Haemodynamics, exercise capacity and clinical events in pulmonary arterial hypertension

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ABSTRACT The purpose of this study was to clarify whether changes in cardiopulmonary haemodynamics induced by pharmacological therapy correlate with exercise capacity and clinical events in patients with pulmonary arterial hypertension.

16 randomised trials including 2353 patients, followed up for 16.4±10.6 weeks, measuring cardiopulmonary haemodynamics by right heart catheterisation 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 haemodynamic changes (pulmonary artery pressure, pulmonary vascular resistance, cardiac index and right atrial pressure) and clinical events.

Treatments significantly reduced all-cause death (OR 0.5, 95% CI 0.3–0.7; $p<0.01$), hospitalisation for pulmonary arterial hypertension (OR 0.4, 95% CI 0.2–0.7; $p<0.01$), initiation of rescue therapy (OR 0.3, 95% CI 0.2–0.6; $p<0.01$) and the composite outcome (OR 0.3, 95% CI 0.3–0.5; $p<0.01$). No relationship was found between changes of haemodynamic parameters and clinical events, whereas changes of cardiac index and pulmonary vascular resistance significantly correlated with changes in the 6-min walking distance ($r=0.64$, $p=0.03$; $r=-0.55$, $p=0.04$, respectively).

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

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In PAH, cardiopulmonary haemodynamic improvements correlate with exercise capacity changes but not with clinical events http://ow.ly/lzTdC

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Introduction

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

Right heart catheterisation (RHC) is recommended by guidelines to measure cardiopulmonary haemodynamic parameters with the purpose of diagnosing PAH, defining its aetiology, guiding therapeutic management and obtaining prognostic information [2, 3]. Yet, although the role of cardiopulmonary haemodynamic parameters is well recognised for the initial diagnostic workup, it is still uncertain whether changes of haemodynamics 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 haemodynamic parameters either represented the primary end-point [4–8] or were reported in several PAH randomised clinical trials [9–19], it has been not extensively investigated whether improvement of haemodynamic parameters correlates with improved exercise capacity. More importantly, the relationship of haemodynamic changes with major clinical events has never been assessed from randomised studies. However, this information is 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 haemodynamic parameters induced by pharmacological therapies and exercise capacity, and clinical events in PAH patients enrolled in randomised 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. 1) Evaluation of cardiopulmonary haemodynamic by RHC at baseline and at end of follow-up; 2) report of clinical events (all-cause death, hospitalisation for PAH and/or lung or heart–lung transplantation, initiation of PAH rescue therapy); 3) comparison of active drug treatment *versus* placebo or of different doses of active drugs; and 4) randomised protocol design. Studies were identified using the major medical subject headings ''pulmonary arterial hypertension'', ''randomised'' and ''haemodynamics''. Hospitalisation was defined as end-point when it lasted at least 24 h 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 fulfilment of inclusion criteria. Baseline characteristics, haemodynamic values (pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), right atrial pressure (P_{ra}) and cardiac index) 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 haemodynamic changes and composite outcome represented the first objective of the study. Additionally, the relationship between changes of haemodynamic parameters and changes of 6-min walking distance (6MWD) was also investigated. The quality of the trials was evaluated by Detsky's method [22], whereas publication bias was assessed using Macaskill's modified test [23].

Of 14 906 articles identified by the initial search, 16 randomised trials including 2353 patients were included in the study (fig. 1). In 13 of these trials, including 1310 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, TX, USA) to test the relationship between cardiopulmonary haemodynamic changes from baseline to end of follow-up and clinical events, as previously reported [25]. For this analysis, the achieved differences between cardiopulmonary haemodynamic changes in active treatment and control groups were considered (ΔPAP, ΔPVR, ΔP_{ra}, and change in cardiac index (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 haemodynamic changes on the relationship with clinical events, for each haemodynamic parameter, studies were divided in tertiles with the

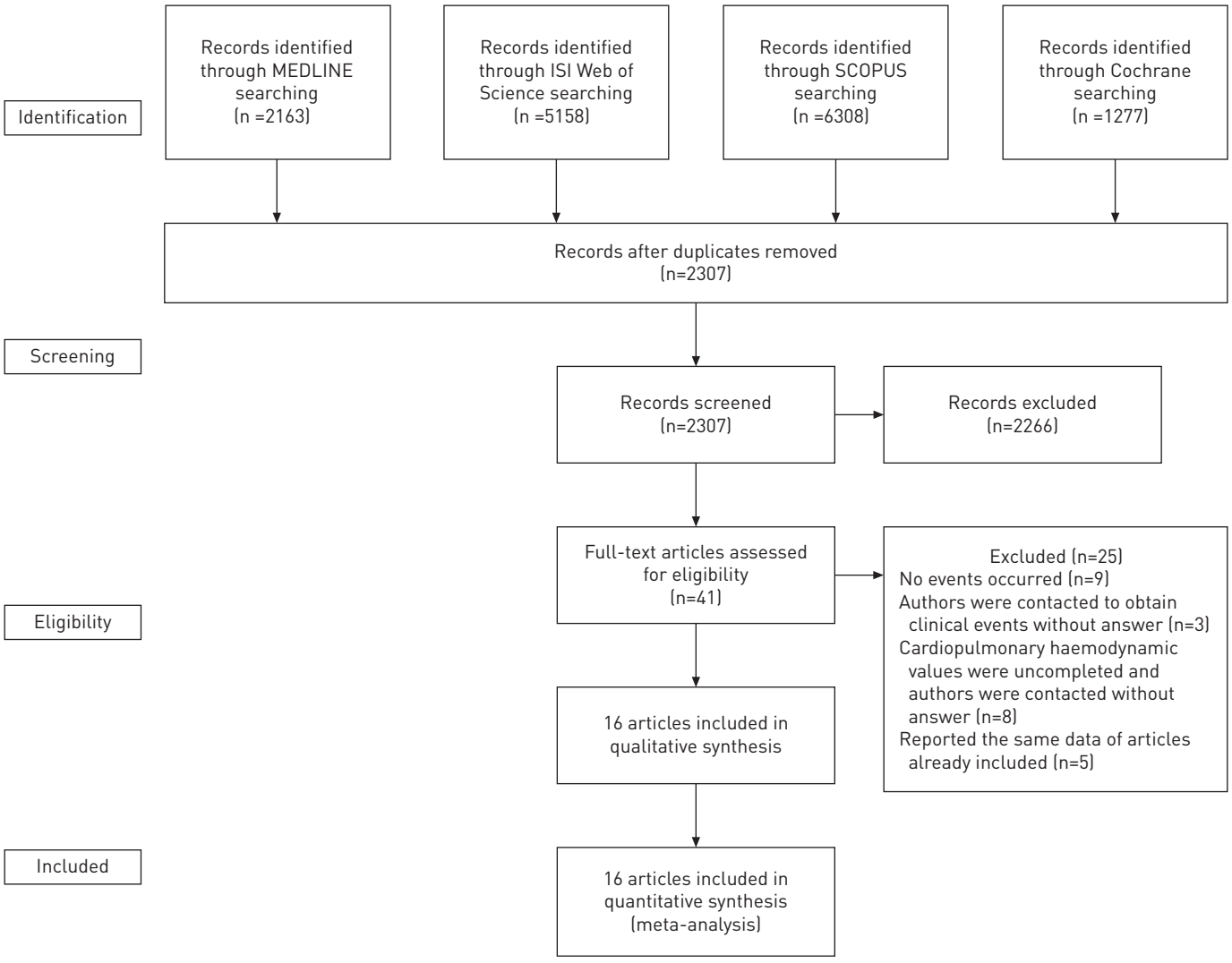

FIGURE 1 Meta-analysis flow chart.

first tertile including trials with the least favourable changes and the upper tertile including studies with the most favourable changes. Then, meta-regression was repeated, for each parameter, only for most favourable 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 haemodynamics and changes in 6MWD.

Outcome meta-analysis

Odds ratios of the effect of treatments were calculated using the metan command (STATA, version 11.0; StataCorp, College Station, TX, USA) [27]. The choice to use odds ratio 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 haemodynamic 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 haemodynamic parameters and tertile of haemodynamic changes.

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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 2353 patients included in the meta-analysis. 385 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 weeks). The overall mean age of patients was 44.4±5.9 years and 76.5% were females.

Effects of therapies on pulmonary haemodynamic parameters and exercise capacity

Pooled weighted analysis of 16 trials reporting haemodynamic changes induced by active treatments showed a 12.7±6.4% increase of mean cardiac index, 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 P_{ra}. 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 ΔP_{ra} (r= -0.57; p=0.19) (fig. 2).

Effects of therapies on outcomes

Pharmacological treatments led to significant reduction of the composite outcome without heterogeneity among studies (OR 0.3, 95% CI 0.3–0.5, comparison p<0.01, heterogeneity p=0.11) (fig. 3). Additionally, each component of the composite outcome was significantly reduced by treatments, including all-cause death (OR 0.5, 95% CI 0.3–0.7, comparison p<0.01, heterogeneity p=0.51) (online supplementary fig. S1), hospitalisation for PAH and/or lung or heart–lung transplantation (OR 0.4, 95% CI 0.2–0.7, comparison p<0.01, heterogeneity p=0.82) (online supplementary fig. S2) and initiation of PAH rescue therapy (OR 0.3, 95% CI 0.2–0.6, comparison p<0.01, heterogeneity p=0.23) (online supplementary fig. S3).

No relationship was found between ΔPAP, ΔPVR, ΔP_{ra}, ΔCI and the composite outcome by meta-regression analysis. Additionally, no relationship was found between ΔPAP, ΔPVR, ΔP_{ra}, ΔCI and each component of the composite outcome (tables 2 and 3) (fig. 4) (online supplementary figs S4–S6). Furthermore, lack of association between each haemodynamic parameter and clinical events was also confirmed for trials belonging to the tertile with the most favourable response.

Sensitivity analysis

Results were confirmed when potential effect modifiers were introduced as covariates in the meta-regression analysis (online supplementary table S1).

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 haemodynamic cardiopulmonary parameters observed during short-term randomised clinical trials investigating pharmacological therapies correlate with changes of exercise capacity evaluated by 6MWD but not with clinical events. In particular, a significant direct correlation was found between cardiac index increase and Δ6MWD, whereas a significant inverse correlation was found between PVR decrease and Δ6MWD. However, no variation of any cardiopulmonary haemodynamic parameter correlated to clinical events occurrence during the short-term follow-up of clinical trials.

Cardiopulmonary haemodynamic parameters in the management of PAH patients

It has been observed in large registry studies that increased PAP and P_{ra}, as well reduced cardiac index, 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 Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) [31] and the French registry [33] include cardiopulmonary haemodynamic as well demographic and functional parameters, whereas in the Pulmonary Hypertension Correction equation, only cardiopulmonary haemodynamic parameters were significantly associated to prognosis [34]. Accordingly, several randomised trials in PAH have reported, as main [4–8] or secondary [9–19] end-points, changes of cardiopulmonary haemodynamic parameters induced by specific PAH therapies.

TABLE 1 Baseline characteristics of trials included in meta-analysis

First author [Ref.]	Trial acronym	Year	Treatment Category	Treatment	Control	Treatment n	Control n	Patients n	Age years	Females	Ethnicity white	Idiopathic and/or familiar PAH	Connective disease PAH	Congenital heart disease PAH	Functional class				Follow-up weeks	Δ6MWD	Detsky quality score
															I	II	III	IV			
Badesch [9]		2000	PGI2 analogues	Epoprostenol + conventional therapy	Conventional therapy	56	55	111	55	86	NA	0	100	0	0	5	78	17	12	NA	17
Barst [10]	PPHSG	1996	PGI2 analogues	Epoprostenol	Conventional therapy	41	40	81	40	73	NA	100	0	0	0	0	74	26	12	16.0	17
Barst [11]		2003	PGI2 analogues	Beraprost	Placebo	60	56	116	42	85	74	75	10	16	0	53	47	0	52	NA	18
Barst [12]	STRIDE-1	2004	ET-receptor antagonists	Sitaxsentan 100 mg	Placebo	55	60	115	47	82	70	52	22	26	0	33	65	2	12	8.7	17
				Sitaxsentan 300 mg	Placebo	63	60	123	46	76	70	58	21	21	0	35	63	2	12	8.2	17
Galiè [13]	ALPHABET	2002	PGI2 analogues	Beraprost	Placebo	65	65	130	45	62	NA	48	10	18	0	49	51	0	12	6.4	19
Galiè [14]	SUPER	2005	PDE5 inhibitors	Sildenafil 20 mg	Placebo	69	70	139	48	76	86	78	31	7	1	40	53	6	12	13.0	19
				Sildenafil 40 mg	Placebo	67	70	137	50	76	87	78	31	7	1	40	57	2	12	13.3	19
				Sildenafil 80 mg	Placebo	71	70	141	48	80	84	79	30	7	1	43	54	3	12	14.6	19
Galiè [4]	EARLY	2008	ET-receptor antagonists	Bosentan	Placebo	93	92	185	45	70	91	61	18	17	0	100	0	26	4.4	19	
Ghofrani [15]		2010	Other drug	Imatinib + conventional therapy	Placebo + conventional therapy	28	31	59	44	51	93	81	10	NA	0	31	61	5	24	6.0	20
Humbert [5]	BREATHE-2	2004	ET-receptor antagonists	Bosentan + epoprostenol	Placebo + epoprostenol	22	11	33	46	70	85	82	18	0	0	0	76	24	16	-10.0	19
Jing [16]	EVALUATION	2011	PDE5 inhibitors	Verdenafil	Placebo	44	20	64	31	83	NA	61	30	9	0	47	53	0	12	21.3	19
McLaughlin [6]	STEP	2006	PGI2 analogues	Iloprost + bosentan	Placebo + bosentan	34	33	67	50	79	81	55	NA	NA	0	1	97	4	12	7.7	19
Olschewski [17]	AIR	2002	PGI2 analogues	Iloprost	Placebo	101	102	203	52	67	NA	50	17	NA	0	0	59	41	12	11.2	16
Oudiz [7]		2004	PGI2 analogues	Treprostinil	Placebo	41	49	90	51	90	NA	0	100	0	0	10	74	16	12	7.3	18
Rubin [8]	CIPPPH	1990	PGI2 analogues	Epoprostenol	Conventional therapy	11	12	23	36	70	NA	100	0	0	NA	NA	NA	NA	8	20.0	17
Simonneau [18]		2002	PGI2 analogues	Treprostinil	Placebo	233	236	469	44	81	84	58	19	23	0	11	81	7	12	NA	18
Simonneau [19]	PACES	2008	PDE5 inhibitors	Sildenafil + epoprostenol	Epoprostenol	134	133	267	48	80	79	79	17	NA	1	25	66	6	16	8.3	192

Data are shown as % unless otherwise stated. PGI2: prostaglandin I2; NA: not available; ET: endothelin; PDE5: type 5 phosphodiesterase.

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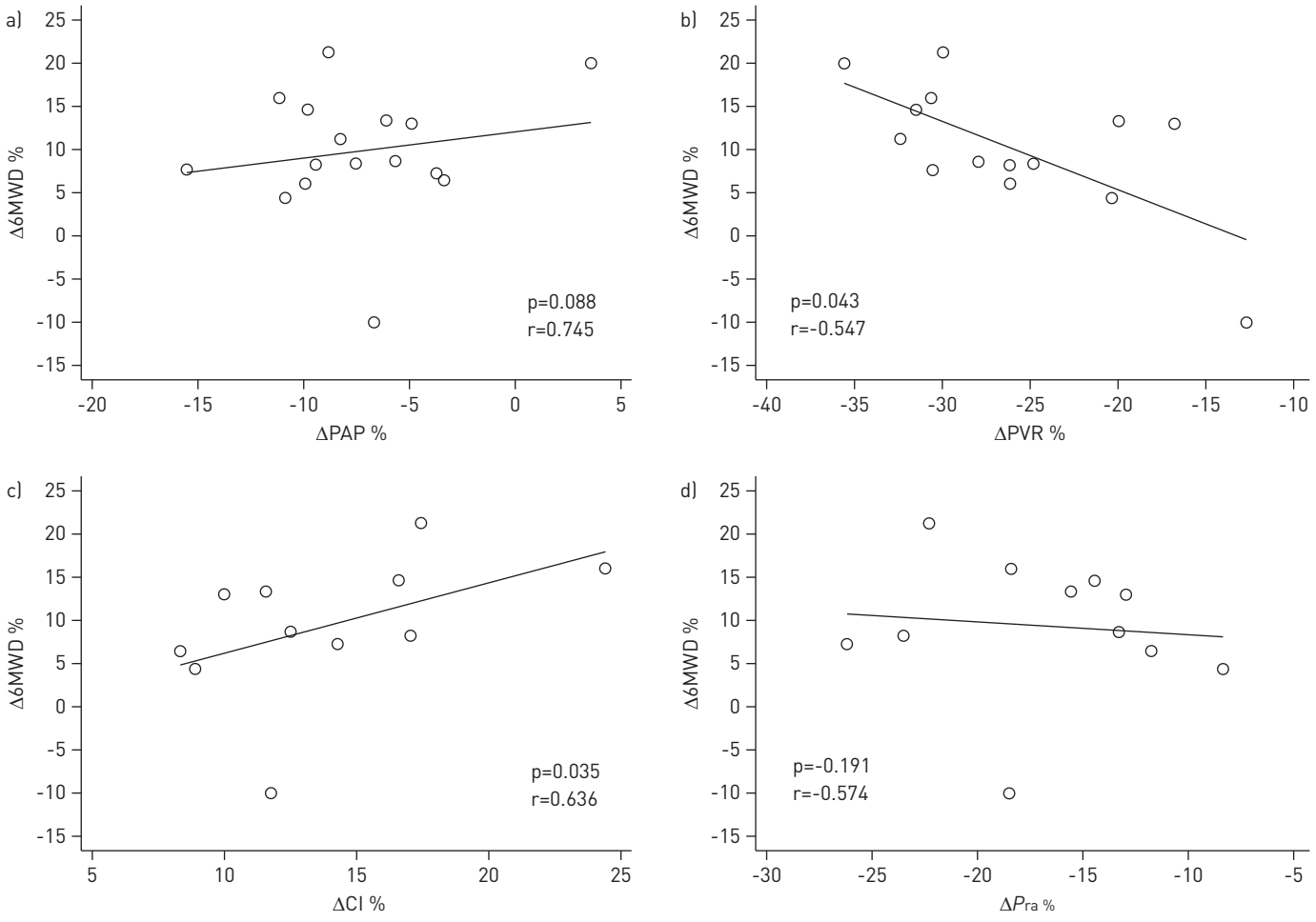

FIGURE 2 Linear regression between change in 6-min walking distance (Δ6MWD) and a) change in pulmonary arterial pressure (ΔPAP), b) change in pulmonary vascular resistance (ΔPVR), c) change in cardiac index (ΔCI), and d) change in right atrial pressure (ΔP_{ra}).

However, the relationship between haemodynamic changes and either changes of exercise capacity or occurrence of clinical events is still unclear, leading the European Society of Cardiology and the European Respiratory Society to consider repeat of RHC after initiation of therapy or, in thr case of clinical deterioration as class II recommendation, with level of evidence C [2], whereas no clear indication for repeating invasive measurement of cardiopulmonary haemodynamic is made by the American College of Cardiology and American Heart Association guidelines on PAH [3].

Cardiopulmonary haemodynamic changes and exercise capacity in PAH

In the current study, a significant association was found by regression analysis between cardiopulmonary haemodynamic changes and exercise capacity, evaluated by the 6MWD test. In particular, the Δ6MWD directly correlated with cardiac index increase and inversely correlated with ΔPVR. Although both haemodynamic and exercise changes were concomitantly assessed in 13 randomised trials [4–8, 10, 12–17, 19], to our knowledge, only BARST *et al.* [10], in their pivotal epoprostenol study, investigated the correlation between haemodynamic and exercise parameters. In agreement with our meta-analysis, they also found a significant association between haemodynamic changes and improvement of 6MWD whereas, at variance with our study, they also reported in 81 patients analysed, a significant association between change in 6MWD and change in mean PAP and change in mean P_{ra}. Thus, our aggregate results, in agreement with those of BARST *et al* [10] from a single clinical trial, indicate that haemodynamic improvement induced by vasodilator therapies in PAH plays a relevant role in the amelioration of exercise capacity.

Cardiopulmonary haemodynamic changes and short-term mortality/morbidity in PAH patients

The relationship between haemodynamic changes and clinical events has been investigated in nonrandomised studies [35–37] indicating that improvement of cardiac index and PAP [36] and decrease

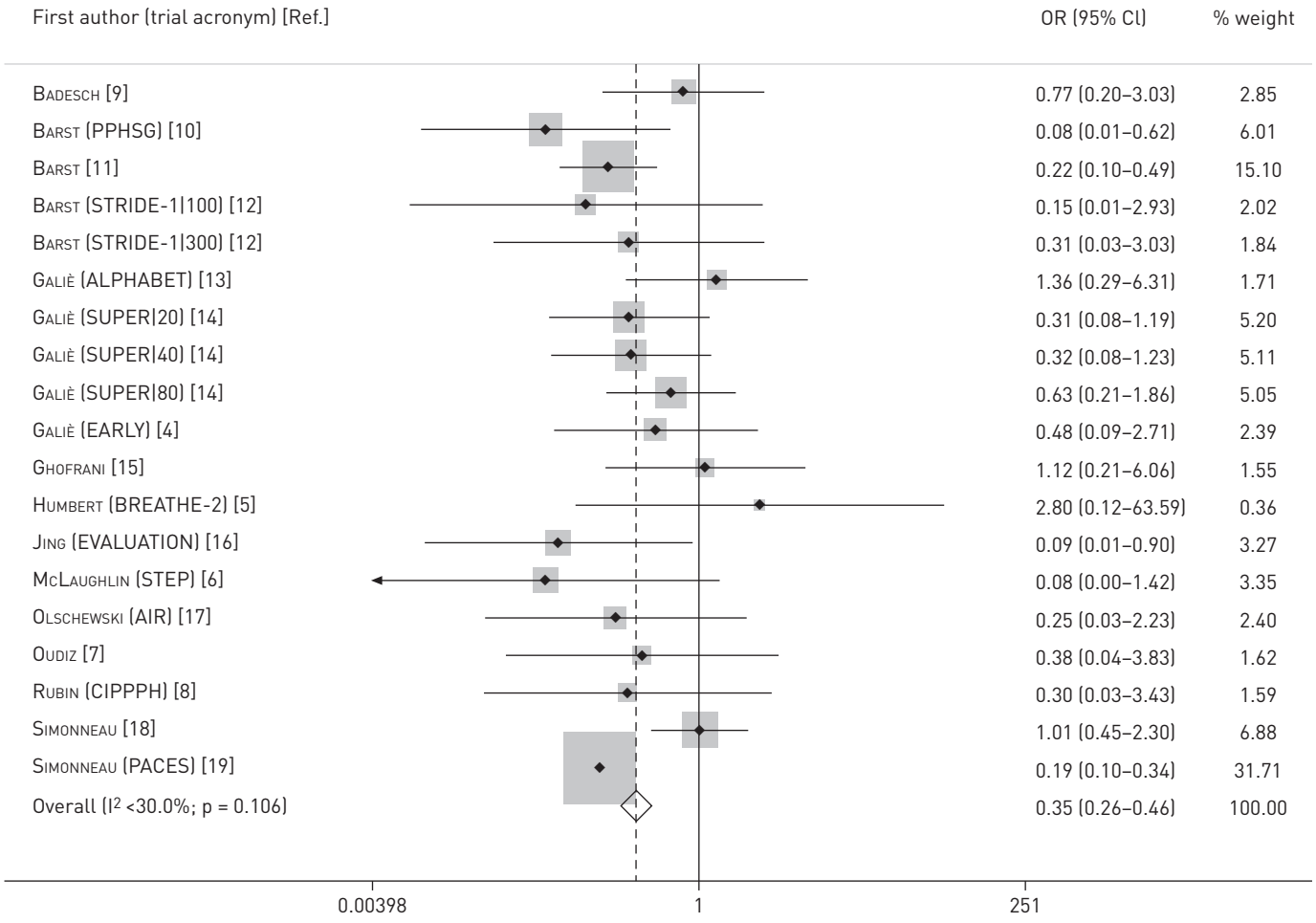

FIGURE 3 Odds ratio (OR) estimate of composite outcome in active treatment groups compared with control groups.

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 cardiac index predicted survival over a 38-month follow-up in 109 patients with PAH.

The association between cardiopulmonary haemodynamic changes observed during randomised 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 haemodynamic changes and clinical events occurring during the short-term follow-up of randomised studies. Explanation for the lack of correlation between haemodynamic improvement and events, and the reasons for the apparent discrepancy with observational nonrandomised studies, can only be hypothesised. It has been suggested that parameters reflecting right ventricular function are more predictive of clinical outcomes compared with cardiopulmonary haemodynamic 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 haemodynamic parameters induced by therapies may occur despite deterioration or no changes in 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 haemodynamic changes and events observed in our study must be interpreted with caution and not as evidence of uselessness of haemodynamic monitoring in PAH patients, for several considerations. First, our findings are restricted to

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TABLE 2 Meta-regession analyses for the different outcomes measured

Outcome	Exp(B)	SE	95% CI	Change in Tau^2	p-value for Tau	REML
ΔPAP						
All-causes death	-0.32	0.67	-0.18–0.11	-0.48	0.64	0.00
Hospitalisation 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
Hospitalisation 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
Hospitalisation 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
Δ*P*ra						
All-causes death	0.01	0.07	0.15–0.17	0.18	0.86	0.00
Hospitalisation 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

Exp(B): exponential value of B coefficient; REML: restricted maximum likelihood; ΔPAP: change in pulmonary arterial pressure; PAH: pulmonary arterial hypertension; ΔPVR: change in pulmonary vascular resistance; ΔCI: change in cardiac index; Δ*P*ra: change in arterial pressure.

randomised clinical trials and to the short period of observation, usually 3–4 months, commonly covered in these trials. This is quite a relevant aspect because, as outlined by MILLER *et al.* [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 haemodynamic changes. In addition, randomised studies include different type of drugs and different

TABLE 3 Haemodynamic values

First author [Ref.]	Trial acronym	Year	Baseline PVR dyn·s^{-1}·cm^{-5}	ΔPVR	Baseline PAP mmHg	ΔPAP	Baseline cardiac index L·min^{-1}·m^{-2}	ΔCI	Baseline *P*ra mmHg	Δ*P*ra
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

Data are presented as % unless otherwise stated. PVR: pulmonary vascular resistance; ΔPVR: change in PVR; PAP: pulmonary arterial pressure; ΔPAP: change in PAP; *P*ra: right atrial pressure; Δ*P*ra: change in *P*ra; NA: not available.

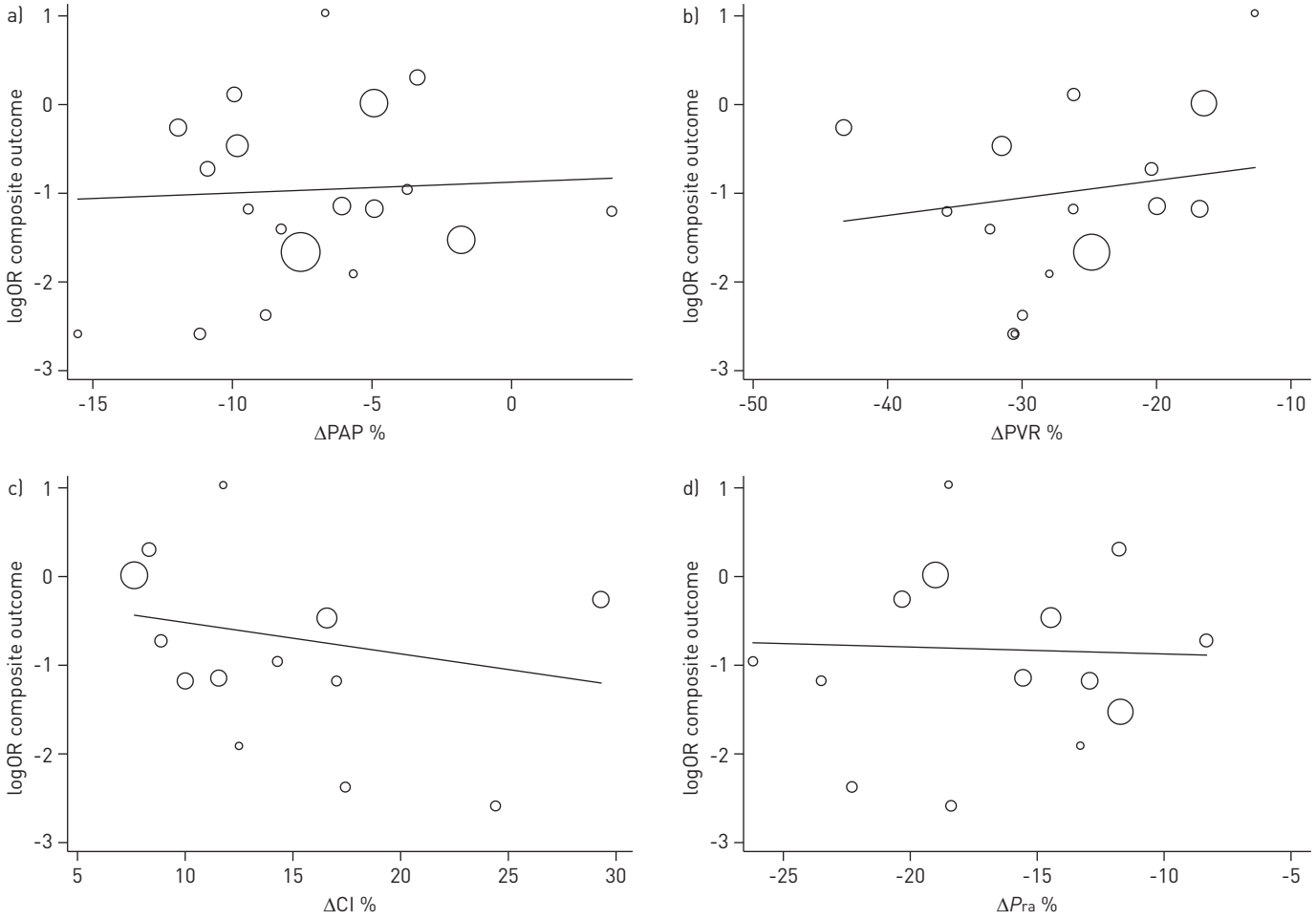

FIGURE 4 Meta-regression between composite outcome and a) change in pulmonary arterial pressure (ΔPAP), b) change in pulmonary vascular resistance (ΔPVR), c) change in cardiac index (ΔCI), d) and change in right atrial pressure (ΔP_{ra}).

degrees of haemodynamic changes, as well as different methods of evaluation of haemodynamic parameters. Thus, it cannot be excluded that an association may exist for responder patients and over a longer follow-up, as reported in nonrandomised studies or registries [45]. In addition, on treatment, haemodynamic 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 haemodynamic benefit provided by therapies under daily life. In this regard, availability of implantable devices that provide a more comprehensive monitoring of haemodynamic changes may turn out to be valuable for risk stratification in PAH patients [46]. Thus, a definitive assessment of the cost-effectiveness of haemodynamic 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 us to exclude potential significant influence of the type of therapy on the association between haemodynamic effects and clinical events, and applies to the short follow-up of clinical trials. Thus, our findings cannot be generalised to long-term treatment of PAH. Furthermore, trials analysed included naive and already treated patients and, therefore, whether reported prognostic differences between naive and treated patients may have influenced our observations cannot be evaluated from our analysis [44]. Finally, since the technique used to measure cardiac index 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.

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Conclusions

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

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