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Pulmonary Arterial Hypertension Diagnosis, Treatment, and Clinical Management in the Contemporary Era

Bradley A. Maron, M.D.¹ and Nazzareno Galiè, M.D.²

¹Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA and Department of Cardiology, Boston VA Healthcare System, Boston, MA, USA

²Department of Experimental, Diagnostic, and Specialty Medicine, University of Bologna, via Massarenti 9, Bologna 40138, Italy

Abstract

Importance—Pulmonary arterial hypertension (PAH) is characterized by severe remodeling of distal pulmonary arteries, increased pulmonary vascular resistance and right ventricular dysfunction that promotes heart failure. Once regarded as largely untreatable, evidence-based decision-making now guides clinical management of patients and improves PAH outcome. Yet, misconceptions regarding the approach to PAH in the modern era are common and associated with substandard clinical care.

Observations—The clinical profile of PAH has changed substantially since its original description: the age at diagnosis is older than previously reported, disease severity appears greater in men compared to women, and PAH in association with connective tissue disease is identified as a particularly high risk patient subgroup. Risk stratification scales for PAH are now available at point of care, which inform treatment goals including: 6-minute walk distance >440 m, peak VO_2 >15 ml/min/kg, right atrial area <18 cm², cardiac index >2.5 l/min/m², and absent/low symptom burden with routine physical activity. Currently, 14 therapies targeting six PAH-specific molecular intermediaries are in use clinically. Recent landmark trial data have demonstrated the critical importance of initial combination therapy in treatment-naïve patients. Taken together, these findings underscore a global shift in PAH coupling early disease detection with aggressive pharmacotherapy. Indeed, recent longitudinal data from combination therapy patients shows that the 3-year survival rate in PAH may be as high as 84% compared with 48% from the original National Institutes of Health registry on idiopathic PAH (1980-1985). Despite these gains, incomplete clinical evaluation and misdiagnosis by referring practitioners is common and associated with inappropriate therapy.

Conclusions and Relevance—Compared to the original clinical experience, PAH has evolved into a contemporary and treatable disease characterized by improved survival and a high standard for defining therapeutic success. However, under-awareness among clinicians regarding the

importance of early and accurate PAH diagnosis persists and is a potentially reversible cause of adverse outcome in this disease.

Introduction

Twenty years ago, the first clinical trial demonstrating superiority of a disease-specific medical intervention in pulmonary arterial hypertension (PAH) was published based on findings from a small cohort of end-stage idiopathic PAH (iPAH) patients.¹ In contradistinction to the original clinical experience, PAH has evolved into a treatable disease characterized by maintained quality of life and improved longevity in many patients.² Despite these gains, the adverse clinical event rate in PAH remains elevated. Fresh epidemiological and clinical trial data suggests that missed opportunity to improve outcome in PAH may exist by virtue of delayed diagnosis and late implementation of disease-specific therapy.³⁻⁵ From this perspective, the contemporary approach to PAH diagnosis, management, and treatment is discussed further in detail.

Demystifying the Approach to PAH Diagnosis

Pulmonary hypertension is diagnosed based on a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg determined by resting supine right heart catheterization (RHC).^{6,7} Although a wide spectrum of conditions promote pulmonary hypertension, PAH is characterized by remodeling of distal pulmonary arteries in the absence of other cardiopulmonary disease. An elevation in mPAP alone does not exclude left atrial hypertension or describe the disease severity, as pulmonary arterial pressure may be only mildly increased in the setting of end-stage right ventricular failure. Therefore, a diagnosis of PAH is considered in mPAP ≥ 25 patients with pulmonary artery wedge pressure (PAWP) ≥ 15 mmHg and pulmonary vascular resistance (PVR) >3.0 Wood Units.^{6,7} Diagnosing PAH requires exclusion of co-morbid cardiac, parenchymal lung, thromboembolic, and other diseases that predispose to abnormal cardiopulmonary hemodynamics (Figure 1).

The approach to PAH will often involve two-dimensional Doppler echocardiography, complete pulmonary function testing, thoracic computed tomography (CT), and nocturnal plethysmography to evaluate sleep disordered breathing. A ventilation/perfusion scan to assess for chronic thromboembolic pulmonary hypertension is critical in all patients suspected of PAH, since this disease is curable by surgical endarterectomy in most cases and treatable medically or by balloon pulmonary angioplasty in patients who are poor operative candidates (Reviewed in detail in ref. 8).

Although iPAH is the most common PAH subgroup, serological analysis for markers of connective tissue disease (CTD), liver failure, and human immunodeficiency virus (HIV) should also be performed as results may inform a diagnosis of CTD-PAH, PAH associated with portal hypertension, and HIV-PAH, respectively. In patients at risk for heritable PAH (HPAH), screening for a mutation in *BMPR-2* or other selected genes may be indicated. Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis are rare PAH subgroups caused by obstructive remodeling of pulmonary venules and proliferation of capillaries, respectively.⁹ Confirming the approach to diagnosing these diseases as well as

PAH in congenital heart disease or pediatric patients requires consultation with a qualified specialist (Table 1).^{6,7}

Delayed Diagnosis in PAH is Common—Inappropriate, incomplete, and delayed diagnosis of pulmonary hypertension is common and reported in up to 85% of at-risk patients.^{10,11} This is likely due, in part, to the high frequency of non-specific symptoms at presentation, such as exertional dyspnea. Nonetheless, patients with PAH on average express symptoms 2 years prior to diagnosis.¹² Misconceptions among clinicians regarding the diagnostic criteria for PAH, declining utilization of RHC despite its favorable safety profile, and over-reliance on echocardiography despite its inadequate accuracy for measuring right heart hemodynamics contribute to misdiagnosis of patients.¹³ In one multi-center cross-sectional analysis of patients diagnosed with PAH in community hospitals and referred to a quaternary specialty center, 37% of patients had not yet undergone RHC, which ultimately resulted in diagnosis reclassification and the identification of prescribed therapy that was inappropriate in 52% and 57% of the cohort, respectively.¹¹

Novel Clues to the Clinical Spectrum of Risk in PAH—There is accumulating evidence to suggest that in CTD-PAH, a mPAP <25 mmHg is abnormal. For example, resting mPAP >17 mmHg corresponds to a significant decrease in 6-minute walk distance (6-MWD) and peak volume of oxygen (pVO₂) extraction during cardiopulmonary exercise testing (CPET) as compared to matched patients with mPAP <17 mmHg.¹⁴ In one study of mixed clinical populations that includes CTD-PAH, resting mPAP ~20-25 mmHg was associated with significantly diminished exercise tolerance and a 4.8-fold increase in the 4-yr mortality rate.¹⁵ It has been shown that increases in pulmonary arterial pressure affect right heart physiology *in vivo* by disrupting RV work distribution in favor of maintaining pulmonary circulatory pressure relative to blood flow (and hence oxygen transport), which is referred to as right ventricular-pulmonary arterial (RV-PA) uncoupling.¹⁶ However, the extent to which RV-PA uncoupling underpins adverse outcome in CTD-PAH with mPAP <25 mmHg requires additional study. Additionally, comprehensive data on the utility of treating any patient based on mPAP <25 mmHg remain forthcoming. Nonetheless, a low clinical index of suspicion for PAH is warranted when encountering CTD patients irrespective of resting cardiopulmonary hemodynamics, and their early referral to specialty care centers is justified (Table 1).

New Trends in the Epidemiology of PAH—The reported prevalence of PAH is 5-25 cases/million (incidence 2-5 cases/million), although referral bias from registry studies is likely to under-estimate the true rate of disease.¹⁷ The mean age of PAH patients in the REVEAL (U.S., 2006-2007)¹⁸ and COMPERA (Europe, 2007-)¹⁹ PAH registries was 54 and 68 yrs, respectively, compared to 36 yrs in the original National Institutes of Health (NIH) iPAH cohort (1980-1985).²⁰ On the other hand, the large variability in mean age of iPAH patients in contemporary registries may also be explained by participation bias among centers and variable accuracy in the diagnostic process. In fact, auditing for diagnostic accuracy is not systematic in large registries and the frequency of misclassification is unknown, particularly in patients with left heart disease risk factors and PAWP >12 mmHg, for whom adjudicating retrospectively PAH vs. pulmonary hypertension due to left heart

disease is difficult. The prevalence of PAH favors women to men by ~3.1-fold;²¹ however, the clinical profile, hemodynamics at diagnosis, and prognosis in men has appears comparatively less favorable.^{17,22}

Natural History—The original NIH registry included mainly HPAP and iPAH, and 64% of patients were incident cases. The median survival was 2.8 yr; the 1- and 3-yr mortality rates were 68% and 48%, respectively, and the use of standard therapy at the time (digitalis, diuretics, or anticoagulants) likely did not influence outcome.²³ In 2010, data were organized for 298 prevalent and 56 incident iPAH, HPAH and anorexigen-PAH patients followed for 3 years in the French Network on Pulmonary Hypertension.¹⁷ In that study, 76% of patients were prescribed PAH-specific therapy, and the 1- and 3-yr survival rates were 85.7% and 54.9%, respectively, although only 2 patients were reported to receive 1 PAH-specific therapy. However, from the REVEAL registry, which tracks PAH patients from 54 U.S. centers, an analysis on outcome that included 40% of patients on combination PAH therapy indicated that the 1- and 3-yr survival rates were 91% and 69%, respectively.²⁴ Directionally similar findings were observed in registries from Spain, UK, and China, as well as a European series reporting that the 3-year survival of PAH combination patients was 84%.²⁵ It is notable that mortality in PAH is now akin to, or perhaps lower than, patients with left ventricular heart failure, for which the age-adjusted 1-yr survival was 69% in 2010 and 67% in 1980-1989.²⁶

Pathogenesis and Current Drug Targets in PAH

Histopathology—In PAH, effacement of distal pulmonary arteries involving the intima, media, and adventitial layers occurs due to hypertrophic, fibrotic, plexogenic, and inflammatory vascular remodeling without primary involvement of the arterial systemic beds. The small pulmonary veins system is also variably affected, particularly in PAH due to the classical form of pulmonary veno-occlusive disease.²⁷ It is now understood that in addition to endothelial dysfunction and dysregulated pulmonary artery smooth muscle cell growth, pathogenic changes to the structure and function of pulmonary arterial pericytes, myofibroblasts, and adventitial fibroblasts also play a key role in the vascular remodeling process.²⁸ Increased vascular reactive oxygen species accumulation, a shift in mitochondrial bioenergetics toward glycolysis, over-activation of HIF-1 α signaling, and maladaptive epigenetic modifications that promote DNA damage are all implicated in apoptosis-resistance, unopposed proliferation, and/or transdifferentiation of pulmonary vascular cells.^{29,30} Ultimately, profound vascular cell proliferation ensues and results in luminal obliteration and impaired vascular reactivity.

The Syndrome of PAH—Structural abnormalities to the alveolar-capillary interface, and to left atrium, and left ventricle (due to underfilling) occur as a consequence of pulmonary vascular remodeling in PAH. Upregulation of neurohumoral signaling in concert with impaired renal or hepatic function is an important systemic manifestation of PAH,³¹ while diminished strength and fiber size in volitional (e.g., quadriceps) and non-volitional (e.g., diaphragm) muscles is well documented and contributes to symptom burden.³²

PAH Pathophysiology and RV involvement—A predominantly vasoconstrictive pathophenotype is observed in only ~10% of PAH patients.^{6,7} By contrast, decreased arterial compliance and elevations in PVR are universal across the PAH spectrum and, ultimately, induce RV dilation, impaired diastolic function, and diminished contractile reserve. Therefore, analyzing the RV is important in PAH, and includes echocardiographic measurement of right atrial and RV volumes, and RV function.³³ In PAH, RV-PA uncoupling measured by transduction catheter and magnetic resonance imaging precedes frank right heart failure and in clinical studies corresponds to decreased exercise tolerance.³⁴ Interestingly, the pathophysiology of CTD-PAH appears somewhat unique, as these patients fail to augment RV contractility during exercise at RV afterload levels that are associated with maintained RV function in iPAH patients.³⁵ Thus, RV performance differs across PAH subgroups, possibly as a function of disease-specific factors rather than solely by elevated RV afterload.

Genetics of PAH—A germline mutation coding for the bone morphogenetic receptor-2 (BMPR-2) gene, which is part of the TGF- β superfamily of receptors, is implicated in 70% of HPAH and up to 40% of iPAH patients.³⁶ Importantly, up to 80% of BMPR-2 carriers are “genotype positive-phenotype negative,” and, thus, the contribution of reduced penetrance to under recognition of BMPR-2 mutation status in PAH patients without a familial history of the disease is not known.³⁷ A smaller percentage of HPAH and PAH-hereditary hemorrhagic telangiectasia is attributed to mutations in genes coding for other TGF- β family receptor proteins including ALK1, endoglin, and SMAD9. Other rarer genetic causes of PAH include mutations in *CAVI*, which regulates SMAD 2/3 and modifies TGF signaling, and *KCNK3*, which encodes for the potassium channel protein TASK-1.³⁸ Mutations in *EIF2AK4* have also been identified as causative of heritable pulmonary veno-occlusive disease.³⁹

Novel Drug Therapies and Care Strategies in PAH

In the previous 5 years, three mainstream trends have emerged in the pharmacotherapeutic management of patients with PAH (reviewed in detail recently in ref. 40). First, the efficacy of phosphodiesterase type-V inhibitors (PDE-Vi), endothelin type-A and type-B receptor antagonists (ERA), and prostaglandin I₂ replacement therapies, administered either as monotherapy or in sequential combination, have each achieved evidence-based validation for their ready use in PAH when patients are under the care of an expert pulmonary hypertension clinician (eFigure 1). Second, recent clinical trials show the effects of 3 novel PAH drug therapies: the SERAPHIN trial with macitentan (ERA),⁴¹ PATENT trial with riociguat (soluble guanylyl cyclase [sGC] stimulator),⁴² and GRIPHON trial with selexipag (prostaglandin I₂ receptor agonist).⁴³ Third, findings from the recent AMBITION trial mark a strategic shift in PAH by providing definitive evidence in favor of initial combination therapy over monotherapy for newly diagnosed, treatment-naïve patients.⁴⁴

In the SERAPHIN trial, 742 PAH patients were randomized to receive placebo or macitentan (10 mg vs. 3 mg daily), which was a modified ERA with optimal receptor binding kinetics. The majority of enrolled patients had iPAH or CTD-PAH (87%), NYHA Functional Class II/III (97%), severe pulmonary hypertension (mPAP ~55 mmHg, CI ~2.3 l/min/m², PVR ~12.5 Wood units), and were on some form of background PAH therapy (64%), the majority

of which was the PDE-Vi sildenafil. Compared to placebo (mean duration of treatment 85.3 wk), the hazard ratio for achieving the composite primary end-point of PAH-related clinical worsening, which included death or disease progression, was 0.70 ($P=0.01$) in the 3 mg dose arm and 0.55 ($P<0.001$) in the 10 mg dose arm (mean duration of treatment: 100 wk for 3 mg arm, 104 wk for 10 mg arm). Directionally similar findings were observed for PVR and cardiac index at 6 months compared to baseline. However, given that the 3 mg dose was associated with only a subtle improvement in other study measures, only the 10 mg dose received approval for use clinically in the U.S. and Europe.

The PATENT-1 study compared the effect of riociguat (2.5 mg t.i.d.) or placebo on change in 6-MWD from baseline at study week 12 in a cohort of 443 PAH patients. The majority of participants in PATENT-1 had iPAH (61%), NYHA Functional Class II/III (95%), and were already prescribed background PAH therapy (50.1%) at the time of study enrollment (mainly bosentan). Compared to placebo, riociguat 2.5 mg t.i.d. was associated with a significant increase in 6-MWD (+30 m vs. +6 m; $P<0.001$), decreased PVR (-2.8 vs. -0.1 Wood units; $P<0.001$) and significant improvements to mPAP, cardiac output, N-terminal pro-b-type natriuretic peptide, World Health Organization (WHO) Functional Class, and dyspnea burden. Riociguat was generally well tolerated; syncope was the most common serious adverse event and occurred in 1% of patients.

The GRIPHON trial randomized 1156 patients from 39 countries to receive placebo (median duration 64 wk) or selexipag (median duration 71 wk) titrated to the maximal tolerated dose. The majority of patients had NYHA Functional Class II/III (98%), and iPAH/HPAP (86%) or PAH due to corrected congenital shunt (9.5%). Baseline PAH therapies included ERA (15%), PDE-Vi (32%), ERA + PDE-Vi (33%), or no drug (20%). The primary end-point of death or PAH complication occurred in 41.6% of placebo-treated patients and 27.0% of selexipag-treated patients ($HR=0.6$; $P<0.001$) (Figure 2A). The effect of therapy on 6-MWD was negligible, and the side effect profile of selexipag was consistent with PGI₂ analogues (e.g., headache, diarrhea, nausea, jaw pain) corresponding to a drug discontinuation rate of 14% due to adverse symptoms.

Strategic Shift in the Management of PAH—Meta-analyses studying sequential combination therapy patients suggested a signal toward superior clinical benefit among patients on multiple drugs compared to patients on placebo or prescribed monotherapy.⁴⁵ To address this further, the AMBITION trial included 500 treatment-naïve newly diagnosed participants that were randomized (2:1:1) to receive initial combination therapy with the selective ET_A receptor antagonist ambrisentan 10 mg daily plus PDE-Vi with tadalafil 40 mg daily or standard of care monotherapy with either drug alone. Patients in AMBITION were diagnosed with PAH on average 20 days prior to study drug day 1 and had NYHA Functional Class II/III and moderate-severe cardiopulmonary haemodynamic severity at enrollment. At a median of 517 d, an end-point of death, PAH hospitalization, disease progression, or unsatisfactory clinical response occurred in 18%, 34% and 28% of patients randomized to combination therapy, ambrisentan monotherapy, and tadalafil monotherapy, respectively. Furthermore, a 50% ($P<0.001$) reduction in the hazard for achieving the primary end-point, which was a composite of the clinical events, was observed in the combination therapy group compared to patients randomized to either monotherapy

treatment (Figure 2B). Initial combination therapy was also associated with a decrease in the hazard for the primary end-point by 79% ($P=0.005$) among patients with NYHA Functional Class II, providing evidence in support of initial combination therapy in mildly symptomatic patients.

Approach to PAH Patients in Practice

Pulmonary Vasoreactivity Testing, Risk Stratification, and Initial Management

Steps—Assessing the effect of inhaled nitric oxide, intravenous prostacyclin, or intravenous adenosine on cardiopulmonary hemodynamics for the purpose of determining vasoreactivity, and, thus, treatment should be confined primarily to HPAH, iPAH, and drug-induced PAH and performed at a PAH referral center. A positive test is defined by a decrease in mPAP ≥ 10 mmHg to reach an mPAP ≤ 40 mmHg with a decrease (or no change) in cardiac output.^{6,7} In such patients, high dose calcium channel antagonism therapy is indicated as first-line treatment owing to relevant improved clinical outcome following treatment in this PAH subgroup.

Systems for classifying patients according to 1-year mortality risk are now available for use in clinical practice.^{6,7} Low ($<5\%/yr$), intermediate ($5\text{--}10\%/yr$), and high ($>10\%/yr$) risk is determined based on a collective analysis of clinical, hemodynamic, biochemical, and echocardiographic data (Table 2). These and other criteria and warning signs that should prompt referral to a pulmonary hypertension expert center are provided in Table 1. Achieving low clinical risk also functions as the principle treatment goal and includes: 6-minute walk distance >440 m, peak $VO_2 >15$ ml/min/kg, right atrial area <18 cm², cardiac index >2.5 l/min/m².

Initiating PAH Therapy—For patients with a positive vasoreactivity study but calcium channel antagonist non-responder status or in patients without a positive vasoreactivity study, treatment selection hinges on risk level (Figure 3). According to evidence in the literature, it is recommended that initial combination therapy with an ERA and a PDE-Vi be adopted for treatment-naïve patients with low or intermediate risk, which often equates to NYHA Functional Class II/III status. As an alternative, monotherapy that includes an ERA, a PDE-Vi, a sGC stimulator or a prostacyclin analogue may be considered as initial treatment in low or intermediate risk patients. For patients at high risk at first clinical encounter, initial combination therapy including intravenous (IV) prostacyclin analogues should be considered, with IV epoprostenol prioritized given its favorable effect on survival in high-risk patients even with administered as monotherapy.¹

Therapeutic Escalation—Medical assessment including 6-MWD testing should be evaluated every 3–6 months (at least twice annually) to observe for a decline in exercise status. Additional studies, such as echocardiography or RHC, are often performed at least annually or if indicated by a change in clinical status. Determining timing of therapeutic escalation is challenging, and should be tailored to individual patients. An overarching goal is to maintain WHO Functional Class II or I status, 6-MWD >440 m and cardiac index ≥ 2.5 l/min/m². Therefore, if drug treatment fails to accomplish this objective within 3–6 months of its initiation, or if clinical decline is precipitous (≥ 1 WHO functional class decrease), then

the addition of therapies is warranted. High-risk findings that suggest advanced RV failure, for example, may alter the timeline of treatment escalation.

The recently proposed strategy of initial combination therapy with oral compounds in newly diagnosed PAH patients in WHO functional class II and III status^{6,7} will leave in the future only one additional escalation step to reach the maximal triple combination medical therapy.

It is common practice to escalate therapy by the sequential addition of PAH-specific drugs in patients with progressive disease despite maximal tolerated dose of the initial treatment selection. The addition of macitentan to sildenafil; riociguat to bosentan; and, selexipag to an ERA or PDE-Vi are each 2005 ESC/ERS Guideline Class I^{6,7} recommendations for most patients, and triple medical therapy in refractory disease is increasingly common. It is important to note that the combination of PDE-Vi and riociguat is prohibited due to severe adverse events.⁴⁶

Referral for lung transplant evaluation is recommended in patients prescribed maximal medical therapy. The preferred procedure in PAH patients is double lung transplantation; importantly, an inverse correlation between pre-operative frailty and post-transplant outcome is observed.⁴⁷ The introduction of a right-to-left shunt using balloon atrial septostomy or Potts shunt may be a consideration to palliate the clinical sequelae of right heart failure in PAH, but should only be implemented on an individualized basis at referral centers expert with these procedures.

Prescription Exercise in PAH Treatment—Once regarded as potentially dangerous in PAH due to concern for provoked sudden death, exercise training has become as an important therapy in the management of patients. Mereles and colleagues⁴⁸ first established prescription aerobic exercise as a safe and effective strategy to improve exercise tolerance and quality of life in patients with severe PAH. A recent meta-analysis of 16 prospective studies in PAH (N=469) showed that exercise was associated with a significant improvement at follow up (median 15 wk) in 6-MWD (+53.3 m), pVO₂ (+1.8 ml/kg), and pulmonary artery systolic pressure (-3.7 mmHg).⁴⁹ Generally, inspiratory muscle training that achieves >30% of maximal inspiratory pressure (30 min session, 1-2/d) and aerobic exercise that achieves 50-85% maximal aerobic capacity (30 min session, 3-7 d/wk) is recommended to patients.⁵⁰ However, the practical application of exercise programs for a rare disease in the real world requires further developments and adaptations to the different healthcare systems.

Difficult Clinical Scenarios

Patients with borderline mean pulmonary arterial pressure increase—Several reports in unselected populations that included patients with left heart and pulmonary disease describe an increase in clinical risk associated with pulmonary arterial pressure beginning at levels classified currently as normal.⁵² In the largest study (N=21,727),⁵³ a continuous relationship between mPAP and the adjusted hazard for all-cause mortality was observed beginning at 19 mmHg. Furthermore, as the range of mPAP 19-24 mmHg, was common and corresponded to a 23% increase in mortality risk. However, It is unknown whether mPAP <25 mmHg is sufficient to induce right heart pathophysiology and account for adverse clinical outcome in these subjects, or if events are due to co-morbid disease.

Determining if this subphenotype is an early disease state has important implications on patient risk-stratification and merits future investigation. At present, data informing clinical decision-making in patients with mPAP 19-24 mmHg does not exist and, therefore, such patients should not be treated with PAH approved therapy.

Mixed Clinical Phenotypes—Encountering patients with multiple risk factors for left heart disease and with cardiopulmonary hemodynamics consistent with PAH is becoming common.^{6,7} A subgroup analysis of the AMBITION study involving PAH patients with 3 risk factors for left heart disease and PAWP ≥ 15 mmHg suggested a signal toward clinical benefit. Determining the manner by which this patient subgroup contrasts with PAH (i.e., pre-capillary PH) and bona fide left heart disease (LHD) with preserved ejection fraction (HFpEF), thus, bears important ramifications on PAH diagnosis and treatment. Opitz and colleagues⁵⁴ showed that PAH patients with risk factors for left heart disease and HFpEF patients in the COMPERA registry were incrementally older and had greater BMI compared to PAH without risk factors. However, PAH patients with risk factors were treated commonly with PAH-specific drugs, which apparently was associated with meaningful improvements in functional status and 6-MWD. However, the magnitude of treatment effects was inferior compared to PAH patients without risk factors, outlining the potential negative effects of comorbidities.

On the other hand, we need to acknowledge the important limitations of the data provided by the COMPERA study, which is a voluntary, not systematically audited, non-interventional registry that, as such, cannot provide definitive results on the comparative effects of treatments in the studied patient groups. The differential diagnosis between iPAH with multiple risk factors for LHD and HFpEF with pulmonary hypertension is based substantially on PAWP, which is ≥ 15 mmHg in the latter clinical phenotype.^{6,7} The assessment of PAWP may present technical difficulties and artifact, which can lead to uncertainties in the PAWP, particularly between 12 – 18 mmHg. In cases of doubt, a direct assessment of left ventricular end-diastolic pressure may be helpful. Fluid challenge or exercise hemodynamics have been suggested in cases of persisting uncertainties, but unfortunately the heterogeneity of protocols and the lack of age-related normal thresholds for PAWP limit their diagnostic reliability. In clinical practice, the differential diagnosis in unclear cases should be based not only on a borderline value of PAWP, but also a comprehensive assessment including the history of the patient, the severity of comorbidities and the response to medications such as diuretics.

Conclusions

Over the preceding two decades, PAH has evolved into a treatable cardiovascular disease associated with improved survival and decreased morbidity. Optimizing clinical outcome hinges on lower clinical index of suspicion for PAH at point of care, understanding the broad clinical spectrum of risk, and the importance of early aggressive therapy in newly diagnosed patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Classification of pulmonary hypertension subgroups

Pulmonary hypertension is defined by a mean pulmonary artery pressure ≥ 25 mmHg measured by right heart catheterization supine at rest. Patients meeting this criterion are classified further according to co-morbid left heart disease causing left atrial hypertension, parenchymal or hypoxic lung disease, chronic thromboembolic pulmonary hypertension (CTEPH), or other predisposing diseases associated with pulmonary vascular remodeling. In the case of CTEPH, in situ thrombotic and fibrotic remodeling of subsegmental pulmonary arterioles occurs in most patients as a maladaptive response to prior luminal pulmonary embolism. By contrast to these forms of pulmonary hypertension, pulmonary arterial hypertension (PAH) is characterized by a plexogenic, hypertrophic, and fibrotic vasculopathy affecting distal pulmonary arterioles that occurs primarily due to interplay between genetic and molecular factors and requires meeting the following additional cardiopulmonary hemodynamic criteria: pulmonary vascular resistance (PVR) >3.0 Wood units and pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg. The most common forms of PAH in industrialized countries are idiopathic PAH, heritable PAH due primarily to a mutation in the gene for bone morphogenetic protein receptor-2, and PAH in association with connective tissue disease (CTD) or congenital heart disease. LV, left ventricle; HIV, human immunodeficiency virus; PH, pulmonary hypertension; COPD, chronic obstructive pulmonary disease; HD, hemodialysis.

Figure 2.

A. The effect of sequential combination therapy of selexipag as monotherapy or as addition to endothelin receptor antagonists and/or phosphodiesterase type5 inhibitors on the outcome. In the GRIPHON study patients were randomised to receive selexipag or placebo. Kaplan–Meier curves for the primary composite end point of death (from any cause) or a complication related to pulmonary arterial hypertension (disease progression or worsening of pulmonary arterial hypertension that resulted in hospitalization, initiation of parenteral prostanoid therapy or long-term oxygen therapy, or the need for lung transplantation or balloon atrial septostomy) up to the end of the treatment period in the selexipag and placebo groups. A significant treatment effect in favor of selexipag versus placebo was observed (hazard ratio, 0.60; 99% CI, 0.46 to 0.78; $P<0.001$ with the use of a one-sided log-rank test). Reproduced with permission from Sitbon et al.⁴³

B. The effect of initial combination therapy with ambrisentan plus tadalafil on pulmonary arterial hypertension (PAH) outcome in treatment-naïve patients on clinical outcome. In the AMBITION trial, treatment-naïve PAH patients were randomized to receive monotherapy standard of care with the selective endothelin-A receptor antagonist ambrisentan (10 mg daily) or the phosphodiesterase-type V inhibitor tadalafil (40 mg daily), or combination therapy with both drugs. The primary end-point included first event of clinical failure, which was a composite of death, hospitalization for worsening pulmonary arterial hypertension, disease progression, or unsatisfactory long-term clinical response. The pooled monotherapy condition refers to all patients randomized to receive either ambrisentan alone or tadalafil alone. Reproduced from Galiè, et al.⁴⁴

Figure 3. Evidence-based treatment algorithm for pulmonary arterial hypertension (PAH) patients

CCB: calcium channel blockers; DPAH, drug-induced PAH; HPAH, heritable PAH; IPAH, idiopathic PAH; i.v., intravenous; PCA: prostacyclin analogues; WHO-FC: World Health Organization Functional Class. ^bInitial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure. ^cIntravenous epoprostenol should be prioritized. ^dConsider also balloon atrial septostomy. Adapted with permission from Galiè N, et al.^{6,7}

Table 1
Conditions that suggest referral to a Pulmonary Hypertension Expert Center

Performance of vasoreactivity tests
PAH patients with intermediate-to-high risk status (Table 2)
Patients in need for patenteral prostanoids
PAH with Connective Tissue Diseases
PAH with congenital heart defects
Suspicion of heritable PAH
Suspicion of pulmonary veno-occlusive disease
Elective surgery in PAH patients
Decision making about pregnancy in PAH patients
Patients with PH due to LHD or lung disease and severe PH or RV dysfunction
Suspicion of chronic thromboembolic pulmonary hypertension
Any severe PH patients with uncertain diagnosis
Pediatric PH patients

PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; LHD, left heart disease; RV, right ventricle.

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Table 2
Point of care risk stratification for patients with pulmonary arterial hypertension (PAH)

Determinants of Prognosis (estimated 1-year mortality)	Low Risk <5%	Intermediate Risk 5-10%	High Risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope	Repeated syncope
WHO Functional Class	I,II	III	IV
6MWD	>440 m	165-440 m	<165 m
Cardiopulmonary exercise testing	Peak VO ₂ >15 ml/kg/min (>65% predicted) VE/VCO ₂ Slope <36	Peak VO ₂ 11-15 ml/kg/min (35-65% predicted) VE/VCO ₂ Slope 36-44.9	Peak VO ₂ <11 ml/kg/min (<35% predicted) VE/VCO ₂ Slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-BNP <300 ng/l	BNP 50-300 ng/l NT-BNP 30-1400 ng/l	BNP >300 ng/l NT-BNP >1400 ng/l
Imaging (ECHO, CMR)	RA area <18 cm ² No pericardial effusion	RA area 18-26 cm ² No or minimal pericardial effusion	RA area >26 cm ² pericardial effusion
Hemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m ² SvO ₂ >65%	RAP 8-14 mmHg CI 2.0-2.4 l/min/m ² SvO ₂ 60-65%	RAP >14 mmHg CI <2.0 l/min/m ² SvO ₂ <60%

Integrated assessment of clinical, functional, biochemical, imaging and cardiopulmonary hemodynamic data is used to risk stratify PAH patients according to low (<5%), intermediate (5-10%), and high (>10%) predicted annual mortality rate. WHO, World Health Organization; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; ECHO, echocardiography, CMR, cardiac magnetic resonance imaging; VO₂, volume of oxygen consumption; RA, right atrial; RAP, right atrial pressure; CI, cardiac index; VE/VCO₂, minute ventilation/carbon dioxide production; SvO₂, mixed venous oxygen saturation. Reproduced Galie N, et al.^{6,7}.