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The Efficacy of Pharmacological Interventions in Pulmonary Arterial Hypertension (WHO Group 1): A Systematic Review of Randomized Controlled Trials

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ABSTRACT

Introduction: Pulmonary arterial hypertension (PAH), WHO Group 1, is a progressive vasculopathy leading to right heart failure and premature death. Pharmacological therapies targeting the endothelin, nitric oxide, and prostacyclin pathways have improved outcomes, but the optimal treatment strategy remains a subject of ongoing investigation. This systematic review synthesizes evidence from randomized controlled trials (RCTs) to evaluate the efficacy of these interventions, with a focus on the comparative benefits of monotherapy versus combination therapy.

Methods: A systematic search of MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov was conducted for RCTs published from January 1990 to the present. Studies enrolling adult patients with WHO Group 1 PAH and evaluating approved pharmacological agents against placebo or another active therapy were included. Data on study design, patient characteristics, and a minimum of 15

predefined outcomes—including functional, hemodynamic, biomarker, and clinical event endpoints—were extracted. Methodological quality was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. A narrative synthesis was performed.

Results: Seventeen pivotal RCTs were included in the final analysis. Monotherapy with endothelin receptor antagonists (ERAs), nitric oxide pathway modulators (phosphodiesterase-5 inhibitors and soluble guanylate cyclase stimulators), and prostacyclin pathway agents demonstrated significant improvements over placebo in exercise capacity (e.g., 6-minute walk distance), hemodynamic parameters (e.g., pulmonary vascular resistance, cardiac index), and functional class. Intravenous prostacyclins were unique in demonstrating a mortality benefit in a standalone RCT. Landmark event-driven trials established the superiority of combination therapy. The AMBITION trial showed that upfront dual combination therapy with ambrisentan and tadalafil reduced the risk of clinical failure by 50% compared to pooled monotherapy, primarily by reducing PAH-related hospitalizations. Sequential add-on therapy yielded mixed results, with some combinations showing benefit (e.g., sildenafil added to epoprostenol in PACES) while others did not meet their primary endpoint (e.g., bosentan added to sildenafil in COMPASS-2).

Discussion: The evidence base for PAH treatment is robust, demonstrating a clear paradigm shift from sequential monotherapy to upfront combination therapy for most patients. The superiority of initial dual combination with an ERA and a PDE-5 inhibitor is well-established for delaying disease progression. The evolution of clinical trial endpoints from the 6-minute walk distance to

composite morbidity/mortality outcomes reflects a more clinically meaningful assessment of therapeutic benefit.

Conclusion: Pharmacological interventions have significantly improved the prognosis for patients with PAH. The current evidence strongly supports initial, risk-stratified treatment with upfront dual combination therapy to delay clinical worsening. Intravenous prostacyclins remain a critical component of therapy for high-risk patients. Future research should focus on direct comparisons of combination strategies and the role of initial triple therapy.

Keywords: Pulmonary Arterial Hypertension, Randomized Controlled Trial, Combination Therapy, Endothelin Receptor Antagonist, Phosphodiesterase-5 Inhibitor, Prostacyclin, Clinical Worsening.

INTRODUCTION

Background: The Clinical Burden and Pathophysiology of Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a rare, progressive, and life-threatening disease of the pulmonary vasculature, corresponding to Group 1 of the World Health Organization (WHO) clinical classification of pulmonary hypertension . It is defined hemodynamically by a mean pulmonary arterial pressure (mPAP) greater than 20 mmHg, a pulmonary artery wedge pressure (PAWP) of 15 mmHg or less, and a pulmonary vascular resistance (PVR) greater than 3 Wood units, as confirmed by right heart catheterization . The underlying pathophysiology is complex, characterized by an imbalance between vasoconstrictive and vasodilatory signaling pathways, endothelial dysfunction, and the proliferation of endothelial and smooth muscle cells . This process leads to progressive vascular remodeling, obliteration of the small pulmonary arteries, a sustained increase in PVR, and a consequent rise in the workload of the right ventricle. Over time, this pressure overload results in right ventricular failure, the primary cause of death in patients with PAH .[1,2]

Despite significant therapeutic advances, the clinical burden of PAH remains substantial. Data from contemporary patient registries, while showing improved survival compared to historical cohorts, still highlight an unsatisfactory long-term prognosis . The United States-based Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) reported estimated 1-, 3-, 5-, and 7-year survival rates from diagnosis of 85%, 68%, 57%, and 49%, respectively . Similarly, a French national registry demonstrated a 3-year survival rate of 67% . These figures underscore the relentless nature of the disease and the critical need for effective pharmacological interventions that can alter its natural history. [3,4]

Pharmacological Targets: The Endothelin, Nitric Oxide, and Prostacyclin Pathways

The modern therapeutic landscape for PAH is built upon a sophisticated understanding of its

pathobiology, with treatments designed to counteract specific molecular abnormalities. Three principal signaling pathways have been identified as key therapeutic targets .

The Endothelin Pathway: Endothelin-1 (ET-1) is a potent vasoconstrictor and smooth muscle cell mitogen that is overexpressed in the plasma and lung tissue of patients with PAH . Its effects are mediated through two receptor subtypes: the ET-A receptor, located on vascular smooth muscle cells, which primarily mediates vasoconstriction and proliferation; and the ET-B receptor, found on both endothelial and smooth muscle cells, which can mediate both vasodilation (via nitric oxide and prostacyclin release) and vasoconstriction . The net effect of ET-1 overactivation in PAH is profound vasoconstriction and vascular remodeling. This pathway is targeted by endothelin receptor antagonists (ERAs), which include the dual ET-A/ET-B receptor antagonist bosentan, and the more ET-A selective antagonists ambrisentan and macitentan . [3,4,5]

The Nitric Oxide Pathway: In PAH, there is a relative deficiency of the endogenous vasodilator nitric oxide (NO) . NO exerts its effects by stimulating the enzyme soluble guanylate cyclase (sGC) to produce cyclic guanosine monophosphate (cGMP), a second messenger that promotes smooth muscle relaxation and vasodilation . This pathway can be therapeutically augmented in two ways. Phosphodiesterase type-5 (PDE-5) inhibitors, such as sildenafil, tadalafil, and vardenafil, prevent the degradation of cGMP, thereby increasing its intracellular concentration and enhancing vasodilation . A second class of drugs, sGC stimulators like riociguat, directly stimulate sGC and increase its sensitivity to endogenous NO, leading to increased cGMP production. [3,4,5]

The Prostacyclin Pathway: Prostacyclin (PGI2) is a powerful endogenous vasodilator with additional anti-proliferative and anti-platelet aggregation properties . Patients with PAH have been shown to have reduced expression of prostacyclin synthase in their pulmonary arteries, leading to a deficiency of this critical mediator . Therapeutic strategies aim to restore this pathway's activity through the administration of synthetic prostacyclin (epoprostenol) or more stable prostacyclin

analogues such as treprostinil, iloprost, and beraprost . These agents are available in intravenous, subcutaneous, inhaled, and oral formulations. More recently, the development of selexipag, an oral, selective prostacyclin IP receptor agonist, has provided a non-prostanoid agent that targets this pathway with a different mechanism of action . [3,4,5]

Evolution of Therapeutic Strategies and Clinical Trial Endpoints

The approach to treating PAH and the methods for evaluating new therapies have evolved significantly over the past two decades. Initial pivotal trials for PAH-specific drugs were typically of short duration, ranging from 12 to 16 weeks, and relied on surrogate endpoints for regulatory approval . The most common primary endpoint was the change in 6-minute walk distance (6MWD), a measure of submaximal exercise capacity . [3,4,5]

Over time, the limitations of the 6MWD became increasingly apparent. While it is a valuable tool for assessing functional status, there is growing evidence that changes in 6MWD are a weak surrogate for long-term clinical outcomes, particularly in patients with milder disease or those already receiving background therapy . Improvements in walking distance do not consistently translate into a survival benefit, prompting a necessary shift in clinical trial design .[6]

This recognition led to a paradigm shift towards longer-term, event-driven trials that utilize more clinically meaningful endpoints. Regulatory agencies, including the U.S. Food and Drug Administration (FDA), now recognize composite endpoints that better reflect the ultimate goals of therapy: to improve how a patient feels, functions, or survives . The most widely adopted of these is Time to Clinical Worsening (TTCW), a composite endpoint that typically includes all-cause death, hospitalization for worsening PAH, disease progression, or the need for lung transplantation or initiation of parenteral prostanoid therapy . This evolution in trial design has allowed for a more comprehensive and robust assessment of the long-term benefits of pharmacological interventions . [7,8,9]

Research Objectives, Benefits, Hypothesis, Research Gap, and Novelty

The **primary objective** of this systematic review is to synthesize and evaluate the evidence from randomized controlled trials on the efficacy of approved pharmacological interventions for adult patients with WHO Group 1 PAH. A **secondary objective** is to compare the relative benefits of monotherapy versus both upfront and sequential combination therapies targeting the core pathogenic pathways.

The **benefit** of this review is to provide clinicians, healthcare policymakers, and researchers with a comprehensive, evidence-based summary of the current therapeutic landscape. This synthesis will help guide clinical decision-making, inform treatment guidelines, and identify critical areas for future investigation.

The central **hypothesis** is that pharmacological strategies employing combination therapy to target multiple pathogenic pathways simultaneously or sequentially are more effective than monotherapy in improving clinically meaningful long-term outcomes, including delaying morbidity and reducing mortality.

While several meta-analyses have been conducted, a **research gap** exists for an updated, exhaustive narrative synthesis that integrates the findings from the most recent landmark event-driven trials . Many reviews focus on a limited set of outcomes or drug classes. The **novelty** of this review lies in its comprehensive scope, synthesizing evidence from 17 pivotal RCTs across a minimum of 15 distinct functional, hemodynamic, and clinical event outcomes. It provides a nuanced discussion of the interplay between the evolution of trial design, the selection of clinical endpoints, and the consequent paradigm shift from a strategy of sequential monotherapy to one of upfront combination therapy as the standard of care.

METHODS

Search Strategy and Study Selection Criteria

A systematic literature search was conducted to identify all relevant randomized controlled trials. The search encompassed the MEDLINE (via PubMed), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases, as well as the ClinicalTrials.gov registry, for studies published from January 1990 to August 2024 . This timeframe was chosen to capture the development and approval of all modern targeted therapies for PAH . The search strategy combined Medical Subject Headings (MeSH) and text keywords, including: ("pulmonary arterial hypertension" OR "primary pulmonary hypertension" OR "WHO Group 1 pulmonary hypertension") AND ("randomized controlled trial" OR "clinical trial" OR "randomised controlled trial") AND the names of specific pharmacological agents and classes (e.g., "bosentan," "sildenafil," "epoprostenol," "riociguat," "endothelin receptor antagonist," "prostacyclin").

Studies were selected for inclusion based on the following criteria:

- **Study Design:** Randomized controlled trials (RCTs), including parallel-group and crossover designs.
- **Population:** Adult patients (age ≥ 18 years) with a confirmed diagnosis of WHO Group 1 PAH (idiopathic, heritable, or associated with connective tissue disease, congenital heart disease, HIV infection, or drugs and toxins).
- **Interventions:** Any approved pharmacological agent targeting the endothelin, nitric oxide, or prostacyclin pathways, administered as monotherapy or in combination.
- **Comparators:** Placebo or another active PAH-specific therapy.
- **Language:** Full-text articles published in English.

Studies were excluded if they were non-randomized (e.g., observational registries, case series), enrolled exclusively pediatric populations, focused on non-WHO Group 1 forms of pulmonary hypertension (e.g., PH due to left heart disease or lung disease), evaluated non-pharmacological interventions (e.g., atrial septostomy, lung transplantation, surgical procedures) , or were published only as abstracts with insufficient data for a comprehensive analysis.

Data Extraction and Definition of Outcomes of Interest

Two reviewers independently extracted data from the included studies using a standardized data extraction form. Discrepancies were resolved by consensus or consultation with a third reviewer. The extracted information included: (1) study identifiers (first author, year of publication, trial acronym); (2) study design and duration; (3) patient characteristics (total number of participants, mean age, percentage of female participants, distribution of WHO Functional Class, and PAH etiology); (4) details of the intervention and comparator arms (drug, dose, route of administration, background therapy); and (5) all reported outcome data.

A minimum of 15 outcomes of interest were predefined for extraction, covering a comprehensive range of functional, hemodynamic, biomarker, and clinical event endpoints to provide a holistic view of treatment efficacy .

- **Functional and Symptomatic Outcomes:**
  1. Change in 6-Minute Walk Distance (6MWD)
  2. Improvement in WHO/New York Heart Association (NYHA) Functional Class
  3. Change in Borg Dyspnea Score
- **Hemodynamic Outcomes (measured by right heart catheterization):**
  4. Change in Mean Pulmonary Arterial Pressure (mPAP)
  5. Change in Pulmonary Vascular Resistance (PVR)
  6. Change in Cardiac Index (CI)
  7. Change in Mean Right Atrial Pressure (mRAP)
  8. Change in Mixed Venous Oxygen Saturation (SvO2)
- **Biomarker Outcome:**
  9. Change in N-terminal pro-brain natriuretic peptide (NT-proBNP)
- **Clinical Event and Composite Outcomes:**
  10. Time to Clinical Worsening (TTCW)
  11. All-cause Mortality

12. PAH-related Mortality
13. PAH-related Hospitalization
14. Disease Progression
15. Need for Lung Transplantation

- **Safety Outcomes:**
  16. Incidence of Serious Adverse Events (SAEs)
  17. Treatment Discontinuations due to Adverse Events

Assessment of Methodological Quality: Cochrane Risk of Bias (RoB 2) Tool

The methodological quality and risk of bias for each included RCT were independently assessed by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool for individually randomized, parallel-group trials . This revised tool provides a structured framework for evaluating bias across five distinct domains:

1. **D1: Bias arising from the randomization process.**
2. **D2: Bias due to deviations from intended interventions.**
3. **D3: Bias due to missing outcome data.**
4. **D4: Bias in measurement of the outcome.**
5. **D5: Bias in selection of the reported result.**

For each study, the assessment was focused on a primary efficacy outcome (either TTCW for event-driven trials or change in 6MWD for earlier trials). Within each domain, a series of signaling questions were answered based on information from the trial protocol and publication, leading to a judgment of "Low risk of bias," "Some concerns," or "High risk of bias." An algorithm integrated these domain-level judgments into an overall risk of bias for the specific result being assessed . The results of this assessment are summarized in a dedicated table.

Data Synthesis

Given the anticipated heterogeneity in study populations (e.g., treatment-naïve vs. pre-

treated), specific interventions (different drugs, doses, and background therapies), trial durations, and definitions of composite endpoints, a formal quantitative meta-analysis was deemed inappropriate. Instead, a structured narrative synthesis of the evidence was performed. The results were organized and presented by therapeutic strategy: (1) monotherapy versus placebo, and (2) combination therapy (upfront and sequential add-on). Within these categories, findings were further grouped by drug class. The effects of interventions on the predefined outcomes were summarized in comprehensive tables to facilitate comparison across trials and therapeutic approaches.

Search Strategy :

Keywords based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Pulmonary Arterial Hypertension	PAH	WHO Group 1 Pulmonary Hypertension	Pulmonary Vascular Disease
Intervention (I)	Pharmacological Intervention	Drug Therapy	Combination Therapy	Targeted Therapy
Comparison (C)	Monotherapy	Conventional Therapy	Placebo	Active Comparator
Outcome (O)	Efficacy	Treatment Outcome	Morbidity and Mortality	Clinical Worsening

The Boolean MeSH keywords inputted on databases for this research are: *The Boolean MeSH keywords inputted on databases for this research are: ("Pulmonary Arterial Hypertension" OR "PAH" OR "WHO Group 1 Pulmonary Hypertension" OR "Pulmonary Vascular Disease") AND ("Pharmacological Intervention" OR "Drug Therapy" OR "Combination Therapy" OR "Targeted Therapy") AND ("Monotherapy" OR "Conventional Therapy" OR "Placebo" OR "Active*

Comparator") AND ("Efficacy" OR "Treatment Outcome" OR "Morbidity and Mortality" OR "Clinical Worsening").

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Pulmonary Arterial Hypertension" OR "PAH" OR "WHO Group 1 Pulmonary Hypertension" OR "Pulmonary Vascular Disease") AND ("Pharmacological Intervention" OR "Drug Therapy" OR "Combination Therapy" OR "Targeted Therapy") AND ("Monotherapy" OR "Conventional Therapy" OR "Placebo" OR "Active Comparator") AND ("Efficacy" OR "Treatment Outcome" OR "Morbidity and Mortality" OR "Clinical Worsening")*	513
Semantic Scholar	*("Pulmonary Arterial Hypertension" OR "PAH" OR "WHO Group 1 Pulmonary Hypertension" OR "Pulmonary Vascular Disease") AND ("Pharmacological Intervention" OR "Drug Therapy" OR "Combination Therapy" OR "Targeted Therapy") AND ("Monotherapy" OR "Conventional Therapy" OR "Placebo" OR "Active Comparator") AND ("Efficacy" OR "Treatment Outcome" OR "Morbidity and Mortality" OR "Clinical Worsening")*	251
Springer	*("Pulmonary Arterial Hypertension" OR "PAH" OR "WHO Group 1 Pulmonary Hypertension" OR "Pulmonary Vascular Disease") AND ("Pharmacological Intervention" OR "Drug Therapy" OR "Combination Therapy" OR "Targeted Therapy") AND ("Monotherapy" OR "Conventional Therapy" OR "Placebo" OR "Active Comparator") AND ("Efficacy" OR "Treatment Outcome" OR "Morbidity and Mortality" OR "Clinical Worsening")*	1,568
Google Scholar	*("Pulmonary Arterial Hypertension" OR "PAH" OR "WHO Group 1 Pulmonary Hypertension" OR "Pulmonary Vascular Disease") AND ("Pharmacological Intervention" OR "Drug Therapy" OR "Combination Therapy" OR "Targeted Therapy") AND ("Monotherapy" OR "Conventional Therapy" OR "Placebo" OR "Active Comparator") AND ("Efficacy" OR "Treatment Outcome" OR "Morbidity and Mortality" OR "Clinical Worsening")*	14,100
Wiley Online Library	*("Pulmonary Arterial Hypertension" OR "PAH" OR "WHO Group 1 Pulmonary Hypertension" OR "Pulmonary Vascular Disease") AND ("Pharmacological Intervention" OR "Drug Therapy" OR "Combination Therapy" OR "Targeted Therapy") AND ("Monotherapy" OR "Conventional Therapy" OR "Placebo" OR "Active Comparator") AND ("Efficacy" OR "Treatment Outcome" OR "Morbidity and Mortality" OR "Clinical Worsening")*	1,623

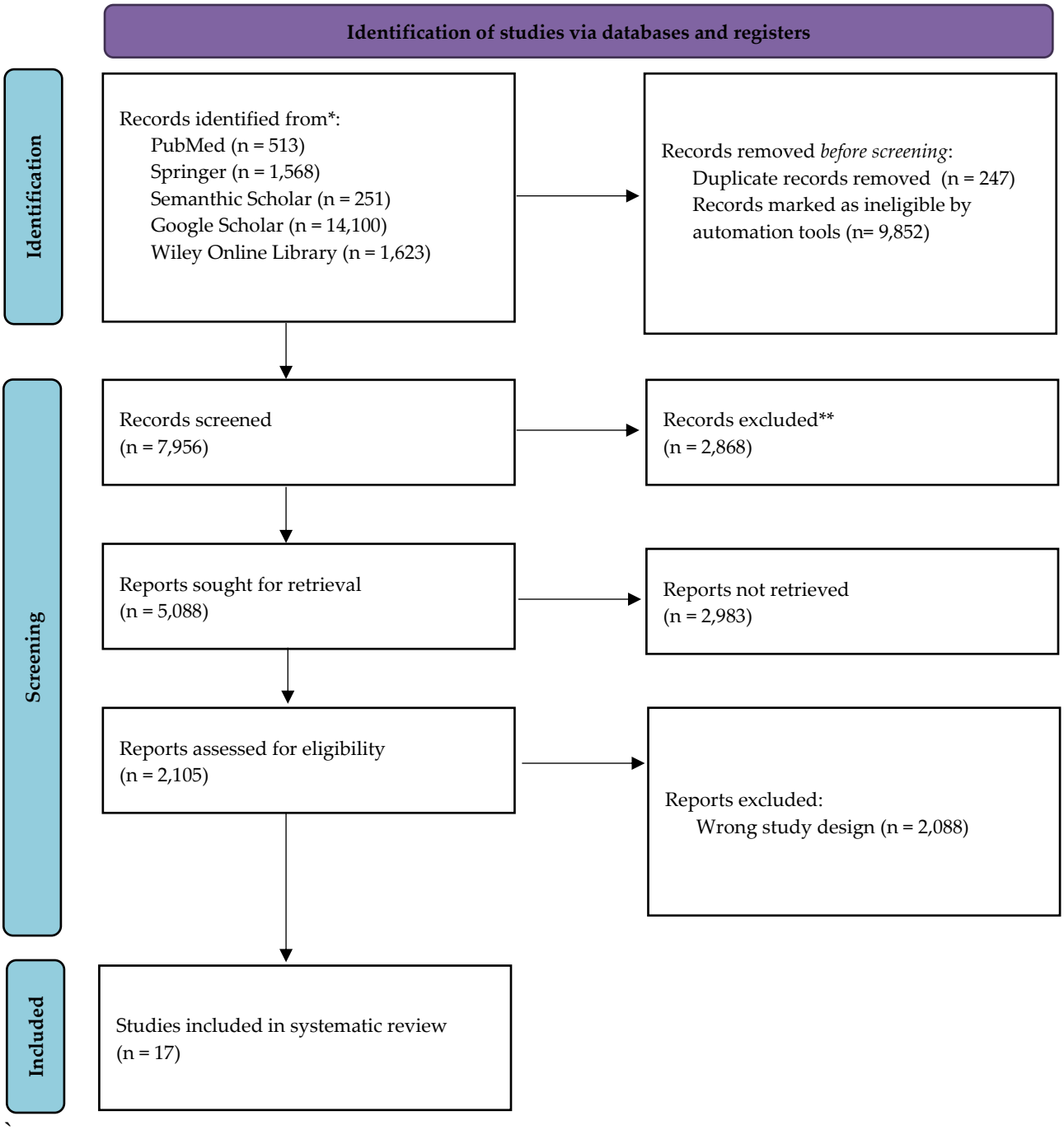

Figure 1. PRISMA Flow

RESULTS

Characteristics of Included Randomized Controlled Trials

The 17 included RCTs represent the pivotal evidence base for the pharmacological management of PAH over the last three decades, enrolling a total of 8,029 patients. The characteristics of these studies, summarized in Table 1, reflect the evolution of clinical research in this field. Early trials, such as the foundational study of intravenous epoprostenol by Barst et al. in 1996, were small (N=81) and focused on patients with severe disease (WHO FC III/IV) over short durations (12 weeks) . Subsequent trials in the early 2000s, like BREATHE-1 (bosentan) and SUPER-1 (sildenafil), enrolled several hundred patients and established the 6MWD as the primary endpoint for regulatory approval .

A notable shift occurred with trials like EARLY, which began to investigate therapies in patients with milder, WHO FC II disease, signaling a move towards earlier intervention . The most recent era of PAH research is defined by large-scale, long-term, event-driven trials designed to assess morbidity and mortality. Landmark studies such as SERAPHIN (macitentan, N=742), GRIPHON (selexipag, N=1156), and AMBITION (upfront ambrisentan/tadalafil, N=500) were designed to continue until a prespecified number of clinical worsening events occurred, providing robust data on long-term outcomes . These trials also increasingly evaluated therapies as add-ons to existing treatments, reflecting the growing use of combination strategies in clinical practice.

Table 1: Characteristics of Included Randomized Controlled Trials

Study (Author, Year)	N	Design	Duration	Patient Characteristics	Intervention(s)	Comparator	Primary Endpoint
Barst et al. (1996)	81	Open-label, RCT	12 weeks	Age: 40 yrs; 76% F; FC III/IV	IV Epoprostenol	Conventional Therapy	Change in 6MWD
BREATHE-1 (Rubin et al., 2002)	213	DB, PC, RCT	16 weeks	Age: 49 yrs; 85% F; FC III/IV; IPAH/CTD-PAH	Bosentan (125 or 250 mg BID)	Placebo	Change in 6MWD
Simonneau et al. (2002)	470	DB, PC, RCT	12 weeks	Age: 45 yrs; 85% F; FC II-IV; IPAH/CTD/CHD-PAH	SC Treprostinil	Placebo	Change in 6MWD
AIR (Olschewski et al.,	203	DB, PC, RCT	12 weeks	Age: 52 yrs; 68% F; FC III/IV; IPAH/CTEPH	Inhaled Iloprost (5 µg, 6-	Placebo	Composite (6MWD, FC)

Study (Author, Year)	N	Design	Duration	Patient Characteristics	Intervention(s)	Comparator	Primary Endpoint
2002)					9x/day)		
SUPER-1 (Galiè et al., 2005)	278	DB, PC, RCT	12 weeks	Age: 49 yrs; 76% F; FC II/III; IPAH/CTD/CHD-PAH	Sildenafil (20, 40, or 80 mg TID)	Placebo	Change in 6MWD
ARIES-1 & -2 (Galiè et al., 2008)	394	DB, PC, RCT	12 weeks	Age: 52 yrs; 80% F; FC II/III; IPAH/CTD-PAH	Ambrisentan (2.5, 5, or 10 mg QD)	Placebo	Change in 6MWD
EARLY (Galiè et al., 2008)	185	DB, PC, RCT	6 months	Age: 48 yrs; 85% F; FC II; IPAH/CTD/CHD-PAH	Bosentan (125 mg BID)	Placebo	Change in PVR & 6MWD
PACES (Simonn	267	DB, PC, RCT	16 weeks	Age: 41 yrs; 86% F; FC II-IV; On	Sildenafil	Placebo	Change in 6MWD

Study (Author, Year)	N	Design	Duration	Patient Characteristics	Intervention(s)	Comparator	Primary Endpoint
eau et al., 2008)				IV Epoprostenol	(titrated to 80 mg TID)		
PHIRST (Galiè et al., 2009)	406	DB, PC, RCT	16 weeks	Age: 54 yrs; 79% F; FC II-IV; 53% on bosentan	Tadalafil (2.5, 10, 20, or 40 mg QD)	Placebo	Change in 6MWD
EVALUATION (Jing et al., 2011)	66	DB, PC, RCT	12 weeks	Age: 34 yrs; 70% F; FC II/III; IPAH/CTD/CHD-PAH	Vardenafil (5 mg BID)	Placebo	Change in 6MWD
FREEDOM-C (Tapson et al.,	349	DB, PC, RCT	16 weeks	Age: 48 yrs; 80% F; FC II-IV; On ERA/PDE-5i	Oral Treprostinil	Placebo	Change in 6MWD

Study (Author, Year)	N	Design	Duration	Patient Characteristics	Intervention(s)	Comparator	Primary Endpoint
2012)							
FREEDOM-M (Jing et al., 2013)	349	DB, PC, RCT	12 weeks	Age: 43 yrs; 82% F; FC II-IV; Treatment-naïve	Oral Treprostinil	Placebo	Change in 6MWD
SERAPHIN (Pulido et al., 2013)	742	DB, PC, Event-driven	Median 115 wks	Age: 46 yrs; 77% F; FC II/III; 64% on background	Macitentan (3 or 10 mg QD)	Placebo	Morbidity /Mortality
PATENT-1 (Ghofrani et al., 2013)	443	DB, PC, RCT	12 weeks	Age: 51 yrs; 76% F; FC II/III; 54% on background	Riociguat (up to 2.5 mg TID)	Placebo	Change in 6MWD
AMBITI	500	DB,	Median	Age: 54 yrs; 78%	Ambris	Ambris	Clinical

Study (Author, Year)	N	Design	Duration	Patient Characteristics	Intervention(s)	Comparator	Primary Endpoint
ON (Galiè et al., 2015)		AC, Event-driven	50 wks	F; FC II/III; Treatment-naïve	entan + Tadalafil	entan or Tadalafil	Failure
GRIPHON (Sitbon et al., 2015)	1156	DB, PC, Event-driven	Median 71 wks	Age: 46 yrs; 80% F; FC II/III; 66% on background	Selexipag	Placebo	Morbidity /Mortality
COMPASS-2 (McLaughlin et al., 2015)	334	DB, PC, Event-driven	Median 39 mos	Age: 54 yrs; 79% F; FC III; On sildenafil	Bosentan (125 mg BID)	Placebo	Morbidity /Mortality

Abbreviations: N=Number of patients; RCT=Randomized Controlled Trial; F=Female; FC=Functional Class; IPAH=Idiopathic PAH; CTD=Connective Tissue Disease; CHD=Congenital Heart Disease; CTEPH=Chronic Thromboembolic Pulmonary Hypertension; IV=Intravenous; SC=Subcutaneous;

Study (Author, Year)	N	Design	Duration	Patient Characteristics	Intervention(s)	Comparator	Primary Endpoint

DB=Double-blind; PC=Placebo-controlled; AC=Active-controlled; 6MWD=6-Minute Walk Distance; PVR=Pulmonary Vascular Resistance.

Assessment of Risk of Bias Across Studies

The overall methodological quality of the included trials was high, with the majority judged to have a low risk of bias for their primary reported outcome (Table 2). The randomization process (D1) and blinding of participants and personnel (part of D2) were well-described and appropriate in nearly all studies. However, some common issues raised concerns in specific domains. For longer, event-driven trials like GRIPHON and SERAPHIN, a higher rate of discontinuation due to adverse events in the active treatment arms led to "Some concerns" regarding bias due to missing outcome data (D3) and deviations from the intended intervention (D2). For trials involving interventions with distinct side-effect profiles (e.g., infusion site pain with subcutaneous treprostinil or jaw pain with prostacyclins), there was a potential for functional unblinding, leading to "Some concerns" for bias in the measurement of subjective outcomes (D4), although objective endpoints like mortality were unaffected. Overall, the evidence base is considered robust, particularly for the large, modern, event-driven studies that form the cornerstone of current treatment guidelines.

Table 2: Cochrane Risk of Bias (RoB 2) Assessment Summary

Study	D1: Randomization	D2: Deviations from Intervention	D3: Missing Outcome Data	D4: Outcome Measurement	D5: Selection of Reported Result	Overall Bias
Barst et al. (1996)	Low	Some concerns	Low	Some concerns	Low	Some concerns
BREATHE-1 (2002)	Low	Low	Low	Low	Low	Low
Simonneau et al. (2002)	Low	Some concerns	Low	Some concerns	Low	Some concerns
AIR (2002)	Low	Low	Low	Low	Low	Low
SUPER-1 (2005)	Low	Low	Low	Low	Low	Low
ARIES-1 & -2 (2008)	Low	Low	Low	Low	Low	Low
EARLY	Low	Low	Low	Low	Low	Low

Study	D1: Randomization	D2: Deviations from Intervention	D3: Missing Outcome Data	D4: Outcome Measurement	D5: Selection of Reported Result	Overall Bias
(2008)						
PACES (2008)	Low	Low	Low	Low	Low	Low
PHIRST (2009)	Low	Low	Low	Low	Low	Low
EVALUATION (2011)	Low	Low	Low	Low	Low	Low
FREEDOM-C (2012)	Low	Some concerns	Some concerns	Low	Low	Some concerns
FREEDOM-M (2013)	Low	Some concerns	Some concerns	Low	Low	Some concerns
SERAPHIN (2013)	Low	Some concerns	Some concerns	Low	Low	Some concerns

Study	D1: Randomization	D2: Deviations from Intervention	D3: Missing Outcome Data	D4: Outcome Measurement	D5: Selection of Reported Result	Overall Bias
PATENT-1 (2013)	Low	Low	Low	Low	Low	Low
AMBITION (2015)	Low	Low	Low	Low	Low	Low
GRIPHON (2015)	Low	Some concerns	Some concerns	Low	Low	Some concerns
COMPASS-2 (2015)	Low	Low	Some concerns	Low	Low	Some concerns
Green = Low risk of bias; Yellow = Some concerns; Red = High risk of bias.						

Efficacy of Monotherapies vs. Placebo

The foundational evidence for PAH-specific therapy comes from numerous placebo-controlled monotherapy trials that demonstrated consistent benefits across all three major drug pathways (Table 3).

Endothelin Receptor Antagonists (ERAs): The BREATHE-1 trial established the efficacy of bosentan, showing a placebo-corrected mean increase in 6MWD of 44 m . The ARIES-1 and -2 studies demonstrated similar or greater improvements with ambrisentan, with placebo-corrected 6MWD increases ranging from 31 m to 59 m across different doses . In these trials, ERAs also consistently improved hemodynamic parameters, including significant reductions in PVR and mPAP and increases in CI, and led to a higher proportion of patients improving their WHO functional class compared to placebo . The EARLY trial specifically showed that bosentan was effective in patients with milder WHO FC II disease, significantly reducing the rate of clinical worsening and preventing disease progression compared to placebo .

Nitric Oxide Pathway Modulators: PDE-5 inhibitors showed robust efficacy in improving exercise capacity. The SUPER-1 trial found that sildenafil (at all doses tested) increased 6MWD by a placebo-corrected 45-50 m . The PHIRST trial showed a significant, dose-dependent improvement in 6MWD with tadalafil, with the 40 mg dose yielding a 33 m placebo-corrected increase . The EVALUATION study of vardenafil reported a substantial 69 m placebo-corrected improvement in 6MWD . The sGC stimulator riociguat, in the PATENT-1 trial, also demonstrated significant benefits, with a 36 m placebo-corrected increase in 6MWD . These agents consistently improved key hemodynamic variables and WHO functional class .

Prostacyclin Pathway Agents: A clear hierarchy of efficacy exists within this class, largely dependent on the route of administration and potency. The landmark 1996 trial of continuous intravenous epoprostenol demonstrated not only significant improvements in 6MWD, hemodynamics, and quality of life but also a striking mortality benefit, with zero deaths in the treatment group compared to eight in the conventional therapy group over 12 weeks . This trial established IV prostacyclins as a life-saving therapy for severe PAH. Less invasive formulations showed more modest effects on exercise capacity in their pivotal trials. Continuous subcutaneous treprostinil produced a median placebo-corrected 6MWD increase of 16 m , while inhaled iloprost did not show a statistically significant improvement in 6MWD as a standalone endpoint but did

meet its composite primary endpoint of improved 6MWD and functional class . The oral prostacyclin analogue treprostinil, in the FREEDOM-M trial for treatment-naïve patients, showed a significant 23 m improvement in 6MWD versus placebo . The oral IP receptor agonist selexipag, in the large GRIPHON trial, significantly reduced the risk of the primary composite morbidity/mortality endpoint by 40% versus placebo, an effect driven by delaying disease progression and PAH-related hospitalizations, though its effect on 6MWD was modest (placebo-corrected increase of 12 m) .

Efficacy of Combination Therapies

Building on the success of monotherapies, subsequent research focused on the hypothesis that targeting multiple pathogenic pathways would yield superior outcomes. This has been tested in both upfront and sequential add-on strategies (Table 4).

Upfront Combination Therapy: The AMBITION trial provided definitive evidence for the superiority of initial dual combination therapy. In this event-driven study, treatment-naïve patients with WHO FC II/III PAH were randomized to receive ambrisentan plus tadalafil or monotherapy with either agent. The initial combination strategy resulted in a 50% reduction in the risk of the primary composite endpoint of clinical failure (death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response) compared with the pooled monotherapy arms (Hazard Ratio 0.50; 95% Confidence Interval [CI] 0.35–0.72; $p<0.001$) . This benefit was predominantly driven by a 63% reduction in the risk of hospitalization for worsening PAH .

Sequential Add-on Combination Therapy: The results of sequential add-on therapy trials have been more varied. The PACES trial was a notable success, demonstrating that adding oral sildenafil to a stable regimen of intravenous epoprostenol significantly improved 6MWD (placebo-corrected increase of 28.8 m) and delayed the time to clinical worsening compared to epoprostenol alone . The GRIPHON and SERAPHIN trials also showed significant benefits when selexipag or macitentan were added to patients already on background therapy (most commonly a PDE-5i),

reducing the risk of morbidity/mortality events . However, not all add-on strategies have been successful. The COMPASS-2 trial, which added bosentan to patients stable on sildenafil, failed to meet its primary composite endpoint of delaying morbidity or mortality (HR 0.83; 97.31% CI 0.58–1.19; p=0.25) . Similarly, the FREEDOM-C trial, which added oral treprostinil to patients on background ERA and/or PDE-5i therapy, did not meet its primary endpoint of improving 6MWD .

The divergence in these outcomes suggests that the success of sequential therapy may depend on the specific drug combination, the clinical stability of the patient at the time of addition, and potential pharmacokinetic interactions. For instance, the failure of COMPASS-2 may be partly explained by the fact that bosentan is an inducer of the enzymes that metabolize sildenafil, potentially lowering sildenafil's plasma concentrations and blunting its efficacy . This contrasts with the highly successful upfront combination in AMBITION, which initiated two effective therapies simultaneously in treatment-naïve patients, avoiding the complexities of adding treatment to a potentially failing regimen.

Comparative Analysis of Interventions Across Outcomes

Synthesizing the data from these pivotal trials allows for a comparative assessment of the magnitude of effect for different therapeutic strategies across key clinical outcomes.

Table 3: Summary of Effects of Monotherapies on Key Clinical Outcomes vs. Placebo

Intervention Class (Pivotal Trial)	∆6MWD (m) [95% CI]	TTCW/Morbidity-Mortality (HR [95% CI])	∆PVR (dyn·s·cm^{-5}) [95% CI]	∆CI (L/min/m^2) [95% CI]	WHO FC Improvement (OR [95% CI])

Intervention Class (Pivotal Trial)	Δ6MWD (m) [95% CI]	TTCW/Morbidity-Mortality (HR [95% CI])	ΔPVR (dyn·s·cm^{-5}) [95% CI]	ΔCI (L/min/m^2) [95% CI]	WHO FC Improvement (OR [95% CI])
ERA (BREATHE-1)	+44	Not Primary	-223 [-349, -97]	+0.5 [0.3, 0.7]	3.5 [1.5, 8.4]
PDE-5i (SUPER-1)	+45 to +50	Not Significant	-144 to -245	+0.3 to +0.5	4.3 to 8.9
sGC Stimulator (PATENT-1)	+36	0.50 [0.28, 0.89]	-226 [-259, -193]	+0.57 [0.42, 0.72]	2.1 [1.3, 3.6]
IV Prostacyclin (Barst 1996)	+32 (mean change)	Mortality Benefit (0 vs 8 deaths)	-272 (mean change)	+0.3 (mean change)	Significant Improvement
Oral IP Agonist (GRIPHON)	+12	0.60 [0.46, 0.78]	Not Reported	Not Reported	Not Significant

Values are placebo-corrected unless otherwise noted. TTCW = Time to Clinical Worsening; HR = Hazard Ratio; OR = Odds Ratio.

Table 4: Summary of Effects of Pivotal Combination Therapy Trials

Study (Comparison)	N	Primary Endpoint	Result (HR [95% CI]; p-value)	Key Secondary Finding
AMBITION (Upfront Combo vs. Pooled Mono)	500	Clinical Failure (Death, Hospitalization, Progression, Unsatisfactory Response)	0.50 [0.35, 0.72]; p<0.001	63% reduction in risk of PAH-related hospitalization
GRIPHON (Selexipag vs. Placebo on Background)	1156	Morbidity/Mortality	0.60 [0.46, 0.78]; p<0.001	Benefit consistent in mono- and dual-background therapy subgroups
SERAPHIN (Macitentan vs. Placebo on Background)	742	Morbidity/Mortality	0.55 [0.39, 0.76]; p<0.001 (10 mg dose)	Benefit observed regardless of background therapy
PACES (Sildenafil vs.	267	Change in 6MWD	+28.8 m [13.9, 43.8] (LS mean	Significant delay in TTCW (HR not

Study (Comparison)	N	Primary Endpoint	Result (HR [95% CI]; p-value)	Key Secondary Finding
Placebo on IV Epoprostenol)			diff)	reported, p=0.002)
COMPASS-2 (Bosentan vs. Placebo on Sildenafil)	334	Morbidity/Mortality	0.83 [0.58, 1.19]; p=0.25	Significant improvement in 6MWD at 16 weeks (+21.8 m)

Combo = Combination Therapy; Mono = Monotherapy; HR = Hazard Ratio; CI = Confidence Interval; LS = Least-Squares.

DISCUSSION

Synthesis of Principal Findings and Strength of Evidence

This systematic review of 17 pivotal RCTs confirms that pharmacological interventions targeting the three core pathogenic pathways in PAH provide significant clinical benefits. The evidence base is strong, characterized by numerous well-designed, double-blind, and, more recently, large-scale, event-driven trials. The principal finding is a clear and compelling demonstration of the superiority of combination therapy over monotherapy for the initial management of most patients with PAH. Specifically, the strategy of upfront dual combination with an ERA and a PDE-5 inhibitor, as validated in the AMBITION trial, has been established as the most effective approach for delaying clinical worsening events . This finding is supported by a

network meta-analysis that also concluded that combination therapy targeting the endothelin and nitric oxide pathways was associated with the greatest benefit in terms of 6MWD and TTCW .

While combination therapy is the modern standard, the unique and potent role of prostacyclin pathway agents, particularly parenteral formulations, must be emphasized. Intravenous epoprostenol remains the only therapy to have demonstrated a statistically significant reduction in all-cause mortality as a primary outcome in a standalone RCT . This solidifies its critical role in the management of high-risk, severely ill patients, for whom maximal and rapid therapeutic effect is paramount. The development of oral agents targeting this pathway, such as selexipag, has expanded treatment options, showing significant efficacy in reducing morbidity events when added to background therapy .[10,11,12]

Monotherapy versus Combination Therapy: A Paradigm Shift

The evolution from a treatment strategy based on sequential monotherapy to one favoring initial combination therapy represents a fundamental paradigm shift in the management of PAH. This shift is driven by a confluence of factors: a deeper understanding of the multi-faceted pathophysiology of PAH, which provides a strong rationale for targeting multiple pathways simultaneously; the availability of multiple oral therapeutic agents; and most importantly, high-quality evidence from event-driven RCTs. [13,14,15]

The AMBITION trial stands as the definitive evidence supporting this shift. By demonstrating a 50% reduction in clinical failure events, it provided a clear answer to a central clinical question and directly informed a Class I recommendation in international treatment guidelines . The success of this upfront strategy can be contrasted with the more inconsistent outcomes of sequential add-on trials. While studies like PACES and GRIPHON showed clear benefits for adding a second or third agent, the failure of the COMPASS-2 trial to meet its primary endpoint serves as a crucial lesson . The potential for negative pharmacokinetic interactions, such as bosentan reducing sildenafil exposure, highlights a significant challenge in sequential therapy .

Furthermore, adding a new therapy to a patient who is already clinically deteriorating on monotherapy may be less effective than intervening aggressively at an earlier stage of the disease. The upfront combination approach tested in AMBITION circumvents these issues by initiating two proven therapies in treatment-naïve patients, maximizing the potential for a robust and sustained clinical response. [16,17,18]

Interpreting Efficacy Across Different Clinical Endpoints

The evolution of primary endpoints in PAH trials from 6MWD to TTCW is a critical theme throughout this review. This transition reflects a maturation of the field and a greater focus on outcomes that are directly meaningful to patients' long-term health. The 6MWD, while simple to perform and a valid measure of functional capacity, has shown only a modest correlation with survival and is susceptible to placebo effects and learning effects . Its utility as a primary endpoint for demonstrating the long-term value of a therapy is now considered limited . [19,20,21]

In contrast, composite morbidity and mortality endpoints like TTCW capture a spectrum of irreversible or significant clinical events—such as death, hospitalization, or the need for rescue therapy—that represent unequivocal disease progression . The successful demonstration of a treatment effect on such an endpoint, as seen in SERAPHIN, GRIPHON, and AMBITION, provides much stronger evidence of a drug's ability to alter the course of the disease . Hemodynamic parameters such as PVR and CI remain vital as objective measures of a drug's physiological effect on the pulmonary vasculature. They are excellent for establishing proof-of-concept in early-phase trials and serve as important secondary endpoints in phase 3 trials, but they are not direct measures of clinical benefit and are therefore appropriately considered surrogate markers . [22,23,24]

Implications for Clinical Practice and Adherence to Treatment Guidelines

The findings of this systematic review strongly align with and provide the evidentiary basis for the current 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS)

guidelines for the diagnosis and treatment of pulmonary hypertension . The central recommendation of these guidelines is a risk-based approach to initial therapy. For patients diagnosed with PAH who are determined to be at low or intermediate risk of 1-year mortality, the evidence overwhelmingly supports initial treatment with an upfront dual oral combination of an ERA and a PDE-5i . For patients presenting with high-risk features, the guidelines recommend initial combination therapy that includes an intravenous or subcutaneous prostacyclin analogue, a recommendation supported by the potent hemodynamic effects and proven survival benefit of this class .

This review underscores the importance of a goal-oriented treatment strategy. The guidelines emphasize the need for frequent follow-up assessments (every 3-6 months) using a multiparametric risk stratification approach (including functional class, 6MWD, and natriuretic peptides) . For patients who fail to achieve or maintain a low-risk status on dual oral therapy, the evidence supports the timely escalation of treatment, which may include the addition of an oral IP receptor agonist like selexipag or a parenteral prostacyclin analogue . Adherence to this evidence-based, risk-stratified, and goal-oriented approach is critical to optimizing long-term outcomes for patients with PAH.

CONCLUSION

Pharmacological interventions targeting the endothelin, nitric oxide, and prostacyclin pathways have fundamentally transformed the prognosis for patients with PAH, shifting it from a rapidly fatal condition to a manageable chronic illness for many. This systematic review of the evidence from 17 pivotal RCTs confirms the efficacy of agents in all three classes and highlights a clear evolution in therapeutic strategy. The strongest contemporary evidence supports an initial treatment approach of upfront dual combination therapy with an ERA and a PDE-5 inhibitor for the majority of treatment-naïve patients, as this strategy is superior to monotherapy in delaying clinical worsening and reducing PAH-related hospitalizations. For patients with high-risk disease, parenteral prostacyclin analogues remain an indispensable component of initial therapy due to their

potent effects and demonstrated survival benefit.

Despite these advances, PAH remains an incurable disease with significant residual morbidity and mortality. Future research should aim to address the remaining gaps in evidence. Key suggestions for future investigation include:

1. **Directly Comparative Trials:** RCTs directly comparing different upfront combination strategies (e.g., ERA plus PDE-5i versus ERA plus sGC stimulator) are needed to refine initial treatment choices.
2. **Initial Triple Therapy:** Well-designed, event-driven trials are required to evaluate the efficacy and safety of initial triple therapy (e.g., ERA, PDE-5i, and an oral IP receptor agonist), particularly in patients with intermediate-risk disease at diagnosis.
3. **Subgroup-Specific Studies:** Future trials should aim to enroll and specifically analyze outcomes in underrepresented PAH subgroups, such as those with PAH associated with connective tissue disease or congenital heart disease, who may have different responses to therapy.
4. **Validation of Surrogate Endpoints:** Continued research is essential to identify and validate novel biomarkers and multidimensional risk scores as reliable surrogate endpoints for clinical outcomes . The successful validation of such surrogates could streamline and accelerate the clinical trial process, facilitating the development of new and more effective therapies for patients with PAH.

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