THURSDAY MARCH 20, 2025

PULMONARY ARTERIAL HYPERTENSION

SONJA BARTOLOME, MD, MPH

UT SOUTHWESTERN

KEYNOTE*: INTERPRETING THE 2024 WORLD SYMPOSIUM ON PULMONARY HYPERTENSION FROM THE US PERSPECTIVE*

Thursday, March 20, 2025 11:00 am -11:45 am

Dr. Sonja Bartolome serves as the Director of the Pulmonary Vascular Disease Program at UT Southwestern in Dallas, TX. She completed her medical training at the University of Kansas, where she later joined the faculty with a focus on the management of patients with pulmonary arterial hypertension. In 2010, she transitioned to UT Southwestern, where she is now a Professor in the Division of Pulmonary and Critical Care Medicine. Dr. Bartolome's clinical expertise is dedicated to the treatment of patients with pulmonary vascular disease. She has served as a principal investigator in numerous clinical trials and has contributed extensively to the field through textbook chapters, scientific publications, and international lectures.

MARC SIMON, MD

UCSF

ECHOCARDIOGRAPHY AND RIGHT HEART CATHETERIZATION FOR THE PULMONOLOGIST

Thursday, March 20, 2025 11:45 am - 12:10 pm

Dr. Marc Simon is a Professor of Medicine, Director of Pulmonary Vascular Disease and the UCSF Pulmonary Hypertension Center of Comprehensive Care, and Program Director of the UCSF Advanced Heart Failure & Transplant Cardiology Fellowship. Dr. Simon has a Bachelor's of Science in Engineering from the University of Pennsylvania, MD from the University of Maryland, and a MS in Bioengineering from the University of Pittsburgh. He trained in Internal Medicine at the University of Colorado, then in cardiology as well as advanced heart failure and cardiac transplant at the University of Pittsburgh. He was a faculty member at the University of Pittsburgh for 14 years prior to moving to UCSF in 2021. Dr. Simon's research has focused on several central themes: 1) translational studies of the right ventricular (RV) adaptation and eventual failure in pulmonary hypertension (PH); 2) extension of studies of the RV to heart failure, cardiomyopathies, and mechanical support; 3) early phase clinical trial design and execution in pulmonary hypertension and heart failure (bench to bedside; first in disease trials). Dr. Simon has received research support from NIH, NSF, AHA, and several local foundations. He has mentored over 40 trainees at all levels of training. Dr. Simon is a guest editor and former senior associate editor for the *Journal of the American Heart Association*. He is on the editorial board and has been a guest editor of *Advances in Pulmonary Hypertension*. Dr. Simon has been an ad hoc member of multiple grant review panels for the NIH and American Heart Association. He currently serves as the chair of the Pulmonary Vascular Disease Interdisciplinary Network of the International Society of Heart & Lung Transplantation.

View a list of Dr. Simon's publications here:
http://www.ncbi.nlm.nih.gov/sites/myncbi/marc.simon.1/bibliography/41155514/public/?sort=date&direction=ascending

Karim El-Kersh, MD

University of Arizona

UNDERSTANDING PAH-SPECIFIC THERAPY AND THE TREATMENT ALGORITHM IN GROUP 1 PAH

Thursday, March 20, 2025 12:10 pm - 12:35 pm

Dr. El-Kersh is a Professor of Medicine in the Division of Pulmonary, Critical Care, and Sleep Medicine at the University of Arizona College of Medicine- Phoenix where he serves as the Pulmonary Section Head and the Director of the Pulmonary Hypertension Program at Banner University Medical Center and Banner lung Institute. Also, Dr. El-Kersh is the Program Director of the Sleep Medicine Fellowship at the University of Arizona College of Medicine, Phoenix. Previously, he served as a faculty member in the University of Louisville, and in the University of Nebraska Medical Center where he helped lead the pulmonary hypertension programs in these academic centers. Dr. El-Kersh's pulmonary hypertension research interest includes risk stratification, healthcare utilization, palliative care and social determinants of health in PH.

JEFFREY S. SAGER, MD
USC
DEBATE: THE HEMODYNAMIC DEFINITION OF PAH SHOULD BE 2 WOOD UNITS

Thursday, March 20, 2025 12:35 pm - 12:50 pm

Dr. Jeffrey S. Sager is a nationally recognized expert in the management and treatment of pulmonary hypertension and advanced lung disease. He received his medical degree from the University of the Witwatersrand in Johannesburg, South Africa. He completed his medical internship, residency, and chief residency at Albert Einstein Medical Center. He then pursued a fellowship in Pulmonary and Critical Care Medicine at the University of Pennsylvania, where he was awarded the Will Rogers Institute Research Fellowship for excellence in research. Additionally, he earned a master's degree in clinical Epidemiology and Biostatistics from the University of Pennsylvania.

Dr. Sager remained at the University of Pennsylvania Medical Center as Associate Medical Director of the Lung Transplantation Program before relocating to the West Coast. He now lives and practices in Santa Barbara, CA, where he runs the local Pulmonary Hypertension Clinic.

He has received numerous accolades, including the American College of Chest Physicians Young Leadership Award. Dr. Sager has contributed to several landmark clinical trials in pulmonary hypertension and has authored multiple publications in the field.

RICHARD CHANNICK, MD

David Geffen School of Medicine at UCLA

DEBATE: THE HEMODYNAMIC DEFINITION OF PAH SHOULD BE 3 WOOD UNITS

Thursday, March 20, 2025 12:50 pm – 1:05 pm

Richard Channick, MD, is Professor of Medicine and Saul Brandman Endowed Chair in Pulmonary Arterial Hypertension at David Geffen School of Medicine at UCLA. He serves as Co-Director of the Pulmonary Vascular Disease Program and Director of the Acute and Chronic Thromboembolic Disease at UCLA Medical Center. Dr. Channick received his medical degree from Temple University Medical School, where he was elected to the Alpha Omega Alpha Medical Honor Society. He did his residency and was Chief Resident at the University of Massachusetts Medical Center. He did a pulmonary and critical care fellowship at the University of California, San Diego Medical Center. Dr. Channick was at UCSD for 20 years helping build the pulmonary vascular program there. From 2009-2018 he was at Massachusetts General Hospital, Harvard Medical School where he built a large Pulmonary Vascular Program. He has been at UCLA since September 2018, directing the UCLA Acute and Chronic Thromboembolic Disease Program. Dr. Channick has published over 200 original articles, chapters and reviews focused on all aspects of pulmonary hypertension and pulmonary embolism. He has served on many national and international leadership committees including the American Thoracic Society Pulmonary Circulation Program Committee and the American College of Chest Physicians Pulmonary Vascular Disease Network steering committee, past Chair of the Pulmonary Hypertension Association (PHA) Scientific Leadership Committee and co-founder and past President of the Pulmonary Embolism Response Team (PERT) Consortium. Dr. Channick has served on the steering committees for numerous pivotal clinical trials in pulmonary vascular disease and lectures nationally and internationally.

ASSOCIATED PULMONARY HYPERTENSION

POOJA PRASAD, MD

UCSF

NOVEL DEVELOPMENTS IN GROUP 2 PH

Thursday, March 20, 2025 2:15 pm – 2:40 pm

Dr. Pooja Prasad is a pulmonary hypertension, advanced heart failure and transplant cardiologist. She earned her medical degree from the University of Rochester School of Medicine. She completed a residency in internal medicine at the University of California, Davis, followed by a fellowship in cardiology at Oregon Health and Science University and a fellowship in advanced heart failure and transplant cardiology at UCSF. Dr. Prasad serves as an Assistant Clinical Professor at UCSF.

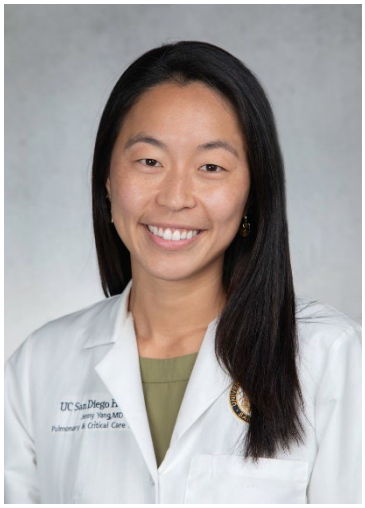
NAMITA SOOD, MD

UC DAVIS

NOVEL DEVELOPMENTS IN GROUP 3 PH

Thursday, March 20, 2025 2:40 pm – 3:05 pm

Dr. Sood is the Director of Advanced Dung disease at University of California- Davis. After completing her fellowship in Pulmonary and critical care medicine from university of North Carolina in 1999; she has focused on pulmonary vascular disease including pulmonary hypertension, pulmonary embolism, lung disease related to rheumatological disease and sickle cell anemia. She has participated in multicenter trials for development of therapies for PH. She has participated in the development of guidelines for the treatment of Pulmonary hypertension, venothromboembolic disease and pulmonary hypertension in sickle cell anemia.



JENNY YANG, MD

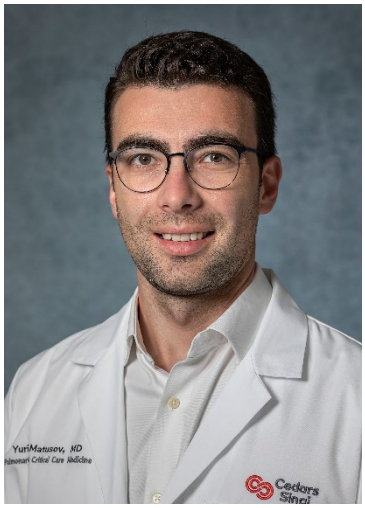
UCSD

NOVEL DEVELOPMENTS IN GROUP 4 PH

Thursday, March 20, 2025 3:05 pm – 3:30 pm

Jenny Yang, MD is a board-certified pulmonologist and critical care physician, who specializes in pulmonary vascular disease. Her clinical and research interests are in pulmonary vascular medicine, including pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. She has developed a special focus in balloon pulmonary angioplasty for chronic thromboembolic pulmonary disease. She also cares for critically ill patients in the intensive care unit. Dr. Yang completed her fellowship and residency at UC San Diego School of Medicine, where she also served as chief fellow. She earned her medical degree at Jefferson Medical College of Thomas Jefferson University.
Dr. Yang is board certified in internal medicine, pulmonary disease and critical care.

CARE DELIVERY FOR UNIQUE POPULATIONS WITH PULMONARY HYPERTENSION



YURI MATUSOV, MD
CEDARS SINAI MEDICAL CENTER

ICU MANAGEMENT OF PATIENTS WITH PAH

Thursday, March 20, 2025 4:20 pm – 4:45 pm

Yuri Matusov, MD, FACP, is an assistant professor of medicine at Cedars-Sinai Medical Center. He completed residency in internal medicine at Santa Barbara Cottage Hospital and fellowship in pulmonary and critical care medicine at Cedars-Sinai, where he served as chief fellow. Dr. Matusov is co-director of the Cedars-Sinai Pulmonary Hypertension Program and chairs the PCCM fellowship research committee. He is actively involved in research and education in pulmonary vascular disease, ARDS, and shock resuscitation.

NICHOLAS KOLAITIS, MD,MAS

UCSF

ECMO AND LUNG TRANSPLANTATION FOR PAH

Thursday, March 20, 2025 4:45 pm – 5:10 pm

Dr. Nicholas Andreas Kolaitis is a specialist in pulmonary and critical care medicine, with a focus on lung transplantation and pulmonary hypertension.

Dr. Kolaitis earned his medical degree at the University of California, San Diego School of Medicine. He completed a residency in internal medicine at UCLA Health, followed by fellowships in lung transplantation and pulmonary and critical care medicine at UCSF. His research focuses on ways to improve quality of life for patients with advanced lung disease. He holds a master's degree in clinical research from UCSF. He is currently serving as the vice chair of the Pulmonary Hypertension Association Registry, and as an editorial board member for the CHEST Journal and the Journal of Heart and Lung Transplantation Open.

Kolaitis is also a member of the executive board of the California Thoracic Society and as one of two representatives to the American Thoracic Society Council of Chapter Representatives. He is involved in health policy reform, currently serving as the vice chair for the American Thoracic Society Health Policy Committee and as a member of the International Society for Heart and Lung Transplantation Advocacy Committee. He also serves as a member of the Pulmonary Vascular Research Institute Lung Transplantation Task Force, the International Society for Heart and Lung Transplantation Standards and Guidelines Committee, and the Pulmonary Hypertension Association Patient and Caregiver Education Committee.

Kolaitis' clinical work has been recognized with various awards, including the Jeffrey Golden Outstanding Clinical Fellow Award, the Michael Stulbarg Outstanding Teaching Award, and the California Thoracic Society Outstanding Clinician Award.

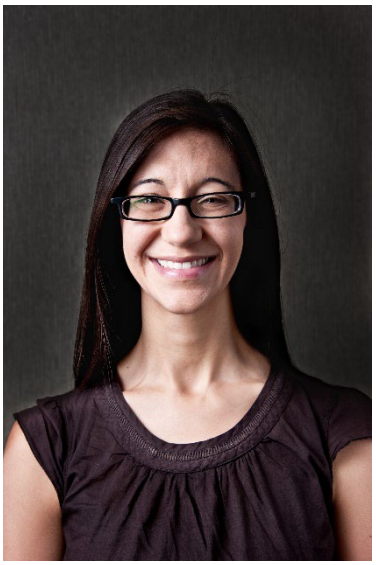
RACHEL HOPPER, MD

STANFORD

UNDERSTANDING PEDIATRIC PH

Thursday, March 20, 2025 5:10 pm – 5:35 pm

Dr. Rachel Hopper earned her medical degree from the University of Michigan Medical school then completed residency in Pediatrics at Boston Children's Hospital and fellowship in Pediatric Cardiology at Stanford with additional fellowship training in pulmonary hypertension. She is currently a Clinical Professor of Pediatrics in the division of Pediatric Cardiology and serves as Associate Director of the Pediatric Pulmonary Vascular Disease Program at Stanford. She is also an active member of the Pulmonary Hypertension Association and the Pediatric PH Network (PPHNet).



DAFNE MORETTA, MD

LOMA LINDA

UNDERSTANDING DISPARITIES IN PULMONARY VASCULAR DISEASE

Thursday, March 20, 2025 5:35 pm – 6:00 pm

Dr. Dafne Moretta earned her medical degree and completed her pulmonary and critical care training at Loma Linda University. She currently serves as the Medical Director of the Pulmonary Hypertension Center at Loma Linda, where she leads efforts to provide comprehensive care for patients with pulmonary vascular disease. In addition to her clinical work, Dr. Moretta is deeply involved in medical education, serving in various leadership roles and championing transformative care for her patients.

Interpreting the 2024 World Symposium on Pulmonary Hypertension from the US Perspective

Sonja Bartolome, MD, MBA
Director, Pulmonary Vascular Disease Program
Professor of Medicine, Pulmonary and Critical Care
University of Texas Southwestern
Dallas, TX

Disclosures

- I have the following relationships with ACCME defined ineligible companies:
- Consultant: Merck, United Therapeutics, Gossamer Bio, Janssen
- Research: United Therapeutics
- I **WILL NOT** discuss off-label use and/or investigational use of any drugs or devices.

A Historical Perspective

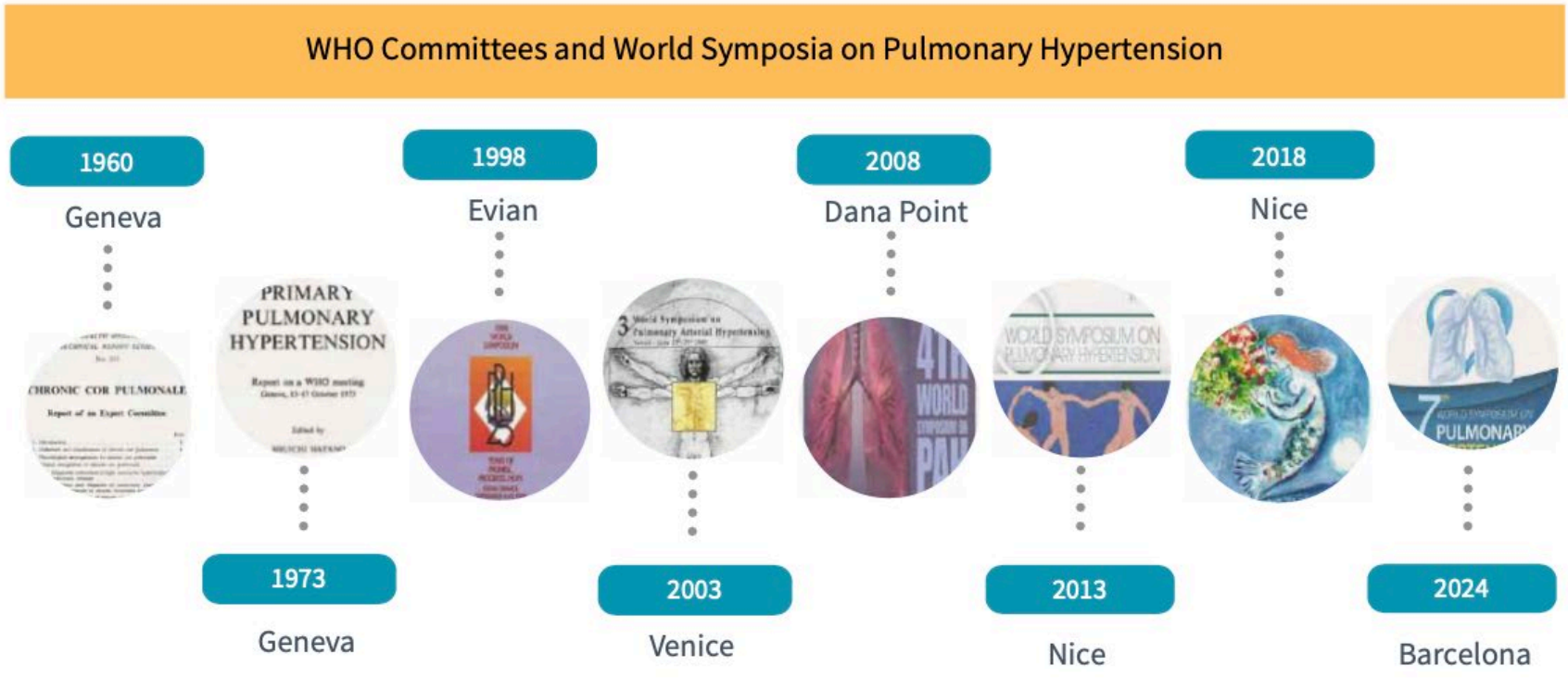
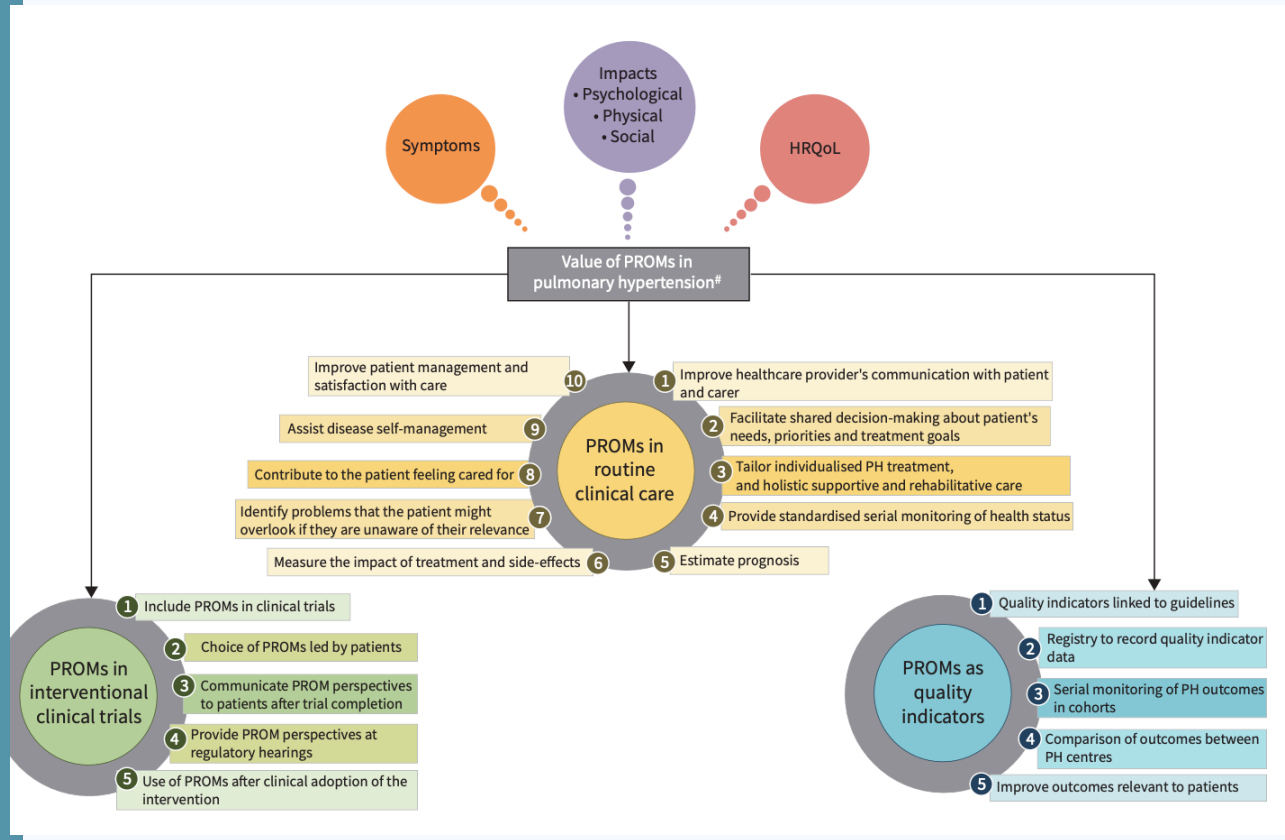


FIGURE 1 Historical perspective of the World Health Organization (WHO) Committees and World Symposia on Pulmonary Hypertension (1960–2024).

• Humbert M, Galiè N, Rubin LJ, et al. The Seventh World Symposium on Pulmonary Hypertension: our journey to Barcelona. Eur Respir J 2024;

7th World Symposium on Pulmonary Hypertension – Patient Perspective



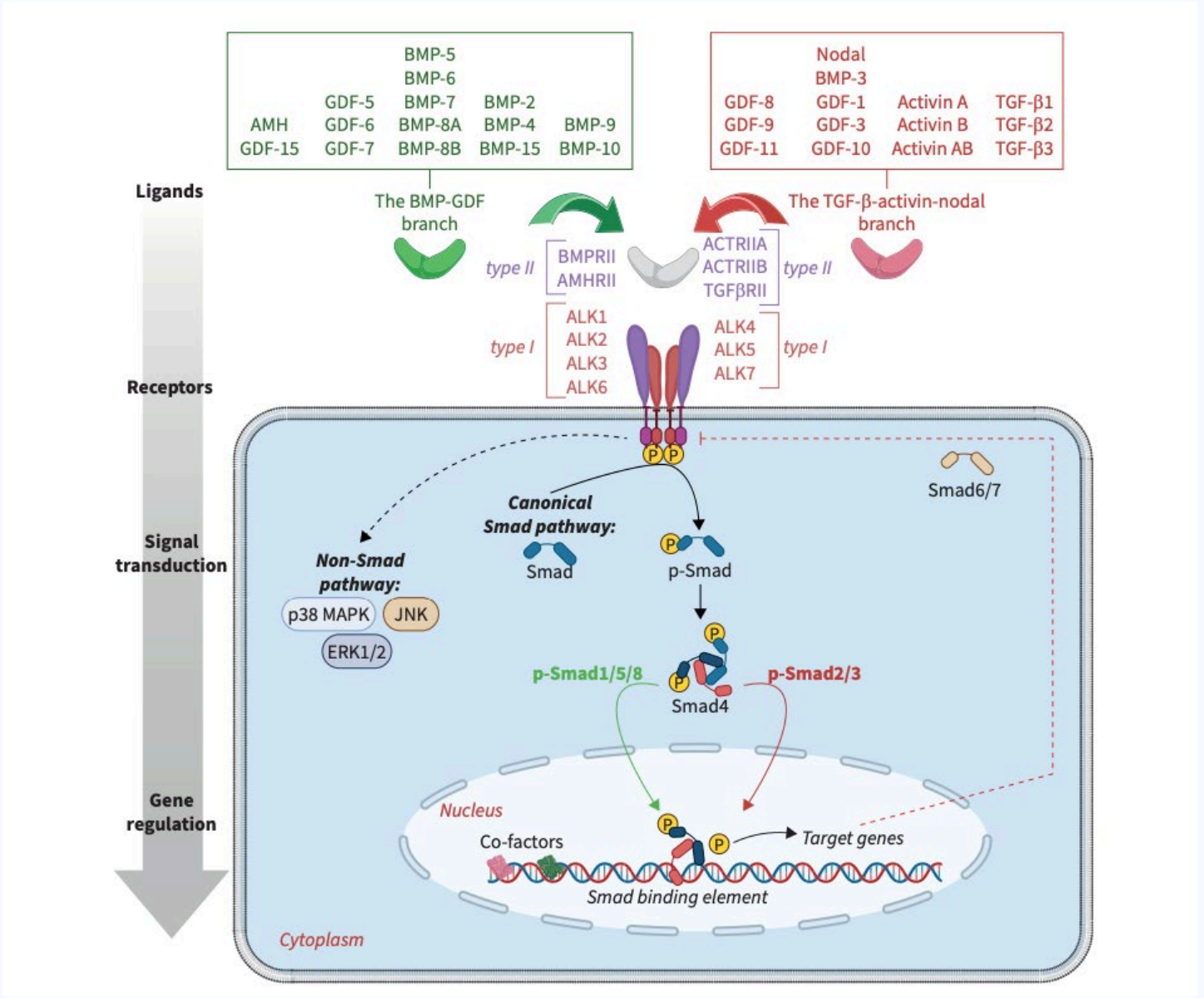
Patient Reported Outcome Measures (PROMs)

- **CAMPHOR** – symptoms, activity, HRQoL
- **EmPHasis-10** – HRQOL
- **Living with PAH** – Physical, emotional
- **PAH- SYMPACT** -- Cardiopulmonary symptoms Cardiovascular symptoms Physical impacts Cognitive/ emotional impacts
- **PAHSIS** – Symptoms
- **EQ-SD** – Mobility, Self-care, Pain, Anxiety/depression, Activity
- **SF-36** -- Physical functioning, Physical limitations, Pain, General health, Energy/vitality, Social functioning, Emotional limitations, Mental health

• Ford HJ, Brunetti C, Ferrari P, et al. Exploring the patient perspective in pulmonary hypertension. Eur Respir J 2024;

7th World Symposium on Pulmonary Hypertension – Pathology and Pathobiology

BMP and TGF-β signaling



Guignabert C, Aman J, Bonnet S, et al. Pathology and pathobiology of pulmonary hypertension: current insights and future directions. Eur Respir J 2024

California Thoracic Society
ATS Chapter Serving California and Arizona

Hemodynamic Definition of Pulmonary Hypertension

mPAP > 20 mmHg

mPAP > 20 mmHg
PAWP ≤ 15 mmHg
PVR > 2 WU

mPAP > 20 mmHg
PAWP > 15 mmHg
PVR ≤ 2 WU

mPAP > 20 mmHg
PAWP > 15 mmHg
PVR > 2 WU

mPAP/CO slope > 3 mmHg/L/min
between rest and exercise

Mild Pulmonary Hypertension and Mortality

Mild PH confers increased mortality in many well-phenotyped causes of PH (scleroderma, sickle cell, LHD)

N=>40,000 VA patients many with prevalent LHD

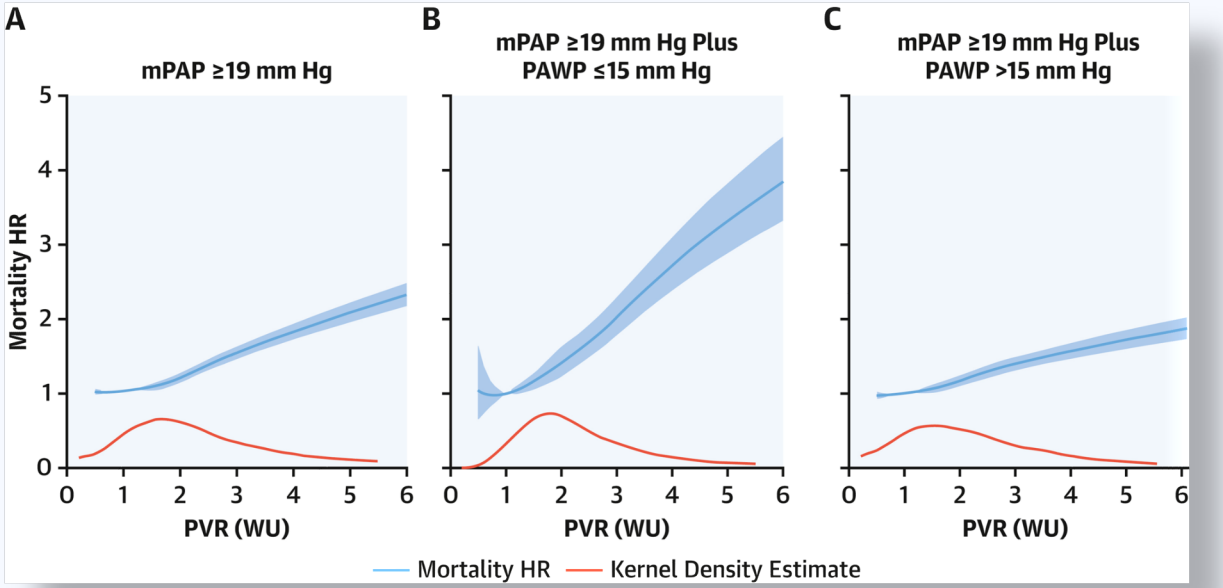
PVR >2.1 captured ~ 55% more at risk patients than a PVR of 3.0

HR mortality 1.47

HR heart failure hospitalization 1.17

Results validated in a study at Vanderbilt University in a sex-matched cohort

No data for treatment affecting this risk



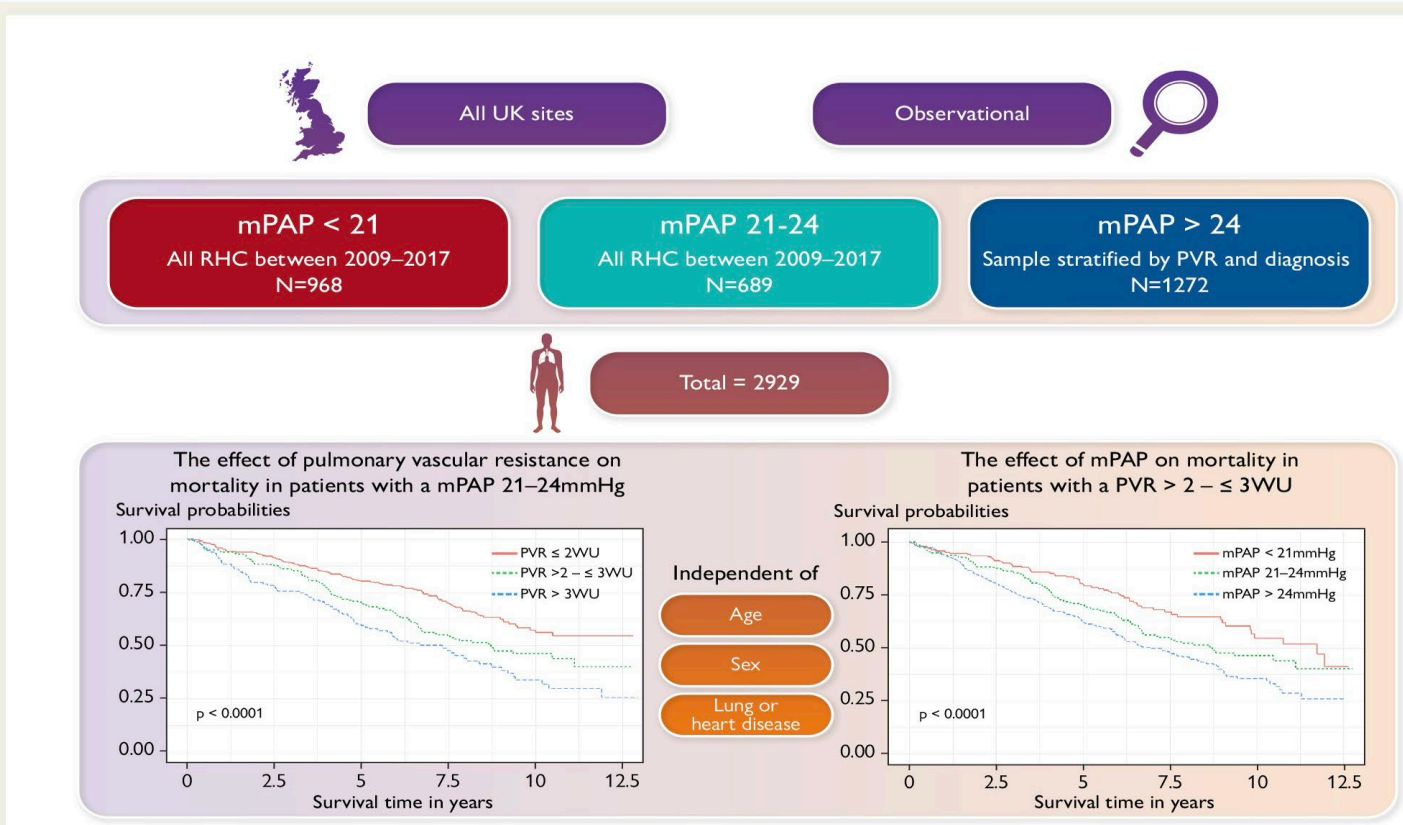
- Maron B.A., Brittain E.L., Hess E., et al. "The association between pulmonary vascular resistance and clinical outcomes in patients with pulmonary hypertension: A retrospective cohort study". Lancet Respir Med 2020;8:873-884.

Outcomes in Patients with "mild PH"

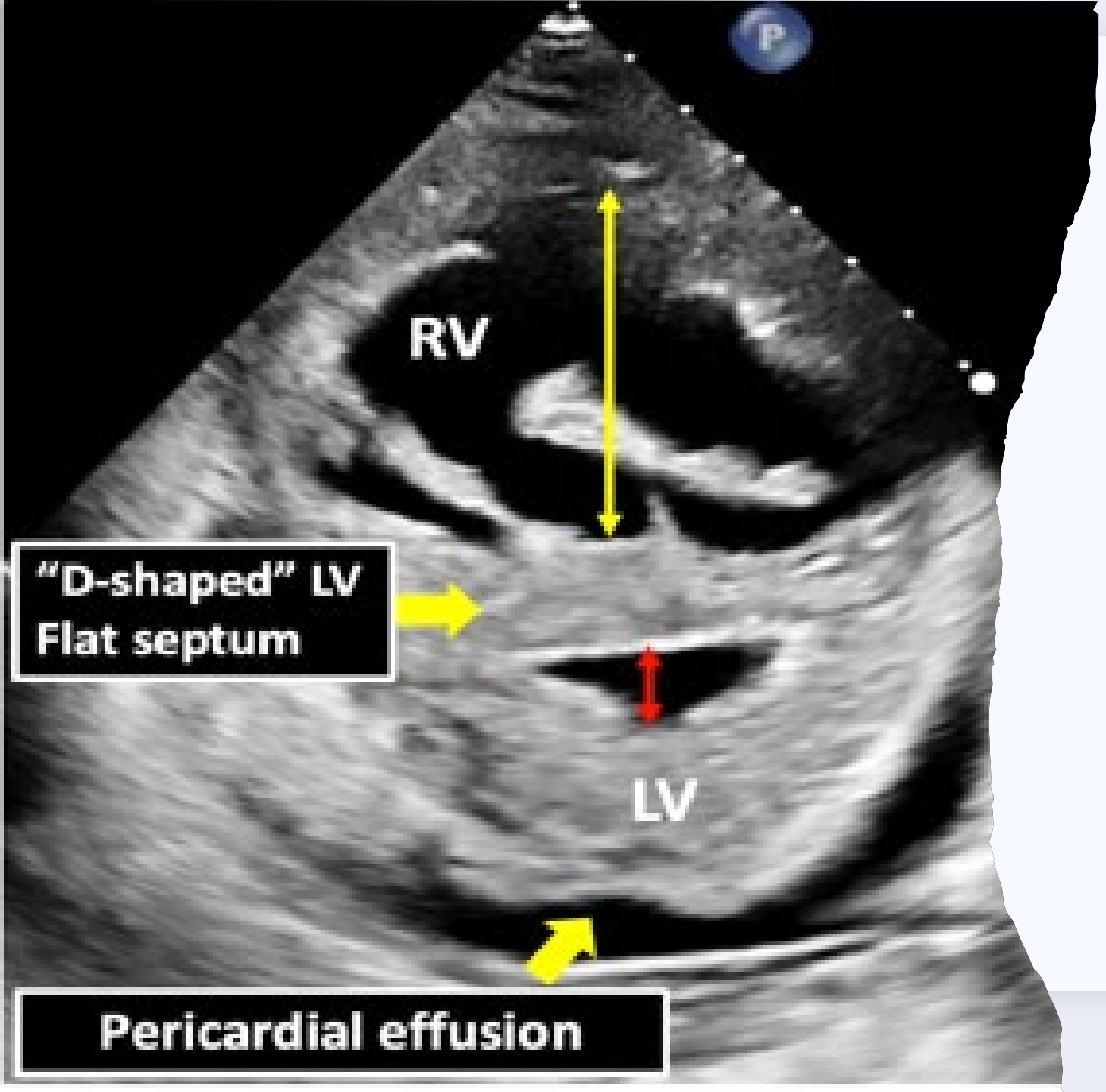
Survival in patients referred for right heart cath in the UK 2009-2017, stratified by hemodynamics

Majority of patients with mPAP 21-24 and PVR 2-3 had underlying heart or lung disease (68% and 79%, respectively)

Mortality is increased in "mild PH"



Karia N, Howard L, Johnson M, Kiely DG, Lordan J, McCabe C, Pepke-Zaba J, Ong R, Preiss M, Knight D, Muthurangu V, Coghlan JG. Predictors of outcomes in mild pulmonary hypertension according to 2022 ESC/ERS Guidelines: the EVIDENCE-PAH UK study. Eur Heart J. 2023 Nov 21;44(44):4678-4691.



Mild PH and Classification

- Mild PH confers increased mortality in referred patients but often occurs in the setting of underlying heart and lung disease
- RHC must be interpreted in a clinical context to avoid misclassification
- Avoid RHC amidst an acute condition
- Comprehensive, deliberate evaluation remains important

Exercise Pulmonary Hypertension

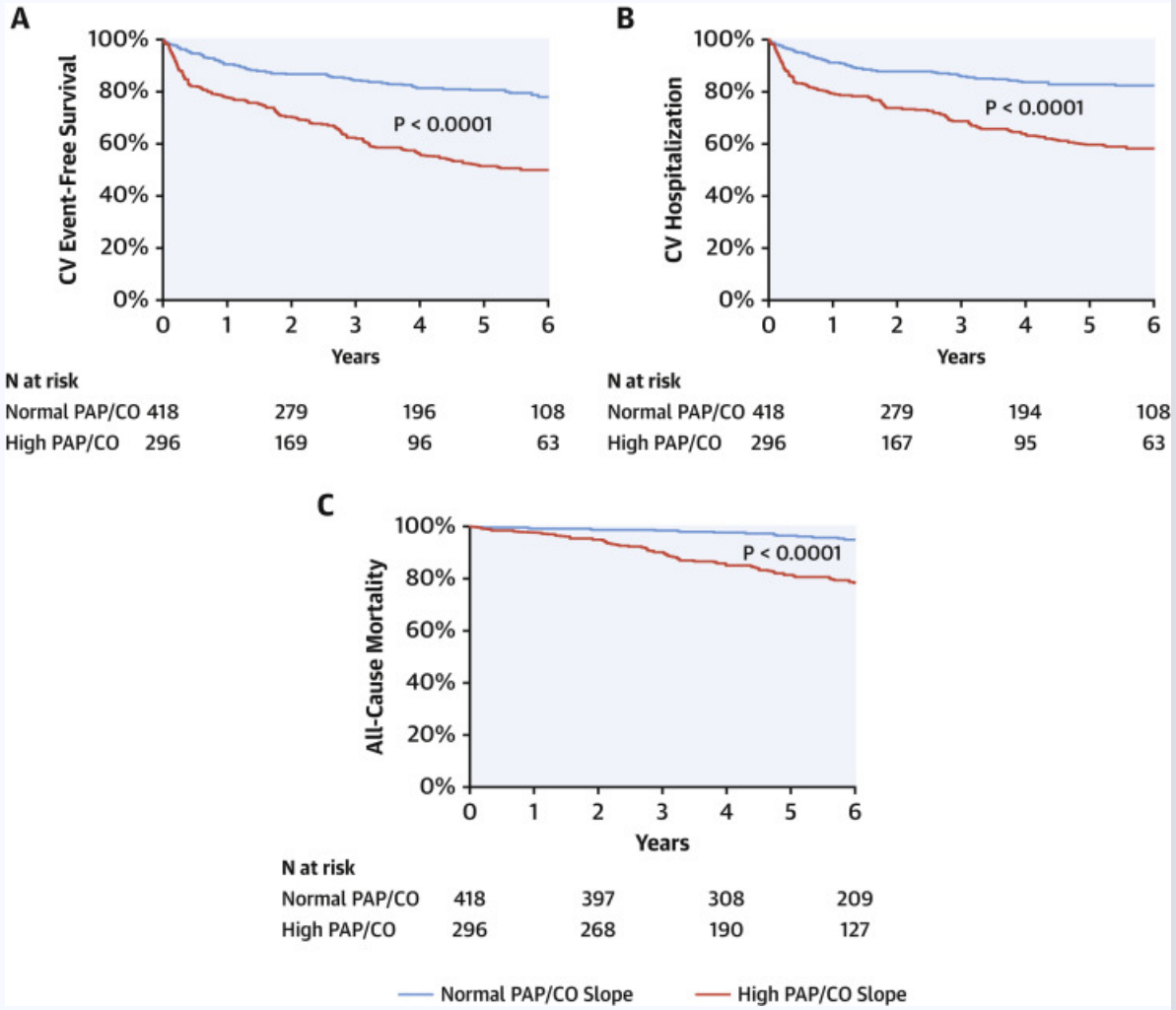
mPAP/CO slope > 3mmHg/L/min is defined as abnormal

In patients with chronic dyspnea, exercise PH is associated with worse event-free survival in patients with dyspnea

This finding holds despite comorbidities

This definition allows future study of this population

No proven therapeutic options



Jennifer E. Ho, Emily K. Zern, Emily S. Lau, Luke Wooster, Cole S. Bailey, Thomas Cunningham, Aaron S. Eisman, Kathryn M. Hardin, Robyn Farrell, John A. Skarbaro, Mark W. Schoenike, Nicholas E. Houstis, Aaron L. Baggish, Ravi V. Shah, Matthew Nayor, Rajeev Malhotra, Gregory D. Lewis, Exercise Pulmonary Hypertension Predicts Clinical Outcomes in Patients With Dyspnea on Effort, Journal of the American College of Cardiology, Volume 75, Issue 1, 2020, Pages 17-26, ISSN 0735-1097.

Clinical Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension (PAH)

1.1 Idiopathic
- 1.1.1 Long-term responders to calcium channel blockers

1.2 Heritable [a]
1.3 Associated with drugs and toxins [a]
1.4 Associated with:
- 1.4.1 Connective tissue disease
- 1.4.2 HIV infection
- 1.4.3 Portal hypertension
- 1.4.4 Congenital heart disease
- 1.4.5 Schistosomiasis

1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
1.6 Persistent PH of the newborn

2. PH associated with left heart disease

2.1 Heart failure:
- 2.1.1 with preserved ejection fraction
- 2.1.2 with reduced or mildly reduced ejection fraction
- 2.1.3 with specific cardiomyopathies (hypertrophic and amyloid)

2.2 Valvular heart disease
- 2.2.1 aortic valve disease
- 2.2.2 mitral valve disease
- 2.2.3 mixed valvular disease

2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3. PH associated with lung diseases and/or hypoxia

3.1 Chronic obstructive pulmonary disease and/or emphysema
3.2 Interstitial lung disease
3.3 Combined pulmonary fibrosis and emphysema
3.4 Other parenchymal lung diseases [b]
3.5 Non-parenchymal restrictive diseases
- 3.5.1 Hypoventilation syndromes
- 3.5.2 Pneumonectomy
- 3.5.3 Musculoskeletal disorders

3.6 Hypoxia without lung disease (e.g. high altitude)
3.7 Developmental parenchymal disorders

4. PH associated with pulmonary artery obstructions

4.1 Chronic thrombo-embolic PH
4.2 Other pulmonary artery obstructions [c]

5. PH with unclear and/or multifactorial mechanisms

5.1 Haematological disorders [d]
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans's cell histiocytosis, and neurofibromatosis type 1
5.3 Metabolic disorders [e]
5.4 Chronic renal failure with or without haemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis
5.7 Complex congenital heart diseases

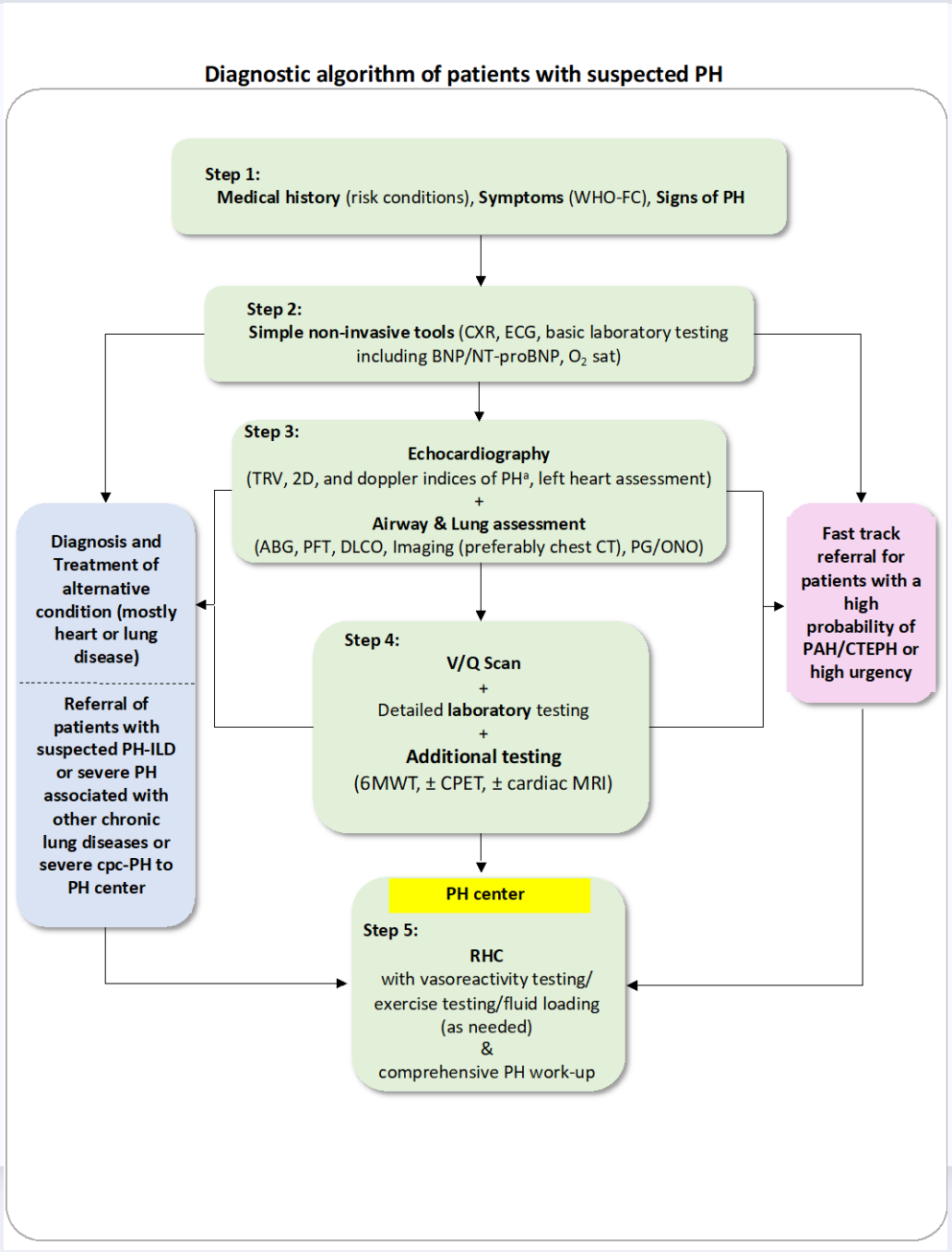
Long-term Responders to Calcium Channel Blockers

- **Long-term Responders Added**
  - Separate pathophysiology and prognosis
  - This does require long-term follow-up
  - Emphasizes the importance of initial vasoreactivity testing

- **Acute vasoresponder removed**
  - A positive response is observed in up to 12% of iPAH or DT-PAH, and 5% of Heritable
  - This group was the only one defined not by pathophysiology but by an initial therapeutic strategy
  - This group includes both those who will be long-term responders and those who will progress similarly to PAH

Diagnosis of Pulmonary Arterial Hypertension

- Simplified Diagnostic Algorithm
- Vasoreactivity testing in IPAH, DPAH, and HPAH
- Emphasize Fast Track Referral for High-Risk Patients

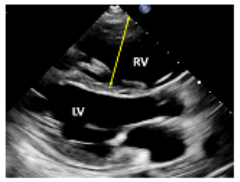


Echocardiographic Measurements

The ventricles	RV/LV basal diameter / area ratio > 1.0
	Flattening of interventricular septum (LVEI > 1.1 in systole and/or diastole)
	TAPSE / sPAP ratio < 0.55 mm/mmHg
Pulmonary artery	RVOT AT < 105 ms and/or mid-systolic notching
	Early diastolic pulmonary regurgitation velocity > 2.2 m/s
	PA diameter > AR diameter; PA diameter > 25 mm
Inferior vena cava and right atrium	IVC diameter > 21 mm with decreased inspiratory collapse
	RA area (end-systole) > 18 cm^2

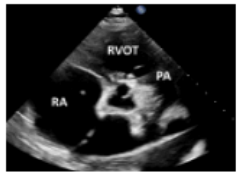
Echocardiographic Measurements by Standard View

Parasternal Long Axis

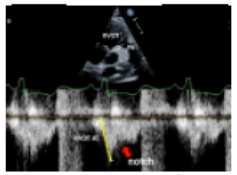


Enlarged RV

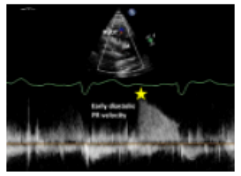
Parasternal Short Axis (at level of valves)



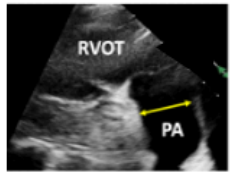
Enlarged RA, RVOT, and PA



Decreased RVOT/PV acceleration time <105 ms with mid-systolic notch

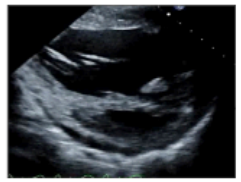


Increased peak diastolic pulmonic regurgitant velocity >2.2 m/s



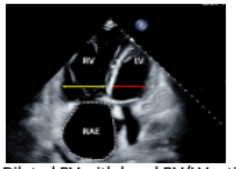
Enlarged PA >25 mm

Parasternal Short Axis (at mid-ventricle)

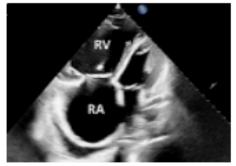


D-Shaped LV; Decreased LV eccentricity index (LVEI, D2/D1) >1; Pericardial effusion

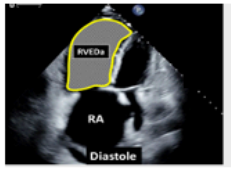
4-Chamber View

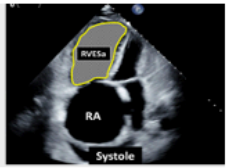


Dilated RV with basal RV/LV ratio > 1.0; Enlarged right atrial area (RAE) >18cm² (end-systole)



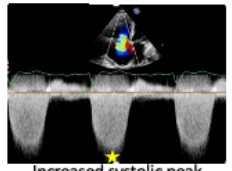
Pericardial effusion



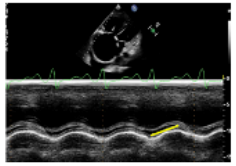


Reduced RV fractional area change (FAC) in systole versus diastole [(RVEDa-RVESa)/RVEDV] <35%

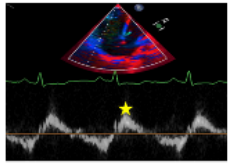
4-Chamber View (Doppler and M-Mode)



Increased systolic peak tricuspid regurgitant velocity >2.8 m/s by Doppler

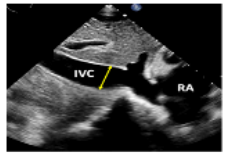


Decreased tricuspid annular plane excursion (TAPSE) <1.8cm by M-mode

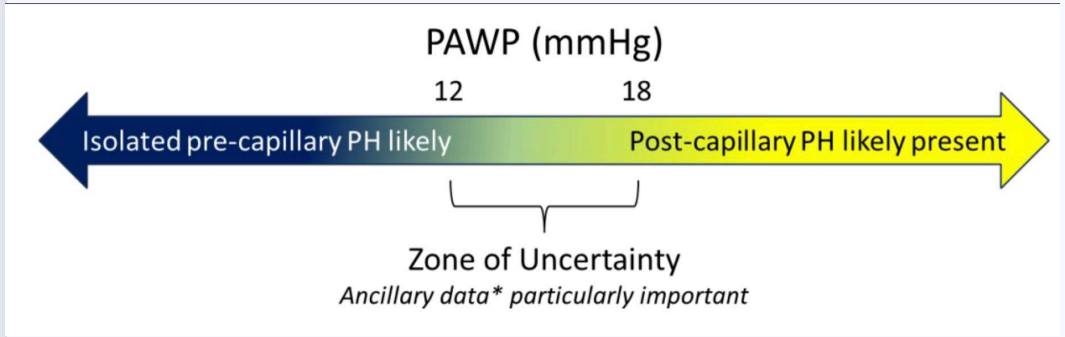


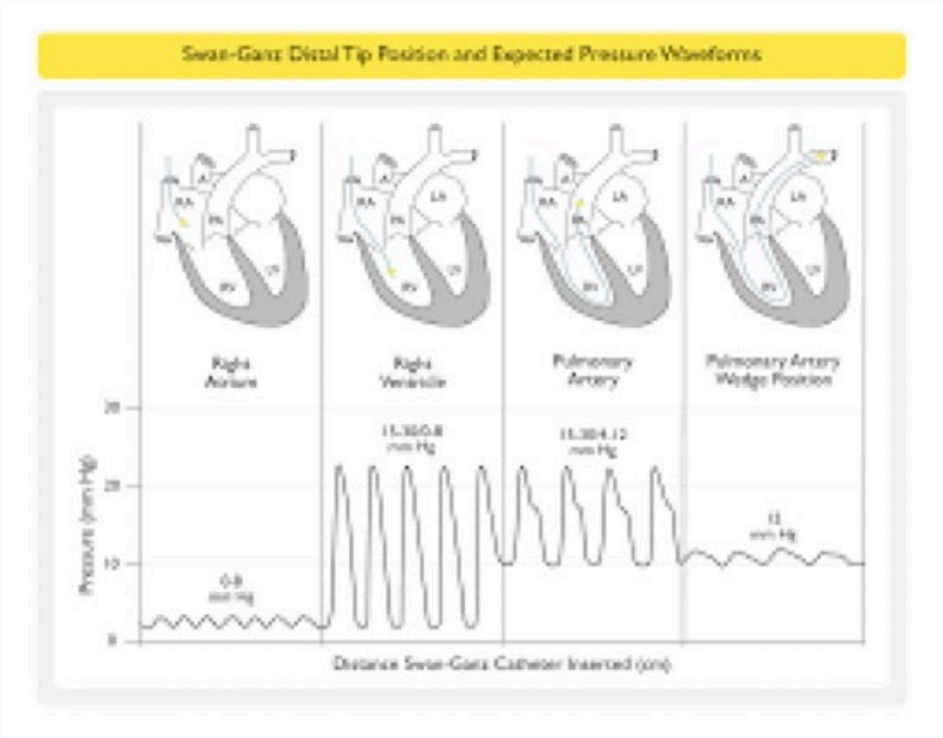
Decreased systolic excursion velocity (S') of tricuspid valve annulus <9.5 cm/s by tissue Doppler imaging

IVC



Distended IVC >2.1 cm with diminished inspiratory collapsibility (<50% with a sniff or <20% with quiet inspiration)





Right Heart Catheterization

Measurements are end-expiratory without breath-hold or averaged over 3-4 respiratory cycles

Direct Fick > TD > Indirect

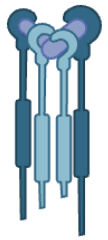
Vasoreactivity testing in IPAH, DPAH, and HPAH

Normal or moderately increased mPAP and PCWP 13-15 may benefit from

Exercise

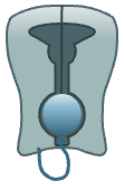
- Exercise PH defined by the mPAP/CO slope > 3 mmHg/L/min

7th World Symposium on Pulmonary Hypertension – Genetics and Precision Genomics



BMP/TGF-β family

ACVRL1 (ALK1)*
BMPR2 (BMPR2)
ENG (endoglin)*
GDF2 (BMP9)
SMAD9 (SMAD8)
CAV1 (caveolin-1)



Channels

ATP13A3 (ATPase 13A3)
KCNK3 (TASK1)
ABCC8 (MRP8)

Transcription factors

EIF2AK4 (GCN2)†
SOX17 (SOX17)‡
TBX4 (TBX4)‡

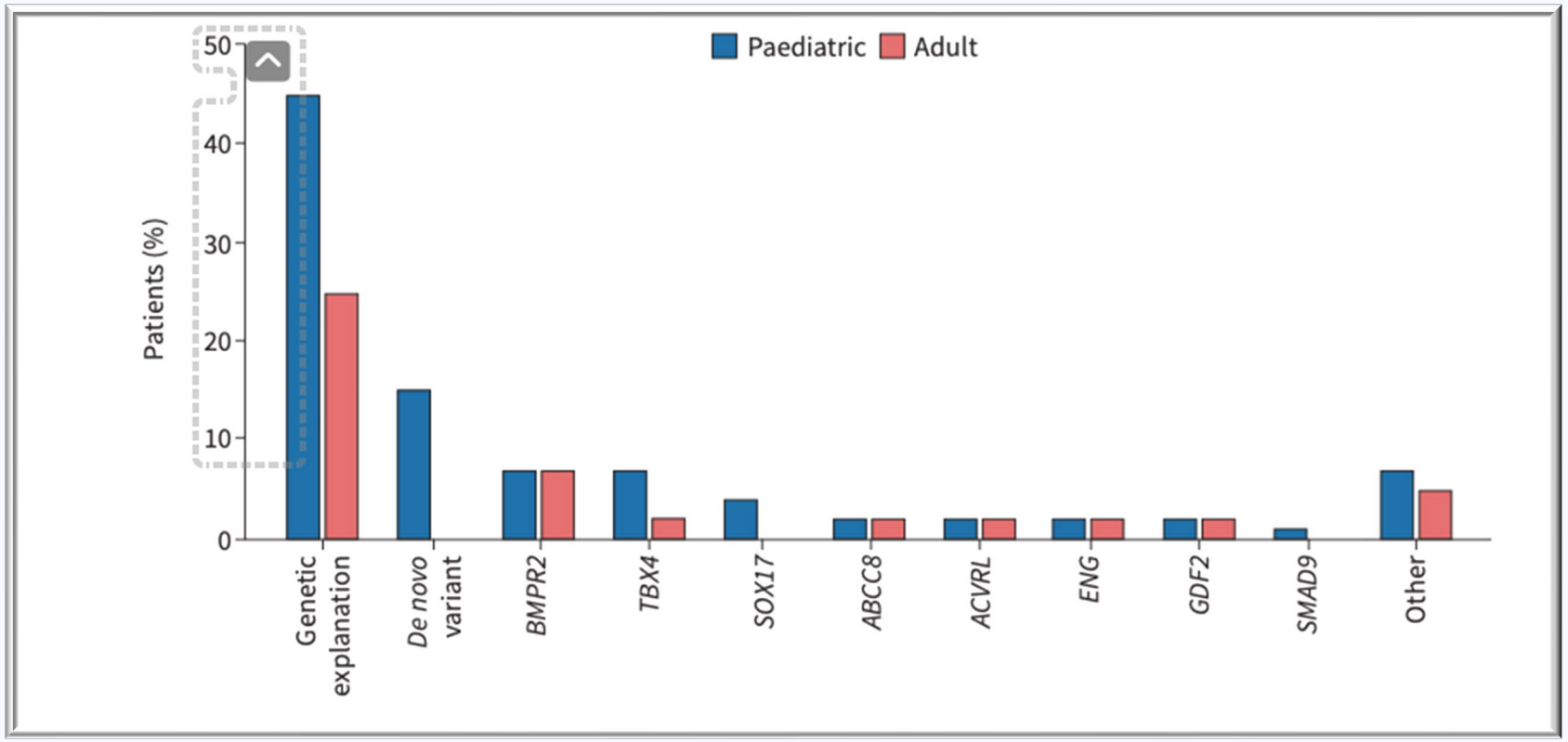
Other

KDR (VEGFR2)
TET2 (TET2)
GGCX (GGCX)

- *Hereditary hemorrhagic telangiectasia. †Pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis.
‡Lung development abnormalities.
Eichstaedt C, *et al. Eur Respir J* 2023; 61:2201471.

7th World Symposium on Pulmonary Hypertension – Genetics and Precision Genomics

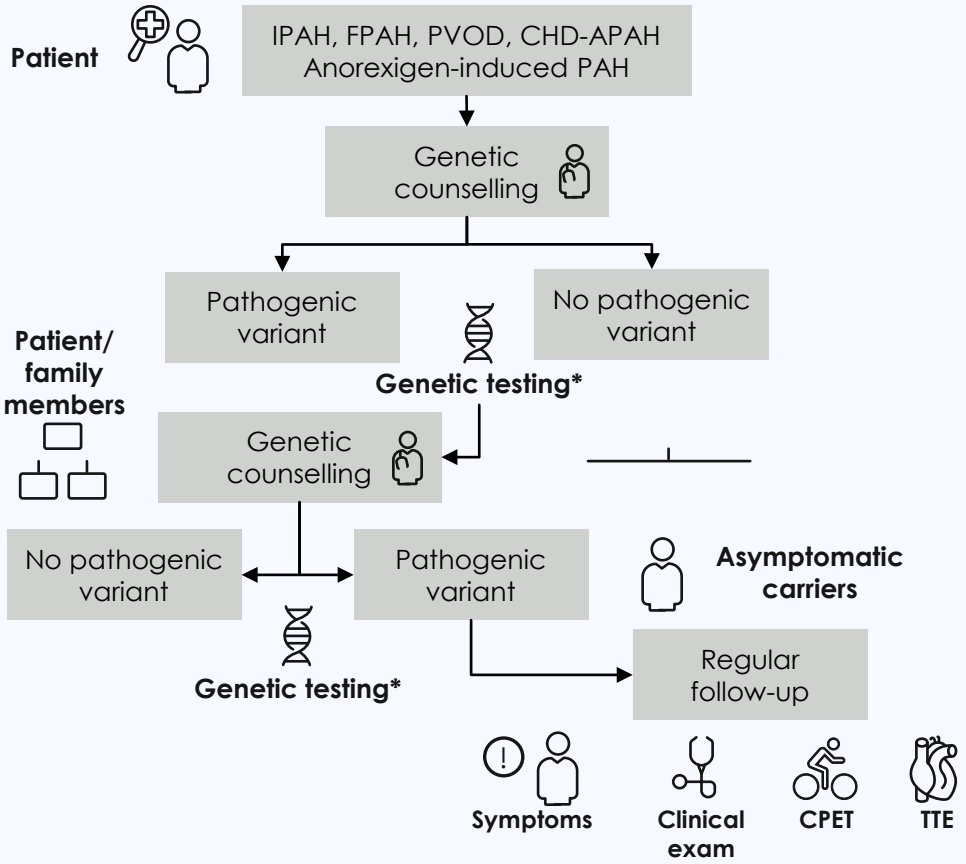
Prevalence of Genetic Predisposition in PH Population



- Austin ED, Aldred MA, Alotaibi M, et al. Genetics and precision genomics approaches to pulmonary hypertension. Eur Respir J 2024

The path of genetic counseling and testing

Genetic counseling path for PAH patients and their relatives[1]

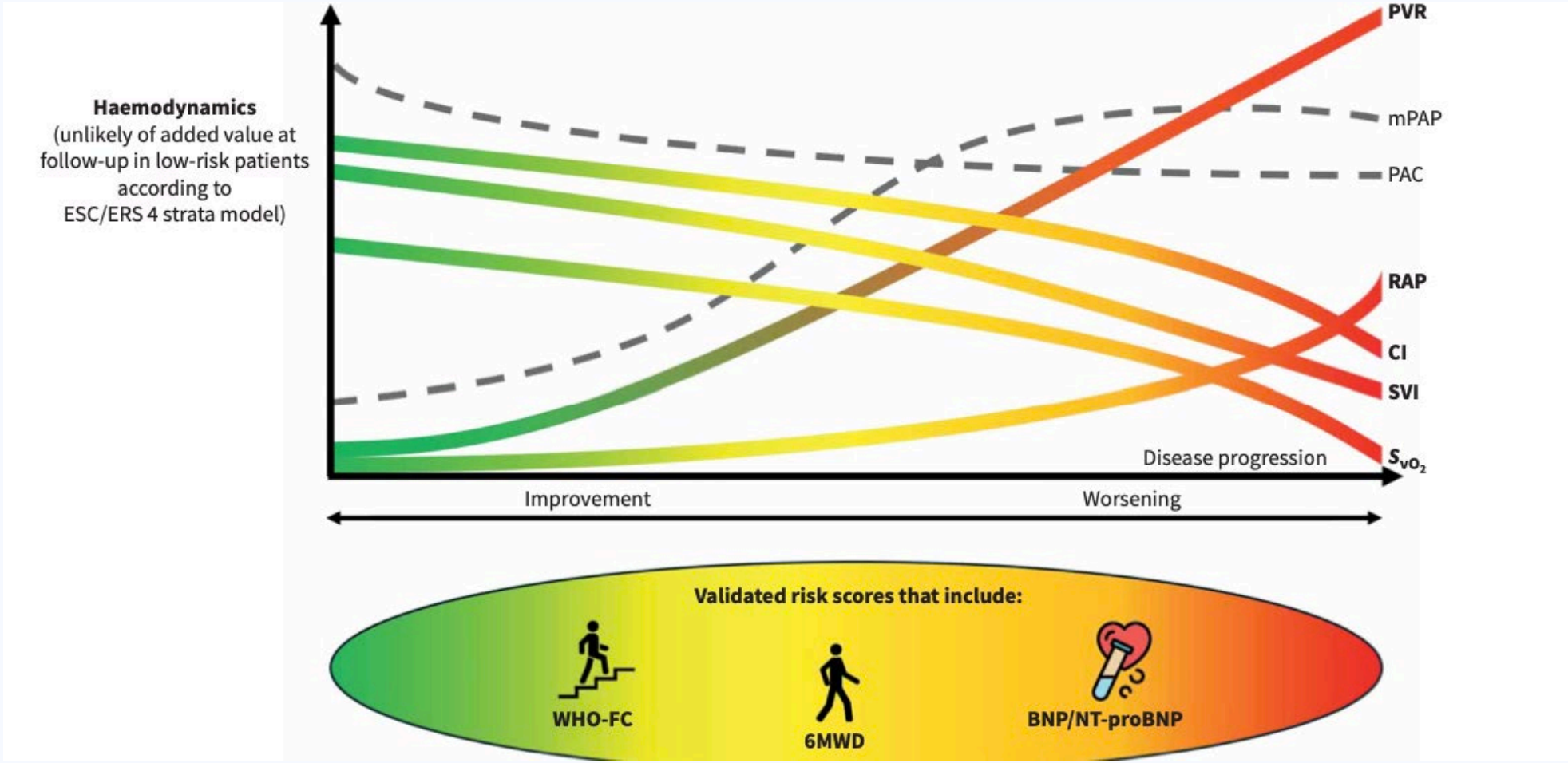


2022 ESC/ERS Guideline recommendations for genetic counseling and testing[2]

- Patients with IPAH/FPAH/PVOD/PCH/anorexigen-induced PAH should be informed about the possibility of a genetic condition that may increase the risk of PAH in family members
- Genetic counseling **prior to** genetic testing can address questions related to penetrance, reproduction, psychosocial impact and at-risk family members
  - Genetic counseling should be performed for symptomatic and asymptomatic family members
- Family members should be made aware of early signs and symptoms, to ensure that a timely and appropriate diagnosis is made
- Prompt counseling for women with PAH who consider **pregnancy** or who become pregnant, to facilitate genetic counseling and shared decision-making, and to provide psychological support

1. Eichstaedt C, *et al. Eur Respir J* 2023; 61:2201471; 2. Humbert M, *et al. Eur Heart J* 2022; 43:3618-731.

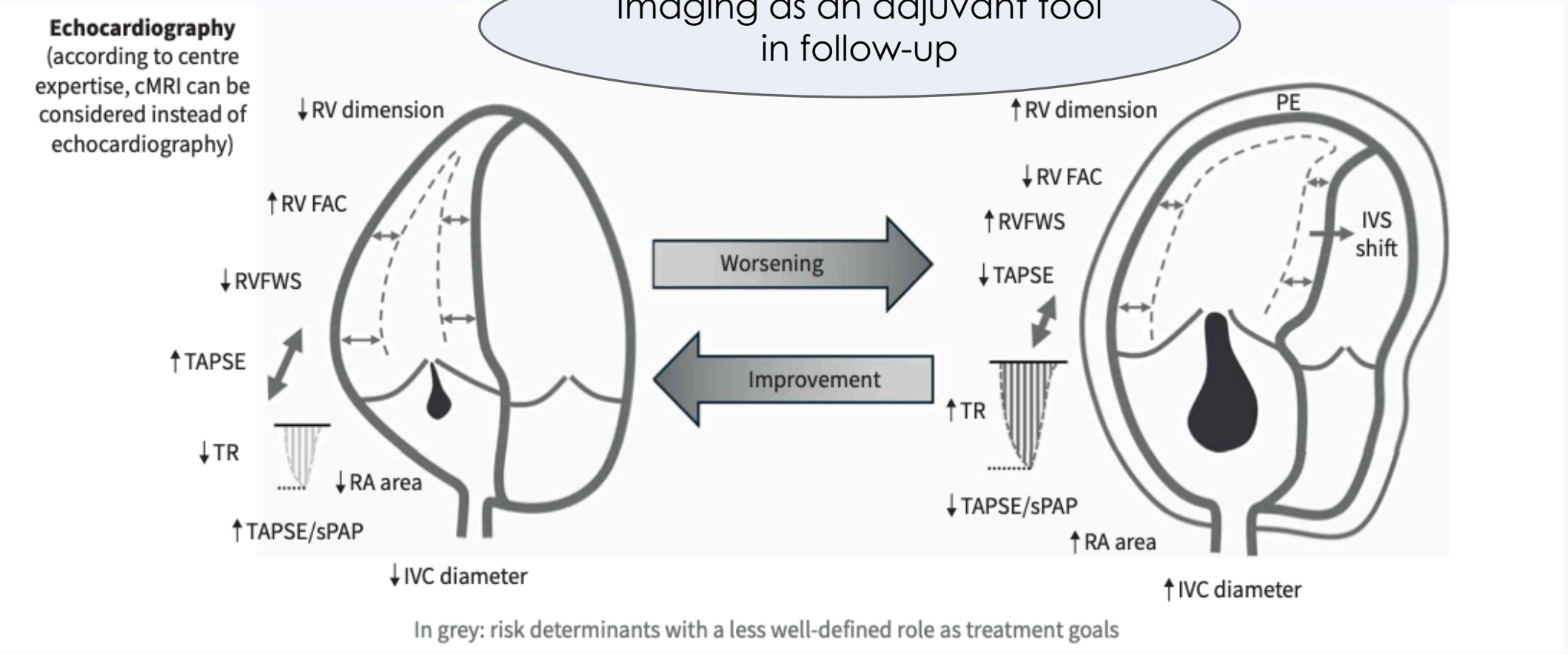
7th World Symposium on Pulmonary Hypertension –Risk Stratification and Treatment Goals



- Dardi F, Boucly A, Benza R, et al. Risk stratification and treatment goals in pulmonary arterial hypertension. Eur Respir J 2024

7th World Symposium on Pulmonary Hypertension –Risk Stratification and Treatment Goals

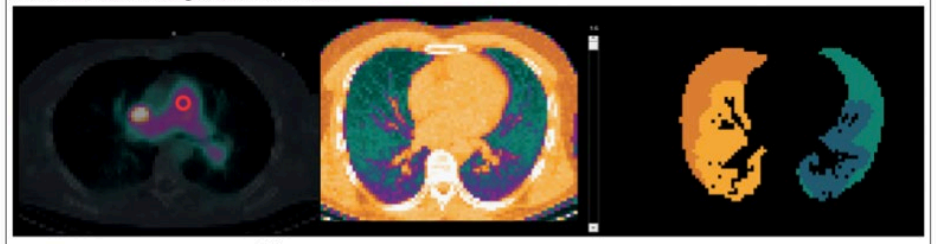
Imaging as an adjuvant tool
in follow-up



- Dardi F, Boucly A, Benza R, et al. Risk stratification and treatment goals in pulmonary arterial hypertension. Eur Respir J 2024

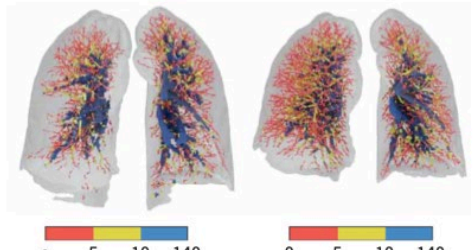
7th World Symposium on Pulmonary Hypertension – emerging Imaging Modalities

a) Aid decision-making in all forms of PH

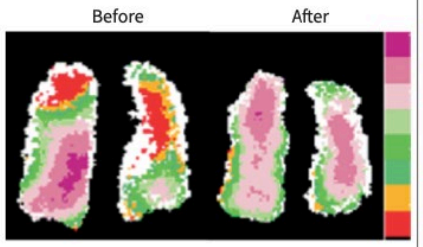


^{18}FLT PET in PAH patients reports on disease activity

b) Assess impact of pharmacological interventions

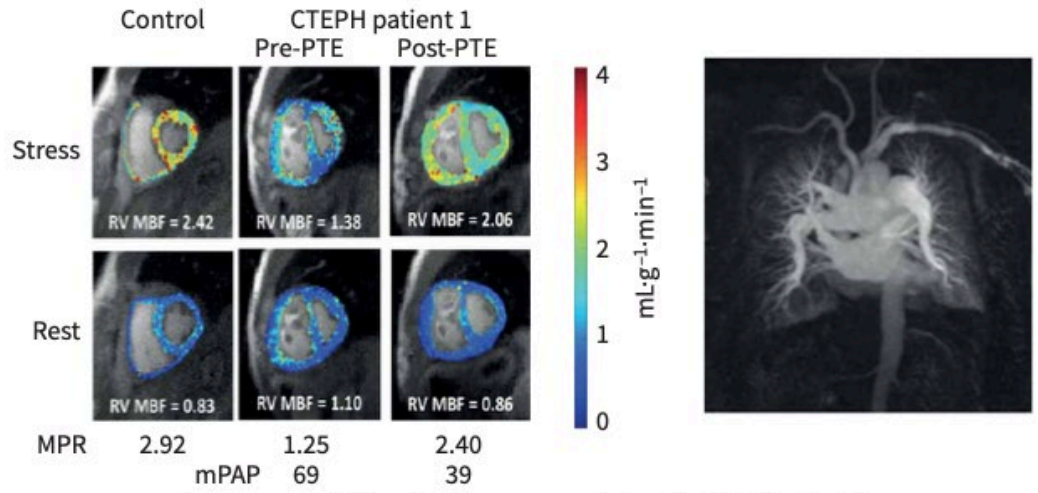


Quantitative CT of small, intermediate and large vessels before and after PEA in CTEPH



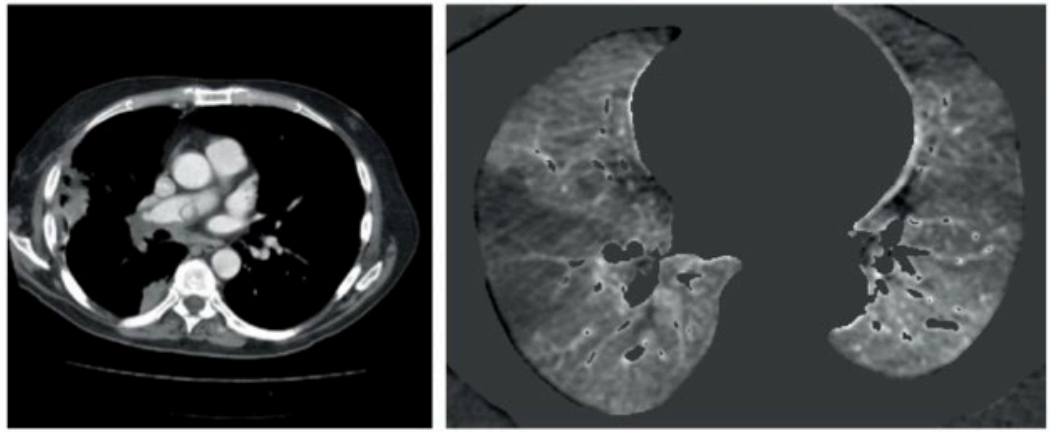
^{129}Xe MRS oscillation imaging monitoring response to PEA surgery in CTEPH

c) Holistic approach to assess impact of therapies



Assessment of RV and pulmonary perfusion in CTEPH with MRI

d) Disease burden in CTEPH to guide treatment



Conventional CT PE with near-total occlusion of RPA

CT angiography with spectral imaging reveals multiple PE-type defects

- Rajagopal S, Bogaard HJ, Elbaz MSM, et al. Emerging multimodality imaging techniques for the pulmonary circulation. Eur Respir J 202

California Thoracic Society
ATS Chapter Serving California and Arizona

Summary

- The definition of PH has been changed based on research, but the treatments are still proven on the previous definition
- The classification scheme of PH has been refined to reflect the patient groups we encounter
- Exercise-induced PH has been added to aid in further research, but no treatment has been proven
- Genetic phenotyping is increasingly important and being studied with treatment modalities
- The diagnostic algorithm has been simplified, but expanded testing can be done based on initial workup
- AI and new imaging techniques may be helpful
- Risk Stratification is important to drive both initial treatment and response

Echocardiography and right heart catheterization for the pulmonologist

Marc A. Simon, MD, MS

Professor of Medicine
Director of Pulmonary Vascular Disease and the UCSF Pulmonary Hypertension Comprehensive Care Center (PHCCC)

UCSF Advanced Heart Failure & Cardiac Transplant Fellowship Director

Disclosures

- I have the following relationships with ACCME defined ineligible companies:
- **Actelion Janssen, Aerovate, Aeromi, Merck, Gossamer Bio**
- **I WILL NOT discuss off-label use and/or investigational use of any drugs or devices.**

Outline/Educational Objectives

1. To review key echocardiography features related to pulmonary hypertension.
2. To review hemodynamics obtained via right heart catheterization, pitfalls, and when to consider exercise testing.

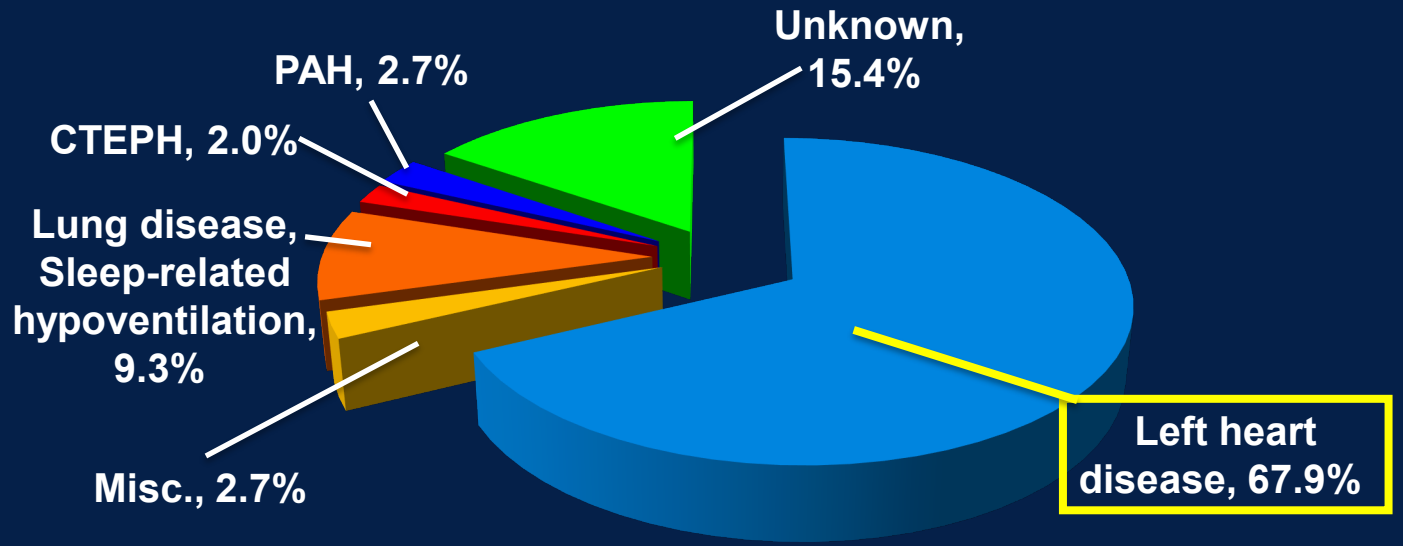
Echocardiography

Basic Objectives

1. Estimate PA pressure
2. Assess Right- vs Left-sided Structures
3. Screen for Congenital Heart Disease

Epidemiology of PH by Echo (PASP >40 mm Hg)

- Single echo lab / Australian community of 165,450
- Etiology of PH noted on echocardiogram



Strange G et al. *Heart*. 2012;98:1805-1811.

N=936 of 10,314 patients with echo PASP >40 mm Hg.

UCSF

Echo Screening – 2022 European Guidelines

A: The ventricles	B: Pulmonary artery	C: Inferior vena cava and RA
RV/LV basal diameter/area ratio >1.0	RVOT AT (PAAT) <105 ms and/or mid-systolic notching	IVC diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the interventricular septum (LVEI >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/s	RA area (end-systole) >18 cm^2
TAPSE/sPAP ratio <0.55 mm/mmHg	PA diameter >AR diameter PA diameter >25 mm	

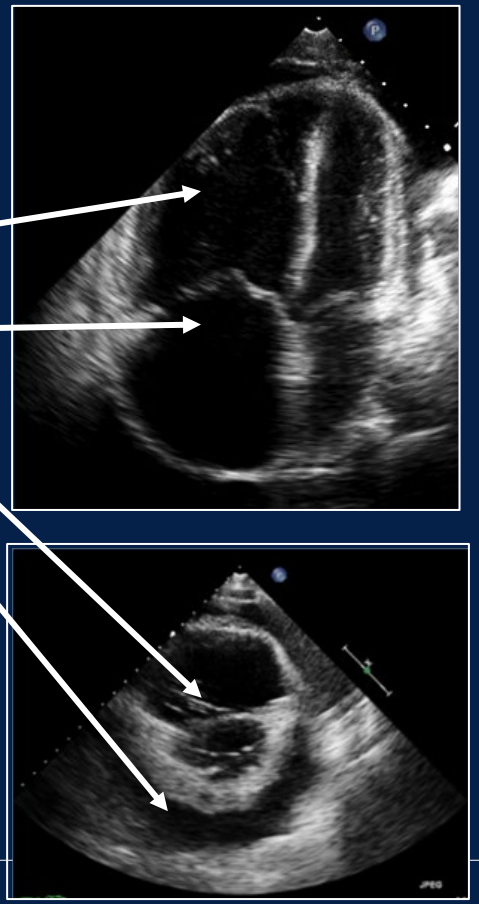
Signs from at least two categories (A/B/C) must be present to alter the level of echocardiographic probability of PH.

Eur Heart J, 2022; 43(38):3618–3731, https://doi.org/10.1093/eurheartj/ehac237

UCSF

Structural Echocardiographic Findings in Patients With PAH

- RV enlargement
- RA enlargement
- Septal flattening
- Pericardial effusion

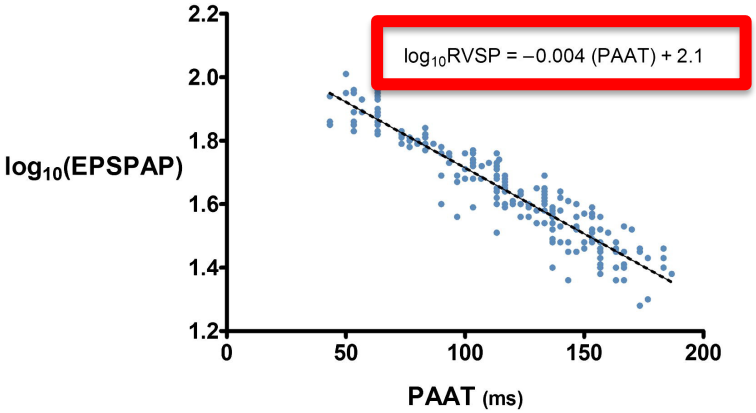


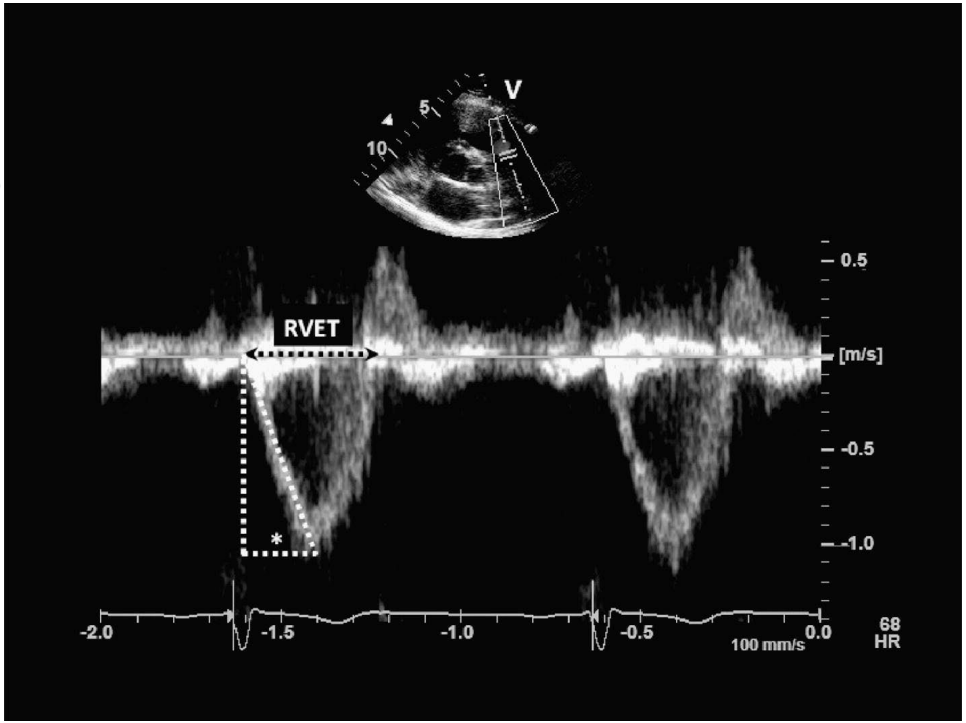
McLaughlin VV et al. *J Am Coll Cardiol.* 2009;53:1573-1619.

UCSF

Echocardiography to Assess PA Pressure

- TR Jet
- PA acceleration time (PAAT)
  - Midsystolic Notching



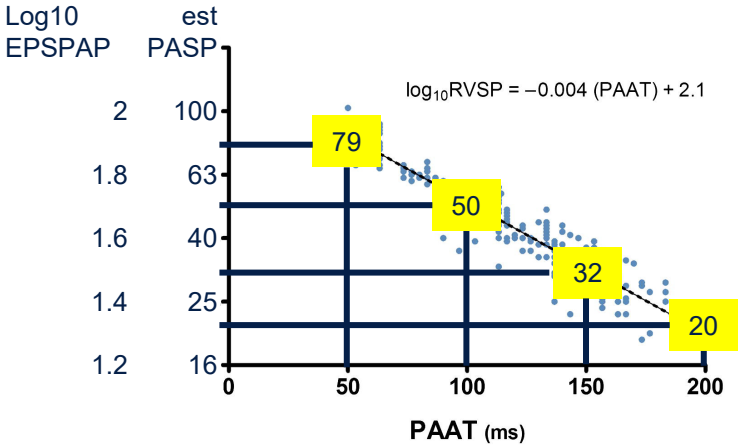


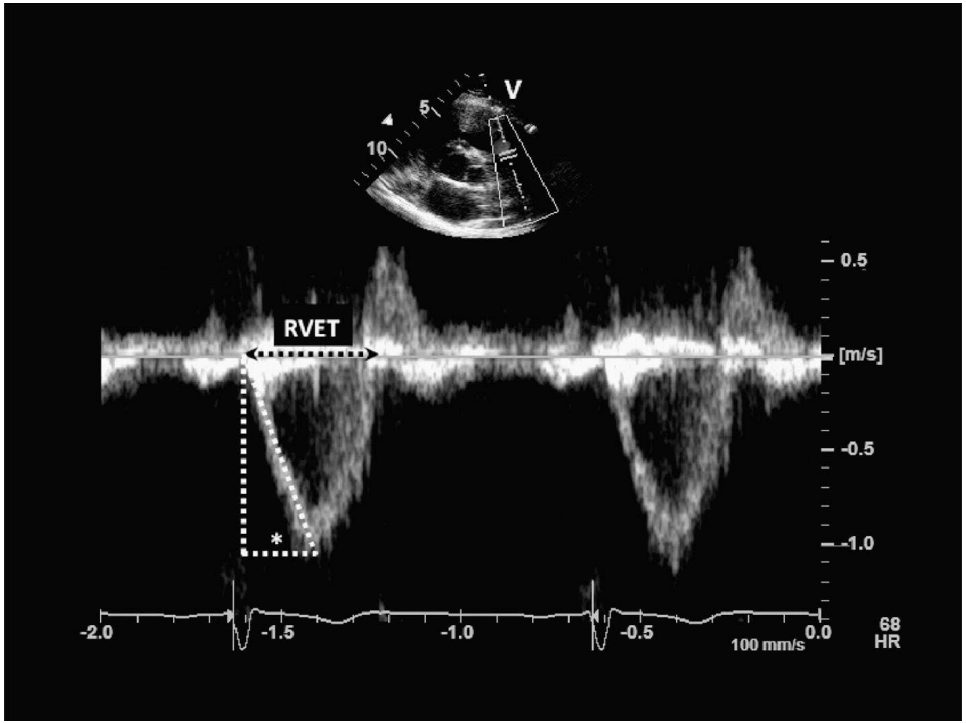
Yared et al. J Am Soc Echo 2011

UCSF

Echocardiography to Assess PA Pressure

- TR Jet
- PA acceleration time (PAAT)
  - Midsystolic Notching

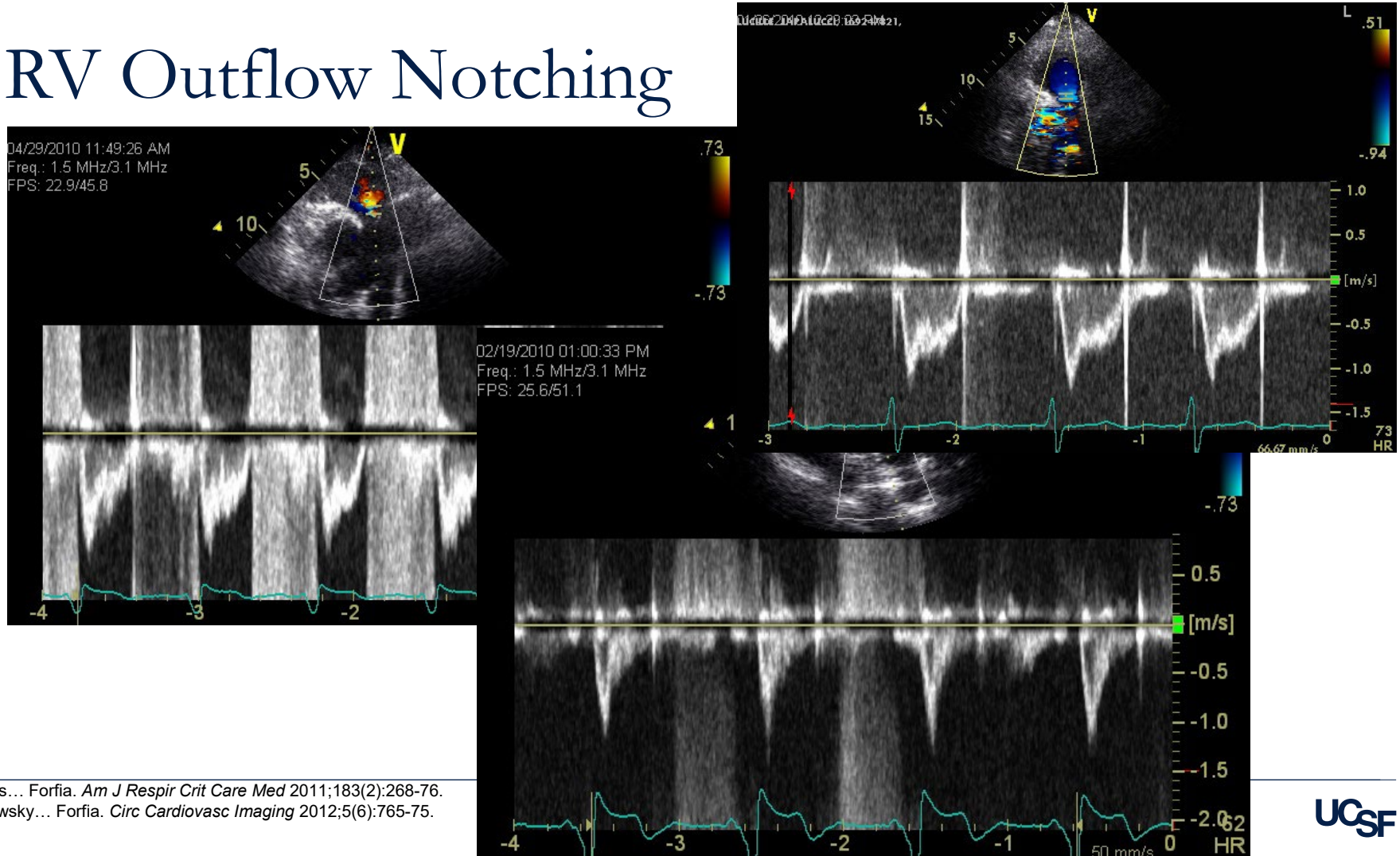




Yared et al. J Am Soc Echo 2011

UCSF

RV Outflow Notching



Arkles… Forfia. *Am J Respir Crit Care Med* 2011;183(2):268-76.
Optowsky… Forfia. *Circ Cardiovasc Imaging* 2012;5(6):765-75.

UCSF

PAAT:

Is this TR jet good enough to estimate PASP?

PAAT: Estimate PASP

log10(EPSPAP) = 0.004(PAAT) + 2.1
PAAT of 100 ms = Estimated PASP of 50 mmHg

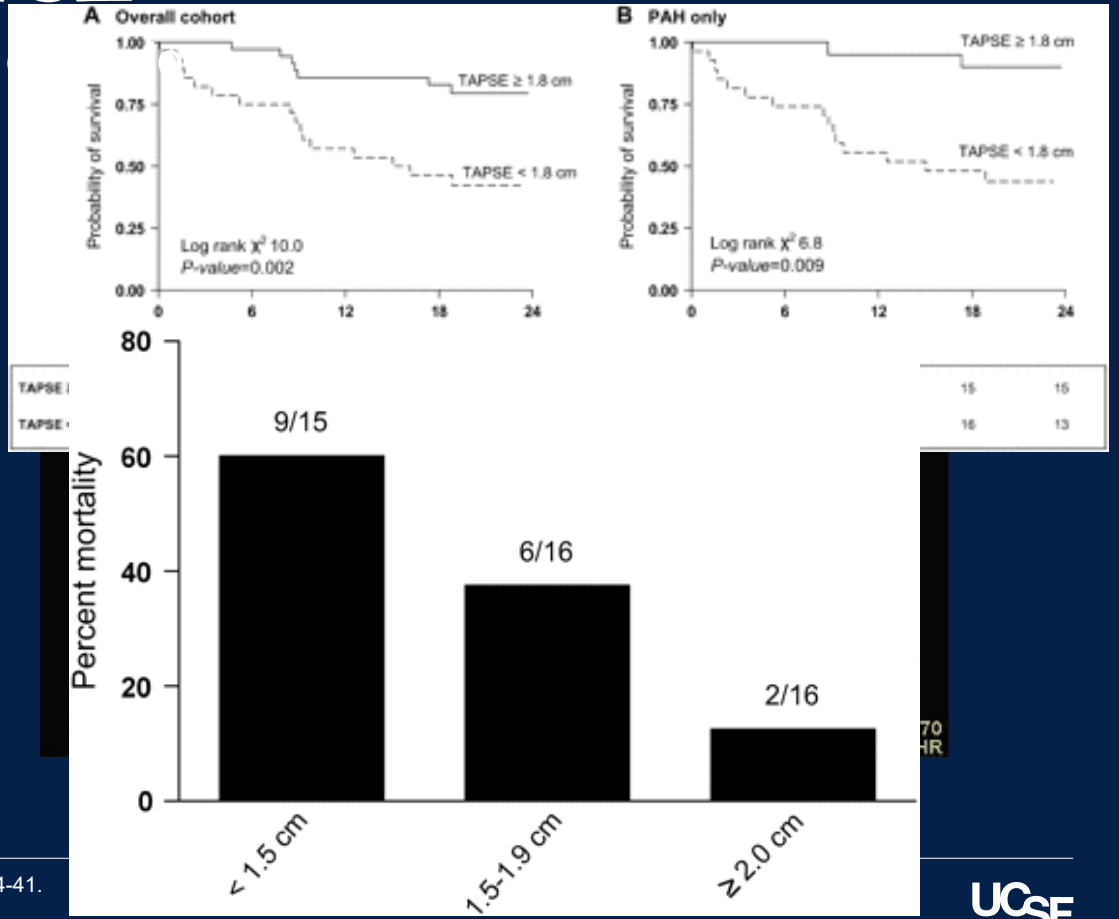
PAAT: Estimate PASP

log10(EPSPAP) = 0.004(PAAT) + 2.1
PAAT of 100 ms = Estimated PASP of 50 mmHg
TR Jet underestimated → minimal TR = poor est

RV Function: TAPSE

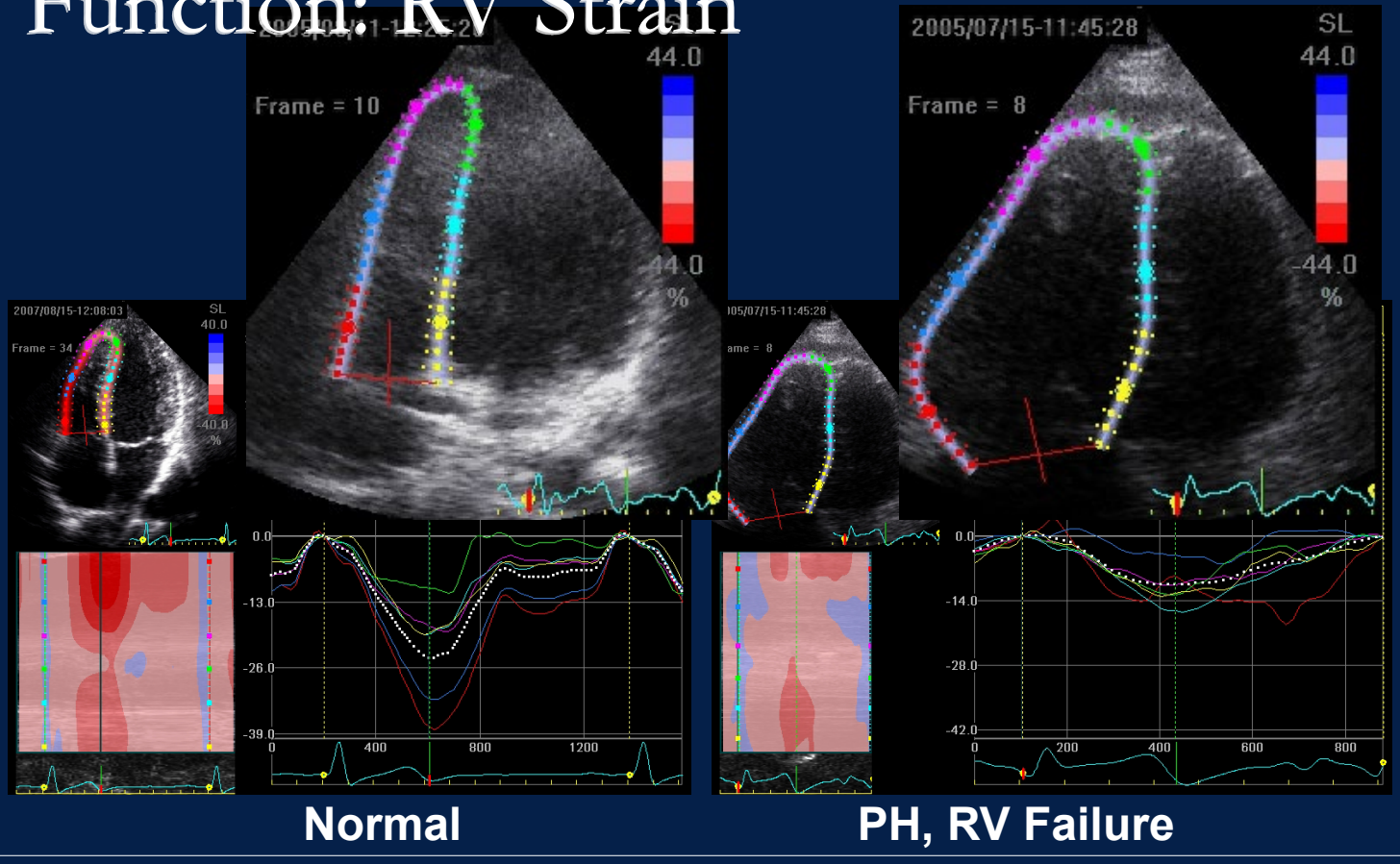
Tricuspid annular plane systolic

- In the four chamber view a straight line (M mode) is drawn through the lateral tricuspid valve annulus (arrow 1).
- The level of excursion of the TV plane during systole (TAPSE) corresponds with RV EF (arrow 2) (5 mm ~ 20%; 10 mm ~ 30%; 15 mm ~ 40%; 20 mm ~ 50%).
- Also associated with poor outcomes at cutoffs of 1.6 – 2.0.



Bleeker, et al. Heart 2006;92;19-26. Forfia, et al. AJRCCM 2006;174(9):1034-41.

RV Function: RV Strain

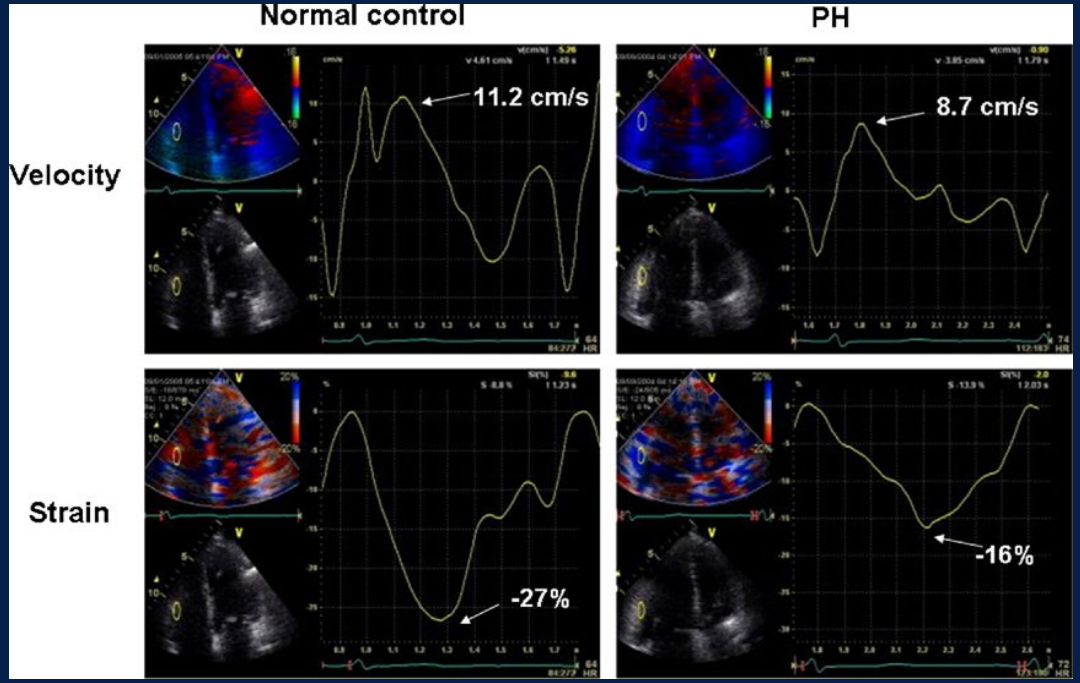


Normal **PH, RV Failure**

Reali M, Rajagopalan N, Lopez-Candales A, Cordero KE, Suffoletto M, Shroff SG, Pinsky MR, Gorcsan III J, Mathier MA, Simon MA. Regional Right Ventricular Myocardial Strain by Echocardiographic Speckle Tracking Distinguishes Clinical and Hemodynamic RV Dysfunction in Pulmonary Hypertension. *Journal of Cardiac Failure* 14(6, Suppl): S17, 2008.

UCSF

RV Function: S' and RV Strain



Rajagopalan N, Simon MA, Mathier MA, Lopez-Candales A,. Identifying right ventricular dysfunction with tissue Doppler imaging in pulmonary hypertension. *International Journal of Cardiology* 128 (2008) 359–363.

UCSF

VEST Echo Screening Tool

Distinguish PAH from PH-LHD

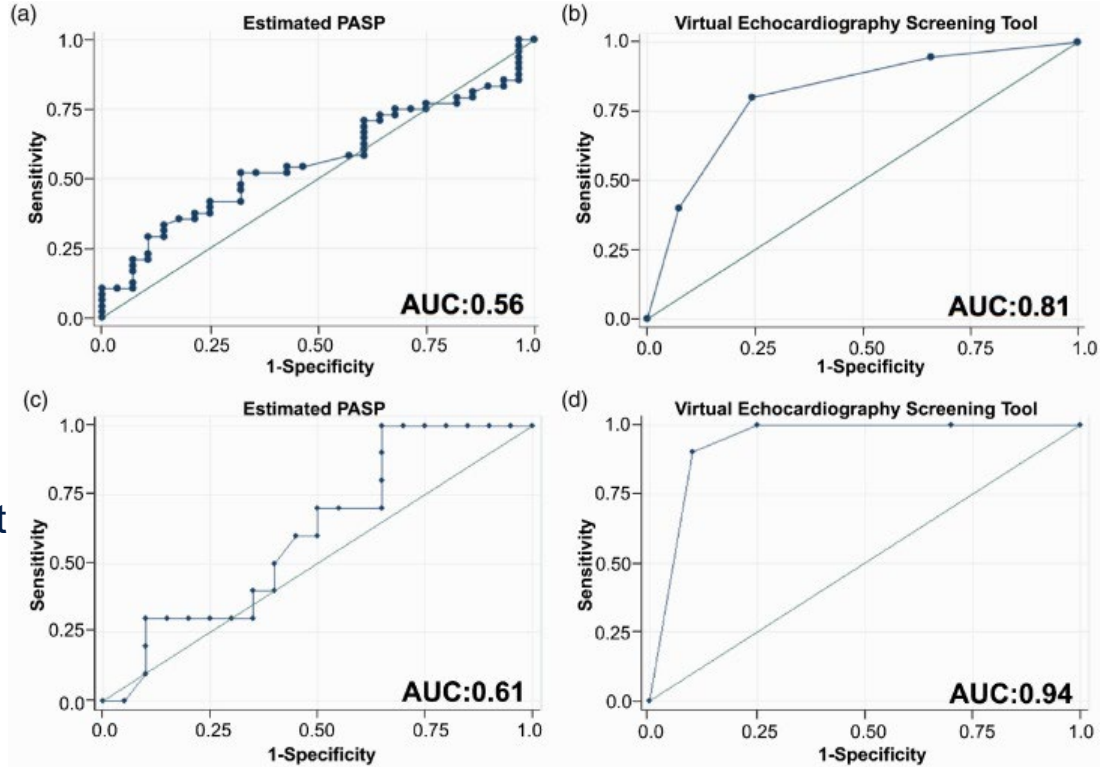
Echocardiographic parameter	Yes	No
Mitral E:e', lateral ≤10[a]	+1	−1
Qualitative left atrial size normal or mildly enlarged	+1	−1
Systolic interventricular septal flattening	+1	−1

VEST Echo Screening Tool

Distinguish PAH from PH-LHD

Original Cohort

Validation Cohort

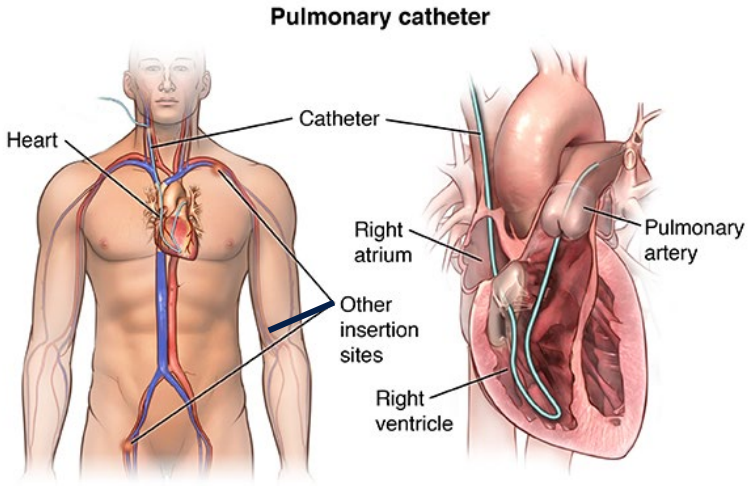


Vaidya… Forfia. Pulm Circ 2020;10(3):2045894020950225.

Right Heart Catheterization

Access

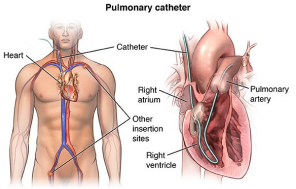
- Brachial vein
- Internal Jugular vein
- Femoral vein



Adapted from MedEdge

Right Heart Catheterization

Common Pitfalls & Sources of Error



Issue	Impact	Solution
Improper zeroing	P consistently > < than expected	Level transducer at mid thorax
Overdamping	False ↓ Sys P & ↑ Dias P	Flush catheter
Catheter whip	False ↓ Sys P & ↑ Dias P	Ignore artifact
Under-wedged PCWP	False ↑ PCWP/similar to PAP	PCWP sat or use LVEDP
Overwedged PCWP	False ↑ PCWP/dampened	Less balloon or use LVEDP
Significant respiratory variation (obesity, lung dz)	Large changes in intrathoracic P	Consider avg (esp COPD) & end-expiratory
MR: tall v-waves on PCWP	False ↑ PCWP	Use a-wave or mean
Inaccurate CO	Thermodil: TR, temps, vol Fick: indirect inaccurate	Thermodil: use avg of 3-5 Use Thermodilution

Adapted from : Rajagopalan et al. JACC: Heart Fail 2024;12(7):1114-1156.

UCSF

Vasoreactivity testing

Definitions of acute and long-term responses	
	Definition
Acute pulmonary vasoreactivity[a] for patients with IPAH, HPAH or drug-induced PAH	• Reduction of mPAP ≥10 mm Hg to reach absolute value of mPAP ≤40 mm Hg • Increased or unchanged cardiac output
Long-term response to CCB	• NYHA FC I or II • With sustained hemodynamic improvement after at least one year on CCBs only

Adenosine i.v. is no longer recommended due to frequent side effects

Compound	Route	Half-life	Dosage	Duration
Nitric oxide	inh	15–30 s	10–20 p.p.m.	5–10 min[a]
Iloprost	inh	30 min	5–10 µg[b]	10–15 min[c]
Epoprostenol	i.v.	3 min	2–12 ng/kg/min	10 min[d]

CCB: calcium channel blockers; FC: functional class
* Inhaled nitric oxide (10-20 ppm) is recommended for performing vasoreactivity testing

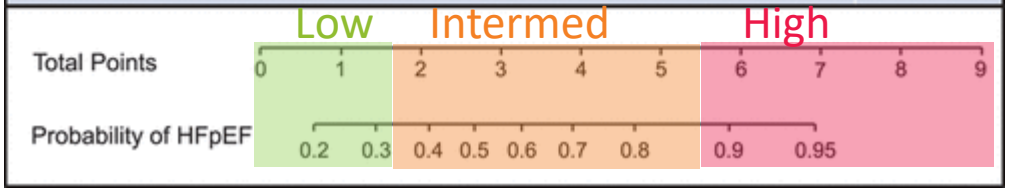
Simonneau G, Eur Respir J 2018

Eur Heart J, 2022; 43(38):3618–3731, https://doi.org/10.1093/eurheartj/ehac237

UCSF

Rule out Occult Group 2 PH… HFpEF !!

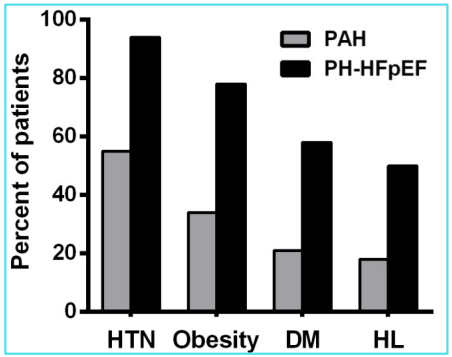
	Clinical Variable	Values	Points
H_2	Heavy	Body mass index > 30 kg/m^2	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial Fibrillation	Paroxysmal or Persistent	3
P	Pulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	Elder	Age > 60 years	1
F	Filling Pressure	Doppler Echocardiographic E/e' > 9	1
	H_2FPEF score		Sum (0-9)

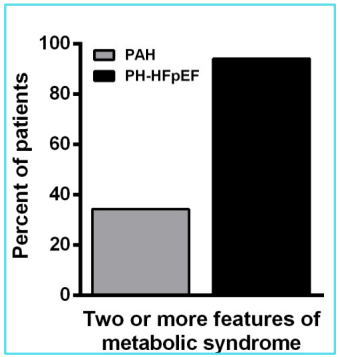


Borlaug et al. Circulation 2018

"Approximately one-third of patients with HFpEF have normal pulmonary capillary wedge pressure (PCWP) at rest, with elevations in filling pressures exclusively during exercise."

Rajagopalan et al. JACC:HF 2024;12(7):1141-1156.





Robbins et al. CHEST 2009;136:31-36.

Rule out Occult Group 2 PH… HFpEF !!

Patient With Unexplained Exertional Dyspnea and No Clear Alternative Cause

H_2FPEF Score

	Definition	Points
Heavy	BMI >30 kg/m^2	2
Hypertension	2 or more antihypertensive medicines	1
Atrial Fibrillation	Any history	3
Pulmonary Hypertension	Pulmonary artery systolic pressure >35 mm Hg (echo)	1
Elder	>60 years	1
Filling pressures	E/e' ratio >9 (echo)	1

HFA-PEFF Score

Domain	Major Criteria (2 Points Max Per Category)	Minor Criteria (1 Point Max Per Category)
Functional	• Average E/e' ratio ≥15 • Septal e' <7 cm/s • Lateral e' <10 cm/s • Tricuspid regurgitation velocity >2.8 m/s	• Average E/e' ratio 9-14 • Global longitudinal strain <16%
Morphological	• Left atrial volume index >34 mL/m^2 • Left ventricular mass index >149/122 g/m^2 (men/women) and relative wall thickness >0.42	• Left atrial volume index 29-34 mL/m^2 • Left ventricular mass index >115/95 g/m^2 (men/women) • Relative wall thickness >0.42 • Left ventricular wall thickness ≥12 mm
Biomarker (sinus)	NTproBNP >220 pg/mL BNP >80 pg/mL	NTproBNP 125-220 pg/mL BNP 35-80 pg/mL
Biomarker (atrial fibrillation)	NTproBNP >660 pg/mL BNP >240 pg/mL	NTproBNP 365-660 pg/mL BNP 105-240 pg/mL

Low probability score
Unlikely HFpEF
(H_2FPEF 0-1 or HFA-PEFF 0-1)

Intermediate probability score
(H_2FPEF 2-5 or HFA-PEFF 2-4)
Further evaluation needed

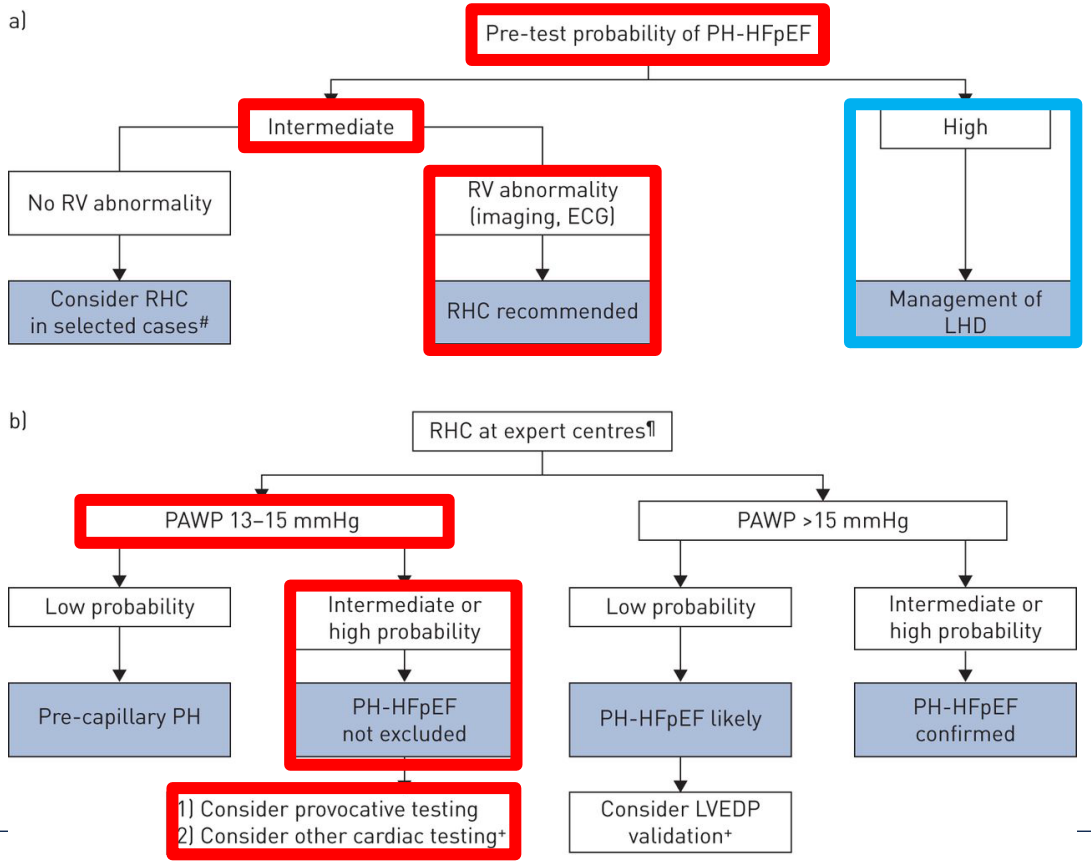
High probability score
Likely HFpEF
(H_2FPEF 6-9 or HFA-PEFF 5-6)

Hemodynamic Stress Test

Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart Failure With Preserved Ejection Fraction: JACC Scientific Statement. JACC 2023;81:1810-1834. doi: 10.1016/j.jacc.2023.01.049

UCSF

Rule out Occult Group 2 PH: Provocative Testing



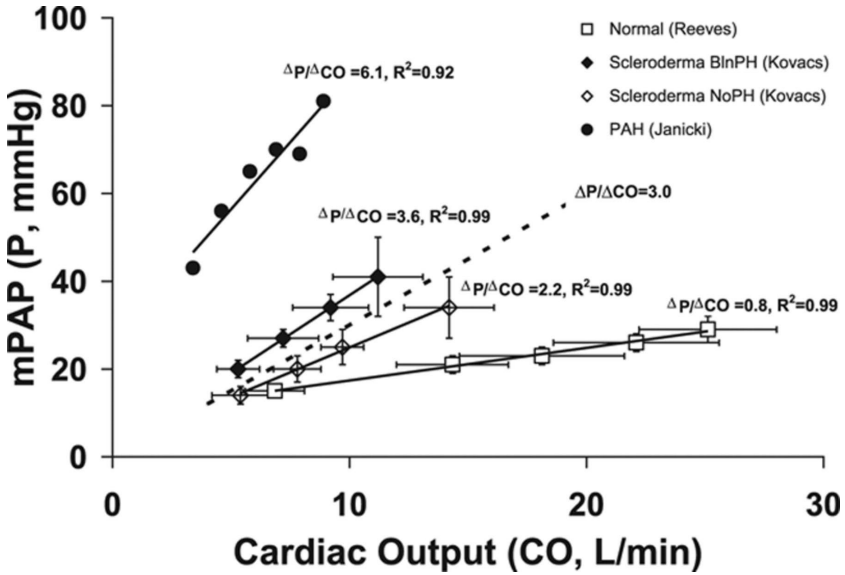
Inampudi C, Silverman D, Simon MA, Leary PJ, Sharma K, Houston BA, Vachiery J, Haddad F, Tedford RJ. Pulmonary Hypertension in the Context of Heart Failure with Preserved Ejection Fraction. CHEST. 2021 Aug 11;S0012-3692(21)03666-7. DOI:https://doi.org/10.1016/j.chest.2021.08.039.

UCSF

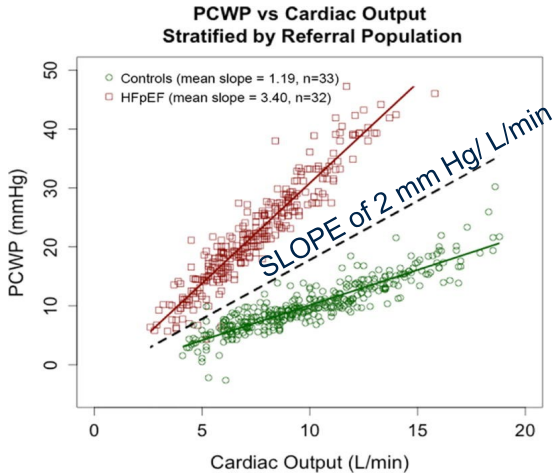
Rule out Occult Group 2 PH: Provocative Testing

Normal response to exercise:

- modest ⬆️ mean PA pressure (<3.0 mm Hg/L/min)
- modest ⬆️ PCWP (<25 mm Hg)
- ⬇️ PVR



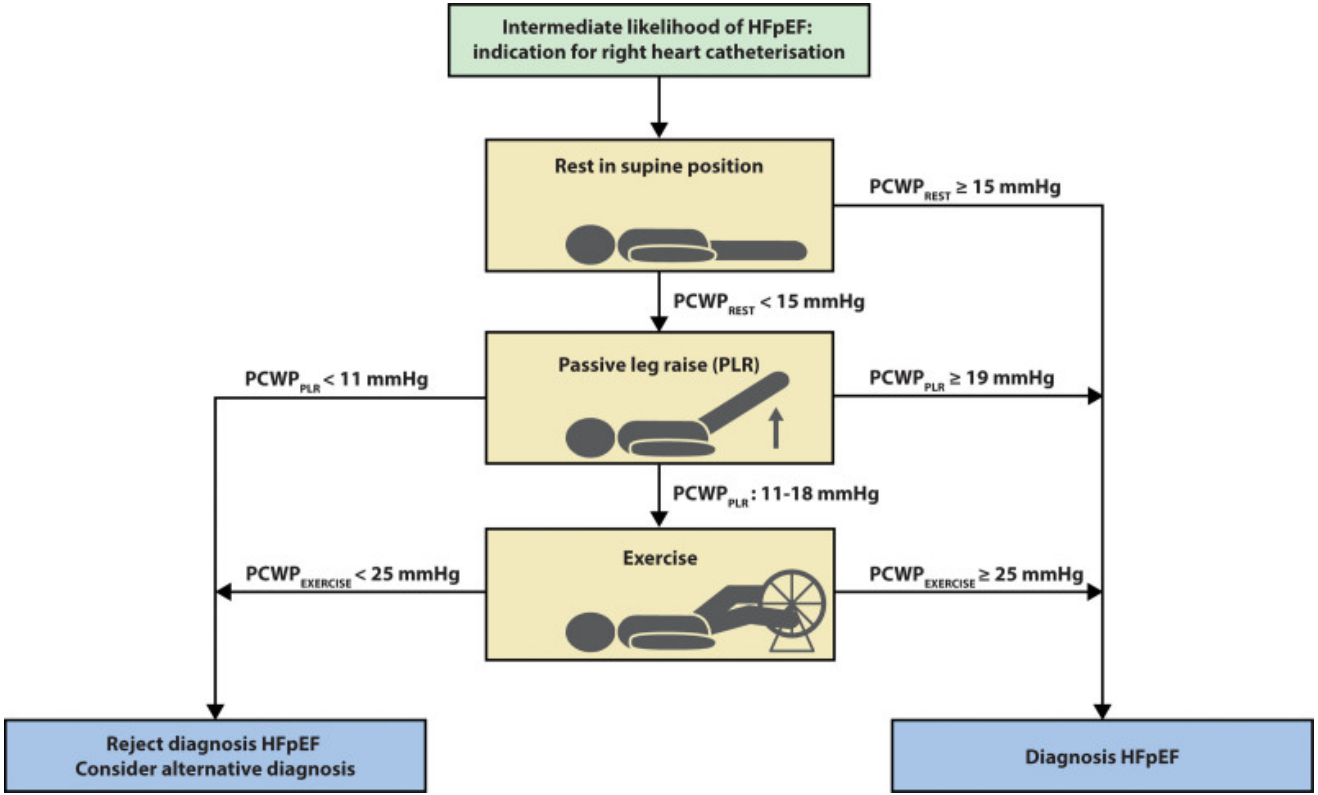
Lewis et al. Circulation 2013;128(13)



Eisman et al. Circ HF 2018

UCSF

Rule out Occult Group 2 PH: Provocative Testing

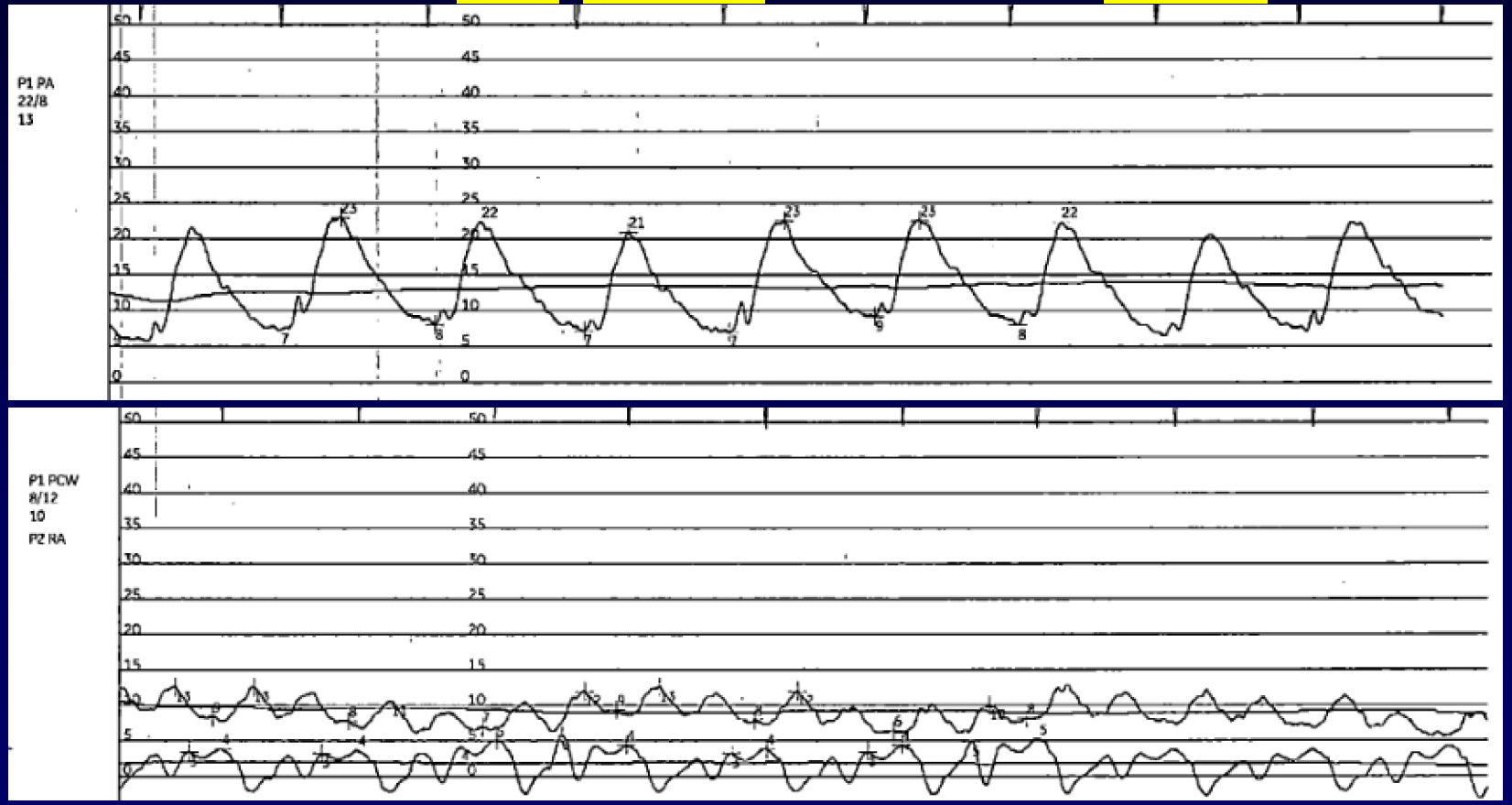


van de Bovenkamp et al. Circ Heart Fail. 2022;15:e008935.

UCSF

Rule out Occult Group 2 PH: Provocative Testing

Rest: RA 1, W 10, MPAP 13, TPG 3, CO 3.6, PVR 0.8



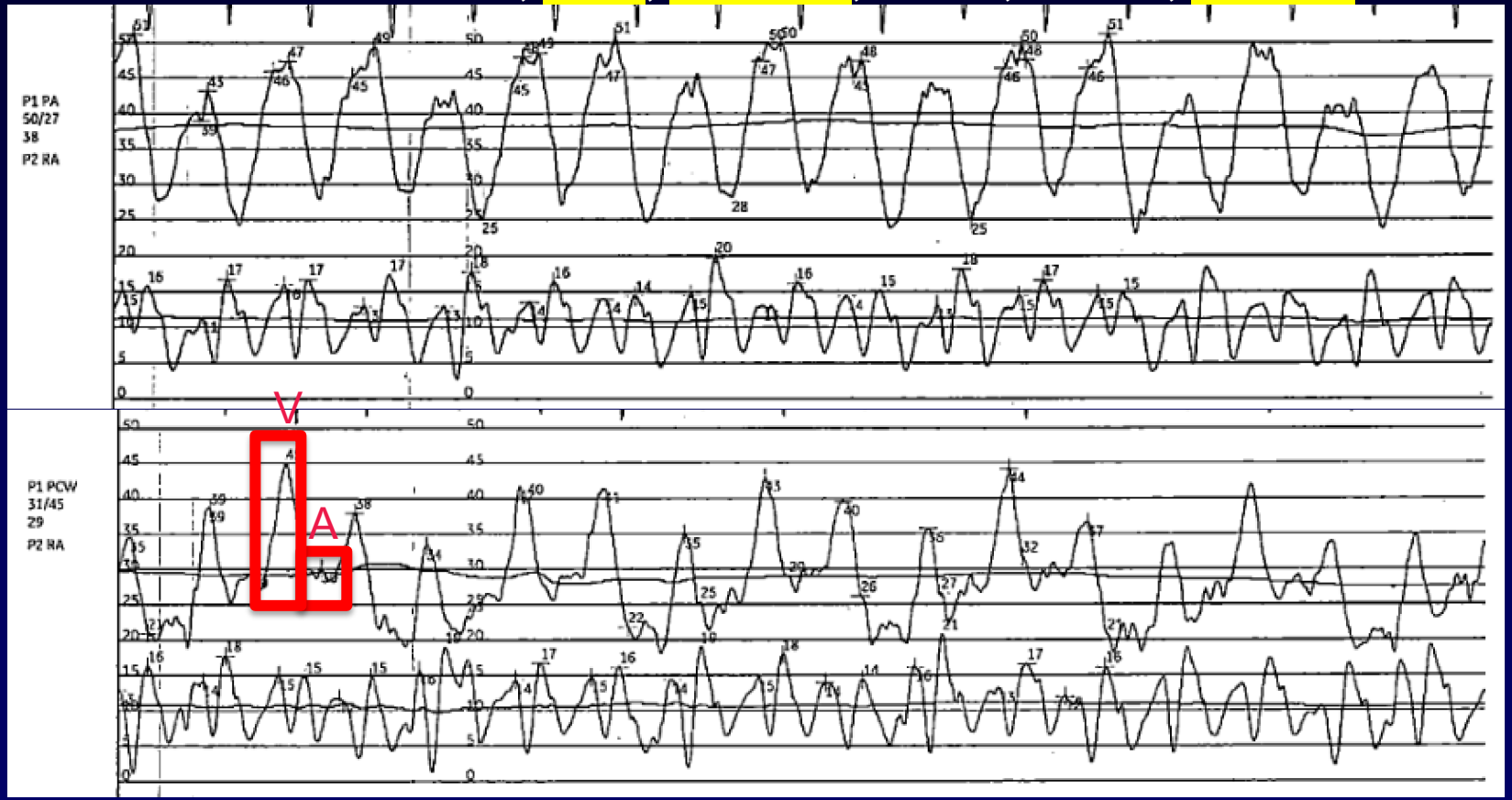
PA

PWP

RA

Rule out Occult Group 2 PH: Provocative Testing

Exercise 2 min: RA 7, W 29, MPAP 38, TPG 9, CO 5.6, PVR 1.6



Summary:

Echocardiography and right heart catheterization for the pulmonologist

- Echo: right vs left-sided findings
- Don’t forget about HFpEF! (LHD is #1 cause of PH – Group 2)
- RHC
  - Be wary of pitfalls when looking at a report (vs pressure tracings)
  - Normal PCWP may not excluded Group II PH (HFpEF)
  - Pre-test probability of HFpEF is helpful to plan invasive testing (H2FPEF score)
  - Even a leg raise can be helpful to identify occult HFpEF
  - Exercise testing can be very useful for those with intermediate pre-test probability of HFpEF

Understanding PAH-specific therapy and the treatment algorithm in Group 1 PAH

Karim El-Kersh, MD

Professor of Medicine, University of Arizona College of Medicine, Phoenix

Director of Pulmonary Hypertension Program Banner University Medical Center, and Banner University Lung Institute, Phoenix

Disclosures

- I have the following relationships with ACCME defined ineligible companies:
- **Consultant Merck, J&J, and United Therapeutics**
- I **WILL NOT** discuss off-label use and/or investigational use of any drugs or devices.

Group 1 PAH

	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR >2 WU
Isolated post-capillary PH (ipcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR ⩽2 WU
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

Group 1: PAH

- 1.1 Idiopathic
  - 1.1.1 Long-term responders to calcium channel blockers
- 1.2 Heritable[#]
- 1.3 Associated with drugs and toxins[#]
- 1.4 Associated with:
  - 1.4.1 connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 portal hypertension
  - 1.4.4 congenital heart disease
  - 1.4.5 schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn

• Kovacs G, et al. Eur Respir J. 2024 Oct 31;64(4):2401324.

Drugs and toxins associated with PAH

Definite association	Possible association
Aminorex	Alkylating agents
Benfluorex	Amphetamines
Carfilzomib	Bevacizumab
Dasatinib	Bortezomib
Dexfenfluramine	Bosutinib
Fenfluramine	Cocaine
Methamphetamines	Diazoxide
Mitomycin C[#]	Direct-acting antiviral agents against hepatitis C virus (sofosbuvir)
Toxic rapeseed oil	Indigo naturalis (Chinese herb Qing-Dai)
	Interferon-α and -β
	Leflunomide
	L-tryptophan
	Phenylpropanolamine
	Ponatinib
	Solvents (trichloroethylene)[#]
	St John's wort

- Kovacs G, et al. Eur Respir J. 2024 Oct 31;64(4):2401324.

European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk tools

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} V'_E/V'_{CO_2}	>15 mL·kg^{-1}·min^{-1} <36	11–15 mL·kg^{-1}·min^{-1} 36–44	<11 mL·kg^{-1}·min^{-1} >44
Biomarkers	BNP NT-proBNP	<50 ng·L^{-1} <300 ng·L^{-1}	50–800 ng·L^{-1} 300–1100 ng·L^{-1}	>800 ng·L^{-1} >1100 ng·L^{-1}
Imaging	Echocardiography RA area TAPSE/sPAP PE	<18 cm^2 >0.32 mm·mmHg^{-1} No	18–26 cm^2 0.19–0.32 mm·mmHg^{-1} Minimal	>26 cm^2 <0.19 mm·mmHg^{-1} Moderate or large
	cMRI RVEF SVI RVESVI	>54% >40 mL·m^{-2} <42 mL·m^{-2}	37–54% 26–40 mL·m^{-2} 42–54 mL·m^{-2}	<37% <26 mL·m^{-2} >54 mL·m^{-2}
RHC	Haemodynamics RAP CI SVI S_{vO_2}	<8 mmHg ≥2.5 L·min^{-1}·m^{-2} >38 mL·m^{-2} >65%	8–14 mmHg 2.0–2.4 L·min^{-1}·m^{-2} 31–38 mL·m^{-2} 60–65%	>14 mmHg <2.0 L·min^{-1}·m^{-2} <31 mL·m^{-2} <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 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}

ESC/ERS risk calculation

SPAHR/COMPERA 1.0

Parameters		
Low risk 1 point	Intermediate risk 2 points	High risk 3 points

Overall risk = sum of the points / n of parameters

- 1.0–1.49= Low risk
- 1.5–2.49= Intermediate risk
- ≥2.5= High risk

FPHR invasive

Low risk parameters	
WHO-FC	I–II
6MWD	>440 m
RAP	<8 mmHg
CI	≥2.5 L·min^{-1}·m^{-2}

Low risk = 4 low risk parameters

FPHR noninvasive

Low risk parameters	
WHO-FC	I–II
6MWD	>440 m
BNP/NT-proBNP	<50/300 ng·L^{-1}

Low risk = 3 low risk parameters

COMPERA 2.0

Parameters			
Low risk 1 point	Intermediate-low risk 2 points	Intermediate-high risk 3 points	High risk 4 points

Overall risk = sum of the points / n of parameters

- 1.0–1.49= Low risk
- 1.5–2.49= Intermediate-low risk
- 2.5–3.49= Intermediate-high risk
- ≥3.5= High risk

• Dardi F, et al. Eur Respir J. 2024 Oct 31;64(4):2401323.

Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) risk tools

REVEAL 2.0

	−2	−1	0	1	2	3
WHO group 1 subgroup			Other	CTD	Heritable	PoPH
Male >60 years			No		Yes	
All-cause hospitalisation ≤6 months			No	Yes		
eGFR <60 mL/min/1.73m^2 or renal insufficiency			No	Yes		
Systolic BP (mmHg)			≥110	<110		
Heart rate (bpm)			≤95	>95		
WHO-FC		I	II	III	IV	
6MWD (m)	≥440	320–440	165–320	<165		
BNP (ng·L^{-1}) or NT-proBNP (ng·L^{-1})	<50 <300		50–200 300–1100	200–800	≥800 ≥1100	
PE on echocardiogram			No	Yes		
D_{LCO} ≤40 % pred			No	Yes		
RAP >20 mmHg within 1 year			No	Yes		
PVR <5 WU		Yes	No			

Overall risk= sum of the points +6 =
- 0–6= Low risk
- 7–8= Intermediate risk
- ≥9= High risk

REVEAL Lite 2

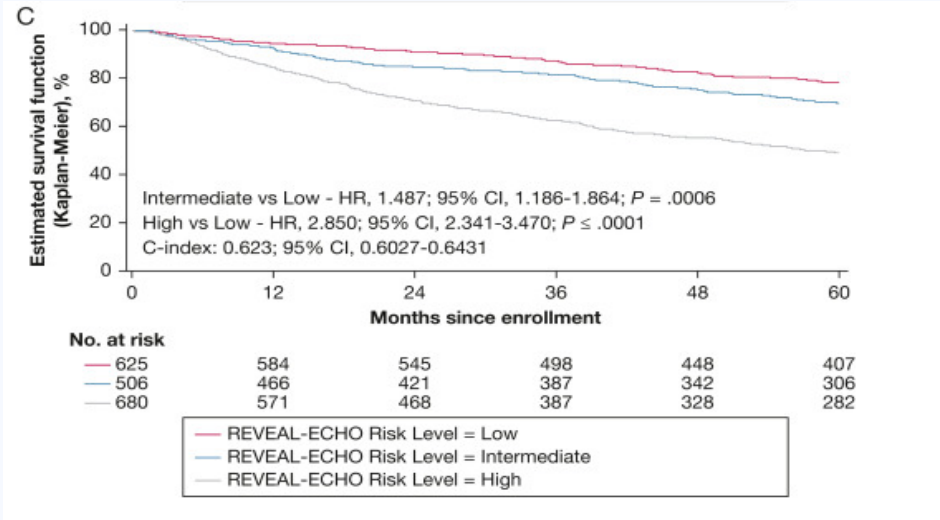
	−2	−1	0	1	2
eGFR <60 mL/min/1.73m^2 or renal insufficiency			No	Yes	
Systolic BP (mmHg)			≥110	<110	
Heart rate (bpm)			≤95	>95	
WHO-FC		I	II	III	IV
6MWD (m)	≥440	320–440	165–320	<165	
BNP (ng·L^{-1}) or NT-proBNP (ng·L^{-1})	<50 <300		50–200 300–1100	200–800	≥800 ≥1100

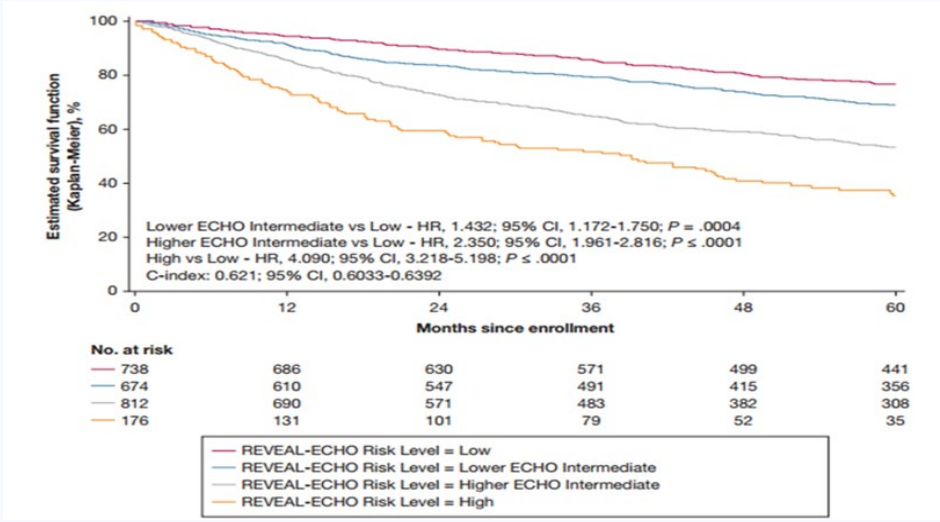
Overall risk= sum of the points +6 =
- 0–5= Low risk
- 6–7= Intermediate risk
- ≥8= High risk

• Dardi F, et al. Eur Respir J. 2024 Oct 31;64(4):2401323.

REVEAL-ECHO

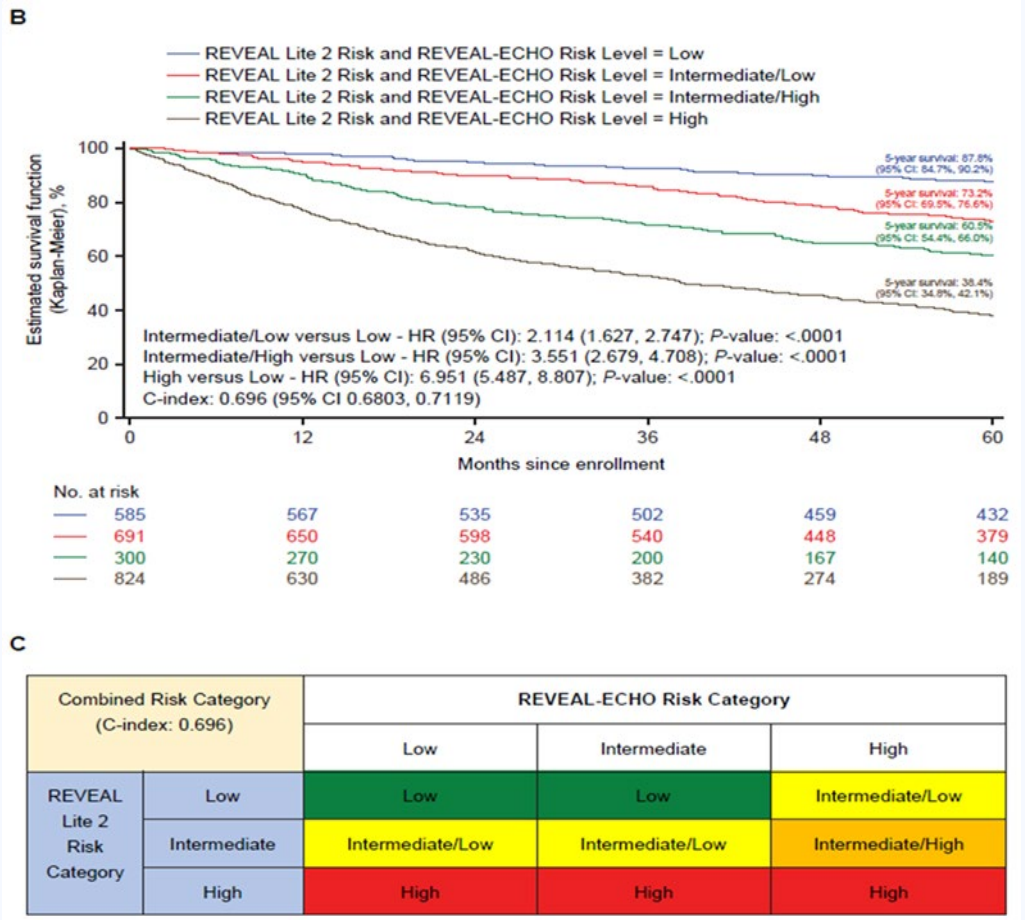
Parameter	Weighting of Each Parameter in the REVEAL-ECHO Score			
Group 1	CTD = 1	HPAH = 2	PoPH = 3	Other = 0
RV chamber enlargement	None = 0	Mild = 0	Moderate = 1	Severe = 2
RV reduced systolic function	None = 0	Mild = 0	Moderate = 1	Severe = 2
TR severity	None or trivial = 0	Mild = 0	Moderate = 1	Severe = 2
Pericardial effusion	None = 0	Mild = 1	Moderate = 2	Severe = 3
REVEAL-ECHO score				= sum of above





• El-Kersh K et al. Chest. 2023 May;163(5):1232-1244.

REVEAL-ECHO

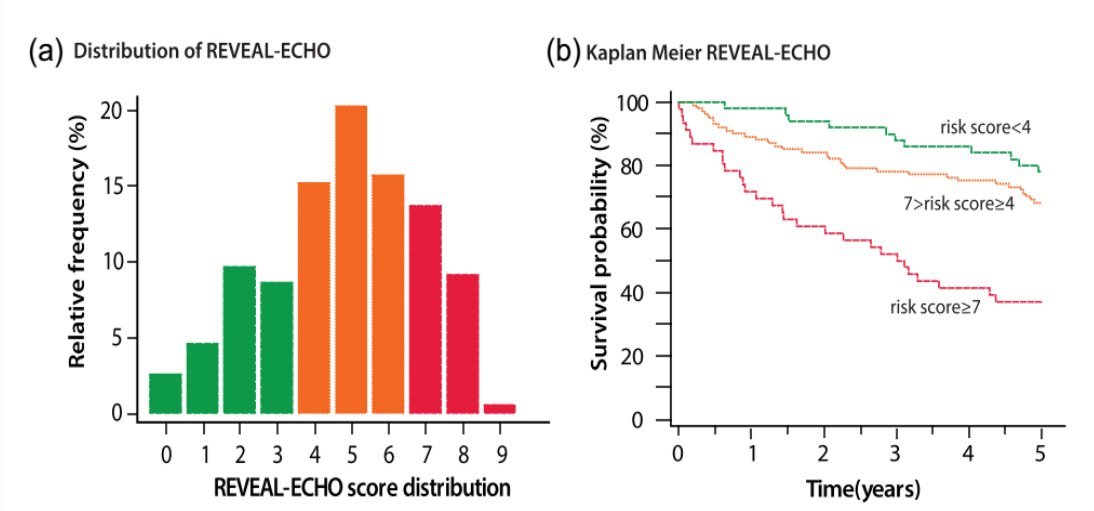


C

Combined Risk Category (C-index: 0.696)		REVEAL-ECHO Risk Category		
		Low	Intermediate	High
REVEAL Lite 2 Risk Category	Low	Low	Low	Intermediate/Low
	Intermediate	Intermediate/Low	Intermediate/Low	Intermediate/High
	High	High	High	High

TABLE 4 | Survival Probability Based on REVEAL Lite 2 and REVEAL-ECHO Risk Categories

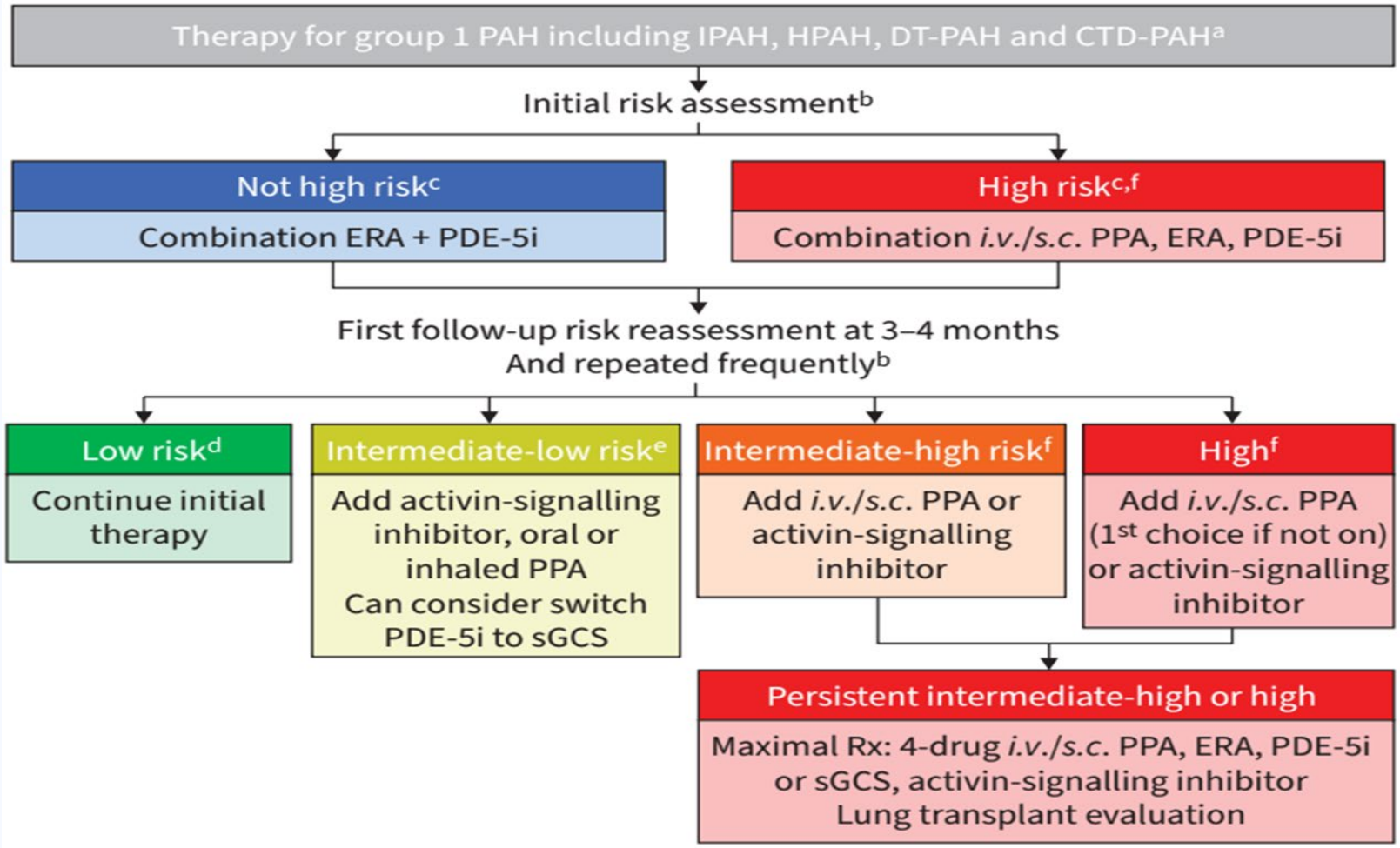
Time Since Enrollment, y	RL: Low, RE: Low (n = 355)	RL: Low, RE: Int (n = 230)	RL: Low, RE: High (n = 196)	RL: Int, RE: Low (n = 257)	RL: Int, RE: Int (n = 238)	RL: Int, RE: High (n = 300)
1	98.9 (97.0-99.6)	96.5 (93.2-98.2)	94.4 (90.1-96.8)	95.3 (91.8-97.3)	95.8 (92.3-97.7)	90.3 (86.4-93.2)
2	95.9 (93.2-97.6)	93.0 (88.9-95.7)	85.6 (79.8-89.8)	92.4 (88.4-95.1)	90.7 (86.1-93.7)	78.2 (73.0-82.5)
3	93.5 (90.3-95.7)	90.8 (86.2-93.9)	82.2 (76.0-87.0)	88.1 (83.4-91.6)	85.4 (80.1-89.3)	71.9 (66.4-76.6)
4	91.2 (87.6-93.8)	87.5 (82.4-91.2)	76.4 (69.6-81.9)	79.8 (74.0-84.4)	79.6 (73.6-84.3)	65.0 (59.2-70.2)
5	89.9 (86.1-92.7)	84.5 (78.9-88.7)	70.0 (62.7-76.2)	75.2 (68.9-80.3)	73.9 (67.4-79.2)	60.5 (54.4-66.0)



• *El-Kersh K et al. Chest. 2023 May;163(5):1232-1244.*
Celestin BE, et al. Pulm Circ. 2024 May 24;14(2):e12361.

California Thoracic Society
ATS Chapter Serving California and Arizona

Treatment Algorithm



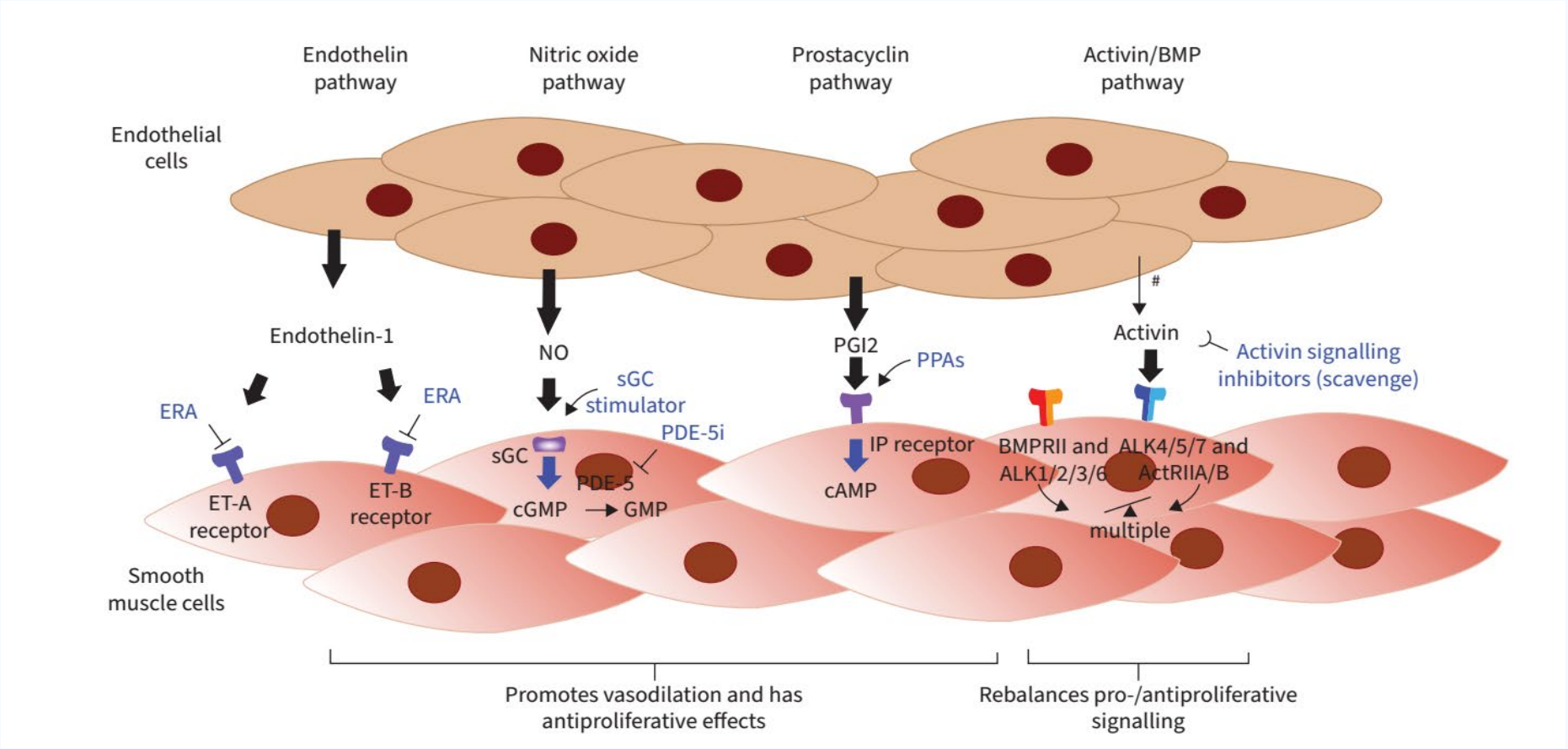
Hemodynamics, RV imaging and other measures should be used to supplement risk assessment

Initial triple therapy with an i.v./s.c. PPA may be considered in non-high risk with severe hemodynamics and/or poor RV function

Patients with confirmed group 1 PAH (phenotypically clear-cut, including mPAP ≥25 mmHg and PVR >3 WU and no significant response on acute vasoreactivity)

• Chin KM, et al. Eur Respir J. 2024 Oct 31;64(4):2401325.

PAH Therapies Pathways

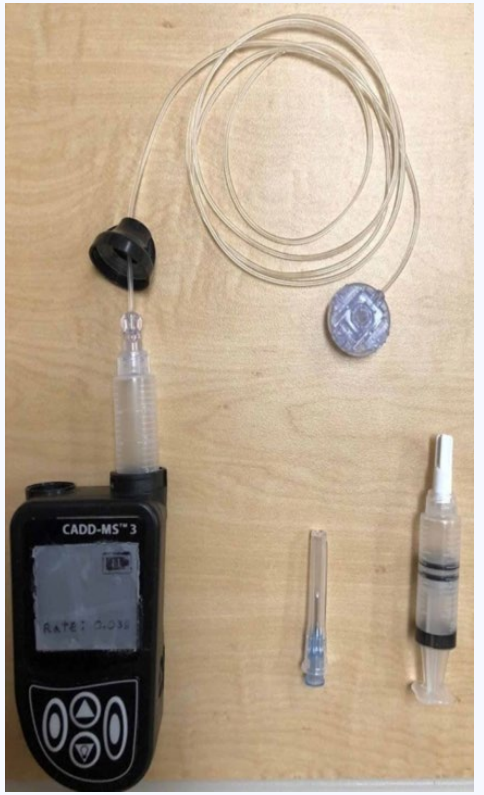


• Chin KM, et al. Eur Respir J. 2024 Oct 31;64(4):2401325.

	Medications	Common adverse reactions	Other information
Oral medications			
PDE-5i	Sildenafil Tadalafil	Headache Flushing, Dyspepsia, Epistaxis	Rare loss of vision or hearing, Avoid with nitrates, riociguat
Guanylyl cyclase stimulators	Riociguat	Headache, Dyspepsia, Dizziness, Hypotension	Avoid in pregnancy# , avoid with nitrates, PDE-5i
Endothelin-1 receptor antagonists	Ambrisentan Bosentan Macitentan	Peripheral oedema, Nasal congestion, Anaemia	Avoid in pregnancy# , monitor Hgb (all), LFTs (monthly for bosentan, as clinically indicated for others)
Prostacyclin receptor agonists	Selexipag	Prostanoid-type AEs	
Prostanoids, p.o	Treprostinil		
Inhaled medications			
Prostanoids, inhaled	Iloprost, Treprostinil	Cough, Prostanoid-type AEs	
Parenteral medications			
Prostanoids, parenteral	Epoprostenol (i.v.), Treprostinil (i.v., s.c.)	Prostanoid-type AE	Sudden discontinuation can be life-threatening
Activin-signaling inhibitor	Sotatercept (s.c.)	Headache, Diarrhea, Nosebleed, Bleeding events, Telangiectasia	Avoid in pregnancy ; potential reduced fertility (animal studies); monitor for thrombocytopenia and increased Hgb for first five doses and periodically

Parenteral Therapy Tips (Epoprostenol/ Treprostinil)

- A dedicated line for infusion (<u>don't flush, or withdraw blood</u>)
- Specialty pharmacy is available 24/7
- Examine the catheter or SQ site.
- If catheter is leaking or broken, switch to a peripheral line.
- Redness at the infusion site (especially if it is a new site) is normal.
- Line priming (Groshong catheter, PICC line, central line...) to avoid interruption of infusion (new line or concentration change)
- Epoprostenol half-life is about 4 minutes & treprostinil half-life is about 4 hours



Parenteral Therapy Tips (Sotatercept)

- Subcutaneous injection once every 3 weeks according to patient weight.
- The starting dose is 0.3 mg/kg.
- Obtain Hgb and platelet count prior to the first dose.
- Do not initiate treatment if platelet count is <50,000/mm3.
- Check Hgb and platelet count before each dose for the first 5 doses *(or longer if values are unstable)*
- Delay treatment for at least 3 weeks if any of the following occur:

1. Hgb increases >2.0 g/dL from the previous dose and is above ULN.

2. Hgb increases >4.0 g/dL from baseline.

3. Hgb increases >2.0 g/dL above ULN.

4. Platelet count decreases to <50,000/mm3

- Recheck Hgb and platelet count before reinitiating treatment.
- For treatment delays lasting >9 weeks, restart treatment at 0.3 mg/kg, and escalate to 0.7 mg/kg after verifying acceptable Hgb and platelet count.

PAH subgroups	Notes
CTD-PAH	• Some limitation of risk assessment tools in CTD-PAH specifically SSc-PAH • Caution with initiation of medications that may increase bleeding risk, such as sotatercept, in CTD patients who are predisposed to GI bleeding due to vascular anomalies • Digital contractures and impaired manual dexterity may impact decisions about parenteral therapies. • Other forms of PH such PH-ILD, CTEPH in SLE *(antiphospholipid syndrome)*
CHD-PAH with unrepaired defects	• Shunt closure is contraindicated in Eisenmenger syndrome • In ASD and a PVR >5 WU despite PAH treatment, shunt closure is not recommended
Drug &toxin PAH	• Partial or full reversal of PAH has been reported after discontinuation of some agents, including dasatinib and interferon • For stimulant-associated PAH spontaneous remission is not typical • Referral for substance use treatment
HIV	• Drug-drug interactions particularly with protease inhibitors and sildenafil/tadalafil.
PoPH	• Distinguish true PoPH from other forms of PH that can occur in liver disease • PORTICO (12 weeks of macitentan 10 mg versus placebo resulted in 35% reduction in PVR with macitentan) • Hemodynamic targets prior to Liver Tx listing by ILTS (mPAP <35 mmHg and a PVR <5 WU, or a mPAP 35–45 mmHg with a PVR <3 WU)
PVOD/PCH	• Life-threatening pulmonary edema may occur with PAH therapy • Lung Tx is the preferred definitive treatment for eligible patients

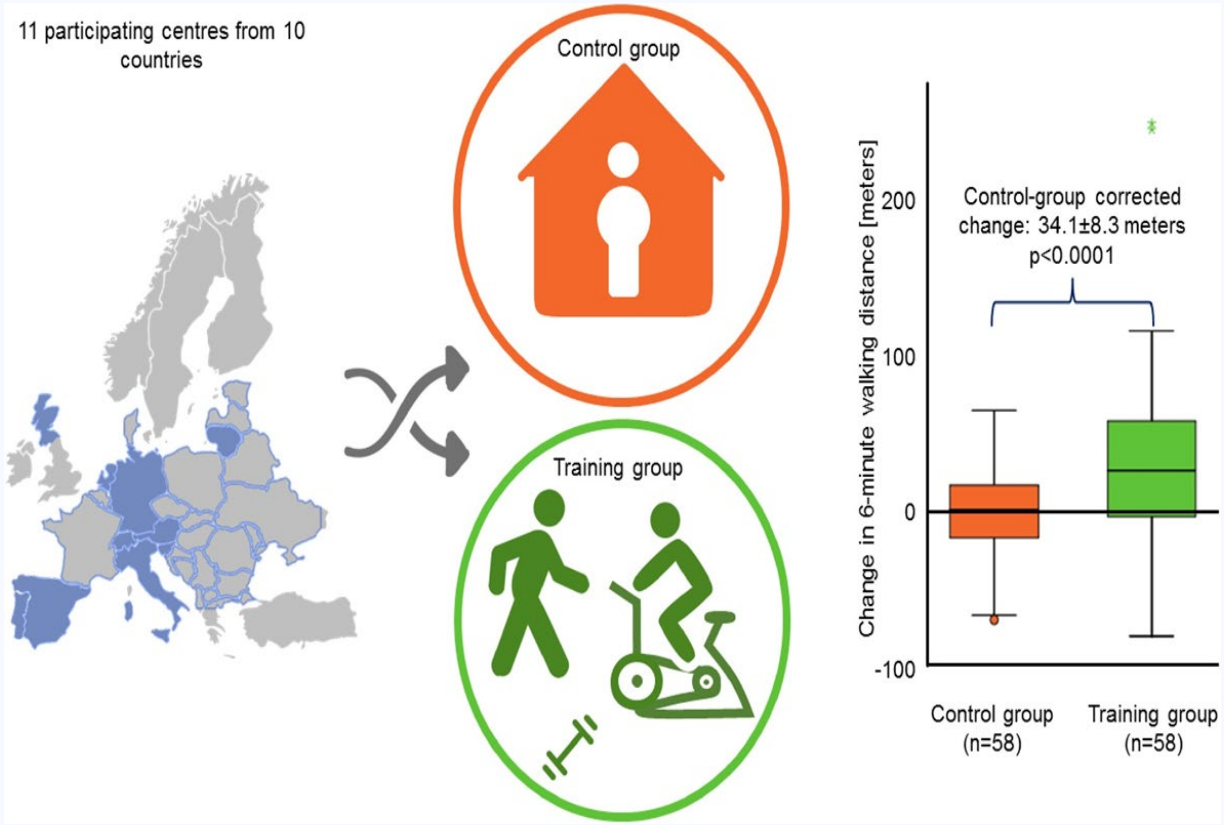
Recommended Supportive Measures

Supervised exercise training
Psychological support
Immunisation against SARS-CoV-2, influenza, *Streptococcus pneumoniae* and consider vaccination against RSV
Diuretic treatment in patients with fluid retention
Continuous LTOT when arterial blood oxygen pressure is consistently <8 kPa (60 mmHg)
Correction of iron status in patients with iron-deficiency anaemia
Advise against pregnancy
Clear contraceptive advice
Pre-transplant counselling

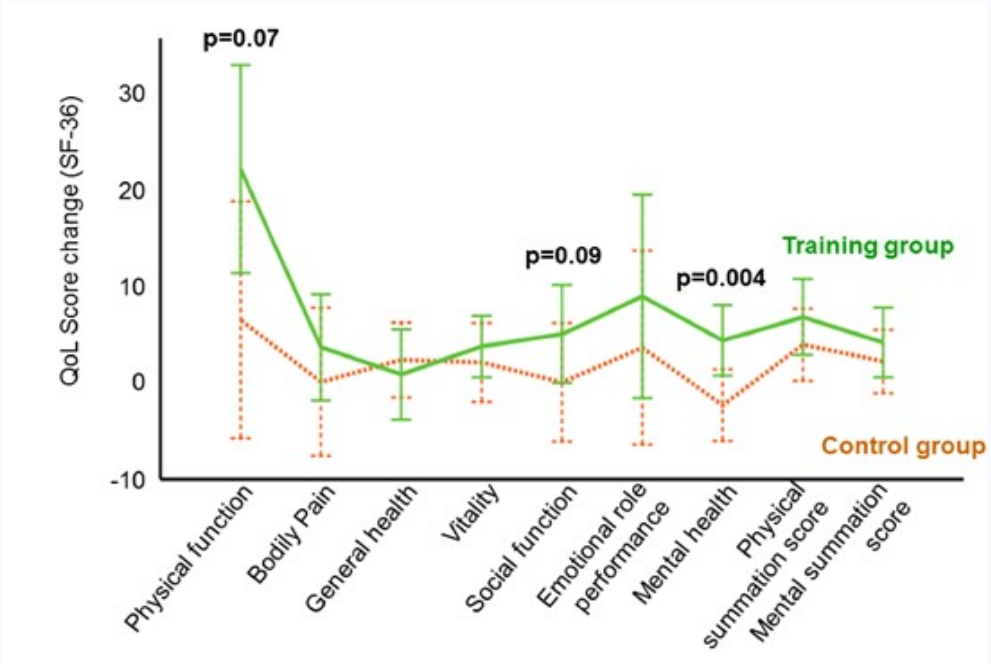
• Chin KM, et al. Eur Respir J. 2024 Oct 31;64(4):2401325.

Rehabilitation and Exercise

Patients with chronic pulmonary hypertension (n=129)
(84% PAH, 16% CTEPH; 53.7±13.0 years, mPAP 56.5±14.7 mmHg,
CO 5.2±1.5 l/min, 6MWD 441±119 metres)
Randomisation into training (n=68) and control group (n=61)



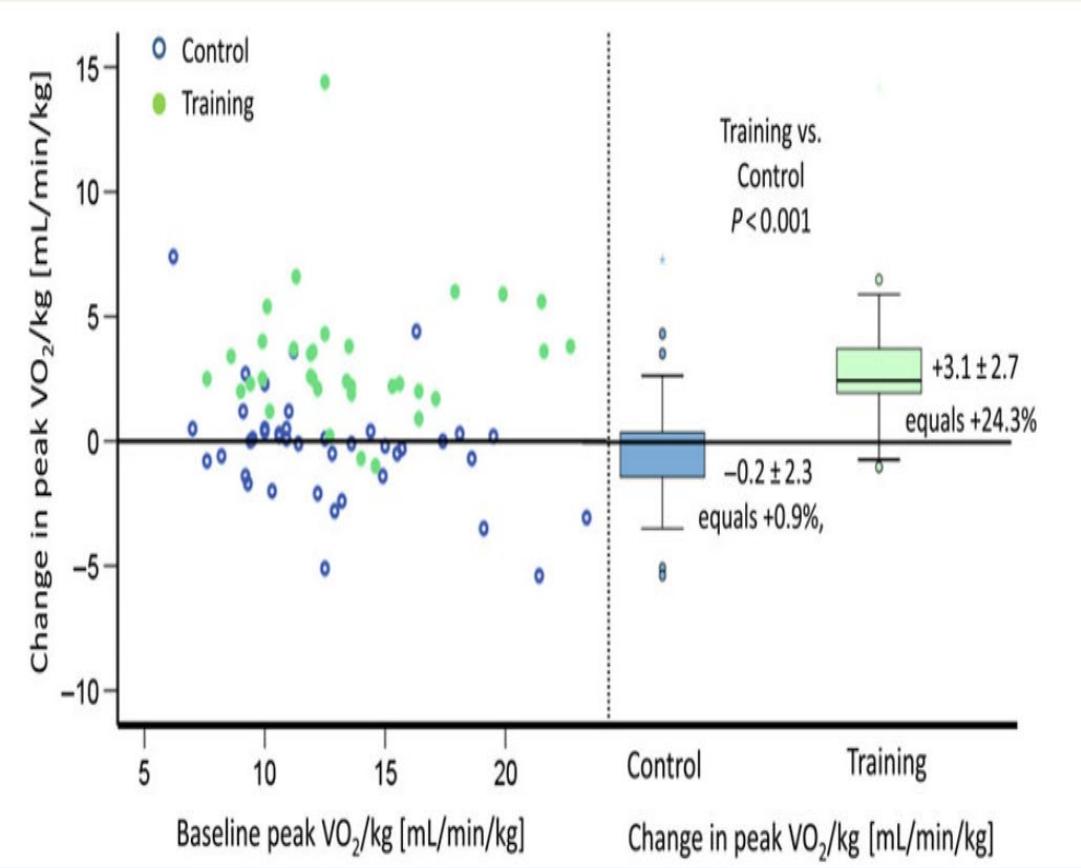
"Patients with PAH should be treated with the best standard of pharmacological treatment and be in a stable clinical condition before embarking on a supervised rehabilitation programme."



• Ekkehard Grünig, et al. *Eur Heart J*, Volume 42, Issue 23, 14 June 2021, Pages 2284–2295

California Thoracic Society
ATS Chapter Serving California and Arizona

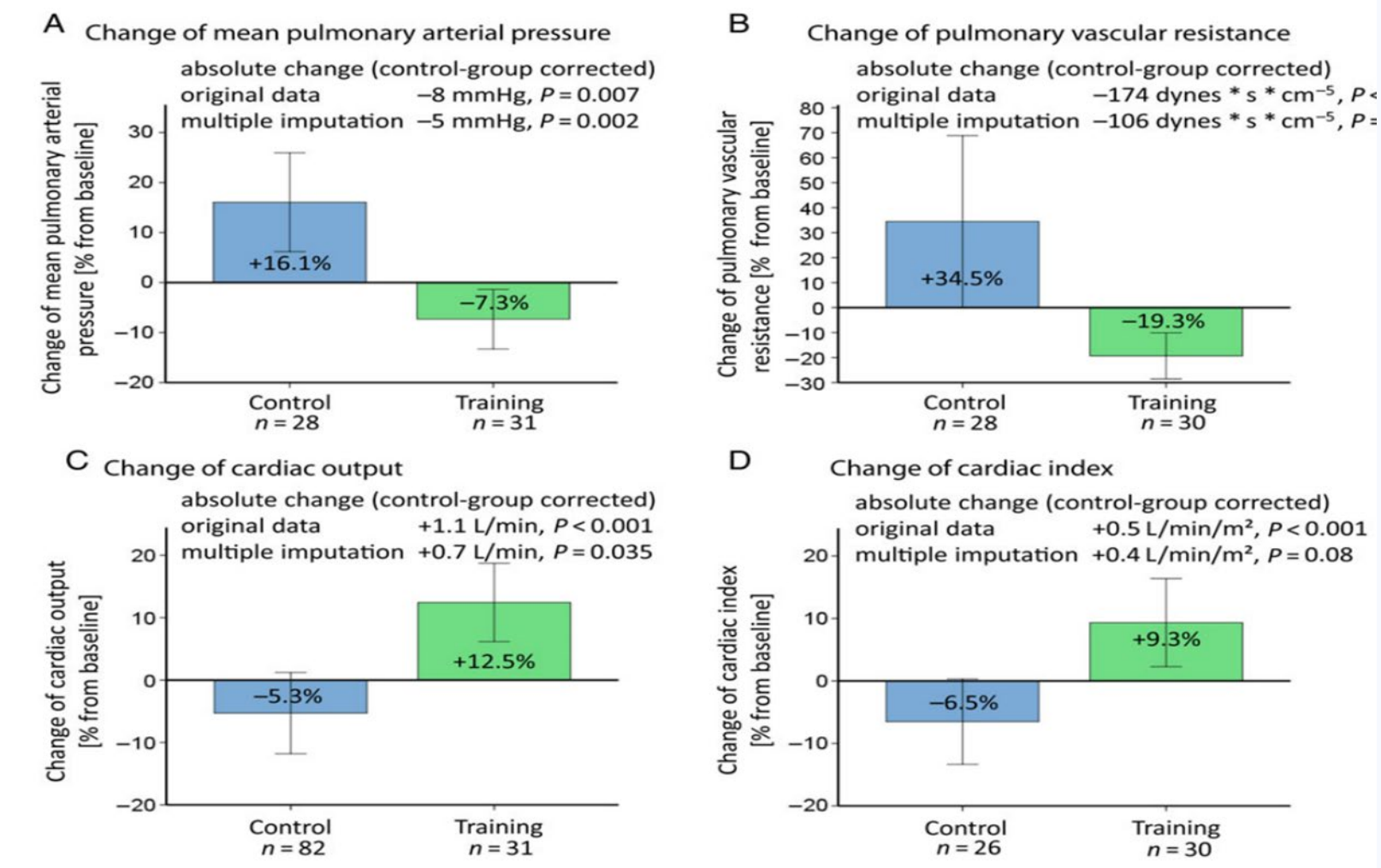
Exercise Training Effect on Peak O2 Consumption and Hemodynamics in PAH and Inoperable CTEPH



Baseline characteristics	Control	Training
Patients, *n*	41	46
Gender, male/female	20/21	20/26
Age (years)	57 ± 15	55 ± 15
Height (cm)	171 ± 8	170 ± 9
Weight (kg)	79 ± 18	75 ± 18
WHO functional class, no. (%) baseline		
II	6 (15%)	8 (18.2%)
III	30 (75%)	36 (81.8%)
IV	4 (10%)	0 (0%)
Diagnosis		
Pulmonary arterial hypertension	26 (63.4%)	35 (76.1%)
CTEPH	15 (36.5%)	11 (23.9%)
NT-proBNP (pg/mL)		
Baseline	1114 ± 1386	1163 ± 2520
Right heart catheterization		
Mean pulmonary arterial pressure (mmHg)	37.6 ± 11.8	41.0 ± 11.7
Pulmonary vascular resistance (dyn × s /cm^5)	512 ± 338	540 ± 267
Central venous pressure (mmHg)	7.1 ± 4.7	7.5 ± 3.7
Pulmonary arterial oxygen saturation (%)	64.3 ± 9.4	64.7 ± 9.9
Pulmonary arterial wedge pressure (mmHg)	9.4 ± 3.8	9.4 ± 3.5
Cardiac index (L/min/m^2)	2.69 ± 0.89	2.68 ± 0.73
PAH-targeted medication		
Endothelin receptor antagonists	29 (70.7%)	33 (71.7%)
Phosphodiesterase-5-inhibitors	30 (73.2%)	31 (67.4%)
Prostanoids inhaled	6 (14.6%)	3 (6.5%)
Prostanoids per os	0 (0%)	1 (2.2%)
Prostanoids intravenous	0 (0%)	0 (0%)
Calcium channel blockers	3 (7.3%)	5 (10.9%)
Imatinib	1 (2.4%)	0 (0%)
Soluble guanylate cyclase-stimulator	3 (7.3%)	6 (13%)
Combination therapy		
Monotherapy	14 (35%)	13 (33.3%)
Dual therapy	22 (55%)	20 (51.3%)
Triple therapy	4 (10%)	6 (15.4%)
Oxygen therapy, yes/no	20/21	17/25

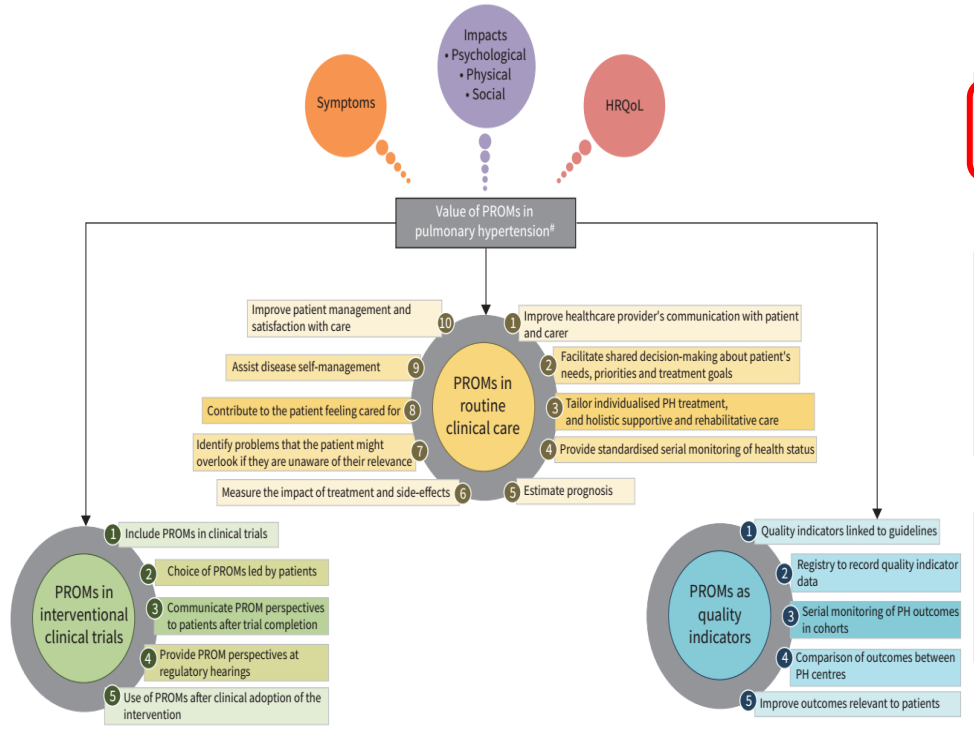
- Ehlken N, et al. Eur Heart J. 2016 Jan 1;37(1):35-44.

Exercise Training Effect on Peak O2 Consumption and Hemodynamics in PAH and Inoperable CTEPH



• Ehlken N, et al. Eur Heart J. 2016 Jan 1;37(1):35-44.

Patient-reported Outcome Measures



PROM	Diseases assessed	Domains assessed	Correlates with	Scale/ scoring	Questions n	Approximate completion time (min)	Time period assessed	Languages available	App or online tool	MCID (points)
CAMPHOR	PAH CTEPH	Symptoms Activity HRQoL	6MWD, FC, Borg dyspnoea score, clinical worsening	Yes/no and 3-point Likert	65	10	Same day	23	No	HRQoL 3 Symptoms 4 Activities 3–4
EmPHasis-10	PAH CTEPH	HRQoL	6MWD, FC, BNP, PVR, REVEAL risk score, survival	6-point semantic differential	10	2–3	At time of assessment	25	Yes	6–8
Living with PH	PAH	Physical Emotional	6MWD, FC	6-point Likert	21	5–10	1 week	English only	No	Overall 7 Subsections 3
PAH-SYMPACT	PAH CTEPH	Cardiopulmonary symptoms Cardiovascular symptoms Physical impacts Cognitive/ emotional impacts	6MWD, FC, REVEAL 2.0 risk score, D_{LCO}, survival	5-point Likert	23	5–7	24 h for symptoms 7 days for impacts	22 for paper version, 33 for electronic version	Yes (research only)	Not available
PAHSIS	PAH	Symptoms	SF-36 scores	11-point Likert	17	<5	1 month	English only	No	Not available
EQ-5D	Generic	Mobility Self-care Pain Anxiety/depression Activity	Not available for PAH	Visual analogue	5	2–5	Same day	208	Yes	Not available
SF-36	Generic	Physical functioning Physical limitations Pain General health Energy/vitality Social functioning Emotional limitations Mental health	6MWD, FC, survival	Variable	36	8–10	4 weeks	193	Yes	Not available

- Ford HJ, et al. Eur Respir J. 2024 Oct 31;64(4):2401129.

Social Determinants of Health

10-item SDoH screener ǂ

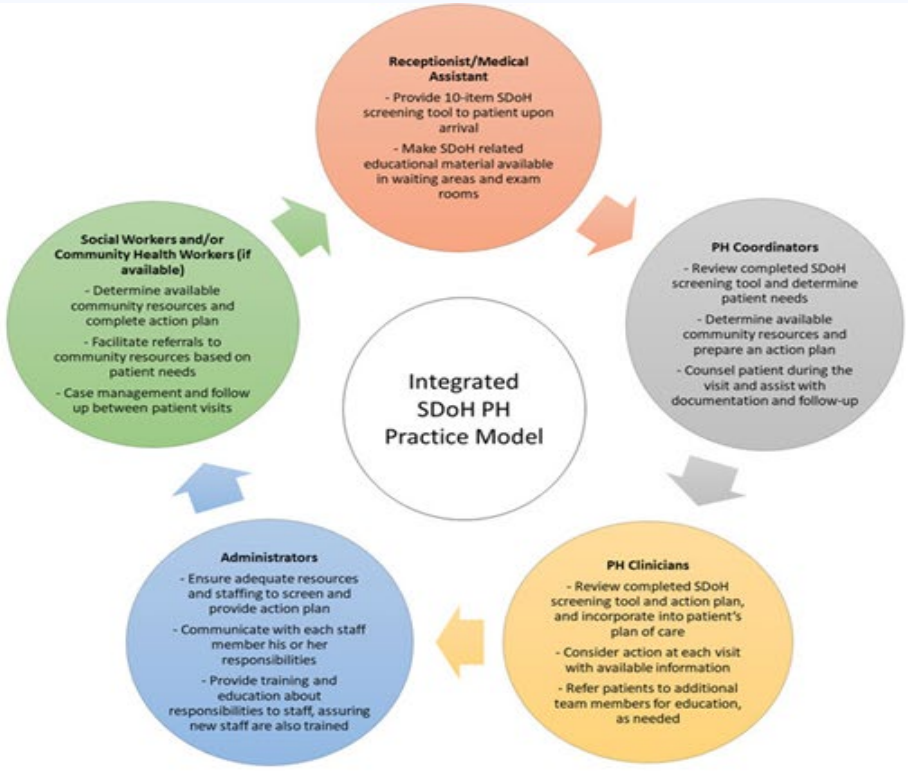
		YES / NO
	Are you worried that in the next 2 months, **you may not have a safe or stable place to live?** (eviction, being kicked out, homelessness)	Y N
	Are you worried that the **place you are living now is making you sick?** (has mold, bugs/rodents, water leaks, not enough heat)	Y N
	In the last 12 months, did you worry that **your food could run out before you got money to buy more?**	Y N
	In the last 3 months, has the **electric, gas, oil or water company threatened to shut off services to your home?**	Y N
	In the last 3 months, has **lack of transportation kept you from medical appointments or getting your medications?**	Y N
	In the last 3 months, did you have to **skip buying medications or going to doctor's appointments to save money?**	Y N
	Do you **need help getting child care or care for an elderly or sick adult?**	Y N
	Do you **need legal help?** (child/family services, immigration, housing discrimination, domestic issues, etc.)	Y N
	Are you **finding it so hard to get along with a partner, spouse, or family members that it is causing you stress?**	Y N
	Does anyone in your life **hurt you, threaten you, frighten you or make you feel unsafe?**	Y N

Do you want help? Y N

Phone Number: _____

Best time to Call: _____

ǂ Reproduced with permission from Montefiore Health System. This screening tool is a derivative of a recommended screening tool by Health Leads (https://healthleadsusa.org/) licensed under a Creative Commons Attribution-ShareAlike 4.0 International License (https://creativecommons.org/licenses/by-sa/4.0/) and was adapted by Montefiore Health System's Office of Community and Population Health."



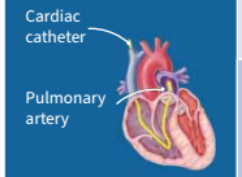
Content adapted from American Academy of Family Physicians. Social Determinants of Health – Guide to Social Needs Screening. Accessed at https://www.aafp.org/dam/AAFP/documents/patient_care/everyone_project/hops19-physician-guide-sdoh.pdf [April 30, 2022]

PH=Pulmonary Hypertension; SDoH = Social Determinants of Health

• Nadipelli VR, et al. Pulm Circ. 2022 Jul 1;12(3):e12111

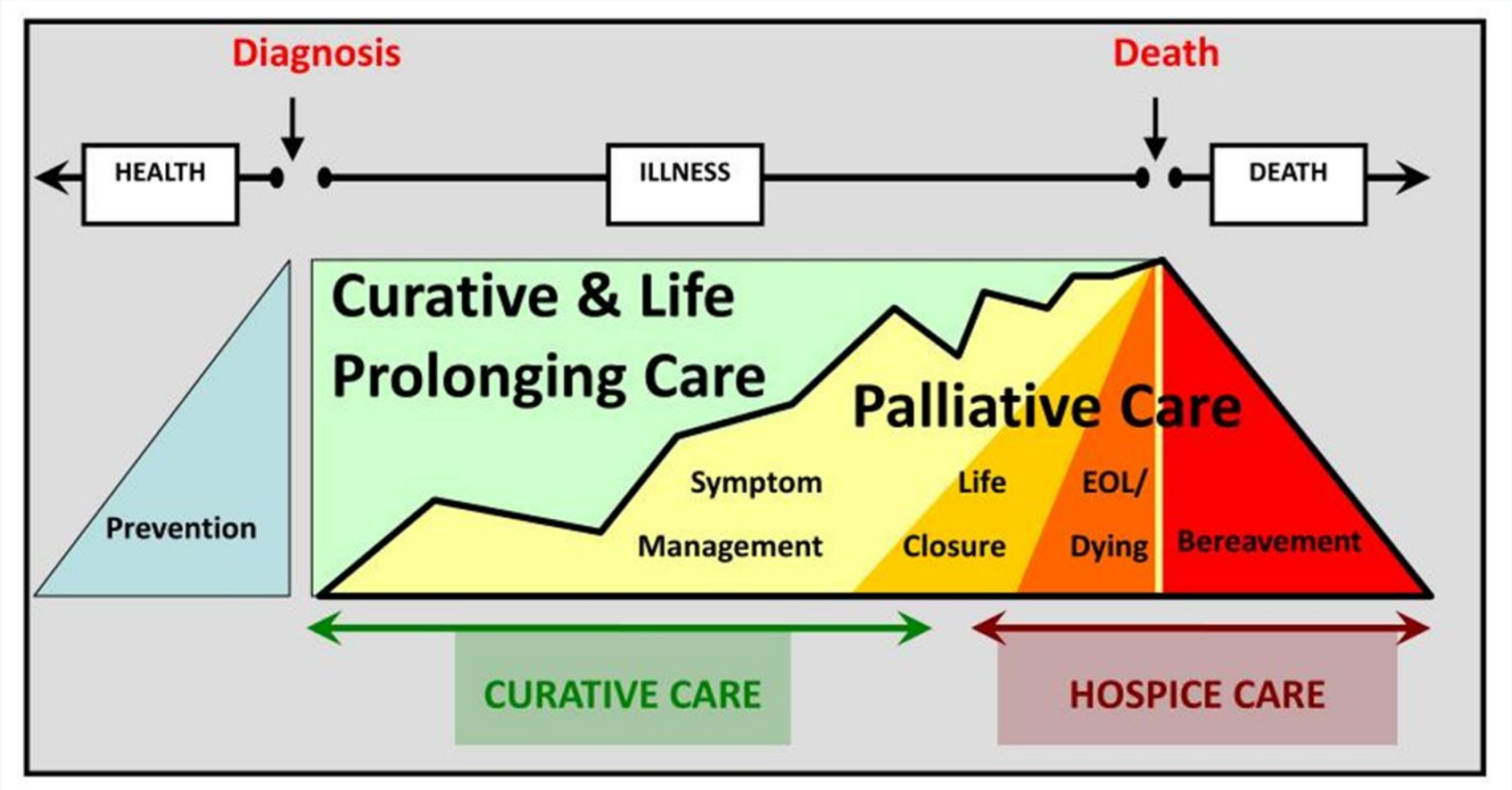
Treatment Goals

- Goals should be personalized, considering subtype, severity, age, side effects, patient preferences, and quality of life.
- A low mortality risk is a valid treatment goal, assessed with a multiparametric risk tool.
- However, achieving a low 1-year mortality risk does not eliminate the risk of clinical deterioration over the medium to long term, especially if low-risk criteria for WHO-FC, 6MWD, and BNP/NT-proBNP are not met (using ESC/ERS 4 strata) or if a REVEAL 2.0 risk score <5/REVEAL Lite 2 risk score <4 is not reached.

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

• Dardi F, et al. Eur Respir J. 2024 Oct 31;64(4):2401323.

Palliative Care



• https://caseyscircle.org/palliative-care/

Debate: The hemodynamic definition of PAH should be 2 wood units

Jeffrey S Sager, MD

Adjunct Clinical Associate Professor of Medicine, USC

Disclosures:

Research grants:

Merck, Johnson and Johnson, United Therapeutics, Bayer Pharmaceuticals, Gossamer Bio, Pliant Therapeutics, Roivant Sciences

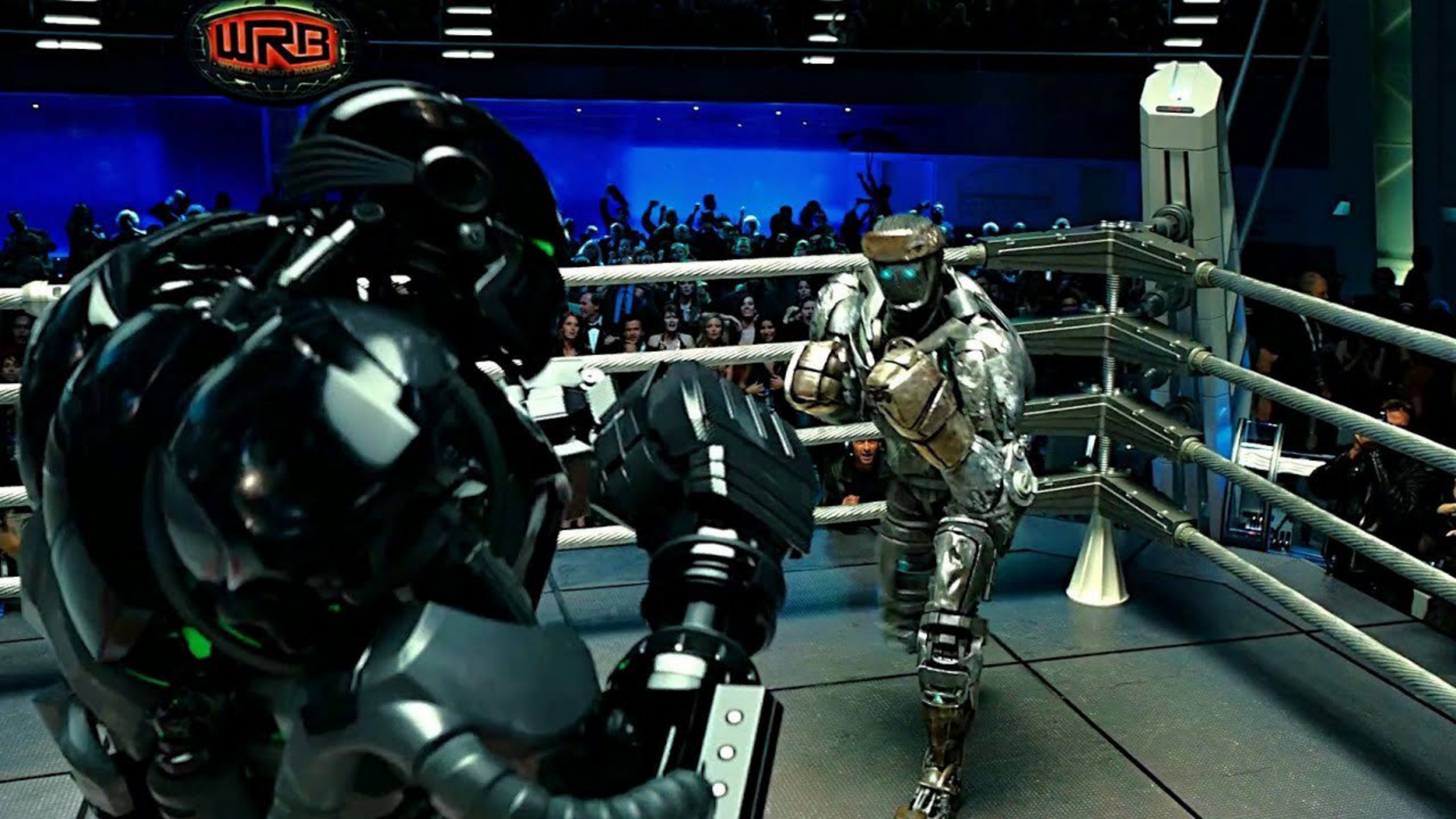
Consulting/Speaking/Advisory boards:

Merck, Johnson and Johnson, Bayer Pharmaceuticals

I **WILL NOT** discuss off-label use and/or investigational use of any drugs or devices.

VS

VS


WRB

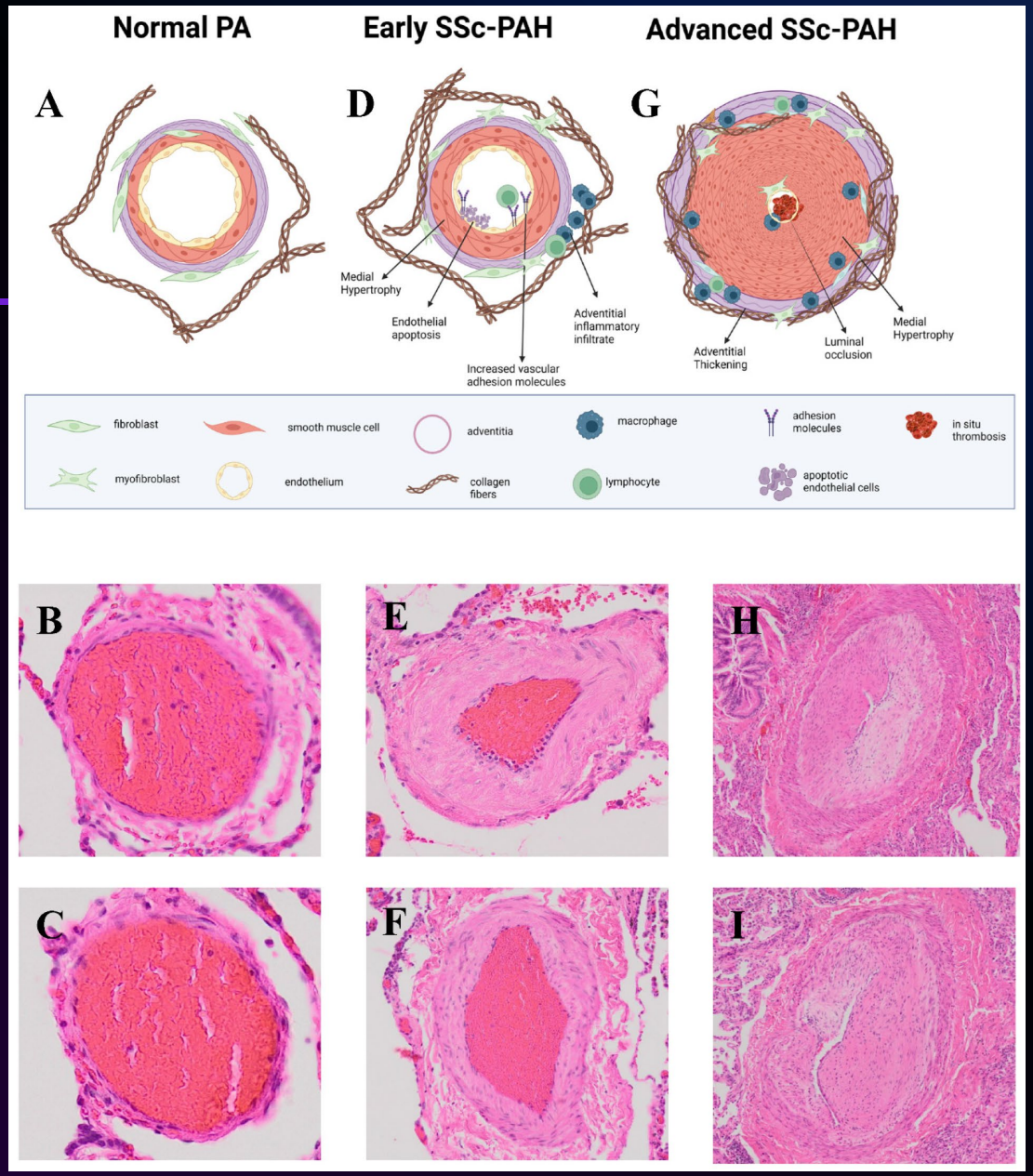
OPENING ARGUMENT

- Pulmonary arterial hypertension is a progressive disease with significant morbidity and mortality.
- Lowering the PVR diagnostic threshold from **≥3 WU to ≥2 WU** allows for earlier detection, earlier intervention, and potentially better patient outcomes.
- Emerging data suggest that even mild elevations in pulmonary vascular resistance (PVR) are associated with worse prognosis and that waiting for the traditional **3 WU** cutoff may delay necessary treatment.

Maron BA, et al. (2022). Eur Heart J. 43(9):943-955

EARLIER DETECTION=BETTER OUTCOMES

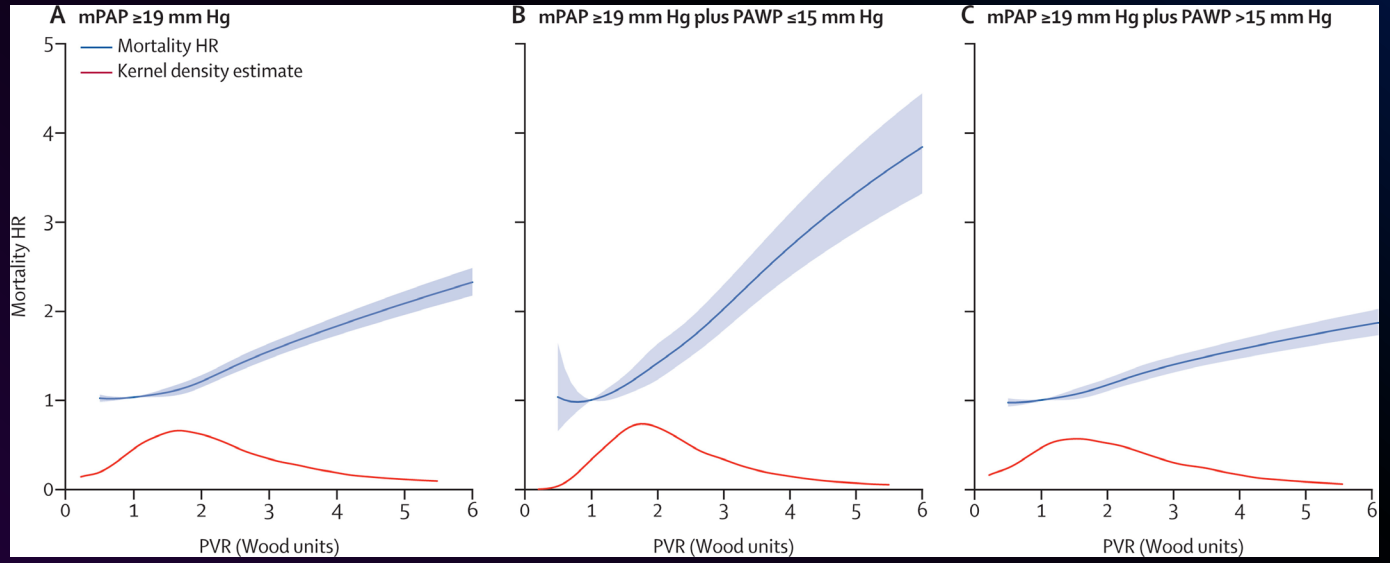
- PAH is a disease with a long preclinical phase where vascular remodeling is already occurring at PVR levels below 3 WU.
- Studies show that patients with **PVR between 2-3 WU** already have subclinical disease, and early treatment could slow progression.



Bahi, M et al Int. J. Mol. Sci. 2024, 25(9), 4728

PROGNOSTIC EVIDENCE SUPPORTS A LOWER THRESHOLD

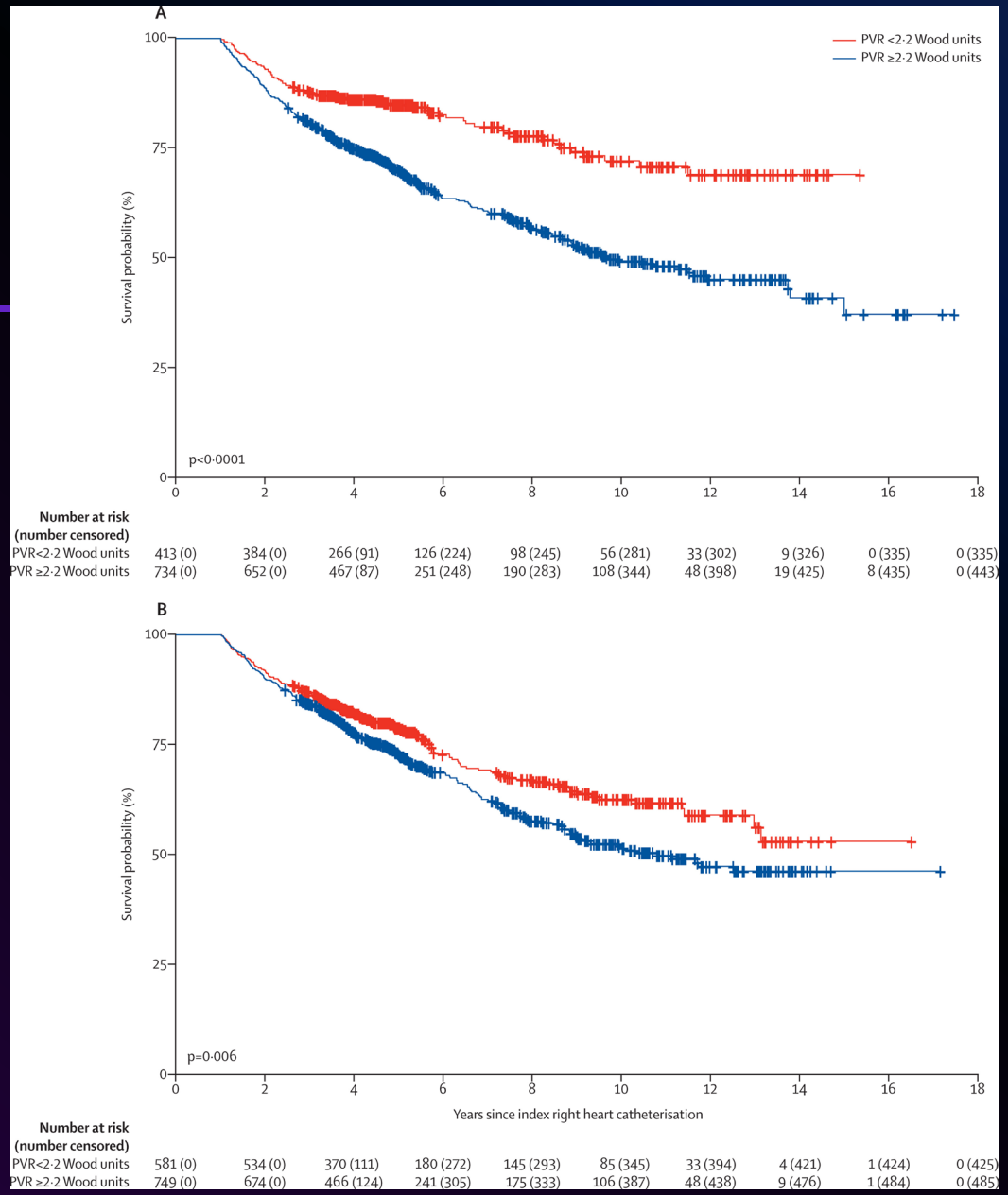
Data from a large retrospective study in VA patients demonstrate that patients with PVR 2-3 WU have worse survival than those with normal PVR (<2 WU).



Maron, Bradley et al, Circulation. 2016;133:1240-1248

LOWER PVR AND SURVIVAL

Even mild elevations in PVR correlate with increased mortality, RV dysfunction, and symptom burden, reinforcing the need for earlier intervention.

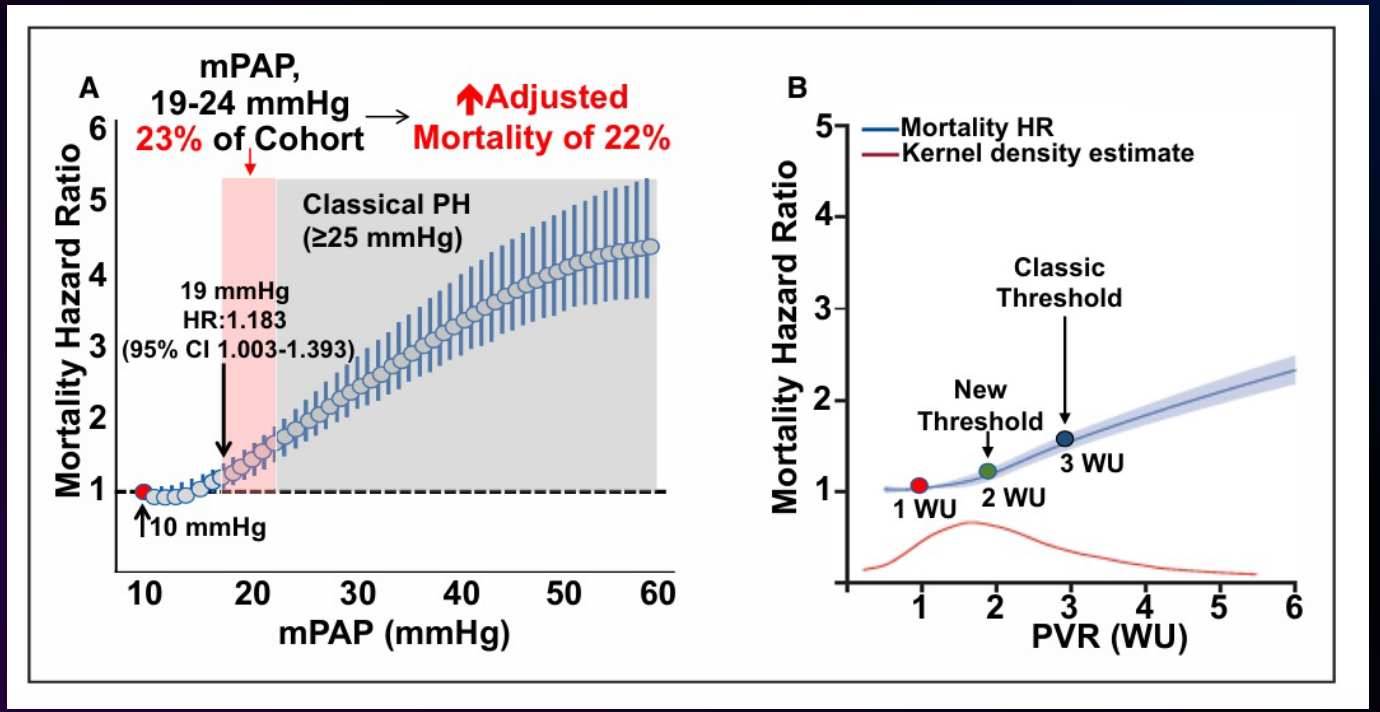


Maron, Bradley et al, Circulation. 2016;133:1240–1248

THE RELATIONSHIP BETWEEN PVR AND ALL-CAUSE MORTALITY

- A national cohort of patients referred for RHC showed significant and continuous increase in mortality beginning at mPAP of 20 mm Hg.

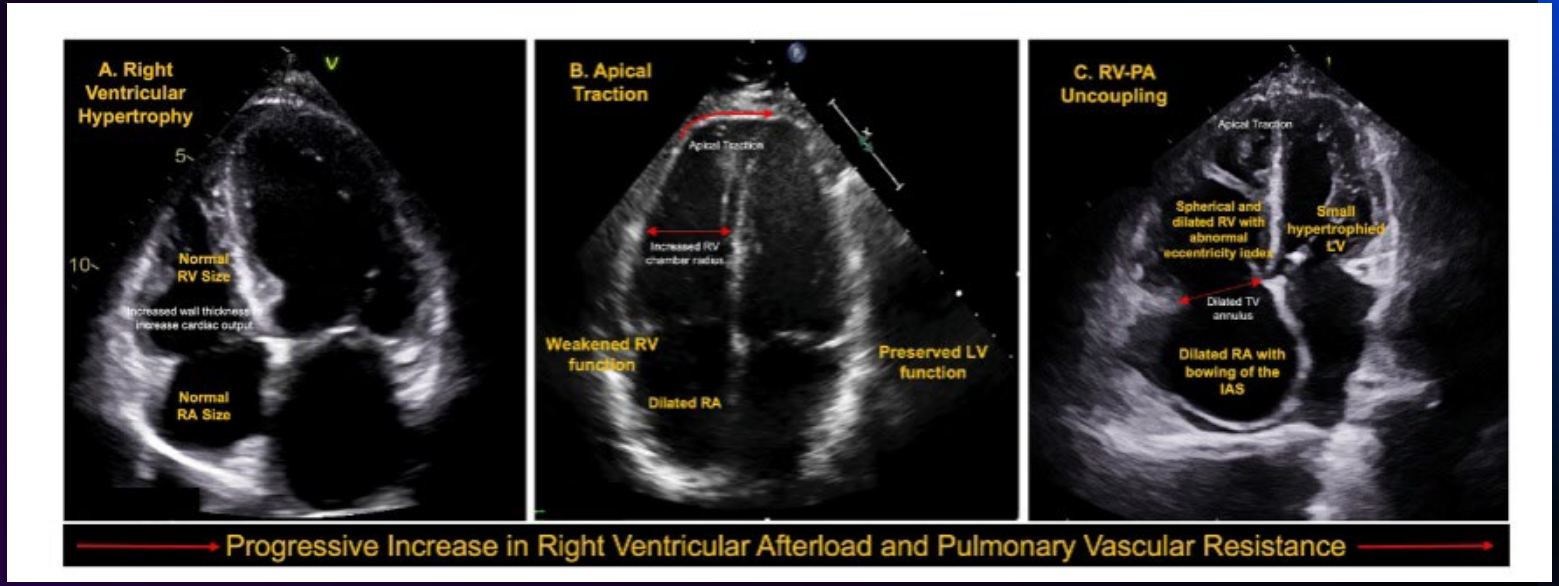
  Among patients with elevated mPAP, a PVR of >2.0 WU was associated with a significant and continuous increase in mortality



Maron, Bradley J Am Heart Assoc. 2023;12:e029024

RV DYSFUNCTION BEGINS EARLY

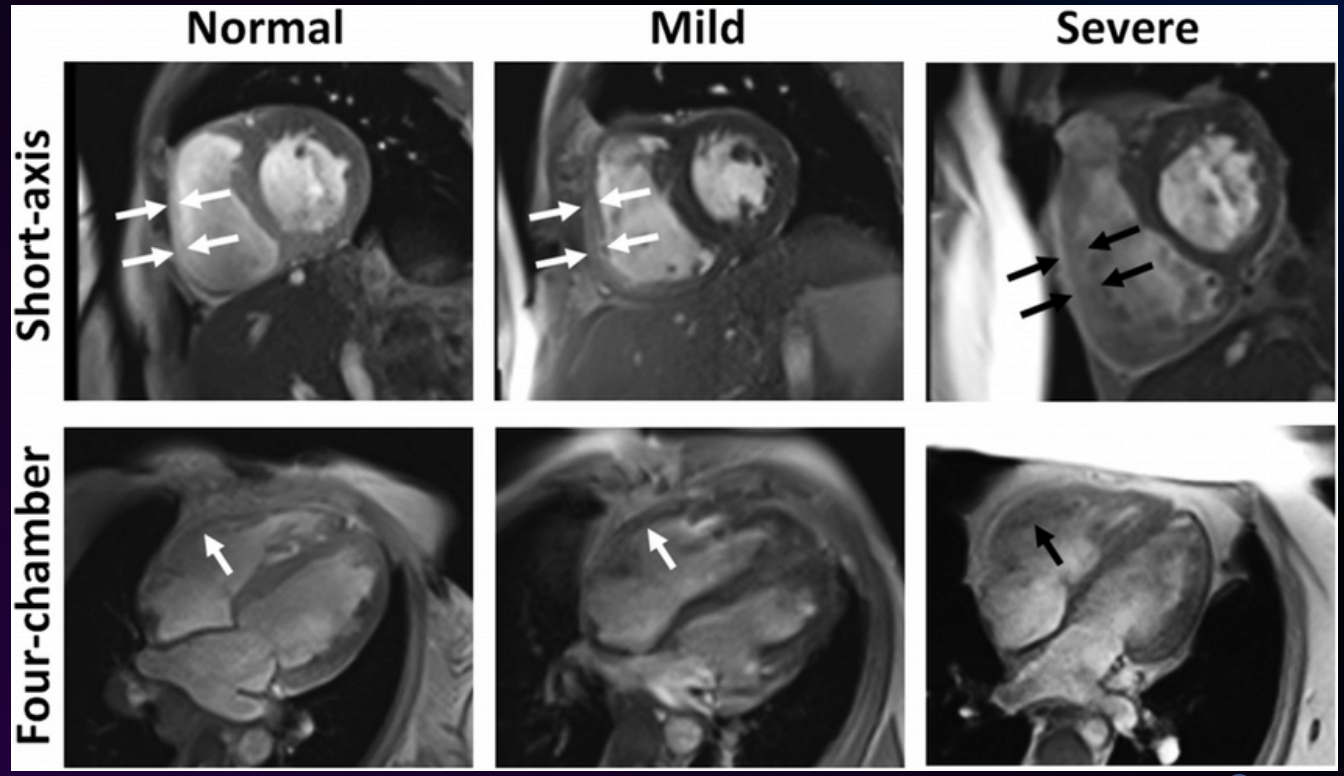
- Right ventricular (RV) function is a critical determinant of PAH outcomes.
- Studies using MRI and echocardiography have shown **early RV changes at PVR levels between 2-3 WU**, suggesting that the disease process is already underway before reaching the traditional 3 WU threshold.



Mukherjee, M et al
J Am Soc Echocardiogr 2025;38:141-86

RV DYSFUNCTION BEGINS EARLY

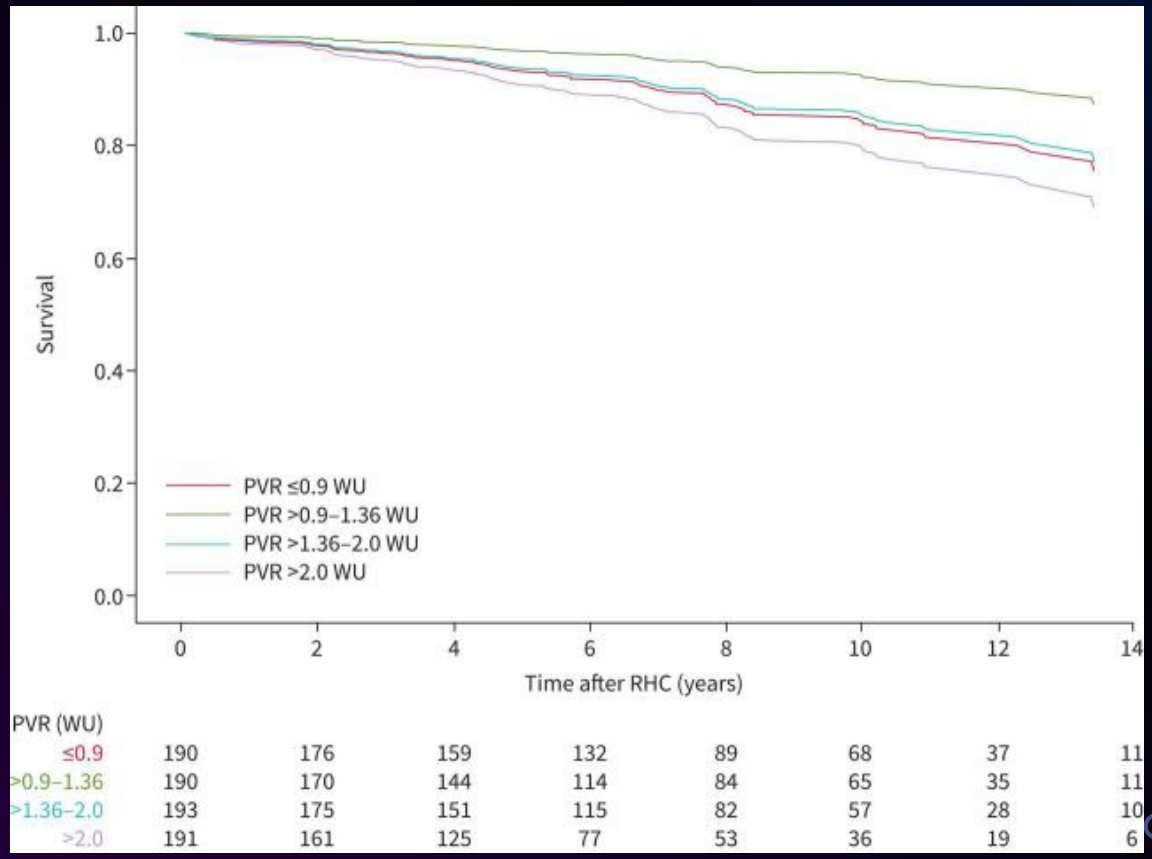
- Right ventricular (RV) function is a critical determinant of PAH outcomes.
- Studies using MRI and echocardiography have shown **early RV changes at PVR levels between 2-3 WU**, suggesting that the disease process is already underway before reaching the traditional 3 WU threshold.



El-Sayed H. Ibrahim et al Tomography September 2015

SURVIVAL BY PVR AT PEAK EXERCISE

- An increased TPG and a lower CO at peak exercise were independently associated with a poor prognosis
- PVR (TPG/CO) at peak exercise has prognostic relevance
- Evidence that treating exercise PH can make a difference, albeit such reports a small and case series.



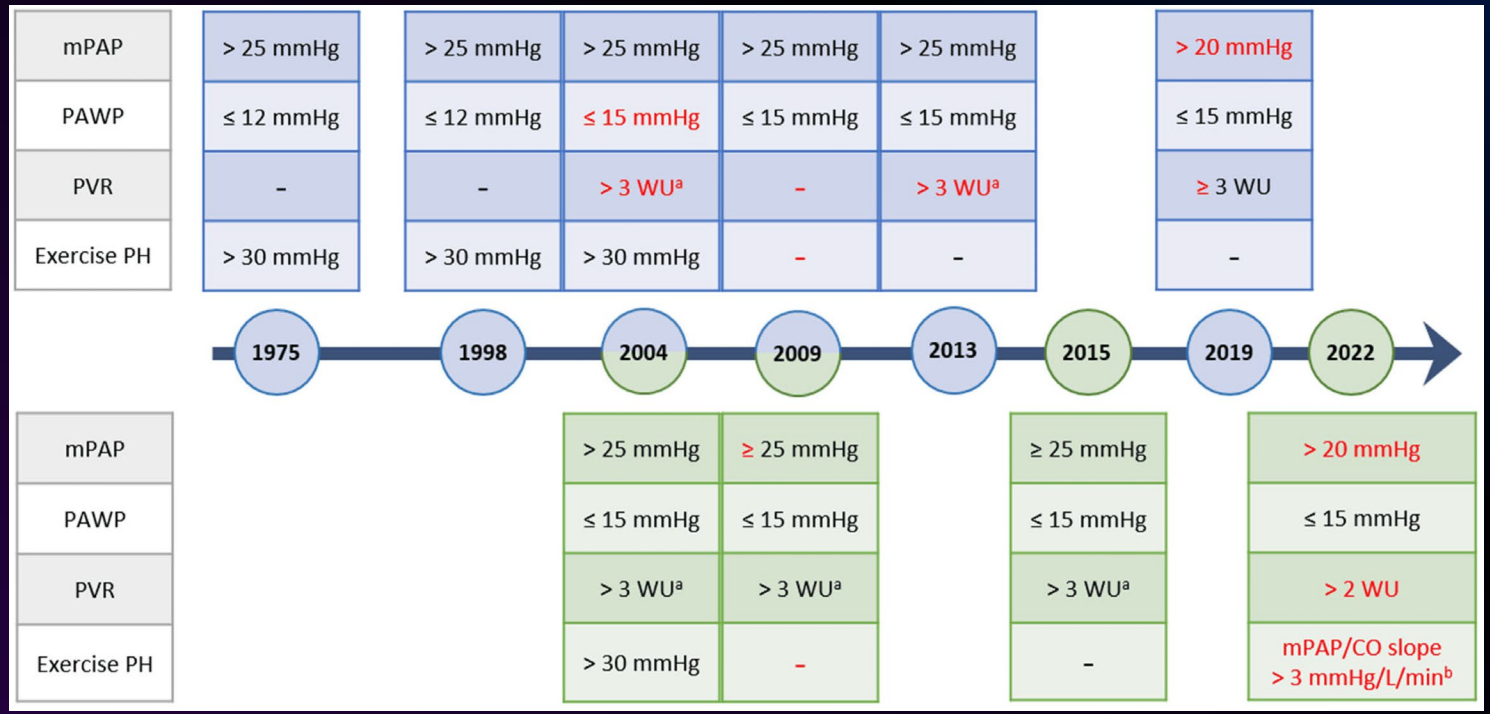
PVR (WU)								
≤0.9	190	176	159	132	89	68	37	11
>0.9–1.36	190	170	144	114	84	65	35	11
>1.36–2.0	193	175	151	115	82	57	28	10
>2.0	191	161	125	77	53	36	19	6

adjusted for age, sex, haemoglobin, resting mean pulmonary arterial pressure, resting PVR and resting diastolic systemic blood pressure.

Kovacs, Gabor et al. Eur Respir J 2024; 64: 2400698
Saggar R, et al Arthritis Rheum. 2012 Dec;64(12):4072-7

ALIGNING WITH A MODERN UNDERSTANDING OF PULMONARY VASCULAR DISEASE

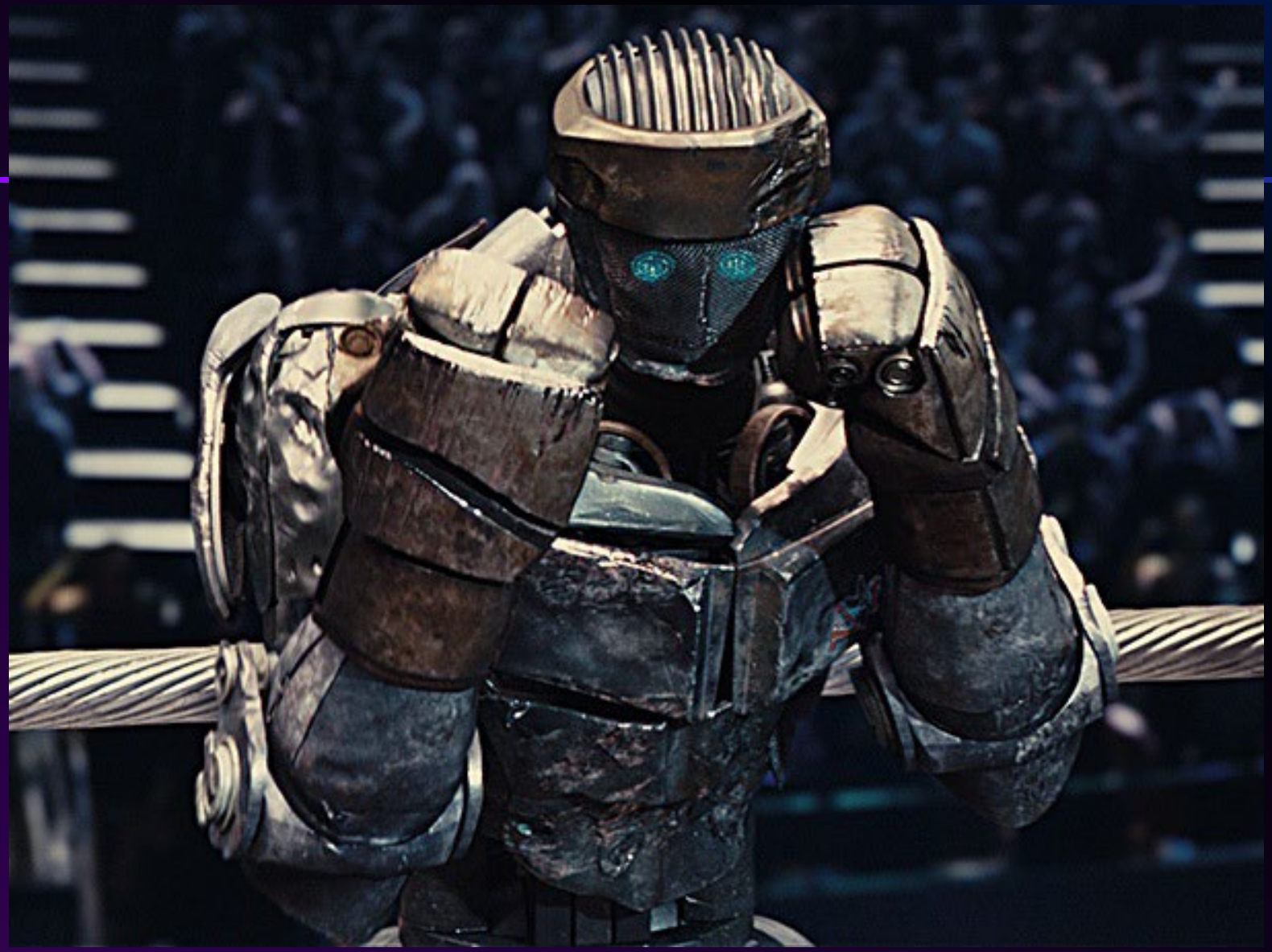
- The 2022 ESC/ERS guidelines already lowered the mPAP definition from ≥25 mmHg to >20 mmHg, recognizing that pulmonary hypertension starts earlier than previously thought.
- PVR is a continuous variable, and there is no physiologic "cliff" at 3 WU—patients deteriorate gradually, and intervention should reflect that.



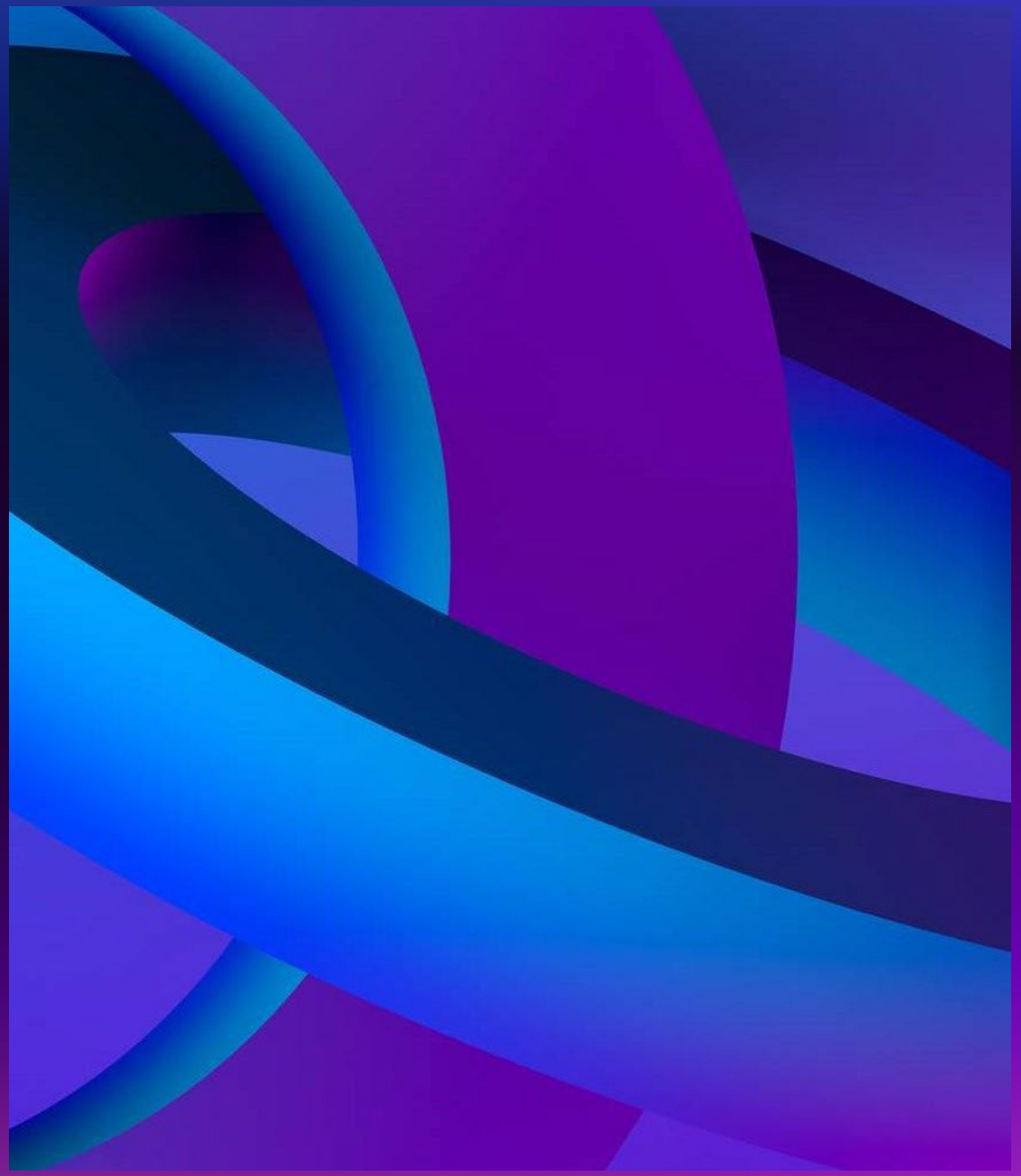
David Montani J. Cardiovasc. Dev. Dis. 2024

CONCLUSION

- The traditional ≥3 WU threshold PVR is arbitrary and outdated.
- A lower PVR threshold of ≥2 WU aligns with modern pathophysiology, allows for earlier diagnosis, and may improve patient outcomes by enabling earlier treatment strategies.
- Given the accumulating evidence, the medical community should embrace this change to optimize care for PAH patients.



REBUTTAL



CONCERN: OVERDIAGNOSIS AND OVERTREATMENT

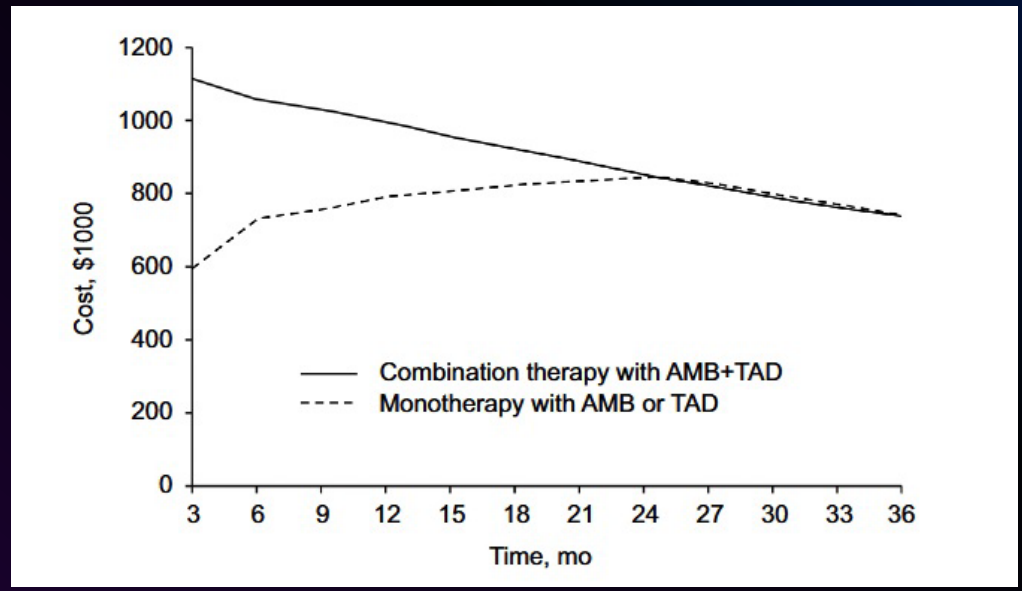
- Not all patients with **PVR 2-3 WU** will require immediate treatment but identifying them allows for **closer monitoring** and potential early intervention before irreversible damage occurs.

LACK OF TRIAL DATA ON TREATMENT IN PVR 2-3 WU RANGE

- The same was once true for treating systemic hypertension at lower thresholds, yet guidelines evolved as evidence accumulated.
- The **current definition excludes a high-risk population from potential research trials** that could prove benefit.

CONCERN: INCREASED HEALTHCARE BURDEN

Catching PAH early reduces hospitalizations and advanced therapy needs later, which may be cost-saving in the long run.



Burger, C et al. ClinicoEconomics and Outcomes Research 2017:9

CONCERN ABOUT CAPTURING PH GROUP II AND III PATIENTS WITH A LOWER PVR THRESHOLD

Hemodynamic exclusions

Patients with COPD/ILD often have elevated mPAP but do not show significant isolated PVR elevation.

Their PH is more driven by increased pulmonary pressures due to hypoxic vasoconstriction, hyperinflation, or left heart disease rather than intrinsic pulmonary vascular remodeling.

In contrast, PAH is a disease of progressive vascular obstruction, which remains distinct from PH caused by lung pathology

CONCERN ABOUT CAPTURING PH GROUP II AND III PATIENTS WITH A LOWER PVR THRESHOLD

Most patients with COPD/ILD have normal or near-normal PVR in early disease.

When PVR rises above 2 WU in ILD/COPD, it often correlates with severe, end-stage lung disease.

If anything, this underscores the need for better risk stratification in PH rather than dismissing early vascular disease outright.

The greater harm is in missing early PAH, as delaying diagnosis leads to worse survival and treatment response.

CONCERN ABOUT CAPTURING PH GROUP II AND III PATIENTS WITH A LOWER PVR THRESHOLD

The Current 3 WU Threshold Is Arbitrary—PAH Doesn't Suddenly Begin at 3 WU

There is no biological justification for setting the threshold at 3 WU instead of 2 WU.

Multiple studies show that PVR is a continuous variable, and even at 2-3 WU, there are early signs of vascular remodeling and worse outcomes.

Lowering the Threshold Encourages Better Diagnostic Pathways, Not Over-Treatment

Redefining PAH to PVR ≥2 WU does not mean blindly treating all patients who meet the new cutoff

CONCERN ABOUT CAPTURING PH GROUP II AND III PATIENTS WITH A LOWER PVR THRESHOLD

It means identifying at-risk patients earlier and refining diagnostic approaches, such as:

- Vasoreactivity testing, exercise hemodynamics, and multimodal imaging to differentiate PAH from PH due to lung disease.
- Stratified monitoring—not every patient with PVR 2-3 WU will need immediate treatment, but they may need closer follow-up.

HOW TO WIN THE DEBATE?

CHANNELING VIC

HOW TO WIN A DEBATE…

- There once was a doc named Channick,

HOW TO WIN A DEBATE…

- There once was a doc named Channick,
- Whose views on PH were archaic.

HOW TO WIN A DEBATE...

- There once was a doc named Channick,
- Whose views on PH were archaic.
- He clung to his three,
- But soon he'll agree—

HOW TO WIN A DEBATE…

- There once was a doc named Channick,
- Whose views on PH were archaic.
- He clung to his three,
- But soon he'll agree—
- Two’s better (and far less dramatic)!

THANK YOU

Jeffrey S Sager, MD

PVR Cutoff Should Have Remained at 3

Richard N. Channick, M.D.
Co-Director, Pulmonary Vascular Disease Program
Saul Brandman Endowed Chair in Pulmonary Arterial Hypertension
Professor of Clinical Medicine
David Geffen School of Medicine at UCLA

Fundamentals: Let's Keep this Simple

$$PVR = \frac{\text{mean PAP- PCWP}}{\text{Cardiac Output}}$$

Mean PAP = PVR x CO + PCWP

- Different components can lead to PH
  - High PVR (loss of cross-sectional area of vasculature, precapillary PAH)
  - High flow (hyperdynamic states)
  - High Wedge (post capillary PH)

Why is Higher PVR Worse?

- Elevated PVR results in restricted blood flow through the pulmonary arterial circulation which causes increased workload of the right ventricle and ultimately right heart failure.
- In other words, high PVR can kill

BUT

How high??

Who Actually Determines Hemodynamic Definitions?

- Guidelines Committees
- Consensus Conferences

EUROPEAN RESPIRATORY JOURNAL
ERS OFFICIAL DOCUMENTS
M. HUMBERT ET AL.

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG)

Marc Humbert[1,2], Gabor Kovacs[3,4], Marius M. Hoeper[5,6], Roberto Badagliacca[7,8], Rolf M.F. Berger[9], Margarita Brida[10,11], Jørn Carlsen[12,13], Andrew J.S. Coats[14,15], Pilar Escribano-Subias[16,17,18], Pisana Ferrari[19,20], Diogenes S. Ferreira[21], Hossein Ardeschir Ghofrani[22,23,24], George Giannakoulas[25], David G. Kiely[26,27,28], Eckhard Mayer[29], Gergely Meszaros[19,30], Blin Nagavci[31], Karen M. Olsson[32], Joanna Pepke-Zaba[33], Jennifer K. Quint[34], Göran Rådegran[35,36], Gerald Simonneau[37,38], Olivier Sitbon[2,37,39], Thomy Tonia[40], Mark Toshner[41], Jean-Luc Vachiery[42], Anton Vonk Noordegraaf[43], Marion Delcroix[44,46], Stephan Rosenkranz[45,46] and the ESC/ERS Scientific Document Group

What Hemodynamic Definitions Are Not

Moses want-to-be

Let's Look At the Evolution of Hemodynamic Definitions

New New New Hemodynamic Definition of PAH:
Who will determine it?

Historic Hemodynamics Definition of PAH:
- mPAP ≥ 25 mmHg
- PAWP ≤15 mmHg
- PVR > 3 Wood units

New Hemodynamic Definition of PAH:
- mPAP ≥ 20 mmHg
- PAWP ≤15 mmHg
- PVR > 3 Wood units

New New Hemodynamic Definition of PAH:
- mPAP ≥ 20 mmHg
- PAWP ≤15 mmHg
- PVR > 2 Wood units

PVR Cutoff of 2 was considered and rejected in 2013 and 2018

“Although the upper level of normal PVR is approximately 2 WU, the PVR cutoff value for PAH should be kept at 3 WU because patients with lower PVR levels are unlikely to have PAH (this is consistent with setting the cutoff for PAPm at 25 mm Hg, despite the upper limit of normal being 20 mm Hg)” Hoeper 2013

- 22298608 Saggar editorial to Kovacs article

- 21885394 Kovacs PVR with exercise 2012

Then This Paper

Published in final edited form as:
Lancet Respir Med. 2020 September ; 8(9): 873–884. doi:10.1016/S2213-2600(20)30317-9.

The Association Between Pulmonary Vascular Resistance and Clinical Outcomes in Patients with Pulmonary Hypertension: A Retrospective Cohort Study

Bradley A. Maron, M.D.[1,2,*,‡], **Evan L. Brittain, M.D.**[3,*], **Edward Hess, M.S.**[4], **Stephen W. Waldo, M.D.**[4], **Anna E. Barón, Ph.D.**[5] **[Prof]**, **Shi Huang, Ph.D.**[6], **Ronald H. Goldstein, M.D.**[1] **[Prof]**, **Tufik Assad, M.D.**[3], **Bradley M. Wertheim, M.D.**[2], **George A. Alba, M.D.**[7], **Jane A. Leopold, M.D.**[2], **Horst Olschewski, M.D.**[8] **[Prof]**, **Nazzareno Galiè, M.D.**[9] **[Prof.]**, **Gerald Simonneau, M.D.**[10] **[Prof]**, **Gabor Kovacs, M.D.**[8], **Ryan J. Tedford, M.D.**[11], **Marc Humbert, M.D.**[10] **[Prof]**, **Gaurav Choudhary, M.D.**[12]

Inflection Point in Mortality at PVR 2.2 when PCW < 16

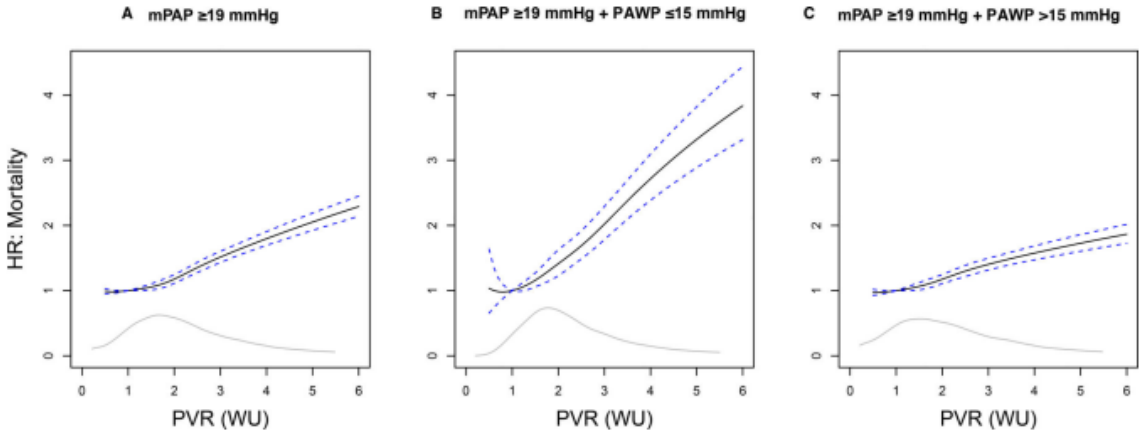


Figure 1. The adjusted hazard ratio for all-cause mortality stratified by pulmonary vascular resistance (PVR) in patients with elevated pulmonary artery pressure.
From the primary cohort, the hazard ratio (95% confidence interval) for all-cause mortality is plotted for PVR 1–6 WU relative to a reference value of 1.0 WU in patients with mean pulmonary artery pressure ≥19 mmHg **(A)**. This population was then restricted to PAWP ≤15 mmHg **(B)** and, alternatively, to PAWP >15 mmHg **(C)**. WU, Wood unit. The grey line inset is the kernel density estimate, representing the relative density of patients across PVR levels.

Maron

“There are several implications of our findings to clinical medicine. First, clarifying the lower limit of PVR that is prognostic when including patients with mildly elevated mPAP favors detection of early PH. We show here that using a PVR threshold of ≥3.0 WU in patients with mPAP ~20–25 mmHg excludes a sizeable group of vulnerable patients with elevated mPAP. Although such an approach may offer higher diagnostic specificity, this also seems to emphasize detection of severe (late) PH”

Maron et al.

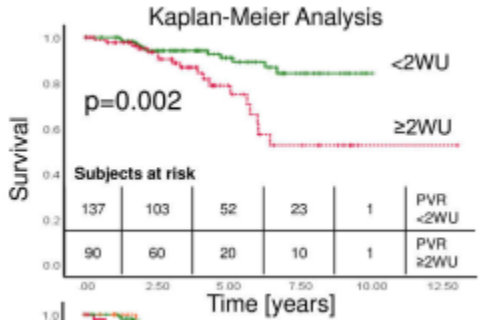
- “These data do not provide information on temporal trends in cardiopulmonary hemodynamics; therefore, patients in this study cannot be regarded as an early PH subgroup”

Maron paper: Is this the typical PAH patient??

Patient demographic, clinical, and hemodynamic characteristics for the primary cohort.

	Primary Cohort (N=40,082)
Age	66.5 [61.1–73.5]
Male	38,751 (96.7)
BMI (kg/m²)	29.6 [25.8–34.4]
Inpatient RHC	16,950 (42.3)
Race	
White	31,994 (79.8)
Black	7,261 (18.1)
Other	827 (2.1)
Clinical Comorbidities	
Systemic hypertension	35,429 (88.4)
Prior MI	11,222 (28.0)
Congestive heart failure	23,201 (57.9)
Atrial arrythmia	11,335 (28.3)
Peripheral arterial disease	8,214 (20.5)
Diabetes mellitus	19,104 (47.7)
Prior CABG	7,625 (19.0)
Prior PCI	8,095 (20.2)
Prior valvular disease	16,739 (41.8)
Prior stroke or TIA	3,413 (8.5)
Pulmonary embolism	1,490 (3.7)
Tobacco use	24,706 (61.6)
COPD	13,348 (33.3)
Interstitial lung disease	252 (0.6)
Obstructive sleep apnea	5,303 (13.2)
Portal hypertension	298 (0.7)
Chronic kidney disease	12,436 (31.0)
Connect tissue disease	1,303 (3.3)
Renal replacement therapy	1,870 (4.7)
Cancer	6,711 (16.7)
Psychiatric disease	1,152 (2.9)
Cardiopulmonary hemodynamics	
mPAP (mmHg)	27 [20–35]
PASP (mmHg)	40 [32–53]
PADP (mmHg)	18 [12–25]
PAWP (mmHg)	16 [11–23]
CO (Td), % (N)	24,567 (61.3)
CO (eFick), % (N)	34,773 (86.8)

Almost all males
42% inpatient rhc
88% HTN
33.3% COPD
13% sleep apnea



Xanthouli P, et al. Ann Rheum Dis 2020;79:370–378. doi:10.1136/annrheumdis-2019-216476

Among the patients in the group with mPAP 21–24 mm Hg, 28 (9.85% of total cohort) had a PVR ≥2 WU with no significant left heart or lung disease and would be newly diagnosed as SSc-APAH using this PVR threshold..

In patients with mPAP 21–24 mm Hg and PVR ≥2 WU, 21 out of 25 patients who received exercise RHC could be defined as exercise PH with mPAP >30 mm Hg and total pulmonary resistance >3 WU. No patient had a PAWP >25 mm Hg. Among patients with mPAP ≥25 mm Hg and PAWP ≤15 mm Hg (n=54), 33 had a PVR ≥3 WU, another 19 patients (6.7% of the total cohort) had a PVR ≥2 WU and would be classified as SSc-APAH with a lower PVR threshold.

The Difference in 6 MWD between the Groups is Statistically Significant but Wide Intervals!

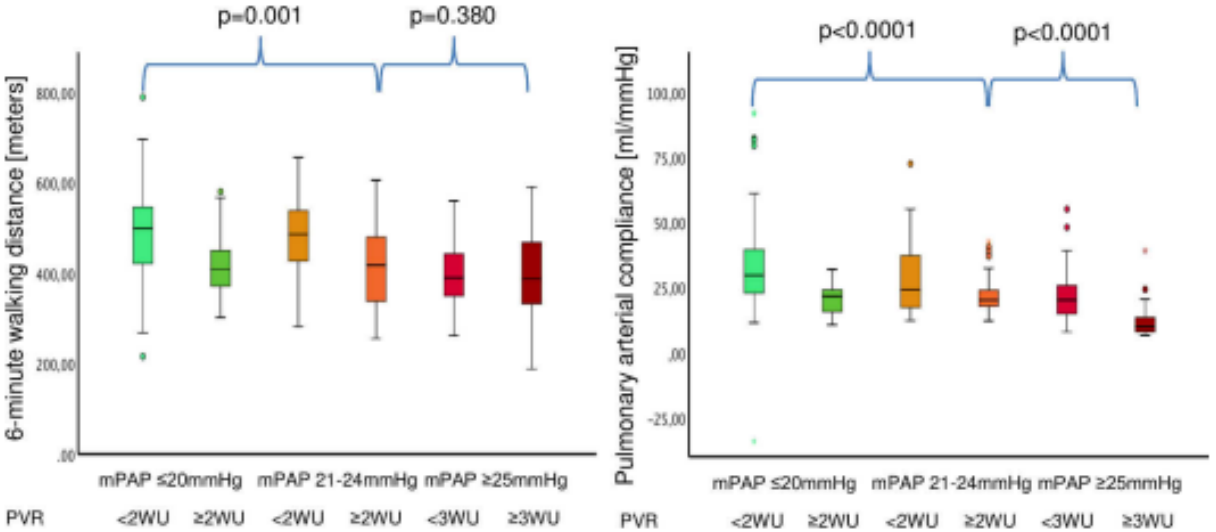


Figure 2 Six-minute walking distance (6MWD) and pulmonary arterial compliance (PAC) in different haemodynamic subgroups. Patients with mPAP 21–24 mm Hg and PVR ≥2 WU showed a significantly lower 6MWD than patients with mPAP ≤20 mm Hg (t-test p=0.001), but did not significantly differ from patients with mPAP ≥25 mm Hg. Patients with mPAP 21–24 mm Hg and PVR ≥2 WU also showed a significantly lower PAC than patients with mPAP ≤20 mm Hg (t-test p<0.0001), and a significantly higher PAC than patients with mPAP ≥25 mm Hg (t-test p<0.0001). The bracket ends in the graph point to the two groups that were compared by Student's t-test. mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; WU, Wood Units.

Two Questions You Should Ask at This Point

- Do patients with PVR 2-3 with increased mortality actually die from PH?
- If not, then why are we changing the definition of a disease?

What Really is Normal?

Acta Medica Scandinavica. Vol. 176, fasc. 4, 1964

The Department of Clinical Physiology, Karolinska sjukhuset, and the Laboratory of Clinical Physiology, Thoracic Clinics, Karolinska sjukhuset, Stockholm, Sweden

Circulation in Healthy Old Men, Studied by Right Heart Catheterization at Rest and During Exercise in Supine and Sitting Position

By

A. GRANATH, B. JONSSON and T. STRANDELL

ESC/ERS Felt These Data Should Lead to a Definition Change

"According to the revised haemodynamic definition, PAH may be diagnosed in patients with mPAP >20 mmHg and PVR >2 WU. Yet, the efficacy of drugs approved for PAH has only been demonstrated in patients with mPAP ≥25 mmHg and PVR greater than 3 No data are available for the efficacy of drugs approved for PAH in patients whose mPAP is greater or equal to 25 mmHg and whose PVR is greater than 3 WU. Hence, for such patients, the efficacy of drugs approved for PAH has not been established"

7th world symposium agrees

- 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 haemodynamic definitions of PH and pre-capillary PH, characterised by mPAP ⩾25 mmHg, PAWP ⩽15 mmHg and PVR >3 WU. Therefore, these drugs should be administered exclusively to patients meeting these definitions. We are aware of the disparity between the current criteria for PH (and pre-capillary PH) and for the indication for targeted therapy. Presently, the treatment of patients with early PH, or mPAP 21–24 mmHg and PVR 2–3 WU, using PH drugs lacks justification due to the absence of sufficient data from clinical trials.

7th WSPH

Definition of early PH

It has been previously shown that elevated mPAP and PVR values above the upper limits of normal are associated with poor survival [6–8]. A large recent nationwide study from the United Kingdom revealed that in patients with mildly elevated mPAP (21–24 mmHg) or PVR (2–3 WU), independent of comorbid lung and heart disease, survival was worse than among those with normal pressures (mPAP <21 mmHg) and normal PVR (PVR ⩽2 WU) [9]. In addition, patients with liver cirrhosis and PVR 2–3 WU frequently develop PVR >3 WU during follow-up, suggesting the presence of an early stage of progressive pulmonary vascular disease in these patients [10]. Similarly, patients with systemic sclerosis presenting with mPAP 21–24 mmHg and PVR 2–3 WU frequently develop mPAP ⩾25 mmHg during follow-up [11]. These observations suggest that the current haemodynamic criteria of PH and pre-capillary PH are clinically relevant and that patients with a risk condition for PH and mPAP 21–24 mmHg and/or PVR 2–3 WU may be at risk of haemodynamic progression. Therefore, this haemodynamic condition may be

What Did Changing The PVR Cutoff Accomplish?

Predictors of outcomes in mild pulmonary hypertension according to 2022 ESC/ERS Guidelines: the EVIDENCE-PAH UK study

Nina Karia [1,2], Luke Howard [3], Martin Johnson [4], David G. Kiely [5], James Lordan[6], Colm McCabe [7,8], Joanna Pepke-Zaba [9], Rose Ong[10], Michael Preiss[11], Daniel Knight [1,2], Vivek Muthurangu[2], and J. Gerry Coghlan [1,2]*

[1]National Pulmonary Hypertension Service, Royal Free Hospital London NHS Foundation Trust, Pond Street, London NW3 2QG, UK; [2]Institute of Cardiovascular Science, University College London, London WC1E 6BT, UK; [3]National Pulmonary Hypertension Service, Hammersmith Hospital, London W12 0HS, UK; [4]Scottish Pulmonary Vascular Unit, Golden Jubilee National Hospital, Glasgow G81 4DY, UK; [5]Sheffield Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield S10 2JF, UK; [6]Pulmonary Vascular Unit, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK; [7]National Pulmonary Hypertension Service, Royal Brompton Hospital, London SW3 6NP, UK; [8]National Heart and Lung Institute, Imperial College, London SW3 6LY, UK; [9]Pulmonary Vascular Disease Unit, Royal Papworth Hospital NHS Foundation Trust, Cambridge CB2 0AY, UK; [10]Actelion Pharmaceuticals Ltd, A Janssen Pharmaceutical Company of Johnson and Johnson, Global Epidemiology, Allschwil CH-4123, Switzerland; and [11]Actelion Pharmaceuticals Ltd, Janssen Pharmaceutical Company of Johnson & Johnson, Global Medical Affairs, Allschwil CH-4123, Switzerland

Received 7 February 2023; revised 21 July 2023; accepted 9 August 2023; online publish-ahead-of-print 24 August 2023

Mild PH is, in fact, associated with higher mortality

Table 6 Adjusted mortality for confounders across mean pulmonary artery pressure groups

	Adjusted for lung disease[a] $n = 2873$		Adjusted for heart disease[a] $n = 2783$		Adjusted for CTD[a] $n = 2929$		Adjusted for lung and heart disease[a] $n = 2736$		Adjusted for all comorbidities[a] $n = 2736$	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
mPAP 21–24 mmHg	1.30 (1.10–1.53)	.00179	1.44 (1.22–1.70)	.0000191	1.41 (1.20–1.66)	.0000257	1.36 (1.14–1.61)	.000442	1.37 (1.15–1.62)	.000330
mPAP ≥25 mmHg	2.29 (1.99–2.63)	<.000001	2.48 (2.15–2.86)	<.000001	2.58 (2.26–2.95)	<.000001	2.24 (1.94–2.60)	<.000001	2.30 (1.98–2.66)	<.000001

[a]Adjusted for age/sex.

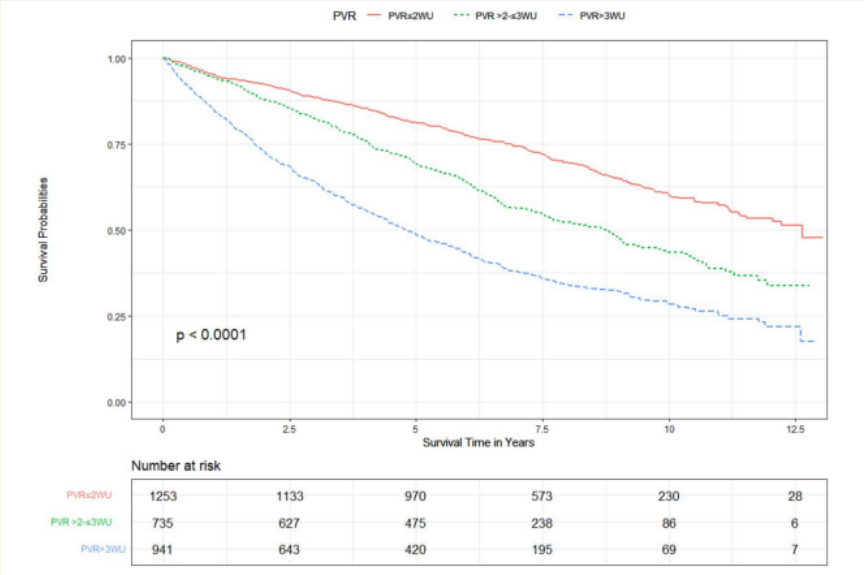


Figure 2 Unadjusted effect of pulmonary vascular resistance on survival.

But, Effect on Mortality of PVR 2-3 Small at Best

Table 7 Adjusted mortality for confounders across pulmonary vascular resistance groups

	Adjusted for lung disease[a] n = 2873		Adjusted for heart disease[a] n = 2783		Adjusted for CTD[a] n = 2929		Adjusted for lung and heart disease[a] n = 2736		Adjusted for all comorbidities[a] n = 2736	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
PVR >2–≤3 WU	1.28 (1.10–1.48)	.00108	1.44 (1.24–1.66)	.00000144	1.43 (1.24–1.65)	.00000129	1.28 (1.10–1.49)	.00119	1.28 (1.10–1.49)	.00147
PVR >3 WU	2.15 (1.89–2.45)	<.000001	2.54 (2.23–2.90)	<.000001	2.47 (2.18–2.81)	<.000001	2.22 (1.93–2.54)	<.000001	2.23 (1.95–2.55)	<.000001

[a]Adjusted for age/sex.

What About the Scleroderma subgroup, in who we are vigilant in screening for even mild PH?

Puigrenier *et al. Respiratory Research* (2022) 23:284
https://doi.org/10.1186/s12931-022-02205-4

Respiratory Research

RESEARCH Open Access

Mild pulmonary hemodynamic alterations in patients with systemic sclerosis: relevance of the new 2022 ESC/ERS definition of pulmonary hypertension and impact on mortality

Sébastien Puigrenier[1,2,3†], Jonathan Giovannelli[4†], Nicolas Lamblin[5,6], Pascal De Groote[5,6], Marie Fertin[5,6], Jean-François Bervar[7], Antoine Lamer[8], Jean-Louis Edmé[9,10], Marie-Hélène Balquet[11], Vincent Sobanski[1,2,12,13], David Launay[1,2,12,13], Éric Hachulla[1,2,12,13] and Sébastien Sanges[1,2,12,13*]

10 of 16 Patients Progressed (We already knew this)

Table 2 (continued)

Pt #	Screening strategies			Follow-up				
	DETECT algorithm	ESC/ERS echocardiographic probability of PH	ASIG algorithm	ESC/ERS risk assessment at baseline (worsening or death at 1 year)	Number of PH drugs (at baseline - during follow-up)	Duration of follow-up (y)	Occurrence of mPAP > 25 mmHg during follow-up (delay from 1st RHC—months)	Death
1	—	—	—	High risk	0—0	0.3	—	Yes
2	RHC recommended	Low	Positive	Intermediate risk	0—0	2.7	No	No
3	—	Intermediate	Positive	High risk	0—0	0.9	—	Yes
4	RHC recommended	Intermediate	Positive	Intermediate risk	1—1	3.4	Yes (11)	No
5	RHC recommended	Intermediate	Positive	Intermediate risk	0—0	3.0	Yes (28)	Yes
6	RHC recommended	Intermediate	Positive	Intermediate risk	0—2	4.9	Yes (24)	No
7	RHC recommended	Intermediate	Positive	High risk	0—0	5.3	Yes (60)	Yes
8	—	Intermediate	Positive	High risk	0—1	1.8	Yes (15)	Yes
9	RHC recommended	Intermediate	Positive	High risk	0—1	3.2	Yes (18)	No
10	—	Intermediate	Positive	Low risk	0—0	4.3	—	Yes
11	—	Intermediate	Positive	Intermediate risk	0—2	8.4	Yes (40)	No
12	—	Low	Negative	Intermediate risk	0—0	3.0	No	Yes
13	—	Intermediate	—	Intermediate risk	0—1	5.4	Yes (60)	No
14	RHC recommended	Intermediate	Positive	Intermediate risk	0-0	4.4	Yes (50)	No
15	—	High	—	Intermediate risk	0—0	2.8	No	No
16	—	Low	—	Intermediate risk	0—3	8.0	Yes (64)	No

6MWD: 6-min walking distance, ACA: anti-centromere antibodies, AFA: anti-fibrillarin antibodies, ASIG: Australian Scleroderma Interest Group, ATA: anti-topoisomerase antibodies, BNP: brain natriuretic peptide, CI: cardiac index, CO: cardiac output, CTE: chronic thrombo-embolism, dc: diffuse cutaneous, diag: diagnosis, diam: diameter, DLCO: diffusing capacity for carbon monoxide, ESC/ERS: European Society of Cardiology/European Respiratory Society, ext: extensive, F: female, FEFRPS: first except for RP symptom, FEV1: forced expired volume in 1 min, fluid ch: fluid challenge, FVC: forced vital capacity, HVPG: hepatic venous pressure gradient, ILD: interstitial lung disease, IVC: inferior vena cava, KCO: carbon monoxide transfer coefficient, LA: left atrium, lc: limited cutaneous, lim: limited, LV: left ventricle, LVEF: left ventricular ejection fraction, LVFP: elevated left ventricular filling pressure, M: male, mPAP: mean pulmonary arterial pressure, mRSS: modified Rodnan skin score, N: normal value, NA: not available; no spec: positive antinuclear antibodies without antibody specificity identified, NYHA: New York Heart Association, PAAT: pulmonary artery acceleration time, PAWP: pulmonary arterial wedge pressure, pericard.: pericardial, PH: pulmonary hypertension, pred: predicted value, Pt: patient, PVOD: pulmonary veno-occlusive disease, PVR: pulmonary vascular resistance, RA: right atrium, RAP: right atrial pressure, RAxD: right axis deviation, RHC: right heart catheterization, RHF: clinical signs of right heart failure, RP: Raynaud phenomenon, RV: right ventricle, SSc: systemic sclerosis, SvO_2: venous saturation in oxygen, TAPSE: tricuspid annular plane systolic excursion, tel: telangiectasias, TLC: total lung capacity, TRV: tricuspid regurgitation velocity, vol: volume, WU: Wood units, y: years; yo: years old

* Of note, patient #1 had triscupid valvular disease, making echographic markers of PH unreliable

Spline modelling relationship between PVR and Survival

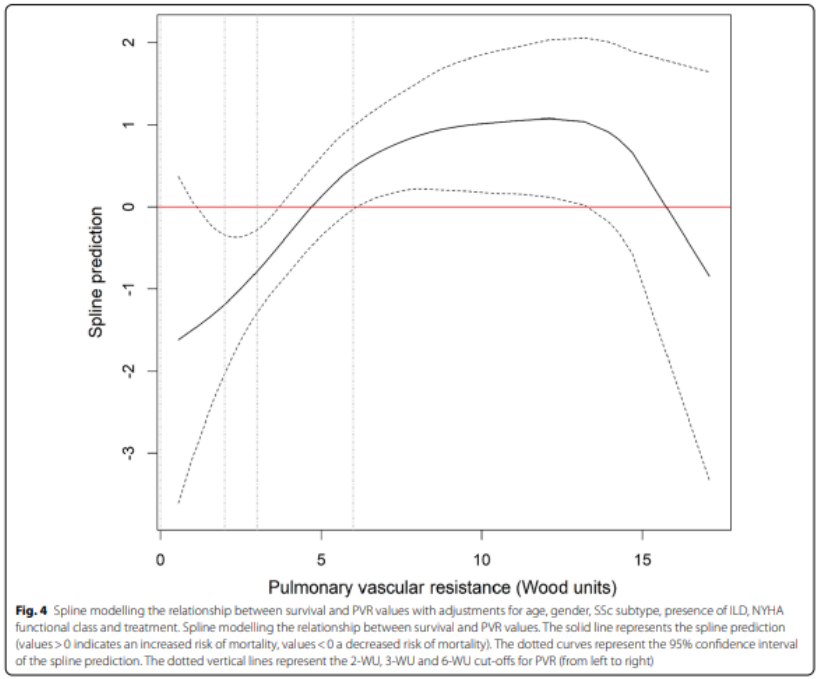


Fig. 4 Spline modelling the relationship between survival and PVR values with adjustments for age, gender, SSc subtype, presence of ILD, NYHA functional class and treatment. Spline modelling the relationship between survival and PVR values. The solid line represents the spline prediction (values > 0 indicates an increased risk of mortality, values < 0 a decreased risk of mortality). The dotted curves represent the 95% confidence interval of the spline prediction. The dotted vertical lines represent the 2-WU, 3-WU and 6-WU cut-offs for PVR (from left to right)

Looks like even mild PVRs infer worse survival

EXCEPT:

For PVR 2-3, HR after adjusting for age, sex SSc subtype, disease duration, NYHA class and treatment was:

0.49 (0.04-5.56)

3 yr Mortality was actually better for 2-3, 5 year only a little worse

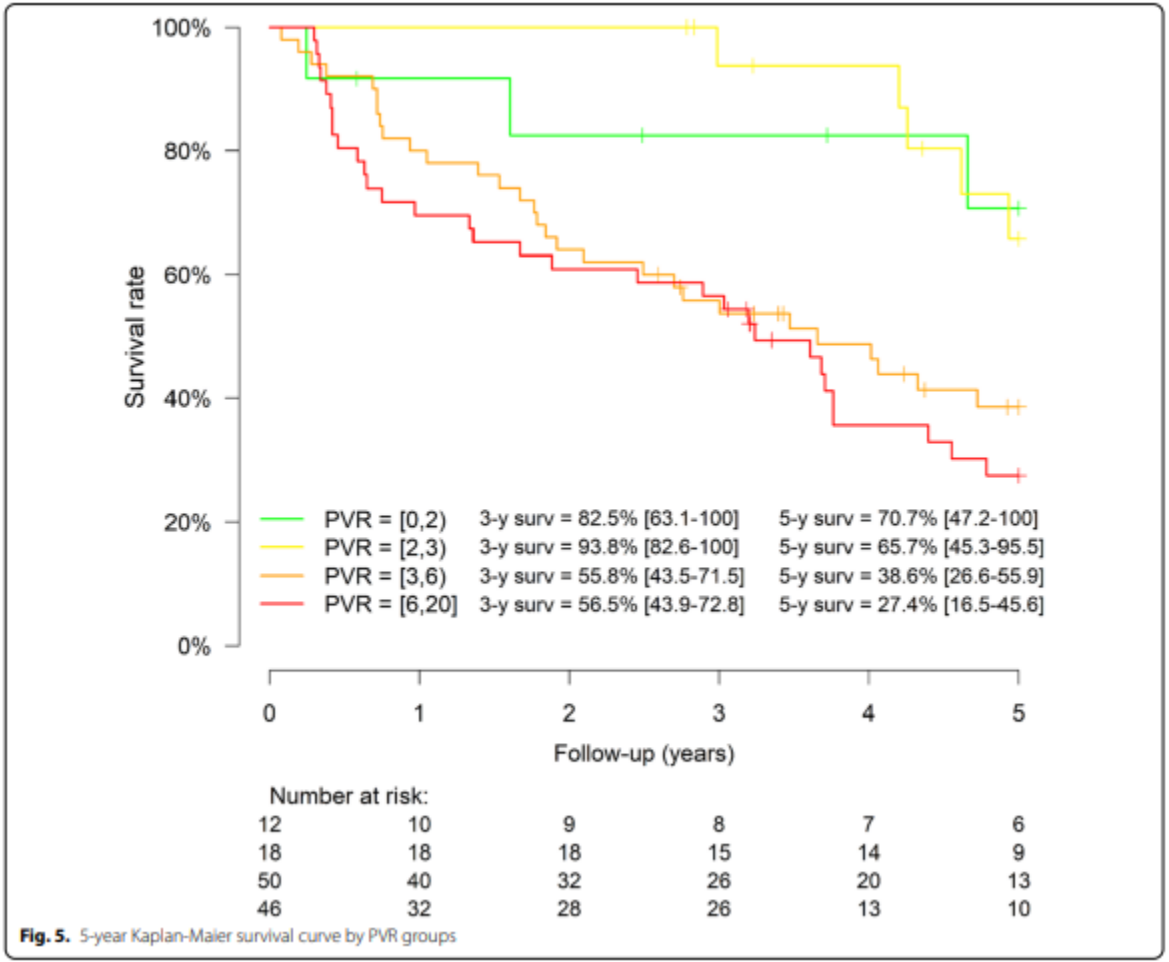


Fig. 5. 5-year Kaplan-Maier survival curve by PVR groups

So if PVR Greater Than 2 is Bad, Why Not Change the Definition?

Let’s Look to Systemic Hypertension

- Hypertension is a common risk factor for several life-threatening cardiovascular and cerebrovascular diseases, including myocardial infarction, cardiomyopathies, and cerebrovascular accidents
- Maintaining optimal blood pressure (BP) control is crucial in managing other significant conditions, including diabetes. Consequently, determining safe cut-off values has remained a primary goal for several organizations, including the American Heart Association (AHA) and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).
- **Over the past years, these organizations have focused on developing guidelines to enable physicians and patients to maintain optimal BP control.**

2014

High blood pressure redefined for first time in 14 years: 130 is the new high

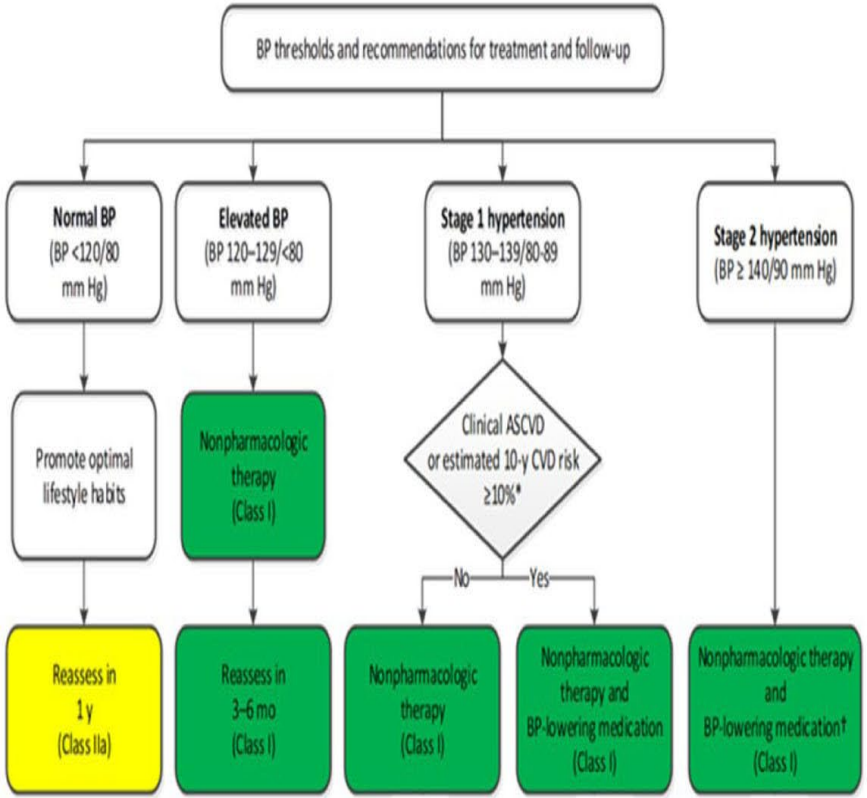
American Heart Association/American College of Cardiology Guidelines

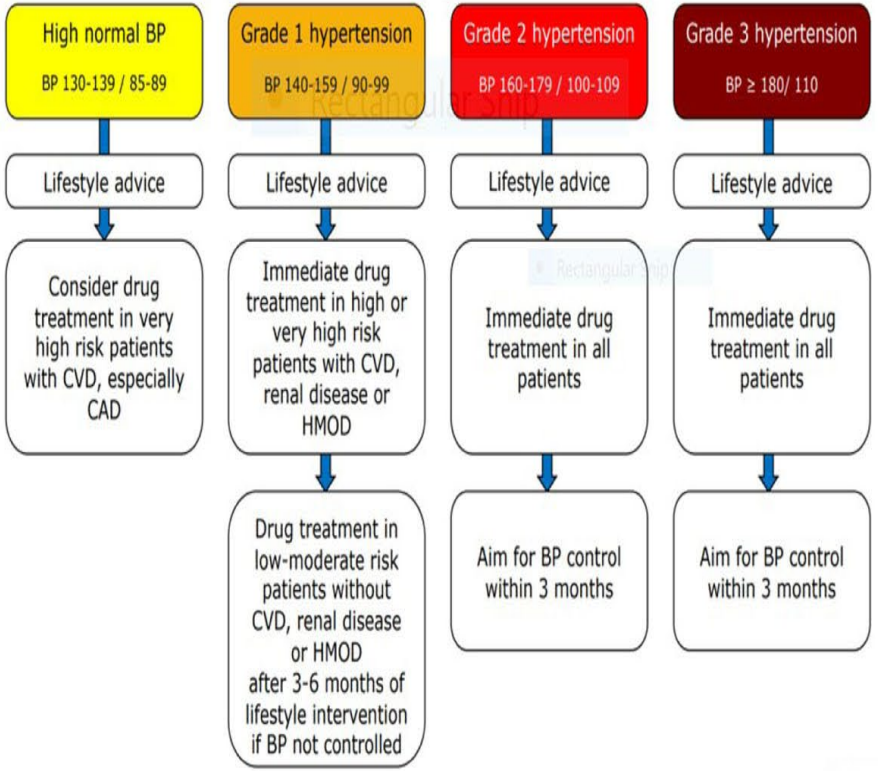
Highlights

- High blood pressure is now defined as readings of 130 mm Hg and higher for the systolic blood pressure measurement, or readings of 80 and higher for the diastolic measurement. That is a change from the old definition of 140/90 and higher, reflecting complications that can occur at those lower numbers.
- In the first update to comprehensive U.S. guidelines on blood pressure detection and treatment since 2003, the category of prehypertension is eliminated.
- While about 14 percent more people will be diagnosed with high blood pressure and counseled about lifestyle changes, there will only be a small increase in those who will be prescribed medication.
- By lowering the definition of high blood pressure, the guidelines recommend earlier intervention to prevent further increases in blood pressure and the complications of hypertension.

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

HTN equals Treatment





Mild HTN Treatment improves CV mortality

Journal of the American Heart Association

ORIGINAL RESEARCH

Stage 1 Hypertension and the 10-Year and Lifetime Risk of Cardiovascular Disease: A Prospective Real-World Study

Xinyi Peng, MD;* Cheng Jin, MD;* Qirui Song, MD; Shouling Wu, MD, PhD; Jun Cai, MD, PhD

BACKGROUND: The 10-year and lifetime cardiovascular disease risk in the population with stage 1 hypertension and the effects of recovery from and progression of stage 1 hypertension remain undetermined.

METHODS AND RESULTS: This prospective cohort study included 96268 individuals with blood pressure measurements obtained in 2006 and again in 2010. The 10-year cardiovascular disease risk was estimated using the multivariable Cox proportional hazards model, and the lifetime risk was calculated using a modified survival analysis that accounted for the competing risk of death. Stage 1 hypertension was detected in 30.83% of the cohort. The 10-year cardiovascular disease risk was 2.80%, and the lifetime risk was 16.61%. Compared with the normal blood pressure group, the stage 1 hypertension group had a 35% higher 10-year risk (hazard ratio [HR], 1.35 [95% CI, 1.19–1.52]) and a 36% higher lifetime risk (HR, 1.36 [95% CI, 1.25–1.49]). By 2010, 12.57% of the participants with stage 1 hypertension had progressed to stage 2, with a significant 156% increase in 10-year risk (HR, 2.56 [95% CI, 2.11–3.11]) and an increased lifetime risk of 129% (HR, 2.29 [95% CI, 1.89–2.77]). There was no appreciable change in risk in those with stage 1 hypertension whose blood pressure returned to the normal-elevated range.

CONCLUSIONS: Stage 1 hypertension was associated with a significant increase in 10-year and lifetime cardiovascular disease risk. Progression to stage 2 hypertension was associated with a marked increase in lifetime risk. The current guidelines require revision to promote early detection and appropriate management of blood pressure.

Table 2. Ten-Year and Lifetime Risk of CVD, According to Antihypertensive Medication Taking

Group	CVD events/N	10-y risk (%)	HR for 10-y risk	Lifetime risk, n (%)	HR for lifetime risk	PAR for lifetime (%)
Total population						
Without antihypertensive medications						
<120/80 mm Hg	199/9753	2.17 (1.87–2.51)	1 (ref)	20.33 (17.70–23.47)	1 (ref)	0.00
120–129/<80 mm Hg	108/2864	2.89 (2.37–3.53)	1.34 (1.06–1.69)	25.95 (21.68–31.06)	1.32 (1.05–1.67)	1.76
130–139/80–89 mm Hg	755/20488	3.16 (2.87–3.48)	1.46 (1.25–1.71)	27.05 (24.52–29.85)	1.39 (1.19–1.62)	13.50
>140/90 mm Hg	1451/18099	5.24 (4.80–5.73)	2.42 (2.08–2.82)	40.43 (37.48–43.61)	2.28 (1.97–2.64)	31.15
With antihypertensive medications						
<120/80 mm Hg	33/369	8.54 (6.04–12.07)	1 (ref)	38.32 (28.52–51.48)	1 (ref)	0.00
120–129/<80 mm Hg	21/284	6.14 (3.98–9.48)	0.72 (0.42–1.25)	32.69 (22.46–47.57)	0.82 (0.47–1.42)	−0.38
130–139/80–89 mm Hg	218/3011	6.64 (5.72–7.71)	0.78 (0.54–1.12)	33.06 (28.72–38.06)	0.83 (0.57–1.21)	−3.91
>140/90 mm Hg	1095/9951	9.32 (8.47–10.26)	1.09 (0.77–1.55)	42.65 (39.00–46.64)	1.15 (0.81–1.64)	9.88

Hazard ratio calculated by Cox proportional hazards regression analysis for 10-y and lifetime CVD risk after adjustments for age, sex, alcohol consumption, smoking, fasting serum glucose, total cholesterol levels, high-density lipoprotein-cholesterol, high-sensitivity C-reactive protein, family history of CVD, and uric acid levels. Antihypertensive medication taking was assessed during the 2010 survey. *P* for the interaction of antihypertensive medications between blood pressure and CVD <0.001. CVD indicates cardiovascular disease; HR, hazard ratio; and PAR, population-attributable risk.

What are the implications of changing the PVR threshold?

Defining a Disease that Requires Treatment? NO

Identifying patients who will progress and die of PH? NO

Creating confusion? YES

My Take Home Message (and Philosophy)

- Hemodynamics, like life, are a continuum, not a series of cutoffs (unless you're in the NBA)
- In other words: 2.9 = 3.1
- Putting patients into buckets, like PVR less than 3 vs. greater than 3, may be nice for research and statistics but not for sophisticated caregivers.

Novel Developments in Group 2 PH

Pooja Prasad, MD

Assistant Clinical Professor

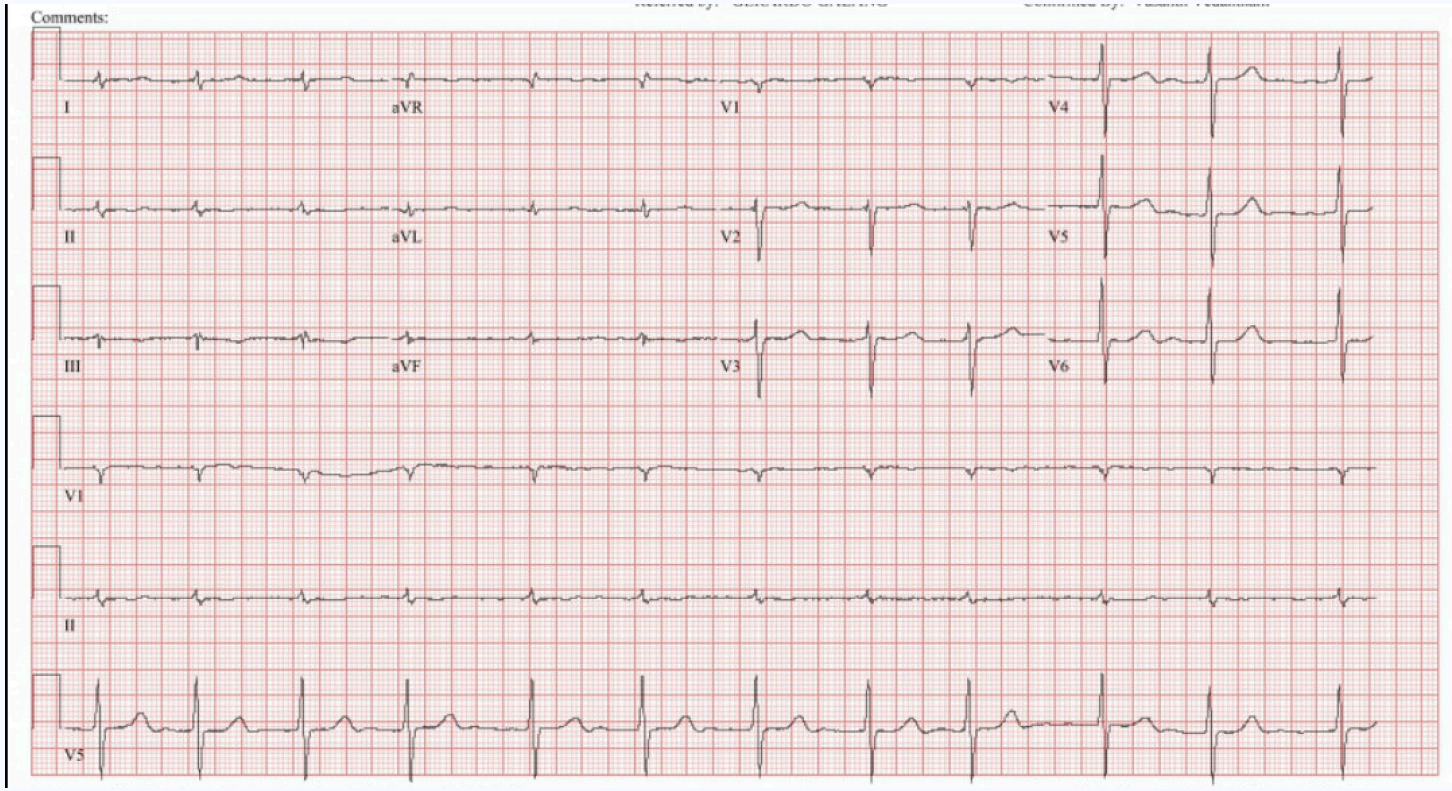
UCSF

Disclosures

- I have the following relationships with ACCME defined ineligible companies:
  - Advisory boards – Bayer
- I **WILL NOT** discuss off-label use and/or investigational use of any drugs or devices.

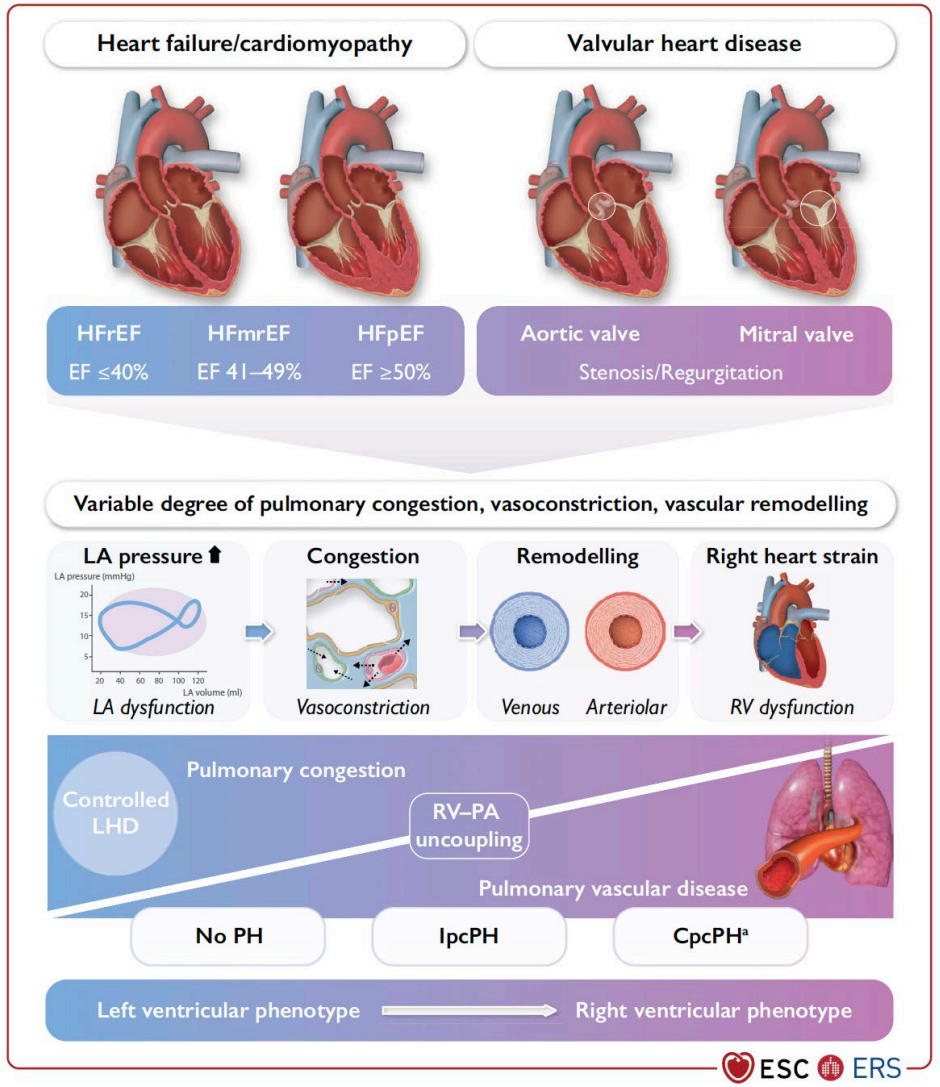
Patient case

- 85 y.o. with permanent atrial fibrillation with shortness of breath and new ascites requiring paracentesis
- Echo: RVSP of 49. reduced RV function, moderate LVH
- RHC: elevated right and left sided filling pressures (PCWP: 22 mm Hg) with elevated LVEDP (14); mPA 30, TPG of 8, consistent with post-capillary disease .
- Started on tadalafil by his local cardiologist, referred to UCSF



What is Group 2 PH?

- Pulmonary Hypertension associated with left heart disease
- Most common; 65-80% of PH
- Common in HFpEF, affecting at least 50% of these patients
- 60–70% of patients with severe and symptomatic mitral valve disease
- 50% of those with symptomatic aortic stenosis



European Heart Journal (2022) 43, 3618–3731

• European Heart Journal (2022) 43, 3618–3731

Diagnosis of group 2 PH

- mPAP > 20 mmHg and a PAWP >15 mmHg.
  - Isolated post-capillary (IpcPH) if PVR ≤2 WU, combined post- and precapillary PH (CpcPH) if PVR >2 WU.
- Challenges: high prevalence of cardiac disease, "mixed phenotype"
- Evaluate for other etiologies
- Biomarkers (BNP/NT-pro BNP), echocardiography, RHC in selected patients
- Specific echo features: LV hypertrophy, increased LA size, and reduced LA strain
- Multiple invasive assessments may be required, for example after optimization of cardiac or renal disease
- Be aware of the patient who has been diuresed aggressively prior to RHC

HFpEF can be missed; scores can help

FIGURE 7 Diagnostic Evaluation of HFpEF

Patient With Unexplained Exertional Dyspnea and No Clear Alternative Cause

H_2FPEF Score

	Definition	Points
Heavy	BMI >30 kg/m²	2
Hypertension	2 or more antihypertensive medicines	1
Atrial Fibrillation	Any history	3
Pulmonary Hypertension	Pulmonary artery systolic pressure >35 mm Hg (echo)	1
Elder	>60 years	1
Filling pressures	E/e' ratio >9 (echo)	1

HFA-PEFF Score

Domain	Major Criteria (2 Points Max Per Category)	Minor Criteria (1 Point Max Per Category)
Functional	• Average E/e' ratio ≥15 • Septal e' <7 cm/s • Lateral e' <10 cm/s • Tricuspid regurgitation velocity >2.8 m/s	• Average E/e' ratio 9-14 • Global longitudinal strain <16%
Morphological	• Left atrial volume index >34 mL/m² • Left ventricular mass index >149/122 g/m² (men/women) and relative wall thickness >0.42	• Left atrial volume index 29-34 mL/m² • Left ventricular mass index >115/95 g/m² (men/women) • Relative wall thickness >0.42 • Left ventricular wall thickness ≥12 mm
Biomarker (sinus)	NTproBNP >220 pg/mL BNP >80 pg/mL	NTproBNP 125-220 pg/mL BNP 35-80 pg/mL
Biomarker (atrial fibrillation)	NTproBNP >660 pg/mL BNP >240 pg/mL	NTproBNP 365-660 pg/mL BNP 105-240 pg/mL

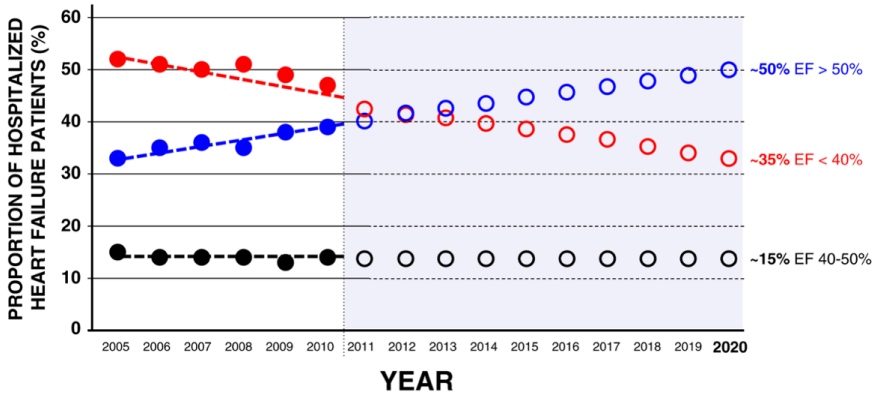
Low probability score
Unlikely HFpEF
(H_2FPEF 0-1 or HFA-PEFF 0-1)

Intermediate probability score
(H_2FPEF 2-5 or HFA-PEFF 2-4)
Further evaluation needed

Hemodynamic Stress Test

High probability score
Likely HFpEF
(H_2FPEF 6-9 or HFA-PEFF 5-6)

- Bourlag et al. JACC 2023

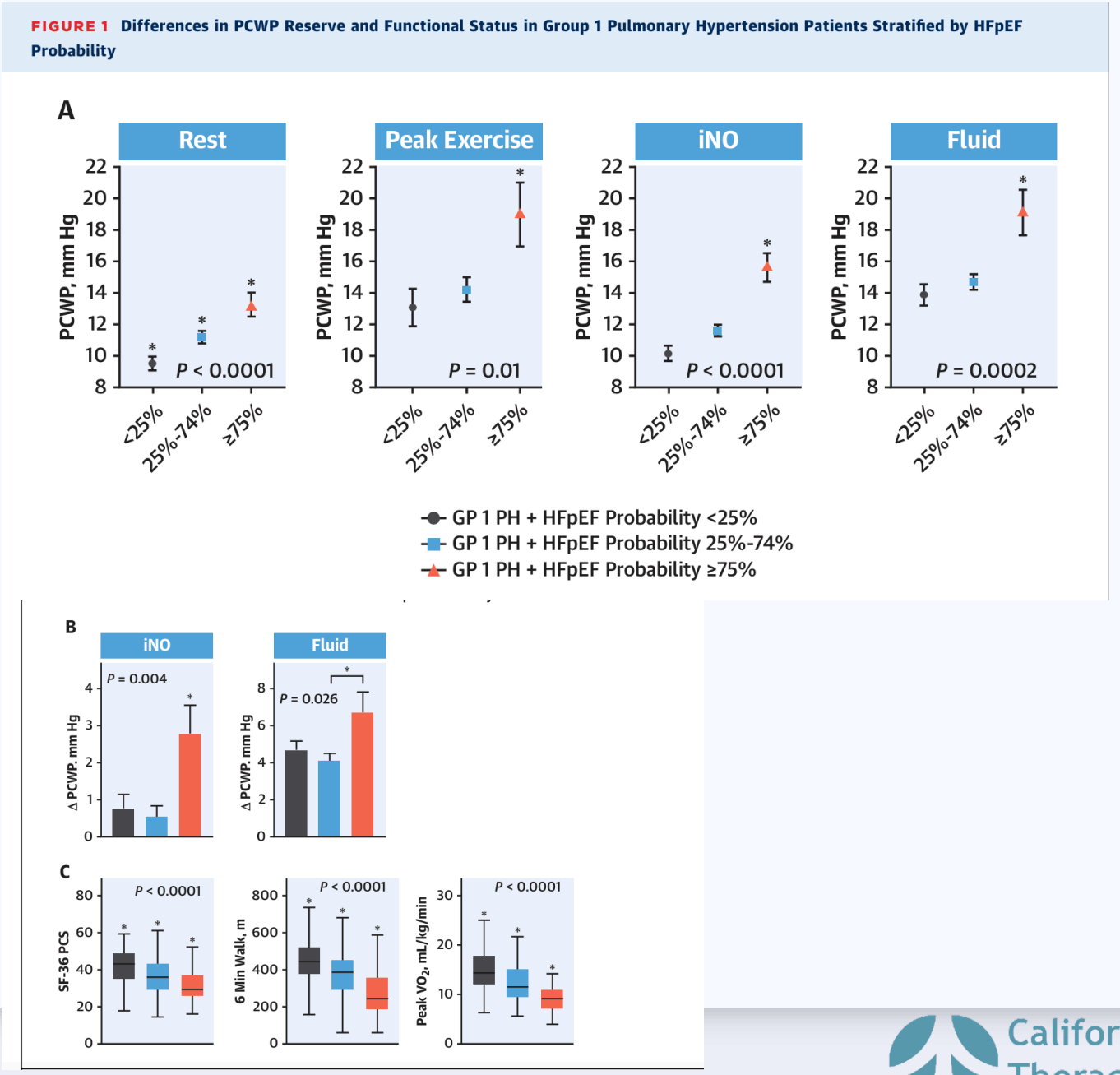


Dunley et al. *Curr Heart Fail Rep* 2013 (based on data from Steinberg BA, et al. *Circulation* 2012)

California Thoracic Society
ATS Chapter Serving California and Arizona

Group 1 PH with risk factors for group 2 PH

- Among 424 patients with group 1 PH, 54% had intermediate HFpeF probability, 15% had high HFpEF probability
- Will response to and safety of therapy differ in patients with Group 1 PH and risk factors for HFpEF compared to those without?



• Reddy et al .JACC 2024

Fluid loading in cardiac catheterization lab

- Perform when intermediate risk probability of HFpEF
- Diagnostic value of PCWP with PLR is comparable to the gold standard (exercise) in a single center study of 109 patients.
- $PCWP_{PLR}$ ≥19 mmHg (24% of cases): specificity of 100% for diagnosing occult-HFpEF, irrespective of diuretic use. $PCWP_{PLR}$ ≥11 mmHg had a 100% sensitivity and negative predictive value for diagnosing occult-HFpEF

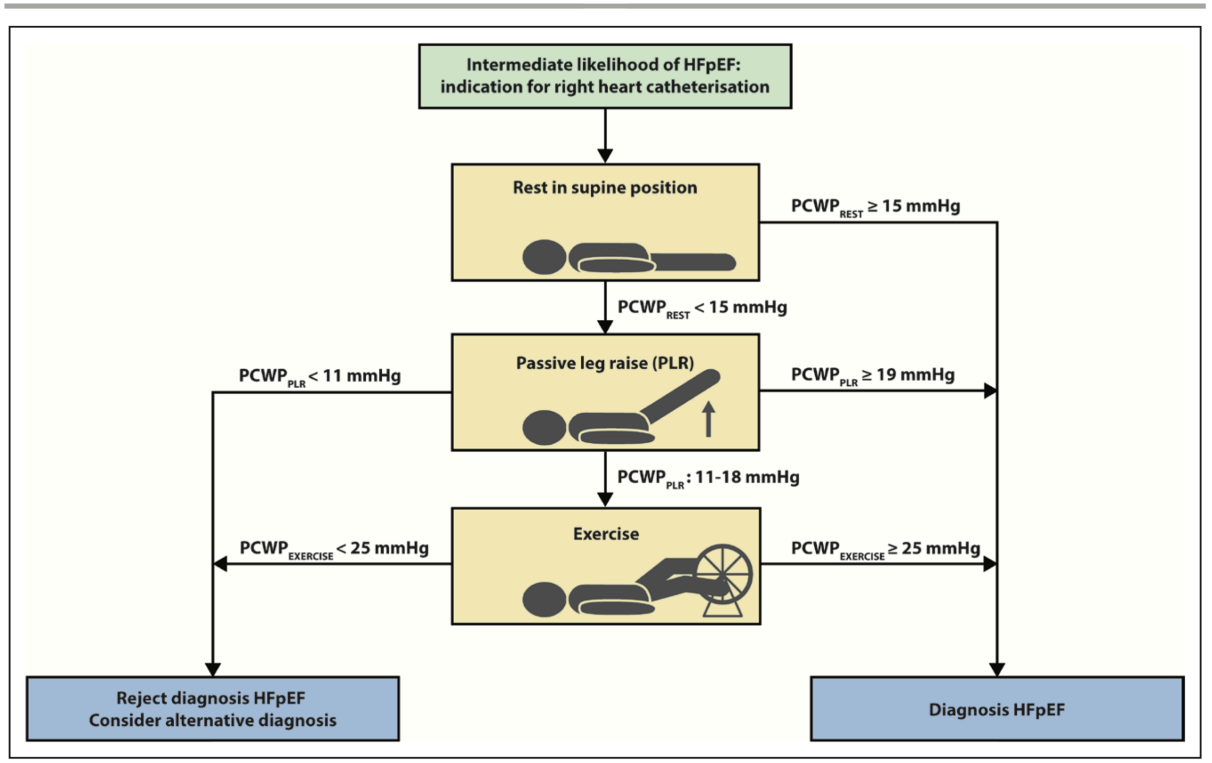


Figure 4. Implementation of passive leg raise test during right heart catheterization.
HFpEF indicates heart failure with preserved ejection fraction; PCWP, pulmonary capillary wedge pressure; and PLR, passive leg raise.

fluid challenge, are treated with PAH drugs, close monitoring is recommended		
In patients with PH at RHC, a borderline PAWP (13–15 mmHg) and features of HFpEF, additional testing with exercise or fluid challenge may be considered to uncover post-capillary PH[133,143]	IIb	C

ERS 2022

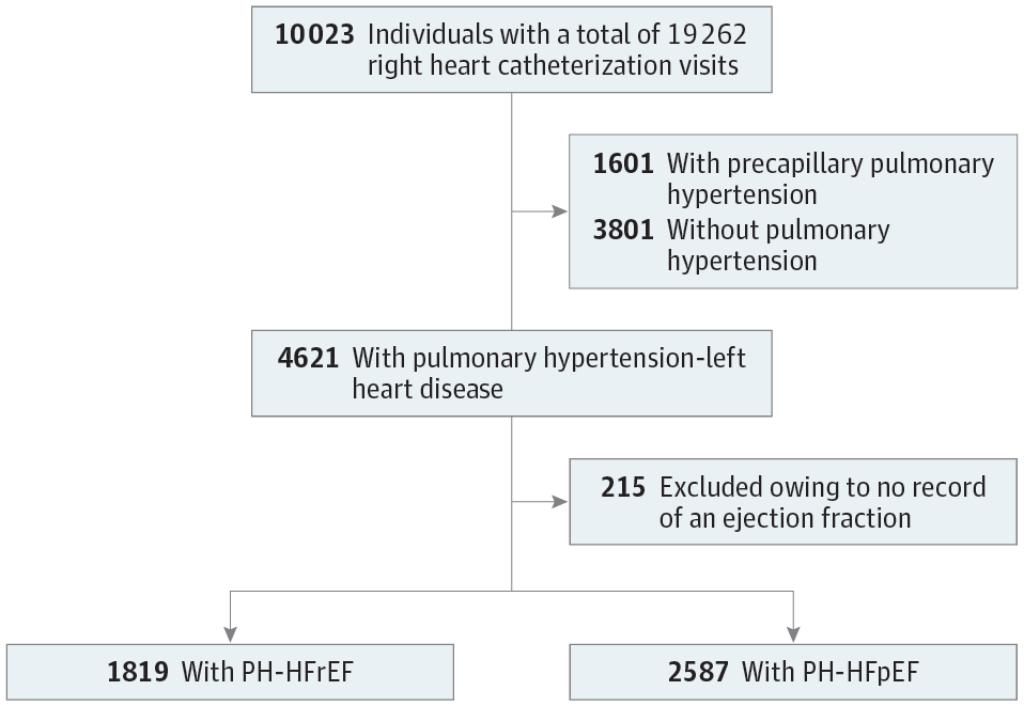
2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
European Heart Journal (2022) 43, 3618–3731

van de Bovenkamp et al.
Circ Heart Fail
. 2022 Apr;15(4):e008935.

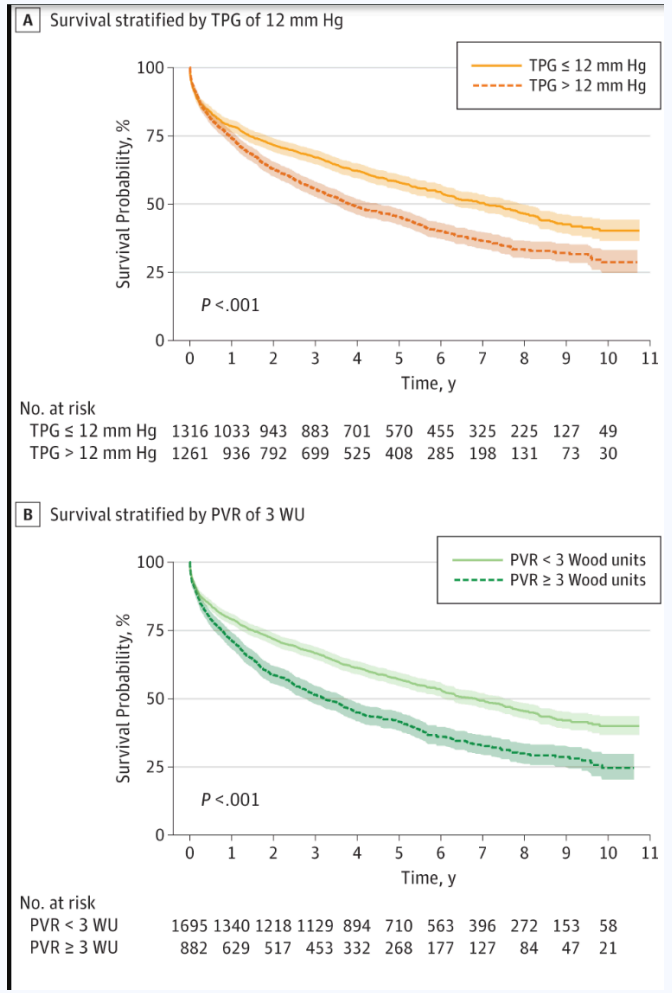
California Thoracic Society
ATS Chapter Serving California and Arizona

Who should I be worried about?

- Risk of mortality and hospitalizations increases with progressive elevation in PVR>5
- RV dysfunction
- Decreased exercise tolerance



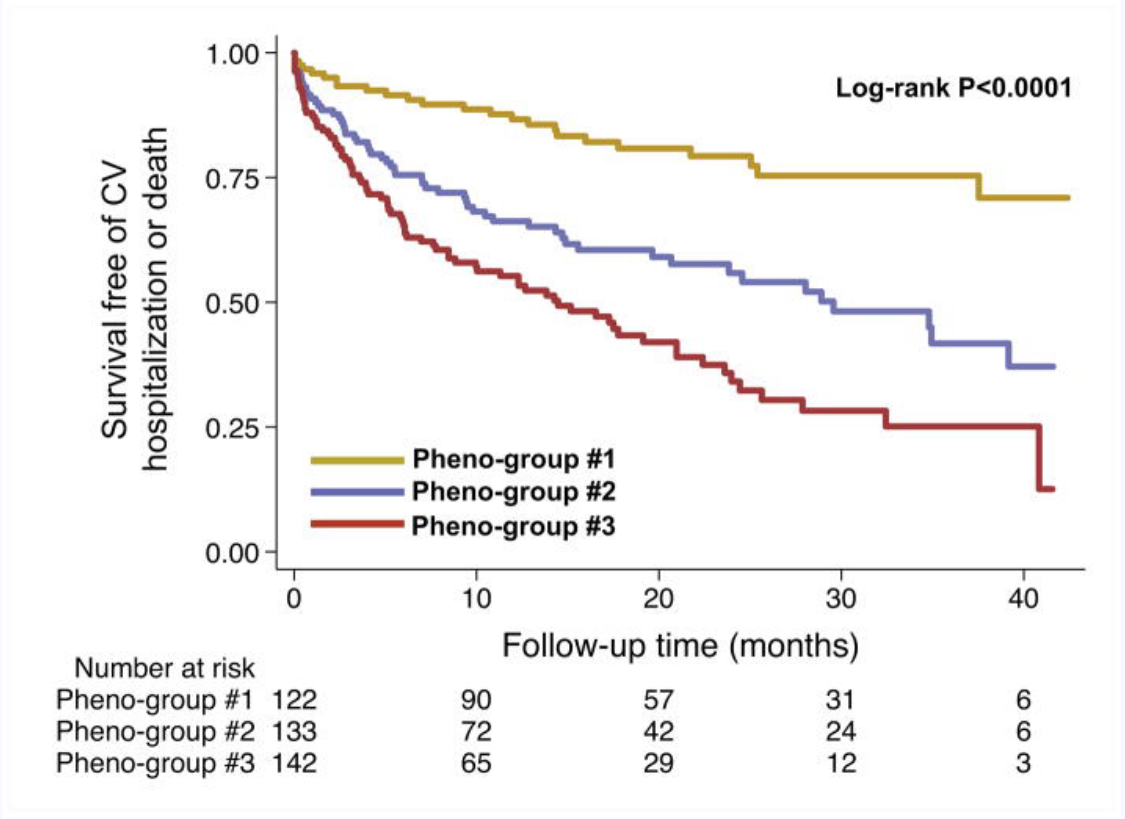
Among PH-HFpEF cohort



• Vanderpool et al. *JAMA Cardiol* 2018

HFpEF with PH is associated with worse prognosis

- 3 clusters of patients
  1) Younger patients with moderate diastolic dysfunction, normal BNP
  2) Obese, diabetic patients with high prevalence of OSA, worst LV relaxation
  3) **Older patients with CKD, myocardial remodeling, pulmonary hypertension & right ventricular dysfunction.**



• Shah et al. Circulation 2015

Treatment of Group 2 PH

- Optimize underlying cardiac disease (medical therapy, valve intervention, etc.).
- RHC will aid management decisions if ordering provider is specific in question
- Do no harm

Recommendation Table 22A

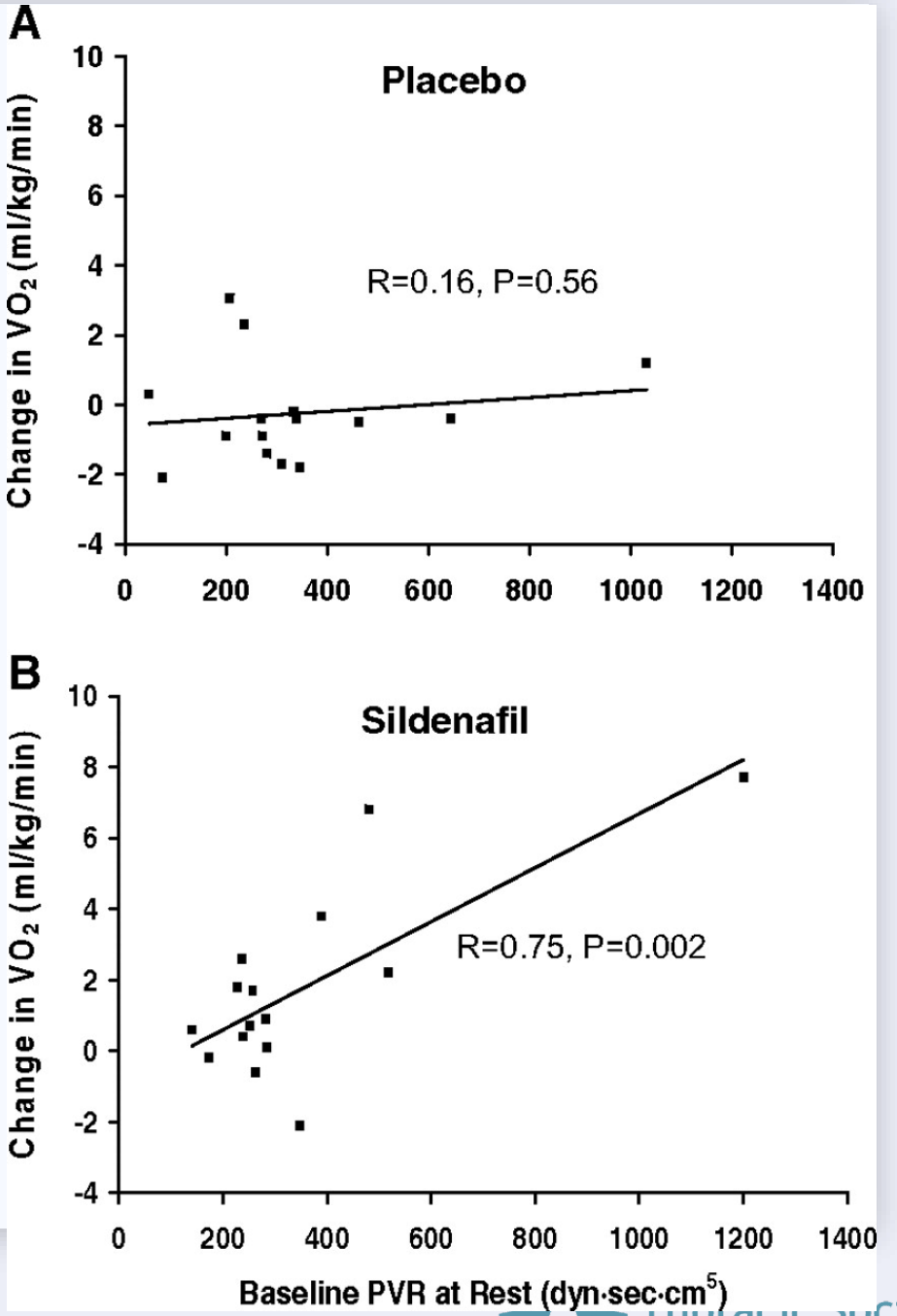
Recommendations	Class[a]	Level[b]
In patients with LHD, optimizing treatment of the underlying condition is recommended before considering assessment of suspected PH[27,28]	I	A
RHC is recommended for suspected PH in patients with LHD, if it aids management decisions	I	C
RHC is recommended in patients with severe tricuspid regurgitation with or without LHD prior to surgical or interventional valve repair	I	C
For patients with LHD and suspected PH with features of a severe pre-capillary component and/or markers of RV dysfunction, referral to a PH centre for a complete diagnostic work-up is recommended[29,47,142]	I	C
In patients with LHD and CpcPH with a severe pre-capillary component (e.g. PVR >5 WU), an individualized approach to treatment is recommended	I	C
When patients with PH and multiple risk factors for LHD, who have a normal PAWP at rest but an abnormal response to exercise or fluid challenge, are treated with PAH drugs, close monitoring is recommended	I	C
In patients with PH at RHC, a borderline PAWP (13–15 mmHg) and features of HFpEF, additional testing with exercise or fluid challenge may be considered to uncover post-capillary PH[133,143]	IIb	C
Drugs approved for PAH are not recommended in PH-LHD[c] 631,678,683,684,701,706	III	A

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
European Heart Journal (2022) 43, 3618–3731

• Humbert et al. EHJ 2023

PA therapies in HFrEF; not recommended

- FIRST trial : increased mortality with IV epoprostenol in patients with class IIIB/IV congestive heart failure (Califf et al. 1997)
- In patients with NYHA class IIIb-IV HF, left ventricular ejection fraction <35% and SPAP >40 mm Hg, bosentan did not change CI or SPAP or any echo parameters (Kaluski et al. 2007)
- Serious AEs occurred more frequently in the bosentan arm (20.3 vs. 7.1%).
  - Weight gain, hemoglobin and hematocrit reduction, leg edema, increased diuretic need
- Sildenafil for 12 weeks associated with improved RV function, augmented peak VO2, increased 6MWD, reduced PVR and increased CO in a study of 34 patients with symptomatic HFrEF and PH (Lewis et al. 2007)



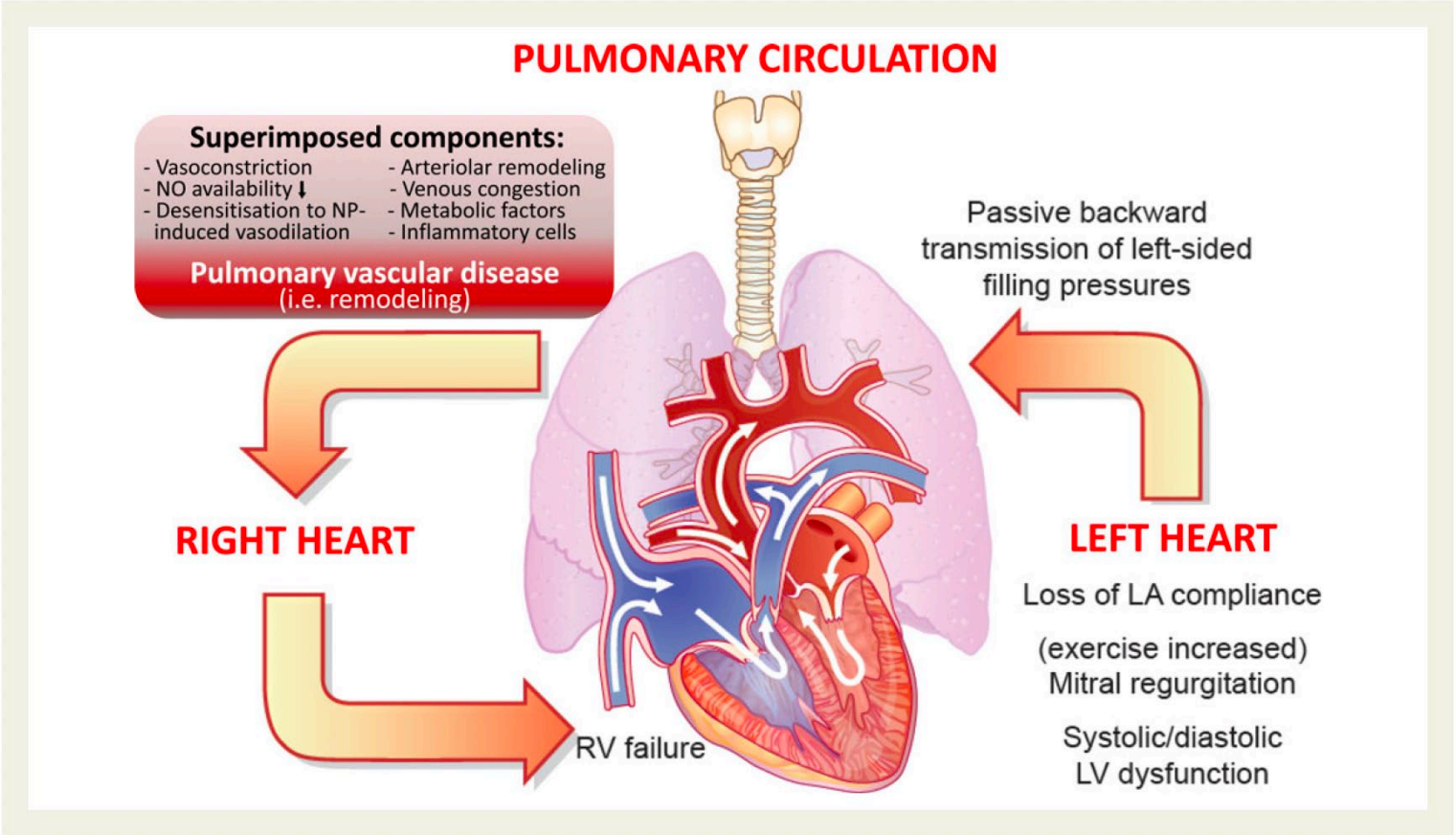
• Lewis et al. Circulation 2014

PH therapies in HFpEF

- MELODY-1 study: macitentan in patients with combined post- and pre-capillary PH with DPG≥7 and PVR 3 WU. Trend towards increased fluid retention and worsening in NYHA class; 10.08% (95% CI -15.07-33.26; p=0.34) with no changes in hemodynamics (Vachiéry et al. 2018)
- Sildenafil did not improve exercise capacity or clinical status in the RELAX trial in patients with HFpEF without PH
- Subsequent metabolomic profiling showed adverse effects on mitochondrial function and endoplasmic reticulum stress (Wang et al. 2017)
- Some small RCTs have shown benefit for PDE5 in HFpEF
  - In 44 patient with HfpEF and PASP>50, reduction in mPAP, improved RV function, reduced RV dimensions, increased CI, reduced RAP, improved alveolar-capillary membrane gas conductance (Guazzi et al. Circ 2011)

Why might these meds not be effective

- Lowering of PVR and increased pulmonary blood flow may lead to increased PCWP & pulmonary edema
- Reduced LA compliance will predispose PCWP to increase



- Rosenkranz et al. EHJ 2016

Management of HFpEF

- The Guidelines: 2022 AHA/ACC/HFSA Guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.

- **3rd top take-home message on HFpEF**

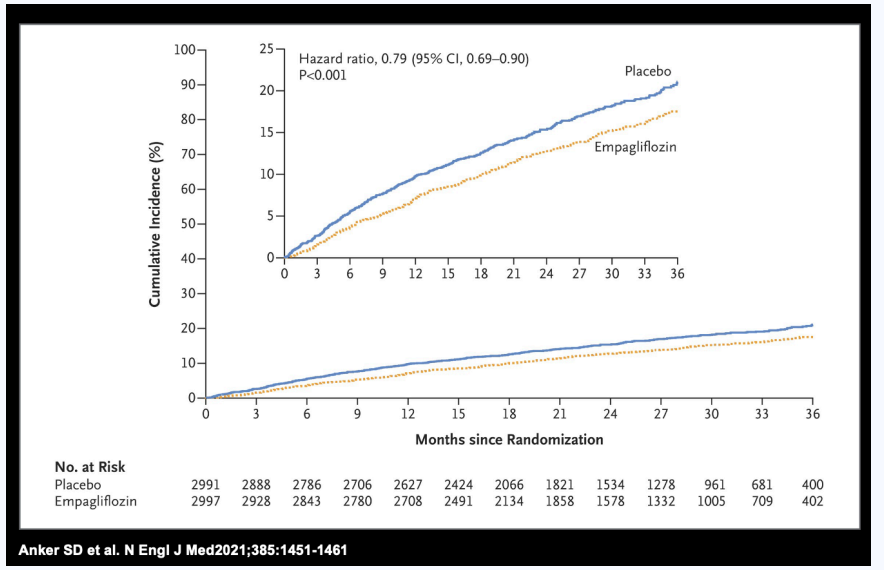
- New recommendations for HFpEF are made for **SGLT2i** (Class of Recommendation 2a), **MRAs** (Class of Recommendation 2b), and ARNi (Class of Recommendation 2b). Prior recommendations: treatment of hypertension (Class of Recommendation 1), treatment of atrial fibrillation (Class of Recommendation 2a), use of ARBs (Class of Recommendation 2b), and avoidance of routine use of nitrates or phosphodiesterase-5 inhibitors (Class of Recommendation 3: No Benefit).

COR	LOE	Recommendations
2a	B-R	In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.[33]
2b	B-R	In selected patients with HFpEF, MRA may be considered to decrease hospitalizations, particularly in patients with LVEF on the lower end of this spectrum.[38,42,43]
2b	B-R	In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly in patients with LVEF on the lower end of this spectrum.

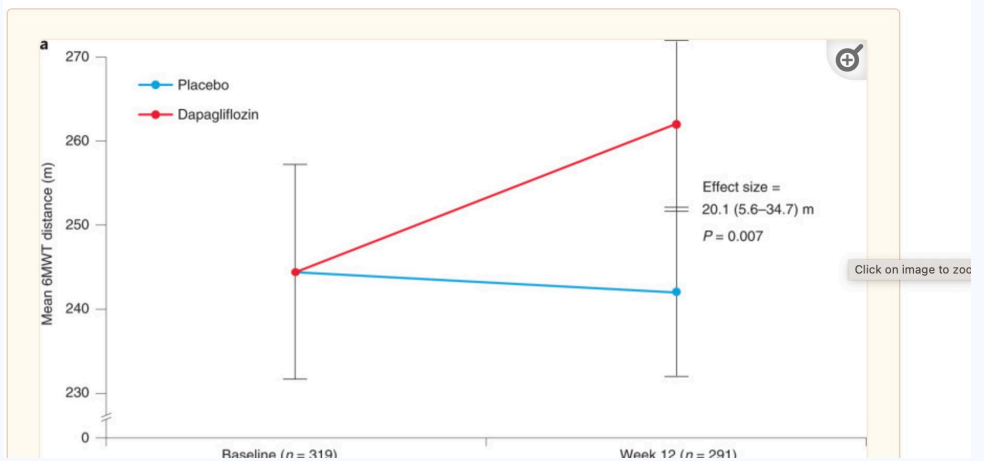
• Heidenreich P, Bozkurt B, Aguilar D, et al. J Card Fail 2022; 28(5): e1-e167

How can SGLT2 inhibitors help in HFpEF?

- 18% - 21% reduction in primary endpoint of HF hospitalization or cardiovascular death
- Nephroprotective
- EMPEROR-Preserved
- DELIVER
- Dapagliflozin has been shown to improve QOL & exercise capacity



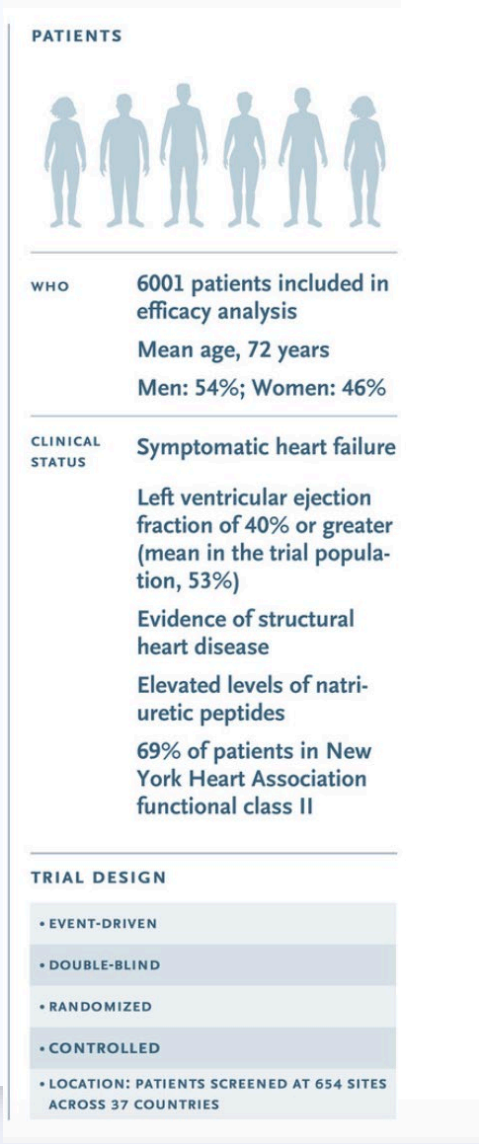
Anker SD et al. N Engl J Med2021;385:1451-1461

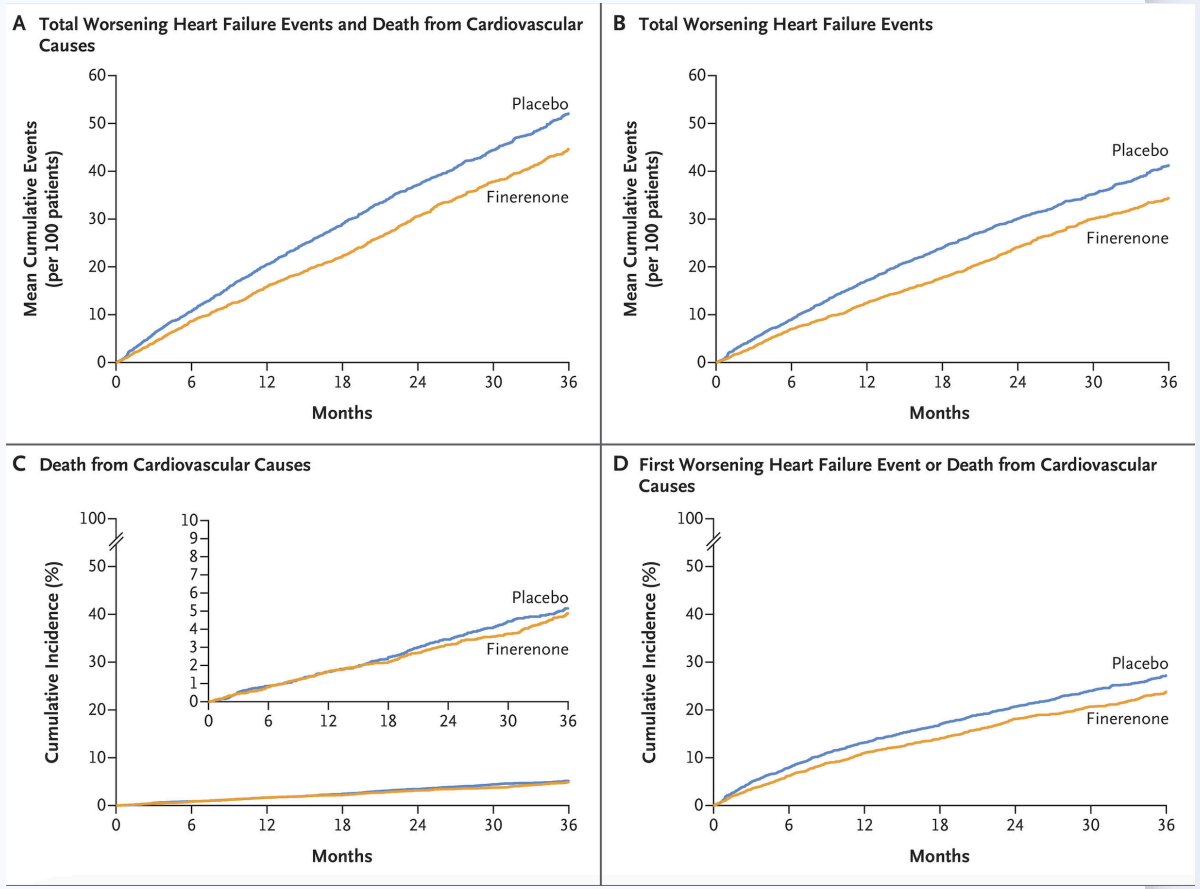


Nassif et al. Nat Med 2021

Non-steroidal MRA in HFpEF; FINEARTS-HF

- Lower rate of composite of total worsening heart failure events and death from cardiovascular causes (the primary outcome) in patients with heart failure and LVEF >40%
- Moderate improvement in KCCQ, no improvement in NYHA Class

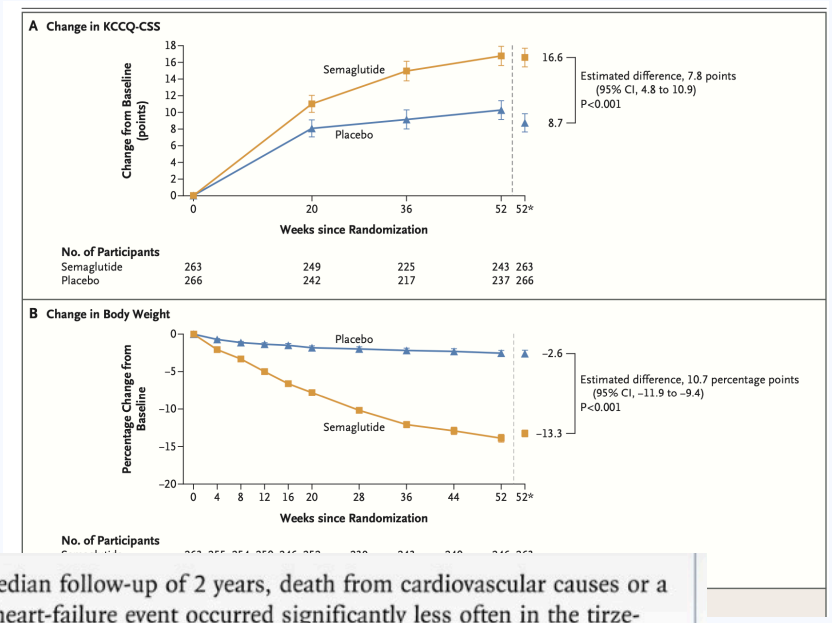




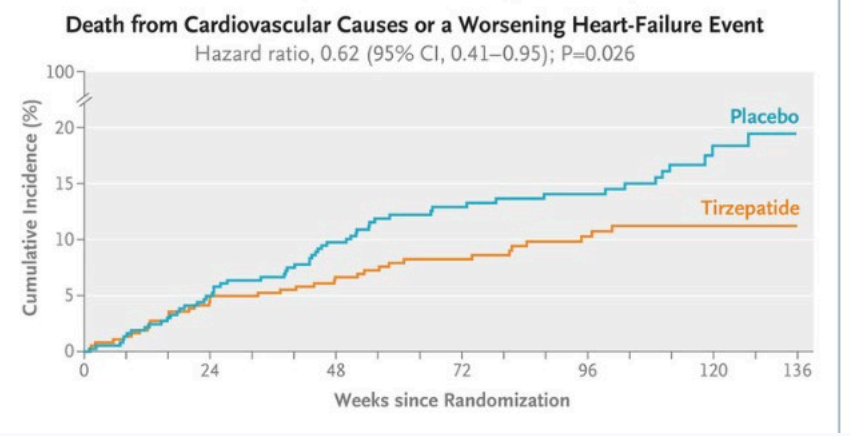
• Soloman et al. NEJM 2024

Obesity management in HFpEF

- STEP-HFpEF; semaglutide reduced symptoms, improved exercise function in patients with BMI >30, and without T2DM. Secondary analysis has also shown reduction in NT-pro BNP
- In patients with BMI>30 tirzepatide=>lower risk of composite of death from CV cause or worsening HF than placebo and improved health status



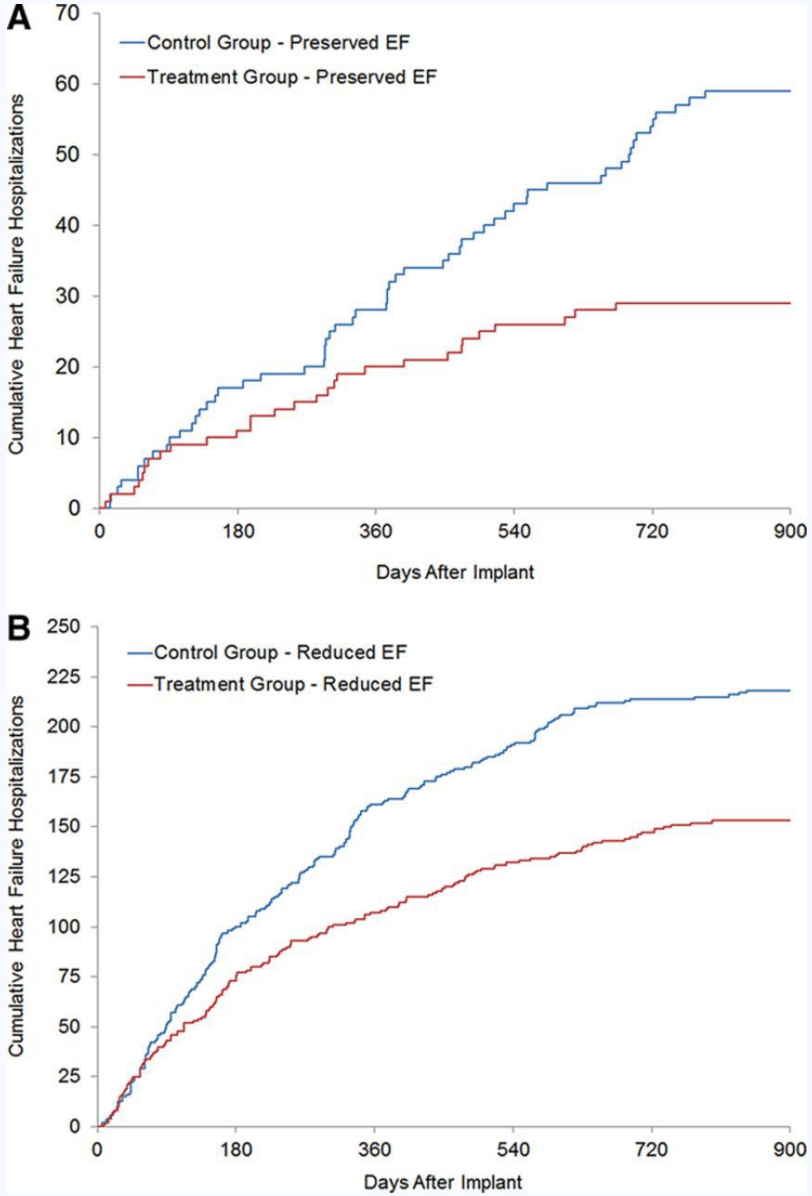
During a median follow-up of 2 years, death from cardiovascular causes or a worsening heart-failure event occurred significantly less often in the tirzepatide group than in the placebo group. At 52 weeks, improvement in the KCCQ-CSS was significantly greater in the tirzepatide group.



Options to consider in select patients

- Champion trial: **PA sensor reduces hospitalizations and stabilizes pulmonary artery pressures**
  - Using AOC methods, treatment group patients had a median reduction of −3.0 mm Hg days versus an increase of 97.7 mm Hg days in control group patients during the 6 months of primary follow-up.
  - Hospitalizations preceded by rise in mPA in both HFrEF and HfpEF

Photo Credit: Endotronix



• Circ Heart Fail 2014 Nov;7(6):935-44.

California Thoracic Society
ATS Chapter Serving California and Arizona

Some final pearls

- Understand severity of co-morbidities
- Invasive testing may be required with provocative maneuvers; **get the most out of the right heart cath**
- De-prescription of Group 1 therapies may be required
- Studies focusing on PDE5is in patients with HFpEF and a CpcPH phenotype are currently ongoing. Is there a PVR cutoff above which there is benefit?
- No recommendation regarding PDE5i use in patients with HFpEF and Cpc- PH but should be avoided in HFrEF
- Treatment options for HFpEF are expanding
- Know your patient's hemodynamics and RV function
- Caution with patients with RV predominant phenotype given risks of decompensated RV failure with intubation and invasive ventilation

Patient Case Conclusion

- PYP scan 10/24/2024 was highly suggestive of ATTR amyloidosis. Excluded AL amyloidosis with normal K/L ratio, normal SPEP.
- Tadalfil stopped
- Started on Tafamadis with reported significant improvement in exertional dyspnea
- Down-trending NT- pro BNP and normalized troponin
- Maintained on spironolactone 25 mg daily, Jardiance 10 mg daily and Lasix 20 mg

	10/1/2024 12:00 PM	3/17/2025 11:00 AM
Cardiology Six Minute Walk Distance		
Distance Traveled (m)	244 Meters	326 Meters

References

- Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S; ESC/ERS Scientific Document Group. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022 Oct 11;43(38):3618-3731. doi: 10.1093/eurheartj/ehac237. Erratum in: Eur Heart J. 2023 Apr 17;44(15):1312. doi: 10.1093/eurheartj/ehad005. PMID: 36017548.

- Rosenkranz S, Gibbs JS, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiery JL. Left ventricular heart failure and pulmonary hypertension. Eur Heart J 2016;37: 942–954. 48.

- Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol 2009;53:1119–1126.

- Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart Failure With Preserved Ejection Fraction: JACC Scientific Statement. J Am Coll Cardiol. 2023 May 9;81(18):1810-1834. doi: 10.1016/j.jacc.2023.01.049. Epub 2023 Apr 19. PMID: 37137592.

References

- Kaluski E, Cotter G, Leitman M, Milo-Cotter O, Krakover R, Kobrin I, Moriconi T, Rainisio M, Caspi A, Reizin L, Zimlichman R, Vered Z. Clinical and hemodynamic effects of bosentan dose optimization in symptomatic heart failure patients with severe systolic dysfunction, associated with secondary pulmonary hypertension--a multi-center randomized study. Cardiology. 2008;109(4):273-80. doi: 10.1159/000107791. Epub 2007 Sep 17. PMID: 17873492.
- van de Bovenkamp AA, Wijkstra N, Oosterveer FPT, Vonk Noordegraaf A, Bogaard HJ, van Rossum AC, de Man FS, Borlaug BA, Handoko ML. The Value of Passive Leg Raise During Right Heart Catheterization in Diagnosing Heart Failure With Preserved Ejection Fraction. Circ Heart Fail. 2022 Apr;15(4):e008935. doi: 10.1161/CIRCHEARTFAILURE.121.008935. Epub 2022 Mar 21. PMID: 35311526; PMCID: PMC9009844.
- Adamson PB, Abraham WT, Bourge RC, Costanzo MR, Hasan A, Yadav C, Henderson J, Cowart P, Stevenson LW. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. Circ Heart Fail. 2014 Nov;7(6):935-44. doi: 10.1161/CIRCHEARTFAILURE.113.001229. Epub 2014 Oct 6. PMID: 25286913.
- Califf RM, Adams KF, McKenna WJ, Gheorghiade M, Uretsky BF, McNulty SE, Darius H, Schulman K, Zannad F, Handberg-Thurmond E, Harrell FE Jr, Wheeler W, Soler-Soler J, Swedberg K. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). Am Heart J. 1997 Jul;134(1):44-54. doi: 10.1016/s0002-8703(97)70105-4. PMID: 9266782.

References

- Reddy YNV, Frantz RP, Hassoun PM, Hemnes AR, Horn E, Leopold JA, Rischard F, Rosenzweig EB, Hill NS, Erzurum SC, Beck GJ, Finet JE, Jellis CL, Mathai SC, Tang WHW, Borlaug BA. Clinical Implications of Pretest Probability of HFpEF on Outcomes in Precapillary Pulmonary Hypertension. J Am Coll Cardiol. 2024 Nov 26;84(22):2196-2210. doi: 10.1016/j.jacc.2024.08.061. Epub 2024 Oct 23. PMID: 39453363; PMCID: PMC11760158.
- Wang H, Anstrom K, Ilkayeva O, Muehlbauer MJ, Bain JR, McNulty S, Newgard CB, Kraus WE, Hernandez A, Felker GM, Redfield M, Shah SH. Sildenafil Treatment in Heart Failure With Preserved Ejection Fraction: Targeted Metabolomic Profiling in the RELAX Trial. JAMA Cardiol. 2017 Aug 1;2(8):896-901. doi: 10.1001/jamacardio.2017.1239. PMID: 28492915; PMCID: PMC5815079.
- Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart Failure With Preserved Ejection Fraction: JACC Scientific Statement. J Am Coll Cardiol. 2023 May 9;81(18):1810-1834. doi: 10.1016/j.jacc.2023.01.049. Epub 2023 Apr 19. PMID: 37137592.
- 2022 AHA/ACC/HFSA Guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Heidenreich P, Bozkurt B, Aguilar D, et al. J Card Fail 2022; 28(5): e1-e167
- Anker SD, Butler J, Filippatos G, et al. Empa- gliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385:1451–1461.

References

- Shah, S. J. *et al.* Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation* **131**, 269–279 (2015).
- Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022;387:1089–1098.
- Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, Khariton Y, Malik AO, Khumri T, Umpierrez G, Lamba S, Sharma K, Khan SS, Chandra L, Gordon RA, Ryan JJ, Chaudhry SP, Joseph SM, Chow CH, Kanwar MK, Pursley M, Siraj ES, Lewis GD, Clemson BS, Fong M, Kosiborod MN. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med. 2021 Nov;27(11):1954-1960. doi: 10.1038/s41591-021-01536-x. Epub 2021 Oct 28. PMID: 34711976; PMCID: PMC8604725.

References

- Solomon SD, McMurray JJV, Vaduganathan M, Claggett B, Jhund PS, Desai AS, Henderson AD, Lam CSP, Pitt B, Senni M, Shah SJ, Voors AA, Zannad F, Abidin IZ, Alcocer-Gamba MA, Atherton JJ, Bauersachs J, Chang-Sheng M, Chiang CE, Chioncel O, Chopra V, Comin-Colet J, Filippatos G, Fonseca C, Gajos G, Goland S, Goncalvesova E, Kang S, Katova T, Kosiborod MN, Latkovskis G, Lee AP, Linssen GCM, Llamas-Esperón G, Mareev V, Martinez FA, Melenovský V, Merkely B, Nodari S, Petrie MC, Saldarriaga CI, Saraiva JFK, Sato N, Schou M, Sharma K, Troughton R, Udell JA, Ukkonen H, Vardeny O, Verma S, von Lewinski D, Voronkov L, Yilmaz MB, Zieroth S, Lay-Flurrie J, van Gameren I, Amarante F, Kolkhof P, Viswanathan P; FINEARTS-HF Committees and Investigators. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2024 Oct 24;391(16):1475-1485. doi: 10.1056/NEJMoa2407107. Epub 2024 Sep 1. PMID: 39225278.

- Vachiéry JL, Delcroix M, Al-Hiti H, Efficace M, Hutyra M, Lack G, Papadakis K, Rubin LJ. Macitentan in pulmonary hypertension due to left ventricular dysfunction. Eur Respir J. 2018 Feb 7;51(2):1701886. doi: 10.1183/13993003.01886-2017. PMID: 29437943.

- Lewis GD, Shah R, Shahzad K, Camuso JM, Pappagianopoulos PP, Hung J, Tawakol A, Gerszten RE, Systrom DM, Bloch KD, Semigran MJ. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation. 2007 Oct 2;116(14):1555-62. doi: 10.1161/CIRCULATIONAHA.107.716373. Epub 2007 Sep 4. PMID: 17785618.

- Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. Circulation. 2011 Jul 12;124(2):164-74. doi: 10.1161/CIRCULATIONAHA.110.983866. Epub 2011 Jun 27. PMID: 21709061.

Novel Developments in Group 3 PH

Namita Sood MD, FCCP

University of California –Davis

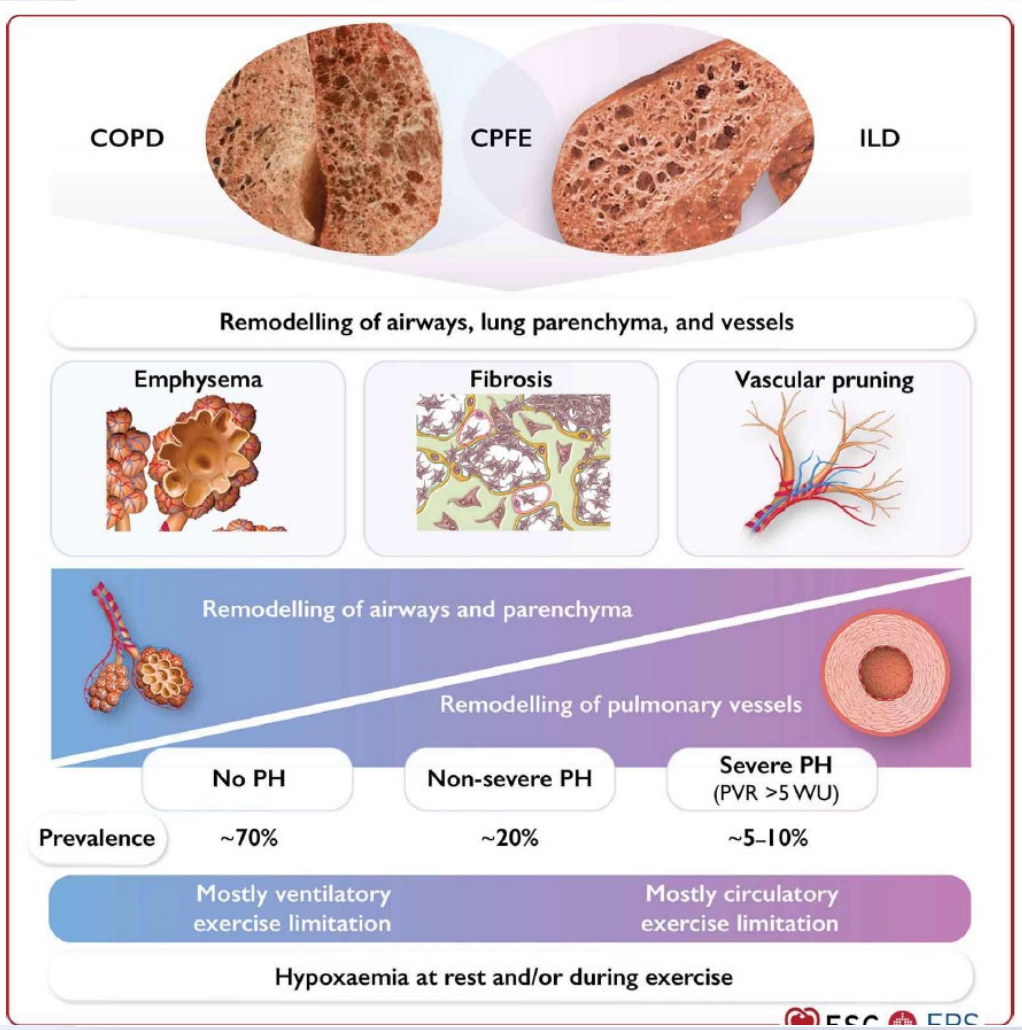
Disclosures

- I have the following relationships with ACCME defined ineligible companies:
- Speakers Bureau : Boehringer Ingelheim, Bayer
- Consulting (Advisory Board) Merck, United Therapeutics
- Research : Bayer, Gossamer, Merck , ?united Therapeutics. Pulmonvant, Insmed
- I **WILL/WILL NOT** discuss off-label use and/or investigational use of any drugs or devices.

PH associated with Lung disease and/or Hypoxia(Group 3)

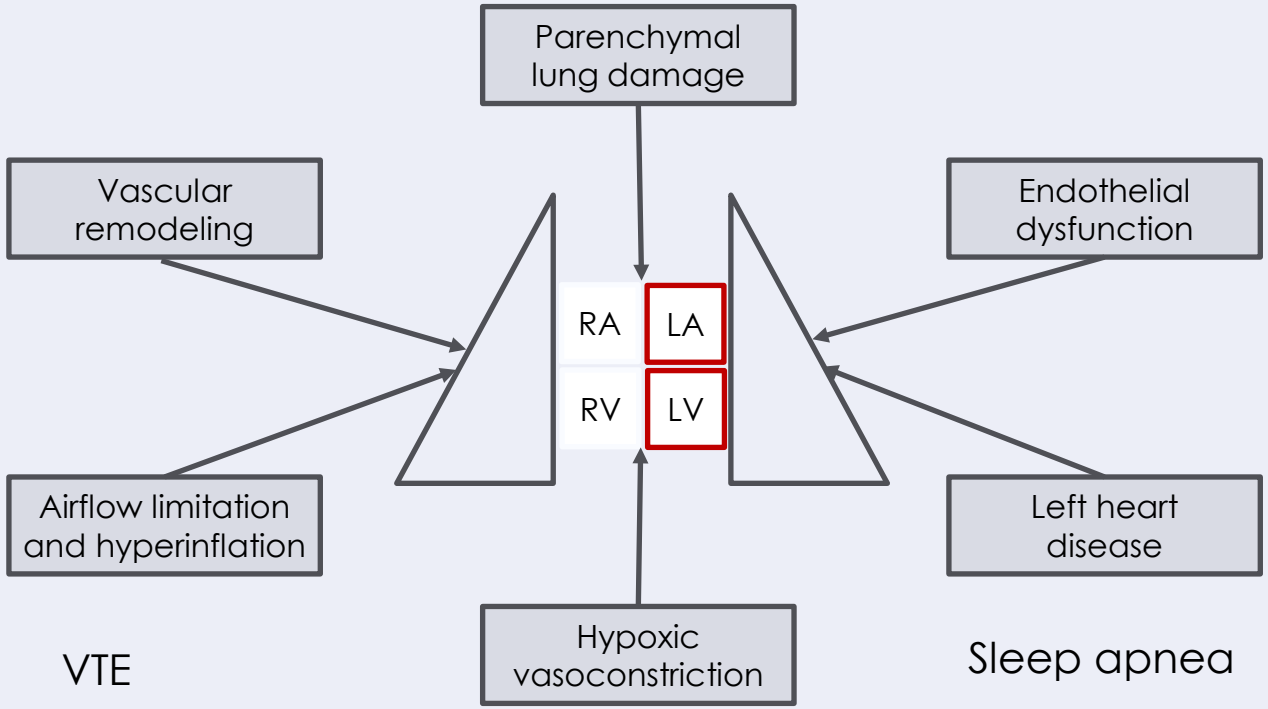
- 3.1 Obstructive lung disease or emphysema
- 3.2 Interstitial Lung Disease
- 3.3 Combined Pulmonary Fibrosis and Emphysema
- 3.4 Nonparenchymal Restrictive lung Disease
  - Hypoventilation syndromes
  - Pneumonectomy
- 3.5 Hypoxia without lung disease (e.g. high altitude)
- 3.6 Developmental lung disorders

Few Considerations



- PH > 20 mmHG PVR >2 WU
- PH >25mmHg PVR >3WU
- Severe PH > 35mmHg
- Severe PH PVR> 5WU a better indicator

The pathophysiology of group 3 PH is multifactorial and complex

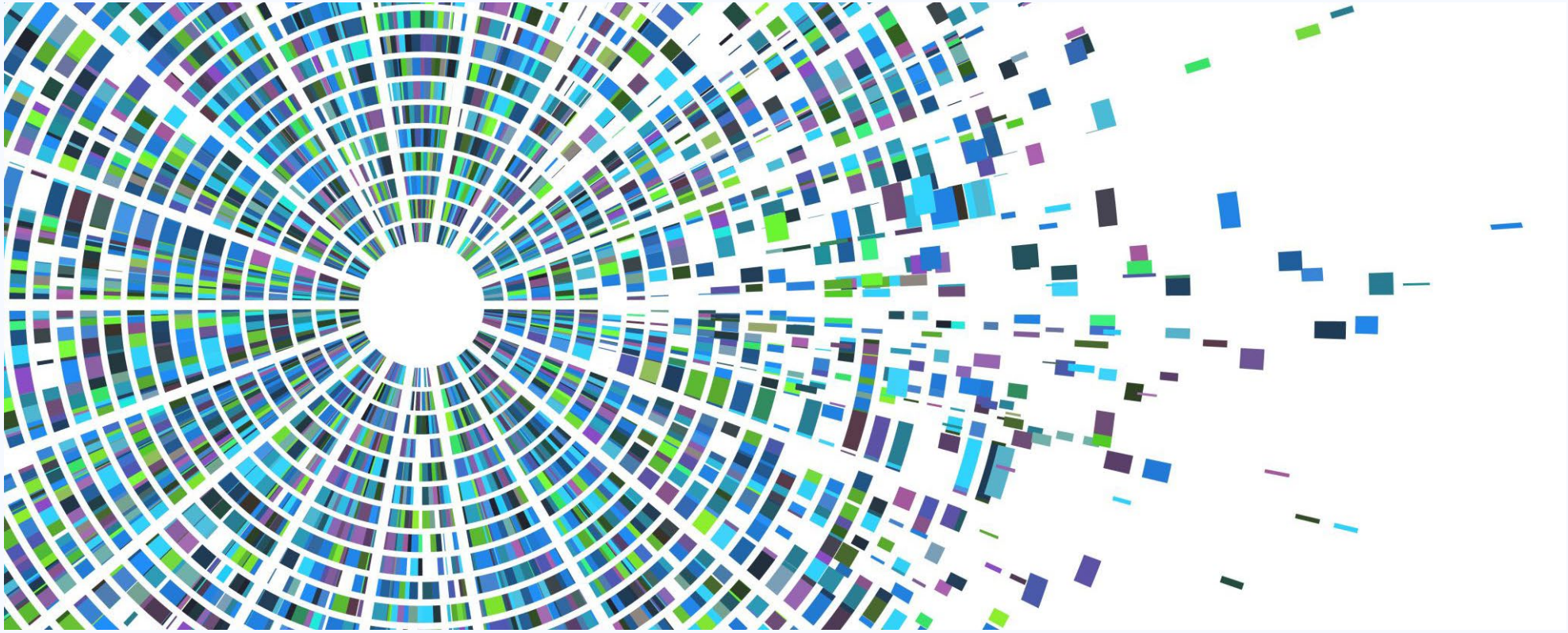


Consider coexistent contributory conditions in CLD-PH patients

- Left heart dysfunction, thromboembolic disease, sleep disordered breathing.

CLD, chronic lung disease; IPAH, idiopathic pulmonary arterial disease; PH, pulmonary hypertension; RA: right atrium; RV: right ventricle; LA: left atrium; LV: left ventricle. Krompa A, et al. *Breathe.* 2022;18:220205.

Prevalence

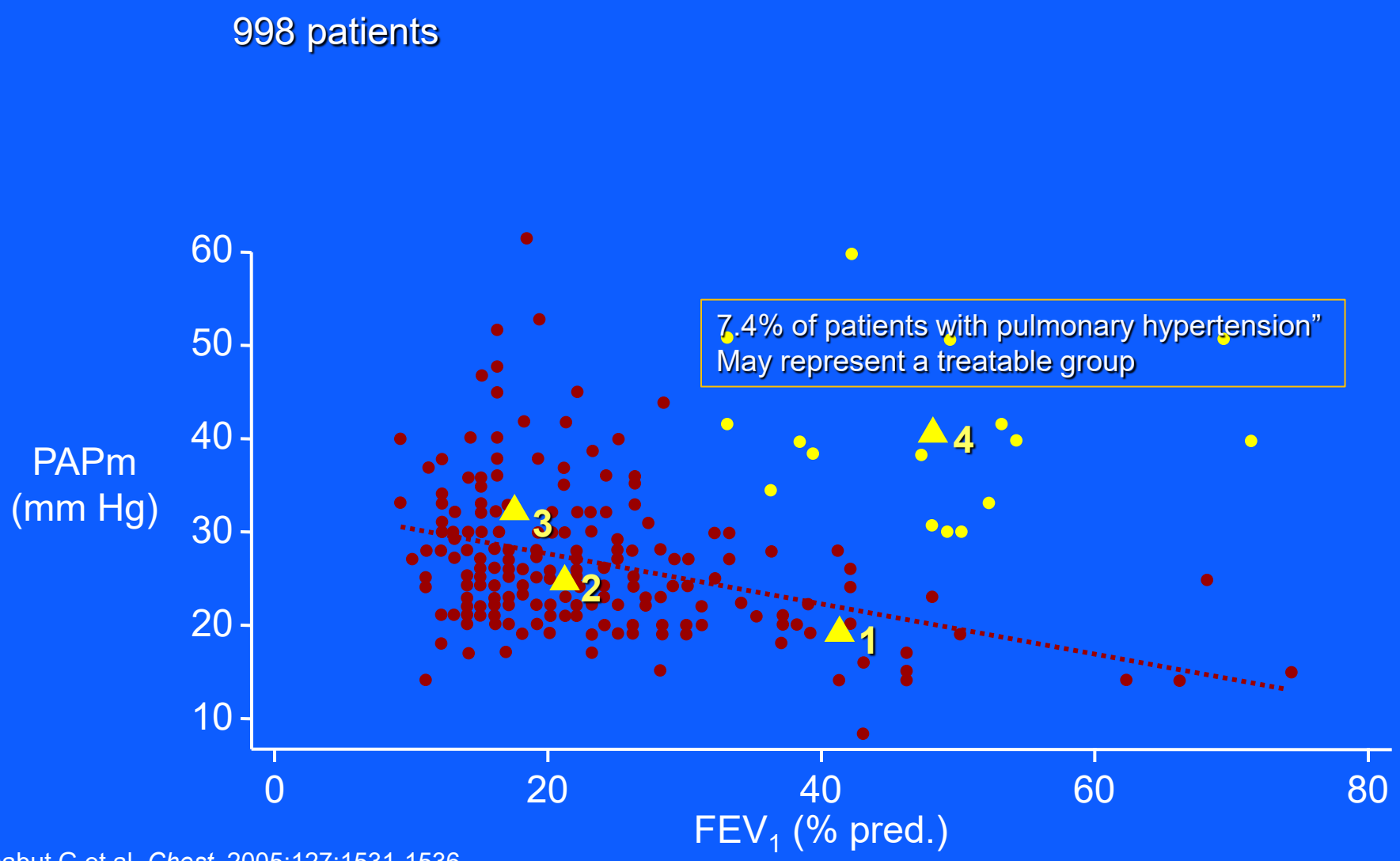


- Prevalence
  - Varies by underlying lung disease
  - Tools used for Diagnosis are varied
  - Data skewed by single center studies and biased populations
    - Tertiary referral centers
    - Transplant evaluation

PH in Lung Disease

- Non Severe PH common in COPD
- - Overall 39%
- - upto 90 % with advanced COPD
- Severe PH uncommon
  - 1-5 %
- Independent of severity of lung Disease

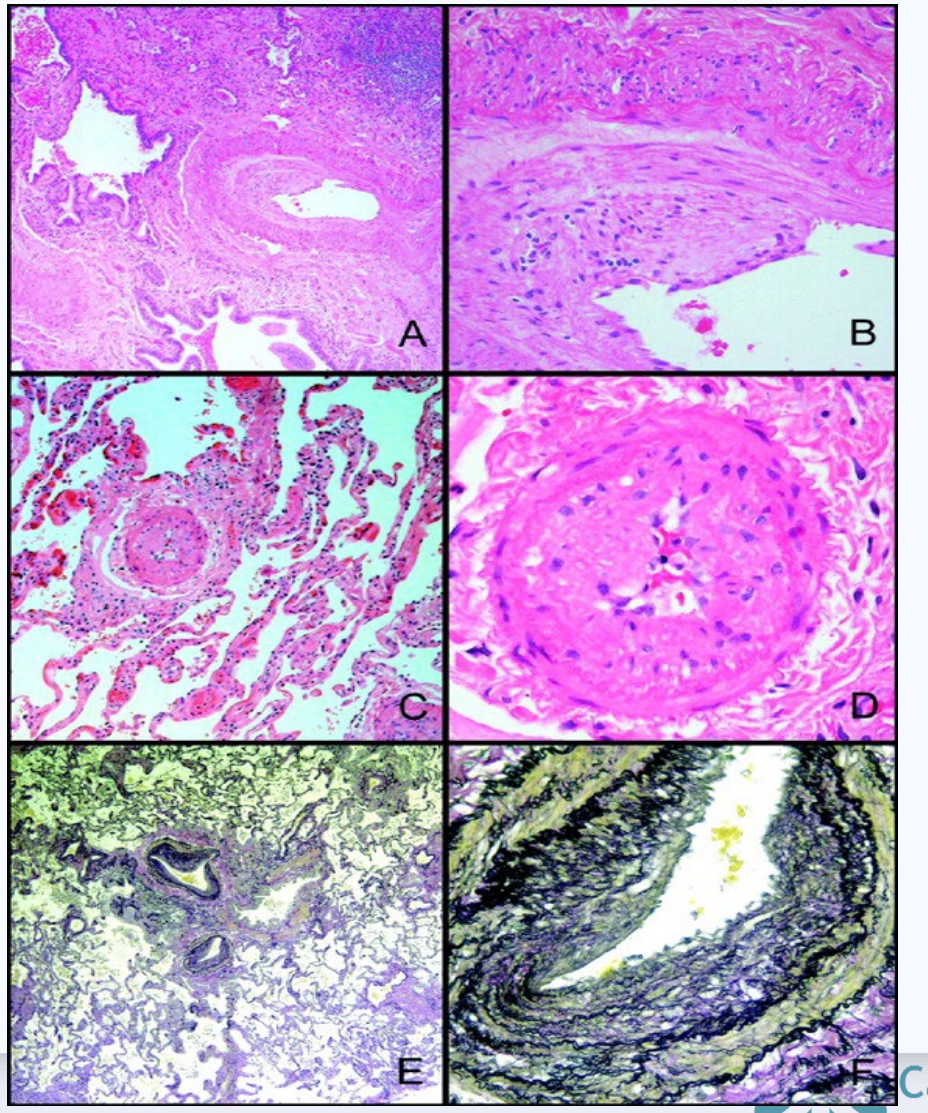
COPD and Pulmonary Hypertension



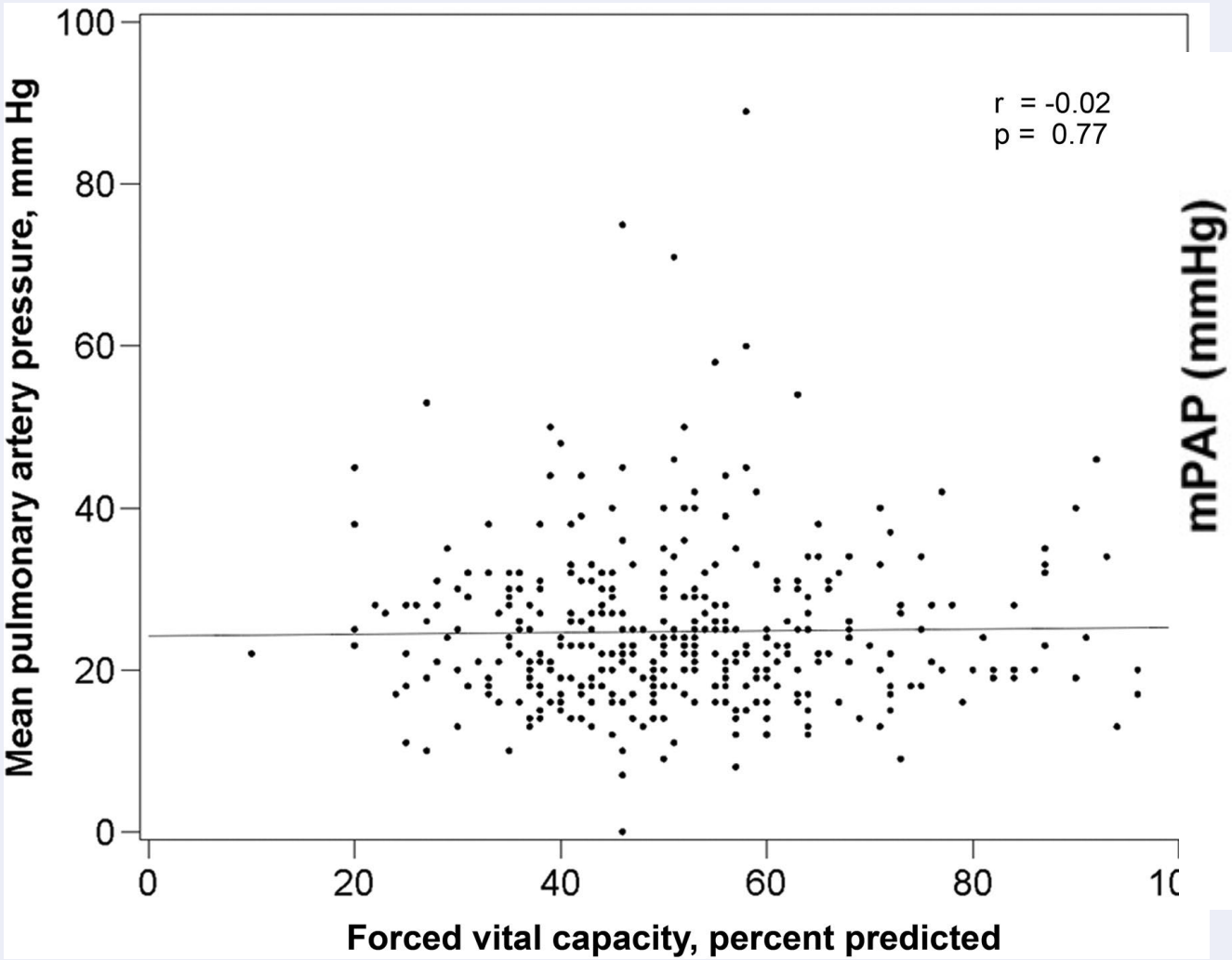
Thabut G et al. *Chest.* 2005;127:1531-1536.

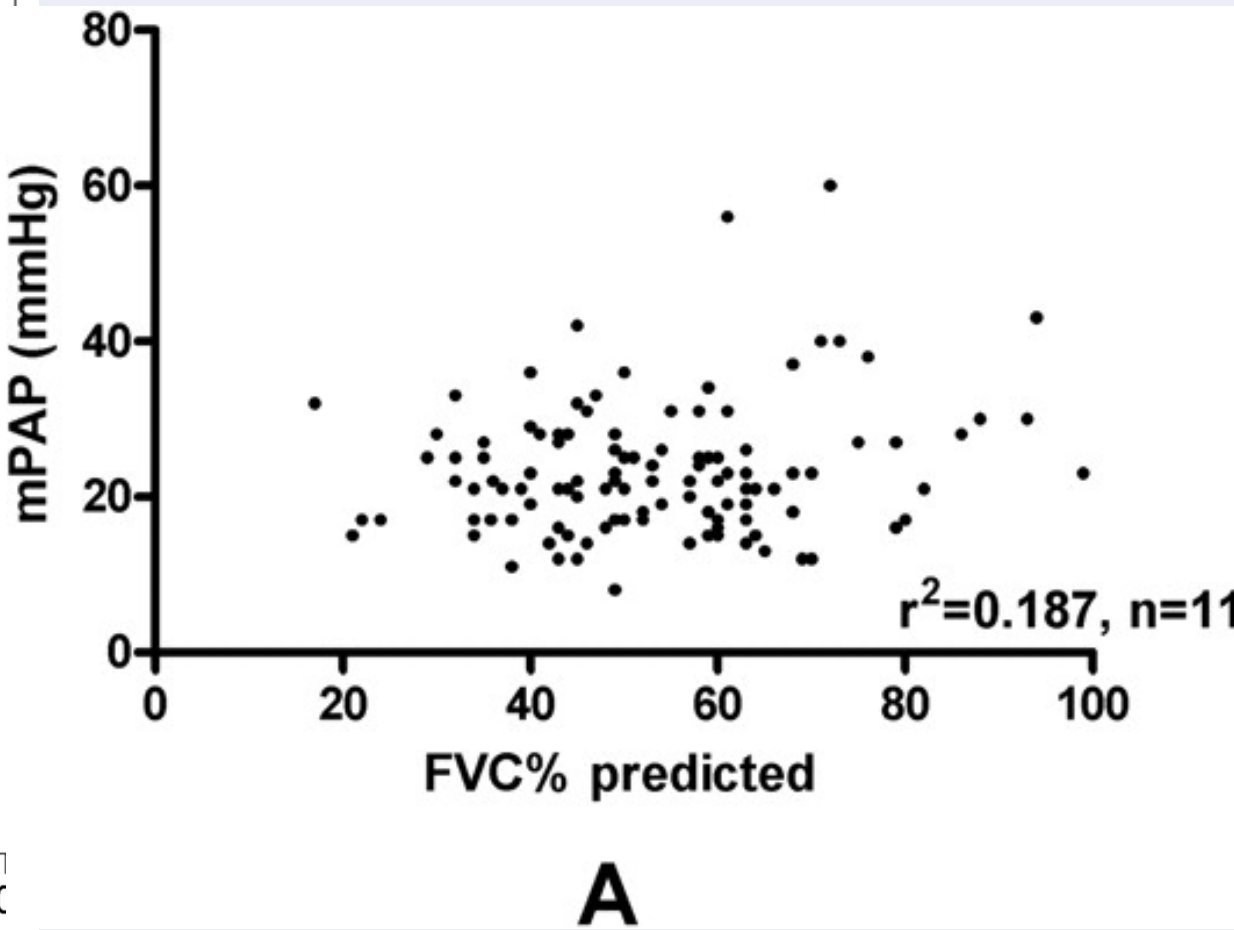
PH in ILD

Diagnosis	
IPF	
- **Time of Dx**	8-15%
- **Advanced Disease**	30-50%
- **End Stage Disease**	>60%
CPFE	30-50%
Chronic HP	20%
CTD -ILD	2-24%
Hypoventilation	
High altitude	5%
Sarcoidosis	5-74%
Lymphangiolieomatosis	5-6%



Scatter plot of FVC% vs mPAP in IPF patients





Patel, N. M. et al. Chest 2007;132:998-1006

Nathan, S. D. et al. Chest 2007;131:657-663

ARTEMIS IPF

TABLE 1 Baseline demographic and disease characteristics of subjects with and without pulmonary hypertension (PH) at baseline

	Group 3# PH	Group 2# PH		No PH, elevated PAWP		No PH, PAWP not elevated	
		Demographics	p-value *versus* Group 3 PH	Demographics	p-value *versus* Group 3 PH	Demographics	p-value *versus* Group 3 PH
Subjects n	68	25		21		374	
Age years	68.0±6.14	67.6±6.28	0.62	66.1±7.65	0.30	65.5±7.44	0.016
Sex male/female	47 (69.1)/ 21 (30.9)	20 (80.0)/ 5 (20.0)	0.44	20 (81.0)/ 4 (19.0)	0.41	267 (71.4)/ 107 (28.6)	0.77
BMI kg·m^{-2}	31.4±5.12	32.8±2.87	0.051	30.4±4.81	0.54	29.2±4.38	<0.001
Smoking status			0.10		0.76		0.78
Never	22 (32.4)	4 (16.0)		5 (23.8)		124 (33.2)	
Current	2 (2.9)	3 (12.0)		0		7 (1.9)	
Former	44 (64.7)	18 (72.0)		16 (76.2)		243 (65.0)	
Ethnicity			0.32		0.46		0.20
American Indian	1 (1.5)	0		0		1 (0.3)	
Asian	0	0		1 (4.8)		4 (1.1)	
Black or African heritage	1 (1.5)	0		0		0	
Collection of data not permitted	0	0		0		3 (0.8)	
Other	7 (10.3)	0		1 (4.8)		34 (9.1)	
White	59 (86.8)	25 (100)		19 (90.5)		332 (88.8)	
FEV$_1$ % predicted	74.1±14.38	77.0±11.95	0.23	75.9±15.31	0.67	76.6±15.0	0.12
FVC % predicted	66.9 (12.09)	69.9 (11.42)	0.18	68.2 (12.07)	0.66	69.5 (13.78)	0.12
***D*$_{LCO}$ % predicted**[¶]	39.1±14.78	40.5 (11.97)	0.41	43.5±9.65	0.064	44.1±13.69	0.002
6MWD m	356±131.3	372±108.3	0.78	400±96.4	0.16	427±115.8	<0.001
Residual volume % predicted	62±27.0	55±19.4	0.38	54±20.5	0.25	61±22.9	0.88
Resting % O_2 saturation	88±20	90±20.8	0.039	92±16.5	0.013	89±21.8	<0.001
Lowest % O_2 saturation on exercise	84±5.8	88±6.3	0.008	87±5.7	0.027	89±5.3	<0.001
Cardiac output L·min^{-1}	5.26±1.31	5.58±1.58	0.65	5.2±1.27	0.95	5.42±1.49	0.47
Cardiac index L·min^{-1}·m^{-2}	2.7±0.68	2.6±0.71	0.5	2.6±0.52	0.44	2.8±0.77	0.53
Mean PAP mmHg	29.6±7.53	33.4±7.35	0.002	21.9±1.90	<0.001	17.7±3.82	<0.001
Pulmonary vascular resistance mmHg·L^{-1}·min	3.9±3.09	2.6±1.46	>0.001	1.0±0.51	<0.001	1.8±0.90	<0.001

Impact of PH-COPD

Compera Registry

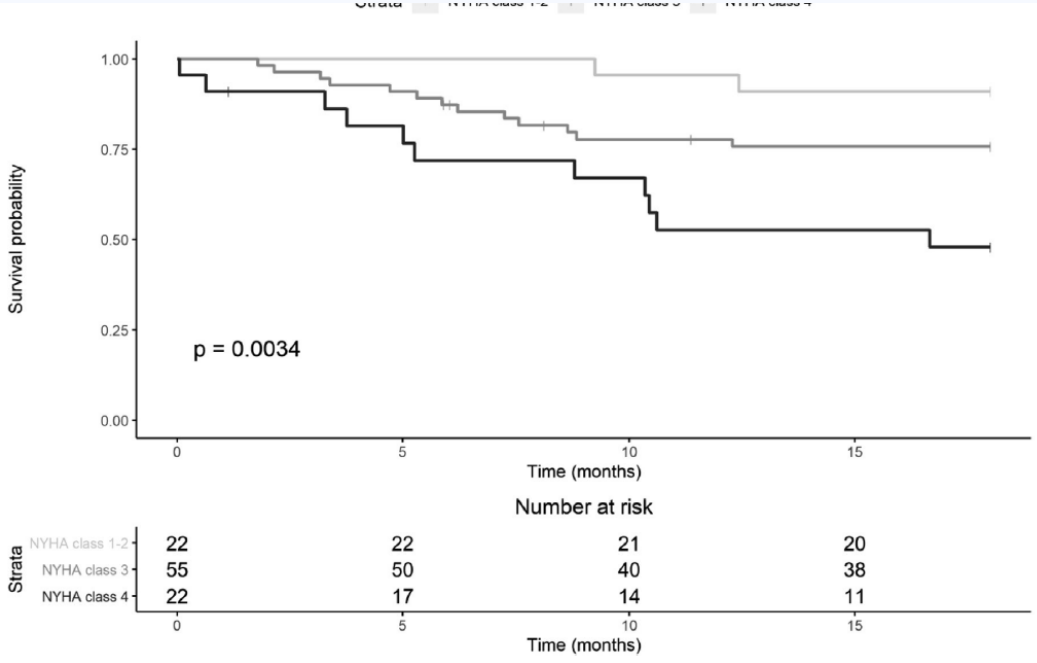
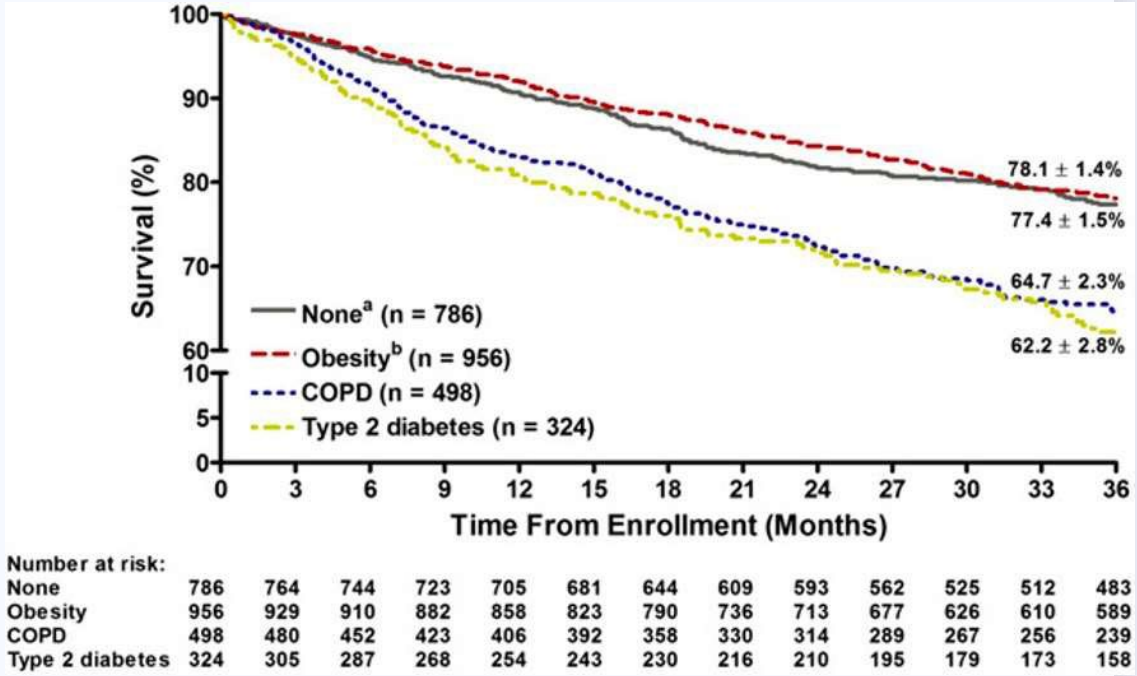
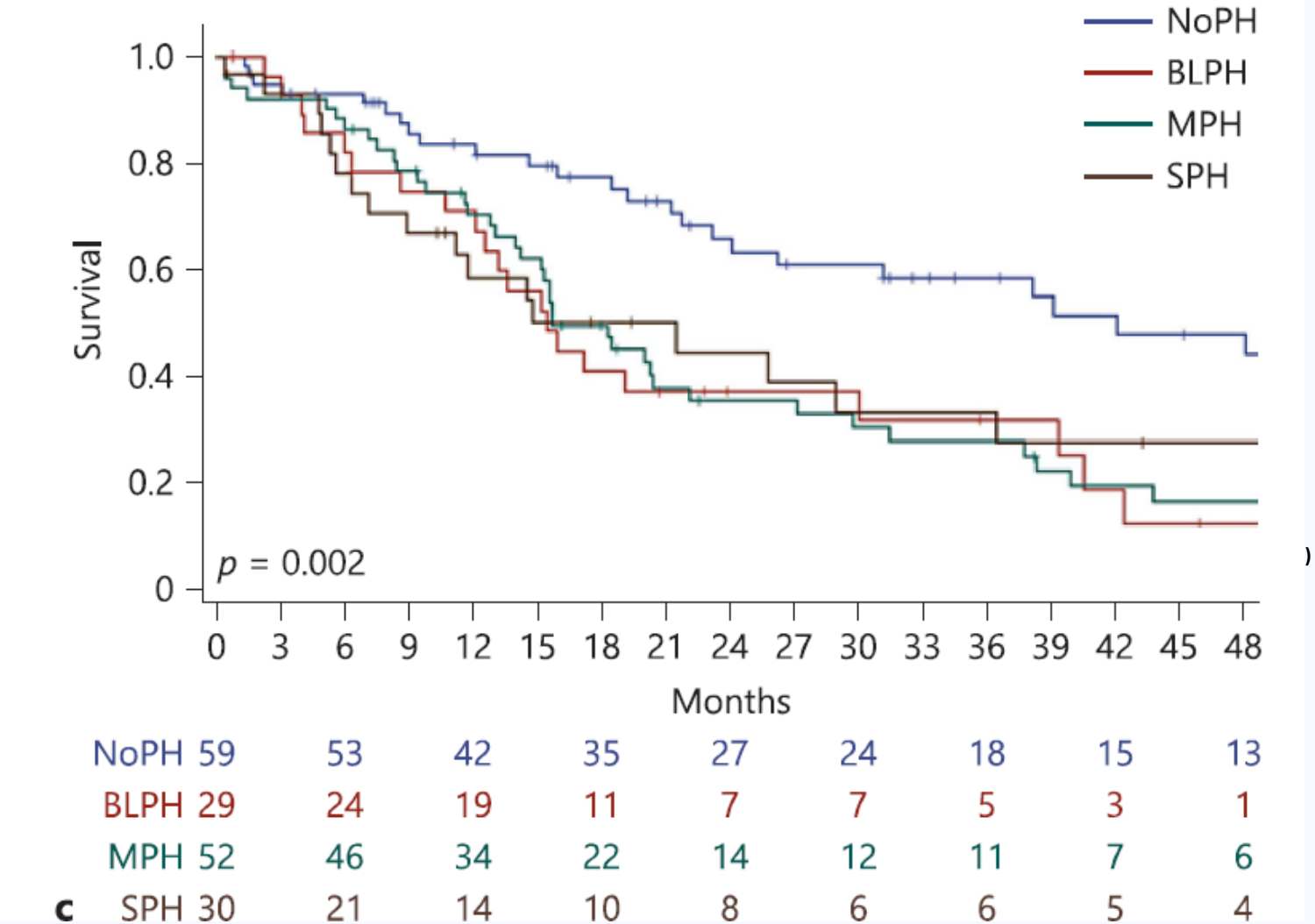


Figure 3 Kaplan-Meier survival curves. (A) Overall survival, (B) Survival stratified by NYHA class.

Reveal Registry



Impact of PH in ILD



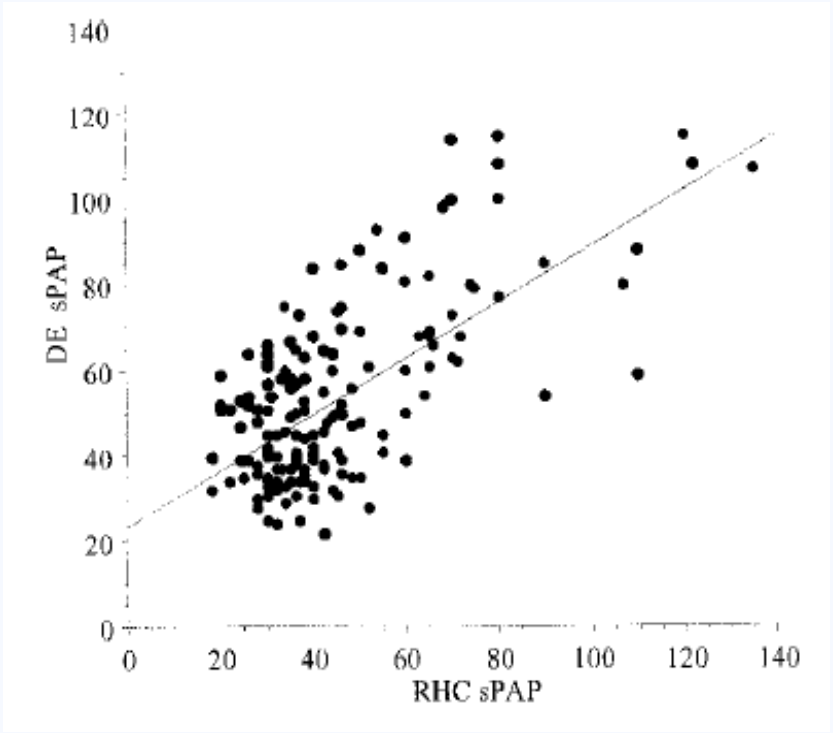
c

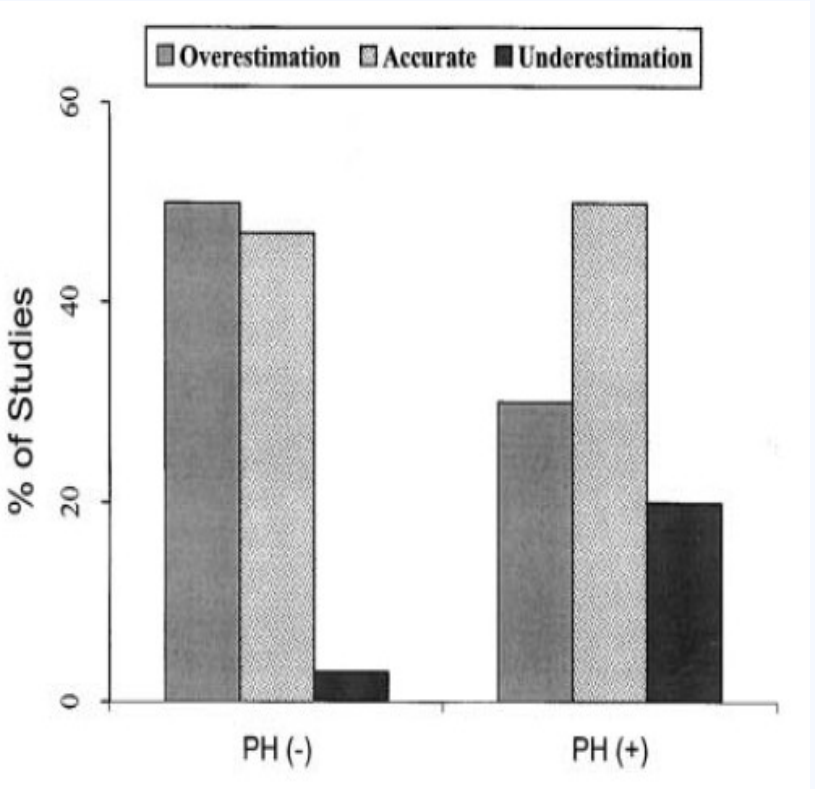
.

Piccary et all Respiration .

Diagnosis

Diagnosis of PH-Lung Disease: Not by Echo Alone





Estimate of RVSP possible in 54% of patients with ILD within 10 mmHg of RHC

RVSP measured sPAP only 37% of time

40% those with RVSP>45 did not have PH

56% of those with normal RVSP had PH

Arcasoy SM, Christie JD, Ferrari VA, et al. *Am J Respir Crit Care Med* 2003;167:735-740.

Diagnosis of PH-COPD: Not by Echo Alone

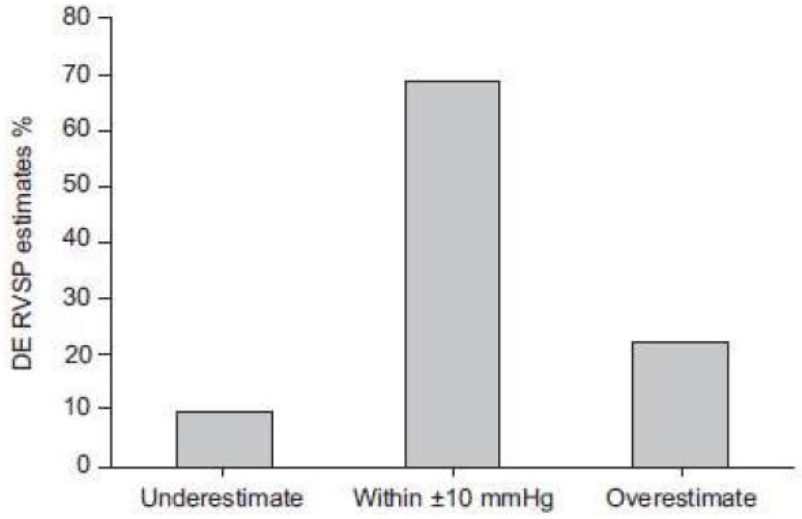
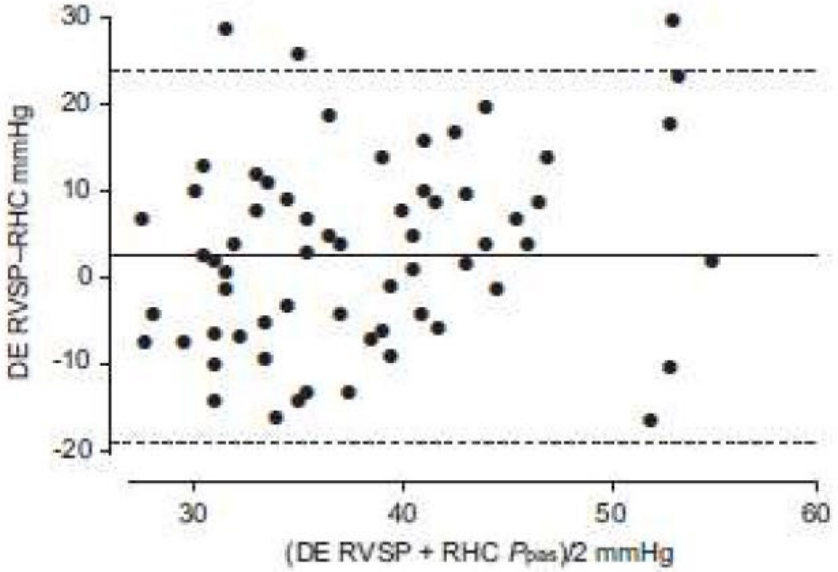


FIGURE 4. Percentage of Doppler echocardiography (DE) estimates of right ventricular systolic pressure (RVSP) within 10 mmHg of the measured pulmonary artery systolic pressure at right heart catheterisation. n=74 paired measurements on 63 patients. 1 mmHg=0.133 kPa.



95% limits of agreement:
-18.7mmHg to 24.3 mmHg

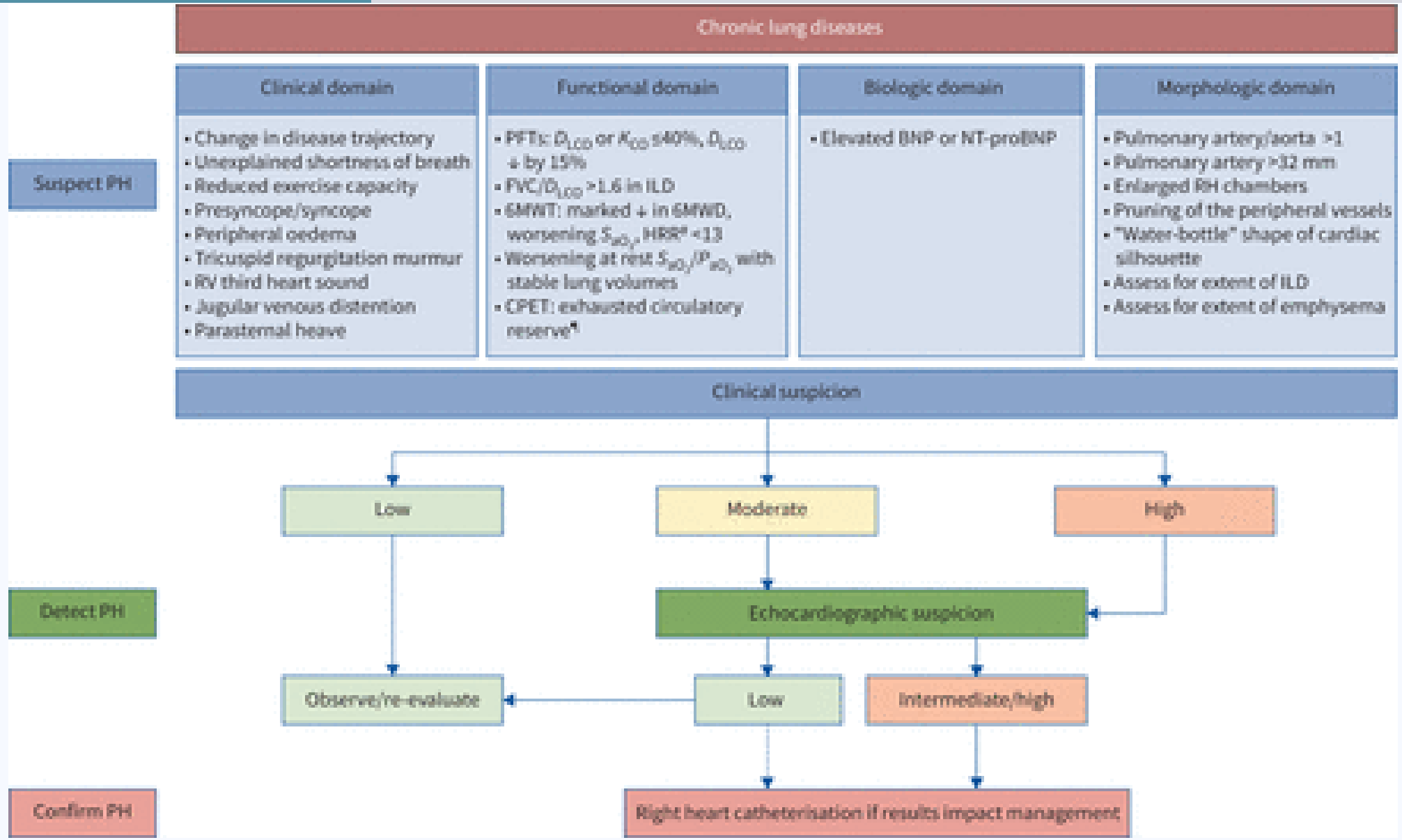
Fisher MR et al. *Eur Respir J* 2007; 30:914-921.

Diagnosis of PH in Lung Disease

Test	Utility as Screening Test
PA size on CT chest	Limited
Spirometry	None
DL_{CO}★ or FVC/DL_{CO}*	Limited
BNP/NT-proBNP	Needs validation
Echocardiography	Limited

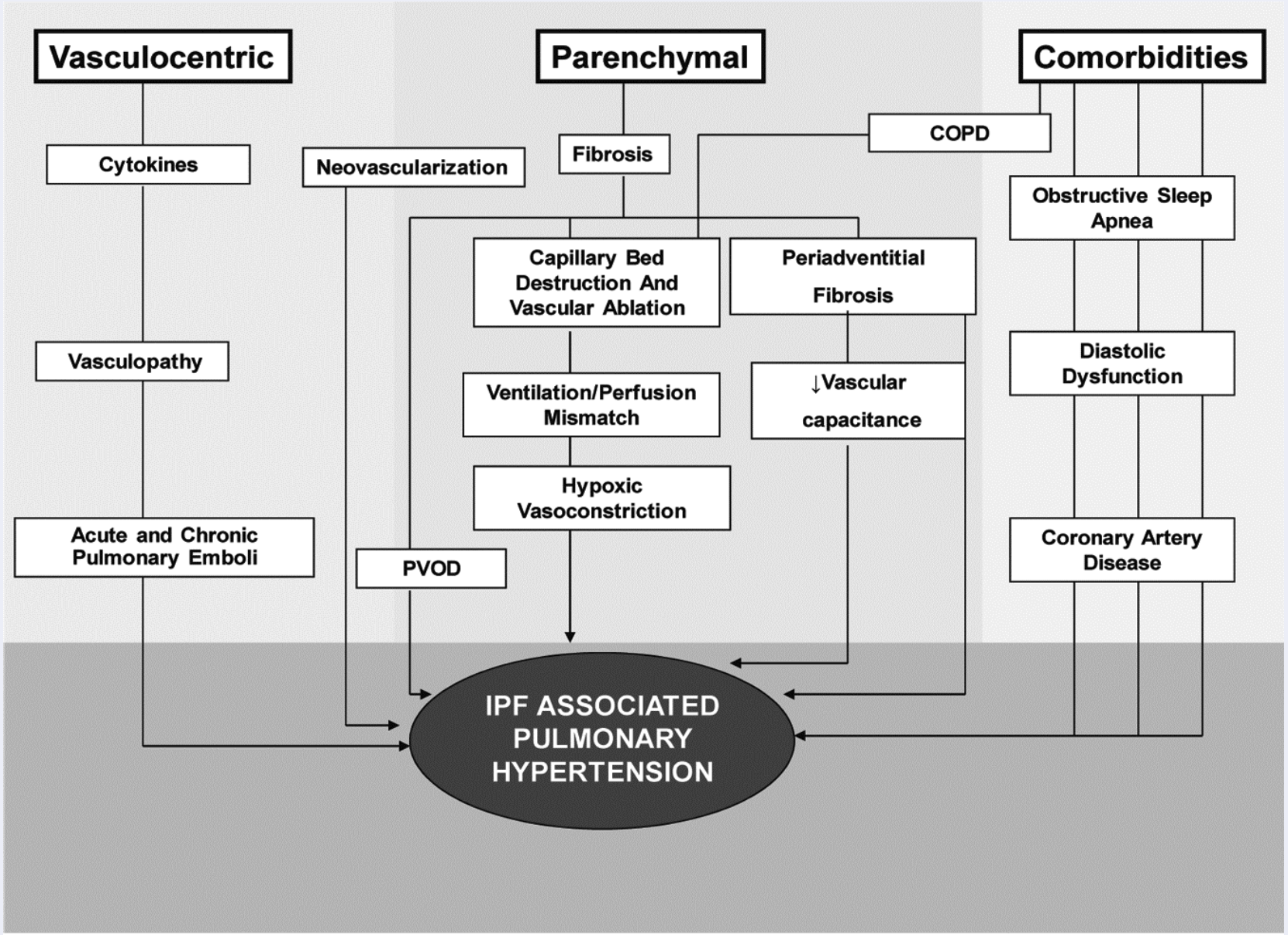
COPD			
KOVACS, 2022	142	TTE NT-proBNP PA/A diameter ratio	Haemodynamically defined pre-capillary severe PH (6th WSPH) PPV 94% NPV 94%
COSTE, 2019]	24	CT-measured bronchial wall thickness % of cross-sectional area of PV <5 mm^2 P_{aO2}	Sensitivity of 87.5% for severe PH (6th WSPH)

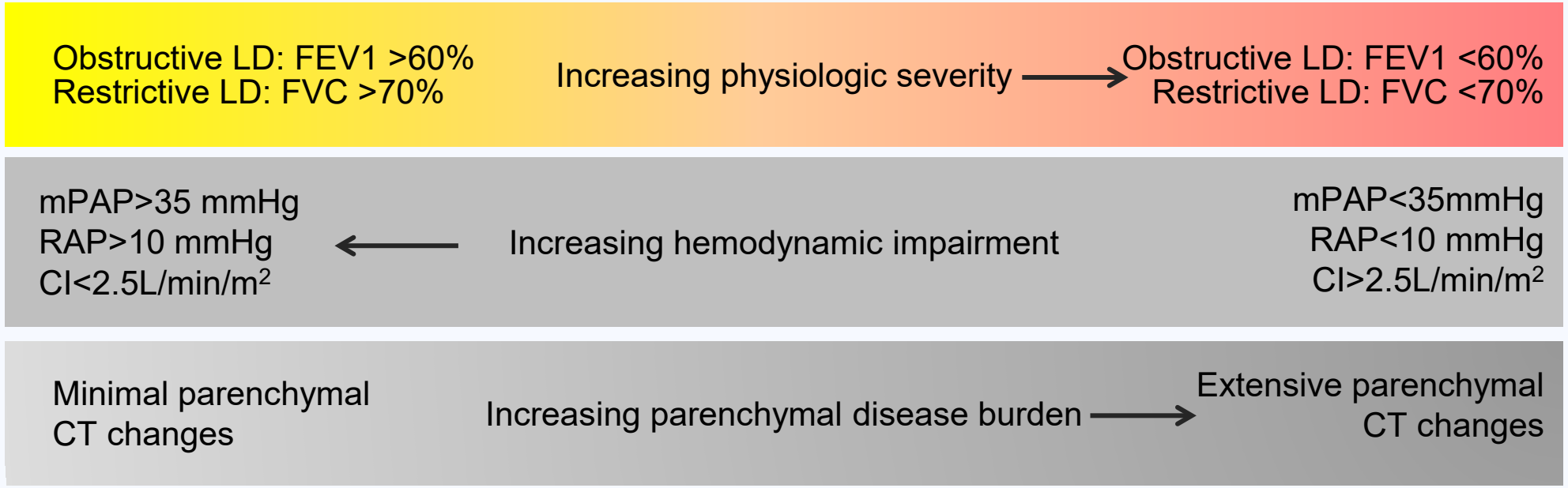
First author, year [reference]	Subjects n	Scoring variables	Outcomes
ILD			
Nathan, 2024#]	Derivation cohort: 481 IPF Validation cohort: 204 IPF	FORD scoring system and FORD index: FVC%/D_{LCO}% ratio Oxygenation nadir during 6MWT Race 6MWD	PH (2022 ESC/ERS) AUC 0.75 Score ≥33 sensitivity 70% specificity 73% Score ≥53 specificity 98%
Joseph, 2023	66 ILD	Gas exchange-derived PVC $\Delta ETCO_2$ (CO measure) TTE sPAP Elevated FVC/D_{LCO}	PH (2022 ESC/ERS) AUC 0.94 sensitivity 0.86 specificity 0.93
Parikh, 2022# Parikh, 2023	Derivation cohort: 154 ILD Validation cohort: 161 ILD	History Exam 6MWD D_{LCO} CTA PA/A ratio BNP/NT-proBNP	PH (6th WSPH) Score ≥6 (0–12) AUC 0.920 sensitivity 86.5% specificity 86.3%
Refini, 2021	37 IPF	TTE sPAP PA area Diameter of the segmental artery to that of the adjacent bronchus in the apicoposterior segment of the left upper lobe ratio	mPAP sensitivity 100% specificity 53%
Sobiecka, 2020	93 ILD	Age 6MWD TLC/D_{LCO} ratio	Echocardiography sPAP AUC ROC 0.867
Tello, 2019#	172 CLD 94 ILD 78 COPD	TAPSE/sPAP ratio	Severe PH (6th WSPH) TAPSE/sPAP ratio 0.26 mm·mmHg^{-1} sensitivity 80.6% specificity 71.2%
Sonti, 2019	105 IPF	sPAP FVC/D_{LCO} PA/A ratio	PH (6th WSPH) NPV 87.2%
Bax, 2018#	Derivation cohort: 210 ILD Validation cohort: 61 ILD	Stepwise echocardiographic algorithm	Severe PH (6th WSPH) Score ≥7 sensitivity 89% specificity 71% PPV 68% NPV 90% AUC 84.8%
Furukawa, 2018	273 IPF	D_{LCO} PA/A ratio on CT ≥0.9 P_{aO2} <80 Torr	mPAP AUC ROC 0.757 (95% CI 0.682–0.833)



Treatment

Pulmonary Hypertension in Lung Disease

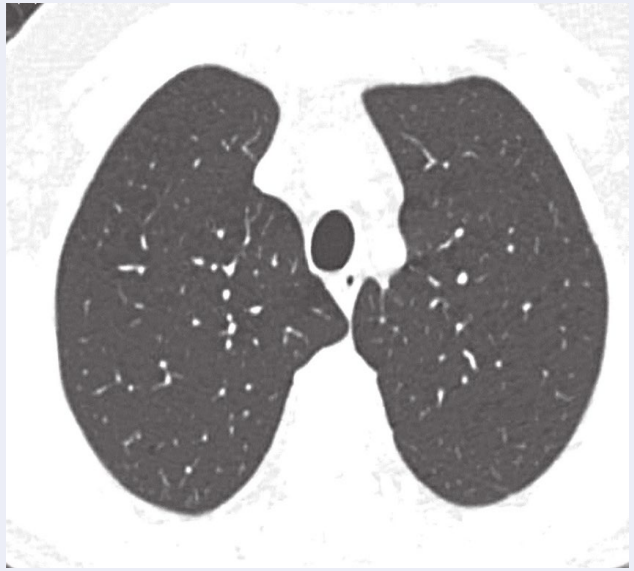




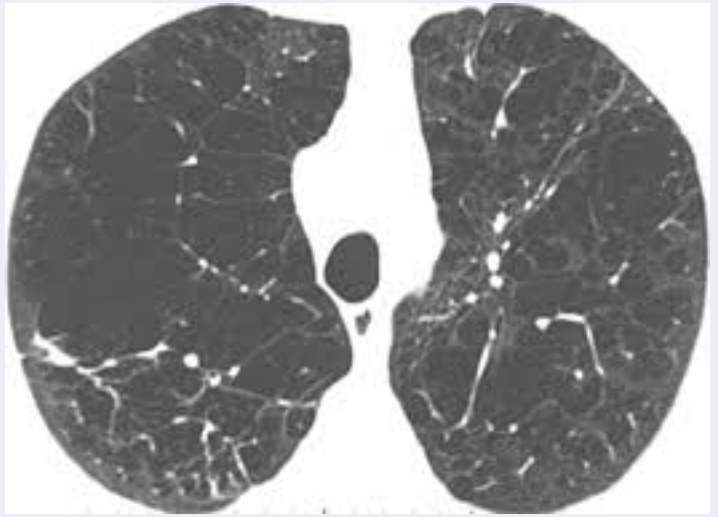
Diagnosisng group 3 PH involves consideration of the extent of lung disease (by PFTs and imaging) versus the severity of hemodynamic impairment

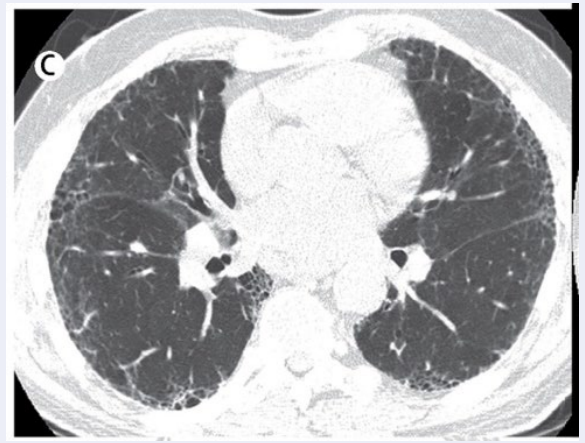
CT, computerized tomography; FEV1, forced expiratory volume; FVC, forced vital capacity; mPAP, mean pulmonary arterial pressure; LD, lung disease; PFTs, pulmonary function tests; PAH, pulmonary arterial pressure; PH, pulmonary hypertension; RAP, right arterial pressure.

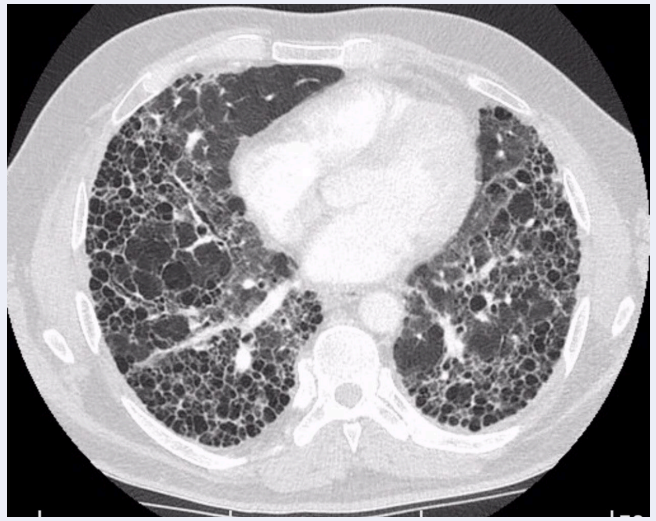
Nathan S et al. *Eur Respir J*. 2019;53(1):1801914.



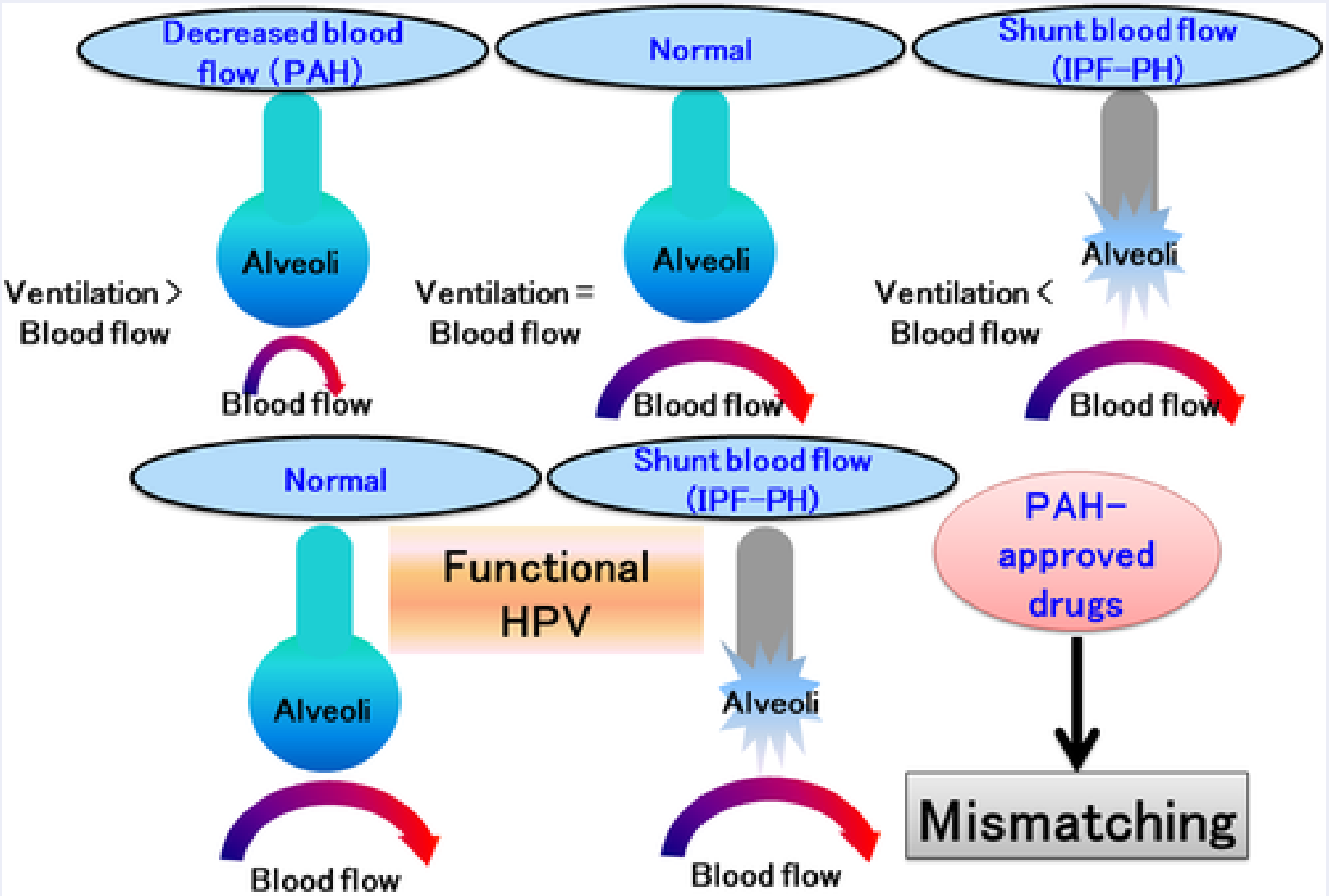
mPAP 30 mmHg
RAP 8 mmHg
CO 4.0L/min/m^2





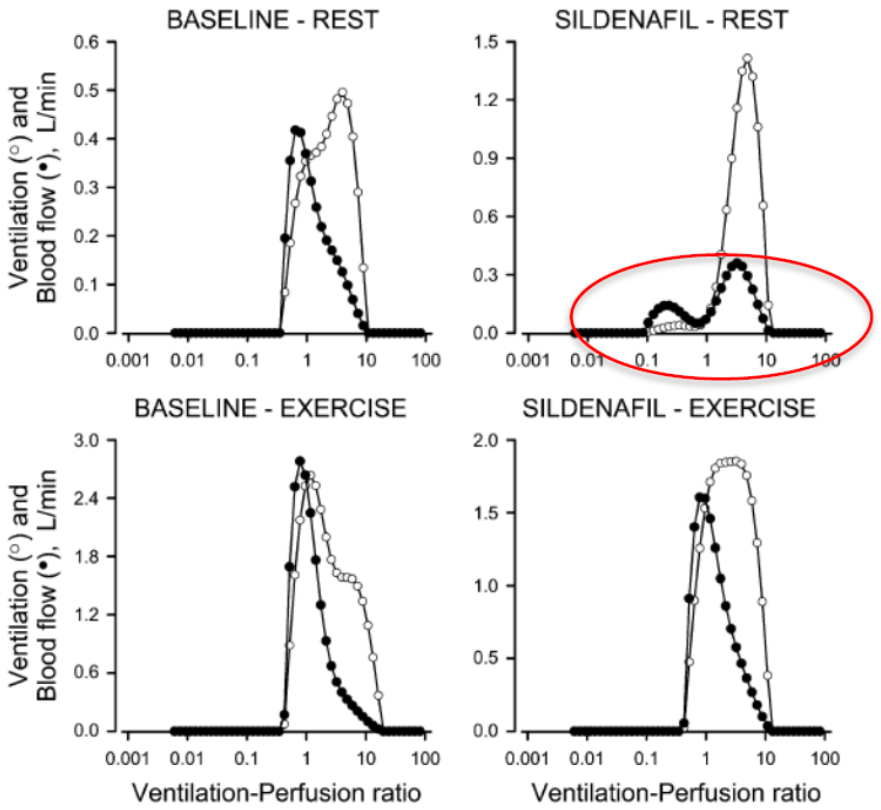


Need to consider V/Q mismatch and effect of Vasodilators



Koichiro Tatsumi. Journal of the American Heart Association. Hypoxic Pulmonary Vasoconstriction and the Diffusing Capacity in Pulmonary Hypertension Secondary to Idiopathic Pulmonary Fibrosis, Volume: 8, Issue: 16, DOI: (10.1161/JAHA.119.013310)

COPD -PH



Assess VQ matching in PH-COPD patients treated with sildenafil

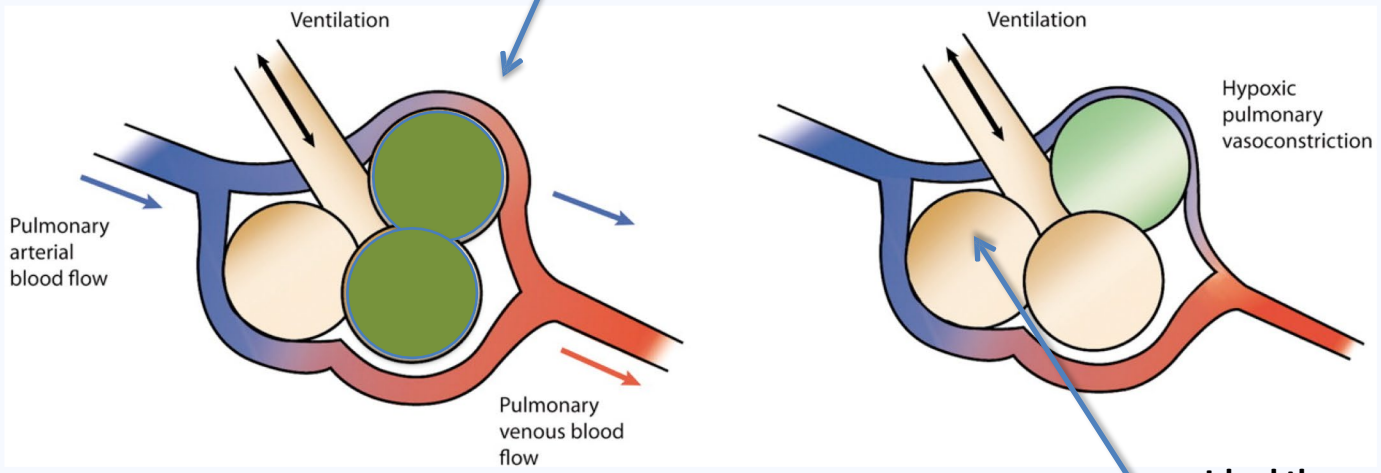
Marked reduction in O2 sats at rest
No difference with exercise

Improved exercise tolerance
Drop in mPAP 20% with exercise
Minimal improvement in CO

Blanco I et al. *Am J Respir Crit Care Med* 2010;181:270-78.

Release of Hypoxic Vasoconstriction

PAH-Therapy*



Ideal therapy: targets ventilated lung

*** Also β-blockers, CCBs, nitrates**

Dhillon R. *Arch Dis Child Fetal Neonatal Dis Ed* 2011.

Inhaled Treprostinil

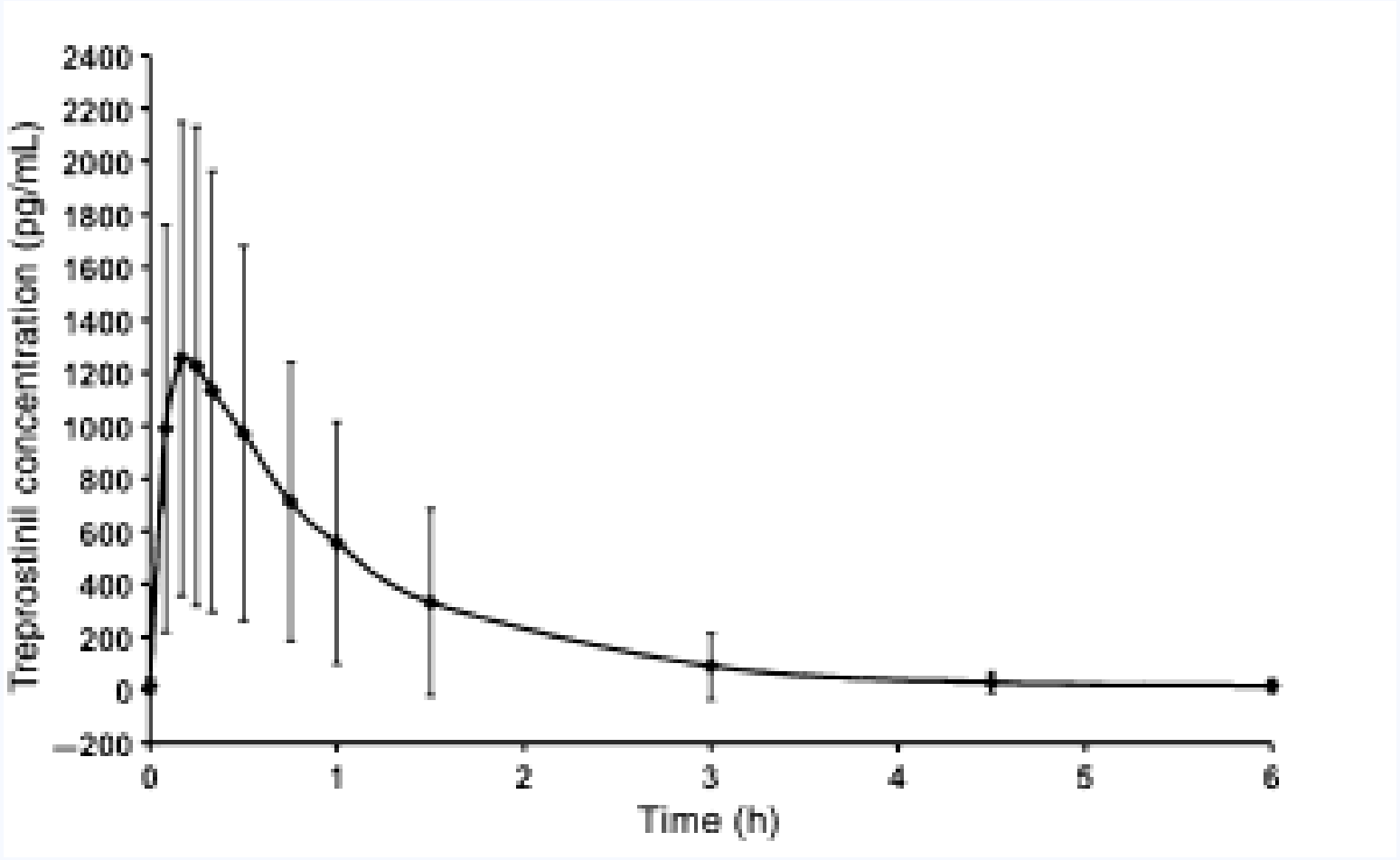
Longer-acting prostacyclin analogue (2.5-4hrs half-life)

Aerosolized delivery system

Approved for WHO Group 1NYHA Class II and PH-ILD

Four times a day dosing

Inhaled Treprostinil



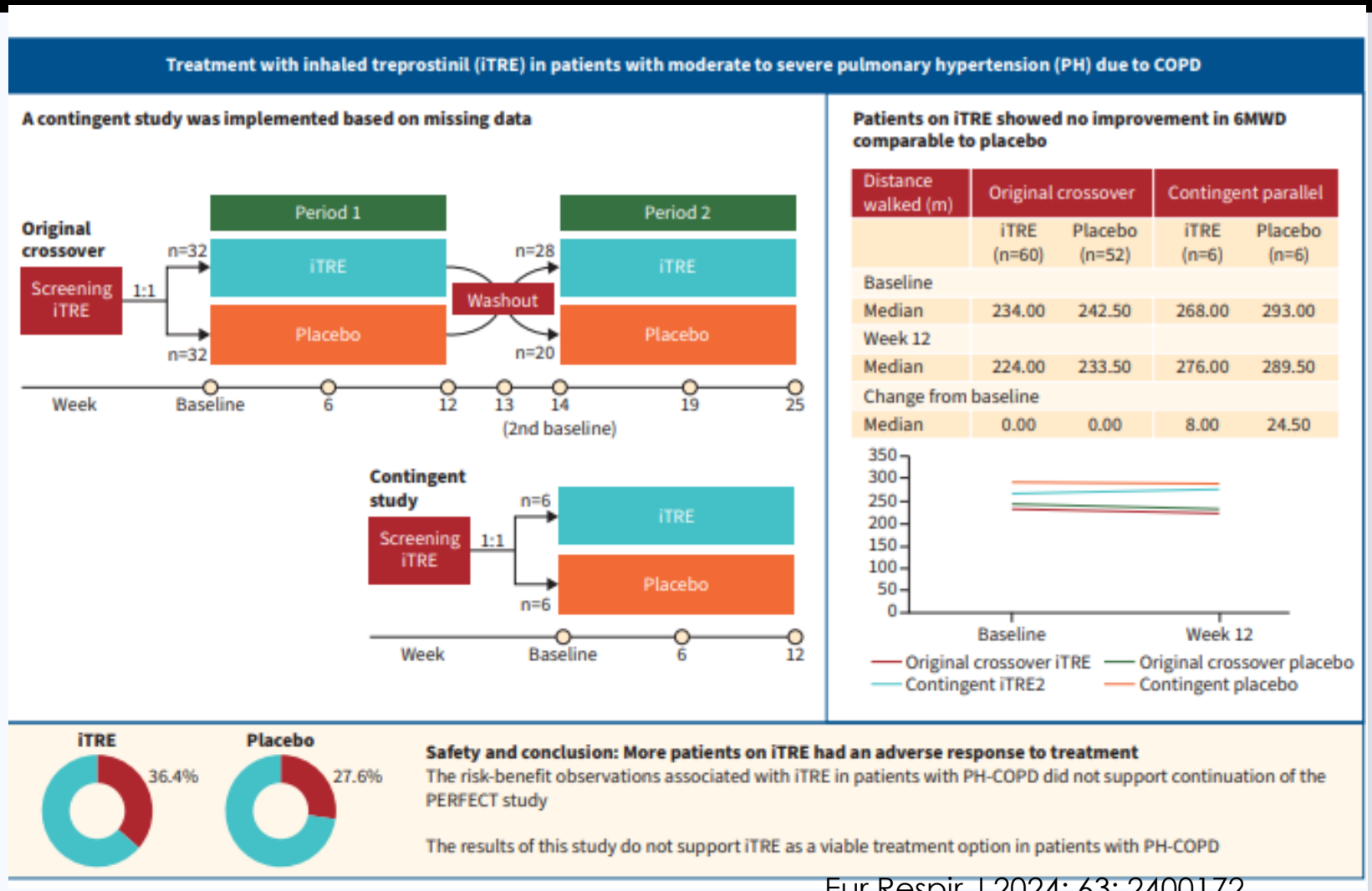
54mcg dose

Inhaled Treprostinil in Patients with Pulmonary Hypertension Due to Chronic Obstructive Pulmonary Disease

Inhaled Treprostinil in Patients with Pulmonary Hypertension Due to Chronic Obstructive Pulmonary Disease

Inhaled treprostinil in pulmonary hypertension associated with COPD: PERFECT study results

188 patients
76 Randomized



Eur Respir J 2024; 63: 2400172

Inhaled treprostinil in pulmonary hypertension associated with COPD: PERFECT study results

	During Part A	During Part B with…		During the extension trial
	Treprostinil Out of 108 participants	**Treprostinil** Out of 66 participants	**Placebo** Out of 58 participants	**Treprostinil** Out of 41 participants
How many participants had serious adverse events?	9 (8%)	17 (26%)	6 (10%)	13 (32%)
How many participants had serious adverse events that were fatal?	1 (1%)	5 (8%)	0	8 (20%)

Eur Respir J 2024; 63: 2400172

COPD trials

irst author, year [reference]	Lung disease	Study design	Subjects n	Therapy	Results	Comments
VITULO, 2017	COPD-PH	RCT	28	Sildenafil (n=18)	Decrease in PVR, improvement in BODE, D_{LCO} and quality of life	No adverse effect on oxygenation
MARON, 2022	COPD-PH	RCT	42	Tadalafil (n=28)	No change in PVR or mPAP at 6 months Improvement in shortness-of-breath questionnaire	No adverse effect on oxygenation
NATHAN, 2024 [	COPD-PH	RCT	136	Inhaled treprostinil (n=66)	Decrease in 6MWD at 12 weeks	Study terminated due to increased SAE in the treated group

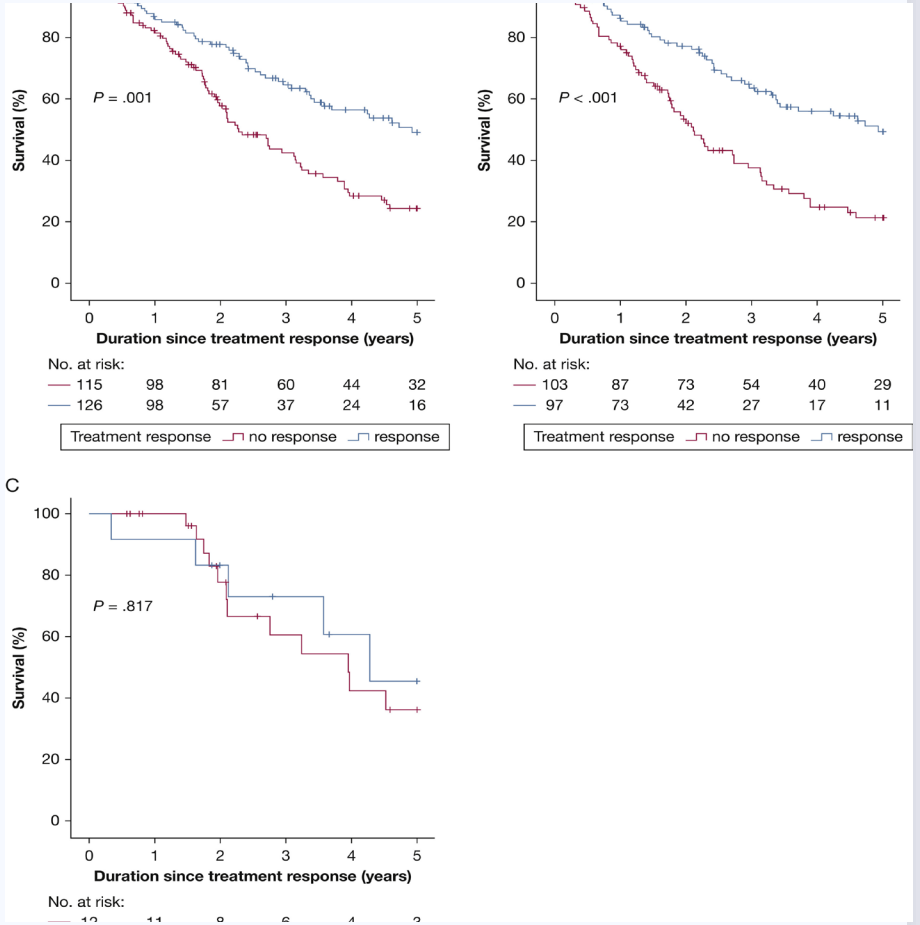
Treatment of PH-COPD

PDE-5i significantly improved hemodynamics in COPD-PH patients, but this did not translate to clinical, functional, or HRQoL benefits.

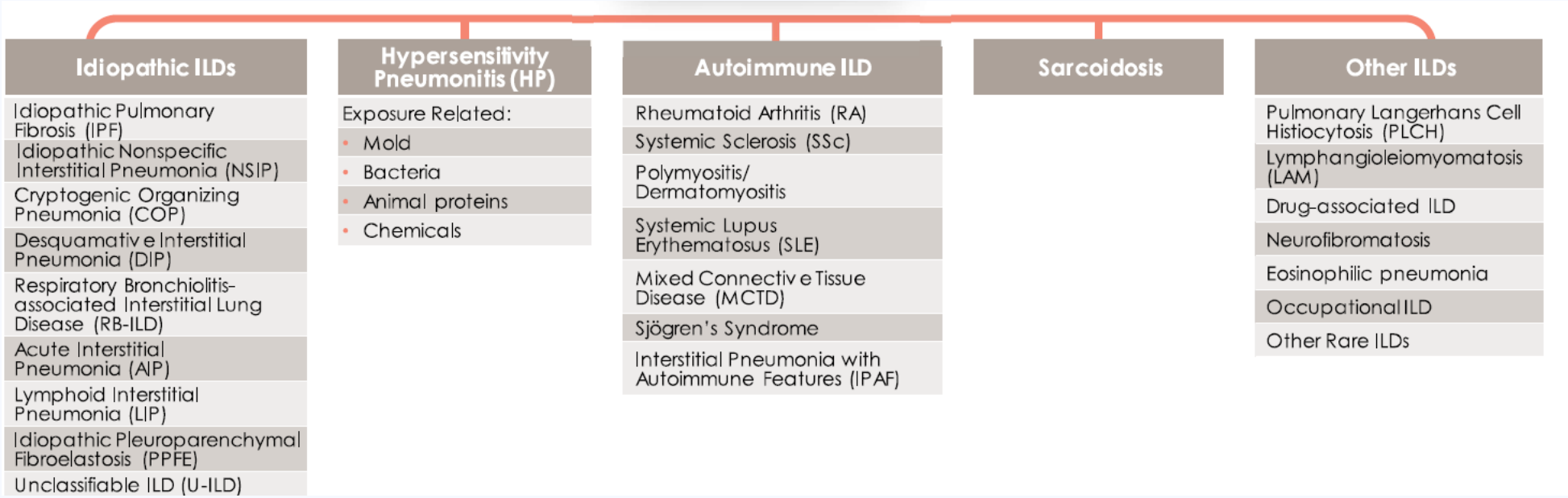
ERAs have limited hemodynamic and uncertain clinical benefits in COPD-PH patients.

Combination PAH-targeted therapy does not improve survival but may offer some transient clinical and/or functional benefits. Patients with objective "response" to therapy, including improved NYHA FC or PVR, may have improved survival.

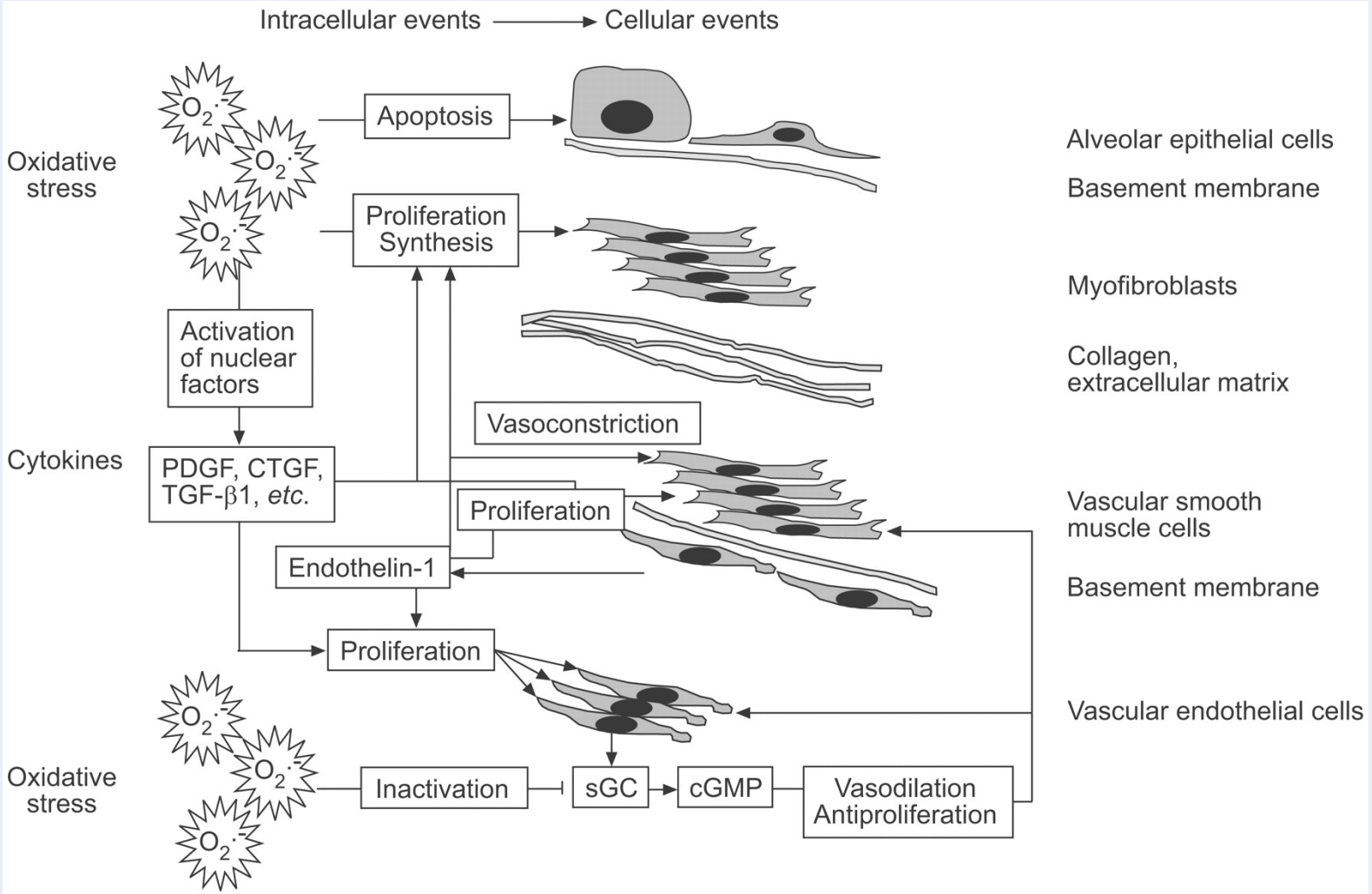
Guidelines recommend against PAH-targeted therapy for mild to moderate COPD-PH



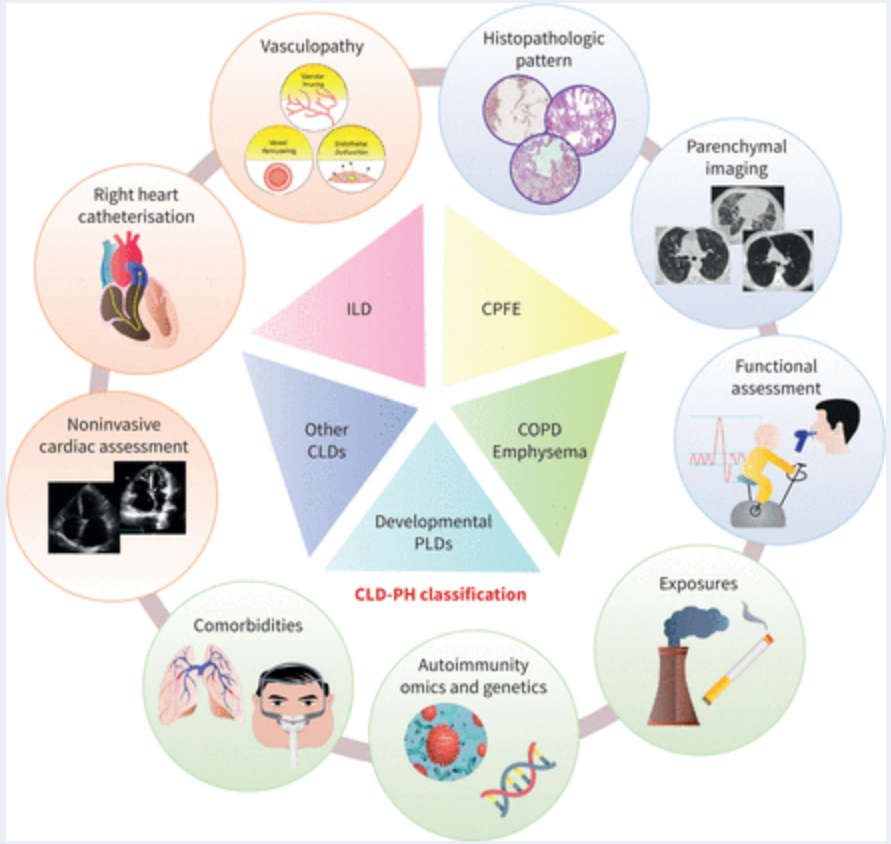
Footnotes are in the speaker notes.
Arif R, et al. *ERJ Open Res.* 2022;8(1):00348-2021.

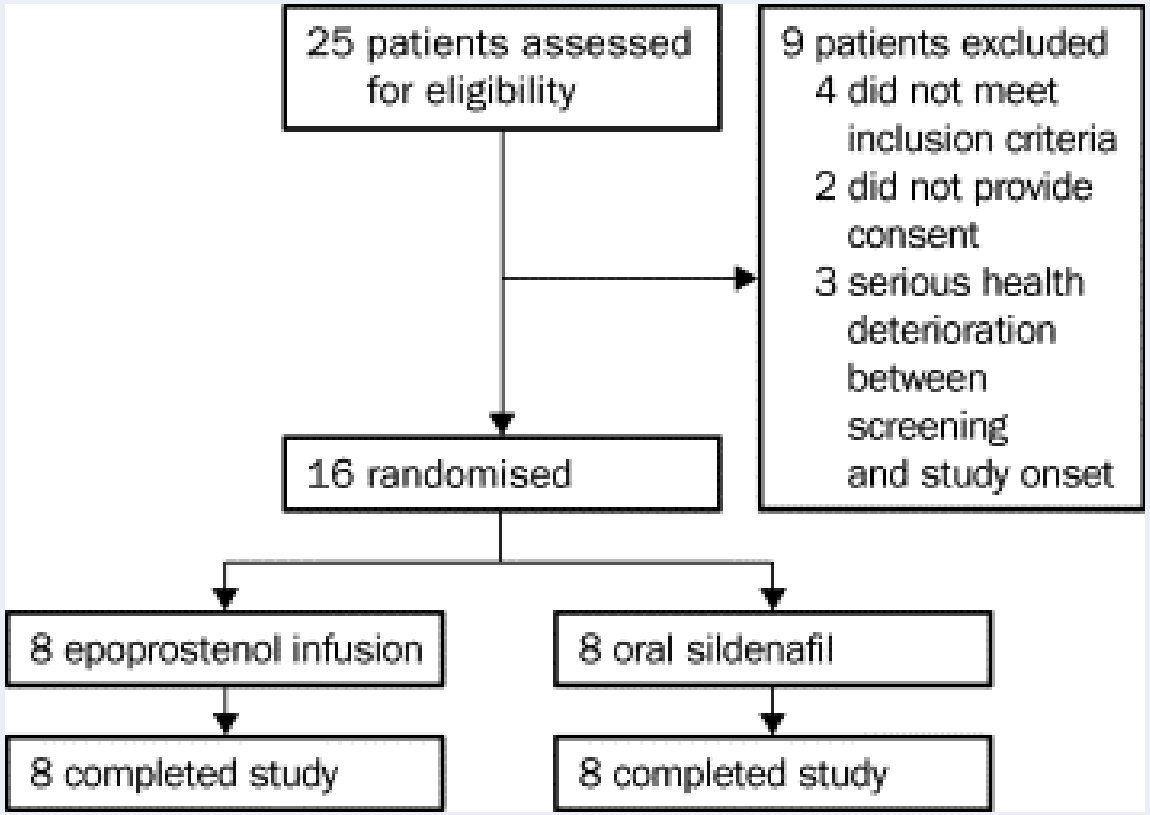

Idiopathic ILDs
Idiopathic Pulmonary Fibrosis (IPF)
Idiopathic Nonspecific Interstitial Pneumonia (NSIP)
Cryptogenic Organizing Pneumonia (COP)
Desquamative Interstitial Pneumonia (DIP)
Respiratory Bronchiolitis-associated Interstitial Lung Disease (RB-ILD)
Acute Interstitial Pneumonia (AIP)
Lymphoid Interstitial Pneumonia (LIP)
Idiopathic Pleuroparenchymal Fibroelastosis (PPFE)
Unclassifiable ILD (U-ILD)
Hypersensitivity Pneumonitis (HP)
Exposure Related:
Mold
Bacteria
Animal proteins
Chemicals
Autoimmune ILD
Rheumatoid Arthritis (RA)
Systemic Sclerosis (SSc)
Polymyositis/ Dermatomyositis
Systemic Lupus Erythematosus (SLE)
Mixed Connective Tissue Disease (MCTD)
Sjögren's Syndrome
Interstitial Pneumonia with Autoimmune Features (IPAF)
Sarcoidosis
Other ILDs
Pulmonary Langerhans Cell Histiocytosis (PLCH)
Lymphangioleiomyomatosis (LAM)
Drug-associated ILD
Neurofibromatosis
Eosinophilic pneumonia
Occupational ILD
Other Rare ILDs

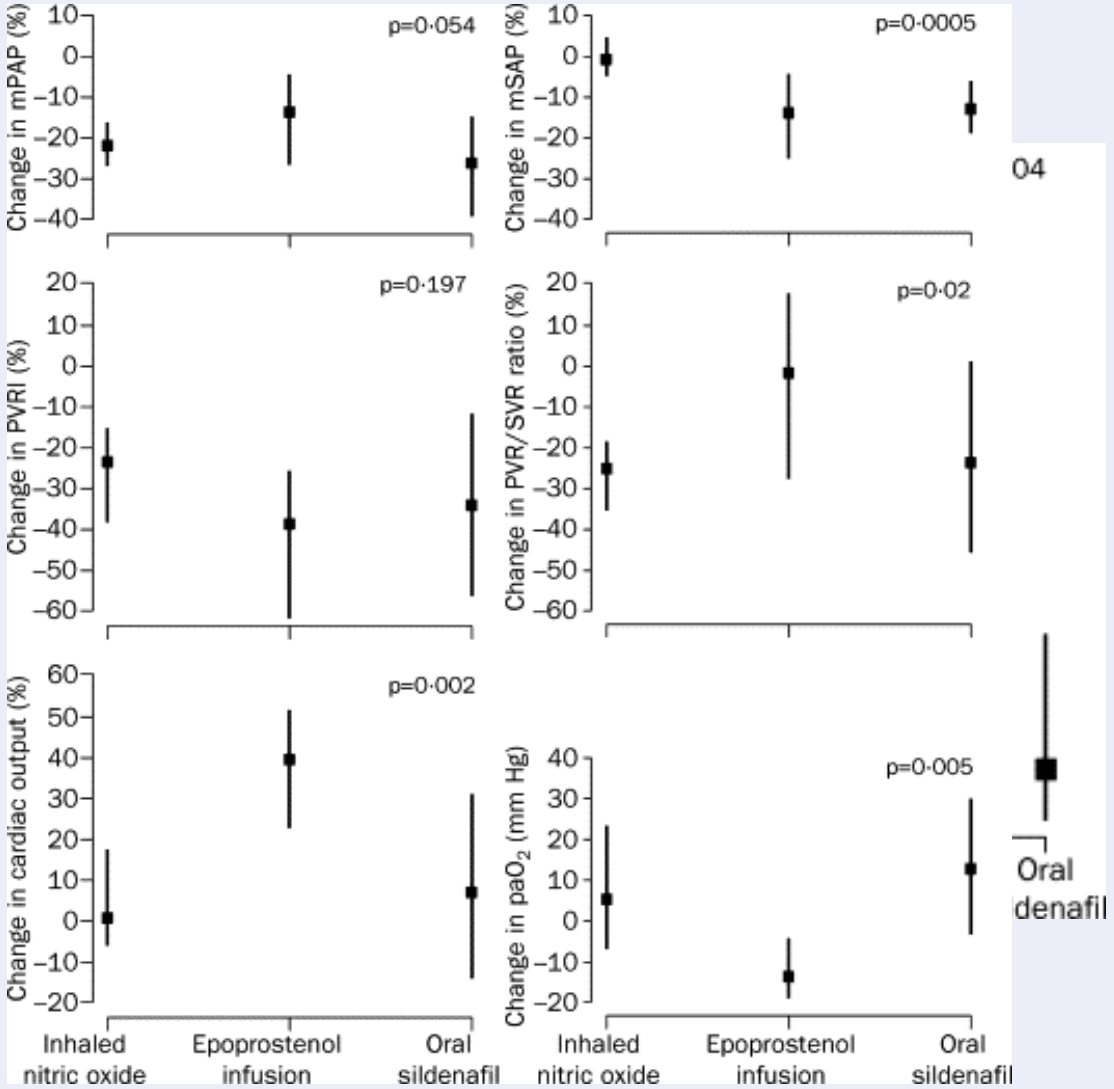
Potential common pathomechanisms of parenchymal and vascular remodelling in interstitial lung disease and pulmonary hypertension.



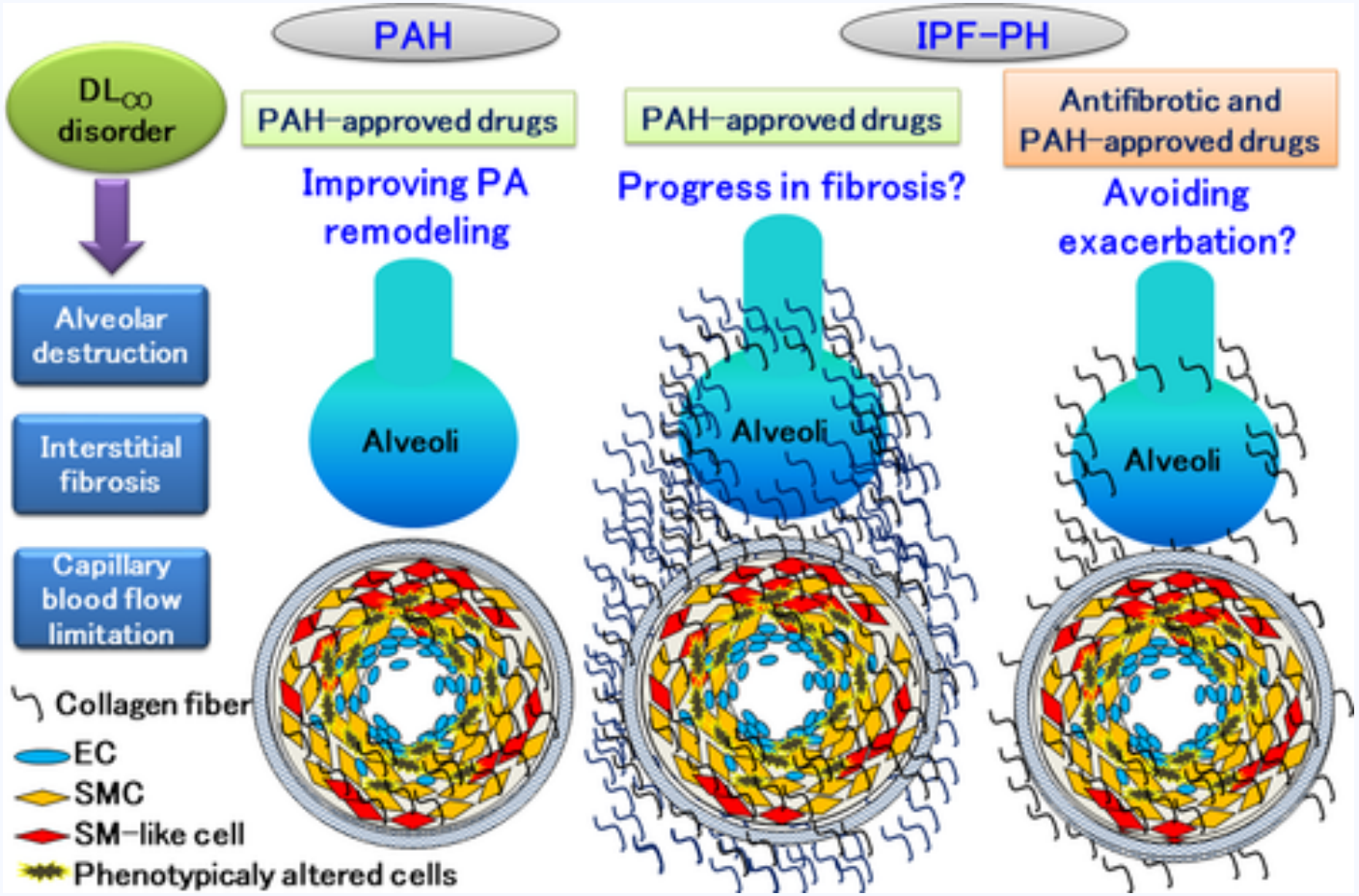
J. Behr, and J. H. Ryu Eur Respir J 2008;31:1357-1367


Vasculopathy
Histopathologic pattern
Parenchymal imaging
Functional assessment
Exposures
Autoimmunity omics and genetics
Comorbidities
Noninvasive cardiac assessment
Right heart catheterisation
ILD
CPFE
Other CLDs
COPD Emphysema
Developmental PLDs
CLD-PH classification


25 patients assessed for eligibility
9 patients excluded
4 did not meet inclusion criteria
2 did not provide consent
3 serious health deterioration between screening and study onset
16 randomised
8 epoprostenol infusion
8 oral sildenafil
8 completed study
8 completed study


Change in mPAP (%)
p=0·054
Change in mSAP (%)
p=0·0005
Change in PVRI (%)
p=0·197
Change in PVR/SVR ratio (%)
p=0·02
Change in cardiac output (%)
p=0·002
Change in paO2 (mm Hg)
p=0·005
Inhaled nitric oxide
Epoprostenol infusion
Oral sildenafil
04
Oral denafil

Olschewski,AJRCCM 1999	**iNO, IV epoprostenol, inhaled Iloprost, CCB**	**Pulm fibrosis**	**PASP >50ormPAP >30**	**8 (IPF=1)**	**Open label**	**All PVR, mPAPEpo O_2CCB ?BP**
Ghofrani, Lancet 2002	iNO, IV epoprostenol or sildenafil	Pulm fibrosis	mPAP =35	16 (IPF=7)	Open label	All PVR, Epo /O_2Sildenafil ? O_2
Krowka, Chest [abstract] 2007	Inhaled iloprost	IPF	PASP =35ormPAP =25	51	DB-RCT	No change in 6MWT, exercise O_2, WHO class in 12 weeks
King, AJRCCM 2008 BUILD-1	Bosentan	IPF	n/a	158	DB-RCT	No change in 6MWD at 12 months. Trend toward delaying time to death or disease progression
King, AJRCCM 2011 BUILD-3	Bosentan	IPF mild, biopsy proven	n/a	616	DB-RCT	No delay in time to death or disease progression
Raghu, Annals 2013 ARTEMIS-IPF	Ambrisentan	IPF	n/a	494	DB-RCT	Stopped early for lack of efficacy and possible risk of disease progression
Collard,Chest 2007	Sildenafil	IPF	mPAP =25orPASP =35	14	Open label-RCT	57% improved 6MWD of 20% at 3 months
IPFnet, NEJM 2010 STEP-IPF	Sildenafil	IPF	n/a	180	DB-RCT	Did not meet 20% change in 6MWD at 12 or 24 weeks. Improvement in sob and QoL
Han,Chest 2013 (STEP-IPF post-hoc analysis)	Sildenafil	IPF	Echo with RV dysfunction	119	DB-RCT	Improved preservation of 6MWD
Sager	Treprostinil	IPF	mPAP>35	15	Open label	Improved PVR no significant improvement in Dyspnea score
Hoeper	Riociguat	IPF	mPAP>25	18	Open label	Improved Hemodynamics
Hoeper	Riociguat	ILD	mPAP>25	147 (73vs74)	DB-RCT	Increase mortality in Riociguat study Clinical worsening 47%vs 49%

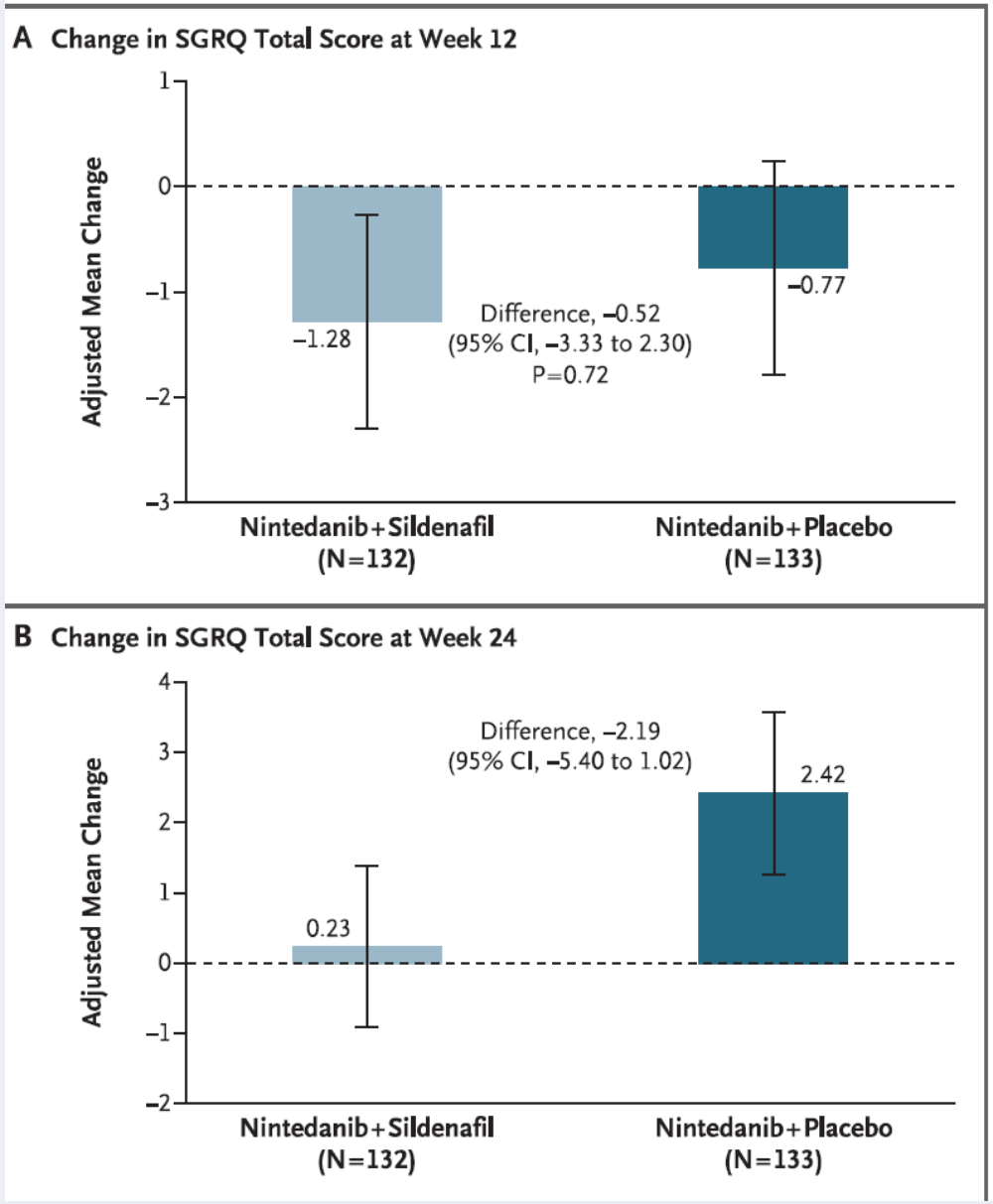


Koichiro Tatsumi. Journal of the American Heart Association. Hypoxic Pulmonary Vasoconstriction and the Diffusing Capacity in Pulmonary Hypertension Secondary to Idiopathic Pulmonary Fibrosis, Volume: 8, Issue: 16, DOI: (10.1161/JAHA.119.013310)

Nintedanib AND Sildenafil

Table 1. Characteristics of the Patients at Baseline.*

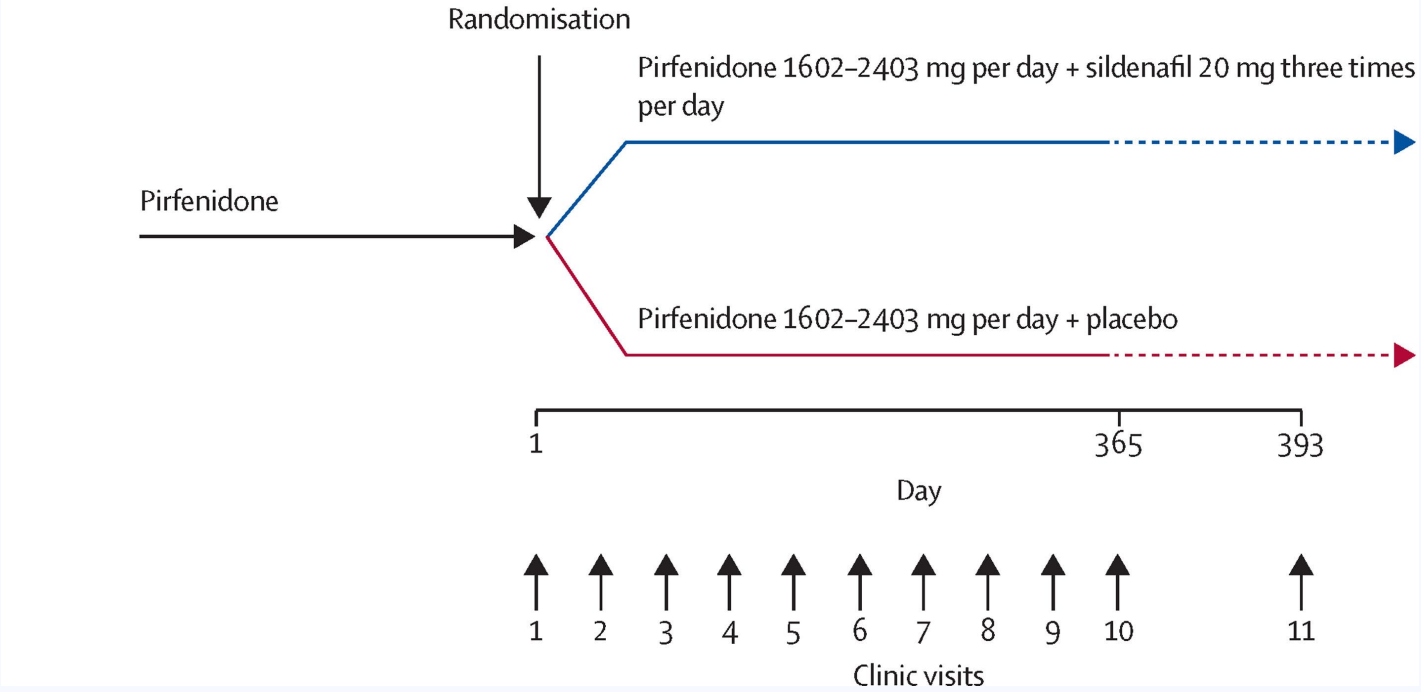
Characteristic	Nintedanib + Sildenafil (N=137)	Nintedanib + Placebo (N=136)
Age — yr	70.3±8.6	70.0±7.9
Male sex — no. (%)	110 (80.3)	106 (77.9)
Weight — kg	73.7±17.7	74.2±15.5
Time since diagnosis of IPF — yr	2.2±1.9	2.1±1.8
Emphysema — no. (%)†	51 (37.2)	45 (33.1)
Nintedanib treatment status — no. (%)		
Not previously treated	76 (55.5)	87 (64.0)
Currently treated	56 (40.9)	46 (33.8)
Previously treated	5 (3.6)	3 (2.2)
Any echocardiographic sign indicative of right heart dysfunction — no. (%)	61 (44.5)	56 (41.2)
FVC		
Mean — ml	2246±749	2181±786
Percentage of predicted value	67.9±19.3	66.1±18.7
FEV_1:FVC	0.82±0.08	0.84±0.08
D_{LCO} — % of predicted value‡	25.8±6.8	25.6±7.0
SGRQ total score§	56.7±18.5	54.0±17.9
UCSD-SOBQ score¶	60.3±26.1	56.5±25.2
EQ-5D VAS score‖	55.8±17.9	60.0±17.8



NEJM 2018 379

Pirfenidone and Sildenafil

Informed consent form	Run-in period	Screening period		Double-blind treatment	Follow-up	
		Washout, days −57 to −29	Screening, days −28 to −1	Days 1 to 365	Days 365 to 393 (±5)	12 months



Lancet Respir Med 2021;9:85–95.

272 enrolled
80 in each group

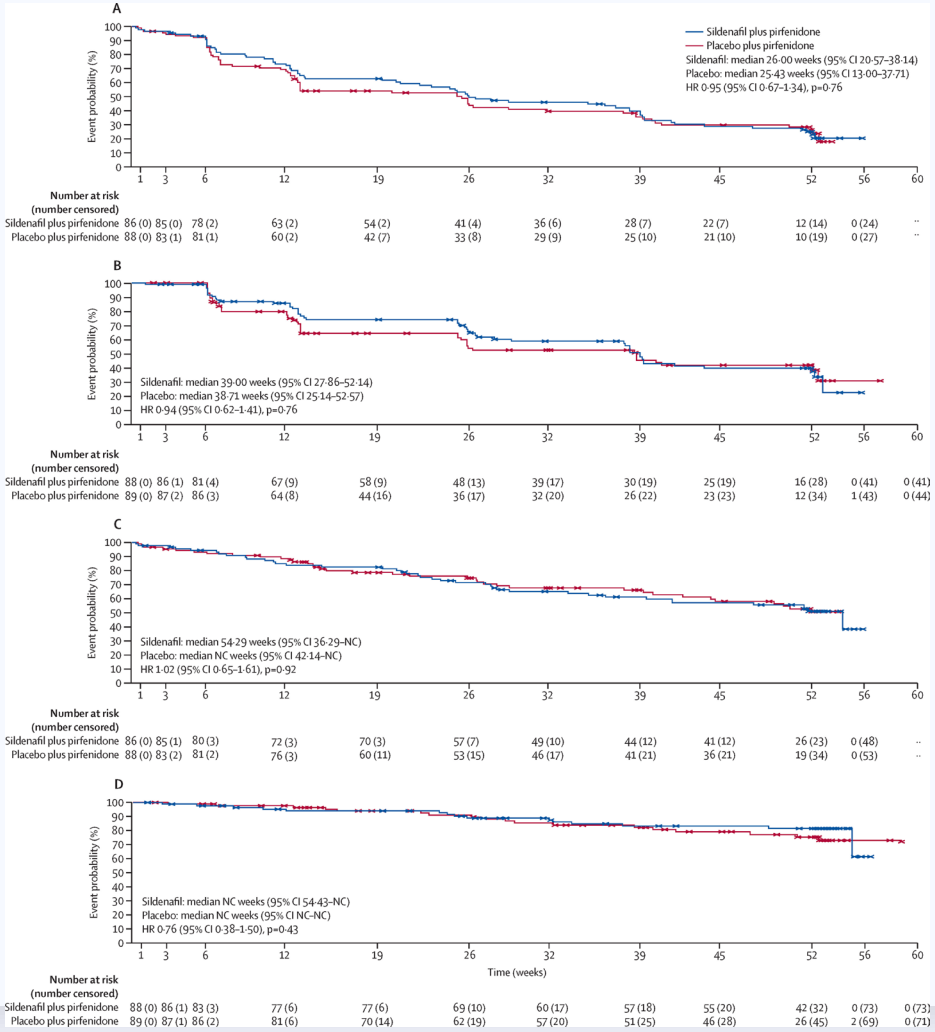
The composite primary endpoint

Disease progression

Decline in 6-min walk distance

Respiratory-related admission to hospital

All-cause mortality, after 52 weeks



The NEW ENGLAND JOURNAL of MEDICINE

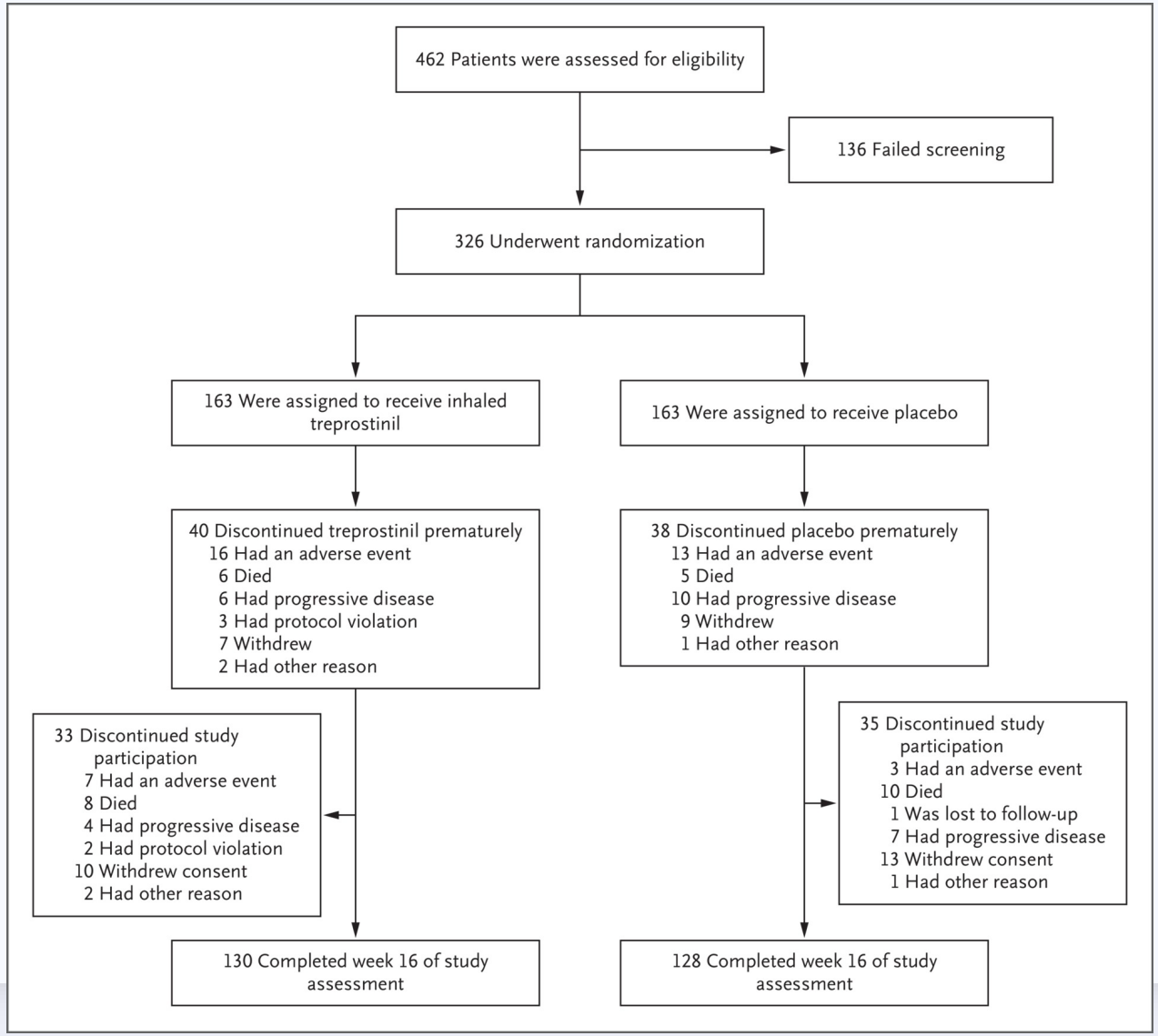
ORIGINAL ARTICLE

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

Aaron Waxman, M.D., Ph.D., Ricardo Restrepo-Jaramillo, M.D., Thenappan Thenappan, M.D., Ashwin Ravichandran, M.D., Peter Engel, M.D., Abubakr Bajwa, M.D., Roblee Allen, M.D., Jeremy Feldman, M.D., Rahul Argula, M.D., Peter Smith, Pharm.D., Kristan Rollins, Pharm.D., Chunqin Deng, M.D., Ph.D., Leigh Peterson, Ph.D., Heidi Bell, M.D., Victor Tapson, M.D., and Steven D. Nathan, M.D.

N Engl J Med 2021

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease



Waxman A et al. N Engl J Med 2021;384:325-334

The NEW ENGLAND JOURNAL of MEDICINE

Characteristics of the Patients at Baseline

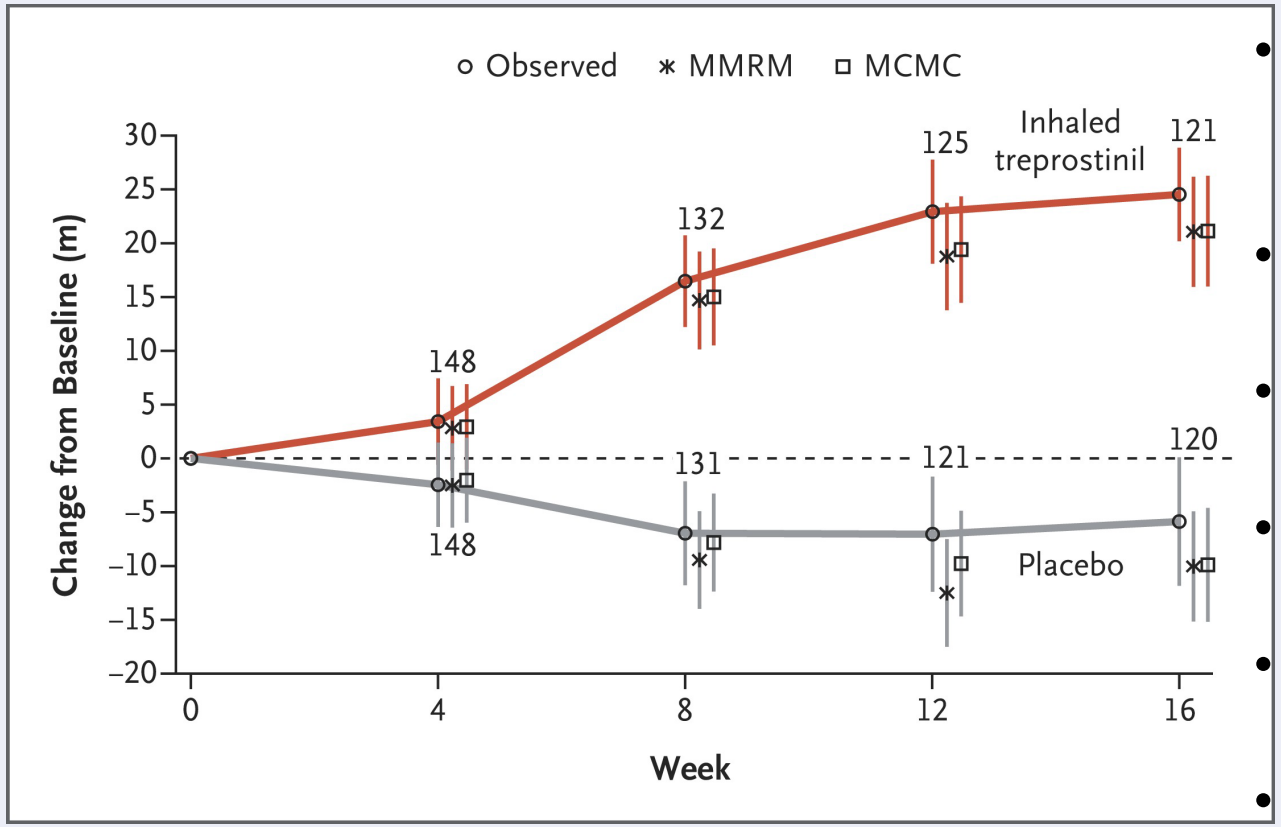
	Inhaled Treprostinil (n=163)	Placebo (n=163)
Women (n,%)	85(52.1)	68(41.7)
Age (yr, range)*	65.6(26-90)	67.4(36-83)
Race White Black	 112(68.7) 41(25.2)	 126(77.3) 30(18.4)
Cause of ILD IPF CPFE CTD	 65(39.9) 42(25.8) 40(24.5)	 81(49.7) 40(24.5) 32(19.6)
Supplemental O2 (n,%)	119(73)	114(69.9)
Background tx* (n,%)	133(81.6)	119(73)

Waxman A et al. N Engl J Med 2021;384:325-334

The NEW ENGLAND JOURNAL of MEDICINE

	Inhaled Treprostinil (n=163)	Placebo (n=163)
6MWT [m; mean(range)]	254.1 (100-538)	265.1 (30-505)
mPAP [mmHg; mean(range)]	37(25-74)	36(25-61)
PCWP [mmHg; mean(range)]	10.1(2-20)	9.6(0-15)
PVR [WU; mean(range)]	6.4(3.1-18.1)	6.0(3.1-17.6)
FVC % predicted [mean(range)]	62.9(25-126)	64.2(30-109)
DLCO % predicted [mean(range)]	30.0(5-86)	28.1(1-86)

Mean Change from Baseline in Peak 6-Minute Walk Distance through Week 16.

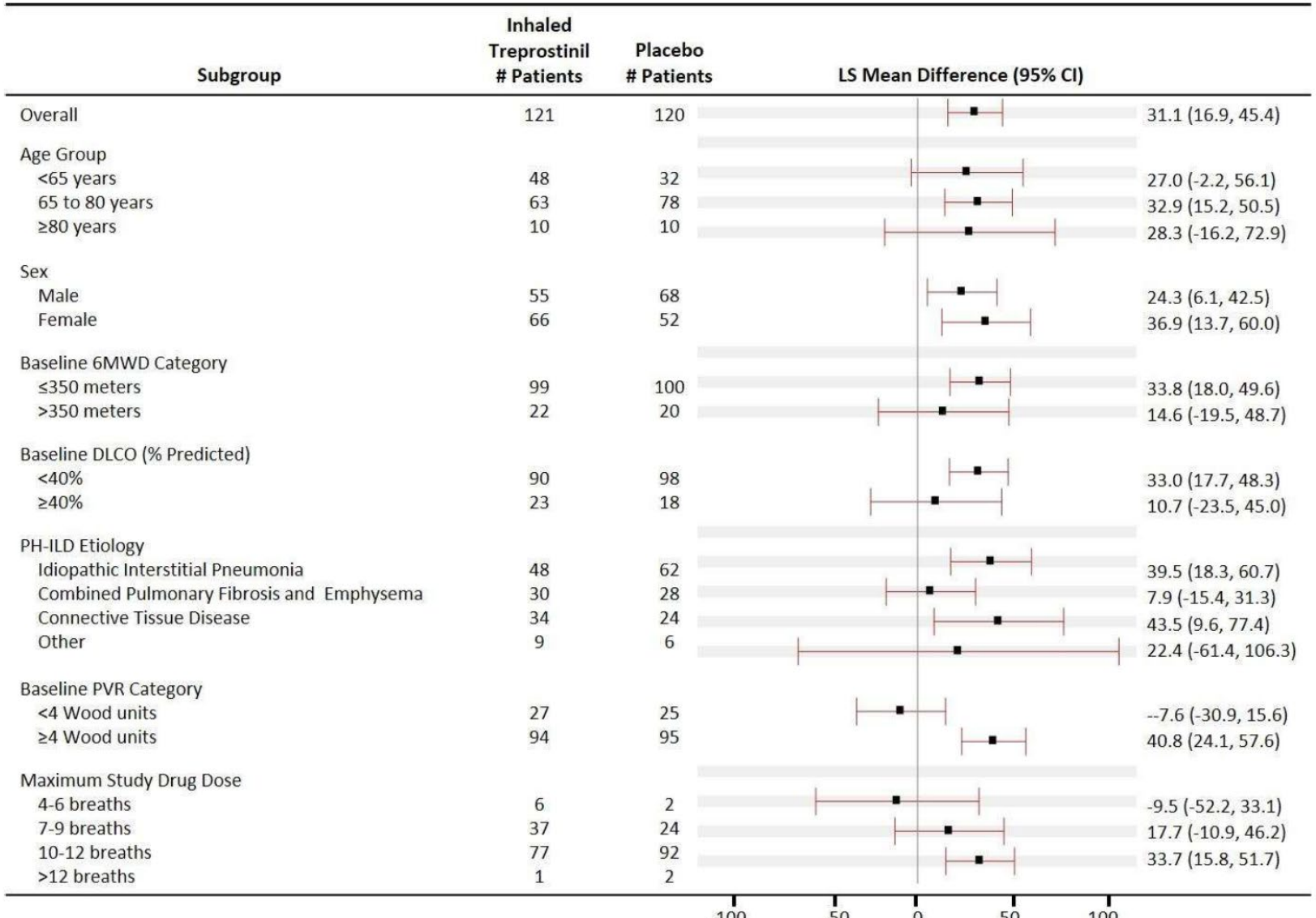


- Placebo corrected change 6 min walk 31.1± 7.3m
- Reduction in ProNT-BNP
- Reduction in clinical worsening
- No Difference AE
- No change in end walk SpO2
- Cough , throat pain

Waxman A et al. N Engl J Med 2021;384:325-334

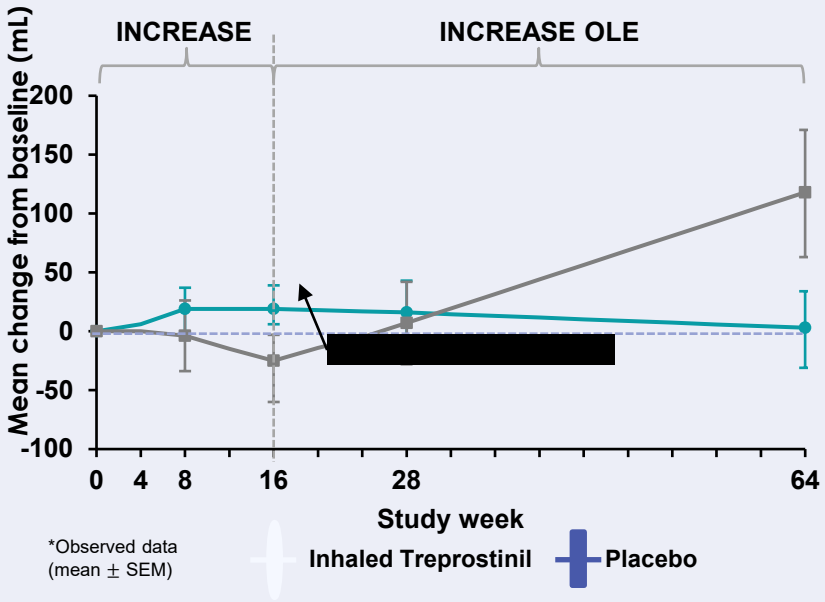
The NEW ENGLAND JOURNAL of MEDICINE

Figure S2. Forest Plot on Subgroup Analyses of Peak 6-Minute Walk Distance (meter) at Week 16.

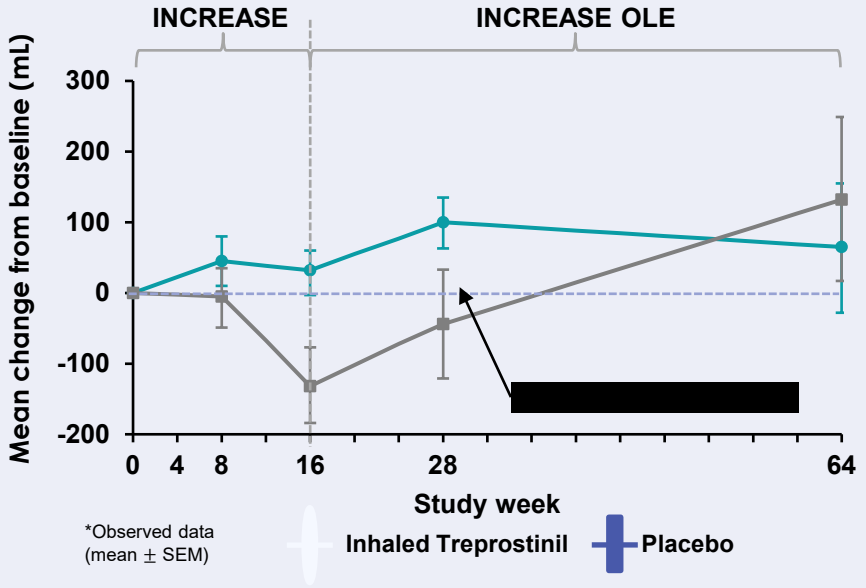


- INCREASE was a 16-week randomized, placebo-controlled trial

Mean Change From Baseline in FVC (mL) for All Patients



Mean Change From Baseline in FVC (mL) for the IPF Subgroup



- FVC improvements in the subgroup of patients with IPF, with a 64 mL and 133 mL increase in FVC at Week 64 in the prior inhaled treprostinil and placebo groups, respectively

FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; OLE, open-label extension.
Waxman AB, et al. ATS 2022. B96.

Management

- Address Underlying Lung Disease
- Optimize Comorbidities – OSA/ Hypertension
- Optimize Supplemental Oxygen
- Rule out VTE
- Inhaled Treprostinil

Exercise Training Outcomes: Absolute Change in 6MWD From Rigorous Program

N=183 participants in open-label, non-comparative cohort of PH of various etiologies

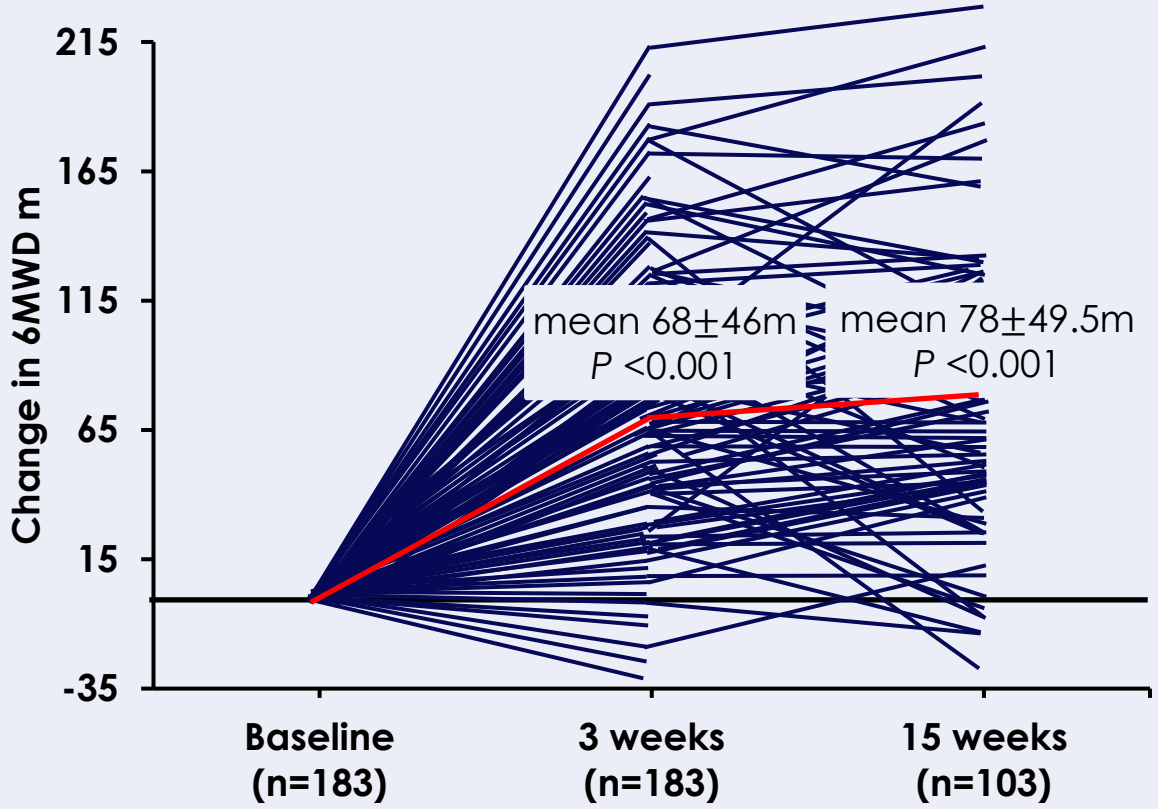
PAH (72%)
, CTEPH (16.9%),
Group 2 PH (4.4%)
, Group 3 PH (6.0%)

PAH/CTEPH patients were stable on optimized PAH-specific therapy at study entry

Program included 3 weeks of clinic-based ≥1.5 h per day exercise training (in intervals distributed over the day) of bicycle ergometer training 7 days per week, and walking, dumbbell training and respiratory training 5 days a week

HR = 60% to 80% of maximum with O2 sat >85%

Weeks 3 through 15 were at-home training ≥30 minutes a day, 5 days a week



Grunig E, et al. *Eur Respir J.* 2012;40:84-92.

Future Directions

Future Directions

- Newer therapies

- - Long acting Treprostinil

- -inhaled Guanylate cyclase

- - Inhaled Seralutinib

Future Directions

- Thorough Phenotyping and characterization

- Identify the which patients most likely to benefit from treatment

    - Use of Biomarkers
    - Use of proteomic and genetic data

- Define Acceptable clinical / research Outcomes
    - Risk stratification
    - QOL measures
    - Functional Improvement

Balance the burden of disease with burden of treatment

THANK YOU

NSOOD@UCDAVIS.EDU

What's New in CTEPH?

Novel Developments in Group 4 PH

Jenny Yang, MD

Assistant Professor of Medicine

University of California San Diego

Division of Pulmonary and Critical Care

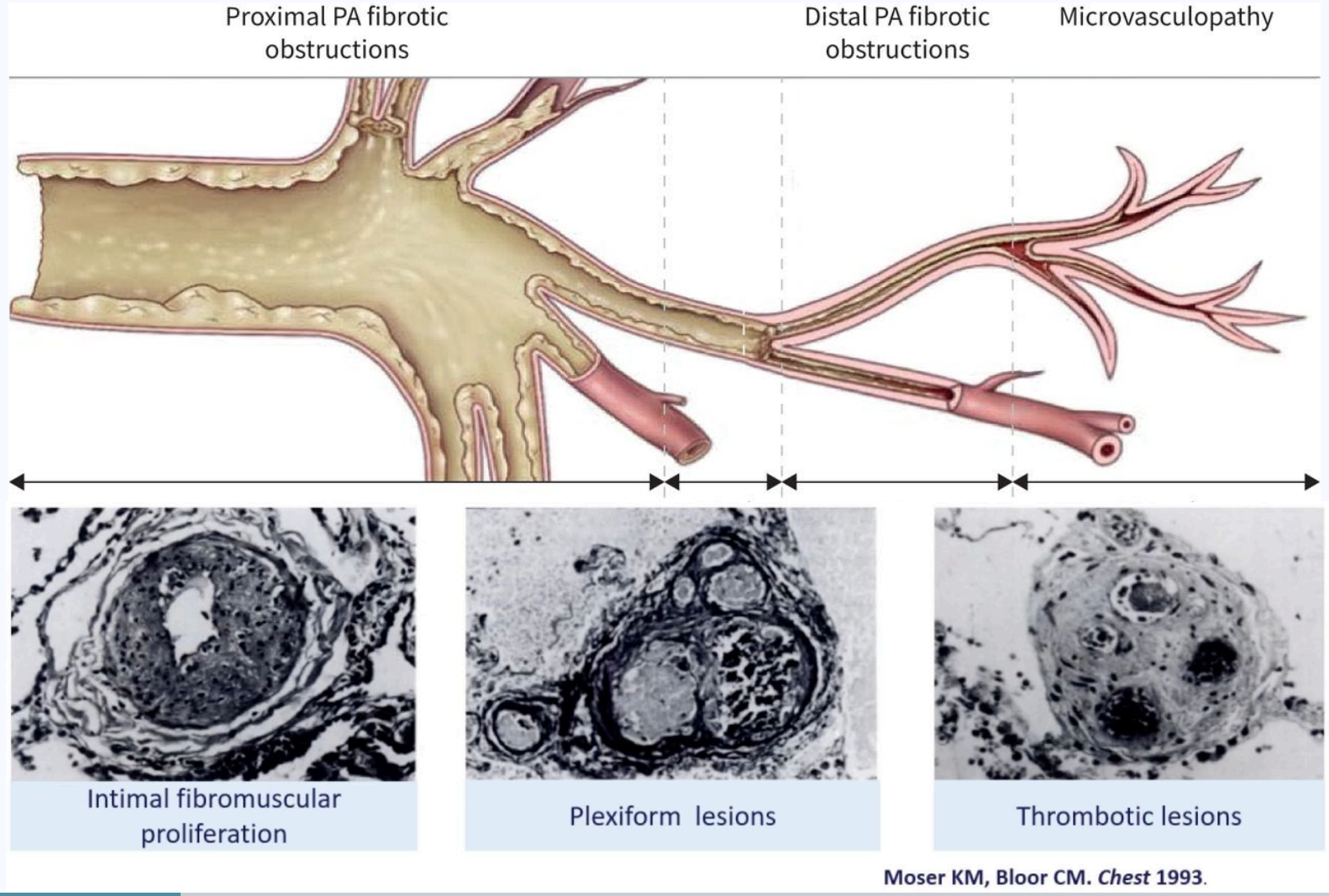
Disclosures

- I have the following relationships with ACCME defined ineligible companies:
  - Speaking/consulting fees – Merck
  - Advisory boards – Janssen, Merck
- I **WILL NOT** discuss off-label use and/or investigational use of any drugs or devices.

Outline

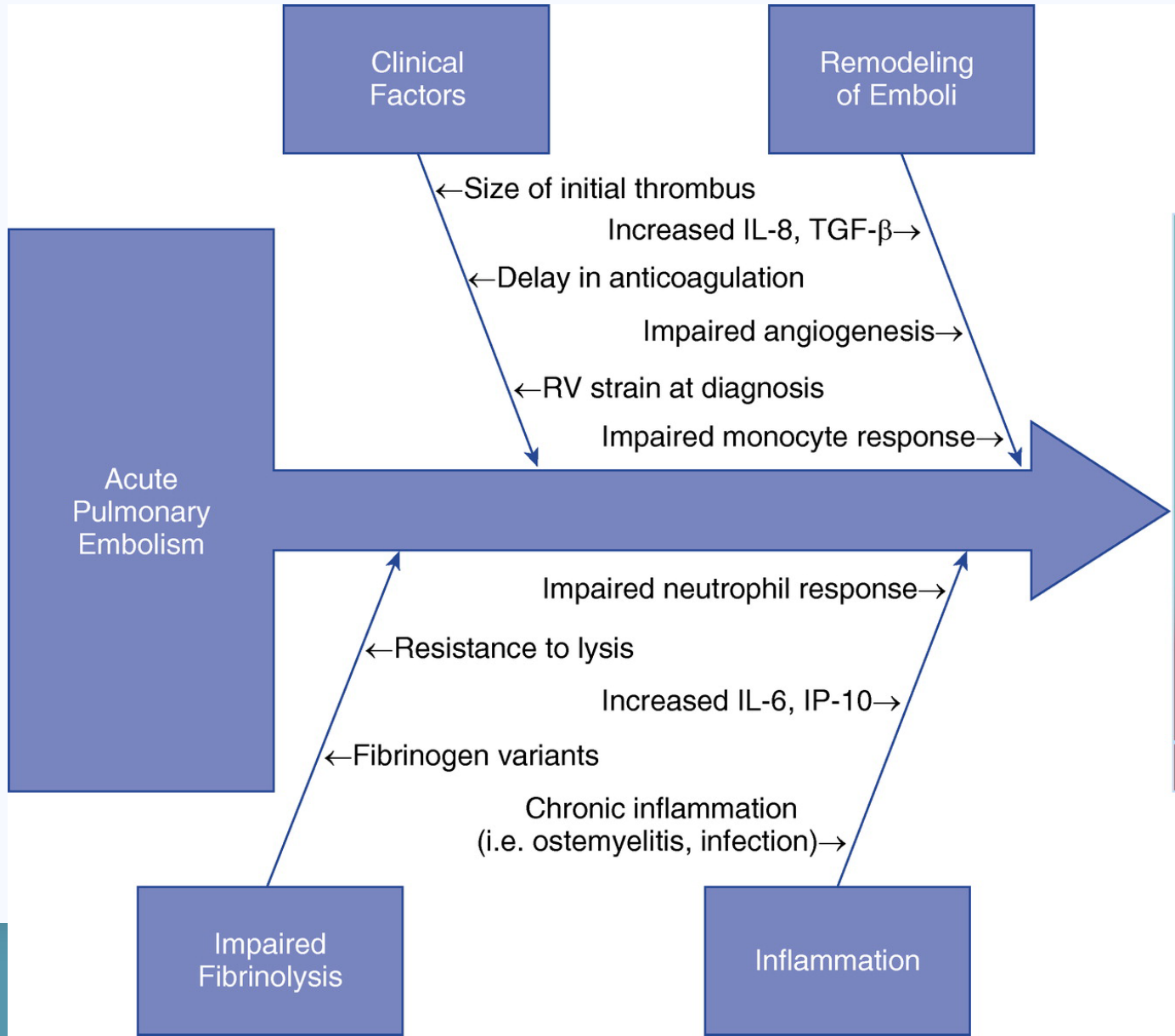
- Screening and diagnosis of CTEPH
- Treatment algorithm for CTEPH
- Follow up of CTEPH
- Challenges with long-term follow up

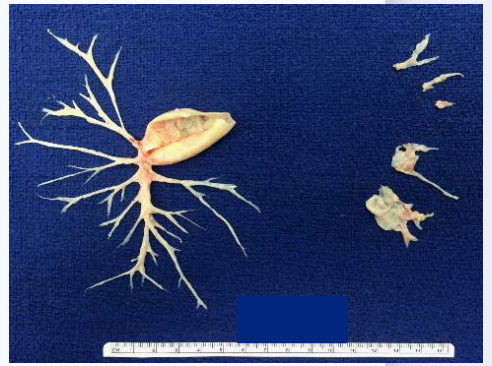
Chronic Thromboembolic Pulmonary Hypertension (CTEPH)



1) Simonneau et al, European Respiratory Review 2023 32(167): 220132; 2) Moser, Chest. 1993 Mar;103(3):685-92

Acute PE may fail to resolve

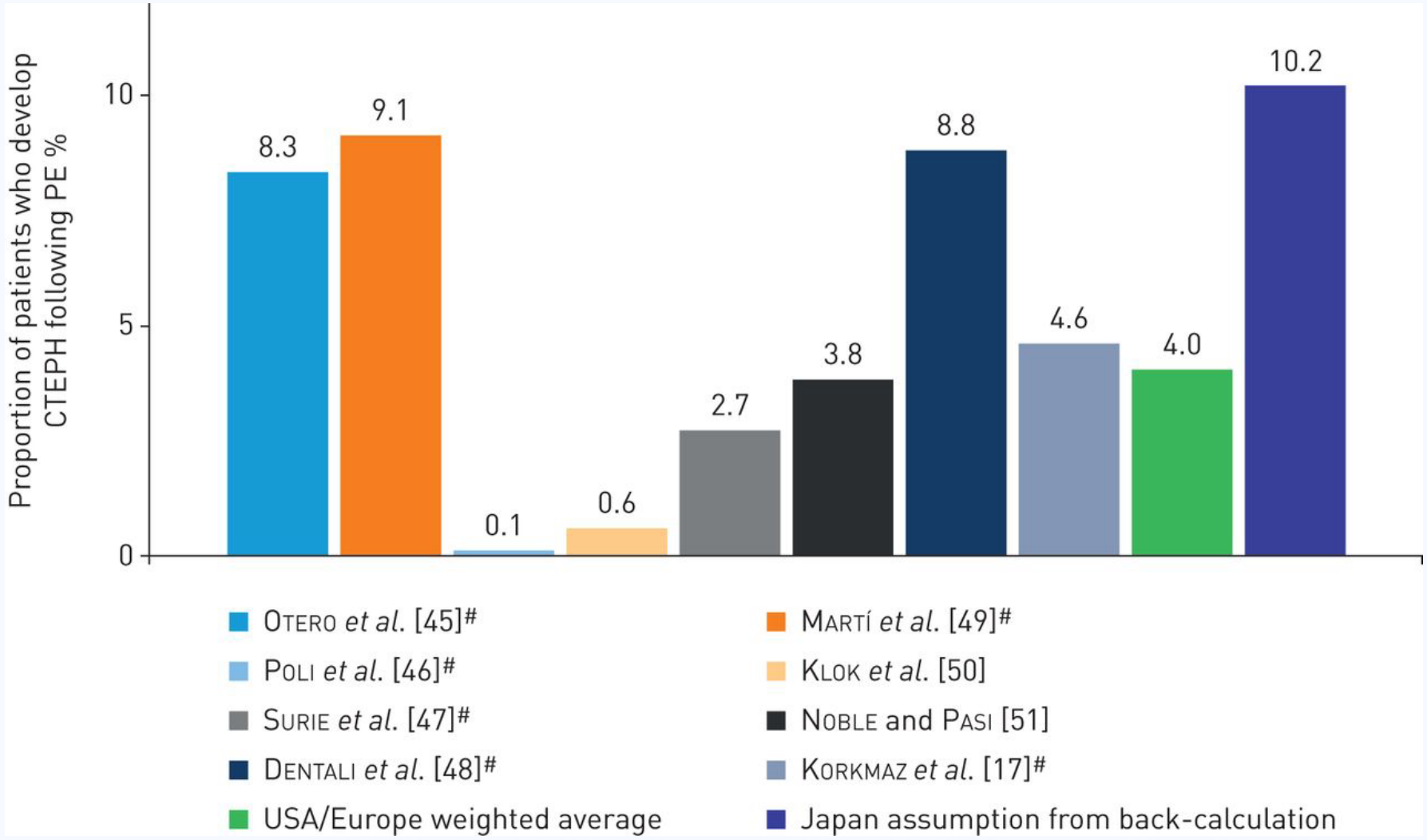




Fernandes T, *et al. Ann Am Thorac Soc.*, 2016;13 Suppl 3:S207-14

California Thoracic Society
ATS Chapter Serving California and Arizona

Incidence of CTEPH after acute PE



Richter et al, Eur Resp Rev 2017; 26:160121

No need for "routine" screening for CTEPH after PE, but…

- All patients should be routinely followed post-PE
- Symptoms should resolve to pre-PE baseline by 3-6 months

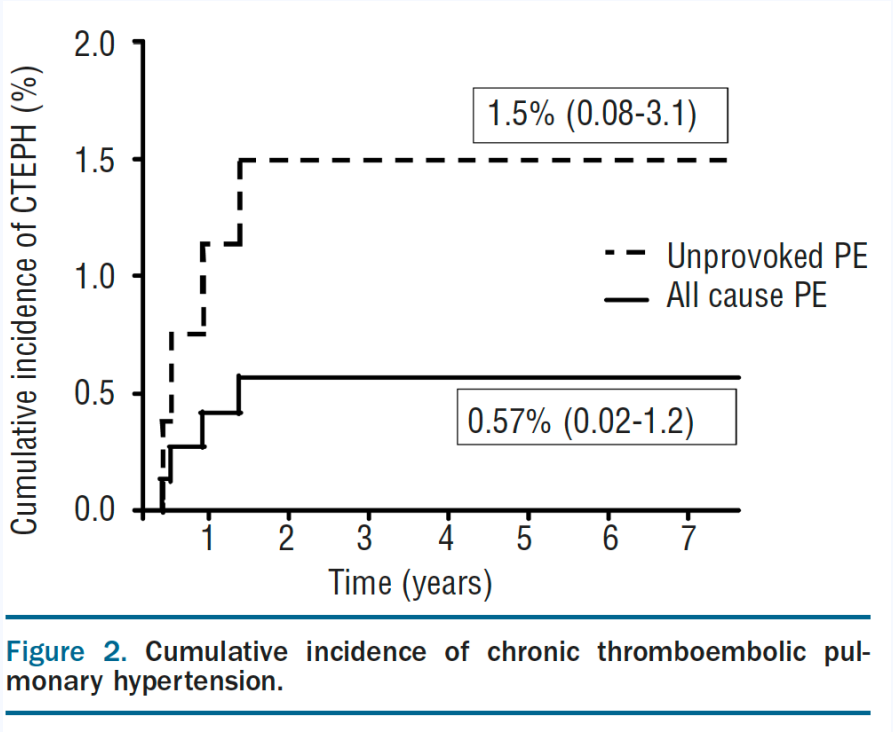
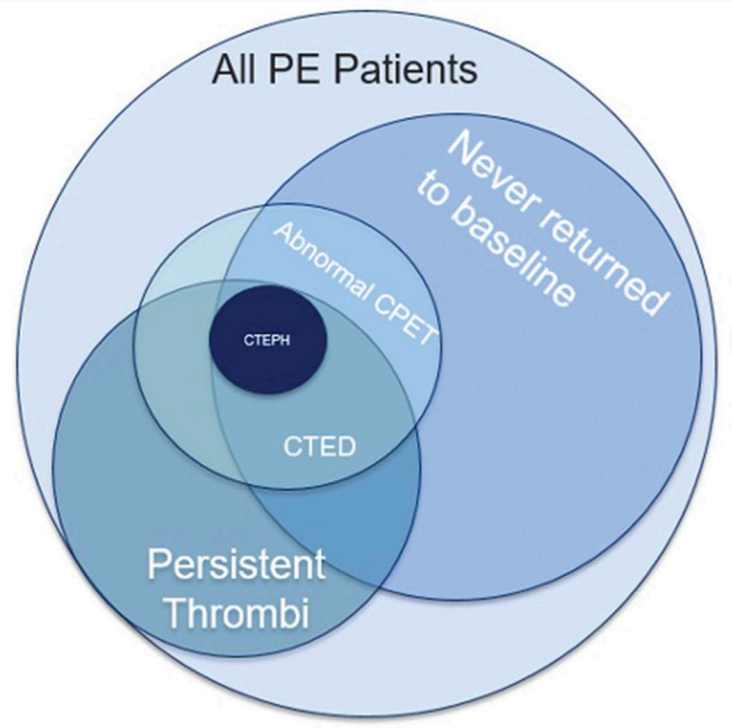
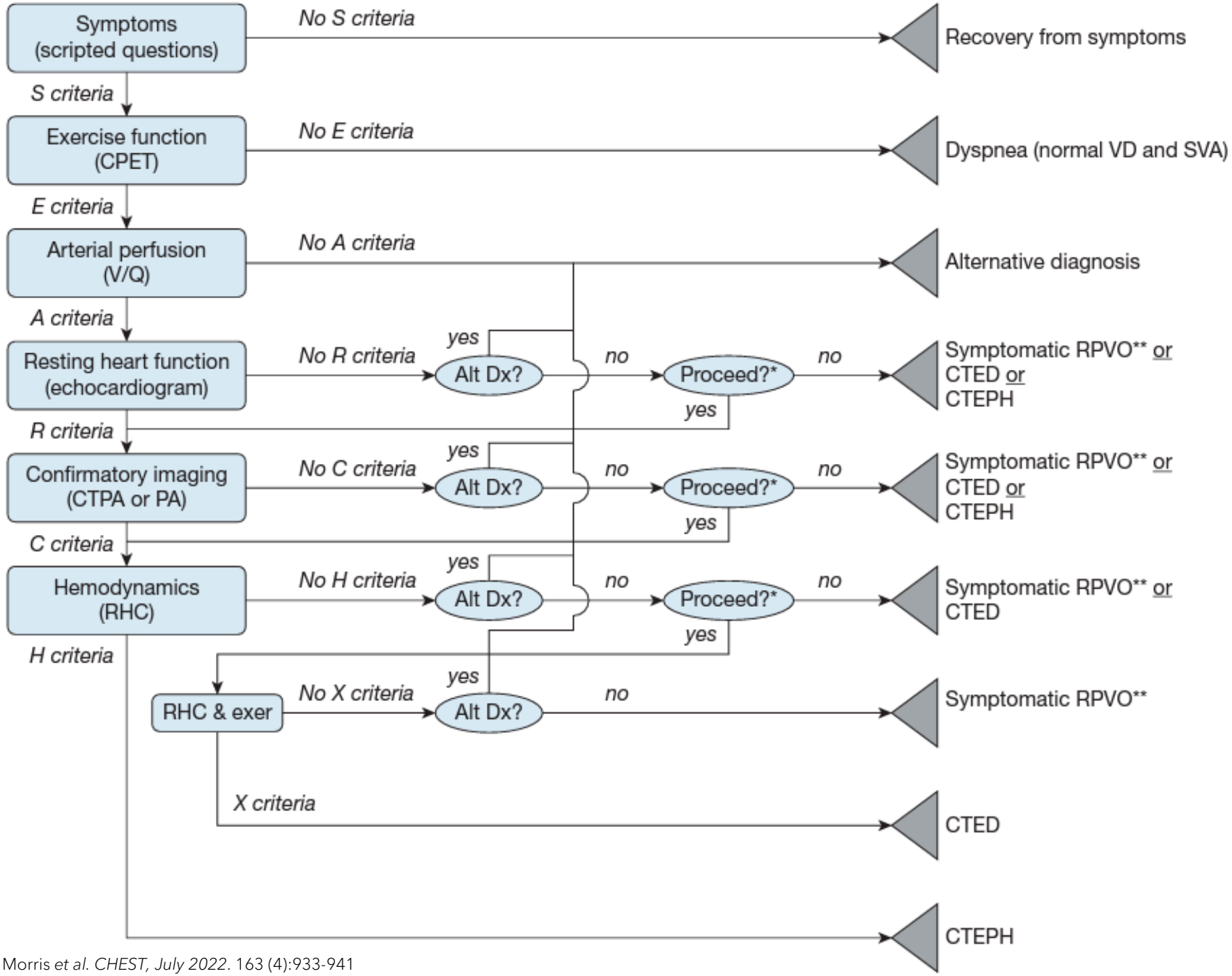


Figure 2. Cumulative incidence of chronic thromboembolic pulmonary hypertension.



1) Klok et al. Haematologica 2010, 95(6):970-5; 2) McGuire et al. Structural Heart 2021, 5(2):120-127.



Morris *et al. CHEST, July 2022*. 163 (4):933-941

"SEARCH"

Symptoms

Exercise (CPET)

Arterial perfusion (VQ)

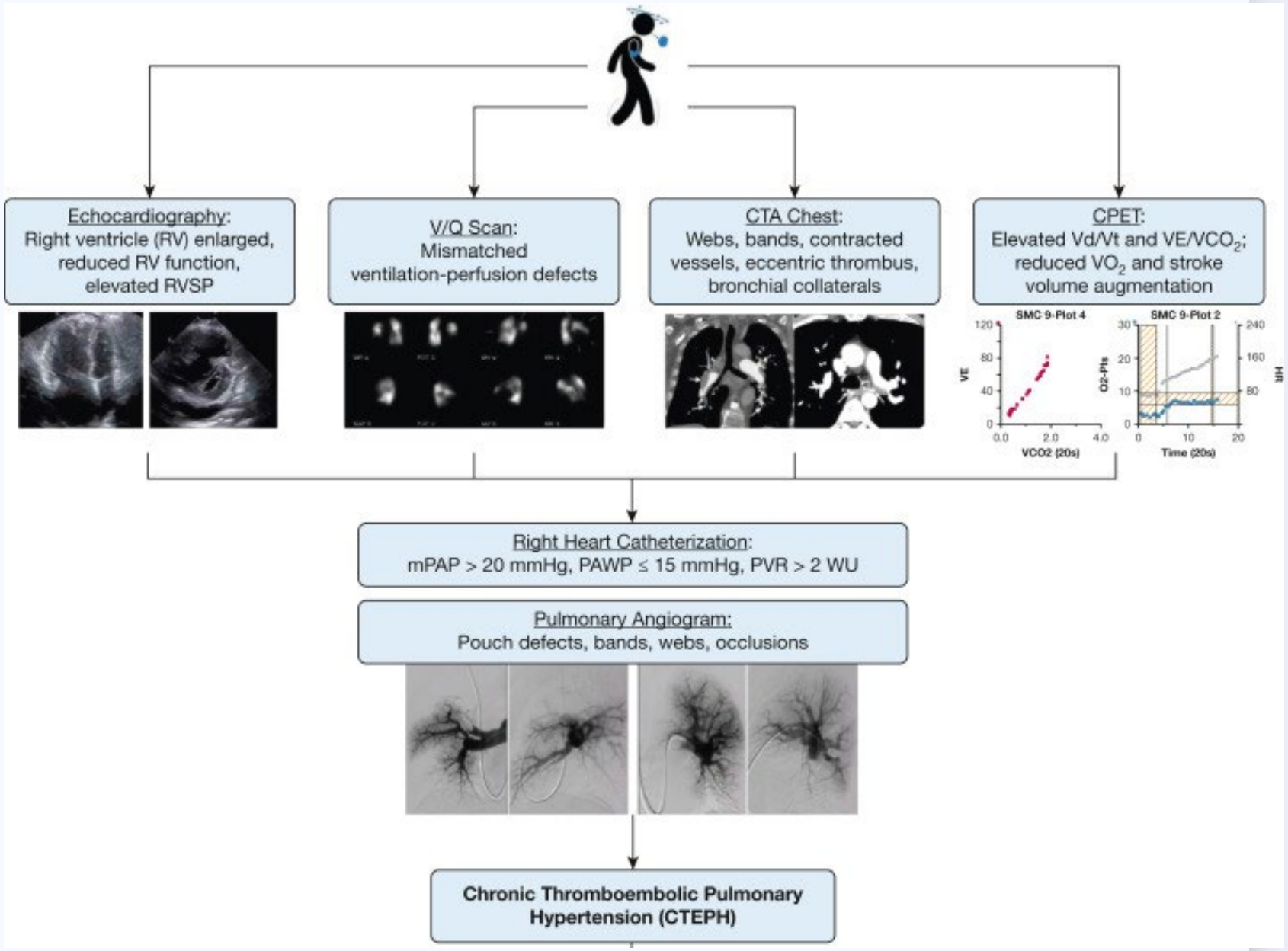
Resting echocardiogram

Confirmatory imaging

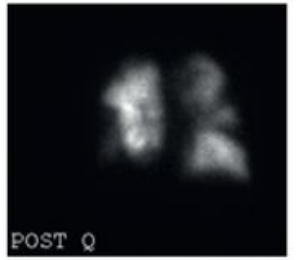
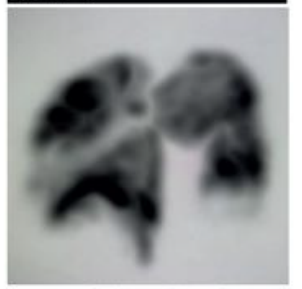
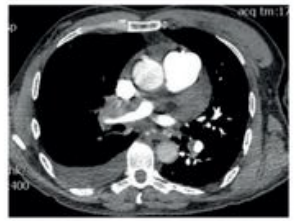
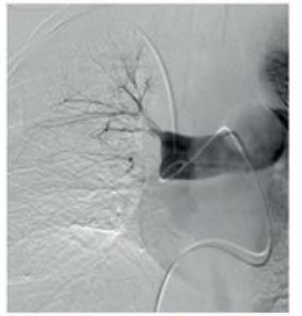
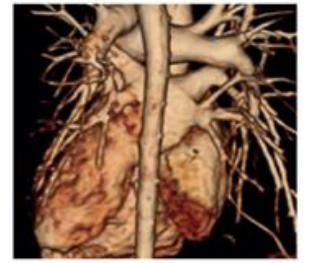
Hemodynamics

California Thoracic Society
ATS Chapter Serving California and Arizona

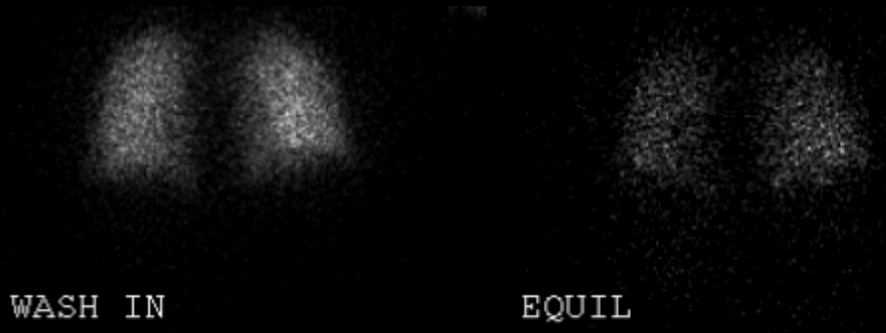
Screening and Diagnostic Tests



Yang et al, CHEST 2023; 164(2):490-502

Test	Pros	Cons	Examples
***V*/*Q* scan**	• Screening test of choice • Specific to pulmonary arterial blood flow • Normal or abnormal	• Perception of being an outdated test or phasing out • Ventilation may not be available (*e.g.* accessibility, pandemic effect)	
SPECT scan	• More sensitive than planar radionucleotide perfusion scan • May become more readily available than *V*/*Q*	• Not additive if planar scan already available	
CT pulmonary angiogram (with or without dual energy)	• Most widely available • Detailed information about pulmonary circulation but also lung parenchyma and mediastinum • Dual energy capable of perfusion map	• False negative results (*e.g.* chronic segmental/subsegmental disease) • Requires radiologist with CTEPD awareness and experience • Contrast necessary	
Pulmonary angiogram	• Direct injection into pulmonary arteries can offer details of the lumen including sequential views as contrast passes • Helpful for surgical or BPA planning	• Requires right heart catheterisation with devices allowing for rapid injection without catheter migration • Limited access to expertise • Can underestimate disease	
MRI	• No radiation • Can offer views of pulmonary circulation, perfusion map and surrounding soft tissues • Valuable for pulmonary arterial tumour evaluation • Additional cardiac morphology and functional assessment	• Requires radiologist with CTEPD awareness and experience • Limited access to expertise	

Kim et al, Eur Resp J. 2024. 2401294

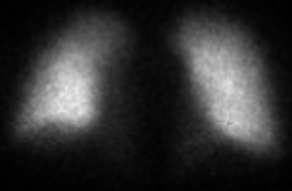


WASH IN

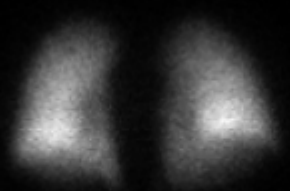
EQUIL

WASHOUT1

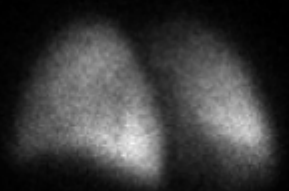
WASHOUT2



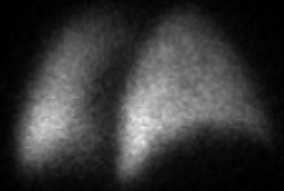
ANT Q



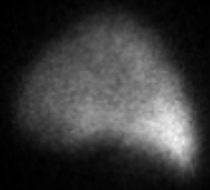
POST Q



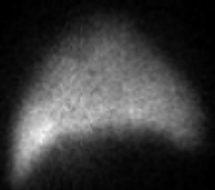
LPO Q



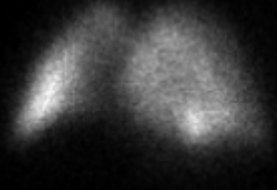
RPO Q



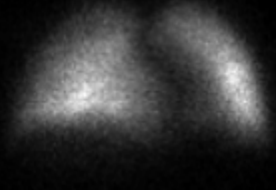
LLAT Q



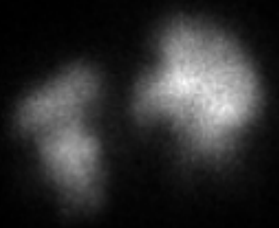
RLAT Q



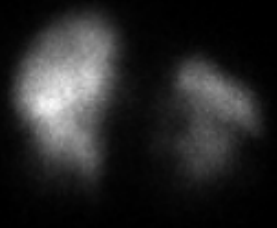
LAO Q



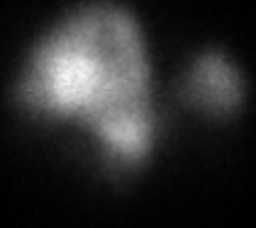
RAO Q



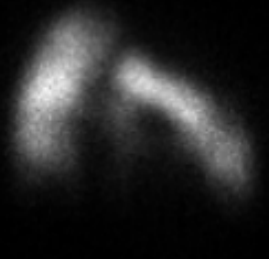
ANT Q



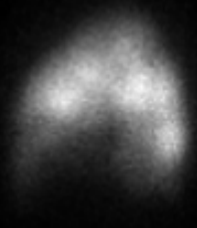
POST Q



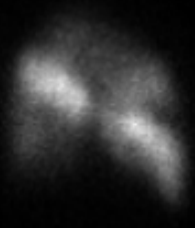
LPO Q



RPO Q

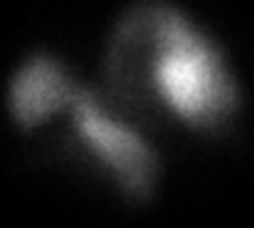


LLAT Q



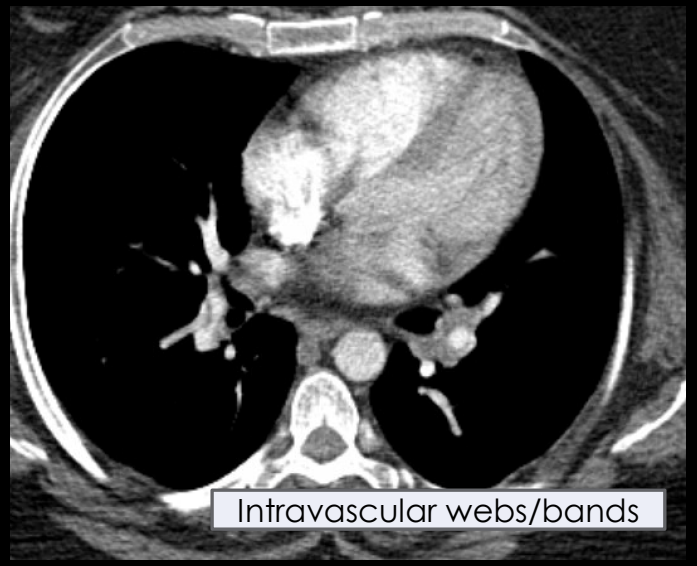
RLAT Q

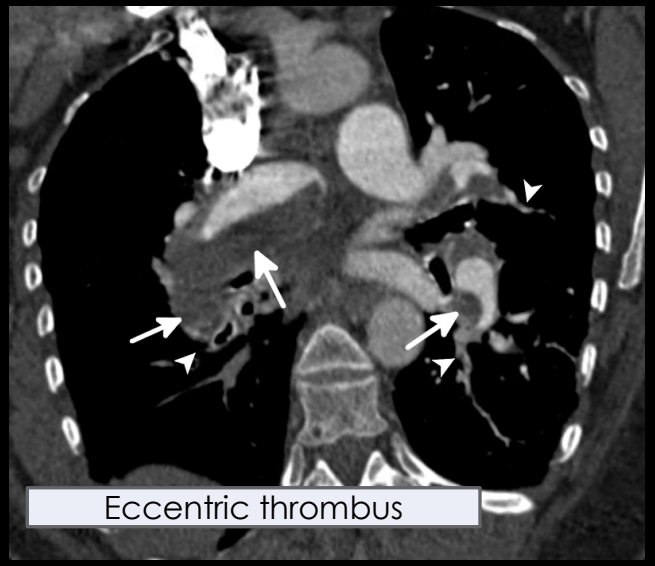
LAO Q

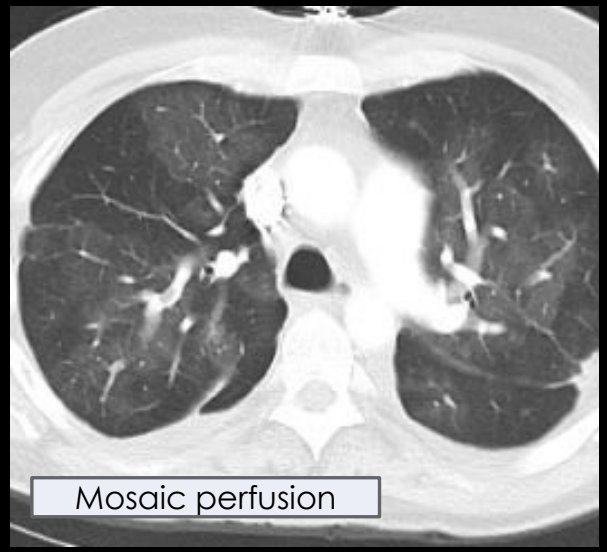


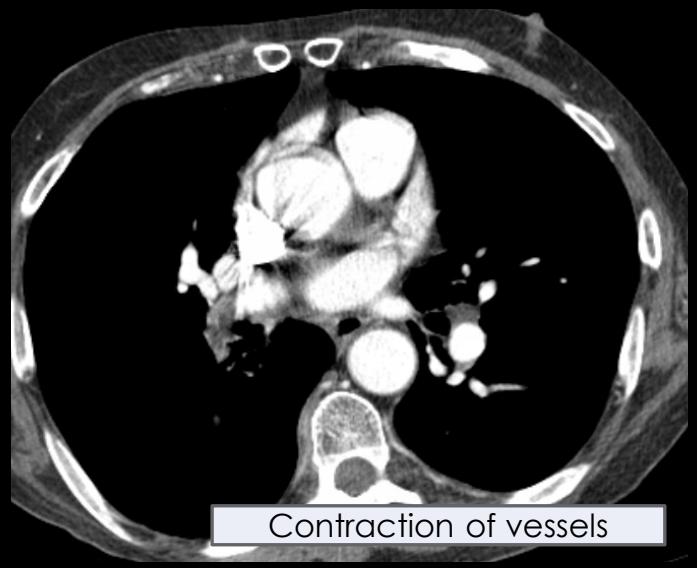
RAO Q

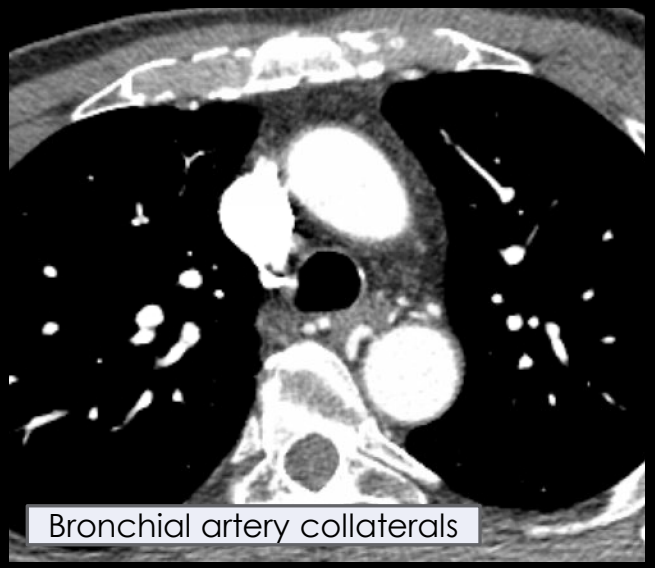
Findings of CTEPH on CT scans

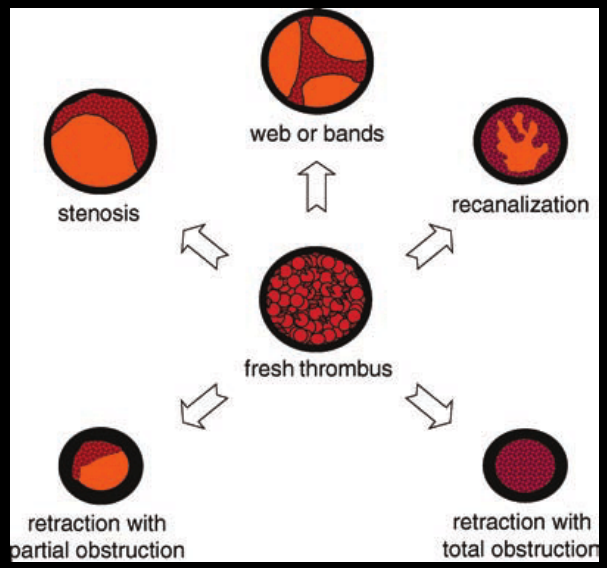

Intravascular webs/bands


Eccentric thrombus


Mosaic perfusion

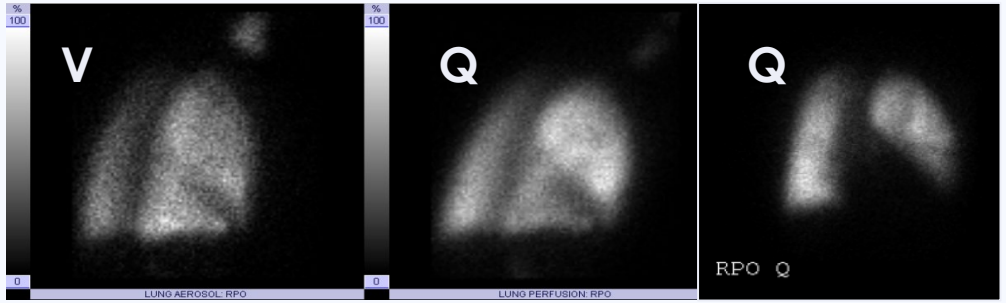

Contraction of vessels


Bronchial artery collaterals



Challenges with Diagnosis

- **VQ scan:** screening test of choice but can be difficult to interpret (Xenon vs Tc99 for ventilation)
- **CTPA:** may miss distal disease or could be misinterpreted



[Pulmonary Vascular Original Research]

CHEST

Preexisting Chronic Thromboembolic Pulmonary Hypertension in Acute Pulmonary Embolism

Check for updates

Stefano Barco, MD, PhD; Anna C. Mavromanoli, MD; Karl-Friedrich Kreitner, MD; Alexander C. Bunck, MD;

- **Misinterpretation → Misdiagnosis → Mismanagement**
  - Mimics: acute PE, PA sarcoma, arteritis/vasculitis, tumor embolism, mediastinal fibrosis, etc.
  - Inappropriate treatments and high-risk interventions: suction thrombectomy, CDT, EBUS etc.

Outcomes Associated With Catheter-Directed Therapies in Chronic Thromboembolic Pulmonary Hypertension

Cautionary Tales From a Single-Center Case Series

Jenny Z. Yang, MD; Nick H. Kim, MD; Seth Kligerman, MD; Timothy M. Fernandes, MD, MPH; Demosthenes G. Papamatheakis, MD; David S. Poch, MD; Mona Alotaibi, MD; Victor G. Pretorius, MD; Michael M. Madani, MD; and Kim M. Kerr, MD

Endobronchial ultrasound with transbronchial needle aspiration resulting in major complications in chronic thromboembolic pulmonary hypertension

Boksoon Chang[1*], Byeong-Ho Jeong[2], Lewis Hahn[3], Seulgi Gu[4], Michael M. Madani[5], Nick H. Kim[4]

[1]Department of Pulmonary, Allergy and Critical Care Medicine, Kyung Hee University Hospital at Gangdong, School of Medicine, Kyung Hee University, Seoul, Korea [2]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [3]Department of Radiology, [4]Pulmonary Vascular Medicine, University of California, San Diego, La Jolla, CA [5]Cardiovascular and Thoracic Surgery, University of California San Diego, La Jolla, CA
*Email of the presenting author: meera.chang@gmail.com

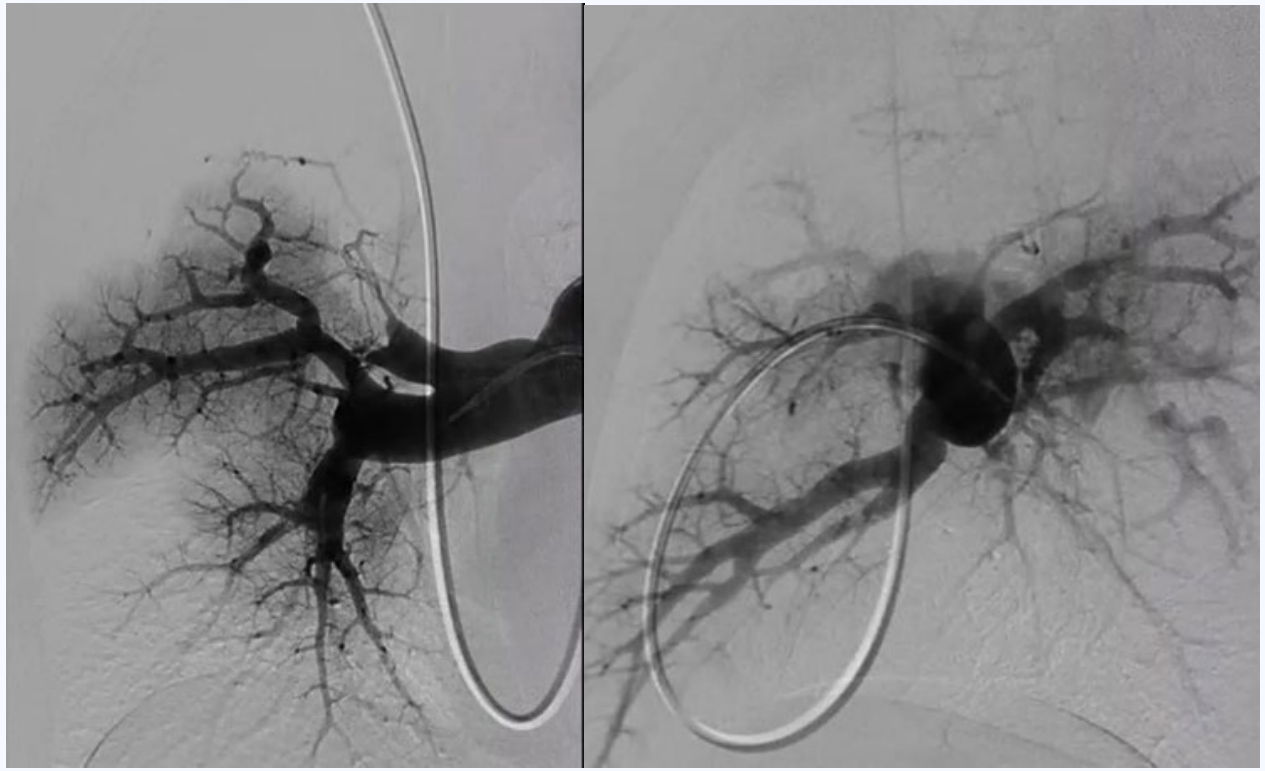
• Barco, *et al. CHEST April 2023;163(4):*923-932; J Nuc Med 2007;48:680; Thorax 2013;68:677; Can J Respir Crit Care Sleep Med 2019;3:177; Eur Heart J 2022;43:3618; Eur Respir J 2021;57:2002828; JACC 2020;76:2155

Diagnosis of CTEPH or CTED

- Confirmatory imaging (invasive pulmonary angiogram or CTPA)
- and,
- mPAP > 20 mmHg, PCWP ≤ 15 mmHg, PVR > 2 WU

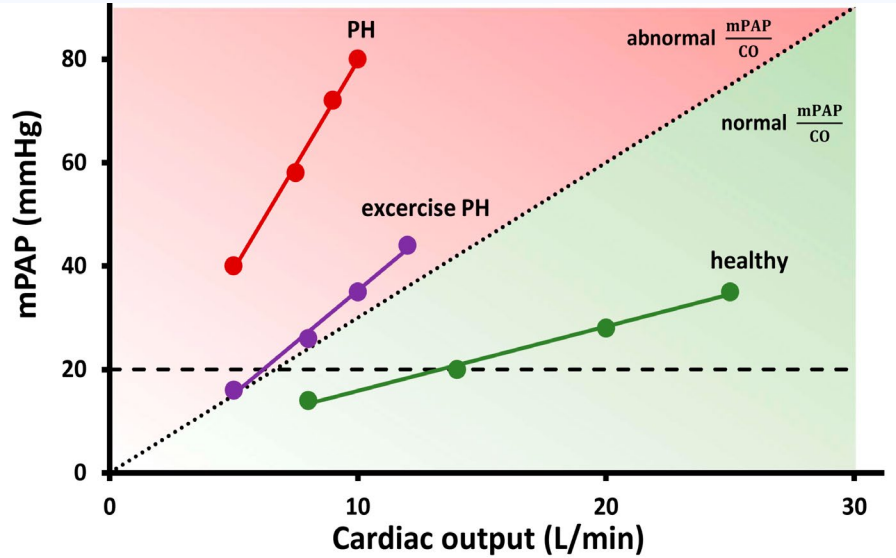
or,

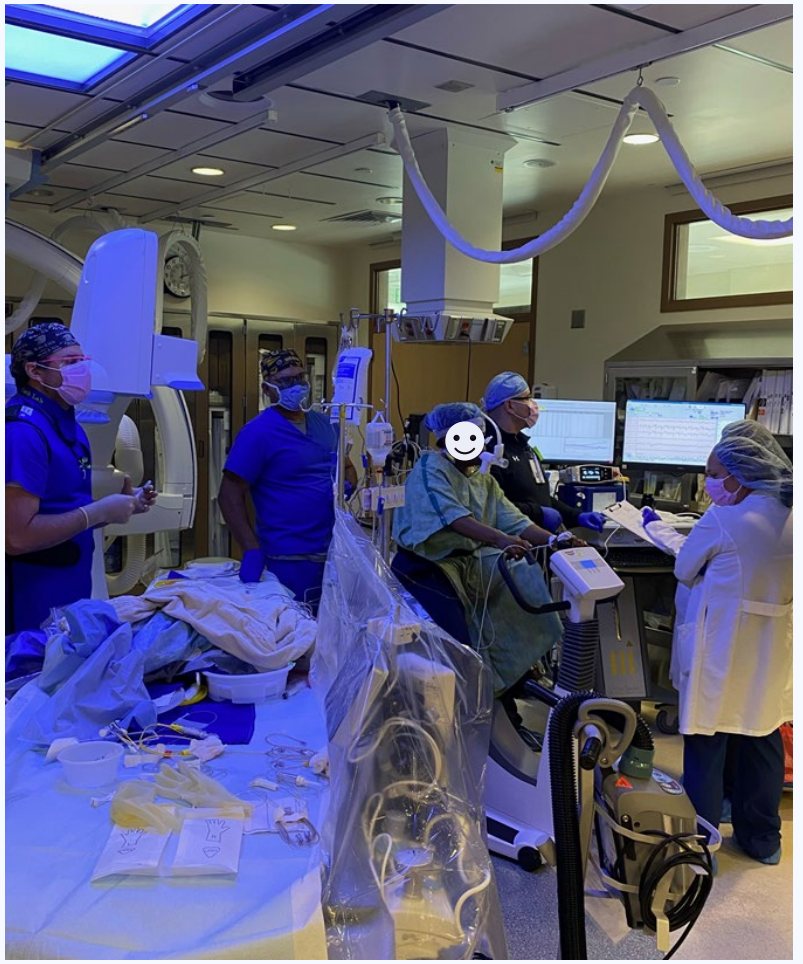
- mPAP/CO slope >3 mmHg/L/min



Quick word on CTEPD without PH (or CTED)

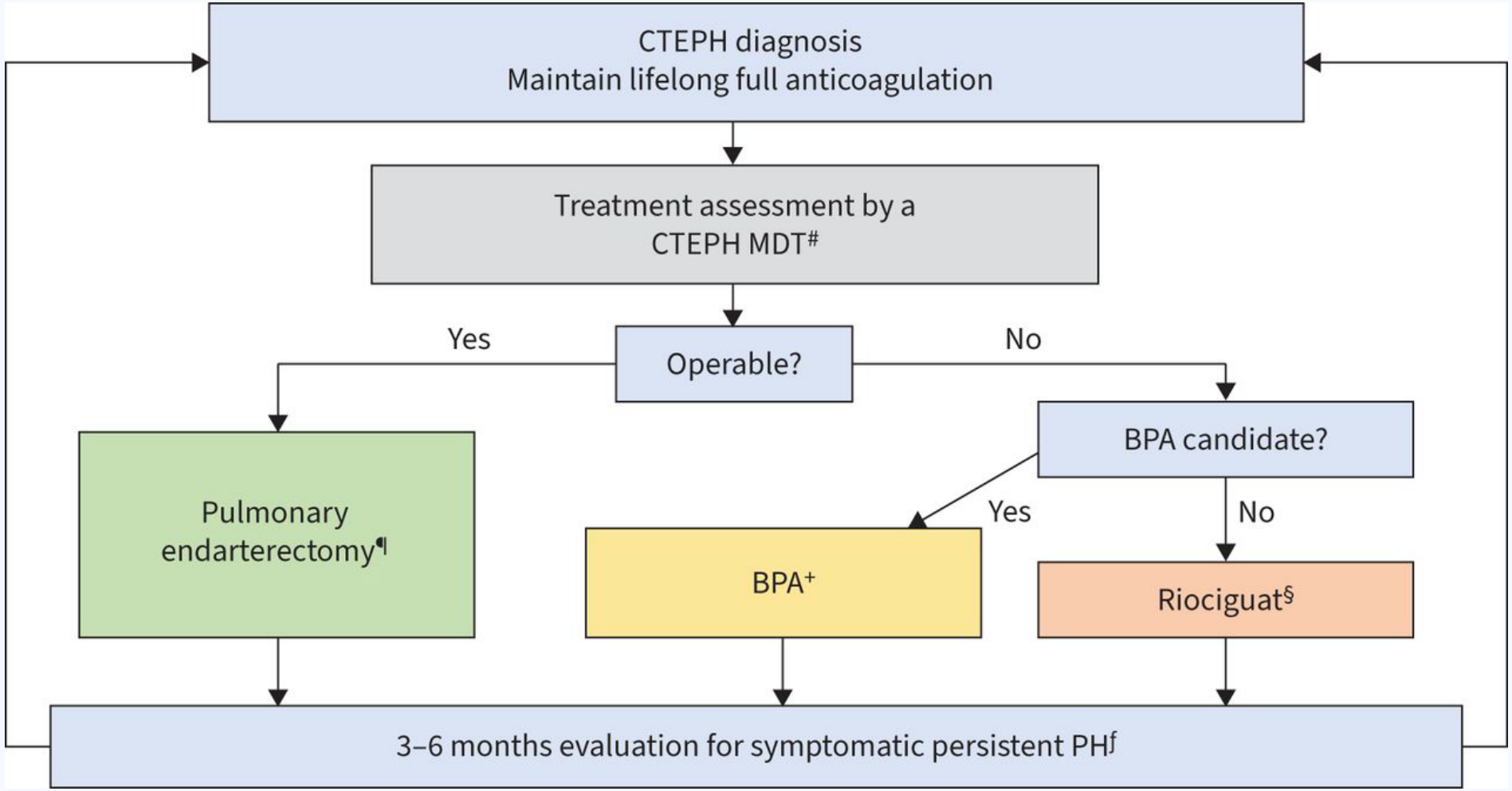
- Diagnosis requires exercise hemodynamics
  - Inefficient ventilation
  - Decreased pulmonary artery compliance
  - Poor RV reserve with inability to augment stroke volume
  - **Elevated P/Q slope (>3 mmHg/L/min)**





Skafar et al, Life 2023, 13(6), 1385

Treatment Algorithm

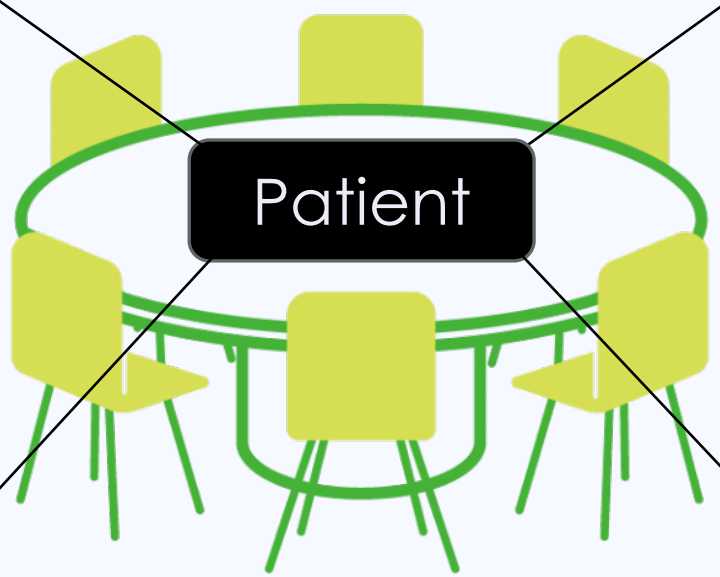


Kim et al, Eur Respj. 2024. 2401294

Multidisciplinary CTEPH team

PTE surgeon

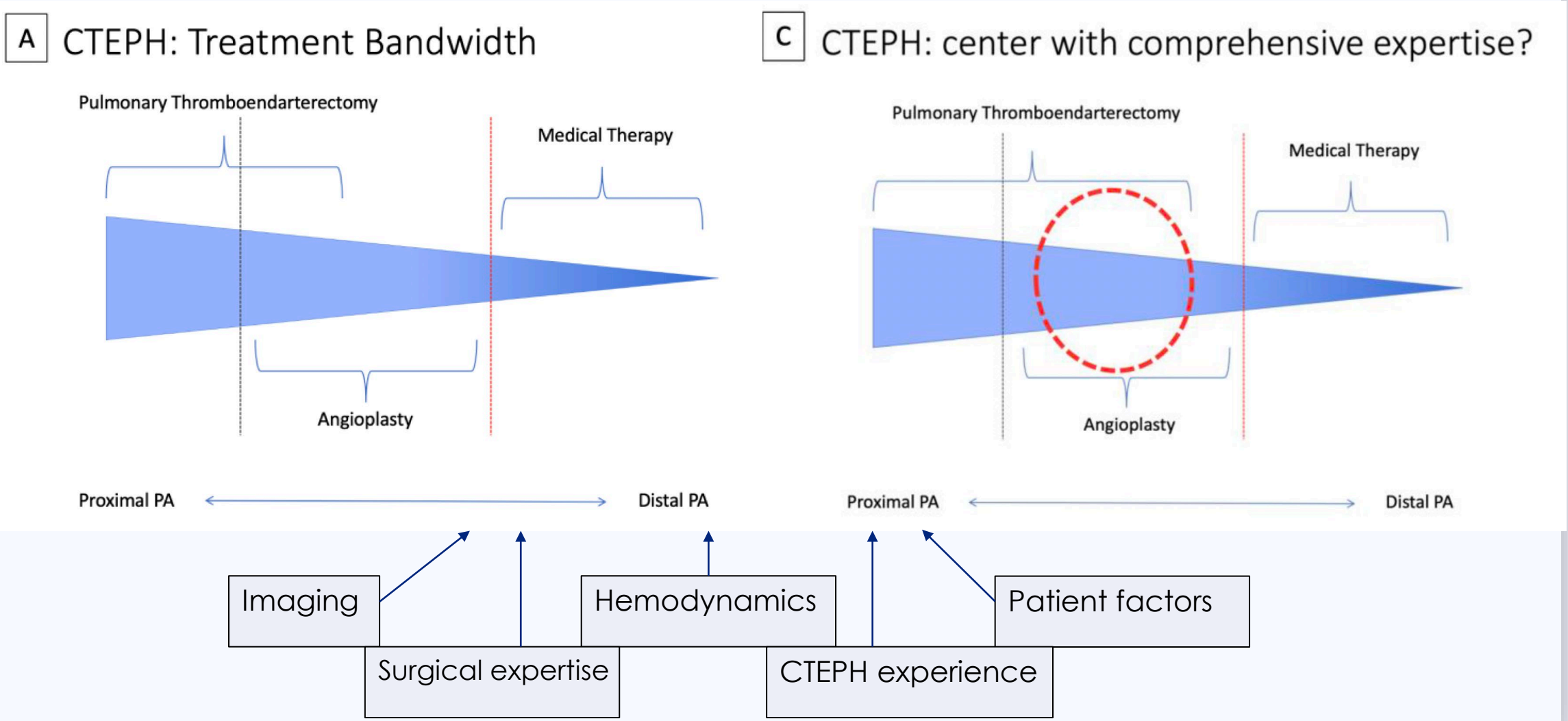
CTEPH/PVM specialist



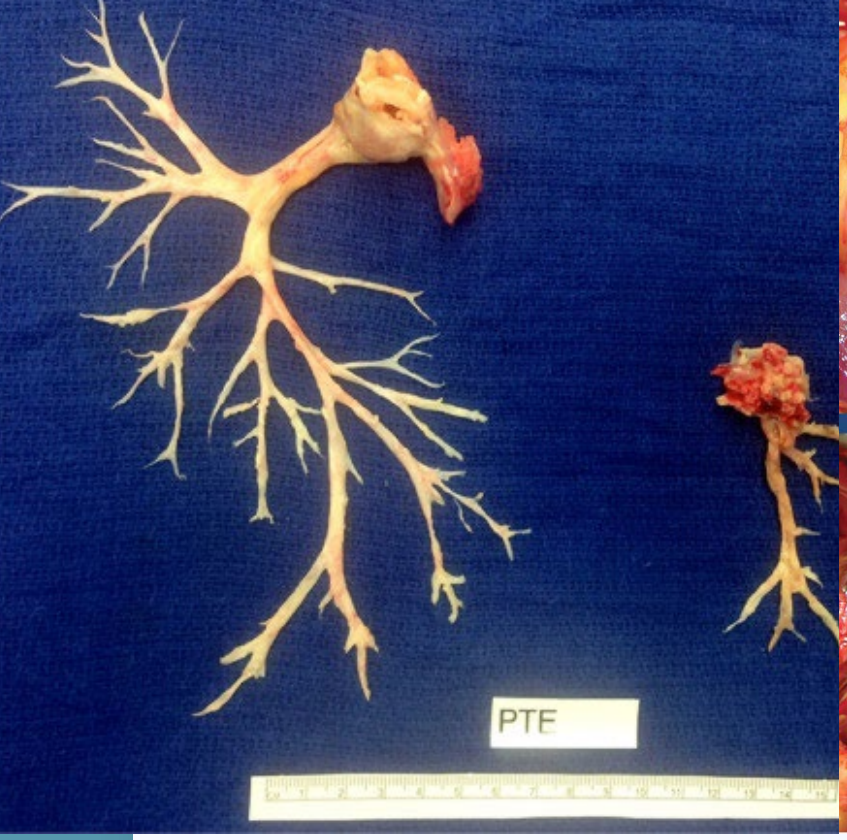
BPA interventionalist

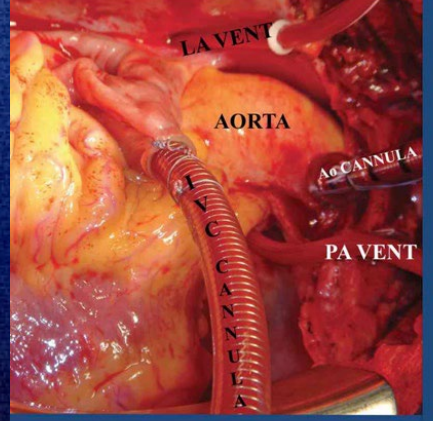
Chest/CTEPH radiologist

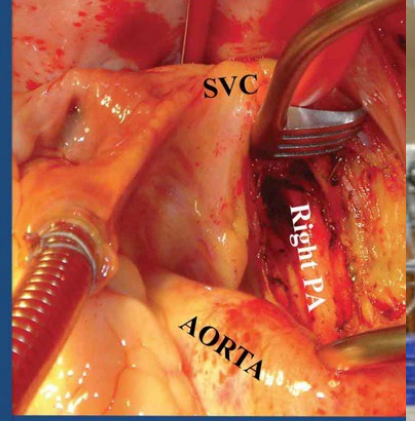
Multidisciplinary CTEPH discussion

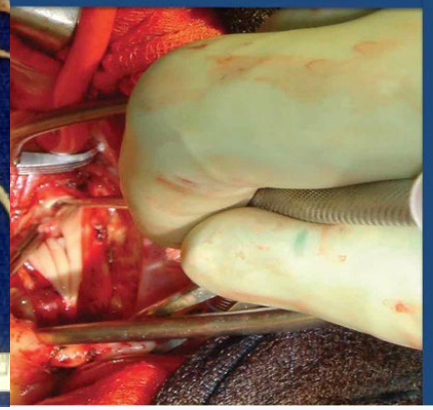


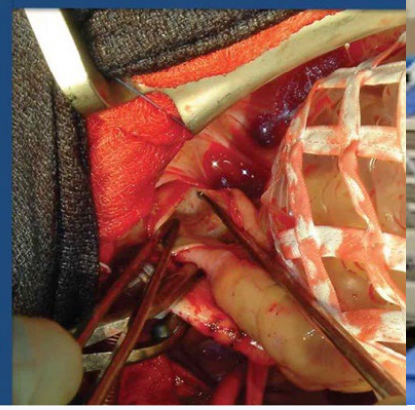
Yang et al, Pulm Circ 2023; 13(4):e12312











PTE Surgery

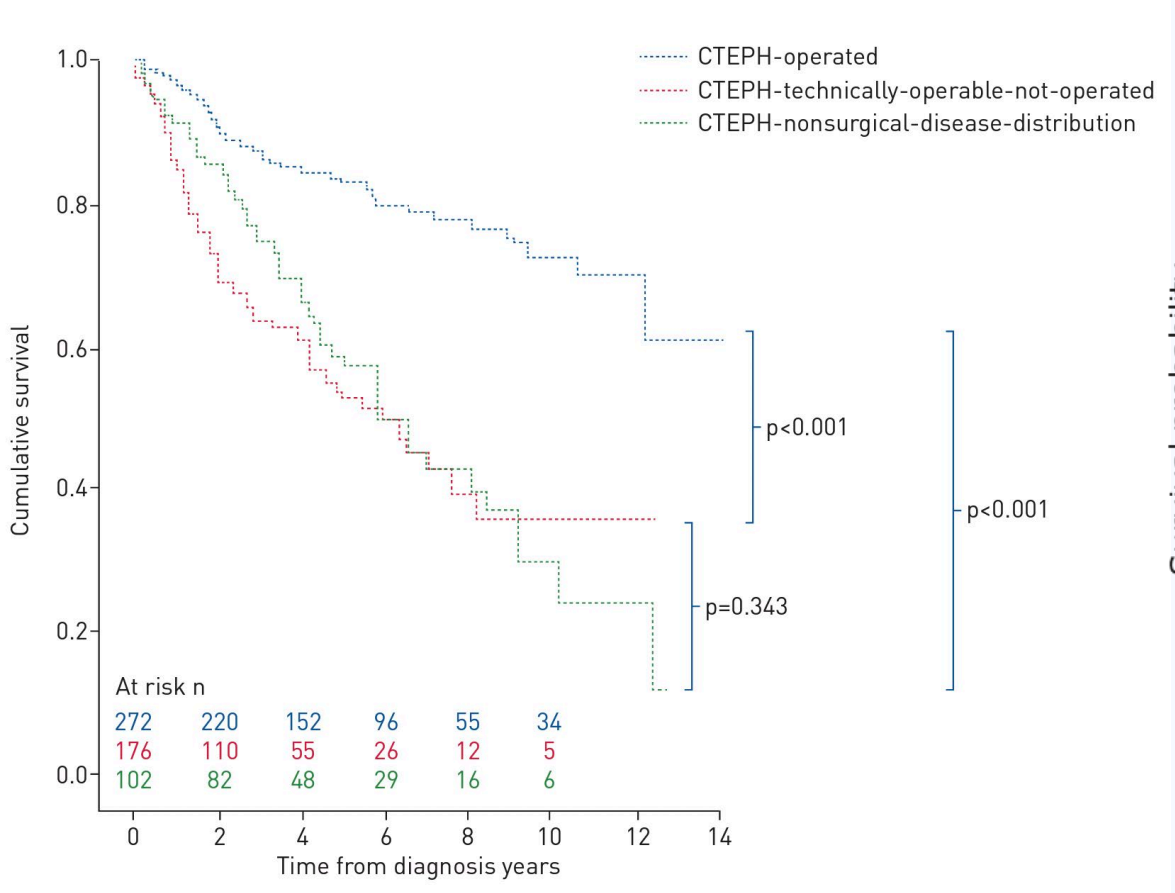
- 8-10 hour surgery
- Median sternotomy
- Cardiopulmonary bypass
- Cooled to 20 degrees Celsius (68F)

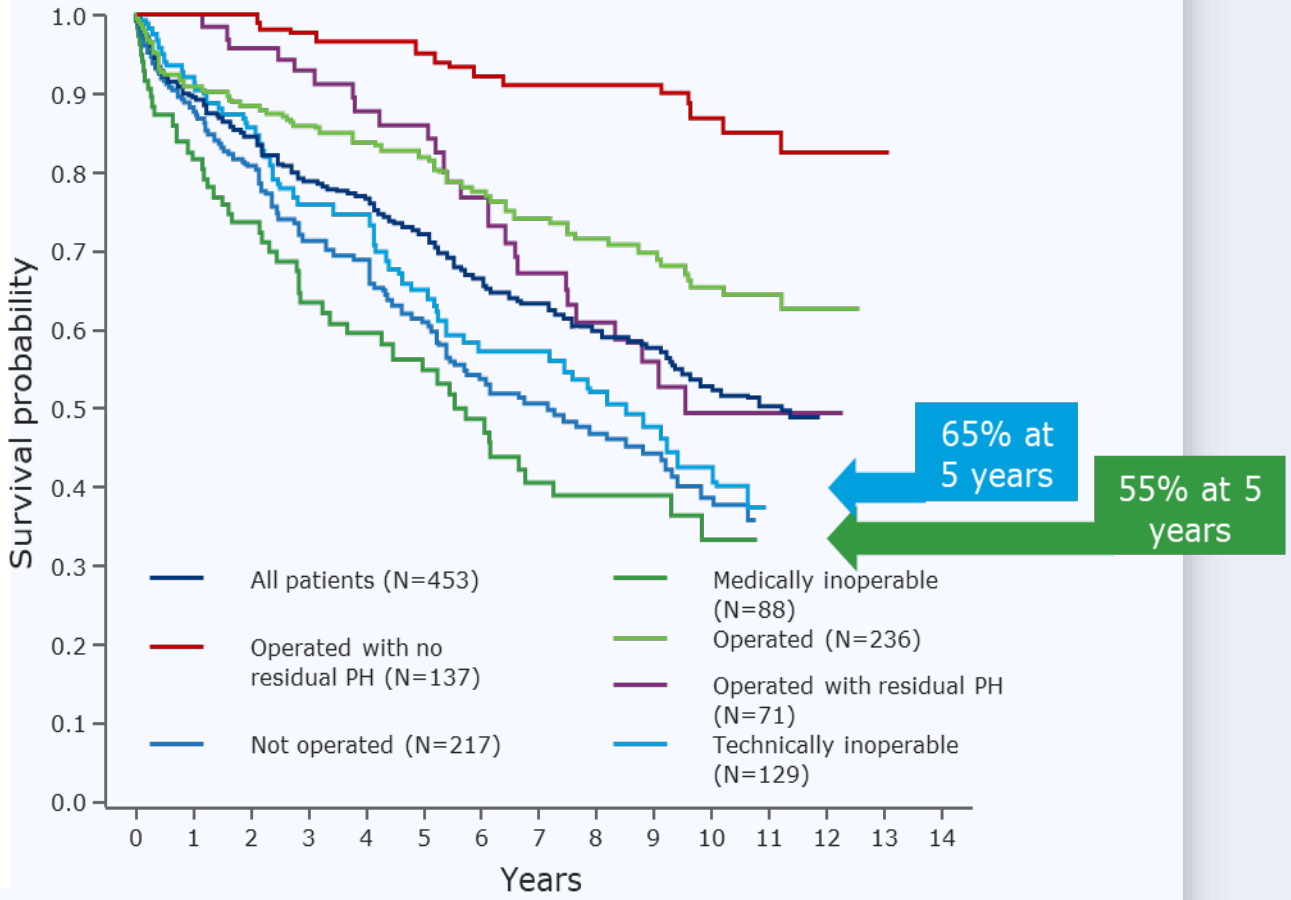
Deep hypothermic circulatory arrest (20C)

Bilateral endarterectomy (not embolectomy)

Rewarming and closure

PTE is treatment of choice for operable disease

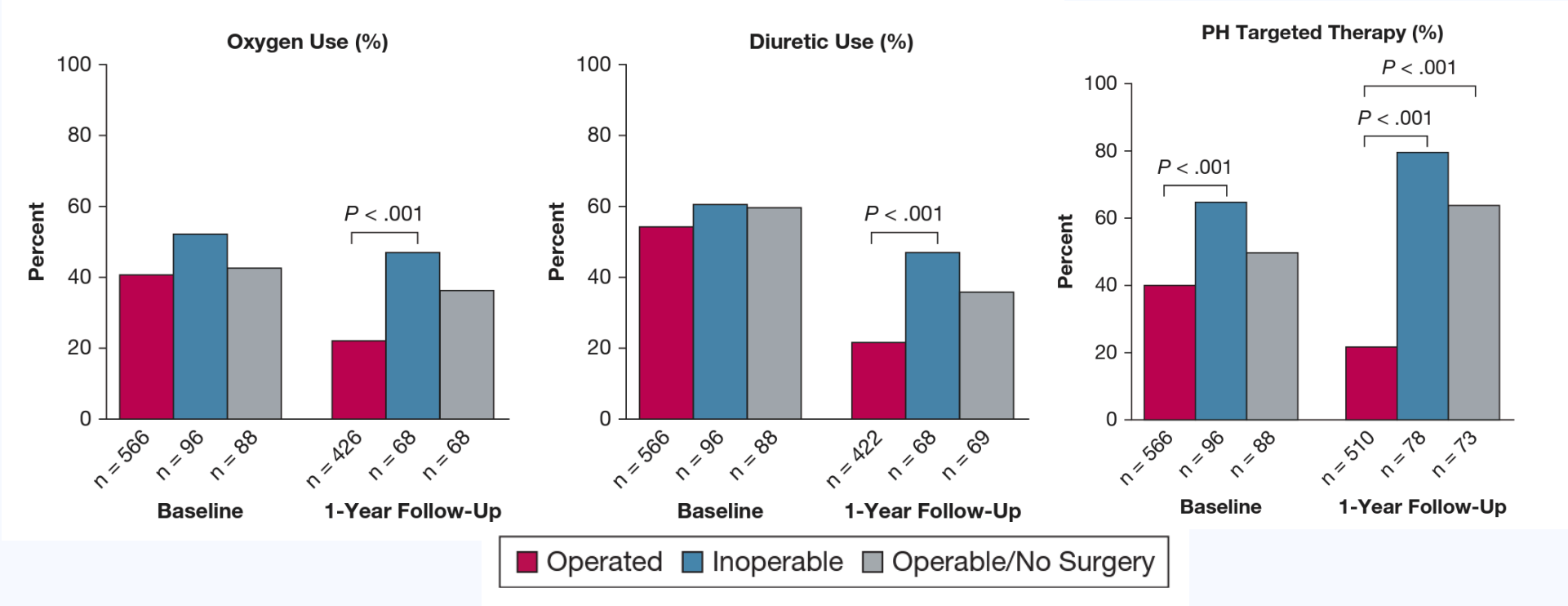




Jansa P, *et al. Pulm Circ* 2022; 12:e12038.
Quadery et al, Eur Resp J 2018, 52(3): 1800589

California Thoracic Society
ATS Chapter Serving California and Arizona

US CTEPH Registry: Operated vs Not Operated



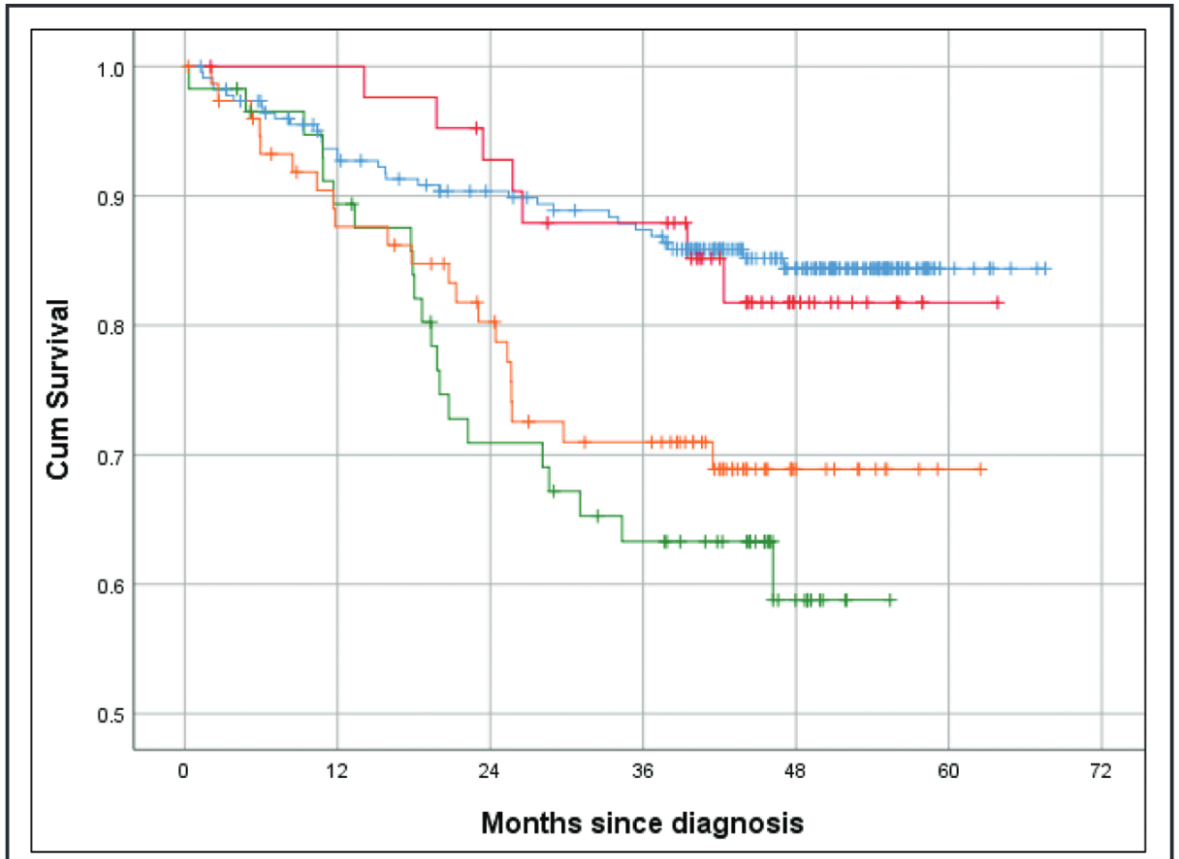
Kerr et al, CHEST 2021; 160(5):1822-31

California Thoracic Society
ATS Chapter Serving California and Arizona

Inoperable CTEPH

Worst survival in patients with:

- Co-morbidities
- Operable disease but did not get surgery



Time (months)	0	12	24	36	48	60
Technically inoperable	226	199	185	175	104	8
Patient refusal	43	42	38	35	12	1
Comorbidity	58	50	38	32	10	
Considered operable	76	62	53	44	11	1

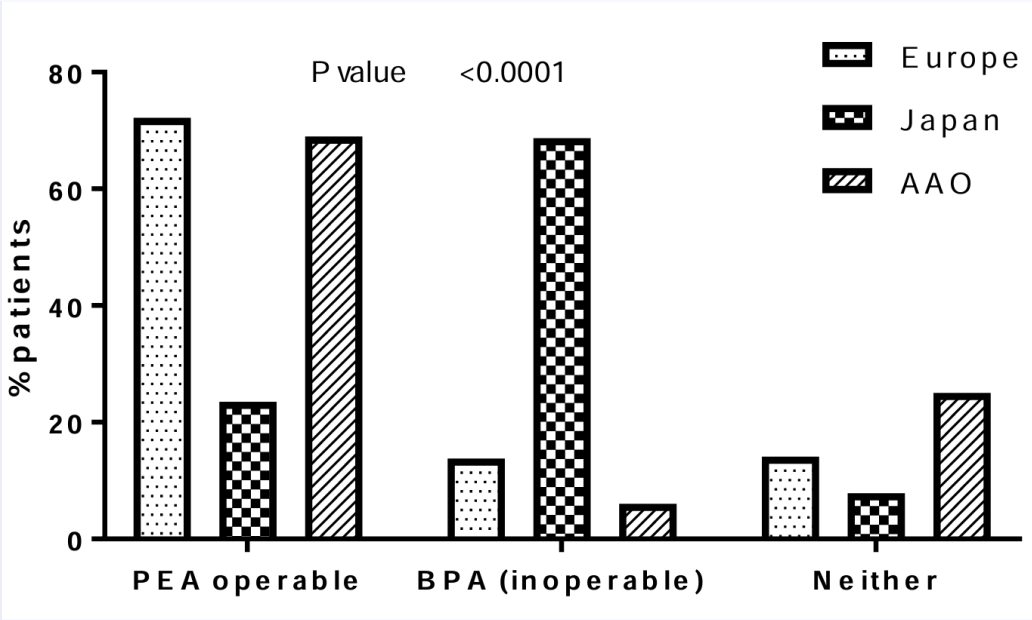
Delcroix et al, Circulation. 2024;150:1354–1365.

California Thoracic Society
ATS Chapter Serving California and Arizona

So how many CTEPH patients are considered inoperable?

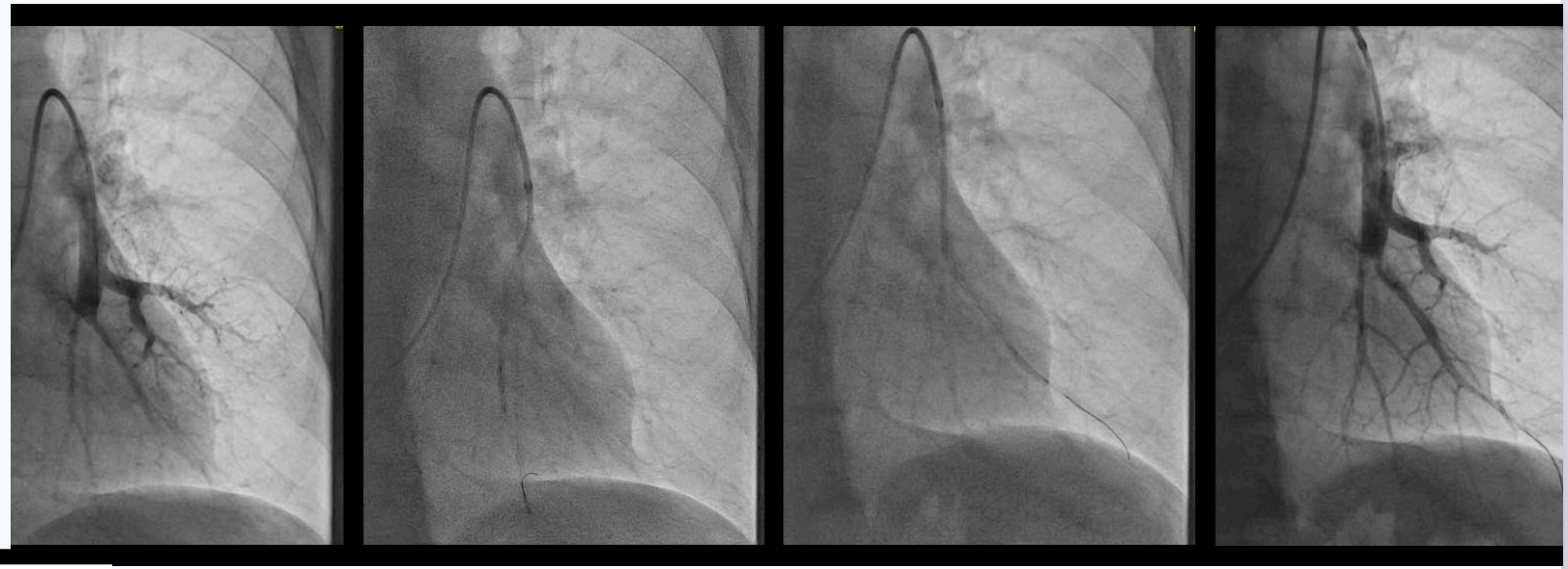
Worldwide CTEPH Registry: Feb 2015-Sept 2016. n=1010

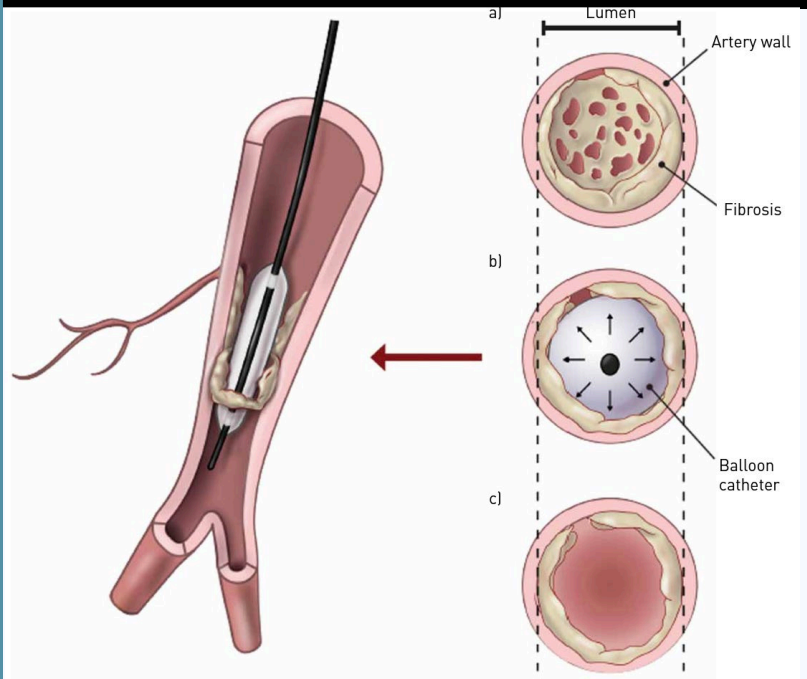
	Europe	Japan	AAO	Total
Subjects, n	779	115	116	1010
PEA, operable	562 (72.1%)	27 (23.5%)	80 (69%)	669 (66.2%)
BPA, not operable	107 (13.7%)	79 (68.7%)	7 (6%)	193 **(19.1%)**
Neither	110 (14.1%)	9 (7.8%)	29 (25%)	148 **(14.7%)**
Total inoperable	**27.8%**	**76.5%**	**31%**	**33.8%**



Guth et al, ERJ Open Res. 2021;7(3):00850-2020

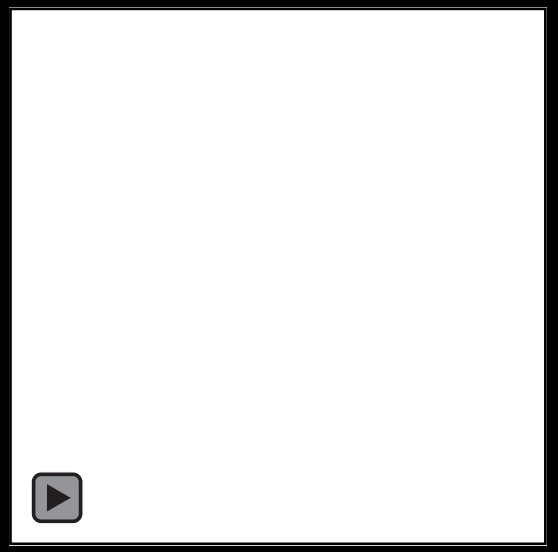
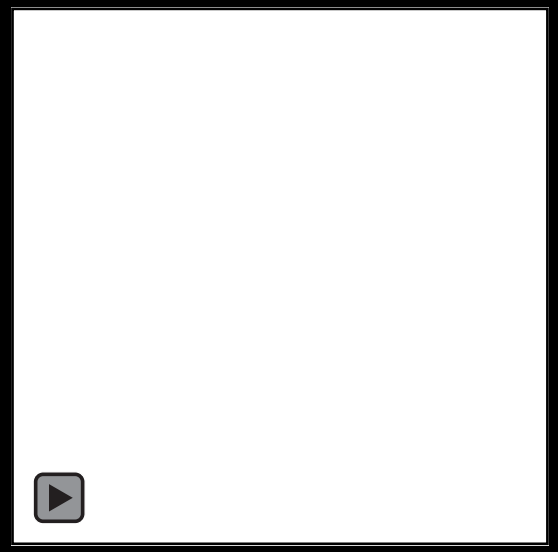
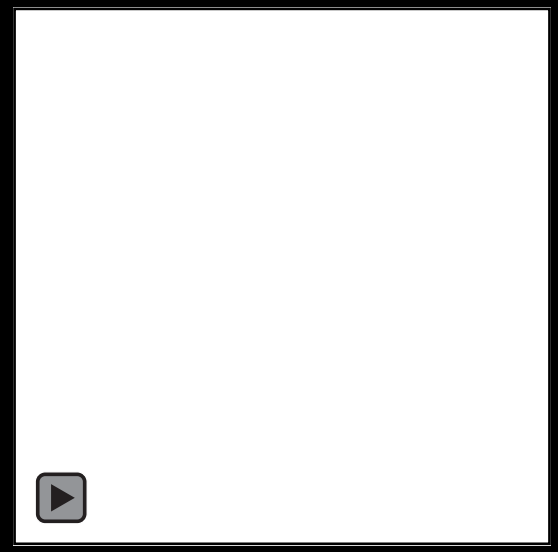
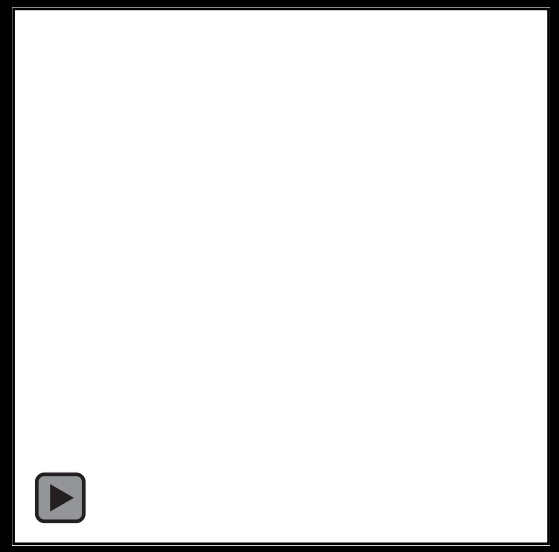
Balloon Pulmonary Angioplasty (BPA)





- Inoperable or post-PTE with residual pulmonary hypertension
- Percutaneous, catheter-based approach
- Femoral (or IJ) venous access
- Selective pulmonary angiography
- Wire passed across lesions then balloon dilated

Delcroix et al, Eur Resp J 2021, 57(6):2002828

BPA Effects on…

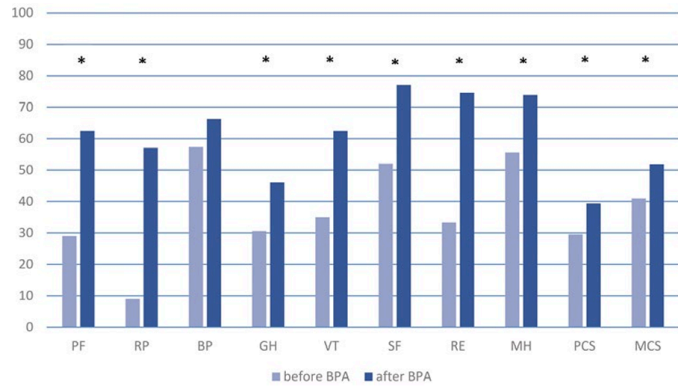
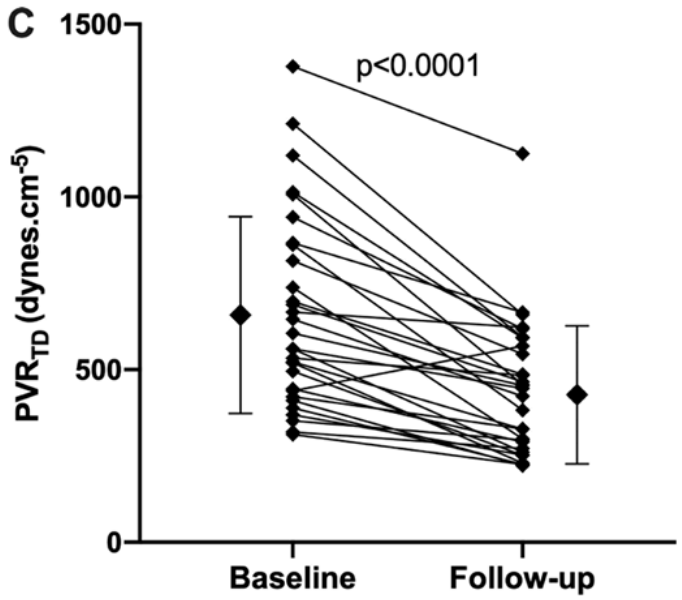
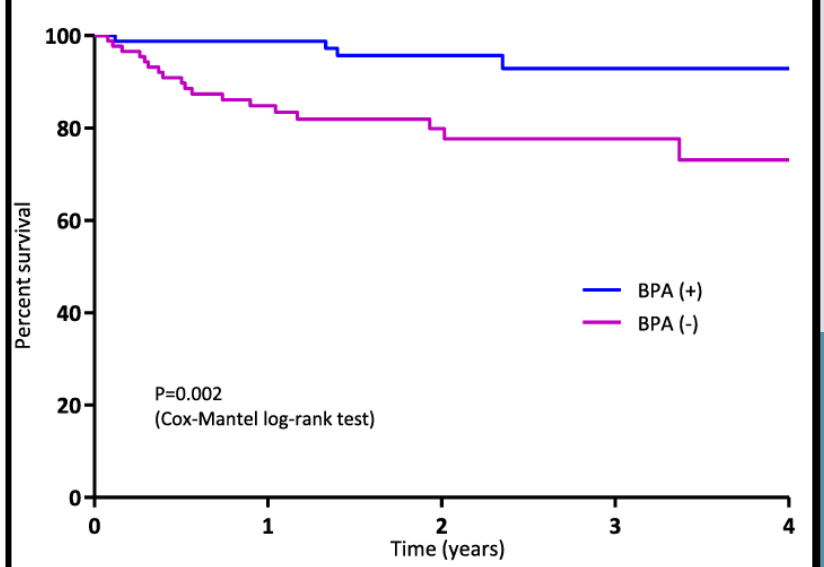


Figure 3. Change in quality of life (36-item Short Form [SF-36v2]) scale scores after the last balloon pulmonary angioplasty (BPA). BP, bodily pain; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; RE, role emotional; RP, role-physical; SF, social functioning; VT, vitality. *P<0.05.





QUALITY OF LIFE

HEMODYNAMICS

SURVIVAL

Circ J 2017; 81(4):552-557
Open Heart 2020;7:e001144
Taniguchi et al, J Heart Lung Transplant 2019; 38(8):833-842

California Thoracic Society
ATS Chapter Serving California and Arizona

Worldwide CTEPH Registry

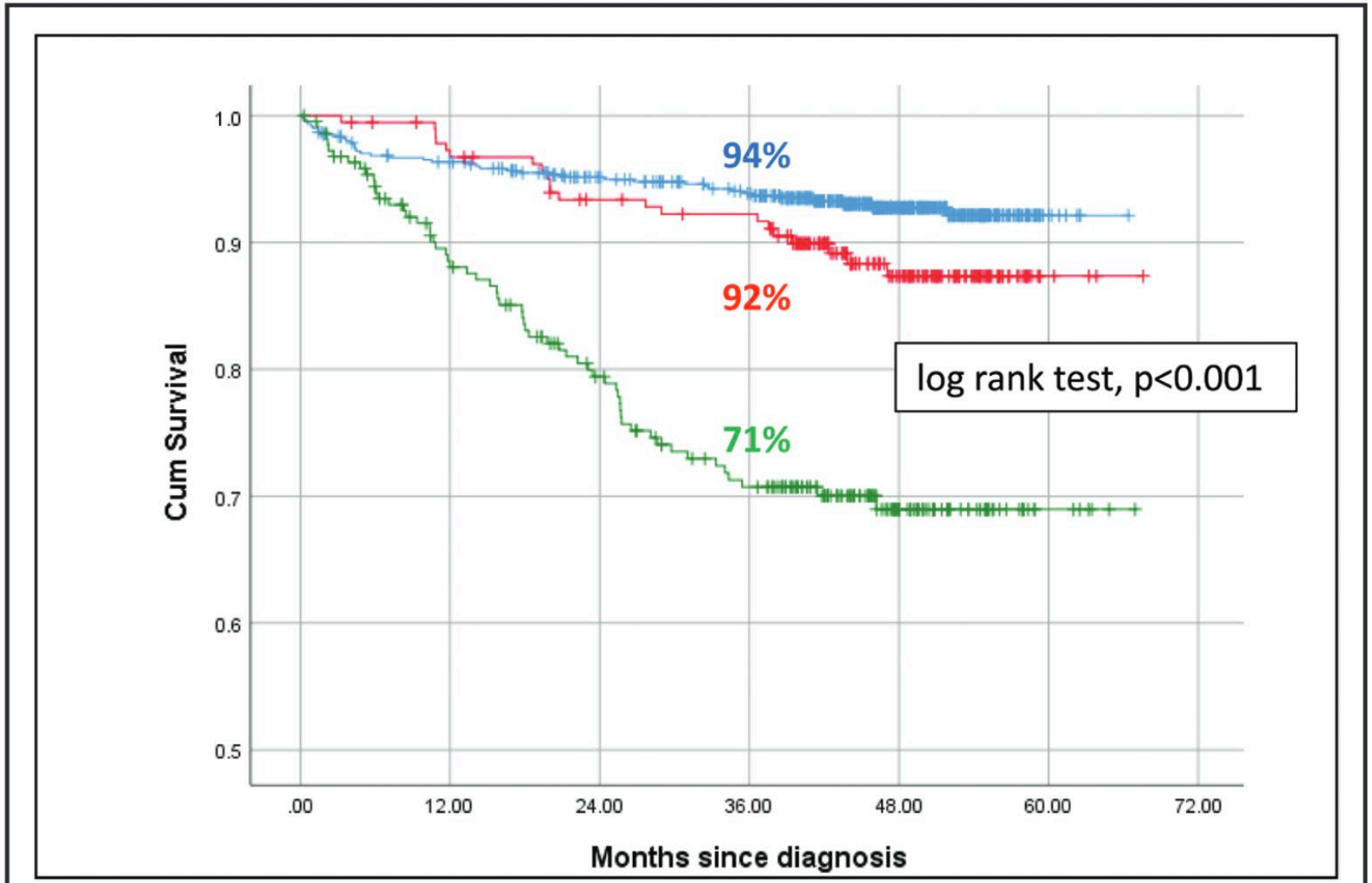
Feb 2015 – Sept 2016

PEA: 60%

BPA: 18%

Neither: 22%

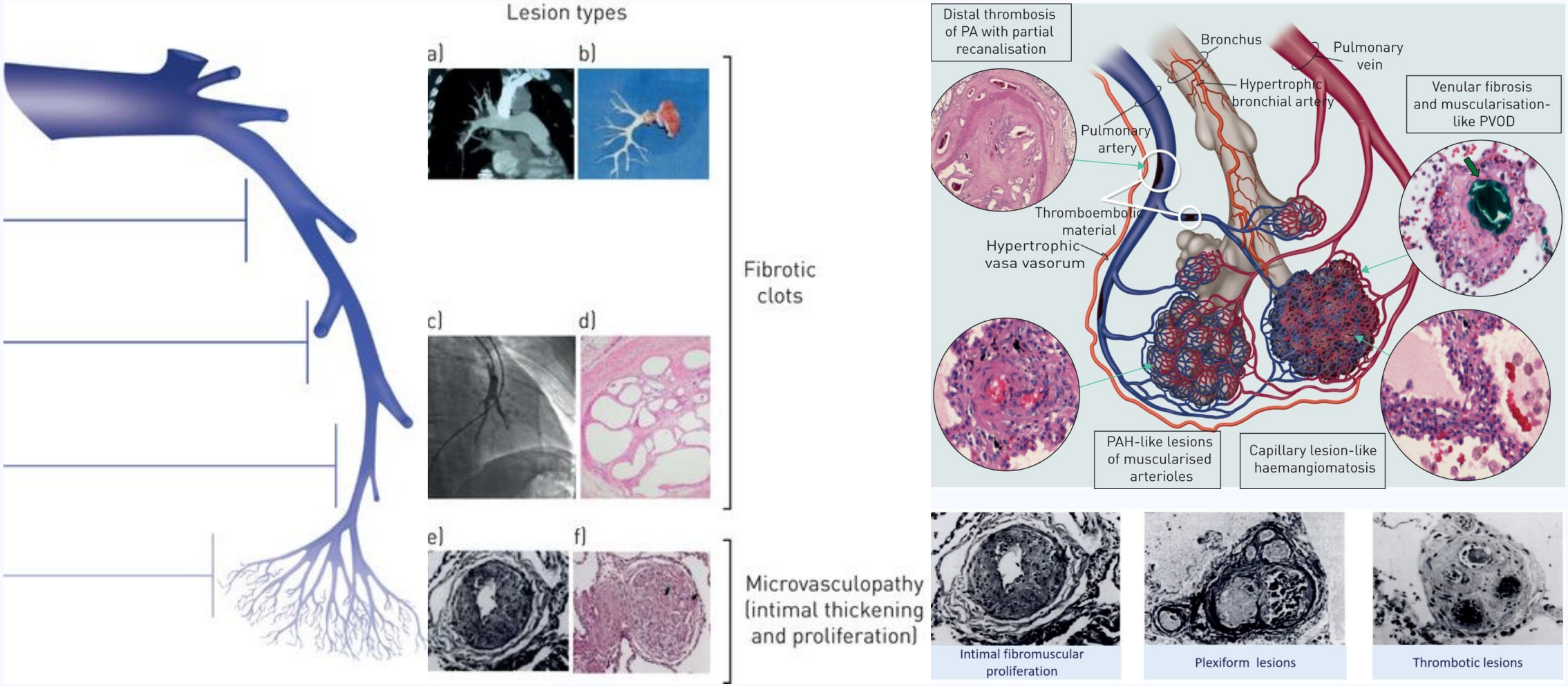
76% of "neither" group on PH therapies



Time (months)	0	12	24	36	48	60
PEA	605	572	535	506	250	7
BPA	185	176	165	161	84	4
No PEA/BPA	219	178	150	126	53	6

Delcroix et al, Circulation. 2024;150:1354–1365.

Medical Therapy



Madani MM et al, European Respiratory Review 2017 26(146): 170105.
Moser and Bloom, Chest. 1993 Mar;103(3):685-92
Dorfmuller et al, Eur Respir J. 2014 Nov;44(5):1275-88

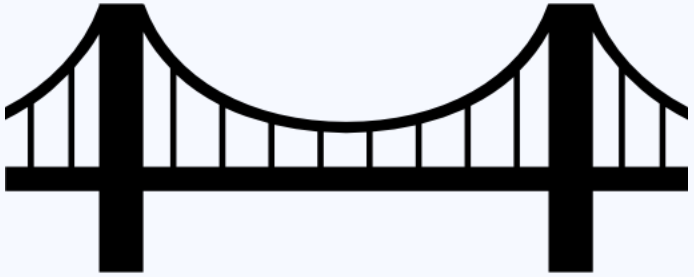
Trials of Medical Therapy in CTEPH

Trial/ Medication	Outcomes
AIR. Iloprost	First study of PH therapies to include CTEPH patients. No adjudication of operability.
Sildenafil	No change in 6MWD. Improved PVR and FC. Insufficiently powered.
BENEFiT. Bosentan	Inoperable and post-PTE. Post-hoc adjudication. Improved PVR.
CHEST-1. **Riociguat**	Inoperable and post-PTE. Prospective adjudication. Improved 6MWD. **Worldwide approval.**
MERIT-1. Macitentan	Combination therapy. Prospective adjudication. Improved PVR, 6MWD, BNPP. No riociguat allowed.
CTREPH. Subcutaneous Treprostinil	Improved 6MWD. No independent adjudication of operability. Approved in Europe.
Selexipag	Improved PVR. Unique CTEPH population in Japan. No central adjudication. Background rio (61%); prior BPA (53%). Approved in Japan
SELECT. Selexipag	Terminated early. No efficacy on primary endpoint (PVR) at week 20
MACiTEPH. Macitentan 75 mg	Terminated early. Futility (6MWD)

When to use medical therapy?

- Inoperable disease

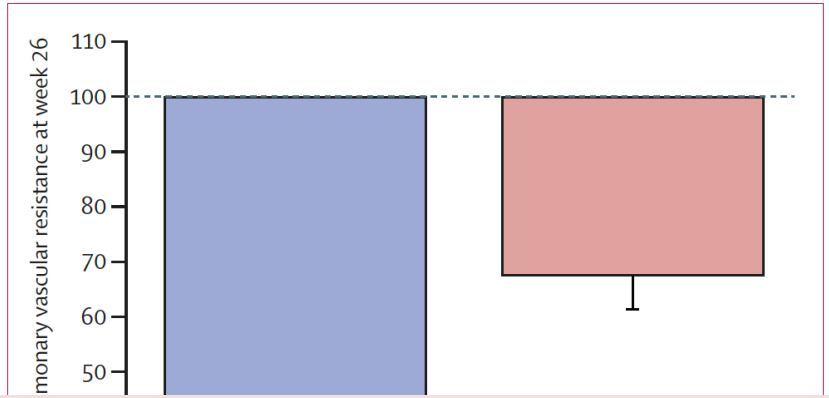
- What about as a "bridge" to…



Currently no data to su
May delay referral for definit
PEA bridging study cancelled (covid)

Can be helpful!
individualized approach…

RACE Trial: BPA vs Riociguat



	BPA group (n=52)	Riociguat group (n=53)
Patients with ≥1 adverse event	33 (63%)	38 (72%)
Patients with ≥1 serious adverse event	26 (50%)	14 (26%)
Patients with ≥1 treatment-related serious adverse event	22 (42%)	5 (9%)
Most frequent adverse events (≥3 patients in either group)		
Gastro-oesophageal reflux	0	10 (19%)
Dizziness	1 (2%)	9 (17%)
Haemoptysis	8 (15%)	0
Headache	0	8 (15%)
Vomiting	0	8 (15%)
Cough	0	7 (13%)
Lung injury	8 (15%)	0

- Improved FC and PVR in upfront riociguat group going into BPA
- Less adverse events in riociguat then BPA group

	1st line BPA	1st line riociguat then BPA	p-value
Functional class II III IV	 12 (23%) 38 (73%) 2 (4%)	 21 (58%) 15 (42%) 0	0.0017
6MWD	379.9	426.9	0.0487
Mean PAP	46.5	43.3	0.102
Cardiac output	4.2	5.2	<0.0001
PVR	767.2	537.6	<0.0001
≥1 BPA-related serious AE	22 **(42%)**	5 **(14%)**	
≥1 AE and/or serious AE related to BPA	32 **(62%)**	12 **(33%)**	

Jais et al, Lancet Respir Med 2022; 10(10)961-971

California Thoracic Society
ATS Chapter Serving California and Arizona

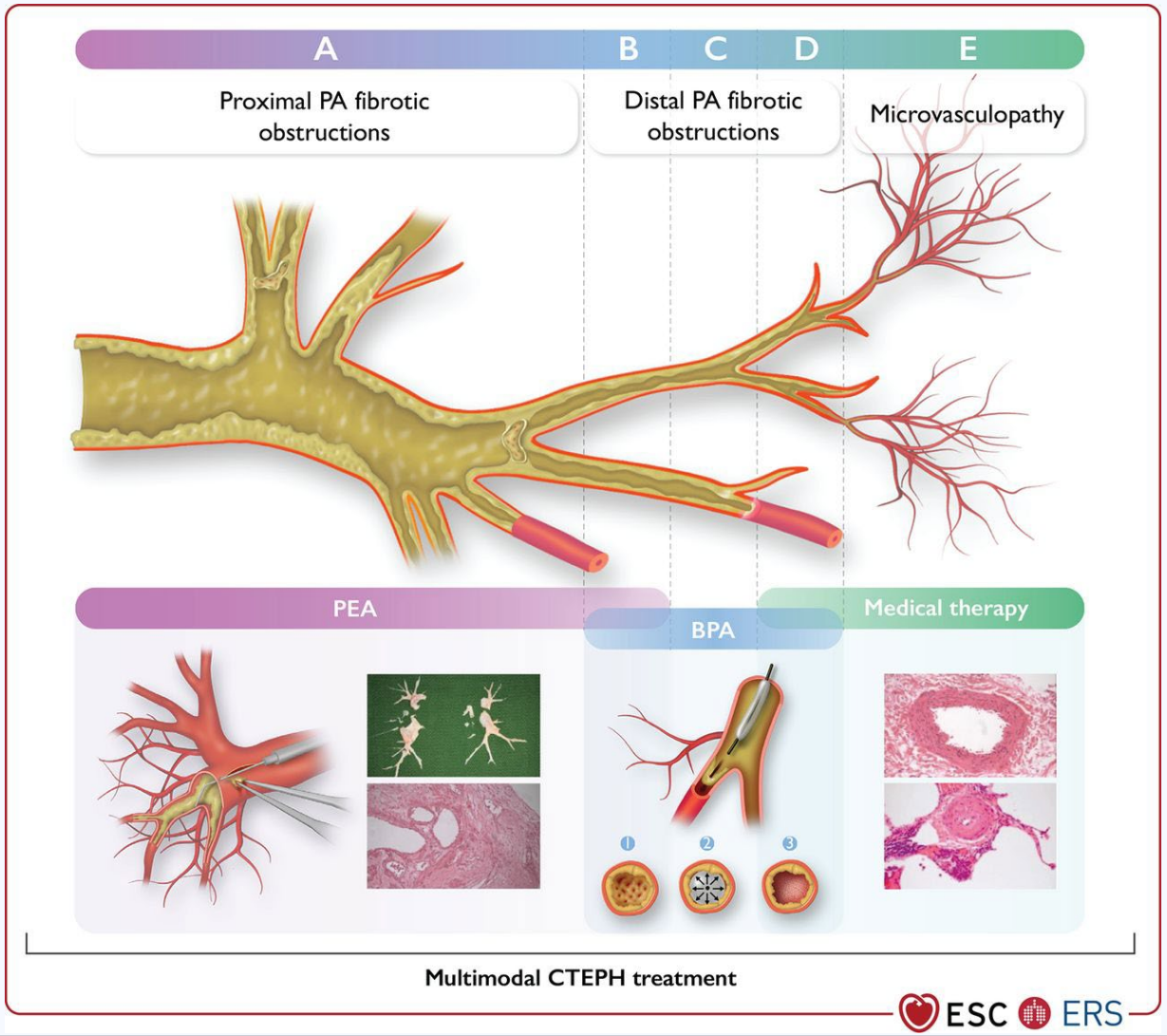
Multimodal Approach to Therapy

PTE

BPA

Medical Therapy

CTEPH is a spectrum



Humbert M, *et al. Eur Heart J* 2022.

California Thoracic Society
ATS Chapter Serving California and Arizona

PTE and BPA are complementary, not in competition with each other

Bautista A, et al. *ATS* 2021.

California Thoracic Society
ATS Chapter Serving California and Arizona

Chronic thromboembolic pulmonary hypertension: realising the potential of multimodal management

Marion Delcroix, Marc de Perrot, Xavier Jaïs, David P Jenkins, Irene M Lang, Hiromi Matsubara, Lilian J Meijboom, Rozenn Quarck, Gérald Simonneau, Christoph B Wiedenroth, Nick H Kim

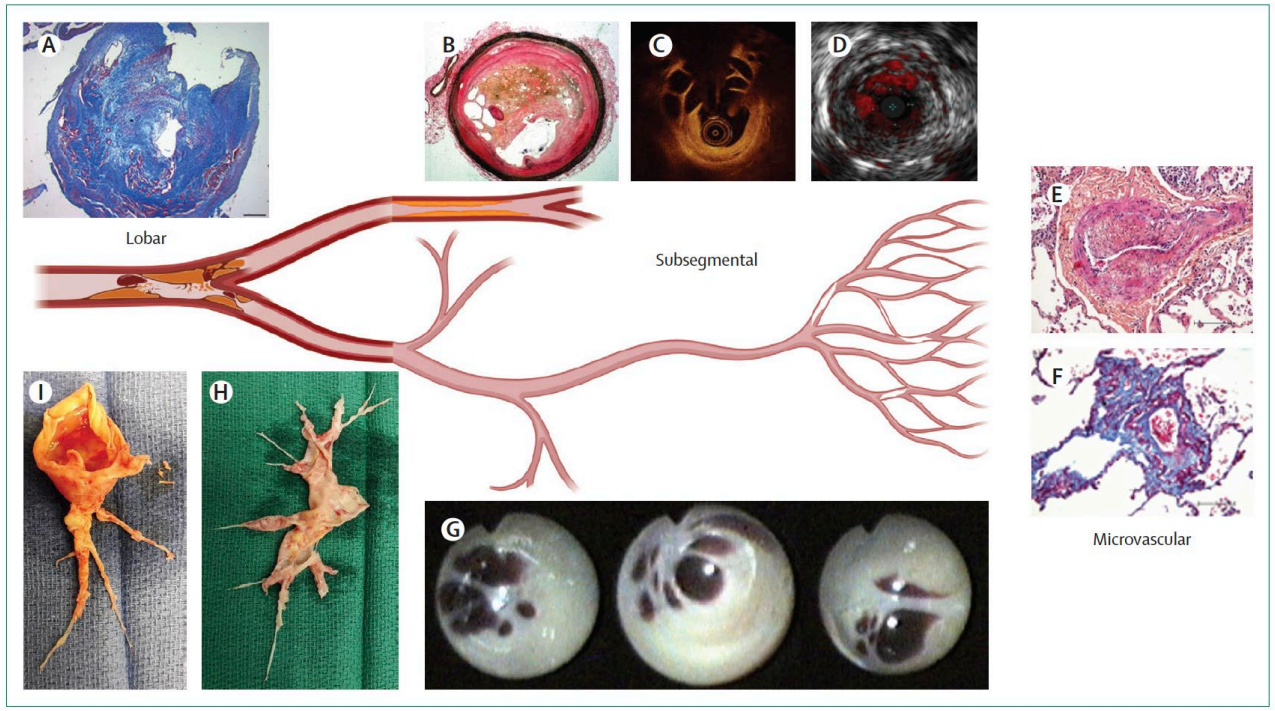
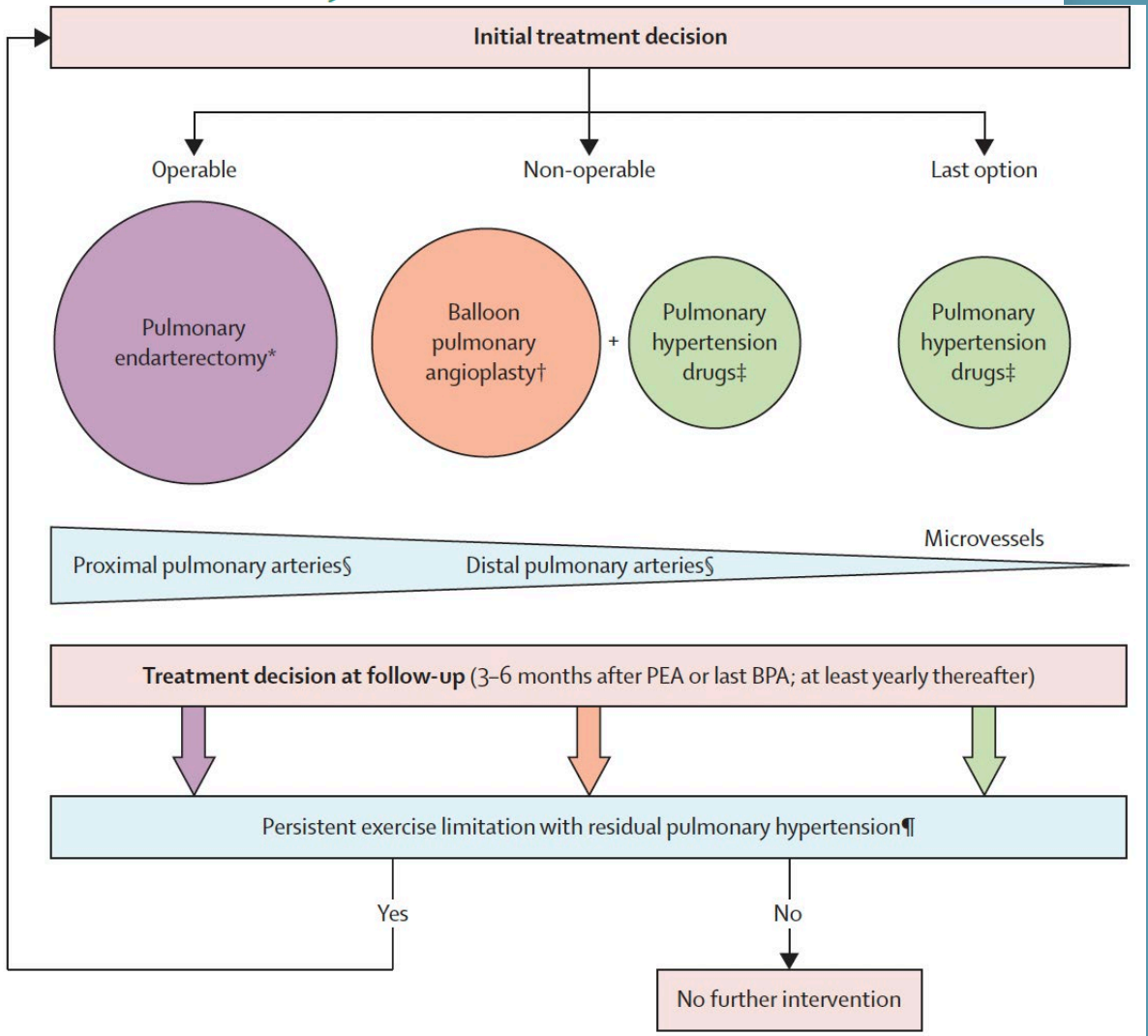


Figure 1: Types of lesion in CTEPH



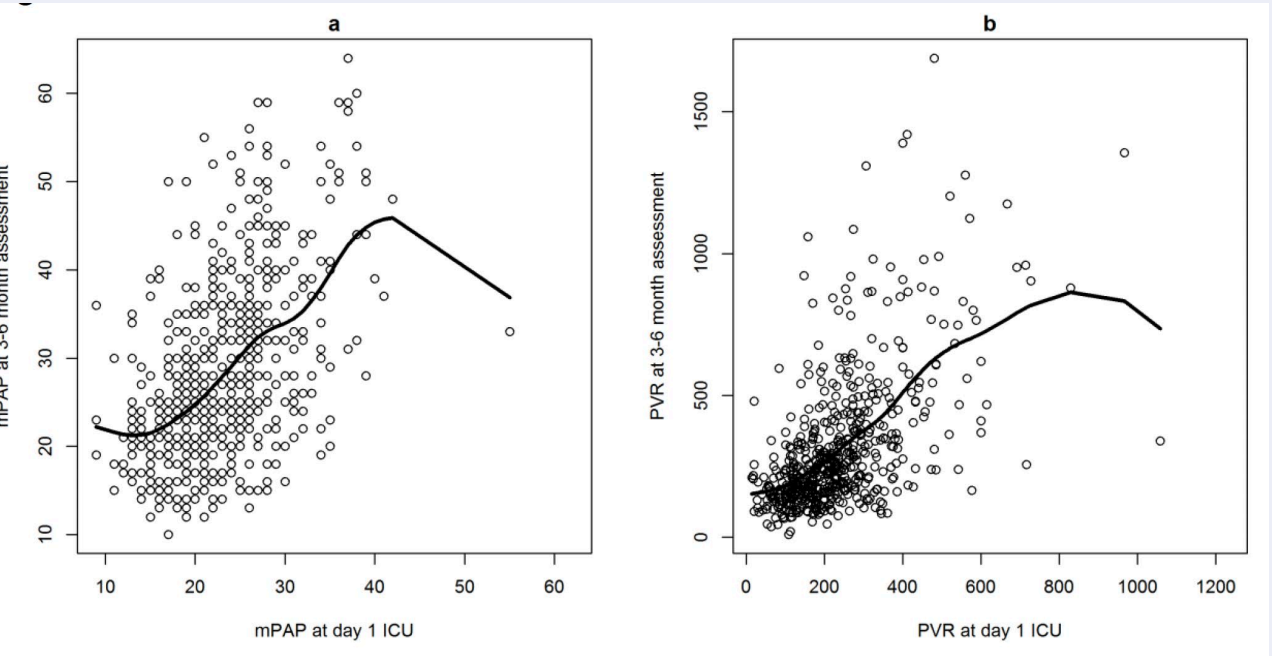
Delcroix et al, Lancet Respir Med 2023; 11:836-50.

Adequate follow-up is necessary to determine if patients need additional therapy

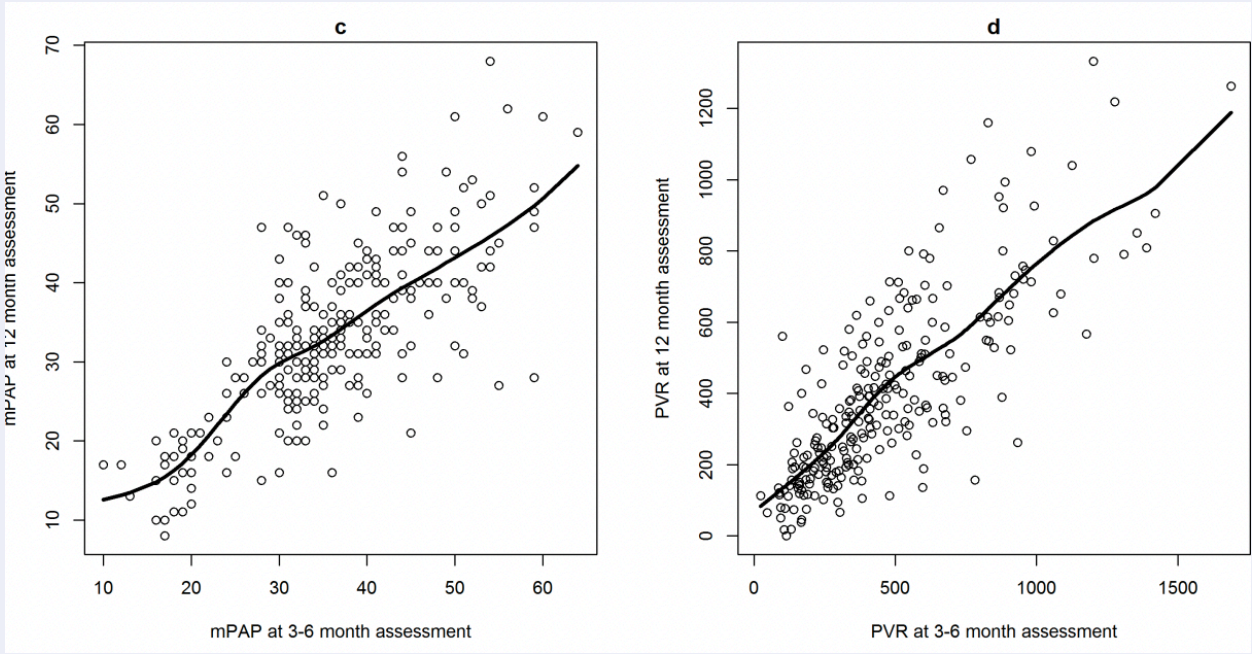
Early Follow-up

- Hemodynamics in the ICU post-PTE
- Echocardiogram prior to discharge post-PTE

NOT predictive of long-term hemodynamics and outcomes



Minimal correlation between hemodynamics in the ICU and at 3-6 months

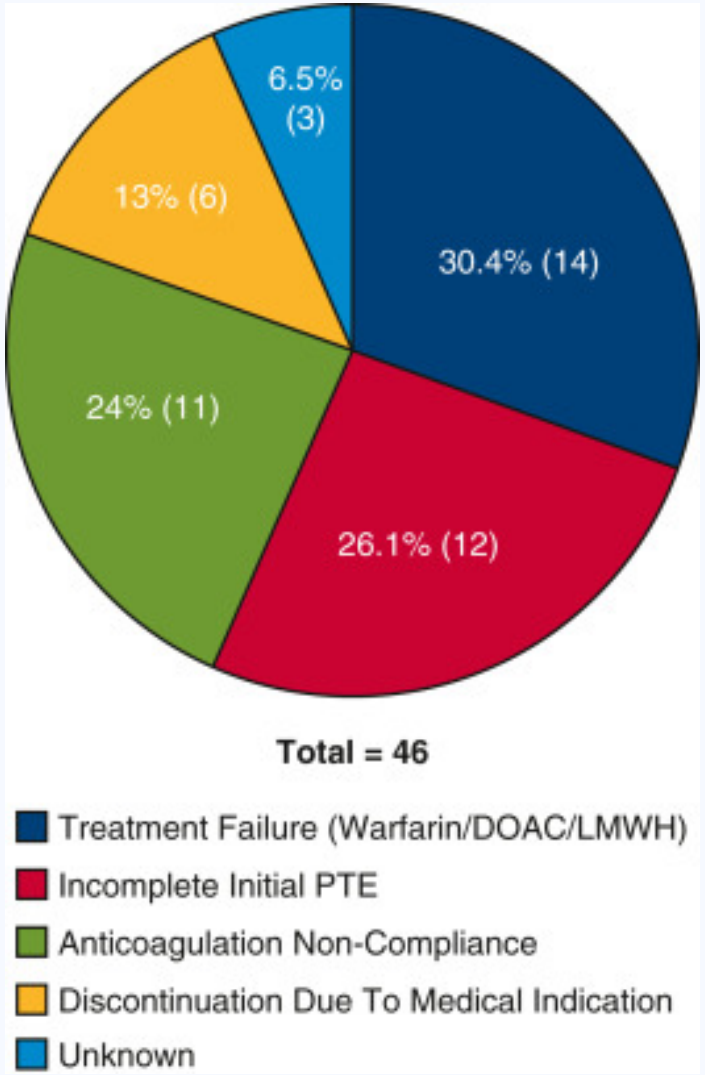


Strong correlation between hemodynamics at 3-6 months and 12 months

Most important to check at follow-up is..

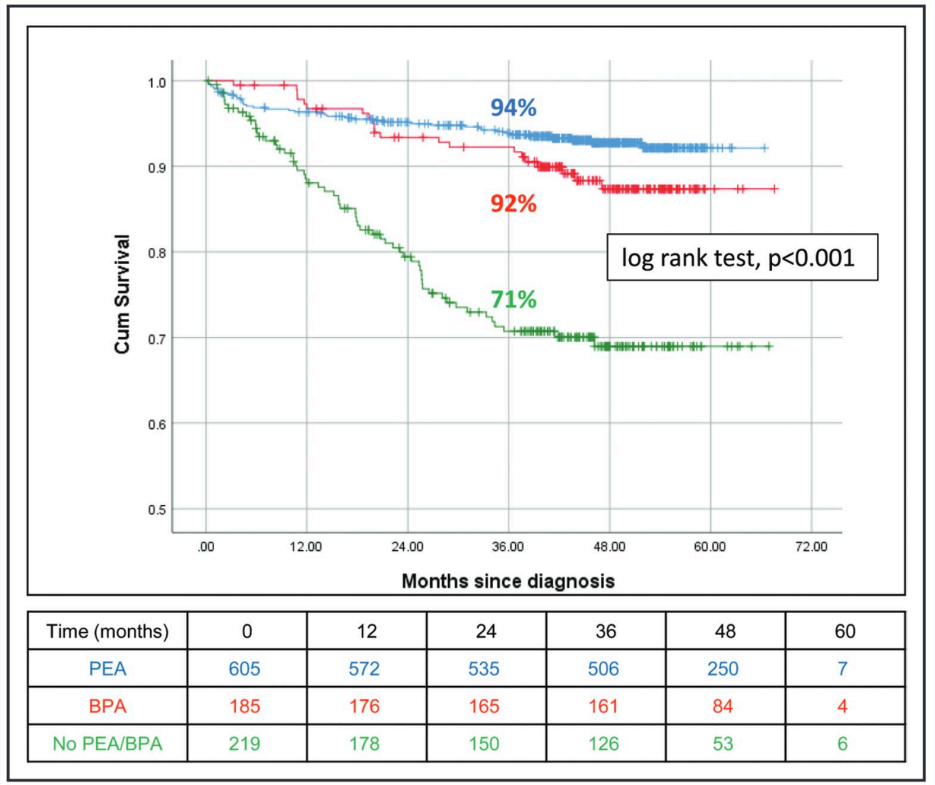
Anticoagulation!

- Indefinite anticoagulation is key!
  - Warfarin vs DOAC vs LMWH
- Antiphospholipid syndrome patients need to be on warfarin, not DOAC

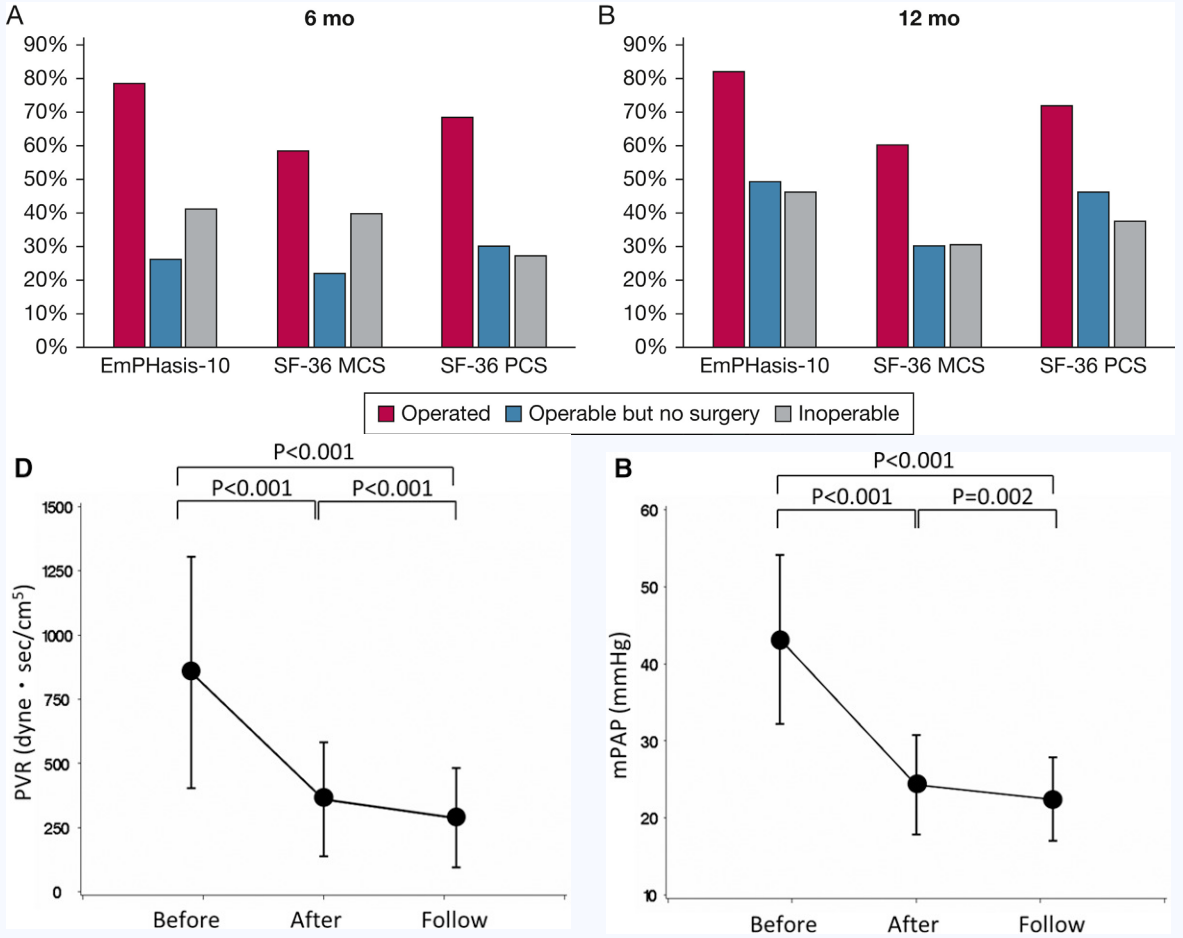


- Astashchanka et al, JHLT 2023. 166 (6): 1512-1519.

Long-term outcomes with PTE and BPA are good!



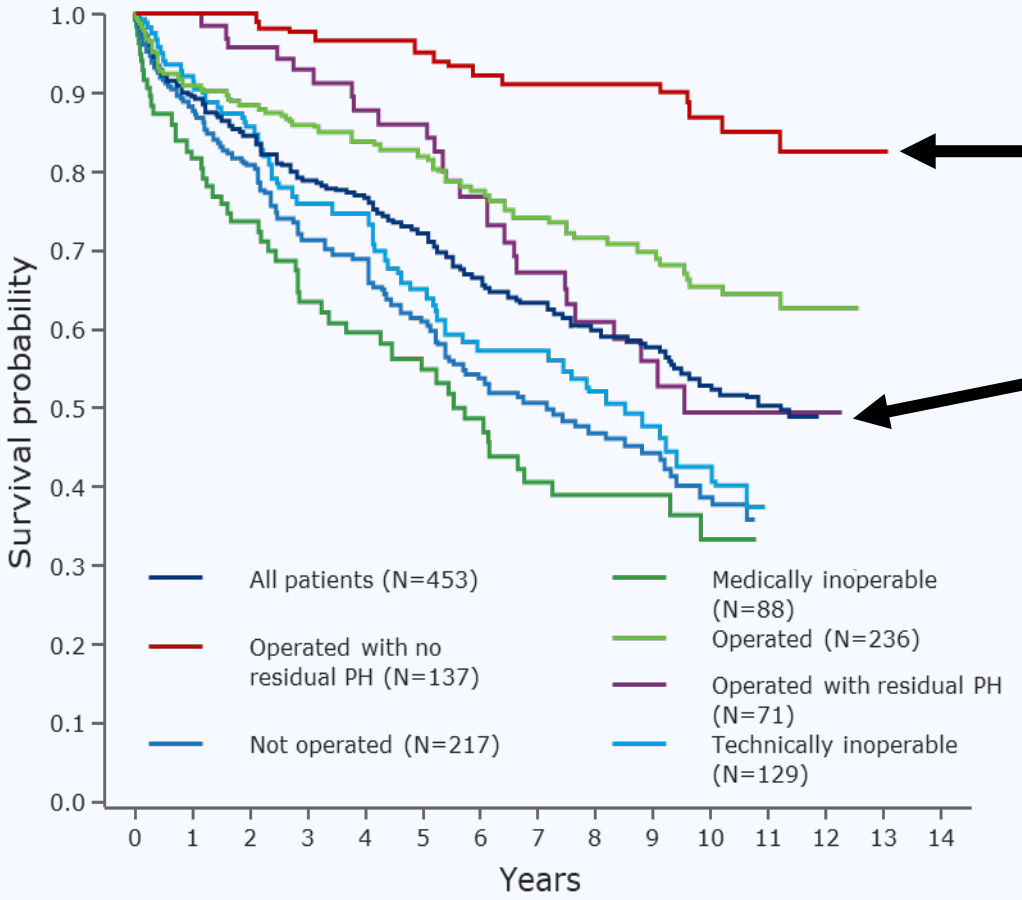
Time (months)	0	12	24	36	48	60
PEA	605	572	535	506	250	7
BPA	185	176	165	161	84	4
No PEA/BPA	219	178	150	126	53	6



1) Delcroix et al, Circulation. 2024;150:1354–1365. 2) Ogawa et al, Circ Cardiovasc Qual Outcomes. 2017; 10(110):e004029. 3) Chin et al, Chest Pulmonary. 2023; 1(2):100008

California Thoracic Society
ATS Chapter Serving California and Arizona

But, we know that is not the case for everyone



Operated without residual PH

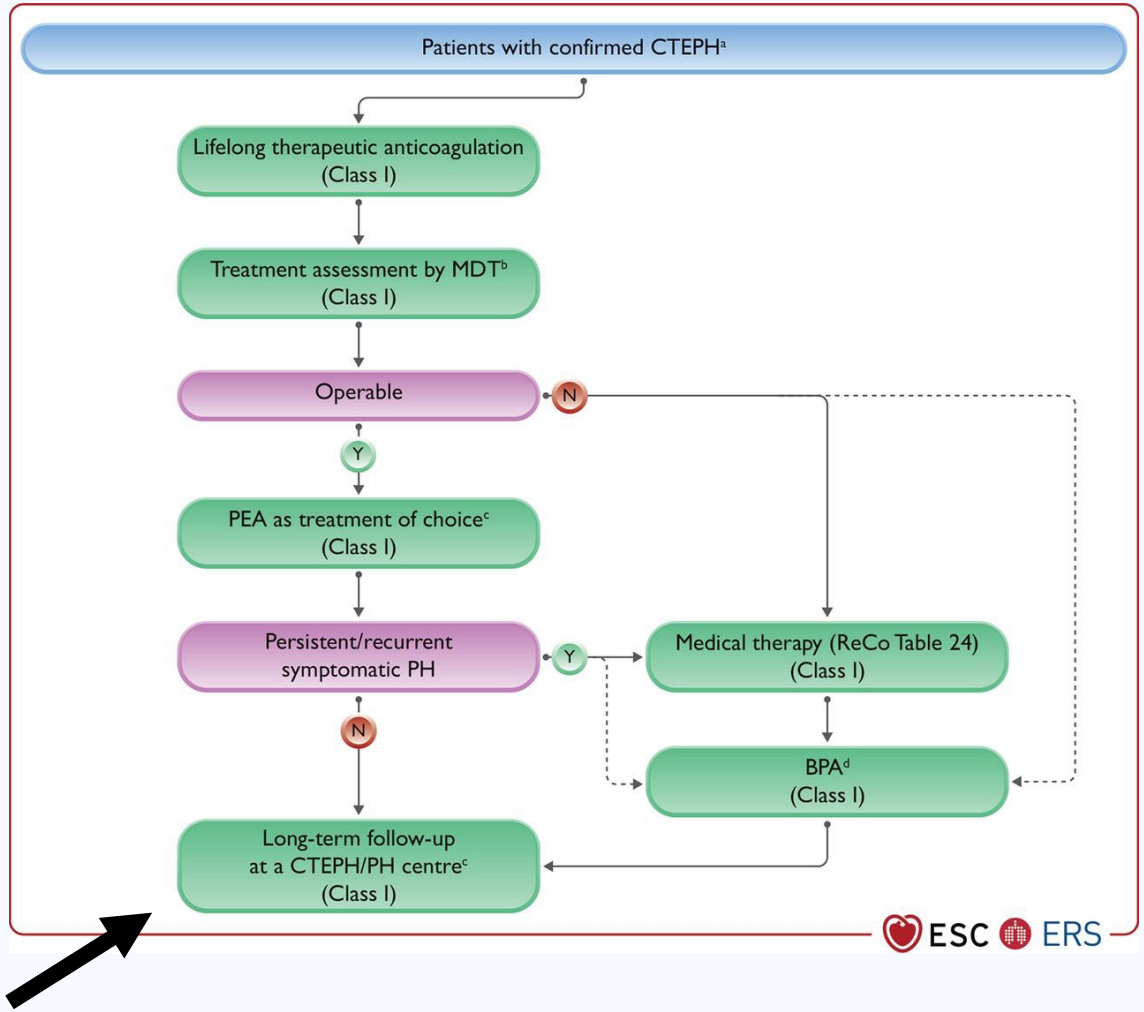
Operated with residual PH

Jansa P, *et al. Pulm Circ* 2022; 12:e12038.

California Thoracic Society
ATS Chapter Serving California and Arizona

Long-term Follow-Up

- We have recognized the need for follow-up
- But there are many challenges…

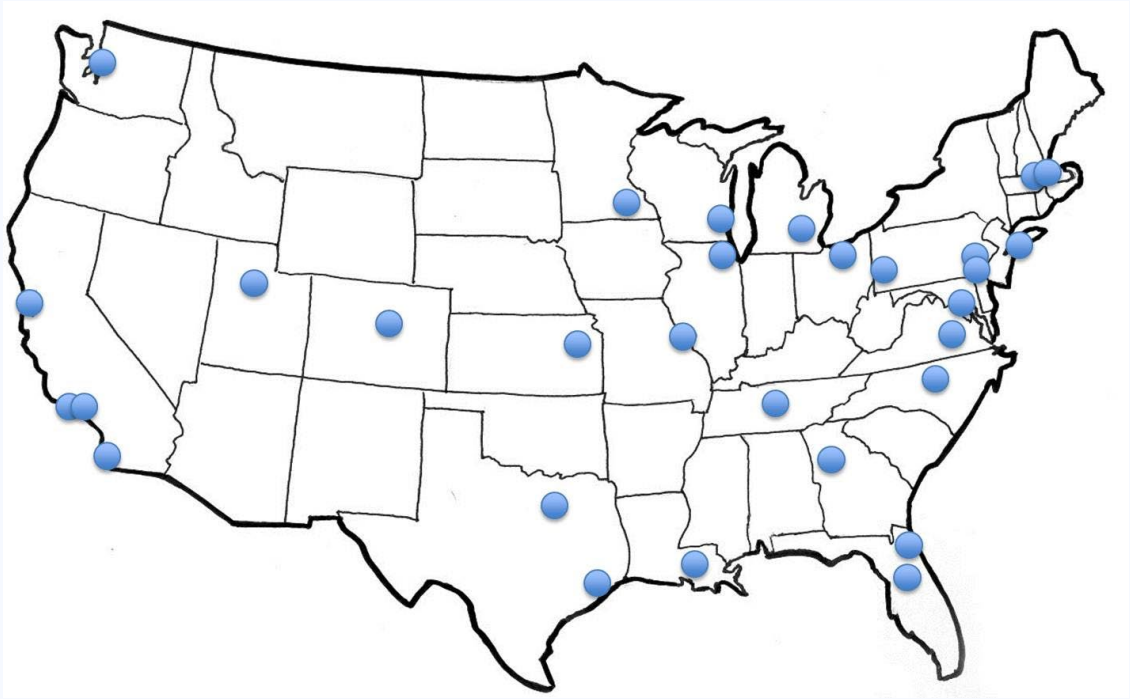


Long-term follow-up is recommended after PEA and BPA, as well as for patients with CTEPH established on medical therapy	I

Humbert M, *et al. Eur Heart J* 2022.

Challenges with Follow-Up

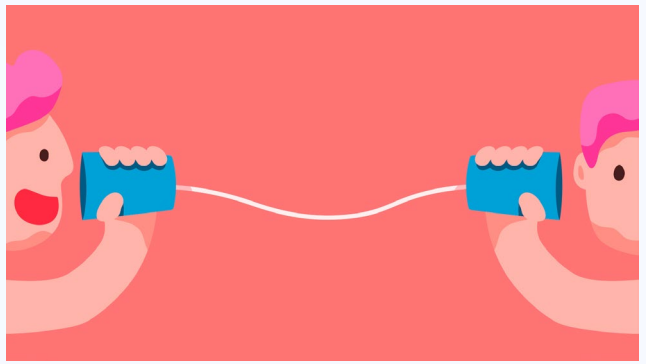
- Geographical
- Patient ability/willingness
- Awareness and recognition
- Selection/referral bias
- How best to follow?
  - Echos
  - RHCs
  - CPET
- Lack of specific follow-up algorithm
- Lack of differentiation between PTE and BPA



30 centers involved in the US-CTEPH registry

But follow-up is still possible though!

- Communication with CTEPH referral centers
- Telehealth visits
- Emails and telephone calls



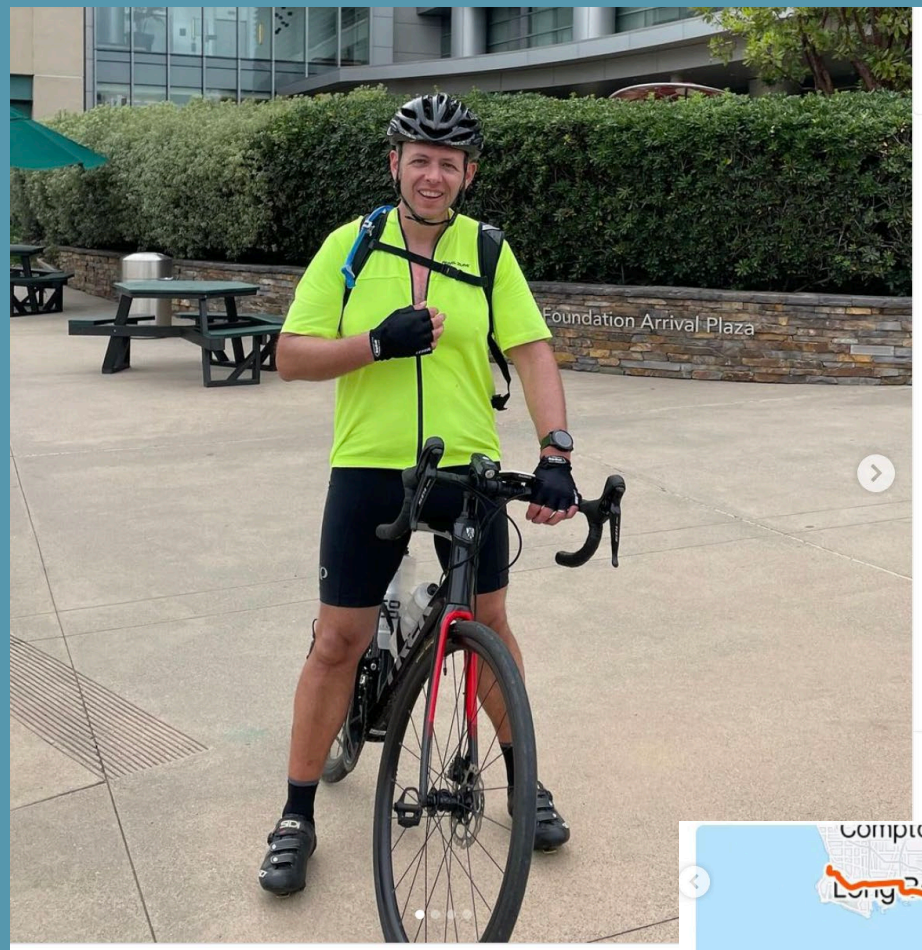
- Increased emphasis on importance of follow-up post-intervention
  - ESC/ERS 2022 PH guidelines
  - 7th World Symposium on Pulmonary Hypertension – CTEPH taskforce
  - International CTEPH Association (ICA) Conference 2023

Best practice and expert definitions

The management of CTEPH has become more demanding, but more satisfying, with the advances in multimodal therapies. Once treated primarily with one modality with even the prospect of lung [illegible] to the individual case. For any of these centres, a structured follow-up should become standard of care and an important aspect of disease management.

Kim et al, Eur Resp J. 2024. 2401294

California Thoracic Society
ATS Chapter Serving California and Arizona



ucsdhealth • Follow
UC San Diego Health

ucsdhealth Within six months since pulmonary thromboendarterectomy (PTE) surgery, Peter Johnson achieved three amazing milestones. He hiked Mt. Baldy (10,062 ft), hiked Mt San Jacinto (21 miles, 10,700 ft) and rode his bicycle 109 miles from Long Beach to San Diego for his six-month follow up visit. All of these accomplishments were thanks to his unwavering determination and expert care team at UC San Diego Health.

Johnson has always been active — hiking, climbing and biking regularly, so he knew when he was falling behind with a backpacking group in Catalina, something was not right.

"Usually, I'm out in front with tons of

Home to hospital for 6mo check in

Distance	Elev Gain	Achiev
109.48 mi	4,423 ft	

Congratulations, this activity is your longest ri on Strava!

PTE in August 2023

Hope all is well. Just wanted to drop a note and say my first rock/ice/mixed climbing up in the Canadian Rockies went well. I took it easy on the technica side and felt great. No issues with the sternum and being over 11k for 3 days was fine. Lungs are feeling awesome. Some pics to go on the adventure wall to hopefully motivate other PTE patients:

And then on my surgery anniversary I climbed Black Peak in the North Cascades in Washington. It's a rock route that's not too crazy, but was good to be back rock climbing now that the sternum is all set.

6-month follow up

1-year follow up

California Thoracic Society
ATS Chapter Serving California and Arizona

What's next for CTEPH?

- Utilizing AI for better recognition and diagnosis
- Zoom conferences and televisits

- Multimodal therapy
  - Double combination therapy prior to BPA
  - Bridging therapy to PTE
  - Hybrid PTE/BPA
- Understanding evolution and optimal management of CTED
- Will catheter directed thrombectomy reduce rates of CTEPH?
- What's considered a "successful" PTE or BPA?

Conclusion

- CTEPH is a spectrum of proximal obstructive, distal obstructive, and microvascular disease
- Multidisciplinary CTEPH team is essential for optimal treatment
  - PTE is treatment of choice for operable disease
  - BPA is highly effective treatment for non-operable disease
- Patients may benefit from multimodal approach to CTEPH treatment
- Long-term follow-up can be especially challenging in the US but is essential in the management of CTEPH

Thank you!

Jenny Yang, MD
University of California San Diego

✉: jey052@health.ucsd.edu

𝕏: @JennyYangMD

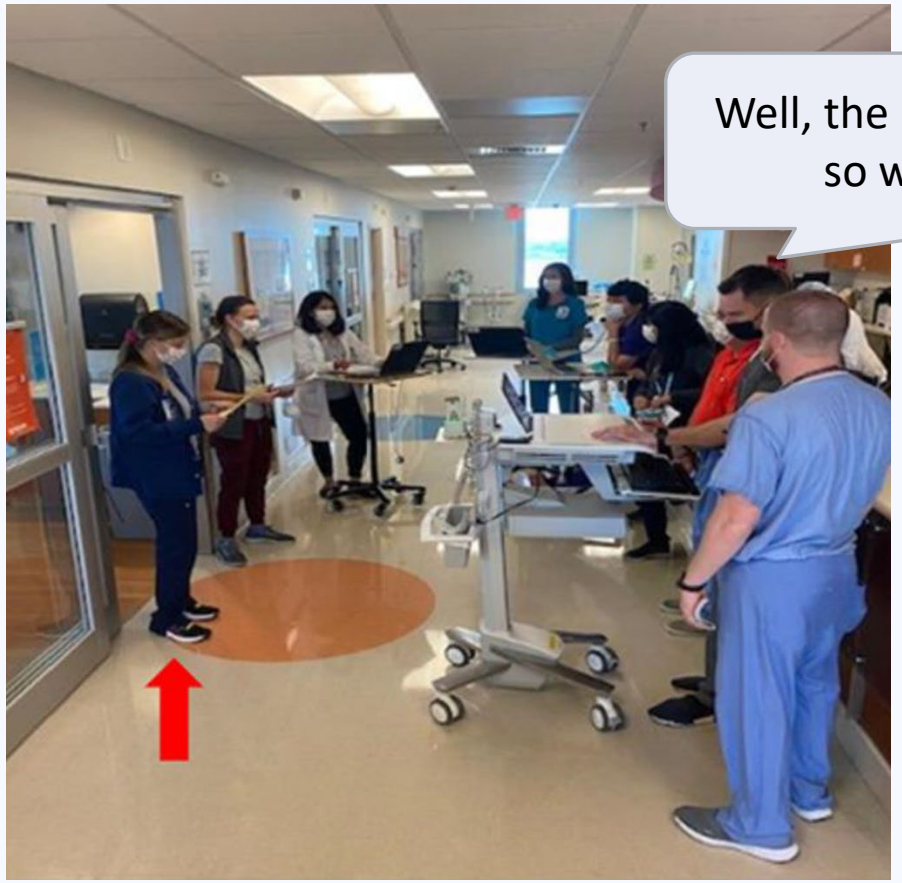
Decompensated right ventricular failure in the ICU

Yuri Matusov, MD, FACP, ATSF
Assistant Professor of Medicine
Cedars-Sinai Medical Center

Disclosures

- I have the following relationships with ACCME defined ineligible companies:
- **Mallinckrodt, Tenax, Penumbra (research funding)**
- **Jupiter Endovascular (consulting)**
- I **WILL** discuss off-label use and/or investigational use of any drugs or devices.

How would you approach supporting RV function in this patient?



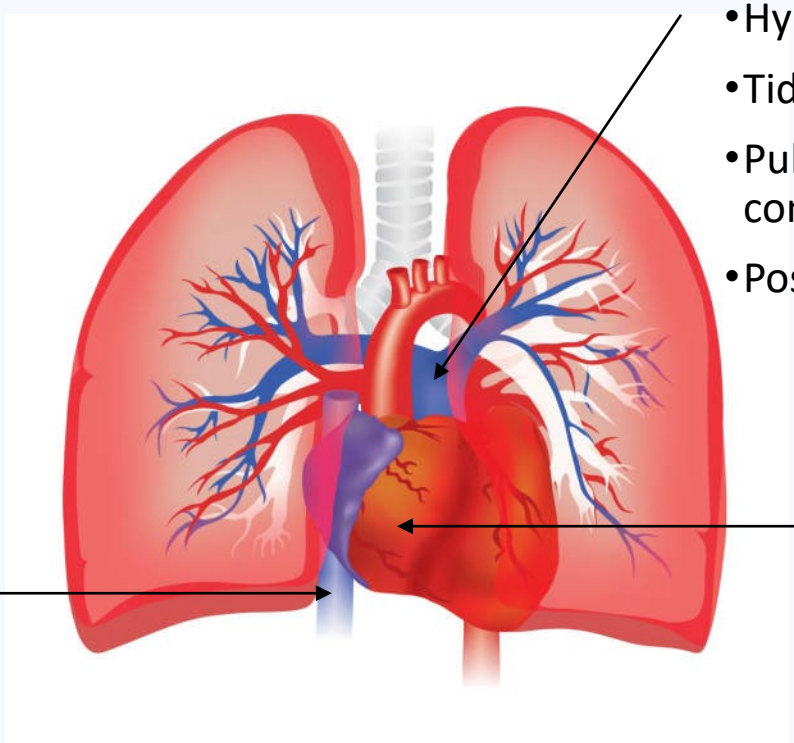
RV failure is never just one "thing"

Afterload issues

- Obstruction
- Acidosis
- Hypoxemia
- Hypercapnia
- Tidal volume
- Pulmonary/thoracic compliance
- Positive pressure ventilation

Preload issues

- Volume
- RV morphology
- Diagnostic challenges
- Positive pressure ventilation



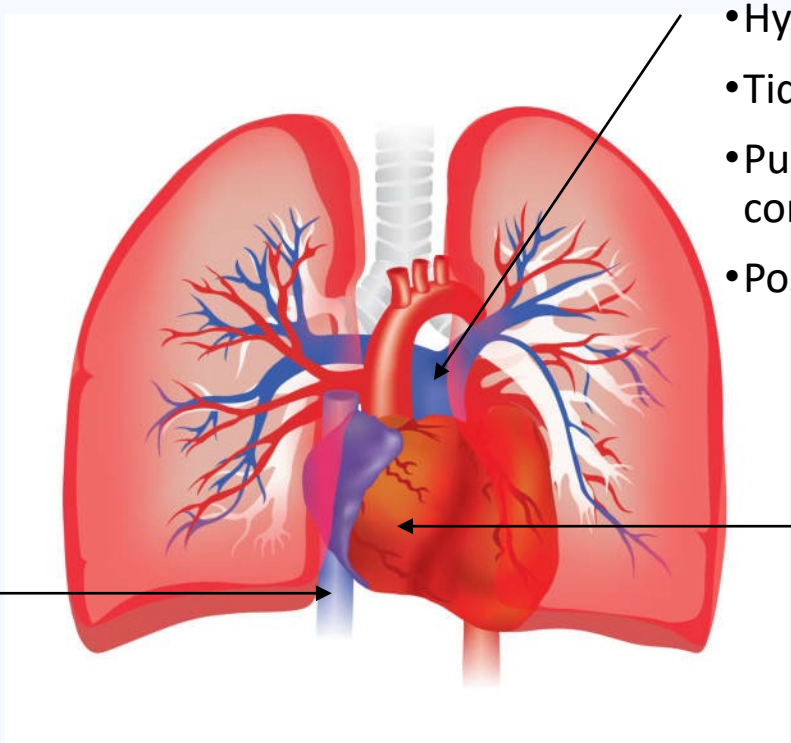
Contractility issues

- O2 deficit
- Wall stress and tension
- Hypoperfusion
- Arrhythmias
- Intracardiac shunting
- Acidosis

RV ~~failure~~ success is determined by addressing all factors

<u>Preload issues</u>

- Volume
- RV morphology
- Diagnostic challenges
- Positive pressure ventilation

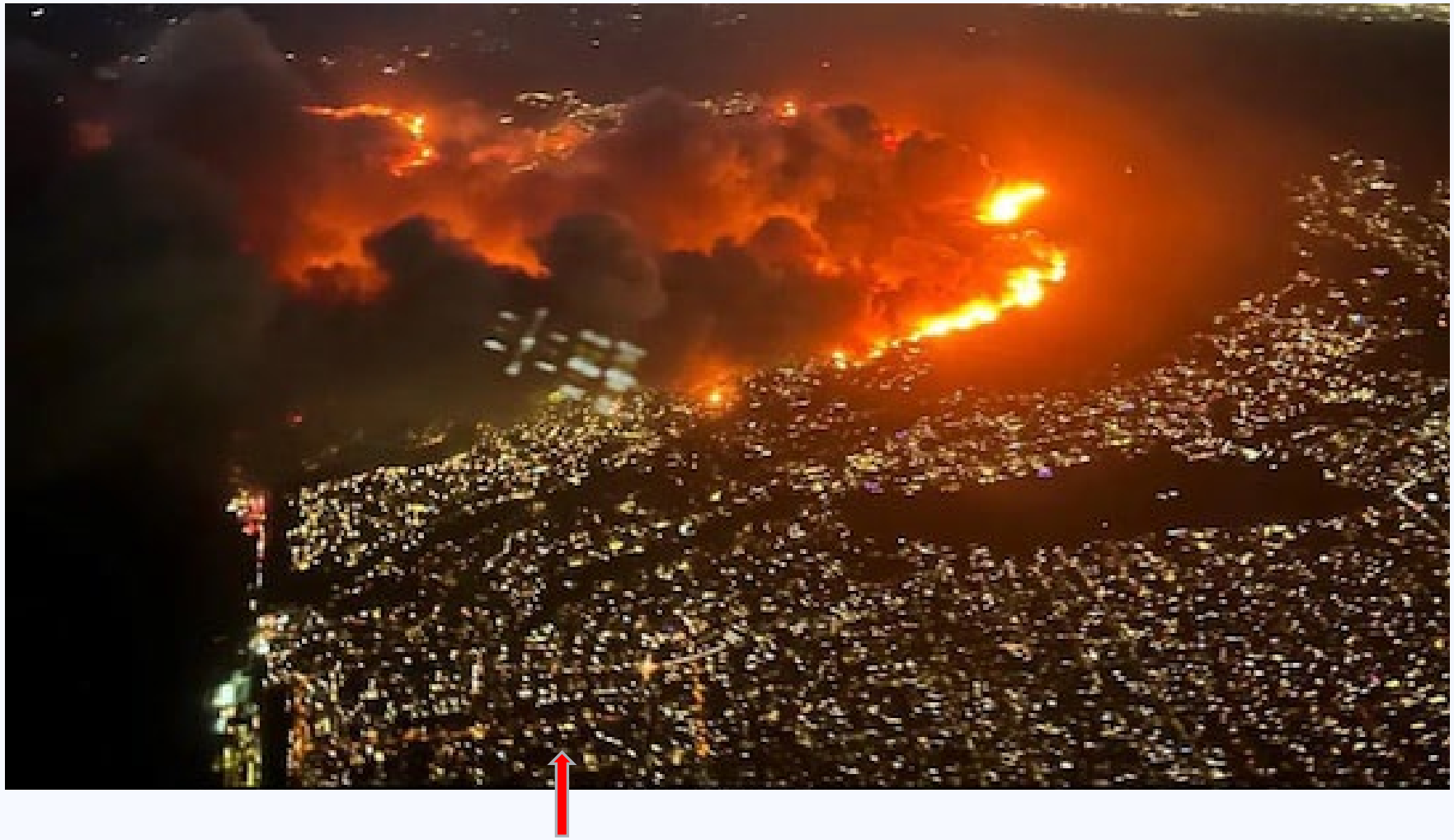


<u>Afterload issues</u>

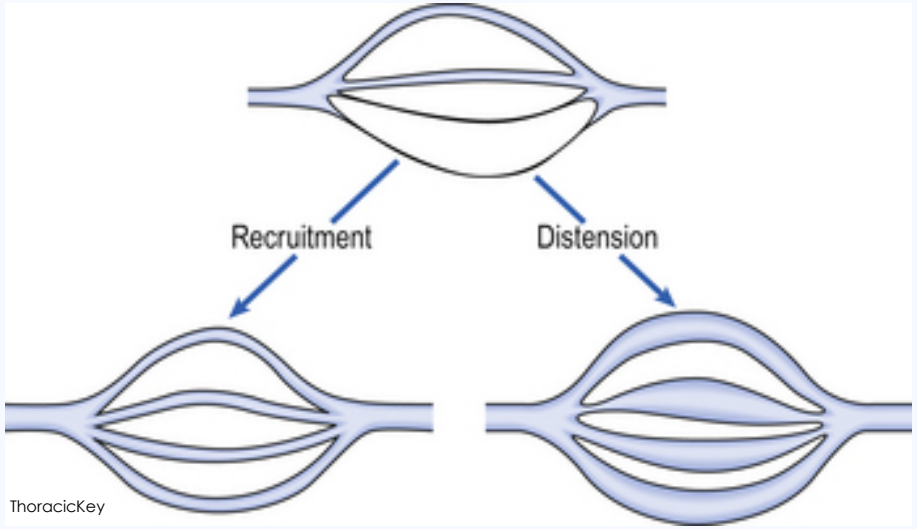
- Obstruction
- Acidosis
- Hypoxemia
- Hypercapnia
- Tidal volume
- Pulmonary/thoracic compliance
- Positive pressure ventilation

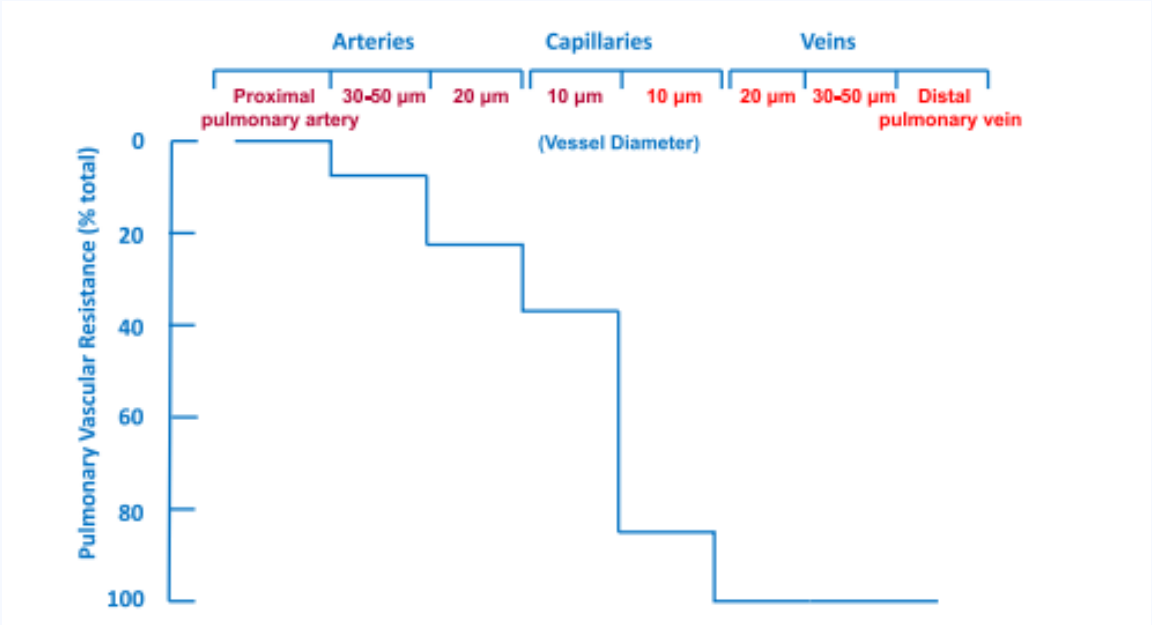
<u>Contractility issues</u>

- O2 deficit
- Wall stress and tension
- Hypoperfusion
- Arrhythmias
- Intracardiac shunting
- Acidosis



Normal RV response to increased cardiac output demand does not significantly change PA pressure or PVR

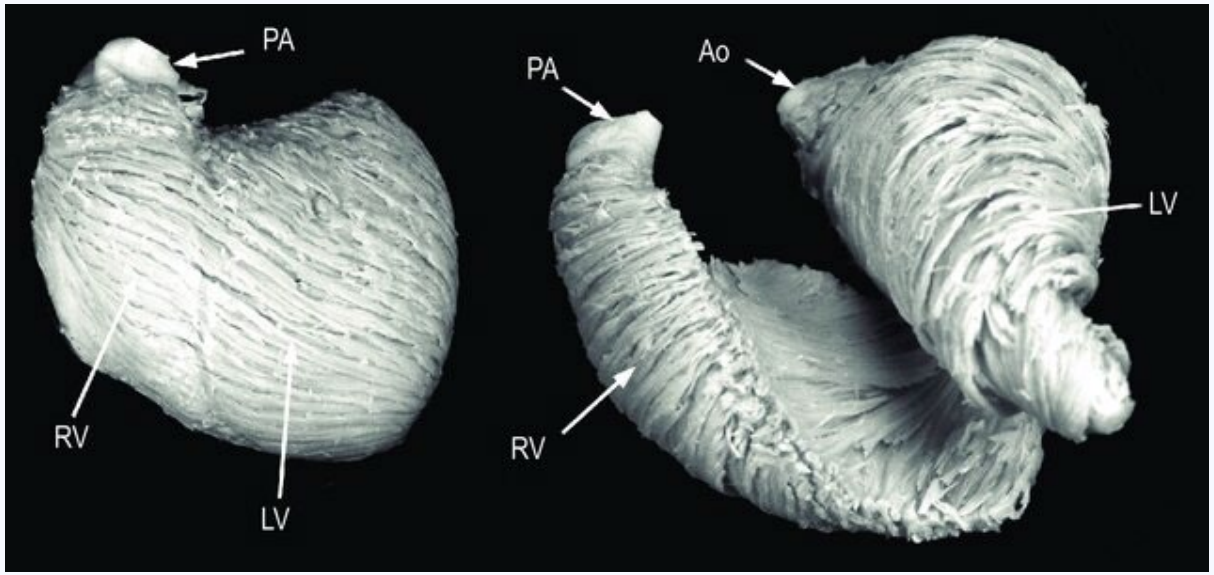


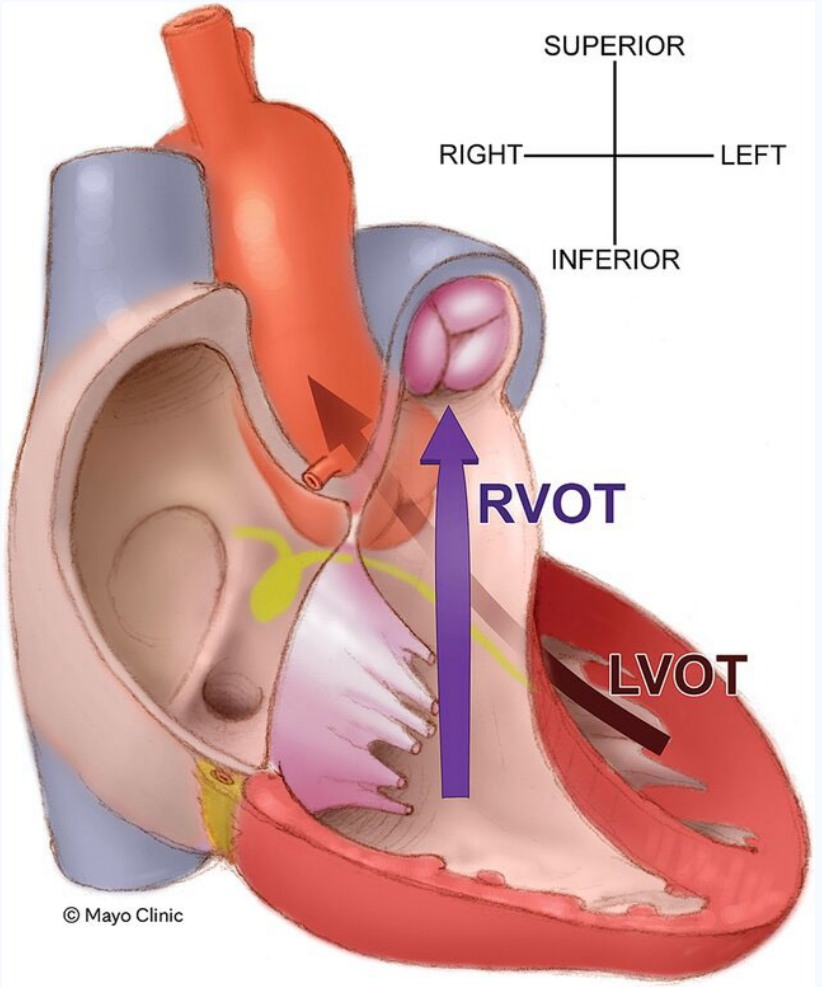


Bhattacharya J, Science 1980
Ventetuolo CE, Annals ATS 2014

California Thoracic Society
ATS Chapter Serving California and Arizona

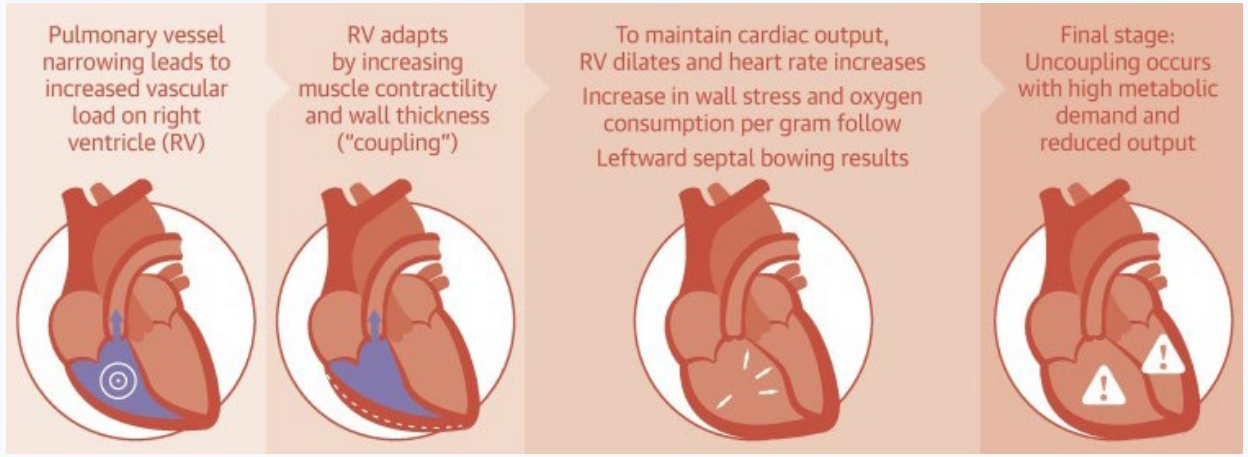
The difference in RV myocardial structure explains why its adaptation to pressure and volume is different than LV

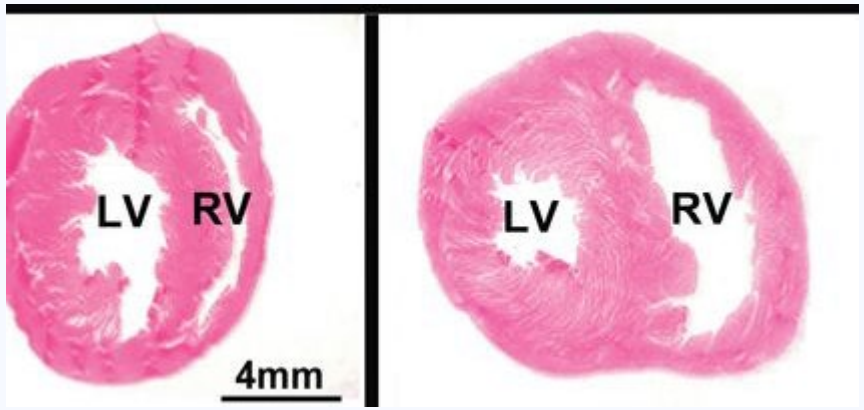


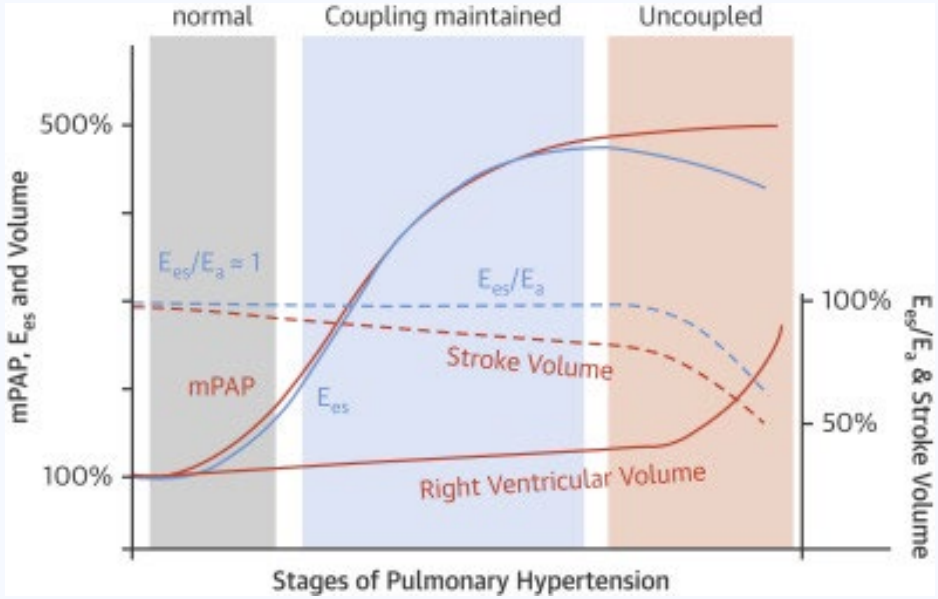


Rocha GM, Arq Bras Cardiol 2015
Ventetuolo CE, Annals ATS 2014
Haq IU, Clin Anatomy 2023

RV morphology and function change in PAH leads to a very different response when stressed







Vonk Noordegraaf A, JACC 2017
Gan C, Am J Physiol Heart Circ Physiol 2006
Gupta S, Transplant Proc 2015
Sharma S, Circulation 2014

Clinical diagnosis of decompensated RV failure is based on history, clinical exam, echo, and invasive measures of hypoperfusion

Triggers for decompensation

- Infection
- Thromboembolism
- Arrhythmias
- Abrupt prostacyclin discontinuation
- Uncontrolled disease
- Surgery/anesthesia
- Pregnancy
- Worsening parenchymal lung disease

Hemodynamic findings

- Markedly elevated RA pressure
- Decreased cardiac index
- Increased PVR

Clinical exam findings

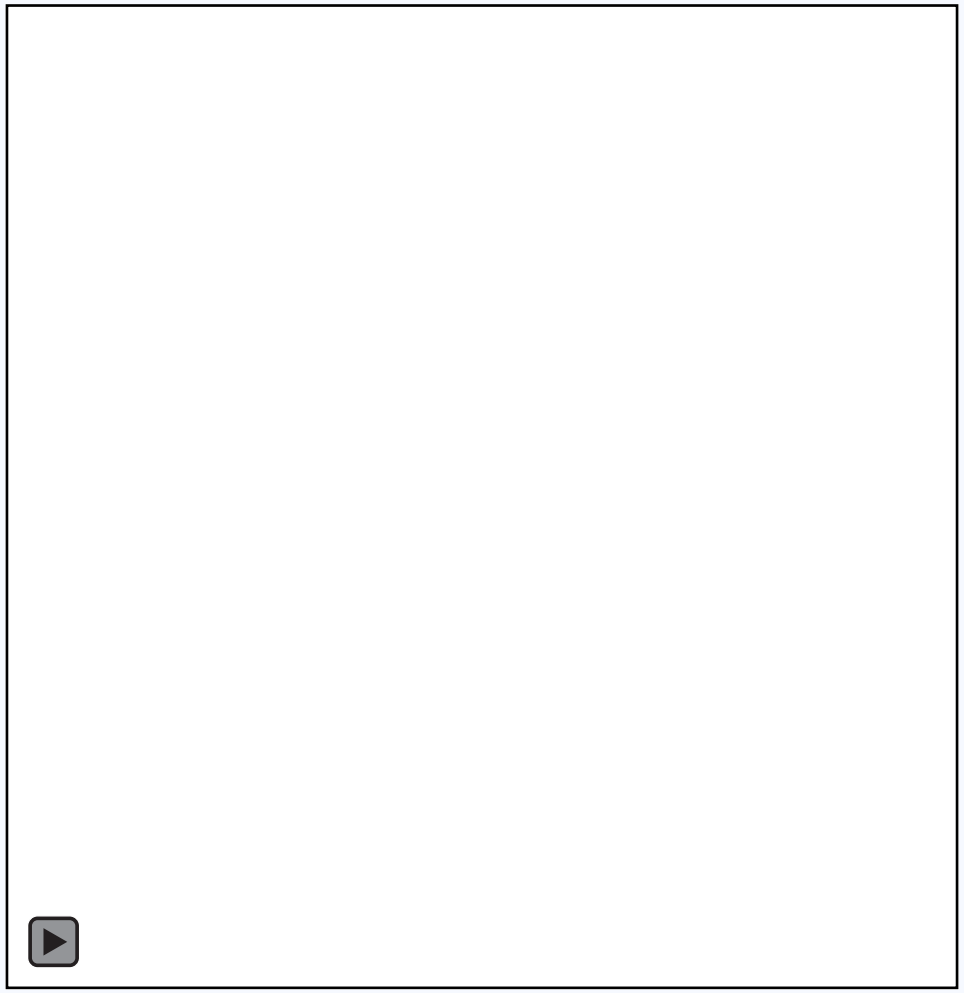
- Elevated JVP; pronounced *v* wave
- Peripheral edema (inc. ascites)
- Split S2 with prominent P2
- RV heave
- Cold extremities

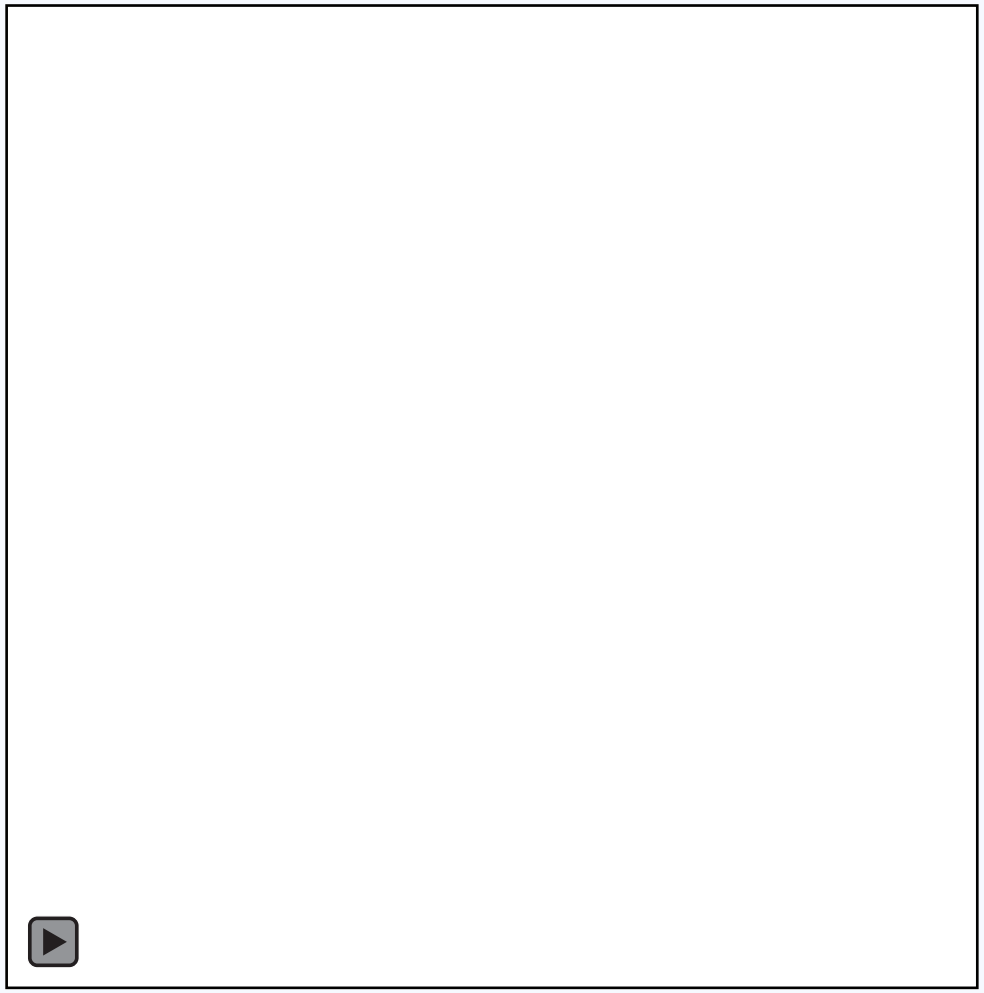
Laboratory findings

- Acute kidney injury
- Troponin/BNP elevation
- Lactate elevation
- Transaminase elevation
- Decreased SvO2

Savale L, Eur Respir Rev 2017
Ventetuolo CE, Annals ATS 2014

Clinical diagnosis of decompensated RV failure is based on history, clinical exam, echo, and invasive measures of hypoperfusion

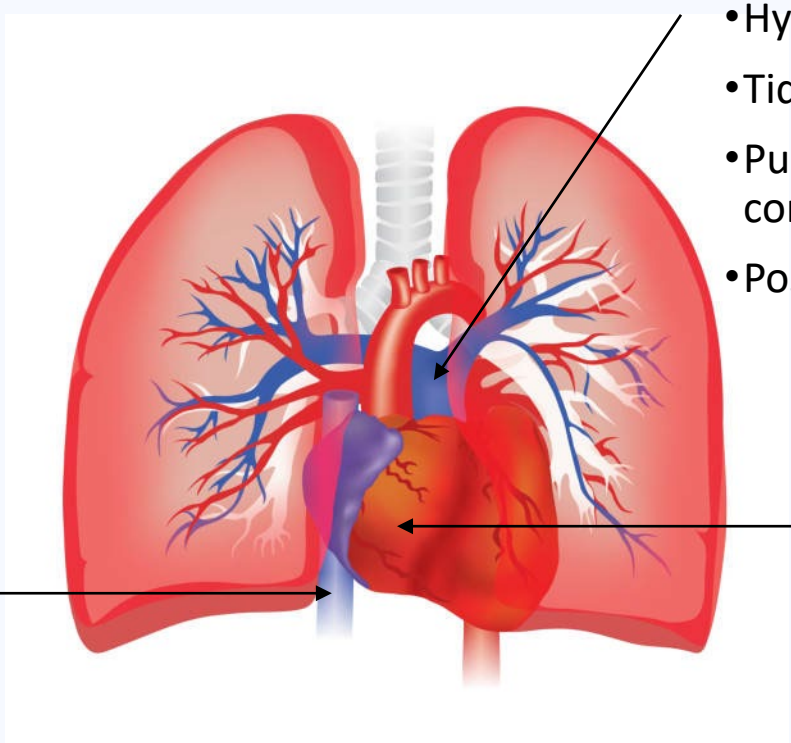




RV ~~failure~~ success is determined by addressing all factors

<u>Preload issues</u>

- Volume
- RV morphology
- Diagnostic challenges
- Positive pressure ventilation



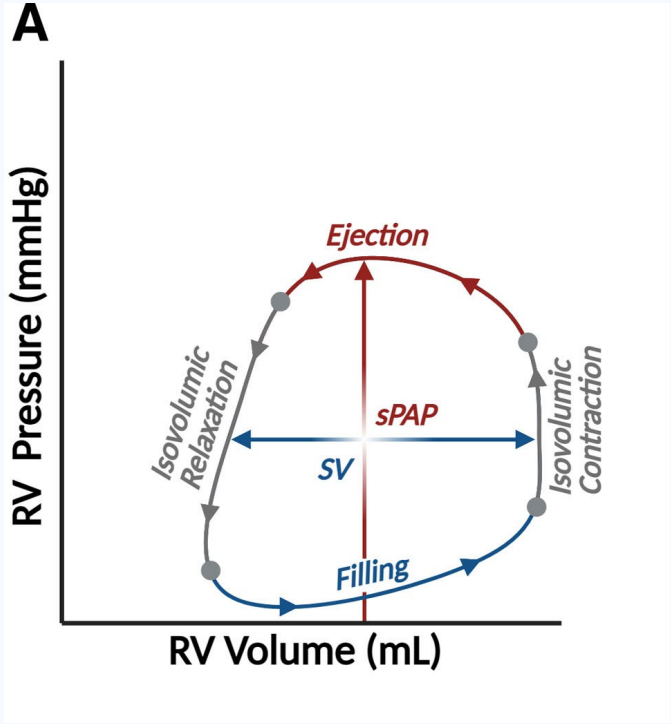
<u>Afterload issues</u>

- Obstruction
- Acidosis
- Hypoxemia
- Hypercapnia
- Tidal volume
- Pulmonary/thoracic compliance
- Positive pressure ventilation

<u>Contractility issues</u>

- O2 deficit
- Wall stress and tension
- Hypoperfusion
- Arrhythmias
- Intracardiac shunting
- Acidosis

Impact of preload on RV function

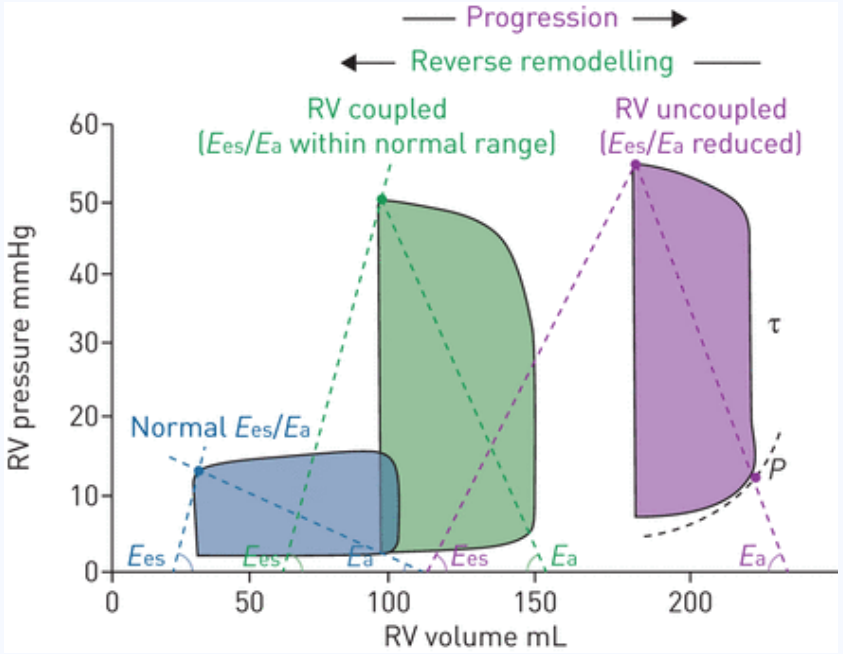


Preload increased by:

- Volume loading
- Negative pressure ventilation

Preload decreased by:

- Sedation/analgesia
- Positive pressure ventilation
- Hypovolemia
- Distributive shock



Brener MI, Circ Heart Fail 2021
Vonk Noordegraaf A, Eur Respir J 2019

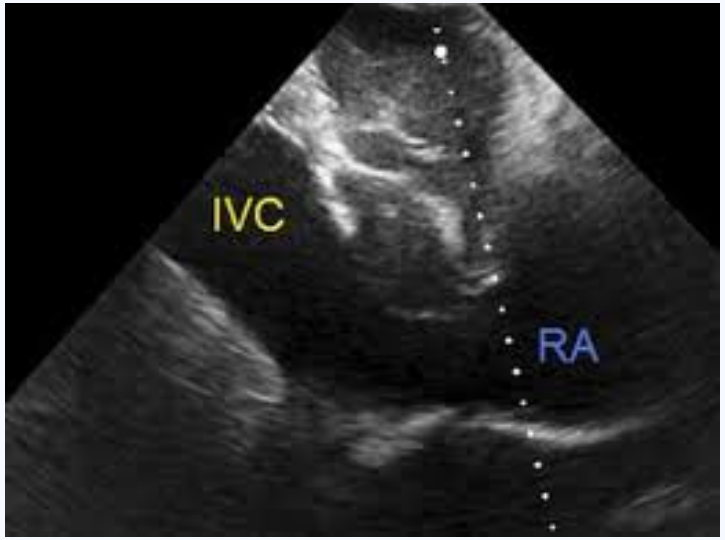
Preload

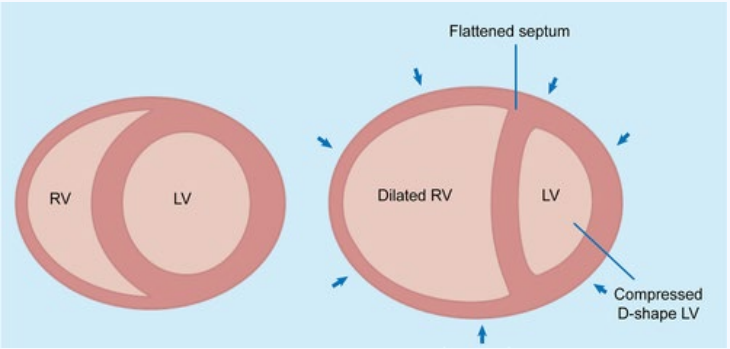
Beware of CVP

- **Pressure ≠ Volume**
- **IVC collapsibility is a normal physiologic state**
- Stiff RV + tricuspid regurgitation = high RAP = high CVP
  - Even when hypovolemic
  - Consider RV myocardial compliance and RV afterload
- IVC (non)collapsibility in longstanding RV failure is not a reliable marker of volume
  - Severity of TR can *decrease* with drop in RV stroke volume → drop in RAP and increased IVC collapsibility
  - Dilation due to portosystemic collaterals in cirrhosis

Volume loading with a dilated RV can worsen LV filling

***Most** patients should be diuresed or dialyzed*

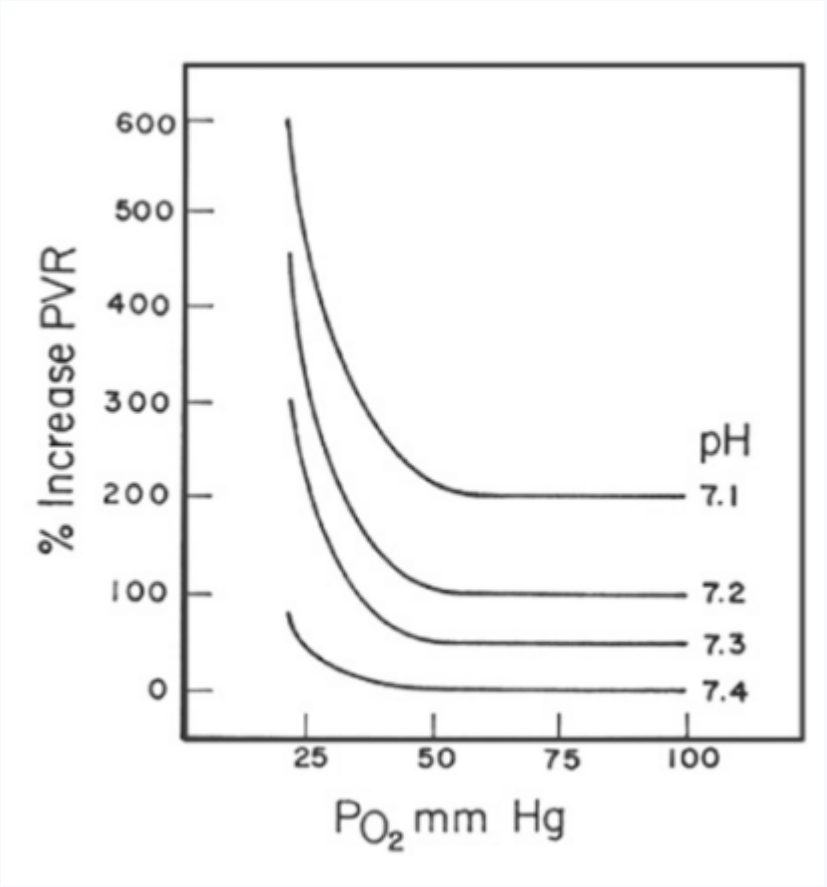




Kan JYL, Chest 2024
Harjola VP, Eur J Heart Fail 2016

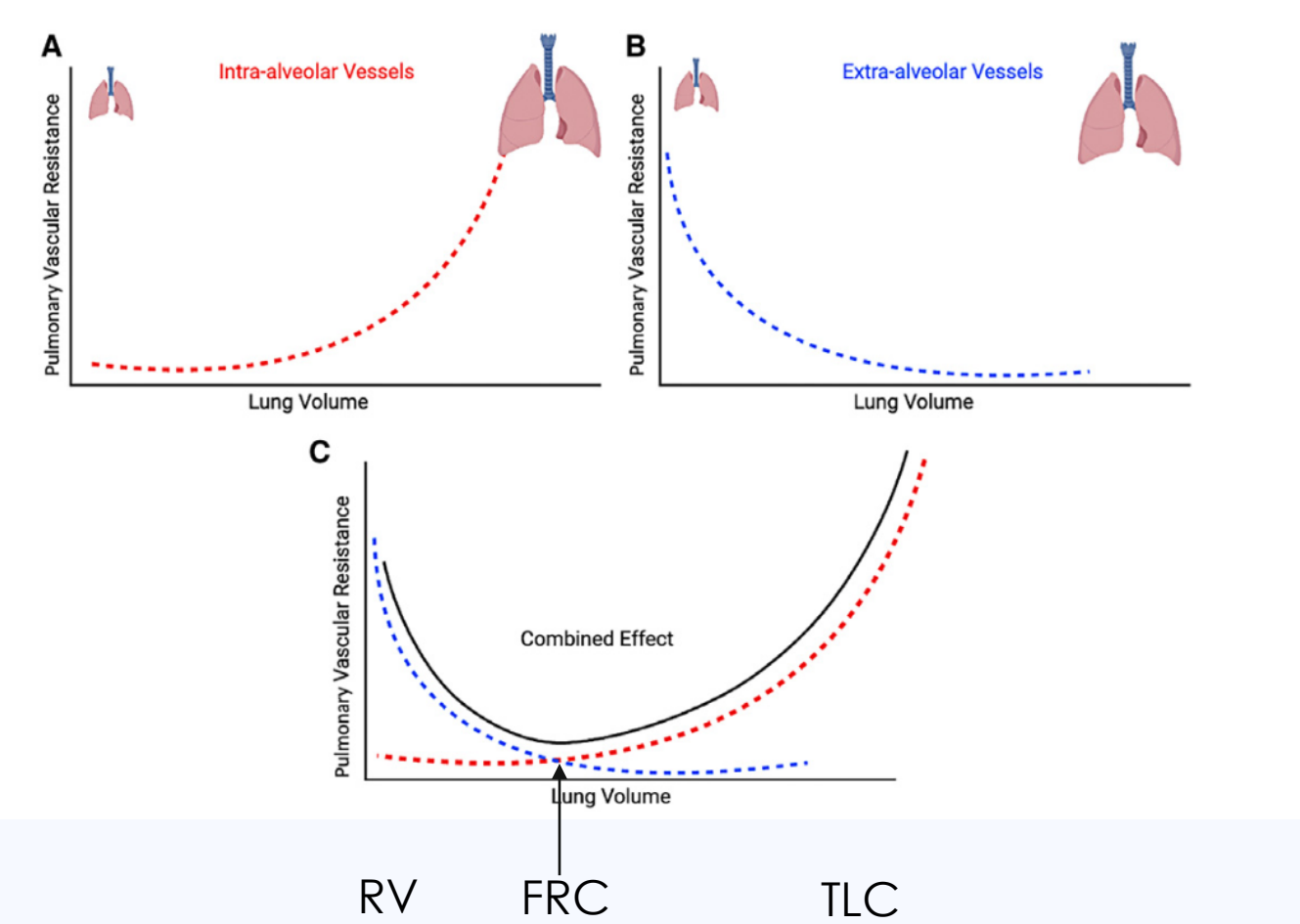
Acute on chronic RV afterload increase can be devastating

- Abrupt rise in PVR → RV dilation
  - Tricuspid stretch → worse TR
  - Increase in RV wall tension → ischemia
  - Leftward septal shift → impaired LV filling
- Thromboembolic disease should be treated aggressively
- PVR increase is significantly driven by:
  - Hypoxia (hypoxic pulmonary vasoconstriction)
  - Hypercapnia
  - Acidosis (additive effect)
- Use HFNC early; keep SaO2 >90-92%
- Use iNO or inhaled epoprostenol early (i.e., through HNFC)
  - Ameliorates hypoxic pulmonary vasoconstriction
  - Directly reduces of RV afterload



Rossaint R, Intensive Care Med 1995
Muzaffar S, J Thorac Cardiovasc Surg 2004
Dembinski R, Intensive Care Med 2004

Positive pressure ventilation in RV failure



- Induction → hypotension → RV hypoperfusion
  - Consider awake intubation
  - Optimize as much as possible pre-intubation
- Ensure arterial and venous access
- Optimize PEEP depending on hemodynamics and RV function
  - No PEEP ladder
- As lung compliance changes, impact of PPV may change

Preload and afterload

Yuriditsky E, ATS Scholar 2025
Johannes J, Crit Care Med 2017
Srour H, J Cardiothorac Vasc Anesth 2020

When should you use systemic pulmonary vasodilators?

- No robust data in acutely decompensated RV failure
- PDE5 inhibitors can increase RV contractility but cause systemic hypotension (at high doses)
- Calcium channel blockers can have negative inotropic effect
- Parenteral prostacyclin therapy is very effective for PAH patients
  - Particularly with low cardiac index
  - Need to consider implications of commitment to parenteral therapy
  - Need to consider rate of uptitration
- If uncertainty of diagnosis, may not be good options

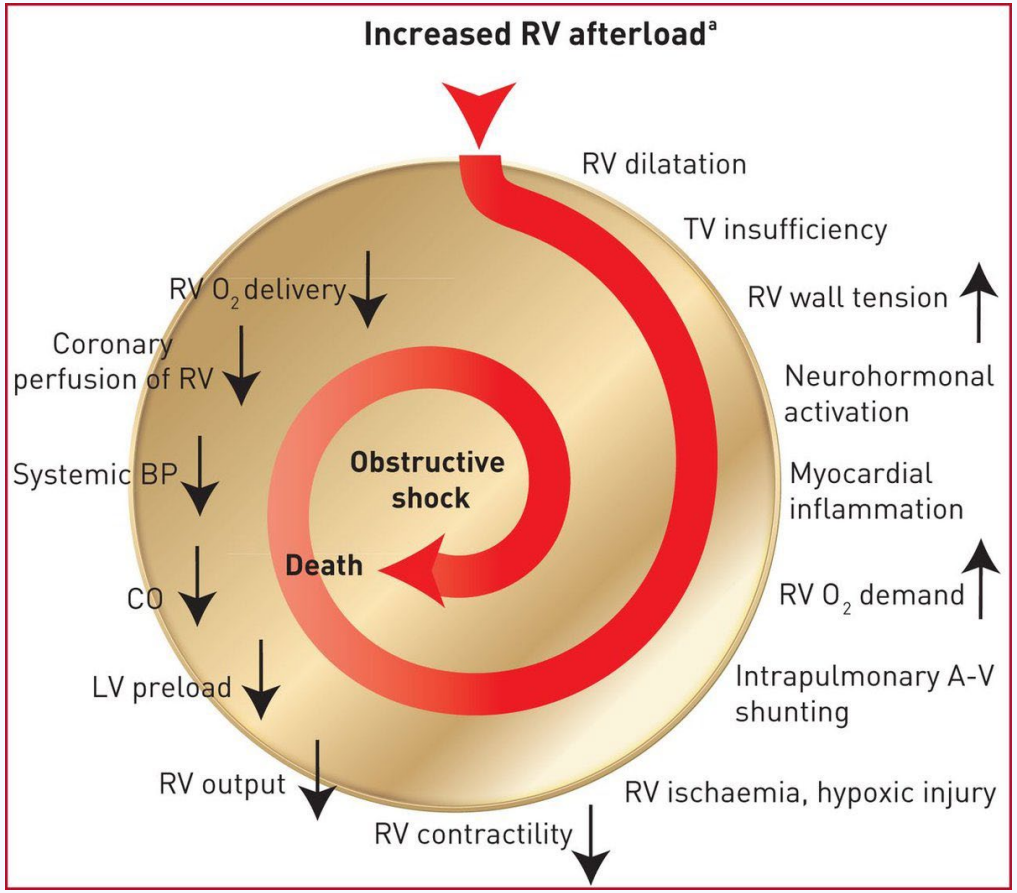
Afterload

Cornet AD, Intensive Care Med 2010
Packer M, JACC 1984

Hemodynamic support facilitates contractility

Contractility

- Fluid resuscitation can worsen RV wall tension, ventricular interdependence
- R → L shunting can develop/worsen → worsening hypoxemia
- RCA blood flow during systole approaches 0 as RVSP approaches systemic levels
- Myocardial supply/demand mismatch much worse if primary process separate from RV failure (e.g., septic shock)
- Myocardial ischemia may come earlier in some PAH subsets (e.g., systemic sclerosis)
- **<u>Avoid systemic hypotension</u>**
  - Using inotropes with inadequate coronary perfusion will lead to worsening RV ischemia



Konstantinides SV, ESC 2019
Ventetuolo CE, Annals ATS 2014
Van Wolferen SA, Eur Heart J 2008

Titrate vasopressors and inotropes to sensible goals

Afterload

Agent	Receptor					Notes
	α_1	β_1	β_2	D	V1	
Norepinephrine	++	+				Some evidence of improved RV/PA coupling, RV myocardial O2 delivery
Phenylephrine	++					May increase PVR, cause bradycardia
Epinephrine	++	++	+			May improve RV contractility
Vasopressin					+	Low dose ($\leq$ 0.03) – some pulmonary vasodilation; higher doses may have coronary artery vasoconstriction
Dopamine						Low-dose vasodilation May stimulate diuresis (not improve renal function), confounding goals Can trigger arrhythmias before vasopressor effect Only drug shown to worsen mortality in sepsis
< 5		+		++		
5-10	+	++		++		
>10	++	++		++		
Dobutamine		++	+			Low dose (5-10) improves RV/PA coupling Risk of hypotension and arrhythmias
Milrinone						PDE3 inhibitor, improves inotropy, some vasodilation; inhaled formulation exists

Ventetuolo CE, Annals ATS 2014
Hollenberg SM, AJRCCM 2011
Schreuder WO, Chest 1989
Rich S, Chest 1990
Le Tulzo Y, Intensive Care Med 1997
Leather HA, Crit Care Med 2002
De Backer D, Crit Care Med 2012
Chen EP, Ann Thorac Surg 2000
Deb B, Crit Care Med 2000

Titrate vasopressors and inotropes to sensible goals

My approach:

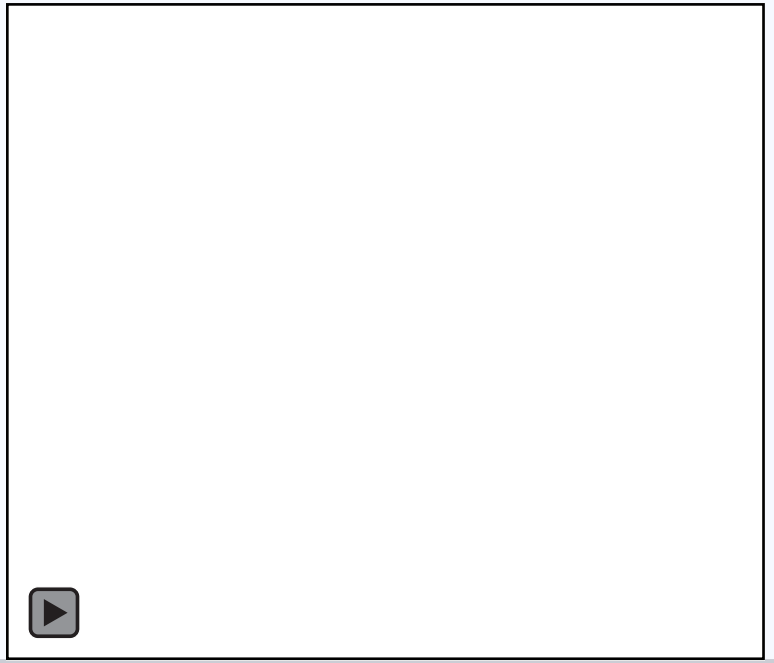
1. Treat the primary cause of shock (if separate from RV failure)
2. Start norepinephrine with a goal MAP >60-70
3. If norepi requirements >8-10 mcg/min (>0.1-0.17 mcg/kg/min), add vasopressin at 0.03 U/min to minimize arrhythmia risk
4. Once BP at goal, start dobutamine @ 2.5-5 mcg/kg/min or milrinone @ 0.125 mcg/kg/min, titrated to MvO2 >60 or clinically improved perfusion.
5. Only use phenylephrine if no other option to keep BP up or very arrhythmia-sensitive.
6. Almost never use dopamine because impossible to logically titrate.

Minimize arrhythmias

- Sinus tachycardia generally ok
- Supraventricular arrhythmias very problematic – no LV filling on an already compressed LV
  - Early cardioversion for unstable supraventricular arrhythmias
  - IV amiodarone generally a good option for rapid atrial fibrillation (?digoxin)
- Avoid negative inotropes (beta blockers, calcium channel blockers)
  - There may be a role for esmolol to allow for improved filling time in certain situations
- Defibrillation for ventricular arrhythmias
- Consider resynchronization and AV pacing when needed
- Avoid bradycardia

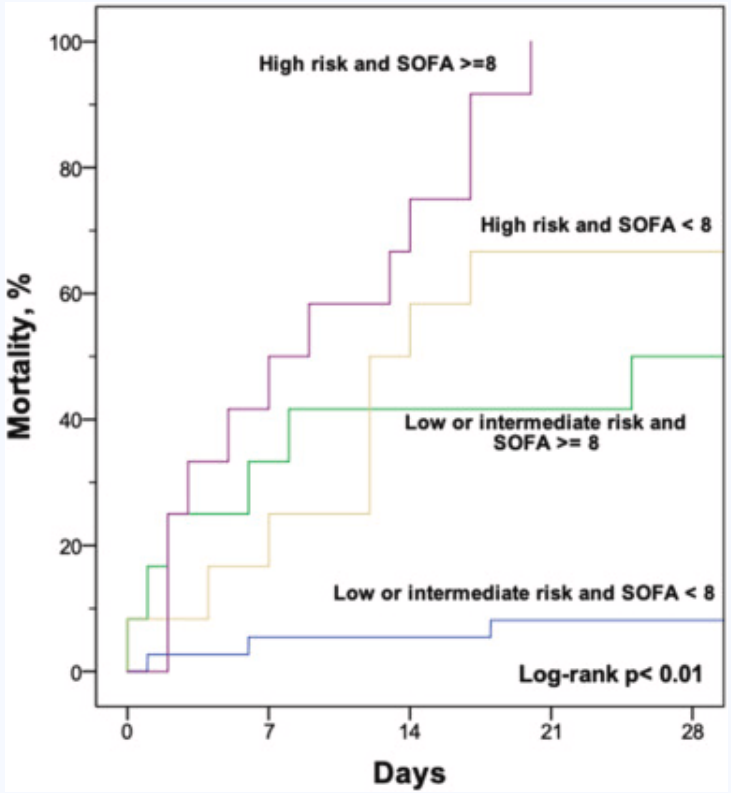
Pericardial effusions in decompensated PAH

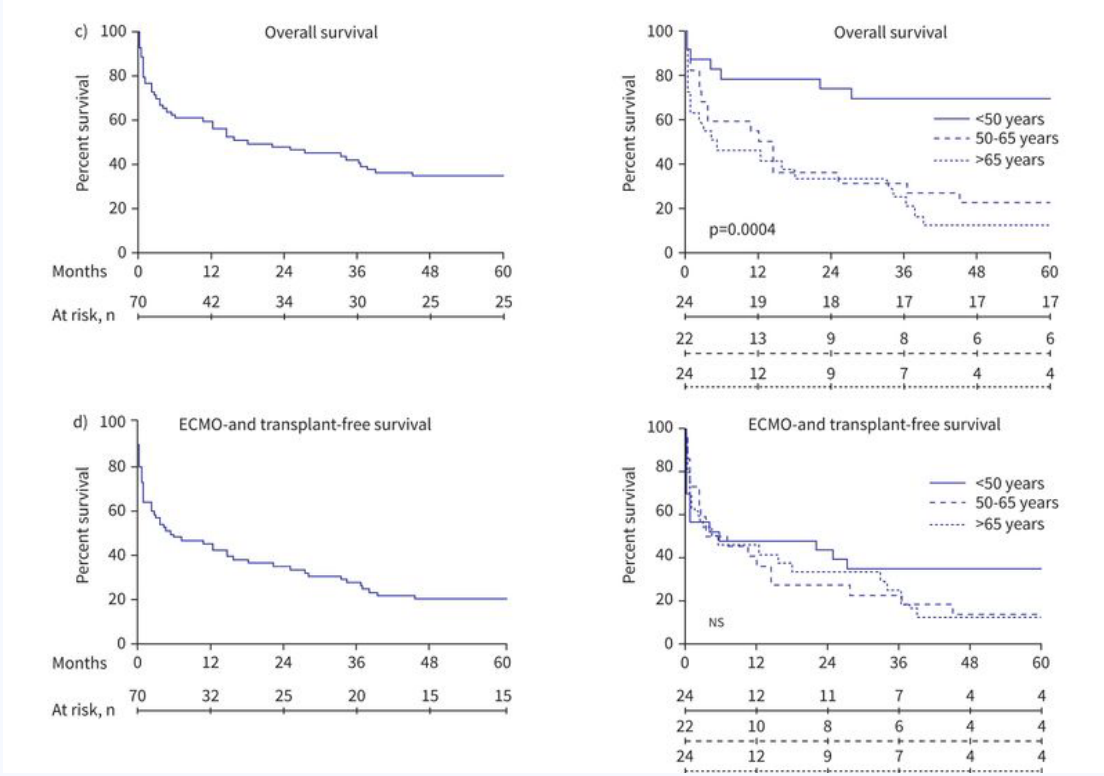
- May be tougher to identify RV/RA collapse with hypertrophied RV and dilated RA
- If tamponade is a concern, can place PAC to guide drainage
  - Equilibration of intracardiac pressure, prominent *x* wave, small/absent *y* wave
- Drain smaller volumes over long period of time
  - Rapid removal → RV dilation → further LV compression by septum



• Sahay S, Pulm Circ 2016

Decompensated PAH associated with high mortality



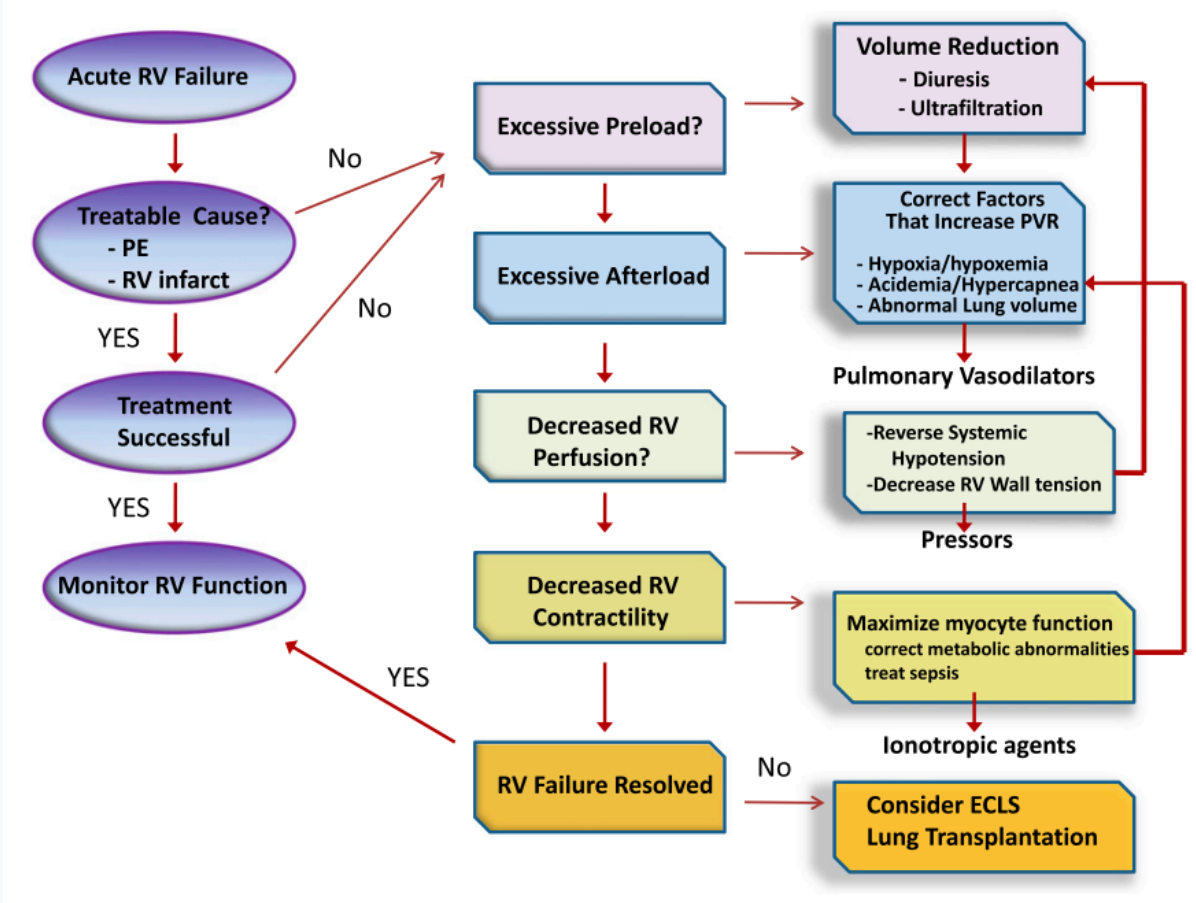


Rates of ROSC ~20%, rates of long-term survival < 10% after CPR

Savale L, Eur Respir J 2021
Fernandes Garcia MV, Respiratory Med 2021
Hoeper MM, AJRCCM 2001
Yang JZ, Pulm Circ 2022

Successful management of decompensated PAH is driven by physiology

- Transfer to experienced facility
- Reverse the cause, if you can
- Optimize volume status, often with volume removal
- Fix hypoxemia, hypercapnia, and acidosis
- Avoid PPV if you can, but if not, optimize vent support
- Optimize RV afterload reduction and contractility
- Consider mechanical support and transplant



Ventetuolo CE, Annals ATS 2014

Thank you

California Thoracic Society
ATS Chapter Serving California and Arizona

ECMO and Lung Transplantation for PAH

Nicholas Kolaitis, MD MAS
University of California, San Francisco

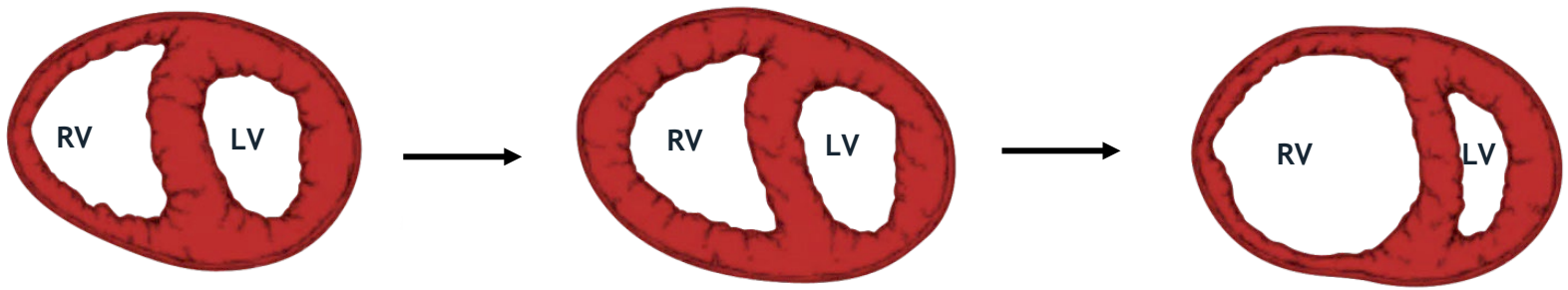
Disclosures

- I have the following relationships with ACCME defined ineligible companies:
- **Merck, Johnson and Johnson, Liquidia, United Therapeutics, Bayer**
- I **WILL NOT** discuss off-label use and/or investigational use of any drugs or devices.

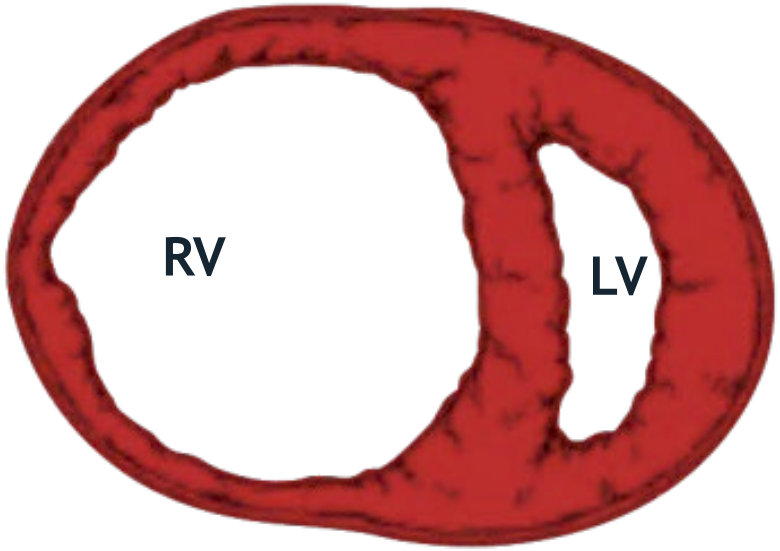
Goals for today

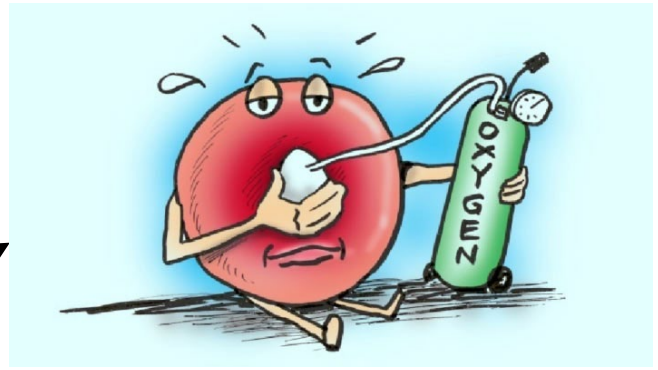
- Background on right ventricular failure in PAH
- How does extracorporeal membrane oxygenation work
- Discuss type of extracorporeal membrane oxygenation used in PAH
- Background on lung transplantation
- Discuss referral for lung transplantation in PAH
- Discuss unique challenges in lung transplantation for PAH
- Results of PVRI Delphi

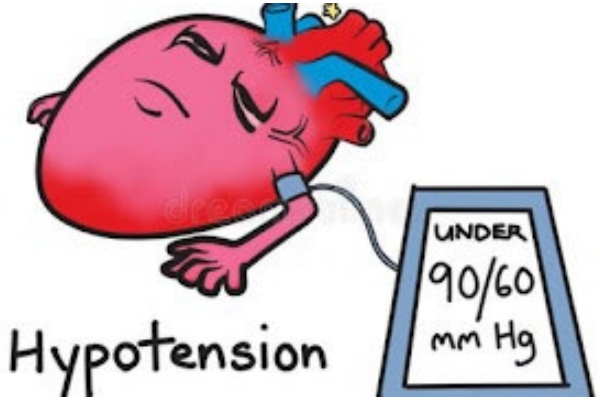
ECMO in pulmonary vascular diseases

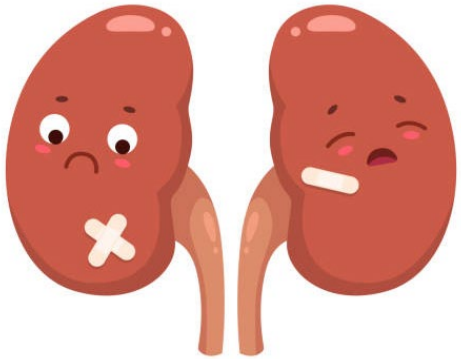


PVR


RV
LV

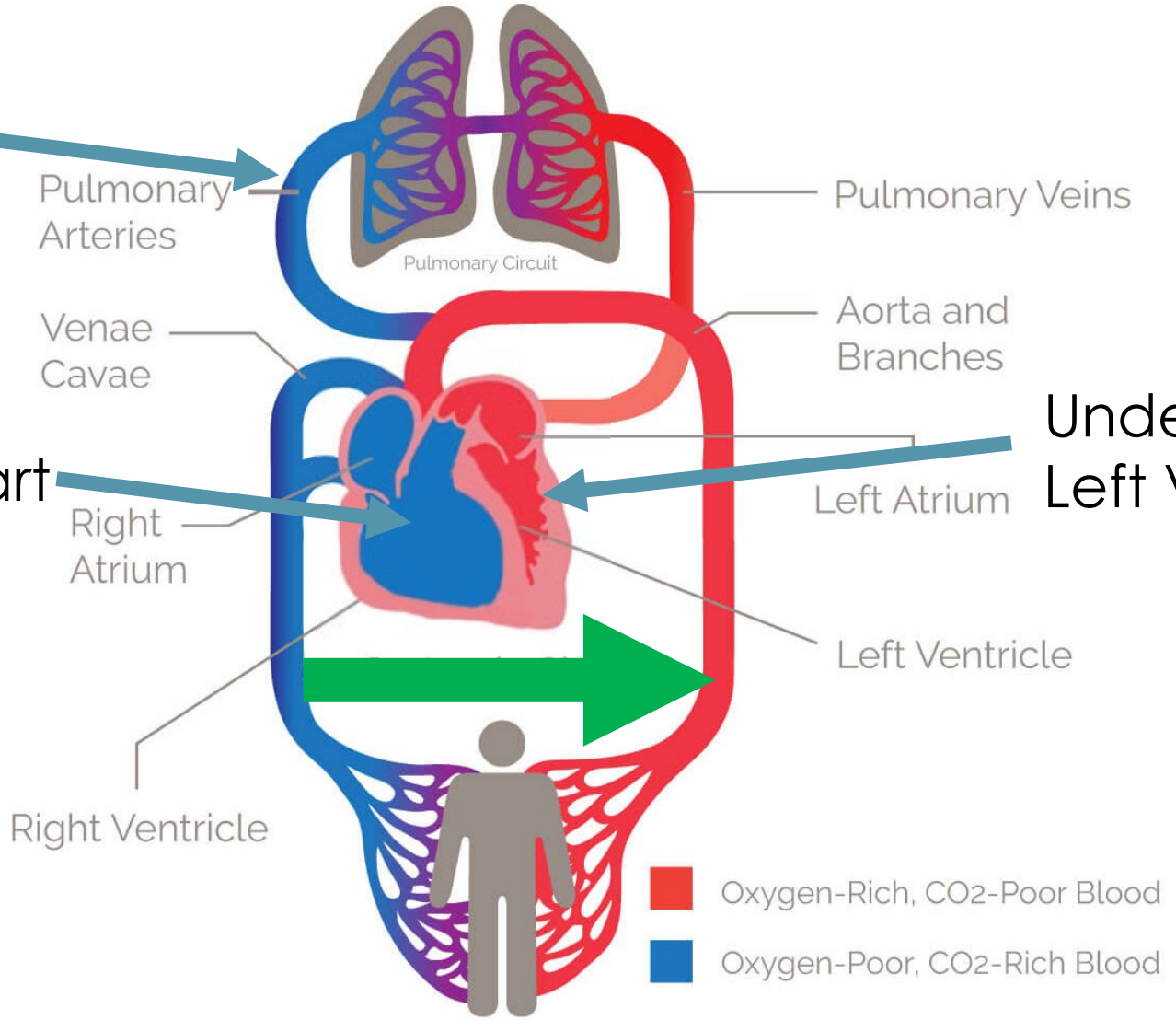

OXYGEN


UNDER
90/60
mm Hg
Hypotension

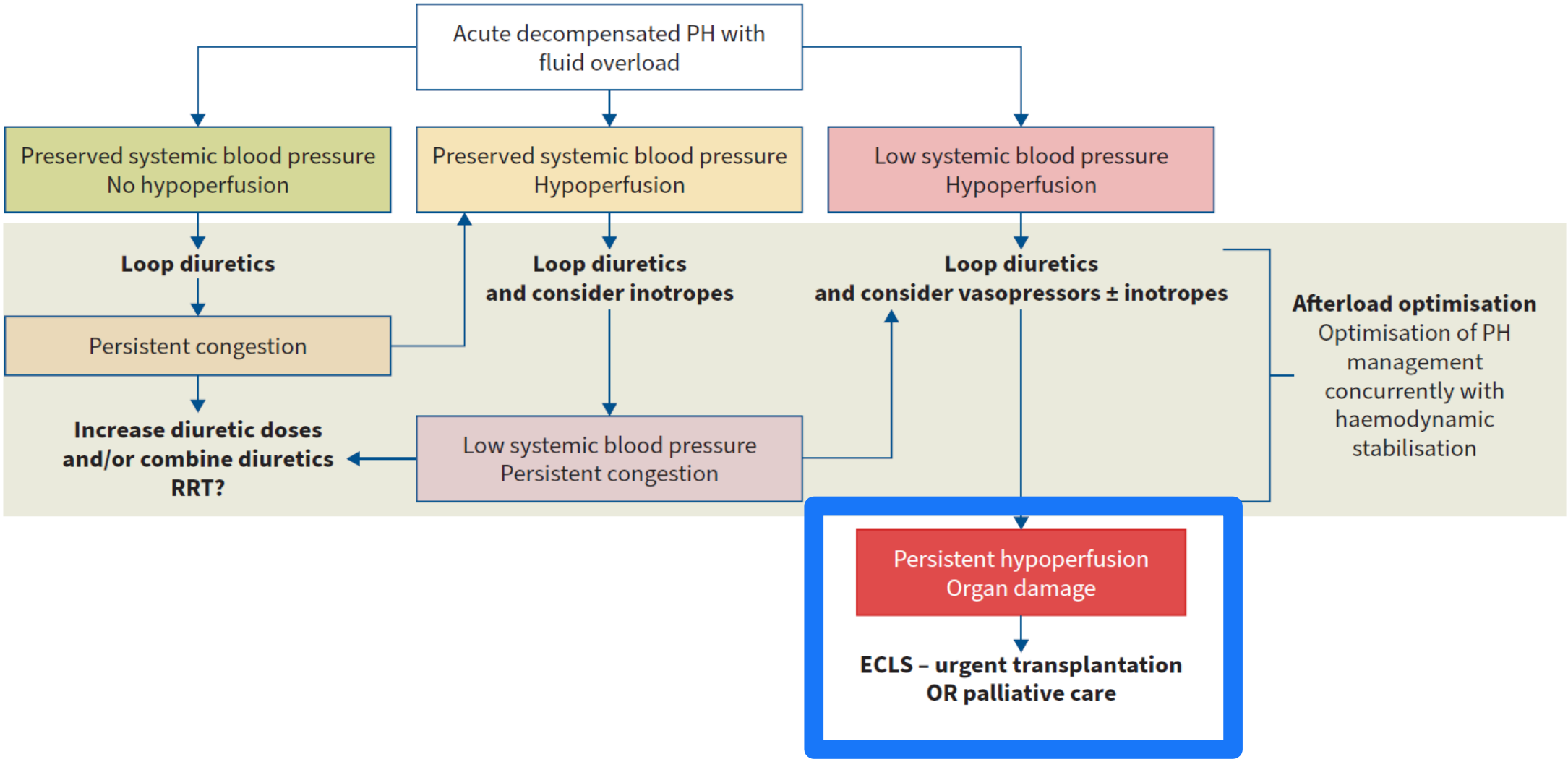


High PVR

Right Heart Failure



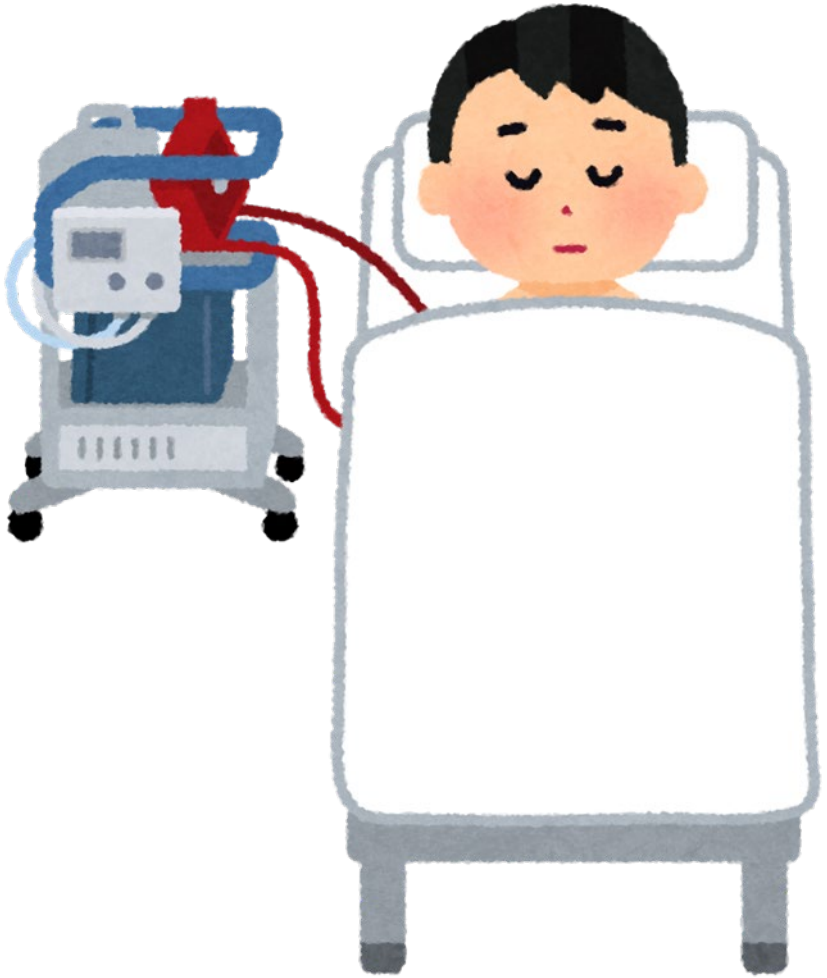
Underfilled Left Ventricle



Savale Eur Respir J 2024

How does ECMO work?

Extracorporeal membrane oxygenation



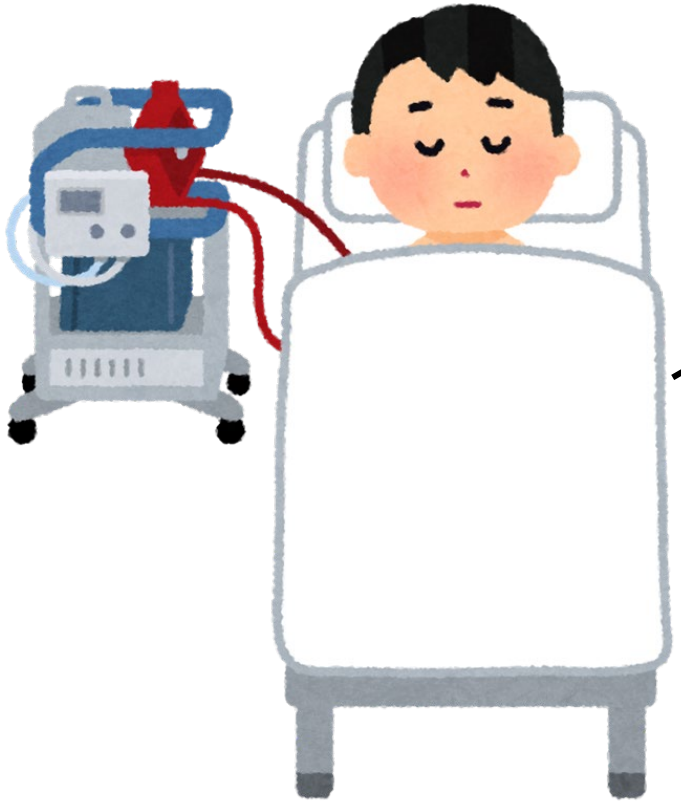
ECMO is a mechanical circulatory device

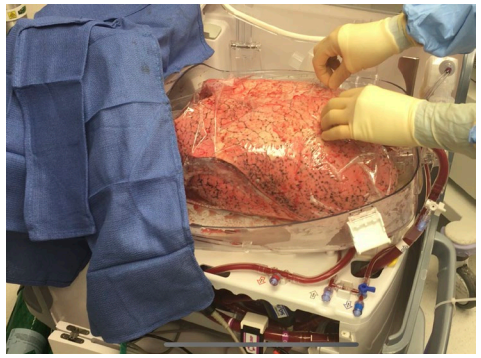
Cannulas placed into major vessels and blood is pumped through an oxygenator and then back into body

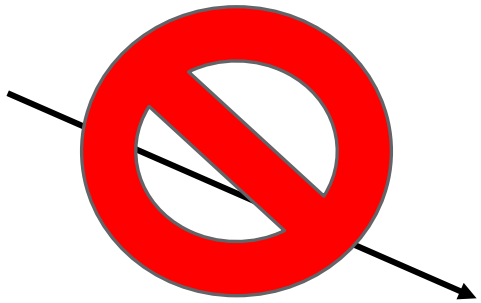
- Three purposes of ECMO

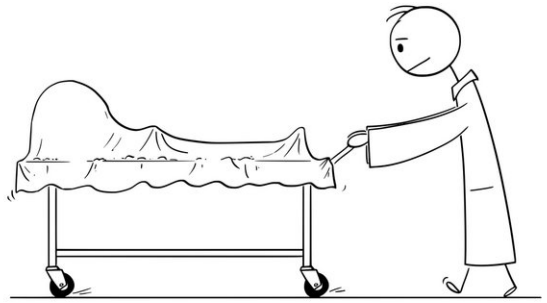
Aim 1	Aim 2	Aim 3

When to use extracorporeal membrane oxygenation







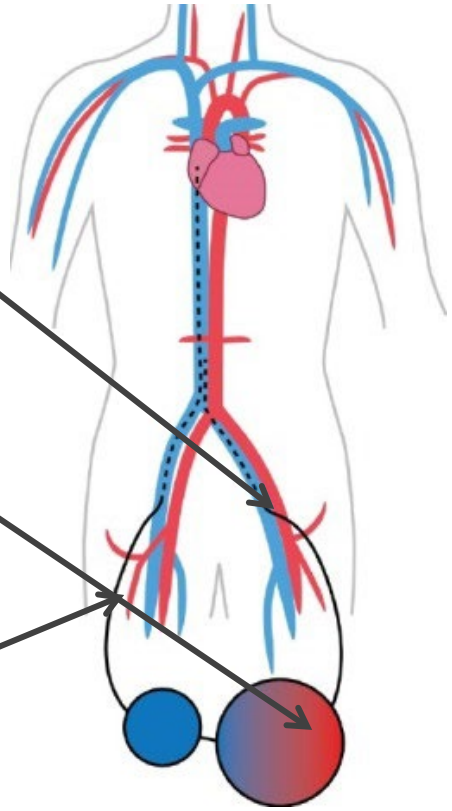


Veno-Venous ECMO versus Veno-Arterial ECMO

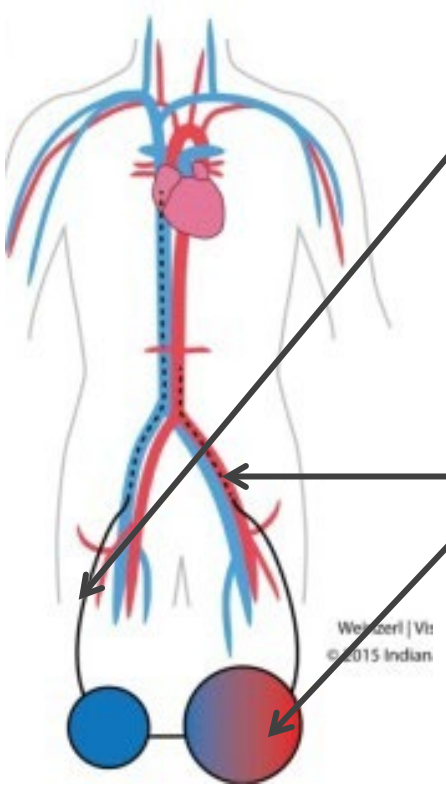
Entered back into body in venous system

Passes through oxygenator

Venous blood comes out of body



Veno-Venous ECMO

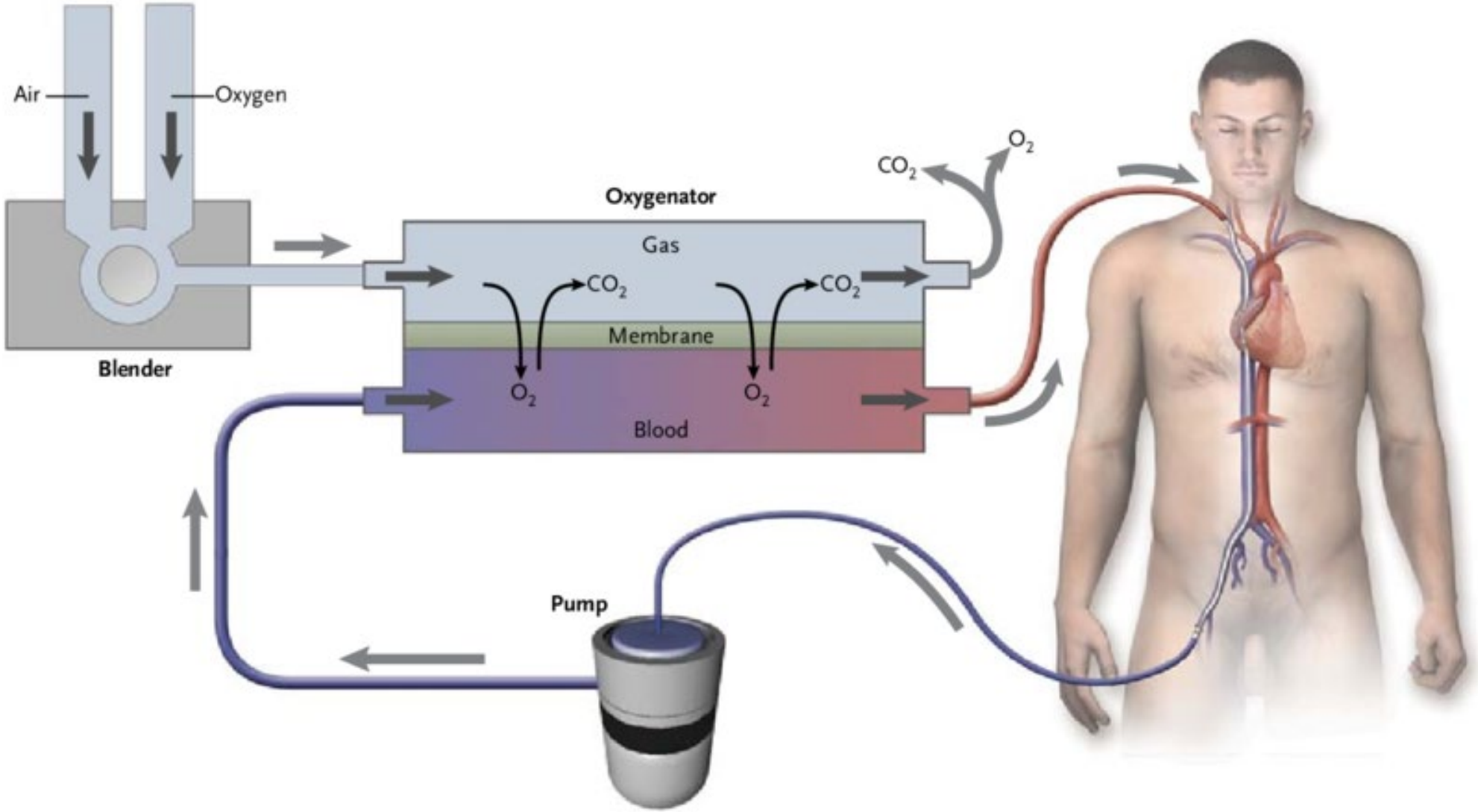


Venous blood comes out of body via femoral vein

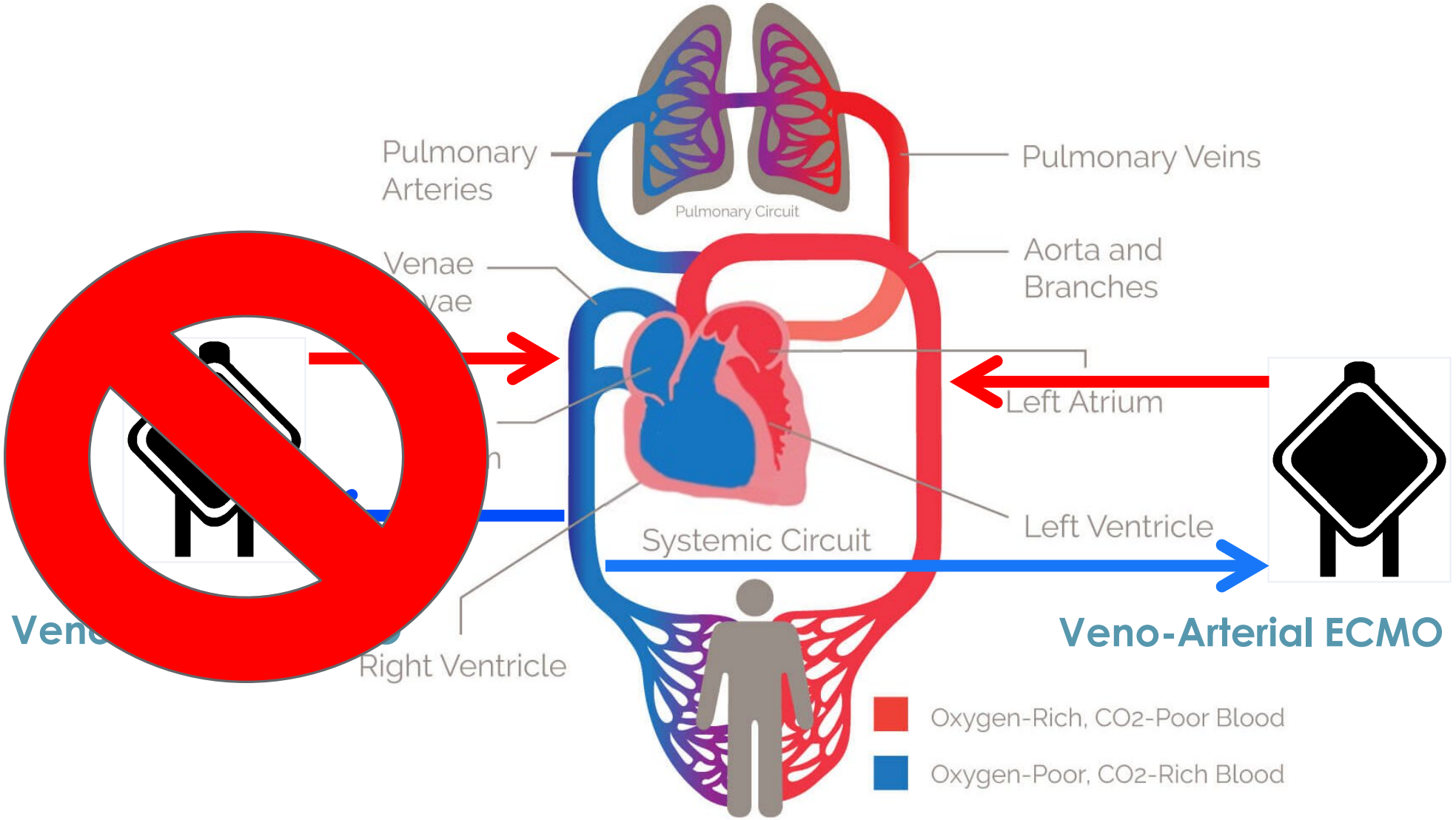
Passes through oxygenator

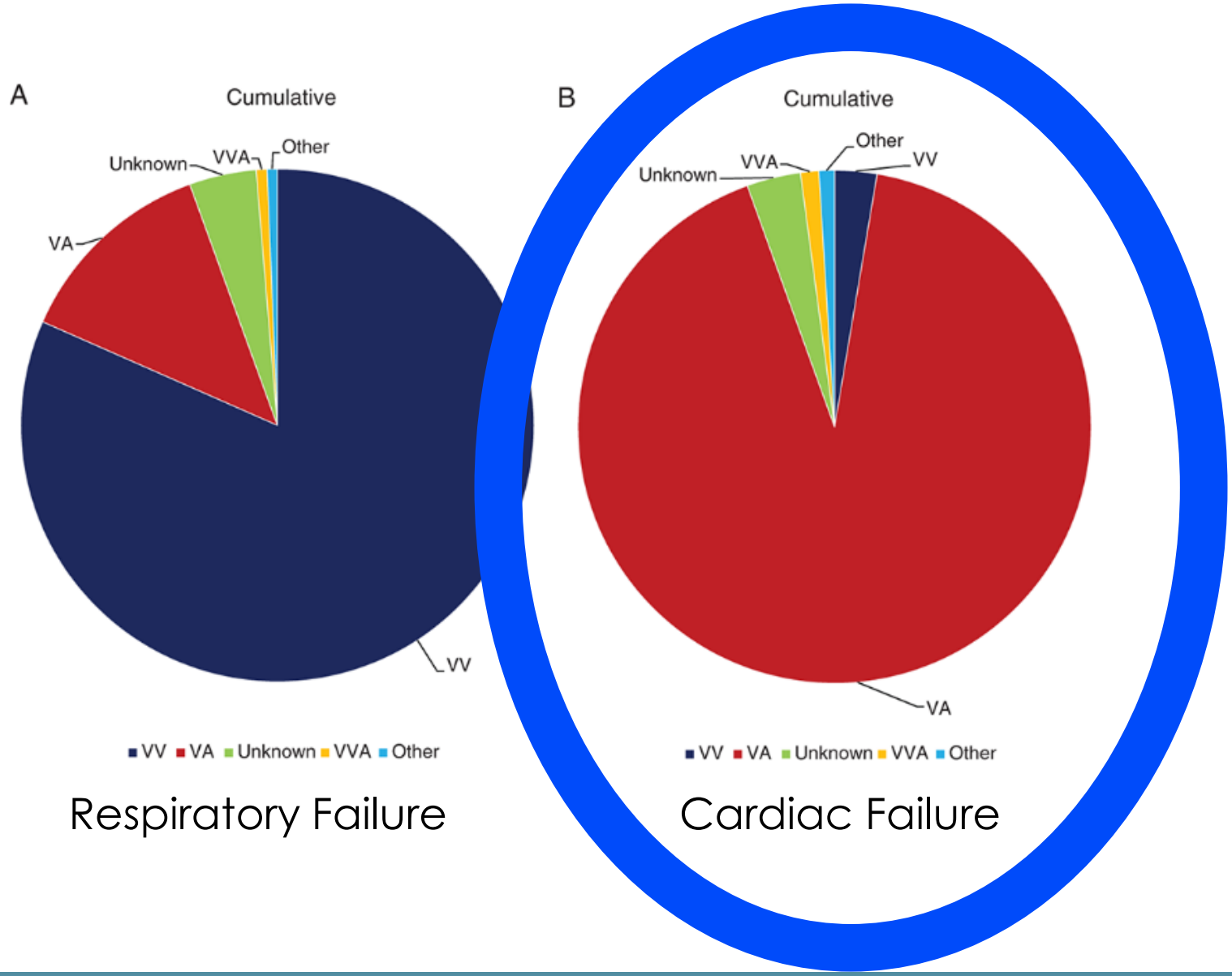
Entered back into body in femoral artery

Veno-Arterial ECMO

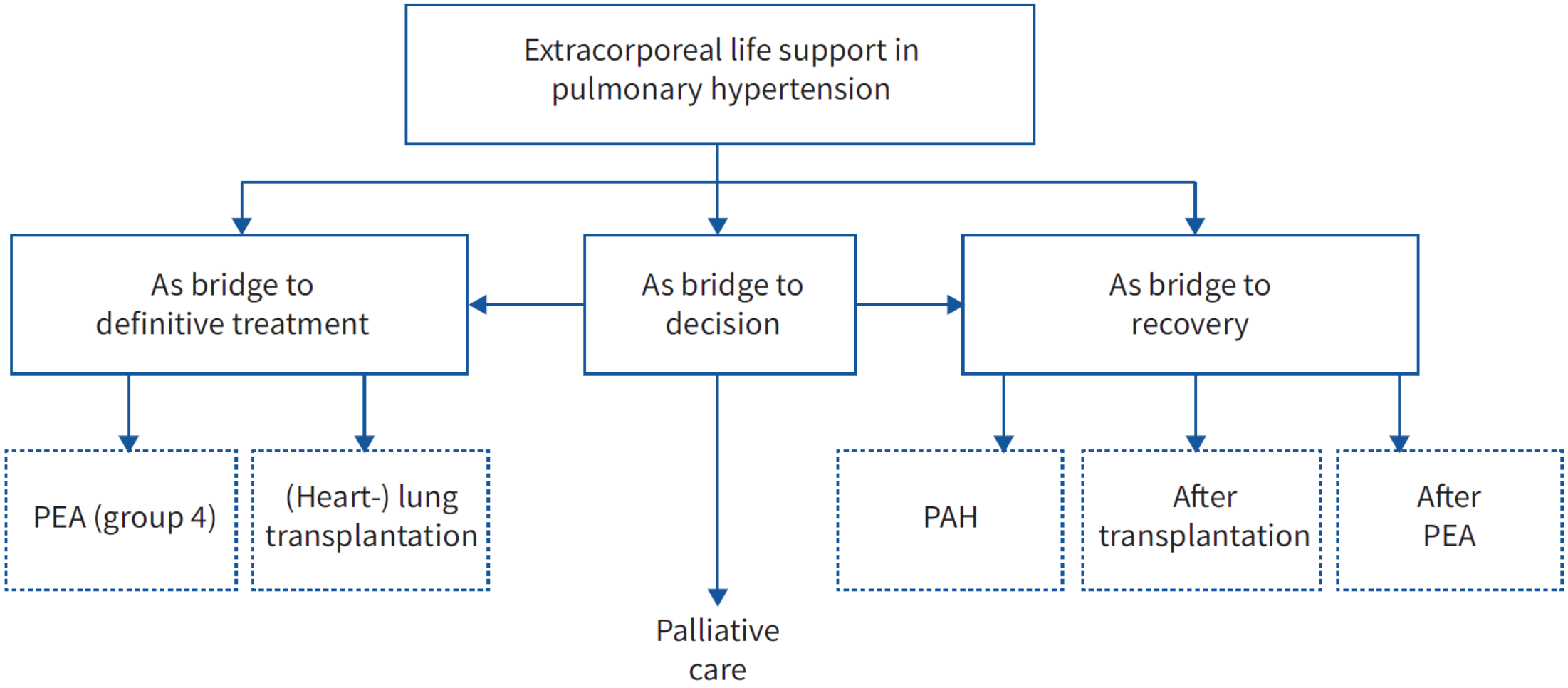

Air
Oxygen
Blender
Oxygenator
Gas
Membrane
Blood
CO_2
O_2
Pump

What kind of ECMO should be used in pulmonary vascular disease?


Pulmonary Arteries
Pulmonary Circuit
Pulmonary Veins
Venae
Aorta and Branches
Left Atrium
Systemic Circuit
Left Ventricle
Right Ventricle
Veno-Arterial ECMO
Oxygen-Rich, CO2-Poor Blood
Oxygen-Poor, CO2-Rich Blood



Sorokin V. et al. Eur J Heart Fail 2017



Savale Eur Respir J 2024

Contraindications to ECMO in PAH

- No defined therapeutic plan after initiation
- No conceivable chance of recovery or transplant (or PEA in CTEPH)
- Vascular access issues
- Severe risk of hemorrhage

Interim Summary

- Right ventricular failure occurs due to high pulmonary vascular resistance
- Extracorporeal membrane oxygenation can be used in appropriate patients
- Typically veno-arterial approaches are needed in PAH
- Use as bridge to something

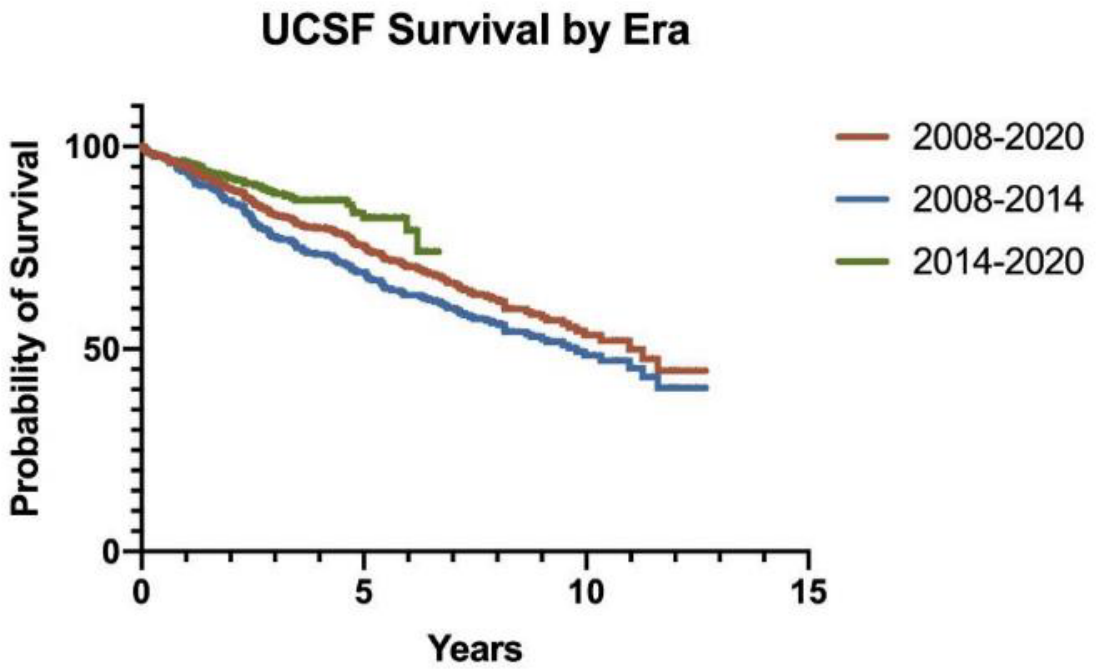
Lung Transplantation

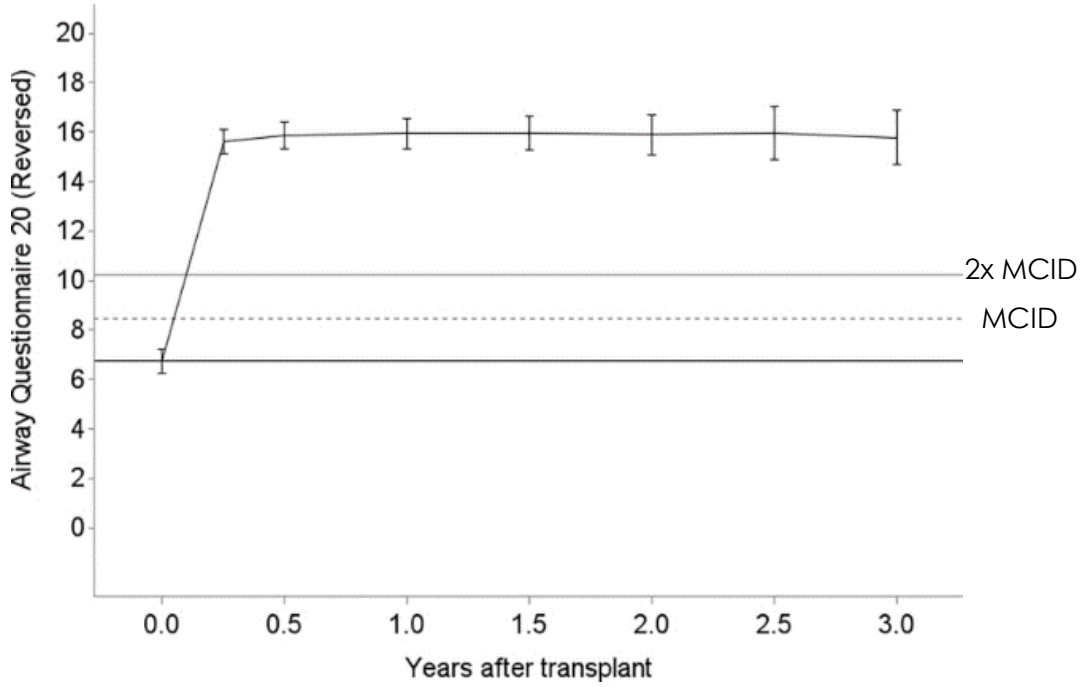
Two Aims of Lung Transplantation

Aim 1

Aim 2

Two Aims of Lung Transplantation

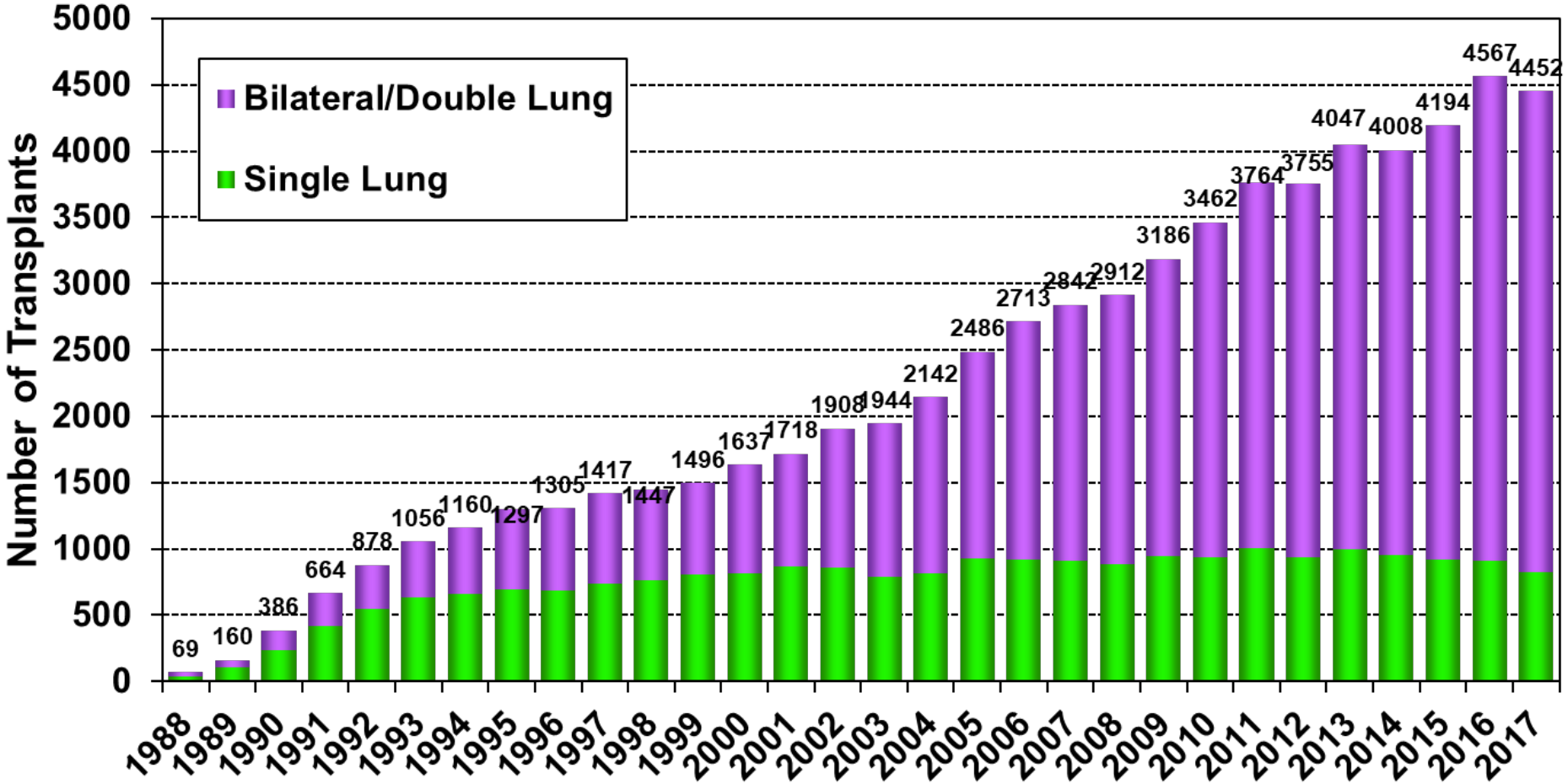




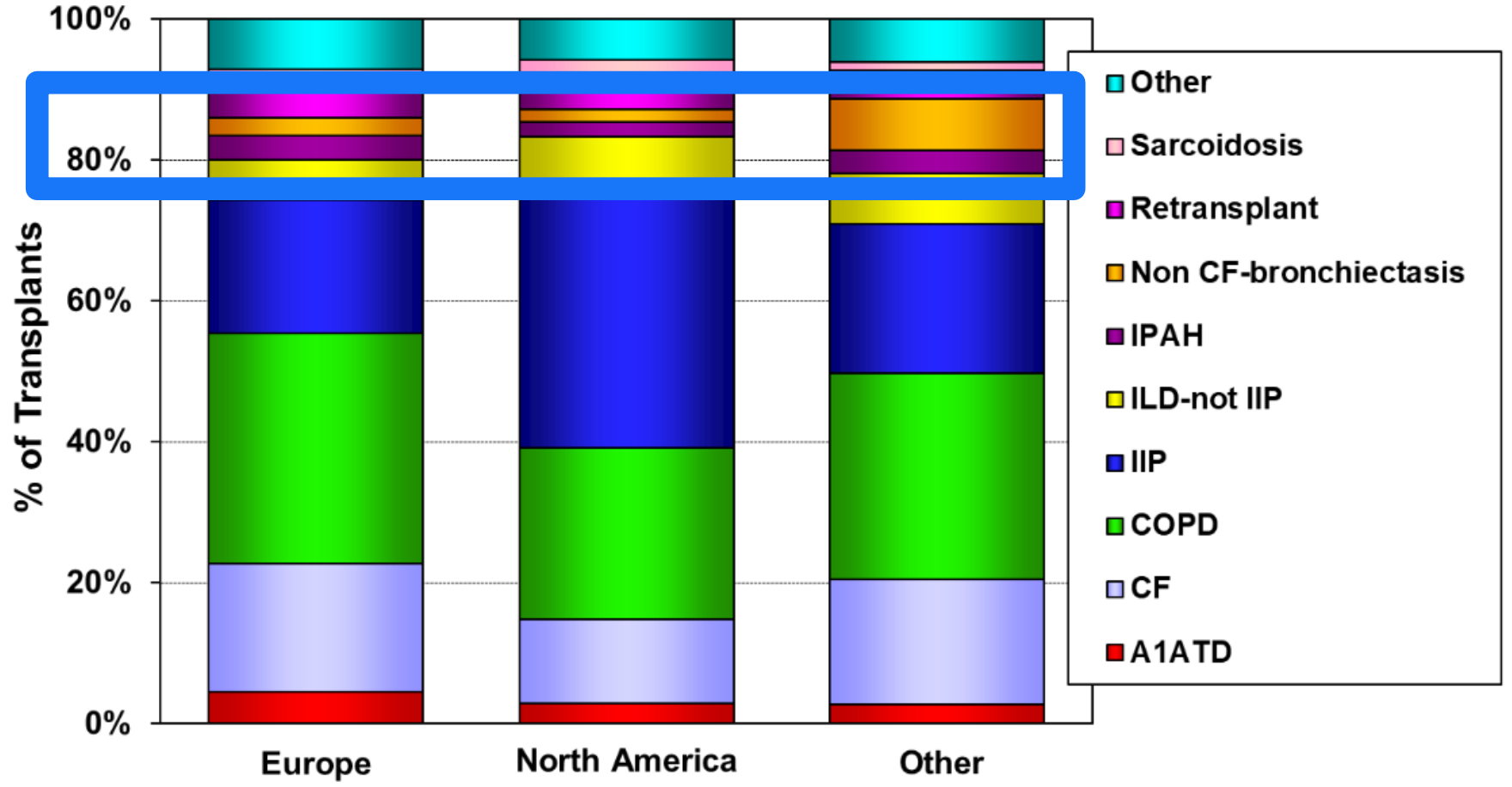
UCSF Internal Data
Singer Am J Transplant 2017

California Thoracic Society
ATS Chapter Serving California and Arizona

Transplant is becoming more popular



Indications for Transplantation



Indications for Referral

Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation

Lorriana E. Leard, MD,[a] Are M. Holm, MD, PhD,[b] Maryam Valapour, MD, MPP,[c] Allan R. Glanville, MBBS, MD,[d] Sandeep Attawar, MBBS, MS, MCh,[e] Meghan Aversa, MD,[f] Silvia V. Campos, MD,[g] Lillian M. Christon, PhD,[h] Marcelo Cypel, MD, MSc,[f] Göran Dellgren, MD, PhD,[i] Matthew G. Hartwig, MD, MHS,[j] Siddhartha G. Kapnadak, MD,[k] Nicholas A. Kolaitis, MD, MAS,[a] Robert M. Kotloff, MD,[l] Caroline M. Patterson, MD,[m] Oksana A. Shlobin, MD,[n] Patrick J. Smith, PhD, MPH,[j] Amparo Solé, MD, PhD,[o] Melinda Solomon, MD, MSc,[p] David Weill, MD,[q] Marlies S. Wijsenbeek, MD, PhD,[r] Brigitte W.M. Willemse, MD, PhD,[s] Selim M. Arcasoy, MD, MPH,[t] and Kathleen J. Ramos, MD, MSc[k]

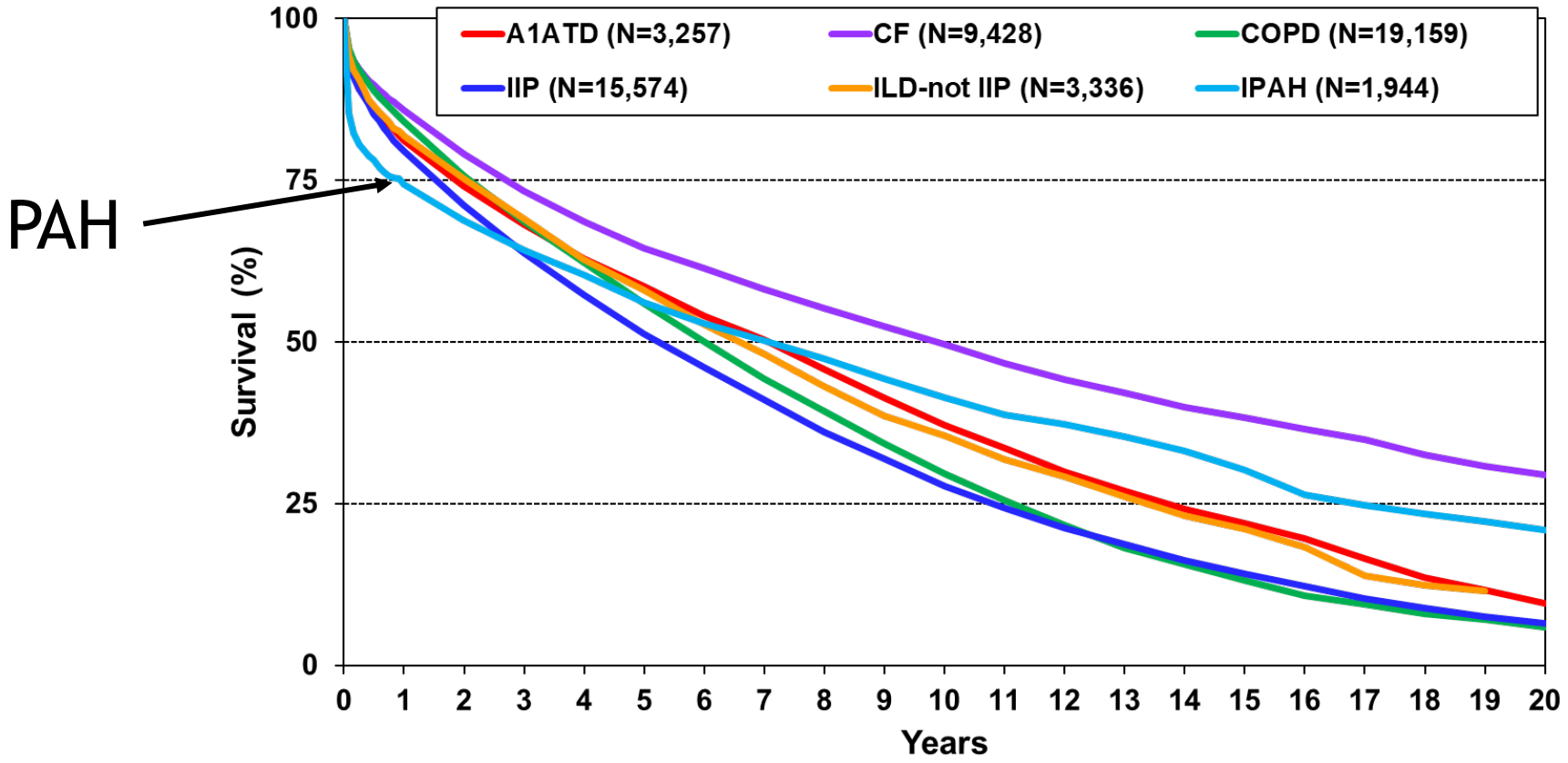
Leard J Heart Lung Transpl 2021

Indications for Referral in PAH

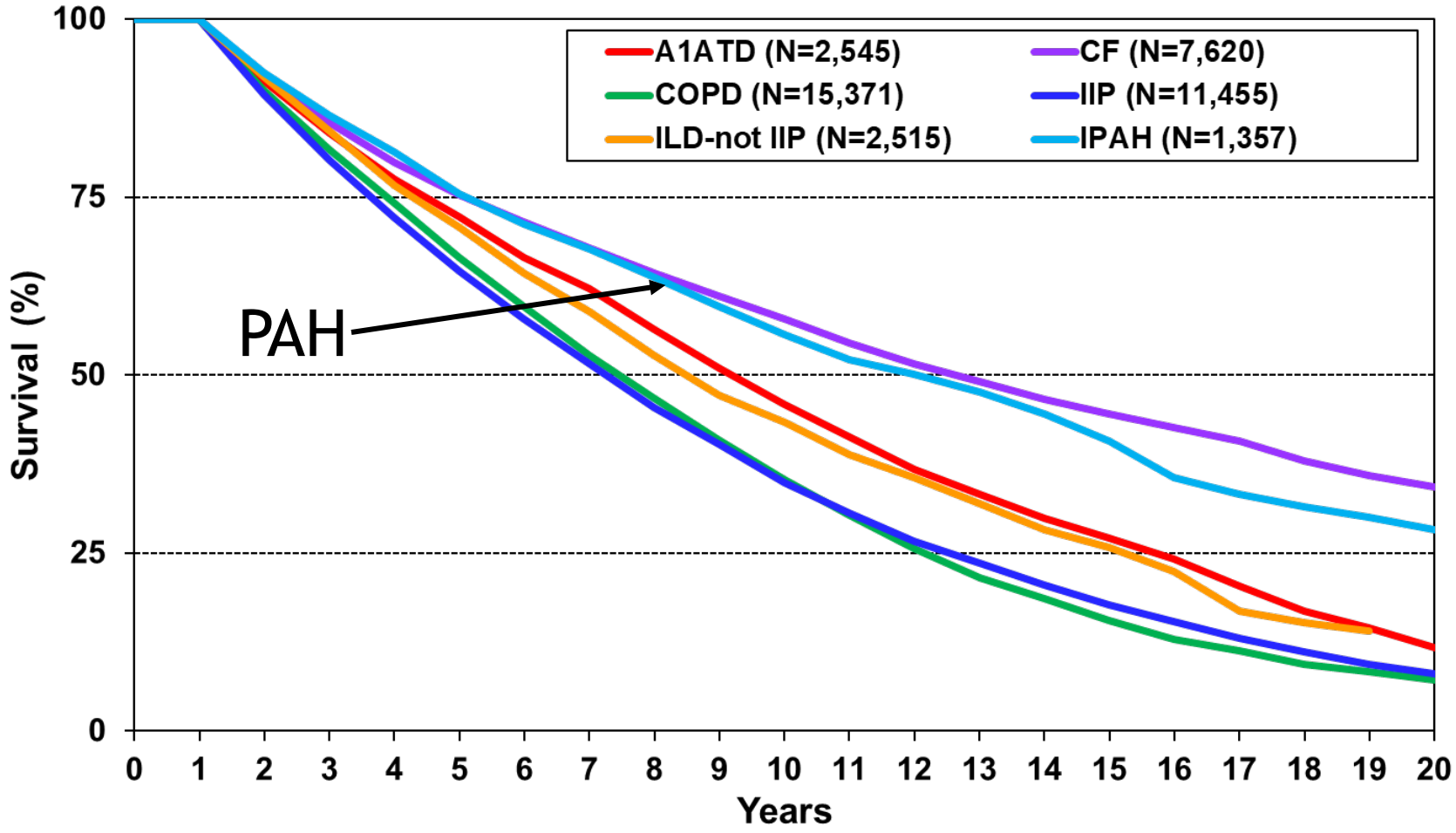
Referral	Listing
ERS/ESC intermediate or high risk or REVEAL ≥8	ERS/ESC high risk or REVEAL >10 on appropriate therapy
RV dysfunction despite appropriate therapy	Progressive hypoxemia, especially in PVOD
Need for IV or SC prostacyclin	Progressive kidney dysfunction or liver dysfunction
High risk variants like PVOD or scleroderma	Hemoptysis

Leard J Heart Lung Transpl 2021

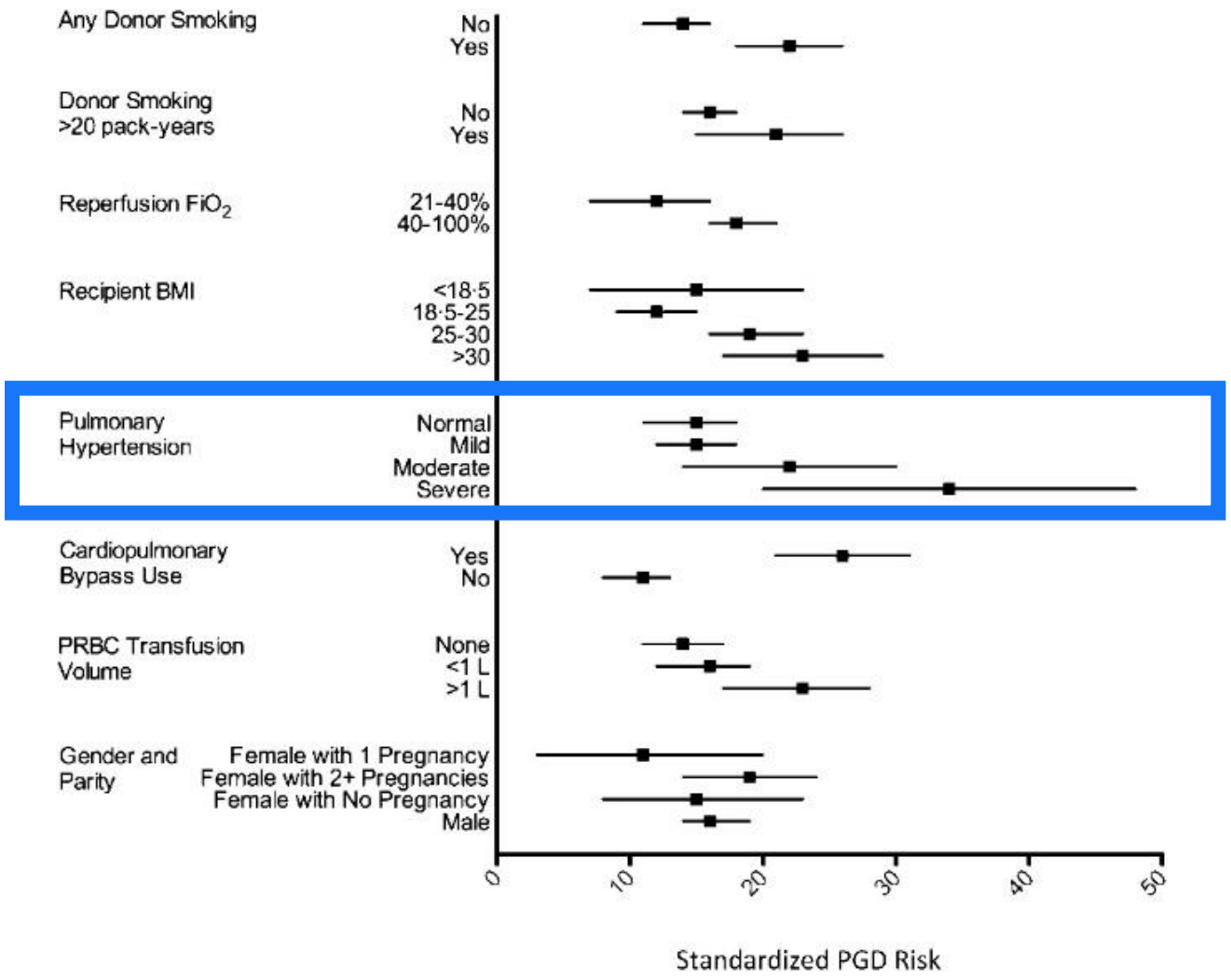
Lung Transplant Survival by Diagnosis

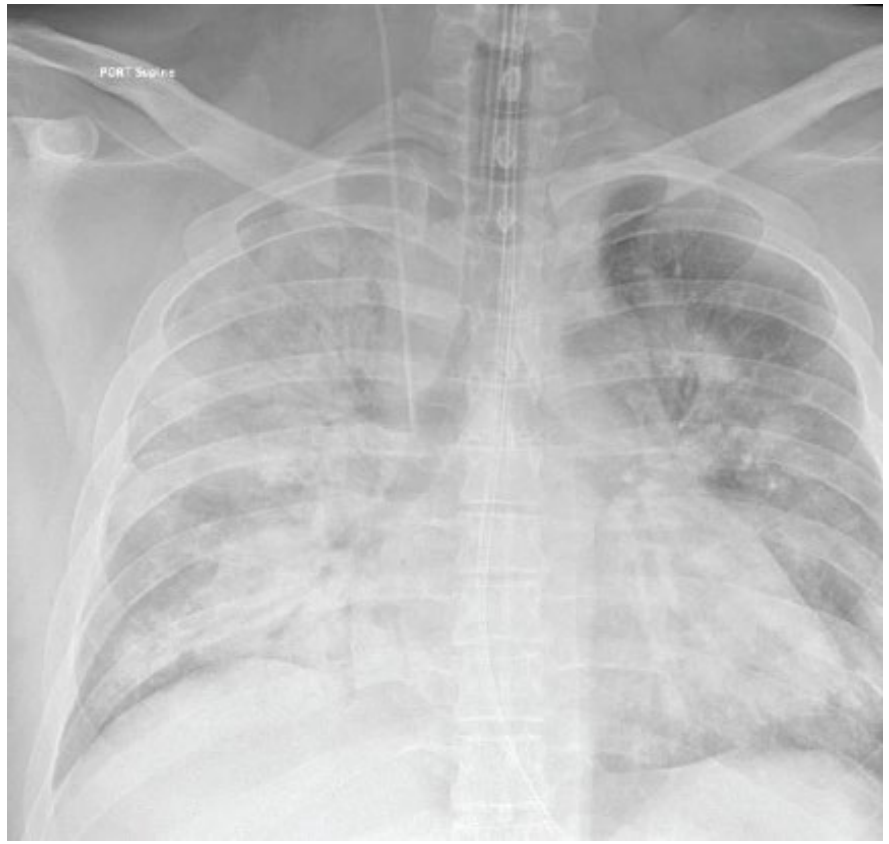


Lung Transplant Survival by Diagnosis (Conditional One Year)



Why do patients with PAH have worse survival than other diagnostic groups?





Diamond et al. Am J Respir Crit Care Med 2013

Is anything else going on?

How are donor lungs allocated?

- Between 2005-2023 donor lungs were allocated via the Lung Allocation Score
  - Calculated score by need based on clinical parameters
    - (e.g., FVC, age, 6MWD, oxygen requirements, CO2)
  - Many parameters not relevant to PAH

- Early reports indicated that patients with PAH had the highest risk of waitlist death and lowest likelihood of survival

Egan et al Am J Transplant 2006
Chen et al Am J Respir Crit Care Med 2009

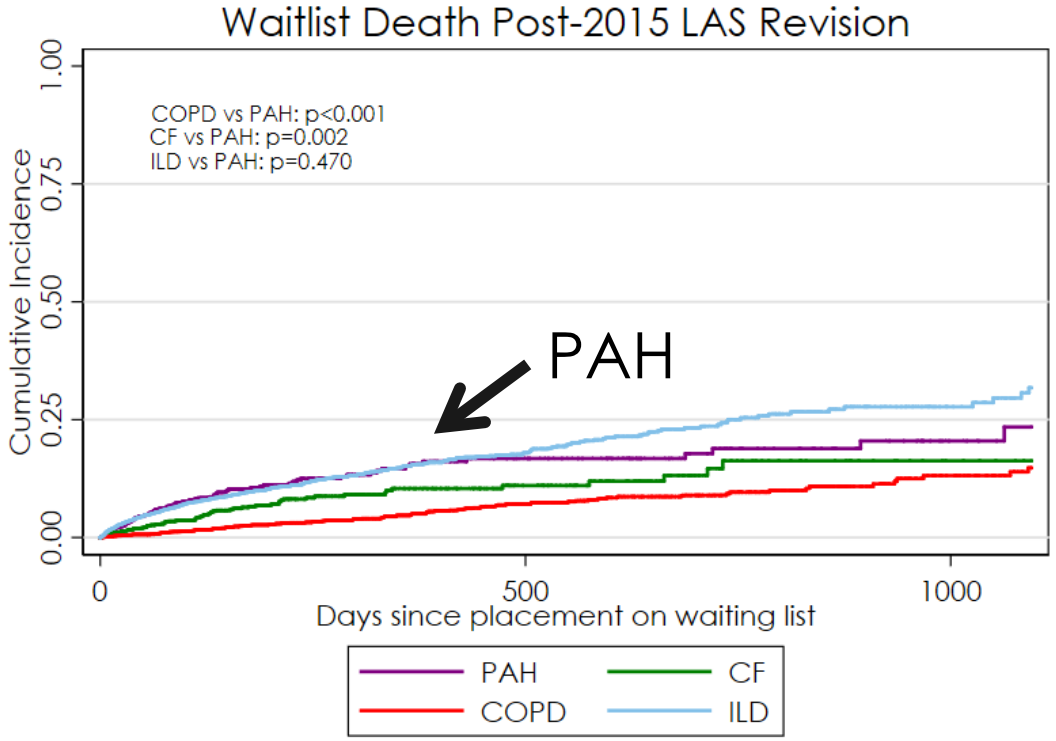
Components of the Lung Allocation Score

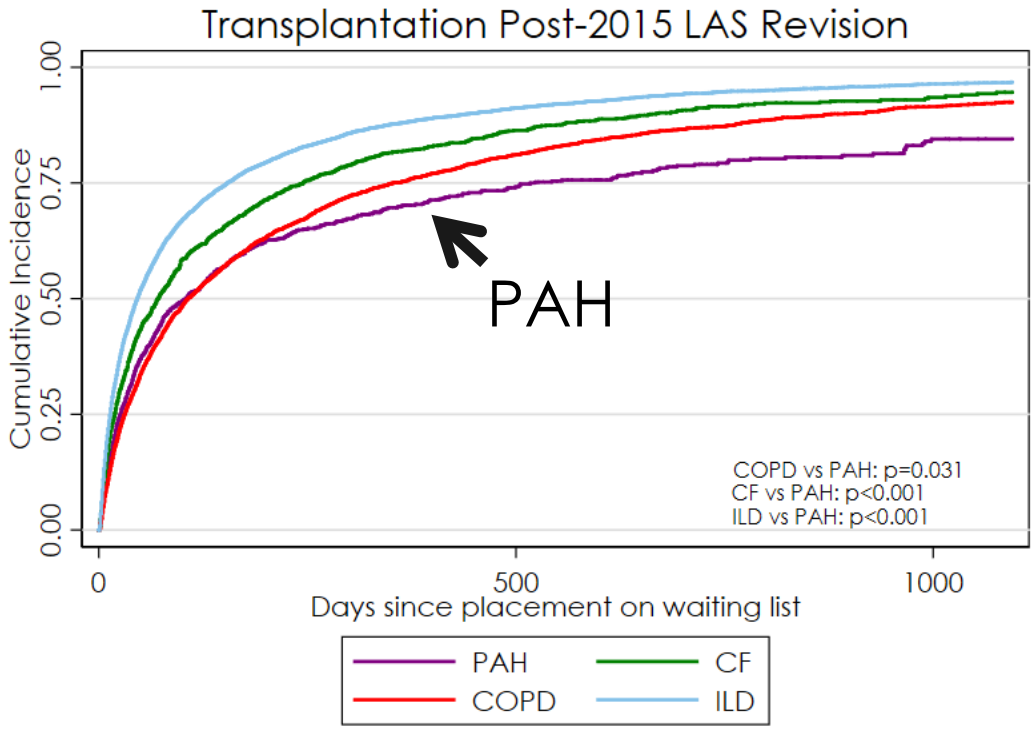
Table 5: Factors used to calculate LAS when the allocation system was implemented

Factors used to predict waiting list survival	Factors used to predict posttransplant survival
FVC (% predicted)	FVC (% predicted)
PA systolic pressure	PCW mean pressure ≥ 20 mmHg
O_2 required at rest (L/min)	Continuous mechanical ventilation
Age at offer	Age at transplant
Body mass index (BMI)	Serum creatinine (mg/dL)
NYHA functional status	NYHA functional status
Diagnosis	Diagnosis
Six-minute walk distance <150 feet	
Continuous mechanical ventilation	
Diabetes	

Source: SRTR.

Egan et al. Am J Transplant 2006





Kolaitis et al. Am J Respir Crit Care 2023

California Thoracic Society
ATS Chapter Serving California and Arizona

TABLE 2] Example of Lung Allocation Scores of Patients Listed for Various Diseases With Similar Allocation Priority

Variable	Patient 1	2	3	4	5	6
Diagnosis	PAH	PAH	COPD	IPF	Bronchiolitis obliterans	IPF
Age, y; sex	34; female	52; female	61; male	71; male	60; female	69; male
O_2 requirement, L/min	2 (at rest)	15 (at rest)	3 (at rest)	6 (at rest)	4 (at rest)	4 (at rest)
Other support	Dobutamine, 2 μg/kg/min	CPAP at night	BiPAP at night	None	None	None
PA pressure (mean), mm Hg	69/29 (48)	97/39 (60)	29/11 (19)	25/14 (21)	25/14 (20)	23/8 (14)
Cardiac output, L/min	3.01	3.95	4.33	4.58	3.90	5.0
Cardiac index, L/min/m^2	1.79	2.34	2.49	2.1	2.74	2.59
6MWD, ft	1,063	1,443	592	1,150	620	787
FVC (%), L	3.67 (87%)	2.45 (80%)	1.81 (41%)	3.30 (72%)	1.38 (49%)	2.09 (50%)
FEV_1 (%), L	3.22 (92%)	1.87 (76%)	0.48 (14%)	2.90 (86%)	0.44 (20%)	1.82 (59%)
CO_2, mm Hg	34	43	46	40	61	58
Creatinine, mg/dL	3.04	0.65	0.68	0.78	0.67	0.97
Total bilirubin, mg/dL	1.5	0.90	0.5	0.7	0.3	0.4
Clinical setting	Cardiac ICU	Cardiac ICU	Home	Home	Home	Home
Notable medications	Treprostinil, 109 ng/kg/min Sildenafil Macitentan	Treprostinil, 65 ng/kg/min Riociguat Macitentan	Albuterol Umeclidinium	Nintedanib	Fluticasone Salmeterol	Pirfenidone
LAS score	33.26	37.56	34.37	35.5	43.35	41.01

Sample of six patients listed for transplant at the University of California, San Francisco with similar range of allocation scores. All patients were listed after the September 2021 update to the LAS. For reference, on December 23, 2022, the iteration of the LAS was as follows: an LAS score of 33.9 represents the 25th percentile, a score of 36.8 represents the 50th percentile, a score of 41 represents the 75th percentile, a score of 49 represents the 90th percentile, a score of 56.5 represents the 95th percentile, and a score of 92.8 represents the 99th percentile. 6MWD = 6-min walk distance; IPF = idiopathic pulmonary fibrosis; LAS = lung allocation score; PA = pulmonary artery; PAH = pulmonary arterial hypertension.

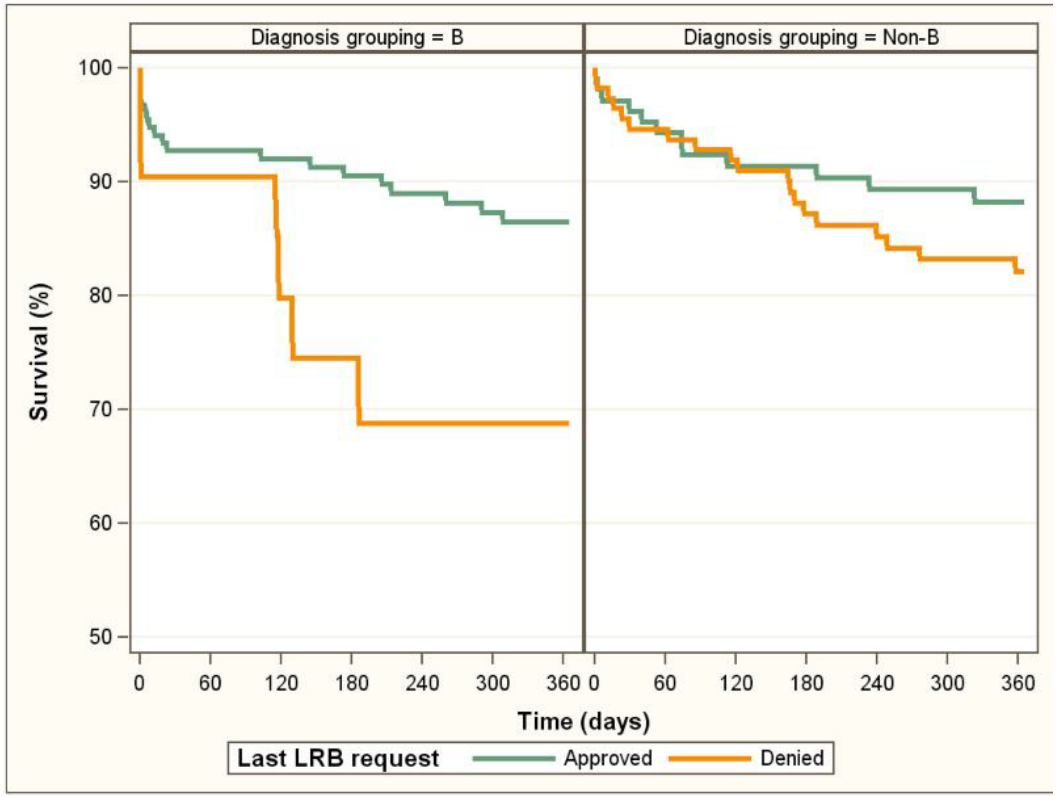
Kolaitis et al. Chest 2024

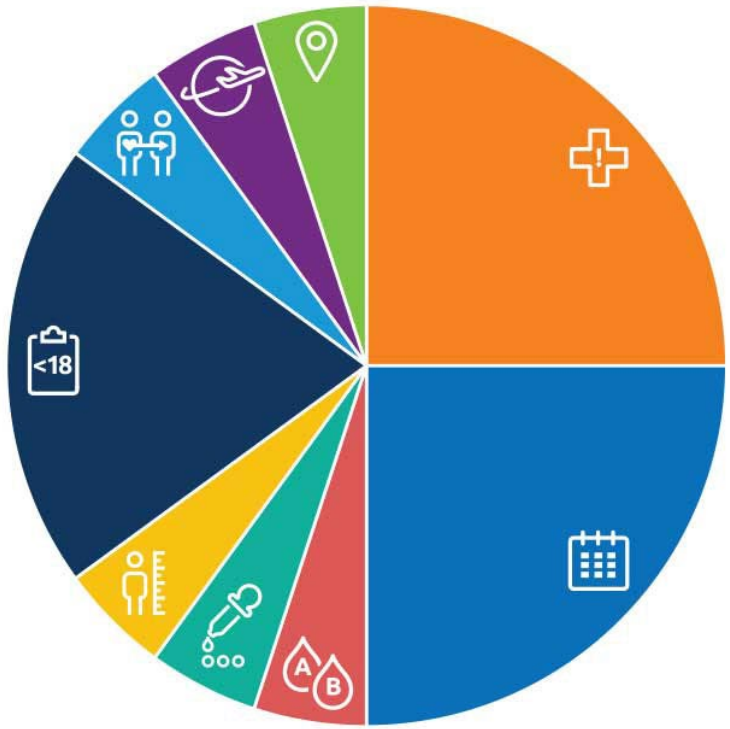
Can't you write an exception?

2006

Automatic Exception (90th percentile)

Deteriorating with RAP >15 mmHg or CI <1.8 L/min/m2



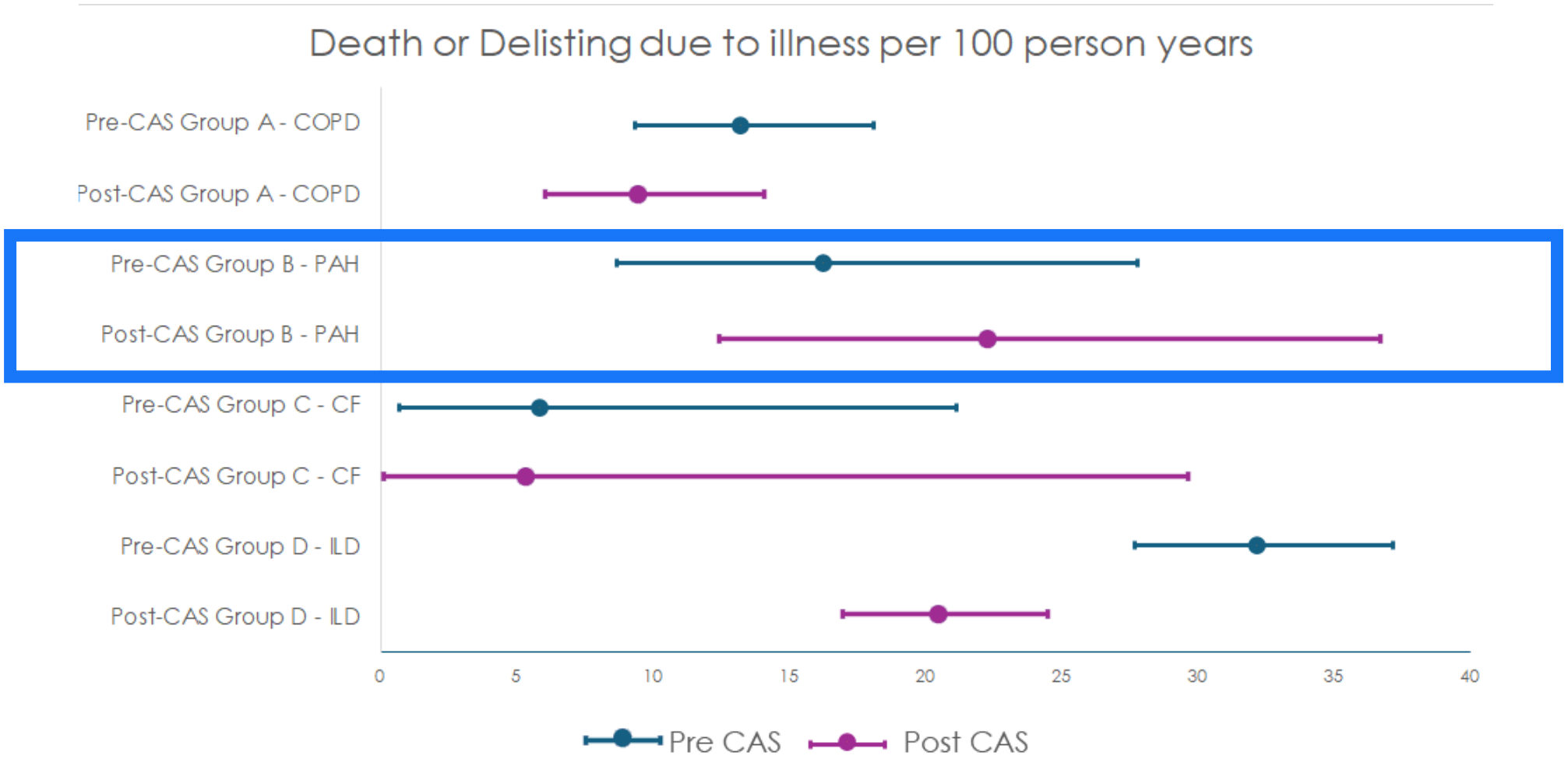


- candidate medical urgency
- likely survival > five years
- blood type match
- immune system matching (CPRA)
- height match
- listed younger than 18
- prior living donor
- travel efficiency
- proximity efficiency

What about now?

CAS Scoring	Maximum Points
Candidate Medical Urgency	25
Likely Survival >5 years	25
Blood Type Match	5
Immune System Match	5
Height Match	5
Listed Younger Than 18	20
Prior Living Donor	5
CAS Subscore	*90*
Travel Efficiency	5
Proximity Efficiency	5
CAS Total Score	100

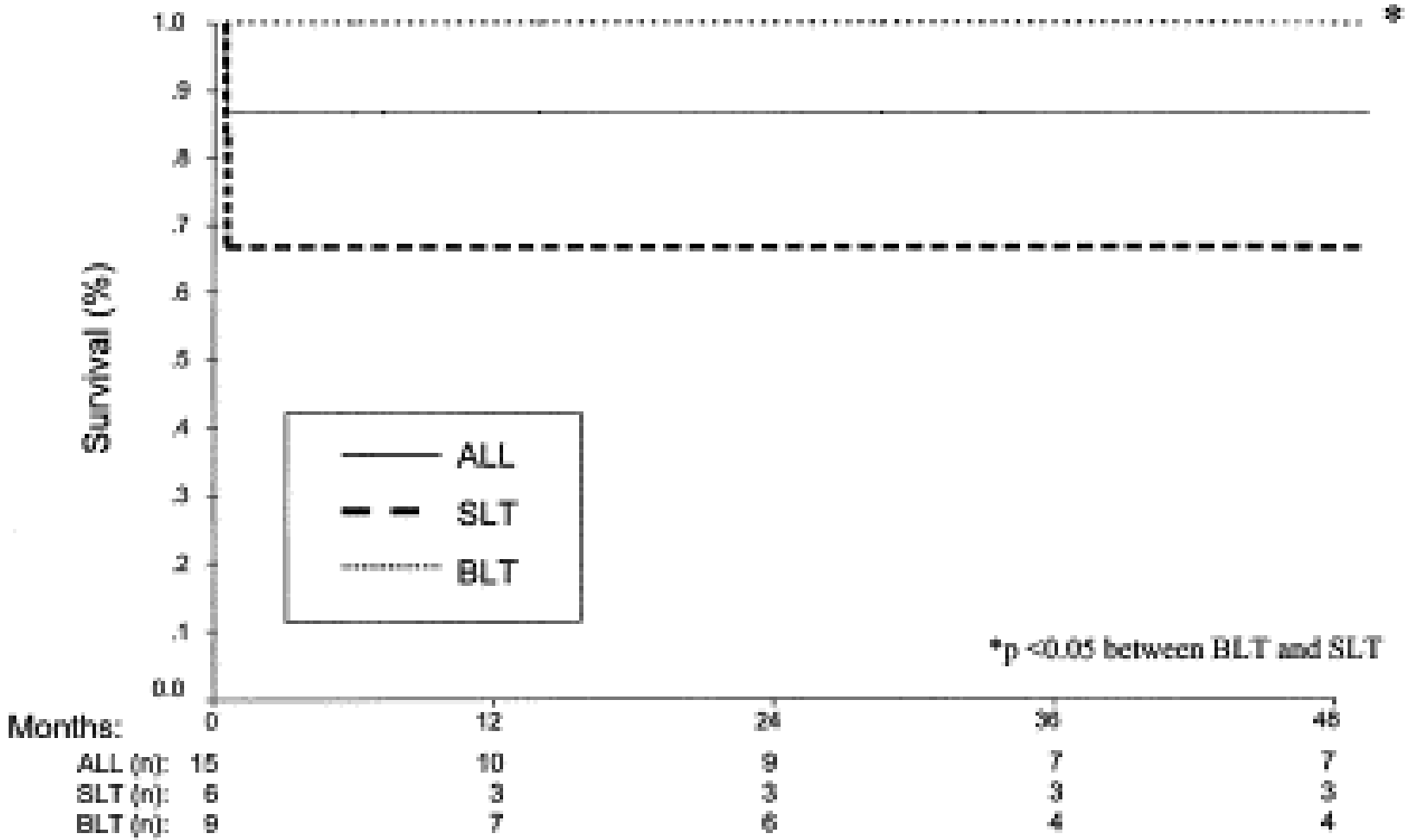
Points change at time of match run based on location


Death or Delisting due to illness per 100 person years
Pre-CAS Group A - COPD
Post-CAS Group A - COPD
Pre-CAS Group B - PAH
Post-CAS Group B - PAH
Pre-CAS Group C - CF
Post-CAS Group C - CF
Pre-CAS Group D - ILD
Post-CAS Group D - ILD
0
5
10
15
20
25
30
35
40
Pre CAS
Post CAS

Do they need two lungs?

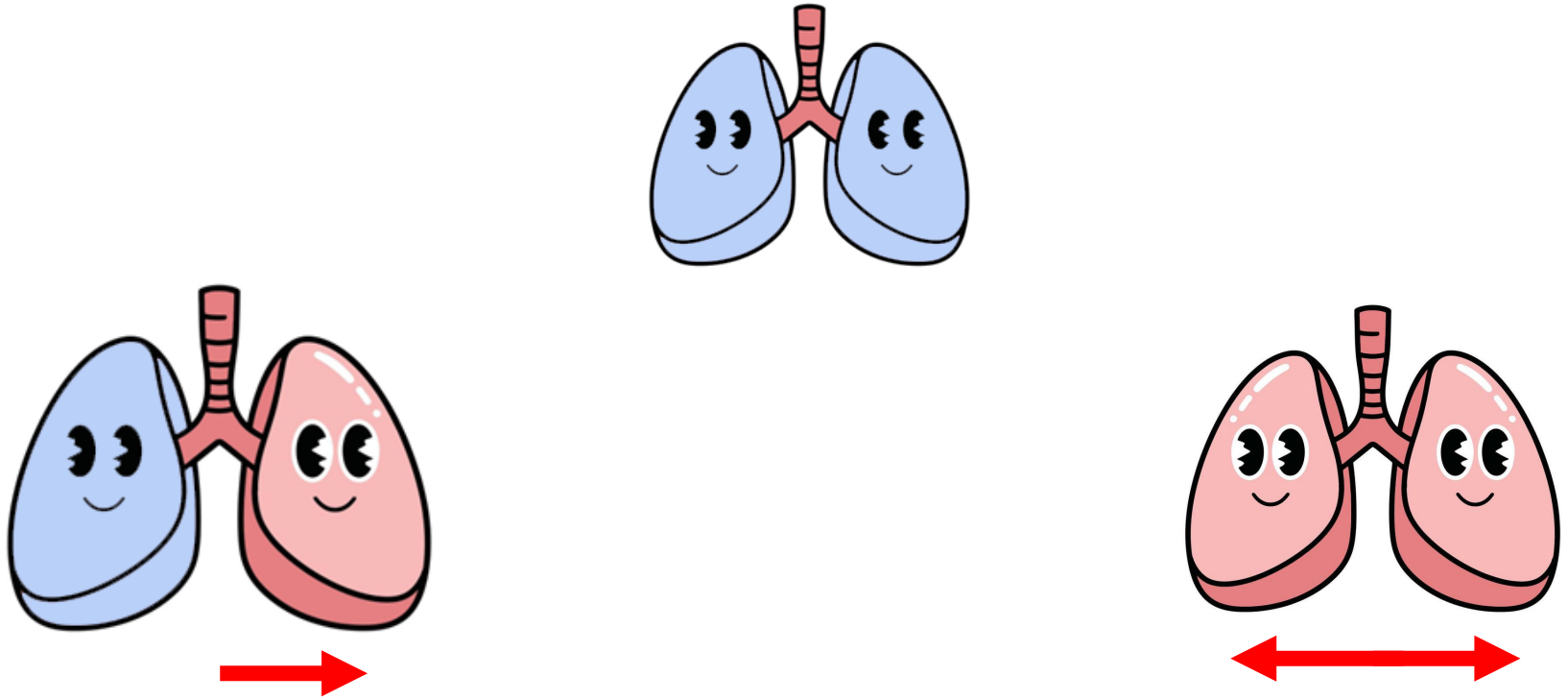
Maybe if we can do one lung they will have more access

Type of organ transplant: Single vs Bilateral

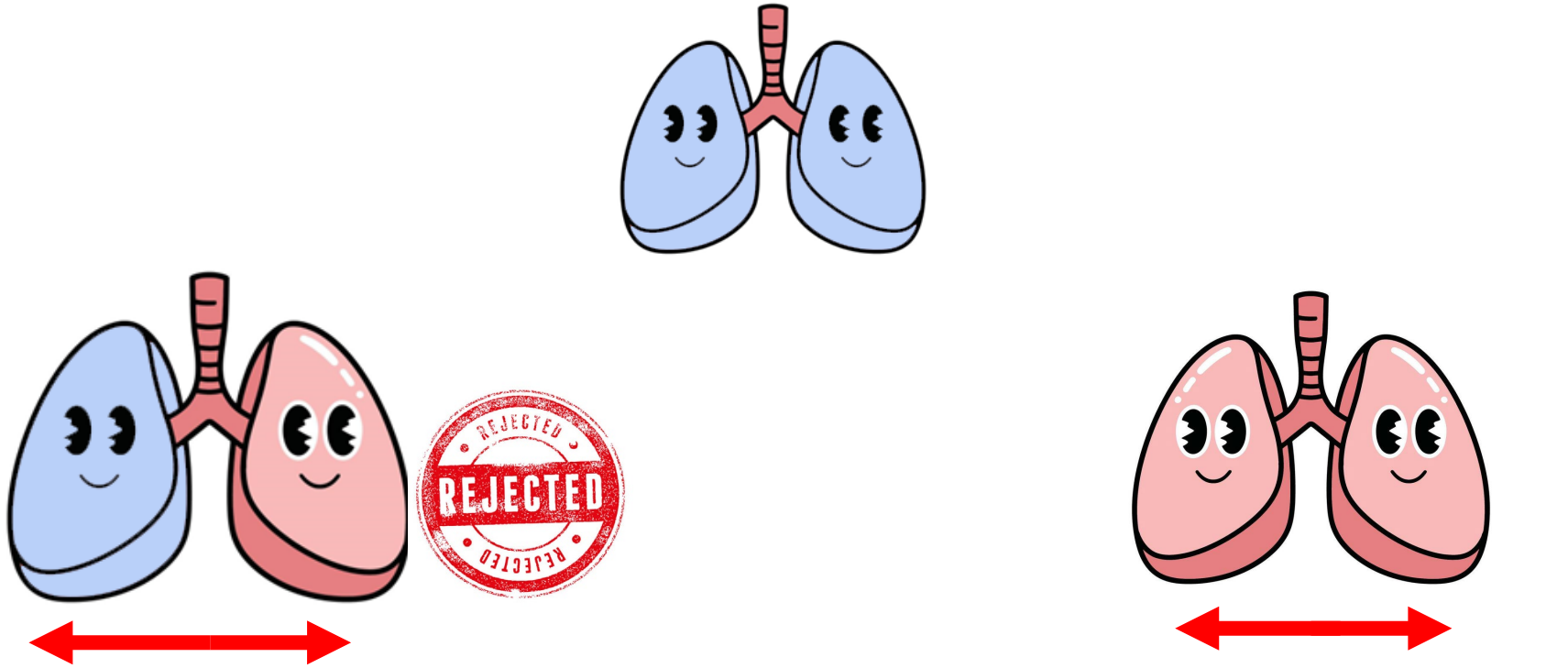


Conte et al Ann Thorac Surg 2001

Issues with single lung transplant

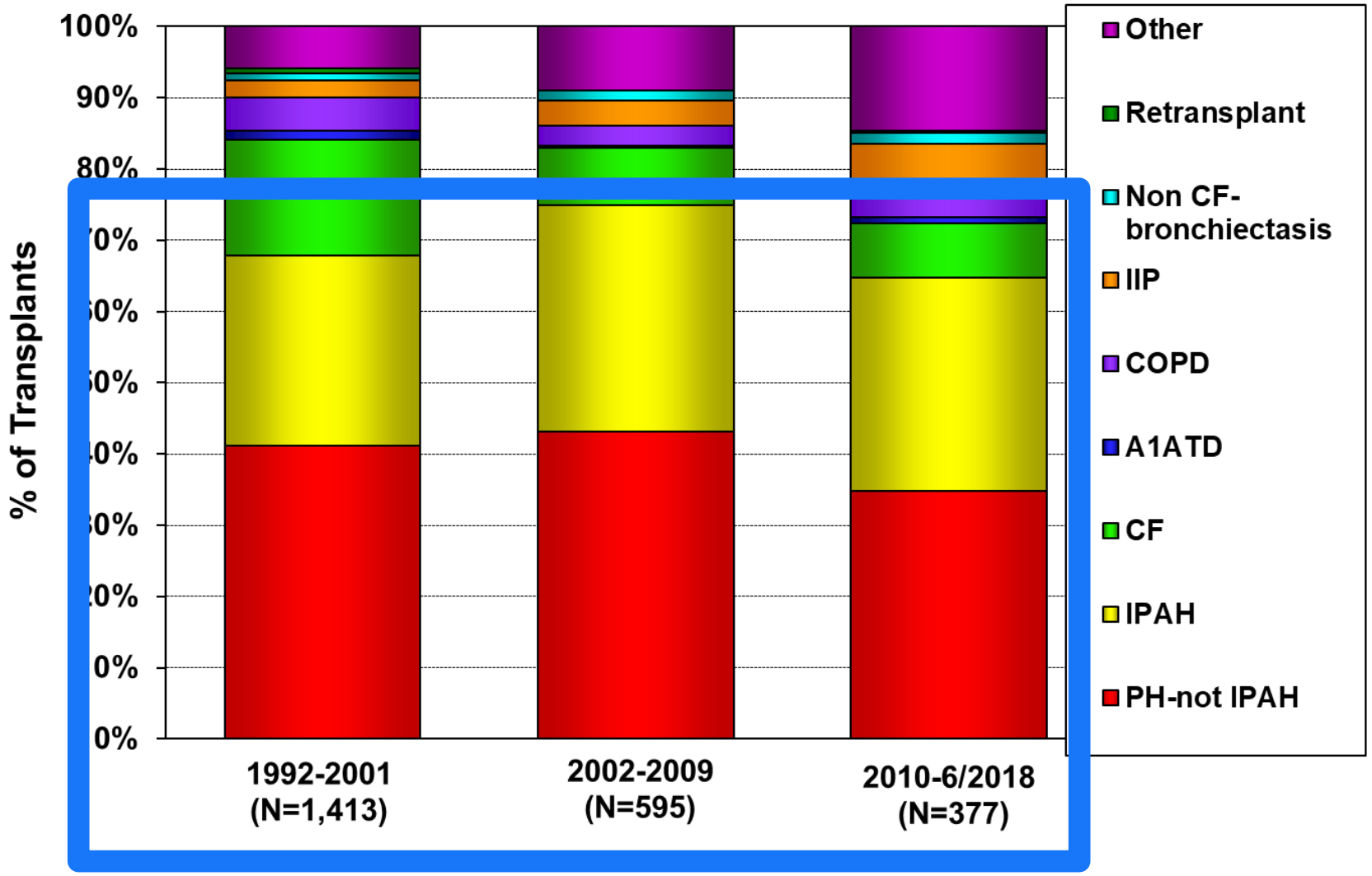


Issues with single lung transplant

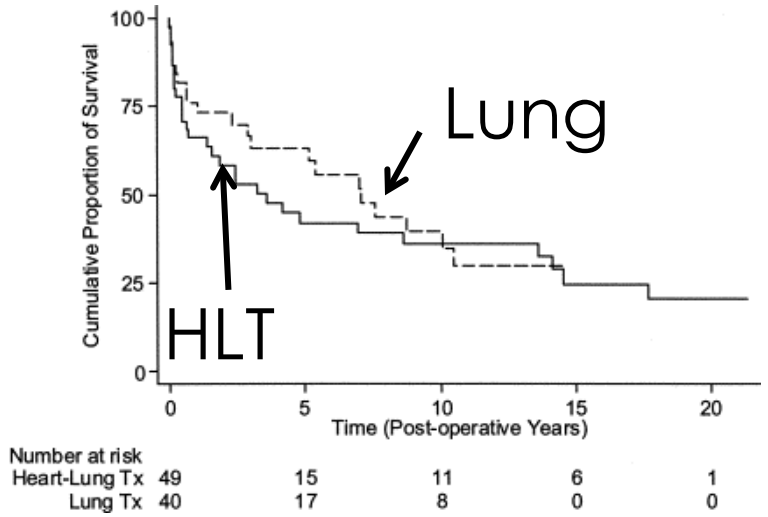


What about heart-lung transplant?

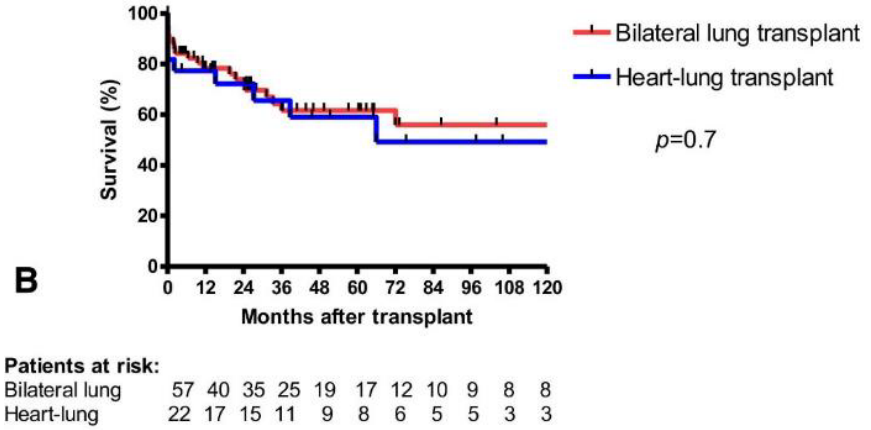
Combined Heart-Lung Transplantation



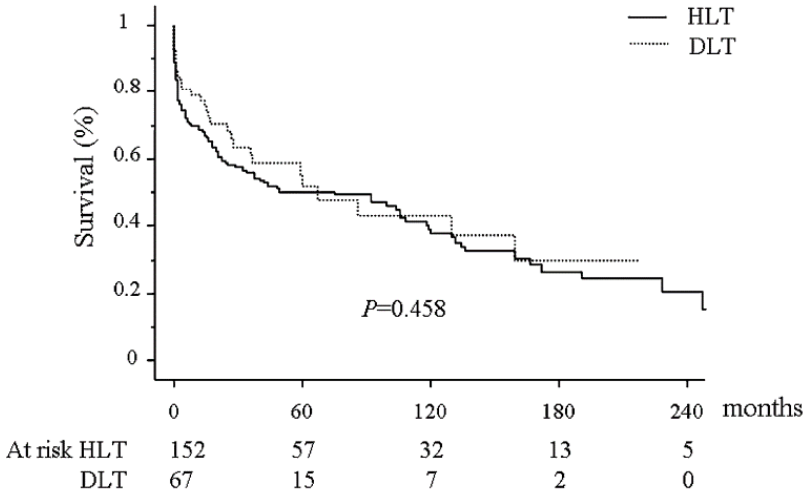
Combined Heart-Lung Transplantation



59 PAH patients undergoing transplant



79 PAH patients undergoing transplant



219 PAH patients undergoing transplant

Toyoda et al. Ann Thorac Surg. 2008
Fadel et al. Eur J Cardiothorac Surg. 2010
De Perrot et al. J Thorac Cardiovasc Surg. 2012

Interim Summary

- Lung Transplantation extends survival and improves quality of life
- Refer early
- Patients with PAH are at increased risk of primary graft dysfunction
- Patients with PAH are disadvantaged in organ allocation
- Bilateral lung transplant is the procedure of choice

PVRI Delphi on Lung Transplant for PAH

Lung Transplant in PAH DELPHI Process

Pre-survey

Open ended questions developed by the IDDI Lung Transplant Workstream experts to identify gaps.

Survey #1

Open ended questions sent to the IDDI Lung Transplant Workstream group for answers.

Answers to the Open-ended questions analyzed by DELPHI leads and made into survey statements.

20/29 Responded

Survey #2

Survey Statements ranked in Likert scale format by each expert of the Lung Transplant Workstream

28/29 Responded

Survey #3

Same as survey 2, each member will re-review their statements and compare their Likert scale ranking according to overall ranking from survey #2.

29/29 Responded

Kolaitis et al. *Under Review*

California Thoracic Society
ATS Chapter Serving California and Arizona

Discussions, Referral, and Listing

Discussions

At Diagnosis:
- ESC/ERS 3 Stratum **High-Risk**
- REVEAL 2.0 ≥9 (**High Risk**)
- Diagnosis of **PVOD/PCH**

At Follow Up:
- ESC/ERS 3 Stratum High-Risk
- ESC/ERS 4 Stratum **Intermediate-High Risk**
- REVEAL 2.0 ≥7 (**Intermediate Risk**)

At Any Time:
- Deteriorating
- **Starting Triple non-Parenteral Therapy**
- Starting Parenteral Therapy
- Hemoptysis
- Renal Insufficiency
- Hepatic Congestion
- Hypoxemia
- **Pregnant or Considering Pregnancy**

Refer

Despite Appropriate Therapy:
- ESC/ERS 3 Stratum High-Risk
- REVEAL 2.0 ≥8 (**Intermediate-Risk**)
- ESC/ERS 4 Strata **Intermediate-High Risk**
- RV Dysfunction
- **Progression of Disease**
- **PAH Hospitalization**
- Hemoptysis
- WHO Functional Class III-IV
- **More than a trivial pericardial effusion**
- **Cardiac index <2 L/min/m2**
- Renal dysfunction
- Hepatic Dysfunction

At Any Time:
- Require Parenteral Therapy
- Suspected PVOD/PCH
- Heritable PAH
- **Large/Progressive PA Aneurysm**
- Concomitant significant Left Heart Dz
- Atrial Septostomy
- Coronary Compression

List

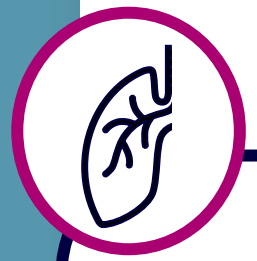
Despite Maximal Medical Therapy:
- ESC/ERS 3 Stratum **High-Risk**
- REVEAL 2.0 ≥9 (**High-Risk**)
- ESC/ERS 4 Stratum **Intermediate-High Risk**
- Severe RV Dilation/Dysfunction
- Progressive but not end-stage renal disease attributable to PAH
- Progressive but not end-stage hepatic disease attributable to PAH
- Hospitalization for right heart failure
- Life Threatening Hemoptysis
- Progressive Hypoxemia

At Any Time:
- Suspected PVOD/PCH with deterioration
- **On ECMO life support**
- On intravenous inotropes
- On vasopressors

Kolaitis et al. *Under Review*

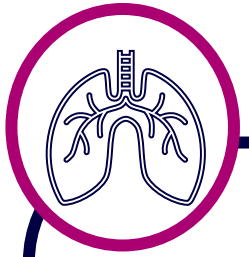
California Thoracic Society
ATS Chapter Serving California and Arizona

Type of Organ Transplant



Single Lung

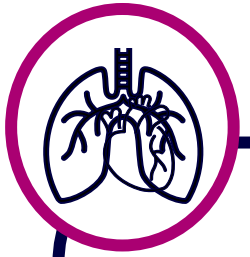
Not Recommended



Bilateral Lung

Right Ventricular Dysfunction:
- **No degree of Right Ventricular Dysfunction precludes lung transplantation alone**

Congenital Heart Disease/Septostomy:
- PAH with simple ASD amenable to surgical repair
- PAH with septostomy amenable to surgical repair
- PAH with open PDA amenable to surgical repair



Heart-Lung

Congenital Heart Disease:
- **Complex Congenital Heart Disease not amenable to surgical repair**

Other Left Heart Disease:
- **Concomitant left heart disease**
- **Coronary disease not amenable to revascularization**

Kolaitis et al. *Under Review*

California Thoracic Society
ATS Chapter Serving California and Arizona

Bridging, Intra-Operative, and Post-Operative

Bridging

When to use ECMO:
- **Refractory Right Heart Failure**
- Refractory Hypoxemia
- **Prophylactic cannulation for deterioration**

Type of Cannulation Strategy:
- **Peripheral VA ECMO**
- PA to LA Pumpless Novalung
- PA to LA Cannulation
- Strategy depends on patient characteristics
- Avoid RA to PA catheter

Non-ECMO Bridging:
- **Reverse Potts Shunt in Pediatric Patients**
- Long Term Continuous Ionotropic Support
- Weigh benefit of interventional procedures against increased surgical risk

Intra-operative

Specifics of Transplant Surgery in PAH:
- **Stop parenteral prostacyclin in surgery at initiation of VA ECMO or cardiopulmonary bypass**
- Holding wires placed before induction
- Surgeon in operating room at induction
- Avoid systemic hypotension
- **Consider pre-emptive awake peripheral VA ECMO in severe RV dysfunction**
- **Prefer VA ECMO over cardiopulmonary bypass**
- **Prefer central VA ECMO over peripheral VA ECMO in surgery**
- Avoid milrinone
- Norepinephrine preferred over epinephrine
- Monitoring with arterial line and PA catheter
- Monitoring with transesophageal echo

Post-Operative

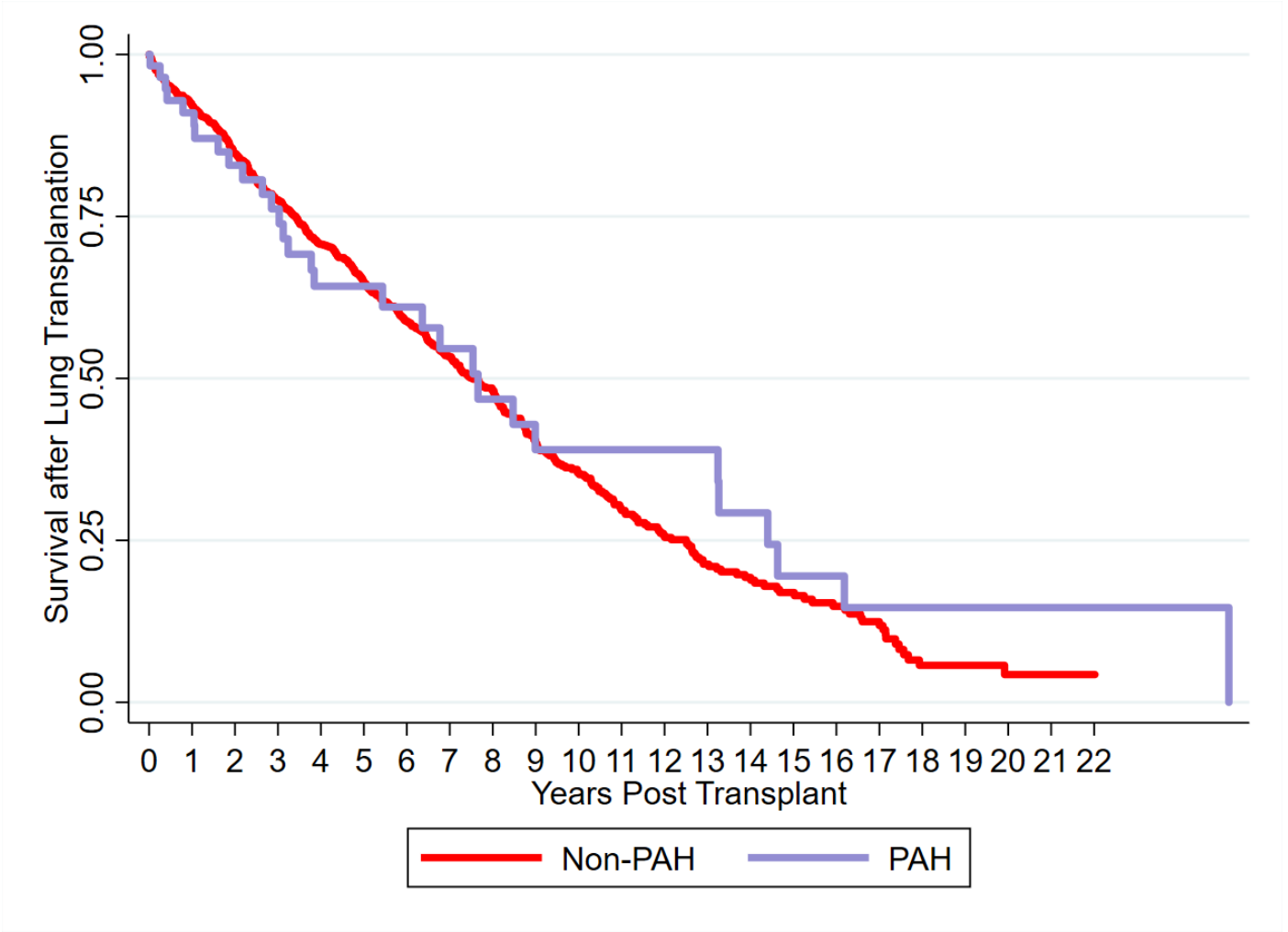
Post-Operative VA ECMO:
- **Guide usage by hemodynamic response and findings on transesophageal echo**

Post-Operative Monitoring:
- Meticulous monitoring of intra-vascular volume
- Avoid Hypervolemia
- Norepinephrine preferred over epinephrine
- Hemodynamic monitoring with a PA catheter for 48 hours
- Hemodynamic monitoring with an arterial line for 48 hours
- Renal function monitoring with a foley catheter for 72 hours

Kolaitis et al. *Under Review*

California Thoracic Society
ATS Chapter Serving California and Arizona

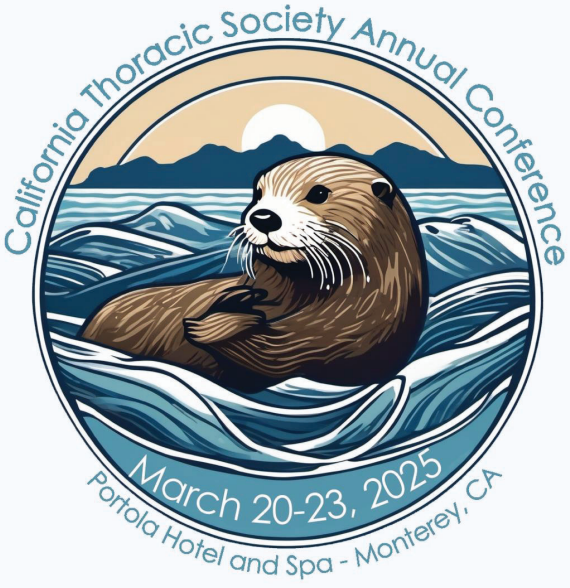
Can good outcomes be achieved?



Conclusions

Conclusions

- ECMO is an option to support patients with progressive RV failure from PAH
- ECMO is typically used as a bridge to recovery or bridge to transplant
- Veno-arterial ECMO is typically necessary
- Lung Transplantation is effective to improve survival and quality of life
- Patients with PAH at an increased risk of death perioperatively
- Patients with PAH have inequitable access to transplantation
- PVRI has a Delphi in review that addresses the complexities of transplant for PAH



Understanding Pediatric Pulmonary Hypertension

Rachel K. Hopper, MD

Stanford University

Disclosures

I have the following relationships with ACCME defined ineligible companies:

None

I **WILL** discuss off-label use and/or investigational use of any drugs or devices.

Introduction

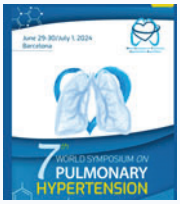
- Despite many similarities, some important differences between adult and pediatric-onset PH
- Many similarities in PAH pathophysiology and presentation
- Children often with higher clinical severity, better RV compensation
- Profound contribution from abnormal lung and/or cardiac development, genetics
- Better response to therapies and/or ability to improve with lung growth

"Children are not just little adults"

But some adults may be big children!

Agarwal et al. *Eur Respir J.* 2024
Barst et al. *Eur Respir J. 2011*

WSPH 2024 Classification

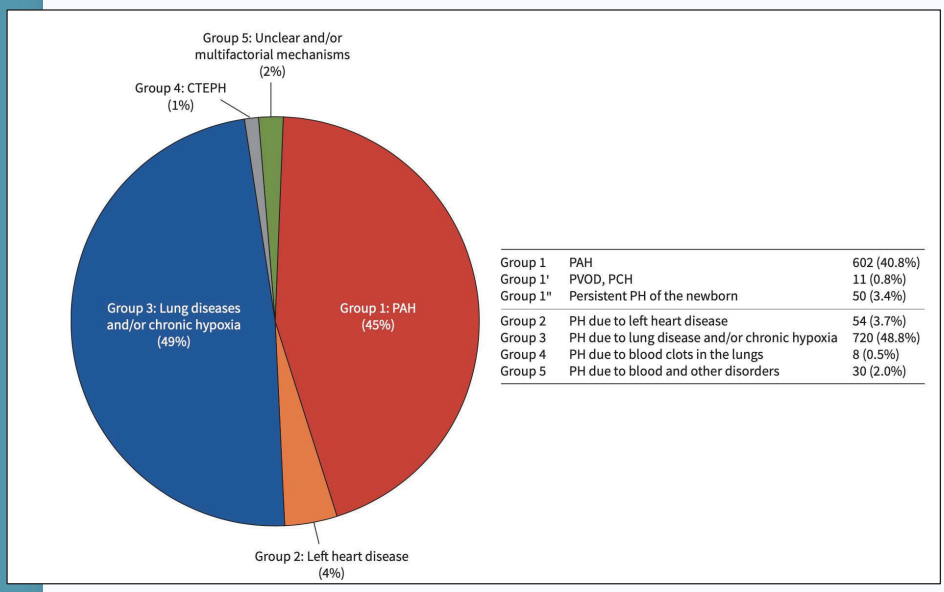


Pulmonary Hypertension (WSPH Classification)

Group 1 Pulmonary Arterial	**Group 2** Left Heart	**Group 3** Lung Disease	**Group 4** CTEPH	**Group 5** Other
Idiopathic **Heritable** Drug/toxin *Associated with:* Connective tissue **Congenital heart** Portal HTN Schistosomiasis HIV PCH/PVOD **PPHN syndrome**	HFpEF HFrEF Cardiomyopathy Valvular **Congenital**	COPD ILD Combined fibrosis & emphysema Other/mixed Restrictive Hypoxia **Developmental**	Thromboembolic PA obstruction	Heme Metabolic Tumor **Complex** **CHD** Other

• Kovacs et al. *Eur Resp J* 2024

PH in pediatrics: PPHNet Registry



Group 1	PAH	602 (40.8%)
Group 1'	PVOD, PCH	11 (0.8%)
Group 1"	Persistent PH of the newborn	50 (3.4%)
Group 2	PH due to left heart disease	54 (3.7%)
Group 3	PH due to lung disease and/or chronic hypoxia	720 (48.8%)
Group 4	PH due to blood clots in the lungs	8 (0.5%)
Group 5	PH due to blood and other disorders	30 (2.0%)

In adults:

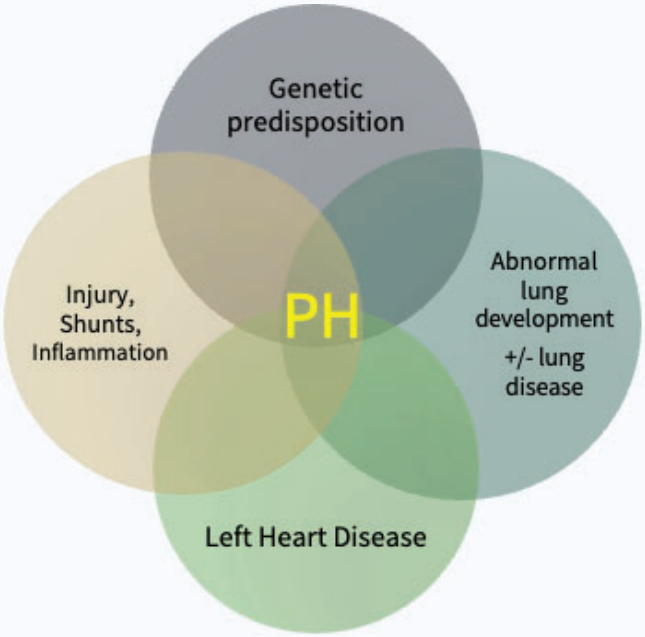
- Age >65 years
- Group 2 (left heart disease)
- Group 3 (lung disease, especially COPD)
- Females (esp. PAH)

In children:

- Group 3 (mostly BPD, CDH)
- Group 1 (CHD, idiopathic, heritable)
- Infant predominance

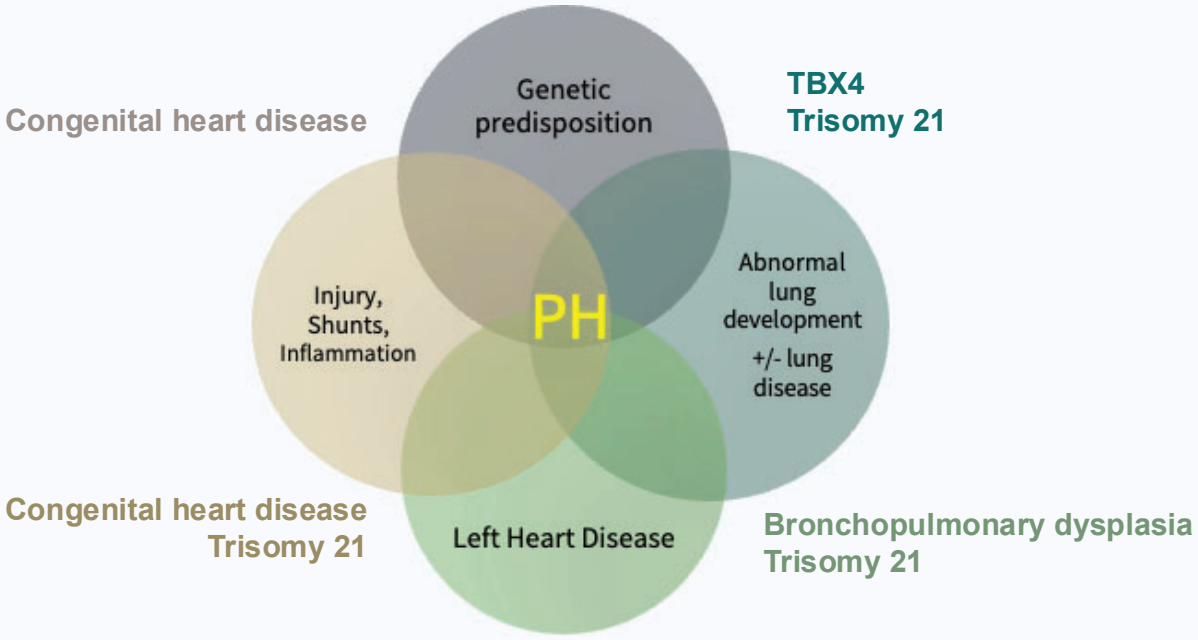
Abman et al. *Eur Resp J*, 2021
Humbert et al. *Eur Heart J*, 2022

The reality in children



• del Cerro MJ et al. *Pulm Circ*, 2011

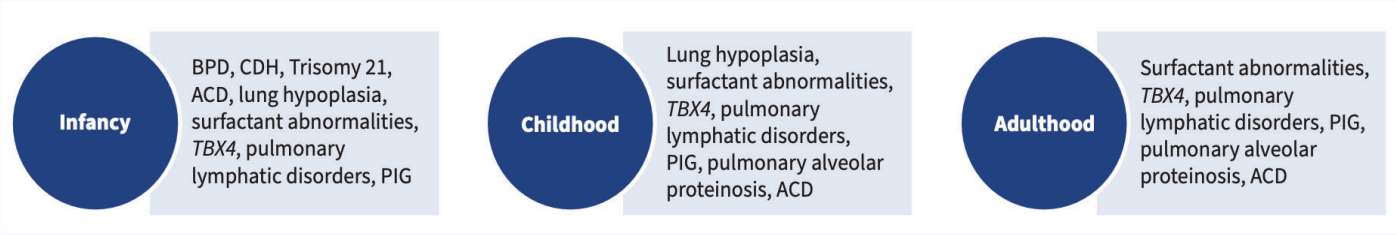
The reality in children



• del Cerro MJ et al. *Pulm Circ*, 2011

Developmental lung diseases

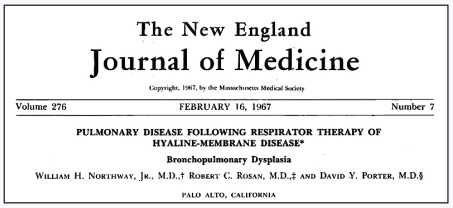
- While more common in infancy, can present at any age



- ”Atypical” or late presentation increasingly recognized (alveolar capillary dysplasia (ACD))
- Increasing survival of infants and children with these diseases into adulthood

• Varghese et al. *Eur Respir. J. 2024*

Bronchopulmonary dysplasia (BPD)



The New England
Journal of Medicine

Copyright, 1967, by the Massachusetts Medical Society

Volume 276 FEBRUARY 16, 1967 Number 7

PULMONARY DISEASE FOLLOWING RESPIRATOR THERAPY OF HYALINE-MEMBRANE DISEASE*

Bronchopulmonary Dysplasia

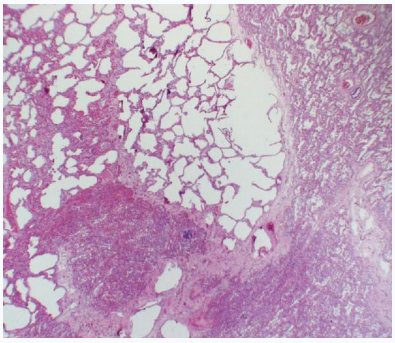
WILLIAM H. NORTHWAY, JR., M.D.,† ROBERT C. ROSAN, M.D.,‡ AND DAVID Y. PORTER, M.D.§

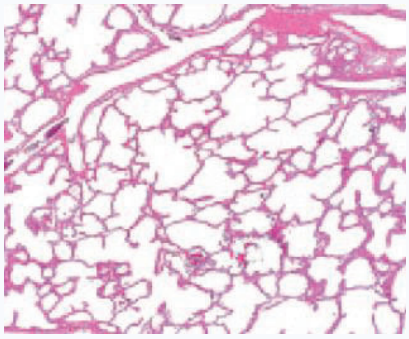
PALO ALTO, CALIFORNIA

Pre-Surfactant
"Old BPD"
(1967-1980s)

Post-Surfactant
"New BPD"
(>1990)

Lung injury
Atelectasis
Hyperinflation



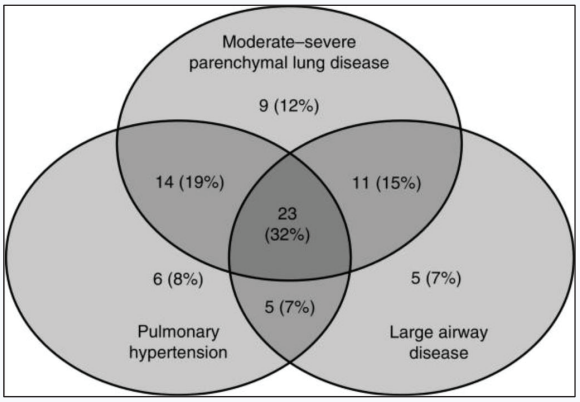


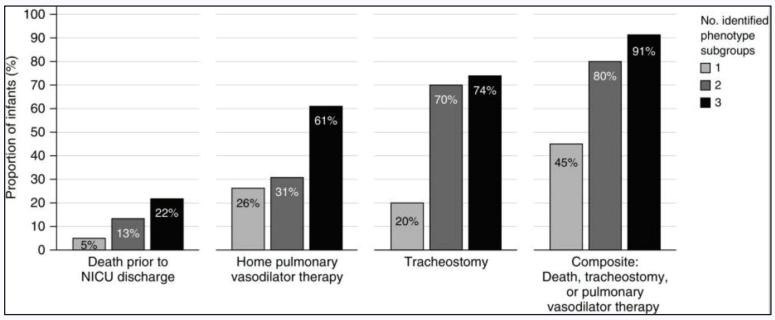
Impaired development
Alveolar simplification
Vascular hypoplasia

Slide courtesy Dr. Michael Tracy

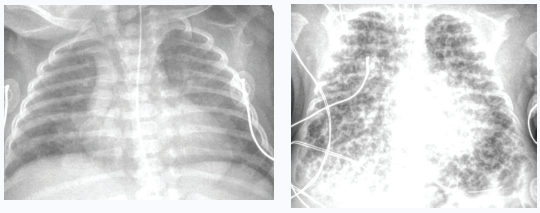
California Thoracic Society
ATS Chapter Serving California and Arizona

BPD phenotypes





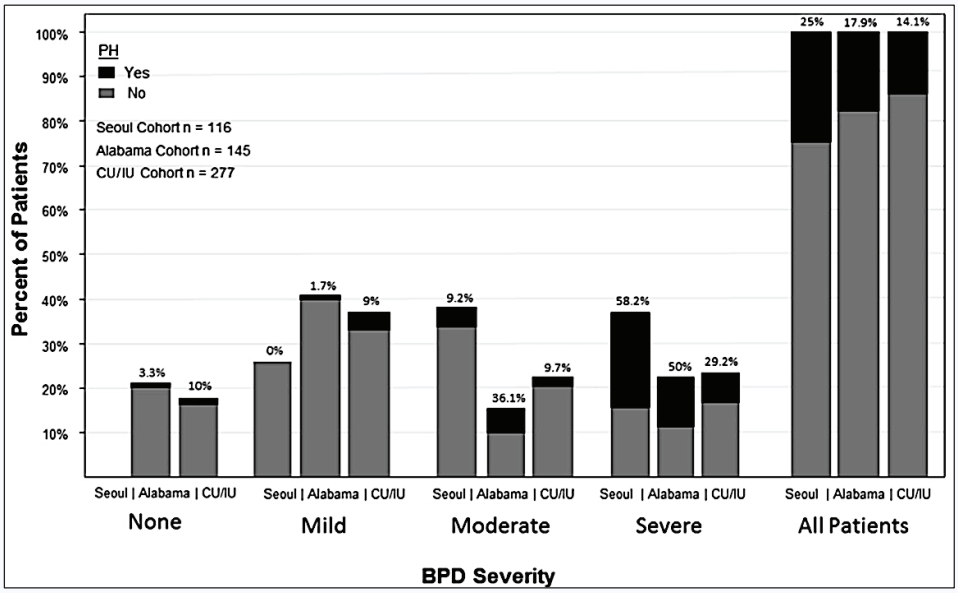
24-week GA, severe BPD
CXR at 36 weeks



PH No PH

• Wu et al *AJRCCM* 2020

PH risk: beyond BPD severity



Seoul: <32w BPD, echo after 2 mo.

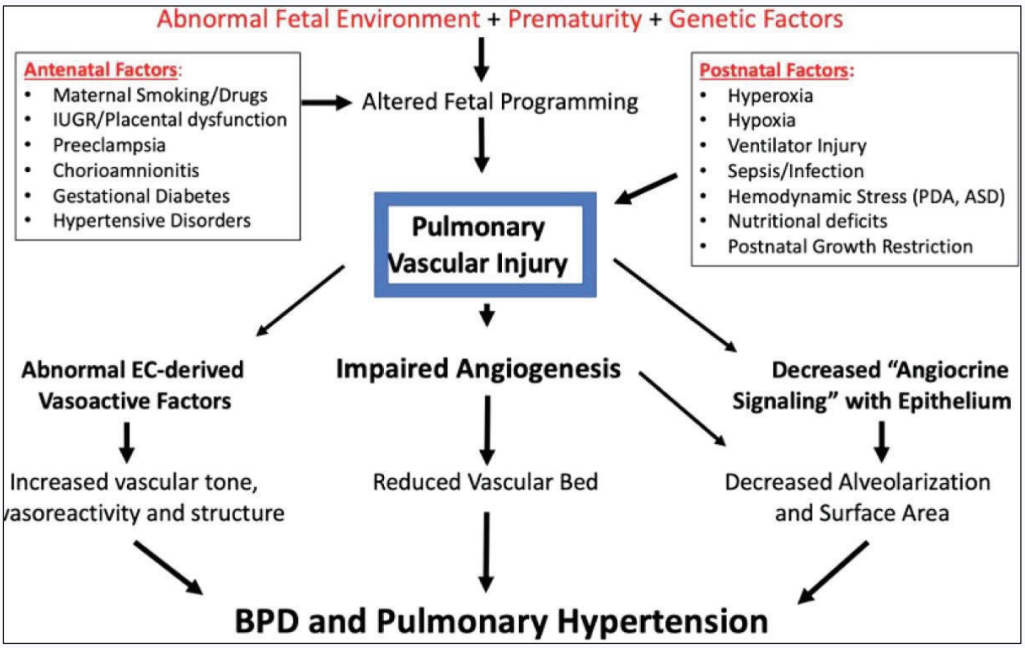
Alabama:<1000g, echo at 4-6w of age, serial

Colorado/Indiana: <34w, BW 500-1250g, echo at 7d, 36w

- Mourani and Abman, *Clin Perinatol*, 2015

California Thoracic Society
ATS Chapter Serving California and Arizona

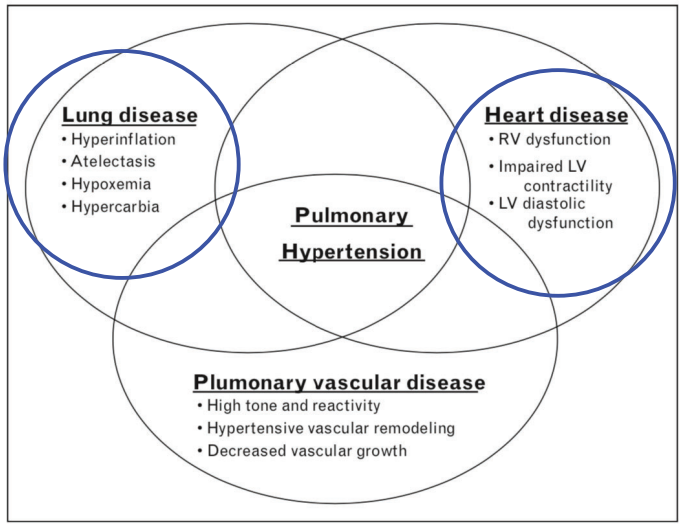
Determinants of PH



• Mirza et al. *J Pediatr*. 2023

Physiologic contributors to PH in BPD

Group 3



Group 2

Group 1

Important treatment implications

• Mourani and Abman. *Curr Opin Pediatr* 2013.

Treatment and outcomes

- Routine echo screening improves early detection
- Addressing modifiable risk factors is important
- Pulmonary vasodilators often used but limited data (off-label)
- Improves/resolves with growth but some abnormalities may persist

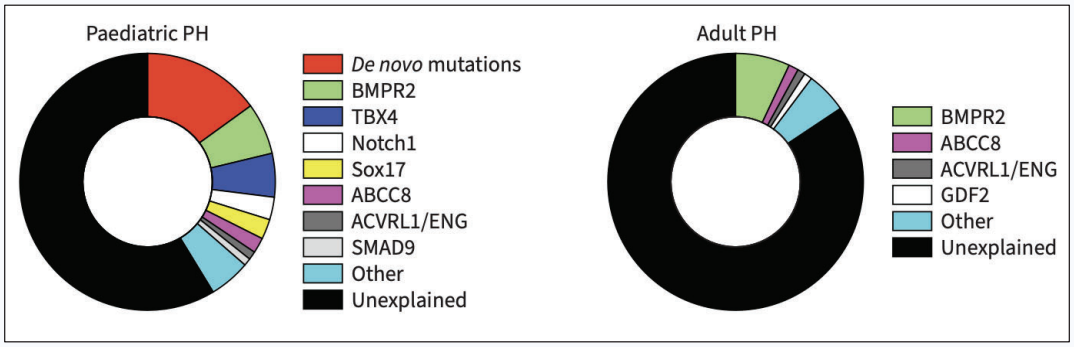
Sildenafil in BPD-PH: meta-analysis

Study	Mean follow-up duration (months)	Mortality rate (%/year)	Improvement in the estimate of the PAP (%)	Improvement in respiratory scores (%)
Mourani et al.[30]	7.9 ± 7.6	25.2	NR	NR
Nyp et al.[31]	12.0 ± 2.9	19.0	70.0	14.3*†,‡
Tan et al.[32]	9.0 ± 3.0	36.2	66.7	0.0§†
Trottier-Boucher et al.[33]	5.6 ± 2.4	74.3	71.4	34.8§†‡
Kadmon et al.[29]	24.0 ± 15.6	2.9	NR	NR
Pooled effect (95% CI)	**11.2 ± 7.5**	**27.6 (12.6–60.4)****	**69.3 (56.8–81.8)††**	**15.0 (0.0–30.4)****
I^2		80.6	0.0	58.2
X^2 *P* value		<0.001	0.9	0.05

• Van der Graaf, *Pulm Circ.* 2019

Genetics of pediatric vs adult onset PH

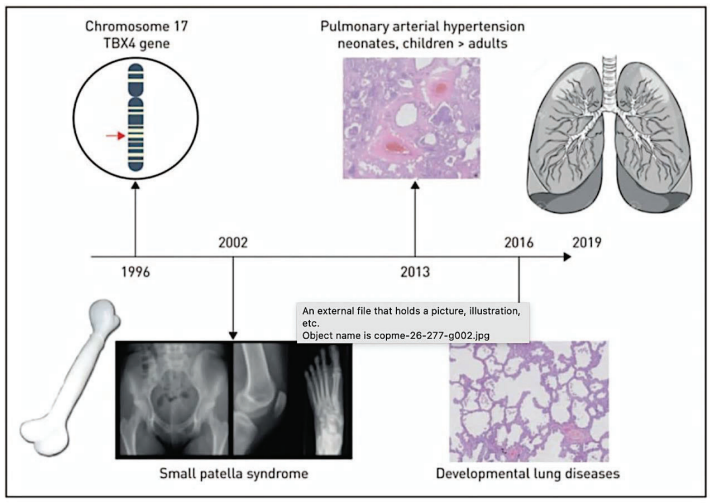
- Genetic etiology identified in ~35-40% pediatric PAH, 10-15% adult PAH
- Testing more common in pediatrics, implications for family members
- Highlights need for increased support for genetic testing/counseling in all PAH patients



- Zhu et al. *Circ Genom Precis Med*. 2018
- Agarwal et al. *Eur Respir J*. 2024

TBX4 (T-box transcription factor 4)

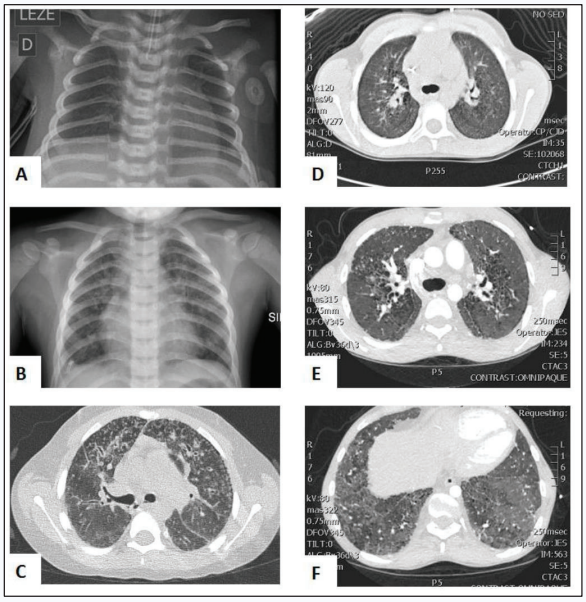
- Regulates limb development, lung morphogenesis
- Majority of patients have some skeletal abnormality (SPS)
- Spectrum of severity and phenotype
- Most commonly diagnosed in infancy, but adult-onset described

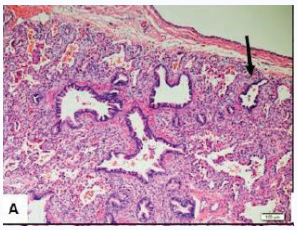


• Haarman et al. *Curr Opin Pulm Med.* 2020

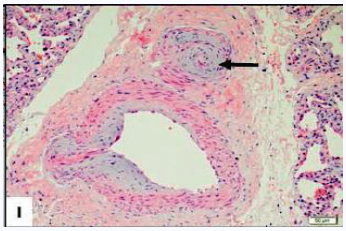
TBX4 clinical phenotypes

- Spectrum of airway, parenchymal lung disease and vascular remodeling

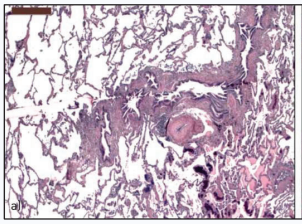




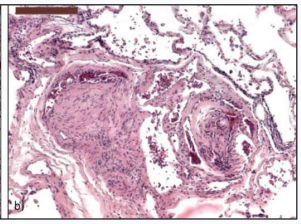
Underdeveloped respiratory lobules



Vascular remodeling



Occluded small PA



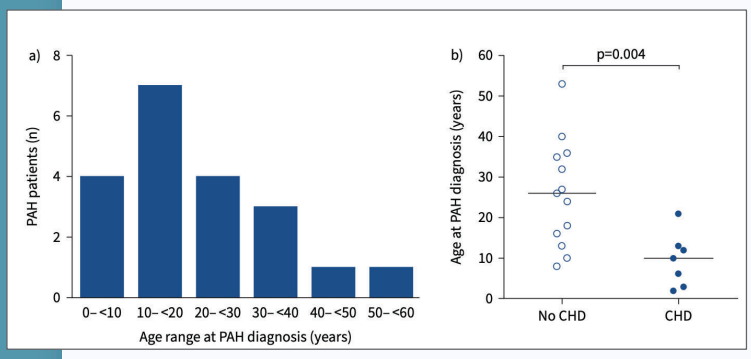
Plexiform lesion

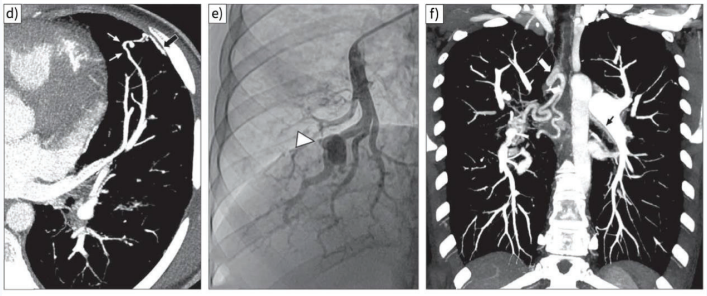
- Thore et al. *Eur Resp J.* 2020

California Thoracic Society
ATS Chapter Serving California and Arizona

SOX17 in PAH

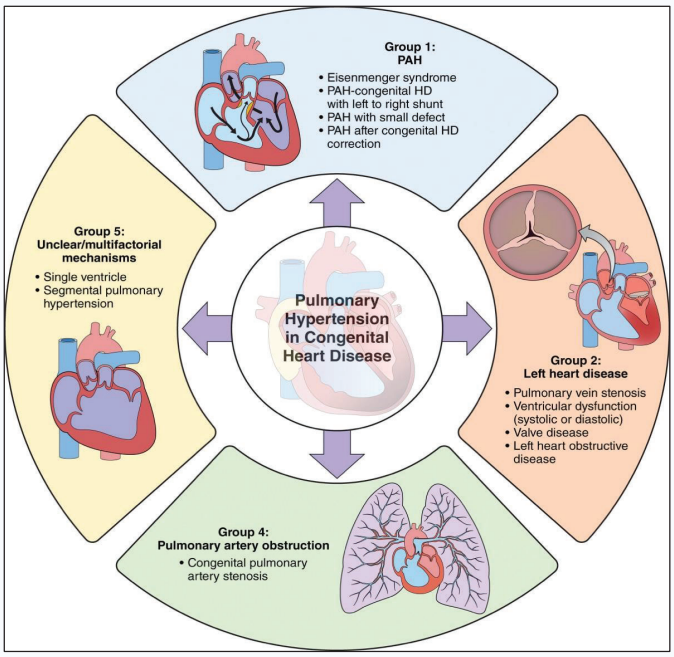
- Transcription factor involved in Wnt/β-catenin and Notch signaling during development
- Identified in 3 different PAH cohorts in 2018 (Europe, US, Japan)
- Associated with PAH-CHD, younger age at onset, severe disease at presentation





- Zhu et al. *Genome Medicine*. 2018
- Montani et al. *Eur Respir. J.* 2022
- Mullen et al. *J Pediatr.* 2025

Congenital Heart Disease (CHD) and PH



WSPH 2024 Classification of CHD-PAH

Group	Condition
A	Eisenmenger syndrome
B	Left-to-right shunt: correctable not correctable
C	Coincidental defects, including all (isolated) ASDs in childhood
D	Corrected CHD
E	Without (prolonged) initial shunt, *e.g.* neonatal arterial switch operation for TGA

ASD: atrial septal defects; TGA: transposition of the great arteries.

- Jone et al. *Circ Heart Fail.* 2023
- Ivy et al. *Eur Respir J.* 2024

California Thoracic Society
ATS Chapter Serving California and Arizona

Operability considerations

- High PVR associated with poor outcome after VSD closure
- PVRi 4-8 WU*m^2 "borderline"
- Not just one metric determines potential success
- "Treat and repair" strategy somewhat controversial – partial or fenestrated repair may be considered

TABLE 8 Intervention in paediatric "borderline" pulmonary vascular resistance associated with congenital heart disease

Favourable parameters for consideration of intervention	
Clinical	Absence of cyanosis (at rest and with exertion) Younger age
Anatomical	Pre-tricuspid shunt (*e.g.* ASD) Multilevel shunts
Haemodynamic	PVRI <4–8 WU·m^2 with reduction on targeted PH therapy and rise in Q_p/Q_s to ⩾2:1
Echocardiographic	Absence of right-to-left shunt
Absence of signs of RV failure	
Toolbox of interventional/surgical approaches	Targeted PAH medical therapies
	Pulmonary arterial banding
	Percutaneous closure of a congenital systemic–pulmonary shunt (*e.g.* ductal occluder)
	Percutaneous downsizing of an ASD (AFR, fenestrated ASD device)
	For multilevel shunts: closure of one defect only leaving a residual shunt
	Surgical repair of a congenital systemic-pulmonary shunt with intentional residual fenestration

RV: right ventricular; ASD: atrial septal defect; PVRI: indexed pulmonary vascular resistance; WU: Wood Units; PH: pulmonary hypertension; Q_p/Q_s: pulmonary-to-systemic blood flow ratio; PAH: pulmonary arterial hypertension; AFR: atrial flow restrictor.

• Ivy et al. *Eur Respir. J.* 2024

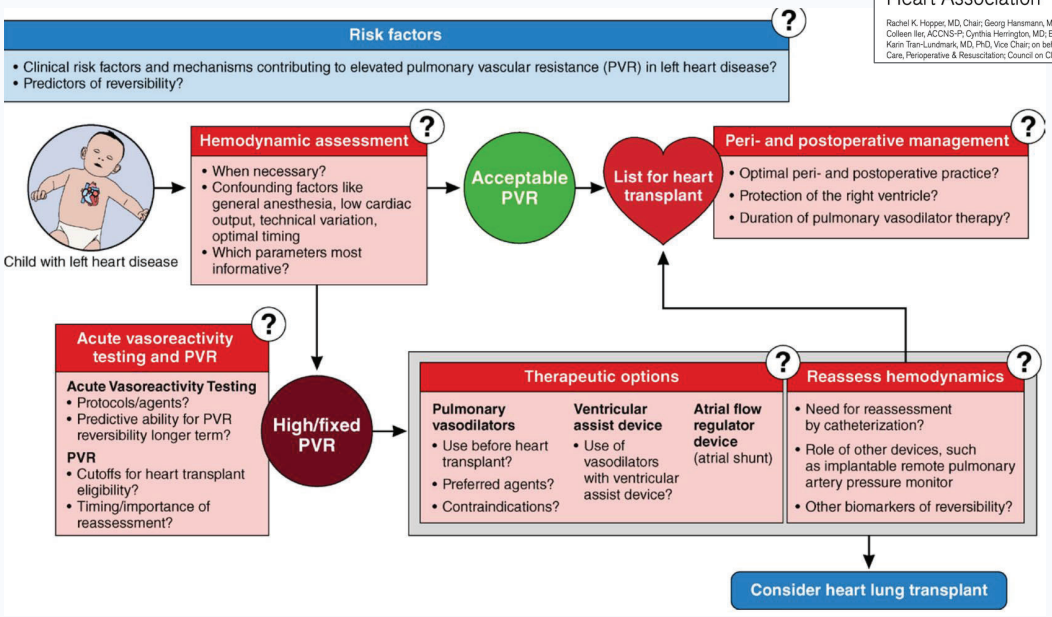
Group 2 PH in children

Etiologies of LHD and response to PH therapies may differ

AHA SCIENTIFIC STATEMENT

Clinical Management and Transplant Considerations in Pediatric Pulmonary Hypertension Due to Left Heart Disease: A Scientific Statement From the American Heart Association

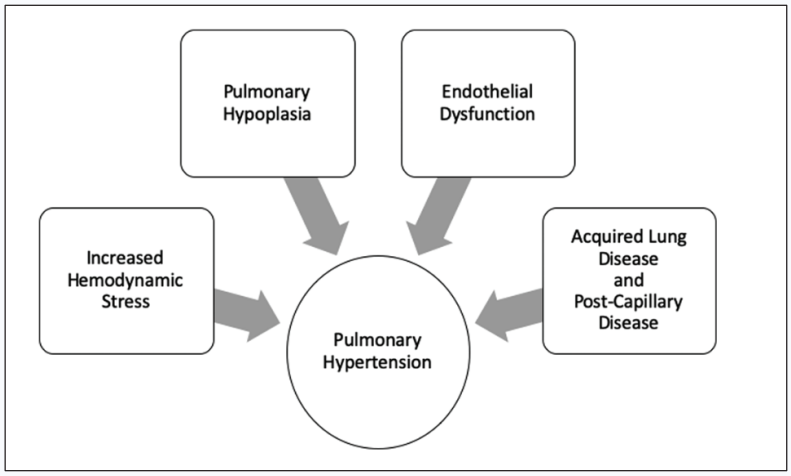
Rachel K. Hopper, MD, Chair; Georg Hansmann, MD, PhD; Seth A. Hollander, MD; Anne I. Dipchand, MD; Oscar van der Have, MD; Colleen Iler, ACCNS-P; Cynthia Herrington, MD; Erika B. Rosenzweig, MD; Juan C. Alejos, MD; Karin Tran-Lundmark, MD, PhD, Vice Chair; on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative & Resuscitation; Council on Clinical Cardiology; and Council on Cardiovascular Stroke Nursing



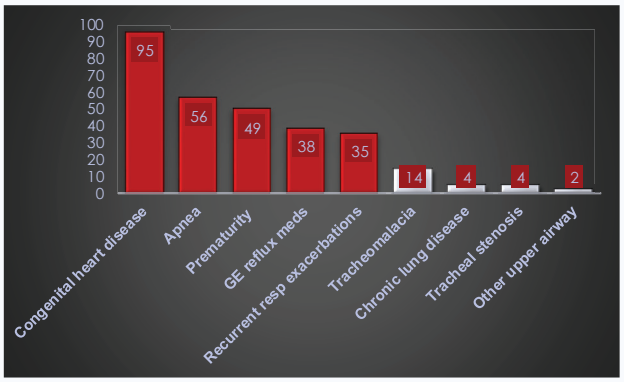
• Hopper et al. *Circ Heart Fail.* 2024

Trisomy 21

- Multifactorial contributors to PH



Comorbidities in T21+PH (%), N=158

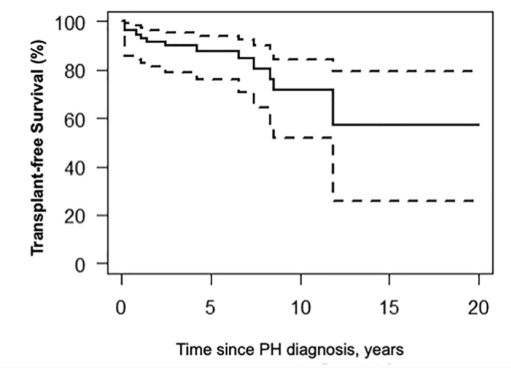


- Bush et al. *Pediatr. Pulmonol.* 2021
- Hopper et al. *J Pediatr.* 2023

California Thoracic Society
ATS Chapter Serving California and Arizona

Trisomy 21 – PPHNet Registry

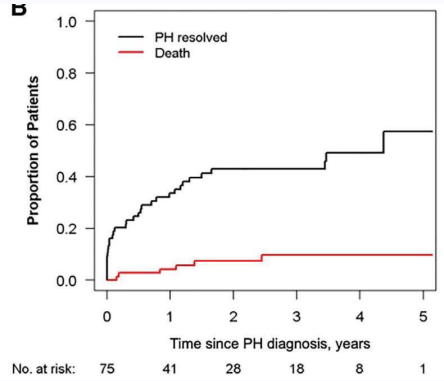
Overall Survival



5-year transplant-free survival 88% (95% CI: 80-97%)

Composite outcome of PH severity met in 34%
(Tracheostomy, HR 3.3 (1.6-6.7), Reflux meds HR 2.1 (1.1-3.9)

Competing risk estimates



PH resolved in 34% at 1 y, 43% after 3 y
(Diagnosis age < 6 months (54% vs 29%, p=0.002), pre-tricuspid shunt (65% vs 38%, p=0.02)

• Hopper et al. *J Pediatr.*, 2023

PH Therapies in Pediatrics

- Focus on growth and protection of immature lungs
- Often good response to pulmonary vasodilators
- Most clinical trials are phase II or rely on retrospective data
  - Published treatment algorithms extrapolate from adult studies
  - Lack of regulatory approval
- Need for clinical trials and real-world data in pediatrics

TABLE 5 Current European Medicines Agency (EMA) and United States Food and Drug Administration (US FDA) approval status for use of pulmonary arterial hypertension drugs in paediatrics and ongoing trials

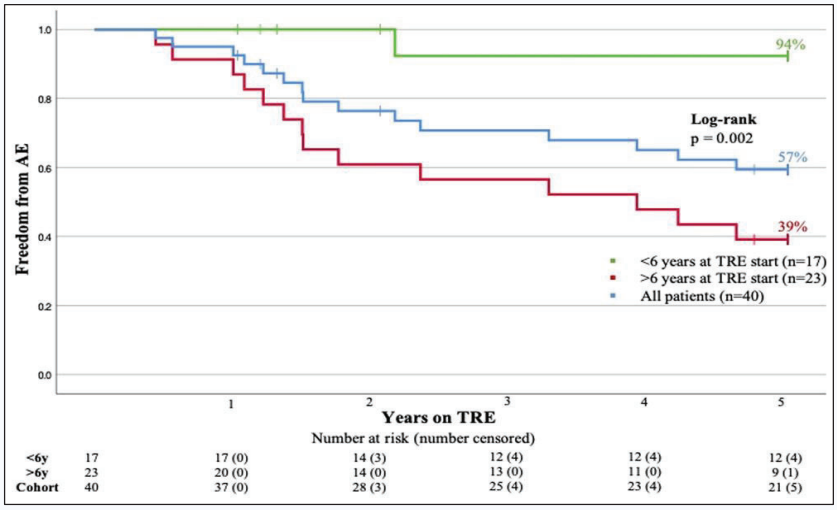
	EMA approval	FDA approval	Comments
PDE-5i			
Sildenafil	Yes	Yes	EMA: age 1–17 years FDA: age 1–17 years
Tadalafil	Yes		EMA: age >2 years
sGC stimulator			
Riociguat	Yes		EMA: >50 kg
ERA			
Bosentan	Yes	Yes	FDA: age >3 years EMA: age >1 year
Ambrisentan	Yes		EMA: age 8–18 years
Macitentan			Ongoing study
PPA			
Epoprostenol			
Treprostinil			
Selexipag (IPR-agonist)			Ongoing study
Activin signalling inhibitor			
Sotatercept			Ongoing study

PDE-5i: phosphodiesterase-5 inhibitor; sGC: soluble guanylate cyclase; ERA: endothelin receptor antagonist; PPA: prostacyclin pathway agent; IPR: selective prostacyclin receptor.

• Ivy et al. *Eur Respir. J*, 2024

Importance of age?

Younger age at initiation of subcutaneous treprostinil is associated with better response in pediatric Group 1 pulmonary arterial hypertension



• Kochanski et al. *Pulm Circ*, 2024

California Thoracic Society
ATS Chapter Serving California and Arizona

Conclusions

- Much of **pediatric PH Is multifactorial** and recognition of contributing factors is important to guide therapy and address reversible factors.
- **Developmental lung disease and CHD** are important drivers of pulmonary vascular disease in infants and children and may contribute to reversibility in some scenarios.
- **Genetics** are increasingly recognized as contributing to PAH in children and adults. Routine clinical testing could identify new genes and develop targeted therapies.
- Children often respond well to PAH therapies, but pediatric-specific data and regulatory approval are lacking for many drugs. **Additional studies are needed** to inform pediatric use.

Thank you

THE WALL CENTER
PULMONARY VASCULAR DISEASE
@STANFORD

Stanford Children's Health | Lucile Packard Children's Hospital Stanford

PPHNet
Pediatric Pulmonary Hypertension Network

California Thoracic Society
ATS Chapter Serving California and Arizona

Understanding Disparities in Pulmonary Vascular Disease

Dafne Moretta, MD

Loma Linda University Medical Center

Disclosures

- No disclosures

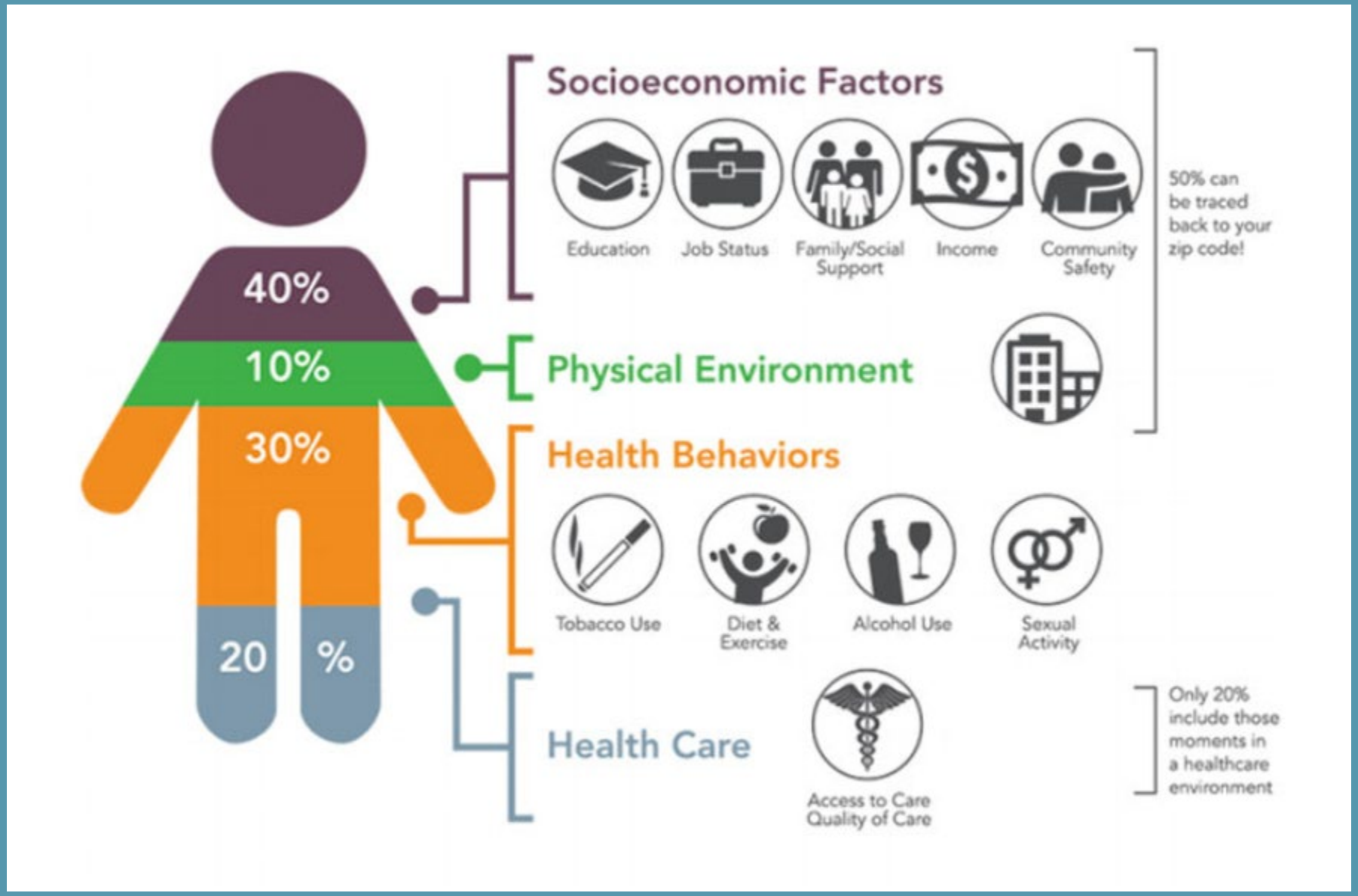
Social Determinants of Health

- "**Circumstances** in which humans are born, develop, live, earn, and age. At the international, regional , and state or local levels, the **distribution** of money, power, and resources shapes these circumstances. "

World Health Organization

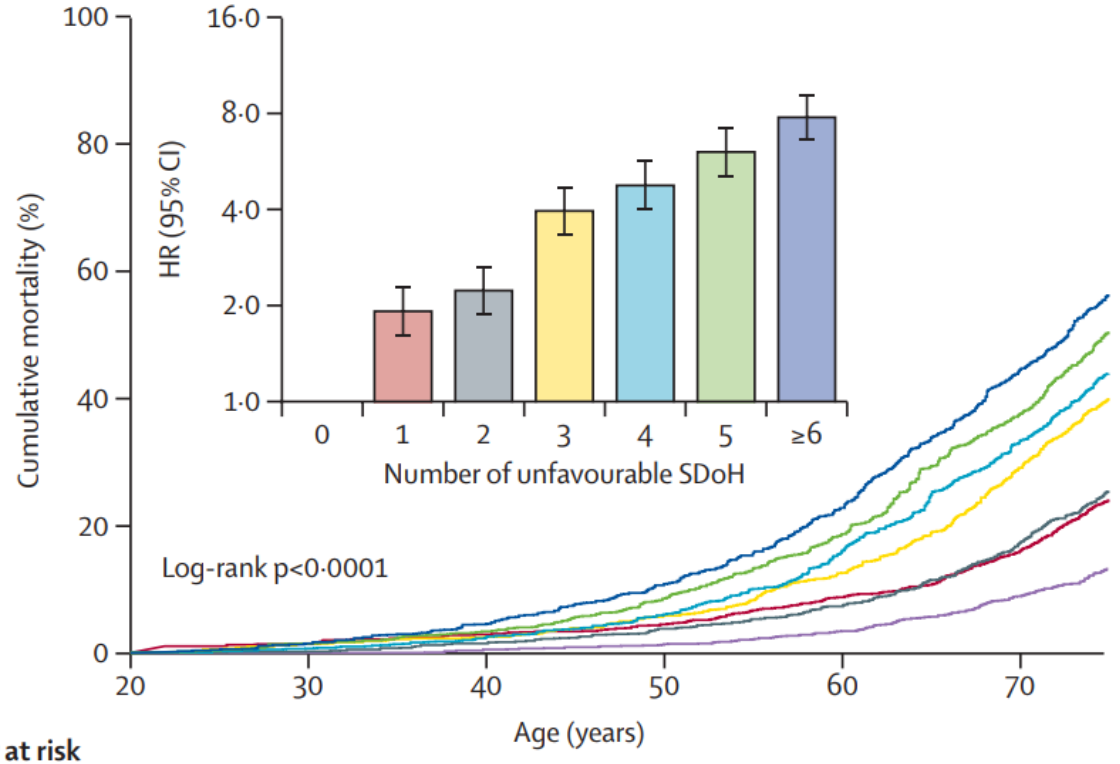
- WHO, 2022; Healthy People 2030 | odphp.health.gov

California Thoracic Society
ATS Chapter Serving California and Arizona



It is estimated that **social determinants of health account for > 40% of health outcomes.**

How much do Social Determinants impact Health Outcomes?

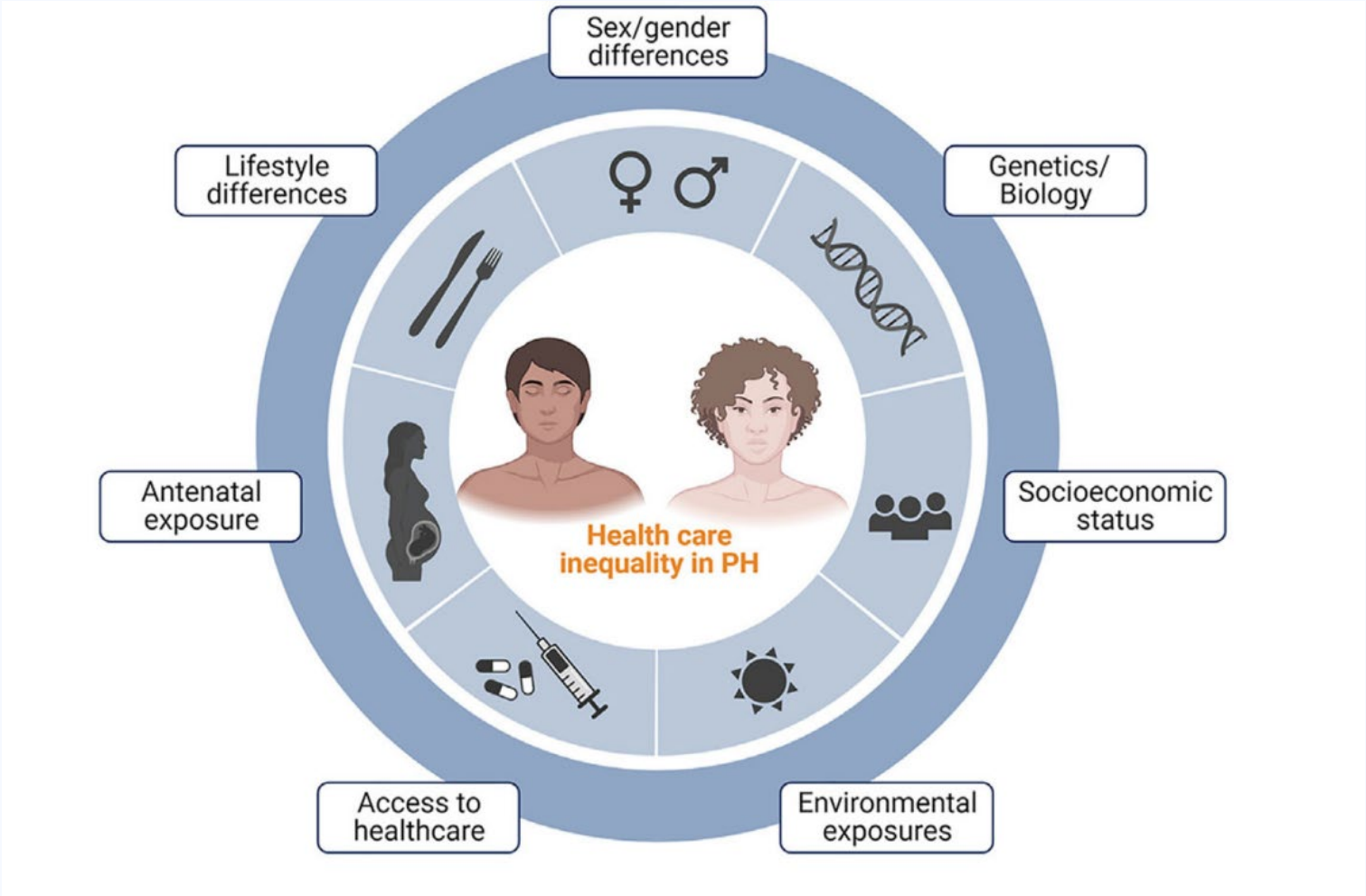


Number at risk

No unfavourable SDoH	106	503	1405	1810	1862	1386
One unfavourable SDoH	158	826	1488	1560	1387	1333
Two unfavourable SDoH	183	1055	1422	1263	1056	1128
Three unfavourable SDoH	319	1337	1360	1123	898	937
Four unfavourable SDoH	353	1369	1312	1125	939	859
Five unfavourable SDoH	312	1189	1173	981	838	681
Six or more unfavourable SDoH	336	1164	1146	959	803	616

Bundy JD, et al. Social determinants of health and premature death among adults in the USA from 1999 to 2018: A National Cohort Study. The Lancet PH, 2023

Social Determinants of Health in PAH



• Bernardo RJ, Dr Jesus Perez VA. Clinic in Chest Medicine, 2023; 44:543-554

Patient's Case

- 32 yo Hispanic female
- Pregnant (26 week- gestation)
- Methamphetamine user
- Lives in Needles
- No reliable transportation
- Partner unemployed
- 3 children
- Intermittent homelessness
- Unreliable income
- Unemployed
- Inconsistent Health Insurance IEHP, previously uninsured
- Poor literacy
- Bilingual
- Poor treatment adherence in the past
- Loss of follow up

Social determinants of Health (social risks/challenges) in our case

- Sex/Gender: Female
- Race/Ethnicity: Hispanic
- Financial/Economical Challenges: Unemployed/ inconsistent income
- Health Care Insurance: Intermittently Uninsured
- Geographic/Social Challenges: Needles, intermittent homelessness
- Education Level: Poor Literacy/ Language Barrier
- Substance Abuse: Methamphetamine User
- Transportation Barriers: No transportation
- Treatment Adherence: Poor Compliance
- Clinical Trial Participation: Failed to enroll

Social determinants of Health (social risks/challenges) in our case

Sex/Gender: Female

Race/Ethnicity: Hispanic

Financial/Economical Challenges: Unemployed/ inconsistent income

Health Care Insurance: Intermittently Uninsured

Geographic/Social Challenges: Needles, intermittent homelessness

Education Level: Poor Literacy/ Language Barrier

Substance Abuse: Methamphetamine User

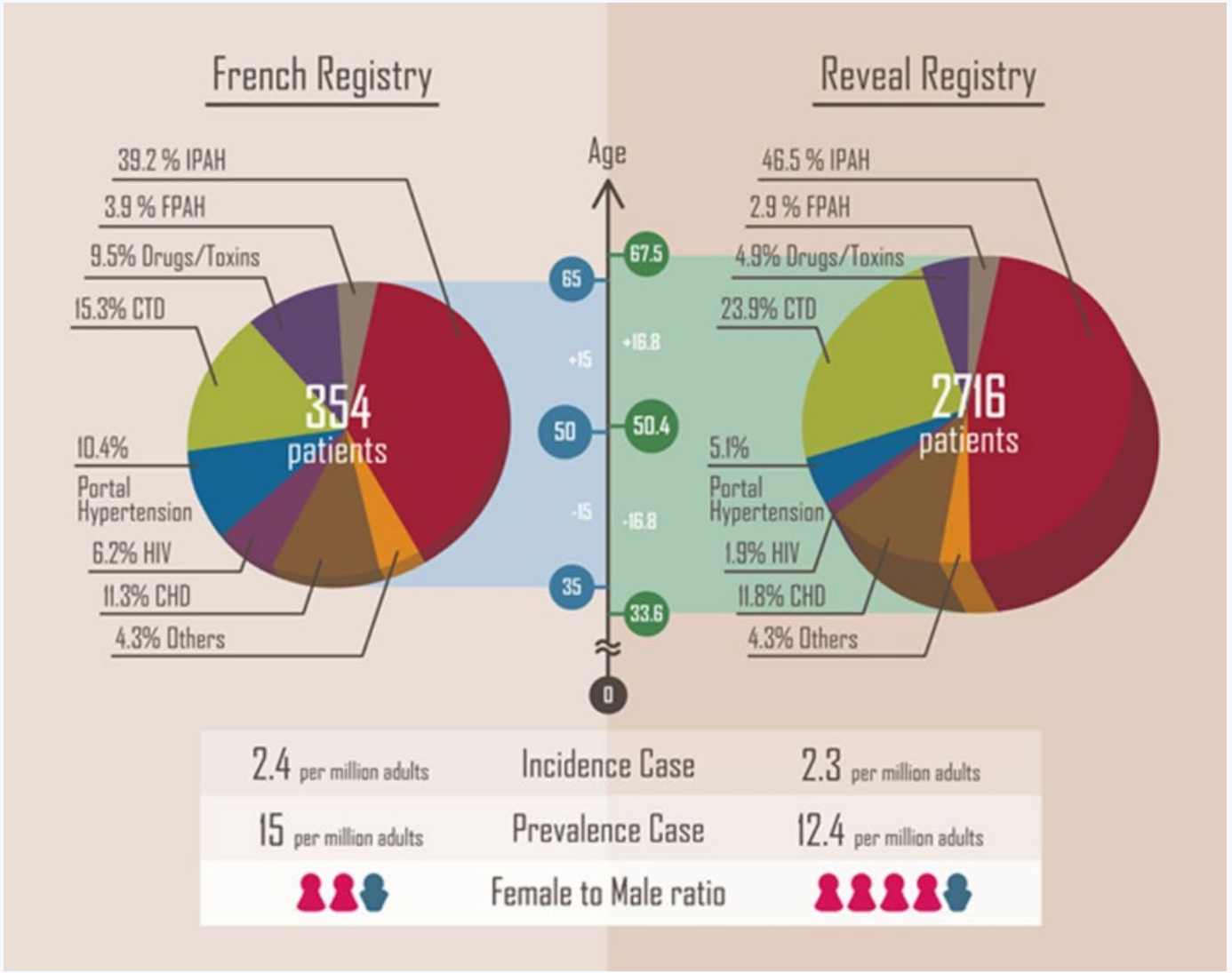
Transportation Barriers: No transportation

Treatment Adherence: Poor Compliance

Clinical Trial Participation: Failed to enroll

Sex Differences in Pulmonary Hypertension

- Disease Severity
- Treatment Response
- Survival Outcomes
- Sex Hormones

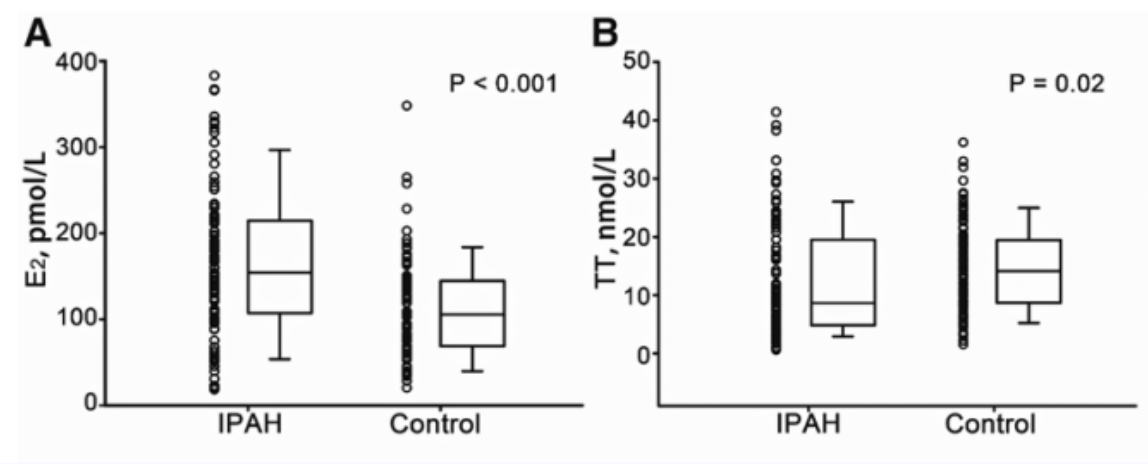


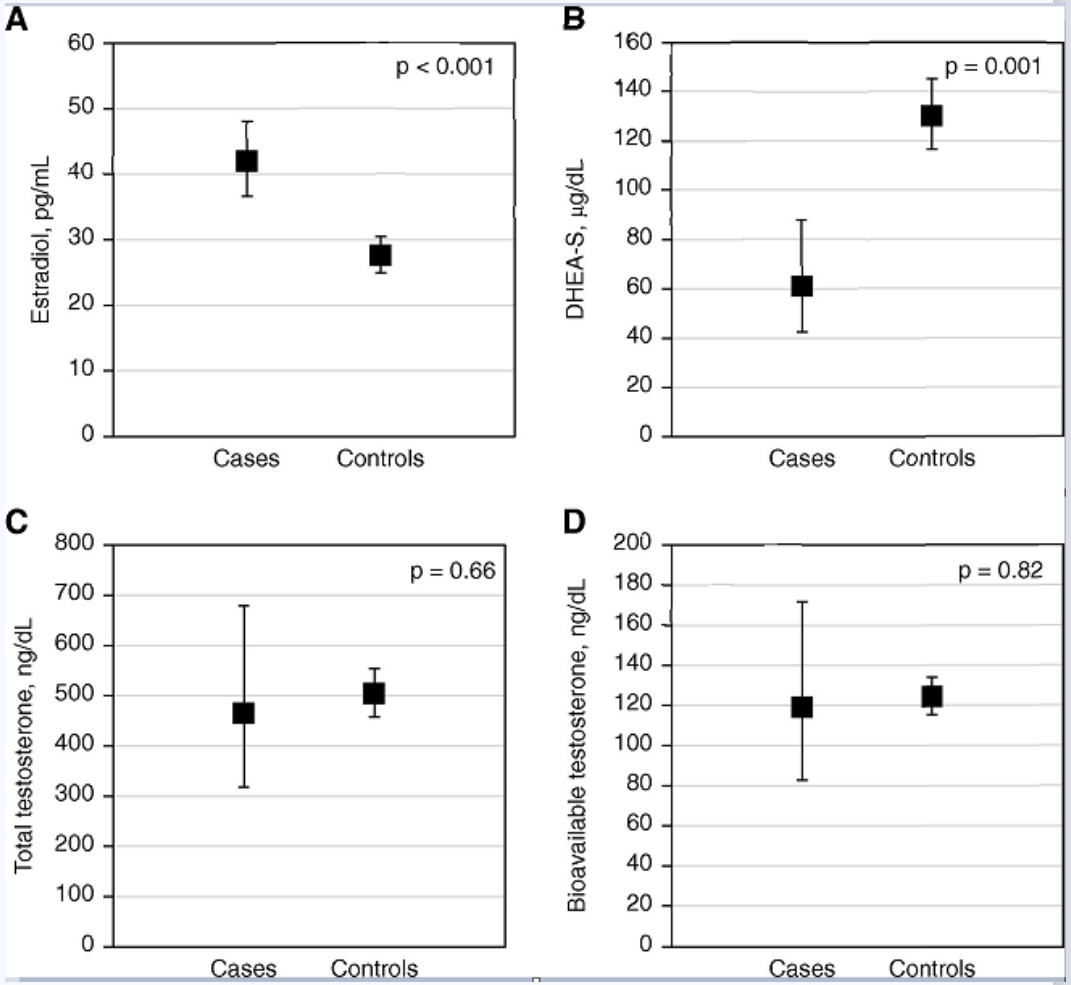
• Yen-Chun Lai et al., Pulmonary Arterial Hypertension: The Clinical Syndrome; *AHA/ASA Journal* , 2014

California Thoracic Society
ATS Chapter Serving California and Arizona

Hormones and PAH

- Higher levels of E2 and lower levels of DHEA-S were associated with PAH in men.
- Wu and Colleagues, 2018
  - Higher E2 levels identified in Chinese men with PAH compared to controls.





• Ventetuolo, CE et al, *AJRCCM*, 2016 Wu WH et al., *Hypertension*, 2018

"Sex Paradox" in PH

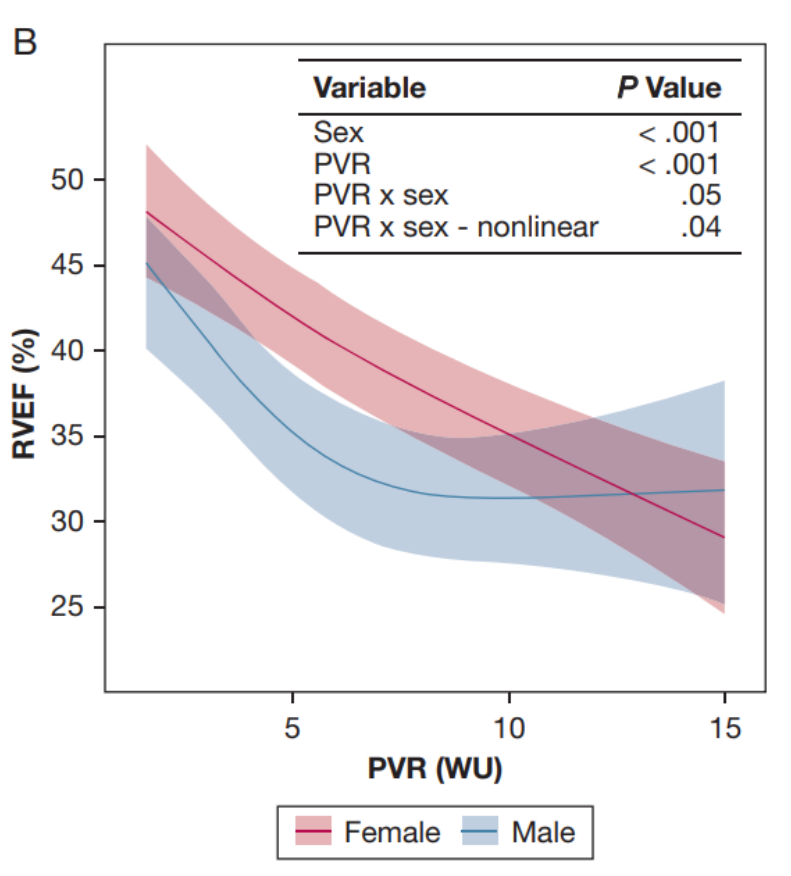
- Sex differences in susceptibility and prognosis in PH are complex, resulting in two significant paradoxical findings:
  - Women have higher incidence of PH, especially in WHO group 1 PAH.
  - Women experience better RV function and improved survival compared to men

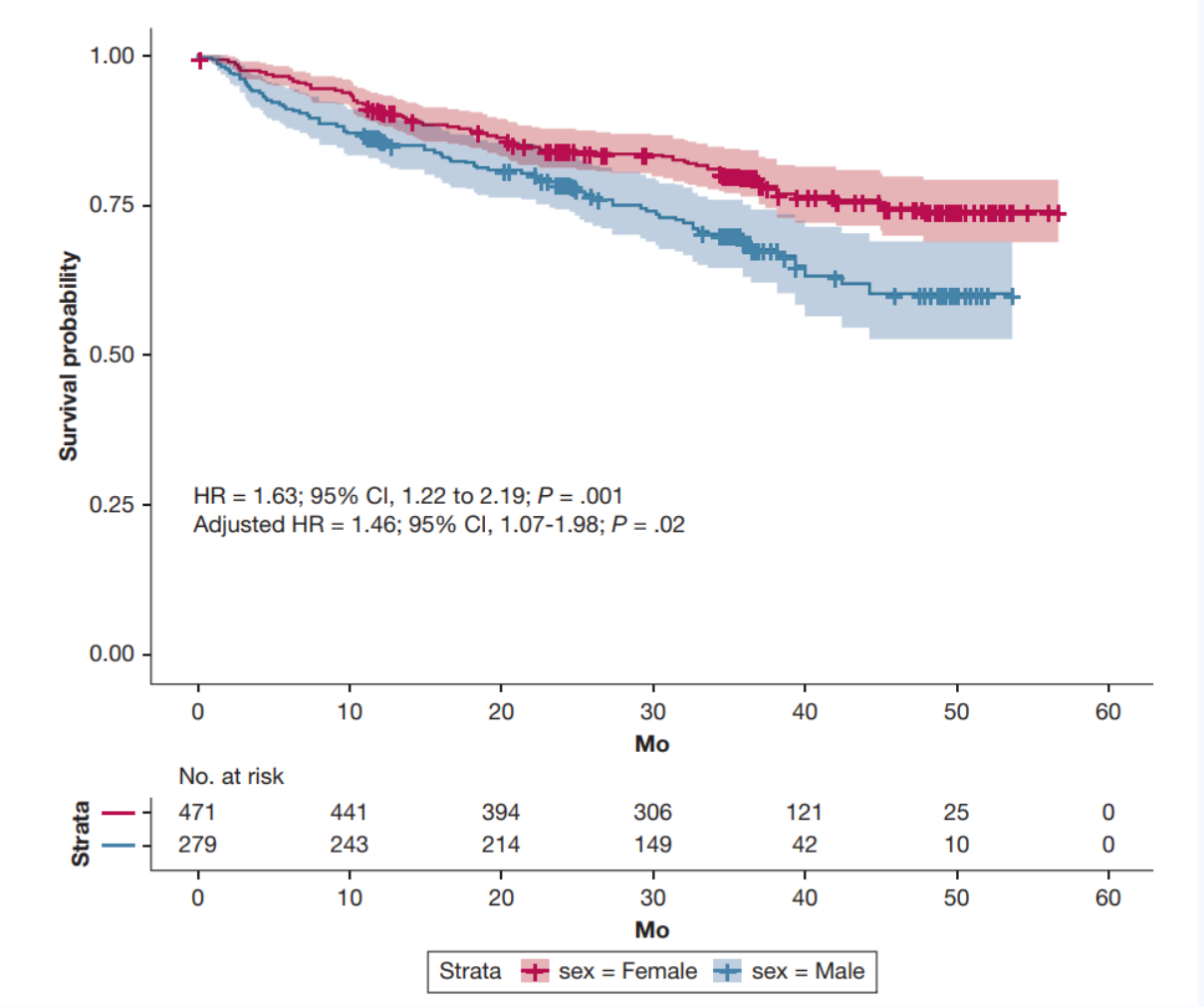
TABLE 1] Patient Characteristics by WSPH Group

Variable	Group					Total (N = 750)
	1 (n = 353)	2 (n = 136)	3 (n = 172)	4 (n = 57)	5 (n = 32)	
Female sex	259 (73.4)	78 (57.4)	88 (51.2)	35 (61.4)	11 (34.4)	471 (62.8)
Postmenopausal	168 (64.9)	75 (96.2)	81 (92.0)	35 (71.4)	7 (63.6)	356 (75.6)
Age at enrollment, y						
Female sex	52 ± 14	68 ± 11	63 ± 12	56 ± 15	57 ± 14	61 ± 15
Male sex	53 ± 14	68 ± 13	65 ± 10	63 ± 12	57 ± 13	57 ± 15

• PVDOMICS, Hemnes et al. *CHEST*, 2024

"Sex Paradox" in PH





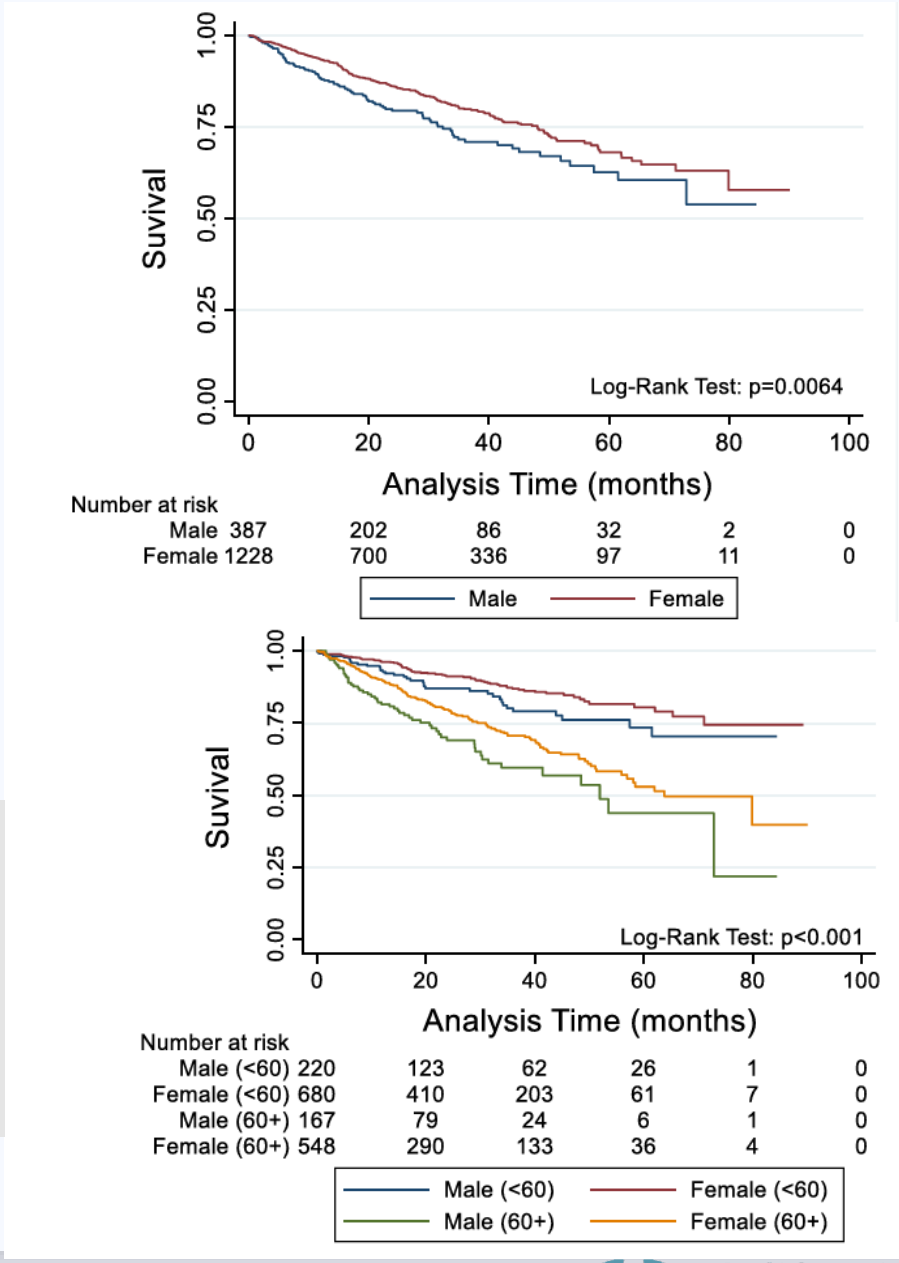
- PVDOMICS, Hemnes et al. *CHEST*, 2024

Sex Differences in PHAR

- Females: 2x higher frequency of CTD-PAH
- Males: Drug/toxin –associated, PoPAH, HIV-related

Table 1 Baseline Characteristics of Adult PAH Patients Enrolled in PHAR by Sex

	Total	Male	Female	*p*-value
PAH Diagnosis, *n* (%N)[b]				
Idiopathic	817 (43%)	193 (41%)	624 (44%)	< 0.01
Connective tissue disease-associated	617 (33%)	85 (18%)	532 (37%)	
Drug/toxin-associated	243 (13%)	91 (20%)	152 (11%)	
Portopulmonary	127 (7%)	60 (13%)	67 (5%)	
Heritable	55 (3%)	14 (3%)	41 (3%)	
HIV-related	32 (2%)	23 (5%)	9 (1%)	



• DesJardin, JT et al. *JHLT*, 2024.

Social determinants of Health (social risks/challenges) in our case

Sex/Gender: Female

Race/Ethnicity: Hispanic

Financial/Economical Challenges: Unemployed/ inconsistent income

Health Care Insurance: Intermittently Uninsured

Geographic/Social Challenges: Needles, intermittent homelessness

Education Level: Poor Literacy/ Language Barrier

Substance Abuse: Methamphetamine User

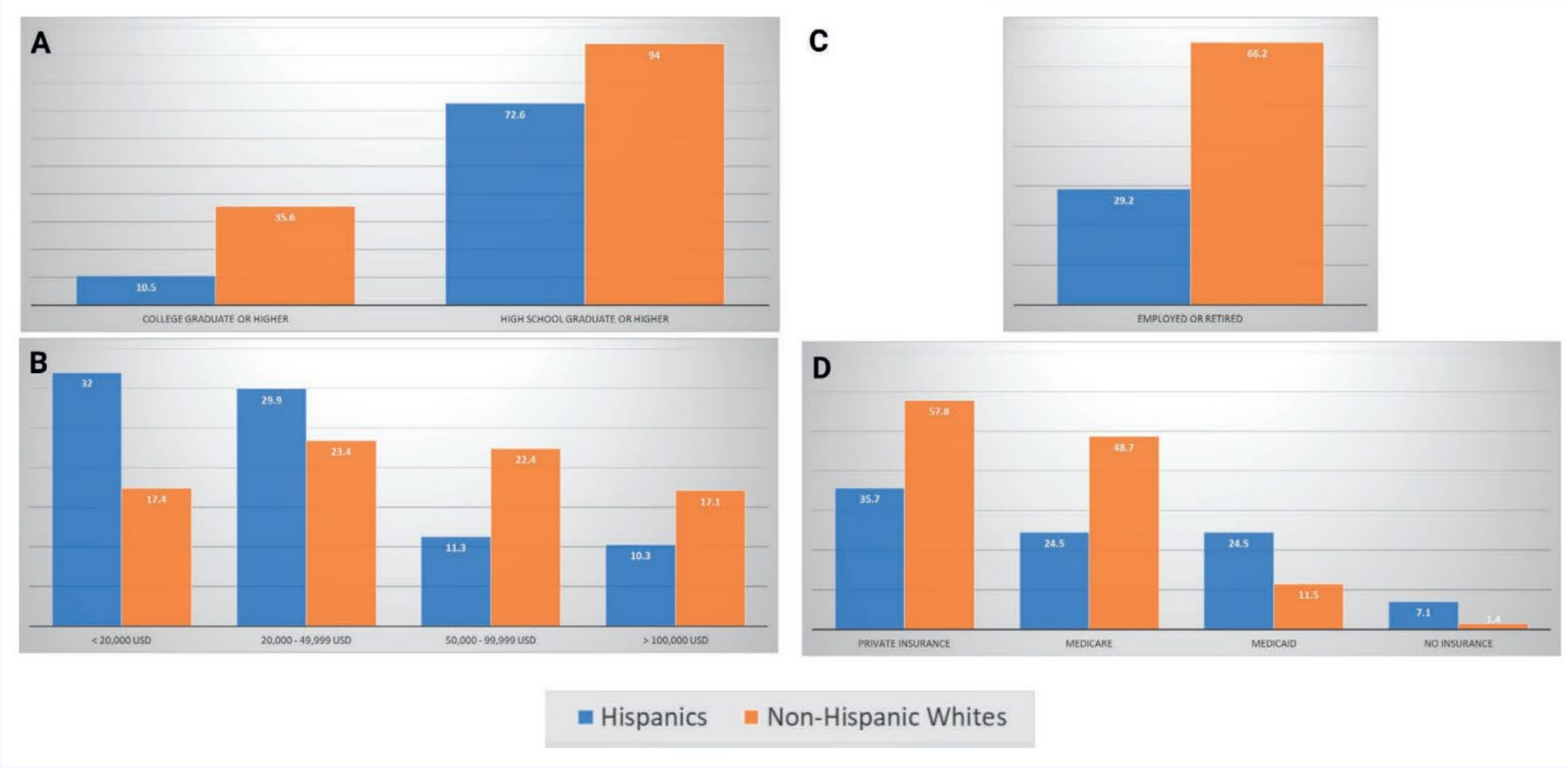
Transportation Barriers: No transportation

Treatment Adherence: Poor Compliance

Clinical Trial Participation: Failed to enroll

REGULAR ARTICLE

Hispanic Ethnicity and Social Determinants of Health: Harnessing Data from The Pulmonary Hypertension Association Registry



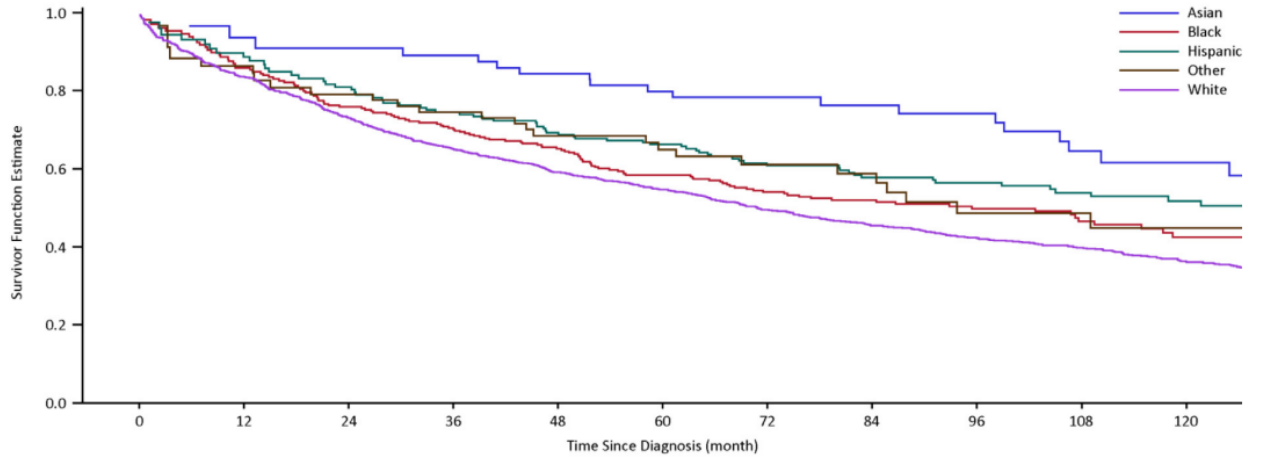
• Bernardo, et al., *Advances in Pulmonary Hypertension*, 2022

California Thoracic Society
ATS Chapter Serving California and Arizona

REVEAL Outcome Based on Race/Ethnicity

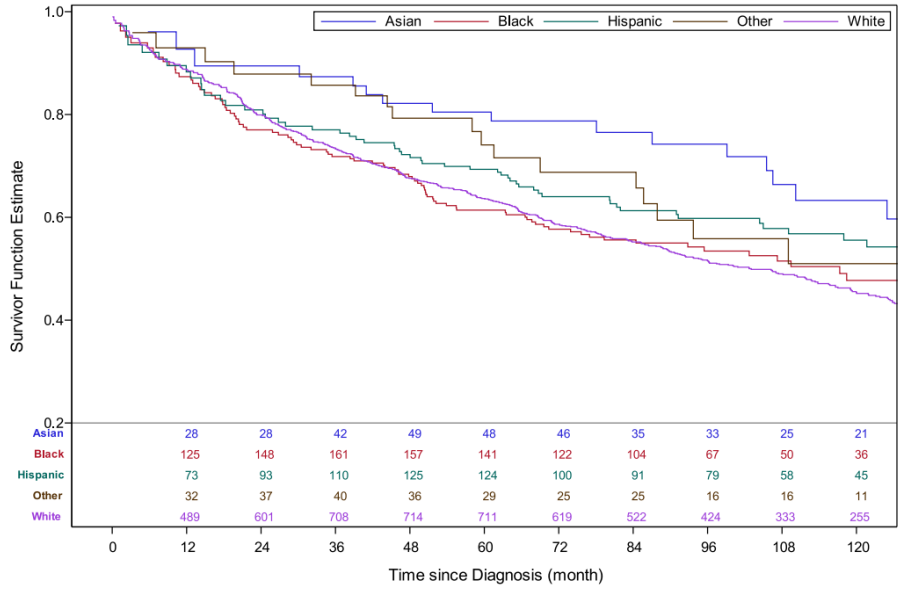
- Unadjusted Survival Analysis: Better Hispanic Survival
- P= 0.0041

Race	n	HR (95% CI) vs white patients	P value
Asian	100	0.541 (0.358–0.819)	0.0037
Black	393	0.813 (0.672–0.982)	0.0319
Hispanic	263	0.709 (0.560–0.897)	0.0041
Other	88	0.788 (0.541–1.149)	0.2157
White	2202	—	—



- Adjusted for age and PAH type: No difference
- P= 0.068

Race	n	HR (95% CI) vs white patients	*P* value
Asian	91	0.654 (0.418–1.023)	0.0630
Black	313	0.881 (0.700–1.110)	0.2827
Hispanic	239	0.782 (0.600–1.019)	0.0683
Other	68	0.841 (0.531–1.331)	0.4587
White	1506	—	—



• Medrek et al., *JHLT*, 2020

PHAR Hispanic Survival Advantage

- Hispanics had:
  - Impaired health access
  - Lower Education
  - Lower Income
  - Higher ER visits and Hospitalizations

- Survival Analysis:
  - Unadjusted: Better survival in Hispanic patients (p=0.032).
  - Adjusted: No survival difference after controlling for SDoH (p=0.474).

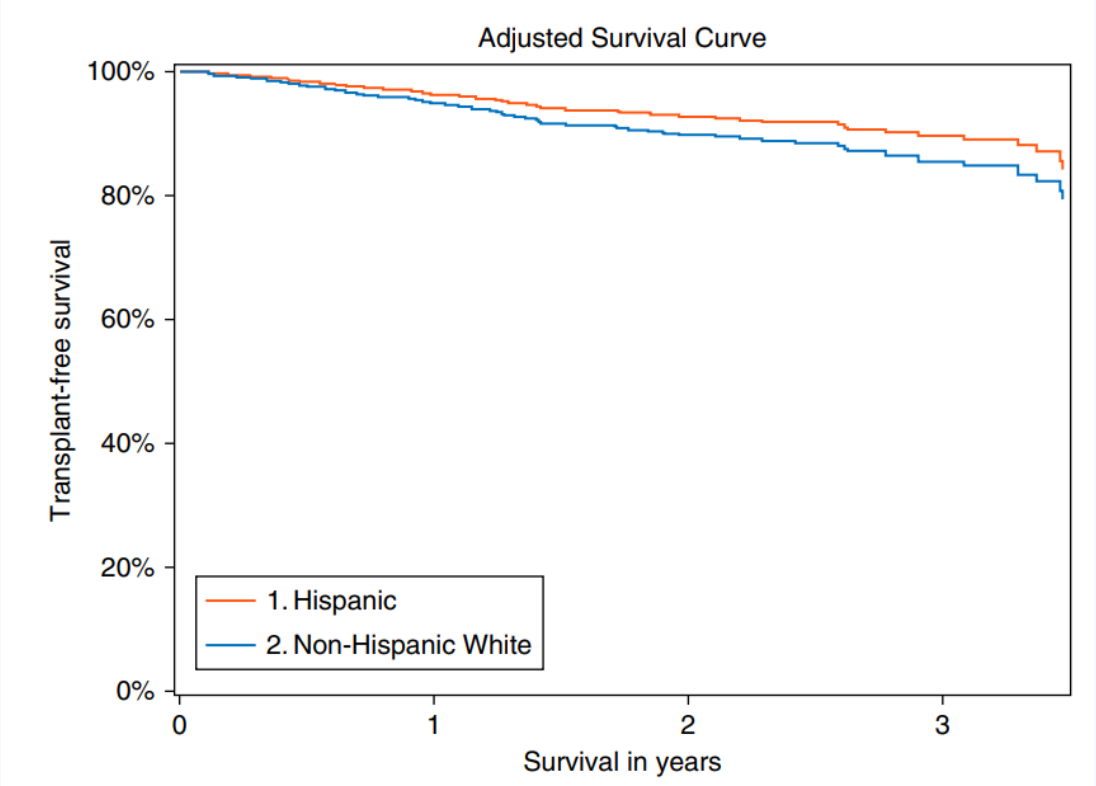


Table 4. Univariate and multivariable Cox proportional hazards model for transplant-free survival

	Univariate Analysis		Multivariable Analysis*	
Variable	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
Hispanics vs. non-Hispanic White patients	0.47 (0.24–0.94)	0.032	0.76† (0.35–1.62) 0.83‡ (0.41–1.68)	0.474 0.601

• Bernardo et al., *Annals ATS*, 2022

Social determinants of Health (social risks/challenges) in our case

Sex/Gender: Female	Race/Ethnicity: Hispanic	**Financial/Economical Challenges: Unemployed/ inconsistent income**	Health Care Insurance: Intermittently Uninsured
Geographic/Social Challenges: Needles, intermittent homelessness	Education Level: Poor Literacy/ Language Barrier	Substance Abuse: Methamphetamine User	Transportation Barriers: No transportation
	Treatment Adherence: Poor Compliance	Clinical Trial Participation: Failed to enroll	

ORIGINAL RESEARCH

Hispanic Ethnicity and Social Determinants of Health in Pulmonary Arterial Hypertension

The Pulmonary Hypertension Association Registry

Roberto J. Bernardo[1], Di Lu[2], Ramon L. Ramirez III[3,4], Haley Hedlin[2], Steven M. Kawut[5], Todd Bull[6], Teresa De Marco[7], H. James Ford[8], Daniel Grinnan[9], James R. Klinger[10], John W. McConnell[11], Erika Berman-Rosenzweig[12], Oksana A. Shlobin[13], Roham T. Zamanian[3,4*], and Vinicio A. de Jesus Perez[3,4*]; on behalf of the PHAR Study Group

Table 2. Social determinants of health

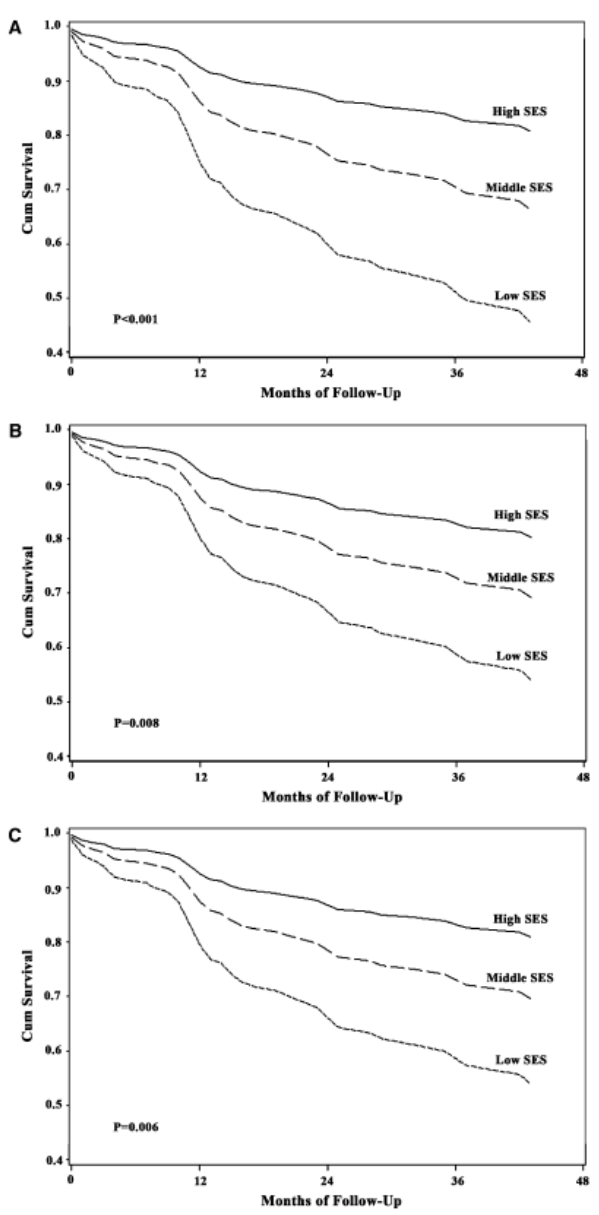
	Hispanic ($n = 98$)	Non-Hispanic White Patients ($n = 585$)	ASD*
Health care insurance			
Private insurance	35 (35.7)	338 (57.8)	0.453
Medicare	24 (24.5)	285 (48.7)	0.520
Medicaid	24 (24.5)	67 (11.5)	0.345
No insurance	7 (7.1)	8 (1.4)	0.289
Education ($n = 679$)			
College graduate or higher	10 (10.5)	208 (35.6)	0.624
High school graduate or higher	69 (72.6)	549 (94.0)	0.598
Income ($n = 682$)			0.474
<$20,000 per year	31 (32.0)	102 (17.4)	
$20,000–$49,999 per year	29 (29.9)	137 (23.4)	
$50,000–$99,999 per year	11 (11.3)	131 (22.4)	
>$100,000 per year	10 (10.3)	100 (17.1)	
Do not know/decline to answer	16 (16.5)	115 (19.7)	
Occupation ($n = 640$)			
Employed or retired	26 (29.2)	365 (66.2)	0.798
Number of household members ($n = 682$)	3.5 ± 1.7	2.4 ± 1.2	0.801
Substance use ($n = 682$)			
Smoked at least 100 cigarettes in their lifetime	30 (30.9)	279 (47.7)	0.381
Current alcohol use	16 (16.5)	239 (40.9)	0.569
History of methamphetamine use	16 (16.5)	85 (14.5)	0.054

• Bernardo et al., *Annals ATS*, 2022

Lower Socioeconomic Status Is Associated with Worse Outcomes in Pulmonary Arterial Hypertension

Wen-Hui Wu[1]*, Lu Yang[1]*† Fu-Hua Peng[1]*, Jing Yao[1], Li-Ling Zou[2], Dong Liu[1], Xin Jiang[1], Jue Li[2], Lan Gao[3], Jie-Ming Qu[4,5], Steven M. Kawut[6,7], and Zhi-Cheng Jing[1]

- Lower SES is associated with increased mortality (ie: 3 year-survival: 50%, 71%, and 86%)
- Mortality risk remained significant even after adjusting for age, sex, disease severity, and treatment type.
- Delayed treatment initiation in patients with lower SES
- Limited Access to Healthcare in patients with lower SES



• Wu et al. *AJRCCM*, 2013

California Thoracic Society
ATS Chapter Serving California and Arizona

ORIGINAL RESEARCH

Socioeconomic status affects pulmonary hypertension disease severity at time of first evaluation

Arunabh Talwar,[1] Sonu Sahni,[1] Ankoor Talwar,[2] Nina Kohn,[3] James R. Klinger[4]

- **Correlation between income and disease severity:** There was a negative relationship between income and initial FC (r= 0.146; p=0.0226)
- **Potential contributing factors:** Delayed diagnosis, healthcare access barriers.

Table 3. World Health Organization functional class (WHO-FC) at diagnosis in relation to socioeconomic status in pulmonary arterial hypertension patients

Median annual income, $	WHO-FC I/II	WHO-FC III/IV	Total
<60,530	5 (15.2)	28 (84.8)	33
60,530–77,351	8 (28.6)	20 (71.4)	28
77,352–94,678	11 (45.8)	13 (54.2)	24
>94,678	14 (45.2)	17 (54.8)	31
Total	38	78	116

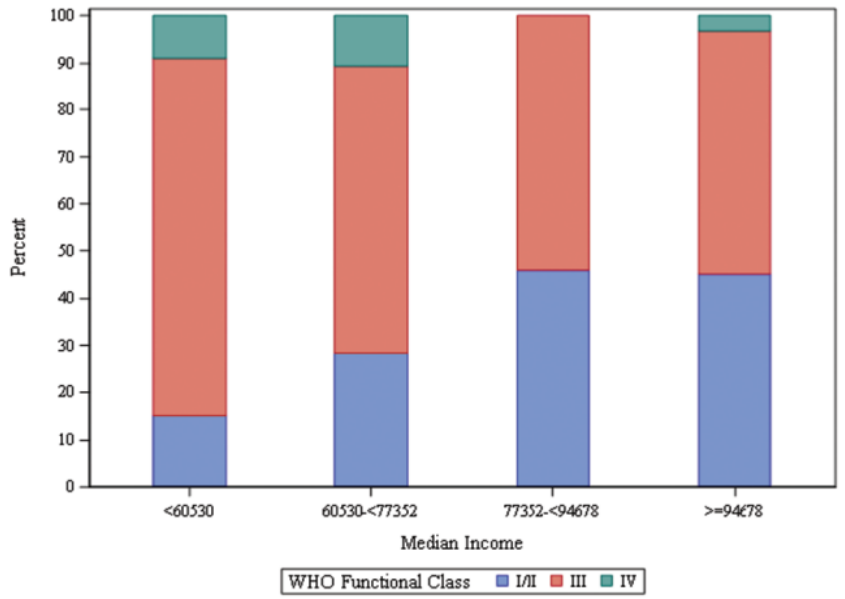


Figure 2. World Health Organization (WHO) functional class at diagnosis in relation to socioeconomic status in pulmonary arterial hypertension patients.

• Talwar et al. *Pulm Circ*, 2016

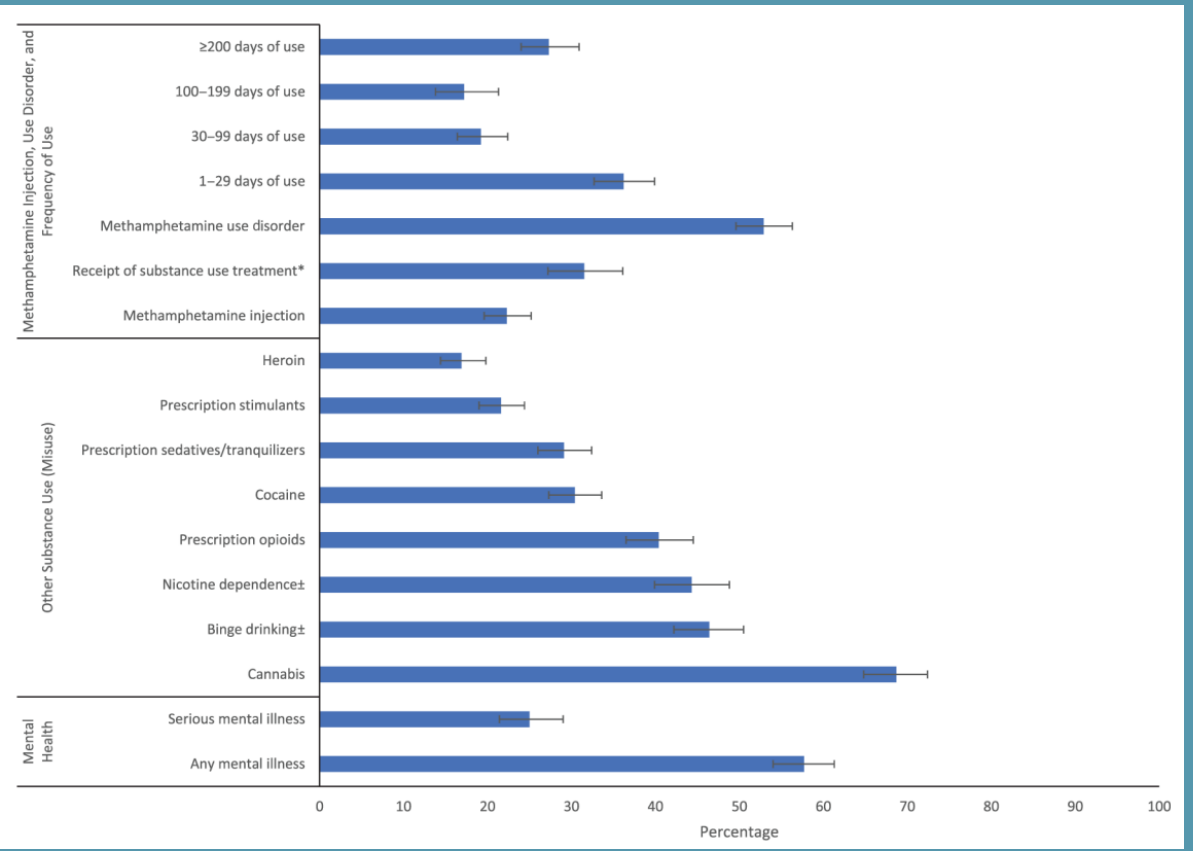
California Thoracic Society
ATS Chapter Serving California and Arizona

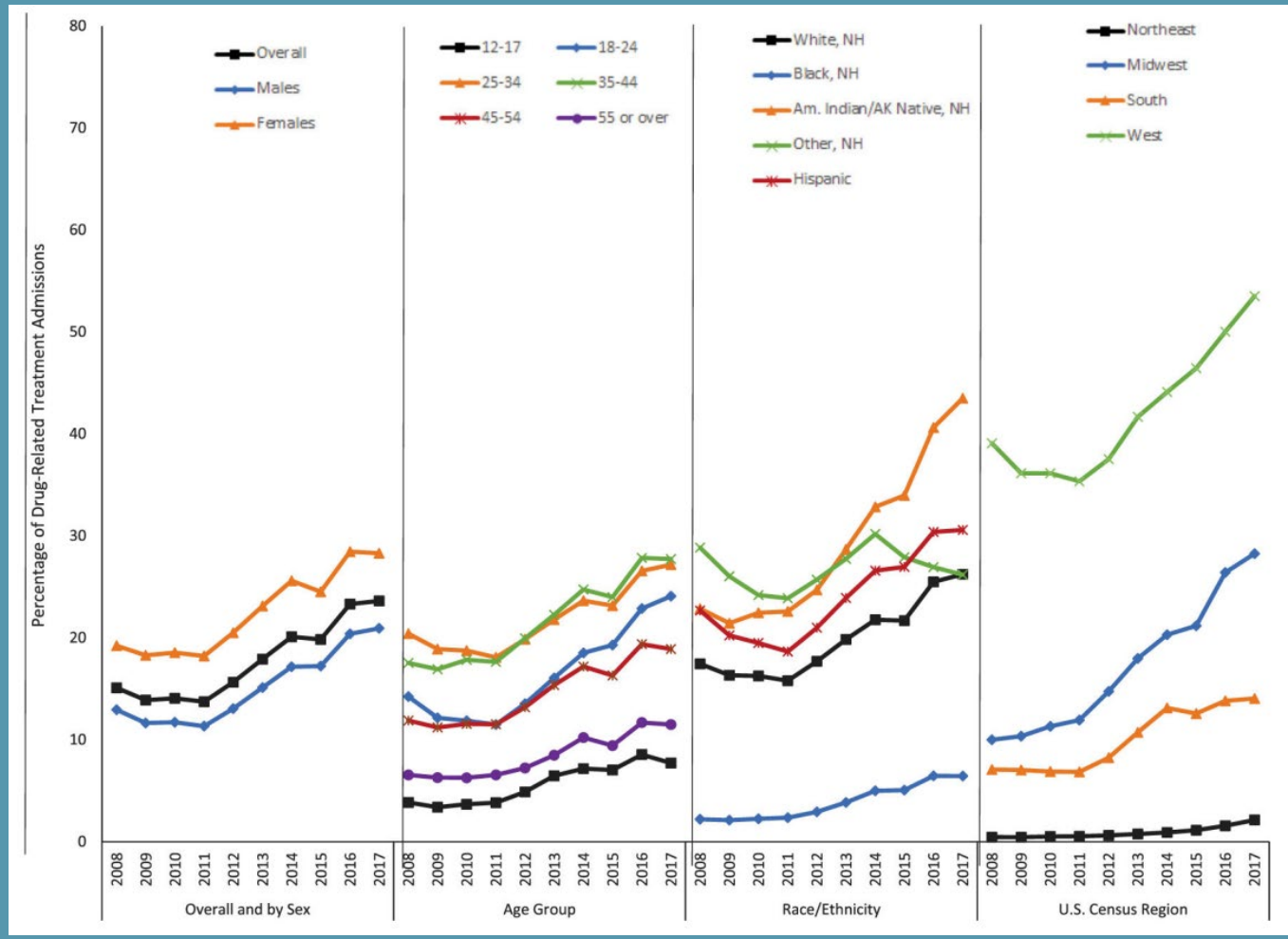
Social determinants of Health (social risks) in our patient

Sex/Gender: Female	Race/Ethnicity: Hispanic	Financial Challenge: Unemployed/ Pattern with inconsistent income	Health Care Insurance: Uninsured
Geographic/Social Challenges: Intermittent Homelessness	Education Level: Poor Literacy/ Language Barrier	**Substance Abuse: Methamphetamine Use**	Transportation Barriers: No transportation
	Treatment Adherence: Poor	Clinical Trial Participation: Failed	

Methamphetamine use in the United States: epidemiological update and implications for prevention, treatment, and harm reduction

Christopher M. Jones[1], Debra Houry[1], Beth Han[2], Grant Baldwin[3], Alana Vivolo-Kantor[3], Wilson M. Compton[2]





• Jones et al., *Ann NY Acad Sci.*, 2022

California Thoracic Society
ATS Chapter Serving California and Arizona

JAMA | Original Investigation

Illicit Substance Use and Treatment Access Among Adults Experiencing Homelessness

Ryan D. Assaf, PhD, MPH; Meghan D. Morris, PhD, MPH; Elana R. Straus, BA; Priest Martinez, AS; Morgan M. Philbin, PhD, MHS; Margot Kushel, MD

- Only 6.7% of regular users currently in treatment
- 21.2% desired but lacked treatment access

Table 3. Regular Illicit Substance Use and Method of Use in the Past 6 Months[a]

	Overall, unweighted No.	Regular use in the last 6 mo, weighted percent (95% CI)[b]				
		Any illicit substance	Methamphetamine	Opioid	Cocaine/crack cocaine	Injection
Total	3200	37.1 (32.9-41.3)	33.1 (29.4-36.7)	10.4 (7.9-12.9)	3.2 (1.8-4.6)	11.8 (9.8-13.8)
Demographics						
Age, y						
18-24	216	29.5 (19.0-40.1)	20.4 (12.7-28.2)	16.9 (6.3-27.5)	7.4 (0.0-16.9)	5.8 (2.0-9.6)
25-49	1543	45.0 (40.4-49.7)	41.9 (37.4-46.5)	13.6 (10.1-17.1)	2.3 (0.9-3.6)	15.6 (12.5-18.7)
50 or older	1441	28.8 (23.6-34.1)	24.2 (19.1-29.2)	5.9 (3.1-8.8)	3.8 (1.4-6.1)	8.0 (5.1-11.0)
Race and ethnicity[e]						
American Indian and Alaska Native	107	40.5 (33.1-47.8)	39.0 (31.5-46.5)	8.7 (4.8-12.7)	4.2 (0.5-7.9)	12.5 (8.2-16.8)
Asian and Pacific Islander[d]	64					
Black and African American	732	28.6 (21.4-35.9)	21.9 (15.7-28.1)	4.9 (0.01-9.7)	6.5 (3.1-9.8)	5.3 (0.0-10.6)
Hispanic and Latine	691	38.2 (32.0-44.3)	36.6 (30.4-42.9)	7.7 (4.0-11.4)	0.8 (0.3-1.3)	12.2 (7.8-16.5)
Multiracial and Multiethnic	441	37.1 (27.4-46.8)	34.0 (24.9-43.1)	16.3 (8.7-23.8)	3.9 (0.4-7.4)	12.3 (7.8-16.8)
White	1089	44.2 (40.6-47.8)	38.9 (35.2-42.5)	15.4 (11.8-18.9)	2.4 (0.9-3.9)	17.2 (14.0-20.4)
Another race not listed[d]	15					

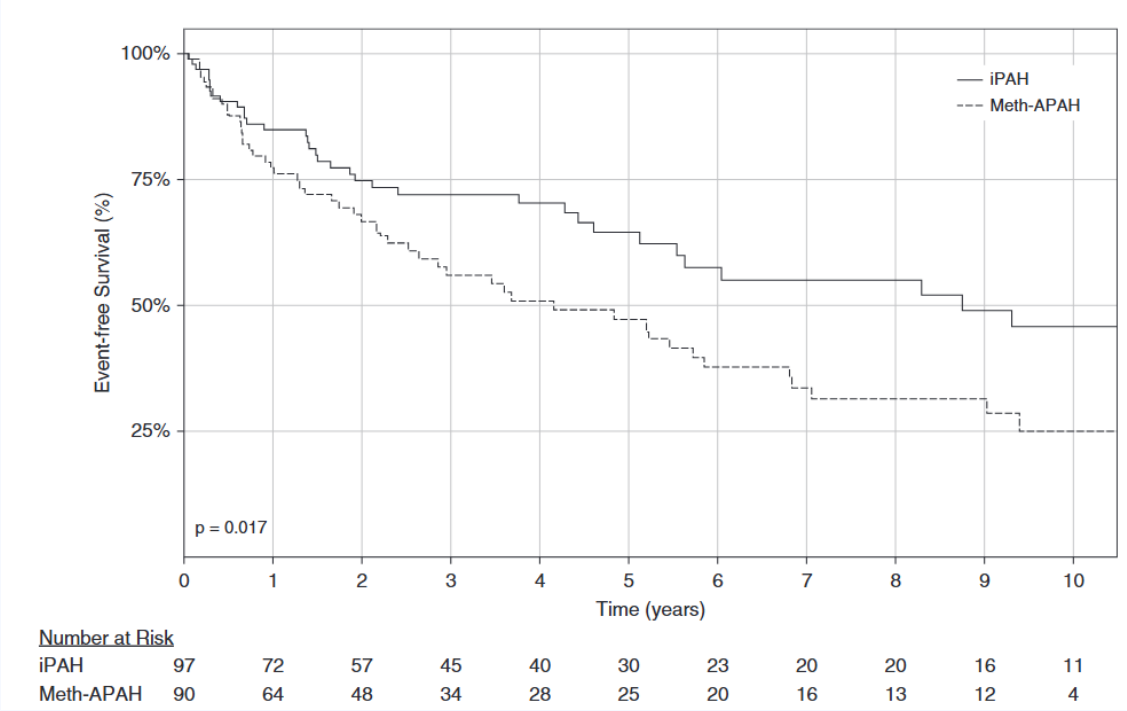
• Assaf et al., *JAMA*, 2025

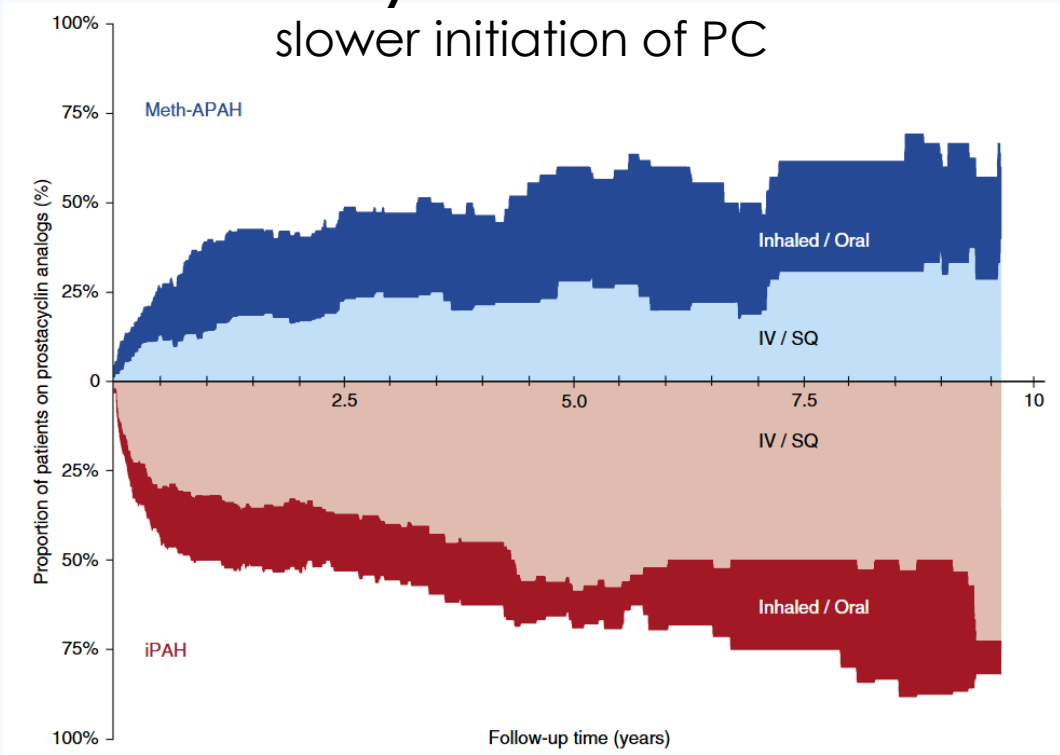
ORIGINAL ARTICLE

Features and Outcomes of Methamphetamine-associated Pulmonary Arterial Hypertension

Roham T. Zamanian[1,2], Haley Hedlin[3], Paul Greuenwald[4], David M. Wilson[5], Joshua I. Segal[6], Michelle Jorden[7], Kristina Kudelko[1,2], Juliana Liu[1,2], Andrew Hsi[1,2], Allyson Rupp[1,2], Andrew J. Sweatt[1,2], Rubin Tuder[8], Gerald J. Berry[6], Marlene Rabinovitch[2,9], Ramona L. Doyle[10], Vinicio de Jesus Perez[1,2*], and Steven M. Kawut[11*]

- **Worse outcomes**: RAP, SVI. Double the risk of clinical worsening or death
- **Poor prognosis:** Event free survival: 64.2% at 2.5 yr, 47.2% at 5 yr, 25% at 10yr
- **Delayed treatment:** MA-APAH slower initiation of PC





Zamanian et al., *AJRCCM*, 2018

California Thoracic Society
ATS Chapter Serving California and Arizona

Clinical Differences and Outcomes between Methamphetamine-associated and Idiopathic Pulmonary Arterial Hypertension in the Pulmonary Hypertension Association Registry

Nicholas A. Kolaitis[1], Roham T. Zamanian[2], Vinicio A. de Jesus Perez[2], David B. Badesch[3], Raymond L. Benza[4], Charles D. Burger[5], Murali M. Chakinala[6], Jean M. Elwing[7], Jeremy Feldman[8], Matthew R. Lammi[9], Stephen C. Mathai[10], John W. McConnell[11], Kenneth W. Presberg[12], Jeffrey C. Robinson[13], Jeffrey Sager[14], Oksana A. Shlobin[15], Marc A. Simon[16], Steven M. Kawut[17], David V. Glidden[18], Jonathan P. Singer[1], and Teresa De Marco[1]; on behalf of the Pulmonary Hypertension Association Registry Investigators

- MA-PAH patients were:
  - Younger and with lower SES
  - Had advanced FC and lower CI (similar PAP)
  - Worse PAH-specific QOL scores
  - Higher ER visits and hospitalizations
  - Less likely to receive Triple or parenteral therapy

Table 6. Healthcare use in participants with methamphetamine-associated PAH

Outcome	Incidence Rate Ratio (95% CI)	*P* Value
Unadjusted		
Emergency department visit	2.30 (1.71–3.10)	<0.001
Hospitalization	1.39 (1.10–1.76)	0.005
Adjusted for age, sex, race/ethnicity, education, body mass index, and the time-dependent covariate of whether the participant was on PAH-specific therapy or not		
Emergency department visit	2.30 (1.71–3.11)	<0.001
Hospitalization	1.42 (1.10–1.83)	0.007

Kolaitis, et al.,*Annals of ATS*, 2021

California Thoracic Society
ATS Chapter Serving California and Arizona

Social determinants of Health (social risks) in our patient

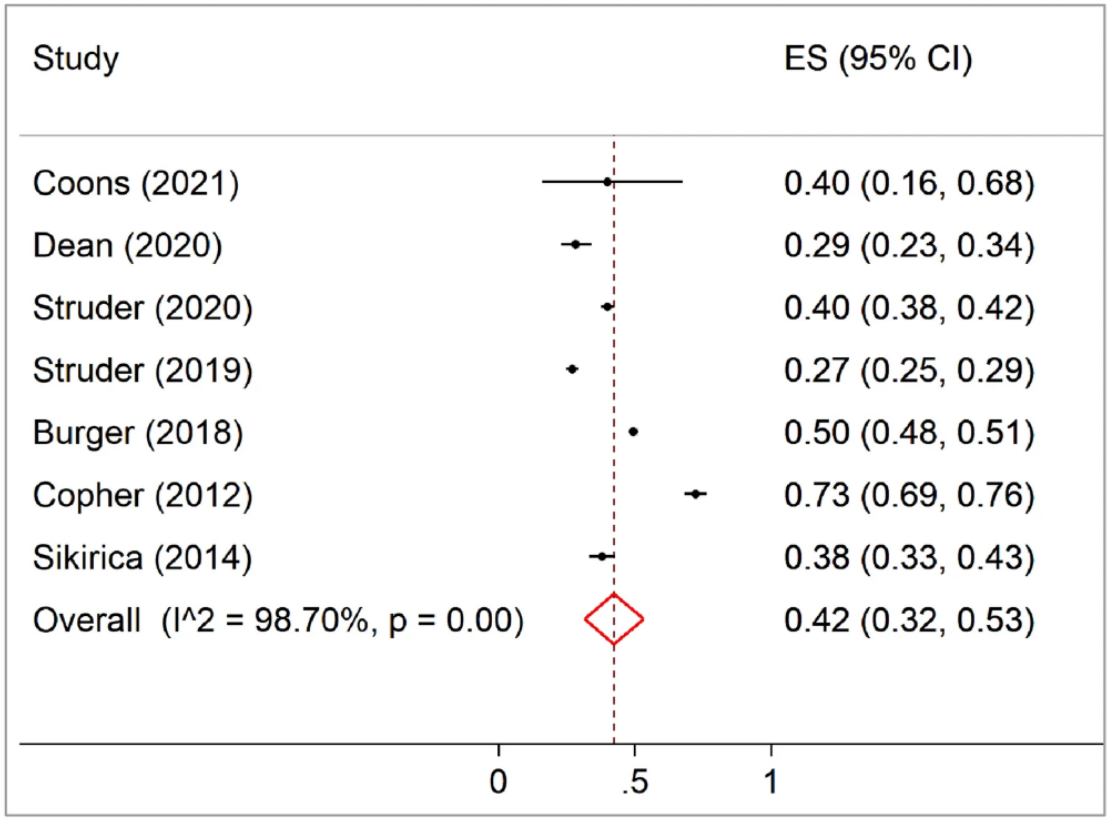
Sex/Gender: Female	Race/Ethnicity: Hispanic	Financial Challenge: Unemployed/ Pattern with inconsistent income	Health Care Insurance: Uninsured
Geographic/Social Challenges: Intermittent Homelessness	Education Level: Poor Literacy/ Language Barrier	Substance Abuse: Methamphetamine Use	Transportation Barriers: No transportation
	Treatment Adherence: Poor	Clinical Trial Participation: Failed	

Adherence and Discontinuation of Disease-Specific Therapies for Pulmonary Arterial Hypertension: A Systematic Review and Meta-Analysis

Sami Qadus[1] · Abdallah Y. Naser[1] · Richard Ofori-Asenso[2] · Zanfina Ademi[2,3] · Safaa Al Awawdeh[4] · Danny Liew[2,5]

Accepted: 4 October 2022 / Published online: 25 November 2022

- Pooled Adherence: 60.9%
- Pooled Discontinuation: 42.3%
- Factors Affecting Adherence:
  - **Adverse Effects**
  - Administration Frequency
  - **Co-payments**
  - Treatment Duration



CI = confidence interval; ES = proportion that discontinued

• Qadus et al., *American Journal of Cardiovascular Drugs*, 2022

RESEARCH ARTICLE

High rates of medication adherence in patients with pulmonary arterial hypertension: An integrated specialty pharmacy approach

Nisha B. Shah[1☯]*, Rhonita E. Mitchell[1☯], Stephanie Terry Proctor[2☯], Leena Choi[3‡], Joshua DeClercq[3‡], Jacob A. Jolly[1‡], Anna R. Hemnes[4‡], Autumn D. Zuckerman[1☯]

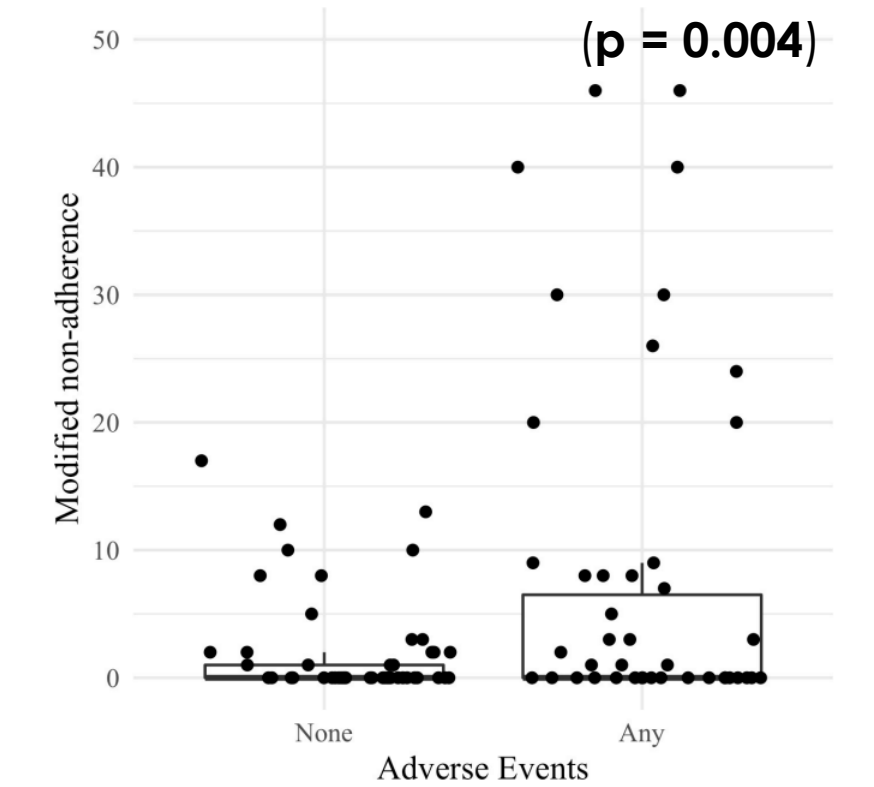


Table 2. Baseline demographics by proportion of days covered (PDC).

	PDC< 80% n (% of sample)	PDC≥ 80% n (% of sample)	*P*-value[a]
Race			0.786
Caucasian	7 (5)	95 (73)	
African American	1 (1)	27 (21)	
Alaska Native/American Indian	0	1 (<1)	
Smoking Status			0.072
Never smoker	8 (6)	73 (56)	
Previous smoker	0	38 (29)	
Current smoker	0	12 (9)	
Phosphodiesterase-5 inhibitor[b]			0.576
Sildenafil	2 (2)	43 (33)	
Tadalafil	6 (5)	81 (61)	
Concomitant therapy			
Endothelin receptor antagonist	4 (3)	64 (49)	0.91
Prostanoid	4 (3)	36 (27)	0.22
Calcium channel blocker	0	6 (5)	0.52
Prostacyclin receptor agonist	0	5 (4)	
Adverse Event			0.002
Yes	8 (6)	54 (41)	
No	0 (0)	69 (53)	
Hospitalization			0.910
Yes	2 (2)	33 (25)	
No	6 (5)	90 (69)	
Monthly out-of-pocket cost			0.838
$0	4 (3)	45 (34)	
>$0-$10	3 (2)	55 (42)	
>$10–100	1 (1)	17 (13)	
>$100	0 (0)	6 (5)	
Financial assistance			0.062
Yes	7 (5)	66 (50)	
No	1 (<1)	57 (44)	

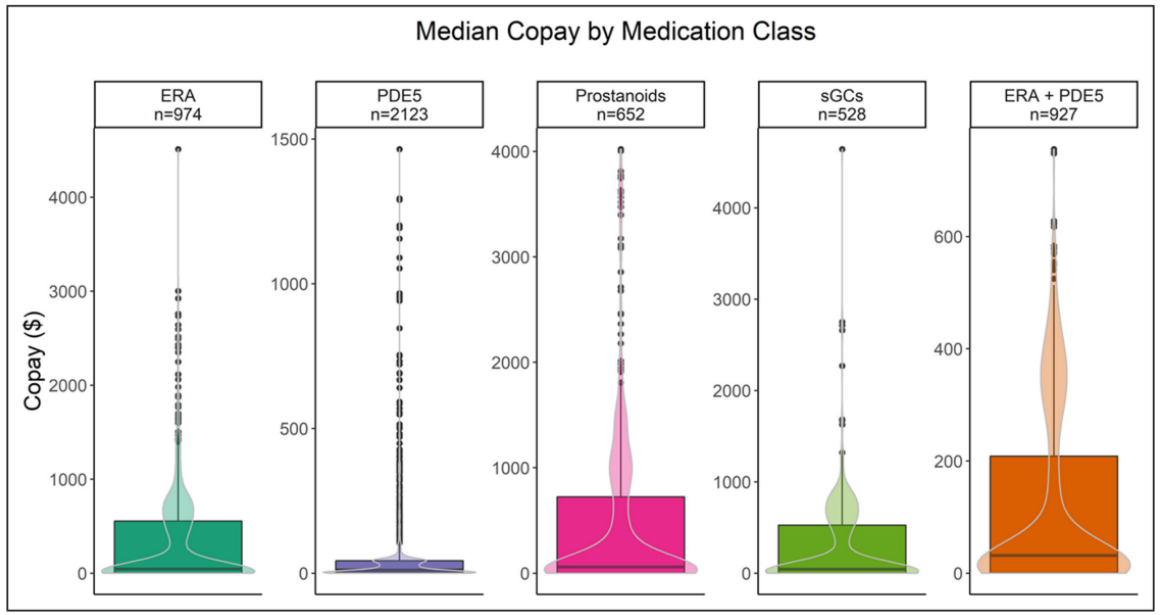
SHAH, *PLOS/ONE*, 2019

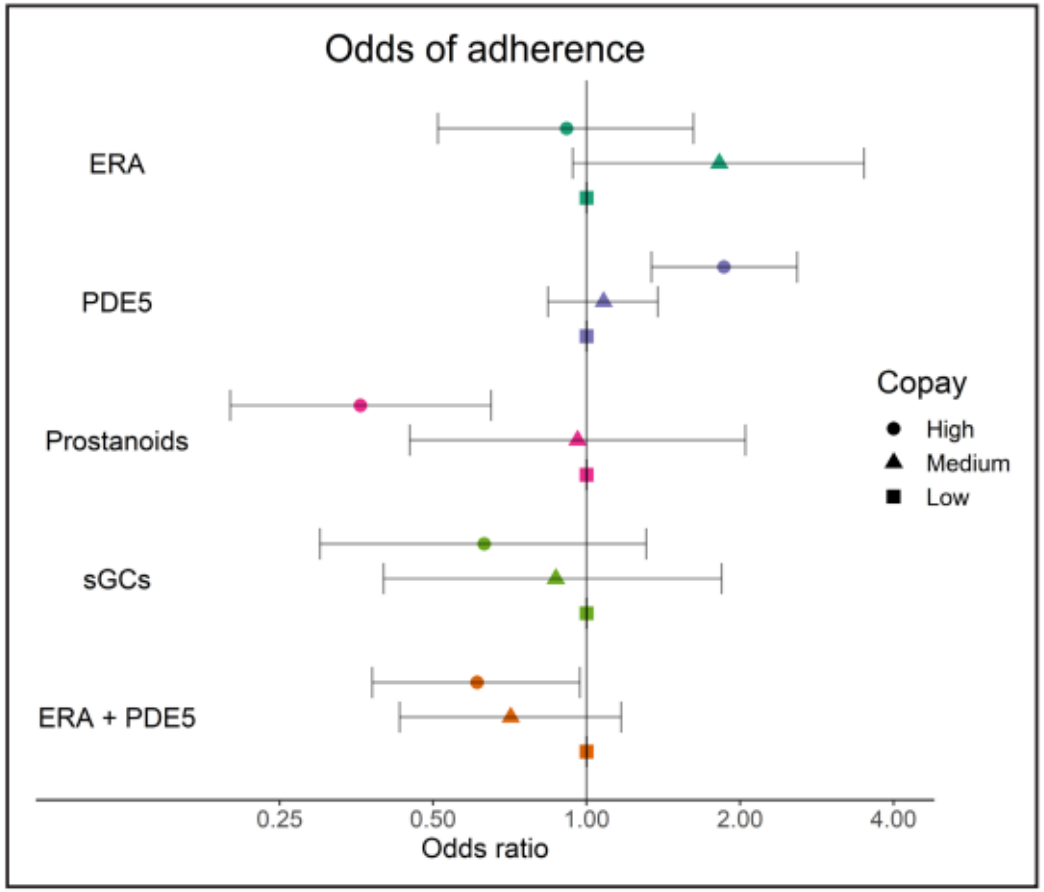
Journal of the American Heart Association

ORIGINAL RESEARCH

Association Between Copayment and Adherence to Medications for Pulmonary Arterial Hypertension

Erin M. Schikowski, MD; Gretchen Swabe, MSc; Stephen Y. Chan, MD, PhD; Jared W. Magnani, MD, MSc





Schikowski, *JAHA*, 2022

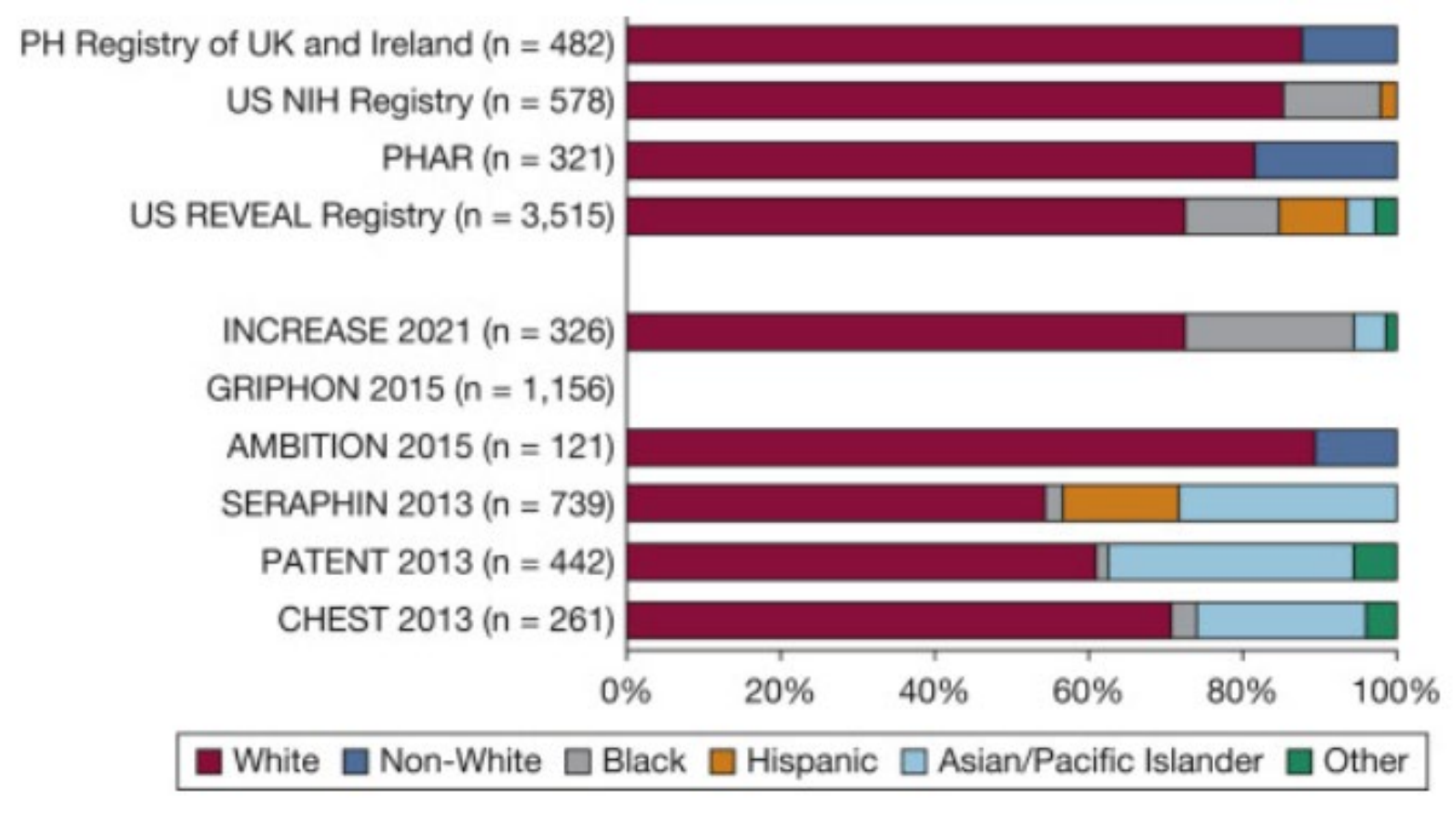
California Thoracic Society
ATS Chapter Serving California and Arizona

Social determinants of Health (social risks) in our patient

Sex/Gender: Female	Race/Ethnicity: Hispanic	Financial Challenge: Unemployed/ Pattern with inconsistent income	Health Care Insurance: Uninsured
Geographic/Social Challenges: Intermittent Homelessness	Education Level: Poor Literacy/ Language Barrier	Substance Abuse: Methamphetamine Use	Transportation Barriers: No transportation
	Treatment Adherence: Poor	**Clinical Trial Participation: Failed**	

Race/Ethnicity Representation in PH Registries and Trials

- Underrepresentation in Registries and Clinical Trials perpetuates health disparities:
  - Limiting applicability of research findings
  - Hindering access to effective treatments
  - Failing to address healthcare needs of minorities



Goel et al. *CHEST*, 2021

California Thoracic Society
ATS Chapter Serving California and Arizona

What Happened to Our Patient?

- In November 2023, she successfully gave birth to a healthy baby girl via an ECMO-supported C-section.
- In December 2024 we received a phone call informing us of the patient's death
- Factors leading to her death: meth use, inability to replenish oxygen supplementation, no access to phone, transportation or childcare.

California
Thoracic Society
ATS Chapter Serving California and Arizona

Proposed Solutions

Objectives:

✓Early Disease Recognition & Treatment

✓Optimize Access to PH Centers

✓Increase Minority Enrollment in Trials

Proposed Solutions:

✓ Develop Community PH Programs & Public Health Initiatives

✓ Increase Racial/Ethnic Diversity Among Providers

✓ Reduce Financial Barriers & Physician Biases

Enhancing Access to Care:

- Community Health Workers
- Telemedicine & Remote Monitoring
- Transportation Assistance

Addressing Language Barriers/Health Literacy:

- Interpreter Services
- Multilingual Resources
- Teach-Back Method & Digital Tools

Addressing Socioeconomic Barriers:

- Financial Assistance & Flexible Scheduling
- Workplace/Community Screenings

Improving Adherence:

- Integrated Care Model with Clinical Pharmacists
- Patient-Centered Care: Collaborative Decision-Making