*Research Article*

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# Chronic use of PAH-specific therapy in World Health Organization Group III Pulmonary Hypertension: a systematic review and meta-analysis

**Kurt W. Prins, Sue Duval, Jeremy Markowitz, Marc Pritzker and Thenappan Thenappan**

Cardiovascular Division, University of Minnesota Medical School, Minneapolis, MN, USA

**Abstract**

Pulmonary hypertension (PH) complicating chronic obstructive pulmonary disease (COPD-PH) and interstitial lung disease (ILD-PH) (World Health Organization [WHO] Group III PH) increases medical costs and reduces survival. Despite limited data, many clinicians are using pulmonary arterial hypertension (PAH)-specific therapy to treat WHO Group III PH patients. To further investigate the utility of PAH-specific therapy in WHO Group III PH, we performed a systematic review and meta-analysis. Relevant studies from January 2000 through May 2016 were identified in the MEDLINE, EMBASE, and COCHRANE electronic databases and www.clinicaltrials.gov. Change in six-minute walk distance (6MWD) was estimated using random effects meta-analysis techniques. Five randomized controlled trials (RCTs) in COPD-PH (128 placebo or standard treatment and 129 PAH-medication treated patients), two RCTs in ILD-PH (23 placebo and 46 treated patients), and four single-arm clinical trials (50 patients) in ILD-PH were identified. Treatment in both COPD-PH and ILD-PH did not worsen hypoxemia. Symptomatic burden was not consistently reduced but there were trends for reduced pulmonary artery pressures and pulmonary vascular resistance with PAH-specific therapy. As compared to placebo, 6MWD was not significantly improved with PAH-specific therapy in the five COPD-PH RCTs (42.7 m; 95% confidence interval [CI], −1.0 – 86.3). In the four single-arm studies in ILD-PH patients, there was a significant improvement in 6MWD after PAH-specific treatment (46.2 m; 95% CI, 27.9–64.4), but in the two ILD-PH RCTs there was not an improvement (21.6 m; 95% CI, −17.8 – 61.0) in exercise capacity when compared to placebo. Due to the small numbers of patients evaluated and inconsistent beneficial effects, the utility of PAH-specific therapy in WHO Group III PH remains unproven. A future clinical trial that is appropriately powered is needed to definitively determine the efficacy of this widely implemented treatment approach.

**Keywords**

pulmonary hypertension, chronic lung disease, COPD, ILD, WHO Group 3 Pulmonary Hypertension

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## Introduction

Pulmonary hypertension (PH) is a frequent complication of chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) (World Health Organization [WHO] Group III PH).[1–9] PH in COPD and ILD increases symptomatic burden, costs, and reduces survival.[1–10] Although not extensively studied in the WHO Group III PH population, many providers are using pulmonary arterial hypertension (PAH)-specific therapy for WHO Group III PH patients. In fact, a recent study showed 80% of PH referral centers in the USA use PAH-specific therapy in WHO Group III PH patients.[11]

Use of PAH-specific therapy in WHO Group III PH patients is controversial as these medications are only approved for WHO Groups I and IV patients, and there is

Corresponding author:

Thenappan Thenappan, Assistant Professor of Medicine, Section of Advanced Heart Failure and Pulmonary Hypertension Cardiovascular Division, University of Minnesota Medical School, 420 Delaware Street SE, Minneapolis, MN 55455, USA.

Email: tthenapp@umn.edu

theoretical concern that the pulmonary vasodilation could result in ventilation perfusion (V/Q) mismatch and subsequently worsen hypoxemia.[10] However, small clinical trials in COPD-PH and ILD-PH patients showed PAH-specific medications were safe, but the therapeutic benefit was unclear.[12–21] In order to gain better insight into the utility of PAH-specific therapy in WHO Group III PH, we conducted a systematic review and meta-analysis.

## Materials and methods

The present review was reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework.[22] A PRISMA checklist was used to verify the methodology of the manuscript (Supplemental Data 1).

*Search strategy:* Studies were identified by working with a biomedical librarian and systematically searching the electronic databases EMBASE, MEDLINE, and COCHRANE from January 2000 through May 2016. We did not include gray literature. The search strategies are depicted in the Supplemental Data. Only articles written in English and conducted in humans were included. Two reviewers (KWP and JM) retrieved and read the full-text articles from those with an abstract that suggested it was relevant. Results from this step were compared and any discrepancies resolved through consensus. We also searched the reference lists from the identified articles and www.clinicaltrials.gov to identify other studies.

*Study selection:* To be eligible, studies had to fulfill the following inclusion criteria: (1) randomized controlled trial (RCT) or single-arm clinical trial; (2) assessed the chronic effects (duration of $\geq 12$ weeks) of PAH-specific therapy in COPD and ILD patients with PH as defined by a mean pulmonary arterial pressure (PAP) of $\geq 25$ mmHg via right heart catheterization or an echo-estimated systolic PAP of $> 30$ mmHg; (3) reported the mean change in six-minute walk distance (6MWD) and its corresponding standard deviation or sufficient data to calculate these measures; and (4) reported at least one of the following outcomes: changes in oxygenation, symptomatic burden, or hemodynamics.

*Data extraction:* The details extracted independently by three reviewers (KWP, JM, and SD) from each study included the following: primary author's last name, year of publication, patient population, number of patients that were treated with PAH-specific therapy and at what dose, number of patients in placebo or standard treatment arm, outcomes assessed, symptomatic changes, hemodynamic changes, and mean change in 6MWD with corresponding standard deviations. Where data were only reported in graphical form, data were digitized with GetData Graph Digitizer V2.26 (Digital River GmbH, Germany). We also contacted the authors to obtain the change in 6MWD when data presented were not amenable to meta-analysis.

*Quality of study analysis:* Assessment of risk of bias in the RCTs was performed using the Cochrane Collaboration risk for bias tool[23] and in the single-arm studies bias analysis was conducted as described by Downs and Black[24] with two independent reviewers scoring the studies (KWP and TT). For the single-arm studies, high, medium, and low risks of bias in reporting, external validity, internal validity-bias, internal validity-confounding, and power were quantified as previously described.[25,26] ARTEMIS-PH risk of bias analysis was performed from the information from www.clinicaltrials.gov (NCT00879229) and from the published results of the ARTEMIS trial,[27] which discussed the trial design and results of ARTEMIS-PH in brief.

*Outcome variables:* Mean change in 6MWD with PAH-specific therapy was the primary outcome. For the RCTs, we calculated the difference in the change in 6MWD in the treated group and the placebo group. In the single-arm studies, we calculated the change in 6MWD after treatment. Secondary outcomes included were changes in: oxygenation, symptomatic burden, and hemodynamics with PAH-specific therapy treatment compared to the placebo or standard treatment.

*Statistical analysis:* Study-specific effects were calculated as the change in 6MWD in the treated group minus the change in 6MWD in the placebo or standard treatment group in the RCTs. In the single-arm studies, the study-specific effect was the change in 6MWD after treatment. Since none of the studies reported the correlation between pre- and post-intervention values, the calculated standard deviations from the RCTs were calculated assuming a correlation of 0.5. The study-specific effects in 6MWD and their standard deviations were combined using a random effects meta-analytic model.[28] $I^2$ statistics were calculated to examine heterogeneity, with a value $> 50\%$ considered severe heterogeneity. Because of the small number of studies, we did not perform any formal test for publication bias. All analyses were performed using Stata Version 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX, USA).

## Results

Our literature search revealed 450 non-duplicate articles in COPD-PH and 834 articles in ILD-PH; 389 articles in COPD-PH and 757 articles were excluded after reviewing the title and abstract (Fig. 1a and 1b). After reviewing the remaining 61 manuscripts in COPD-PH and 77 manuscripts in ILD-PH, final analysis was conducted from five RCTs in the COPD-PH and two RCTs and four single-arm clinical trials in ILD-PH (Fig. 1a and 1b). One of the RCTs was identified from www.clinicaltrials.gov in ILD-PH (NCT00879229). Studies are summarized in Table 1. Of studies that were amenable to meta-analysis, there were 128 placebo or standard treatment patients and 129 treated patients in COPD-PH studies, 23 placebo and 46 treated patients in ILD-PH RCTs, and 50 patients in ILD-PH single-arm studies.

We conducted a risk of bias analysis of all the identified studies to assess overall quality of the studies. In the RCTs

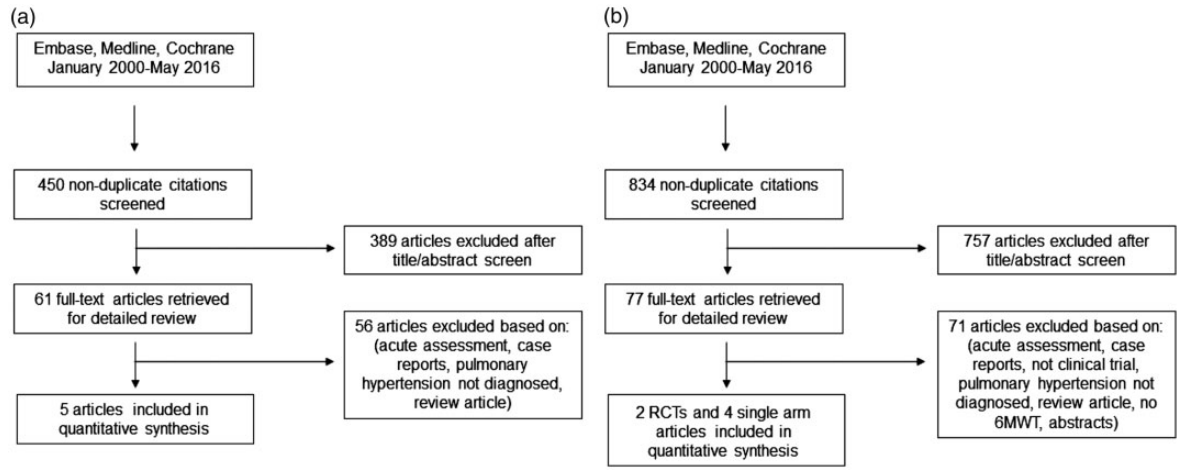


**Fig. 1.** Study flow diagram for COPD-PH (a) and ILD-PH studies (b).

in both COPD-PH and ILD-PH, there was favorable risk of bias. There was increased risk of bias in the Valerio trial due to non-blinding and ARTEMIS-PH had increased risk of bias due to early termination of the trial (Fig. 2a). In the ILD-PH single-arm studies, there was comparable bias analysis (Fig. 2b) and hence these four studies were meta-analyzed separately without including the ILD-PH RCT.

Next, we performed meta-analyses of change in exercise capacity in both COPD-PH and ILD-PH patients. 6MWD was not significantly improved with PAH-specific therapy when compared to placebo or standard treatment in COPD-PH patients (42.7 m; 95% confidence interval [CI], –1.0 – 86.3) (Fig. 3) and there was significant heterogeneity ($I^2 = 92.2\%$) in these five studies. The treatment effects of PAH-specific therapy in ILD-PH were examined in the four single-arm studies and the two RCT separately. 6MWD was improved after treatment with PAH-specific therapy (46.2 m; 95% CI, 27.9–64.4) (Fig. 4a) and there was not significant heterogeneity in the four single-arm studies ($I^2 = 14.7\%$). However, in the two ILD-PH RCTs, there was no significant improvement in 6MWD when comparing PAH-treated to placebo patients (21.6 m; 95% CI, –17.8 – 61.0) (Fig. 4b). There was no heterogeneity in the two ILD-PH RCTs ($I^2 = 0.0\%$).

Although not amenable to meta-analysis, we examined how symptomatic burden changed with PAH-specific therapy. In COPD-PH, three of the studies showed PAH-specific therapy did not reduce symptomatic (Table 2);[12,16,20] however, Vitulo et al. showed an improvement in quality of life with sildenafil treatment.[21] In ILD-PH, five of the studies examined symptomatic burden. Only, Saggar et al. showed a significant improvement in University of San Diego Shortness of Breath questionnaire score with treprostinil treatment, but the rest of the studies showed no improvement in symptomatic burden (Table 2).

Next, we examined the safety profile of PAH-specific therapy with special attention to oxygenation because of the concern that PAH-specific therapy could worsen V/Q mismatch in WHO Group III PH. None of the studies reported any major differences in adverse events. With regards to oxygenation, in COPD-PH, Blanco et al., Valerio et al., and Vitulo et al. showed no difference in oxygenation with treatment (Table 2).[12,20,21] In the ILD-PH, Corte et al. 2014 showed no change in oxygen levels.[15] In the single-arm studies, Hoeper et al., Corte et al., and Saggar et al. reported no alteration of oxygen levels at completion (Table 2).[14,17,19]

Finally, we assessed the hemodynamic changes with PAH-specific therapy. In the COPD-PH studies, Rao et al. showed reduced estimated PAP using echocardiography in the treated group,[18] Valerio et al. found invasively measured mean PAP and pulmonary vascular resistance (PVR) decreased significantly,[20] Vitulo showed reduced PVR but no change in mean PAP,[21] and Goudie et al. showed diminished estimated mean PAP in the treated arm using echocardiography (Table 3).[16] In ILD-PH studies, inconsistent effects on hemodynamics were observed. In the RCTs, Corte et al. showed no improvement in mean PAP and PVR with PAH-specific therapy comparing treated to placebo.[15] Raghu et al. reported the hemodynamic effects of the ARTEMIS-PH trial and found mean PAP or PVR were not significantly reduced with ambrisentan as compared to placebo.[29] In the open-label studies, Hoeper et al. reported no difference in mean PAP but reduced PVR,[17] Corte et al. showed no change in estimated right ventricular systolic pressure, and Saggar et al. showed pulmonary artery pressures and PVR dropped (Table 3).[19]

## Discussion

In this systematic review and meta-analysis, we examined the effects of PAH-specific therapy in WHO Group III PH. PAH-specific therapy was not associated with worsening hypoxemia in this small group of patients and there were signs of favorable hemodynamic changes especially in the COPD-PH group. However, there were not consistent

**Table 1.** Summary of studies identified for systematic review and meta-analysis.

| Author | PH definition | Treatment | Dose | Duration | Placebo (n) | Treated (n) | Mean age (years) | Sex M:F |
|---|---|---|---|---|---|---|---|---|
| COPD-PH | | | | | | | | |
| Blanco | Echo estimated PA systolic >34 mmHg or RHC mPAP ≥ 25 mmHg | Sildenafil | 20 mg TID | 3 months | 27 | 24 | P: 65 ± 8<br>T: 66 ± 8 | P: 26:5<br>T: 28:1 |
| Rao | Echo estimated PA systolic pressure >40 mmHg | Sildenafil | 20 mg TID | 12 weeks | 18 | 15 | P: 63.6 ± 6.7<br>T: 60.7 ± 8.5 | NR |
| Valerio | RHC mPAP ≥ 25 mmHg | Bosentan | 125 mg BID | 18 months | 16 | 16 | P: 65 ± 10<br>T: 66 ± 9 | P: 12:4<br>T: 13:3 |
| Goudie | Echo estimated PA systolic pressure >30 mmHg or PA-AT < 120 ms | Tadalafil | 10 mg daily | 12 weeks | 57 | 56 | P: 70 ± 7<br>T: 68 ± 8 | P: 40: 20<br>T: 42:18 |
| Vitulo | RHC mPAP ≥ 35 mmHg if $FEV_1$ ≥30% after bronchodilator or mPAP ≥ 30 mmHg if $FEV_1$ >30% after bronchodilator | Sildenafil | 20 mg TID | 16 weeks | 10 | 18 | P: 64.1 ± 11<br>T: 66.4 ± 6.5 | P: 8:2<br>T: 13:5 |
| ILD-PH | | | | | | | | |
| Corte, 2014 | RHC mPAP ≥ 25 mmHg | Bosentan | 125 mg BID | 16 weeks | 14 | 25 | P: 66.4 ± 9.2<br>T: 66.9 ± 9.3 | P: 15:5<br>T: 27:13 |
| Artemis-PH | RHC mPAP ≥ 25 mmHg | Ambrisentan | 10 mg daily | 16 weeks | 9 | 21 | P: 68 ± 5.2<br>T: 68 ± 7.7 | P: 10:5<br>T: 20:5 |
| Collard | RHC mPAP ≥ 25 mmHg or echo estimated PA pressure >35 mmHg | Sildenafil | 20–50 mg TID | 12 weeks | NA | 11 | 72 ± 7 | 8:6 |
| Hoeper | RHC mPAP ≥ 25 mmHg | Riociguat | 1.0–2.5 mg TID | 12 weeks | NA | 18 | 60.5 (33–80) | 14:8 |
| Corte, 2010 | RHC or echo | Sildenafil | 20 mg TID | 6 months | NA | 6 | 55 ± 15 | 8:7 |
| Saggar | RHC mPAP ≥ 35 mmHg | Treprostinil | 34 ± 21 ng/kg/min | 12 weeks | NA | 15 | 63 ± 15 | 12:3 |

Saggar treprostinil dose listed as mean ± standard deviation.

Age and sex distribution is from patients that started trial not from those that completed.

BID, two times daily; mPAP, mean pulmonary arterial pressure; PA, pulmonary artery; PA-AT, pulmonary artery acceleration time; RHC, right heart catheterization; TID, three times daily.

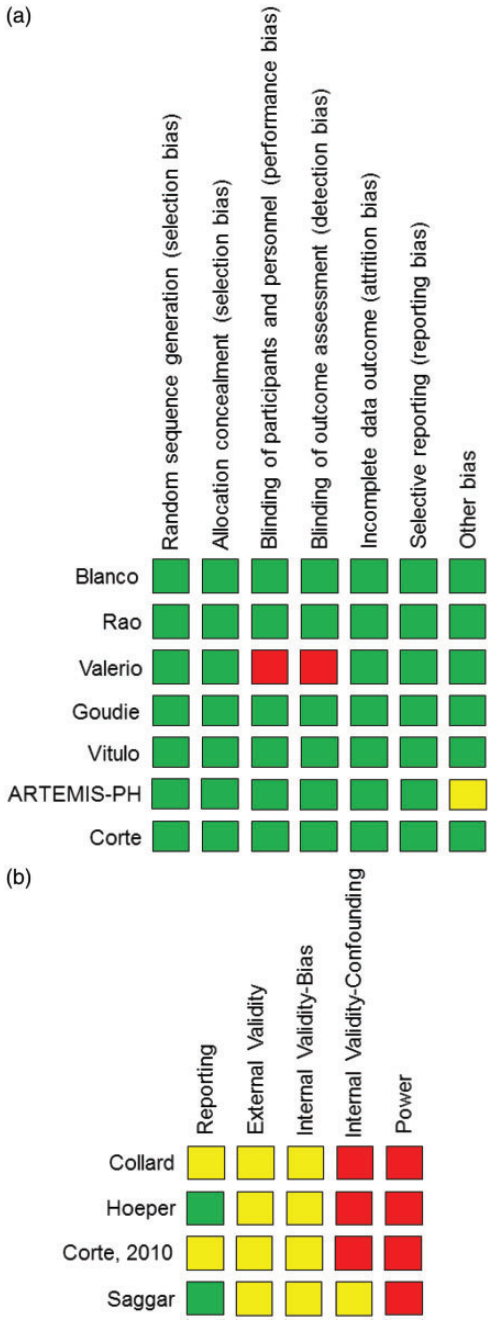


**Fig. 2.** Risk of bias assessment in randomized trials (a) and single-arm studies (b). Green indicates low risk of bias, yellow indicates medium risk of bias, and red indicates high risk of bias.

improvements when symptomatic burden and exercise capacity were examined, which is similar to the results observed in two recent retrospective studies.[30,31] In conclusion, our results do not validate the routine use of PAH-specific therapy in WHO Group III PH patients.

When comparing the different studies identified in our search, we found significant heterogeneity in the COPD-PH which may have been due to the following reasons. First, there were different PAH-specific therapies used which may have different therapeutic benefits in WHO Group III PH. While no PAH-specific oral medication has been shown to be superior to another in WHO Group 1 PAH, a definitive trial has not been conducted to answer that question so it is possible that the different medications have different efficacies. While, the AMBITION trial did not find significant differences between the ambrisentan and tadalfil treated groups,[32] the SERAPH study showed sildenafil had greater effects on cardiac performance as compared to bosentan.[33] Moreover, there is preclinical evidence that blockage of endothelin receptors can alter carotid body hypoxia sensing,[34] which could be deleterious in patients with lung disease. Second, there were different definitions of PH used in these studies with PH determined either via invasive hemodynamics or echocardiography. While echocardiography is an acceptable screening tool for PH, a definitive diagnosis requires invasive hemodynamic assessment. This is important because echocardiography can lead to inaccurate estimates of pulmonary artery pressure as the study by Fisher et al. showed that approximately half of echo-estimated pulmonary artery pressures were discrepant by $\pm 10$ mmHg.[35] Moreover, estimates of pulmonary artery pressures in patients with coexisting lung disease are frequently overestimated.[36] Hence, there could have been variability in the severity of PH studied in the different trials or some patients may not have had PH at all. Third, the severity of underlying lung disease may have affected outcomes. Overall, the baseline pulmonary function profiles of the studies were comparable (Supplemental Table 1), but there was some variability which may have contributed to differences in outcomes. Lastly, there were a small number of patients examined in all of the studies. Small sample sizes are more susceptible to the effects of chance, which may have partially explained why there were heterogeneous results. In summary, there were multiple reasons for heterogeneity in the identified studies, which may have explained the variations in the outcomes measured.

Although not statistically significant, there was a trend for improved exercise capacity with PAH-specific therapy in the COPD-PH population. When comparing the individual studies, Rao et al., Valerio et al., and Vitulo et al. showed the most improvements in 6MWD with PAH-specific therapy, but only the Rao et al. changes were statistically significant. On the other hand, Blanco et al. and Goudie et al. showed no difference in 6MWD with PAH-specific therapy. One possible explanation for the divergent effects is PH severity. When comparing hemodynamics of these studies, there was a trend for increased severity of PH being associated with improved exercise capacity. The treated patients from Valerio et al. (mPAP $37 \pm 5$ mmHg and PVR of $442 \pm 2$ dynes s/cm$^5$) and Vitulo et al. (mPAP of $39.3 \pm 7.6$ and PVR of $7.0 \pm 2.6$ Wood Units) had severe WHO Group III PH, and both of these studies showed trends for improved exercise performance. However, the patients from Rao et al. study, which had the greatest benefit from

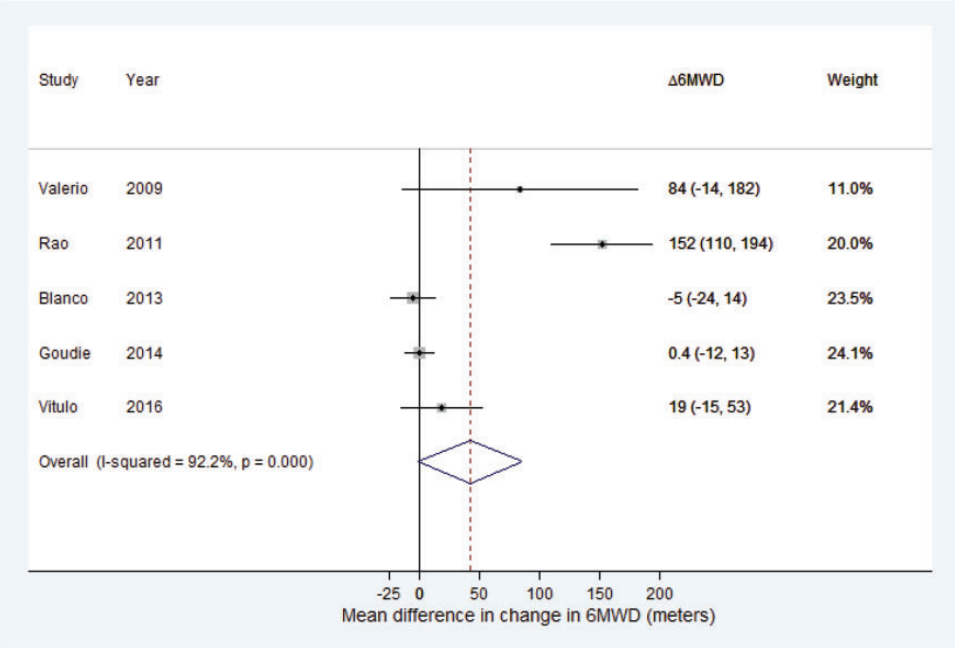


**Fig. 3.** Forest plot for difference in 6MWD in COPD-PH. PAH-specific therapy did not significantly increase walking distance when compared to placebo or standard treatment (42.7 m; 95% CI, −1.0 – 86.3). Δ6MWD: Difference in change in 6MWD as compared to placebo or standard treatment. Data are presented as mean difference and 95% CI.

PAH-specific therapy, had echo estimated systolic PAP of $53 \pm 12$ mmHg which equates to an estimated mean PAP of approximately $32 \pm 2$ mmHg, and that was only slightly higher than that of the Goudie et al. (echo estimated mean PAP $30.1 \pm 5.2$ mmHg) and Blanco et al. (mean PAP 31 [range, 29–33] mmHg) studies. As discussed above, the inaccuracies of echocardiography based estimates of pulmonary pressures makes this comparison imperfect and thus more information is needed to determine how PH severity affects response to PAH-specific therapy in COPD-PH. Beyond PH severity, other factors must be taken under consideration when evaluating the trend for improved exercise in the COPD-PH studies. First, Rao et al. showed extraordinary increases in 6MWD, beyond what is often reported in WHO Group 1 PAH studies. This may have skewed the overall result, which is possible when there was such a small numbers of patients examined. Moreover, the Valerio et al. study was unblinded which may have also contributed to the documented improvements. Taken together, these results suggest severity of PH may be a factor that dictates response to PAH-specific therapy in COPD-PH, but a large double-blind study is needed to validate this hypothesis-generating result.

In the ILD-PH studies, small sample sizes and different trial designs may have contributed to the inconsistent results observed. The improvement in exercise capacity in the single-arm studies could have been due to bias as frequently occurs when blinding is absent. Consistent with this hypothesis, the RCTs showed no improvement in 6MWD (Fig. 4b). Furthermore, there were less consistent hemodynamic benefits with PAH-specific therapy in ILD-PH. As discussed above with COPD-PH, both the severity of lung disease and PH and the different medications employed may have resulted in the divergent effects. However, severity of PH in the Hoeper et al., Corte et al., and Saggar et al. trials was similar and all used invasive hemodynamics to assess pulmonary vascular disease, suggesting PAH-therapy type or ILD subtype may be more important in ILD-PH. Finally, right ventricular function may also play a role in response to therapy in ILD-PH. Saggar et al. showed improvements in 6MWD, symptomatic burden, and right ventricular function (right atrial pressure dropped, cardiac output increased, and BNP decreased) with treprostinil in severe ILD-PH patients (mPAP $47.0 \pm 8.0$).[19] Although pulmonary pressures were not assessed in all patients, Han et al., showed sildenafil improved exercise capacity and quality of life in patients with ILD and right ventricular dysfunction.[37] Clearly there is much to learn about ILD-PH moving forward.

Although our meta-analysis did not reveal significant improvements in patients with WHO Group III PH treated with PAH-specific therapy, there were trends for benefits in COPD-PH and safety did not appear to be an issue suggesting the utility of this approach should be explored further. With regards to safety, we found PAH-specific therapy did not worsen hypoxemia in the small number of patients examined. This is in contrast to two previous clinical trials that showed impaired oxygenation with sildenafil[38] and bosentan[39] in COPD patients, but these patients did not have specified PH. In ILD-PH, there are more safety

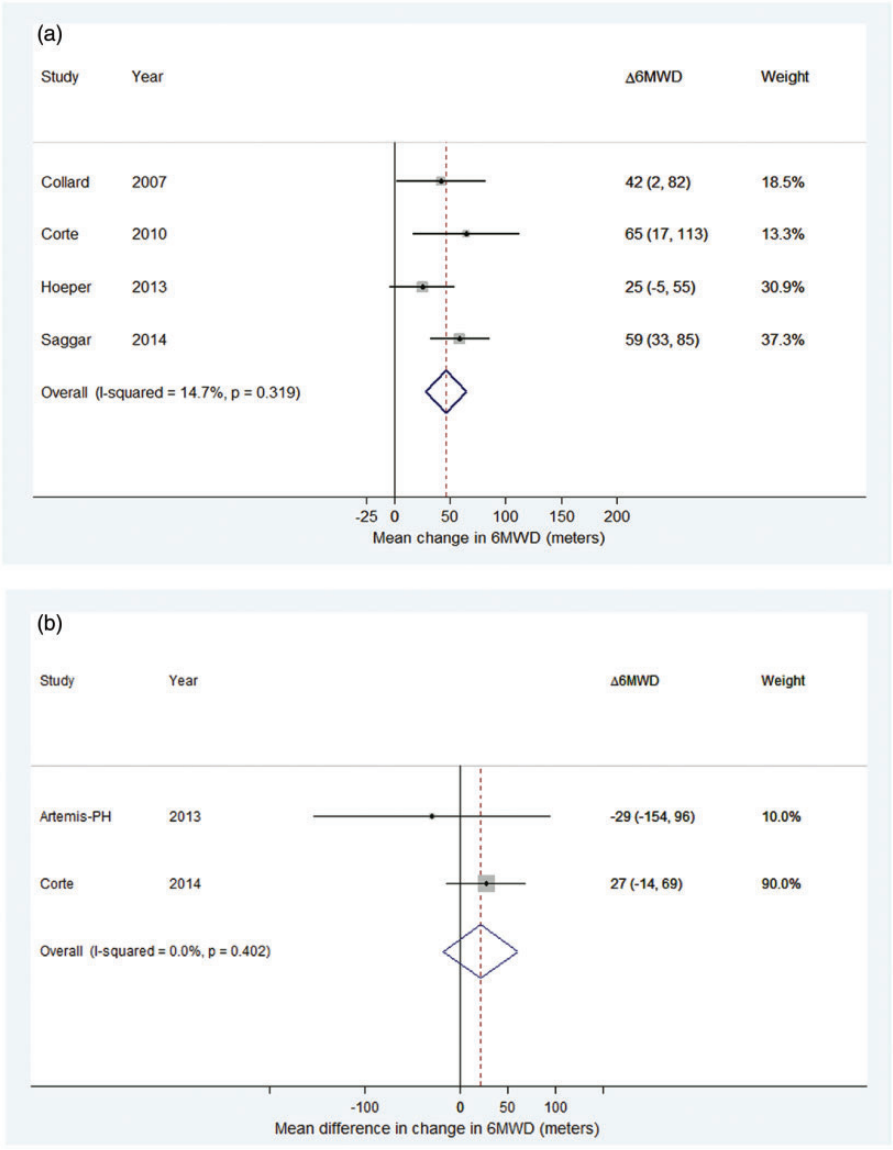


**Fig. 4.** Meta-analysis of the effects of PAH-specific therapy on 6MWD in ILD-PH. (a) Change in 6MWD post treatment from four single-arm studies. PAH-specific therapy improved exercise capacity (46.2 m; 95% CI, 27.9–64.4). (b) Difference in 6MWD comparing placebo to PAH-specific therapy from two randomized controlled studies. There was not a significant difference in 6MWD (21.6 m; 95% CI, −17.8 – 61.0). Δ6MWD: Change in 6MWD post treatment in (a) and difference in change in 6MWD as compared to placebo in (b). Data are presented as mean difference and 95% CI.

concerns for PAH-specific therapy as ambrisentan treatment led to worsening outcomes in ILD patients in the ARTEMIS trial, but patients with PH were not examined as rigorously because the trial was halted early.[27] However, the recent premature termination of the RISE- IIP trial (NCT02138825) due to increased mortality in patients treated with riociguat further raises safety concerns for use of PAH-specific therapy in ILD-PH, and thus perhaps, COPD-PH would be a better patient population for future examination.

Thus, a future clinical trial examining the short-term (12–16 weeks) effects of PAH-specific therapy should be conducted in a properly selected group of patients with severe WHO group III PH and right ventricular dysfunction. We would propose to select COPD-PH patients with invasively measured mPAP of $\geq 35$ mmHg and right ventricular dysfunction as determined by echocardiography or cardiac MRI. Endpoints could be an integrative approach to patient symptomatic burden such as that implemented in the SPHERIC trial,[21] and secondary endpoints could include: change in pulmonary hemodynamics as determined by invasive hemodynamics, NT pro-BNP levels, change in exercise capacity, oxygenation assessments, and change in right ventricular function. Given the costs of PAH-specific

**Table 2** Assessment of symptomatic burden and oxygenation changes.

| Author | Symptomatic assessment | Treated-placebo difference | Post treatment | *P* value | Oxygenation assessment | Treated-placebo difference | Post treatment | *P* value |
|---|---|---|---|---|---|---|---|---|
| COPD-PH | | | | | | | | |
| Blanco | St. George's Respiratory Questionnaire | 1.3 (–3.5 –6.9) | – | 0.526 | Arterial oxygen tension (mmHg) | 2.5 (–2.6 – 6.5) | – | 0.287 |
| Rao | NR | NR | NR | NR | NR | NR | NR | NR |
| Valerio | St. George's Respiratory Questionnaire | NR | C: 43 ± 13<br>T: 46 ± 13 | NS | Arterial oxygen tension (mmHg) | NR | C: 55 ± 12<br>T: 61 ± 8 | NS |
| Goudie | St. George's Respiratory Questionnaire | –2.64 (–6.53 – 1.15) | NR | 0.17 | NR | NR | NR | NR |
| Vitulo | QoL | 9.85 (9.07–10.63) | – | 0.04 | Arterial oxygen tension (mmHg) | –1.02 (–11.57 – 11.6) | – | NS |
| ILD-PH | | | | | | | | |
| Corte, 2014 | CAMPHOR | P: 1.57 ± 8.46<br>T: 1.41 ± 9.28 | NR | 0.69 | $SpO_2$% | P: –0.57 ± 3.9<br>T: –0.76 ± 4.0 | NR | 0.74 |
| Artemis-PH | Transition Dyspnea Index | P: –1.4 ± 3.8<br>T: –1.5 ± 3.1 | NR | NS | NR | NR | NR | NR |
| Collard | Borg Dyspnea Index | NA | Pre: 10.9 ± 3.2<br>Post: 10 ± 2.8 | NS | NR | NA | NR | NR |
| Hoeper | Borg Dyspnea Index | NA | NR | NS | $PaO_2$ (mmHg) | NA | –7 ± 12 | NS |
| Corte, 2010 | NR | NA | NR | NR | $PaO_2$ (kPa) | NA | Pre: 7.3 ± 1.8<br>Post: 7.8 ± 2.4 | NS |
| Saggar | UCSD SOB | NA | Pre: 87 ± 17.1<br>Post: 73.1 ± 21 | 0.002 | $SpO_2$% | NA | Pre: 83 ± 7<br>Post: 80 ± 10 | 0.078 |

Data are presented as mean ± standard deviation or median (95% CI) for Blanco or mean (95% CI) for Goudie.
NA, not applicable; NR, not reported; NS, not statistically significant; QoL, quality of life questionnaire; UCSD SOB, University of San Diego Shortness of Breath questionnaire.

**Table 3.** Hemodynamic effects of PAH-specific therapy.

| Author | PA Pressure Baseline (mm Hg) | Post Treatment Pressure (mm Hg) | *p*-value | PVR Baseline (dynes s/cm$^5$ or Wood Units) | Post Treatment PVR (dynes s/cm$^5$ or Wood Units) | *p*-value |
|---|---|---|---|---|---|---|
| COPD-PH | | | | | | |
| Blanco | P: 26 (26,27), $n=5$<br>T: 31 (29,33), $n=9$ | NR | NR | NR | NR | NR |
| Rao | P: 48 ± 13 (PASP)<br>T: 53 ± 12 (PASP) | P: 44 ± 12 T: 41 ± 8 | 0.025 (pre/post treatment) | NR | NR | NR |
| Valerio | P: 36 ± 5 9 (mPAP)<br>T: 37 ± 5 (mPAP) | P: 38 ± 7 (mPAP)<br>T: 31 ± 6 (mPAP) | 0.002 (pre/post treatment) | P: 420 ± 170<br>T: 442 ± 192 | P: 435 ± 189<br>T: 250 ± 170 | 0.012 (pre/post treatment) |
| Goudie | P: 30.8 ± 6.8 (mPAP)<br>T: 30.1 ± 5.2 (mPAP) | P: 30.8 ± 7.5 (mPAP)<br>T: 26.6 ± 5.2 (mPAP) | 0.025 (mean difference between groups) | NR | NR | NR |
| Vitulo | P: 39.1 ± 2.9 (mPAP)<br>T: 39.3 ± 2.1 (mPAP) | P: 36.7 ± 2.9 (mPAP)<br>T: 35.5 ± 2.3 (mPAP) | NS (difference in change) | P: 6.3 ± 0.8<br>T: 7.01 ± 0.6 | P: 6.4 ± .08<br>T: 5.72 ± 0.6 | 0.04 (difference in change of PVR) |
| ILD-PH | | | | | | |
| Corte, 2014 | P: 33.5 ± 6.1 (mPAP)<br>T: 37.2 ± 9.9 (mPAP) | P: 0.2 ± 7.4 T: −1.3 ± 5.6 | 0.43 | P: 11.4 ± 4.5<br>T: 13.9 ± 7.5 (Wood units/m$^2$) | P: 0.8 ± 4.2<br>T: −1.1 ± 3.9 (Wood units/m$^{2)}$ | 0.19 |
| Artemis-PH | NR | P: −1.1 ± 9.39 (mPAP)<br>T: −5.3 ± 4.27 (mPAP) | NS | NR | P: −0.51 ± 1.56<br>T: −0.70 ± 1.31 (mmHg/L*min) | NS |
| Collard | NR | NR | NR | NR | NR | NR |
| Hoeper | 40 ± 10 (mPAP) | 41 ± 7 (mPAP) | NS | 648 ± 207 (dyn*s$^{-1}$*cm$^{-5}$) | 528 ± 181 (dyn*s$^{-1}$*cm$^{-5}$) | <0.05 |
| Corte, 2010 | 73.8 ± 17.8 (RVSP) | 72.6 ± 28.0 (RVSP) | NS | NR | NR | NR |
| Saggar | 47.0 ± 8.0 | 38.9 ± 13.4 | 0.005 | 698 ± 278 (dyn*s$^{-1}$*cm$^{-5}$) | 496 ± 229 (dyn*s$^{-1}$*cm$^{-5}$) | <0.001 |

Data are presented as mean ± standard deviation or median (25th, 75th percentiles).
$^{m}$PAP, mean pulmonary arterial pressure; NR, not reported; NS, not statistically significant; P, placebo or usual treatment (Valerio); PA, pulmonary arterial; PASP, pulmonary arterial systolic pressure; PVR, pulmonary vascular resistance; RVSP, right ventricular systolic pressure.

therapy and potential side effects, it is difficult to justify the widespread use of these agents in WHO Group III PH patients until such a trial is conducted.

## Limitations

Our search strategy included only English language papers and thus we could have missed an article that was not in English. Moreover, due to the small number of patients examined, our study does not allow for a definitive statement on the safety or efficacy of PAH-specific therapy in WHO Group III PH.

## Conclusions

The utility of PAH-specific therapy in WHO Group III PH is unclear because of the small numbers of patients evaluated and inconsistent beneficial effects observed. There is an unmet need for a future clinical trial that is appropriately powered to definitively determine the efficacy of this widely implemented treatment approach.

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### Conflict of interest

The author(s) declare that there is no conflict of interest.

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### References

1. Andersen CU, Mellemkjaer S, Hilberg O, et al. Pulmonary hypertension in interstitial lung disease: Prevalence, prognosis and 6 min walk test. *Respir Med* 2012; 106: 875–882.
2. Andersen KH, Iversen M, Kjaergaard J, et al. Prevalence, predictors, and survival in pulmonary hypertension related to end-stage chronic obstructive pulmonary disease. *J Heart Lung Transplant* 2012; 31: 373–380.
3. Behr J and Ryu JH. Pulmonary hypertension in interstitial lung disease. *Eur Respir J* 2008; 31: 1357–1367.
4. Burrows B, Kettel LJ, Niden AH, et al. Patterns of cardiovascular dysfunction in chronic obstructive lung disease. *N Engl J Med* 1972; 286: 912–918.
5. Hamada K, Nagai S, Tanaka S, et al. Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. *Chest* 2007; 131: 650–656.
6. Kimura M, Taniguchi H, Kondoh Y, et al. Pulmonary hypertension as a prognostic indicator at the initial evaluation in idiopathic pulmonary fibrosis. *Respiration* 2013; 85: 456–463.
7. Minai OA, Santacruz JF, Alster JM, et al. Impact of pulmonary hemodynamics on 6-min walk test in idiopathic pulmonary fibrosis. *Respir Med* 2012; 106: 1613–1621.
8. Nathan SD, Shlobin OA, Ahmad S, et al. Serial development of pulmonary hypertension in patients with idiopathic pulmonary fibrosis. *Respiration* 2008; 76: 288–294.
9. Seeger W, Adir Y, Barbera JA, et al. Pulmonary hypertension in chronic lung diseases. *J Am Coll Cardiol* 2013; 62: D109–116.
10. Barbera JA and Blanco I. Gaining insights into pulmonary hypertension in respiratory diseases. *Eur Respir J* 2015; 46: 1247–1250.
11. Trammell AW, Pugh ME, Newman JH, et al. Use of pulmonary arterial hypertension-approved therapy in the treatment of non-group 1 pulmonary hypertension at US referral centers. *Pulm Circ* 2015; 5: 356–363.
12. Blanco I, Santos S, Gea J, et al. Sildenafil to improve respiratory rehabilitation outcomes in COPD: A controlled trial. *Eur Respir J* 2013; 42: 982–992.
13. Collard HR, Anstrom KJ, Schwarz MI, et al. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. *Chest* 2007; 131: 897–899.
14. Corte TJ, Gatzoulis MA, Parfitt L, et al. The use of sildenafil to treat pulmonary hypertension associated with interstitial lung disease. *Respirology* 2010; 15: 1226–1232.
15. Corte TJ, Keir GJ, Dimopoulos K, et al. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2014; 190: 208–217.
16. Goudie AR, Lipworth BJ, Hopkinson PJ, et al. Tadalafil in patients with chronic obstructive pulmonary disease: A randomised, double-blind, parallel-group, placebo-controlled trial. *Lancet Respir Med* 2014; 2: 293–300.
17. Hoeper MM, Halank M, Wilkens H, et al. Riociguat for interstitial lung disease and pulmonary hypertension: A pilot trial. *Eur Respir J* 2013; 41: 853–860.
18. Rao RS, Singh S, Sharma BB, et al. Sildenafil improves six-minute walk distance in chronic obstructive pulmonary disease: A randomised, double-blind, placebo-controlled trial. *Indian J Chest Dis Allied Sci* 2011; 53: 81–85.
19. Saggar R, Khanna D, Vaidya A, et al. Changes in right heart haemodynamics and echocardiographic function in an advanced phenotype of pulmonary hypertension and right heart dysfunction associated with pulmonary fibrosis. *Thorax* 2014; 69: 123–129.
20. Valerio G, Bracciale P and Grazia D'Agostino A. Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease. *Ther Adv Respir Dis* 2009; 3: 15–21.
21. Vitulo P, Stanziola A, Confalonieri M, et al. Sildenafil in severe pulmonary hypertension associated with chronic obstructive pulmonary disease: A randomized controlled multicenter clinical trial. *J Heart Lung Transplant* 2016. DOI: 10.1016/j.healun.2016.04.010.
22. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* 2009; 6: e1000097.
23. Higgins JP, Altma DG, Gotzsche PC, et al. Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.

24. Downs SH and Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998; 52: 377–384.
25. Galvagno SM Jr, Thomas S, Stephens C, et al. Helicopter emergency medical services for adults with major trauma. *Cochrane Database Syst Rev* 2013; 3: CD009228.
26. Prins KW, Neill JM, Tyler JO, et al. Effects of beta-blocker withdrawal in acute decompensated heart failure: A systematic review and meta-analysis. *JACC Heart Fail* 2015; 3: 647–653.
27. Raghu G, Behr J, Brown KK, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan: A parallel, randomized trial. *Ann Intern Med* 2013; 158: 641–649.
28. DerSimonian R and Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177–188.
29. Raghu G, Nathan SD, Behr J, et al. Pulmonary hypertension in idiopathic pulmonary fibrosis with mild-to-moderate restriction. *Eur Respir J* 2015; 46: 1370–1377.
30. Hoeper MM, Behr J, Held M, et al. Pulmonary hypertension in patients with chronic fibrosing idiopathic interstitial pneumonias. *PLoS One* 2015; 10: e0141911.
31. Brewis MJ, Church AC, Johnson MK, et al. Severe pulmonary hypertension in lung disease: Phenotypes and response to treatment. *Eur Respir J* 2015; 46: 1378–1389.
32. Galie N, Barbera JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015; 373: 834–844.
33. Wilkins MR, Paul GA, Strange JW, et al. Sildenafil versus endothelin receptor antagonist for pulmonary hypertension (SERAPH) study. *Am J Respir Crit Care Med* 2005; 171: 1292–1297.
34. Chen J, He L, Dinger B, et al. Role of endothelin and endothelin A-type receptor in adaptation of the carotid body to chronic hypoxia. *Am J Physiol Lung Cell Mol Physiol* 2002; 282: L1314–1323.
35. Fisher MR, Forfia PR, Chamera E, et al. Accuracy of doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med* 2009; 179: 615–621.
36. Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med* 2003; 167: 735–740.
37. Han MK, Bach DS, Hagan PG, et al. Sildenafil preserves exercise capacity in patients with idiopathic pulmonary fibrosis and right-sided ventricular dysfunction. *Chest* 2013; 143: 1699–1708.
38. Lederer DJ, Bartels MN, Schluger NW, et al. Sildenafil for chronic obstructive pulmonary disease: A randomized crossover trial. *COPD* 2012; 9: 268–275.
39. Stolz D, Rasch H, Linka A, et al. A randomised, controlled trial of bosentan in severe COPD. *Eur Respir J* 2008; 32: 619–628.