable studies. Furthermore, the tertile (1,2 or 3) to which each study belonged, was tested as potential effect modifier in sensitivity analysis.

Unweighted Spearman correlation was used to test the relationship between changes in hemodynamics and changes in 6MWD.

Outcome Meta-Analysis. Odds ratios (ORs) of the effect of treatments were calculated using the metan command (STATA version 11.0, StataCorps)[27]. The choice to use OR was driven by the retrospective design of the meta-analysis [27-29]. Overall estimates of effect were calculated with a fixed-effect model, random-effects model or Peto method as appropriate. Statistical homogeneity was assessed using Q and I^2 statistics.

Sensitivity Analysis. To assess the influence of potential effect modifiers on the association between hemodynamic changes and clinical events, meta-regression analyses were conducted, including the following variables as covariates, each separately: mean age,

sex, race, type of PAH, baseline functional class, changes in 6MWD (Δ6MWD) from baseline to the end of follow-up, Detsky quality score, duration of follow-up, study publication year, baseline hemodynamic parameters, tertile of hemodynamic changes.

RESULTS

Characteristics of included trials. Baseline characteristics of the 16 trials included in the study are reported in Table 1. A total of 254 clinical events were reported in 2,353 patients included in the meta-analysis. Three hundred and eighty-five patients were assigned to phosphodiesterase type 5 inhibitor inhibitors treatment, 942 to prostaglandin I2 analogues, 300 to endothelin receptor antagonists, 28 to imatinib, 107 to conventional therapy and 1047 to placebo. Conventional therapy was defined as any combination of therapy including diuretics, anticoagulants and oxygen supply, but not including specific PAH drugs. Mean follow-up duration was 16.4±10.6 weeks (range 8-52). The overall mean age of patients was 44.4±5.9 years and 76.5% were women.

Effects of therapies on pulmonary hemodynamic parameters and exercise capacity. Pooled weighted analysis of 16 trials reporting hemodynamic changes induced by active treatments showed a 12.7±6.4% increase of mean CI, a 24.6±7.9% decrease of mean PVR, a 7.1±4.3% decrease of mean PAP and a 16.5±5.1% decrease of mean RAP. In 13 trials reporting exercise capacity, a 9.8±7.2% increase of mean 6MWD was observed.

A significant correlation was found between Δ6MWD and ΔCI (r=0.6; p=0.03) and between Δ6MWD and ΔPVR (r=-0.55; p=0.04), but not between Δ6MWD and ΔPAP (r=0.74; p=0.09) and between Δ6MWD and ΔRAP (r=-0.57; p=0.19)(Figure 2).

Effects of therapies on outcomes. Pharmacological treatments led to significant reduction of the composite outcome without heterogeneity among studies (OR: 0.3, 95% confidence interval (IC): 0.3 to 0.5, comparison p<0.01, heterogeneity p=0.11)(Figure 3). Additionally, each component of the composite outcome was significantly reduced by

treatments, including all-cause death (OR: 0.5, 95% IC: 0.3 to 0.7, comparison p<0.01, heterogeneity p=0.51)(Supplementary Material Figure 1), hospitalization for PAH and/or lung or heart-lung transplantation (OR: 0.4, IC: 0.2 to 0.7, comparison p<0.01, heterogeneity p=0.82)(Supplementary Material Figure 2) and initiation of PAH rescue therapy (OR: 0.3, IC: 0.2 to 0.6, comparison p<0.01, heterogeneity p=0.23)(Supplementary Material Figure 3).

By meta-regression analysis no relationship was found between ΔPAP, ΔPVR, ΔRAP, ΔCI and the composite outcome. Additionally, no relationship was found between ΔPAP, ΔPVR, ΔRAP, ΔCI and each component of the composite outcome (Tables 2,3)(Figure 4)(Supplementary Material Figures 4-6). Furthermore, lack of association between each hemodynamic parameter and clinical events was also confirmed for trials belonging to the tertile with the most favorable response.

Sensitivity Analysis. Results were confirmed when potential effect modifiers were introduced as covariates in the meta-regression analysis (Supplementary Material Table 1).

Publication Bias. No publication bias was detected by Macaskill's modified test for composite or single outcomes analysis.

DISCUSSION

The main findings of the present analysis indicate that, in patients with PAH, changes of hemodynamic cardiopulmonary parameters observed during short-term randomized clinical trials investigating pharmacologic therapies correlate with changes of exercise capacity evaluated by 6MWD but not with clinical events. In particular, a significant direct correlation was found between CI increase and Δ6MWD, whereas a significant inverse correlation was found between PVR decrease and Δ6MWD. However, no variation of any cardiopulmonary hemodynamic parameter correlated to clinical events occurrence during the short-term follow up of clinical trials.

Cardiopulmonary hemodynamic parameters in the management of PAH patients. It has been observed in large registry studies that increased PAP and RAP, as well reduced CI, are associated with worse prognosis in patients with PAH [30-34]. From these observations, survival equations have been developed, that represent a useful tool to predict prognosis in PAH patients. Survival equations developed from the REVEAL [31] and French [33] registries include cardiopulmonary hemodynamic as well demographic and functional parameters, whereas in the Pulmonary Hypertension Correction equation only cardiopulmonary hemodynamic parameters resulted significantly associated to prognosis [34]. Accordingly, several randomized trials in PAH have reported, as main [4-8] or secondary [9-19] end-points, changes of cardiopulmonary hemodynamic parameters induced by specific PAH therapies. However, the relationship between hemodynamic changes and either changes of exercise capacity or occurrence of clinical events is still unclear, leading the European Society of Cardiology and European Respiratory Society to consider repeat of RHC after initiation of therapy or in case of clinical deterioration as class II recommendation, with level of evidence C [2] whereas no clear indication for repeating invasive measurement of cardiopulmonary hemodynamic is made by the American College of Cardiology and American Heart Association guidelines on PAH [3].

Cardiopulmonary hemodynamic changes and exercise capacity in PAH. In the current study a significant association was found by regression analysis between cardiopulmonary hemodynamic changes and exercise capacity, evaluated by 6MWD test. In particular Δ6MWD directly correlated with CI increase and inversely with ΔPVR. Although both hemodynamic and exercise changes were concomitantly assessed in 13 randomized trials [4-8,10,12-17,19], to our knowledge only Barst et al [10], in their pivotal epoprostenol study, investigated the correlation between hemodynamic and exercise parameters. In agreement with our meta-analysis, they also found a significant association between hemodynamic

changes and improvement of 6MWD, whereas, at variance with our study, they also reported in 81 patients analyzed, a significant association between Δ6MWD and Δ mean PAP and Δ mean RAP. Thus, our aggregate results, in agreement with those of Barst et al [10] from a single clinical trial, indicate that hemodynamic improvement induced by vasodilator therapies in PAH plays a relevant role in the amelioration of exercise capacity.

Cardiopulmonary hemodynamic changes and short-term mortality/morbidity in PAH patients. The relationship between hemodynamic changes and clinical events has been investigated in non-randomized studies [35-37] indicating that improvement of CI and PAP [36] and decrease or no changes of PVR [35,37] are associated with long term clinical outcome in PAH patients. More recently, an analysis of patients undergoing subcutaneous treprostinil therapy followed up for 3 years, also reported that on-treatment changes of mixed oxygen venous saturation and of 6MWD predicted survival in PAH patients [38] whereas Nickel et al [39] showed that changes of mixed oxygen venous saturation and CI predicted survival over a 38 months follow up in 109 patients with PAH.

The association between cardiopulmonary hemodynamic changes observed during randomized clinical studies and occurrence of clinical events using has never been systematically evaluated. The results of our meta-regression analysis indicate that no statistically significant association exists between pulmonary hemodynamic changes and clinical events occurring during the short-term follow-up of randomized studies. Explanation for the lack of correlation between hemodynamic improvement and events, and the reasons for the apparent discrepancy with observational non-randomized studies, can only be hypothesized. It has been suggested that parameters reflecting right ventricular function are more predictive of clinical outcomes compared to cardiopulmonary hemodynamic changes. In a recent study, van de Veerdonk et al. [40] observed that right ventricular function, evaluated by magnetic resonance imaging, deteriorated in a subgroup of a population of 110 patients

with treated PAH, despite reduction of PVR, and that in these patients prognosis was poor irrespective of PVR changes. Thus, it is conceivable that improvement of hemodynamic parameters induced by therapies may occur despite deterioration or no changes of right ventricular function, thus correlating in the short-term with exercise capacity but not with clinical events [41,42]. In fact, consistent with the current findings, in a recent meta-analysis exercise capacity changes reflected by 6MWD test in PAH did not correlate with clinical events [43].

Despite potential pathophysiological explanations, the lack of association between hemodynamic changes and events observed in our study must be interpreted with caution and not as evidence of uselessness of hemodynamic monitoring in PAH patients, for several considerations. First, our findings are restricted to randomized clinical trials and to the short period of observation, usually three to four months, commonly covered in these trials. This is quite a relevant aspect to point out since, as nicely outlined by Miller et a. [44], clinical trials usually include stable patients with potential survival bias, for whom a short-term period of observation may prevent the occurrence of a number of events statistically adequate to be tested for association with hemodynamic changes. In addition, randomized studies include different type of drugs and different degrees of hemodynamic changes, as well different methods of evaluation of hemodynamic parameters. Thus, it cannot be excluded that an association may exist for responder patients and over a longer follow up, as reported in non-randomized studies or registries [45]. In addition, on treatment hemodynamic changes are usually defined as the difference between baseline value and a snap-shot repeat evaluation under resting conditions, and may, therefore, not be representative of the full hemodynamic benefit provided by therapies under daily life. In this regard, availability of implantable devices that provide a more comprehensive monitoring of hemodynamic changes may turn out to be valuable for risk stratification in PAH patients [46]. Thus, a definitive assessment of

the cost-effectiveness of hemodynamic changes measurement in PAH patients cannot be made from the present analysis and deserve further exploration in prospective studies using different techniques [47].

Study limitations. Our study has some limitations. First, the analysis reported was based on aggregate rather than individual patient data. In addition, the current analysis does not allow to exclude potential significant influence of the type of therapy on the association between hemodynamic effects and clinical events, and applies to the short follow-up of clinical trials. Thus, our findings cannot be generalized to long-term treatment of PAH. Furthermore, trials analyzed included naïve and already treated patients, and, therefore, whether reported prognostic differences between naïve and treated patients may have influenced our observations cannot be evaluated from our analysis [44]. Finally, since the technique used to measure CI was not reported in several trials included in our meta-regression, an influence of the technique used, i.e., thermodilution or estimated or actual Fick method, on the association with clinical outcome cannot be excluded. Yet, there are also strengths of this analysis that are represented by the lack of publication bias and by the sensitivity analysis that confirmed that our findings were not influenced by several potential effect modifiers.

Conclusions. In the short duration of clinical trials, drug therapy favorably affects pulmonary hemodynamic parameters, exercise capacity and clinical outcome in PAH patients. Pulmonary hemodynamic changes, reported in randomized clinical trials, correlate with exercise capacity but not with clinical events, emphasizing the need to keep on searching for markers of disease modification in PAH patients.

REFERENCES

1. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine SP, Gladwin MT, Jing ZC, Krowka MJ, Langleben D, Nakanishi N, Souza R. *J Am Coll Cardiol* 2009; 54: S43–S54.
2. Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC); European Respiratory Society (ERS); International Society of Heart and Lung Transplantation (ISHLT), Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; 34: 1219-1263.
3. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J; American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association; American College of Chest Physicians; American Thoracic Society, Inc; Pulmonary Hypertension Association. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009; 53: 1573-1619.
4. Galiè N, Rubin Lj, Hoeper M, Jansa P, Al-Hiti H, Meyer G, Chiossi E, Kusic-Pajic A, Simonneau G. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008; 371: 2093-2100.

5. Humbert M, Barst RJ, Robbins IM, Channick RN, Galiè N, Boonstra A, Rubin LJ, Horn EM, Manes A, Simonneau G. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004; 24: 353-359.

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

7. Oudiz RJ, Schilz RJ, Barst RJ, Galié N, Rich S, Rubin LJ, Simonneau G; Treprostinil Study Group. Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. *Chest* 2004; 126: 420-427.

8. Rubin LJ, Mendoza J, Hood M, McGoon M, Barst R, Williams WB, Diehl JH, Crow J, Long W. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. *Ann Intern Med* 1990; 112: 485-491.

9. Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, Rich S, Barst RJ, Barrett PS, Kral KM, Jöbsis 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. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000; 132: 425-434.

10. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996; 334: 296-302.

11. 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; Beraprost Study Group. Beraprost therapy for pulmonary arterial hypertension. Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2003; 41: 2119-2125.

12. Barst RJ, Langleben D, Frost A, Horn EM, Oudiz R, Shapiro S, McLaughlin V, Hill N, Tapson VF, Robbins IM, Zwicke D, Duncan B, Dixon RA, Frumkin LR; STRIDE-1 Study Group. Sitaxsentan therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2004; 169: 441-447.

13. Galiè N, Humbert M, Vachiéry 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; Arterial Pulmonary Hypertension and Beraprost European (ALPHABET) Study Group 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* 2002; 39: 1496-1502.

14. Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G; Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005; 353: 2148-2157.

15. Ghofrani HA, Morrell NW, Hoeper MM, Olschewski H, Peacock AJ, Barst RJ, Shapiro S, Golpon H, Toshner M, Grimminger F, Pascoe S. Imatinib in pulmonary arterial hypertension patients with inadequate response to established therapy. *Am J Respir Crit Care Med* 2010; 182: 1171-1177.

16. Jing ZC, Yu ZX, Shen JY, Wu BX, Xu KF, Zhu XY, Pan L, Zhang ZL, Liu XQ, Zhang YS, Jiang X, Galiè N; Efficacy and Safety of Vardenafil in the Treatment of

Pulmonary Arterial Hypertension (EVALUATION) Study Group Vardenafil in pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled study. *Am J Respir Crit Care Med* 2011; 183: 1723-1729.

17. Olschewski H, Simonneau G, Galiè 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; Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002; 347: 322-329.
18. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, Keogh A, Oudiz R, Frost A, Blackburn SD, Crow JW, Rubin LJ; Treprostinil Study Group. 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* 2002; 165: 800-804.
19. Simonneau G, Rubin LJ, Galiè N, Barst RJ, Fleming TR, Frost AE, Engel PJ, Kramer MR, Burgess G, Collings L, Cossons N, Sitbon O, Badesch DB; PACES Study Group. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008; 149: 521-530.
20. Moher D, Liberati, A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Ann Intern Med* 2009; 151: 264-269.
21. Costanzo P, Perrone-Filardi P, Petretta M, Marciano C, Vassallo E, Gargiulo P, Paolillo S, Petretta A, Chiariello M. Calcium channel blockers and cardiovascular outcomes: a meta-analysis of 175,634 patients. *J Hypertens* 2009; 27: 1136-1151.

22. Detsky A, Naylor C, O'Rourke K, McGeer A, L'Abbé K. Incorporating variations in the quality of individual randomized trials into meta-analysis. *J Clin Epidemiol* 1992; 45: 255–265.

23. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *JAMA* 2006; 295: 676–680.

24. Sharp SJ. Meta-analysis regression. *Stata Tech Bull* 1998; 42: 16–22.

25. Costanzo P, Savarese G, Rosano G, Musella F, Casaretti L, Vassallo E, Paolillo S, Marsico F, Rengo G, Leosco D, Perrone-Filardi P. Left ventricular hypertrophy reduction and clinical events. A meta-regression analysis of 14 studies in 12,809 hypertensive patients. *Int J Cardiol* 2012; doi:10.1016/j.ijcard.2012.06.084.

26. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 1999; 18: 2693–2708.

27. Sharp S, Sterne J. Meta-analysis. *Stata Tech Bull Reprints* 1998; 7: 100–108.

28. Whitehead A. *Meta-Analysis of Controlled Clinical Trials.* England: John Wiley & Sons; 2002: 4.

29. Davies HT, Crombie IK, Tavakoli M. When can odds ratios mislead? *Br Med J* 1998; 316: 989–991.

30. McLaughlin VV, MD, McGoon MD. Pulmonary Arterial Hypertension. *Circulation* 2006; 114: 1417-1431.

31. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG, Liou TG, McGoon MD. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010; 122: 164-172.

32. 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. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991; 115: 343–349.

33. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaïci A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C,Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Cottin V, Degano B, Jaïs X, Montani D, Souza R, Simonneau G. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010; 122: 156-163.

34. Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. *Eur Respir J* 2010; 35: 1079-1087.

35. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Hervé P, Rainisio M, Simonneau G. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002; 40: 780-788.

36. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002; 106: 1477-1482.

37. Provencher S, Sitbon O, Humbert M, Cabrol S, Jaïs X, Simonneau G. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. *Eur Heart J* 2006; 27: 589-595.

38. Benza RL, Gomberg-Maitland M, Naeije R, Arneson CP, Lang IM. Prognostic factors associated with increased survival in patients with pulmonary arterial hypertension

treated with subcutaneous treprostinil in randomized, placebo-controlled trials. *J Heart Lung Transplant* 2011; 30: 982-989.

39. Nickel N, Golpon H, Greer M, Knudsen L, Olsson K, Westerkamp V, Welte T, Hoeper MM. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2012; 39: 589-96.

40. van de Veerdonk MC, Kind T, Marcus JT, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *J Am Coll Cardiol* 2011; 58: 2511-2519.

41. Girgis RE. Predicting long-term survival in pulmonary arterial hypertension: more than just pulmonary vascular resistance. *J Am Coll Cardiol* 2011; 58: 2520-2521.

42. Dellegrottaglie S, Perrone-Filardi P, García-Alvarez A, Moral S, Stevens GR, Fuster V, Sanz J. Serial phase-contrast MRI for prediction of pulmonary hemodynamic changes in patients with pulmonary arterial hypertension. *Int J Cardiol* 2012; 157: 140-142.

43. Savarese G, Paolillo S, Costanzo P, D'Amore C, Cecere M, Losco T, Musella F, Gargiulo P, Marciano C, Perrone-Filardi P. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? *J Am Coll Cardiol* 2012; 60: 1192-1201.

44. Miller DP, Gomberg-Maitland M, Humbert M. Survivor bias and risk assessment. *Eur Respir J* 2012; 40: 530-532.

45. Gomberg-Maitland M, Dufton C, Oudiz RJ, Benza RL. Compelling evidence of long-term outcomes in pulmonary arterial hypertension? A clinical perspective. *J Am Coll Cardiol* 2011; 57: 1053-1061.

46. Frantz RP. Hemodynamic monitoring in pulmonary arterial hypertension. *Expert Rev Respir Med* 2011; 5: 173-178.

47. Farber HW, Foreman AJ, Miller DP, McGoon MD. REVEAL Registry: correlation of right heart catheterization and echocardiography in patients with pulmonary arterial hypertension. *Congest Heart Fail* 2011; 17: 56-64.

FIGURE LEGENDS

Figure 1. Meta-analysis flow chart.

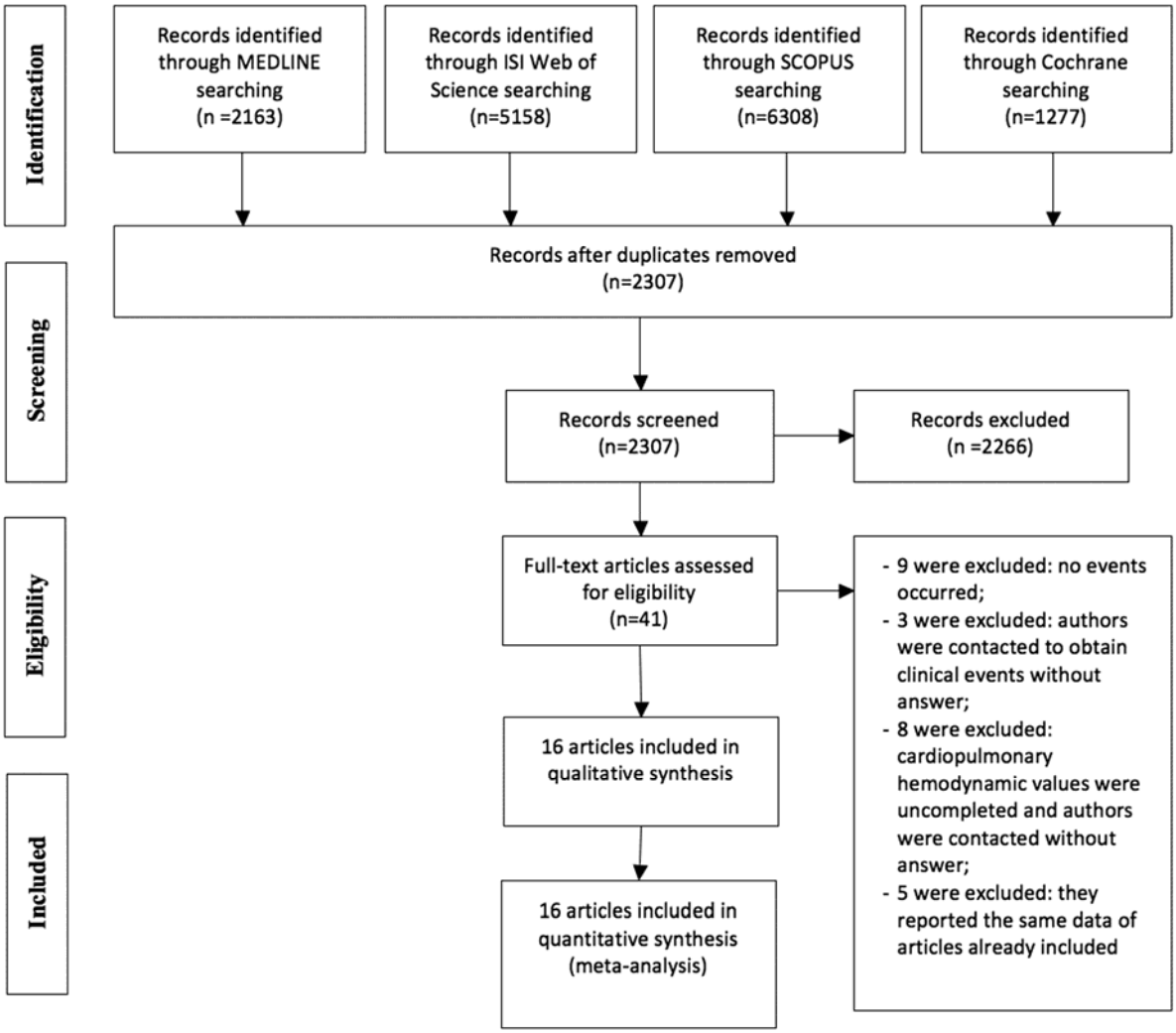

Figure 2. Linear regression between Δ6MWD and ΔPAP (A), ΔPVR (B), Δ CI (C), ΔRAP (D).

6MWD: 6 minute walking distance

PAP: pulmonary artery pressure

PVR: pulmonary vascular resistance

CI: cardiac index

RAP: right atrial pressure

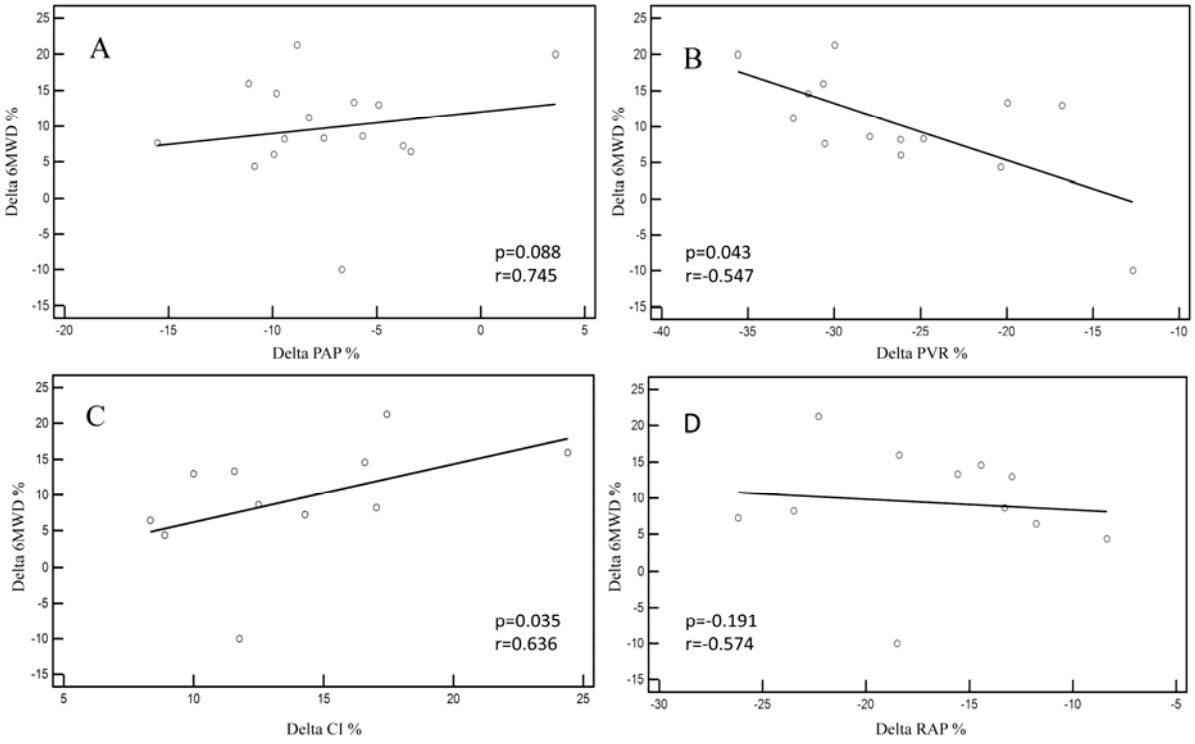

Figure 3. OR estimate of composite outcome in active treatment groups compared with control groups.

OR: Odds Ratio

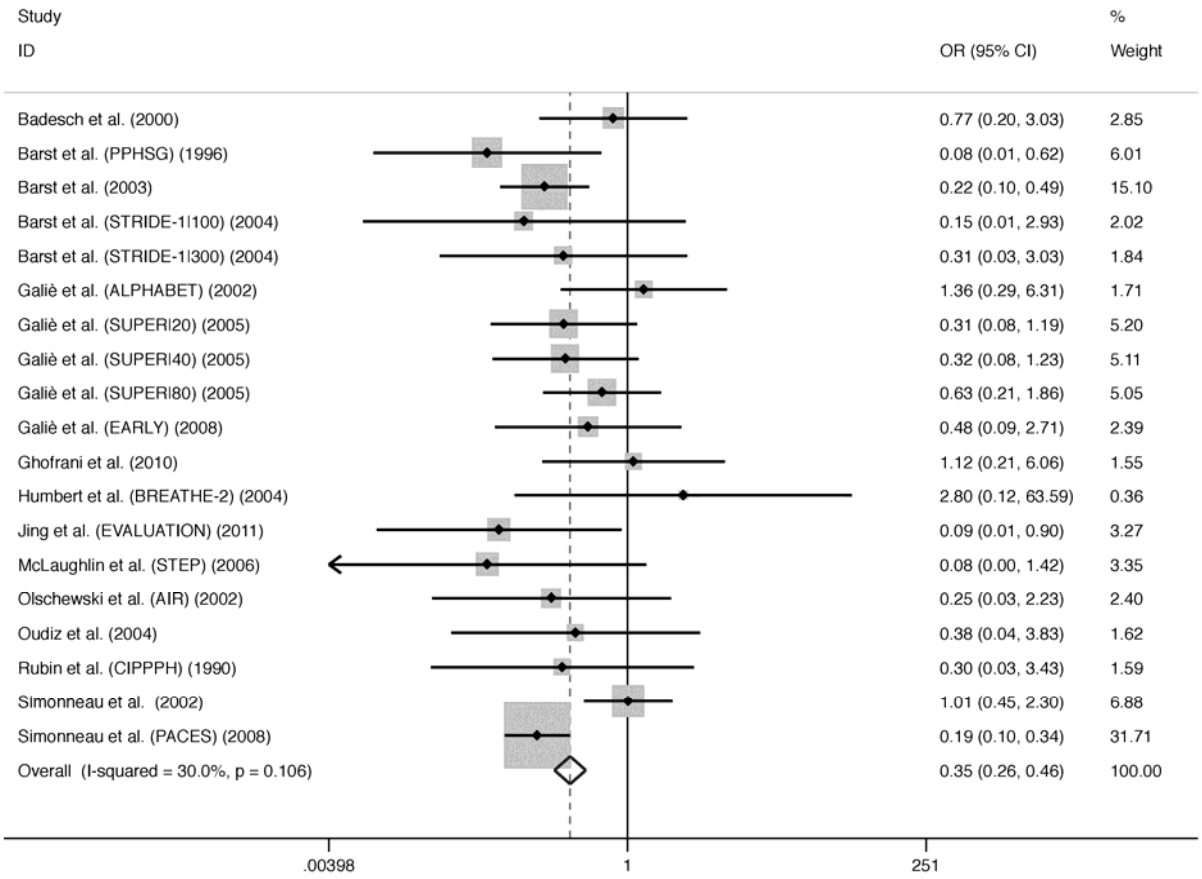

Figure 4. Meta-regression between composite outcome and ΔPAP (A), ΔPVR (B), ΔCI (C) and ΔRAP (D).

PAP: pulmonary artery pressure

PVR: pulmonary vascular resistance

CI: cardiac index

RAP: right atrial pressure

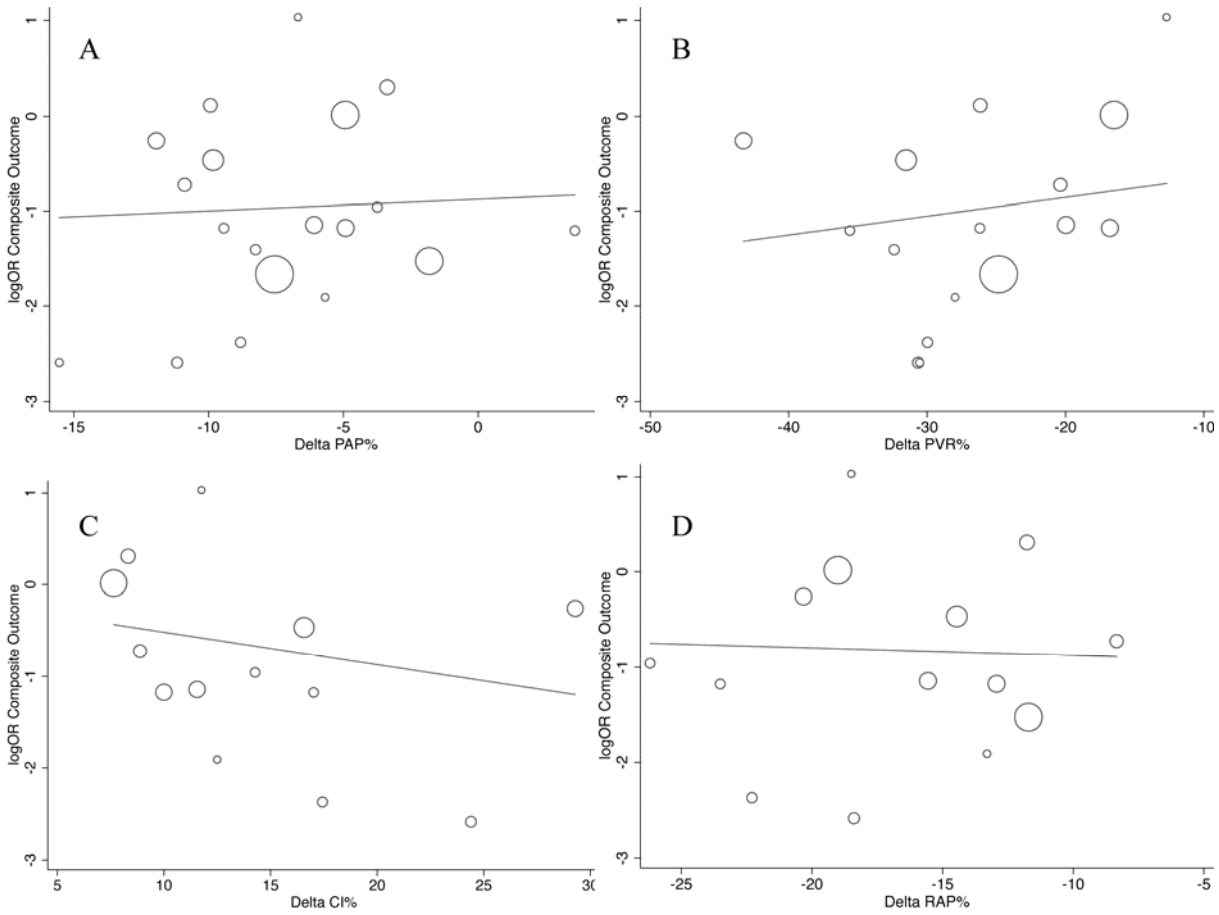
A
logOR Composite Outcome
Delta PAP%
B
logOR Composite Outcome
Delta PVR%
C
logOR Composite Outcome
Delta CI%
D
logOR Composite Outcome
Delta RAP%

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

Article	Trial Acronym	Year	Treatment Category	Treatment	Control	Treatment (n)	Control (n)	Patients (n)	Age (yrs)	Women (%)	White Race (%)
Badesch[9]		**2000**	PGI2 analogues	Epoprostenol + Conventional Therapy	Conventional Therapy	56	55	111	55	86	NA
Barst[10]	**PPHSG**	**1996**	PGI2 analogues	Epoprostenol	Conventional Therapy	41	40	81	40	73	NA
Barst[11]		**2003**	PGI2 analogues	Beraprost	Placebo	60	56	116	42	85	74
Barst[12]	**STRIDE-1**	**2004**	ET-receptor antagonists	Sitaxsentan 100mg	Placebo	55	60	115	47	82	70
				Sitaxsentan 300 mg	Placebo	63	60	123	46	76	70
Galiè[13]	**ALPHABET**	**2002**	PGI2 analogues	Beraprost	Placebo	65	65	130	45	62	NA
Galiè[14]	**SUPER**	**2005**	PDE5 inhibitors	Sildenafil 20 mg	Placebo	69	70	139	48	76	86
				Sildenafil 40 mg	Placebo	67	70	137	50	76	87
				Sildenafil 80 mg	Placebo	71	70	141	48	80	84
Galiè[4]	**EARLY**	**2008**	ET-receptor antagonists	Bosentan	Placebo	93	92	185	45	70	91
Ghofrani[15]		**2010**	Other drug	Imatinib + Conventional Therapy	Placebo + Conventional Therapy	28	31	59	44	51	93
Humbert[5]	**BREATHE-2**	**2004**	ET-receptor antagonists	Bosentan+Epoprostenol	Placebo +	22	11	33	46	70	85

					Epoprostenol						
Jing[16]	**EVALUATION**	**2011**	PDE5 inhibitors	Verdenafil	Placebo	44	20	64	31	83	NA
McLaughlin[6]	**STEP**	**2006**	PGI2 analogues	Iloprost+Bosentan	Placebo+Bosentan	34	33	67	50	79	81
Olschewski[17]	**AIR**	**2002**	PGI2 analogues	Iloprost	Placebo	101	102	203	52	67	NA
Oudiz[7]		**2004**	PGI2 analogues	Treprostinil	Placebo	41	49	90	51	90	NA
Rubin[8]	**CIPPPH**	**1990**	PGI2 analogues	Epoprostenol	Conventional Therapy	11	12	23	36	70	NA
Simonneau[18]		**2002**	PGI2 analogues	Treprostinil	Placebo	233	236	469	44	81	84
Simonneau[19]	**PACES**	**2008**	PDE5 inhibitors	Sildenafil+Epoprostenol	Epoprostenol	134	133	267	48	80	79

PAH: pulmonary arterial hypertension

PDE5: type 5 phosphodiesterase

ET: endothelin

PGI2: prostaglandin I2

NA: not available

Table 1. Continued

Article	Trial Acronym	Year	Idiopatic and/or familiar PAH (n%)	Connective disease PAH (n%)	Congenital heart disease PAH (n%)	Functional class I (%)	Functional class II (%)	Functional class III (%)	Functional class IV (%)	Follow-up (wks)	Δ6MWD	Detsky quality score
Badesch[9]		**2000**	0	100	0	0	5	78	17	12	NA	17
Barst[10]	**PPHSG**	**1996**	100	0	0	0	0	74	26	12	16.0	17
Barst[11]		**2003**	75	10	16	0	53	47	0	52	NA	18
Barst[12]	**STRIDE-1**	**2004**	52	22	26	0	33	65	2	12	8.7	17
			58	21	21	0	35	63	2	12	8.2	17
Galiè[13]	**ALPHABET**	**2002**	48	10	18	0	49	51	0	12	6.4	19
Galiè[14]	**SUPER**	**2005**	78	31	7	1	40	53	6	12	13.0	19
			78	31	7	1	40	57	2	12	13.3	19
			79	30	7	1	43	54	3	12	14.6	19
Galiè[4]	**EARLY**	**2008**	61	18	17	0	100	0	0	26	4.4	19
Ghofrani[15]		**2010**	81	10	NA	0	31	61	5	24	6.0	20
Humbert[5]	**BREATHE-2**	**2004**	82	18	0	0	0	76	24	16	-10.0	19
Jing[16]	**EVALUATION**	**2011**	61	30	9	0	47	53	0	12	21.3	19
McLaughlin[6]	**STEP**	**2006**	55	NA	NA	0	1	97	4	12	7.7	19
Olschewski[17]	**AIR**	**2002**	50	17	NA	0	0	59	41	12	11.2	16
Oudiz[7]		**2004**	0	100	0	0	10	74	16	12	7.3	18

Rubin[8]	**CIPPPH**	**1990**	100	0	0	NA	NA	NA	NA	8	20.0	17
Simonneau[18]		**2002**	**58**	19	23	0	11	81	7	12	NA	18
Simonneau[19]	**PACES**	**2008**	**79**	17	NA	1	25	66	6	16	8.3	19

Table 2. Exp[(b)] of ΔPAP, ΔPVR, ΔRAP and ΔCI changes from baseline, 95% IC, change in Tau^2, statistical significance and REML statistics for each outcome.

Outcome	Exp[(b)]	SE	95% IC	Change in Tau^2	P Tau	REML
		ΔPAP				
All-causes death	-0.32	0.67	-0.18 0.11	-0.48	0.64	0.00
Hospitalization for PAH and/or lung or heart-lung transplantation	0.07	0.13	-0.23 0.37	0.55	0.60	0.07
Initiation of PAH rescue therapy	-0.01	0.13	-0.32 0.30	-0.07	0.94	0.64
Composite outcome	0.01	0.06	-0.11 0.14	0.20	0.84	0.28
		ΔPVR				
All-causes death	0.03	0.03	-0.04 0.09	0.90	0.39	0.00
Hospitalization for PAH and/or lung or heart-lung transplantation	0.00	0.06	-0.14 0.15	0.07	0.95	0.09
Initiation of PAH rescue therapy	0.05	0.09	-0.19 0.28	0.51	0.63	0.75
Composite outcome	0.02	0.03	-0.05 0.09	0.62	0.54	0.28
		ΔCI				
All-causes death	-0.03	0.04	-0.12 0.06	-0.83	0.43	0.00
Hospitalization for PAH and/or lung or heart-lung transplantation	0.01	0.08	-0.19 0.22	0.16	0.88	0.00
Initiation of PAH rescue therapy	-0.07	0.12	-0.45 0.30	-0.61	0.59	0.00
Composite outcome	-0.03	0.03	-0.11 0.04	-1.02	0.33	0.07
		ΔRAP				
All-causes death	0.01	0.07	0.15 0.17	0.18	0.86	0.00
Hospitalization for PAH and/or lung or heart-lung transplantation	0.00	0.11	-0.27 0.28	0.05	0.96	0.00
Initiation of PAH rescue therapy	-0.08	0.12	-0.40 0.25	-0.67	0.54	0.291
Composite outcome	-0.01	0.55	-0.13 0.11	-0.14	0.89	0.220

IC: confidence intervals

REML: restricted maximum likelihood

SE: standard error

PAH: pulmonary arterial hypertension

PAP: pulmonary artery pressure

PVR: pulmonary vascular resistance

CI: cardiac index

RAP: right atrial pressure

Table 3. Hemodynamic values.

Article	Trial acronym	Year	Baseline PVR dyn*sec*cm^{-5}	ΔPVR %	Baseline PAP mmHg	ΔPAP %	Baseline CI liters/min/m^2	ΔCI %	Baseline RAP mmHg	ΔRAP %
Badesch[9]		**2000**	1017	-43.3	50	-11.9	2.0	29.3	12	-20.3
Barst[10]	**PPHSG**	**1996**	1280	-30.6	60	-11.2	2.0	24.4	13	-18.4
Barst[11]		**2003**	NA	NA	56	-1.8	2.5	NA	9	-11.7
Barst[12]	**STRIDE-1**	**2004**	966	-27.9	53	-5.7	2.4	12.5	8	-13.3
			929	-26.1	53	-9.4	2.3	17.0	9	-23.5
Galiè[13]	**ALPHABET**	**2002**	NA	NA	59	-3.4	2.4	8.3	8	-11.8
Galiè[14]	**SUPER**	**2005**	1019	-16.8	55	-4.9	2.3	10.0	8	-12.9
			962	-20.0	53	-6.1	2.2	11.6	9	-15.5
			984	-31.5	54	-9.8	2.3	16.6	9	-14.4
Galiè[4]	**EARLY**	**2008**	822	-20.3	52	-10.9	2.7	8.9	7	-8.3
Ghofrani[15]		**2010**	1121	-26.1	60	-9.9	NA	NA	NA	NA
Humbert[5]	**BREATHE-2**	**2004**	1483	-12.7	60	-6.7	1.7	11.8	12	-18.5
Jing[16]	**EVALUATION**	**2011**	1255	-30.0	61	-8.8	2.3	17.4	9	-22.3
McLaughlin[6]	**STEP**	**2006**	802	-30.5	51	-15.5	NA	NA	NA	NA

Olschewski[17]	**AIR**	**2002**	1035	-32.4	53	-8.2	NA	NA	NA	NA
Oudiz[7]		**2004**	NA	NA	54	-3.7	2.1	14.3	11	-26.2
Rubin[8]	**CIPPPH**	**1990**	1686	-35.6	61	3.6	3.4	NA	NA	NA
Simonneau[18]		**2002**	2040	-16.5	61	-4.9	2.3	7.7	10	-19.0
Simonneau[19]	**PACES**	**2008**	806	-24.8	52	-7.55	NA	NA	NA	NA

PVR: pulmonary vascular resistance

PAP: pulmonary artery pressure

CI: cardiac index

RAP: right atrial pressure

NA: not available