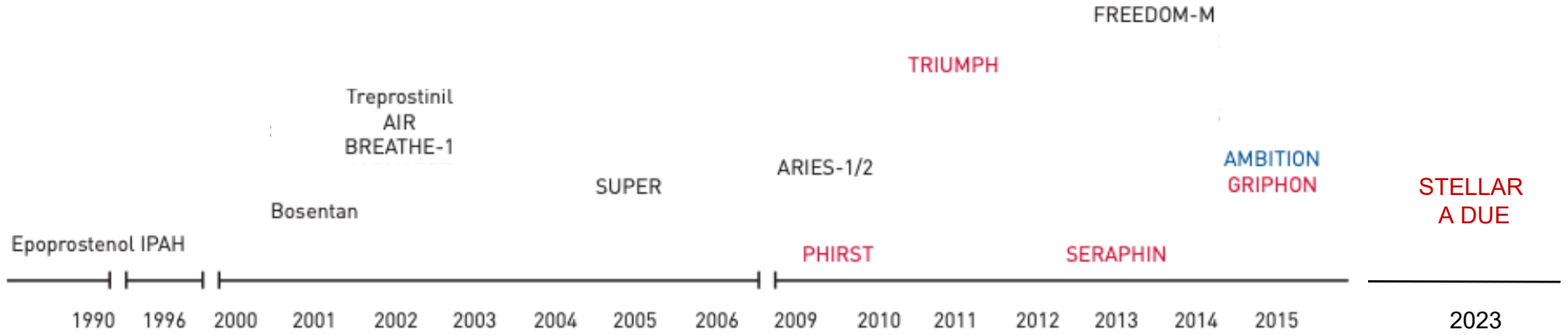
Update in Pulmonary Arterial Hypertension Therapies

Victor Moles, MD
Clinical Associate Professor
University of Michigan
Ann Arbor, MI

TOTAL CME

Several Treatment Options Are Available

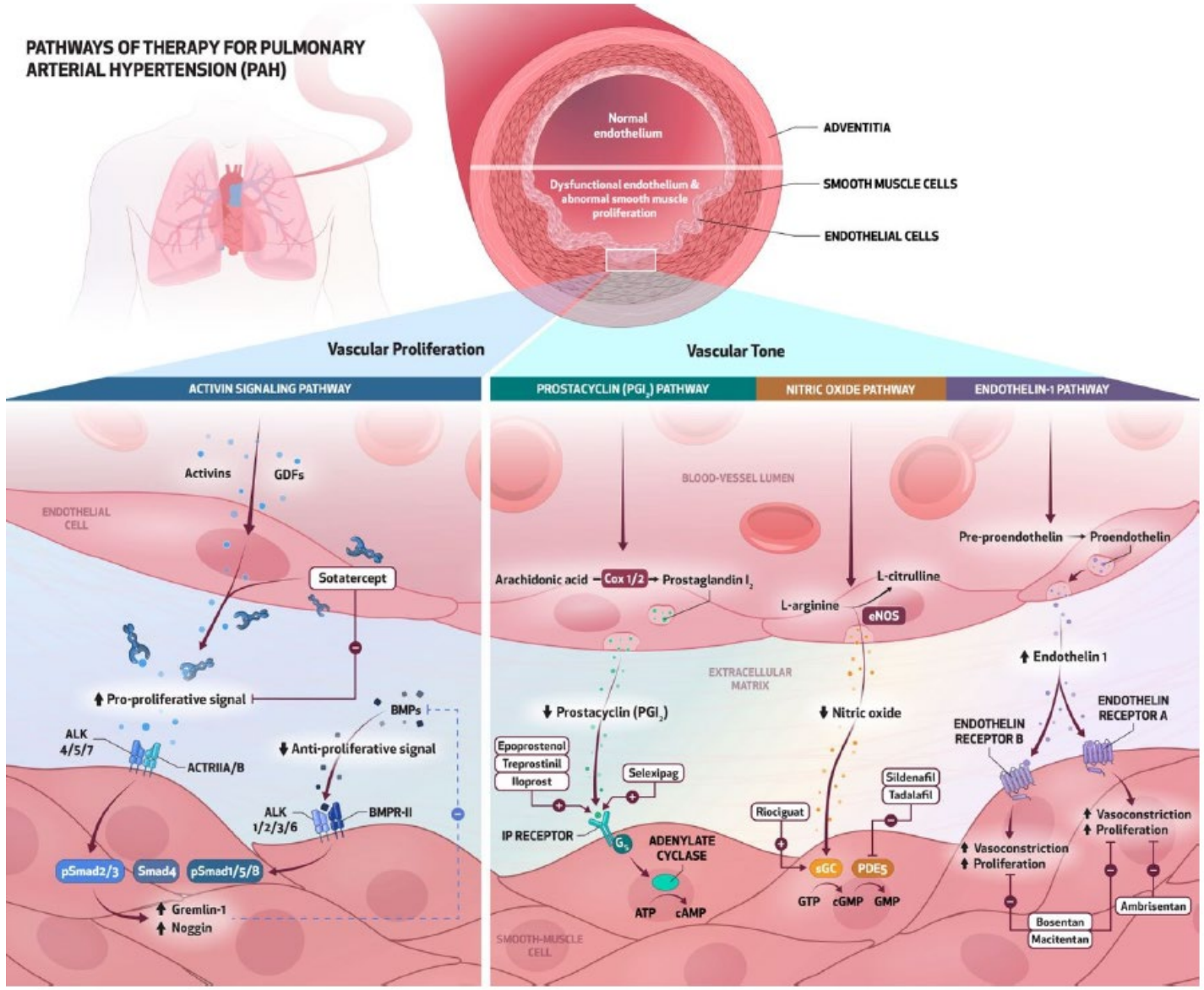


FDA-Approved Medication/Year

- Epoprostenol IV (Flolan) – Approved 1995
- Bosentan PO (Tracleer) – Approved 2001
- Treprostinil SQ (Remodulin) – Approved 2002
- Iloprost Inh (Ventavis) – Approved 2004
- Treprostinil IV – Approved 2005
- Sildenafil PO (Revatio) – Approved 2005
- Ambrisentan PO (Letairis) – Approved 2007
- Tadalafil PO (Adcirca) – Approved 2009
- Treprostinil IH (Tyvaso) – Approved 2009
- Epoprostenol IV (Veletri) – Approved 2010
- Riociguat PO (Adempas) – Approved 2013
- Macitentan PO (Opsumit) – Approved 2013
- Treprostinil PO (Orenitram) – Approved 2013
- Selexipag PO (Uptravi) – Approved 2015
- Sotatercept (Winrevair) – Approved 2024
- Tadalafil/Macitentan (Opsynvi) – Approved 2024

Adapted from Galiè N, et al. *Eur Respir J*. 2019;53(1):1802148.

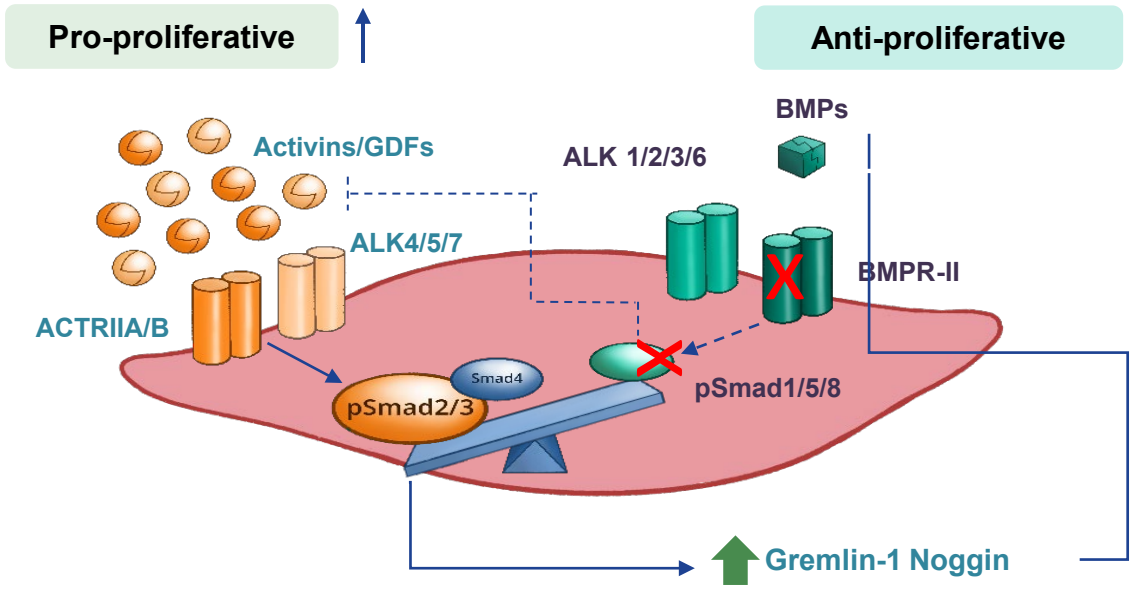
Current Pathways of Therapy for Pulmonary Arterial Hypertension



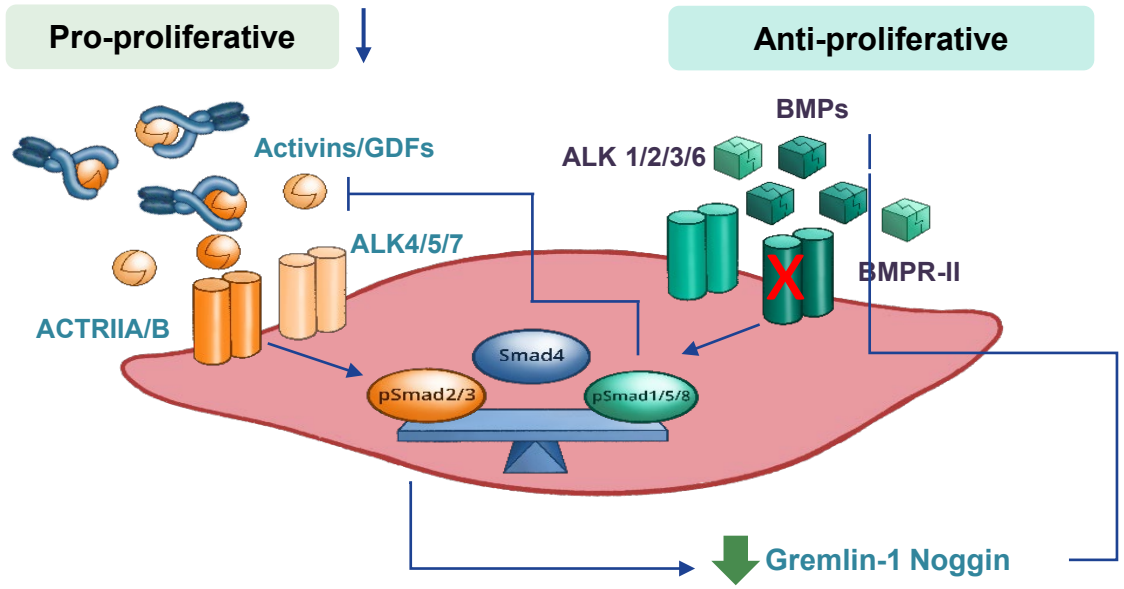
Sahay S, et al. *Am J Respir Crit Care Med.* 2024;210(5):581-592.

BMPR2 / Activin Signaling Pathway

PAH



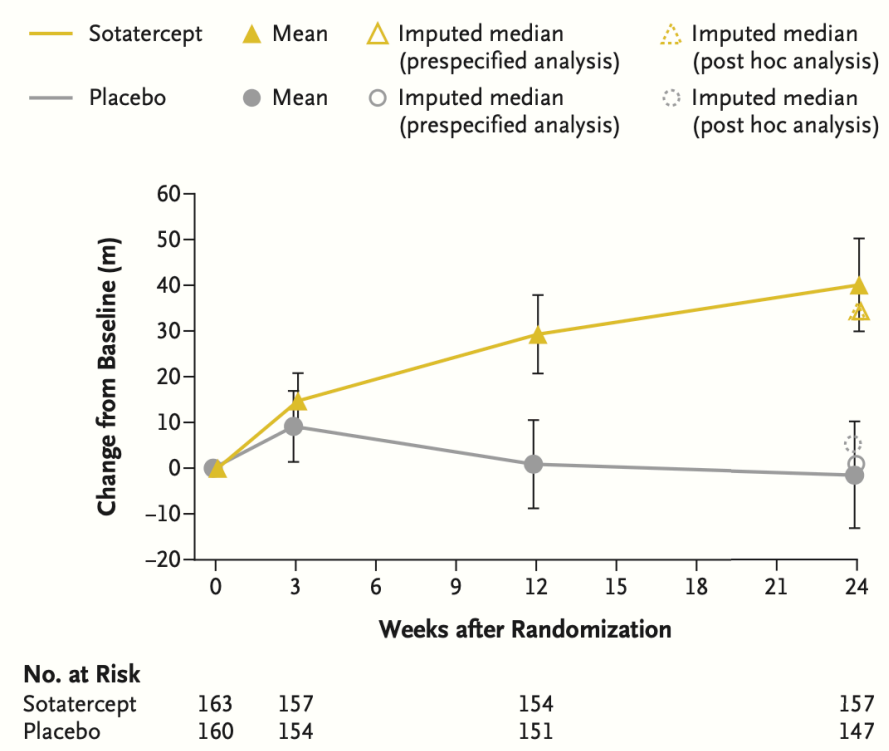
Sotatercept



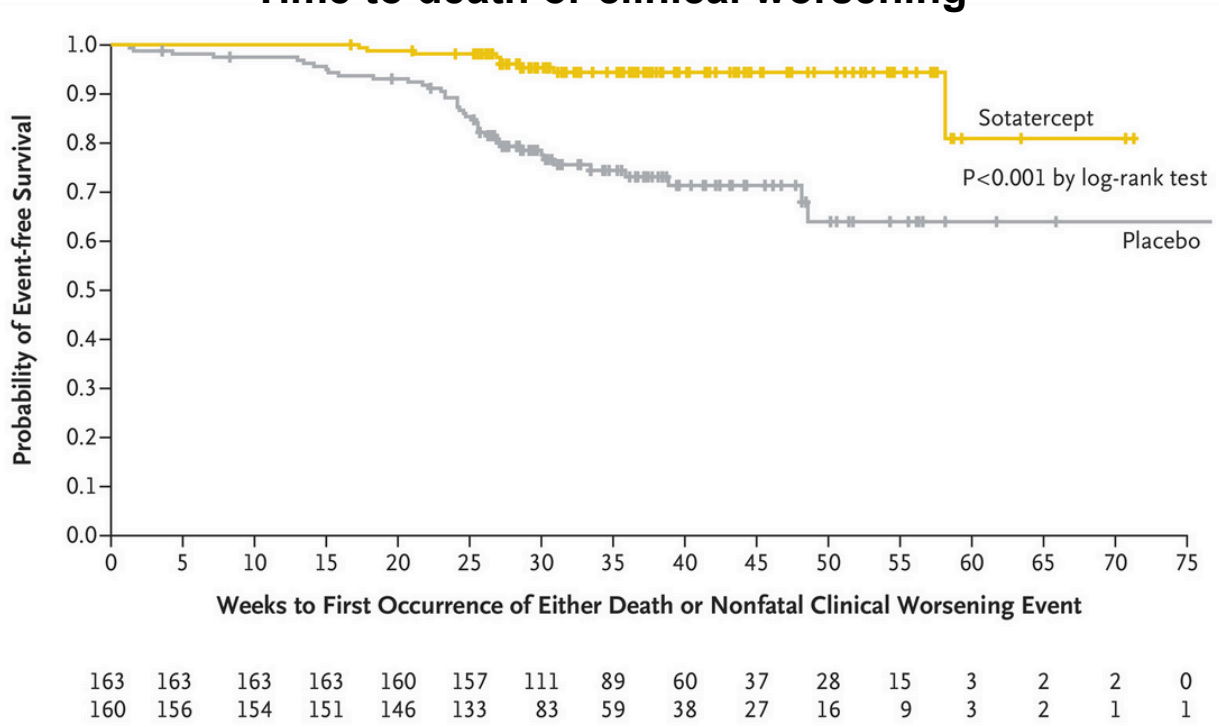
Galkin A, et al. *Eur Respir J.* 2022;60(6):2102356.

STELLAR – Sotatercept

6-minute walk distance (6MWD)



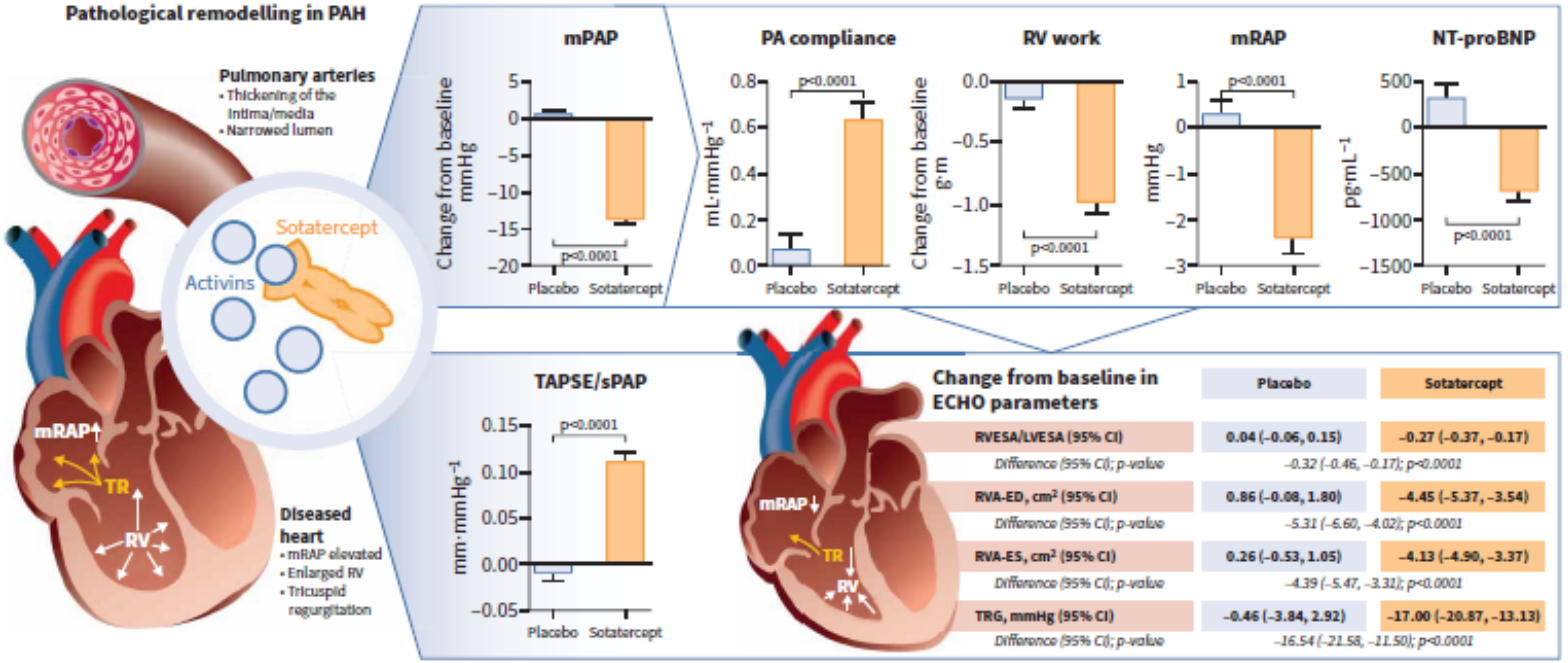
Time to death or clinical worsening



FDA approval in March 2024

Hoeper MM, et al. *N Engl J Med*. 2023;388(16):1478-1490.

Sotatercept Improves Hemodynamics and Produces Significant RV Remodeling



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*	

CO (L·min^{-1})	4.8±1.2 (160)	4.7±1.2 (144)	−0.2 (−0.3, −0.0) (144)	4.9±1.3 (163)	4.8±1.3 (154)	−0.1 (−0.3, 0.0) (154)	0.1 (−0.2, 0.3); p=0.5900
CI (L·min^{-1}·m^{-2})	2.7±0.6 (160)	2.6±0.6 (144)	−0.1 (−0.2, −0.0) (144)	2.7±0.6 (163)	2.6±0.6 (154)	−0.1 (−0.2, 0.0) (154)	0.0 (−0.1, 0.2); p=0.6212
RVFAC (%)	29.28±8.94 (151)	30.24±9.26 (139)	1.42 (−0.04, 2.88) (139)	28.45±8.81 (155)	32.19±9.94 (148)	3.46 (2.04, 4.89) (148)	2.04 (0.03, 4.05); p=0.0462
RVA-ED (cm²)	30.22±9.51 (151)	30.77±9.91 (139)	0.86 (−0.08, 1.80) (139)	30.69±8.87 (155)	25.93±8.75 (148)	−4.45 (−5.37, −3.54) (148)	−5.31 (−6.60, −4.02); p<0.0001
RVA-ES (cm²)	21.75±8.70 (151)	21.85±8.62 (139)	0.26 (−0.53, 1.05) (139)	22.26±8.07 (155)	17.91±7.82 (148)	−4.13 (−4.90, −3.37) (148)	−4.39 (−5.47, −3.31); p<0.0001

Significant decrease in PVR and PA compliance

↓ PAP = CO

Positive RV remodeling

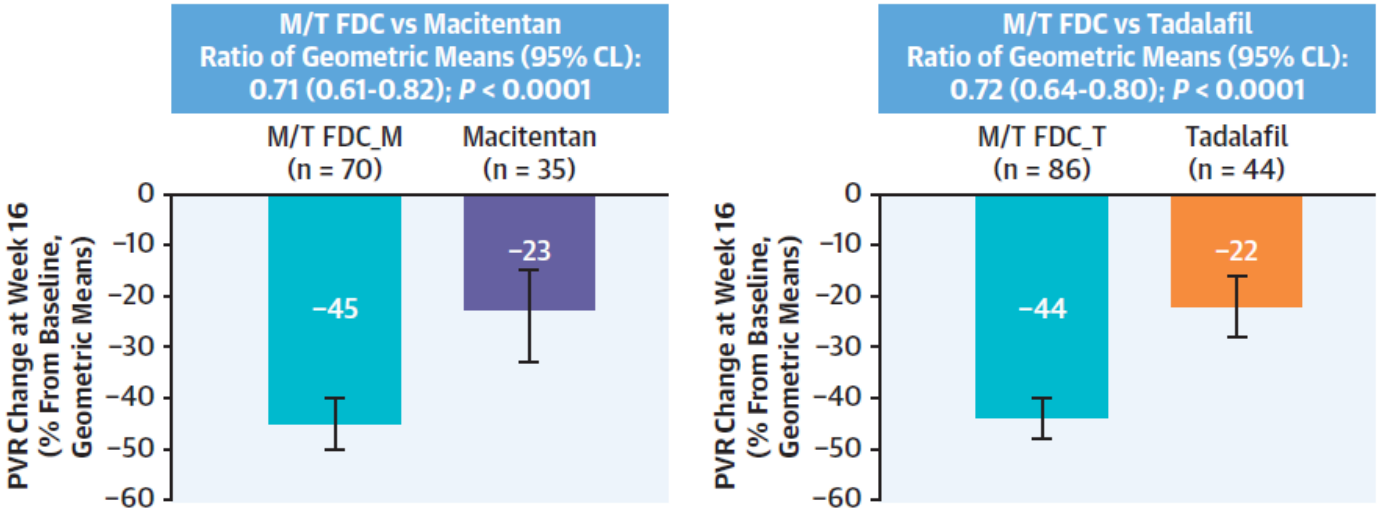
↓ Size ↑ Function

Souza R, et al. *Eur Respir J.* 2023;62(3):2301107.

A-DUE: Single-Tablet Combination Therapy of Macitentan/Tadalafil (M/T)

- Safety and efficacy of M/T
- Both treatment naïve and prior treatment with ERA or PDE5i
- Primary endpoint: change in PVR at 16 weeks

Figure 2 Primary Endpoint: Change in PVR at Week 16



FDA approval in March 2024

Grünig E, et al. *J Am Coll Cardiol*. 2024;83(4):473-484.

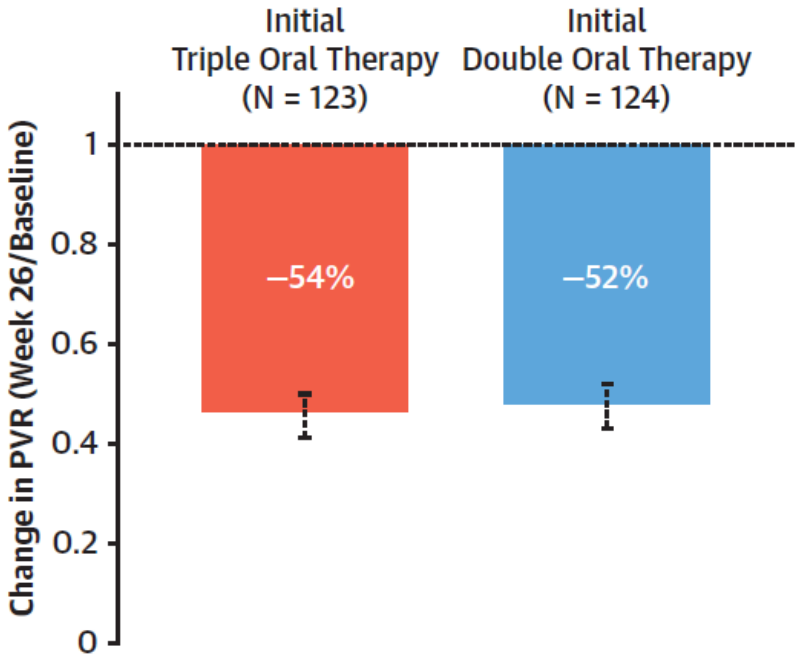
Not All Up-Front Triple Combination Therapy Is Equal

TRITON

- Initial triple (tadalafil, macitentan, selexipag) versus initial double (tadalafil, macitentan, placebo) therapy in newly diagnosed treatment-naïve patients with PAH
- No change in PVR at 26 weeks
- Non-statistically significant trend to time of first disease progression event

❖ Triple up-front combination including selexipag is not recommended

Figure 2 Change in Pulmonary Vascular Resistance from Baseline to Week 26

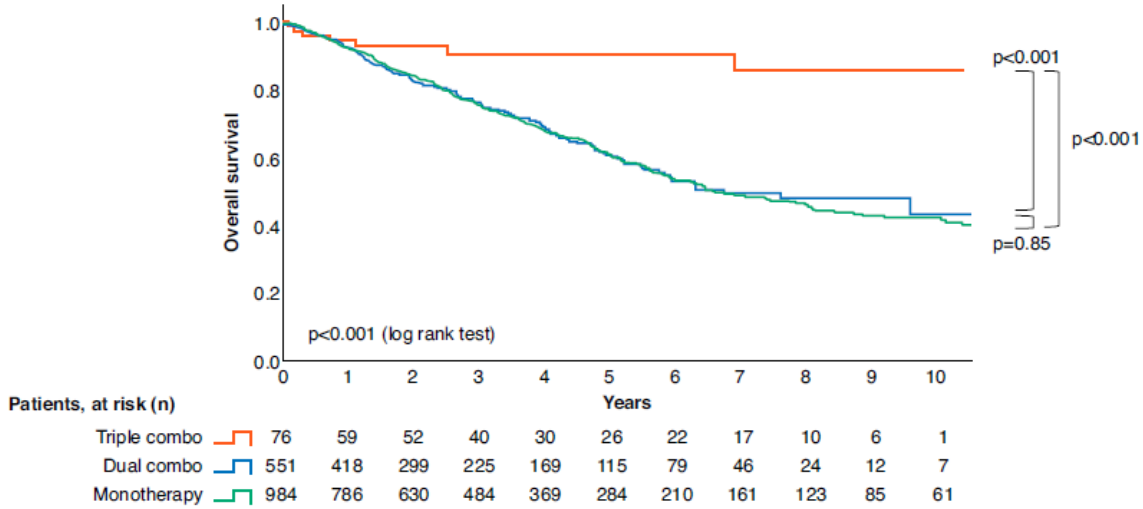


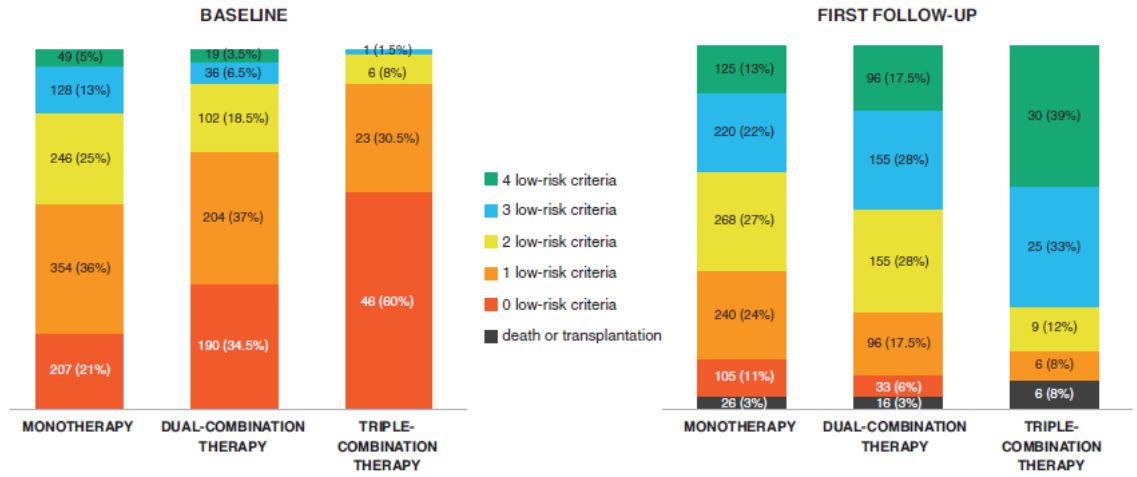
Chin KM, et al. *J Am Coll Cardiol*. 2021;78(14):1393-1403.

Not All Up-Front Triple Combination Therapy Is Equal

French PH Network and Registry

- A retrospective analysis of incident patients with idiopathic, heritable, or anorexigen-induced PAH enrolled in the FPHR (1/2006 to 12/2018)
- Survival was assessed according to the initial strategy: monotherapy, dual therapy, or triple-combination therapy (2 oral medications and a parenteral prostacyclin)
- ❖ Initial triple-combination therapy that includes parenteral prostacyclin was associated with a higher survival rate in PAH





Boucly A. *Am J Respir Crit Care Med*. 2021;204(7):842-854.

Conclusions

- Many therapies are available for the management of PAH.
- The activin-signaling pathway is a novel therapeutic target for the management of PAH.
- Sotatercept is FDA-approved in PAH and has a distinct hemodynamic effect.
- Tadalafil/macitentan combination tablet is now FDA-approved and may improve medication adherence.
- Not all triple up-front combination therapy is equal.

Updated PAH Treatment Algorithm

Vallerie V. McLaughlin, MD

Director, Pulmonary Hypertension Program

University of Michigan

Ann Arbor, MI

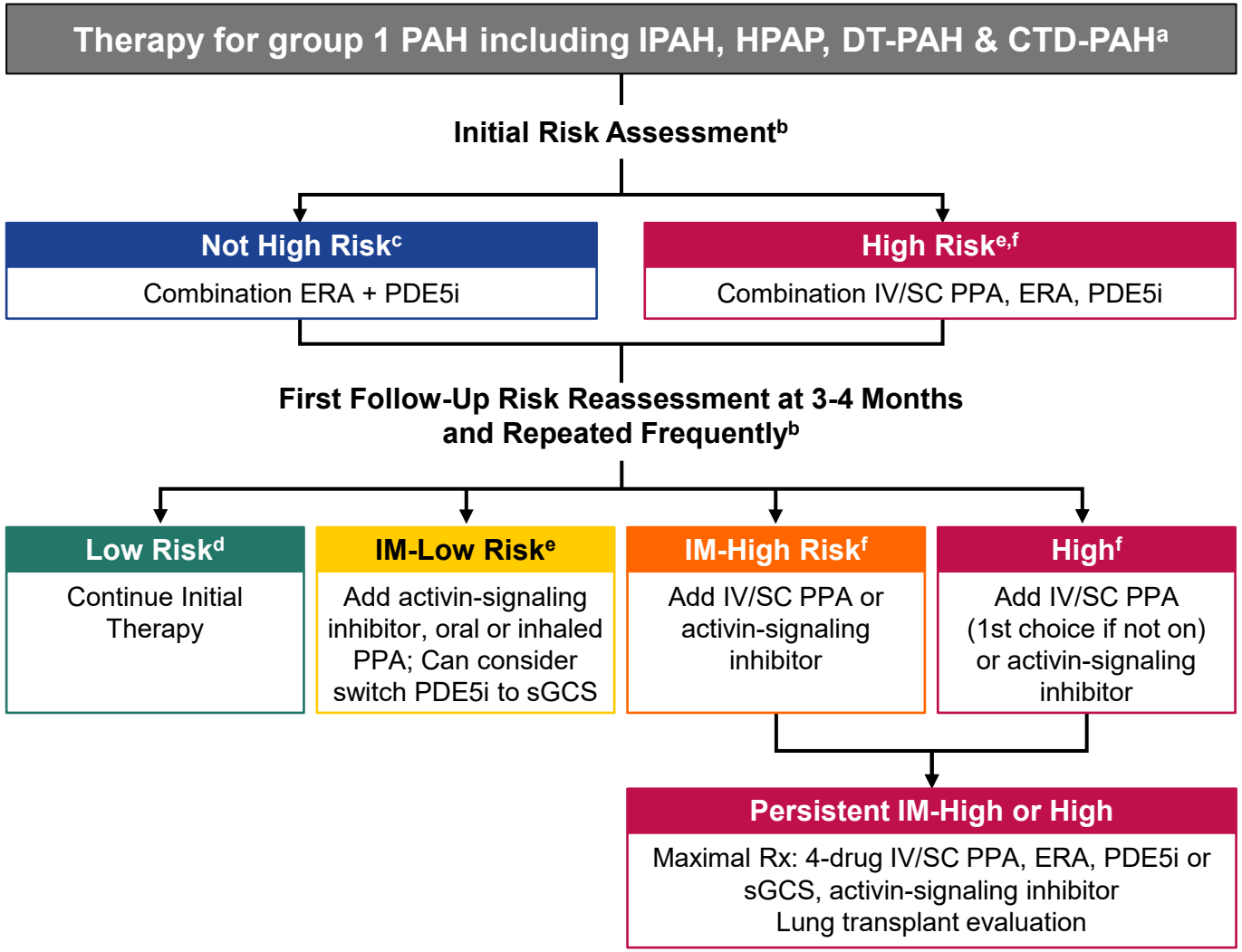
TOTAL CME

7th WSPH: Recommended Supportive Measures

- Supervised exercise training
- Psychological support
- Immunization against SARS-CoV-2, influenza, Streptococcus pneumoniae, and consider vaccination against RSV
- Diuretic treatment in patients with fluid retention
- Continuous long-term oxygen therapy when arterial blood O_2 pressure is consistently <8 kPa (60 mm Hg)
- Correction of iron status in patients with iron-deficiency anemia
- Advise against pregnancy
- Clear contraceptive advice
- Pre-transplant counseling

Chin KM, et al. *Eur Respir J*. Published online August 29, 2024. doi:10.1183/13993003.01325-2024

7th WSPH Treatment Algorithm: First Follow-Up Risk Assessment at 3-4 Months and Repeat Frequently



Treatment Algorithm Key Points

a. Treatment algorithm is intended for patients with confirmed group 1 PAH (phenotypically clear-cut, ***mPAP ≥25 and PVR >3*** and no significant response on acute vasoreactivity testing). Treatment nuances in PAH with complex phenotypes.

b. Risk assessment should be performed at baseline, within 3-4 months, and periodically thereafter, and using FC, 6MWD, and natriuretic peptides as a part of a validated risk calculator. Hemodynamics, RV imaging, and other measures should be used to supplement risk assessment.

c. Initial triple therapy with an IV/SC PPA is recommended in high-risk patients and may be considered in non-high risk with severe hemodynamics and/or poor RV function.

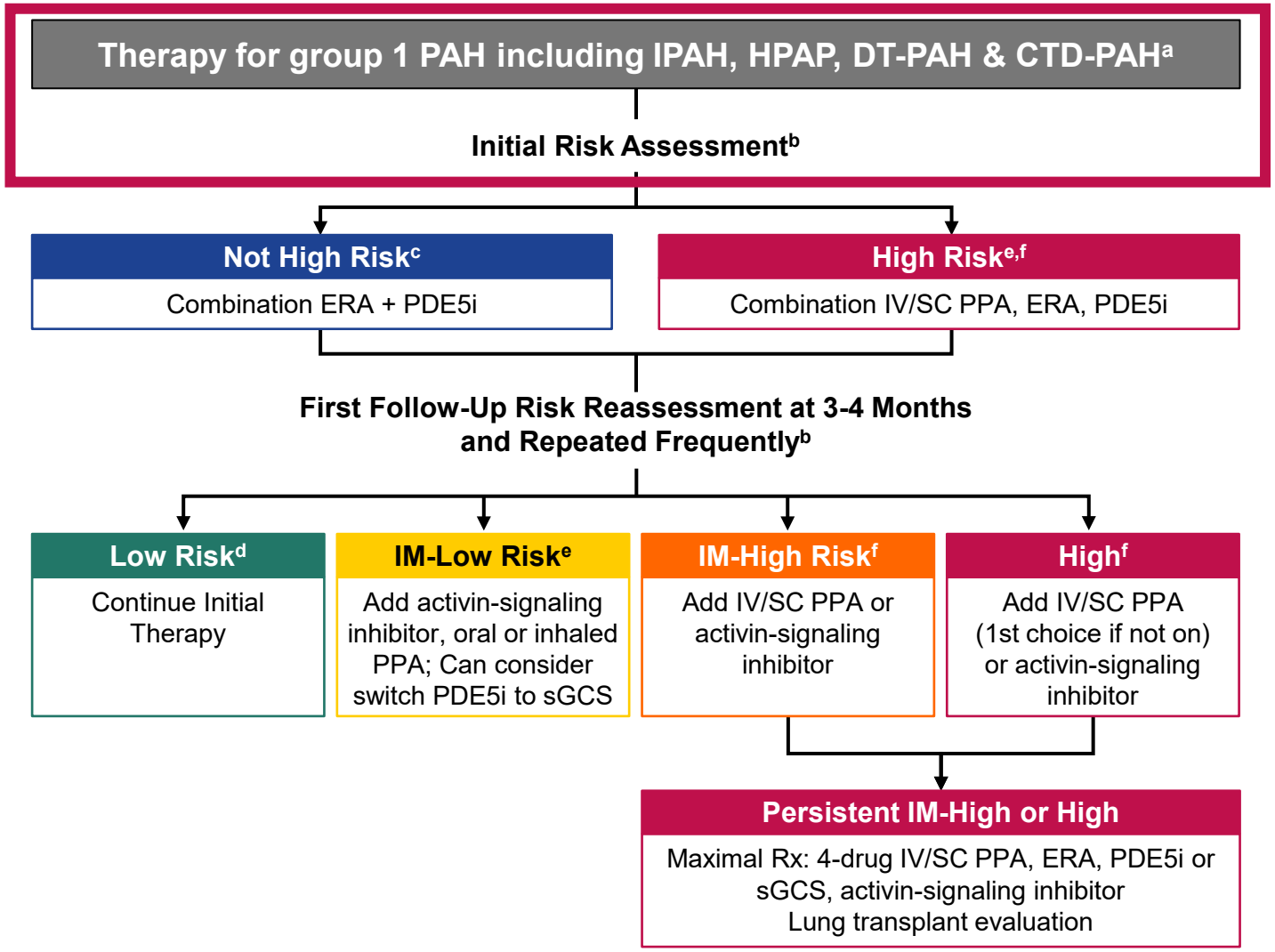
d. Most ***low risk*** at follow-up patients should continue initial therapy.

e. Clinical trials with oral and inhaled treprostinil included ***only patients on monotherapy***, while studies of selexipag and sotatercept included patients on combination therapy.

f. Transplant referral should be considered for select high-risk patients **at diagnosis**, and for IM-high and high-risk patients at ***first*** or subsequent follow-up.

Chin KM, et al. *Eur Respir J*. Published online August 29, 2024. doi:10.1183/13993003.01325-2024

7th WSPH Treatment Algorithm: First Follow-Up Risk Assessment at 3-4 Months and Repeat Frequently



Treatment Algorithm Key Points

a. Treatment algorithm is intended for patients with confirmed group 1 PAH (phenotypically clear-cut, ***mPAP ≥25 and PVR >3*** and no significant response on acute vasoreactivity testing). Treatment nuances in PAH with complex phenotypes.

b. Risk assessment should be performed at baseline, within 3-4 months, and periodically thereafter, and using FC, 6MWD, and natriuretic peptides as a part of a validated risk calculator. Hemodynamics, RV imaging, and other measures should be used to supplement risk assessment.

c. Initial triple therapy with an IV/SC PPA is recommended in high-risk patients and may be considered in non-high risk with severe hemodynamics and/or poor RV function.

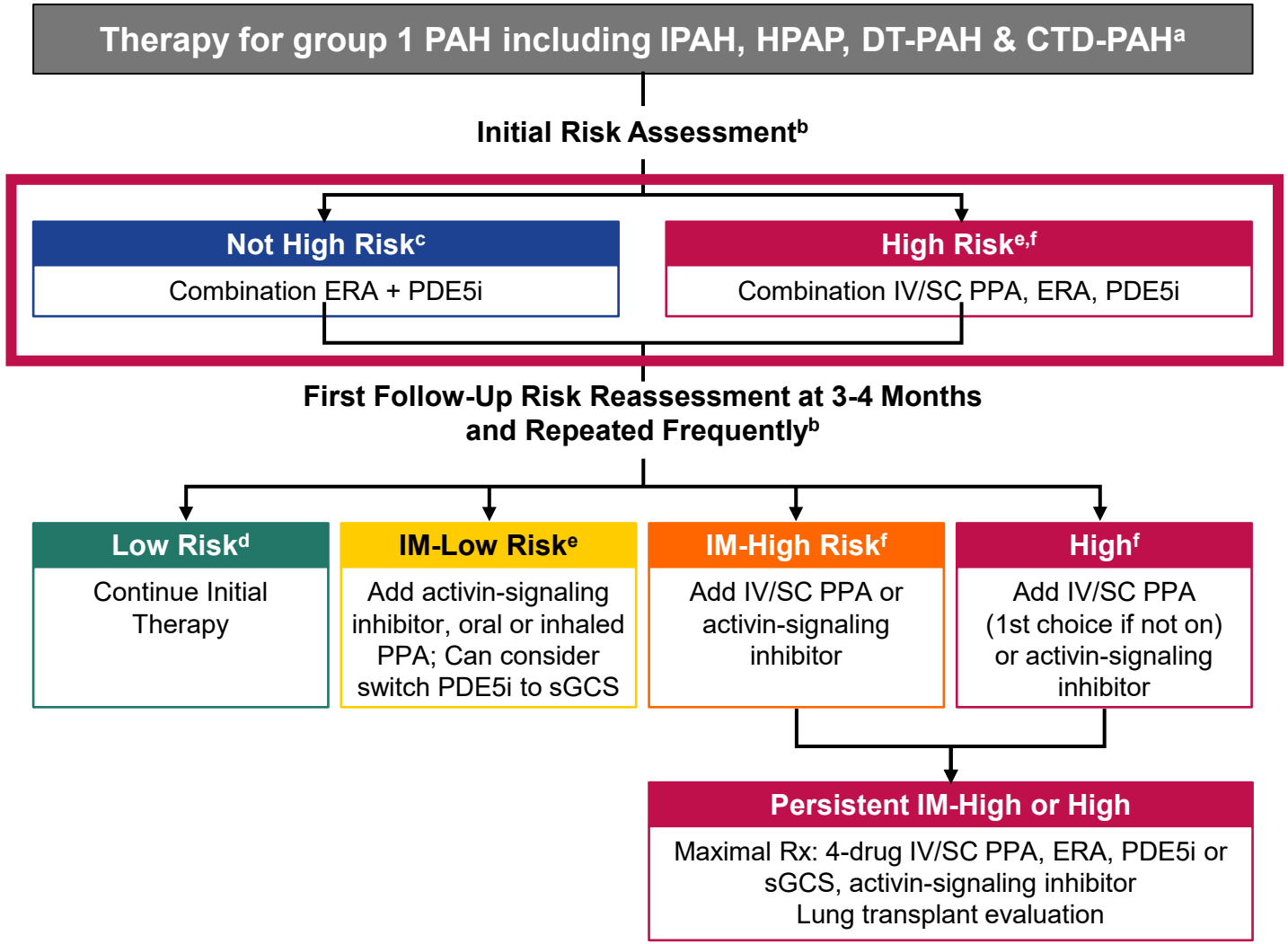
d. Most ***low risk*** at follow-up patients should continue initial therapy.

e. Clinical trials with oral and inhaled treprostinil included ***only patients on monotherapy***, while studies of selexipag and sotatercept included patients on combination therapy.

f. Transplant referral should be considered for select high-risk patients **at diagnosis**, and for IM-high and high-risk patients at ***first*** or subsequent follow-up.

Chin KM, et al. *Eur Respir J.* Published online August 29, 2024. doi:10.1183/13993003.01325-2024

7th WSPH Treatment Algorithm: First Follow-Up Risk Assessment at 3-4 Months and Repeat Frequently



Treatment Algorithm Key Points

a. Treatment algorithm is intended for patients with confirmed group 1 PAH (phenotypically clear-cut, mPAP ≥25 and PVR >3 and no significant response on acute vasoreactivity testing). Treatment nuances in PAH with complex phenotypes.

b. Risk assessment should be performed at baseline, within 3-4 months, and periodically thereafter, and using FC, 6MWD, and natriuretic peptides as a part of a validated risk calculator. Hemodynamics, RV imaging, and other measures should be used to supplement risk assessment.

c. ***Initial triple therapy*** with an IV/SC PPA is recommended in high-risk patients and may be considered in non-high risk with severe hemodynamics and/or poor RV function.

d. Most ***low risk*** at follow-up patients should continue initial therapy.

e. Clinical trials with oral and inhaled treprostinil included ***only patients on monotherapy***, while studies of selexipag and sotatercept included patients on combination therapy.

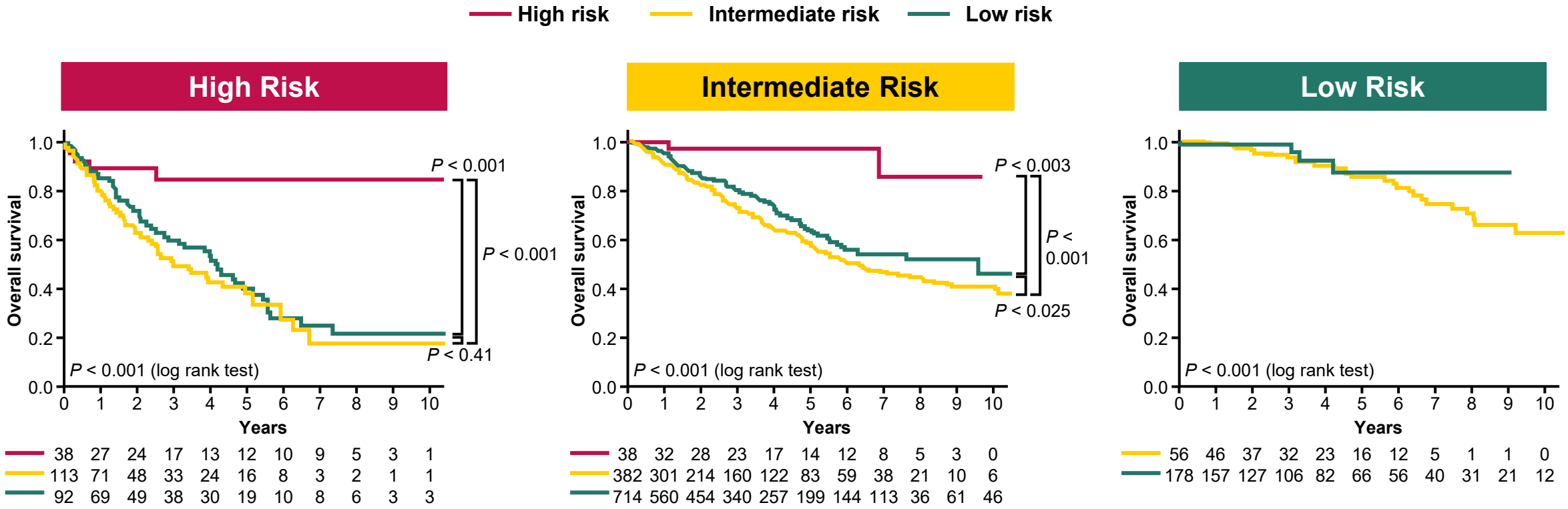
f. ***Transplant referral*** should be considered for select high-risk patients **at diagnosis**, and for IM-high and high-risk patients at ***first*** or subsequent follow-up.

Chin KM, et al. *Eur Respir J.* Published online August 29, 2024. doi:10.1183/13993003.01325-2024

FDA-Approved Therapy for PAH

Pathway	Therapy	Dosage
Endothelin	Ambrisentan	5, 10 mg po qd
	Bosentan	125 mg po bid
	Macitentan	10 mg po bid
Nitric Oxide	**PDE5 Inhibitors**	
	Sildenafil	20 mg po tid
	Tadalafil	40 mg po qd
	sGC Stimulator	
	Riociguat	0.5-2.0 mg po tid
Prostacyclin	Epoprostenol	IV
	Treprostinil	IV/SC
		9 inhalations qid
		Oral tid
	Iloprost	Inhale 6-9 times daily
	Selexipag	200-1600 mcg bid
Activin-Signaling inhibitor	Sotatercept	0.3-0.7 mg/kg every 3 wk

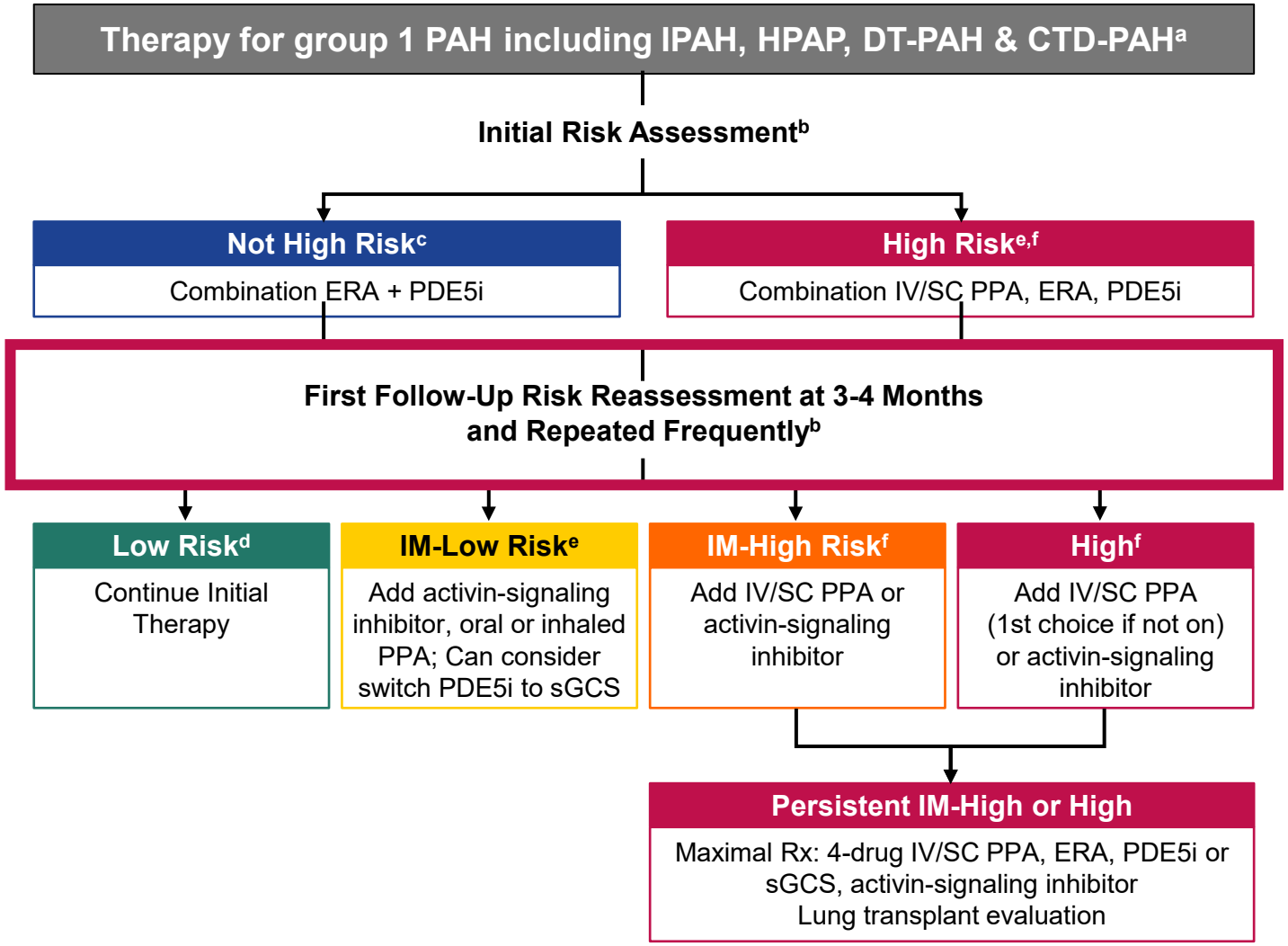
Initial Triple Combination Is Also Better in Patients at Intermediate Risk



Initial triple combination is superior to other strategies in patients at **high risk** and **intermediate risk**

Boucly A, et al. *Am J Respir Crit Care Med*. 2021;204(7):842-854.

7th WSPH Treatment Algorithm: First Follow-Up Risk Assessment at 3-4 Months and Repeat Frequently



Treatment Algorithm Key Points

a. Treatment algorithm is intended for patients with confirmed group 1 PAH (phenotypically clear-cut, mPAP ≥25 and PVR >3 and no significant response on acute vasoreactivity testing). Treatment nuances in PAH with complex phenotypes.

b. Risk assessment should be performed at baseline, within 3-4 months, and periodically thereafter, and using FC, 6MWD, and natriuretic peptides as a part of a validated risk calculator. Hemodynamics, RV imaging, and other measures should be used to supplement risk assessment.

c. Initial triple therapy with an IV/SC PPA is recommended in high-risk patients and may be considered in non-high risk with severe hemodynamics and/or poor RV function.

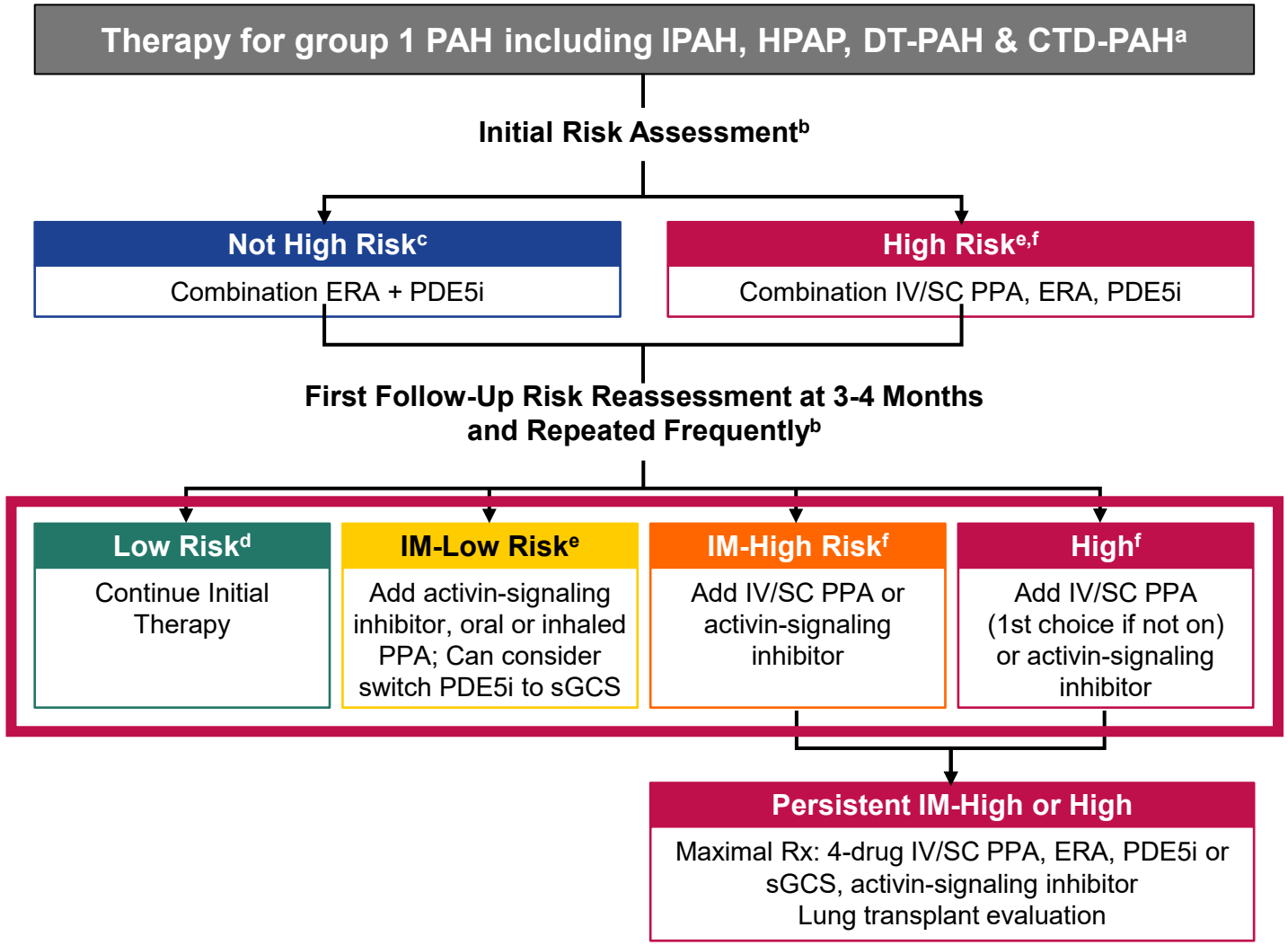
d. Most ***low risk*** at follow-up patients should continue initial therapy.

e. Clinical trials with oral and inhaled treprostinil included ***only patients on monotherapy***, while studies of selexipag and sotatercept included patients on combination therapy.

f. Transplant referral should be considered for select high-risk patients **at diagnosis**, and for IM-high and high-risk patients at ***first*** or subsequent follow-up.

Chin KM, et al. *Eur Respir J*. Published online August 29, 2024. doi:10.1183/13993003.01325-2024

7th WSPH Treatment Algorithm: First Follow-Up Risk Assessment at 3-4 Months and Repeat Frequently



Treatment Algorithm Key Points

a. Treatment algorithm is intended for patients with confirmed group 1 PAH (phenotypically clear-cut, mPAP ≥25 and PVR >3 and no significant response on acute vasoreactivity testing). Treatment nuances in PAH with complex phenotypes.

b. Risk assessment should be performed at baseline, within 3-4 months, and periodically thereafter, and using FC, 6MWD, and natriuretic peptides as a part of a validated risk calculator. Hemodynamics, RV imaging, and other measures should be used to supplement risk assessment.

c. Initial triple therapy with an IV/SC PPA is recommended in high-risk patients and may be considered in non-high risk with severe hemodynamics and/or poor RV function..

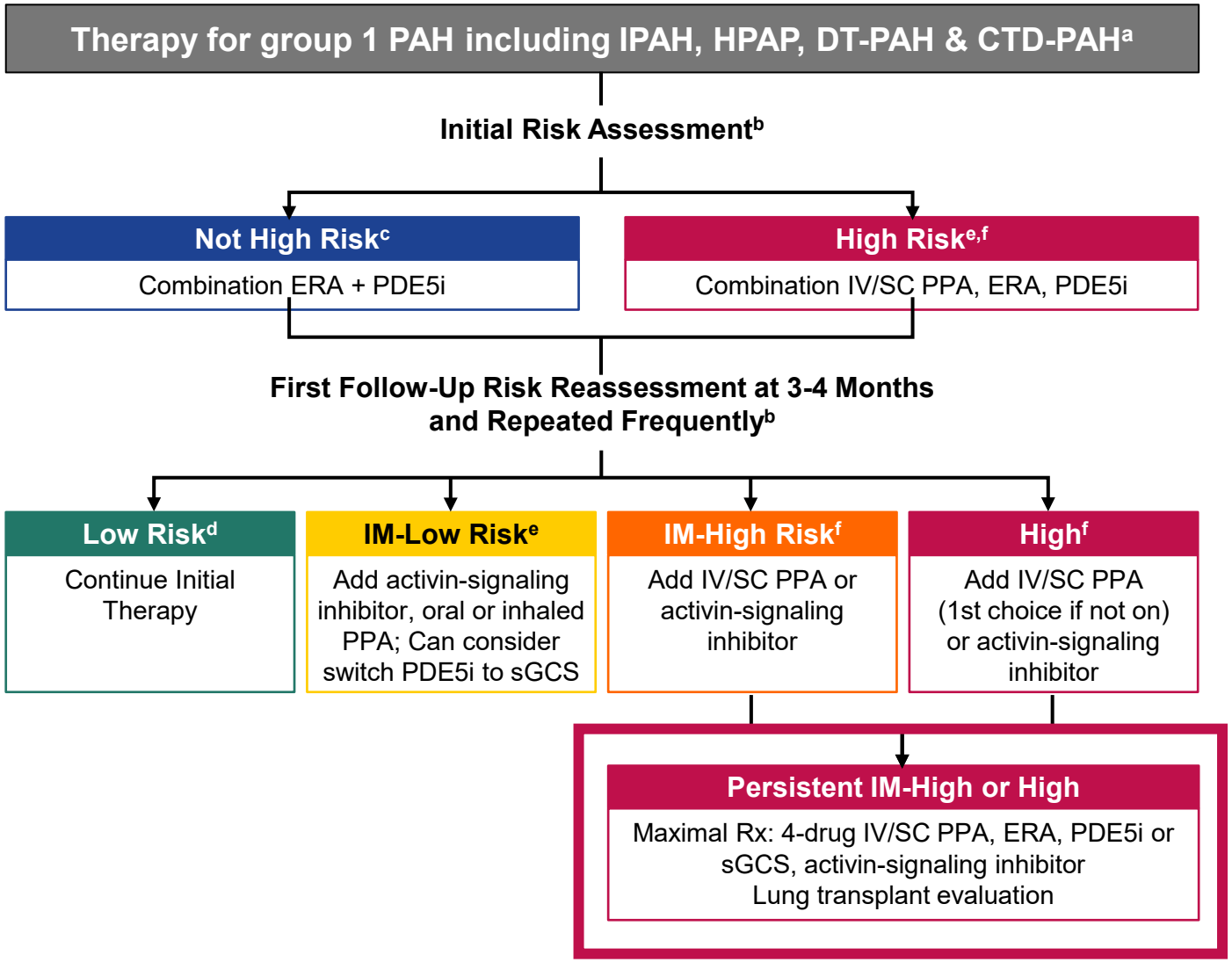
d. Most ***low risk*** at follow-up patients should continue initial therapy.

e. Clinical trials with oral and inhaled treprostinil included ***only patients on monotherapy***, while studies of selexipag and sotatercept included patients on combination therapy.

f. ***Transplant referral*** should be considered for select high-risk patients **at diagnosis**, and for IM-high and high-risk patients at ***first*** or subsequent follow-up.

Chin KM, et al. *Eur Respir J*. Published online August 29, 2024. doi:10.1183/13993003.01325-2024

7th WSPH Treatment Algorithm: First Follow-Up Risk Assessment at 3-4 Months and Repeat Frequently



Treatment Algorithm Key Points

a. Treatment algorithm is intended for patients with confirmed group 1 PAH (phenotypically clear-cut, ***mPAP ≥25 and PVR >3*** and no significant response on acute vasoreactivity testing). Treatment nuances in PAH with complex phenotypes.

b. Risk assessment should be performed at baseline, within 3-4 months, and periodically thereafter, and using FC, 6MWD, and natriuretic peptides as a part of a validated risk calculator. Hemodynamics, RV imaging, and other measures should be used to supplement risk assessment.

c. Initial triple therapy with an IV/SC PPA is recommended in high-risk patients and may be considered in non-high risk with severe hemodynamics and/or poor RV function.

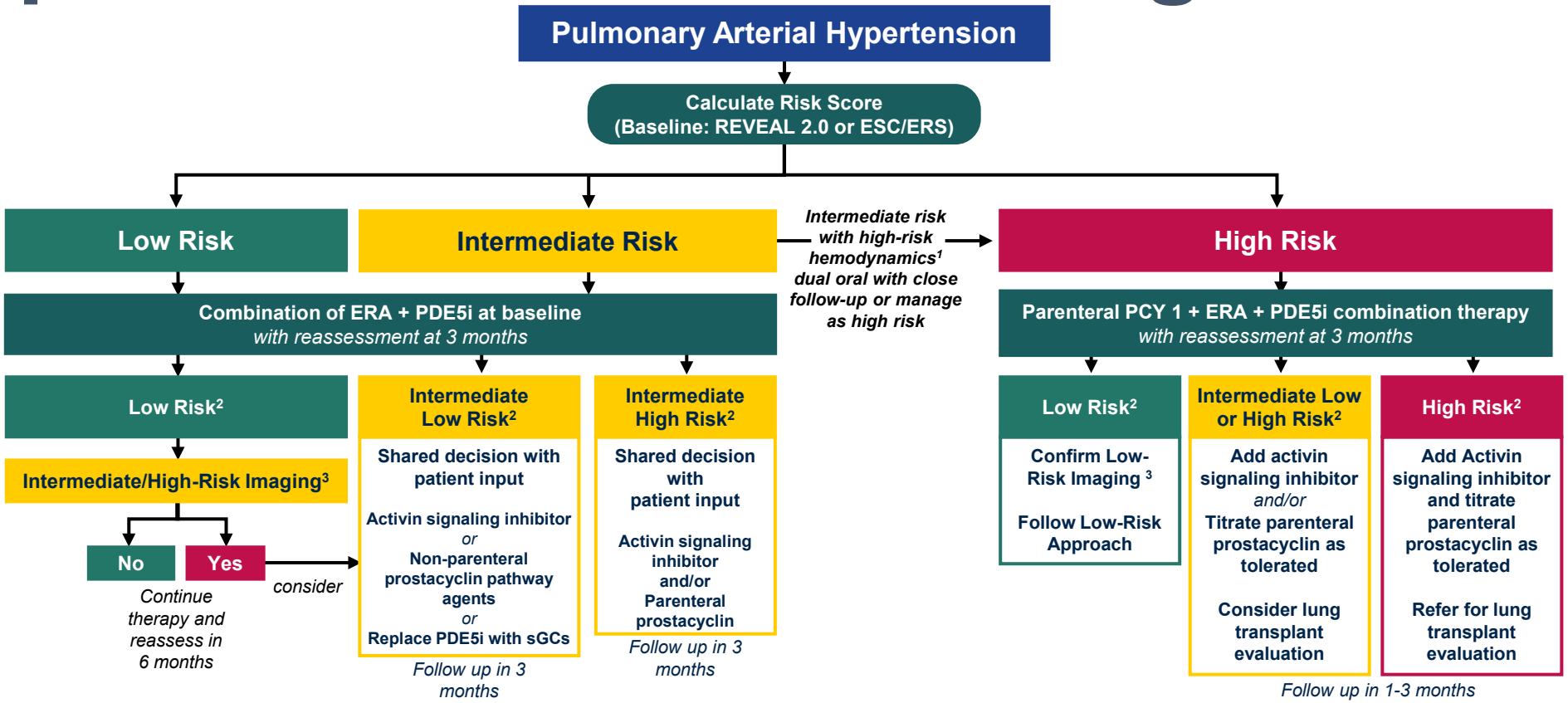
d. Most ***low risk*** at follow-up patients should continue initial therapy.

e. Clinical trials with oral and inhaled treprostinil included ***only patients on monotherapy***, while studies of selexipag and sotatercept included patients on combination therapy.

f. Transplant referral should be considered for select high-risk patients **at diagnosis**, and for IM-high and high-risk patients at ***first*** or subsequent follow-up.

Chin KM, et al. *Eur Respir J*. Published online August 29, 2024. doi:10.1183/13993003.01325-2024

Proposed PAH Treatment Algorithm



1. High-risk hemodynamics as defined in the ESC/ERS guidelines
2. Follow-up risk assessment: REVEAL 2.0 Lite or ESC/ERS 4-strata
3. Imaging risk: Suggest referring to the risk table in the 2022 ESC/ERS guidelines. In patients with intermediate- and high-risk imaging, parameters should be considered for further escalation of therapy (this is based on the expert opinion only)

* Among patients not able to tolerate therapies as indicated above, alternative approaches can be adopted as an individualize d approach.

PAH Special Circumstances: Mean PA 21-24 mmHg

Ioana Preston, MD
Associate Professor of Medicine
Tufts University School of Medicine
Boston, MA

TOTAL CME

Hemodynamic Criteria of Pulmonary Hypertension

PH	mPAP >20 mmHg	
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR >2 WU	← Groups 1, 3, 4, 5
Isolated post-capillary PH (ipcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR ⩽2 WU	← Group 2
Combined post- and pre-capillary PH (cpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU	
Exercise PH	mPAP/CO slope >3 mmHg/L/min between rest and exercise	← All Groups

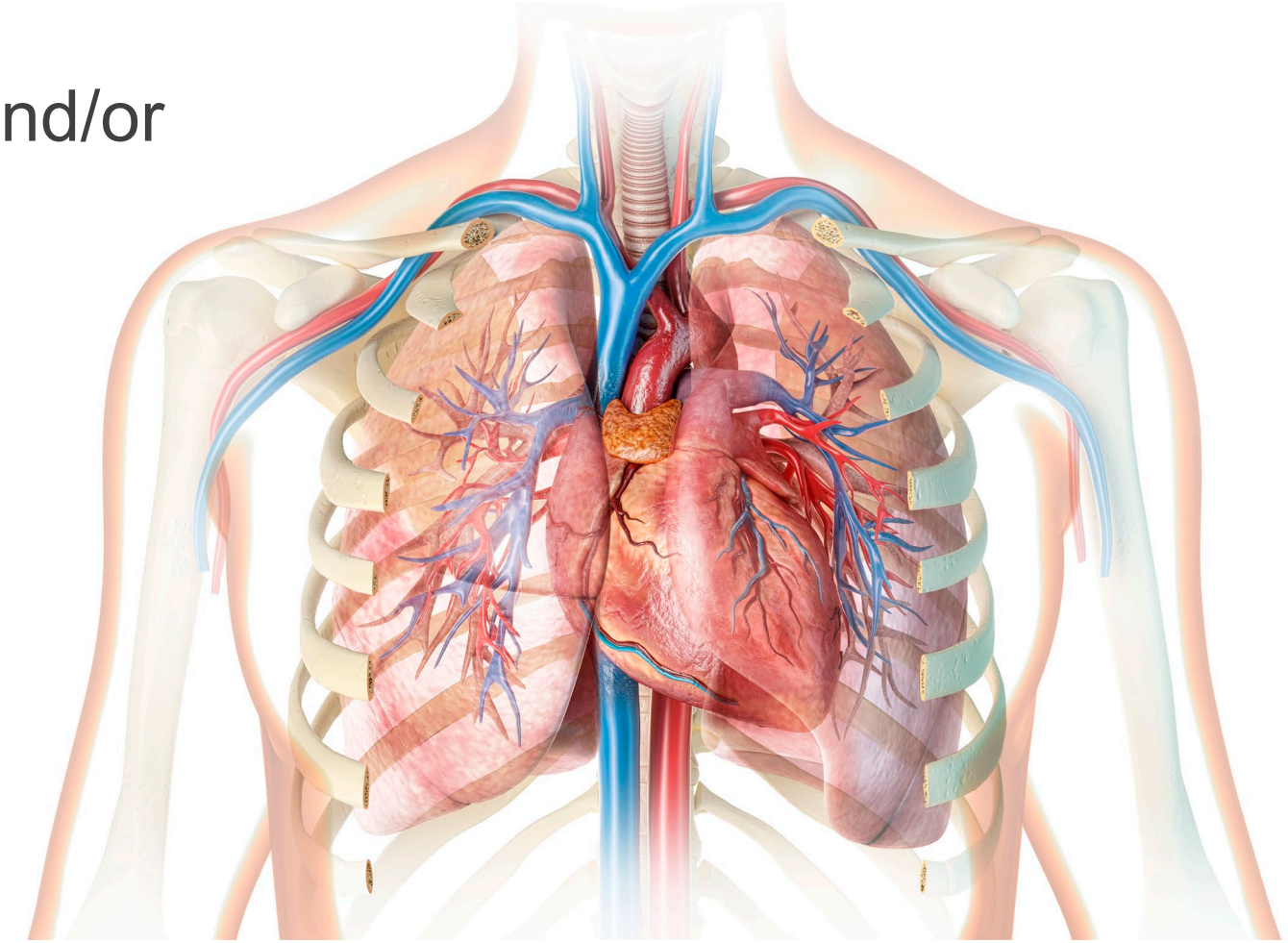
mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood Units; CO: cardiac output.

Noninvasive methods such as echocardiography or cardiac MRI lack precision or are not sufficiently validated to accurately assess pulmonary hemodynamics

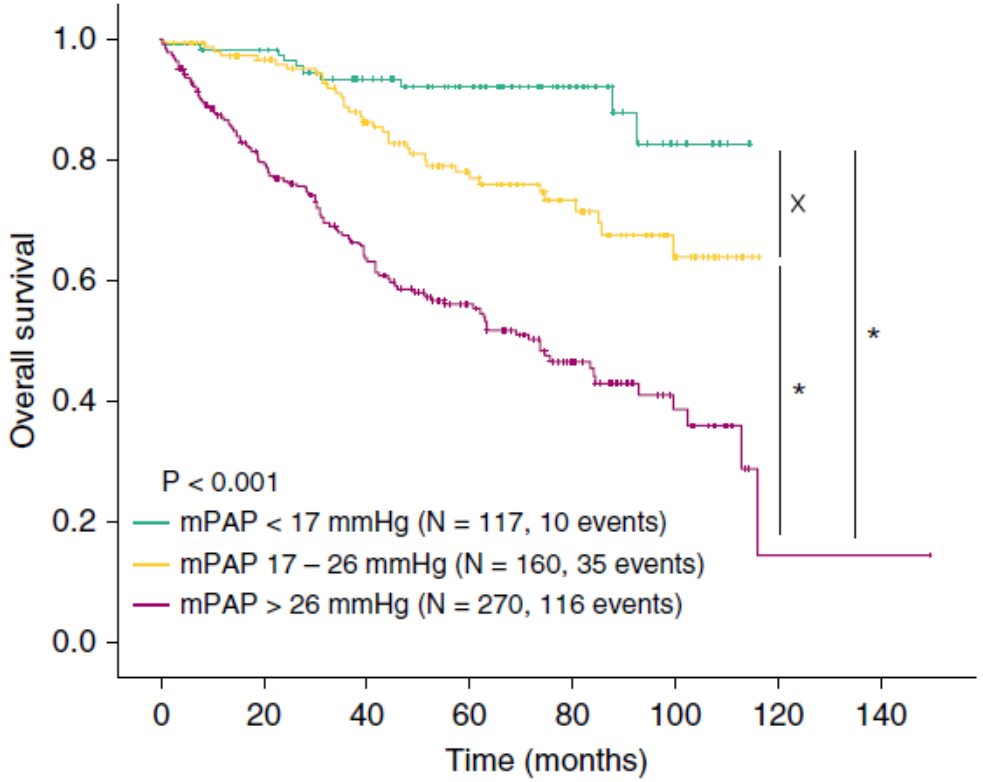
Kovacs G, et al. *Eur Respir J*. Published online August 29, 2024. doi:10.1183/13993003.01324-2024

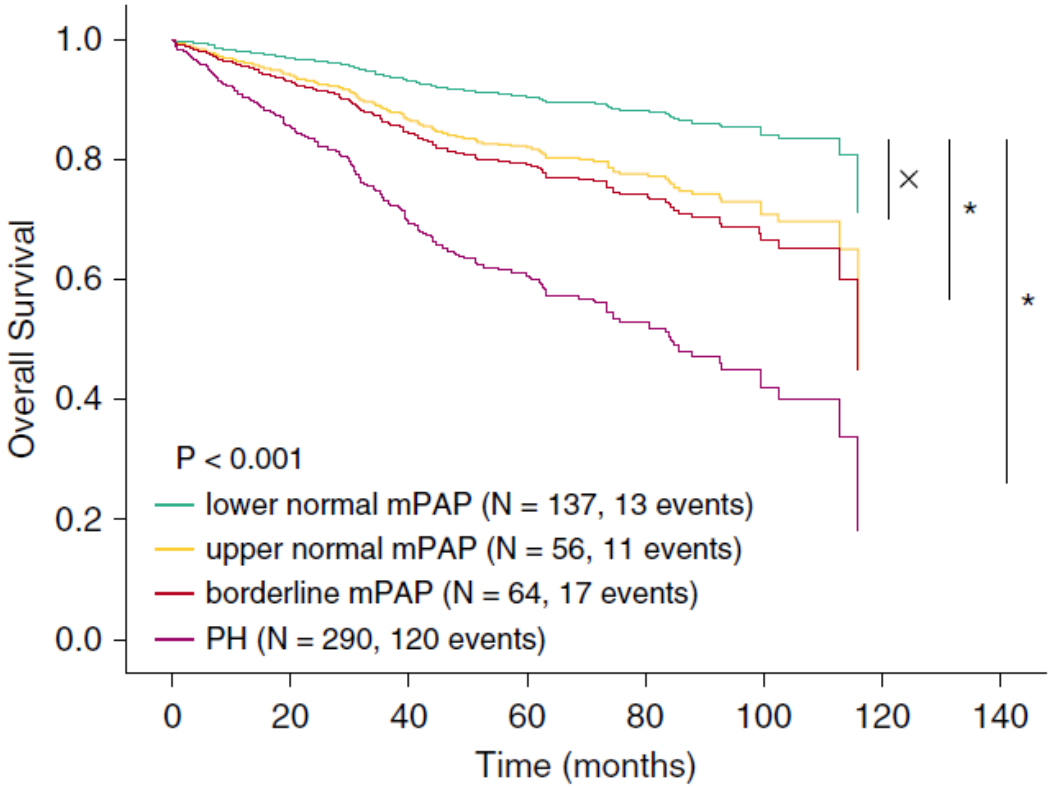
Early PH

- Mean PAP 21–24 mmHg and/or
- PVR 2–3 WU



Borderline mPAP: Catheterization for Clinical Reasons

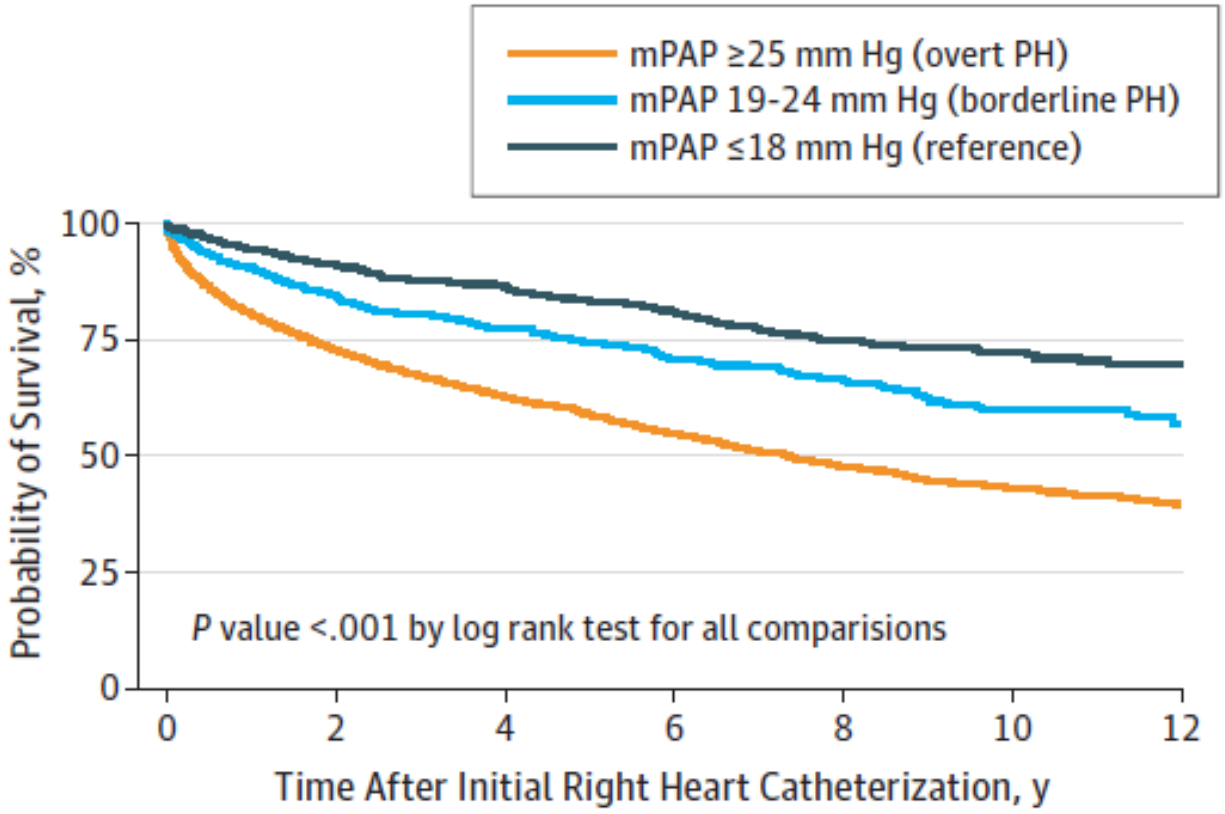


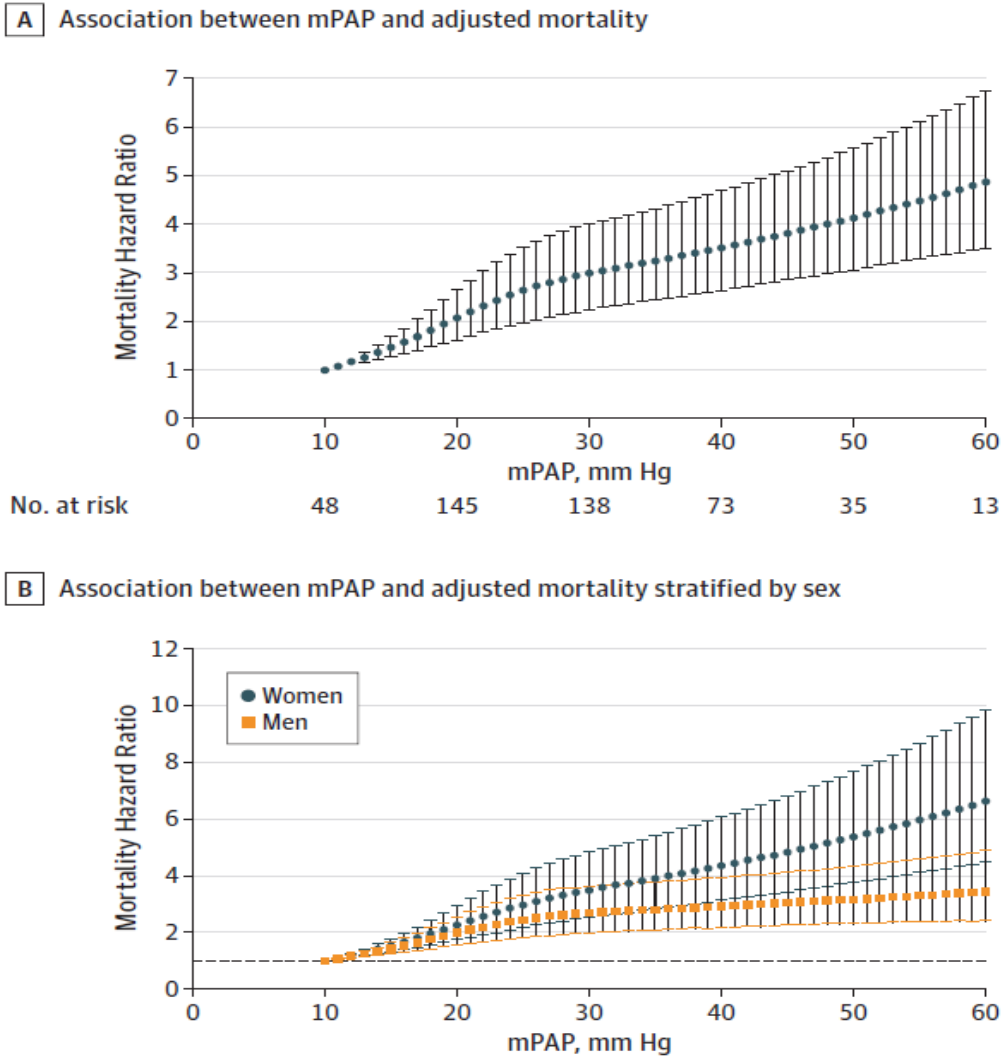


* Control mean 14 ± 3.3, LN ≤ 17.3, UN 17.4-20.6, borderline PH >20.6-25 and PH ≥ 25 mmHg

Douschan P, et al. *Am J Respir Crit Care Med*. 2018;197(4):509-516.

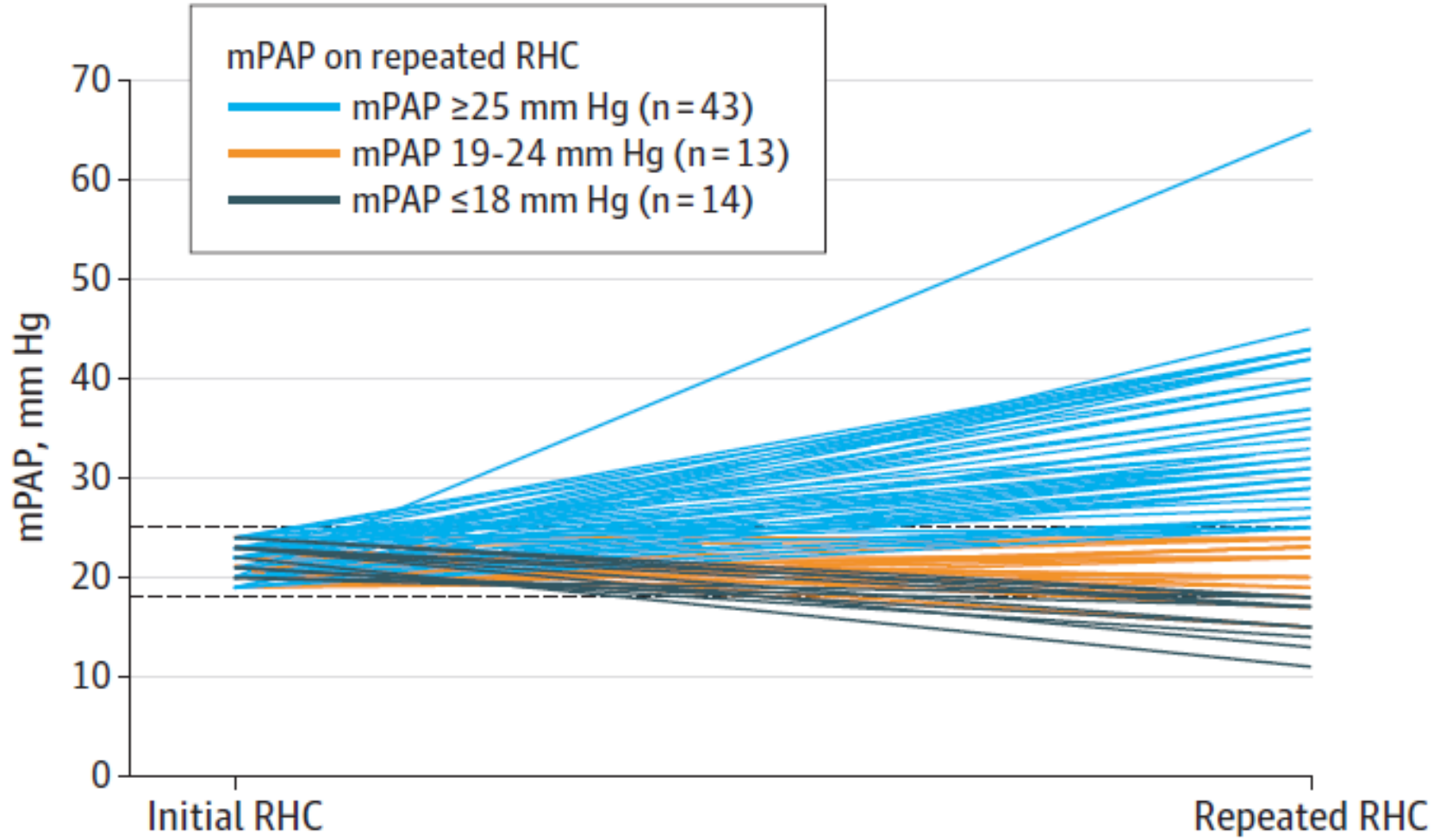
Borderline PA Pressures at Cath Associated With Survival





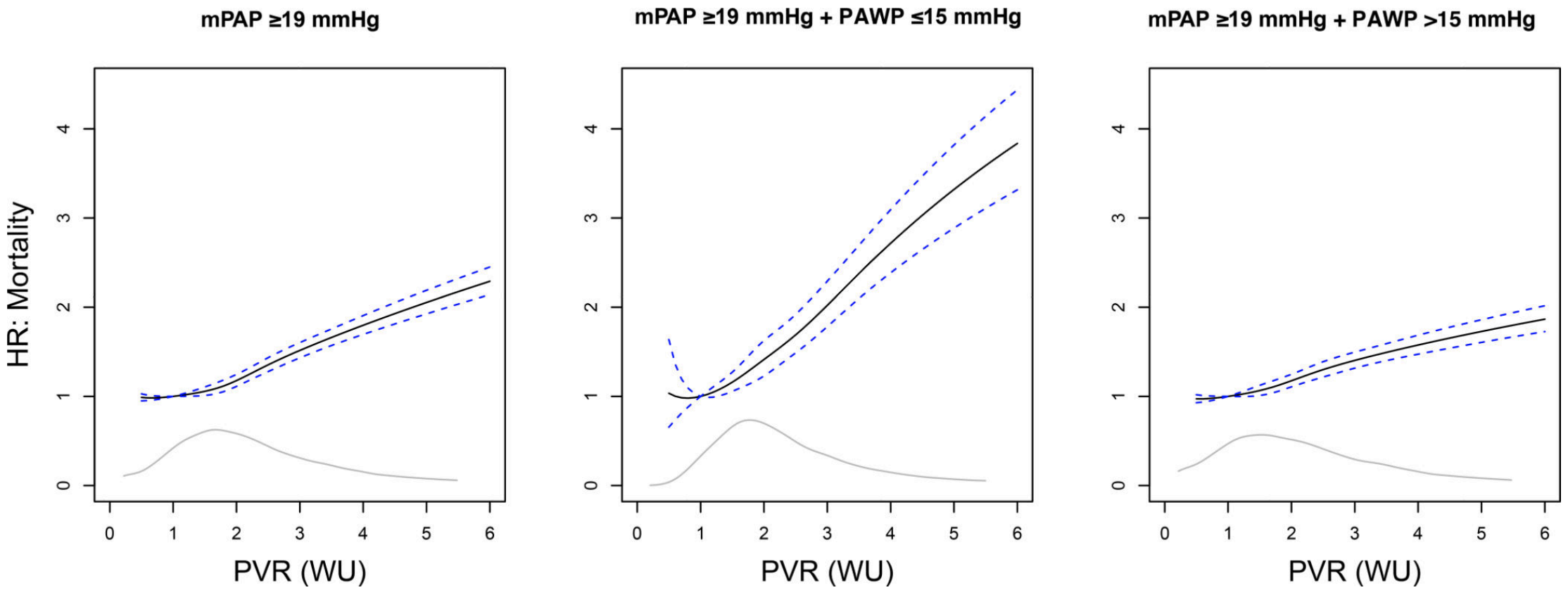
Assad TR, et al. *JAMA Cardiol*. 2017;2(12):1361-1368.

Borderline mPAP Progresses

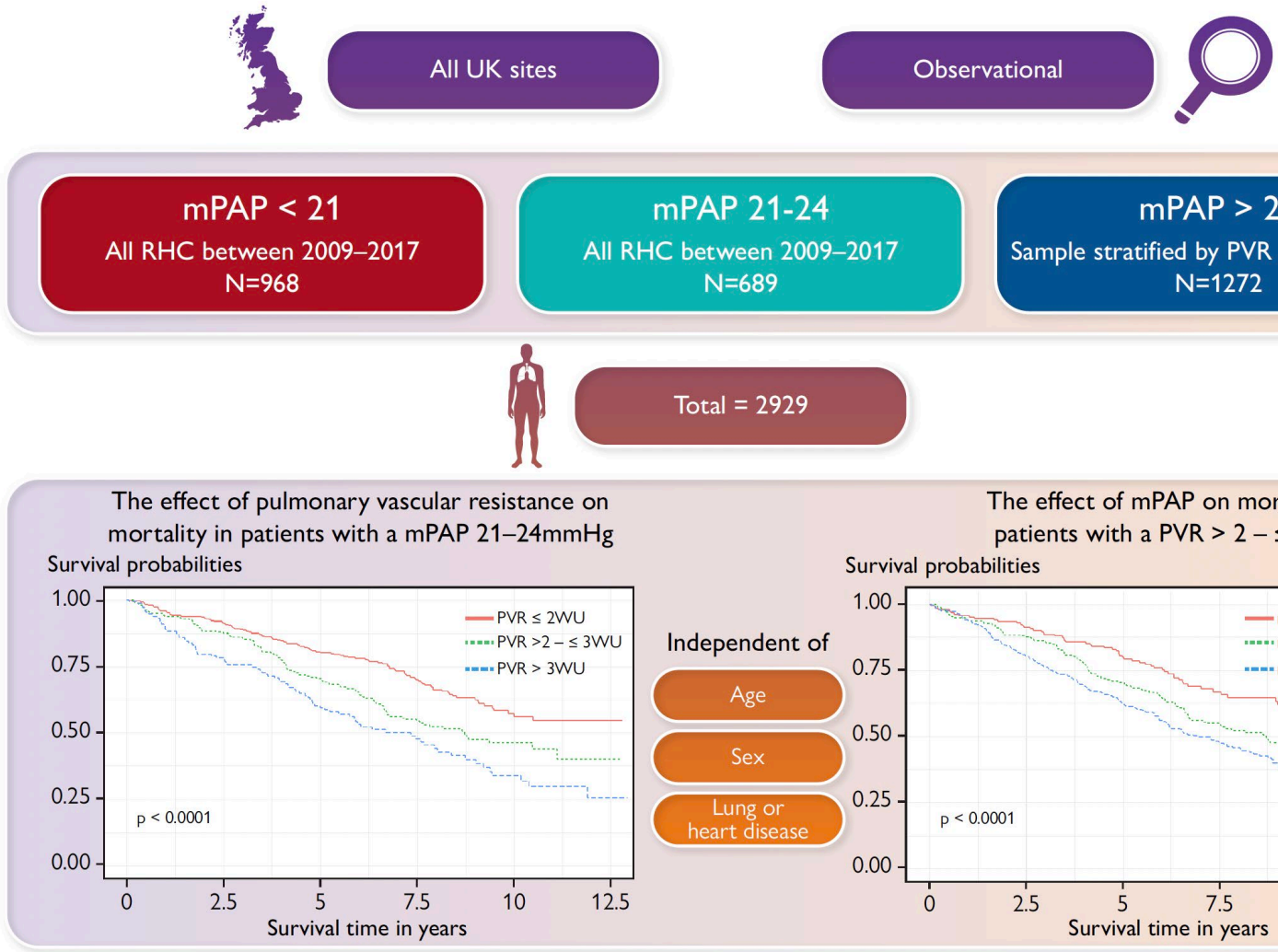


Assad TR, et al. *JAMA Cardiol*. 2017;2(12):1361-1368.

Survival Is Influenced by PVR: VA Cohort



Maron BA, et al. *Lancet Respir Med*. 2020;8(9):873-884.



Number at risk

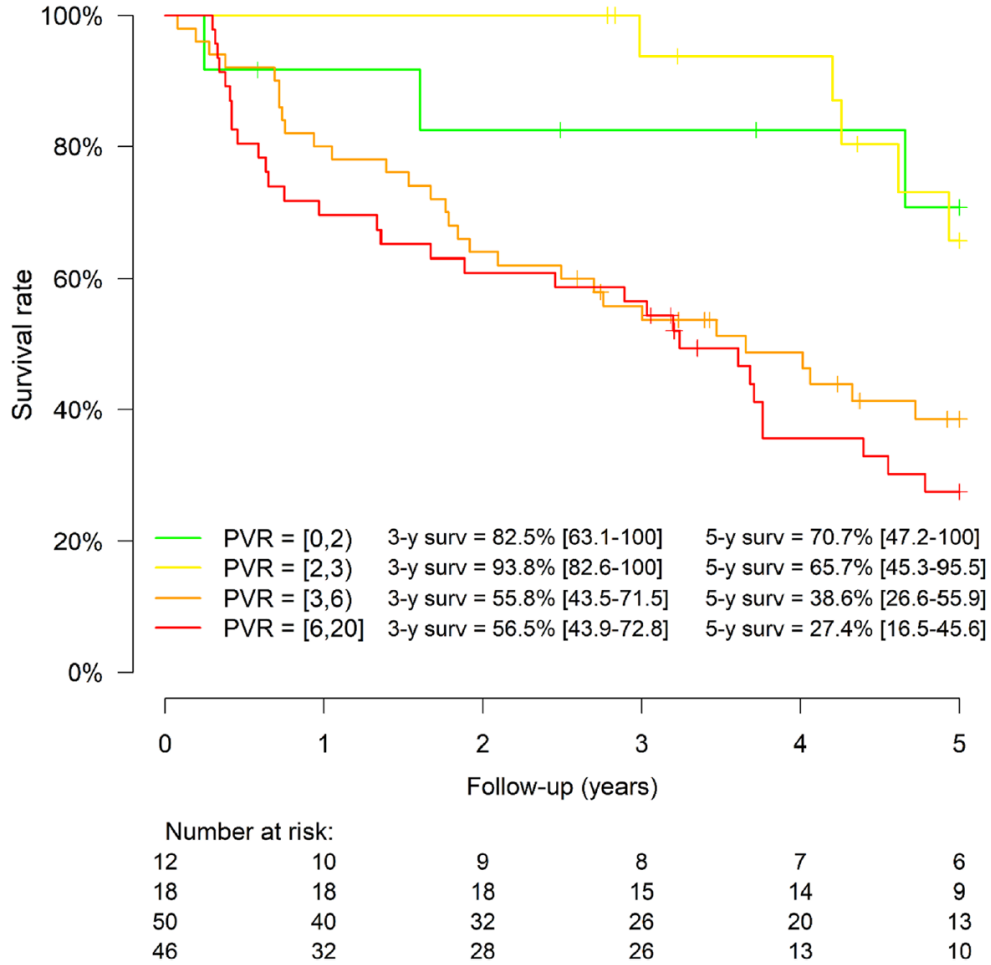
mPAP<21mmHg	968	882	750	436	183	29
mPAP 21-24mmHg	689	601	477	260	93	9
mPAP ≥25mmHg	1272	920	638	310	109	3

Number at risk

PVR≤2WU	1253	1133	970	573	230	28
PVR >2-≤3WU	735	627	475	238	86	6
PVR>3WU	941	643	420	195	69	7

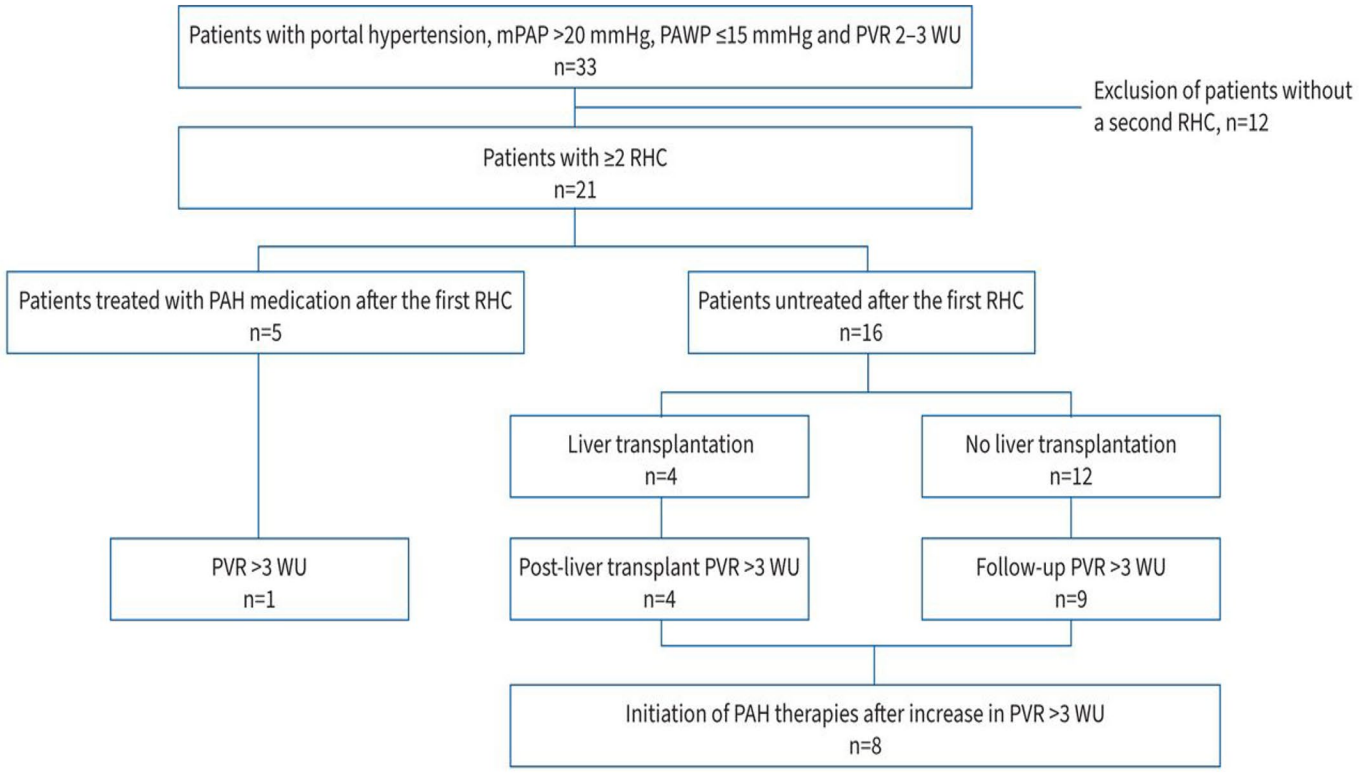
Karia N, et al. *Eur Heart J*. 2023;44(44):4678-4691.

Mild Pulmonary Hemodynamic Alterations in Patients With Systemic Sclerosis

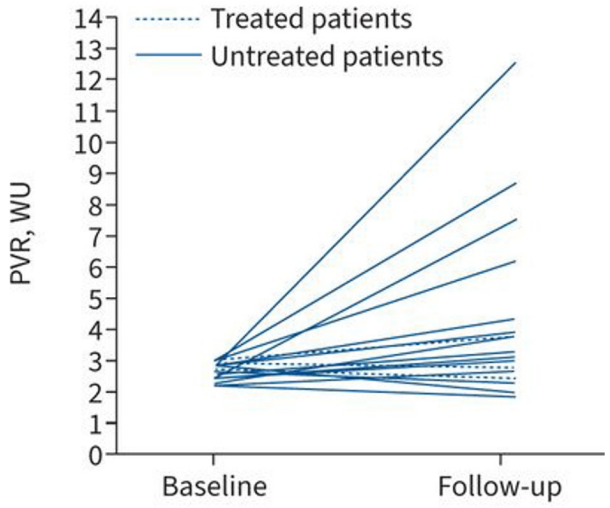


Puigrenier S, et al. *Respir Res*. 2022;23(1):284.

Early PH in Cirrhotic Patients: Outcomes and Treatment



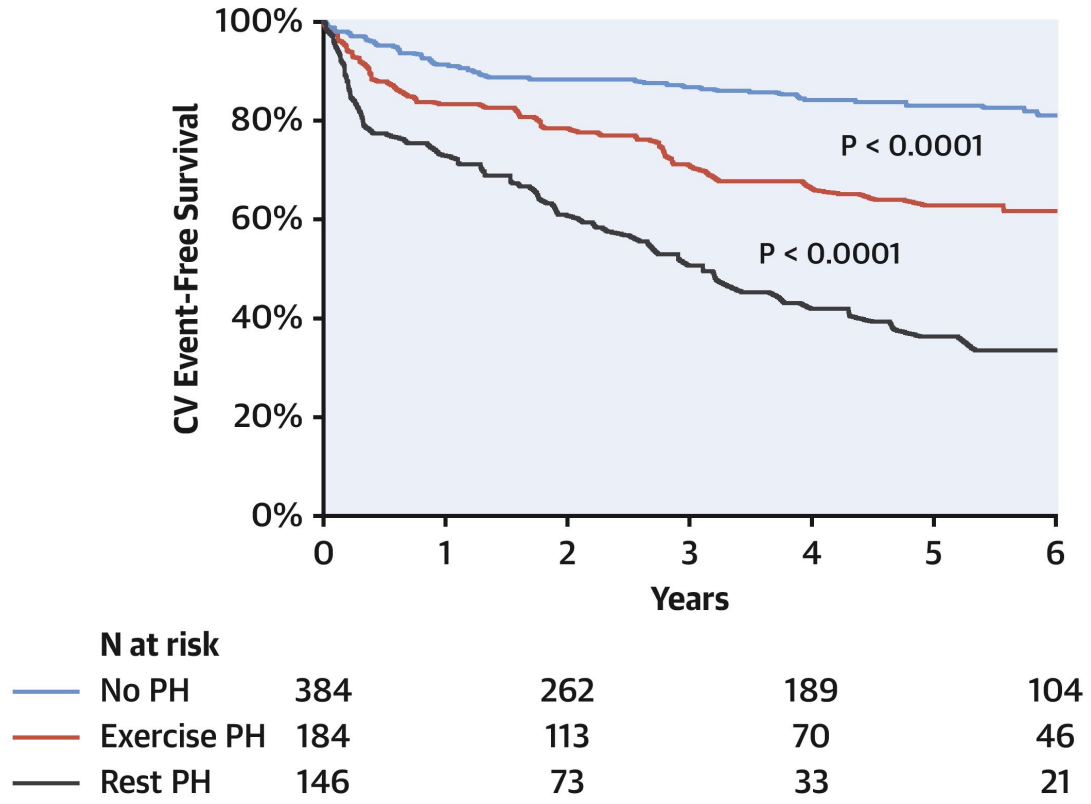
Untreated patients after first RHC (n=16)	Baseline visit	Follow-up visit	p-value
NYHA functional class III–IV, n (%)	6 (37)	8 (50)	0.47
6MWD, m, median (IQR)	451 (384–560)	440 (384–560)	0.08
Haemodynamics, mean±SD			
mPAP, mmHg	31±4	35±11	0.09
PAWP, mmHg	9±3	10±5	0.6
Right atrial pressure, mmHg	6±3	8±4	0.01
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	4.4±0.9	3.3±0.9	0.001
PVR, WU	2.7±0.3	4.6±2.9	0.001



Certain MC, et al. *Eur Respir J*. 2022;60(2):2200107.

Exercise PH Is Associated With Increased Cardiovascular Event-Free Survival

- Individuals with abnormal PAP/CO slope had a 2-fold increased hazard of future CV or death event (multivariable-adjusted hazard ratio: 2.03; 95% confidence interval: 1.48 to 2.78; $P < 0.001$)
- The association of abnormal PAP/CO slope with outcomes remained significant after excluding rest PH (n = 146, hazard ratio: 1.75; 95% confidence interval: 1.21 to 2.54; $P = 0.003$)
- Both pre- and post-capillary contributions to exercise PH independently predicted adverse events ($P < 0.001$ for both)



Ho JE, et al. *J Am Coll Cardiol*. 2020;75(1):17-26.

What Don’t We Know

- Both early and exercise PH need further refinement and study
- All currently available drugs for the treatment of PAH, chronic thromboembolic PH (CTEPH), or PH associated with lung diseases were approved based on clinical trials using previous hemodynamic definitions of PAH and pre-capillary PH, characterized by mPAP ≥ 25 mmHg, PAWP ≤15 mmHg and PVR >3 WU

Summary

- Early PH and exercise PH are entities associated with worse outcomes compared with normal population
- In many subpopulations, early PH progresses
- Presently, the treatment of patients with early PH with specific therapies is not recommended due to the absence of sufficient data from clinical trials