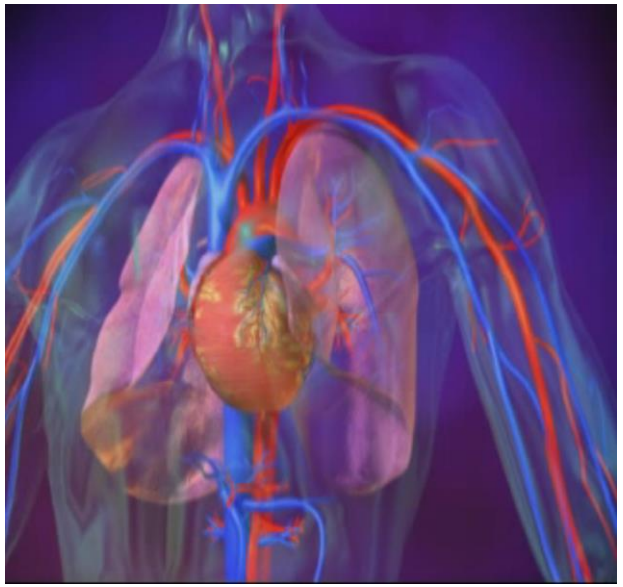
2023 Updates in Pulmonary Hypertension Management



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Potential Conflicts of Interest

- Consultant/Advisory Panel (J&J Actelion, Acceleron, United Therapeutics
- Speaker (J&J Actelion, Bayer, United Therapeutics)
- Research Funding (Respira, Bellerophon, Acceleron)

Sobering Initial Comments

- Although updates to the field exist and will be discussed, the biggest challenges to patients and management have remained largely unchanged for >25 years.
- Failure of timely appropriate diagnosis.
  - The diagnosis of PAH is typically missed and delayed until late stages. Approximately 74-88.5% of patients present at FC III-IV.[1-4] Statistical survival at these late stages are poor even in the era of modern therapeutics.[4]
- Misdiagnosis
  - Significant numbers of patients referred to PAH centers, even those placed on PAH specific medications are mis-diagnosed.[5]
- Undertreatment
  - Patients treated initially in non-PAH specialty centers and then referred have poorer survivals compared to patients treated throughout their course at such centers.[6]

[1]Farber HW, et al. *Chest.* 2015;148:1043-54; 137:367-87
[2]Humbert M, et al. *Am J Respir Cir Care Med.* 2006;179:1023-30
[3]Kyellstrem B, et al. Swedish Pulmonary Arterial Hypertension Registry Annual Report 2019
[4]Hoeper M, et al. *Eur Respir J.* 2017; 50: 1700740.
[5]Deaño RC, et al. JAMA Intern Med. 2013;173(10):887-893.
[6]Badagliacca ,et al. J Heart Lung Transplant. 2012;31:364-37.2

Objectives: Identify key elements of PAH diagnosis which are changing

- Diagnosis
  - Definition and separation of physiologies associated with PH
  - Focus on accelerated workup and risk based on RV findings at initial echo
- Revision of goals of therapy and time frames for therapeutic decision making*
  - 3 strata model of risk assessment
  - 4 strata model of risk assessment
- Trends in experimental therapies – what is on the horizon?
  - Sotatercept
  - Other molecular targets
  - Prn rescue vardenafil

ESC European Society of Cardiology

European Heart Journal (2022) **00**, 1–114
https://doi.org/10.1093/eurheartj/ehac237

ESC/ERS GUIDELINES

2022 ESC/ERS Guidelines for the diagnosis and 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).

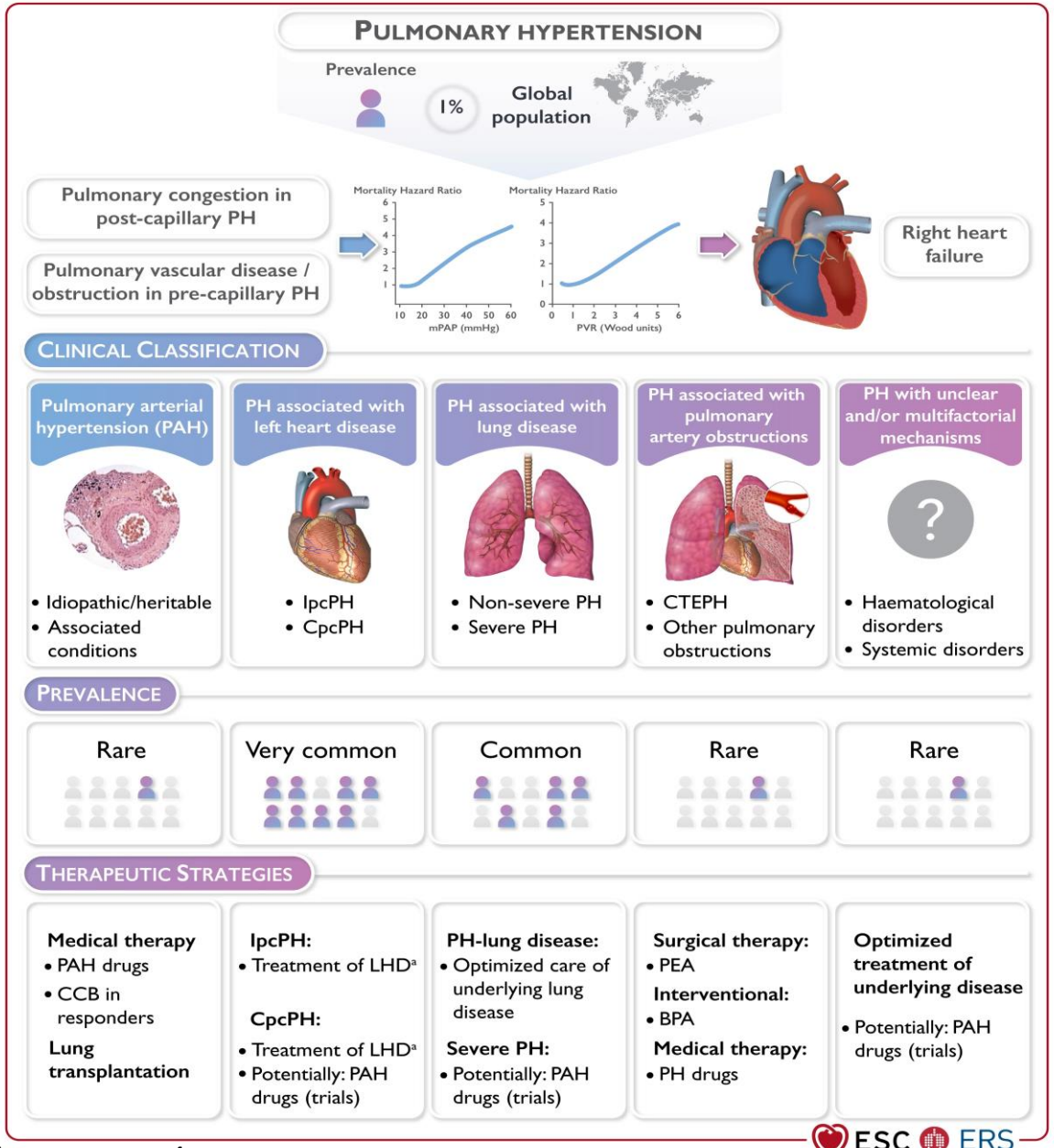
Definition

Hemodynamic and Physiologic Classifications of PH

Definition	Hemodynamic characteristics	
PH	mPAP >20 mmHg	Previous mPAP >25 mm Hg
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR >2 WU	
IpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR ⩽2 WU	
CpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU	
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min	

European Heart Journal, ehac237, https://doi.org/10.1093/eurheartj/ehac237 26 August 2022

- Classification System for PH
  - I - Pulmonary Arterial Hypertension
  - II - PH Associated with Left Heart Disease
  - III - PH Associated with Lung Disease
  - IV- PH Associated with Pulmonary Artery Occlusions
  - V - PH with Unclear and/or Multifactorial Mechanisms



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PAH Classification (Expanded)

- 1.1 Idiopathic
  - 1.1.1 Non-responders at vasoreactivity testing
  - 1.1.2 Acute responders at vasoreactivity testing
- 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

Adapted from:European Heart Journal, ehac237, https://doi.org/10.1093/eurheartj/ehac237 26 August 2022

Diagnosis

When to Suspect PAH/CTEPH/PH-ILD?
Unexplained chronic dyspnea + one or more of the following:

- Presence of a systemic disorder or drug exposure known to be associated with PAH
- Review of systems/Exam/Testing Consistent
  - Physical exam findings consistent with PH
  - Study findings consistent with PH
- Presence of interstitial lung disease
- History of pulmonary embolism (PE) or risk for PE

- Focus of a primary PH workup
  - The primary goal is to raise early suspicion of PH and ensure fast-track referral to PH centers in patients with a high likelihood of PAH, CTEPH, or other forms of severe PH.
  - The second objective is to identify underlying diseases, especially LHD (group 2 PH) and lung disease (group 3 PH), as well as comorbidities, to ensure proper classification, risk assessment, and treatment.

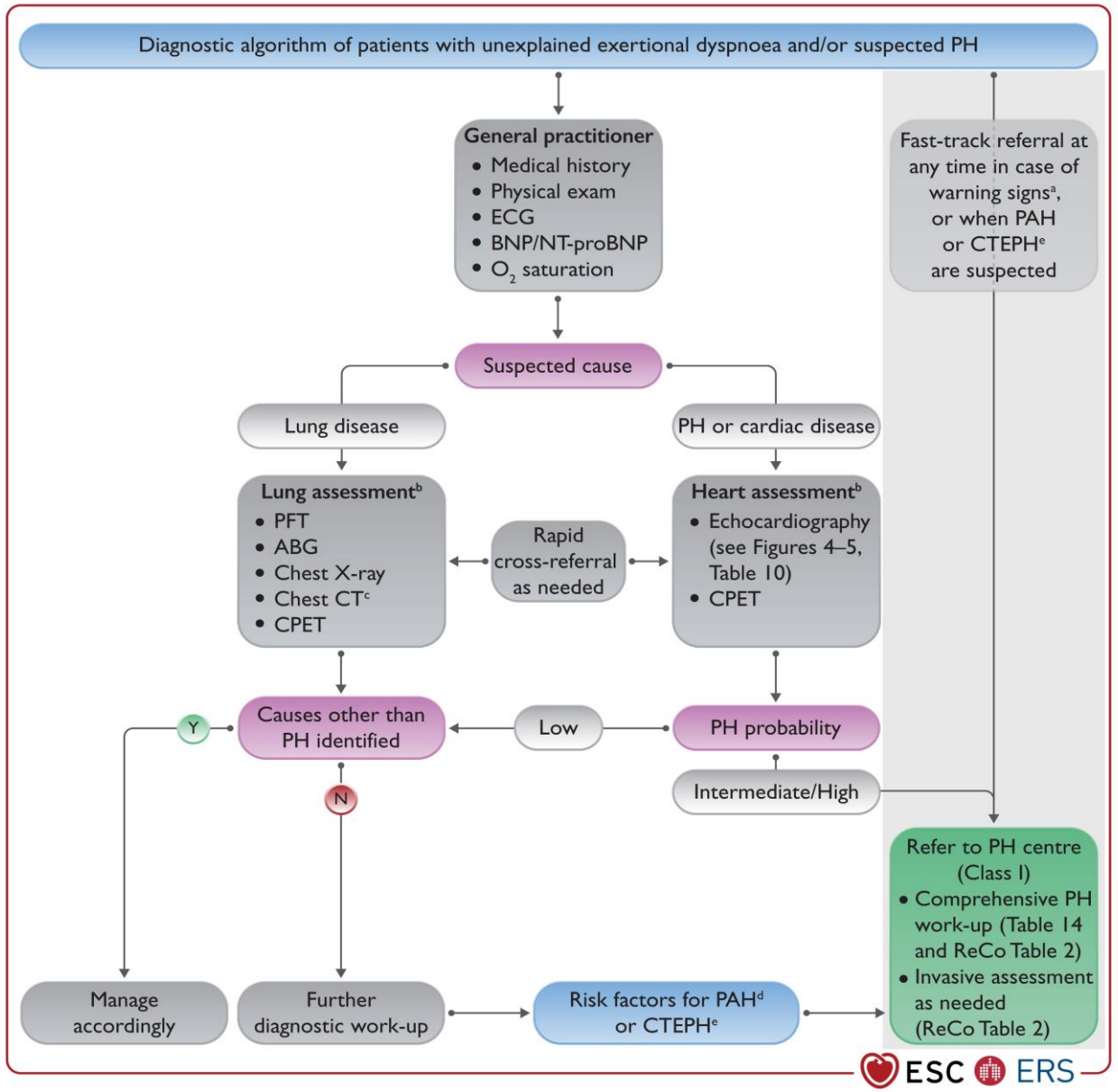

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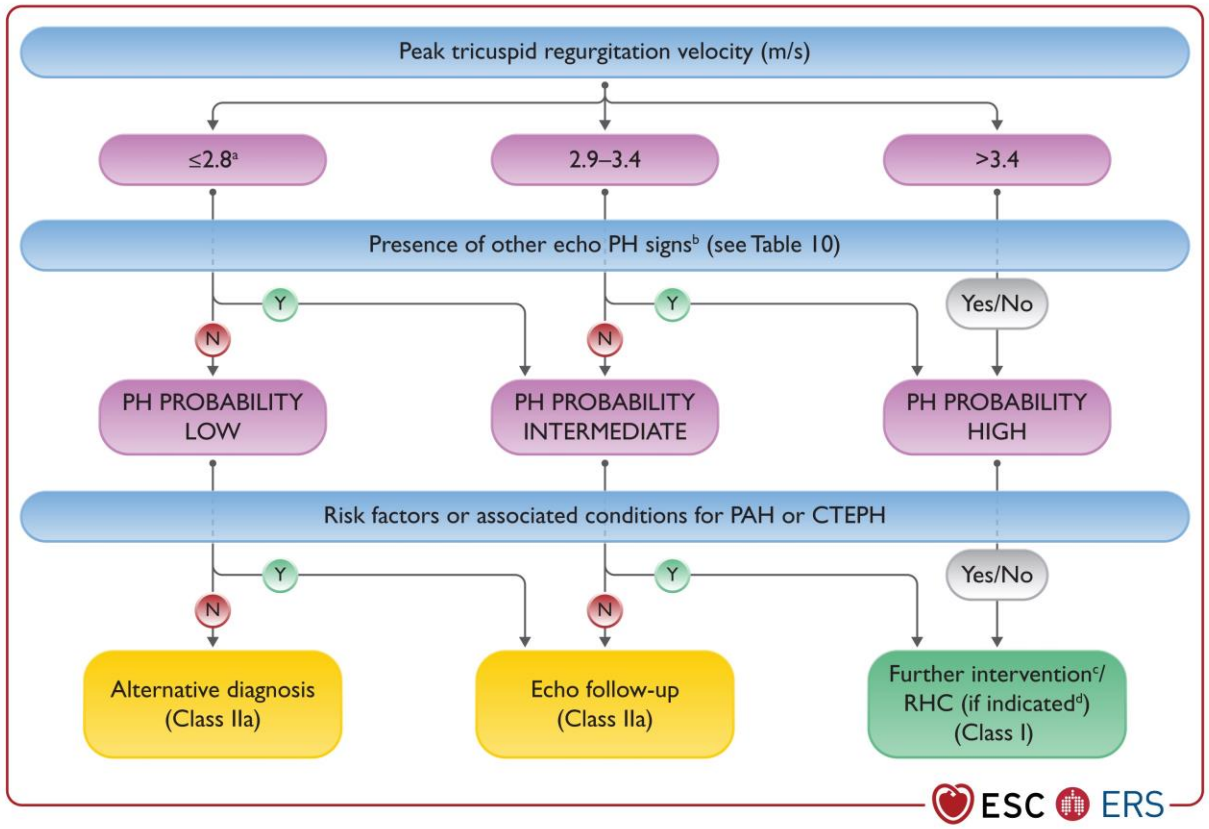
Figure 5 Echocardiographic probability of pulmonary hypertension and recommendations for further assessment.
CPET, ...



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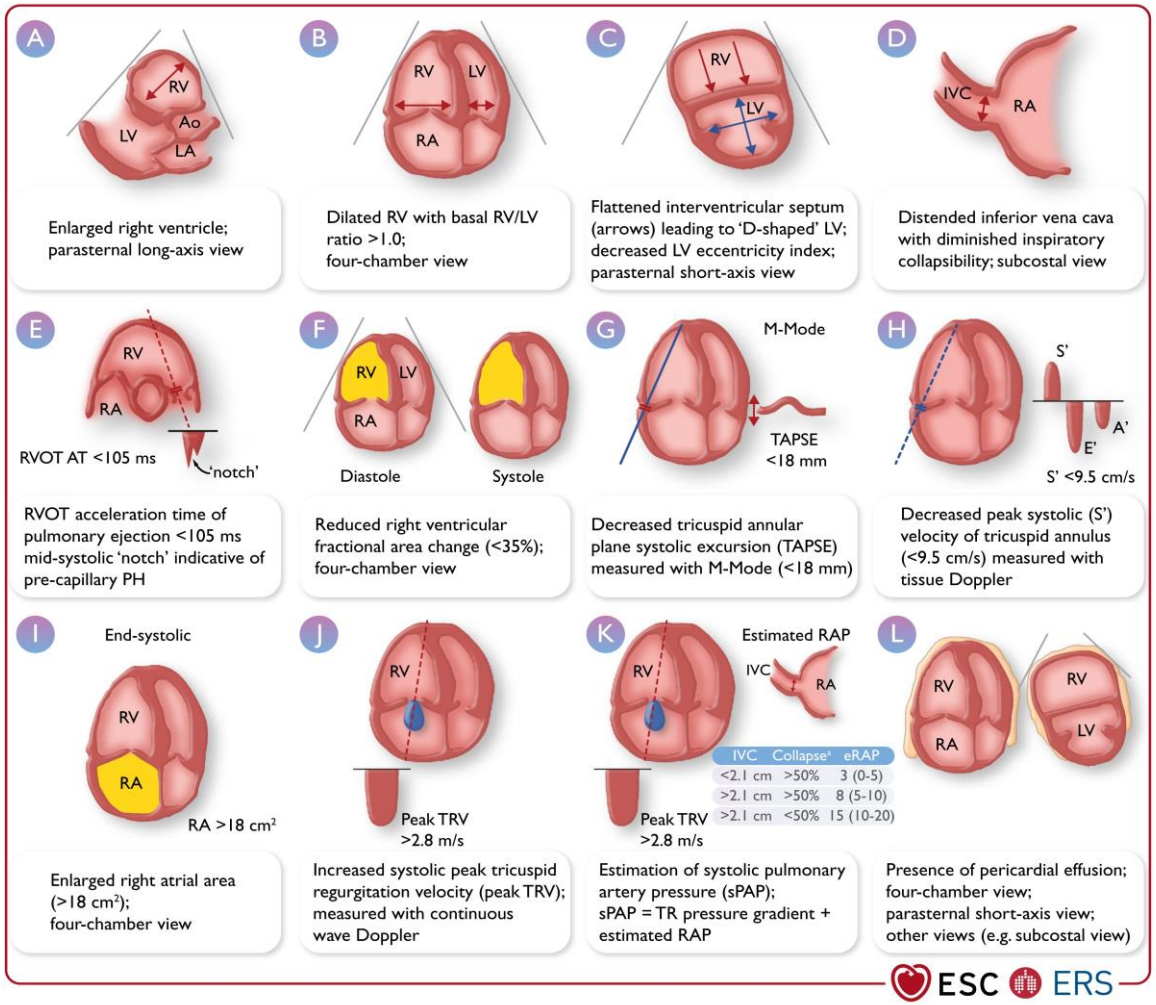
Transthoracic echocardiographic parameters associated with pulmonary hypertension.



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Risk Stratification and Implications on Escalation of Therapy

STABILITY IS NO LONGER AN ACCEPTABLE GOAL OF THERAPY

INTERMEDIATE RISK STATUS IS NO LONGER AN ACCEPTABLE GOAL OF THERAPY

ACHIEVMENT OF LOW RISK STATUS IS CURRENTLY PROPOSED RECOMMENDATION OF GOAL OF THERAPY

3 STRATA RISK ASSESSMENT

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%

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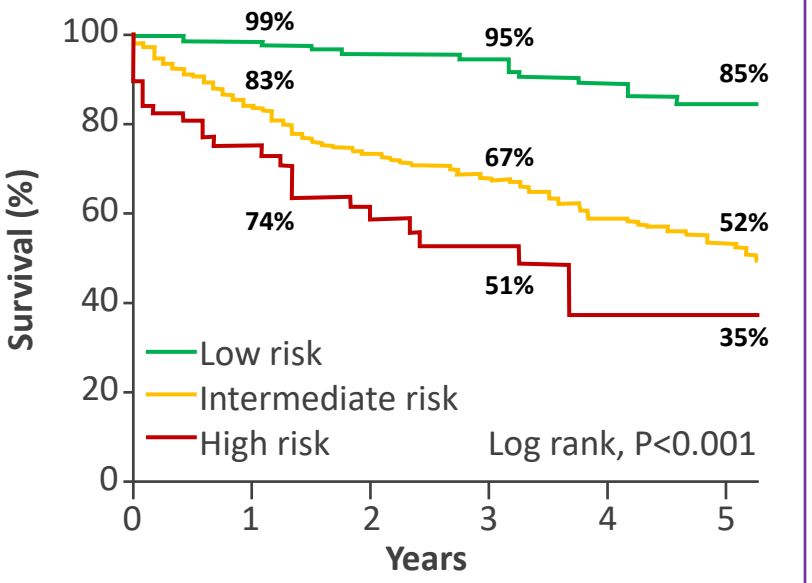
Importance of Risk Assessment at Baseline

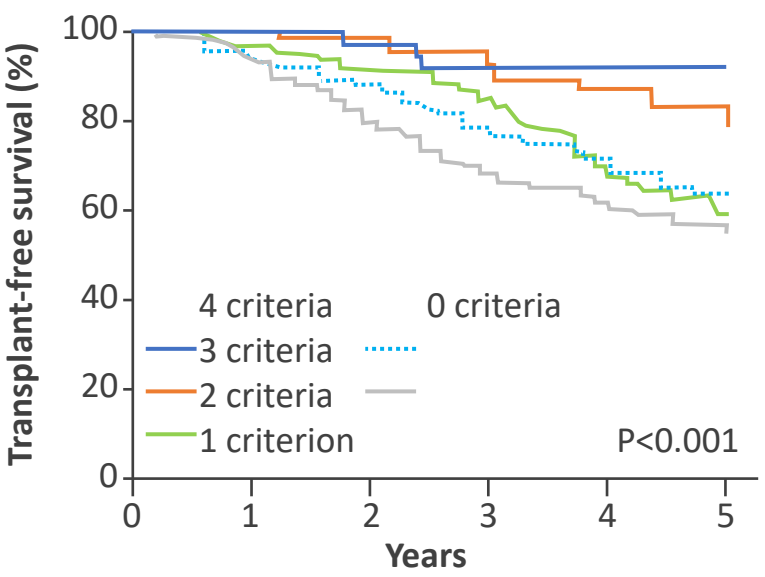
Swedish PAH Register[1]



No. at risk:

Low risk	120	100	86	73	58	42
Intermediate risk	355	246	176	124	80	51
High risk	55	35	22	13	5	4

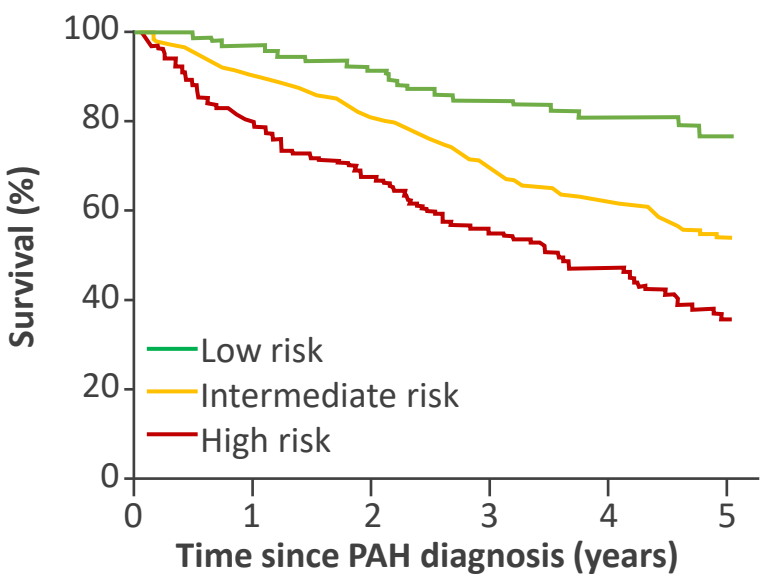
French Pulmonary Hypertension Registry[2]



No. at risk:

4 criteria	59	52	46	35	26	20
3 criteria	112	94	74	59	36	26
2 criteria	217	173	149	104	63	45
1 criterion	371	302	233	176	128	89
0 criteria	258	212	158	117	76	53

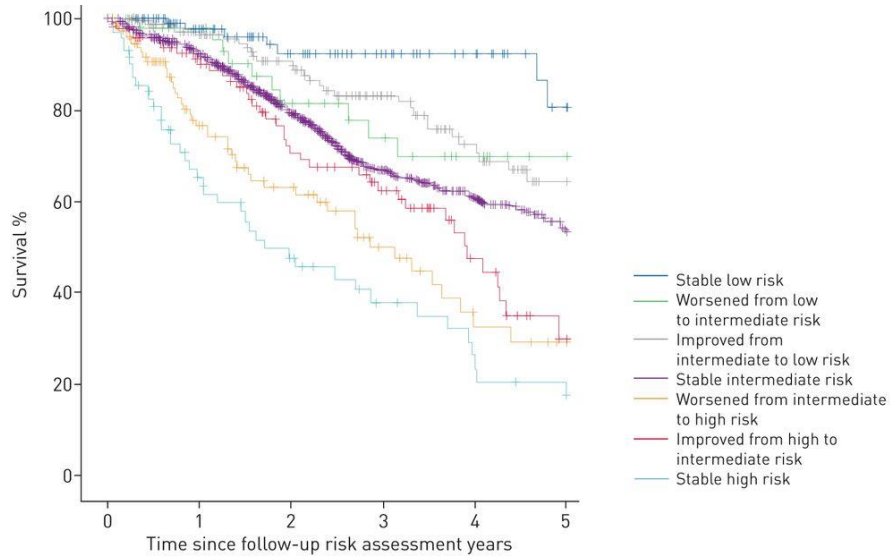
COMPERA[3]



Years after enrollment	Survival (%)			Cases left (n)		
	Low risk	Intermediate risk	High risk	Low risk	Intermediate risk	High risk
0	100	100	100	196	1116	276
1	97.2	90.1	78.8	156	764	170
2	91.5	80.3	66.0	111	540	117
3	84.2	68.1	53.2	75	376	77
4	80.2	60.1	44.7	47	252	47
5	75.9	51.9	32.4	31	149	24

1. Kylhammar D et al. *Eur Heart J.* 2017 Jun 1. doi: 10.1093/eurheartj/ehx257. [Epub ahead of print] 2. Boucly A et al. *Eur Respir J.* 2017;50(2).
3. Hoeper MM et al. *Eur Respir J.* 2017;50(2).

Analysis showing survival according to change in risk category from baseline to follow-up within 3 months and 2 years in patients with pulmonary arterial hypertension.



	Survival %						
Years after enrolment	Stable low risk	Worsened from low to intermediate risk	Improved from intermediate to low risk	Stable intermediate risk	Worsened from intermediate to high risk	Improved from high to intermediate risk	Stable high risk
0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
1	97.4	97.8	96.3	91.6	76.5	89.9	65.3
2	92.2	81.4	90.7	79.1	63.1	70.4	47.7
3	92.2	73.8	83.1	67.0	49.9	62.3	38.2
4	92.2	69.7	72.4	60.5	32.6	47.5	23.5
5	80.6	69.7	64.4	53.3	29.3	30.0	17.1

	Patients at risk n						
Years after enrolment	Stable low risk	Worsened from low to intermediate risk	Improved from intermediate to low risk	Stable intermediate risk	Worsened from intermediate to high risk	Improved from high to intermediate risk	Stable high risk
0	93	49	152	504	110	95	70
1	71	39	118	391	63	74	35
2	46	26	88	282	42	47	23
3	31	19	62	181	21	34	14
4	22	12	40	117	10	16	8
5	13	7	21	68	6	4	5

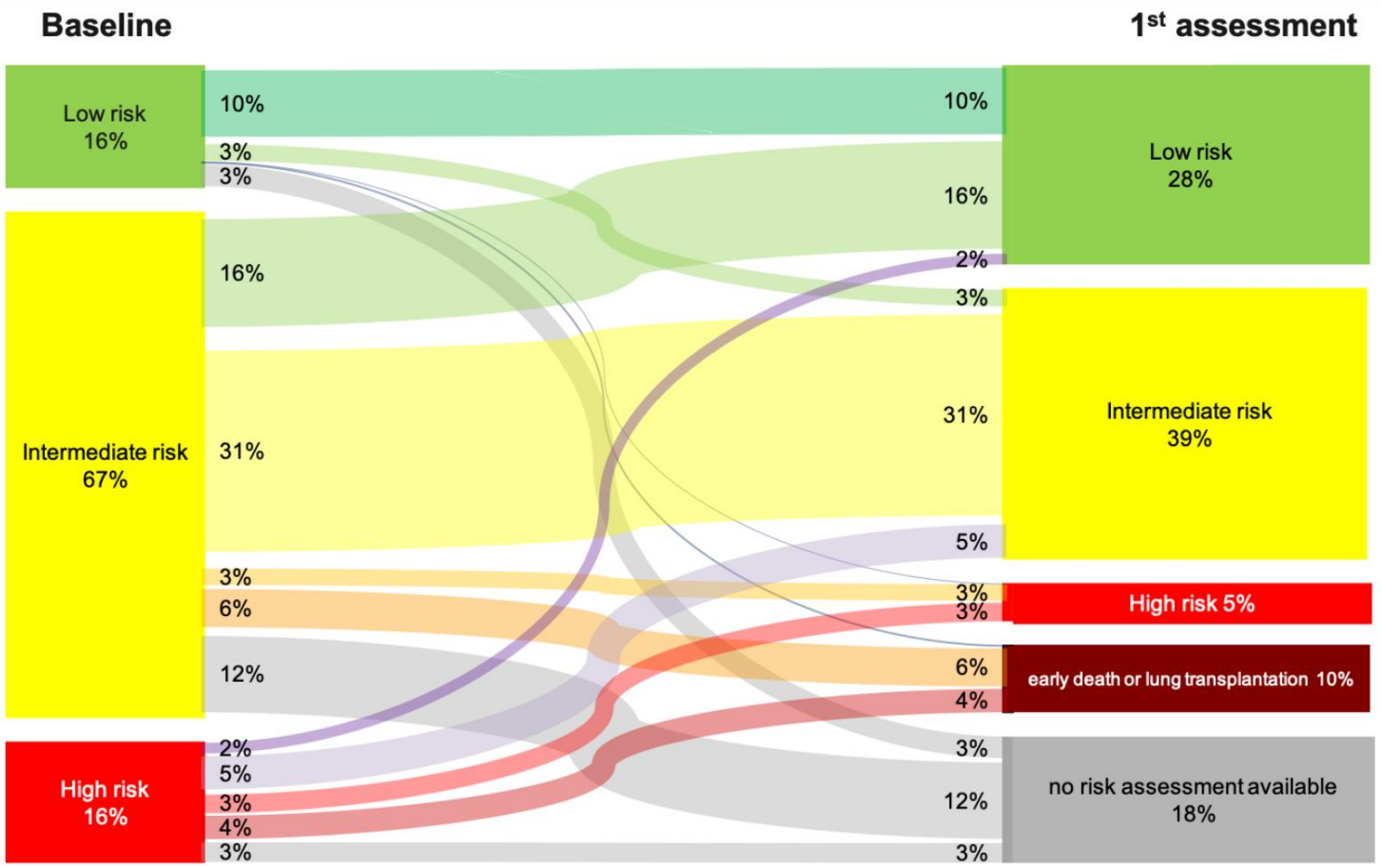
Marius M. Hoeper et al. Eur Respir J 2017;50:1700740

Initial Observations with Risk Assessment

- The vast majority of patients present as intermediate risk (67%)
- Only low risk patients demonstrated satisfactory survivals
- Failure to achieve low risk criteria incrementally added to death
- There was a large variability in survivals among patients with intermediate risk with time and trajectory: Low->Intermediate > Stable intermediate > High->Intermediate
- Few patients “moved” to low risk.
- Gestalt suggested that when analyzing intermediate patients that intrinsically, they likely looked more like high risk or more like low risk and this this may be a more logic stratification schema.

Four Strata Risk Assessment

Limited ability for French PAH Registry patients to "move" to a more favorable risk strata using usual standards of care. (Sankey diagram)



Boucly et al. Eur Respir J 2022 Jun 30;59(6):2102419.

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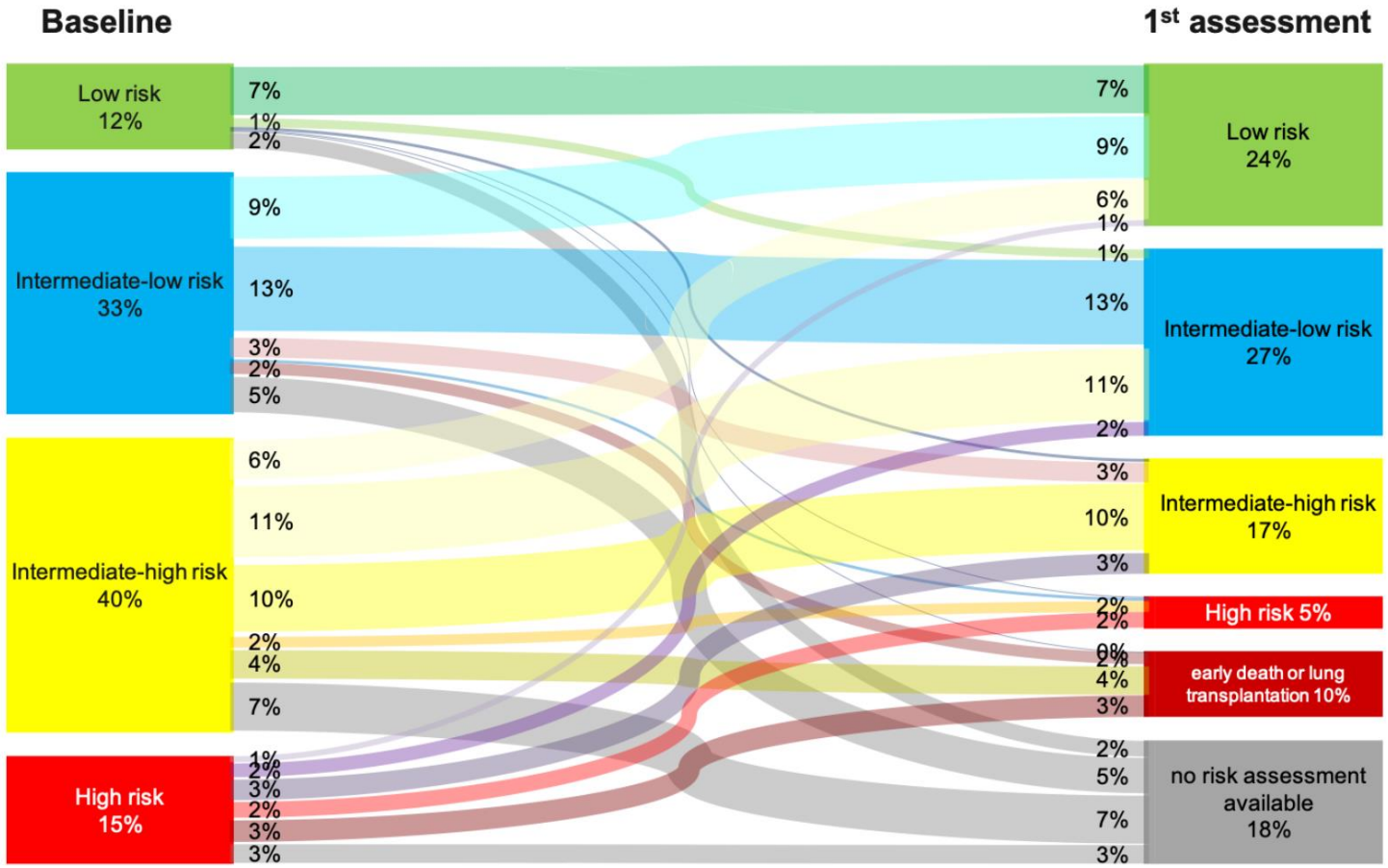


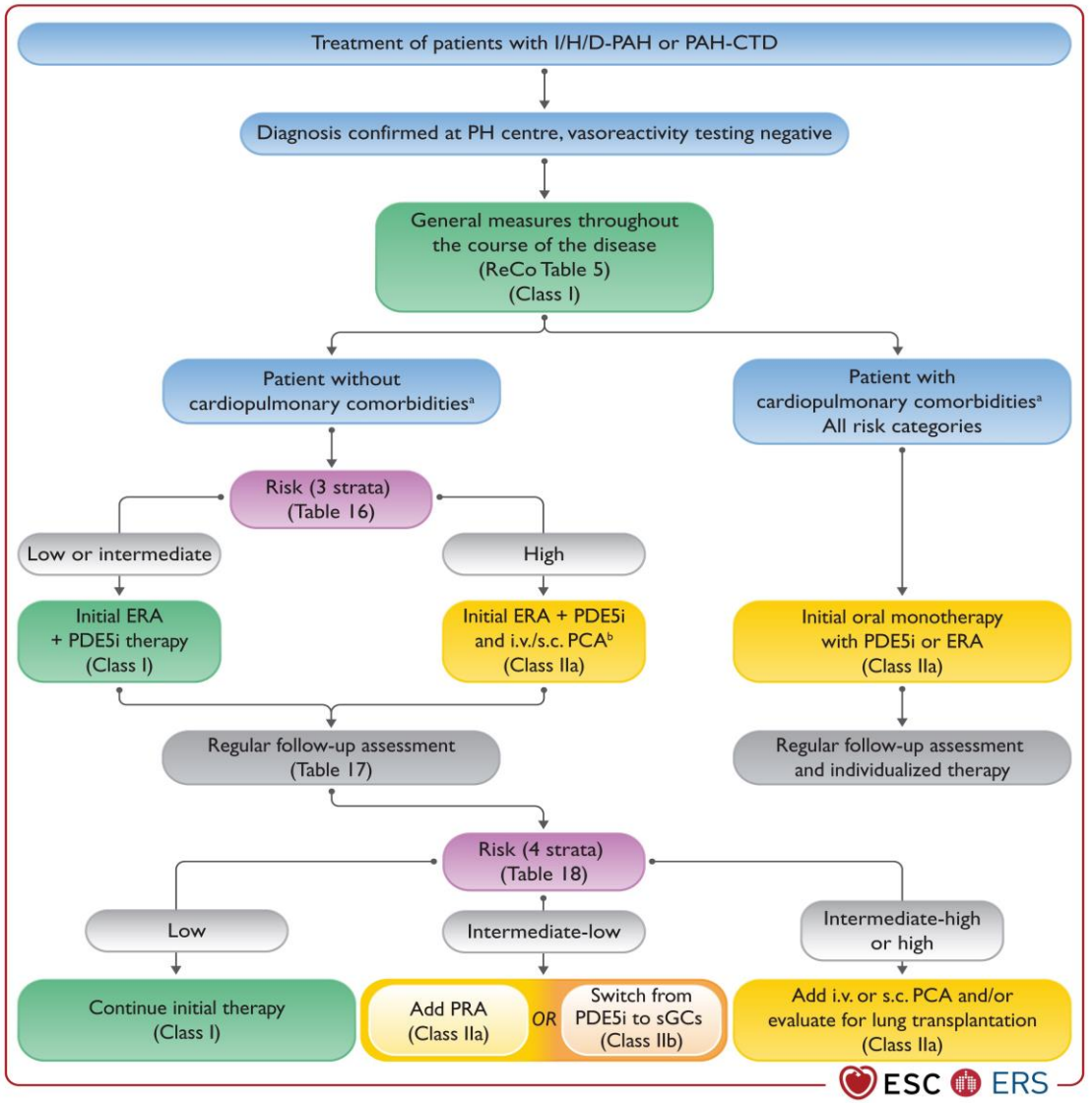
Boucly et al. Eur Respir J 2022 Jun 30;59(6):2102419.

Four Strata Risk Assessment

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

European Heart Journal, ehac237, https://doi.org/10.1093/eurheartj/ehac237 26 August 2022

Figure 9 Evidence-based pulmonary arterial hypertension treatment algorithm for patients with idiopathic, heritable, ...



Eur Heart J, ehac237, https://doi.org/10.1093/eurheartj/ehac237

Recommendations for the treatment of non-vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension who present without cardiopulmonary comorbidities

Recommendations	Class[b]	Level[c]
Recommendations for initial therapy		
In patients with IPAH/HPAH/DPAH who present at high risk of death, initial combination therapy with a PDE5i, an ERA, and i.v./s.c. prostacyclin analogues should be considered[d]	IIa	C
Recommendations for treatment decisions during follow-up		
In patients with IPAH/HPAH/DPAH who present at intermediate–low risk of death while receiving ERA/PDE5i therapy, the addition of selexipag should be considered[419]	IIa	B
In patients with IPAH/HPAH/DPAH who present at intermediate–high or high risk of death while receiving ERA/PDE5i therapy, the addition of i.v./s.c. prostacyclin analogues and referral for LTx evaluation should be considered	IIa	C
In patients with IPAH/HPAH/DPAH who present at intermediate–low risk of death while receiving ERA/PDE5i therapy, switching from PDE5i to riociguat may be considered[429]	IIb	B

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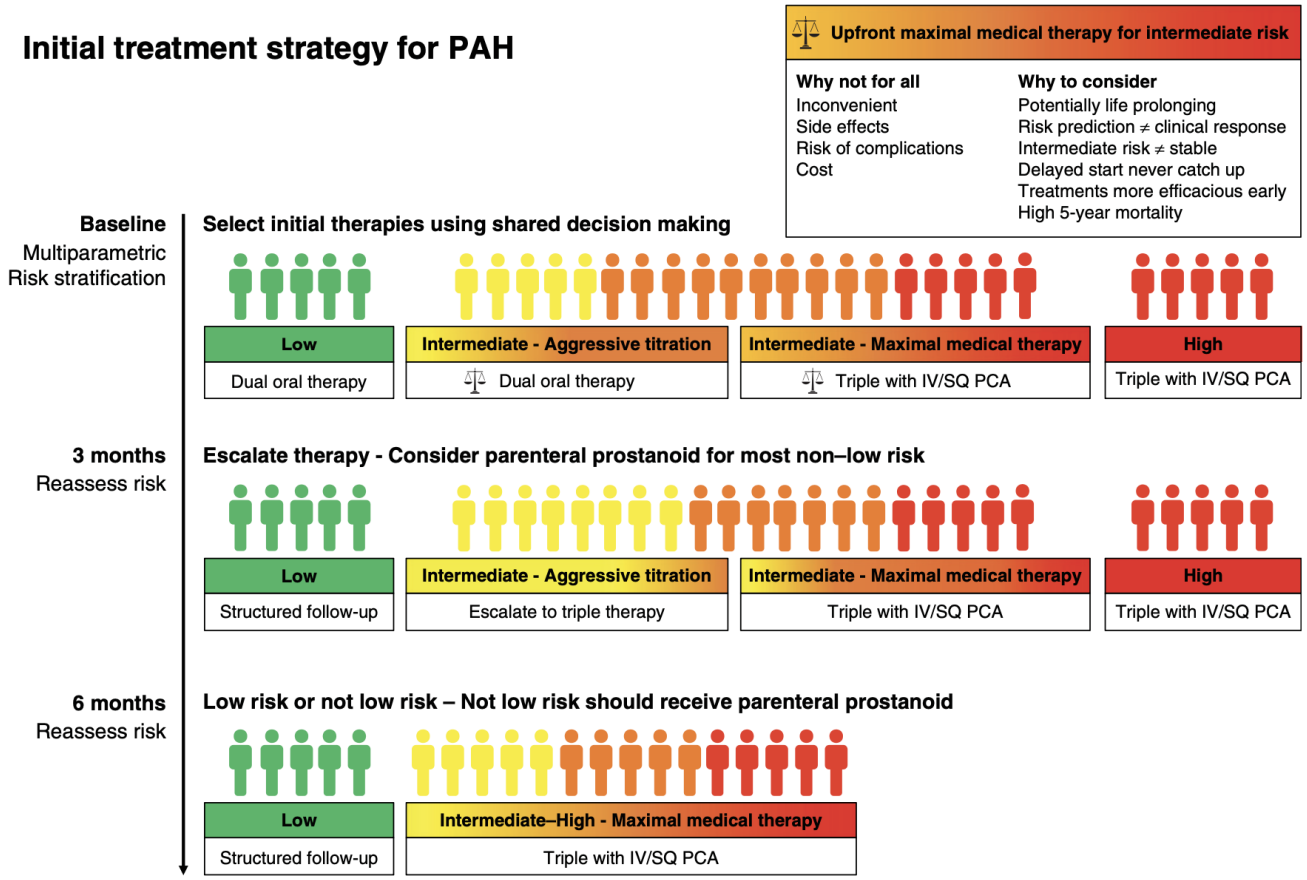
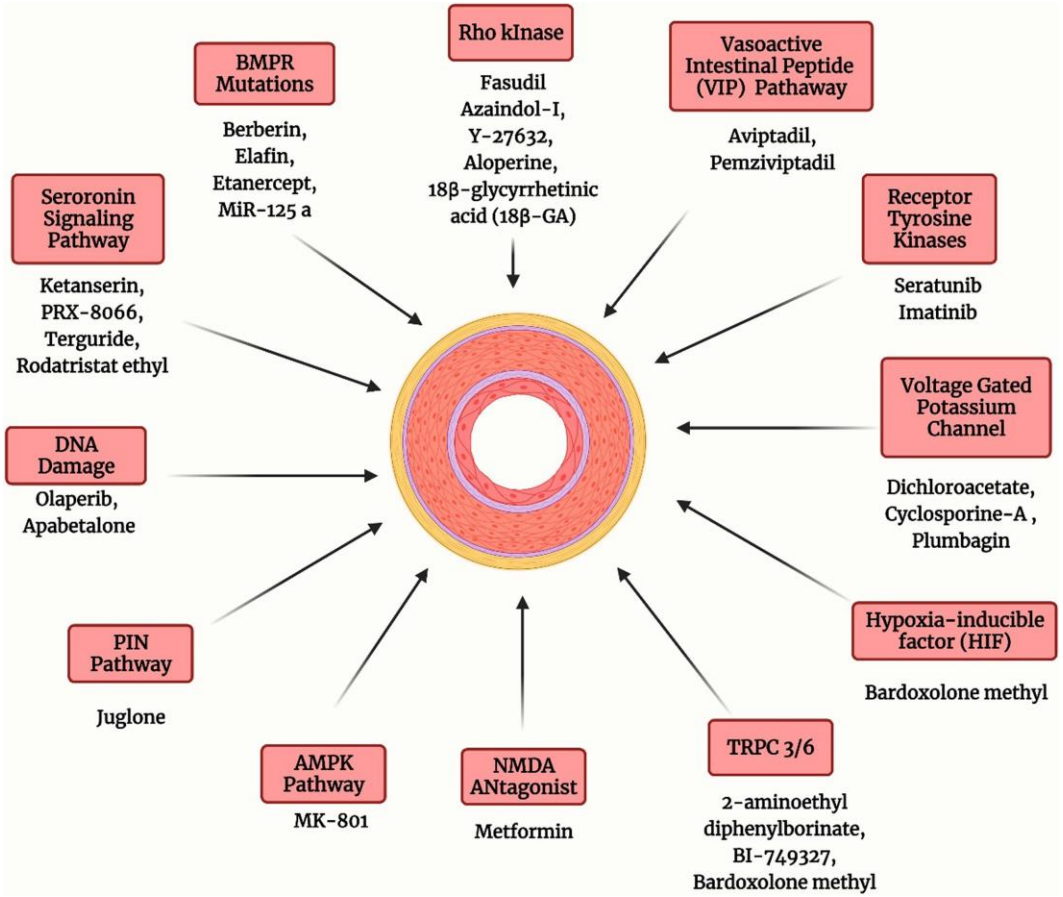
Proposed initial treatment strategy based on 4 strata risk stratification



Cascino et al. AJRCCM Volume 204 Number 7 | October 1 2021

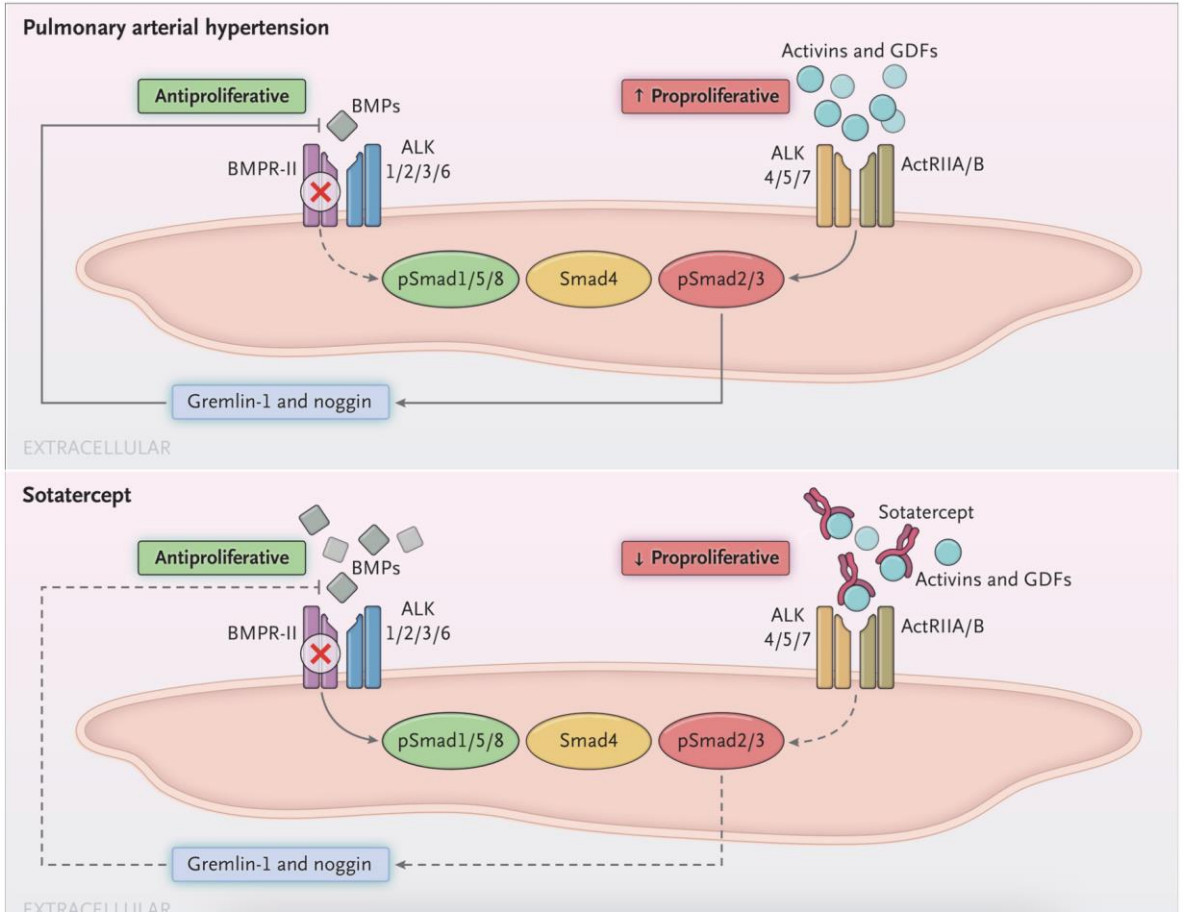
Future Therapeutics

Some Select Molecular Targets Being Evaluated for PAH Therapeutics



Dhoble S *et al.* International Journal of Pharmaceutics 621 (2022) 121792

Novel Target for PAH Therapeutics: Activin/BMPR-II with Sotatercept



Humbert M et al. N Engl J Med 2021; 384:1204-1215.

Demographic and Clinical Characteristics of the Patients at Baseline.*

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Sotatercept (N=163)	Placebo (N=160)	Total (N=323)
Female sex — no. (%)	129 (79.1)	127 (79.4)	256 (79.3)
Age — yr	47.6±14.1	48.3±15.5	47.9±14.8
Geographic region — no. (%)			
North America	49 (30.1)	56 (35.0)	105 (32.5)
South America	13 (8.0)	15 (9.4)	28 (8.7)
Europe	91 (55.8)	77 (48.1)	168 (52.0)
Asia–Pacific	10 (6.1)	12 (7.5)	22 (6.8)
Race — no. (%)†			
White	147 (90.2)	141 (88.1)	288 (89.2)
Black	2 (1.2)	5 (3.1)	7 (2.2)
Asian	1 (0.6)	6 (3.8)	7 (2.2)
Other	7 (4.3)	6 (3.8)	13 (4.0)
Missing	6 (3.7)	2 (1.2)	8 (2.5)
Body-mass index‡	26.1±5.7	26.6±6.1	26.4±5.9
Body-mass index ≥30 — no. (%)‡	36 (22.1)	38 (23.8)	74 (22.9)
Time since diagnosis of pulmonary arterial hypertension — yr§	9.2±7.3	8.3±6.7	8.8±7.0
Classification of pulmonary arterial hypertension — no. (%)			
Idiopathic	83 (50.9)	106 (66.2)	189 (58.5)
Heritable	35 (21.5)	24 (15.0)	59 (18.3)
Associated with connective-tissue disease	29 (17.8)	19 (11.9)	48 (14.9)
Drug-induced or toxin-induced	7 (4.3)	4 (2.5)	11 (3.4)
Associated with corrected congenital shunts	9 (5.5)	7 (4.4)	16 (5.0)
WHO functional class — no. (%)¶			
II	79 (48.5)	78 (48.8)	157 (48.6)
III	84 (51.5)	82 (51.2)	166 (51.4)
Background therapy for pulmonary arterial hypertension — no. (%)‖			
Prostacyclin infusion therapy**	65 (39.9)	64 (40.0)	129 (39.9)
Monotherapy	9 (5.5)	4 (2.5)	13 (4.0)
Double therapy	56 (34.4)	56 (35.0)	112 (34.7)
Triple therapy	98 (60.1)	100 (62.5)	198 (61.3)
Hemoglobin — g/dl	13.9±1.7	13.7±1.6	13.8±1.6
Estimated glomerular filtration rate — ml/min/1.73 m^2	91.2±34.6	88.3±35.8	89.8±35.2
6-Minute walk distance — m	397.6±84.3	404.7±80.6	401.1±82.4
NT-proBNP — pg/ml	1037.5±2498.6	1207.8±2694.4	1121.1±2593.8
Pulmonary vascular resistance — dyn·sec·cm^{-5}	781.3±398.5	745.8±313.5	763.7±358.8
Cardiac output — liters/min	4.9±1.3	4.8±1.2	4.8±1.2
Cardiac index — liters/min/m^2	2.7±0.6	2.7±0.6	2.7±0.6
Mean pulmonary artery pressure — mm Hg	53.0±14.6	52.2±13.0	52.6±13.8
Right atrial pressure — mm Hg	8.0±4.3	8.5±4.5	8.2±4.4
Pulmonary arterial wedge pressure — mm Hg	9.7±3.2	9.8±3.1	9.8±3.1
Mixed venous oxygen saturation — %	66.8±7.1	67.4±7.9	67.1±7.5

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. NT-proBNP denotes N-terminal pro–B-type natriuretic peptide.
† Race was reported by the patient.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The length of time since diagnosis of pulmonary arterial hypertension was calculated by adding the number of days from the date of diagnosis to the date of informed consent (enrollment) plus 1 day, then dividing by 365.25.
¶ World Health Organization (WHO) functional classes range from I to IV, with higher numbers indicating greater functional limitations.
‖ Background therapy was not prespecified in the protocol; rather, patients were treated according to their respective physicians and countries. Treatments included monotherapy, double therapy, or triple therapy with combinations of endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues, and prostacyclin-receptor agonists. Patients who were receiving prostacyclin infusion therapy were also included in one of the other categories of therapy.
** Prostacyclin infusion therapy includes intravenous epoprostenol and intravenous or subcutaneous treprostinil.

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

Change from Baseline at Week 24 in Primary and Secondary Efficacy End Points (Intention-to-Treat Population).*

Table 2. Change from Baseline at Week 24 in Primary and Secondary Efficacy End Points (Intention-to-Treat Population).*

End Point	Sotatercept (N = 163)	Placebo (N = 160)
Primary end point		
6-Minute walk distance — m		
Median change estimate (95% CI) from baseline at wk 24†	34.4 (33.0 to 35.5)	1.0 (−0.3 to 3.5)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	40.8 (27.5 to 54.1)§¶	
Secondary end points		
Multicomponent improvement		
Patients who met all three criteria for 6-min walk distance, NT-proBNP level, and WHO functional class — no./total no.	63/162‖	16/159‖
Percentage of patients (95% CI)	38.9 (31.3 to 46.9)¶**	10.1 (5.9 to 15.8)
Pulmonary vascular resistance — dyn·sec·cm^{-5}		
Median change estimate (95% CI) from baseline at wk 24†	−165.1 (−176.0 to −152.0)	32.8 (26.5 to 40.0)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−234.6 (−288.4 to −180.8)§¶	
NT-proBNP — pg/ml		
Median change estimate (95% CI) from baseline at wk 24†	−230.3 (−236.0 to −223.0)	58.6 (46.0 to 67.0)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−441.6 (−573.5 to −309.6)§¶	
WHO functional class		
Patients with improvement at wk 24 from baseline — no./total no.	48/163¶**	22/159‖
Percentage of patients (95% CI)	29.4 (22.6 to 37.1)	13.8 (8.9 to 20.2)
Time to first occurrence of death or nonfatal clinical worsening event		
Hazard ratio (95% CI)††	0.16 (0.08 to 0.35)¶‡‡	
French risk score§§		
Patients with a low-risk score with the use of the simplified French model at wk 24 — no./total no.	64/162‖	29/159‖
Percentage of patients (95% CI)	39.5 (31.9 to 47.5)¶**	18.2 (12.6 to 25.1)
PAH-SYMPACT Physical Impacts domain score¶¶		
Median change estimate (95% CI) from baseline at week 24†	−0.13 (−0.15 to 0.00)	0.01 (0.00 to 0.13)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−0.26 (−0.49 to −0.04)¶‖	
PAH-SYMPACT Cardiopulmonary Symptoms domain score¶¶		
Median change estimate (95% CI) from baseline at week 24†	−0.12 (−0.14 to −0.08)	−0.01 (−0.03 to 0.00)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−0.13 (−0.26 to −0.01)¶‖	
PAH-SYMPACT Cognitive/Emotional Impacts domain score¶¶		
Median change estimate (95% CI) from baseline at week 24†	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−0.16 (−0.40 to 0.08)	

* All analyses were performed in the intention-to-treat population with the prespecified multiple-imputation methods for handling missing data. Missing values at week 24 owing to death or nonfatal clinical worsening events were assigned worst and second-worst rank scores, respectively. Missing values at week 24 owing to reasons other than death or nonfatal clinical worsening events were populated with the use of a fully conditional specification regression model in which the data were assumed to be missing at random (see the Statistical Analyses section in the Supplementary Appendix). The widths of the confidence intervals have not been adjusted for multiple comparisons; the intervals should therefore not be used to infer definitive treatment effects for the secondary end points.

† Shown is the average of the medians across the imputed data sets (with 95% confidence interval) if missing data were imputed.

‡ The Hodges–Lehmann location shift from placebo estimate is the median of all paired differences.

§ P<0.001 for the comparison of sotatercept with placebo on the basis of the aligned-rank stratified Wilcoxon test with randomization factors of background therapy (monotherapy or double therapy vs. triple therapy) and baseline WHO functional class (II vs. III) as strata.

¶ P<0.05 as derived by means of a gatekeeping method to control the type I error rate for secondary end points by hierarchical testing that proceeded successively in the order of the end points listed in the table with a two-sided alpha level of 0.05.

‖ One patient in the group had missing data owing to coronavirus disease 2019 (Covid-19) and was excluded from the analysis.

** P<0.001 for the comparison of sotatercept with placebo on the basis of a Cochran–Mantel–Haenszel method stratified according to randomization factors of background therapy (monotherapy or double therapy vs. triple therapy) and baseline WHO functional class (II vs. III).

†† The hazard ratio (sotatercept vs. placebo) was derived from a Cox proportional-hazards model with trial group as the covariate and stratification according to the randomization factors of background therapy (monotherapy or double therapy vs. triple therapy) and baseline WHO functional class (II vs. III).

‡‡ P<0.001 for the comparison of sotatercept with placebo on the basis of a Cox proportional-hazards model with trial group as the covariate and stratification according to randomization factors of background therapy (monotherapy or double therapy vs. triple therapy) and baseline WHO functional class (II vs. III).

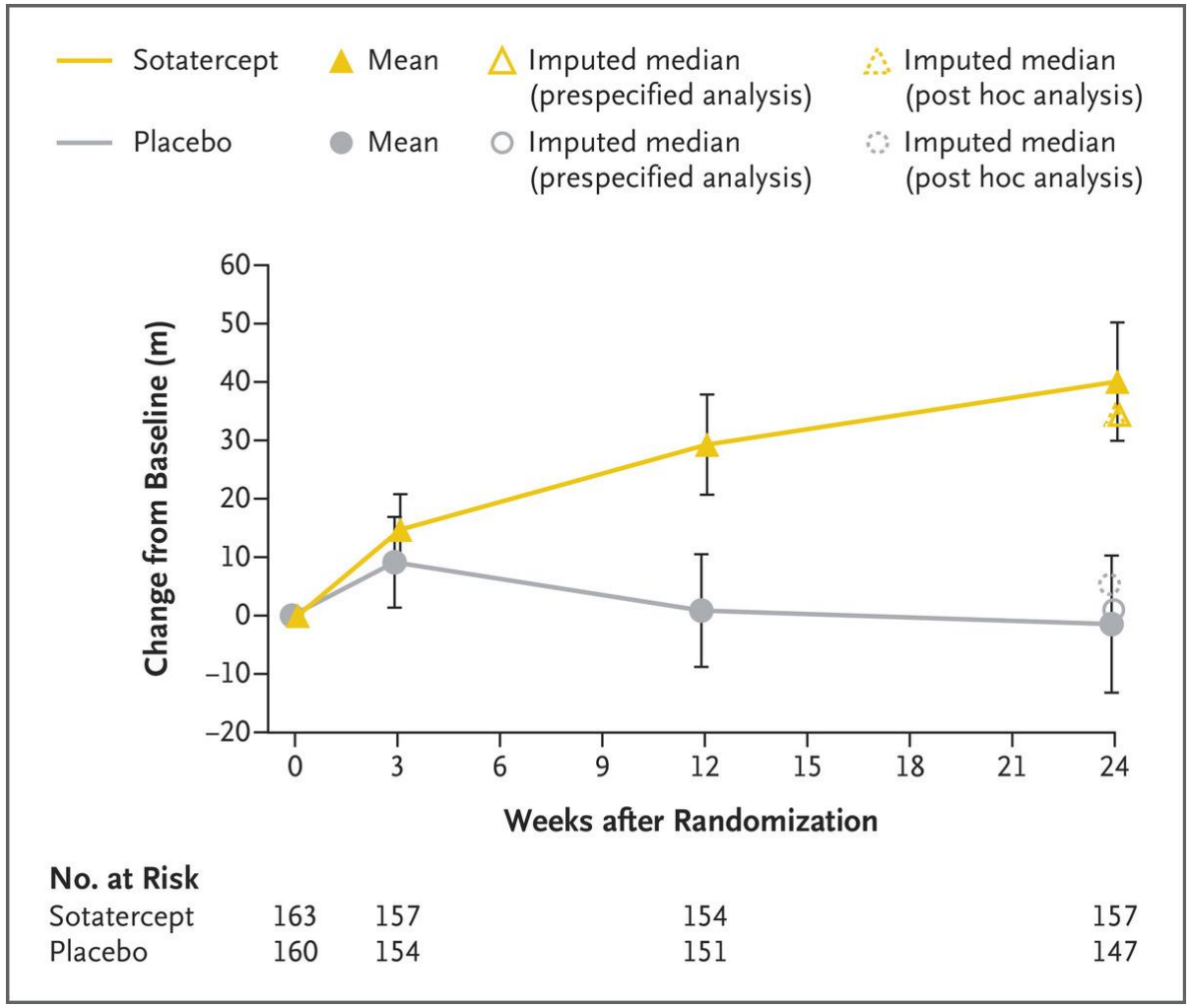
§§ A low French risk score was defined by the meeting of all three criteria for low risk: a WHO functional class of I or II, a 6-minute walk distance of more than 440 m, and an NT-proBNP level of less than 300 pg per milliliter.

¶¶ The Pulmonary Arterial Hypertension–Symptoms and Impact (PAH-SYMPACT) questionnaire is a disease-specific patient-reported outcome instrument. Domain scores range from 0 to 4, with higher scores indicating greater severity of symptoms.

‖‖ P<0.05 for the comparison of sotatercept with placebo on the basis of the aligned-rank stratified Wilcoxon test with randomization factors of background therapy (monotherapy or double therapy vs. triple therapy) and baseline WHO functional class (II vs. III) as strata.

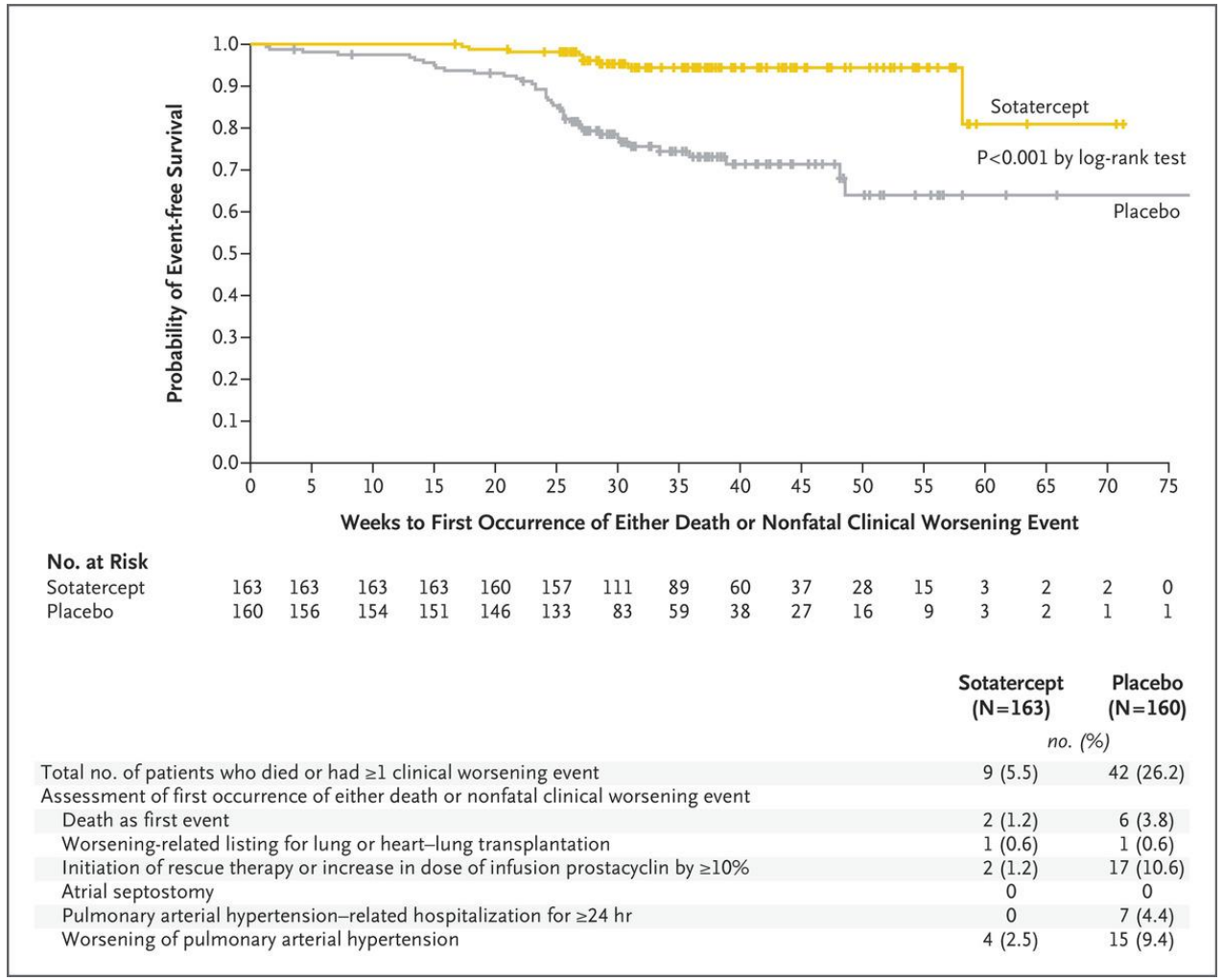
MM Hoeper et al. N Engl J Med 2023. DOI: 10.1056/NEJMoa2213558

Change in 6-Minute Walk Distance through Week 24.



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

Time to First Occurrence of Death or Nonfatal Clinical Worsening Event (Intention-to-Treat Population).



	Sotatercept (N=163)	Placebo (N=160)
	no. (%)	
Total no. of patients who died or had ≥1 clinical worsening event	9 (5.5)	42 (26.2)
Assessment of first occurrence of either death or nonfatal clinical worsening event		
Death as first event	2 (1.2)	6 (3.8)
Worsening-related listing for lung or heart–lung transplantation	1 (0.6)	1 (0.6)
Initiation of rescue therapy or increase in dose of infusion prostacyclin by ≥10%	2 (1.2)	17 (10.6)
Atrial septostomy	0	0
Pulmonary arterial hypertension–related hospitalization for ≥24 hr	0	7 (4.4)
Worsening of pulmonary arterial hypertension	4 (2.5)	15 (9.4)

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

Adverse Events through Week 24 (Safety Population).*

Table 3. Adverse Events through Week 24 (Safety Population).*

Variable	Sotatercept (N = 163)	Placebo (N = 160)	Difference†
	number (percent)		*percentage points*
Adverse events			
Any	138 (84.7)	140 (87.5)	−2.8 (−10.5 to 4.8)
Related to sotatercept or placebo‡	67 (41.1)	41 (25.6)	15.5 (5.2 to 25.5)
Leading to discontinuation of sotatercept or placebo	3 (1.8)	10 (6.2)	−4.4 (−9.5 to −0.1)
Leading to withdrawal from the trial	3 (1.8)	5 (3.1)	−1.3 (−5.5 to 2.5)
Leading to death	0	6 (3.8)	−3.8 (−7.9 to −1.4)
Severe adverse event§	13 (8.0)	21 (13.1)	−5.1 (−12.2 to 1.6)
Serious adverse events¶			
Any	23 (14.1)	36 (22.5)	−8.4 (−16.9 to 0.1)
Related to sotatercept or placebo‡	2 (1.2)	2 (1.2)	−0.0 (NR)
Leading to discontinuation of sotatercept or placebo	1 (0.6)	8 (5.0)	−4.4 (−9.0 to −1.0)
Leading to withdrawal from the trial	1 (0.6)	5 (3.1)	−2.5 (−6.6 to 0.6)
Adverse events of interest or special interest‖			
Increased hemoglobin level: increased hematocrit or increased red-cell count	9 (5.5)	0	5.5 (2.9 to 10.2)
Thrombocytopenia	10 (6.1)	4 (2.5)	3.6 (−0.9 to 8.8)
Bleeding events	35 (21.5)	20 (12.5)	9.0 (0.8 to 17.2)
Increased blood pressure	6 (3.7)	1 (0.6)	3.1 (−0.2 to 7.3)
Telangiectasia	17 (10.4)	5 (3.1)	7.3 (2.0 to 13.3)
Adverse events reported in ≥10% of patients in either group	138 (84.7)	140 (87.5)	−2.8 (−10.5 to 4.8)
Headache	33 (20.2)	24 (15.0)	5.2 (−3.1 to 13.6)
Covid-19	24 (14.7)	21 (13.1)	1.6 (−6.1 to 9.3)
Nausea	16 (9.8)	18 (11.2)	−1.4 (−8.4 to 5.4)
Diarrhea	20 (12.3)	12 (7.5)	4.8 (−1.8 to 11.6)
Fatigue	17 (10.4)	12 (7.5)	2.9 (−3.5 to 9.5)
Epistaxis	20 (12.3)	3 (1.9)	10.4 (5.2 to 16.6)
Telangiectasia	17 (10.4)	5 (3.1)	7.3 (2.0 to 13.3)
Dizziness	17 (10.4)	3 (1.9)	8.6 (3.6 to 14.4)

* Shown are adverse events that occurred up to and including day 56 after the last dose of sotatercept or placebo. The safety population includes all randomly assigned patients who received at least one dose of sotatercept or placebo. NR denotes not reported.
† Shown is the point estimate for the between-group difference. The 95% confidence intervals were calculated with the use of the Miettinen and Nurminen method. The confidence interval is not provided when the incidence is less than 4 in both trial groups.
‡ These events were suspected to be related to sotatercept or placebo by the trial investigator.
§ A severe adverse event was any adverse event that was deemed to be severe in intensity by the trial investigator.
¶ A serious adverse event was defined as any untoward medical event that results in death, is life-threatening, warrants hospitalization or causes prolongation of existing hospitalization, results in persistent or clinically significant disability or incapacity, may have caused a congenital abnormality or birth defect, or warrants intervention to prevent permanent impairment or damage.
‖ Adverse events of interest (bleeding events, cardiac events, embryo or fetal toxic effects, hepatic toxic effects, immunogenicity, increased blood pressure, increased hemoglobin levels, leukopenia, neutropenia, renal toxic effects, suppression of follicle-stimulating hormone, thrombocytopenia, and thromboembolic events) and special interest (telangiectasia) were predefined variables that were monitored to assess the overall safety profile of sotatercept. Only those adverse events of interest and special interest in which the point estimate for the between-group difference excluded zero in the 24-week analysis (Table S20), the cumulative analysis (Table S21), or both are shown here. These two supplementary tables include details on the prespecified search strategies for adverse events of interest and special interest.

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A Phase 2b, Open-label, Single Dose Study to Evaluated the Safety and Efficacy of RT234 on Exercise Parameters Assessed by Cardiopulmonary Exercise Testing (CPET) in Subjects With Pulmonary Arterial Hypertension (PAH)

Study Elements

- Novel Treatment Concept – prn vasodilation to improve exercise tolerance.
- Agent: Inhaled Vardenafil
- Documented PAH
- Inclusion: Ve/VCO2 >35

Study Analysis and Endpoint

- Safety
- Pharmacokinetics
- Primary endpoint is improvement in exercise tolerance as judged by $VO2_{max}$
- Secondary endpoint is 6 minute walk difference

Summary

- Diagnosis
  - Definition and separation of physiologies associated with PH
  - Focus on accelerated workup and risk based on RV findings at initial echo
- Revision of goals of therapy and time frames for therapeutic decision making*
  - 3 strata model of risk assessment
  - 4 strata model of risk assessment
- Trends in experimental therapies – what is on the horizon?
  - Sotatercept
  - Other molecular targets
  - Prn rescue vardenafil