ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original research article

Treatment of pulmonary hypertension associated with chronic obstructive pulmonary disease: a systematic review

Ragdah Arif, Arjun Pandey, Ying Zhao, Kyle Arsenault-Mehta, Danya Khoujah, Sanjay Mehta

Please cite this article as: Arif R, Pandey A, Zhao Y, *et al*. Treatment of pulmonary hypertension associated with chronic obstructive pulmonary disease: a systematic review. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00348-2021).

Title: Treatment of Pulmonary Hypertension Associated with Chronic Obstructive Pulmonary Disease: A Systematic Review

Authors: Ragdah Arif[1,2] MD FRCPC, Arjun Pandey[3] BSc, Ying Zhao[2] MD, Kyle Arsenault-Mehta[4] MD, Danya Khoujah[5] MBBS MEHP, Sanjay Mehta[2,6] MDCM FRCPC

From: [1]Respirology Division, Department of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia, [2]Southwest Ontario Pulmonary Hypertension Clinic, Division of Respirology, Department of Medicine, London Health Sciences Center, Schulich Faculty of Medicine & Dentistry, University of Western Ontario, London, [3]Faculty of Medicine, McMaster University, Hamilton, Ontario, [4]Faculty of Medicine, University of Ottawa, Ottawa, Ontario, [5]Department of Emergency Medicine, University of Maryland School of Medicine Baltimore. and [6]Pulmonary Hypertension Association (PHA) of Canada.

Correspondence: Dr. Sanjay Mehta, Division of Respirology, London Health Sciences Centre - Victoria Hospital, Room E6.201, 800 Commissioner's Road East, London, Ontario, Canada N6A 5W9. Tel: (519)-667-6723, Fax: (519)-685-8406
Email: sanjay.mehta@lhsc.on.ca

Keywords: COPD, emphysema, pulmonary hypertension, oxygen, calcium-channel blockers, sildenafil, bosentan, ambrisentan, survival, 6 minute walk test

ABSTRACT

Chronic obstructive pulmonary disease-associated pulmonary hypertension (COPD-PH) is an increasingly recognized condition which contributes to worsening dyspnea and poor survival in COPD. It is uncertain whether specific treatment of COPD-PH, including use of medications approved for pulmonary arterial hypertension (PAH), improves clinical outcomes. This systematic review and meta-analysis assesses potential benefits and risks of therapeutic options COPD-PH.

We searched Medline and Embase for relevant publications until Sep 2020. Articles were screened for studies on treatment of COPD-PH for at least 4 weeks in 10 or more patients. Screening, data extraction, and risk of bias assessment were performed independently in duplicate. When possible, relevant results were pooled using the random effects model.

Supplemental long-term O_2 therapy (LTOT) mildly reduced mean pulmonary artery pressure (PAP), slowed progression of PH, and reduced mortality, but other clinical or functional benefits were not assessed. Phosphodiesterase type-5 inhibitors significantly improved systolic PAP (pooled treatment effect -5.9 mmHg; 95%CI -10.3, -1.6), but had inconsistent clinical benefits. Calcium-channel blockers and endothelin receptor antagonists had limited hemodynamic, clinical, or survival benefits. Statins had limited clinical benefits despite significantly lowering systolic PAP (pooled treatment effect -4.6 mmHg; 95% CI: -6.3, -2.9).

This review supports guideline recommendations for LTOT in hypoxemic COPD-PH patients as well as recommendations against treatment with PAH-targeted medications, Effective treatment of COPD-PH depends upon research into the pathobiology, and future high-quality studies comprehensively assessing clinically relevant outcomes are needed.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive and incurable disease that represents one of the five leading causes of death worldwide[1; 2]. COPD is characterized by exertional dyspnea, functional limitation, poor health-related quality of life (HRQoL), recurrent exacerbations and hospitalization, as well as shortened survival[1; 2]. The presence of pulmonary hypertension (PH) in patients with COPD is increasingly recognized as an important contributing factor to its clinical manifestations and adverse clinical outcomes including increased mortality[3; 4]. For example, severe PH and resulting right ventricular (RV) failure are associated with more severe dyspnea and limited exercise capacity[5; 6]. Indeed, the presence of PH has a stronger association with mortality in COPD than forced expiratory volume in 1s (FEV1) or gas exchange variables[7; 8].Moreover, enlarged pulmonary artery diameter on computed tomography scan is independently associated with a higher risk of acute COPD exacerbations and related hospitalizations[8; 9].

Estimates of the prevalence of PH in COPD (COPD-PH) vary widely (20-91%)[5; 10; 11] , with increasing prevalence with greater severity of COPD[4]**.** For example, the most severe Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV COPD is associated with mild-moderate PH in up to 90% of patients[5]**.** PH in a patient with COPD could be due to a broad range of underlying conditions, such as left-heart disease[12], concomitant interstitial lung diseases or sleep disordered-breathing, or chronic thromboembolic PH. Management of associated cardiac and respiratory conditions can improve the clinical status and outcomes in COPD-PH patients[4; 13]**.**

Specific medical treatment of COPD-PH may also offer clinical benefits, including improved dyspnea, functional capacity, and long-term outcomes. Thus, we conducted a systematic review and meta-analysis for benefits and risks of treatment options for COPD-PH.

METHODS

Search Strategy and Eligibility Criteria

According to the referred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we searched MEDLINE and Embase databases from 1947 to September 30, 2020, using the search terms pulmonary hypertension" AND "chronic obstructive airway disease or chronic obstructive pulmonary disease or COPD" AND "treatment or management"

We also reviewed bibliographies, identifying additional relevant studies. Titles and abstracts were screened, and full-text articles were reviewed independently and in duplicate (RA, SM) in order to identify studies meeting the predefined inclusion and exclusion criteria (Supp Table 1): studies of 10 or more patients reporting the effects of at least four weeks of treatment on pulmonary hemodynamics, survival, and other clinical outcomes in patients with COPD-PH. Risk of bias was assessed using the Newcastle Ottawa Scale for observational studies and the Cochrane Collaboration tool for Randomized Controlled Trials (RCTs). Disagreements were resolved by consensus.

Data Collection

Data collection was performed independently by at least 2 authors (RA, AP, YZ). The data extracted included: study characteristics, patients demographics and comorbidities, method of PH diagnosis, intervention type, dosage and frequency, duration of and loss to follow-up, as

well as outcomes, including clinical outcomes (eg. survival), cardio-pulmonary hemodynamics (eg. mean pulmonary artery pressure [mPAP]), pulmonary vascular resistance (PVR), cardiac output [CO], and others) as listed in Supp Table 1.

Data Analysis

Subgroups based on the method of PH diagnosis were defined a priori and a sensitivity analysis performed; patients diagnosed using right-heart catheterization (RHC)-determined mPAP vs those diagnosed using non-invasive echocardiography by estimating systolic PAP (sPAP) or calculating mPAP. During data analysis, another subset of COPD-PH patients was identified; those with more severe PH and RV failure, often in the setting of only mild -moderate COPD without resting hypoxemia. This subgroup was analyzed separately.

RESULTS

We retrieved and screened 4577 reports, and an additional 26 records were identified through other sources (Figure 1). 4557 studies were excluded, leaving 46 studies reporting treatment of COPD-associated PH, including 23 RCTS (1159 patients) and 23 non-RCTs (1187 patients). Patients ranged from 35-85 yrs in age and were predominantly male in the majority of studies (range 32-100%). Lung function varied widely (FEV1 13-94% predicted), but most patient s had moderate-severe COPD, many with hypoxemia at rest.

We identified five categories of COPD-PH therapies, including supplemental O2 (Table1), calcium-channel blockers (Supp Table 2), PAH-targeted therapy (Table 2), statins (Supp Table 3), and miscellaneous therapies (Supp Table 4).

Long-term Oxygen Therapy (LTOT)

In COPD-PH patients, LTOT may have hemodynamic and clinical benefits. The evidence base consists of 8 reports (n=596; 72-100% men), including one RCT[14], two randomized parallel group studies comparing LTOT vs nocturnal O_2(NOT), and four case series [15; 16; 17; 18](Table 1). All patients underwent RHC which documented the presence and severity of baseline PH. Most studies report outcome data over longer than one year (range 2-6 yrs), but two studies were < 8 weeks duration[15; 19]. Most LTOT studies had an unclear or high risk of bias in at least one domain; only one study had a low risk of bias (Supp Tables 5 and 6)[20], which limits our confidence in the effects of LTOT in COPD-PH.

The hemodynamic benefit of LTOT varied, with small reductions (3-5 mmHg) in mPAP in 4 of 8 studies[15; 16; 19; 21], and/or PVR in three[19; 20; 21], but no reported change in CO (3 studies). Even in the absence of actual improvement in the severity of PH, LTOT may be associated with less progression of PH over time[14; 16]. For example, a progressive increase in mPAP in control patients was completely attenuated in LTOT patients in the Medical Research Council (MRC) trial[14].

No studies assessed clinical or functional patient outcomes other than mortality benefits of LTOT. Survival was assessed in four studies (n=480), of which three (n=408) reported improved survival[14; 20; 21], but one study found no effect[17]. Pulmonary hemodynamic improvement may be associated with greater survival[20; 21], but this was not consistently observed[22].

In summary, in COPD-PH patients with hypoxemia, LTOT may mildly reduce severity of PH, slow PH progression over time, and reduce mortality, but without any other clinical or functional benefit (Table 3). There are limited, conflicting data on NOT, with hemodynamic benefit in only one of two RCTs[22; 23], and no clinical benefits in either.

Calcium channel blockers (CCBs)

our studies defining PH using mPAP threshold of 20 mmHg, including 2 RCTs (n=80)[24; 25] and 2 case series[26; 27] , evaluated effects of CCBs over at least eight weeks (Supp Table 2)**.** All studies had an unclear or high risk of bias in at least one domain. Two small studies found no RHC-assessed hemodynamic benefit of nifedipine[25; 26], but felodipine decreased echo-calculated mPAP and total pulmonary resistance (TPR) as well as increased CO in a case-series[27]. Only one study assessed symptoms, reporting decreased dyspnea scores but found no difference in survival[24] Another study reported no change in exercise capacity[27]. Side effects of CCBs were common and many patients required dose reduction (50%) and/or withdrawal of therapy (7-27%).

In summary, based on limited evidence, CCBs may mildly improve hemodynamics with no evidence to suggest any clinical or survival benefits, and they are generally poorly tolerated (Table 3).

PAH-Targeted Medications

Based on strong benefits in the treatment of PAH, fifteen reports describe potential benefits of PAH-targeted therapies, including oral phosphodiesterase type-5 inhibitors (PDE-5i), oral endothelin receptors antagonists (ERA), and prostanoids in patients with COPD-PH (Table 2).

PDE-5'i

Six studies (n=459) assessed effects of PDE-5i, including sildenafil (5 studies)[28; 29; 30; 31; 32] and tadalafil[33], in five of which PH was echo-defined using variable thresholds (sPAP> 30-40 mmHg)[28; 29; 31; 33]**,** whereas a single study variably defined PH by RHC (mPAP>30-35 mmHg), depending on FEV1% predicted[30]**.** Three studies had a low risk of bias , one RCT was unclear [28]**,** and two had a high risk of bias.[31; 32] All 5 studies assessing hemodynamics reported benefits of PDE-5i. Sildenafil improved echo-sPAP[28; 31], echo-calculated mPAP[32], and RHC-mPAP[30], and tadalafil improved both echo-sPAP and calculated mPAP[33]. Pooled analyses showed favourable effects on both sPAP and mPAP (Figure 2).

Of 6 studies assessing functional capacity[28; 29; 30; 31; 32; 33], sildenafil improved six-minute walk distance (6MWD) in two RCTs[28; 31] and 1 cohort study[32], but had no effect in 2 other RCTs.[29; 30] The one study of tadalafil showed a similar lack of benefit [33]. The pooled analysis of 6MWD showed no clear benefit with a trend towards improvement (Figure 3). PDE-5i's were generally well-tolerated with expected side-effects and did not worsen hypoxemia.

There were inconsistent benefits in HRQoL in 4 RCTs using different measurement tools[29; 30; 31; 33]. Sildenafil improved mMRC dyspnea[30; 31]**,** 36-item Short Form survey (SF-36) score, and the multi-parameter COPD BODE index (body mass index [BMI], obstruction by

FEV1, mMRC dyspnea, and 6MWD)[30], but not HRQoL in an unspecified questionnaire[29]. Tadalafil had no effect using different scores (SF-36, SGRQ, MLHFQ)[33].

In summary, PDE-5i's significantly improved hemodynamics in COPD-PH patients, but this did not translate to clinical, functional, or HRQoL benefits (Table 3).

ERAs.

Two placebo-controlled RCTs assessed the effects of bosentan in severe COPD. In a non-blinded study in RHC-diagnosed moderate-severe PH, bosentan had mild hemodynamic benefit associated with improved exercise capacity and limited symptomatic benefit[34]. In contrast, bosentan had inconsistent hemodynamic effects, uncertain clinical benefits (6MWD fell slightly, HRQoL improved), and reduced PaO_2 in mild echo-defined PH[35]. Ambrisentan treatment in a case series (n=24) of RHC-diagnosed severe PH decreased brain natriuretic peptide (BNP) with no change in 6MWD[36]. Two studies had a high risk of bias and one RCT had a low risk of bias35.

In summary, ERAs have limited hemodynamic and uncertain clinical benefits in COPD-PH patients.

Studies of multiple PAH-targeted therapies

Four retrospective cohort studies assessed the effects of multiple PAH-targeted therapies individually in RHC-defined COPD-PH[37; 38; 39; 40], reporting hemodynamic improvement with no clinical or functional benefits[37; 38], or no effects at all[39; 40]. Three other retrospective cohort studies[41; 42; 43] reported no survival benefit of PAH-targeted therapies in various combinations in RHC-defined PH, but one found short-term clinical (improved New York Heart association

[NYHA] functional class) and functional (improved 6MWD) benefits up to 1 year which were not sustained at 2 yrs[41]. Three studies suggested greater improvements with PAH-targeted therapy in patients with more severe PH, including greater RHC-measured hemodynamic effects[37; 38; 41], and one showed clinical and functional benefits up to 1 year[41]. Risk of bias was high for six of seven studies of multiple PAH-targeted therapies, and unclear for one study, which limits confidence in the results.

In summary, combination PAH-targeted therapy does not improve survival but may offer some transient clinical and/or functional benefits. Patients with objective "response" to therapy, including improved mNYHA FC or PVR, may have improved survival[39].

Statins

Statins are widely used in COPD due to the prevalence of cardiovascular diseases, and have been used for treatment of COPD-PH in six studies (n=394; Supp Table 3), including five RCTs using echo-defined PH[44; 45; 46; 47; 48] and one RHC-defined PH cohort study[49]**.** Only one study had low risk of bias[44], but the other five studies had an unclear risk of bias.

Three RCTs showed statins decreased echo sPAP at rest[46; 47; 48] or during exercise[44], whereas another RCT showed no change[45]**.** Clinical and functional outcomes were infrequently assessed, and changes in dyspnea, HRQoL, and functional capacity are inconsistent [44; 45; 47]**.** In summary, statins are well-tolerated, significantly reduced sPAP (Figure 4), but had no clinical or functional benefits.

Other Therapies

Single studies have reported on several miscellaneous, non-traditional potential therapies

in patients with COPD-PH (Supp Table 4)[50; 51; 52]. Some therapies demonstrated improved pulmonary hemodynamic at rest (eg. Dipyridamole[53]**,** Cicletanine[54]**,** ACE inhibitors[55; 56], inhaled nitric oxide [iNO][57]) or on exercise (eg. Waon therapy[58]), and/or reduced dyspnea (eg. Waon therapy[58]*),* or improved exercise capacity (eg. iNO[57]*),* whereas many other therapies had no reported benefits. Combinations of such therapies may improve multiple parameters, eg. combination of azithromycin, simvastatin, and LTOT decreased RHC sPAP and increased 6MWD[59]**.**

DISCUSSION

Our systematic review focuses on the effect of various therapeutic options in COPD-PH. We identified studies that focused on treatment of COPD-PH for at least 4 weeks, and captured hemodynamics and clinical outcomes including survival. Overall, many treatments improve PH hemodynamics, some may improve survival, but few are associated with improved symptoms, functional capacity, or HRQoL. For example, supplemental LTOT mildly reduces PH hemodynamic severity, may slow PH progression over time, and reduces mortality. However, other clinical and functional benefits of LTOT were not assessed. Similarly, PAH-targeted therapy using sildenafil improved PH hemodynamics, but had uncertain clinical and functional benefits. In contrast, other PAH-targeted medications, e.g. ERAs had inconsistent effects, as did other therapies including CCBs and statins.

The presence and severity of PH in COPD patients is a significant contributor to clinical morbidity, including worse dyspnea, functional capacity and HRQoL[5; 6; 30], as well as being a prognostic marker for more frequent exacerbations and worse survival. However, there are no specific treatments for COPD-PH, and current guidelines for management of WHO group 3 PH, including COPD-PH, simply suggest LTOT for resting hypoxemia and optimization of underlying chronic cardiopulmonary conditions[4; 13].

COPD-PH is believed to be largely the result of hypoxemia. As such, LTOT could be effective in the treatment of hypoxemic COPD-PH. The data suggest mild improvements in severity of PH, some evidence for slowing progression of PH, and importantly, improved survival. However, O_2 did not normalize mPAP and there were no other symptomatic or functional clinical benefits reported. As for NOT, the limited available data shows no clear benefits in COPD-PH patients with either daytime or isolated nocturnal hypoxemia. We did not

find studies that assessed the long-term effect of supplemental O_2 in COPD-PH patients with exertional hypoxemia.

Besides hypoxemia, COPD-PH may also be driven through other potential mechanisms[60], including pathophysiologic features similar to PAH, including pulmonary micro-vessel rarefaction and endothelial dysfunction, e.g. decreased expression of endothelial nitric oxide synthetase (eNOS)[3; 4; 60;]. Thus, PAH-targeted therapy may have a potential role in COPD-PH management. However, guidelines generally recommend against PAH-targeted therapy for mild to moderate WHO group 3 PH, including COPD-PH[13; 61].

In our systematic review, PAH-targeted therapy in patients with COPD-PH had inconsistent effects, including limited clinical benefits, eg. symptoms, functional capacity HRQoL, but no assessment of hospitalization or survival. Overall, our findings are similar to other analyses[4; 62; 63]. Some PAH-targeted medications may offer benefits, as PDE-5i's (sildenafil and tadalafil) significantly improved pulmonary hemodynamics, and sildenafil improved mMRC[30; 31], BODE index and SF-36[30]. In our pooled analysis, 6MWD increased slightly but not significantly with PDE-5i treatment (+16m; Figure 3), which was less than the significant pooled effect of sildenafil on 6MWD (+29m) in another review of COPD-PH[64]. Differences include our inclusion of a negative trial on tadalafil, possibly due to an ineffective small dose[33], and exclusion of several positive studies from China. Comparatively, there are fewer studies of other PAH-targeted therapies such as ERAs, but similar overall limited clinical benefits despite some hemodynamic effects. Combination PAH-targeted therapy is now standard of care in PAH[13; 61], but there are limited data in COPD-PH to suggest any benefit.

Interestingly, an objective "response" to PAH-targeted therapy (PDE-5i or ERA), as characterized by improved mNYHA FC or PVR (>20% fall), was predictive of better survival[39].

Furthermore, some COPD patients with more severe PH, generally defined as mPAP≥35mmHg may respond better to PAH-targeted therapy[37; 38; 41]. A subset of COPD patients with this severe precapillary PH and possibly RV failure, often in the setting of only mild-moderate COPD has been labeled , and may reflect a "vascular" phenotype[65], which may be at particularly high risk of long-term PH-related morbidity and mortality[5; 66]. This group of patients may have a genetic predisposition to PH, similar to heritable PAH, which may become manifest in the context of COPD, either driven by hypoxemia, cigarette smoke, airway or systemic inflammation[60; 65], or simply due to concurrent COPD and unrelated PAH. This subset of COPD patients merits further study, and may benefit clinically from referral to expert PH centers for further assessment and consideration of treatment[4;13].

Concerns over potential risks of PAH-targeted therapies worsening ventilation/perfusion (V/Q) matching and hypoxemia, because of non-selective widespread pulmonary vasodilation, are not supported by any evidence for any adverse effect on oxygenation[29; 30; 31; 33; 34]. Expected side-effects of PAH-targeted therapy were observed, e.g. flushing, headache, diarrhea, but did not lead to high rates of medication discontinuation.

Among other treatment options, CCBs may mildly improve hemodynamics, but there is no evidence to suggest any clinical or survival benefits, and they are generally poorly tolerated. Statins reduced sPAP (mPAP in one study), but had limited clinical benefits. Although the statin effect in PH could be mediated through systemic vascular and/or left-ventricular effects rather than direct pulmonary vascular action, a multiple regression analysis suggested statins reduce mPAP independent of pulmonary artery wedge pressure (PAWP)[49]. Statins may also prevent COPD progression and improve PH by reducing C-reactive protein and other inflammatory factors[67]. Several other therapies (eg. iNO, Waon, cicletanine) improved pulmonary

hemodynamics with minimal clinical benefits.

Limitations of this review include paucity of RHC diagnosed PH, as only some studies reported RHC-mPAP, whereas most studies only reported echo-estimated sPAP +/- calculated mPAP[68]. A systemic vascular effect of a putative treatment could result in apparent pulmonary hemodynamic benefit as assessed simply by echocardiogram, eg. decrease in sPAP with statins. Moreover, studies used various thresholds for both RHC and echo measurements to define presence of PH. In addition, study populations exhibited marked heterogeneity, including severity of COPD and presence of hypoxemia. There was also treatment heterogeneity, as studies used various doses and duration of therapy, and in some studies of combination PAH-targeted therapies, specific combinations were not clearly defined. Most importantly, very few studies provided a comprehensive assessment of the potential benefits of PAH-targeted therapies, including multi-parameter characterization of hemodynamic, clinical, and functional benefits.

In conclusion, this systematic review identifies the large number of studies assessing multiple treatments for patients with COPD-PH, and highlights the limited evidence base. This review supports recent guidelines which recommend LTOT in hypoxemic COPD-PH patients, but do not recommend other treatments for COPD-PH, including PAH-targeted medications. Development of future therapies depends upon new ideas on the pathobiology of COPD-PH, as well as higher-quality studies on more homogeneous populations, including patients with more severe PH or a "vascular" phenotype, using a standardized RHC diagnosis of PH and comprehensive assessment of outcomes.

Take home message.

The presence of PH in COPD patients is associated with worsening morbidity and mortality. Our findings support guideline recommendations for LTOT in hypoxemic COPD-PH patients as well as recommendations against treatment using PAH-targeted medications

Table 1. Effects of supplemental oxygen therapy including long term oxygen therapy (LTOT) and nocturnal oxygen therapy (NOT) in patients with COPD-PH .

Study	Design	Population	Intervention	Significant outcomes
Stark 1972[19]	Randomized parallel-group	n=11: LTOT of different duration ● Age: 39-67 yrs ● Gender: 100% male ● FEV_1: 0.80 L ● PaO_2: 49 mmHg ● RHC mPAP: 41.9 mmHg	LTOT (2 L/min) for 18 hrs/d (n=4), 15 hrs/d (n=4), or 12 hrs/d (n=3) x 3-7 wks	Outcomes with LTOT: ▪ Decreased mPAP (18 hrs/d: 51 to 31 mmHg, p<0.05; 12 hrs/d: 37 to 30, p<0.05) ▪ Decreased PVR (18 hrs/d: 10 to 5.6 WU, p<0.05; 15 hrs/d: 6.2 to 5 WU, p<0.05)
NOTT 1980[20]	Randomized parallel-group	n=203: LTOT (n=101) vs NOT (n=102) Inclusion criteria: - PaO_2 ≤55 OR - PaO_2 ≤59 mmHg AND either edema OR hematocrit ≥55% OR ECG P pulmonale ● Age: 65 yrs ● Gender: 78.8% male ● FEV_1: 29.7% ● PaO_2: 51.2 mmHg ● RHC mPAP: 29.5 mmHg	LTOT (17.7±4.8 [SD] hrs/d) vs NOT (12±2.5 hrs/d) to target PaO_2 60 to 80 mmHg x >1 yr (Mean 19.3 mos)	Outcomes in LTOT (n=87/101) vs NOT (n=80/102): ▪ Decreased PVR (11.1%; n=52) vs increased (6.5%; n=49) at 6 mos (p=0.04) ▪ Lower 12 mos mortality (11.9±3.2 vs 20.6±4.0%; n= 87 vs 80, respectively; p=0.01) ▪ Lower 24 mos mortality (22.4±4.6 vs 40.8±5.5%; n= 37 vs 29, respectively; p=0.01) ▪ Survival benefit of LTOT in patient s with baseline mPAP <27 (p=0.03), PVR <3.5 WU (p=0.03)

MRC 1981[14]	RCT	n=87: LTOT (n=42) vs control (n=45) Inclusion criteria: PaO_2 40-60 mmHg ● Age: 58.2 yrs ● Gender: 75.9% male ● FEV_1: Males 0.70 vs Females 0.61 L ● PaO_2: 51 mmHg ● RHC mPAP: 34.4 (male) vs 32.7 (female) mmHg	LTOT (>15 hrs/d) to target PaO_2 >60 mmHg vs control (room air) x 5 yrs	Outcomes in LTOT vs control: ▪ Change in mPAP (-0.06 vs +2.79 mmHg/yr; n=21 men surviving >500 d; "significant" but p value not specified) ▪ Change in TPR (0 vs +1.4 WU/yr) ▪ Decreased mortality in females (p <0.05) ▪ Decreased mortality in males only after 500 d (n=19 vs 30; 12%/yr vs 29%/yr, p=0.04)
Gluskowski 1983[15]	Case series	n=16 Inclusion criteria: PaO_2 <60mmHg or hematocrit >60% ● Age: 50.4 yrs ● Gender: 81.3% male ● FEV_1: 0.84±0.33 L (SD) ● PaO_2: 51.8±8.8 mmHg ● RHC mPAP: 42.5±13.3 mmHg	LTOT (17 hrs/d) on 28% facemask x 6 wks	Outcomes with LTOT: ▪ Decreased mPAP (42.5±13.3 to 38.1±10.4 mmHg; p<0.001) ▪ Increased FEV_1 (0.84±0.33 to 1.06±0.55; p<0.05) ▪ No change in cardiac index or PaO_2
Weitzenblum 1985[16]	Case series	n=16 Inclusion criteria: - PaO_2 <60mmHg, AND - RHC mPAP >20 mmHg OR history of right heart failure OR ECG RVH ● Age: 58.1±7.9 yrs (SD) ● Gender: 93.8% male ● FEV_1: 0.89±0.28 L ● PaO_2: 50.2±6.6 mmHg ● RHC mPAP: 28.0±7.4 mmHg	LTOT (>15 h/d) to target PaO_2 ≥65 mmHg (Mean 31±19 mos)	Outcomes with LTOT: ▪ Decreased mPAP (28.0±7.4 to 23.9±6.6 mmHg; annual change -2.2±4.4 mmHg/yr, p <0.05) vs increased mPAP pre-LTOT (23.3±6.8 to 28.0±7.4 mmHg; +1.5±2.3 mmHg/yr, p<0.005)

Timms 1985[21]	Randomized parallel-group	n=118/203 with RHC at baseline and 6 mos: LTOT (n=61) vs NOT (n=57) Inclusion criteria: PaO_2 ≤55 or PaO_2 ≤59 with signs of right heart failure or erythrocytosis: ● Age: 65.6±7.7 yrs (SD) ● Gender: 83.1% male ● FEV_1: 32.7±14.1% (n=114) ● PaO_2: 51.9±4.9 mmHg (n=117) ● RHC mPAP: 29±10 mmHg (n=178)	LTOT vs NOT (12 hrs/d) x mean 32 mos	Outcomes in LTOT vs NOT: ▪ Decreased resting mPAP 3±11mmHg (p=0.02) and PVR 0.85±2.2 WU (p=0.007) vs no change; differences between LTOT and NOT were not significant ▪ Decreased exercise mPAP (p=0.005) and exercise PVR (p=0.001), increased exercise SVI (p=0.004) vs no change ▪ Changes in mPAP during first 6 mos associated with subsequent survival after adjustment for baseline values (p <0.01) in both LTOT and NOT
Cooper 1987[17]	Case series	n=72 Inclusion: FEV_1 <50% AND PaO_2 <60 mmHg AND ≥1 episode of peripheral edema ● Age: 60.5±7.5 yrs (SD) ● Gender: 73.6% male ● FEV_1: 29±10 % ● PaO_2: 45.8±7.5 mmHg ● RHC mPAP: 28.3±10.2 mmHg (n=45) ● PVR: 5.0±2.2 WU (n=45)	LTOT (1.5 - 2.5 L/min) to target PaO_2 ≥60 mmHg 15 hrs/d x 5 yrs	▪ No difference in mPAP at 1-year vs baseline (n=40) ▪ No association of survival with PAP or PVR
Fletcher 1992[22]	RCT	N=16/38: NOT (n=7) vs sham (n=9) Inclusion criteria: Daytime PaO_2 ≥60 mmHg, episodic desaturation in REM sleep ● Age: 61.6±2.2 yrs (SEM) ● Gender: not specified ● FEV_1: 1.42±0.20 vs 1.42±0.14 L ● PaO_2: 73.7±2.6 vs 76.7±3.4 mmHg ● RHC mPAP: 26.7±2.2 vs 22.5±1.8 mmHg	NOT (3L/min) vs sham x 3 yrs	Outcomes in NOT vs sham: ▪ Change in mPAP -3.7 vs +3.9 mmHg /3 yrs (p <0.02) ▪ No difference in PVR, CO, mortality

Zielinski 1998[18]	Case series	n=73/95 who survived at least 2 yrs Inclusion criteria: - PaO2 ≤55 mmHg OR – PaO2 56–65 mmHg with cor pulmonale (ECG RVH, PH on CXR) OR hematocrit ≥55% ● Age: 58±9 yrs (SD) ● Gender: 72% male ● FEV_1: 0.84±0.31 L ● PaO_2: 55±6 mmHg ● RHC mPAP: 28±11 mmHg	LTOT (mean 13.5-14.7 hrs /d) x 2 - 6 yrs	Outcomes at 2 yr (n=39), 4 yr (n=20), and 6 yr (n=12): ▪ No change in mPAP, PVR or CO at any timepoint vs baseline ▪ Increased mPAP at 4 yr ($p<0.05$) and 6 yr ($p<0.01$) vs 2 yr (n=12) ▪ Decreased PaO_2 at 2 yr ($p<0.05$), 4 yr ($p<0.05$), and 6 yr ($p<0.001$) vs baseline
Chaouat 1999[23]	RCT	N=76: NOT (n=41) vs Ragdah xxx control (n=35) Inclusion: PaO_2 56-69 mmHg AND nocturnal desaturation (SaO_2 <90% for ≥30% of time in bed) Exclusion: OSA with AHI ≥10 events/hrs ● Age: 63.5±7.1 yrs (SD) ● Gender: not specified ● FEV_1: 1.1±0.5 vs 1.0±0.3 L ● PaO_2: 62.6±3 vs 62.8±3 mmHg ● RHC mPAP: 19.7±5.3 vs 19.5±5.3 mmHg ● PH at baseline (mPAP ≥20 mmHg): n=36/76	NOT: 8.9±1.9 hrs/night) to target SpO_2 >90% x 2 yrs (mean 35.1±14.3 mos)	Outcomes in NOT vs control at 2 yrs: ▪ No difference in mPAP or CO at rest or with exercise (n=24 vs 22) ▪ No difference in mPAP in patients with PH at baseline (n=9 vs 10) ▪ No difference in mortality (n=9 vs 7)

Data are mean±SEM, unless otherwise specified.

Abbreviations: AHI, apnea-hypopnea index; CI, cardiac index; CO, cardiac output; CXR, chest X-ray; DB, double-blinded; EKG, electrocardiogram; FEV_1, forced expiratory volume in one second; hrs/d; hours per day; LTOT, long-term oxygen therapy; mos; months; mPAP, mean pulmonary artery pressure; NOT, nocturnal oxygen therapy; OSA, obstructive sleep apnea; PaO_2, partial pressure of

oxygen in arterial blood; PC, placebo-controlled; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RCT, randomized controlled trial; REM, rapid eye movement; RHC, right heart catheterization; RVH, right ventricular hypertrophy; SaO_2, arterial oxygen saturation (%); SpO_2, transcutaneous pulse oximetry oxygen saturation (%); SVI, stroke volume index; TPR, total pulmonary resistance, wks, weeks; WU, Wood unit (mmHg/L/min); yrs, years.

Table 2. Effects of PAH-targeted therapies in patients with COPD-PH.

Study	Design	Population	intervention	Significant Outcomes	Adverse Effects
Stolz 2008[35]	RCT	N=30: Bosentan (n=20) vs placebo (n=10) Inclusion criteria: - COPD GOLD stage III–IV ● Age: 68±8.5 yrs (SD) ● Gender: 60% male ● FEV1: 39±13.3 % ● 6MWD: 336.3±92.6 m ● SpO2: 92.6±3.3 % ● Echo sPAP: 32 (median; IQR 29–38) vs 37 mmHg (20–42) in (n=14) bosentan vs (n=6) placebo	Bosentan 62.5 mg PO BID x 2 wks then 125 mg PO BID x12 wks Note: (n=8 on LTOT) in Bosentan vs (n=3) placebo	Outcomes in Bosentan (n=14/20) vs placebo (n=9/10): ▪ No change in echo PVR vs increase (p=0.006) ▪ No difference in sPAP or CI ▪ Improved SF-36 total and physical domain scores ▪ Decreased 6MWD 339±81 to 329±94 m (p=0.04) vs no change ▪ No change in BDI ▪ Decreased PaO2 (p=0.029)	Bosentan (n=6) vs placebo (n=1) withdrew (p=0.37) Bosentan (n=2) dose reduction (elevated liver enzymes)
Valerio 2009[34]	RCT (not-blinded)	N=40: Bosentan (n=20) vs placebo (n= 20) Inclusion criteria: - RHC mPAP >20 mmHg AND PAWP <15 mmHg ● Age: 65.5±9.5 yrs ● Gender: 78,1% male (n=32/40) ● FEV_1: 38±18 % ● 6MWD: 257±118 vs 270±150 m ● PaO2: 57±10 vs 58±9 mm Hg ● mPAP: 37±5 mmHg (Variance not defined)	Bosentan 125 mg PO BID vs placebo x 18 mos Note: 40 % of each group were on LTOT	Outcomes in Bosentan (n=16/20) vs placebo (n=16/20): ▪ Decreased mPAP (37±5 to 31±6 mmHg; p=0.002) vs no change ▪ Decreased PVR (5.5±2.4 to 4.9±2.3 WU; p=0.012) vs no change ▪ Increased 6MWD (257±118 to 321±122 m; p=0.003) vs no change ▪ Decreased mNYHA FC (3.2±0.8 to 2.8±1.2; p=0.05) vs no change ▪ Decreased BODE index (6.6±2.8 to 5.5±3; p=0.002) vs no change ▪ No change in PaO2	n=8 withdrew (noncompliance, other health problems)

Rao 2011[28]	RCT	N=37: Sildenafil (n=17) vs placebo (n=20) Inclusion criteria: - Echo sPAP >40 mmHg ● Age: 62.3±7.5 yrs (SD) ● Gender: not specified ● FEV_1: 32.5±11.1 vs 28.5±7.5 % ● 6MWD: 268.9±139.9 vs 323.1±165.6 m ● Echo sPAP: 52.7±11.9 vs 47.8±13.4 mmHg	Sildenafil 20 mg PO TID vs placebo x 12 wks Note: none of the study participants used LTOT	Outcomes in sildenafil (n=15/17) vs placebo (n=18/20): At 4 wks ▪ Increased mean 6MWD 150±123 vs 24±117 m (p<0.05) At 12 wks ▪ Increased mean 6MWD 191±127 vs 39±87 m (p<0.025) ▪ Decreased echo sPAP 53±12 to 41±8 mmHg (p<0.05) vs no change	Sildenafil n=2 (epigastric pain and lost to follow up) vs placebo n=2 (acute exacerbation and lost to follow up)
Badesch 2012[36]	Case-series	N=24 (11 %) with COPD-PH of n=224 with PH Inclusion criteria: – FEV1 ≥50% – RHC mPAP >35 mmHg AND PVR >3.5 mmHg/L/min – 6MWD (150-450 m) ● Age: 68±11 yrs (SD) ● Gender: 71% male ● 6MWD:241±84 m ● BNP: 243±245 ng/L ● mPAP: 45±10 mmHg	Ambrisentan 5 mg PO daily for 24 weeks Note: 52.2 % receiving background PH therapy	Outcomes in COPD-PH: ● No change in 6MWD (-5 m; 95%CI: -34, 24) ● Change in BNP (-38%; 95%CI -54, -17) Outcomes in all PH: ● 181 patients (81%) contributed to the primary endpoint, 34 patient s (15%) discontinued prior to the week 24 visit ● Six patients died during the 24-week treatment period ● Improved mNYHA FC in 23%, worse in 7% (p<0.001). ● Change in BDI (-0.5; 95%CI: -0.8, -0.3)	No specific data in COPD-PH.

Hurdman 2013[39]	Retrospective non-randomized cohort analysis of prospective registry (ASPIRE)	N=59: PH-targeted therapy (n=43) vs no therapy (n=16) Inclusion criteria: – Post bronchodilator FEV1 ≤0.7 – RHC mPAP ≥40 mmHg ("severe") ● Age: 70±9 yrs (SD) ● Gender: 47% male (n=28/59) ● FEV1: 65±23% ● ISWD: 40 (Median:IQR 18–100) m ● PaO2: 45.8±11.3 mmHg ● mPAP: 49±8 mmHg	PDE-5I (n=31), ERA (n=10), SC treprostinil (n=1), nebulised iloprost (n=1), Treatment for ≥3 mos or until death Note: 85% received LTOT	Outcomes with PH-targeted therapy vs no therapy: ● No change in survival 72% vs 63% /1yr (p=0.67) PH-targeted therapy responder subgroup: ● N=8 (19%) objective response to PH therapy based on improved mNYHA FC or >20% fall in PVR ● Better survival vs non-responder (p<0.05)	No difference in SpO2 between groups; no discontinuation of medication (median 178 d)
Blanco 2013[29]	RCT	N=63: Sildenafil per-protocol (n=32) vs placebo (n=31) Inclusion criteria: – Echo sPAP >34 or RHC mPAP ≥25 mmHg ● Age 65.5±8 yrs (SD) (n=60) ● Gender: 90% male (n=60) ● FEV1: 32±12% (SD) ● 6MWD: 392±81 vs 379±100 m (n=60) ● Echo sPAP: 42±10 or RHC mPAP mean 31±5 mmHg in 22% of patient s.	Sildenafil 20 mg TID vs placebo x3 mos All patients underwent pulmonary rehabilitation 3 times per week x3 mos Note: n=18 on LTOT	Primary outcome in sildenafil-treated (n=29/32) vs placebo (n=31) per protocol: ● No significant difference in improvement in cycle endurance time (p=0.77) Outcomes in sildenafil-treated (n=24/29) vs placebo (n=27/31) who completed study: ● No statistically significant differences in incremental exercise test, 6MWD, HRQoL	COPD exacerbation which occurred in about third of patients lead to 10% d/c and 8% hospitalization with no difference between groups
Goudie 2014[33]	RCT	N=120: Tadalafil (n=60) vs placebo (n=60) Inclusion criteria: – Age 35-85 yrs – Post-bronchodilator FEV1 <80% AND FEV1/FVC <70%	Tadalafil 10 mg daily vs placebo x12 weeks N=13 (11%) of patients were on LTOT	Outcomes in tadalafil (n=56/60) vs placebo (n=57/60): ● Primary end point: No difference in 6MWD (p=0.94) ● No significant changes in HRQoL (SF-36, SGRQ, MLHFQ), BNP	Expected Tadalafil side-effects (eg. dyspepsia, headache) more common than placebo.

		– Echo sPAP >30 mmHg OR PAAT ≤120 ms ● Age: 69±7.5 yrs (SD) ● Gender: 68.5% male ● FEV1: 40.5±16% ● 6MWD: 347.5±104.5 m ● SpO2: 95.4±2.9% ● Echo sPAP: 42±9.5 mmHg		● Mean placebo-corrected decreased sPAP from baseline (12.3 mmHg; p=0.007; n=12 tadalafil vs n=13 placebo) ● Mean placebo-corrected decreased calculated mPAP from baseline (3.5 mmHg; p=0.025)	No difference in SpO2 between groups
Fossati 2014[41]	Retrospective cohort	N=27 /48 with COPD-PH, of n=463 attending PH clinic Inclusion criteria: – FEV1/FVC <0.7 – RHC mPAP ≥25 mmHg AND PAWP ≤15 mmHg – PH targeted therapy for at least 3 mos ● Age: 70 (Median:IQR 60-76) yrs ● Gender: 74% male ● FEV1: 60 (46-78) % ● 6MWD: 373 (236-452) m ● SpO2: 92 (86-94) % ● NT-pro-BNP: 653 (159-1,194) ng/L ● mPAP: 39 (32- 44) mmHg	Sequential combination therapy; final: ERA (n=15), PDE-5i (n=25), Prostanoids: inhaled (n=10), s/c (n=2), iv (n=3) Note: 60 % of patients used supplemental oxygen at least during nights	Median f/u 5.9 yrs: ● mNYHA FC improved at 3 and 6 mos (p=0.02 and p=0.008, respectively), not significant at 1 and 2yrs ● 6MWD increased significantly at 3, 6, and 12 mos (p≤0.01 at each timepoint), not significant at 2 yrs ● No change in NT-pro-BNP and resting SpO2 ● Peak exercise Spo2 during 6MWD decreased at 3, 6, and 24 mos (p<0.05 at each timepoint) ● No difference in transplant-free survival between PH-targeted therapies	None reported
Lange 2014[42]	Retrospective, non-randomized cohort	N=29 COPD-PH of N=72 WHO Group 3 PH Inclusion criteria: – FEV1/FVC <0.7 – FEV1 <70 % OR more than mild CT emphysema – RHC mPAP >25 mmHg and PAWP ≤15 mmHg	PDE-5i (n=29), ERA (n=11), nebulised iloprost (n=6) Note: dual therapy (n=8), triple therapy (n=2) x median 25.5 mos Note: PH-targeted therapy in 65% of	***COPD-PH subgroup*** Outcomes with PH-targeted therapy (n=12) vs no therapy (n=17) in: ● Reduced mortality (HR 0.235, p=0.075) ***Entire WHO group 3 PH cohort*** Outcomes with PH-targeted therapy (n=34; including n=26 severe PH) vs	Not reported.

		(N=72) ● Age: 67±9 yrs (SD) ● Gender: 68% male ● FEV1: 70±24% ● 6MWD: 300±100 m ● mPAP: 37.3±9.1 mmHg (n=12 severe mPAP ≥35 mmHg)	severe PH and 25% of less severe PH	no therapy (n=38; including 14 severe PH): ● Reduced mortality (HR 0.262, p=0.004)	
Girard 2015[37]	Retrospective non-randomized cohort) analysis of prospective registry data.	N=26 Inclusion criteria: – Post bronchodilator FEV1/FVC <0.7 – Precapillary PH: RHC mPAP ≥25 AND PAWP ≤15 mm Hg – Severe PH: mPAP >35 mmHg AND/OR CI <2 liters/min/m-2 ● Age: 66±11 yrs (SD) ● Gender: 96% male ● FEV1: 57±20% ● 6MWD: 212±104 m ● NT-proBNP: 3,205±4,250 ng/L ● Nuclear RVEF: 22±6% ● mPAP: 48±9 mmHg	PDE-5i (n=11), ERA (n=11), CCB (n=1), prostanoids (n=2), dual therapy (n=3) x median 6±3 mos Note all study participants were on optimal COPD treatment including LTOT	Outcomes with PH-targeted therapy: ● RHC (3-12 mos post-treatment) mPAP decreased 48±9 to 42±10 mmHg (p= 0.008) ● PVR decreased 8.5±3.0 to 6.6±2.0 WU (p= 0.001) ● TD CI improved 2.4±0.4 to 2.7±0.6 L/min/m2 (p= 0.015) ● Nuclear RVEF increased (p=0.03) ● No significant differences in mNYHA FC, 6MWD, echo parameters, or NT-proBNP levels	Decreased SpO2 % in n=2 (ERA), leading to discontinuation of study treatment
Tanabe 2015[43]	Multi-centre, retrospective cohort study	N=18 COPD-PH of N=70 WHO Group 3 PH Inclusion criteria: – RHC mPAP ≥35 mmHg and "normal" PAWP ● Age: 67±9 yrs (SD) ● Gender: 94% male ● FEV1: 58±33 % ● 6MWD: 263±97 m ● BNP: 397±608 pg/ml ● PaO2: 52±16 mmHg ● mPAP: 47±15	78% (n=14) treated with PH-targeted therapy: PDE-5i (n=14), ERA (n=8), beraprost (n=7) x mean 1.9 ±1.7 yrs Note: 96% (n=67) of study participants used LTOT	***COPD-PH subgroup*** ● Cumulative survival 50% /3yrs ● No change in survival with PDE-5i treatment: 53.6% vs 37.5% /3yrs (p= 0.56) ***Entire WHO group 3 PH cohort*** ● Improved survival with PDE-5i treatment (multivariate analysis, p=0.01)	Not reported

Brewis 2015[40]	Retrospective cohort study	N=40: COPD-PH of N=118 WHO Group 3 PH Inclusion criteria: – FEV1/FVC <0.7 either FEV1 <60% or emphysema on CT with FEV1 <80% – RHC mPAP ≥35 mmHg and PAWP ≤15 mmHg ● Age: 64±10 yrs (SD) ● Gender: 55% male ● FEV1: 56±16% ● 6MWD: 216±110 m ● NT-proBNP: 2169 (median; IQR 769–3919) pg/mL ● PaO2: 57±10.5 mmHg ● mPAP: 49±10 mmHg	Initial: ERA (N=10), PDE-5i (n=26), CCB (n=2), Prostanoid (n=2) x ≥3 mos Note: n=5 on LTOT	***COPD-PH subgroup*** ● No change in 6MWD ● No change in mNYHA FC ● No change in NT-proBNP ***Entire WHO group 3 PH cohort*** ● No change in 6MWD ● No change in mNYHA FC ● NT-proBNP improved (p=0.015) ● No change in PaO2	
Calcaianu 2016[38]	Single center, retrospective cohort study	N=28/537 (inclusion criteria) – FEV1/FVC <70% AND FEV1 >50% – RHC mPAP ≥35 mmHg PAWP <15 mmHg ● Age: 71.2±9.4 yrs (SD) ● Gender: 79% male ● FEV1: 69.3±13.8 % ● 6MWD: 259±104 m ● BNP: 296±389 ng/L ● PaO2: 49.6±9.5 mmHg ● mPAP: 44.2±8.7 mmHg	Initial: ERA (n=23), PDE-5i (n=1), prostanoid (n=1), CCB (n=1), combination therapy (n=2); x 6-12 mos (median 3 yrs) Note: All study participants used LTOT	Outcomes with PH-targeted therapy at 6-12 mos (n=16/28): ● PVR decreased 8.4±4.2 to 5.0±1.7 WU (p= 0.008) ● CI increased 2.5±0.7 to 3.2±0.6 L/min/m2 (p= 0.003) ● No change in mPAP ● No change in mNYHA FC (3 mos) ● No change in 6MWD, PaO2 ● Cumulative survival 57.2 % /3yrs (sequential combination therapy in n=10)	No side-effects leading to withdrawal of study treatment

Alkhayat 2016[32]	Parallel group cohort study	N=139: Sildenafil (n=69) vs placebo (n=70) Inclusion criteria: – COPD diagnosis: unclear criteria. – Echo calculated mPAP ≥25 mmHg – 6MWD (100-450) m ● Age: 48±15.5 yrs (SD) ● Gender: 76% male ● 6MWD: 345.5±84.5 m ● Calculated mPAP: 45±13 vs 56±16 mmHg	Sildenafil 20 mg po TID vs placebo x 12 wks	Outcomes in Sildenafil vs placebo: ● Mean placebo-corrected increase in 6MWD 51 m from baseline (p<0.001) ● Decreased mPAP from baseline 2.1 mmHg (-4.3, 0.0) vs increased 0.6 (-0.8, 2.0; p= 0.04)	Expected Sildenafil side-effects (eg. flushing, dyspepsia, and diarrhea)

Vitulo 2016[30]	Multicenter, RCT	N=28: Sildenafil (n=18) vs placebo (n=10) Inclusion criteria: - RHC mPAP ≥30 mmHg for FEV1 >30 % post−BD OR - RHC mPAP ≥35 mmHg if FEV1 <30 % post−BD - PAWP ≤15 mmHg - LTOT ≤6 L/min - PaCO2 ≤55 mmHg - No decrease in PaO2 ≤55 mmHg after first dose of blinded study medication ● Age: 67.9±8.1 yrs (SD) ● Gender: 75% male ● FEV1: 52.3±23.4 % ● 6MWD: 229.2±101.4 vs 308.5±99.6 m ● PaO2: 74.3±14.5 mmHg ● mPAP: 39.2±9.35 mmHg	Sildenafil 20 mg TID vs placebo x 16 wks	Outcomes in Sildenafil (n=15/18) vs placebo (n=10): ● PVR decreased 1.4 WU (p=0.04) ● CI increased 0.4 L/min/m2 (p=0.004) Secondary end points: ● BODE index improved 0.40 units (p=0.02) ● mMRC dyspnea improved (0.6 units; p=0.03) ● No change in 6MWD	Expected Sildenafil side-effects (eg. (headache, flushing, myalgia) mild-moderate in n=5; no interruption of study treatment. No difference in SpO2 between groups
Shrestha 2017[31]	Non placebo-RCT	N=72: Sildenafil (n=36) vs standard medical therapy (n=36) Inclusion criteria: - Echo sPAP >36 mmHg ● Age: 64.2±5 yrs ● Gender: not specified ● FEV1: 46.1±12.8 % ● 6MWD: 183±78 m ● mPAP: 71.3±14.7 mmHg (Variance not defined)	Sildenafil 25 mg po TID vs standard medical therapy x 4 wks Note: LTOT permitted	Outcomes in Sildenafil (n=30) vs standard medical therapy (n=31): ● Decreased sPAP 9.9±7.8 vs 5.9±7.4 mmHg (p=0.048) ● Increased 6MWD 48±26 vs 33±33 m (p=0.047) Secondary outcomes: ● Decreased mMRC (p=0.037) ● No difference in mNYHA FC, BDI	Expected Sildenafil side-effects (eg. flushing, diarrhea, syncope), no interruption of study treatment. No difference in SpO2 between groups

Data are mean±SEM unless otherwise specified

Abbreviations: 6MWD, 6-minute walk distance (m); BDI, Borg dyspnea index; BID, twice daily; BNP, brain natriuretic peptide; BODE index; Body mass index, Obstruction by FEV1, Dyspnea by mMRC grade, and Exercise capacity by 6MWD; CCB, calcium channel blockers; CT, computerized tomography scan; ERA, endothelin receptor antagonist; FEV1/FVC, ratio of forced expiratory volume in one second to forced vital capacity, GOLD, Global Initiative for Chronic Obstructive Lung Disease; IQR, interquartile range; IV; intravenous; ISWD, incremental shuttle walk distance; mMRC, modified Medical Research Council; mNYHA FC, modified New York Heart Association functional class; NT-proBNP, N-terminal propeptide of brain natriuretic peptide; PAAT, Pulmonary artery acceleration time; PaCO2; partial pressure of carbon dioxide in arterial blood; PAWP, pulmonary arterial wedge pressure; PDE-5i, phosphodiesterase type-5 inhibitors; PO, per os; HRQoL, health-related quality of life; SGRQ, St. George's Respiratory Questionnaire; SC, subcutaneous; sPAP, systolic pulmonary arterial pressure (mmHg); TID, three times a day; WHO, world health organization.

Table 3. Summary of outcomes in treatment of COPD-PH

Treatment	PH Outcomes		Clinical Outcomes				
	Cardiopulmonary Hemodynamic	*RV Function*	*Symptoms*	*Functional Capacity*	*HRQoL*	*Hospitalization*	*Survival*
O2 (n=4)							
LTOT (n=8)	+	NA	NA	NA	NA	NA	+
NOT (n=2)	+/-	NA	NA	NA	NA	NA	0
CCBs (n=4)							
Nifedipine (n=3)	0	NA	+	NA	NA	NA	0
Felodipine (n=1)	+	NA	NA	0	NA	NA	NA
PH-targeted therapy (n=9)							
PDE type 5 inhibitors (PDE-5i)							
Sildenafil (n=5)	+	NA	+/-	+/-	+/-	NA	NA
Tadalafil (n=1)	+	NA	0	0	0	NA	NA
ERA							
Bosentan (n=2)	+/-	NA	+	+/-	+	NA	NA
Ambrisentan (n=1)	NA	+	+/-	0	NA	NA	NA
Statins (n=6)							
Atorvastatin (n=4)	+	0	NA	0	NA	NA	NA
Rosuvastatin (n=1)	+	0	0	+	0	NA	NA
Pravastatin (n=1)	+	NA	+	+	NA	NA	NA

Clinically relevant effects: +, significant; +/-, uncertain; 0, none; NA, not assessed

Reference List

[1] VESTBO, J. et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. **Am.J.Respir.Crit Care Med.,** v. 187, n. 4, p. 347-365, 2013.

[2] RABE, K. F.; WATZ, H. Chronic obstructive pulmonary disease. **Lancet,** v. 389, n. 10082, p. 1931-1940, May 2017. ISSN 1474-547X.

[3] GREDIC, M. et al. Pulmonary hypertension in chronic obstructive pulmonary disease. **Br.J.Pharmacol.**, 2020.

[4] NATHAN, S. D. et al. Pulmonary hypertension in chronic lung disease and hypoxia. **Eur Respir J,** v. 53, n. 1, 01 2019. ISSN 1399-3003.

[5] CHAOUAT, A. et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. **Am.J.Respir.Crit Care Med.,** v. 172, n. 2, p. 189-194, 2005.

[6] HILDE, J. M. et al. Haemodynamic responses to exercise in patients with COPD. **Eur.Respir.J.,** v. 41, n. 5, p. 1031-1041, 2013.

[7] OSWALD-MAMMOSSER, M. et al. Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. **Chest,** v. 107, n. 5, p. 1193-1198, 1995.

[8] SEEGER, W. et al. Pulmonary hypertension in chronic lung diseases. **J.Am.Coll.Cardiol.,** v. 62, n. 25 Suppl, p. D109-D116, 2013.

[9] WELLS, J. M. et al. Pulmonary arterial enlargement and acute exacerbations of COPD. **N.Engl.J.Med.,** v. 367, n. 10, p. 913-921, 2012.

[10] THABUT, G. et al. Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. **Chest,** v. 127, n. 5, p. 1531-1536, 2005.

[11] SCHARF, S. M. et al. Hemodynamic characterization of patients with severe emphysema. **Am.J.Respir.Crit Care Med.,** v. 166, n. 3, p. 314-322, 2002.

[12] SIMONNEAU, G. et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. **Eur.Respir.J.,** v. 53, n. 1, p. 1801913, 2019.

[13] HIRANI, N. et al. Canadian Cardiovascular Society/Canadian Thoracic Society Position Statement on Pulmonary Hypertension. **Can.J.Cardiol.,** v. 36, n. 7, p. 977-992, 2020.

[14] PARTY, M. W. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. **Lancet,** v. 1, n. 8222, p. 681-686, 1981.

[15] GLUSKOWSKI, J. et al. Effects of prolonged oxygen therapy on pulmonary hypertension and blood viscosity in patients with advanced cor pulmonale. **Respiration,** v. 44, n. 3, p. 177-183, 1983.

[16] WEITZENBLUM, E. et al. Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. **Am Rev Respir Dis,** v. 131, n. 4, p. 493-8, Apr 1985. ISSN 0003-0805.

[17] COOPER, C. B.; WATERHOUSE, J.; HOWARD, P. Twelve year clinical study of patients with hypoxic cor pulmonale given long term domiciliary oxygen therapy. **Thorax,** v. 42, n. 2, p. 105-110, 1987.

[18] ZIELIŃSKI, J. et al. Effects of long-term oxygen therapy on pulmonary hemodynamics in COPD patients: a 6-year prospective study. **Chest,** v. 113, n. 1, p. 65-70, Jan 1998. ISSN 0012-3692.

[19] STARK, R. D.; FINNEGAN, P.; BISHOP, J. M. Daily requirement of oxygen to reverse pulmonary hypertension in patients with chronic bronchitis. **Br.Med.J.,** v. 3, n. 5829, p. 724-728, 1972.

[20] NOTT. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. **Ann.Intern.Med.,** v. 93, n. 3, p. 391-398, 1980.

[21] TIMMS, R. M.; KHAJA, F. U.; WILLIAMS, G. W. Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. **Ann.Intern.Med.,** v. 102, n. 1, p. 29-36, 1985.

[22] FLETCHER, E. C. et al. A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO2 above 60 mm Hg. **Am.Rev.Respir.Dis.,** v. 145, n. 5, p. 1070-1076, 1992.

[23] CHAOUAT, A. et al. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. **Eur.Respir.J.,** v. 14, n. 5, p. 1002-1008, 1999.

[24] VESTRI, R. et al. One-year clinical study on nifedipine in the treatment of pulmonary hypertension in chronic obstructive lung disease. **Respiration,** v. 54, n. 2, p. 139-144, 1988.

[25] SAADJIAN, A. Y. et al. Long-term treatment of chronic obstructive lung disease by Nifedipine: an 18-month haemodynamic study. **Eur.Respir.J.,** v. 1, n. 8, p. 716-720, 1988.

[26] AGOSTONI, P. et al. Nifedipine reduces pulmonary pressure and vascular tone during short- but not long-term treatment of pulmonary hypertension in patients with chronic obstructive pulmonary disease. **Am.Rev.Respir.Dis.,** v. 139, n. 1, p. 120-125, 1989.

[27] SAJKOV, D. et al. Felodipine improves pulmonary hemodynamics in chronic obstructive pulmonary disease. **Chest,** v. 103, n. 5, p. 1354-1361, 1993.

[28] RAO, R. S. 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.,** v. 53, n. 2, p. 81-85, 2011.

[29] BLANCO, I. et al. Sildenafil to improve respiratory rehabilitation outcomes in COPD: a controlled trial. **Eur.Respir.J.,** v. 42, n. 4, p. 982-992, 2013.

[30] VITULO, P. et al. Sildenafil in severe pulmonary hypertension associated with chronic obstructive pulmonary disease: A randomized controlled multicenter clinical trial. **J.Heart Lung Transplant.,** v. 36, n. 2, p. 166-174, 2017.

[31] SHRESTHA, S. K. et al. Effect of Sildenafil Citrate on Pulmonary Arterial Systolic Pressure and Sub-maximal Exercise Capacity in Chronic Obstructive Pulmonary Disease. **Kathmandu.Univ Med.J.,** v. 15, n. 60, p. 271-278, 2017.

[32] ALKHAYAT, K.; EID, M. Sildenafil citrate therapy for secondary pulmonary arterial hypertension due to chronic obstructive lung disease. **Egyptian Journal of Chest Diseases and Tuberculosis,** v. 65, p. 805-809, 2016.

[33] GOUDIE, A. R. et al. Tadalafil in patients with chronic obstructive pulmonary disease: a randomised, double-blind, parallel-group, placebo-controlled trial. **Lancet Respir.Med.,** v. 2, n. 4, p. 293-300, 2014.

[34] VALERIO, G.; BRACCIALE, P.; GRAZIA, D. A. A. Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease. **Ther.Adv.Respir.Dis.,** v. 3, n. 1, p. 15-21, 2009.

[35] STOLZ, D. et al. A randomised, controlled trial of bosentan in severe COPD. **Eur.Respir.J.,** v. 32, n. 3, p. 619-628, 2008.

[36] BADESCH, D. B. et al. ARIES-3: ambrisentan therapy in a diverse population of patients with pulmonary hypertension. **Cardiovasc.Ther.,** v. 30, n. 2, p. 93-99, 2012.

[37] GIRARD, A. et al. Severe pulmonary hypertension associated with COPD: hemodynamic improvement with specific therapy. **Respiration,** v. 90, n. 3, p. 220-228, 2015.

[38] CALCAIANU, G. et al. Pulmonary Arterial Hypertension-Specific Drug Therapy in COPD Patients with Severe Pulmonary Hypertension and Mild-to-Moderate Airflow Limitation. **Respiration,** v. 91, n. 1, p. 9-17, 2016.

[39] HURDMAN, J. et al. Pulmonary hypertension in COPD: results from the ASPIRE registry. **Eur.Respir.J.,** v. 41, n. 6, p. 1292-1301, 2013.

[40] BREWIS, M. J. et al. Severe pulmonary hypertension in lung disease: phenotypes and response to treatment. **Eur.Respir.J.,** v. 46, n. 5, p. 1378-1389, 2015.

[41] FOSSATI, L. et al. Long-term effect of vasodilator therapy in pulmonary hypertension due to COPD: a retrospective analysis. **Lung,** v. 192, n. 6, p. 987-995, 2014.

[42] LANGE, T. J. et al. Outcome of patients with severe PH due to lung disease with and without targeted therapy. **Cardiovasc.Ther.,** v. 32, n. 5, p. 202-208, 2014.

[43] TANABE, N. et al. Multi-institutional retrospective cohort study of patients with severe pulmonary hypertension associated with respiratory diseases. **Respirology.,** v. 20, n. 5, p. 805-812, 2015.

[44] LEE, T. M. et al. Effects of pravastatin on functional capacity in patients with chronic obstructive pulmonary disease and pulmonary hypertension. **Clin.Sci.(Lond),** v. 116, n. 6, p. 497-505, 2009.

[45] MOOSAVI, S. A. et al. Evaluation of the Effects of Atorvastatin on the Treatment of Secondary Pulmonary Hypertension due to Chronic Obstructive Pulmonary Diseases: A Randomized Controlled Trial. **Iran Red.Crescent.Med.J.,** v. 15, n. 8, p. 649-654, 2013.

[46] LIU, H. F. et al. Atorvastatin improves endothelial progenitor cell function and reduces pulmonary hypertension in patients with chronic pulmonary heart disease. **Exp.Clin.Cardiol.,** v. 18, n. 1, p. e40-e43, 2013.

[47] CHOGTU, B. et al. A prospective, randomized study: Evaluation of the effect of rosuvastatin in patients with chronic obstructive pulmonary disease and pulmonary hypertension. **Indian J.Pharmacol.,** v. 48, n. 5, p. 503-508, 2016.

[48] ARIAN, A. et al. The Effects of Statins on Pulmonary Artery Pressure in Patients with Chronic Obstructive Pulmonary Disease: A Randomized Controlled Trial. **J.Res.Pharm.Pract.,** v. 6, n. 1, p. 27-30, 2017.

[49] REED, R. M. et al. Statin therapy is associated with decreased pulmonary vascular pressures in severe COPD. **COPD.,** v. 8, n. 2, p. 96-102, 2011.

[50] SCHONHOFER, B. et al. Long term effects of non-invasive mechanical ventilation on pulmonary haemodynamics in patients with chronic respiratory failure. **Thorax,** v. 56, n. 7, p. 524-528, 2001.

[51] MORRELL, N. W. et al. Pilot study of losartan for pulmonary hypertension in chronic obstructive pulmonary disease. **Respir.Res.,** v. 6, p. 88, 2005.

[52] FALLAHI, M. J.; GHAYUMI, S. M.; MOARREF, A. R. Effects of pentoxifylline on oxygenation and exercise tolerance in patients with severe chronic obstructive pulmonary disease. **Iran J.Med.Sci.,** v. 38, n. 2 Suppl, p. 163-168, 2013.

[53] NENCI, G. G. et al. Effects of dipyridamole on the hypoxemic pulmonary hypertension of patients with chronic obstructive pulmonary disease. **Respiration,** v. 53, n. 1, p. 13-19, 1988.

[54] SAADJIAN, A. et al. Long-term effects of cicletanine on secondary pulmonary hypertension. **J.Cardiovasc.Pharmacol.,** v. 31, n. 3, p. 364-371, 1998.

[55] PISON, C. M. et al. Effects of captopril combined with oxygen therapy at rest and on exercise in patients with chronic bronchitis and pulmonary hypertension. **Respiration,** v. 58, n. 1, p. 9-14, 1991.

[56] MARTINIUC, C.; BRANISTE, A.; BRANISTE, T. Angiotensin converting enzyme inhibitors and pulmonary hypertension. **Rev.Med.Chir Soc.Med.Nat.Iasi,** v. 116, n. 4, p. 1016-1020, 2012.

[57] VONBANK, K. et al. Controlled prospective randomised trial on the effects on pulmonary haemodynamics of the ambulatory long term use of nitric oxide and oxygen in patients with severe COPD. **Thorax,** v. 58, n. 4, p. 289-293, 2003.

[58] UMEHARA, M. et al. Repeated waon therapy improves pulmonary hypertension during exercise in patients with severe chronic obstructive pulmonary disease. **J.Cardiol.,** v. 51, n. 2, p. 106-113, 2008.

[59] WANG, P. et al. Effect of azithromycin in combination with simvastatin in the treatment of chronic obstructive pulmonary disease complicated by pulmonary arterial hypertension. **Pak.J.Med.Sci.,** v. 33, n. 2, p. 260-264, 2017.

[60] BLANCO, I.; PICCARI, L.; BARBERÀ, J. A. Pulmonary vasculature in COPD: The silent component. **Respirology,** v. 21, n. 6, p. 984-94, 08 2016. ISSN 1440-1843.

[61] GALIE, N. et al. Risk stratification and medical therapy of pulmonary arterial hypertension. **Eur.Respir.J.,** v. 53, n. 1, 2019.

[62] PRINS, K. W. et al. Chronic use of PAH-specific therapy in World Health Organization Group III Pulmonary Hypertension: a systematic review and meta-analysis. **Pulm Circ,** v. 7, n. 1, p. 145-155, Mar 2017. ISSN 2045-8932.

[63] CHEN, X. et al. Therapy in stable chronic obstructive pulmonary disease patients with pulmonary hypertension: a systematic review and meta-analysis. **J Thorac Dis,** v. 7, n. 3, p. 309-19, Mar 2015. ISSN 2072-1439.

[64] HAO, Y. et al. Efficacy and safety of Sildenafil treatment in pulmonary hypertension caused by chronic obstructive pulmonary disease: A meta-analysis. **Life Sci,** v. 257, p. 118001, Sep 2020. ISSN 1879-0631.

[65] KOVACS, G. et al. Pulmonary Vascular Involvement in Chronic Obstructive Pulmonary Disease. Is There a Pulmonary Vascular Phenotype? **Am J Respir Crit Care Med,** v. 198, n. 8, p. 1000-1011, 10 2018. ISSN 1535-4970.

[66] BOERRIGTER, B. G. et al. Ventilatory and cardiocirculatory exercise profiles in COPD: the role of pulmonary hypertension. **Chest,** v. 142, n. 5, p. 1166-1174, Nov 2012. ISSN 1931-3543.

[67] LU, Y. et al. Effectiveness of long-term using statins in COPD - a network meta-analysis. **Respir Res,** v. 20, n. 1, p. 17, Jan 2019. ISSN 1465-993X.

FIGURE LEGENDS

Figure 1. Prisma flow diagram of identification of relevant articles for inclusion in systematic review and quantitative analysis.

Figure 2. The effect of treatment with PDE-5i on mean pulmonary artery pressure (mPAP; UPPER PANEL) and systolic PAP (sPAP; LOWER PANEL) in COPD-associated PH. Note: mean PAP was measured by right heart catheterization (Vitulo 2017) or estimated from echo measurement of systolic PAP (Goudie 2014).

Figure 3. The effect of treatment with phosphodiesterase type-5 inhibitors (PDE-5i) on six-minute walk distance (6MWD) in subjects with COPD-associated PH. Note: PH was diagnosed either by right heart catheterization (Vitulo 2017) or by echocardiogram in the other studies.

Figure 4. The effect of treatment with atorvastatin on systolic PAP in COPD-associated PH. Note: PH was diagnosed by echocardiogram in all studies.

Figure 1. Prisma flow diagram of identification of relevant articles for inclusion in systematic review and quantitative analysis.

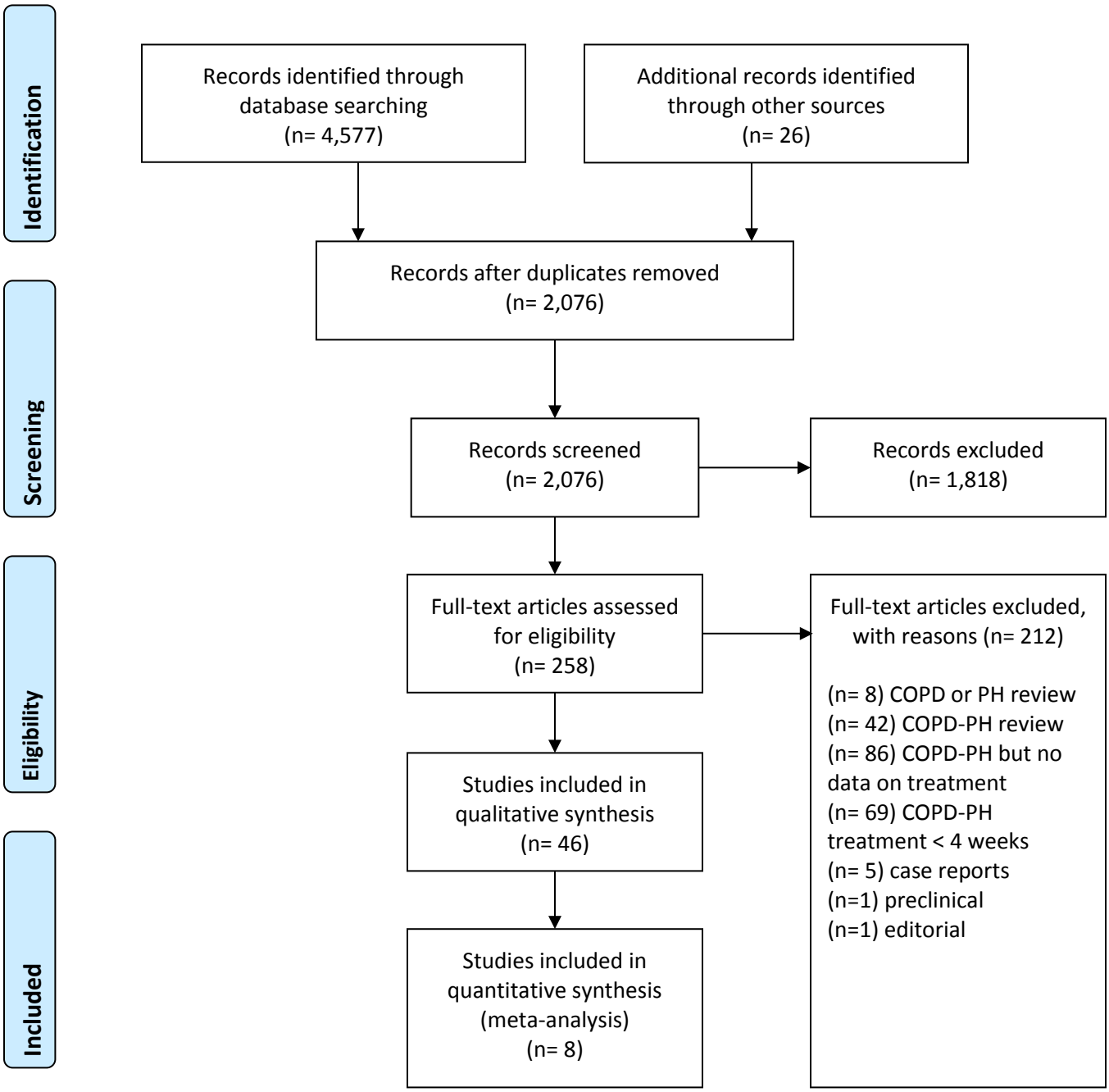


Figure 2. The effect of treatment with PDE-5i on mean pulmonary artery pressure (mPAP; UPPER PANEL) and systolic PAP (sPAP; LOWER PANEL) in COPD-associated PH. Note: mean PAP was measured by right heart catheterization (Vitulo 2017) or estimated from echo measurement of systolic PAP (Goudie 2014).

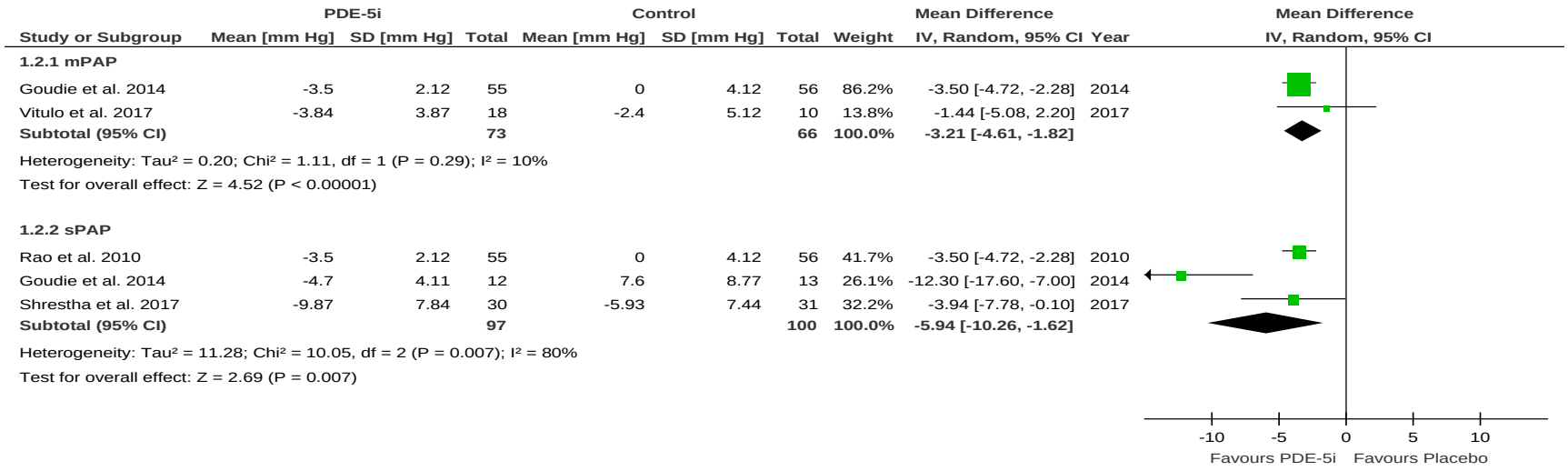


Figure 3. The effect of treatment with phosphodiesterase type-5 inhibitors (PDE-5i) on six-minute walk distance (6MWD) in subjects with COPD-associated PH. Note: PH was diagnosed either by right heart catheterization (Vitulo 2017) or by echocardiogram in the other studies.

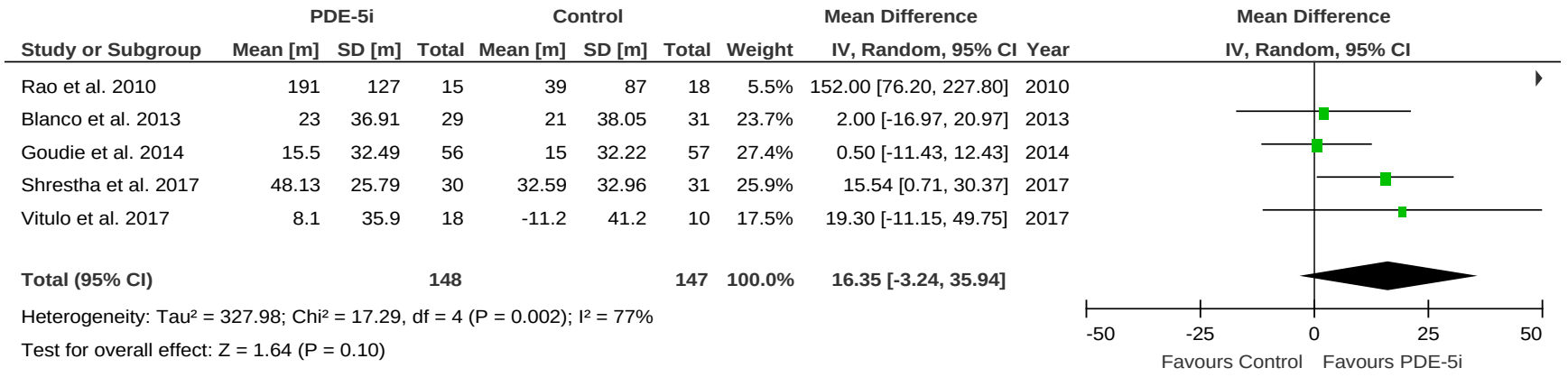
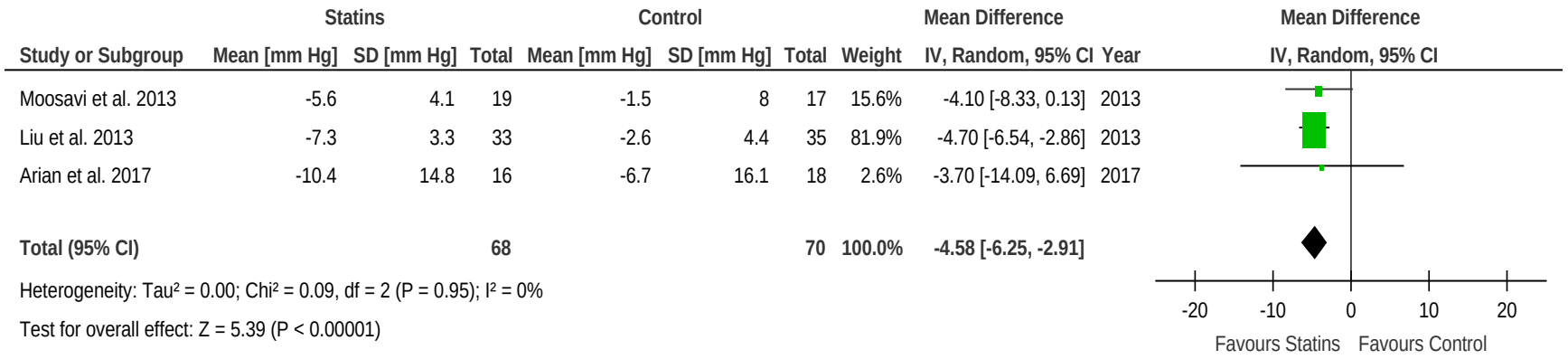


Figure 4. The effect of treatment with atorvastatin on systolic PAP in COPD-associated PH. Note: PH was diagnosed by echocardiogram in all studies.



SUPPLEMENTARY FILE

TITLE: Treatment of Pulmonary Hypertension Associated with Chronic Obstructive Pulmonary Disease: A Systematic Review

AUTHORS: Ragdah Arif MD FRCPC, Arjun Pandey BSc, Ying Zhao MD FRCPC, Kyle Arsenault-Mehta MD, Danya Khoujah MBBS MEHP, Sanjay Mehta MDCM FRCPC

Registration name / number: PROSPERO 2020 CRD42020170662

Appendix 1: SUPPLEMENTARY METHODS

Assessment of Risk of Bias.

Risk of bias was assessed using the Newcastle Ottawa Scale for observational studies[1] and the Cochrane Collaboration tool for Randomized Controlled Trials (RCTs)[2].

Statistical Analysis.

Summary measures of treatment effect. Expecting heterogeneity among trials, we used a random effects model and the method of DerSimonian and Laird[3] to pool relevant results. Results are presented as risk ratios (RR) with 95% confidence intervals (95% CI) for dichotomous outcomes. For continuous outcomes and categorical variables, results are presented as mean difference (95% CI). We assessed all outcomes for clinical and methodological heterogeneity which would make pooling of results inappropriate. The Chi squared test was used to assess homogeneity and the I^2 statistic for heterogeneity. Publication bias was assessed by funnel plot analysis. Studies that compare the pharmacologic intervention with usual care only (not placebo/sham) were included in the systematic review but not in the meta-analysis. When data for a particular outcome (either continuous or dichotomous) were inadequate to perform meta-analysis, the results of each study were presented in a table. All analyses were performed using Revman 5.31.

Reference List.

1. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Appl Eng Agric. 2014 Dec;18(6):727-34.

2. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. **Bmj**. 2011 Oct 18;343.
3. DERSIMONIAN, R.; LAIRD, N. Meta-analysis in clinical trials. Control Clin Trials, v. 7, n. 3, p. 177-88, Sep 1986. ISSN 0197-2456. https://www.ncbi.nlm.nih.gov/pubmed/3802833.

Appendix 2: SUPPLEMENTARY TABLES

Supplementary Table 1: Inclusion and exclusion criteria

Inclusion Criteria	
Study design	English or French-language, published, retrospective or prospective, cohort studies and randomized controlled trials.
Population	Adult patients (≥18 years) diagnosed with COPD (clinical diagnosis or by spirometry criteria [FEV1/FVC <70%]) AND Pulmonary Hypertension (PH diagnosed by either echo sPAP ≥30 mmHg OR RHC mPAP ≥20 mmHg).
Intervention	Any treatment for COPD-PH for at least 4 weeks
Comparator	Placebo or sham or standard medical therapy
Outcomes	1. Clinical outcomes: symptoms (improved, stable, worsening), Borg dyspnea index, functional status (improved, stable, worsening mNYHA), hospitalization, survival 2. Exercise (functional) capacity (6MWD) 3. Cardiopulmonary hemodynamic parameters: mPAP, PVR, and cardiac output/index 4. Echo parameters: sPAP, RV size/function, RA size 5. Health-related quality of life 6. Arterial partial pressure of oxygen and pulse oximetry saturation 7. Adverse effects and serious adverse effects 8. Withdrawals due to adverse effects

Exclusion Criteria	1. Letter or abstract 2. Pre-clinical studies (animal, pathology) 3. Pediatric studies 4. Studies with no clinical features (genetics, blood parameters, imaging, hemodynamics) 5. Acute therapeutic study 6. Review articles 7. Studies presenting combined data for multiple types of PH with no specific data for COPD-PH (including studies on WHO Group 3 PH patients) 8. Acute therapeutic studies defined as treatment duration <4 weeks 9. Case reports or case series with sample size <10

Abbreviations: 6MWD, six-minute walk distance; COPD, chronic obstructive pulmonary disease; COPD-PH, COPD-associated pulmonary hypertension; echo, echocardiogram; FEV1/FVC, ratio of forced expiratory volume in first second to forced vital capacity; mNYHA, modified New York Heart Association functional classification; mPAP, mean pulmonary arterial pressure; PA, pulmonary artery; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RA, right atrium; RV, right ventricle; sPAP, systolic pulmonary arterial pressure;

Supplementary Table 2. Effects of Treatment with calcium-channel blockers in patients with COPD-PH

Study	Design	Population	Intervention	Significant Outcomes	Adverse Effects
Vestri 1988[24]	RCT	N=60: Nifedipine (n=30) vs undefined control (n=30) Inclusion: PaO_2 <80 mmHg AND RHC mPAP >20 mmHg ● Age: 63.3±1.5 yrs ● Gender: 93.3% male ▪ FEV_1: 35±3 % ▪ Pao_2: 64.8±2.1 mmHg ▪ mPAP: 31.3±2.2 mmHg (Variance not defined)	Nifedipine 10 mg PO TID vs control X mean 12 mos (n=15 on LTOT >12 hrs/d)	Outcomes in Nifedipine (n=19/30) vs control (n=22/30) ▪ Decreased dyspnea score (both with and without LTOT) ▪ No difference in PaO_2, mortality	n=7 died and n=4 withdrew (ankle edema) vs n=8 died (nifedipine vs control)
Saadjian 1988[25]	RCT	n=20: Nifedipine (n=10) vs undefined control (n=10) Inclusion criteria: - RHC mPAP >20 mmHg ● Age: 62±2.3 yrs ● Gender: 100% male ● FEV_1: 32±2 % ● PaO_2: 63.3±2.7 mmHg ● mPAP: 31.7±2.3 mmHg	Nifedipine 10 mg PO TID vs control X mean 18 mos (n=10 on LTOT)	Outcomes in Nifedipine vs control ● No difference in mPAP, TPR, PaO2 ● Stable CI vs decreased CI ($p<0.05$)	n=1 (edema)

Agostoni 1989[26]	Case series	N=15 Inclusion criteria: - FEV_1 <60% - RHC mPAP ≥20 mmHg ● Age: 55 yrs ● Gender: 86.7% male ● FEV_1: 50.3 % ● PaO2: 54.8 mmHg ● mPAP: 32.8±4.1 mmHg	Nifedipine up to 180 mg daily x 8 wks	Outcomes in n=10/15 ▪ No change in mPAP (repeat RHC wks 1, 8, 9)	n=5 withdrew (intolerance)
Sajkov 1993[27]	Case series	N=13 Inclusion criteria: - PaO_2 <70 mmHg - Echo sPAP >30 AND/OR echo-calculated mPAP >20 mmHg ● Age: 66.6±2.1 yrs (SD) ● Gender: 80% male ● FEV_1: 37.4±19.5% ● PaO_2: 60.9±13.1 mmHg ● mPAP: 33.0±6.6 mmHg	Felodipine 2.5 mg PO BID x 5d, then 5 mg BID x 5d, then 10 mg BID x 10 wks (n=4 on LTOT)	Outcomes in n=10/13 ▪ Decreased echo mPAP 33.0±6.6 to 24.0±5.6 mmHg ($p<0.05$) ▪ Increased CO 6.1±1.2 to 7.2±1.3 L/min ($p<0.05$) ▪ Decreased TPR 5.6±1.7 to 3.5±1.1 WU ($p<0.05$) ▪ No change in cycle ergometry exercise capacity	n=3 withdrew (edema, dizziness); n=6 dose reduction (edema, headache)

Data are mean±SEM, unless otherwise specified.

Abbreviations: BID, twice daily; CI, cardiac index; CO, cardiac output; FEV_1, forced expiratory volume in one second; hrs; hours; LTOT, long-term oxygen therapy; mos, months; NOT, nocturnal oxygen therapy; PaO_2, partial pressure of oxygen in arterial blood; PO, per os (by mouth); RCT, randomized controlled trial; TID, three times a day; TPR, total pulmonary resistance; wks, weeks; WU, wood unit; yrs, years.

Supplementary Table 3. Effects of Statin therapy in patients with COPD-PH.

Study	Design	Population	intervention	Significant Outcomes	Adverse effect
Lee 2009[44]	RCT	N=65: Pravastatin (n=32) vs placebo (n=33) Inclusion criteria: – Age 40-80 yrs – FEV1/FVC <70% AND FEV1 <80% – Exercise echo sPAP ≥35 mmHg ● Age: 71.5±7 yrs (SD) ● Gender: 74 % male ● FEV_1: 56.6±16.8 % ● Exercise echo sPAP: 47±7.5 mmHg	Pravastatin 40 mg daily x 6 mos NOT was permitted (n=2)	Outcomes in Pravastatin (n=27/32) vs placebo (n= 26/33): ▪ Increased exercise time 660±352 to 1006±316s (p<0.05) vs no change (653±274 to 629±181) ▪ Decreased exercise sPAP 47±8 to 40±6 mmHg (p<0.05) vs no change (47±7 to 46±7) ▪ Decreased exercise BDI 6.7±1.0 to 3.9±0.7 (p<0.05) vs no change (6.9±0.9 to 6.8±1.2)	None reported. N=2 discontinued pravastatin (no reason mentioned)
Reed 2011[49]	Retrospective, non - randomized cohort	N=112/259 evaluated for lung transplant who had hemodynamics: Statin user (n=34/112) vs non-statin user (n=78/112) Inclusion criteria:	Atorvastatin (53%), Simvastatin (35%)	Outcomes in Statin vs non-statin: ● Lower mPAP independent of PAWP (p=0.03; multiple regression analysis)	

		– mPAP ≥20 mmHg (92%), and 66% had PAWP ≤15 mmHg ● Age: 58±6 vs 55±9 yrs (SD) ● Gender: 41 % male ● FEV1: 21±8 % ● 6MWD: 249 ±111 m (n=60) ● mPAP: 26±7 vs 29±7 mmHg ● PAWP: 12±6 vs 15±5 mmHg	(90% on LTOT)	● Lower PAWP (p<0.001; multiple regression analysis)	
Moosavi 2013[45]	RCT	N=45: Atorvastatin (n=24) vs placebo (n=21) Inclusion criteria: – Age: > 18 years – FEV1 <80% AND FEV1/FVC <70% – mNYHA FC 2 or 3 – Echo sPAP >40 mmHg ● Age: 66.4±12.4 yrs (SD) ● Gender: 62 % male ● FEV1: 43.7±19.5 % ● 6MWD: 259.5±112.8 m ● sPAP: 49.1±9 mmHg	Atorvastatin 20 mg BID x 6 mos	Outcomes in Atorvastatin (n=19/24) vs placebo (n=17/21): ● No difference in sPAP, CO, Echo RV size, 6MWD, spirometry	None

Liu 2013[46]	RCT	N=68: Atorvastatin (n=33) vs standard COPD treatment (n=35) Inclusion criteria: - Age 60-85 yrs - FEV1 ≤65% and FEV1/FVC ≤70% - mNYHA FC 1 or 2 - Echo sPAP >30 mmHg ● Age: 65.5±7.8 yrs (SD) ● Gender: 63% male ● sPAP: 52.2±8 mmHg	Atorvastatin 20 mg daily x 6 mos. Note: All study participants used LTOT	Outcomes in Atorvastatin vs control: ● Decreased sPAP 52.7±8.1 to 45.4±6.8) vs no change (51.7±7.9 to 49.1±7.3)	None
Chogtu 2016[47]	RCT	N=62: Rosuvastatin (n=32) vs placebo (n=30) Inclusion criteria: - Age 40-80 yrs - Echo sPAP >30 AND <75 mmHg ● Age: 61.4±8.4 vs 65.9±9.7 yrs (SD)	Rosuvastatin 10 mg daily X 12 wks. Note: Background sildenafil treatment (n=3 in each group)	Outcomes in Rosuvastatin (n=30) vs placebo (n=30): ● Decreased placebo-corrected sPAP (3mmHg; p=0.07) ● No difference in placebo-corrected RV myocardial tissue systolic and diastolic motion velocities ● Increased 6MWD by 25.1 m (p=0.033) ● No difference in BDI ● No difference in HRQoL (Clinical COPD Questionnaire)	Rosuvastatin: n=5 elevated AST at 3 mos which reversed after discontinuation. N=2 muscle pain / elevated CK at 3 mos, reversed after discontinuation.

Arian 2017[48]	RCT	N=42: Atorvastatin (n=21) vs undefined control (n=21) Inclusion criteria: – Echo sPAP >25 mmHg ● Age: 64.7±9.4 yrs (SD) ● Gender: 32% male ● sPAP: 48.6±15.9 mmHg	Atorvastatin 40 mg daily x 6 mos. None of the patients on LTOT	Outcomes in Atorvastatin (n=16/21) vs control (n=18/21): ● Change in sPAP (-10.4, 95%CI: -3.2, -17.7) vs no change (-6.7, 95 %CI: -14.2, +0.7); placebo-corrected change in sPAP -3.7 mmHg (p=0.008)	No "major" (not defined) side effects observed. No drug discontinuation due to side effects.

Data are mean±SEM unless otherwise specified
Abbreviations: AST, aspartate aminotransferase; BDI, Borg dyspnea index; CK, creatine kinase; FEV1/FVC, ratio of forced expiratory volume in first second to forced vital capacity; mNYHA FC, modified New York Heart Association Functional Class; PAWP, pulmonary arterial wedge pressure; HRQoL, health-related quality of life; RV; right ventricle.

Supplementary Table 4. Effects of Miscellaneous therapies in patients with COPD-PH .

Study	Design	Population	intervention	Significant Outcomes	adverse Effects
Nenci 1988[53]	Cross-over, RCT	n=11 Inclusion criteria: – FEV_1 <60% – PaO_2 <60 mmHg – RHC sPAP >30 and dPAP >15 mmHg ● FEV1: 36.3±11.8 % (SD) ● paO2: 51.6±7.4 mmHg ● sPAP 52.2±9.7 mmHg	Dipyridamole 100 mg po QID + NAC 100 mg po QID vs NAC alone x 3 mos LTOT was not permitted in the study observational period.	Outcomes with Dipyridamole + NAC vs NAC (N=8/11): ▪ Lower RHC sPAP 46.8±16 vs 56.1±14 mmHg (p<0.05)	n=3 withdrew (AECOPD)
Pison 1991[55]	Case series	n=11 Inclusion criteria: – Resting PaO2 <60 mmHg – RHC mPAP >20 mmHg ● Age: 64±6 yrs (SD) ● Gender: 91% male ● FEV_1: 0.90±0.28 L ● PaO2: 54±6 mmHg ● mPAP: 25±6 mmHg	Captopril 12.5 mg po TID x 8 wks. Note: All subjects on LTOT	Outcomes in n=9/11 who had repeat RHC at 8 weeks: ● Decreased resting mPAP from 25±6 to 22±7 mmHg (p<0.05) ● Decreased exercise mPAP from 56±16 to 50±16 mmHg (p<0.05) ● No difference in resting or exercise CI or PaO_2	None reported
Saadjian 1998[54]	RCT	N=23 cicletanine (n=11) vs placebo (n=12) Inclusion criteria: – RHC mPAP ≥20 mmHg	Cicletanine 50 mg daily x 12 mos	Outcomes in cicletanine (n=9/11) vs placebo (n=10/12): ▪ Decreased mPAP 22±1.5 vs 29±2.5 (p<0.02)	None reported

		– FEV1/FVC <70% ● Age: 62.5±2 yrs ● Gender: 100% male ● FEV_1: 1.09±0.20 L ● PaO_2: 62±3 mmHg ● mPAP: 29±2 mmHg	Note: n=6 cicletanine and n=7 placebo on LTOT >15 hrs/d	▪ Increased CI 3.2±0.2 vs 2.7±0.1 L/min/m^2 ($p<0.05$) ▪ Decreased PVR ($p<0.05$) ▪ Decreased PaO2 at 3 and 12 mos ($p<0.05$) vs no change; not significant vs placebo	
Schonhofer 2001[50]	Case series	n=13/31 provided consent Inclusion criteria: ● FEV_1 <1 L AND FEV_1/FVC <0.5 ● Age: 50.7±8.2 yrs (SD) ● Gender: 92 % male ● FEV1: 0.85±0.32 L ● PaO_2: 46±6 mmHg ● $PaCO_2$: 60.0±7.5 mmHg ● RHC mPAP: 25.3±6 mmHg	Nocturnal mechanical ventilation ± LTOT if hypoxemic x 1 yr (mean O2 use 15.2 hrs/d)	Outcomes ▪ No change in mPAP, PVRI	None reported
Vonbank 2003[57]	RCT	N=40: LTOT+NO (n=20) vs LTOT alone (n=20) Inclusion criteria: – RHC mPAP >25 mmHg – LTOT >15 hrs/d x >6 mos ● Age: 61.6±8.15 yrs (SD) ● Gender: 67.5 % male ● FEV_1: 1.2±0.6 L ● mPAP: 26±5.1 mmHg	Pulsed LTOT+NO (20 ppm) vs LTOT alone x 3 mos	Outcomes in LTOT+NO (n=15/20) vs LTOT alone (n=17/20): ● Decreased mPAP 27.6±4.4 to 20.6±4.9 mmHg vs no change ($p<0.001$) ● Decreased PVR ($p=0.001$) ● Increased CO 5.6±1.3 to 6.1±1.0 L/min vs no change ($p=0.025$) ● Improved physical performance score in 38.5% vs 12.5% of subjects ($p=0.047$) ● No difference in PaO_2	N=8 withdrawn (AECOPD, non-compliance, undetected CAD)

Morrell 2005[51]	RCT	N=40: losartan (n=20) vs placebo (n=20) Inclusion criteria: - Age: 50-80 yrs - FEV1/FVC ratio ≤ 70% - Echo TTPG ≥30 mmHg ● Age: 67±7.8 yrs (SD) ● Gender: 47.5% Male ● FEV_1: 35±16.5% ● TTPG 43.1±9.3 mmHg	Losartan 25 mg PO daily x 1 wk then 50 mg PO daily x 12 mos	Outcomes in losartan (n=12/20) vs placebo(n=15/20) ● No difference in TRvel, TTPG, RAP ● No difference in RV wall thickness ● No difference in SGRQ scores (symptoms) or exercise capacity	N=2 withdrew losartan due to (nausea, rash, hypotension) N=5 withdrew placebo due to (rash, hypotension, dizziness, tremor)
Umehara 2008[58]	Case series	N=13 Inclusion criteria: - FEV1/FVC <0.7 - MRC 4-5/5 despite conventional therapy ● Age: 75 yrs ● Gender: 100% male ● FEV_1: 39.0±13.8 % (SD) ● Echo sPAP: 41±8.3 mmHg	Waon therapy (far infrared-ray sauna at 60°C for 15 min, then bed rest with warm blanket x30 min) daily, 5 d/wk x 4 wks	Outcomes: ▪ No change in Echo sPAP ▪ Decreased exercise sPAP 64±18.0 to 51.3±13.1 mmHg (p=0.028) ▪ Increased exercise time 359.6±106.5 to 391.5±97.0 sec (p=0.032) ▪ Increased nadir SpO2 during exercise 89±5 to 91±4% (p=0.022) ▪ Decreased SGRQ scores including total score (p=0.002), symptoms (p=0.007), impact (p=0.024)	None reported
Martiniuc 2012[56]	Case series	N=111 Inclusion criteria:	Enalapril 10-40 mg daily (n=61),	Outcomes: Echo sPAP ● improved 46.3±3.3 to 32.1±2.6 (p<0.01) with enalapril	None reported

		– Moderate COPD (FEV1 50 - 80%) – Associated with systemic hypertension and NYHA class 1 or 2 LV failure ● Age: 47.5±2.2 yrs ● Gender: 54% male ● Echo sPAP: 43.6±2.7 mmHg (variance not defined)	fosinopril 5-10 mg daily (n=26), or moexipril 7.5 mg daily (n=24) for 8 weeks	● improved 42.1±1.1 to 28.2±0.8 ($p<0.05$) with moexipril ● improved 38.3±3.1 to 27.1±2.6 ($p<0.01$) with fosinopril	
Fallahi 2013[52]	RCT	N=28: Pentoxifylline (n=15) vs placebo (n=13) inclusion criteria: – FEV1 <50% – Echo SPAP >40 mmHg ● Age: 65.5±10.3 yrs (SD) ● Gender: 75 % male ● FEV1: 962.1±266.1 ml ● sPAP: 48.3±6.9 mmHg ● 6MWD: 340.8±71.9 m ● SpO2: 87.5±3.5 %	Pentoxifylline: 400 mg three times daily or 200 mg for patients also receiving Theophylline. x 12 weeks	Outcomes in Pentoxifylline (n=10/15) vs placebo (n=10/13) at 12 weeks. ● 6MWD increased by 41m in Pentoxifylline vs 25 m in placebo group (p=0.142) ● No difference in resting oxygen saturation (p=676) ● No difference in baseline and exercise BDI	N=3 withdraw Pentoxifylline due to gastrointestinal upset

Wang 2017[59]	RCT	N=86: azithromycin (n=43) vs placebo (n=43) Inclusion criteria: – RHC: mPAP ≥20 mmHg at rest and mPAP ≥30 mmHg on exercise ● Age: 71.5±8.21 yrs (SD) ● Gender: 59 % male ● FEV1: 0.67±0.1 L ● 6MWD: 254.5±42.3 m ● PaO2: 40.34±3.1 mmHg ● sPAP at rest: 36.7±0.8 mmHg	azithromycin 250 mg daily and simvastatin 20 mg daily vs simvastatin 20 mg daily alone x 6 mos. Note: All patients on LTOT	Outcomes with azithromycin+simvastatin vs simvastatin alone: ● RHC sPAP decreased 36.7±0.7 to 35.4±0.6 mmHg ($p<0.05$) vs no change ● Greater increase in 6MWD 251±34 to 380±31 vs 257±50 to 302±30 m ($p<0.05$) ● Greater increase in PaO_2 ($p<0.05$) ● Greater decrease in $PaCO_2$ ($p<0.05$)	None reported

Data are mean±SEM unless otherwise specified
Abbreviations: AECOPD, acute exacerbation of COPD; dPAP, diastolic pulmonary artery pressure; QID, four times a day; RAP, right atrial pressure; TRvel, tricuspid regurgitation velocity; TTPG, trans-tricuspid pulmonary gradient.

Supplementary Table 5. Risk of bias assessment using the Cochrane Collaboration tool for RCTs.

	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias		
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall assessment
COPD-PH diagnosed by RHC								
(NOTT) 1980	low	low	low	low	low	low	-	low
MRC 1981	low	unclear	low	low	low	high	-	high
Fletcher 1992	low	unclear	low	low	high	low	-	high
Chaouat 1999	low	unclear	unclear	low	low	low	-	unclear
Vestri 1988	unclear	unclear	unclear	unclear	low	low	-	unclear
Saadjian 1988	unclear	unclear	unclear	unclear	low	low	-	unclear
Valerio 2009	unclear	unclear	high	high	low	low	-	high
Saadjian 1998	unclear	unclear	low	low	low	low	-	unclear
Vonbank 2003	low	low	low	low	low	low	-	low
Vitulo 2016	low	low	low	low	low	low	-	low
Wang 2017	unclear	unclear	unclear	unclear	unclear	unclear	-	unclear
COPD-PH diagnosed by echo								
Morrell 2005	unclear	unclear	low	low	high	low	-	high
Stolz 2008	low	low	low	low	low	low	-	low
Lee 2009	low	low	low	low	low	low	-	low
Rao 2011	low	low	low	low	low	unclear	-	unclear
Fallahi 2012	low	unclear	low	low	unclear	unclear	-	unclear
Blanco 2013	low	low	low	low	low	low	-	low
Moosavi 2013	low	low	low	low	low	unclear	-	unclear
Liu 2013	unclear	unclear	unclear	unclear	unclear	unclear	-	unclear
Goudie 2014	low	low	low	low	low	low	-	low
Chogtu 2016	unclear	low	low	low	low	unclear	-	unclear
Shrestha 2017	low	low	low	high	unclear	unclear	-	high
Arian 2017	low	low	low	low	unclear	unclear	-	unclear

Supplementary Table 6. Risk of bias assessment using the **Newcastle-*Ottawa* scale for cohort studies.**

Study/study type	Selection				Comparability		Outcome			Total score
	Representativeness of the exposed (treated) COPD-PH cohort	Selection of the non-exposed Cohort	Ascertainment of exposure (treatment)	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts (demographic)	Comparability of cohorts (other factors)	Assessment of outcome	Length of follow-up: 6 MONTHS	Adequacy of follow-up / drop-out rate	
COPD-PH diagnosed by RHC										
Stark 1972	★			★			★		★	4
Gluskowski 1983	★			★			★		★	4
Weitzenblum 1985	★		★	★			★	★	★	6
Timms 1985	★		★	★			★	★	★	6
Cooper 1987	★		★	★			★	★	★	6
Zielinski 1998	★		★	★			★	★	★	6
Bratel 1990	★		★	★			★		★	5
Pison 1991	★		★	★			★		★	5
Agostoni 1989	★		★	★			★		★	5
Schonhofer 2001	★		★	★			★	★	★	6
Reed 2011		★		★	★	★	★			5
Badesch 2012	★		★	★			★	★		5
Hurdman 2013	★	★		★			★		★	5
Fossati 2014	★			★			★	★		4
Lange 2014	★			★	★	★	★	★		5
Girard 2015	★			★			★	★	★	5
Brewis 2015	★			★	★	★	★		★	6
Tanabe 2015	★			★			★	★	★	5
Calcaianu 2016	★			★			★	★		4
COPD-PH diagnosed by echo.										
Sajkov 1993	★			★			★		★	4
Umehara 2008	★		★	★			★		★	5
Martiniuc 2012	★			★			★			3
Alkhayat2016	★	★		★			★			4