Pulmonary Hypertension Update and Case Studies 2022

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Disclosures

Speakers Bureau – BMS, BI, Pfizer, Actelion Pharmaceuticals/ Johnson & Johnson

Case Study

Paul is a 66 year old male who presented to his primary care physician's office with complaints of cough, increased fatigue and dyspnea on exertion. Past medical history includes hypertension, smoking and osteoarthritis. He had a recent Cardiolite stress test which was negative. BP in office is 160/90. An echocardiogram was ordered.

Height 64 inches. Weight 275 lbs.

Physical Exam- III/VI SEM, 1+ lower extremity edema

Case Study

Britney is a 26 year old female who presented to her primary care physician's office with complaints of cough, increased fatigue and dyspnea which has been worsening over the past 1 year. She now c/o SOB at rest. No previous significant past medical history. Was seen by her PCP and placed on an inhaler and steroids. BP in office is 110/70. An echocardiogram was ordered.

Height 64 inches. Weight 145 lbs.

Physical Exam- III/VI SEM

1+ lower extremity edema

https://www.google.com/search?q=britney&source=lnms&tbm=isch&sa=X&ved=2ahUKEwjk2MWuwbvpAhXSU80KHSBPDJgQ_AUoAnoECCIQBA&biw=1280&bih=913

Case Study

Denise is a 46 year old female who presented to her primary care physicians office with complaints of cough, increased fatigue and dyspnea on exertion. Past medical history includes hypertension, smoking and scleroderma. She had a recent Cardiolite stress test which was negative. BP in office is 130/80. An echocardiogram was ordered.

Height 64 inches. Weight 195 lbs.

Physical Exam- III/VI SEM

1+ lower extremity edema

Case Study

Agnes is a 96 year old female smoker who presented to her primary care physician's office with complaints of cough, increased fatigue and dyspnea on exertion. Past medical history includes hypertension, smoking x 70 years and osteoarthritis. She had a recent Cardiolite stress test which was negative. BP in the office is 140/800. An echocardiogram was ordered.

Height 64 inches. Weight 175 lbs.

Physical Exam- III/VI SEM, 1+ lower extremity edema

Case Study

2D Echo results:

LVEF: 65%

Reduced RV function

Severe right atrial and ventricular size

Severe tricuspid regurgitation

Small pericardial effusion

RVSP 60 mmHg

Case Study

Based on the initial presentation and echocardiogram your next step would be as follows?

A. No further testing or treatment is indicated
B. Start on oral diuretics
C. Set up for a PFT, VQ Scan and Sleep Study
D. Place on anti-hypertensive medications
E. Set up for a Right Heart Cath

What is PAH?

- PAH is a syndrome characterised by a progressive increase in pulmonary vascular resistance (PVR)
  - leads to right ventricular overload
  - eventually leads to right ventricular failure and premature death[1]
  - If untreated, the median survival is 2.8 years[2] which is comparable with some malignancies

- Increased PVR is related to progressive changes in the pulmonary arterioles
  - vasoconstriction
  - obstructive remodelling of the pulmonary vessel wall
  - inflammation
  - in-situ thrombosis

1. Sitbon O *et al. Circulation* 2005
2. D'Alonzo GE *et al*. *Ann Intern Med* 1991

Clinical Classification of Pulmonary Hypertension (2018)

1. PAH

- Idiopathic PAH
- Heritable
- Drug- and toxin-induced
- Associated with:
  - CTD
  - HIV infection
  - portal hypertension
  - Systemic to pulmonary shunts
  - Chronic hemolytic anemia
  - Schistosomiasis
  - PVOD

2. PH Owing to Left Heart Disease

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

3. PH Owing to Lung Diseases and/or Hypoxia

- COPD
- ILD
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities
- Broncho pulmonary dysplasia (BPD)

4. CTEPH

5. PH With Unclear Multifactorial Mechanisms

- Hematologic disorders
- Systemic disorders
- Metabolic disorders
- Congenital heart Disease- Other than systemic to pulmonary shunt
- Others chronic hemolytic anemia

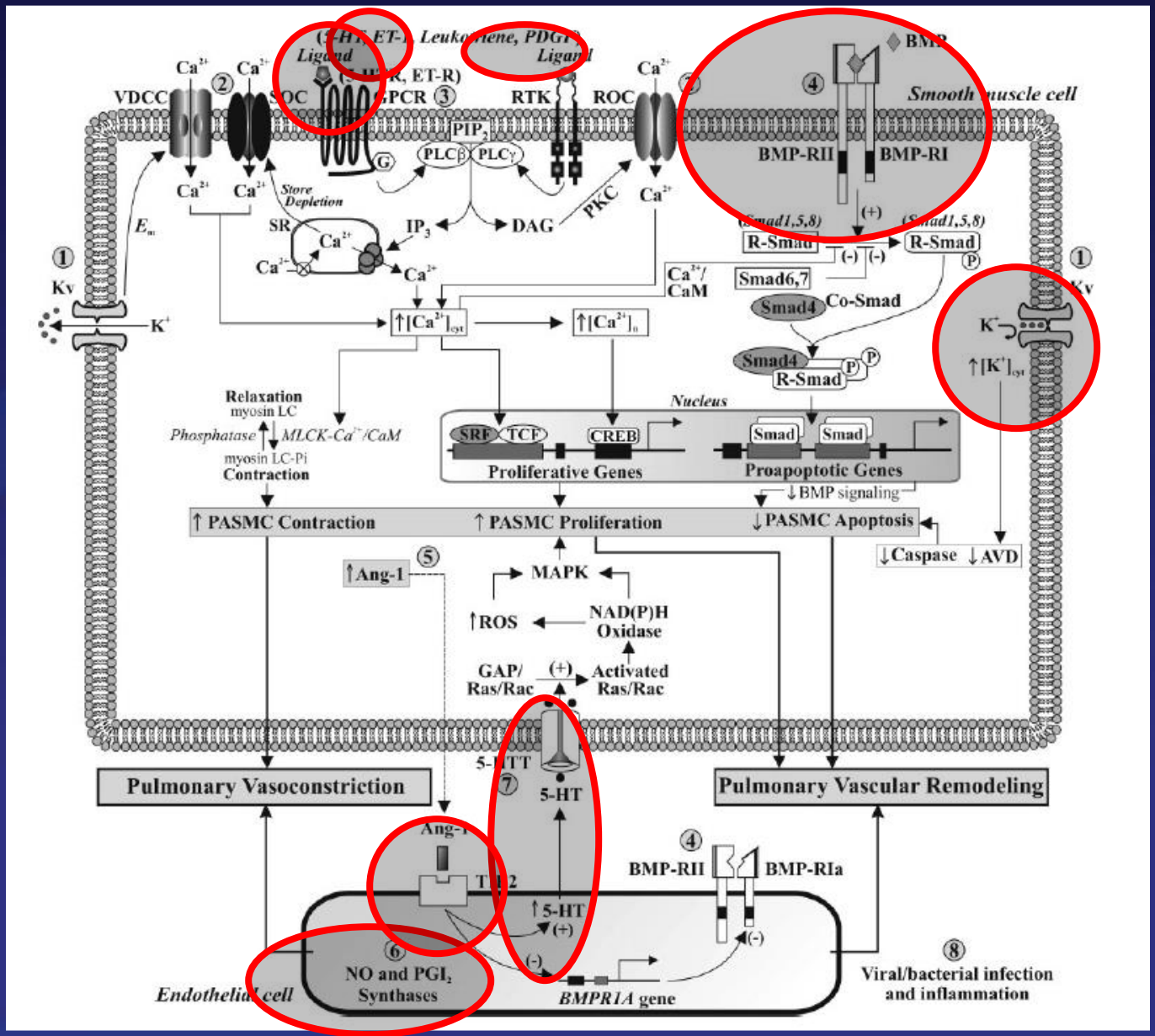
BMJ 2018.

Pulmonary Arterial Hypertension (PAH)

PAH: why does it develop?

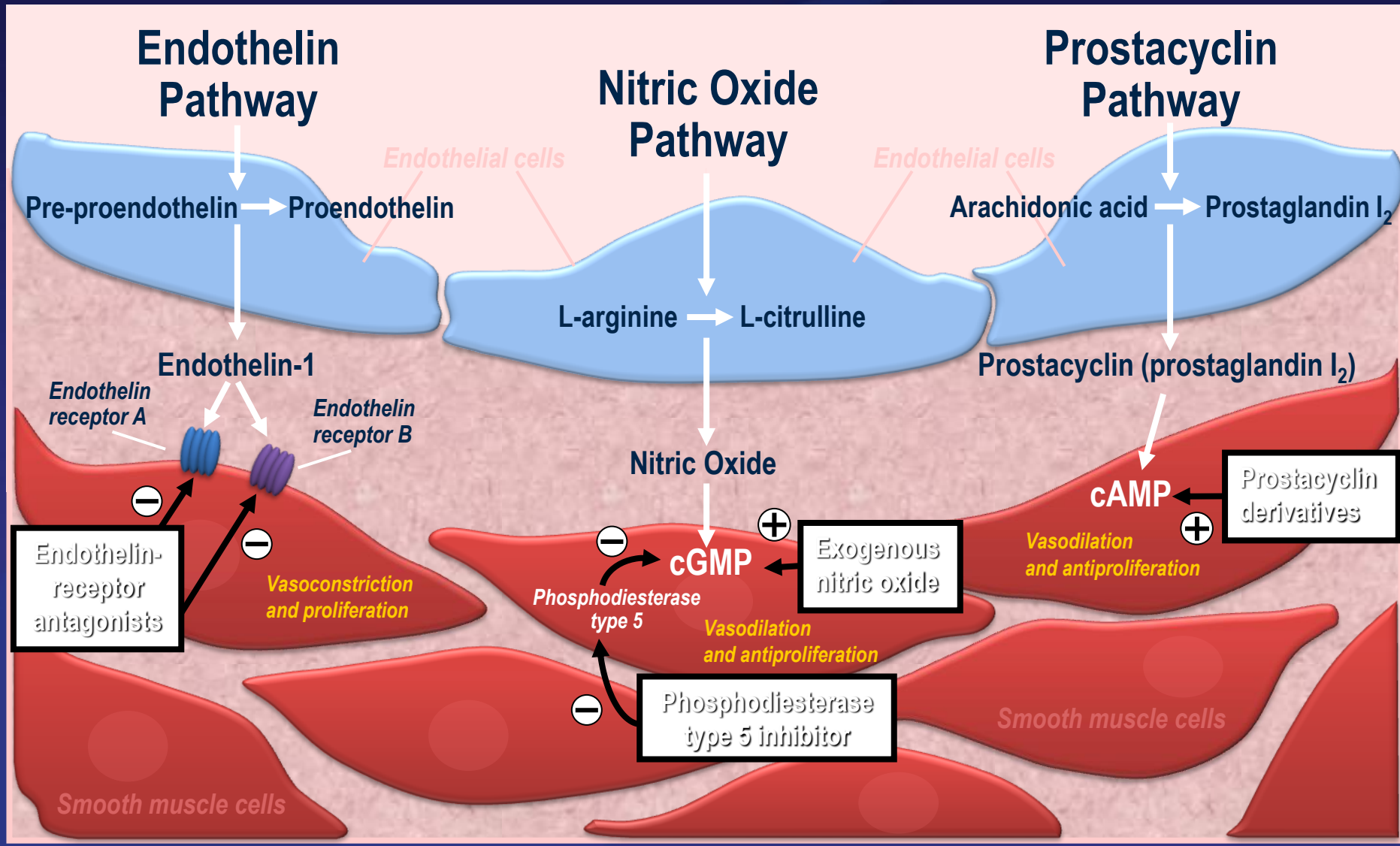
- Exact cause of PAH remains unknown
- Endothelial dysfunction occurs early on in the disease process
- Endothelial dysfunction results in
  - reduced production of vasodilators
  - over production of vasoconstrictors
  - endothelial and smooth muscle cell proliferation
  - remodelling of the pulmonary vascular bed and increased vascular resistance

Potential Targets



Yuan JXJ, Rubin LJ. *Circulation.* 2005;111:534-538.

Approved Therapeutic Targets



Humbert M et al. *N Engl J Med*. 2004;351:1425-1436.

PAH: why does it develop?

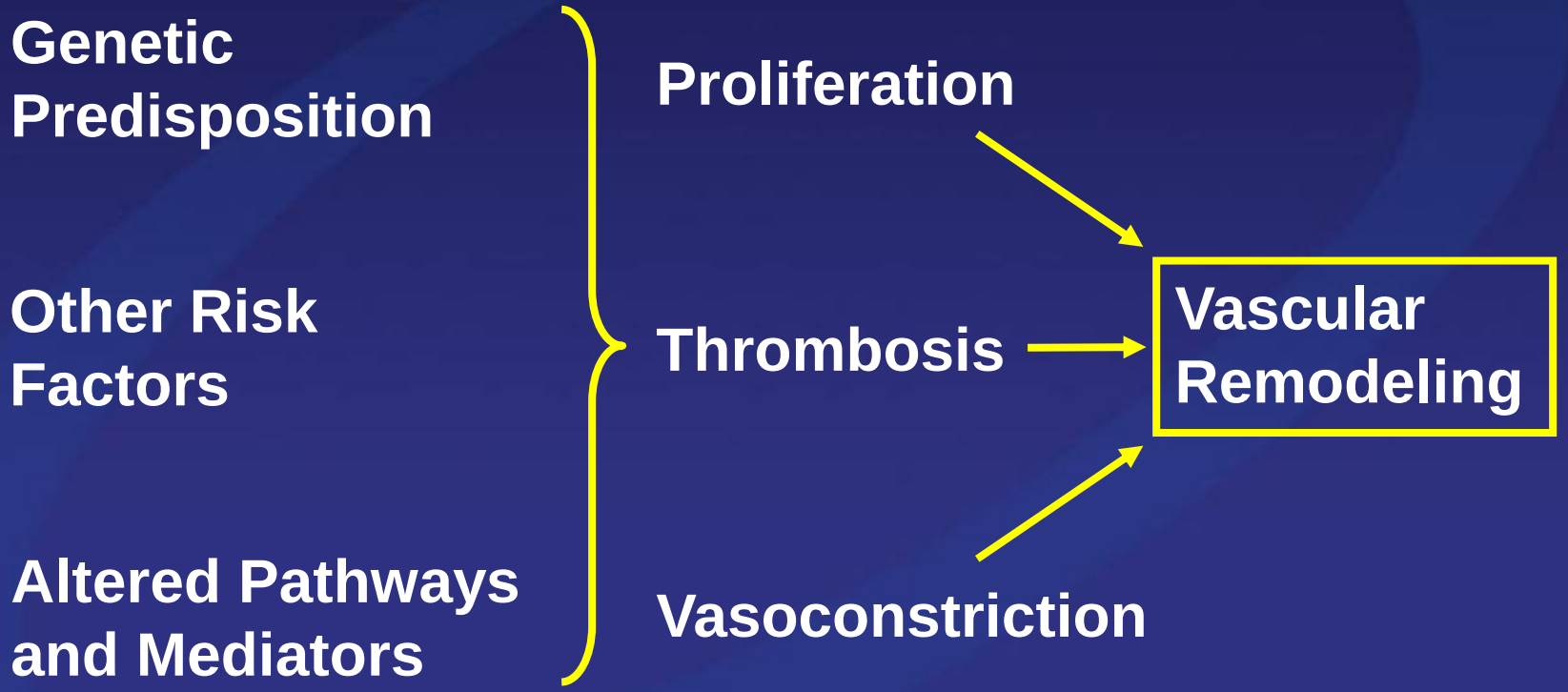
- Reduced production of vasodilators
  - Prostacyclin
    - potent vasodilator
    - potent inhibitor of platelet activation
    - therapy with synthetic forms of prostacyclin may help to correct this deficiency
  - Nitric oxide
    - potent vasodilator
    - possesses anti-proliferative properties
    - vasodilatory effect is mediated by cGMP
      - rapidly degraded by phosphodiesterases

PAH: why does it develop?

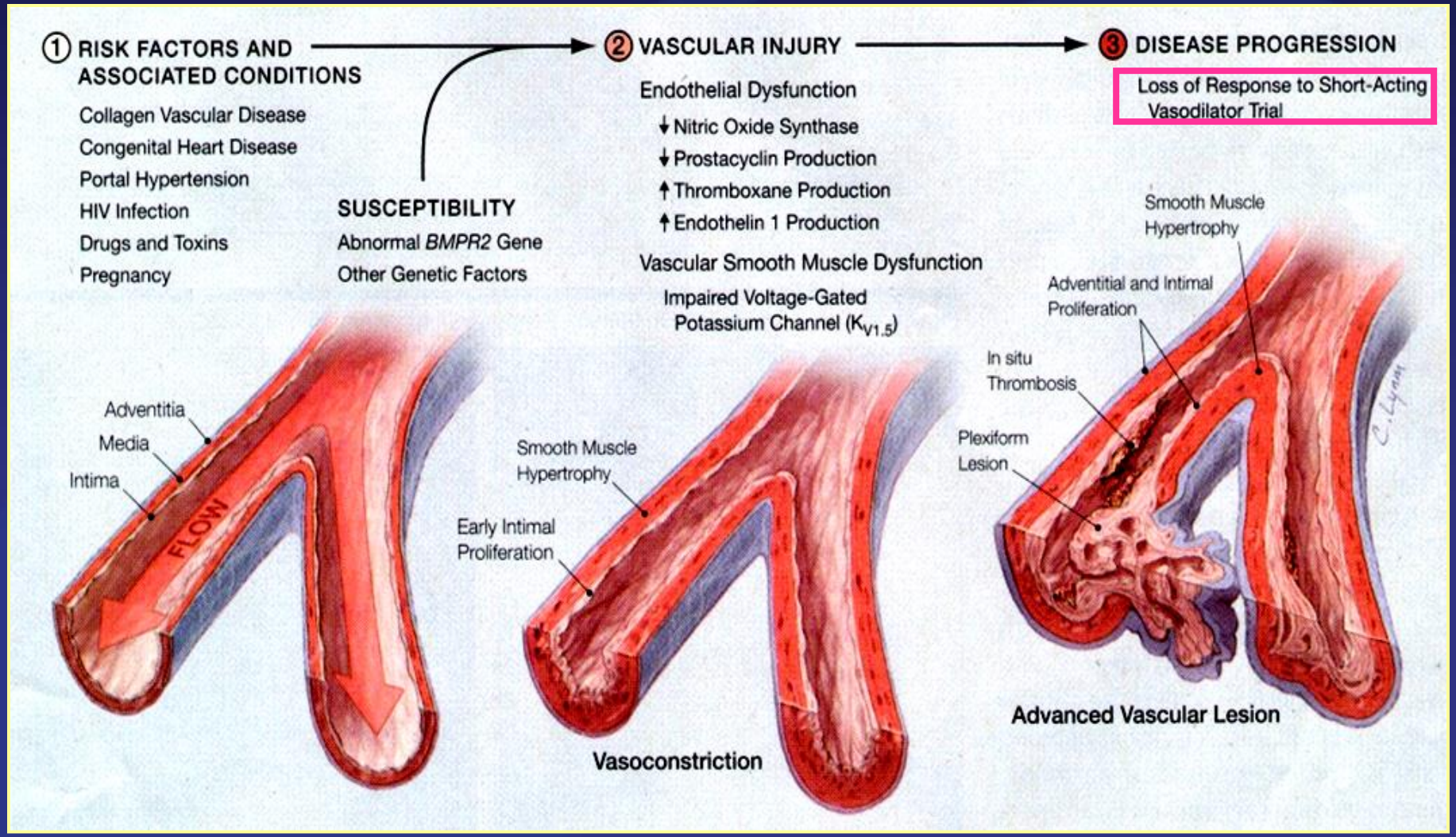
- Increased production of vasoactive compounds
  - Endothelin (ET)
    - elevated levels are seen in PAH patients[1–3]
    - levels correlate with disease severity[4]
    - deleterious effects mediated through endothelin receptors[5]
      - fibrosis
      - hypertrophy and cell proliferation
      - inflammation
      - vasoconstriction
    - endothelin receptor antagonists can block these effects
- Endothelin, nitric oxide and prostacyclin have been the principal focus of research into treatments for PAH

1. Stewart DJ *et al. Ann Inter Med* 1991
2. Vancheeswaran R *et al. J Rheum* 1994
3. Yoshibayashi M *et al*. *Circulation* 1991
4. Galiè N *et al. Eur J Clin Invest* 1996
5. Channick RN *et al*. *Lancet* 2001

Pathophysiology of PAH: An Integrated View



Pathogenesis of Pulmonary Arterial Hypertension



1. Barst RJ *et al. J Am Coll Cardiol* 2004

PAH: how common is it?

- PAH is rare
  - an estimated prevalence of 30–50 cases per million[1]
  - most common in young women
- Mean age of diagnosis 36 years[2]
- The prevalence in certain at-risk groups is higher
  - HIV-infected patients (0.50%)[3]
  - sickle cell disease (20–40%)[4]
  - systemic sclerosis (16%)[5]
- True prevalence may be higher

1. Peacock AJ. *BMJ* 2003
2. Gaine SP *et al. Lancet* 1998
3. Sitbon O *et al. Am J Resp Crit Care Med* 2008
4. Lin EE *et al*. *Curr Hematol Rep* 2005
5. McGoon M *et al. Chest* 2004

PAH Related to Connective Tissue Disease

- Connective tissue diseases
  - scleroderma (most common)
  - systemic lupus erythematosus
  - Sjogren's syndrome
  - rheumatoid arthritis
  - MCTD

- PH is one of the top causes of death in scleroderma
- Similar to IPAH pathology
- Medical treatment same as for IPAH, but benefits less than for IPAH

Hachulla E et al. *Rheumatology.* 2009;48:304-308.

Survival in Pulmonary Arterial Hypertension

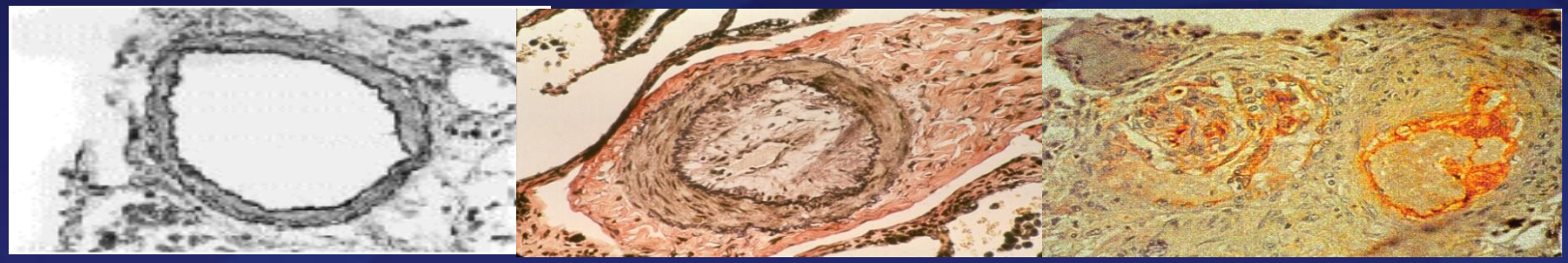
- Survival rates (patients with IPAH) at 1, 3 and 5 years were 68%, 48% and 34% respectively

- PAH mortality contributed to
  - Right heart failure 47%
  - Sudden Death 26%
  - Other (pneumonia) 27%

- Although new treatments have improved mortality rates, there is little evidence to support reversal of aberrant remodeling

D'Alonzo GE, et al. Ann Intern Med 1991;115:343-349.

Schematic Progression of PAH



Pre-symptomatic/ Compensated

Symptomatic/ Decompensating

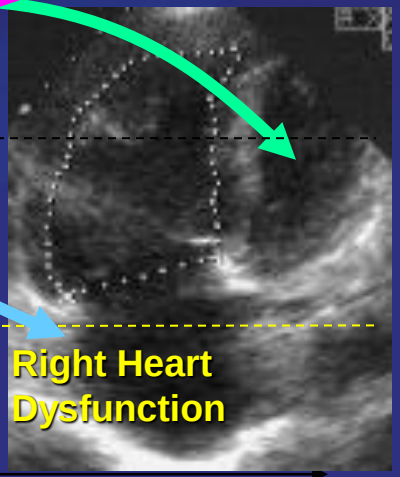
Declining/ Decompensated

CO

Symptom Threshold

PAP

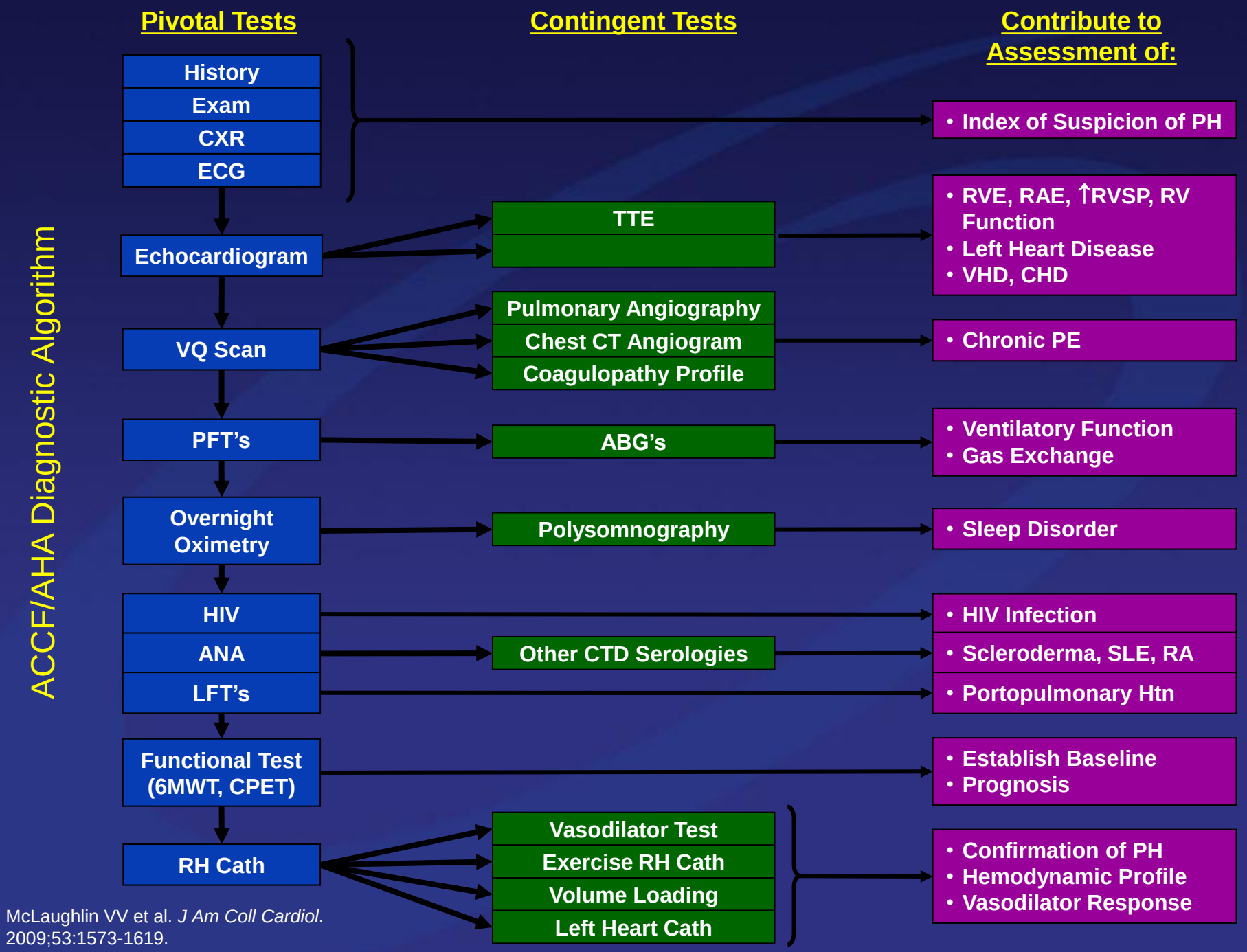
PVR



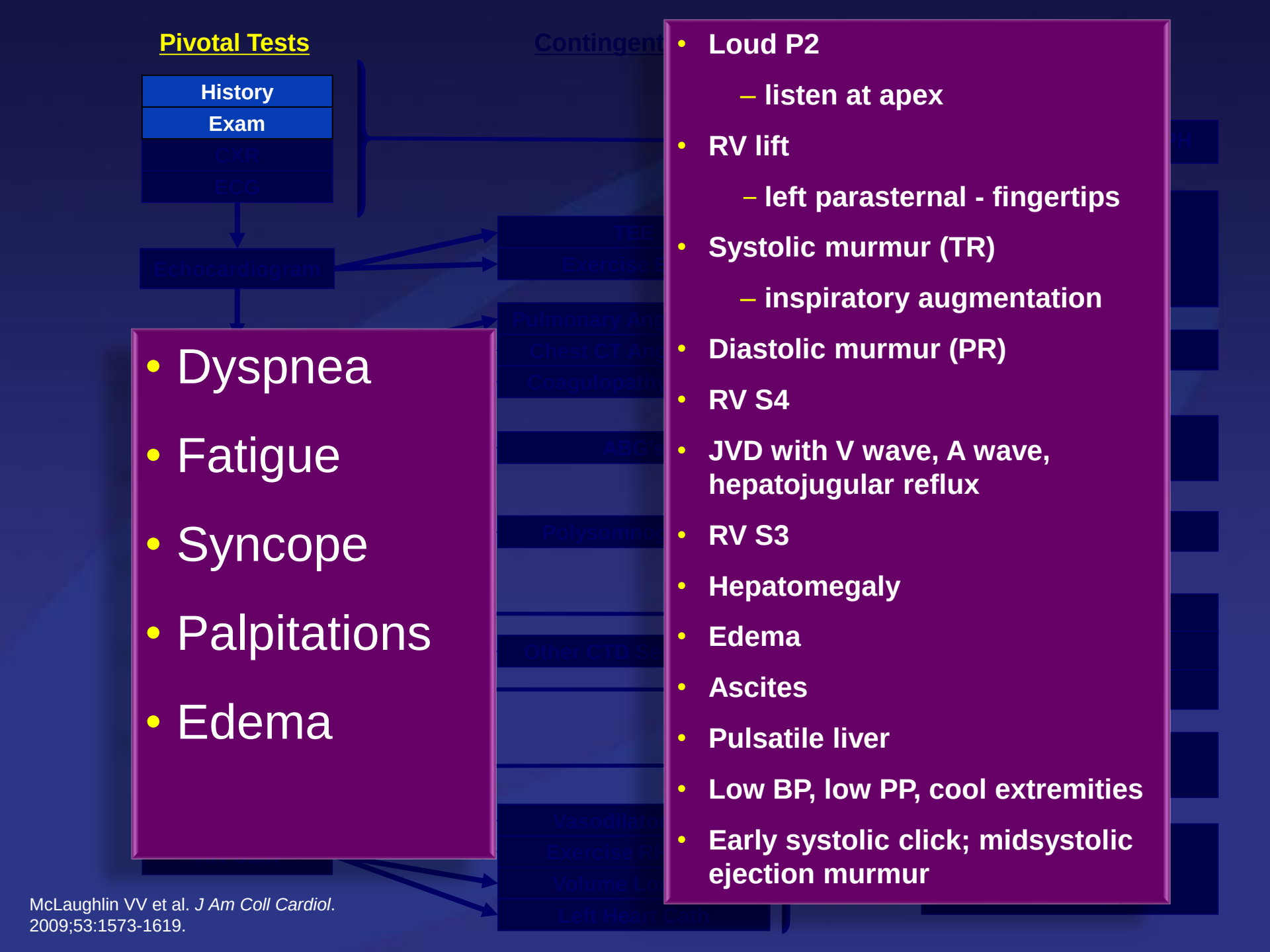
Time

$$PVR = \frac{PAP - PCW}{CO}$$

Diagnosis of Pulmonary Arterial Hypertension (PAH)



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



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

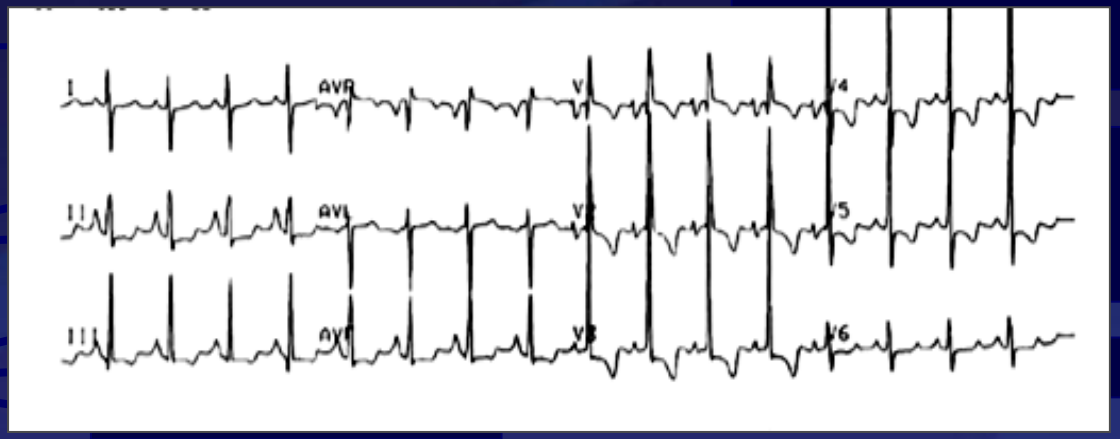
Pivotal Tests

Contingent Tests

Contribute to Assessment of:

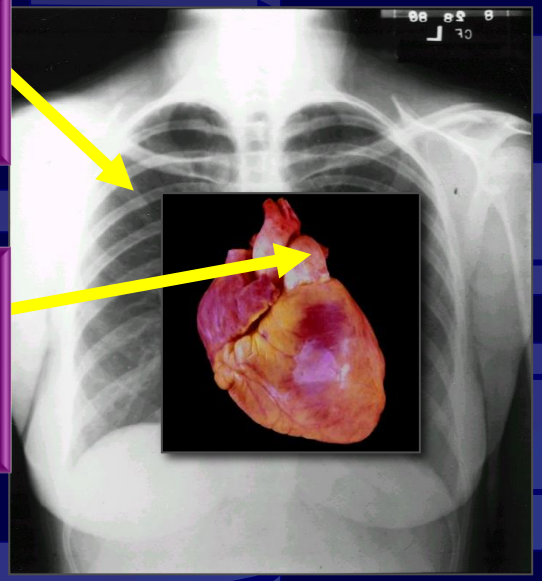
CXR

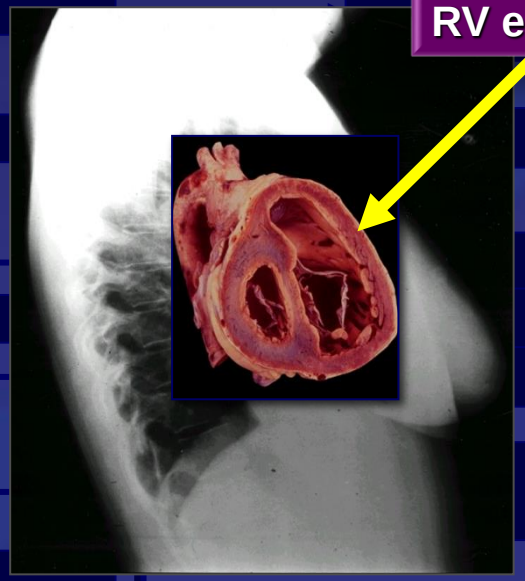
ECG



Peripheral hypovascularity (pruning)

Prominent central pulmonary artery





RV enlargement

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

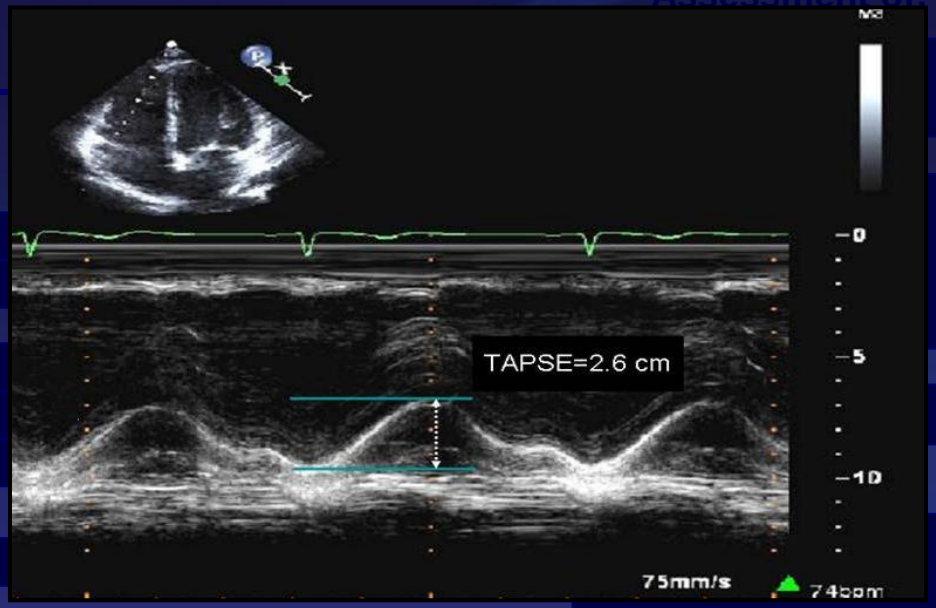
Pivotal Tests

Contingent Tests

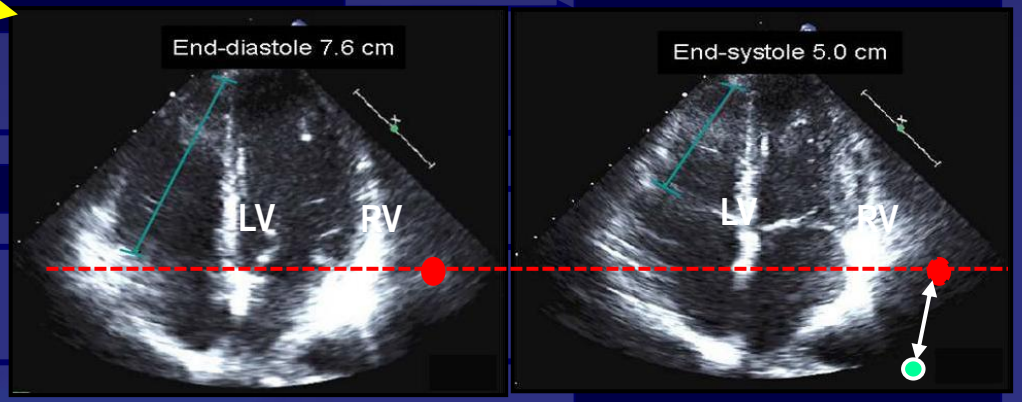
Contribute to Assessment of:

Echocardiogram

- **RA, RV enlargement, IVS straightening**
- **RV systolic dysfunction**
  - **TAPSE**
- **IVC diameter and inspiratory collapse**
- **TR severity**
- **Estimated PVR, MPAP, DPAP**



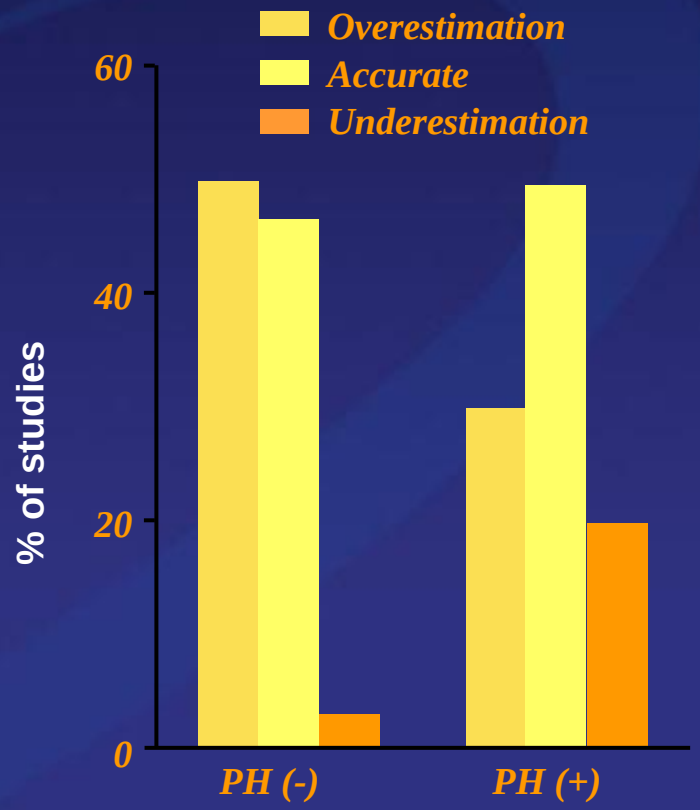
$$RVSP = 4(V_{TR})^2 + RAP$$



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

Echo estimate of PAP often inaccurate in advanced lung disease

- Cohort: 374 lung txp pts
- Echo 24–48 h prior to RHC
- Prevalence of PH: 25%
- Echo frequently leads to over-diagnosis of PH in patients with advanced lung disease



Arcasoy SM et al. Am J Respir Crit Care Med. 2003;167:735-740. General Overview of Pulmonary Hypertension Tasbirul Islam MD,FCCP,MRCP(UK)
Indiana University Hospital Arnett
Lafayette , IN

Arbitrary criteria for detecting the presence of PH based on tricuspid regurgitation peak velocity and Doppler-calculated PA systolic pressure at rest*

- **Echocardiographic diagnosis: PH unlikely**
  - Tricuspid regurgitation velocity ≤ 2.8 m/sec, PA systolic pressure ≤ 36 mmHg and no additional echocardiographic variables suggestive of PH
- **Echocardiographic Diagnosis PH possible**
  - Tricuspid regurgitation velocity ≤ 2.8 m/sec, PA systolic pressure ≤ 36 mmHg but presence of additional echocardiographic variables suggestive of PH.
  - Tricuspid regurgitation velocity 2.8-3.4 m/sec, PA systolic pressure 36-50 mmHg with or without additional echocardiographic variables suggestive of PH
- **Echocardiographic diagnosis: PH likely**
  - Tricuspid regurgitation velocity > 3.4 m/sec, PA systolic pressure > 50 mmHg with/without additional echocardiographic variables suggestive of PH

Arcasoy SM et al. Am J Respir Crit Care Med. 2003;167:735-740. General Overview of Pulmonary Hypertension Tasbirul Islam MD,FCCP,MRCP(UK)
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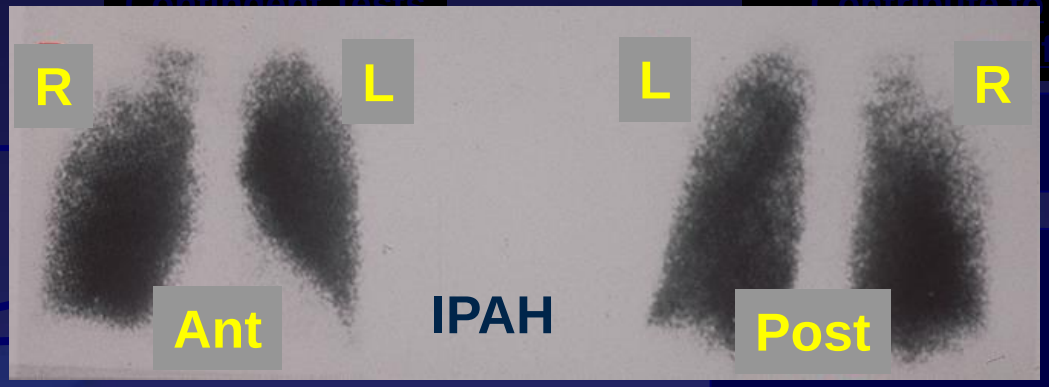
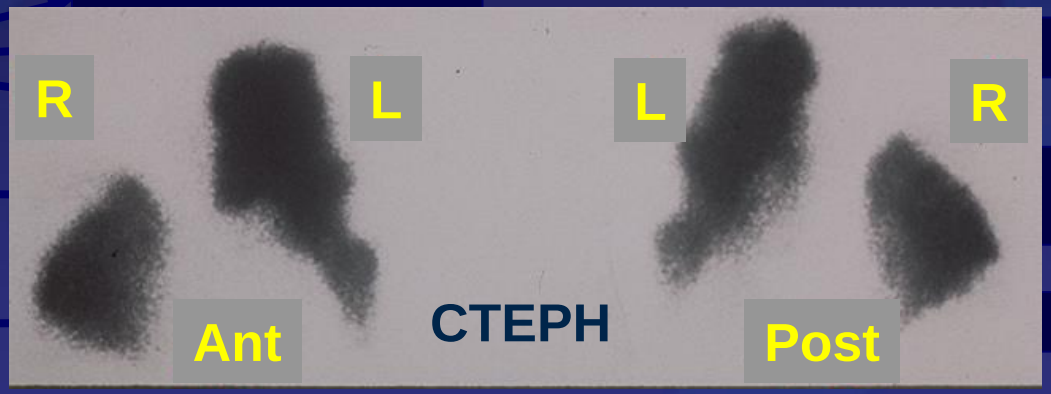
Lafayette , IN

European Heart Journal 2009;30:2493-2537

Pivotal Tests

VQ Scan



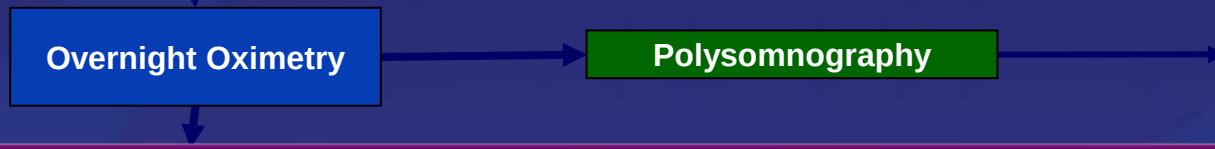


- 3-4% of acute PE do not entirely resolve
- ½ of those with CTEPH do not have an apparent history of acute PE
- Normal or very low probability VQ essentially excludes chronic PE
- CTEPH should be excluded, even when another explanation for PH is present

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

Pivotal Tests | Contingent Tests | Contribute to Assessment of:

- 17% (37/220) of patients with OSA have daytime mPAP >20 mm Hg *Chaouat A et al. Chest. 1996;109:380-386.*
  - 16 had mPAP >25 mm Hg; only 2 had mPAP >35 mm Hg
  - Marked ↑ with sub-max exercise (mean mPAP 47 mm Hg) – in part due to ↑ PCWP
  - Contributing factors: obesity, hypoxemia, COPD



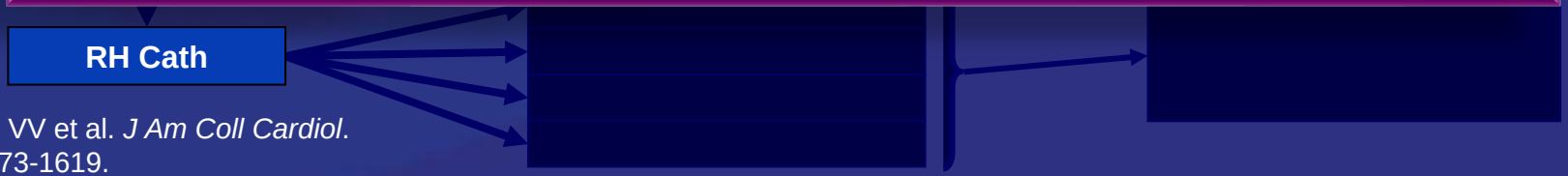
- In patients with OSA, ↓PAP reported in response to CPAP therapy

  See: *Somers VK et al. J Am Coll Cardiol. 2008;52:686-717.*

- Untreated – response to other treatment likely less effective

Pivotal Tests | **Contingent Tests** | **Contribute to Assessment of:**

- Oxygen saturations (SVC, IVC, PA, SA)
- Right atrial pressure
- RV systolic and end-diastolic pressure
- PA systolic, diastolic, and mean pressure
- PAWP, LVEDP, or LAP
- Thermodilution or Fick CO, CI
- Pulmonary vascular resistance
- Systemic systolic, diastolic, and mean pressure
- Heart rate
- Vasodilator response



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

Proposed Hemodynamic Definition of PH/PAH- Updated 2019 6th World Symposium

PH	Mean PAP ≥20 mm Hg
PAH	Mean PAP ≥20 mm Hg *plus* PCWP/LVEDP ≤15 mm Hg, PVR > 3 Woods Units

https://www.acc.org/latest-in-cardiology/articles/2019/10/30/08/08/the-6th-world-symposium-on-ph-part-1

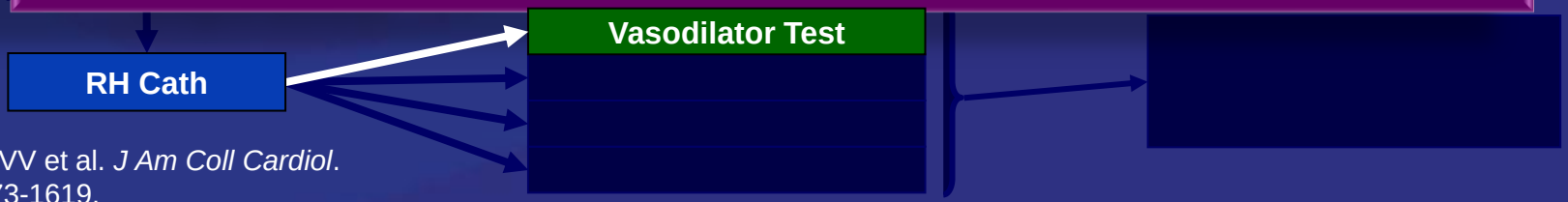
Proposed Hemodynamic Definition of PH/PAH- Updated 2019 6th World Symposium

Definitions	Characteristics
Pre-Capillary PH	mPAP >20 mmHg
	Pulmonary artery wedge pressure ≤15 mmHg
	PVR ≥3 Wood units
Isolated Post-Capillary PH	mPAP >20 mmHg
	Pulmonary artery wedge pressure >15 mmHg
	PVR <3 Wood units
Combined Pre- and Post-Capillary PH	mPAP >20 mmHg
	Pulmonary artery wedge pressure >15 mmHg
	PVR ≥3 Wood units

https://www.acc.org/latest-in-cardiology/articles/2019/10/30/08/08/the-6th-world-symposium-on-ph-part-1

Pivotal Tests

- Vasodilator response
  - iNO recommended
  - Decrease in mPAP by ≥10 mm Hg
  - Decrease of mPAP to ≤40 mm Hg
  - rare in scleroderma, hereditary, diet-pill-induced
  - risk of pulmonary edema with left heart disease or PVOD
- RHC is safe (1.1% serious events)
  - hematoma, pneumothorax, arrhythmias, hypotension
    (*Hoeper M et al. JACC. 2006;48:2546-2552.*)
- Minimize spontaneous variability
  - take measurements over 2-3 respiratory cycles at end-expiration



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

Treating PAH

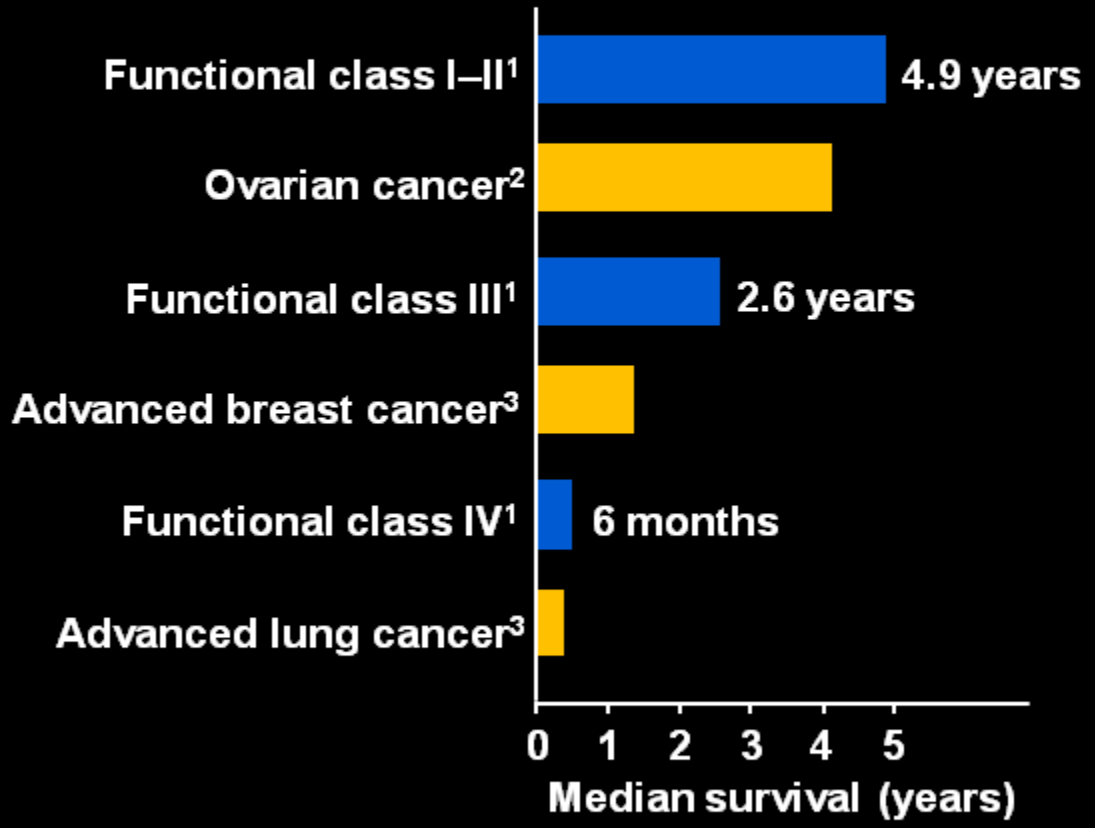
PAH: How is it treated?

- There is currently no cure for PAH
- Prognosis is influenced by the status of WHO FC when treatment is started – those who start therapy in WHO FC I or II demonstrate a better prognosis than those whose therapy is started in the more severe stages[1]
- By recognizing and treating patients as early as possible, disease progression may be delayed
- Without treatment, patients in WHO FC II can rapidly deteriorate within 6 months to more advanced PAH as evidenced by progression of symptoms.[2]

1. Sitbon O *et al*. J *Am Coll Cardiol* 2002
2. Galiè N *et al*. *Lancet* 2008

Early Recognition and Treatment of PAH is Essential

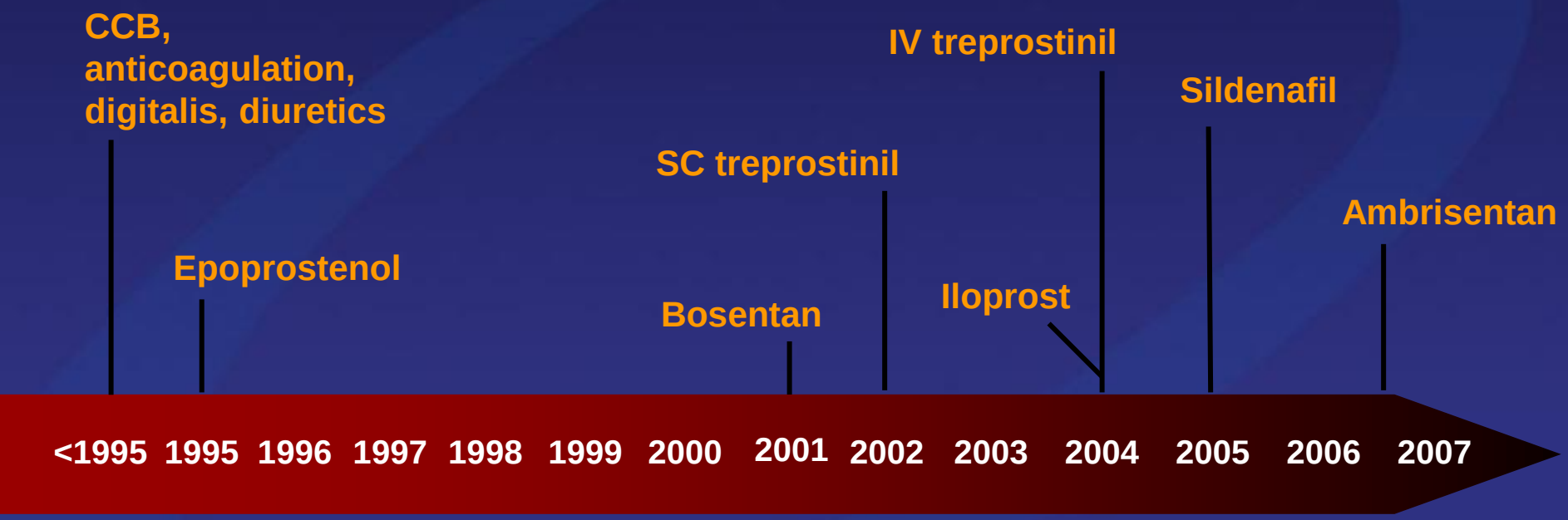
Prognosis of untreated PAH is poor, even when mildly symptomatic (WHO FC II)



FC=functional class; PAH=pulmonary arterial hypertension; WHO=World Health Organization.

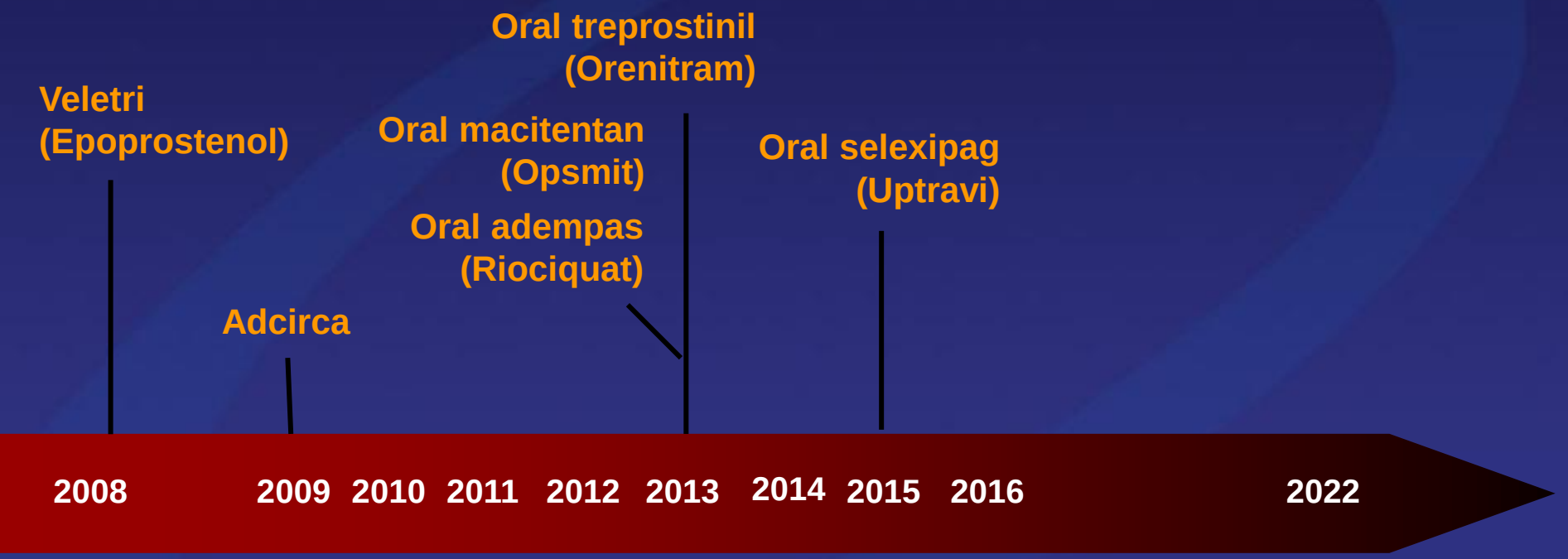
1. D'Alonzo GE et al. *Ann Intern Med.* 1991;115:343-349. 2. Armstrong DK et al. *N Engl J Med.* 2006;354:34-43. 3. Kato I et al. *Cancer.* 2001;92:2211-2219.

PAH Treatments—a Historical Overview



CCB = calcium channel blocker.

PAH Treatments—a Historical Overview



When to use a Calcium Antagonist ?

CCB Therapy is Effective in Only a Small Percent of PAH Patients

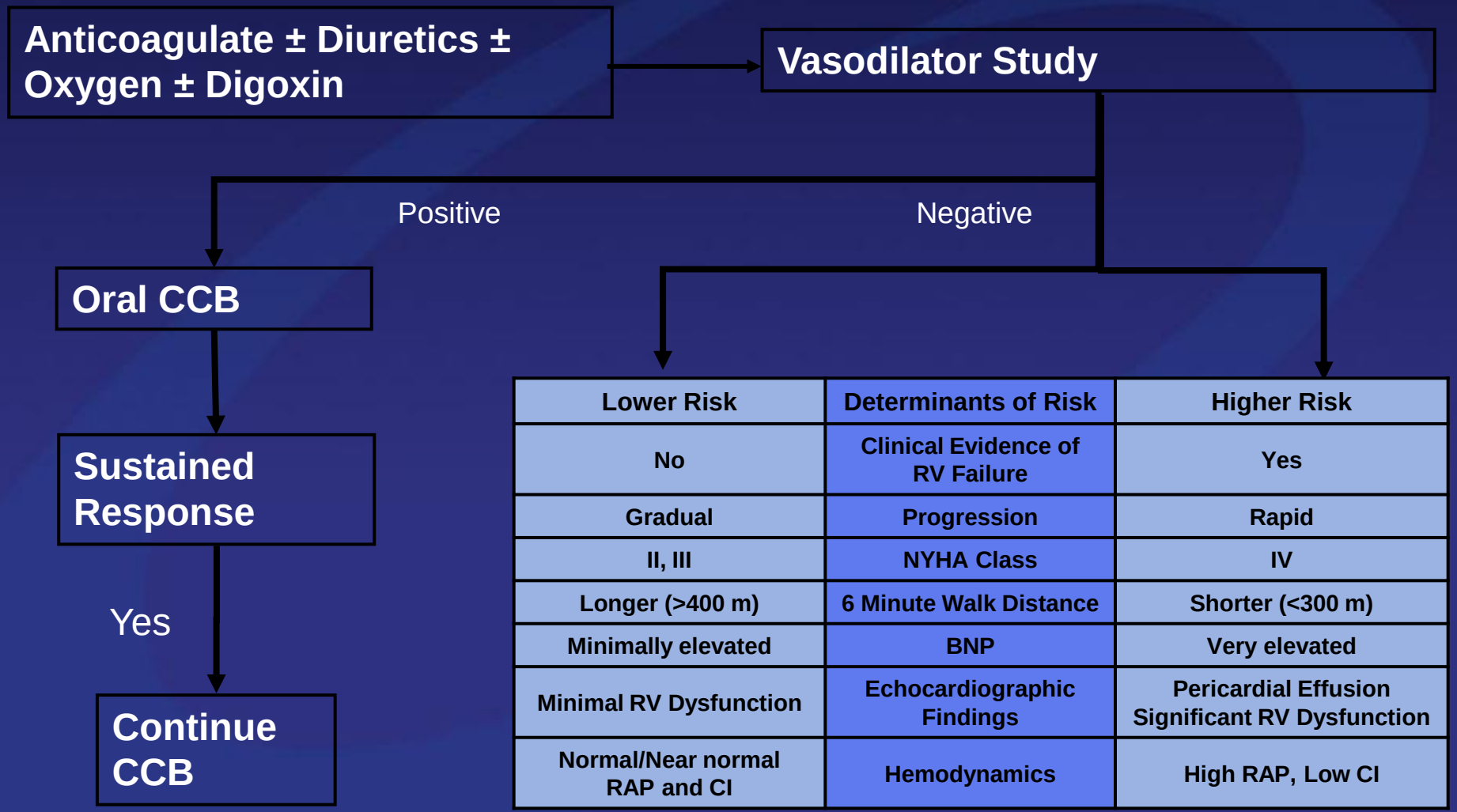
A retrospective study of 557 patients who were tested for acute vasoreactivity:

- 70 (12.6%) patients responded and were put on CCB therapy
- Of those 70 patients, only 38 improved
- Therefore only 6.8% of the total number of patients benefited from long-term CCB therapy
- For the 32 patients who responded positively to acute vasoreactivity testing but who failed to respond to CCB therapy, the 5-year survival rate was 48%

Long-term CCB responders represent <10% of iPAH patients

Sitbon O et al. *Circulation.* 2005;111:3105-3111.

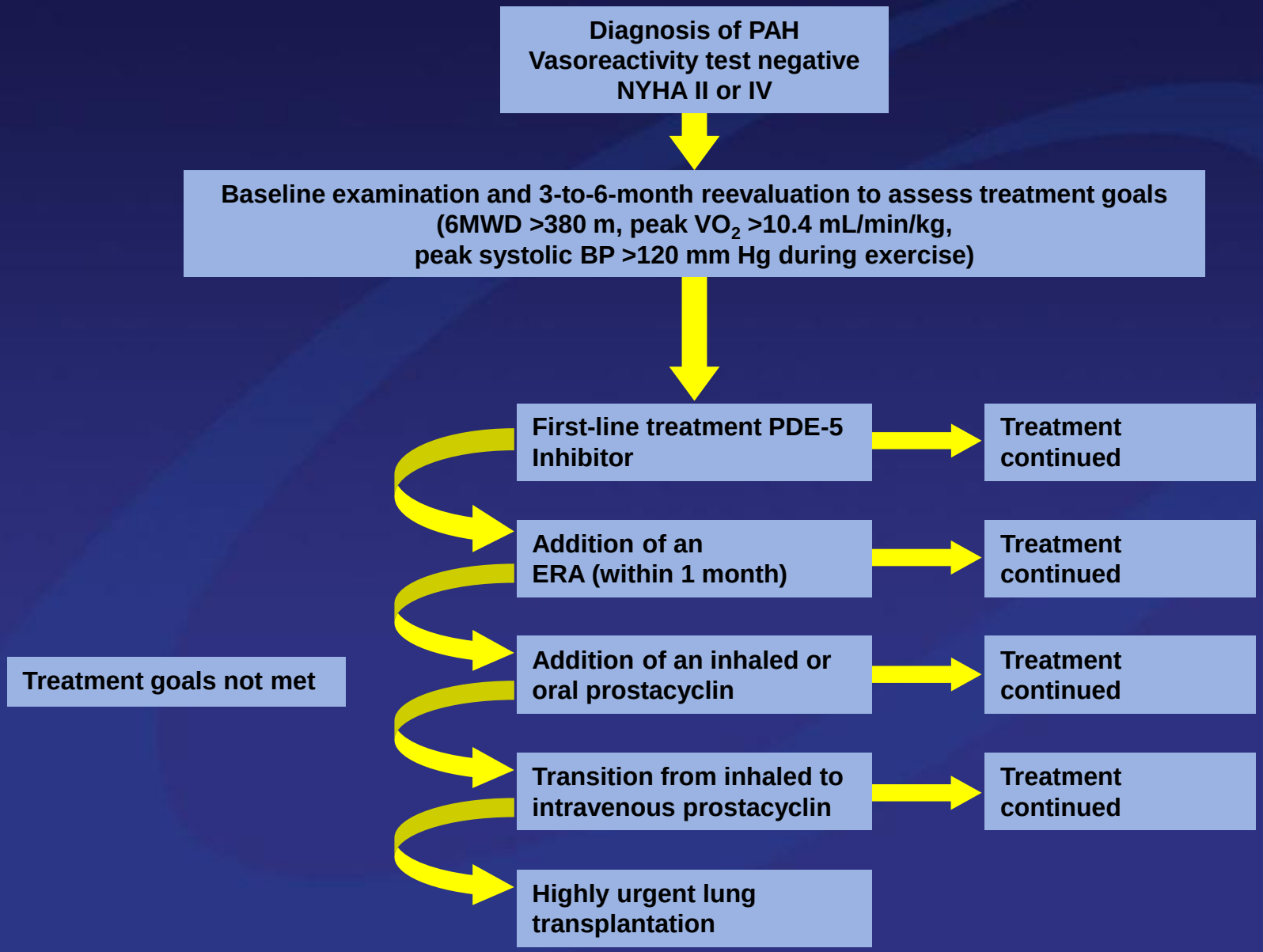
What is the Optimal Treatment Strategy?



Lower Risk	Determinants of Risk	Higher Risk
No	Clinical Evidence of RV Failure	Yes
Gradual	Progression	Rapid
II, III	NYHA Class	IV
Longer (>400 m)	6 Minute Walk Distance	Shorter (<300 m)
Minimally elevated	BNP	Very elevated
Minimal RV Dysfunction	Echocardiographic Findings	Pericardial Effusion Significant RV Dysfunction
Normal/Near normal RAP and CI	Hemodynamics	High RAP, Low CI

McLaughlin VV and McGoon M. *Circulation*. 2006;114:1417-1431.

Goal-Oriented Therapy



Modified from Hoeper et al. *Eur Respir J.* 2005;26:858-863.

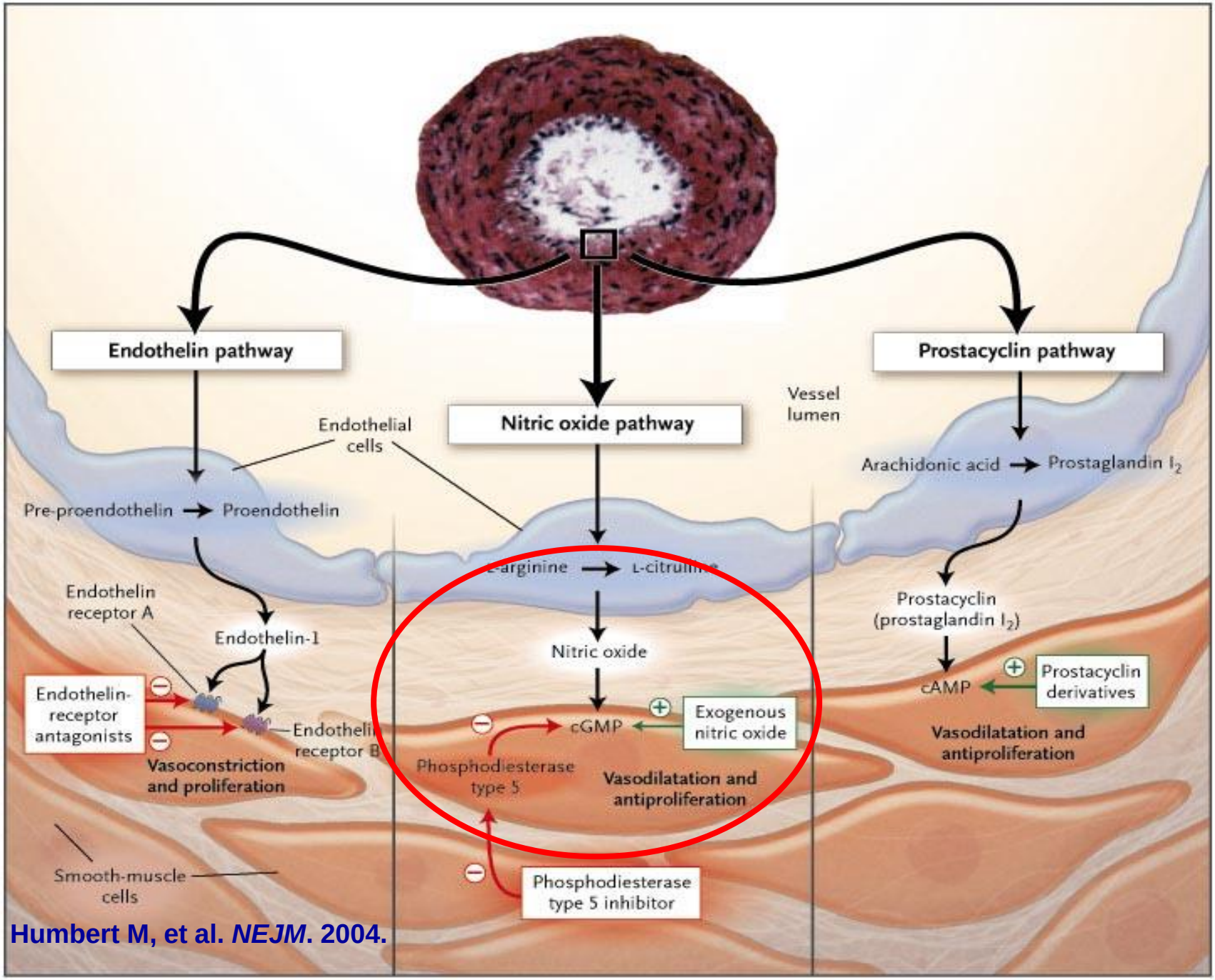
Treatment Targets for Pulmonary Arterial Hypertension Patients (WHO Group I)

Phosphodiesterase 5 Inhibitors

- Oral
  - Sildenafil (Viagra)
  - Tadalafil (Adcirca)

Soluble Guanylate Cyclase (sGC) Stimulator

- Oral
  - Riociguat (Adempas)



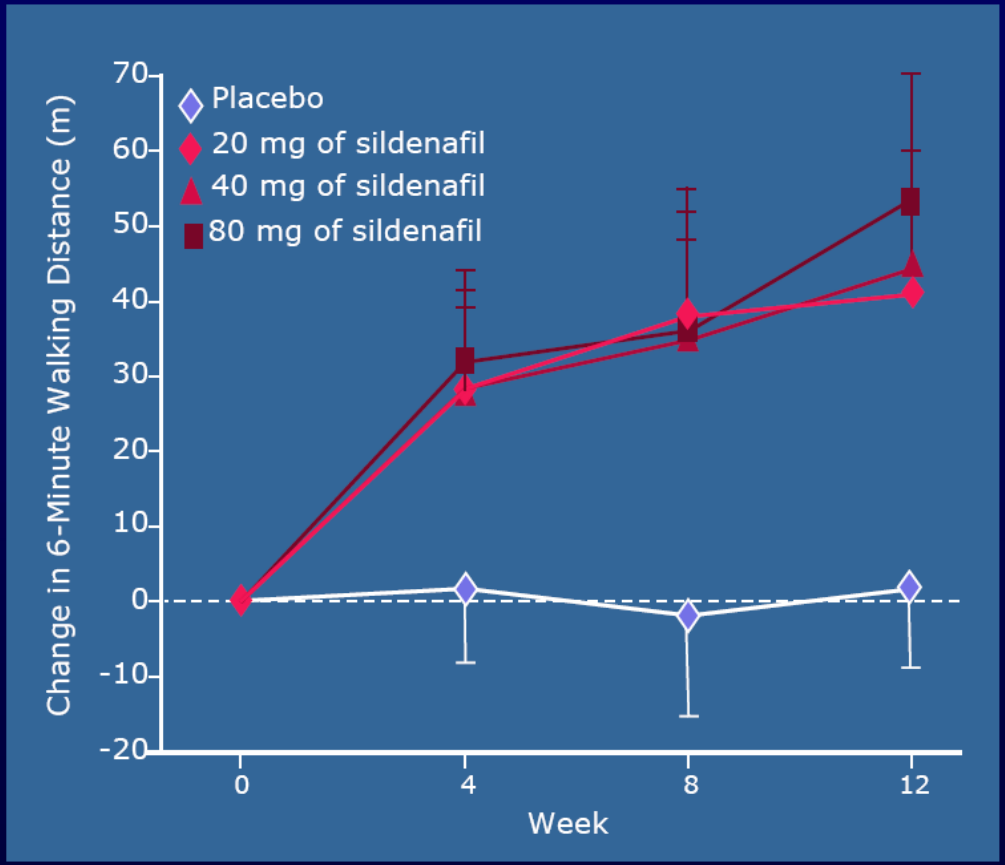
Humbert M, et al. *NEJM*. 2004.

Phosphodiesterase 5 Inhibitors

- Prevent breakdown of cGMP the downstream mediator of nitric oxide
- Major side effects
  - Vasodilatory- headaches, flushing, sinus congestion
  - Visual color changes and blurriness

Sildenafil (Revatio)

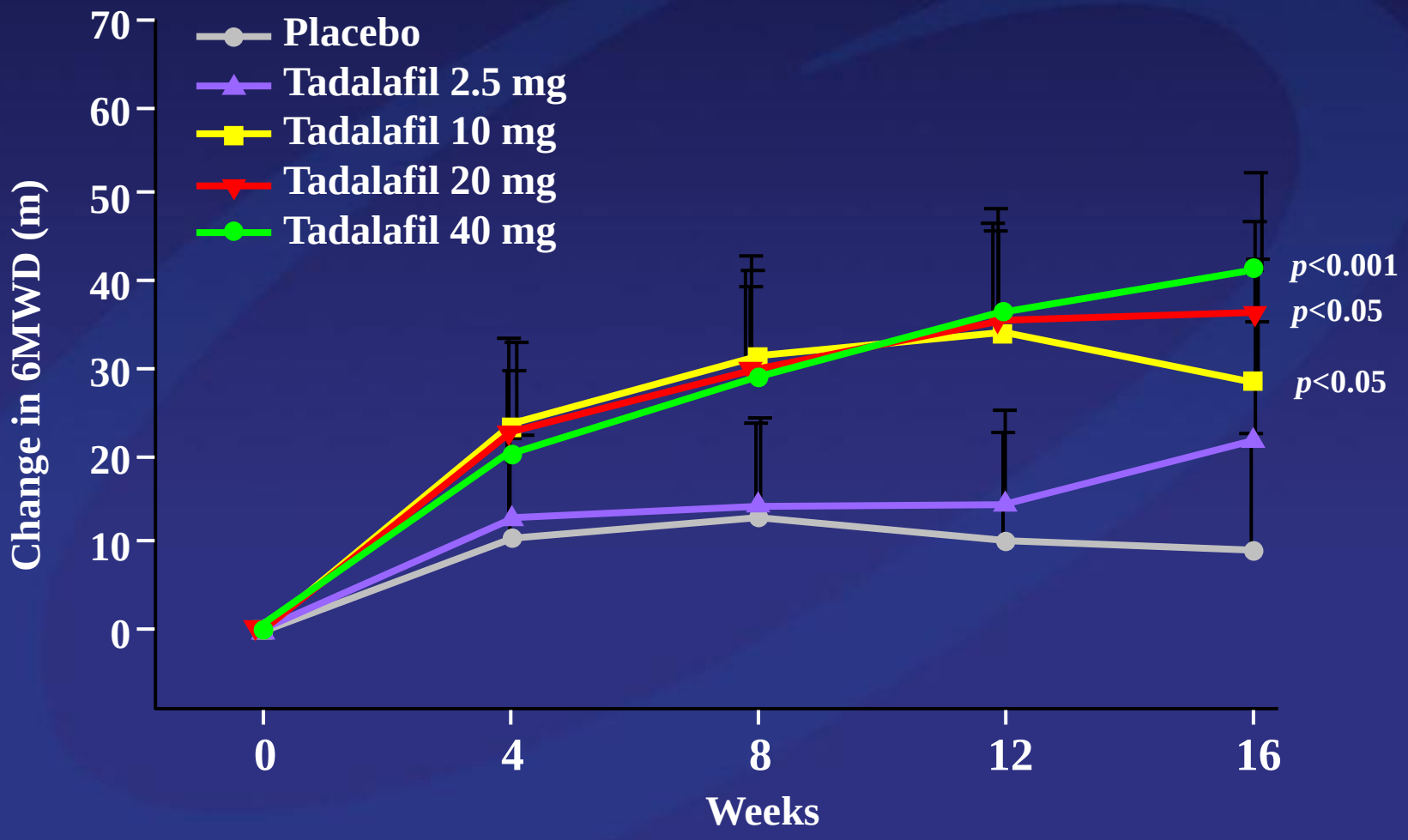
- 278 patients[1]
  - 65% IPAH
  - 40% Class II and 56% Class III
- Treatment effect ~45 meters
- No difference in 6 MWD between doses



[1]Galie N et al. *N Engl J Med* 2005;353:2148-57

Adapted from Hill, N. NJ Fellows Conf in PAH 12/2/06

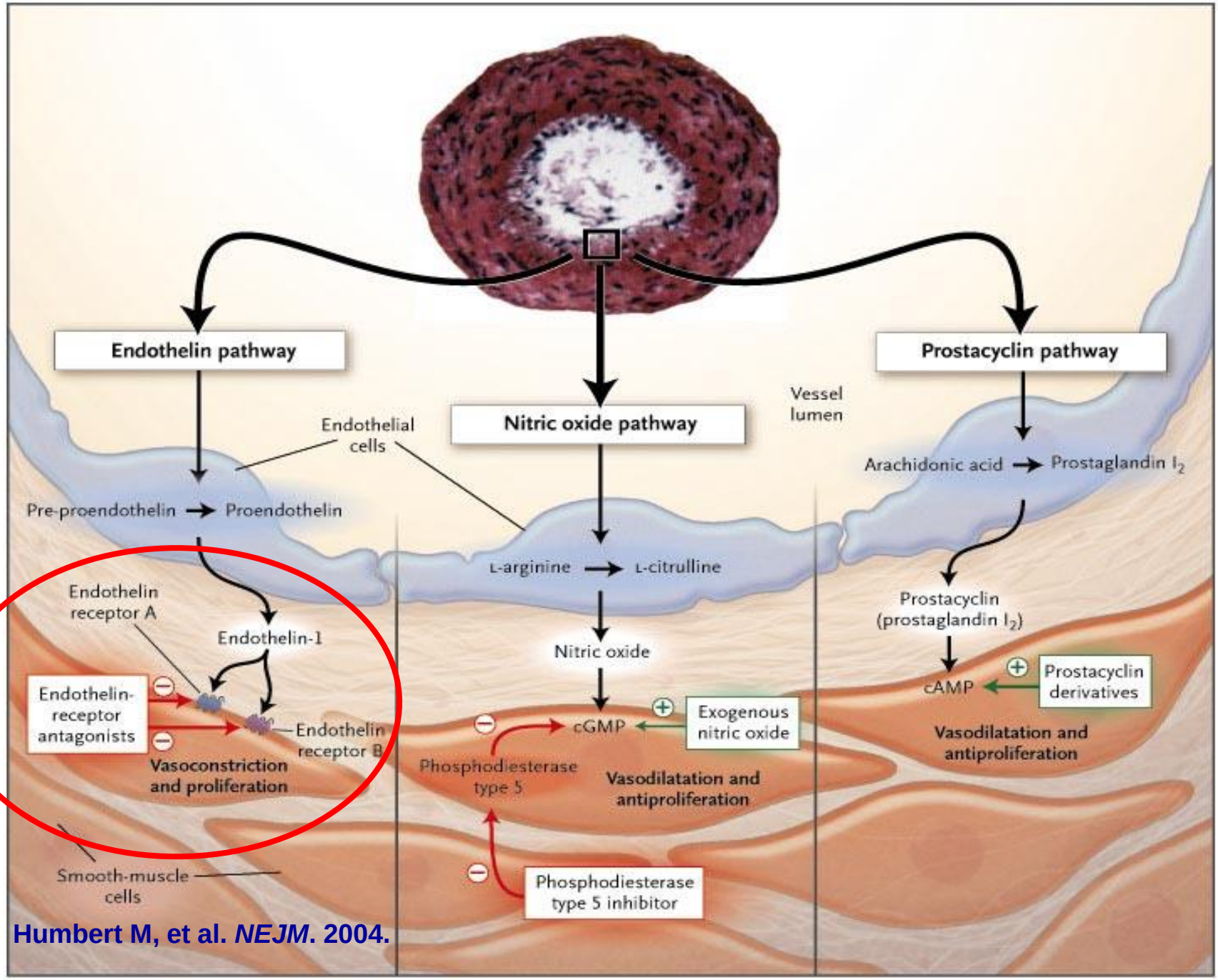
Effect of Tadalafil on 6MWD (PHIRST)



Galiè N et al. *Circulation.* 2009;119;2894-2903..

Endothelin Antagonists (ERAs)

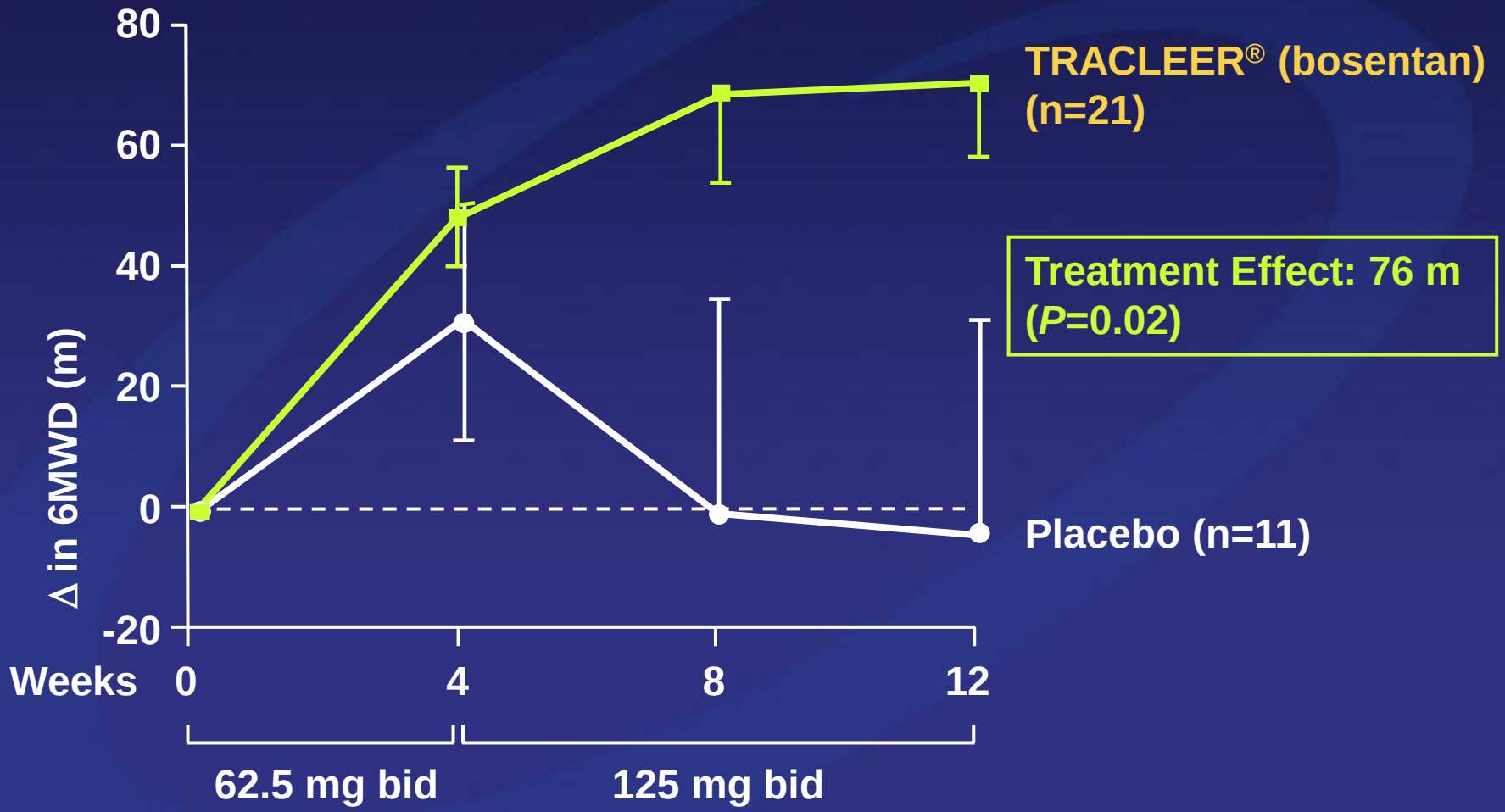
- Oral
  - **Bosentan (Tracleer)**
  - **Ambrisentan (Letairis)**
  - **Macitentan (Opsumit)**



Humbert M, et al. *NEJM*. 2004.

Significant Change in 6MWD*

Study 351



*Data are mean ± SEM.

Channick RN et al. *Lancet.* 2001;358:1119-1123.

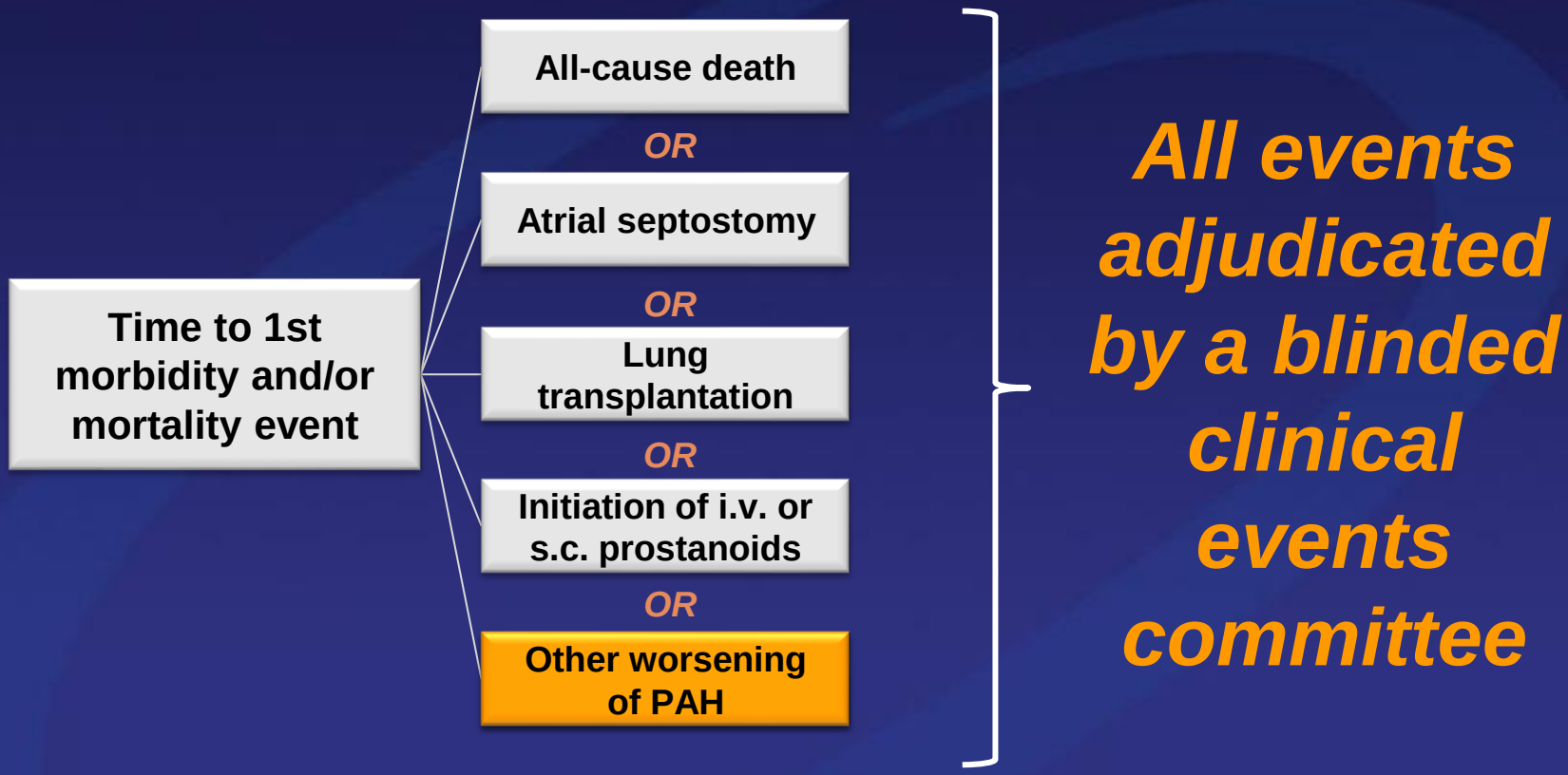
SERAPHIN: A landmark study in PAH

Drug	Study	Duration	Primary endpoint	No. of patients
Bosentan	Study-351[1,2]	12 wks	6-MWD	32
	BREATHE-1[3]	16 wks	6-MWD	213
	EARLY[4]	26 wks	PVR, 6-MWD	185
Ambrisentan	ARIES-1[5,6]	12 wks	6-MWD	202
	ARIES-2[5,7]	12 wks	6-MWD	192
Sildenafil	SUPER-1[8]	12 wks	6-MWD	277
Tadalafil	PHIRST[9]	16 wks	6-MWD	405
Macitentan	**SERAPHIN[10]**	**96 wks***	**Time to first morbidity/mortality event**	**742**

1. Channick RN, *et al*. *Lancet* 2001. 2. Badesch D, *et al*. *Curr Ther Res* 2002. 3. Rubin LJ, *et al*. *N Engl J Med* 2002. 4. Galiè N, *et al*. *Lancet* 2008. 5. Galiè N, *et al*. *Circulation* 2008. 6. Oudiz R, *et al*. *Chest* 2006. 7. Oudiz RJ, *et al*. *J Am Coll Cardiol* 2009. 8. Galiè N, *et al*. *N Engl J Med* 2005. 9. Galiè N, *et al*. *Circulation* 2009. 10. www.clinicaltrials.gov, NCT00660179.

*Mean study drug exposure

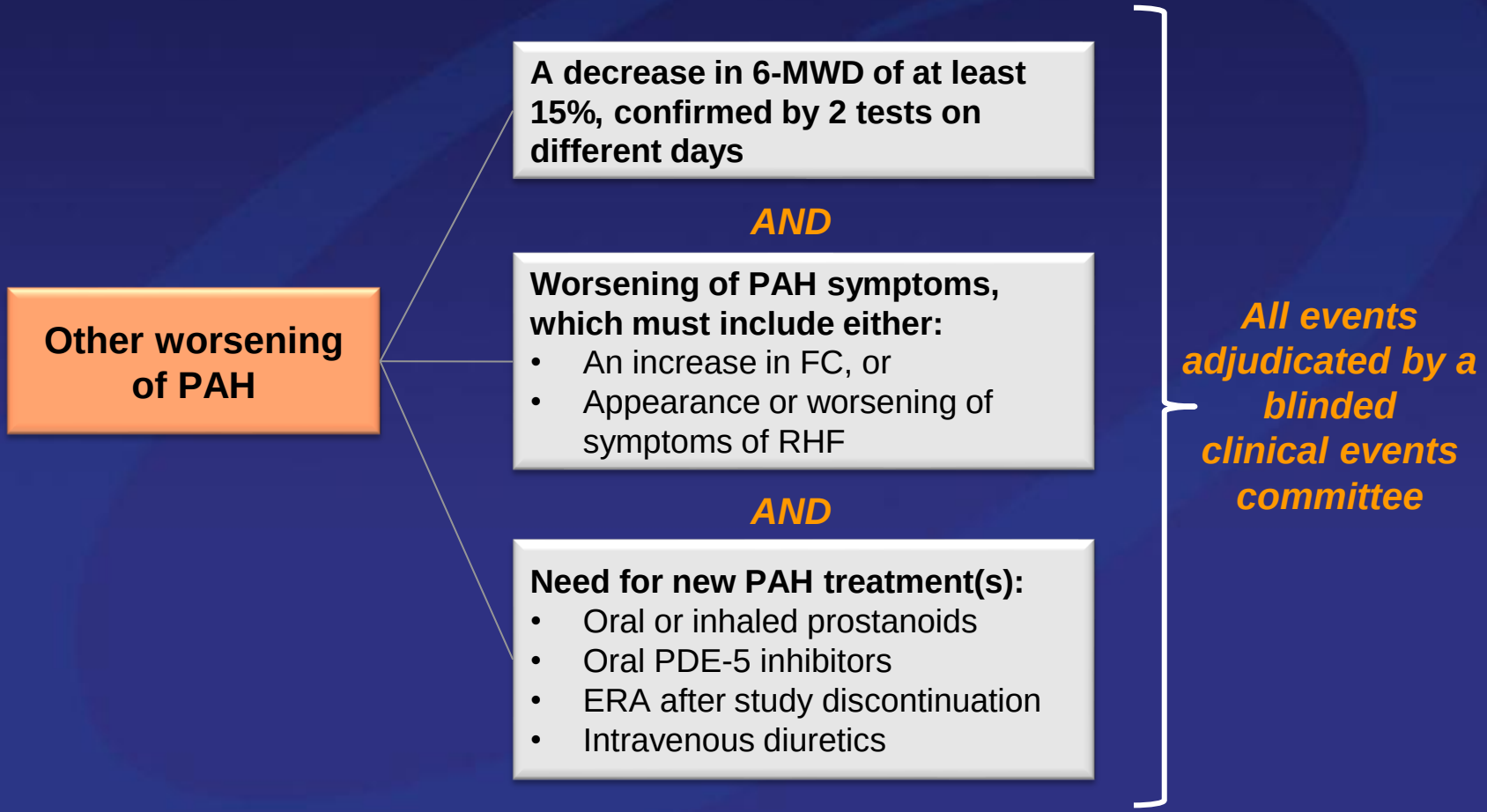
SERAPHIN morbidity and/or mortality primary endpoint



- Robust nature of the primary endpoint = only clinically relevant events are captured
- Morbidity/mortality as primary endpoint is considered more clinically relevant as it reflects the true progression of PAH

Pulido T et al. NEJM 2013; 369:809-18

SERAPHIN primary endpoint: Other worsening of PAH



Pulido T et al. NEJM 2013; 369:809-18

Summary

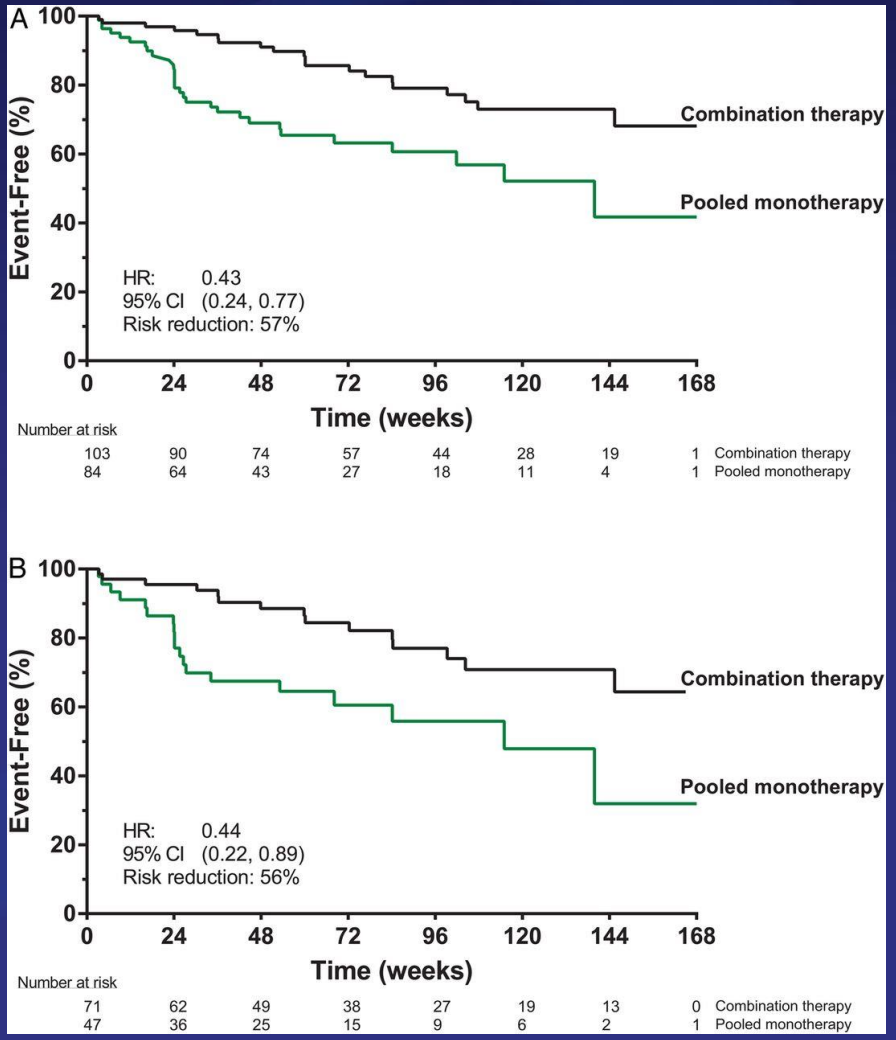
- Macitentan also significantly improved clinically important secondary endpoints including 6-MWD,
  WHO FC and hospitalization

- There was no mortality benefit.

Combination therapy with a PDE-5 and a Endothelin Receptor Antagonist

- Oral
  - **Tadalafil (Adcirca)**
  - **Ambrisentan (Letairis)**

Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial

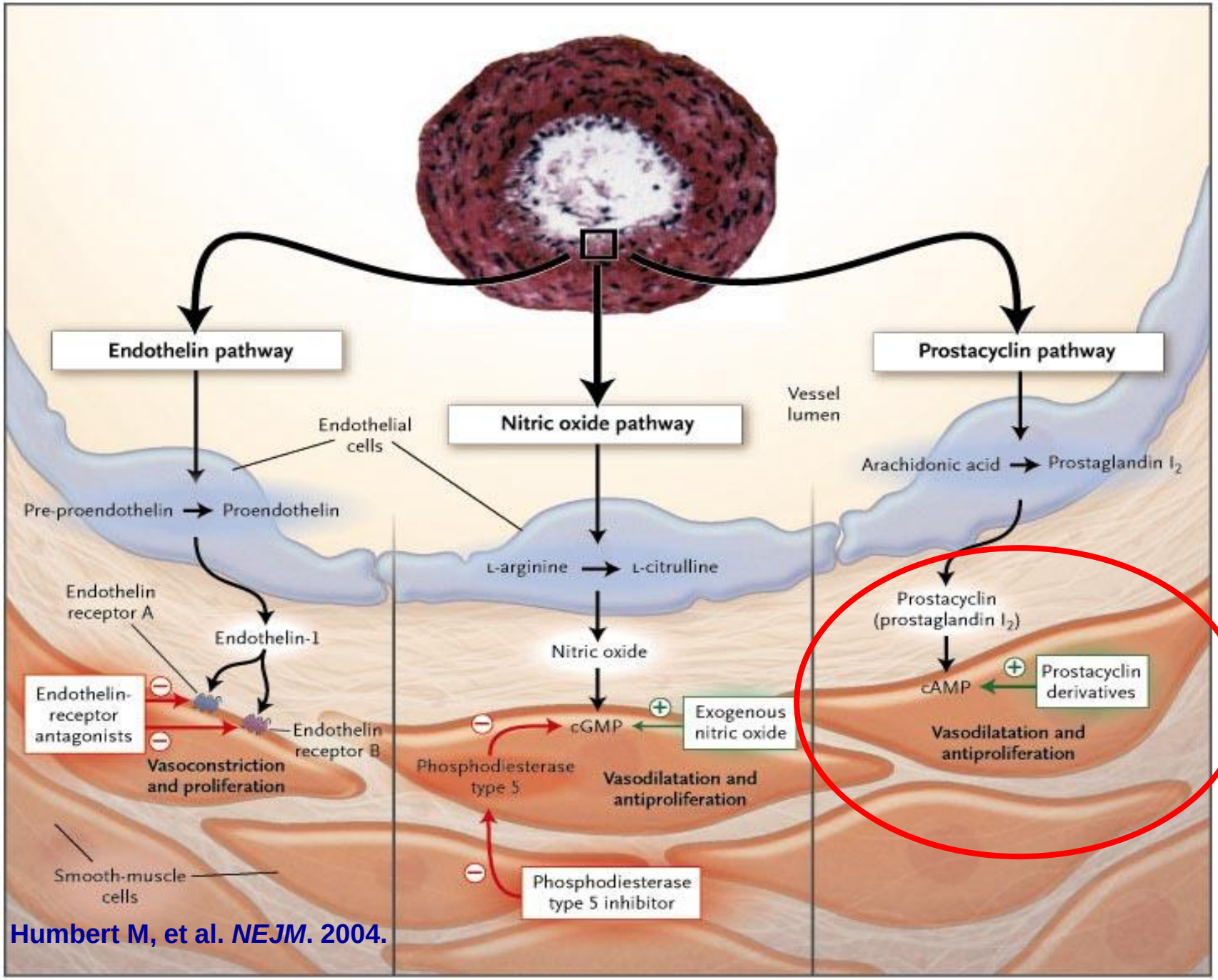


***FDA approved**

Prostacyclins

- Intravenous (epoprostenol, treprostinil)
- Subcutaneous (treprostinil)
- Inhaled (iloprost, treprostinil)
- Oral (selexipag, treprostinil)

*FDA approved



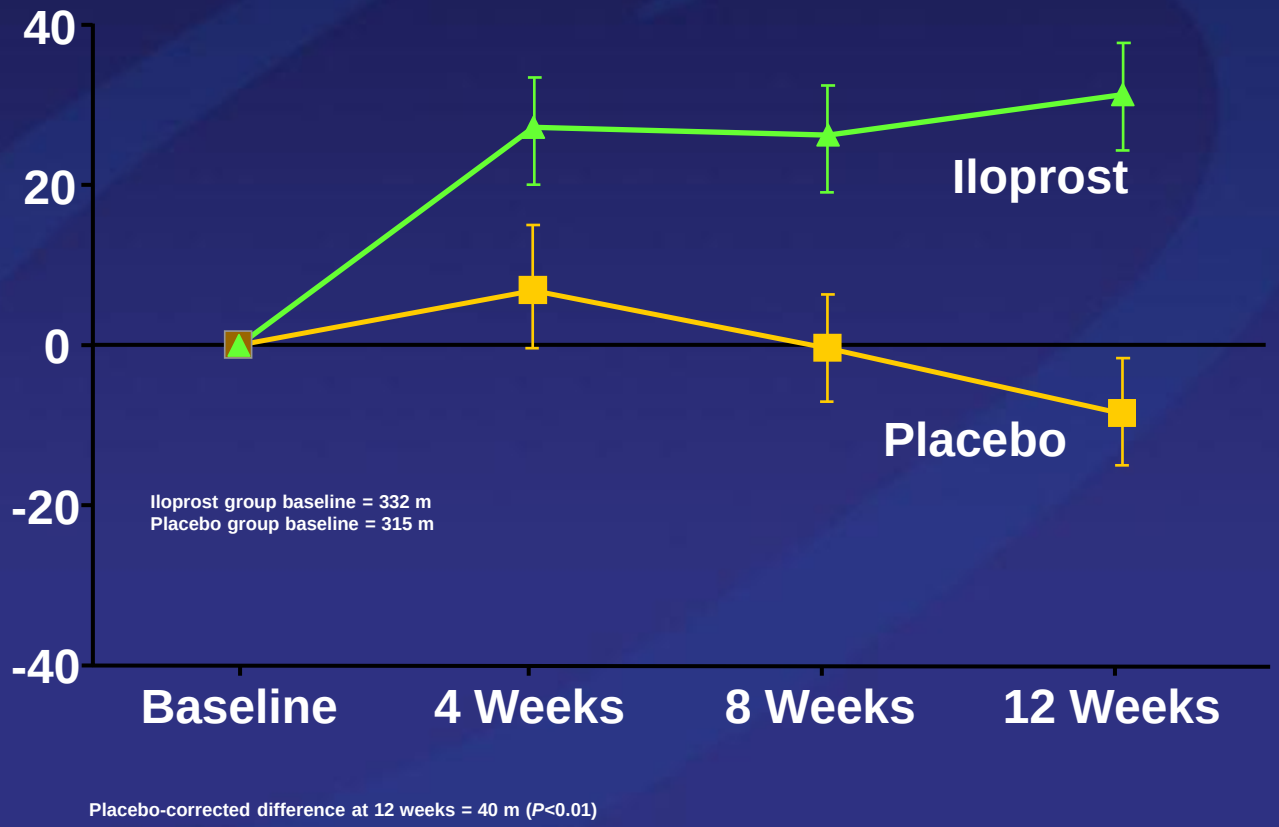
Humbert M, et al. *NEJM*. 2004.

Ventavis® (iloprost) Inhalation Solution:
Dosage and Administration

- Indicated for inhalation via the Prodose® AAD® system only
- 2.5 mcg initial dose
  - increase to 5 mcg if 2.5 mcg dose is tolerated
  - maintain at maximum tolerable dose (2.5 mcg or 5 mcg)
- 6-9 inhalations daily during waking hours; 8-10 minutes each

Inhaled Iloprost: Change in 6MWD in PAH Patients

Mean (± SEM) absolute change vs baseline (m) 30 minutes postinhalation



Placebo-corrected difference at 12 weeks = 40 m (*P*<0.01)

Olschewski H, et al: *N Engl J Med.* 2002;347:322.

Uptravi® - Selexipag Clinical Application

- Indications:
  - Treatment of pulmonary arterial hypertension (PAH), WHO Group I, to delay disease progression and reduce risk of hospitalization for PAH
- Place in therapy:
  - As monotherapy or in combination with other classes of PAH medications

Uptravi® [package insert].

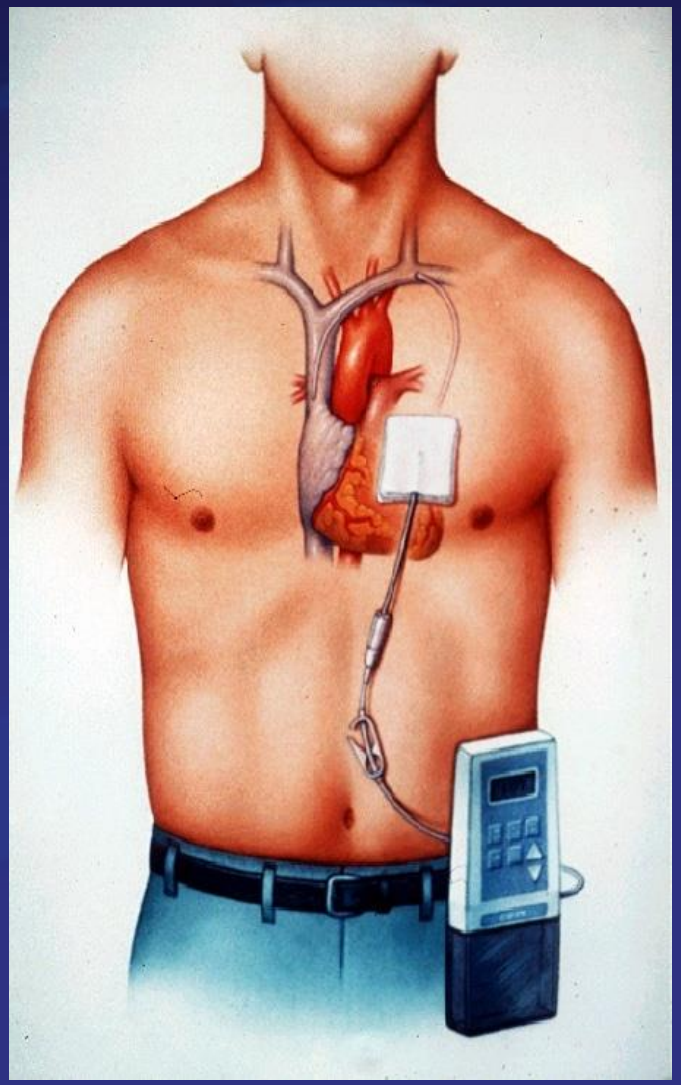
Uptravi® - Selexipag Literature Review

- Conclusions:
  - Selexipag lowers complication related to PAH vs. placebo (Hospitalization or disease progression)
  - No difference in mortality between groups
  - Addition of selexipag to baseline regimen of two meds gave benefits consistent with overall treatment effect
  - Similar efficacy regardless of dose range

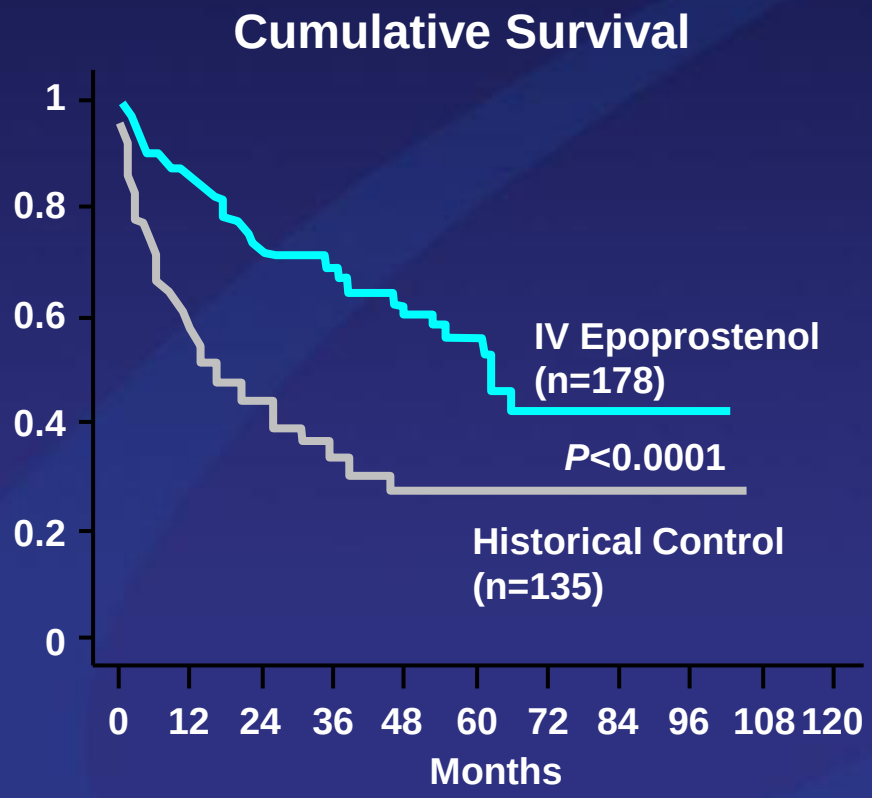
Sitbon O, et al. N Engl J Med. 2015;373(26):2522-33.

Epoprostenol

- Synthetic salt of prostacyclin
- Rapid efficacy; short, 3- to 5-min half-life
- Approved for Class III and IV
- Invasive: requires continuous IV infusion
- Individualized dosing regimen required
- Two RCTs showing efficacy



Long-term Outcome in IPAH With Epoprostenol



No. at risk:

178	129	85	57	36	21	7	3	1	IV Epoprostenol
135	59	34	20	11	4	2	2	1	Historical Control

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

Prostanoid Side Effects

- Flushing
- Headache
- Diarrhea, nausea, vomiting
- Jaw pain
- Leg pain
- Hypotension
- Dizziness
- Syncope
- Cough (inhaled)
- Delivery site complications

Vary according to drug and route of delivery

The Real Cost of PAH Drugs

- History of expensive PAH drugs
  - IV epoprostenol/SC treprostinil: ~ $90,000/year
  - Bosentan: ~ $80,000/year
  - Ambrisentan: ~ $80,000/year
  - Oral treprostinil
    - ~ $500,000/year [12 mg, three times daily → patients transitioning from parenteral treprostinil (ongoing trial[c])]
    - Compared with placebo: improved 6MWD, Borg dyspnea score (intent-to-treat population → 26.0 m; *P* = .0001)[d]

a. McLaughlin VV, et al. *Circulation*. 2009;119:2250-2294[11]; b. Frumkin LR, et al. *Pharmacol Rev.* 2012;64(3):583-620.[12]; c. White RJ, et al. ATS 2013. Abstract B64.[13]; d. Jing ZC, et al. *Circulation*. 2013;127:624-633[14]

Longitudinal Evaluation

Stable; no increase in symptoms and/or decompensation	Clinical course	Unstable; increase in symptoms and/or decompensation
Every 3-6 months	Frequency of evaluation	Every 1-3 months
Every clinic visit	Functional class assessment	Every clinic visit
Every clinic visit	6MW distance	Every clinic visit
Every 12 months or center dependent	Echocardiography	Every 6-12 months or center dependent
Center dependent	BNP	Center dependent
Clinical deterioration and center dependent	Right heart catheterization	Every 6-12 months or clinical deterioration

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

Case Studies

Case Study

Paul is a 66 year old male who presented to his primary care physicians office with complaints of cough, increased fatigue and dyspnea on exertion. Past medical history includes hypertension, smoking and osteoarthritis. He had a recent Cardiolite stress test which was negative. BP in office is 160/90. An echocardiogram was ordered.

Height 64 inches. Weight 275 lbs.

Physical Exam- III/VI SEM, 1+ lower extremity edema

Case Study

2D Echo results:

LVEF: 65%

Normal RV function

Stage I diastolic dysfunction

Mild LVH

Mild biatrial chamber size enlargement

Normal left and right ventricular size

Severe tricuspid regurgitation

RVSP 60 mmHg

Case Study

Based on the initial presentation and echocardiogram your next step would be as follows?

A. No further testing or treatment is indicated
B. Start on oral diuretics
C. Set up for a PFT, VQ Scan and Sleep Study
D. Place on anti-hypertensive medications
E. Set up for a Right Heart Cath

Case Study

You decided to place Paul on HCTZ 25 mg and lisinopril 5 mg daily. He returns one month later with continued dyspnea. BP in office is improved at 138/80.

Given RVSP of 60 mmHg a sleep study, PFT was performed, both of which were severely abnormal. Patient was treated with a CPAP and treatments for COPD. Symptoms improving.

An Echocardiogram was performed in 12 months demonstrating an RVSP of 48 mmHg with normal LV/RV function.

Patient continued medical therapy.

Case Study

Britney is a 26 year old female who presented to her primary care physician's office with complaints of cough, increased fatigue and dyspnea on exertion which has been worsening over the past 1 year. She now c/o SOB at rest. No previous significant past medical history. Was seen by her PCP and placed on an inhaler and steroids. BP in office is 110/70. An echocardiogram was ordered.

Height 64 inches. Weight 145 lbs.

Physical Exam- III/VI SEM

1+ lower extremity edema

Case Study

2D Echo results:

LVEF: 65%

Reduced RV function

Severe right atrial and ventricular size

Severe tricuspid regurgitation

Small pericardial effusion

RVSP 60 mmHg

Case Study

Based on the initial presentation and echocardiogram your next step would be as follows?

A. No further testing or treatment is indicated
B. Start on oral diuretics
C. Set up for a PFT, VQ Scan and Sleep Study
D. Place on anti-hypertensive medications
E. Set up for a Right Heart Cath

Case Study

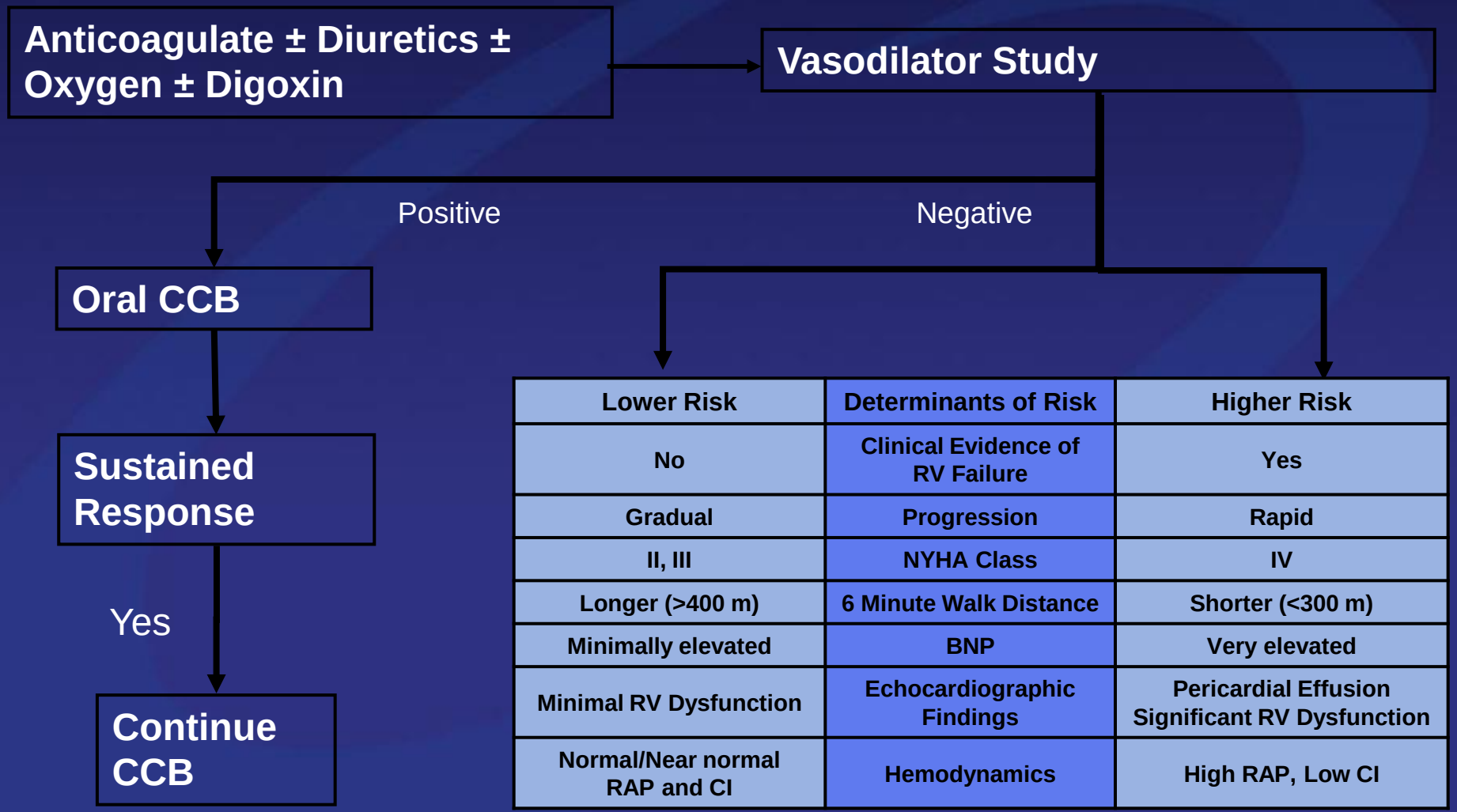
You decided to set up patient with a right heart cath.

Findings:

mPAP- 56, PAOP- 6. CO 2 L/m, negative NO vasodilator study

You diagnose patient with severe pulmonary hypertension.

What is the Optimal Treatment Strategy?



Lower Risk	Determinants of Risk	Higher Risk
No	Clinical Evidence of RV Failure	Yes
Gradual	Progression	Rapid
II, III	NYHA Class	IV
Longer (>400 m)	6 Minute Walk Distance	Shorter (<300 m)
Minimally elevated	BNP	Very elevated
Minimal RV Dysfunction	Echocardiographic Findings	Pericardial Effusion Significant RV Dysfunction
Normal/Near normal RAP and CI	Hemodynamics	High RAP, Low CI

McLaughlin VV and McGoon M. *Circulation*. 2006;114:1417-1431.

Case Study

You perform a 6 MWT in the office and she is able to walk 250 meters

Based on her echo, RHC and clinical findings you refer her for IV epoprostenol therapy.

In the meantime, laboratory studies are ordered to exclude CTD, HIV, liver disease, etc.

Case Study

Agnes is a 96 year old female smoker who presented to her primary care physician's office with complaints of cough, increased fatigue and dyspnea on exertion. Past medical history includes hypertension, smoking x 70 years and osteoarthritis. She had a recent Cardiolite stress test which was negative. BP in the office is 140/800. An echocardiogram was ordered.

Height 64 inches. Weight 175 lbs.

Physical Exam- III/VI SEM, 1+ lower extremity edema

Case Study

2D Echo results:

LVEF: 65%

Reduced RV function

Stage I diastolic dysfunction

Mild LVH

Mild biatrial chamber size enlargement

Mild right ventricular enlargment

Severe tricuspid regurgitation

RVSP 60 mmHg

Case Study

Based on the initial presentation and echocardiogram your next step would be as follows?

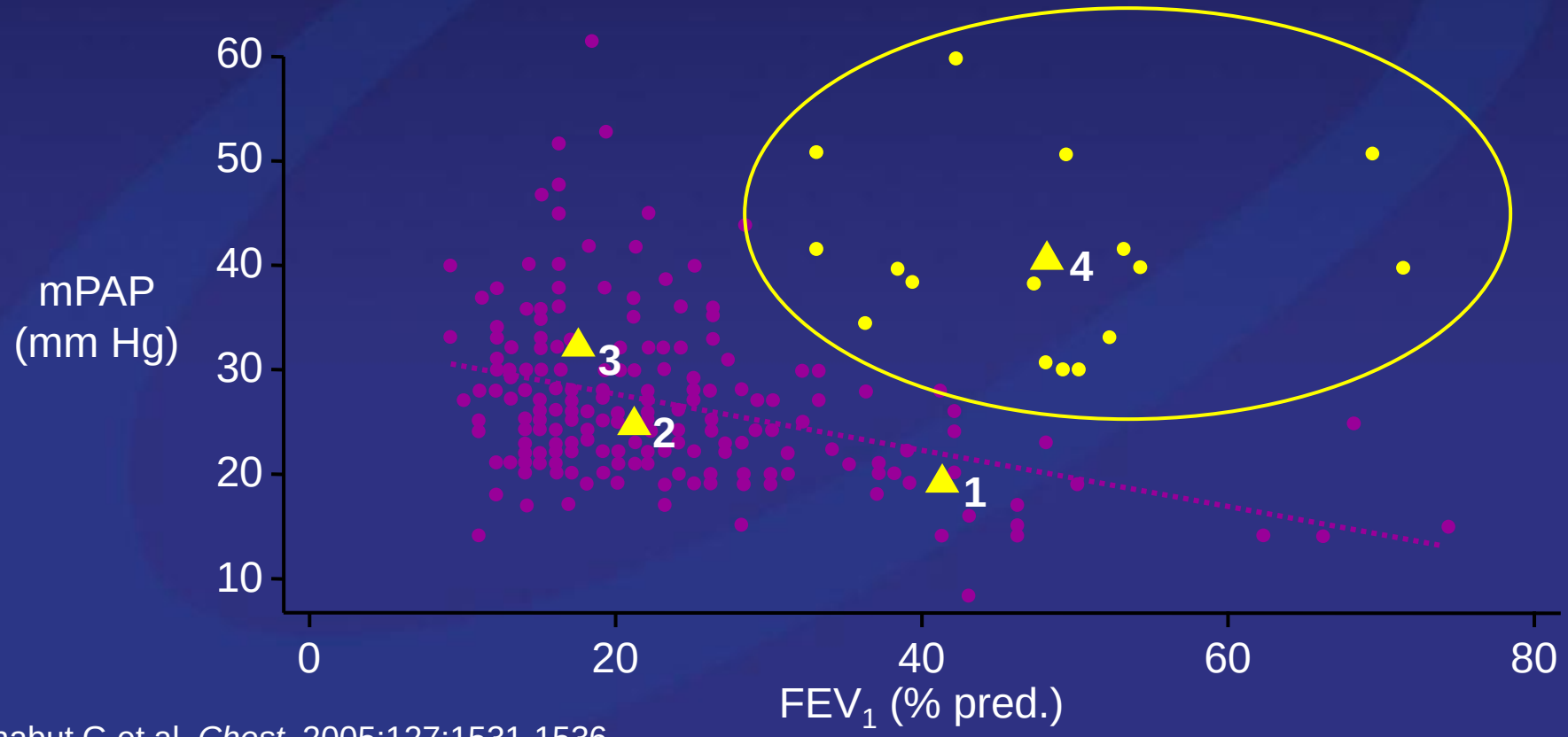
A. No further testing or treatment is indicated
B. Start on oral diuretics
C. Set up for a PFT, VQ Scan and Sleep Study
D. Place on anti-hypertensive medications
E. Set up for a Right Heart Cath

Case Study

No further workup for her pulmonary hypertension is warranted given her age and unlikely nature it would be from PAH.

COPD and PH

- Retrospective study of 215 COPD patients
- 13% had a PA mean >35 mm Hg
- Correlated best (inversely) with PaO2
- A small number had only moderate obstruction: treatable sub-group?



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

Case Study

Denise is a 46 year old female who presented to her primary care physicians office with complaints of cough, increased fatigue and dyspnea on exertion. Past medical history includes hypertension, smoking and scleroderma. She had a recent Cardiolite stress test which was negative. BP in office is 130/80. An echocardiogram was ordered.

Height 64 inches. Weight 195 lbs.

Physical Exam- III/VI SEM

1+ lower extremity edema

Case Study

2D Echo results:

LVEF: 65%

Normal RV function

Stage I diastolic dysfunction

Mild LVH

Mild biatrial chamber size enlargement

Normal left and right ventricular size

Severe tricuspid regurgitation

RVSP 60 mmHg

Case Study

Based on the initial presentation and echocardiogram your next step would be as follows?

A. No further testing or treatment is indicated
B. Start on oral diuretics
C. Set up for a PFT, VQ Scan and Sleep Study
D. Place on anti-hypertensive medications
E. Set up for a Right Heart Cath

Case Study

Given her symptoms and history of scleroderma a comprehensive evaluation is performed including:

- PFT with DLCO
- Sleep Study
- VQ Scan

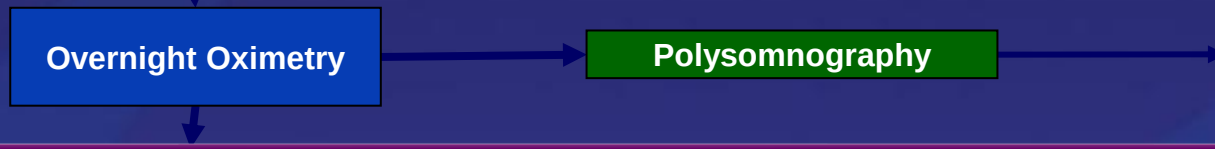
PFT was normal with abnormal DLCO. Moderate obstructive sleep apnea, normal VQ Scan

Patient continues to have SOB. Given this you decide to proceed with a RHC.

Findings: mPAP 42 mmHg, PAOP 19 mmHg, Normal CO/CI

Pivotal Tests | Contingent Tests | Contribute to Assessment of:

- 17% (37/220) of patients with OSA have daytime mPAP >20 mm Hg *Chaouat A et al. Chest. 1996;109:380-386.*
  - 16 had mPAP >25 mm Hg; only 2 had mPAP >35 mm Hg
  - Marked ↑ with sub-max exercise (mean mPAP 47 mm Hg) – in part due to ↑ PCWP
  - Contributing factors: obesity, hypoxemia, COPD



- In patients with OSA, ↓PAP reported in response to CPAP therapy

  See: *Somers VK et al. J Am Coll Cardiol. 2008;52:686-717.*

- Untreated – response to other treatment likely less effective

Case Study

Findings: mPAP 42 mmHg, PAOP 19 mmHg, Normal CO/CI

Given moderate sleep apnea and hypervolemia you decide to place on low dose Lasix and recommend CPAP with plans to repeat a RHC.

Treatment with CPAP and Lasix 3 months, feeling better but still SOB. RHC mPAP 35 mmHg, PAOP 15 mmHg, Normal CO/CI

Patient diagnosed with PAH WHO Group I out of proportion to underlying medical conditions and you place patient on a PDE-5 inhibitor followed by a ERA one month later.

Emerging Therapies

Reducing Hospitalizations
Impact of Current and Emerging Therapies

- Macitentan (ERA): SERAPHIN trial[a,b]
  - Included pts on macitentan mono- and combination therapy (PDE-5 inhibitors, oral or inhaled prostanoids, CCBs, l-arginine)
  - Macitentan reduced primary end point (composite of death, atrial septostomy, lung transplantation, initiation of treatment with IV or SC prostanoids, worsening PAH) by 30%-45% (dose dependent; *P* = .01; *P* < .001)
  - Reduced all-cause hospitalization by 32% (HR, 0.677; *P* = .0051)
- Ambrisentan (ERA) ± tadalafil (PDE-5 inhibitor) vs monotherapy: AMBITION Trial[c]
  - **Reduced clinical failure events by 50% (HR, 0.502; *P* = .0002); superior to each individual monotherapy (*P* < .01) → main treatment effect driven by hospitalizations**
- Selexipag (selective IP receptor agonist): GRIPHON top-line data[d]
  - **80% of pts receiving oral PAH therapy at onset**
  - **Reduced morbidity/mortality event vs placebo by 39% (*P* < .0001)**

a. Pulido T, et al. *N Engl J Med*. 2013;369:809-818[8]; b. Mehta S, et al. ATS 2014. Abstract B17[9]; c. Galiè N, et al. ERS 2014. Abstract 2916[6]; d. Actelion press release.[10]

Final Thoughts

- Comprehensive history and physical is foundation for diagnosis
- Noninvasive screening as indicated
- Treat any identified factor(s) that could contribute to or exacerbate pulmonary hypertension
- Invasive hemodynamics are crucial
- Refer early

Thank You!

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- 1. Taylor B, Rumbak M, Taylor SP, Solomon D. Early versus delayed right heart catheterization in evaluation of pulmonary arterial hypertension. *J Heart Lung* Transplant. 2013;32:137-138.

- 2. Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: 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 of Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2009;30:2493-2537.

- 3. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126(1 suppl):14S-34S.

- 4. Burger CD, Long PK, Shah MR, et al. Characterization of first-time hospitalizations in patients with newly diagnosed pulmonary arterial hypertension in the REVEAL registry. *Chest*. 2014;146:1263-1273.

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- 5. Johnson S, Delate T, Boka A, et al. Characterizing the financial burden of pulmonary arterial hypertension within an integrated healthcare delivery system. *J Med Econ*. 2013;16:1414-1422.

- 6. Galiè N. The AMBITION study: design and results. Presented at: 2014 European Respiratory Society Annual Meeting; June 9-14, 2014; Munich, Germany. Abstract 2916.

- 7. McGoon MD, Kane GC. Pulmonary hypertension: diagnosis and management. *Mayo Clin Proc*. 2009;84:191-207.

- 8. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369:809-818.

- 9. Mehta S, Delcroix M, Galiè N, et al. Macitentan reduced all-cause hospitalizations in patients with pulmonary arterial hypertension: data from the randomized controlled SERAPHIN trial. Presented at: 2014 American Thoracic Society Annual Meeting; May 16-21, 2014; San Diego, CA. Abstract A2458.

References (cont)

- 10. Actelion press release. Selexipag meets primary endpoint in pivotal phase III GRIPHON outcome study in patients with pulmonary arterial hypertension. http://www1.actelion.com/en/our-company/news-and-events.page?newsId=1793163. Accessed December 15, 2014.

- 11. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation*. 2009;119:2250-2294.

- 12. Frumkin LR. The pharmacological treatment of pulmonary arterial hypertension. *Pharmacol Rev*. 2012;64(3):583-620.

- 13. Jing ZC, Parikh K, Pulido T, et al. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized, controlled trial. *Circulation*. 2013;127:624-633.

References (cont)

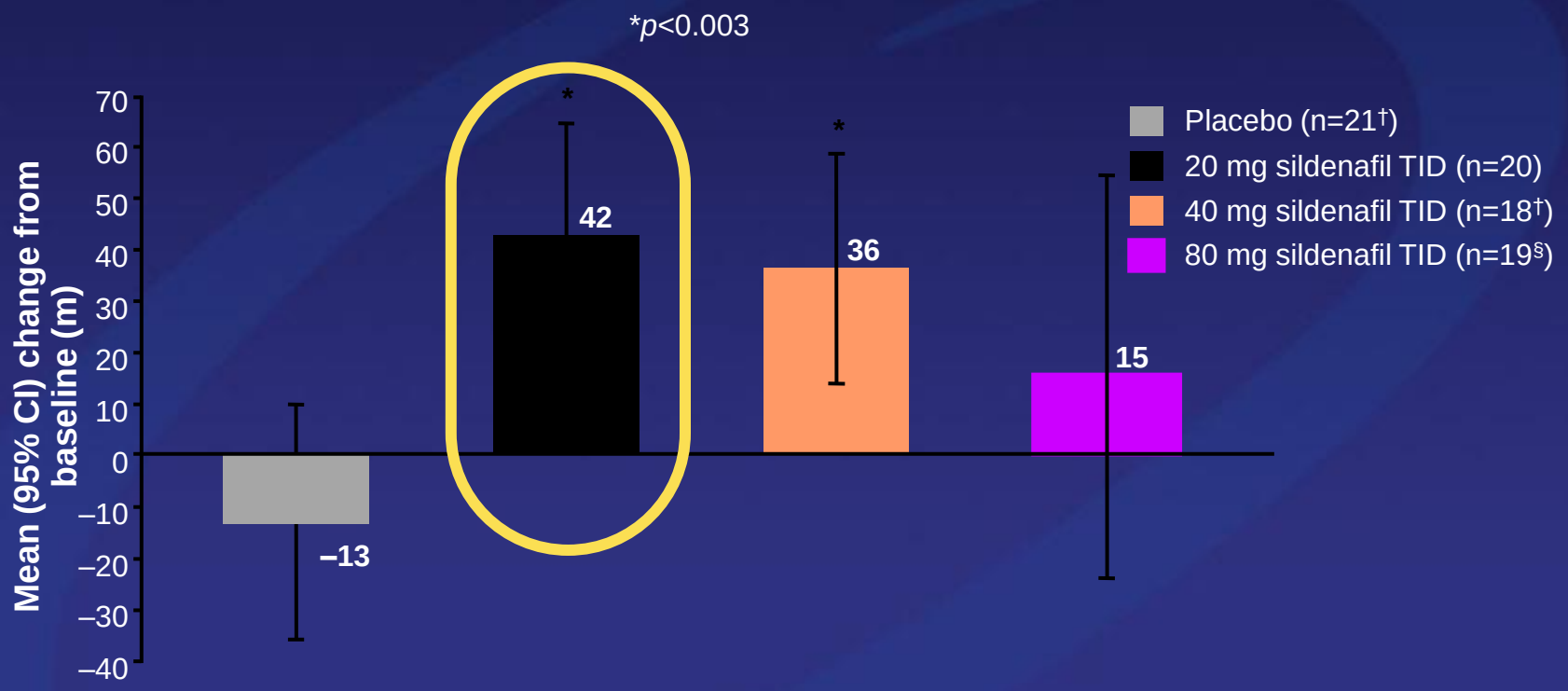
•14. White RJ, Chakinala MM, Mathier M, et al. Safety and tolerability of transitioning from parenteral treprostinil to oral treprostinil in patients with pulmonary arterial hypertension. Presented at: 2013 American Thoracic Society Annual Meeting; May 17-23, 2013; Philadelphia, PA. Abstract A3303.

•15. Ghofrani HA, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2013;369:330-340.

•16. Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med*. 2013;369:319-329.

•17. Walker T. FDA approves first drug to treat two forms of pulmonary hypertension. Drug Topics. October 10, 2013. http://drugtopics.modernmedicine.com/drug-topics/content/clinical/clinical-pharmacology/fda-approves-first-drug-treat-two-forms-pulmonary?page=full. Accessed December 15, 2013.

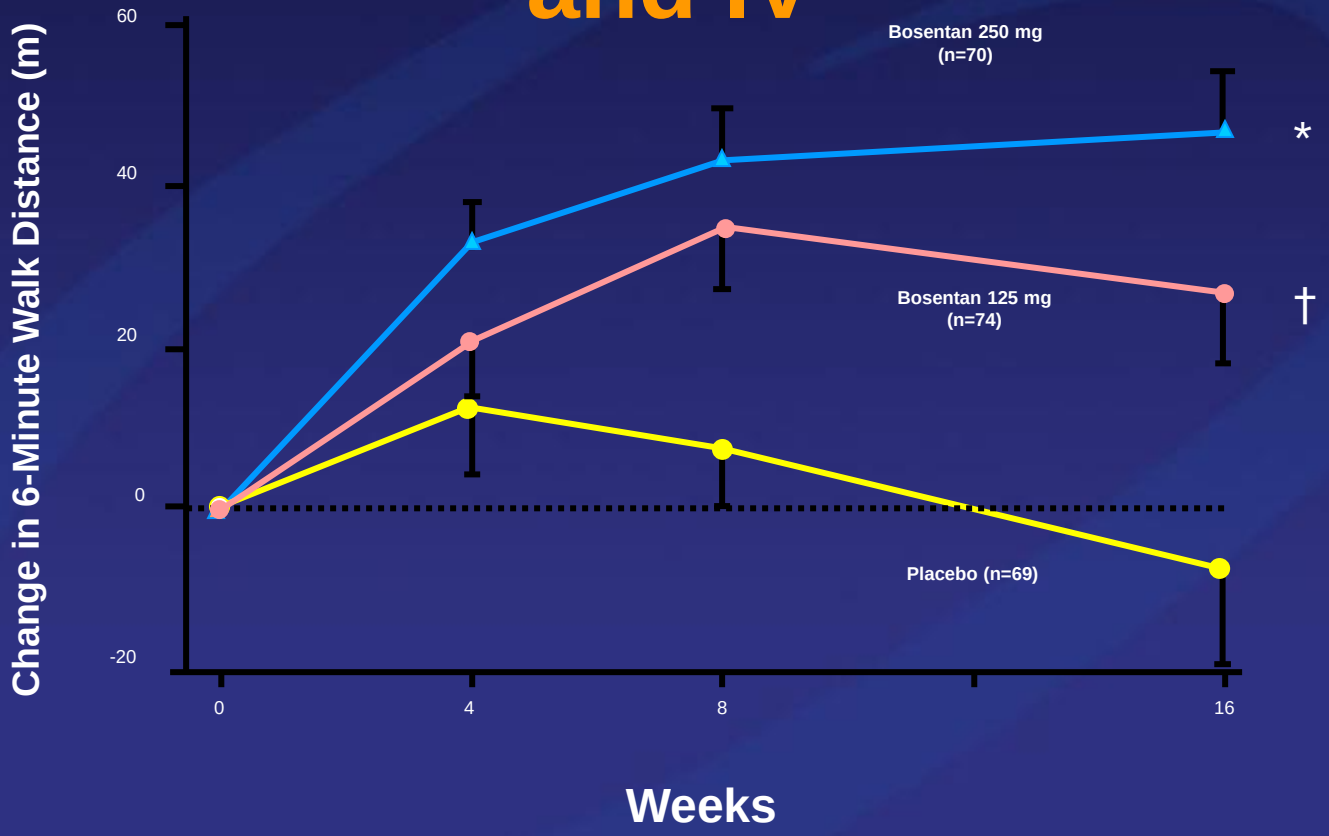
SUPER-1: improvements in 6MWD with sildenafil in PAH-CTD patients



†Patients without baseline 6MWD: 1 in placebo group and 2 in 40 mg group; §2 patients discontinued due to adverse events after 4-week evaluation

Badesch DB, *et al*. *J Rheumatol* 2007;34:2417–22.

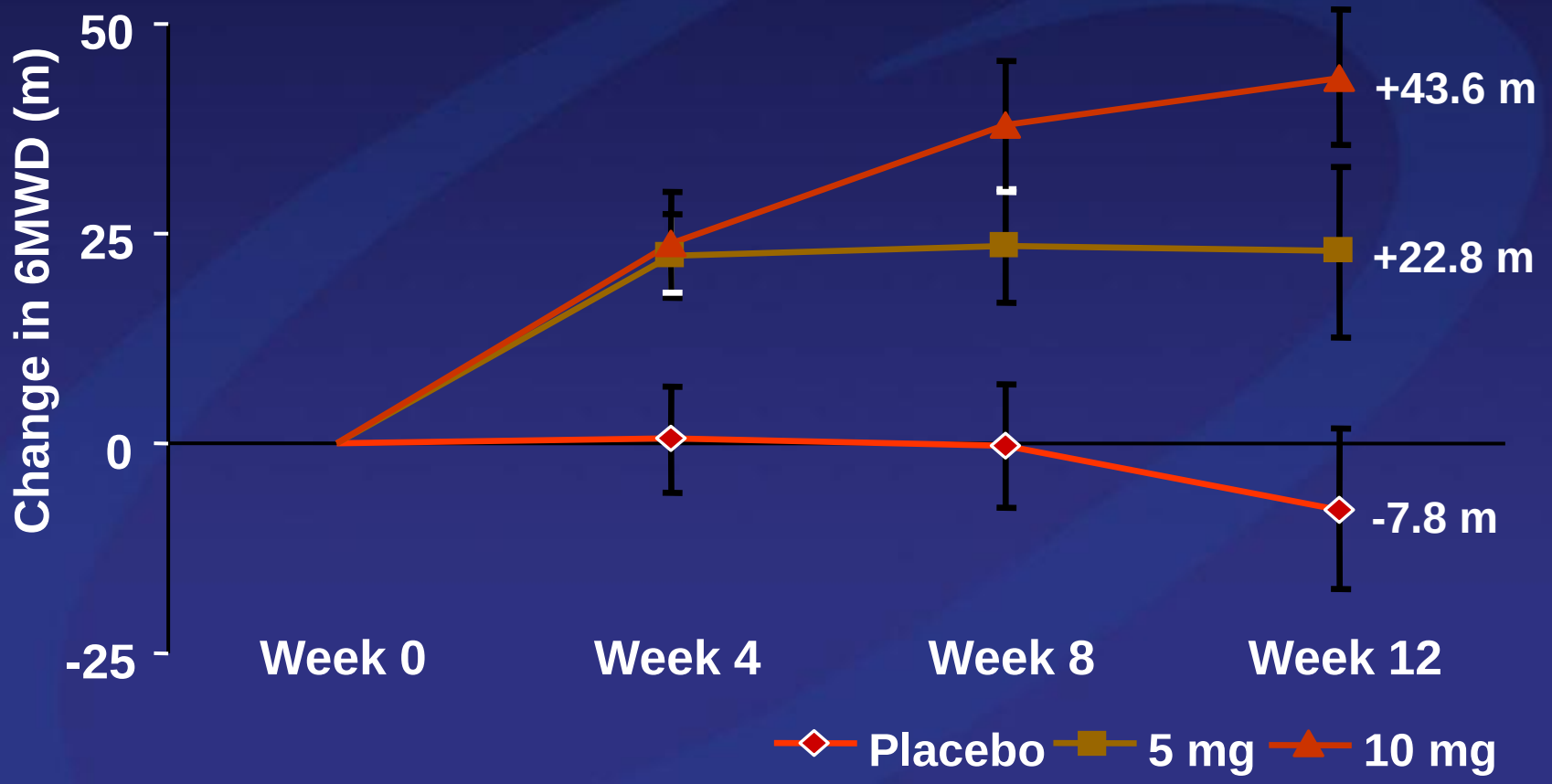
BREATHE-1: Impact of Bosentan on 6-Minute Walk Distance in WHO Classes III and IV



*P<0.001 vs placebo. †P<0.01 vs placebo.

Rubin LJ, et al. *N Engl J Med*. 2002;346:896-903.

Ambrisentan ARIES-1 Primary Endpoint: Change in 6MWD at Week 12



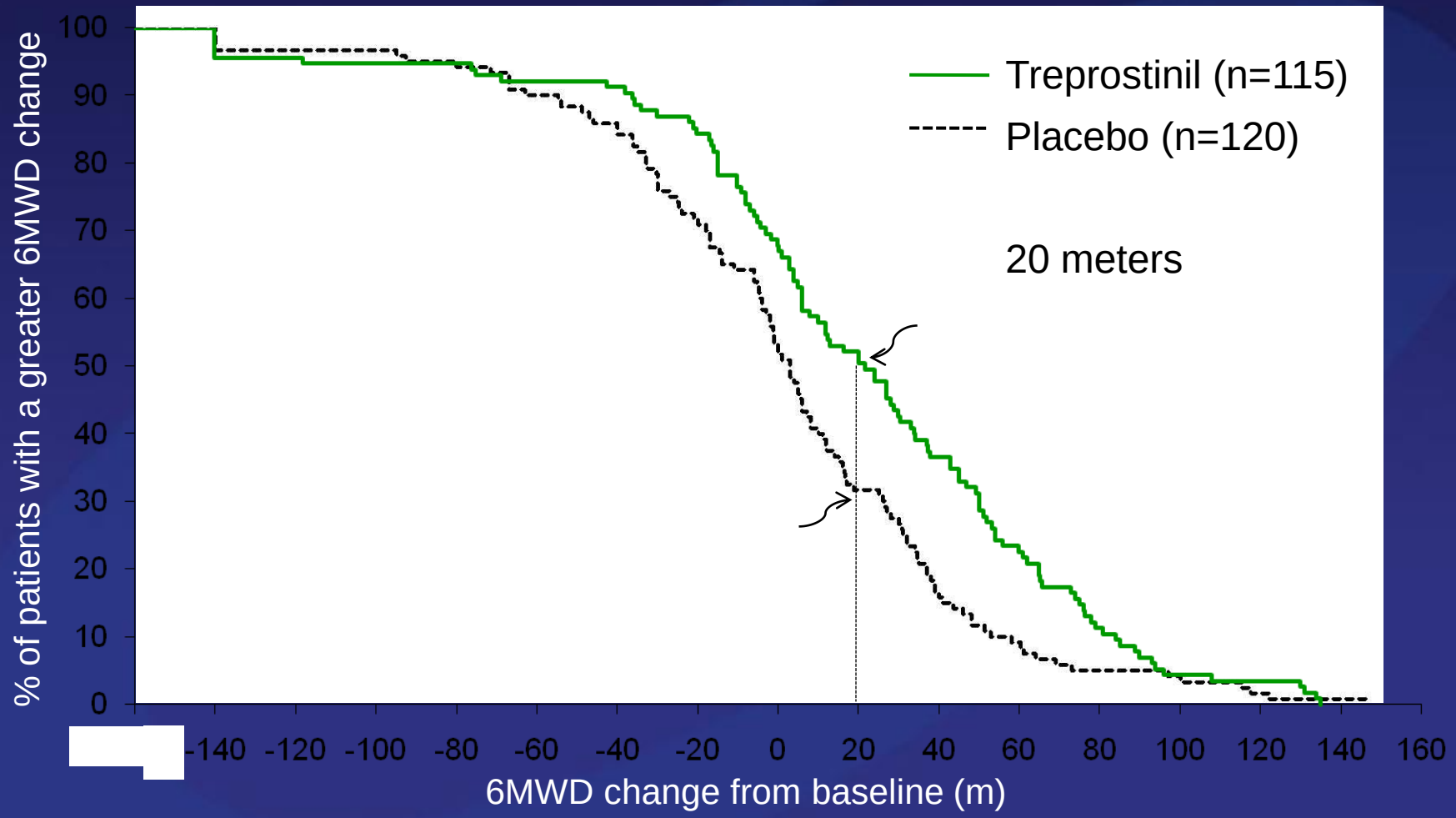
N=202.
Placebo-adjusted changes: 10 mg = +51.4 m (*P*=0.0001)
5 mg = +30.6 m (*P*=0.0084)

Oudiz RJ, et al. *Chest*. 2006;130:Abstract 121S.

Inhaled Treprostinil (Tyvaso)

- Inhaled prostacyclin
- Administered 4 times daily
- Proprietary nebulizer
- TRIUMPH study showed improvements in 6MWD

Inhaled Treprostinil Distribution of Changes in 6MWD

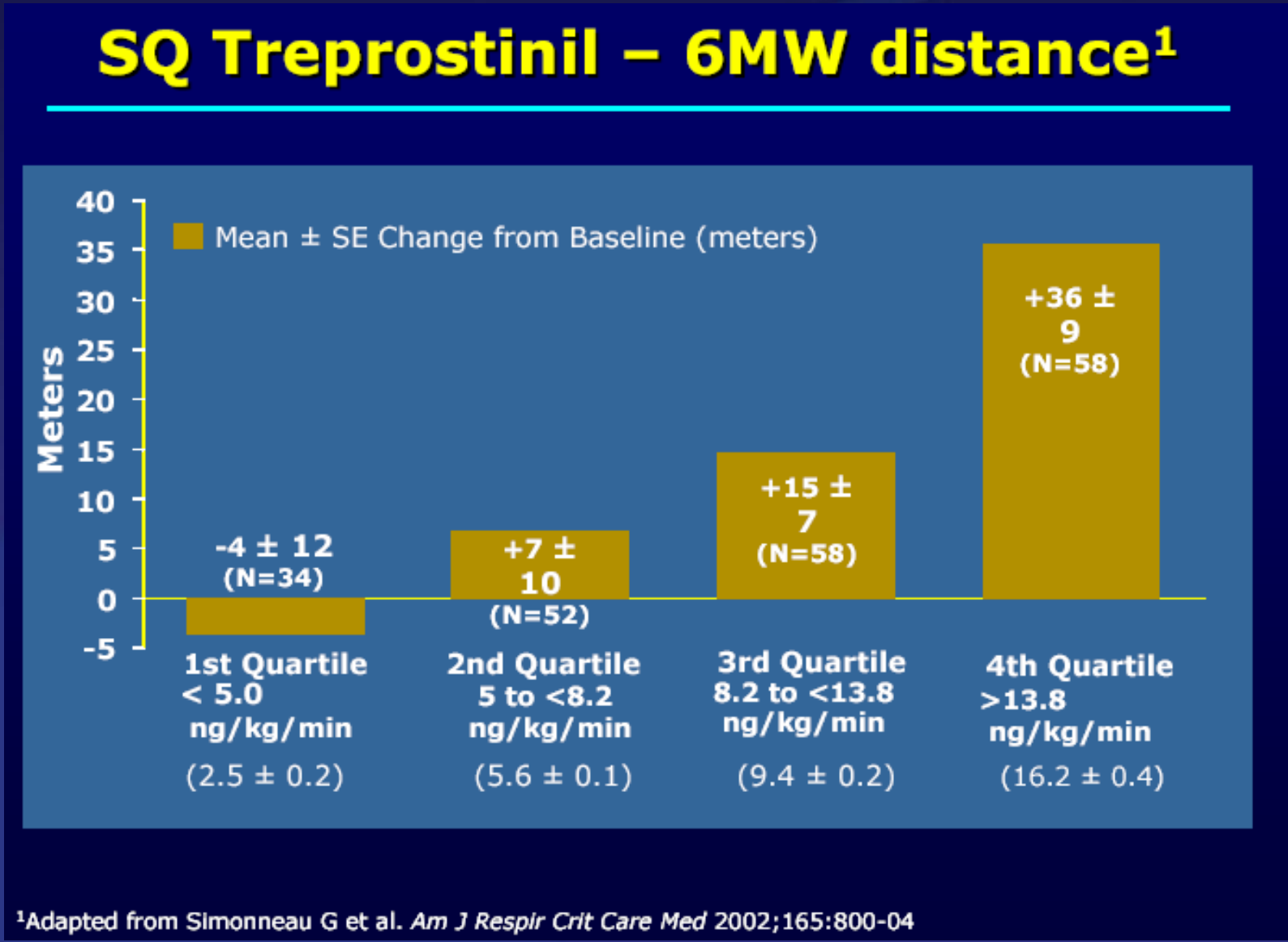


6MWD, 6-minute walk distance.

SC Treprostinil

- Requires capable patient
- Site pain is major impediment
  - Affects 85%
  - Local measures: ice, heat, lidocaine, capsaicin, collagenase ± effective
  - NSAIDs, narcotics, gabapentin ± effective

Treprostinil (Remodulin)



[1]Adapted from Simonneau G et al. *Am J Respir Crit Care Med* 2002;165:800-04

Adapted from Hill, N. NJ Fellows Conf in PAH 12/2/06