Choosing the Right Therapy: Adult and Pediatric Perspectives on PH Risk Assessment

Speakers:
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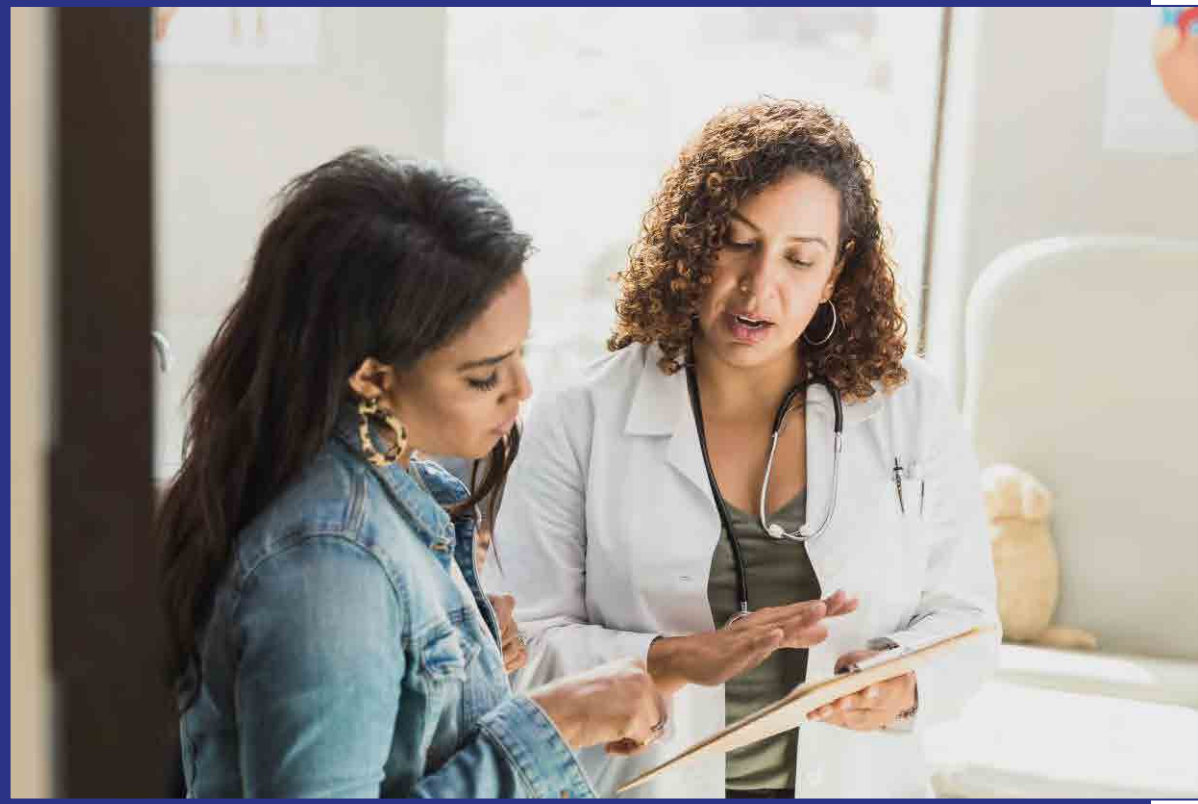

Disclosures:

Namita Sood, MD, FCCP - UC -Davis

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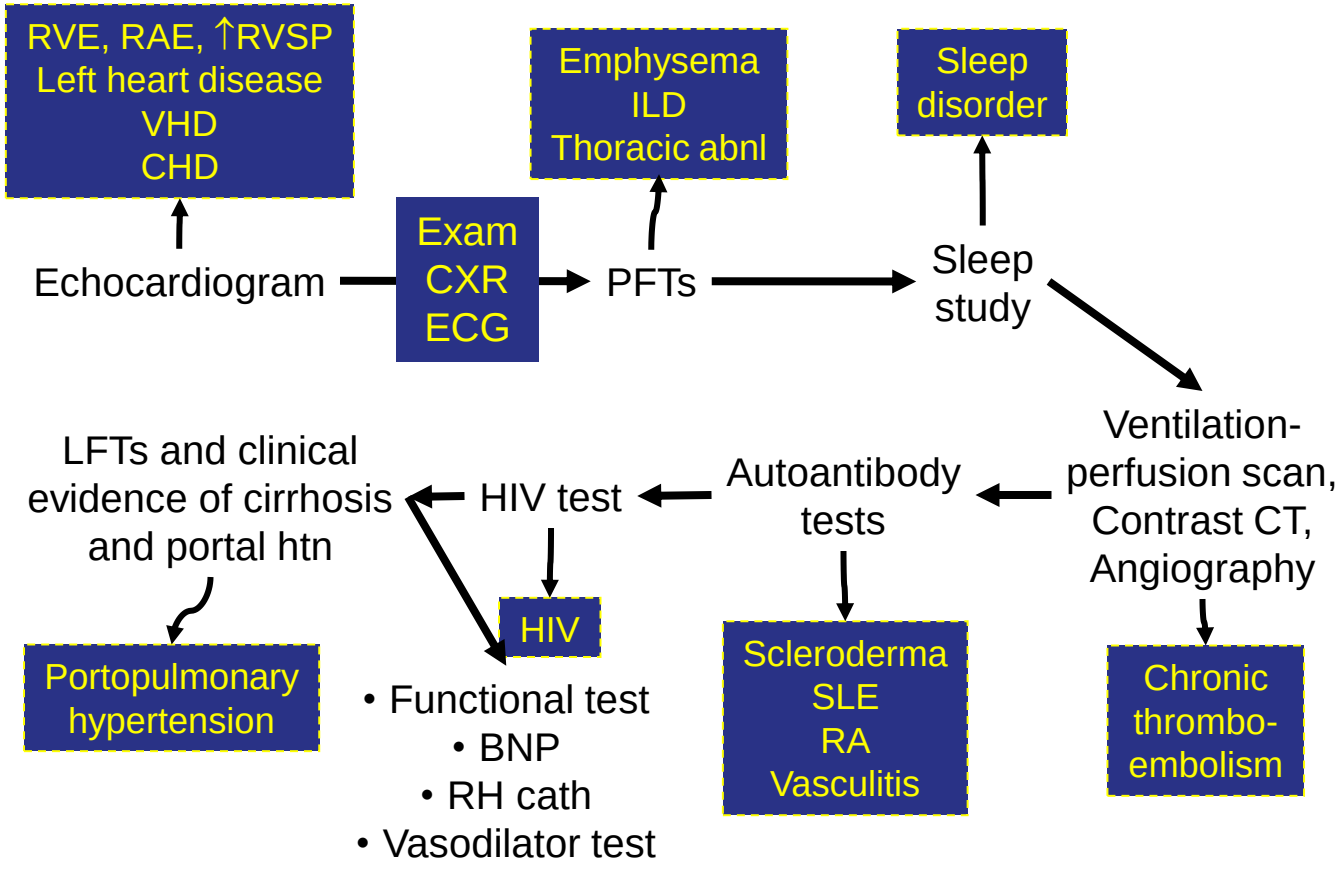
Diagnostic Approach



McLaughlin VV, McGoon Michael D. *Circulation.* 2006;114:1417-1431.

2022 ERS ESC Clinical Classification of PH

1. Pulmonary Arterial Hypertension
1.1 Idiopathic PAH
1.1.1 Non-responders at vasoreactivity testing
1.1.2 Acute responders at vasoreactivity testing
1.2 Heritable PAH
1.3 Drugs and toxins induced
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 syndrome

2. PH due to left heart disease
2.1 Heart failure:
2.1.1 with preserved ejection fraction
2.1.2 with reduced or mildly reduced ejection fraction
2.2 Valvular heart disease
2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

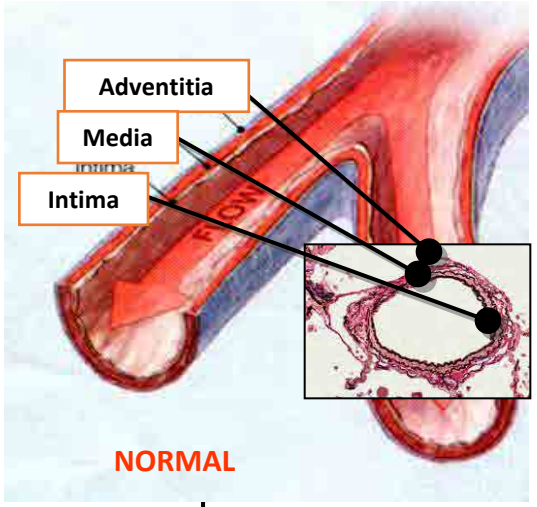
3. PH associated with lung diseases and/or hypoxia
3.1 Obstructive lung disease or emphysema
3.2 Restrictive lung disease
3.3 Lung disease with mixed restrictive/obstructive pattern
3.4 Hypoventilation syndromes
3.5 Hypoxia without lung disease (e.g. high altitude)
3.6 Developmental lung disorders

4. PH associated with pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions

5. PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorder
5.2 Systemic disorders
5.3 Metabolic disorders
5.4 Chronic renal failure with or without haemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis

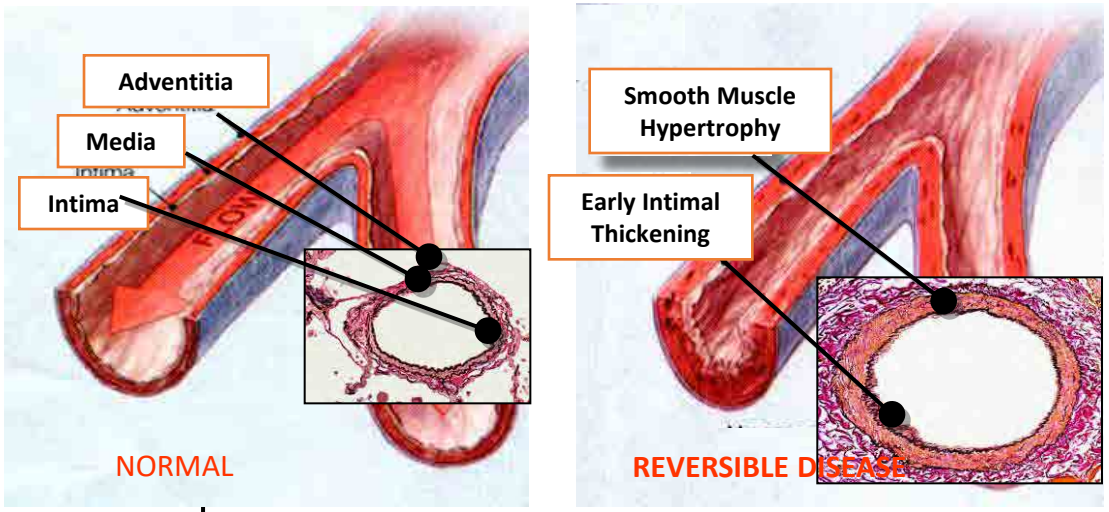
Marc Humbert, et al. ESC/ERS Scientific Document Group , 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension, European Heart Journal, Volume 43, Issue 38, 7 October 2022, Pages 3618–3731.

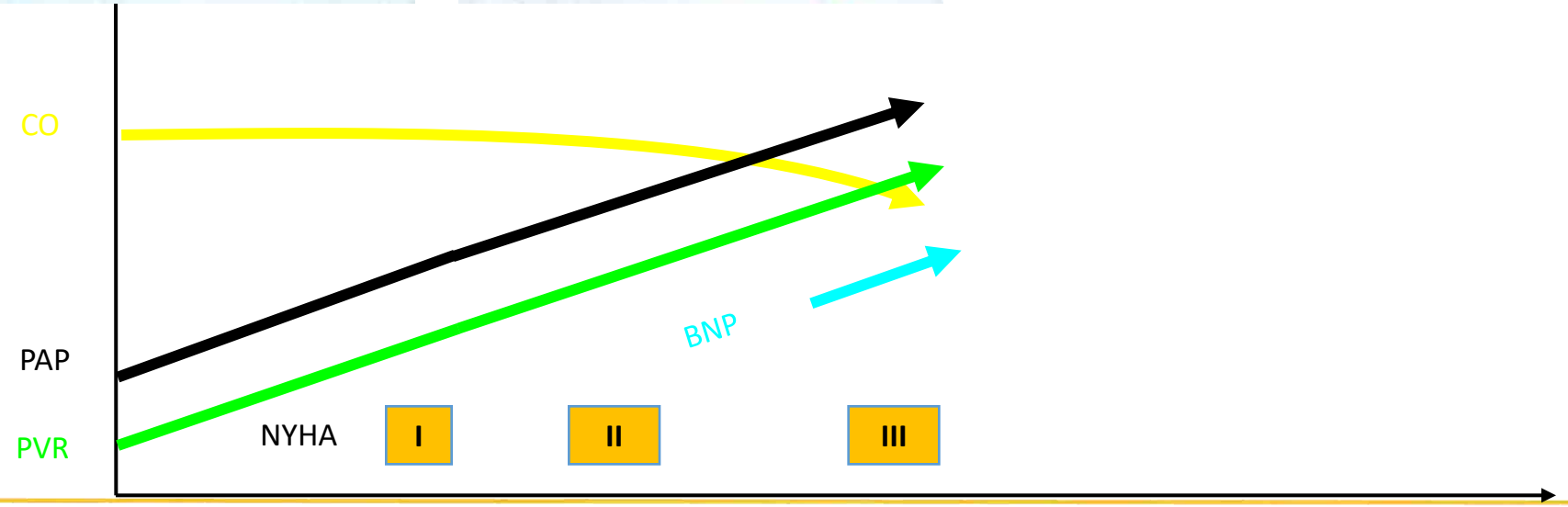
PAH: Hemodynamic and Clinical Course



Adapted from Gaine S. *JAMA.* 2000;284:3160-3168.

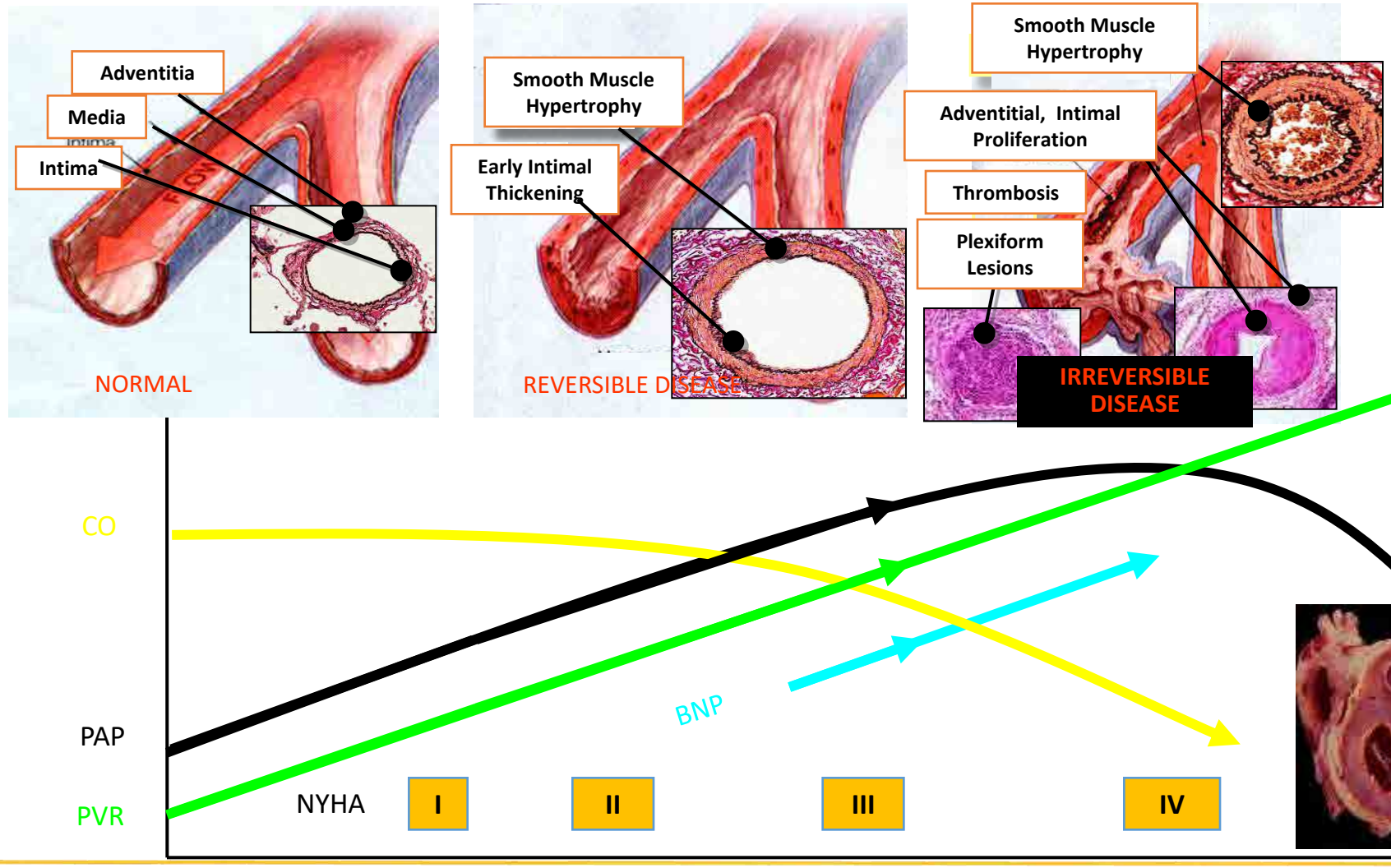
PAH: Hemodynamic and Clinical Course





Adapted from Gaine S. *JAMA*. 2000;284:3160-3168.

PAH: Hemodynamic and Clinical Course



Adapted from Gaine S. *JAMA.* 2000;284:3160-3168.

What Does Risk Stratification Mean in PAH?

Risk stratification uses population-level outcome data to estimate an individual patient's risk of clinical deterioration and mortality.

They combine clinical, functional, biomarker, imaging, and/or hemodynamic variables associated with outcomes.

Applied to an individual patient, they provide an **estimate of prognosis and not a prediction of exactly what will happen to that patient**.

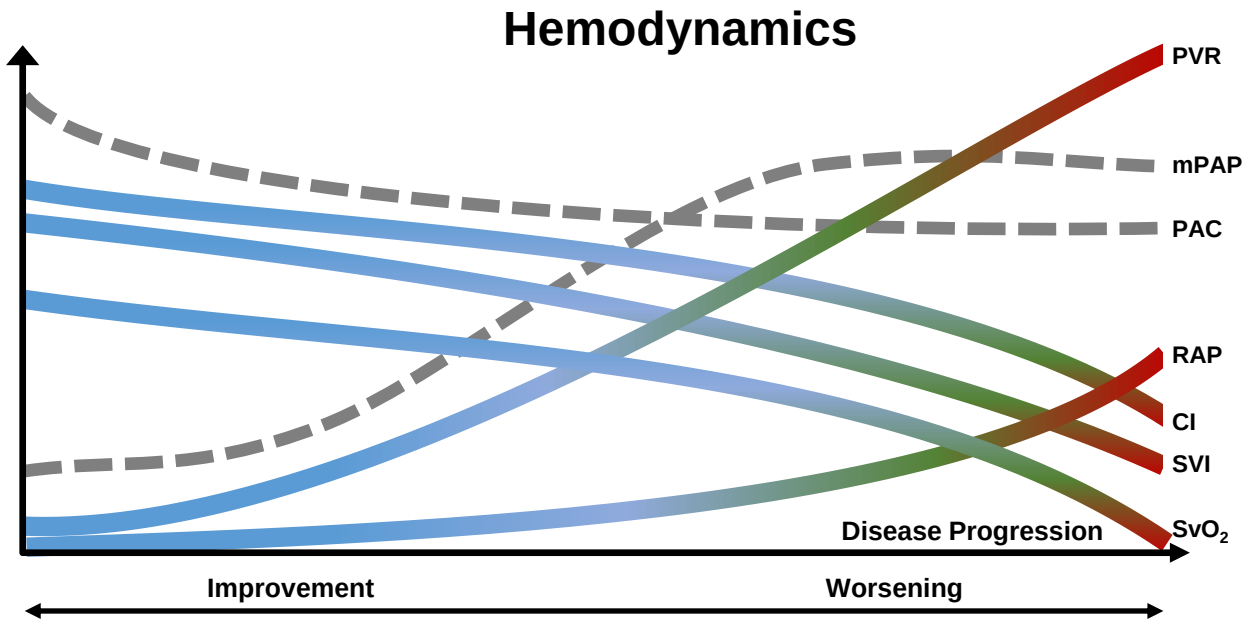
Risk should be **reassessed over time** and used with clinical judgment to guide treatment decisions.

Move patients toward and maintain LOW RISK

Assess Risk → Treat → Reassess → Optimize

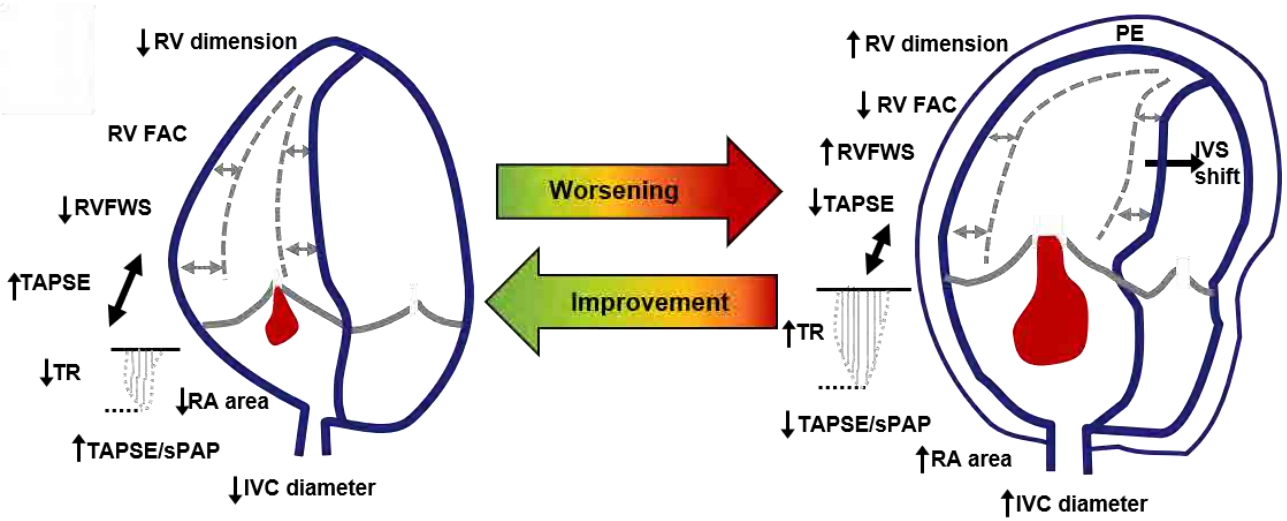
Humbert M, et al. *Eur Heart J.* 2022;43:3618–3731. **2022 ESC/ERS Guidelines for pulmonary hypertension.**
Benza RL, et al. *Chest.* 2019;156:323–337. **REVEAL 2.0 risk score.**
Hoeper MM, et al. *Eur Respir J.* 2022;60:2102311. **COMPERA 2.0 four-strata risk assessment.**

Multidimensional Strategy for Assessing Risk



Echocardiography

(according to center expertise, cMRI can be considered instead of echocardiography)



Acronyms are in the speaker notes. Dardi F, et al. *Eur Respir J.* 2024;64(4),2401323.

European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk

ECS/ERS 3 risk-strata

Determinants of prognosis (according to 1-year estimated mortality)		Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical parameters	Signs of right HF	Absent	Absent	Present
	Symptom progression	No	Slow	Rapid
	Syncope	No	Occasional	Repeated
	WHO-FC	I, II	III	IV
Exercise tests	6MWD	>440 m	165–440 m	<165 m
	CPET			
	Peak V'_{O_2}	>15 mL·kg^{-1}·min^{-1}	11–15 mL·kg^{-1}·min^{-1}	<11 mL·kg^{-1}·min^{-1}
	V'_E/V'_{CO_2}	<36	36–44	>44
Biomarkers	BNP	<50 ng·L^{-1}	50–800 ng·L^{-1}	>800 ng·L^{-1}
	NT-proBNP	<300 ng·L^{-1}	300–1100 ng·L^{-1}	>1100 ng·L^{-1}
Imaging	Echocardiography			
	RA area	<18 cm^2	18–26 cm^2	>26 cm^2
	TAPSE/sPAP	>0.32 mm·mmHg^{-1}	0.19–0.32 mm·mmHg^{-1}	<0.19 mm·mmHg^{-1}
	PE	No	Minimal	Moderate or large
	cMRI			
	RVEF	>54%	37–54%	<37%
	SVI	>40 mL·m^{-2}	26–40 mL·m^{-2}	<26 mL·m^{-2}
	RVESVI	<42 mL·m^{-2}	42–54 mL·m^{-2}	>54 mL·m^{-2}
RHC	Haemodynamics			
	RAP	<8 mmHg	8–14 mmHg	>14 mmHg
	CI	≥2.5 L·min^{-1}·m^{-2}	2.0–2.4 L·min^{-1}·m^{-2}	<2.0 L·min^{-1}·m^{-2}
	SVI	>38 mL·m^{-2}	31–38 mL·m^{-2}	<31 mL·m^{-2}
	S_{vO_2}	>65%	60–65%	<60%

ECS/ERS 4 risk-strata

Determinants of prognosis	Low	Intermediate-low	Intermediate-high	High
WHO-FC	I, II		III	IV
6MWD	>440 m	320–440 m	165–319 m	<165 m
BNP	<50 ng·L^{-1}	50–199 ng·L^{-1}	200–800 ng·L^{-1}	>800 ng·L^{-1}
NT-proBNP	<300 ng·L^{-1}	300–649 ng·L^{-1}	650–1100 ng·L^{-1}	>1100 ng·L^{-1}

ESC/ERS risk calculation

SPAHR/COMPERA 1.0

Parameters		
Low risk 1 point	Intermediate risk 2 points	High risk 3 points

Overall risk = sum of the points = n of parameters
- 1.0–1.49= Low risk
- 1.5–2.49= Intermediate risk
- ≥2.5= High risk

FPHR invasive

Low risk parameters	
WHO-FC	I–II
6MWD	>440 m
RAP	<8 mmHg
CI	≥2.5 L·min^{-1}·m^{-2}

Low risk = 4 low risk parameters

FPHR noninvasive

Low risk parameters	
WHO-FC	I–II
6MWD	>440 m
BNP/NT-proBNP	<50/300 ng·L^{-1}

Low risk = 3 low risk parameters

COMPERA 2.0

Parameters			
Low risk 1 point	Intermediate-low risk 2 points	Intermediate-high risk 3 points	High risk 4 points

Overall risk = sum of the points = n of parameters
- 1.0–1.49= Low risk
- 1.5–2.49= Intermediate-low risk
- 2.5–3.49= Intermediate-high risk
- ≥3.5= High risk

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

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REVEAL Risk ScoresTools

REVEAL 2.0 Risk Calculator

Select all variables that apply. A minimum of 7 variables are required to generate a score. Calculation accuracy increases with more selections.

					Score
WHO Group 1 Subgroup	CTD-PAH 1	Heritable 2	PoPH 3	Other 0	--
Demographics – Male age > 60 years		No 0	Yes 2		--
eGFR<60mL/min/1.73m² or renal insufficiency		No 0	Yes 1		--
NYHA/WHO Functional Class	I -1	II 0	III 1	IV 2	--
Systolic BP (mm Hg)		SBP≥110 0	SBP<110 1		--
Heart Rate (BPM)		HR≤96 0	HR>96 1		--
All-Cause Hospitalizations ≤ 6 mo		No 0	Yes 1		--
6-Minute Walk Test (m)	≥440 -2	320 to 440 -1	<320 to 165 0	<165 1	--
BNP (pg/mL)	50 -2	50 to <200 0	200 to <800 1	≥800 2	--
or					
NT-proBNP (pg/mL)	<300 -2	300 to <1100 0	≥1100 2		--
Pericardial Effusion on Echocardiogram		No 0	Yes 1		--
% predicted DL_{CO} ≤40		No 0	Yes 1		--
mRAP ≥20 mm Hg Within 1 Year		No 0	Yes 1		--
PVR ≥ 5 Wood units on right heart catheterization		No 0	Yes -1		--
					+6
				Risk score	--

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

REVEAL Lite 2 Risk Calculator

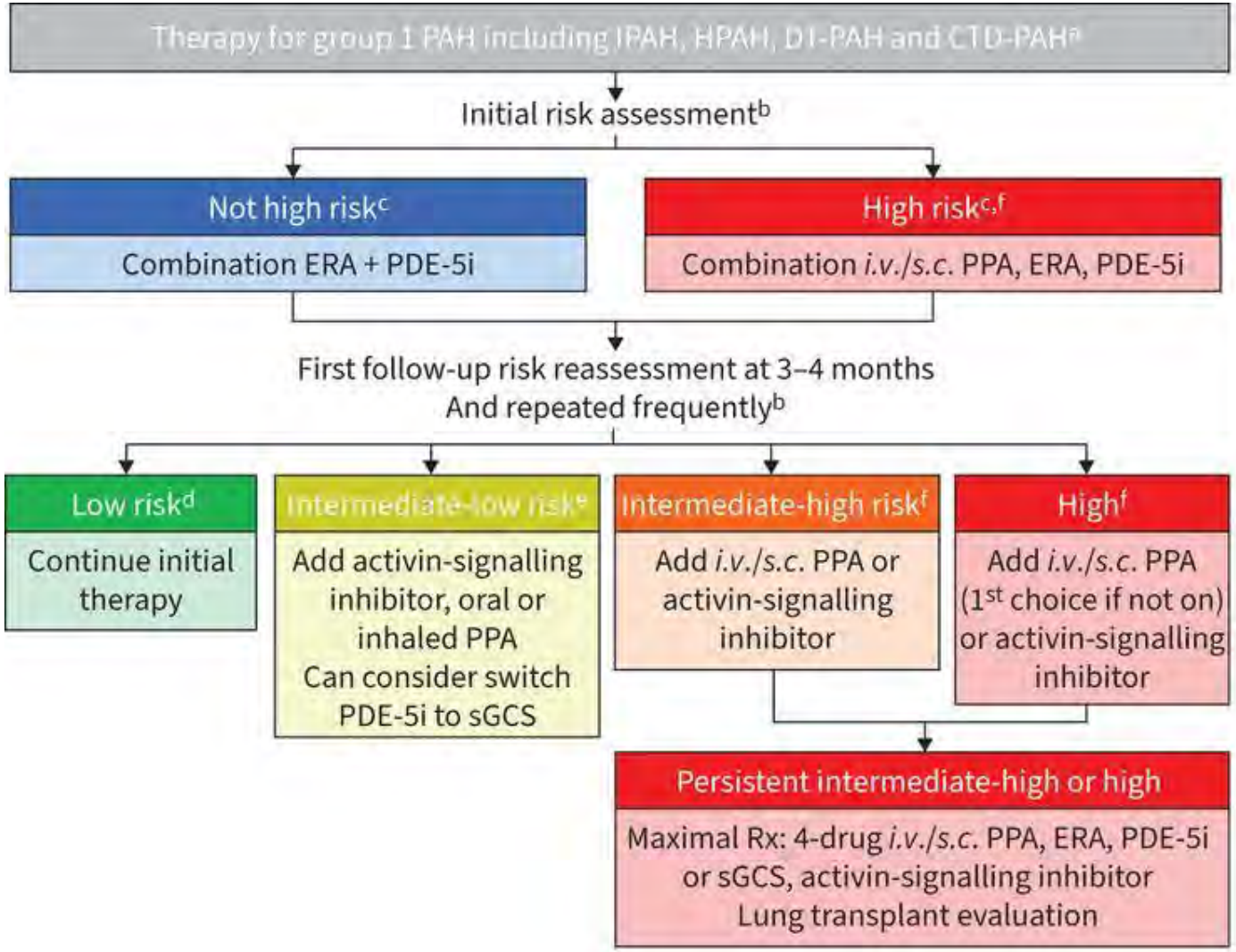
Select all variables that apply. A minimum of 3 variables are required to generate a score where at least 2 are of the most predictive variables - denoted **.

					Score
BNP (pg/mL)**	<50 -2	50 to <200 0	200 to <800 1	≥800 2	--
or					
NT-proBNP (pg/mL)**	<300 -2	300 to <1100 0	≥1100 2		--
6-Minute Walk Test (m)**	≥440 -2	320 to 440 -1	<320 to 165 0	<165 1	--
NYHA/WHO Functional Class**	I -1	II 0	III 1	IV 2	--
Systolic BP (mm Hg)		SBP≥110 0	SBP<110 1		--
Heart Rate (BPM)		HR≤96 0	HR>96 1		--
eGFR<60mL/min/1.73m² or renal insufficiency		No 0	Yes 1		--
					+6
				Risk score	--

Risk score	Low risk	Intermediate risk	High risk
	≤5	6-7	≥8

Acronyms are in the speaker notes. Benza RL, et al. *Chest*. 2021;159(1):337-346; Dardi F, et al. *Eur Respir J.* 2024;64(4):2401323.

Treatment Algorithm



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.

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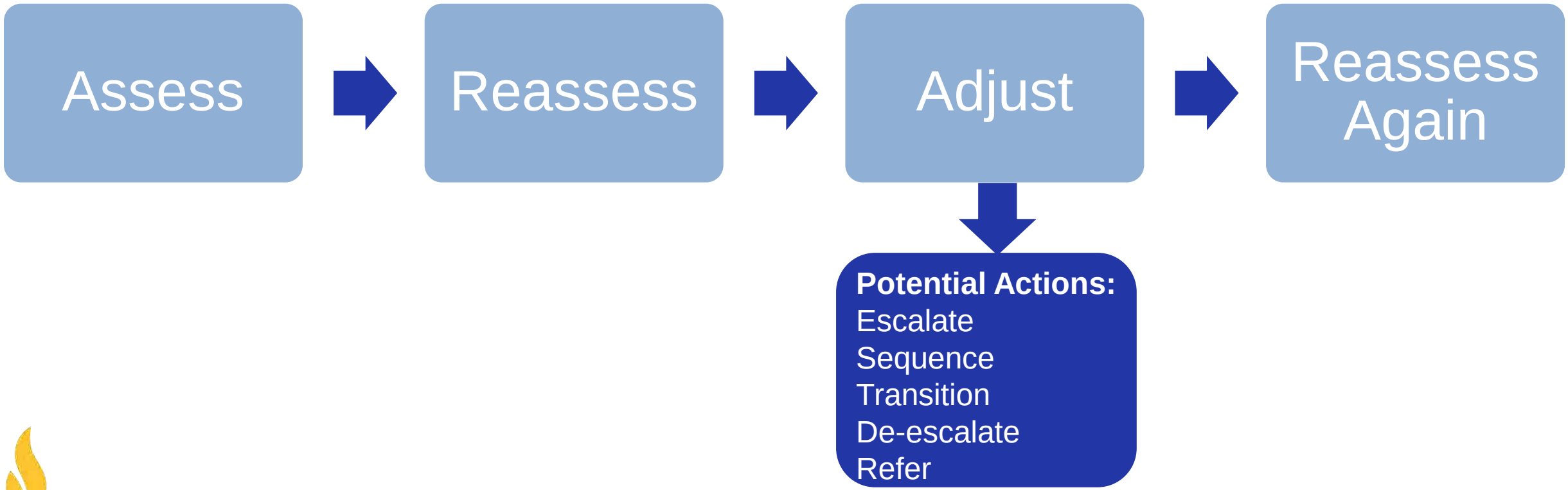
Kelly M. Chin et al. Eur Respir J
doi:10.1183/13993003.01325-2024

Clinical Decision Framework



ESC/ERS 4-Strata Risk Assessment — Follow-Up

Treatment goal → Achieve and maintain LOW RISK.

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	<50	50–199	200–800	>800
NT-proBNP,[a] ng/L	<300	300–649	650–1100	>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.

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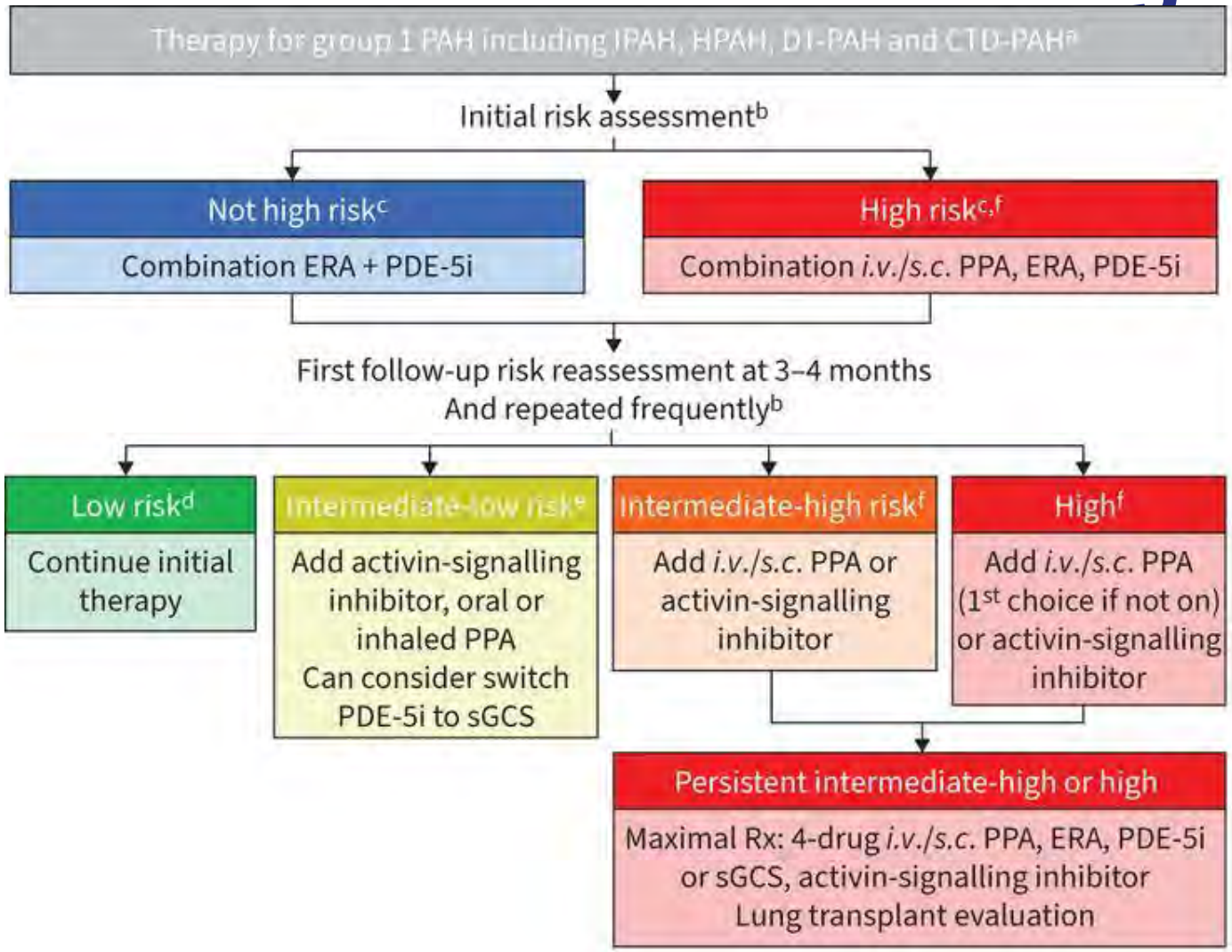
Humbert M, et al. *Eur Heart J.* 2022;43:3618–3731.

Treatment Algorithm



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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.

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Risk Assessment Guides Treatment Decisions Actions for Tomorrow's Clinic

Consider These Questions at Every Follow-Up

- ✓ Has the patient's risk status changed?
- ✓ Is the current therapy achieving its intended goals?
- ✓ Is the patient tolerating treatment?
- ✓ Can the patient realistically sustain the regimen?
- ✓ Is treatment intensity still aligned with disease severity?
- ✓ Is escalation, transition, de-escalation, or referral warranted?

Treat → Reassess → Optimize

Risk Assessment in Pediatric PH

How to choose the right therapy for a child?

- Similar approach to that in adults with some important differences:
  - **No validated risk scores** for children
  - **Fewer research studies** in children to guide us
  - Some PAH medicines are **not FDA-approved** for children
  - Standard treatment approaches are based on **expert consensus**, limited pediatric data and adopting adult practice

Children are not just small adults

Pediatric pulmonary hypertension has unique features, and it requires a different approach.

Adults
(often with acquired causes)

Children
(often with different causes and needs)

Adults		Children
Most often idiopathic or associated with common risk factors (e.g., connective tissue disease, left heart disease).	**Causes**	More often related to congenital heart disease, genetic conditions, or developmental lung disease.
Less often has a genetic cause.	**Genetics**	Higher likelihood of genetic and developmental causes (e.g., BMPR2, chromosomal conditions).
Fully developed organs and systems.	**Development**	Growing and developing — with unique effects on treatment, monitoring, and long-term outcomes.
May present with more subtle symptoms, often later in life.	**Diagnosis**	Symptoms can be different (e.g., poor weight gain, feeding issues, excessive sweating, or exercise intolerance) and may be harder to recognize.
Treatment options and doses are well established.	**Treatment**	Dosing, formulations, and side effects must be tailored to a child's size, development, and daily life.
Focus on symptom control, slowing progression, and quality of life.	**Goals**	In addition to these goals, we also focus on growth, development, school participation, and the best possible long-term future.

chatGPT

Tools Used in Risk Assessment

- Symptoms
- Growth
- Functional Class
- 6-minute Walk Test
- Exercise Test (treadmill/bike)
- Labs: BNP/NT-proBNP
- Echocardiogram
- Cardiac Catheterization
- Cardiac MRI

Unique Challenges in Children

- Symptoms
- Growth
- Functional Class

Ability to recognize, express symptoms evolves
Vary by age, developmental stage

- 6-minute Walk
- Exercise Test

Normal varies by age/size
Consideration of size, ability to perform the test

- BNP/NT-proBNP
- Echocardiogram

Normal values vary by age/size

- Cardiac Cath
- Cardiac MRI

Often requires anesthesia/sedation in young children

Age-Specific Functional Assessment

2011 “Panama Functional Class” developed age-specific equivalents of the WHO Functional Class

Table 4: Pediatric functional classification for children aged 0.5–1 years

Class	Children with pulmonary hypertension
I	Asymptomatic, growing along own centiles, no limitation of physical activity. Mobile, sitting, grasping, starting to stand, crawling, playing
II	Slight limitation of physical activity, unduly dyspnoeic and fatigued when playing. Delayed physical development. Comfortable at rest. Continues to grow along own centiles
IIIa	Marked limitation of physical activity. Regression of learned physical activities. Stops crawling. Quiet and needs frequent naps. Hesitant and unadventurous. Comfortable at rest. Less than ordinary activity causes undue fatigue or syncope and/or presyncope. Growth compromised. Poor appetite. Requires excessive medical attention
IIIb	Growth severely compromised. Poor appetite. Supplemental feeding. Less than ordinary activity causes undue fatigue or syncope. Plus features of Class IIIa
IV	Unable to carry out any physical activity without undue dyspnoea, fatigue or syncope, not interacting with family. Syncope and/or right heart failure. Plus features of Class III

Lammers et al. *Pulm Circ.* 2011

Higher vs. Lower Risk

Lower Risk

Growing well
Attending school, activities
Minimal symptoms
No signs of right heart failure on exam
Better 6 min walk distance
Normal NT-proBNP
Preserved right heart size and function by echo, MRI
Milder pressure elevation by cath

Higher Risk

Poor growth
Frequent hospitalizations
Symptoms with activity
Signs of right heart failure
Lower 6 min walk distance
Elevated NT-proBNP
Impaired right heart function, dilation on echo, MRI
Higher pressures, PVR by cath

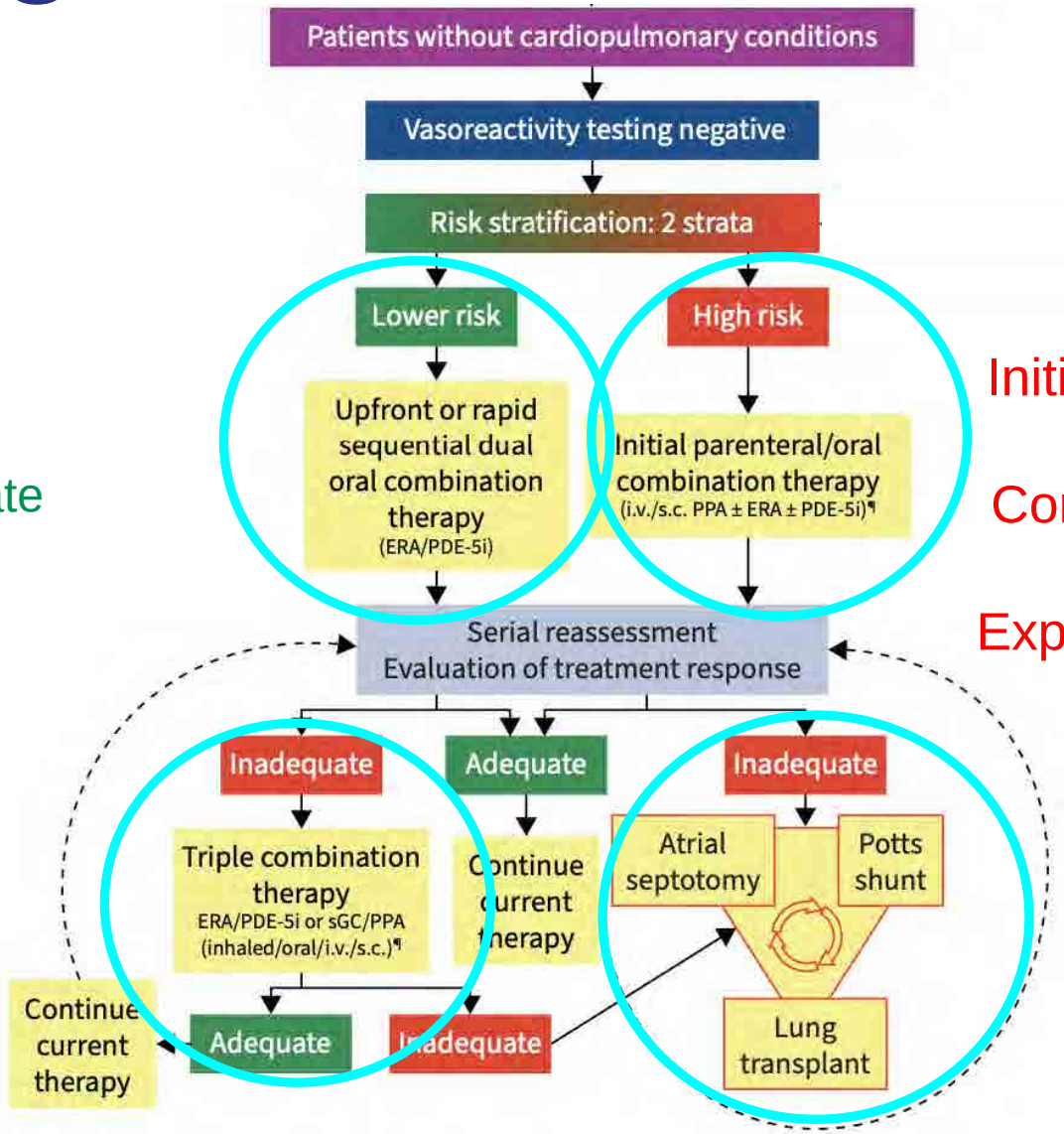
Treatment Algorithm for PAH

Lower Risk

Upfront dual oral therapy

(usually PDE5i + ERA)

Add/change therapy if inadequate



Higher Risk

Initial prostacyclin therapy

Triple therapy early

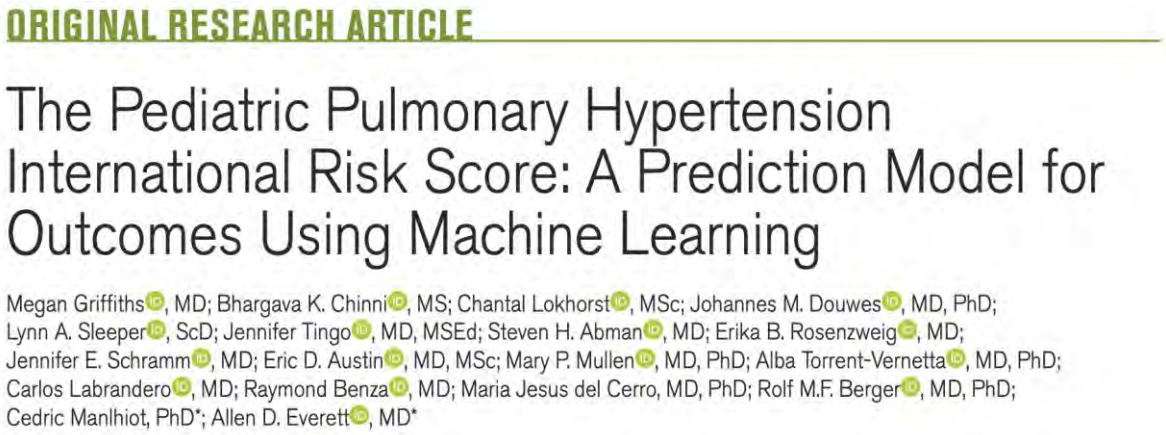
Consider novel therapies

(sotatercept)

Explore other options early

Ivy et al. *Eur Respir J*. 2024

Can We Use AI to Improve Prediction?



ORIGINAL RESEARCH ARTICLE

The Pediatric Pulmonary Hypertension International Risk Score: A Prediction Model for Outcomes Using Machine Learning

Megan Griffiths, MD; Bhargava K. Chinni, MS; Chantal Lokhorst, MSc; Johannes M. Douwes, MD, PhD; Lynn A. Sleeper, ScD; Jennifer Tingo, MD, MSEd; Steven H. Abman, MD; Erika B. Rosenzweig, MD; Jennifer E. Schramm, MD; Eric D. Austin, MD, MSc; Mary P. Mullen, MD, PhD; Alba Torrent-Vernetta, MD, PhD; Carlos Labrandero, MD; Raymond Benza, MD; Maria Jesus del Cerro, MD, PhD; Rolf M.F. Berger, MD, PhD; Cedric Manlhiot, PhD*; Allen D. Everett, MD*

Multicenter, validated model using data from 3 registries provided good 1-year risk prediction in children using 16 clinical variables

Summary

- **Caregiver input** is so important
- **Growth and development** are strong indicators in infants and children
- The right treatment **depends on the child** and family
- **Reassessment** is critical
- **Options** are always changing
- More pediatric **research is needed** to improve care