Journal of the American Heart Association

CONTEMPORARY REVIEW

Revised Definition of Pulmonary Hypertension and Approach to Management: A Clinical Primer

Bradley A. Maron, MD

ABSTRACT: The definition of pulmonary hypertension (PH) has changed recently based, in part, on contemporary outcome data and to focus on early disease detection. Now, PH includes patients with mean pulmonary artery pressure >20 mm Hg measured by right heart catheterization. In contrast to the classical era, pulmonary vascular resistance >2.0 Wood units is also used for diagnosis and prognostication. These lowered thresholds aim to identify patients early in the disease course, which is important because delay to diagnosis of PH is common and linked to elevated morbidity and shortened lifespan. This clinical primer highlights key changes in diagnosis and approach to PH management, focusing on concepts that are likely to be encountered frequently in general practice. Specifically, this includes hemodynamic assessment of at-risk patients, pharmacotherapeutic management of pulmonary arterial hypertension, approach to PH in patients with heart failure with preserved ejection fraction, and newly established indications for early referral to PH centers to prompt comanagement of patients with pulmonary vascular disease experts.

Key Words: definition ■ pulmonary hypertension ■ treatment

Pulmonary hypertension (PH) is a heterogeneous and highly morbid disease encountered commonly in general medicine, cardiology, and pulmonary medicine clinical practices.[1] The original definition of PH used mean pulmonary artery pressure (mPAP) ≥25 mm Hg, but this was derived from expert consensus opinion originally reported 45 years ago in the absence of sufficiently powered clinical data. Largely unaddressed over the ensuing period, the emergence of normative data and information from large patient cohort studies linked to adverse outcomes provided much-needed insight on the relationship between clinical risk and mPAP.[2] Investigations from these studies showed, for the first time, that a significant increase in mortality and hospitalization risk emerges with mPAP >20 mm Hg. This finding reclassifies to PH a sizeable subgroup of patients considered previously as normal. In doing so, this and other similar changes to the PH definition emphasize earlier diagnosis.[3] Contemporary recommendations also now clarify treatment strategies as well as the indications and timing for expert center referral.[4] It is important for the practicing community to understand these changes because an ≈2-year delay in PH diagnosis is reported and linked to substantial and potentially modifiable disease burden.[5]

There are 5 broad PH clinical categories that focus on the underlying cause of abnormal pulmonary artery pressure: pulmonary arterial hypertension (PAH); left heart disease; lung diseases and/or hypoxia; pulmonary artery obstructions (particularly thromboembolic syndromes); and undifferentiated or multifactorial causes, including sickle cell disease and sarcoidosis (Figure 1). Among these, PH attributable to left heart and lung diseases are the most prevalent subtypes, with an estimated prevalence of 50% to 70% and 30% to 50%, respectively.[4] Risk factors for left heart disease PH include age >70 years, systemic hypertension, obesity, glucose intolerance, or prior coronary intervention. Numerous pharmacotherapeutic options are available to treat PAH, which may be idiopathic,

Correspondence to: Bradley A. Maron, MD, Brigham and Women's Hospital, 77 Ave Louis Pasteur, NRB Room 0630-N, Boston, MA 02115.
Email: bmaron@bwh.harvard.edu

For Sources of Funding and Disclosures, see page 7.

JAHA is available at: www.ahajournals.org/journal/jaha

Nonstandard Abbreviations and Acronyms

mPAP	mean pulmonary artery pressure
PAH	pulmonary arterial hypertension
PH	pulmonary hypertension
WHO-FC	World Health Organization Functional Class

hereditary, induced by specific pharmacotherapies or methamphetamines,[6,7] or associated with predisposing diseases, particularly limited cutaneous systemic sclerosis,[8] HIV,[9] and various primary liver diseases.[10] Chronic thromboembolic PH is often overlooked[11] but potentially curable by surgical endarterectomy, whereas balloon pulmonary angioplasty and medical therapy are available in poor surgical candidates (reviewed separately in the study by Matusov et al[12]). Thus, a high index of clinical suspicion for PH is needed to ensure appropriate diagnosis and clinical management of patients.

Dyspnea and mildly reduced exercise capacity are indicative of early PH; in patients with advanced disease, chest pain, syncope, and symptomatic heart failure are common. Most often, a PH diagnosis is suggested initially by findings on transthoracic echocardiography. Specifically, a tricuspid regurgitant jet velocity >2.8 m/s, which corresponds to a pulmonary artery systolic pressure of ≈35 mm Hg or greater, suggests PH (Figure 2A).[4,13] More important, however, echocardiography estimates pulmonary artery systolic pressure, is subject to inaccuracy in patients with suboptimal acoustic windows (ie, large anterior-posterior chest diameter, observed commonly in patients with obesity or obstructive lung disease), and does not provide key data, such as pulmonary artery wedge pressure, that indicate pulmonary venous hypertension (ie, left heart disease PH). Furthermore, one-third of patients without a measurable tricuspid regurgitant jet have PH when assessed by cardiac catheterization.[14] Therefore, it is helpful to consider tricuspid regurgitant jet velocity results in combination with echocardiographic parameters that increase the probability of PH, including right atrial dilation, right ventricular (RV)/left ventricular basal diameter >1.0, flattening of the interventricular septum, and decreased RV systolic function (Figure 2B and 2C).[4] The latter can be quantitated by analyzing RV strain or displacement of the tricuspid annulus, referred to as the tricuspid annular plane of systolic

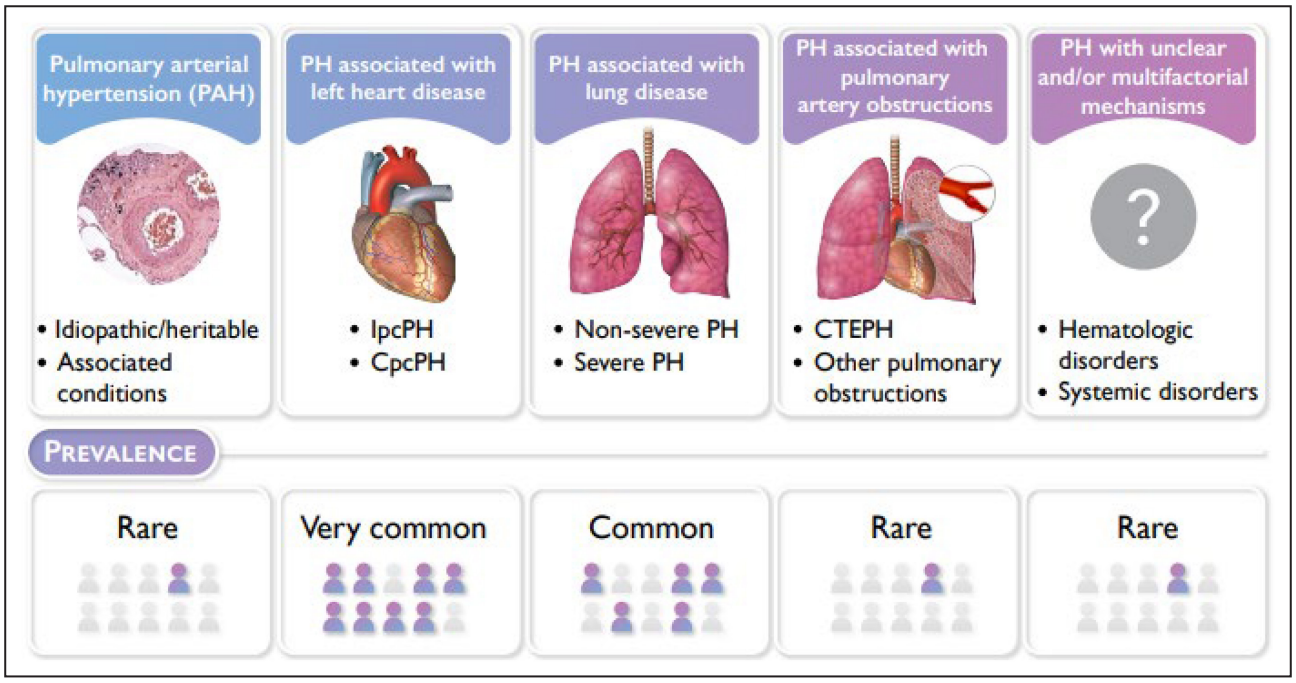

Figure 1. Clinical classification of pulmonary hypertension (PH).
There are 5 broad PH clinical groups that reflect the circumstances underlying elevated pulmonary artery pressure and other pathogenic cardiopulmonary hemodynamic findings on right heart catheterization (RHC). In pulmonary arterial hypertension (PAH), fibromuscular and plexigenic remodeling of distal pulmonary arterioles is caused by interplay between genetic and molecular events, induced by certain toxic drugs (eg, methamphetamines, desatinib, or anorexigens) or observed in association with systemic sclerosis, liver disease, HIV, or other predisposing conditions. Patients with PH attributable to left heart disease present with pulmonary venous hypertension, manifest by postcapillary PH on RHC, whereas PH severity in patients with underlying lung disease is variable. Thrombotic mechanical obstruction to normal pulmonary blood flow is the cornerstone feature of chronic thromboembolic PH (CTEPH). Reproduced from Humbert et al[4] with permission. Copyright ©2023 European Society of Cardiology and European Respiratory Society. Cpc indicates combined precapillary+postcapillary PH; and Ipc, isolated postcapillary PH.

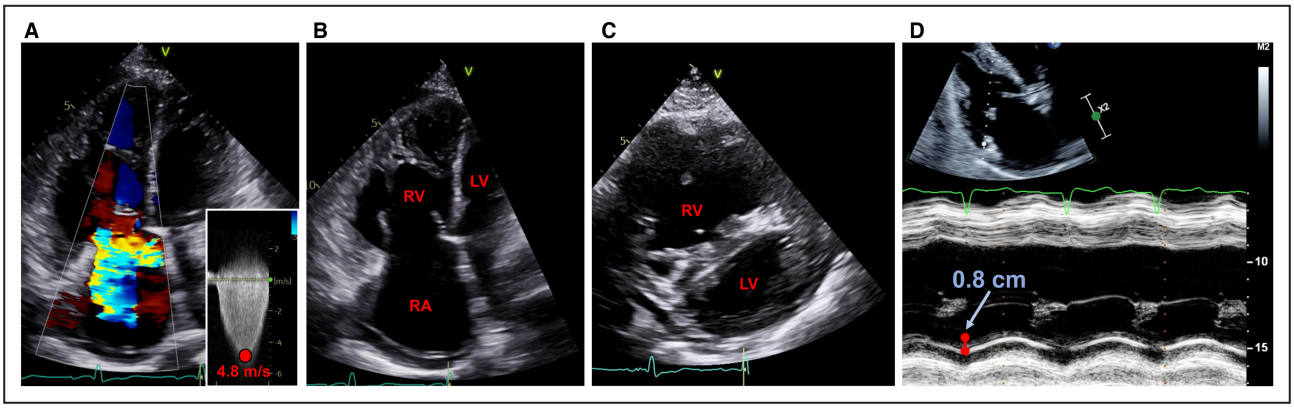

Figure 2. Selected transthoracic echocardiographic findings in pulmonary arterial hypertension (PAH).
A, Continuous-wave Doppler imaging acquired from the apical 4-chamber view in a patient with advanced-stage PAH demonstrates severe tricuspid regurgitation. In the inset, the velocity of the tricuspid regurgitant jet is 4.8 m/s, well above the threshold of 2.8 m/s that suggests mild pulmonary hypertension (PH), and corresponds to an estimated right ventricular systolic pressure of 98 mm Hg and estimated pulmonary artery systolic pressure of 108 mm Hg. **B**, From the same view, severe right ventricular (RV) and right atrial (RA) dilation is noted. **C**, In the short-axis 2-chamber view, the interventricular septum imaged at end systole is flat ("D sign"), indicative of RV volume and pressure overload. **D**, Assessment of RV systolic function accomplished by measuring the tricuspid annular plane of systolic excursion (TAPSE), which quantitates the apical displacement of the tricuspid annulus between diastole and systole measured by M-mode echocardiography. In patients with PH, TAPSE <1.7 cm is prognostic for adverse outcome. LV indicates left ventricle.

excursion, which is a clinically useful tool for prognosticating adverse outcome when <1.7 cm (Figure 2D).[15] Increased left atrial volume (>0.34 mL/m^2), left ventricular hypertrophy, and early/late diastolic inflow velocity 1 to 1.5 with decreased early diastolic mitral annulus velocity (<7 cm/s) and a ratio of early diastolic mitral inflow velocity/early diastolic mitral annulus velocity average >14 are all suggestive of a left heart contribution to PH.

Ultimately, right heart catheterization is required to diagnose PH, clarify PH subtype, and stage disease severity. The classic definition of PH used mPAP ≥25 mm Hg and required pulmonary vascular resistance

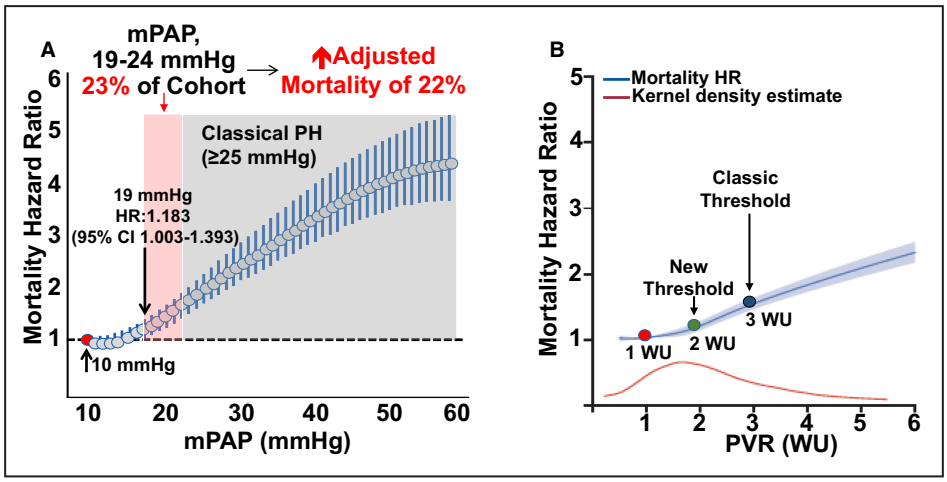

Figure 3. The relationship between pulmonary hypertension (PH) hemodynamic parameters and all-cause mortality.
In a national cohort of patients referred for right heart catheterization, mean pulmonary artery pressure (mPAP) (N=21 727) (**A**) and pulmonary vascular resistance (PVR) restricted to patients with mPAP ≥19 mm Hg (N=32 725) (**B**) were modeled continuously, and the association with all-cause mortality risk is shown. These results converge with normative data,[18,19] suggesting that the upper limits of normal for mPAP and PVR are ≈20 mm Hg and 2 WU, respectively. Taken together, these data establish an evidence-based framework for the new hemodynamic definition of PH. The red disc represents the referent group. Adapted with permission from Maron BA, et al[16] © 2016, American Heart Association, Inc (**A**); and Maron BA, et al[17] © 2020, Elsevier Ltd (**B**). HR indicates hazard ratio; and WU, Wood units.

Table 1. New Hemodynamic Definitions for PH

Definition	Hemodynamic profile	Typical clinical group
PH	mPAP >20 mm Hg	All
Precapillary PH	mPAP >20 mm Hg PVR >2 WU PAWP ≤15 mm Hg	Pulmonary arterial hypertension PH attributable to lung disease CTEPH
Combined precapillary+postcapillary PH	mPAP >20 mm Hg PVR >2 WU PAWP >15 mm Hg	Left heart disease Left heart+lung disease overlap
Isolated postcapillary PH	mPAP >20 mm Hg PVR ≤2 WU	Left heart disease
Exercise PH	mPAP/CO slope between rest and exercise >3 mm Hg/L per min	Exertional dyspnea with preserved LV ejection fraction with normal resting PAWP

The new hemodynamic definitions for PH emphasize mPAP >20 mm Hg and PVR >2 WU as a strategy by which to capture patients earlier in the disease arc. Some clinical groups are exclusive to specific hemodynamic categories. For example, pulmonary arterial hypertension is only observed in patients with isolated precapillary PH, and an elevated PAWP (as a measure of pulmonary venous hypertension) is reserved for patients with left heart disease. Patients with exertional dyspnea, preserved LV function, and normal resting PAWP referred for exercise invasive right heart catheterization in whom the mPAP/CO slope is >3 mm Hg/L per min represent an emerging clinical syndrome characterized by abnormal pulmonary vascular response to exercise. Reproduced from Humbert et al[4] with permission. Copyright ©2023 European Society of Cardiology and European Respiratory Society. CTEPH indicates chronic thromboembolic PH; CO, cardiac output; LV, left ventricular; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; and WU, Wood units.

(PVR) ≥3.0 Wood units (WU) for patients with PAH only. Our group studied a national cohort of patients referred for right heart catheterization to show a significant and continuous increase in mortality is observed beginning at mPAP of 20 mm Hg.[16] Moreover, among patients with elevated mPAP, a PVR of >2.0 WU was associated with a significant and continuous increase in mortality (Figure 3).[17] Both mPAP of 20 mm Hg and PVR of 2.0 WU also are the upper limit of normal for each parameter.[18,19] In well-phenotyped populations at risk for PAH[20] or PH from primary cardiac or lung disease,[21] mPAP >20 mm Hg and PVR >2.0 WU are associated with impaired exercise tolerance or other measures of PH disease burden. In patients with mPAP >20 mm Hg and PVR >2.0 WU, pathogenic changes are also observed to the pulmonary vasculature,[22] whereas pathogenic

Table 2. Approved Medications for the Treatment of PAH

Generic name	Route of administration	Drug class	Indication
Epoprostenol	Intravenous	Prostacyclin derivative	Treatment of PAH to improve exercise capacity
Iloprost	Inhaled	Prostacyclin derivative	Treatment of PAH to improve a composite end point consisting of exercise tolerance, symptoms (NYHA class), and lack of deterioration
Treprostinil	Intravenous or subcutaneous	Prostacyclin derivative	Treatment of PAH to diminish symptoms associated with exercise
Treprostinil	Inhaled	Prostacyclin derivative	Treatment of PAH to improve exercise ability Treatment of interstitial lung disease–associated pulmonary hypertension to improve walk distance
Treprostinil	Oral	Prostacyclin derivative	Treatment of PAH to improve exercise ability
Selexipeg	Oral	Selective prostacylin (IP) receptor agonist	Treatment of PAH to improve a composite end point lack of clinical deterioration
Bosentan	Oral	Endothelin receptor antagonist	Treatment of PAH to improve exercise capacity and to decrease clinical worsening
Ambrisentan	Oral	Endothelin receptor antagonist	Treatment of PAH to improve exercise capacity and delay clinical worsening
Macitentan	Oral	Endothelin receptor antagonist	Treatment of PAH to improve a composite end point of delay of clinical worsening
Sildenafil	Oral or intravenous	PDE5 inhibitor	Treatment of PAH to improve exercise capacity and delay clinical worsening
Tadalafil	Oral	PDE5 inhibitor	Treatment of PAH to improve exercise ability
Riociguat	Oral	Soluble guanylyl cyclase stimulator	Treatment of PAH to improve exercise ability

Adapted with modifications from Maron BA et al.[37] Copyright ©2022, McGraw Hill. NYHA indicates New York Heart Association; PAH, pulmonary arterial hypertension; and PDE5, phosphodiesterase type-5.

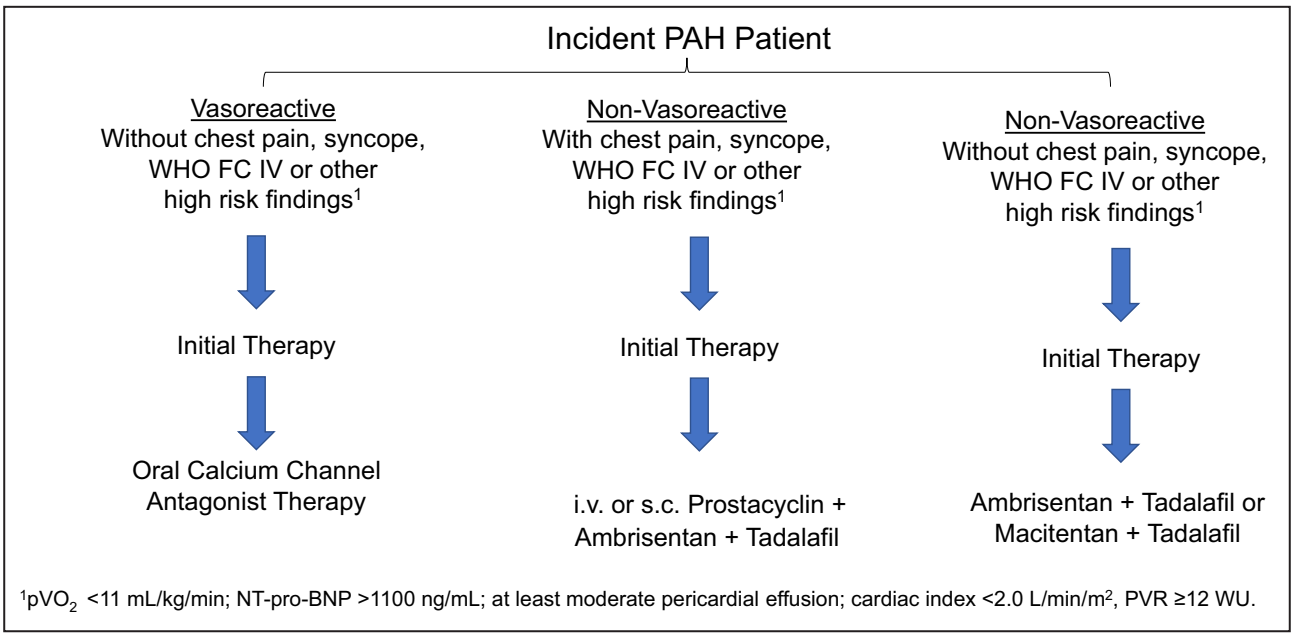

Figure 4. Approach to the management of patients with incident pulmonary arterial hypertension (PAH).
Newly diagnosed patients with idiopathic, hereditary, or drug-induced PAH should be considered for vasoreactivity testing in the cardiac catheterization laboratory at an expert pulmonary hypertension center. In the absence of a high-risk clinical profile, patients who demonstrate a positive vasoreactivity response, defined by decrease in mean pulmonary artery pressure ≥10 mm Hg from baseline to ≤40 mm Hg without a decrease in cardiac output, should be initiated on calcium channel antagonist therapy dose titrated to optimal clinical benefit/adverse effect balance. For patients with PAH without evidence of vasoreactivity but with high-risk findings, consideration to up-front therapy with the prostacyclin analogue treprostinil administered by intravenous (i.v.) or subcutaneous (s.c.) route plus the phosphodiesterase type-5 inhibitor tadalafil and endothelin receptor antagonist ambrisentan is indicated. For patients with PAH without vasoreactivity or high-risk findings, initial combination therapy with the tadalafil and ambrisentan or the alternate endothelin receptor antagonist macitentan should be considered. NT-proBNP indicates N-terminal pro-B-type natriuretic peptide; pVO_2, peak volume of oxygen consumption; PVR, pulmonary vascular resistance; and WHO-FC, World Health Organization Functional Class; and WU, Wood units.

changes to RV size and function[23,24] are often indicative of increased RV afterload,[25] itself an independent risk factor for right heart failure progression.[4] These collective observations indicate that mild PH is pathogenic per se, and associated adverse outcome is unlikely attributable solely to comorbidities.

For these reasons, the PH definition has been changed recently to include mPAP, 20 mm Hg, and PVR, 2.0 WU, for distinguishing each of the hemodynamic PH subgroups: isolated precapillary, combined precapillary/postcapillary, and isolated postcapillary PH (Table 1).[4] This is an important step in patient assessment, as certain causes of PH can be excluded on the basis of hemodynamic classification. For example, PAH is not compatible with isolated postcapillary PH because in those patients pulmonary venous hypertension drives elevated mPAP. The new mPAP and PVR criteria greatly increase the PH cohort encountered clinically, capturing ~60% more patients compared with the classic definition in one large referral population.[17] It is possible, however, that (abnormally) high cardiac output states, such as liver failure or large arterio-venous fistula, may result in mPAP >20 mm Hg and PVR <2 WU.

Although the new mPAP >20 mm Hg and PVR >2.0 WU criteria for PH are positioned to identify at-risk patients earlier in the disease arc, most patients with PH are, in fact, diagnosed late and at a time point when hemodynamics are severely abnormal. In the largest clinical trial studying patients with incident PAH, for example, the average mPAP and PVR were ≈48 mm Hg and 10.3 WU, respectively.[26] It is incumbent on practitioners to consider PH in patients with unexplained dyspnea or in the presence of tricuspid regurgitant jet velocity >2.8 cm/s on echocardiography. This includes screening patients for sleep-disordered breathing and assessing exertional hypoxemia. Fast-track referral to a PH expert center is indicated in patients with rapid progression of symptoms (eg, change in World Health Organization Functional Class [WHO-FC] status within 3 months or patients with WHO-FC III/IV), presyncope or syncope on mild exertion, clinical signs of right heart failure, or qualitative evidence of right ventricular dilation or abnormal tricuspid annular plane of systolic excursion.[4] For patients who are pregnant or wish to become pregnant despite PAH risk factors, fast-track referral to an expert center is warranted, as

well as for those with cardiopulmonary symptoms in whom a diagnosis of chronic thromboembolic PH or cardiac shunt is suspected.[27] It is also advised that patients under consideration for pulmonary vasodilatory treatment be comanaged with a PH expert for detailed risk stratification (using any of several validated scales[4,28–31]) and drug selection, because these medications are notably associated with significant adverse effects[32] and overprescribing is common.[33]

Patients with idiopathic, hereditary, or drug-induced PAH (but not other PH subtypes) are considered for vasoreactivity testing with inhaled nitric oxide (NO) (or another suitable agent) performed at an expert PH center. A decrease in mPAP ≥10 mm Hg from baseline to ≤40 mm Hg without a decrease in cardiac output generally warrants initiation of oral calcium channel antagonist therapy, such as nifedipine or amlodipine, with dose titrated based on efficacy/adverse effect profile. Although vasoreactivity is uncommon (≈12%), this is an important subgroup because >50% will achieve dramatic (ie, near curative) long-term clinical response to treatment.[34] If patients with PAH do not demonstrate vasoreactivity but are at high risk for adverse outcome (eg, WHO-FC III/IV symptoms, syncope, chest pain, other parameters, cardiac index <2.0 L/min per m^2, or PVR ≥12 WU), parenteral (which is preferred)[35] or subcutaneous prostacyclin therapy, followed closely by initiation of dual endothelin receptor antagonist+phosphodiesterase type-5 inhibitor oral therapy, is recommended (Table 2 and Figure 4).[4,36,37] For patients with PAH without vasoreactivity and not at a high-risk clinical profile, up-front endothelin receptor antagonist+phosphodiesterase type-5 inhibitor[26,36] therapy is a common therapeutic strategy, although other evidence-based approaches focusing on combination PAH therapy are also used.[38,39]Therapeutic escalation should be pursued in patients who do not achieve low-risk status (Table 3) with initial therapy, administered in conjunction with a PH center of excellence. This may include the addition of oral prostacyclin receptor agonist treatment in patients with 6-minute walk distance of 320 to 440 m and NT-proBNP (N-terminal pro-B-type natriuretic peptide) level of 300 to 649 ng/L,[4] or patients with WHO-FC II symptoms and elevated right atrial pressure (8–14 mm Hg), decreased cardiac index (2.0–2.4 L/min per m^2), and mixed venous O_2 saturation of 60% to 65%, among other clinical scenarios.[40] Parenteral/subcutaneous prostacyclin therapy or lung transplantation referral is indicated in patients with WHO-FC III/IV, 6-minute walk distance of <320 m, and NT-pro-BNP level of ≥650 ng/L.[4]

The use of endothelin receptor antagonist or prostacyclin analogue/receptor therapies for patients with left heart disease, including heart failure with preserved ejection fraction, is not associated with a consistent clinical benefit and may cause adverse events.[41] For patients with PH attributable to heart failure with preserved ejection fraction who remain symptomatic despite aggressive salt and fluid restriction, diuretic treatment, mineralocorticoid receptor antagonism, and sodium-glucose transport protein-2 pharmacotherapy,[42] referral to a specialty PH center for clinical study enrollment is encouraged. If clinical trial enrollment is not possible, then an individualized care plan that includes a trial of phosphodiesterase type-5 inhibitor therapy could be attempted to palliate symptoms or, potentially, improve exercise capacity (particularly when PVR is >5 WU) but must include serial follow-up evaluations that use objective measures to guide treatment (dis)continuation, such as WHO-FC, 6-minute walk distance, NT-proBNP level, or peak volume of oxygen consumption on cardiopulmonary exercise testing.[4] Similarly, the initiation of inhaled prostacyclin therapy is reasonable to consider in patients with interstitial lung disease and PH, particularly when PVR >4.0 WU. This is based on the results of a single randomized clinical trial showing an average 6-minute walk distance improvement of +33 m compared with placebo.[43] However, the translational benefit of therapy with inhaled prostacyclin (or any other pulmonary vasodilators) to real-world practice in interstitial lung disease PH has not yet been established but is an important consideration to routine therapy use given challenges associated with medication compliance, off-target effects, and expense.[44]

Table 3. Determinants of Low-Risk Status in PAH

Determinants of prognosis	<5% 1-y Mortality
Signs of heart failure	Absent
Progression of clinical manifestations	No
Syncope	No
WHO-FC	I, II
6-min Walk distance	>440 m
Cardiopulmonary exercise test	Peak VO_2>15 mL/min per kg (>65% predicted)
Biomarkers BNP or NT-proBNP	BNP <50 ng/L NT-proBNP <300 ng/L
Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mm Hg No pericardial effusion
Cardiac magnetic resonance imaging	RVEF >54% SVI >40 mL/m^2
Hemodynamics	RAP <8 mm Hg CI ≥2.5 L/min per m^2 SVI >38 mL/m^2 SvO_2>65%

Reproduced from Humbert et al[4] with permission. Copyright ©2023, European Society of Cardiology and European Respiratory Society. BNP indicates brain natriuretic peptide; CI, cardiac index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; RA, right atrium; RAP, right atrial pressure; RVEF, right ventricular ejection fraction; sPAP, systolic pulmonary arterial pressure; SVI, stroke volume index; SvO_2, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; VO_2, oxygen uptake; and WHO-FC, World Health Organization Functional Class.

In conclusion, the definition of PH has changed recently to emphasize earlier diagnosis. In patients with mPAP of 20 to 25 mm Hg and PVR of 2 to 3 WU, the focus of clinical management includes clarifying causes of mild PH, risk factor modification, close follow-up for symptom progression, and consideration to clinical trial enrollment. All prior PAH pharmacotherapeutic intervention studies used the classical mPAP and PVR definition of >25 mm Hg and ≥3.0 WU, respectively, and therefore the therapeutic benefit of such medications in patients under the revised definition remains to be determined. Invasive exercise hemodynamics can be helpful diagnostically in patients with mild PH at rest and exercise limitation,[45] as an exaggerated increase in pulmonary artery wedge pressure relative to cardiac output (>2 mm Hg/L per min) suggests exercise-induced pulmonary venous hypertension.[46] The initiation of pulmonary vasodilator therapy is reserved mainly for patients with PAH with mPAP of >25 mm Hg and PVR of >3.0 WU, and should align with clinical trial data and consensus guideline recommendations. Certain patients with PH from interstitial lung disease could also be considered for inhaled prostacyclin. However, there are insufficient data to recommend pulmonary vasodilator use in heart failure with preserved ejection fraction with PH. On the basis of the prognostic implications of severely elevated PVR (>5.0 WU) in this subgroup, devising individualized care plans that include trialing phosphodiesterase type-5 inhibitor therapy under close monitoring in conjunction with a PH expert may be reasonable if enrollment in clinical trials is not possible. Fast-track referral to specialty centers is indicated in these clinical situations as well as for patients with suspected lung disease PH PAH or chronic thromboembolic PH and increased risk for adverse outcome.

ARTICLE INFORMATION

Affiliations

Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and Divisions of Cardiology and Pulmonary and Critical Care Medicine, VA Boston Healthcare System, West Roxbury, MA.

Sources of Funding

This work was supported by National Institutes of Health grants R01HL139613-01, R01HL163960, R01HL153502, and R01HL155096; and McKenzie Family Trust.

Disclosures

Dr Maron reports the following conflicts of interest: Actelion Pharmaceuticals (outside the scope of the current work), Deerfield Company (outside the scope of the current work), and Tenax Therapeutics (outside the scope of the current work).

REFERENCES

1. Maron BA, Galiè N. Diagnosis, treatment, and clinical management of pulmonary arterial hypertension in the contemporary era: a review. *JAMA Cardiol.* 2016;1:1056–1065. doi: 10.1001/jamacardio.2016.4471
2. Maron BA, Brittain EL, Choudhary G, Gladwin MT. Redefining pulmonary hypertension. *Lancet Respir Med.* 2018;6:168–170. doi: 10.1016/S2213-2600(17)30498-8
3. Maron BA, Humbert M. Finding pulmonary arterial hypertension-switching to offense to mitigate disease burden. *JAMA Cardiol.* 2022;7:369–370. doi: 10.1001/jamacardio.2022.0011
4. Humbert M, Kovacs G, Hoeper MM, Badaglacia R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, et al. ESC/ERS Scientific Document Group. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J.* 2022;2022:2200879.
5. McGoon MD, Miller DP. REVEAL: a contemporary US pulmonary arterial hypertension registry. *Eur Respir Rev.* 2012;21:8–18. doi: 10.1183/09059180.00008211
6. Maron BA, Abman SH, Elliott CG, Frantz RP, Hopper RK, Horn EM, Nicolls MR, Shlobin OA, Shah SJ, Kovacs G, et al. Pulmonary arterial hypertension: diagnosis, treatment, and novel advances. *Am J Respir Crit Care Med.* 2021;203:1472–1487. doi: 10.1164/rccm.202012-4317SO
7. Zamanian RT, Hedlin H, Greuenwald P, Greuenwald P, Wilson DM, Segal JI, Jorden M, Kudelko K, Liu J, His A, et al. Features and outcomes of methamphetamine-associated pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2018;197:788–800. doi: 10.1164/rccm.201705-0943OC
8. Hassan HJ, Naranjo M, Ayoub N, Housten T, Hsu S, Balasubramanian A, Simpson CE, Damico RL, Mathai SC, Kolb TM, et al. Improved survival for patients with systemic sclerosis-associated pulmonary arterial hypertension: the Johns Hopkins Registry. *Am J Respir Crit Care Med.* 2023;207:312–322. doi: 10.1164/rccm.202204-0731OC
9. Brittain EL, Duncan MS, Chang J, Patterson OV, DuVall SL, Brandt CA, So-Armah KA, Goetz M, Akgun K, Crothers K, et al. Increased echocardiographic pulmonary pressure in HIV-infected and -uninfected individuals in the Veterans Aging Cohort study. *Am J Respir Crit Care Med.* 2018;197:923–932. doi: 10.1164/rccm.201708-1555OC
10. Hoeper MM, Krowka MJ, Strassburg CP. Portopulmonary hypertension and hepatopulmonary syndrome. *Lancet.* 2004;363:1461–1468. doi: 10.1016/S0140-6736(04)16107-2
11. Maron BA, Choudhary G, Khan UA, Jankowich MD, McChesney H, Ferrazzani SJ, Gaddam S, Sharma S, Opotowsky AR, Bhatt DL, et al. Clinical profile and underdiagnosis of pulmonary hypertension in US veteran patients. *Circ Heart Fail.* 2013;6:906–912. doi: 10.1161/CIRCHEARTFAILURE.112.000091
12. Matusov Y, Singh I, Yu YR, Chun HJ, Maron BA, Tapson VF, Lewis MI, Rajagopal S. Chronic thromboembolic pulmonary hypertension: the bedside. *Curr Cardiol Rep.* 2021;23:147. doi: 10.1007/s11886-021-01573-5
13. Jankowich M, Maron BA, Choudhary G. Mildly elevated pulmonary artery systolic pressure on echocardiography: bridging the gap in current guidelines. *Lancet Respir Med.* 2021;9:1185–1191. doi: 10.1016/S2213-2600(21)00072-2
14. O'Leary JM, Assad TR, Xu M, Farber-Eger E, Wells QS, Hemnes AR, Brittain EL. Lack of a tricuspid regurgitation Doppler signal and pulmonary hypertension by invasive measurement. *J Am Heart Assoc.* 2018;7:e009362. doi: 10.1161/JAHA.118.009362
15. Forfia PR, Fisher MR, Mathai SC, Housten-Harris T, Hemnes AR, Borlaug BA, Chamera E, Corretti MC, Champion HC, Abraham TP, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med.* 2006;174:1034–1041. doi: 10.1164/rccm.200604-547OC
16. Maron BA, Hess E, Maddox TM, Opotowsky AR, Tedford RJ, Lahm T, Joynt KE, Kass DJ, Stephens T, Stanislawski MA, et al. Association of borderline pulmonary hypertension with mortality and hospitalization in a large patient cohort: insights from the Veterans Affairs Clinical Assessment, Reporting, and Tracking program. *Circulation.* 2016;133:1240–1248. doi: 10.1161/CIRCULATIONAHA.115.020207
17. Maron BA, Brittain EL, Hess E, Waldo SW, Baron AE, Huang S, Goldstein RH, Assadd T, Wertheim BM, Alba GA, et al. Pulmonary vascular resistance and clinical outcomes in patients with pulmonary hypertension: a retrospective cohort study. *Lancet Respir Med.* 2020;8:873–884. doi: 10.1016/S2213-2600(20)30317-9
18. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J.* 2009;34:888–894. doi: 10.1183/09031936.00145608
19. Kovacs G, Olschewski A, Berghold A, Olschewski H. Pulmonary vascular resistances during exercise in normal subjects: a systematic review. *Eur Respir J.* 2012;39:319–328. doi: 10.1183/09031936.00008611

20. Xanthouli P, Jordan S, Milde N, Marra A, Blank N, Egenlauf B, Gorenflo M, Harutyunova S, Lorenz HM, Nagel C, et al. Haemodynamic phenotypes and survival in patients with systemic sclerosis: the impact of the new definition of pulmonary arterial hypertension. *Ann Rheum Dis.* 2020;79:370–378. doi: 10.1136/annrheumdis-2019-216476
21. Douschan P, Kovacs G, Avian A, Foris V, Gruber F, Olschewski A, Olschewski H. Mild elevation in pulmonary artery pressure as a predictor of mortality. *Am J Respir Crit Care Med.* 2018;197:509–516. doi: 10.1164/rccm.201706-1215OC
22. Maron BA, Kleiner D, Arons E, Wertheim BM, Sharma NS, Haley KJ, Samokhin AO, Rowin EJ, Maron MS, Rosing DR, et al. Evidence of advanced pulmonary vascular remodeling in obstructive hypertrophic cardiomyopathy with pulmonary hypertension [published online October 12, 2022]. *Chest.* 2022:3912. doi: 10.1016/j.chest.2022.09.040
23. Huston JH, Maron BA, French J, Huang S, Thayer T, Farber-Eger EH, Wells QS, Choudhary G, Hemnes AR, Brittain EL. Association of mild echocardiographic pulmonary hypertension with mortality and right ventricular function. *JAMA Cardiol.* 2019;4:1112–1121. doi: 10.1001/jamacardio.2019.3345
24. Strange G, Stewart S, Celermajer DS, Prior D, Scalia GM, Harwick TH, Gabbay E, Ilton M, Joseph M, Codde J, et al. Threshold of pulmonary hypertension associated with increased mortality. *J Am Coll Cardiol.* 2019;73:2660–2672. doi: 10.1016/j.jacc.2019.03.482
25. Hsu S, Kokkonen-Simon KM, Kirk JA, Kolb TM, Damico RL, Mathai SC, Mukherjee M, Shah AA, Wigley FM, Margulies KB, et al. Right ventricular myofilament functional differences in humans with systemic sclerosis-associated versus idiopathic pulmonary arterial hypertension. *Circulation.* 2018;137:2360–2370. doi: 10.1161/CIRCULATIONAHA.117.033147
26. Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery JL, Grunig E, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med.* 2015;373:834–844. doi: 10.1056/NEJMoa1413687
27. Rudder M, Russo M, Ventetuolo CE. Breathing for two. *N Engl J Med.* 2021;384:61–68. doi: 10.1056/NEJMcps2006666
28. Benza RL, Millder DP, Gomberg-Maitland M, Frantz RP, Froeman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation.* 2010;122:164–172. doi: 10.1161/CIRCULATIONAHA.109.898122
29. Benza RL, Kanwar MK, Raina A, Scott JV, Zhao CL, Selej M, Elliott CG, Farber HW. Development and validation of an abridged version of the REVEAL 2.0 risk score calculator, REVEAL Lite 2, for use in patients with pulmonary arterial hypertension. *Chest.* 2021;159:337–346. doi: 10.1016/j.chest.2020.08.2069
30. Olsson KM, Delcroix M, Ghofrani HA, Henning T, Huscher D, Speich R, Grunig E, Staehler G, Rosenkranz S, Halank M, et al. Anticoagulation and survival in pulmonary arterial hypertension: results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). *Circulation.* 2014;129:57–65. doi: 10.1161/CIRCULATIONAHA.113.004526
31. Boucly A, Weatherald J, Savale L, Jais X, Cottin V, Prevot G, Picard F, de Groote P, Jevnikar M, Bergot E, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir. J.* 2017;50:1700889. doi: 10.1183/13993003.00889-2017
32. Leary PJ, Kang S, Kolb TM, Maron BA, Ralph DD, Rao Y, Tedford RJ, Zamanian RT. What's in a side effect? The association between pulmonary vasodilator adverse drug events and clinical outcomes in patients with pulmonary arterial hypertension. *Int J Cardiol.* 2017;240:386–391. doi: 10.1016/j.ijcard.2017.04.016
33. Maron BA, Ryan JJ. A concerning trend for patients with pulmonary hypertension in the era of evidence-based medicine. *Circulation.* 2019;139:1861–1864. doi: 10.1161/CIRCULATIONAHA.118.037613
34. Sitbon O, Humbert M, Jaïs X, Loos V, Hamid AM, Provencher S, Garcia G, Parent F, Hervé P, Simonneau GA. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation.* 2005;111:3105–3111. doi: 10.1161/CIRCULATIONAHA.104.488486
35. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med.* 1996;334:296–301. doi: 10.1056/NEJM199602013340504
36. Sitbon O, Jaïs X, Savale L, Cottin V, Bergot E, Artaud Macari E, Bouvaist H, Dauphin C, Picard F, Bulifon S, et al. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. *Eur Respir J.* 2014;43:1691–1697. doi: 10.1183/09031936.00116313
37. Maron BA, Loscalzo J. Pulmonary hypertension. In: Loscalzo J, Kasper DL, Longo DL, Fauci AS, Hauser SL, Jameson JL, eds *Harrison's Principles of Internal Medicine*. Vol 2. 21st ed. McGraw Hill; 2022:2121–2129.
38. Sitbon O, Cottin V, Canuet M, Clerson P, Gressin V, Perchenet L, Bertoletti L, Bouvaist H, Picard F, Prévot G, et al. Initial combination therapy of macitentan and tadalafil in pulmonary arterial hypertension. *Eur Respir. J.* 2020;56:2000673. doi: 10.1183/13993003.00673-2020
39. Sitbon O, Chin KM, Channick RN, Benza RL, Di Scala L, Gaine S, Ghofrani H-A, Lang IM, McLaughlin VV, Preiss R, et al. Risk assessment in pulmonary arterial hypertension: insights from the GRIPHON study. *J Heart Lung Transpl.* 2020;39:300–309. doi: 10.1016/j.healun.2019.12.013
40. McLaughlin VV, Channick R, Marco TD, Farber HW, Gaine S, Galié N, Krasuki RA, Preston I, Souza R, Coghlan JG, et al. Results of an expert consensus survey on the treatment of pulmonary arterial hypertension with oral prostacyclin pathway agents. *Chest.* 2020;157:955–965. doi: 10.1016/j.chest.2019.10.043
41. Vachiery JL, Delcroix M, Al-Hiti H, Efficace M, Hutyra M, Lack G, Papdakis K, Rubin LJ. Macitentan in pulmonary hypertension due to left ventricular dysfunction. *Eur Respir J.* 2018;51:1701886. doi: 10.1183/13993003.01886-2017
42. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca H-P, Choi D-J, Chopra V, Chuquiure-Valenzuela E, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;385:1451–1461. doi: 10.1056/NEJMoa2107038
43. Waxman A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P, Bajwa A, Allen R, Feldman J, Argula R, Smith P, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med.* 2021;384:325–334. doi: 10.1056/NEJMoa2008470
44. Johnson SW, Finlay L, Mathai SC, Goldstein RH, Maron BA. Real-world use of inhaled treprostinil for lung disease-pulmonary hypertension: a protocol for patient evaluation and prescribing. *Pulm Circ.* 2022;12:e12126. doi: 10.1002/pul2.12126
45. Berry NC, Manyoo A, Oldham WM, Stephens TE, Goldstein RH, Waxman AB, Tracy JA, Leary PJ, Leopold JA, Kinlay S, et al. Protocol for exercise hemodynamic assessment: performing an invasive cardiopulmonary exercise test in clinical practice. *Pulm Circ.* 2015;5:610–618. doi: 10.1086/683815
46. Bentley RF, Barker M, Esfandiari S, Wright SP, Valle FH, Granton JT, Mak S. Normal and abnormal relationships of pulmonary artery to wedge pressure during exercise. *J Am Heart Assoc.* 2020;9:e016339. doi: 10.1161/JAHA.120.016339