Pulmonary Hypertension: When to Initiate Advanced Therapy

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Disclosures

- Medtronic, Abbott: Consultant

Hemodynamic Definition of PH/PAH

PH	**Mean PAP ≥ 25 mm Hg**
PAH	**Mean PAP ≥ 25 mm Hg *plus* PCWP/LVEDP ≤ 15 mm Hg**

ACCF/AHA includes PVR > 3 Wood units

McLaughlin VV, et al. *J Am Coll Cardiol*. 2009;53:1573-1619.
Badesch D, et al. *J Am Coll Cardiol*. 2009;54:S55-S66.

5th World Symposium on PH: Modified Classification of PH

1. Pulmonary arterial hypertension

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
  - 1.2.3 Unknown
- 1.3 Drug- and toxin-induced
- 1.4 Associated with
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (update)
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1''. PPHN

2. PH due to LHD

- 2.1 LV systolic dysfunction
- 2.2 LV diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital/acquired left heart inflow/outflow obstruction

3. PH due to lung diseases and/or hypoxia

- 3.1 COPD
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases

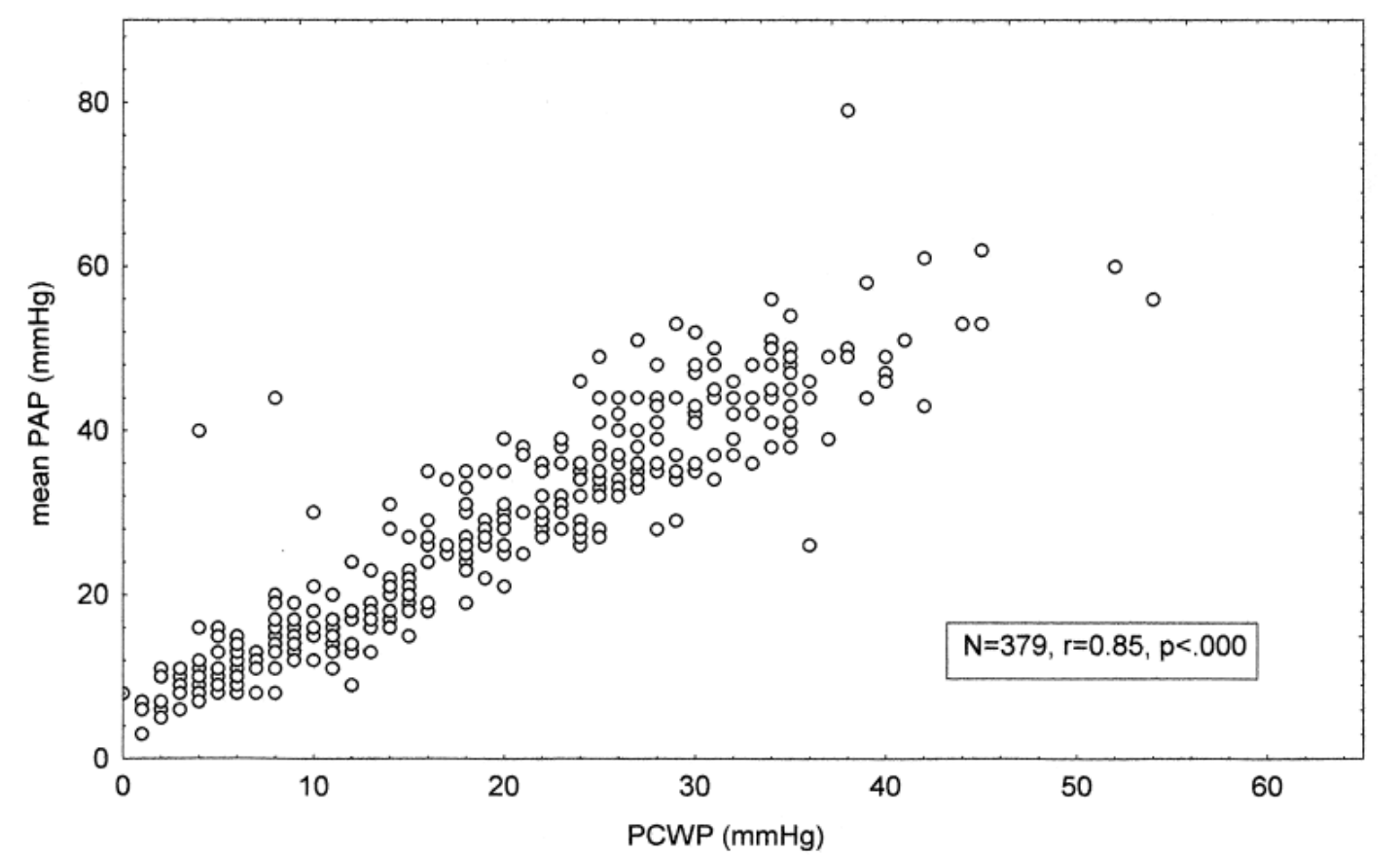
4. CTEPH

5. PH with unclear multifactorial mechanisms

- 5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Simonneau G et al. *JACC 2013*;62:D34-41.

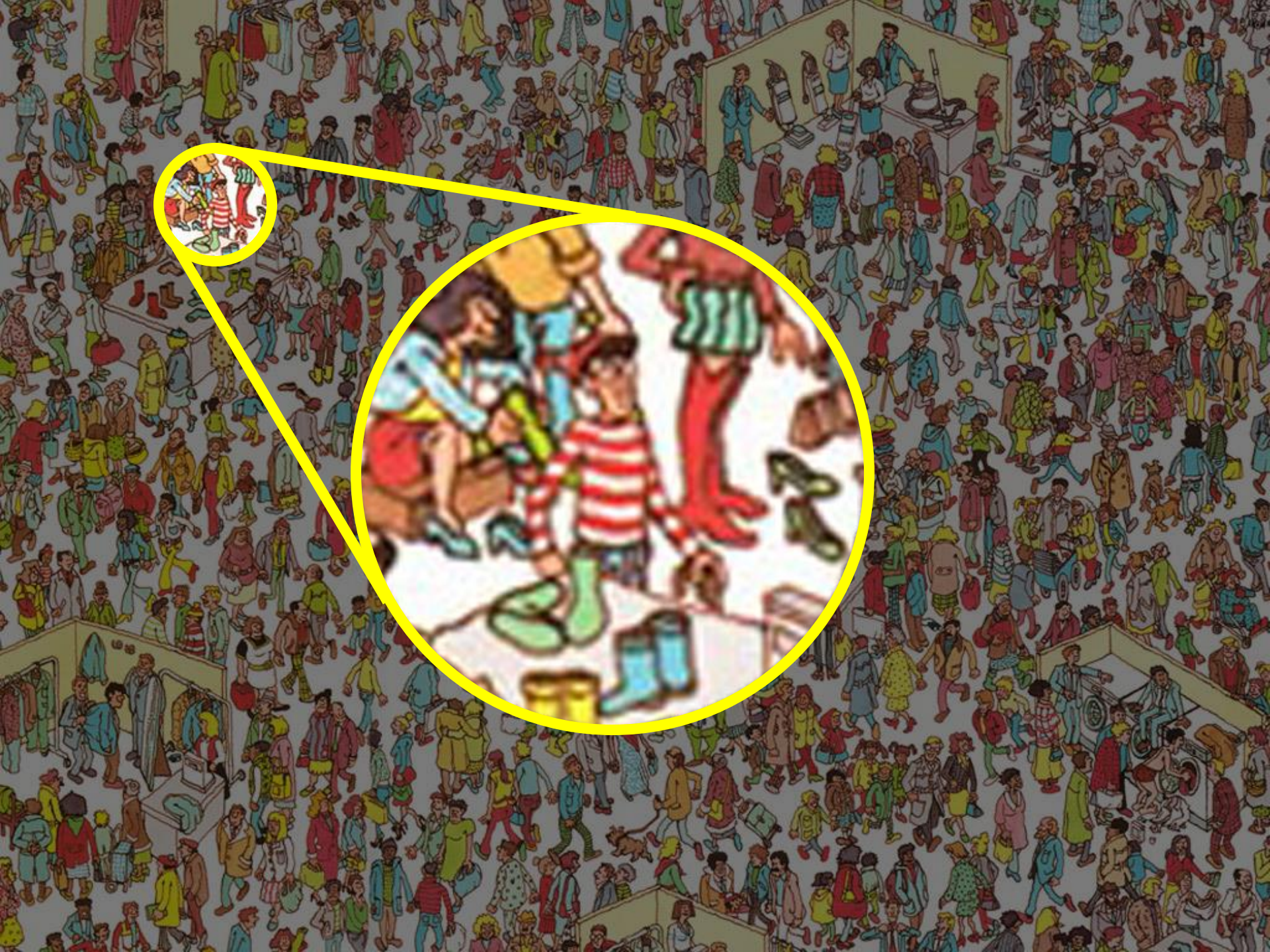
Why does Group 2 PH occur?
It's simple: As PCWP goes up, PAP goes up



Ghio JACC 2001

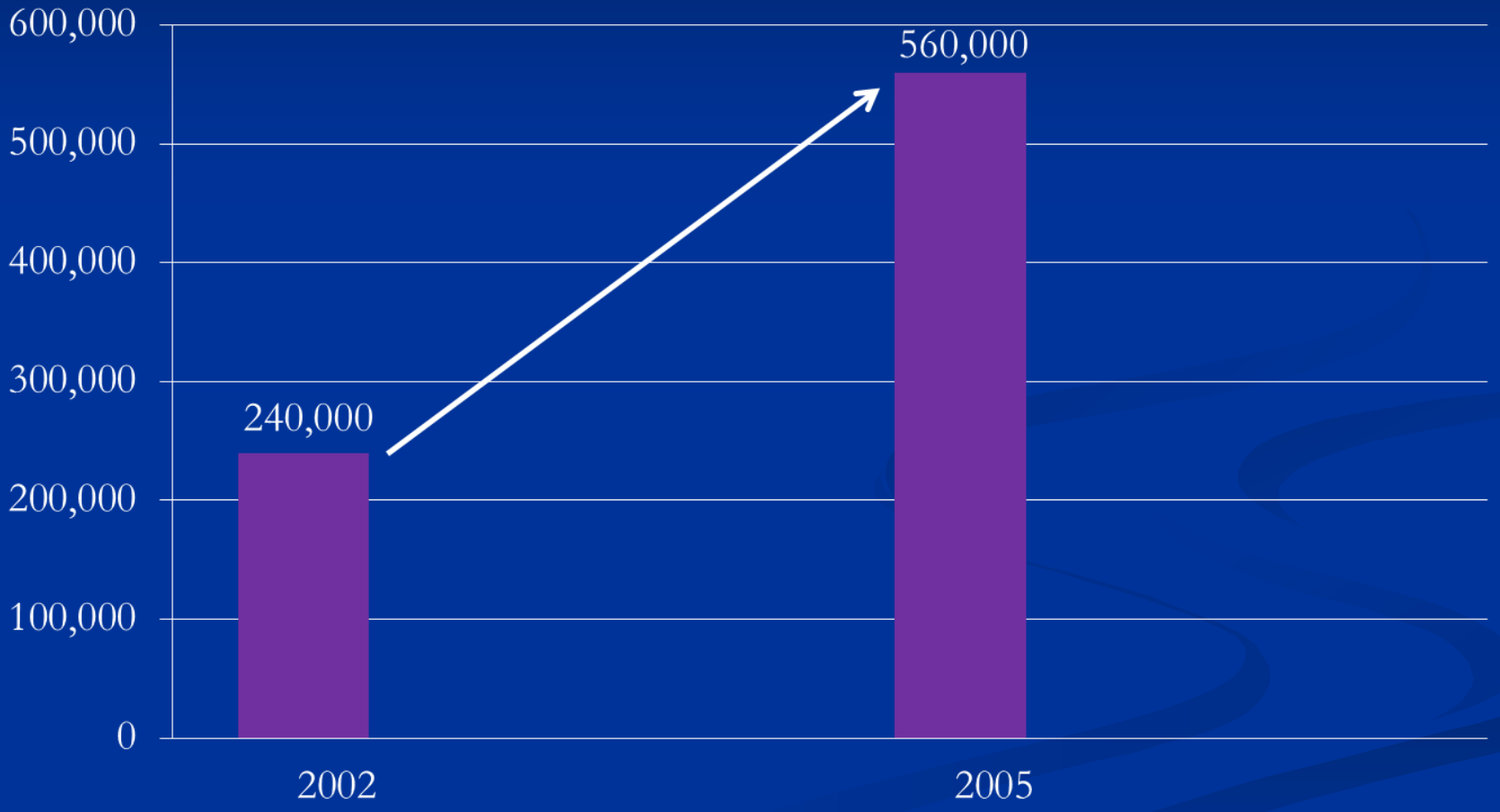
Prevalence of PAH

- WHO Group 1 PAH:
  - Prevalence: 15/million
  - US population: 311 million
  - US cases of PAH: 4,665 (orphan disease < 200K in U.S.)
- *WHO Group 1 PAH is a rare, orphan disease*



A PH Epidemic?

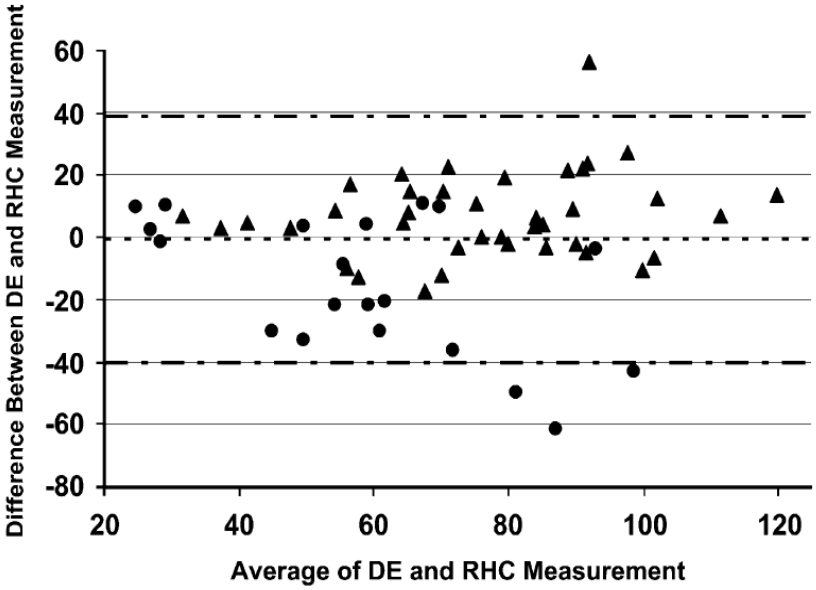
Data from CMS of hospitalized patients with a discharge diagnosis of pulmonary hypertension in 2005 compared with 2002



HCUP CCS. Healthcare Cost and Utilization Project (HCUP). August 2006. U.S. Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp

Doppler echo is too unreliable

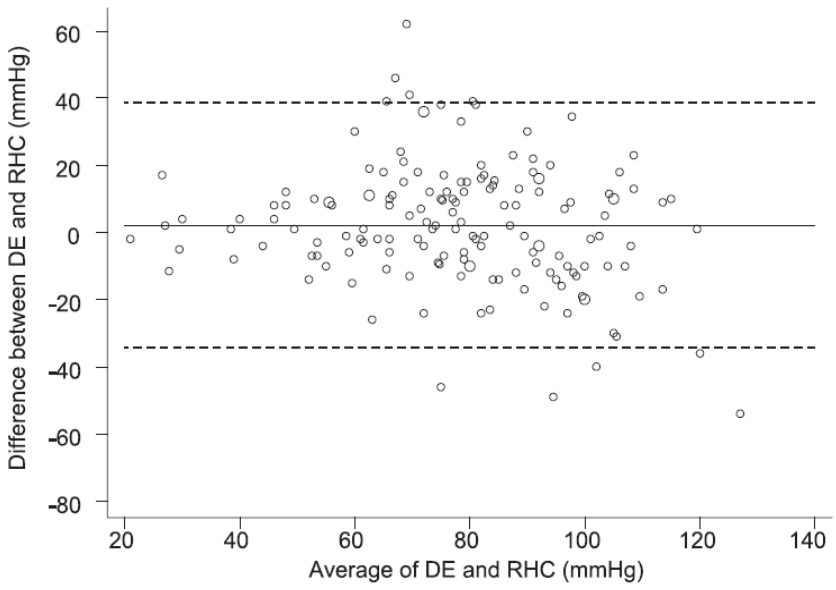
- Correlation: r=0.66; p<0.001



Inaccurate cases: 48%!

Fisher M, et al. AJRCCM 2009

- Correlation: r=0.68; p<0.001



Inaccurate cases: 51%!

Rich J, et al. Chest 2010

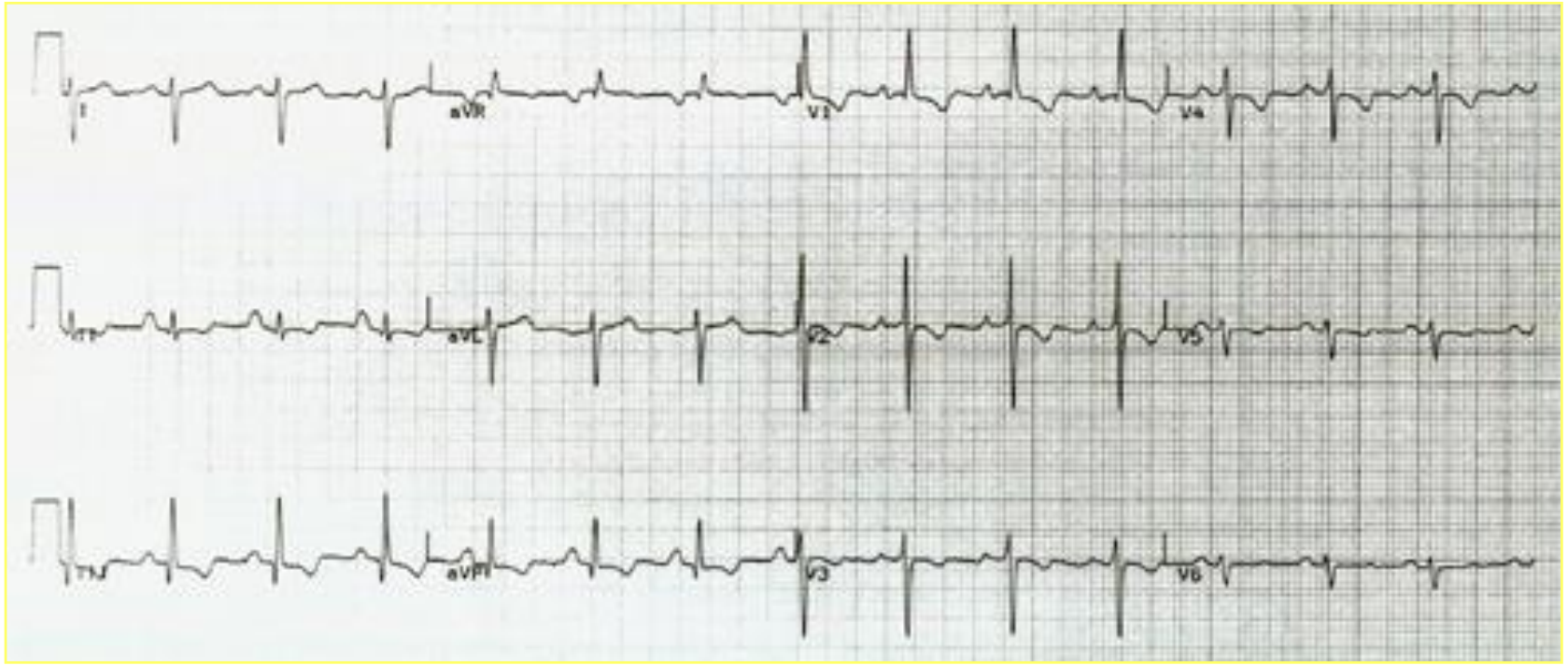
Cardiac Catheterization

- To exclude congenital heart disease
- To measure wedge pressure or LVEDP
- To establish severity and prognosis
- To test vasodilator therapy

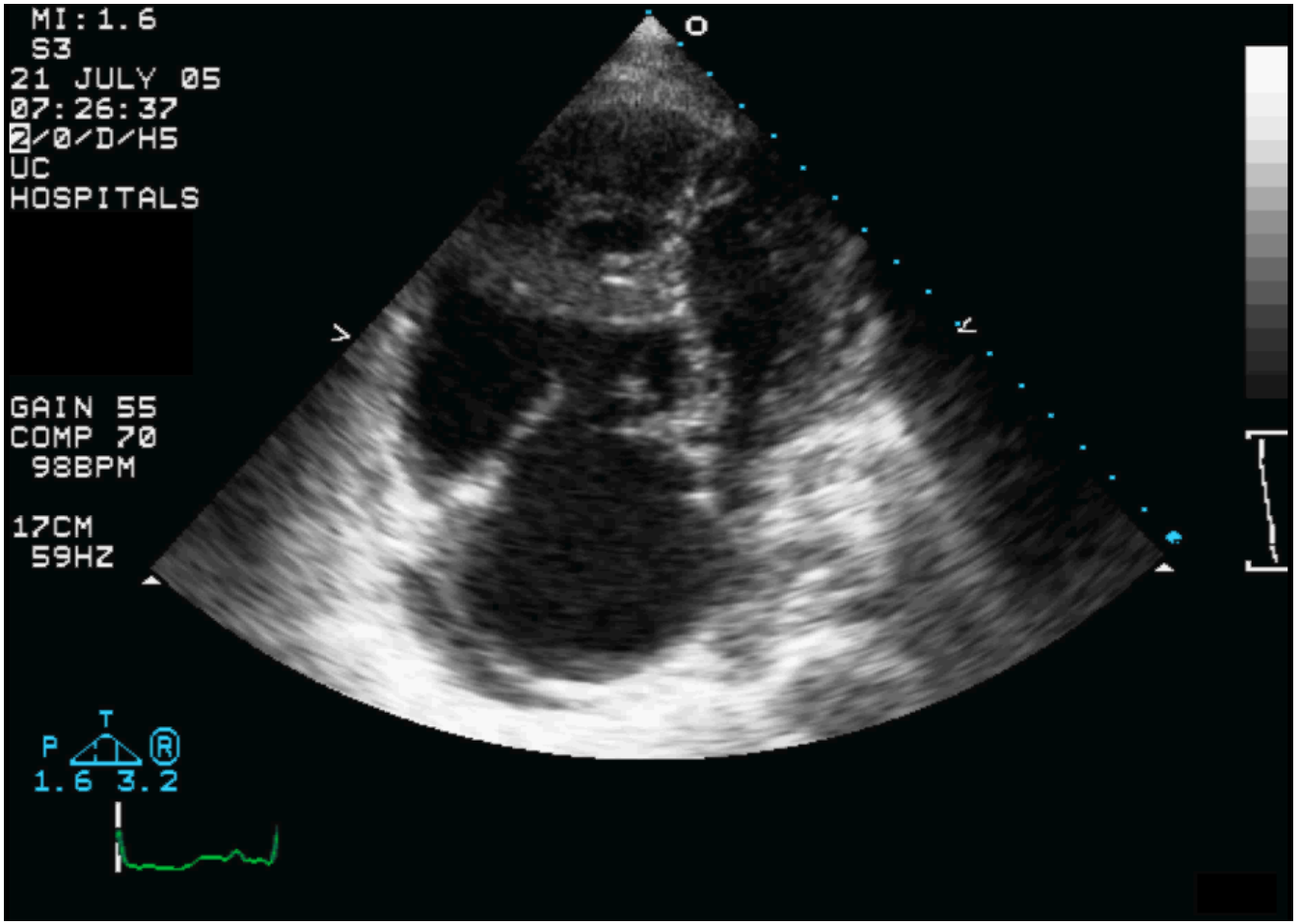
Catheterization is required for nearly every patient with suspected pulmonary hypertension

Findings on Electrocardiogram

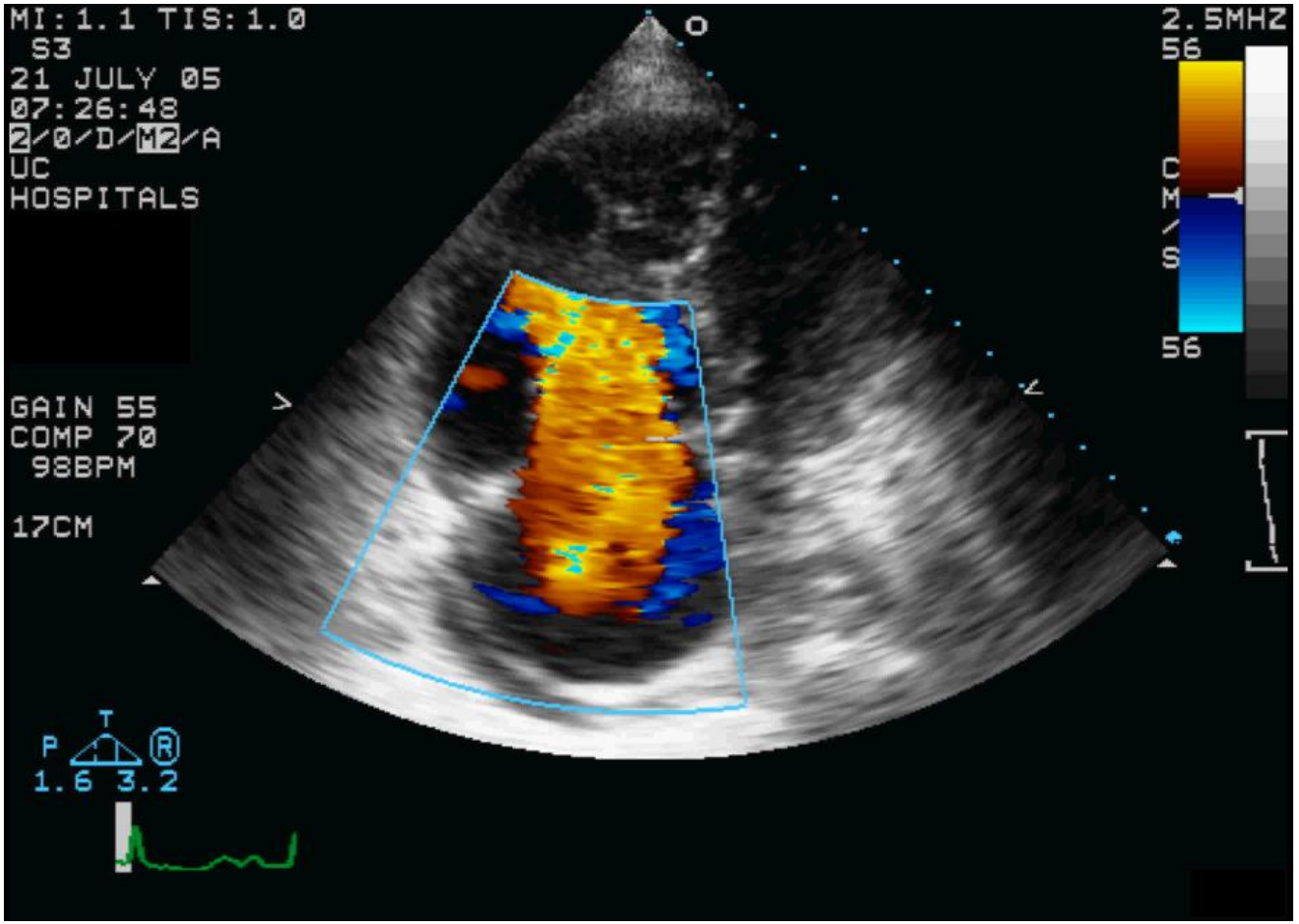
RAD, RVH, RAE, IRBBB



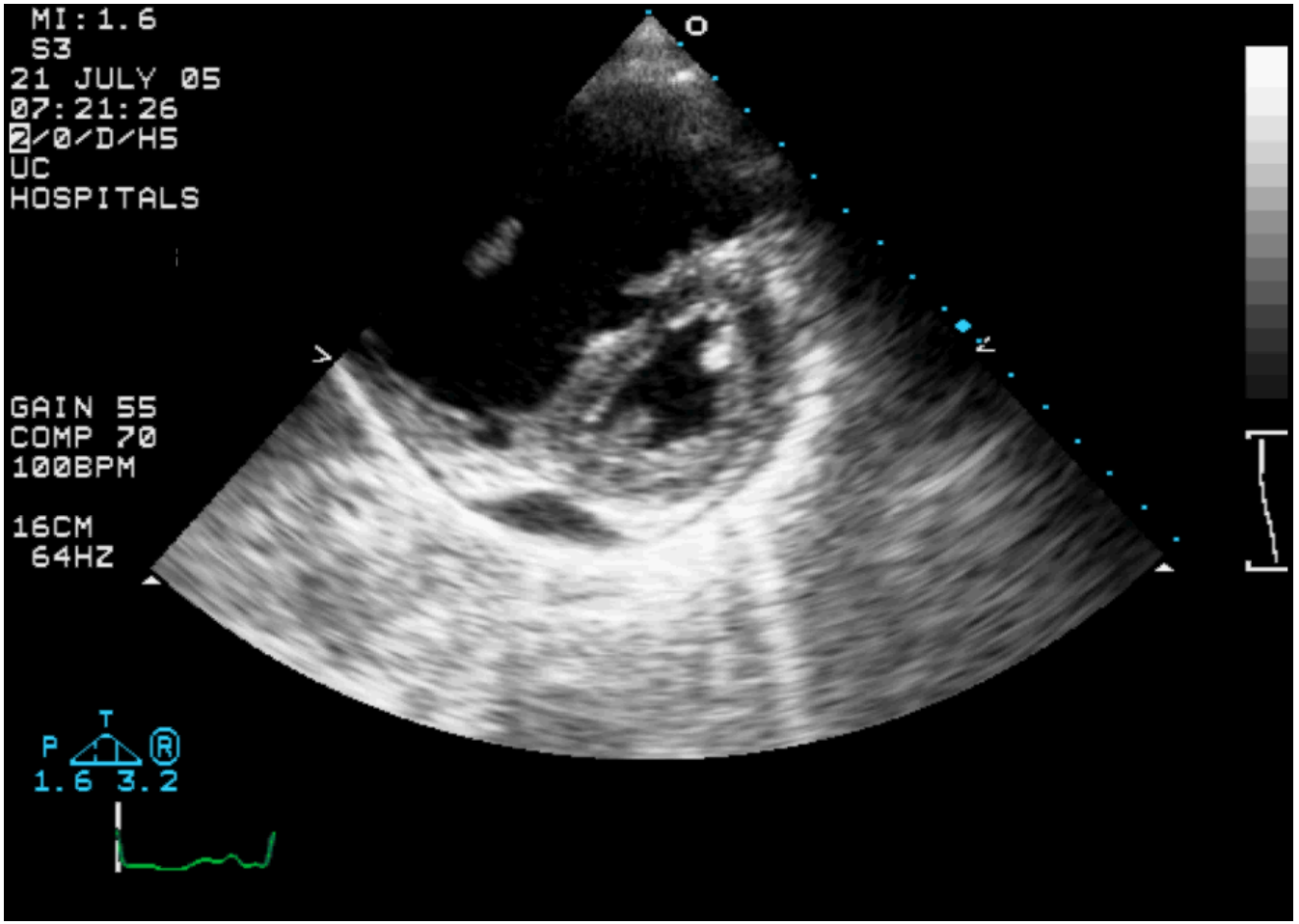
Echocardiogram



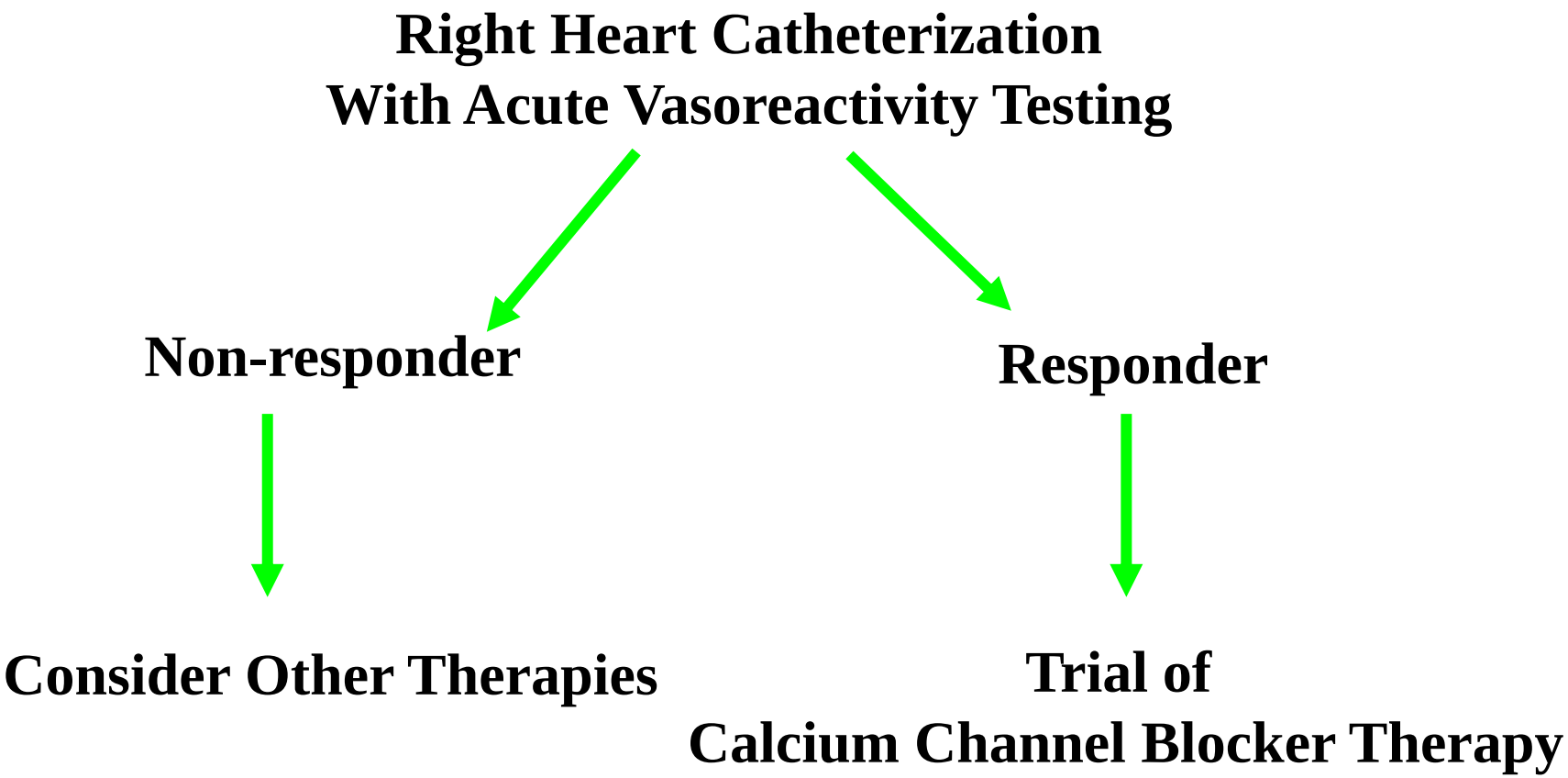
Echocardiogram



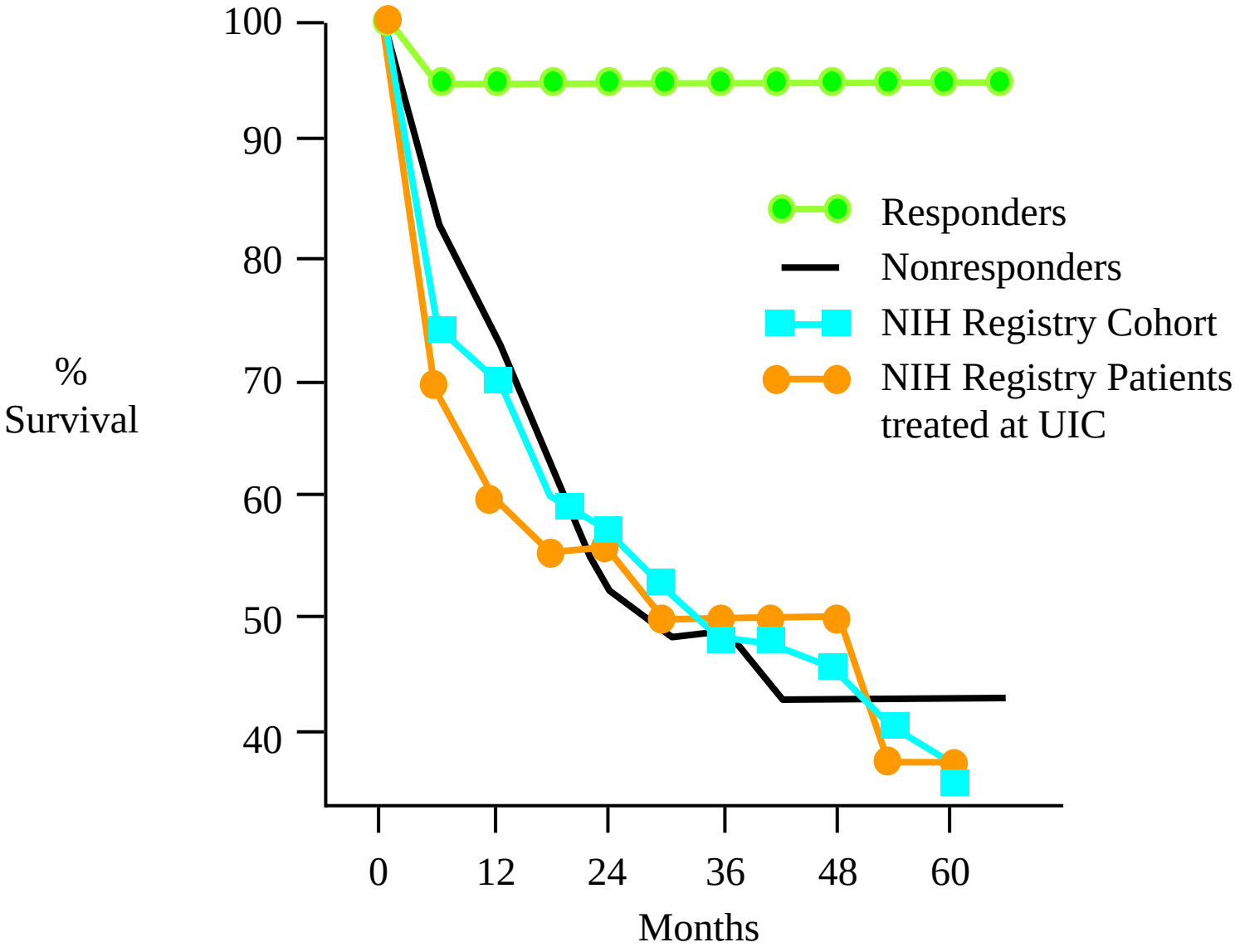
Echocardiogram



Algorithm for Assessment of Vasoreactivity in Patients with PAH

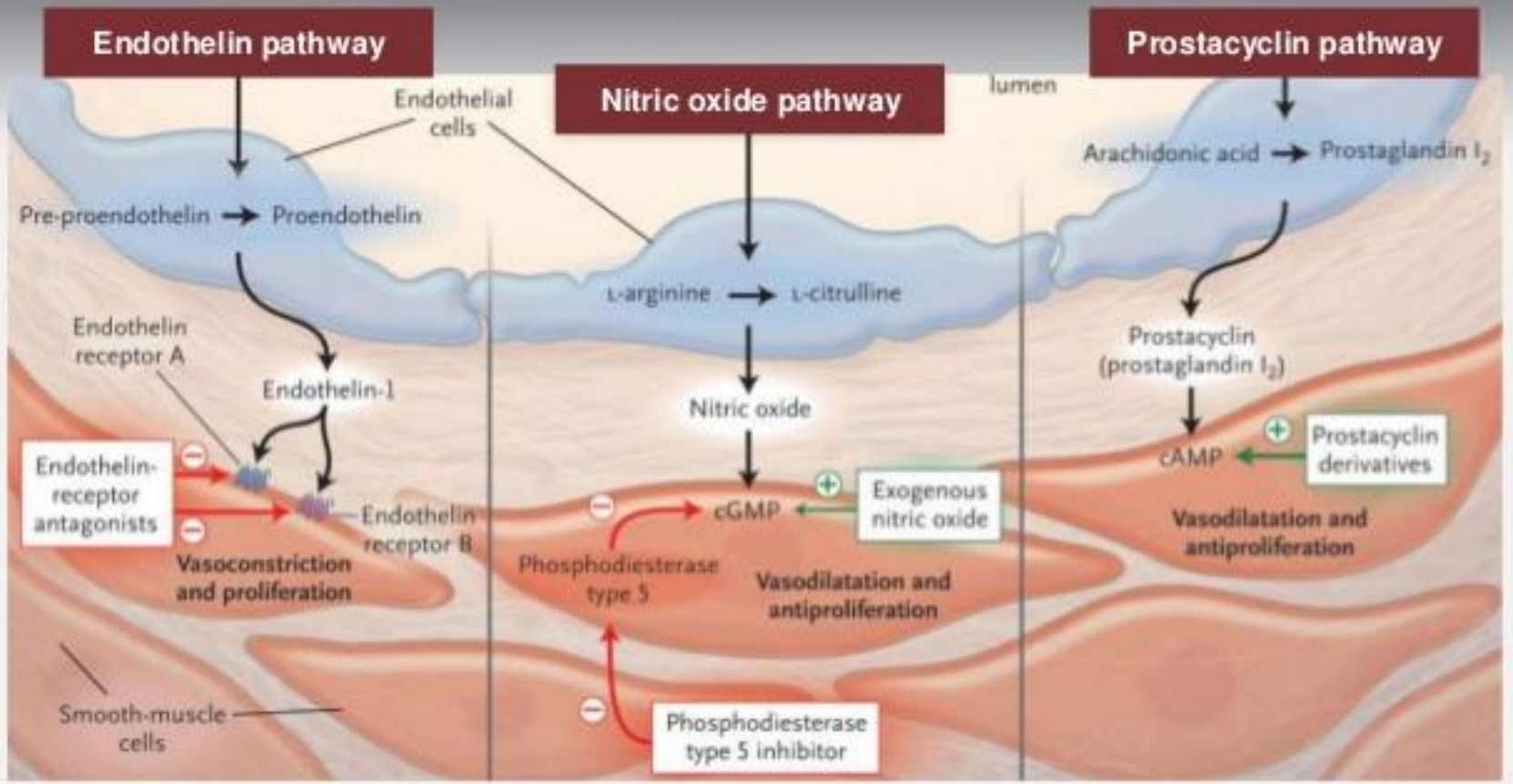


Effect of High-Dose CCBs on Survival in PPH

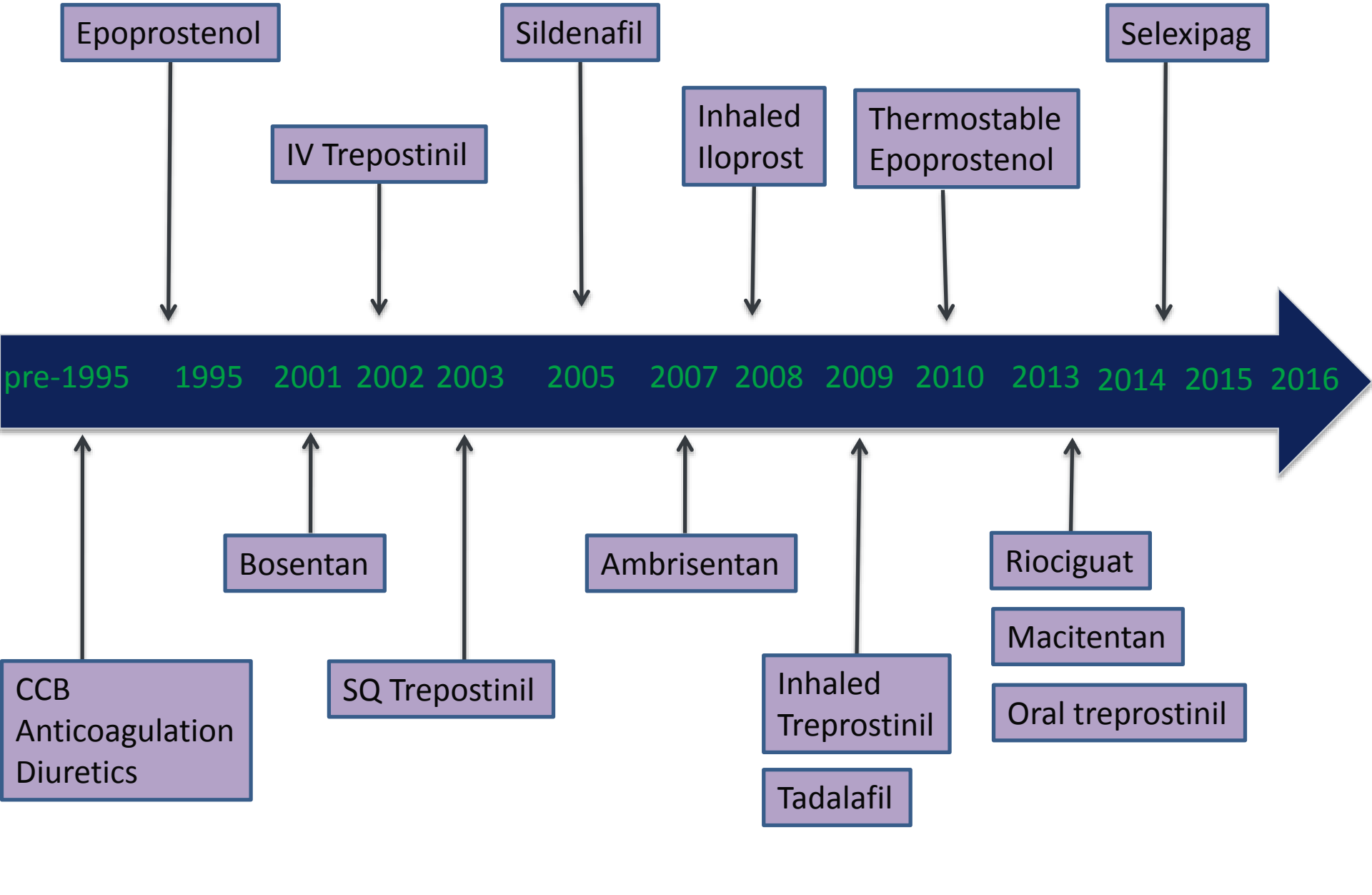


Rich S et al. *N Engl J Med.* 1992;327:76-81.

3 Key Signaling Pathways in PAH



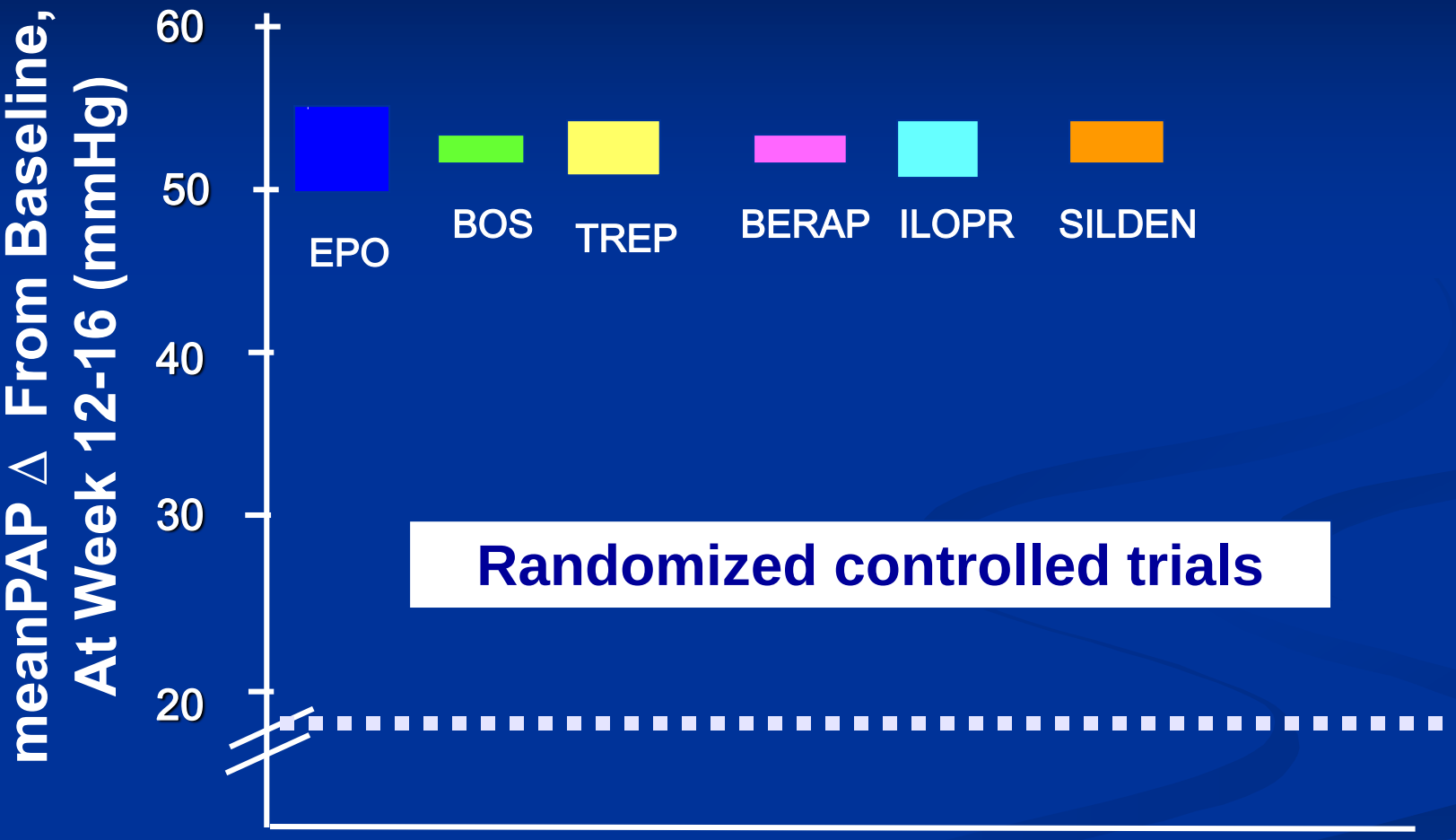
Humbert M, et al. *N Engl J Med*. 2004;351:1425-36.


Epoprostenol
IV Trepostinil
Sildenafil
Inhaled Iloprost
Thermostable Epoprostenol
Selexipag
pre-1995
1995
2001
2002
2003
2005
2007
2008
2009
2010
2013
2014
2015
2016
CCB
Anticoagulation
Diuretics
Bosentan
SQ Trepostinil
Ambrisentan
Inhaled Treprostinil
Tadalafil
Riociguat
Macitentan
Oral treprostinil

There is a general misunderstanding of the role of vasodilator pathways in PAH

- PAH is NOT caused by…
  - Over expression of endothelin
  - Inadequate production of nitric oxide
  - Inability to produce endogenous prostacyclin
- It is unknown if these pathways…
  - Are all active
  - Have additive effects
  - Have any influence over each other

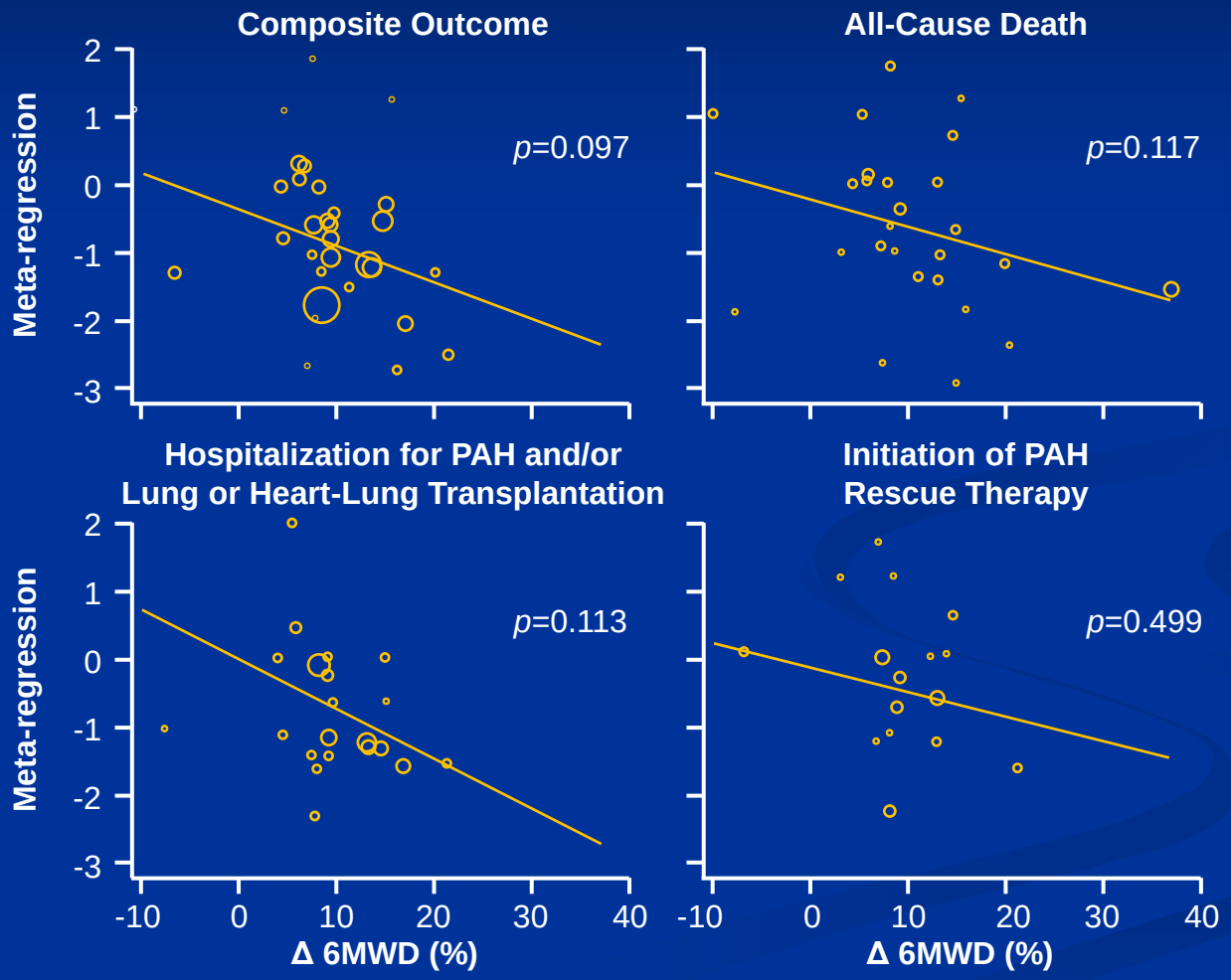
Mean Improvements on Monotherapy Do Not Restore Normal PAP



Barst 1996, 2003, 2003; Rubin 2002; Simmoneau 2002; Galie 2002, 2005; Ghofrani 2004

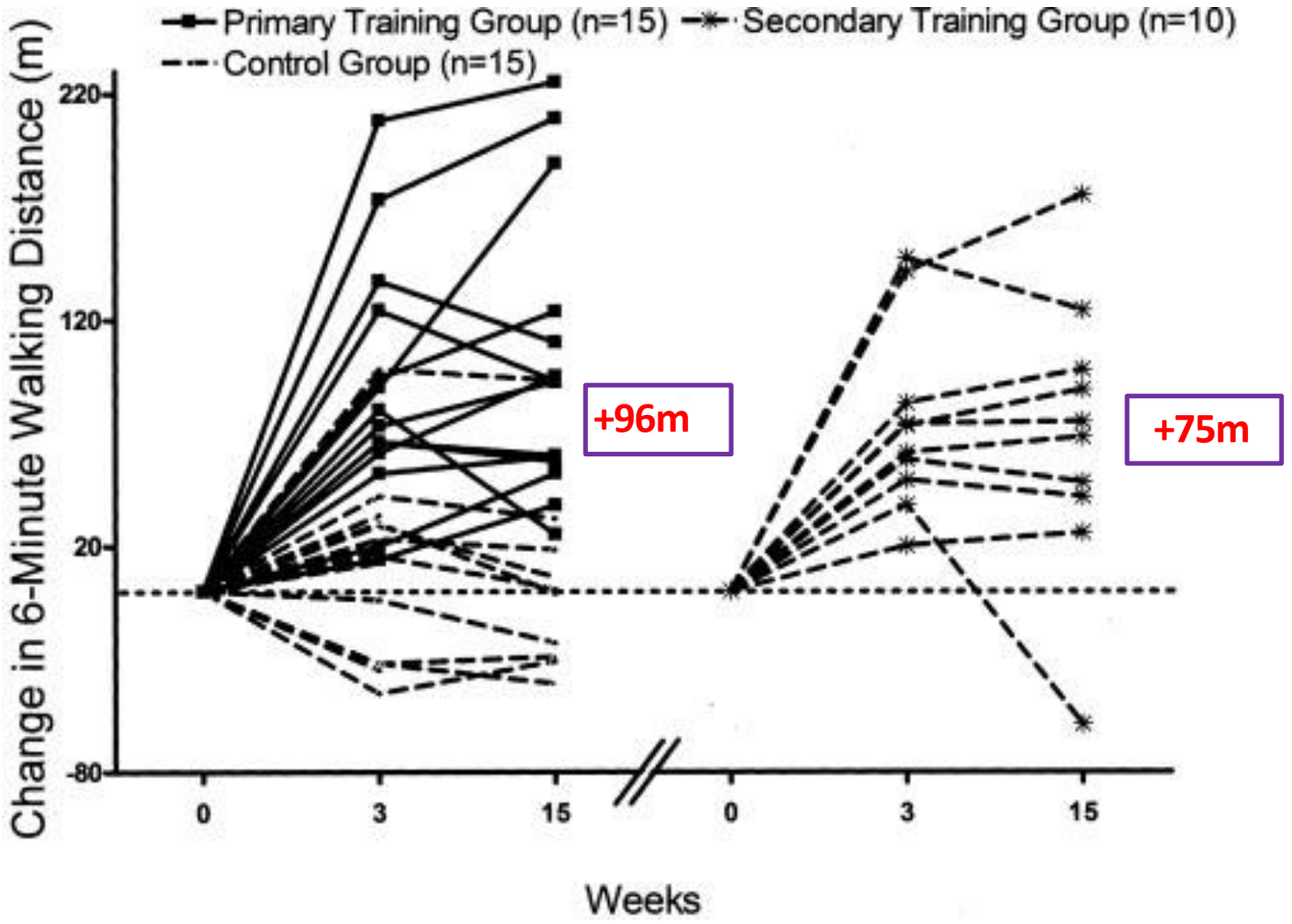
Meta-analysis of 22 RCTs

No relationship between 6MWD changes and outcomes



Savarese G et al. *J Am Coll Cardiol.* 2012

Could walking be superior to medical therapy?



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Mereles et al Circulation 2006

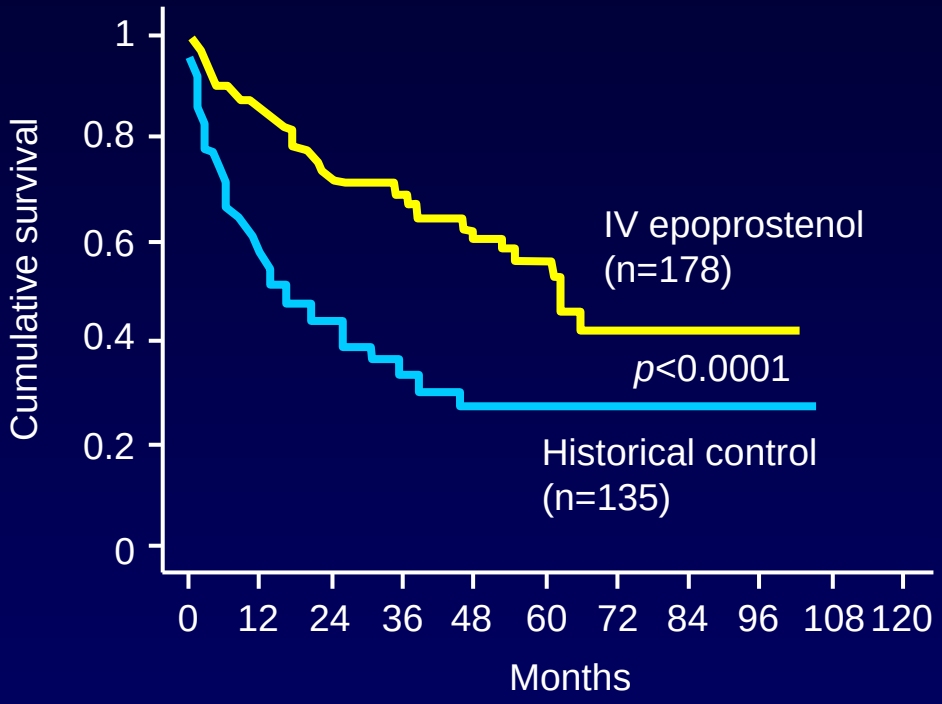
Dosing and cost of pulmonary arterial hypertension treatment options

	Labeled indication	Route	Dosing	Annual Cost (USD)
CCBs	Off-label	Oral	Based on clinical response	$1,136[a]
PDE-5				
Sildenafil	WHO FC I-IV	Oral	20 mg three times daily	$18,788 (20 mg three times daily) to $75,152 (80 mg three times daily)
Tadalafil	WHO FC I-IV	Oral	40 mg once daily	$14,910
ERAs				
Ambrisentan	WHO FC II or III	Oral	10 mg once daily	$79,278
Bosentan	WHO FC II-IV	Oral	125 mg twice daily	$79,278
Prostacyclins				
Epoprostenol	NYHA FC III and IV	Intravenous	2 ng/kg/min IV continuous infusion, ↑dose every 15 min to achieve clinical response[b]	$19,111 (2 ng/kg/min) to $34,054 (16 ng/kg/min)[c]
Iloprost	NYHA FC III and IV	Inhaled	2.5–5.0 µg inhalation 6-9x/day, ↑2.5 µg to achieve desired clinical response to maximum dose of 45 µg/day	$162,936 (6 times per day) to $244,404 (9 times per day)[d]
Treprostinil	NYHA FC II–IV	SC Intravenous	IV/SC – 1.25 ng/kg/min, ↑2.5ng/kg/min per week to achieve clinical response	$17,688 (2.5 ng/kg/min) to $176,880 (40 ng/kg/min)[c]
Treprostinil	NYHA FC III	Inhaled	Inhale – 3 breaths (18 µg/breath) 4x/day, ↑1-2 breaths every 1–2 weeks to maximum of 9 (54 µg) breaths 4x/day[b]	$162,670

Abbreviations: CCBs, calcium channel blockers; PDE-5, phosphodiesterase type-5 inhibitors; WHO, World Health Organization; ERAs, endothelin receptor antagonists; NYHA, New York Heart Association; FC, functional classification; SC, subcutaneous

PharmacoEconomics (2016) 34:509–520

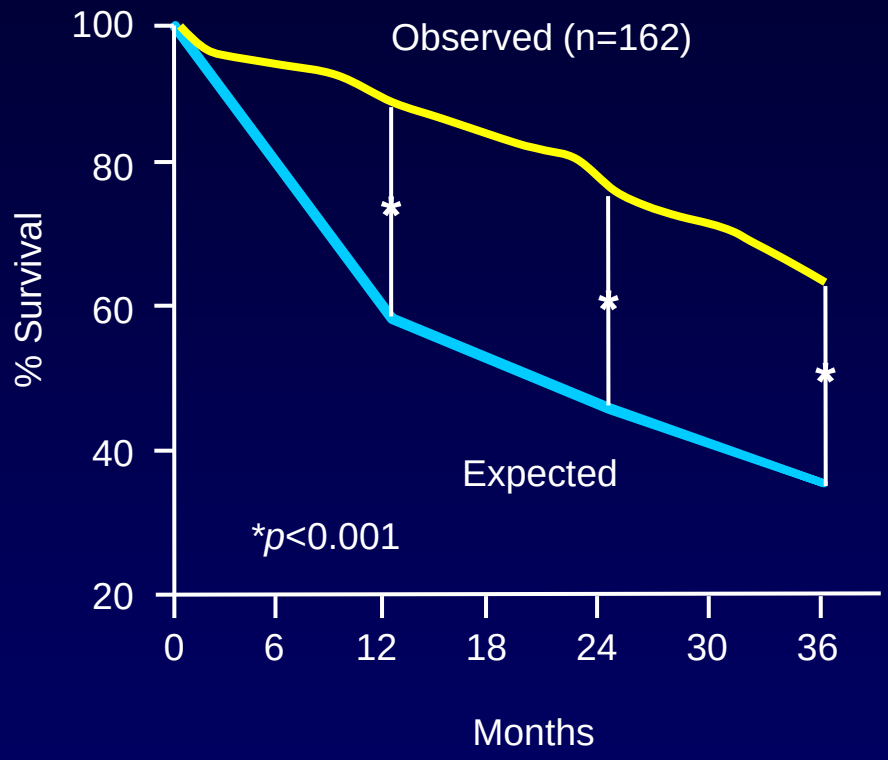
Long-Term Survival in IPAH With Epoprostenol



No. at risk

178	129	85	57	36	21	7	3	1	IV epo
135	59	34	20	11	4	2	2	1	Hist. control

Sitbon O et al. *J Am Coll Cardiol.* 2002;40:780-788.



McLaughlin VV et al. *Circulation.* 2002;106:1477-1482.

PAH Determinants of Risk

Determinants of Prognosis (estimated 1-year mortality)	Low Risk <5%	Intermediate Risk 5-10%	High Risk >10%
Clinical evidence of RV failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Rare Syncope	Repeated Syncope
WHO class	I,II	III	IV
Cardiopulmonary exercise testing	Peak VO_2 > 15 ml/min/kg VE/VCO_2 slope < 36	Peak VO2 11-15 ml/min/kg VE/VCO2 slope 36-44.9	Peak VO2 < 11 ml/min/kg VE/VCO2 slope ≥ 45
6MW distance	>440 m	165-440 m	<165 m
NT-proBNP	BNP < 50 ng/l NT-proBNP < 300 ng/ml	BNP 50-300 NT-proBNP 300-1400	BNP > 300 NT-proBNP > 1400
Echocardiographic findings	RA area < 18 cm^2 No pericardial eff	RA area 18-26cm2 No or minimal pericardial eff	RA area > 26cm2 pericardial eff
Hemodynamics	RAP < 8 mmHg CI ≥ 2.5 l/min/m^2 SvO_2 >65%	RAP 8-14 mmHg CI 2.0-2.4 l/min/m2 SvO2 60-65%	RAP > 14 mmHg CI < 2.0 l/min/m2 SvO2 <60%

Delayed initiation of proper treatment

RePHerral study

- At the time of referral 61% of patients were in advanced stages of disease
- 30% on PAH-specific medications
- 57% of those on PAH medications not in adherence to published guidelines

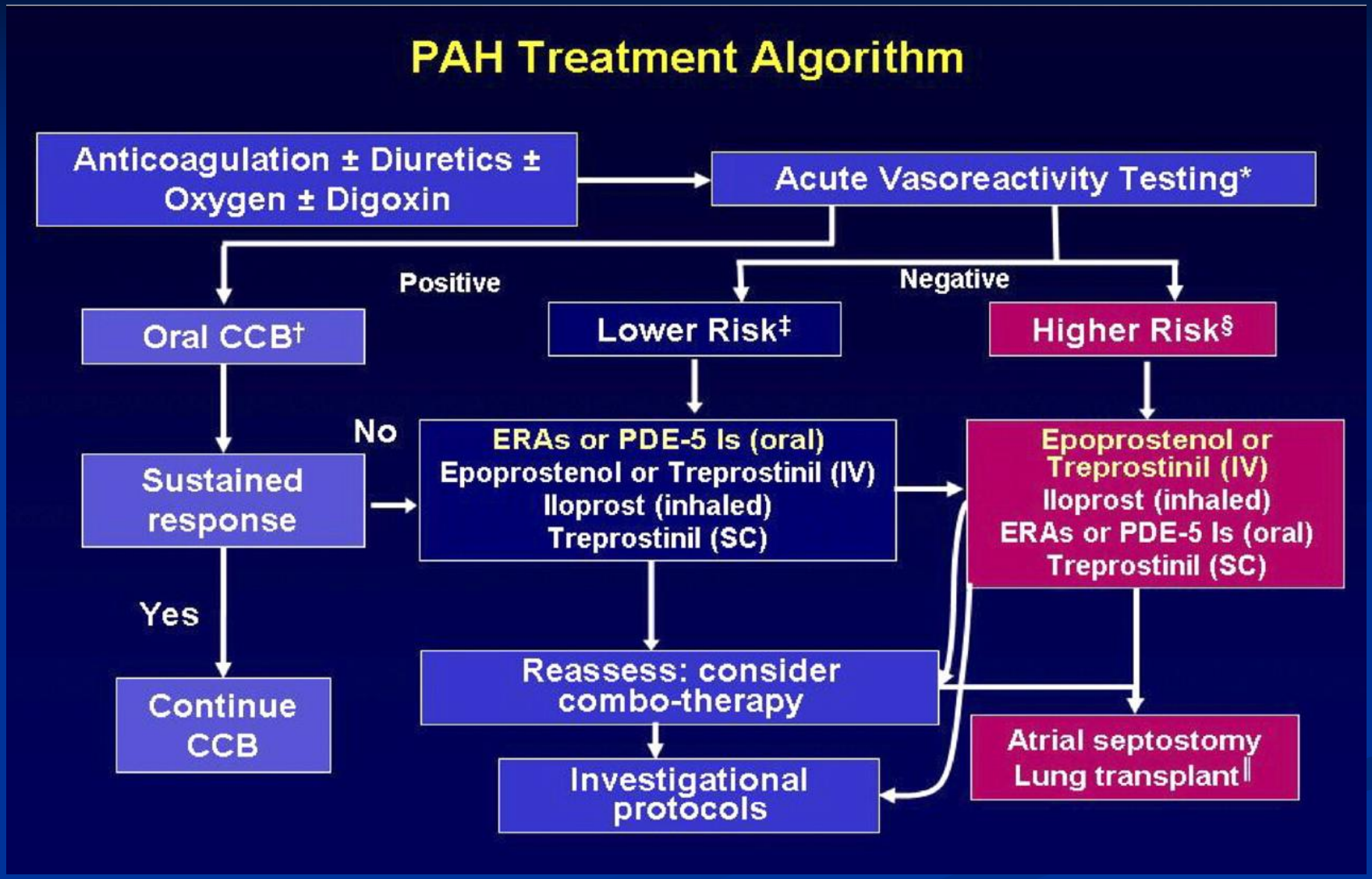
CHEST 2014 and ESC/ERS 2015 recommended infused prostacyclin in patients with severe disease

- REVEAL Registry demonstrated that only 56% of patients with PAH-related death were treated with an infused prostacyclin analog.

PAH-QuERI

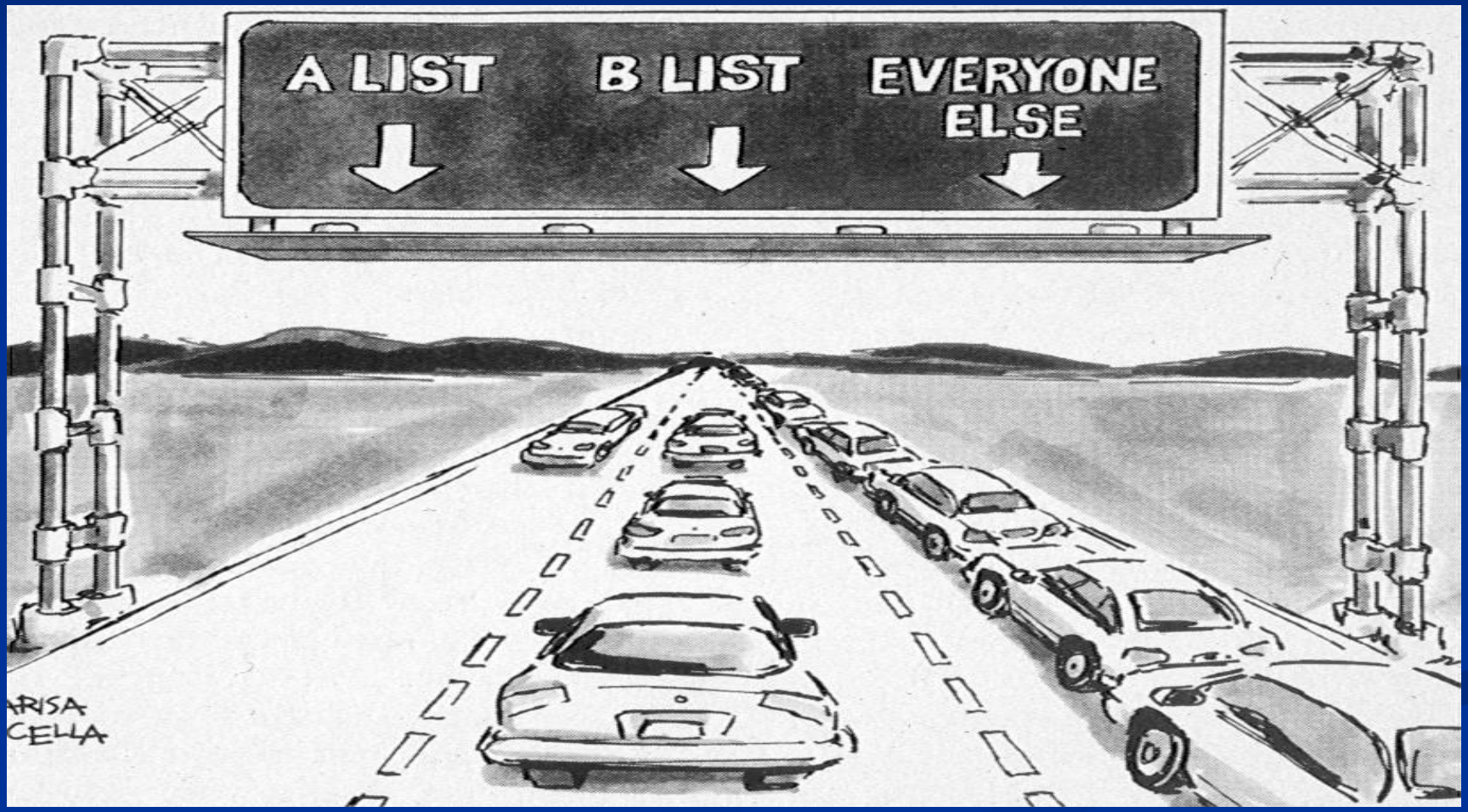
- Only 7% of patients treated with Calcium channel blockers met vasoreactivity testing on RHC

JAMA int med, 2013;173(10)887-93 Eur Heart J, 2016;37(1):67-119
Chest, 2014;146(2):449-75 Chest 2013;143(2):324-32



McLaughlin, V. V. et al. J Am Coll Cardiol 2009;53:1573-1619

Lung Transplantation

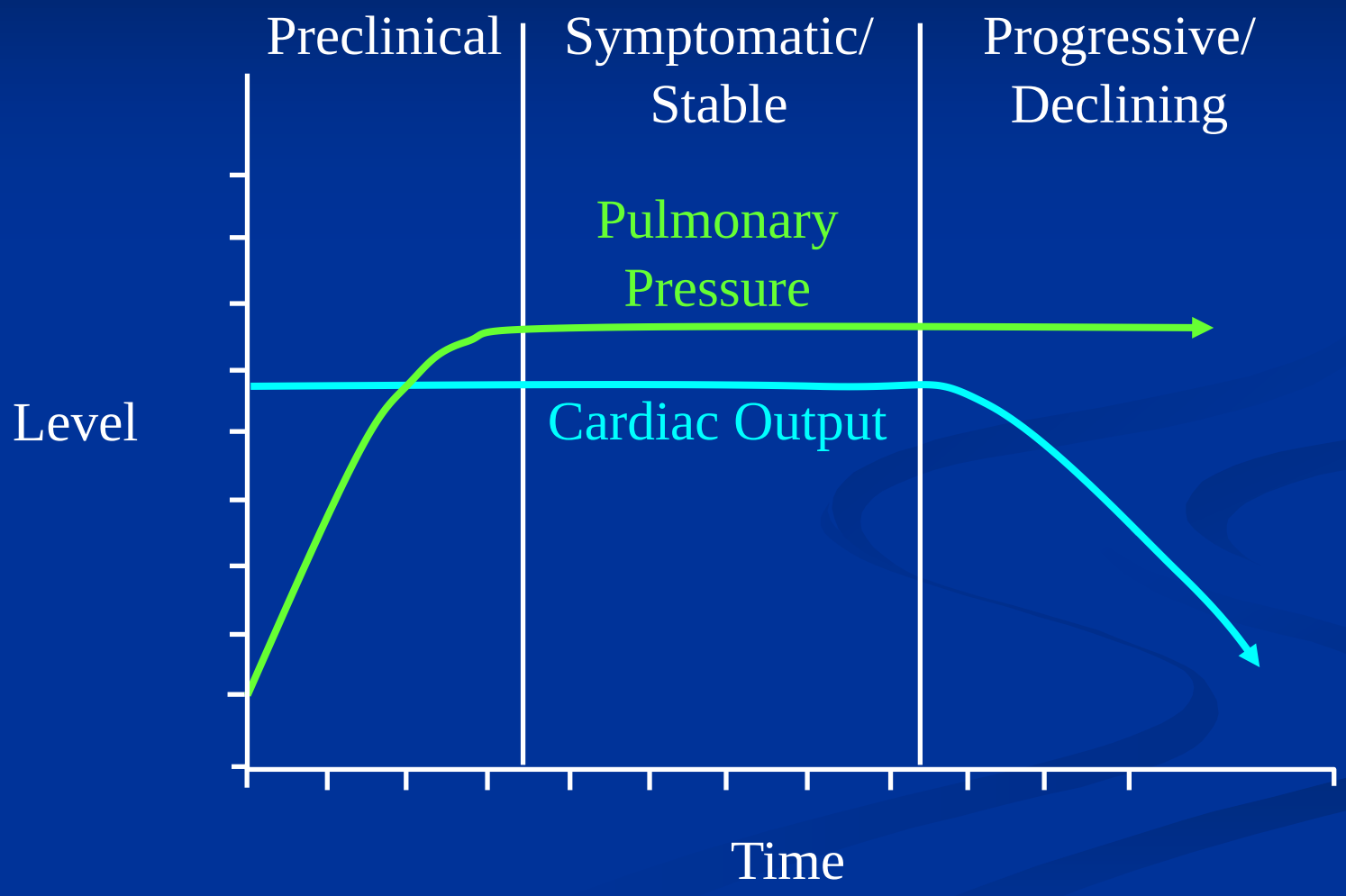


Poor Prognostic Indicators in PAH
It's all about the RV!

- RV dysfunction by hemodynamics
  - High right atrial pressure
  - Low cardiac index
- RV dysfunction by echocardiography
  - TAPSE <1.8 cm
- RV dysfunction by labs
  - Elevated BNP levels
- Other:
  - NYHA/WHO functional class III or IV
  - Poor exercise capacity (eg, 6MWD <380 m)
  - **Higher pulmonary artery pressures NOT a consistent predictor**

Sitbon O et al. *J Am Coll Cardiol*. 2002;40:780-788; McLaughlin VV et al. *Circulation*. 2002;106:1477-1482; Wensel R et al. *Circulation*. 2002;106:319-324.

Hemodynamic Progression of PAH




thank you!