



Ipertensione arteriosa polmonare: le sfide per il futuro

CONGRESSO

ROMA, 25 - 27 Giugno 2026

SEDE DEI LAVORI

A. Roma Lifestyle Hotel
Via Giorgio Zoega 59, Roma

Dott.C.Raineri

Divisione di Cardiologia

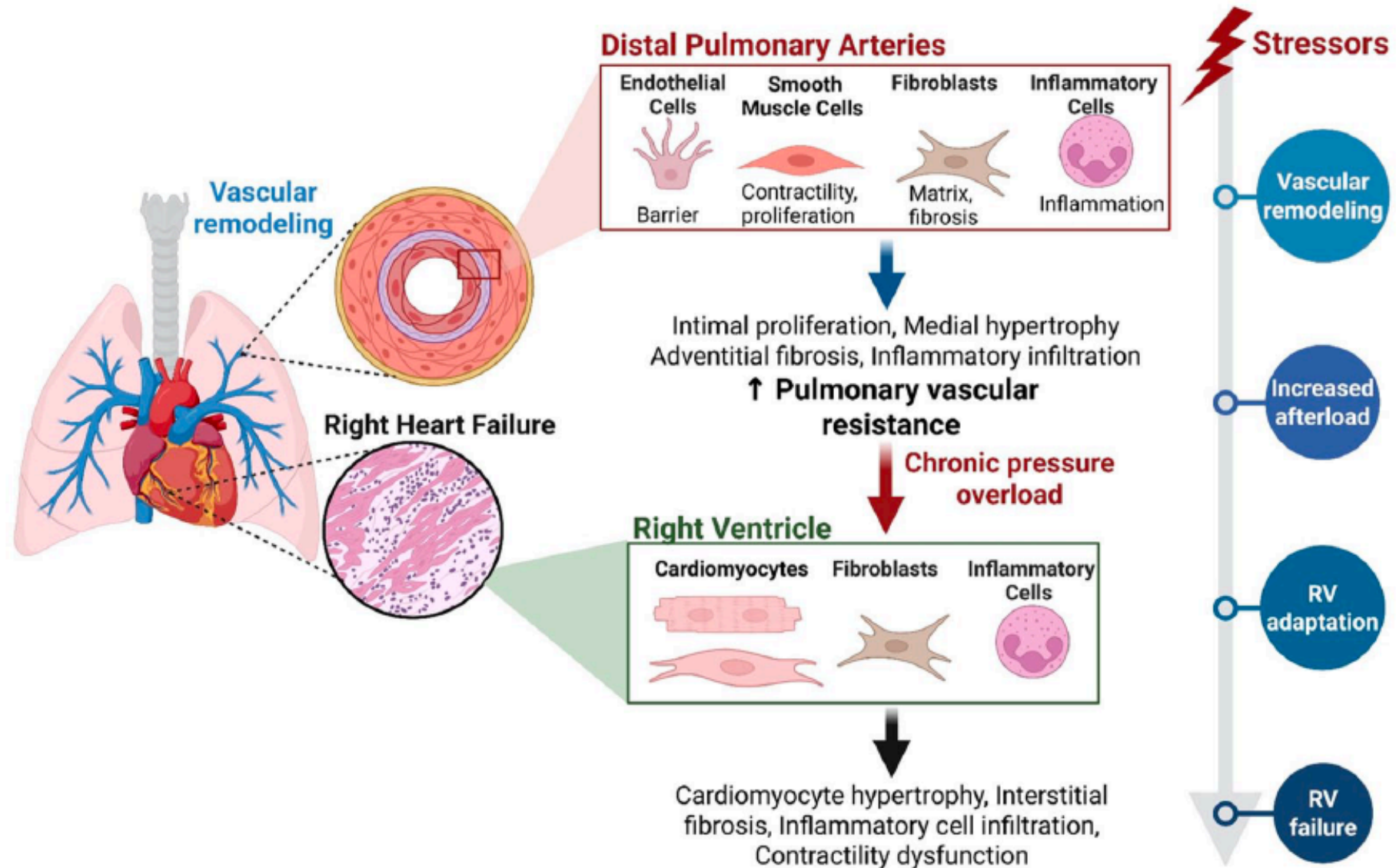
Città della Salute e della Scienza- Ospedale Molinette



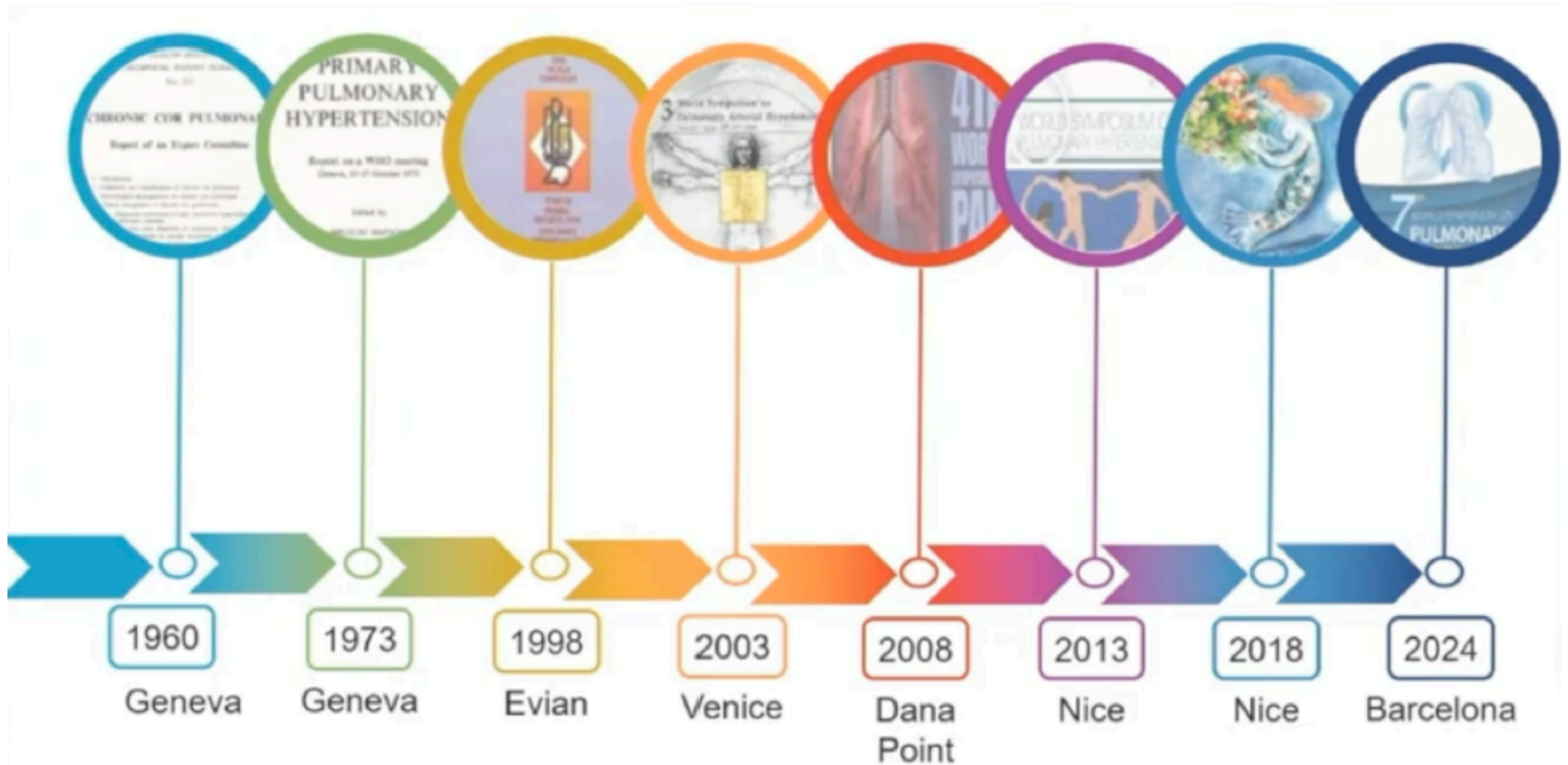
Disclosure

- MSD
- Johnson & Johnson

Pulmonary Arterial hypertension



Timeline PAH



History of PH and development of therapeutic drugs

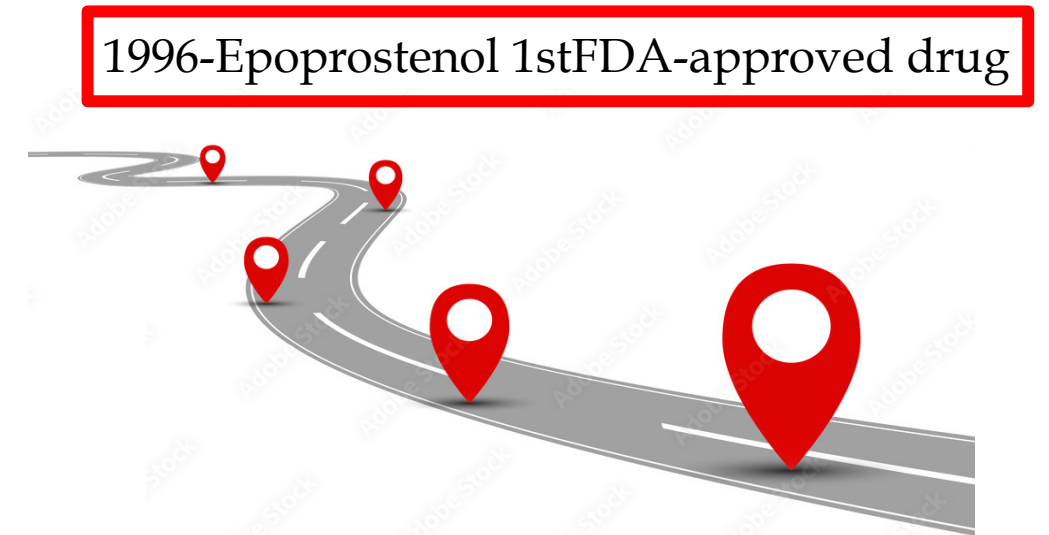
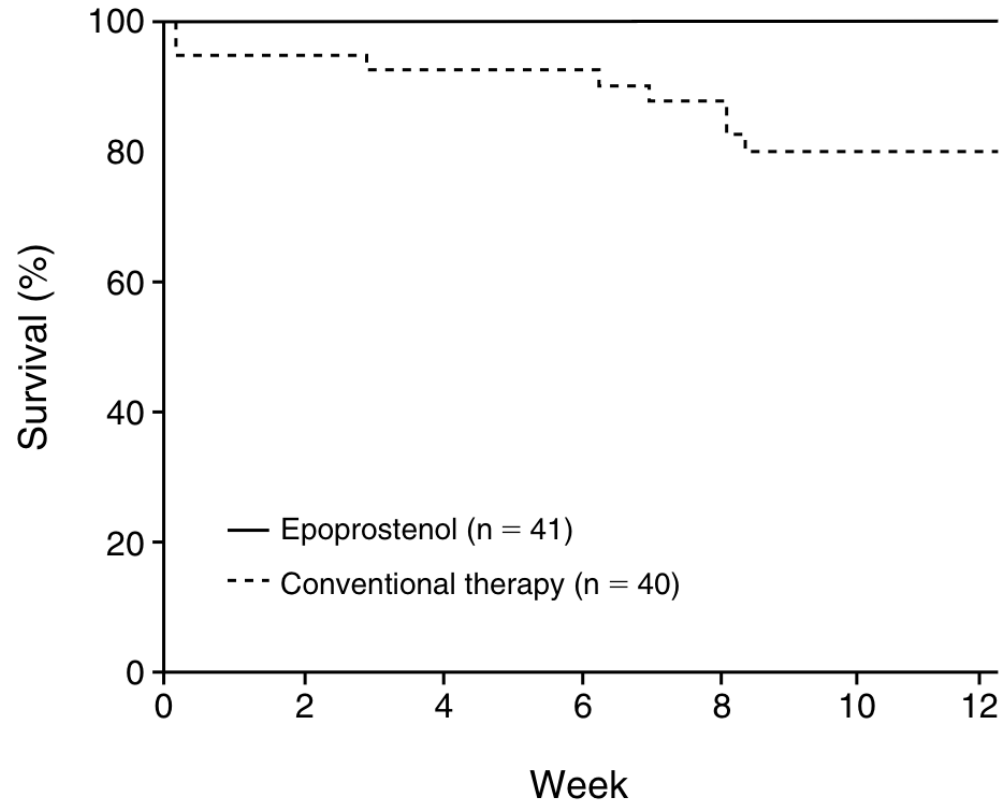
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THE NEW ENGLAND JOURNAL OF MEDICINE

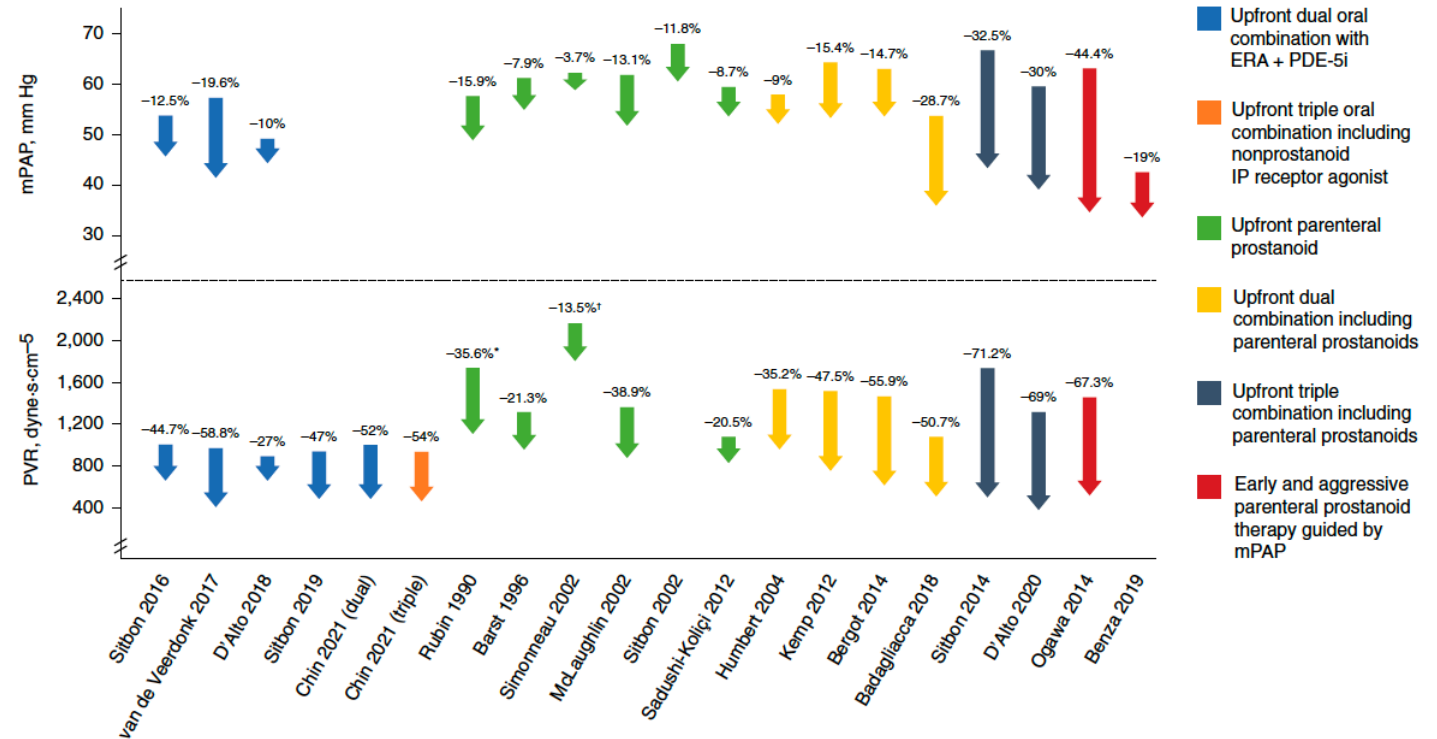
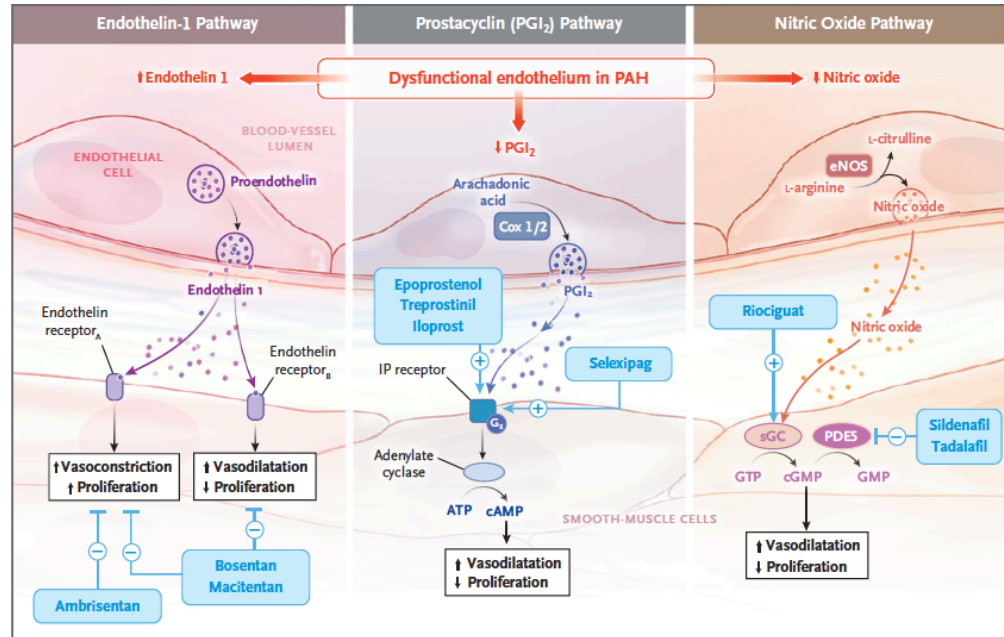
Feb. 1, 1996

A COMPARISON OF CONTINUOUS INTRAVENOUS EPOPROSTENOL (PROSTACYCLIN) WITH CONVENTIONAL THERAPY FOR PRIMARY PULMONARY HYPERTENSION

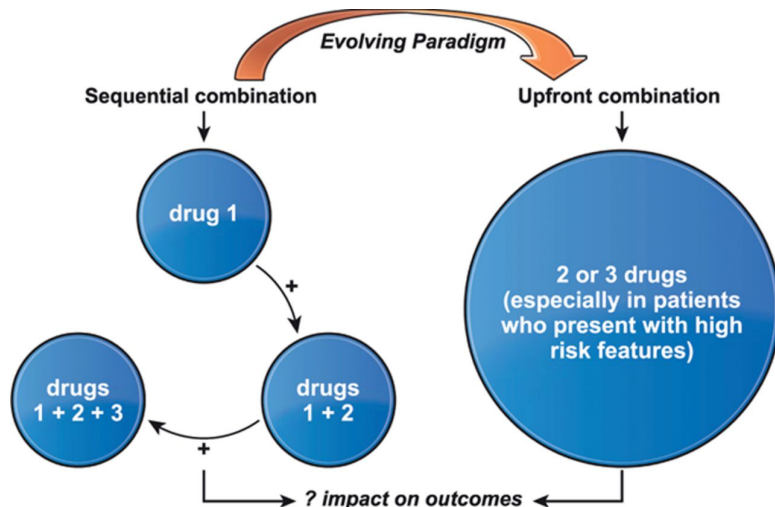
ROBYN J. BARST, M.D., LEWIS J. RUBIN, M.D., WALKER A. LONG, M.D., MICHAEL D. MCGOON, M.D.,
STUART RICH, M.D., DAVID B. BADESCH, M.D., BERTRON M. GROVES, M.D., VICTOR F. TAPSON, M.D.,
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SHELMER D. BLACKBURN, JR., B.A., DENISE SHORTINO, M.S., JAMES W. CROW, PH.D.,
FOR THE PRIMARY PULMONARY HYPERTENSION STUDY GROUP*



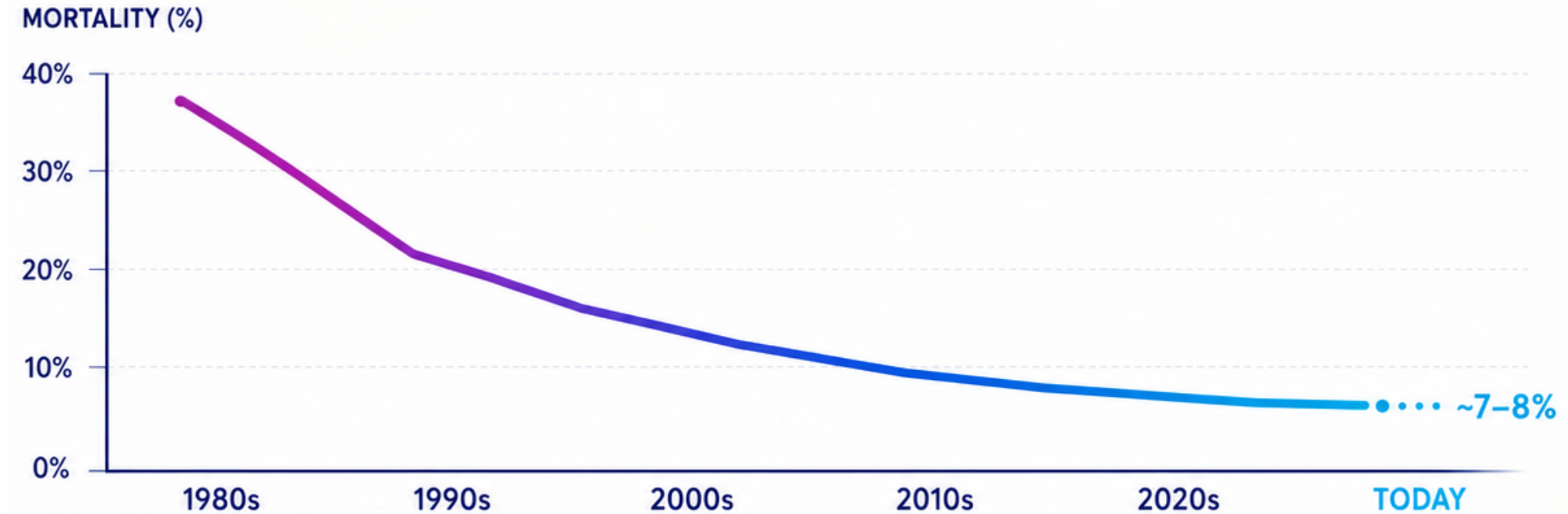
From sequential to initial up-front combination therapy



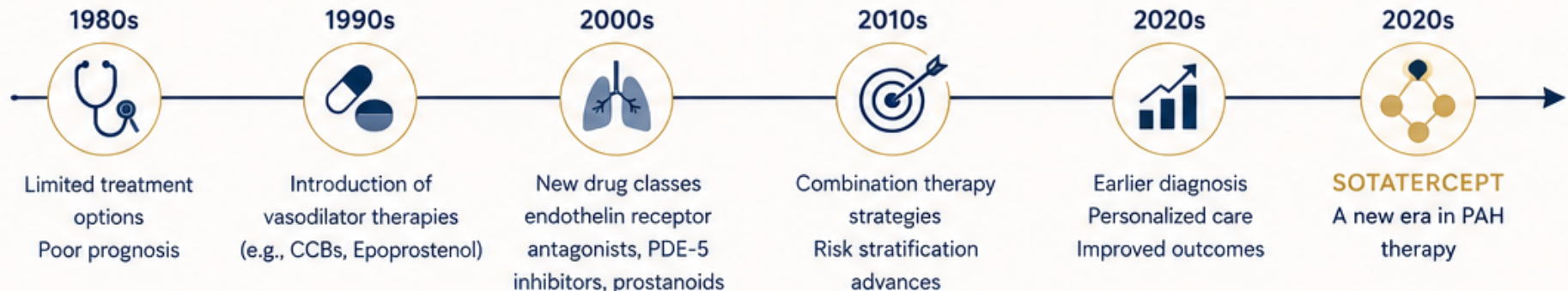
Aggressive Afterload Lowering to Improve the RV



Mortality progress in PAH



MILESTONES IN PAH CARE AND THERAPY



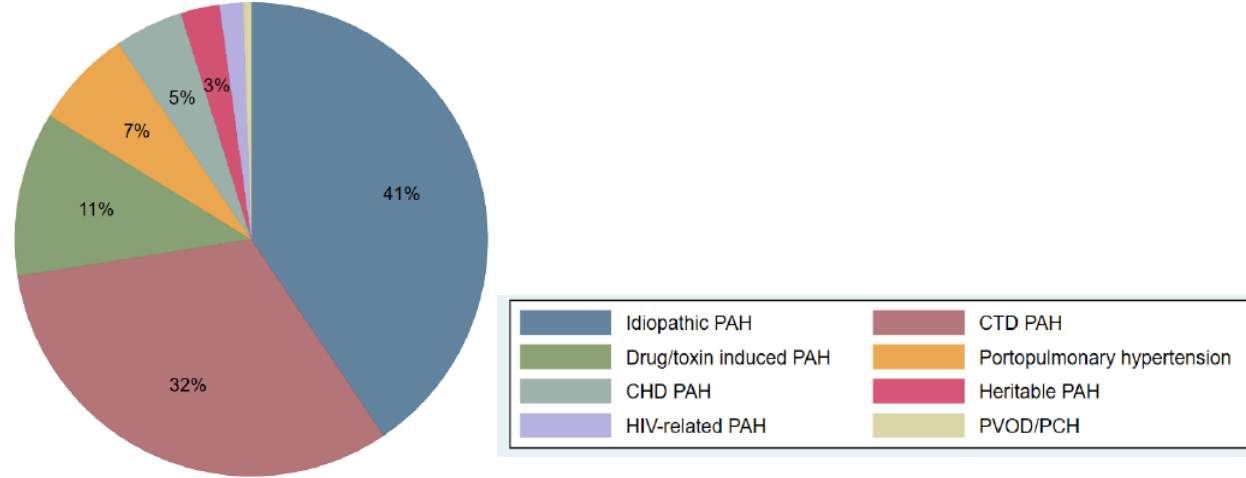
Mortality in Pulmonary Arterial Hypertension in the Modern Era

J Am Heart Assoc. 2022;11:e024969

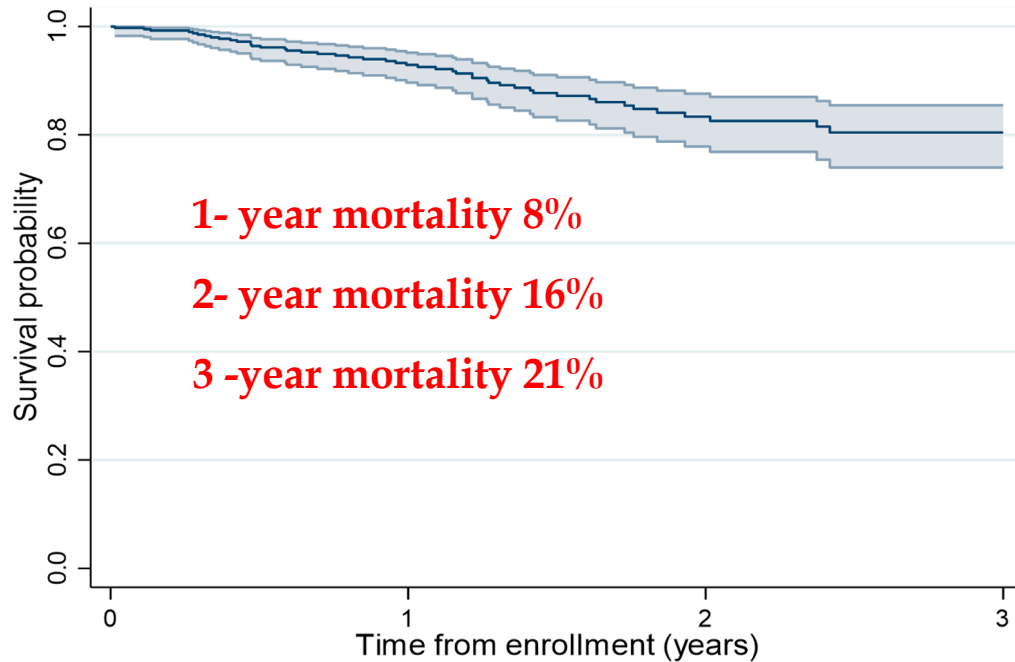
- 935 adult PAH Pts enrolled in the PHAR between 2015 and 2020
- Median age of 56 years; 76% women

12.9% of pts died

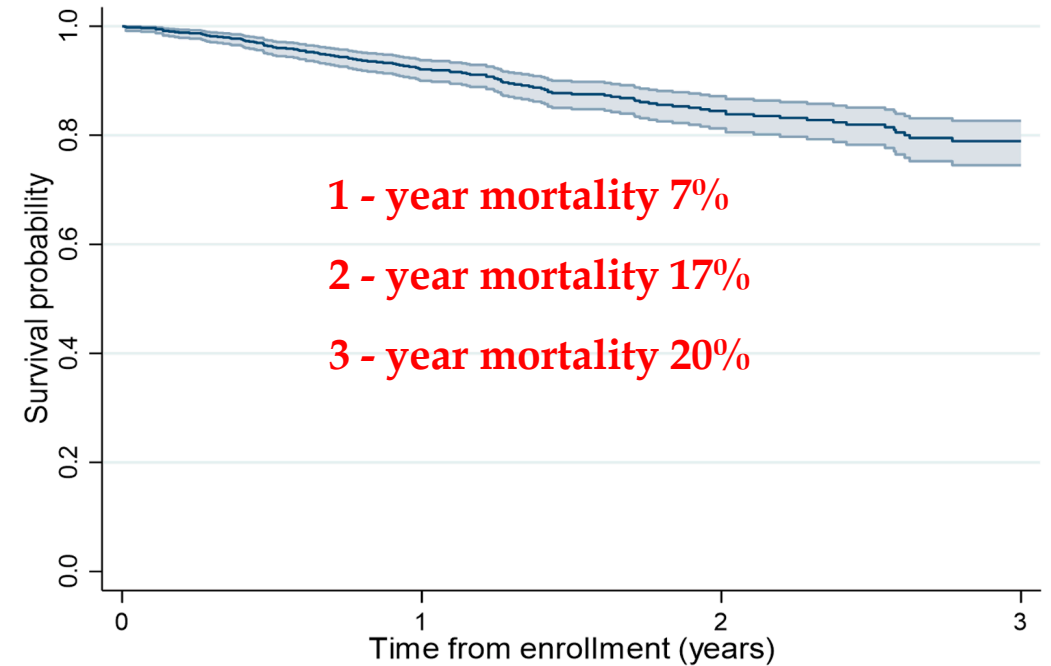
1.3% of pts underwent lung transplantation



All PAH



Idiopathic and heritable PAH

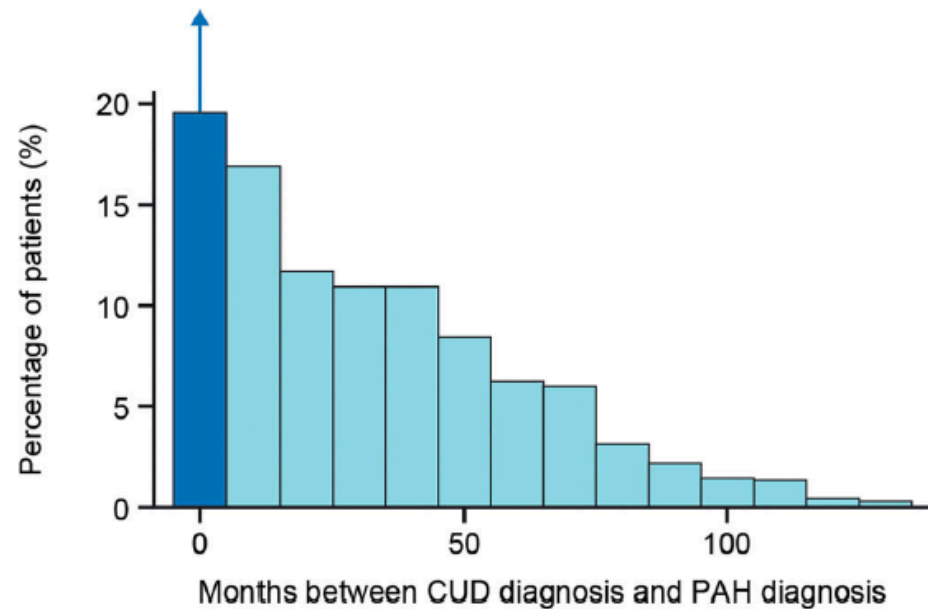
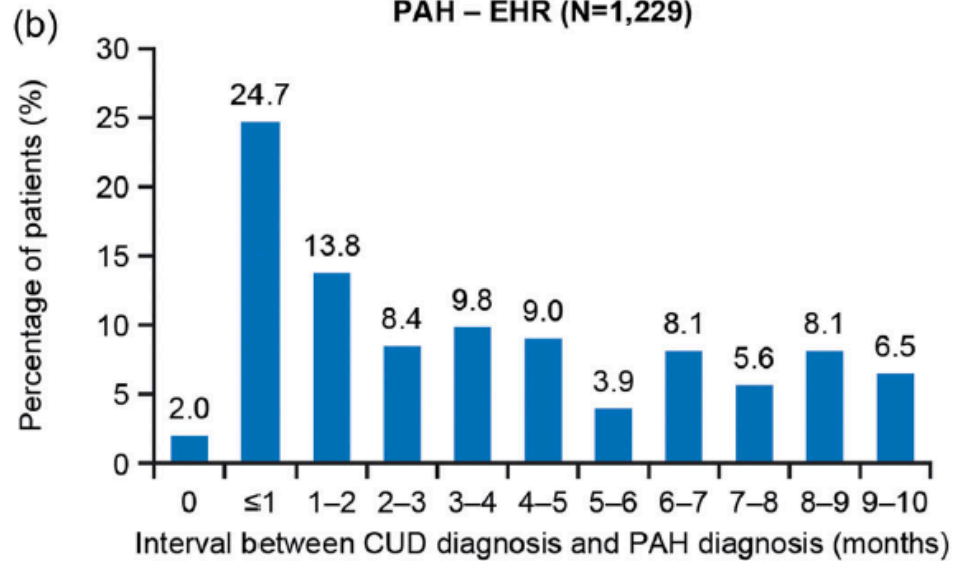


**How do we move beyond disease control
toward disease modification?**

How do we move beyond disease control toward disease modification?

✓ Earlier diagnosis

Time to diagnosis of PAH

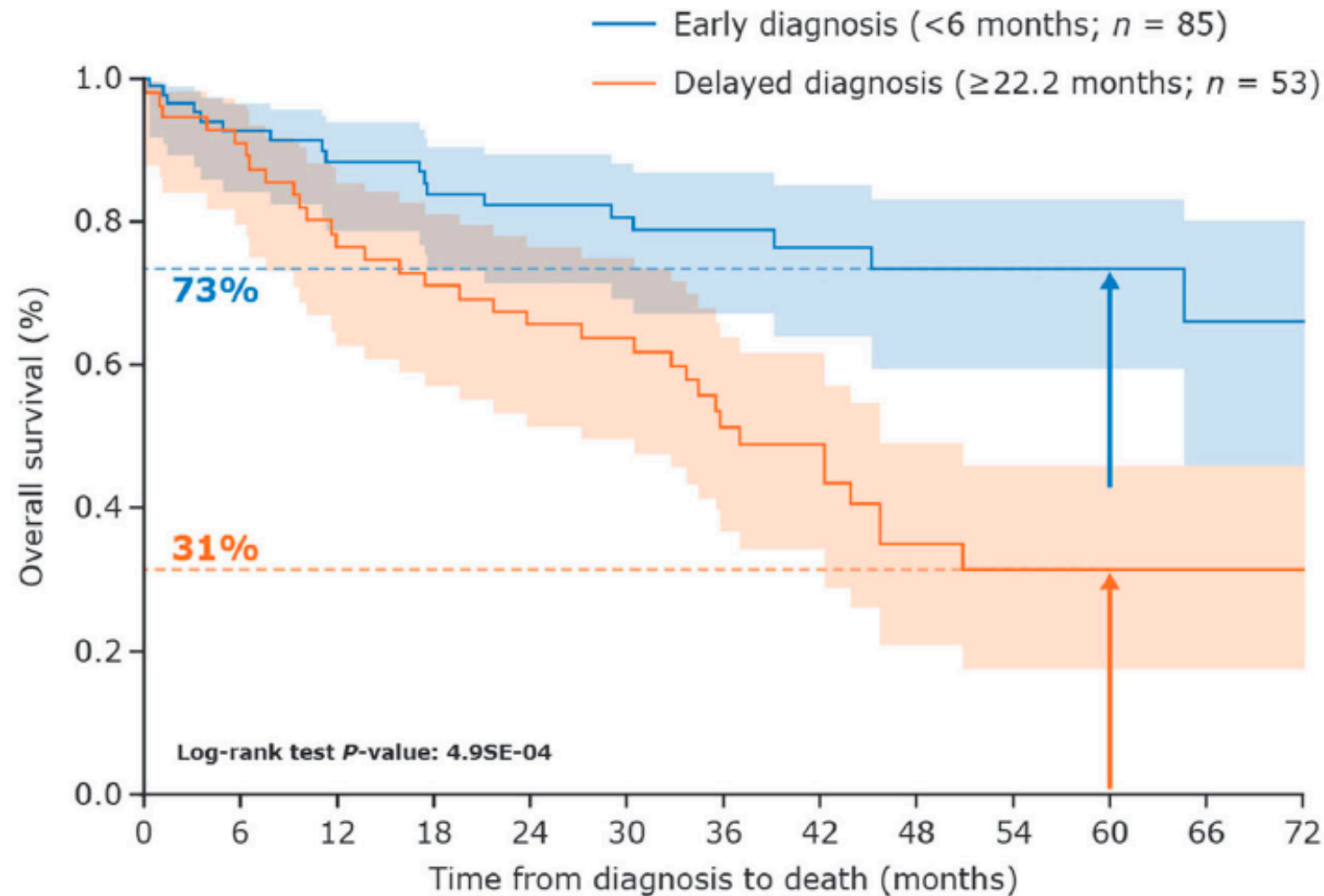


	Years to PAH dx	Months to PAH dx
Median	2.18	26.15
Q1, Q3	0.67, 4.15	8.05, 49.74
Min, max	0, 11.24	0, 134.83

CUD: chronic unexplained dyspnoea

The Impact of Time to Diagnosis and Treatment for Patients With PAH

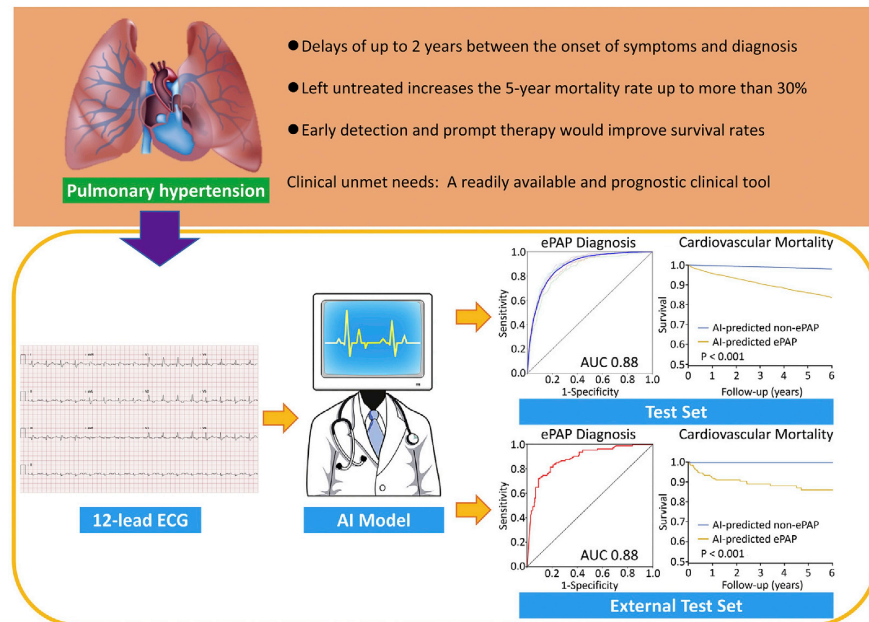
Initial patient selection criteria	Further criteria for formation of eligible PAH cohort (PAH cohort)
• Aged ≥ 18 years • mPAP > 20 mmHg • Limit to precapillary patients (PVR > 2.0 WU and PCWP ≤ 15 mmHg) • No CTEPH according to ICD codes • No use of PAH medications before mPAP (“diagnosis”) date • ≥ 1 PAH medication after diagnosis date	• ≥ 1 eligible event (symptom/non-PAH diagnosis) before diagnosis



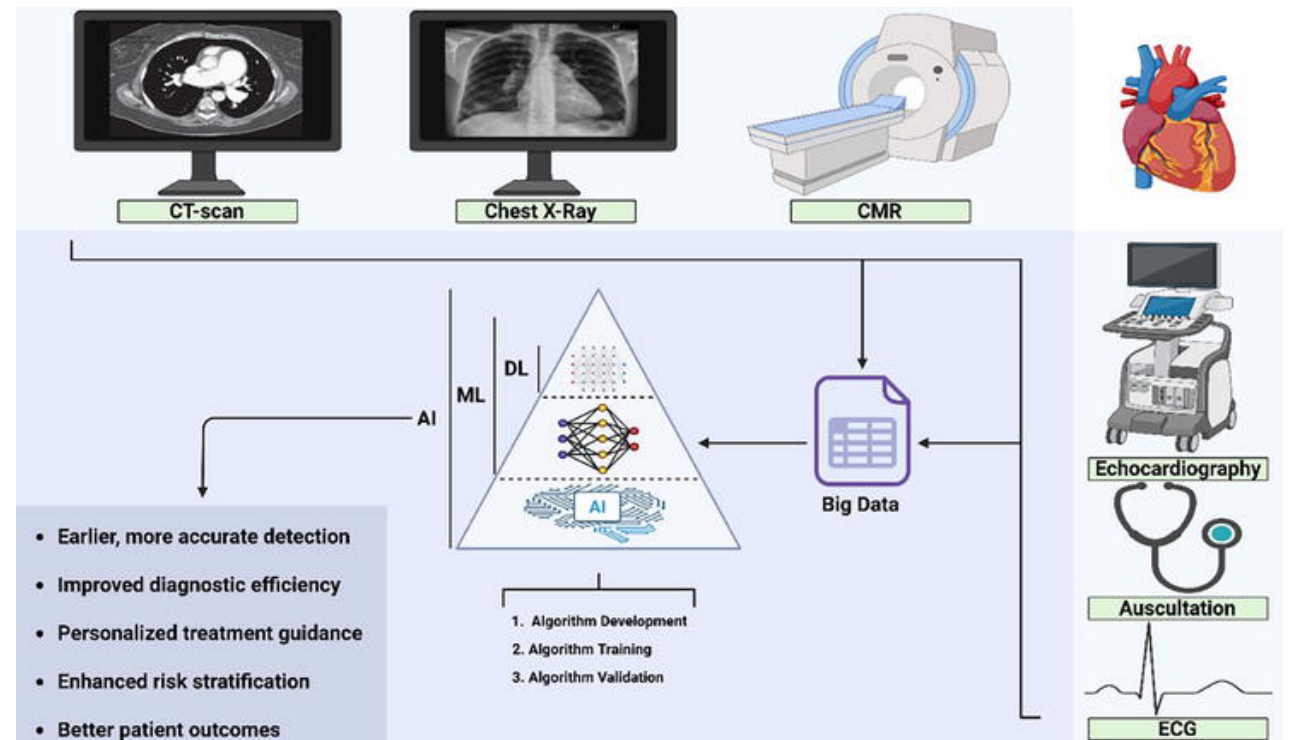
Goal: detect disease before irreversible vascular remodeling

- High-risk population surveillance
- AI-assisted screening
- Digital phenotyping

CENTRAL ILLUSTRATION: An Electrocardiogram-Enabled Artificial Intelligence Model for Detecting Elevated Pulmonary Arterial Hypertension and Assessing Risk of Cardiovascular Mortality



Liu C-M, et al. JACC: Asia. 2022;2(3):258-270.

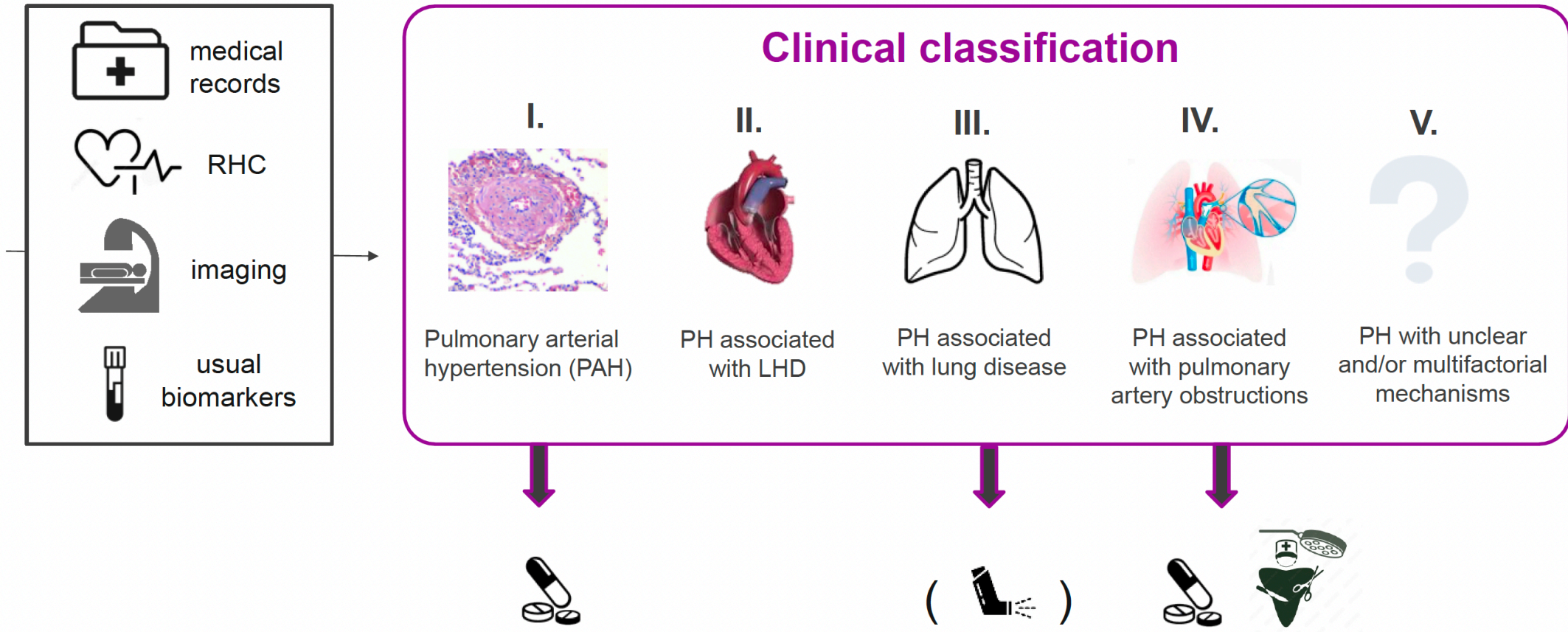


How do we move beyond disease control toward disease modification?

- ✓ Earlier diagnosis

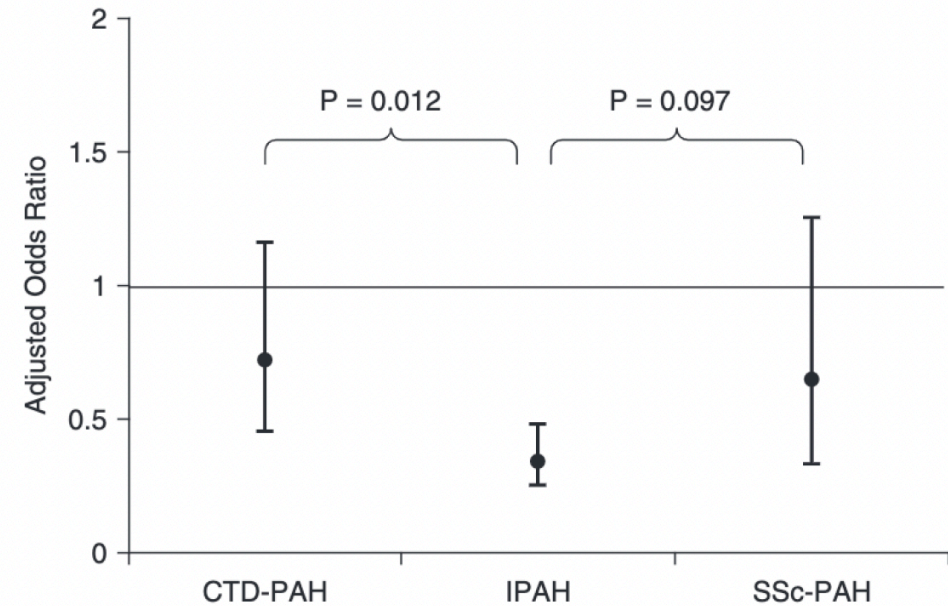
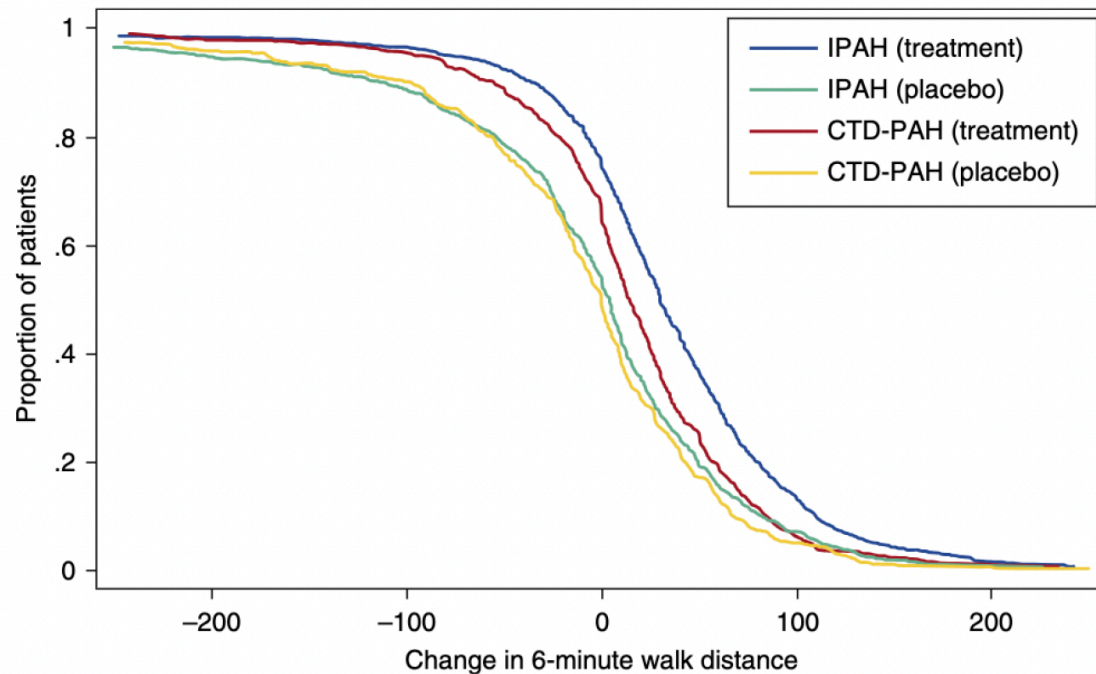
- ✓ **Individualized therapeutic strategies**

Clinical classification guides treatment strategy



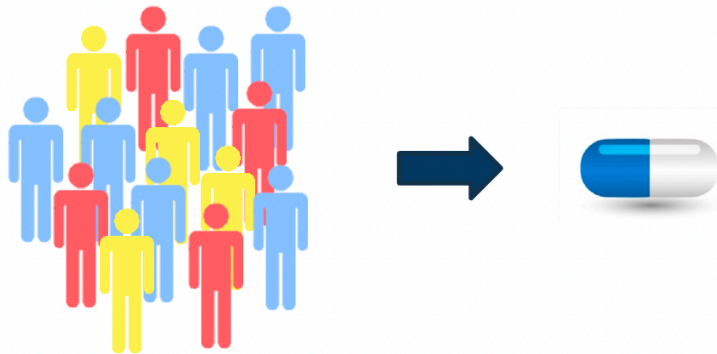
Response to PAH-specific therapies are variable

2,762 PAH patients included in 11 phase III RCT

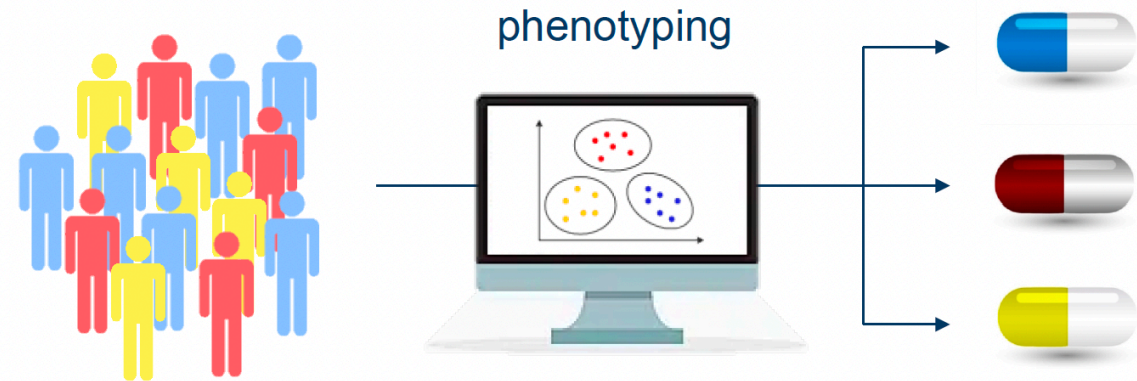


Current medicine

“ One treatment fits all ”

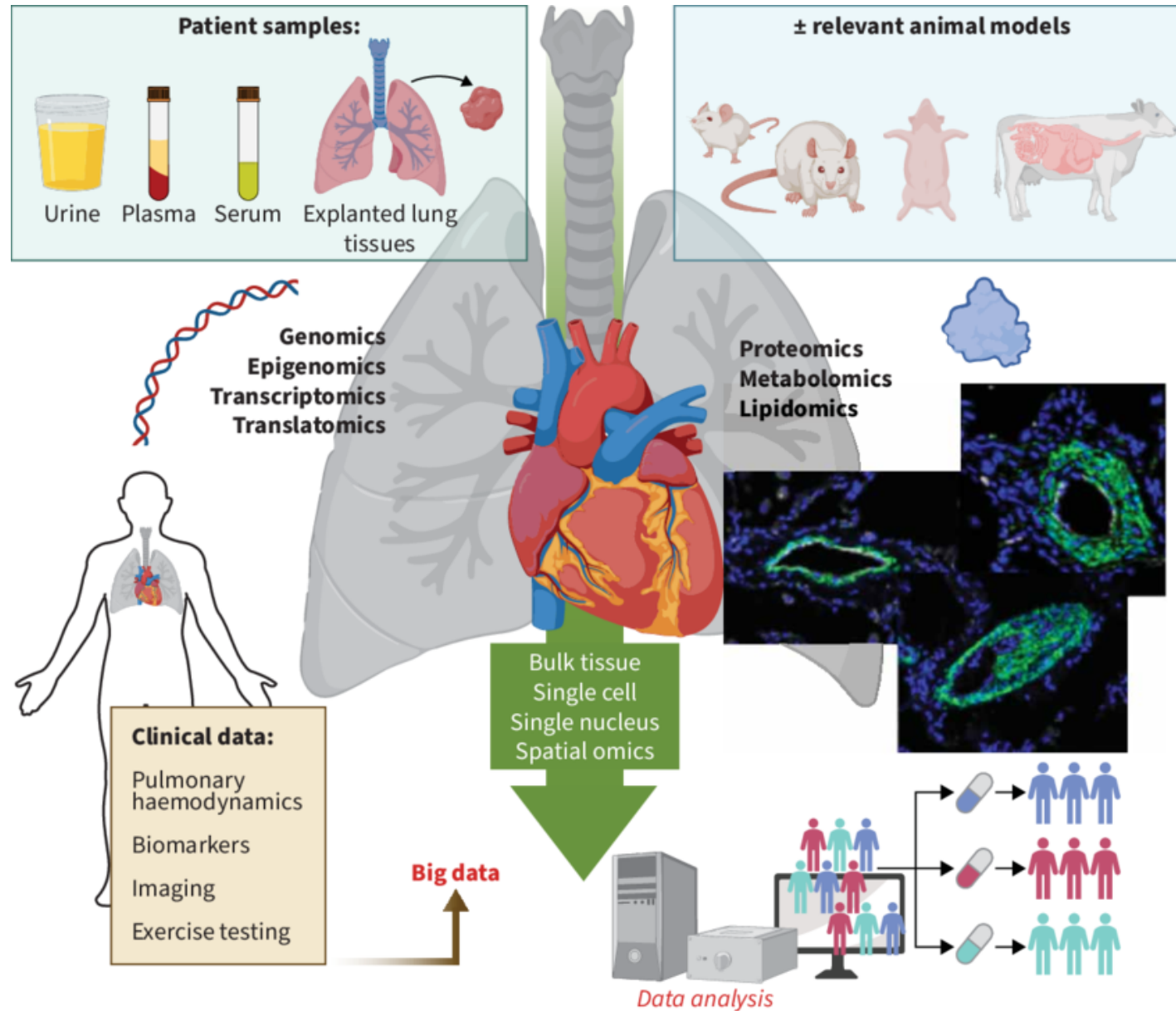


Precision medicine

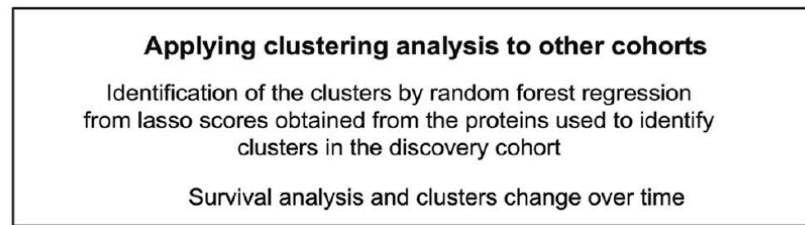
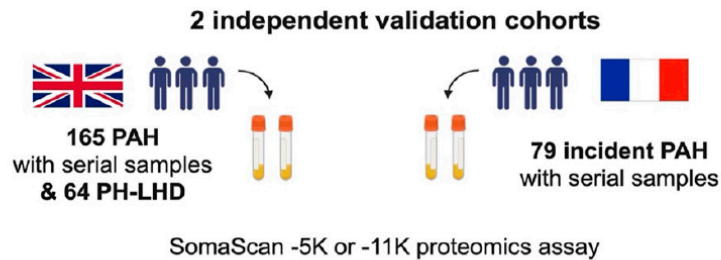
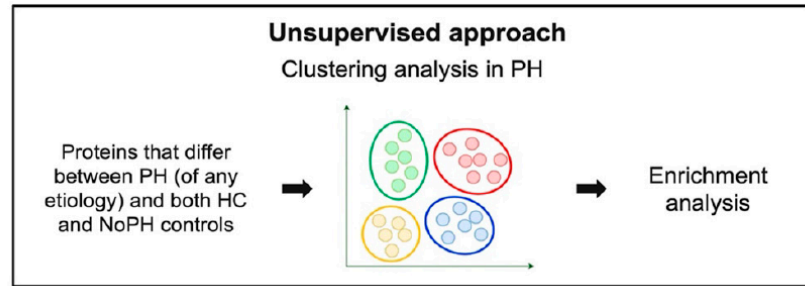


The goal of precision medicine is to **target the right treatment(s) to the right patient at the right time**, by taking into account differences in people's genes, environments, and lifestyles.

Precision Medicine

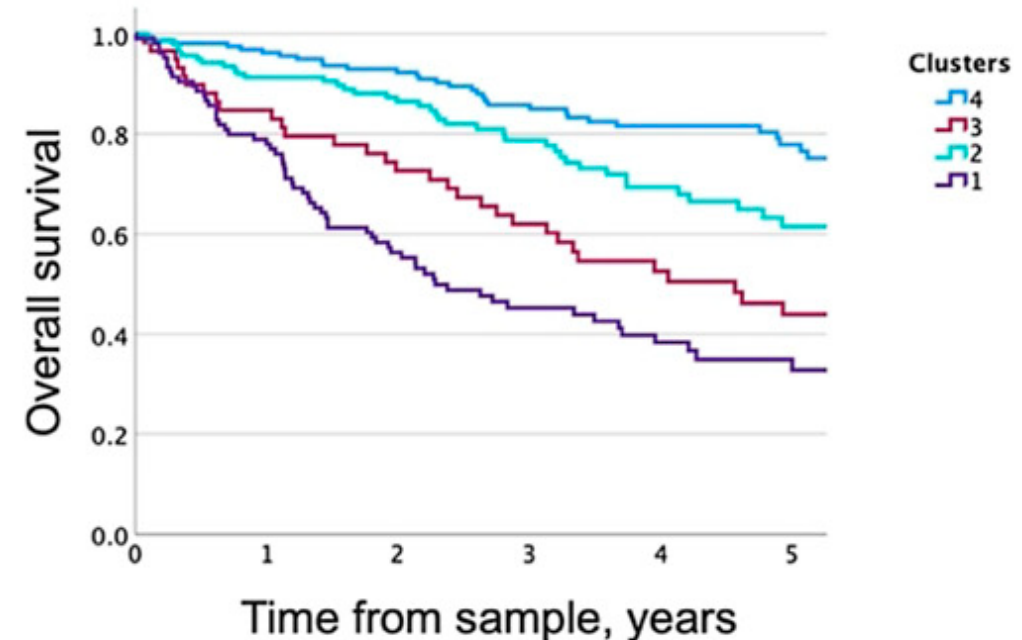
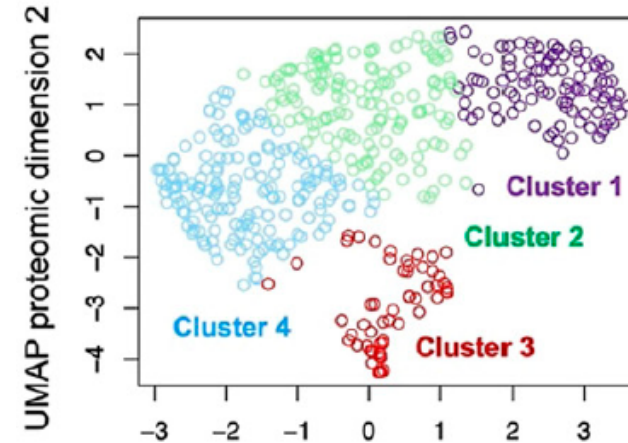


Clustering Patients with PH using the Plasma Proteome



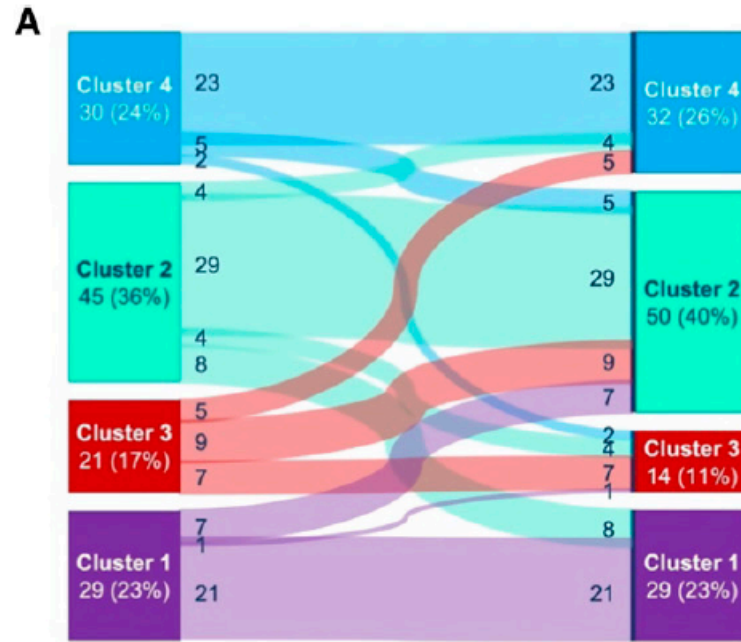
Plasma levels of 7,288 proteins

156 plasma proteins distinguished PAH from PH-KHD and healthy control subjects formed four clusters with diverse 5-year survival rates

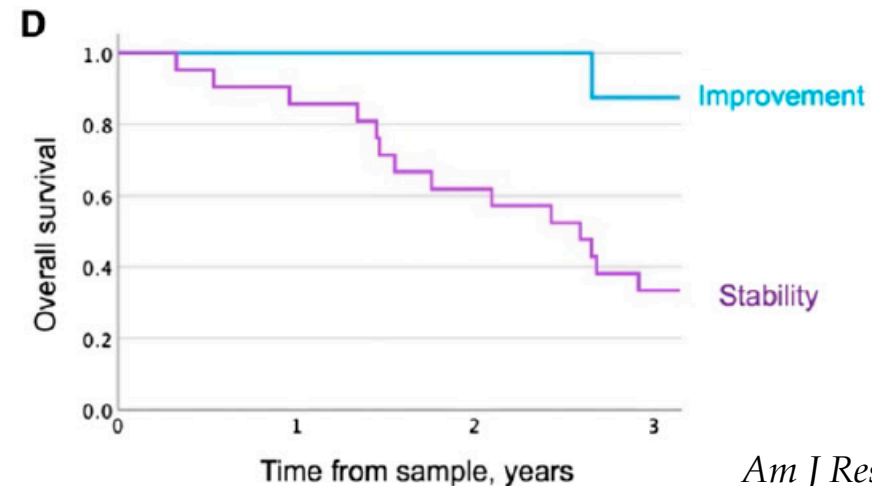
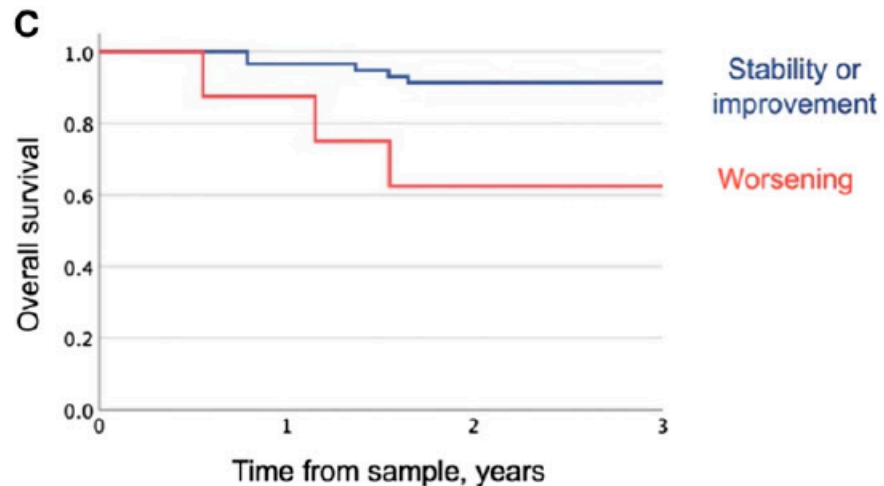
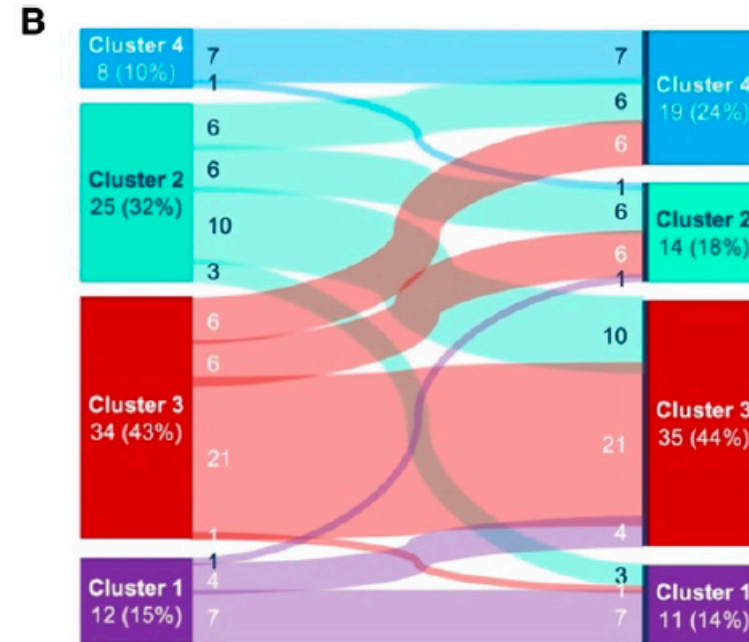


Clustering Patients with PH Using the Plasma Proteome

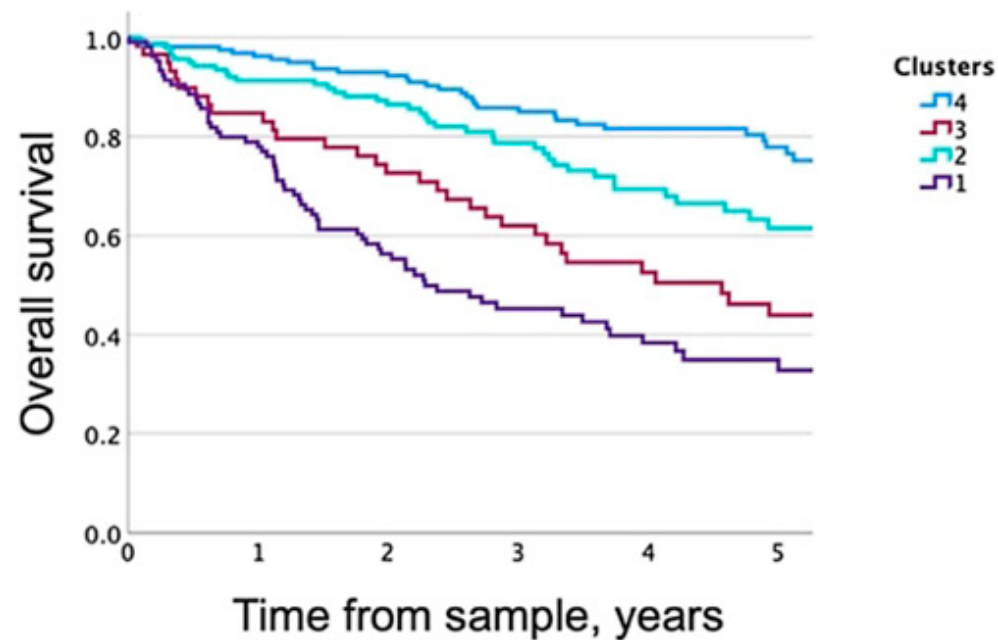
UK Cohort



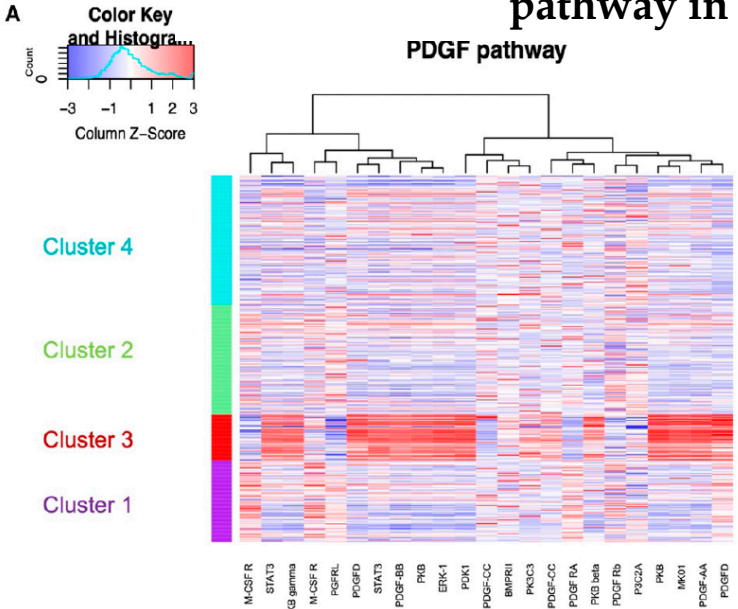
French cohorts



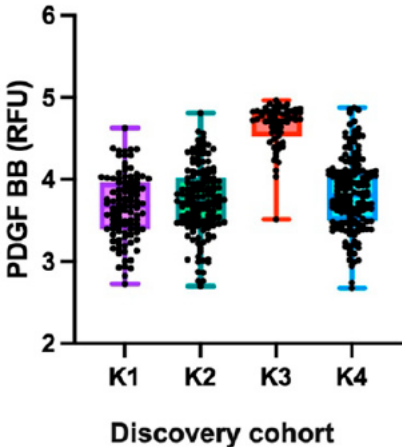
Clustering Patients with PH Using the Plasma Proteome



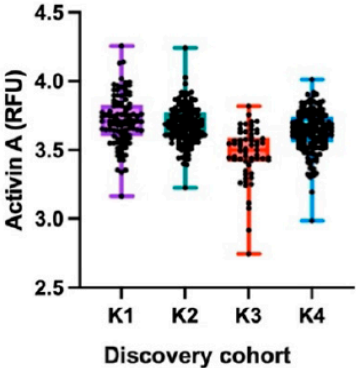
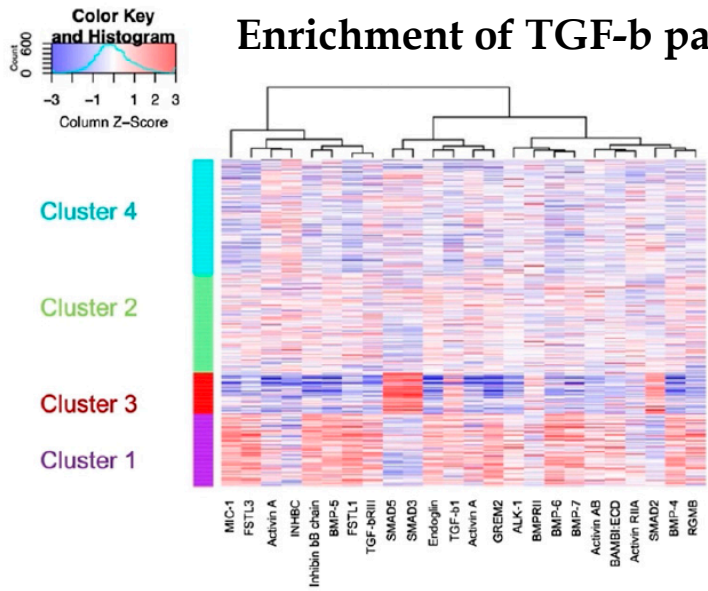
Enrichment of Platelet-Derived Growth Factor pathway in cluster 3



Seralutinib?

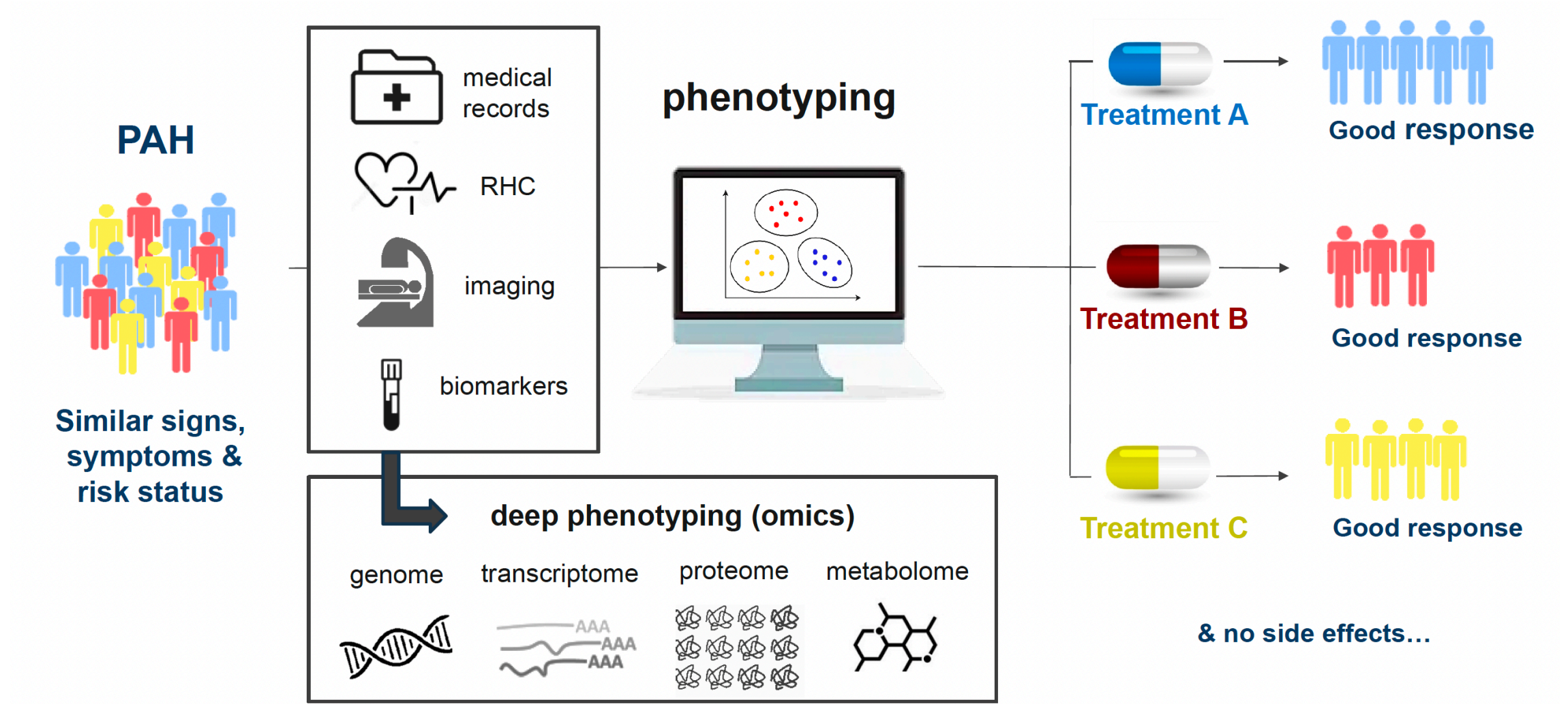


Enrichment of TGF-b pathway in cluster 1



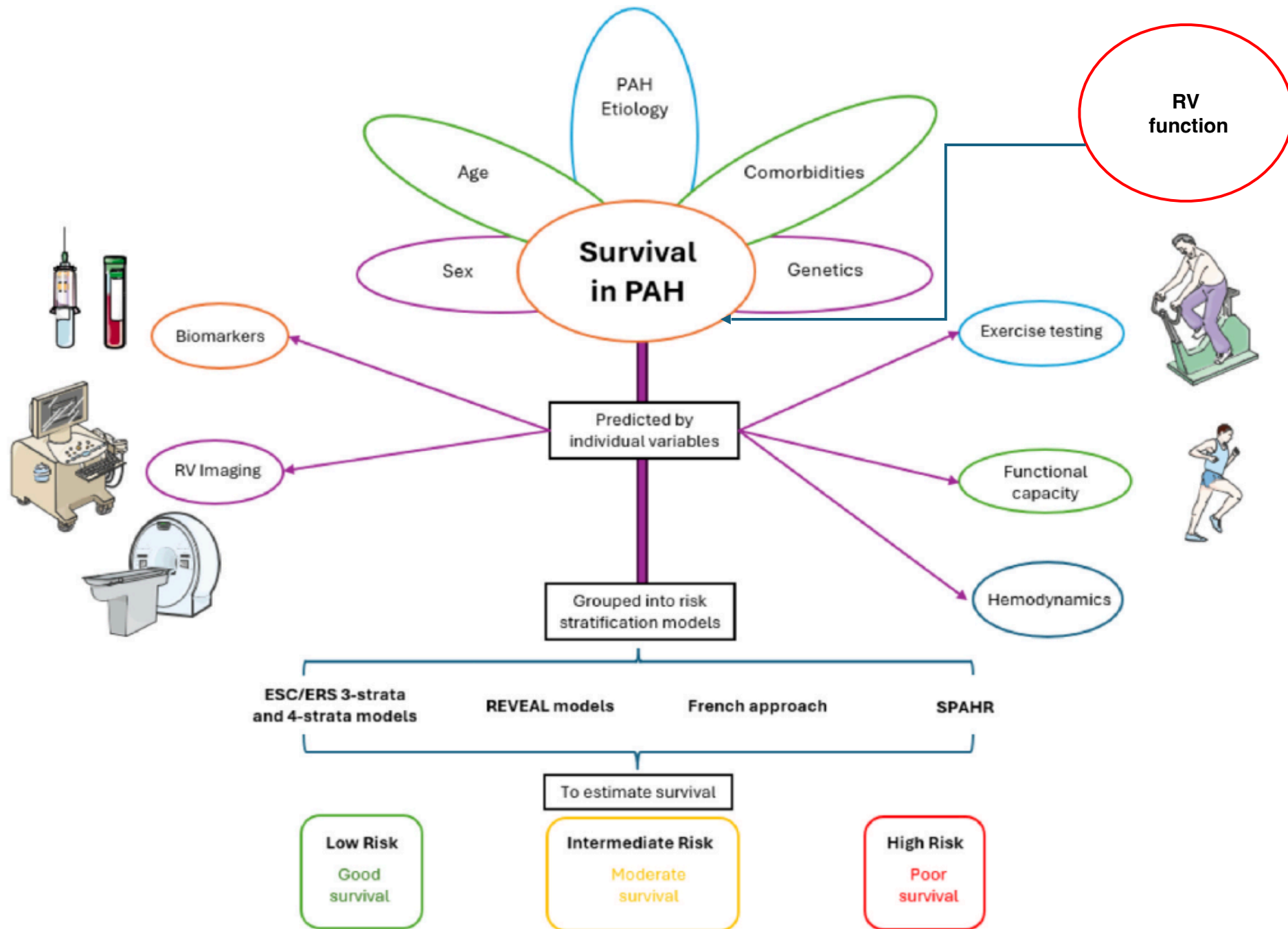
Sotatercept?

The ultimate goal

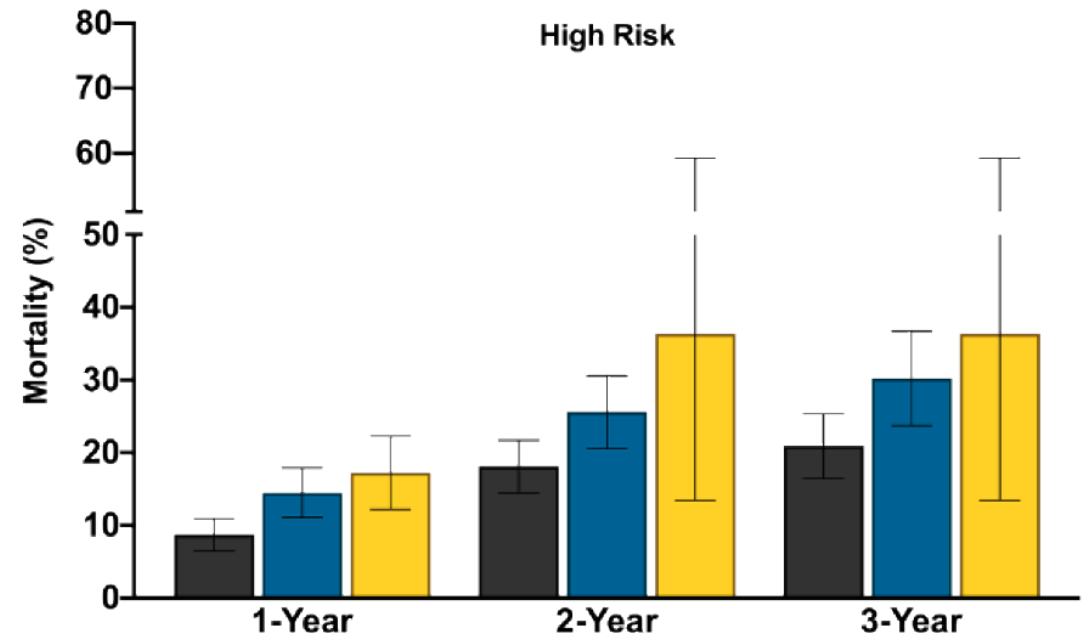
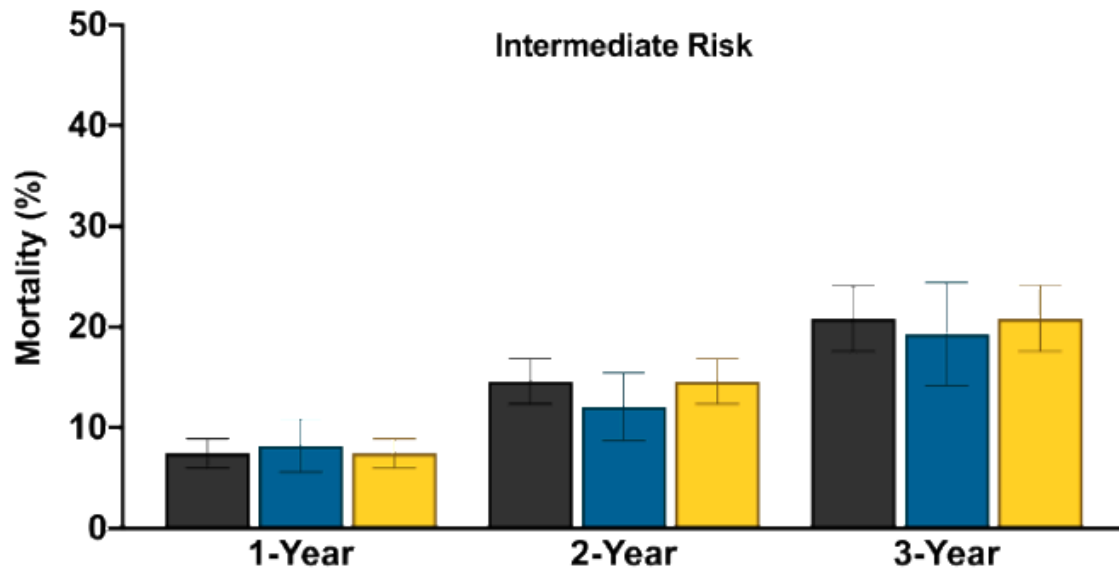
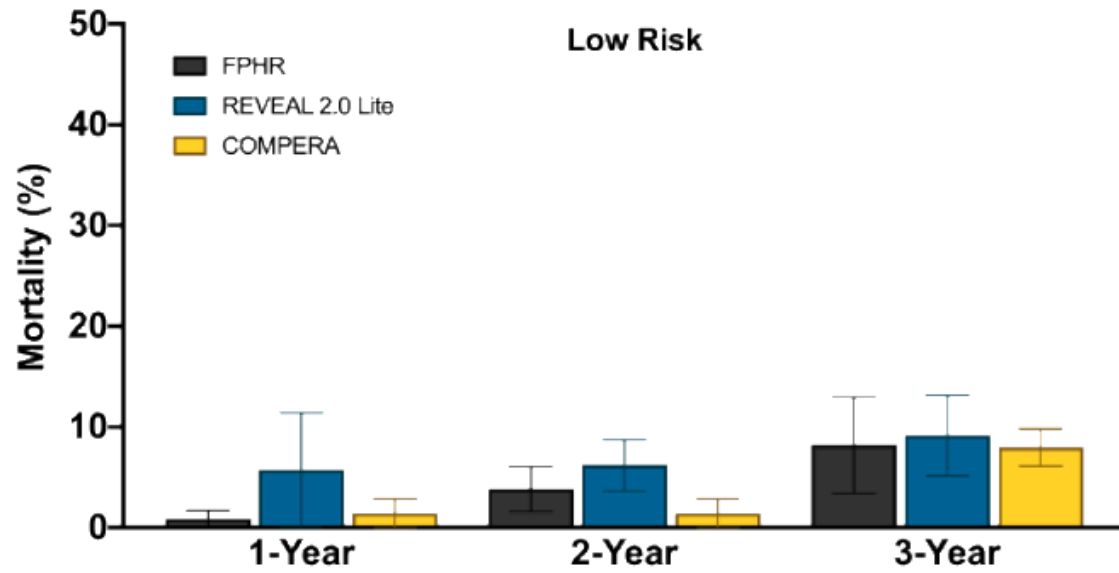


How do we move beyond disease control toward disease modification?

- ✓ Earlier diagnosis
- ✓ Individualized therapeutic strategies
- ✓ **Risk Stratification: Beyond Traditional Models**



Mortality in Pulmonary Arterial Hypertension in the Modern Era



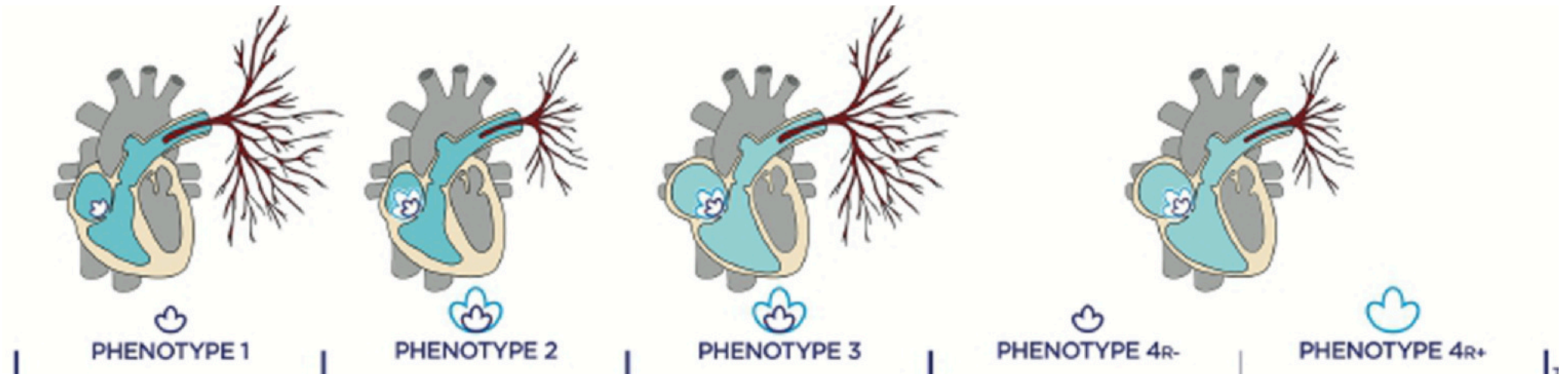
Right ventricular phenotyping to improve risk assessment at follow-up

- $RVEDA/LVEDA \leq 1$
- $TAPSE/PAPs \geq 0.33$

- $RVEDA/LVEDA \leq 1$
- $TAPSE/PAPs \leq 0.33$
- all TR

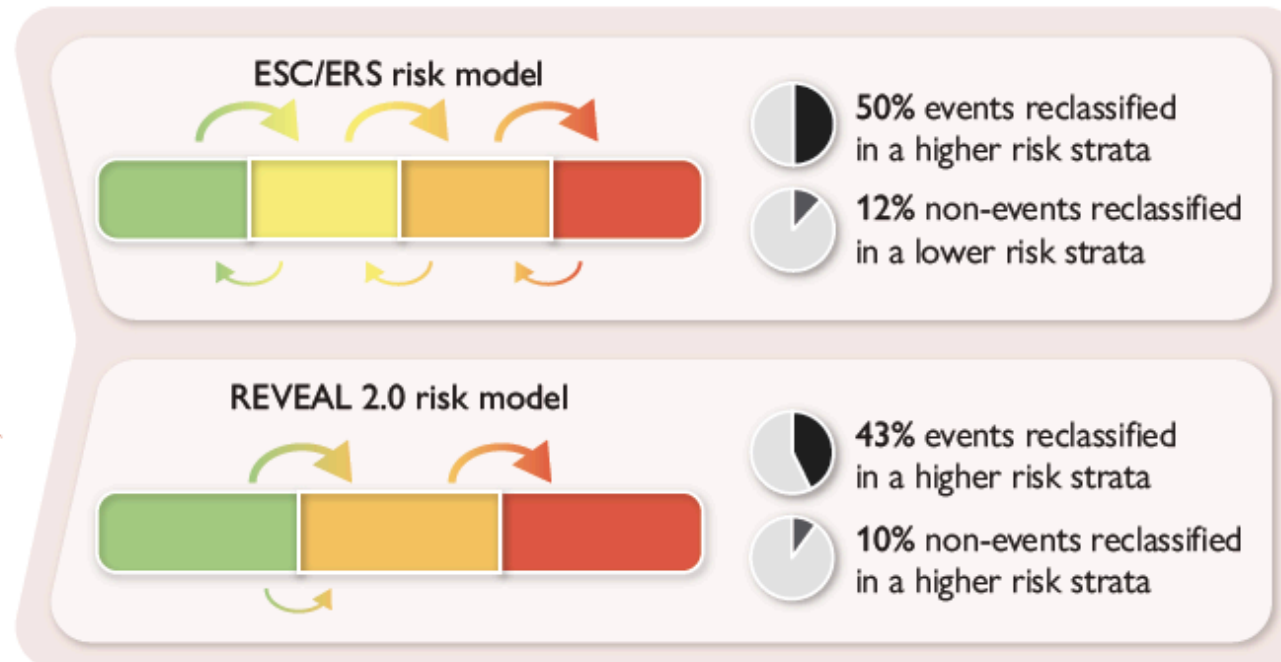
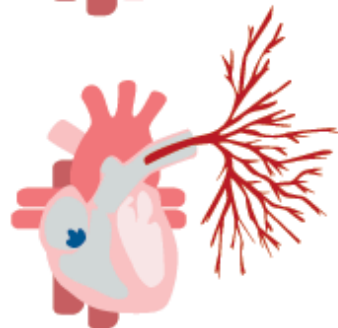
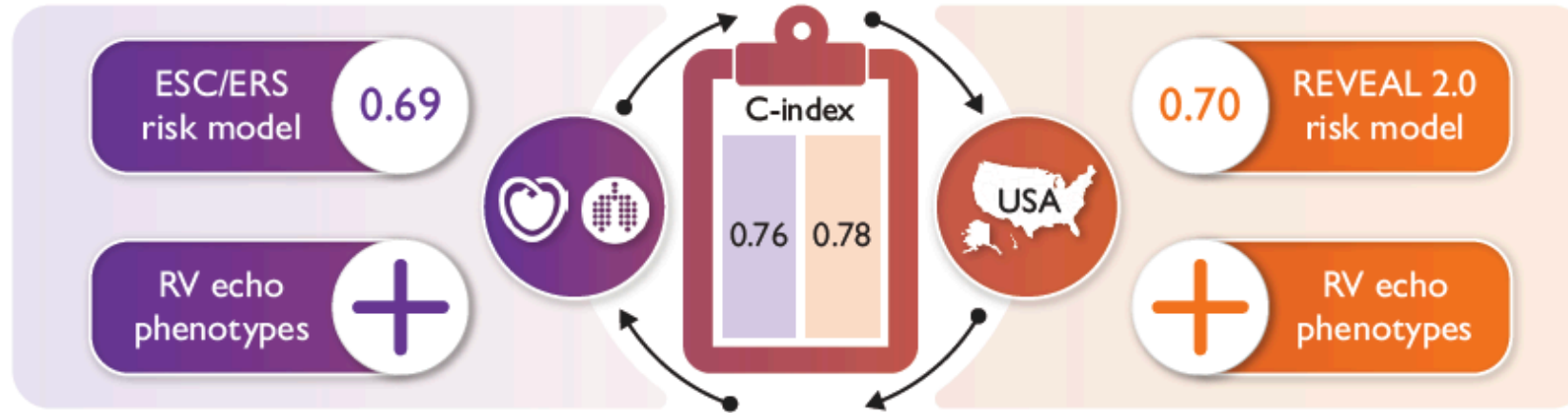
- $RVEDA/LVEDA > 1$
- $TAPSE/PAPs > 0.33$
- all TR

- $RVEDA/LVEDA > 1$
- $TAPSE/PAPs \leq 0.33$

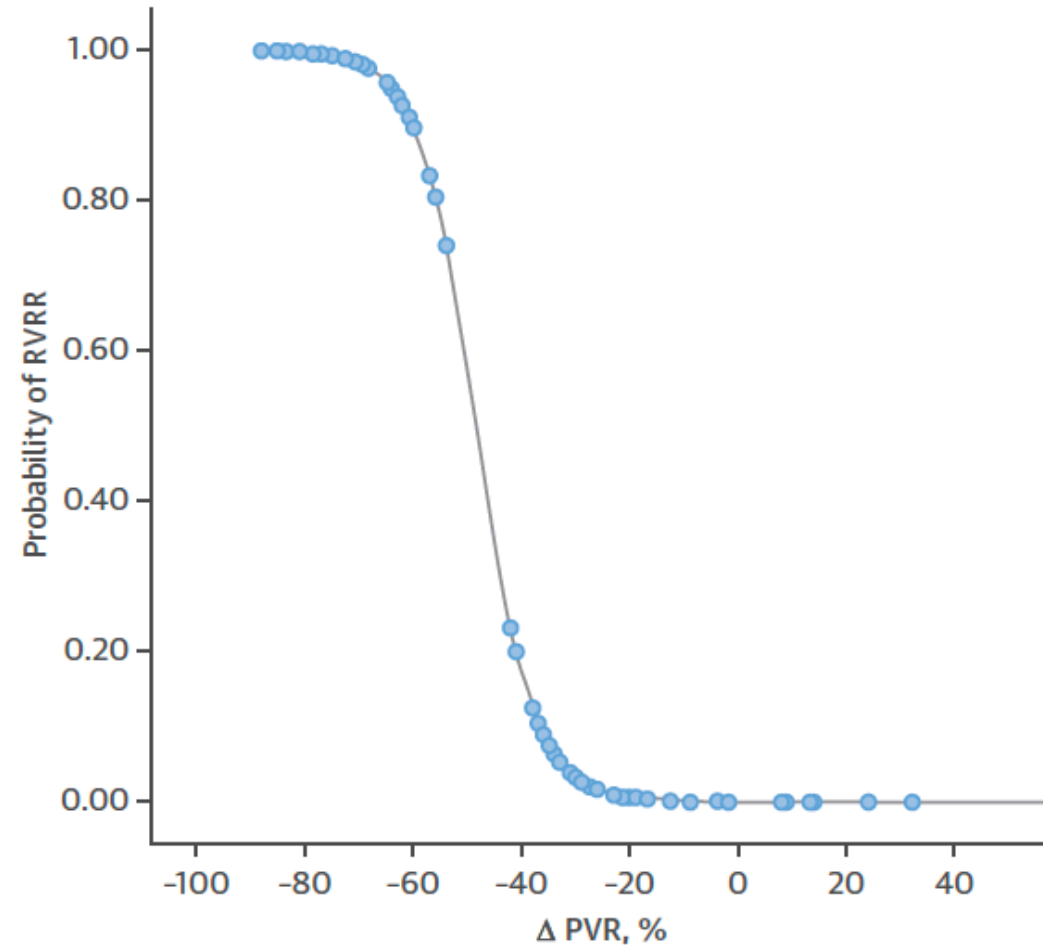


Right ventricular phenotyping to improve risk assessment at follow-up

Eur Heart J 2026; 00, 1–12



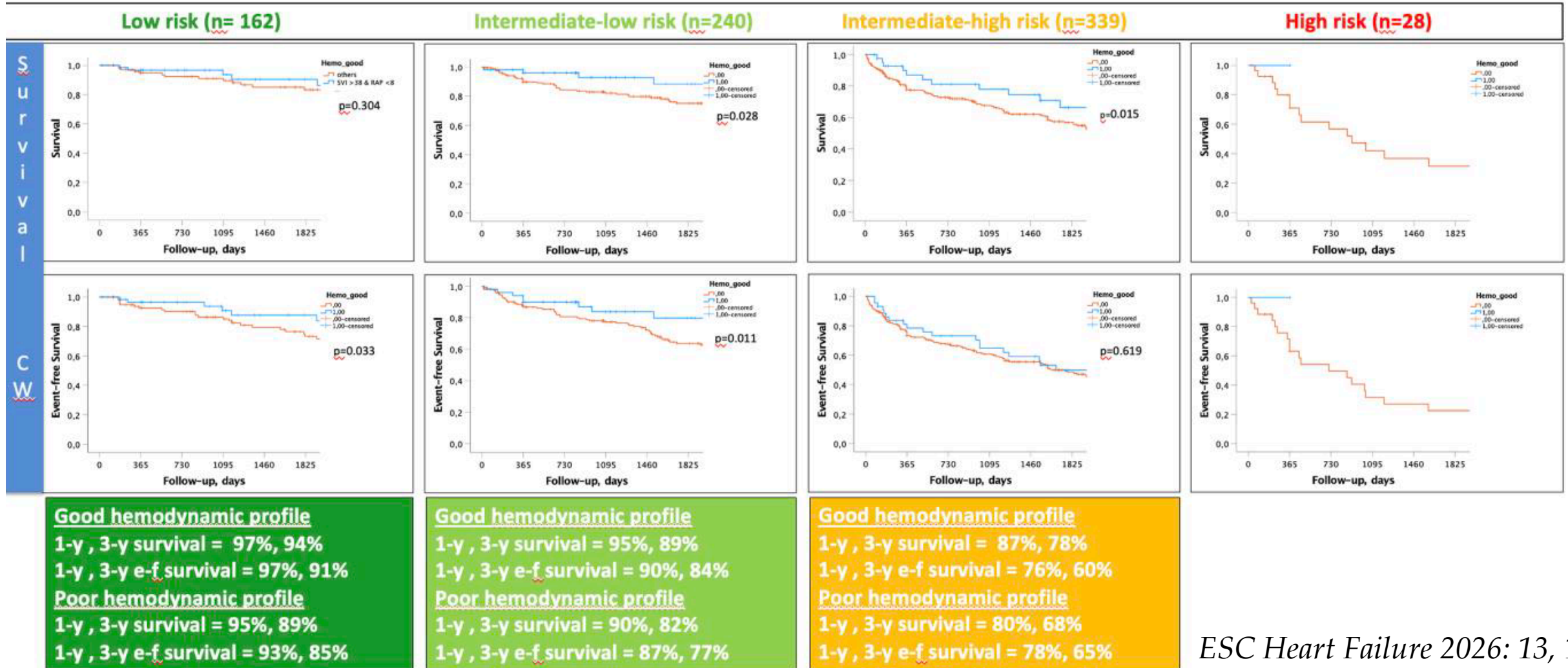
Aggressive Afterload Lowering to Improve the RV



Value of right heart haemodynamics for risk stratification at follow-up

769 PAH patients from the IPHNET registry reassessed at first follow-up by non-invasive variables (functional class, 6MWT and BNP/NT-proBNP) and by hemodynamic variables (SVi and RAP)

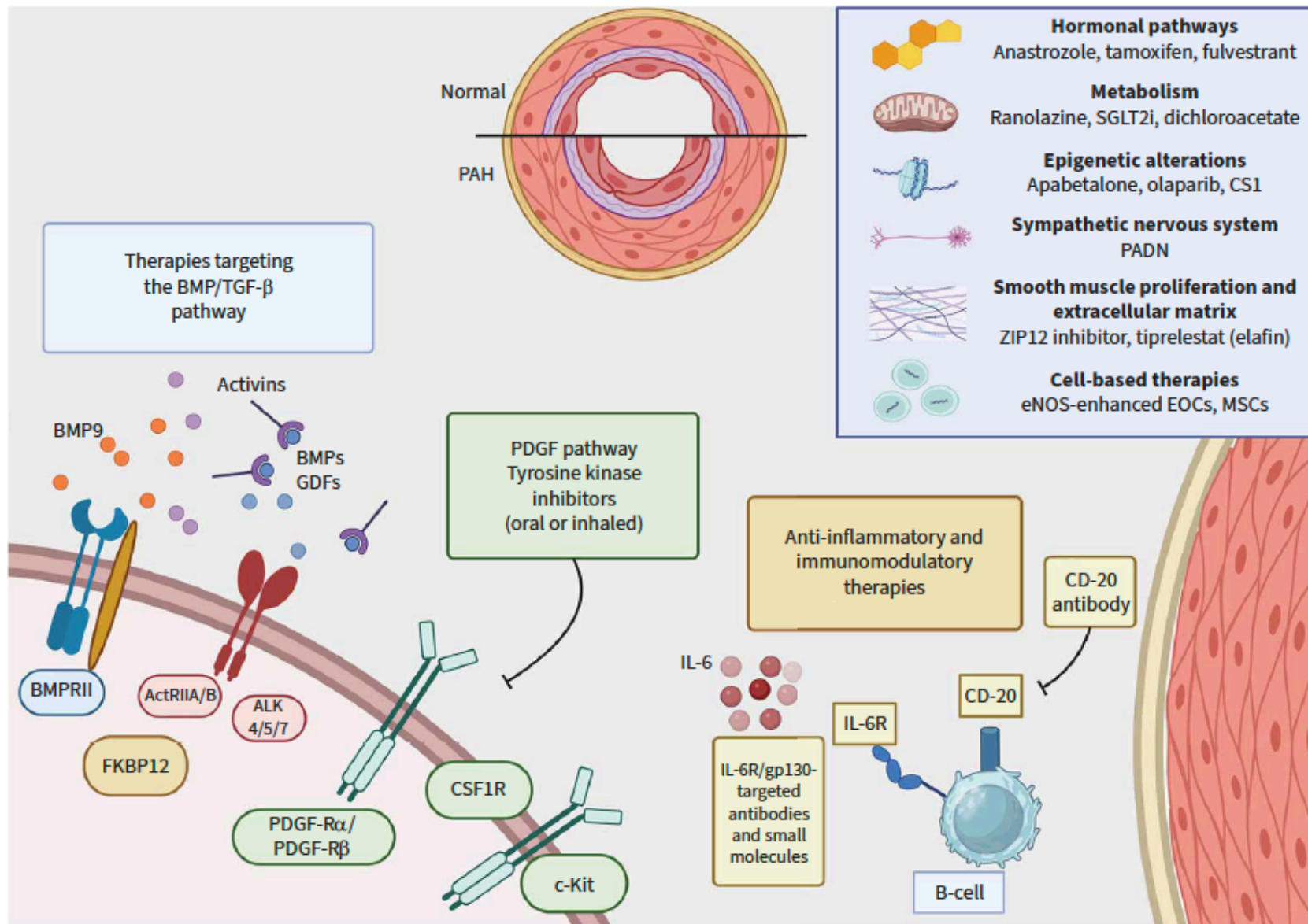
Good Hemodynamic profile = $SV_i > 38 \text{ ml/m}^2$ and $RAP < 8 \text{ mmHg}$ - Poor Hemodynamic profile = either both or one of the two: $SV_i \leq 38 \text{ ml/m}^2$, $RAP \geq 8 \text{ mmHg}$



How do we move beyond disease control toward disease modification?

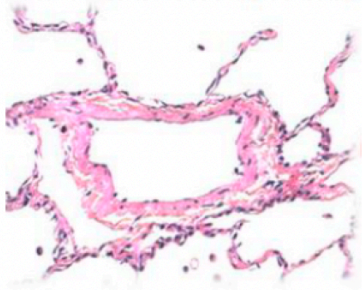
- ✓ Earlier diagnosis
- ✓ Individualized therapeutic strategies
- ✓ Risk Stratification: Beyond Traditional Models
- ✓ **Novel Therapeutic Targets**

Emerging pathways in PAH

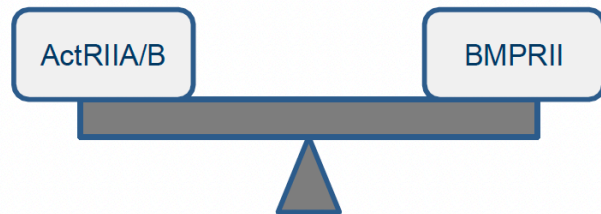


Sotatercept: rebalancing growth-promoting and growth-inhibiting signaling

Normal Pulmonary Artery

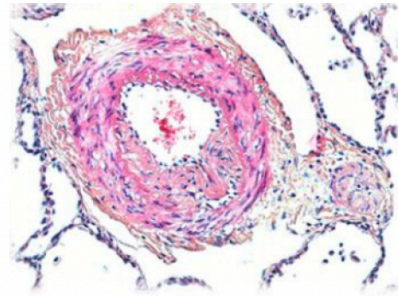


Vascular homeostasis

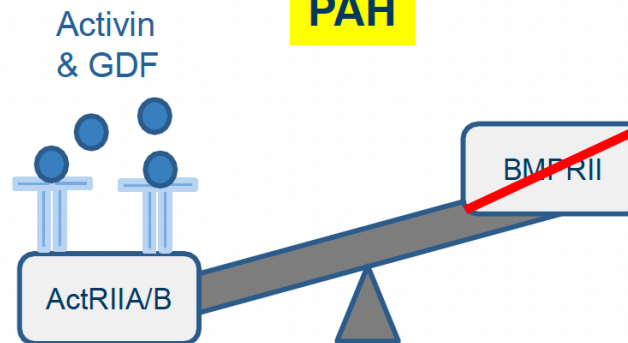


↑ proliferation ↓ proliferation

PAH Pulmonary Artery



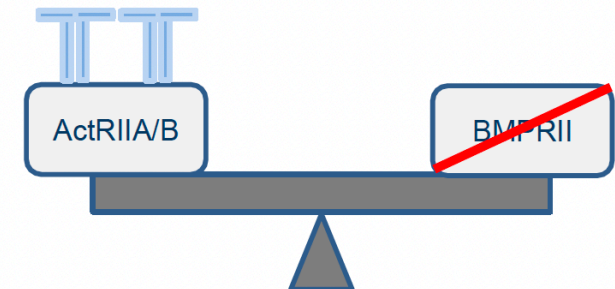
PAH



↑ ↑ proliferation

PAH treated with sotatercept

(Activin signaling inhibitor
Ligand trap)



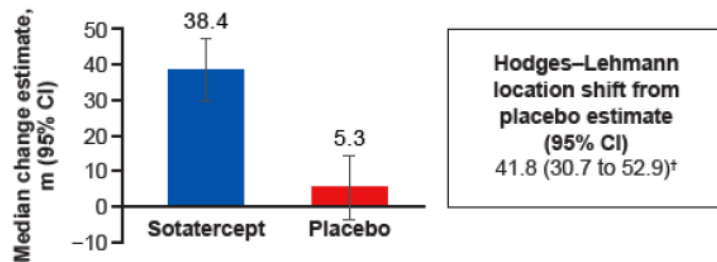
balance restored

Efficacy and safety sotatercept, in a pooled analysis of PULSAR and STELLAR studies

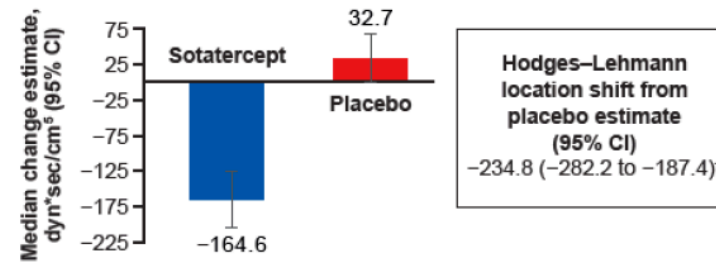
- This post-hoc, exploratory, pooled analysis combines data from the double-blind placebo periods of the phase 2 PULSAR (NCT03496207) and phase 3 STELLAR (NCT04576988) studies
- A total of 429 patients with Group 1 PAH were randomised and treated; 237 received sotatercept and 192 received placebo

Efficacy

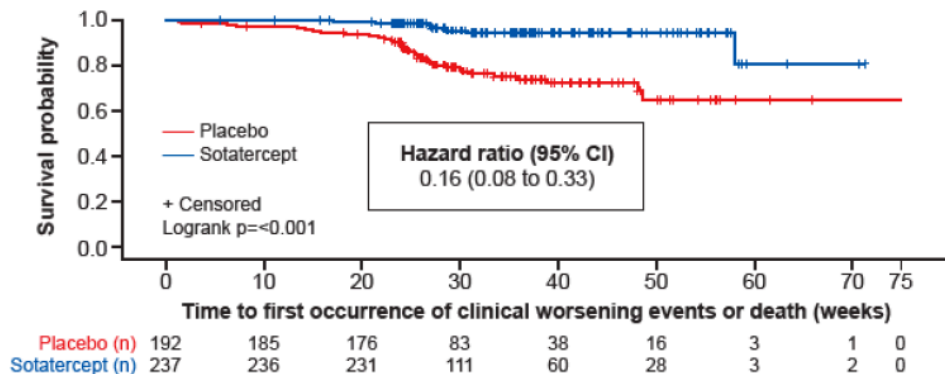
6MWD



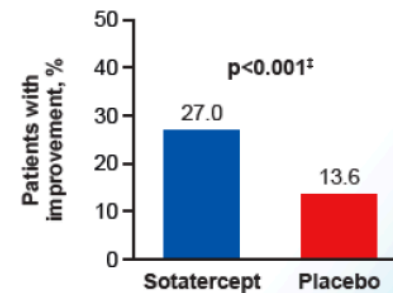
PVR



Time to first occurrence of clinical worsening events or death



WHO functional class



Safety

Sotatercept had favorable safety in patients with PAH

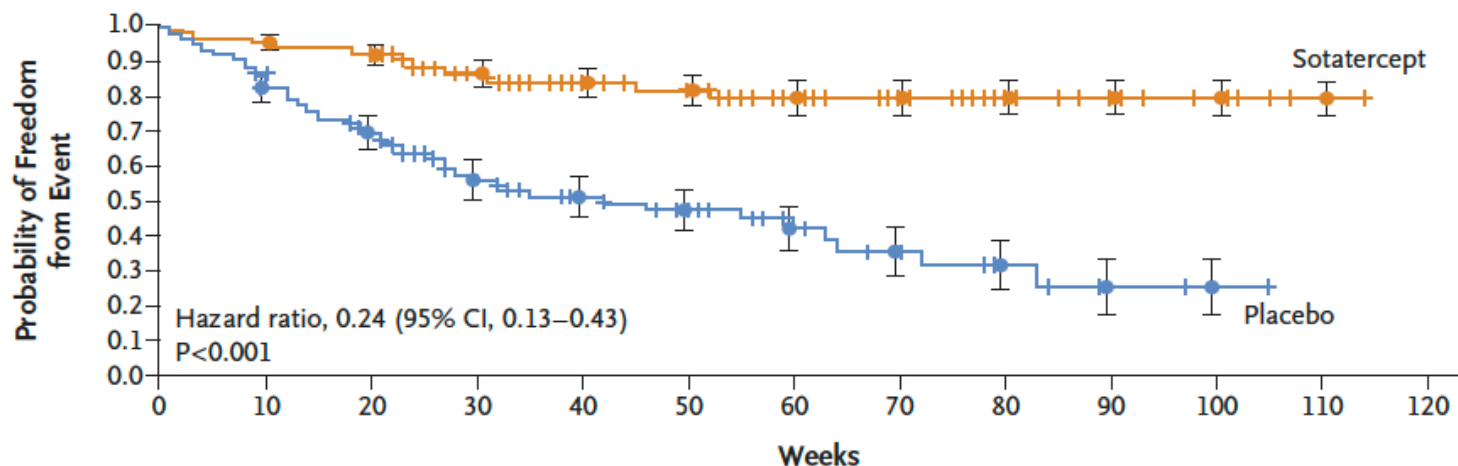
	Sotatercept (n=237)	Placebo (n=192)
Number of patients with any adverse event, n (%)		
Any	202 (85.2)	169 (88.0)
Related to study treatment	104 (43.9)	50 (26.0)
Leading to discontinuation of study treatment	9 (3.8)	11 (5.7)
Leading to death	1 (0.4)	6 (3.1)
Number of patients with an adverse event of interest and special interest, n (%)		
Increased blood pressure	8 (3.4)	3 (1.6)
Increased haemoglobin	18 (7.6)	0
Thrombocytopenia	17 (7.2)	4 (2.1)
Bleeding event	49 (20.7)	28 (14.6)
Telangiectasia	17 (7.2)	5 (2.6)

ZENITH TRIAL

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

Primary Composite End point:

Death from any cause, Lung Transplantation, or Hospitalization lasting at least 24 hours for worsening PAH pulmonary arterial



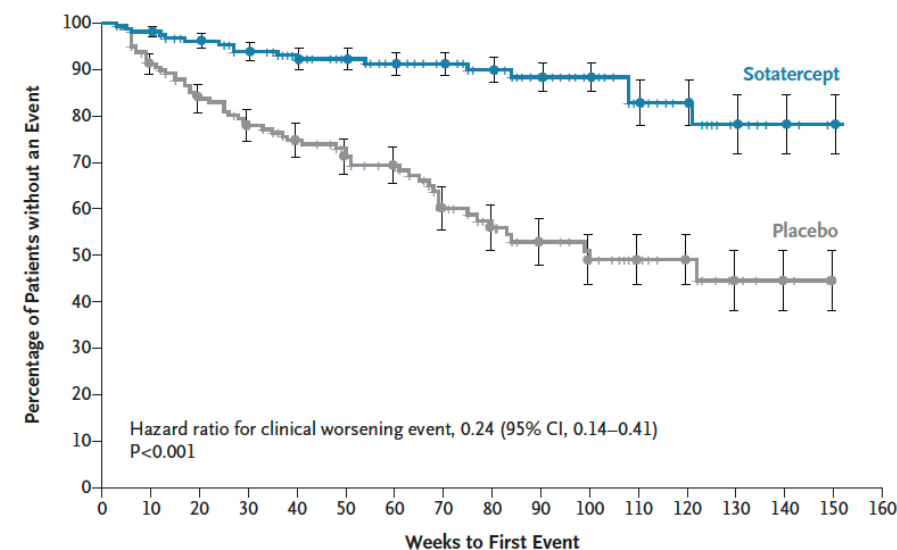
N Engl J Med 2025;392:1987-2000

HYPERION TRIAL

Sotatercept for Pulmonary Arterial Hypertension within the First Year after Diagnosis

The primary end point:

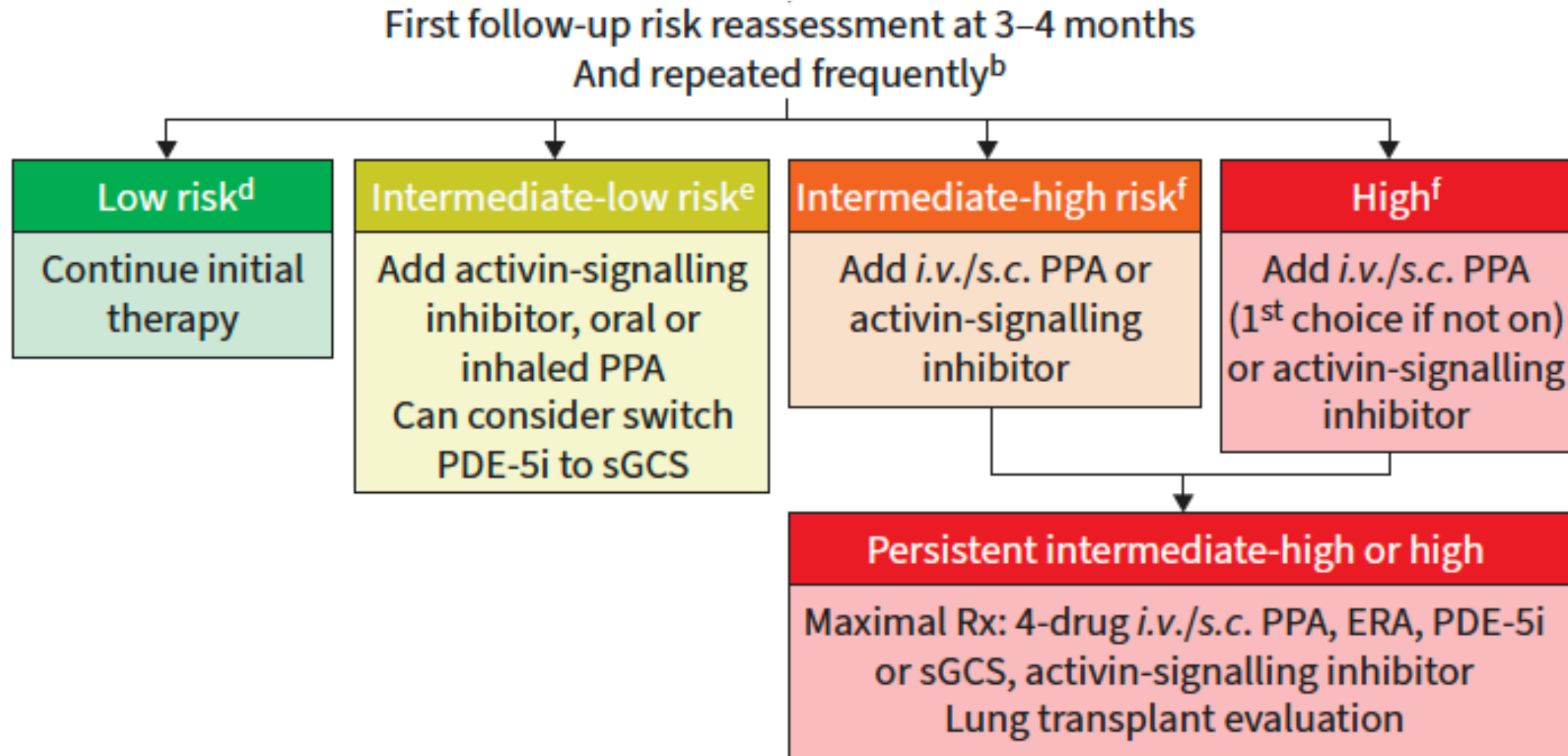
composite of death from any cause, unplanned hospitalization for worsening PAH, atrial septostomy, lung transplantation, or deterioration in performance in exercise testing



N Engl J Med 2025 Sep 30

Treatment algorithm for pulmonary arterial hypertension

*The Seventh World Symposium on
Pulmonary Hypertension*

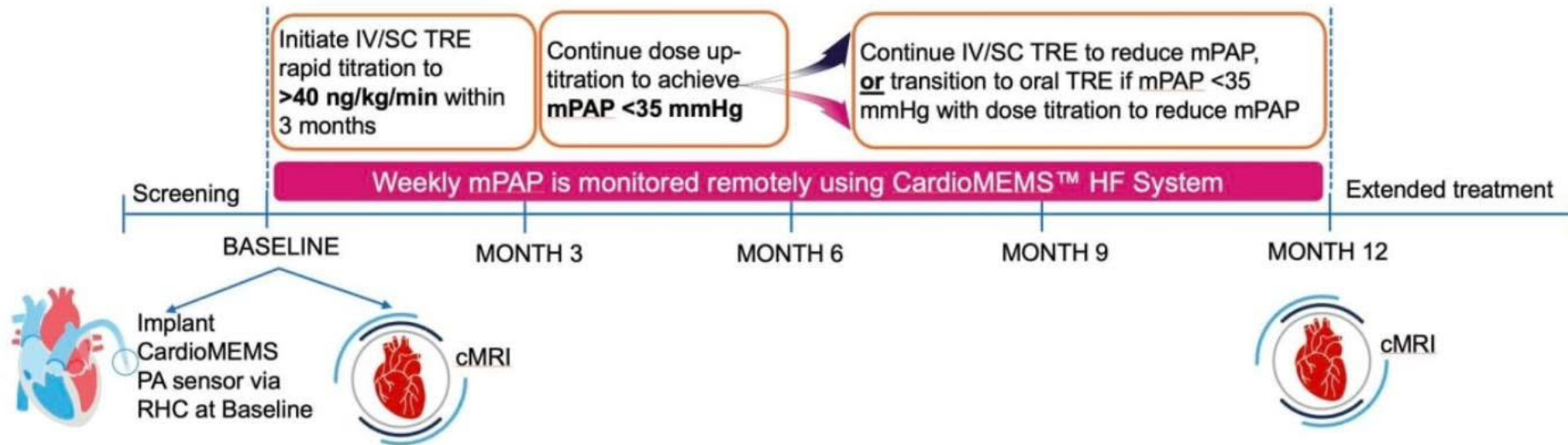


ARTISAN: Mean PAP-Targeted Approach with Early and Rapid Treprostinil Therapy to Reverse RV Remodeling in PAH

Methods



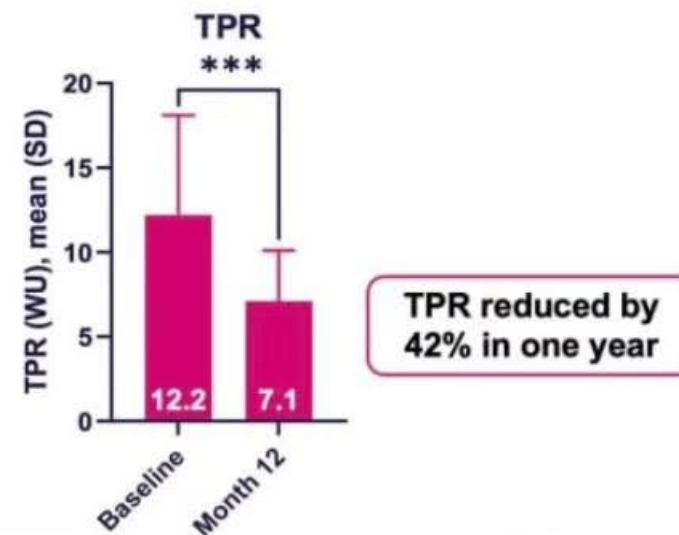
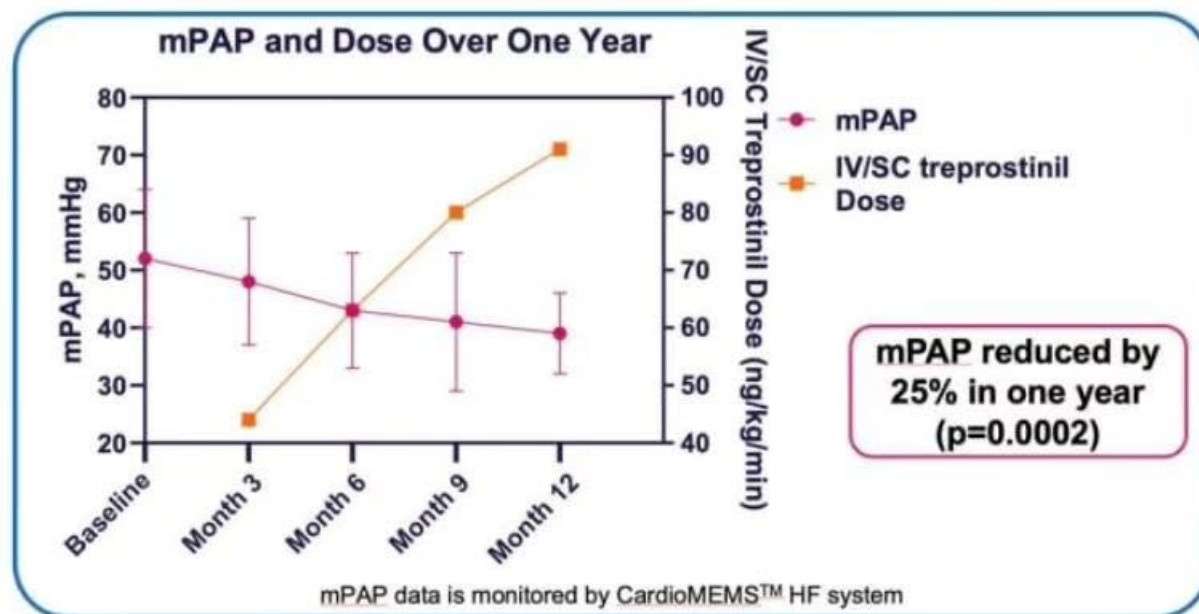
- **Eligibility Criteria:** Newly diagnosed PAH with background therapy <6 months or treatment naïve; baseline mPAP >35 mmHg, PVR >2 WU, PAWP ≤15 mmHg; REVEAL Lite 2 risk score ≤9; WHO FC II or III.



- At Baseline and Month 12, RV function are measured by cMRI and centrally reviewed.
- Primary endpoint: Change in RVEF from baseline to Month 12.

cMRI: cardiac magnetic resonance imaging; IV: intravenous; mPAP: mean pulmonary artery hypertension; PA: pulmonary artery; PAH: pulmonary arterial hypertension; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; RHC: right heart catheterization; RVEF: right ventricular ejection fraction; SC: subcutaneous; TRE: treprostinil; WHO FC: World Health Organization functional class; WU: Wood Units.

Results – Early TRE Dosing to mPAP and TPR



TPR (Total Pulmonary Resistance)= mPAP/CO, mPAP is from CardioMEMS and CO is from cMRI

mPAP reduction of >20% may contribute to greater PVR reduction and CO increase.¹

	Month 3	Month 6	Month 9	Month 12
IV/SC treprostinil dose, ng/kg/min	43±14 (n=17)	64±16 (n=17)	83±17 (n=12)	91±19 (n=9)
Oral treprostinil dose, total daily dose, mg	19.5 (n=1)	11.75 (n=1)	24±11 (n=6)	27±10 (n=9)

Variables are reported as mean ± SD, with p values calculated using paired t-tests, except for mPAP calculated using repeated measures ANOVA.

1. Farmakis IT, et al. ERJ Open Res. 2024;10:00706-2023

Levels of clinical response in pulmonary arterial hypertension

Symptom free

Wellness

Symptoms

Symptoms

Disability

Death

Symptomatic



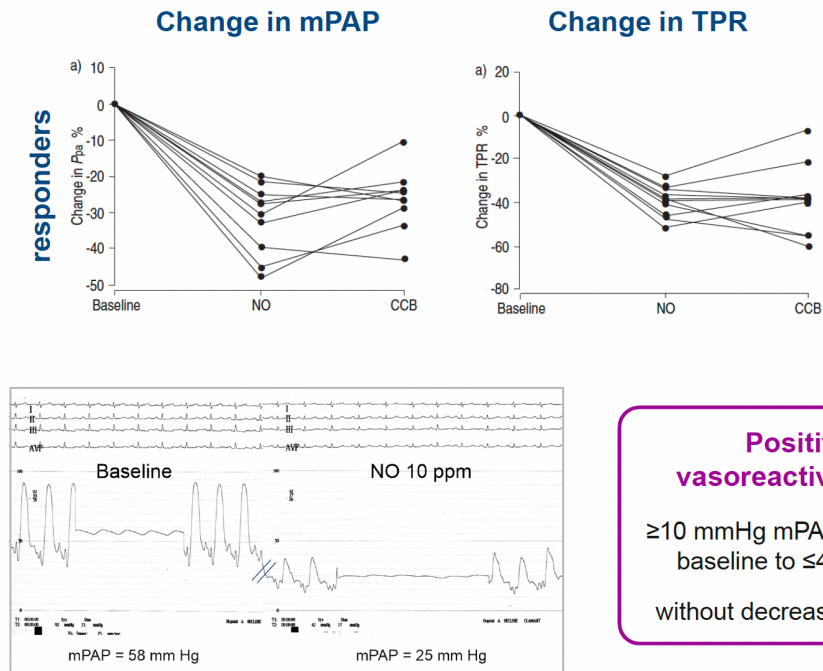
	Haemodynamics	Right heart functions	Mortality risk	Symptoms	Function	Disease course
Complete remission (PAH medication continued)	mPAP $\leq$ 20 mm Hg and PVR $\leq$ 2 Wood units at rest	Normal right atrium and right ventricle size and function	Low	No pulmonary hypertension related symptoms	WHO function class I	Life expectancy no longer affected by PAH
Partial remission (PAH medication continued)	Substantial improvement in pulmonary haemodynamics to mPAP $\leq$ 35 mm Hg or PVR <5 Wood units	Improvement in right atrium and right ventricle size and function	Low	Mild pulmonary hypertension related symptoms	WHO function class I-II	Major improvement in progression-free survival or overall survival
Improvement	Any decrease (improvement) in mPAP and PVR not fulfilling the partial remission criteria	Improvement in right atrium and right ventricle size and function	Improved risk category	Moderate pulmonary hypertension related symptoms	WHO function class II-III	Improvement in progression-free survival possible

Time



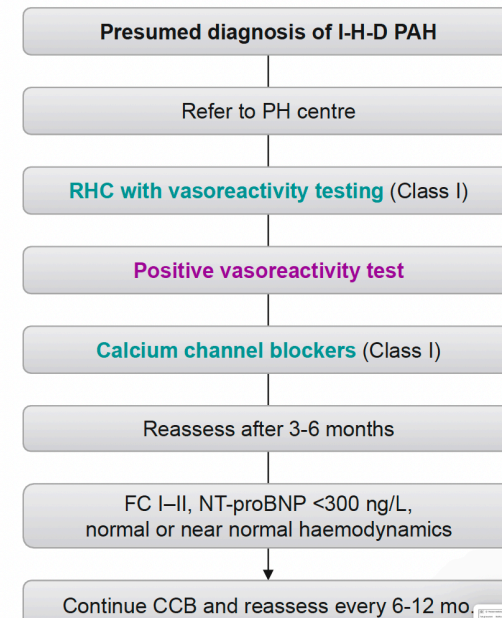
cloud.raineri@gmail.com
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Vasoreactivity testing identifies patients who will be initiated by calcium channel blockers



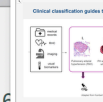
Positive vasoreactivity test

≥10 mmHg mPAP drop from baseline to ≤40 mmHg without decrease in CO/CI

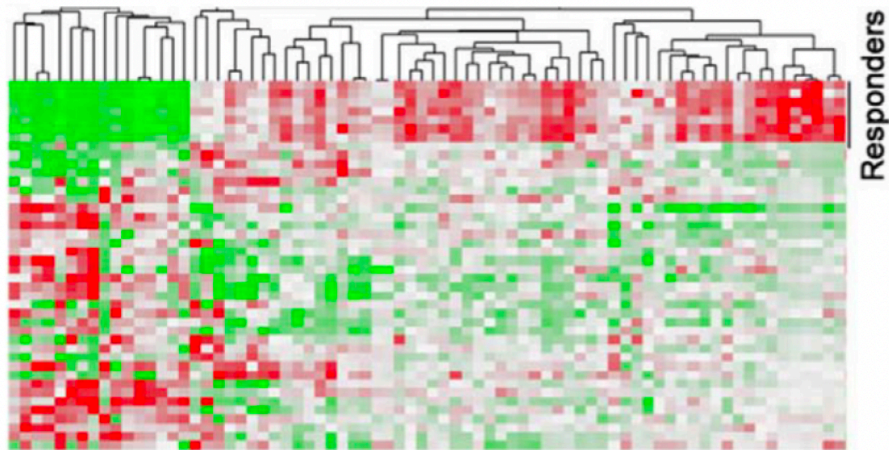


Sitbon O, et al. *Eur Respir J* 1998; 12: 265–270.

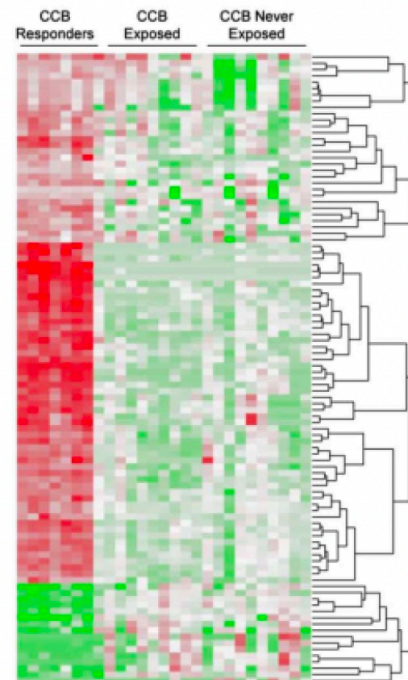
Humbert M, et al. *Eur Heart J* 2022; 43: 3618-3731; Humbert M, et al. *Eur Respir J* 2023; 6



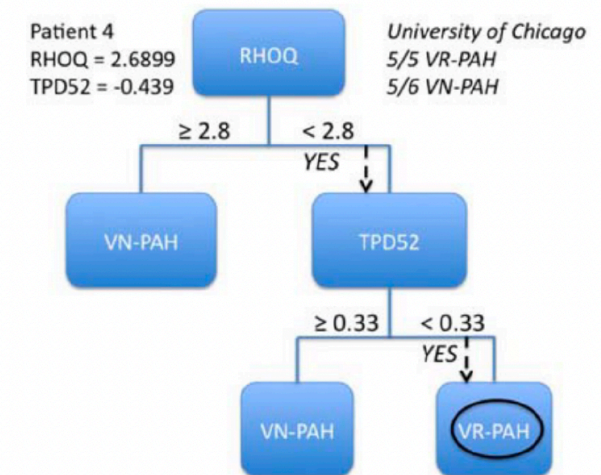
RNA expression patterns in peripheral blood of 9 vasodilator-responsive PAH (>1y CCB) and 32 patients with negative VR test



Non responders



Decision Tree based on 2 genes (RHOQ and TPD52) to predict long-term responders in a validation cohort



Differences in peripheral blood RNA expression profiles between CCB long-term responders and non vasoreactive patients were not explained by CCB exposure