Una visión personal de los desafíos en la Hipertensión Arterial Pulmonar

DRA PILAR ESCRIBANO SUBIAS

European Reference Network for rare or low prevalence complex diseases
Network Respiratory Diseases (ERN-LUNG)

UHP Unidad de Hipertensión Pulmonar 12 de Octubre

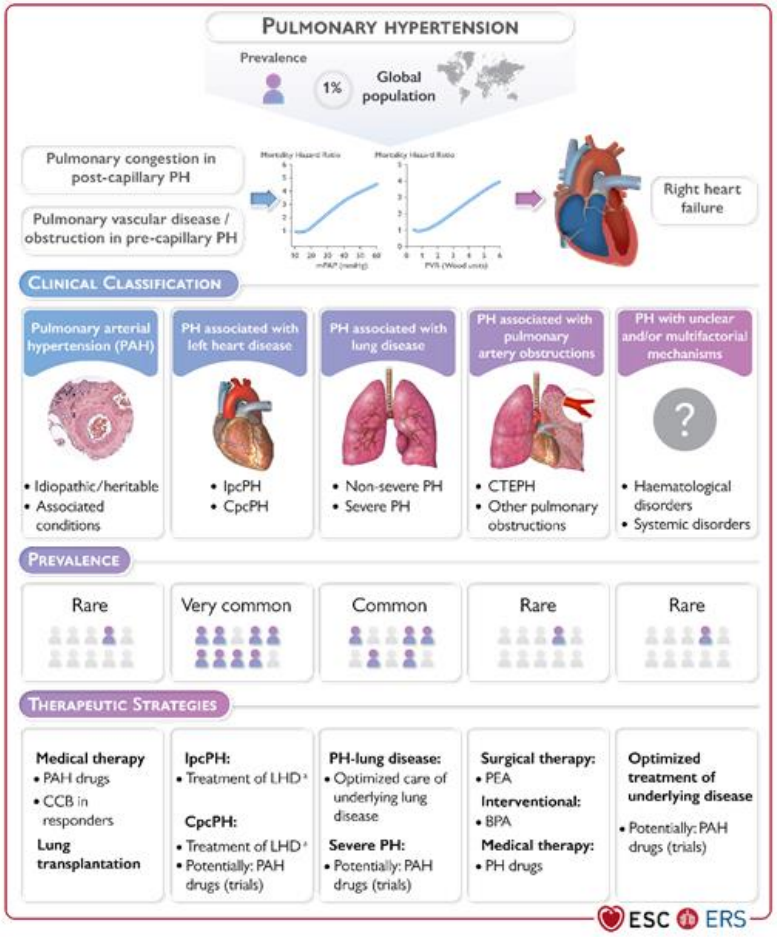
ciberCV Centro de Investigación Biomédica en Red Enfermedades Cardiovasculares

Hospital Universitario 12 de Octubre
SaludMadrid
Comunidad de Madrid

CONFLICTO DE INTERESES

Relevant financial relationships with a commercial interest:

- Gossamer: board or advisory committee
- Bayer/Merck: board or advisory committee, speaker
- AOP Orphan Pharmaceuticals: board and speaker
- Ferrer: speaker, board or advisory committee
- Janssen: board or advisory committee, speaker, research support

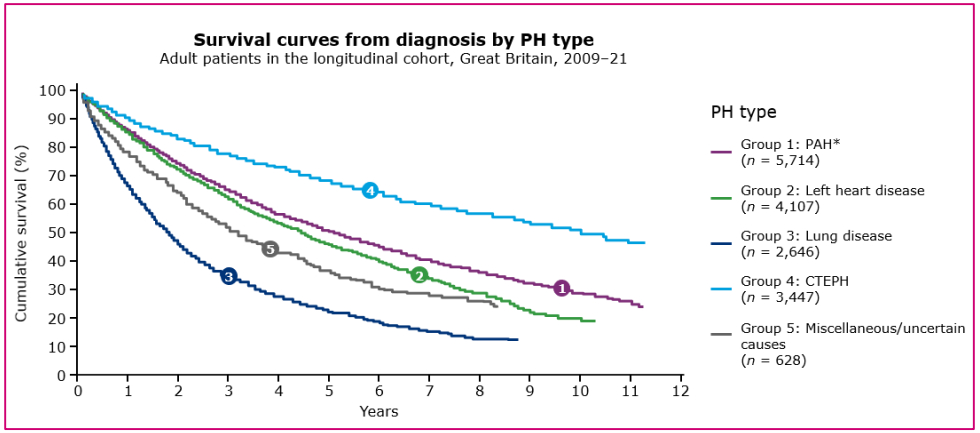


Epidemiologia PAH :

- ✓ Incidencia 3-6 casos millón /año en el adulto
- ✓ Prevalencia : 48–55 casos/millón en el adulto

Epidemiologia HPTBEC

- ✓ Incidencia 2-6 casos millón /año en el adulto
- ✓ Prevalencia: 26–38 casos/millón en el adulto



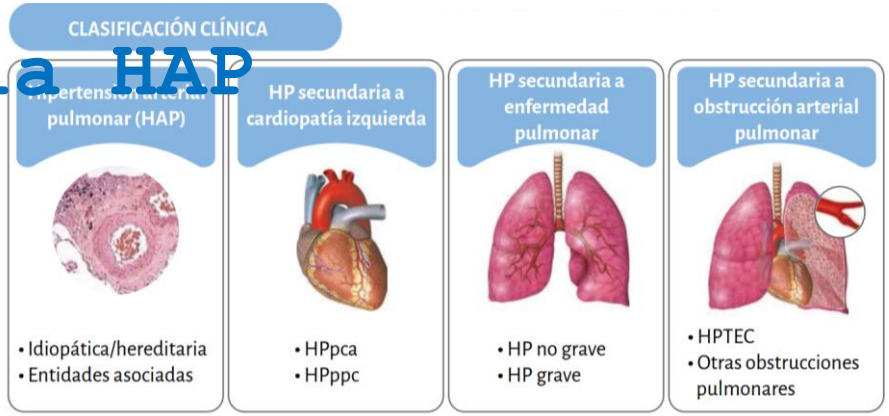
2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

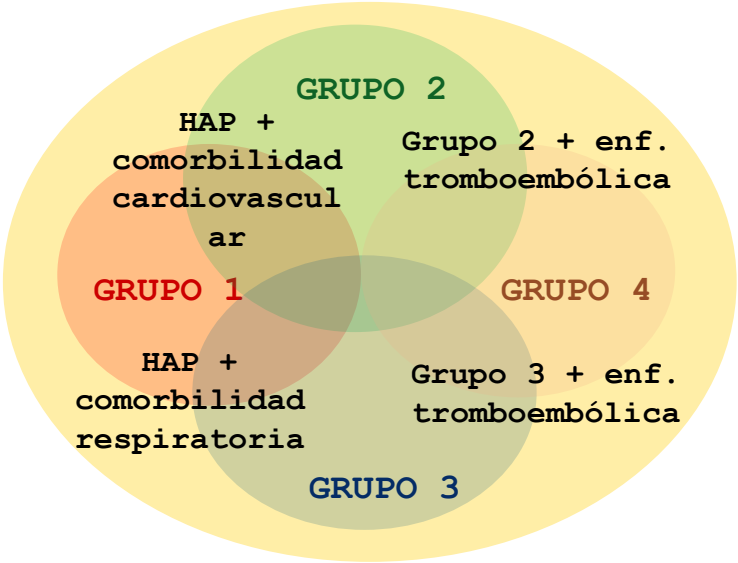
Comorbilidades en la HAP

Comorbilidad: coexistencia en un mismo individuo de dos o más enfermedades

Un problema de COMPLEJIDAD y CLASIFICACIÓN

~~cada vez más frecuente~~



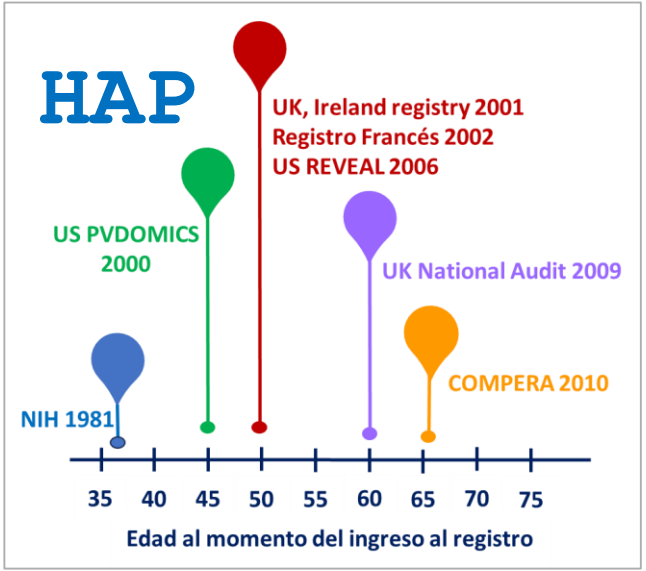


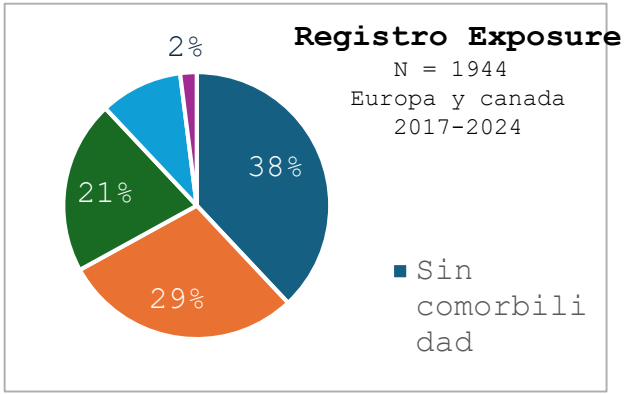
Comorbilidades en la HAP

La epidemiología de la HAP ha cambiado a lo largo del tiempo.

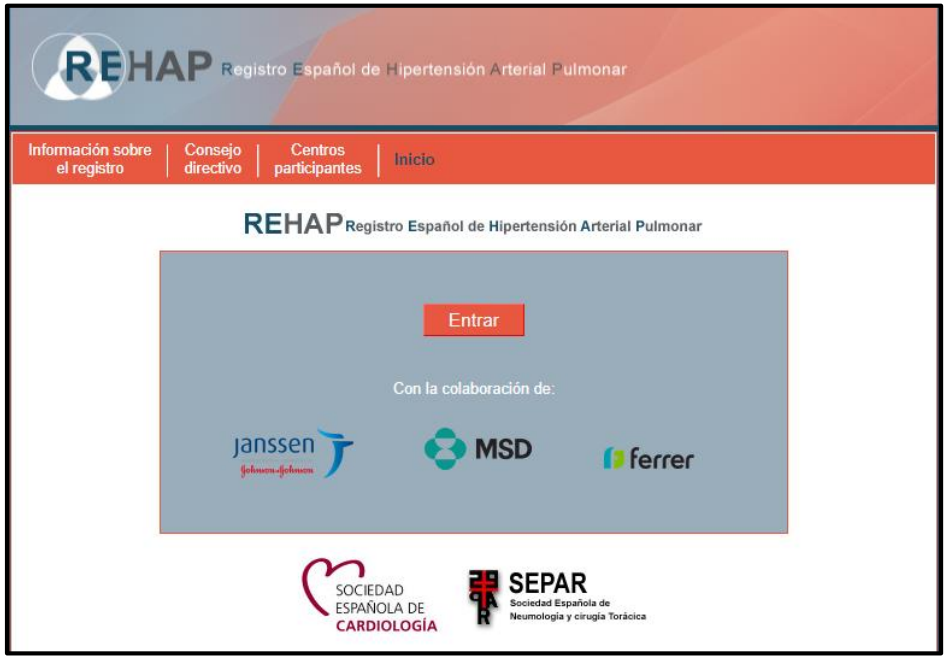
Cada vez vemos pacientes mayores y con más carga de comorbilidad

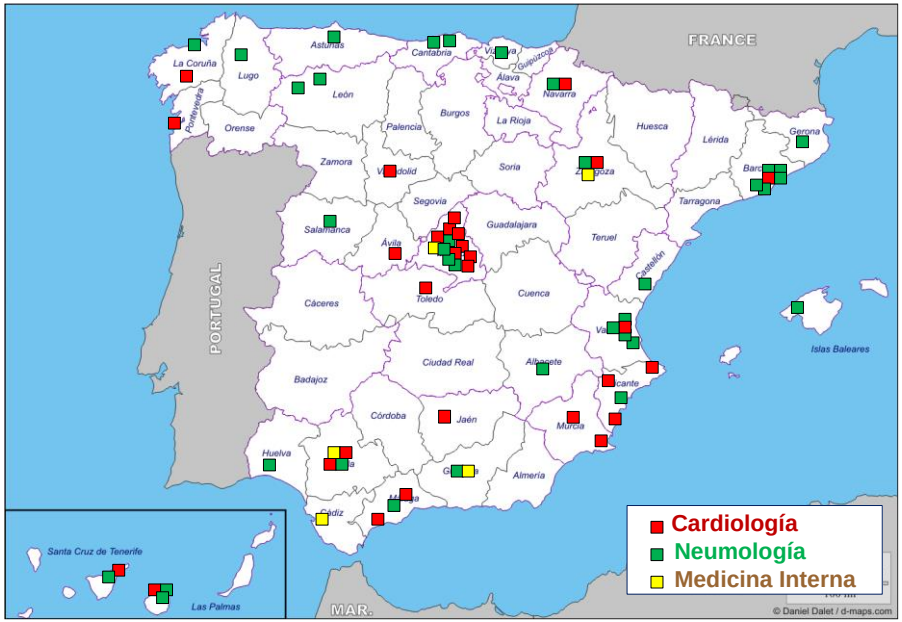
La evidencia del tratamiento en estos pacientes es menor.





Adv Ther (2024) 41:1103–1119


REHAP Registro Español de Hipertensión Arterial Pulmonar
Información sobre el registro
Consejo directivo
Centros participantes
Inicio
REHAP Registro Español de Hipertensión Arterial Pulmonar
Entrar
Con la colaboración de:
janssen
MSD
ferrer
SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA
SEPAR
Sociedad Española de Neumología y cirugía Torácica


FRANCE
PORTUGAL
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Asturias
Cantabria
Guipuzcoa
Alava
Navarra
La Coruña
Lugo
León
Orense
Palencia
Burgos
La Rioja
Huesca
Lérida
Gerona
Zamora
Soria
Tarragona
Segovia
Salamanca
Ávila
Guadalajara
Teruel
Cáceres
Toledo
Cuenca
Islas Baleares
Ciudad Real
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Badajoz
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Cádiz
Santa Cruz de Tenerife
Las Palmas
Cardiología
Neumología
Medicina Interna
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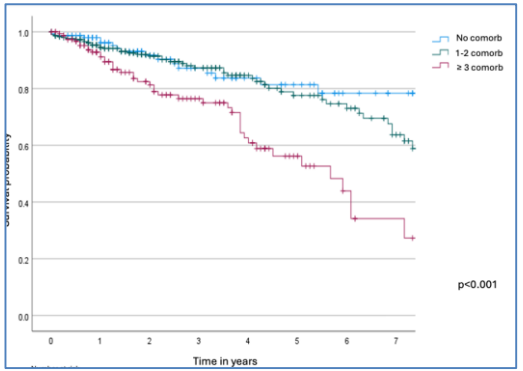
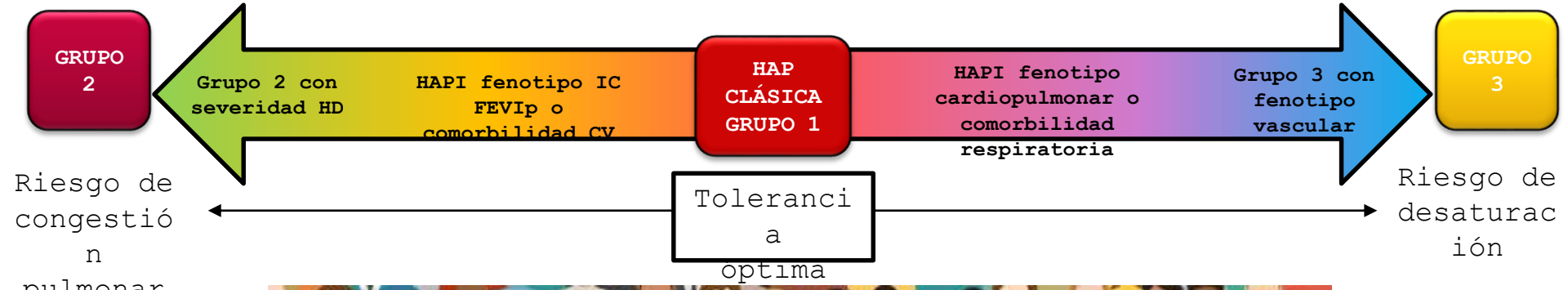
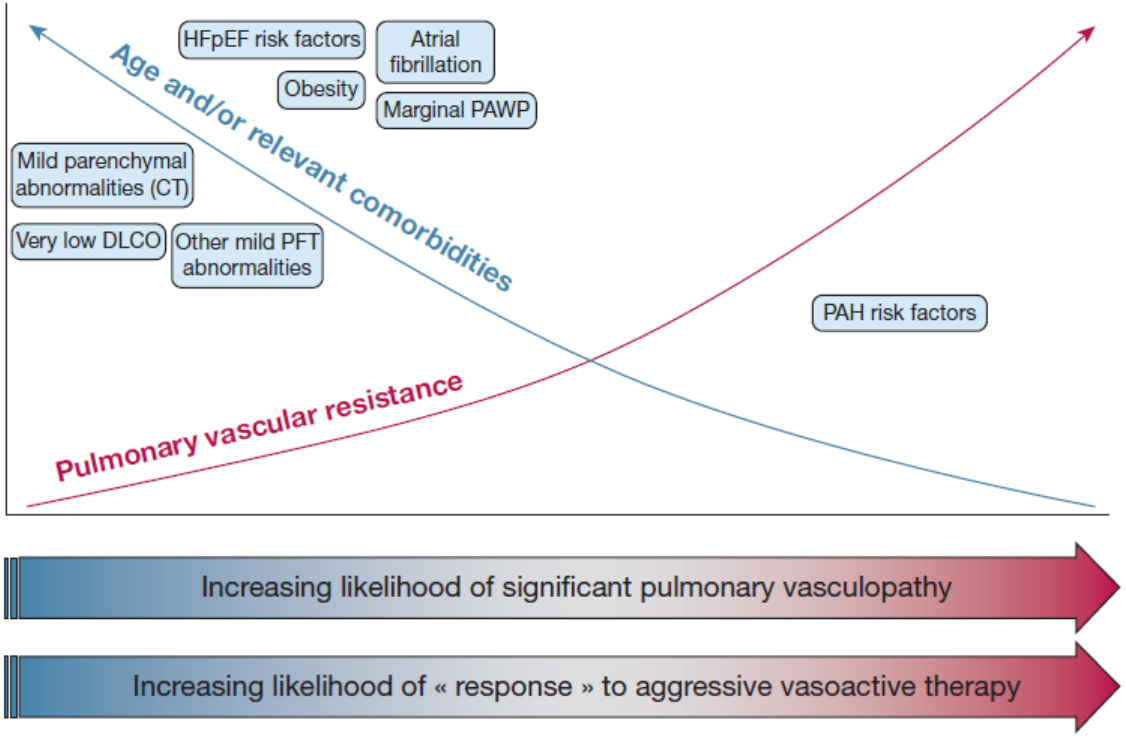
Comorbidities	All n = 757	No comorb n = 186 (24.6%) 49 ± 17	1-2 comorb n = 373 (49.3%) 59 ± 15	≥ 3 comorb n = 198 (26.2%) 67 ± 10	p - value
Smoking history	351 (46.4%)	0 (0%)	211 (56.6%)	140 (70.7%)	<0.001
Hypertension	314 (41.5%)	0 (0%)	141 (37.8%)	173 (87.4%)	<0.001
BMI ≥ 30 Kg/m²	186 (24.6%)	0 (0%)	80 (21.4%)	106 (53.5%)	<0.001
CKD (GFR CKD-EPI equation < 60 ml/min/1.73 m²)	145 (19.2%)	0 (0%)	51 (13.7%)	94 (47.5%)	<0.001
Diabetes mellitus	124 (16.4%)	0 (0%)	14 (3.8%)	110 (55.6%)	<0.001
Atrial fibrillation	64 (8.5%)	0 (0%)	21 (5.6%)	43 (21.7%)	<0.001
Coronary heart disease	62 (8.2%)	0 (0%)	10 (2.7%)	52 (26.3%)	<0.001



Discriminar fenotipos



Relationship between relevant cardiorespiratory comorbidities and disease p



➢ *Proyectos – FIS de GENÉTICA:*

BASES GENÉTICO MOLECULARES DE LA HIPERTENSIÓN ARTERIAL PULMONAR Y SU EXPRESIÓN FENOTÍPICA EN LA POBLACIÓN ESPAÑOLA.
FIS : 15/02012

UHP · Hospital Universitario 12 de Octubre · SaludMadrid · Comunidad de Madrid

BASES GENÉTICO MOLECULARES DE LA MEDICINA DE PRECISIÓN EN LA HIPERTENSIÓN ARTERIAL PULMONAR.
FIS : 18/01233

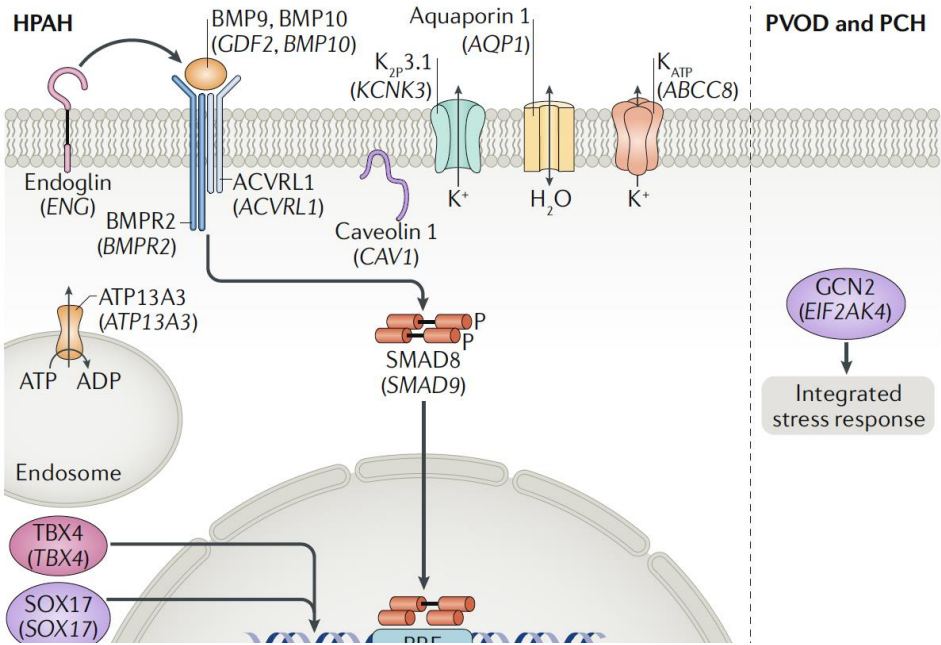
UHP · Hospital Universitario 12 de Octubre · SaludMadrid · Comunidad de Madrid

➢ *BIOBANCO ESPAÑOL DE HIPERTENSIÓN PULMONAR*

bioBANC · IDIBAPS · CLÍNIC BARCELONA Hospital Universitari

Genética actual en la HAP

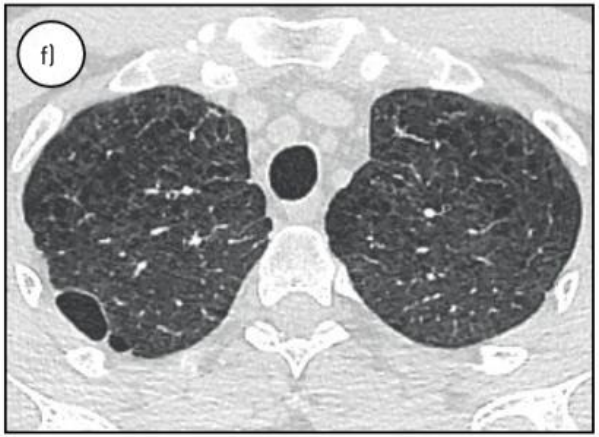
Gene	Number of reported mutation-positive cases by PAH category[a]						Female (%)	Mean age of onset and range (years)	Associate clinical features
	HPAH	IPAH	APAH	PCH/ PVOD	Unknown	Total			
BMPR2	284	415	22	3	82	806	67.9	33 (1–72)	CHD, IPF, PVOD
EIF2AK4	8	6	0	38	14	66	48.1	32 (11–72)	PCH, PVO
ACVRL1	8	21	42	0	5	76	78.9	27 (1–63)	HHT
TBX4	4	30	14	0	0	48	58.5	25 (<1 to 72)	SPS
GDF2	1	32	0	0	0	33	71	33 (3–54)	–
SOX17	0	13	13	0	0	26	55.2	19 (<1 to 51)	CHD
ENG	0	8	9	0	0	17	62.5	30 (<1 to 59)	HHT, CHD
KCNK3	5	11	0	0	0	16	58.8	23 (<1 to 44)	–
ABCC8	2	8	2	0	0	12	58.3	29 (<1 to 79)	CHD
ATP13A3	0	11	0	0	0	11	90.9	48 (42–58)	–
SMAD9	1	8	2	0	0	11	80	25 (<1 to 58)	CHD
AQP1	3	6	0	0	0	9	44.4	32 (25–46)	–
CAV1	2	1	1	0	0	4	75	28 (1–67)	CHD
BMP10	0	1	1	0	0	2	100	20 (11–28)	CHD
SMAD4	0	2	0	0	0	2	50	35	–
SMAD1	0	1	0	0	0	1	100	47	–

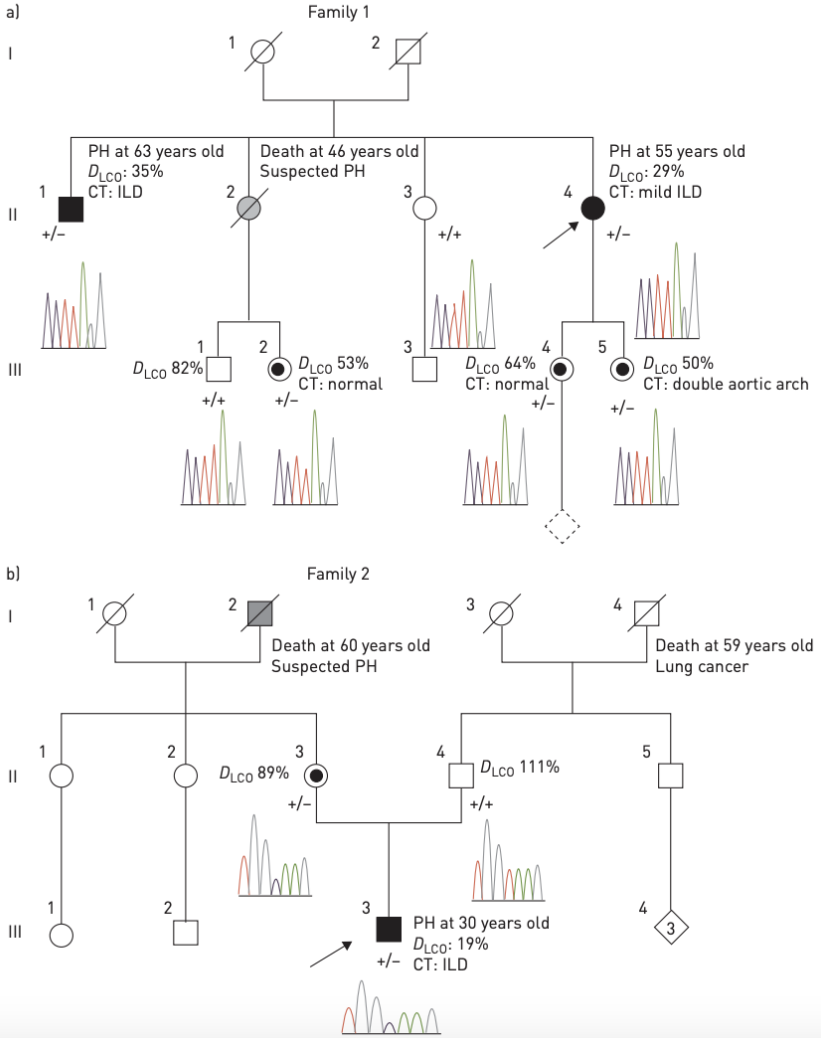


Southgate L. *Nat Rev Cardiol*. 2020;17(2):85-95.

Familial pulmonary arterial hypertension by *KDR* heterozygous loss of function

Mélanie Eyries[1,2,13], David Montani[3,4,5,13], Barbara Girerd[3,4], Nicolas Favrolt[6], Marianne Riou[7], Laurence Faivre[8], Grégoire Manaud[5], Frédéric Perros[5], Stefan Gräf[9,10,11], Nicholas W. Morrell[9,12], Marc Humbert[3,4,5] and Florent Soubrier[1,2]





Eyries M, Montani D, Girerd B, et al. Familial pulmonary arterial hypertension by KDR heterozygous loss of function. *Eur Respir J*. 2020;55(4).

European Reference Network
for rare or low prevalence complex diseases
Network Respiratory Diseases (ERN-LUNG)

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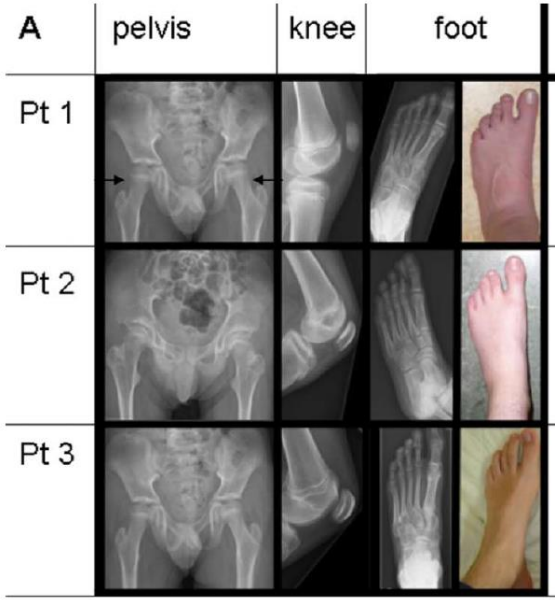
UNIDAD DE HIPERTENSIÓN PULMONAR 12 DE OCTUBRE

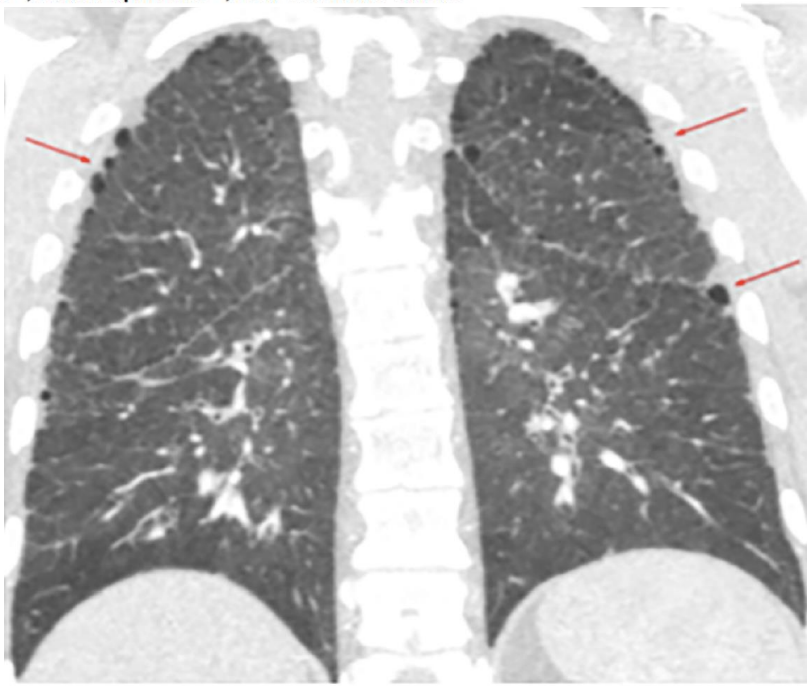
TBX4 mutations (small patella syndrome) are associated with childhood-onset pulmonary arterial hypertension

Wilhelmina S Kerstjens-Frederikse,[1] Ernie M H F Bongers,[2] Marcus T R Roofthooft,[3] Edward M Leter,[4] J Menno Douwes,[3] Arie Van Dijk,[5] Anton Vonk-Noordegraaf,[6] Krista K Dijk-Bos,[1] Lies H Hoefsloot,[2] Elke S Hoendermis,[7] Johan J P Gille,[4] Birgit Sikkema-Raddatz,[1] Robert M W Hofstra,[1] Rolf M F Berger[3]



Clinical heterogeneity of Pulmonary Arterial Hypertension associated with variants in *TBX4*

Ignacio Hernandez-Gonzalez[1]*, Jair Tenorio[2,3], Julian Palomino-Doza[4,5,6], Amaya Martinez Meñaca[7], Rafael Morales Ruiz[8], Mauro Lago-Docampo[9], María Valverde Gomez[4], Javier Gomez Roman[10], Ana Belén Enguita Valls[11], Carmen Perez-Olivares[5], Diana Valverde[9], Joan Gil Carbonell[12], Elvira Garrido-Lestache Rodríguez-Monte[13], Maria Jesus del Cerro[13], Pablo Lapunzina[2,3], Pilar Escribano-Subias[5,6]*



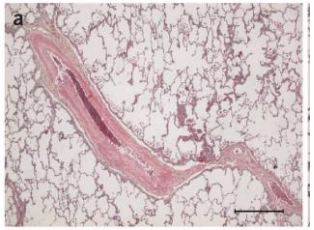
Kerstjens-Frederikse WS, et al. J Med Genet 2013;50:500–506.

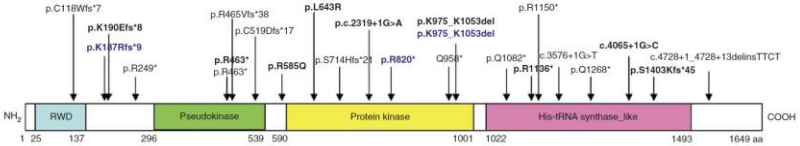
. PLoS ONE 15(4): e0232216.

Enfermedad venooclusiva pulmonar (EVOP)

EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension

Mélanie Eyries[1–3], David Montani[4–6], Barbara Girerd[4–6], Claire Perret[3,7], Anne Leroy[2], Christine Lonjou[8], Nadjim Chelghoum[8], Florence Coulet[2,3], Damien Bonnet[9,10], Peter Dorfmüller[6,11], Elie Fadel[6,12], Olivier Sitbon[4–6], Gérald Simonneau[4–6], David-Alexandre Tregouët[3,7], Marc Humbert[4–6] & Florent Soubrier[1–3]



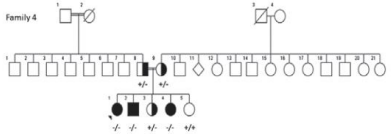


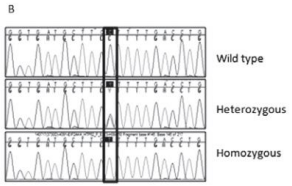
Nat Genet. 2014 Jan;46(1):65-9.

A founder *EIF2AK4* mutation causes an aggressive form of pulmonary arterial hypertension in Iberian Gypsies

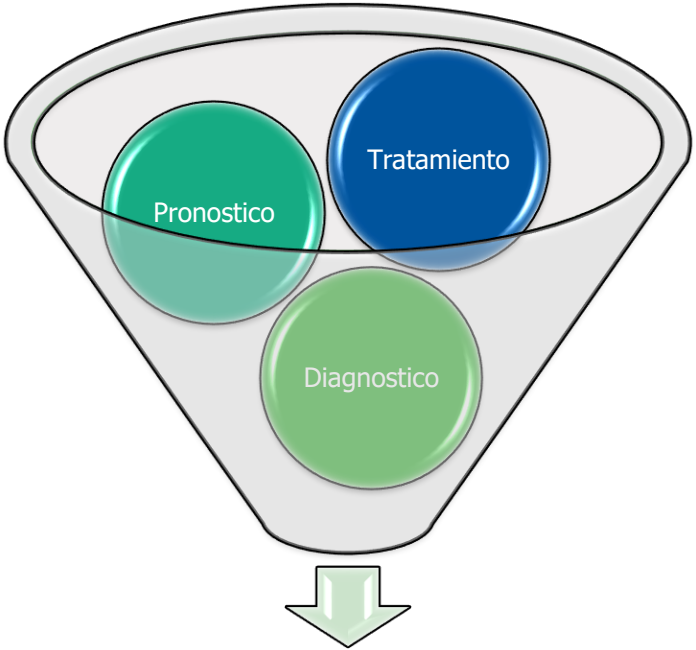
Tenorio J., Navas P., Barrios E., Fernández L., Nevado J., Quezada C.A., López-Meseguer M., Arias P., Mena R., Lobo J.L., Alvarez C., Heath K., Escribano-Subías P., Lapunzina P. A founder *EIF2AK4* mutation causes an

J. Tenorio[a,b,†], P. Navas[c,d,†], E. Barrios[a], L. Fernández[a,b], J. Nevado[a,b], C.A. Quezada[a],





Clin Genet. 2015 Dec;88(6):579-83.



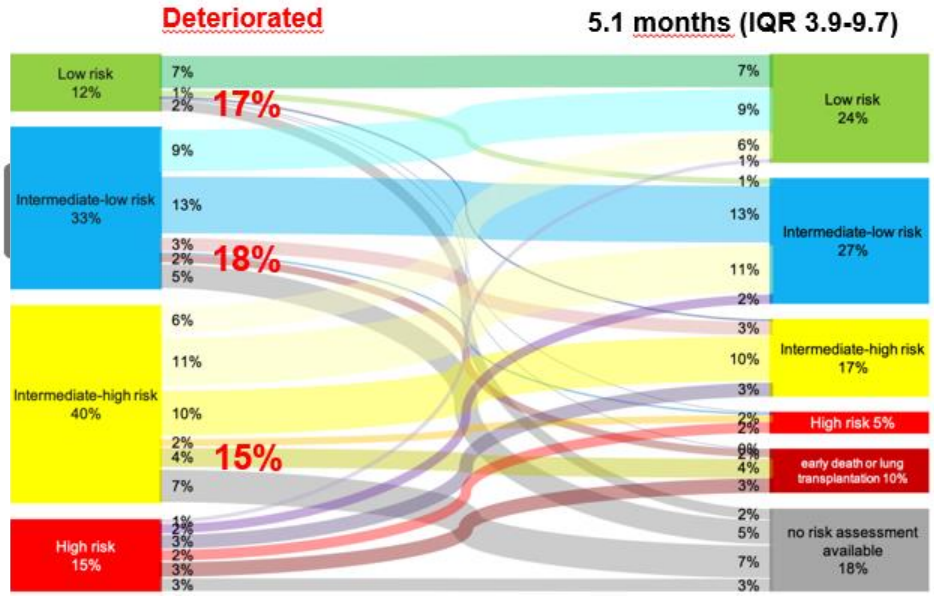
Cada minuto cuenta

ECS/ERS 3 risk-strata

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

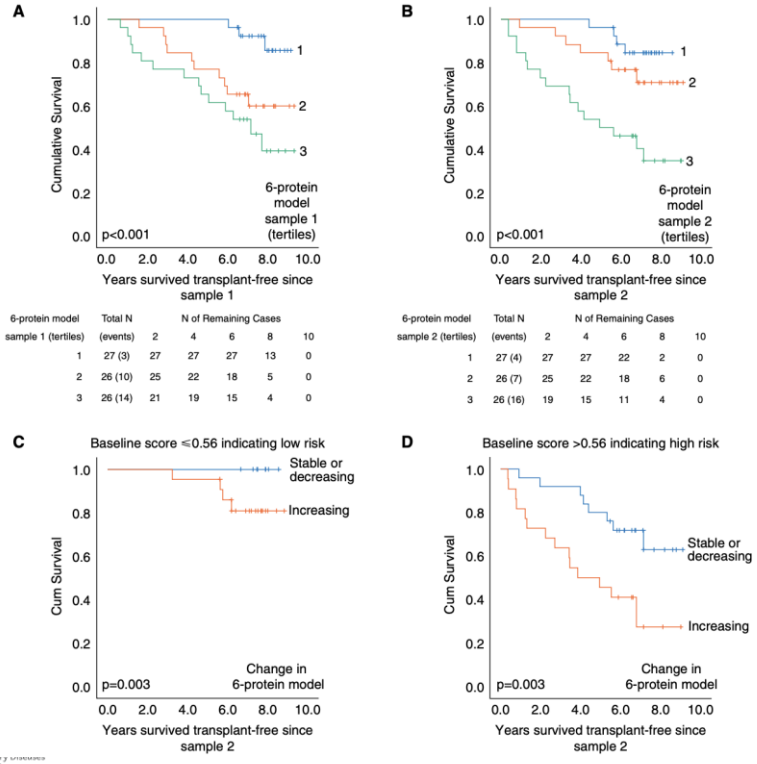
ECS/ERS 4 risk-strata

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



Using the Plasma Proteome for Risk Stratifying Patients with Pulmonary Arterial Hypertension

Christopher J. Rhodes[1], John Wharton[1], Emilia M. Swietlik[2], Lars Harbaum[1], Barbara Girerd[3], J. Gerry Coghlan[4], James Lordan[5], Colin Church[6], Joanna Pepke-Zaba[7], Mark Toshner[2], Stephen J. Wort[1], David G. Kiely[8,9], Robin Condliffe[8,9], Allan Lawrie[8], Stefan Gräf[2,10], David Montani[3], Athénaïs Boucly[3], Olivier Sitbon[3], Marc Humbert[3], Luke S. Howard[1], Nicholas W. Morrell[2], and Martin R. Wilkins[1]; on behalf of the UK National PAH Cohort Study Consortium

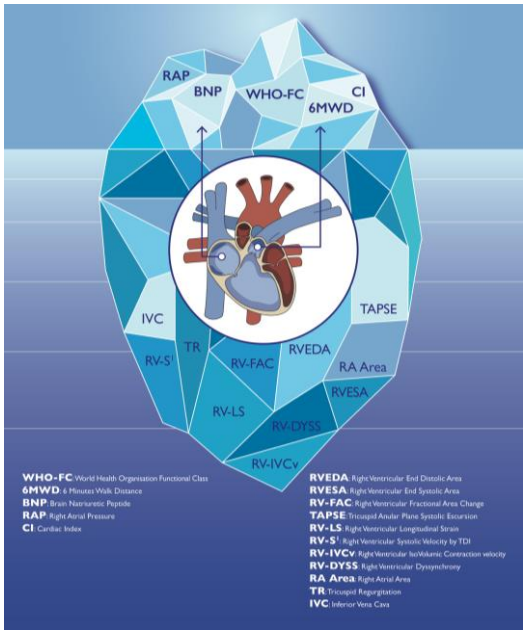


The plasma proteome informs prognosis beyond established factors in PAH and may provide a more sensitive measure of therapeutic response.

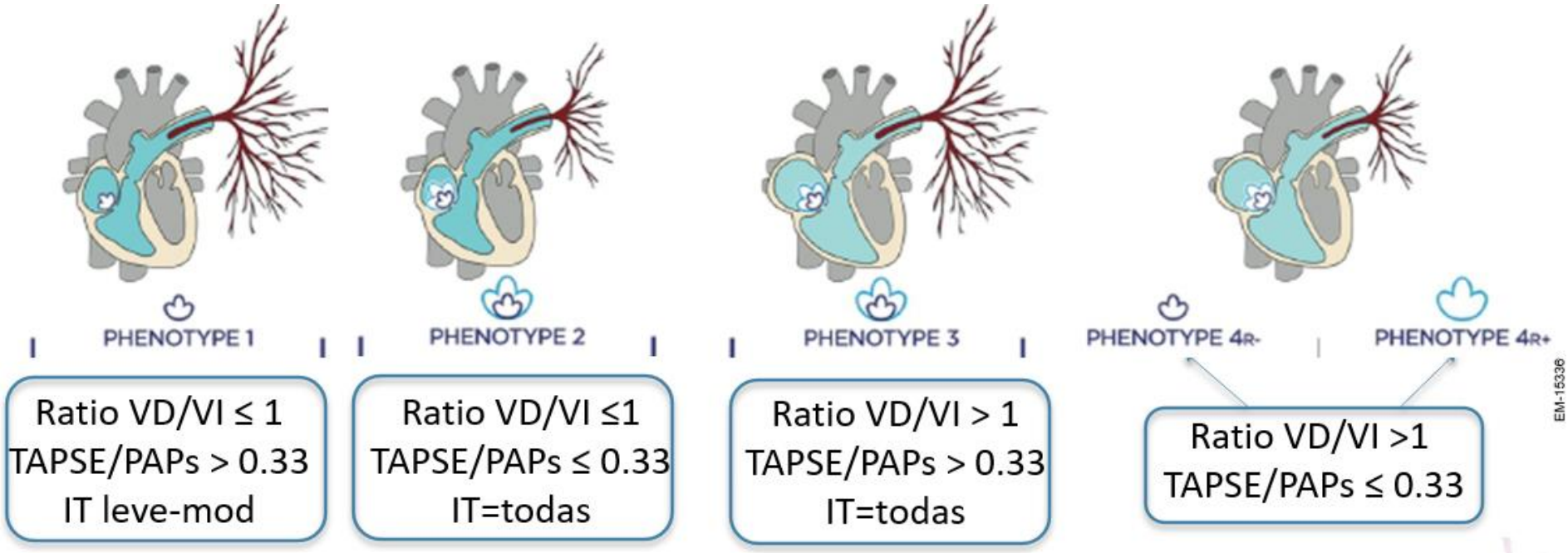
Am J Respir Crit Care Med 2022 May 1;205(9):988-990.

The importance of the RV in risk assessment

PAH and RV afterload mismatch

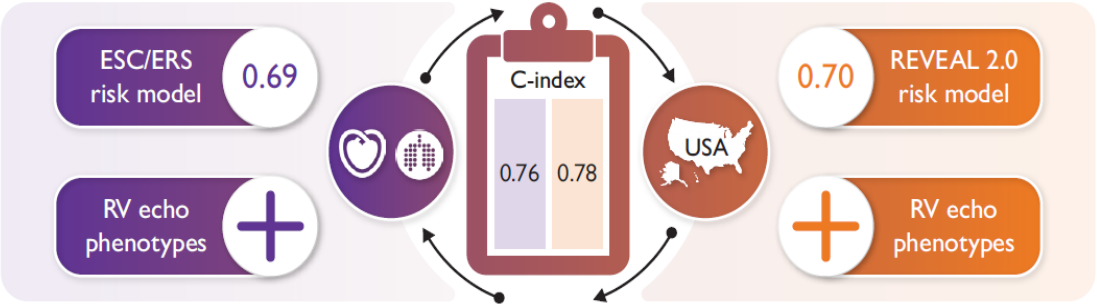


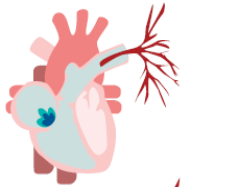
Prognostic relevance of RV phenotyping

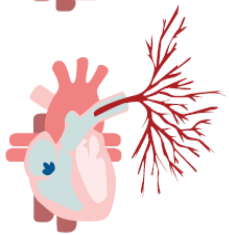


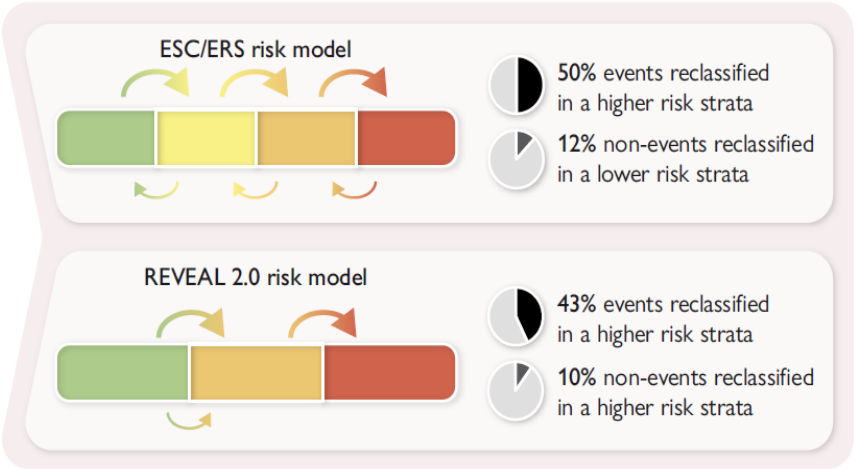
- J Heart Lung Transplant. 2024 Oct;43(10):1668-1676. doi: 10.1016/j.healun.2024.06.003.

Do echocardiography-derived phenotypes describing different degrees of RV remodelling add prognostic information to current risk stratification tools ?









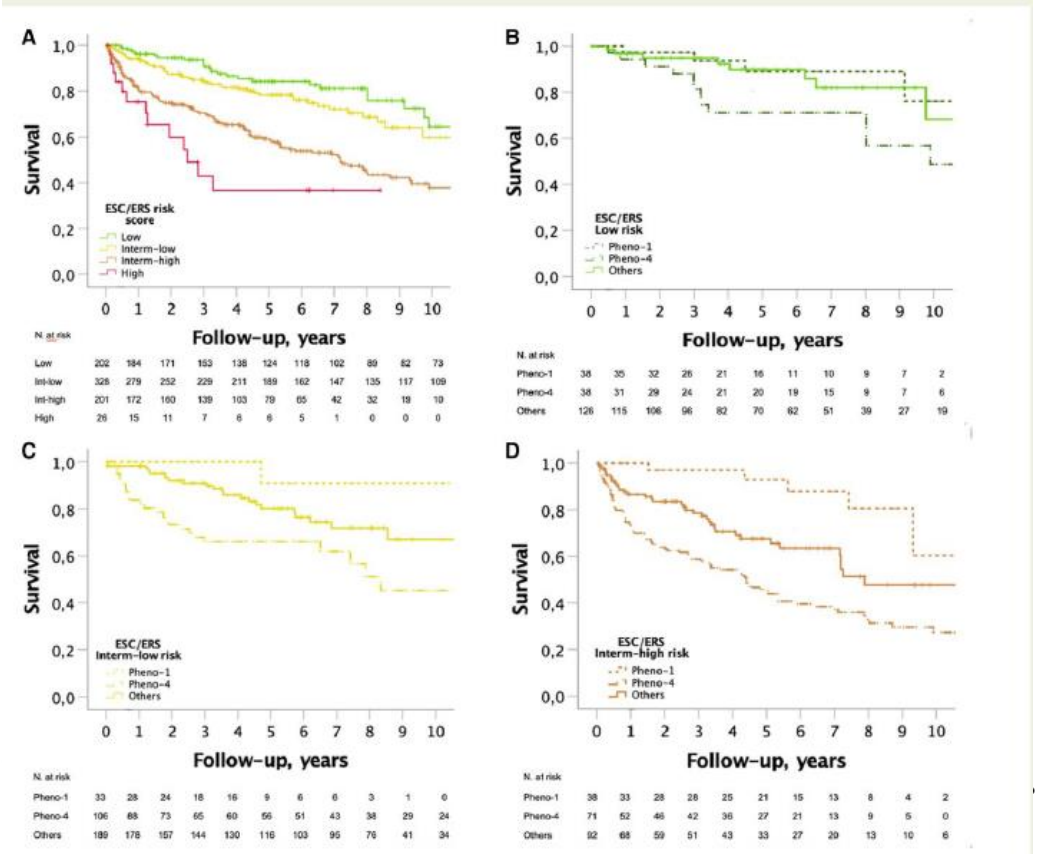
719 pacientes prevalentes

Echocardiographic phenotypes (ECO) were present in all ESC/ERS risk groups, except for the high-risk groups which included only phenotypes 3 and 4.

Eco phenotypes provide prognostic information which is independent and additional to the score Risk

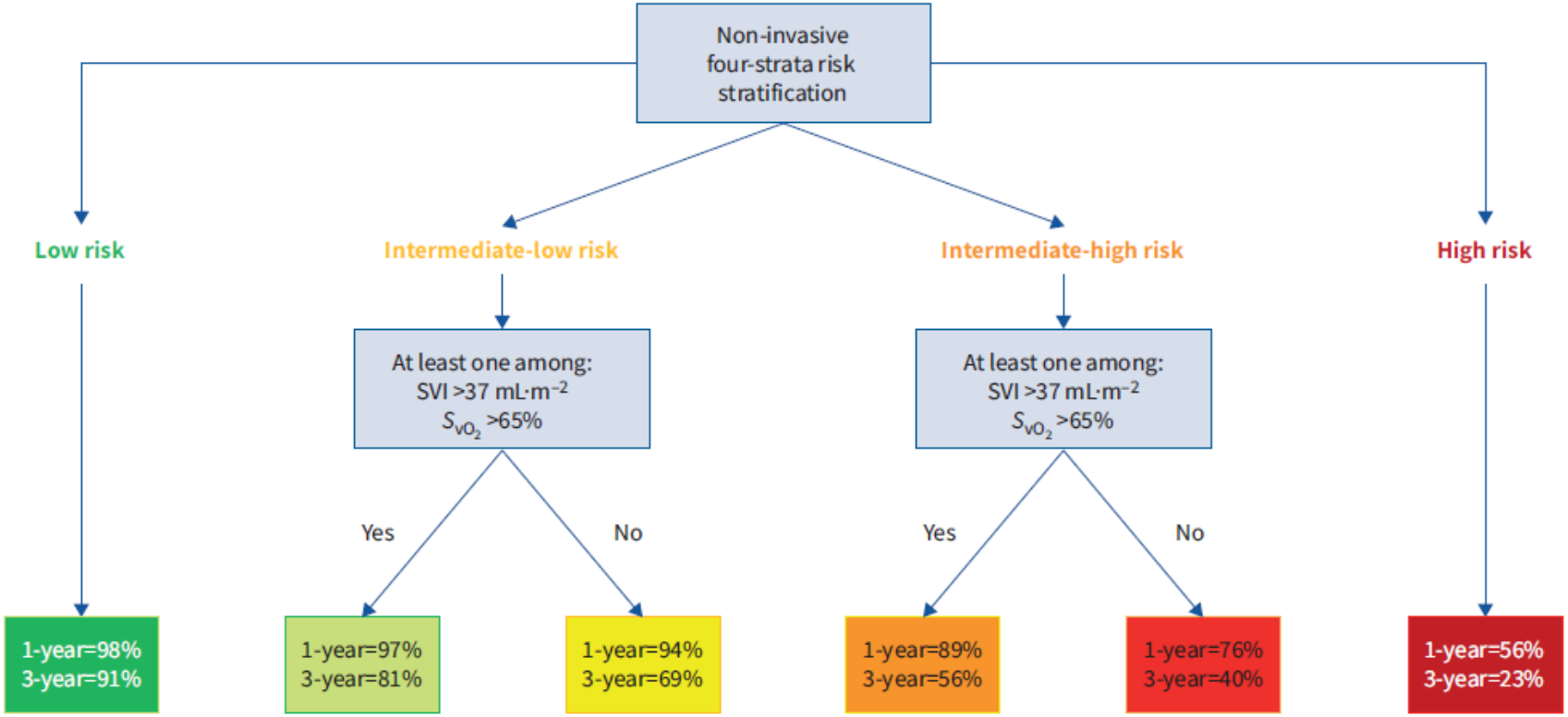
European Heart Journal (2026) **00**, 1–12

Do echocardiography-derived phenotypes describing different degrees of RV remodelling add prognostic information to current risk stratification tools ?

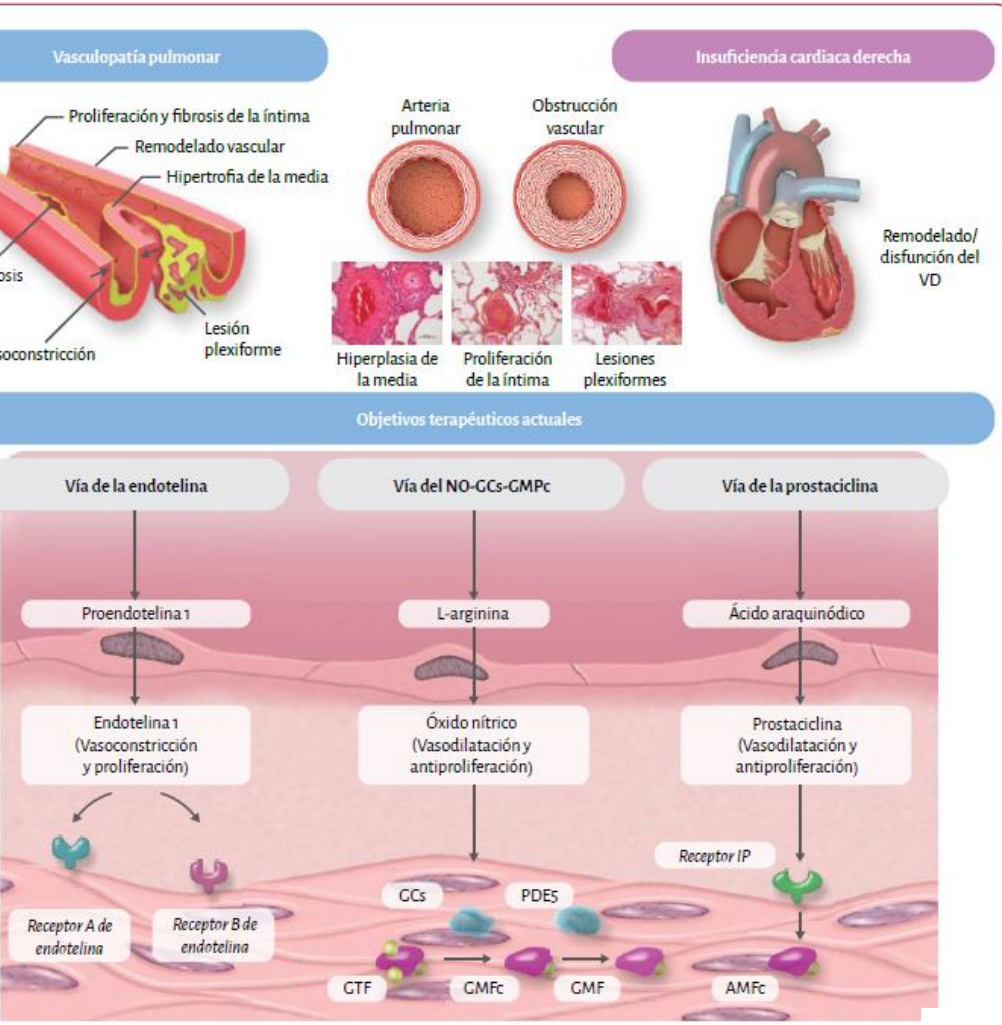


	Phenotype 1 (n = 109)	Phenotype 2 (n = 143)	Phenotype 3 (n = 290)	Phenotype 4_{R-} (n = 166)	Phenotype 4_{R+} (n = 49)
HR, bpm	70 ± 11	76 ± 11	74 ± 12	78 ± 13	79 ± 13
RAP, mm Hg	5.1 ± 3	6.5 ± 4	5.8 ± 3	8.3 ± 4	11.0 ± 5
mPAP, mm Hg	27 ± 6	45 ± 11	35 ± 6	51 ± 11	59 ± 16
PAWP, mm Hg	9 ± 2	10 ± 2	9 ± 3	9 ± 3	10 ± 3
CI, l/min/m^2	2.9 ± 0.6	2.6 ± 0.6	2.8 ± 0.6	2.5 ± 0.6	2.2 ± 0.4
PVR, WU	3.7 ± 1.5	8.4 ± 2.9	6.1 ± 2.3	10.6 ± 5.1	14.7 ± 6.7
PAC, mm Hg/mL	3.2 ± 1.7	1.4 ± 0.6	2.2 ± 0.8	1.2 ± 0.5	1.1 ± 0.7

1240 PAH patients from the French PH registry reassessed at first follow-up visit by three non-invasive variables (WHO/NYHA FC, 6MWD, BNP/NT-proBNP) and right heart catheterisation

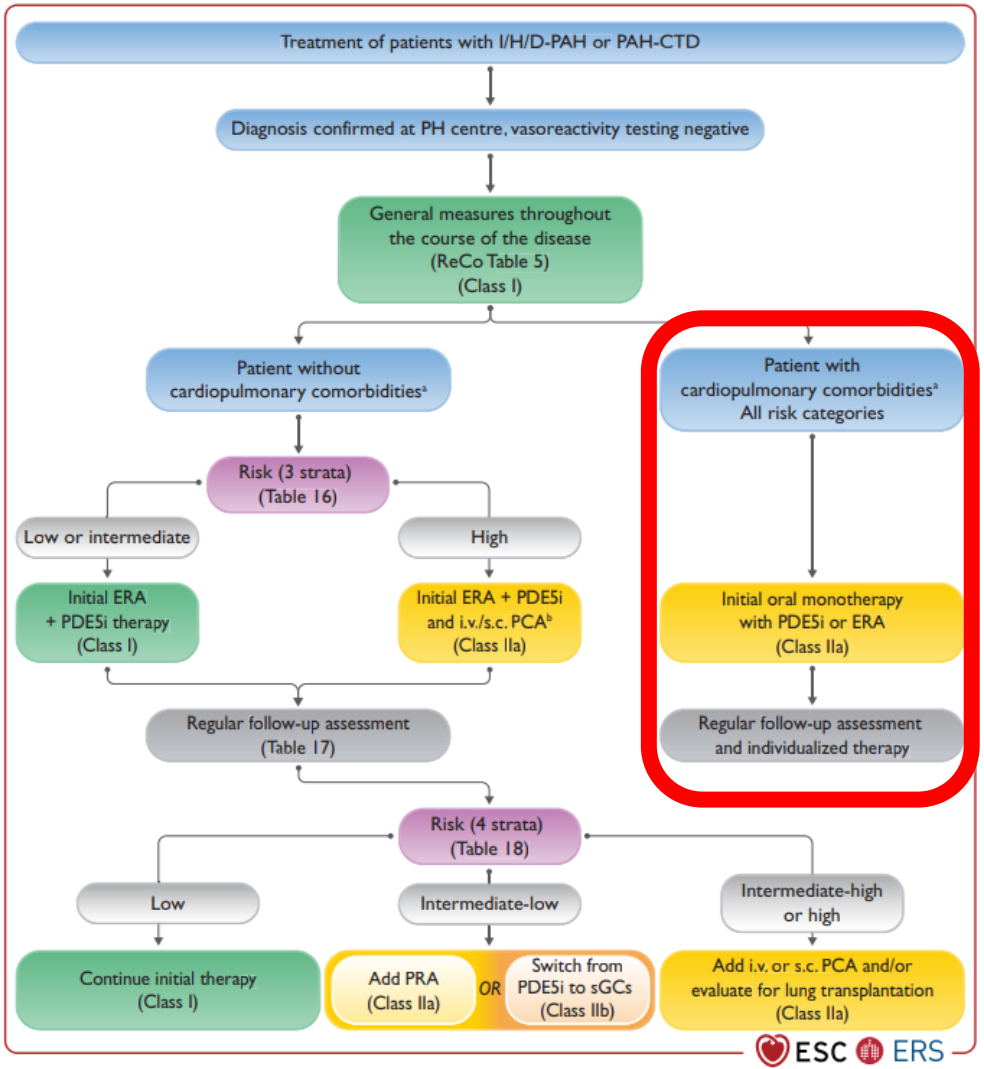


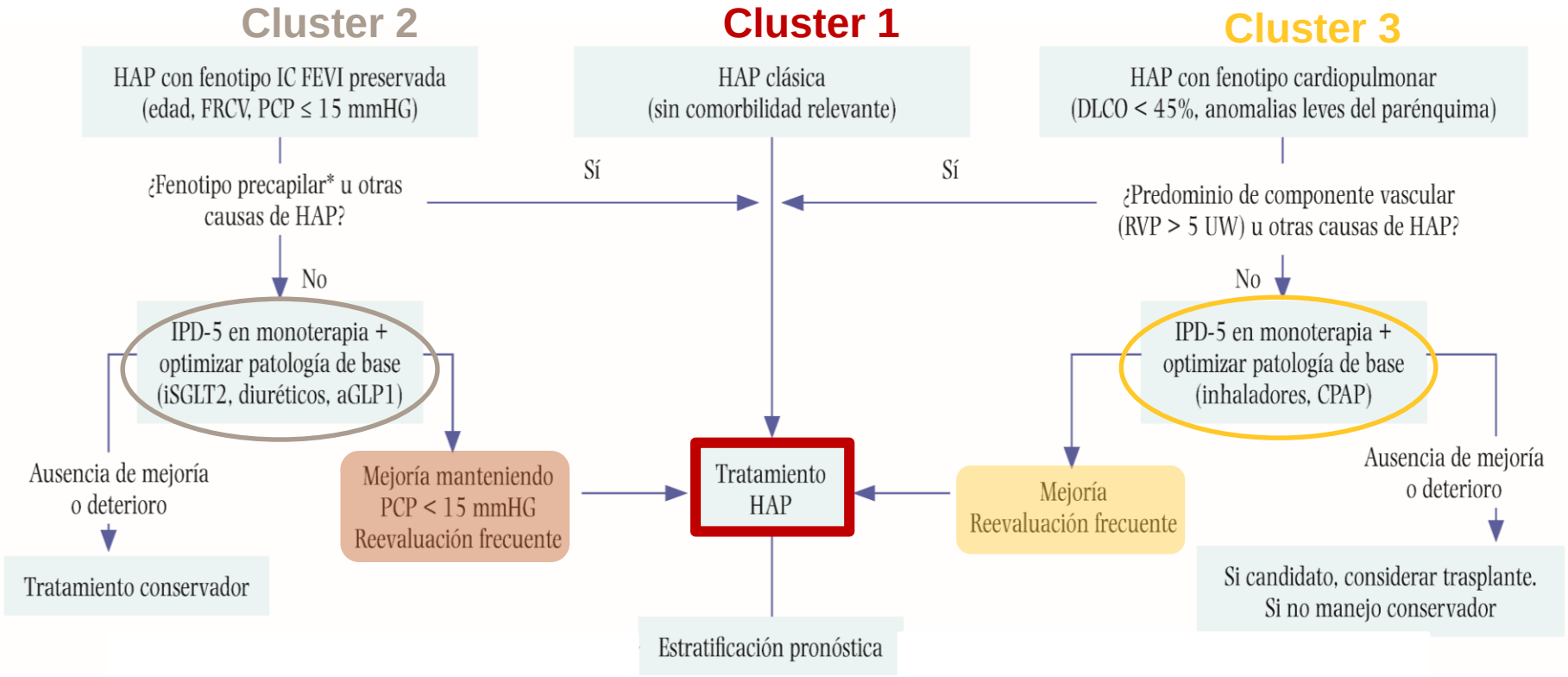
Eur Respir J 2024; 64: 2400197



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)

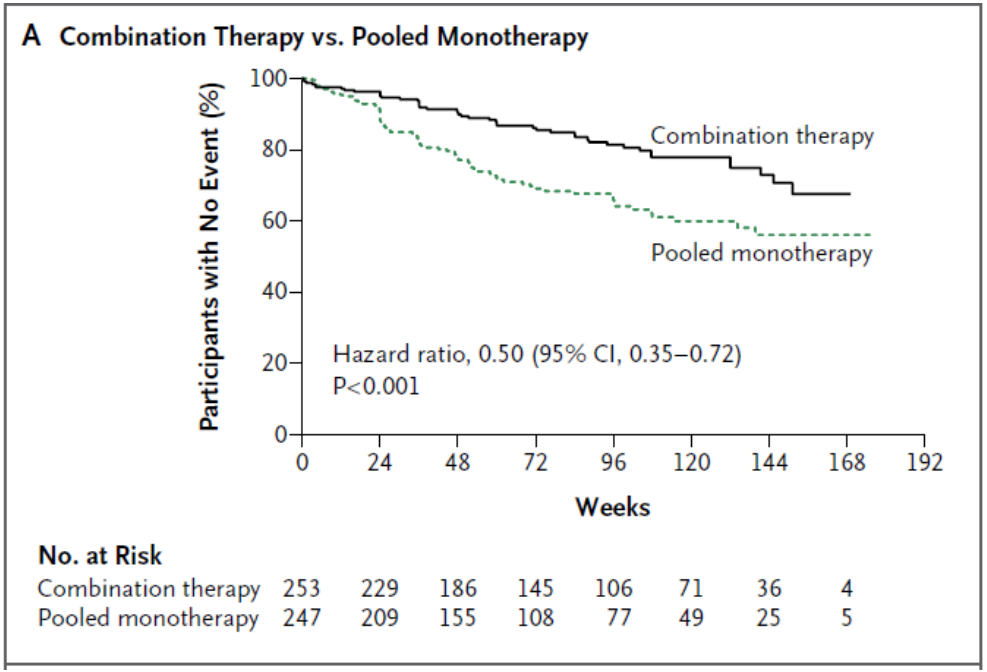
¿Qué implican las comorbilidades en el manejo de la hipertensión pulmonar?





Protocolos H12O. 2025

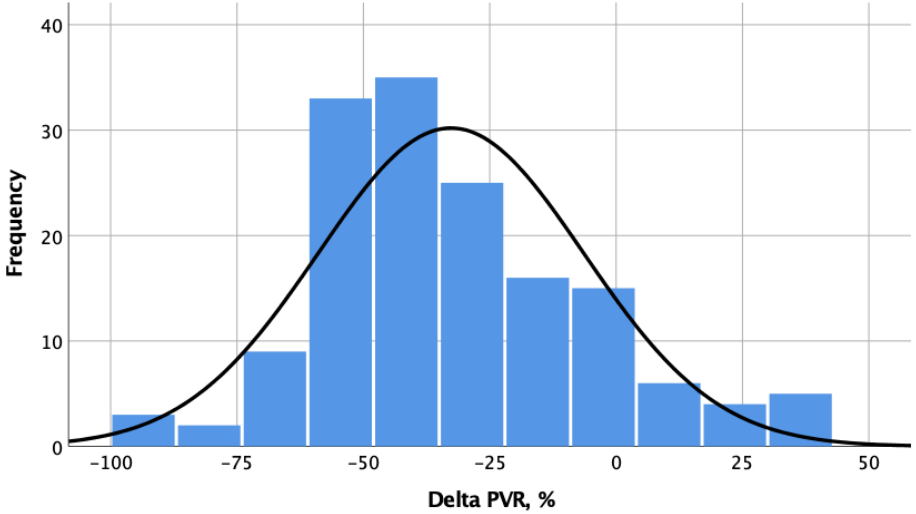
Ambition: up front combination



N Engl J Med 2015;373:834-44.
DOI: 10.1056/NEJMoa1413687

PVR and treatment response

181 naive PAH patients (IPAH, CTD) treated with upfront double oral combination
11 italian centers – iPHNET -
Ambrisentan-Tadalafil most common combi (62%)
median follow-up 180 days (IQR 79-394)



PVR reduction : median - 40 % (mean -35%)

Badagliacca R, Am J Respir Crit Care Med. 2020;10.1164/rccm.202004-1006OC.

CLI

CENTRAL ILLUSTRATION Initial Triple Versus Double Oral Combination Therapy in Pulmonary Arterial Hypertension

TRITON: Multicenter, double-blind, randomized, placebo-controlled, phase 3b study

Newly diagnosed, treatment-naive patients with pulmonary arterial hypertension (PAH)

n = 123	Macitentan 10 mg o.d.	Tadalafil 40 mg o.d.	Selexipag 200-1,600 µg b.i.d.
n = 124	Macitentan 10 mg o.d.	Tadalafil 40 mg o.d.	Placebo 200-1,600 µg b.i.d.

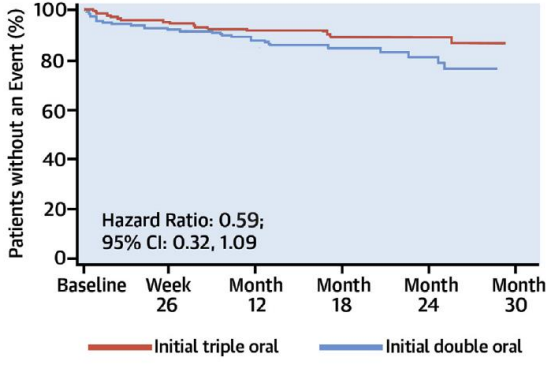
Change from Baseline to Week 26

	Initial triple	Initial double	Treatment effect
Primary Endpoint			
Pulmonary vascular resistance 	-54%	-52%	No difference
Secondary Endpoints (Exploratory Analyses)			
6-Minute walk distance 	+55 m	+56 m	No difference
NT-proBNP 	-74%	-75%	

Time to First Disease Progression Event

Secondary Endpoints (Exploratory Analyses)

41% reduction in risk of disease progression with initial triple oral vs initial double oral combination therapy



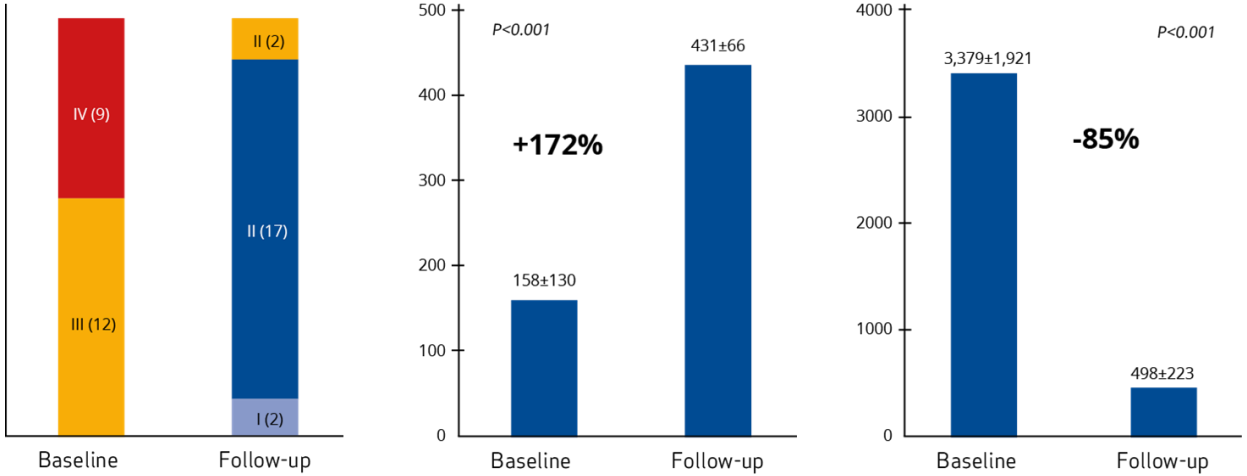
Chin, K.M. et al. J Am Coll Cardiol. 2021;78(14):1393-1403.

J Am Coll Cardiol 2021;78:1393-1403)

Hospital Universitario 12 de Octubre

Upfront combination treatment including parenteral prostanoids in critical ill patients

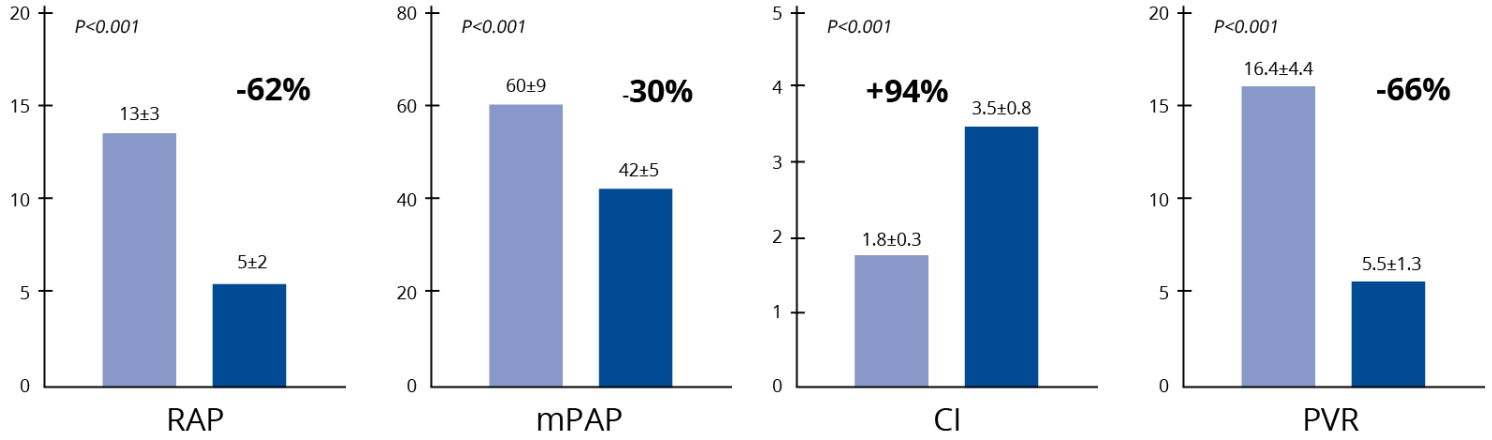
Upfront triple combination therapy with ambrisentan, tadalafil and SC treprostinil in severe PAH patients
21 patients treated - 24 months Follow-up - 21/21 patients alive on triple combination therapy



D'Alto et al. Risk reduction and right heart reverse remodeling by upfront triple combination therapy in pulmonary arterial hypertension. CHEST 2019

Upfront combination treatment including parenteral prostanoids in critical ill patients

- Right-sided atrial pressure decreased from 13 ± 3 to 5 ± 2 mm Hg
- Mean pulmonary artery pressure decreased from 60 ± 9 to 42 ± 5 mm Hg
- Cardiac index increased from 1.8 ± 0.3 to 3.5 ± 0.8 L/min/m2
- Pulmonary vascular resistance (PVR) decreased from 16.4 ± 4.4 to 5.5 ± 1.3 WU



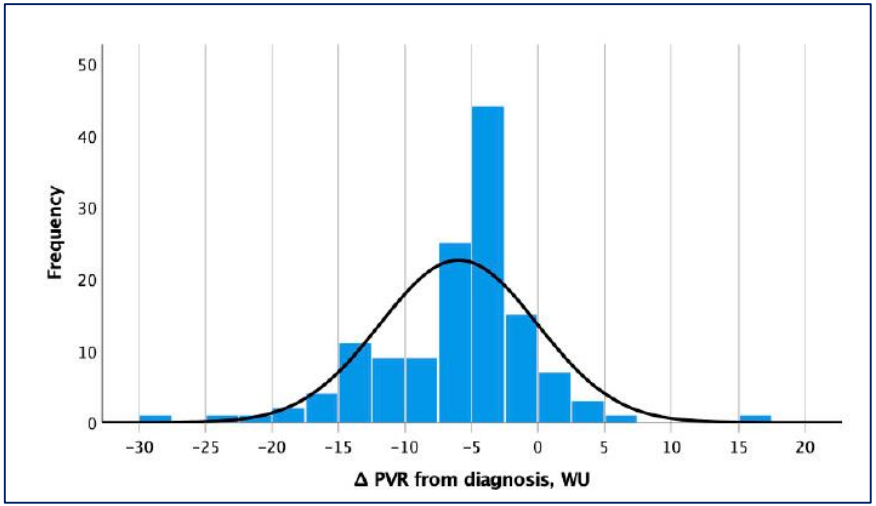
D'Alto et al. Risk reduction and right heart reverse remodeling by upfront triple combination therapy in pulmonary arterial hypertension. CHEST 2019

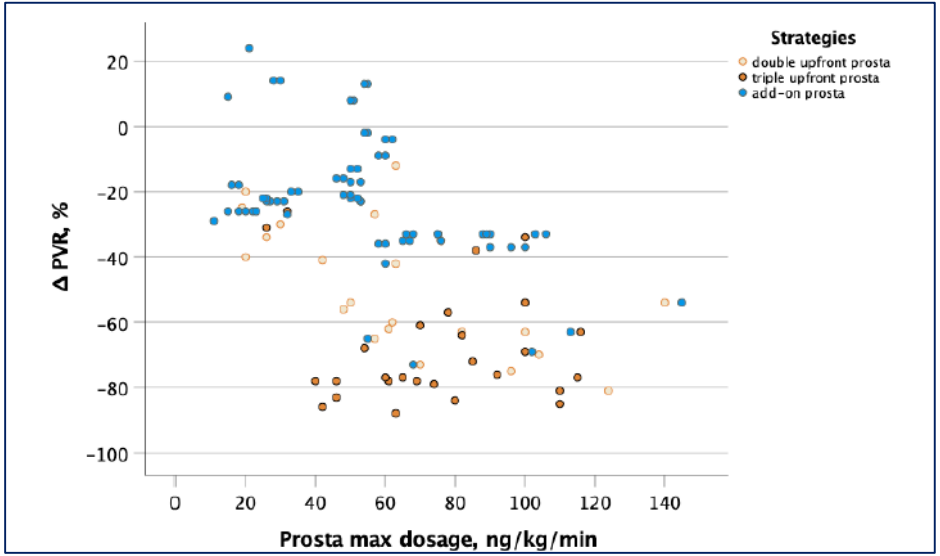
Journal of
Clinical Medicine

MDPI

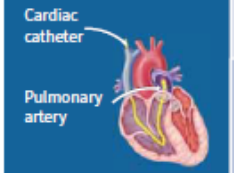
Article

Impact of Parenteral Prostanoids in Pulmonary Arterial Hypertension: The Relevance of Timing





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; in press: 2401323

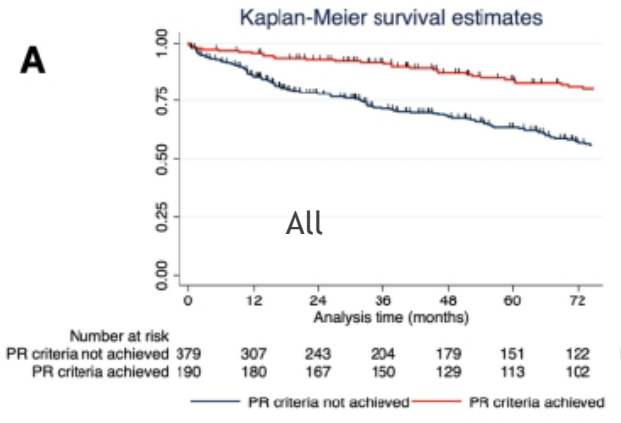
ERJ open research

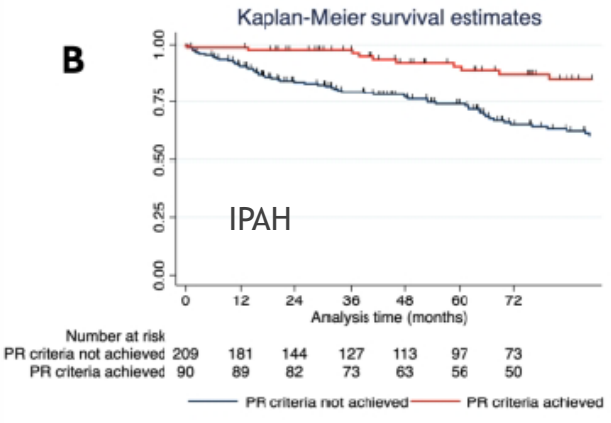
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

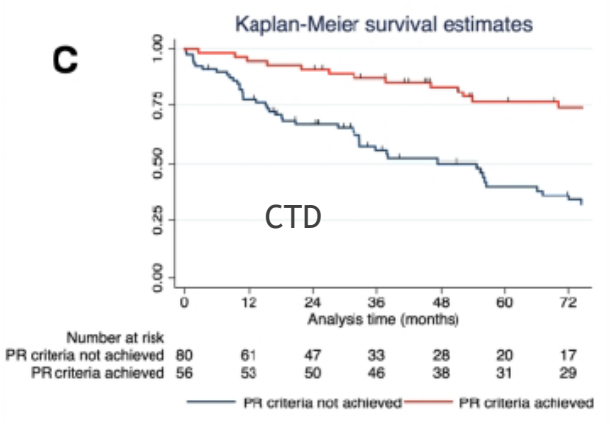
569 pacientes

Remisión parcial en seguimiento

PVR< 5UW y/o mPP < 35 mmhg

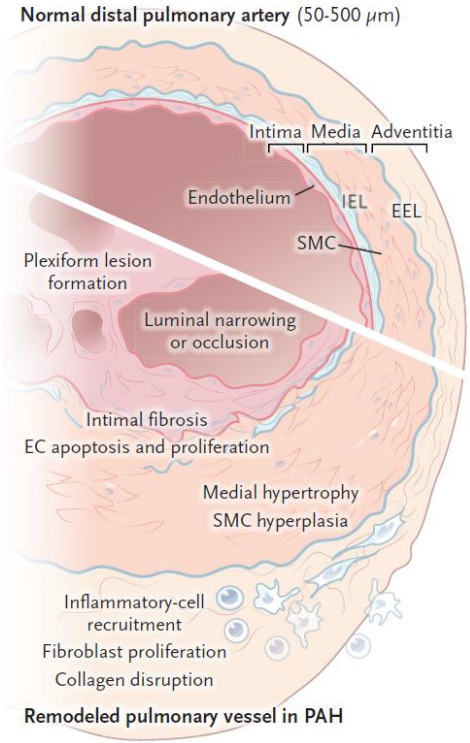


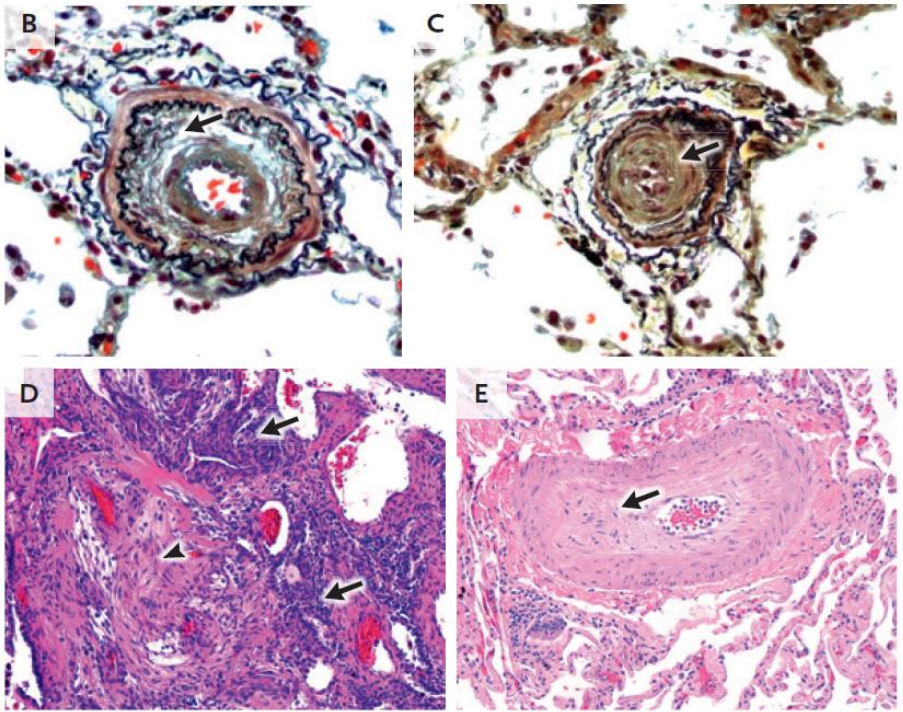




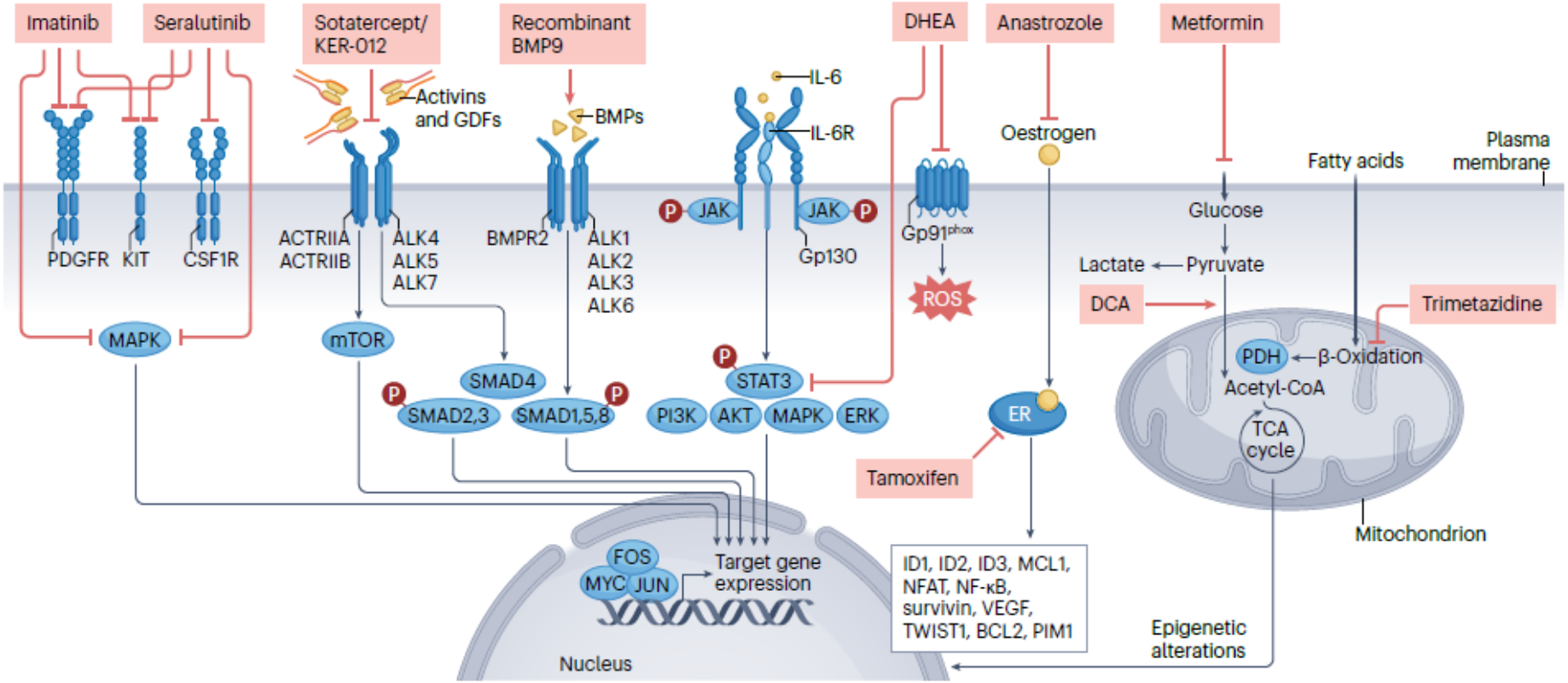
Cruz-Utrilla A. Accepted for publication

Pathobiology of pulmonary hypertension

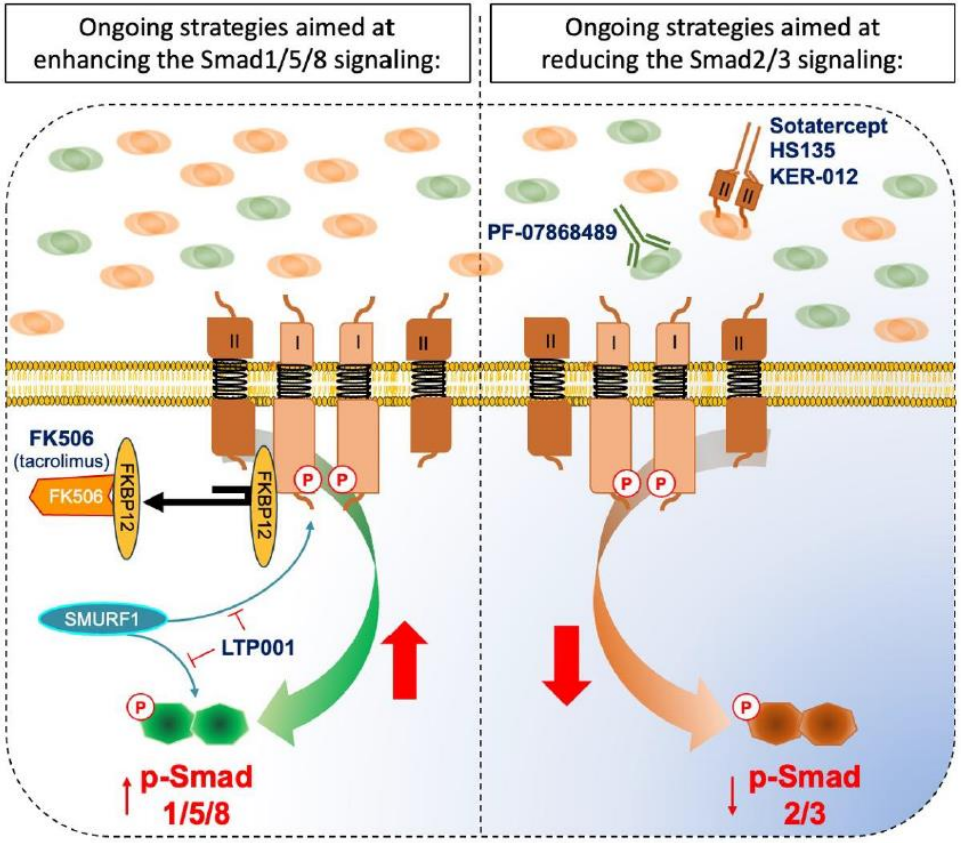




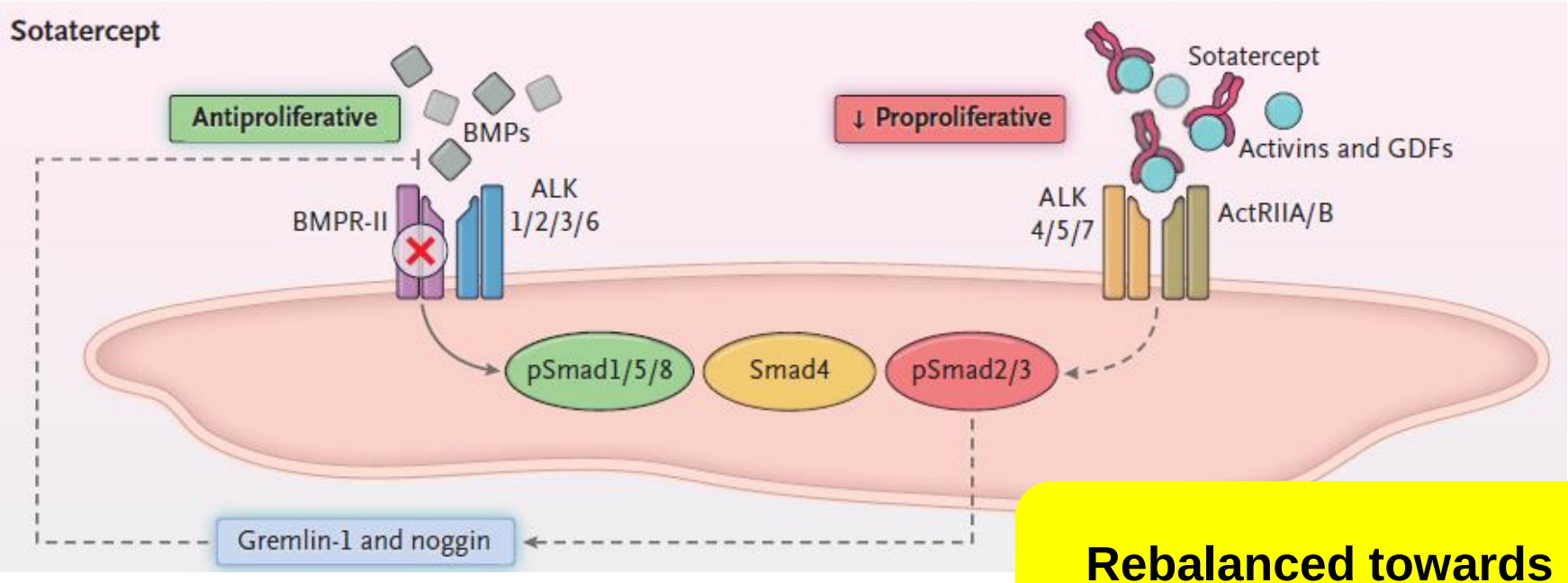
Hassoun, N Engl J Med 2021;385:2361-76



nature reviews Cardiology. Ghofrani H et al. https://doi.org/10.1038/s41569-024-01064-4


Ongoing strategies aimed at enhancing the Smad1/5/8 signaling:
Ongoing strategies aimed at reducing the Smad2/3 signaling:
Sotatercept
HS135
KER-012
PF-07868489
FK506
(tacrolimus)
FK506
FKBP12
FKBP12
P
SMURF1
LTP001
p-Smad
1/5/8
p-Smad
2/3
Smad1/5/8 pathway activator ligand:
Smad2/3 pathway activator ligand:

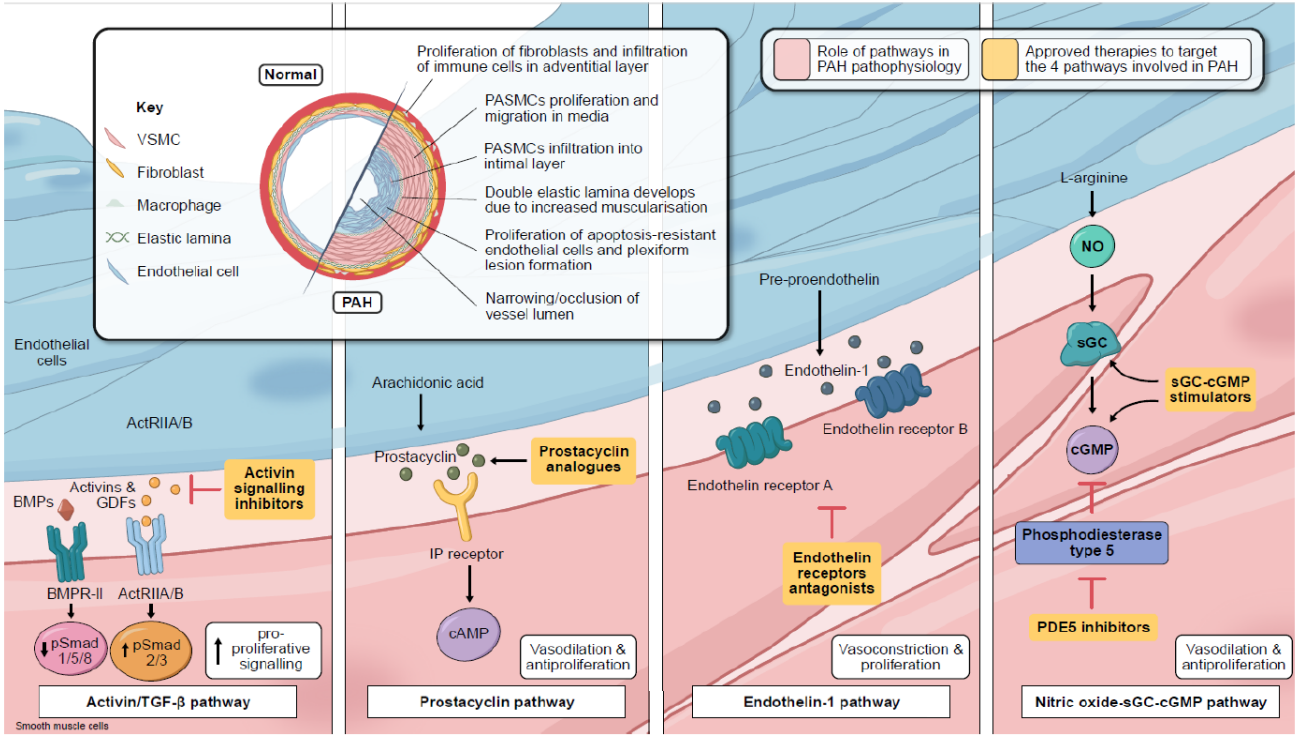
Mechanism of action: Sotatercept



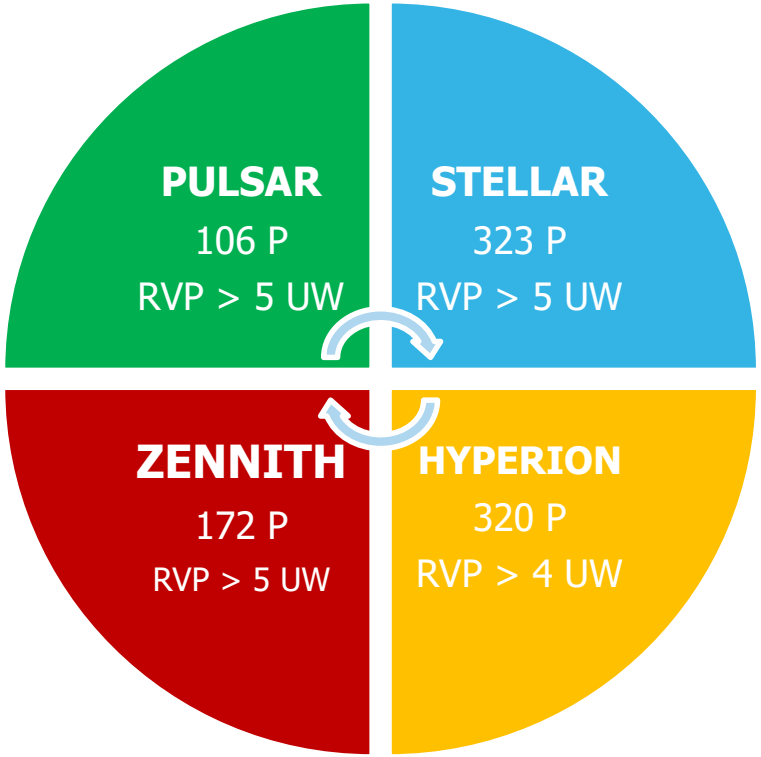
Rebalanced towards vascular homeostasis

Humbert et al. N Engl J Med 2021;384:1204-15

ASI class to target a the ACTIVIN/TGFB pathway and treat PAH



- Hoeper MM, Gomber-Mailand M, Badesh B, et al.. Eur Respir J 2025; in press



SOTERIA
426 P

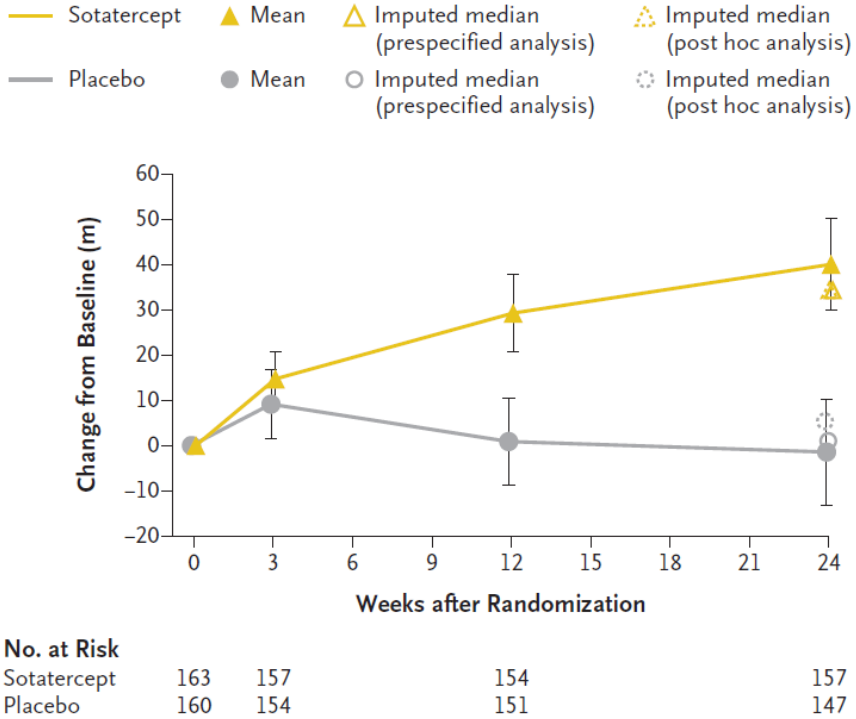
STELLAR: demographics and baseline clinical characteristics

Parameter		Placebo N = 160	Sotatercept N = 163	Total N = 323
Classification of PAH, n (%)	Idiopathic	106 (66.3)	83 (50.9)	189 (58.5)
	Heritable	24 (15.0)	35 (21.5)	59 (18.3)
	Associated with CTD	19 (11.9)	29 (17.8)	48 (14.9)
	Drug-induced or toxin-induced	4 (2.5)	7 (4.3)	11 (3.4)
	Associated with corrected congenital shunts	7 (4.4)	9 (5.5)	16 (5.0)
WHO FC, n (%)†	Class II	78 (48.8)	79 (48.5)	157 (48.6)
	Class III	82 (51.3)	84 (51.5)	166 (51.4)
Age		47.6(14.1)	48.3 (15.5)	47.9 (14.8)
Background therapy‡, n (%)	Prostacyclin infusion therapy§	64 (40.0)	65 (39.9)	129 (39.9)
	Mono	4 (2.5)	9 (5.5)	13 (4.0)
	Double	56 (35.0)	56 (34.4)	112 (34.7)
	Triple	100 (62.5)	98 (60.1)	198 (61.3)
Time since diagnosis of PAH		9.2 (7.3)	8.3 (6.7)	8.8(7.0)

STELLAR: demographics and baseline clinical characteristics of study patients

Parameter	Placebo N = 160	Sotatercept N = 163	Total N = 323
Hb, g/dL	13.7 ± 1.6	13.9 ± 1.7	13.8 ± 1.6
eGFR, mL/min/1.73 m^2	88.3 ± 35.8	91.2 ± 34.6	89.8 ± 35.2
6MWD, m	407.0 ± 78.2	398.5 ± 83.5	402.7 ± 80.9
NT-proBNP, pg/mL	1207.8 ± 2694.4	1037.5 ± 2498.6	1121.1 ± 2593.8
PVR, dyn sec cm^{-5}	745.8 ± 313.5	781.3 ± 398.5	763.7 ± 358.8
CO, L/min	4.8 ± 1.2	4.9 ±1.3	4.8 ± 1.2
Cardiac index, L/min/m^2	2.7 ± 0.6	2.7 ± 0.6	2.7 ± 0.6
Mean pulmonary artery pressure, mm Hg	52.2 ± 13.0	53.0± 14.6	52.6 ± 13.8
RA pressure, mm Hg	8.5 ± 4.5	8.0 ± 4.3	8.2 ± 4.4
Pulmonary arterial wedge pressure, mm Hg	9.8 ± 3.1	9.7 ± 3.2	9.8 ± 3.1
Mixed venous oxygen saturation, %	67.4 ± 7.9	66.8 ± 7.1	67.1 ± 7.5

Sotatercept – STELLAR trial

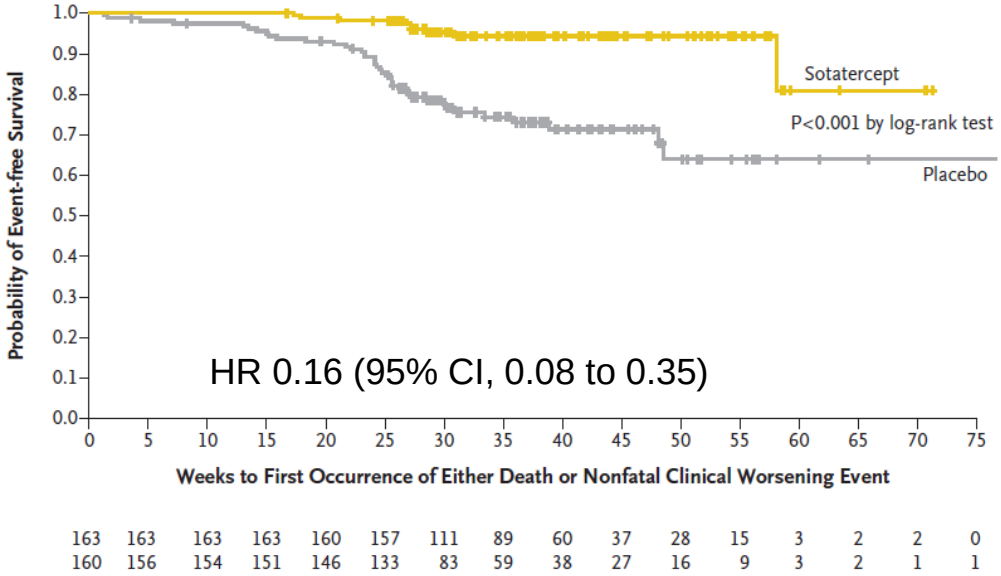


	Placebo (N=160)	Sotatercept (N=163)
Baseline mean (±SD)*	404.7 (±80.6)	397.6 (±84.3)
Observed mean change from baseline (±SD)*	-1.4 (±72.0)	40.1 (±64.3)
Observed median*	6.0	34.5
Imputed median†	1.0	34.4
Hodges-Lehmann location shift (95% CI)‡		40.8 (27.5, 54.1)
Wilcoxon p-value§		< 0.001

Hoeper et al. N Engl J Med 2023;388:1478-90

Sotatercept – STELLAR trial

84 reduction in the risk of fatal and nonfatal outcomes after a median follow-up of 32.7 weeks

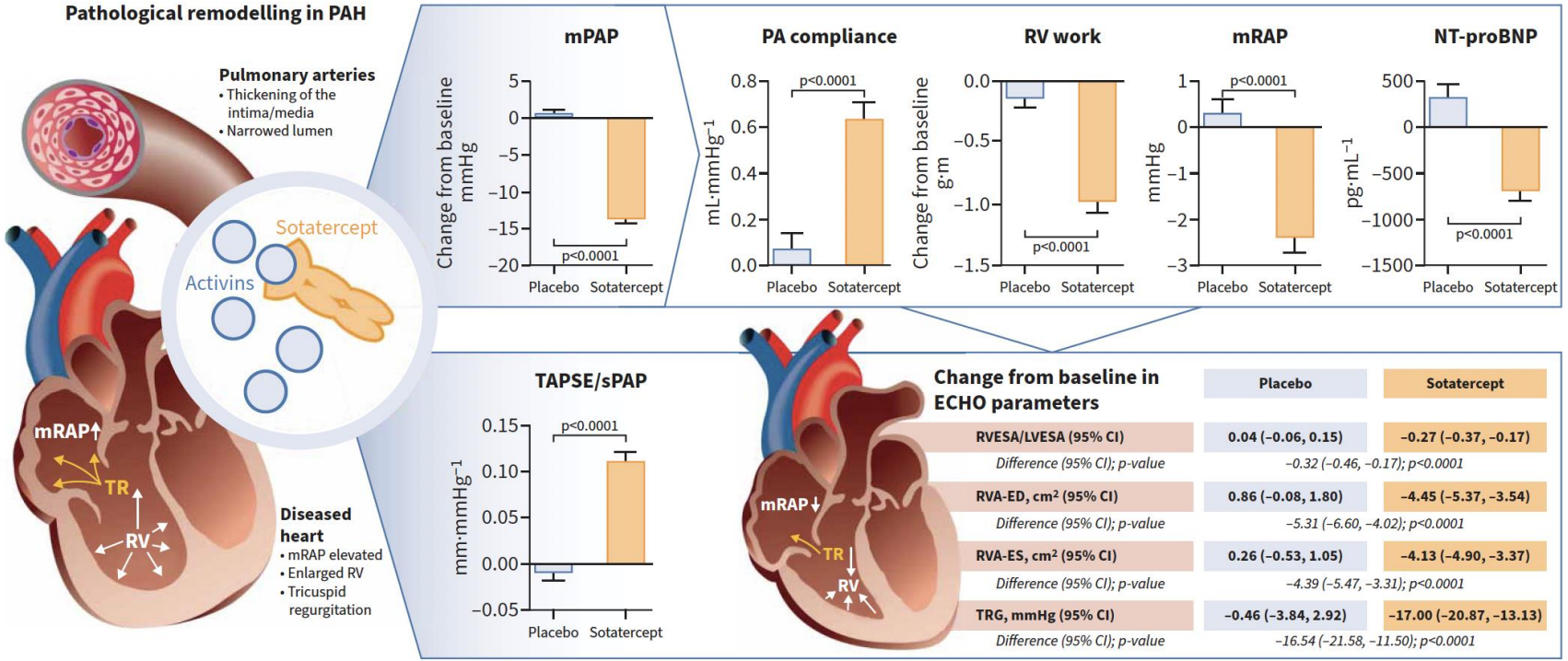


	Sotatercept (163)	Placebo (160)
Pts with worsening/death	9 (5.5)	42 (46.2)
Death	2 (1.2)	6 (3.8)
Listing HL transplant	1 (0.6)	1 (0.6)
Rescue therapy	2 (1.2)	17 (10.6)
Atrial septostomy	0	0
Hospitalization	0	7 (4.4)
Worsening PAH	4 (2.5)	15 (9.4)

Cinical worsening events : listing for transplantation, initiation or rescue therapy with an approved background treatment or increase in the prostacyclin dose by ≥10%, hospitalization ≥24 hours for PAH or worsening of PAH relative to baseline as defined by both a worsened WHO-FC and a decrease in 6MWD ≥15%

Hoeper et al. N Engl J Med 2023;388:1478-90

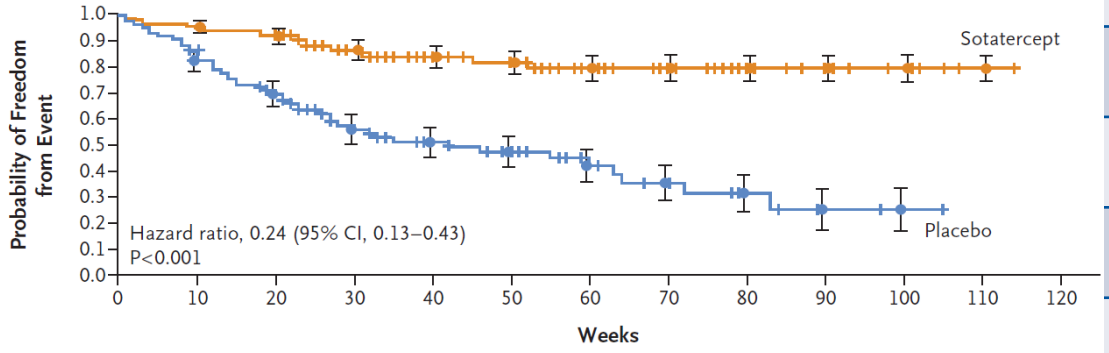
Effects of sotatercept on haemodynamics and right heart function: analysis of the STELLAR trial



Change from baseline in ECHO parameters	Placebo	Sotatercept
RVESA/LVESA (95% CI)	0.04 (−0.06, 0.15)	−0.27 (−0.37, −0.17)
Difference (95% CI); p-value	*−0.32 (−0.46, −0.17); p<0.0001*	
RVA-ED, cm² (95% CI)	0.86 (−0.08, 1.80)	−4.45 (−5.37, −3.54)
Difference (95% CI); p-value	*−5.31 (−6.60, −4.02); p<0.0001*	
RVA-ES, cm² (95% CI)	0.26 (−0.53, 1.05)	−4.13 (−4.90, −3.37)
Difference (95% CI); p-value	*−4.39 (−5.47, −3.31); p<0.0001*	
TRG, mmHg (95% CI)	−0.46 (−3.84, 2.92)	−17.00 (−20.87, −13.13)
Difference (95% CI); p-value	*−16.54 (−21.58, −11.50); p<0.0001*	

ZENITH: Primary endpoint results

Kaplan-Meier Estimates of Primary Composite Endpoint

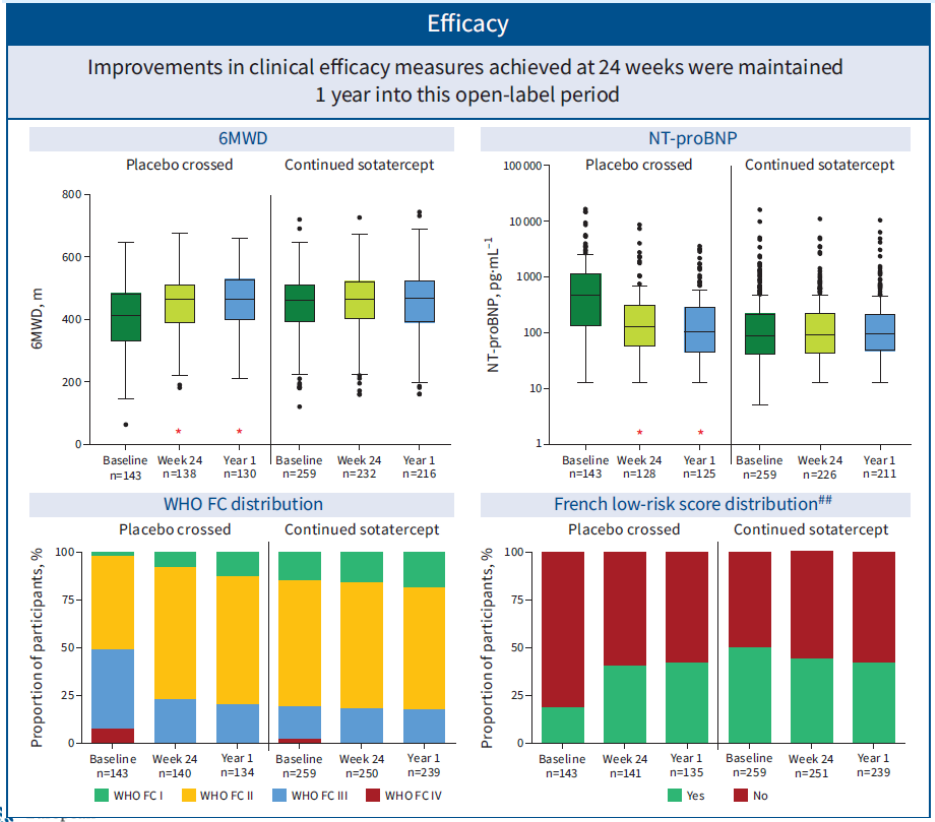


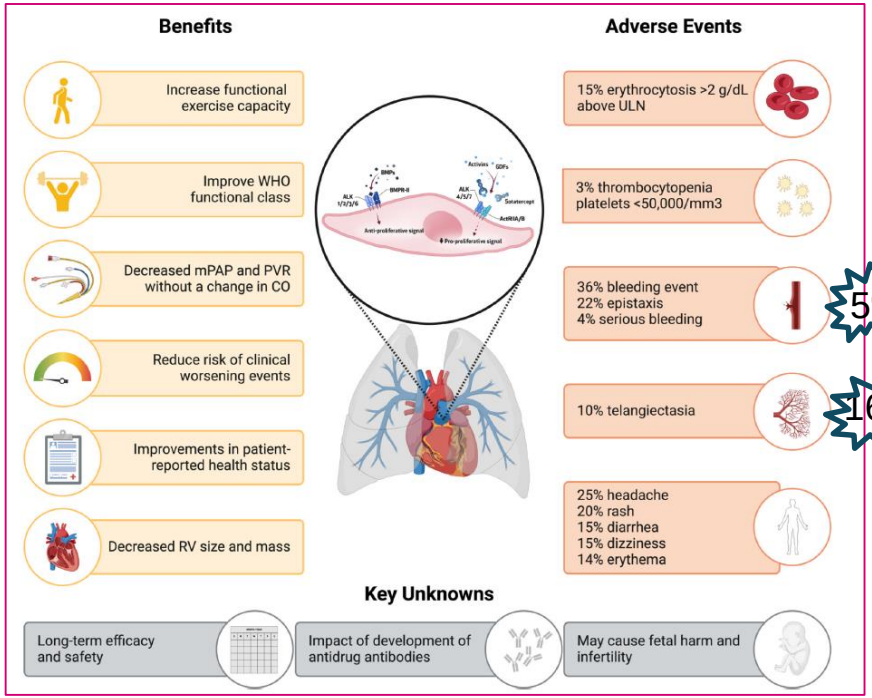
No. at Risk													
Sotatercept	86	82	79	61	51	40	28	21	13	9	5	1	0
Placebo	86	74	59	38	28	23	15	10	5	2	1	0	0
No. of Events													
Sotatercept	4	3	4	2	1	1	0	0	0	0	0	0	0
Placebo	12	13	10	4	2	1	3	1	1	0	0	0	0

Components of the primary endpoint, n (%)	Placebo (n=86)	Sotatercept (n=86)
Patients with one or more primary events	**47 (54.7)**	**15 (17.4)**
Components of the primary endpoint as a standalone outcome[d]		
All-cause death[e]	13 (15.1)	7 (8.1)
Lung transplantation	6 (7.0)	1 (1.2)
PAH worsening–related hospitalization of ≥24 hours	43 (50.0)	8 (9.3)

Analysis of Time to First Morbidity-Mortality Events

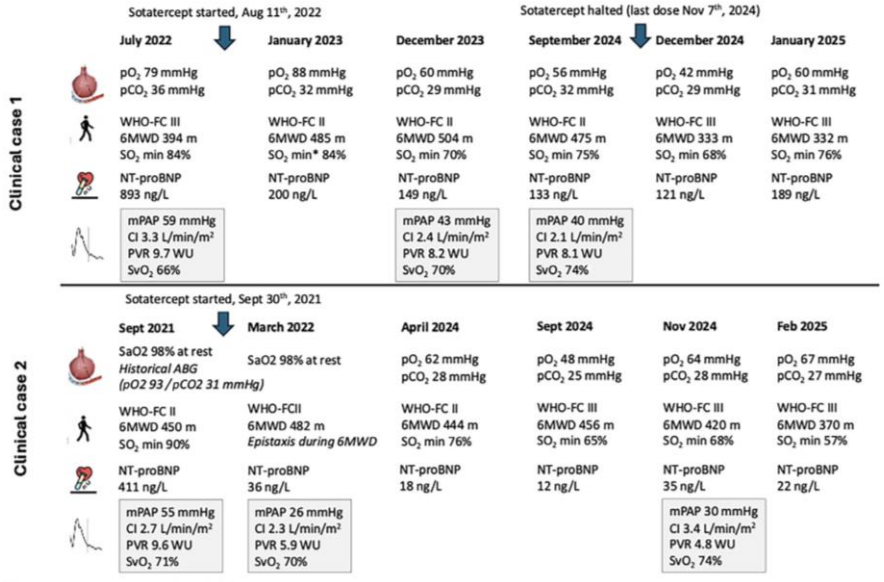
A long-term follow-up study of Sotatercept: interim results of SOTERIA

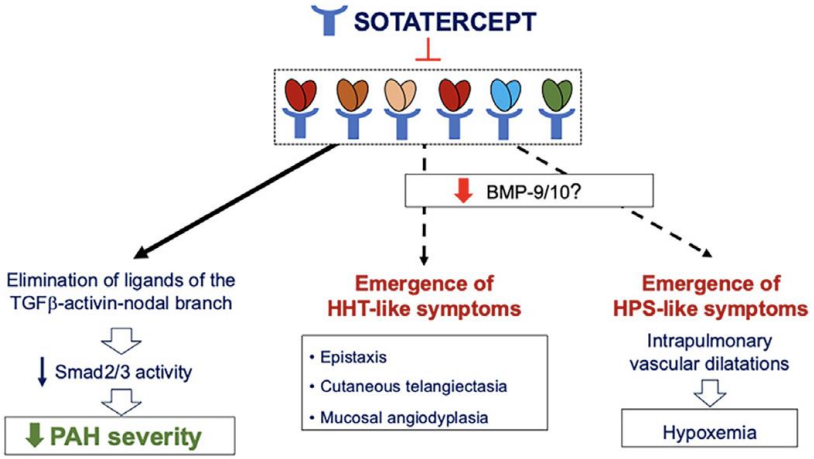




Severe Hypoxemia and Pulmonary Capillary Dilatations in Pulmonary Arterial Hypertension Patients Treated with Sotatercept

Karen M. Olsson[1,2], Laurent Savale[3,4,5], Christophe Guignabert[3,4], Da-Hee Park[1,2], Jan C. Kamp[1,2], Athénaïs Boucly[3,4,5], David Montani[3,4,5], Olivier Sitbon[3,4,5], Marc Humbert[3,4,5], and Marius M. Hoeper[1,2]

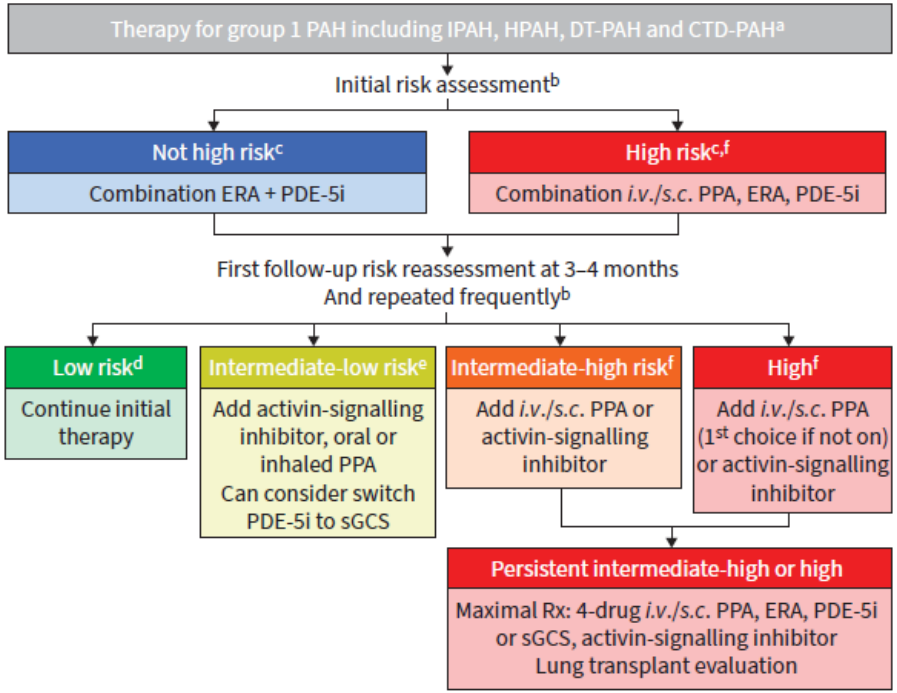




Am J Respir Crit Care Med. 2025 Jul;211(7):1303-1305

Pericardial effusions and sotatercept therapy in PAH: a multicentre, real-world experience

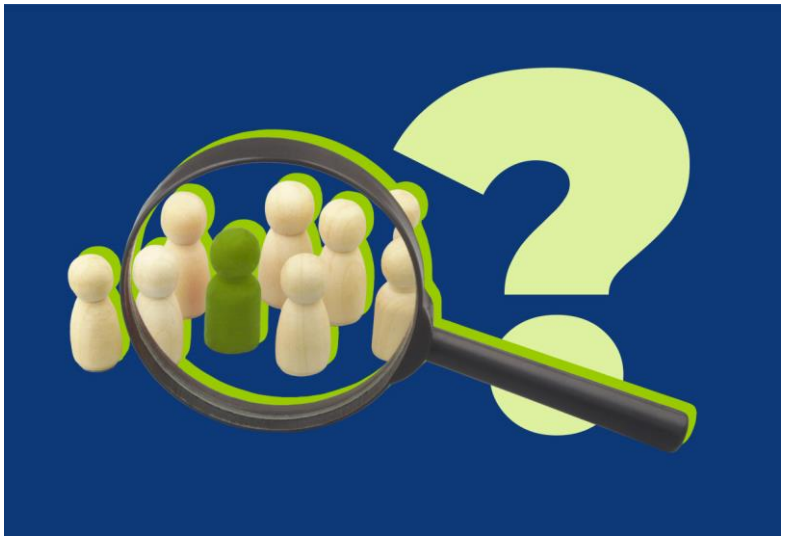
- Among 391 adults with PAH who were consecutively treated with sotatercept as add-on therapy at six comprehensive care centres. 70.3% were on a prostacyclin pathway agent
- 165 (42.2%) IPAH, 133 (34.0%) had PAH -CTD, 34 (8.7%) had drug- and toxin-associated PAH, 26 (6.6%) had heritable PAH (HPAH), 25 (6.4%) had PAH associated with CHD
- All events occurred among patients on 0.7 $mg \cdot kg^{-1}$ dose of sotatercept with a median exposure:136 days
- 20 patients (5%): Seven patients (35.0%) developed new-onset effusions, while 13 (65.0%) developed worsening of an existing pericardial effusion The cumulative incidence was 9,8% in PAH-CTD and 3,9% IPAH
- Pericardial effusions were associated with improvement in haemodynamics and/or right heart function, as opposed to the progression of cardiopulmonary vascular disease
- 11 patients (48%) required intervention either by pericardiocentesis or by the creation of a pericardial window.



Eur Respir J 2024. DOI: 10.1183/13993003.01325-2024].

EUROPEAN RESPIRATORY JOURNAL
EDITORIAL
M.M. HOEPER

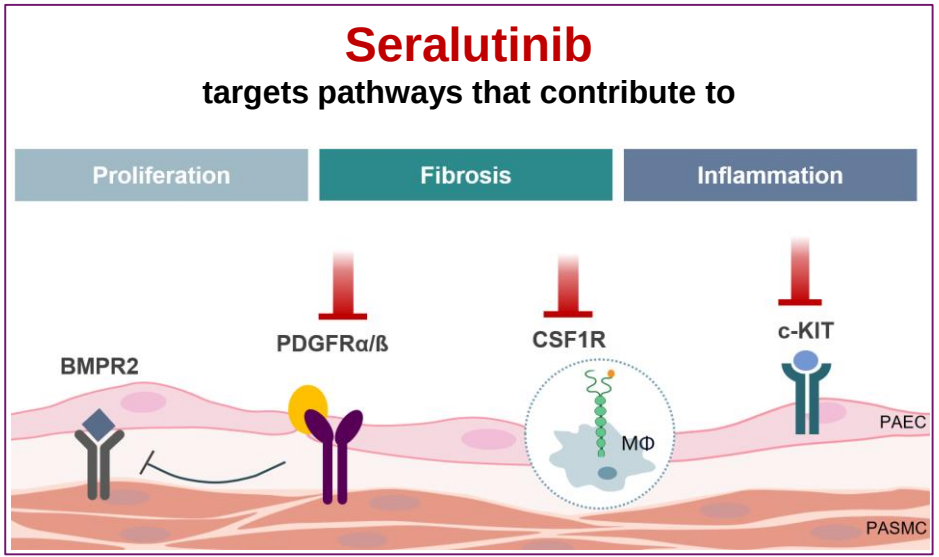
Sotatercept in pulmonary arterial hypertension: revolution, risk and the road ahead



Eur Respir J 2025; 66: 2501633

Seralutinib inhibits key drivers of PH pathophysiology

- Proliferation, inflammation, and fibrosis play critical, interconnected, roles in vascular remodeling in PAH
- Seralutinib potently and selectively inhibits PDGFRα/ß, CSF1R, and c-KIT kinases, key pathogenic drivers of PAH progression
- By inhibiting PDGFR signaling, seralutinib restores BMPR2 expression
- Seralutinib is an inhaled, novel, TKI designed to normalize vascular remodeling

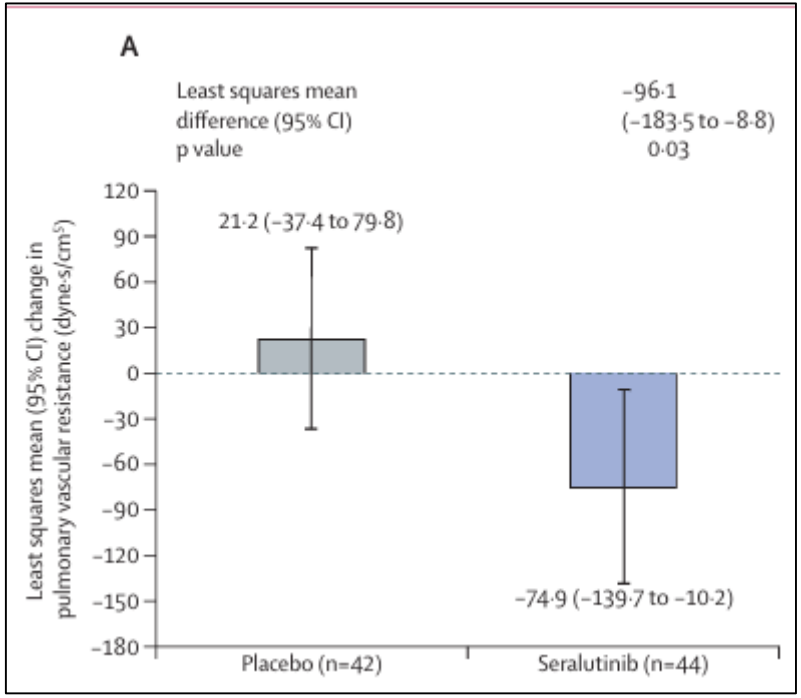


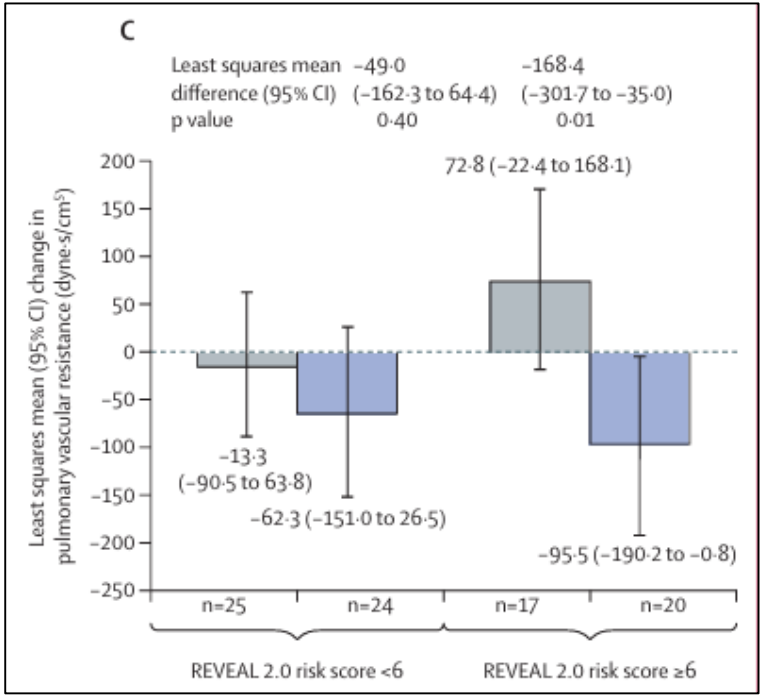
BMPR2, bone morphogenetic protein receptor type 2; c-KIT, mast/stem cell growth factor; CSF1(R), colony stimulating factor 1 (receptor); MΦ, macrophage; PAEC, pulmonary artery endothelial cell; P(A)H, pulmonary (arterial) hypertension; PASMC, pulmonary artery smooth muscle cell; PDGF(R), platelet-derived growth factor (receptor); TKI, tyrosine kinase inhibitor.

1 Schermuly RT, et al. *J Clin Invest.* 2005;115(10):2811-2821. **2** Antoniu SA. *Expert Opin Ther Targets.* 2012;16(11):1055-1063. **3** Hoeper MM, et al. *Circulation.* 2013;127(10):1128-1138. **4** Galkin A, et al. *Eur Respir J.* 2022;6(6)0:2102356.

Seralutinib in adults with pulmonary arterial hypertension (TORREY): a randomised, double-blind, placebo-controlled phase 2 trial

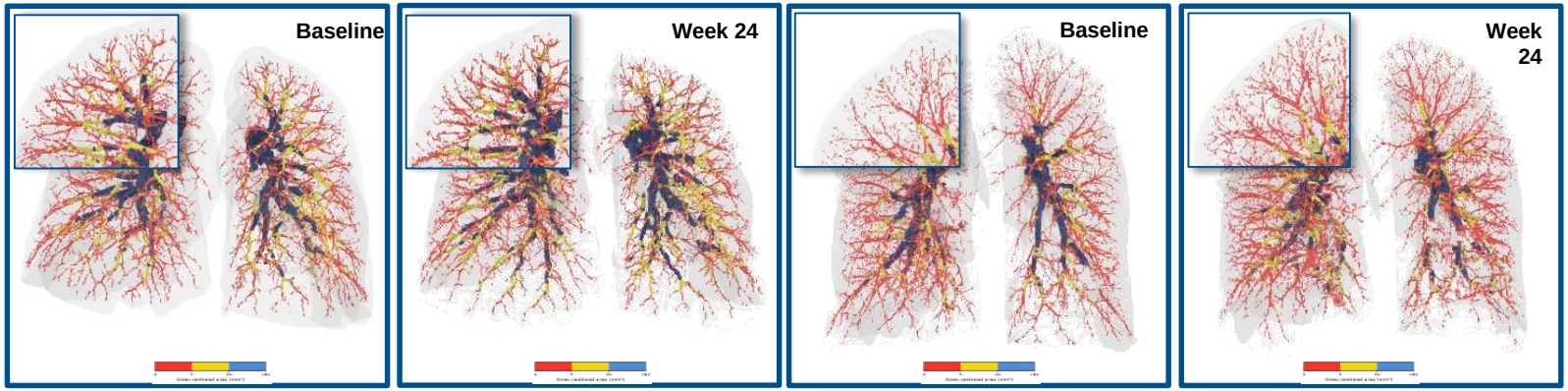
*Robert P Frantz, Vallerie V McLaughlin, Sandeep Sahay, Pilar Escribano Subías, Ronald L Zolty, Raymond L Benza, Richard N Channick, Kelly M Chin, Anna R Hemnes, Luke S Howard, Olivier Sitbon, Jean-Luc Vachiéry, Roham T Zamanian, Matt Cravets, Robert F Roscigno, David Mottola, Robin Osterhout, Jean-Marie Bruey, Erin Elman, Cindy-ann Tompkins, Ed Parsley, Richard Aranda, Lawrence S Zisman, Hossein-Ardeschir Ghofrani, on behalf of the TORREY Study Investigators**





European Reference Network for rare or low prevalence complex diseases
Network Respiratory Diseases (ERN-LUNG)
UHP Unidad de Hipertensión Pulmonar 12 de Octubre
ciberCV Centro de Investigación Biomédica en Red Enfermedades Cardiovasculares
Hospital Universitario 12 de Octubre SaludMadrid Comunidad de Madrid

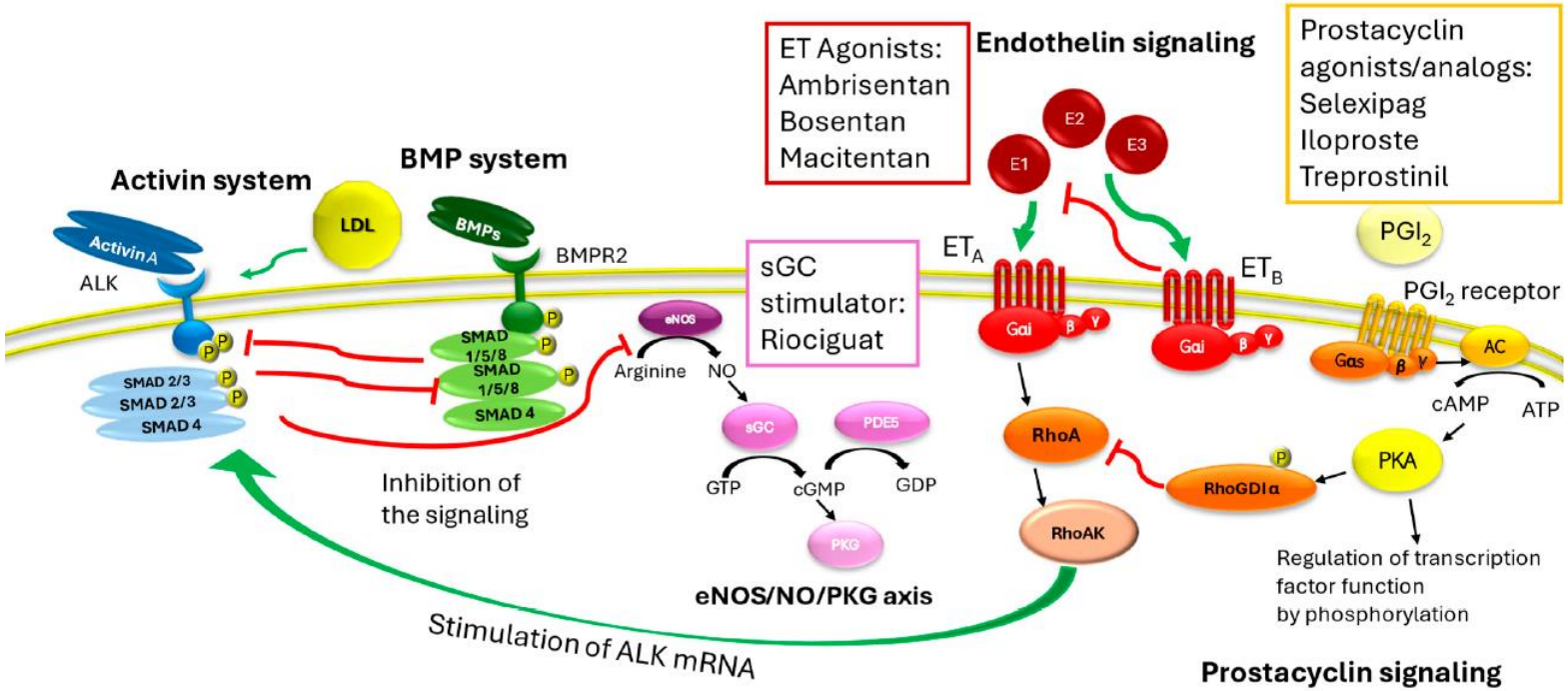
Changes in the pulmonary vasculature after 24 weeks of seralutinib treatment are suggestive of a reverse remodeling effect

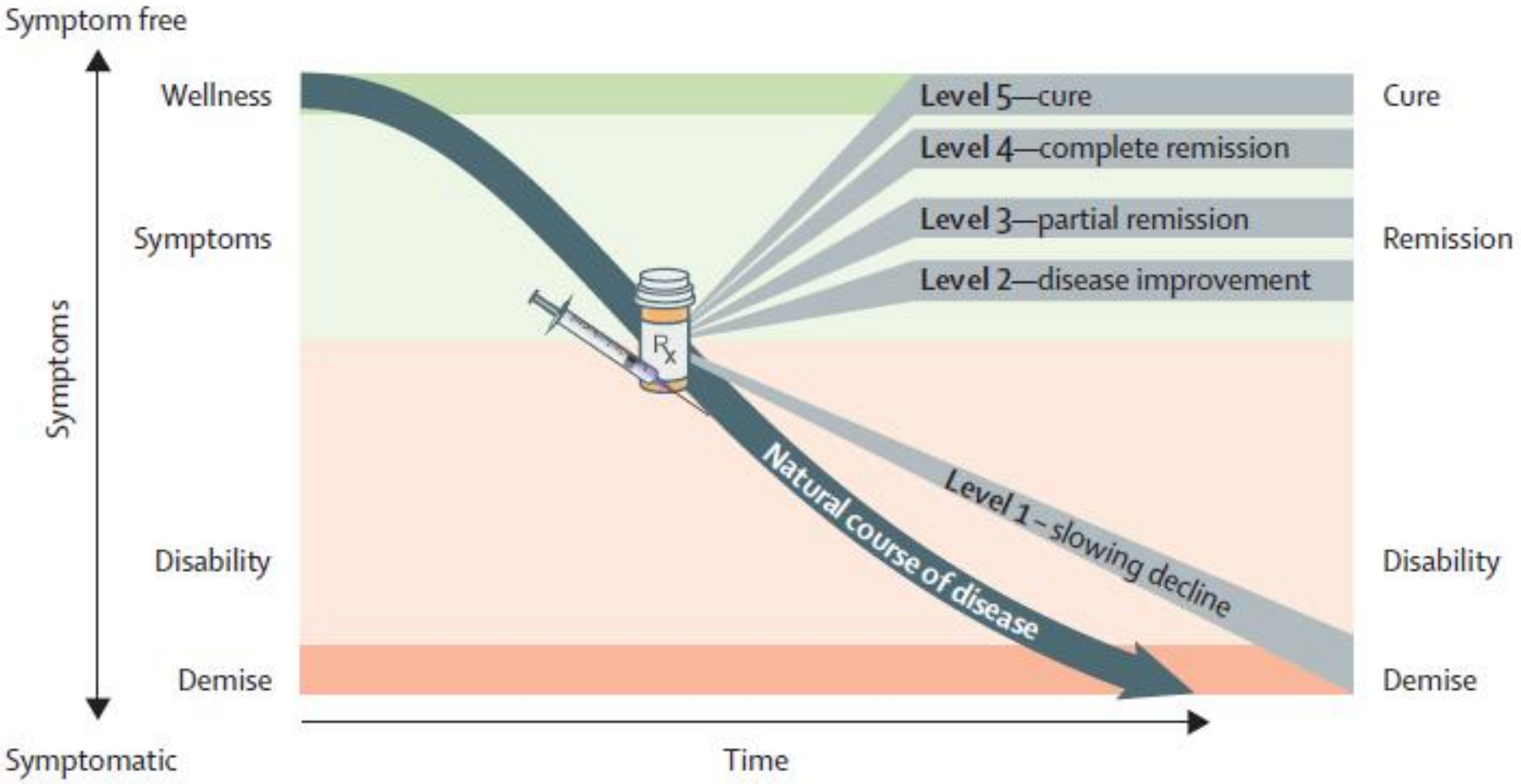


Placebo patient		Seralutinib patient	
Female, 24 y, IPAH, FC II, treated with PDE5-i + prostacyclin		Female, 58 y, IPAH, FC II, treated with ERA + PDE5-i + prostacyclin	
PVR change, dyne·s/cm^5 (%)	283 (+65.4)	PVR change, dyne·s/cm^5 (%)	-159 (-39.0)
ΔBV510A ratio (% change)	-0.70 (-28.9)	ΔBV510A ratio (% change)	+2.5 (+78.0)

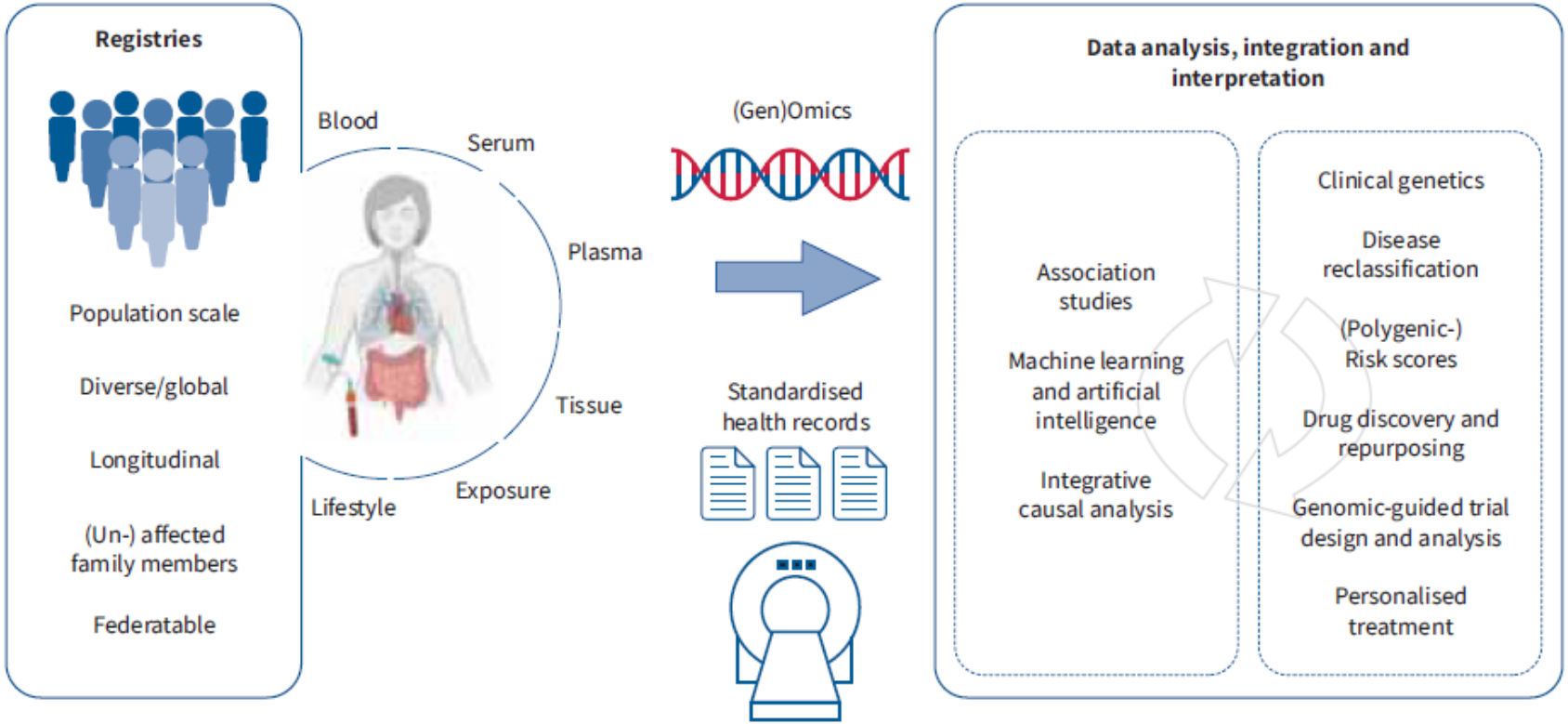
The images shown are representative examples. The highlighted sections were chosen to illustrate changes in the pulmonary vasculature.

Crosstalk Between the Activin System and Other Signaling




Symptom free
Wellness
Symptoms
Disability
Demise
Symptomatic
Symptoms
Level 5—cure
Level 4—complete remission
Level 3—partial remission
Level 2—disease improvement
Level 1—slowing decline
Natural course of disease
Cure
Remission
Disability
Demise
Time

Medicina de precisión en la HAP



René Magritte. El falso Espejo

https://historia-arte.com/obras/el-falso-espejo