Peer-to-Peer Educational Toolkit

Navigating the Latest in Pulmonary Arterial Hypertension: Implementing Guidelines Amidst a Changing Treatment Landscape

Content adapted from a PAH webcast

Faculty:

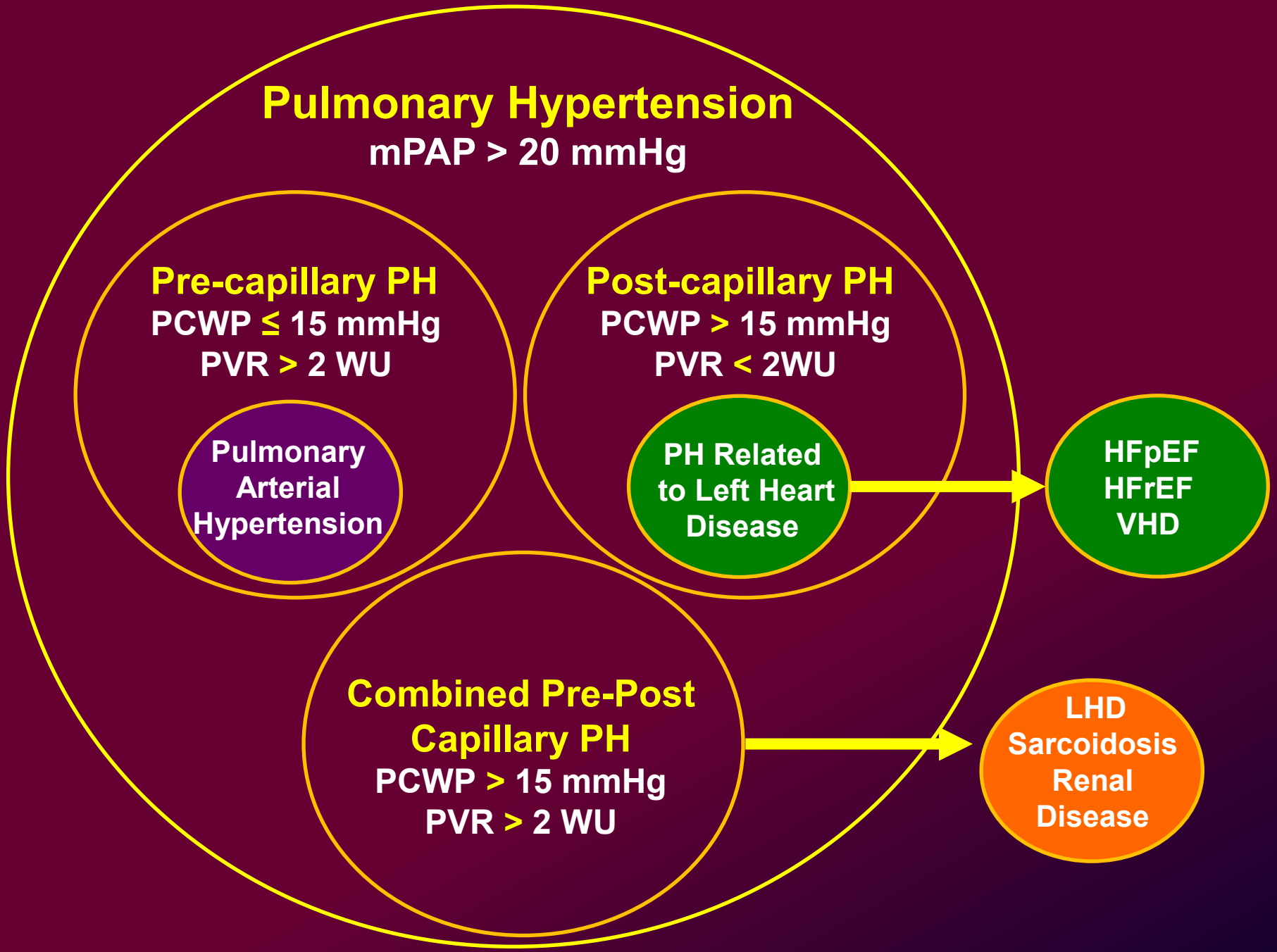
Vallerie V. Mclaughlin, MD, FACC, FAHA
Kim A. Eagle, MD Endowed Professor of Cardiovascular Medicine
Director, Pulmonary Hypertension Program
University of Michigan
Ann Arbor, MI

Richard N. Channick, MD
Saul Brandman Endowed Chair in Pulmonary Arterial Hypertension
Co-Director, Pulmonary Vascular Disease Program
Director, Acute and Chronic Thromboembolic Disease Program
Director, Advanced Pulmonary Vascular Disease Fellowship
Professor of Medicine
Pulmonary and Critical Care Division
David Geffen School of Medicine at UCLA
Los Angeles, CA

7th WSPH Hemodynamic Definition of PH/PAH

Definitions	Characteristics	Clinical Groups
PH	mPAP >20 mmHg	1, 2, 3, 4, 5
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR >2 WU	1, 3, 4, 5
Isolated post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR ⩽2 WU	2, 5
Combined pre- and post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU	2, 5
Exercise PH	mPAP/CO slope >3 mm Hg/L/min between rest and exercise	

Adapted from Kovacs G et al. *Eur Respir J.* 2024; 2401324 [DOI: 10.1183/13993003.01324-2024].


Pulmonary Hypertension
mPAP > 20 mmHg
Pre-capillary PH
PCWP ≤ 15 mmHg
PVR > 2 WU
Pulmonary Arterial Hypertension
Post-capillary PH
PCWP > 15 mmHg
PVR < 2WU
PH Related to Left Heart Disease
HFpEF
HFrEF
VHD
Combined Pre-Post Capillary PH
PCWP > 15 mmHg
PVR > 2 WU
LHD
Sarcoidosis
Renal Disease

Symptoms in Patients With PH

Early

Late

Symptoms

- Dyspnea on exertion (WHO-FC)
- Fatigue and rapid exhaustion
- Dyspnea when bending forward (bendopnea)
- Palpitations
- Hemoptysis
- Exercise-induced abdominal distention and nausea
- Weight gain due to fluid retention
- Syncope (during or shortly after physical exertion)

Rare symptoms due to pulmonary artery dilation

- Exertional chest pain:
  dynamic compression of the left main coronary artery
- Hoarseness (dysphonia):
  compression of left laryngeal recurrent nerve (cardiovocal or Ortner's syndrome)
- Shortness of breath, wheezing, cough, lower respiratory tract infection, atelectasis:
  compression of the bronchi

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.
Eur Heart J. 2022— doi:10.1093/eurheartj/ehac237 and Eur Resp J. 2022—doi:1183/13993003.00879-2022.

Functional Assessment: WHO Functional Class

Modified From NYHA Classification

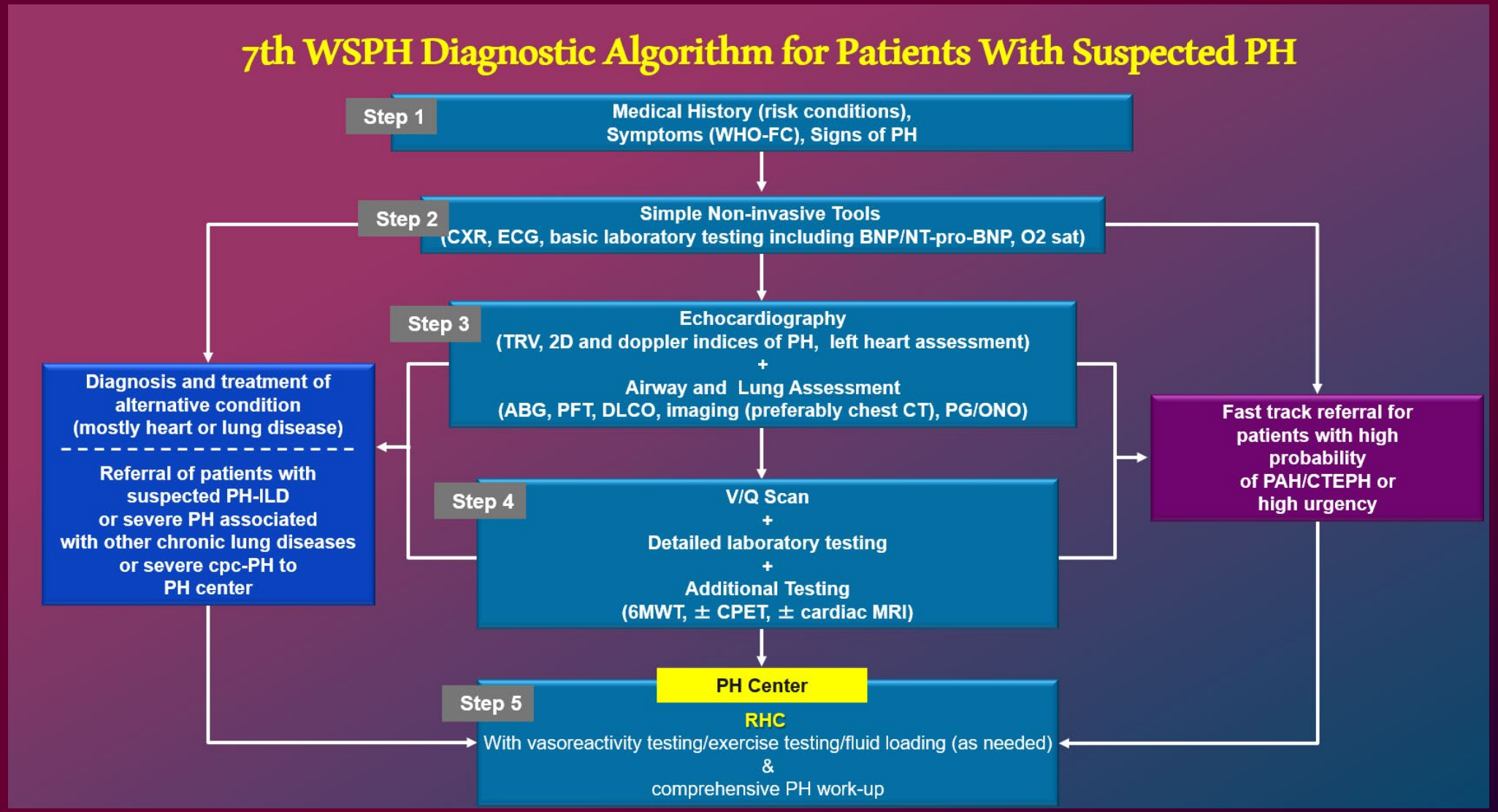
Class	Description
I	No limitation of physical activity; ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope
II	Slight limitation of physical activity; no discomfort at rest; ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
III	Marked limitation of physical activity; no discomfort at rest; less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope
IV	Unable to carry out any physical activity without symptoms; signs of right-heart failure; dyspnea and/or fatigue may be present at rest; discomfort is increased by any physical activity

Rubin LJ. Chest. 2004;126:7S-10S.

Recommendations for Improved Screening and Detection of PAH in Patients With Systemic Sclerosis

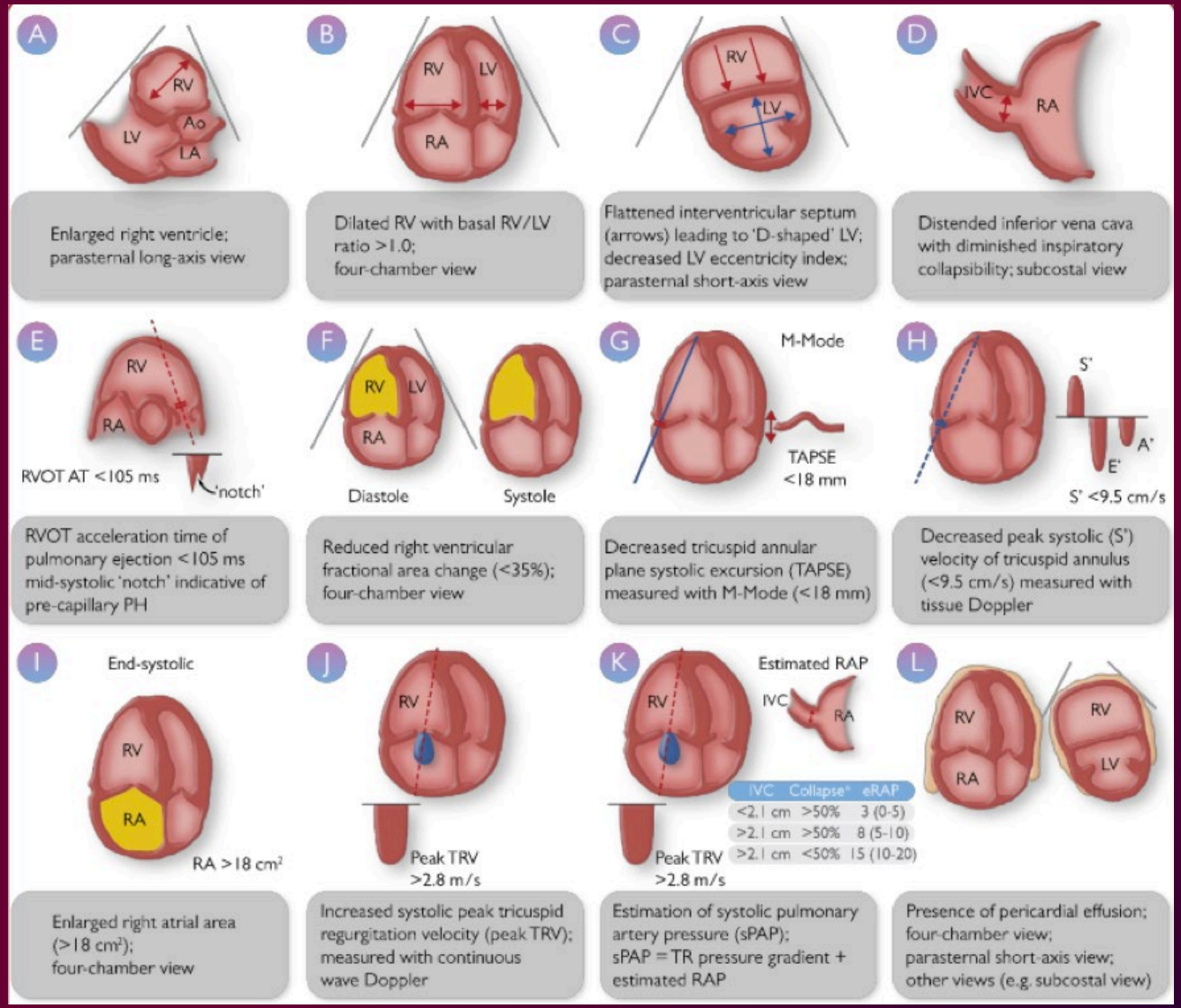
Recommendations	Class	Level
In patients with SSc, annual evaluation of risk of having PAH is recommended	I	B
In adult patients with SSc with >3 year's disease duration, FVC ≥40%, and DLCO <60%, DETECT algorithm is recommended to identify asymptomatic patients with PAH	I	B
In patients with SSc, where breathlessness remains unexplained following noninvasive assessment, RHC is recommended to exclude PAH	I	C

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022— doi:10.1093/eurheartj/ehac237 and Eur Resp J. 2022—doi:1183/13993003.00879-2022.



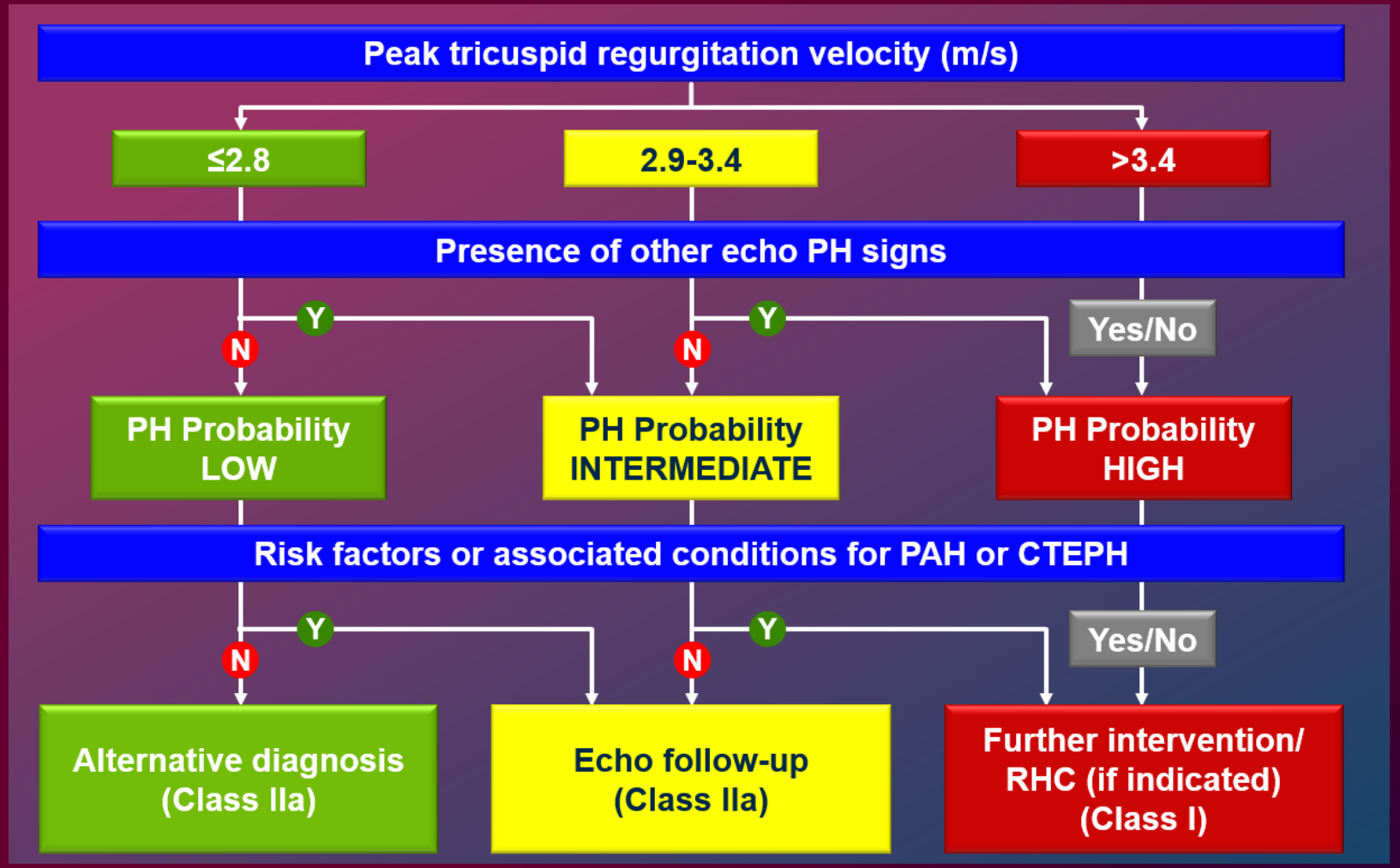
Kovacs G et al. Eur Respir J. 2024; 2401324 [DOI:10.1183/13993003.01324-2024].

Transthoracic Echo Parameters in Assessment of PH



2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.
Eur Heart J. 2022— doi:10.1093/eurheartj/ehac237 and Eur Resp J. 2022—doi:1183/13993003.00879-2022.

Echocardiographic Probability of PH and Recommendations for Further Assessment



2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.
Eur Heart J. 2022— doi:10.1093/eurheartj/ehac237 and Eur Resp J. 2022—doi:1183/13993003.00879-2022.

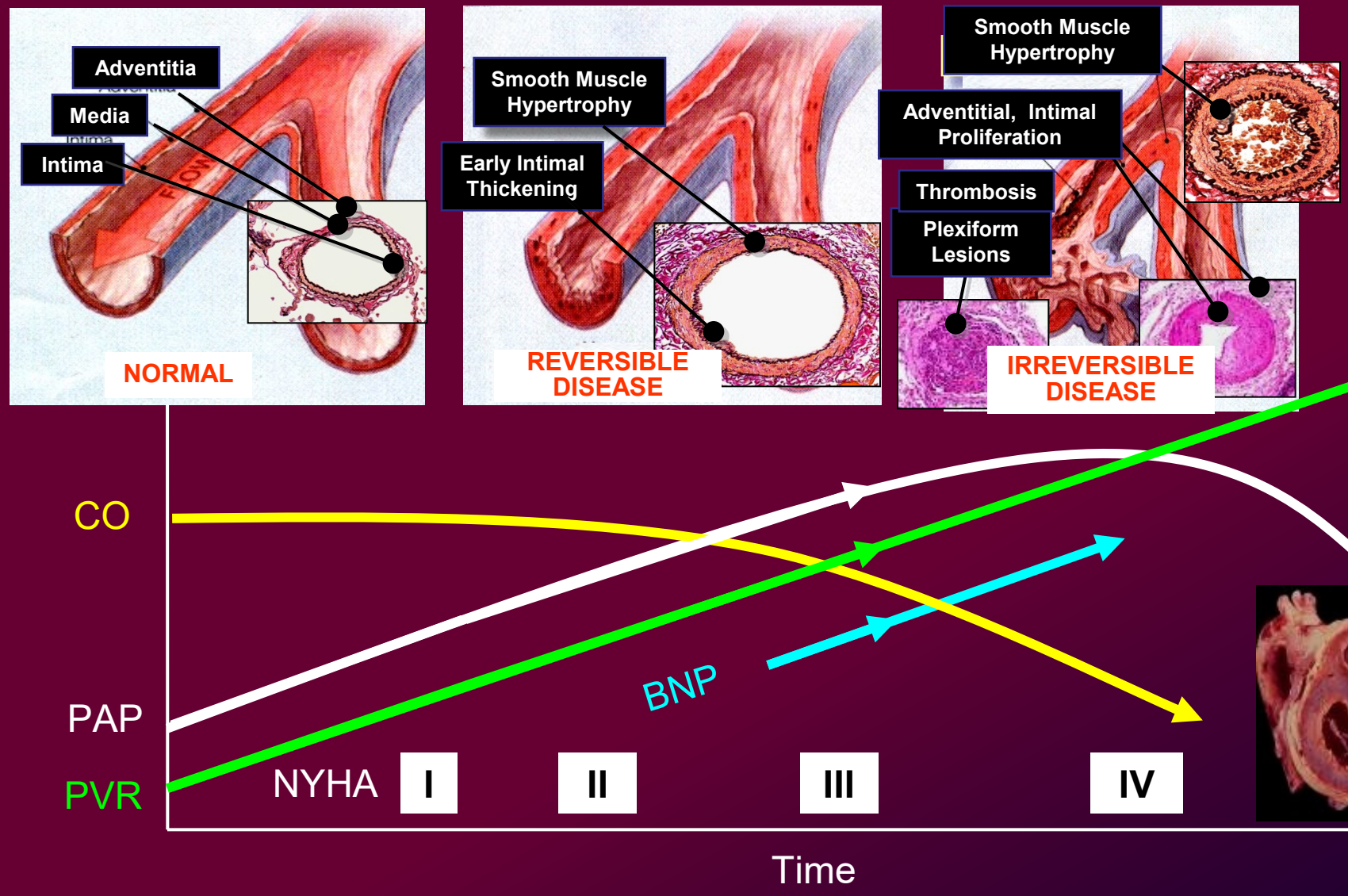
RHC to Obtain These Hemodynamic Measures

Measured Variables	Normal Value
Right atrial pressure (RAP)	2-6 mm Hg
Systolic pulmonary artery pressure (PAP; sPAP)	15-30 mm Hg
Diastolic PAP (dPAP)	4-12 mm Hg
Mean PAP (mPAP)	8-20 mm Hg
Mean pulmonary artery wedge pressure (PAWP)	≤15 mm Hg
Cardiac output (CO)	4-8 L/min
Mixed venous oxygen saturation (SvO_2)	65-80%
Arterial oxygen saturation (SaO_2)	95-100%
Systemic blood pressure	120/80 mm Hg

Calculated Parameters	Normal Value
Pulmonary vascular resistance (PVR)	0.3-2.0 WU
PVR index (PVRI)	3-3.5 WU*m^2
Total pulmonary resistance (TPR)	<3 WU
Cardiac index (CI)	2.5-4.0 L/min·m^2
Stroke volume (SV)	60-100 mL
SV index (SVI)	33-47 mL/m^2
Pulmonary arterial compliance (PAC)	>2.3 mL/mm Hg

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.
Eur Heart J. 2022— doi:10.1093/eurheartj/ehac237 and Eur Resp J. 2022—doi:1183/13993003.00879-2022.

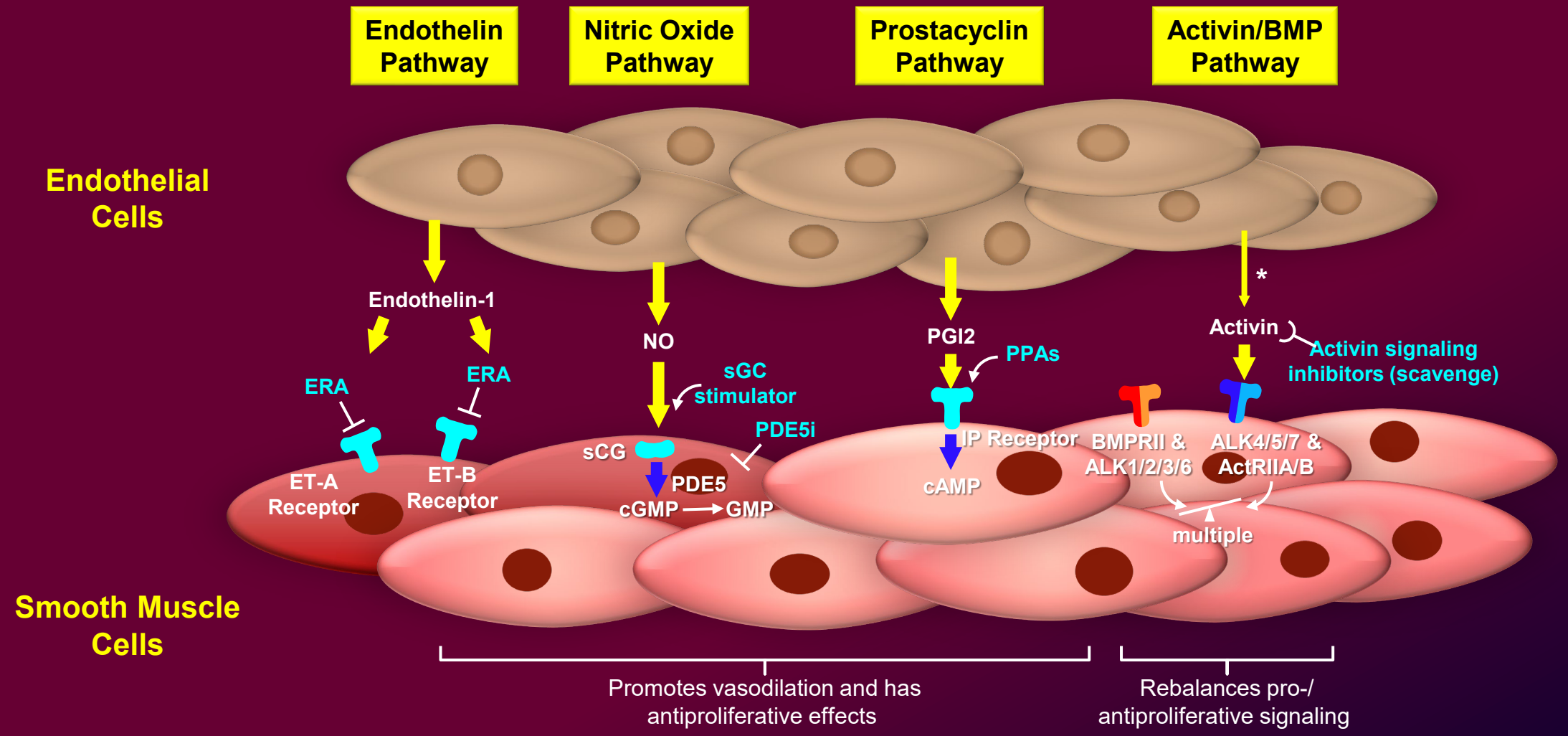
PAH: Hemodynamic and Clinical Course



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

Current and Emerging Treatments for PAH

Current Treatment Pathways in PAH



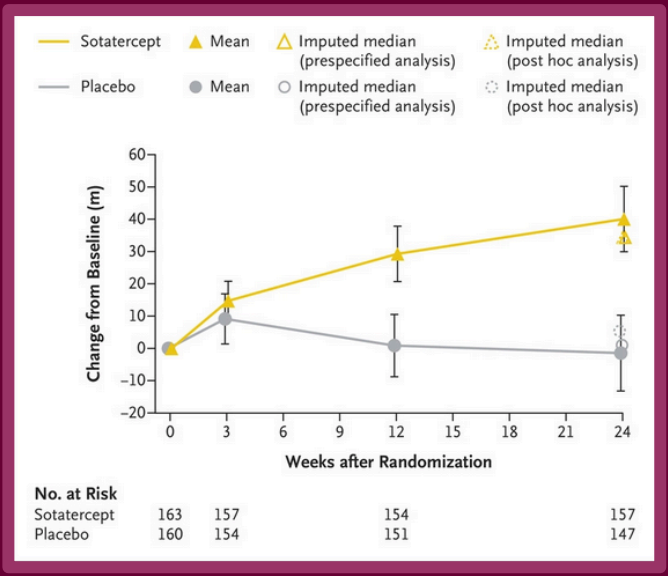
*Signaling mediators also originate from multiple other cell types, particularly for activin.

Chin KM et al. Eur Respir J. 2024; in press: 2401325 [DOI: 10.1183/13993003.01325-2024].

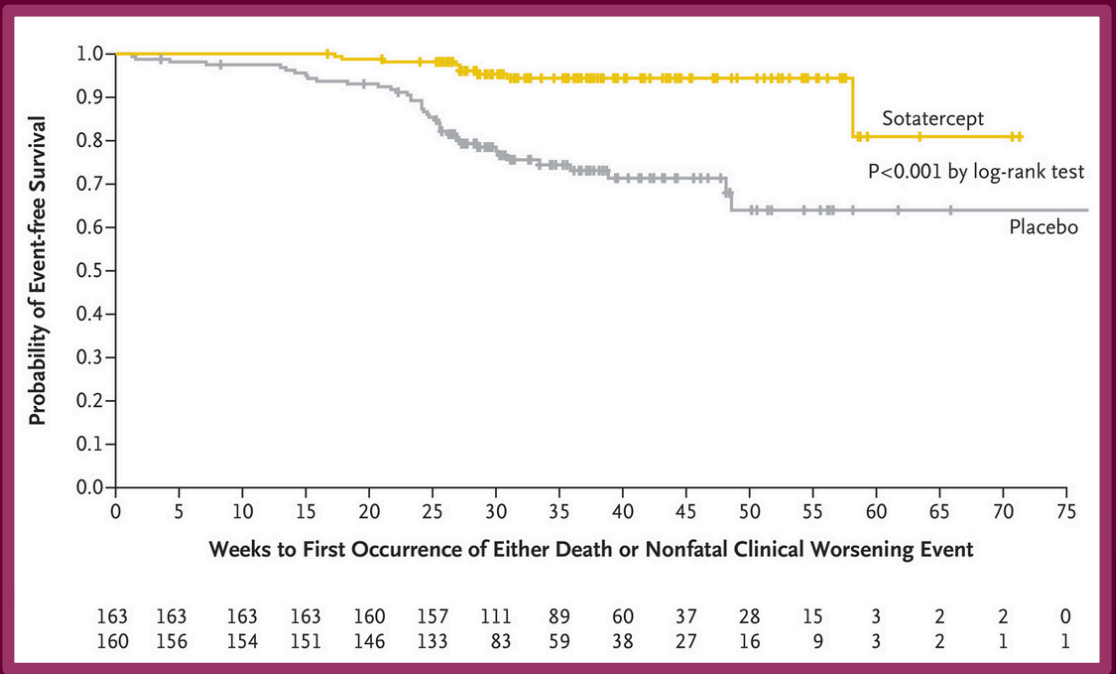
FDA-Approved Therapy for PAH

Pathway	Therapy	Dosage
Endothelin	ambrisentan	5,10 mg po qd
	bosentan	125 mg po bid
	macitentan	10 mg po bid
Nitric Oxide	*PDE 5 Inhibitors*	
	sildenafil	20 mg po tid
	tadalafil	40 mg po qd
	sGC Stimulator	
	riociguat	0.5-2.0 mg po tid
Prostacyclin	epoprostenol	IV
	treprostinil	IV/SC
		9 inhalations qid
		Oral tid
	iloprost	Inhale 6-9 times daily
	selexipag	200-1600 mcg bid
Activin-signaling inhibitor	sotatercept	0.3-0.7 mg/kg every 3 wk

STELLAR: Effect of sotatercept in PAH



6MWD

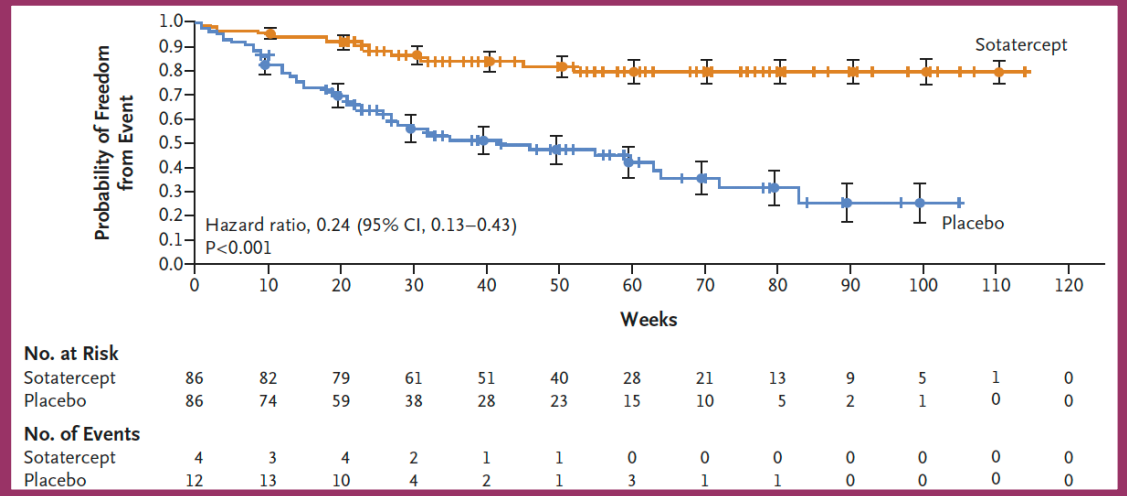


Time to Death / Clinical Worsening

100% on background therapy:
-13% on monotherapy
-35% on double therapy
-61% on triple therapy

Hoeper MM et al. N Engl J Med. 2023. DOI: 10.1056/NEJMoa2213558

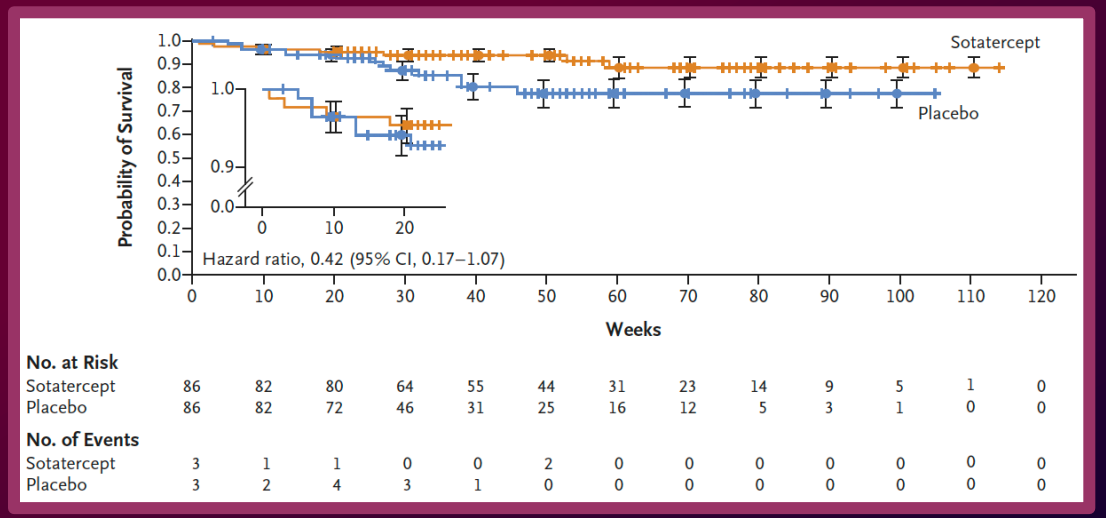
ZENITH: Phase 3 study of Sotatercept in high-risk PAH WHO FC III and IV



Primary Composite End-Point*

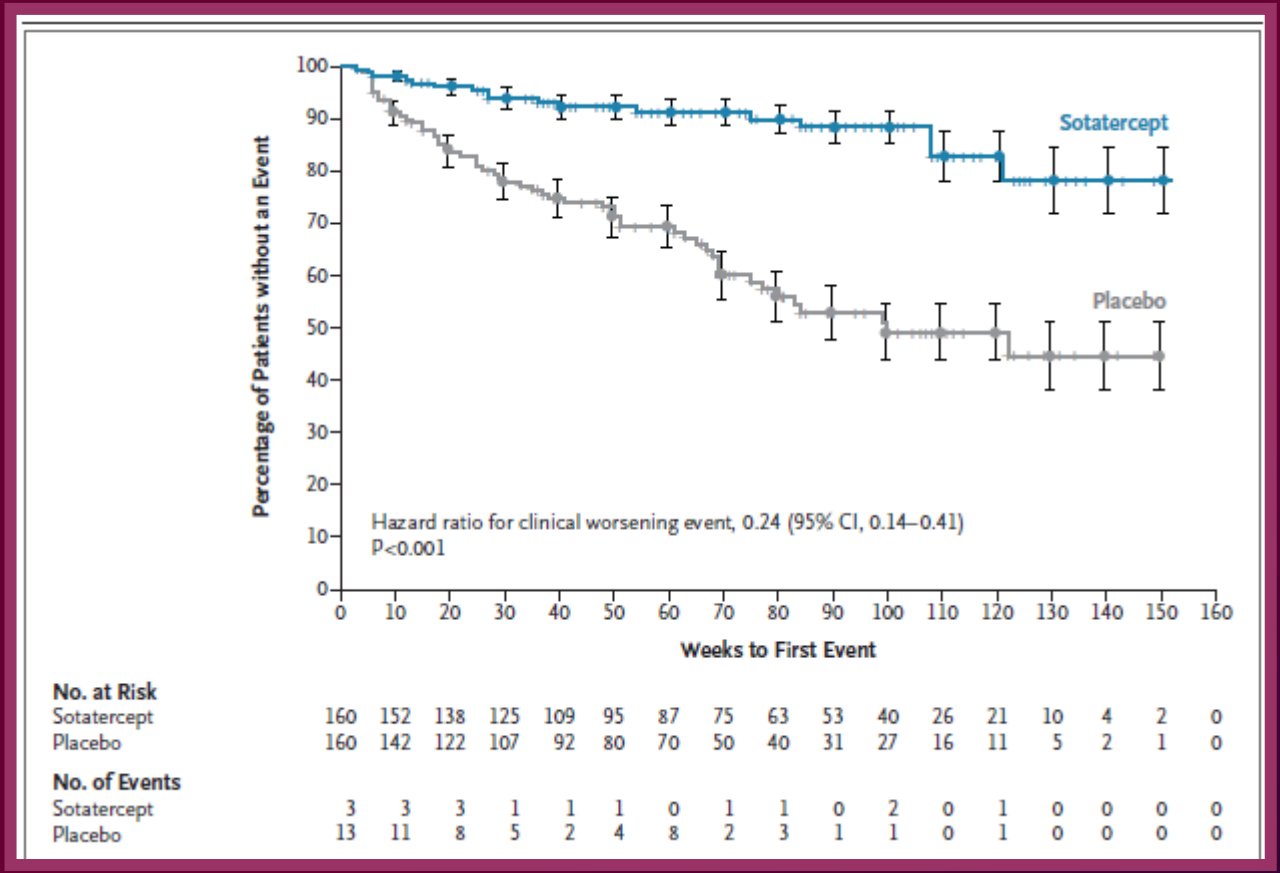
*Death from any cause, lung tx, or hospitalization (≥24 h) for worsening PAH (time-to-first-event analysis)

Overall Survival



Humbert M et al. N Engl J Med. 2025;DOI: 10.1056/NEJMoa2415160

HYPERION: Sotatercept in PAH patients within the first year of diagnosis

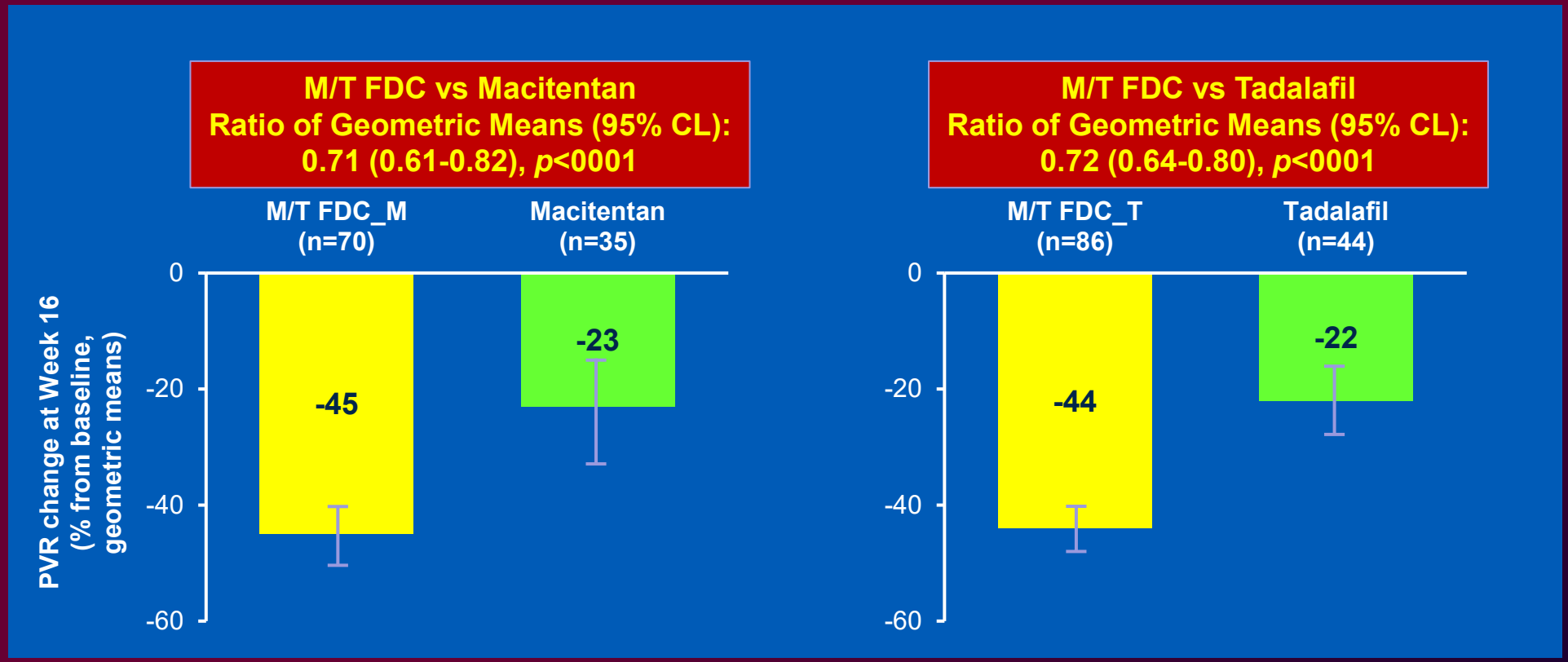


No. at Risk																	
Sotatercept	160	152	138	125	109	95	87	75	63	53	40	26	21	10	4	2	0
Placebo	160	142	122	107	92	80	70	50	40	31	27	16	11	5	2	1	0
No. of Events																	
Sotatercept	3	3	3	1	1	1	0	1	1	0	2	0	1	0	0	0	0
Placebo	13	11	8	5	2	4	8	2	3	1	1	0	1	0	0	0	0

McLaughlin et al, NEJM epub ahead of print, 2025

A DUE: Macitentan-Tadalafil Single-Tablet Combination

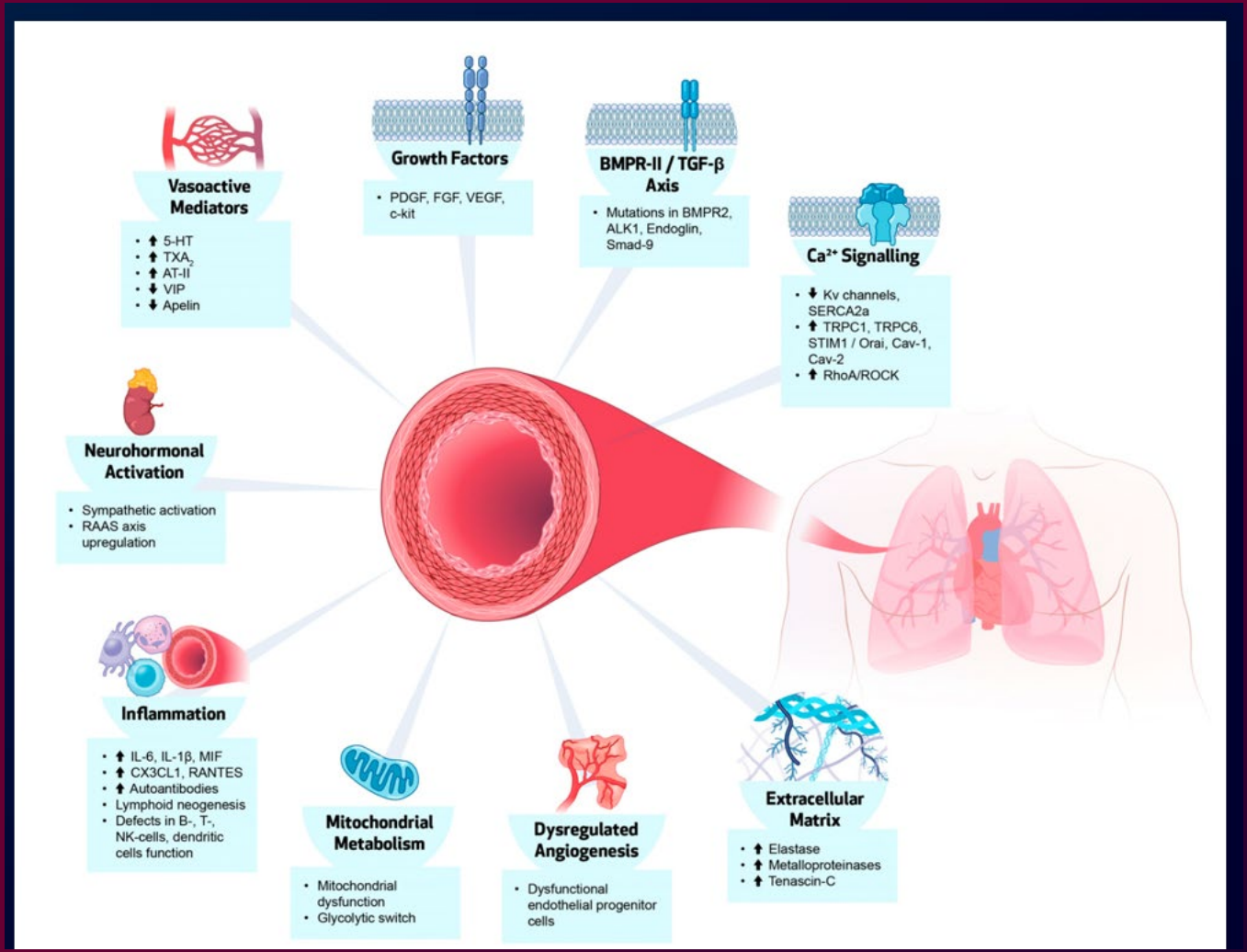
Primary Endpoint: Change in PVR at Week 16



Grünig E et al. J Am Coll Cardiol. 2024;83:473-84.

Potential Therapeutic Targets for PAH Treatment

- Circulating hormones
- Epigenetic alterations
- Growth factors
- Vasoactive factors
- Inflammatory mediators
- Ion channels
- Mitochondrial and metabolic adaptations
- Oxidative stress modulator
- Stem cell therapy

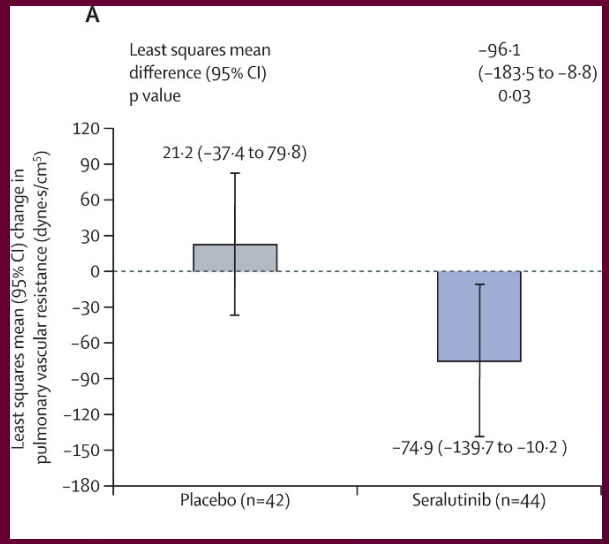


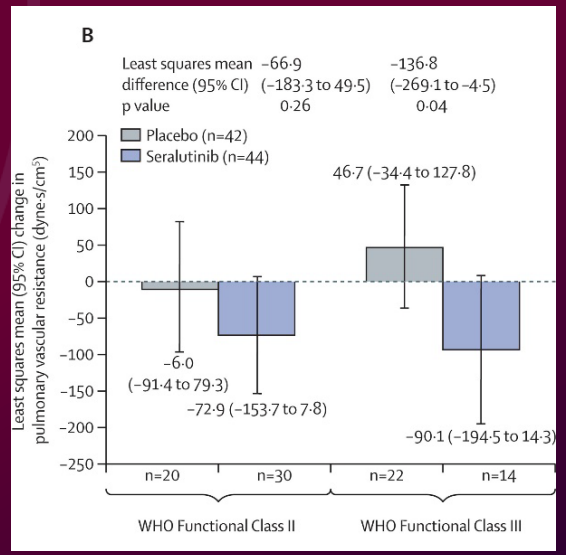
Sahay S et al. Am J Respir Crit Care Med. 2024; 210:581–592.

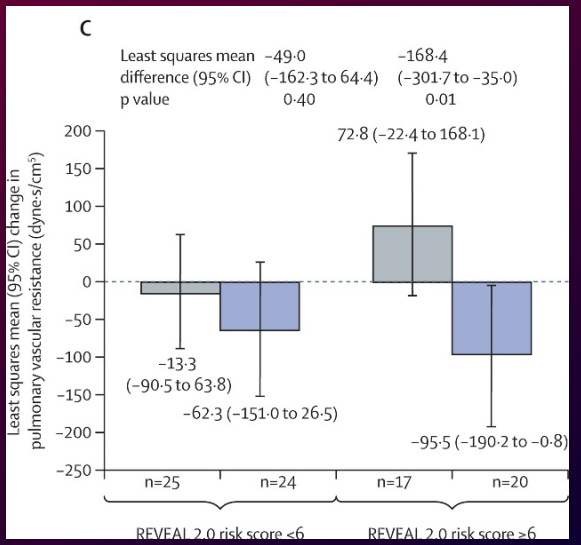
Seralutinib - TORREY

Frantz, RP. *Lancet Respir Med*. 2024; 12(7)

- *Primary Endpoint: PVR*







Ralinepag – Selective IP receptor agonist- Phase III (Advance)- Nearing the end of enrollment

SOURCE: *clinicaltrials.gov*

- Target enrollment: ~1000 subjects
  - **Once-daily dosing (1:1)**
  - **50 mcg titrate as tolerated**
- Primary: **TTCW (adjudicated event)**
  - Death, hospitalization for PAH, parenteral/inhaled PPA or disease progression
- Inclusion/Exclusion:
  - Functional class II – IV
  - 6MWD ≥ 150 meters
  - No parenteral prostacyclin analogues

Nearing the end of enrollment

Macitentan 75 mg

SOURCE: *clinicaltrials.gov*

- Phase 3 study (935 pts randomized)
- Macitentan 75 mg vs 10 mg
- mPAP > 20 mmHg, PVR ≥ 3 WU; 6MWD > 50 m and ≤ 440 m
- Primary: Time to first adjudicated mortality and morbidity event
- Death, PAH-related hospitalization, +parenteral prostanoid, PAH-related disease progression (↓15% 6MWD and additional PAH therapy or ↑ functional class)

Enrollment completed
Sufficient accrual of clinical events estimated to be Aug 2025

TPIP – Once daily dosing

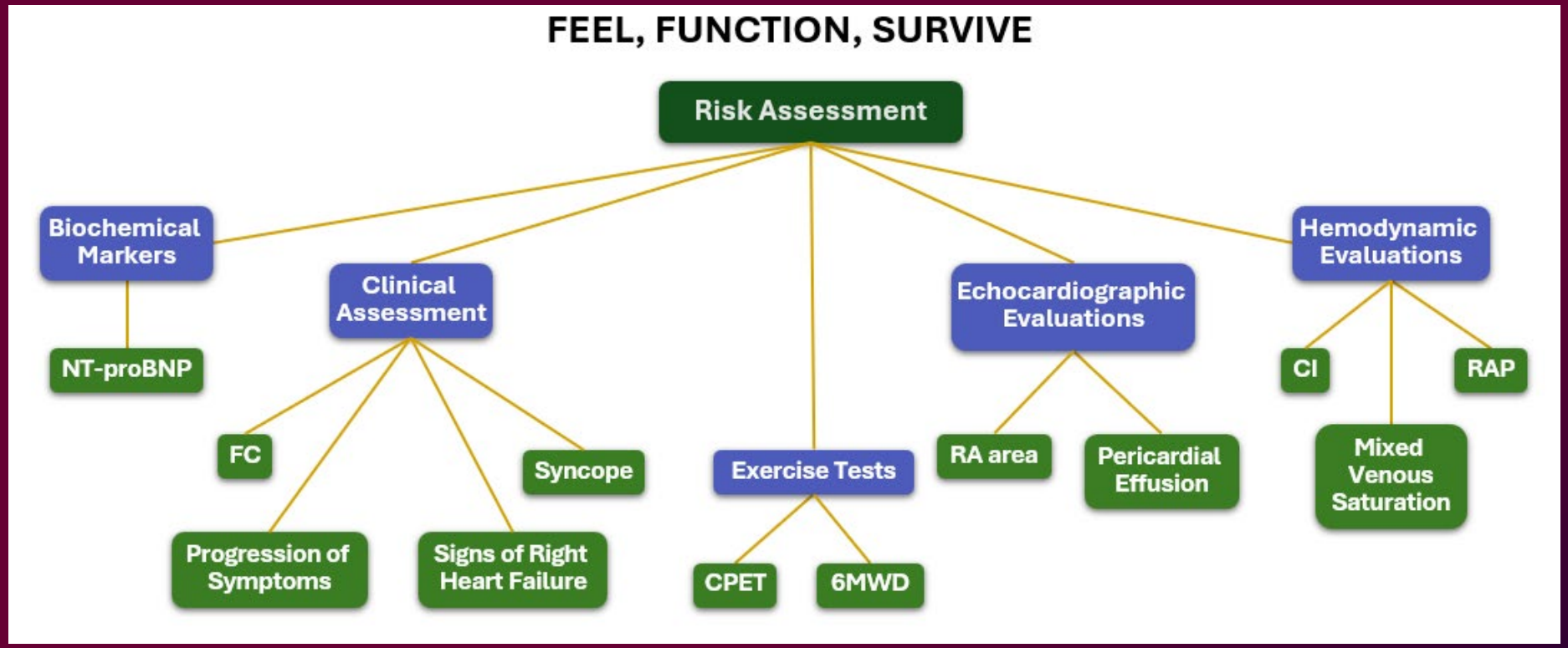
https://investor.insmed.com/2025-06-10-Insmed-Announces-Positive-Topline-Results-from-Phase-2b-Study-of-Treprostinil-Palmitil-Inhalation-Powder-TPIP-as-Once-Daily-Therapy-in-Patients-with-Pulmonary-Arterial-Hypertension

Positive topline results from phase 2 study-announced June 10

- Statistically Significant 35% Placebo-Adjusted Reduction from Baseline in Pulmonary Vascular Resistance for the Primary Endpoint ($p<0.001$)
- 35.5 Meter Placebo-Adjusted Improvement in Six-Minute Walk Distance for the Secondary Efficacy Endpoint ($p=0.003$)
- 60% Placebo-Adjusted Reduction from Baseline in NT-proBNP Concentrations for the Secondary Efficacy Endpoint ($p<0.001$)
- Results Were Assessed Approximately 24 Hours After Administration, Demonstrating Sustained Benefit Throughout the 24-Hour Dosing Period
- Engaging with FDA to plan phase 3 for both PH-ILD and PAH

Risk Assessment & Treatment Monitoring in Patients with PAH

PAH Requires Multi-Parameter Risk Assessment



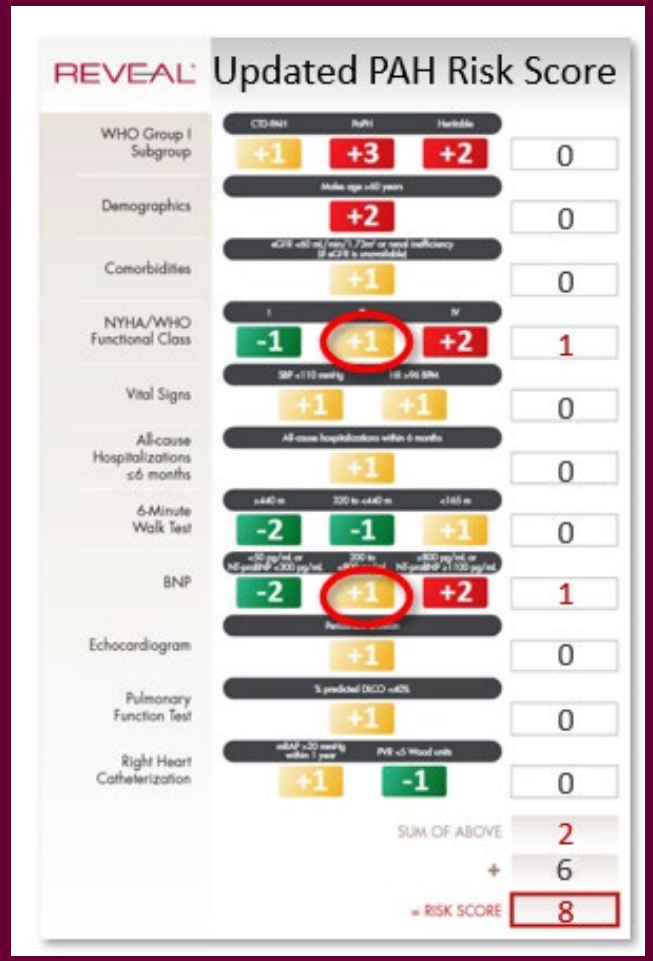
FC, functional class; CPET, cardiopulmonary exercise test; CI, cardiac index; RAP, right atrial pressure; Adapted from: Galiè N, et al. Eur Heart J 2016;37:67-119

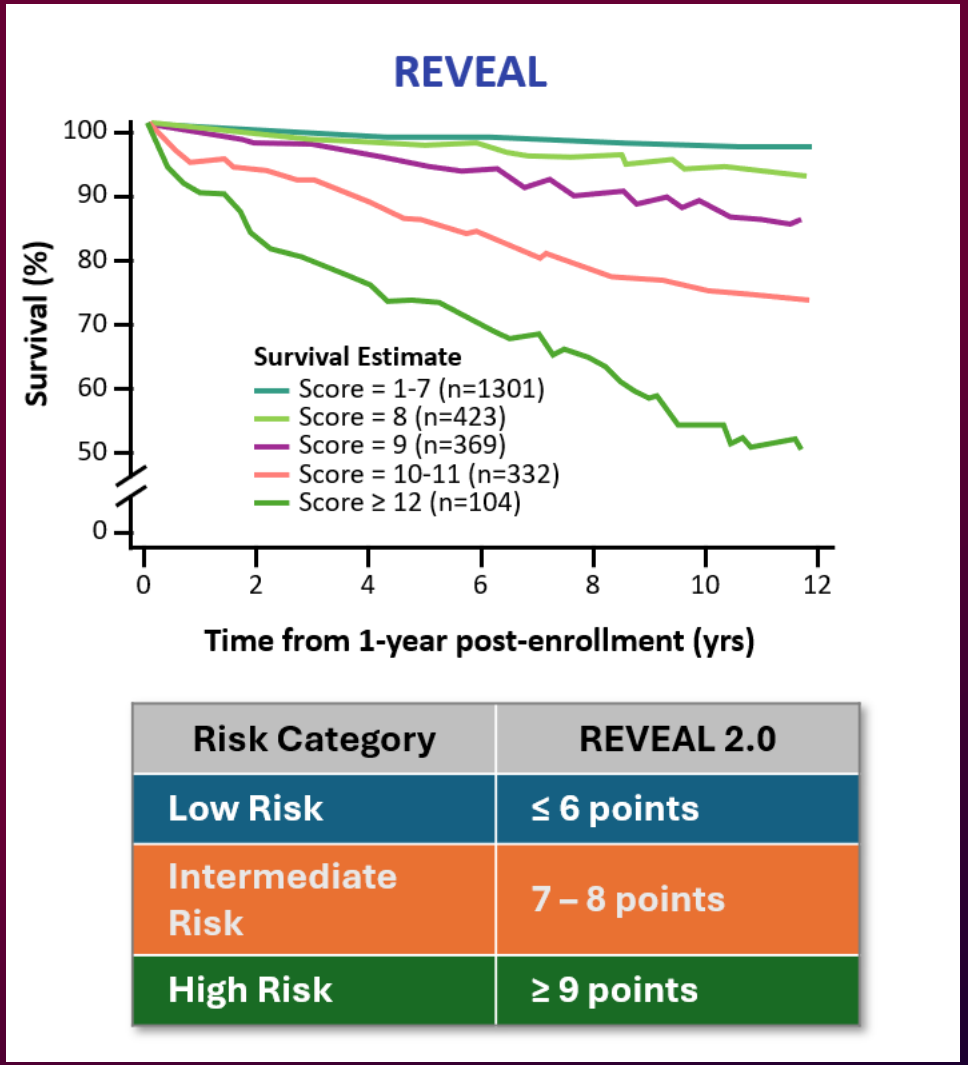
Risk Stratification: Key Component of Assessment

Updates in ERS/ESC Guidelines 2022
Added Emphasis on RV Function as a predictor of outcome

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%

Assessing risk at diagnosis: REVEAL





Risk Category	REVEAL 2.0
Low Risk	≤ 6 points
Intermediate Risk	7 – 8 points
High Risk	≥ 9 points

Benza RL et al: Chest. 2019 Aug;156(2):323-337

Risk Stratification at Follow-Up: Improving Predicted Outcome

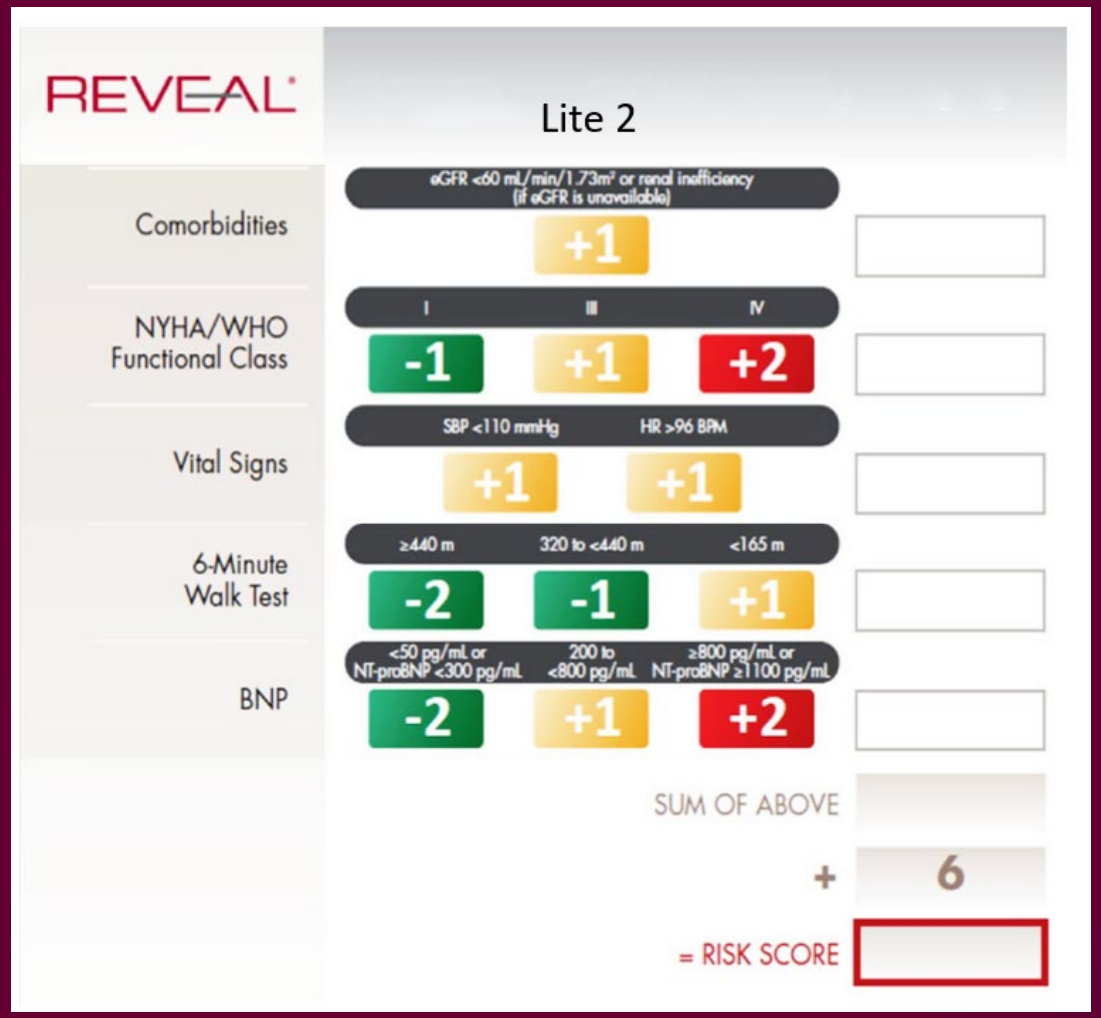
4-strata risk-assessment tool

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

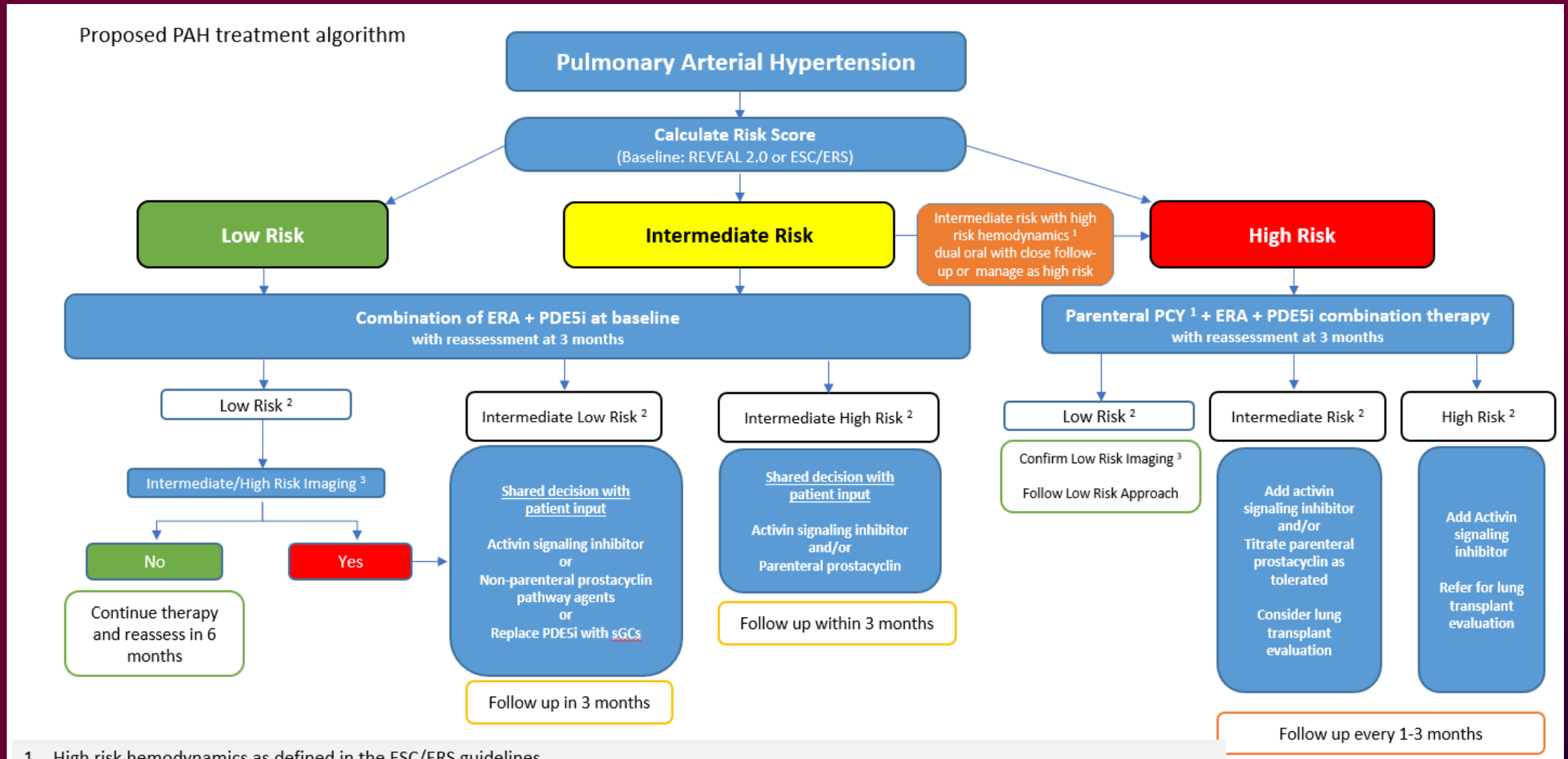
Each variable is graded from 1 to 4, and the mean is calculated by dividing the sum of all grades by the number of variables and rounding to the next integer

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(European Heart Journal; 2022 – doi: 10.1093/eurheartj/ehac237 and European Respiratory Journal; 2022 – doi: 10.1183/13993003.00879-2022)

REVEAL Lite 2- Risk Stratification at Follow-Up



Risk Category	REVEAL 2.0	REVEAL Lite 2
Low Risk	≤ 6 points	1-5 points
Intermediate Risk	7 – 8 points	6-7 points
High Risk	≥ 9 points	> 8 points



1. High risk hemodynamics as defined in the ESC/ERS guidelines
2. Follow-up risk assessment: REVEAL 2.0 Lite or ESC/ERS 4-strata
3. Imaging risk: Suggest referring to the risk table in the 2022 ESC/ERS guidelines. In patients with intermediate and high-risk imaging parameters should be considered for further escalation of therapy

** Among patients not able to tolerate therapies as indicated above alternative approaches can be adopted as an individualized approach*

Sahay S, et al. Am J Respir Crit Care Med. Published online July 10, 2024