Pulmonary Hypertension: Do this, not that!

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Disclosures

- Clinical Trial PI
  - United Therapeutics, Janssen, Acceleron.
- Research Advisory Committee
  - Janssen, Altavant

Goals:

- Understand the key diagnostics needed to make the diagnosis of pulmonary arterial hypertension (PAH)
- To understand risk stratification and application to modern treatment approaches
- To review some common clinical scenarios and how to approach them
  - Group 2 pulmonary hypertension (PH related to left heart disease)
  - Methamphetamine-associated PAH

PAH Definitions

- PAH results from an increased pulmonary vascular **resistance**[1]

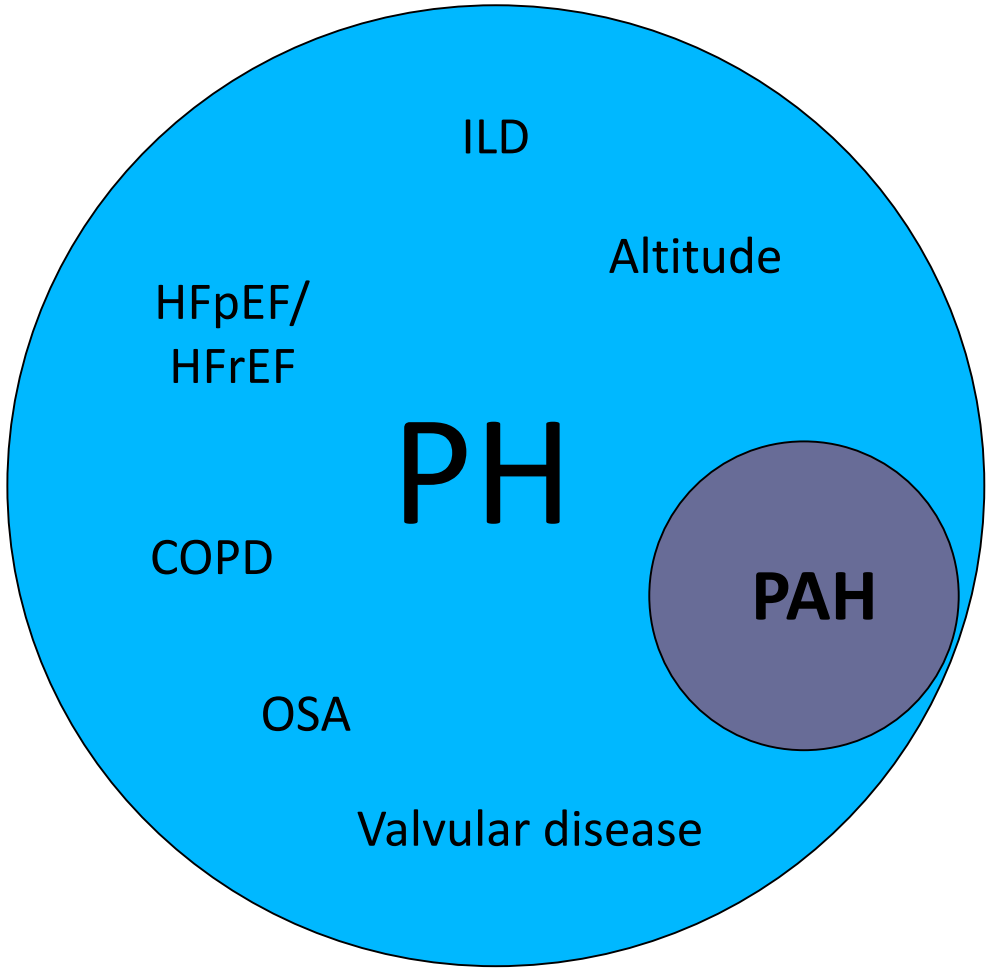
	2015 ESC/ERS[2]	6th WSPH[3]
Hemodynamic definition of PAH:	**mPAP ≥25 mmHg**	**mPAP >20 mmHg**
	PAWP ≤15 mmHg	**PAWP ≤15 mmHg**
	PVR >3 Wood units	**PVR ≥3 Wood units**

- The increase in pulmonary vascular resistance[4]:
  - Restricts blood flow through the pulmonary arterial circulation
  - Ultimately leads to **right heart failure**

ERS=European Respiratory Society. ESC=European Society of Cardiology; PAWP=pulmonary arterial wedge pressure; PVR=pulmonary vascular resistance; WSPH=World Symposium on Pulmonary Hypertension.

1. McLaughlin VV, et al. *J Am Coll Cardiol.* 2015;65:1976-1997. 2. Galiè N, et al. *Eur Respir J.* 2015;46:903-975. 3. Simonneau G, et al. *Eur Respir J*. 2019;24:53.
4. McLaughlin VV, et al. *J Am Coll Cardiol.* 2009;53:1573-1619.

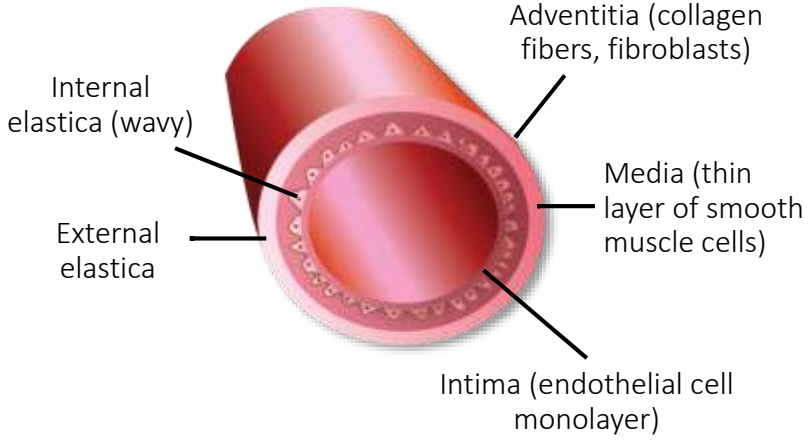
PH is distinct from PAH



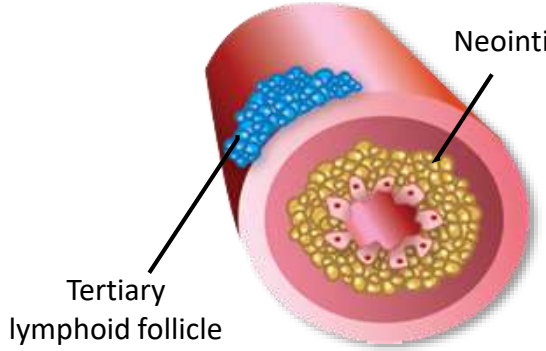
- All patients with PAH have PH
- Not all patients with PH have PAH

PAH is the result of remodeling of the pulmonary vasculature

Normal pulmonary artery



Pulmonary arterial changes in PAH

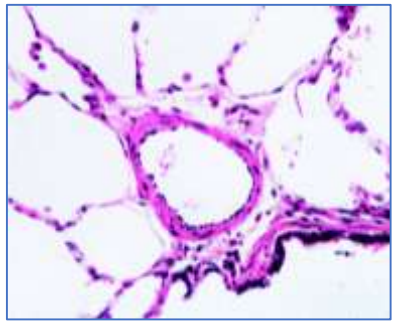


Arterial remodeling and inflammation

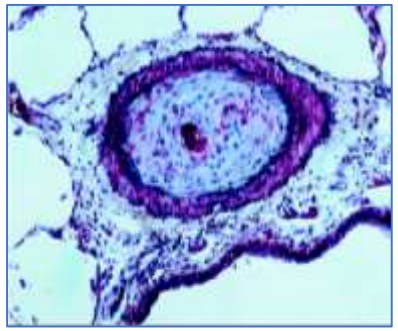
- Thickening of adventitia and media
- Neointima formation, caused by proliferation and migration of smooth muscle cells and fibroblasts
- Pulmonary lymphoid neogenesis

Adapted from: McLaughlin VV, et al. *J Am Coll Cardiol.* 2015;65:1976-1997.

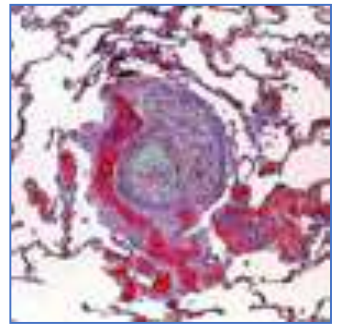
Natural history of PAH



Healthy Vasculature[1]



Symptomatic/Decompensating[1]



Declining/Decompensated[2]

Right Heart Dysfunction

Right Heart Failure

CO

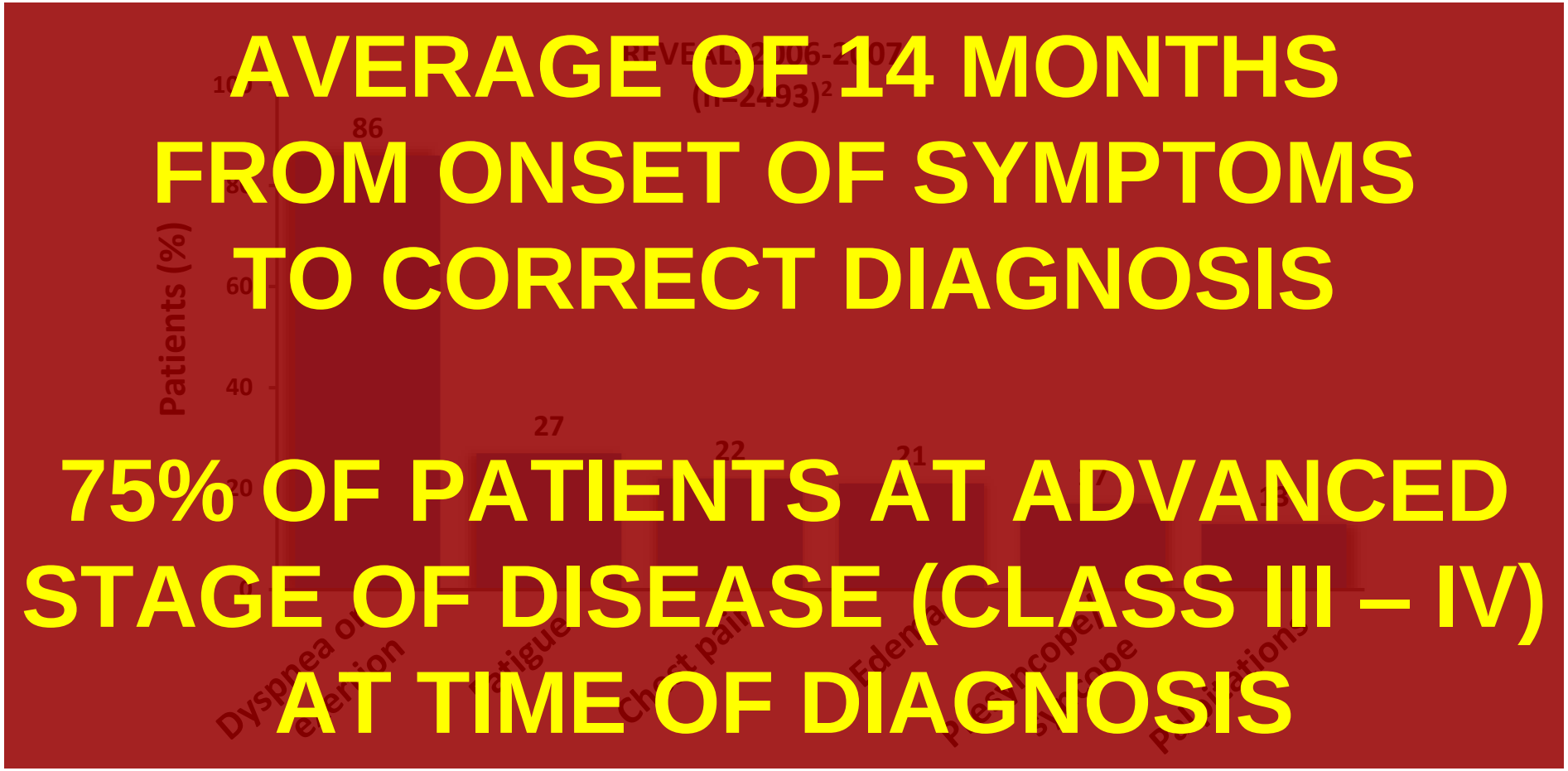
PAP

PVR

RAP

Time

PAH: Symptoms are non-specific



Brown LM, et al. *Chest.* 2011;140:19-26. 3. McGoon MD, et al. *Eur Respir Rev*. 2012;21:8-18.

Clinical classification of pulmonary hypertension

1. PAH

1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH
1.4 PAH 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 long-term responders to calcium channel blockers
1.6 PAH with overt features 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 LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3. PH due to lung diseases and/or hypoxia

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 obstructions

4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions

5. PH with unclear and/or multifactorial mechanisms

5.1 Haematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

HIV=human immunodeficiency virus; LVEF=left ventricular ejection fraction; PCH=pulmonary capillary haemangiomatosis; PVOD=pulmonary veno-occlusive disease.
Simonneau G, et al. *Eur Respir J.* 2019;24:53(1). doi:10.1183/13993003.01913-2018.

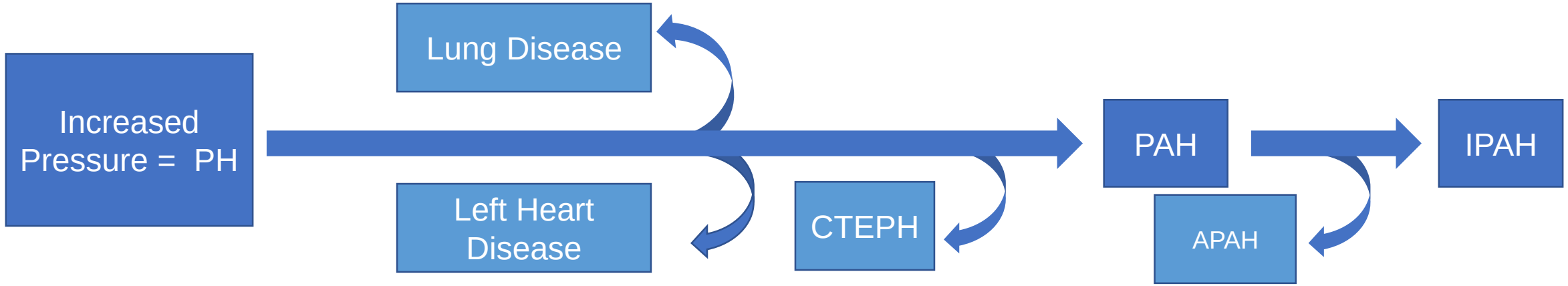
Screening for PAH

Risk Factor	Estimated Prevalence of PAH
HIV infection	≈0.5%[1]
Portal hypertension	2% to 6%[2,3]
Connective tissue disease	3% to 13%[4]

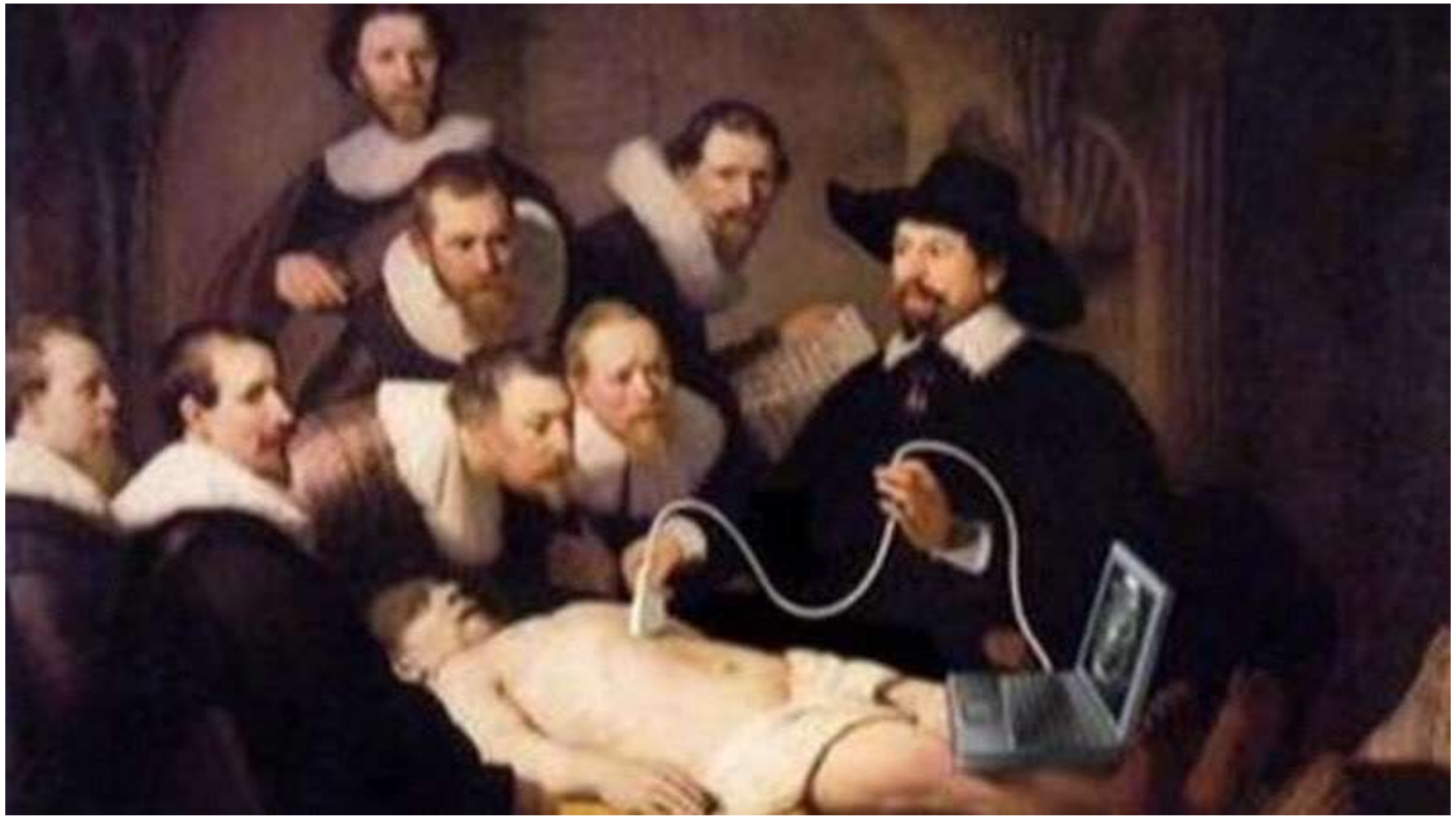
1. Sitbon O, et al. *Am J Respir Crit Care Med.* 2008;177:108-113. 2. Hadengue A, et al. *Gastroenterology.* 1991;100:520-528. 3. Colle IO, et al. *Hepatology.* 2003;37:401-409. 4. Chung L, et al. *Chest*. 2010;138:1383-1394.

PH Diagnosis: Diagnosis of Exclusion

PH Suspicion	PH Detection	PH Group Identification	PAH Type	PAH – Hemodynamics	PAH – Exercise Capacity
• Symptoms and physical examination • Screening procedures • Incidental findings	• ECG (EKG) • Chest x-ray • TT Echocardiogram	• Pulmonary function tests and ABG • V/Q lung scan • High resolution CT • Pulmonary angiography	• Blood tests and immunology • HIV test • Abdominal ultrasound scan	• Right heart catheterization • Acute vasoreactivity test	• 6-minute walk test • Peak VO_2 • Functional class

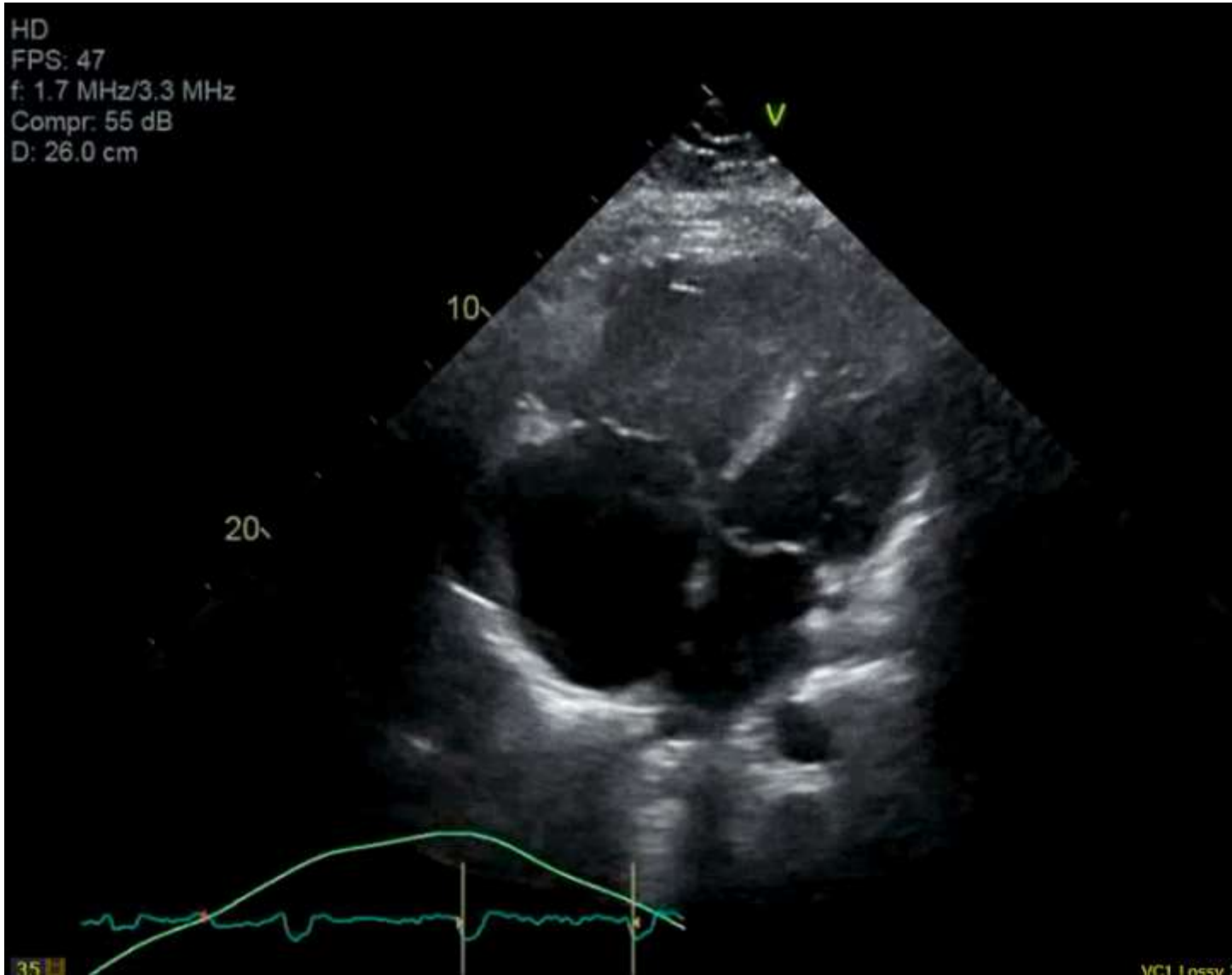


Use echocardiogram as a **screening** tool



Use echocardiogram as a **screening** tool

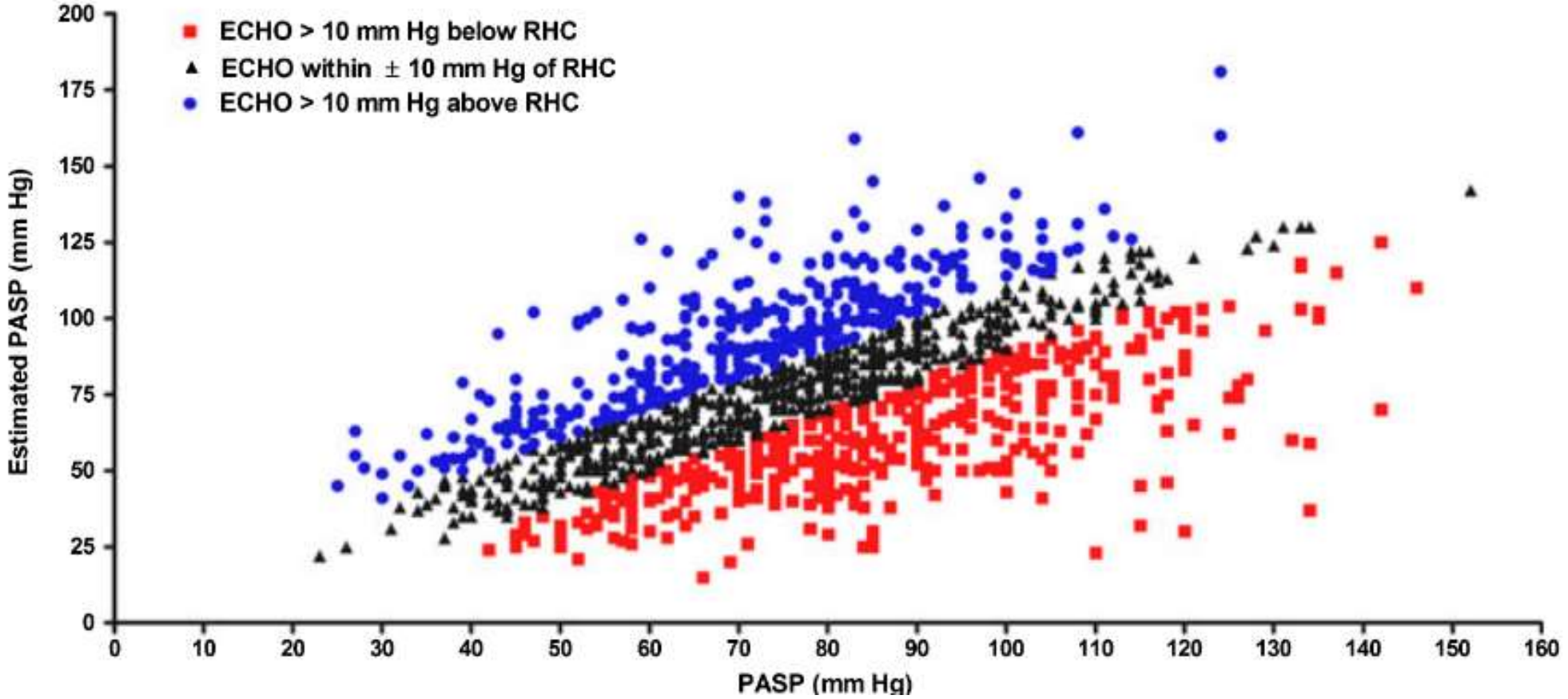
- Assess RV morphology and function
- Pericardial effusion?
- Hints of left sided disease
  - Left atrial enlargement?
  - Aortic or mitral disease?
- RVSP…



Where echo fails as a **diagnostic** tool…

- If volume overloaded, RVSP is likely to be overestimated
  - Get patient euvolemic on physical exam prior to echo!
- Diagnosis of elevated left sided filling pressures and diastolic dysfunction is imperfect
- Does RVSP correlate to true RVSP on right heart catheterization?

Where echo fails as a **diagnostic** tool…



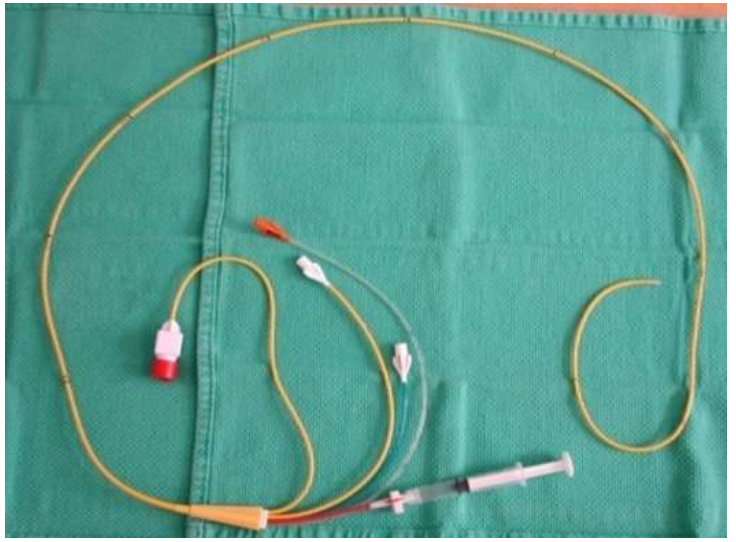
Only 50% of echo-derived RVSPs will be within 10 mmHg of RHC RVSP!

Farber HW, et al. Congest Heart Fail. 2011;17:56–63.

Right heart catheterization is crucial!

- Outpatient procedure
- Ensures accurate diagnosis
  - ↑ PCWP may indicate elevated LVEDP or mitral regurgitation
  - Allows for cardiac output measurement
  - Pulmonary vascular resistance measurement

- <u>Absolutely necessary prior to treatment of PAH</u>
- If PAH found, **vasodilator challenge MUST be performed**



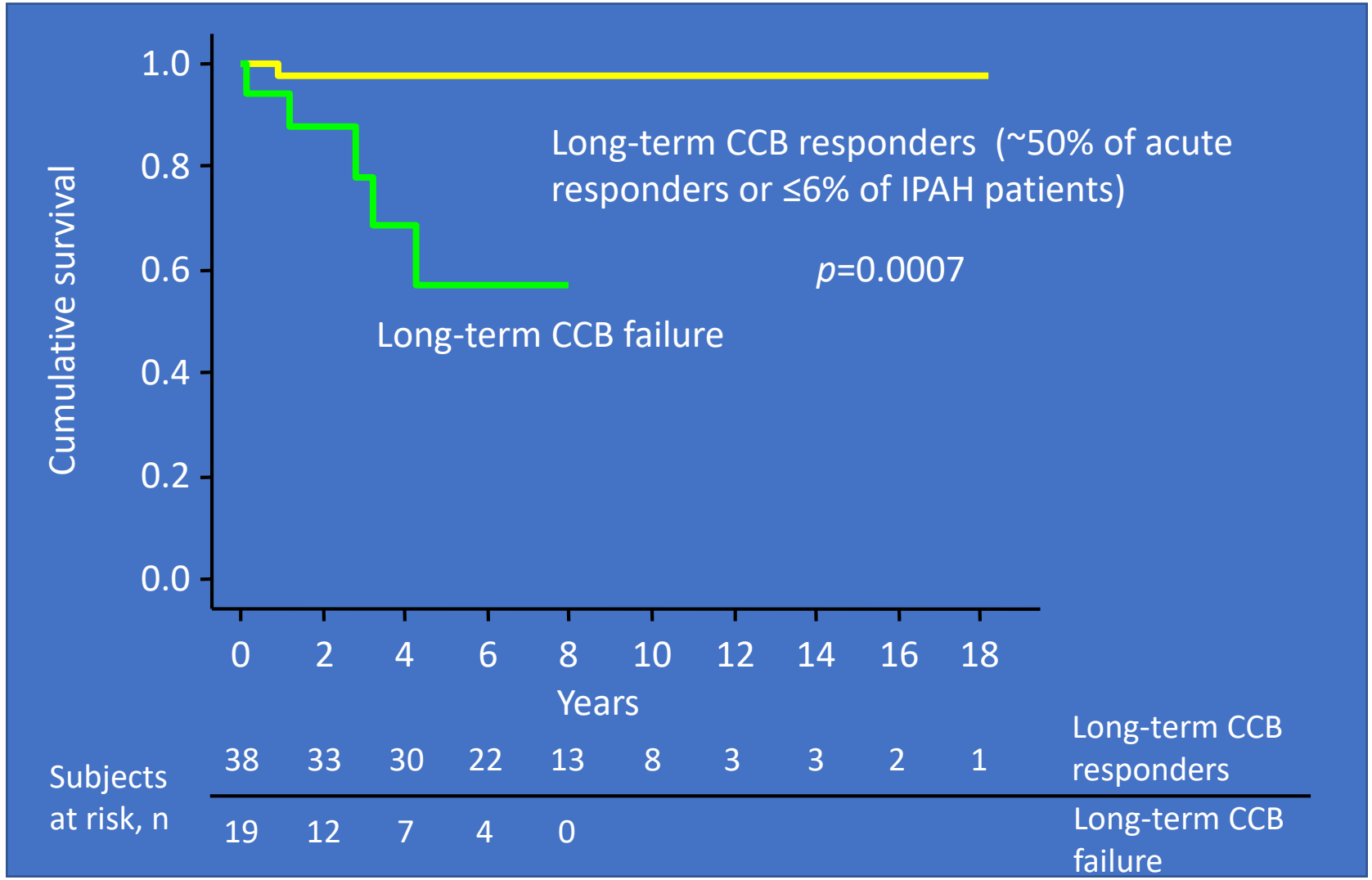
A quick detour….

“Vasodilator Response”

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

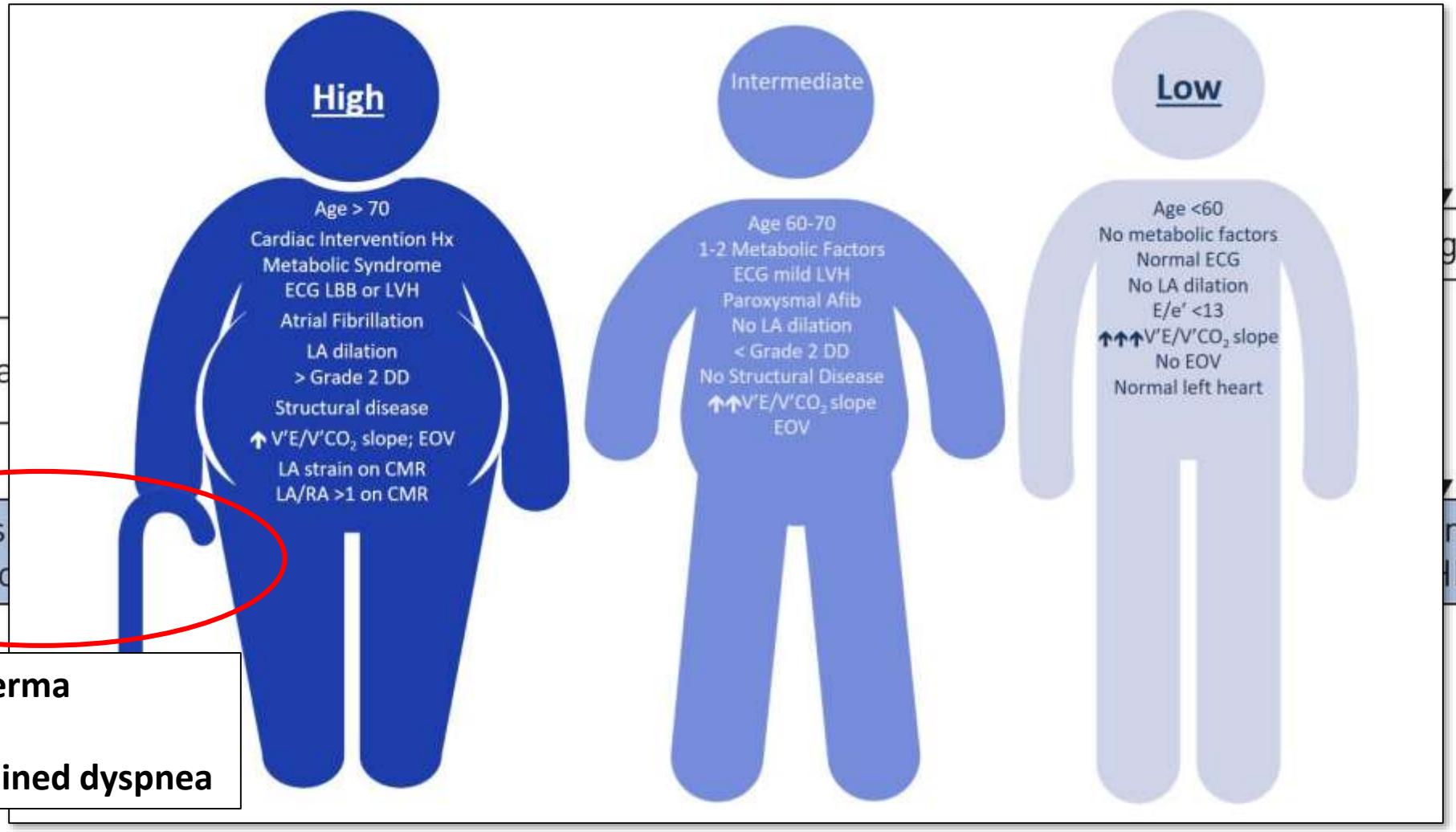
McLaughlin VV, et al. American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association. J Am Coll Cardiol. 2009 Apr 28;53(17):1573-619.

Survival in IPAH: *Long-term CCB Responders*



Sitbon O, Humbert M, Jais X, Ioos V, Hamid AM, Provencher S, Garcia G, Parent F, Herve P, Simonneau G. *Circulation.* 2005;111:3105-3111.

When should you pursue invasive testing?



No RV a

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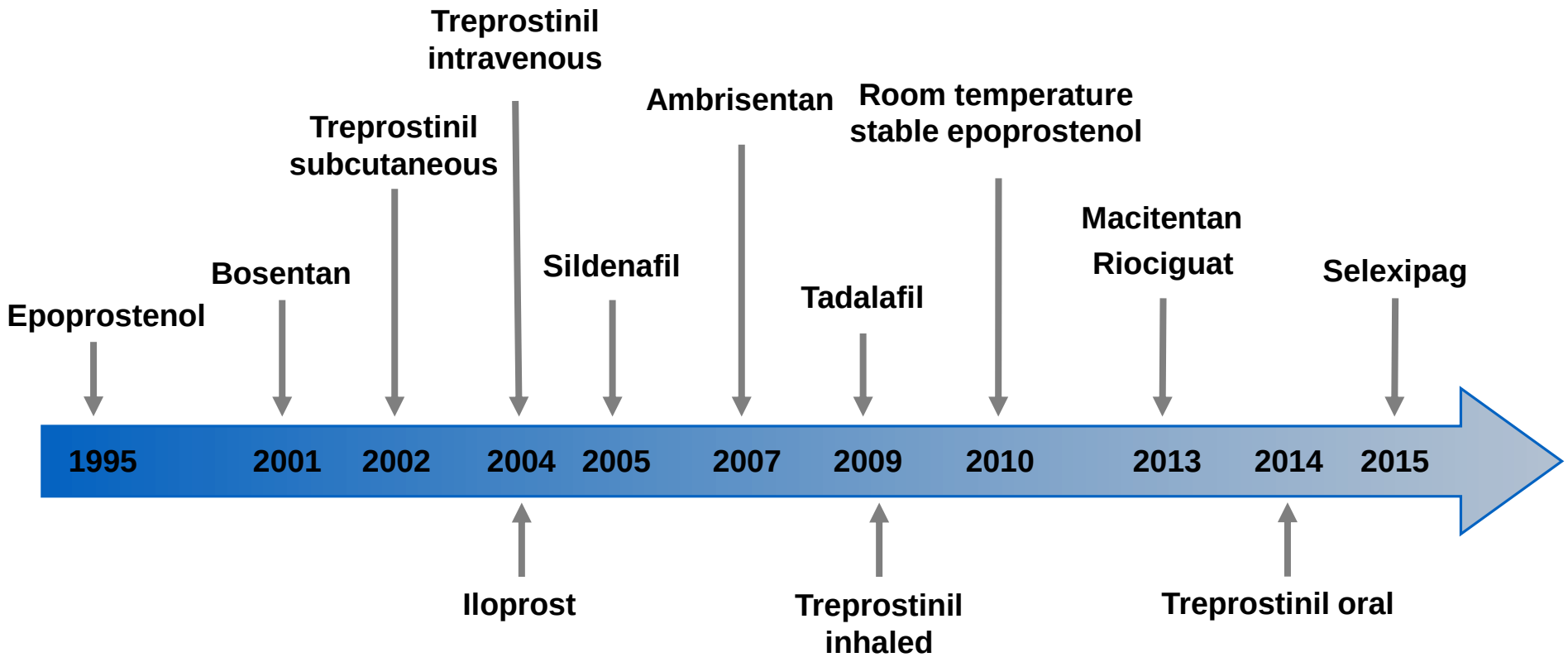
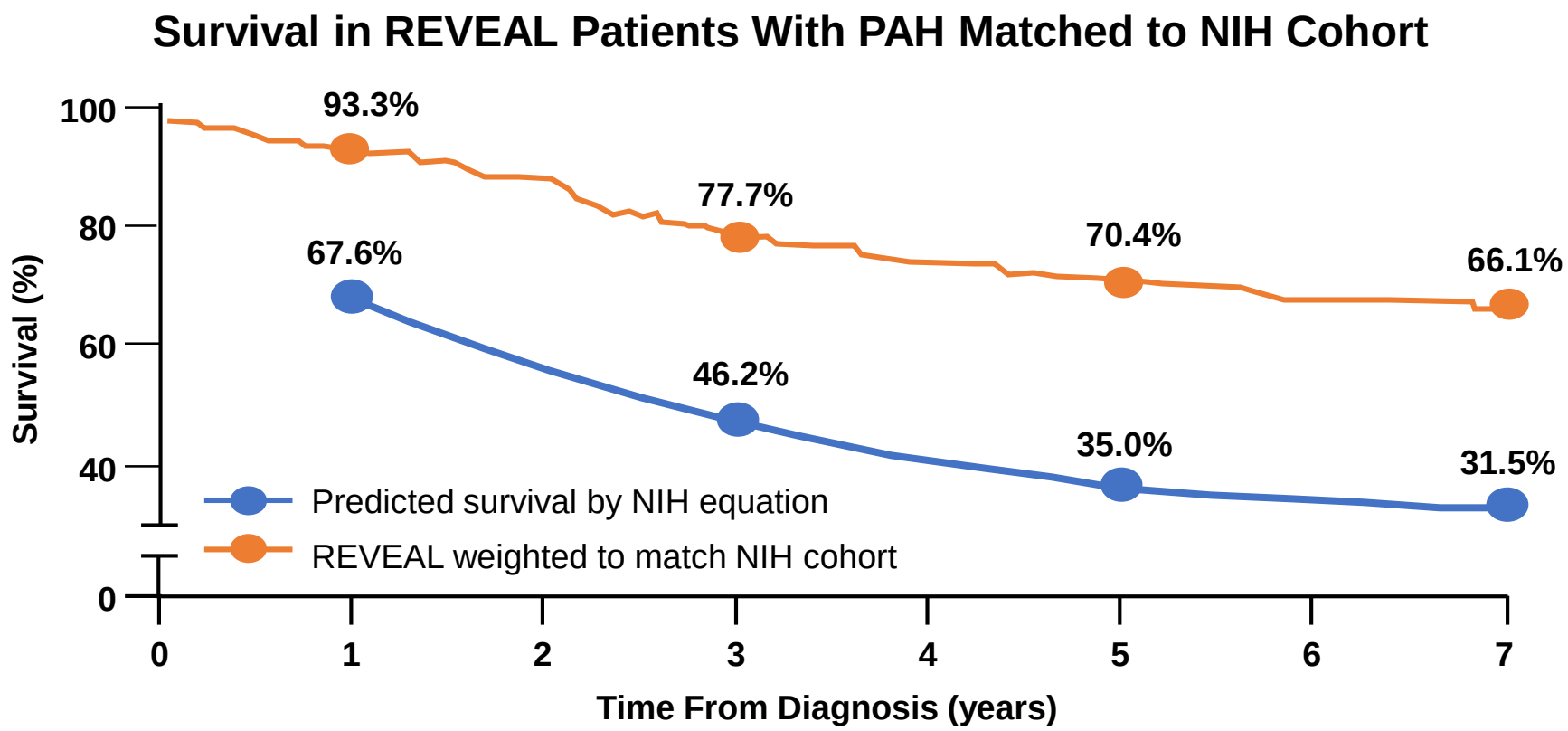
Scleroderma
CTEPH
Unexplained dyspnea

PAH Drug Development

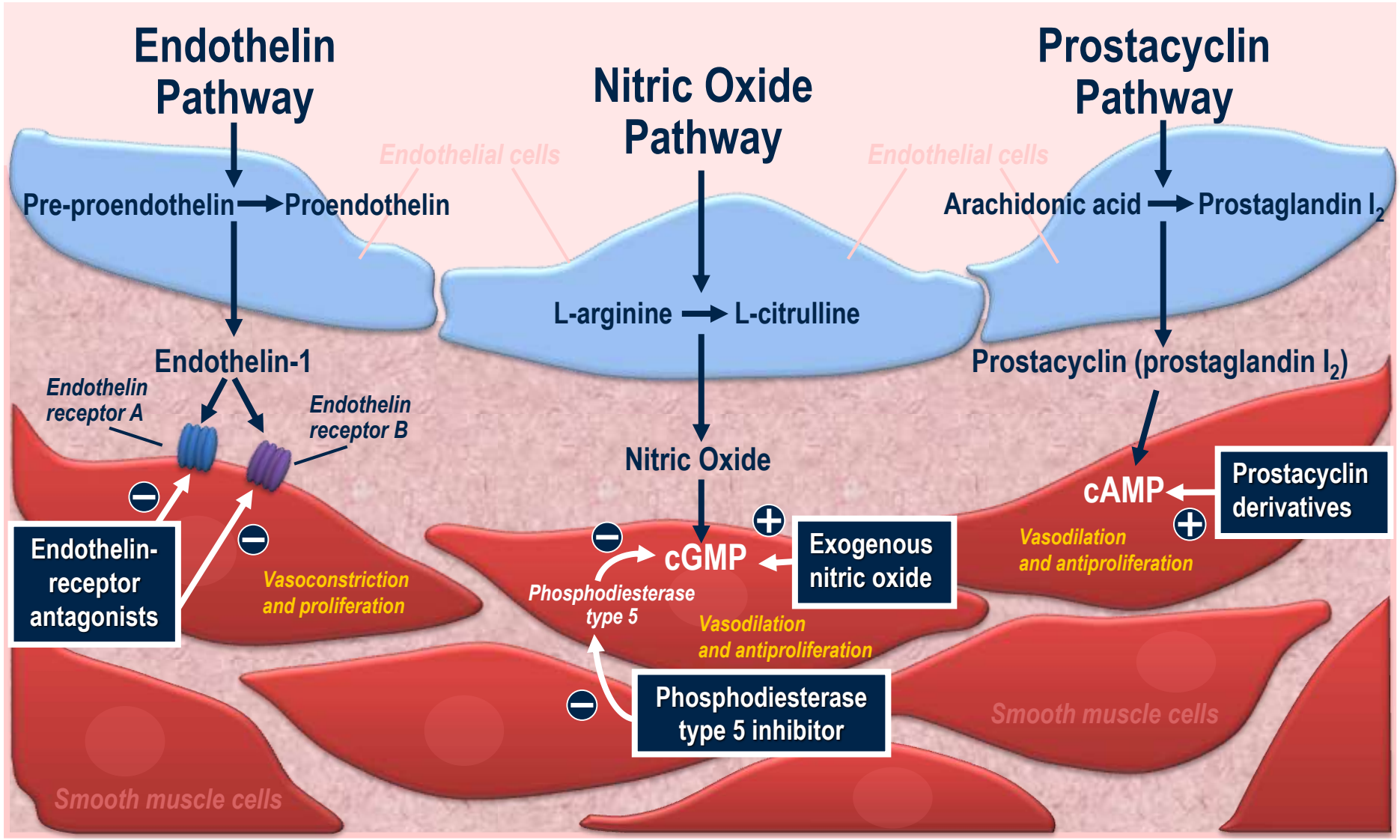


Long-term Survival From Time of Diagnosis of PAH in the REVEAL Registry



Benza RL, et al. *Chest*. 2012;142:448-456.

Modern PAH Treatments



Humbert M, Sitbon O, Simonneau G. *N Engl J Med*. 2004;351:1425-1436.

Use risk assessment to guide therapy

REVEAL 2.0 Risk Calculator

Print | Reset

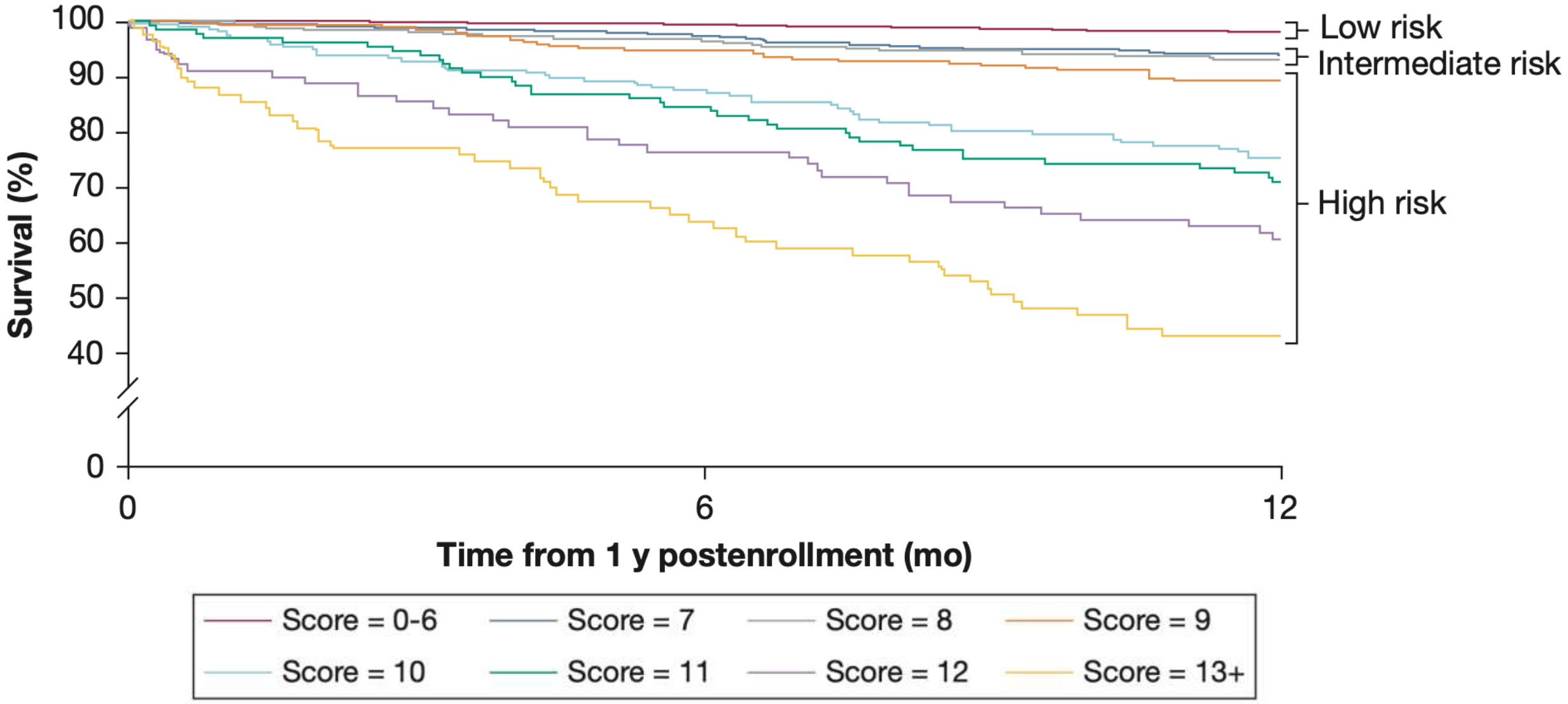
Select all variables that apply. A minimum of 7 variables are required to generate a score. Calculation accuracy increases with more selections.

					Score
WHO Group 1 Subgroup	CTD-PAH 1	Heritable 2	PoPH 3	Other 0	-
Demographics - Male age > 60 years		No 0	Yes 2		-
eGFR<60mL/min/1.73m² or renal insufficiency		No 0	Yes 1		-
NYHA/WHO Functional Class	I -1	II 0	III 1	IV 2	-
Systolic BP (mm Hg)		SBP≥110 0	SBP<110 1		-
Heart Rate (BPM)		HR≤96 0	HR>96 1		-
All-Cause Hospitalizations ≤ 6 mo		No 0	Yes 1		-
6-Minute Walk Test (m)	>440 -2	320 to 440 -1	<320 to 165 0	<165 1	-

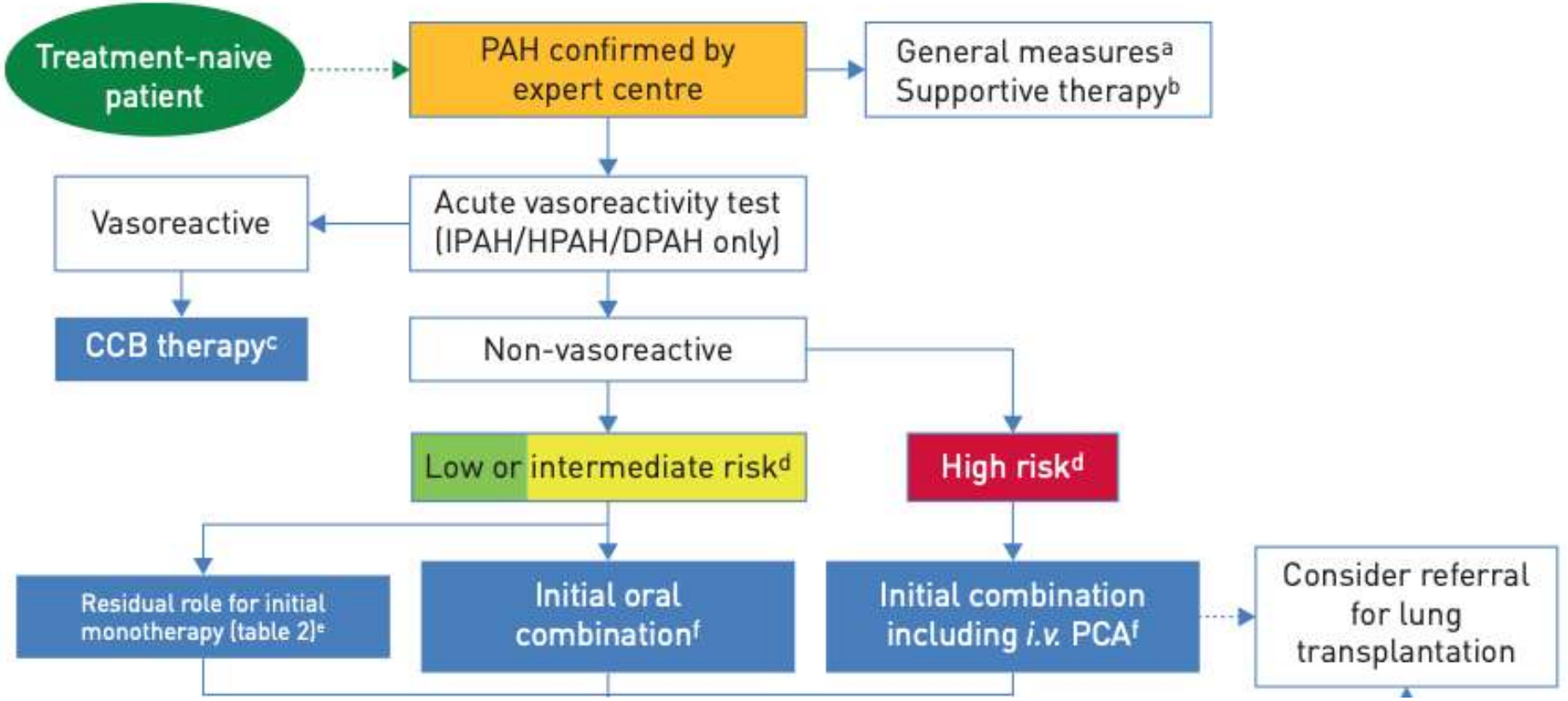
BNP (pg/mL)	<50 -2	50>200 0	200>800 1	≥800 2	-
or					
NT-proBNP (pg/mL)	<300 -2	300≤1100 0	≥1100 2		-
Pericardial Effusion on Echocardiogram		No 0	Yes 1		-
% predicted DL_{CO} ≤40		No 0	Yes 1		-
mRAP >20 mm Hg Within 1 Year		No 0	Yes 1		-
PVR < 5 Wood units on right heart catheterization		No 0	Yes -1		-
					+6
				Risk score	--

	Low risk	Intermediate risk	High risk
Risk score	0-6	7-8	≥9

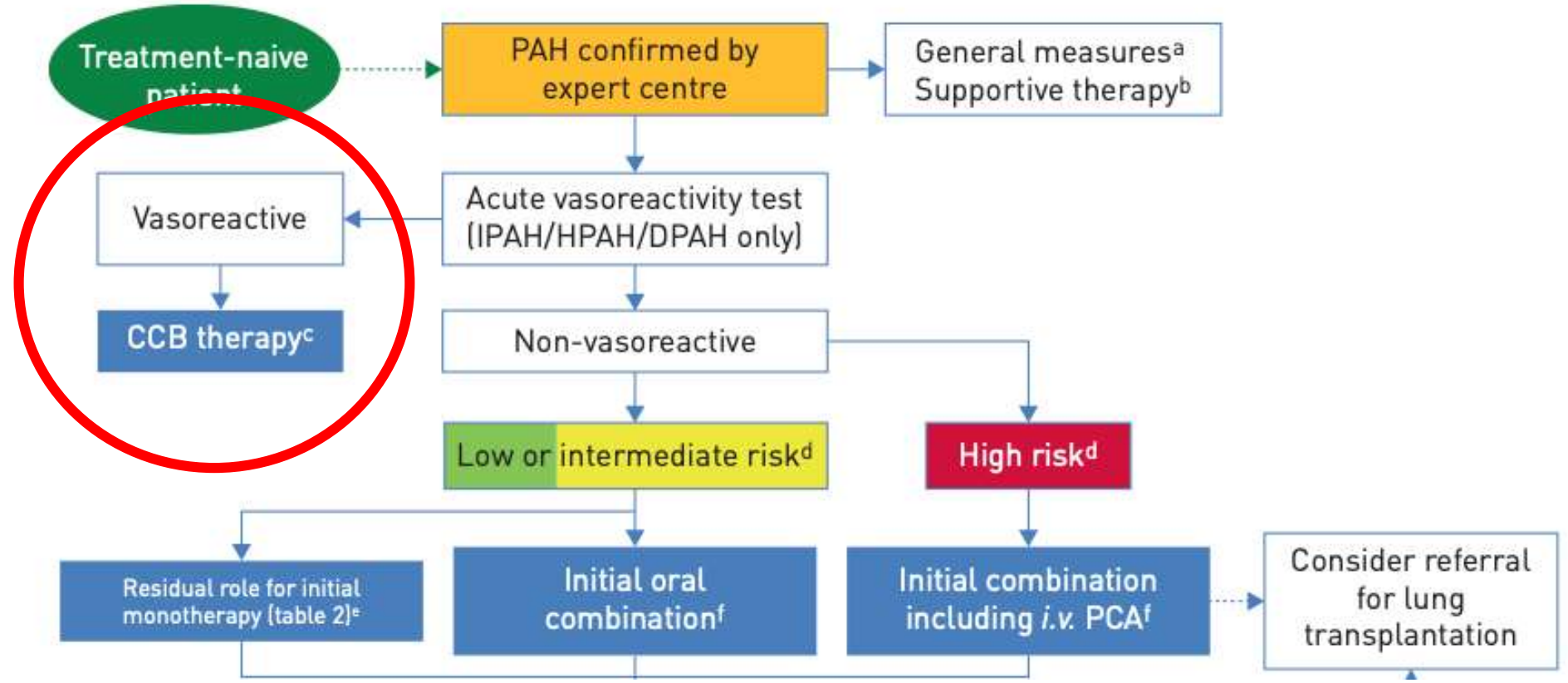
Calculated risk correlates with outcomes



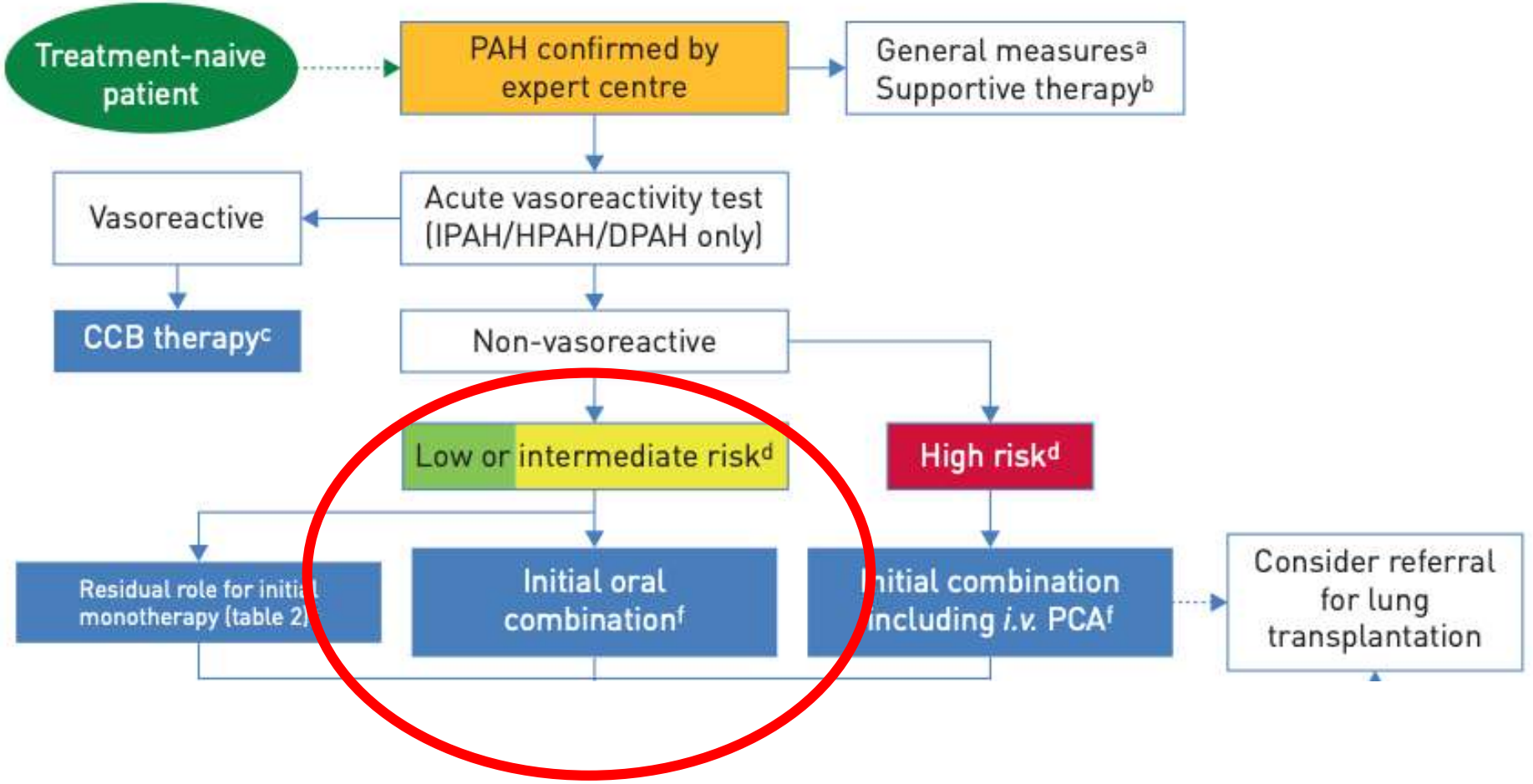
Initial treatment strategy



Initial treatment strategy



Initial treatment strategy



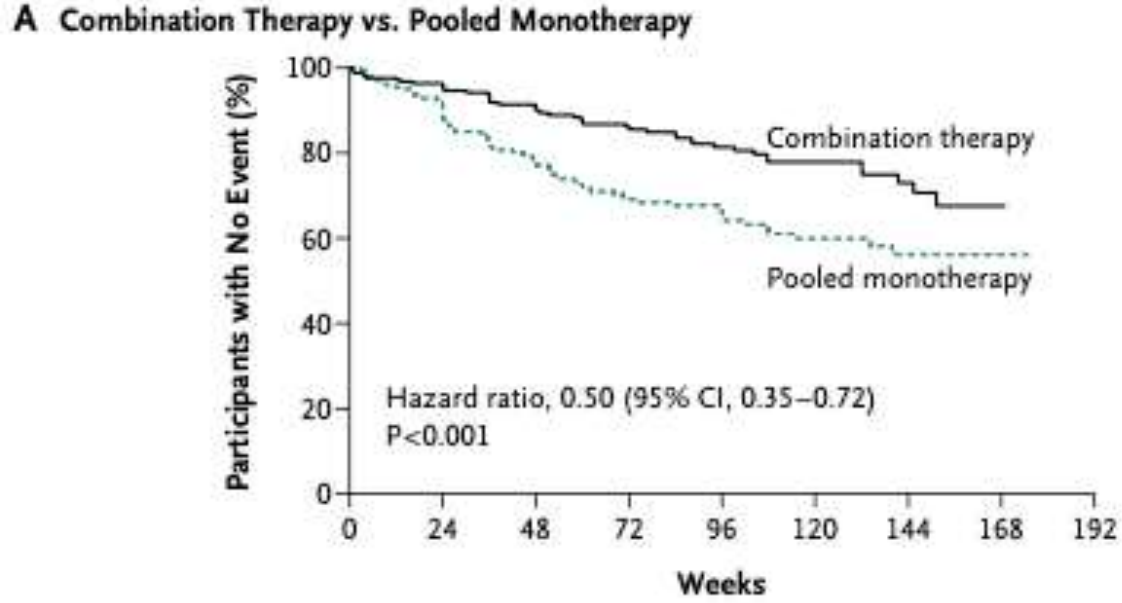
Most new diagnoses should be treated with upfront combination oral therapy

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension

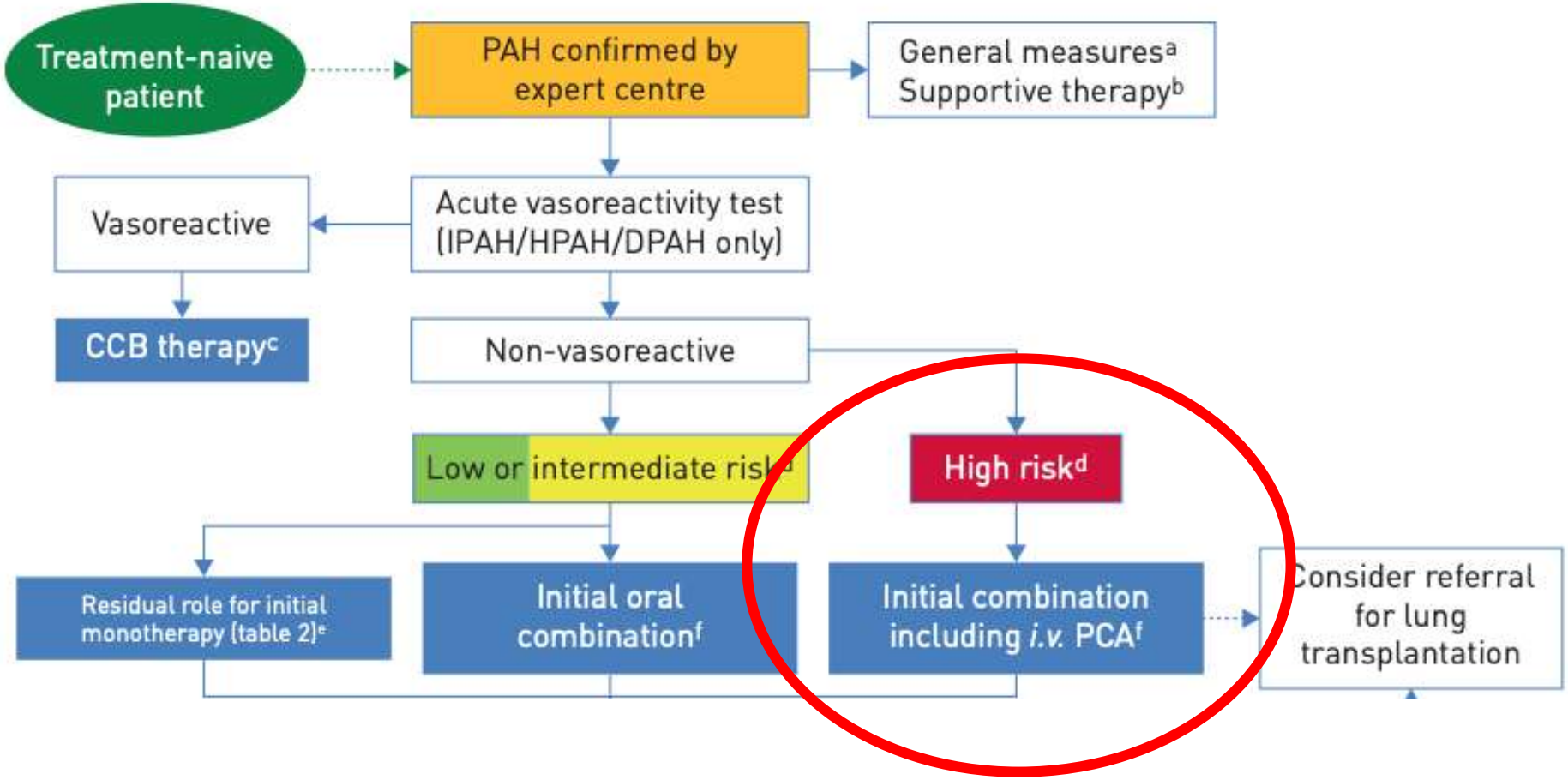
N. Galiè, J.A. Barberà, A.E. Frost, H.-A. Ghofrani, M.M. Hoeper, V.V. McLaughlin, A.J. Peacock, G. Simonneau, J.-L. Vachiery, E. Grünig, R.J. Oudiz, A. Vonk-Noordegraaf, R.J. White, C. Blair, H. Gillies, K.L. Miller, J.H.N. Harris, J. Langley, and L.J. Rubin, for the AMBITION Investigators*

- 605 subjects
  - 302 combination therapy
  - 152 Ambrisentan monotherapy
  - 151 Tadalafil monotherapy

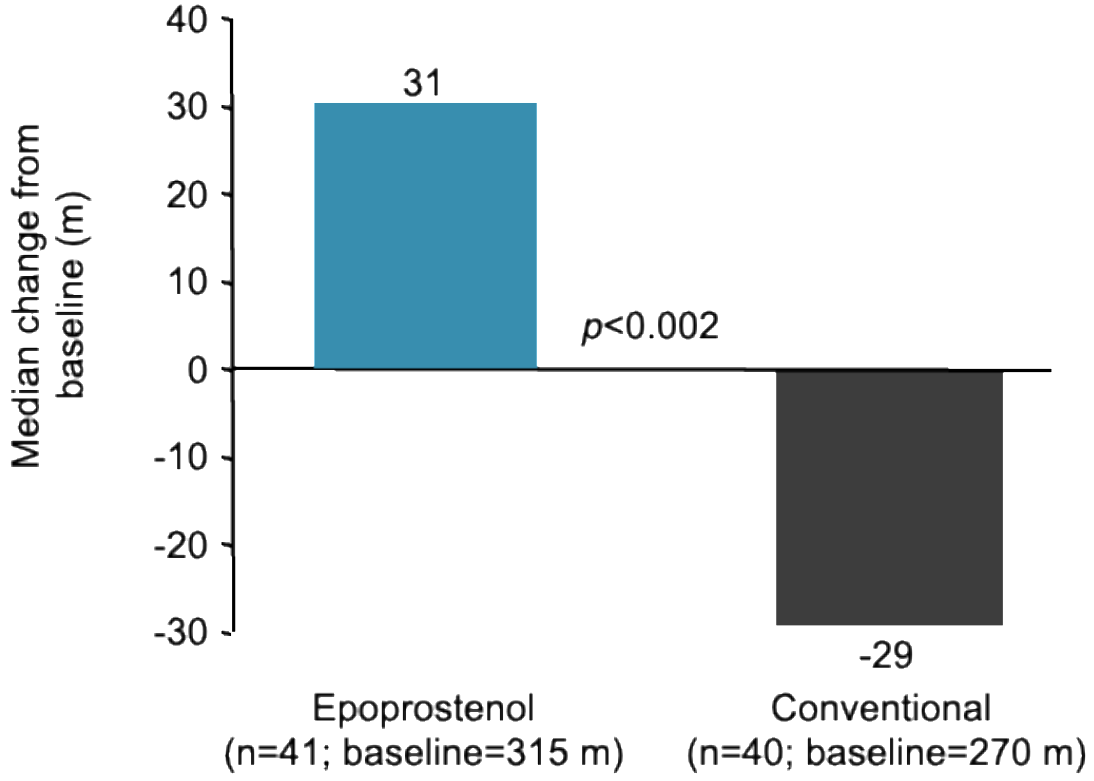
- Primary outcome: Time to clinical failure
  - Death
  - Hospitalization for worsening PAH
  - Disease progression (decrease 15% in 6MWD or worsening FC)
  - Unsatisfactory response (consistently worsening 6MWD, FCIII for over 6 months)

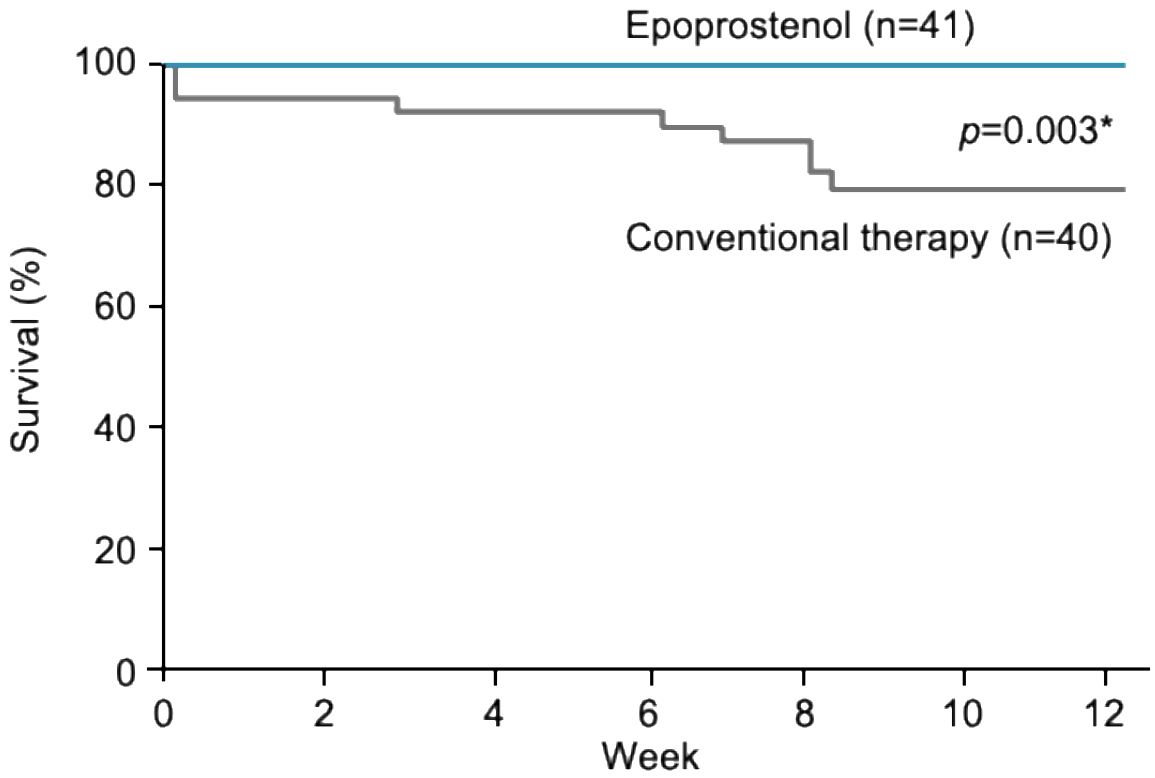


Initial treatment strategy



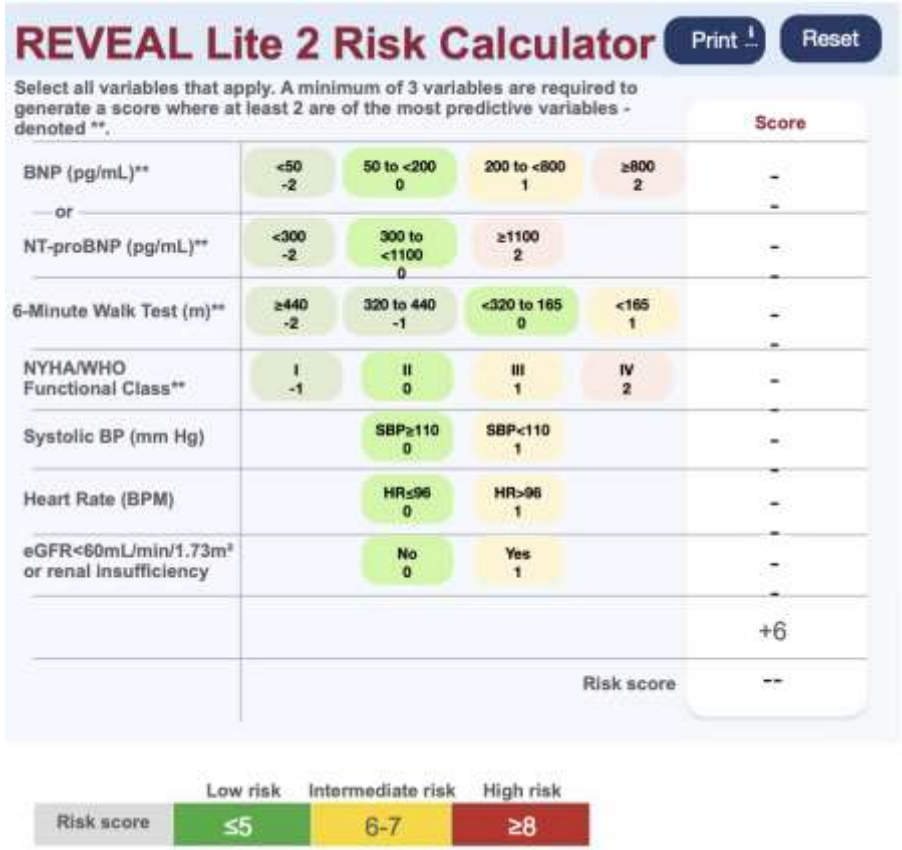
Epoprostenol vs. Conventional therapy





Barst RJ, et al. *NEJM.* 1996; 334:296-301

Assessing treatment efficacy and changes



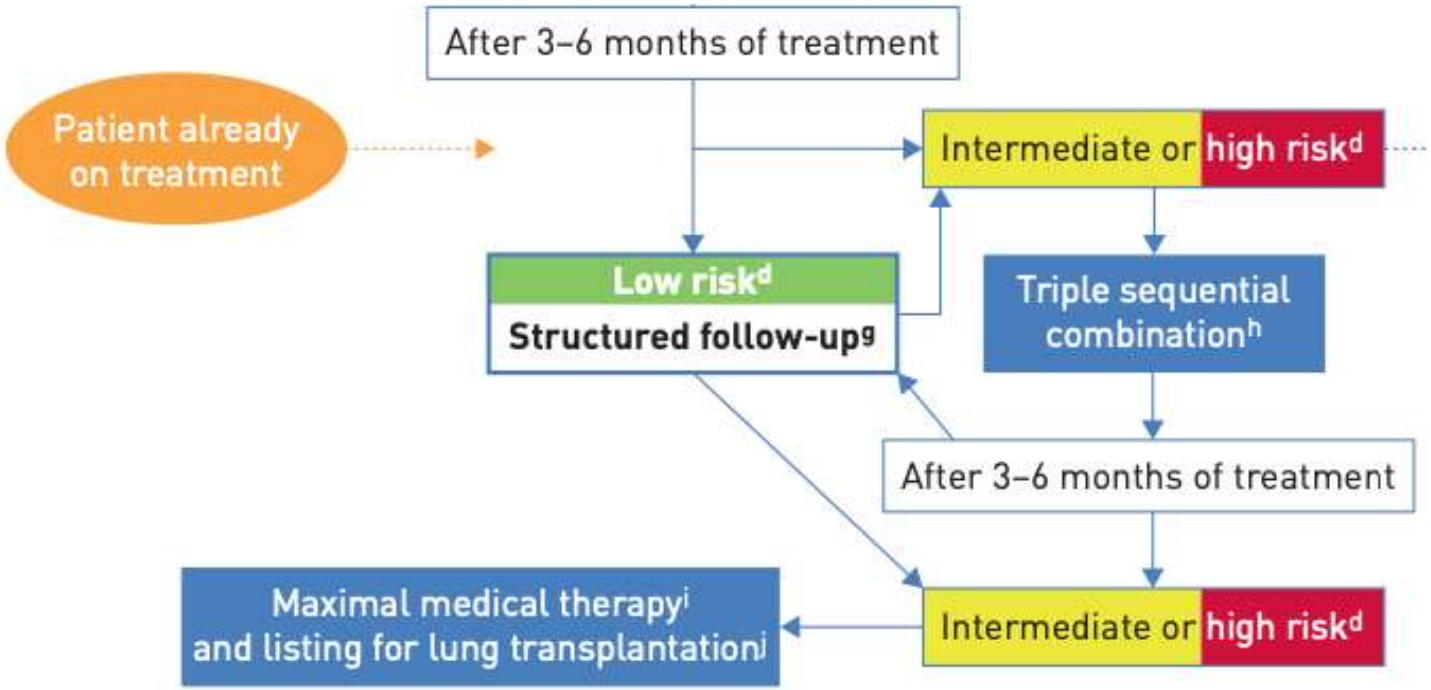
REVEAL Lite 2 Risk Calculator

Print Reset

Select all variables that apply. A minimum of 3 variables are required to generate a score where at least 2 are of the most predictive variables - denoted **.

					Score
BNP (pg/mL)**	<50 -2	50 to <200 0	200 to <800 1	≥800 2	-
or					-
NT-proBNP (pg/mL)**	<300 -2	300 to <1100 0	≥1100 2		-
6-Minute Walk Test (m)**	≥440 -2	320 to 440 -1	<320 to 165 0	<165 1	-
NYHA/WHO Functional Class**	I -1	II 0	III 1	IV 2	-
Systolic BP (mm Hg)		SBP≥110 0	SBP<110 1		-
Heart Rate (BPM)		HR≤96 0	HR>96 1		-
eGFR<60mL/min/1.73m² or renal insufficiency		No 0	Yes 1		-
					+6
				Risk score	--

	Low risk	Intermediate risk	High risk
Risk score	≤5	6-7	≥8



Should PAH treatment be used in **group 2 PH?**

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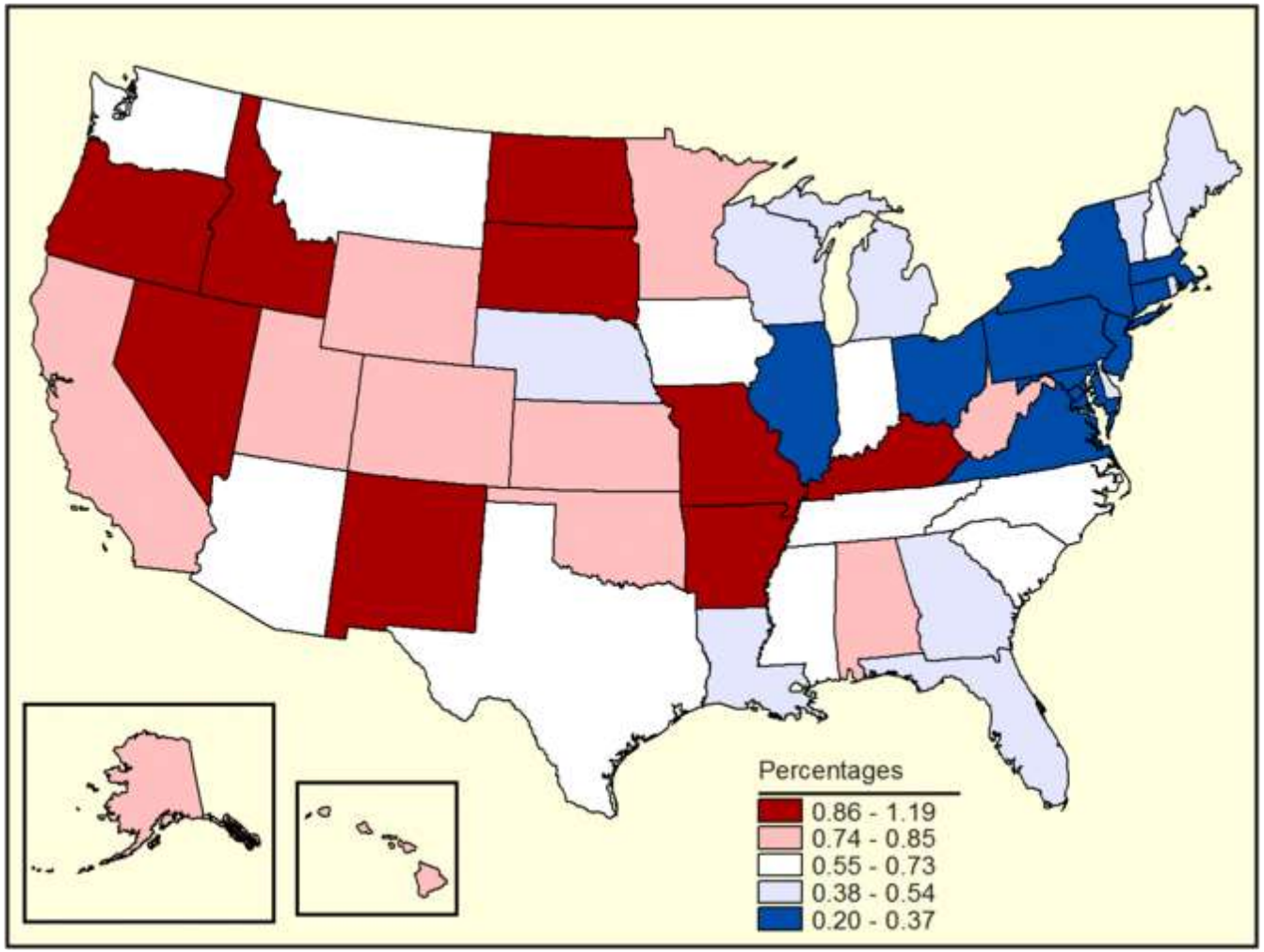
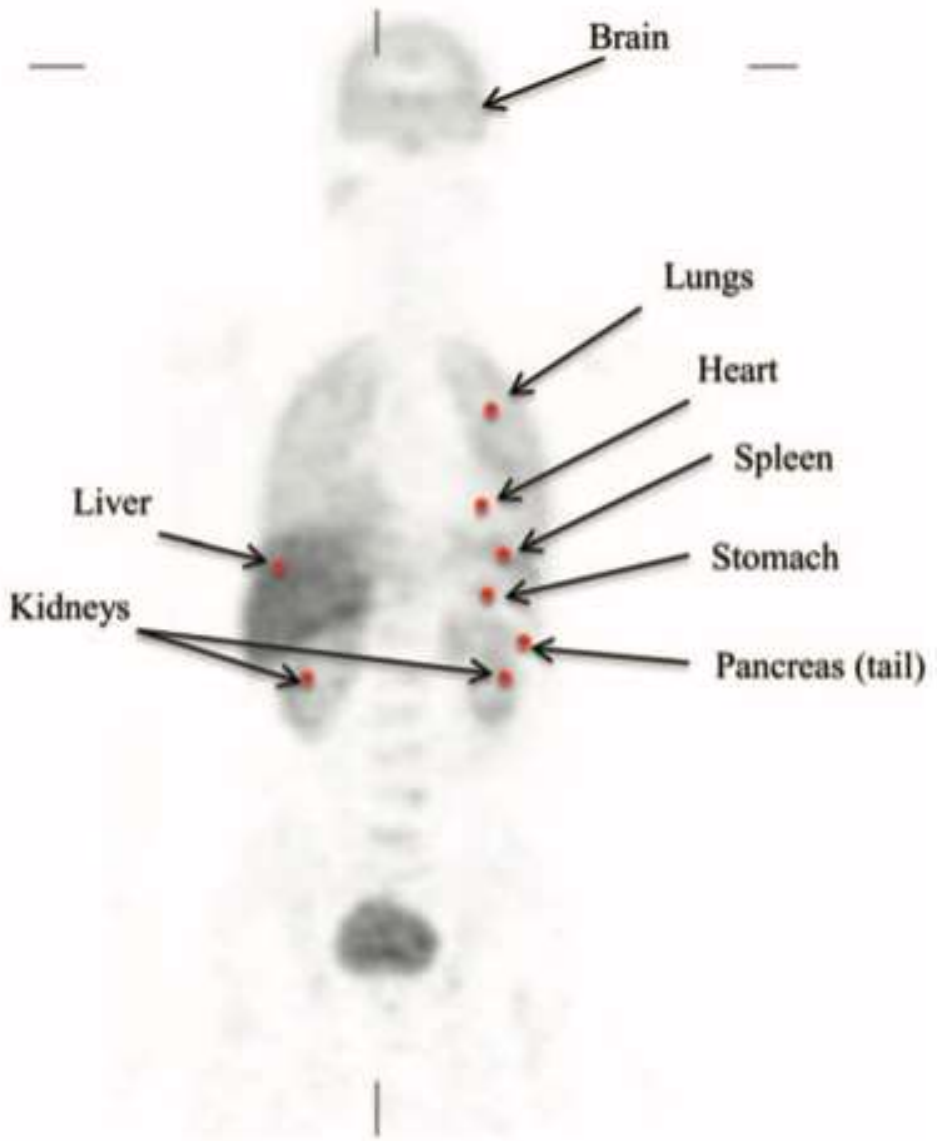
Meth-APAH: A major issue in Oregon

Methamphetamine Use in the Past Year among Individuals Aged 12 or Older

by State: Percentages, Annual Averages Based on 2016 and 2017 NSDUHs



Meth and the Lungs



Meth-APAH Regional Distribution

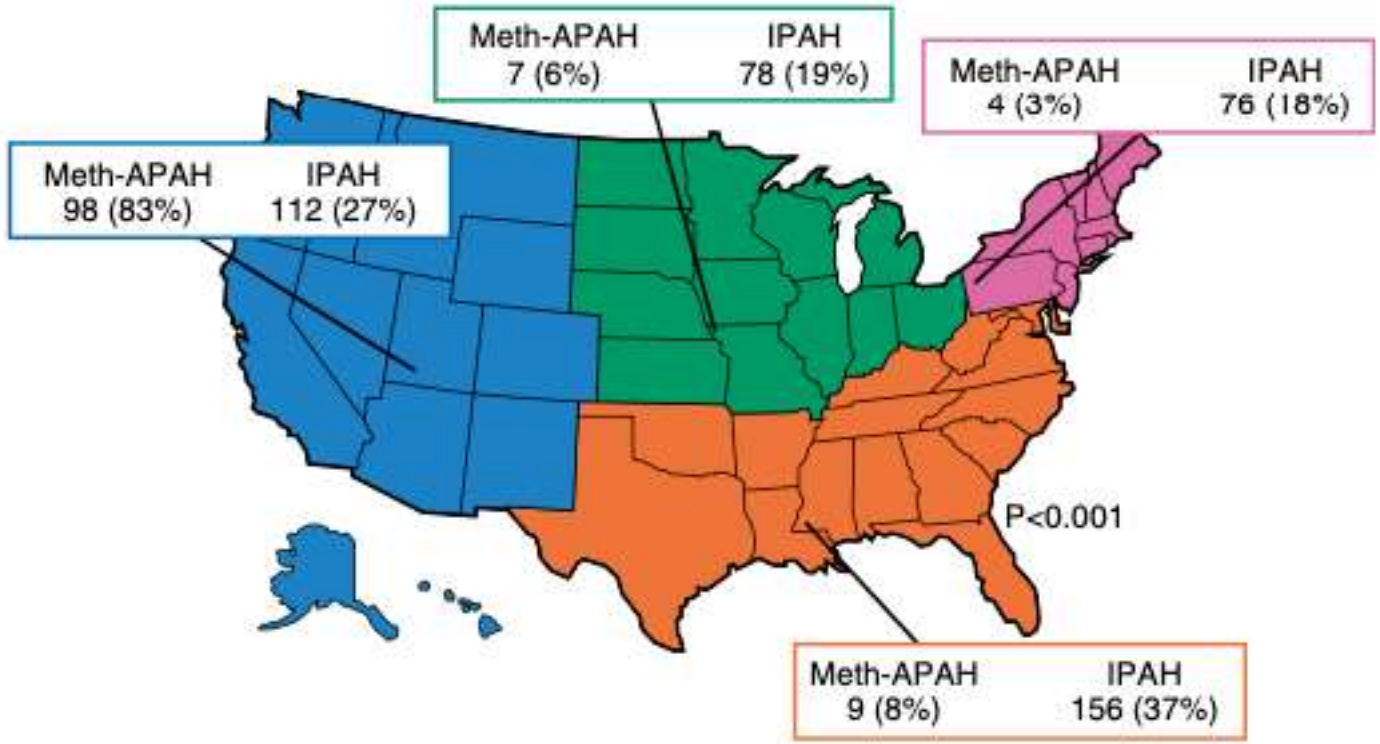


Figure 1. Distribution of Meth-APAH and IPAH in the Pulmonary Hypertension Association Registry. IPAH = idiopathic pulmonary arterial hypertension; Meth-APAH = methamphetamine-associated pulmonary arterial hypertension.

Kolaitis, et al. 10.1513/AnnalsATS.202007-774OC

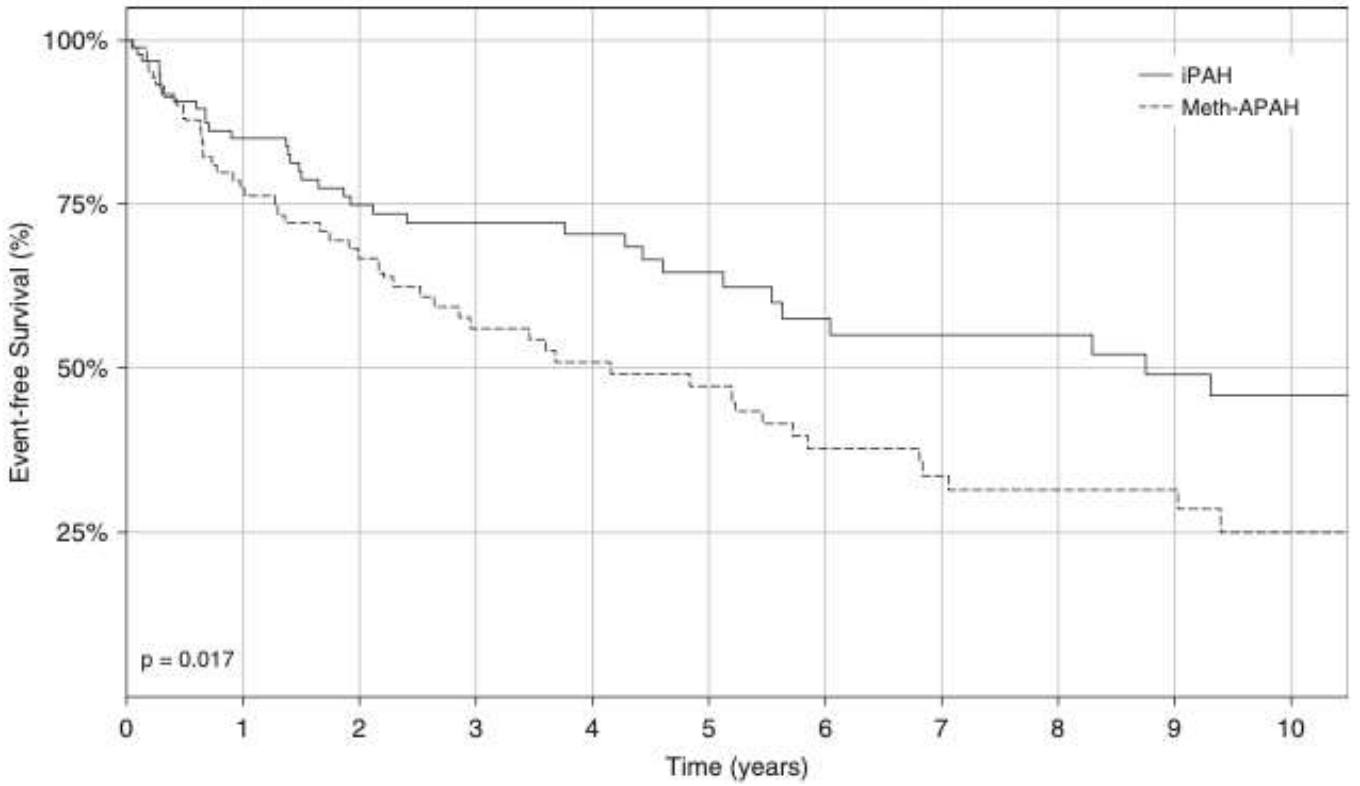
Meth-APAH Treatment Patterns

	Meth-APAH (n = 118)	IPAH (n = 423)
Therapy at enrollment		
On PAH specific therapy	86%	88%
Dual combination	52%	52%
Triple therapy	11%	20%
Parenteral prostacyclin	6%	28%

Treatment	Odds Ratio (95% CI)	*P* Value
Adjusted for age, sex, race/ethnicity, education, body mass index, and the time-dependent covariates of 6-minute walk distance and World Health Organization functional class		
Digoxin	1.83 (0.91–3.70)	0.091
On PAH-specific treatment	0.73 (0.31–1.71)	0.465
Dual combination	1.23 (0.79–1.92)	0.361
Triple therapy	0.43 (0.24–0.77)	0.005
Parenteral prostacyclin	0.10 (0.04–0.24)	<0.001
Supplemental oxygen	0.49 (0.30–0.81)	0.005

Kolaitis, et al. 10.1513/AnnalsATS.202007-774OC

Meth-APAH and Increased Mortality



Zamanian, et al: 10.1164/rccm.201705-0943OC

Meth-APAH Treatment Challenges

Initial Contact with PH team

- Referral and patient making initial contact can be difficult

Maintaining patient engagement/follow-up

- Normalizing and encouraging transparent interactions
- Often requires extra nursing and physician time
- Participation in an active recovery program is typically extremely helpful

Pharmacologic limitations

- Unclear efficacy if continued methamphetamine use
- Complexities of prostacyclin IP receptor agonists and oral prostacyclin titrations are sometimes too difficult
- Risk/safety issues with parenteral therapies

Takeaways:

- Pulmonary arterial hypertension is a progressive disease with a high index of suspicion required to diagnose
- Accurate diagnosis is crucial, followed by **risk assessment to guide initial treatment strategy and treatment escalation**
- There is **little data** to support treatment of pulmonary hypertension due to left heart disease with pulmonary vasodilators, and some evidence of harm
- Meth-APAH is a **major** regional issue, and we believe that a multidisciplinary treatment program helps improve adherence and outcomes.

Thank You!

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Gwen Myers, MA

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Jeff Robinson, MD

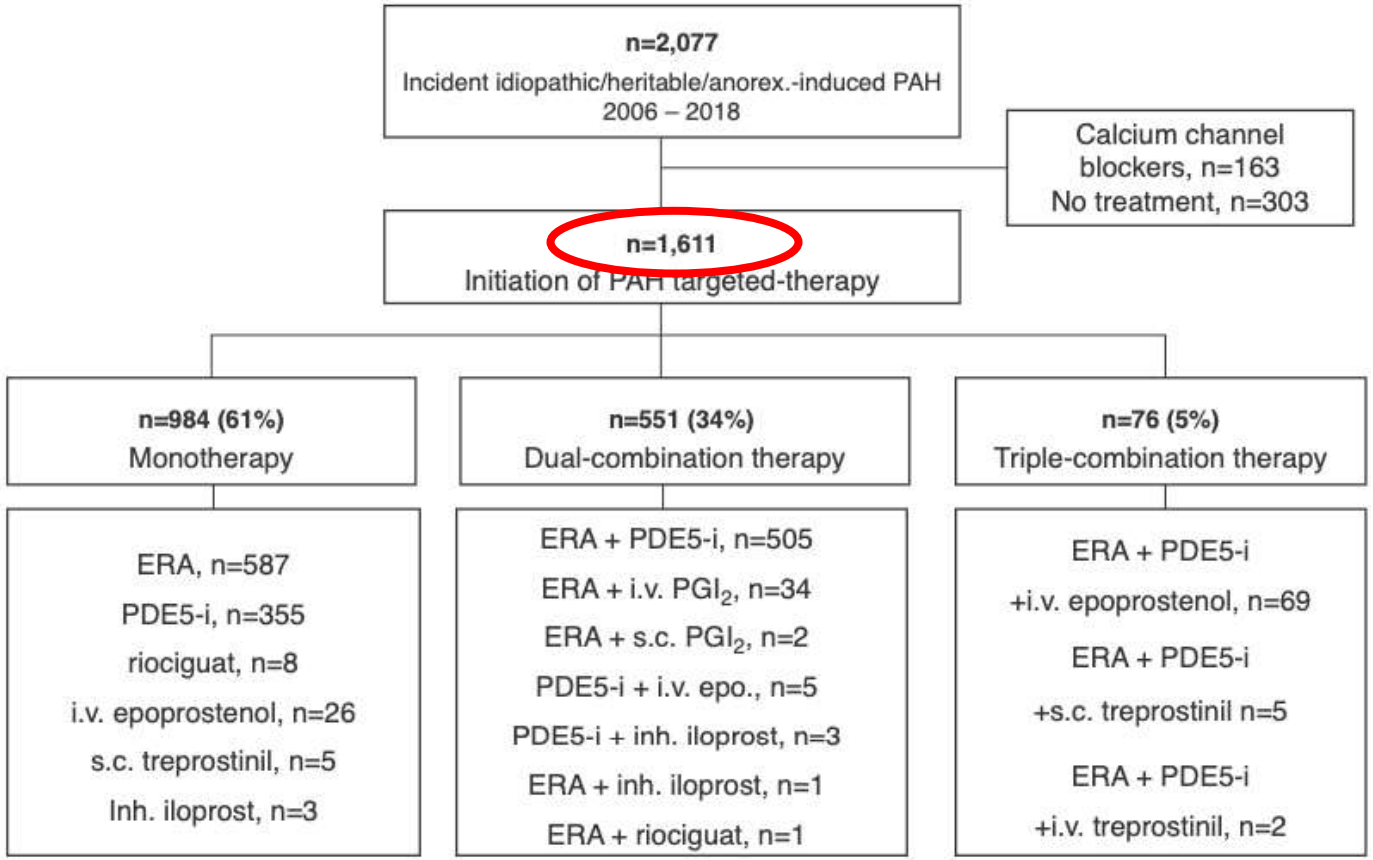
Pulmonary and Cardiology Divisions

MICU and CVICU teams

OHSU School of Pharmacy

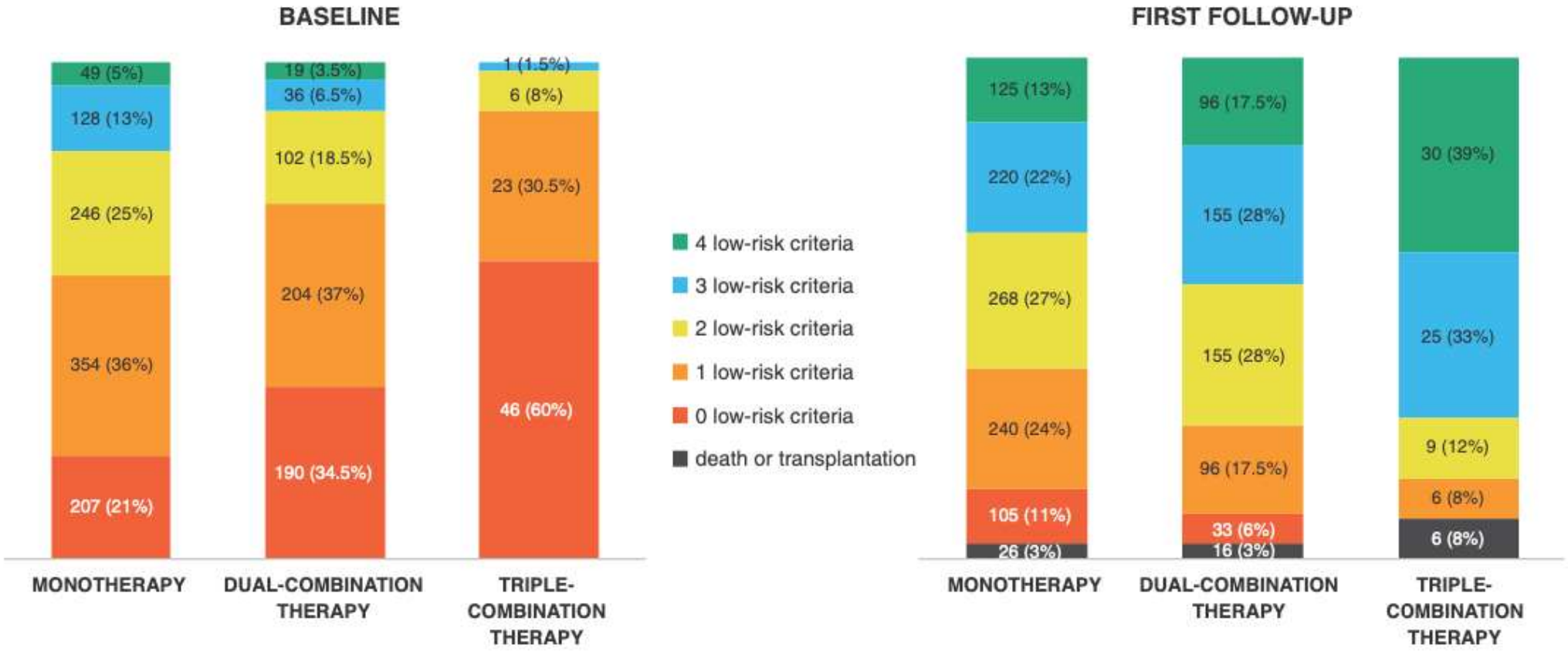
Extra Slides

Is there a role for upfront *triple* therapy?



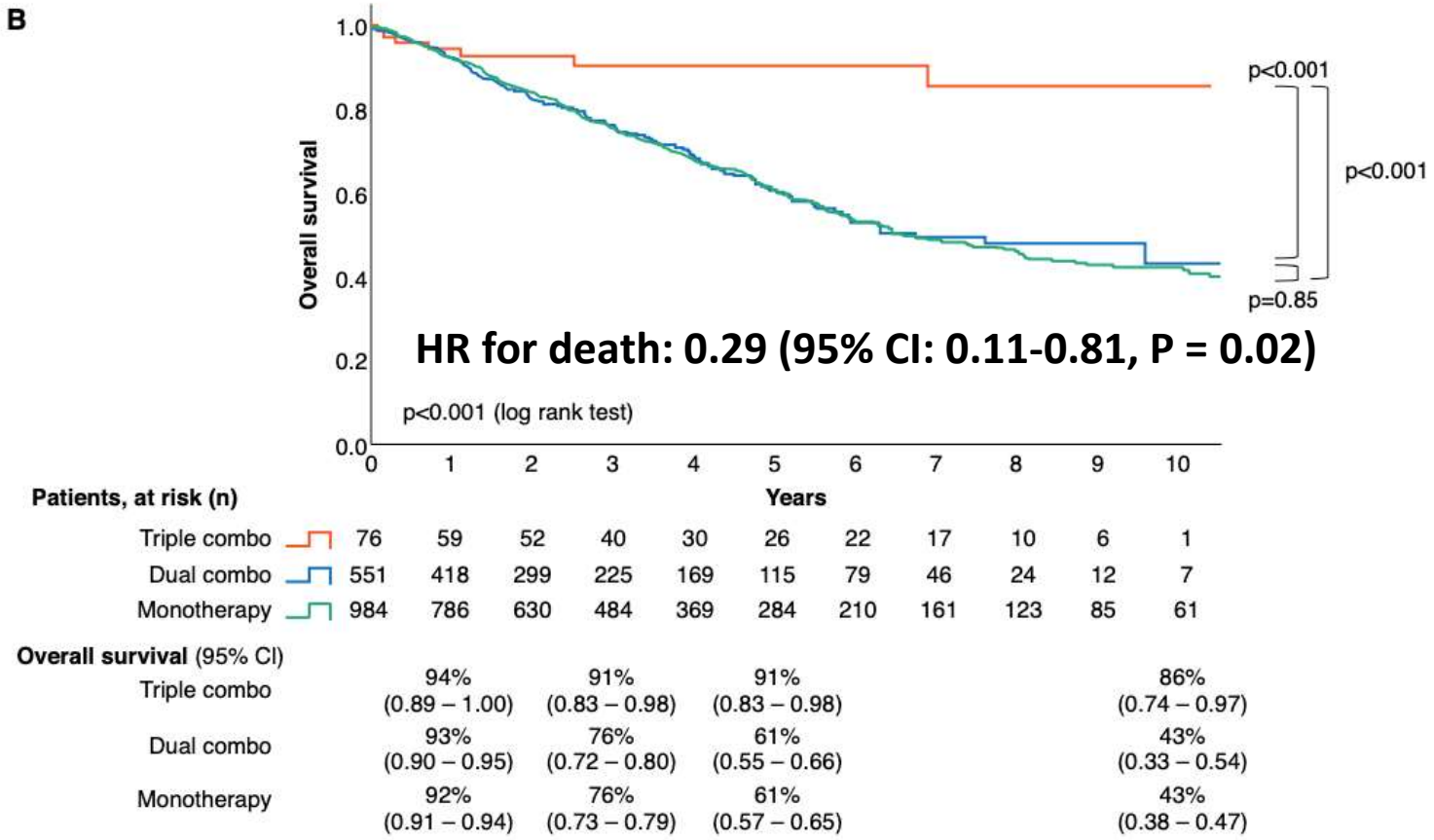
Boucly, et al. Am J Respir Crit Care Med. 2021 Oct 1;204(7):842-854.

Boucly Study



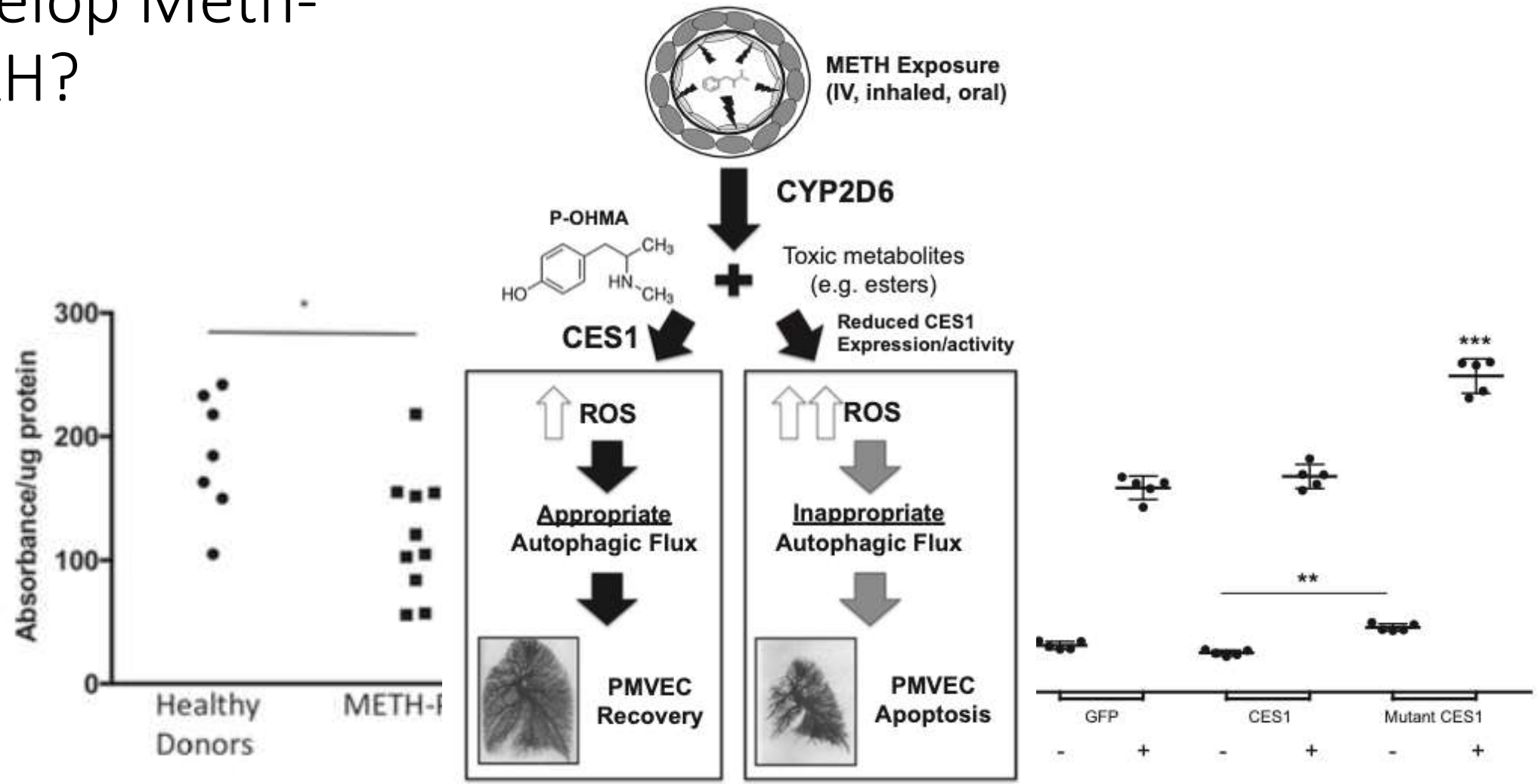
Boucly, et al. Am J Respir Crit Care Med. 2021 Oct 1;204(7):842-854.

Boucly: Survival according to initial treatment



Boucly, et al. Am J Respir Crit Care Med. 2021 Oct 1;204(7):842-854.

Why do only some develop Meth-APAH?



Orcholski, et al. doi:10.1152/ajplung.00453.2016

Meth-APAH Clinical Features

	Meth-APAH (n = 118)	IPAH (n = 423)
WHO functional class		
Class 1	9%	10%
Class 2	28%	34%
Class 3	54%	49%
Class 4	10%	6%
6-minute walk distance	375 ± 118	343 ± 139
Brain natriuretic peptide (BNP)	104 [32.5 – 370]	114 [41-332]
Baseline Hemodynamics		
RAP - Right Atrial Pressure (mmHg)	11.9 ± 5.0	10.2 ± 6.1
mPAP - Mean Pulmonary Artery pressure (mmHg)	51.8 ± 12.7	50.9 ± 14.2
PCWP - Pulmonary Capillary Wedge Pressure (mmHg)	11.5 ± 7.6	11.4 ± 5.7
PVR - Pulmonary Vascular Resistance (WU)	11.1 ± 5	10.4 ± 5.7
CI - Cardiac index (L/min/m^2)	2.06 ± 0.66	2.22 ± 0.70

Kolaitis, et al. 10.1513/AnnalsATS.202007-774OC