# Contribution of pressure and flow changes to resistance reduction after pulmonary arterial hypertension treatment: a meta-analysis of 3898 patients

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**In PAH, the contribution of mPAP and CI changes to PVR reduction through targeted therapy use are equally significant. Oral combo and oral plus parenteral prostanoid strategies lead to similar mPAP reduction but differ significantly in CI increase.** https://bit.ly/3Gk5boY

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## Abstract

*Background* Pulmonary arterial hypertension (PAH)-targeted therapies exert significant haemodynamic changes; however, systematic synthesis is currently lacking.

*Methods* We searched PubMed, CENTRAL and Web of Science for studies evaluating mean pulmonary artery pressure (mPAP), cardiac index/cardiac output (CI/CO) and pulmonary vascular resistance (PVR) of PAH-targeted therapies either in monotherapy or combinations as assessed by right heart catheterisation in treatment-naïve PAH patients. We performed a random-effects meta-analysis with meta-regression.

*Results* We included 68 studies (90 treatment groups) with 3898 patients (age 47.4±13.2 years, 74% women). In studies with small PVR reduction (<4 WU), CI/CO increase ($R^2$=62%) and not mPAP reduction ($R^2$=24%) was decisive for the PVR reduction (p<0.001 and p=0.36, respectively, in the multivariable meta-regression model); however, in studies with large PVR reduction (>4 WU), both CI/CO increase ($R^2$=72%) and mPAP reduction ($R^2$=35%) contributed significantly to the PVR reduction (p<0.001 and p=0.01, respectively). PVR reduction as a percentage of the pre-treatment value was more pronounced in the oral+prostanoid intravenous/subcutaneous combination therapy (mean difference −50.0%, 95% CI −60.8– −39.2%), compared to oral combination therapy (−41.7%, −47.6– −35.8%), prostanoid *i.v./s.c.* monotherapy (−31.8%, −37.6– −25.9%) and oral monotherapy (−21.6%, −25.4– −17.8%). Changes in haemodynamic parameters were significantly associated with changes in functional capacity of patients with PAH as expressed by the 6-min walking distance.

*Conclusion* Combination therapies, especially with the inclusion of parenteral prostanoids, lead to remarkable haemodynamic improvement in treatment-naïve PAH patients and may unmask the contribution of mPAP reduction to the overall PVR reduction in addition to the increase in CO.

## Introduction

Pulmonary arterial hypertension (PAH) involves a complex pathobiology that includes dysfunction in the pulmonary endothelium and the vascular smooth muscle, as well as persistent vascular inflammation and

immune dysregulation [1]. In patients who do not show vasoreactivity, PAH therapies address various pathways involved in the pathogenesis of PAH, such as the nitric oxide, endothelin and prostanoid pathway [2]. Existing PAH therapies aim to decrease the afterload of the pulmonary circulation by inducing vasodilatation and inhibiting the proliferation of the endothelial and smooth muscle cell of the pulmonary vasculature, which lead to vascular narrowing and the heightening of pulmonary vascular resistance (PVR) [3]. Their efficacy in exerting significant haemodynamic changes and improving patient outcomes is established in prospective observational cohorts as well as randomised controlled trials, and current guidelines recommend the use of combination treatments for all patients with PAH without comorbidities aiming to achieve a lower risk stratification level [4]. However, given the variety of both treatment combinations and disease subtypes, a systematic overview of the haemodynamic effects of PAH therapies is currently lacking. We therefore aimed to systematically synthesise the literature and summarise the haemodynamic effects of PAH therapies, as well as to explore the pulmonary pressure and flow changes in relation to the resistance changes in treatment-naïve patients with PAH.

## Methods

This systematic review was performed according to the PRISMA Guidelines [5] and its protocol has been registered in the Open Science Framework (DOI 10.17605/OSF.IO/XTMW8). No ethical approval is required for this type of study.

The PubMed, CENTRAL and Web of Science databases were searched on August 2022 with a search strategy including terms for "pulmonary hypertension", "PAH therapies" and "haemodynamics" (supplementary material 1). We considered eligible both prospective and retrospective studies which included treatment-naïve PAH patients at baseline. Eligible studies were designed to evaluate the haemodynamic effects as assessed by right heart catheterisation (RHC) – *i.e.* changes in mean pulmonary artery pressure (mPAP), cardiac index/cardiac output (CI/CO) and PVR – of PAH therapies comprising endothelin receptor antagonists (ERA), phosphodiesterase type 5 inhibitors (PDE5i), prostanoids (either *i.v.*/*s.c.* or *p.o.*/inhaled therapy), riociguat and selexipag. PAH therapies could be administered either as monotherapy or as combination therapy. For the purposes of our analysis, we categorised PAH therapies as oral monotherapy (O-mono, including oral prostacyclin analogues and inhaled prostanoids in this group), prostanoid *i.v.*/*s.c.* monotherapy (P-mono), oral combination therapy (O-combo), and combination of oral plus prostanoid *i.v.*/*s.c.* therapy (OP-combo). We also extracted data regarding the 6-min walking distance (6MWD) in metres before and after the administration of PAH therapies. No changes in administered pharmacotherapy should have been performed from treatment initiation until follow-up RHC (this does not exclude changes in the dose titration of the administered initial therapy). Exclusion criteria included patients with Eisenmenger syndrome, pulmonary hypertension group other than group 1 and studies assessing acute haemodynamic effects of PAH therapies (measurements performed before and after single dose of a drug). The study selection and data extraction processes were performed independently from two review authors (A. Baroutidou and V. Patsiou), while a third review author (I.T. Farmakis) was consulted to resolve disagreements according to standard procedures as described in the Cochrane Handbook [6]. Quality assessment of the included studies was performed with a modified Newcastle–Ottawa scale for single-arm studies [7].

We performed a single-arm random effects model meta-analysis of eligible studies to evaluate the effect of PAH therapies on haemodynamic parameters as described above. The mean difference (MD) or the standardised mean difference with corresponding 95% confidence intervals was the effect measure. Standard Der–Simonian–Laird equations were used to produce estimates of variance. Heterogeneity was assessed with the Cochran's Q and the $I^2$ statistic. Publication bias was assessed with the use of funnel plots and the Egger's test. We used meta-regression to evaluate the contribution of mPAP reduction and CI/CO increase to the PVR reduction in the whole population divided into two groups by separating with the median PVR reduction across studies and evaluating the $R^2$ corresponding to the explained variation. We used meta-regression to evaluate the contribution of changes in haemodynamic parameters to change in 6MWD from baseline to follow-up. All analyses were performed with the *meta* package in R.

## Results

The search strategy resulted in 3343 studies; after evaluation of 273 full-text articles, 68 studies were considered eligible (supplementary material 2). Eligible studies comprised 90 treatment arms with 3898 patients who underwent RHC before and after initiation of PAH therapy [8–75]. Mean age was 47.4 ±13.2 years, and 74% of patients were women. World Health Organization (WHO) functional class of I or II was reported in 21.6% of patients, while the mean baseline 6MWD was 334.8±103.6 m. Of included patients, 64.5% concerned idiopathic or heritable PAH, 18.9% connective tissue disease-associated PAH and 7.6% congenital heart disease-associated PAH. Mean baseline mPAP was 54.7±12.3 mmHg. In total, 1867 (48%) patients received O-mono (46 treatment arms), 834 (21%) received P-mono (19 treatment

arms), 857 (22%) received O-combo (14 treatment arms) and 157 (4%) patients received OP-combo therapy (seven treatment arms), while 183 (5%) patients (four treatment arms) could not be grouped. Characteristics of patients according to the groups of PAH treatment are presented in table 1. Characteristics of individual studies are presented in supplementary material 3.

In the quality assessment, 29 and 25 studies received total score 6 and 5 out of 6, respectively, while nine and five studies received total score 4 and 3 out of 6, respectively, indicating a high participation rate of studies of adequate quality in the review (supplementary material 4 ).

### *Effects of PAH therapies on haemodynamics*

In the random effect meta-analysis, mean reduction of PVR was −4.1 WU (95% CI −4.7– −3.5). In studies with PVR reduction <4 WU (n=39 treatment arms), the mPAP reduction contribution to the PVR reduction was $R^2$=24%, while the CI increase contribution was $R^2$=62% (figure 1). In studies with PVR reduction >4 WU (n=41 treatment arms), the mPAP reduction contribution to the PVR reduction was $R^2$=35%, while the CI increase contribution was $R^2$=72% (figure 1). In the multivariable meta-regression analysis by introducing simultaneously the CI and mPAP as independent terms, the contribution of CI was significant both in the smaller PVR reduction group (p<0.0001) as well as in the larger PVR reduction group (p<0.0001). However, the mPAP contribution was not significant for the smaller PVR reduction group (p=0.35), while it reached statistical significance in the larger PVR reduction group (p=0.01).

PVR reduction as a percentage of the pre-treatment value was more pronounced in the OP-combo therapy (MD −50.0%, 95% CI −60.8– −39.2%), compared to O-combo (MD −41.7%, 95% CI −47.6– −35.8%), P-mono (MD −31.8%, 95% CI −37.6– −25.9%) and O-mono (MD −21.6%, 95% CI −25.4– −17.8%) (figure 1). The % reduction of PAH therapy on mPAP was −21.2% (OP-combo), −19.4% (O-combo), −11.0% (P-mono) and −8.2% (O-mono), while the % increase on CO/CI was 64.0% (OP-combo), 34.1% (O-combo), 29.3% (P-mono) and 13.6% (O-mono) (figure 2). Absolute reduction of mPAP was −4.3 mmHg (95% CI −5.2– −3.5) with O-mono, −5.4 mmHg (95% CI −6.9– −3.8) with P-mono, −10.1 mmHg (95% CI −12.2– −8.0) with O-combo and −12.8 mmHg (95% CI −16.7– −8.9) with OP-combo (supplementary material 5). The % reduction of PVR was more evident in the subgroups of initial combination therapy and studies with longer follow-up duration (possibly because of better dose treatment titration), while there was no difference according to the subgroups of PAH populations (figure 3).

### *Functional capacity and haemodynamics*

The mean increase in 6MWD with PAH therapies was +57.8 (95% CI 48.5–67.1) m or +18.7% relative to baseline. The increase was significantly greater with OP-combo therapies (+141.1 m or +68.4%) than

**TABLE 1** Characteristics of the included population according to pulmonary arterial hypertension therapy groups

| Characteristic | Oral monotherapy[#] | Prostanoid monotherapy[¶] | Oral combination therapy[+] | Oral plus parenteral prostanoid combination therapy[§] |
|---|---|---|---|---|
| **Age years** | 46±13.7 | 44.5±8.7 | 52.1±16.5 | 44.7±15.5 |
| **Female %** | 73.3 | 77.7 | 72 | 72.8 |
| **IPAH/HPAH** | 55.7 | 74.5 | 66.4 | 89.2 |
| **CTD-PAH** | 20.8 | 13 | 23.3 | 5.1 |
| **CHD-PAH** | 10.2 | 8.2 | 3.2 | 2.5 |
| **WHO FC I/II** | 29.9 | 3.8 | 25.2 | 0.6 |
| **6MWD m** | 352±97 | 287±105 | 344±115 | 264±124 |
| **mPAP mmHg** | 54.2±14.6 | 58.3±8.2 | 51.9±11.2 | 60.7±11.2 |
| **CI L·min$^{-1}$·m$^{-2}$** | 2.4±0.7 | 2.1±0.3 | 2.3±0.7 | 1.8±0.3 |
| **PVR WU** | 12.9±7.3 | 16.4±6.3 | 11.8±5.5 | 16.7±5.1 |

Data are presented as mean±SD or %. 183 patients (4 treatment arms) could not be grouped. IPAH: idiopathic pulmonary arterial hypertension; HPAH: hereditary pulmonary arterial hypertension; CTD-PAH: connective tissue disease-associated pulmonary arterial hypertension; CHD-PAH: congenital heart disease-associated pulmonary arterial hypertension; WHO FC: World Health Organization functional class; 6MWD: 6-min walking distance; mPAP: mean pulmonary artery pressure; CI: cardiac index; PVR: pulmonary vascular resistance; WU: Wood units. [#]: 46 treatment arms, n=1867 patients; [¶]: 19 treatment arms, n=834 patients; [+]: 14 treatment arms, n=857 patients; [§]: 7 treatment arms, n=157 patients.

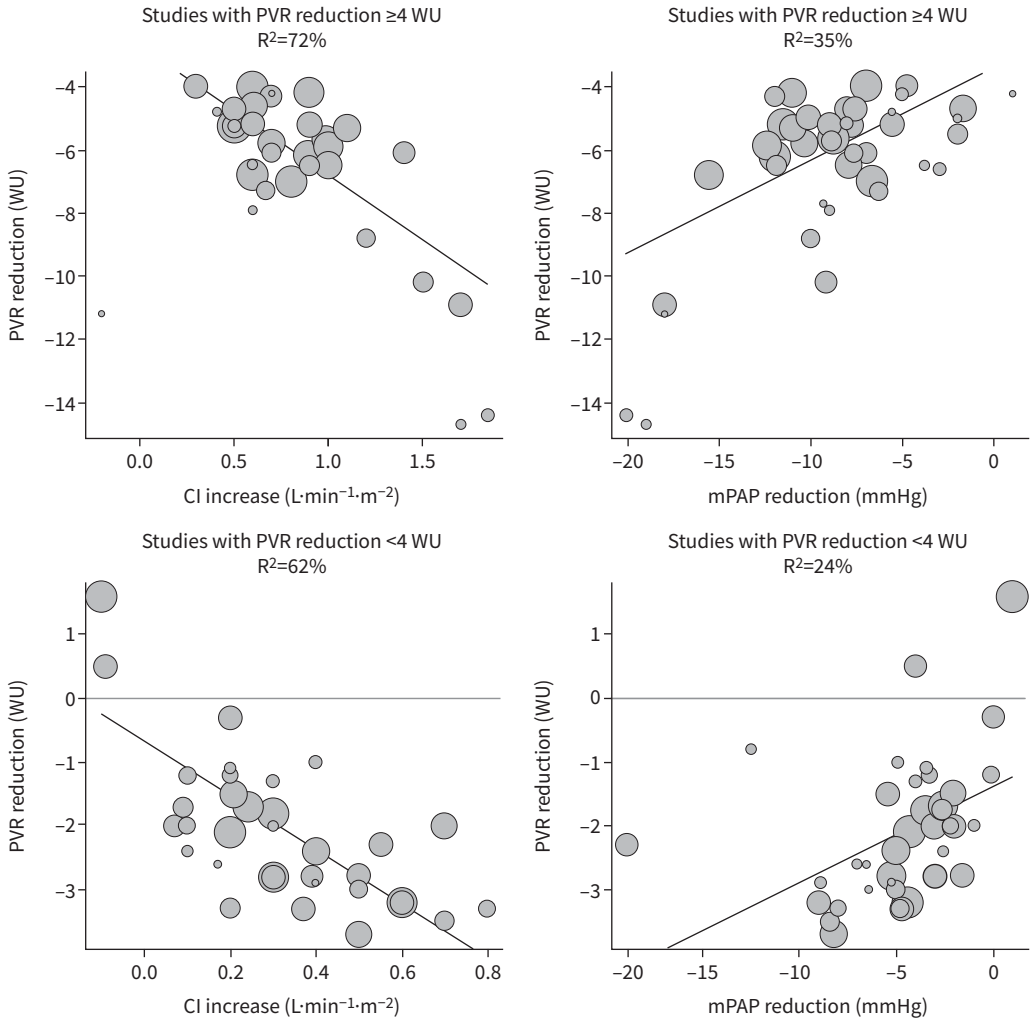


FIGURE 1 The contribution of mean pulmonary artery pressure (mPAP) reduction (right panels) and of cardiac index/cardiac output (CI/CO) increase (left panels) on the pulmonary vascular resistance (PVR) % reduction across studies with small and large PVR reduction.

O-combo (+58.3 m or +17.2%), P-mono (+75.8 m or +29.5%) and O-mono (+43.3 m or +12.7%) therapies (supplementary material 5). The contribution of PVR change to 6MWD change reached an $R^2$ of 22.5%, while the contributions of mPAP changes and CO/CI changes to 6MWD were 32.4% and 52.6%, respectively (all significant with $p<0.001$) (figure 4).

## Discussion

To our knowledge, this is the most comprehensive analysis of the effects of PAH therapies on haemodynamic parameters, synthesising results from ∼4000 PAH patients. Combination therapies, especially when including parenteral prostanoids, led to a remarkable haemodynamic improvement in treatment-naïve PAH patients. These findings aligned with our previous work [76]. The results of the present study suggest that PAH medical treatment exerts significant PVR reduction through vasodilation and increase in cardiac output, which contributes more to the resistance reduction than the reduction in the mPAP. This may reflect changes in the intravascular proliferation and could suggest remodelling in the pulmonary vasculature. Especially in cases where the overall drop of PVR is not large, the contribution of cardiac output increase though PAH treatment is dominant. However, in cases where PVR is significantly reduced, such as in triple upfront PAH therapy with the inclusion of parenteral prostanoids, the contribution through mPAP reduction and, thus, through remodelling of the pulmonary vasculature is becoming apparent. Summarising, it may be suggested that with the currently available PAH treatments, the initial mild decrease in mPAP (*i.e.* oral therapy) is initially accompanied by a more potent CO increase,

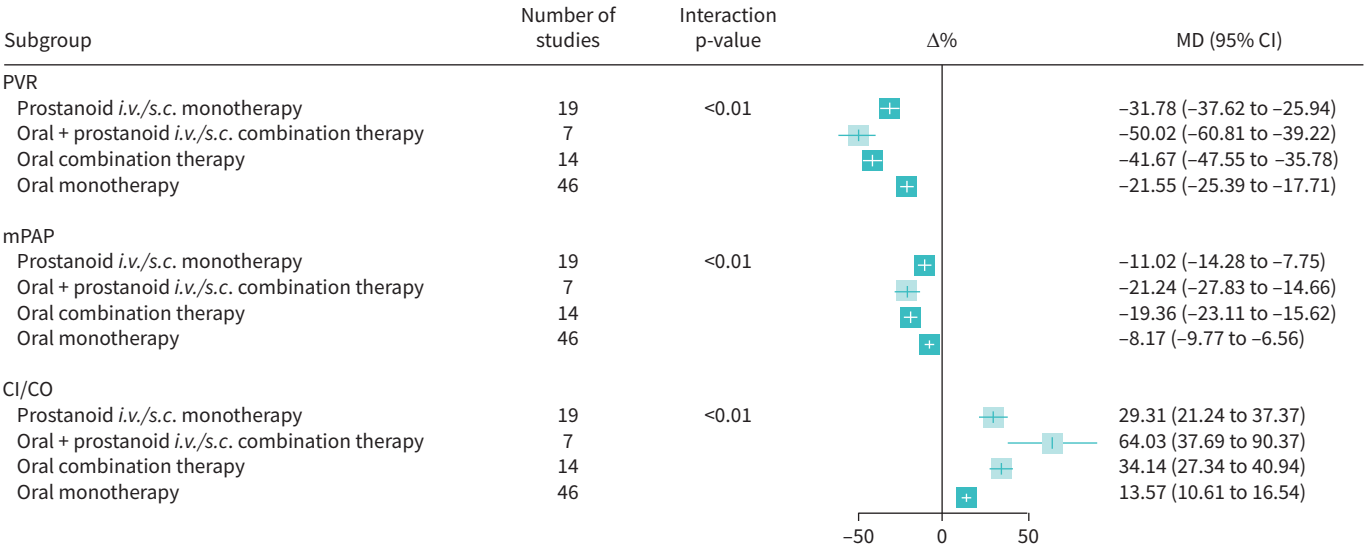


FIGURE 2 Effects of different groups of pulmonary arterial hypertension (PAH) therapies on haemodynamic parameters as a percentage difference from baseline in treatment-naïve PAH patients. PVR: pulmonary vascular resistance; mPAP: mean pulmonary artery pressure; CI/CO: cardiac index/cardiac output; MD: mean difference.

and a more aggressive approach (*i.e.* triple including parenteral prostanoids) is able to obtain a relevant PVR decrease resulting from a combined CO increase plus mPAP decrease.

Interestingly, strategies involving oral combination therapies and oral plus prostanoid *i.v./s.c.* therapies led to a similar reduction in mPAP (−19% and −21% from baseline, respectively), but significantly differed in CI/CO increase (34.1% and 64% from baseline, respectively), although with large confidence intervals due to the limited number of studies. This finding could be explained by the additive vasodilatory effects on the pulmonary vasculature combined with the positive inotropic effects of prostanoid therapies [77, 78]. In addition, the prominent effect of prostanoid therapies on systemic vascular resistance could consequently lead to an additional increase in the cardiac output.

We believe that our findings may support current recommendations for the early initiation of parenteral prostanoids, especially for patients at high risk at initial assessment and with severely impaired haemodynamics [4, 79], as this has also been shown to achieve reverse right ventricular remodelling [9] and lead to survival benefit [80]. In addition, as was also shown with our analysis, the OP-combo therapies led to the greatest improvement in the functional capacity with an approximate 70% relative increase in the 6-min walking test. It has to be mentioned that patients eligible for parenteral prostanoids also had the worst baseline 6MWD values and thus the greatest room for clinical improvement; however, even when expressed in absolute values, the difference was significantly greater with OP-combo therapies. In addition, changes in haemodynamic variables significantly explained a large part of the heterogeneity of 6MWD change through follow-up as also shown by a previous study [81]. Nonetheless, due to the small number of identified studies to evaluate the haemodynamic effects of triple combination therapy including parenteral prostanoids and because of the wide CI changes in cardiac output observed in the available literature, further studies with larger cohorts of patients treated with triple combo including parenteral prostanoid are essential to clarify the true vasodilatory effect of such an aggressive approach on the pulmonary circulation.

Alternative strategies including combined vasodilation and vascular remodelling inhibition with antiproliferative mechanisms, which could potentially result in stronger afterload reduction, are currently under investigation [82, 83]. In general, research in PAH treatment has focused on therapies that stall or reverse pulmonary vascular remodelling [1]. Recently, sotatercept, a ligand trap for members of the transforming growth factor-β superfamily, which restores the balance between the growth-promoting activin growth differentiation factor pathway and the growth-inhibiting BMP pathway, has shown in the phase II PULSAR trial a significant reduction in PVR compared to placebo in patients already on either monotherapy or combination therapy [84]. Notably, the effect was driven by a reduction in mPAP and no

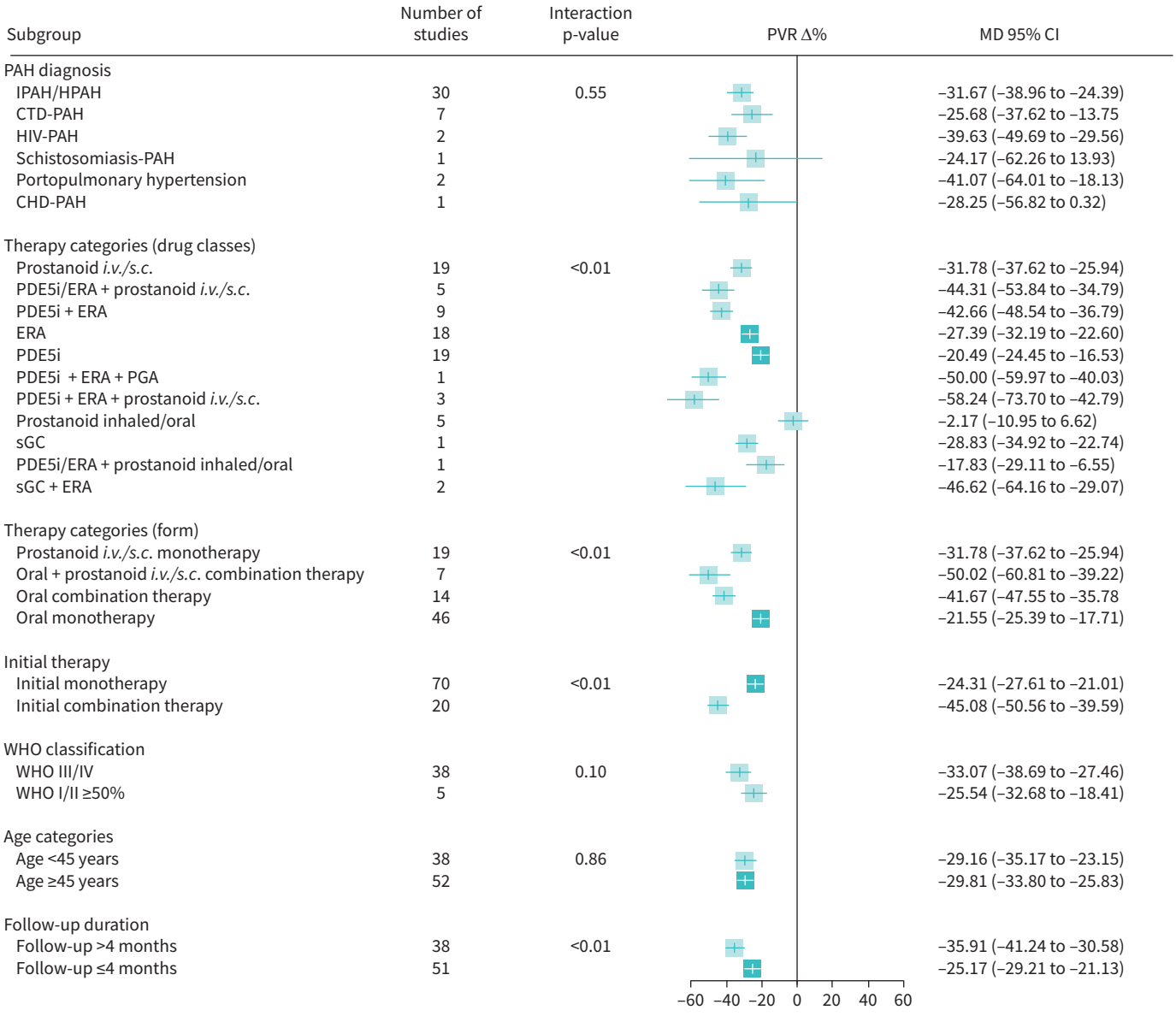


**FIGURE 3** Key subgroup analyses for the effect of pulmonary arterial hypertension (PAH) therapies on pulmonary vascular resistance (PVR) as a percentage difference from baseline. MD: mean difference; IPAH: idiopathic pulmonary arterial hypertension; HPAH: hereditary pulmonary arterial hypertension; CTD-PAH: connective tissue disease associated pulmonary arterial hypertension; HIV-PAH: HIV-associated pulmonary arterial hypertension; CHD-PAH: congenital heart disease associated pulmonary arterial hypertension; PDE5i: phosphodiesterase type 5 inhibitors; ERA: endothelin receptor antagonists; PGA: oral prostacyclin receptor agonist; sGC: soluble guanylate cyclase; WHO: World Health Organization.

increase in the CO was observed, suggesting that sotatercept has a direct effect on pulmonary vascular remodelling [84, 85]. The phase III STELLAR trial of sotatercept showed clinical benefit in patients receiving the drug compared to placebo [83]. KER-012, another modified ACTRIIB ligand trap, is also currently under investigation in an effort to mitigate adverse events of sotatercept such as telangiectasia and bleeding. Other novel pathways involve tyrosine kinase inhibitors that target the platelet-derived growth factor (PDGF) and platelet-derived growth factor receptor (PDGFR) overexpression that has been shown in lung tissues from patients with PAH [86]. Seralutinib is an inhaled PDGFR, CSF1R, and Kit tyrosine kinase inhibitor and recently demonstrated a significant 14% PVR reduction *versus* placebo in the phase II TORREY trial [87].

Limitations of this meta-analysis include a study-level design, and variability in the components of the PAH therapy groups, in the aetiology of PAH as well as in baseline risk assessment of patients, and in the

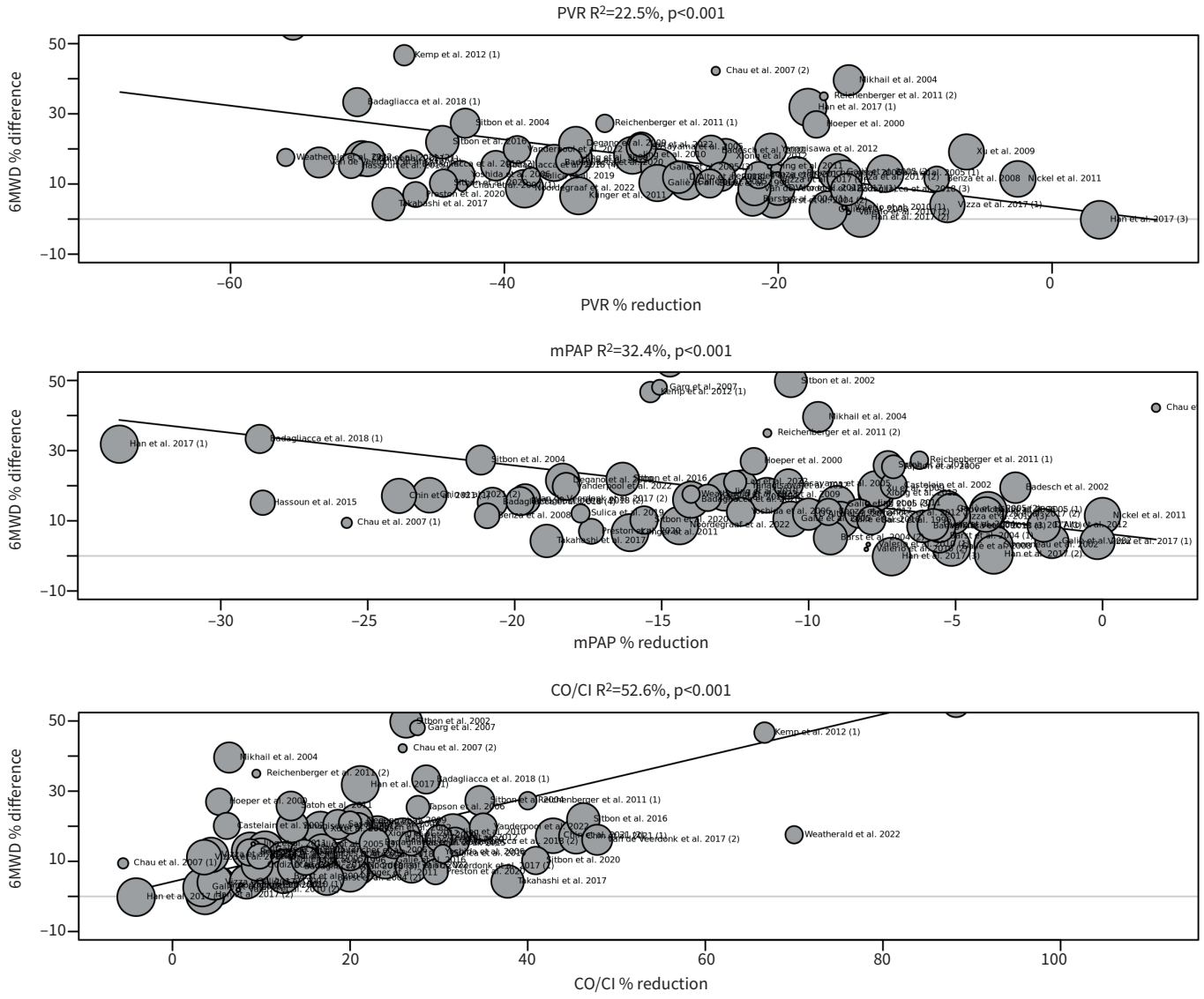


**FIGURE 4** The contribution of haemodynamic changes to the 6-min walking distance (6MWD) changes in patients with pulmonary arterial hypertension (PAH). PVR: pulmonary vascular resistance; mPAP: mean pulmonary artery pressure; CI/CO: cardiac index/cardiac output.

methods of CI/CO calculation. In addition, the group of oral plus prostanoid *i.v./s.c.* combination therapy comprised a restricted number of studies and patients, thus limiting the power of the analysis.

In conclusion, combination therapies, especially with the inclusion of parenteral prostanoids, are associated with remarkable haemodynamic improvement in treatment-naïve PAH patients and a subsequent improvement in functional capacity. Smaller PVR reductions are mainly attributed to the CI/CO increase, while the effect of mPAP reduction is unmasked in greater PVR reduction, *i.e.* as with triple upfront therapy. This increases the likelihood of pulmonary vascular and right ventricular reverse remodelling.

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