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HEART FAILURE (HJ EISEN, SECTION EDITOR)

Pulmonary Arterial Hypertension: a Pharmacotherapeutic Update

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Abstract

Purpose of Review Pulmonary arterial hypertension (PAH) leads to progressive increases in pulmonary vascular resistance (PVR), right heart failure, and death if left untreated. This review will summarize and discuss recent updates in the classification and management of patients with PAH.

Recent Findings PAH requires careful hemodynamic assessment and is defined by a mean pulmonary artery pressure > 20 mmHg with normal left-sided filling pressures and a PVR ≥ 3 Wood units. Most patients with PAH require targeted pharmacotherapy based on multiparametric risk stratification. Significant improvements in clinical outcome have been realized through the approval of 14 unique pharmacotherapeutic options.

Summary The latest clinical recommendations provide the updated hemodynamic definition and clinical classification as well as evidence-based treatment recommendations. An important change is the focus on initial upfront combination therapy for most patients with PAH. Structured follow-up and escalation of treatment for those not achieving low-risk status is paramount.

Keywords Pulmonary hypertension · Pulmonary arterial hypertension · WHO group 1 pulmonary hypertension · Chronic thromboembolic pulmonary hypertension (CTEPH)

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by increases in pulmonary vascular resistance (PVR) that ultimately lead to right ventricular (RV) failure and death if left untreated [1]. Registry data report an overall incidence of PAH in 15 per 1 million people [2]. Although pulmonary hypertension (PH) can affect all ages, genders, and races, the preponderance of patients diagnosed with PAH are younger females (mean age of 50 ± 14 years; 80% female) [3]. Since 1990, there have been 41 randomized controlled trials that have led to advancements in PAH treatment [4••]. Significant improvements in PAH outcome have been realized in the modern era (median survival 7 years) compared to the National Institutes of Health registry from the early 1980s (median survival 2.8 years) [3, 5].

Hemodynamic Diagnosis and Classification

PH is defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg, measured by right heart catheterization (RHC), and was recently updated at the Sixth World Symposium on

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Pulmonary Hypertension (WSPH) in 2018 [6••, 7]. PAH is distinguished from PH by an mPAP > 20 mmHg plus a pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg, and a PVR ≥ 3 Wood units (WU) [6••].

The Sixth WSPH updated the clinical classification based on the World Health Organization (WHO) PH groups, which are based on shared pathological features, hemodynamics, and therapeutic approaches (Table 1) [6••]. Pre-capillary PH (PAWP ≤ 15 mmHg) refers to patients from groups 1, 3, 4, and some from 5, but rarely patients from group 2 (post-capillary PH). Patients in group 1 are classified as PAH and include the following subtypes based on etiology: idiopathic, heritable, drug, and toxin-induced (i.e., aminorex, benfluorex, dexfenfluramine, fenfluramine, methamphetamines, dasatinib, toxic rapeseed oil), associated conditions (connective tissue disease, human immunodeficiency virus infection, portal hypertension, congenital heart disease, and schistosomiasis). Newly included in WHO group 1 is long-term responders to calcium channel blockers. Other subtypes include PH with overt features of venous/capillary disease (pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis) and persistent PH of the newborn.

Table 1 WHO group classification in pulmonary hypertension [6••]

1. PAH
Idiopathic PAH
Heritable PAH
Drug- and toxin-induced PAH
PAH associated with
Connective tissue disease
HIV
Congenital heart disease
Schistosomiasis
PAH long-term responders to calcium channel blockers
PAH with overt features of venous/capillary involvement
Persistent PH of the newborn syndrome
2. PH due to left heart disease
PH due to heart failure with preserved ejection fraction
PH due to heart failure with reduced ejection fraction
Valvular heart disease
Congenital/acquired cardiovascular conditions leading to post-capillary PH
3. PH due to lung diseases and/or hypoxia
Obstructive lung disease
Restrictive lung disease
Other lung diseases with mixed obstructive/restrictive pattern
Hypoxia without lung disease
Developmental lung disorders
4. PH due to pulmonary obstructions
Chronic thromboembolic PH
Other pulmonary artery obstructions
5. PH with unclear and/or multifactorial mechanisms
Hematological disorders
Systemic and metabolic disorders
Others
Complex congenital heart disease

PAH pulmonary arterial hypertension, *PH* pulmonary hypertension

(Reproduced with permission of the © ERS 2019: *European Respiratory Journal 53 (1) 1801913; DOI:* https://doi.org/10.1183/13993003.01913-2018 *Published 24 January 2019*) [6••]

Pathophysiology

The pathophysiology of PAH is multifactorial and complex. It is hypothesized that there may be specific risk factors and/or sources of vascular injury that may lead to pulmonary vascular remodeling. Some patients may have a genetic predisposition or be exposed to an environmental factor (e.g., dasatinib or methamphetamine), or have a dysfunctional immune/inflammatory response [8]. When a patient accumulates enough "hits" to the pulmonary vasculature, it leads to pulmonary endothelial cell dysfunction and smooth muscle cell proliferation. Researchers are investigating mechanisms by which cellular dysfunction in PAH mirrors that of cancer cells, with aberrant cellular signaling, cellular proliferation, and metabolic perturbations leading to vascular dysfunction [9].

Central features for vascular dysfunction include vasoconstriction, vascular wall remodeling, and in situ thrombosis coalescing to an increase in PVR [1]. Vasculopathy affects primarily the distal pulmonary arteries through intimal hyperplasia, medial hypertrophy, adventitial proliferation, inflammation, thrombosis, and development of plexiform lesions [10]. A dysregulation and imbalance of vasodilators (i.e., nitric oxide (NO), prostacyclins) and vasoconstrictors (i.e., thromboxane A2, endothelin-1 [ET-1]) exists within vascular endothelium and smooth muscle [1]. These are primary pathways and therapeutic targets for PAH. Deficiency in NO, a potent vasodilator that inhibits platelet activation and vascular smooth muscle cell proliferation, results from impairment in the NO–soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) pathway [11]. NO activates its molecular target, sGC, which leads to increases in cGMP. Degradation of cGMP is regulated by the enzyme phosphodiesterase type 5 (PDE-5) [10]. ET-1, a potent vasoconstrictor and mitogen that exerts its effects on pulmonary vascular smooth muscle cells by ET type A (ETA) and ET type B (ETB) receptors [11], is increased in PH patients. Finally, prostacyclin (prostaglandin I2) is a major metabolite of arachidonic acid metabolism and has significant effects on pulmonary vascular smooth muscle via production of cyclic adenosine monophosphate (cAMP). It is a potent vasodilator, inhibits platelet activation, and has antiproliferative effects [10].

Diagnostic Approach

Echocardiography plays an integral part in the initial diagnostic approach to PH and is used to evaluate PH effects on the heart. Several parameters exist, namely tricuspid regurgitant velocity (TRV), indicating elevated pulmonary artery systolic pressures (PASP) by determining RV systolic pressure. A

peak TRV of ≥ 3.4 m/s indicates a high likelihood of PH. A peak TRV exceeding 2.8 m/s warrants invasive evaluation with RHC. If a patient has a lower velocity but has other echocardiographic signs of right atrial, RV, or pulmonary artery enlargement or RV dysfunction invasive evaluation is also warranted (Fig. 1) [12••].

Patients with PH often have discrepant echocardiographically measured PA pressures compared to invasive RHC. Therefore, the diagnosis cannot end with echocardiogram but rather should be used to assign a level of probability of PH to determine if invasive evaluation is necessary [13].

Lastly, echocardiography can help with assessing RV function and risk stratification. The variables involved include RV area as well as LV eccentricity index. Additionally, RV contractility can be measured by RV fractional change, Tei index as well as tricuspid annular plane systolic excursion (TAPSE). Pericardial effusion and indexed right atrial (RA) area can add to prediction of mortality in these patients and should be noted [14].

Biomarkers

Biomarkers can add a non-invasive variable to monitor disease progression and risk stratification. For this reason, guidelines and risk stratification models use BNP/NT-proBNP [12, 15–19]. BNP/NT-proBNP are markers of myocardial stress and dysfunction and although there are no clear advantages in using BNP versus NT-proBNP, BNP appears to have a stronger correlation with hemodynamic effects of pulmonary hypertension in addition to being less affected by kidney function, while NT-proBNP seems to be a stronger predictor of prognosis as well as often the only natriuretic biomarker available in a given institution [20].

Other biomarkers reflecting vascular dysfunction, inflammation, myocardial stress, low cardiac output, and/or tissue hypoxia are recommended to be regularly monitored per the PH guidelines [12••, 21]. Despite the plethora of biomarkers available, BNP/NT-proBNP are the mainstay in PH and the only biomarkers used in major risk stratification models [12••, 15–19].

Risk Assessment

Despite progress in treatment options, PAH patients continue to experience disease progression and events associated with right ventricular failure such as frequent hospitalizations and death [22]. Frequent hospitalizations indicate disease progression and mortality in patients with RV failure [23–25]. Appropriate and accurate risk assessment is imperative to affect disease progression and identify those at high risk of early and rapid progression.

Multiple risk stratification schemas have been developed since the first was proposed in 1991 [5]. The most recent models are derived from European and North American cohorts [15–19]. The European risk stratification schema is consensus-based and proposed by the European guidelines [12••]. The North American risk stratification system was derived through multivariate modeling and incorporates 14 different variables [16]. A simplified version of the REVEAL score has still shown to be predictive; nonetheless, 2015 ESC/ERS PH guidelines have recommended an approach utilizing only 8 variables [26]. Those include modifiable clinical (clinical signs of RV failure such as right-sided volume

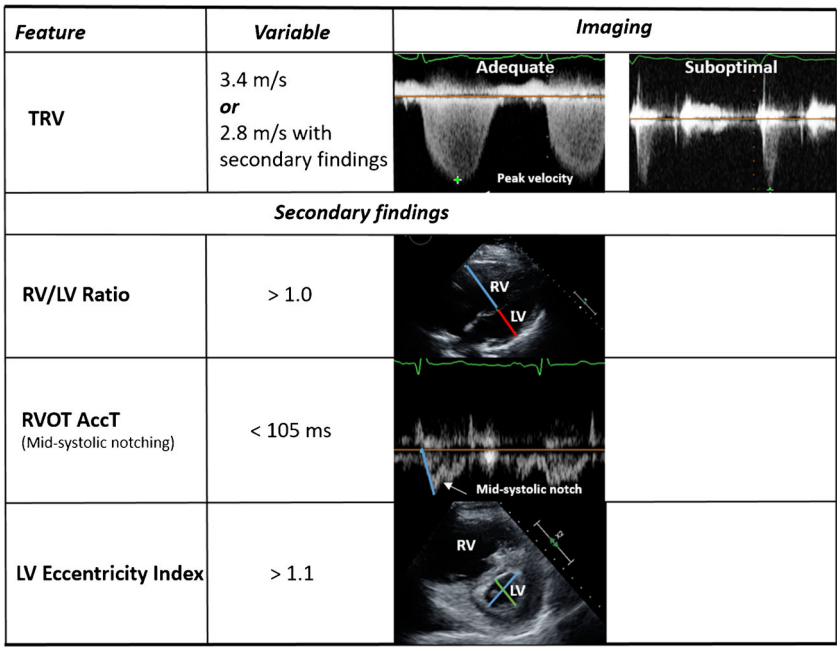

Fig. 1 Echocardiographic variables in the diagnosis and screening of PAH. TRV, tricuspid regurgitation velocity; RVOT AccT, right ventricular outflow tract acceleration time

overload as well as rapidity of progression of symptoms and syncope), functional (WHO functional class (WHO FC)), exercise [6 min walk distance (6MWD) as well as cardiopulmonary stress testing], biochemical (biomarkers indicative of myocardial stress), echocardiographic (right atrial enlargement and pericardial effusion), and hemodynamic (right atrial pressure, cardiac index, and central venous saturation) variables with known prognostic significance [12••].

The most recent iteration of the REVEAL score (REVEAL 2.0) has demonstrated greater risk discrimination compared to other risk stratification schemas revealing that COMPERA underestimated risk in 80% and French Pulmonary Hypertension Registry underestimated risk in 58% of high-risk patients. In the process, REVEAL 2.0 has been updated with additional variables, such as renal function as well as hospitalizations within 6 months of risk stratification [16].

The majority of morbidity and mortality of patients with PH depends on RV function and myocardial stress. Variables involved in risk stratification algorithms reflect RV dysfunction severity and use of risk stratification methods help provide a regimented evaluation to determine which therapies to initiate and/or when to escalate therapy to prevent progression to RV failure and enable patients to achieve their best functional status.

Overview of Pharmacotherapeutic Options for PAH

The first therapy approved for the treatment PAH, continuous infusion intravenous epoprostenol, was made available in 1995. It took 10 years for two oral agents to come to market in the United States and since then there has been an exponential increase in approvals targeting the three pathophysiologic pathways. There are currently 14 pharmacotherapeutic options to choose from which encompass four administrative routes. While early trials focused on improvements in short-term, surrogate endpoints, there has been a shift to long-term morbidity and mortality-based trials. Table 2 provides a summary of recent PAH trials evaluating newer pharmacotherapies for improving clinical outcomes.

Acute pulmonary vasoreactivity testing is typically used to identify patients with idiopathic, heritable, or drug-induced PAH who may favorably respond to high doses of calcium channel blockers (CCBs) before consideration for targeted PAH therapies. Inhaled NO is often used; however, alternatives may include inhaled or IV epoprostenol or IV adenosine. A positive vasoreactivity response is defined as a reduction in mPAP of ≥ 10 to ≤ 40 mmHg with no change or an increase in cardiac output [6••]. Most patients tested are not vasoreactive, and of those with a positive response, less than 10% maintain response to CCBs [27]. Patients who are not vasoreactive or who do not have a long-term response to a CCB should be treated with targeted PAH therapies [4••].

PDE-5 Inhibitors

PDE-5 inhibitors target the NO pathway by preventing the breakdown of cGMP. Both sildenafil (20 mg TID) and tadalafil (40 mg daily) have been shown to improve exercise capacity, measured by 6MWD, compared to placebo in patients with predominantly WHO FC II and III symptoms. Sildenafil has also been shown to improve hemodynamics (mPAP, PVR, and cardiac index) and WHO FC in treatment-naïve patients, while tadalafil was associated with improvements in time to clinical worsening (TTCW) for both treatment naïve and those patients on background endothelin receptor antagonist (ERA) therapy [28, 29].

Adverse effects are mainly vasodilatory and include headache, flushing, dyspepsia, myalgias, epistaxis, and visual and auditory alterations. Both agents are contraindicated with concomitant nitrates or riociguat due to hypotension. Other interactions include concomitant use of strong inhibitors of CYP3A4 which require dose adjustment or avoidance [30, 31]. Additionally, tadalafil requires dose adjustment with mild to moderate renal impairment [31]. Finally, this is the only class of agents available without Risk Evaluation and Mitigation Strategy (REMS) and/or specialty pharmacy requirements.

Soluble Guanylate Cyclase Stimulators

Soluble guanylate cyclase stimulators (sGCS) also target the NO pathway by acting in synergy with endogenous NO and directly stimulating sGC independently to increase cGMP. Riociguat (1 mg TID titrated to 2.5 mg TID) has been shown to improve exercise capacity (6MWD), WHO FC, and delay TTCW compared to placebo in those with WHO FC II to III symptoms. Improvements in PVR and NT-proBNP were also noted. Treatment effect was consistent regardless of background therapy, with nearly half of patients on a stable regimen (predominantly ERA therapy) [32].

Adverse effects are similar to those with the PDE-5 inhibitors and include headache, dizziness, hypotension, syncope, and dyspepsia. Riociguat is contraindicated with concomitant nitrates or PDE-5 inhibitors. As a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and various CYP isoenzymes, drug interaction screening, particularly for strong CYP and P-gp/BCRP inhibitors, is crucial in determining the starting dose of riociguat. Smoking is also an important consideration for dosing as it is associated with reduced drug exposure and potential need for increased maintenance dosing. Subsequent dose titration should be performed at 2-week intervals as tolerated [33]. Due to teratogenic effects, female patients can only receive riociguat through the Adempas REMS Program from a certified prescriber and pharmacy and must undergo baseline and monthly pregnancy testing

Table 2 Recent clinical trials of pharmacotherapy for patients with PAH

Clinical trial	Study type	Number of patients	Intervention	WHO functional class	Background therapy	Primary endpoint
SERAPHIN [36]	Double-blind, randomized, placebo-controlled trial	742	Macitentan (3 mg or 10 mg daily) vs. placebo	II (52%) III (46%)	PDE5 inhibitor (61%) Oral or inhaled prostanoid (5%)	Time to first occurrence of clinical composite (death, atrial septostomy, lung transplantation, initiation of intravenous or subcutaneous prostanoids, or worsening of PAH) Macitentan 10 mg vs. placebo 31.4% vs. 46.4% HR 0.55; 97.5% CI 0.39–0.76; $P < 0.001$
PATENT-1 [32]	Double-blind, randomized, placebo-controlled trial	443	Riociguat (up to 1.5 or 2.5 mg TID) vs. placebo	II (42%) III (53%)	ERA (44%) Non-intravenous prostanoid (6%)	Change from baseline in 6MWD at week 12 Riociguat 2.5 mg vs. placebo 36 m (least-squares mean difference); 95% CI 20–52; $P < 0.001$
GRIPHON [49]	Double-blind, randomized, placebo-controlled trial	1156	Selexipag (200–1600 mcg BID) vs. placebo	II (46%) III (52%)	ERA (15%) PDE5 inhibitor (32%) ERA + PDE5 inhibitor (32%)	Time to first morbidity/mortality event (disease progression, hospitalization for worsening PAH, PAH worsening, death) Selexipag vs. placebo 27% vs. 41.6% HR 0.60; 99% CI 0.46–0.78; $P < 0.0001$
AMBITION [50]	Double-blind, randomized, controlled trial	500	Tadalafil 40 mg daily + ambrisentan 10 mg daily vs. monotherapy with either	II (31%) III (69%)	None	Time to clinical failure (death, hospitalization for worsening PAH, disease progression, unsatisfactory long-term clinical response) Dual vs. monotherapy 18% vs. 31% HR 0.50; 95% CI 0.35–0.72; $P < 0.001$

PAH pulmonary arterial hypertension, *ERA* endothelin receptor antagonist, *6MWD* 6 min walk distance, *WHO* World Health Organization

during and for 1 month after treatment, with defined contraception requirements.

Endothelin Receptor Antagonists

The ERAs bosentan, ambrisentan, and macitentan block the effects of ET-1 with varying receptor selectivity. Bosentan (62.5 mg BID titrated to 125 mg BID) was the first oral agent approved for PAH and has been shown to improve exercise capacity, TTCW, and various hemodynamic measures in patients with WHO FC II–IV symptoms [34]. Ambrisentan (10 mg daily) has similar effects on exercise capacity and TTCW [35]. These effects were seen in treatment-naïve patients in comparison to placebo.

Macitentan (10 mg daily) was the first agent to demonstrate benefits in a long-term event-driven trial, with significant improvements in time to first PAH-related event or all-cause mortality in WHO FC II and III patients. This benefit was consistent regardless of background therapy and was driven largely by reductions in PAH-related hospitalizations [36].

Tolerability is comparable but variable across this class, with similar vasodilatory side effects as the other classes previously discussed. Bosentan is associated with increased serum transaminases and requires baseline and ongoing measurement of liver function tests during treatment. Ambrisentan does not carry the same hepatotoxicity risk; however, it is associated with more peripheral edema. All three are associated with anemia. As with riociguat, the ERAs are teratogenic and only available through REMS programs from certified prescribers and pharmacies with unique laboratory and contraception requirements. All three are CYP substrates, and bosentan induces CYP 3A4 and 2C9, which makes drug-drug interaction screening essential [37–39].

Prostacyclin Analogues

Prostacyclin analogues offer the widest array of administration options at the expense of increased complexity. These agents act on the prostacyclin pathway to increase cAMP, promoting vasodilation and inhibiting both platelet aggregation and smooth muscle cell proliferation. Injectable agents include epoprostenol and treprostinil, administered by continuous IV infusion due to short half-lives. Treprostinil is also available for subcutaneous (SC) infusion, as well as both inhaled and oral routes. Finally, iloprost is available only as an inhaled agent in the US.

IV epoprostenol remains the only agent associated with improved mortality in patients with WHO FC III–IV symptoms [40]. Improvements in 6MWD and hemodynamics have also been demonstrated. The initial formulation is not stable at room temperature and requires use of ice packs as well as a special diluent for stability. A newer thermostable formulation is available and, while not bioequivalent, offers advantages from a logistical perspective. Dosing is generally initiated at 2 ng/kg/min and titrated based upon tolerability (usual range 20–40 ng/kg/min).

Treprostinil has a longer half-life (4–5 h as compared to 4–6 min for epoprostenol) and most recently has been approved for IV infusion via a fully implantable pump [Implantable System for Remodulin® (ISR)]. More data exist for the SC administration of treprostinil with dose-related increases in 6MWD and hemodynamics and is preferred to IV administration with data in WHO FC II–IV [41, 42]. Dosing is similar to epoprostenol with an initial rate of 1.25 ng/kg/min for both routes and up-titration based on tolerability (usual range 40–80 ng/kg/min). All injectable agents require continuous infusion without interruption via a dedicated line with sterile preparation.

Injectable prostanoids have comparable tolerability, with vasodilatory effects as outlined previously. Unique adverse effects to this class include jaw pain, nausea/vomiting, and musculoskeletal pain. Additional distinctive adverse effects include thrombocytopenia (epoprostenol); gram negative bacteremia (IV treprostinil); and dose- and treatment-limiting infusion site pain/erythema (SC treprostinil). These agents are contraindicated in patients with heart failure with reduced ejection fraction due to increased mortality seen with IV epoprostenol [43]. These agents are available only through specialty pharmacy and require significant teaching and investment by the patient and caregivers to ensure success with drug admixture, administration, and maintenance of the infusion pump and access site.

Inhaled iloprost (2.5 mcg titrated to 5 mcg 6–9 times daily, max dose 45 mcg/day) improves 6MWD, WHO FC, hemodynamics, and TTCW in WHO FC III–IV patients. This has largely been replaced by inhaled treprostinil due to decreased administration time and frequency (3 breaths titrated to 9 breaths QID), and has demonstrated improvements in exercise capacity in WHO FC III patients. Both agents are associated with the systemic adverse effects of the prostacyclin class, with the addition of cough and throat irritation. Agent-specific delivery systems are required for administration and both agents are available only through specialty pharmacies.

Treprostinil diolamine was the first oral prostacyclin approved for PAH. The early studies showed improvement in exercise capacity for patients on monotherapy, despite no benefit when used in combination [44–46]. However, these trials were limited by subtherapeutic and suboptimal twice daily dosing related to a high prevalence of gastrointestinal-adverse effects. Higher doses have been achieved in practice owing in part to three-times daily administration and smaller tablet strengths (as low as 0.125 mg) for titration [47, 48]. The FREEDOM-EV trial (clinicaltrials.gov NCT 01560624) recently reported an improvement in time to first clinical worsening event with oral treprostinil versus placebo among patients on background therapy. Dosing was titrated based on tolerability to a maximum of 12 mg three-times daily.

Prostacyclin Receptor Agonists

The newest drug approved for the treatment of PAH, selexipag, targets the prostacyclin pathway by selectively stimulating the IP receptor to promote vasodilation and antiproliferation. It has demonstrated improvements in a composite endpoint including death or PAH-related complications in WHO FC II and III patients. Dosing was initiated at 200 mcg BID and titrated weekly to a maximum of 1600 mcg BID. Outcomes were consistent regardless of achieved dose or background therapy and was driven largely by reductions in disease progression and hospitalizations [49]. Adverse effects are similar to the prostacyclin class, including myalgia and jaw pain in addition to diarrhea. Selexipag is a substrate of CYP2C8 and is contraindicated with concomitant gemfibrozil. As with most PAH-targeted therapies, selexipag is available only through specialty pharmacies.

Sixth WSPH Guidelines

The Sixth WSPH recently published evidence-based treatment recommendations [4••]. The algorithm provides treatment recommendations with emphasis on the utility of initial upfront combination therapy versus monotherapy based on positive outcomes from the AMBITION trial [50]. This study demonstrated a significant improvement in the composite of time to clinical failure with the combination of tadalafil and ambrisentan compared to either agent alone (HR 0.50; 95% CI 0.35–0.72) in patients with WHO FC II–III symptoms [50]. Therefore, the guideline recommendation for upfront combination applies to most treatment-naïve and non-vasoreactive patients with low or intermediate-risk status.

The Sixth WSPH guidelines also address the residual role for initial monotherapy in low- or intermediate-risk patients. Subgroups of patients who should be considered for monotherapy include those not well-represented in the AMBITION trial (HIV, portal hypertension, uncorrected congenital heart disease, and mild disease [WHO FC I, PVR 3–4 Wood units, normal RV function, mPAP < 30 mmHg]). Additional considerations for monotherapy include the following groups: long-term response to calcium channel blockers, long-term treated patients with stable, low-risk profile on monotherapy, idiopathic PAH and > 75 years of age with multiple risk factors for heart failure with preserved ejection fraction, suspected pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis, and those in whom combination therapy is either unavailable or contraindicated [4••].

Patients with high-risk status as defined in the treatment guidelines are recommended to receive initial combination therapy which includes an IV prostacyclin analogue [4••]. Epoprostenol has the highest recommendation based on mortality benefit [40]. The initial choice of medication is often based on a variety of factors (i.e., route of administration, adverse effects, drug interaction potential, patient preferences, comorbidities, prescriber experience, and cost) since most studies did not include head-to-head comparisons. These patients should also be considered for referral for lung transplant evaluation.

Regardless of initial risk status, patients should be re-evaluated 3 to 6 months after treatment has been initiated. The same treatment can be continued if low-risk status is achieved. For intermediate-risk status, treatment should be escalated to triple combination therapy (or dual therapy if initial monotherapy was chosen). Note that the following combinations have the highest recommendation and evidence for sequential treatment: macitentan and sildenafil; riociguat and bosentan; selexipag and an ERA and/or PDE5 inhibitor [4••, 32, 36, 49]. For high-risk status, maximal medical therapy is recommended (triple combination therapy including a SC or IV prostacyclin analogue, although IV is preferred) and referral for lung transplantation [4••].

Despite advancements in medical therapies and use of combination therapeutic strategies, PH is still a chronic and progressive disease, and in patients who progress despite medical therapy, it is important to consider lung transplantation. The International Society for Heart and Lung Transplantation (ISHLT) guidelines recommend referring PH patients that show WHO FC III or IV symptoms during escalating therapy, or who have progressive disease, or who are on parenteral therapy, or have known or suspected pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis [51]. It is important to recognize that early referral is helpful so that patients can be fully evaluated and educated about lung transplantation and make a decision for themselves about listing when they are not in the throes of clinical worsening. Additionally, early referral does not necessarily mean automatic listing, especially if the patient is too well for transplant. Rather, it allows the transplant center to also follow the patient and be able to do whatever testing is needed to lower their transplant risk, as well as follow them and be ready for when the time comes for listing. ISHLT guidelines recommend listing for transplant when a patient still has WHO FC III or IV symptoms despite at least 3 months of combination therapy including prostanoids, a cardiac index of less than 2 L/min/m^2, mean right atrial pressure > 15 mmHg, 6MWD < 650 m, or development of significant hemoptysis, pericardial effusion, or progressive right heart failure (HF) [51]. Timing of listing and transplantation is key in any patient with end-stage lung disease, as the current median survival for PAH patients after double lung transplant is 6.3 years [52]. PAH patients can have a challenging course in the immediate post-operative period, so when they make it past the initial 3 months, the overall medial survival improves to 9.8 years [52]. In summary, it is important to consider lung transplant as a treatment option in PAH patients.

New Insights into Management of PAH

A newer therapeutic approach being investigated for patients with PAH is the use of upfront triple combination therapy using medications which target different disease pathways. A pilot study demonstrated improvements in exercise capacity, WHO FC, and hemodynamics at 4 months among nineteen patients with WHO FC III or IV symptoms [53]. These patients were treatment naïve and initiated with the combination of epoprostenol, bosentan, and sildenafil. This study prompted the ongoing TRITON study (ClinicalTrials.gov Identifier: NCT02558231) which is investigating upfront triple therapy (macitentan, tadalafil, and selexipag) compared to dual therapy (macitentan, tadalafil, and placebo). The primary outcome is change in PVR at 26 weeks [54].

Multidisciplinary Team

Despite a paucity of data documenting improved outcomes associated with multidisciplinary care of the PH patient population, it is still deemed an important consideration in assuring optimal care. The importance of the multidisciplinary team in the management of patients with pulmonary hypertension is supported by international guideline recommendations [4••, 12••]. The multidisciplinary team includes a PH specialist (pulmonologist or cardiologist) and may consist of physicians from varying subspecialties (pulmonary, cardiology, interventional cardiology, transplant surgery, PTE surgery, rheumatology, and hematology), pharmacists, advanced practice providers, nurses, psychologists, and social workers. This care extends to comorbid conditions including, but not limited to, depression, systemic sclerosis, thrombophilia, and cardiovascular and pulmonary diseases. Issues with medication access and cost, agent selection and dose titration, and adverse event management also lend themselves well to a multidisciplinary approach and may support attainment of goals determined by patient risk and goals of care [55–57].

Non-group 1 PH Overview and General Treatment Approach

The treatment modality for secondary forms of PH (groups 2 through 5) is to address the underlying causes. A brief overview of each WHO non-group 1 is summarized below.

WHO Group 2 PH—PH due to Left Heart Disease

The most common cause of PH is left heart disease (LHD), including HF or valvular heart disease, which lead to passive increases in left atrial pressure [12••, 58]. Patients with PH-LHD are categorized as having post-capillary or group 2 PH [6••]. According to the new guidelines, these patients are further defined according to hemodynamics: isolated post-capillary PH (PAWP > 15 mmHg, mPAP > 20 mmHg, and PVR < 3 WU) and combined pre- and post-capillary PH (PAWP > 15 mmHg, mPAP > 20 mmHg, and PVR ≥ 3 WU) [6]. Readers are referred to a recently published focused review on this topic for further information [59].

WHO Group 3 PH—PH due to Lung Diseases and/or Hypoxia

Elevated pulmonary artery pressures are commonly seen in chronic lung disease, and associated with worse outcomes including increased mortality [60, 61•]. PH is most commonly described in chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD), but is also found in other chronic lung diseases such as cystic fibrosis and bronchopulmonary dysplasia. In COPD, PH is associated with more severe COPD, and the presence of pulmonary hypertension has been associated with more frequent hospitalizations for COPD exacerbations [60, 62]. In ILD, PH has not been associated with disease severity as measured by fibrosis score on CT scan or by pulmonary function tests [61•].

Although PH is common in chronic lung disease, to date there is a paucity of evidence for the use of vasodilator therapy in chronic lung disease. In fact, in the case of some agents, vasodilator therapy worsened mortality, and thus the guidelines recommend against the use of vasodilator therapy in WHO group 3 PH [61•].

Because PH is common in chronic lung disease, but the use of vasodilator therapy is uncommon, experts recommend judicious use of right heart catheterization in patients with lung disease so that it is used in cases where the data are likely to influence the patient's outcome. Such cases include evaluation for lung transplantation, clinical trials, or investigating whether there is concomitant left-sided heart disease. It may also be used when a patient's symptoms are not felt to be explained by their lung disease (i.e., they have relatively mild lung disease), or making an accurate prognosis is important to the patient.

In recent years meetings of the WSPH, experts gather to discuss the concepts of WHO group 3 PH (PH due to chronic lung disease) versus those instances where patients may have significant PAH-type numbers and limited lung disease (PAH with concomitant lung disease, but not resultant from the lung disease). The WSPH and Cologne conference distinguished these patients as having an mPAP ≥ 35 mmHg and PVR ≥ 6 Wood units [61•, 63]. When this is found, it is recommended that the patient be referred to expert centers for PH and lung disease for possible clinical trials or further consideration for treatment. However, first-line therapy in WHO group 3 PH specifically excludes vasodilator therapy and focuses on the treatment of the underlying lung disease [61•]. This includes bronchodilator therapy or antiproliferative therapy for the patient's lung disease, supplemental oxygen, pulmonary rehabilitation, and lung transplant evaluation.

WHO Group 4 PH—PH due to Pulmonary Artery Obstructions

Chronic thromboembolic PH (CTEPH) occurs primarily after an acute venous thromboembolic event and is a major cause of chronic PH [64•]. The exact incidence of CTEPH after symptomatic pulmonary embolism is uncertain but has been estimated at 0.4 to 6.2% with diagnostic confirmation by RHC, with an overall incidence of 3.4% [64•, 65]. While the exact mechanism is unclear, it appears to result from one or more pulmonary emboli. The resultant obstruction in blood flow is a result of fibrotic thrombi and leads to progressive vascular remodeling and the development of PH with resultant right heart failure [64•].

Current guidelines recommend that all patients with CTEPH be considered for pulmonary endarterectomy (PEA) surgery at an expert center due to favorable survival rates (90% at 3 years with surgery) and potential for cure [64•, 66]. For those patients who are not candidates for PEA, or who have residual disease despite PEA, the recommendations are less clear. There are continually emerging data evaluating outcomes after balloon pulmonary angioplasty (BPA). However, this too should be confined to expert centers with review by a multidisciplinary team given the training, expertise, and complications associated BPA [64•].

Lifelong anticoagulation is indicated for all patients diagnosed with CTEPH. Vitamin K antagonists have typically been the agents used as there are limited data evaluating the use of the direct-acting oral anticoagulants (DOACs) or low-molecular-weight heparin products. This is regardless of operable candidacy or any additional therapies [64•, 67].

For patients who are not candidates for PEA, there are limited prospective data to support the use of PH-targeted therapies used in group 1 disease. Bosentan was evaluated in patients with predominantly WHO FC II–III symptoms who were either deemed to have inoperable or persistent disease despite PEA. While it failed to improve exercise capacity or WHO FC at 16 weeks, bosentan was associated with improvements in hemodynamics [68]. Macitentan was evaluated exclusively in WHO FC II–III inoperable patients and improved PVR at 16 weeks, with several other secondary outcomes also improved (CI, mixed venous oxygen saturation, and NT-proBNP). Exercise capacity was also improved with macitentan at the end of the 24-week follow-up [69]. Riociguat represents the only therapy with a labeled indication for the treatment of both PAH and CTEPH. In the largest trial of WHO FC II–III patients with inoperable or persistent disease, riociguat was found to improve exercise capacity at 16 weeks. Improvements were also seen in a number of hemodynamic parameters, WHO FC, NT-proBNP, and quality of life scores [70].

Based upon currently available data, riociguat is the sole agent with a class I recommendation in patients with CTEPH that is deemed inoperable or persistent despite PEA. Off-label use of other agents approved for PAH should be reserved for patients with inoperable disease (class IIb). The decision for medical therapy should be made after evaluation by an experienced PEA surgeon [12••].

Conclusions

Updated recommendations for PH include a revised hemodynamic definition, clinical classification, and evidence-based treatment algorithm. Careful clinical and hemodynamic evaluation with multivariable risk assessment are essential to proper diagnosis and treatment. The pharmacotherapy for PAH has evolved to include several medications which have demonstrated improvements in clinical outcome. The treatment approach has also advanced to include upfront combination therapy for treatment-naïve patients. Structured risk assessment and treatment escalation is an important component of patient management. A multidisciplinary approach to PAH care is advised. Investigation continues into newer treatment paradigms including upfront triple combination therapy for PAH. For patients with non-group 1 PH, treatment should focus on the underlying etiology. Studies for the management of these patients are ongoing.

Compliance with Ethical Standards

Conflict of Interest James C. Coons reports a grant from United Therapeutics.

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- • Of importance
- •• Of major importance

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