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REDEFINING PULMONARY HYPERTENSION AND EMERGING THERAPEUTIC STRATEGIES

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ABSTRACT

Introduction and objective: This narrative review summarizes recent advances in the understanding and treatment of elevated pulmonary vascular pressure disorders between 2017 and 2025. Particular emphasis is placed on evolving classification criteria, the emergence of novel therapies, and their impact on clinical practice.

Materials and Methods: Rather than presenting a formal systematic search, this review integrates findings from key clinical trials, international guidelines, and major publications indexed in PubMed/MEDLINE, Cochrane Library, Embase, Web of Science, and CINAHL. Special attention is given to studies addressing the role of sotatercept, activin signaling, and the BMP pathway, which have shaped current perspectives.

Brief description of the state of knowledge: The past years have witnessed a redefinition of hemodynamic thresholds, lowering the diagnostic criterion for mean pulmonary arterial pressure from ≥ 25 mmHg to >20 mmHg, enabling earlier diagnosis and broader recognition of disease burden. Epidemiological estimates suggest approximately 192,000 cases worldwide, with a predominance in women. On the therapeutic front, sotatercept represents a landmark advance, acting through the BMP/activin axis and shifting the paradigm toward disease modification. The STELLAR Phase 3 trial demonstrated a 40.8-meter improvement in six-minute walk distance and a 76% reduction in composite adverse outcomes, underscoring its clinical relevance.

Summary: Between 2017 and 2025, pulmonary vascular medicine has undergone substantial transformation. The redefinition of diagnostic criteria and the development of sotatercept mark a decisive move from purely symptomatic management toward therapies capable of altering disease progression. These changes not only improve patient prognosis but also redefine future directions in the field.

KEYWORDS

Pulmonary Hypertension, Hemodynamic Definition, Vascular Remodeling, Sotatercept Therapy, Activin Signaling

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1. Introduction

Pulmonary hypertension (PH) is a progressive and life-threatening cardiovascular disease characterized by increased pulmonary arterial pressure, right ventricular dysfunction, and high mortality. Its heterogeneous clinical presentation and complex pathophysiology make early diagnosis and effective treatment a major challenge for clinicians worldwide (Guignabert et al. 2024). Recent epidemiological analyses, including the Global Burden of Disease Study, estimate a prevalence of approximately 192,000 cases of pulmonary arterial hypertension worldwide, with a predominance in women (Leary et al. 2024).

This narrative review aims to synthesize advances achieved between 2017 and 2025, with particular focus on changes in hemodynamic definitions, novel therapeutic strategies, and their impact on clinical outcomes. A pivotal change was introduced in the 2022 ESC/ERS guidelines, which redefined the diagnostic threshold of mean pulmonary arterial pressure to >20 mmHg, representing a paradigm shift with significant clinical and epidemiological consequences (Ntiloudi et al. 2024).

On the therapeutic front, sotatercept has emerged as the first-in-class activin signaling inhibitor that targets pulmonary vascular remodeling rather than vasodilatory dysfunction. This innovation marks the most important breakthrough in pulmonary arterial hypertension (PAH) therapy in more than a decade, with the potential to alter long-term outcomes (Cascino et al. 2024). At the same time, combination therapy strategies, advances in risk stratification, and personalized medicine approaches are reshaping the management of PH (Hoeper et al. 2025; Dardi et al. 2024).

In addition, surgical and interventional procedures such as pulmonary endarterectomy, lung transplantation, and emerging mechanical circulatory support remain critical options for advanced disease. Future perspectives include the development of anti-inflammatory and metabolic modulators, regenerative therapies, and the integration of artificial intelligence and genetic profiling into clinical decision-making (Hajra et al. 2022).

2. Research materials and methods

This review is based on a broad and integrative analysis of peer-reviewed literature published between 2017 and 2025, capturing the most relevant advances in the understanding, diagnosis, and treatment of pulmonary hypertension. The emphasis was placed on high-impact journals in cardiovascular and respiratory medicine, major international guidelines, and proceedings from leading scientific meetings, including the World Symposium on Pulmonary Hypertension, the European Society of Cardiology Congress, the American Thoracic Society International Conference, and the European Respiratory Society International Congress.

The search strategy combined established medical databases (PubMed/MEDLINE, Embase, Cochrane Library, Web of Science, and CINAHL) with targeted exploration of landmark journals such as The New England Journal of Medicine, The Lancet Respiratory Medicine, European Respiratory Journal, Circulation, and Chest. Particular attention was given to studies addressing pathophysiological mechanisms (especially the BMP/activin axis and BMPR2 signaling), novel diagnostic tools, and therapeutic innovations including sotatercept, as well as to updated clinical guidelines issued by international societies.

The review prioritised evidence from clinical trials, systematic reviews, and consensus statements, while also considering important observational studies and epidemiological reports to provide context on disease burden. Rather than following a rigid systematic protocol, evidence was organised thematically to highlight progress in key domains: redefined hemodynamic criteria, epidemiology, pathophysiology, diagnostic strategies, therapeutic advances, risk stratification, surgical and interventional approaches, and future perspectives.

The integration of findings from both mechanistic studies and clinical trials allowed for a comprehensive overview of pulmonary hypertension research in its current state. This narrative approach ensures that emerging discoveries are discussed alongside established concepts, illustrating the dynamic evolution of the field and its implications for clinical practice.

3. State of knowledge

3.1 Updated Classification and Hemodynamic Definition

Recent years have brought profound changes in pulmonary hypertension (PH) classification and diagnostic definitions. The 2022 ESC/ERS Guidelines lowered the threshold for mean pulmonary arterial pressure (mPAP) from ≥ 25 to >20 mmHg and set pulmonary vascular resistance (PVR) ≥ 2 Wood units as part of the definition of precapillary PH (Ntiloudi et al. 2024). These changes were supported by registry data showing worse outcomes in patients with borderline mPAP (20–24 mmHg) (Levine 2021).

The updated classification retains the five traditional PH groups but refines them with more detailed phenotyping, particularly within Group 1 PAH. Genetic background, associated conditions, and hemodynamic profiles are now increasingly used to guide personalised medicine approaches (Montani et al. 2025). The key modifications in diagnostic thresholds and classification refinements are summarised in Table 1.

Table 1. Changes in hemodynamic definition and classification of pulmonary hypertension (PH)

Criterion	Previous definition (before 2022)	Updated definition (2022 ESC/ERS)	Clinical significance
Mean pulmonary arterial pressure (mPAP)	≥ 25 mmHg	>20 mmHg	Enables earlier recognition and diagnosis
Pulmonary vascular resistance (PVR)	≥ 3 Wood units	≥ 2 Wood units	Captures patients with borderline disease and subtle vascular changes
PH Classification	Five WHO groups (basic phenotypes)	Five WHO groups + refined phenotyping (genetic, associated conditions, hemodynamic profiles)	Facilitates personalised medicine and targeted therapies

Abbreviations: mPAP – mean pulmonary arterial pressure; PVR – pulmonary vascular resistance; WHO – World Health Organization; ESC – European Society of Cardiology; ERS – European Respiratory Society.

These updates emphasise earlier recognition of disease, provide more precise phenotyping, and create opportunities for a more personalised treatment approach.

3.2 Global Epidemiological Insights and Disease Burden

The Global Burden of Disease Study 2021 estimated approximately 192,000 cases of PAH worldwide, corresponding to an age-standardised prevalence of 2.28 per 100,000 population, with women disproportionately affected (62% of cases) (Leary et al. 2024). Despite being traditionally labelled a “rare disease,” PH represents a significant global health burden with substantial years of life lost.

Epidemiological differences reflect both real variation and disparities in diagnostic access. Studies report prevalence ranging widely due to methodological differences, while data from Ontario, Canada, illustrate rising incidence and prevalence over time, likely reflecting both improved recognition and ageing populations (Wijeratne et al. 2018).

3.3 Pathophysiological Advances and Molecular Understanding

Advances in molecular research have clarified the central role of the TGF- β superfamily, particularly the balance between activin (pro-proliferative) and BMP (anti-proliferative) signalling. Mutations in BMPR2, present in ~70% of heritable and up to 20% of idiopathic PAH, highlight its role as a key driver of disease pathogenesis (Cascino et al. 2024).

Vascular remodelling results from endothelial dysfunction, smooth muscle hypertrophy, and adventitial fibroblast activation, amplified by imbalances in endothelin, nitric oxide, and prostacyclin pathways. New technologies, such as single-cell RNA sequencing, have revealed cellular heterogeneity and metabolic changes, providing novel therapeutic targets (Guignabert et al. 2024).

3.4 Contemporary Diagnostic Evolution and Risk Assessment

Early recognition of PH relies on structured algorithms combining clinical suspicion with non-invasive tools. Echocardiography remains the primary screening method, while right heart catheterisation continues as the gold standard for definitive diagnosis and hemodynamic profiling (Anderson and Lau 2022)

Additional imaging, including cardiac MRI and CT pulmonary angiography, supports structural and etiological assessment. Risk stratification tools such as the REVEAL score and ESC/ERS strategies integrate functional, biochemical, imaging, and hemodynamic parameters to classify patients into low-, intermediate-, or high-risk categories, guiding therapy escalation and personalised management (Dardi et al. 2024).

3.5 Revolutionary Therapeutic Advances: The Sotatercept Era

Sotatercept represents the most important therapeutic innovation in PAH in more than a decade. As an activin receptor type IIA ligand trap, it targets pulmonary vascular remodelling rather than vasodilatory dysfunction (Hoeper et al. 2025).

The PULSAR Phase 2 trial evaluated sotatercept in 106 adults with PAH receiving optimized background therapy. The study met its primary endpoint, showing a dose-dependent reduction in pulmonary vascular resistance: $-145.8 \text{ dyn s cm}^{-5}$ with 0.3 mg/kg and $-239.5 \text{ dyn s cm}^{-5}$ with 0.7 mg/kg, alongside improvements in six-minute walk distance and NT-proBNP levels (Hoeper et al. 2023)

The pivotal STELLAR Phase 3 trial enrolled 323 patients with WHO FC II–III PAH. At week 24, sotatercept improved six-minute walk distance by 40.8 m versus placebo ($p < 0.001$) and significantly reduced the risk of clinical worsening. Benefits were consistent across secondary outcomes (functional class, PVR, quality of life), even in patients already receiving dual or triple therapy (Hoeper et al. 2023).

Key data from the PULSAR and STELLAR trials are summarised in Table 2.

Table 2. Key clinical trials of sotatercept in pulmonary arterial hypertension (PAH)

Trial	Population	Intervention	Key outcomes	Clinical significance
PULSAR (Phase II)	106 adults with PAH on background therapy	Sotatercept 0.3 or 0.7 mg/kg SC every 3 weeks	Dose-dependent ↓PVR: $-145.8 \text{ dyn s cm}^{-5}$ (0.3 mg/kg), $-239.5 \text{ dyn s cm}^{-5}$ (0.7 mg/kg); improvements in 6MWD and NT-proBNP	First proof of efficacy; showed vascular remodelling target can modify disease course
STELLAR (Phase III)	323 patients, WHO FC II–III PAH	Sotatercept vs placebo (on dual/triple therapy)	↑6MWD by 40.8 m vs placebo ($p < 0.001$); reduced risk of clinical worsening; benefits across FC, PVR, QoL	Confirmed clinical efficacy; supports sotatercept as first disease-modifying agent in PAH

Abbreviations: 6MWD – six-minute walk distance; PVR – pulmonary vascular resistance; QoL – quality of life; SC – subcutaneous.

In 2024, sotatercept (Winrevair®) became the first new disease-modifying agent approved for PAH in over a decade. Administered subcutaneously every three weeks, it has a manageable safety profile, with side effects such as epistaxis, hypertension, and mild hematological changes (Torbic and Tonelli 2024).

3.6 Enhanced Understanding of Traditional Therapeutic Pathways

Despite the arrival of sotatercept, established therapeutic targets remain central in PAH care. Endothelin receptor antagonists, PDE-5 inhibitors, and prostacyclin analogues/agonists continue to provide vasodilatory and antiproliferative effects (Hajra et al. 2022; Ghofrani et al. 2024).

Combination therapy has become the standard of care, offering superior outcomes to sequential escalation. Current strategies increasingly consider early dual or triple therapy, with the prospect of incorporating sotatercept into multipathway regimens, moving towards a four-pathway approach for comprehensive disease control (Weatherald et al. 2018).

4. Conclusions

Pulmonary hypertension management has advanced remarkably in the past decade, reflecting new hemodynamic definitions, deeper mechanistic insights, and the arrival of transformative therapies. Yet PH remains a progressive, life-limiting condition with substantial global burden, highlighting the need for continued scientific and clinical innovation (Guignabert et al. 2024; Ntiloudi et al. 2024).

4.1 Transformative Clinical Implications

Lowering the diagnostic threshold of mPAP to >20 mmHg marks a paradigm shift, enabling earlier recognition and intervention. This change, however, requires healthcare systems to adapt in terms of screening, provider training, and economic planning (Levine 2021). The approval of sotatercept represents the most significant therapeutic advance since prostacyclin, targeting pulmonary vascular remodelling and offering the potential for true disease modification (Cascino et al. 2024; Hoeper et al. 2023).

4.2 Therapeutic Evolution and Multi-Pathway Targeting

Combination therapy has become standard in PAH, reflecting the disease's multifactorial pathophysiology. The introduction of sotatercept adds a fourth pathway (BMP/activin), expanding treatment strategies and improving outcomes, particularly in high-risk patients. Future practice will likely integrate sotatercept into multi-pathway regimens, demanding careful timing and patient selection (Dardi et al. 2024; Torbic and Tonelli 2024).

4.3 Global Health and Equity Challenges

Epidemiological data confirm PH as a significant global burden, disproportionately affecting women and older adults, with marked regional disparities in diagnosis and treatment (Leary et al. 2024). Inequalities in healthcare access, diagnostics, and drug availability remain critical barriers. Addressing these gaps requires international collaboration, training initiatives, and equitable distribution of therapies to resource-limited settings (Emmons-Bell et al. 2022; Wijeratne et al. 2018).

4.4 Future Research Directions

Emerging fields such as anti-inflammatory therapies, metabolic modulators, regenerative medicine, and precision approaches based on genomics and biomarkers hold promise for further progress (Kasse et al. 2024; Montani et al. 2025). Artificial intelligence and multi-omics platforms may refine patient stratification, support earlier diagnosis, and enable personalised therapy.

4.5 Persistent Challenges and Outlook

Despite advances, PAH remains incurable with 5-year survival near 60% (Hajra et al. 2022). Limited access to specialised care and the high cost of therapies restrict the benefits of innovation for many patients (Mocumbi et al. 2024). Sustainable healthcare policies and global equity in access to treatment are therefore crucial to realise the full potential of scientific progress.

4.6 Final Perspective

Sotatercept and the refinement of diagnostic criteria mark a historic milestone in PH management. Still, further breakthroughs, earlier diagnosis, and equitable access are essential to translate research achievements into lasting patient benefit. The future of pulmonary hypertension care will depend on integrating mechanistic discoveries, multidisciplinary cooperation, and a global commitment to health equity.

Disclosure**Author's contribution:**

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supervision: Michał Wabiszczewicz

project administration: Łukasz Woźniak, Patrycja Krysiak

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