**Review (Guideline)**

2020 KSC/KATRD guideline for the diagnosis and treatment of pulmonary hypertension:

Executive summary

Joint Task Force for the diagnosis and treatment of pulmonary hypertension of the Korean Society of Cardiology (KSC) and the Korean Academy of Tuberculosis and Respiratory Diseases (KATRD)

Endorsed by: Korean College of Rheumatology (KCR), Korean Heart Rhythm Society (KHRS), Korean Pediatric Heart Society (KPHS), Korean Society of Heart Failure (KSHF), Korean Society of Cardiovascular Imaging (KOSCI), Korean Society of Echocardiography (KSE), Korean Society of Interventional Cardiology (KSIC), Korean Society for Transplantation (KST), Korean Society for Laboratory Medicine (KSLM), Korean Pulmonary Hypertension Society in Korean Society of Hypertension (KPHS/KSH), and Korean Association of Clinical Cardiology (KACC)

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Short running title: Summary of KSC/KATRD PH guideline

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Abstract

Pulmonary hypertension (PH) is a condition of increased blood pressure in the pulmonary arteries and is diagnosed with increased a mean pulmonary artery pressure ≥25mmHg. It may involve multiple clinical situations. There are five clinical groups according to similar pathophysiological mechanisms, clinical presentation, hemodynamic profiles, and treatment strategies. Although there have been major advances in the management of PH, it is still associated with significant morbidity and mortality. The diagnosis and treatment of PH have mainly been performed following European guidelines in Korea because the country lacks localized PH guidelines. Since foreign treatment guidelines do not reflect regional actual status, diagnosis and treatment have not been tailored well in Korean patients with PH. Thus, we have developed this guideline to facilitate the diagnosis and treat PH appropriately in Korea, where the consensus for diagnosing and treating PH remains insufficient. This is the first edition of the guidelines for the diagnosis and treatment of PH in Korea primarily based on the ‘2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension’ with the acceptance and adaptation of recent publications of PH.

Keywords: Pulmonary hypertension; Treatment; Pulmonary arterial hypertension; Guidelines
Introduction

The purpose of establishing the guidelines is to help medical staff choose the best approach for individual patients, considering the impact on outcomes and the severity of the effects that can be obtained against the risks from specific diagnoses or treatment methods. There have been many treatment guidelines related to various diseases from several international and domestic academic societies. However, the diagnosis and treatment of pulmonary hypertension (PH) have mainly been performed following European guidelines in Korea because the country lacks domestic guidelines. Since foreign treatment guidelines do not reflect our actual status, the strategies of diagnosis and treatment have not been fully implemented for the patients with PH in Korea. Thus, we developed this guideline to help diagnose and treat PH appropriately in Korea, where the basis for the diagnosis and treatment of PH remains insufficient. The basic purpose of treatment guidelines is to assist in the decision-making process through appropriate communication between physicians and patients in clinical practice. This guideline is the first edition of the guidelines for the diagnosis and treatment of PH in Korea based on the ‘2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension’ with the acceptance and adaptation of recent publications of PH, where we try to include as many articles based on Korean data as possible.¹

The joint task force for the diagnosis and treatment of PH included writing and reviewing panels without conflict of interest. The writing panel, including five members of the Korean Society of Cardiology (KSC) and the Korean Academy of Tuberculosis and Respiratory Diseases (KATRD), made a draft that included ‘up-to-date’ published evidence for diagnosis, treatment, prevention, and rehabilitation regarding PH, including Korean data. The review panel comprising 15 members represented the opinions of 11 associated academic societies,
including the Korean College of Rheumatology (KCR), the Korean Heart Rhythm Society (KHRS), the Korean Pediatric Heart Society (KPHS), the Korean Society of Heart Failure (KSHF), the Korean Society of Cardiovascular Imaging (KOSCI), the Korean Society of Echocardiography (KSE), the Korean Society of Interventional Cardiology (KSIC), the Korean Society for Transplantation (KST), the Korean Society for Laboratory Medicine (KSLM), the Korean Pulmonary Hypertension Society in Korean Society of Hypertension (KPHS/KSH), and the Korean Association of Clinical Cardiology (KACC). This task force for the preparation of guidelines for PH was conducted without financial support from related industries to avoid conflicts of interests.

For the accommodation and adaptation of guideline, we searched a total of 31,077 articles across a 10-year period from three databases (MEDLINE, PubMed, and EMBASE). After assessing these articles with K-AGREE II (Appraisal of Guideline for Research and Evaluation II), including six domains and 23 items, we finally selected the ‘2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension’ as a reference of standard, and partially adapted the ‘Guidelines for the Treatment of Pulmonary Hypertension (Japanese Circulation Society 2017/ Japanese Pulmonary Circulation and Pulmonary Hypertension Society 2017)’. We reviewed consensus manuscripts and included these in this process. The level of evidence and the strength of recommendations for each item were graded and presented according to a predefined scale, as shown in Tables 1 and 2.

This guideline represents the official position on PH of the KSC, KATRD, KPHS, and KPHS/KSH, and it will be updated periodically. The full version of the PH guideline can be found at the official websites of the KSC (www.circulation.or.kr), the KATRD (www.lungkorea.org), and the Korean Medical Guideline Information Center (https://www.guideline.or.kr/evaluation/index.php?sub=1). The recommendations mentioned
in this guideline were prepared to help experts make decisions in their daily work by evaluating and summarizing existing evidence on individual issues, but the final decision for each patient should be made by an attending physician after careful discussion with the patients and their caregivers. In addition, it is the responsibility of the individual medical practitioner to check related regulations such as various permits and insurance benefits that change concerning medications and devices when prescribing.

In the future, follow-up investigations should be conducted to verify whether the actual daily practice is performed in accordance with the recommendations of these PH guidelines, and through this process, it is necessary to create a series of virtuous cycles, including clinical research, guideline preparation, and the dissemination and clinical application of these guidelines.

**Definition and classification of PH**

1. To confirm the diagnosis of PH and to support treatment decisions, right heart catheterization (RHC) should be performed at rest (*Strength of recommendation I, Level of evidence C*)

2. It is recommended to perform RHC at expert centers (*Strength of recommendation I, Level of evidence B*)

3. Vasoreactivity testing is recommended in patients with idiopathic pulmonary arterial hypertension (IPAH), hereditary PAH (HPAH), and PAH induced by drugs or toxins to detect patients who can have long-term benefit with high doses of a calcium channel blocker (CCB, *Strength of recommendation I, Level of evidence C*)
**Definition of PH**

The normal mean pulmonary arterial pressure (mPAP) at rest is 14 ± 3 mmHg, and the upper limit of normal value is about 20 mmHg, which is twice the standard deviation assuming a normal distribution of PAP. PH is defined as an increase in mPAP to ≥25 mmHg at rest, and mPAP should be assessed by RHC.1, 4

Recently, the sixth World Symposia on Pulmonary Hypertension (WSPH) took place in Nice, France. The task forces presented their consensus opinion that PH should be defined as mPAP >20 mmHg rather than mPAP ≥25 mmHg because two standard deviations above the normal mPAP value is the threshold for abnormal PAP.5 After active debate over changing the criteria for PH to mPAP >20 mmHg in this guideline, we kept the threshold of PH as mPAP ≥25 mmHg because additional researches are needed to support these new criteria and consensus from expert.

PH can be defined hemodynamically according to various combinations of PAP, pulmonary artery wedge pressure (PAWP), cardiac output (CO), diastolic pressure gradient (DPG), and pulmonary vascular resistance (PVR); Table 3 describes the different hemodynamic classifications of PH.

RHC should be done to define PH, to assess the severity, and to check the acute vasoreactivity in expert centers. When performed in expert centers, the complication rate and mortality rate are both very low (1.1% and 0.06%, respectively).6 Vasoreactivity testing is recommended in patients with IPAH, HPAH, and PAH induced by drugs or toxins to detect patients who can have long-term benefits from high-dose of a CCB.7, 8
Classifications of PH

PH is categorized into five clinical classifications with similar pathophysiological mechanisms, clinical presentation, hemodynamic profiles, and treatment strategies (Table 4).\textsuperscript{1, 9} Since PAH patients with an acute vasodilator response had dramatically improved survival when treated with long-term CCB,\textsuperscript{7, 8} identifying these patients where pulmonary vasoconstriction plays an important role in PAH pathophysiology is vital. Thus, these PAH long-term responders to CCBs were incorporated into group 1.5. Pulmonary veno-occlusive disease (PVOD)/pulmonary capillary hemangiomatosis (PCH) share similar causes and associated conditions with PAH, and it was included in group 1.6. Persistent pulmonary hypertension of the newborn (PPHN), which exhibits different patterns from conventional PAH, was classified as a separate disease category within group 1.7

Both congenital and acquired heart diseases causing post-capillary PH were included in group 2. Patients with PAH associated with congenital heart disease are classified into four groups (Eisenmenger’s syndrome, PAH associated with prevalent systemic to pulmonary shunts, PAH with small/coincidental defects, and PAH after defect correction) according to their clinical profiles.\textsuperscript{1, 10}

Group 3 PH is due to lung diseases and/or hypoxemia. The common causes of group 3 PH are interstitial lung disease and chronic obstructive pulmonary disease (COPD). Severe PH is usually uncommon in patients with severe interstitial lung disease or COPD. However, severe PH can be associated with the combined emphysema/fibrosis syndrome.

Group 4 PH was changed to include chronic thromboembolic pulmonary hypertension (CTEPH), and other pulmonary artery obstructions, including pulmonary sarcoma or
angiosarcoma, other intravascular tumors, arteritis without connective tissue disease, congenital pulmonary artery stenosis, and parasites.10

Chronic hemolytic anemia is associated with an increased risk of PH. Pre-capillary PH associated with chronic hemolytic anemia is different from other types of PAH in terms of pathological characteristics (plexiform lesions), hemodynamic characteristics (low PVR and increased CO), and response to specific treatments for PAH (no response). This group was considered a different clinical condition, and the classification was changed from group 1 to group 5.

Epidemiology and genetics of PAH

Epidemiology of PAH

The data on global PH incidence are insufficient. The prevalence and incidence of PAH in Europe are in the range 15-60 patients per million adult population and 5-10 cases per million adult population per year, respectively.1, 11

Epidemiologic data in Korea are also scant. In a retrospective study based on data from the Health Insurance Review and Assessment Service (HIRA) claim database (for 2008-2016), there were 1,307 newly diagnosed PAH patients in total. The mean age at diagnosis was 44 ± 13 years, and 69.3% were females.12 The incidence of PAH in Korea was 4.8 patients per million adult population per year. In total, 625 PAH patients were enrolled in the Korean Registry of Pulmonary Arterial Hypertension (KORPAH) study, the first prospective registry in which four domestic societies (KSC, KRS, KPHS, and KATRD) participated.13 Their mean age was 48±16 years, and 503 (80.5%) were female. The incidence of PAH was 1.9 per million adult population per year.13 This data showed that the proportion of PAH patients
who are diagnosed and treated remains low, indicating that a more-active patient screening programs are needed to be implemented in Korea. However, clinicians should interpret these data with caution because the frequency of RHC performance was very low (39.8%), and the degree of participation in each academic society varied. Systemic sclerosis is the most common cause of associated PAH globally. In Korea, it seems that there are many associated PAH patients due to systemic lupus erythematosus.

The clinical pattern and incidence of PAH may change depending on the clinical situation. The mean age of patients with IPAH in the U.S. National Institutes of Health registry, first implemented in 1981, was 36 years. With the inclusion of more PAH patients, the average age of patients is currently 50-65 years. The overall prognosis seems to have improved over time.

According to HIRA data, the average age of group 1 PAH patients was 44 ± 13 years, and the mean age of IPAH patients was 48 ± 13 years in Korea. The average age of PAH patients in the KORPAH registry was 48±16 years, and the average age of IPAH patients was 45 years.

Genetics of PAH

Mutations of bone morphogenic receptor protein 2 (BMPR2) are the most well-known genetic anomalies, and heterogynous BMPR2 mutations account for about 75% of familial PAH and approximately 25% of sporadic PAH patients. The BMPR2 gene encodes a type 2 receptor for bone morphogenetic proteins which control vascular cell proliferation. The results of the PILGRIM study, which examined the genetic mutation and clinical features of BMPR2 in Korea in 73 patients, indicated that 22% of patients with IPAH had mutations in BMPR2
Patients with BMPR2 mutation were younger (27 vs. 47 years; p = 0.02) and had a higher mPAP than non-carriers (64 vs. 51 mmHg; p<0.05).

Bi-allelic mutations of eukaryotic translation initiation factor 2 alpha kinase 4 (EIF2AK4), which encodes a serine-threonine kinase in all eukaryotes, can be associated with heritable PVOD/PCH.17

**Diagnosis of PH**

1. Transthoracic echocardiography is a first-line non-invasive diagnostic test in clinically suspected PH cases (*Strength of recommendation I, Level of evidence C*).

2. Ventilation/perfusion lung scan should be performed in cases with unexplained PH to exclude CTEPH (*Strength of recommendation I, Level of evidence C*).

3. Computerized tomography (CT) pulmonary angiography is recommended to evaluate patients with CTEPH (*Strength of recommendation I, Level of evidence C*).

4. Biochemistry, hematology, immunology, human immunodeficiency virus (HIV), and thyroid function tests are recommended to evaluate the specific associated condition in all patients with PAH (*Strength of recommendation I, Level of evidence C*).

**Diagnostic tests of PH**

Diagnosis of PH begins with clinical suspicion of the disease based on symptoms or findings from physical examination. Although RHC to determine hemodynamic criteria is mandatory for diagnosis, a comprehensive evaluation of several diagnostic tests is necessary. In addition
to the cause of PH, it is essential to evaluate a PH patient’s disease severity systematically and consistently with a comprehensive evaluation of the patient's functional classification, exercise capacity, echocardiographic findings, blood tests, and hemodynamic status.\textsuperscript{18}

Transthoracic echocardiography is a first-line non-invasive diagnostic test in clinically suspected cases of PH. The probability of PH can be assessed with transthoracic echocardiography to evaluate the effects of PH and estimate PAP with Doppler measurement.\textsuperscript{1, 19} When PH is probable, further evaluation including RHC is recommended to confirm the diagnosis of PH.

Since a normal result or low probability of ventilation/perfusion lung scan can exclude CTEPH effectively, this test should be performed to evaluate CTEPH in patients with unexplained PH.

CT imaging can provide important information on pulmonary vascular, parenchymal and mediastinal abnormalities, that may suggest PH. In addition, CT pulmonary angiography is recommended for the evaluation of patients with CTEPH.

Biochemistry, hematology, immunology, HIV, and thyroid function tests are recommended to evaluate the specific associated condition involved in all patients with PAH.

\textit{Diagnostic algorithm}

Figure 1 describes the diagnostic algorithm of PH. Patients with suspected PH by symptoms, signs, or clinical history should undergo echocardiographic examination to assess the probability of PH. More common clinical groups of PH [group 2 (PH due to left heart disease) and group 3 (PH due to lung disease and/or hypoxia)] should be initially identified in
patients with echocardiographic findings compatible with PH. Then, group 4 (CTEPH) should be discriminated with ventilation/perfusion lung scan in PH patients without evidence of group 2 or group 3 PH. PH patients without group 4 PH should be determined by the presence of various causes of PAH (group 1) and rarer causes of PH (group 5).

**Prognostic evaluation and risk assessment in PAH**

In evaluating patients with PAH, clinical evaluation is a necessary process that provides valuable information to determine the disease severity, improvement, deterioration, or stability. The basic history-taking items performed between follow-up visits include changes in exercise capacity; episodes of chest pain, arrhythmia, hemoptysis or fainting; and changes in concomitant medications in addition to the evaluation of compliance with prescribed medications. Through physical examination, information on the presence or absence of distal or central cyanosis, dilatation of the jugular vein, edema, ascites, pleural effusion, heart rate, rhythm, and blood pressure should be collected.

Although there are considerable differences among clinicians, the evaluation of dyspnea according to the World Health Organization (WHO) functional class criterion is the most powerful indicator that can predict clinical prognosis during a follow-up as well as at the diagnosis.

The 6-minute walking test (6MWT), which evaluates submaximal exercise capacity, is the most widely used exercise test at many PH centers. This test is easy to perform, inexpensive, and familiar to both patients and medical staff. The results of the 6MWT-like those of other PH assessments-should always be interpreted in the clinical context. The cardiopulmonary exercise test (CPET) generally evaluates maximal exercise capacity and provides important information on gas exchange, ventilator efficiency, and cardiac function during exercise and
on exercise capacity. It offers information on the end-tidal partial pressure of carbon dioxide (PCO₂), ventilator equivalents for carbon dioxide (VE/VCO₂), oxygen/pulse (VO₂/HR), and peak oxygen uptake (peak VO₂). PAH patients can have low PCO₂, high VE/VCO₂, low VO₂/HR, and low peak VO₂.²¹

Various biochemical markers have been studied, but no specific indicator has been developed to reflect the degree of pulmonary vascular remodeling or severity of PAH. Among these markers, B-type natriuretic peptide (BNP) and N terminal pro-BNP (NT-proBNP) concentrations correlate with myocardial dysfunction and give prognostic information both during follow-up at the time of diagnosis.²² Since they are nonspecific for PH and can be elevated in many cardiovascular diseases, these levels should be interpreted in the clinical context.

Traditionally, risk assessment can be done in a multidimensional approach considering symptoms, functional class, clinical signs of right heart failure, results of 6MWT or CPET, BNP/NT-proBNP, presence of pericardial effusion and right atrial area by imaging studies, and hemodynamic profiles. Since these variables are partially overlapped and it is difficult to measure all variables at each visit, the sixth WSPH presented a simplified evaluation system to facilitate the risk assessment, which we adapted and included in our guideline (Table 5). It is unnecessary to evaluate these criteria for all patients with PAH at every visit. However, clinicians should evaluate the functional class and check the exercise capacity with using 6MWT or CPET. It is also recommended to measure BNP/NT-proBNP or obtain information on the right ventricular function through an echocardiographic examination.

However, most of the variables included in the risk assessment proposed above are based on published data and expert opinion. Thus, it should be applied to individual patients with caution.
Treatment of PH

1. CCBs are recommended in patients with IPAH, HPAH and drug-induced PAH who have a positive vasoreactivity test (Strength of recommendation I, Level of evidence C).

2. Initial monotherapy or combination therapy with approved drugs is recommended in treatment-naïve patients with PAH and PAH patients with low- or intermediate-risk (Strength of recommendation I, Level of evidence A).

3. Sequential combination therapy with approved drugs is recommended in PAH patients who show inadequate treatment response to initial monotherapy or initial double combination therapy (Strength of recommendation I, Level of evidence B).

4. The use of PAH-approved drugs is not recommended in PH patients due to left heart disease or lung disease (Strength of recommendation III, Level of evidence C).

5. Surgical pulmonary endarterectomy with deep hypothermic circulatory arrest is recommended for CTEPH patients with operability (Strength of recommendation I, Level of evidence B).

6. Riociguat is recommended in symptomatic CTEPH patients with persistent or recurrent lesions after surgical treatment or in inoperable CTEPH patients (Strength of recommendation I, Level of evidence B).

PAH patients should be managed initially with general measures including physical activity and supervised rehabilitation, inhibition of pregnancy, birth control and post-menopausal hormonal therapy, elective surgery, infection prevention, psychosocial support, adherence to
treatments, genetic counseling, and travel. Supportive therapy for PAH patients includes oral anticoagulants, diuretics, oxygen, and digoxin.

Drug treatment for PAH should be determined based on the diagnosis, symptoms, and result of the acute vasoreactivity test. Without contraindication to using CCBs, CCBs should be considered for PAH patients who show a favorable response to the acute vasoreactivity test at the time of RHC. The choice of CCB is based on the heart rate at baseline, and nifedipine (120 – 240 mg/day) and diltiazem (240 – 720 mg/day) are frequently used CCBs in the treatment of PAH patients.7, 8

PAH specific drugs can be used in PAH patients without vasoreactivity according to the grade of recommendation and level of evidence for treatment. However, the use of PAH specific drugs is not necessary for PAH patients without symptoms (WHO functional class I). Close follow-up is required to determine if and when symptoms occur for deciding when PAH-specific drugs should be started.18 PAH patients in WHO functional class II or higher require treatment according to their individual indications. Figure 2 shows the treatment algorithm.

PAH-specific drugs include endothelin receptor antagonists (ERA), phosphodiesterase type-5 inhibitors (PDE-5i), guanylate cyclase stimulators (cGC), prostanoids, and IP-receptor agonists. Initial monotherapy or combination therapy with PAH-specific drugs is recommended in newly diagnosed PAH patients and PAH patients with low- or intermediate-risk without vasoreactivity. Initial combination therapy, including intravenous prostacyclin analogs, should be considered for PAH patients in WHO functional class IV. Intravenous epoprostenol is the first option since it has reduced the initial mortality in high-risk PAH. Since this drug is not available in Korea (as of October 2020), it is necessary to actively implement other types of initial upfront combination therapy. If there is inadequate treatment
response to initial monotherapy or initial double combination therapy in the reassessment after 3 – 6 months, sequential double or triple combination therapy with approved drugs is recommended in symptomatic PAH patients. The combination of PDE-5I and cGC is contraindicated.

Pulmonary endarterectomy (PEA) in deep hypothermic circulatory arrest is recommended for CTEPH patients with operability assess by a multidisciplinary team. In inoperable CTEPH patients or in patients with persistent or recurrent lesions after PEA, riociguat is recommended. Interventional balloon pulmonary artery angioplasty may be considered in CTEPH patients without operability.

If the clinical response to initial monotherapy or combination therapy is inadequate, it seems reasonable to refer PAH patients for lung transplantation evaluation.

Conclusions

Over the past decades, there have been major advances in the management of PH. However, it is still associated with significant morbidity and mortality, and the strategy of diagnosis and treatment of PH have mainly been followed European guidelines in Korea because the country lacks localized PH guidelines. Since foreign treatment guidelines do not reflect our actual status, diagnosis and treatment have not been performed well in Korean patients with PH. Thus, we have developed this guideline to help diagnose and treat PH appropriately in Korea, where the basis for diagnosing and treating PH remains insufficient.
Acknowledgement

We sincerely appreciate Sun Bok Kang for her dedication and a great title illustration.
References


Table 1. Strength of recommendations

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<tr>
<th>Criterion</th>
<th>Definition</th>
<th>Suggestion</th>
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<tbody>
<tr>
<td>Class I</td>
<td>Benefit &gt;&gt; risk</td>
<td>Procedure/treatment should be performed. Is recommended/ is indicated</td>
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<tr>
<td></td>
<td>Procedure or treatment is beneficial, useful and effective</td>
<td></td>
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<td></td>
<td>Benefit &gt; risk</td>
<td>It is reasonable to perform procedure/treatment</td>
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<tr>
<td>Class IIa</td>
<td>Evidence or opinion is useful or efficacious</td>
<td>Should be considered</td>
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<tr>
<td></td>
<td>Benefit ≥ risk</td>
<td>Procedure/treatment may be considered</td>
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<tr>
<td>Class IIb</td>
<td>Additional studies with broad objectives needed because usefulness/efficacy is less well established</td>
<td></td>
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<tr>
<td></td>
<td>Benefit ≤ risk</td>
<td>Procedure/treatment should not be performed</td>
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<tr>
<td>Class III</td>
<td>Procedure or treatment are not useful or potentially harmful</td>
<td>Is not recommended</td>
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<tr>
<td>Level</td>
<td>Definition</td>
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<tr>
<td>A</td>
<td>Multiple populations evaluated in multiple randomized clinical trials or meta-analyses</td>
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<tr>
<td>B</td>
<td>Limited populations evaluated in a single randomized trial, or large non-randomized studies</td>
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<tr>
<td>C</td>
<td>Consensus opinion of the experts, or very limited populations evaluated in small studies, retrospective studies or registries</td>
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<tr>
<td>Definition</td>
<td>Characteristics</td>
<td>Clinical PH group</td>
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<tr>
<td>Pre-capillary PH</td>
<td>mPAP ≥25mmHg</td>
<td>1, 3, 4, 5</td>
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<td></td>
<td>PAWP ≤15mmHg</td>
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<tr>
<td>Post-capillary PH</td>
<td>mPAP ≥25mmHg</td>
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<td></td>
<td>PAWP &gt;15mmHg</td>
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<tr>
<td>Isolated post-capillary PH</td>
<td>DPG&lt;7mmHg and/or PVR ≤3WU(^b)</td>
<td>2, 5</td>
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<td>(Ip PH)</td>
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<tr>
<td>Combined post-capillary and</td>
<td>DPG ≥7mmHg and/or PVR &gt;3WU</td>
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<td>pre-capillary PH (Cpc-PH)</td>
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CO: cardiac output; DPG: diastolic pressure gradient; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; WU: Wood units

\(^{a}\) DPG = diastolic PAP – mean PAWP

\(^{b}\) WU are preferred to dynes.s.cm\(^{-5}\), and 1 WU is about 80 dynes.s.cm\(^{-5}\).
<table>
<thead>
<tr>
<th>Group 1. Pulmonary arterial hypertension (PAH)</th>
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<tr>
<td>1.1 Idiopathic PAH</td>
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<td>1.2 Heritable PAH</td>
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<td>1.3 Drug- and toxin-induced PAH</td>
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<td>1.4 PAH associated with diseases</td>
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<td>1.4.1 Connective tissue disease</td>
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<td>1.4.3 Portal hypertension</td>
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<td>1.4.4 Congenital heart disease</td>
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<td>1.4.5 Schistosomiasis</td>
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<td>1.5 PAH long-term responders to calcium channel blockers</td>
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<td>1.6 Pulmonary venoocclusive disease and/or pulmonary capillary hemangiomatosis</td>
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<td>1.7 Persistent pulmonary hypertension of the newborn</td>
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<td>2.2 PH due to heart failure with reduced ejection fraction</td>
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<td>2.3 PH due to valvular heart disease</td>
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<td>2.4 PH due to congenital/acquired cardiovascular conditions</td>
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<thead>
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<th>Group 3. PH due to lung diseases and/or hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Obstructive lung disease</td>
</tr>
<tr>
<td>3.2 Restrictive lung disease</td>
</tr>
<tr>
<td>3.3 Other lung disease with mixed restrictive/obstructive pattern</td>
</tr>
<tr>
<td>3.4 Hypoxia without lung disease</td>
</tr>
<tr>
<td>3.5 Developmental lung disorders</td>
</tr>
</tbody>
</table>
Group 4. Chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions

4.1 CTEPH

4.2 Other pulmonary artery obstructions

Group 5. PH with unclear and/or multifactorial mechanisms

5.1 Hematological disorders
Table 5. Risk assessment in patients with pulmonary arterial hypertension

<table>
<thead>
<tr>
<th>Prognostic criterion</th>
<th>Low risk(^a)</th>
<th>Intermediate risk(^b)</th>
<th>High risk(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated 1-year mortality (%)</td>
<td>&lt;5</td>
<td>5 - 10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>I, II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6-minute walking distance (m)</td>
<td>&gt; 440</td>
<td>16 – 440</td>
<td>&lt; 165</td>
</tr>
<tr>
<td>Biochemical test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP (ng/L)</td>
<td>&lt;50</td>
<td>50 – 300</td>
<td>&gt; 300</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>&lt;300</td>
<td>300 – 1400</td>
<td>&gt;1400</td>
</tr>
<tr>
<td>Hemodynamic profile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA pressure (mmHg)</td>
<td>&lt;8</td>
<td>8 – 14</td>
<td>&gt; 14</td>
</tr>
<tr>
<td>CI (L/min/m(^2))</td>
<td>≥2.5</td>
<td>2.0 – 2.4</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>SvO(_2) (%)</td>
<td>&gt;65</td>
<td>60 - 65</td>
<td>&lt;60</td>
</tr>
</tbody>
</table>

a. at least three low risk criteria and no high-risk criterion  
b. definitions of low or high risk are not fulfilled  
c. at least two high-risk criteria including CI or SvO\(_2\)  

BNP: b type natriuretic peptide; CI: cardiac index; NT-proBNP: N terminal-pro B type natriuretic peptide; RA: right atrial; SvO\(_2\): Mixed venous oxygen saturation
Figure legends

Figure 1. Diagnostic algorithm of pulmonary hypertension.

CT: computed tomography; CTEPH: chronic thromboembolic pulmonary hypertension; HIV: human immunodeficiency virus; mPAP: mean pulmonary artery pressure; PA: pulmonary angiography; PAH: pulmonary arterial hypertension; PAWP: pulmonary artery wedge pressure; PH: pulmonary hypertension; PVOD/PCH: pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis; PVR: pulmonary vascular resistance; RHC: right heart catheterization; RV: right ventricular
Figure 2. Treatment algorithm of pulmonary arterial hypertension

CCB: calcium channel blocker; DPAH: drug- or toxin-induced pulmonary arterial hypertension; HPAH: heritable pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension; PAH: pulmonary arterial hypertension; PCA: prostacyclin analogue; WHO-FC: World Health Organization functional class