Clinical Practice Guideline

Executive Summary Thai Pulmonary Hypertension Guidelines 2020

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In 2011, the Heart Association of Thailand (HAT) approved the first Thai guideline for the diagnosis and management of patients with pulmonary hypertension (PH). Since then, significant changes have occurred in the diagnosis and management of patients with PH, such as risk assessment and new strategies for combination therapies based on the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension guidelines. The most recently updated definition of PH was from the Sixth World Symposium on Pulmonary Hypertension in 2018. Hence, HAT has revised the Thai guidelines for the diagnosis and management of patients with PH, which was approved by the Royal College of Physicians of Thailand in 2019. These guidelines are intended for use by 1) general practitioners for preliminary diagnoses and referral to a PH referral center and 2) specialist physicians such as cardiologists and pulmonologists, to collaborate in the caring process and diagnosis and management, including the use of Pulmonary artery hypertension (PAH)-specific drugs.

The guidelines were written in Thai language to be easily understood and approved by HAT and the Royal College of Physicians of Thailand in 2019. The current executive summary is aimed to highlight important details of the 2020 Thai Pulmonary Hypertension Guidelines for a broader distribution. This updated version of the executive summary of the guidelines is aimed to achieve three objectives, 1) early diagnosis by using the algorithm, including pathophysiology into one of five PH groups, 2) risk assessment for PAH patients into low, intermediate, or high risk, and 3) sequential combination therapy as indicated by the risk assessment for PAH-specific drugs to maintain PAH patients within the low-risk group as much as possible to improve their long-term survival.

Keywords: Guideline, Pulmonary hypertension, Diagnosis, Management

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Development of the Guidelines

These guidelines follow the template of the Appraisal of Guidelines for Research and Evaluation II (AGREE II)[1]. The review process includes a summary of the most up-to-date and important local and international publications by experts in each specialty. Eight official meetings were held in 2018 and 2019. At each meeting, representatives of the subspecialties were asked to present their views on the revised recommendations and a consensus was reached among all the subspecialties. The quality of evidence was graded into levels from one to four and the strength of the recommendations were categorized into five levels from high confidence and should be done (++), to potentially harmful with excess morbidity and mortality (– –). These recommendations are not to be taken as regulations for conduct, and users may act differently from the

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guidelines in situations where facilities are restricted or when resources are limited, or for other justifiable reasons, based on reasonable judgment, academic principles, and ethics.

Quality of evidence and strength of recommendations (adapted from the Royal College of Physicians of Thailand guidelines)

Quality of evidence

Level 1: Evidence obtained from systematic review of well-controlled randomized clinical trials or well-designed randomized clinical trials.

Level 2: Evidence obtained from systematic review of controlled or designed clinical trials or other research models that clearly demonstrate significant benefits or risks.

Level 3: Evidence obtained from descriptive or cohort studies.

Level 4: Evidence obtained from a consensus of a panel of experts or other evidence.

Strength of recommendations

++, High confidence of the recommendation. Such action is worthwhile and should be done.

+, Medium level of confidence of the recommendation and such action may be worthwhile.

+/–, Such action may be considered though its usefulness is not well established.

–, Such actions are not recommended, indicated, or beneficial.

– –, Such actions are potentially harmful and associated with excess morbidity or mortality.

1. Definition and classification of pulmonary hypertension

The signs and symptoms of patients with pulmonary hypertension (PH) are often vague and non-specific. Patients may experience tiredness, fatigue, chest pain, dizziness, and syncope without specific etiology. Heaving of right ventricle (RV) with cardiomegaly and loud P2 on auscultation can also be found on cardiac examination. Signs of right-sided heart failure such as hepatomegaly and engorged neck vein are often difficult to detect. Although 90% of idiopathic pulmonary artery hypertension (IPAH) patients have abnormal chest X-ray (CXR) with enlargement of pulmonary artery trunk, right atrium, or RV[2,3], patients in the early stage of PAH may still have a normal CXR. We recommend screening patients with CXR (3, ++) and electrocardiography (ECG) (3, ++), and consider other blood tests such as complete blood count (CBC), creatinine (Cr), liver function test (LFT), anti-human immune deficiency virus (HIV) according to specific history or physical signs, and antinuclear antibody (ANA) if autoimmune disease is suggested (3, ++). In the event of the patient having severe symptoms, appropriate management should be undertaken rather than waiting for an established diagnosis of pulmonary artery hypertension (PAH) such as treatment of heart failure or shock before the patient is sent to a PH referral center.

The current Thai PH guidelines use the same definition of PAH as in the Sixth World Symposium on Pulmonary Hypertension 2018[4-7], where the mean pulmonary arterial pressure (mPAP) at rest is greater than 20 millimeter of mercury (mmHg), which was reduced from the previous guideline of 25 mmHg or greater, pulmonary arterial wedge pressure (PAWP) of 15 mmHg or less, and pulmonary vascular resistance (PVR) of 3 wood unit (WU) or more, which can be diagnosed by right heart catheterization (RHC) (++, 1) in pediatric and adult populations. While this updated criterion alone cannot be used to consider PAH-specific drug therapy, it is useful for monitoring at-risk patients (1, ++). The current guidelines are also aimed to increase the efficiency of diagnosis and initiate specific treatments for primarily PAH or Group 1 patients[4-6,8].

The following classification is based on clinical features of PH, which responds to each treatment strategy according to the pathophysiology[6,7]:

Group 1, PAH (all etiologies)

Group 2, PH due to left heart disease

Group 3, PH due to lung disease or hypoxemia or both

Group 4, Chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions

Group 5, PH with unclear or multifactorial mechanisms or both

The following flow chart (Figure 1) shows the diagnosis algorithm for PH and echocardiography (also see Table 1, 2).

1. The first step is to establish whether the patient has PH based on echocardiography parameters used to differentiate the likelihood of PH and "PH signs" from echocardiography[5]. Echocardiography can also differentiate structural heart lesions such as congenital heart disease with left to right shunt or valvular heart disease. Group 2 (PH) due to left heart systolic or diastolic dysfunction can also be diagnosed from the echocardiography examination.
2. Investigations such as the pulmonary function

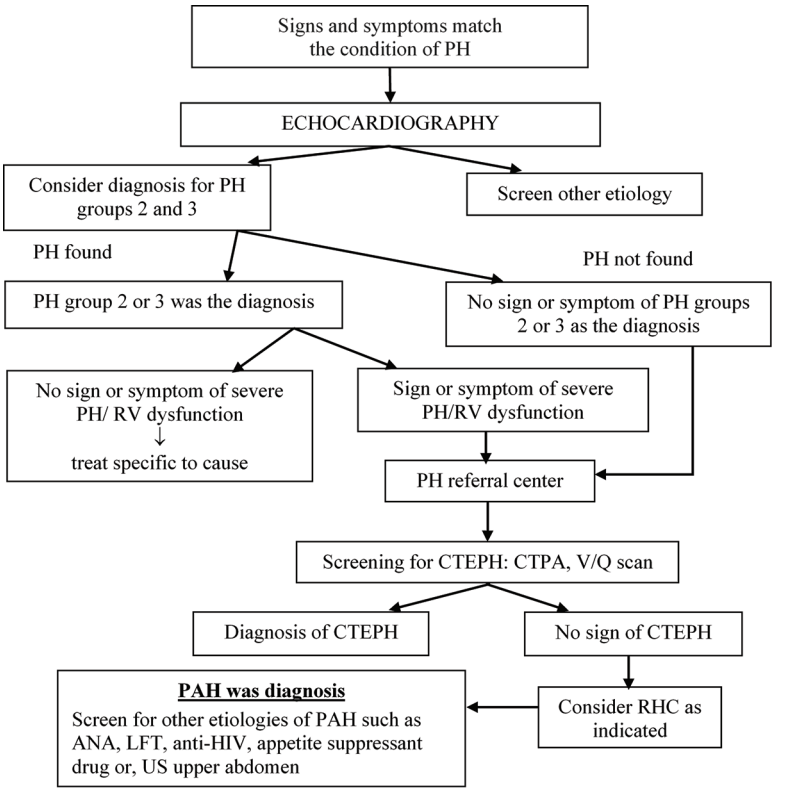

Figure 1. Algorithm for diagnosis of pulmonary hypertension.

PH=pulmonary hypertension; RV=right ventricle; CTEPH=chronic thromboembolic pulmonary hypertension; CTPA=computerized tomography of pulmonary artery; V/Q=ventilation perfusion; PAH=pulmonary artery hypertension; ANA=antinuclear antibody; LFT=liver function test; anti-HIV=anti-human immune deficiency virus; US=ultrasound; RHC=right heart catheterization

test (PFT) (3, +), diffusing capacity for carbon monoxide (DLCO) ± bronchodilator (3, +), oxygen (O_2) saturation and arterial blood gas (3, +), high resolution computerized tomography scan (HRCT) (3, +), sleep monitoring (polysomnography; PSG) and ventilation-perfusion lung scan (V/Q scan) (3, ++) can be used to diagnose patients in Group 3 (PH due to lung disease and/or hypoxemia).

3. If Group 2 or 3 PH is diagnosed, the patient should be treated accordingly. However, the patient showing signs of severe PH or right-sided heart failure should be sent to a PH referral center for other etiological examinations, such as a combination of several groups of PH.

4. In patients suspected of PAH, CTEPH, or other pulmonary artery obstructions, these may be excluded by a V/Q scan or computerized tomography of the pulmonary artery (CTPA) (3, +).

5. Cardiac catheterization should be performed to diagnose PAH with definitions of mPAP at rest greater than 20 mmHg, PAWP of 15 mmHg or less, and PVR of 3 WU or more (1, ++).

6. Patients in Group I with a history of congenital heart disease or connective tissue disease or with any other underlying pathology should receive coordinated care with the primary specialist to assess the risk of pulmonary arterial hypertension periodically.

7. Patients with a history of suspected familial PAH or pulmonary vascular obstructive disease (PVOD) or pulmonary capillary hemangiomatosis (PCH) should have a genetic consultation to recognize the possibility of inherited transmission (3, ++). A genetic test such as Bone morphogenetic protein receptor type II (BMPR2) for specific disease can be performed if applicable (3, +/–).

8. Patients should be referred if any of the investigations cannot be performed or if the patient appears to have more than one group of etiologies of PH.

2. Right heart catheterization and acute vaso-reactivity testing

RHC should be performed by a physician who is

Table 1. Risk assessment in pulmonary arterial hypertension adapted from Galie et al[6] and Frost et al[5] using hemodynamic parameters from cardiac catheterization and echocardiography[13]

Determinants of prognosis	Low risk	Intermediate risk	High risk
Mortality rate within 1st year	<5%	5 to 10%	>10%
Sign of right heart failure	Absent	Absent	Present
Worsening of symptoms	No	Slow	Rapid worsening
Syncope	No	Occasional syncope	Repeated syncope
WHO functional class	I or II	III	IV
6MWD (m)	>440	165 to 440	<165
BNP or NT-proBNP	BNP <50 ng/L, NT-proBNP <300 ng/L	BNP 50 to 300 ng/L, NT-proBNP 300 to 1,400 ng/L	BNP >300 ng/L, NT-proBNP >1,400 ng/L
Echocardiography/hemodynamic measurement	RAP <8 mmHg*, CI ≥2.5 L/minute/m^2, SvO_2>65%	RAP 8 to 14 mmHg*, CI 2.0 to 2.4 L/minute/m^2, SvO_2 60 to 65%	RAP >14 mmHg*, CI <2.0 L/minute/m^2, SvO_2<60%

6MWD=6-minute walk distance; BNP=brain natriuretic peptide; CI=cardiac index; NT-proBNP=N-terminal pro-brain natriuretic peptide; RA=right atrium; RAP=right atrial pressure; SvO_2=mixed venous oxygen saturation; WHO=World Health Organization

* RAP can be calculated from established formula or by echocardiography[13]

familiar with catheter movement in the right side of the heart that can be enlarged or that the pulmonary artery is difficult to enter. The right heart pressure should be measured with an accurate measurement of the pulmonary artery wedge pressure[7,9]. The O_2 saturation or the thermodilution method should be used to measure cardiac output and to calculate PVR. The indication for RHC is as follows:

1. Confirm the diagnosis of pulmonary arterial hypertension or acute vasoreactivity, before giving medication (3, +).

2. Differentiate between pre-capillary PH that has a mean PA greater than 20 mmHg, PAWP of 15 mmHg or less, and PVR of 3 WU or more and post-capillary PH that has a mean PA greater than 20 mmHg, PAWP of more than 15 mmHg, and PVR of less than 3 WU or the combined pre- and post-capillary PH that has a mean PA more than 20 mmHg, PAWP of more than 15 mmHg, and PVR of 3 WU or more (3, +).

3. Determine the operability in the patient with pulmonary artery hypertension and congenital heart disease (PAH-CHD) (3, +).

4. Confirm the diagnosis and guidelines for the treatment of CTEPH (3, +).

5. Assess the severity and prognosis, with monitoring and treatment plan adjustments in patients with pulmonary arterial hypertension (3, +/–).

The acute vasoreactivity test (AVT) performed by inhaled nitric oxide predicts the response to the calcium channel blocker. Only patients with a diagnosis of IPAH, heritable PAH, or drug-related PAH should undergo the AVT when a calcium channel blocker has been indicated for treatment (3, ++). "Responder" denotes that the mPAP was lowered by at least 10 mmHg from the previous value while the overall mPAP is 40 mmHg or less and the cardiac output is stable or increased[6,7]. For a non-responder, PAH-specific drugs should be initiated according to the risk assessment (Table 1). Patients who had PAH other than above three PAH etiologies do not need AVT before being given a PAH-specific drug. Care should be taken for cardiac catheterization and AVT in patients with unstable circulatory conditions or those who are in World Health Organization (WHO) functional class (FC) IV.

3. Risk assessment of pulmonary arterial hypertension[6,10]

This risk assessment has been adapted from the 2015 European Society of Cardiology (ESC)/ European Respiratory Society (ERS) Pulmonary Hypertension Guidelines that use three levels of risk based on the estimated mortality rate within one year (Table 1). Low risk is less than 5%, intermediate risk is 5% to 10%, and high risk is more than 10%[6]. Certain low risk such as 1) WHO FC I or II, 2) 6MWD greater than 440 m, 3) right atrial pressure less than 8 mmHg, and 4) cardiac index of 2.5 L/minute/m^2 or more are associated with better prognoses of PAH[11,12]. In addition, further assessments show that the low-risk criteria at diagnosis and during the first year of treatment can discriminate the risk of death or lung transplantation.

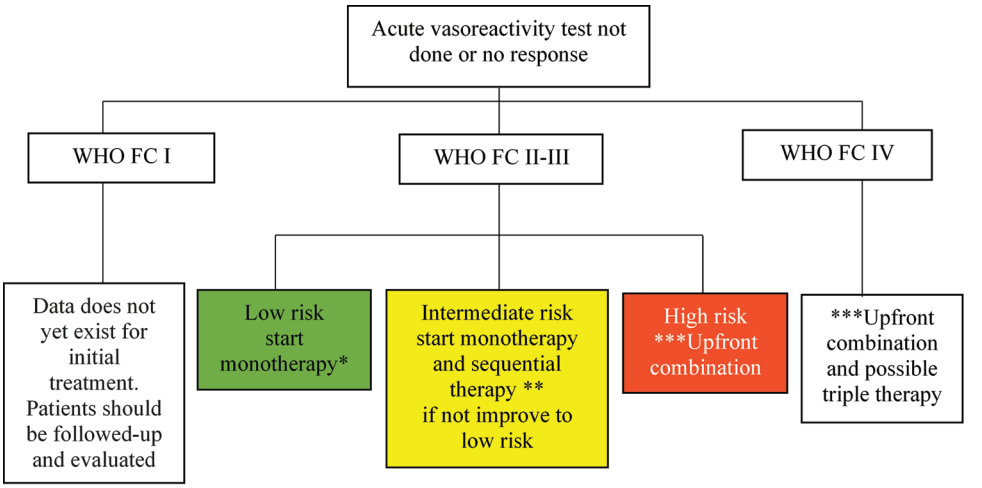

Figure 2. Guidelines for PAH-specific drugs.

FC=WHO functional class, * PAH-specific drugs with monotherapy (Table 2), ** PAH-specific drugs for sequential combination therapy (Table 3), *** PAH-specific drugs for upfront combination (Table 3)

One PAH-specific drug can be given to monitor the side-effects and the second drug can be given within a short time (i.e., 1 to 2 weeks).

4. PAH-specific drugs

Recommendations for PAH-specific drugs are based on the risk assessment criteria in Table 1. In Thailand, a limited number of PAH-specific drugs are available[6,10,14-22]. PAH-specific drugs should be initiated in patients who are in WHO class II or worse[6,10].

In Thailand, the PAH-specific drugs belong to the following drug groups:

1. Calcium channel blockers (CCB): amlodipine, nifedipine, and diltiazem. The CCB are effective in IPAH patients who respond to pulmonary vasoreactivity testing. Since the drugs have an effect on the heart rate, patients with a slow heart rate should be given nifedipine or amlodipine. Diltiazem can be given to patients with a fast heart rate. CCB should be started in small doses and then gradually increased to a level that the patient can tolerate.

2. Endothelin receptor antagonists (ERA): bosentan and macitentan. Patients with PH have elevated levels of endothelin-1 in both blood and lung tissue. Endothelin-1 (ET-1) causes vasoconstriction and stimulates smooth muscle cell proliferation. ERA can bind to endothelin receptor type A or B or both at the muscle cells of the pulmonary arteries and cause relaxation of the vascular wall.

3. Phosphodiesterase type 5 inhibitors (PDE-5i): sildenafil and tadalafil. PDE5i inhibit the action of phosphodiesterase type 5 enzyme that causes the breakdown of cyclic guanosine monophosphate (cGMP). The amount of cGMP acts to expand the pulmonary arteries via nitric oxide (NO)/cGMP. Another type of drug that acts via stimulation of soluble guanylate cyclase (sGC) is riociguat, which has been approved for CTEPH patients.

4. Prostacyclin analogues: beraprost, iloprost, and selexipag. Prostacyclin has a strong vasodilator effect on endothelial cells. It also causes anti-platelet aggregation.

Monotherapy (any class of drugs) can be initiated in patients who are in the low-risk group (Figure 2). In practice, most patients are given sildenafil at 20 mg three times daily, a drug that is listed in the National List of Essential Medication (Thailand) unless a contraindication is present[17,18,23]. Sequential therapy, with the addition of a second drug such as ERA to sildenafil may be considered if the patient's symptoms are assessed to show no improvement from intermediate to low risk (2, +). An upfront combination treatment (sildenafil + ERA) should be considered for high-risk patients[17,24]. Currently, in Thailand generic formularies are available for both sildenafil[17] and bosentan[25] with some evidence from clinical trials. The present study of combinations (both international and local) with PDE-5i in combination with each ERA or triple therapy (PDE-5i + ERA + Selexipag) showed improved morbidity and mortality than monotherapy alone. For patients who are in WHO FC IV, epoprostenol has supportive evidence, but since Thailand does not have this drug, the recommended treatment is to use drugs that are used for patients in WHO FC III.

Table 2. Recommendation for initiating PAH-specific drug for monotherapy[6] (adapted from Galie et al[6] and Frost et al[5])#

Medication		Class-level		
Group	Name	WHO-FC II Level of evidence and strength of recommendation	WHO-FC III Level of evidence and strength of recommendation	WHO-FC IV* Level of evidence and strength of recommendation
CCB		3, ++	3, ++	–
ERA	Ambrisentan	1, ++	1, ++	3, +
	Bosentan	1, ++	1, ++	3, +
	Macitentan	2, ++	2, ++	3, +
PDE-5i	Sildenafil	1, ++	1, ++	3, +
	Tadalafil	2, ++	2, ++	3, +
Prostacyclin analogue and IP receptor	Epoprostenol*		1, ++	1, ++
	Iloprost	–	2, ++	3, +
	Beraprost	–	2, +/–	–
	Selexipag	2, ++	2, ++	2, +
Guanylate cyclase stimulators	Riociguat	2, ++	2, ++	3, +

CCB=calcium channel blockers; ERA=endothelin receptor antagonist; PDE-5i=phosphodiesterase type 5 inhibitor; WHO-FC=World Health Organization functional classification; IP=prostaglandin I2 receptor

* In WHO FC IV patients, epoprostenol is supported by evidence for its effectiveness, but since Thailand does not have this drug, the recommended treatment is to use drugs that are used in WHO FC III patients.

All of the medications except epoprostenol are available in Thailand.

Table 3. Recommendation for sequential combination therapy in intermediate risk patients who did not improved to low risk after receiving monotherapy (adapted from Galie et al[6] and Frost et al[5])

Sequential combination PAH-specific drug	Class-level		
	WHO-FC II Level of evidence and strength of recommendation	WHO-FC III Level of evidence and strength of recommendation	WHO-FC IV Level of evidence and strength of recommendation
Bosentan added to sildenafil	3, +/–	2, +	3, +
Sildenafil added to bosentan	3, +/–	3+/–	3+/–
Macitentan added to sildenafil	2, ++	2, ++	3, +
Iloprost added to bosentan	2, +/–	2, +/–	3, +/–
Tadalafil added to bosentan	3, +	3, +	3, +
Riociguat added to bosentan	2, ++	2, ++	3, +
Ambrisentan added to sildenafil	3, +/–	3, +/–	3, +/–
Upfront combination in high-risk patients			
Ambrisentan + tadalafil*	2, ++	2, ++	3, +/–
Other ERA + PDE-5i**	3, +	3, +	3, +/–

WHO-FC=World Health Organization functional classification; ERA=endothelin receptor antagonist; PDE-5i=phosphodiesterase type 5 inhibitor

* Combination therapy in WHO FC III/IV or intermediate/high-risk patients showed better outcomes than monotherapy. The study of combinations (both international and local) with PDE-5i in combination with each ERA or triple therapy (PDE-5i + ERA + Selexipag) showed different outcomes including morbidity/mortality. The committee considers that all ERA drugs are useful for treating patients and can be substituted for each other.

** Consider using upfront combination in patients with high risk. Using more than two PAH-specific drug should be done in PH referral center

Further considerations for PAH-specific drugs:

1. A patient who has symptoms for the first time and has no underlying disease should be diagnosed according to Figure 1 and should have RHC to confirm the PAH diagnosis and to exclude Group 2-PH from left heart disease (3, +).

2. Patients with symptom of hypotension or right heart failure should have supportive treatment. The initiation of PAH-specific drugs is at the discretion of the physician in charge, before RHC can be

Table 4. PAH-specific drugs and dosages available in Thailand. Recommended starting dose, maximal dose (maximum dosage for a child is no more than for adults, unless otherwise specified), and side effects[6,18]

PAH drug	Adult		Child		Side effects
	Starting dose	Maximal dose	Starting dose	Maximal dose	
Nifedipine	30 mg BID	120 to 240 mg/day	0.1 to 0.2 mg/kg/dose BID-TID	2 to 3 mg/kg/day BID-TID	Hypotension, leg edema, bradycardia, rash, gum hyperplasia, constipation
Diltiazem	60 mg TID	240 to 720 mg/day	0.5 mg/kg/dose TID	3 to 5 mg/kg/day BID-TID	
Amlodipine	2.5 mg OD	20 mg/day	0.1 to 0.3 mg/kg/day OD	2.5 to 7.5 mg/kg/day OD	
Ambrisentan Tab 5 mg	5 mg OD	10 mg OD	5 to 10 mg OD		Abnormal liver function 0.8 to 3%, peripheral edema
Bosentan Tab 125 mg	62.5 mg BID	125 mg BID	BW <10 kg: 2 mg/kg BID BW 10 to 20 kg: 31.25 mg BID BW 20 to 40 kg: 62.5 mg BID BW >40 kg: 125 mg BID		↑Hepatic aminotransferases 10%, contraindication in pregnancy
Macitentan	10 mg OD		Patients who are older than 12 years old.		Anemia, contraindication in pregnancy
Sildenafil Tab 20, 50, 100 mg	5 mg TID	20 mg TID	Age <1 year: 0.5 to 1 mg/kg/dose TID BW <20 kg: 10 mg TID BW ≥20 kg: 20 mg TID		LFT, avoid using with nitrates, color vision disturbance
Beraprost sodium 20 mcg	20 mcg TID				Flushing, headache, hypotension, reactive airway symptoms worsening
Iloprost IV/ inhale 20 mcg	IV 0.5 to 2 ng/kg/minute or 2.5 to 5 mcg inhalation q 4 to 6 hours		IV 0.5 to 2 ng/kg/minute or 2.5 to 5 mcg inhalation q 4 to 6 hours		
Selexipag	200 mcg BID	1,600 mcg BID	Not established in children		

mg=milligram; kg=kilogram of body weight; OD=once daily; BID=twice daily; TID=three times daily; BW=body weight; LFT=liver function test; mcg=microgram

Table 5. Recommendations for considering congenital heart surgery with high pulmonary artery pressure due to systemic-pulmonary shunts (modified from Galie et al[6])

PVRi (WU•m^2)	PVR (WU)	Correctable	Level of evidence and strength of recommendation
<4	<2.3	Yes	3, +
>6 to 8*	>4.6	No	3, +
4 to 8	2.3 to 4.6	Individual patient evaluation in tertiary centers	3, +

PVR=pulmonary vascular resistance; PVRi=pulmonary vascular resistance index; WU=wood units.

* Survival was improved in local study if PVRi cut-off was used as 6 WU•m^2[26].

performed.

5. Operability in pulmonary artery hypertension with congenital heart disease patients

Recommendations for considering corrective surgery in patients with congenital heart disease with PAH due to systemic-to-pulmonary shunts are shown in Table 5. According to the 2015 ESC, surgery is recommended in patients with pulmonary vascular resistance index (PVRi) to body surface area values of less than 4 WU•meter^2 (m^2) and PVR of less than 2.3 WU (3, +)[6]. Calculation of PVR in pediatric patients with a body surface area of less than 1 m^2 should be done with some reservation. For example, if a child with a body surface area of 0.5 m^2 has a calculated PVR of 6 WU and based on the table for surgical repair, the surgery is not recommended, the same child will have a calculated PVRi of 3 WU•m^2, which would permit the corrective surgery according to the same table.

Corrective surgery in patients with PAH-CHD is a complex procedure and the treatment results will depend on many factors. Clear benefits are seen when the patient has a PVRi of less than 4 WU•m^2 and PVR, which is systemic vascular resistance (SVR) of less than 0.3[27]. Nevertheless, if the PVRi is between 4 to 8 WU•m^2, the patient will be classified as high risk. Survival was improved in a local study when the PVRi cut-off of 6 WU•m^2 was used[26]. Experts on the American Heart Association (AHA)/

Table 6. Several clinical factors (i.e., physical examination and arterial saturation) were used to determine surgical or transcatheter repair for shunt closure in atrial septal defect (ASD) or ventricular septal defect (VSD) patients or in patent ductus arteriosus (PDA). Right heart catheterization was also used to measure systolic pressure and calculate the ratio of pulmonary blood flow: systemic blood flow (Qp: Qs), PVR, and SVR (adapted from Stout et al[28])

Level of recommendation	Symptom	Qp: Qs	PASP: SBP	PVR: SVR
3, +	Present	Qp: Qs ≥1.5:1	<50%	<1/3
3, +	Absent	Qp: Qs ≥1.5:1	<50%	<1/3
3, +	Present	net left to right shunt	≥50%	>1/3
3, – –	Present	net right to left shunt	≥67%	≥2/3

Qp: Qs=pulmonary blood flow: systemic blood flow; PASP=pulmonary artery systolic pressure; SBP=systolic blood pressure; PVR=pulmonary vascular resistance; SVR=systemic vascular resistance

Table 7. Recommendation for PAH-specific drugs for Eisenmenger syndrome group (adapted from Galie et al[6] and Frost et al[5])

Recommendation	Level of evidence and strength of recommendation
Bosentan could be used for Eisenmenger syndrome for patients in WHO-FC III or worse.	2, ++
ERA, PDE-5i and prostanoid can be considered in Eisenmenger syndrome	3, +
Oral anticoagulant should be considered in patients with pulmonary artery thrombosis or severe congestive heart failure. Contraindication for this medication is patients with hemoptysis	3, + –
Consider using O_2 therapy if arterial O_2 saturation or symptoms improve	3, +
Phlebotomy should only be done for patients with hyperviscosity with hematocrit more than 65% by using isovolumic replacement	3, +
Supplemental iron should be considered for patients with low plasma ferritin	3, +
Combination drug therapy should be used for Eisenmenger syndrome	3, +
CCB are contraindicated in Eisenmenger syndrome	3, – –

PAH=pulmonary artery hypertension; WHO-FC=World Health Organization functional class; ERA=endothelin receptor antagonists; PDE5i=phosphodiesterase type 5 inhibitor; O_2=oxygen; CCB=calcium channel blocker

American College of Cardiology (ACC) Guidelines for the Management of Adults with Congenital Heart Disease[28] and from the Cologne consensus[29,30] have suggested using the ratio of pulmonary artery systolic pressure (PASP) to systolic blood pressure (SBP) or PVR to systemic vascular resistance (PVR:SVR), which has been used in combination with the primary lesion (Table 6).

Patients with Eisenmenger syndrome who have long-standing PH are known to benefit from bosentan treatment given as a monotherapy for 16 weeks. The PVRi was significantly reduced by 472.0 dyne•s•cm-5 and the 6-minute walk distance (6MWD) was significantly increased by 53.1 m in the BREATH-5 study(31-34). Several small studies have also shown a short-term benefit from sildenafil for patients with Eisenmenger syndrome[17,19,35]. Nevertheless, all PAH-CHD patients virtually reach time to clinical worsening within one to two years[19]. A meta-analysis with 456 pooled PAH-CHD patients who had bosentan added on to sildenafil showed significant improvement in the 6MWD, WHO FC, mPAP, and PVRi[36]. Interestingly, in a recent MAESTRO study[37], Eisenmenger patients treated with macitentan for 16 weeks showed results that differed from those of the BREATHE-5 study[31]. The patients in the MAESTRO study had less pronounced improvements in 6MWD and no significant improvement when compared to the placebo group. The limited treatment effect of macitentan was attributed to the large improvement in 6MWD in the placebo group, though a clear explanation was not given. The recommendation suggests that ERA (bosentan or macitentan) be added on to sildenafil in patients with PAH-CHD (3, +) (as shown in Table 7).

6. PAH associated with connective tissue disease

Systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) are two of the most common connective tissue diseases associated with PAH[38,39]. Every SSc patient is recommended to have echocardiography examination after a diagnosis of SSc, and echocardiography should be repeated every year in subjects with WHO-FC level II or higher (2,

++)[39]. Echocardiography should be done sooner if a worsening occurs in the WHO-FC without any explainable causes (2, ++) or it can be used with the PFT to improve the sensitivity of a diagnosis of PAH[40].

PH in SSc can be caused by several etiologies such as pulmonary vascular disease creating PAH, interstitial lung disease (ILD), or left heart disease. Risk factors for PAH in SSc include age over 60 years, Forced vital capacity (FVC)/DLCO ratio over 1.6, abnormal NT-proBNP levels, and increased blood uric acid levels[41,42]. PAH associated with SSc patients can be seen in both diffuse and limited subtypes[39]. Generally, an anticoagulant is not recommended due to the unclear benefit and increased risk of complications (2, –)[39]. Corticosteroids and immunosuppressive drugs are not recommended for the treatment of PAH in SSc patients (3, –)[43-45].

CCBs are not recommended for use in the treatment of patients with PAH-SSc as most cases of PAH-SSc do not respond to the AVT from RHC. PAH-specific drugs should be used for patients with WHO class II or higher[46].

PH in SLE is usually caused by pulmonary vasculitis, pulmonary embolism, or PH due to heart disease[38]. Anticoagulant drugs should be considered for patients with PH-associated anti-phospholipid syndrome (2, ++). High doses of corticosteroids such as prednisolone 1 mg/kg/day[47] (3, +/–) can be used in combination with immunosuppressive drugs (2, ++) if the PAH is suspected due to pulmonary vasculitis or other systemic inflammation. CCBs are not recommended for treating PH-SLE (3, –), because of inconclusive results[44,47].

PAH can rarely be seen in other connective tissue disease, such as rheumatoid arthritis, polymyositis, Sjogren's syndrome, or vasculitis. Other causes of PH should be excluded prior to providing the diagnosis of PAH in these diseases. Use of PAH specific drugs should follow that of PAH in SSc. Corticosteroids, immunosuppressive drugs, or anti-coagulants use should be based on the indication of their primary diseases.

7. Pulmonary arterial hypertension in children

Children can often have a transient PH situation that differs from adults, including persistent PH of newborns and children undergoing surgical repair from left to right shunt congenital heart defect[4]. Persistent pulmonary hypertension of the newborn (PPHN) is considered as a subgroup of pulmonary arterial hypertension. Patients often have temporary high pulmonary artery pressure, which is approximately 30 cases per 1,000,000 children per year. Patients with this condition need specific management by the neonatal intensive care unit (NICU)[48]. The definition of PH in adults (Table 2) can also be applied in children. The incidence of IPAH in children is 0.67 to 2 per 1,000,000 children[49], while the prevalence is about 2.1 to 4.4 people per 1,000,000 people. Children often experience common dyspnea, fatigue, and failure to thrive. Syncope is more common in young patients than in adults and sudden cardiac death is not uncommon. The prognosis in children is worse than in adults. Children with IPAH if not treated have an average survival rate of eight months, compared to 2.8 years in adults[4]. Due to the poor prognosis, the use of a combination of drugs is more common in children.

Risk assessment in pediatric patients with PH has been simplified into low or high-risk groups due to the limited history that can be obtained and the poorer prognosis, compared to that in adults (Table 8).

Because few randomized controlled trials have been conducted in children for the use of PAH-specific drugs, the guidelines for adults have been adapted for children. The dosages of these medications are shown in Table 4.

8. Pulmonary hypertension due to left heart disease

Patients with heart failure with reduced left ventricular ejection fraction (HFrEF), heart failure with preserved left ventricular ejection fraction (HFpEF), heart valve disease, and other mitral or aortic valve disease including certain types of congenital heart disease are considered as having left heart disease. If PH is found within these patients, they usually experience more symptoms of heart failure than that of their underlying condition[6,50,51]. The diagnosis is based on the same hemodynamic definitions in the PH table. Isolated post-capillary PH (Ipc-PH) (Group 2: PH due to left heart disease) is diagnosed with mPAP of more than 20 mmHg, PAWP of more than 15 mmHg, and PVR of less than 3 WU. This should be excluded from pre-capillary PH (Group 1: PAH, Group 3: PH due to lung disease, Group 4: CTEPH, or Group 5) with mPAP of more than 20 mmHg, PAWP of 15 mmHg or less, and PVR of 3 WU or more. In the case of mPAP of more than 20 mmHg, PAWP of more than 15 mmHg, and PVR of 3 WU or more, the patient is considered to have a combination of post-capillary and pre-capillary PH (Cpc-PH)[7].

Table 8. Risk assessment for pulmonary arterial hypertension in children (adapted from Rosenzweig et al[4])

Low risk	Risk factor	High risk
Not found	Symptom of right heart failure	Appear
Stable or slow progress	Worsening of symptom	Rapid
Normal	Growth	Failure to thrive
I or II	WHO functional class	III, IV
>350 meters	6MWD (>6 years old)	<350 meters
Slightly high value for age	BNP or NT-proBNP	Very high value for age
	Echocardiography	RA/RV enlargement, reduce LV size, increase RV/LV ratio, reduce TAPSE, low RV FAC, pericardial effusion
CI ≥3.0 L/minute/m^2, SvO_2 >65% Acute vasoreactivity	Hemodynamics	mRAP >10 mmHg CI <2.5 L/minute/m^2, SvO_2 <60% PVRI >20 WU•m^2

6MWD=6-minute walk distance; BNP=brain natriuretic peptide; CI=cardiac index; NT-proBNP=N-terminal pro-brain natriuretic peptide; RA=right atrium; RV=right ventricle; LV=left ventricle; TAPSE=tricuspid annular plane systolic excursion; FAC=fractional area change; mRAP=mean right atrial pressure; SvO_2=mixed venous oxygen saturation; WHO=World Health Organization; IV=intravenous; WU.m^2=wood unit meter^2

The treatment for PH from left heart disease is focused on management of the underlying left ventricular dysfunction, valvular or congenital lesion, and the symptoms of heart failure[52]. To date, no evidence supports benefits of PAH-specific drugs for this condition and their routine use in patients with PH-LHD is not recommended. Patients with combined pre and post capillary pulmonary hypertension (Cpc-PH) with severe pre-capillary considerations should be referred to a PH referral center for other treatments on a case-by-case basis.

9. Pulmonary hypertension due to lung disease and/or hypoxia

Chronic obstructive pulmonary disease (COPD), ILD, or hypoxemia caused by obstructive sleep apnea or high altitude, can cause PH. Most patients will have mild symptoms. Patients with severe respiratory symptoms should be evaluated with PFT, including DLCO and echocardiography (3, ++)[53,54]. PFT in patients with PH often indicate very low DLCO levels. No specific treatment is available for PH in this group of patients except in COPD, where patients can benefit from long-term O_2 therapy and can have a reduced mortality from COPD (3, ++). No conclusive evidence supports the use of PAH-specific therapy in this group of patients.

10. Pulmonary hypertension due to chronic thromboembolic pulmonary hypertension

Incidents of CTEPH after an episode of acute pulmonary embolism have been reported and is ranging from 0.1% to 9.1% within the first two year[55]. The diagnosis of PAH is made using the same definition of PAH in Group 1 with a mismatched perfusion defect in the lung scan and radiological characteristics such as ring-like stenosis, webs, pouch, or tapered lesions from CT, MRI, or pulmonary angiography.

A ventilation/perfusion (V/Q) scan is recommended to screen patients with suspected CTEPH, as it has a 96% sensitivity and is 90% to 95% specific[56,57]. The V/Q scan is especially sensitive for diagnosing CTEPH that occurs in the small peripheral blood vessels[58]. Normal V/Q or low probability can usually exclude CTEPH that is more likely to be a moderate, high-intermediate, or high probability test result.

CTPA with slices as close as 0.5 mm has a 76% sensitivity and is 96% specific for diagnosing CTEPH (3, +)[59]. The test is especially useful for confirming the diagnosis but may not be appropriate for screening, because the sensitivity is not very high. In addition, CTPA can be used to assess the location of a blockage when considering a treatment with pulmonary endarterectomy.

A conventional pulmonary angiography (CPA) during RHC is considered the gold standard for diagnosing CTEPH and it can help assess whether pulmonary endarterectomy can be used as a treatment. Magnetic resonance pulmonary angiography (MRPA) may be used in cases where CTPA cannot be performed, such as with allergic or opaque substances. In any case, the image resolution is still inferior to CTPA.

Surgical pulmonary endarterectomy is the best, specific treatment for CTEPH (3, ++) in operable cases[60-63]. The indication for pulmonary

Table 9. Recommended drugs for cardiovascular support during management of PH crisis[87]

	Dosage	Side-effects
Vasopressors		
Norepinephrine	0.01 to 0.4 mcg/kg/minute	Tachycardia and increase in SVR and lactic acidosis;
Vasopressin (Glypressin)[88,89]	0.6 to 1.3 mcg/kg/hour (max 10 mcg/kg/hour)	Increase in SVR, bradycardia, higher doses may lead to cardiac depression; Recommended for adjunctive or rescue therapy
Inotropes		
Dobutamine	2.5 to 10 mcg/kg/minute	Hypotension, tachycardia
Dopamine	0.5 to 10 mcg/kg/minute	Tachyarrhythmia, increased SVR and/or PVR
Inodilators		
Milrinone	Initial dose with 25 to 50 mcg/kg iv over 10 minutes then 0.375 to 0.75 mcg/kg/minute	Hypotension
Levosimendan	0.05 to 0.1 mcg/kg/minute and may increase to 0.2 mcg/kg/minute within 24 hours	
Pulmonary vasodilators		
Iloprost	IV 1 to 2 mcg/hour increase as tolerated with initial target 6 mL/hour after 48 to 72 hour (100 mcg in 100 mL NSS); Nebulized 5 mcg 6 to 9 times/day nebulized 5 to 80 ppm	Hypotension, flushing, headache, jaw and leg pain
Nitric oxide	Initial dose 10 to 40 ppm	Rebound PH, methemoglobinemia

mcg=microgram; kg=kilogram; SVR=systemic vascular resistance; PVR=pulmonary vascular resistance; IV=intravenous; NSS=normal saline; ppm=part per million; PH=pulmonary hypertension

endarterectomy is the WHO FC II-IV combined with the surgical location of the obstruction being in the main, lobar, or segmental pulmonary artery[6].

Other recommended medications include:

- Anticoagulants to be given to all and lifelong if no contraindications are present[6,64] (4, ++)
- Diuretics in cases of right-sided heart failure
- O_2 may be given to patients with hypoxemia, with the goal of O_2 saturation equal to 92%[65]
- PAH-specific drugs may be considered for CTEPH patients who are inoperable or are contraindicated for surgery, and patients with high pulmonary artery pressure after surgery[6,64,66-73]

The current PAH-specific drugs are:

1. Endothelin receptor antagonists such as bosentan (2, +)[66,70,74-76], macitentan (2, ++)[72]
2. Phosphodiesterase-5 inhibitors such as sildenafil (3, +)[67,69,71]
3. Prostacyclin analogs such as iloprost, epoprostenol, trepostinil, and beraprost (3, +/–)[77-82]
4. Soluble guanylyl cyclase (sGC) stimulators such as riociguat (2, ++)[23,73]

Balloon pulmonary angioplasty (BPA) is an alternative treatment for CTEPH patients with WHO FC of 2 or greater and who are unable to undergo surgical Pulmonary thromboendarterectomy (PEA) (3, +)[83]. PVR was found to be reduced with right ventricular reverse remodeling and an improved exercise capacity was found after BPA[84-86].

An inferior vena cava (IVC) filter may be used if the anticoagulant could not be used or if anticoagulants had to be stopped in preparation for PEA surgery (4, +/–)[6].

11. Perioperative and critical care management in pulmonary hypertension

PH crisis is a condition where the pulmonary artery pressure is so high that it causes right ventricular failure and hemodynamic compromise. The condition is seen in patients that have undergone surgery or within the intensive care unit. The goal of management is to avoid any factors that may aggravate an increase in PVR such as severe respiratory and metabolic acidosis, hypercarbia, tissue hypoxia, ventilation with high positive end-expiratory pressure (PEEP) or intrinsic PEEP (auto PEEP), or V/Q mismatch. Table 9 shows the recommendations for drug use for cardiovascular support during a PH crisis. Clinical, hemodynamic, and laboratory parameters should be monitored and managed accordingly (Table 10).

PAH-specific drugs recommended to reduce PVR and improve RV function and cardiac output are as follows:

1. Inhaled NO for PH patients with RV dysfunction in ARDS, after heart surgery with PH (2, +).
2. Inhaled iloprost (2, ++).
3. Intravenous iloprost in cases when patient does not respond to inhaled iloprost (3, +/–). This

Table 10. Clinical and hemodynamic parameters for patients with severe pulmonary hypertension

	Clinical or hemodynamic parameters	Target for management
Renal	Urine output	Fluid balance
	Serum creatinine	Normalize renal function
Hepatic	AST, ALT, bilirubin	Normalization of liver function
Cardiac	CVP	Decreasing RAP
	$ScvO_2$, SvO_2	$ScvO_2$ >70%, SvO_2 >65%
	Echocardiography	Improved LV filling and function
Tissue perfusion/oxygenation	Lactate	<2 mmol/L
Biomarkers	BNP	BNP decreasing
Myocardial perfusion	SBP	DBP >60 mmHg
	ECG	Avoid tachyarrhythmias
	Troponin	Troponin to normal level

AST=aspartate aminotransferase; ALT=alanine transaminase; $ScvO_2$=central venous oxygen saturation; SvO_2=mixed venous oxygen saturation; RAP=right atrial pressure; LV=left ventricle; BNP=brain natriuretic peptide; SBP=systolic blood pressure; DBP=diastolic blood pressure; ECG=electrocardiogram

medication must be used with caution due to side-effects such as hypotension.

4. Other oral medications may be considered in conjunction with this medication according to the patient's condition and the route of administration (3, +/–).

12. Interventional and surgical treatment in pulmonary hypertension

Some indications must be made for the following groups of patients:

1. Pulmonary thromboendarterectomy (PEA) in CTEPH patients
2. Atrial septostomy in severe PAH[90]
3. Bilateral lung transplantation or heart-lung transplantation should be considered in patients who had appropriate PAH-specific drugs but are still in WHO FC III or worse, or their risk assessment is still at a high-risk level.
4. Extracorporeal life support or ECMO
5. Ventricular assist devices

All treatments should be considered in terms of socio-economic factors and the resources in the context for each hospital.

13. Pulmonary hypertension referral centers

A PH referral center should be an institution that can diagnose pulmonary arterial hypertension and provide planning and appropriate treatment for various types of pulmonary arterial hypertension. The institute should maintain a patient database via the patient's registration for assessing the effect of treatment in a broader context.

1. Subspecialist physicians such as cardiologists or pulmonologists must be involved in the diagnosis of pulmonary arterial hypertension and provide primary care for PH patients.

2. The institute must be able to perform all important and relevant laboratory tests, including echocardiography, ultrasonography, computed tomography of chest, spirometry, PSG, V/Q scan, 6MWD, and RHC.

3. A multidisciplinary team of consultants in related diseases must be available. The team should include pediatricians, cardiologists, rheumatologists, and physicians who have access to PAH-specific drugs.

4. The institute must be able to provide treatments or plan for pulmonary endarterectomy and heart-lung/lung transplantation.

14. Independence of the committee

A grant from the HAT was used to fund meeting expenses including travel fees and all other expenses. No conflict of interest, holding of shares in an industrial pharmaceutical, or related medical device company was found. The committee does not promote the use of any specific PAH drug but suggests using generic drugs or classes of drugs instead. All recommendations are made with consideration of the context of the Kingdom of Thailand.

What is already known on this topic?

The 2015 ESC/ERS pulmonary hypertension guidelines[6] stated the risk assessment and new strategies for combination therapies and then the definition of PH was updated from the Sixth World Symposium on Pulmonary Hypertension in 2018. However, some of the recommendations are not suitable in Thailand.

What this study adds?

The 2020 Thai Pulmonary Hypertension Guidelines simplified the algorithm for diagnosis of pulmonary hypertension. This guideline also uses risk assessment criteria with the present study assessment for initiating PAH-specific drug for monotherapy and sequential combination therapy in intermediate risk patients. The guideline also covered certain subspecialty such as congenital heart disease, PAH with connective tissue disease, pulmonary hypertension due to lung disease or hypoxia, and PH with left heart disease including perioperative and critical care management of PH.

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Conflicts of interest

The authors declare no conflict of interest.

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