

Diagnosis and Treatment of Pulmonary Arterial Hypertension

A Review

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 Multimedia

IMPORTANCE Pulmonary arterial hypertension (PAH) is a subtype of pulmonary hypertension (PH), characterized by pulmonary arterial remodeling. The prevalence of PAH is approximately 10.6 cases per 1 million adults in the US. Untreated, PAH progresses to right heart failure and death.

OBSERVATIONS Pulmonary hypertension is defined by a mean pulmonary artery pressure greater than 20 mm Hg and is classified into 5 clinical groups based on etiology, pathophysiology, and treatment. Pulmonary arterial hypertension is 1 of the 5 groups of PH and is hemodynamically defined by right heart catheterization demonstrating a mean pulmonary artery pressure greater than 20 mm Hg, a pulmonary artery wedge pressure of 15 mm Hg or lower, and a pulmonary vascular resistance of 3 Wood units or greater. Pulmonary arterial hypertension is further divided into subgroups based on underlying etiology, consisting of idiopathic PAH, heritable PAH, drug- and toxin-associated PAH, pulmonary veno-occlusive disease, PAH in long-term responders to calcium channel blockers, and persistent PH of the newborn, as well as PAH associated with other medical conditions including connective tissue disease, HIV, and congenital heart disease. Early presenting symptoms are nonspecific and typically consist of dyspnea on exertion and fatigue. Currently approved therapy for PAH consists of drugs that enhance the nitric oxide–cyclic guanosine monophosphate biological pathway (sildenafil, tadalafil, or riociguat), prostacyclin pathway agonists (epoprostenol or treprostinil), and endothelin pathway antagonists (bosentan and ambrisentan). With these PAH-specific therapies, 5-year survival has improved from 34% in 1991 to more than 60% in 2015. Current treatment consists of combination drug therapy that targets more than 1 biological pathway, such as the nitric oxide–cyclic guanosine monophosphate and endothelin pathways (eg, ambrisentan and tadalafil), and has shown demonstrable improvement in morbidity and mortality compared with the previous conventional single-pathway targeted monotherapy.

CONCLUSIONS AND RELEVANCE Pulmonary arterial hypertension affects an estimated 10.6 per 1 million adults in the US and, without treatment, typically progresses to right heart failure and death. First-line therapy with drug combinations that target multiple biological pathways are associated with improved survival.

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Pulmonary arterial hypertension (PAH) is a life-threatening disorder characterized by elevated pressure in the pulmonary arteries due to increased pulmonary vascular resistance.¹ Symptoms of PAH are nonspecific but commonly include dyspnea on exertion and fatigue.² The estimated prevalence of PAH is 10.6 per 1 million adults in the US. Untreated, PAH typically progresses to right ventricular failure and death.³ Treatment has significantly improved outcomes in the last decade.⁴ The diagnosis should be considered in any patient presenting with unexplained exertional dyspnea. This Review summarizes current evidence regarding diagnosis and treatment of PAH.

arterial hypertension. Articles were selected for inclusion based on relevance to current clinical practice. Randomized clinical trials, large longitudinal observational studies, and more recent articles were prioritized. Bibliographies of retrieved articles were searched for other relevant articles. Of the articles identified, 99 were included, consisting of 23 randomized clinical trials, 3 meta-analyses and systematic reviews, 36 observational studies, 16 registry-based studies, and 21 clinical practice guidelines or other reports.

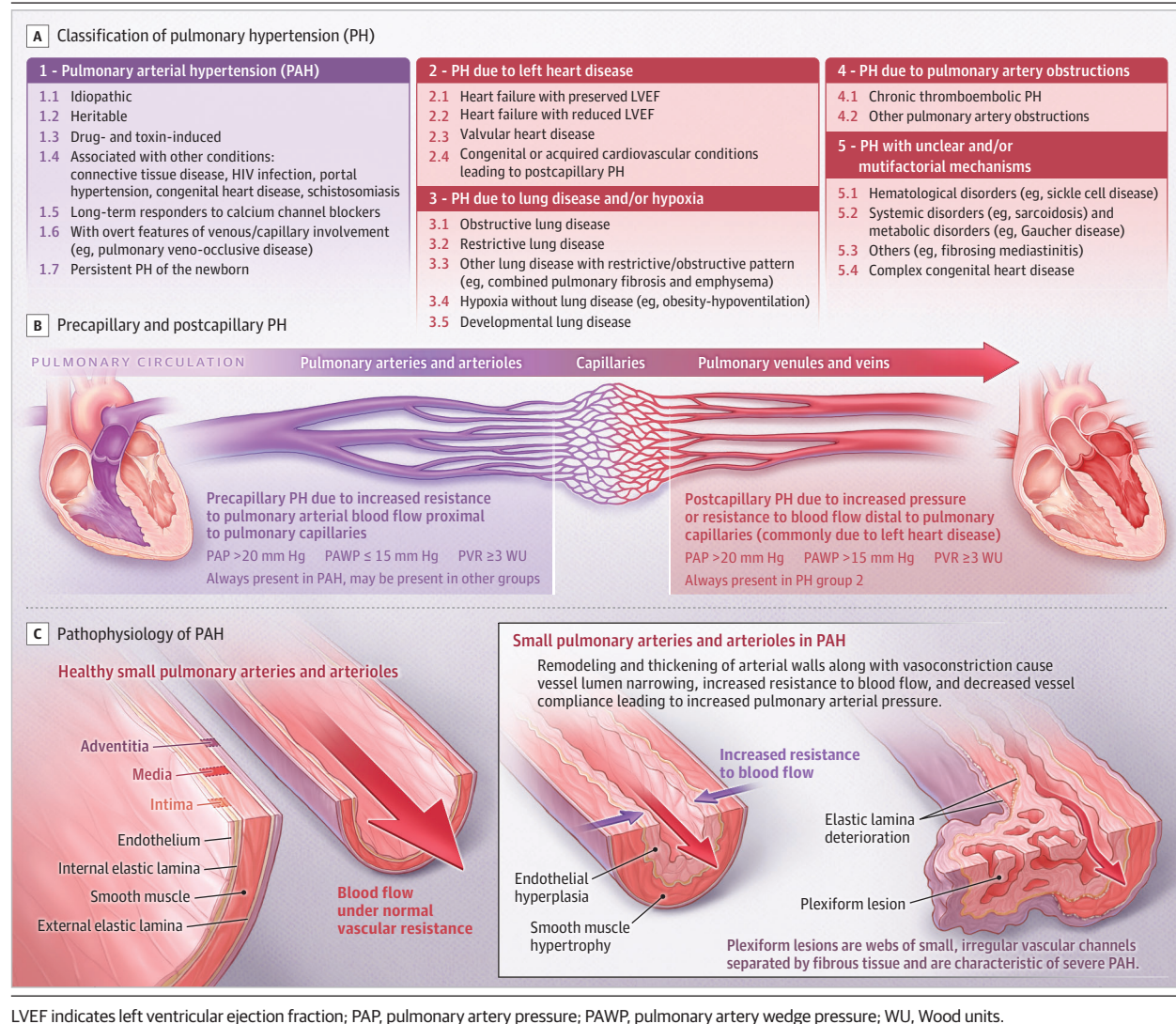
Definition and Classification of Pulmonary Hypertension

The clinical classification of pulmonary hypertension (PH), of which PAH is a subtype, is important for understanding the approach to both diagnosis and treatment of PAH. Pulmonary hypertension is

Methods

PubMed was searched for English-language articles from 1985 through December 30, 2021, using search terms for pulmonary

Figure 1. Classification of Pulmonary Hypertension and Pathophysiology of Pulmonary Arterial Hypertension



LVEF indicates left ventricular ejection fraction; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; WU, Wood units.

currently defined by a mean pulmonary artery pressure greater than 20 mm Hg on supine right heart catheterization at rest.⁵ This definition differs from the previous threshold of 25 mm Hg or greater in recognition that patients with a mean pulmonary artery pressure of 21 mm Hg to 24 mm Hg are at increased risk of mortality and hospitalization compared with those with a mean pulmonary artery pressure of 20 mm Hg or lower.⁶

Pulmonary hypertension is classified into 5 groups (Figure 1A). Group 1 PH (PAH) is defined as a mean pulmonary artery pressure greater than 20 mm Hg, pulmonary artery wedge pressure of 15 mm Hg or lower, and pulmonary vascular resistance of 3 Wood units or greater.⁵ Group 2 is PH associated with left heart disease. Group 3 is PH associated with lung disease such as chronic obstructive pulmonary disease or idiopathic pulmonary fibrosis and/or hypoxemia. Group 4 disease is PH due to pulmonary artery obstruction, typically chronic thromboembolic disease. Group 5 is PH associated with an unclear cause or multifactorial causes. Thus, all PAH, the subject of this Review, is also classified as PH, whereas only Group 1 PH is considered PAH.^{5,7}

Pathophysiology of PAH

Distinguishing between PH due to prepulmonary vs postpulmonary capillary vascular abnormalities is essential to understanding the pathophysiology of PAH (Figure 1B). Pulmonary hypertension is defined by elevation of the pressure within the pulmonary arteries. Normally, cardiac output from the right ventricle flows through the pulmonary arteries and arterioles, pulmonary capillaries, pulmonary venules, and veins, eventually reaching the left atrium. Precapillary PH exists when the elevation in pulmonary artery pressure is due to increased resistance in the pulmonary arteries proximal to the pulmonary capillaries, and is always present in PAH.

The pathophysiologic mechanisms of PAH remain unclear.^{5,8,9} Vascular pathology consists of arterial medial and intimal remodeling, plexiform lesions, and fragmentation of the elastic lamina (Figure 1C).^{8,9} Vascular remodeling, defined as thickening of the vascular wall via hypertrophy or hyperplasia, primarily contributes to increased pulmonary vascular resistance and, subsequently, an in-

crease in mean pulmonary artery pressure. Vasoconstriction is an important component of PAH; however, whether it is an inciting event or a complication of pulmonary vascular remodeling is uncertain.⁸ Eventually, the small precapillary arteries and arterioles are obliterated, leading to an isolated reduction in diffusing capacity for carbon monoxide (DLCO) in patients with PAH.¹⁰ Effective treatments ideally target remodeling of pulmonary arteries as well as vasoconstriction. Initially, the right ventricle compensates for increased afterload by increasing contractility and wall thickness. Eventually, the right ventricle dilates and fails, resulting in death due to right heart failure if left untreated.¹¹

Prevalence of PAH and Patient Characteristics

Pulmonary arterial hypertension is uncommon. A French registry (n = 674; 2002-2003) reported an incidence of about 2.4 cases per 1 million per year and a prevalence of 15 cases per 1 million adults.¹² The US-based REVEAL registry (n = 2525; 2006-2007), a multicenter prospective cohort study involving 54 centers, reported an incidence of 2.0 cases per 1 million per year and a prevalence of 10.6 cases per 1 million adults.¹

Patient characteristics vary by registry. In contrast to findings from a National Institutes of Health registry initiated in 1981 (n = 187),¹³ the REVEAL registry (n = 2525; 2006-2007) reported that patients with PAH were older (aged 50.1 [SD, 14.4] years vs 35 [SD, 15] years at diagnosis) and had a greater predominance among women (ratio of female to male patients, 4.07:1 vs 1.7:1).¹⁴ It is uncertain whether these differences represent temporal changes in characteristics of people with PAH or are related to increased awareness.¹⁴ Prior to the development of PAH-specific therapy, 5-year survival after diagnosis was 34% (n = 187).³ More recent data reported 1-year survival rates of approximately 61% (REVEAL registry; n = 2749; 2006-2009) and 64% (French registry; n = 1611; 2006-2018).^{15,16}

Subgroups of PAH

Pulmonary arterial hypertension is further categorized into subgroups based on pathophysiology, etiology, and response to treatment.

Idiopathic PAH (Group 1.1)

Previously referred to as primary PH, idiopathic PAH meets the hemodynamic criteria for PAH but is not associated with another disease process, such as collagen vascular disease or liver disease. The REVEAL registry and French registry reported that 46% of 2525 patients with PAH and 39% of 674 patients with PAH had idiopathic PAH, respectively.^{1,12}

Heritable PAH (Group 1.2)

Heritable PAH (or familial PAH) affects approximately 6% to 10% of people with PAH.¹⁷ Variants in the bone morphogenetic protein receptor 2 gene (*BMPR2*) account for nearly 75% of heritable PAH and are associated with an autosomal dominant/incomplete penetrance pattern of inheritance.¹⁸ When genotyping is performed, *BMPR2* variants are present in approximately 25% of patients ini-

tially diagnosed with idiopathic PAH, underscoring the need for genetic counseling for patients who have either heritable or idiopathic PAH.¹⁸ Currently, approximately 15 additional variants have been identified in people with heritable PAH,¹⁹ including variants present in hereditary hemorrhagic telangiectasia.²⁰ Compared with nonheritable idiopathic PAH, heritable PAH due to *BMPR2* variants typically presents earlier (age 37 years vs age 46 years), has more severe hemodynamic characteristics at diagnosis, and has a poorer response rate to therapy.^{21,22}

Drug- and Toxin-Induced PAH (Group 1.3)

Pulmonary arterial hypertension is associated with specific drug and toxin exposures, such as methamphetamine, dasatinib, or fenfluramine.⁵ A study of patients hospitalized from 2003 to 2015 reported that the incidence of likely PAH-related hospitalization per *International Classification of Diseases* coding was more than twice as high in users vs nonusers of methamphetamine (984.6 cases per 1 million [meth]amphetamine users compared with 373.2 cases per 1 million in non-[meth]amphetamine users; relative risk [RR], 2.64; 95% CI, 2.18-3.2; *P* < .001).²³ In 90 patients with methamphetamine-associated PAH and 97 patients with idiopathic PAH, those with methamphetamine-associated PAH had more severe clinical disease and rapid progression of PAH compared with those with idiopathic PAH (5-year and 10-year event-free survival rates of 47.2% and 25% vs 64.5% and 45.7%, respectively).²³

Dasatinib, a targeted cancer therapy tyrosine kinase inhibitor, is associated with development of PAH. In a French registry of 2900 patients receiving dasatinib, 9 patients developed PH (mean length of treatment prior to diagnosis, 31 months; range, 8-48 months), and 4 additional cases of dasatinib-associated PH were reported to French regulatory agencies; therefore, the lowest estimate of PH in patients with a history of dasatinib use was 0.45%, compared with 10 to 15 cases per 1 million in a population that was not associated with use of dasatinib.²⁴ Dasatinib-associated PAH typically resolves with discontinuation of the drug.^{25,26} In a pharmaceutical vigilance database, 34 of 36 patients with dasatinib-associated PAH had improvement or resolution of their symptoms with discontinuation of the drug.²⁷

Associated PAH (Group 1.4)

Connective Tissue Disease–Associated PAH (Group 1.4.1)

Connective tissue disease–associated PAH affects 15% to 25% of people with PAH, most commonly patients with scleroderma, although it also occurs with systemic lupus erythematosus, mixed connective tissue disease, rheumatoid arthritis, and Sjögren syndrome.^{1,12,14} The prevalence of PAH in patients with scleroderma is 8% to 14%.^{24,28} Patients with scleroderma-associated PAH have a worse prognosis compared with other forms of connective tissue disease–associated PAH and have a higher prevalence of pericardial effusions, shorter 6-minute walk distance, and worse DLCO compared with people with idiopathic PAH.²⁹ Patients with scleroderma who have PAH have a higher rate of mortality than those without PAH (3-year survival, 94% vs 56%; n = 546).³⁰ Annual echocardiogram screening is recommended by the World Symposium on Pulmonary Hypertension for patients with scleroderma to facilitate early diagnosis and treatment of PAH.^{2,30,31} However, no clinical trials have shown

that annual echocardiogram screening improves outcomes. A cross-sectional international study of 466 patients with scleroderma at high risk of PAH found that 87 of 466 patients (19%) had PAH confirmed by right heart catheterization.³²

HIV-Associated PAH (Group 1.4.2)

Pulmonary arterial hypertension is a potential complication of HIV infection. In 7658 patients with HIV infection, the prevalence of PAH was 0.46% (95% CI, 0.32%-0.64%), compared with 10 to 15 cases per 1 million in a population that was not HIV positive.³³ Echocardiographic assessment is recommended by the World Symposium on Pulmonary Hypertension in all patients with HIV infection with unexplained dyspnea or in patients with asymptomatic HIV infection who have additional risk factors such as female sex, intravenous drug or cocaine use, or hepatitis C infection.² However, this approach has not been shown to improve outcomes in patients with HIV.

Portal Hypertension-Associated PAH (Group 1.4.3)

Portopulmonary hypertension, defined as PAH in association with portal hypertension, can develop in patients with portal hypertension due to cirrhosis, periportal fibrosis without cirrhosis, portal vein thrombosis, hepatic vein sclerosis, and congenital portal circulation abnormalities. Survival is worse with portopulmonary hypertension when cirrhosis is present.³⁴ In a prospective study of 1235 patients evaluated for liver transplant, PAH was diagnosed in 5%.³⁵ The pathophysiologic connection between portal hypertension and PAH is unclear. It is hypothesized that the dysfunctional liver and portosystemic shunts expose the pulmonary vascular bed to factors that may adversely affect it via abnormal estrogen signaling in genetically susceptible individuals.^{36,37} Practice guidelines recommend obtaining an echocardiogram in all patients with portal hypertension to assess for PH, although this approach has not been shown to improve clinical outcomes.² The American Society of Transplantation recommends screening for portopulmonary hypertension with echocardiogram as part of a comprehensive evaluation prior to liver transplant.^{35,38} Portopulmonary hypertension may improve or resolve following liver transplant. In a 10-year follow-up study of patients with portopulmonary hypertension who underwent liver transplant (n = 27), 45% had resolution of PH while 55% required ongoing pulmonary vasodilator therapy.³⁹

Congenital Heart Disease-Associated PAH (Group 1.4.4)

Congenital heart disease-associated PAH consists of a diverse spectrum of pathophysiology and includes 4 subgroups: Eisenmenger syndrome, PAH associated with systemic-to-pulmonary shunts, PAH with small/incidental cardiac defects (such as small atrial septal defects or ventricular septal defects), and PAH after cardiac defect closure.⁴⁰ In 192 patients with congenital heart disease-associated PAH, 20-year survival rates were 87% for those with Eisenmenger syndrome, 86% for those with systemic-to-pulmonary shunts, and 36% for those with corrected abnormalities such as atrial and ventricular septal defects.⁴¹ Survival in patients with Eisenmenger syndrome is better than that of patients with idiopathic PAH (89% vs 46%) at 10 years, possibly because of better right ventricular function in patients with Eisenmenger syndrome.^{41,42}

Schistosomiasis-Associated PAH (Group 1.4.5)

Schistosomiasis-associated PAH represents the leading cause of PAH in countries where schistosomiasis is endemic, thus possibly representing the largest burden of PAH worldwide.^{43,44} Among patients with severe schistosomal liver disease, approximately 5% to 8% develop schistosomiasis-associated PAH.⁴⁵ Schistosomiasis-associated PAH should be considered or suspected in patients with PAH who are from an endemic area and who have *Schistosoma* parasite eggs in stool, a history of treatment for schistosomiasis, or ultrasound evidence of hepatosplenic schistosomiasis, such as portal hypertension with portal fibrosis with or without splenomegaly.^{44,46}

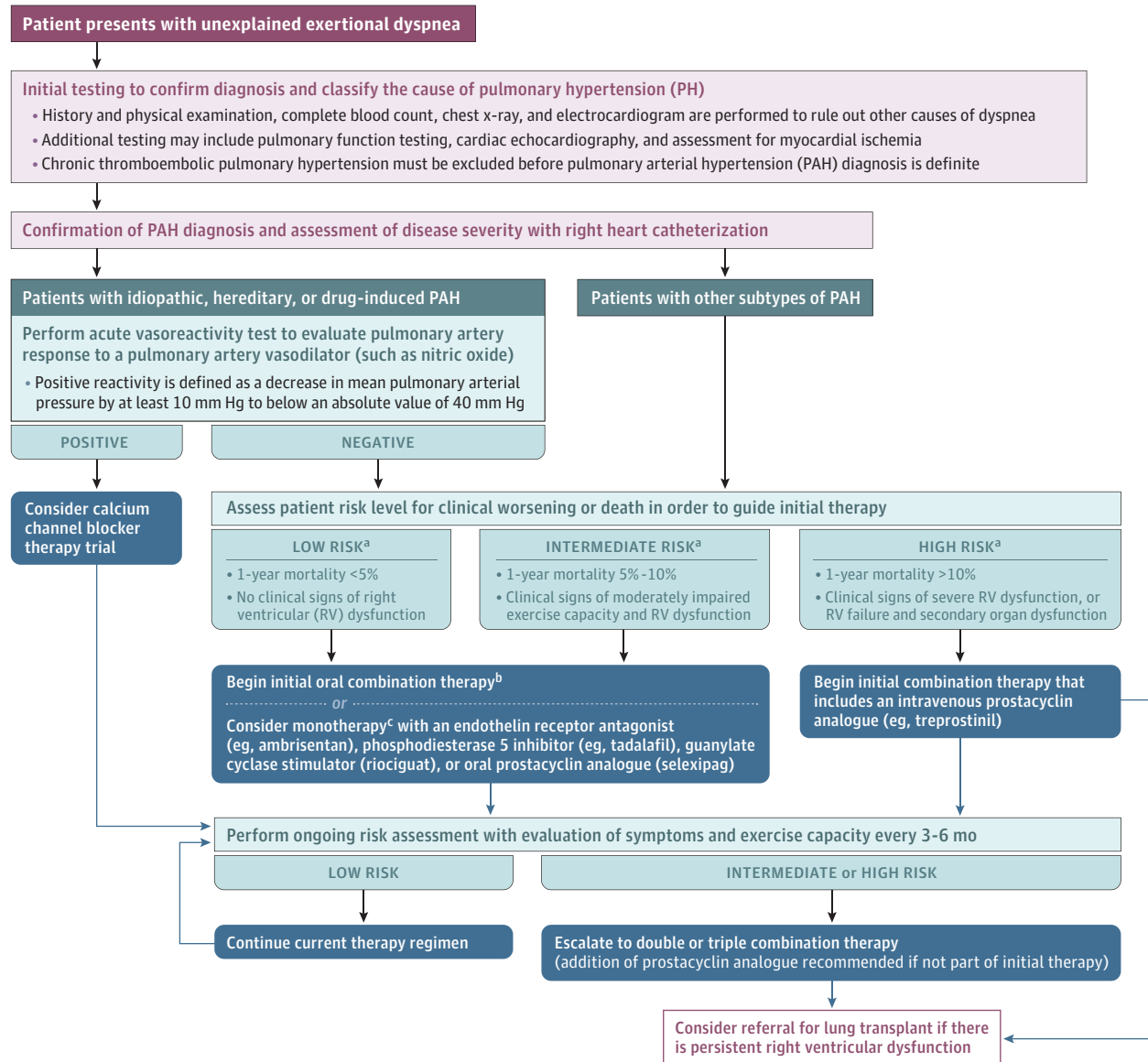
PAH in Long-term Responders to Calcium Channel Blockers (Group 1.5)

First recognized in 2018, long-term responders to calcium channel blockers are defined as patients with PAH who demonstrate acute vasodilation of the pulmonary vasculature in response to inhaled nitric oxide challenge and improvement in New York Heart Association function class (to class I or II) and unchanged or improved hemodynamics at 1 year when treated with calcium channel blockers alone.⁵ Acute vasodilator testing is performed during right heart catheterization, with measurement of hemodynamics typically before and after inhaled nitric oxide. Testing may alternatively be performed with inhaled or intravenous epoprostenol, adenosine, or inhaled iloprost. A positive test result is defined as a decrease in mean pulmonary artery pressure by 10 mm Hg or greater to less than 40 mm Hg without a decrease in cardiac output.⁵ In a study of 557 patients with PAH, 12.5% had an acute vasodilator response and 6.8% had a sustained response with long-term improvement while taking calcium channel blockers.⁴⁷ Patients with long-term calcium channel blocker responsiveness possess unique molecular signatures in human lung fibroblasts enriched for vascular smooth muscle-related genes that differentiate them from non-calcium channel blocker-responsive idiopathic PAH.⁴⁸ Survival is better for patients with PAH who are long-term responders to calcium channel blockers.^{47,49}

PAH With Overt Features of Venous/Capillary Involvement (Group 1.6)

Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis account for 5% to 10% of patients initially diagnosed as having idiopathic PAH (estimated incidence of 0.1 to 0.2 cases per 1 million; prevalence of 1 case per 1 million).^{40,50} Patients with pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis present with severe reductions in DLCO, severe hypoxemia, and typical imaging findings including diffuse septal thickening, centrilobular ground-glass opacities, and mediastinal lymphadenopathy.⁵¹ The distinction between pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis has been questioned since both have features of a pan-pulmonary vasculopathy with prominent septal vein/venule involvement and capillary congestion/proliferation with varying degrees of small arteriolar involvement.⁵⁰ Unlike idiopathic PAH, both entities have significant involvement of small vessels distal to the pulmonary arterioles, which makes treatment with pulmonary vasodilators dangerous due to the risk of precipitating pulmonary edema.⁵² Heritable forms of pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis have been reported in association with *EIF2AK4* and *BMPR2* variants.^{51,53}

Figure 2. Diagnosis and Medical Management of Pulmonary Arterial Hypertension



^a Risk assessment as defined in Galiè et al.⁴⁰

^b Oral combinations of ambrisentan and tadalafil; macitentan added sequentially to sildenafil; selexipag added sequentially to phosphodiesterase 5 inhibitors and/or endothelin receptor antagonists; or oral treprostinil added sequentially to phosphodiesterase 5 inhibitors and/or endothelin receptor

antagonists have been found to be efficacious compared with placebo and/or monotherapy.

^c Monotherapy can be considered in very low-risk populations or in patients who have been stable with monotherapy for more than 1 to 2 years.

Persistent PH of the Newborn Syndrome (Group 1.7)

Persistent PH of the newborn syndrome occurs when fetal circulation fails to transition from intrauterine circulation to extrauterine circulation at birth, resulting in persistently elevated pulmonary vascular resistance, low pulmonary blood flow, right-to-left shunting across the patent ductus arteriosus and patent foramen ovale, and severe hypoxemia.⁵⁴ The incidence of persistent PH of the newborn syndrome is 0.18% (3277 cases per 1 781 156 live births), with a mortality rate of 7.6% at 1-year follow-up for all newborns with persistent PH of the newborn syndrome.⁵⁵

Clinical Presentation

Symptoms of PAH may be nonspecific and have an insidious onset (Figure 2). In the National Institutes of Health registry of 187 people with PAH, dyspnea was the first symptom in 60%, although 98% reported dyspnea at the time of PAH diagnosis.¹³ Fatigue (19%), near syncope (5%), syncope (8%), and chest pain (7%) also occur (Box 1).¹³ With advanced disease, these symptoms may occur with minimal exertion or at rest.

Box 1. Presenting Symptoms, Signs, and Echocardiogram Findings in Pulmonary Arterial Hypertension**Common Symptoms**

Dyspnea on exertion
 Fatigue
 Lower extremity edema
 Palpitations
 Lightheadedness
 Syncope

Physical Signs

Loud pulmonic component of second heart sound
 Elevated jugular venous pressure
 Pulmonary artery tap
 Tricuspid regurgitation murmur
 Lower extremity edema
 Ascites

Echocardiogram Findings

Elevated estimated right ventricular systolic pressure
 Right ventricular dilation
 Right ventricular dysfunction
 Peak tricuspid regurgitant jet >2.8 m/s
 Flattening of interventricular septum
 Tricuspid annular plane systolic excursion <17 mm

Physical examination findings are subtle in early disease. Of 187 patients, 93% had a loud second heart sound.¹³ Other distinctive findings (right-sided third heart sound, tricuspid regurgitation murmur, increased jugular venous distension, right ventricular heave) occur in more advanced disease. As right ventricular dysfunction worsens, lower extremity edema, abdominal distension, and ascites may develop.

Diagnosis is often delayed: 21.1% of patients in the REVEAL registry (n = 2967) had symptoms for more than 2 years before diagnosis.⁵⁶ Younger age (<36 years) and coexistence of common respiratory disorders such as asthma and obstructive sleep apnea increase delayed diagnosis.⁵⁶ Prognosis is associated with disease severity at presentation. Expert consensus recommends that early diagnosis and early initiation of therapy may improve survival.^{4,15} A high degree of clinical suspicion in a patient with unexplained exertional dyspnea or fatigue is required.

Assessment and Diagnosis

Evaluation of patients with possible PH should focus on confirming the diagnosis, classifying the cause of PH, and ascertaining severity (Box 2). If a thorough history, physical examination, complete blood count, chest x-ray, and electrocardiogram do not explain dyspnea, recommended testing may include pulmonary function tests, cardiac echocardiography, and assessment for myocardial ischemia, depending on a patient's history and risk factors.^{2,57} Chronic thromboembolic PH, defined by progressive pulmonary artery vascular remodeling leading to PH as a consequence of pulmonary embolism, must be excluded before PAH can be diagnosed.^{5,40}

Box 2. Commonly Asked Questions in Pulmonary Arterial Hypertension**Can Pulmonary Arterial Hypertension Be Diagnosed With an Echocardiogram?**

No. An echocardiogram is an excellent first test; however, diagnosis of pulmonary arterial hypertension requires a right heart catheterization to accurately assess hemodynamic status and eliminate left heart disease as a contributor to elevated pulmonary artery pressure.

How Dangerous Is a Right Heart Catheterization?

When performed at a center with experience in the procedure, right heart catheterization is associated with a low risk of serious complications (1.1%) or death (0.055%), even for patients with significant right ventricular dysfunction.

What Is the Initial Laboratory Evaluation of Pulmonary Hypertension?

Initial tests should include complete blood count, basic metabolic panel, thyrotropin, B-type natriuretic peptide or N-terminal pro-brain natriuretic peptide, antinuclear antibody, and liver function tests. Additional autoimmune serologic testing, HIV screening, and hepatitis panel screening can be obtained when PAH is diagnosed, if indicated.

Electrocardiogram

In 61 patients with PAH, 13% of electrocardiogram findings were normal.⁵⁸ Typical abnormalities include right axis deviation (79%), right ventricular hypertrophy (87%), and right ventricular strain (74%).¹³ A prospectively validated diagnostic decision tree (n = 251) found that electrocardiographic variables with the strongest diagnostic accuracy for the presence of PAH on right heart catheterization were heart rate and right ventricular strain (sensitivity, 79%; specificity, 60%).⁵⁹

Laboratory Testing

Plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) increase in patients with PAH and right ventricular dysfunction. Elevated NT-proBNP levels are associated with an increased risk of death (n = 2017; hazard ratio, 1.84; 95% CI, 1.62-2.10; *P* < .001 [absolute rate data were not included in the published article]).⁶⁰ Laboratory testing may help diagnose PAH associated with HIV/AIDS (HIV antibody), connective tissue disorder (positive antinuclear antibody >1:160 and other associated autoantibodies), or portopulmonary hypertension (liver function test abnormalities).^{2,40}

Echocardiography

Two meta-analyses (n = 3947 and n = 4386) reported sensitivity and specificity of echocardiographic assessment for presence of PH of approximately 85% and 70% to 74%, respectively.^{61,62} Echocardiography-based estimates of pressure may be imprecise and may overestimate or underestimate true values.^{63,64} Right heart catheterization should be considered for accurate measurement of pulmonary artery pressure in the presence of other signs, including increased tricuspid regurgitation velocity and/or signs of right ventricular pressure/volume overload such as right ventricular enlargement or dysfunction, flattening of the interventricular septum, or pulmonary artery enlargement.⁴⁰ A retrospective study

($n = 1262$) reported that the absence of significant tricuspid regurgitation on a transthoracic echocardiogram performed within 2 days of a right heart catheterization had a negative predictive value for excluding PH of 53%.⁶⁵ This study was not limited to patients with suspected PAH, and the negative predictive value of a transthoracic echocardiogram for PAH is not known.

Pulmonary Function Testing

Pulmonary vascular disease is characterized by normal spirometry findings, normal lung volumes, and a low DLCO due to destruction of the pulmonary vasculature.¹⁰ Of 79 consecutive patients with documented PAH, 78% had a low DLCO.¹⁰ In a retrospective study of 166 patients with PAH, DLCO values less than 45% were associated with 38% 5-year survival compared with 80% in those with a DLCO of 45% or greater.⁶⁶

Specialty Center Evaluation

Care of patients with PAH is complex. Clinicians should consider referring patients with possible PH to a PH specialty center.^{2,67} In a retrospective observational study of 580 patients within a 40-hospital system, after adjustment for age and comorbidities, care at a specialty center is associated with decreased hospitalizations (hazard ratio, 0.68; $P = .01$ [absolute rate data were not included in the published article]) and increased survival (incidence ratio, 0.54; $P < .001$).⁶⁷ The retrospective design and lack of specific information regarding possible referral bias are limitations of this study.

Right Heart Catheterization

Right heart catheterization is required for definitive diagnosis of PAH and to assess disease severity, which guides treatment (Box 3).^{2,40} When performed at expert centers, the procedure has a low morbidity (1.1%) and mortality (0.055%) ($n = 7218$).⁶⁸ The most common serious adverse effects from the procedure consist of hematoma at puncture site (0.0014%), vagal reactions with bradycardia and hypotension (0.0015%), and supraventricular tachycardia (0.001%).⁶⁸

Medical Treatment for PAH

Current therapies for PAH pulmonary vasodilator treatment target 3 pathways: stimulating the nitric oxide–cyclic guanosine monophosphate biological pathway, increasing prostacyclin effects on receptors, and antagonizing the endothelin pathway (Table 1). Medical therapy with combinations of pulmonary vasodilators that target multiple therapeutic pathways were superior to monotherapy-based regimens for outcomes of survival and time to clinical worsening.^{4,69-73} Treatment of PAH discussed herein does not apply to patients with non-Group 1 PH, particularly Group 2 and Group 3 disease, for which treatment with pulmonary vasodilators remains controversial.

Phosphodiesterase 5 Inhibitors

Phosphodiesterase 5 inhibitors inhibit phosphodiesterase 5–based degradation of cyclic guanosine monophosphate, causing vasodilation, particularly in the pulmonary vasculature. In a randomized clinical trial of 278 patients with PAH, compared with placebo, sildenafil improved 6-minute walk distance by 45 m to 50 m, World

Box 3. Right Heart Catheterization Diagnostic Testing for Pulmonary Arterial Hypertension

- Verify mean pulmonary artery pressure >20 mm Hg.
- Assess cardiac output and right ventricular function.
- Exclude postcapillary disease and confirm pulmonary artery wedge pressure ≤ 15 mm Hg.
- Verify pulmonary vascular resistance >3 Wood units.
- Perform acute vasodilator testing if indicated (idiopathic, hereditary, and drug- and toxin-induced pulmonary arterial hypertension) to identify the subset of patients for whom calcium channel blockers may be effective treatment.

Health Organization (WHO) functional class by at least 1 class in 28% to 42% of patients, and mean pulmonary artery pressure by 2.1 mm Hg to 4.7 mm Hg.⁷⁴ In a randomized clinical trial of 405 patients, tadalafil improved 6-minute walk distance by 31 m compared with placebo.⁷⁵

Soluble Guanylate Cyclase Stimulators

Soluble guanylate cyclase stimulators, such as oral riociguat, enhance cyclic guanosine monophosphate production, causing vasodilation. In a randomized clinical trial of 444 patients, compared with placebo, riociguat improved WHO functional class (21% vs 14%; $P = .003$), improved 6-minute walk distance by 30 m ($P < .001$), and reduced pulmonary vascular resistance by 223 dyne·s·cm⁻⁵ ($P < .001$).⁷⁶ The combination of riociguat and phosphodiesterase 5 inhibitors can cause severe hypotension and should be avoided.⁷⁷

Endothelin Receptor Antagonists

Endothelin 1, a potent endogenous vasoconstrictor, is overexpressed in the pulmonary vasculature of patients with PAH. Endothelin receptor antagonists, such as bosentan and ambrisentan, block the activity of endothelin 1, resulting in vasodilation. In 2 randomized clinical trials of 32 and 213 participants, compared with placebo, bosentan improved 6-minute walk distance by 44 m to 70 m and WHO functional class in approximately 42% to 43% of patients.^{78,79} Ambrisentan ($n = 500$) improved time to clinical worsening and 6-minute walk distance while macitentan improved time to clinical worsening, defined as worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, lung transplant, or atrial septostomy.^{69,71}

Prostacyclins and Prostacyclin Agonists

Prostacyclin, a potent pulmonary artery vasodilator, is endogenously produced by endothelial cells. Synthetic prostacyclins (epoprostenol, treprostinil, and iloprost) also cause vasodilation. Epoprostenol remains the only pulmonary vasodilator to demonstrate a mortality benefit in a clinical trial of 82 people randomized to receive epoprostenol or placebo (mortality rate, 0% vs 5%; $P = .003$).⁸⁰ Treprostinil increases time to clinical worsening and improves symptoms and 6-minute walk distance.^{73,81} Selexipag is an oral selective prostacyclin receptor agonist that increases time to clinical worsening.⁷⁰

Monotherapy vs Combination Therapy

Three large randomized trials demonstrated that initial treatment with combination therapies improved clinical outcomes more than

Table 1. US Food and Drug Administration–Approved Medications for Group 1 Pulmonary Hypertension^a

	Phosphodiesterase 5 inhibitors			Endothelin receptor antagonists			Guanylate cyclase stimulator: riociguat		Prostacyclin analogues and prostacyclin receptor agonists			
	Sildenafil	Tadalafil	Bosentan	Ambrisentan	Macitentan				Epoprostenol	Treprostinil	Iloprost	Selexipag
Mechanism of action	Enhances the nitric oxide–cGMP pathway and slows cGMP degradation; acts as a pulmonary vasodilator	Enhances the nitric oxide–cGMP pathway and slows cGMP degradation; acts as a pulmonary vasodilator	Binds to endothelin receptors types A and B; blocks endothelin-mediated vasoconstriction	Binds to endothelin receptor type A and some type B; blocks endothelin-mediated vasoconstriction	Binds to endothelin receptors types A and B; blocks endothelin-mediated vasoconstriction			Enhances cGMP production; acts as a vasodilator	Mimics endogenous prostacyclin; potent vasodilator; inhibits platelet aggregation	Mimics endogenous prostacyclin; potent vasodilator; inhibits platelet aggregation	Mimics endogenous prostacyclin; potent vasodilator; inhibits platelet aggregation	Selective prostacyclin receptor agonist; acts as a vasodilator and inhibits platelet aggregation
Common adverse effects	Headache (16%-46%), flushing (10%-19%), dyspepsia (3%-17%), epistaxis (9%-13%), hypotension (<2%)	Headache (4%-42%), flushing (2%-13%), nausea (11%), myalgia (1%-14%), hypotension (<2%)	Increased hepatic transaminases (about 12%; dose dependent), edema (11%), respiratory tract infections (22%), fluid retention (≤3%)	Peripheral edema (14%-38%), abnormal liver function test results (<1%), anemia (7%), cough (13%)	Anemia (13%), headache (14%), nasopharyngitis (20%), increased liver enzymes (>8× upper limit of normal; 2%)			Hypotension (3%-10%), headache (27%), dizziness (20%), respiratory hemoptysis (1%), epistaxis	Flushing (23%-58%), headache (46%-83%), diarrhea (37%-50%), jaw pain (54%-75%), musculoskeletal pain (3%-84%), potential for line-associated complications	Flushing (15%-45%), headache (27%-75%), diarrhea (25%-69%), jaw pain (11%-18%), limb pain with all forms (14%-18%); potential line-associated complications with intravenous form; infusion site pain with subcutaneous form (83%), cough with inhaled form (54%)	Flushing (27%), headache (30%), jaw pain (12%), cough (39%)	Flushing (12%), headache (65%), diarrhea (42%), jaw pain (26%)
Available forms	Oral, intravenous	Oral	Oral	Oral	Oral			Oral	Continuous intravenous infusion	Continuous intravenous infusion, inhaled via specialized nebulizer	Inhaled via specialized nebulizer	Oral
Notes	Combination with riociguat contraindicated due to similar mechanism of action; caution with use in kidney failure	Combination with riociguat contraindicated due to similar mechanism of action; use not recommended in severe hepatic impairment (Child-Pugh Class C); caution with use in kidney failure	Teratogenic; requires negative pregnancy test prior to initiation and monthly monitoring of hepatic amino transaminases required; avoid use in moderate to severe hepatic impairment (Child-Pugh Class B or C)	Teratogenic; requires negative pregnancy test prior to initiation and monthly monitoring of enzymes and hemoglobin prior to initiation of therapy, at 1 mo, and as needed during therapy; avoid use in moderate to severe hepatic impairment (Child-Pugh Class B or C)	Teratogenic; requires negative pregnancy test prior to initiation and monthly monitoring of enzymes and hemoglobin prior to initiation of therapy, at 1 mo, and as needed during therapy; avoid use in moderate to severe hepatic impairment (Child-Pugh Class B or C)			Teratogenic; requires negative pregnancy testing prior to initiation and monthly during use; combination with phosphodiesterase 5 inhibitors is contraindicated due to similar mechanism of action; use not recommended in kidney failure or severe hepatic impairment (Child-Pugh Class C)	Avoid abrupt dose discontinuation or dose reductions as rebound pulmonary hypertension may result; backup pump/device and medication are necessary to avoid interruptions; use of oral form contraindicated in severe hepatic impairment (Child-Pugh Class C)	Avoid abrupt dose discontinuation or dose reductions as rebound pulmonary hypertension may result; backup pump/device and medication are necessary to avoid interruptions; use of oral form contraindicated in severe hepatic impairment (Child-Pugh Class C)	Avoid abrupt dose discontinuation or dose reductions as rebound pulmonary hypertension may result; backup pump/device and medication are necessary to avoid interruptions; use of oral form contraindicated in severe hepatic impairment (Child-Pugh Class C)	Avoid use in severe hepatic impairment (Child-Pugh Class C)

Abbreviation: cGMP, cyclic guanosine monophosphate.

^a See Table 2 for efficacy data.

Table 2. Randomized Clinical Trials of Combination Therapy in PAH

Source	Trial name	Participants, No.	PAH baseline treatment	Therapeutic group	Comparator	Duration	Primary end point	Results		
								Absolute data	Outcome difference	P value
Gal�� et al, ⁶⁹ 2015	AMBITION	500	None ^a	Ambrisentan and tadalafil	Ambrisentan or tadalafil	24 wk	Time to first event of clinical failure	End-point event occurred in 18%	End-point event occurred in 31% ^b	<.001
Humbert et al, ⁸² 2004	BREATHE-2	33	None ^a	Epoprostenol and bosentan	Epoprostenol and placebo	16 wk	Total pulmonary resistance	Mean change, -36.3% (SEM, 4.3%)	Mean change, -22.6% (SEM, 6.2%)	.08
Hoepfer et al, ⁸³ 2006	COMBI	40	Bosentan (100%)	Inhaled iloprost	None ^c	12 wk	GMWD	Mean change, -9 m (SD, 100 m)	Mean change, -10 m	.49
McLaughlin et al, ⁸⁴ 2015	COMPASS-2	334	Sildenafil (100%)	Bosentan	Placebo	114 wk ^d	Time to first event of clinical failure	End-point event occurred in 42.8%	End-point event occurred in 51.4%	.25
Gal�� et al, ⁸⁵ 2008	EARLY	185	None (84%); sildenafil (16%)	Bosentan	Placebo	26 wk	PVR and GMWD	Geometric mean change in PVR: 83.2%; mean change in GMWD: 11.2 m	PVR: -22.6% (95% CI, -33.5% to -10.0%); GMWD: 19.1 m (95% CI, 3.6-41.8 m)	.08
Tapson et al, ⁸⁶ 2012	FREEDOM-C	350	ERA (30%); PDE5 inhibitor (25%); ERA and PDE5 inhibitor (45%)	Oral treprostinil	Placebo	16 wk	GMWD	Median, 14.5 m (IQR, -10 to 47.0 m)	Median, 4.8 m (IQR, -22.0 to 35.5 m)	.07
Tapson et al, ⁸⁷ 2013	FREEDOM-C2	310	ERA (17%); PDE5 inhibitor (43%); ERA and PDE5 inhibitor (40%)	Oral treprostinil	Placebo	16 wk	GMWD		Median difference, 10.0 m (95% CI, -2 to 22 m)	.09
White et al, ⁷³ 2020	FREEDOM-EV	690	PDE5 inhibitor or soluble guanylate cyclase (72%); ERA (28%)	Oral treprostinil	Placebo	60 wk	Time to first event of clinical failure	End-point event occurred in 26%	End-point event occurred in 36%	.28 ^e
Sitbon et al, ⁷⁰ 2015	GRIPHON	1156	None (20%); ERA (15%); PDE5 inhibitor (32%); ERA and PDE5 inhibitor (33%)	Selexipag	Placebo	70.7 wk	Time to first event of clinical failure	End-point event occurred in 27%	End-point event occurred in 41.6%	<.001 ^e
Simonneau et al, ⁸⁸ 2008	PACES	267	Intravenous epoprostenol (100%)	Sildenafil	Placebo	16 wk	GMWD	Mean change, 29.8 m	Mean change, 1.0 m	<.001
Ghofrani et al, ⁷⁶ 2013	PATENT-1	443	None (50%); ERA (44%); prostacyclin (6%)	Riociguat	Placebo	12 wk	GMWD	Mean change, 30 m	Mean change, -6 m	<.001 ^e
Gal�� et al, ⁷⁵ 2009	PHIRST	405	None (47%); bosentan (53%)	Tadalafil	Placebo	16 wk	GMWD		33 m (95% CI, 15-50 m) ^f	<.01
Pulido et al, ⁷¹ 2013	SERAPHIN	742	None (36%); PDE5 inhibitor (61%); oral/inhaled prostacyclin (5%)	Macitentan	Placebo	115 wk	Time to first event of clinical failure	End-point event occurred in 31.4% ^g	End-point event occurred in 46.4%	<.001 ^e
McLaughlin et al, ⁸⁹ 2006	STEP	67	Bosentan (100%)	Inhaled iloprost	Placebo	12 wk	GMWD	Mean change, 30 m	Mean change, 4 m	.051

(continued)

Table 2. Randomized Clinical Trials of Combination Therapy in PAH (continued)

Source	Trial name	Participants, PAH baseline treatment No.	Therapeutic group	Comparator	Duration	Primary end point	Results		
							Absolute data	Intervention	Outcome difference
Chin et al, ⁹⁰ 2021	TRITON	247	Macitentan, tadalafil, and selexipag	Macitentan and tadalafil	26 wk	PVR	Change, -54%	Change, -52%	Ratio of geometric means, 0.096 (95% CI, 0.86-1.07) ^h
McLaughlin et al, ⁹¹ 2010	TRIUMPH	235	Bosentan (70%); sildenafil (30%)	Placebo	12 wk	6MWD	Median, 21.6 m (IQR, -8.0 to 54.0 m)	Median, 3.0 m (IQR, -26.0 to 31.5 m)	20.0 m (95% CI, 8.0-32.8 m)
Zhuang et al, ⁹² 2014		124	Ambrisentan (100%)	Placebo	16 wk	6MWD	Mean change, 54.4 m	Mean change, 18.3 m	<.001

Abbreviations: ERA, endothelin receptor antagonist; HR, hazard ratio; 6MWD, 6-minute walk distance; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase 5; PVR, pulmonary vascular resistance.

^a Initial combination therapy in treatment-naïve patients.

^b Pooled monotherapy.

^c Patients received bosentan and inhaled iloprost or bosentan only.

^d Mean bosentan treatment duration.

^e Results for subgroup of patients receiving background therapy consistent with the overall study findings.

^f Mean placebo-adjusted treatment difference for 40-mg tadalafil dose.

^g For 10-mg macitentan dose.

^h Data presented as available from primary study.

initial therapy with a single drug⁶⁹⁻⁷¹ (Table 2). Combination pulmonary vasodilator therapy consists of either simultaneous initiation of treatment with multiple therapies or sequential addition over several weeks of an additional agent or agents to a single agent initiated at baseline.

In a clinical trial of 500 participants randomized to receive either ambrisentan combined with tadalafil, ambrisentan alone, or tadalafil alone, combination therapy decreased rates of a composite end point of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response, compared with monotherapy with either agent (hazard ratio for the combination group vs the pooled monotherapy group, 0.5; 95% CI, 0.35-0.72; $P < .001$ [absolute rate data were not included in the published article]), in addition to statistically significant improvements in 6-minute walk distance and NT-proBNP.⁶⁹

In a clinical trial of 1156 patients with PAH who were randomized to receive placebo or selexipag, selexipag reduced clinical failure events, defined as death from any cause or a complication related to PAH, compared with placebo (hazard ratio, 0.60; 99% CI, 0.46-0.78; $P < .001$ [absolute rate data were not included in the published article]).⁷⁰ Nearly 47% of patients were receiving background PAH-specific monotherapy (15% with an endothelin receptor antagonist; 32% with a phosphodiesterase 5 inhibitor) and 33% were receiving dual therapy (combination of an endothelin receptor antagonist and a phosphodiesterase 5 inhibitor).⁷⁰ Prespecified subgroup analysis found that the effect of selexipag was similar in the subgroup of patients who were already receiving treatment at baseline.⁷⁰

In a clinical trial of 742 participants, in which 66.8% were taking a background phosphodiesterase 5 inhibitor or oral or inhaled prostacyclin, macitentan decreased rates of clinical failure events, defined as death, atrial septostomy, lung transplant, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of PAH, compared with placebo (hazard ratio, 0.55; 97.5% CI, 0.39-0.76; $P < .001$ [absolute rate data were not included in the published article]).⁷¹ In the background therapy subgroup, the risk of the composite primary end point was reduced by 38% ($P = .009$) compared with placebo.^{71,93}

In sum, several large randomized clinical trials and a subsequent meta-analysis ($n = 4095$; relative risk, 0.65; 95% CI, 0.58-0.72; $P < .001$ [absolute rate data were not included in the published article]) support combination therapy as first-line therapy in PAH over monotherapy.⁷² However, it remains unclear whether the efficacy findings from these trials can be generalized to their respective drug classes or to only the specific drugs, or combination, tested. Although they are all endothelin receptor antagonist/phosphodiesterase 5 inhibitor combinations, ambrisentan and tadalafil as well as macitentan and a phosphodiesterase 5 inhibitor in combination have shown efficacy in a randomized clinical trial, but the combination of bosentan and sildenafil were not efficacious in a randomized clinical trial.^{69,71,84} This concept extends not only to individual drug selection but also to the number of drugs used in combination. For example, a clinical trial of 247 treatment-naïve patients with PAH randomized to initial 2-drug therapy with macitentan and tadalafil vs 3-drug therapy with macitentan, tadalafil, and selexipag reported no statistically significant difference in pulmonary vascular resistance at 26 weeks between groups (decreased by 52% and 54%, respectively; $P = .42$), further underscoring the need for efficacy testing of individual regimens.⁹⁰

Some subgroups of PAH are not well represented in combination therapy clinical trials (eg, portopulmonary hypertension), and the efficacy of monotherapy vs combination therapy in these subgroups remains unclear.

Initiation of Guideline-Based Therapy

Practice guidelines recommend that patients who have not received prior therapy for PAH who are at low to intermediate risk of death by risk assessment and do not meet criteria for vasoreactivity should start oral combination therapy.^{4,40,94} Oral combinations of ambrisentan and tadalafil, macitentan added sequentially to a phosphodiesterase 5 inhibitor, selexipag added sequentially to a phosphodiesterase 5 inhibitor and/or an endothelin receptor antagonist, or oral treprostinil added sequentially to a phosphodiesterase 5 inhibitor, soluble guanylate cyclase stimulator, and/or endothelin receptor antagonist have been found to be efficacious compared with placebo and/or monotherapy.^{69-71,73} If low-risk status according to a risk calculator is not achieved within 3 to 6 months, the addition of a prostacyclin analogue is recommended.^{4,40,94} Combination therapy, including an intravenous prostacyclin, is recommended for patients initially classified as high-risk by a risk calculator.^{4,40,94} Monotherapy can be considered in very low-risk populations or in patients who have been stable with monotherapy for more than 1 to 2 years.⁴

Progressively titrated high-dose calcium channel blockers are the treatment of choice for the subset of patients who are candidates for and meet criteria for vasoreactivity, defined as demonstrating acute vasodilation of the pulmonary vasculature in response to inhaled nitric oxide challenge.^{4,40,49} Calcium channel blockers may cause hypotension and syncope in patients who do not meet criteria for vasoreactivity.⁴⁰

Adjunctive Therapy

Standard diuretics are a mainstay of PAH therapy in patients with clinical signs of right ventricular failure and volume overload. Aldo-

sterone antagonists such as spironolactone can be initiated for neurohormonal blockade or renin-angiotensin-aldosterone modulation, diuresis, and prevention of hypokalemia.⁹⁵

Although no PAH-specific evidence exists regarding the benefit of oxygen therapy, oxygen is recommended when Pao₂ is consistently less than 60 mm Hg, following guidelines for chronic obstructive pulmonary disease.⁹⁶ Patients may require additional supplemental oxygen for travel by air or to high altitudes due to the risk of hypoxemia.

In premenopausal women, birth control counseling is critical because pregnant patients with PAH are at high risk of right ventricular failure and death as a result of pregnancy-related changes in cardiac output and volume.⁹⁷ Maternal mortality can be 13% to 16.7% in patients with PAH who continue pregnancy.⁹⁸ Estrogen-containing contraception should be avoided due to the increased risk of thromboembolism.⁹⁹

Limitations

This review has several limitations. First, the quality of the evidence is limited by the quality of the published studies on PAH. Second, it is possible that some relevant articles have been missed. Third, a formal quality assessment of the included articles was not performed.

Conclusions

Pulmonary arterial hypertension affects 10.6 per 1 million adults in the US and without treatment typically progresses to right heart failure and death. First-line therapy with drug combinations that target multiple biological pathways are associated with improved survival.

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