



Systematic Review

Pulmonary Vasodilators in COPD-Associated Pulmonary Hypertension: An Updated Meta-Analysis of Randomized Evidence

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Abstract

Background: Pulmonary hypertension (PH) is a common complication of chronic obstructive pulmonary disease (COPD), termed COPD-associated pulmonary hypertension (COPD-PH), and is associated with worse clinical outcomes. The efficacy and safety of pulmonary vasodilators in COPD-PH remain uncertain. **Methods:** We performed a systematic review and meta-analysis of randomized studies evaluating pulmonary vasodilators in adults with COPD-PH. Fifteen studies were identified, with 11 contributing to quantitative analyses. Outcomes included six-minute walk distance (6MWD), mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR), partial pressure of arterial oxygen (PaO₂), and systolic pulmonary arterial pressure (sPAP). **Results:** Pulmonary vasodilators significantly reduced mPAP (MD −3.88 mmHg, 95% CI −7.23 to −0.53) and PVR (SMD −0.90, 95% CI −1.70 to −0.10). However, no significant improvements were observed in 6MWD or PaO₂. An exploratory composite hemodynamic score supported an overall hemodynamic benefit. Subgroup analyses suggested a more favorable profile for nitric oxide donors, whereas endothelin receptor antagonists were associated with worsened oxygenation. **Conclusions:** Pulmonary vasodilators improve pulmonary hemodynamics in COPD-PH but do not consistently improve exercise capacity or oxygenation. Current evidence does not support routine use outside specialized centers or clinical trials, and treatment effects appear to vary by drug class.

Keywords: chronic obstructive pulmonary disease; pulmonary hypertension; pulmonary vasodilators; meta-analysis; sildenafil; mean pulmonary arterial pressure; six-minute walk distance; endothelin receptor antagonist; nitric oxide; phosphodiesterase-5 inhibitor



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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major global cause of morbidity, mortality, and healthcare expenditure, affecting an estimated 300 million people worldwide and responsible for approximately 3.2 million deaths annually [1,2]. Its cardinal pathophysiological features, chronic airflow limitation, mucus hypersecretion, small-airway remodeling, and alveolar destruction, are accompanied by systemic consequences that extend well beyond the lung parenchyma. Among these, pulmonary hypertension (PH) occupies a position of particular clinical importance; when it arises in the context of COPD, it is termed COPD-associated pulmonary hypertension (COPD-PH) and is defined by most included studies using historical criteria, typically $\text{mPAP} \geq 25$ mmHg by right heart catheterization or elevated echocardiographic estimates. PH develops in an estimated 20–35% of patients with moderate-to-severe COPD and correlates inversely with exercise tolerance, health-related quality of life, and survival. Notably, even modestly elevated pulmonary pressures, falling below the formal diagnostic threshold, are associated with excess hospitalizations and accelerated functional decline, underscoring the clinical and prognostic importance of vascular involvement in this disease [3,4].

The pathogenesis of COPD-associated PH is multifactorial. Chronic alveolar hypoxia drives hypoxic pulmonary vasoconstriction and stimulates vascular smooth muscle hypertrophy and intimal remodeling [5,6]. Endothelial dysfunction, characterized by impaired nitric oxide (NO) synthesis and upregulation of vasoconstrictive mediators such as endothelin-1 and thromboxane A_2 , further promotes vascular remodeling and increased pulmonary vascular resistance (PVR) [5,6]. These mechanisms share broad mechanistic similarities with pulmonary arterial hypertension (PAH), the condition for which the four major classes of pulmonary vasodilators were developed: PDE5 inhibitors (sildenafil, tadalafil), NO donors (inhaled nitric oxide), prostanoids (iloprost, epoprostenol), and ERAs (bosentan, ambrisentan). This mechanistic overlap provides the rationale for their repurposing in COPD-PH. The hemodynamic plausibility of PDE5 inhibition has been substantiated by dose-ranging physiological studies, including Blanco et al. [7] who demonstrated dose-dependent reductions in mPAP and PVR with sildenafil using right heart catheterization at rest and during exercise—providing mechanistic proof-of-concept for this class even in the absence of a placebo-controlled comparator in that study [8,9].

Each vasodilator class targets a distinct node in this pathway. PDE5 inhibitors (sildenafil, tadalafil) prolong the vasodilatory action of endogenous nitric oxide by blocking cGMP degradation, and are the most extensively studied class in COPD-PH. NO donors (inhaled nitric oxide) directly supply the vasodilatory mediator whose endogenous synthesis is impaired by endothelial dysfunction, with the theoretical advantage of preferentially reaching ventilated alveoli. Prostanoids (iloprost, epoprostenol, treprostinil) act through the prostacyclin pathway to induce smooth muscle relaxation and inhibit vascular remodeling, but lack the ventilation-selectivity of inhaled NO, which may explain the safety signal described in the Discussion. ERAs (bosentan, ambrisentan) block endothelin-1, a vasoconstrictive mediator upregulated in COPD-PH, but act non-selectively across the pulmonary vasculature, including poorly ventilated regions, providing a mechanistic basis for the oxygenation risk observed with this class.

However, COPD-PH differs fundamentally from PAH in ways that may limit the translatability of efficacy data. In COPD, hypoxic pulmonary vasoconstriction, while contributing to elevated pressures, serves an adaptive role in directing blood flow away from poorly ventilated alveoli, thereby optimizing ventilation–perfusion (V/Q) matching. Non-selective pulmonary vasodilation risks disrupting this mechanism, redistributing blood to poorly ventilated lung units, and worsening arterial oxygenation. Furthermore, the elevated right ventricular afterload in COPD-PH is generally modest compared with

PAH; hemodynamic improvements, even if genuine, may not be sufficient to overcome the ventilatory and musculoskeletal determinants of exercise limitation that dominate in COPD [7,10–15].

Prior systematic reviews and meta-analyses of vasodilators in COPD-PH have been constrained by small evidence bases, narrow outcome selection, and an absence of drug-class-stratified analyses. The most recent comprehensive synthesis predates several important trials, including the TADA-PH study (Maron et al., 2022) [16] and the SPHERIC-1 trial (Vitulo et al., 2017) [13]. The present study addresses these gaps with an updated systematic review incorporating 15 trials across 6MWD, mPAP, PVR, PaO₂, sPAP, and a novel composite hemodynamic z-score, with drug-class-stratified subgroup analyses conducted for all primary outcomes [7,12–24].

2. Materials and Methods

2.1. Protocol and Registration

This systematic review and meta-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Figure 1 and Supplementary File S1) [11]. The review protocol was registered on PROSPERO (CRD420261324168, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=1324168, accessed on 30 April 2026) before data extraction (Supplementary File S2) [25]. Two refinements were made after registration and are reported here per PRISMA 2020 item 24c. First, the registered protocol specified assessment of risk of bias using ROBINS-I (2016 version); during full-text review we determined that risk of bias for the randomized trials comprising the great majority of the evidence base was more appropriately assessed using the Cochrane Risk of Bias 2 (RoB 2; 2019 revision) tool, with ROBINS-I reserved for the non-randomized studies retained for narrative synthesis. Second, the registered protocol specified inclusion of randomized study types only; one non-randomized trial (Valerio et al., 2009 [22]) was subsequently retained for narrative synthesis and sensitivity evaluation only, and did not contribute to quantitative pooling, in order to provide fuller context on bosentan's effects in COPD-PH given the paucity of ERA trials in this population.

2.2. Eligibility Criteria

Studies were eligible for quantitative pooling if they were randomized parallel-group or crossover trials in adults with confirmed COPD and co-existing PH (mPAP $\geq$ 25 mmHg by right heart catheterization or sPAP $\geq$ 35 mmHg by echocardiography), comparing any pulmonary vasodilator against placebo, sham, or usual care, and reporting at least one pre-specified outcome. Single-arm studies, dose-comparison studies without a placebo or standard-care control arm, and randomized trials in which control arm outcome data were not reported in a form permitting computation of between-group effect sizes were excluded from primary pooling but retained for sensitivity evaluation or narrative synthesis where appropriate. Studies enrolling subjects with PAH, pulmonary embolism, or heart failure as the primary diagnosis were excluded.

2.3. Search Strategy

A comprehensive search of PubMed/MEDLINE, Embase, the Cochrane CENTRAL, Scopus and ClinicalTrials.gov was conducted from inception through 12 March 2026 (Supplementary File S3). Search terms combined MeSH headings and free-text keywords for COPD, PH, and vasodilator therapy. Two independent reviewers (I.A.Y) and (I.A) screened titles and abstracts, followed by full-text review; disagreements were resolved by intervention of a third reviewer (M.O).

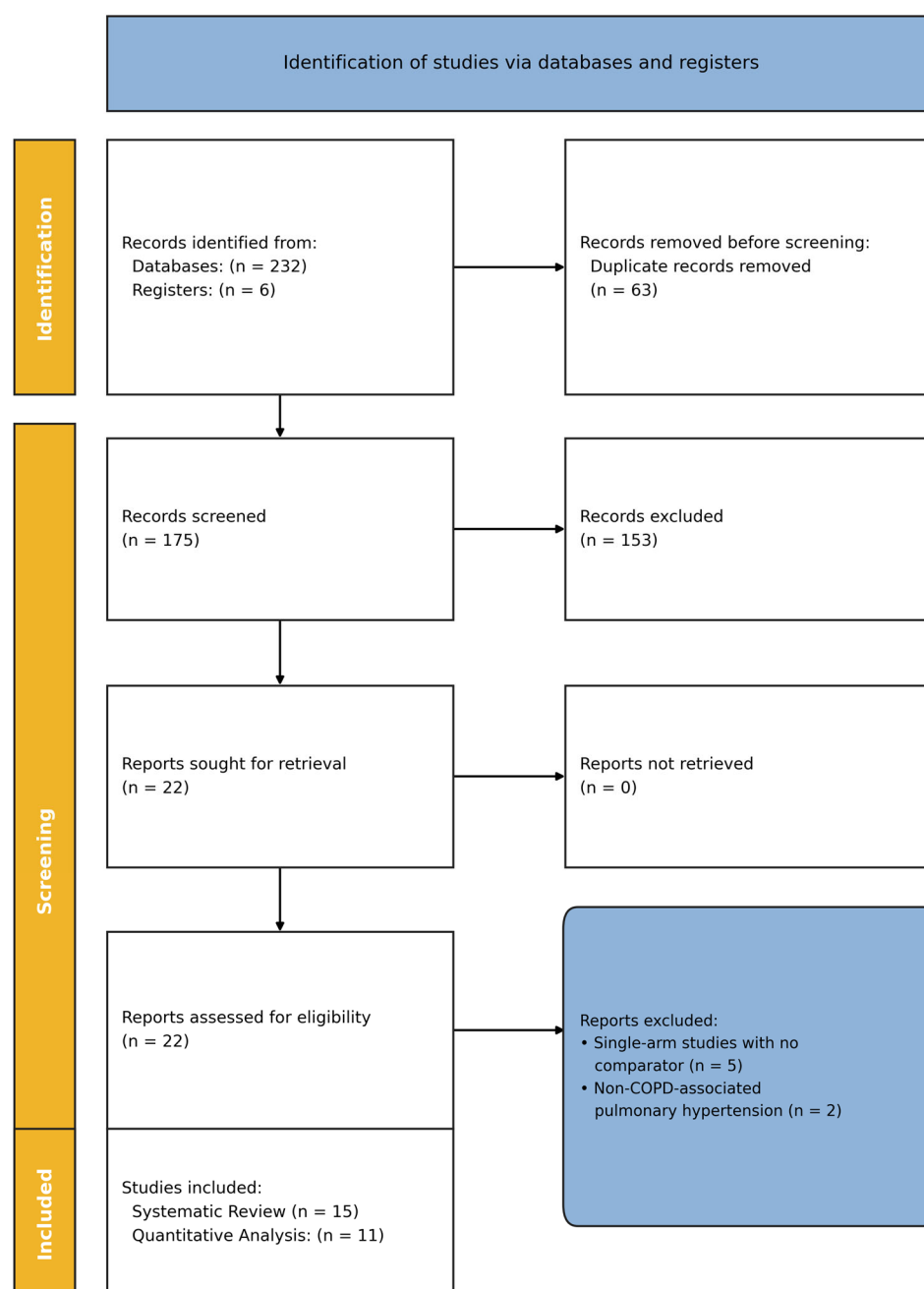


Figure 1. PRISMA Flow Chart.

2.4. Data Extraction and Study Quality

Data extraction was performed in duplicate using a pre-piloted structured form capturing study design, year, intervention, and comparator details, sample sizes, and pre- and post-treatment means and SDs for each outcome. Risk of bias for randomized studies was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. The following domains were evaluated: bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was rated as “low risk,” “some concerns,” or “high risk,” and an overall judgment was assigned according to Cochrane guidance. Risk of bias for the two non-randomized studies retained for narrative synthesis was assessed using the ROBINS-I tool. These non-randomized studies were not included in the quantitative meta-analysis (Figure 2). RoB 2 and ROBINS-I ratings were independently assessed by two reviewers (I.A.Y and I.A.), with discrepancies resolved by a third reviewer (M.O).

Randomized Studies (RoB 2)

	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Blanco et al, 2013						
Boeck et al, 2012						
Goudie et al, 2014						
Lederer et al, 2012						
Maron et al, 2022						
Rao et al, 2011						
Roger et al, 1997						
Shrestha et al, 2017						
Stolz et al, 2008						
Vitulo et al, 2017						
Vonbank et al, 2003						
Nathan et al, 2024						

Domains:

D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement

 High risk
 Some concerns
 Low risk

Non-randomized Studies (ROBINS-I)

	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Rietema et al, 2008								
Valerio et al, 2009								

Domains:

D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement

 Serious
 Moderate
 Low

Figure 2. Risk of bias assessment [12–24,26].**2.5. Outcomes**

Primary outcomes were 6MWD, mPAP, PVR, PaO₂, and sPAP. A pre-specified exploratory composite hemodynamic z-score was computed as a supportive summary measure integrating mPAP, PVR, and sPAP. For each study contributing to the mPAP, PVR, or sPAP pooled analyses, a standardized effect size (z) was calculated as the study's observed effect estimate divided by its standard error. For each study, the available standardized values across the three hemodynamic outcomes were averaged, weighted by inverse variance, to produce a single per-study composite z-score; these per-study composite scores were then pooled using the same REML random-effects model used for the primary outcomes. A negative composite z-score denotes overall hemodynamic improvement favoring vasodilator therapy.

2.6. Statistical Analysis

All primary analyses used restricted maximum-likelihood (REML) random-effects models with inverse-variance weighting, implemented in R (version 4.3.1) using the *meta* and *metafor* packages. Continuous outcomes were expressed as mean differences (MD) for outcomes on a common scale, and standardized mean differences (SMD) for PVR due to unit heterogeneity. For crossover trials, within-subject variance was estimated using the method described by Follmann et al., [27] assuming a within-pair correlation of $\rho = 0.50$ as the primary assumption; sensitivity analyses explored $\rho = 0.25$ and $\rho = 0.75$. In crossover trials, the total N reported in Table 1 reflects the number of unique participants, not the number of observations per treatment period, consistent with unit-of-analysis recommendations for crossover designs.

Table 1. General characteristics of all included studies.

Study	Year	Intervention	Control	Design	N (I/C)	Total N	Primary Outcomes
Blanco et al., 2010 [7]	2010	Sildenafil 20 mg vs. 40 mg	None (dose comparison)	Parallel RCT	11/9	20	mPAP, PVR, PaO ₂
Blanco et al., 2013 [12]	2013	Sildenafil + PR	Placebo + PR	Parallel RCT	29/31	60	6MWD, PaO ₂
Boeck et al., 2012 [13]	2012	Iloprost aerosol	Placebo	Crossover RCT	16 (X-over)	16	6MWD
Goudie et al., 2014 [14]	2014	Tadalafil	Placebo	Parallel RCT	60/60	120	6MWD, mPAP
Lederer et al., 2012 [15]	2012	Sildenafil	Placebo	Crossover RCT	10/10	10	6MWD, PaO ₂
Maron et al., 2022 [16]	2022	Tadalafil	Placebo	Parallel RCT	28/14	42	6MWD, mPAP
Nathan et al., 2024 (PERFECT) [26]	2024	Inhaled treprostinil (iTRE)	Placebo	Crossover RCT † (early term)	66/58	76	6MWD (safety)
Rao et al., 2011 [17]	2011	Sildenafil	Placebo	Parallel RCT	17/20	37	6MWD, sPAP
Rietema et al., 2008 [18]	2008	Sildenafil	None (single-arm)	Single-arm	15/—	15	6MWD, PVR
Roger et al., 1997 [19]	1997	Inhaled NO	Room air	Crossover RCT	9/9	9	mPAP, PaO ₂
Shrestha et al., 2017 [20]	2017	Sildenafil	Standard therapy	Parallel RCT	36/36	72	6MWD, sPAP
Stolz et al., 2008 [21]	2008	Bosentan	Placebo	Parallel RCT	20/10	30	6MWD, PVR, PaO ₂
Valerio et al., 2009 [22]	2009	Bosentan	Best care support	Non-Randomized Trial	16/16	32	mPAP, PVR, 6MWD
Vitulo et al., 2017 [23]	2017	Sildenafil	Placebo	Parallel RCT	18/10	28	6MWD, mPAP, PVR, PaO ₂
Vonbank et al., 2003 [24]	2003	O ₂ + Nitric oxide	O ₂ alone	Parallel RCT	20/20	40	mPAP, PVR
TOTAL				15 Trials	Pooled: 464/ All included: 607		

PR, RCT, randomized controlled trial; pulmonary rehabilitation; NO, nitric oxide. For crossover trials, N (I/C) and Total N reflect unique randomized participants, not observations per treatment period. Boeck et al. (2012) [13]: N = 16 unique participants in a 2-period crossover (not 2 independent groups). Nathan et al., 2024 (PERFECT) [26]: terminated early for harm; included for contextual completeness; did not contribute to quantitative efficacy pooling. †: crossover trial.

Between-study heterogeneity was quantified using I^2 and Cochran's Q. Publication bias was assessed by visual inspection of funnel plots and Egger's regression test for outcomes with ≥ 10 studies. Baujat plots, leave-one-out sensitivity analyses, bubble meta-regression, cumulative meta-analysis, and radial (Galbraith) plots were used to assess heterogeneity sources and influential studies. Pre-specified subgroup analyses stratified results by drug class (PDE5 inhibitors, NO donors, ERAs, prostanoids). All tests were two-tailed; statistical significance was set at $\alpha = 0.05$.

2.7. Certainty of Evidence

Certainty of evidence for the main pooled outcomes was assessed using the GRADE framework across the domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias. Summary judgments were generated for 6MWD, mPAP, PVR, and PaO₂. GRADE ratings were independently assessed by two reviewers (I.A.Y and I.A), with discrepancies resolved by a third reviewer (M.O). The overall certainty of evidence for each outcome was categorized as high, moderate, low, or very low. Findings are reported in the results section of this study.

3. Results

3.1. Study Selection and Characteristics

In total, 15 trials met final eligibility criteria, of which 11 were included in the quantitative analysis [7,12–24]. Four trials did not contribute to quantitative pooling: one dose-comparison trial without a placebo/control arm (Blanco et al., 2010 [7]), one single-arm trial (Rietema et al., 2008 [18]), one non-randomized trial (Valerio et al., 2009 [22]), and one trial terminated early for safety (PERFECT; Nathan et al., 2024 [26]); these are retained for narrative synthesis or sensitivity evaluation as detailed below. The PERFECT trial, a Phase 3 randomized, double-blind, placebo-controlled crossover study of inhaled treprostinil in patients with PH-COPD, was terminated early by the data and safety monitoring committee due to excess serious adverse events. A full efficacy analysis was not possible, and PERFECT does not contribute to quantitative efficacy pooling. Its safety findings are described narratively. Formal risk-of-bias rating (Figure 2) was performed for 14 of the 15 trials; Blanco et al. (2010) [7] was excluded because its dose-comparison design without a placebo or standard-care control arm precludes assessment of the between-group bias domains defined by RoB 2. Characteristics of all included studies are summarized in Table 1.

The 15 trials enrolled 607 subjects across intervention and control arms. A total of 464 subjects were enrolled across the 11 trials contributing to quantitative efficacy pooling. Trials were published between 1997 and 2022. Sample sizes in the pooled trials ranged from 9 to 120 subjects. Follow-up ranged from a single acute session to 12 months, with most trials employing treatment periods of 8–16 weeks. Seven trials used a parallel-group design; four were crossover. Of the trials included in the quantitative analysis, the most studied drug class was PDE5 inhibitors (7 trials), followed by NO donors (2 trials), ERAs (1 trial), and prostanoids (1 trial).

3.2. Summary of Pooled Effects

An overview of pooled effect sizes and heterogeneity is presented in Table 2. The summary plot confirms statistically significant reductions in mPAP and PVR with vasodilator therapy, while 6MWD, PaO₂, and sPAP did not reach significance. The composite hemodynamic z-score provides an overall confirmatory hemodynamic signal.

Table 2. Summary of pooled meta-analysis results.

Outcome	Studies (n)	Total N	Pooled Effect (95% CI)	pValue	I ² (%)
6MWD	10	424	MD +10.09 m (−12.95 to +33.13)	p = 0.43	8.3
mPAP	5	239	MD −3.88 mmHg (−7.23 to −0.53)	p = 0.02	36.1
PVR (SMD)	3	98	SMD −0.90 (−1.70 to −0.10)	p = 0.03	0
PaO ₂	5	137	MD +2.10 mmHg (−4.91 to +9.11)	p = 0.56	44.7
sPAP	2	109	Descriptive only	—	0
Composite z-score	8	378	z −0.61 (−0.88 to −0.34)	p < 0.001	—

MD, mean difference; SMD, standardized mean difference; 6MWD, six-minute walk distance; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; PaO₂, partial pressure of arterial oxygen; sPAP, systolic pulmonary arterial pressure.

3.3. GRADE Certainty of Evidence

GRADE assessment showed moderate certainty for 6MWD because the evidence was downgraded for imprecision despite low inconsistency; moderate certainty for mPAP, downgraded from high for imprecision because the 95% CI (-7.23 to -0.53 mmHg) spans a range from a large treatment effect to one approaching the threshold of trivial clinical importance; low certainty for PVR, downgraded for very serious imprecision given only three contributing studies and a 95% CI spanning a similarly wide range of clinical importance (-1.70 to -0.10); low certainty for PaO₂ due to concerns regarding inconsistency and imprecision; and low certainty for the composite hemodynamic z-score, downgraded for indirectness, as it is an exploratory, non-validated summary measure combining variables of different physiological meaning, and for imprecision. Overall, the certainty profile indicates that confidence in the individual hemodynamic outcomes is only moderate-to-low even where point estimates are directionally consistent, and confidence in functional and oxygenation outcomes remains limited (Table 3).

Table 3. GRADE Certainty of Evidence Table.

Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty
Six-Minute Walk Distance (6MWD)	Not serious	Not serious	Not serious	Serious	Undetected	Moderate
Mean Pulmonary Arterial Pressure (mPAP)	Not serious	Not serious	Not serious	Serious	Undetected	Moderate
Pulmonary Vascular Resistance (PVR)	Not serious	Not serious	Not serious	Very serious	Undetected	Low
Partial Pressure of Arterial Oxygen (PaO ₂)	Not serious	Serious	Not serious	Serious	Undetected	Low
Composite Hemodynamic Z-Score	Not serious	Not serious	Serious	Serious	Undetected	Low

3.4. Six-Minute Walk Distance

Ten trials contributed 6MWD data (Figure 3) [12–17,19–21,23]. The pooled mean difference favored pulmonary vasodilator therapy numerically but did not reach statistical significance (MD +10.09 m, 95% CI -12.95 to $+33.13$; $p = 0.43$; $I^2 = 8.3\%$). Importantly, the magnitude of improvement was well below the accepted minimum clinically important difference (MCID) of approximately 20 m, indicating that the observed effect is unlikely to represent a meaningful functional benefit. The very low heterogeneity suggests that this null finding was consistent across studies rather than being driven by outliers. Funnel plot inspection showed no evidence of asymmetry, and Egger's test did not indicate small-study effects ($p = 0.49$). Leave-one-out analyses did not materially change the pooled estimate, supporting the robustness of the finding. The PERFECT trial (Nathan et al., 2024 [26]) was not included in the 6MWD pooling: early termination precluded a valid between-group effect size estimate, as the published report did not provide the group-level means and standard deviations required for a poolable mean difference. Its safety findings are discussed separately.

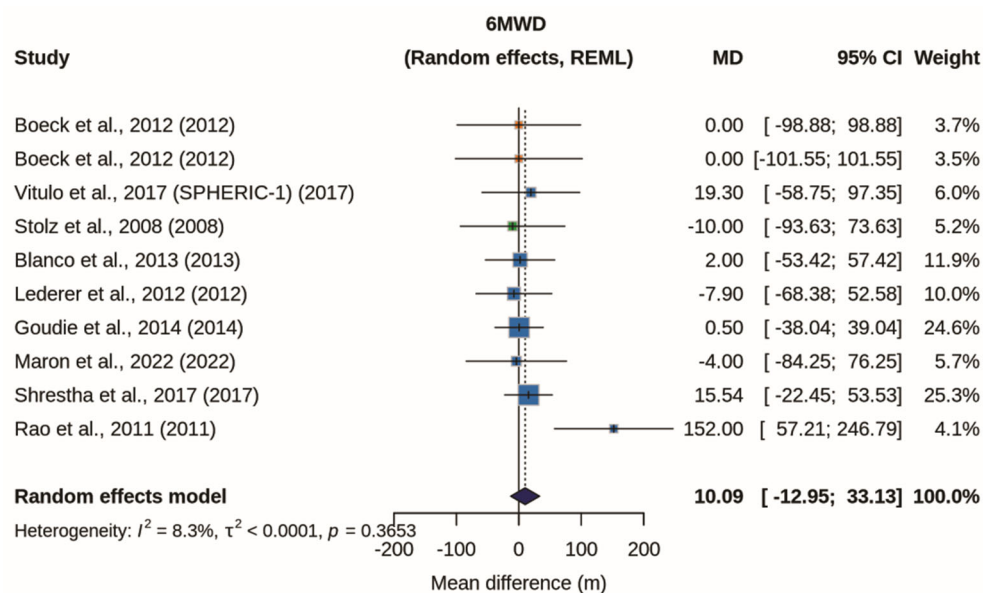


Figure 3. Six-Minute Walk Distance. Forest plot of pooled mean difference in six-minute walk distance (6MWD) with pulmonary vasodilator therapy versus placebo/control [12–17,20,21,23]. Square size is proportional to study weight; square color denotes drug class (blue = phosphodiesterase-5 inhibitors, orange = prostanoids, green = endothelin receptor antagonists). The diamond represents the pooled random-effects estimate.

3.5. Mean Pulmonary Arterial Pressure

Figure 4 presents the Forest Plots for mPAP, PVR and PaO₂. Five trials reported mPAP data [14,16,19,22,24]. Pulmonary vasodilator therapy was associated with a statistically significant reduction in mPAP (MD −3.88 mmHg, 95% CI −7.23 to −0.53; $p = 0.02$; $I^2 = 36.1\%$). Heterogeneity was moderate and largely attributable to Vonbank et al. (2003) [24], which was identified as influential on Baujat and influence analyses. Sensitivity analysis excluding this study attenuated the effect but did not abolish significance (MD −2.91 mmHg, 95% CI −5.48 to −0.34), confirming that the overall result was not dependent on a single study. Cumulative meta-analysis demonstrated early stabilization of the mPAP estimate. Bubble meta-regression showed no significant relationship between baseline mPAP and treatment effect size ($\beta = 0.09$; $p = 0.18$), suggesting that baseline severity did not meaningfully modify treatment response.

3.6. Pulmonary Vascular Resistance

Three trials contributed PVR data [13,21,24]. Due to heterogeneity in measurement units, PVR was pooled using standardized mean differences. Pulmonary vasodilator therapy significantly reduced PVR (SMD −0.90, 95% CI −1.70 to −0.10; $p = 0.03$; $I^2 = 0\%$). The absence of heterogeneity indicates a consistent direction of effect across studies. Leave-one-out analysis excluding Vitulo et al. (2017) [23] yielded a similar estimate (SMD −1.08, 95% CI −1.86 to −0.30), confirming directional stability. Radial plots further demonstrated a consistently negative regression slope, reinforcing the presence of a true pulmonary vascular effect despite the limited number of contributing trials.

3.7. Partial Pressure of Arterial Oxygen

Five trials reported PaO₂ data [7,12,15,19,21]. The pooled mean difference was +2.10 mmHg (95% CI −4.91 to +9.11; $p = 0.56$; $I^2 = 44.7\%$), indicating no significant overall effect of vasodilator therapy on arterial oxygenation. The wide confidence interval reflects uncertainty in the direction and magnitude of effect. Moderate heterogeneity was driven primarily by Stolz et al. (2008) and Blanco et al. (2013) [12,21]. Subgroup analysis revealed impor-

tant class-specific differences: nitric oxide donors showed a directionally favorable effect on PaO₂, whereas endothelin receptor antagonists were associated with a clinically relevant decline (−4.10 mmHg), consistent with potential worsening of ventilation–perfusion matching due to inhibition of hypoxic pulmonary vasoconstriction.

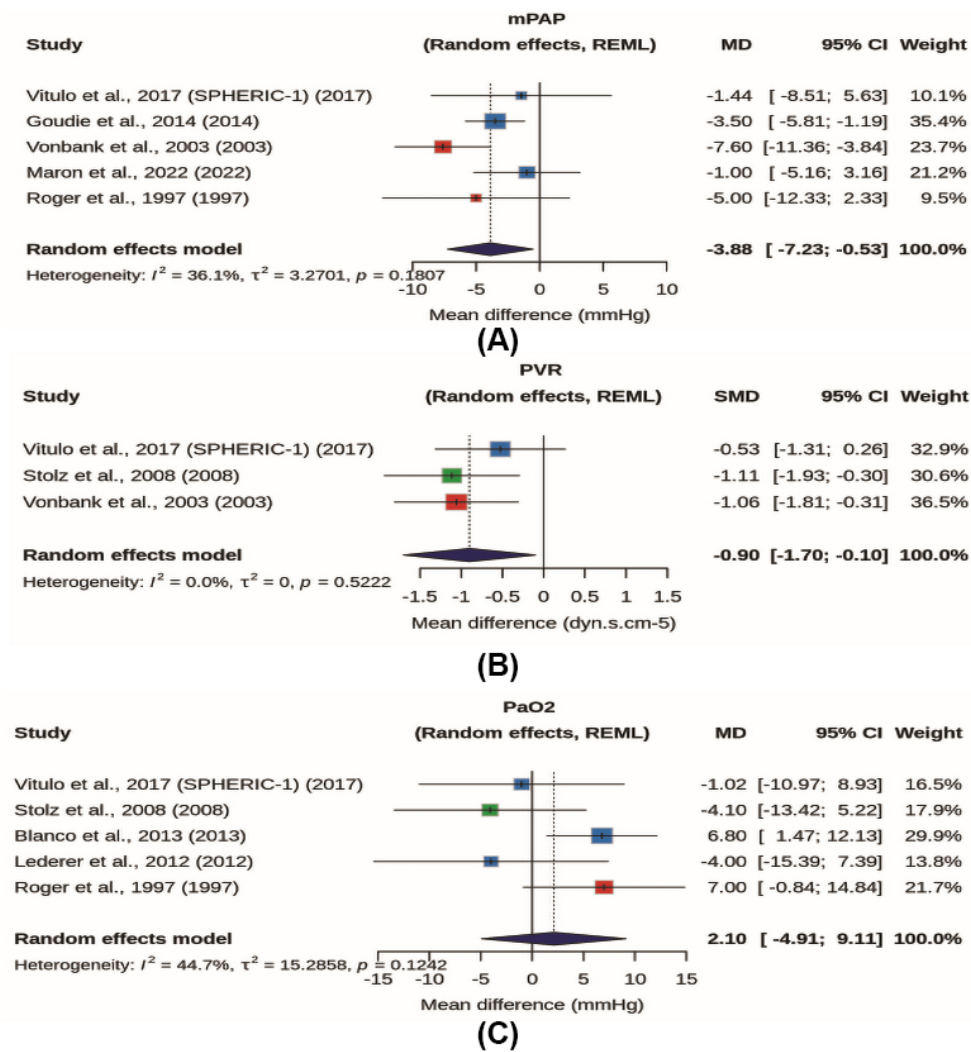


Figure 4. Forest Plots for MPAP, PVR and PaO₂. (A) mean pulmonary arterial pressure (mPAP) [14,16,19,23,24]; (B) pulmonary vascular resistance (PVR) [21,23,24]; (C) partial pressure of arterial oxygen (PaO₂) [12,15,19,21,23]. Square size is proportional to study weight; square color denotes drug class (blue = phosphodiesterase-5 inhibitors, orange = prostanoids, green = endothelin receptor antagonists). The diamond represents the pooled random-effects estimate.

3.8. Composite Hemodynamic Z-Score

Figure 5 presents both the composite hemodynamic score and subgroup analysis of hemodynamic performance stratified by drug class. The pooled estimate demonstrated a statistically significant overall hemodynamic benefit ($z = -0.61$, 95% CI -0.88 to -0.34 ; $p < 0.001$). This composite integrates mPAP, PVR, and sPAP to provide a global assessment of pulmonary vascular response. The consistency of this result with individual hemodynamic outcomes supports the robustness of the physiological signal. However, as an exploratory measure, it should be interpreted as supportive rather than definitive evidence of clinical benefit.

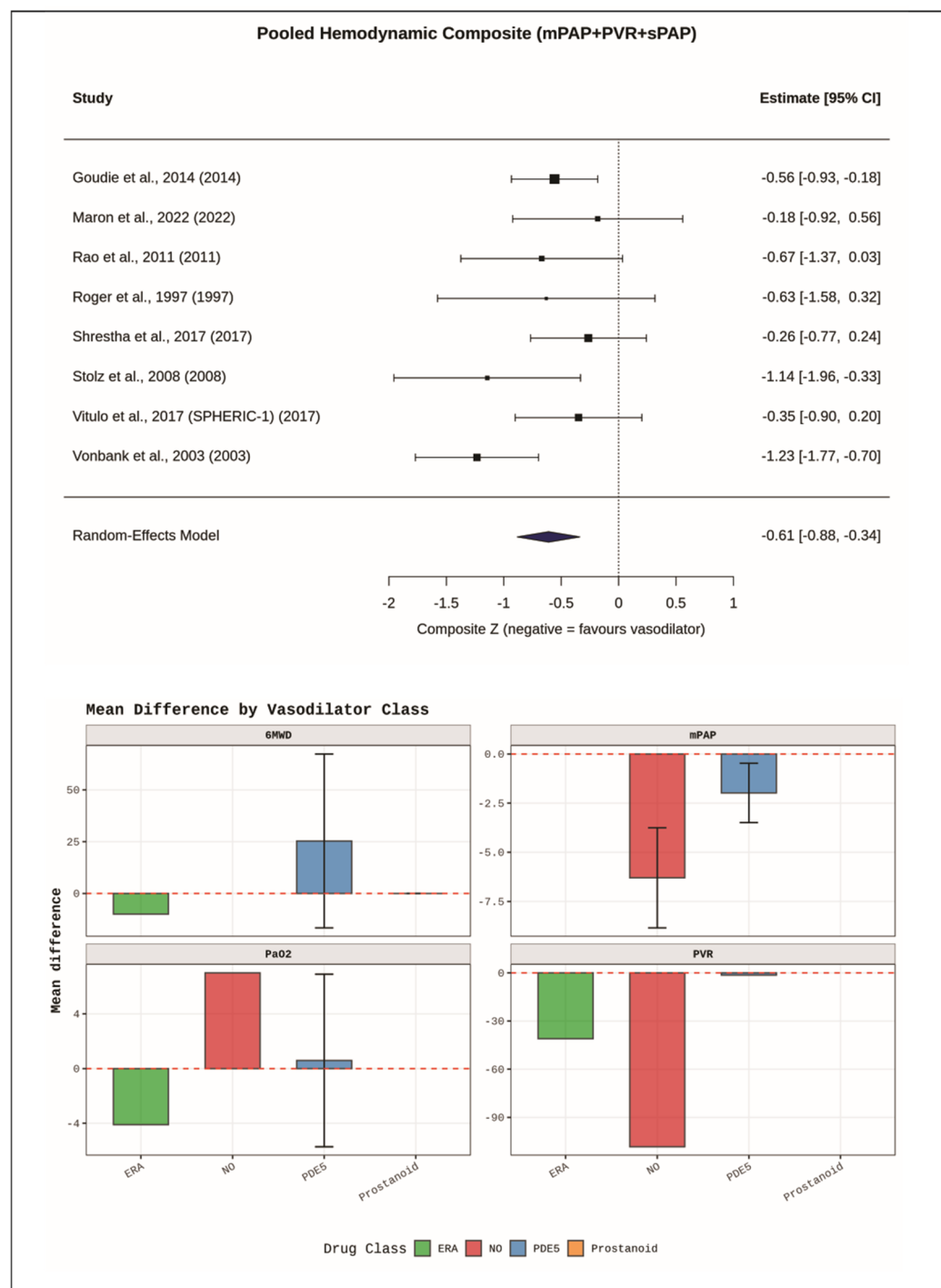


Figure 5. Composite hemodynamic Z-Score and subgroup analysis of hemodynamic performance stratified by class. The composite score aggregates standardized mPAP and PVR effect estimates [14,16,17,19–21,23,24]. Bars are grouped by drug class (phosphodiesterase-5 inhibitors, prostanoids, endothelin receptor antagonists); the dashed line denotes the line of no effect ($Z = 0$).

3.9. Drug Class Subgroup Analyses

PDE5 inhibitors demonstrated modest hemodynamic improvements and a small, non-clinically meaningful increase in 6MWD (~12 m), with a generally neutral effect on oxygenation. Nitric oxide donors showed the most favorable balance, with favorable directional hemodynamic improvement and preserved oxygenation, likely reflecting selective vasodilation of well-ventilated lung units. Endothelin receptor antagonists were associated with worsening oxygenation and minimal functional benefit, raising concerns about their

safety in this population. A single trial represented prostanoids and did not demonstrate a meaningful benefit. These findings suggest that pulmonary vasodilators should not be considered a homogeneous therapeutic class in COPD-associated PH.

3.10. Additional Diagnostics

Baujat and Influence analyses were consistent with primary findings. Baujat plots identified Vonbank et al. (2003) [24] as influential for mPAP and composite outcomes and Vitulo et al. (2017) [23] for PVR, but exclusion of these studies did not alter overall conclusions. Bubble meta-regression showed no significant association between baseline disease severity and treatment effect for any outcome (all $p > 0.10$). Cumulative meta-analysis demonstrated temporal stability for mPAP and PVR effects, whereas 6MWD and PaO₂ estimates fluctuated before converging toward null effects. Sensitivity analyses varying the assumed within-subject correlation for crossover trials ($\rho = 0.25$ to 0.75) did not materially change pooled estimates, supporting the robustness of results across analytic assumptions (Supplementary File S4).

4. Discussion

4.1. Evidence Synthesis

This updated systematic review and meta-analysis of 15 randomized trials yields a clinically important finding: pulmonary vasodilators produce statistically significant and consistent reductions in pulmonary arterial pressure and resistance in COPD-associated PH, yet these hemodynamic improvements do not translate into meaningful gains in exercise capacity or arterial oxygenation. The composite hemodynamic z-score, an exploratory summary measure pre-specified for this analysis, is directionally consistent with the individual hemodynamic findings across mPAP, PVR, and sPAP, but combines variables of different physiological meaning and should not be interpreted as an independently validated clinical endpoint; it is presented as supportive of, rather than additional evidence for, the individual hemodynamic findings. Meanwhile, the non-significant 6MWD result (pooled MD +10.09 m, well below the MCID of ~20 m) and near-null PaO₂ effect collectively indicate that hemodynamic improvement is a surrogate that does not reliably predict patient-centered outcomes in this disease (Figure 6) [28,29].

The hemodynamic–functional dissociation is supported by existing research and deserves careful mechanistic consideration [30]. In PAH, right ventricular afterload is the primary determinant of exercise intolerance, and reductions in mPAP and PVR reliably predict functional improvement. This mechanistic chain appears disrupted in COPD-PH. Exercise limitation in COPD is multidetermined: ventilatory capacity constrained by dynamic hyperinflation and expiratory flow limitation, peripheral skeletal muscle dysfunction driven by systemic inflammation and deconditioning, and inspiratory muscle overloading all contribute comparably or dominantly to exercise intolerance relative to right ventricular afterload. Even a clinically meaningful reduction in mPAP of 4–5 mmHg is therefore unlikely to shift the primary exercise-limiting factor in most patients [30–36].

A second critical consideration is the effect of non-selective pulmonary vasodilation on V/Q matching and arterial oxygenation [34]. In COPD, hypoxic pulmonary vasoconstriction (HPV) plays a cardinal adaptive role in minimizing perfusion of under-ventilated lung units. Systemic or non-selective vasodilators risk abrogating HPV, redistributing blood flow to poorly ventilated regions, and worsening V/Q mismatch. This mechanism is most plausible for ERAs: the decline in PaO₂ associated with bosentan in Stolz et al. (2008) [21] is consistent with this hypothesis. In contrast, inhaled NO, delivered directly to ventilated alveoli, preferentially vasodilates well-ventilated units, potentially improving

V/Q matching. The directionally positive PaO₂ signal for NO donors in our subgroup analysis supports this interpretation [37].

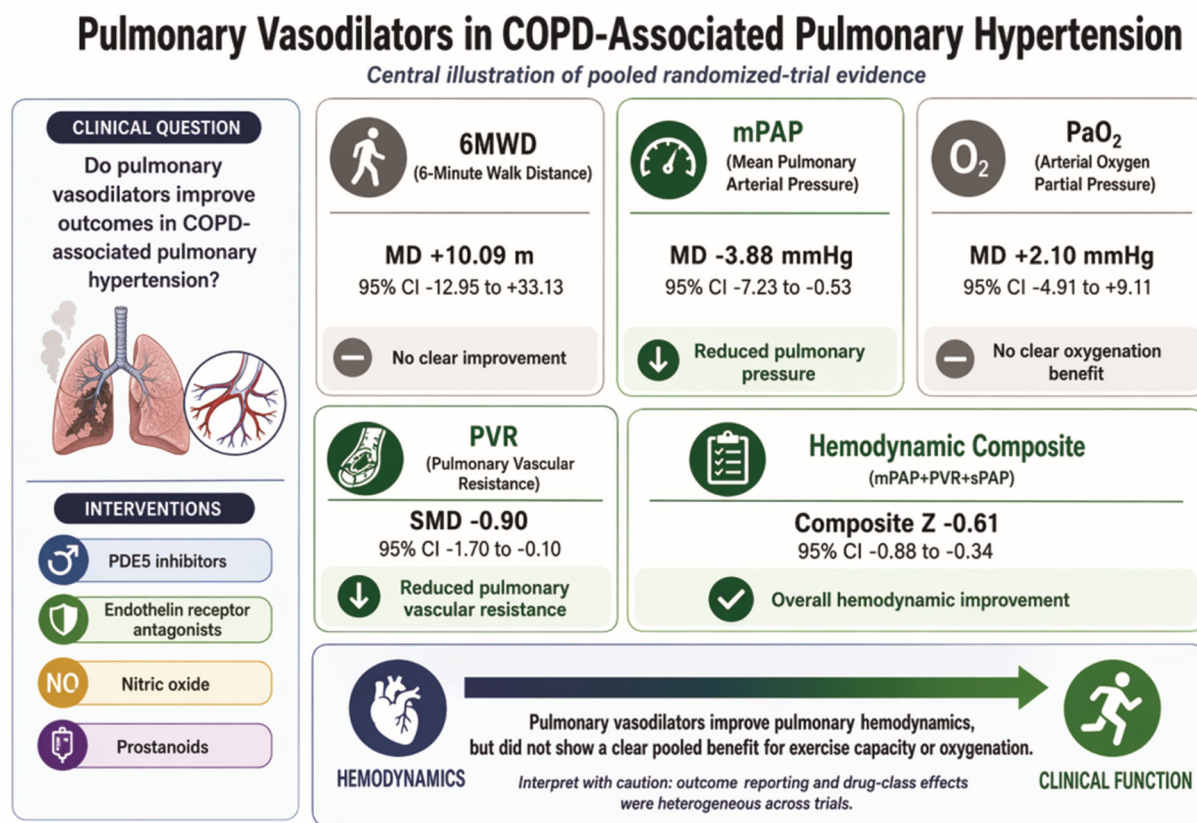


Figure 6. Central illustration of all pooled functional and hemodynamic outcomes. Bars/points represent pooled effect estimates (mean difference or standardized mean difference) for 6MWD, mPAP, PVR, and PaO₂ [7,12–17,19,21,22,24]; color denotes direction of effect (favors treatment vs. favors control). Error bars represent 95% confidence intervals. This Figure was created using CorelDRAW Graphics Suite 2022.

The PDE5 inhibitor class, which accounts for the majority of available trial evidence, occupies an intermediate position. The hemodynamic effects are modest but consistent; oxygenation effects are near-neutral in most trials. Complementary physiological evidence from Blanco et al. (2010), a dose-comparison study of sildenafil 20 mg versus 40 mg using right heart catheterization at rest and during exercise [7], confirms dose-dependent hemodynamic responses with a modest ceiling effect, suggesting that dose escalation alone is unlikely to produce functional benefit. The TADA-PH trial (Maron et al., 2022) [16], the most recent and largest included study, demonstrated numerically favorable mPAP effects with tadalafil but failed to demonstrate 6MWD improvement over 12 months, directly echoing the aggregate findings of this meta-analysis [38–40].

The most definitive contemporary evidence on inhaled prostanoids in PH-COPD comes from the PERFECT trial (Nathan et al., 2024) [26], a Phase 3, randomized, double-blind, placebo-controlled crossover study of inhaled treprostinil (up to 72 mcg four times daily) in patients with moderate-to-severe COPD and hemodynamically confirmed PH (mPAP ≥ 30 mmHg, PVR ≥ 4 Wood units). The trial enrolled 76 subjects and was terminated early by the data and safety monitoring committee due to evidence of increased serious adverse events in the treprostinil arm, including acute respiratory failure and COPD exacerbations, and a potential excess mortality signal (6 deaths, all in subjects with DLCO ≤ 25% predicted). The incidence of an adverse response was 36.4% with

treprostinil versus 27.6% with placebo, and a full efficacy analysis was not possible due to insufficient sample size after early termination; 6MWD change was numerically similar between treprostinil and placebo. These results represent a critically important safety signal for inhaled prostanoids in PH-COPD and directly challenge the assumption that inhaled delivery confers a consistently favorable V/Q profile. Severe emphysema and impaired diffusion capacity may limit the selectivity of alveolar drug deposition in COPD, and systemic prostacyclin receptor activity beyond the pulmonary vasculature may provoke adverse cardiopulmonary effects in this vulnerable population. A post hoc analysis of PERFECT identified a potential responder subgroup—subjects with mPAP ≥ 40 mmHg and FEV1 $\geq 40\%$ predicted—suggesting that pulmonary vascular phenotype enrichment may be necessary for future prostanoid trials in PH-COPD [26]. This finding, combined with recent registry data from the GoDeep meta-registry demonstrating an association between PDE5 inhibitor use and improved survival in PH-COPD [41], reinforces the importance of drug-class specificity and patient phenotyping when evaluating vasodilator therapy in COPD-associated PH.

These findings have important clinical practice implications. No pulmonary vasodilator holds regulatory approval specifically for COPD-associated PH, and the totality of evidence does not support routine off-label use, particularly ERAs, which carry a specific oxygenation risk signal. Patients with significant out-of-proportion PH should be referred to specialist PH centers and, where possible, enrolled in prospective trials. Future trial design should prioritize phenotypically defined subgroups most likely to benefit (severe out-of-proportion PH with preserved ventilatory reserve), patient-centered co-primary endpoints including quality of life, hospitalization, and survival, and inhaled delivery mechanisms that confer V/Q selectivity [42,43].

It is important to state plainly that this dissociation between hemodynamic and functional benefit is not a secondary or incidental finding, but arguably the central clinical message of this review: six-minute walk distance did not improve, arterial oxygenation did not improve, and no trial in this evidence base reported quality of life, hospitalization, or survival as an outcome. In the absence of patient-centered data, the hemodynamic improvements demonstrated here cannot be assumed to translate into meaningful clinical benefit and should not, on their own, be used to justify treatment decisions outside of specialized centers or clinical trials.

4.2. Study Strengths

This study has several strengths. It provides the most comprehensive updated synthesis of randomized evidence in COPD-associated PH to date, incorporating 15 trials totaling 607 participants across all included studies and spanning nearly three decades of investigation. It incorporates GRADE certainty assessment for all primary outcomes, formal risk of bias evaluation using RoB 2 and ROBINS-I, pre-specified subgroup analyses stratified by drug class, and an extensive suite of heterogeneity and influence diagnostics including Baujat plots, bubble meta-regression, cumulative meta-analysis, and radial plots. The inclusion of PERFECT (Nathan et al., 2024) [26] as a contextual study ensures that the most recent and consequential safety evidence is represented in the evidence map, even where formal pooling was not possible.

4.3. Study Limitations

The limitations of this review must be understood in the context of the field itself. COPD-associated PH represents a particularly challenging area for clinical trial conduct: the population is heterogeneous, diagnostic thresholds have shifted over time, the condition lacks regulatory approval for any targeted therapy, industry investment has been

limited following early negative trials, and concerns about worsening V/Q mismatch have historically deterred large-scale drug development programs. As a result, the available evidence base consists predominantly of small, investigator-initiated, single-centre physiologic studies with short follow-up periods and surrogate haemodynamic endpoints. The total pooled N of 464 participants across 11 trials accumulated over nearly three decades reflects structural barriers to trial conduct in this population rather than a selective literature search. This review does not claim to resolve these evidence gaps; rather, it attempts to comprehensively map all available randomized evidence, apply rigorous methodology to maximize inferential value from the existing data, and provide the clearest possible summary of what is and is not known to inform both clinical decision-making and future trial design. Within these field-level constraints, several study-level limitations should be acknowledged. We wish to emphasize that clinical heterogeneity, rather than statistical heterogeneity, constitutes the principal limitation of this synthesis. The included trials differed substantially in COPD severity, PH diagnostic method (right heart catheterization vs. echocardiographic estimation), study design (acute physiological studies vs. long-term therapeutic trials), follow-up duration, and pharmacological class (PDE5 inhibitors, NO donors, ERAs, and prostanoids). Low I^2 values in this context should not be interpreted as evidence of clinical homogeneity; with as few as 2–10 studies per outcome, these statistics have limited power to detect true heterogeneity, and confidence intervals should be interpreted as reflecting this residual clinical diversity. Pooled estimates are therefore best understood as an approximate summary signal across a mechanistically and clinically heterogeneous literature rather than as the precisely estimated effect of a single, well-defined intervention. First, PH diagnostic criteria were inconsistent across trials: some trials relied on echocardiographic sPAP estimates rather than right heart catheterization. Second, COPD severity, background therapy, baseline oxygenation, vasodilator dose, route of delivery, and follow-up duration varied markedly across trials. These sources of clinical heterogeneity are partially addressed by the pre-specified subgroup analyses stratified by drug class, and by the absence of statistically significant heterogeneity for most outcomes ($I^2 = 0$ –36%). Nevertheless, residual clinical heterogeneity that is not captured by statistical measures cannot be excluded. Third, a few of included trials were published before 2005, including Roger et al. (1997) and Vonbank et al. (2003) [19,24], and may have limited contemporary applicability. Fourth, for crossover trials, the total N in Table 1 reflects unique randomized participants, not observations per treatment period, consistent with Cochrane unit-of-analysis guidance. Within-subject variance was estimated using the Follmann et al. [27] method and was confirmed to be robust across sensitivity analyses, varying the assumed within-pair correlation from $\rho = 0.25$ to $\rho = 0.75$. Finally, the composite hemodynamic z-score was pre-specified as an exploratory measure and should be interpreted as supportive of the individual hemodynamic findings rather than as independent evidence of clinical efficacy. None of the 15 included trials reported quality of life, hospitalization, or survival as an outcome; a meta-analysis of these patient-centered endpoints was therefore not feasible with the currently available randomized evidence, and this remains an important gap for future trial design.

5. Conclusions

Pulmonary vasodilator therapy in COPD-associated pulmonary hypertension was associated with modest but consistent improvement in pulmonary hemodynamic parameters, including mPAP and PVR. However, these physiologic benefits did not translate into clinically meaningful improvement in exercise capacity or arterial oxygenation: the pooled 6MWD improvement (+10.09 m) fell well short of the ~20 m minimal clinically important difference and should not be interpreted as a clinically meaningful functional benefit. The available evidence suggests important drug-class differences, with a potential oxygenation

risk signal for endothelin receptor antagonists and a more favorable physiologic profile for nitric oxide donors in limited data. These findings should not be interpreted as evidence of clinical efficacy: pulmonary vasodilators improve pulmonary hemodynamics in COPD-PH, but the absence of consistent functional or oxygenation benefit, together with the complete absence of quality-of-life, hospitalization, or survival data, means the evaluated medications cannot currently be considered clinically efficacious for this indication outside specialized centers or clinical trials. Current randomized evidence does not support routine pulmonary vasodilator use in unselected subjects with COPD-associated pulmonary hypertension. Use should be restricted to specialist pulmonary hypertension centers, carefully selected subjects with disproportionate pulmonary vascular disease, or clinical trial settings. The premature termination of the PERFECT trial due to excess serious adverse events with inhaled treprostinil further confirms that vasodilator class and patient phenotype are critical determinants of safety, and that all pulmonary vasodilators—including inhaled formulations—should be considered investigational in unselected PH-COPD populations.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/jor6030018/s1>, Supplementary File S1: PRISMA 2020 Checklist [25]; Supplementary File S2: PROSPERO Registration Record (CRD420261324168); Supplementary File S3: Detailed Search Strategy; Supplementary File S4: Supplementary Figures, Sensitivity Analyses, Publication Bias Assessments, and Additional Meta-Analytic Results [12,13,15–17,19–21,23,24].

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Abbreviations

The following abbreviations are used in this manuscript:

6MWD	Six-Minute Walk Distance
COPD	Chronic Obstructive Pulmonary Disease
ERA	Endothelin Receptor Antagonist
GRADE	Grading of Recommendations Assessment, Development and Evaluation
mPAP	Mean Pulmonary Arterial Pressure

NO	Nitric Oxide
PAH	Pulmonary Arterial Hypertension
PaO ₂	Partial Pressure of Arterial Oxygen
PDE5	Phosphodiesterase-5
PH	Pulmonary Hypertension
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PVR	Pulmonary Vascular Resistance
RCT	Randomized Controlled Trial
REML	Restricted Maximum Likelihood
RoB2	Risk of Bias 2 Tool
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions
sPAP	Systolic Pulmonary Arterial Pressure
V/Q	Ventilation–Perfusion

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