Housekeeping Items

- Welcome to L.A. Care Provider Continuing Education (PCE) Program's Live Webinar!
- The Live Webinar is being recorded.
- Webinar participants are muted upon entry and exit of webinar.
- ***Webinar attendance will be noted via log in and call in with assigned unique Attendee ID #. Please log in through a computer (instead of cell phone) to Join Webinar / Join Event and choose the Call In option to call in by telephone with the event call in number, event access code and assigned unique attendee ID number. If your name does not appear on our WebEx Final Attendance and Activity Report (only as Caller User #) and no submission of online survey, no CME or CE certificate will be provided.***
- Questions will be managed through the Chat feature and will be answered at the end of the presentation. ***Please keep questions brief and send to All Panelists. One of our Learning and Development Team members and/or webinar host***, will read the questions via Chat when it's time for Q & A session (last 30 minutes of live webinar).
- Please send a message to the Host via Chat if you cannot hear the presenter or see the presentation slides.

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- ***Partial credits are not allowed at L.A. Care's CME/CE activities for those who log in late (more than 15 minutes late) and/or log off early.***

- PowerPoint Presentation is allotted 60 minutes and last 30 minutes for Q&A session, total of 90-minute webinar, 1.50 CME credits for L.A. Care Providers and other Physicians, 1.50 CE credits for NPs, RNs, LCSWs, LMFTs, LPCCs, LEPs, and other healthcare professionals. Certificate of Attendance will be provided to webinar attendees without credentials.

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- Within two (2) weeks after webinar and upon completion of the online survey, you will receive the PDF CME or CE certificate based on your credential and after verification of your name and attendance duration time of at least 75 minutes for this 90-minute webinar.

- The PDF webinar presentation will be available within 6 weeks after webinar date on lacare.org website located at https://www.lacare.org/providers/provider-central/provider-programs/classes-seminars

- Any questions about L.A. Care Health Plan's Provider Continuing Education (PCE) Program and our CME/CE activities, please email Leilanie Mercurio at lmercurio@lacare.org

Presenter's Bio

Dael Geft, M.D. is board certified in advanced heart failure/transplant cardiology, internal medicine, cardiovascular diseases, echocardiography and nuclear cardiology. He earned his bachelor's degree in philosophy and religion at Columbia University and his medical degree at the Sackler School of Medicine, Tel Aviv University, Israel.

He completed his internship and residency at Cedars-Sinai Medical Center followed by fellowship in cardiology and subspecialty training in advanced heart failure, heart transplant and mechanical circulatory support at Cedars-Sinai as well.

In addition to clinical practice, Dr. Geft has a keen interest in research, clinical trials and teaching. He has published and lectured on various topics including pulmonary hypertension, heart transplant, advanced heart failure and MCS. As a resident, Dr. Geft was awarded the Ben Newman Award for Excellence in Patient Care. During fellowship, he received the award for Outstanding Fellow of the Year.

Pulmonary Hypertension
From Diagnosis to Treatment

Dael Geft, M.D.
Cardiologist, Advanced Heart Failure/Transplant/MCS
Associate Director, Pulmonary Hypertension Research and Education
Assistant Professor, Dept. of Cardiology
Cedars-Sinai Smidt Heart Institute

May 30, 2024 Live Webinar, 12:00 pm – 1:30 pm PST, 1.50 CME/CE Credits
Directly Provided CME/CE Activity by L.A. Care Health Plan

Disclosures

The following CME planners and faculty do not have relevant financial relationships with ineligible companies in the past 24 months:

- Leilanie Mercurio, L.A. Care PCE Program Manager, CME Planner.
- Dael Geft, MD, Associate Director, Pulmonary Hypertension Research & Education; Assistant Professor, Dept. of Cardiology, Cedars-Sinai Smidt Heart Institute, CME Planner and Faculty.

An ineligible company is any entity whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Commercial support was not received for this CME/CE activity.

Learning Objectives

- List four (4) signs and symptoms of pulmonary hypertension and identify patients at risk.
- Specify at least two (2) ways how to accurately diagnose and risk stratify patients with pulmonary hypertension.
- State four (4) ways to monitor response to treatment.
- Formulate a long term treatment plan for patients with pulmonary hypertension.

Case - J.R.

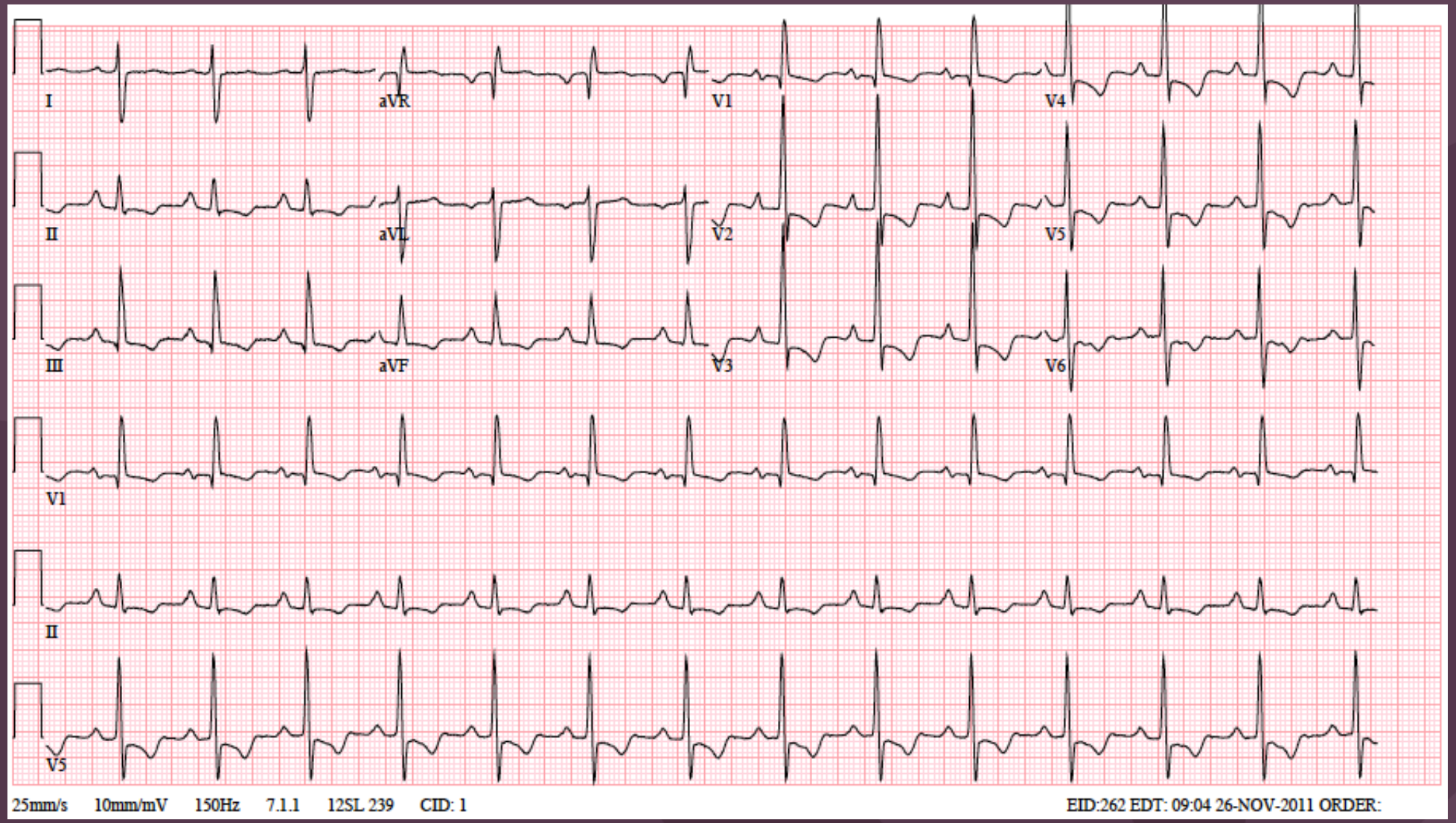
- 33-year old Female who began having shortness of breath during her sixth month of pregnancy
- Delivered healthy baby boy by C-section
- 3 months post partum, continues to have dyspnea on exertion

- Physical Exam:
  - HR 88 bpm, BP 110/75, O2 sat 98% RA
  - JVP to angle of jaw
  - Prominent S2
  - Lungs clear

- 6MWT: 390 meters

- CXR unremarkable

- Referred to cardiologist


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
II
V5
25mm/s 10mm/mV 150Hz 7.1.1 12SL 239 CID: 1
EID:262 EDT: 09:04 26-NOV-2011 ORDER:

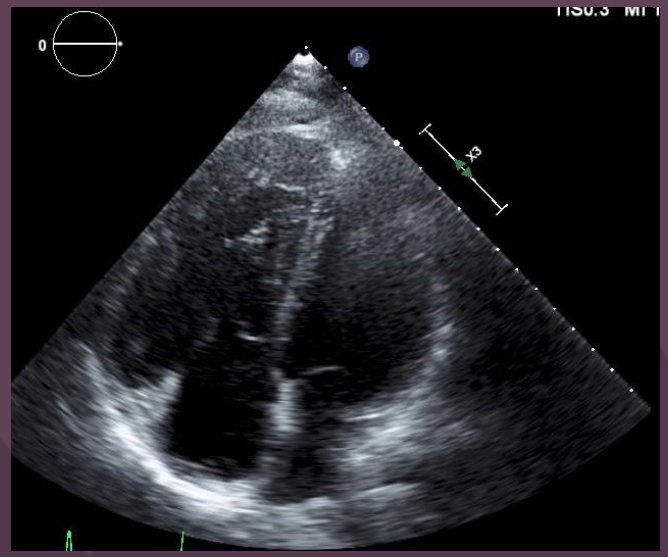
Case J.R.

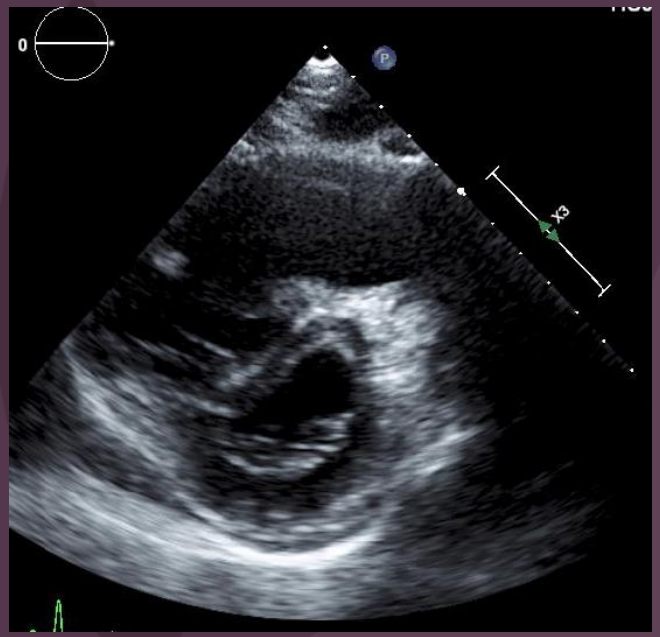
- Echocardiogram:
  - –Normal LV size , wall thickness and function
  - –Severely dilated right ventricle, mild RV dysfunction
  - –D-shaped septal flattening
  - –RA enlargement
  - –Moderate tricuspid regurgitation
  - –Estimated PA pressure 77 mmHg
  - –Small pericardial effusion
  - –Bubble study negative

- Labs: LFT, HIV, ANA, RF negative. Drug screen negative. BNP 132.

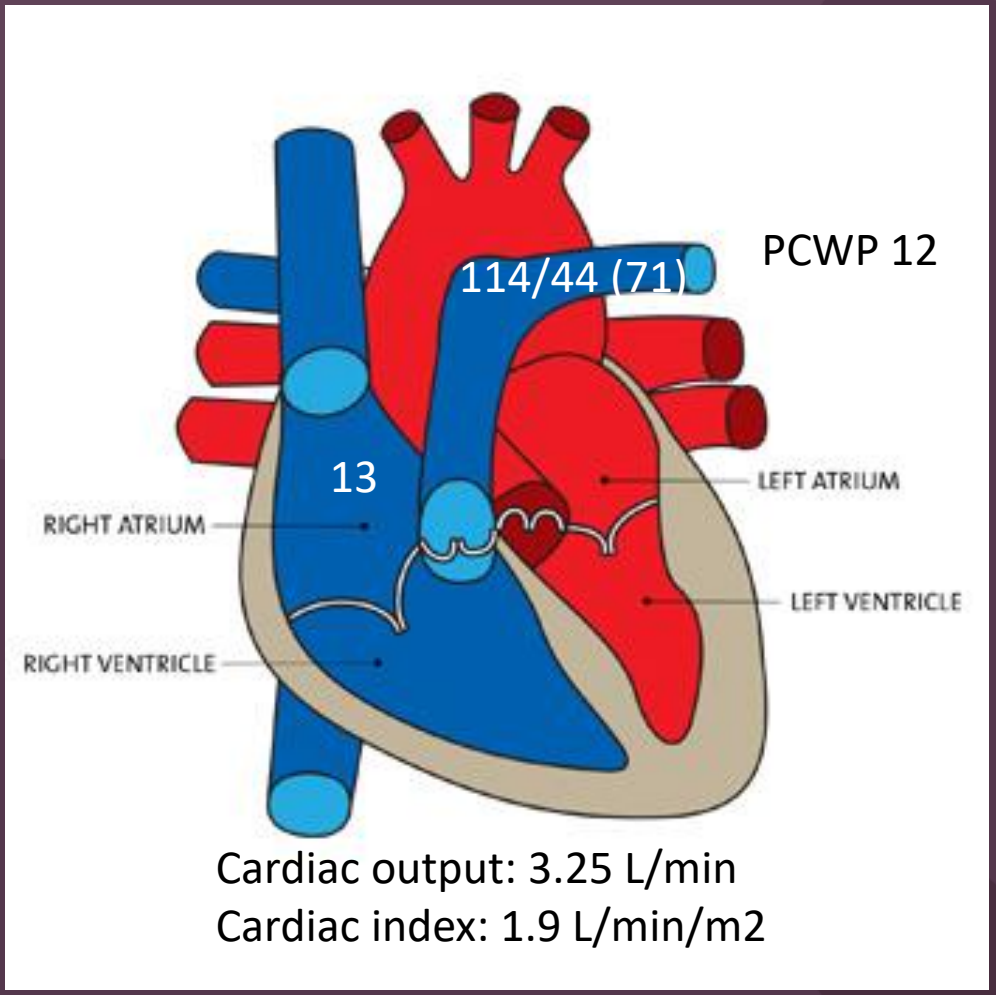
- CT chest: no e/o emphysema or ILD

- V/Q scan: low probability for PE





Right Heart Catheterization

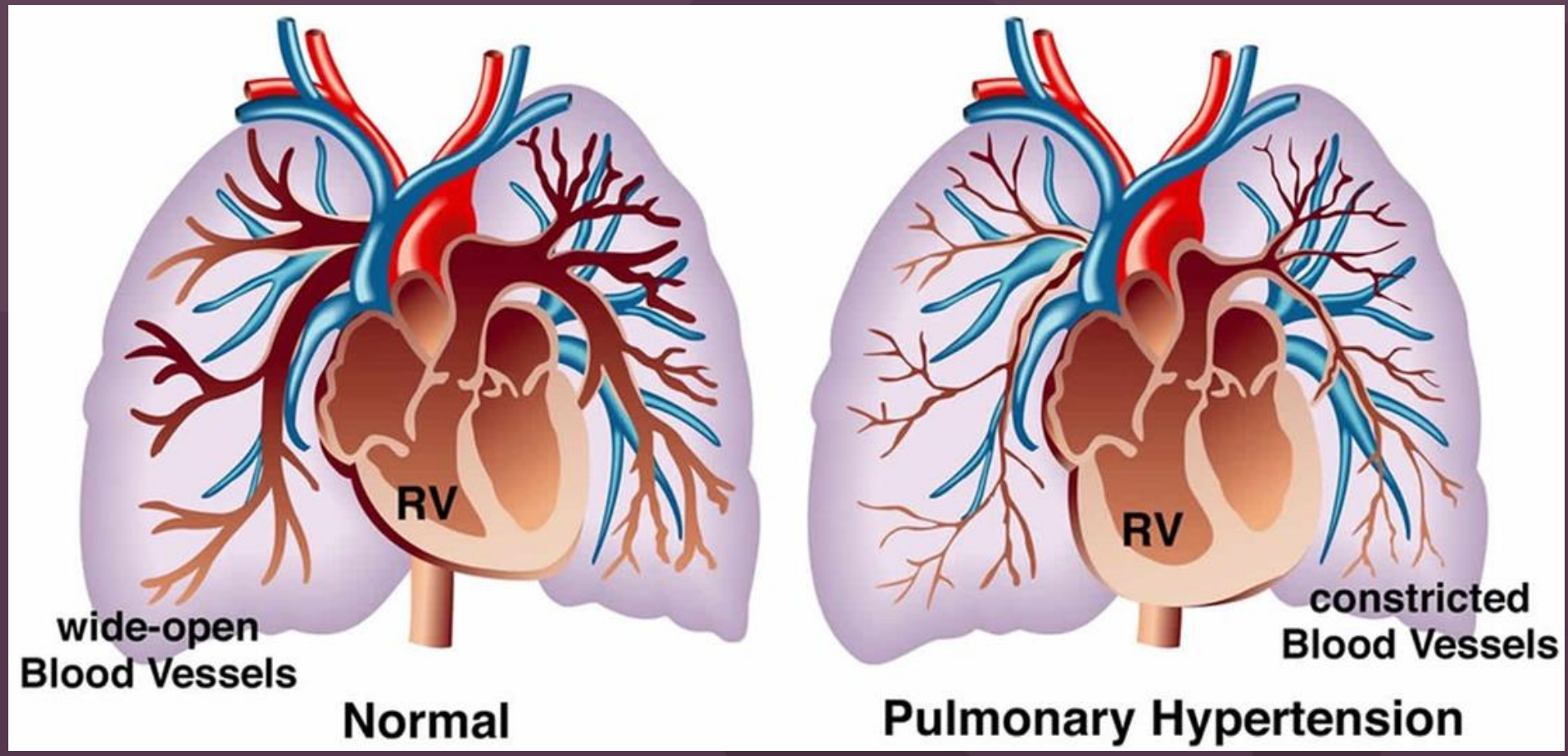


RA 13 mmHg (nml <6)
PA 114/44 (71) mmHg (nml 25/12)
PCWP 12 mmHg (nml < 12)
Cardiac output: 3.25 L/min
Cardiac index: 1.9 L/min/m2 (nml >2.2)
PVR: 18 Wood units (nml <2)

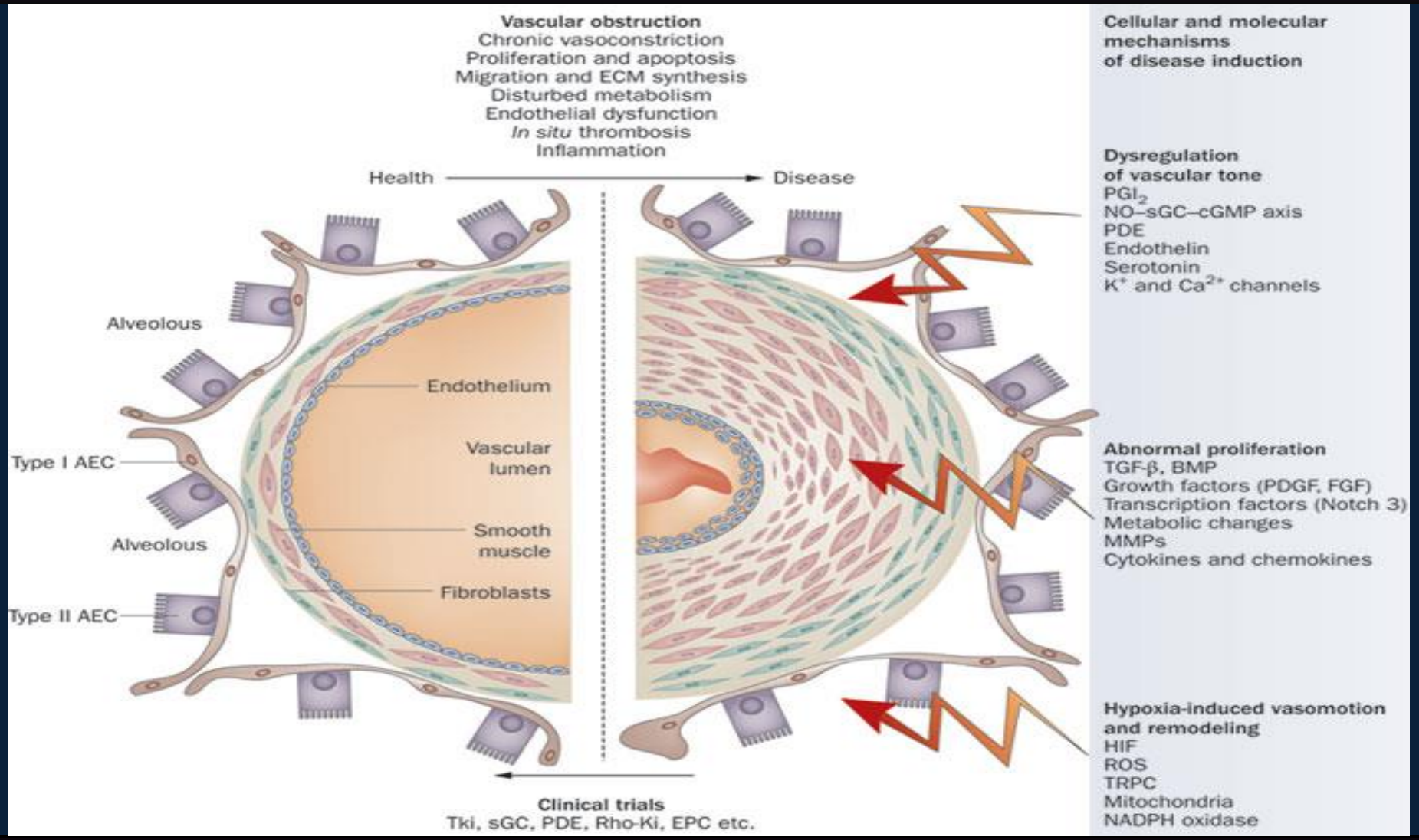
Inhaled nitric oxide study: non-reactive

Dx: Idiopathic PAH confirmed

What is Pulmonary Hypertension?



Vascular Remodeling in Pulmonary Arterial Hypertension



Schermuly, R. T. *et al.* (2011) Mechanisms of disease: pulmonary arterial hypertension
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2011.87

Previous “arbitrary” definition

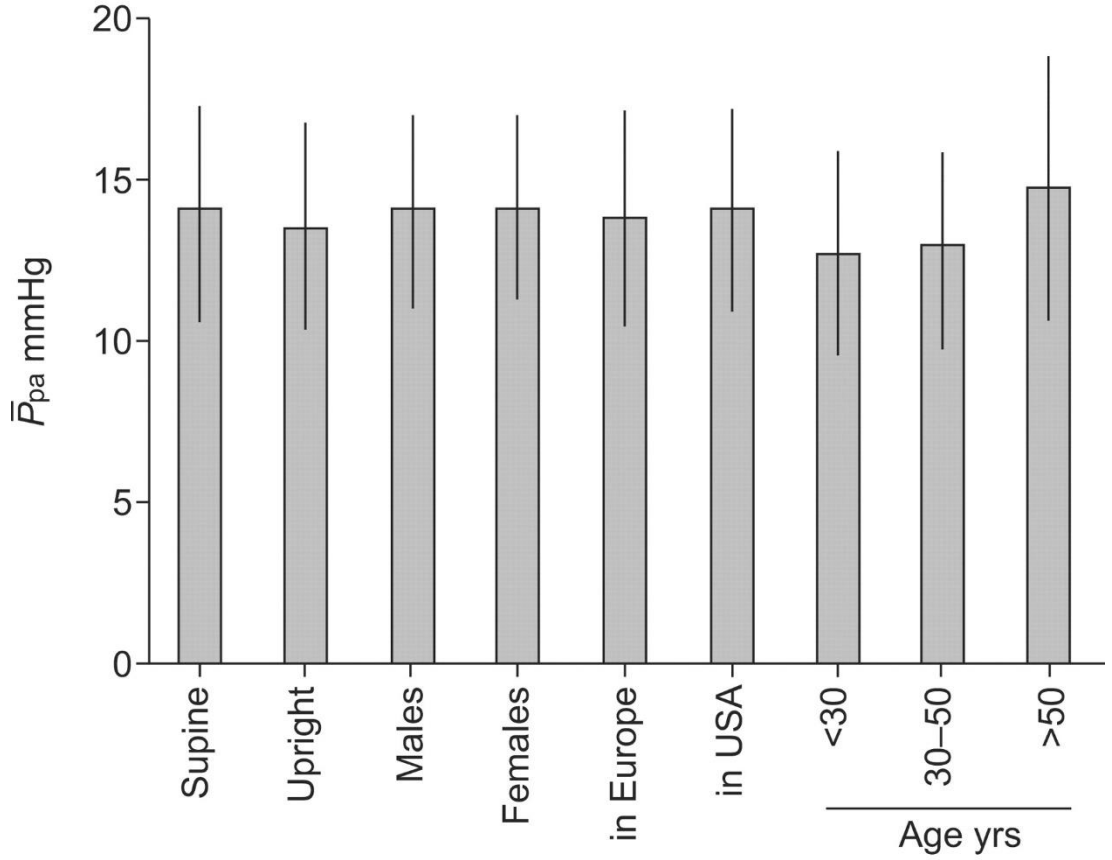
From the 5th World Symposium on PH: This was the Hemodynamic Definition of PH/PAH

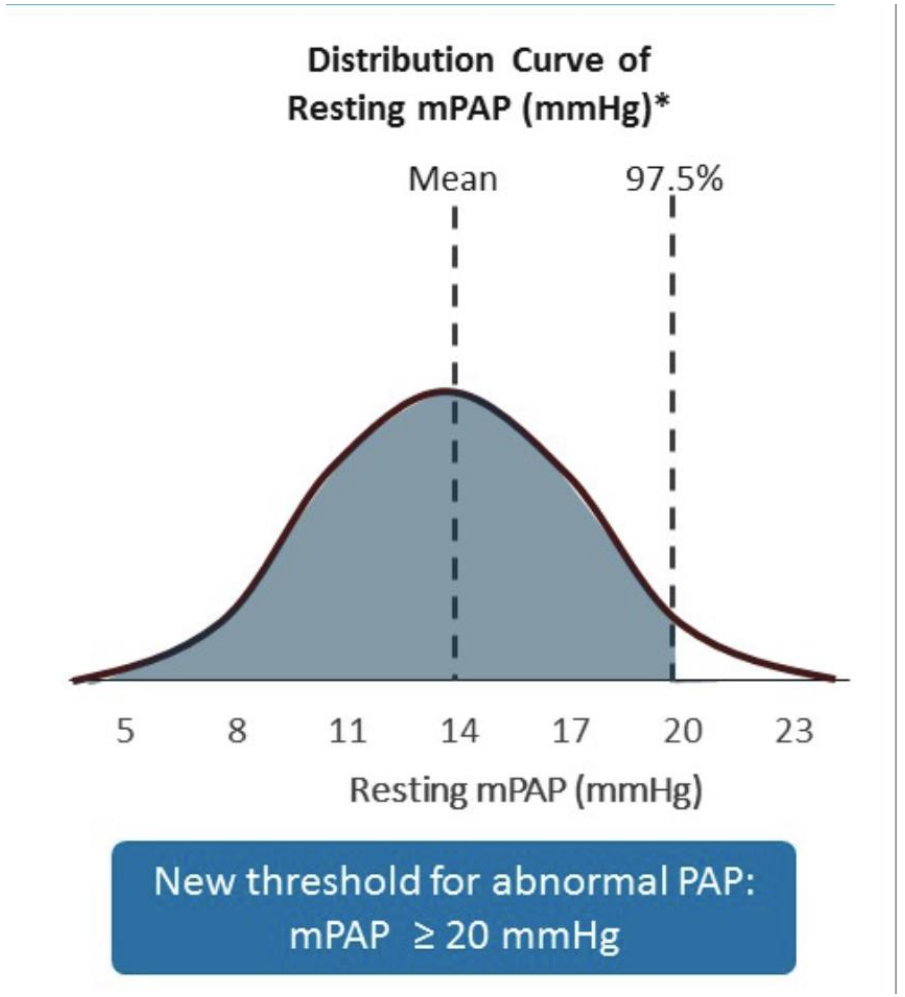
PH Mean PAP ≥25 mm Hg at rest during RHC

PAH Mean PAP ≥25 mm Hg *plus* PAWP ≤15 mm Hg *plus* PVR >3 Wood units

Hoeper MM, Bogaard HJ, Condliffe R, *et al.* Definitions and Diagnosis of Pulmonary Hypertension. *J Am Coll Cardiol.* 2013;62:D42-D50.

Mean Pulmonary Arterial Pressure ($\bar{P}$pa) of Healthy Subjects at Rest According to Different Strata.

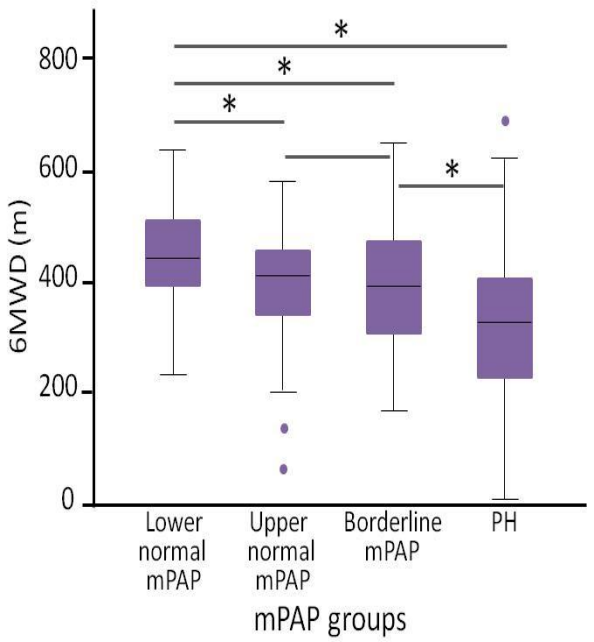




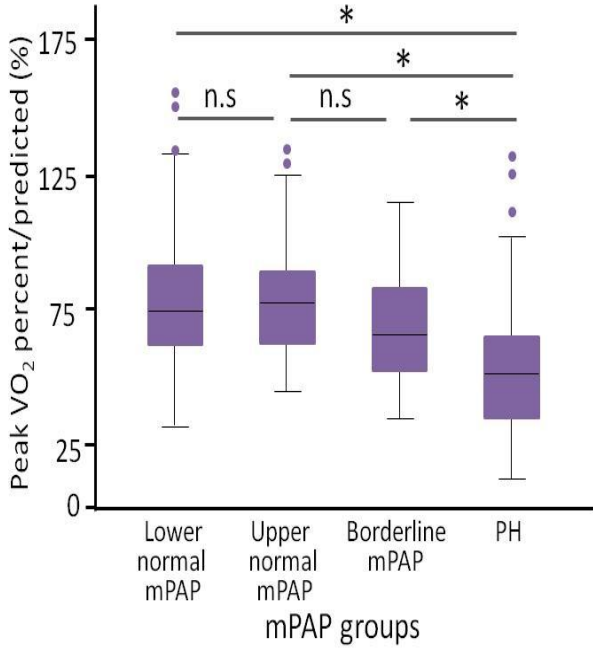
G. Kovacs et al. Eur Respir J 2009;34:888-894

Mild Increase in mPAP is Associated with Decreased Physical Activity and Increased Mortality

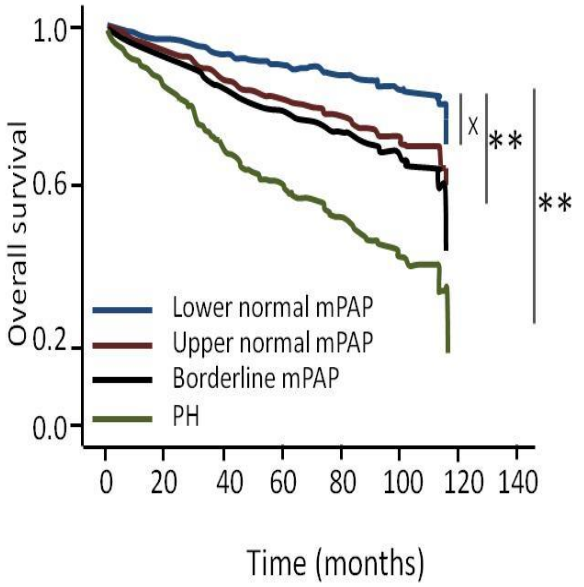
6MWD



Peak VO_2



All-Cause Mortality



Lower normal mPAP	≤17 mm Hg
Upper normal mPAP	17.4 – 20.6 mm Hg
Borderline mPAP	20.6 – 24.9 mm Hg
PH	≥25 mm Hg

* P <0.05; ** P<0.001; mPAP = mean pulmonary arterial pressure; 6MWD = 6-minute walking distance; VO_2 = peak oxygen uptake

Douschan P, Kovacs G, Avian A, *et al.* Mild Elevation of Pulmonary Arterial Pressure as a Predictor of Mortality. *Am J Respir Crit Care Med* 2018 ;197(4):509–516

Hemodynamic Definition of PH/PAH- WSPH 2018

"Out With the Old, In With the New"

Old "arbitrary" Definition

PH

Mean PAP ≥25 mm Hg

PAH

- Mean PAP ≥25 mm Hg *plus*
- PCWP/LVEDP ≤15 mm Hg and
- PVR > 3 WU (ESC/ERS >2 WU)

New Definition (WSPH 2018)

PH

Mean PAP ≥20 mm Hg

PAH

- Mean PAP ≥20 mm Hg *plus*
- PCWP/LVEDP ≤15 mm Hg and
- PVR > 3 WU (ESC/ERS >2 WU)

Simonneau,G et al. WSPH 2018. European Respiratory Journal.

Updates to Hemodynamic Definition of PH

Definition	Hemodynamic Characteristics
Pulmonary hypertension	mPAP > 20 mmHg
Precapillary pulmonary hypertension	mPAP > 20 mmHg PAWP ≤ 15 mmHg PVR > 2 Wood Units
Isolated postcapillary pulmonary hypertension (IpcPH)	mPAP > 20 mmHg PAWP > 15 mmHg PVR ≤ 2 Wood Units
Combined pre- and postcapillary pulmonary hypertension	mPAP > 20 mmHg PAWP > 15 mmHg PVR > 2 Wood Units
Exercise pulmonary hypertension	mPAP/CO Slope between rest and exercise > 3 mmHg/L/min.

CO, cardiac output; CpcPH, combined post- and pre-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units. Some patients present with elevated mPAP (> 20 mmHg) but low PVR (≤ 2 WU) and low PAWP (≤ 15 mmHg); this hemodynamic condition may be described by the term ‘unclassified PH’ (see text for further details).
Copied with permission from Humbert et al. (2022).

WSPH 2018: New Clinical Classification of PH

1. Pulmonary Arterial Hypertension

1.1 Idiopathic PAH
1.2 PAH with vasoreactivity
1.3 Heritable PAH
1.4 Drugs and toxins induced
1.5 Associated with:
- 1.5.1 Connective tissue disease
- 1.5.2 HIV infection
- 1.5.3 Portal hypertension
- 1.5.4 Congenital heart disease
- 1.5.5 Schistosomiasis

1.6 PAH with overt signs of venous/capillaries (PVOD/PCH) involvement
1.7 Persistent PH of the Newborn syndrome

2. PH due to left heart disease

2.1 PH due to heart failure with preserved E.F
2.2 PH due to heart failure with reduced E.F
2.3 Valvular heart disease
2.4 Congenital/acquired CV conditions leading to post-capillary obstructive lesions

3. PH due to lung diseases and/or hypoxia (Table 6)

3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders

4. PH due to pulmonary artery obstruction

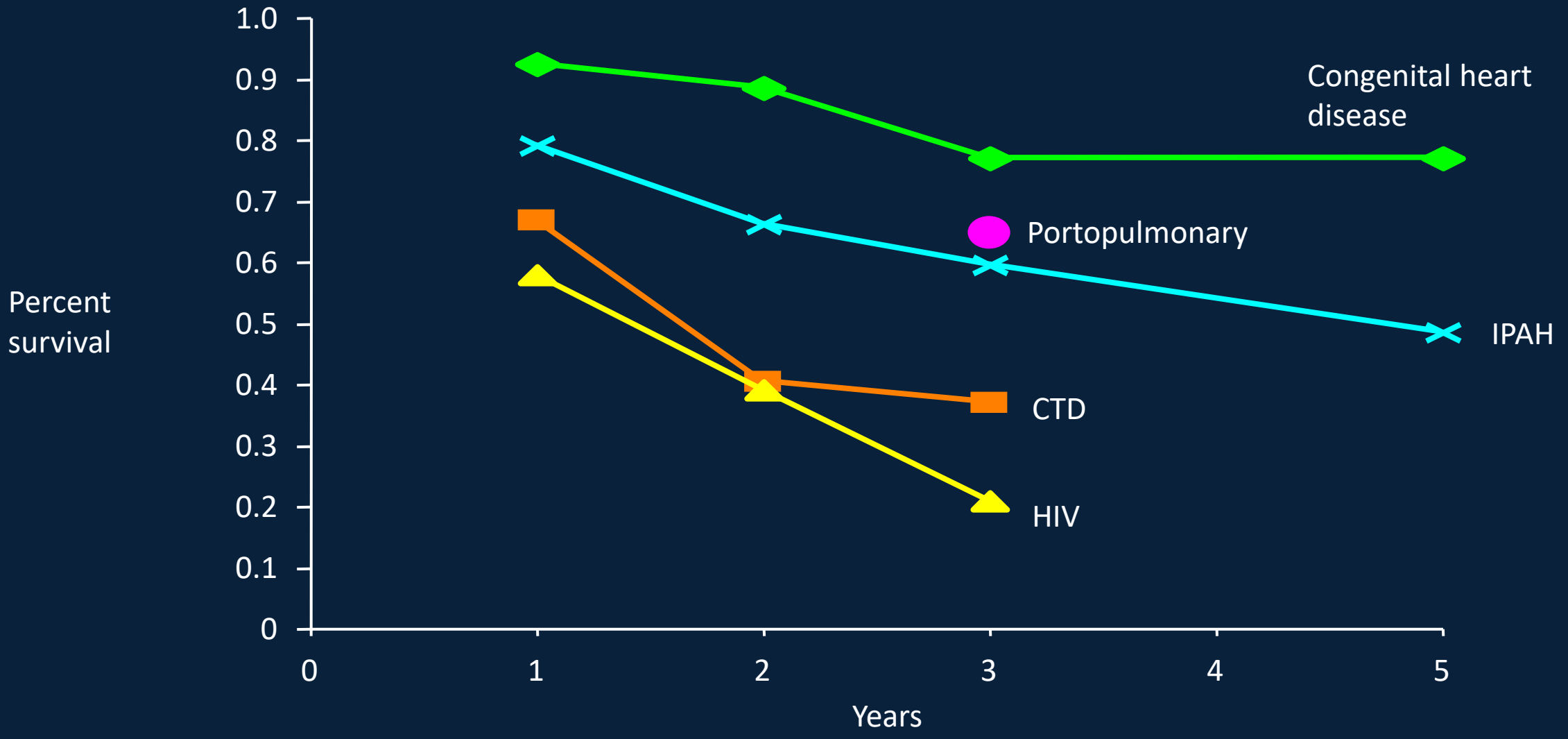
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions

5. PH with unclear mechanisms (Table 8)

5.1 Haematologic disorders (MPD/MDS, chronic hemolytic anemia)
5.2 Systemic disorders (sarcoidosis, Gaucher, histiocytosis…)
5.3 Others (ESRD +/- hemodialysis/fistula, Fibr. Mediastinitis)
5.4 Complex congenital heart disease

Simonneau, G et al. 2019. Eur Respirat Journal

Survival in PAH



McLaughlin VV et al. *Chest.* 2004;126:78S-92S.

Epidemiology – pulmonary hypertension

- Group I PAH) – lowest estimate 2.4 cases/million adult population per year (range 5-10 cases/mil)
  - ~50% idiopathic, heritable or drug-induced
  - CTD (Systemic sclerosis) leading cause among associated conditions
  - 1981 mean age 36, female:male 1.8:1 → today mean age 50-65 and female predominance is quite variable
- Group II (LHD)
  - 60% of patients with severe LV dysfxn (HFrEF) and 70% of HFpEF
  - Virtually all patients with symptomatic mitral valve dz and 65% aortic stenosis

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
Galie, N et al: Eur Heart J. 37: 67-119; Galie N, et al. Eur Respir J 2015; 46:903-975

Epidemiology – pulmonary hypertension

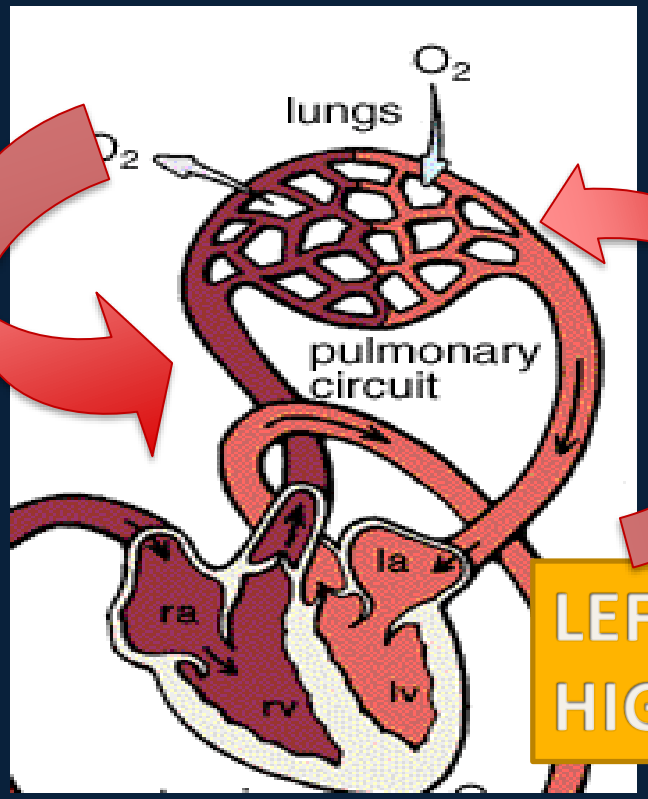
- Group III (Lung dz) – mild PH in severe ILD/COPD but severe PH is uncommon

- Group IV (CTEPH)
  - prevalence 3.2 cases per million
  - incidence of CTEPH after acute PE is 0.5-2%
  - 75% of CTEPH have h/o acute PE

Pepke-Zaba, et al, CTEPH: results from an international prospective registry. Circulation 2011;124: 1973-1981

Pathophysiology of PH in Left Heart Disease

PULMONARY HYPERTENSION



Rx that decreases PCWP normalizes PAP (Reversible)
No structural PA abnormalities at early stage.

Passive component
Increased PCWP/PA

Reactive

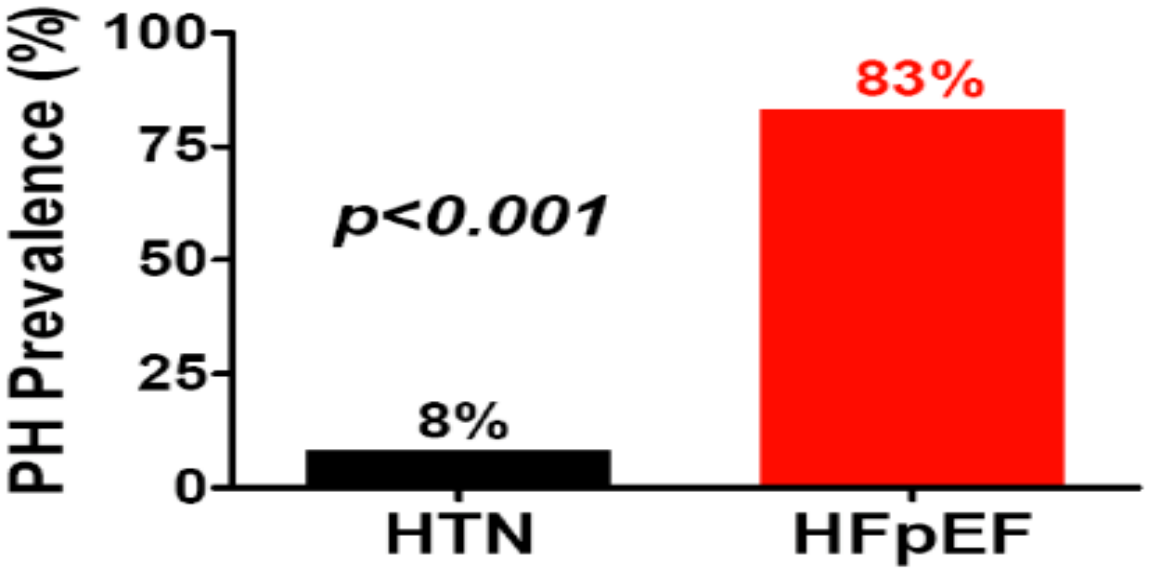
Chronic increase in PA pressure causes "intrinsic" PH, reversible or fixed .
TPG & PVR increases ("**REACTIVE**").
Lowering PCWP and PAP may require vasodilators and/or inotropes.
If PAP, TPG, and PVR cannot be normalized, PH is called fixed.
Structural PA abnormalities may exist.
RV failure may follow

LEFT HEART DISEASE/ HIGH LAP or LVEDP

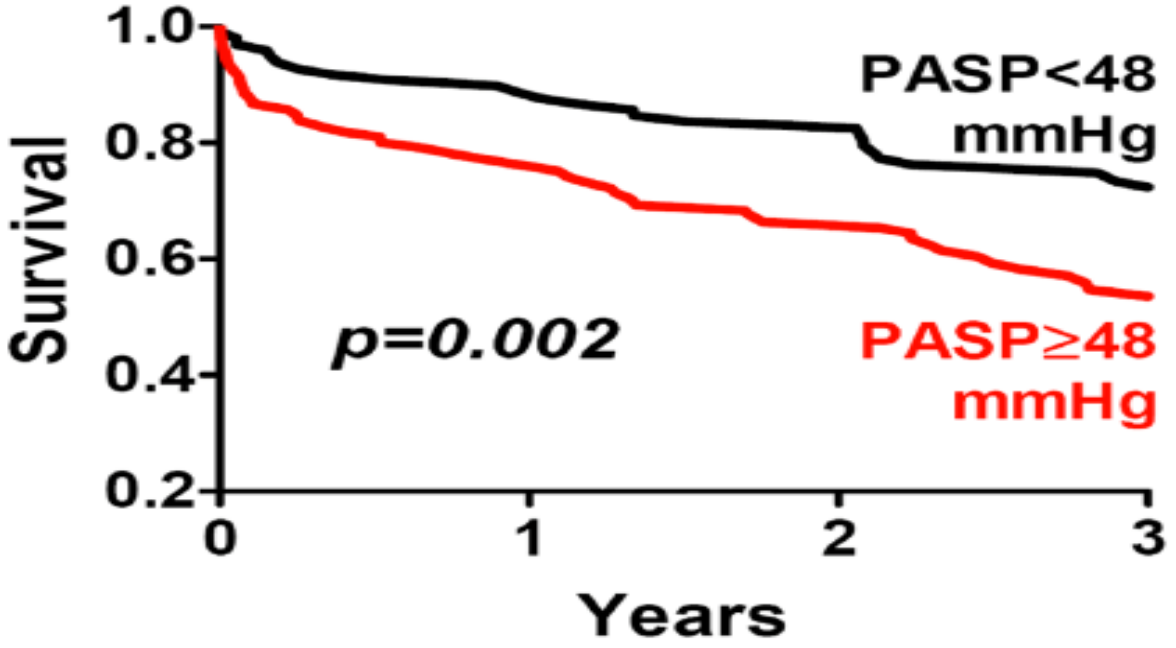
Drazner, M et al, JHLT 1999,18: 1126-1132 and Circ Heart Fail, 2010,3: 202-206

Epidemiology and Prognostic Impact of PH in Diastolic Heart Failure

Prevalence



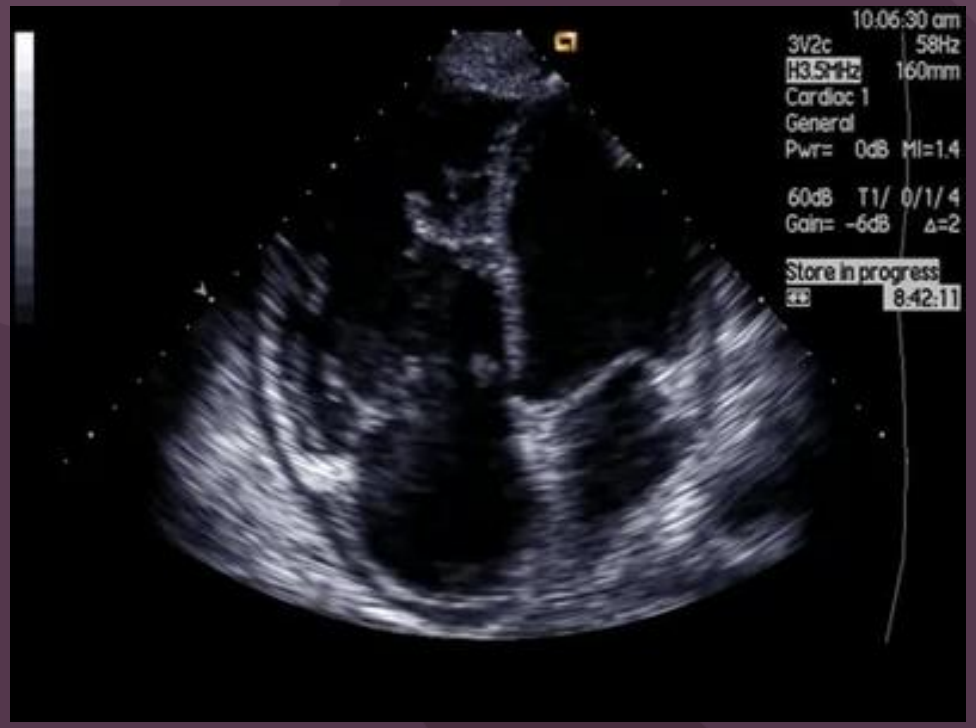
Survival



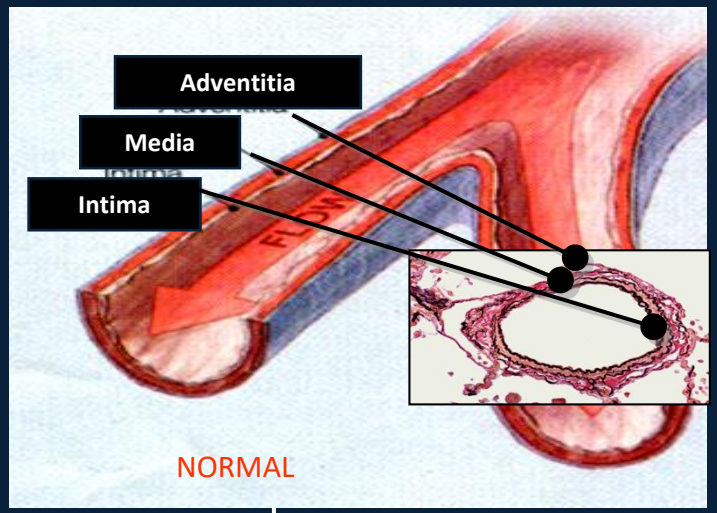
HFpEF: PASP > 35 mmHg present in 83% (median PASP 48 mmHg)
PVH does not fully account for the severity of PH in HFpEF

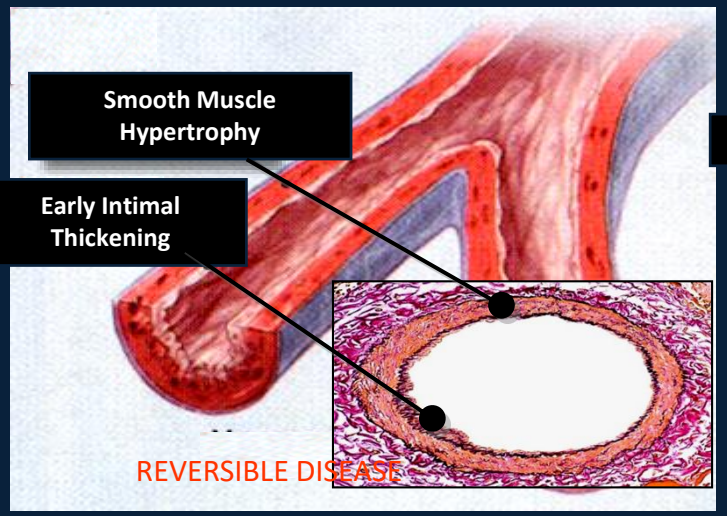
Lam et al., *JACC* 2009; 53: 1119-1126

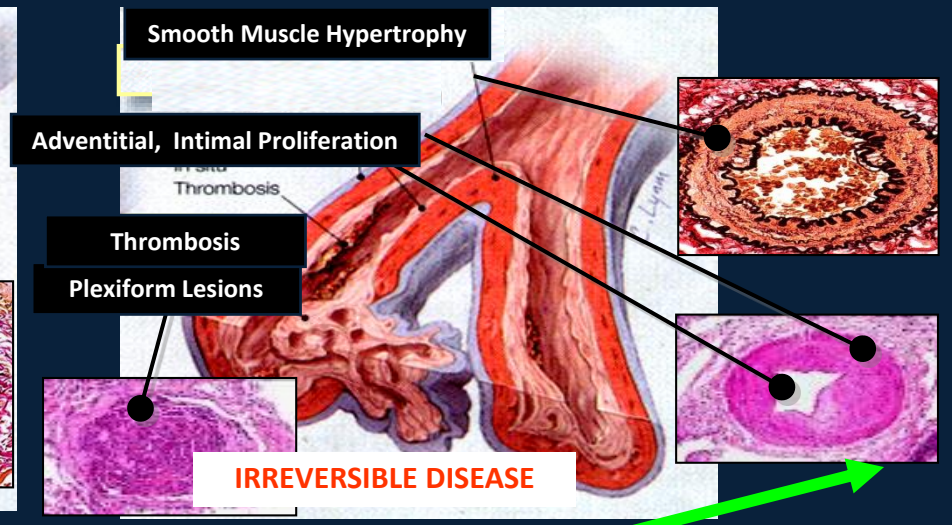
We cannot succeed if the RV fails

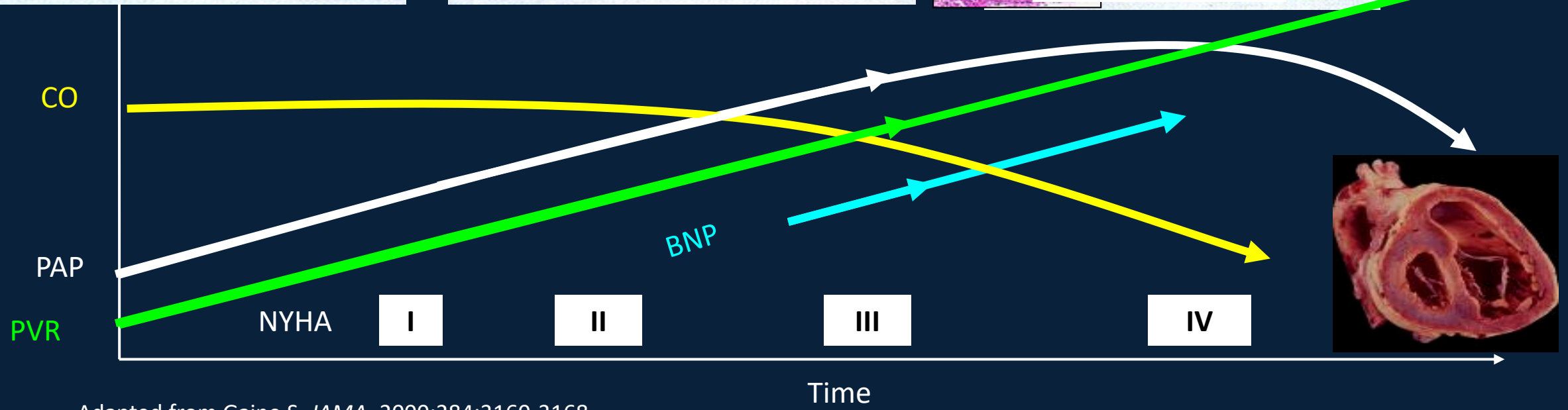


PAH: Hemodynamic and Clinical Course



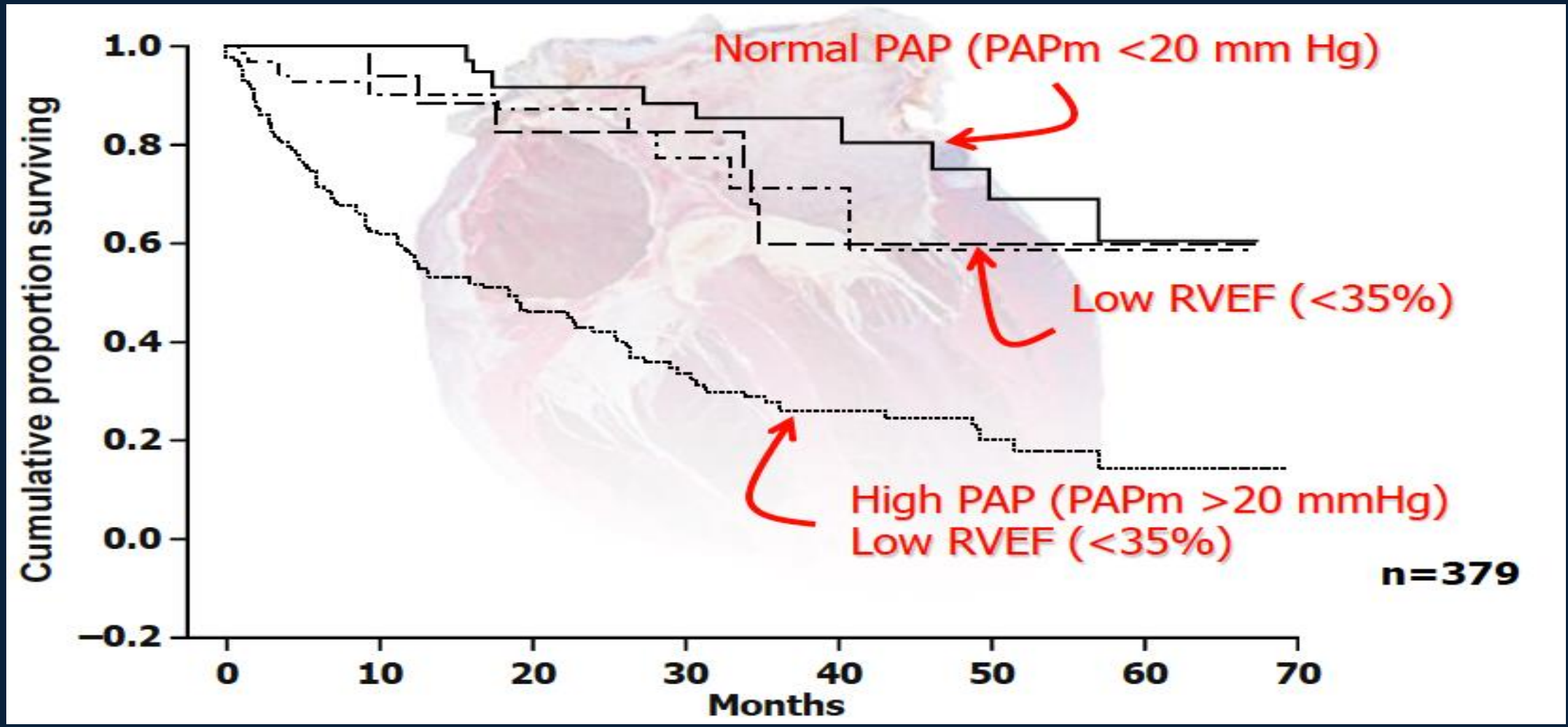






Adapted from Gaine S. *JAMA.* 2000;284:3160-3168.

Survival rates without urgent heart transplantation in patients grouped according to the coupling between mean pulmonary artery pressure (PAP) and right ventricular ejection fraction (RVEF)

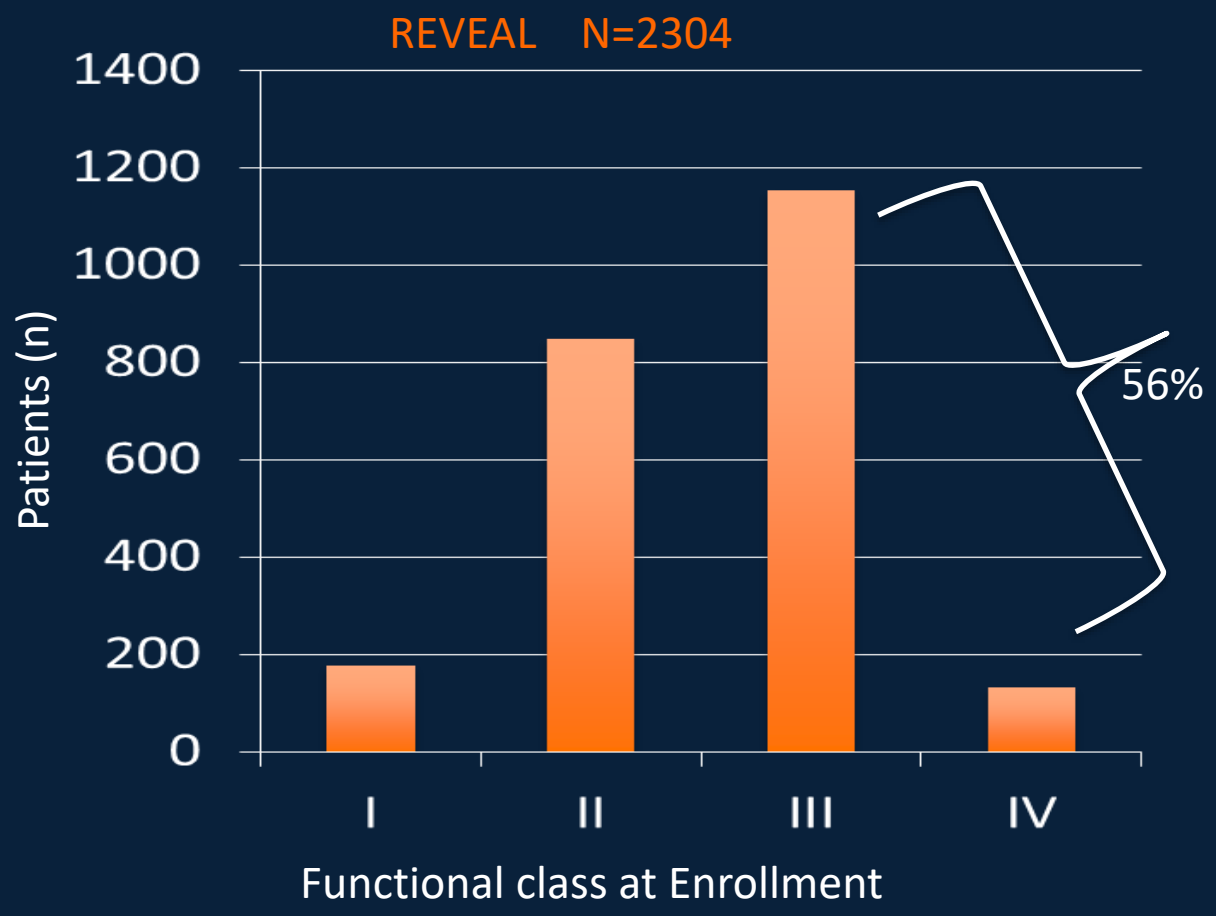


Ghio, S. et al. J Am Coll Cardiol 2001;37:183-188

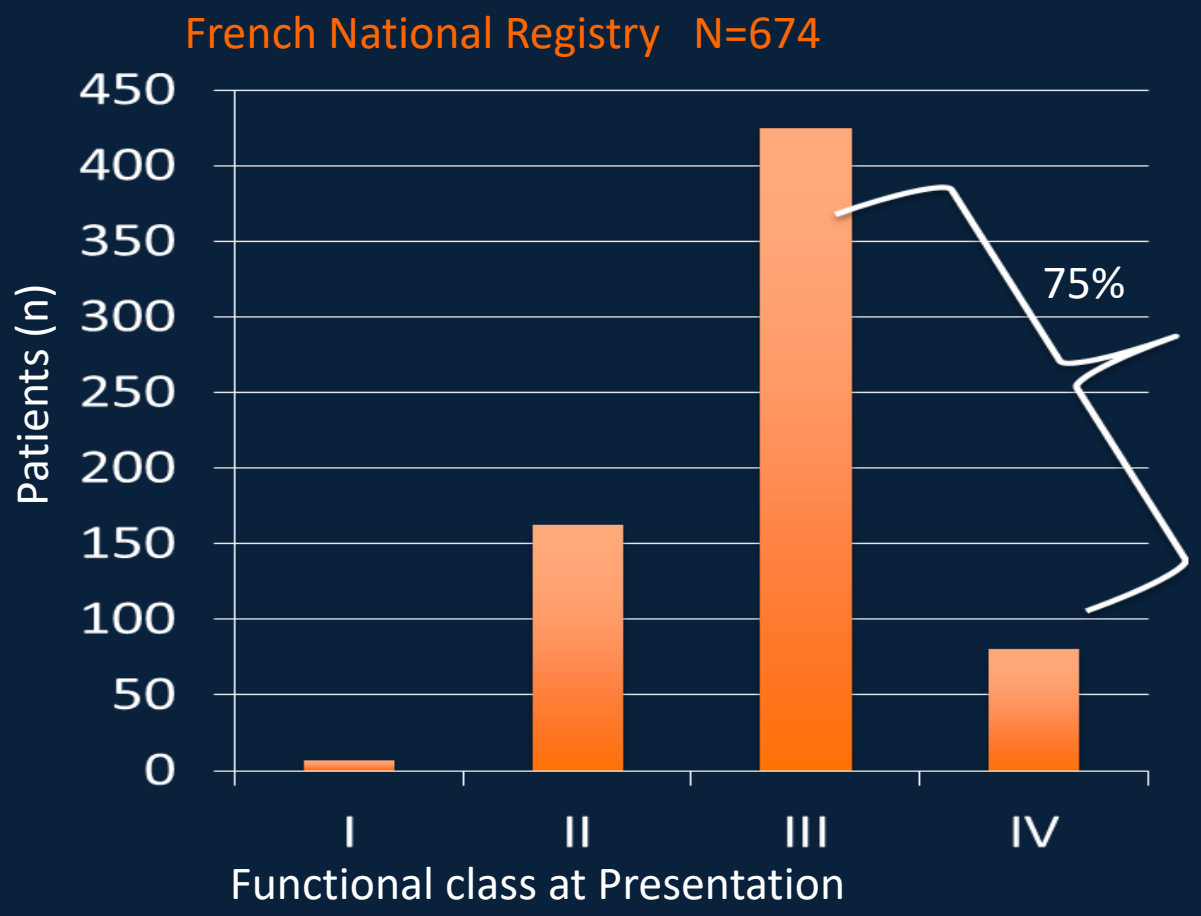

IT'S NEVER TOO LATE!

Diagnosis of PAH is Often Late

Mean time between symptom onset and diagnosis: 2.8 years



Mean time between symptom onset and diagnosis: 2.3 years

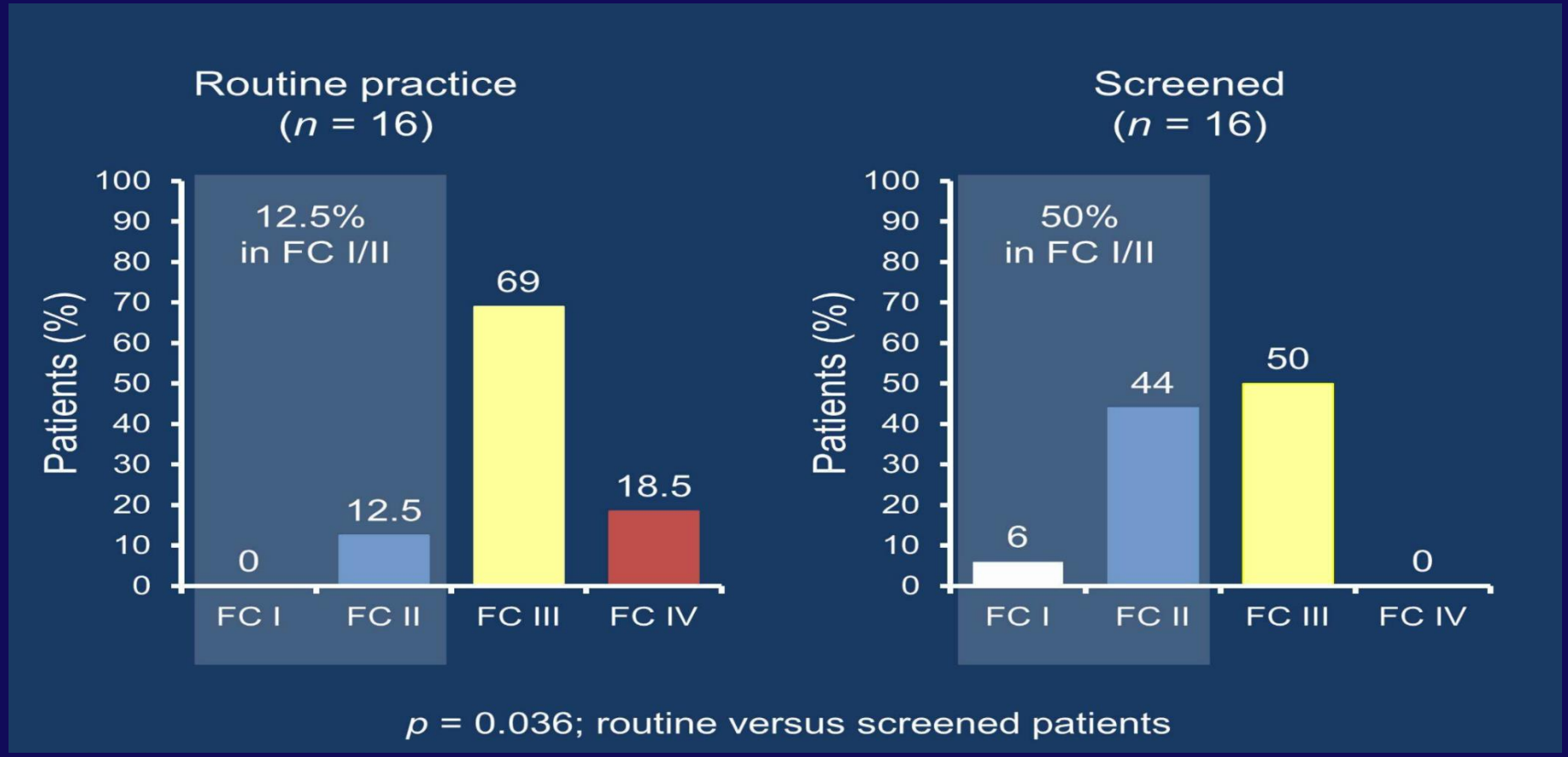


REVEAL= Registry to Evaluate Early and Long-term PAH Disease Management

Badesh DB et al. Chest 2010, 137:376-387.

Humbert M et al. Am J Resp Crit Care Med 2006; 173: 1023-1030

Screening Can Help in Diagnosing the Disease in an Early Stage



Without screening, the majority of patients were diagnosed in WHO FC III or FC IV, and only 12.5% were in WHO FC II

Humbert, M et al. Eur Respir Rev 2012; 21: 126, 306–312

Humbert , M et al. Arthritis Rheum 2011; 63: 3522-3530

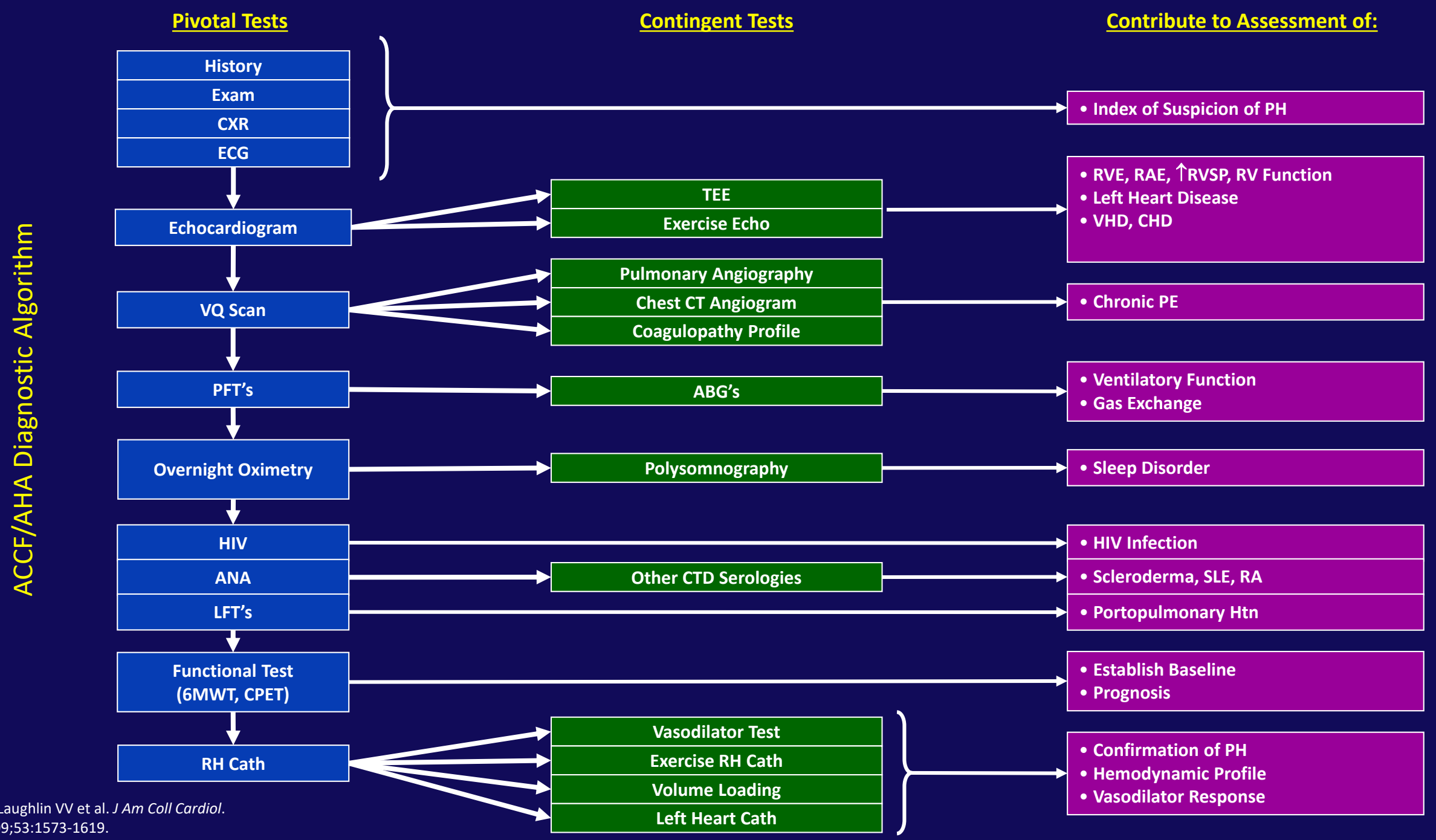
Pivotal Tests

History
Exam

- Dyspnea
- Fatigue
- Angina
- Syncope
- Palpitations
- Edema

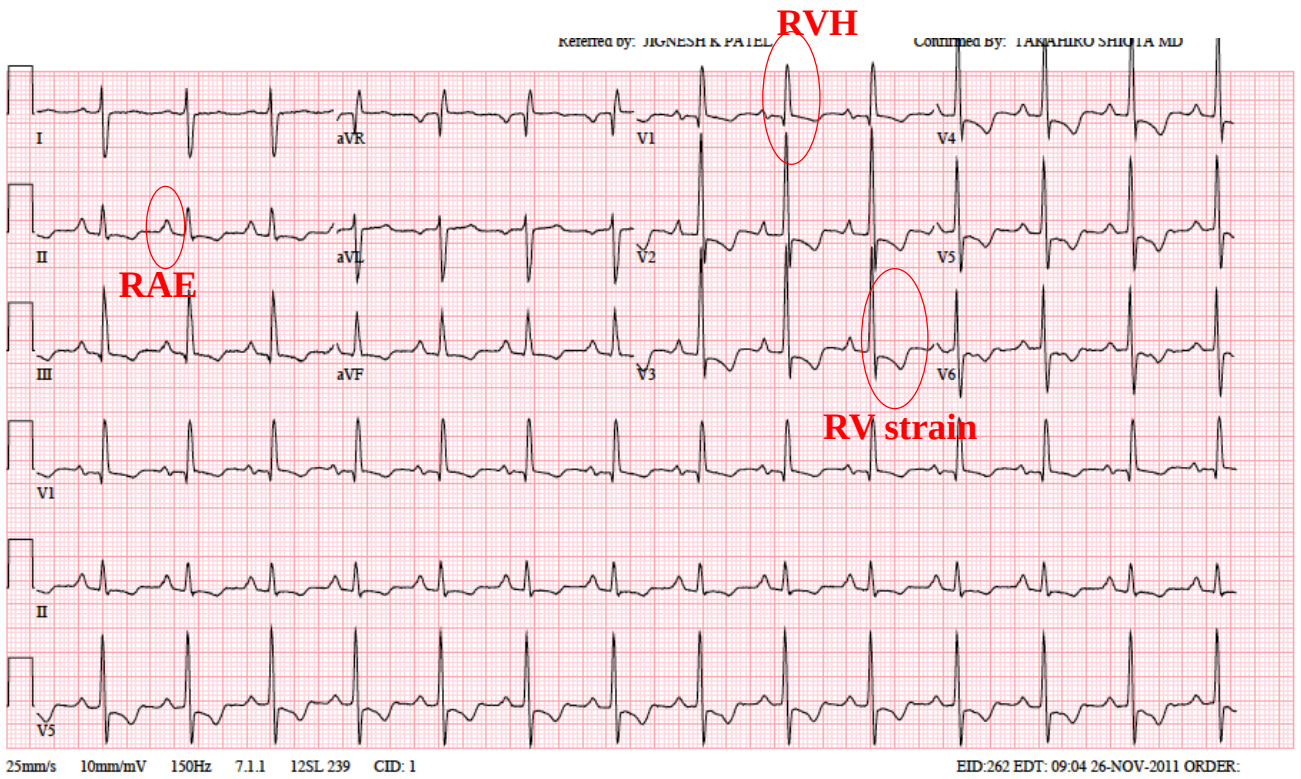
- **Loud P2**
  - **listen at apex**
- **RV lift**
  - **left parasternal - fingertips**
- **Systolic murmur (TR)**
  - **inspiratory augmentation**
- **Diastolic murmur (PR)**
- **RV S4**
- **JVD with V wave, A wave, hepatojugular reflux**
- **RV S3**
- **Hepatomegaly**
- **Edema**
- **Ascites**
- **Pulsatile liver**
- **Low BP, low PP, cool extremities**
- **Early systolic click; midsystolic ejection murmur**

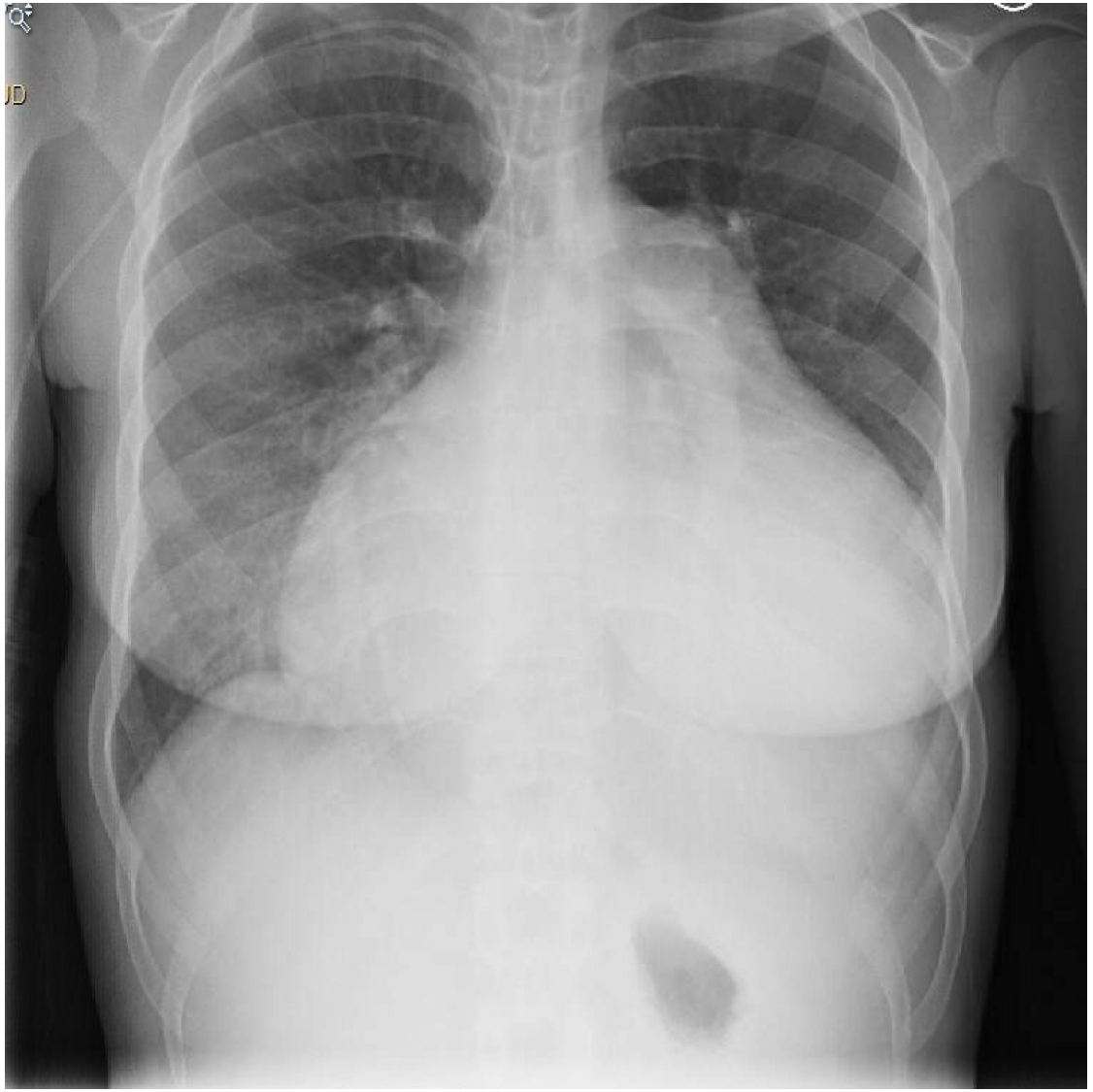
McLaughlin VV et al. *J Am Coll Cardiol*. 2009;53:1573-1619.



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

CXR and EKG of a Patient with IPAH



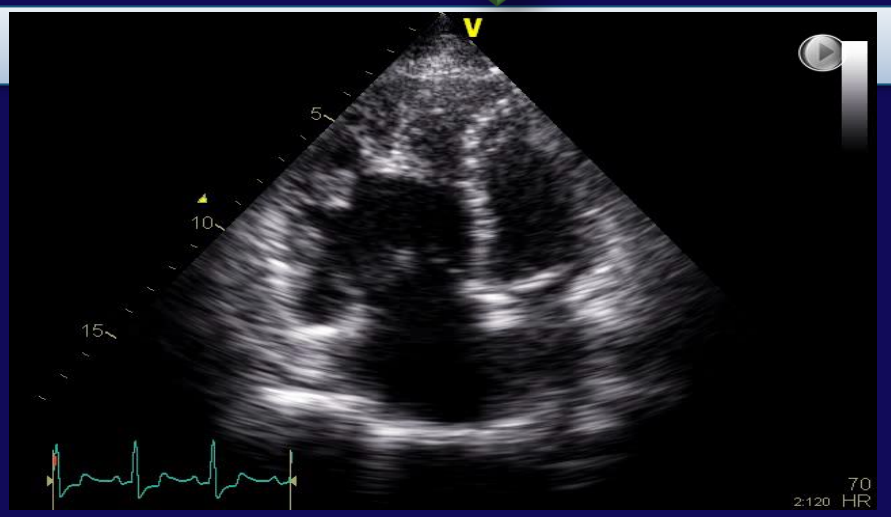


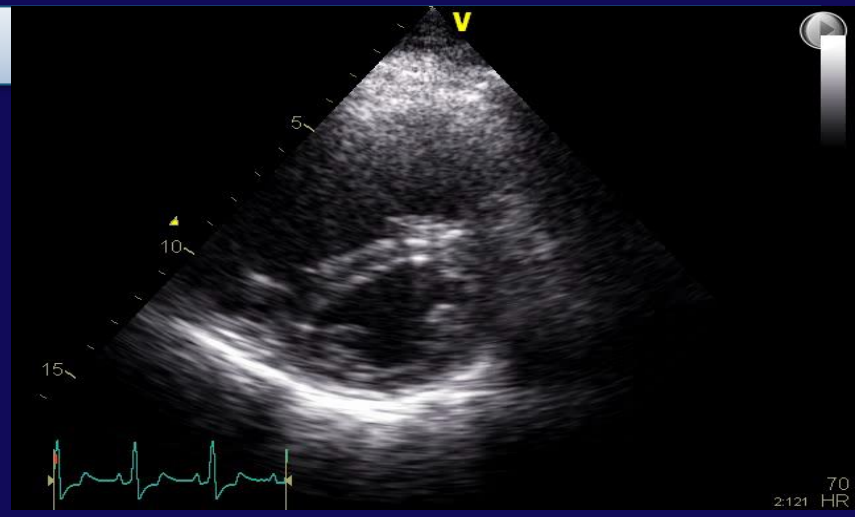
Diagnosis of PAH

Screening and Detection: Echocardiography

High Level of suspicion.
Screening High Risk Populations

Key to early Diagnosis

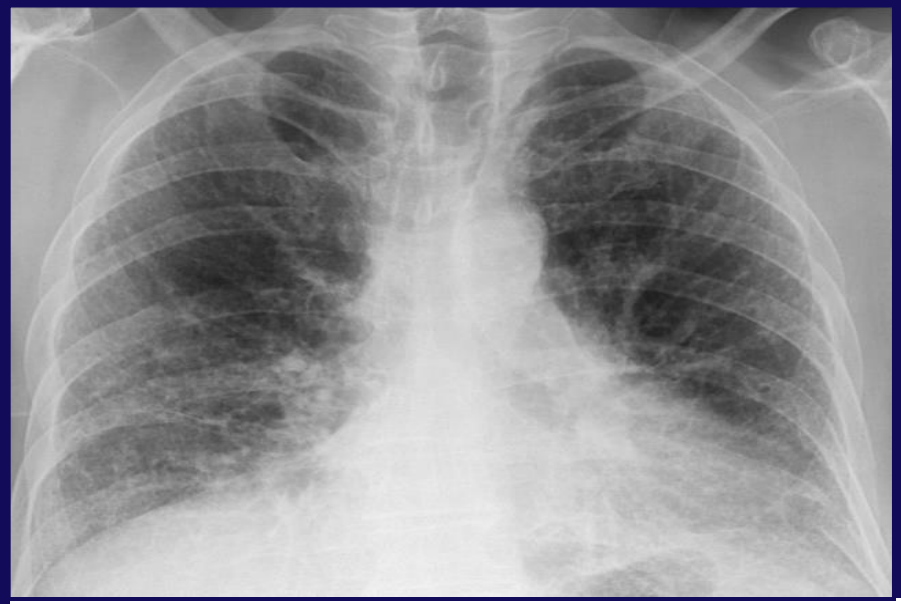


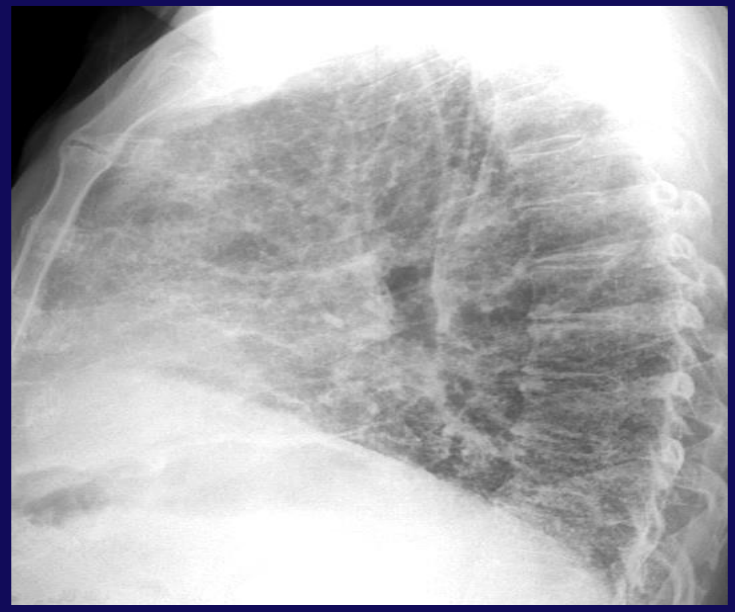


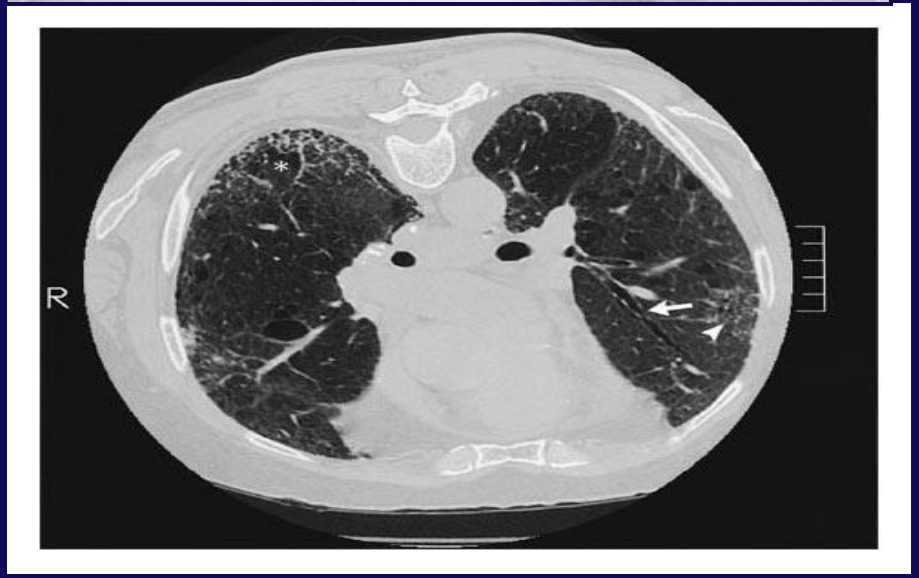
Right Heart Catheterization
Mandatory to confirm and characterize disease

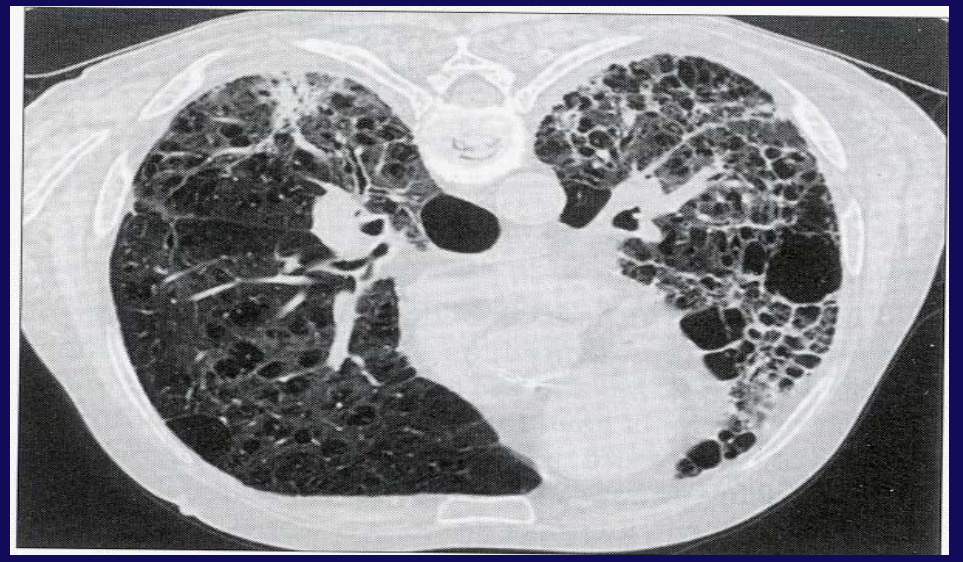
Adapted from Harrison's principles of internal medicine, 148th ed.

PH Owing to Lung Disease: IPF

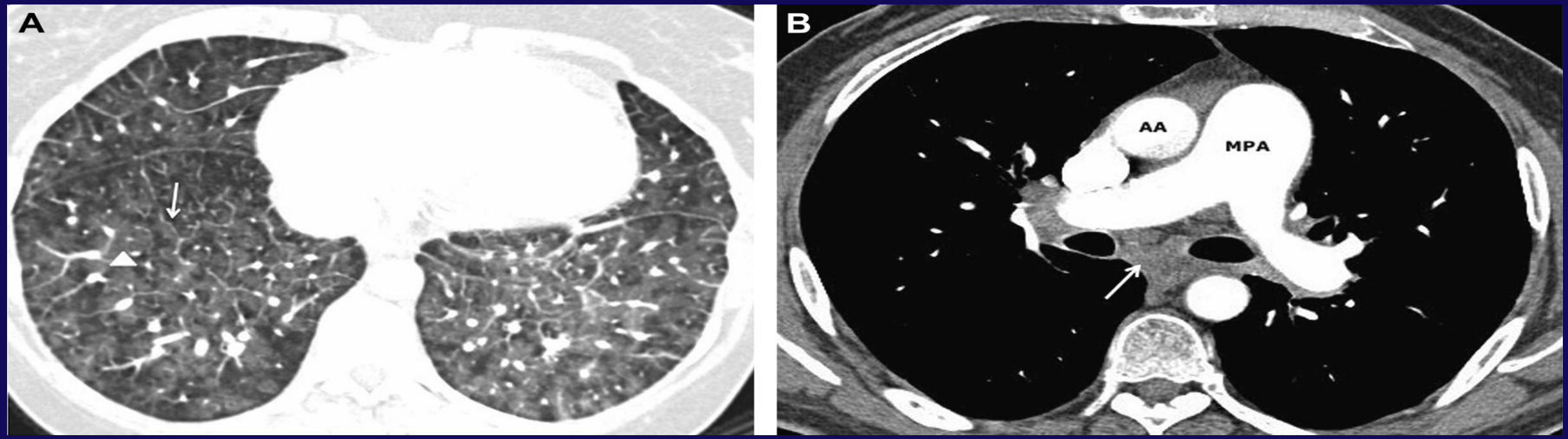






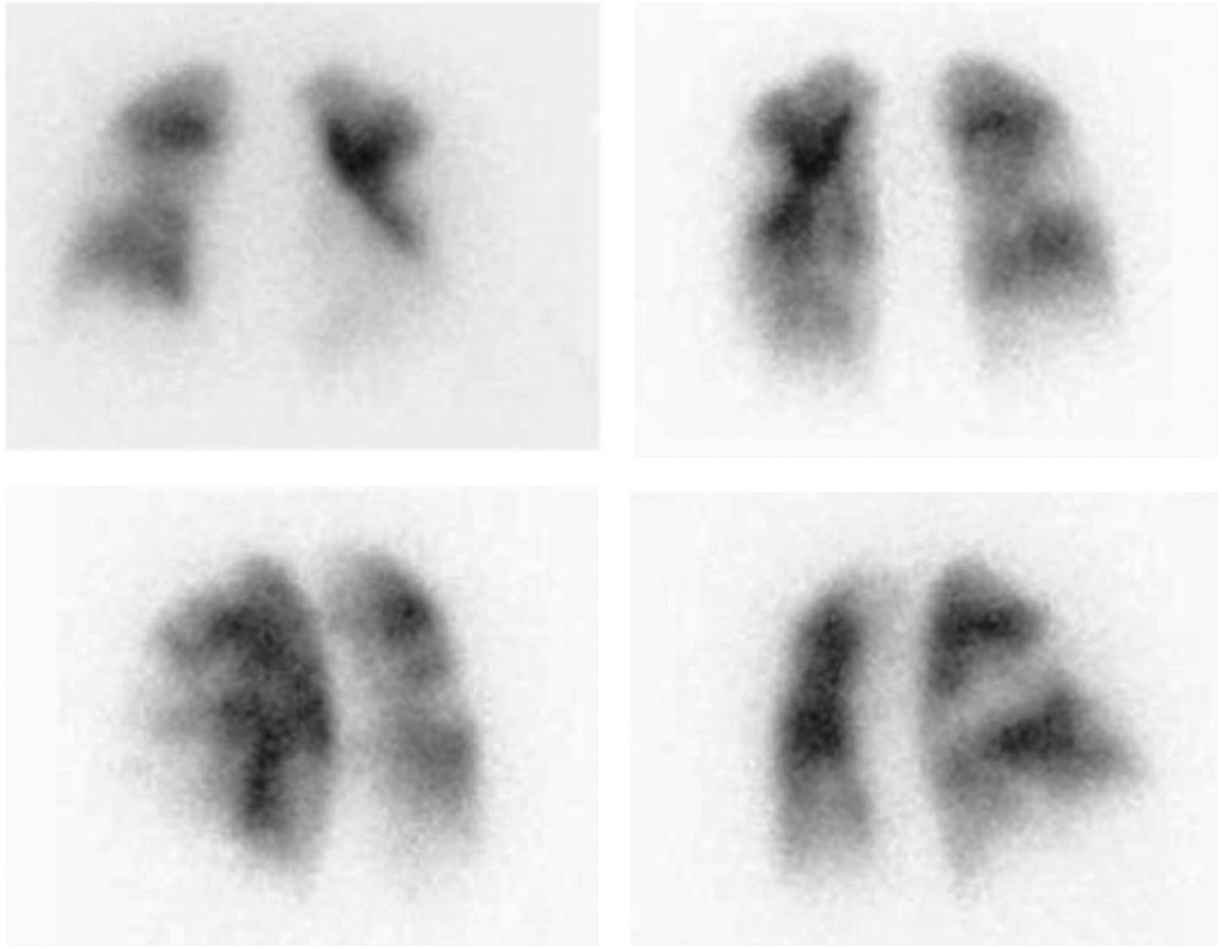


Multidetector CT features of pulmonary veno-occlusive disease in a 35-year-old male subject.

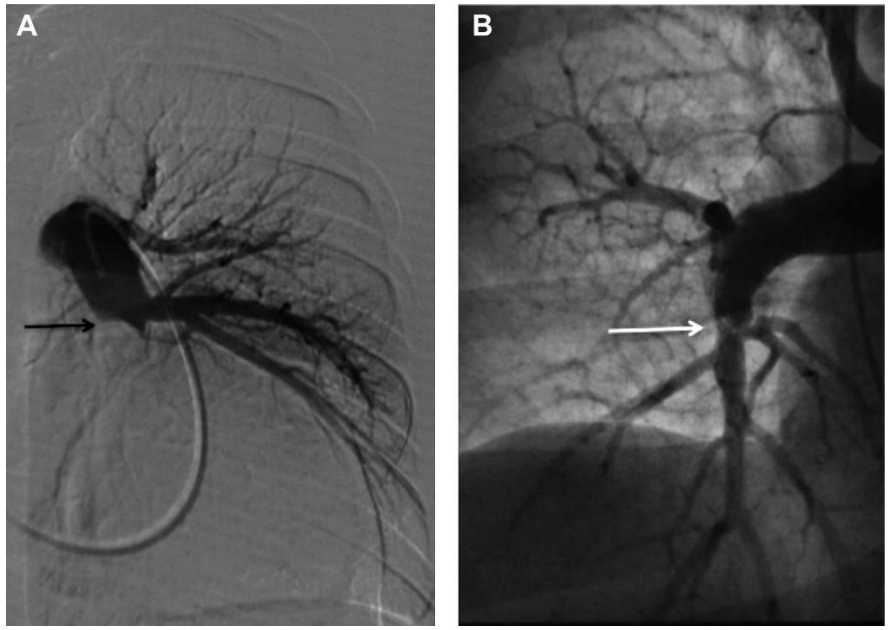


Gopalan D et al. Postgrad Med J 2012;88:397-406

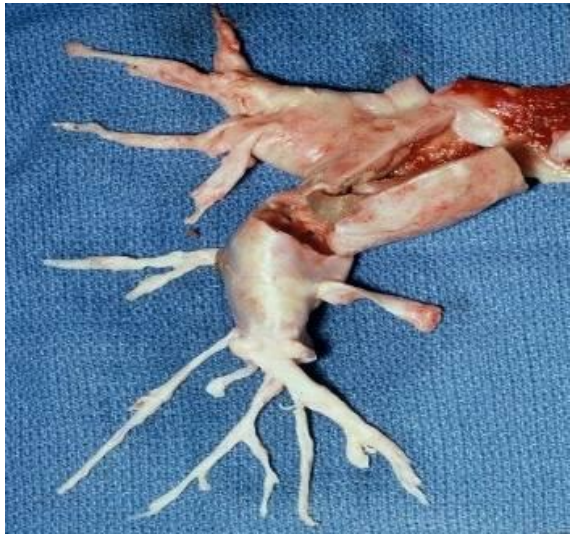
CTEPH : A “Curable” Form of PH Not to Be Missed



V/Q scan of a patient with CTEPH



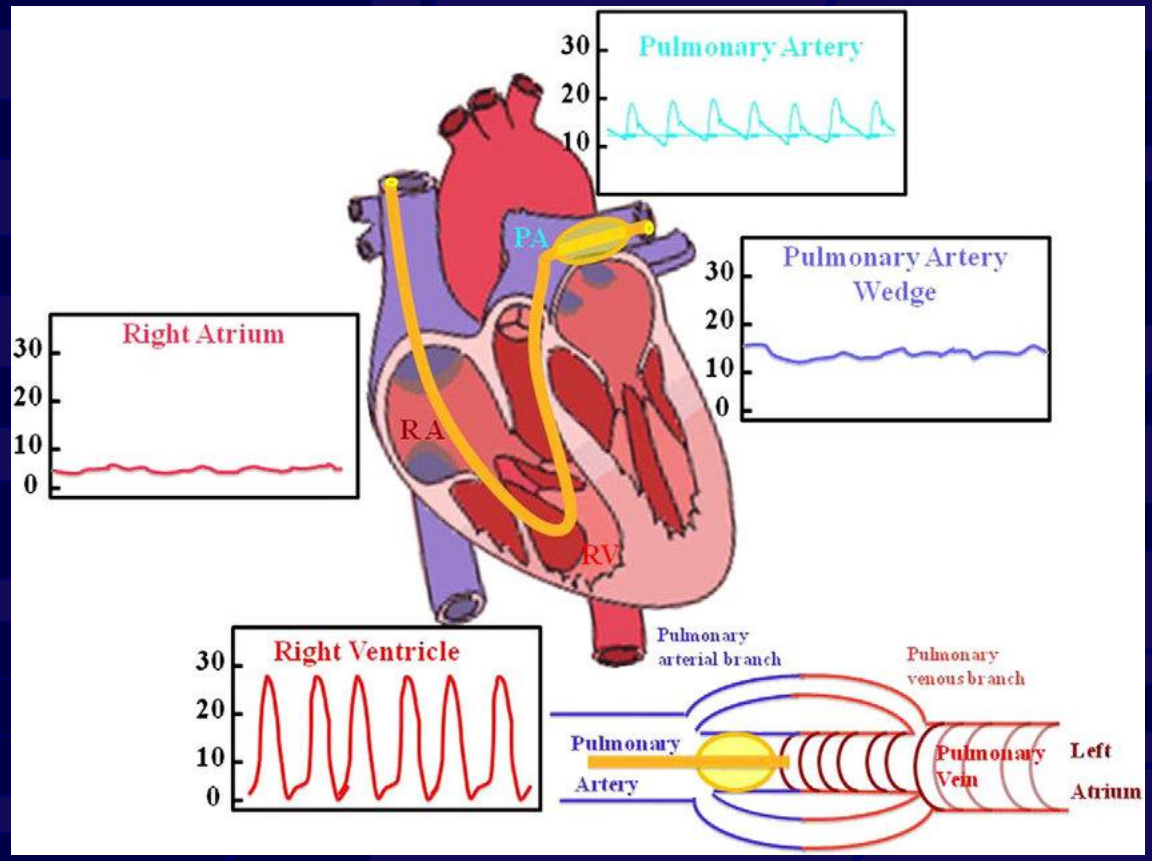
Catheter pulmonary angiogram in a patient with chronic thromboembolic pulmonary hypertension.



PTE specimen

McCann C et al. Postgrad Med J 2012;88:271-279

Right Heart Catheterization



- Oxygen saturations (SVC, IVC, RA, RV, PA, wedge, SA)
- Right atrial pressure
- RV systolic and end-diastolic pressure
- PA systolic, diastolic, and mean pressure
- PCWP, LVEDP, or LAP (if entered via PFO or ASD)
- Thermodilution or Fick CO, CI
- Pulmonary vascular resistance (TPG/CO)
- Systemic systolic, diastolic, and mean pressure
- Heart rate
- Vasodilator response

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

Calcium Channel Blockers
Only If "Vasodilator Responsive"

"Vasodilator Response"

- Fall in mPAP ≥10 mm Hg
  + mPAP (absolute) <40 mm Hg
  + Normal CO

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

Risk Assessment in Pulmonary Arterial Hypertension

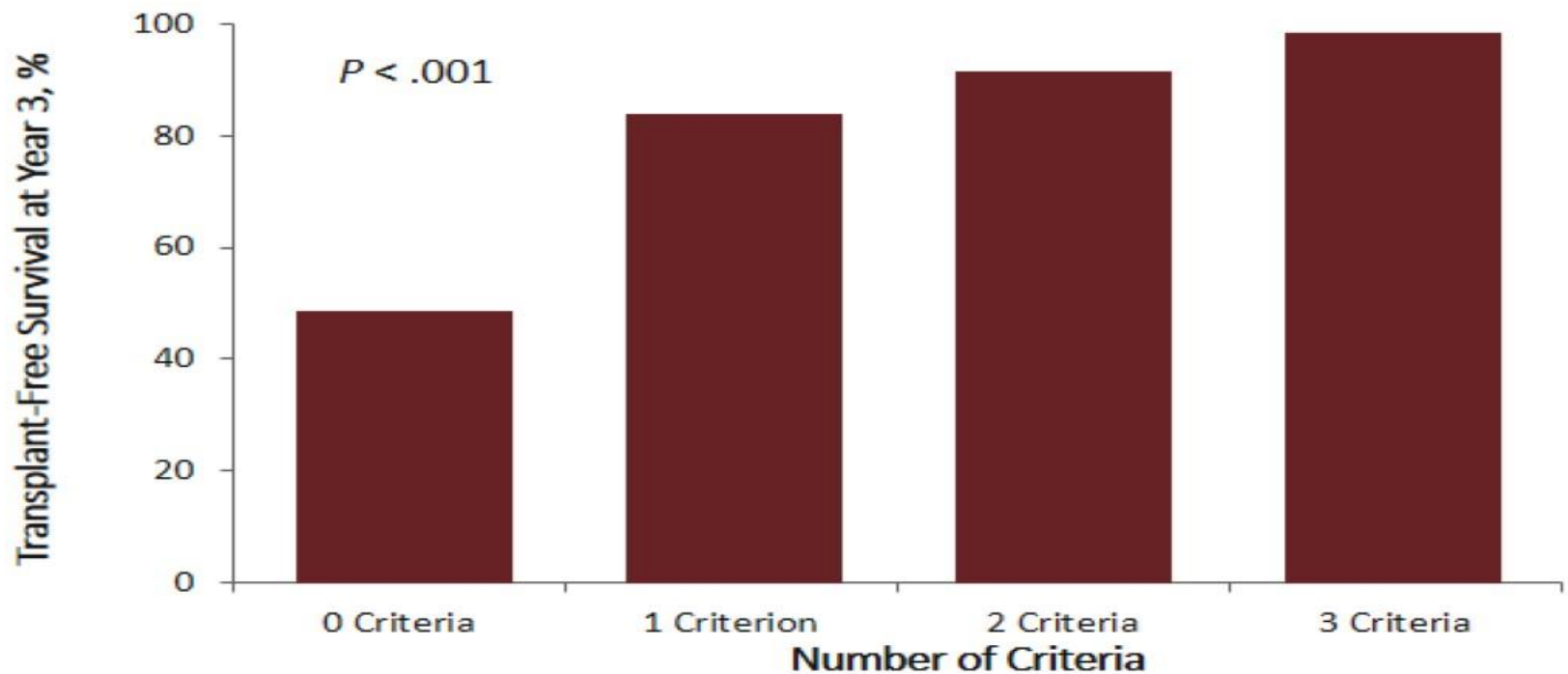
Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

pahriskcalculatorre.com
pahriskcalculatoreu.com

Galie, N et al: Eur Heart J. 37: 67-119; Galie N, et al. Eur Respir J 2015; 46:903-975

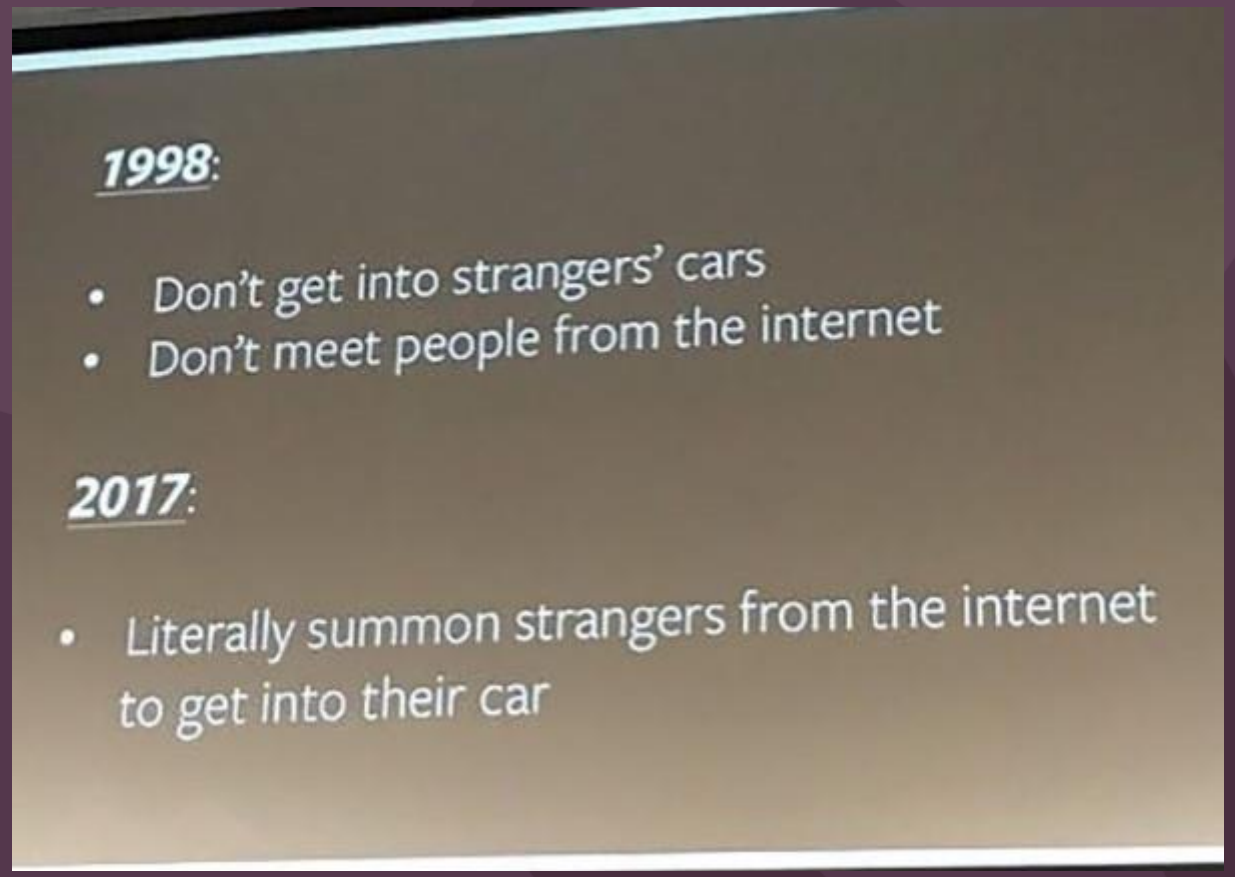
French PH Registry
Number of Noninvasive Low-Risk Criteria Achieved and Survival

- Noninvasive low-risk criteria: WHO/NYHA FC I to II, 6MWD > 440 m, BNP < 50 ng/L or NT-proBNP < 300 ng/L



Boucly A, et al. *Eur Respir J.* 2017;50:1700889.

PAH Therapies
How far have we come?



Medications Approved for the Management of PAH

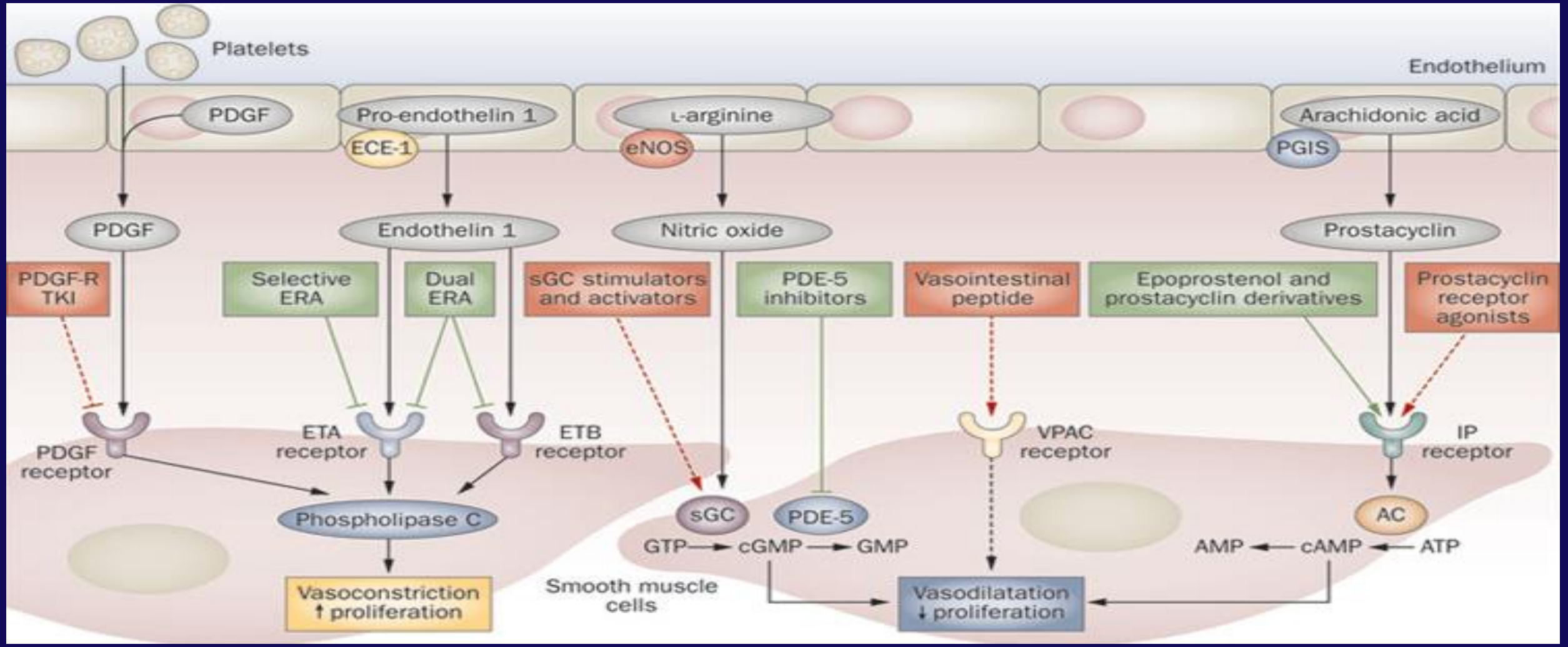
PAH Specific Therapies

Mode of Administration

- Prostacyclin analogs
  - Epoprostenol (Flolan, Veletri) — Intravenous (IV)
  - Treprostinil (Remodulin) — IV or SQ
  - Treprostinil (Tyvaso) — Inhalation
  - Treprostinil (Orenitram) — Oral
  - Iloprost (Ventavis) — Inhalation
- Non Prostanoid IP Receptor Agonist
  - Selexipag (Uptravi) — Oral
- Endothelin receptors Antagonists
  - Bosentan (Tracleer) — Oral
  - Ambrisentan (Letairis) — Oral
  - Macitentan (Opsumit) — Oral
- Phosphodiesterase Type-5 Inhibitors
  - Sildenafil (Revatio) — Oral
  - Tadalafil (Adcirca) — Oral
- Direct Stimulator s-Guanylate Cyclase
  - Riociguat (Adempsa) (PAH +CTEPH) — Oral
- Activin Signaling Inhibitor (PAH) — SQ
  - Sotatercept

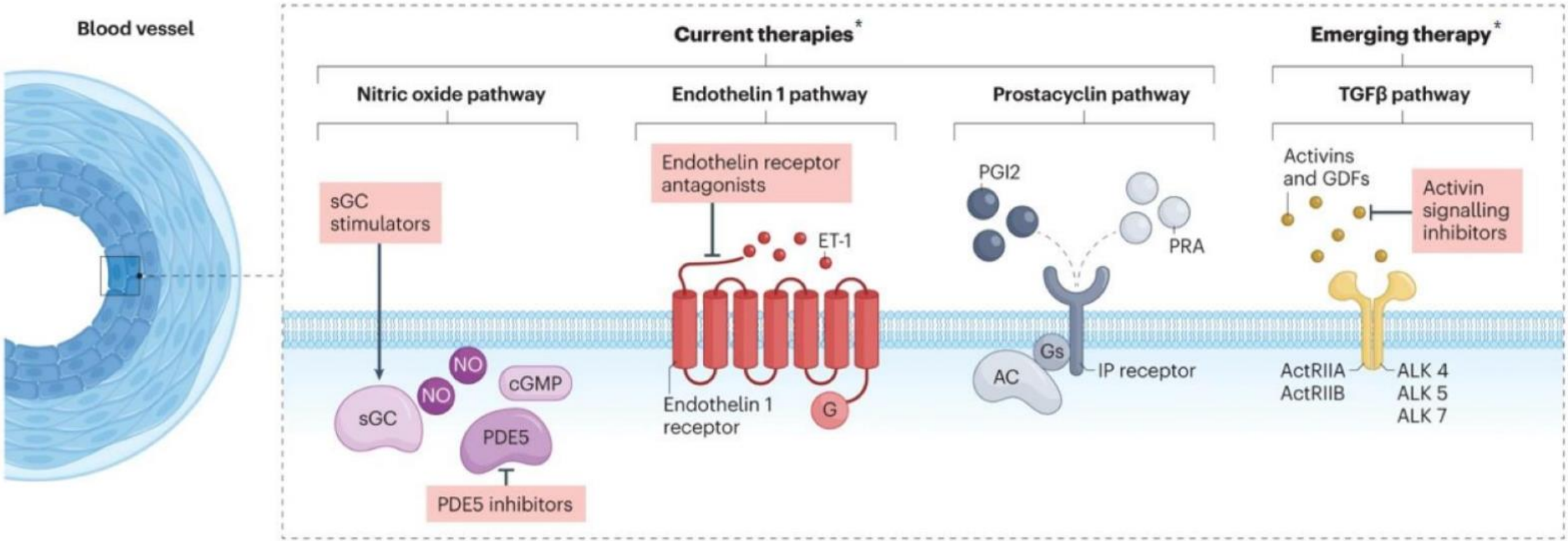
Class I Recommendation for use As Monotherapy in WHO FC II-III

Current and Emerging Targets and Therapies for Pulmonary Arterial Hypertension



O'Callaghan, D. S. *et al.* (2011) Treatment of pulmonary arterial hypertension with targeted therapies
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2011.104

PAH-Specific Therapeutic Pathways



*The main targets for current therapies in PAH are shown including prostacyclin, nitric oxide and endothelin pathways, and a previously emerging but now established, new therapy pathway with the approval of sotatercept-csrk – the activin pathway. The therapies used are represented next to each target.

AC, adenylyl cyclase; ActRIIA/B, activin receptor IIA/B; BMP, bone morphogenetic protein; BMPR-II, BMP receptor type II; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ET-1, endothelin-1; GDF, growth differentiation factor; IP, prostaglandin I2; NO, nitric oxide; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; PG12, prostaglandin 12; PRA, prostacyclin receptor agonist; sGC, soluble guanylate cyclase.

Mocumbi A, et al. *Nav Rev Dis Primers*. 2024;10(1):1.

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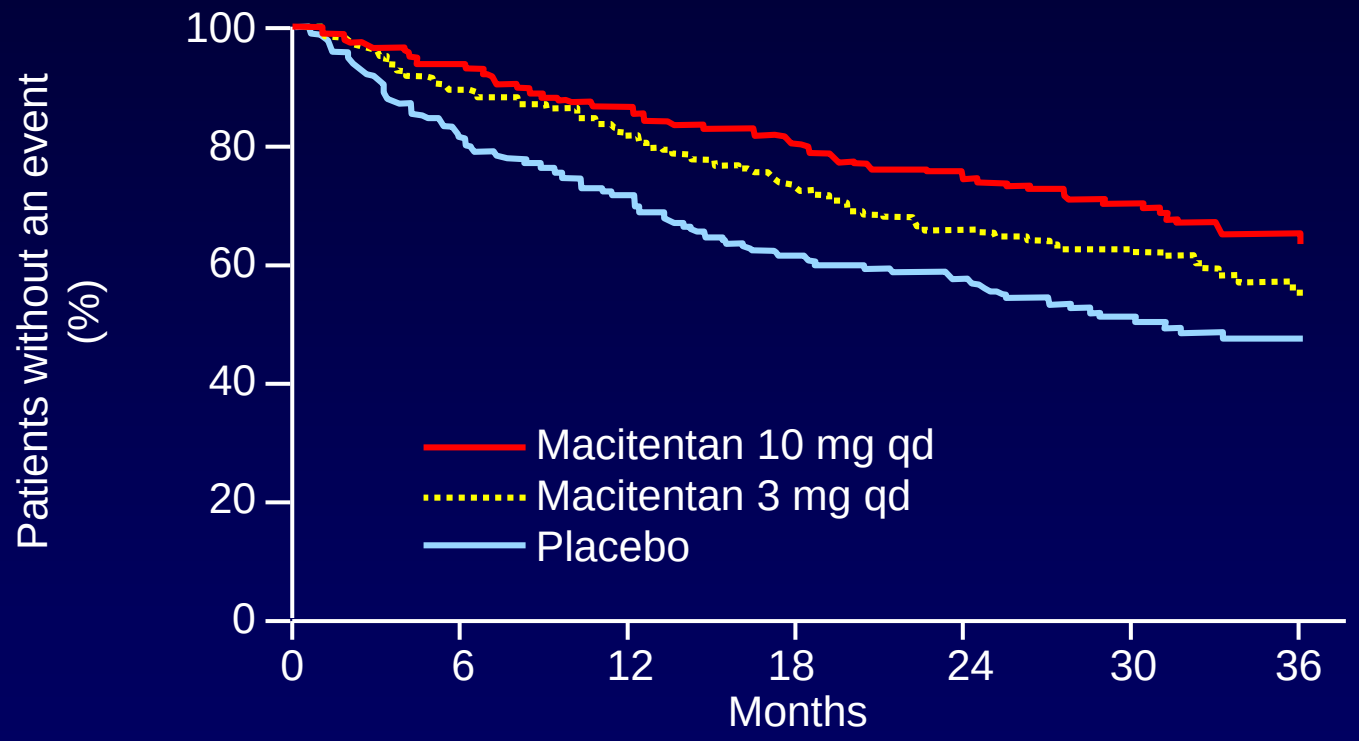
ERA—Macitentan

Effect on Composite First Event Related to PAH* or Death from Any Cause



No. at risk:							
Placebo	250	188	160	135	122	64	23
Macitentan 3 mg	250	213	188	166	147	80	32
Macitentan 10 mg	242	208	187	171	155	91	41

742 patients
2/3 of patients receiving background therapy

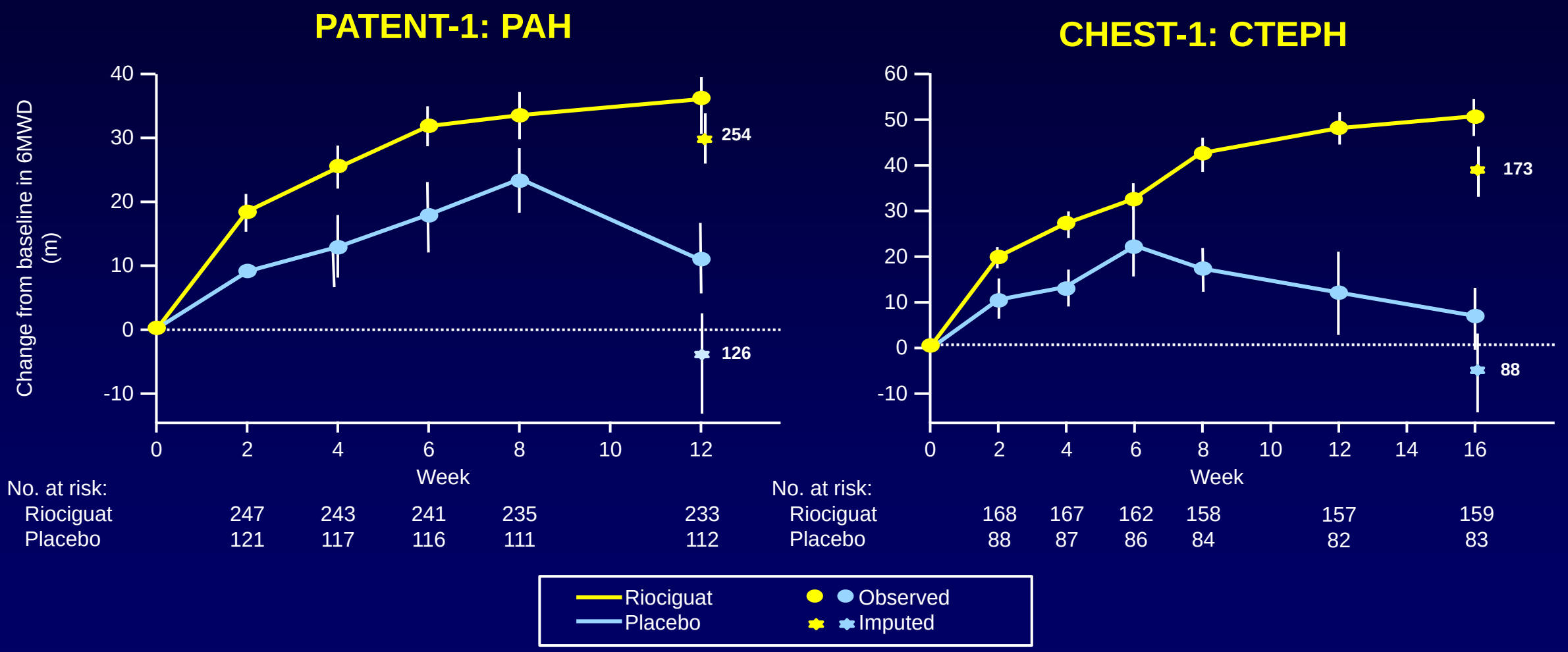
45% Risk Reduction of Primary Endpoint Events*
Macitentan 10 mg vs Placebo

HR: 0.55
***P* value: < .001**

*Worsening of PAH, initiation of treatment with IV or SC prostanoids, lung transplantation or atrial septostomy

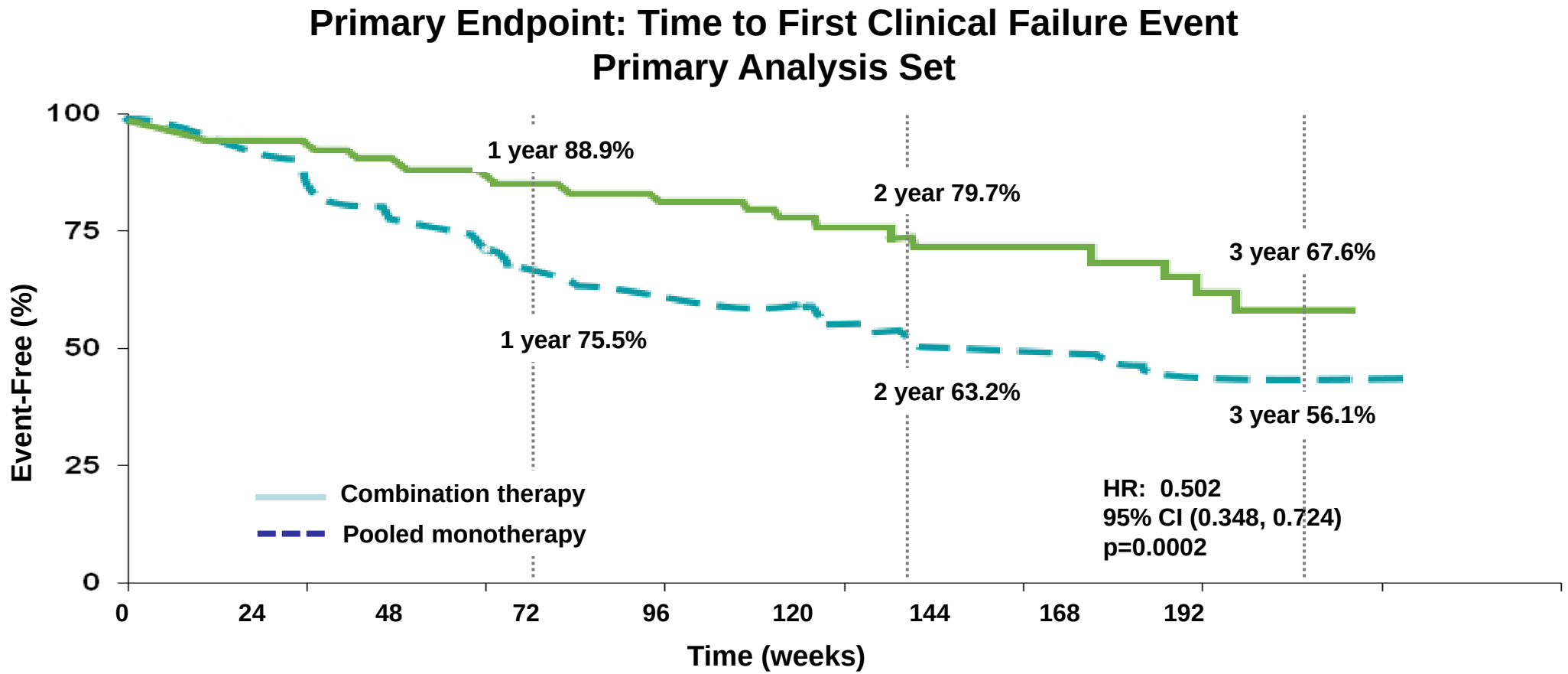
Pulido T et al. *N Engl J Med*. 2013;369:809-818

Nitric Oxide Pathway—Riociguat



Ghofrani AH et al. N Engl J Med 2013; 369:319-329.
Ghofrani AH et al. N Engl J Med 2013; 369:330-340.

AMBITION: Initial Combination Therapy With Ambrisentan-Tadalafil Primary Study Endpoint

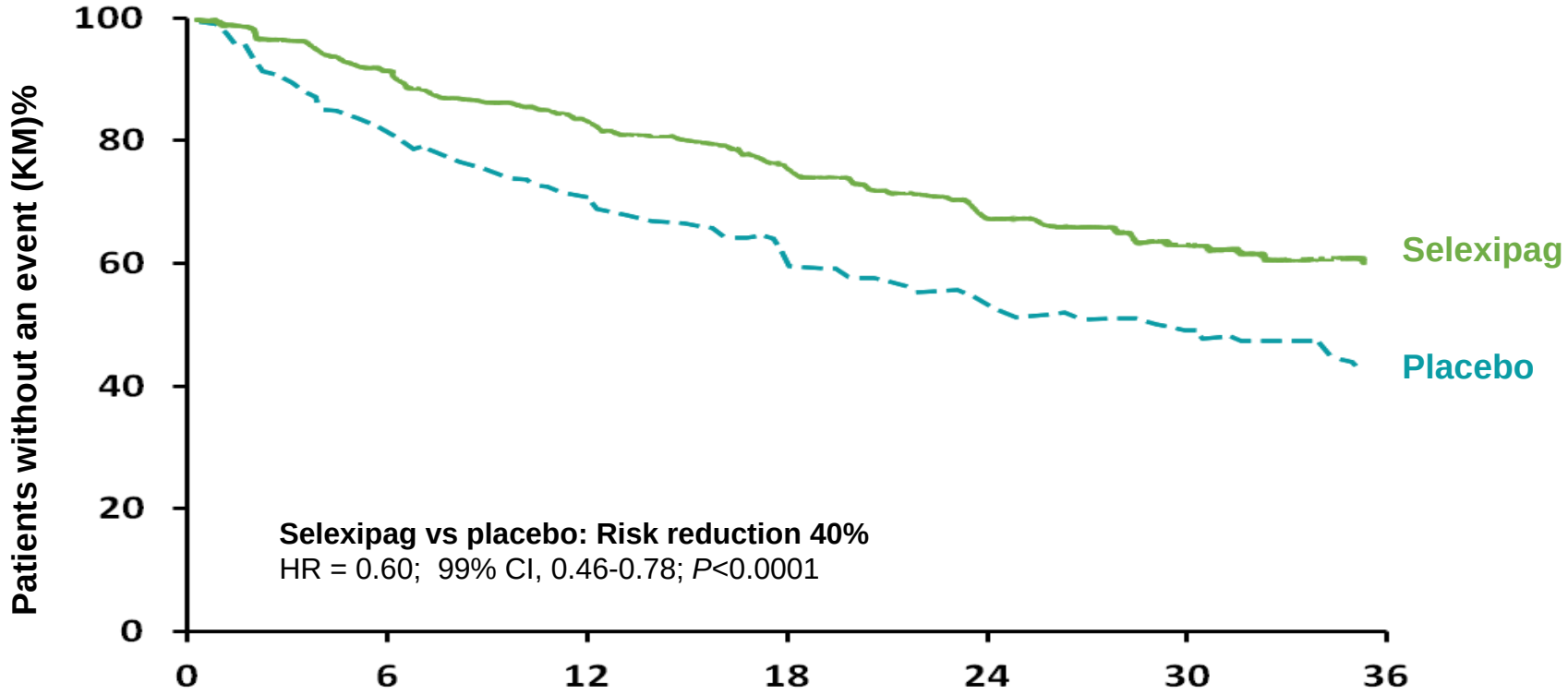


Number at risk:

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

Galie N, et al. *N Engl J Med*. 2015;373:834-844.

Selexipag Primary Endpoint: Time to First Event

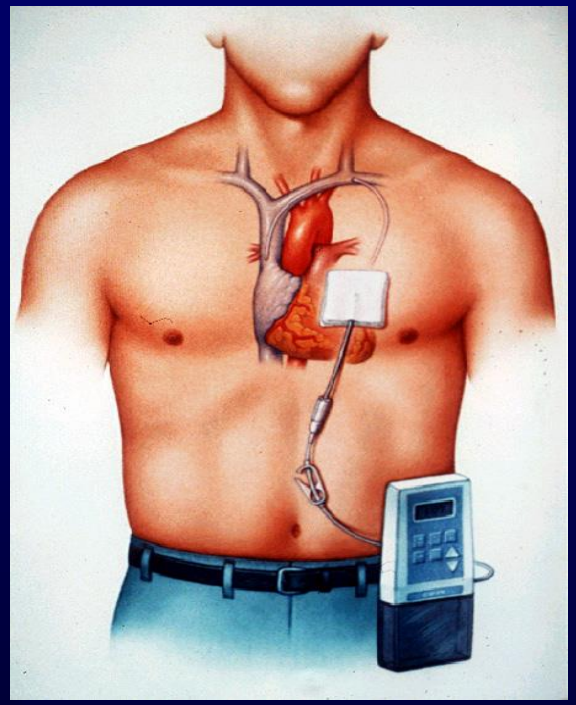


No. at Risk:

Placebo	582	433	347	220	149	88	28
Selexipag	574	455	361	246	171	101	40

McLaughlin VV. *J Am Coll Cardiol*. 2015:65(10S):A1538.

Prostacyclin Analogues: Intravenous, Subcutaneous, or Inhaled



Epoprostenol (Flolan®)

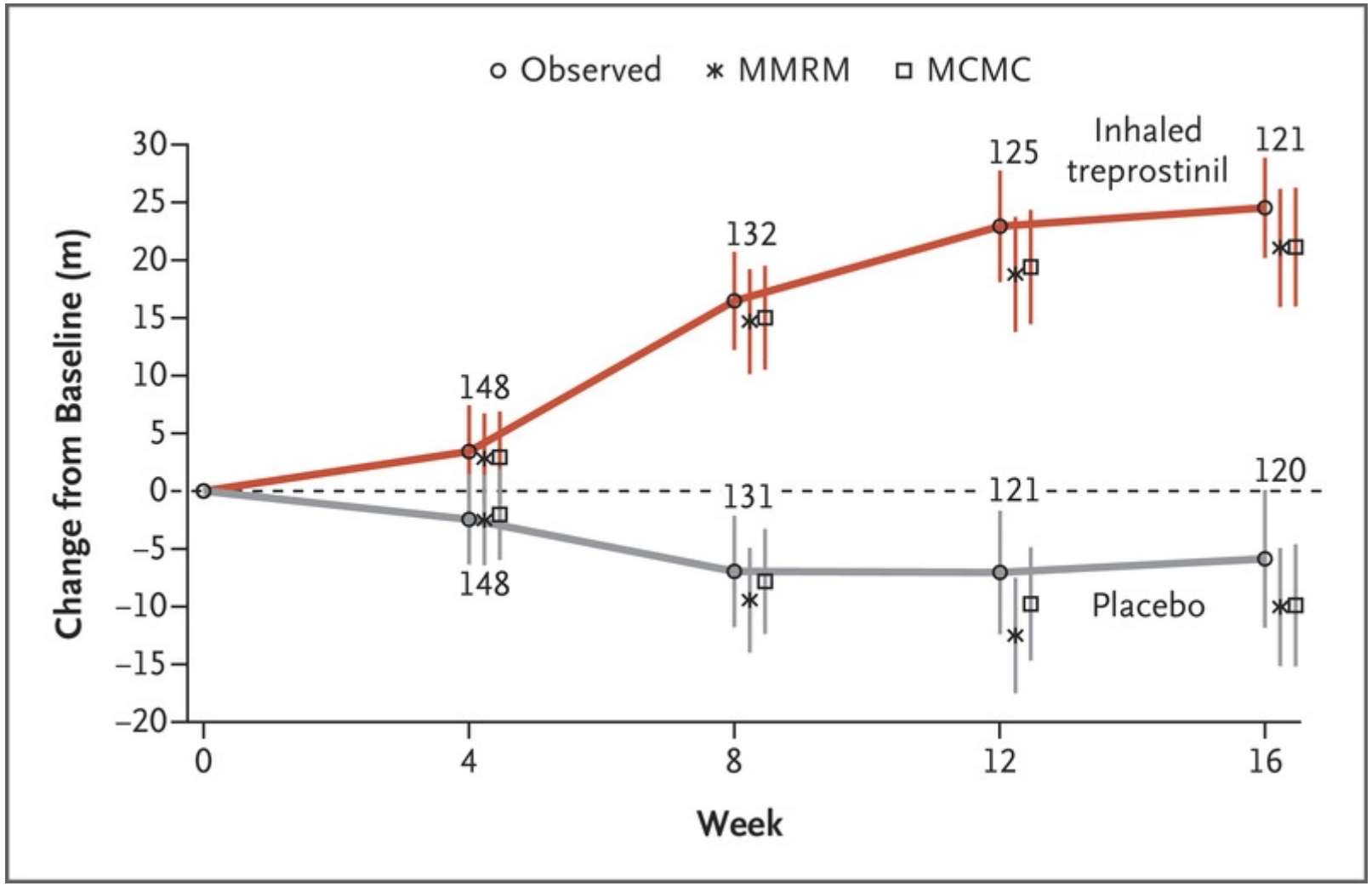
Treprostinil (Remodulin®)

Treprostinil (Remodulin®)

Iloprost (Ventavis®)

Treprostinil (Tyvaso®)

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

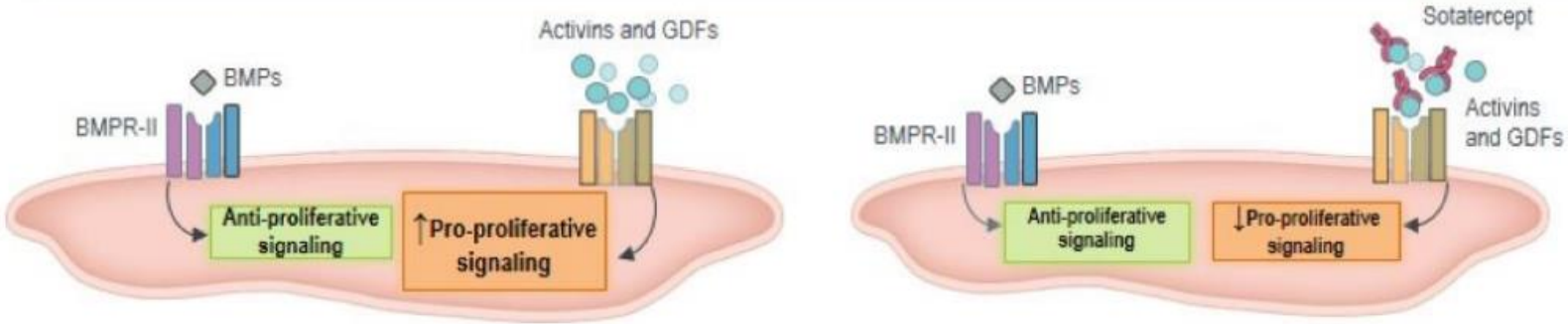


N Engl J Med 2021; 384:325-334

Sotatercept is a First-in-Class Activin Signaling Inhibitor

In rat models of PAH, a sotatercept analog reduced inflammation and inhibited proliferation of endothelial and smooth muscle cells in diseased vasculature, which were associated with thinner vessel walls, partial reversal of right ventricular remodeling, and improved hemodynamics.[10]

Molecular Level Impact of Sotatercept[1-10]



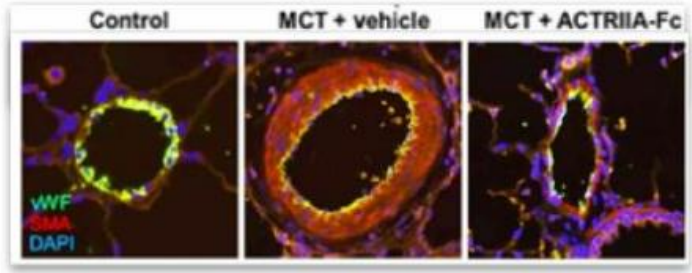
Imbalanced activin/BMPR-II pathways

Pro-proliferative signaling shift increases the risk of PAH and contributes to disease pathogenesis by modulating cell survival and vascular proliferation.

Rebalanced toward vascular homeostasi[0]

Sotatercept a recombinant activin receptor type IIA-Fc (ActRIIA-Fc) fusion protein, is an activin signaling inhibitor that binds to activin A and other TGF- β superfamily ligands. As a result, sotatercept improves the balance between the pro-proliferative (ActRIIA/Smad2/3-mediated) and anti-proliferative (BMPRII/Smad1/5/8-mediated) signaling to modulate vascular proliferation.

Cellular Level Impact of Sotatercept[1,10]



Adapted from Yung LM, et al. Sci Transl Med. 2020;12(543):

In preclinical models of PAH, a sotatercept analog reduced inflammation and inhibited proliferation of endothelial and smooth muscle cells in diseased vasculature. These cellular changes were associated with thinner vessel walls, partial reversal of right ventricular remodeling, and improved hemodynamics.

ActRIIA/B, activin receptor IIA/B; BMP, bone morphogenetic protein; BMPR-II, BMP receptor type II; DAPI, 4',6-diamidino-2-phenylindole; GDF, growth differentiation factor; Fc, fusion protein; MCT, monocrotaline; PAH, pulmonary arterial hypertension; SMA, α-smooth muscle actin; vWF, von Willebrand factor.

1. Yung LM, et al. *Sci Transl Med.* 2020;12(543):eeaz5660. doi:10.1126/scitranslmed.aaz5660. 2. Morrell NW, et al. *Eur Respir J.* 2019;53(1):1801899. doi:10.1183/13993003.01899-2018. 3. Humbert M, et al. *N Engl J Med.* 2021;384(13):1204-1215. 4. Humbert M, et al. PULSAR open label extension: long term efficacy and safety of sotatercept for the treatment of pulmonary arterial hypertension (PAH). Presented at: ATS 2022 International Conference; May 13 15, 2022; San Francisco, CA. 6956. 5. Humbert M, et al. *Eur Respir J.* 2019;53(1):1801887. doi:10.1183/13993003.01887-2018. 6. Rol N, et al. *Int J Mol Sci.* 2018;19(9):2585. doi:10.3390/ijms19092585. 7. Guignabert C, et al. *Eur Respir J.* 2021;57(2):2002341. doi:10.1183/13993003.02341-2020. 8. Yndestad A, et al. *J Appl Physiol (1985).* 2009;106(4):1356-1364. 9. Carrancio S, et al. *Br J Haematol.* 2014;165(6):870-882. 10. Winrevair (sotatercept-csrk) [package insert]. Rahway, NJ: Merck & Co, Inc; 2024.

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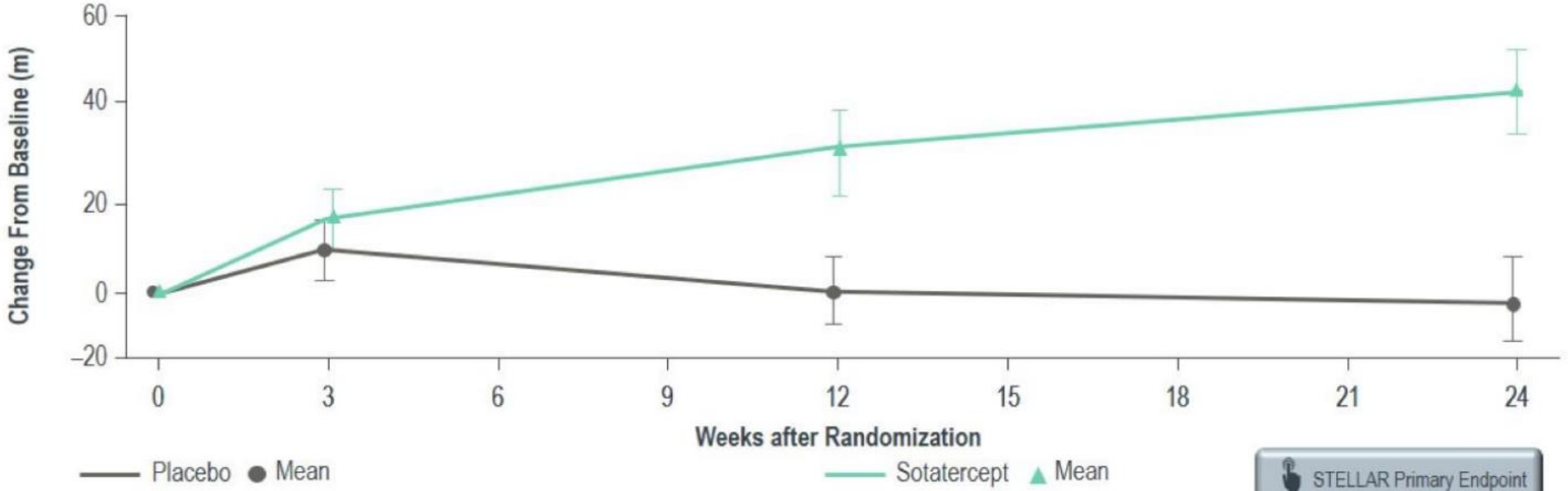
STELLAR TRIAL

Primary Endpoint – Change in 6-minute Walk Distance through Week 24

- The observed mean change from baseline at week 24 in 6-minute walk distance was 40.1 m (95% CI, 29.9 to 50.2) in the sotatercept group and −1.4 m (95% CI, −13.2 to 10.3) in the placebo group (see figure)
- The H-L location shift was 40.8 m (95% CI, 27.5 to 54.1; P<0.001), favoring sotatercept



6MWD, 6-minute walk distance; CI, confidence interval.
The line graph shows the observed mean changes from baseline in 6-minute walk distance (in meters) in the sotatercept group (solid triangles) and placebo group (solid circles) with 95% confidence intervals (indicated by I bars). Walking distance was recorded at prespecified trial visits (i.e., week 0 [baseline], week 3, week 12, and week 24) during the first 24 weeks of the trial. The data shown are for patients with available data (observed) over time. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects..

Hoeper MM, et al. *N Engl J Med*. 2023;10.1056/NEJMoa2213558.

STELLAR Primary Endpoint

SOTERIA Long-term Clinical Efficacy

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For more details on **STELLAR**, click here:

For more details on **SOTERIA**, click here:

Sotatercept Primer Deck: Clinical Trial Summary

STELLAR

- **Δ6MWD**: The H-L location shift was 40.8 m (95% CI: 27.5, 54.1) (P<0.001), favoring sotatercept
- The **most common AEs (≥10%) at week 24** (any group) were COVID-19, headache, nausea, diarrhea, epistaxis, fatigue, and dizziness
  - **Telangiectasia**: 3.1% (placebo) & 10.4% (sotatercept)
- **Serious AEs leading to (at week 24):**
  - **Tx discontinuation**: 5.0% (placebo) and 0.6% (sotatercept)
  - **Study withdrawal**: 3.1% (placebo) and 0.6% (sotatercept)
- 8 out of the 9 **secondary endpoints** met statistical significance, including time to death or the first occurrence of clinical worsening, with a risk reduction of 84%, favoring sotatercept

Post Hoc Analyses:

- In a highly treated patient group, **RHC and ECHO** parameters showed significant improvement in RV function and structure
- Based on post hoc analyses treatment effect of sotatercept showed consistently greater improvement compared to placebo across subgroups based on **background PAH therapy**, **2022 ESC/ERS risk strata**, and **cardiometabolic comorbidities**

SOTERIA

- Improvements in **clinical efficacy** measures were **maintained** in patients on sotatercept **at 1 year** during this open-label period
- **TEAEs** related to treatment were reported in 210 (49.3%) patients
  - **TEAE leading to Tx discontinuation**: 15 (3.5%)
  - **Serious TEAEs** related to treatment: 11 (2.6%)
  - **Death** due to a serious TEAE: 12 (2.8%)
- **Bleeding events** related to treatment were reported in 71 (16.7%) patients
- **Increased hemoglobin** related to treatment was reported in 55 (12.9%) patients
- **Thrombocytopenia** related to treatment was reported in 22 (5.2%) patients
- **Telangiectasia** (occurring on or after rollover) related to treatment was reported in 71 (16.7%) patients
- While on sotatercept treatment, 46 (16.1%) patients were able to **discontinue or de-intensify** their **prostacyclin** dosing
- Only 56 (13.2%) patients on other background PAH therapy **needed additional therapies** when sotatercept was added

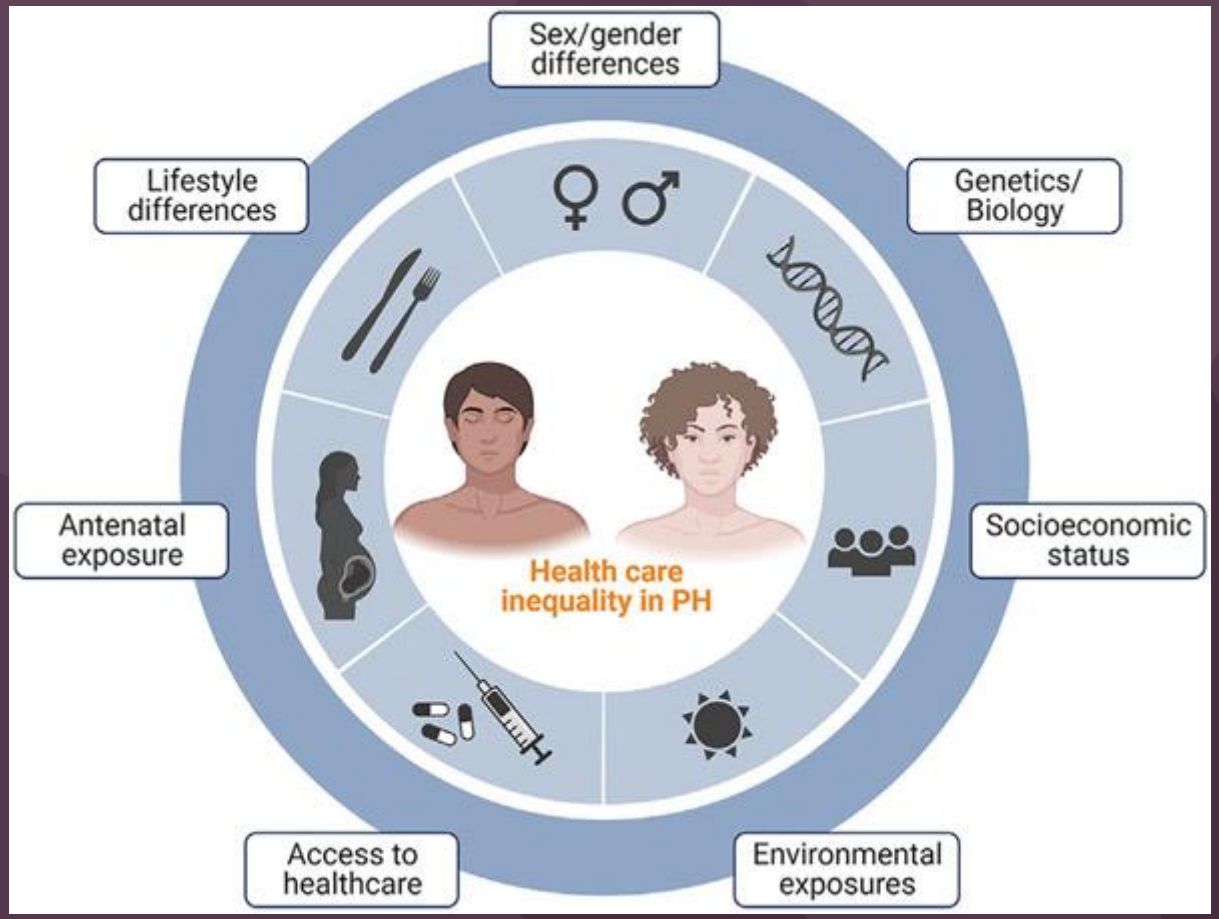
6MWD, 6-minute walk distance; AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; ECHO, echocardiography; ERS, European Respiratory Society; ESC, European Society of Cardiology; MCI, multicomponent improvement; NT-proBNP, N-terminal-pro–B type natriuretic peptide; PA, pulmonary arterial ; PAH, pulmonary arterial hypertension; Tx, treatment; TEAE, treatment-emergent adverse event; RV, right ventricle; WHO FC, World Health Organization Functional Class.

. 2023 Sep;44(3):543-554.

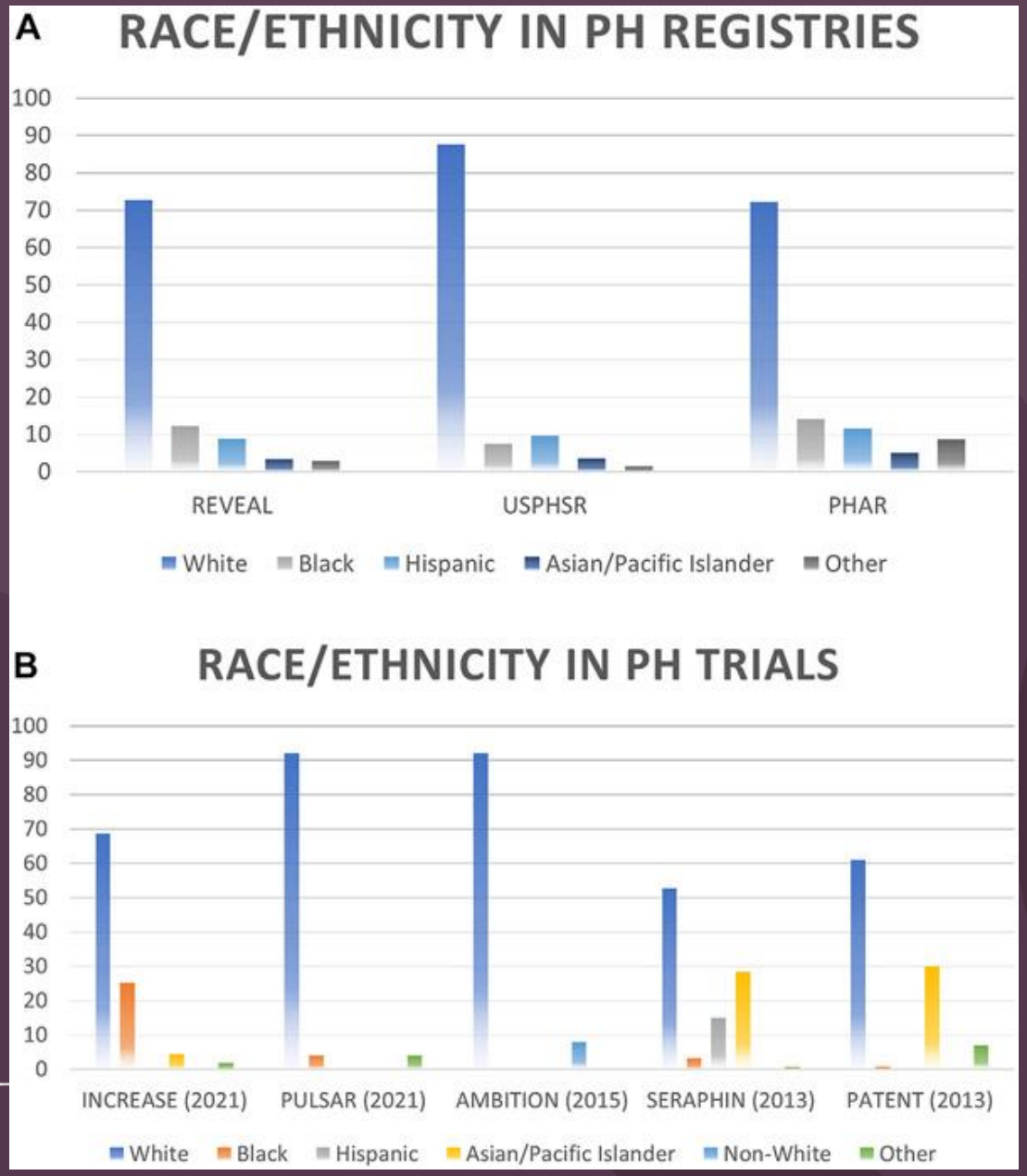
How to monitor response to treatment

- Clinical
  - –NYHA functional class
  - –6MWT
- Biomarkers
  - –BNP or NT proBNP
- Echocardiographic
  - –RV size and function
  - –Tricuspid regurgitation
  - –Estimated RA pressure
- Hemodynamics
  - –Not routine but used when change in clinical status or consideration for change in therapy or preop

Healthcare Inequality in Pulmonary Hypertension



Bernardo, RJ, Clin Chest Med, 2023 Sep;44(3):543-554



CEDARS-

cedars-sinai.edu

Bernardo, RJ, Clin Chest Med, 2023 Sep;44(3):543-554

- Gender
  - PAH predominantly affects females although disease in males tends to be more severe
  - Access to reproductive health care

Cheron C, McBride SA, Antigny F, et al. Sex and gender in pulmonary arterial hypertension. *Eur Respir Rev* 2021;(162):30.

- Race/Ethnicity
  - Black patients with PAH have higher frequency of CTD (scleroderma) than White patients
  - In one study from Hopkins, Black patients had worse functional class and hemodynamics on presentation although REVEAL registry did not show a difference in survival
  - Hispanic patients with PAH tend to be younger and have a higher frequency of congenital heart disease and portopulmonary hypertension. Some studies have suggested improved survival among Hispanic patients with PAH.

Blanco I, Mathai S, Shafiq M, et al. Severity of systemic sclerosis-associated pulmonary arterial hypertension in African Americans. *Medicine (Baltim)* 2014;93(5):177–85

- Low and Middle Income Countries
  - Disparity in etiologies (HIV, Schistosomiasis), education

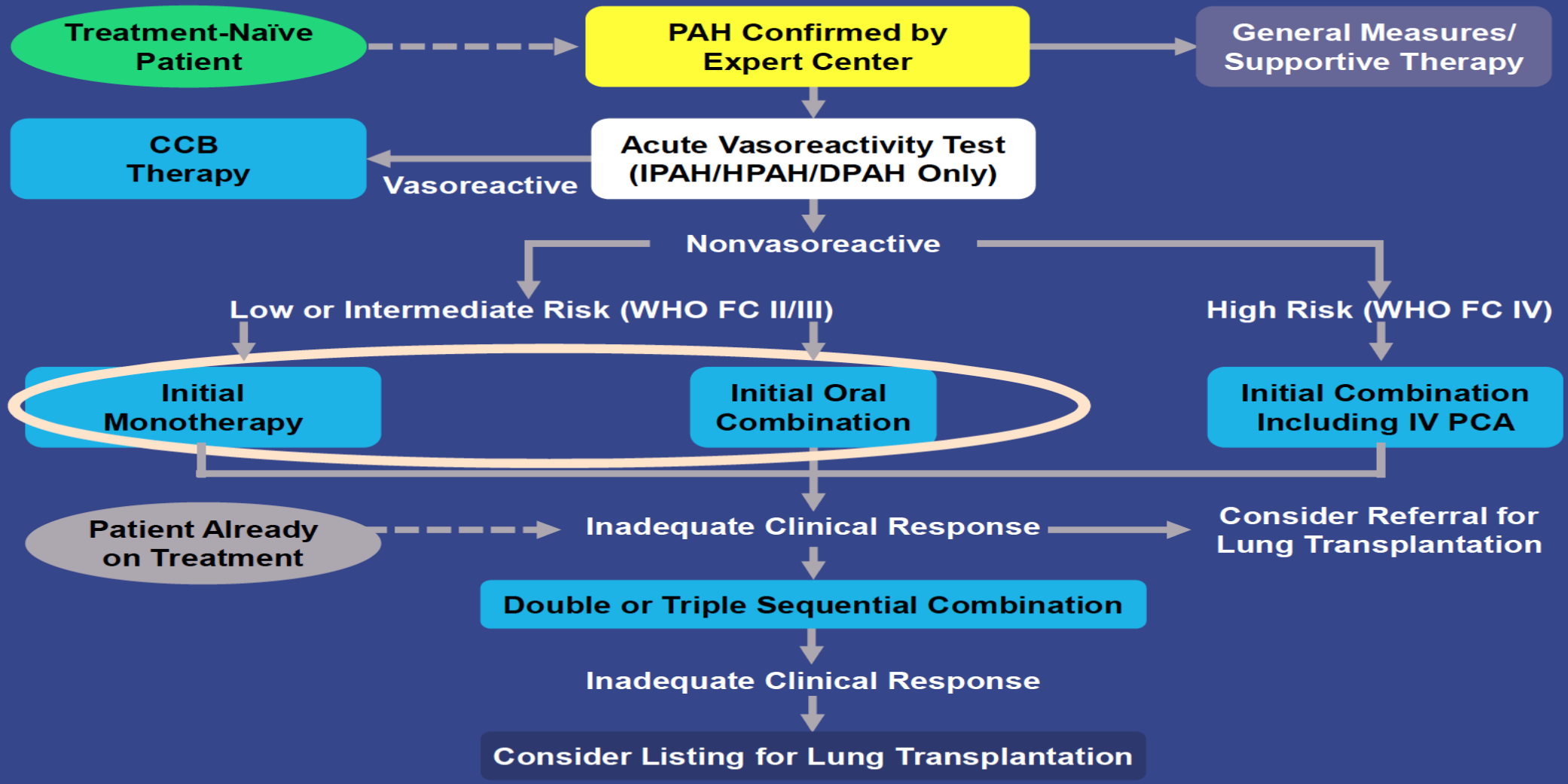
Medrek SK, Sahay S. Ethnicity in pulmonary arterial hypertension: possibilities for novel phenotypes in the age of personalized medicine. *Chest* 2018;153(2):310–20

- PAH in Rural populations
  - Transportation barriers limiting access to PAH specialty centers (?telemedicine), clinic appointments, specialty pharmacies
  - Higher mortality?

Syed ST, Gerber BS, Sharp LK. Traveling towards disease: transportation barriers to health care access. *J Community Health* 2013;38(5):976–93

- Patient Resources
  - PAH Initiative – www.pahinitiative.com
  - Pulmonary Hypertension Association – www.phassociation.org

2015 ESC/ERS PAH Treatment Guidelines



Galiè N, et al. *Eur Heart J*. 2016;37:67-119.

Conclusions

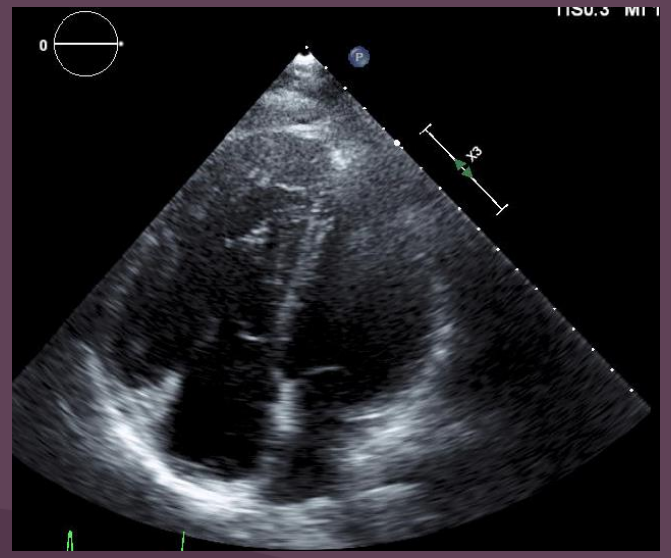
- Keep a high index of suspicion for PH/PAH
- Start by ruling out PH secondary to LHD (R/O Diastolic dysfunction with normal PAWP in dry/diuresed patients) or Lung disease.
- Get V/Q scan: Never miss CTEPH. Pulmonary thrombo-endarcterectomy is potentially curative
- RHC is mandatory for accurate diagnosis and treatment of PH/PAH
- Using PAH medications for PH related to HFpEF is not recommended

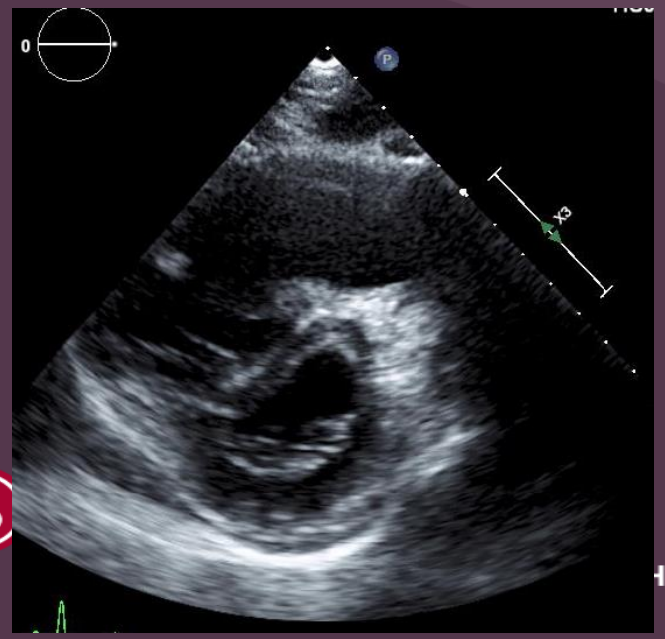
And now back to our case…

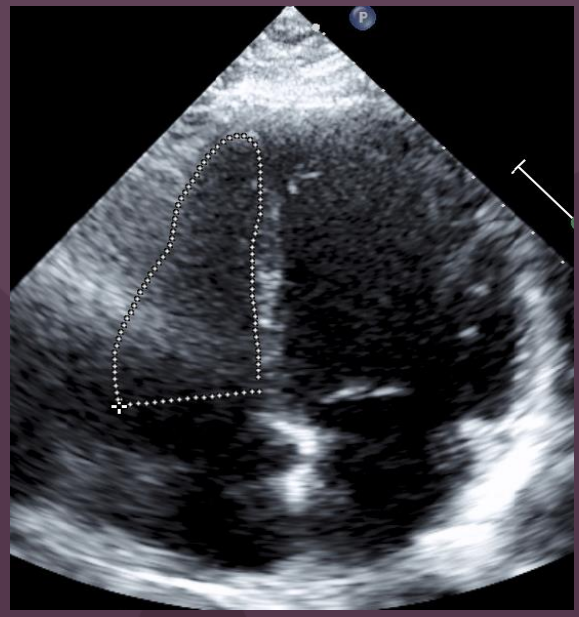
Patient was treated with triple therapy

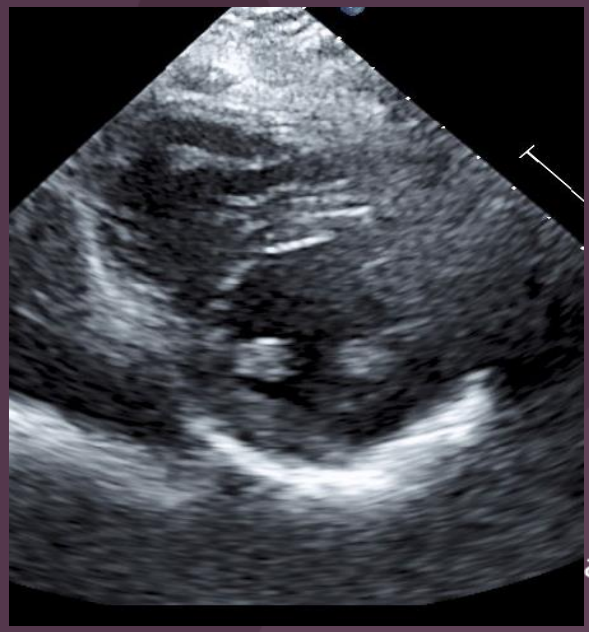
Pre-treatment

Post-treatment









Thank you!

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LEADING THE QUEST

cedars-sinai.edu

FAQs

1. What is the current definition of pulmonary hypertension?
Mean pulmonary artery pressure >20.

2. What are the signs and symptoms of pulmonary hypertension?
Often nonspecific but usually shortness of breath, fatigue, edema, and possibly syncope (a bad sign).

3. Who is at risk of developing group 1 pulmonary hypertension?
Genetics, connective tissue disease, drug use, congenital heart disease, HIV, liver cirrhosis among others.

4. Is there effective treatment for pulmonary hypertension?
Yes, several medication options in every route of administration (PO, IV, SC, inhaled).

Q & A Session

L.A. Care PCE Program Friendly Reminders

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Please note: ***the online survey may appear in another window or tab after the webinar ends.***

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Webinar participants will only have up to two weeks after webinar date to email Leilanie Mercurio at lmercurio@lacare.org to request the evaluation form if the online survey is not completed yet. No name, no survey or completed evaluation and less than 75 minutes attendance duration time via log in means No CME or CE credit, No CME or CE certificate.

Thank you!