Pharmacology and clinical application of PAH target agents

2025-06-21 2025 폐혈관 School

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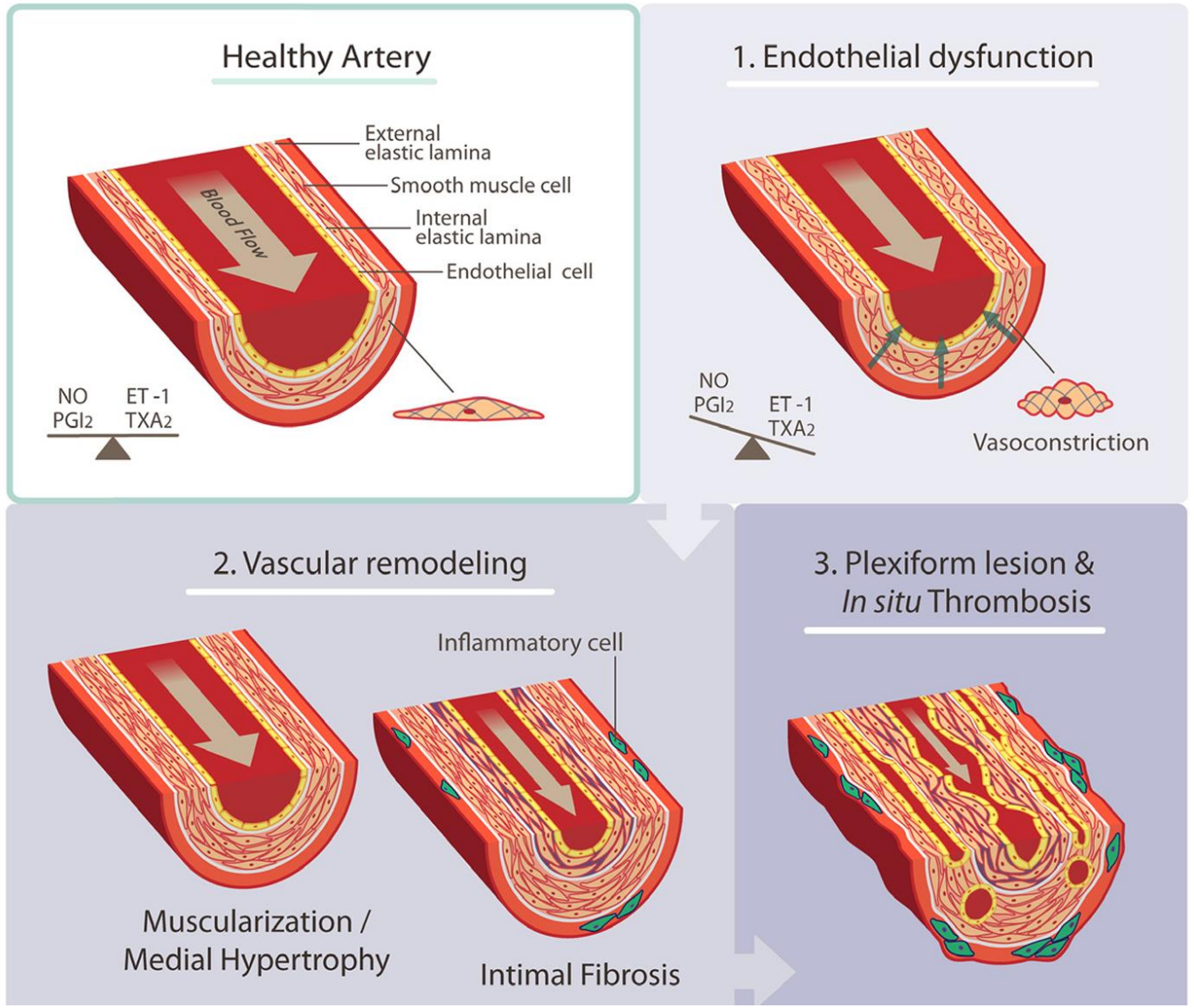
Contents

Pulmonary arterial hypertension

- Pulmonary vasculopathy, characterized by pathologic remodeling and vasoconstriction of the pulmonary arteries.

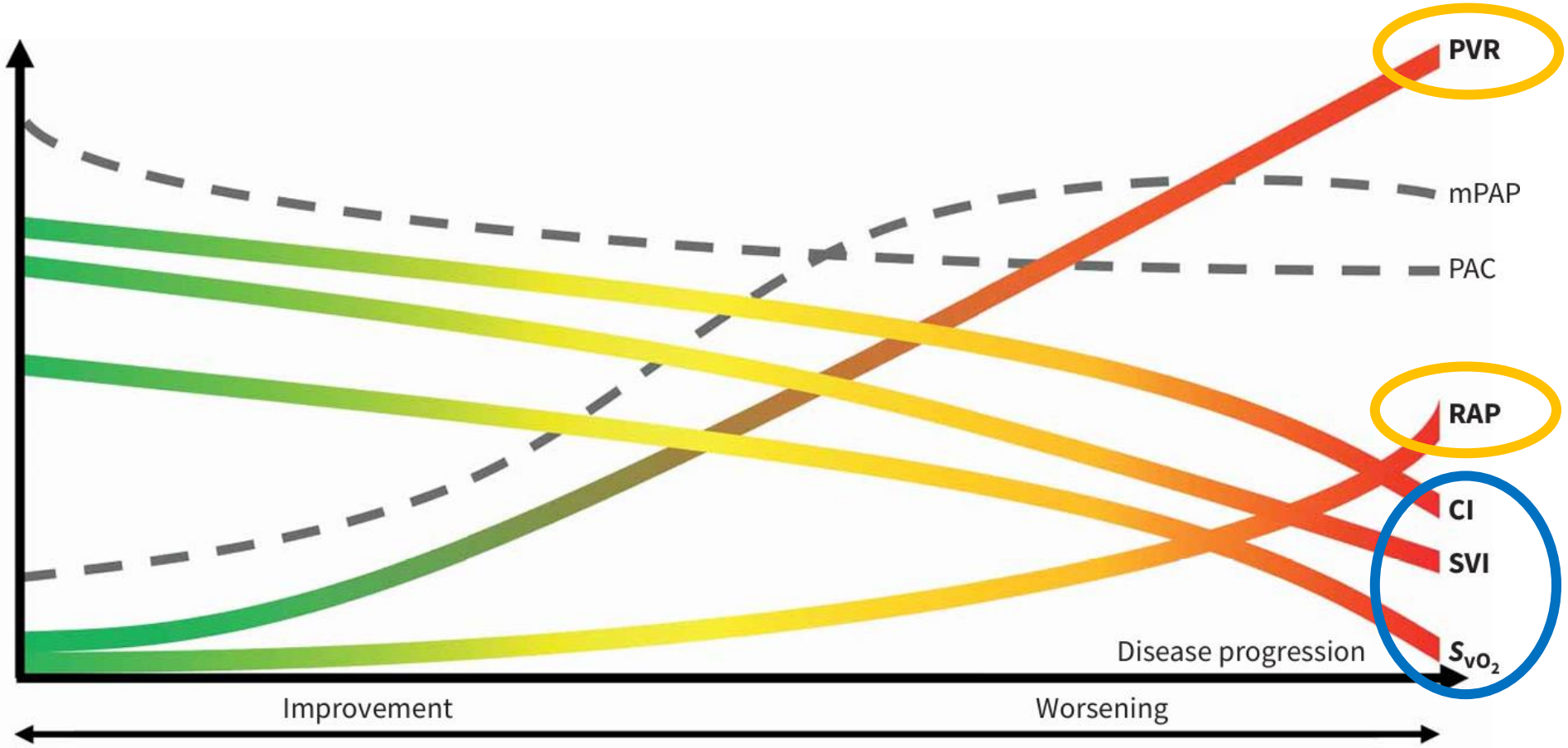
- PAH results in chronic RV pressure overload, development of RV failure and death.



Circ Res. 2014;115:115-130.

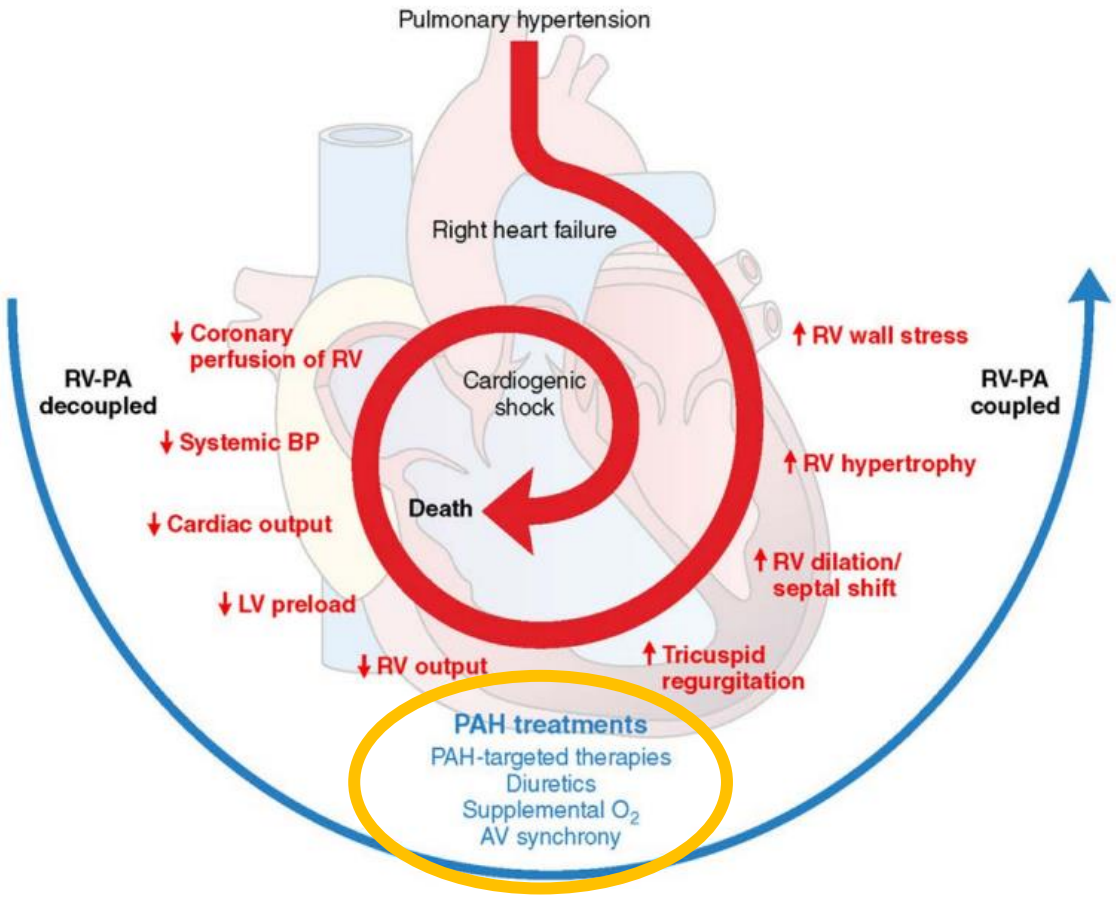
Progressive hemodynamic nature of PAH

Haemodynamics
(unlikely of added value at follow-up in low-risk patients according to ESC/ERS 4 strata model)



Eur Respir J. 2024 Oct 31;64(4):2401323

Pulmonary arterial hypertension



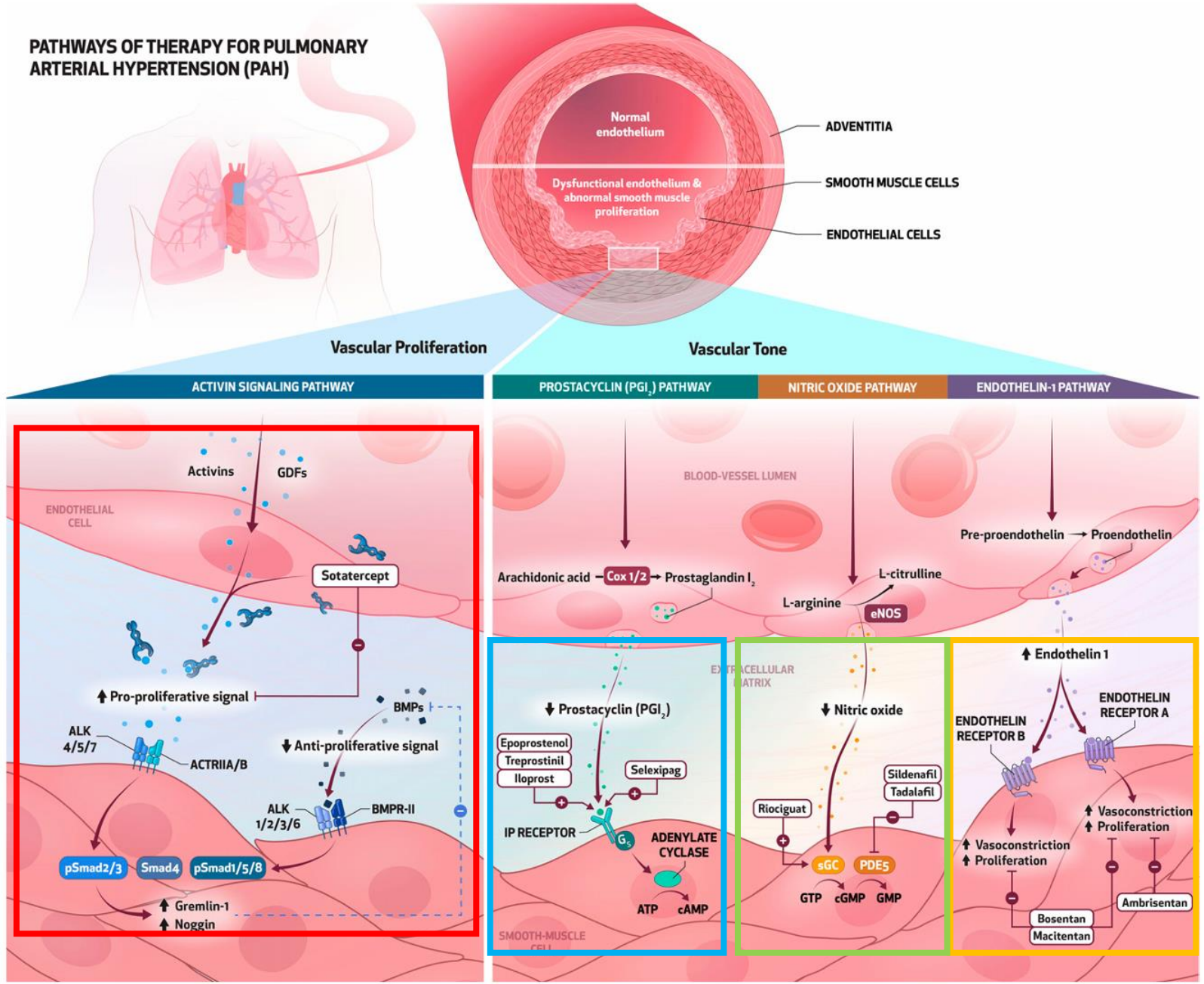
- **Treatment goal in PAH**
  - To reduce the RV afterload in order to accomplish favorable RV adaptation, stable RV function and low mortality rates

Circulation. 2023 Apr 25;147(17):1317-1343

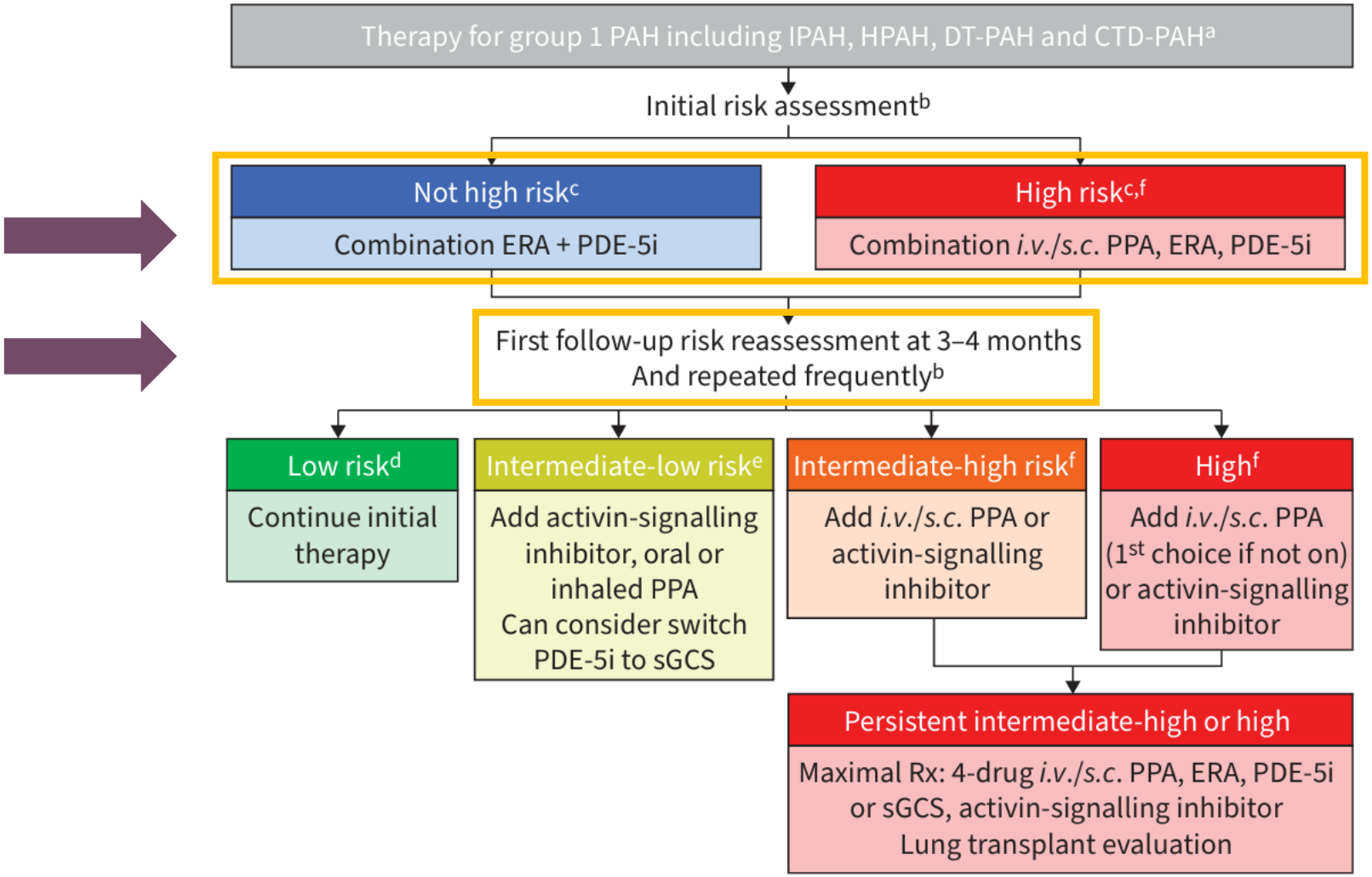
Pulmonary arterial hypertension

- **Treatment goal in PAH**
  - To reduce the RV afterload in order to accomplish favorable RV adaptation, stable RV function and low mortality rates

- **PAH medication**
  - ERA: Bosentan, Ambrisentan, Macitentan
  - PDE5i: Tadalafil, Sildenafil
  - sGC stimulator: Riociguat
  - Prostacyclin analogues: Epoprostenol (IV), Trepostinil (IV,SQ,Inh,Oral), Iloprost (Inh)
  - Selective IP receptor agonist: Selexipag
  - Recombinant activin receptor fusion protein: Sotatercept



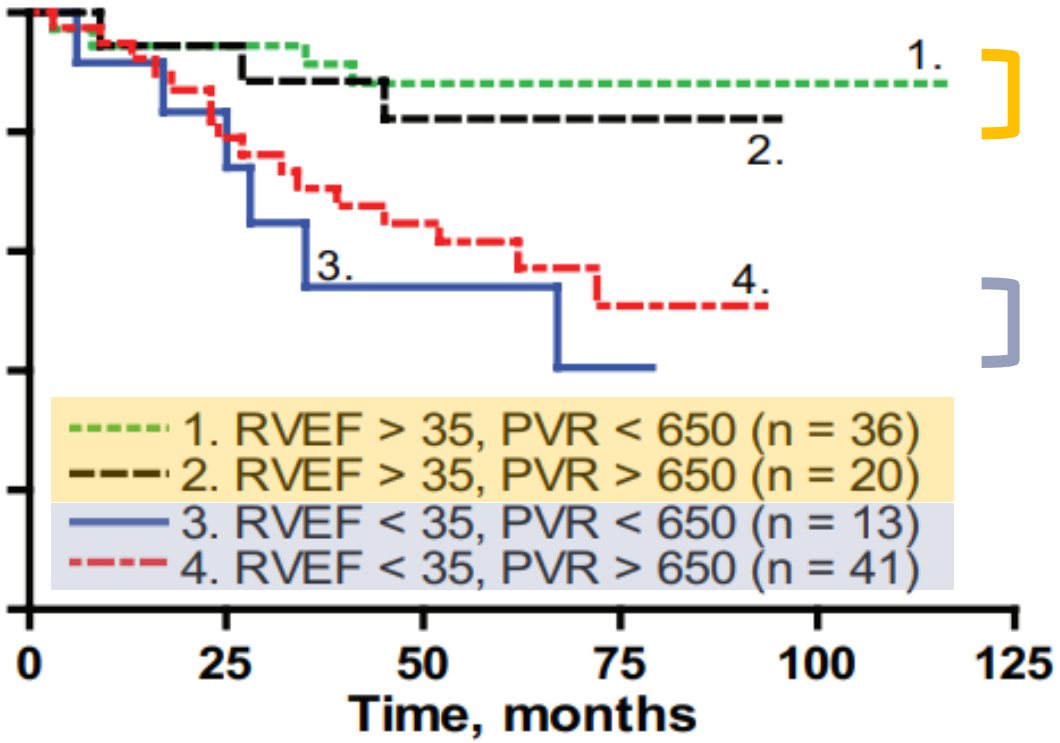
Am J Respir Crit Care Med. 2024 Sep 1;210(5):581-592



Eur Respir J. 2024 Oct 31;64(4):2401325

Importance of achieving treatment goals early

- Baseline RVEF is a more important prognostic factor than the baseline PVR



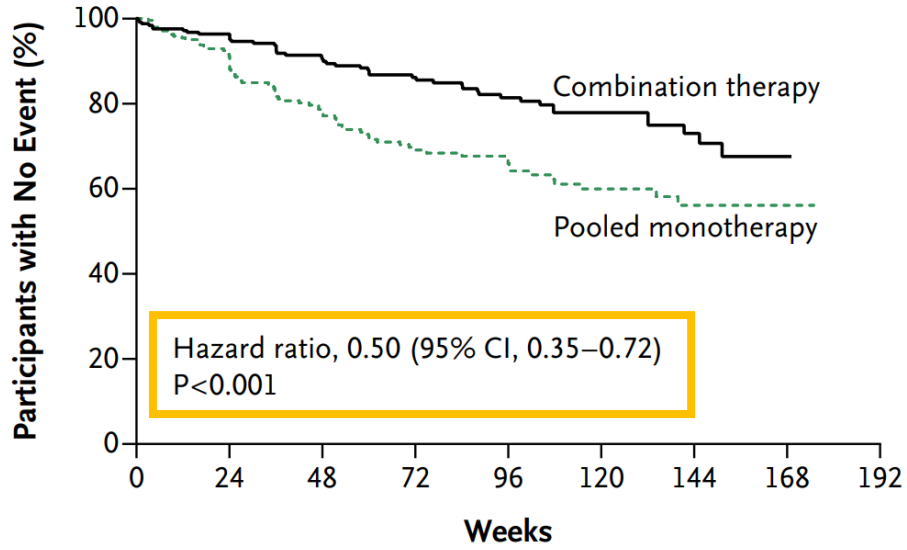
J Am Coll Cardiol 2011;58:2511-99


늦었다고 생각할 때가
진짜 너무 늦었다


늦었다고 생각할 땐 너무 늦은 거다
그러니 지금 당장 시작해라

Efficacy of upfront dual combination therapy

- **AMBITION study**
  - ✓ Ambrisentan + Tadalafil (*n* = 253) *vs.* Ambrisentan (*n* = 126) *vs.* Tadalafil (*n* = 121)
  - ✓ Eligible participants
    - ✓ Group 1 PH with NYHA FC II/III
    - ✓ mPAP ≥25mmHg
    - ✓ Naïve or less than 14 days for PAH treatment
  - ✓ Primary outcome (Composite outcome)
    - ✓ any-cause death
    - ✓ hospitalization for worsening PAH
    - ✓ Disease progression (6MWD 15%↓ & WHO Fc 3 or 4)
    - ✓ Unsatisfactory long-term clinical response (6MWD ↓ & WHO Fc 3 or 4)



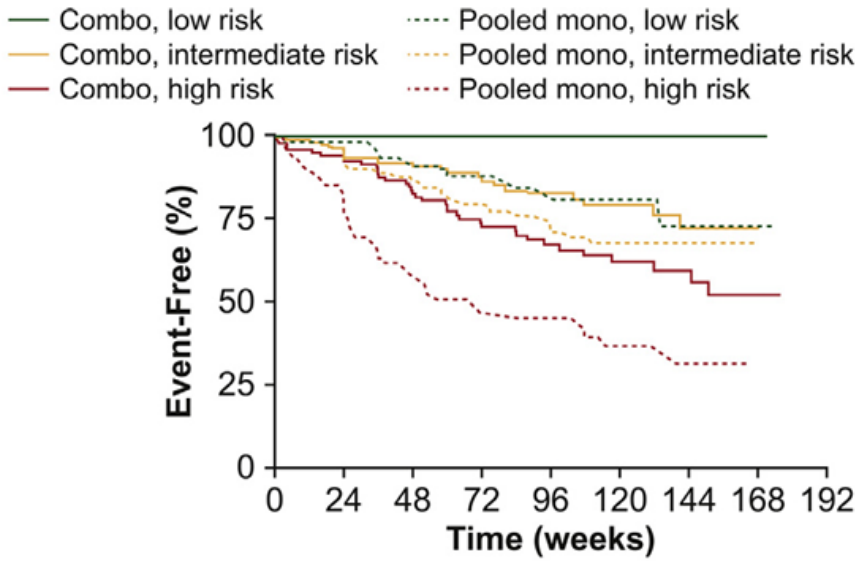
No. at Risk

Combination therapy	253	229	186	145	106	71	36	4
Pooled monotherapy	247	209	155	108	77	49	25	5

N Engl J Med 2015;373:834-44

Efficacy of upfront dual combination therapy

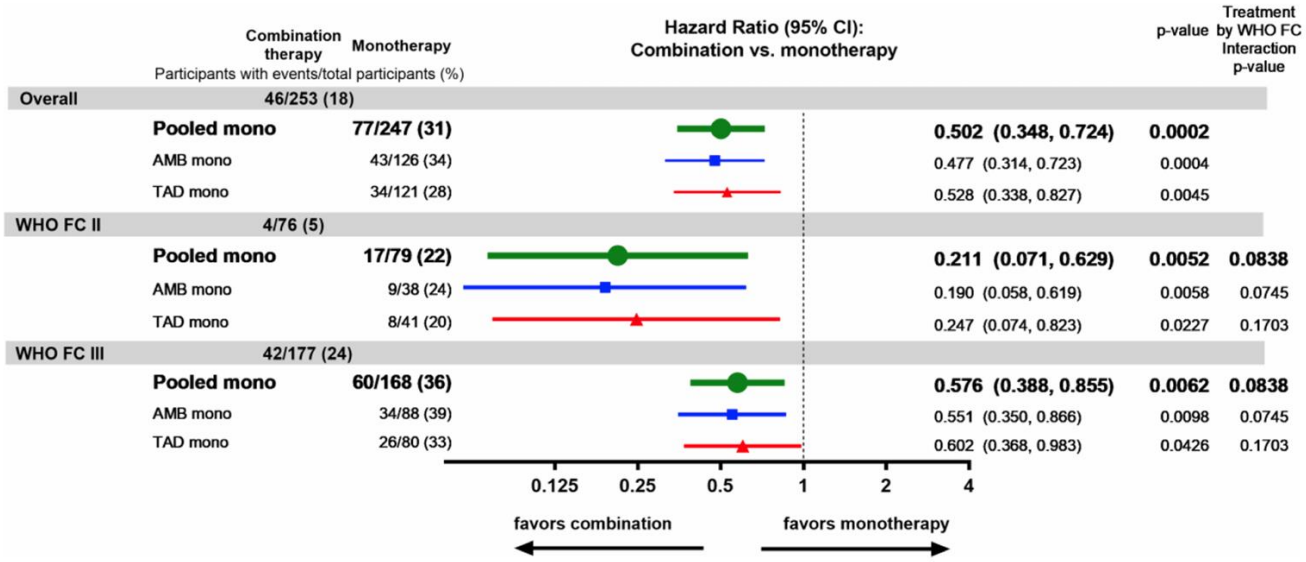
Risk score



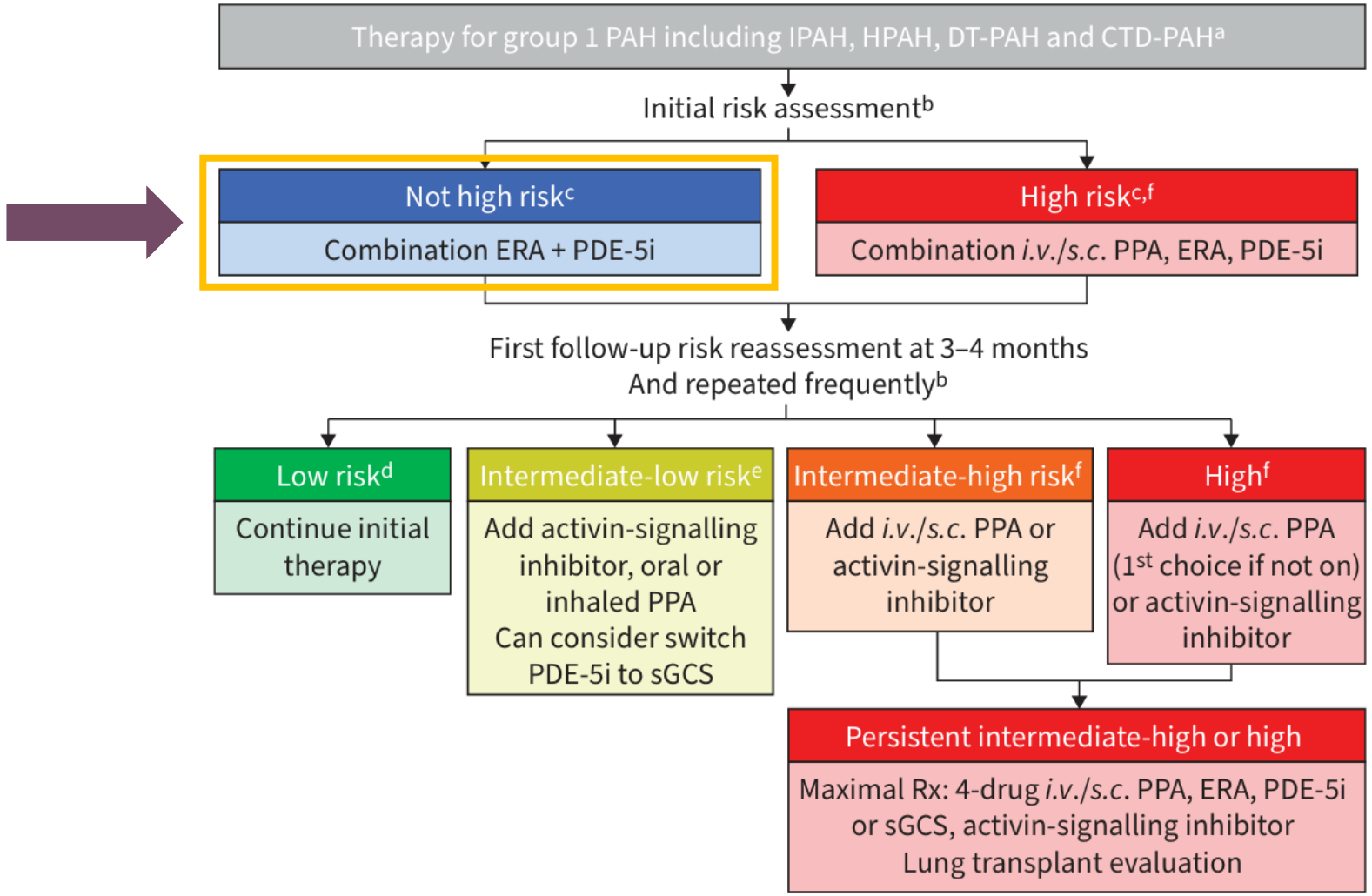
Number at risk:

Combo, High risk (>8)	119	106	83	65	46	28	19	3
Combo, Intermediate risk (6–8)	135	119	99	72	57	39	17	3
Combo, Low risk (<6)	48	45	35	33	23	18	9	3
Pooled mono, High risk (>8)	110	83	50	32	23	11	5	0
Pooled mono, Intermediate risk (6–8)	143	124	102	75	55	37	19	3
Pooled mono, Low risk (<6)	50	44	36	29	23	15	8	3

WHO Fc



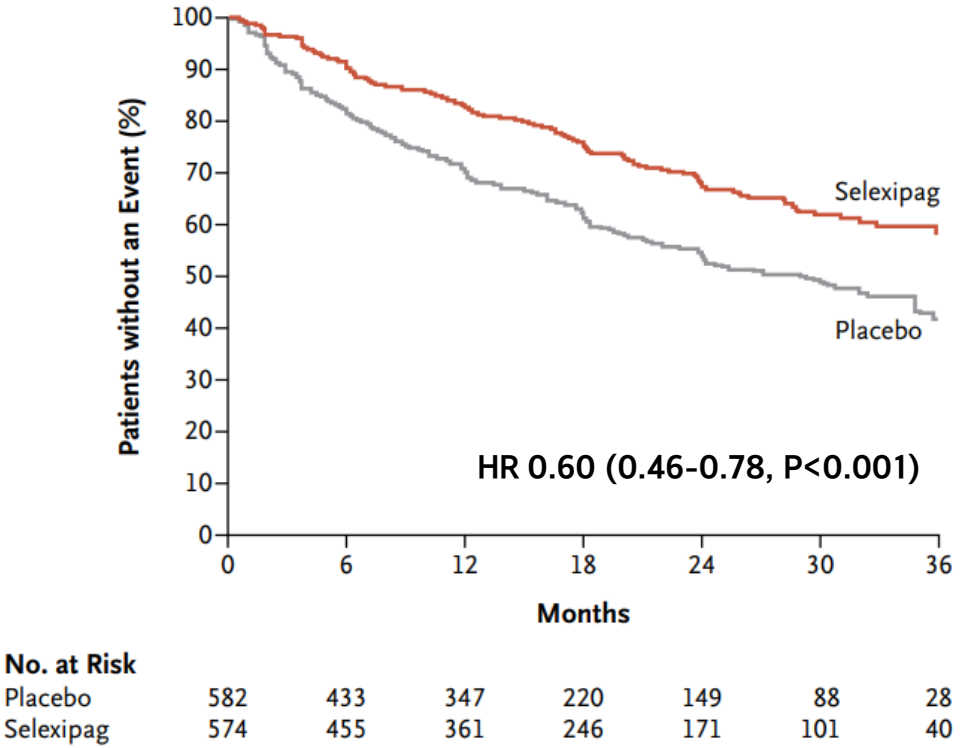
J Heart Lung Transplant 2018;37:1410 1417, Respiratory Research (2019) 20:208



Eur Respir J. 2024 Oct 31;64(4):2401325

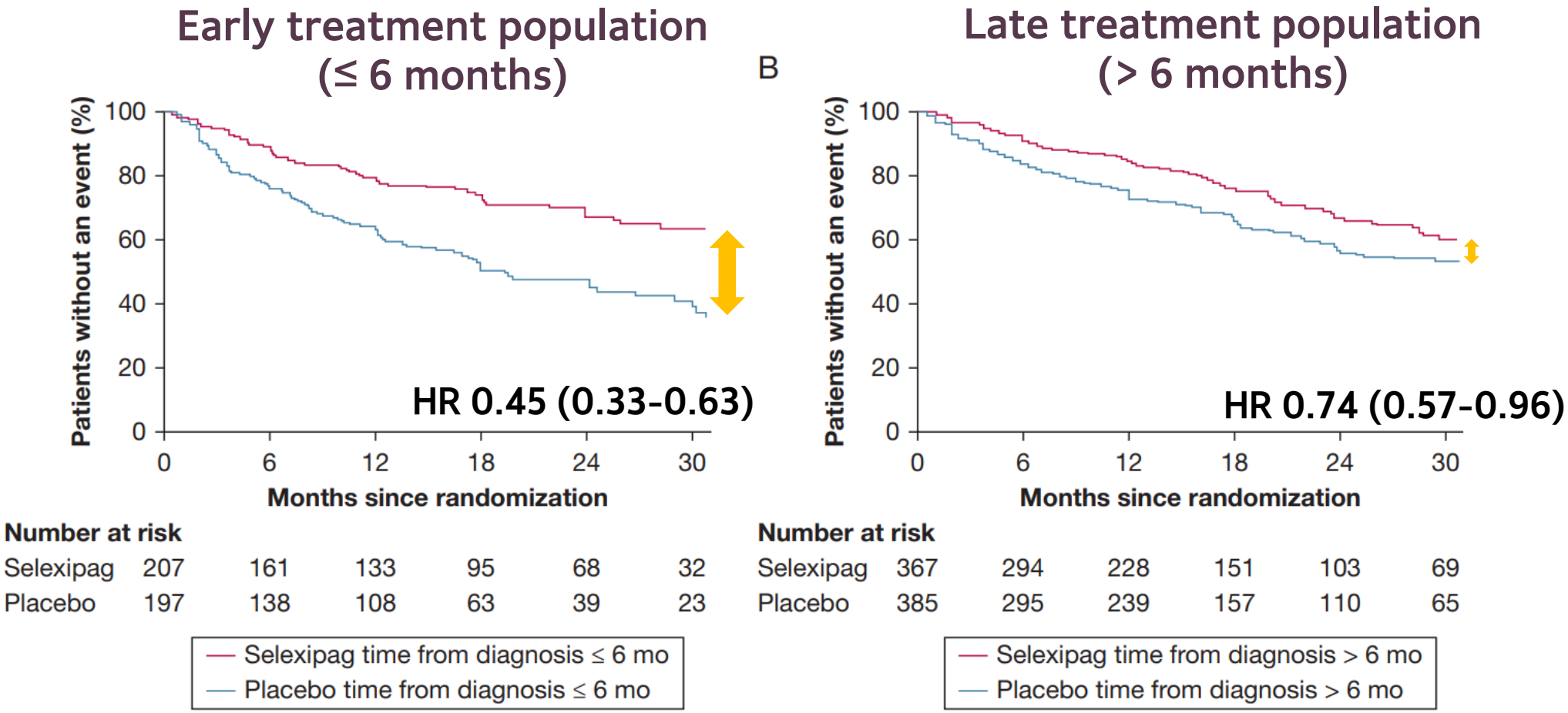
Effect of early treatment

- **GRIPHON study**
  - ✓ Selexipag (*n* = 574) *vs.* Placebo (*n* = 582)
  - ✓ Eligible participants
    - ✓ Group 1 PH
    - ✓ PVR ≥ 5WU & 6MWT 50m to 450m
    - ✓ Naïve/ERA mono/PDEi mono/ERA+PDEi
  - ✓ Primary outcome (composite outcome)
    - ✓ any-cause death
    - ✓ hospitalization for worsening PAH
    - ✓ Disease progression
    - ✓ Parenteral PPA use
    - ✓ Long term oxygen therapy
    - ✓ Lung transplantation
    - ✓ Balloon atrial septostomy



N Engl J Med 2015;373:834-44

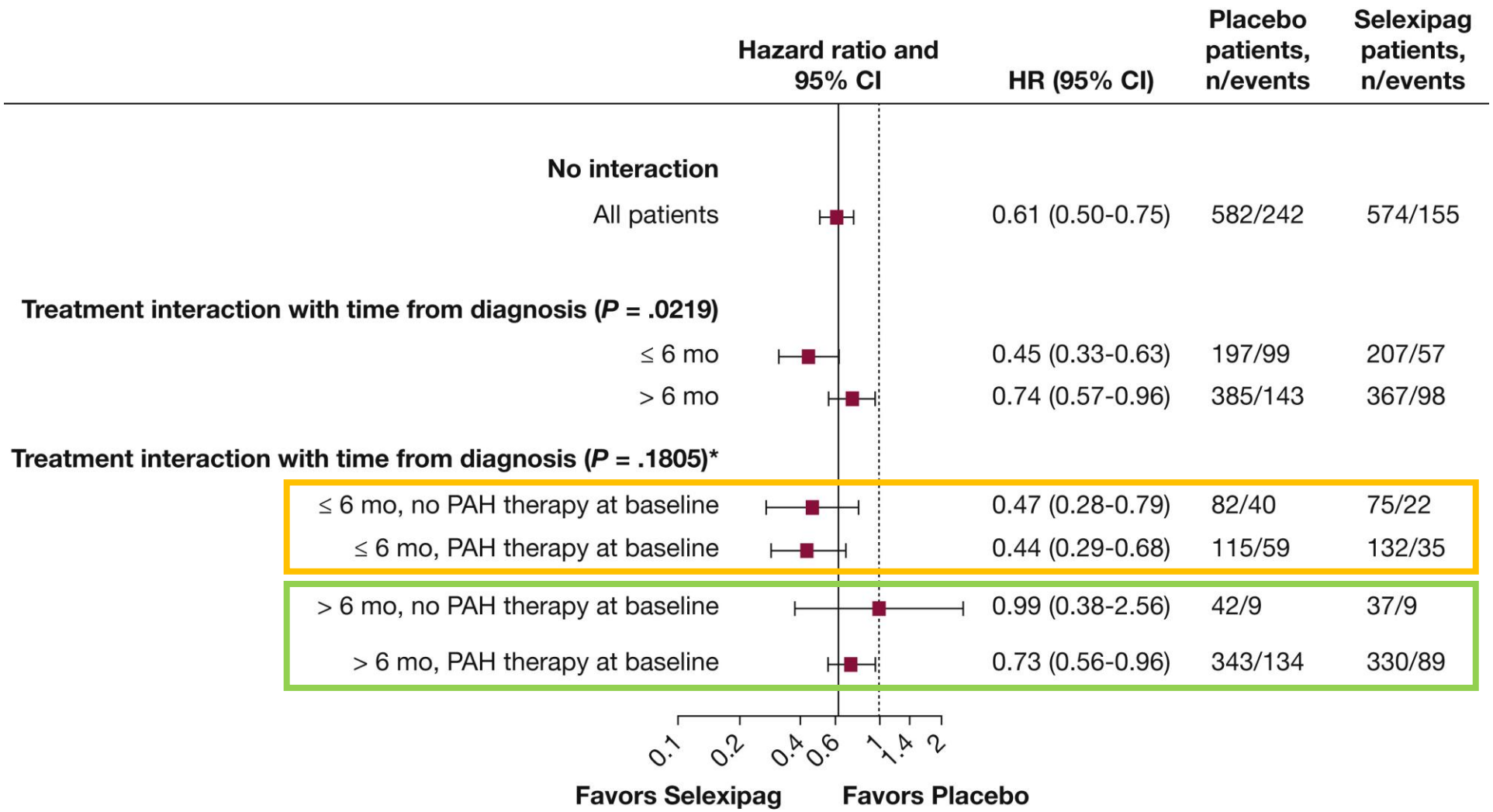
GRIPHON post hoc study



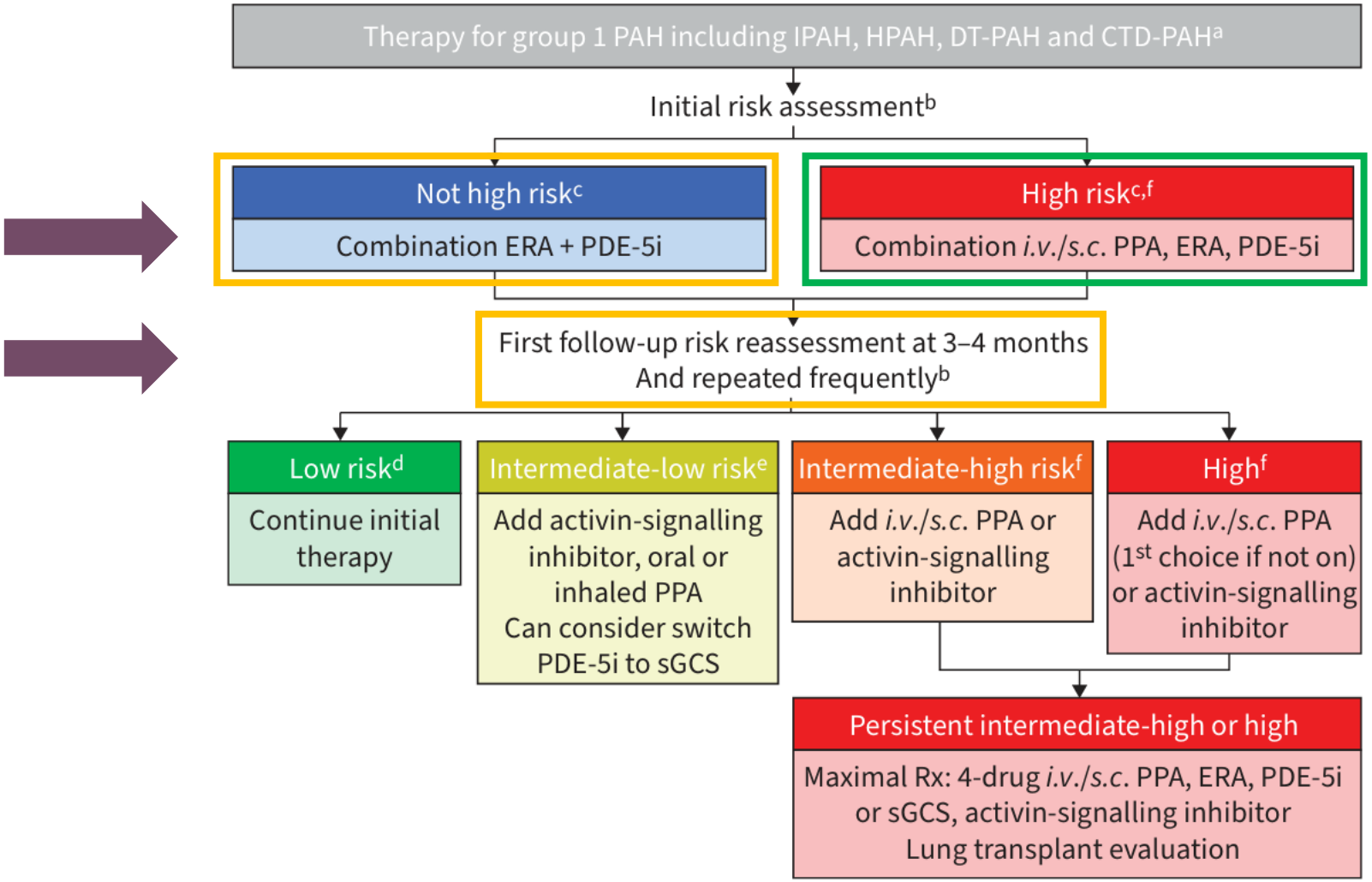
- Selexipag showed beneficial effects, with **a more pronounced treatment effect** seen in patients **treated earlier**

CHEST 2021; 160(1):277-296

GRIPHON post hoc study



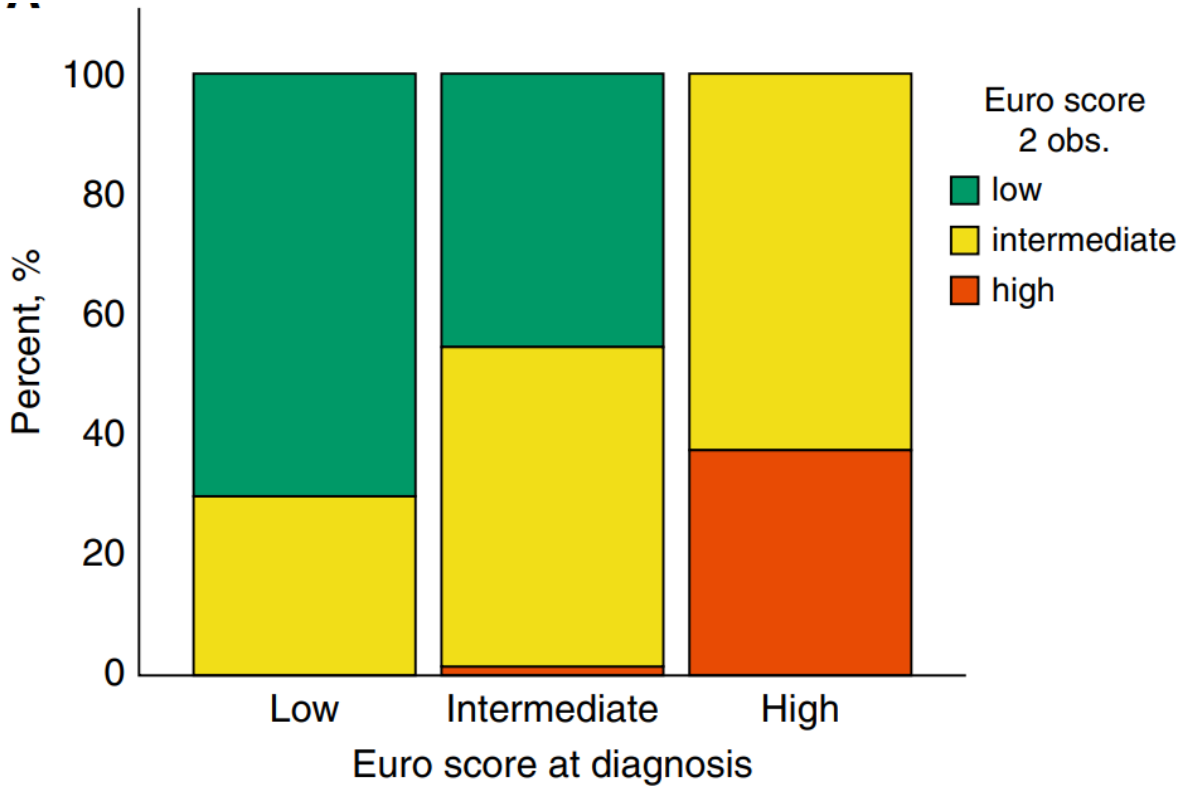
CHEST 2021; 160(1):277-286



Eur Respir J. 2024 Oct 31;64(4):2401325

Limitation of dual combination therapy

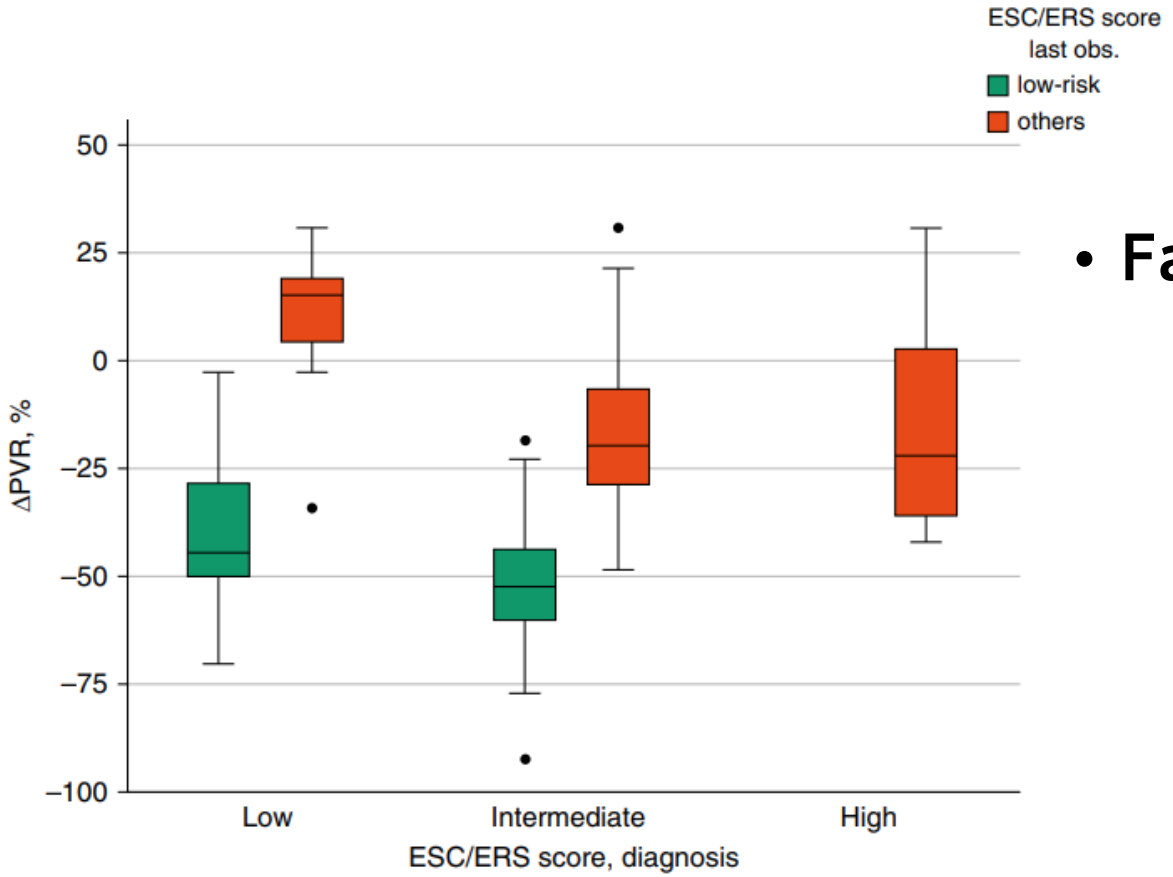
- **iPHNET database study**
  - ✓ 181 treatment-naïve PAH patients
  - ✓ Upfront dual (ERA + PDE-5i) combination therapy



At diagnosis	Low	Intermediate	High
Low (n =14)	11 (78.6%)	3 (21.4%)	
Intermediate (n = 83)	41 (49.4%)	41 (49.4%)	1 (1.2%)
High (n =16)		9 (56.3%)	7 (43.8%)

Am J Respir Crit Care Med. 2021 Feb 15;203(4):484-492

Limitation of dual combination therapy

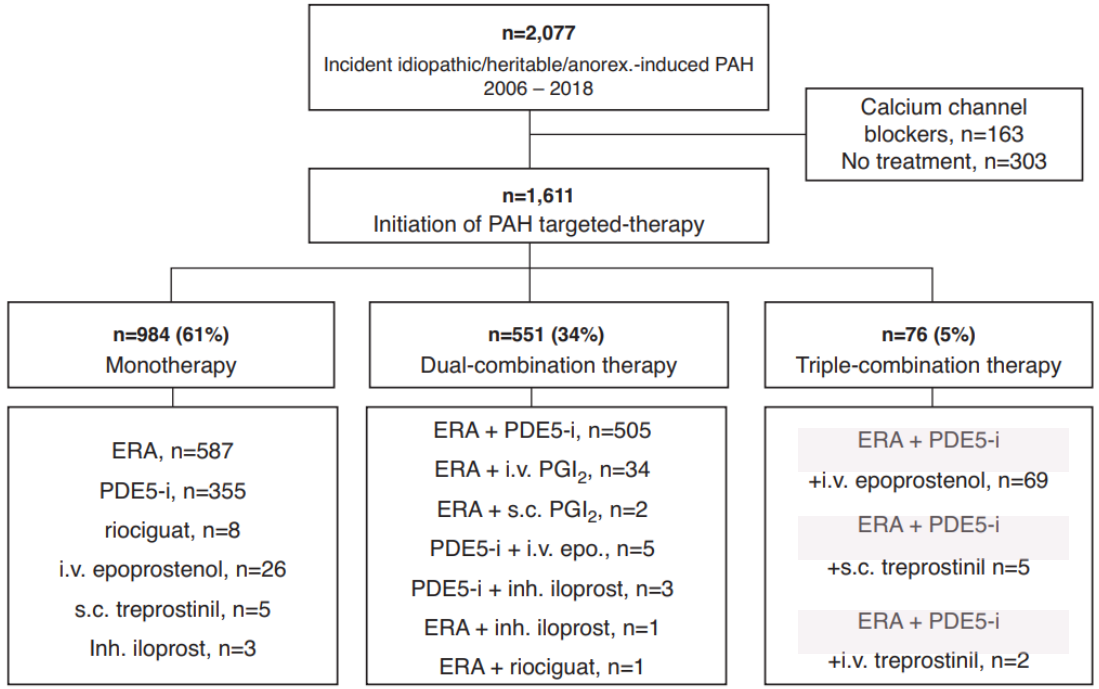


- Factors related to poor PVR response
  - ✓ Risk status at baseline
  - ✓ Poor PVR reduction response prediction factor
    - ✓ Age≥60
    - ✓ Male
    - ✓ mPAP ≥48mmHg & CI <2.5L/min/m²
    - ✓ RVEDA/LVEDA >1 & low TAPSE <18mm

Am J Respir Crit Care Med. 2021 Feb 15;203(4):484-492

Upfront triple therapy

- **French PAH registry analysis**
  - ✓ Eligible participants
    - ✓ Idiopathic, heritable, or anorexigen-induced PAH
      with mPAP ≥25mmHg, mPAWP ≤15mmHg & PVR >3WU
    - ✓ Patients receiving PAH therapy within the first 3 months



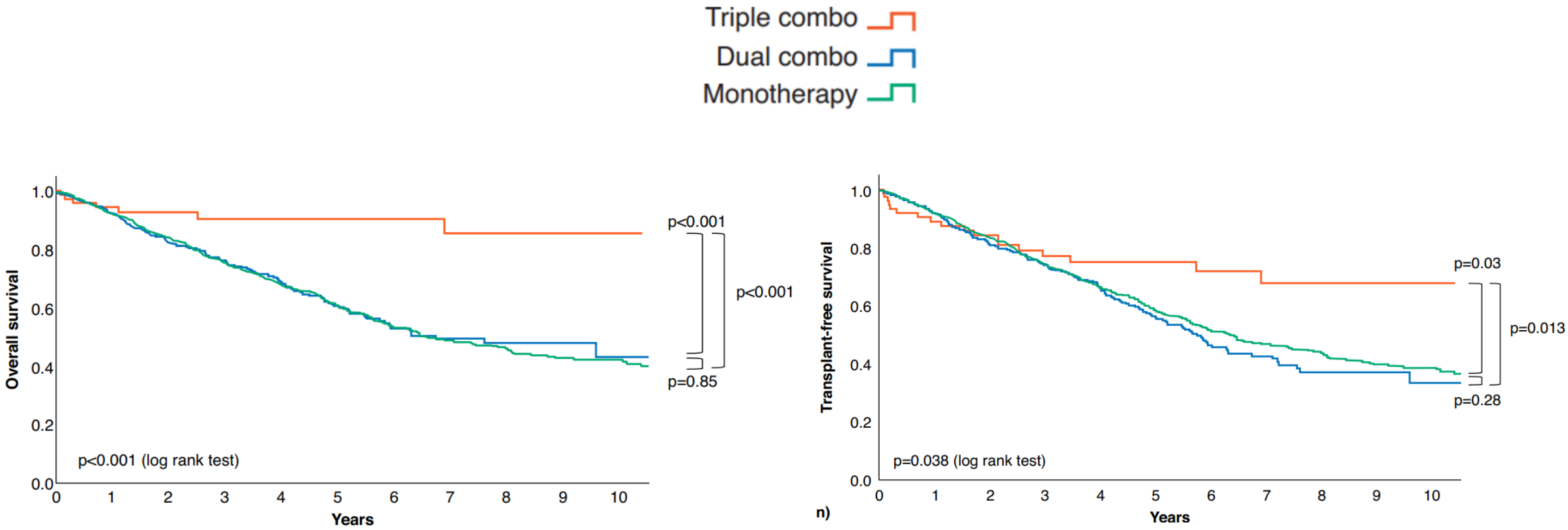
Am J Respir Crit Care Med. 2021 Oct 1;204(7):842-854

Upfront triple therapy

	Overall Study Population (*N* = 1,611)	Initial Monotherapy (*n* = 984)	Initial Dual-Combination Therapy (*n* = 551)	Initial Triple-Combination Therapy (*n* = 76)	*P* Value*
Sex, F, *n* (%)	909 (56)	538 (55)	313 (57)	58 (77)	<0.001
Age, yr	60 ± 17	63 ± 15	57 ± 17	42 ± 17	<0.001
Type of PAH, *n* (%)					<0.001
Idiopathic	1,201 (75)	735 (75)	418 (76)	48 (63)	—
Heritable	133 (8)	52 (5)	54 (10)	27 (36)	—
Anorexigen-induced	277 (17)	197 (20)	79 (14)	1 (1)	—
Comorbidities, *n* (%)					—
Hypertension	798 (50)	524 (53)	259 (47)	15 (20)	<0.001
Obesity	518 (32)	331 (34)	172 (31)	15 (20)	0.037
Diabetes	406 (25)	246 (25)	152 (28)	8 (11)	0.006
Coronary heart disease	233 (14)	147 (15)	79 (14)	7 (9)	0.39
Sleep disorders	176 (11)	114 (12)	57 (10)	5 (7)	0.34
Thyroid disorders	175 (11)	105 (11)	65 (12)	5 (7)	0.37
Atrial fibrillation	150 (9)	95 (10)	54 (10)	1 (1)	0.048
History of cancer	112 (7)	67 (7)	44 (8)	1 (1)	0.10
Renal insufficiency	79 (5)	55 (5)	24 (4)	5 (7)	0.49
Body mass index, kg/m^2	28 ± 9	29 ± 9	28 ± 7	26 ± 6	0.015
NYHA functional class, *n* (%)					<0.001
II	401 (25)	295 (30)	105 (19)	1 (2)	—
III	964 (60)	581 (59)	341 (62)	42 (55)	—
IV	246 (15)	108 (11)	105 (19)	33 (43)	—
6-minute-walk distance, m	280 ± 154	286 ± 145	277 ± 165	226 ± 179	0.011
BNP, ng · L^{-1} (*n* = 855)	253 (100–543)	205 (79–430)	316 (134–697)	404 (182–585)	<0.001
NT-proBNP, ng · L^{-1} (*n* = 380)	1,288 (454–3,003)	1,021 (289–2,344)	1,368 (645–3,174)	3,010 (1,150–3,801)	<0.001
Hemodynamics					—
Right atrial pressure, mm Hg	9 ± 5	9 ± 5	9 ± 5	11 ± 6	<0.001
Mean pulmonary artery pressure, mm Hg	49 ± 13	46 ± 11	52 ± 12	63 ± 19	<0.001
Pulmonary artery wedge pressure, mm Hg	10 ± 4	10 ± 4	9 ± 4	9 ± 4	0.001
Cardiac index, L · min^{-1} · m^{-2}	2.4 ± 0.7	2.5 ± 0.7	2.2 ± 0.6	1.8 ± 0.5	<0.001
Pulmonary vascular resistance, Wood units	10 ± 5	9 ± 4	12 ± 5	19 ± 7	<0.001
Sv_{O2}, % (*n* = 832)	61 ± 11	63 ± 10	60 ± 11	53 ± 11	<0.001
Risk status, *n* (%)					<0.001
Low risk	234 (15)	178 (18)	56 (10)	0	—
Intermediate risk	1,134 (70)	714 (73)	382 (69)	38 (50)	—
High risk	243 (15)	92 (9)	113 (21)	38 (50)	—

Am J Respir Crit Care Med. 2021 Oct 1;204(7):842-854

Upfront triple therapy



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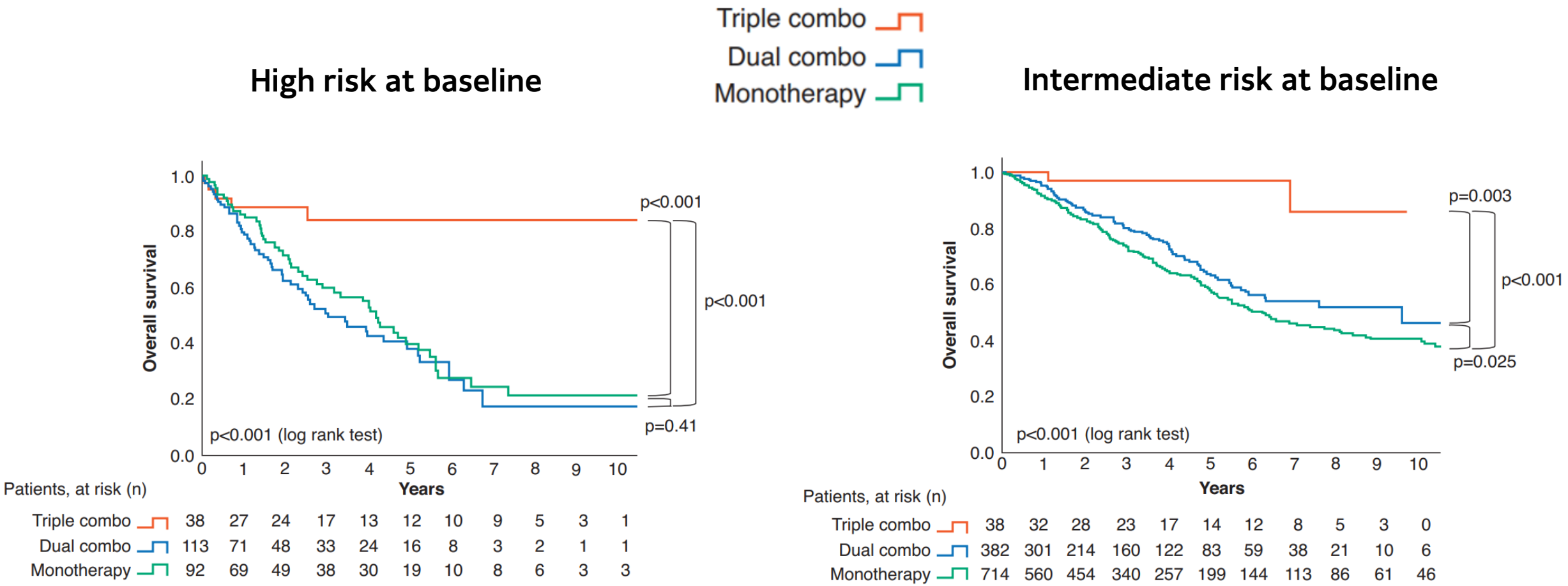
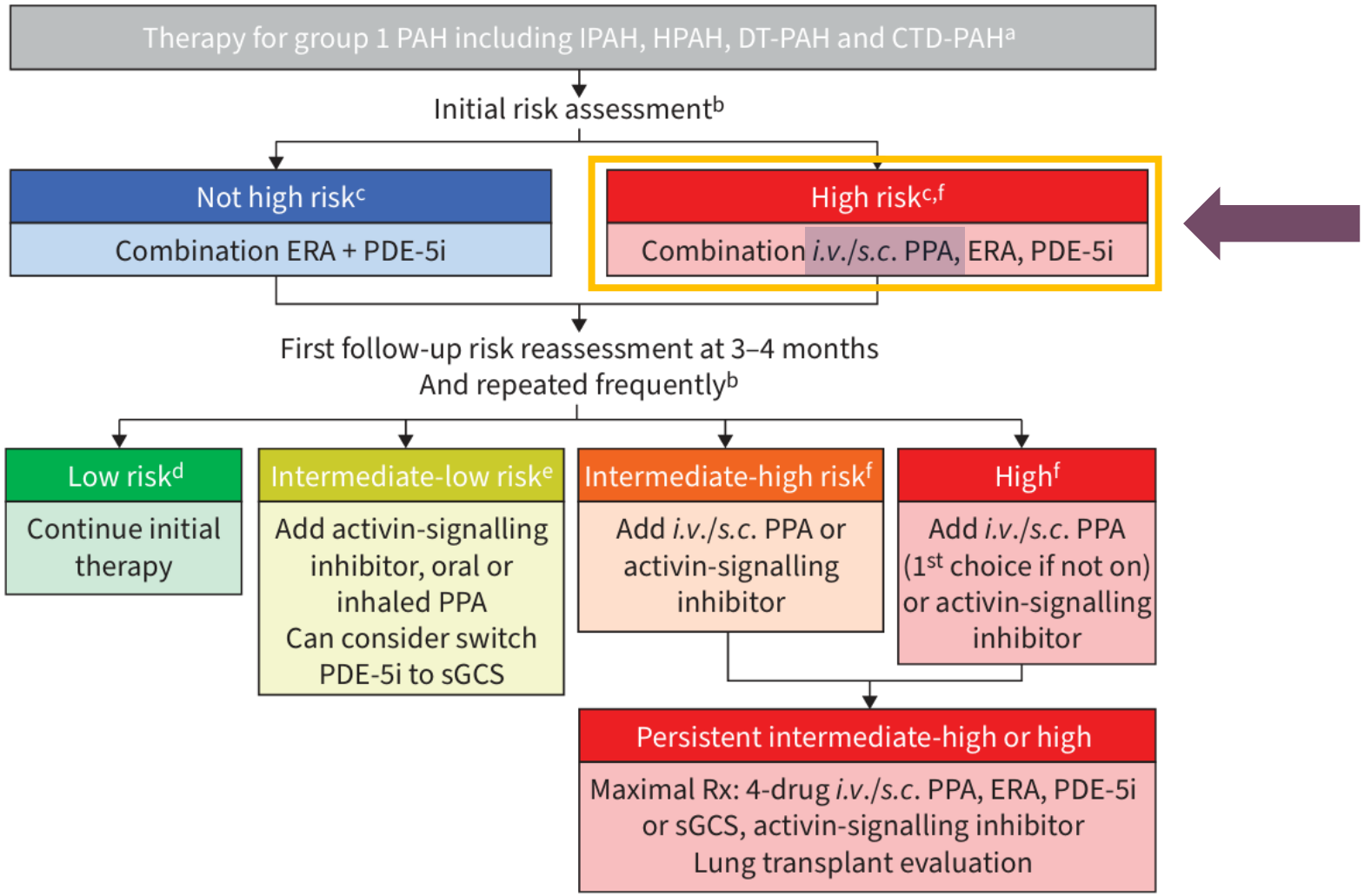
Upfront triple therapy



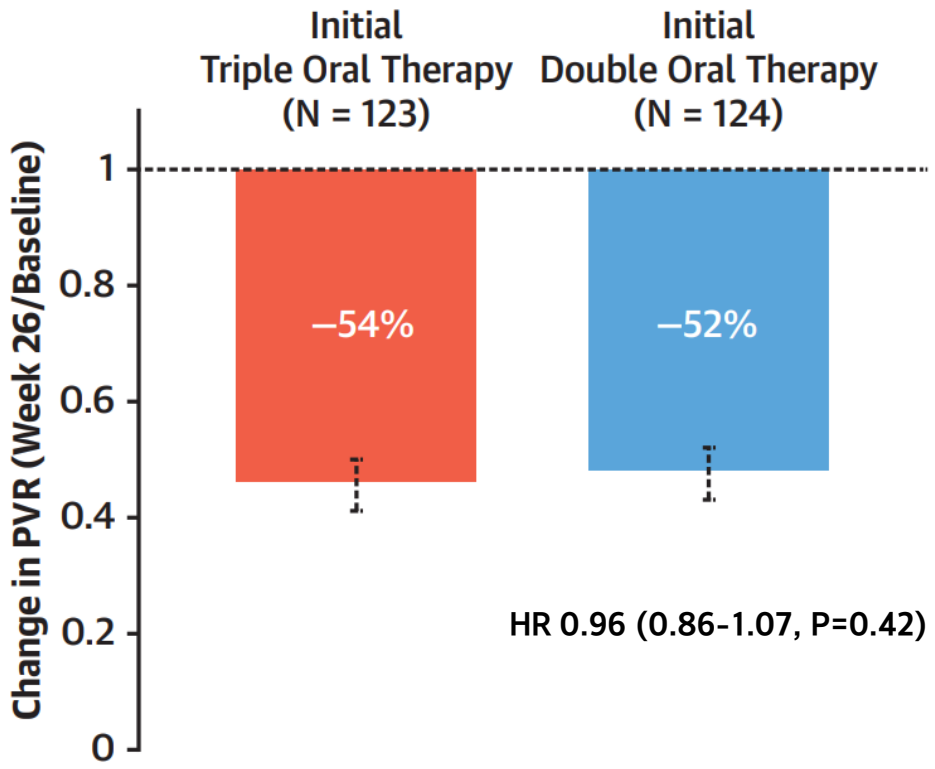
Am J Respir Crit Care Med. 2021 Oct 1;204(7):842-854



Eur Respir J. 2024 Oct 31;64(4):2401325

Upfront triple therapy with PO PPA

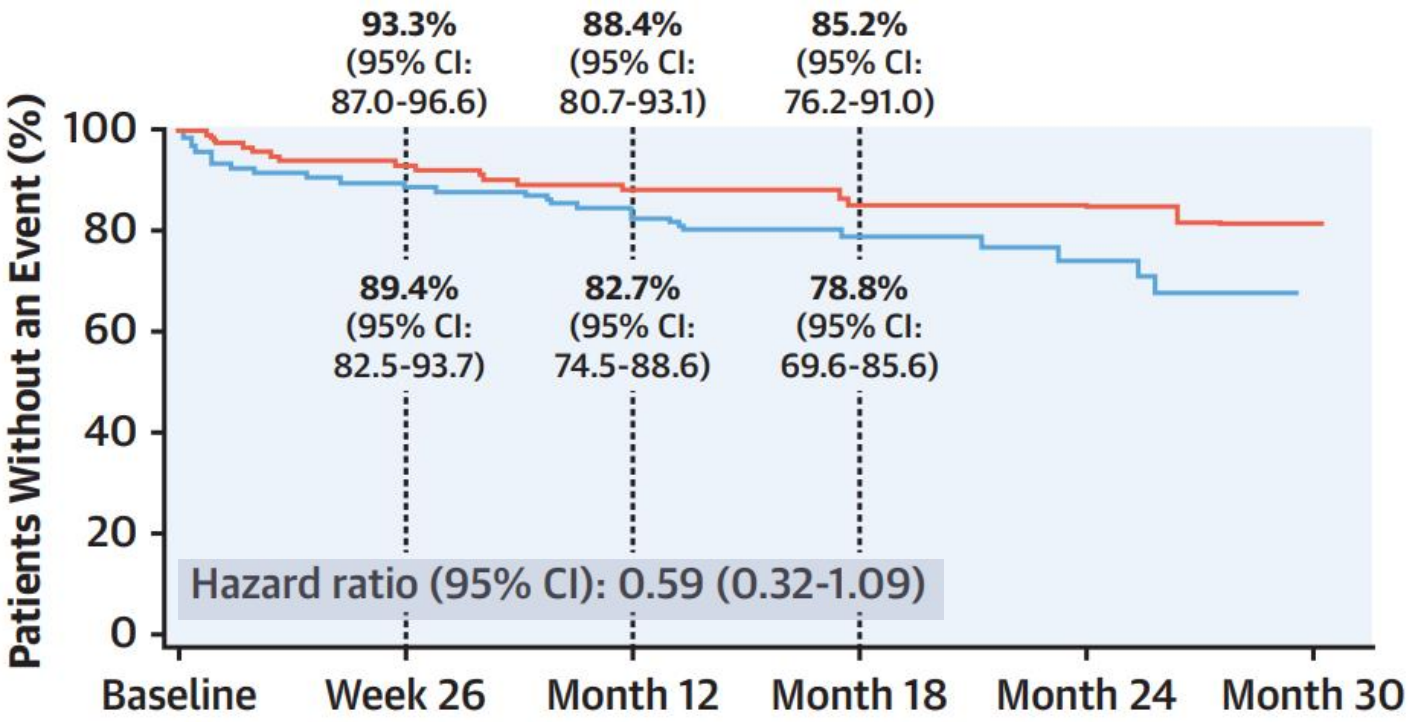
- **TRITON study**
  - ✓ Macitentan + Tadalafil + Selexipag (*n* = 123)
    vs. Macitentan + Tadalafil + Placebo (*n* = 124)
  - ✓ Eligible participants
    - ✓ Group 1 PH
    - ✓ PVR ≥6WU & 6MWT ≥50m
    - ✓ Naïve to PAH treatment
  - ✓ Primary outcome
    - ✓ PVR at 26 weeks



J Am Coll Cardiol. 2021 Oct 5;78(14):1393-1403

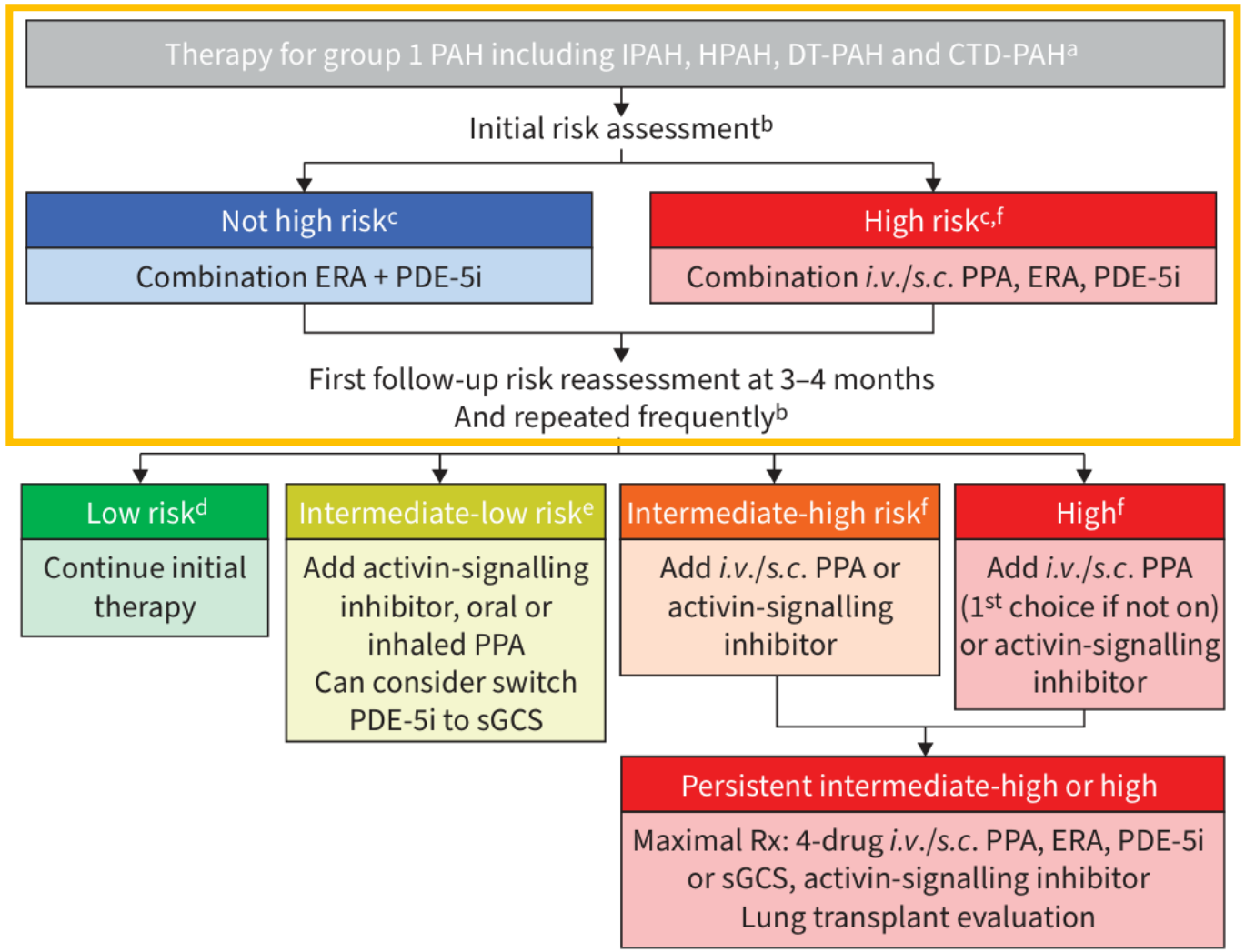
Upfront triple therapy with PO PPA

Disease progression event
- Hospitalization for worsening
- Clinical worsening of PAH
- Initiation of prostacyclin for worsening
- Death



Patients at risk:						
Initial Triple Oral Therapy	123	108	78	53	31	15
Initial Double Oral Therapy	124	109	80	48	25	12

J Am Coll Cardiol. 2021 Oct 5;78(14):1393-1403

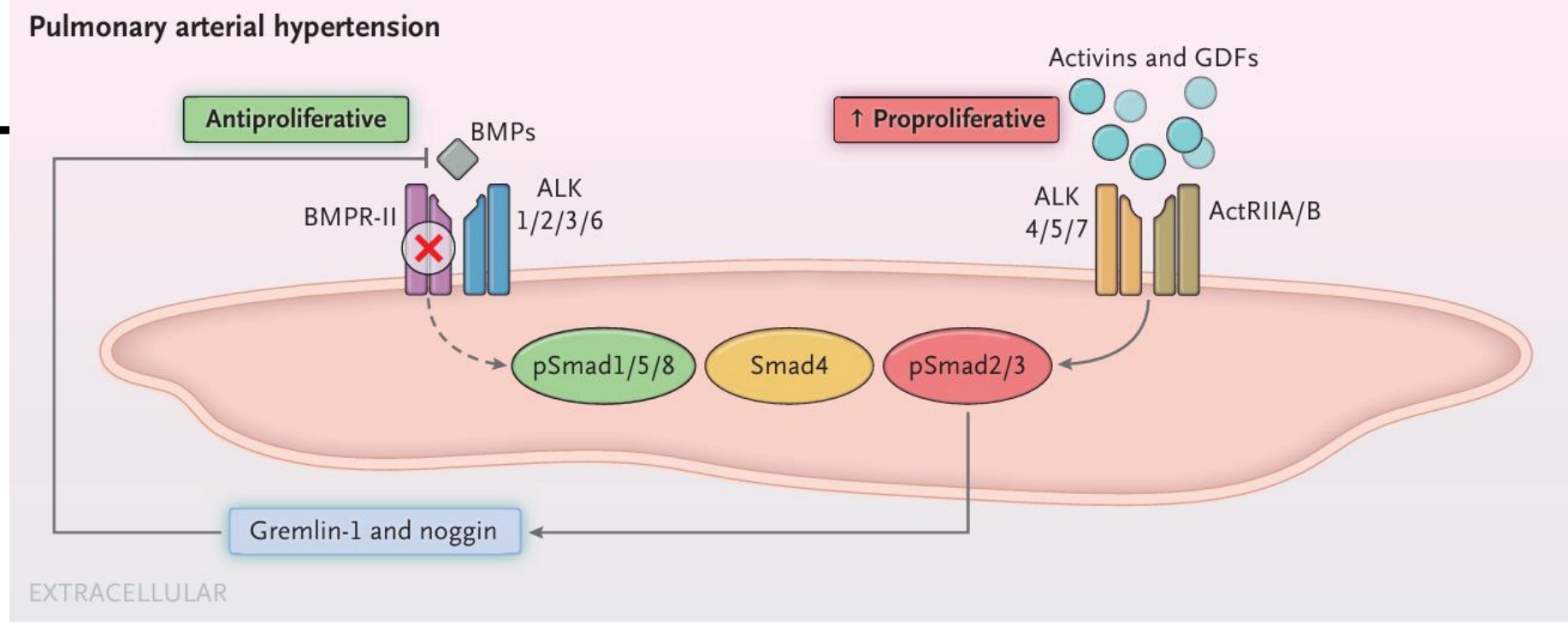


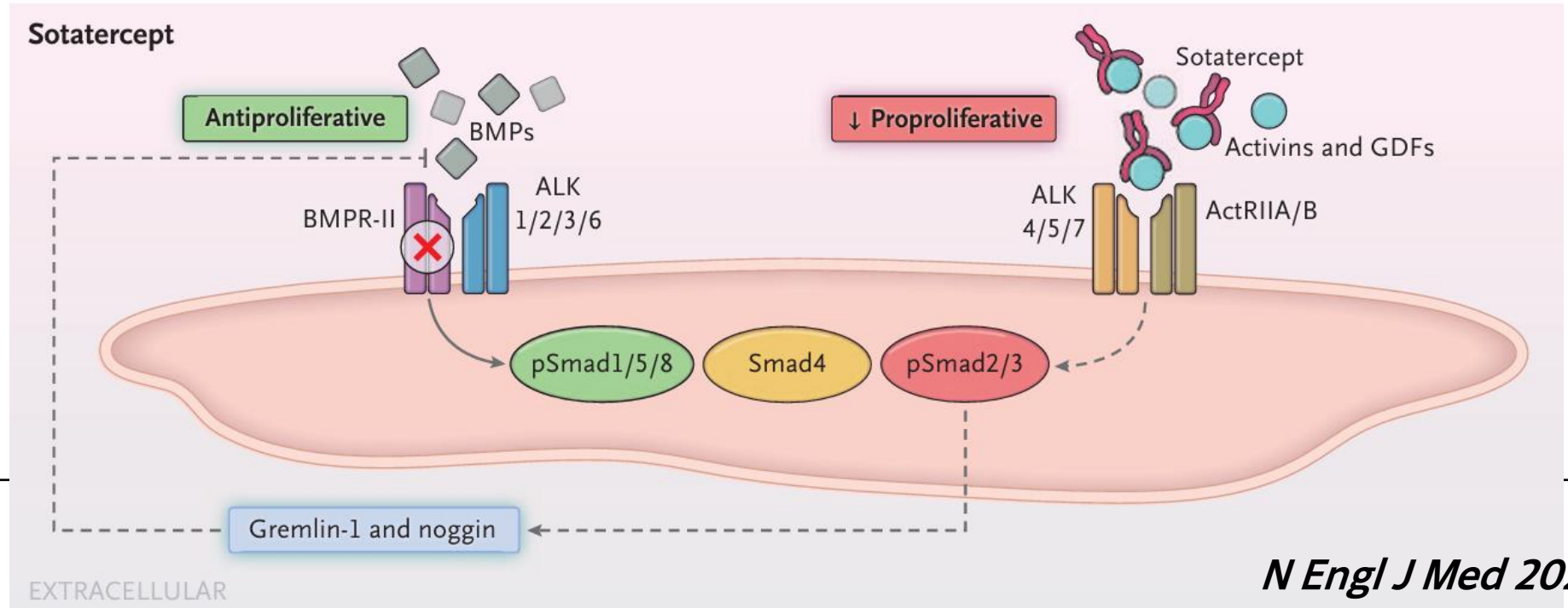
Eur Respir J. 2024 Oct 31;64(4):2401325

Adverse Effects of PAH Target Agents

Class	Major Adverse Effects	Frequency
ERA	LFT elevation, peripheral edema, anemia, headache	Common
PDE5i	Headache, flushing, visual disturbance, myalgia	Common
sGC stimulator	Hypotension, headache, nausea, dizziness	Common
Prostacyclin analogues	Flushing, headache, jaw pain, nausea, diarrhea, hypotension, site reaction	Very common
IP receptor agonist	Headache, diarrhea, jaw pain, myalgia, nausea, vomiting	Very common

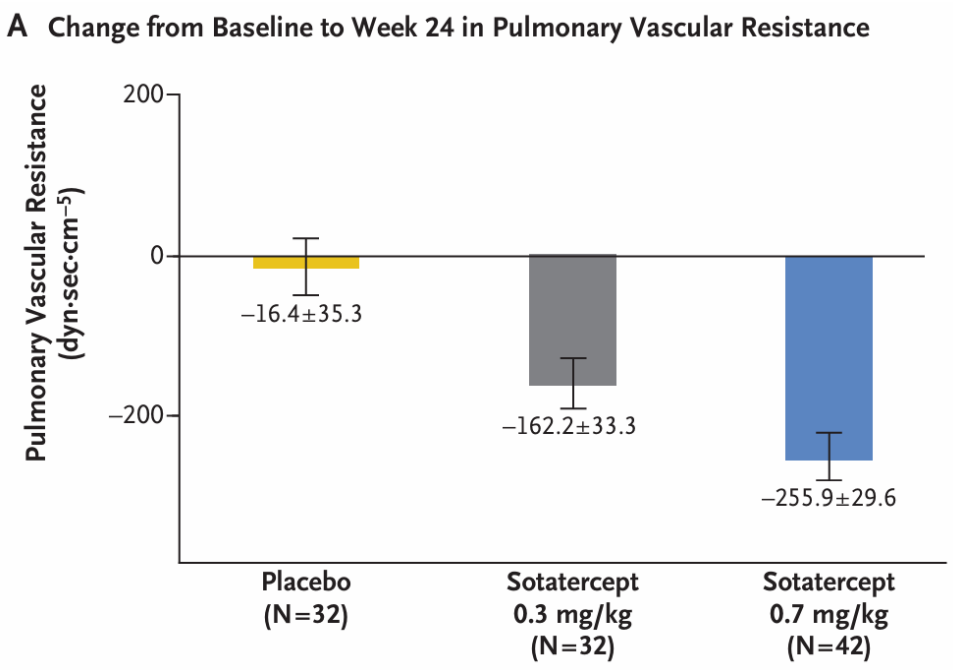
	Starting dose	Target dose
Calcium channel blockers		
Amlodipine	5 mg o.d.	15–30 mg o.d.[a]
Diltiazem	60 mg b.i.d.[b]	120–360 mg b.i.d.[b]
Felodipine	5 mg o.d.	15–30 mg o.d.[a]
Nifedipine	10 mg t.i.d.	20–60 mg b.i.d. or t.i.d.
Endothelin receptor antagonists (oral administration)		
Ambrisentan	5 mg o.d.	10 mg o.d.
Bosentan	62.5 mg b.i.d.	125 mg b.i.d.
Macitentan	10 mg o.d.	10 mg o.d.
Phosphodiesterase 5 inhibitors (oral administration)		
Sildenafil	20 mg t.i.d.	20 mg t.i.d.[c]
Tadalafil	20 or 40 mg o.d.	40 mg o.d.
Prostacyclin analogues (oral administration)		
Beraprost sodium	20 µg t.i.d.	Maximum tolerated dose up to 40 µg t.i.d.
Beraprost extended release	60 µg b.i.d.	Maximum tolerated dose up to 180 µg b.i.d.
Treprostinil	0.25 mg b.i.d. or 0.125 mg t.i.d.	Maximum tolerated dose
Prostacyclin receptor agonist (oral administration)		
Selexipag	200 µg b.i.d.	Maximum tolerated dose up to 1600 µg b.i.d.
Soluble guanylate cyclase stimulator (oral administration)		
Riociguat[d]	1 mg t.i.d.	2.5 mg t.i.d.
Prostacyclin analogues (inhaled administration)		
Iloprost[e]	2.5 µg 6–9 times per day	5.0 µg 6–9 times per day
Treprostinil[e]	18 µg 4 times per day	54–72 µg 4 times per day
Prostacyclin analogues (i.v. or s.c. administration)		
Epoprostenol i.v.	2 ng/kg/min	Determined by tolerability and effectiveness; typical dose range at 1 year is 16–30 ng/kg/min, with wide individual variability
Treprostinil s.c. or i.v.	1.25 ng/kg/min	Determined by tolerability and effectiveness; typical dose range at 1 year is 25–60 ng/kg/min, with wide individual variability

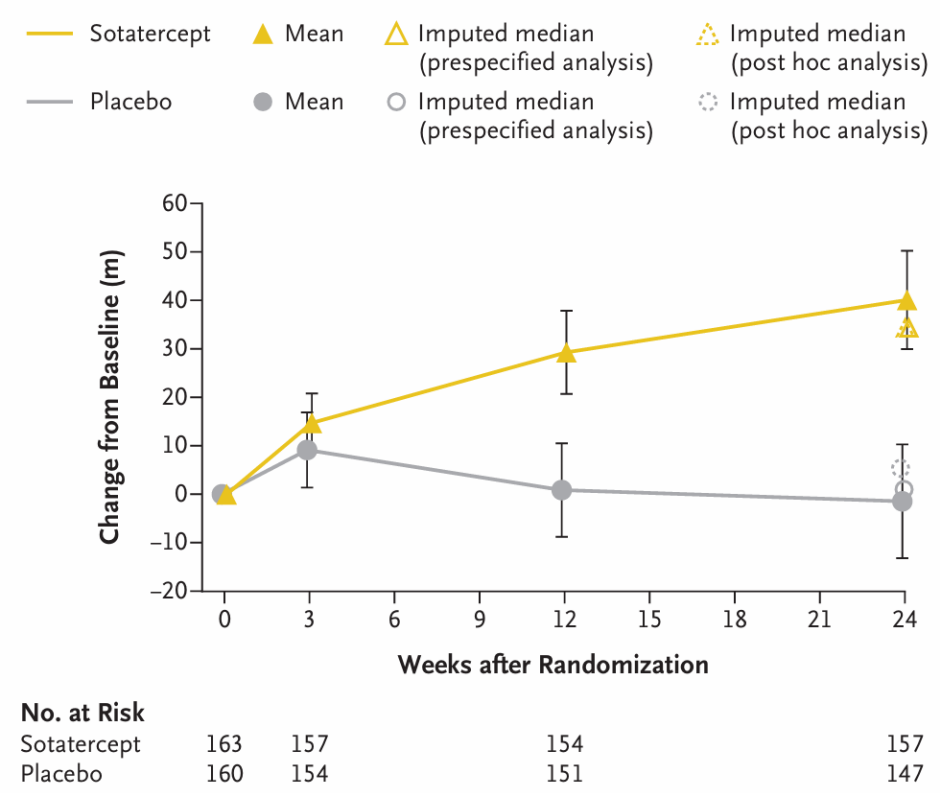




N Engl J Med 2021;384:1204-15

Sotatercept





N Engl J Med 2021;384:1204-15, N Engl J Med 2023;388:1478-90

Sotatercept

Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension

M.M. Hoeper, D.B. Badesch, H.A. Ghofrani, J.S.R. Gibbs, M. Gomberg-Maitland, V.V. McLaughlin, I.R. Preston, R. Souza, A.B. Waxman, E. Grünig, G. Kopeć, G. Meyer, K.M. Olsson, S. Rosenkranz, Y. Xu, B. Miller, M. Fowler, J. Butler, J. Koglin, J. de Oliveira Pena, and M. Humbert, for the STELLAR Trial Investigators*

Sotatercept in Patients with Pulmonary Arterial Hypertension at High Risk for Death

Marc Humbert, M.D., Ph.D.,[1] Vallerie V. McLaughlin, M.D.,[2] David B. Badesch, M.D.,[3] H. Ardeschir Ghofrani, M.D.,[4] J. Simon R. Gibbs, M.D.,[5] Mardi Gomberg-Maitland, M.D.,[6] Ioana R. Preston, M.D.,[7] Rogerio Souza, M.D., Ph.D.,[8] Aaron B. Waxman, M.D., Ph.D.,[9] Victor M. Moles, M.D.,[2] Laurent Savale, M.D., Ph.D.,[1] Carmine Dario Vizza, M.D.,[10] Stephan Rosenkranz, M.D.,[11] Yaru Shi, Ph.D.,[12] Barry Miller, M.S.,[12] Harald S. Mackenzie, M.B., Ch.B.,[12] Samuel S. Kim, Ph.D.,[12] Maria José Loureiro, M.D.,[12] Mahesh J. Patel, M.D.,[12] Joerg Koglin, M.D., Ph.D.,[12] Alexandra G. Cornell, M.D.,[12] and Marius M. Hoeper, M.D.,[13] for the ZENITH Trial Investigators*

N Engl J Med 2023;388:1478-90, N Engl J Med 2025;392:1987-2000

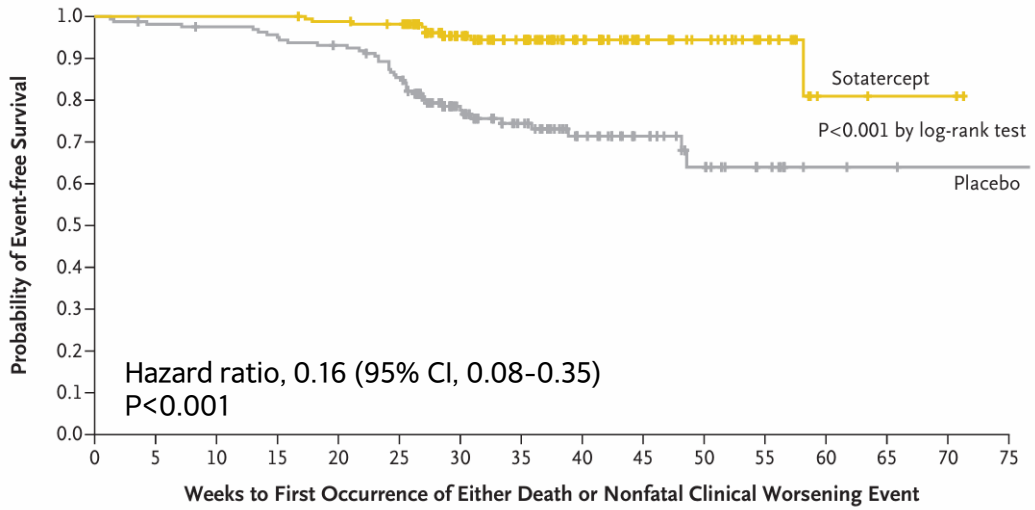
Study design

- **STELLAR study**
  - ✓ Sotatercept (*n* = 163) *vs.* Placebo (*n* = 160)
  - ✓ Eligible participants
    - ✓ Group 1 PH & ≥18 years of age
    - ✓ WHO FC II or III
    - ✓ PVR ≥5WU & 500m≥ 6MWD ≥150m
    - ✓ Stable background therapy for PAH
  - ✓ Primary outcome
    - ✓ Change in 6MWD at 24 weeks
- **ZENITH study**
  - ✓ Sotatercept (*n* = 86) *vs.* Placebo (*n* = 86)
  - ✓ Eligible participants
    - ✓ Group 1 PH & 18-75 years of age
    - ✓ WHO FC III or IV
    - ✓ REVEAL Lite 2 risk score ≥8 & PVR ≥5WU
    - ✓ Stable maximum tolerated doses of double or triple therapy
  - ✓ Primary outcome
    - ✓ All-cause death + Lung T + hospitalization for worsening PAH

N Engl J Med 2023;388:1478-90, N Engl J Med 2025;392:1987-2000

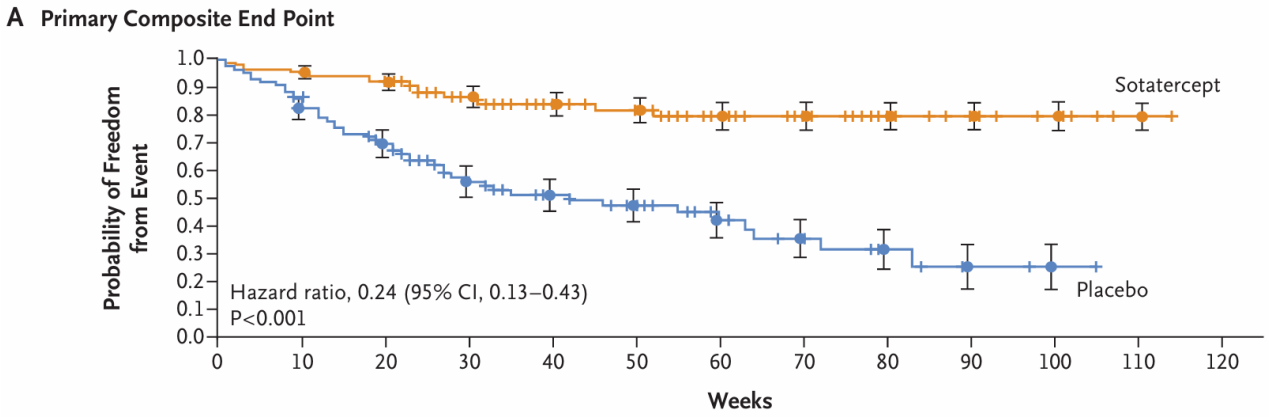
Study outcome

STELLAR study



No. at Risk															
Sotatercept	163	163	163	163	160	157	111	89	60	37	28	15	3	2	2	0
Placebo	160	156	154	151	146	133	83	59	38	27	16	9	3	2	1	1

ZENITH study



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

N Engl J Med 2023;388:1478-90, N Engl J Med 2025;392:1987-2000

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

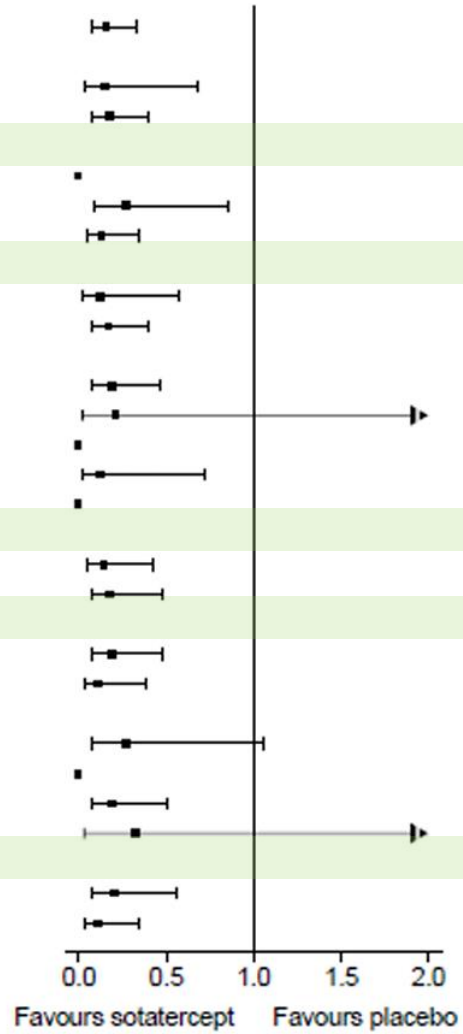
Characteristic	Sotatercept (N=163)	Placebo (N=160)	Total (N=323)
Female sex — no. (%)	129 (79.1)	127 (79.4)	256 (79.3)
Age — yr	47.6±14.1	48.3±15.5	47.9±14.8
Geographic region — no. (%)			
North America	49 (30.1)	56 (35.0)	105 (32.5)
South America	13 (8.0)	15 (9.4)	28 (8.7)
Europe	91 (55.8)	77 (48.1)	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)

Table 1. Demographic and Baseline Clinical Characteristics.*

Characteristic	Sotatercept (N=86)	Placebo (N=86)	Total (N=172)
Female sex — no. (%)	61 (70.9)	71 (82.6)	132 (76.7)
Age — yr	55.3±14.3	53.5±14.3	54.4±14.3
Race — no. (%)†			
White	73 (84.9)	76 (88.4)	149 (86.6)
Other‡	12 (14.0)	10 (11.6)	22 (12.8)
Missing	1 (1.2)	0	1 (0.6)
Body-mass index ≥30 — no. (%)§	14 (16.3)	19 (22.1)	33 (19.2)
Time since diagnosis of pulmonary arterial hypertension — yr¶	7.2±5.6	8.2±6.7	7.7±6.2
Classification of pulmonary arterial hypertension — no. (%)			
Idiopathic	42 (48.8)	44 (51.2)	86 (50.0)
Heritable	11 (12.8)	7 (8.1)	18 (10.5)
Associated with connective-tissue disease	22 (25.6)	26 (30.2)	48 (27.9)
Drug-induced or toxin-induced	6 (7.0)	5 (5.8)	11 (6.4)
Associated with corrected congenital shunts	5 (5.8)	4 (4.7)	9 (5.2)
REVEAL Lite 2 risk score — no. (%)‖			
8–10	60 (69.8)	60 (69.8)	120 (69.8)
≥11	26 (30.2)	26 (30.2)	52 (30.2)
WHO functional class — no. (%)**			
III	66 (76.7)	62 (72.1)	128 (74.4)
IV	20 (23.3)	24 (27.9)	44 (25.6)
Background therapy for pulmonary arterial hypertension — no. (%)††			
Prostacyclin infusion therapy‡‡	53 (61.6)	49 (57.0)	102 (59.3)
Double therapy	21 (24.4)	27 (31.4)	48 (27.9)
Triple therapy	65 (75.6)	59 (68.6)	124 (72.1)
6-Minute walk distance — m	270.3±104.8	270.7±99.9	270.5±102.1
NT-proBNP — pg/ml	3603.1±4101.2	2687.3±2771.2	3145.2±3519.8
Mean pulmonary artery pressure — mm Hg	57.0±13.4	55.2±12.1	56.1±12.8
Pulmonary vascular resistance — dyn·sec·cm^{-5}	883.2±410.9	874.7±344.2	879.0±378.2
Cardiac index — liters/min/m^2	2.6±0.6	2.6±0.8	2.6±0.7
Pulmonary artery wedge pressure — mm Hg	10.0±3.3	9.8±3.1	9.9±3.2
Hemoglobin — g/dl	12.9±1.9	12.9±1.9	12.9±1.9
Estimated glomerular filtration rate — ml/min/1.73 m^2	65.1±24.6	73.5±29.7	69.3±27.5

b)

Subgroup	Placebo (n=192) n	Sotatercept (n=237) n	Sotatercept *versus* placebo Hazard ratio (95% CI)	Sotatercept *versus* placebo Hazard ratio† (95% CI)
Overall	192	237		0.16 (0.08, 0.33)
Sex				
Male	39	42		0.15 (0.03, 0.67)
Female	153	195		0.18 (0.08, 0.40)
Background therapy at baseline				
Monotherapy	6	17		0.00 (NE, NE)‡
Double	69	80		0.27 (0.09, 0.85)
Triple	117	140		0.13 (0.05, 0.34)
Baseline WHO FC				
Class II	95	119		0.13 (0.03, 0.57)
Class III	97	118		0.17 (0.08, 0.40)
PAH aetiological subgroups				
iPAH	125	125		0.19 (0.08, 0.47)
hPAH	31	45		0.21 (0.02, 2.08)
Drug/toxin-induced PAH	4	13		0.00 (NE, NE)‡
Connective tissue disease	23	44		0.13 (0.02, 0.71)
Congenital heart disease with s/p shunt repair	9	10		0.00 (NE, NE)‡
Prostacylin infusion therapy at baseline				
Yes	74	94		0.15 (0.05, 0.43)
No	118	143		0.18 (0.07, 0.48)
Baseline PVR				
≤800 (dynes*sec/cm^5)	129	157		0.20 (0.08, 0.48)
>800 (dynes*sec/cm^5)	63	80		0.11 (0.03, 0.39)
Region				
North America	63	69		0.27 (0.07, 1.05)
South America	24	30		0.00 (NE, NE)‡
Europe	88	116		0.19 (0.07, 0.51)
Asia or Pacific	17	22		0.33 (0.03, 3.19)
Cardiac index				
<2.5L/min/m^2 intermediate/high risk	84	95		0.21 (0.08, 0.56)
≥2.5L/min/m^2 low risk	108	142		0.12 (0.04, 0.34)

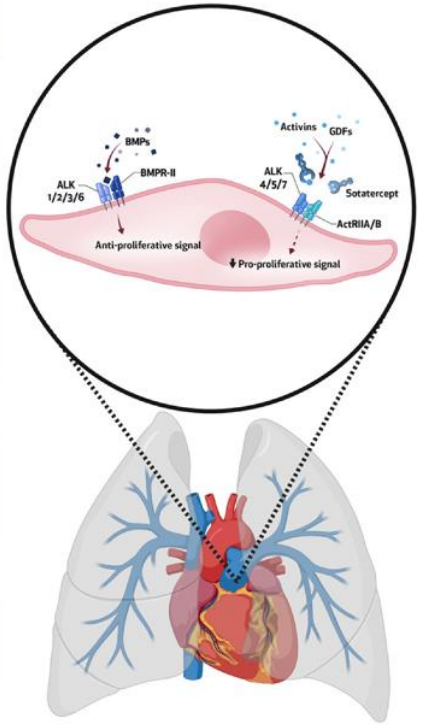


European Respiratory Journal 2025 2401424

Sotatercept for the management of pulmonary arterial hypertension

Benefits

- Increase functional exercise capacity
- Improve WHO functional class
- Decreased mPAP and PVR without a change in CO
- Reduce risk of clinical worsening events
- Improvements in patient-reported health status
- Decreased RV size and mass



Adverse Events

- 15% erythrocytosis >2 g/dL above ULN
- 3% thrombocytopenia platelets <50,000/mm3
- 36% bleeding event
  22% epistaxis
  4% serious bleeding
- 10% telangiectasia
- 25% headache
  20% rash
  15% diarrhea
  15% dizziness
  14% erythema

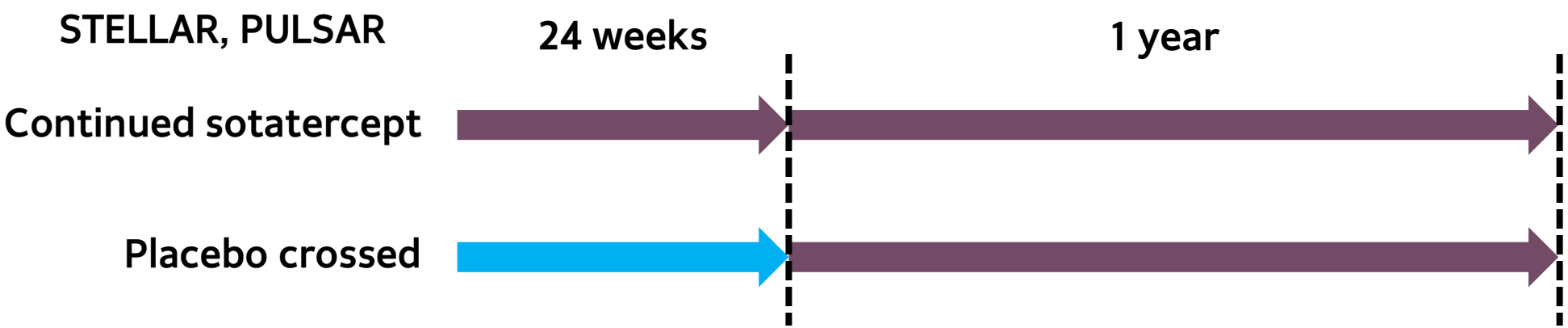
Key Unknowns

- Long-term efficacy and safety
- Impact of development of antidrug antibodies
- May cause fetal harm and infertility

J Heart Lung Transplant. 2025 Jan;44(1):1-10

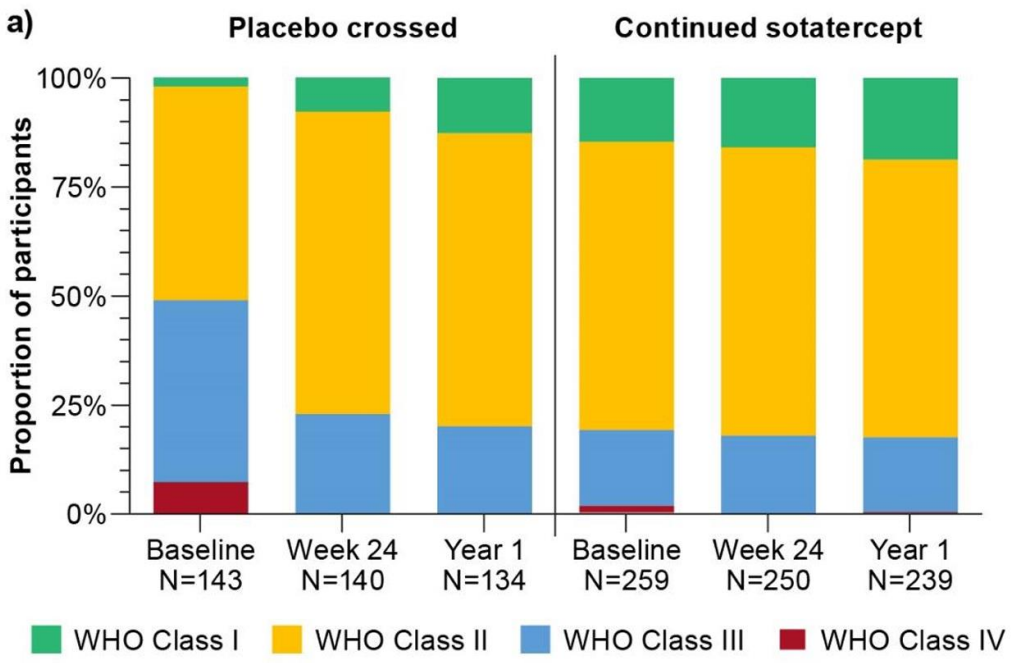
Original Research Article

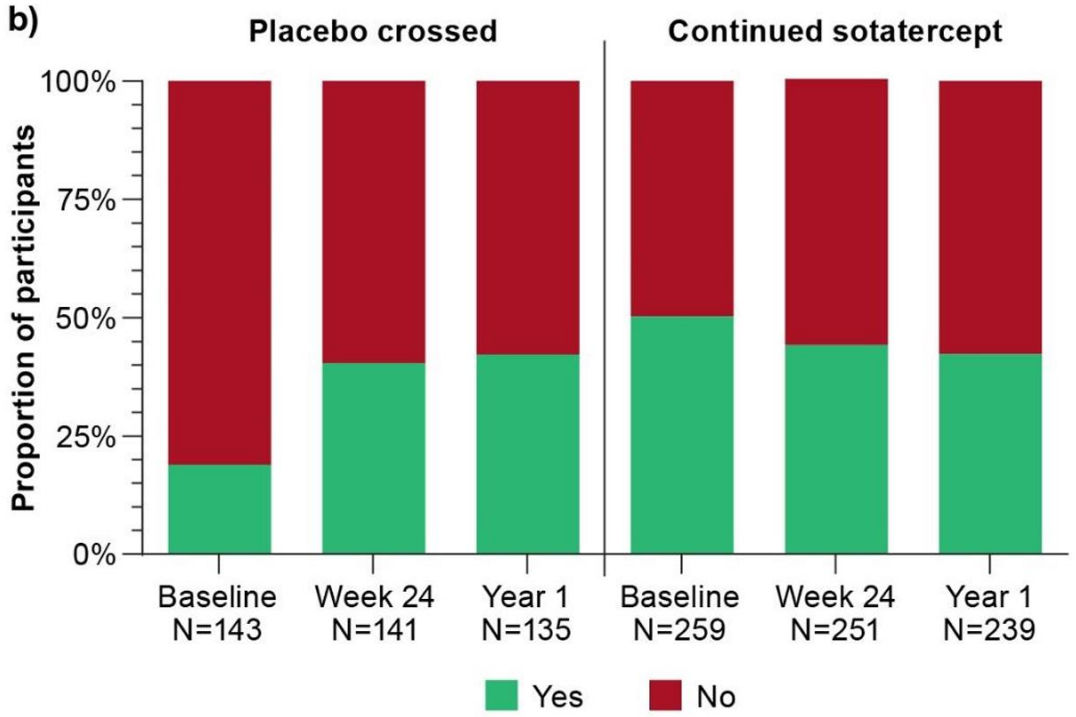
A Long-Term Follow-Up Study of Sotatercept for Treatment of Pulmonary Arterial Hypertension: Interim Results of SOTERIA



Eur Respir J. 2025 Feb 20:2401435

SOTERIA Study



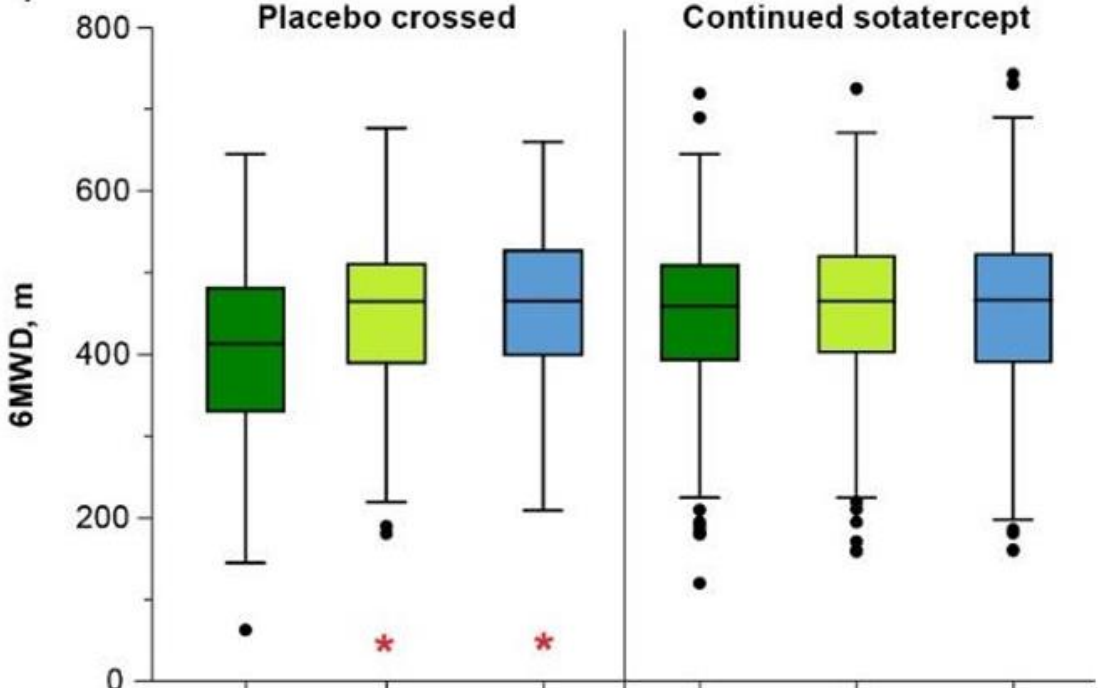


Simplified French low risk

Eur Respir J. 2025 Feb 20:2401435

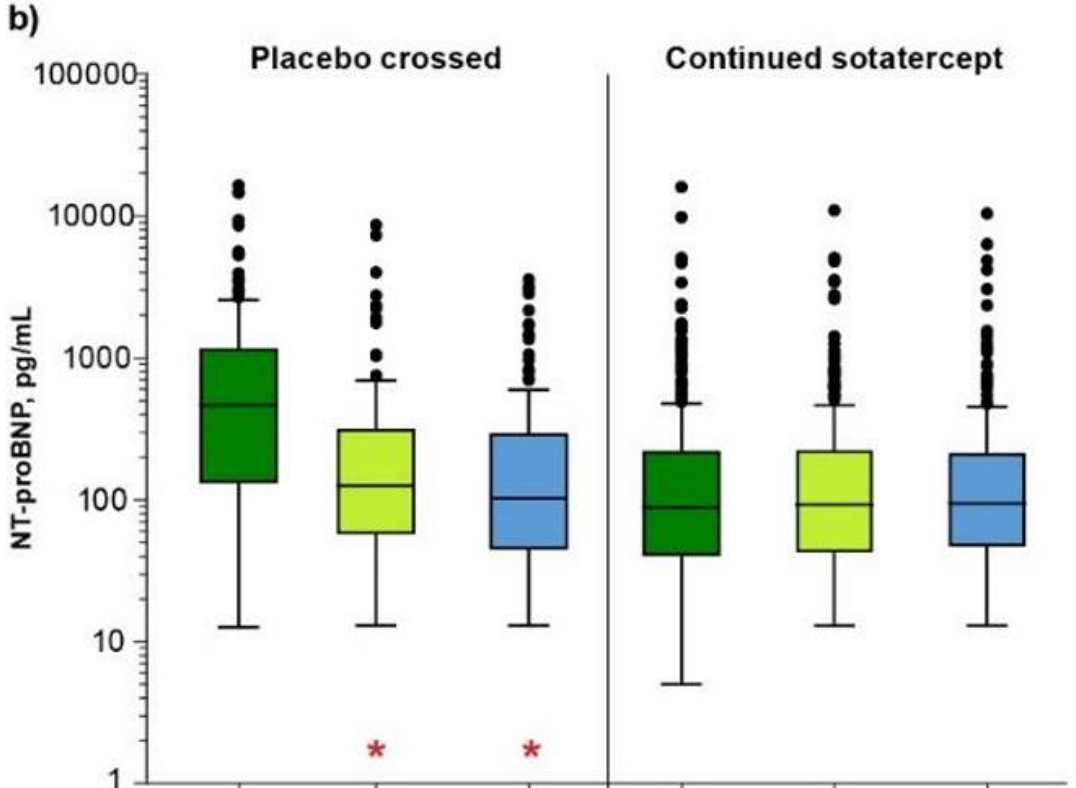
SOTERIA Study

a)



	Baseline	Week 24	Year 1	Baseline	Week 24	Year 1
	n=143	n=138	n=130	n=259	n=232	n=216
Mean	404.5	448.3	455.3	446.3	455.9	453.3
Median	413	464.6	465.3	459	465.5	466.6
Q1	330	389.3	400	393	401	390.3
Q3	482	510	527.3	510	521	522.5
Min	63	181	209	120	159	160
Max	645	677	660	719.3	725.5	743.3
*P-value Δ from baseline	–	<0.0001	<0.0001	–	0.7962	0.7532

b)



	Baseline	Week 24	Year 1	Baseline	Week 24	Year 1
	n=143	n=128	n=125	n=259	n=226	n=211
Mean	1245.5	437.9	339.9	364.8	314.7	326.6
Median	467	126	102	88	92	94
Q1	135.5	58.8	47	41	44	47.5
Q3	1137.5	307.3	290	216	221.5	211.5
Min	12.7	13	13	5	13	13
Max	16477	8674	3561	16007	11017	10431
*P-value Δ from baseline	–	<0.0001	<0.0001	–	0.3910	0.5215

Eur Respir J. 2025 Feb 20:2401435

SOTERIA Study

Table S5. Change From Baseline[a] at Week 24 and Year 1 in Clinical Parameters

	Placebo-Crossed			Continued Sotatercept			Blinded			Total		
	Baseline	Week 24	Year 1	Baseline	Week 24	Year 1	Baseline	Week 24	Year 1	Baseline	Week 24	Year 1
6MWD, m												
N	143	138	130	259	232	214	24	10	3	426	380	347
Mean (SD)	404.5 (103.3)	448.3 (93.1)	455.3 (91.8)	446.3 (104.6)	455.9 (100.7)	452.8 (106.1)	235.0 (129.1)	300.2 (99.6)	364.0 (63.5)	420.4 (116.4)	449.0 (100.8)	453.1 (100.7)
Mean (SD) change from baseline	—	41.3 (74.3)	47.3 (80.7)	—	−0.02 (37.2)	−1.7 (47.6)	—	92.9 (94.2)	122.0 (201.3)	—	17.4 (59.9)	17.8 (68.7)
p-value	—	<0.0001	<0.0001	—	0.80	0.75	—	0.02	0.08	—	<0.0001	<0.0001
NT-proBNP, pg/mL												
N	143	128	125	259	226	211	24	9	3	426	363	339
Mean (SD)	1245.5 (2519.8)	437.9 (1124.7)	339.9 (642.3)	364.8 (1279.1)	314.7 (953.0)	326.6 (981.9)	4926.8 (6668.9)	828.7 (1397.0)	189.7 (147.1)	917.5 (2579.1)	370.9 (1029.7)	330.3 (866.4)
Mean (SD) change from baseline	—	−828.3 (1861.5)	−826.9 (2099.1)	—	−31.0 (987.4)	−32.8 (1145.3)	—	−3436.0 (4388.3)	−1806.3 (2165.3)	—	−396.6 (1620.6)	−341.3 (1620.1)
p-value	—	<0.0001	<0.0001	—	0.39	0.52	—	<0.0001	0.01	—	<0.0001	<0.0001
WHO-FC II/I												
N	143	140	134	259	250	239	24	10	3	426	400	376
n (%)	73 (51.0)	108 (77.1)	107 (79.9)	209 (80.7)	205 (82.0)	197 (82.4)	1 (4.2)	3 (30)	1 (33.3)	283 (66.4)	316 (79.0)	305 (81.1)
Low French risk score												
N	143	141	135	259	251	239	24	10	3	426	402	377
Yes[b], n (%)	27 (18.9)	57 (40.4)	57 (42.2)	130 (50.2)	110 (43.8)	101 (42.3)	0	0	0	157 (36.9)	167 (41.5)	158 (41.9)

Eur Respir J. 2025 Feb 20:2401435

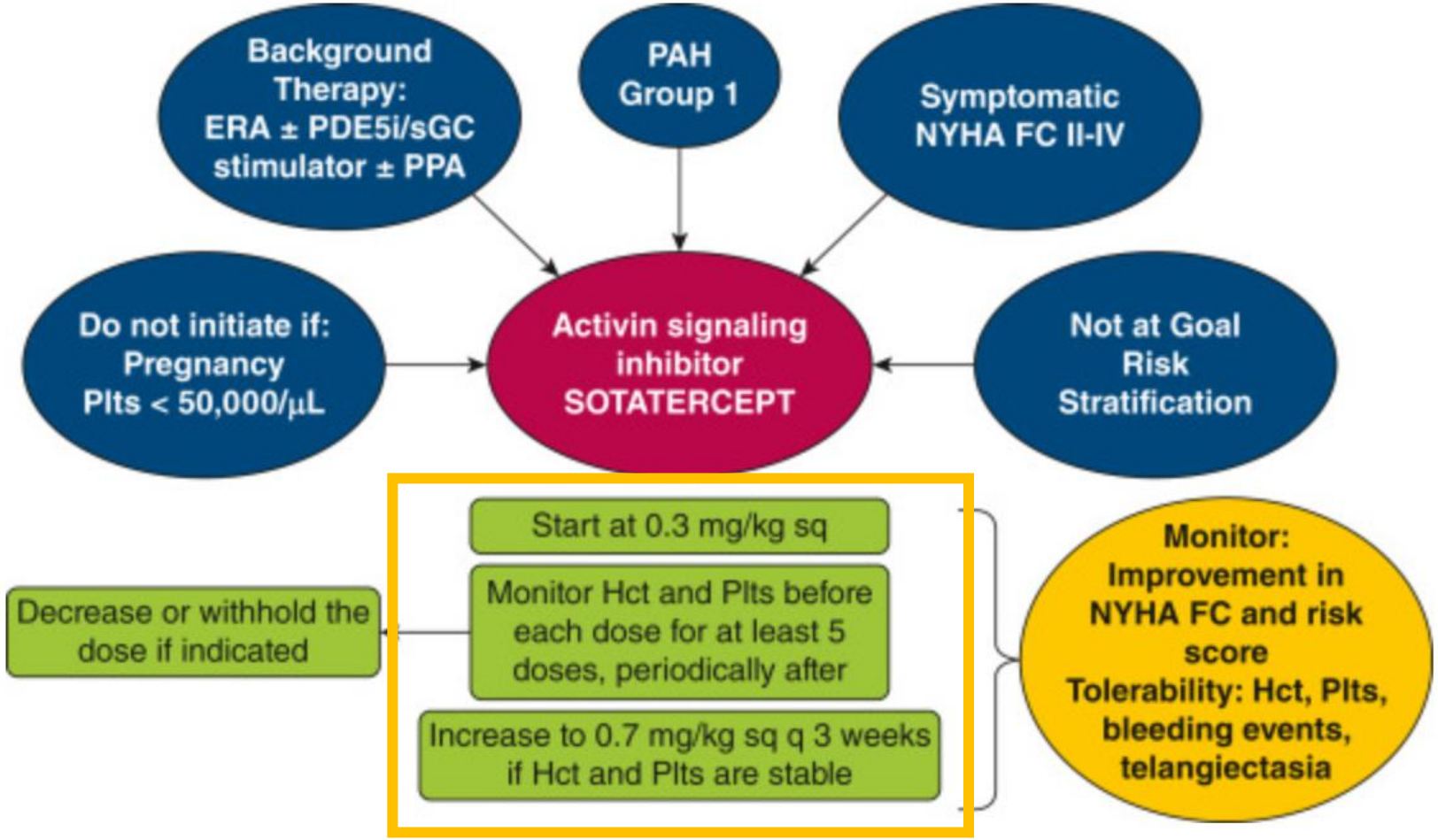
No. (%) of participants	Placebo Crossed (N=143)	Continued Sotatercept (N=259)	Blinded (N=24)	All Participants (N=426)
Any TEAE	131 (91.6)	240 (92.7)	16 (66.7)	387 (90.8)
TEAE related to treatment	79 (55.2)	126 (48.6)	5 (20.8)	210 (49.3)
TEAE leading to treatment discontinuation	2 (1.4)	12 (4.6)	1 (4.2)	15 (3.5)
TEAE leading to study discontinuation	4 (2.8)	10 (3.9)	2 (8.3)	16 (3.8)
TEAE leading to death	4 (2.8)	6 (2.3)	2 (8.3)	12 (2.8)
Any serious TEAE	41 (28.7)	80 (30.9)	8 (33.3)	129 (30.3)
Serious TEAE related to treatment	5 (3.5)	6 (2.3)	0 (0.0)	11 (2.6)
Serious TEAE leading to treatment discontinuation	1 (0.7)	9 (3.5)	1 (4.2)	11 (2.6)
Serious TEAE leading to study discontinuation	3 (2.1)	8 (3.1)	2 (8.3)	13 (3.1)
Serious TEAE leading to death	**4 (2.8)**	**6 (2.3)**	**2 (8.3)**	**12 (2.8)**
Adenocarcinoma of colon	1 (0.7)	0	0	1 (0.2)
Brain neoplasm malignant	0	1 (0.4)	0	1 (0.2)
Bronchopulmonary aspergillosis	0	1 (0.4)	0	1 (0.2)
Gastrointestinal hemorrhage	1 (0.7)	1 (0.4)	0	2 (0.5)
Multiple organ dysfunction syndrome	1 (0.7)	0	0	1 (0.2)
Pneumonia	0	1 (0.4)	0	1 (0.2)
Respiratory failure	0	0	1 (4.2)	1 (0.2)
Right ventricular failure	0	2 (0.8)	1 (4.2)	3 (0.7)
Sepsis	1 (0.7)	0	0	1 (0.2)
Dose holds				
One dose hold	19 (13.3)	33 (12.7)	4 (16.7)	56 (13.1)
Two or more dose holds	16 (11.2)	43 (16.6)	0	59 (13.8)
Median (range) time to first dose hold, days	220 (1 to 492)	165.5 (1 to 722)	45.5 (23 to 85)	168 (1 to 722)
Dose reductions				
One dose reduction	28 (19.6)	43 (16.6)	2 (8.3)	73 (17.1)
Two or more dose reductions	8 (5.6)	16 (6.2)	0	24 (5.6)
Median (range) time to first dose reduction, days	174 (1 to 501)	114.0 (1 to 624)	96.5 (86 to 107)	147 (1 to 624)

115 (27.0%)

97 (22.8%)

Eur Respir J. 2025 Feb 20:2401435

Sotatercept



CHEST 2024; 166(3):604-611

Completed

Study of Sotatercept in Newly Diagnosed Intermediate- and High-Risk PAH Participants (MK-7962-005/A011-13) (HYPERION)

ClinicalTrials.gov ID NCT04811092

Sponsor Acceleron Pharma, Inc., a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ USA

Information provided by Acceleron Pharma, Inc., a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ USA (Responsible Party)

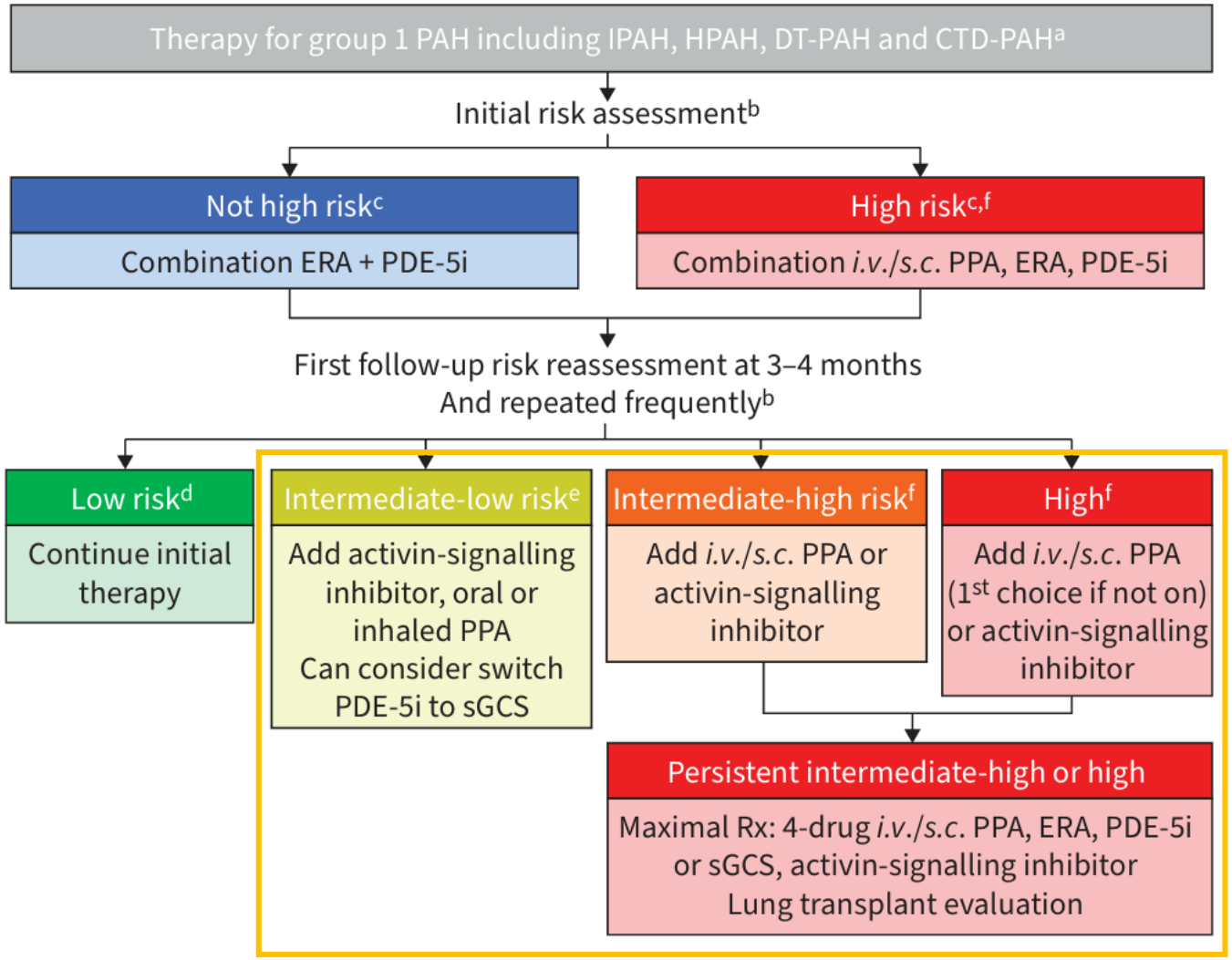
Last Update Posted 2025-05-13

Study Overview

Brief Summary

The objective of this study is to evaluate the effects of sotatercept (MK-7962, formerly called ACE-011) treatment (plus background pulmonary arterial hypertension (PAH) therapy) versus placebo (plus background PAH therapy) on time to clinical worsening (TTCW) in participants who are newly diagnosed with PAH and are at intermediate or high risk of disease progression.

Symptomatic PAH Group 1 diagnosed within 12 months

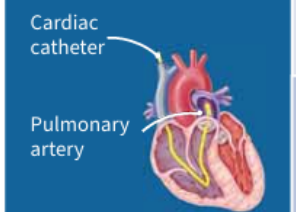


Eur Respir J. 2024 Oct 31;64(4):2401325

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 NT-proBNP	<50 ng·L^{-1} <300 ng·L^{-1}	50–199 ng·L^{-1} 300–649 ng·L^{-1}	200–800 ng·L^{-1} 650–1100 ng·L^{-1}	>800 ng·L^{-1} >1100 ng·L^{-1}

Eur Respir J. 2024 Oct 31;64(4):2401323

Domain	Treatment goals	Comments	Limitations
Exercise tolerance 	**6MWD >440 m** **WHO-FC I or II**	Not disease-specific, potentially affected by conditions other than PAH	Goals may not be achievable in patients with other conditions limiting exercise capacity
RV function and strain 	**BNP <50 ng·L^{-1}** **NT-proBNP <300 ng·L^{-1}**	Not disease-specific, potentially affected by conditions other than PAH	Goals may not be achievable in patients with interfering conditions
	Need for research prioritisation: RA area <18 cm^2 TR, none or trace TAPSE/sPAP >0.32 mm·mmHg^{-1}	Other imaging parameters from echocardiography and MRI are emerging	TAPSE/sPAP threshold requires further validation
Haemodynamics 	**RAP <8 mmHg** **CI ≥2.5 L·min^{-1}·m^{-2}** **SVI >37 mL·m^{-2}** **S_{vO_2} >65%** **PVR <5 WU**	Uncertain added value in low-risk patients according to ESC/ERS 4 strata model PVR <5 WU treatment goal may not apply to patients with congenital heart disease	Established prognostic value; however, not necessarily independent of noninvasive parameters
	Need for research prioritisation: mPAP <30–35 mmHg PAC ≥2.5 mL·mmHg^{-1}	With emerging therapies and effective combination treatment strategies, comprehensive haemodynamic assessment of treatment response is expected to play a prominent role in the management of patients with PAH	The proposed thresholds may be associated with long-term survival; however, this is not evidence-based and requires further validation

Eur Respir J. 2024 Oct 31;64(4):2401323

보험기준
(Sildenafil, ambrisentan, macitentan)

- 대상환자
  - Group 1 PAH (특발성, 가족성, 교원성혈관질환, 선천성 심질환, 문맥고혈압 동반)
  - WHO FC 2 or 3
- 2제 요법으로 추가
  - 단독요법으로 3개월 이상 투여 후 반응이 충분하지 않을 때 (A & B)
  - A: 우심실부전의 증거, 빠른 진행 속도, 실신, WHO-FC 3 이상
  - B: 6MWD ≤440m, Peak VO2 ≤15mL/Kg*min
    BNP≥50, NT-proBNP ≥300
    Pericardial effusion, TAPSE<1.5cm
    RAP≥8mmHg, CI <2.5L/min/m2

보험기준 (Selexipag)

- 대상환자
  - Group 1 PAH (특발성, 가족성, 교원성혈관질환, 선천성 심질환, 문맥고혈압 동반)
  - ERA ± PDE 5 inhibitor 반응이 충분하지 않거나, 둘 다 금기일 경우
- 기본적으로 병용 투여만 인정
  - 단독요법으로 3개월 이상 투여 후 반응이 충분하지 않을 때 (A & B)
  - A: 우심실부전의 증거, 빠른 진행 속도, 실신, WHO-FC 3 이상
  - B: 6MWD ≤440m, Peak VO2 ≤15mL/Kg*min
    BNP≥50, NT-proBNP ≥300
    Pericardial effusion, TAPSE<1.5cm
    RAP≥8mmHg, CI <2.5L/min/m2

보험기준 (Treprostinil)

- 대상환자
  - Group 1 PAH (특발성, 가족성, 교원성혈관질환, 선천성 심질환, 문맥고혈압 동반)
  - NYHA 3 or 4
- 단독 요법
  - WHO FC 4
  - 6MWD <165m, Peak VO2 <11mL/Kg*min, VE/CO2 slope ≥45
    BNP >300, NT-proBNP >1400
    Pericardial effusion, RA area >26cm
    RAP >14mmHg, CI <2.0L/min/m2, SvO2<60%

보험기준 (Treprostinil)

- 대상환자
  - Group 1 PAH (특발성, 가족성, 교원성혈관질환, 선천성 심질환, 문맥고혈압 동반)
  - NYHA 3 or 4
- 병용 요법
  - 단독요법으로 3개월 이상 투여 후 반응이 충분하지 않을 때 (A & B)
  - A: 우심실부전의 증거, 빠른 진행 속도, 실신, WHO-FC 3 이상
  - B: 6MWD ≤440m, Peak VO2 ≤15mL/Kg*min
    BNP≥50, NT-proBNP ≥300
    Pericardial effusion, TAPSE<1.5cm
    RAP≥8mmHg, CI <2.5L/min/m2

보험기준
(Iloprost inhalation)

- 대상환자
  - Group 1 PAH (특발성, 가족성, 교원성혈관질환, 선천성 심질환, 문맥고혈압 동반)
  - NYHA 3 or 4
- 병용 요법 (1일 최대 3amp, 1amp 당 20ug)
  - 단독요법으로 3개월 이상 투여 후 반응이 충분하지 않을 때 (A & B)
  - A: 우심실부전의 증거, 빠른 진행 속도, 실신, WHO-FC 3 이상
  - B: 6MWD ≤440m, Peak VO2 ≤15mL/Kg*min
    BNP≥50, NT-proBNP ≥300
    Pericardial effusion, TAPSE<1.5cm
    RAP≥8mmHg, CI <2.5L/min/m2

THANK YOU FOR YOUR ATTENTION