Emerging therapies and new directions in the treatment of pulmonary arterial hypertension

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a severe and progressive disease with limited survival prospects under currently available therapies. Since the 2022 edition of the European Society of Cardiology and European Respiratory Society guidelines on pulmonary hypertension, substantial clinical evidence has emerged, supporting a new treatment algorithm for PAH as presented at the 7th World Symposium on Pulmonary Hypertension 2024 and the following proceeding papers. Key updates include the introduction of sotatercept as a second-line therapy leading to a revised definition of maximal medical therapy now encompassing agents from four therapeutic groups (phosphodiesterase-5 inhibitors/soluble guanylate cyclase stimulators, endothelin receptor antagonists, prostacyclin pathway agents, and sotatercept), instead of three (phosphodiesterase-5 inhibitors/soluble guanylate cyclase stimulators, endothelin receptor antagonists, prostacyclin pathway agents). Other novelties include the elimination of a distinct pathway for patients with cardiopulmonary comorbidities in favor of an individualized approach, a reduction in the initial patient assessment risk categories from three to two, and a follow-up interval shortened from 3–6 months to 3–4 months post-treatment initiation. This review presents these advancements and emphasizes the need for their widespread implementation in clinical practice. At the end, we present new opportunities and challenges in the treatment of pulmonary arterial hypertension in eight Central and Eastern European countries.

Key words: activin signaling inhibitors, novel therapies, risk assessment, treatment strategy, sotatercept

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by the narrowing of small pulmonary arteries, leading to increased pulmonary vascular resistance (PVR), right heart failure, and premature death [1]. It is a rare condition, with a prevalence of 47.6–54.7 cases per million and an average annual incidence of 5.8 cases per million worldwide [2, 3].

The current treatment strategy for PAH emphasizes early initiation and combination of PAH-targeted therapies to reduce mortality and achieve a low-risk status (defined as a 1-year mortality rate of <5%). This approach requires regular risk assessments and escalation of therapy when treatment goals are not met. To date, therapeutic interventions have focused on targeting three main pathways: the endothelin, nitric oxide/cyclic guanosine

monophosphate, and prostacyclin pathway, with combinations of up to three medications [4].

Despite improvement in prognosis after the introduction of specific PAH therapies including the use of early treatment in double or triple combination regimens, the prognosis for PAH patients remains poor [5]. A recent analysis of one multicenter registry did not find significant improvement in 1- or 3-year survival rates when comparing data from the years 2010–2014 and 2015–2019. The estimated 1-year survival rates in this study were 89.0% (95% confidence interval [CI], 87.2%–90.9%) and 90.8% (95% CI, 89.3%–92.4%) for these periods, respectively, while the 3-year survival rates were 67.8% (95% CI, 65.0%–70.8%) and 70.5% (95% CI, 67.8%–73.4%), respectively.

These findings underscore the need for novel therapies that target alternative pathways and new treatment paradigms. The latest edition of the European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines on pulmonary hypertension was published in 2022 [4]. Since then, significant clinical evidence has emerged, including the approval of sotatercept, a breakthrough therapy for PAH. This prompted experts to revise existing treatment strategies, which were thoroughly discussed at the 7th World Symposium on Pulmonary Hypertension (WSPH) and subsequently published [6].

However, implementing these new treatment algorithms into clinical practice presents challenges, with potential geographical variations in adoption. We, the authors of this review, represent eight Central and Eastern European countries: Croatia, Czech Republic, Latvia, Lithuania, Poland, Romania, Slovakia, and Slovenia. These countries transitioned to Western healthcare system models only in the early 1990s following political changes. This might have impacted these countries' ability to adopt new paradigms, particularly given the associated economic burden (in some of them, this is an ongoing problem). Therefore, this review aims to popularize the latest recommendations, highlight their key messages for improving patient prognosis, and provide a regional perspective on the challenges of implementing these recommendations.

NEW TREATMENT OPTIONS

Since the release of the 2022 ESC/ERS guidelines on pulmonary hypertension, three new treatment options have been approved by regulatory agencies: sotatercept, a fixed-dose combination of tadalafil and macitentan, and sildenafil at an 80 mg dose three times a day (TID).

Sotatercept

PAH is characterized by both vasoconstriction and vascular remodeling, the latter involving the proliferation of vascular smooth muscle cells and infiltration of inflammatory cells. This pathological process arises from an imbalance between vasoconstrictive and vasodilatory mediators, as well as pro- and anti-proliferative signals within the pulmonary artery wall. While current therapeutic options — such as phosphodiesterase-5 inhibitors (PDE5i), soluble guanylate cyclase stimulators, endothelin receptor antagonists (ERA), and prostacyclin and its analogs, or prostacyclin receptor agonists (prostacyclin pathway agents [PPA]) — primarily target vasoconstriction, they have limited effects on reversing the vascular remodeling process [7].

One of the key mechanisms implicated in vascular remodeling in PAH is the reduced anti-proliferative signaling *via* the bone morphogenetic protein receptor type II (BMPR-II) pathway, alongside enhanced pro-proliferative signaling through the activin receptor type IIA (ActRIIA) pathway [8–11].

Sotatercept, a novel activin signaling inhibitor, addresses this imbalance by binding to activin and members of the transforming growth factor β superfamily, thereby disrupting downstream signaling *via* the Smad pathway. This intervention helps to restore the balance between growth-promoting activin pathways and growth-inhibiting BMP pathways. The unique mechanism of sotatercept represents a novel therapeutic approach that targets the underlying vascular remodeling in PAH, offering an alternative to the traditional vasodilation-focused treatment strategies.

In the phase III STELLAR study [13], at week 24 from baseline, sotatercept added to background mono-, dual-, or triple-combination therapy demonstrated significant clinical efficacy. The addition of sotatercept resulted in an improvement in the six-minute walk distance test (6MWD) by 40.8 meters compared to placebo, surpassing the established minimum clinically important difference of 33 meters for PAH patients [14]. Beyond improvements in exercise capacity, sotatercept also led to significant reductions in key hemodynamic parameters, including PVR, mean pulmonary arterial pressure (mPAP), and N-terminal pro-B-type natriuretic peptide levels, alongside enhancements in the World Health Organization functional class (WHO-FC). The therapy additionally increased the chance for multicomponent improvement, delayed time to clinical worsening, and improved quality of life, as measured by the SYMPACT score.

Notably, sotatercept induced a 13.6 mm Hg decline in mPAP, an unprecedented reduction in the context of oral PAH therapies, previously observed only in some subsets with parenteral prostacyclin treatment [15, 16]. This substantial reduction in mPAP highlights the potential of sotatercept as a powerful therapeutic option in PAH with a simpler and less complicated treatment modality compared to parenteral PPA.

The favorable effects of sotatercept were sustained for 18 to 24 months, as demonstrated in the open-label extension of the phase II Pulsar study [17].

Adverse events included telangiectasia, increased hemoglobin levels, and bleeding events (mainly epistaxis and gingival bleeding), though drug discontinuation due

to serious adverse events was rare. In 2024, both the Food and Drug Administration (FDA) and the European Medical Agency approved sotatercept as an add-on therapy for adult patients with PAH in WHO-FC class II or III.

Although the long-term impact of sotatercept on survival remains to be fully established, a population health model indicates that the addition of sotatercept to background therapy could potentially, in 30 years, extend life expectancy from 5.1 years to 16.5 years. Furthermore, this approach may increase prostacyclin-free life years from 3.1 to 14.7 and prevent up to 683 hospital admissions and four lung or heart-lung transplantations per 1000 patients [18]. Conversely, delaying the initiation of sotatercept therapy by two years could lead to a loss of 4.1 life years per patient and an increase of 210 additional hospital admissions per 1000 patients over a 30-year time horizon, as recently argued at the 2024 American Thoracic Society Conference.

Fixed dose combination (FDC) of macitentan and tadalafil

In a recently published (A DUE) study, the efficacy of a single-tablet combination of the endothelin receptor antagonist macitentan (10 mg) and the 5PDEi tadalafil (40 mg) was evaluated against monotherapy with either macitentan or tadalafil in their respective doses. Patients with PAH classified as WHO-FC II or III, treatment-naïve or currently receiving ERA or PDE5i monotherapy, were eligible for inclusion [19].

The primary endpoint of the study was the change in PVR from baseline to week 16. Results indicated that the change in PVR was similar in patients randomized to monotherapy with macitentan (23%) and tadalafil (22%). In contrast, patients receiving the FDC treatment exhibited significantly greater reductions in PVR. The FDC demonstrated a reduction in PVR of 29% compared to macitentan monotherapy and 28% compared to tadalafil monotherapy; these effects were similar in treatment-naïve patients and those with prior exposure to ERA or PDE5i.

No significant differences were observed between the treatment groups in the 6MWD test. Considering the absence of statistically significant results in these primary outcomes, subsequent secondary endpoints within the predefined hierarchical testing framework were not formally analyzed. The safety profile of the FDC was consistent with that of macitentan and tadalafil, with no new or unexpected safety concerns identified.

Sildenafil 80 mg TID

Following safety concerns regarding the use of higher doses of sildenafil in the pediatric population, as observed in the open-label extension of the STARTS trial (Sildenafil in Treatment Children, Aged 1 to 17 Years, With Pulmonary Arterial Hypertension) [20], the FDA mandated that the sponsor evaluate the effect of sildenafil on mortality risk in adults with PAH at three oral dosage levels: 5 mg, 20 mg, and 80 mg, administered three times a day.

The AFFILIATE trial [21] was a phase IIIB/IV randomized, double-blind study designed to demonstrate the non-inferiority of sildenafil 80 mg administered TID compared to 5 mg TID concerning all-cause mortality in adult PAH patients. Key inclusion criteria included patients aged ≥18 and <75 years, a diagnosis of PAH in 12 months before randomization, a diagnosis of idiopathic PAH, PAH associated with connective tissue disease, or PAH related to congenital heart disease that had been corrected at least 12 months before randomization. Participants were required to have a WHO-FC of II to IV and a baseline 6MWD test of ≥50 meters.

The study was terminated prematurely after the enrollment of 385 patients when 50% of the predetermined mortality events occurred, indicating that the non-inferiority endpoint was achieved, alongside an observed increase in mortality in the 5 mg group. Additionally, the time to clinical worsening and the 6MWD test were significantly more favorable for the 80 mg dose compared to the 5 mg dose. However, it is noteworthy that discontinuations due to adverse events were more frequent in the 80 mg group. Importantly, no significant differences in mortality, clinical worsening, or 6MWD test were observed between the 80 mg TID and 20 mg TID sildenafil groups.

Consequently, the US FDA updated the labeling for sildenafil in the treatment of PAH, which included the withdrawal of the 5 mg oral dose recommendation. The updated labeling also permits titration of the sildenafil dose to 80 mg administered TID when necessary, based on patient symptoms and tolerance. Furthermore, the recommendation for a standard dose of 20 mg TID was reinforced.

Ongoing advanced-phase studies in PAH

Sotatercept has been approved for the treatment of PAH based on the results of the STELLAR study. However, further data are awaited to evaluate its efficacy and safety in patients with more advanced disease (WHO-FC III and IV) through the ZENITH trial. On November 25, 2024, Merck announced that the ZENITH trial met its primary endpoint — time to first morbidity or mortality event — at an interim analysis, leading to the early termination of the study to allow all participants access to sotatercept. Additionally, the HYPERION trial is assessing sotatercept in patients with recently (up to 1 year) diagnosed PAH. The long-term safety and efficacy of sotatercept are currently being evaluated in the open-label SOTERIA study. The concept of targeting the activin signaling pathway is also being explored using cibotercept (KER-012) in the phase II TROPOS study (on January 15, 2025 the study was halted by the sponsor due to the risk of pericardial effusion in patients treated with cibotercept). Furthermore, the tyrosine kinase inhibitor seralutinib is undergoing evaluation in PAH patients in the phase III PROSERA study, following positive outcomes reported in the phase II TORREY trial [22].

TREATMENT GOALS AND RISK ASSESSMENT

The 2022 ESC and ERS guidelines emphasize that the primary therapeutic objective in the management of PAH patients is to achieve and maintain a low-risk profile, defined by a one-year mortality rate of <5%. In the context of the four-stratum risk model, classification of patients as low risk requires meeting the low-risk thresholds in at least two of the following parameters during follow-up assessments: WHO-FC I or II, 6MWD test exceeding 440 meters, and plasma levels of BNP <50 ng/l or N-terminal pro-B-type natriuretic peptide <300 ng/l. Patients meeting two of these low-risk criteria demonstrate an estimated five-year survival rate of approximately 80%. Importantly, when all three criteria are fulfilled, the five-year survival rate increases to 90% [23].

An analysis of data from three major randomized controlled trials in PAH — AMBITION, GRIPHON, and SERAPHIN — demonstrated that more than 20% of patients initially classified as low risk, based on multiparameter risk scores, experienced clinical worsening events within three years of study enrollment [24]. These findings highlight that achieving a low-risk profile according to the ESC/ERS four-stratum risk model may not reliably predict favorable medium- or long-term outcomes. As such, recent proceedings from the WSPH [25] have underscored the necessity of incorporating additional hemodynamic and echocardiographic variables into the risk stratification process to guide therapeutic decision-making more effectively. Emerging data suggest that the stroke volume index may enhance risk stratification, particularly in patients categorized as intermediate risk during follow-up assessments [26].

The concept of hemodynamic normalization, or near normalization, has been discussed as a potential therapeutic target in PAH management. This has been observed mainly in young, newly diagnosed patients with idiopathic, heritable, or PAH associated with drugs and toxins (I/H/DT PAH) who received initial combination therapy with PDE5i, ERA, and intravenous or subcutaneous PPA [15, 16]. Achieving such ambitious objectives in PAH treatment may become increasingly feasible with the advent of novel therapeutic agents. For instance, in the recent STELLAR trial, the addition of sotatercept to background double or triple combination therapy resulted in a mean reduction in mPAP of approximately 14 mm Hg.

Achieving a low-risk profile in patients with PAH presents particular challenges in specific subpopulations, such as older individuals or those with significant comorbidities requiring disease-specific management. Additionally, patients who are unable to tolerate or who decline advanced therapies may struggle to reach low-risk status. Notably, conventional markers of risk stratification, such as improvements in the 6MWD test or functional class, may not reliably reflect meaningful improvements in pulmonary hemodynamics in patients with concurrent diseases such as untreated coronary artery disease or obesity. In these populations, comorbidities must be intensively treated in parallel with the introduction of PAH therapies.

CHANGES IN THE PAH TREATMENT ALGORITHM

ESC/ERS 2022 algorithm

According to the 2022 ESC/ERS guidelines, treatment decisions for PAH patients are based on PAH etiology, calculated risk of death, and the presence of cardiopulmonary comorbidities.

Patients with IPAH, HPAH, DPAH, and PAH associated with connective tissue disease or corrected congenital heart disease without cardiovascular comorbidities are recommended to follow the classical treatment algorithm if they have mPAP ≥25 mm Hg and PVR >3 Wood units and do not respond on acute vasoreactivity testing. Patients at high risk or intermediate risk but with high-risk hemodynamics at diagnosis are recommended to receive up-front combination therapy with 2 oral medications (a PDE5 inhibitor and an ERA) along with subcutaneous or intravenous PPA, while patients classified as low and intermediate risk are offered dual oral therapy. Treatment escalation is recommended for patients who do not achieve or maintain a low-risk status despite initial therapy during follow-up assessment 3-6 months after initiation of therapy. The follow-up risk assessment based on the four-stratum risk model determines treatment escalation. Patients who maintain or achieve low-risk status are recommended to continue initial therapy. In patients with intermediate-low risk, addition of prostacyclin receptor agonists or switching PDE5i to soluble guanylate cyclase stimulators is a treatment option. Patients at intermediated-high or high risk are recommended maximal medical therapy, including ERA, PDE5i, and intravenous or subcutaneous PPA. Additionally, patients should be referred to the lung transplantation center.

A separate arm in the 2022 treatment algorithm is dedicated to patients with cardiopulmonary comorbidities which include conditions associated with increased risk of left ventricular diastolic dysfunction such as obesity, hypertension, diabetes mellitus, and coronary heart disease and pulmonary comorbidities such as mild parenchymal lung disease usually associated with a low diffusing capacity for carbon monoxide of <45% of the predicted value.

This part of the treatment algorithm assumes starting therapy with a single medication regardless of the initial risk of mortality, strict observation of effectiveness and safety, and treatment escalation if required.

WSPH 2024 PAH treatment algorithm

The modification of the classical treatment algorithm, as presented at WSPH 2024 (Figure 1) and outlined in a subsequent proceeding paper [6], introduces several key changes

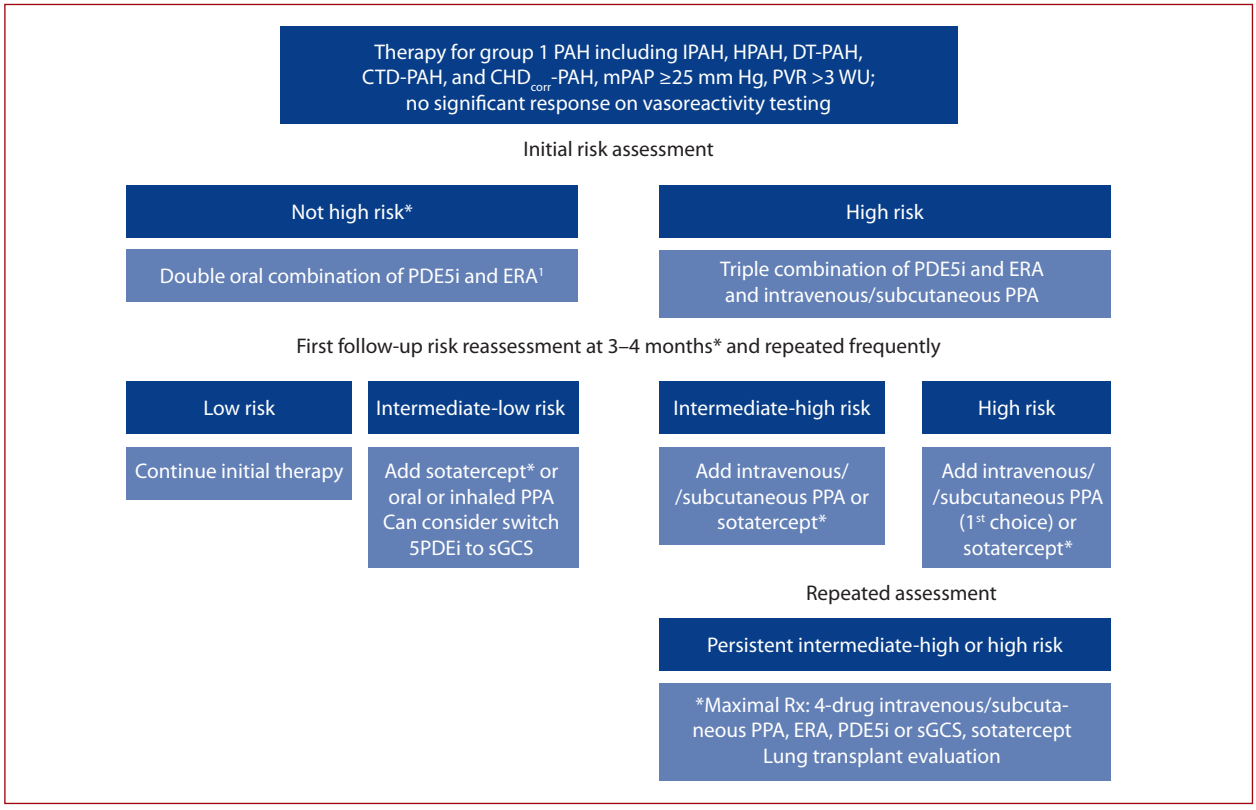

Figure 1. New (2024) treatment algorithm of pulmonary arterial hypertension

[1]Ambrisentan or macitentan plus tadalafil preferred over other combinations of ERA and PDE5i;
*Changes in the 2024 therapeutic algorithm as compared to the ESC/ERS 2022 guidelines (see Table 1)
Abbreviations: CHD_{corr}-PAH, PAH associated with congenital heart disease after correction; ERA, endothelin receptor antagonist; HPAH, heritable PAH; IPAH, idiopathic PAH; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; DT-PAH PAH associated with drugs and toxins; PDE5i, phosphodiesterase 5 inhibitors; PPA, prostacyclin pathway agents; PVR, pulmonary vascular resistance; sGCS, soluble guanylate cyclase stimulator

Table 1. Main modifications of the pulmonary arterial hypertension treatment algorithm

Two vs. three risk categories at initial patient assessment
Reduced time to the first follow-up visit after treatment initiation from 3–6 to 3–4 months
Sotatercept incorporated as a second-line therapeutic option
New definition of maximal medical therapy including PDE5i, ERA, PPA and sotatercept
Lack of a separate pathway for patients with comorbidities is substituted by an individualized approach based on careful diagnostics, including right heart catheterization, with strict monitoring for efficacy and safety

Abbreviations: ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase 5 inhibitors; PPA, prostacyclin pathway agents

(Table 1) including: a simplified decision-making process for newly diagnosed patients, now based on 2 risk categories (high and non-high) and replacing the previous three-category model (high, intermediate, and low risk). The time to the first follow-up visit after treatment initiation has been reduced to 3–4 months. Sotatercept has been incorporated as a second-line therapeutic option. Additionally, a new definition of maximal medical therapy has been introduced, and the algorithm no longer includes a separate pathway for patients with comorbidities. The standard treatment algorithm primarily applies to patients with a negative response to vasoreactivity testing, including those with IPAH, HPAH, DPAH, PAH associated with drugs and toxins, connective tissue disease, and corrected congenital heart defects. No significant changes have been proposed for the treatment of other PAH subgroups.

As previously recommended, the preferred treatment for newly diagnosed patients who are not categorized as high-risk remains the combination of tadalafil with either macitentan or ambrisentan, based on superior evidence supporting this regimen over alternative combinations [19, 27, 28]. A novel approach under consideration is the escalation of sildenafil dosage to 80 mg TID to enhance efficacy; however, this strategy is associated with a higher incidence of adverse events, warranting careful consideration of the risk-benefit profile in individual patients. The regular interval from treatment initiation to the first follow-up, previously recommended at 3–6 months, has been shortened to 3–4 months. This adjustment is based on evidence that most prognostic parameters either stabilize or approach a plateau by this time, making the 3-6 month period a critical window for reassessment. However, earlier assessment should be considered in cases of clinical deterioration or lack of improvement. Early identification of suboptimal response allows for timely treatment escalation, which has been shown to be more effective when implemented

earlier in the disease course, potentially improving long-term outcomes in PAH patients [29].

The risk assessment at follow-up visits should involve WHO FC, 6MWD test, and natriuretic peptide level evaluation to group patients into one of four risk categories. However, these measures should be supplemented with other diagnostic parameters including hemodynamics, echocardiography, and others.

Sotatercept has been recommended as an adjunctive therapy for patients classified as intermediate-low or intermediate-high risk, where it competes with oral or inhaled PPA in the former group, and with intravenous or subcutaneous PPA in the latter. It should also be part of a triple combination therapy as a second-choice option (subcutaneous or intravenous PPA is a first-choice option) in patients who are at high risk despite double oral therapy.

Maximal medical therapy has been upgraded from the conventional combination of three agents — ERA, PDE5i, and IV/SC PPA — to a 4-drug regimen that includes sotatercept. This enhanced therapeutic approach is now indicated for patients classified as intermediate-high or high-risk who do not achieve optimal clinical outcomes despite treatment with the three-drug combination. The inclusion of sotatercept in this regimen reflects its emerging role in addressing more advanced disease states and improving patient outcomes in those who remain inadequately controlled on existing therapies.

The 2024 WSPH proceedings, in contrast to the 2022 ESC/ERS guidelines, omit a distinct treatment algorithm for patients with PAH and cardiopulmonary comorbidities. This decision reflects the considerable heterogeneity in pathophysiology and phenotypes in this group. Patients with PAH and comorbidities include those with well-defined group 1 PAH, who may benefit from PAH-specific therapies, as well as those who may not benefit or could even be harmed, such as individuals with occult group 2 pulmonary hypertension. The latter group is characterized by borderline pulmonary artery wedge pressure values (12–15 mm Hg), relatively low PVR (3–5 Wood units), and echocardiographic evidence of left heart disease, including left atrial enlargement, grade 2 or higher diastolic dysfunction, reduced left ventricular ejection fraction, or left-sided valve dysfunction. Additionally, these patients often present with medical conditions associated with left heart disease, such as hypertension, diabetes, obesity, sleep apnea, atrial fibrillation, and coronary artery disease [30]. In such cases, hemodynamic evaluation using fluid or exercise challenge may reveal underlying left ventricular dysfunction, helping to differentiate these patients from those who would benefit from PAH-targeted therapies.

The treatment decisions in PAH patients with comorbidities may depend on the relation between the severity of pulmonary vascular disease as measured by PVR and the comorbidity burden. In PAH patients with relatively low PVR and high comorbidity burden, the comorbidities should be controlled and monotherapy should be considered with strict monitoring of efficacy and safety. In such cases, PDE5i is preferred over ERA due to its favorable safety profile. If the risk does not improve to low or right ventricular function and PVR does not improve, additional therapy should be considered. In patients with suspected risk of side effects, especially fluid retention, sotatercept may be preferred over ERA.

Conversely, patients who meet strict PAH criteria and present with elevated PVR may be suitable candidates for combination therapy, as outlined in the classical treatment algorithm. However, due to the potential complexity introduced by comorbidities, these patients require rigorous monitoring for adverse effects, particularly in the context of advanced therapies. Careful assessment of treatment tolerance and regular follow-up are essential to mitigate the risk of side effects and to optimize clinical outcomes in this subgroup.

An illustrative example of a tailored therapeutic approach in patients with comorbidities has been presented by US pulmonary hypertension [31] experts. In the case of an elderly woman with hypertension, diabetes, and obesity (representing a high burden of comorbidities) and a PVR of 3.2 Wood units (indicating a low burden of pulmonary vascular disease), the recommended strategy focuses on optimizing the management of her underlying medical conditions, with consideration of PDE5i monotherapy if symptoms persist. Conversely, for a 45-year-old woman with a history of well-controlled hypertension (low burden of comorbidities) and a PVR of 12 Wood units (indicating a high burden of pulmonary vascular disease), the recommendation is to pursue an aggressive treatment regimen for PAH, in line with the classical treatment algorithm. This approach underscores the importance of careful evaluation of patients including hemodynamic data and tailoring therapy based on the balance between comorbidity burden and the severity of pulmonary vascular disease.

In certain patients with comorbidities, treatment with PAH-specific medications may unmask an underlying condition, leading to a change in diagnosis. A common scenario involves a 60-year-old obese woman with systemic hypertension who experiences clinical deterioration while on sildenafil therapy. On physical examination, this patient may present with crackles over the lower lung fields, and RHC would reveal a decrease in PVR accompanied by a significant rise in pulmonary artery wedge pressure, indicative of left heart dysfunction. In such cases, PAH therapy should be discontinued, and the management strategy should shift towards treating left ventricular failure, as this is likely the primary underlying condition. This highlights the importance of re-evaluating the diagnosis and therapeutic approach when PAH-specific treatments lead to unexpected clinical outcomes.

The new treatment algorithm with some modifications has been recently endorsed by US [31] and Belgian [32] pulmonary hypertension experts.

Table 2. Prevalence and incidence of pulmonary arterial hypertension and access to specific therapies in Central and Eastern European Countries

	Croatia	Czech Republic [36, Reply registry]	Latvia [37-39]	Lithuania	Poland [40]	Romania	Slovakia	Slovenia
No of patients with PAH/million adults	41.2[a]	49.6[a]	45.7[a]	55.8[a]	30.8[a]	50[b]	43[b]	35[b]
New diagnosis of PAH per year/million adults	5–6[b]	8.5[a]	9.0–12.04[a]	7–8[b]	5.2[a]	4–5[b]	5.4[b]	5[b]
National PAH registry [Yes/No]	No	Yes	Yes	Yes	Yes	No	No	No
Reimbursed therapies								
Bosentan po [Yes/No]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Macitentan po [Yes/No]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Ambrisentan po [Yes/No]	No	Yes	Yes	Yes	No	No	Yes	Yes
Sildenafil po [Yes/No]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tadalafil po [Yes/No]	Yes	Yes	Yes	No	No	No	Yes	No
Riociguat po [Yes/No]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Treprostinil sc/iv [Yes/No]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Treprostinil inh [Yes/No]	No	No	No	No	No	No	No	No
Treprostinil po [Yes/No]	No	No	No	No	No	No	No	No
Epoprostenol iv [Yes/No]	No	Yes	No	No	Yes	No	Yes	Yes
Selexipag [Yes/No]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Iloprost iv [Yes/No]	No	No	No	No	No	No	No	Yes
Iloprost inh [Yes/No]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Sotatercept sc [Yes/No]	Yes	Yes[c]	No	No	No	No	No	Yes[c]
Double oral combination ERA + PED5i [Yes/No]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Triple combination ERA + PDE5i + Treprostinil sc/iv or Epoprostenol iv [Yes/No]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Quadruple combination ERA + PDE5i + Treprostinil sc/iv or Epoprostenol iv [Yes/No] + sotatercept	Yes	Yes[c]	No	No	No	No	No	No

[a]Based on registry data. [b]Based on estimation. [c]Early access program only

Abbreviations: inh, inhalation; iv, intravenous; PAH, pulmonary arterial hypertension; po, per os; sc, subcutaneous; other — see Table 1

Additional treatments and supportive measures [33–35] in PAH management were not significantly changed.

Perspective of the Central-Eastern European Countries and Call for Action

In the Central and Eastern European Countries, it was not until the early 21st century that therapies specifically targeting PAH began to be formally included in reimbursement schemes. Consequently, the availability of advanced diagnostic tools and targeted treatment options for PAH was somehow delayed compared to Western Europe — even by nearly 2 decades in some countries. Additionally, in several countries, certain therapies, including PPA and triple combination regimens, have only recently been introduced, and their use remains limited.

In Table 2 we present a review of epidemiological data and current therapeutic options in selected Central/Eastern European countries based on observational studies or expert opinion. It shows that the prevalence and incidence of PAH are similar to those reported in Western countries. The availability of oral treatment is wide, and all countries declare access to subcutaneous or intravenous treprostinil; however, epoprostenol and sotatercept are not available in most countries.

With new therapies recently approved by US and European regulatory agencies, there is an urgent expectation from both PAH patients and healthcare providers for these treatments to become widely accessible when indicated. The remarkable efficacy and safety profile of sotatercept positions it as a potentially life-saving therapy, particularly for patients who either cannot tolerate or do not adequately respond to maximal vasodilatory therapy. Despite the potentially high cost of this novel treatment, its favorable efficacy-to-safety ratio and the low prevalence of PAH, which limits the overall cost burden, support our advocacy for its availability in all regions where it has been approved.

Article information

Conflict of interest: GK received lecture honoraria from MSD, AOP Orphan, Janssen, Pfizer, travel expenses coverage from MSD, Janssen, AOP Orphan, research grants from Ferrer, consultancy fees from MSD, AOP Orphan, Janssen, Acceleron, Aerovate, Liquidia and Gossamer BIO; AS received lecture honoraria from Liquidia and Merck, travel expenses coverage from Gossamer bio, AOP Orphan and Liquidia; EE received travel expenses and consultancy fee from MSD; IS received: lecture honoraria from MSD, travel expenses coverage from MSD, AOP, Viatris, consultancy fees from MSD; RE received travel expenses coverage from MSD, AOP Orphan Pharmaceuticals, Janssen; MS has received honoraria as a speaker and as a part of advisory board from Roche, MSD, Pfizer, AstraZeneca, Swixx Biopharma and BMS; BS received lecture honoraria from MSD, AOP Orphan, Janssen, Chiesi, coverage from MSD, AOP Orphan, Providens, consultancy fees from MSD, Chiesi, Janssen; PJ has received lecture honoraria from MSD, AOP Health, AstraZeneca, travel expenses coverage from AOP Health and Janssen Pharmaceutical Companies of Johnson & Johnson, research grants from Janssen Pharmaceutical Companies of Johnson & Johnson, AOP Health, Bayer Healthcare, MSD and AstraZeneca, consultancy fees

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REFERENCES

1. Kopeć G. Sotatercept as a next-generation therapy for pulmonary arterial hypertension: Insights from the STELLAR trial. Cardiovasc Res. 2023; 119(16): e155–e157, doi: 10.1093/cvr/cvad121, indexed in Pubmed: 37584249.
2. Leber L, Beaudet A, Muller A. Epidemiology of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: Identification of the most accurate estimates from a systematic literature review. Pulm Circ. 2021; 11(1): 2045894020977300, doi: 10.1177/2045894020977300, indexed in Pubmed: 33456755.
3. Kopeć G, Kurzyna M, Mroczek E, et al. Characterization of Patients with Pulmonary Arterial Hypertension: Data from the Polish Registry of Pulmonary Hypertension (BNP-PL). J Clin Med. 2020; 9(1): 173, doi: 10.3390/jcm9010173, indexed in Pubmed: 31936377.
4. Kularatne M, Gerges C, Jevnikar M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022; 43(38): 3618–3731, doi: 10.1093/eurheartj/ehac237, indexed in Pubmed: 36017548.
5. Hoeper MM, Pausch C, Grünig E, et al. Temporal trends in pulmonary arterial hypertension: results from the COMPERA registry. Eur Respir J. 2022; 59(6): 2102024, doi: 10.1183/13993003.02024-2021, indexed in Pubmed: 34675047.
6. Chin KM, Gaine SP, Gerges C, et al. Treatment algorithm for pulmonary arterial hypertension. Eur Respir J. 2024; 64(4): 2401325, doi: 10.1183/13993003.01325-2024, indexed in Pubmed: 39209476.
7. Guignabert C, Aman J, Bonnet S, et al. Pathology and pathobiology of pulmonary hypertension: current insights and future directions. Eur Respir J. 2024; 64(4): 2401095, doi: 10.1183/13993003.01095-2024, indexed in Pubmed: 39209474.
8. Ryanto GRT, Ikeda K, Miyagawa K, et al. An endothelial activin A-bone morphogenetic protein receptor type 2 link is overdriven in pulmonary hypertension. Nat Commun. 2021; 12(1): 1720, doi: 10.1038/s41467-021-21961-3, indexed in Pubmed: 33741934.
9. Guignabert C, Humbert M. Targeting transforming growth factor-β receptors in pulmonary hypertension. Eur Respir J. 2021; 57(2): 2002341, doi: 10.1183/13993003.02341-2020, indexed in Pubmed: 32817256.
10. Yung LM, Yang P, Joshi S, et al. ACTRIIA-Fc rebalances activin/GDF versus BMP signaling in pulmonary hypertension. Sci Transl Med. 2020; 12(543), doi: 10.1126/scitranslmed.aaz5660, indexed in Pubmed: 32404506.
11. Andre P, Joshi SR, Briscoe SD, et al. Therapeutic approaches for treating pulmonary arterial hypertension by correcting imbalanced TGF-β superfamily signaling. Front Med (Lausanne). 2021; 8: 814222, doi: 10.3389/fmed.2021.814222, indexed in Pubmed: 35141256.
12. Joshi SR, Liu J, Bloom T, et al. Sotatercept analog suppresses inflammation to reverse experimental pulmonary arterial hypertension. Sci Rep. 2022; 12(1): 7803, doi: 10.1038/s41598-022-11435-x, indexed in Pubmed: 35551212.
13. Hoeper MM, Badesch DB, Ghofrani HA, et al. Phase 3 trial of sotatercept for treatment of pulmonary arterial hypertension. N Engl J Med. 2023; 388(16): 1478–1490, doi: 10.1056/NEJMoa2213558, indexed in Pubmed: 36877098.
14. Moutchia J, McClelland RL, Al-Naamani N, et al. Minimal clinically important difference in the 6-minute-walk distance for patients with pulmonary arterial hypertension. Am J Respir Crit Care Med. 2023; 207(8): 1070–1079, doi: 10.1164/rccm.202208-1547OC, indexed in Pubmed: 36629737.
15. Sitbon O, Jaïs X, Savale L, et al. Upfront triple combination therapy in pulmonary arterial hypertension: A pilot study. Eur Respir J. 2014; 43(6): 1691–1697, doi: 10.1183/09031936.00116313, indexed in Pubmed: 24627535.
16. D'Alto M, Badagliacca R, Argiento P, et al. Risk reduction and right heart reverse remodeling by upfront triple combination therapy in pulmonary arterial hypertension. Chest. 2020; 157(2): 376–383, doi: 10.1016/j.chest.2019.09.009, indexed in Pubmed: 31563498.
17. Gomberg-Maitland M, McLaughlin VV, Badesch DB, et al. Long-term effects of sotatercept on right ventricular function: Results from the PULSAR study. JACC Heart Fail. 2023; 11(10): 1457–1459, doi: 10.1016/j.jchf.2023.05.030, indexed in Pubmed: 37452806.
18. McLaughlin V, Alsumali A, Liu R, et al. Population health model predicting the long-term impact of sotatercept on morbidity and mortality in patients with pulmonary arterial hypertension (PAH). Adv Ther. 2024; 41(1): 130–151, doi: 10.1007/s12325-023-02684-x, indexed in Pubmed: 37851297.
19. Grünig E, Jansa P, Fan F, et al. Randomized trial of macitentan/tadalafil single-tablet combination therapy for pulmonary arterial hypertension. J Am Coll Cardiol. 2024; 83(4): 473–484, doi: 10.1016/j.jacc.2023.10.045, indexed in Pubmed: 38267108.
20. Barst RJ, Beghetti M, Pulido T, et al. STARTS-2: Long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension. Circulation. 2014; 129(19): 1914–1923, doi: 10.1161/CIRCULATIONAHA.113.005698, indexed in Pubmed: 24637559.
21. Hoeper MM, Ewert R, Jansa P, et al. Randomized, multicenter study to assess the effects of different doses of sildenafil on mortality in adults with pulmonary arterial hypertension. Circulation. 2024; 149(25): 1949–1959, doi: 10.1161/CIRCULATIONAHA.123.068107, indexed in Pubmed: 38752352.
22. Frantz RP, McLaughlin VV, Sahay S, et al. Seralutinib in adults with pulmonary arterial hypertension (TORREY): A randomised, double-blind, placebo-controlled phase 2 trial. Lancet Respir Med. 2024; 12(7): 523–534, doi: 10.1016/s2213-2600(24)00072-9, indexed in Pubmed: 38705167.
23. Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J. 2017; 50(2): 1700889, doi: 10.1183/13993003.00889-2017, indexed in Pubmed: 28775050.
24. Blette BS, Moutchia J, Al-Naamani N, et al. Is low-risk status a surrogate outcome in pulmonary arterial hypertension? An analysis of three randomised trials. Lancet Respir Med. 2023; 11(10): 873–882, doi: 10.1016/S2213-2600(23)00155-8, indexed in Pubmed: 37230098.
25. Dardi F, Boucly A, Benza R, et al. Risk stratification and treatment goals in pulmonary arterial hypertension. Eur Respir J. 2024; 64(4): 2401323, doi: 10.1183/13993003.01323-2024, indexed in Pubmed: 39209472.
26. Boucly A, Beurnier A, Turquier S, et al. PulmoTension Network. Risk stratification refinements with inclusion of haemodynamic variables at follow-up in patients with pulmonary arterial hypertension. Eur Respir J. 2024; 64(3): 2400197, doi: 10.1183/13993003.00197-2024, indexed in Pubmed: 38663975.
27. Galiè N, Barberà JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med. 2015; 373(9): 834–844, doi: 10.1056/NEJMoa1413687, indexed in Pubmed: 26308684.
28. McLaughlin V, Channick RN, Ghofrani HA, et al. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. Eur Respir J. 2015; 46(2): 405–413, doi: 10.1183/13993003.02044-2014, indexed in Pubmed: 26113687.
29. Gaine S, Sitbon O, Channick RN, et al. Relationship between time from diagnosis and morbidity/mortality in pulmonary arterial hypertension: Results from the phase III GRIPHON study. Chest. 2021; 160(1): 277–286, doi: 10.1016/j.chest.2021.01.066, indexed in Pubmed: 33545163.
30. Sahay S, Chakinala MM, Kim NH, et al. Contemporary treatment of pulmonary arterial hypertension: A U.S. perspective. Am J Respir Crit Care Med. 2024; 210(5): 581–592, doi: 10.1164/rccm.202405-0914SO, indexed in Pubmed: 38984912.
31. Jonas K, Kurzyna M, Mroczek E, et al. Impact of diabetes mellitus on disease severity and patient survival in idiopathic pulmonary arterial hypertension: data from the Polish multicentre registry (BNP-PL). Cardiovasc Diabetol. 2023; 22(1): 177, doi: 10.1186/s12933-023-01885-6, indexed in Pubmed: 37443009.
32. Vachiéry JL, Belge C, Cools B, et al. A Belgian consensus on sotatercept for the treatment of pulmonary arterial hypertension. Acta Cardiol. 2024; 79(9): 978–983, doi: 10.1080/00015385.2024.2408130, indexed in Pubmed: 39377139.

33. Kopeć G, Araszkiewicz A, Magoń W, et al. Results of atrial flow regulator implantation in pulmonary arterial hypertension patients with severe heart failure despite maximal medical therapy. Pol Heart J. 2024; 82(1): 75–78, doi: 10.33963/KP.a2023.0167, indexed in Pubmed: 37537913.
34. Havranek S, Fingrova Z, Dusik M, et al. Benefits from catheter ablation in patients with pulmonary hypertension: Recent advances. Pol Heart J. 2024; 82(6): 602–608, doi: 10.33963/v.phj.101246, indexed in Pubmed: 38973418.
35. Cruz-Utrilla A, García-Martín EP, Domínguez Pérez L, et al. ECMO in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension as a bridge to therapy. Kardiol Pol. 2023; 81(5): 500–504, doi: 10.33963/KP.a2023.0055, indexed in Pubmed: 36871299.
36. Jansa P, Jarkovsky J, Al-Hiti H, et al. Epidemiology and long-term survival of pulmonary arterial hypertension in the Czech Republic: A retrospective analysis of a nationwide registry. BMC Pulm Med. 2014; 14: 45, doi: 10.1186/1471-2466-14-45, indexed in Pubmed: 24629043.
37. Skride A, Sablinskis K, Lejnieks A, et al. Characteristics and survival data from Latvian pulmonary hypertension registry: Comparison of prospective pulmonary hypertension registries in Europe. Pulm Circ. 2018; 8(3): 2045894018780521, doi: 10.1177/2045894018780521, indexed in Pubmed: 29767576.
38. Kaulins R, Rudzitis A, Lejnieks A, et al. Pulmonary arterial hypertension incidence in Latvia in 2019. Pulm Circ. 2022; 12(4): e12161, doi: 10.1002/pul2.12161, indexed in Pubmed: 36465603.
39. Kigitovica D, Sablinskis M, Sablinskis K, et al. Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension incidence in Latvia in 2018. Eur J Intern Med. 2019; 65: e9–e10, doi: 10.1016/j.ejim.2019.04.022, indexed in Pubmed: 31101467.
40. Kopeć G, Kurzyna M, Mroczek E, et al. Database of Pulmonary Hypertension in the Polish Population (BNPPL): Design of the registry. Kardiol Pol. 2019; 77(10): 972–974, doi: 10.33963/KP.14988, indexed in Pubmed: 31553328.