REVIEW ARTICLE

Darren B. Taichman, M.D., Ph.D., *Editor*

Pulmonary Arterial Hypertension

Paul M. Hassoun, M.D.

PULMONARY HYPERTENSION IS A SYNDROME CHARACTERIZED BY MARKED remodeling of the pulmonary vasculature and a progressive rise in the pulmonary vascular load, leading to hypertrophy and remodeling of the right ventricle. Death results from right ventricular failure if pulmonary hypertension is left untreated. Pulmonary hypertension is currently defined hemodynamically by a mean pulmonary arterial pressure of higher than 20 mm Hg at rest, as measured by right heart catheterization.[1] Precapillary pulmonary hypertension due to pulmonary vascular disease is further defined by an elevation in pulmonary vascular resistance of at least 3 Wood units (WU), in contrast to isolated postcapillary pulmonary hypertension, in which the pulmonary vascular resistance is less than 3 WU and the elevation in the mean pulmonary arterial pressure is due to elevated filling pressures on the left side of the heart.

The several forms of pulmonary hypertension are categorized into five clinical groups (Fig. 1). This review focuses on the relatively rare form of pulmonary arterial hypertension (group 1). Immense progress has been achieved in gaining an understanding of the mechanisms, natural history, and genetic features of pulmonary arterial hypertension and in establishing targeted therapy. A full appreciation of the pathophysiology of the syndrome is important, since the diagnosis requires a thorough clinical investigation to rule out other, more common forms of pulmonary hypertension, for which treatment of the underlying disease should be the primary goal.

The first anatomical description of pulmonary hypertension is credited to von Romberg.[2] However, it is the advent of human right heart catheterization, first performed by Forssmann on himself in 1929,[3] that led to a flurry of physiological observations on the heart and pulmonary circulation by Cournand and Richards in the 1940s. The three investigators received the Nobel Prize in Physiology or Medicine in 1956 for their seminal work. In his illuminating Nobel Lecture, Richards noted that, as a result of their collective work, many forms and degrees of failure were defined, and their responses to treatment measured. [4]

In 1951, Dresdale, a disciple of Cournand and Richards, and colleagues presented the first case series of patients with pulmonary hypertension of unknown cause, defined as primary pulmonary hypertension. [5] Greater awareness of the disease developed in the 1960s, after an epidemic of primary pulmonary hypertension that was associated with the use of the appetite suppressant aminorex.[6] This prompted the World Health Organization to convene a first meeting of pulmonary hypertension experts in 1973, to standardize the clinical and pathological nomenclature of primary pulmonary hypertension, the first attempt at an organized classification.[7] The first and second meetings about pulmonary hypertension were separated by 25 years, but thereafter the World Symposium on Pulmonary Hypertension (WSPH) was convened every 5 years. The meetings brought further refinement to the classification of pulmonary hypertension, with five distinct groups

From the Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore. Dr. Hassoun can be contacted at phassoun@jhmi.edu or at the Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, 1830 E. Monument St., Baltimore, MD 21287.

N Engl J Med 2021;385:2361-76.
DOI: 10.1056/NEJMra2000348

CME at NEJM.org

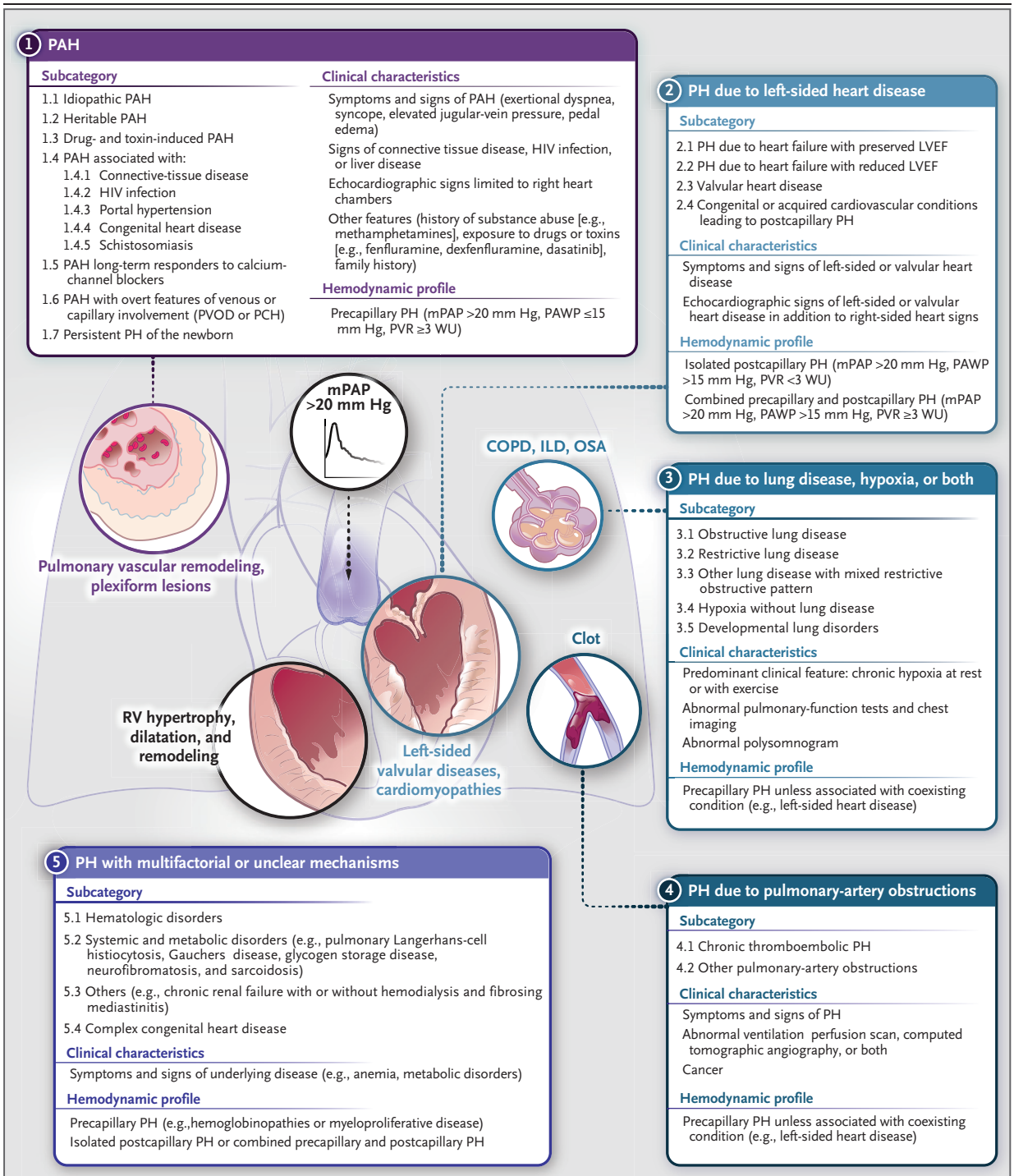

Figure 1. Clinical Classification of Pulmonary Hypertension (PH).

The PH classification based on the 2018 meeting of the World Symposium on Pulmonary Hypertension is shown, along with the clinical characteristics and hemodynamic profile of each group.[1] COPD denotes chronic obstructive pulmonary disease, HIV human immunodeficiency virus, ILD interstitial lung disease, LVEF left ventricular ejection fraction, mPAP mean pulmonary arterial pressure, OSA obstructive sleep apnea, PAH pulmonary arterial hypertension, PAWP pulmonary arterial wedge pressure, PCH pulmonary capillary hemangiomatosis, PVOD pulmonary veno-occlusive disease, PVR pulmonary vascular resistance, RV right ventricular, and WU Wood units.

based on similar clinical and pathological findings and treatment responses (for a discussion of the historical background, see the Supplementary Appendix, available with the full text of this article at NEJM.org). Idiopathic pulmonary arterial hypertension has replaced the term primary pulmonary hypertension, in recognition of the hemodynamic and clinical similarities to other conditions that directly affect the pulmonary arterial vasculature and for which targeted therapy is available.

The recognition that some persons have a genetic predisposition to the disorder (familial pulmonary arterial hypertension) led to the landmark discovery of mutations in the gene encoding bone morphogenetic protein (BMP) receptor type 2 (*BMPR2*).[8,9] Since 80% of cases of familial pulmonary arterial hypertension and up to 20% of sporadic cases have germline *BMPR2* mutations, and since additional mutations in various genes have been identified, the term familial pulmonary arterial hypertension was subsequently changed to heritable pulmonary arterial hypertension.

In the first two decades of this century, a flurry of novel oral, injectable, and inhaled drugs emerged, prompted by a growing interest in and understanding of pulmonary arterial hypertension. The development of these drugs followed and was based on various well-conducted, placebo-controlled studies (Fig. S1 in the Supplementary Appendix).

A GLOBAL HEALTH PROBLEM

The prevalence of pulmonary hypertension varies according to the WSPH group classification. Pulmonary arterial hypertension (group 1) affects 25 persons (most of whom are women) per 1 million population in Western countries, with an annual incidence of 2 to 5 cases per million.[10] The disease is most severe in elderly men,[11] although it is less common in this population, which is more likely to have group 2 disease. For other groups in the pulmonary hypertension classification, the prevalence varies according to the cause and disease state but is likely to be greatly underestimated worldwide.[12]

Many widespread diseases of the cardiopulmonary systems are complicated by pulmonary hypertension, which greatly increases morbidity and mortality. Owing to the high prevalence of congenital heart diseases worldwide, particularly in developing countries,[13] it is estimated that there are 25 cases of congenital heart disease associated pulmonary arterial hypertension per 1 million population worldwide.[14] Valvular and left-sided heart disease are much more common,[15,16] and more than 100 million persons may have pulmonary hypertension due to left-sided heart disease (group 2) worldwide.

Similarly, pulmonary hypertension complicates chronic lung diseases, such as chronic obstructive pulmonary disease (worldwide burden, >500 million cases) and interstitial lung disease (estimated incidence, 10 to 70%); the prevalence is increased among patients with advanced disease.[14] In addition, more than 140 million persons live at high altitude (above 2500 m),[17] but the prevalence of pulmonary hypertension due to chronic hypoxia among persons living in high-altitude areas or persons relocating to such areas is unclear. Furthermore, pulmonary hypertension complicates highly prevalent viral infections (e.g., human immunodeficiency virus [HIV] infection) and parasitic diseases (e.g., schistosomiasis), as well as hemoglobinopathies such as sickle cell disease and thalassemia; therefore, very large numbers of patients are affected in low- and middle-income areas of Africa, Asia, and South and Central America.[18,19]

Thus, it is estimated that 1% of the world population and up to 10% of persons older than 65 years of age have pulmonary hypertension.[14] Moreover, 80% of these persons live in developing countries and, because of prohibitive cost,[20] lack of approved drugs, or limited access to necessary medical and surgical support (e.g., for the treatment of chronic thromboembolic pulmonary hypertension [group 4]), are unlikely to receive therapy.[12,14]

PATHOLOGICAL FEATURES

The histologic features of pulmonary arterial hypertension are complex and variable because of the multiplicity of underlying diseases. However, there are common pathological features of the disorder, such as remodeling of the three layers of the distal pulmonary vasculature (Fig. 2), which involves uncontrolled growth of endothelial and smooth-muscle cells and fibroblasts,[22] and infiltration of inflammatory cells,[23] which affects primarily precapillary vessels with a caliber of 50 to 500 μm. There is also extension of the smooth-muscle cell layer to typically

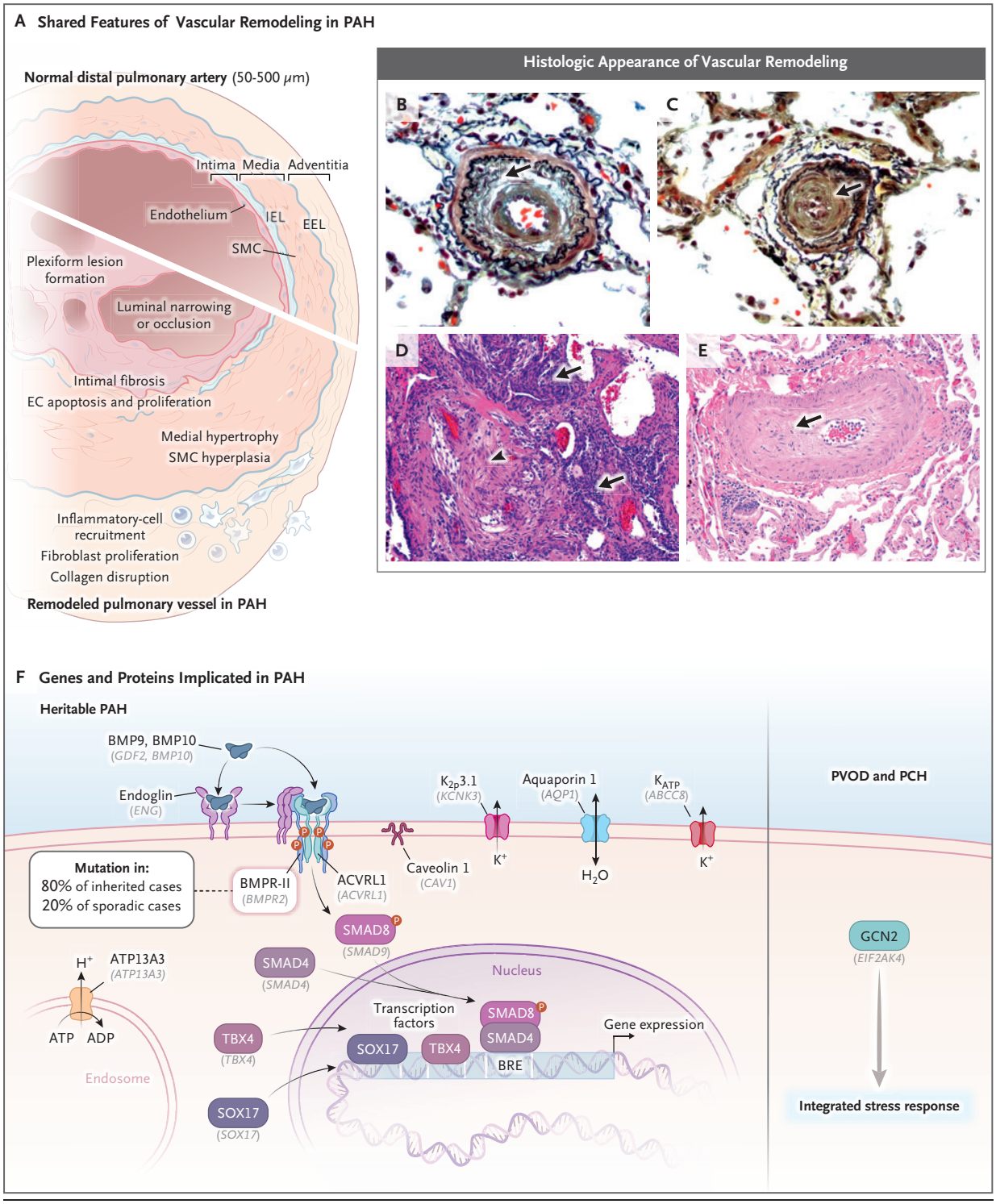

Figure 2 (facing page). Pathobiologic Features of Pulmonary Arterial Hypertension.

Panel A shows a normal distal pulmonary artery and a PAH vessel characterized by remodeling of the three vessel-wall layers (intima, media, and adventitia [EEL denotes external elastic lamina, IEL internal elastic lamina, and SMC smooth-muscle cells]). Endothelial-cell (EC) apoptosis and proliferation cause intimal thickening, smooth-muscle cell hyperplasia causes medial thickening, and infiltration of inflammatory cells such as monocytes, B and T lymphocytes, and dendritic cells, along with collagen disruption, contribute to adventitial remodeling. In Panel B, an elastic stain of a distal pulmonary vessel shows marked narrowing of the arterial lumen, with concentric laminar intimal proliferation and fibrosis, and destruction of the IEL (arrow). The elastic stain in Panel C shows total occlusion of a small pulmonary artery (arrow). Panel D (hematoxylin and eosin) shows a plexiform lesion with an occlusive lesion proximally (arrowhead) and excessive, poorly formed capillaries and large clusters of endothelial-like cells distally (arrows). Panel E (hematoxylin and eosin) shows a characteristic lesion of PVOD, with intimal fibrosis (arrow) and marked obliteration of the vessel lumen. The diagram in Panel F (adapted from Southgate et al.[21]) shows signal transduction by transforming growth factor β (TGF-β) superfamily members and related genes and proteins implicated in heritable PAH, including membrane-bound receptors such as bone morphogenetic protein receptor type II (*BMPR2*); activin A receptor type II like 1 (*ACVRL1*), also known as activin receptor like kinase 1 (*ALK1*); endoglin (*ENG*); caveolin-1 (*CAV1*); and transcription factors SMAD4 and SMAD8 (*SMAD4* and *SMAD9*). Bone morphogenetic protein (BMP) signaling is mediated, in a cell specific manner, by the binding of ligands BMP9 and BMP10 to a heterometric complex of BMPR-II, a cognate type 1 receptor (ACVRL1 or ALK1), and endoglin, an auxiliary receptor thought to sequester ligand, inhibiting receptor binding and thus modulating the effects of BMPs. Activation of the receptor complex results in phosphorylation of the receptor and SMAD8, which then associates with SMAD4 before translocation to the nucleus, regulating genes that contain BMP-responsive elements (BREs). *KCNK3*, the gene encoding potassium-channel subfamily K, member 3 ($K_{2P}3.1$), contributes to pulmonary vascular tone and is a subunit of the ATP-sensitive potassium (K_{ATP}) channel (ABCC8). SOX17 and TBX4 (transcription factors important for organogenesis) also participate in BMP signaling. The probable cation-transporting ATPase 13A3 (*ATP13A3*) is not directly related to BMP signaling. However, loss-of-function mutations in *ATP13A3* disrupt polyamine homeostasis and lead to endothelial dysfunction, thus contributing to PAH pathogenesis. Aquaporin 1 (AQP1), also not a member of the TGF-β superfamily, mediates the migration and proliferation of pulmonary-artery smooth-muscle cells by interacting with β-catenin to activate cell growth related target genes. Biallelic mutations in *GCN2* (general control nonderepressible 2), also known as *EIF2AK4* (eukaryotic translation initiation factor 2 alpha kinase 4), which encodes an important kinase in the integrated stress response, are associated with the pathogenesis of PVOD and PCH.

nonmuscularized distal capillaries. Postcapillary vessels with similar vein remodeling may be involved in specific syndromes, such as pulmonary veno-occlusive diseases and pulmonary capillary hemangiomatosis, scleroderma-associated pulmonary arterial hypertension,[24] chronic thromboembolic pulmonary hypertension,[25] and group 2 cardiac diseases in which vascular remodeling may start in the postcapillary compartment.[26] In situ thrombosis involving small muscular arteries has long been recognized[22] as being due to platelet activation and loss of endothelial integrity.[27]

These changes result in luminal narrowing or complete obliteration of small vessels. Plexiform lesions, which may arise from anastomoses involving bronchial arteries or vasa vasorum penetrating the wall structure of pulmonary vessels,[28] are common features of pulmonary arterial hypertension (Fig. 2). Events leading to severe remodeling have not been clearly identified, although endothelial dysfunction induced by shear stress, hypoxia, autoimmune phenomena, viral infections, drugs and toxins, or genetic alterations may initiate the process of excess vasoconstriction, inflammation, and uncontrolled cellular growth.[27] The findings of highly organized lymphoid follicles juxtaposed against pulmonary arterial hypertension lesions, infiltration of T and B lymphocytes,[29] and circulating inflammatory markers correlating with disease severity,[30] combined with the fact that pulmonary arterial hypertension often complicates autoimmune or inflammatory diseases, have all lent substantial credence to a role of inflammation in the pathogenesis of pulmonary arterial hypertension.[23,31]

RIGHT VENTRICLE

Right ventricular function is the major determinant of clinical outcomes and survival among patients with pulmonary hypertension.[32] In response to an increase in pulmonary vascular resistance by a factor of 5 to 10, the right ventricle undergoes hypertrophy, chamber dilatation, fat deposition, fibrosis, and metabolic shifts as pulmonary hypertension progresses.[32]

Right ventricular remodeling may be adap-

tive, with concentric hypertrophy, preservation of myocardial microcirculation, and minimal fibrosis, or it may be maladaptive, with eccentric hypertrophy, microvascular rarefaction leading to an imbalance between oxygen demand and supply, and myocardial fibrosis.[32] The mechanisms leading to such changes, or to the transition between these two states, remain poorly understood but may involve altered angiogenesis, a shift from glucose oxidation to glycolysis and fatty acid oxidation, and altered mitochondrial bioenergetics.[33]

Pressure–volume loop technology with a high-fidelity conductance catheter, the standard for assessing right ventricular intrinsic myocardial function and right ventricular–pulmonary vascular coupling, is invasive and requires special expertise.[32] Surrogate noninvasive techniques (echocardiography or cardiac magnetic resonance imaging [MRI])[34-36] remain to be validated against this standard, although they do predict outcomes.[34,37] The mechanisms of right ventricular dysfunction, lack of current right ventricle–targeted therapeutics, and remaining gaps in progress have recently been emphasized.[32,38]

Better right ventricular ejection fractions in women than in men free of cardiovascular disease[39] have been attributed to sex hormone differences[40] and sex-related responses to certain drugs (e.g., phosphodiesterase inhibitors and endothelin receptor antagonists).[41] However, further research is warranted.

In vitro study of cardiomyocytes has provided great insight into intrinsic myocardial contractility, revealing a hypercontractile phenotype in patients with idiopathic or congenital heart disease–associated pulmonary arterial hypertension,[42] in sharp contrast to a hypocontractile phenotype in patients with scleroderma-associated pulmonary arterial hypertension.[43] These findings, correlating with in vivo measurements of right ventricular contractility, may explain the worse clinical outcomes and shorter survival in the latter group. The molecular underpinnings of these phenotypes remain poorly studied.

GENETIC FEATURES

A major breakthrough occurred in 2000, when two independent groups[8,9] described heterozygous mutations in *BMPR2*, a member of the transforming growth factor β (TGF-β) superfamily. This breakthrough, combined with advances in genetic technology such as whole-genome and whole-exome sequencing, has substantially advanced our understanding of the role certain genes play in the pathogenesis of pulmonary arterial hypertension.

BMPR2 mutations are identified in approximately 80% of patients with familial pulmonary arterial hypertension, with variable penetrance between male and female carriers, and in up to 20% of patients with sporadic disease. Identification of mutations in *ACVRL1* (encoding activin A receptor type II–like 1 [also known as activin receptor–like kinase 1]) and *ENG* (encoding endoglin)[44,45] in families with hereditary hemorrhagic telangiectasia, a syndrome occasionally complicated by pulmonary arterial hypertension, followed rapidly. Both ACVRL1 and endoglin participate in BMPR-II signaling through dimerization (Fig. 2).

Further analysis of large cohorts of patients with pulmonary arterial hypertension has identified additional mutations[21] in genes coding for the transcription factors SMAD1, SMAD4, and SMAD9,[46] part of the complex BMPR-II downstream signaling, and other genes in families that are negative for *BMPR2* mutations,[47] including the gene encoding caveolin-1 (*CAV1*)[48] (which serves to colocalize BMP receptors) and the gene encoding potassium-channel subfamily K, member 3 (*KCNK3*),[49] which is implicated in membrane potential maintenance and pulmonary vascular tone. Mutations in *TBX4* (encoding T-box transcription factor 4), a gene associated with the small patella syndrome,[50] were detected in a number of children with intellectual disabilities and dystrophic features, in some of their parents, and in an additional small cohort of adults with pulmonary arterial hypertension.[50] *BMPR2* mutations predominate in large cohorts (Fig. S2). Other new mutations involve *ATP13A3* (encoding ATPase 13A3); *SOX17*, which encodes SRY-box 17 and is a major risk factor for congenital heart disease–associated pulmonary arterial hypertension)[51]; *AQP1* (encoding aquaporin 1); and *GDF2* (encoding growth differentiation factor 2, also known as BMP9).[47]

Biallelic mutations in *EIF2AK4*, which encodes the eukaryotic translation initiation factor 2 alpha kinase 4, have been reported in heritable pulmo-

nary capillary hemangiomatosis[52] and pulmonary veno-occlusive disease[53] and in up to 25% of sporadic cases of these diseases. More recently, germline mutations of *TET2*, encoding ten-eleven translocation (tet) methylcytosine dioxygenase 2, a key enzyme in DNA demethylation, were reported in a large cohort of patients with pulmonary arterial hypertension.[54]

The role of altered BMPR-II signaling in the pathogenesis of pulmonary arterial hypertension cannot be overestimated. Most discovered mutations involve *BMPR2* or genes encoding proteins that form complexes or interact with BMP or BMPR-II signaling (Fig. 2). BMPR-II functional loss leads to endothelial dysfunction and the altered balance between proliferation and apoptosis that is characteristic of pulmonary arterial hypertension, which explains the growing interest in therapy aimed at increasing BMPR-II expression[55] or ligand levels, as attempted in preclinical models of BMP9 administration.[56]

Clinicians have an ethical obligation to inform patients and their families about any existing genetic condition, particularly in the case of idiopathic or heritable pulmonary arterial hypertension, pulmonary veno-occlusive disease, or pulmonary capillary hemangiomatosis, and congenital heart disease associated pulmonary arterial hypertension. The implications for family members and their offspring who may be mutation carriers should be considered, along with screening, genetic and psychological counseling by a multidisciplinary team of experts, and patient education.[57] Several affordable technologies and platforms can be used to probe multiple genes simultaneously.

Genetic testing, which promises to further our understanding of the disease and improve therapy through specific targeting, is a task of several national and international collaborative studies[58] and the National Institutes of Health sponsored PVDOMICS (Pulmonary Vascular Disease Phenomics) initiative.[59]

DIAGNOSIS

HISTORY AND PHYSICAL EXAMINATION

Symptoms of pulmonary arterial hypertension are nonspecific (exertional dyspnea, fatigue, chest pain, and fluid retention, as well as syncope in advanced cases), which accounts for a substantially delayed diagnosis in many cases. The presence of an underlying disease such as HIV infection or liver or connective-tissue disease or a history of exposure to drugs or toxins should heighten suspicion concerning pulmonary arterial hypertension (Fig. 1). A major diagnostic challenge is to rule out other forms of pulmonary hypertension for which management should focus principally on the underlying disease, so risk factors for or symptoms of left-sided heart disease or chronic lung disease are important to consider.

Physical findings that are suggestive of pulmonary hypertension include an increased second pulmonic sound, a murmur of tricuspid regurgitation, and evidence of right ventricular fluid overload (e.g., increased jugular venous pressure and pedal edema). Other findings might suggest an underlying cause of pulmonary hypertension, including sequelae of chronic liver or rheumatologic disorders.

DIAGNOSTIC TESTING

Transthoracic echocardiography (TTE), the single most important screening test (Fig. 3), provides a set of measures for gauging the prevalence, cause, and severity of the disease. These measures include dilatation of right-sided chambers; presence and severity of tricuspid regurgitation, which allows for an estimation of right ventricular systolic pressure; the presence of pericardial effusion; and abnormal septal deviation due to right ventricular volume and pressure overload. TTE can also identify left ventricular systolic or diastolic dysfunction and valvular abnormalities, findings that shift the focus toward group 2 pulmonary hypertension.

In addition to a complete blood count and metabolic panel, measurement of antinuclear antibody titers and HIV serologic testing may help uncover a specific underlying disorder such as connective-tissue disease or HIV disease, respectively. The serum N-terminal natriuretic peptide level, measured as a nonspecific cardiac biomarker, can be incorporated into risk stratification (see the discussion below), since the value tracks with the severity of pulmonary arterial hypertension and can be used to predict survival.[61]

A chest radiograph may suggest cardiac enlargement and dilated pulmonary arteries, as

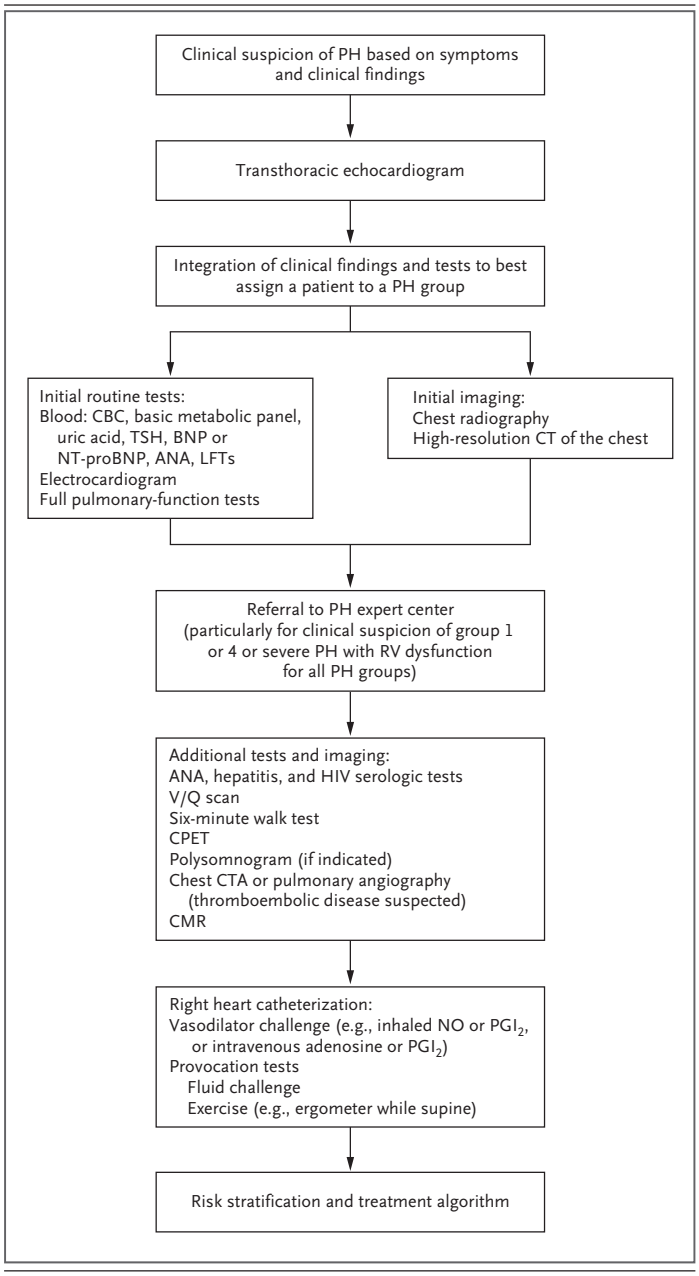

Figure 3. Diagnostic Algorithm for Suspected PH.

When PH is suspected on the basis of symptoms and signs, transthoracic echocardiography is the single most important screening test ordered by the general practitioner. Additional routine blood and imaging tests are integrated in the clinical assessment to determine the best approach in diagnosing PH and possible subgroups or associated conditions (group 1) or other diseases (e.g., groups 2 through 5). Patients suspected of having group 1 (PAH), group 4 (chronic thromboembolic PH), or other forms of severe PH with right ventricular (RV) dysfunction (on echocardiography) are typically referred to specialized PH centers, where additional tests, imaging, and right heart catheterization are performed to further define the nature and severity of PH. A polysomnogram helps rule out associated sleep disorders, which may contribute to or worsen PH. A vasodilator challenge with inhaled nitric oxide (NO), or alternatively, an inhaled prostacyclin (PGI_2) analogue or intravenous adenosine or PGI_2 analogue, is usually reserved for patients with idiopathic PAH, heritable PAH, or PAH associated with drugs or toxins.[60] Provocation tests with fluid challenge or exercise are used to unmask left-sided heart disease or exercise-induced PH, respectively. Cardiopulmonary exercise testing (CPET) can help identify cardiac versus pulmonary causes of dyspnea and obtain measures (e.g., the maximum oxygen consumption or peak) that can be incorporated into the European Society of Cardiology European Respiratory Society (ESC-ERS) risk stratification (see Fig. S4 in the Supplementary Appendix for details of the ESC-ERS risk score and the REVEAL [Registry to Evaluate Early and Long-Term PAH Disease Management] score). The algorithm is adapted from Gali et al.[60] ANA denotes antinuclear antibody, BNP B-type natriuretic peptide, CBC complete blood count, CMR cardiac magnetic resonance, LFTs liver-function tests, NT-proBNP N-terminal proBNP, and TSH thyrotropin.

well as parenchymal lung or chest-wall abnormalities. Computed tomography (CT) of the chest is routinely performed to rule out parenchymal disease. A ventilation perfusion scan remains essential in the clinical algorithm, since normal perfusion makes chronic thromboembolic pulmonary hypertension (CTEPH) an unlikely diagnosis. CT angiography of the chest, although considered less sensitive than a ventilation perfusion scan, may reveal signs of chronic thromboembolic disease such as filling defects or wedge-shaped or irregular linear opacities from previous thrombi. It also helps to determine the surgical accessibility of the lesions and can rule out other diagnoses (e.g., pulmonary-artery stenosis or tumor and fibrosing mediastinitis).

Pulmonary-function tests may suggest obstructive or restrictive lung disease. The single-breath diffusing capacity of the lungs for carbon monoxide, which is typically decreased in pulmonary arterial hypertension, can be incorporated, along with other clinical findings and TTE findings (right atrial enlargement and tricuspid regurgitation velocity), in an evidence-based algorithm to detect pulmonary arterial

hypertension in asymptomatic patients with the scleroderma spectrum of diseases.[62] An electrocardiogram is important to look for evidence of atrial or ventricular hypertrophy, signs of ischemic heart disease, or dysrhythmias.

Cardiac MRI (Fig. S3) is the standard for right ventricular assessment because it provides accurate measurements of the cardiac chamber anatomy and volume, mass, function, and flow, as well as myocardial perfusion.[38] Not widely available, it is increasingly used in centers with expertise in diagnosing and managing pulmonary hypertension. Other advanced imaging techniques that remain in the realm of research include three-dimensional echocardiography, four-dimensional flow MRI, and positron-emission tomography, which can provide unique insights into right ventricular metabolic activity.[63]

HEMODYNAMICS

Right heart catheterization is required for the diagnosis of pulmonary arterial hypertension in order to directly assess pulmonary hemodynamics and cardiac output and to calculate pulmonary vascular resistance. This is a necessary step in the diagnostic algorithm before treatment (Fig. 3). It is essential for confirmation of the presence and type of pulmonary hypertension (precapillary, postcapillary, or combined) and provides essential measures for risk stratification. A structured clinical assessment (Fig. 3) helps assign a patient to a specific pulmonary hypertension group (Fig. 1), which is essential in determining the appropriate therapy, although it is increasingly clear that any given patient may belong in more than one group.

RISK STRATIFICATION

The importance of risk assessment was recognized early in the study of idiopathic pulmonary arterial hypertension, at which time the focus was essentially on baseline hemodynamics.[64] The 2015 European Society of Cardiology European Respiratory Society (ESC-ERS) guidelines for pulmonary hypertension[65] highlighted as an increasing priority the stratification of patients, at baseline and follow-up, into low-, intermediate-, and high-risk groups on the basis of a combination of clinical, functional, and hemodynamic measures, as a tool for choosing therapy. The ESC-ERS risk table and other risk scores (e.g., the REVEAL [Registry to Evaluate Early and Long-Term PAH Disease Management] risk score calculator[66]) (Fig. S4) have been successfully used to assess survival in retrospective analyses of data from pulmonary arterial hypertension registries[67-69] and a post hoc analysis of data from a large prospective clinical trial.[70] The predictive ability of stratification methods is improved by machine-learning algorithms, which reveal a dynamic interdependent influence of multiple risk factors, thus avoiding the assumption that limited clinical measures have independent relationships to a specific outcome.[71]

THERAPY

Basic supportive measures, a constant component of treatment long before the availability of targeted therapy, include diuretics to achieve euvolemia and supplemental oxygen when needed at rest, during sleep, or with exercise, to maintain adequate hemoglobin oxygen saturation (Fig. 4). Sleep-disordered breathing, which can complicate any form of cardiopulmonary disorder, is prevalent among patients with precapillary pulmonary hypertension[72] and should be diagnosed and treated when appropriate. Anticoagulant therapy, once recommended on the basis of retrospective analyses showing a survival benefit,[73,74] is now recommended only for idiopathic pulmonary arterial hypertension (not for other forms of pulmonary arterial hypertension, according to data from a European registry),[75] on a case-by-case basis and risk benefit analysis, and for group 4 pulmonary hypertension (CTEPH), in which increased clotting is a primary issue. A cardiopulmonary exercise program is advised on the basis of a meta-analysis of controlled trials,[76] as tolerated by the patient (Fig. 4). Immunizations should be kept up to date.

Although four decades separated the initial clinical description of pulmonary hypertension and approval of the first effective therapy for pulmonary arterial hypertension, based on a randomized, non-placebo-controlled trial of prostacyclin in patients with primary pulmonary hypertension, [77] the past 20 years have witnessed a series of clinical trials targeting essentially three signaling pathways identified in pulmonary arterial hypertension[78] (Fig. 5). These trials have

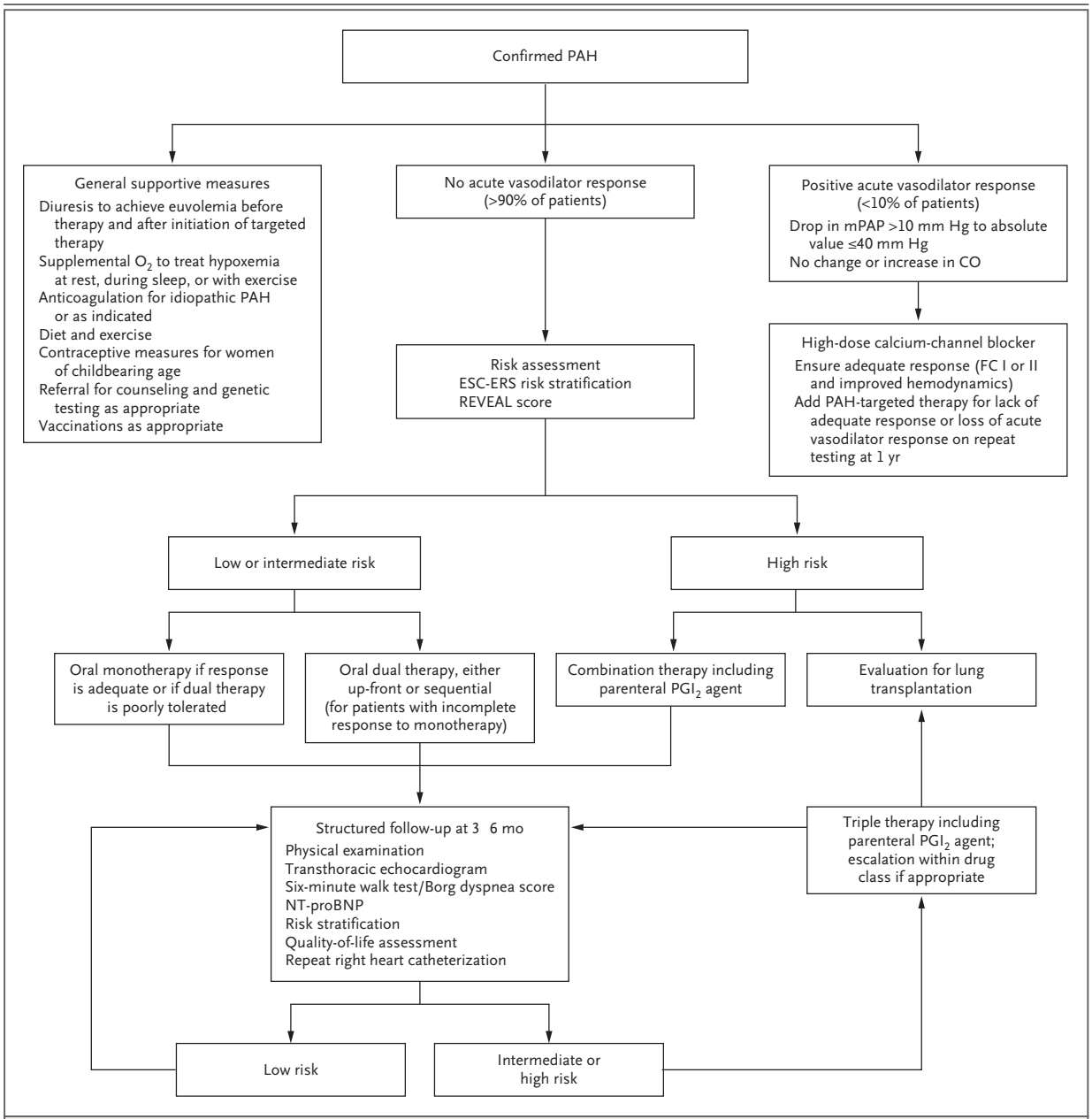

Figure 4. Treatment Algorithm for Confirmed PAH.

The algorithm is adapted from Gali et al.[60] See Fig. S4 for details of the ESC-ERS risk score and the REVEAL score. The Borg dyspnea scale is used to assess dyspnea as reported by a patient during the 6-minute walk test; the scale ranges from 0 to 10, with higher scores indicating more severe dyspnea. Patients in whom triple therapy is recommended are typically evaluated for lung transplantation while a structured follow-up is being performed. FC denotes functional class.

established current targeted therapy for pulmonary arterial hypertension (group 1) and CTEPH (group 4). The findings do not apply to other groups in the WSPH classification, with the exception of inhaled treprostinil, which is now approved by the Food and Drug Administration (FDA) for pulmonary hypertension associated with interstitial lung disease (group 3) on the

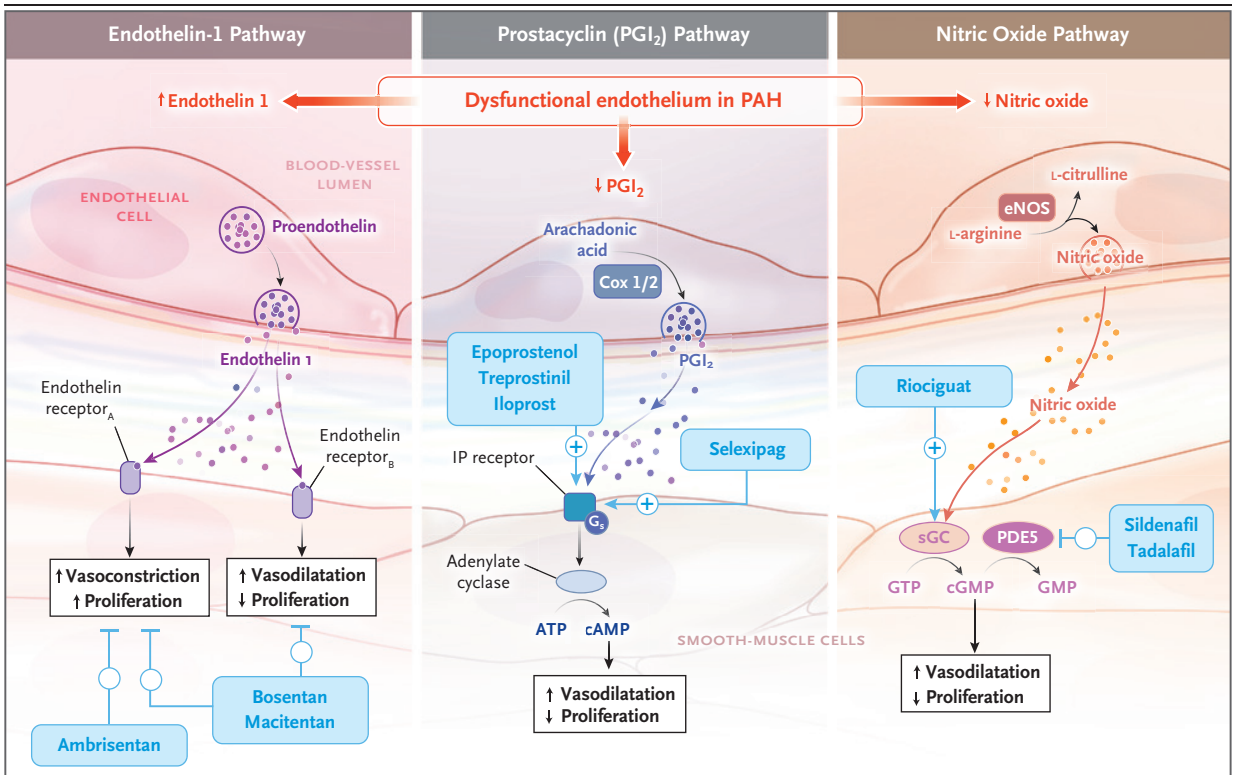

Figure 5. Three Classic Pathways of Targeted Therapy for PAH.

Current targeted therapy is aimed at correcting endothelial dysfunction[27] by inhibiting the endothelin pathway and enhancing the prostacyclin (PGI_2) and NO pathways. Endothelin 1 (ET_1), which is increased in PAH, can bind to either the endothelin A (ET_A) receptor, causing vasoconstriction (of smooth-muscle cells) and cell proliferation, or the endothelin B (ET_B) receptor, causing vasodilatation and antiproliferation. Thus, there are dual ET_A ET_B receptor antagonists (e.g., bosentan and macitentan) or selective ET_A receptor antagonists (e.g., ambrisentan), which leave the ET_B receptor functional. The expression and function of the PGI_2 and NO pathways are decreased in PAH, resulting, respectively, in diminished cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which are second messengers responsible for vasodilatation and antiproliferation. Agents that increase cAMP include PGI_2 analogues given intravenously (e.g., epoprostenol and treprostinil), subcutaneously (e.g., treprostinil), by inhalation (e.g., iloprost and treprostinil), orally (treprostinil), or with the use of oral PGI_2 receptor (IP) agonists (e.g., selexipag). Increased cGMP release can be achieved with inhaled NO (used essentially in the cardiac catheterization laboratory or intensive care unit), which stimulates soluble guanylate cyclase (sGC), or by inhibiting phosphodiesterase type 5 (PDE5, which degrades cGMP into GMP) with the use of oral PDE5 inhibitors (sildenafil or tadalafil). Direct sGC stimulators (e.g., oral riociguat) can increase the release of cGMP independently of NO release. These drugs have been approved by the Food and Drug Administration for patients with PAH who have an mPAP of 25 mm Hg or higher. Although they usually are associated with acceptable adverse-event profiles, these drugs have common side effects that are due essentially to their vasodilatory effects, including headache and lightheadedness (particularly at the initiation of treatment), flushing and upper respiratory congestion, systemic hypotension (more frequent with systemically administered drugs but also common with certain drugs that need slower dose escalation, such as riociguat and selexipag), gastrointestinal symptoms (e.g., bloating, nausea or vomiting, and diarrhea), and rash (PGI_2 analogues). Fluid retention (e.g., pedal edema) is a common problem with the initiation of therapy and requires adjustment of diuretic doses. Additional specific side effects include cough (e.g., with inhaled treprostinil), elevation of aminotransferase levels (with bosentan), anemia (with macitentan), visual changes (with PDE5 inhibitors but very rare), skin irritation or cellulitis (with subcutaneous treprostinil), and thrombocytopenia or bone marrow suppression (with systemically administered PGI_2 analogues). AA denotes arachidonic acid, AC adenylate cyclase, Cox 1/2 cyclooxygenase 1/2, eNOS endothelial isoform of nitric oxide synthase, G_S G-protein coupled receptor, and GTP guanosine triphosphate.

basis of a recent randomized phase 3 clinical trial.[79] An assessment for CTEPH is best performed at specialized centers, where definitive therapy with pulmonary endarterectomy should be considered first. Medical therapy, pulmonary balloon angioplasty, or both are considered for

patients with inoperable disease or residual pulmonary hypertension after endarterectomy.

There have been important changes in the design of randomized, controlled trials (RCTs) over approximately the past decade. The 6-minute walk distance was the primary end point in most early RCTs, typically with a 12-week study period. However, in response to various calls for establishing more relevant end points,[80] RCTs shifted to composite end points, including a combination of hospital admission, worsening of pulmonary arterial hypertension, mortality, and escalation of therapy. Another important change in RCT design was an evaluation of the new therapy added to background treatment for pulmonary arterial hypertension or up-front combined therapy rather than monotherapy. These changes required the enrollment of many more patients and a longer time to reach the primary outcomes. An example is SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome), which revealed the efficacy of macitentan, a dual endothelin receptor antagonist, in reducing the first occurrence of a composite primary end point in a study population of more than 700 patients with symptomatic pulmonary arterial hypertension who were receiving placebo or background therapy (inhaled or oral drugs, excluding other endothelin receptor antagonists).[81] A subsequent RCT, the AMBITION (Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) trial, compared up-front combination therapy with two FDA-approved drugs (ambrisentan and tadalafil) with each drug alone in patients who had received no previous treatment for pulmonary arterial hypertension.[82] The risk of the primary end point (the first event of clinical failure in a time-to-event analysis) was reduced with combination therapy as compared with monotherapy with either drug. In both of these large trials, however, the primary end point was driven predominantly by decreased hospitalization rates (essentially due to worsening pulmonary arterial hypertension), a clinically relevant outcome, since admission for right ventricular failure, the main cause of hospitalization among patients with pulmonary arterial hypertension, portends a very poor prognosis.[83]

Despite the lack of an effect of combined oral therapy on survival in most of the more recent large RCTs,[81,82,84] a large meta-analysis of early RCTs evaluating therapy for pulmonary arterial hypertension, averaging 12 to 16 weeks in duration, showed a significant reduction in mortality with therapy as compared with placebo,[85] which is consistent with data obtained from large registries.[86,87]

Treatment algorithms designed to guide therapy, with classes of recommendations and the level of evidence for the various therapies approved for pulmonary arterial hypertension, are available in comprehensive guidelines.[65] Patients who have pulmonary vasoreactivity (typically to inhaled nitric oxide during initial right heart catheterization), based on strict criteria (a reduction in mean pulmonary arterial pressure of ≥10 mm Hg, to an absolute value of ≤40 mm Hg, accompanied by an increase or no change in cardiac output), can be treated with high-dose calcium-channel blockers alone, provided that this therapy results in New York Heart Association (NYHA) functional class I or II with hemodynamic improvement maintained on repeat testing after at least 1 year of therapy[1] (achieved in less than 10% of patients with idiopathic pulmonary arterial hypertension[88]). In case of clinical deterioration or loss of vasoreactivity, pulmonary arterial hypertension specific therapy should be added according to accepted algorithms.

Monotherapy can be used for patients with a positive response to acute vasoreactivity and those with a good historical response (NYHA functional class I or II with sustained hemodynamic improvement), elderly patients (>75 years old) with important risk factors for left-sided heart disease (e.g., systemic hypertension, coronary artery disease, or atrial fibrillation), those suspected of having pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis, patients with very mild disease (NYHA functional class I and pulmonary vascular resistance of 3 to 4 WU, with normal right ventricular function on echocardiography), and patients in whom combination therapy is associated with an unacceptable side-effect profile.[60] Otherwise, most patients with pulmonary arterial hypertension are currently treated with up-front combination therapy consisting of two oral agents, with dose escalation within a drug class when

appropriate, or sequential combination therapy. Referral for evaluation for lung transplantation is recommended when medical therapy fails to reduce the risk to a low or intermediate level. The role of up-front triple combination therapy in patients with pulmonary arterial hypertension remains unclear.

Atrial septostomy is considered occasionally in patients with end-stage pulmonary arterial hypertension or those awaiting lung transplantation. Atrial septostomy has the advantage of unloading the right atrium and right ventricle and delaying right ventricular failure while improving left ventricular preload and cardiac output at a cost of reduced oxygenation from right to left shunting.

FUTURE DIRECTIONS

Increasingly sophisticated computational power, combined with advanced proteomics platforms[89] or imaging,[90] has led to machine-learning techniques that can be used to develop promising and powerful diagnostic tools for pulmonary arterial hypertension. The current trend to push large-scale investigation into biomarkers and various other -omics (proteomics and genomics) should facilitate characterization of specific mechanistic pathways (common or distinct among pulmonary hypertension groups) in a totally agnostic fashion; the trend should also lead to precision medicine that accounts for genetic, environmental, and lifestyle factors, a process similar to the one that led to current cancer therapy. However, to be successful, this will require strong collaborative efforts among centers, at the national and international levels, to create large registries (for clinical and imaging phenotyping) and biobanks for tissue, biomarkers, genetics, and proteomics. This is particularly important in the case of a rare syndrome such as pulmonary arterial hypertension. Integrating a molecular classification into the current classification is now a realistic goal, as indicated by proteomics studies[91] and genomics studies.[59]

In keeping with the notion that dysregulated immunity may trigger or contribute to the pathogenesis of pulmonary hypertension, clinical trials targeting specific immune pathways have recently been launched. Targeting B cells in scleroderma-associated pulmonary arterial hypertension appeared to benefit a subgroup of patients identified by machine-learning analysis of biomarkers, suggesting a potential role as adjunctive immunotherapy for this disease.[92] Similarly, targeting altered growth factor signaling continues to generate interest, despite the cautionary tale of the tyrosine kinase inhibitor imatinib, which showed encouraging results in a phase 2 trial but serious side effects (i.e., subdural hemorrhage) in a phase 3 trial, preventing FDA approval of imatinib for the treatment of pulmonary arterial hypertension.[93]

Finally, a trial of the calcineurin inhibitor FK506,[94] which was shown to up-regulate BMPR-II expression,[55] is noteworthy, considering the importance of rescuing BMPR-II signaling to counterbalance proproliferative and proinflammatory TGF-β pathways. Similarly, a recent phase 2 clinical trial showed that sotatercept (a first-in-class fusion protein designed to bind the TGF-β ligand activin) reduced pulmonary vascular resistance and serum N-terminal pro B-type natriuretic peptide levels and improved functional capacity in patients with pulmonary arterial hypertension who were receiving background therapy.[95] This very promising new treatment is now being tested in phase 3 clinical trials.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

I thank Carol Farver, University of Michigan, and Jody Hooper, Johns Hopkins University, for providing the histopathological images.

REFERENCES

1. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:1801913.
2. von Romberg E. ber sklerose der lungenarterie. Dtsch Arch Klin Med 1891;48:197-206.
3. Forssmann W. Die sondierung des rechten herzens. Klin Wochenschr 1929;8:2085-7.
4. Richards DW. The contributions of right heart catheterization to physiology and medicine, with some observations on the physiopathology of pulmonary heart disease. Am Heart J 1957;54:161-71.
5. Dresdale DT, Schultz M, Michtom RJ. Primary pulmonary hypertension. I. Clinical and hemodynamic study. Am J Med 1951;11:686-705.
6. Kay JM, Smith P, Heath D. Aminorex and the pulmonary circulation. Thorax 1971;26:262-70.
7. Hatano S, Strasser T, eds. Primary pulmonary hypertension: report on a WHO meeting, Geneva, 15 17 October, 1973. Geneva: World Health Organization, 1975.
8. Lane KB, Machado RD, Pauciulo MW, et al. Heterozygous germline mutations in BMPR2, encoding a TGF-beta receptor, cause familial primary pulmonary hypertension. Nat Genet 2000;26:81-4.

9. Deng Z, Morse JH, Slager SL, et al. Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene. Am J Hum Genet 2000;67:737-44.

10. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006;173:1023-30.

11. Hoeper MM, Huscher D, Ghofrani HA, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. Int J Cardiol 2013;168:871-80.

12. Rich S, Haworth SG, Hassoun PM, Yacoub MH. Pulmonary hypertension: the unaddressed global health burden. Lancet Respir Med 2018;6:577-9.

13. Wu W, He J, Shao X. Incidence and mortality trend of congenital heart disease at the global, regional, and national level, 1990 2017. Medicine (Baltimore) 2020;99(23):e20593.

14. Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. Lancet Respir Med 2016;4:306-22.

15. Gorter TM, Hoendermis ES, van Veldhuisen DJ, et al. Right ventricular dysfunction in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Eur J Heart Fail 2016;18:1472-87.

16. Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. JACC Heart Fail 2013;1:290-9.

17. Moore LG, Niermeyer S, Zamudio S. Human adaptation to high altitude: regional and life-cycle perspectives. Am J Phys Anthropol 1998;107:Suppl 27:25-64.

18. Deol AK, Fleming FM, Calvo-Urbano B, et al. Schistosomiasis — assessing progress toward the 2020 and 2025 global goals. N Engl J Med 2019;381:2519-28.

19. GBD 2017 HIV collaborators. Global, regional, and national incidence, prevalence, and mortality of HIV, 1980 2017, and forecasts to 2030, for 195 countries and territories: a systematic analysis for the Global Burden of Diseases, Injuries, and Risk Factors Study 2017. Lancet HIV 2019;6(12):e831-e859.

20. Sikirica M, Iorga SR, Bancroft T, Potash J. The economic burden of pulmonary arterial hypertension (PAH) in the US on payers and patients. BMC Health Serv Res 2014;14:676.

21. Southgate L, Machado RD, Gr f S, Morrell NW. Molecular genetic framework underlying pulmonary arterial hypertension. Nat Rev Cardiol 2020;17:85-95.

22. Wagenvoort CA. The pathology of primary pulmonary hypertension. J Pathol 1970;101:Pi.

23. Price LC, Wort SJ, Perros F, et al. Inflammation in pulmonary arterial hypertension. Chest 2012;141:210-21.

24. Launay D, Sobanski V, Hachulla E, Humbert M. Pulmonary hypertension in systemic sclerosis: different phenotypes. Eur Respir Rev 2017;26:170056.

25. Gerges C, Gerges M, Friewald R, et al. Microvascular disease in chronic thromboembolic pulmonary hypertension: hemodynamic phenotyping and histomorphometric assessment. Circulation 2020;141:376-86.

26. Fayyaz AU, Edwards WD, Maleszewski JJ, et al. Global pulmonary vascular remodeling in pulmonary hypertension associated with heart failure and preserved or reduced ejection fraction. Circulation 2018;137:1796-810.

27. Budhiraja R, Tuder RM, Hassoun PM. Endothelial dysfunction in pulmonary hypertension. Circulation 2004;109:159-65.

28. Galambos C, Sims-Lucas S, Abman SH, Cool CD. Intrapulmonary bronchopulmonary anastomoses and plexiform lesions in idiopathic pulmonary arterial hypertension. Am J Respir Crit Care Med 2016;193:574-6.

29. Perros F, Dorfm ller P, Montani D, et al. Pulmonary lymphoid neogenesis in idiopathic pulmonary arterial hypertension. Am J Respir Crit Care Med 2012;185:311-21.

30. Soon E, Holmes AM, Treacy CM, et al. Elevated levels of inflammatory cytokines predict survival in idiopathic and familial pulmonary arterial hypertension. Circulation 2010;122:920-7.

31. Hassoun PM, Mouthon L, Barber JA, et al. Inflammation, growth factors, and pulmonary vascular remodeling. J Am Coll Cardiol 2009;54:Suppl 1:S10-S19.

32. Vonk Noordegraaf A, Chin KM, Haddad F, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. Eur Respir J 2019;53:1801900.

33. Ryan JJ, Archer SL. The right ventricle in pulmonary arterial hypertension: disorders of metabolism, angiogenesis and adrenergic signaling in right ventricular failure. Circ Res 2014;115:176-88.

34. Vanderpool RR, Pinsky MR, Naeije R, et al. RV-pulmonary arterial coupling predicts outcome in patients referred for pulmonary hypertension. Heart 2015;101:37-43.

35. Trip P, Kind T, van de Veerdonk MC, et al. Accurate assessment of load-independent right ventricular systolic function in patients with pulmonary hypertension. J Heart Lung Transplant 2013;32:50-5.

36. Sanz J, Kariisa M, Dellegrottaglie S, et al. Evaluation of pulmonary artery stiffness in pulmonary hypertension with cardiac magnetic resonance. JACC Cardiovasc Imaging 2009;2:286-95.

37. Nie L, Li J, Zhang S, et al. Correlation between right ventricular-pulmonary artery coupling and the prognosis of patients with pulmonary arterial hypertension. Medicine (Baltimore) 2019;98(40):e17369.

38. Lahm T, Douglas IS, Archer SL, et al. Assessment of right ventricular function in the research setting: knowledge gaps and pathways forward. An official American Thoracic Society research statement. Am J Respir Crit Care Med 2018;198(4):e15-e43.

39. Kawut SM, Lima JAC, Barr RG, et al. Sex and race differences in right ventricular structure and function: the multi-ethnic study of atherosclerosis-right ventricle study. Circulation 2011;123:2542-51.

40. Ventetuolo CE, Ouyang P, Bluemke DA, et al. Sex hormones are associated with right ventricular structure and function: the MESA-right ventricle study. Am J Respir Crit Care Med 2011;183:659-67.

41. Jacobs W, van de Veerdonk MC, Trip P, et al. The right ventricle explains sex differences in survival in idiopathic pulmonary arterial hypertension. Chest 2014;145:1230-6.

42. Rain S, da Silva Goncalves Bos D, Handoko ML, et al. Protein changes contributing to right ventricular cardiomyocyte diastolic dysfunction in pulmonary arterial hypertension. J Am Heart Assoc 2014;3(3):e000716.

43. Hsu S, Kokkonen-Simon KM, Kirk JA, et al. Right ventricular myofilament functional differences in humans with systemic sclerosis-associated versus idiopathic pulmonary arterial hypertension. Circulation 2018;137:2360-70.

44. Trembath RC, Thomson JR, Machado RD, et al. Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. N Engl J Med 2001;345:325-34.

45. Harrison RE, Berger R, Haworth SG, et al. Transforming growth factor-beta receptor mutations and pulmonary arterial hypertension in childhood. Circulation 2005;111:435-41.

46. Nasim MT, Ogo T, Ahmed M, et al. Molecular genetic characterization of SMAD signaling molecules in pulmonary arterial hypertension. Hum Mutat 2011;32:1385-9.

47. Gr f S, Haimel M, Bleda M, et al. Identification of rare sequence variation underlying heritable pulmonary arterial hypertension. Nat Commun 2018;9:1416.

48. Austin ED, Ma L, LeDuc C, et al. Whole exome sequencing to identify a novel gene (caveolin-1) associated with human pulmonary arterial hypertension. Circ Cardiovasc Genet 2012;5:336-43.

49. Ma L, Roman-Campos D, Austin ED, et al. A novel channelopathy in pulmo-

nary arterial hypertension. N Engl J Med 2013;369:351-61.
50. Kerstjens-Frederikse WS, Bongers EMHF, Roofthooft MTR, et al. TBX4 mutations (small patella syndrome) are associated with childhood-onset pulmonary arterial hypertension. J Med Genet 2013;50:500-6.
51. Zhu N, Welch CL, Wang J, et al. Rare variants in SOX17 are associated with pulmonary arterial hypertension with congenital heart disease. Genome Med 2018;10:56.
52. Best DH, Sumner KL, Austin ED, et al. EIF2AK4 mutations in pulmonary capillary hemangiomatosis. Chest 2014;145:231-6.
53. Eyries M, Montani D, Girerd B, et al. EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension. Nat Genet 2014;46:65-9.
54. Potus F, Pauciulo MW, Cook EK, et al. Novel mutations and decreased expression of the epigenetic regulator *TET2* in pulmonary arterial hypertension. Circulation 2020;141:1986-2000.
55. Spiekerkoetter E, Tian X, Cai J, et al. FK506 activates BMPR2, rescues endothelial dysfunction, and reverses pulmonary hypertension. J Clin Invest 2013;123:3600-13.
56. Long L, Ormiston ML, Yang X, et al. Selective enhancement of endothelial BMPR-II with BMP9 reverses pulmonary arterial hypertension. Nat Med 2015;21:777-85.
57. Morrell NW, Aldred MA, Chung WK, et al. Genetics and genomics of pulmonary arterial hypertension. Eur Respir J 2019;53:1801899.
58. Zhu N, Swietlik EM, Welch CL, et al. Rare variant analysis of 4241 pulmonary arterial hypertension cases from an international consortium implicates FBLN2, PDGFD, and rare de novo variants in PAH. Genome Med 2021;13:80.
59. Hemnes AR, Beck GJ, Newman JH, et al. PVDOMICS: a multi-center study to improve understanding of pulmonary vascular disease through phenomics. Circ Res 2017;121:1136-9.
60. Gali N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J 2019;53:1801889.
61. Fijalkowska A, Kurzyna M, Torbicki A, et al. Serum N-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. Chest 2006;129:1313-21.
62. Coghlan JG, Denton CP, Gr nig E, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 2014;73:1340-9.
63. Rengier F, Melzig C, Derlin T, Marra AM, Vogel-Claussen J. Advanced imaging in pulmonary hypertension: emerging techniques and applications. Int J Cardiovasc Imaging 2019;35:1407-20.
64. D Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991;115:343-9.
65. Gali N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Eur Respir J 2015;46:903-75.
66. Benza RL, Farber HW, Frost A, et al. REVEAL risk scores applied to riociguat-treated patients in PATENT-2: impact of changes in risk score on survival. J Heart Lung Transplant 2018;37:513-9.
67. Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J 2017;50:1700740.
68. Kylhammar D, Kjellstr m B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. Eur Heart J 2018;39:4175-81.
69. Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J 2017;50:1700889.
70. Gali N, Jansa P, Pulido T, et al. SERAPHIN haemodynamic substudy: the effect of the dual endothelin receptor antagonist macitentan on haemodynamic parameters and NT-proBNP levels and their association with disease progression in patients with pulmonary arterial hypertension. Eur Heart J 2017;38:1147-55.
71. Kanwar MK, Gomberg-Maitland M, Hoeper M, et al. Risk stratification in pulmonary arterial hypertension using Bayesian analysis. Eur Respir J 2020;56:2000008.
72. Thurnheer R, Ulrich S, Bloch KE. Precapillary pulmonary hypertension and sleep-disordered breathing: is there a link? Respiration 2017;93:65-77.
73. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992;327:76-81.
74. Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. Circulation 1984;70:580-7.
75. Olsson KM, Delcroix M, Ghofrani HA, 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.
76. Buys R, Avila A, Cornelissen VA. Exercise training improves physical fitness in patients with pulmonary arterial hypertension: a systematic review and meta-analysis of controlled trials. BMC Pulm Med 2015;15:40.
77. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996;334:296-301.
78. Humbert M, Lau EM, Montani D, Ja s X, Sitbon O, Simonneau G. Advances in therapeutic interventions for patients with pulmonary arterial hypertension. Circulation 2014;130:2189-208.
79. Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. N Engl J Med 2021;384:325-34.
80. Gaine S, Simonneau G. The need to move from 6-minute walk distance to outcome trials in pulmonary arterial hypertension. Eur Respir Rev 2013;22:487-94.
81. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013;369:809-18.
82. Gali N, Barber JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015;373:834-44.
83. Campo A, Mathai SC, Le Pavec J, et al. Outcomes of hospitalisation for right heart failure in pulmonary arterial hypertension. Eur Respir J 2011;38:359-67.
84. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med 2015;373:2522-33.
85. Gali N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani ML, Branzi A. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J 2009;30:394-403.
86. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 2010;122:156-63.
87. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest 2012;142:448-56.
88. Sitbon O, Humbert M, Ja s X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005;111:3105-11.
89. Sweatt AJ, Hedlin HK, Balasubrama-

nian V, et al. Discovery of distinct immune phenotypes using machine learning in pulmonary arterial hypertension. Circ Res 2019;124:904-19.
90. Swift AJ, Lu H, Uthoff J, et al. A machine learning cardiac magnetic resonance approach to extract disease features and automate pulmonary arterial hypertension diagnosis. Eur Heart J Cardiovasc Imaging 2021;22:236-45.
91. Rhodes CJ, Wharton J, Ghataorhe P, et al. Plasma proteome analysis in patients with pulmonary arterial hypertension: an observational cohort study. Lancet Respir Med 2017;5:717-26.
92. Zamanian RT, Badesch D, Chung L, et al. Safety and efficacy of B-cell depletion with rituximab for the treatment of systemic sclerosis-associated pulmonary arterial hypertension: a multicenter, double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2021;204:209-21.
93. Hoeper MM, Barst RJ, Bourge RC, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation 2013;127:1128-38.
94. Spiekerkoetter E, Sung YK, Sudheendra D, et al. Randomised placebo-controlled safety and tolerability trial of FK506 (tacrolimus) for pulmonary arterial hypertension. Eur Respir J 2017;50:1602449.
95. Humbert M, McLaughlin V, Gibbs JSR, et al. Sotatercept for the treatment of pulmonary arterial hypertension. N Engl J Med 2021;384:1204-15.

IMAGES IN CLINICAL MEDICINE

The *Journal* welcomes consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal* s website at NEJM.org. At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal*, the electronic version, or both.