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2018 TSOC guideline focused update on diagnosis and treatment of pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH) is characterized as a progressive and sustained increase in pulmonary vascular resistance, which may induce right ventricular failure. In 2014, the Working Group on Pulmonary Hypertension of the Taiwan Society of Cardiology (TSOC) conducted a review of data and developed a guideline for the management of PAH.[4] In recent years, several advancements in diagnosis and treatment of PAH has occurred. Therefore, the Working Group on Pulmonary Hypertension of TSOC decided to come up with a focused update that addresses clinically important advances in PAH diagnosis and treatment. This 2018 focused update deals with: (1) the role of echocardiography in PAH; (2) new diagnostic algorithm for the evaluation of PAH; (3) comprehensive prognostic evaluation and risk assessment; (4) treatment goals and follow-up strategy; (5) updated PAH targeted therapy; (6) combination therapy and goal-orientated therapy; (7) updated treatment for PAH associated with congenital heart disease; (8) updated treatment for PAH associated with connective tissue disease; and (9) updated treatment for chronic thromboembolic pulmonary hypertension.

Introduction

Pulmonary arterial hypertension (PAH), defined by a resting mean pulmonary arterial pressure (mPAP) $\geq$25 mmHg, and pulmonary artery wedge pressure (PAWP) $\leq$15 mmHg with pulmonary vascular resistance (PVR) $>$ 3 Wood units, is a life-threatening condition.[1–4] During the 2018 6th World Symposium on Pulmonary Hypertension held in Nice, France, PH was redefined as both mPAP $\geq$ 20 mmHg and PVR$\geq$3 Wood units.[5] However, the new definition did not change the criteria for initiation of PAH therapy, because most evidences were based on previous definition. PAH is characterized as a progressive and sustained increase in pulmonary vascular resistance, which may induce right ventricular failure.

In 2014, the Working Group on Pulmonary Hypertension of the Taiwan Society of Cardiology (TSOC) conducted a review of data and developed a guideline for the management of PAH.[4] In recent years, several advancements in diagnosis and treatment of PAH has occurred. Therefore, the Working Group on Pulmonary Hypertension of TSOC decided to come up with a focused update that addresses clinically important advances in PAH diagnosis and treatment. This 2018 focused update deals with: (1) the role of echocardiography in PAH; (2) new diagnostic algorithm for the evaluation of PAH; (3) comprehensive prognostic evaluation and risk assessment; (4) treatment goals and follow-up strategy; (5) updated PAH targeted therapy; (6) combination therapy and goal-orientated therapy; (7) updated treatment for PAH associated with congenital heart disease; (8) updated treatment for PAH associated with connective tissue disease; and (9) updated treatment for chronic thromboembolic pulmonary hypertension. The recommendations were developed with the same methodology used for the initial 2014 guidelines.

Echocardiography

Transthoracic echocardiographic (TTE) examination is the first step in the assessment of patients presenting with a relevant history, symptoms and signs showing a high index of suspicion for pulmonary hypertension (PH).[6] The primary purpose of this examination is to determine the probability of PH. Based on echocardiographic findings, the probability of PH is classified into low, intermediate, or high.[6]

Systolic pulmonary artery pressure (SPAP) can be estimated using continuous wave Doppler echocardiography via assessment of the peak tricuspid regurgitation velocity (TRV) and taking into account the right atrial pressure (RAP), which is calculated using the modified Bernoulli equation (SPAP $= 4 \times TRV^2 + RAP$).[7] The RAP can be estimated echocardiographically based on the diameter and inspiratory collapsibility of the inferior vena cava (IVC) — an IVC diameter $<$ 2.1 cm with collapsibility $>$ 50% during a sniff suggests a normal RAP of 3 mmHg (range 0—5 mmHg), whereas an IVC diameter $>$ 2.1 cm with

List of abbreviations

ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
ASD	atrial septal defect
BNP	brain natriuretic peptide
BPA	balloon pulmonary angioplasty
BREATHE	Bosentan Randomised trial of Endothelin Antagonist THErapy
CCB	calcium channel blocker
CHD	congenital heart disease
CMR	cardiac magnetic resonance
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise testing
CTD	connective tissue disease
CTED	chronic thromboembolic disease
CTEPH	chronic thromboembolic pulmonary hypertension
CTPA	computed tomography pulmonary angiogram
DECT	dual-energy CT
DL_{CO}	diffusing capacity of the lung for carbon monoxide
ECG	electrocardiogram
EIF2AK4	eukaryotic translation initiation factor 2 alpha kinase 4
ERA	endothelin receptor antagonist
ESC/ERS	European Society of Cardiology/European Respiratory Society
ET	endothelin
FDA	US Food and Drug Administration
HIV	human immunodeficiency virus
HFpEF	heart failure with preserved left ventricular ejection fraction
HRCT	high resolution computed tomography
INR	international normalized ratio
IPAH	idiopathic pulmonary arterial hypertension
IPF	idiopathic pulmonary fibrosis
IV	intravenous
IVC	inferior vena cava
LSIM	lung subtraction iodine mapping
LV	left ventricle/ventricular
mPAP	mean pulmonary arterial pressure
MR	magnetic resonance
NO	nitric oxide
NT-proBNP	N-terminal pro-brain natriuretic peptide
PA	pulmonary artery
PaCO2	arterial carbon dioxide pressure
PAH	pulmonary arterial hypertension
PAP	pulmonary arterial pressure
PAWP	pulmonary artery wedge pressure
PDA	patent ductus arteriosus
PDE-5i	phosphodiesterase type 5 inhibitor
PE	pulmonary embolism
PEA	pulmonary endarterectomy
PFTs	pulmonary function tests
PH	pulmonary hypertension
PoPH	porto-pulmonary hypertension
PVOD	pulmonary veno-occlusive disease
PVR	pulmonary vascular resistance
PVRi	pulmonary vascular resistance index
RA	right atrium/atrial
RAP	right atrial pressure
RCT	randomized controlled trial
RHC	right heart catheterization
RV	right ventricle/ventricular
RVOT	right ventricular outflow tract
6MWD/6MWT	6-minute walking distance/6-minute walking test
SC	subcutaneous
sGC	soluble guanylate cyclase
sPAP	systolic pulmonary arterial pressure
SSc	systemic sclerosis
SvO2	mixed venous oxygen saturation
TEE	transesophageal echocardiography
TRPG	tricuspid regurgitation peak gradient
TRV	tricuspid regurgitant velocity
TSOC	Taiwan Society of Cardiology
TTE	transthoracic echocardiography
VE/VCO2	minute ventilation − carbon dioxide production relationship
V/Q	ventilation/perfusion
VSD	ventricular septal defect
WHO FC	World Health Organization functional class

collapsibility $<$ 50% during a sniff or $<$ 20% on quiet inspiration suggests a high RAP of 15 mmHg (range 10−20 mmHg). Other than these, RAP 8 mmHg (range 5−10 mmHg) can be used.[8] Despite the strong correlation between SPAP determined echocardiographically and that determined via right heart catheterization (RHC); Doppler-derived SPAP cannot be used as a cut-off value to define PH because of a common overestimation of $>$10 mmHg for SPAP estimated from echocardiographic evaluation. Additionally, underestimation and inaccurate measurements are observed in patients presenting with severe TR.[9] Owing to inaccuracies in estimation of SPAP and RAP, the peak TRV rather than the estimated SPAP is used as a primary parameter to determine the echocardiographic probability of PH (Table 1[6]).

However, in approximately 10−25% of patients with PH who are referred for evaluation, the TRV cannot be assessed because of trivial or mild TR with a weak Doppler profile.[10] In such cases, the use of contrast-enhanced echocardiographic examination by agitated saline may increase Doppler signals and enable assessment of the peak TRV.[11] Additionally, other echocardiographic parameters that raise the suspicion of PH independent of TRV should be sought. These signs include assessment of the RV size and pressure overload, the pattern of blood flow at the right ventricular outflow tract (RVOT), the diastolic pulmonary regurgitation velocity, the PA diameter, an estimated RAP, and the RA area (Table 2).[6]

In summary, a TRV that cannot be measured or a peak TRV $<$ 2.8 m/s with no associated echocardiographic signs of PH indicates a low probability of PH; however, when associated with echocardiographic signs of PH, the probability of PH is determined to be intermediate. A peak TRV of 2.9−3.4 m/s with no associated echocardiographic signs of

PH indicates an intermediate probability of PH; however, when associated with echocardiographic signs of PH, the probability of PH is high. A peak TRV of >3.4 m/s indicates that the probability of PH is high even without associated echocardiographic signs of PH (Table 1).[6]

The recommended plan for the management of symptomatic patients in terms of further investigation based on echocardiographic probability of PH is shown in Table 3[6] and that for asymptomatic patients is shown in Table 4[6], considering the association with or without risk factors of pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH).[6] Following interpretation of all clinical contexts and echocardiographic results, the primary concern that needs to be addressed is to decide the need for cardiac catheterization.

In addition to the detection of PH, echocardiographic evaluation can identify the most common cause of PH, which is related to left-sided heart disease such as valvular heart disease, particularly mitral or aortic valve disease as well as LV systolic and/or diastolic dysfunction. Moreover, Doppler and contrast echocardiography are useful aids to diagnose congenital heart disease (CHD).

Diagnostic algorithm for the evaluation of pulmonary arterial hypertension

When echocardiographic findings are suggestive of a high or intermediate probability of PH, further clinical surveys including chest radiograph, pulmonary function tests, and high resolution computed tomography (HRCT) of the chest are requested to identify the presence of Group 2 or Group 3 PH (Fig. 1). If the diagnosis of left heart or lung parenchymal diseases is excluded, a ventilation/perfusion (V/Q) lung scan should be performed for the differential diagnosis between CTEPH and PAH. If the V/Q scan shows multiple segmental perfusion defects, a diagnosis of Group 4 PH (CTEPH) should be suspected. For patients with suspected Group 4 PH, CT pulmonary angiography (CTPA) and selective pulmonary arterial angiogram on top of right heart catheterization (RHC) is indicated to confirm the diagnosis and to evaluate the feasibility of pulmonary endarterectomy (PEA). When the V/Q scan shows normal or minimal perfusion defect, group 1 (PAH) or rare conditions of group 5 PH should be considered.

The diagnostic algorithm is illustrated in Fig. 1, it starts immediately when clinical symptoms and signs, and the echocardiographic features are compatible with PH to identify the most common etiologies of PH (Groups 2 and 3 PH), then to differentiate Group 4 PH (CTEPH) from Group 1 PAH and the rare conditions in Group 5 PH.

Group 2 (left heart disease) PH

The most common etiology of PH is left heart disease, which accounts for about two-third of patients with increased tricuspid regurgitation peak gradient (TRPG).[12] The phenotypes of left heart diseases varies from heart failure with either reduced or preserved ejection fraction (HFpEF) due to ischemic or non-ischemic causes, valvular heart diseases, and pericardial diseases. The mechanism of PH in patients with left heart disease is primarily related to the backward transmission of the elevated left atrial pressure to the pulmonary vein. Borlaug et al. have demonstrated every increase of pulmonary artery wedge pressure (PAWP) was almost identical to the changes of systolic pulmonary artery pressure (SPAP) during exercise in a study population of HFpEF and healthy controls.[13] However, pulmonary arteries may undergo remodeling due to prolonged pressure overload, resulting in further increases of pulmonary arterial pressure and PVR. The hemodynamic study may therefore illustrate a combined pre and post capillary PH rather than an isolated post-capillary PH.[6]

TTE is usually the standard examination to make the diagnosis. Given there is a growing population of HFpEF, it would be helpful to survey whether the patients have typical heart failure symptoms (paroxysmal nocturnal dyspnea, orthopnea), multiple morbidities, atrial arrhythmia, and absence of right axis deviation to conduct diagnosis.[14] Eventually, RHC is the gold standard to diagnose Group 2 PH by showing an elevated PAWP of ≥15 mmHg.

Group 3 (lung disease) PH

The limited data available has shown that PH was present in 31.6% and 50.2% of patients with idiopathic pulmonary fibrosis (IPF) or chronic obstructive pulmonary disease (COPD), respectively, when they were referred for lung transplantation or lung volume reduction surgery.[15,16] HRCT, pulmonary function tests (PFTs), including diffusing capacity for carbon monoxide (DLco), and arterial blood gas are essential to identify significant airway obstruction, lung parenchymal disease, hypercapnia or mechanical defects of lung. Screening overnight oximetry or polysomnography will

Table 1 Echocardiographic probability of pulmonary hypertension.

Peak TRV (m/s)	Presence of associated echocardiographic signs of PH	Echocardiographic probability of PH
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

PH: pulmonary hypertension, TRV: tricuspid regurgitation velocity.

Table 2 Echocardiographic signs suggesting pulmonary hypertension in addition to tricuspid regurgitation velocity measurement.

A. The ventricles	B. Pulmonary artery	C. Inferior vena cava and right atrium
1. Right ventricle/left ventricle basal diameter ratio >1.0	1. Right ventricular outflow Doppler acceleration time <105 ms and/or mid-systolic notching	1. Inferior vena cava diameter >2.1 cm with decreased inspiratory collapse (<50% with a sniff or < 20% with quiet inspiration).
2. Flattening of the interventricular septum (LV eccentricity index > 1.1 during systole and/or diastole	2. Early diastolic pulmonary regurgitation velocity >2.2 m/s	2. Right atrial area (end-systole) > 18 cm^2
	3. PA diameter >2.5 cm	

PA: pulmonary artery, LV: left ventricle.
Echocardiographic signs suggesting pulmonary hypertension from at least two different categories (A/B/C).

Table 3 Suggested diagnostic management based on echocardiographic probability of pulmonary hypertension in **symptomatic** patients with or without associated risk factors for pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension.

Echocardiographic probability of PH	Without risk factors or associated conditions for PAH or CTEPH	With risk factors or associated conditions for PAH or CTEPH
Low	Alternative diagnosis should be considered	Echocardiographic follow-up should be considered
Intermediate	Alternative diagnosis, echocardiographic follow-up, should be considered Further investigation of PH may be considered	Further assessment of PH including RHC should be considered
High	Further investigation of PH (including RHC) is recommended	Further investigation of PH including RHC is recommended

CTEPH: chronic thromboembolic pulmonary hypertension, PAH: pulmonary arterial hypertension, PH: pulmonary hypertension, RHC: right heart catheterization.

Table 4 Suggested diagnostic management based on echocardiographic probability of pulmonary hypertension in **asymptomatic** patients with or without associated risk factors for pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension.

Echocardiographic probability of PH	Without risk factors or associated conditions for PAH or CTEPH	With risk factors or associated conditions for PAH or CTEPH
Low	No work-up required for PAH	Echocardiographic follow-up may be considered
Intermediate	Echocardiographic follow-up should be considered	Echocardiographic follow-up is recommended In the presence of associated scleroderma, RHC should be considered
High	RHC should be considered	RHC is recommended

CTEPH: chronic thromboembolic pulmonary hypertension, PAH: pulmonary arterial hypertension, PH: pulmonary hypertension, RHC: right heart catheterization.

disclose whether patients have significant sleep apnea/hypopnea.[17]

Group 4 PH (CTEPH)

Although CTPA has been the gold standard to diagnose patients with acute pulmonary emboli, the sensitivity to disclose the chronic distal pulmonary artery obstruction is low. The V/Q scan is the best screening tool for CTEPH when multiple segmental perfusion defects are present.[18] The selective pulmonary angiogram and RHC may clearly demonstrate the extent of CTEPH to evaluate the operability, while PEA provides the most appropriate intervention as a potential cure for this debilitating disorder.

Group 1 PAH

The etiologies of developing PAH include idiopathic or hereditary, connective tissue disease (CTD), CHD, drugs or toxins, portopulmonary hypertension (PoPH), human

immunodeficiency virus (HIV) infection, and schistosomiasis. A number of drugs or toxins have been reported to be associated with the development of PAH (Table 5).[6] Therefore, a careful history taking may disclose whether the patients have been exposed to these drugs or toxins to confirm the etiology of PAH.

CTD is a well-known risk factor of developing PAH. In addition to blood tests, including anti-nuclear antibodies (ANA), sclerodema-70, anti-phospholipid antibodies, anti-ribonuclear protein, rheumatoid factors, etc., consultation with a rheumatologist is recommended.

PAH is common in adult patients with CHD.[19] The transesophageal echocardiography (TEE) is essential to identify the intra- or extra-cardiac defects with systemic-to-pulmonary shunts. In addition, blood gas analysis during RHC may also disclose the presence of intra- or extra-cardiac shunts.

Otherwise, the tests for viral infections, including HIV antibody, hepatitis B surface antigen (HbsAg), anti-hepatitis C antibody are warranted. If patients have chronic viral hepatitis, work-up of liver cirrhosis, such as abdominal sonography, should be performed. During RHC, we may also measure the pressures of hepatic vein and portal vein to survey for portal hypertension. Although schistosomiasis is supposed to be the most prevalent etiology of PAH, the treatment of schistosomiasis-PAH has not been well studied. Identification of eggs in stools or urine, or antibody detection may confirm the infection of schistosomiasis.

Pulmonary veno-occlusive disease (PVOD) is a special entity of PAH. When the therapeutic effects with PAH-specific drugs are with uncertainty, it is suggested to refer the patients to a transplant center once the diagnosis of PVOD is confirmed. PVOD mostly affects small pulmonary veins, leading to an elevation of pulmonary capillary pressure and pre-capillary pulmonary arterial pressure. The patients may have low DLco and the HRCT may show typical findings of ground-glass opacities with centrilobular pattern, poorly defined nodular opacities, septal lines and mediastinal lymphadenopathy. In addition, the bronchial alveolar lavage may disclose hemosiderin-laden macrophages. A combination of clinical findings, physical examination, bronchoscopy and radiological findings or the identification of a bi-allelic EIF2AK4 mutation are recommended to diagnose PVOD without histological confirmation.[6]

Comprehensive prognostic evaluation and risk assessment

In Taiwan, PH has high mortality, especially in females, and patients with older age and with chronic diseases.[20] Idiopathic PAH (IPAH) still has a poor prognosis despite advances in drug therapy that target the endothelin, nitric

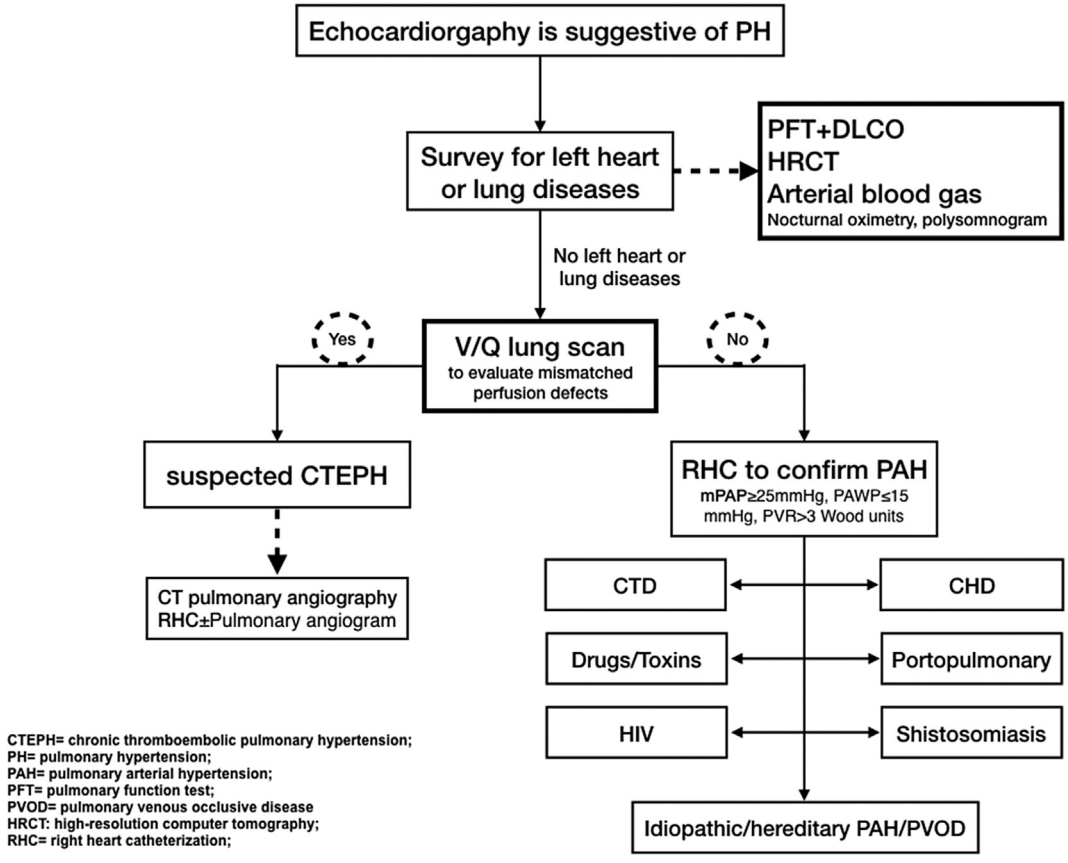

Figure 1 Diagnostic algorithm for the evaluation of pulmonary arterial hypertension. CTEPH = chronic thromboembolic pulmonary hypertension; PH = pulmonary hypertension; PAH = pulmonary arterial hypertension; PFT = pulmonary function test; PVOD = pulmonary veno-occlusive disease; HRCT = high-resolution computed tomography; RHC = right heart catheterization.

oxide, and prostacyclin pathways. Right heart failure is the most common cause of death in PAH and measures that reflect right ventricle (RV) performance predict outcome at baseline and during follow-up.[6,21,22] Regular evaluation of patients with PAH is strongly recommended based on variables with predictive importance. A comprehensive assessment is necessary since no single variable could offer sufficient diagnostic and prognostic information. A multidimensional approach is required and stepwise evaluation at each visit should include the following: any evidence of clinical deterioration, the etiology of clinical deterioration, stability and sufficiency of RV function, and the achievement of the stable and satisfactory criteria. Table 6[6] demonstrates prognostic variables that are most frequently advised in clinical practice guidelines.[21] Not all these parameters must to be evaluated at each visit. The basic programme should comprise determination of the functional class (FC) and at least one measurement of exercise capacity, e.g. 6MWD or CPET. It is also recommended to acquire some information on RV function, either by measuring BNP/NT-proBNP or by performing echocardiography. Most of the proposed variables and cut-off values are based on expert opinions. These prognostic parameters may be used to guide therapeutic decisions, but application to individual patients must be done carefully. In recent investigations of risk assessment in PAH from three European registries, an abbreviated version of the risk stratification strategy listed in Table 6 has validated the benefit of reaching a stable and satisfactory profile.[22–24] RHC remains the gold standard of diagnosis of PAH, and the data acquired by RHC remain the standard hemodynamic values. The magnitude of the PAP correlates poorly with clinical symptoms since it is influenced by the degree of PVR and CO. Therefore, the PAP alone should not be used for therapeutic decision making. The indicated mortality rates are crude estimates and the illustrated variables have been studied mostly in patients with IPAH. Not all variables may be in the same risk group, and it is the comprehensive assessment of individual patients that should guide treatment decisions. Patients often do not completely fall into one of the three categories, and in these cases the patient's overall risk should be judged based on the worse parameters. The individual risk is further modified by other factors, such as the rate of disease progression, the presence or absence of signs of right heart failure, syncope, comorbidities, age, sex, background therapy, and PAH subtype. Finally, the assessment of PAH patients should provide information on clinical worsening, disease complications and hospitalization for PAH. ECGs should be acquired on a regular basis to detect clinically relevant arrhythmias found frequently in the PAH population. Since PAH patients may be candidates for long-term O_2 therapy and a low $PaCO_2$ is associated with reduced pulmonary blood flow and has prognostic implications, arterial or capillary blood gases provide important information and should be part of the regular clinical assessment, at least in case of clinical deterioration. Peripheral O_2 saturation may be used alternatively, but it is less reliable and does not provide information on $PaCO_2$. The recommended basic laboratory workup includes complete blood counts, BNP/NT-proBNP, International normalized ratio (INR) in patients receiving vitamin K antagonists, sodium, potassium, creatinine, aspartate aminotransferase (ASAT)/alanine aminotransferase (ALAT) (in patients receiving ERAs) and bilirubin. The extended laboratory workup comprising troponin, uric acid, iron status and thyroid function should be checked at least once a year or whenever PAH patient presents with clinical worsening.

Table 7 demonstrates comprehensive recommendations on the follow-up assessments of patients with PAH.[6]

Definition of patient status

PAH patients can be categorized as stable and satisfactory, stable but not satisfactory or unstable and deteriorating based on the prognostic evaluation and risk assessment defined in Table 6.[6] Although reliable individual predictions are always difficult, patients categorized as stable and satisfactory have an estimated 1-year mortality $<5\%$. Basically, these patients present with non-progressive disease in WHO-FC I or II with a 6MWD of at least 440 m and no signs of clinically relevant RV dysfunction. The estimated 1-year mortality in the stable but not satisfactory category is 5—10%. These patients typically present in WHO-FC III, with moderately impaired exercise capacity and signs of RV dysfunction, but not with RV failure. Patients in the unstable and deteriorating category have an estimated 1-year mortality $>10\%$. These patients present in WHO-FC III or IV with progressive disease and signs of severe RV dysfunction, or with RV failure and secondary organ dysfunction.

PAH patients often do not completely fall into one of the three categories, and the overall risk should be judged based on the worse parameters. Importantly, the assessment of PAH patients should provide information on clinical

Table 5 Drugs and toxins known to induce pulmonary arterial hypertension.

Definite	Likely	Possible
Aminorex	Amphetamines	Cocaine
Fenfluramine	Dasatinib	Phenylpropanolamine
Dexfenfluramine	L-tryptophan	St. John's wort
Toxic rapeseed oil	Chemotherapeutic agents	Amphetamine-like drugs
Benfluorex	Methamphetamines	Interferon α and β
SSRIs (PPHN only)		Some chemotherapeutic agents such as alkylating agents (mytomycine C, cyclophosphamide)[a]

[a] Alkylating agents are possible causes of pulmonary veno-occlusive disease.

worsening, disease complications and hospitalization for PAH. Again, these risk categories are intended for risk assessment before initiating treatment and can be used for further disease management decisions. Aggressive and timely intervention based on multi-parameter and individualized assessment offers the best chance of gaining control over disease progression and subsequently optimizing the long-term outlook for every patient with PAH.

Treatment goals and follow-up strategy

Treatment goals for PAH patients are those listed in the 'stable and satisfactory' category of Table 6. Treatment goals and target values are not the same in all patients, and which are adjusted according to the individual patient. For example, the value of 6MWD depends on the age and >400 m is acceptable for older PAH patients, and younger patients can aim to walk 500 m or more despite the presence of severe PH and RV dysfunction. More tests such as CPET and/or RHC should be performed in these patients in order to obtain more reliable assessments of RV function. Severe PAH patients with accompanying cardiac arrhythmias or acute RV failure, increasing frequency of syncope are contraindicated for maximal exercise testing. Peak VO_2, an abnormally high VE/VCO_2 slope, O_2 pulse, peak systolic blood pressure during exercise and diminished aerobic capacity are typically seen in patients with RV failure, and these are also important information about RV function during exercise. In addition, biomarkers, echocardiography, and RHC are valuable tools to determine whether the patient can be considered stable.

RHC is required to assess the severity of the hemodynamic impairment and is essential during the initial evaluation of new patient. There is no accepted consensus about the timing for follow-up RHC worldwide. However, some expert centers perform RHC every once a year. It mostly depends on the centers and in case of clinical worsening and/or changes in treatment. Some centers perform RHC 3–6 months after initiation or change of treatment to determine whether hemodynamics is in the desired range. The most important prognostic indicators are those variables that reflect RV function, and these are CO, RA pressure, and mixed-venous oxygen saturation.

Not all parameters need to be assessed at every visit. Recommendations for evaluation of severity and follow-up are summarized in Table 7 [6] and as follows:

1) Clinical evaluation, CPET, biochemical markers, echocardiographic and hemodynamic assessments by RHC while making the diagnosis should be performed.
2) For every patient, regular follow-up with clinical evaluation, 6MWD and BNP/NT-pro-BNP should be performed every 3–6 months even in stable PAH patients.
3) A goal-oriented treatment is recommended in PAH. Treatment goals for PAH patients are those listed in the "stable and satisfactory definition".
4) Echocardiography should be performed in presence of deterioration of symptoms and RHC should be performed

Table 6 Risk assessment in patients with pulmonary arterial hypertension.

Determinants of prognosis[a]	Stable and satisfactory	Stable but not satisfactory	Unstable and deteriorating
estimated 1-year mortality	<5%	5–10%	>10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing (CPET)	Peak VO_2 > 15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 < 11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
BNP or NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 TAPSE > 2.0 cm No pericardial effusion	RA area 18–26 cm^2 TAPSE 1.5–2.0 cm No or minimal pericardial effusion	RA area >26 cm^2 TAPSE < 1.5 cm Pericardial effusion
Hemodynamics	RAP <8 mmHg CI ≥ 2.5 l/min/m^2 SvO2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO2 60–65%	RAP >14 mmHg CI < 2.0 l/min/m^2 SvO2 <60%

6MWD = 6-minute walking distance; BNP = brain natriuretic peptide; CI = cardiac index; CMR = cardiac magnetic resonance; NT-proBNP = N-terminal pro-brain natriuretic peptide; pred. = predicted; RA = right atrium; RAP = right atrial pressure; SvO_2 = mixed venous oxygen saturation; TAPSE = tricuspid annular plane systolic excursion; VE/VCO_2 = ventilatory equivalents for carbon dioxide; VO_2 = oxygen consumption; WHO = World Health Organization.

[a] Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for IPAH and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

[b] Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.

[c] Repeated episodes of syncope, even with little or regular physical activity.

if clinical worsening is suspected and we would like to change the treatment.

Prostacyclin analogues and prostacyclin receptor agonists

Prostacyclin, a prostanoid metabolized from arachidonic acid through the cyclooxygenase pathway, is produced predominantly by endothelial cells and induces vasodilatation of vessels. It is also a potent endogenous inhibitor of platelet aggregation and has both cytoprotective and antiproliferative activities.[25] In PAH patients' pulmonary arteries, the decrease of prostacyclin synthase expression was found, which may contribute to the pathogenesis of PAH.[26] Clinically it has been identified as one of the most effective drugs for the treatment of PAH.

Epoprostenol

Intravenous (IV) epoprostenol (synthetic prostacyclin) is the first prostacyclin analogue used for the treatment of PAH and is a first-line treatment for patients with severe PAH (WHO FC IV). Epoprostenol is available as a stable freeze-dried preparation that needs to be dissolved in alkaline buffer for intravenous infusion. Epoprostenol has a short half-life (3—5 minutes) and a rapid onset of action, reaching plasma steady-state concentrations within 15 minutes. It is stable at room temperature for only 8 hours after dissolution in buffer. It needs to be given continuously by an infusion pump via a permanent catheter. Continuous intravenous administration of epoprostenol improves survival in patients with IPAH[27,28] and those with PAH associated with the scleroderma spectrum of diseases.[29] Epoprostenol improves symptoms, exercise capacity and hemodynamics, and is the only treatment shown to improve survival in treating IPAH patients[28] and was approved by the FDA in 1995 for the long-term treatment in severe symptomatic IPAH and PAH associated with scleroderma patients.[30] It was only approved for the treatment of IPAH in Taiwan. Long-term efficacy has also been shown in open label registries of IPAH[31] as well as in other APAH conditions[32—34] and non-operable CTEPH.[30,35] Treatment with epoprostenol is initiated at a dose of 2—4 ng/kg/min and increased gradually if no severe side effects. Side effects include flushing, headache, jaw pain, diarrhea and leg pain. The optimal dose varies between individual patients, ranging between 20 and 40 ng/kg/min in majority of the patients.[31] Serious adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction and sepsis. Guidelines for the prevention of central venous catheter bloodstream infections have been proposed.[36] Abrupt discontinuation of the epoprostenol infusion should be avoided as it may lead to rebound increases in PAP with severe symptomatic deterioration and even death. Due to this safety concern, epoprostenol should be used in experienced PAH center and patient should be well educated before starting epoprostenol. Because of the complexity of its administration, epoprostenol is generally reserved for patients with advanced PAH and those who have had poor response to oral therapies. For the FC IV PAH patients, it could be used initially, either as mono or combination therapy. A

Table 7 Suggested assessment and timing for the follow-up of patients with pulmonary arterial hypertension.

	At baseline	Every 3—6 months[a]	Every 6—12 months[a]	3—6 months after changes in therapy[a]	In case of clinical worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnea score	+	+	+	+	+
CPET	+		+		+[e]
Echo	+		+	+	+
Basic lab[b]	+	+	+	+	+
Extended lab[c]	+		+		+
Blood gas analysis[d]	+		+	+	+
Right heart catheterization	+		+[e]	+[e]	+[e]

ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; BNP = brain natriuretic peptide; CPET = cardiopulmonary exercise testing; Echo = echocardiography; ECG = electrocardiogram; ERAs = endothelin receptor antagonists; INR = international normalized ratio; lab = laboratory assessment; NT-proBNP = N-terminal pro-brain natriuretic peptide; TSH = thyroid stimulating hormone; 6MWT = 6-minute walking test.

[a] Intervals to be adjusted according to patient needs.

[b] Basic lab includes blood count, INR (in patients receiving vitamin K antagonists), serum creatinine, sodium, potassium, ASAT/ALAT (in patients receiving ERAs), bilirubin and BNP/NT-proBNP.

[c] Extended lab includes TSH, troponin, uric acid, iron status (iron, ferritin, and soluble transferrin receptor) and other variables according to individual patient needs.

[d] From arterial or arterialized capillary blood; may be replaced by peripheral oxygen saturation in stable patients or if blood gas analysis is not available.

[e] Should be considered.

thermostable formulation of epoprostenol has been developed and does not usually require cooling packs to maintain stability beyond 8—12 hours.[37] However, this formulation is not available in Taiwan as of 2017.

Iloprost

Iloprost is a synthetic analogue of prostacyclin available for intravenous (IV) and inhaled administrations. Inhaled iloprost was approved in 2004 by the FDA for the treatment of WHO FC III/IV PAH and has the theoretical advantage of being selective for the pulmonary circulation with less systemic hypotension. Inhaled iloprost has been evaluated in one randomized controlled trial (RCT) in which daily repetitive iloprost inhalations (6—9 times, 2.5—5 μg/inhalation, median 30 μg daily) were compared with placebo inhalation in patients with PAH and CTEPH.[38] The study showed an increase in exercise capacity and improvement in symptoms, PVR and clinical worsening events in enrolled patients. A second RCT with 60 patients on background oral bosentan did not reach its endpoint but did demonstrate safety in the subjects randomized to the addition of inhaled iloprost in comparison with placebo.[39] With these two (2) trials the FDA approved iloprost for PAH. Overall, inhaled iloprost was well tolerated, with flushing and jaw pain being the most frequent side-effects. Inhaled iloprost is initiated at a dose of 2.5 μg/inhalation and increased to 5 μg/inhalation as tolerated (as delivered at the mouthpiece of the inhalation device). The different nebulization device need different volume to provide a total dose of 5 μg of iloprost delivered at the mouthpiece.[40] The maximum recommended dose is 45 μg/day. Because of the short half-life of iloprost (20—30 minutes), daily inhalations for 6 to 9 times is suggested. Continuous intravenous administration of iloprost appears to be as effective as epoprostenol in a small series of patients with PAH and CTEPH.[41] Inhaled iloprost has been approved for group I PAH. The IV formulation is approved for group I PAH in New Zealand. Effects of oral iloprost have not been assessed in PAH. Only inhaled iloprost is available in Taiwan now.

Treprostinil

Treprostinil is a tricyclic benzidine analogue of epoprostenol, with sufficient chemical stability to be administered at room temperature. This characteristic allows administration of the compound by the IV, SC and oral routes. The effects of SC treprostinil in PAH were studied in a worldwide RCT and showed improvements in exercise capacity, hemodynamics and symptoms.[42] The greatest exercise improvement was observed in patients who were more compromised at baseline and in subjects who were able to tolerate the upper quartile dose (>13.8 ng/kg/min). Infusion site pain is the most common adverse effect of SC treprostinil which often leads to withdrawal of the therapy or insufficient dosage titration. Infusion site pain was independent of treprostinil dose or infusion rate but dependent on the volume. Further support of its efficacy was reported in an open-label study in patients with IPAH or CTEPH followed up for a mean of 26 months.[43] Treatment with SC treprostinil is started at a dose of 1—2 ng/kg/min, with doses increasing at a rate limited by side-effects (injection site pain, flushing, headache). The optimal dose varies between individual patients, ranging between 20 and 80 ng/kg/min in majority of patients.

Bioequivalence data on IV versus SC treprostinil prompted clinical trials to explore dosing and safety in PAH.[44] Tapson et al. reported that newly diagnosed patients started on intravenous therapy dramatically improved 6MWD and hemodynamics.[45] Gomberg-Maitland's data suggested that transition from intravenous epoprostenol to intravenous treprostinil is safe and effective.[46] The intravenous treprostinil effects appear to be comparable with those of epoprostenol, but at a dose which is two to three times higher.[45—47] The FDA approved the use of intravenous (IV) treprostinil in WHO FC II, III and IV PAH patients in whom SC infusion is not tolerated. IV and SC treprostinil are available but not approved for the treatment of IPAH in Taiwan. Oral treprostinil has been evaluated in two (2) RCTs in PAH patients on background therapy patients, however both the primary endpoints of 6MWD did not reach statistical significance.[48,49] An additional RCT in PAH treatment-naïve patient showed improvement in 6MWD by 26 m at peak dose.[50] FDA has approved oral treprostinil for the treatment of PAH in Group I PAH patients to improve exercise capacity on December 2013. Oral treprostinil is not available in Taiwan.

Beraprost

Beraprost is the first oral prostacyclin analogue. In two (2) clinical trials it showed an improvement in exercise capacity but no hemodynamic improvements nor long-term outcome benefits.[51,52] Headache, flushing, jaw pain and diarrhea were the most frequent adverse events. It has been approved for the treatment of PAH only in Japan and South Korea but not in Taiwan.

Selexipag

Selexipag is an orally available, selective prostacyclin IP receptor agonist. The vasodilator effect of prostacyclin works via IP receptor; thus, IP receptor agonist may have similar therapeutic effect as prostacyclin in PAH patients. In GRIPHON study, a large RCT in PAH patients (either not receiving PAH-specific treatment or receiving a stable dose of an endothelin-receptor antagonist, a phosphodiesterase type 5 inhibitor, or both), selexipag alone or on top of mono- or double therapy with ERAs and/or PDE-5i was able to reduce the composite morbidity and mortality endpoint (including all causes mortality, hospitalization for worsening of PAH, clinical worsening of PAH resulting in the need for lung transplantation or atrial septostomy, initiation of parenteral prostanoids or chronic O_2 for worsening of PAH and disease progression) by 40% (hazard ratio 0.60, 99% CI 0.46 to 0.78, $P < 0.001$) in median duration of 1.4 years.[53] Common side effects observed in those treated with selexipag in the trial include headache, diarrhea, jaw pain, nausea, muscle pain (myalgia), vomiting, pain in an extremity, and flushing. In a subgroup analysis of CTD-PAH patients from GRIPHON trial, selexipag also reduced the risk of composite morbidity/mortality events in patients

with PAH-CTD by 41% (HR 0.59; 95% CI 0.41—0.85).[54] It has been approved for Group I PAH treatment by FDA, but not officially available in Taiwan as of 2017. Generally it can be used as mono or combination therapy in WHO FC I-III PAH patients. For WHO FC IV PAH patients, IV form prostacyclins, especially epoprostenol, should still be considered as first-line treatment choice.

Endothelin receptor antagonists

Overexpression of endothelin-1 (ET-1), a vasoconstrictive peptide, is the result of the endothelial cell dysfunction observed in PAH and plays a prominent role in the pathogenesis of PAH.[55] ET-1 exerts its vascular effects by binding to two distinct receptor isoforms in the pulmonary vascular smooth muscle cells, endothelin-A (ET_A) and endothelin-B (ET_B) receptors. Dual ET_A and ET_B receptor antagonist and the selective ET_A receptor antagonist drugs have been developed for treatment of PAH.[56—58] There are currently three available FDA-approved endothelin receptor antagonists, including bosentan, ambrisentan, and macitentan.

Bosentan

Bosentan is an oral active dual ET_A/ET_B receptors antagonist that received FDA approval in 2001. Bosentan was approved for the treatment of PAH (idiopathic, CTD-APAH and Eisenmenger syndrome) in patients of WHO FC II—IV to improve exercise ability, functional class, hemodynamics, and to decrease clinical worsening.[56,59—61]

COMPASS-2 was a long term, prospective, double-blind, event-driven trial evaluating 334 PAH patients who were symptomatic on at least 3 months of stable dose sildenafil and were randomized to receive placebo or bosentan. The study did not demonstrate adding bosentan to stable sildenafil therapy was superior to sildenafil monotherapy in delaying the time to first morbidity/mortality event, defined as all-cause death, hospitalization for PAH worsening or intravenous prostanoid initiation, atrial septostomy, lung transplant, or PAH worsening (HR = 0.83; 95% CI 0.58 to 1.19; p = 0.2508).[62] However, on exploratory secondary analysis, bosentan and sildenafil combination therapy improved 6MWD 21.8m (95% CI + 5.9—37.8 m; p = 0.0106) at 16 weeks. There were several limitations of the COMPASS-2 trial and the results must be interpreted with caution.[62] Bosentan is available and approved for the treatment of IPAH and CHD with Eisenmenger syndrome patients in Taiwan.

Ambrisentan

Ambrisentan is a selective ET_A receptor antagonist that received FDA approval in 2007 for patients with PAH WHO FC II—III. According to the clinical trials, ambrisentan led to improved exercise capacity, symptoms, WHO FC, hemodynamics and time to clinical worsening of patients with IPAH and PAH associated with CTD, anorexigen and HIV infection.[63,64] The AMBITION (Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects with PAH) trial was a multicenter, double-blind, phase 3 trial of 500 treatment-naïve WHO FC II and III PAH patients, randomly assigned to receive monotherapy with tadalafil or ambrisentan or both tadalafil and ambrisentan to show dual combination is better than monotherapy.[65] Initial combination with tadalafil and ambrisentan showed marked improvement in a primary composite endpoint of death, hospitalization for worsening PAH, disease progression, and unsatisfactory long-term clinical response in comparison to ambrisentan and tadalafil monotherapy. Ambrisentan is available but only approved for the treatment of IPAH in Taiwan.

Macitentan

Macitentan is the newest dual ERA and approved by FDA in 2013 for PAH patients with FC II and III symptoms. Macitentan has been evaluated in a long-term, event-driven SERAPHIN (Study with an Endothelin Receptor Antagonist in PAH to Improve Clinical Outcomes) study.[58] The primary endpoint was the time from the initiation of treatment to the first occurrence of a composite endpoint of death, worsening PAH, atrial septostomy, lung transplantation, initiation of treatment with parenteral prostanoids or death. Macitentan significantly reduced this composite endpoint of morbidity and mortality, and reduced secondary endpoints at 6 months (Functional class and exercise capacity) among patients with PAH. Benefits were shown both for patients who had not received treatment previously and for those receiving additional therapy for PAH. Macitentan also significantly reduced risk of all-cause hospitalization and PAH-related hospitalization[66] and improved quality of life[67] in the SERAPHIN study. Macitentan was also shown to reduce disease progression in the treatment-naïve cohort of SERAPHIN in both incident (diagnosed <6 months) and prevalent (>6 months) patients taking macitentan.[68] Macitentan is available and approved for the treatment of IPAH and WHO Group I PAH in Taiwan.

Soluble guanylate cyclase (SGC) stimulator

Riociguat

The first 'sGC stimulator', YC-1, was discovered by Taiwanese researchers in the mid-1990s.[69,70] Riociguat is the first sGC stimulator approved for use in PAH or CTEPH. Riociguat directly stimulates the native sGC while also increasing the sensitivity to low levels of nitrogen oxide (NO).[71,72] It is a new agent for the treatment of PAH and CTEPH.[71,72] The Phase III PATENT study focusing on patients with PAH revealed a statistically significant improvement of 36 meters in the 6MWD ($p < 0.0001$) after 12 weeks in the group treated with riociguat compared with placebo.[71] In another Phase III CHEST study, patients with non-operable CTEPH or persistent/recurrent PH after PEA presented with a mean increase of 39 meters in the 6MWD ($P < 0.001$) and an improvement of PVR ($P < 0.001$) post treatment with riociguat for 16 weeks.[72] In the sub-group analysis of PATENT study, riociguat was well tolerated and associated with positive trends in 6MWD in patients with PAH-CTD and PAH-CHD.[73,74] Riociguat did not show any effect on PAP in patients with left heart disease induced PH compared to placebo.[75] Notably, the combination of riociguat and PDE-5 inhibitor is contraindicated due to hypotension.[76] Nevertheless, according to the results of RESPITE study in PAH

patients not responding adequately to previous PDE-5i, treatment with riociguat led to improvements in 6MWD, NT-proBNP levels, and WHO FC.[77] Collectively, riociguat has been approved by FDA in 2013 and is available and also approved for the treatment of IPAH and persistent/recurrent and inoperable CTEPH in Taiwan.

PAH treatment algorithm (Table 8) (Fig. 2)

Combination therapy and goal-orientated therapy

The term combination therapy describes the simultaneous use of more than one PAH-specific class of drugs, e.g. ERAs, PDE-5 inhibitors, prostanoids, sGC stimulator and investigational therapies. Combination treatment causes a synergism between administered drugs, increasing the effectiveness of the treatment and allowing dose reductions of the individual agents with a subsequent lower risk of toxicity. As the field of PAH progresses, combination therapy has become the standard of care in many PAH centers. Numerous case reports have suggested that various drug combinations appear to be safe and effective.[39,60,78–84] The use of combination therapy according to predefined treatment goals proved to be better in all objective outcomes compared with a historical control group from the authors' own practice.[80]

Concomitant administration of drugs may cause drug–drug interactions, compromising efficacy or increasing side effects, with a negative influence on disease progression. For example, a pharmacokinetic interaction exists between bosentan and sildenafil, acting as inducers and inhibitors of CYP3A4, respectively. The co-administration of both substances results in a decline of sildenafil plasma levels and in an increase in bosentan plasma levels.[85] So far there is no indication that these interactions are associated with decreased safety,[86] but the issue of whether the clinical efficacy of sildenafil is significantly reduced is still under debate. A pharmacokinetic interaction is also known with tadalafil and bosentan.[87] The PHIRST study's substudy of subjects on background bosentan demonstrated clinical improvements despite this pharmacokinetic interaction. Other drug–drug interactions are listed on Table 9 and should be taken into consideration.

There are many open questions regarding combination therapy, including the selection of combination medications, when to switch and when to combine. Goal-orientated strategies may provide predefined, structure, and reproducible ways for clinicians to assess response to treatment. Goal-orientated therapy is becoming a standardized treatment strategy, but the selection of goals needs refinement to correlate closely with clinical outcome. Sequential combination therapy is mostly preferred at present time. However, there are more and more evidences supporting initial combination therapy in recent years. The first initial combination therapy RCTs started with the BREATHE-2 study, which failed to demonstrate any significant difference between patients treated initially with the combination epoprostenol and bosentan as compared with epoprostenol alone.[60] A pilot study on initial triple combination in 19 severe PAH patients (WHO FC III and IV) provided preliminary evidence of the long-term benefits of upfront triple combination therapy in patients with severe PAH.[88] A recent multicenter, multinational, blinded, placebo-controlled trial compared first-line monotherapy with tadalafil or ambrisentan with upfront combination therapy with tadalafil and ambrisentan in de novo WHO FC II and III PAH patients. The results revealed a 50% reduction in risk for clinical failure events in the combination group versus pooled monotherapy group. In addition, improvements were observed in exercise capacity, rate of satisfactory clinical response and NT-proBNP plasma levels.[65] According to these results, a higher grade of recommendation was given to this initial combination with

Table 8 Recommendations for initial monotherapy for PAH.

Drugs			WHO Functional Class Level					
			II		III		IV	
Calcium channel blocker			I	C	I	C	–	–
Endothelium receptor antagonists	Ambrisentan		I	A	I	A	IIb	C
	Bosentan		I	A	I	A	IIb	C
	Macitentan		I	A	I	A	IIb	C
Phosphodiesterase type 5 inhibitors	Sildenafil		I	A	I	A	IIb	C
	Tadalafil[a]		I	A	I	A	IIb	C
Soluble guanylate cyclase stimulators	Riociguat		I	A	I	A	IIb	C
Prostacyclin analogues	Epoprostenol	I.V.	–	–	I	A	I	A
	Iloprost	IH	–	–	I	B	IIb	C
		I.V.[a]	–	–	IIa	C	IIb	C
	Treprostinil	SC	–	–	I	B	IIb	C
		IH	–	–	I	B	IIb	C
		I.V.	–	–	IIa	C	IIb	C
		Oral[a]	–	–	IIb	B	–	–
	Beraprost[a]		–	–	IIb	B	–	–
IP receptor agonists	Selexipag		I	B	I	B	–	–

I.V.: intravenous, IH: inhaled, SC: subcutaneous.
[a] Beraprost, tadalafil, I.V. iloprost and oral treprostinil are not available for PAH in Taiwan.

ambrisentan plus tadalafil. Initial combination therapy was also recommended by 2015 ESC/ERS PH guidelines, especially for intermediate to high risk patients.[6] Initial combination therapy including IV prostacyclin was recommended for WHO FC IV patients (Table 10).[60,65,88,89] In case of inadequate clinical response to initial combination therapy or initial monotherapy, sequential double or triple combination therapy is recommended according to Table 11.[53,58,71,84,90–92] The combination of riociguat and PDE-5i is contraindicated.[6]

Pulmonary arterial hypertension associated with congenital heart disease

PAH is found in about 5–10% of adults with CHD.[93] Systemic-to-pulmonary shunts due to the congenital cardiac defects led to increased PVR. If an early correction cannot be made, a wide range of cardiac defects can lead to PAH, including ventricular septal defects, atrial septal defects, atrioventricular septal defects, and patent ductus arteriosus.[93] Eisenmenger syndrome, PAH with reversed central shunt, represents the most severe form. Patients of PAH associated with CHD (PAH-CHD) can be classified clinically into four (4) subgroups (Table 12): Eisenmenger syndrome, PAH associated with systemic-to-pulmonary shunts, PAH associated with small defects, and PAH after cardiac defect correction.[6,94] Two additional types of pulmonary vascular disease, segmental pulmonary arterial hypertension and raised PVR in Fontan patients, should be included in the spectrum of PAH-CHD due to their distinct features and clinical outcomes (Table 12).[95] Furthermore, to better characterize each individual patient, an anatomical-pathophysiological classification[6,94] can be applied to describe the type and severity of the defects, direction of shunt, associated abnormalities and the repair status (Table 13). For pediatric patients, pulmonary vascular disease is characterized by complex heterogeneity.[96] The 2011 Panama classification further categorize pediatric PH into 10 subgroups.[97]

Table 9 Drug–Drug interaction of pulmonary hypertension medication.

Class/Drug	CYP interaction	Other interaction
PDE5 inhibitor		
Sildenafil	CYP3A, CYP2C9	Amlodipine Doxazosin Nitrates
Tadalafil	CYP3A	Alpha-blockers
sGC stimulator		
Riociguat	CYP3A	Nitrates Nitric oxide donors PDE-5 inhibitors Antacids
Endothelin Receptor Antagonists		
Ambrisentan	CYP2C9, CYP3A4, CYP1A2	Cyclosporine
Bosentan	CYP2C9, CYP3A4, CYP2C19	Cyclosporine Glyburide Hormonal contraceptives
Macitentan	CYP3A4	Rifampin HIV medication
Prostanoids		
Epoprostenol	Not known	Diuretics Anti-hypertensives Vasodilators Anti-platelets Anticoagulants Digoxin
Iloprost	Not known	Anti-hypertensives Anticoagulants Platelet inhibitors Vasodilators
Treprostinil	CYP2C8	Diuretics Anti-hypertensives Vasodilators Anticoagulants Gemfibrozil Rifampin
Selective Prostacyclin Receptor Agonist		
Selexipag	CYP2C8, CYP2C9, CYP3A4	

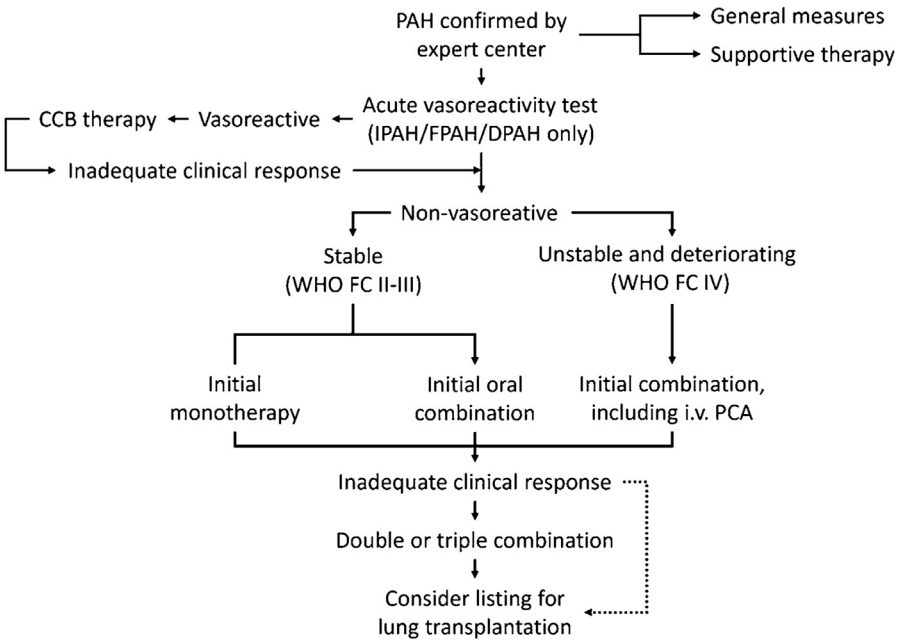

Figure 2 Treatment algorithm for pulmonary arterial hypertension (PAH). CCB = calcium channel blocker; IPAH = idiopathic pulmonary arterial hypertension; FPAH = familiar idiopathic pulmonary arterial hypertension; DPAH = drugs and toxins related pulmonary arterial hypertension; WHO FC: World Health Organization functional class; IV: intravenous; PCA = prostacyclin analogue.

Table 10 Recommendations for efficacy of initial drug combination therapy for pulmonary arterial hypertension (WHO Group 1) according to World Health Organization functional class.

Drugs	WHO Functional Class Level					
	II		III		IV	
Ambrisentan + tadalafil[65]	I	B	I	B	IIb	C
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C
Bosentan + sildenafil + I.V. epoprostenol[88]	—	—	IIa	C	IIb	C
Bosentan + I.V. epoprostenol[60,89]	—	—	IIa	C	IIa	C
Other ERA or PDE-5i + SC treprostinil			IIb	C	IIb	C
Other ERA or PDE-5i + other I.V. prostacyclin analogues			IIb	C	IIb	C
Riociguat + PDE-5i	III	B	III	B	III	B

Modified from 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.
ERA = endothelium receptor antagonist; PDE-5i = Phosphodiesterase type 5 inhibitor; I.V. = intravenous; SC = subcutaneous.

Table 11 Recommendations for efficacy of sequential drug combination therapy for pulmonary arterial hypertension (WHO Group 1) according to World Health Organization functional class.

Drugs	WHO Functional Class Level					
	II		III		IV	
Macitentan added to sildenafil[58]	I	B	I	B	IIa	C
Riociguat added to bosentan[71]	I	B	I	B	IIa	C
Selexipag added to ERA and/or PDE-5i[53,91]	I	B	I	B	IIa	C
Sildenafil added to epoprostenol (I.V.)[84]	—	—	I	B	IIa	B
Treprostinil (IH) added to sildenafil or bosentan[90]	IIa	B	IIa	B	IIa	C
Tadalafil added to bosentan[92]	IIa	C	IIa	C	IIa	C
Bosentan added to epoprostenol (I.V.)	—	—	IIb	C	IIb	C
Other double combinations	IIb	C	IIb	C	IIb	C
Other triple combinations	IIb	C	IIb	C	IIb	C
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B

Modified from 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.
ERA = endothelium receptor antagonist; PDE-5i = Phosphodiesterase type 5 inhibitor; I.V. = intravenous; SC = subcutaneous.

Table 12 Clinical classification of pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD).

A. Eisenmenger syndrome	1.Reversed (pulmonary-to-systemic) or bidirectional shunt. 2.Cyanosis, erythrocytosis, and multiple organ involvement are present
B. Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts	1. Moderate to large defects with increased PVR (mild to moderate) 2. No cyanosis is present at rest.
C. Pulmonary arterial hypertension with small defects	1.Small defects (usually ventricular septal defects $<$ 1 cm and atrial septal defects $<$ 2 cm of effective diameter assessed by echocardiography) 2. The clinical picture is very similar to idiopathic PAH
D. Pulmonary arterial hypertension after corrective cardiac surgery	1.Congenital heart disease has been corrected but PAH is either still present immediately after surgery or has recurred several months or years after surgery 2. Absence of significant post-operative residual congenital lesions or defects that originate as sequelae to previous surgery.
*Additional types of pulmonary vascular disease related to CHD[95]	
Segmental Pulmonary arterial hypertension	In pulmonary atresia with multiple aortopulmonary collateral arteries, or right/left pulmonary artery stenosis in truncus arteriosus. Only part of the lung vasculature develops pulmonary vascular disease.
Raised PVR in Fontan patients	Patients with a previous Fontan-type operation can develop a rise in PVR, despite low pulmonary arterial pressures

Based on Taiwan's National Health Insurance Administration database between 1999 and 2011, PAH-CHD accounts for 11% of patients with a discharge diagnosis of pulmonary hypertension.[20] Patients with PAH-CHD were younger (mean age 27 years old) and had a better outcome (estimated survival rates at 1, 5, and 10 years were 95.3%, 91.64% and 87.09%) compared with patients with other etiologies of pulmonary hypertension.

Considering the four (4) different clinical groups of PAH-CHD (Table 12), data from a single-center cohort in Italy showed that patients with PAH after cardiac defect correction have a worse outcome than patients with Eisenmenger syndrome or those with systemic-to-pulmonary shunts.[98] These findings suggest careful evaluation of the operability before the shunt closure is extremely important.

Therapy

The treatment strategy comprises early surgical repair (or interventional therapy) of the shunt prior to the onset of pulmonary vascular disease, and the treatment of existing PAH. The only curative option for end-stage disease is heart-lung transplantation or lung transplantation in combination with repair of CHD. The issue of organ availability and the prolonged survival of patients of Eisenmenger syndrome make it difficult to determine optimal timing for transplantation.[99] Furthermore, the results of disease-targeting therapies are reassuring, with two (2) recent reports showing disease-targeting therapies offer better survival in Eisenmenger syndrome.[100,101]

Surgical (or interventional therapy) treatment

An early correction can prevent subsequent development of PAH among patients with systemic-to-pulmonary shunt. However, the patients who develop or have persistent PAH after cardiac defect correction have a worse prognosis than patients with unrepaired shunt.[98] Assessment of the operability, which is defined based on the likelihood of a favorable versus an unfavorable outcome, is crucial.[102,103] Traditionally, a baseline pulmonary vascular resistance index (PVRi) of $<$6 Wood units•m^2 with a pulmonary to systemic resistance ratio of $<$0.3 has been interpreted as indicative of favorable outcome following shunt closure, and a vasoreactivity test may be considered in patients with PVRi between 6 and 9 Wood units•m^2 and resistance ratio between 0.3 and 0.5 to see if at least 20% decrease of the value can be achieved.[104] In 2015 ESC/ERS guidelines, a modified threshold was proposed to define PVRi $<$ 4 Wood units•m^2 as "correctable", PVRi $>$ 8 Wood units•m^2 as "not correctable", and individualized evaluation in tertiary centers is suggested in patients with PVRi between 4 and 8 Wood units•m^2.[6]

Medical treatment

General measures and supportive therapies of PAH-CHD are mostly based on clinical experiences rather than evidence-based data, and follow similar principles to IPAH, including patient education, supplemental oxygen therapy, diuretic and digoxin treatment in RV failure, and correction of anemia and iron status.[6] Several issues on treatment; however, are distinct from IPAH. First, the use of calcium channel blockers (CCBs) should be avoided in patients with PAH-CHD,[105] because CCBs may decrease systemic arterial pressure and increase right-to-left shunting, leading to syncope and sudden death. Second, the use of anticoagulation is controversial, concerning the increased risk of hemoptysis.[106] Third, phlebotomy may be considered in patients of PAH-CHD if symptoms of hyperviscosity are present, usually when the hematocrit is $>$65%.[107]

With the advances in disease-targeting therapies, the outcomes of Eisenmenger syndrome has improved. Two of

Table 13 Anatomical-pathophysiological classification of congenital systemic-to-pulmonary shunts associated with pulmonary arterial hypertension (modified from Venice 2003).

1. Type
1.1 Simple pre-tricuspid shunts
1.1.1 Atrial septal defect (ASD)
1.1.1.1 Ostium secundum
1.1.1.2 Sinus venosus
1.1.1.3 Ostium primum
1.1.2 Total or partial unobstructed anomalous pulmonary venous return
1.2 Simple post-tricuspid shunts
1.2.1 Ventricular septal defect (VSD)
1.2.2 Patent ductus arteriosus
1.3 Combined shunts
Describe combination and define predominant defect
1.4 Complex congenital heart disease
1.4.1 Complete atrioventricular septal defect
1.4.2 Truncus arteriosus
1.4.3 Single ventricle physiology with unobstructed pulmonary blood flow
1.4.4 Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus
1.4.5 Other
2. Dimension (specify for each defect if more than one congenital heart defect exists)
2.1 Hemodynamic (specify Qp/Qs)
2.1.1 Restrictive (pressure gradient across the defect)
2.1.2 Non-restrictive
2.2 Anatomic (applied to adult patients)
2.2.1 Small to moderate (ASD $\leq$2.0 cm and VSD $\leq$1.0 cm)
2.2.2 Large (ASD$>$2.0 cm and VSD $>$1.0 cm)
3. Direction of shunt
3.1 Predominantly systemic-to-pulmonary
3.2 Predominantly pulmonary-to-systemic
3.3 Bidirectional
4. Associated cardiac and extracardiac abnormalities
5. Repair status
5.1 Unoperated
5.2 Palliated [specify type of operation(s), age at surgery]
5.3 Repaired [specify type of operation(s), age at surgery]

these agents, bosentan and sildenafil, are currently approved in Taiwan for patients with PAH-CHD.

1) Endothelin receptor antagonists: Bosentan has the strongest supporting dataset of all targeted therapies for CHD-PAH. The double-blind, placebo-controlled BREATHE-5 (Bosentan Randomized Trial of Endothelin Antagonist Therapy-5) study, the only such study in patients with Eisenmenger syndrome, demonstrated that bosentan was well tolerated and improved exercise capacity and hemodynamics without compromising transcutaneous oxygen saturation.[108] These findings were sustained in the open-label extension study.[109] Early experiences with ambrisentan and macitentan on PAH-CHD have been reported recently.[110,111]
2) Prostanoids: Several compounds and administration methods of prostacyclin (prostaglandin I2) analogues have been studied, such as intravenous epoprostenol,[32] subcutaneous treprostinil[42] and inhaled iloprost,[112] and demonstrated improved functional status and hemodynamic parameters.
3) Phosphodiesterase type 5 inhibitors (PDE-5i): Sildenafil[113] and tadalafil[114] have been shown to improve exercise capacity and hemodynamics in patients with Eisenmenger syndrome.
4) Soluble guanylate cyclase (sGC) stimulator: Riociguat has been shown to be well tolerated in patients with PAH-CHD and to improve clinical outcomes including 6MWD, PVR, functional class and NT-proBNP level in a subgroup analysis of PATENT study.[74]
5) Combination therapy: In one randomized study, adding sildenafil to bosentan in Eisenmenger syndrome did not significantly improve walking distance but did increase O_2 saturation at rest.[115] Despite the scarce evidence supporting the use of combination therapy in Eisenmenger syndrome, recently published cohort studies on Eisenmenger syndrome reported around 30—50% of these patients were receiving two or more disease targeting therapies.[100,101]

The strategy of "treat and repair", which means treating the inoperable patients with disease targeting therapies to

reduce PVR and to increase their chances of successful defect closure, is under study.[116] More data are needed to determine the long-term benefits and risks of this strategy.[117]

Pulmonary arterial hypertension associated with connective tissue disease

PAH is a well-known complication of CTDs, such as SSc, SLE, rheumatoid arthritis, MCTD, dermatomyositis, and Sjogren syndrome.[17,118] Previous experience found that ankylosing spondylitis rarely develops PH. SSc represents the main CTD associated with PAH in Europe and the USA.[45] However, SLE is more common in Asia.[119,120]

Diagnosis

Clinical presentations of CTD associated with PAH are very similar to IPAH, CTD may be confirmed by immunological screening studies. Thus, the diagnosis of CTDs usually will not be missed if we follow the proposed diagnostic algorithm, which can be obtained from previous section of this guideline (Fig. 1). There are a few specific rheumatologic markers that should be studied during diagnosis of PH in CTDs.

Systemic sclerosis (SSc)

From previous reports, the prevalence of PAH in patients with SSc, confirmed by right heart catheterization, ranged from 7.9% to 12%.[118,121] In these patients, PAH may be a result of an isolated pulmonary arteriopathy, interstitial lung fibrosis, and/or pulmonary venous hypertension due to venous fibrosis or left heart disease. It is important to determine which mechanism is operative because current specific PAH medications are only reimbursed in Group 1 PAH (IPAH) in Taiwan. Pulmonary involvement of SSc patients can be detected by chest x-ray, HRCT, and DLco studies. Echocardiography and RHC are useful in confirming the PAH and evaluating the left ventricular systolic and diastolic functions.

Systemic lupus erythematosus

Cardiac involvements in SLE include pericardial effusion, pericarditis, endocarditis, myocarditis, coronary artery disease, and cardiac valvular involvement.

Echocardiography and cardiac catheterization are useful in evaluating and defining the cardiac involvement in patients with SLE.

Pericardial effusion may be a sign of serositis due to SLE[122] or a sign of advanced PAH with right heart failure.[123] Since the presence of pericardial effusion in SLE patients indicates the lupus activation phenomenon, it demands multidisciplinary consultation to ascertain the cause of pericardial effusion and to treat the underlying disease.

Therapy

Treatment of patients with CTD-associated PAH is similar to the treatment algorithm for IPAH.[17] Sildenafil and macitentan had been approved for the treatment of CTD-associated PAH in Taiwan. Several important issues should be mentioned about treatment. First, retrospective studies concluded that a substantial portion of patients with SLE or MCTD may benefit from concomitant immunosuppressive therapy.[124] Second, therapy in patients with CTD-associated PAH is more complex than that of IPAH. In CTD-associated PAH patients, the long-term favorable response to CCB treatment is reported in $<1\%$ of cases.[105] Third, in SSc, the long-term risk to benefit ratio of oral anticoagulation is less favorable in SSc patients compared to the IPAH patients because of an increased risk of bleeding in SSc patients.[125]

Follow-up

The long-term survival of CTD-PAH patients, especially SSc-PAH patients, is lower than that of IPAH patients.[120,126] When CTD-PAH patients received PAH-specific medications, the one-year survival rates of SLE, MCTD and SSc with PAH patients were 94%, 88% and 82%, respectively.[126] Thus, early diagnosis and early management is important in this specific population.

Chronic thromboembolic pulmonary hypertension (CTEPH)

Epidemiology

As it is challenging to diagnose CTEPH, limited epidemiological studies have been reported. Based on recent studies, the incidence of CTEPH after an acute pulmonary embolism (PE) is 0.1—9.1% in Europe and the USA, and 10% in Japan. The estimated annual incidence of CTEPH is

Table 14 Chronic thromboembolic pulmonary hypertension prediction score.

Unprovoked PE	+6 points
Known hypothyroidism	+3 points
Symptom onset >2 weeks before PE diagnosis	+3 points
RV dysfunction on CT or echocardiography	+2 points
Known diabetes mellitus	−3 points
Thrombolytic therapy or embolectomy for the acute PE event	−3 points
• Low risk −6 to 6 points	
• High risk >6 points	

RV: right ventricular, CT: computed tomography.

Table 15 Chronic thromboembolic pulmonary hypertension rule out criteria.

1. ECG criteria (absence of signs of RV overload)
   - Right axis
   - rSR' or RSr' in lead V1
   - R:S > 1, R > 0.5 mV in lead V1
2. Normal NT-proBNP

Table 16 Comparison of computed tomography images between acute pulmonary embolism vs. chronic thromboembolic pulmonary hypertension.

Findings	Acute pulmonary embolism	Chronic thromboembolic pulmonary hypertension
Total occlusion	Vessel expanded	Vessel narrowing/ amputation
Partially occlusive filling defects	Acute angles with the vessel lumen; polo mint sign; railway track sign	Obtuse angles with the vessel lumen; webs; bands; intimal irregularities; laminated thrombus
Systemic findings	RV dilation	RV dilation and hypertrophy; dilation of the central pulmonary arteries; collateral vessels, including bronchial artery dilation
Lung parenchymal findings	Triangular subpleural consolidation; ground-glass opacity with fine reticular changes	Mosaic attenuation; fibrotic bands, which could be resolved infarcts, subpleural scar/ cavitation; focal pleural thickening

30—50 per million population per year in Europe and the USA, and 19.4 per million population per year in Japan.[127] Different genetic backgrounds, population demographics and lifestyles may account for the discrepancy among Japan, Europe, and the USA.

Risk factors

Apart from pulmonary embolism, other risk factors associated with CTEPH include deep vein thrombosis, thyroid replacement therapy, malignancy, anti-phospholipid antibodies/lupus anticoagulant, Factor VIII, von Willebrand factor, non-O blood group, ventriculoatrial shunt, cardiac pacemaker, splenectomy, inflammatory bowel disease, chronic inflammatory disorders, infection with Staphylococcal species, and aging.[128—130]

Screening

Owing to the low incidence of CTEPH after PE and multifactorial mechanism of CTEPH, routine screening for CTEPH in asymptomatic survivors of PE is not recommended by 2015 ESC/ERS.[6] Recently, CTEPH prediction score (Table 14)[131] was proposed and it might be used with rule-out criteria (Table 15).[132,133] An ongoing trial may give us more information whether the screening algorithm is accurate and cost effective.

Diagnosis

If CTEPH is suspected according to clinical assessments and basic examinations, TTE is recommended as the first-line diagnostic modality. Nevertheless, 10—31% of cases may be missed by TTE alone. Previous retrospective studies[134,135] and a prospective cohort study[136] showed CPET and V/Q scan could serve as complementary tools in diagnosing CTEPH by using "4-parameter-CPET (4-P-CPET) score".[134] Although further clinical trials are warranted, other tools may be considered for symptomatic patients with normal echocardiography.

For the diagnosis of CTEPH, V/Q scan and newer generation CTPA may both be accurate methods.[137] Several findings on CT can help to differentiate acute PE from CTEPH (Table 16).[138,139] However, some pitfalls should be noted. First, mismatched defect, mosaic pattern, and bronchial hypervascularization could be seen not only in patients with CTEPH but also other conditions.[129,138,140] Second, subsegmental disease is more difficult to be detected by CTPA. For pulmonary vascular interventions distal to subsegmental arteries, cone-beam CT or electrocardiogram-gated area detector CT may be helpful.[141—144]

Dual-energy CT (DECT) is a promising tool that permits a simultaneously combined functional and morphological analysis of the lung. Excellent correlation has been shown between perfusion maps and mismatched defect on V/Q scan.[145] By using automated quantification of perfused blood volume (PBV), pulmonary hemodynamics, especially mPAP and PVR, could be estimated.[146,147] Similar to DECT, lung subtraction iodine mapping (LSIM) CT may offer "one-stop" assessment without extra radiation exposure.[148] However, further validation of LSIM is needed due to limited data.

Magnetic resonance (MR) imaging has significant advances in many techniques recently, such as cine techniques, tissue feature tracking, contrast enhanced MR angiography, phase-contrast MR imaging, 4D phase contrast sequences, and lung perfusion MR imaging. Although MR imaging is less accurate at the subsegmental level,[149] MR imaging can provide anatomical and hemodynamic information in single examination without radiation exposure.

Apart from differential diagnosis,[129] positron emission tomography may be also useful for monitoring right ventricle metabolic functions in severe pulmonary hypertension.[150]

An algorithm for CTEPH diagnosis is shown in Fig. 3.

Vasoreactivity testing

If CTEPH is highly suspected by imaging study, RHC must be performed for hemodynamic confirmation. Although vasoreactivity testing is not recommended in patients with CTEPH by 2015 ESC/ERS guideline,[6] a decrease in mPAP to vasoreactivity testing is associated with better survival.[151—153]

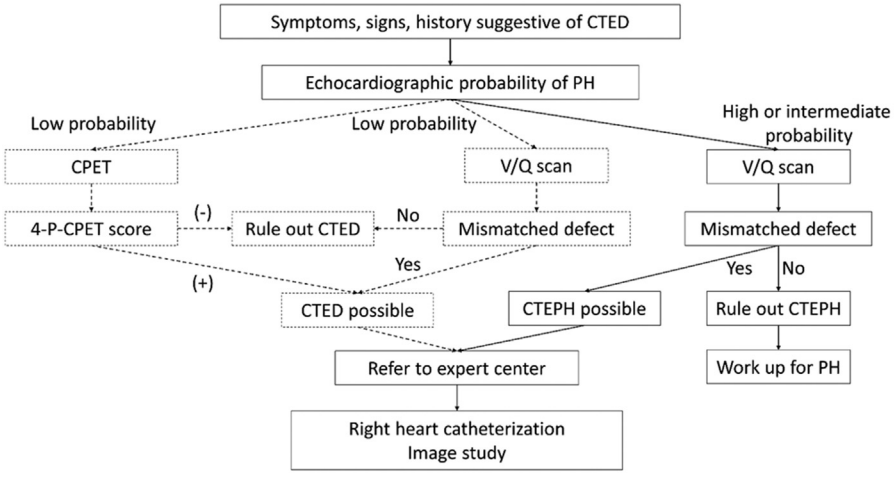

Figure 3 Diagnostic algorithm for chronic thromboembolic pulmonary hypertension (CTEPH) or chronic thromboembolic disease (CTED). Dash-lines or boxes indicate the diagnostic algorithm for CTED, and solid ones for CTEPH. CTED = chronic thromboembolic disease; PH = pulmonary hypertension; CPET = cardiopulmonary exercise testing; V/Q = ventilation-perfusion; CTEPH = chronic thromboembolic pulmonary hypertension.

Treatment

Surgical

CTEPH is a potential curable disease and PEA is the first-line treatment.[6] Hemodynamics, functional parameter, and quality of life improved in most patients after PEA.[154–157] After PEA, up to one third of patients after PEA may have persistent pulmonary hypertension because of incomplete removal of thrombi or concomitant distal pulmonary vasculopathy. Recurrent pulmonary hypertension after PEA may also occur due to poor anticoagulation therapy. However, the definition of persistent or recurrent PH is not well defined. A recent cohort study suggested that mPAP $\geq$38 mmHg and PVR $\geq$425 dynes•s^{-1}•cm^{-5} are correlated with worse long-term survival in patients undergoing PEA.[158] This level of mPAP is much higher than the definition of pulmonary hypertension. On the other hand, some studies that enrolled symptomatic patients with normal mPAP, a condition known as chronic thromboembolic disease (CTED), showed significant improvement in terms of hemodynamics, functional status, and quality of life after PEA.[135,159] However, with limited evidence, PEA is only confined to this patient group with symptoms.

Interventional

Balloon pulmonary angioplasty (BPA) is an emerging treatment for inoperable,[6] persistent, or recurrent CTEPH.[160] Initially, high complication rates raised the concern about the safety of BPA.[161] Growing body of experience has demonstrated "refined BPA" is able to improve, though not immediately, hemodynamics, functional parameters, and quality of life,[162] with low complication rates and post-procedural mortality.[163] Although there is no consensus about the "refined BPA", following strategies may be applied - starting with soft device,[164] image-guided interventions,[144,165] stepwise balloon size-up approach,[144] angioplasty guided by "Pulmonary Edema Predictive Scoring Index (PEPSI)",[166] and pressure-wire-guided technique.[167] With improved outcomes and safety of the procedure, BPA can be considered for symptomatic CTED patients. One study demonstrated further improvement in symptoms, exercise capacity and hemodynamics by extensive revascularization beyond hemodynamic normalization.[168] A meta-analysis reported the improvement in mPAP and PVR were significantly greater for BPA than targeted medical therapy.[169] However, BPA for CTEPH still lacks large randomized control trials and long-term results.

Apart from BPA, some techniques used for treatment of other causes of pulmonary hypertension have been studied in patients with CTEPH, such as atrial septostomy[170] and pulmonary artery denervation.[171] Further studies to confirm the results are required.

Medical

Diuretic agent and oxygen supplement may be considered when patients with CTEPH suffered from acute decompensated heart failure and hypoxia. Although there are no

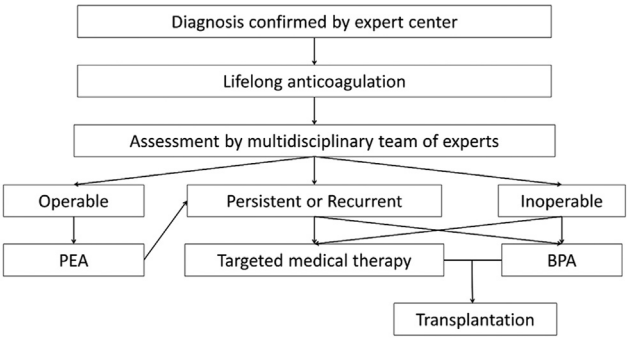

Figure 4 Treatment algorithm for chronic thromboembolic pulmonary hypertension. The operability may be different according to the facility and experience of different centers. Some "inoperable" patients may be operable in high PEA volume centers.[180] For those with inoperable, persistent or recurrent CTEPH, either medical therapy or BPA can be served as the treatment of choice. PEA = pulmonary endarterectomy; BPA = balloon pulmonary angioplasty.

Table 17 Recommendations for chronic thromboembolic pulmonary hypertension.

Recommendations	Class	Level
Routine screening asymptomatic survivors of PE for CTEPH is not recommended.	III	C
The possibility of CTEPH should be evaluated for symptomatic survivors of PE.	IIa	C
Patients with CTEPH should be treated by a multidisciplinary team of experts.	I	C
PEA for patients with CTEPH is recommended to perform in deep hypothermia circulatory arrest.	I	C
BPA may be considered in symptomatic patients with inoperable, persistent, or recurrent CTEPH.	IIa	B
Lifelong anticoagulation is recommended in patients with CTEPH.	I	C
Riociguat and macitentan are recommended in symptomatic patients with inoperable, persistent, or recurrent CTEPH.	I	B
Targeted medical therapies approved for PAH may be considered in symptomatic patients with inoperable CTEPH.	IIb	B

PE = pulmonary embolism; CTEPH = Chronic thromboembolic pulmonary hypertension; PEA = pulmonary endarterectomy; BPA = Balloon pulmonary angioplasty.

randomized studies, lifelong anticoagulation therapy is strongly recommended by 2015 ESC/ERS guideline[6] irrespective of pulmonary arterial pressure. Non-vitamin K oral anticoagulants have demonstrated superior safety and non-inferior efficacy in venous thromboembolism with some experience in CTEPH, but clinical studies in patients with CTEPH are lacking.[156]

Among all targeted therapies, riociguat, a soluble guanylate cyclase stimulator, is still the only approved medication for CTEPH. Randomized controlled CHEST-1 study,[72] extension CHEST-2 study,[172] and long term extension study have shown sustained benefits in exercise and functional capacity for up to 4 years.[173] Another randomized controlled trial, MERIT-1, treated CTEPH patients with macitentan reported significantly improved PVR and exercise capacity.[174] Other randomized trials have failed to show significant improvement in patients treated with bosentan, sildenafil, intravenous epoprostenol, subcutaneous treprostinil, or inhaled iloprost.[175,176] Riociguat is approved for the treatment of persistent/recurrent and inoperable CTEPH in Taiwan.

Recently, in MERIT-1 study, a multicenter, phase 2, randomized, double-blind, placebo-controlled study, macitentan significantly improved PVR in patients with inoperable CTEPH. In this patients, 61% received background therapy, including PDE-5i and/or oral/inhaled prostanoids.[174,177] In another study, initial combination therapy with ERA and PDE-5i was shown to improves exercise capacity and hemodynamics in patients with inoperable CTEPH.[178]

However, medical therapy should be considered only for patients with inoperable, persistent, or recurrent CTEPH rather than as an alternative therapy to potentially curative PEA. Operable patients should proceed to PEA without delay since bridging therapy with targeted therapies before PEA yielded worse surgical outcomes.[179] Although riociguat as a bridge to BPA may potentially enhance procedural safety, the results had been reported only in a couple of conferences.

An algorithm is shown in Fig. 4. The recommendations for CTEPH are summarized in Table 17.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

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