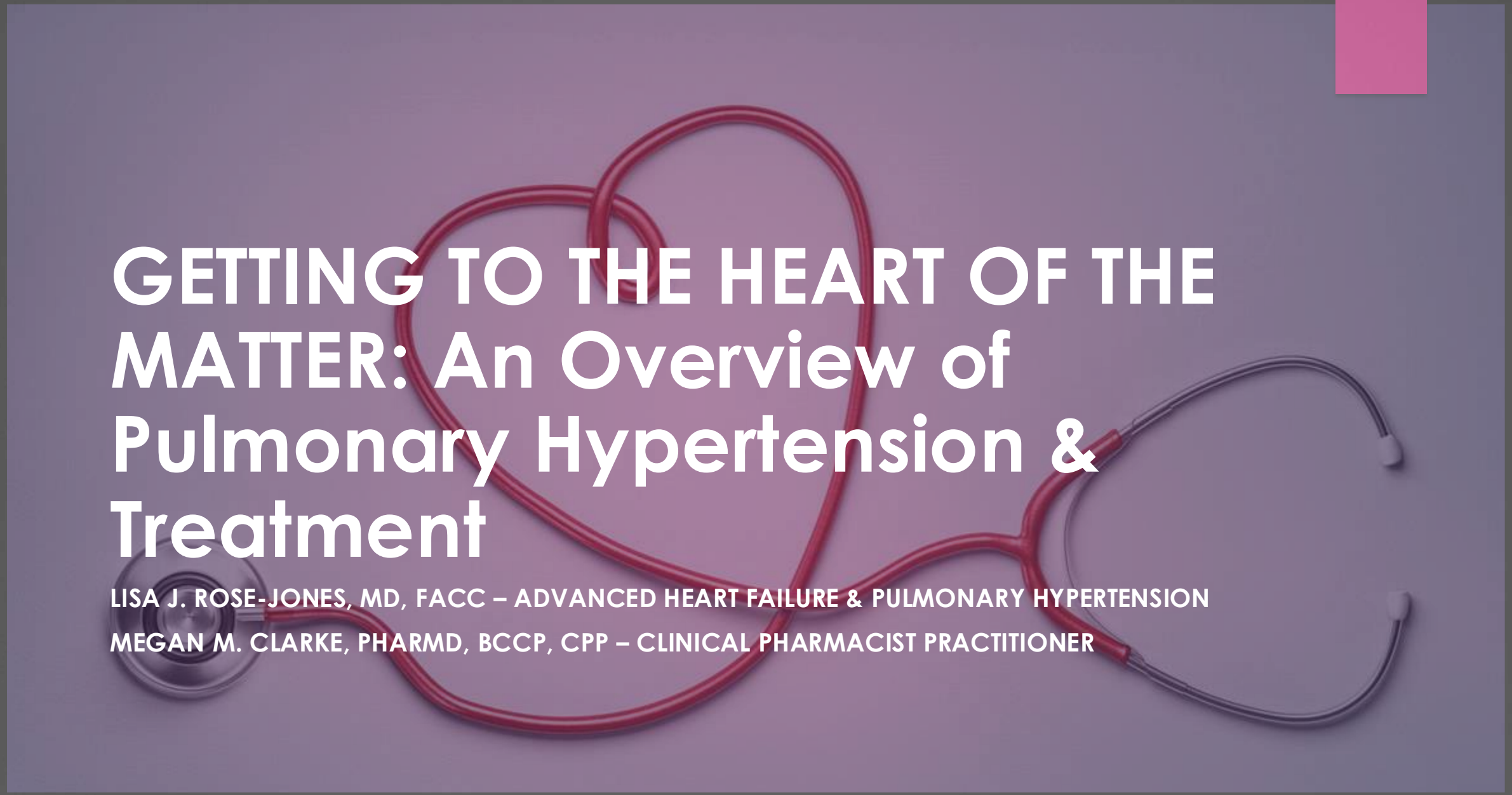


GETTING TO THE HEART OF THE MATTER: An Overview of Pulmonary Hypertension & Treatment

LISA J. ROSE-JONES, MD, FACC – ADVANCED HEART FAILURE & PULMONARY HYPERTENSION

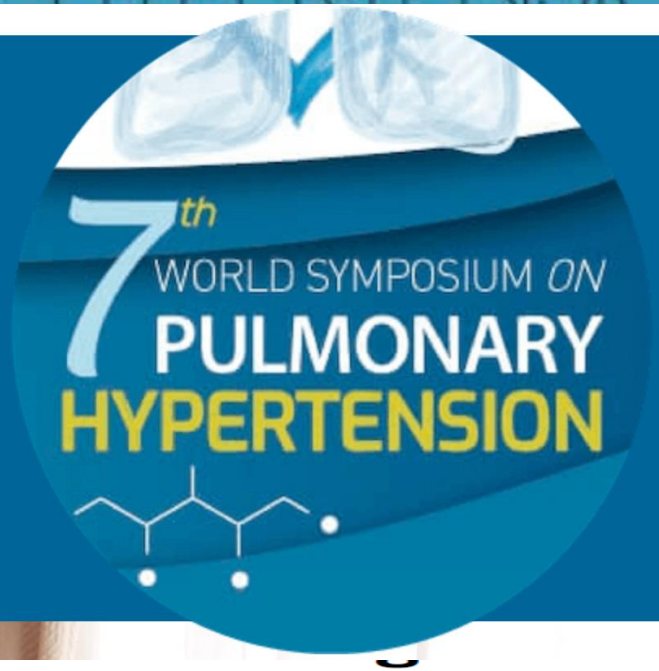
MEGAN M. CLARKE, PHARMD, BCCP, CPP – CLINICAL PHARMACIST PRACTITIONER

Objectives:

- Examine Pathophysiology of PH
- Review hemodynamic definition of PH
  - Define Pulmonary Hypertension & Pulmonary Arterial Hypertension
- Describe categorization
- Outline goals of treatment and risk stratification for patients
- Describe non-pharmacologic treatment option for patients
- Review pharmacologic treatment options for patients
- Create a treatment plan

7TH World Symposium on Pulmonary Hypertension

2024

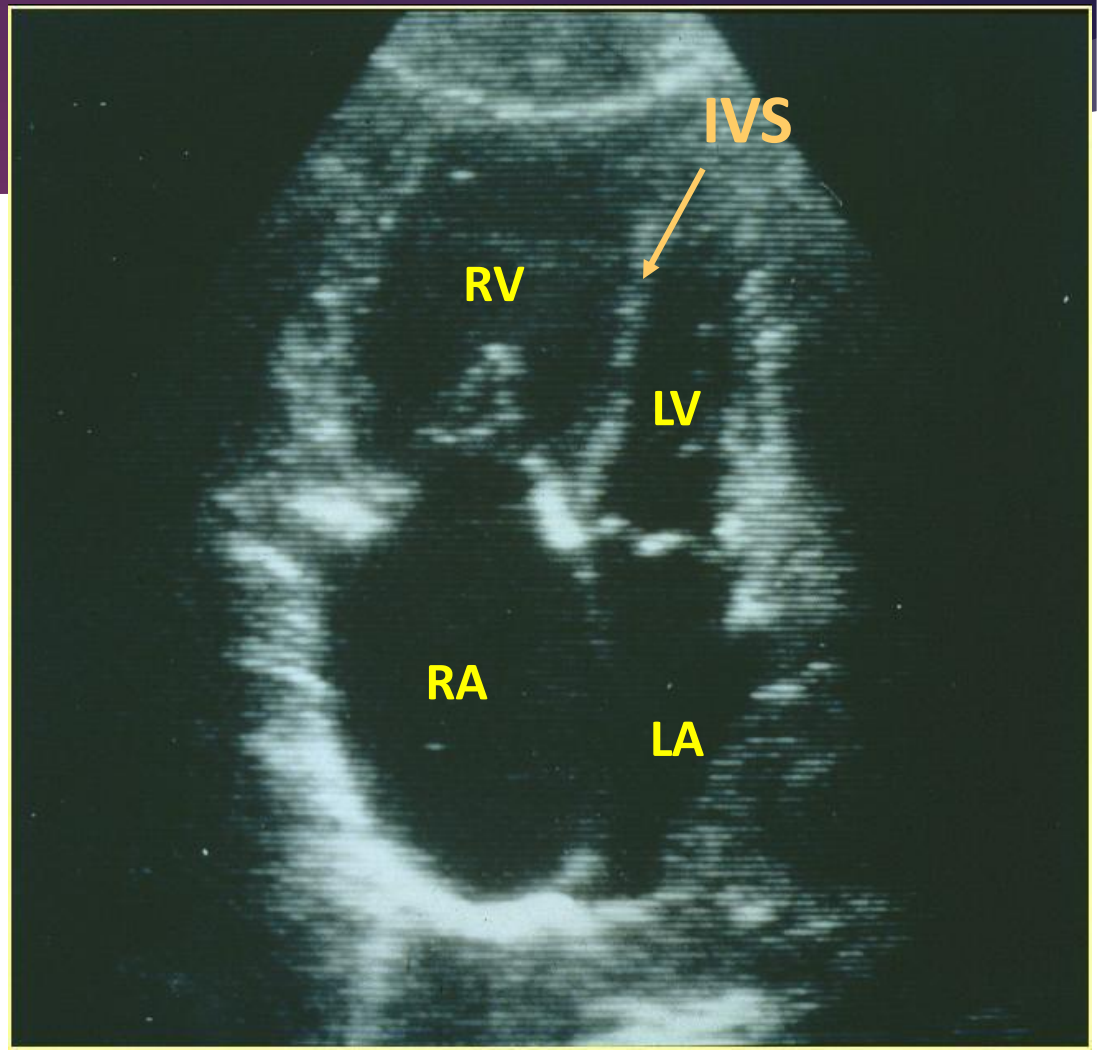


treatment of pulmonary hypertension

Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS).

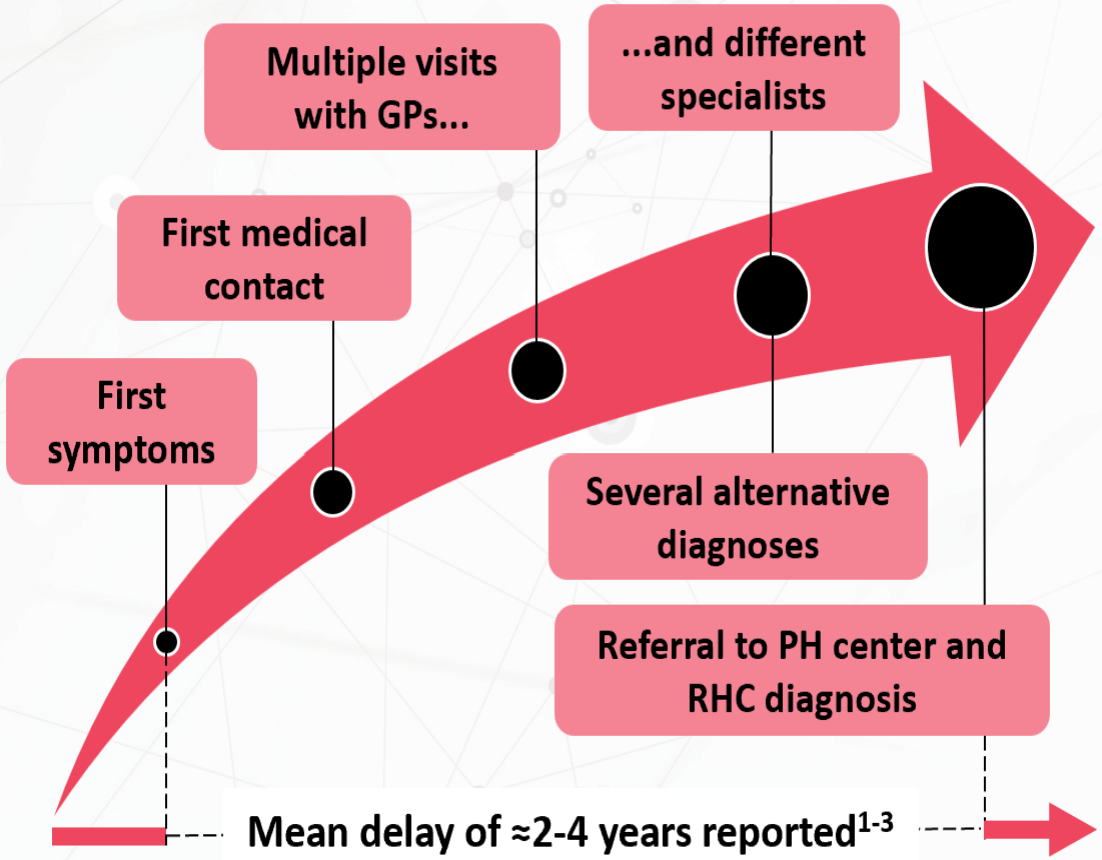
Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG).

How It Begins……

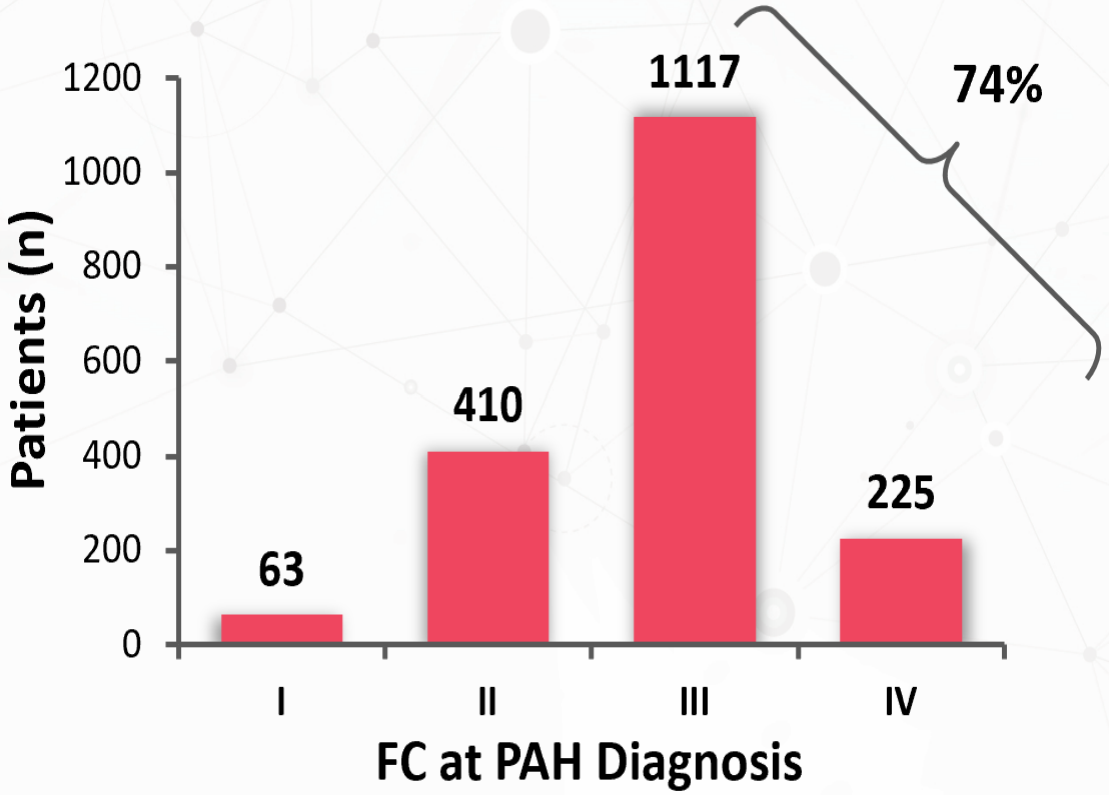


Diagnosis is often LATE

Diagnostic journey is fraught with delays[1]



REVEAL (n=1815): More patients present with worse FC at diagnosis[4*]



*The study population consisted of 2493 patients, of whom 526 (21.1%) had recognition of PAH >2 years after the onset of symptoms and 1967 (78.9%) had recognition ≤2 years. Data presented above do not sum to the total study population due to missing data.[4]

GP=general practitioner; SD=standard deviation.

Adapted with permission from: Strange G, et al. *Pulm Circ*. 2013;3(1):89-94.

1. Strange G, et al. *Pulm Circ*. 2013;3(1):89-94. 2. Badesch DB, et al. *Chest*.2010;137(2):376-387. 3. Khou V, et al. *Respirology*. 2020;25(8):863-871. 4. Brown LM, et al. *Chest*. 2011;140(1):19-26.

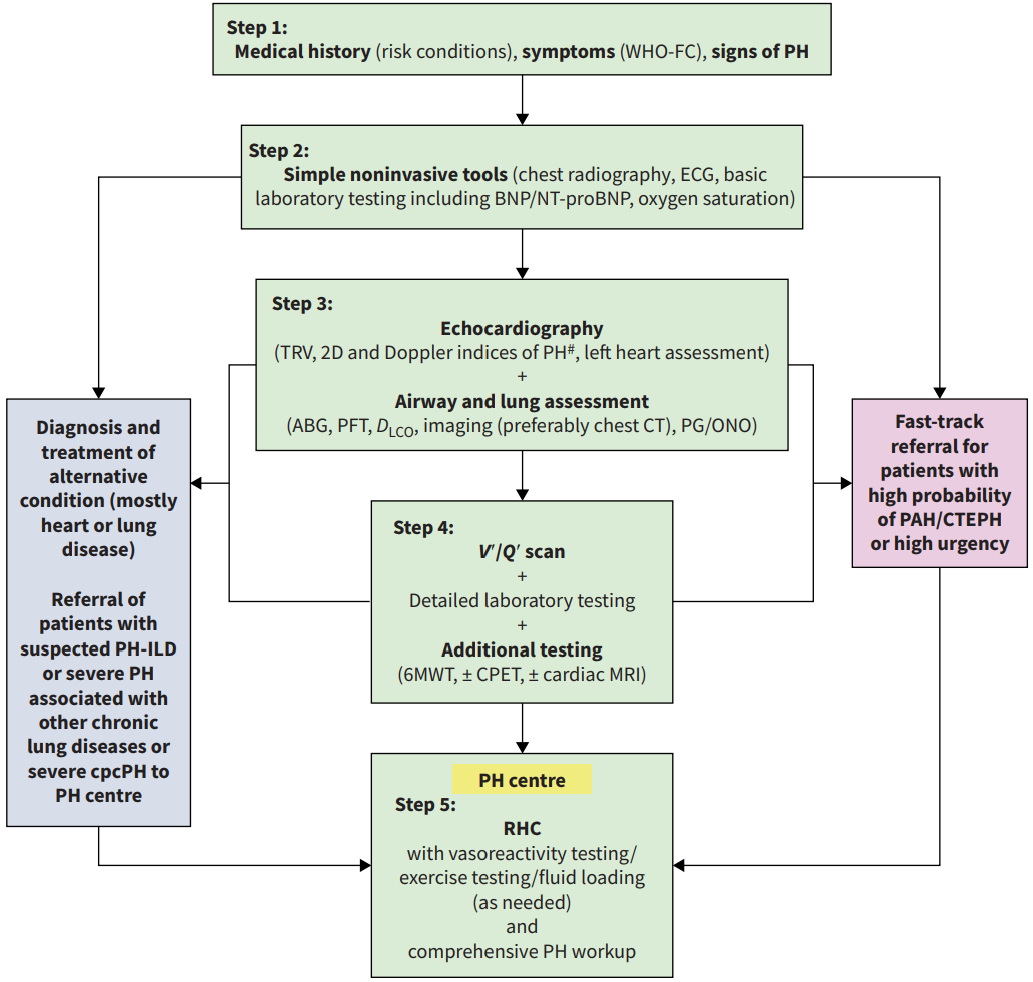


FIGURE 1 Suggested diagnostic approach to pulmonary hypertension (PH). Steps 1–5 represent the most important diagnostic steps of PH from the first presentation of the patient with symptoms or an existing risk condition towards final diagnosis with invasive assessment. WHO-FC: World Health Organization functional class; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; TRV: tricuspid regurgitation velocity; 2D: two-dimensional; ABG: arterial blood gases; PFT: pulmonary function testing; D_{LCO}: diffusion capacity of the lung for carbon monoxide; CT: computed tomography; PG: polygraphy; ONO: overnight oximetry; V'/Q' scan: ventilation/perfusion scan of the lung; 6MWT: 6-min walk test; CPET: cardiopulmonary exercise testing; MRI: magnetic resonance imaging; RHC: right heart catheterisation; PH-ILD: pulmonary hypertension associated with interstitial lung disease; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; cpcPH: combined post- and pre-capillary PH. #: refer to figure 2.

Definition, classification and diagnosis of pulmonary hypertension
Gabor Kovacs, Sonja Bartolome, Christopher P. Denton, Michael A. Gatzoulis, Sue Gu, Dinesh Khanna, David Badesch, David Montani
European Respiratory Journal Jan 2024, 2401324; **DOI:** 10.1183/13993003.01324-2024

PAH is one Cause of PH and is defined HEMODYNAMICALLY

- PH refers to the presence of abnormally high pulmonary vascular **pressure**[1]

Hemodynamic Definition[1]

mPAP >20 mmHg at rest

- PAH results from an increased pulmonary vascular **resistance**, which[2]:
  - Restricts blood flow through the pulmonary arterial circulation[3]
  - Ultimately leads to right heart failure[3]

mPAP >20 mmHg

PAWP ≤15 mmHg

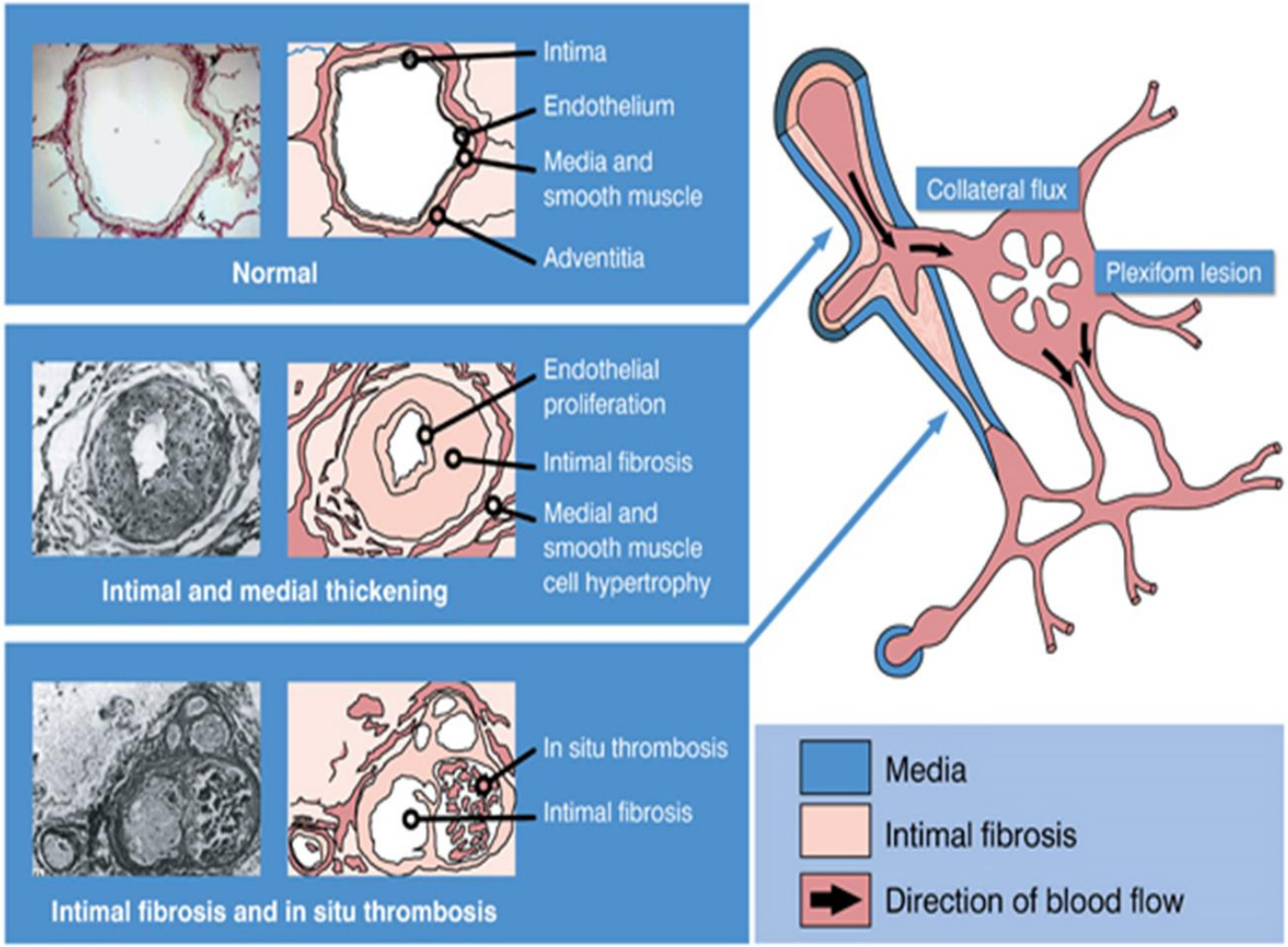
PVR >2 Wood units

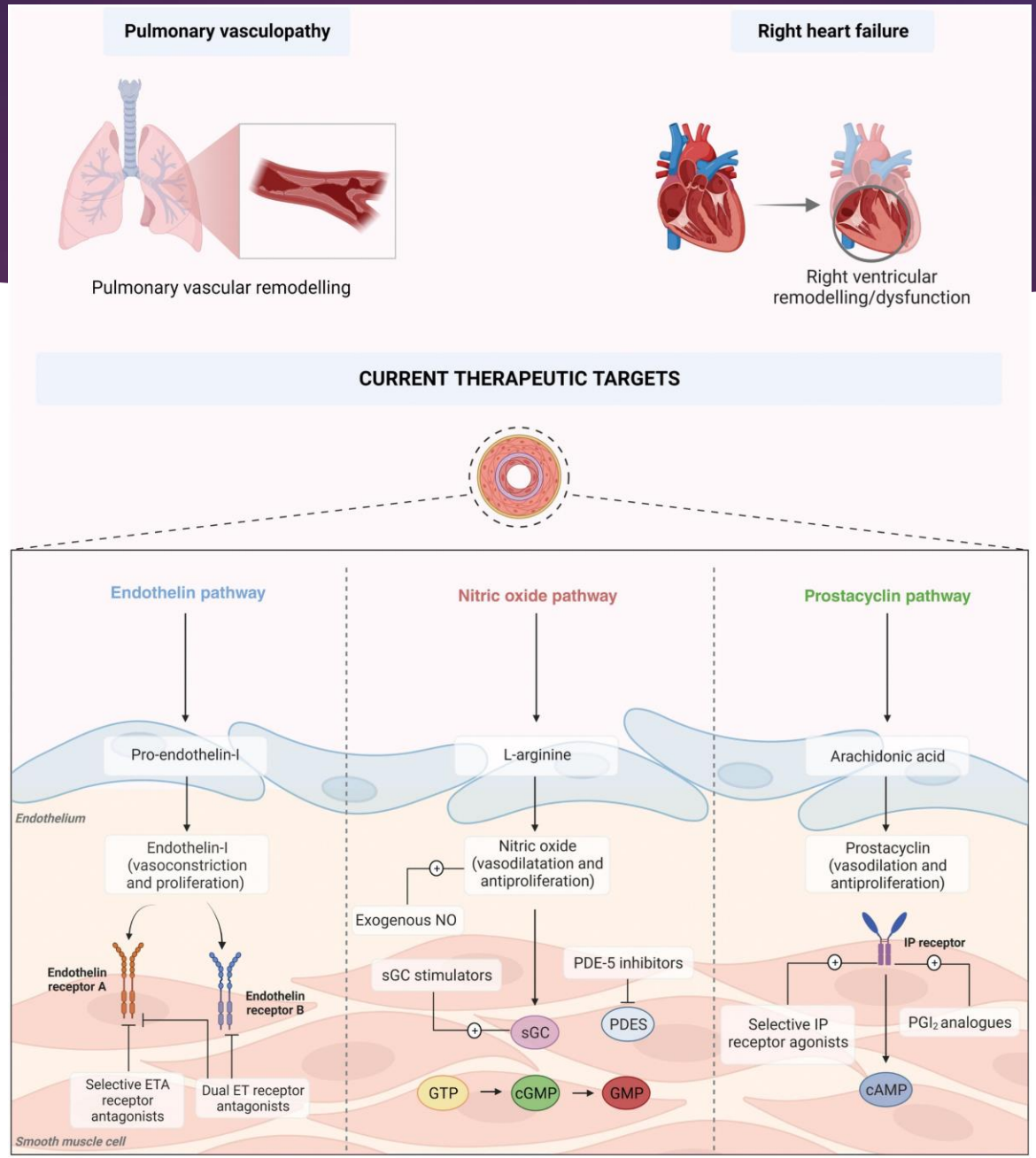
RHC required to confirm diagnosis[1]

ERS=European Respiratory Society; ESC=European Society of Cardiology; mPAP=mean pulmonary artery pressure; PAWP=pulmonary arterial wedge pressure; PVR=pulmonary vascular resistance; RHC=right heart catheterization.

1. Humbert M, et al. *Eur Heart J*. 2022;43(38):3618-3731. 2. McLaughlin VV, et al. *J Am Coll Cardiol*. 2015;65(18):1976-1997. 3. McLaughlin VV, et al. *J Am Coll Cardiol*. 2009;53(17):1573-1619.

Pulmonary Arterial Hypertension: histopathological features

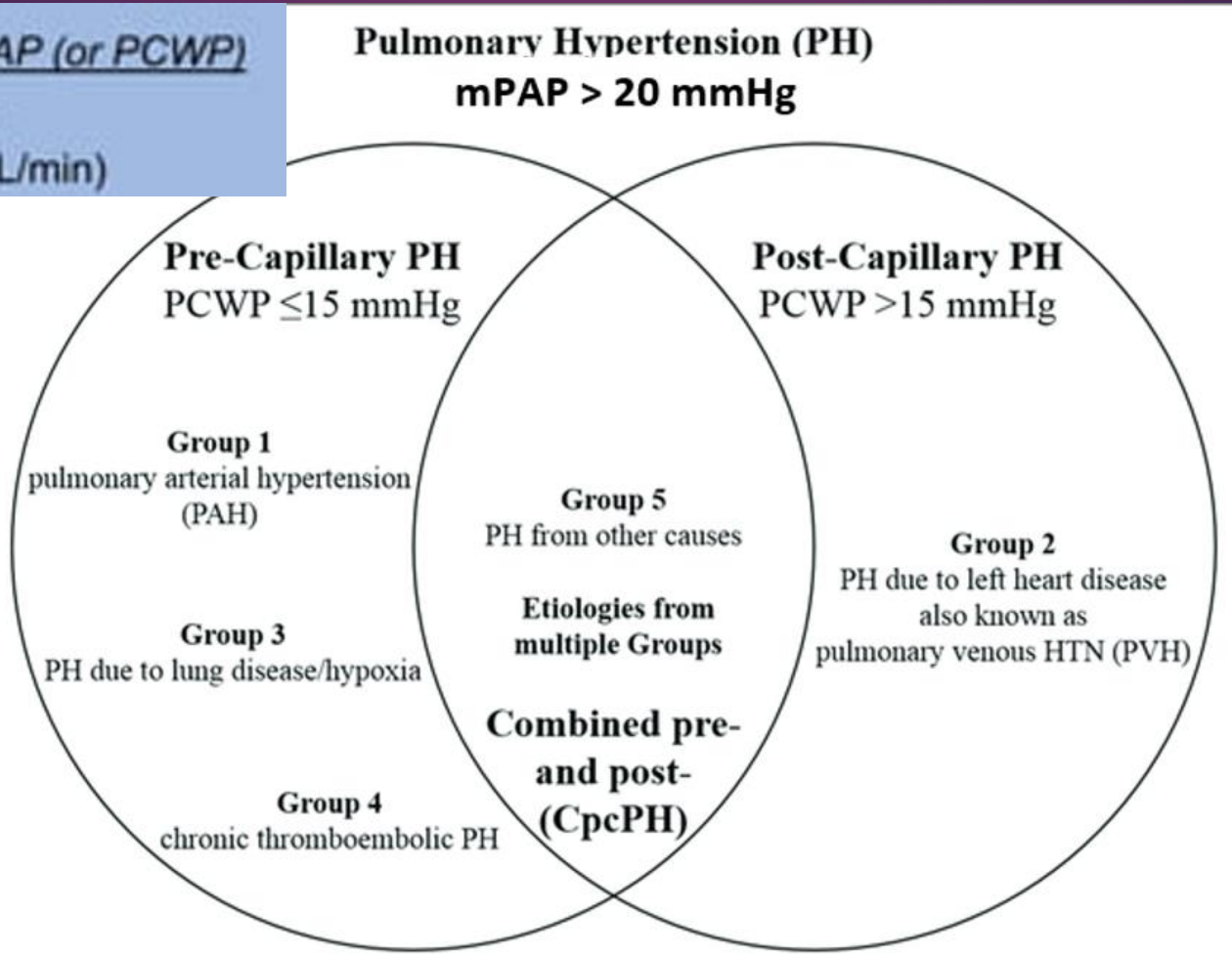



Pulmonary vasculopathy
Right heart failure
Pulmonary vascular remodelling
Right ventricular remodelling/dysfunction
CURRENT THERAPEUTIC TARGETS
Endothelin pathway
Nitric oxide pathway
Prostacyclin pathway
Pro-endothelin-I
L-arginine
Arachidonic acid
Endothelium
Endothelin-I (vasoconstriction and proliferation)
Nitric oxide (vasodilatation and antiproliferation)
Prostacyclin (vasodilation and antiproliferation)
Exogenous NO
IP receptor
sGC stimulators
PDE-5 inhibitors
Endothelin receptor A
Endothelin receptor B
sGC
PDES
Selective IP receptor agonists
PGI2 analogues
Selective ETA receptor antagonists
Dual ET receptor antagonists
GTP
cGMP
GMP
cAMP
Smooth muscle cell

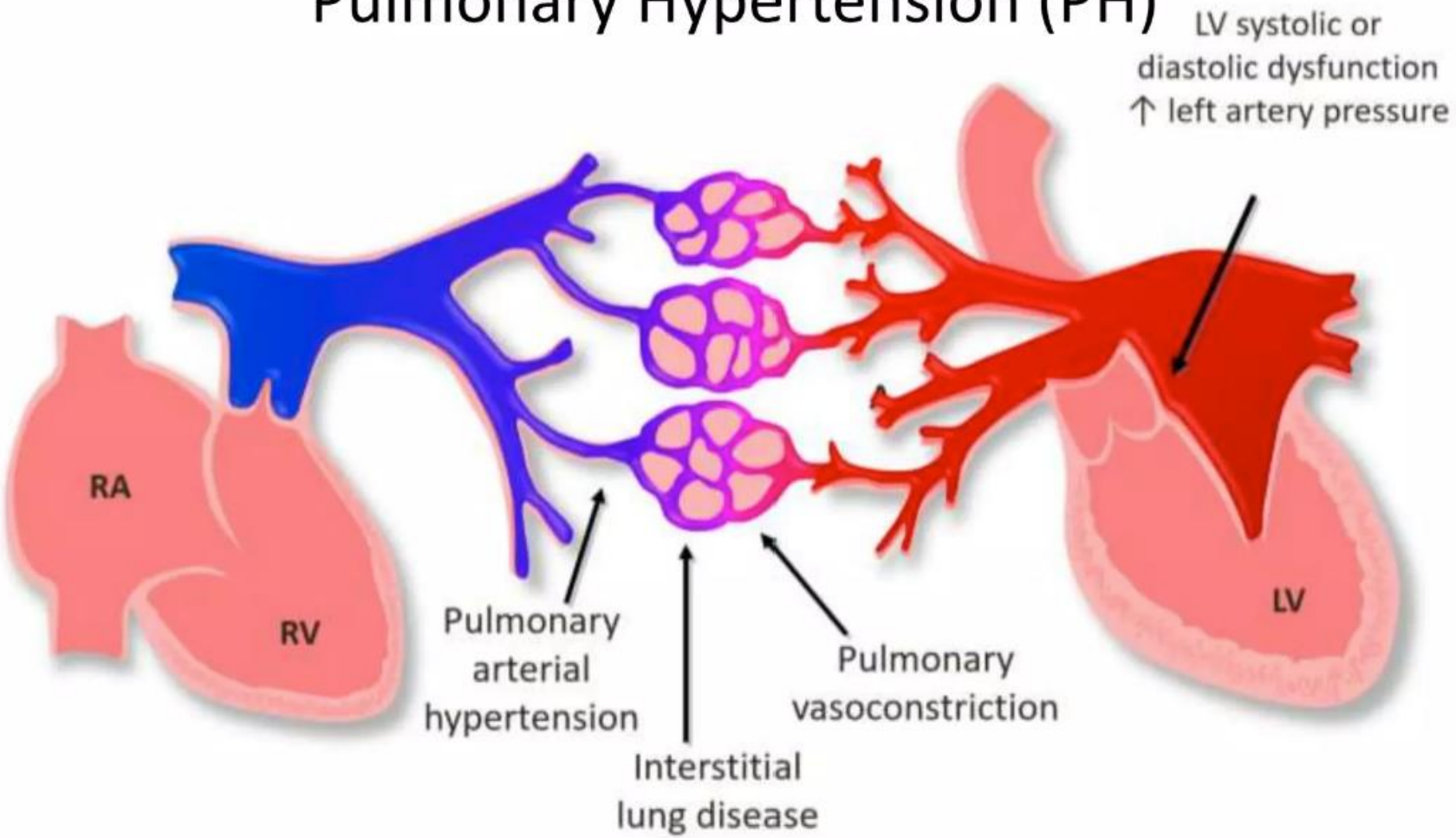
Pulmonary Hypertension: Elevated Pressures in Pulmonary Vascular Bed

PVR = $\frac{\text{mean PAP – mean LAP (or PCWP)}}{Qp}$

-in Woods Unit (mmHg/L/min)



Pulmonary Hypertension (PH)



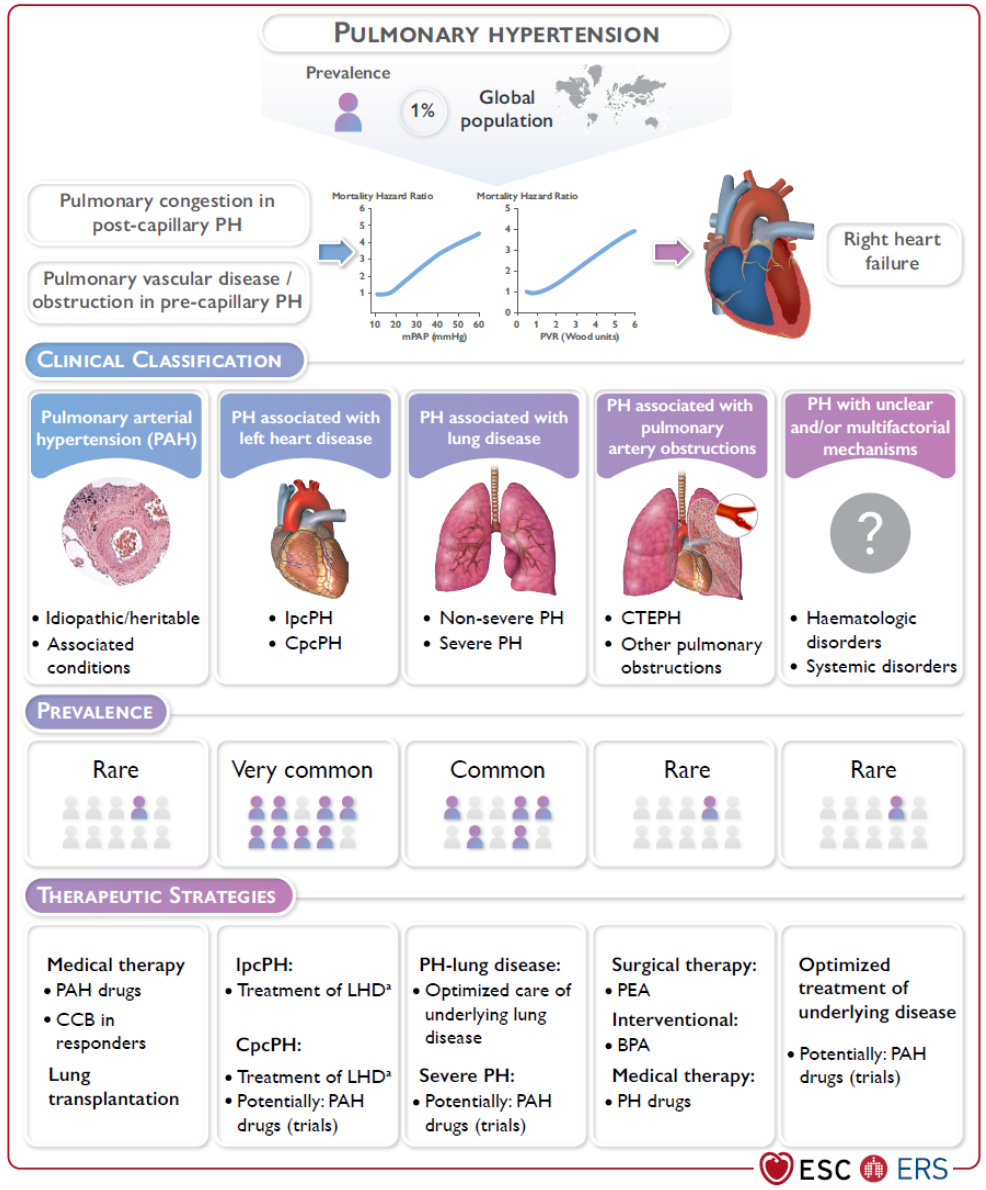


Figure 1 Central illustration. BPA, balloon pulmonary angioplasty; CCB, calcium channel blocker; CTEPH, chronic thrombo-embolic pulmonary hypertension; CpCPH, combined post- and pre-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension; LHD, left heart disease; PAH, pulmonary arterial hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension. [a]Treatment of heart failure according to the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.[27] Treatment of left-sided valvular heart disease according to the 2021 ESC/EACTS Guidelines for the management of valvular heart disease.[28]

Definition, classification and diagnosis of pulmonary hypertension
Gabor Kovacs, Sonja Bartolome, Christopher P. Denton, Michael A. Gatzoulis, Sue Gu, Dinesh Khanna, David Badesch, David Montani
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Group 1: PAH
1.1 Idiopathic
1.1.1 Long-term responders to calcium channel blockers
1.2 Heritable#
1.3 Associated with drugs and toxins#
1.4 Associated with:
1.4.1 connective tissue disease
1.4.2 HIV infection
1.4.3 portal hypertension
1.4.4 congenital heart disease
1.4.5 schistosomiasis
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
1.6 Persistent PH of the newborn

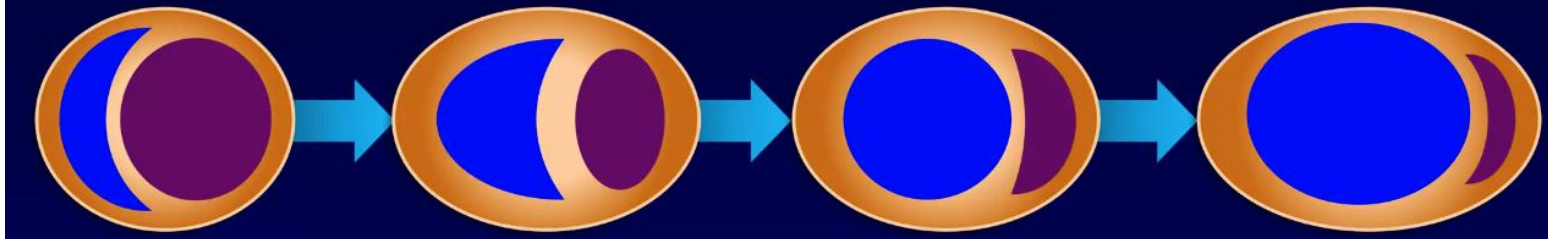
Group 4: PH associated with pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions§

Group 2: PH associated with left heart disease
2.1 Heart failure:
2.1.1 with preserved ejection fraction
2.1.2 with reduced or mildly reduced ejection fraction
2.1.3 cardiomyopathies with specific aetiologies¶
2.2 Valvular heart disease:
2.2.1 aortic valve disease
2.2.2 mitral valve disease
2.2.3 mixed valvular disease
2.3 Congenital/acquired cardiovascular conditions leading to

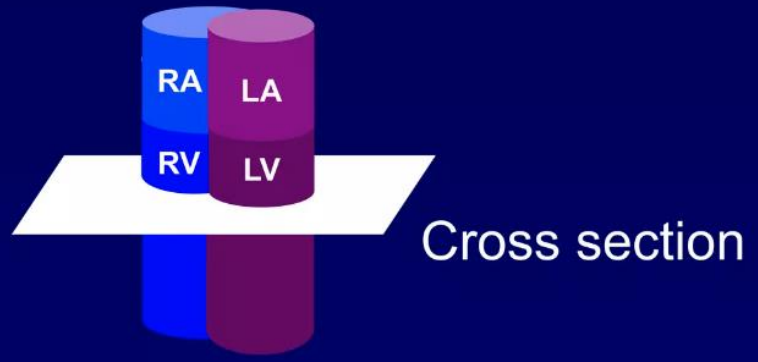
Group 5: PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders‡
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis and neurofibromatosis type 1
5.3 Metabolic disorders##
5.4 Chronic renal failure with or without haemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis
5.7 Complex congenital heart disease

The Right Ventricle in PAH

- RV pressure/volume overload
- RV failure

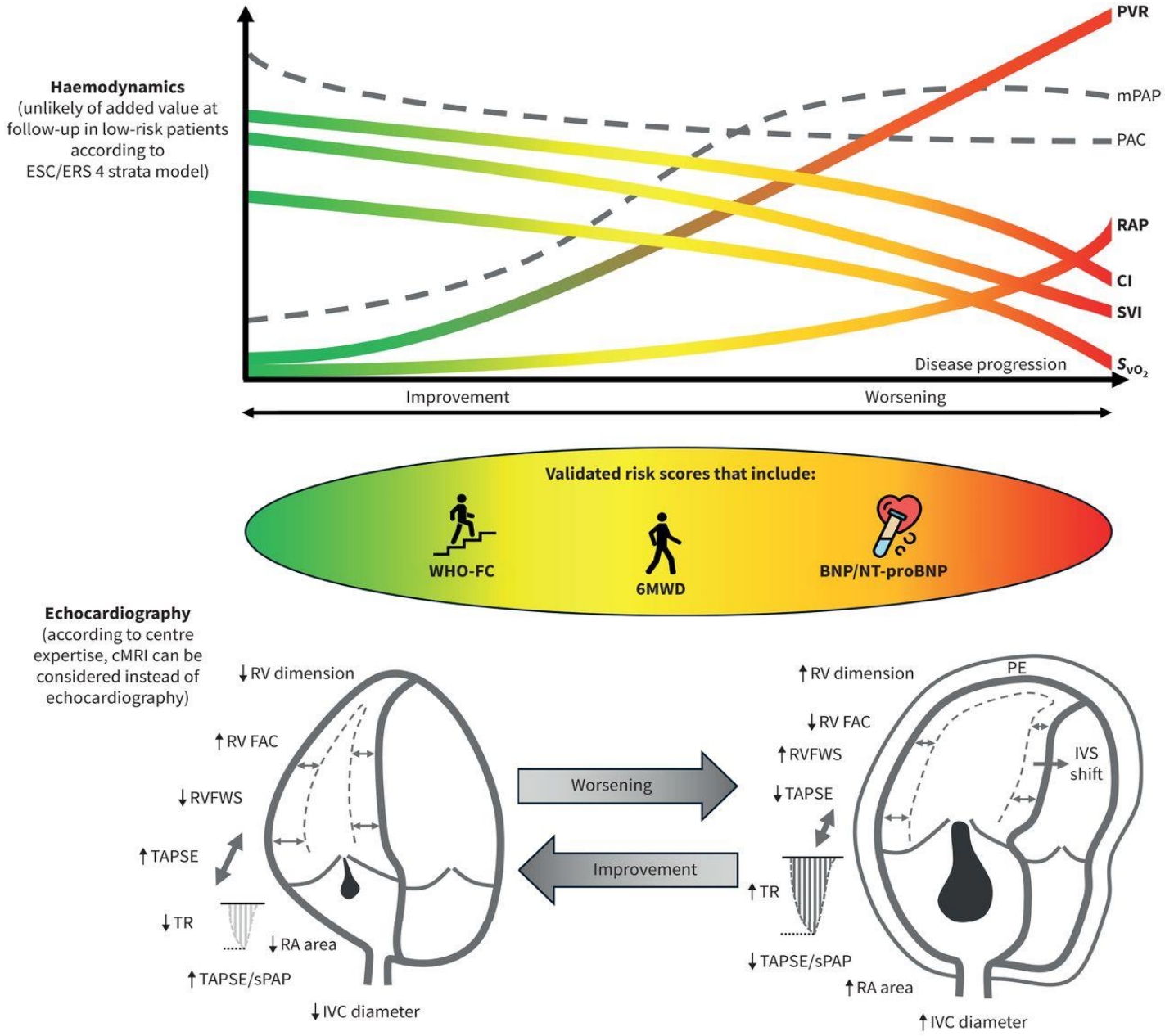


Progressive structural changes in the RV due to poor adaptation to increasing PVR



Cross section

Multidimensional strategy for risk stratification and treatment decisions in pulmonary arterial hypertension (PAH).



Fabio Dardi et al. Eur Respir J
doi:10.1183/13993003.01323-2024

Risk Stratification

Table 16 Comprehensive risk assessment in pulmonary arterial hypertension (three-strata model)

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope[a]	Repeated syncope[b]
WHO-FC	I, II	III	IV
6MWD[c]	>440 m	165–440 m	<165 m
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	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope >44
Biomarkers: BNP or NT-proBNP[d]	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
cMRI[e]	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF <37% SVI <26 mL/m^2 RVESVI >54 mL/m^2
Haemodynamics	RAP <8 mmHg CI ≥2.5 $L/min/m^2$ SVI >38 mL/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 $L/min/m^2$ SVI 31–38 mL/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 $L/min/m^2$ SVI <31 mL/m^2 SvO_2 <60%

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; pred., predicted; RA, right atrium; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; SvO_2, mixed venous oxygen saturation; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; VE/VCO_2, ventilatory equivalents for carbon dioxide; VO_2, oxygen uptake; WHO-FC, World Health Organization functional class.

[a]Occasional syncope during heavy exercise or occasional orthostatic syncope in a stable patient.

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

[c]Observe that 6MWD is dependent upon age, height, and burden of comorbidities.

[d]To harmonize with the four-strata model shown in *Table 18*, the BNP and NT-proBNP cut-off levels have been updated from the 2015 version based on data from the REVEAL registry, acknowledging that the European validation studies have used the original cut-off levels.[274,292,293,295,296,302]

[e]cMRI parameters adapted from *Section 6.2.2.2*.

REVAL Score Risk Assessment

		Score
WHO Group 1 Subgroup	APAH-CTD +1 · APAH-PoPH +3 · FPAH +2	
Demographics	Males Age >60 yr +2	
Comorbidities	eGFR <60 mL/min/1.73 m² or renal inefficiency (if eGFR is unavailable) +1	
NYHA/WHO Functional Class	I -1 · III +1 · IV +2	
Vital Signs	SBP <110 mm Hg +1 · HR >96 BPM +1	
All-Cause Hospitalizations ≤6 mo	All-Cause Hospitalizations within 6 mo +1	
6-Minute Walk Test	≥440 m -2 · 320 to <440 m -1 · <165 m +1	
BNP	<50 pg/mL or NT-proBNP <300 pg/mL -2 · 200 to <800 pg/mL +1 · ≥800 pg/mL or NT-proBNP ≥1100 pg/mL +2	
Echocardiogram	Pericardial Effusion +1	
Pulmonary Function Test	% predicted DL_{CO} ≤40 +1	
Right Heart Catheterization	mRAP >20 mm Hg Within 1 Year +1 · PVR <5 Wood Units -1	
	Sum of above	
		+6

	Low risk	Intermediate risk	High risk
Risk score	0-6	7-8	≥9

Table 18 Variables used to calculate the simplified four-strata risk-assessment tool

Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II[a]	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP,[a] ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO-FC, World Health Organization functional class.
Risk is calculated by dividing the sum of all grades by the number of variables and rounding to the next integer.
[a]WHO-FC I and II are assigned 1 point as both are associated with good long-term survival.

Risk Assessment on FU

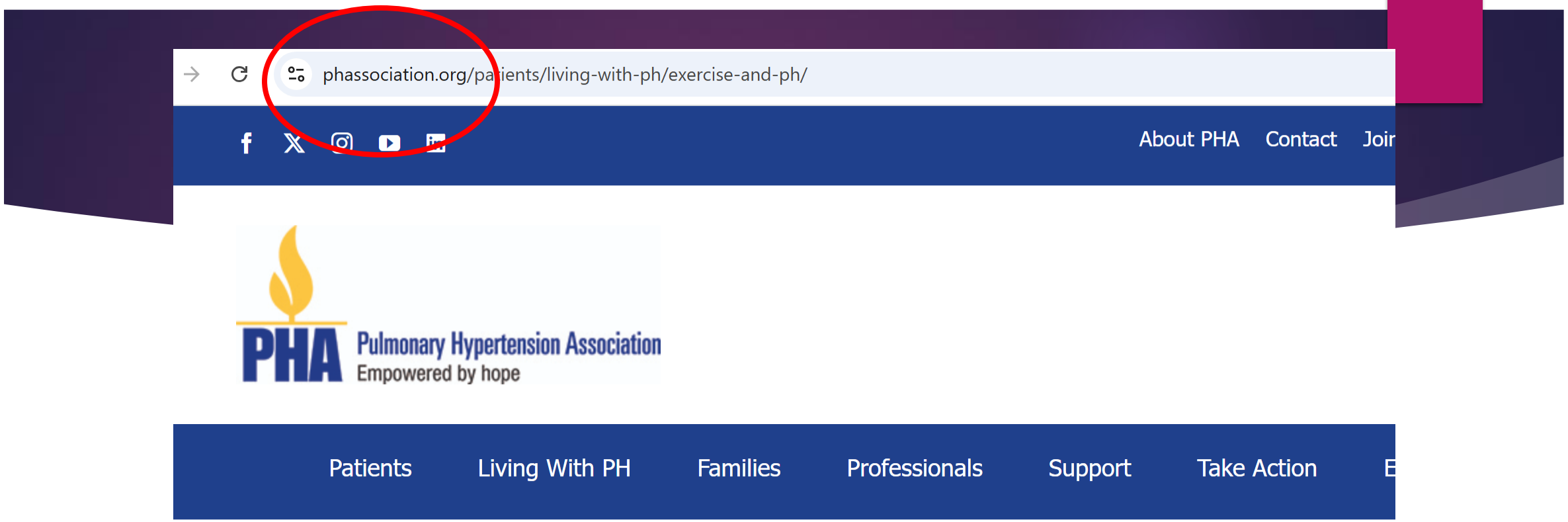
Goals of Therapy in PAH

- Achieve and maintain a low-risk status
- Improve symptoms
- Enhance functional capacity
- Improve hemodynamics
- Increase quality of life
- Prevent disease progression
- Advance survival

Galie N et al. *Euro Heart J*. 2016; 37: 67 – 119.
McLaughlin V et al. *Circulation*. 2009; 119(16): 2250 -2294.

Nonpharmacologic Treatment of PAH

- Vaccination up to date
- Oxygen if hypoxic with ambulation
- Nocturnal O2/CPAP if warranted
- Participate in a supervised exercise program
- Avoid Pregnancy
- Low Sodium/Heart Healthy Diet



EXERCISE AND PH

Regular exercise can improve exercise capacity, muscle function and quality of life for patients with pulmonary hypertension (PH).

Because the severity of PH and other health-related factors vary from patient to patient, recommendations on exercise differ for each individual. These recommendations may change over time depending on an individual's symptoms and response to treatment.

Pulmonary hypertension

A Cochrane review demonstrated that exercise training compared to usual care significantly improves exercise capacity and health-related quality of life (low quality evidence).[16] Sub-group analyses demonstrated similar results for pulmonary arterial hypertension group 1 for exercise, and that in- and out-patient PR are associated with improved exercise capacity, but in-patient PR is associated with a greater magnitude of improvement. Only one study reported one adverse event (light-headedness) during exercise. A more recent systematic review confirmed that exercise training compared to usual care significantly improves exercise capacity. [17]

16. Morris NR, Kermeen FD, Holland Exercise-based rehabilitation programmes for pulmonary hypertension. *Cochrane Database of Systematic Reviews* 2017.
17. Yan L, Shi W, Liu Z, et The benefit of exercise-based rehabilitation programs in patients with pulmonary hypertension: a systematic review and meta-analysis of randomized controlled trials. *Pulmonary Circulation* 2021;11:20458940211007810.

Pharmacologic Treatment

Therapeutic Landscape for WHO Group 1 PAH

- **Medications targeting four different pathways**

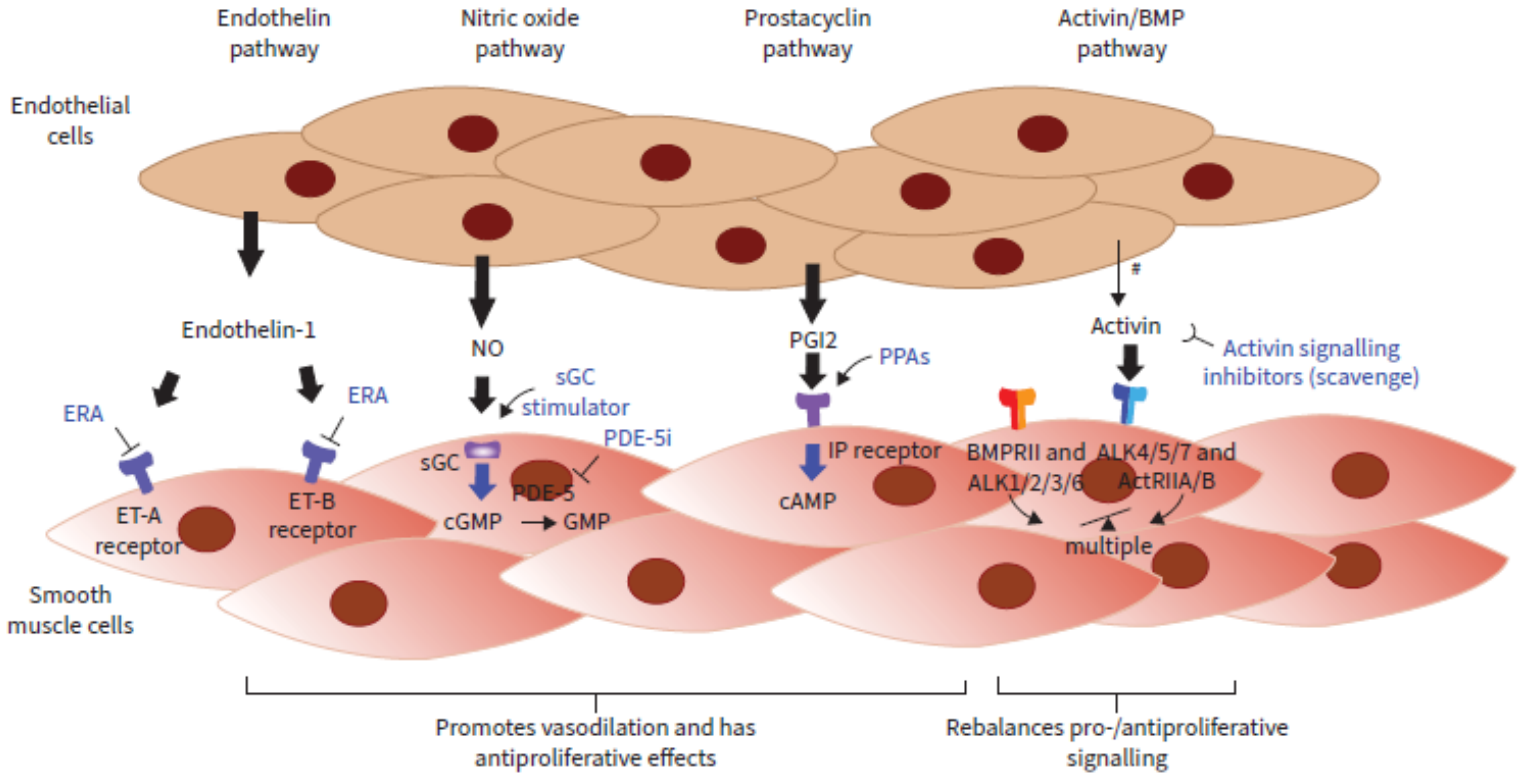
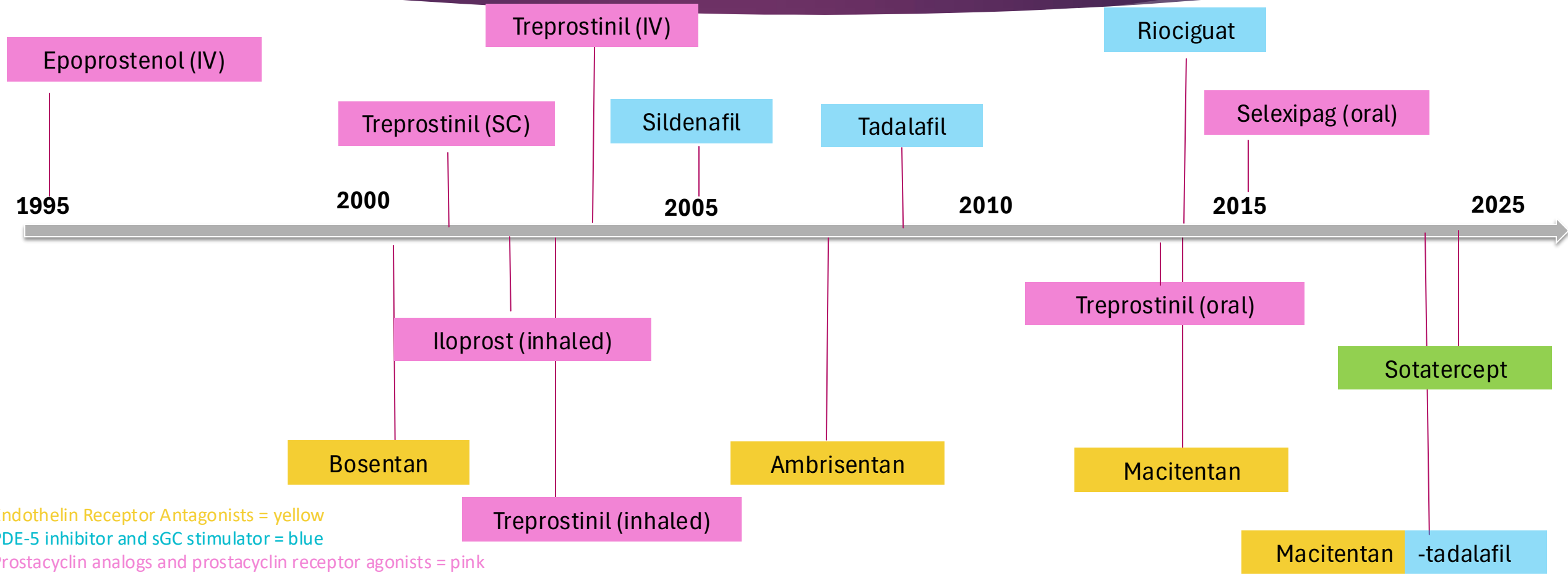


FIGURE 2 Pulmonary arterial hypertension (PAH) therapies work through four major pathways: endothelin-1 receptor antagonists (ERAs) block the endothelin (ET)-1 receptor. Phosphodiesterase-5 inhibitors (PDE-5i) and soluble guanylyl cyclase (sGC) stimulators increase signalling in the nitric oxide (NO) and cyclic GMP (cGMP) pathway, resulting in increased cGMP levels, and prostacyclin (PGI2) and other prostacyclin pathway agents (PPAs) bind the prostacyclin receptor (IP receptor), promoting the production of cAMP, leading to vasodilation and inhibiting vascular cell growth. Sotatercept, a novel biologic agent targeting the transforming growth factor-β superfamily, acts as a ligand trap for activins and related growth factors. This helps rebalance growth-promoting and growth-inhibiting signalling pathways, with multiple downstream effects. Signalling is shown as proceeding from endothelial cell to smooth muscle cell for simplicity, but is bidirectional. BMPR: bone morphogenetic protein receptor; ALK: anaplastic lymphocyte kinase; ActR: activin receptor. #: in addition, signalling mediators also originate from multiple other cell types, particularly for activin.

Eur Respir J 2024 64(4): 2401325

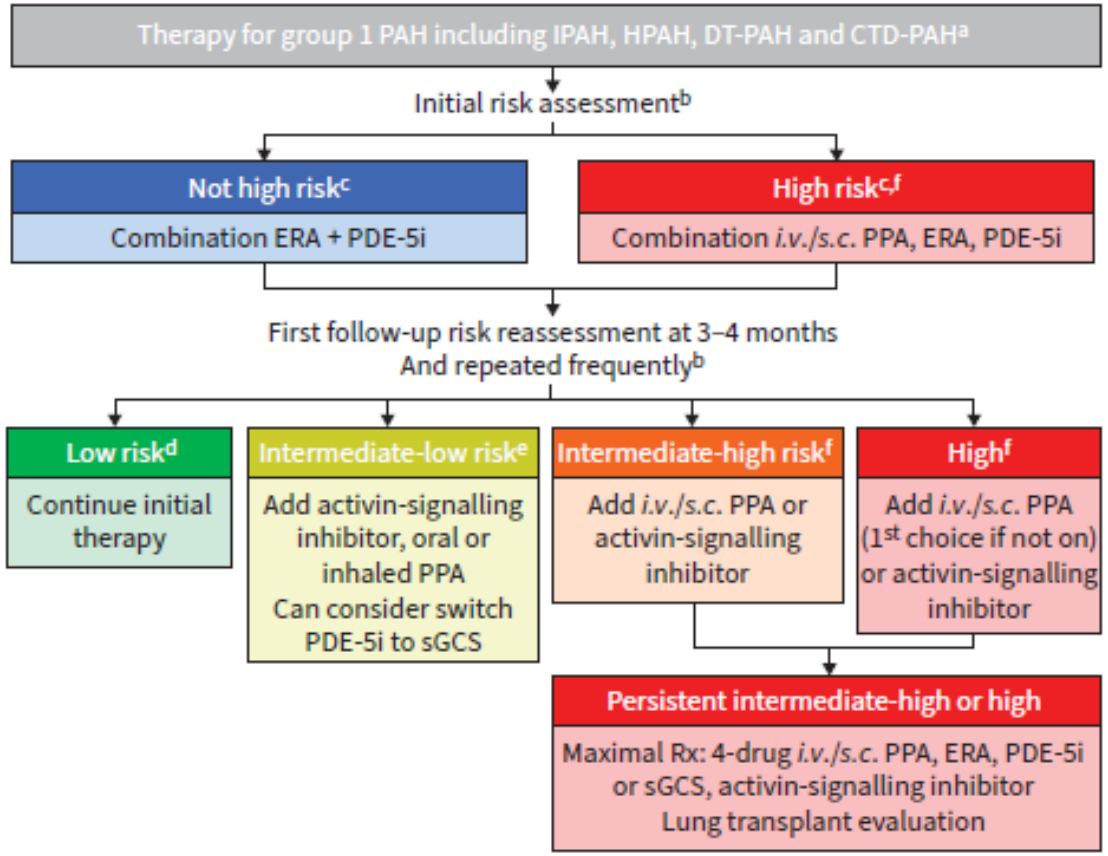
Timeline of Medication Approval



Endothelin Receptor Antagonists = yellow
PDE-5 inhibitor and sGC stimulator = blue
Prostacyclin analogs and prostacyclin receptor agonists = pink
Activin signaling inhibitor = green

Adapted from Gaine et al. Eur Respir Rev 2017; 26(146): 170095.

WHO Group 1 PAH Treatment



Treatment algorithm key points

a. The treatment algorithm is intended for patients with confirmed group 1 PAH (phenotypically clear-cut, including **mPAP ≥25 mmHg and PVR >3 Wood Units** and no significant response on acute vasoreactivity testing). See text for treatment in PAH with complex phenotypes.
b. ***Risk assessment*** should be performed at baseline, within 3–4 months and periodically thereafter, and using FC, 6MWD and natriuretic peptides as a part of a validated risk calculator. Haemodynamics, RV imaging and other measures should be used to supplement risk assessment.
c. ***Initial triple therapy*** with an *i.v./s.c.* PPA is recommended in high-risk patients and may be considered in non-high risk with severe haemodynamics and/or poor RV function.
d. Most ***low-risk patients*** at follow-up should continue initial therapy.
e. Clinical trials with oral and inhaled treprostinil included ***only patients on monotherapy***, while studies of selexipag and sotarcept included patients on combination therapy.
f. ***Transplant referral*** should be considered for select high-risk patients at diagnosis, and for intermediate-high and high-risk patients at first or subsequent follow-up.

FIGURE 1 Treatment algorithm. PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: hereditary PAH; DT: drug and toxin; CTD: connective tissue disease; ERA: endothelin-1 receptor antagonist; PDE-5i: phosphodiesterase-5 inhibitor; *i.v.*: intravenous; *s.c.*: subcutaneous; PPA: prostacyclin pathway agent; sGCS: soluble guanylyl cyclase stimulator; Rx: prescription; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; FC: functional class; 6MWD: 6-min walk distance; RV: right ventricle.

Eur Respir J 2024 64(4): 2401325

WHO Group 1 PAH – Key Clinical Trials

TABLE 4 Key randomised trials of prostacyclin pathway agents, riociguat and sotatercept in studies of patients on background endothelin-1 antagonists and/or phosphodiesterase-5 inhibitors

Study [reference] drug	Subjects n	Blinded	Duration weeks	Background medical treatments %				Primary end-point	Primary end-point results (95% CI)	Positive primary end-point	Other key positive end-points
				0	1	2	3				
GRIPHON [28] selexipag	1156	Yes	~71	20	47	33	0	TTCW	HR 0.60 (0.46–0.78)	Yes	6MWD, NT-proBNP
STELLAR [8] sotatercept	323	Yes	24	0	4	35	61	6MWD	HLE 40.8 (27.5–54.1) m	Yes	6MWD, PVR, NT-proBNP, FC, TTCW, others
TRIUMPH [33] inhaled treprostinil	235	Yes	12	0	100	0	0	6MWD	HLE 20.0 (8.0–32.8) m	Yes	6MWD, NT-proBNP, QoL
FREEDOM-EV [11] treprostinil *p.o.*	690	Yes	~52	0	100	0	0	TTCW	HR 0.74 (0.56–0.97)	Yes	NT-proBNP, FC
REPLACE [15] riociguat	226	No	24	0	29	71	0	Clinical improvement	OR 2.78 (1.53–5.06)	Yes	6MWD, FC

TTCW: time to clinical worsening; HR: hazard ratio; 6MWD: 6-min walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; HLE: Hodges–Lehmann estimate; PVR: pulmonary vascular resistance; FC: functional class; QoL: quality of life.

Eur Respir J 2024 64(4): 2401325

Endothelin Receptor Antagonist

Drug	Class	ROA	Typical Dose	Monitoring	Adverse Effects
Bosentan (Tracleer)	Endothelin-A and -B receptor antagonist	PO	Initial 62.5 mg BID x 4 weeks, then up to 125 mg BID	LFTs (baseline & monthly) - ***REMS** Contraindicated in pregnancy	Hepatic impairment, embryo-fetal toxicity, edema, nasal congestion, flushing, headache, anemia, decreased sperm counts
Ambrisentan (Letairis)	Endothelin-A receptor antagonist	PO	5 to 10 mg daily	Baseline Hgb and LFTs Contraindicated in pregnancy	
Macitentan (Opsumit)	Endothelin-A and -B receptor antagonist	PO	10 mg daily		

Nitric Oxide Pathway

Drug	Class	ROA	Typical Dose	Monitoring	Adverse Effects
Sildenafil (Revatio)	PDE-5i	PO	20 to 80 mg TID	Vital signs	Headache, flushing, epistaxis, vision changes, tinnitus
Tadalafil (Adcirca)	PDE-5i	PO	40mg daily	Vital signs	Headache, flushing, myalgia, vision changes, tinnitus
Riociguat (Adempas)	Soluble guanylate cyclase stimulator	PO	0.5-1 mg TID, may increase by 0.5 mg TID every 2 weeks to 2.5 mg TID	Monthly pregnancy test ***REMS**	Embryo-fetal toxicity, dyspepsia, nausea, diarrhea, headache, flushing, vision changes, tinnitus

Prostacyclin Pathway

Drug	Class	ROA	Typical Dose	Monitoring	Adverse Effects
Epoprostenol (Veletri, Flolan)	Synthetic prostacyclin	IV	Initiate at 2 ng/kg/min and titrate every 4-6 hours to goal max tolerated dose, 25-60 ng/kg/min or greater over time	Vital signs, signs of rebound PH	Flushing, N/V, jaw pain, HA, myalgia, hypotension
Iloprost (Ventavis)	Synthetic prostacyclin	INH	Initial 2.5 mcg, if tolerated give 5 mcg 6-9 times per day	Vital signs, asthma, pulmonary infections	Bronchospasm, cough, vasodilation, flushing, HA
Treprostinil (Remodulin) – IV or SC (Orenitram) - oral (Tyvaso neb) - inhaled (Tyvaso DPI) - inhaled (Yutrepia) – inhaled	Synthetic prostacyclin	INH IV, SC PO	INH: four times daily IV/SC: 1.25 ng/kg/min continuous infusion, titrate as tolerated PO: 0.25 mg BID or 0.125 TID, titrate every 3 to 4 days as tolerated	Vital signs, pulmonary irritation (INH)	Flushing, N/V, jaw pain, HA, myalgia, hypotension, injection site reactions (SC), blood stream infections (IV)
Selexipag (Uptravi)	Prostacyclin IP-receptor agonist	PO	200 to 1600 mcg BID	LFTs, vital signs	HA, N/V, jaw pain

Parenteral Prostacyclin Devices

Intravenous

CADD-Legacy® 1
Portable electronic infusion pump

CADD®-SOLIS AMBULATORY INFUSION PUMP

Subcutaneous

Smiths Medical CADD-MS® 3
Microinfusion pump

It is very important these medications are not stopped!
IV Line should not be used for any other purpose and should not be flushed!

Activin Pathway

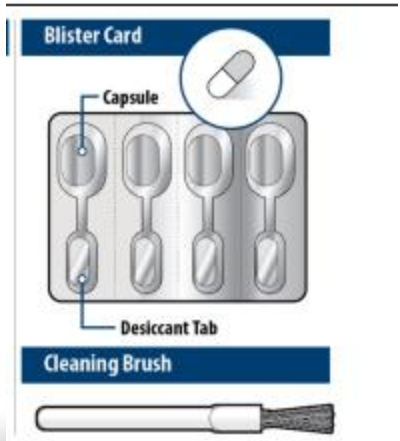
Drug	Class	ROA	Typical Dose	Monitoring	Adverse Effects
Sotatercept (Winrevair)	Activing signaling inhibitor	Subcutaneous Injection (done at home)	Initial dosing: 0.3 mg/kg Maintenance dose: 0.7 mg/kg every 3 weeks	Hgb and platelets before each dose for the first 5 doses, then periodically thereafter	Headache, bleeding (epistaxis), telangiectasia, diarrhea

Inhaled Prostacyclin Devices

Iloprost (Ventavis)

Treprostinil (Tyvaso)

Treprostinil (Yutrepia)



Inhaled Prostacyclin

Iloprost (Ventavis)	
Device	~~Home: iNeb inhaler~~ Hospital: Aero Neb
Dosing	2.5 to 5 mcg 6-9 times daily • during waking hours, minimum 2 hours between doses
Half-life	20 to 30 minutes
Important Note	Ampules come in several concentrations

Device discontinued

Inhaled Prostacyclin

Treprostinil (Tyvaso) nebulized	
Device	Tyvaso Inhalation System • Patient specific device • With start of therapy patients are supplied with <u>two devices</u>
Dosing	• 1 breath =6 mcg • Initial: 1-3 breaths QID • Titrated by 1-3 breaths (typically weekly) • Maintenance Dose: 9-12 breaths QID *higher dosing may be used
Half-life	4 hours
Important Note	• One ampule of medication supplies doses for all day • Outpatient mediation and supplies come from specialty pharmacy; must have home supply before discharge

TIPS FOR DEVICE SETUP

Before setting up your device, wash your hands.

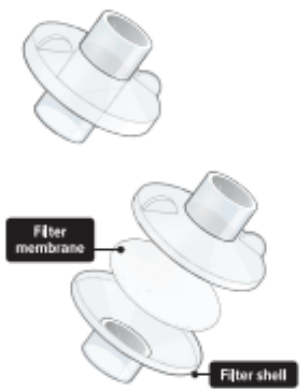
- **Fill the water chamber with distilled water only.** Distilled water is highly purified and can be purchased at most grocery stores and pharmacies.
- **Place 1 new medicine cup into the water chamber of the device.** Placing multiple cups will prevent the flow of medicine. Do not use a cup that is damaged, dirty, or was used before.

ONE AMPULE OF TYVASO WILL COVER A FULL DAY OF TREATMENTS.

One ampule contains enough medicine for all 4 treatment sessions in a day. Be sure to discard any remaining medicine at the end of the day. If you get any medicine from the ampule on your hands, wash them to prevent irritation.

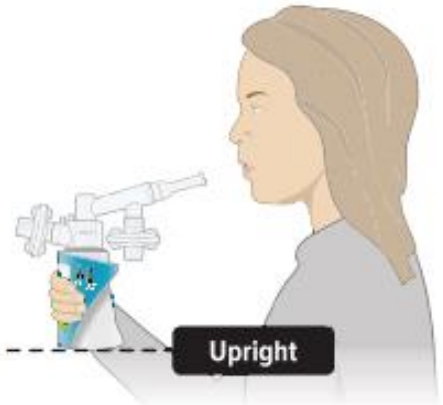
Once you have prepared the medicine and are assembling your device:

- **Do not force the parts together.** When the device is assembled correctly, the parts fit together easily.
- **Each day, you will need to replace the filter membrane within each filter shell.** New filter shells (which you will receive once a month in your refill kit) come with fresh filter membranes already installed.



TIPS FOR TAKING TYVASO

- **Ensure the base of the device is level.** Use a mirror if you want to check your positioning.*
- **Sit or stand upright.** Don't lean down to the mouthpiece on the device when taking TYVASO. Look forward and keep the device level to your mouth.



- **Do not hold your breath after inhaling.** Take a normal full breath for 3 seconds. When the lights stop flashing, remove your lips from the mouthpiece, breathe out normally, and prepare for your next breath. You may not be able to see the medication moving through the mouthpiece, but even if you cannot see it, it is being delivered.
- **Inhale your prescribed number of breaths, 4x daily.** Take your treatments during waking hours, approximately 4 hours apart. You may want to set an alarm on your phone or consider asking family members to help remind you.

*It is recommended that you pick up and hold the device, as it is lightweight.

CLEANING TIPS

DISCARD ANY EXTRA MEDICATION AFTER FINAL TREATMENT OF THE DAY.

Any remaining medication should NOT be used the following day.

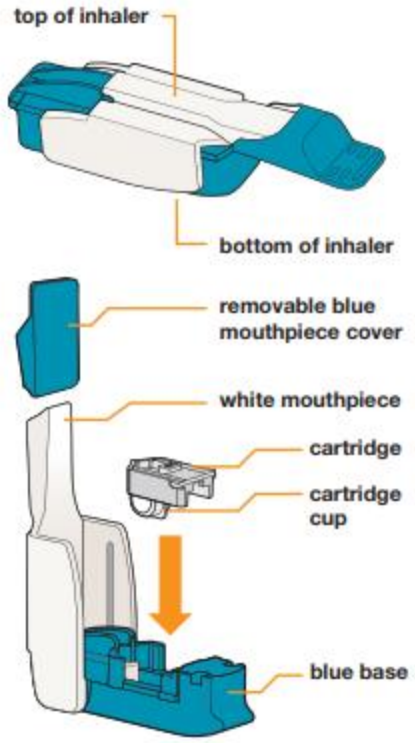
- **Discard the used filter membranes and medicine cup at the end of each day.** These components should not be reused.
- **At the end of each day, clean the reusable accessories by hand in warm, soapy water and allow them to air-dry overnight.** Do not place your device in water; simply empty it and turn it upside down to dry. Do not place your device or its accessories in a dishwasher, an oven, or a microwave.
- **Replace your device's accessories monthly.** You will receive new accessories with each monthly refill of your TYVASO prescription.

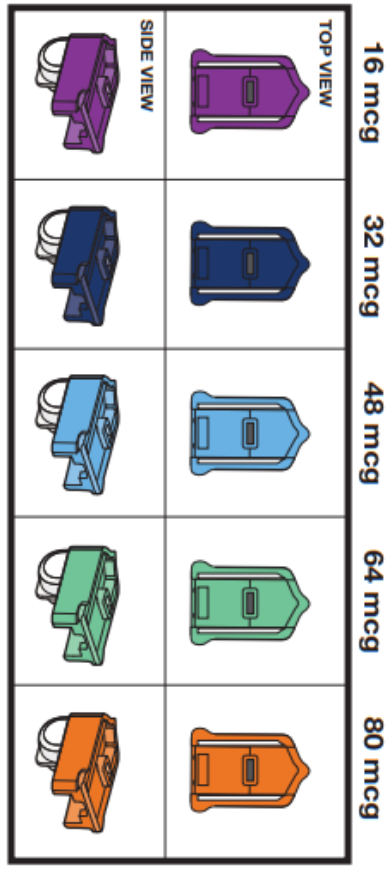
IT IS RECOMMENDED TO CHARGE YOUR DEVICE OVERNIGHT.

A fully charged device will last at least a full day. If there is not enough charge to conduct a treatment session, "Charge battery" appears on the screen. You can also charge the device in between uses if needed. Your device can be used while charging (just like your cell phone).

Inhaled Prostacyclin

Treprostinil (Tyvaso DPI) – dry powder	
Device	Tyvaso DPI inhaler • Inhaler replaced every 7 days
Dosing	Initial dose: 16 mcg QID Titrate by 16 mcg every 1-2 weeks Maintenance dose: usually 64 mcg QID *higher doses can be used
Half-life	4 hours
Important Note	• Do not wash the inhaler, must be kept dry • May use multiple different cartridges based on dose prescribed





Inhaled Prostacyclin

Tyvaso DPI

Position Inhaler in Mouth

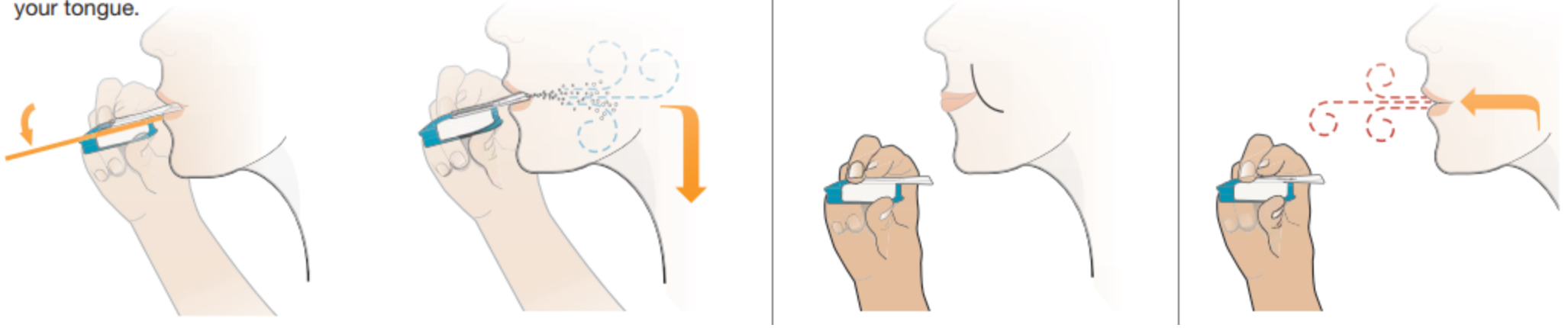
- Keeping your head level, place the mouthpiece in your mouth and close your lips around the mouthpiece to form a seal.
- Tilt the inhaler slightly downward while keeping your head level (see **Figure W**).

Note: This helps prevent the powder from being blocked by your tongue.

Inhale Deeply, Hold Breath, then Exhale

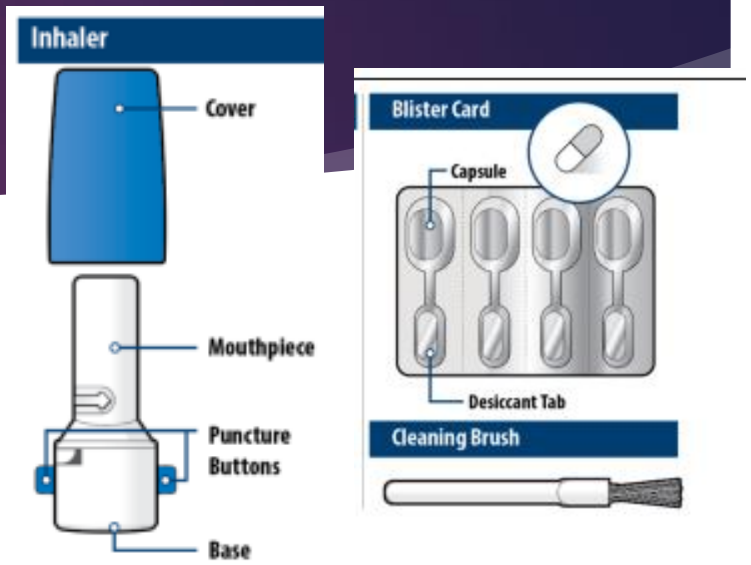
- With your mouth closed around the mouthpiece, **inhale** deeply through the inhaler (see **Figure X**).
- Then remove the inhaler from your mouth and **hold your breath** for as long as you comfortably can (see **Figure Y**).
- Then **blow out** (exhale) and continue to breathe normally (see **Figure Z**).

9



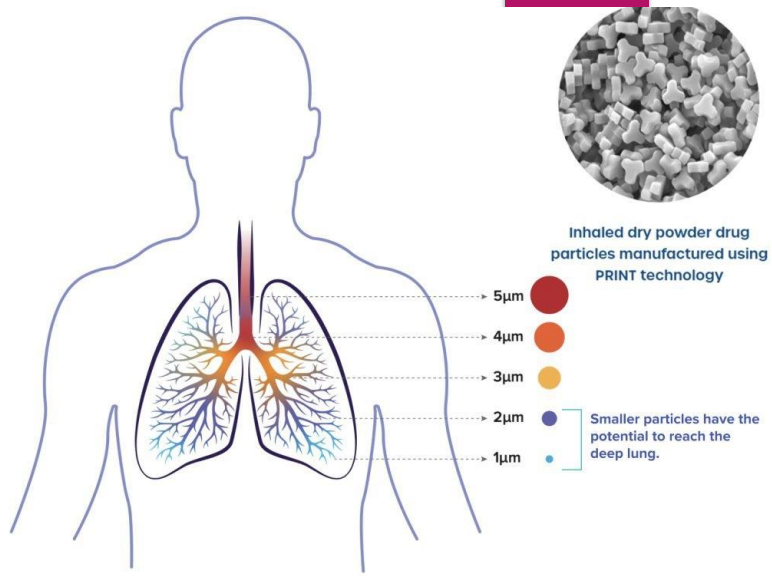
Inhaled Prostacyclin

Treprostinil (Yutrepia) – dry powder	
Device	• Inhaler replaced every 7 days
Dosing	Initial dose: 26.5 mcg QID Titrate by 26.5 mcg every 1-2 weeks Maintenance dose: usually 106 mcg QID *higher doses can be used
Half-life	4 hours
Important Note	• Use **two breaths** with each dose • Outpatient mediation and supplies come from specialty pharmacy; must have home supply before discharge • Ensure patients do not swallow capsules • Clean capsule chamber with brush, new brush each day • Clean mouthpiece with dry cloth



		Capsules Needed
Dose (mcg)	26.5	1 Yellow (26.5 mcg)
	53	1 Green (53 mcg)
	79.5	1 Blue (79.5 mcg)
	106	1 Purple (106 mcg)
	132.5	1 Green (53 mcg) + 1 Blue (79.5 mcg)
	159	2 Blue (79.5 mcg)
	185.5	1 Blue (79.5 mcg) + 1 Purple (106 mcg)
	212	2 Purple (106 mcg)

Inhaled Prostacyclin



Yutrepia

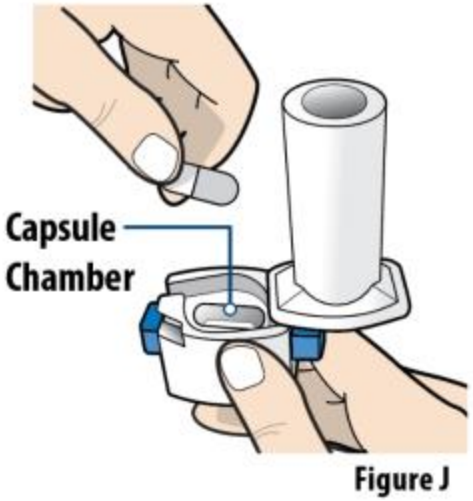


Figure J

STEP 7. Puncture the capsule.

a. Put one finger on top of the capsule to hold it down **(See Figure K)**.
b. While still holding down the capsule, firmly press both puncture buttons all the way in with your other hand **(See Figure L).** Then let go of (release) the puncture buttons. This will puncture the capsule. You only need to press the puncture buttons 1 time.
c. Hold the base of the inhaler and rotate the mouthpiece to close it.

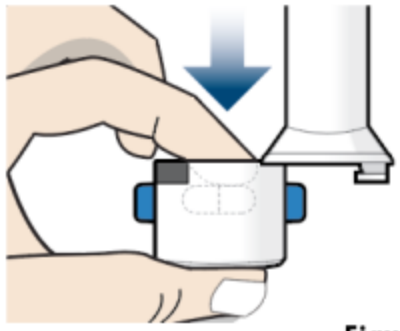
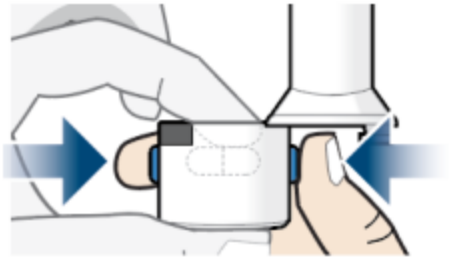
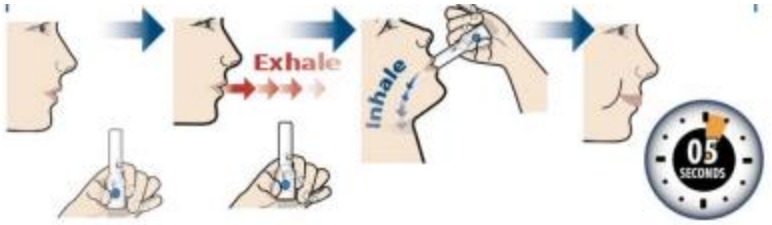


Figure K





Two breaths per dose

Inhaled Prostacyclin

- Selection of nebulized or dry-powder products is based in part on patient's respiratory function
- **SHOULD NOT INTERCHANGE BETWEEN INHALED FORMULATIONS** without consulting pulmonary hypertension specialist

Dosage for Transition from Tyvaso® (treprostinil) Inhalation Solution:

The following regimens of Tyvaso DPI and Tyvaso give similar exposure:

Tyvaso DPI Cartridge Strength	**Tyvaso Number of Breaths**
16 mcg	≤5 (≤30 mcg)
32 mcg	6 to 7 (36 to 42 mcg)
48 mcg	8 to 10 (48 to 60 mcg)
64 mcg	11 to 13 (66 to 78 mcg)
80 mcg	14 to 15 (84 to 90 mcg)

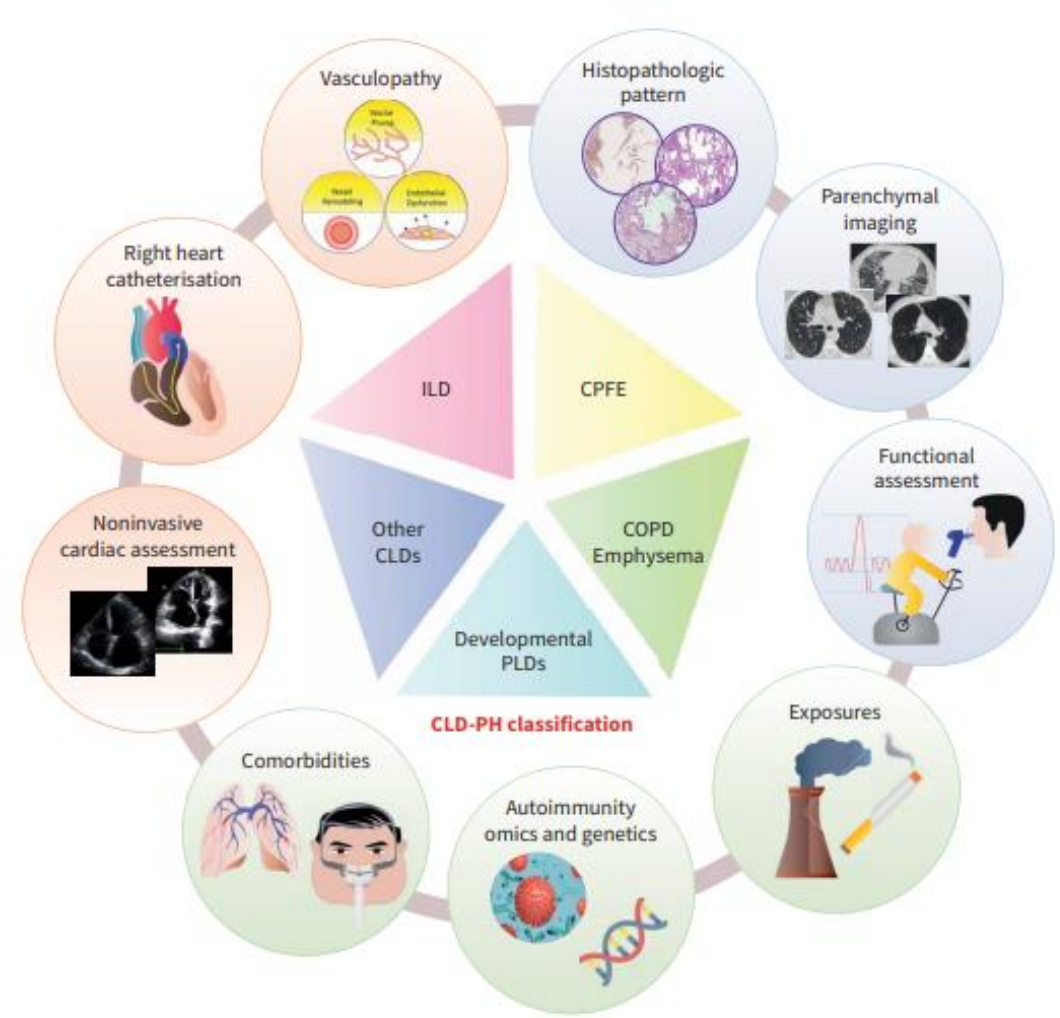
Current Tyvaso Dose*	**YUTREPIA Dose**
(Number of Breaths)	**mcg**
5 or less breaths	26.5 mcg
6 to 8 breaths	53 mcg
9 to 11 breaths	79.5 mcg
12 to 14 breaths	106 mcg
15 to 17 breaths	132.5 mcg
18 or more breaths	159 mcg

*Each breath of Tyvaso delivers approximately 6 mcg of treprostinil.

WHO Group 3

WHO Group 3 Treatment

- Important to treat underlying condition
- Use of pulmonary hypertension therapies should be carefully considered, as some treatments can cause harm
- Treatment with inhaled prostacyclin therapy can be beneficial in treating pulmonary hypertension in some patients with ILD



Eur Respir J 2024; 64: 2401200

WHO Group 3 – Clinical Trials

PERFECT Trial	
Design	Multi-center, randomized, double-blind, placebo-controlled, crossover
Population	Adult **COPD patients** (n=64) with pre-capillary PH with mPAP ≥30 mmHg and PVR ≥4 WU
Treatment	Inhaled treprostinil (neb) vs. placebo
Outcome	**Stopped early for increasing risk of serious events and suggestive evidence of increased risk of mortality**

Eur Respir J 2024; 63: 2400172

WHO Group 3 – Clinical Trials

INCREASE Trial	
Design	Multi-center, randomized, double-blind, placebo-controlled
Population	Adults with ILD and pulmonary hypertension (mPAP≥ 25 mm Hg, PVR > 3 wood units, PWCP ≤ 15 mm Hg) (n=326)
Treatment	Inhaled treprostinil (nebulizer) vs. placebo
Primary Outcome	Change in 6MWD at 16 weeks
Secondary Outcome	Change in NT-proBNP and time to clinical worsening at 16 weeks

N Engl J Med 2021;384:325-34.

Table 2. Summary of Primary and Secondary End Points.*

End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
Primary end point				
Change in peak 6-minute walk distance from baseline to wk 16 — m†	21.08±5.12	−10.04±5.12	31.12±7.25 (16.85 to 45.39)‡	<0.001
Secondary end points§				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change — pg/ml	−396.35±1904.90	1453.95±7296.20		
Median — pg/ml	−22.65	20.65		
Range — pg/ml	−11,433.0 to 5373.1	−5483.3 to 87,148.3		
Ratio to baseline	0.85±0.06	1.46±0.11	0.58±0.06 (0.47 to 0.72)‖	<0.001
Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		
Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m†	18.77±4.99	−12.52±5.01	31.29±7.07 (17.37 to 45.21)‡	<0.001
Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m	9.3±5.5	−12.7±5.5	21.99±7.7 (6.85 to 37.14)‡	0.005††

PATIENT CASE

Patient Case

- DB is a 30-year-old female who presents to the hospital with worsening shortness of breath.
- She noticed that over the past 3 months she has not been able to walk her dog as far throughout her neighborhood.
- PMH: Seasonal allergies
- Current medications: ibuprofen 400 mg if needed (reports use of 800 mg twice daily for 2-3 days/month during menstrual period)

Patient Case

- Height: 5'6''
- Weight: 66 kg
- Vitals: HR 80 bpm, BP 110/78 mm Hg, O_2 Sat 95% (room air)
- Laboratory results:
  - pro-BNP 55 pg/mL

140	105	16	87
4.6	27	0.9	

- 6MWD= 450 meters
- ECHO: Moderately dilated right ventricle, LVEF 60% with normal systolic function, no pericardial effusion
- Right Heart Catheterization:
  - PA 70/30 mm Hg, mPAP 43 mm Hg
  - PA saturation 64%
  - RA pressure 5 mm Hg
  - PVR 6.7 Woods units
  - Cardiac index 2.3 L/min/m^2
  - SVR 1482 dynes·sec·cm^{-5}
  - PAWP 10 mm Hg

Patient Case

- After further diagnostic testing, DB is diagnosed **idiopathic PAH**.
- Her current symptoms are significant consistent with WHO functional class II, HR 85 bpm, BP 115/79 mm Hg

- Baseline
  - PA 70/30 mm Hg
  - mPAP 43 mm Hg
  - PVR 6.7 Woods units
  - Cardiac index 2.3 L/min/m^2

- Vasoreactivity testing
  - PA 60/23 mm Hg
  - mPAP 38 mm Hg
  - PVR 6.7 Woods units
  - Cardiac index 2.5 L/min/m^2

Patient Case

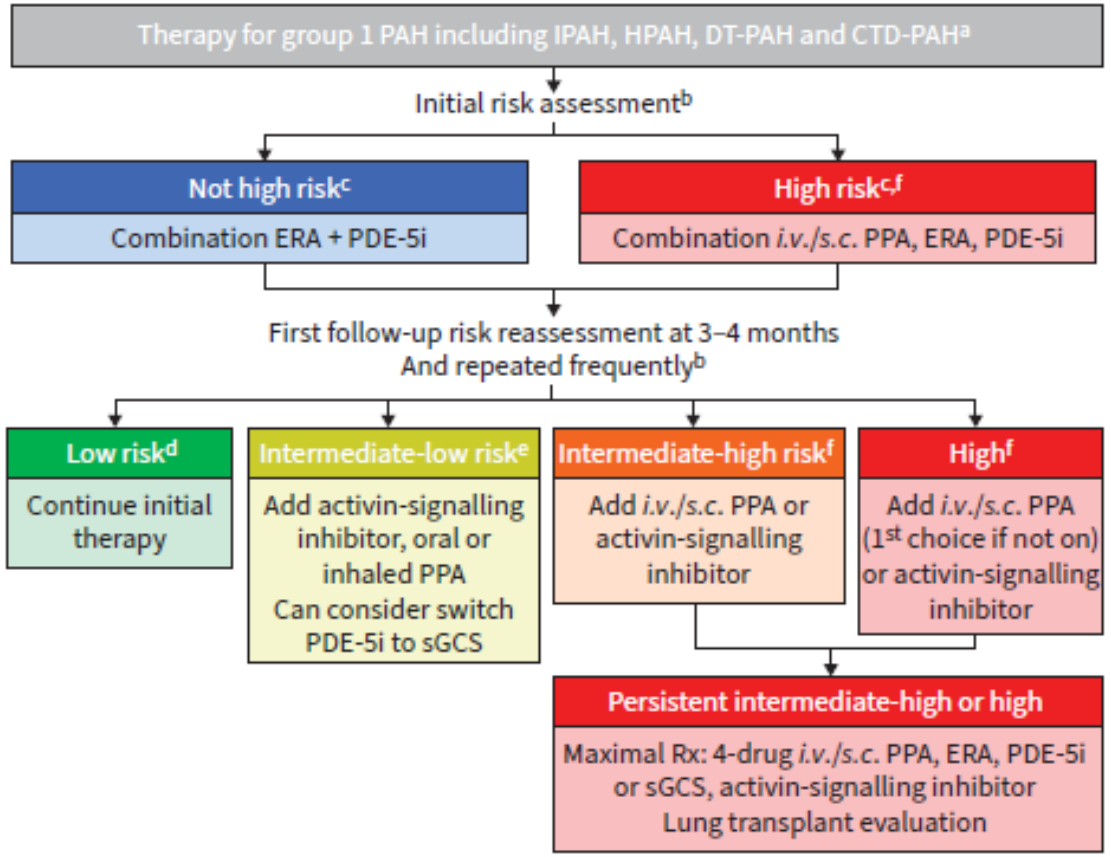
Which is appropriate initial medication treatment for DB?

A. Inhaled treprostinil

B. Sildenafil

C. Oral treprostinil and sildenafil

D. Tadalafil and macitentan



Patient Case

- Pregnancy DB returns to clinic in 3 months after initiating treatment
- DB reports one episode of syncope in the past week.
- 6MWD = 300 meters (previously 450 meters)
- Laboratory results:
  - pro-BNP 1643 pg/mL
  - AST 40 U/L, ALT 54 U/L
  - Pregnancy test: negative

- Vitals: HR 90 bpm, BP 105/70 mm Hg, O_2 Sat 91% (room air)

140	105	25	97
4.6	27	1.2	

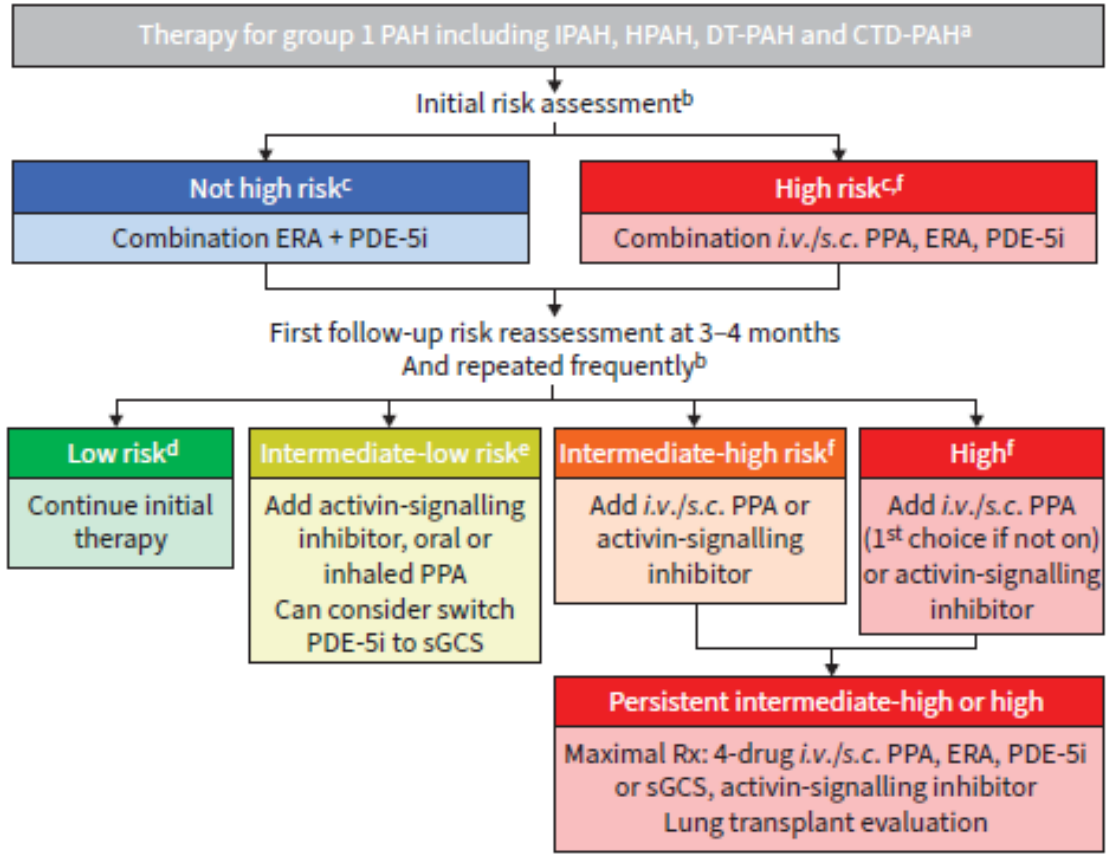
ECHO results:

Severely dilated right ventricle, LVEF 40%, no pericardial effusion

Patient Case

What should be the next step in treatment?

A. Add inhaled treprostinil
B. Add intravenous epoprostenol
C. Add selexipag
D. No changes needed



Thank You!