CMHC Cardiometabolic Health Congress

WEBCAST

Navigating the Latest in Pulmonary Arterial Hypertension

Implementing Guidelines Amidst a Changing Treatment Landscape

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Screening & Diagnosis of PAH

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Key Points

- Review the classification of pulmonary hypertension
- Discuss the current hemodynamic definition
- Explain the diagnostic algorithm for pulmonary hypertension

7th World Symposium on PH Classification

1. Pulmonary Arterial Hypertension

- 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 diseases
  - 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/ capillaries (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn

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 etiologies
- 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 post-capillary PH

3. PH Associated With Lung Diseases and/or Hypoxia

- 3.1 Chronic obstructive pulmonary disease and/or emphysema
- 3.2 Interstitial lung disease
- 3.3 Combined pulmonary fibrosis and emphysema
- 3.4 Other parenchymal lung diseases
- 3.5 Nonparenchymal restrictive diseases
  - 3.5.1 Hypoventilation syndromes
  - 3.5.2 Pneumonectomy
- 3.6 Hypoxia without lung disease (eg high altitude)
- 3.7 Developmental lung diseases

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 Hematological disorders
- 5.2 Systemic disorders (sarcoidosis, pulmonary Langerhans cell histiocytosis, neurofibromatosis type 1)
- 5.3 Metabolic disorders
- 5.4 Chronic kidney failure (+/-hemodialysis)
- 5.5 Pulmonary tumor thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis
- 5.7 Complex congenital heart diseases

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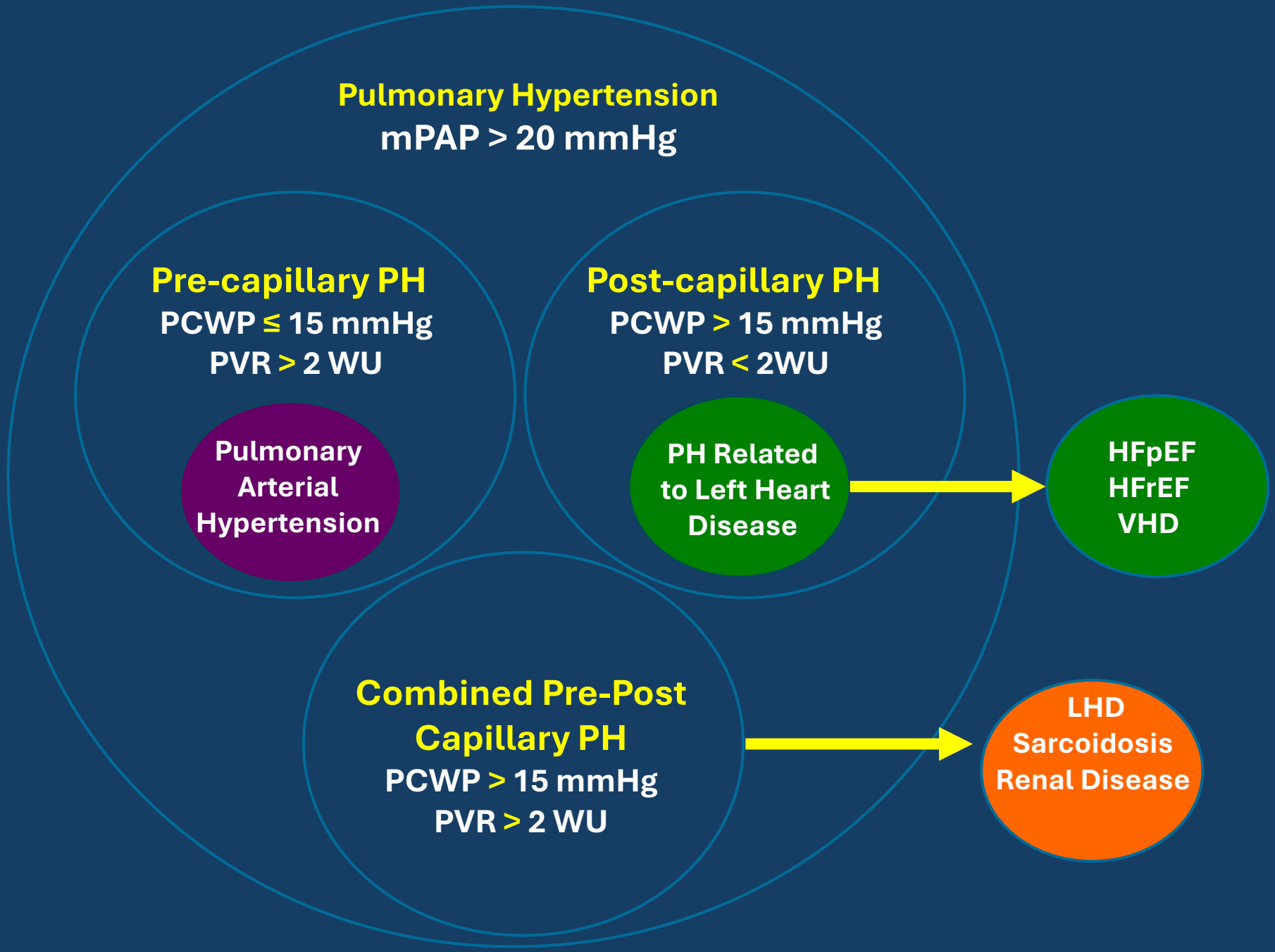
Kovacs G et al. *Eur Respir J.* 2024; 2401324 [DOI: 10.1183/13993003.01324-2024].

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

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

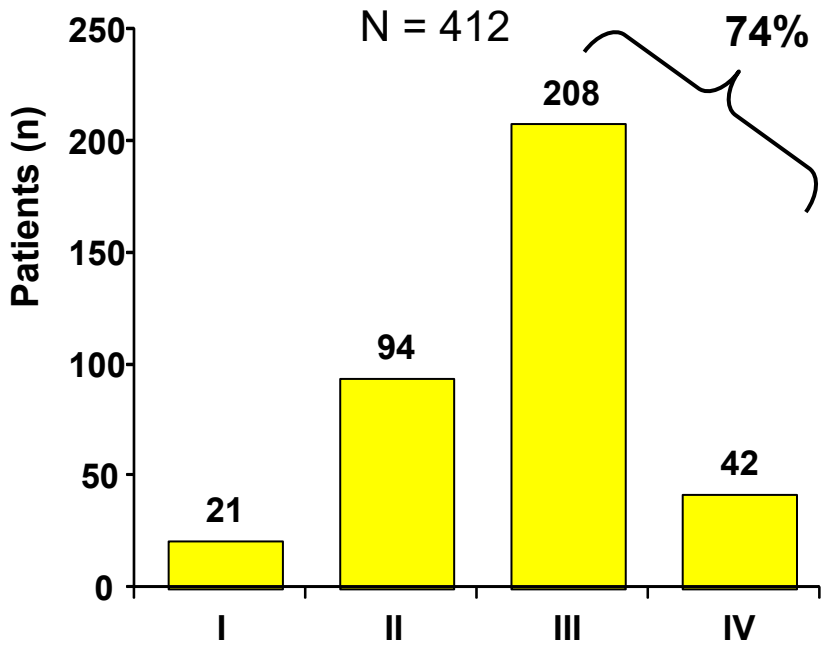
Class	Description
I	No limitation of physical activity; ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope
II	Slight limitation of physical activity; no discomfort at rest; ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
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.

Diagnosis of PAH Is Often Late

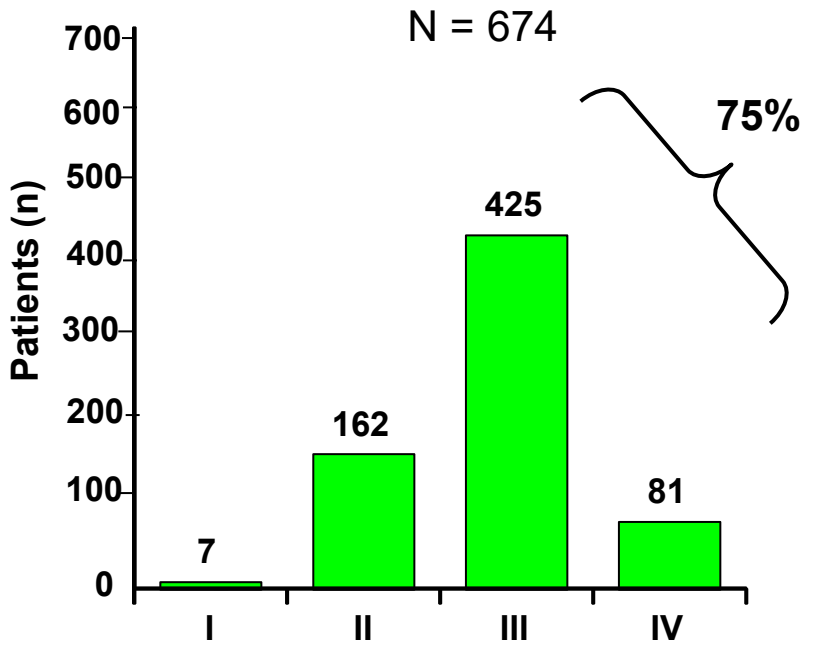
Mean time between symptom onset and diagnosis: 27-34 months

REVEAL Registry[1]



Functional Class at Diagnosis

French National Registry[2]



Functional Class at Presentation

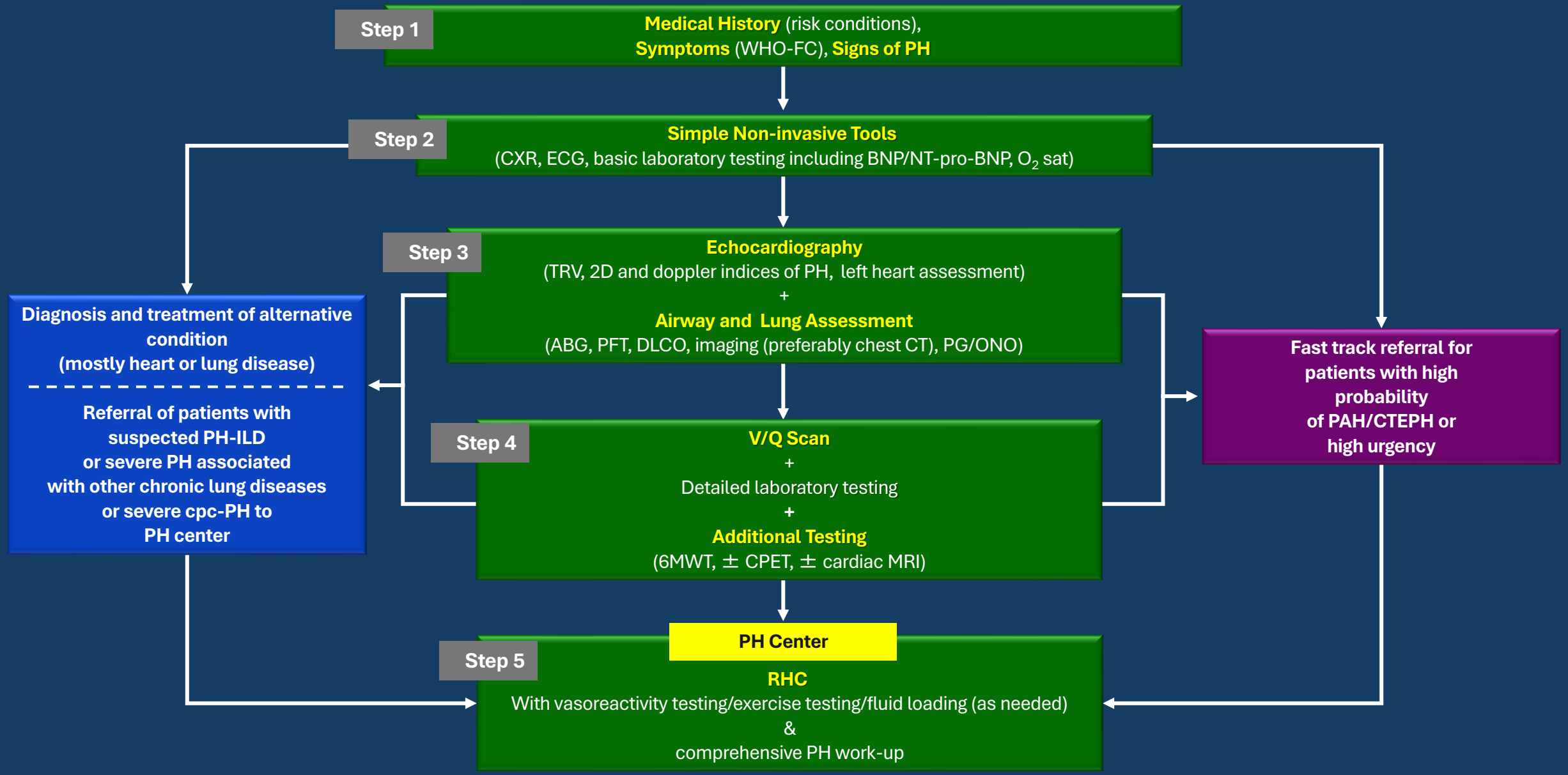
[1]Adapted from Badesch DB. *Chest.* 2010;137:376-387.
[2]Humbert M et al. *Am J Respir Crit Care Med.* 2006;173:1023-1030.

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

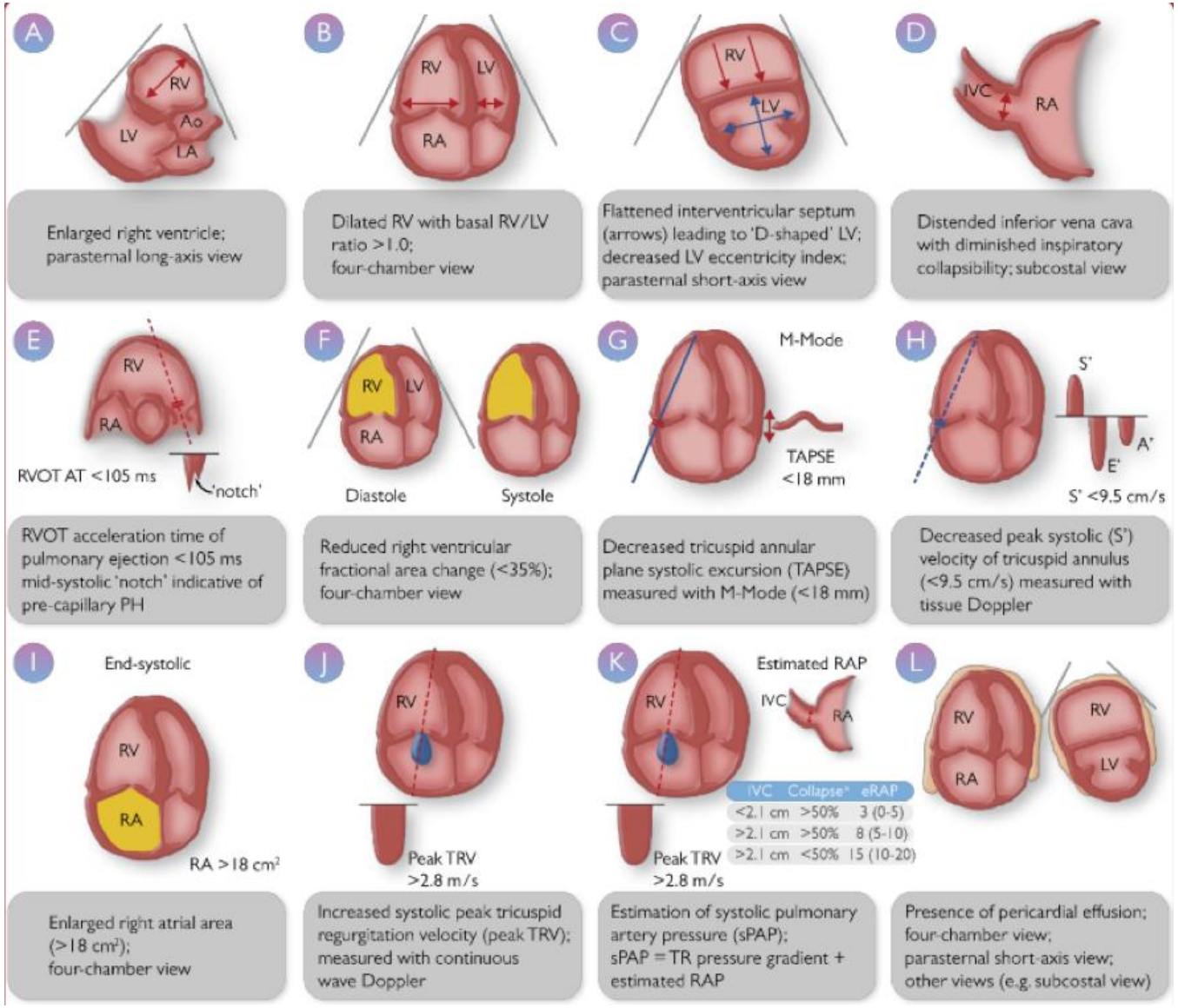
2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2022—doi:10.1093/eurheartj/ehac237 *and* *Eur Resp J.* 2022—doi:1183/13993003.00879-2022.

7th WSPH Diagnostic Algorithm for Patients With Suspected PH



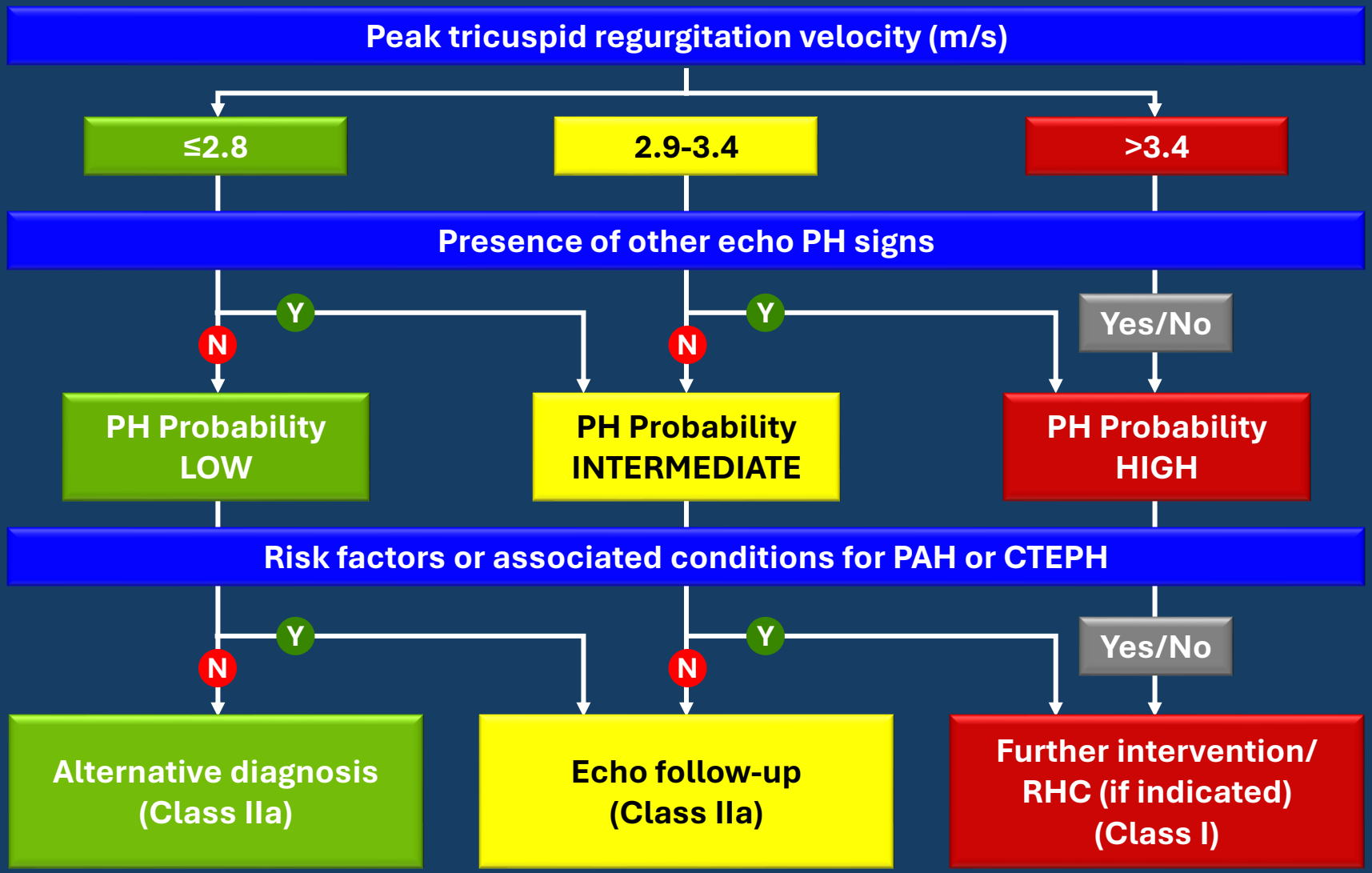
Kovacs G et al. *Eur Respir J.* 2024; 2401324 [DOI:10.1183/13993003.01324-2024].

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.

Cardiac Catheterization

Required when PAH is suspected

- Confirm echo findings
- Survey for left heart disease
  - measure wedge pressure or LVEDP
- Measure CO; calculate PVR
- Exclude systemic to pulmonary shunts
- Establish severity and prognosis
- Acute vasodilator challenge

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.

Vasodilator Challenge

- iNO (most commonly) at 40 ppm
- Positive if:
  - drop in mPAP ≥10 mmHg to a mean ≤40 mmHg
  - no decline in CO/CI
  - no rise in PCWP
- Suggests response to calcium channel blocker
- Caveats:
  - only indicated for IPAH/HPAH/DPAH patients
  - many patients responding acutely lose vasoreactivity over time, thus close monitoring is required

Galiè N et al. *J Am Coll Cardiol.* 2013;62:D60-72.
Sitbon O et al. *Circulation.* 2005;111:3105-3111.

Screening and Diagnosis Summary

- High index of suspicion
- Thorough diagnostic evaluation
- Exclude thromboembolic disease
- Evaluate potential causes/contributing issues
- RHC required prior to initiating PAH therapy

Current & Emerging Treatments in PAH

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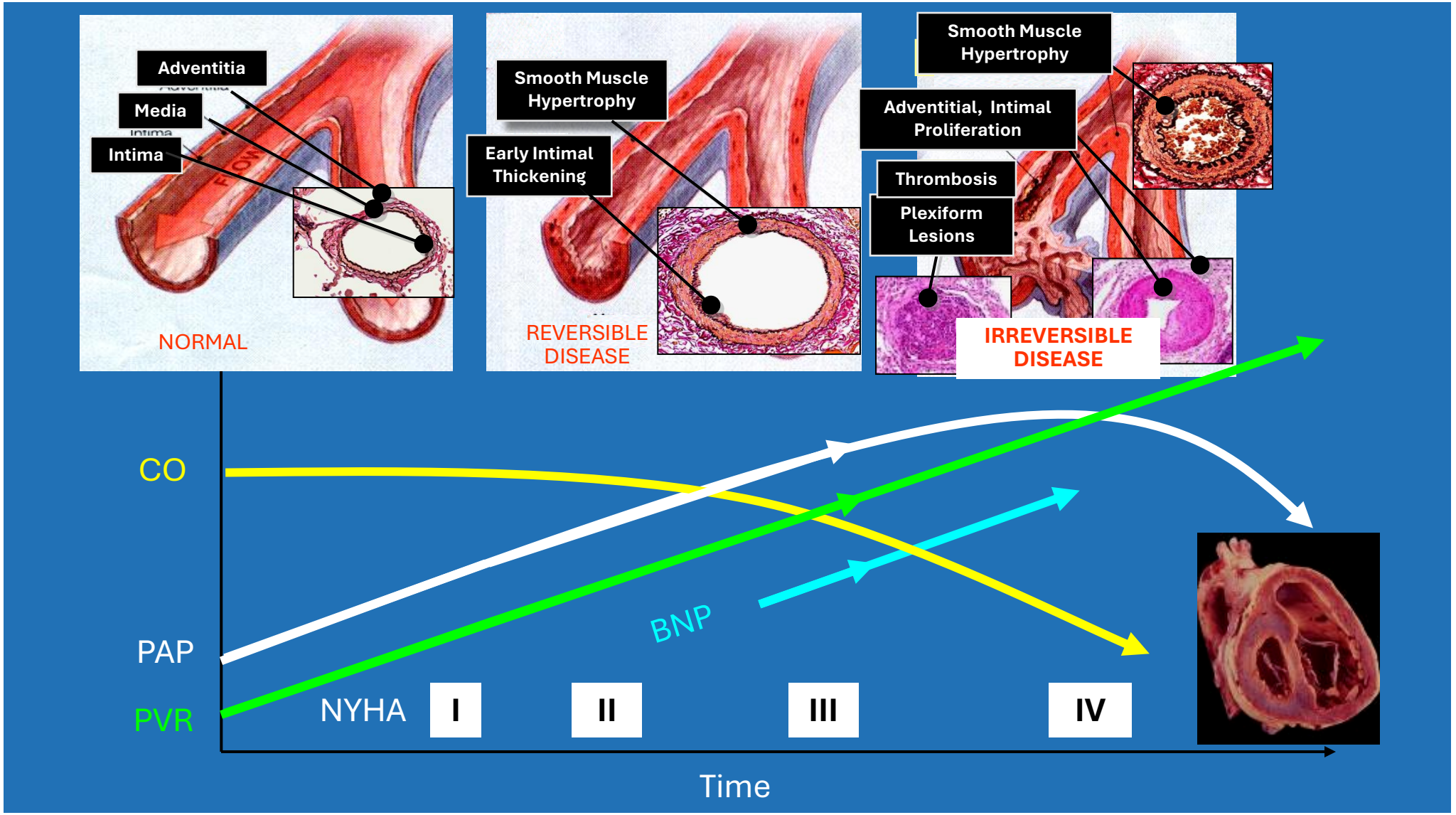
Key Points

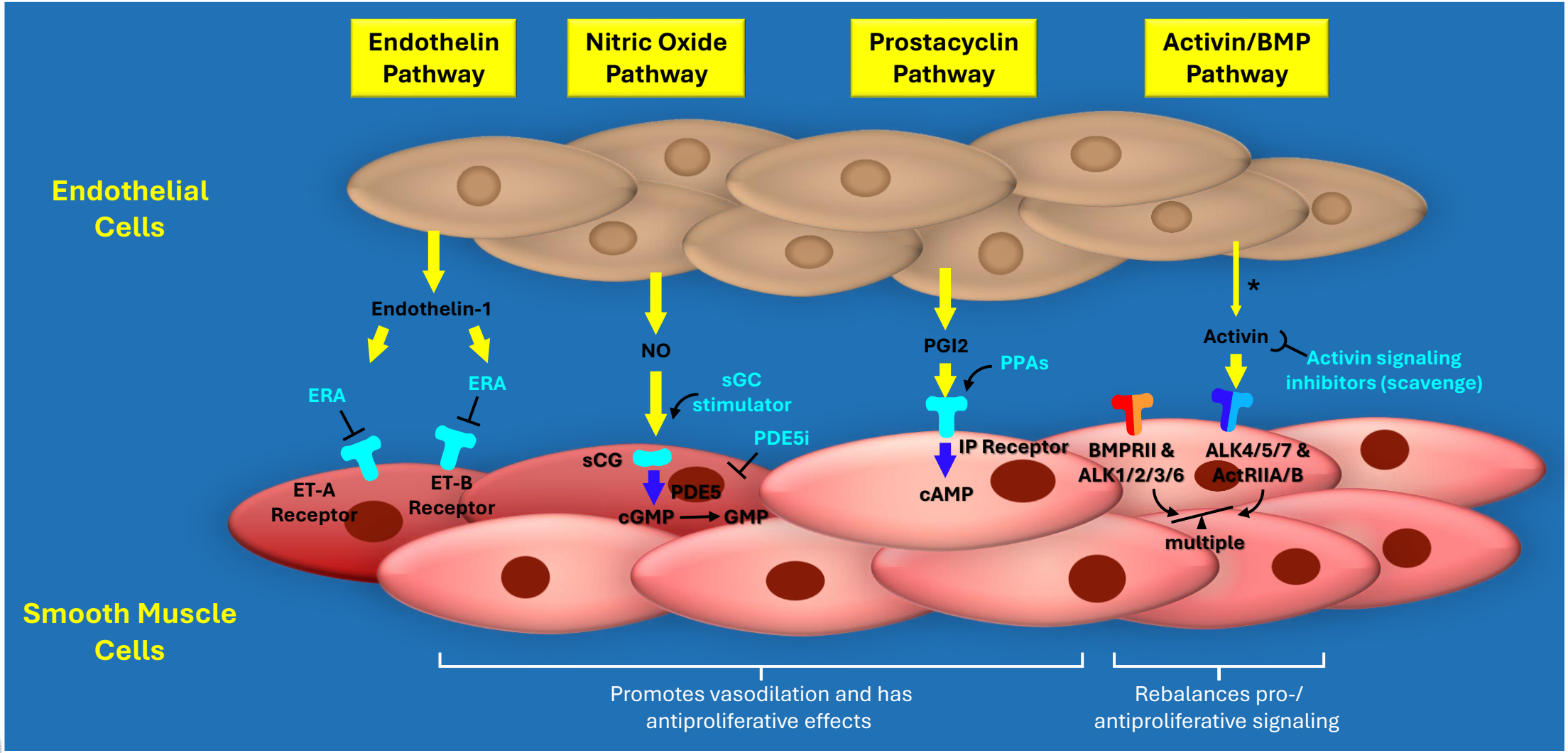
- Review disease pathophysiology
- Explain mechanism of action of current therapies
- Discuss safety and efficacy of current therapies
- Highlight investigational and emerging treatment options

PAH: Hemodynamic and Clinical Course



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

Current Treatment Pathways in PAH



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

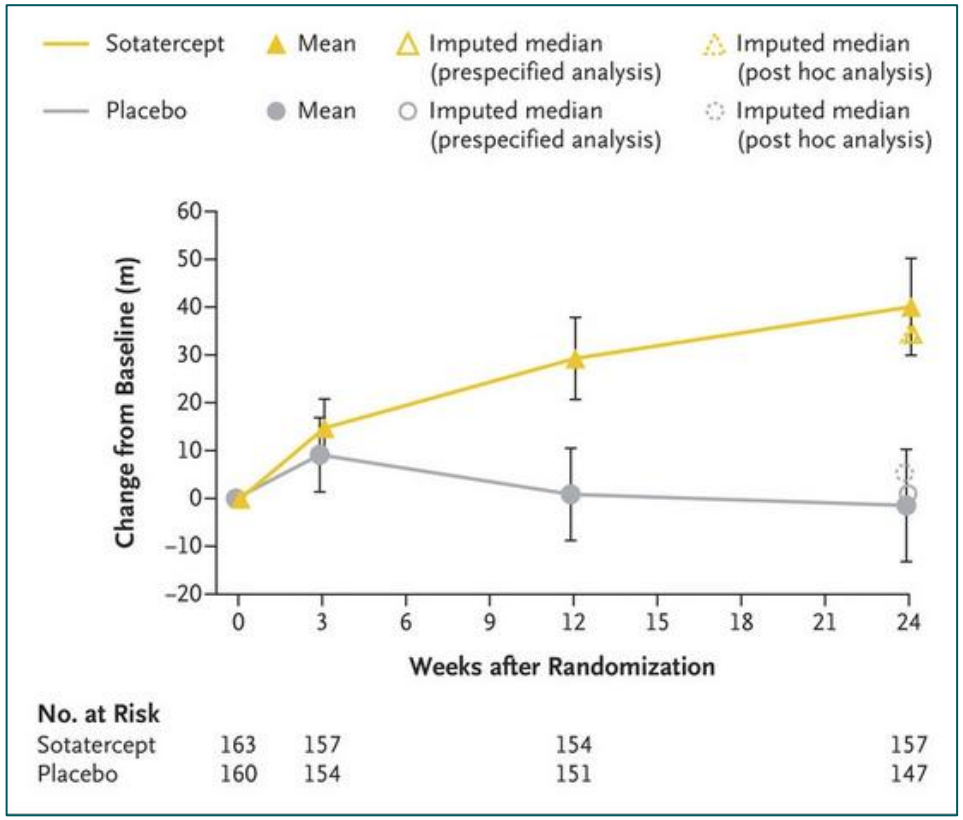
*Signaling mediators also originate from multiple other cell types, particularly for activin.

FDA-Approved Therapy for PAH

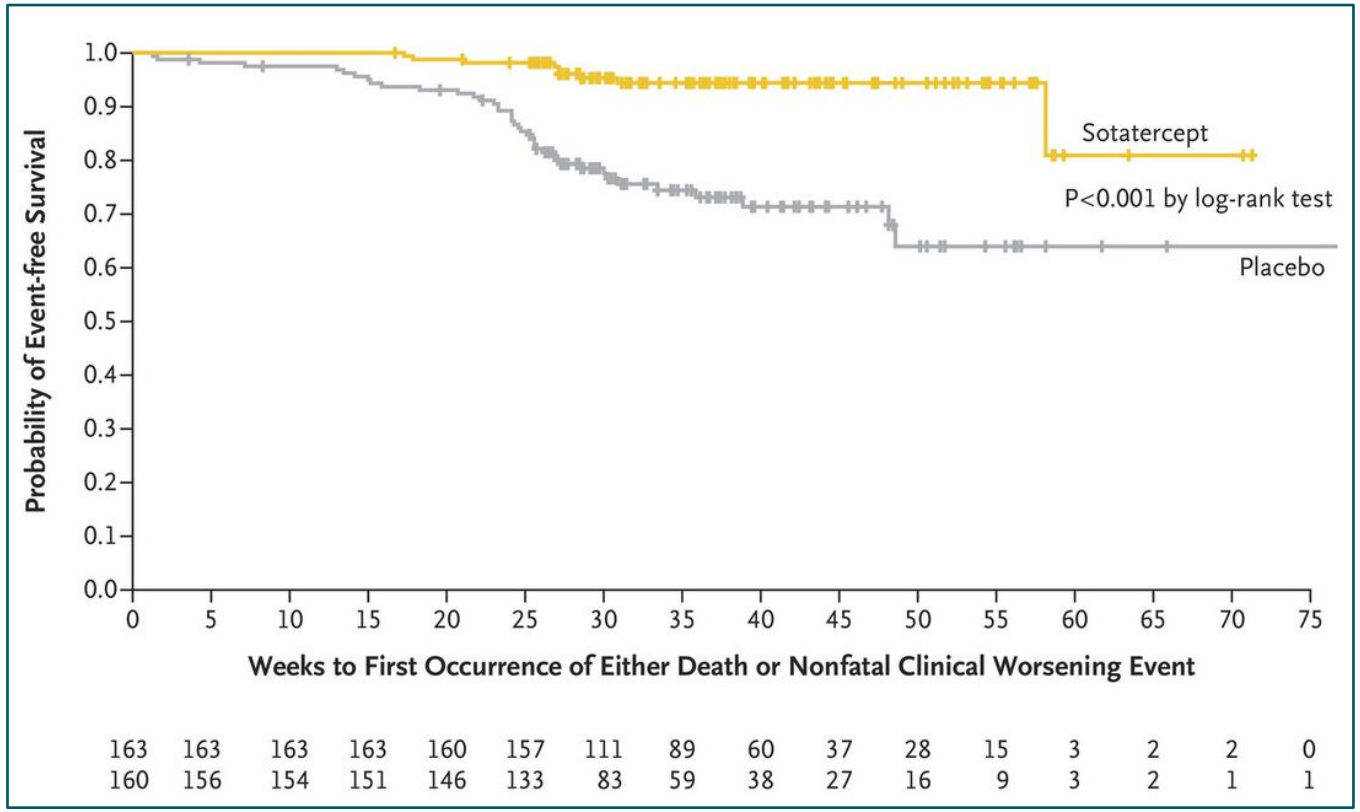
Pathway	Therapy	Dosage
Endothelin	ambrisentan	5,10 mg po qd
	bosentan	125 mg po bid
	macitentan	10 mg po bid
Nitric Oxide	*PDE 5 Inhibitors*	
	sildenafil	20 mg po tid
	tadalafil	40 mg po qd
	sGC Stimulator	
	riociguat	0.5-2.0 mg po tid
Prostacyclin	epoprostenol	IV
	treprostinil	IV/SC
		9 inhalations 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

Summary of Secondary Endpoints

8 of 9 Secondary hypothesis tests also were significant (accounting for testing strategy):

	Secondary Endpoint	Placebo (N = 160)	sotatercept (N = 163)	sotatercept vs. placebo	
				HL Location Shift (95% CI)	p-value
1	Multicomponent Improvement, n/N (%)	16 (10.1)*	63 (38.9)*	--	<0.001
2	PVR — dyn·sec·cm^{-5}			-234.6 (-288.4 to -180.8)	<0.001
3	NT-proBNP - pg per milliliter			-441.6 (-573.5 to -309.6)	<0.001
4	WHO FC, n/N (%)	22 (13.8)*	48 (29.4)	--	<0.001
5	TTCW or all-cause death			0.16 (0.08 to 0.35)†	<0.001†
6	French low-risk score, n/N (%)	29 (18.2)*	64 (39.5)*	--	<0.001
7	PAH-SYMPACT® Physical Impacts			-0.26 (-049 to -0.04)	0.01
8	PAH-SYMPACT® Cardiopulmonary			-0.13 (-0.26 to -0.01)	0.03
9	PAH-SYMPACT® Cognitive/Emotional			-0.16 (-0.40 to 0.08)	0.16

†Expressed as Hazard ratio (95% CI) and Log-rank p-value.

*For multicomponent improvement and French risk score, N= 159 (placebo) and N= 162 (sotatercept) due to one patient in each treatment group with missing data due to COVID-19 and excluded from analysis. For WHO functional class, N= 159 (placebo) and N= 163 (sotatercept) due to a placebo-treated patient with missing data due to COVID-19 and excluded from analysis.
†Defined as meeting all 3 of the following criteria at week 24: improvement in 6MWD [increase of ≥30 meters]; improvement in NT-proBNP level [decrease of ≥30%] or maintenance/achievement of NT-proBNP level <300 pg per milliliter; and improvement in WHO functional class [shift from class III to II or I, or class II to I] or maintenance of class II).

6MWD: 6-minute walk distance; CI: confidence interval; COVID-19: coronavirus of 2019; HL: Hodges-Lehmann; N: number of patients in the treatment group or overall; n: number of patients in the category; NT-proBNP: N-terminal pro–B-type natriuretic peptide; PAH SYMPACT®: pulmonary arterial hypertension symptoms and impact patient-reported questionnaire; PVR: pulmonary vascular resistance; TTCW: time to clinical worsening; WHO: World Health Organization; WHO FC: World Health Organization functional class.

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

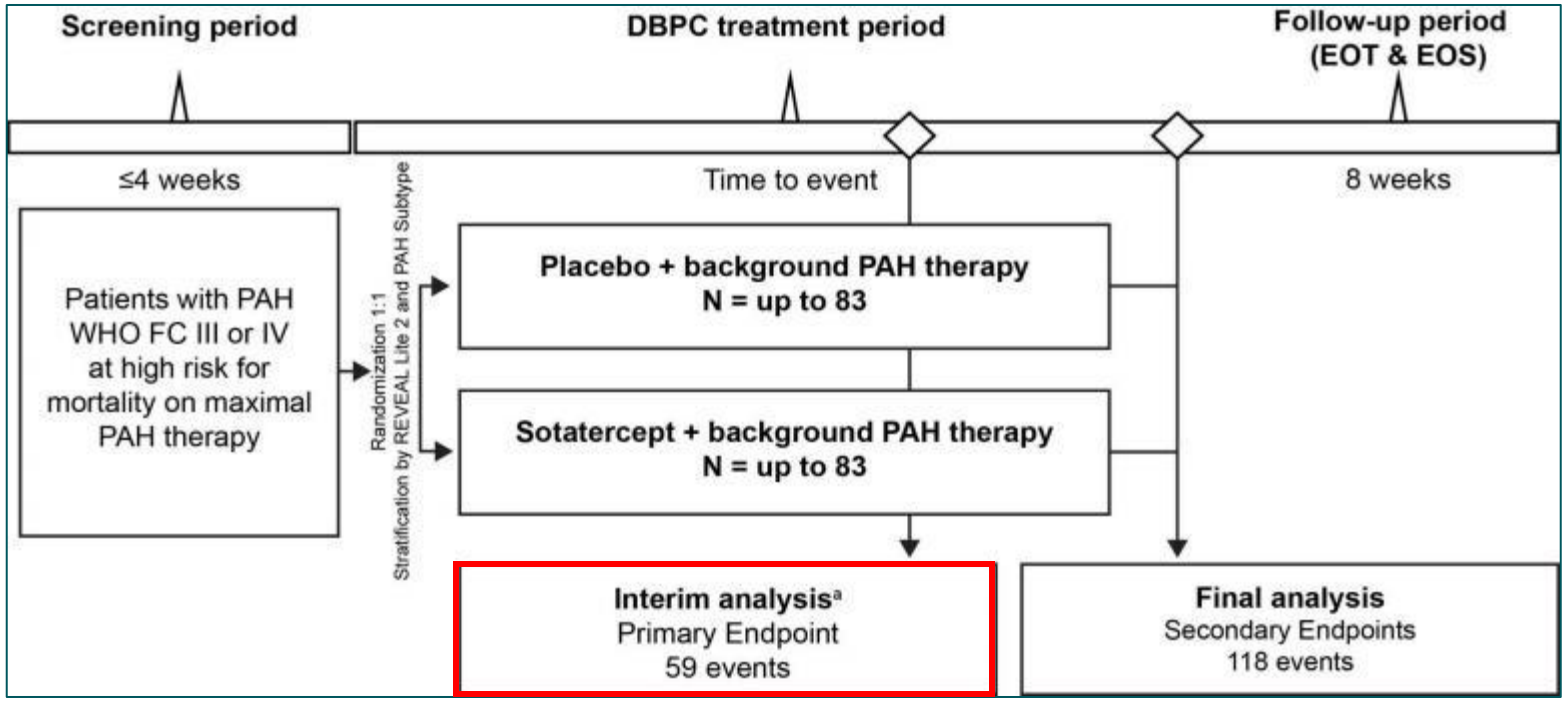
Safety of sotatercept treatment in PAH

TEAEs of interest: bleeding events, cardiac events, embryo-fetal toxicity, hepatic toxicity, immunogenicity, increased blood pressure, increased hemoglobin, leukopenia, neutropenia, renal toxicity, suppression of follicle stimulating hormone, thrombocytopenia, thromboembolic events
TEAE of special interest: telangiectasia

Number of patients with any	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)
TEAEs of interest†	72 (45.0)	97 (59.5)
Bleeding events	25 (15.6)	52 (31.9)
Telangiectasia	6 (3.8)	23 (14.1)
Increased hemoglobin (increased hematocrit, increased RBC count)	0	10 (6.1)
Thrombocytopenia	5 (3.1)	14 (8.6)
Increased blood pressure	1 (0.6)	7 (4.3)

Hoeper M N Engl J Med 2023

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



Primary Endpoint
Time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥ 24 hours

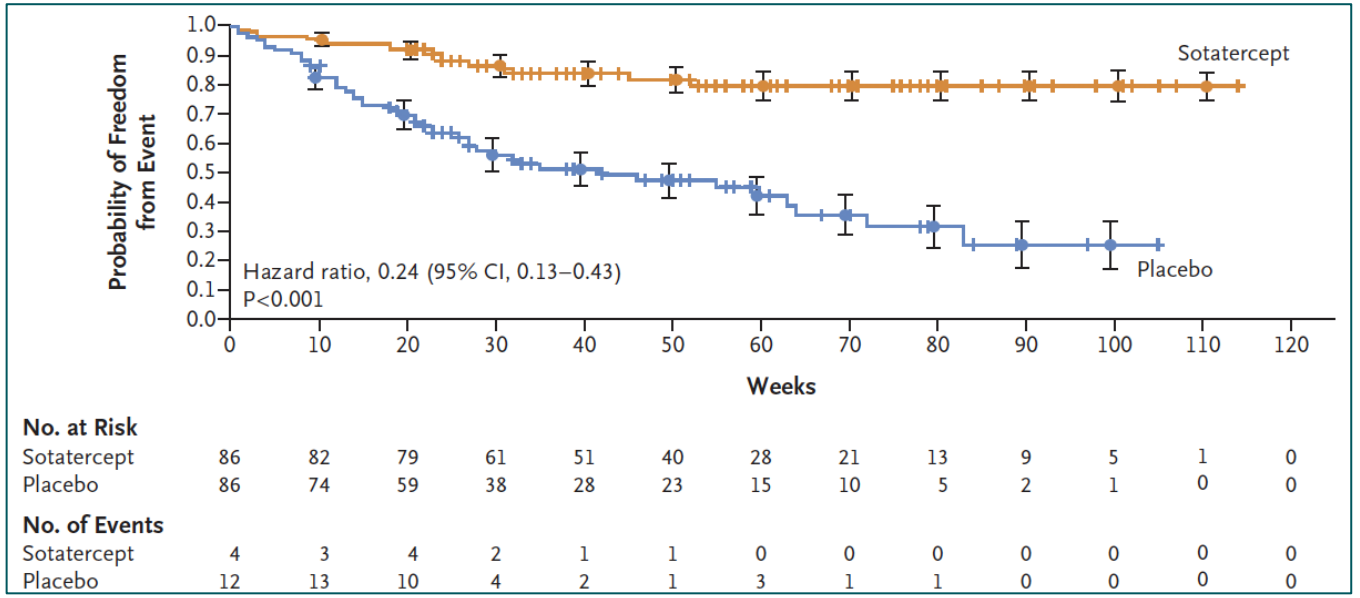
Secondary Endpoints
Prespecified hierarchical testing
• Overall and transplant-free survival • Week 24 changes in: Reveal Lite 2, NT-pro-BNP, mPAP, PVR, WHO FC, 6MWD, CO

[a] **Interim analysis occurred when approximately 50% of the clinical events were accrued (July 26, 2024)**

Humbert *et al*, *New Engl J Med*, DOI: 10.1056/NEJMoa2415160

ZENITH: sotatercept in High-Risk PAH Patients

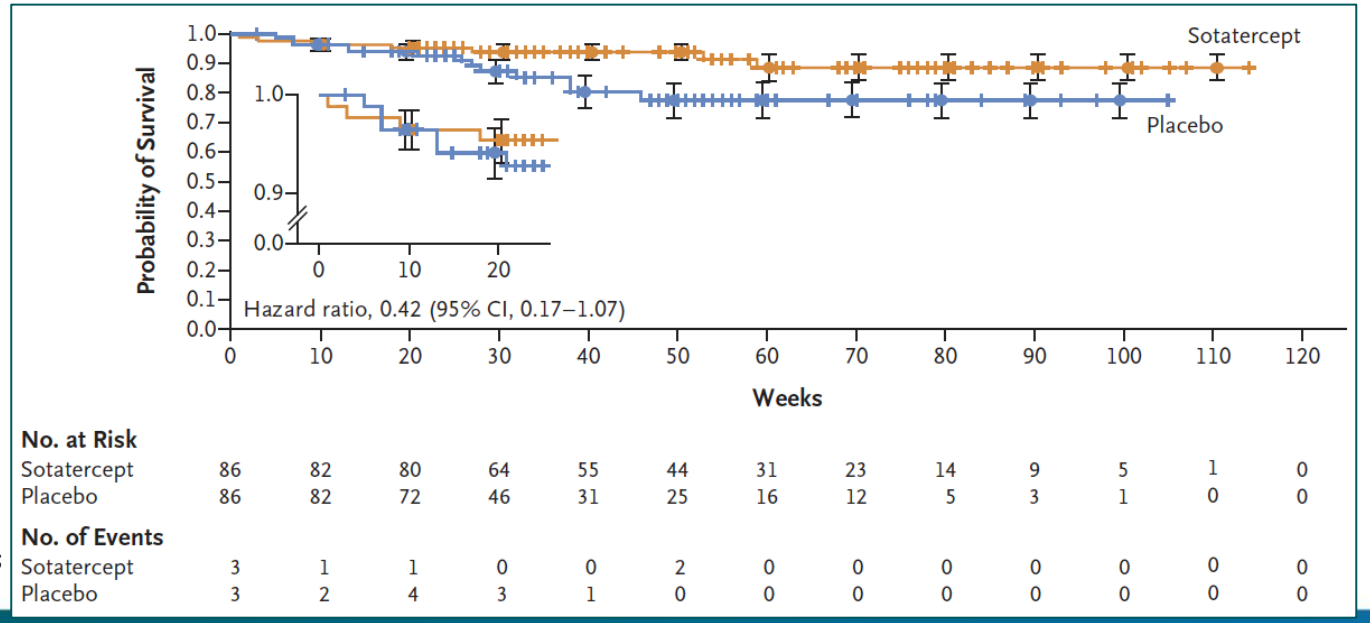
Primary Composite End-Point*



No. at Risk													
Sotatercept	86	82	79	61	51	40	28	21	13	9	5	1	0
Placebo	86	74	59	38	28	23	15	10	5	2	1	0	0
No. of Events													
Sotatercept	4	3	4	2	1	1	0	0	0	0	0	0	0
Placebo	12	13	10	4	2	1	3	1	1	0	0	0	0

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

Overall Survival

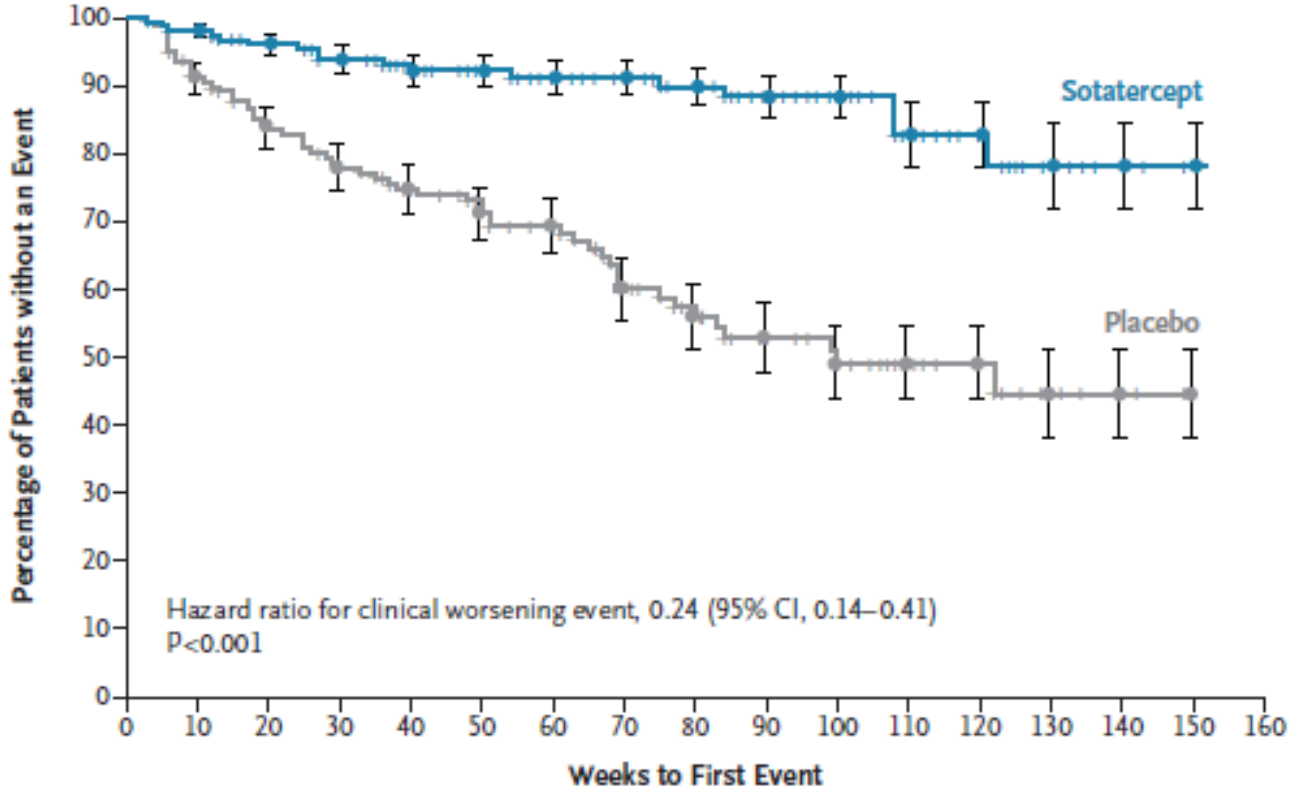


No. at Risk													
Sotatercept	86	82	80	64	55	44	31	23	14	9	5	1	0
Placebo	86	82	72	46	31	25	16	12	5	3	1	0	0
No. of Events													
Sotatercept	3	1	1	0	0	2	0	0	0	0	0	0	0
Placebo	3	2	4	3	1	0	0	0	0	0	0	0	0

Patients were FC III or IV, on maximized background therapy

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

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



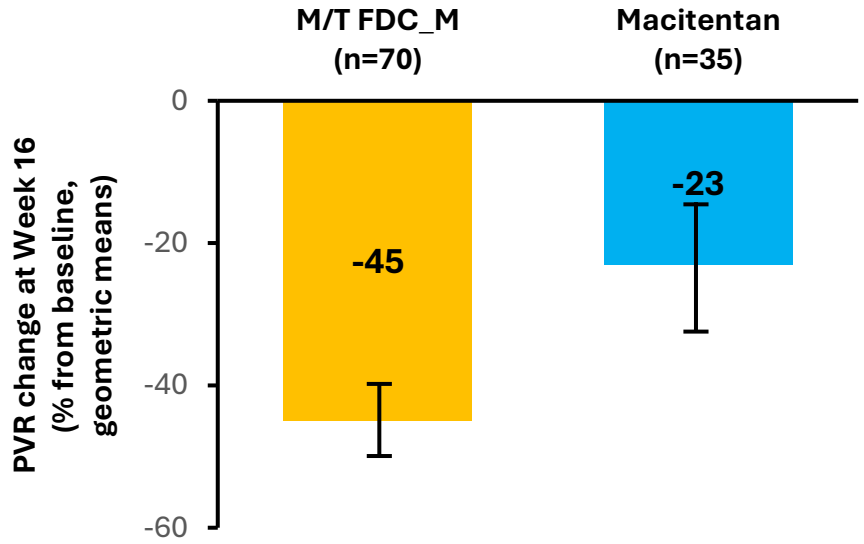
No. at Risk																	
Sotatercept	160	152	138	125	109	95	87	75	63	53	40	26	21	10	4	2	0
Placebo	160	142	122	107	92	80	70	50	40	31	27	16	11	5	2	1	0
No. of Events																	
Sotatercept	3	3	3	1	1	1	0	1	1	0	2	0	1	0	0	0	0
Placebo	13	11	8	5	2	4	8	2	3	1	1	0	1	0	0	0	0

McLaughlin et al, NEJM epub ahead of print, 2025

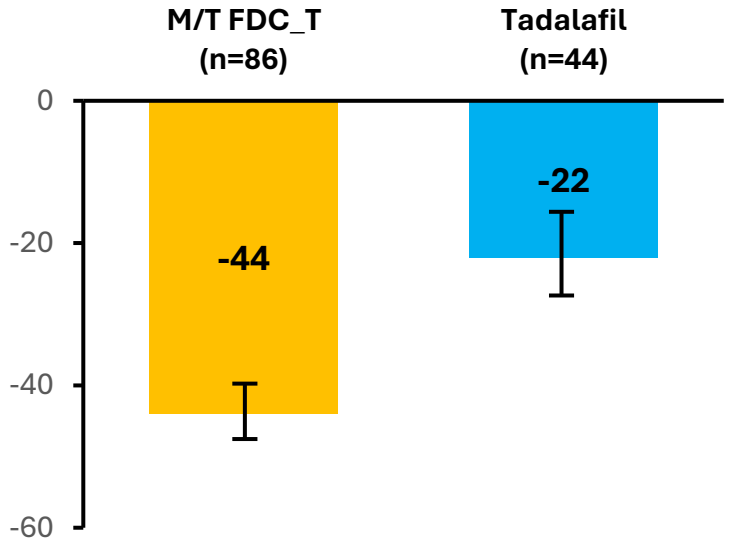
A DUE: Macitentan-Tadalafil Single-Tablet Combination

Primary Endpoint: Change in PVR at Week 16

M/T FDC vs Macitentan
Ratio of Geometric Means (95% CL): 0.71 (0.61-0.82), *p*<0001



M/T FDC vs Tadalafil
Ratio of Geometric Means (95% CL): 0.72 (0.64-0.80), *p*<0001



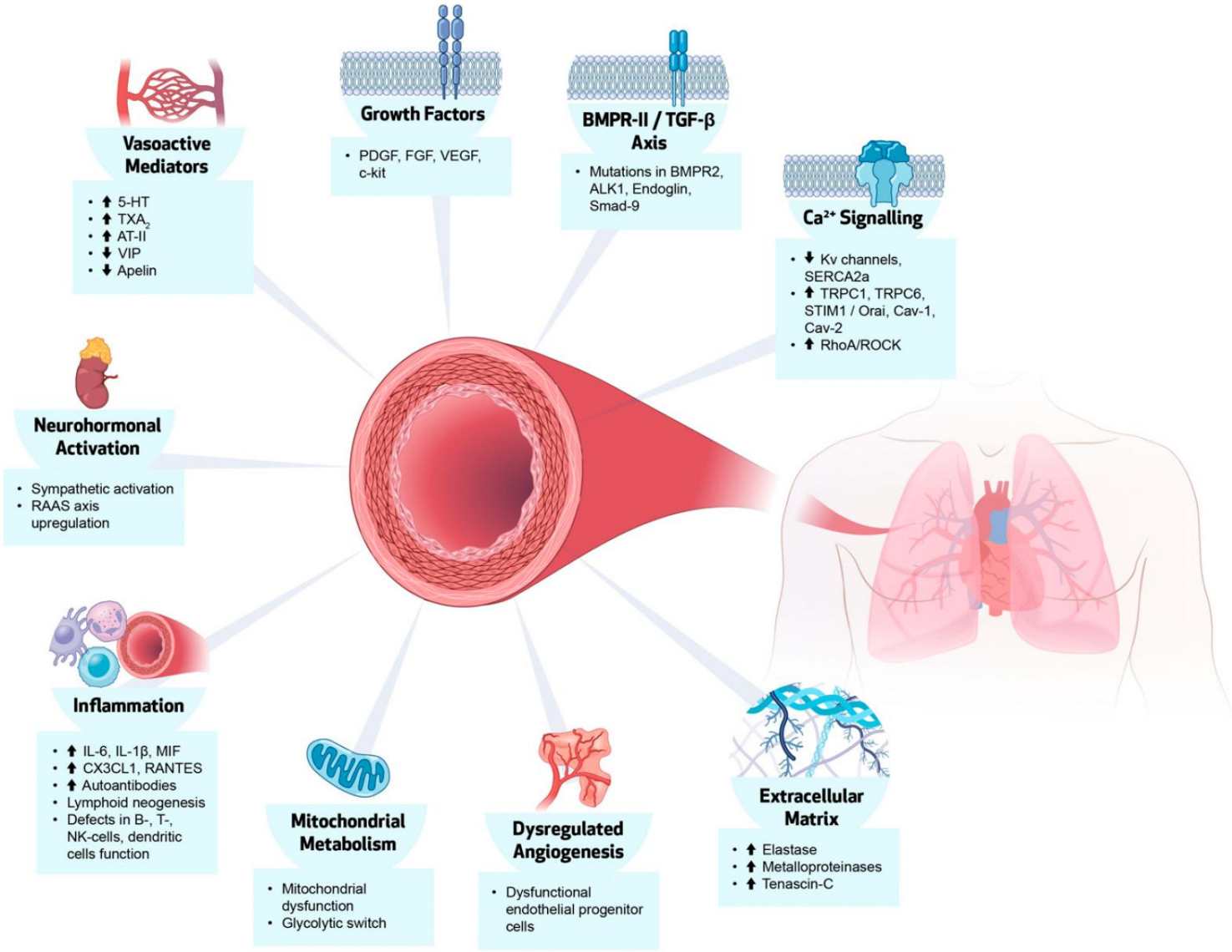
Secondary Endpoint: Mean Change in 6MWD at Week 16

	M/T FDC_M (n=70)			Macitentan (n=35)			Treatment Effect, LS Mean (95% CL), *p* value
	Baseline	Week 16	Change	Baseline	Week 16	Change	
6MWD (m)	354.3 ±12.4	413.6 ± 13.2	52.9 ± 10.6	347.2 ± 15.0	383.2 ± 15.4	38.5 ± 11.9	16.0 (-17.0 to 49.1), *p*=0.380
	M/T FDC_T (n=86)			Tadalafil (n=44)			Treatment Effect LS Mean (95% CL), *p* value
	Baseline	Week 16	Change	Baseline	Week 16	Change	
6MWD (m)	351.0 ± 10.7	398.3 ± 11.7	43.4 ± 8.4	361.8 ± 10.6	381.1 ± 12.2	15.9 ±6.8	25.4 (-0.9 to 51.6), *p*=0.059

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

Potential Therapeutic Targets for PAH Treatment

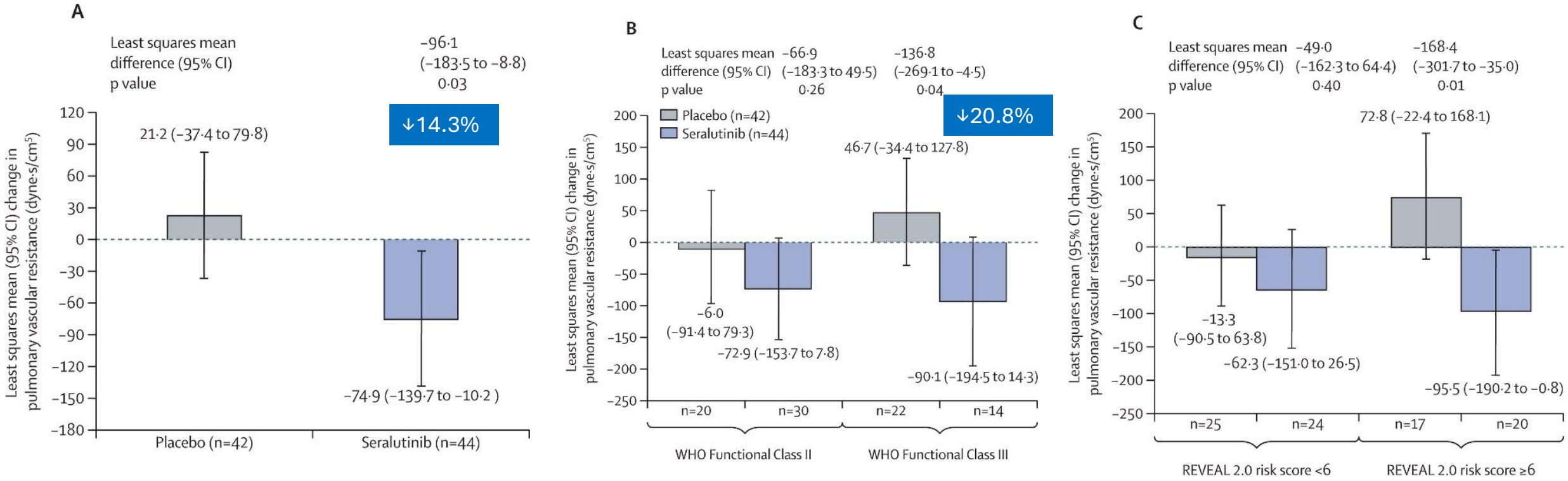
- Circulating hormones
- Epigenetic alterations
- Growth factors
- Vasoactive factors
- Inflammatory mediators
- Ion channels
- Mitochondrial and metabolic adaptations
- Oxidative stress modulator
- Stem cell therapy



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

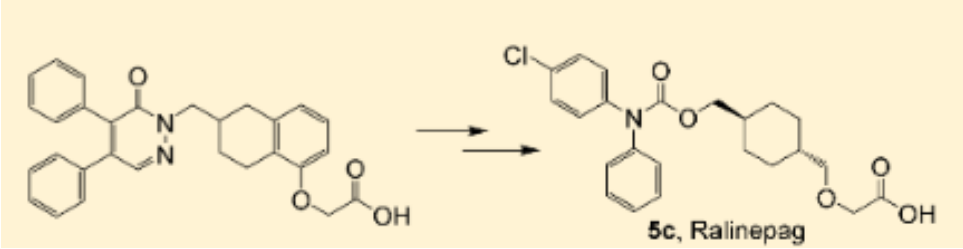
Seralutinib - TORREY

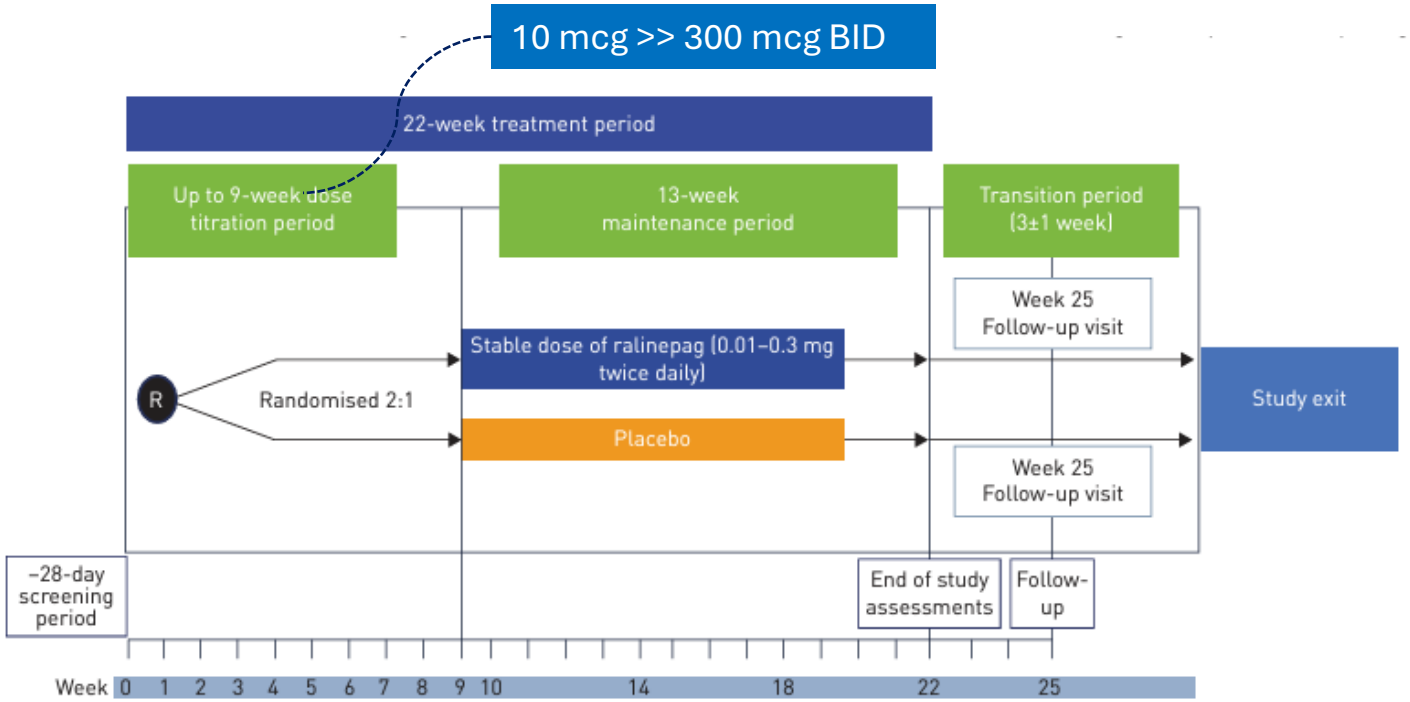
Primary Endpoint: PVR

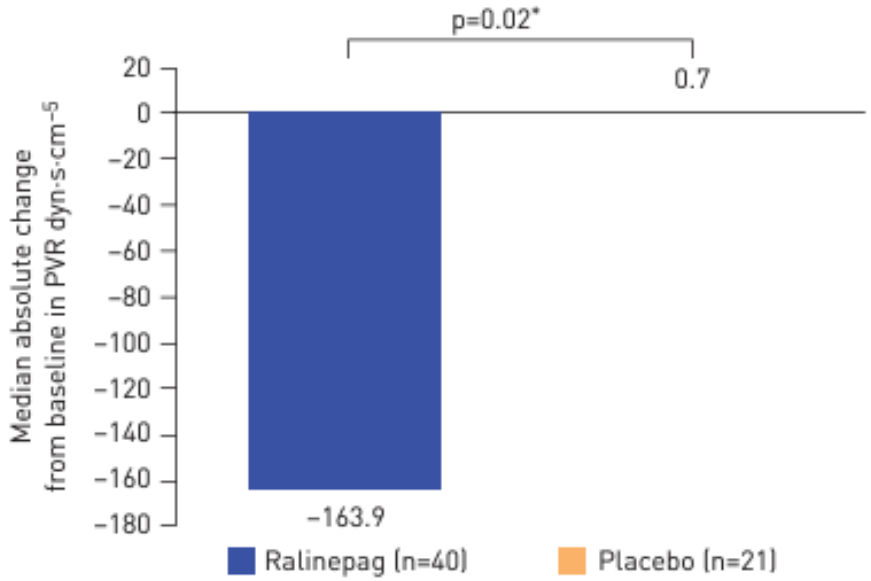


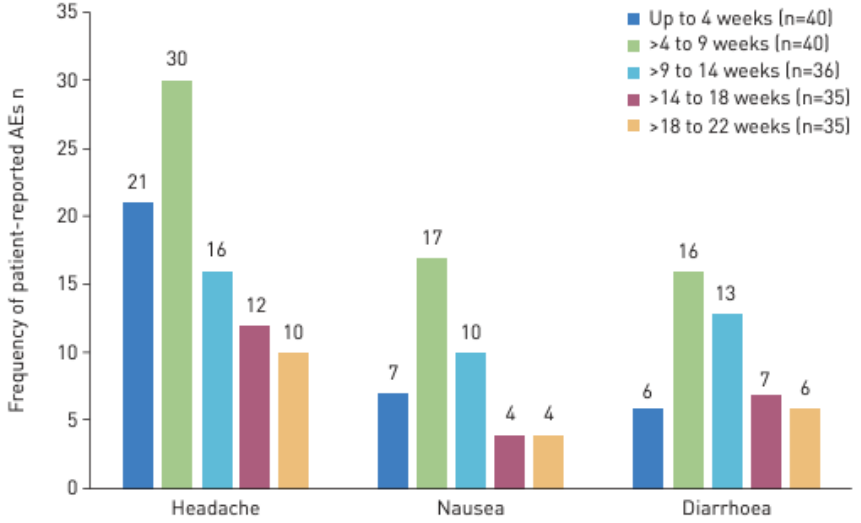
Frantz, RP. *Lancet Respir Med*. 2024; 12(7)

Ralinepag – Selective IP receptor agonist







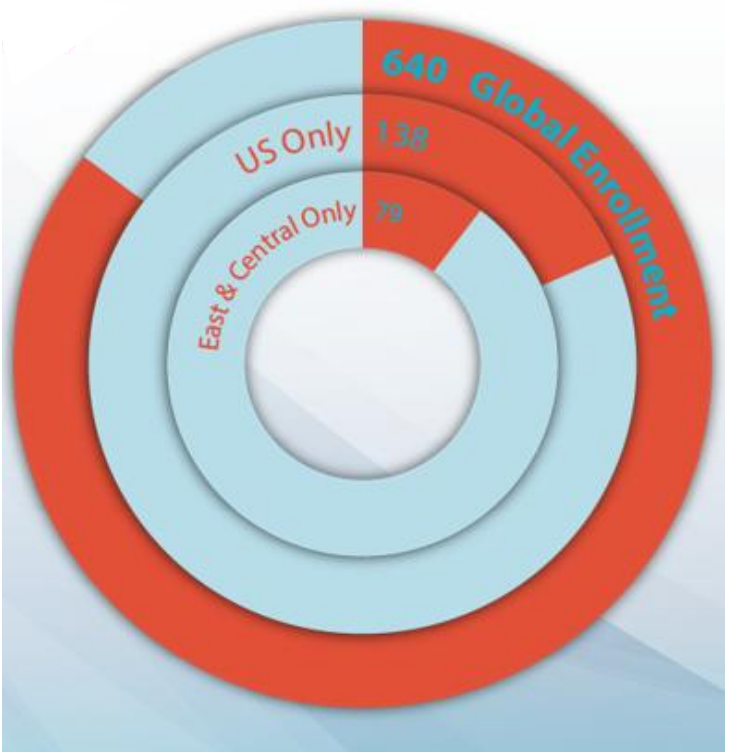


Torres F. *Eur Respir J.* 2019; 54

Ralinepag – Phase III (ADVANCE)

Nearing then end of enrollment

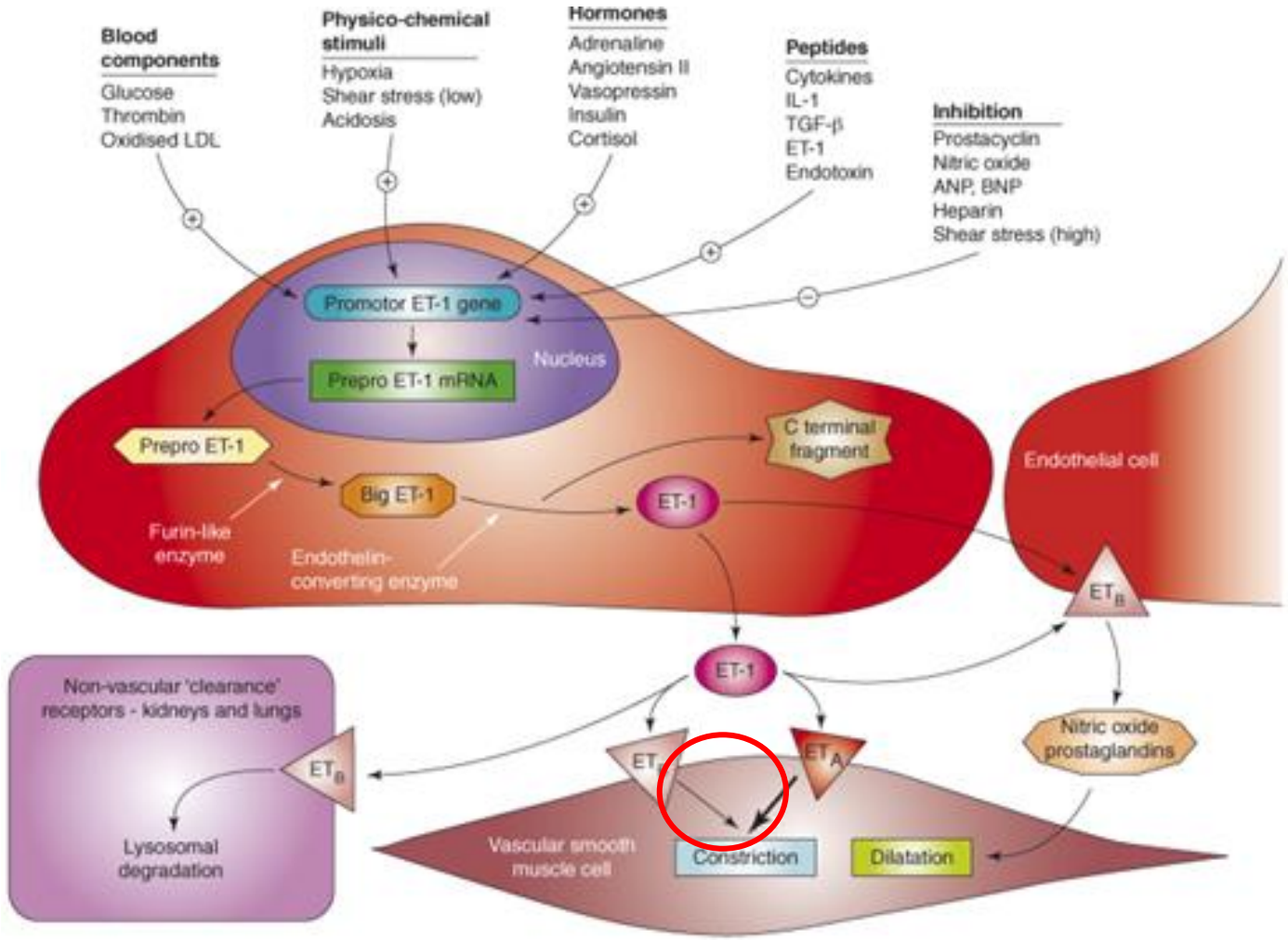
- Target enrollment: ~1000 subjects
  - **Once-daily dosing (1:1)**
  - **50 mcg → titrate as tolerated**
- Primary: **TTCW (adjudicated event)**
  - Death, hospitalization for PAH, parenteral/inhaled PPA or disease progression
- Inclusion/Exclusion:
  - Functional class II – IV
  - 6MWD ≥ 150 meters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



SOURCE: *clinicaltrials.gov*

Macitentan 75 mg
Rationale

- Inadequate blockade of ET_B receptors with 10 mg dose
- P*re*-clinical data: dose-dependent efficacy in terms of hemodynamics and RV hypertrophy in a human equivalent dose of 100 mg/day
- Glioblastoma studies: doses up to 300 mg/day (median 150 mg/day)



Mutsumi K-T. *J Cardiovasc Pharmacol*. 2014; 64(5)
Dhaun N. *TRENDS in Pharmacologic Sciences*. 2007; 28(11)

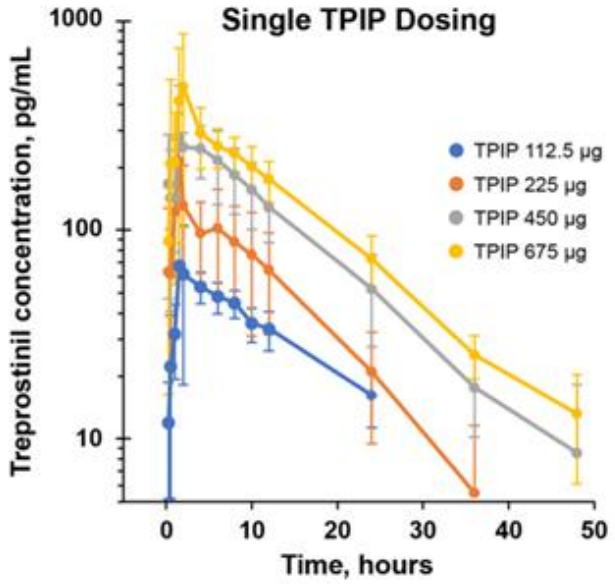
Macitentan 75 mg
UNISUS

- 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)

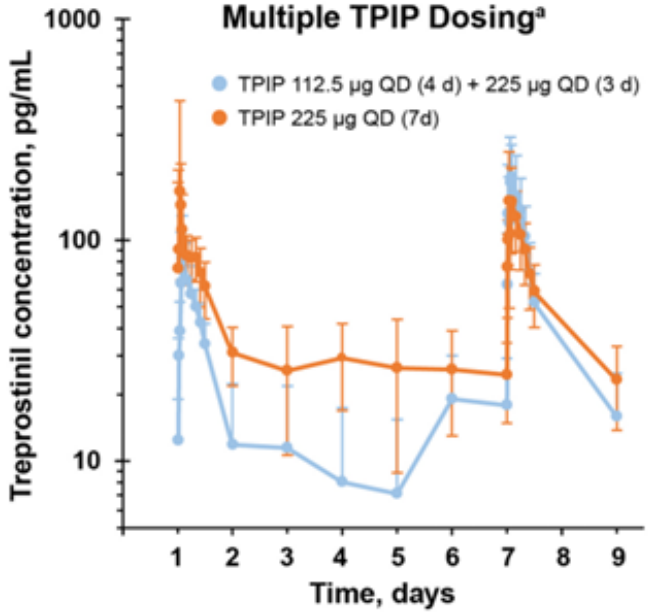
Enrollment completedaccrual of clinical events estimated to Sufficient be Aug 2025

SOURCE: *clinicaltrials.gov*

TPIP – Once daily dosing



PK parameter, mean (CV%)	TPIP single-dose groups			
	112.5 µg (n = 6)	225 µg (n = 6)	450 µg (n = 6)	675 µg (n = 6)
$AUC_{0-\infty}$, pg·h/mL	1090 (19.8)	2130 (30.0)[a]	4040 (27.4)	5480 (11.5)
AUC_{τ}, pg·h/mL	815 (15.0)	1710 (48.6)	3840 (27.5)	5260 (11.7)
C_{max}, pg/mL	78.4 (72.9)	287 (46.6)	387 (38.6)	717 (52.8)
t_{max}, h[b]	3.00 (1.00–4.00)	1.50 (0.32–4.00)	1.78 (0.25–6.15)	2.00 (0.50–4.00)
$t_{1/2}$, h	11.6 (19.4)	8.67 (10.2)[a]	9.36 (22.6)	9.76 (9.99)
CL/F, L/h	106 (18.9)	112 (24.7)[a]	119 (28.5)	124 (10.6)
Vd/F, L	1740 (20.0)	1430 (32.7)	1590 (35.0)	1760 (16.2)



Ismat FA. *Adv Ther*. 2022; 39

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*

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

Key Points

- Complex pathophysiology and vascular dysfunction
- Available therapeutic options target 4 known pathways
- Despite available therapies, many patients have suboptimal outcomes
- Investigational therapies are promising

Risk Assessment & Treatment Monitoring in Patients with PAH

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

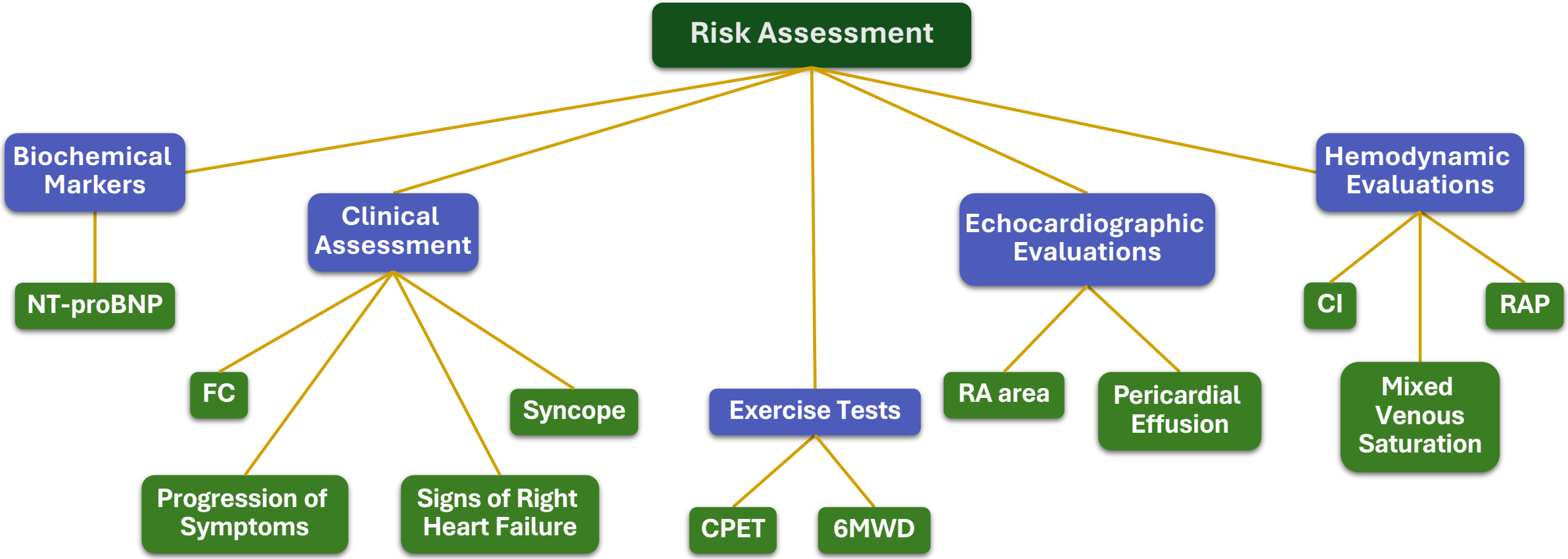
CMHC Cardiometabolic Health Congress

Evolution of Treatment Goals for PAH

- Prior to 2017, no validated risk scores, goal was improving functional Class or hemodynamics
- Of course, as more therapies have become available, evaluating response to therapy to make decisions regarding changes in treatment become more important.
- In 2017, 3 papers published with validated risk scores
- These papers ushered in the era of “treat to low risk”
- Risk scores are prognostic but also include clinically important goals (how a person feels, functions, or survives)

PAH Requires Multi-Parameter Risk Assessment

FEEL, FUNCTION, SURVIVE



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

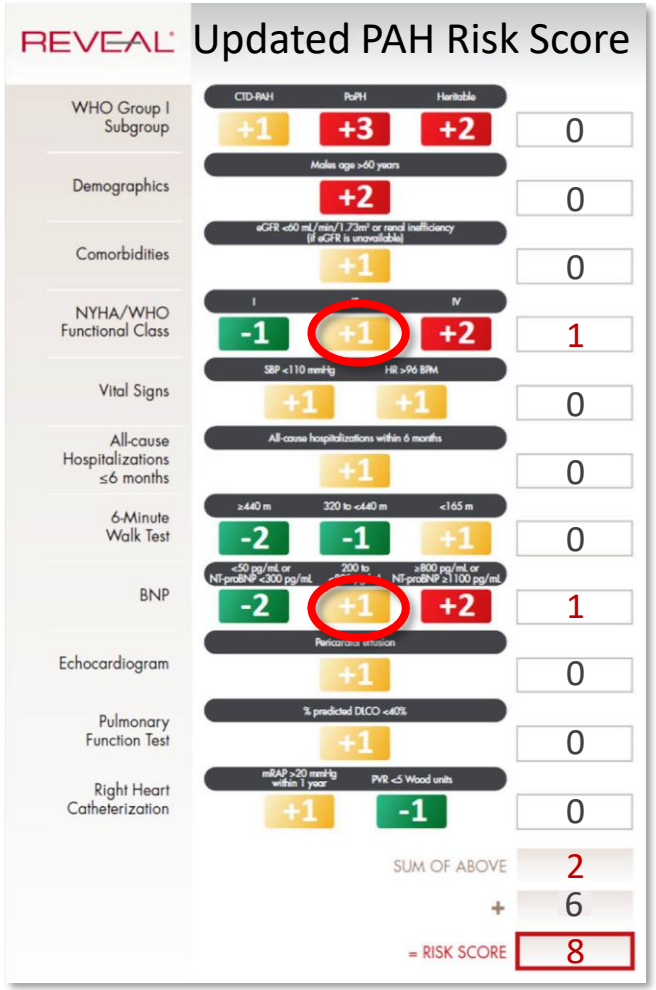
Risk Stratification: Key Component of Assessment

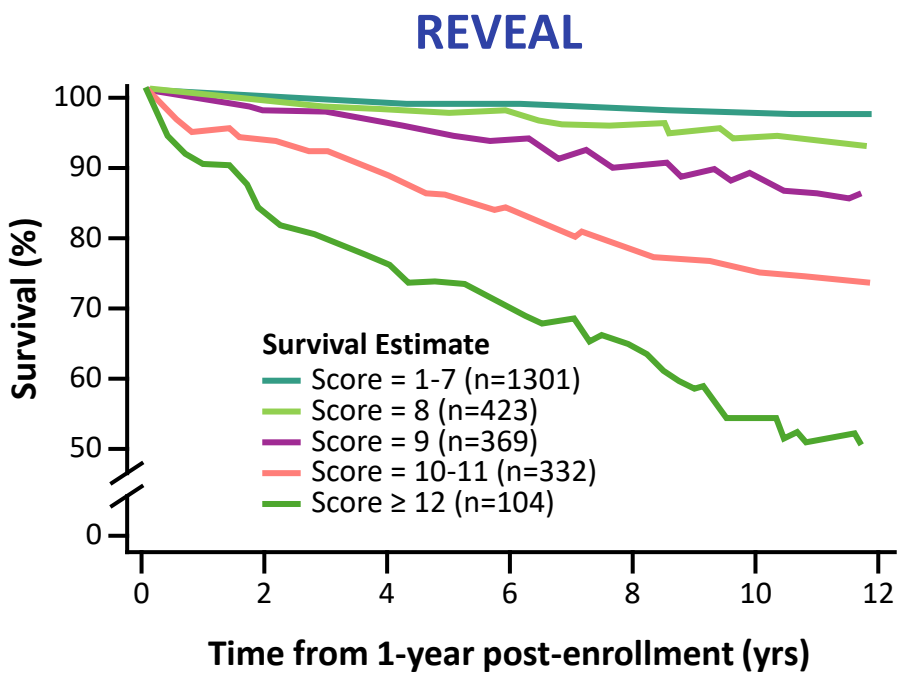
Updates in ERS/ESC Guidelines 2022

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





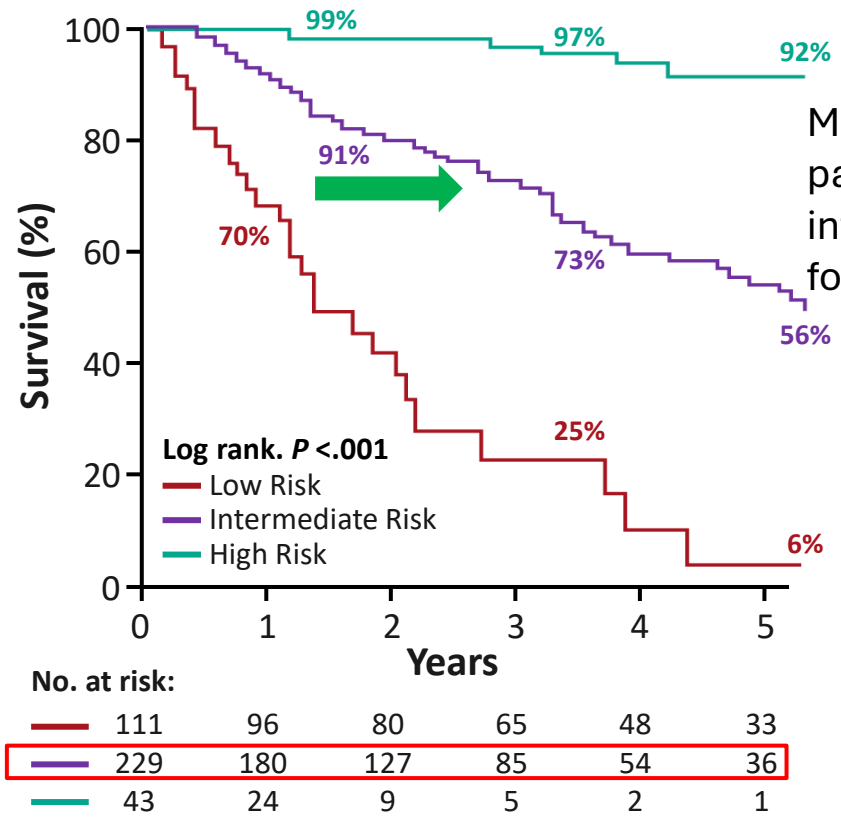
Risk Category	REVEAL 2.0
Low Risk	≤ 6 points
Intermediate Risk	7 – 8 points
High Risk	≥ 9 points

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

Risk Assessment at Follow-up Is Crucial to Evaluate Response to Therapy

Importance of assessing risk at follow up

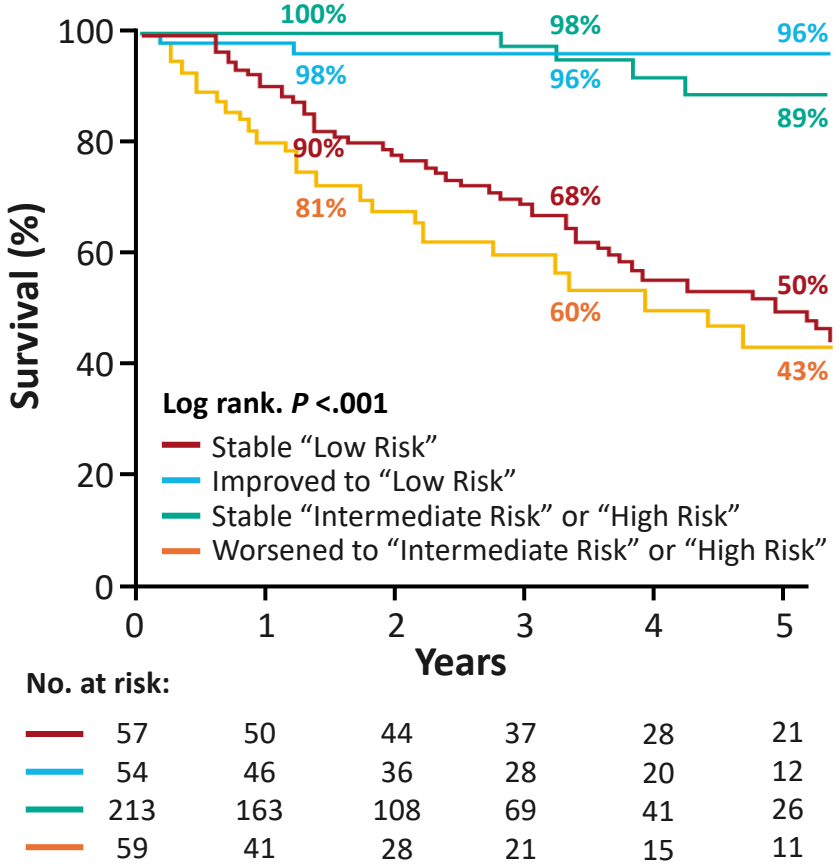
Swedish PAH Registry



More than ½ of patients are intermediate risk at follow up

Importance of achieving of low-risk status

Swedish PAH Registry



Galiè N. N Engl J Med. 2015 Aug 27;373(9):834-844; Akagi S et al. Acta Med. 2015;69(3):129-36.

Risk Stratification at Follow-Up: Improving Predicted Outcome

4-strata risk-assessment tool

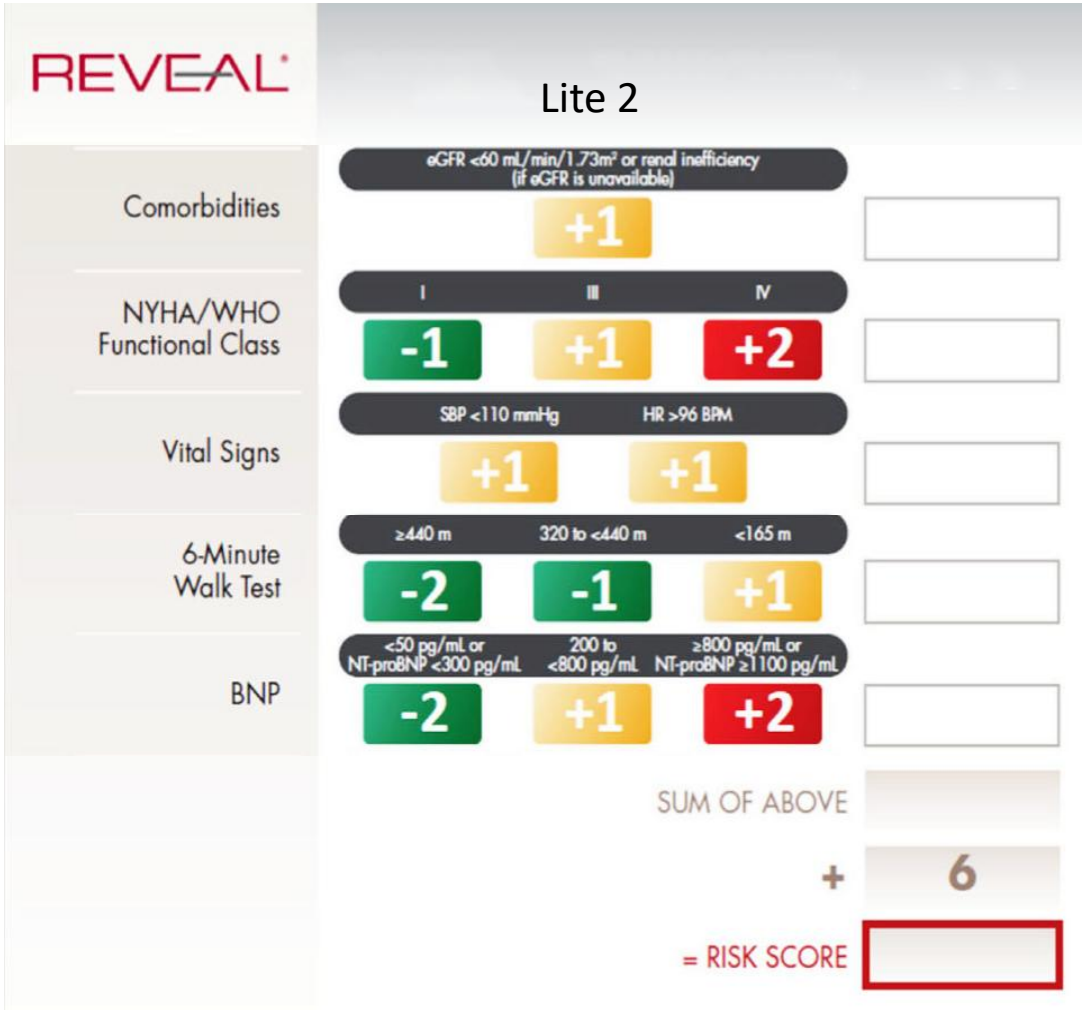
Determinants of prognosis	Low risk	Intermediate-low risk	Intermediate-high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP, ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

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)

Risk Stratification at Follow-Up

REVEAL Lite 2



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

Do Follow-Up Hemodynamics Improve Risk Based Outcome Predictions?

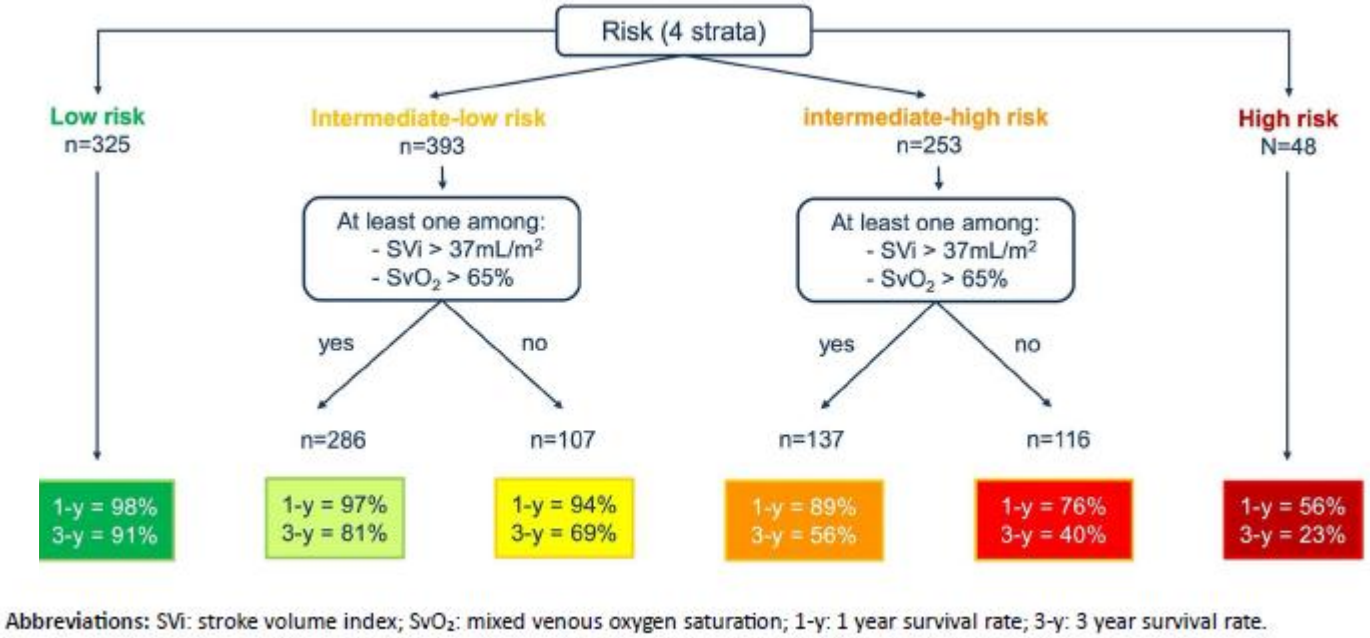
EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Risk stratification refinements with inclusion of haemodynamic variables at follow-up in patients with pulmonary arterial hypertension

Athénaïs Boucly, Antoine Beurnier, Ségolène Turquier, Mitja Jevnikar, Pascal de Groote, Ari Chaouat, Céline Cheron, Xavier Jaïs, François Picard, Grégoire Prévot, Anne Roche, Sabina Solinas, Vincent Cottin, Fabrice Bauer, David Montani, Marc Humbert, Laurent Savale, Olivier Sitbon

(https://doi.org/10.1183/13993003.00197-2024).

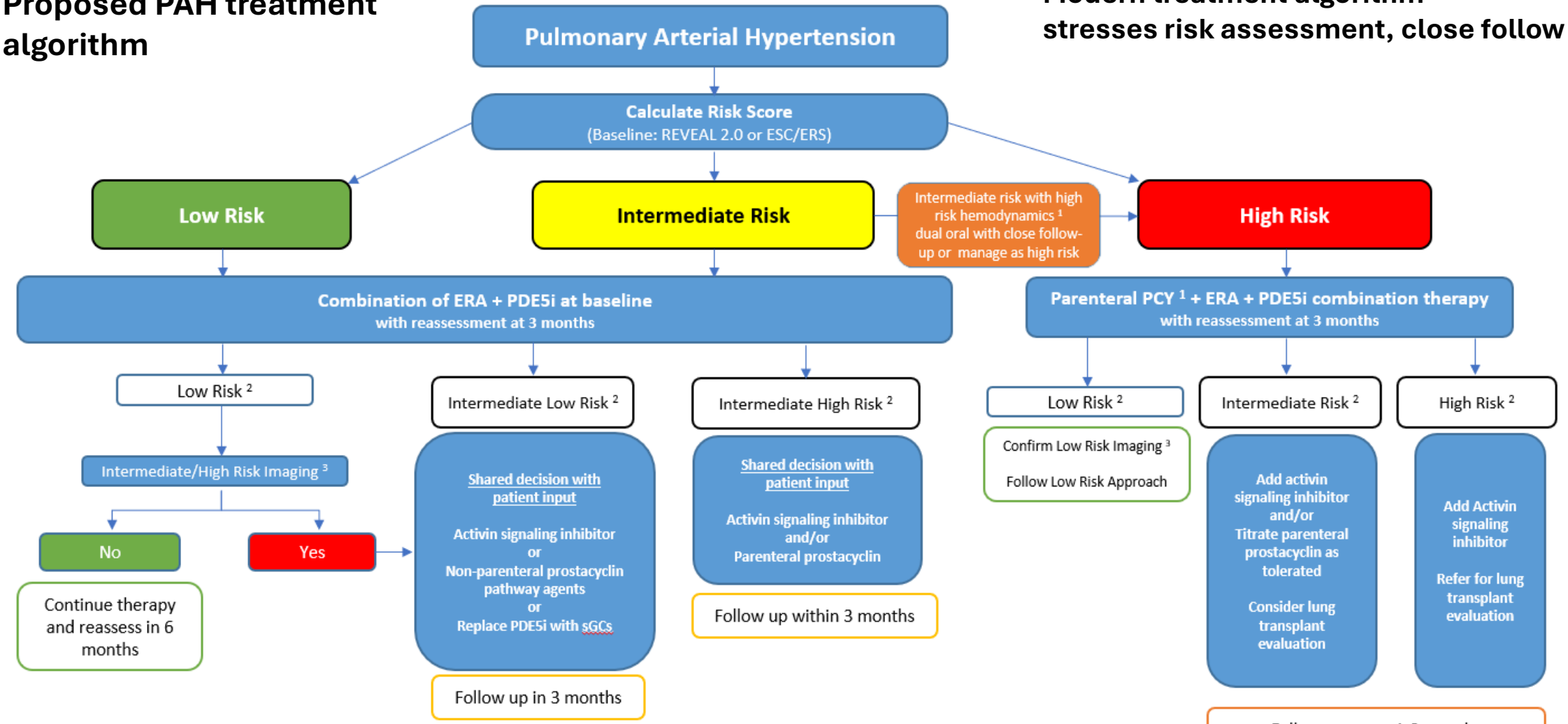


Abbreviations: SVi: stroke volume index; SvO_2: mixed venous oxygen saturation; 1-y: 1 year survival rate; 3-y: 3 year survival rate.

Stroke Volume Index (CI/HR) > 37 ml/m² or SvO_2 >65% at first follow-up RHC predicted better survival in both low- and high-intermediate risk patients

Proposed PAH treatment algorithm

Modern treatment algorithm stresses risk assessment, close follow up



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

Teaching Points

- Risk stratification has emerged as a vital tool in assessing PAH patients both at baseline and on treatment. It should be done in every patient!
- Risk category is a predictor of mortality
- Risk assessment also quantifies clinically relevant goals of therapy
- Current treatment algorithms are based on risk assessment to guide therapy

Patient Cases & Expert Discussion

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

Case 1: Matt

- 60 yo man, with a history of diffuse cutaneous system sclerosis
- Presented in February of 2019
  - Hospitalized locally in December of 2018 with dyspnea, echo and RHC consistent with PAH, referred to rheumatology and PH program
  - Functional class late 3 at time of clinic visit, also limitations due to musculoskeletal weakness
  - Denied chest pain, light headedness, syncope, PND, orthopnea, LE edema
- Medications-fluoxetine 20 mg, simvastatin 40 mg, fluticasone-vilanteral disk inhaler
- No FH of PH, scleroderma, thromboembolic disease
- Former smoker, d/c 2014, no alcohol or drugs

Matt: Initial Evaluation

- EKG: normal sinus rhythm, right axis deviation, NSSTTW abnormality
- Echo: RAE, severe RV enlargement and dysfunction, EF 55%, RVPO, severe TR, estimated PASP 50-55 mmHg PFTs: FVC 77%. FEV1 87%,FEV1/FVC 88%, TLC 95%, DLCO 24%
- V/Q scan: low probability
- PE: CT no PE
- HRCT: Bibasilar reticulation/septal thickening c/w fibrosis, dilated patulous esophagus
- HIV: nonreactive
- 6MWD: 120 m, 99-95% nadir on room air
- BNP: 860 ng/L

Matt: Right Heart Catheterization, December 2018 (OSH)

- RA: 22 mmHg
- PA: 66/23/40 mmHg
- PCWP: 13 mmHg
- iFick CO: 3.23 L/min
- iFick CI: 1.40 L/min/m^2
- PVR: 8.3 WU
- PA saturation: 47%

Matt: Initial Management

- Discussed therapy options
  - Reviewed severity of disease and discussed parenteral prostacyclins in detail
  - Had concerns about the use of parenteral therapy give joint contractures
- Chose oral dual combination therapy with close follow up

Matt: Follow-up, August 2019

- Improved dyspnea but still FC 3
- PAH Meds: macitentan 10 mg, tadalafil 40 mg
- 6MWD: 137 m, nadir saturation 94%
- BNP: 347 ng/L
- Echo: Severe RVE, moderate RV dysfunction, moderate TR, RVSP 82+15 mmHg
- Discussed escalation to a parenteral prostacyclin and patient declined.
- Recommend inhaled treprostinil

Matt: Follow-up, November 2019

- Improved dyspnea but still FC 3
- PAH Meds: macitentan 10 mg, tadalafil 40 mg, inhaled Treprostinil at 9 breaths qid
- 6MWD: 141 m, nadir saturation 92%
- BNP: 422 ng/L
- Still declines parenteral prostacyclin
- Recommend increasing inhaled Treprostinil dose, diuretics also increased
- Inhaled Treprostinil dose increased to 12 breaths qid
- Misses a number of visits related to the COVID pandemic
- Has a VV in January of 2020 and agrees to repeat RHC

Matt: Right Heart Catheterization, February 2021

- RA: 4 mmHg
- PA: 82/29/47 mmHg
- PCWP: 5 mmHg
- TD CO: 5.23 L/min
- TD CI: 2.47 L/min/m^2
- PVR: 8.0 WU
- PA saturation: 60%
- Patient agrees to transition from inhaled to SQ treprostinil

Matt: Follow-up, Further course

- Improved dyspnea but still FC 3
- PAH Meds: SQ Treprostinil, titrated to maximal tolerated dose of 55 ng/kg/min, macitentan 10 mg, tadalafil 40 mg
- Highest 6MWD: 213 m, nadir saturation 92%
- Lowest BNP: 105 ng/L
- Echo: Severe RVE, moderate RV dysfunction, moderate TR, RVSP 78+5 mmHg
- Seen by transplant, deemed not a good candidate related to insurance and compliance issues (would not have necessary dental work), and severe esophageal disease
- Discussed potential risks and benefits of sotatercept, repeated RHC

Matt: Hemodynamics

Date	December 2018	February 2021	July 2024
RAP, mmHg	22	4	10
PAP, mmHg	66/23/40	82/29/47	85/31/49
PCWP, mmHg	13	5	11
CO, L/min	3.23	5.23	5.33
CI, L/min/m^2	1.4	2.47	2.70
PVR, Woods Units	8.3	8.0	7.1

Matt-Sotatercept discussion

- Reviewed hemodynamics and further treatment options
  - Could not tolerate higher doses of Treprostinil due to GI side effects
  - Not a lung transplant candidate
- Discussed potential risks of sotatercept
  - Patient has not h/o GI bleeding
  - Normal Hb and Plt
- Sotatercept started on August 5, 2024

Matt: Hemodynamics

Date	December 2018	February 2021 Maci, tad, inh tre	July 2024 Maci, tad, SQ trep	March 2025 Maci, tad, SQ trep, sota
RAP, mmHg	22	4	10	5
PAP, mmHg	66/23/40	82/29/47	85/31/49	71/24/40
PCWP, mmHg	13	5	11	10
CO, L/min	3.23	5.23	5.33	5.13
CI, L/min/m^2	1.4	2.47	2.70	2.52
PVR, Woods Units	8.3	8.0	7.1	5.8

Case 2: Jenna

- 32 yo woman, without significant past medical history
- Presented in September of 2023 with a 6 month history of exertional dyspnea, FC 3
- No medications, no known drug allergies
- No FH of PH, scleroderma, thromboembolic disease
- Non-smoker, social drinker
- Diagnostic work up-nl PFT's, neg VQ, neg ANA
- 6MWD: 490 m, HR 97 to 137, 95% nadir on room air
- BNP: 366 ng/L

Jenna: Right Heart Catheterization, October 2023

- RA: 6 mmHg
- PA: 100/45/65 mmHg
- PCWP: 10 mmHg
- TD CO: 3.40 L/min
- TD CI: 2.06 L/min/m^2
- PVR: 16.2 WU
- PA saturation: 63%
- Nitric oxide at 40 ppm: mPAP was unchanged at 63 mmHg

Jenna: Initial Management

- Discussed therapy options
  - Reviewed severity of disease and discussed parenteral prostacyclins in detail
- Chose oral combination therapy with close follow up
- Video visit at 4 weeks, tolerating therapies well, dyspnea improving

Jenna: Follow-up at 4 Months

- Improved dyspnea, FC 2
- Meds: macitentan 10 mg, tadalafil 40 mg
- 6MWD: 571 m, nadir saturation 99%
- BNP: 20 ng/L
- Echo: mild RV enlargement, mild RV dysfunction, min TR, UTE RVSP, RVPO
- Low risk by 4 strata

Jenna: Right Heart Catheterization, March 2024

- RA: 6 mmHg
- PA: 85/35/52 mmHg
- PCWP: 8 mmHg
- TD CO: 5.50 L/min
- TD CI: 3.33 L/min/m^2
- PVR: 8 WU
- PA saturation: 74%

Jenna: Subsequent Management

- Reviewed RHC results
  - While meeting low risk criteria, she still had elevated mPAP and PVR
  - Given young age we discussed the risks and benefits of therapy escalation with sotatercept
- Sotatercept started in June of 2024

Jenna: Follow-up September 2024

- Improved dyspnea, FC 1
- Meds: macitentan 10 mg, tadalafil 40 mg, sotatercept
- 6MWD: 689 m, nadir saturation 98%
- BNP: 6 ng/L
- Echo: mild RV enlargement, normal RV function, min TR, UTE RVSP
- Low risk by 4 strata

Jenna: Right Heart Catheterization, December 2024

- RA: 5 mmHg
- PA: 46/25/32 mmHg
- PCWP: 9 mmHg
- TD CO: 5.70 L/min
- TD CI: 3.45 L/min/m^2
- PVR: 4.0 WU
- PA saturation: 74%

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Closing Remarks/Final Thoughts