

# **Recent Advances in the Management of Pulmonary Arterial Hypertension**

**K T Prasad**

# Seminar outline

- ⌚ Introduction
- ⌚ Diagnosis
  - Changes in the recent definition/classification
  - Alternatives to RHC for the diagnosis of PAH
- ⌚ Treatment
  - Specific therapies for PAH
  - Role of combination therapy
  - Status of emerging therapies
- ⌚ Prognosis and prognosis assessment tools
- ⌚ Management algorithm

# Disease burden

- ⌚ Prevalence: 15–50 patients per million population
- ⌚ Annual incidence: 2-7 cases per million population
- ⌚ No systematic data on prevalence/incidence from India

Humbert M et al. Am. J. Respir. Crit. Care Med. 173, 1023–1030 (2006)  
Peacock AJ et al. Eur. Respir. J. 30, 104–109 (2007)

# PAH Prevalence & Incidence

- ② **Pulmonary Arterial Hypertension in France. Results from a National Registry. Humbert M et al. Am. J. Respir. Crit. Care Med. 173, 1023–1030 (2006).** A total of 674 patients (mean  $\pm$  SD age,  $50 \pm 15$  yr; range, 18–85 yr) were entered in the registry. Idiopathic, familial, anorexigen, connective tissue diseases, congenital heart diseases, portal hypertension, and HIV-associated PAH accounted for 39.2, 3.9, 9.5, 15.3, 11.3, 10.4, and 6.2% of the population, respectively. The low estimates of prevalence and incidence of PAH in France were 15.0 cases/ million of adult inhabitants and 2.4 cases/million of adult inhabitants/yr. One-year survival was 88% in the incident cohort.
- ② **An epidemiological study of pulmonary arterial hypertension. Peacock AJ et al. Eur. Respir. J. 30, 104–109 (2007).** Using the linked Scottish Morbidity Record scheme, data from all adults aged 16–65 yrs admitted with PAH (idiopathic PAH, pulmonary hypertension associated with congenital heart abnormalities and pulmonary hypertension associated with connective tissue disorders) during the period 1986–2001 were identified. The annual incidence of PAH was 7.1 cases per million population. On December 31, 2002, there were 165 surviving cases, giving a prevalence of PAH of 52 cases per million population.

# **Definition & Classification**

# Old definition

- ⊙ Pulmonary arterial hypertension (PAH) was defined by
  - Mean PAP >25 mmHg at rest or >30 mmHg with exercise
  - PAWP ≤15 mmHg and
  - PVR >3 mmHg/L/min (Wood units)

# Definition

- ⊗ Pulmonary hypertension (PH) is defined as a resting mPAP  $\geq 25$  mmHg at right heart catheterization (RHC)
- ⊗ PAH is defined as a subgroup of PH with:
  - PAWP  $\leq 15$  mmHg (Pre-capillary PH)
  - Normal or reduced cardiac output
  - Absence of other causes of pre-capillary PH (PH due to lung diseases, chronic thromboembolic PH, or other rare diseases)

Badesch et al. J Am Coll Cardiol 2009;54:S55–66

ESC/ERS Guidelines. Galie N et al. European Heart Journal (2009)30, 2493–2537

# Why this cut-off?

- ④ Systematic review of 47 studies describing 72 healthy populations (1187 patients)
  - Normal resting mPAP:  $14 \pm 3.3$  mmHg
  - Upper limit of normal (ULN = Mean + 2SD): 20.6 mmHg

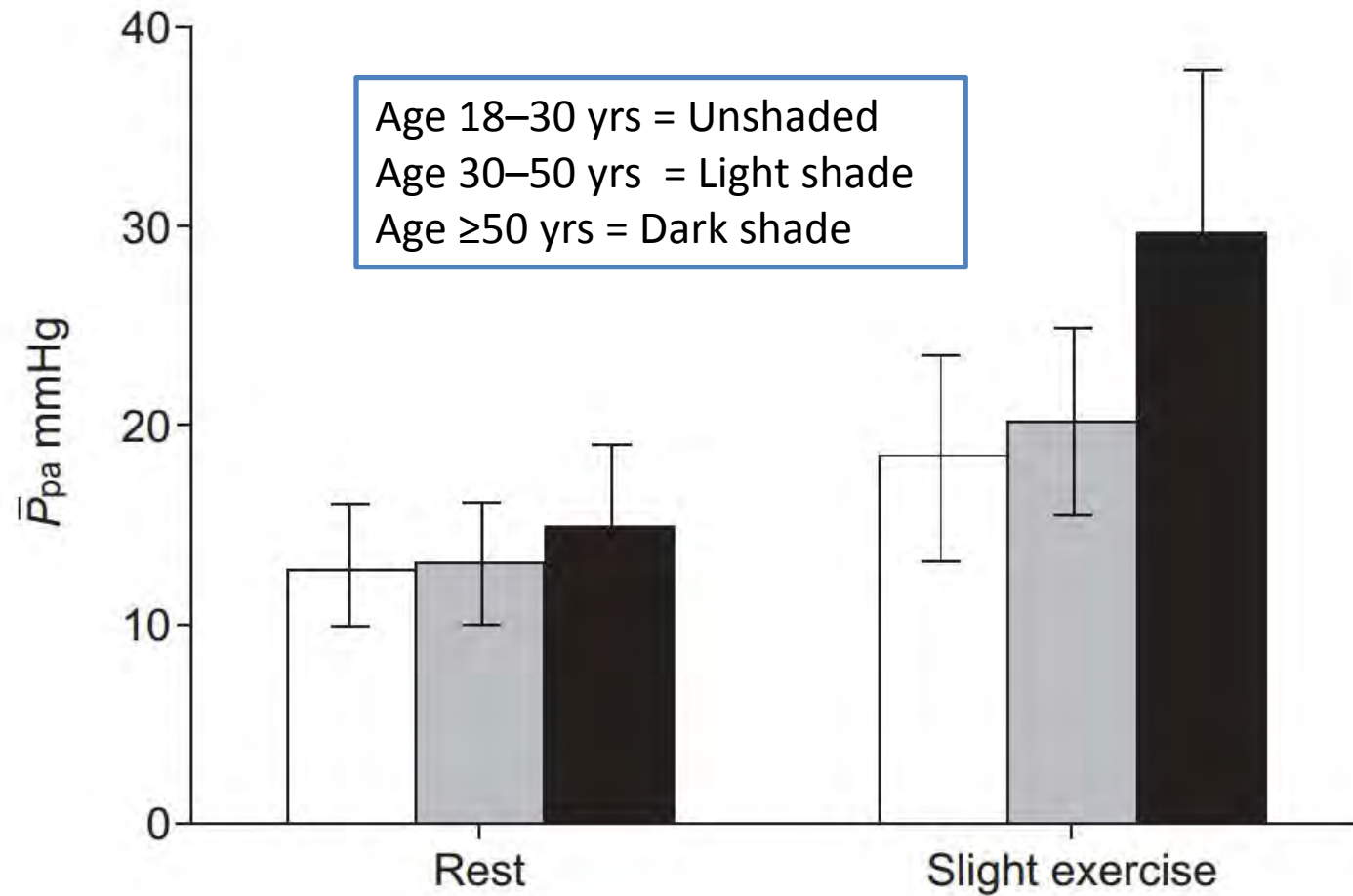
**mPAP 21-24 mmHg: Borderline PAH?**



# Why this cut-off? Explanation

- ⊙ During the 4th World Symposium on Pulmonary Hypertension, which took place in Dana Point, California, in early 2008, members of the Working Group on Diagnosis and Assessment of PAH reviewed the literature and identified 47 studies describing 72 healthy populations. The consequences of the findings by Kovacs et al. were intensively discussed at the Fourth World Symposium on Pulmonary Hypertension in Dana Point and it was decided to abandon the exercise criterion. With regard to the definition of PH at rest, it was proposed to introduce the term “**borderline PH**” for patients with  $\bar{P}_{pa}$  20–25 mmHg, but this term was eventually rejected, as it was felt that patients presenting with  $P_{pa}$  in this range should be further studied before being labelled with a diagnosis of PH. Thus, in the proceedings of the Dana Point meeting, the new haemodynamic definition of PH will be a  $\bar{P}_{pa}$  at rest  $\geq 25$  mmHg. (Source: Diagnosis and Assessment of Pulmonary Arterial Hypertension. Badesch et al. J Am Coll Cardiol 2009;54:S55–66, The new definition of pulmonary hypertension. Hoeper MM. Eur Respir J 2009; 34: 790–791)
- ⊙ If a threshold of 20.6 is used, one in 40 healthy people will be above this threshold, i.e. 25,000 per million population. (Source: The new definition of pulmonary hypertension. Hoeper MM. Eur Respir J 2009; 34: 790–791)

# Why was exercise cut-off (>30mmHg) eliminated?



## Why was exercise cut-off (>30mmHg) eliminated?

- ② mPAP at rest is virtually ***age-independent*** and rarely exceeds 20 mmHg
- ② mPAP at exercise is ***age-dependent*** and frequently exceeds 30 mmHg, especially in elderly individuals (>50 years)

Table 2

## Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)

### 1. Pulmonary arterial hypertension (PAH)

#### 1.1. Idiopathic PAH

#### 1.2. Heritable

##### 1.2.1. BMPR2

##### 1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)

##### 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 diseases

##### 1.4.5. Schistosomiasis

##### 1.4.6. Chronic hemolytic anemia

#### 1.5. Persistent pulmonary hypertension of the newborn

### 1'. Pulmonary veno-occlusive disease (PVOD) and hemangiomatosis (PCH)

### 2. Pulmonary hypertension owing to left heart disease

#### 2.1. Systolic dysfunction

#### 2.2. Diastolic dysfunction

#### 2.3. Valvular disease

### 3. Pulmonary hypertension owing to lung diseases and chronic hypoxemia

#### 3.1. Chronic obstructive pulmonary disease

#### 3.2. Interstitial lung disease

#### 3.3. Other pulmonary diseases with mixed restrictive and obstructive components

#### 3.4. Sleep-disordered breathing

#### 3.5. Alveolar hypoventilation disorders

#### 3.6. Chronic exposure to high altitude

#### 3.7. Developmental abnormalities

### 4. Chronic thromboembolic pulmonary hypertension

### 5. Pulmonary hypertension with unclear multifactorial origin

#### 5.1. Hematologic disorders: 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 on dialysis

### 1. Pulmonary arterial hypertension (PAH)

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#### 1.5. Persistent pulmonary hypertension of the newborn

### 1'. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

# History

- ⊙ The **first classification** was proposed in 1973 at an international conference on primary PH (PPH) endorsed by the **World Health Organization**. The initial classification designated only 2 categories, PPH or secondary PH, depending on the presence or absence of identifiable causes or risk factors.
- ⊙ Twenty-five years later, the **2nd World Symposium on PAH was held in Evian, France (1998)**. The “Evian classification” attempted to create categories of PH that shared pathologic and clinical features as well as similar therapeutic options. The term “secondary PH” was abandoned. This was a much broader, more encompassing classification, with 5 major categories; it allowed investigators to conduct clinical trials in a well-defined group of patients with a shared underlying pathogenesis.
- ⊙ The **3rd World Symposium on PAH was held in Venice, Italy**, 5 years after the Evian conference (2003). The most notable change was to abandon the term PPH in favor of IPAH); familial PAH if there is a family history of PAH; or associated PAH if another cause, such as connective tissue disease or HIV, is present. The other prominent change made at the Venice meeting was to move PVOD and PCH from separate categories into a single subcategory of PAH.
- ⊙ The **2008 4th World Symposium on PH was held in Dana Point, California**

## History (Contd.)

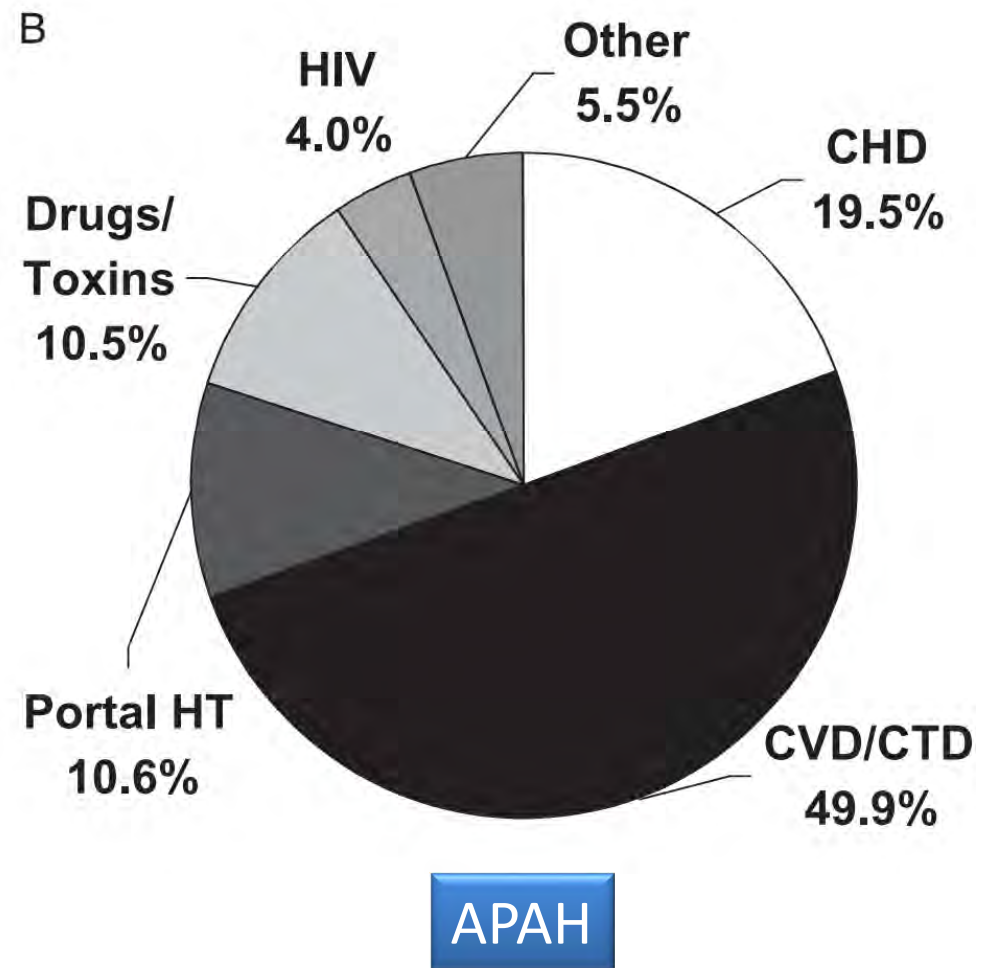
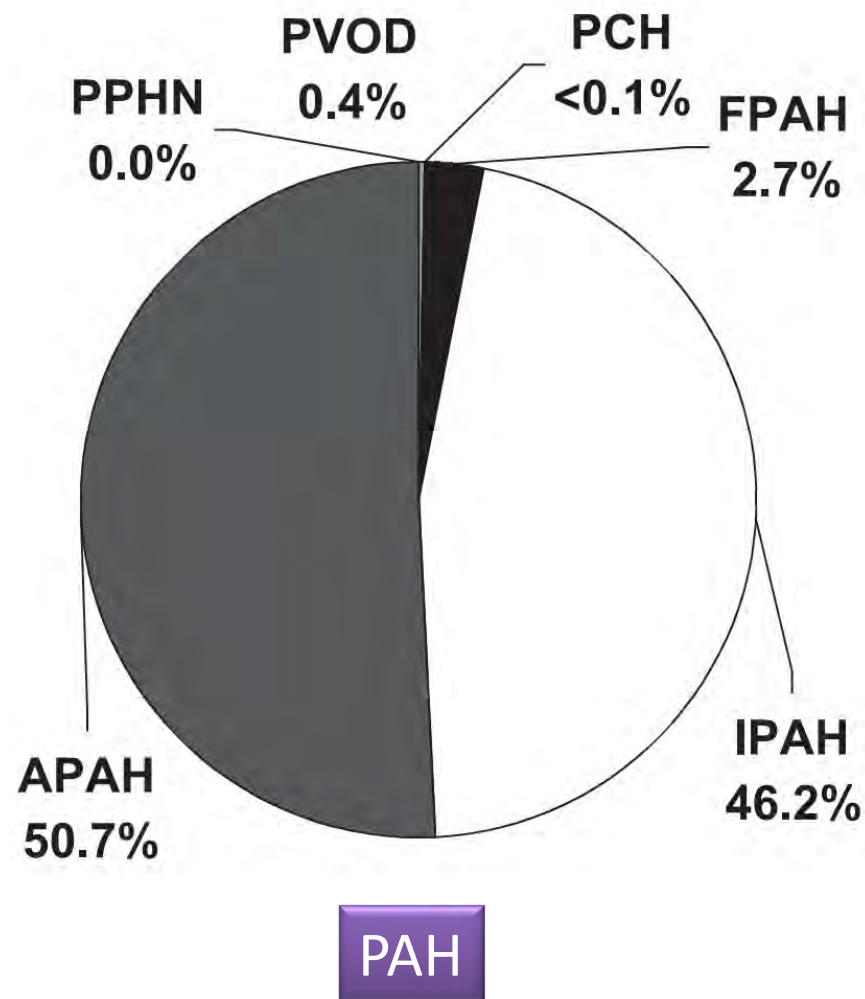
- ② The term primary pulmonary hypertension (PPH) was first coined in 1951 after Dresdale et al reported data on 39 patients with unexplained pulmonary hypertension.
- ② A sudden rise in incidence of pulmonary hypertension (PH) in Europe attributed to the diet pill, aminorex, prompted the World Health Organization (WHO) in 1973 to propose a classification scheme for PH, consisting of 2 categories: PPH or secondary PH.



# Venice (2003) Vs Dana Point (2008)

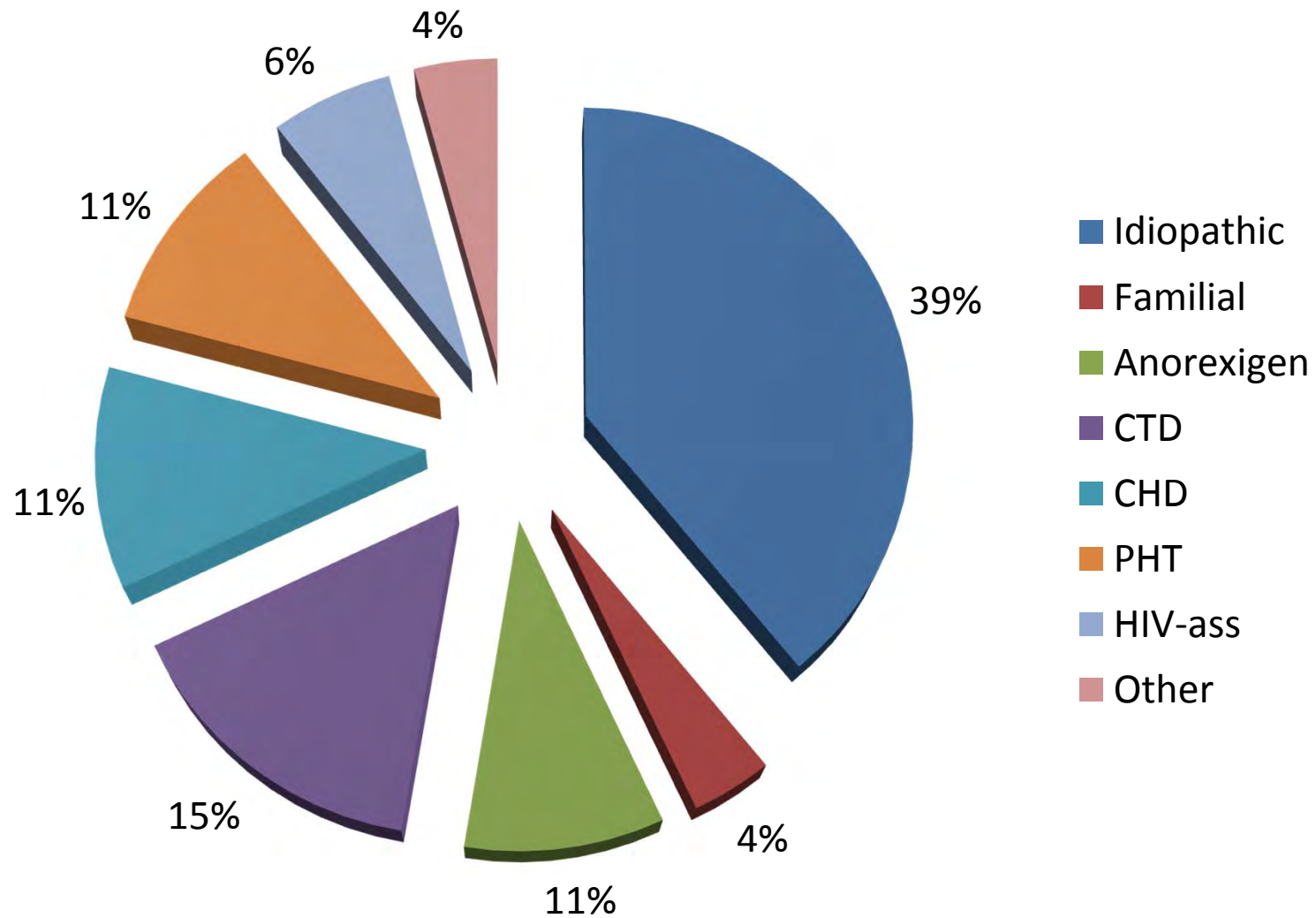
- ④ **'Familial' renamed as 'Heritable'** (to include IPAH with mutations & Familial cases with or without mutation as 11-40% of IPAH cases with no family history have BMPR2 mutation and 30% of familial cases have no BMPR2 mutation)
- ④ **Schistosomiasis included** (Previously under group 4 i.e. CTEPH as it was thought to be due to embolic obstruction of pulmonary arteries by schistosoma eggs. Presentation and histology similar to IPAH with multifactorial etiology: portopulmonary hypertension, inflammation induced by impacted eggs with mechanical obstruction having minor role)
- ④ **Chronic hemolytic anemia made separate** (Previously under 'other' of group 1) as more data strongly linking PAH to this category has emerged
- ④ **PVOD & PCH made separate as 1'** because it shares characteristics with IPAH (similar histological changes, similar clinical presentation, share similar risk factors, may have BMPR2 mutations) but also has a number of distinct differences (presence of crackles, clubbing, GGO, septal thickening, mediastinal adenopathy, hemosiderin-laden macrophages in BAL, decreased DLCO, decreased PaO<sub>2</sub>)

# PAH subtypes: REVEAL registry





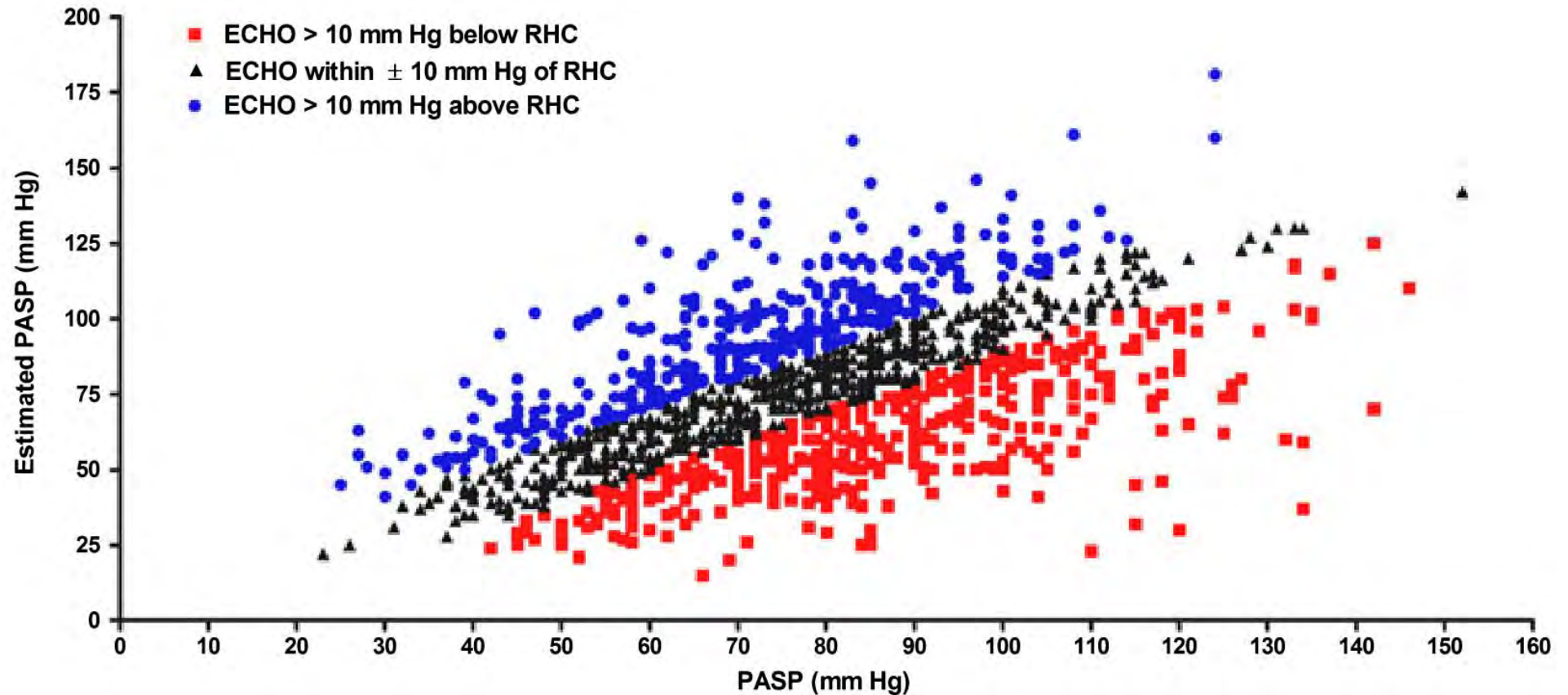
# PAH subtypes: French registry



Humbert M et al. Am. J. Respir. Crit. Care Med. 173, 1023–1030 (2006)

**Do we have an alternative to RHC for  
the diagnosis of PAH?**

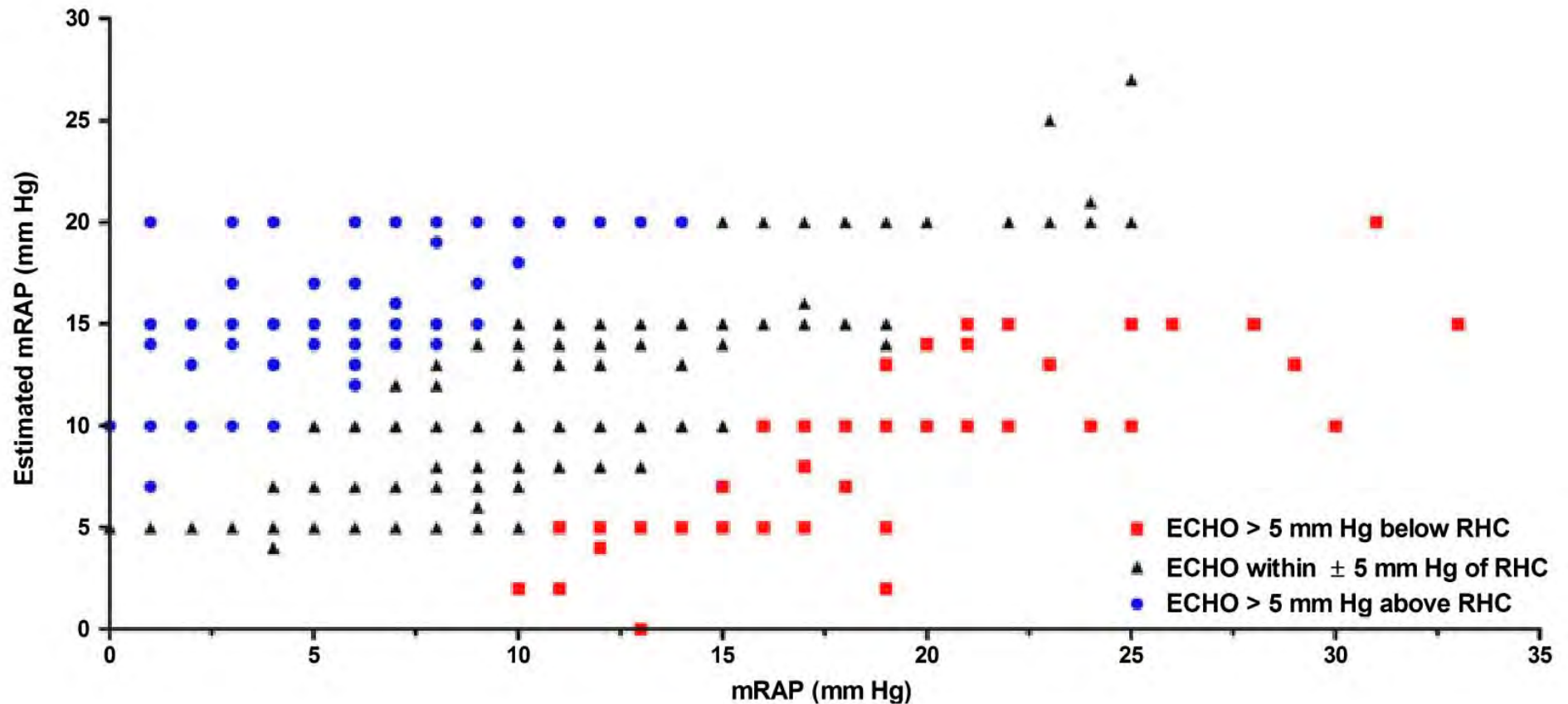
# REVEAL: Echo vs RHC (PASP)



ECHO inaccurate in 57.4% of PASP estimates  
(>10 mmHg higher or lower than RHC)

Farber H. Congest Heart Fail.2011;17:56–63

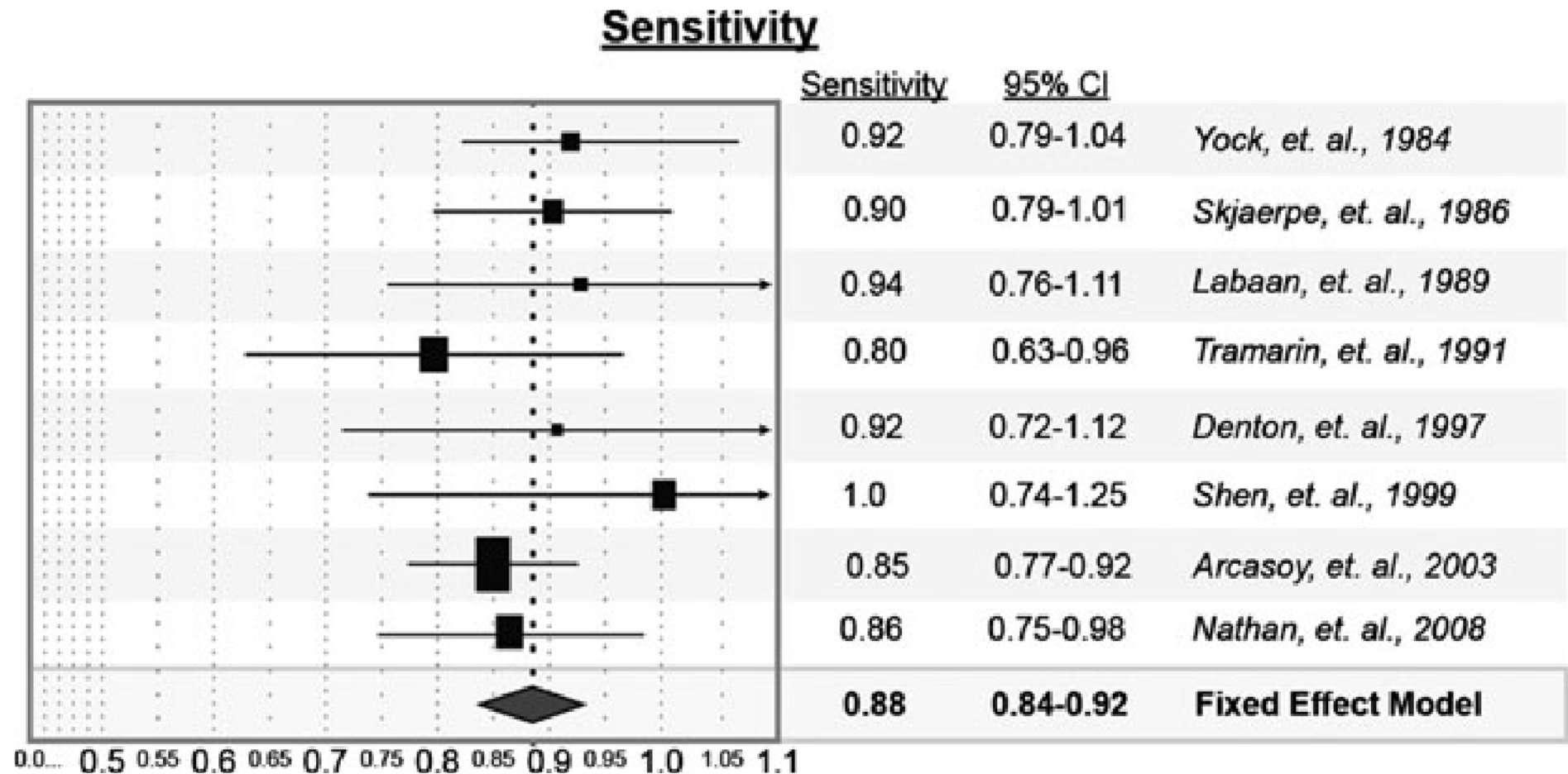
# REVEAL: Echo vs RHC (mRAP)



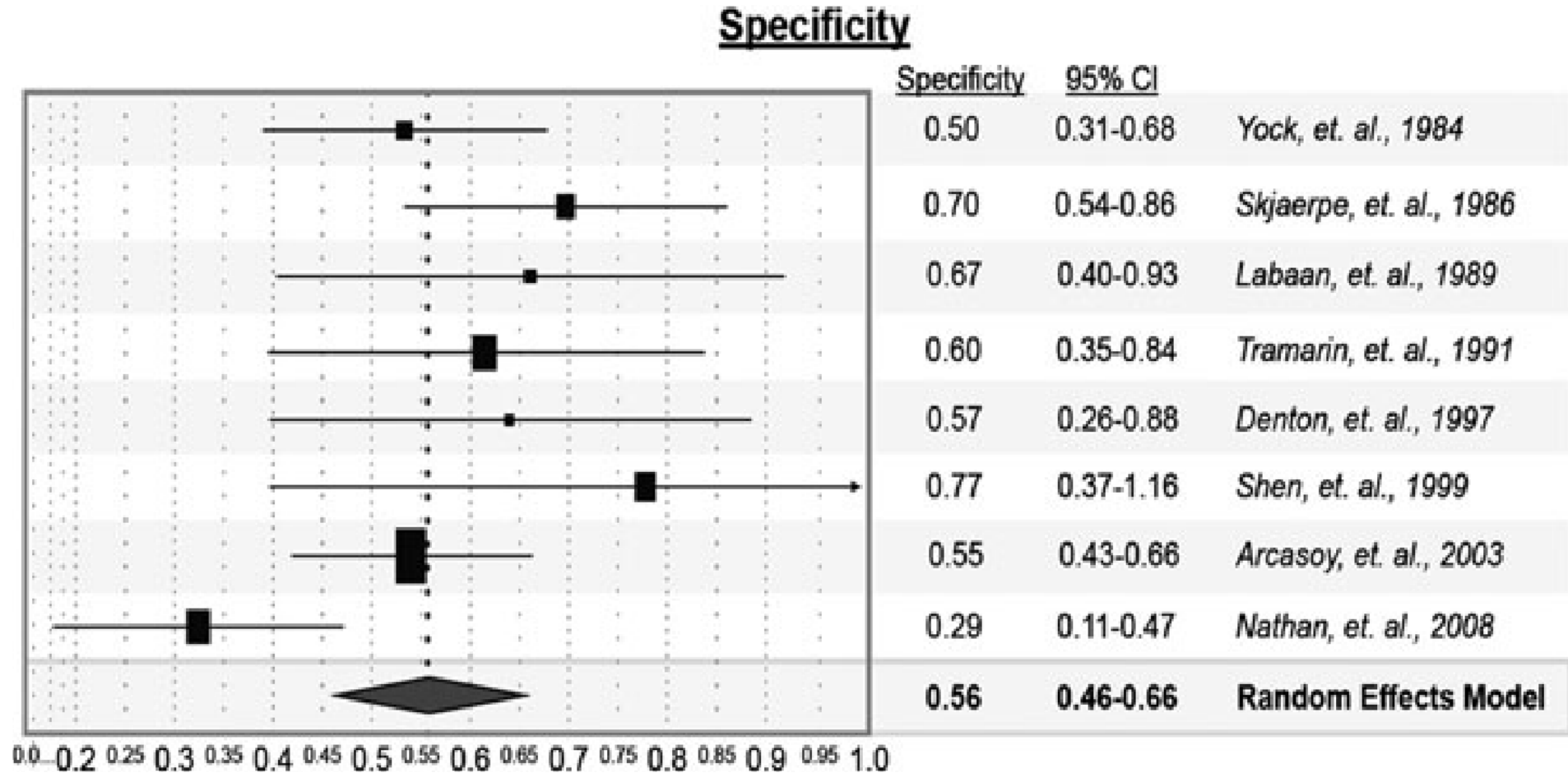
ECHO inaccurate in 36.5% of mPAP estimates  
(>5 mmHg higher or lower than RHC)

Farber H. Congest Heart Fail.2011;17:56–63

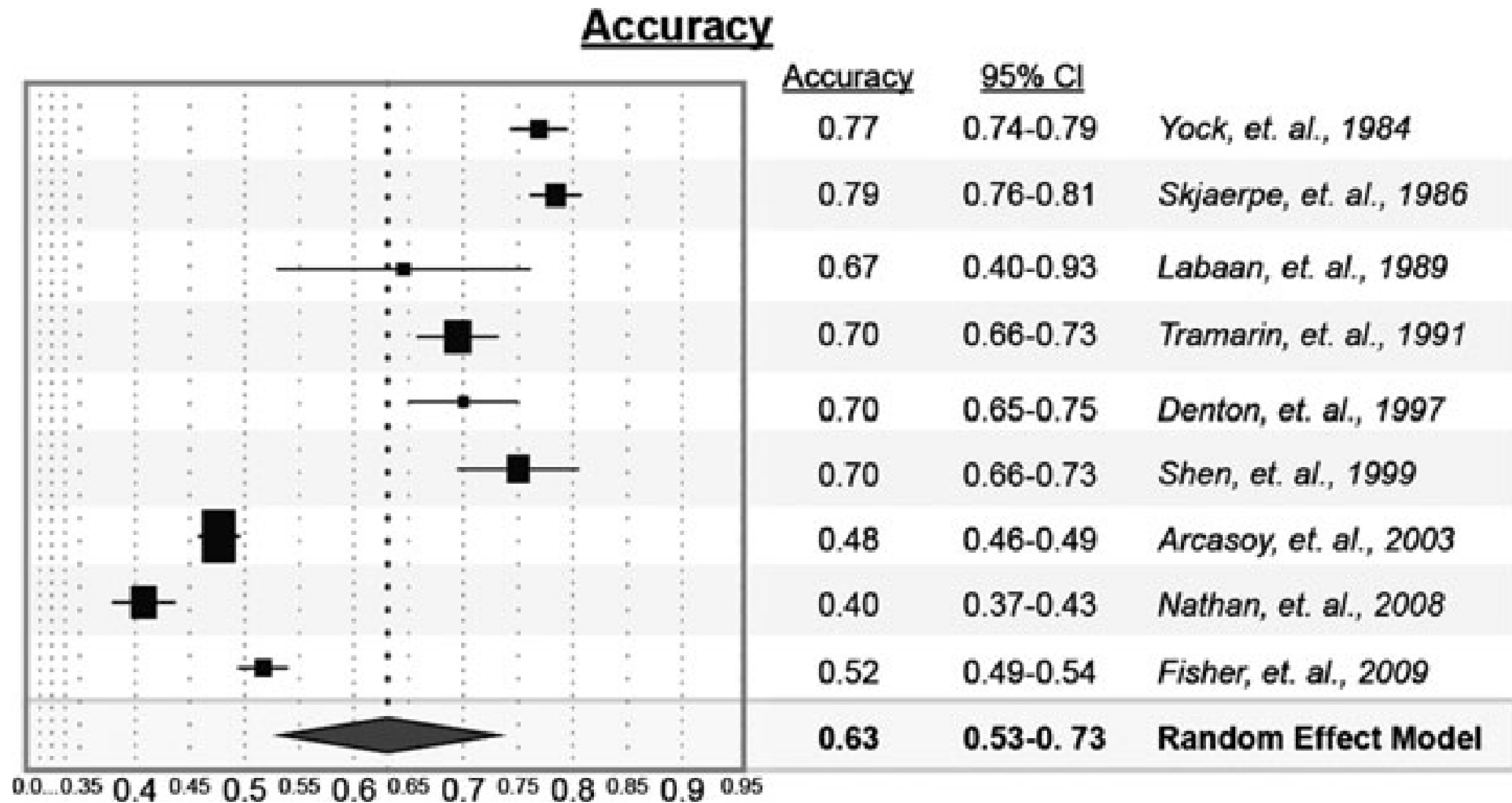
# Echo in PAH



# Echo in PAH

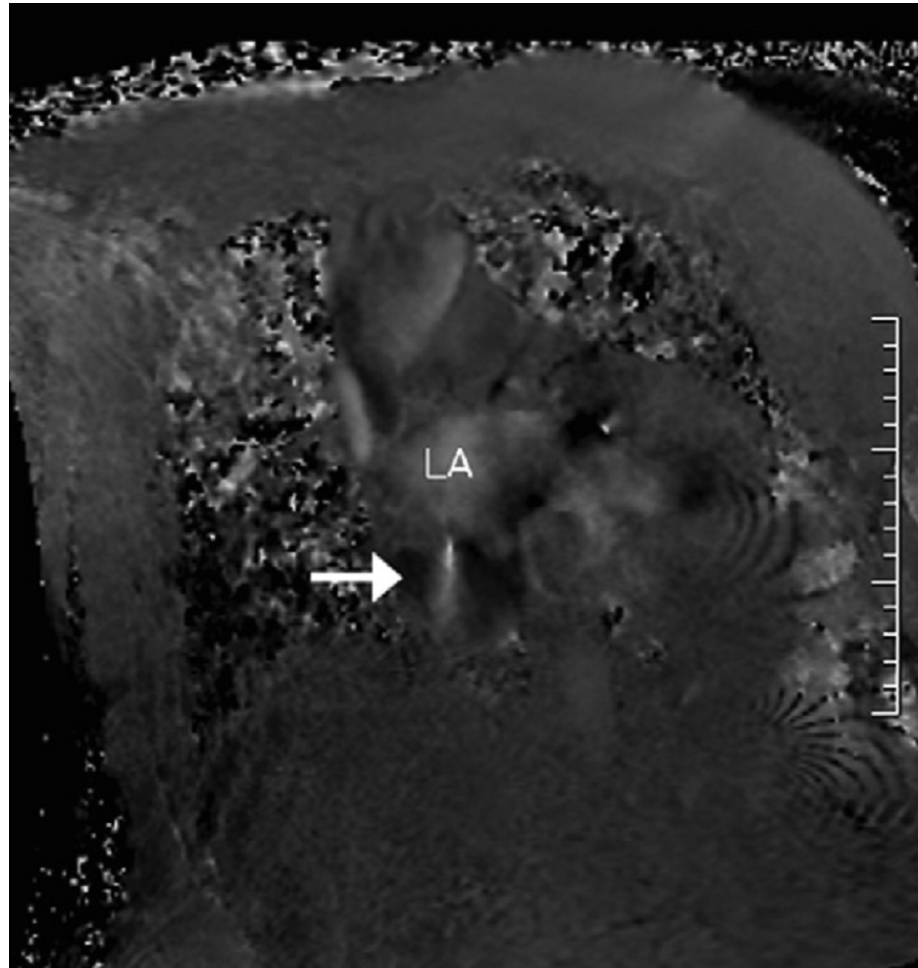


# Echo in PAH



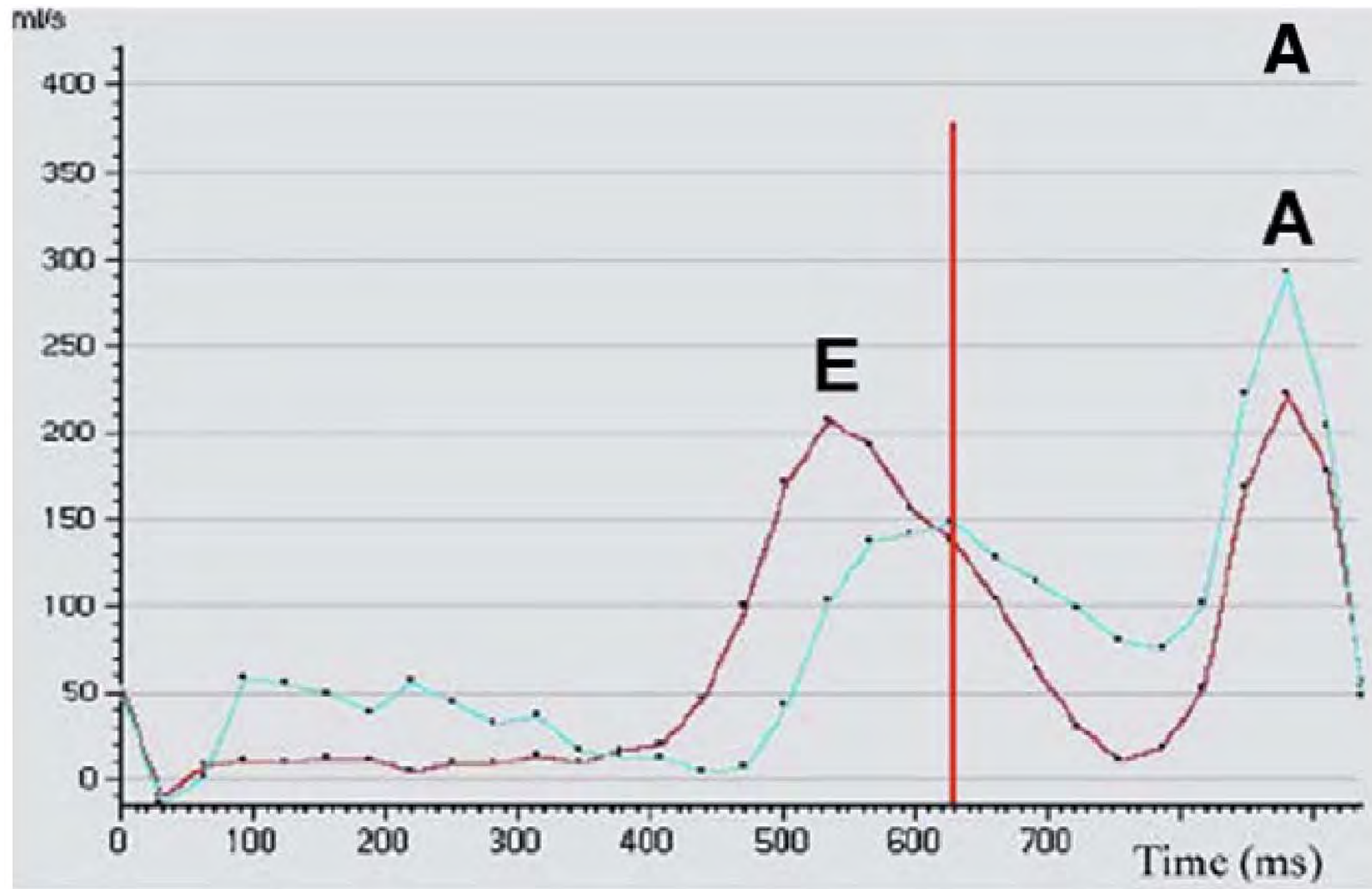


# Phase contrast cardiac MRI (CMR)



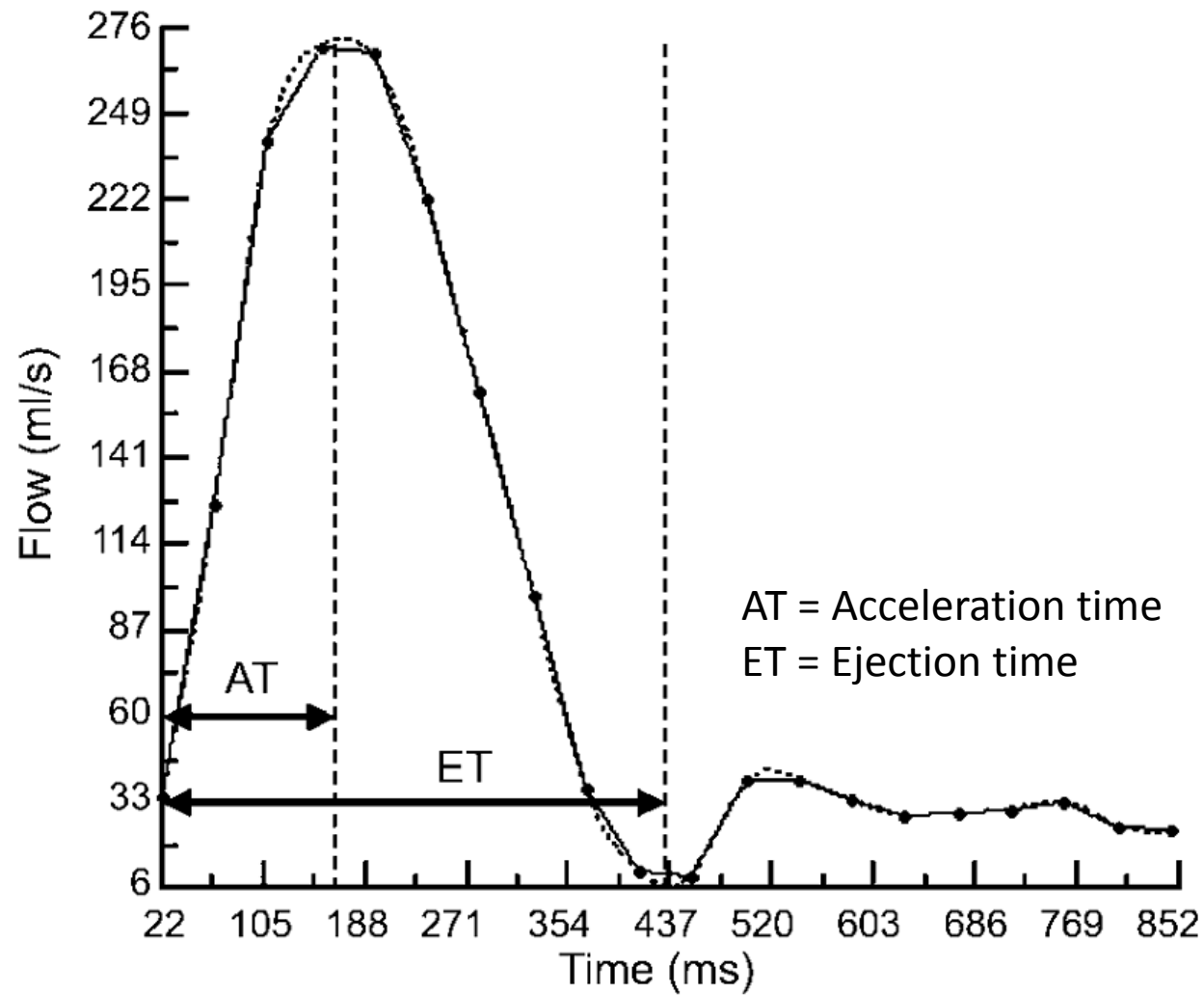


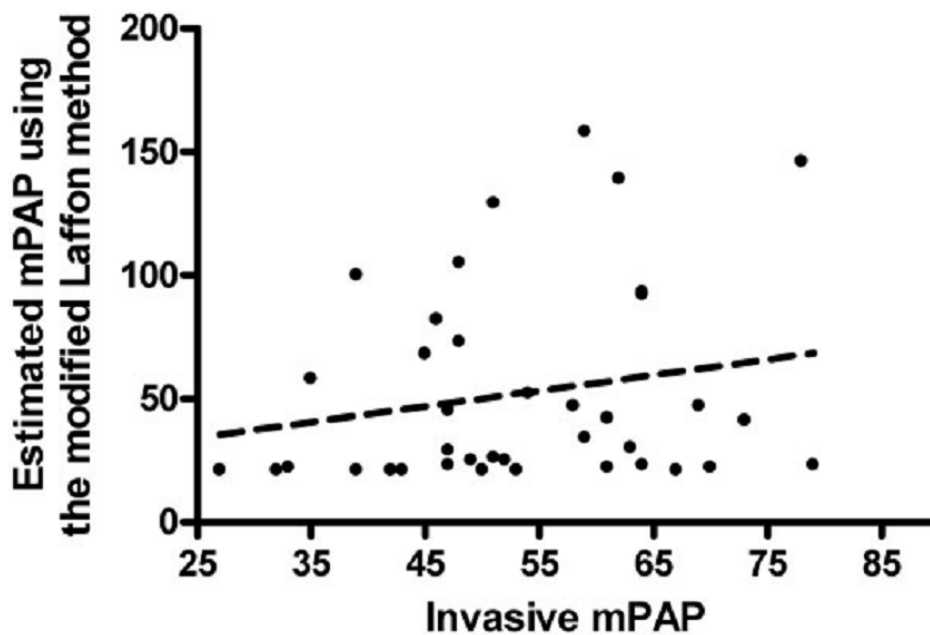
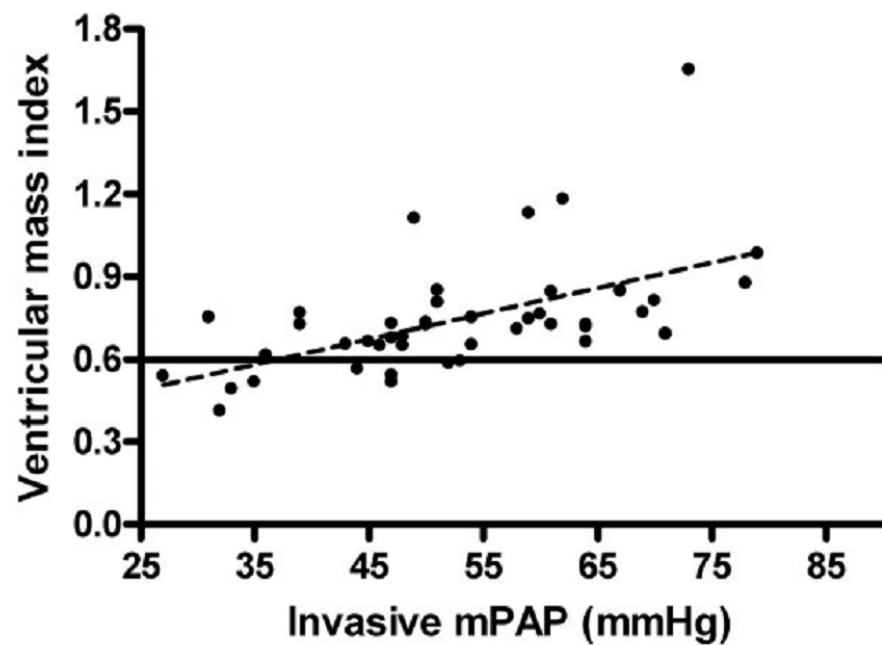
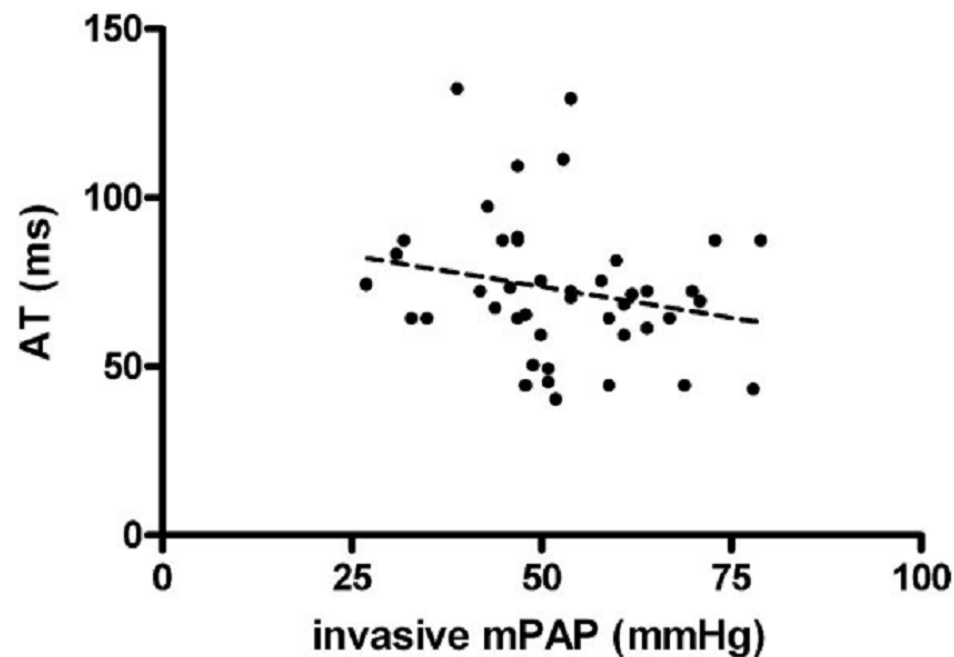
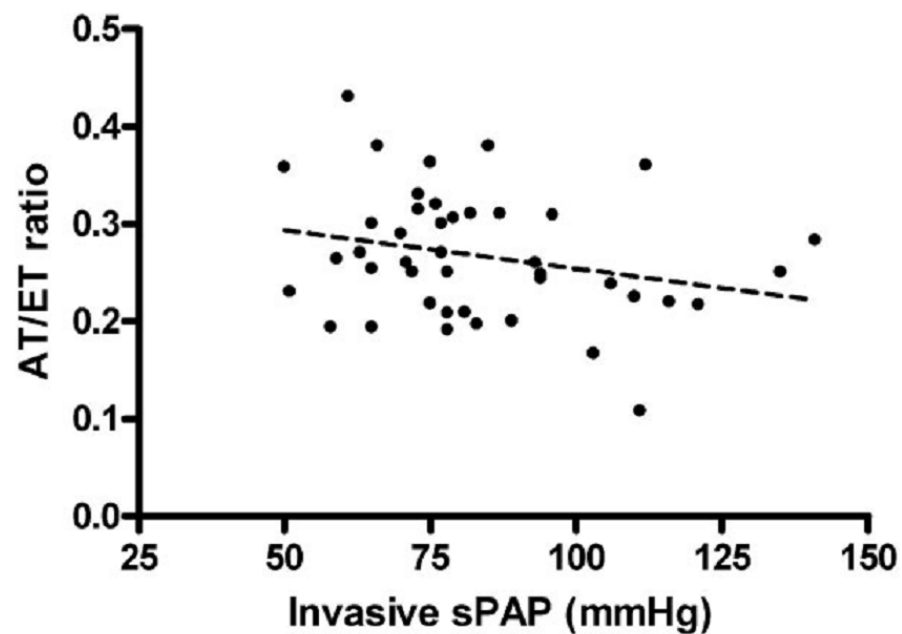
# CMR-based techniques for estimation of PAP



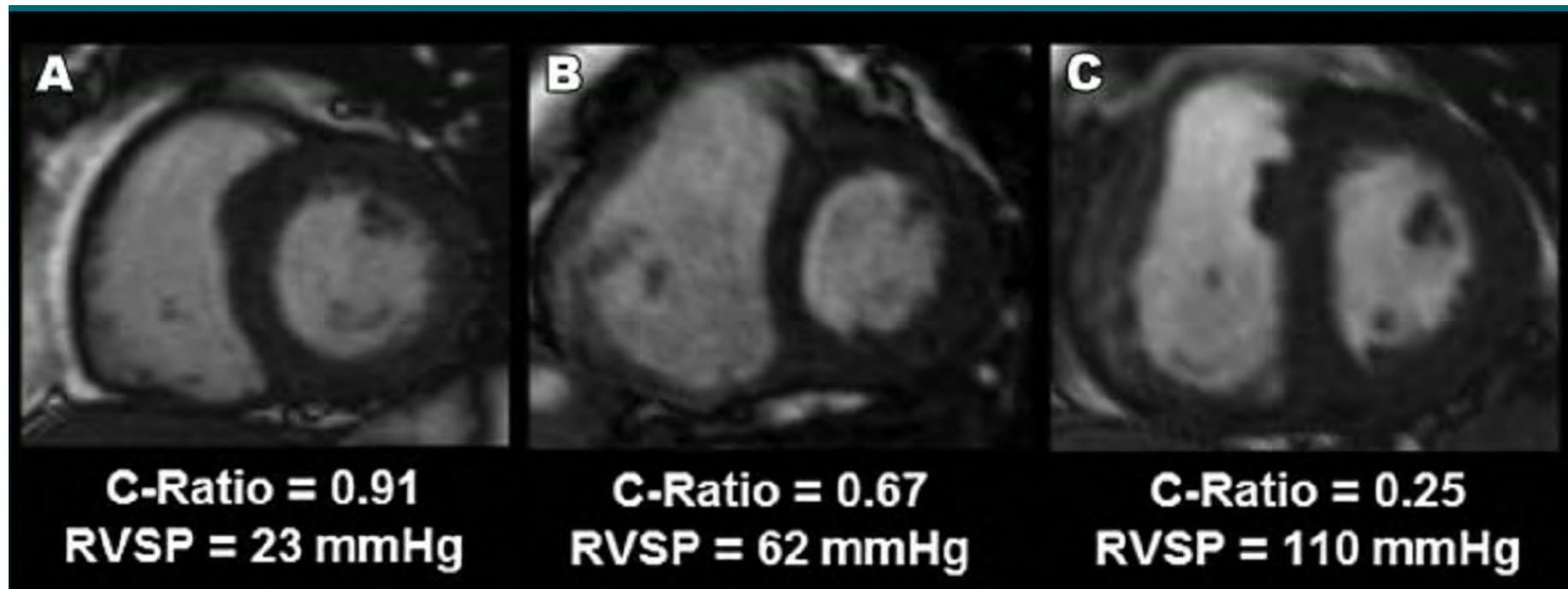
Stevens GR, Fida N, Sanz J. Progress in Cardiovascular Diseases 55 (2012) 161–171

# Flow curve of PA





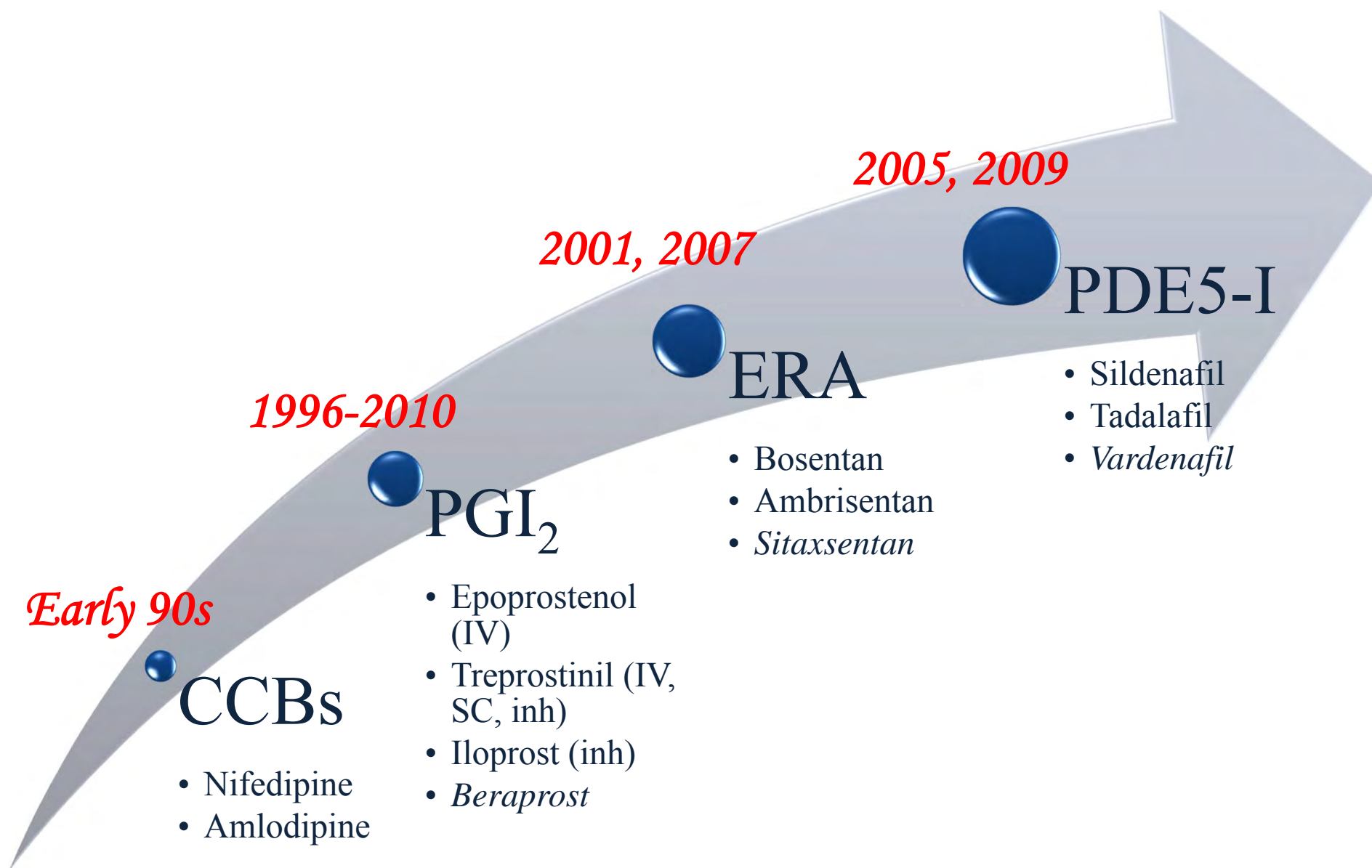
# Cardiac MR–derived curvature ratio



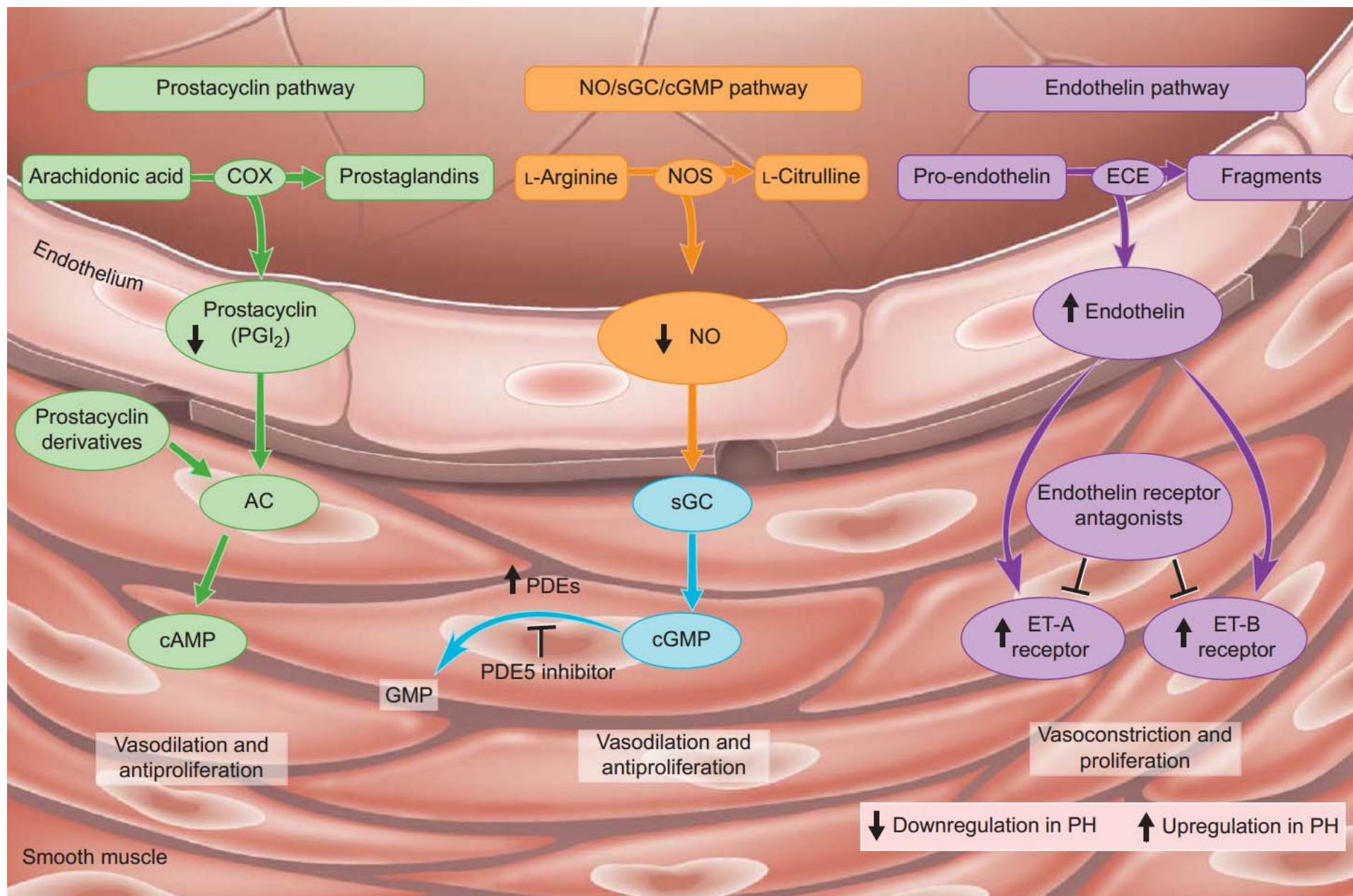
## **Current treatment options**

# Currently available therapies

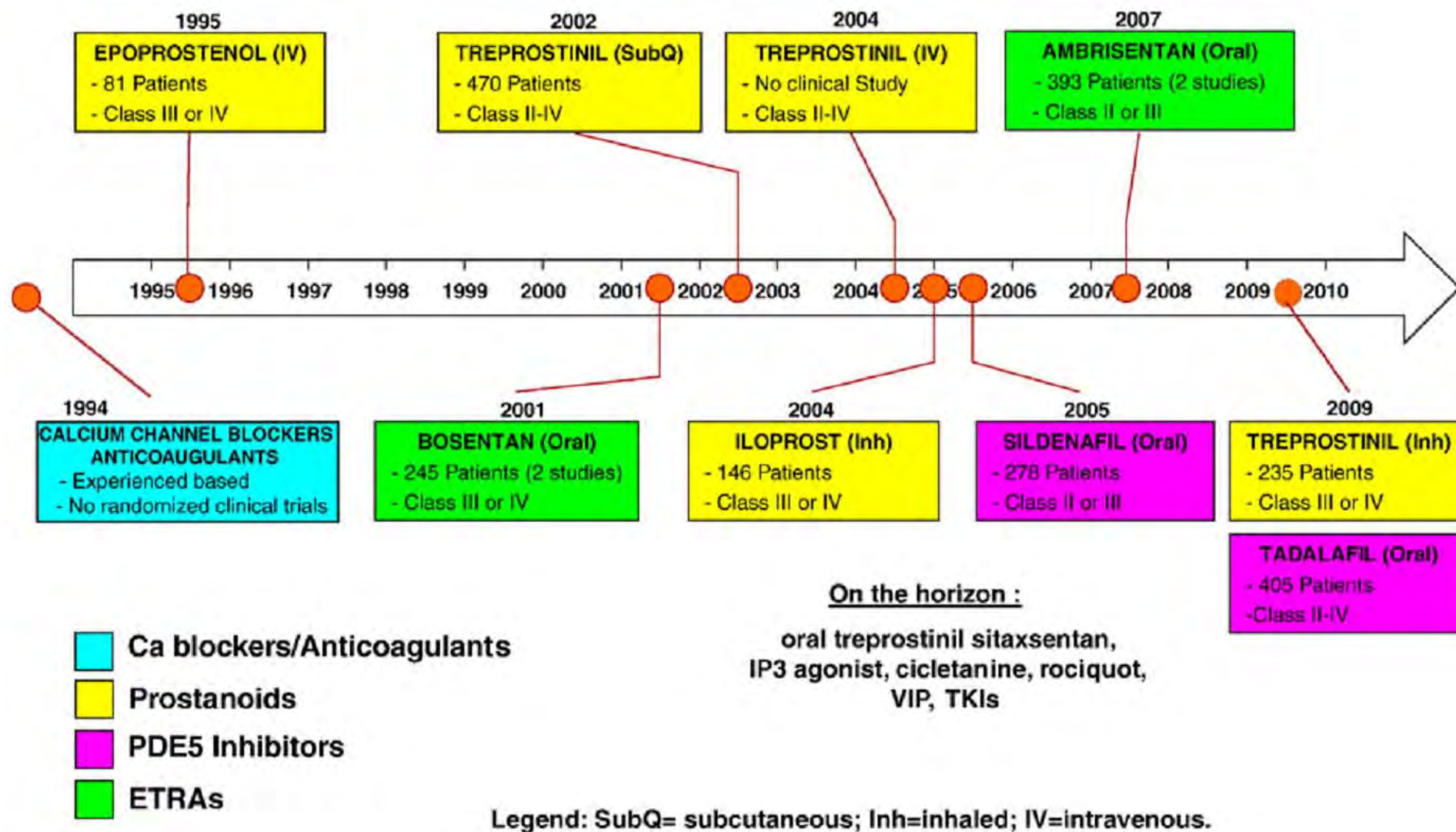
- ⊙ Calcium channel blockers (CCBs): Nifedipine, Amlodipine
- ⊙ Prostacyclins (PGI<sub>2</sub>)
  - Epoprostenol IV (FLOLAN) GlaxoSmithKline 1996
  - Treprostinil SC REMODULIN United Therapeutics May 2002
  - Treprostinil IV REMODULIN United Therapeutics 2004
  - Iloprost (inhaled) VENTAVIST 2004 AIR study
  - Treprostinil (inhaled) TYVASO United Therapeutics May 2009
  - Epoprostenol (room temperature stable preparation) (VELETRI) Actelion Pharmaceuticals 2010
  - *Beraprost*
- ⊙ Endothelin receptor antagonists (ERA)
  - Bosentan (TRACLEER) Nov 2001 BREATHE-1
  - Ambrisentan (LETAIRIS) Gilead June 2007
  - *Sitaxsentan*
  - *Macitentan*
- ⊙ Phosphodiesterase type 5 inhibitors (PDE5-I)
  - Sildenafil (REVATIO) June 2005
  - Tadalafil (ADCIRCA) Eli Lilly May 2009
  - *Vardenafil*











# What was the need for newer therapies?

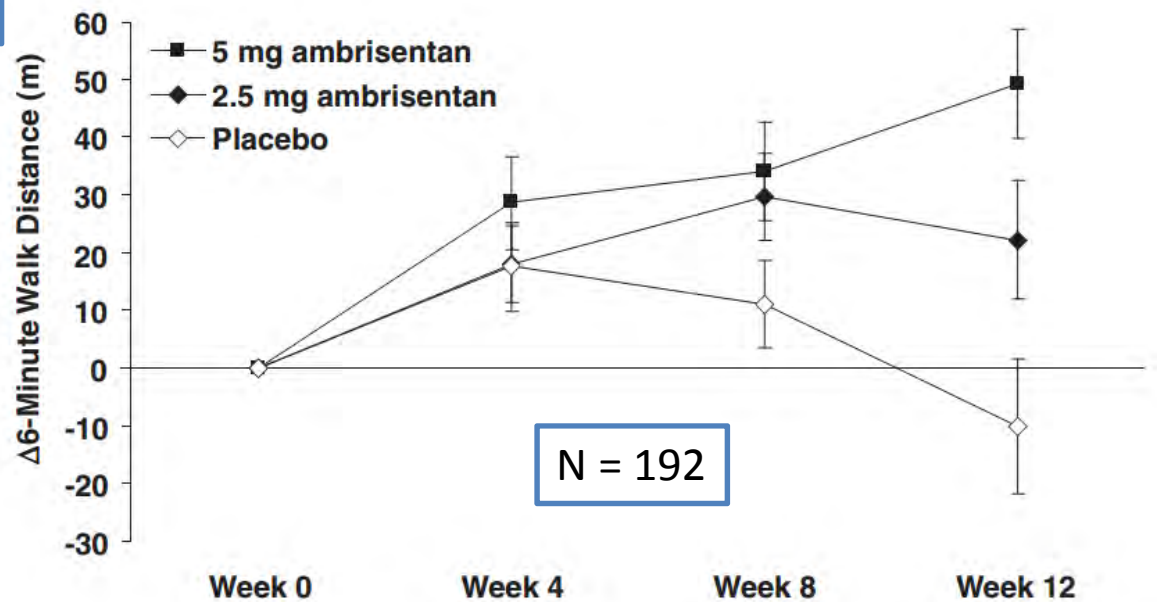
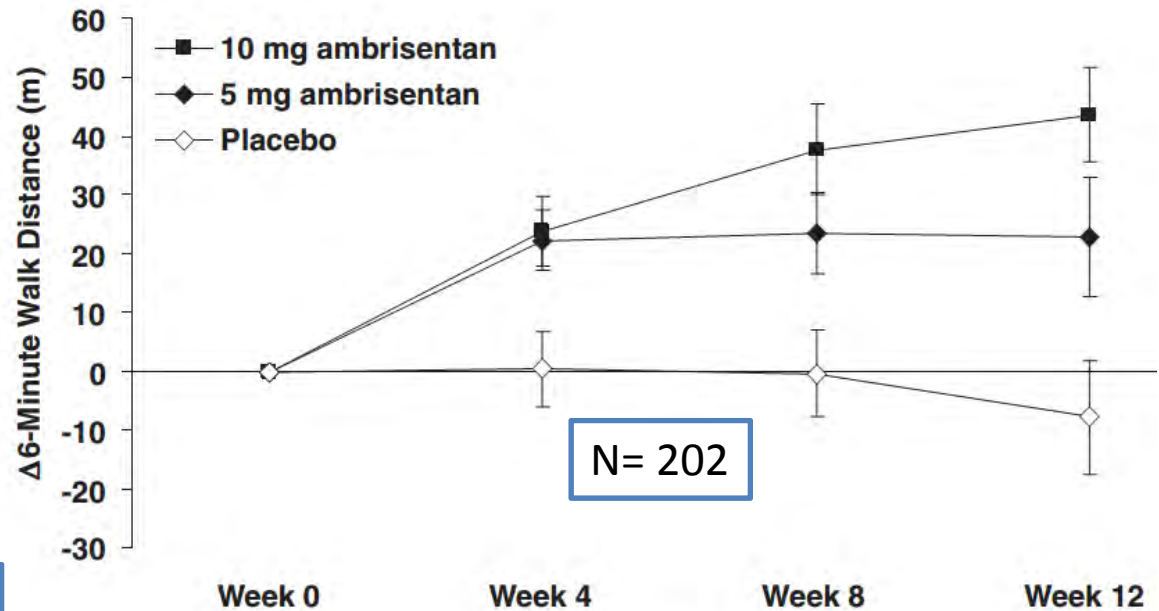
- ⌚ Only 13-26% of IPAH patients demonstrate a vasoactive response to acute vasoreactivity testing
- ⌚ Of them, CCBs are convincingly effective (sustained response for >1 year) in only 5%

Rich S, Kaufmann E, Levy PS. N Engl J Med. 1992 Jul 9;327(2):76-81  
Sitbon et al. Circulation. 2005 Jun 14;111(23):3105-11

**Specific therapies for PAH that have become available or in advanced stages of development over the last 5 years**

# ARIES 1 & 2: Ambrisentan

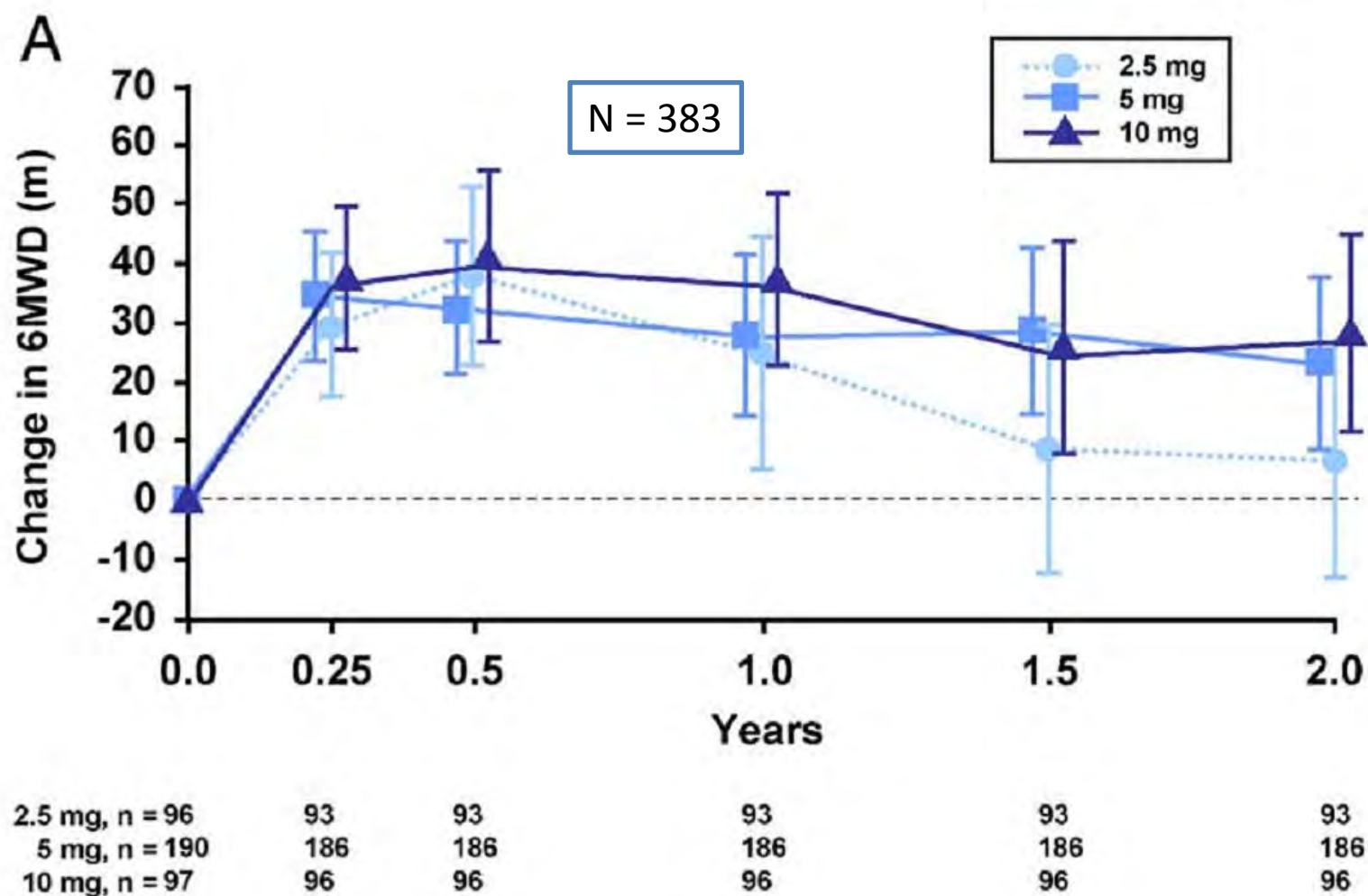
All WHO FC included, but consisted predominantly of WHO FC II, III



# ARIES 1 & 2: Ambrisentan

- Ⓒ Background— Ambrisentan is a propanoic acid-based, **A-selective endothelin receptor antagonist** for the **once-daily treatment** of pulmonary arterial hypertension.
- Ⓒ Methods and Results— Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study 1 and 2 (ARIES-1 and ARIES-2) were concurrent, double-blind, placebo-controlled studies that randomized 202 and 192 patients with pulmonary arterial hypertension, respectively, to placebo or ambrisentan (**ARIES-1, 5 or 10 mg; ARIES-2, 2.5 or 5 mg**) orally once daily for **12 weeks**. The primary end point for each study was change in 6-minute walk distance from baseline to week 12. Clinical worsening, World Health Organization functional class, Short Form-36 Health Survey score, Borg dyspnea score, and B-type natriuretic peptide plasma concentrations also were assessed. In addition, a long-term extension study was performed. **The 6-minute walk distance increased in all ambrisentan groups; mean placebo-corrected treatment effects were 31 m (P=0.008) and 51 m (P<0.001) in ARIES-1 for 5 and 10 mg ambrisentan, respectively, and 32 m (P=0.022) and 59 m (P<0.001) in ARIES-2 for 2.5 and 5 mg ambrisentan, respectively.** Improvements in time to clinical worsening (ARIES-2), World Health Organization functional class (ARIES-1), Short Form-36 score (ARIES-2), Borg dyspnea score (both studies), and B-type natriuretic peptide (both studies) were observed. **No patient treated with ambrisentan developed aminotransferase concentrations >3 times the upper limit of normal.** In 280 patients completing 48 weeks of treatment with ambrisentan monotherapy, the improvement from baseline in 6-minute walk at 48 weeks was 39 m.
- Ⓒ Conclusions— Ambrisentan improves exercise capacity in patients with pulmonary arterial hypertension. Improvements were observed for several secondary end points in each of the studies, although statistical significance was more variable. Ambrisentan is well tolerated and is associated with a low risk of aminotransferase abnormalities.

# ARIES extension: Ambrisentan



All WHO FC included, but predominantly II, III

Am Coll Cardiol. 2009 Nov 17;54(21):1971-81

# ARIES extension: Ambrisentan

- Ⓒ Objectives: This study evaluated the safety and efficacy of ambrisentan for a period of 2 years in patients with pulmonary arterial hypertension (PAH).
- Ⓒ Background: **Ambrisentan is an oral, once-daily endothelin receptor antagonist that is selective for the endothelin type A receptor.** The ARIES-1 (Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies) and ARIES-2 trials were the pivotal 12-week, placebo-controlled studies that led to the regulatory approval of ambrisentan (5 and 10 mg) for the treatment of PAH.
- Ⓒ Methods: In the ARIES-1 and -2 studies, and the subsequent long-term extension protocol, the ARIES-E study, 383 patients received ambrisentan (2.5, 5, or 10 mg). Efficacy and safety assessments are presented from the time of the first dose of ambrisentan for all patients with post-baseline data.
- Ⓒ Results: **After 2 years of ambrisentan exposure, the mean change from baseline in 6-min walk distance was improved for the 5-mg (+23 m; 95% confidence interval: 9 to 38 m) and 10-mg (+28 m; 95% confidence interval: 11 to 45 m) groups.** Estimates of survival and freedom from clinical worsening for the combined dose group were 94% and 83%, respectively, at 1 year and 88% and 72%, respectively, at 2 years. **The annualized risk of aminotransferase abnormalities >3× the upper limit of normal was ~2% per year; most of these events were mild and did not lead to discontinuation of drug.**
- Ⓒ Conclusions: Two years of ambrisentan treatment was associated with sustained improvements in exercise capacity and a low risk of clinical worsening and death in patients with PAH. Ambrisentan was generally well tolerated and had a low risk of aminotransferase abnormalities over the 2-year study period. (A Long Term Study of Ambrisentan in Pulmonary Arterial Hypertension Subjects Having Completed AMB-320 or AMB-321; NCT00578786)



# Ambrisentan: Safety

- ⊙ Peripheral edema, nasal congestion and sinusitis
- ⊙ Hepatotoxicity (AST or ALT > 3 times the ULN)
  - None in ARIES 1 & 2 (12 weeks)
  - Bosentan 9% in BREATHE-1 (12 weeks)
  - However, in ARIES extension (2 years), 1.8% in first year and 3.9% in the second year

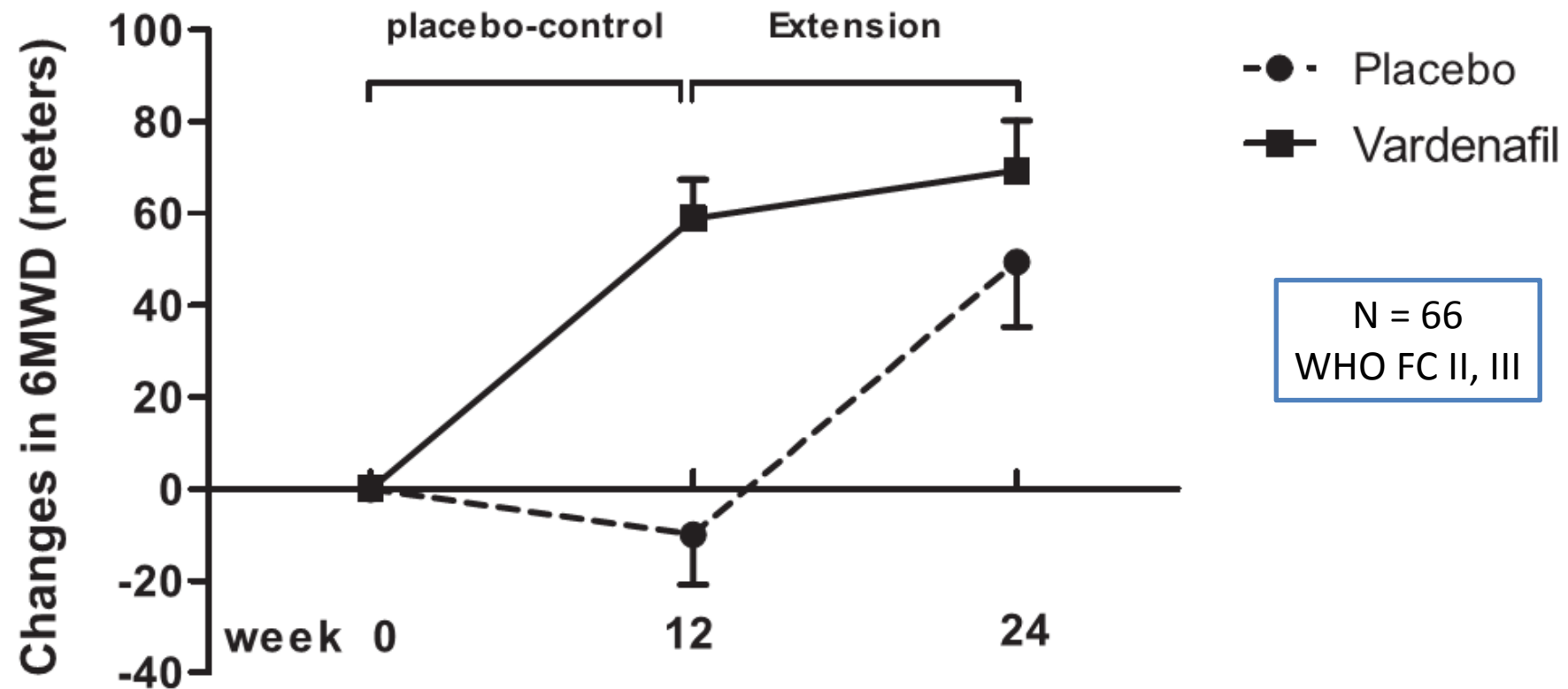


# PHIRST-1: Tadalafil

- Ⓒ Background— Treatment options for pulmonary arterial hypertension target the prostacyclin, endothelin, or nitric oxide pathways. **Tadalafil, a phosphodiesterase type-5 inhibitor**, increases cGMP, the final mediator in the nitric oxide pathway.
- Ⓒ Methods and Results— In this **16-week**, double-blind, placebo-controlled study, 405 patients with pulmonary arterial hypertension (idiopathic or associated), **either treatment-naïve or on background therapy with the endothelin receptor antagonist bosentan**, were randomized to **placebo or tadalafil 2.5, 10, 20, or 40 mg orally once daily**. The primary end point was the change from baseline to week 16 in the distance walked in 6 minutes. Changes in World Health Organization functional class, clinical worsening, and health-related quality of life were also assessed. Patients completing the 16-week study could enter a long-term extension study. **Tadalafil increased the distance walked in 6 minutes in a dose-dependent manner; only the 40-mg dose met the prespecified level of statistical significance ( $P<0.01$ ). Overall, the mean placebo-corrected treatment effect was 33 m (95% confidence interval, 15 to 50 m). In the bosentan-naïve group, the treatment effect was 44 m (95% confidence interval, 20 to 69 m) compared with 23 m (95% confidence interval, -2 to 48 m) in patients on background bosentan therapy.** Tadalafil 40 mg improved the time to clinical worsening ( $P=0.041$ ), incidence of clinical worsening (68% relative risk reduction;  $P=0.038$ ), and health-related quality of life. The changes in World Health Organization functional class were not statistically significant. **The most common treatment-related adverse events reported with tadalafil were headache, myalgia, and flushing.**
- Ⓒ Conclusions— In patients with pulmonary arterial hypertension, tadalafil 40 mg was well tolerated and improved exercise capacity and quality of life measures and reduced clinical worsening.

Galie et al. Circulation. 2009 Jun 9;119(22):2894-903.

# EVALUATION: Vardenafil



# EVALUATION: Vardenafil

- Ⓢ Rationale: Although the phosphodiesterase type 5 inhibitors sildenafil and tadalafil have demonstrated efficacy in patients with pulmonary arterial hypertension (PAH), monotherapy with these agents has not been conclusively shown to reduce clinical worsening events.
- Ⓢ Objectives: To evaluate the safety and efficacy of the phosphodiesterase type 5 inhibitor vardenafil in Chinese patients with PAH.
- Ⓢ Methods: In a randomized, double-blind, placebo-controlled study, 66 patients with PAH were **randomized 2:1 to vardenafil (5 mg once daily for 4 wk then 5 mg twice daily; n = 44) or placebo (n = 22) for 12 weeks**. Patients completing this phase were then treated with open-label vardenafil (5 mg twice daily) for a further 12 weeks.
- Ⓢ Measurements and Main Results: **At Week 12, the mean placebo-corrected 6-minute walking distance was increased with vardenafil (69 m;  $P < 0.001$ ), and this improvement was maintained for at least 24 weeks**. Vardenafil also increased the mean placebo-corrected cardiac index ( $0.39 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ;  $P = 0.005$ ) and decreased mean pulmonary arterial pressure and pulmonary vascular resistance ( $-5.3 \text{ mm Hg}$ ,  $P = 0.047$ ;  $-4.7 \text{ Wood U}$ ,  $P = 0.003$ ; respectively) at Week 12. Four patients in the placebo group (20%) and one in the vardenafil group (2.3%) had clinical worsening events (hazard ratio 0.105; 95% confidence interval, 0.012–0.938;  $P = 0.044$ ). Vardenafil was associated with only mild and transient adverse events.
- Ⓢ Conclusions: Vardenafil is effective and well tolerated in patients with PAH at a dose of 5 mg twice daily.

Jing et al. Am J Respir Crit Care Med. 2011 Jun 15;183(12):1723-9

# Sitaxsentan

## **Pfizer Stops Clinical Trials Of Thelin® And Initiates Voluntary Product Withdrawal In The Interest Of Patient Safety**

**Decision based on review of emerging safety information from clinical trials and post-marketing reports**

NEW YORK, N.Y., December 10, 2010 - Pfizer Inc. announced today that, in the interest of patient safety, it is voluntarily withdrawing Thelin® (sitaxentan) for the treatment of pulmonary arterial hypertension (PAH) in regions where it is approved (the European Union, Canada and Australia). In addition, Pfizer is discontinuing clinical studies of Thelin worldwide.

[http://www.pfizer.ca/en/media\\_centre/news\\_releases/article?year=2010&article=340](http://www.pfizer.ca/en/media_centre/news_releases/article?year=2010&article=340)

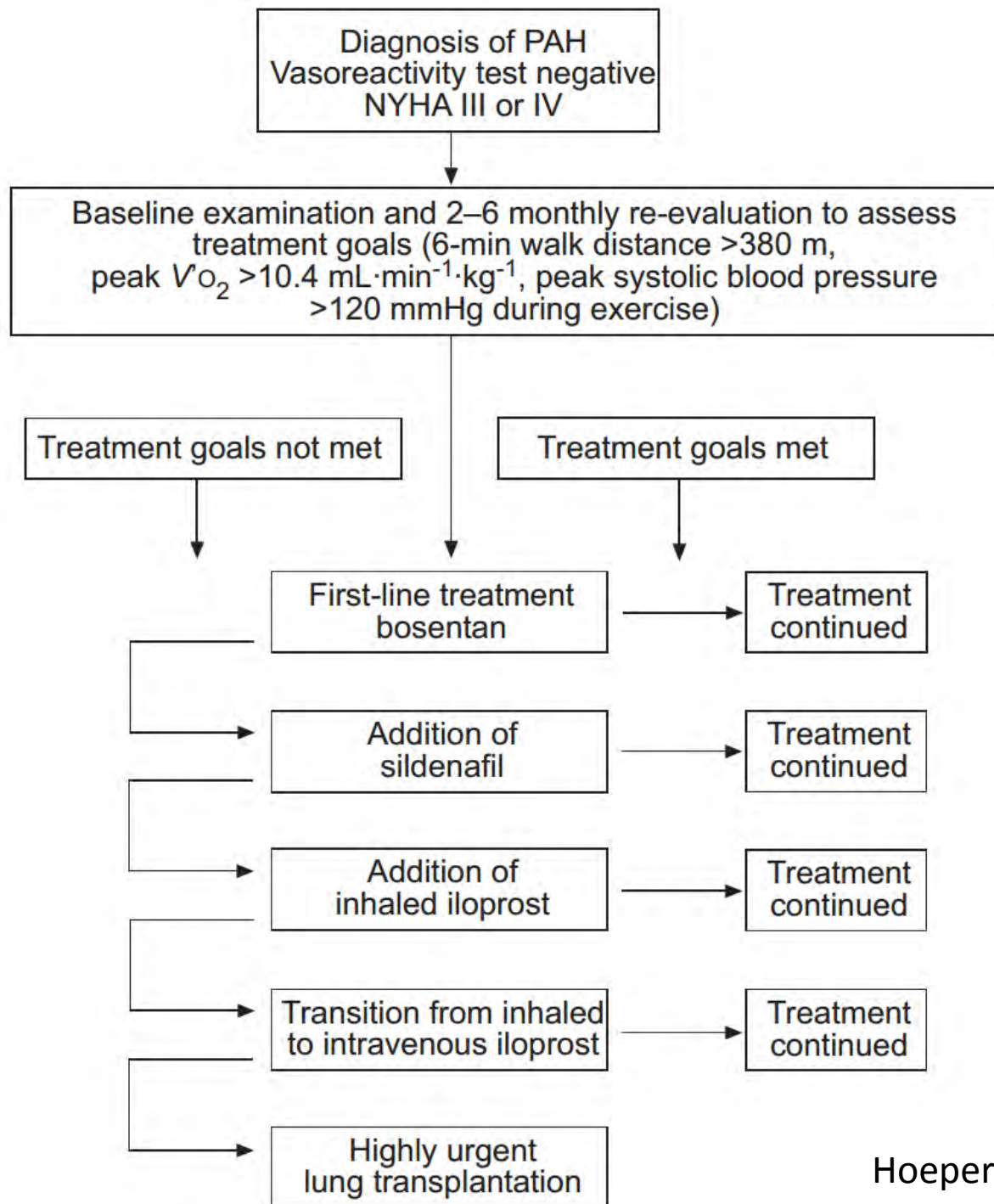
(accessed on 3<sup>rd</sup> February 2013)

# Cost analysis

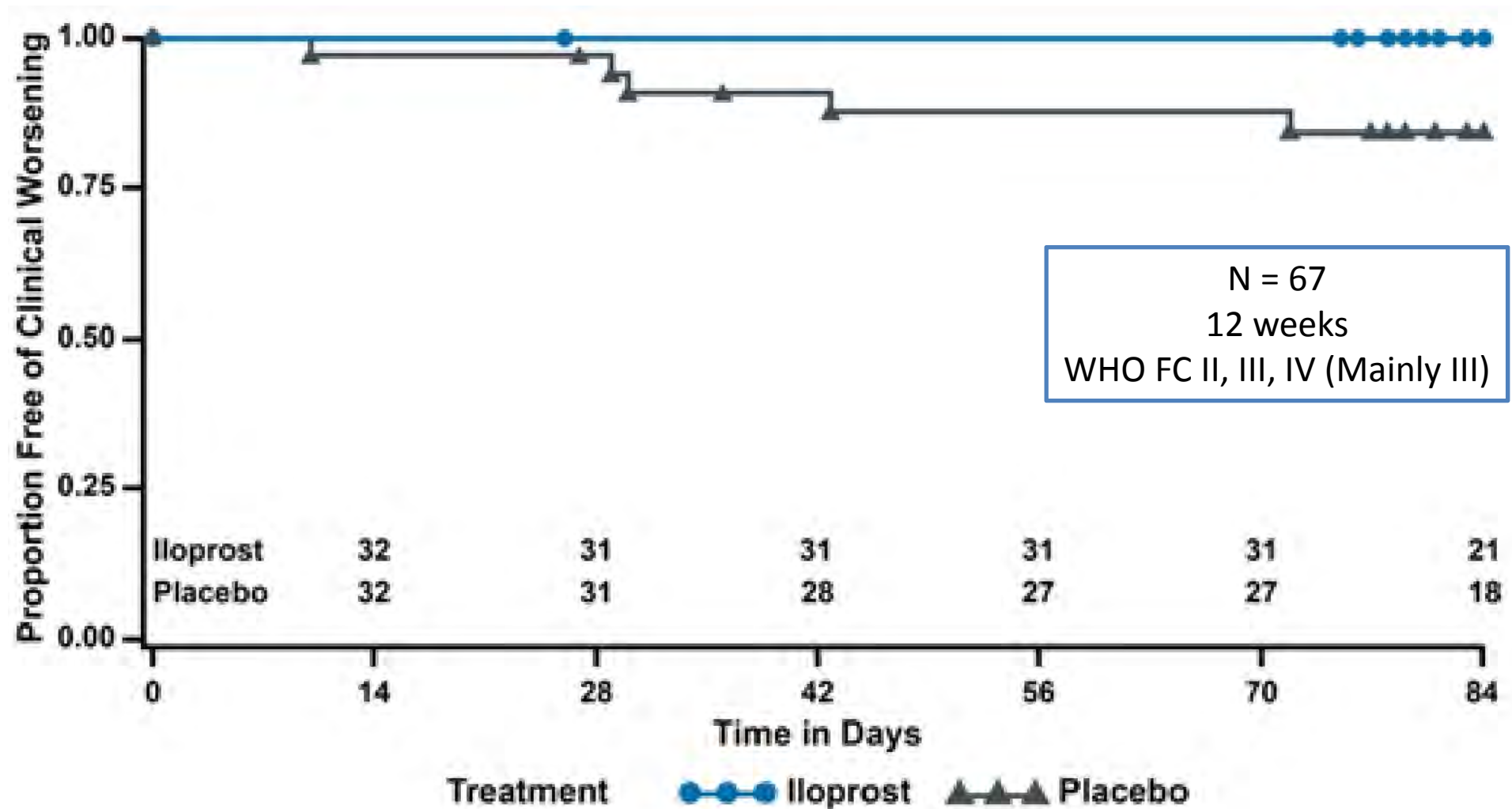
Drug	Estimated annual cost	Availability in India
Sildenafil	\$18,815	Yes
Tadalafil	\$16,228	Yes
Bosentan	\$71,358	Yes
Ambrisentan	\$73,391	?
Epoprostenol	\$100,000	Yes
Treprostinil	\$120,000 to \$160,000	?
Iloprost	\$145,635	?

Source: [www.phassociation.org](http://www.phassociation.org) (accessed 1<sup>st</sup> March, 2013)

**What is the role of combination therapy  
in PAH?**



## STEP-1: Addition of Iloprost to Bosentan

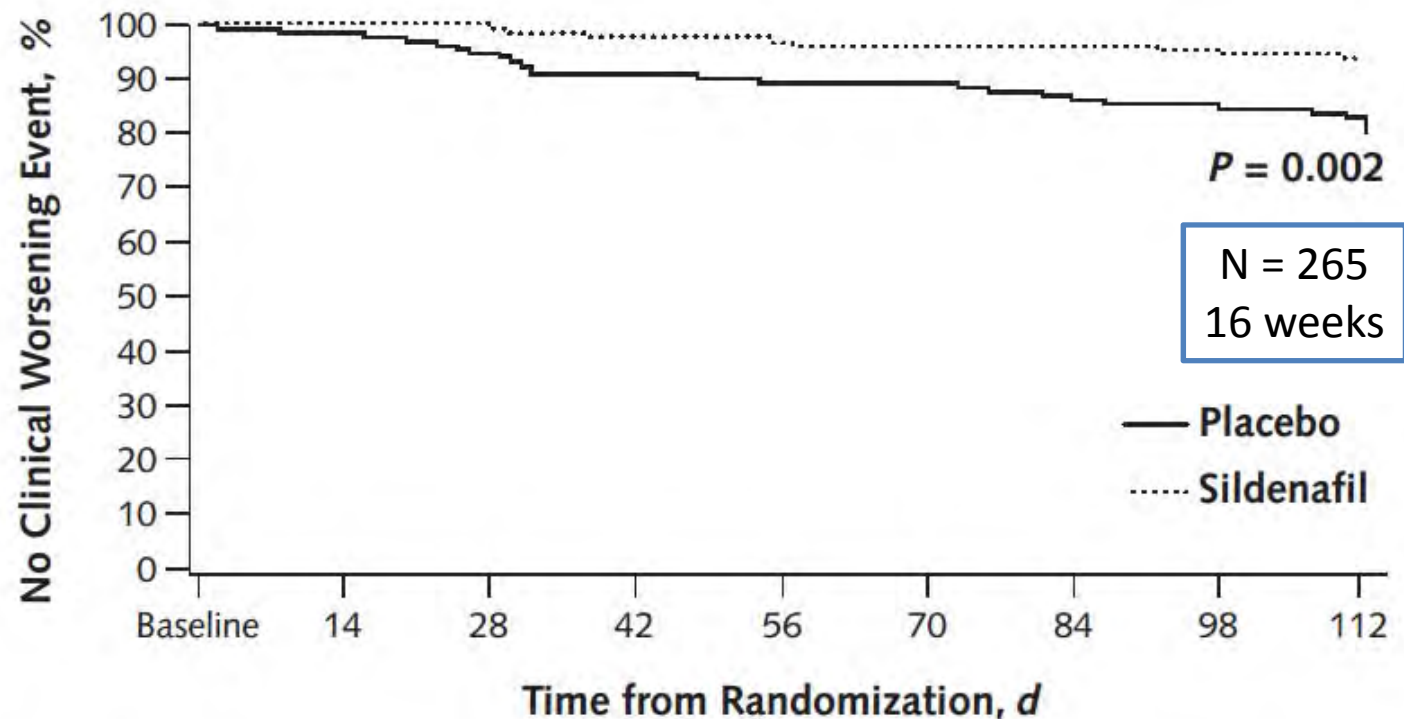




# STEP-1: Addition of Iloprost to Bosentan

- Ⓢ Rationale: Small, open-label studies suggest that combinations of existing therapies may be effective for pulmonary arterial hypertension (PAH).
- Ⓢ Objective: To evaluate the safety and efficacy of adding inhaled iloprost, a prostacyclin analog, to the endothelin receptor antagonist bosentan in patients with PAH.
- Ⓢ Methods: In a randomized, multicenter, double-blind trial, inhaled iloprost (5 µg) or placebo was added to stable monotherapy with bosentan for **12 wk**. Efficacy endpoints included change from baseline in 6-min-walk distance (6-MWD), modified New York Heart Association (NYHA) functional class, hemodynamic parameters, and time to clinical worsening.
- Ⓢ Measurements and Main Results: A total of 67 patients with PAH (55% idiopathic PAH, 45% associated PAH, 94% NYHA class III, and mean baseline 6-MWD of 335 m) were randomized. **At Week 12, patients receiving iloprost had a mean increase in 6-MWD of 30 m ( $p = 0.001$ ); placebo patients had a mean 6-MWD increase of 4 m ( $p = 0.69$ ), with a placebo-adjusted difference of +26 m ( $p = 0.051$ ).** NYHA status improved by one class in 34% of iloprost versus 6% of placebo patients ( $p = 0.002$ ). **Iloprost delayed the time to clinical worsening ( $p = 0.0219$ ).** Improvements were noted in postinhalation placebo-adjusted change in mean pulmonary artery pressure ( $-8$  mm Hg;  $p < 0.001$ ) and pulmonary vascular resistance ( $-254$  dyn  $\cdot$  s  $\cdot$  cm $^{-5}$ ;  $p < 0.001$ ). Combination therapy was well tolerated.
- Ⓢ Conclusions: Within the limitations of a relatively small sample size, results of this study demonstrate that the addition of inhaled iloprost in patients with PAH with reduced exercise capacity on bosentan monotherapy is safe and efficacious.

# PACES: Addition of sildenafil to epoprostenol



Treatment	Persons at Risk (Censored), <i>n</i>				
	Baseline	Day 28*	Day 56†	Day 84‡	Day 112§
Epoprostenol + placebo	131	123 (1)	116 (0)	111 (2)	70 (36)
Epoprostenol + sildenafil	134	134 (0)	128 (2)	125 (2)	78 (44)

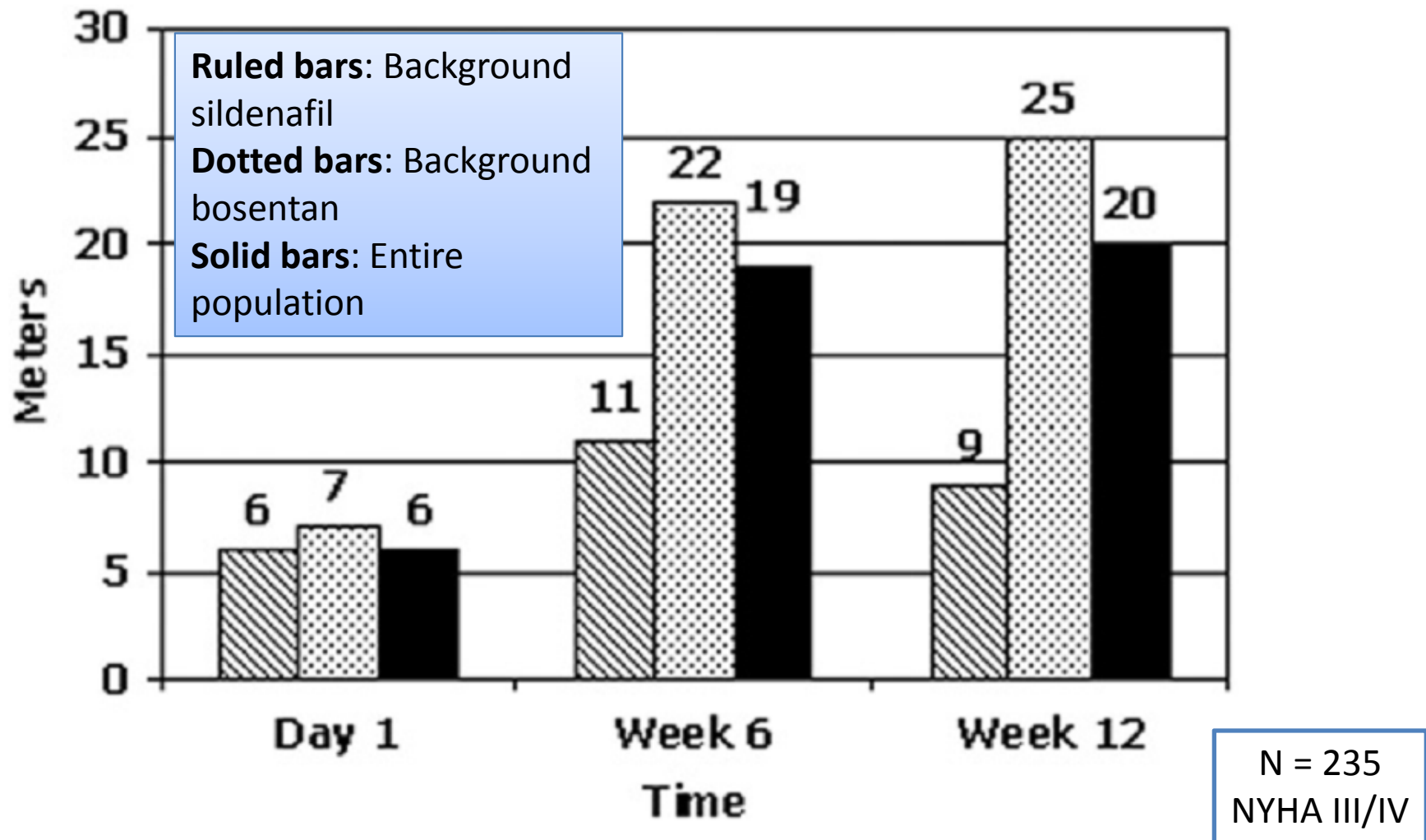
All WHO FC included, but predominantly II, III

Ann Intern Med. 2008 Oct 21;149(8):521-30

# PACES: Addition of sildenafil to epoprostenol

- ⊙ OBJECTIVE: To investigate the effect of adding oral sildenafil to long-term intravenous epoprostenol in patients with pulmonary arterial hypertension.
- ⊙ DESIGN: A **16-week**, double-blind, placebo-controlled, parallel-group study.
- ⊙ SETTING: Multinational study at 41 centers in 11 countries from 3 July 2003 to 27 January 2006.
- ⊙ PATIENTS: 267 patients with pulmonary arterial hypertension (idiopathic, associated anorexigen use or connective tissue disease, or corrected congenital heart disease) who were receiving long-term intravenous epoprostenol therapy.
- ⊙ INTERVENTION: Patients were randomly assigned to receive placebo or sildenafil, 20 mg three times daily, titrated to 40 mg and 80 mg three times daily, as tolerated, at 4-week intervals. Of 265 patients who received treatment, 256 (97%) patients (123 in the placebo group and 133 in the sildenafil group) completed the study.
- ⊙ MEASUREMENTS: Change from baseline in exercise capacity measured by 6-minute walk distance (primary end point) and hemodynamic measurements, time to clinical worsening, and Borg dyspnea score (secondary end points).
- ⊙ RESULTS: **A placebo-adjusted increase of 28.8 meters (95% CI, 13.9 to 43.8 meters) in the 6-minute walk distance occurred in patients in the sildenafil group**; these improvements were most prominent among patients with baseline distances of 325 meters or more. Relative to epoprostenol monotherapy, addition of sildenafil resulted in a greater change in mean pulmonary arterial pressure by -3.8 mm Hg (CI, -5.6 to -2.1 mm Hg); cardiac output by 0.9 L/min (CI, 0.5 to 1.2 L/min); and longer time to clinical worsening, with a smaller proportion of patients experiencing a worsening event in the sildenafil group (0.062) than in the placebo group (0.195) by week 16 ( $P = 0.002$ ). Health-related quality of life also improved in patients who received combined therapy compared with those who received epoprostenol monotherapy. There was no effect on the Borg dyspnea score. Of the side effects generally associated with sildenafil treatment, the most commonly reported in the placebo and sildenafil groups, respectively, were headache (34% and 57%; difference, 23 percentage points [CI, 12 to 35 percentage points]), dyspepsia (2% and 16%; difference, 13 percentage points [CI, 7 to 20 percentage points]), pain in extremity (18% and 25%; difference, 8 percentage points [CI, -2 to 18 percentage points]), and nausea (18% and 25%; difference, 8 percentage points [CI, -2 to 18 percentage points]).
- ⊙ LIMITATIONS: The study excluded patients with pulmonary arterial hypertension associated with other causes. There was an imbalance in missing data between groups, with 8 placebo recipients having no postbaseline walk assessment compared with 1 sildenafil recipient. These patients were excluded from the analysis.
- ⊙ CONCLUSION: In some patients with pulmonary arterial hypertension, the addition of sildenafil to long-term intravenous epoprostenol therapy improves exercise capacity, hemodynamic measurements, time to clinical worsening, and quality of life, but not Borg dyspnea score. Increased rates of headache and dyspepsia occurred with the addition of sildenafil.

# TRIUMPH I: Addition of inhaled treprostinil to oral therapy (Bosentan/Sildenafil)

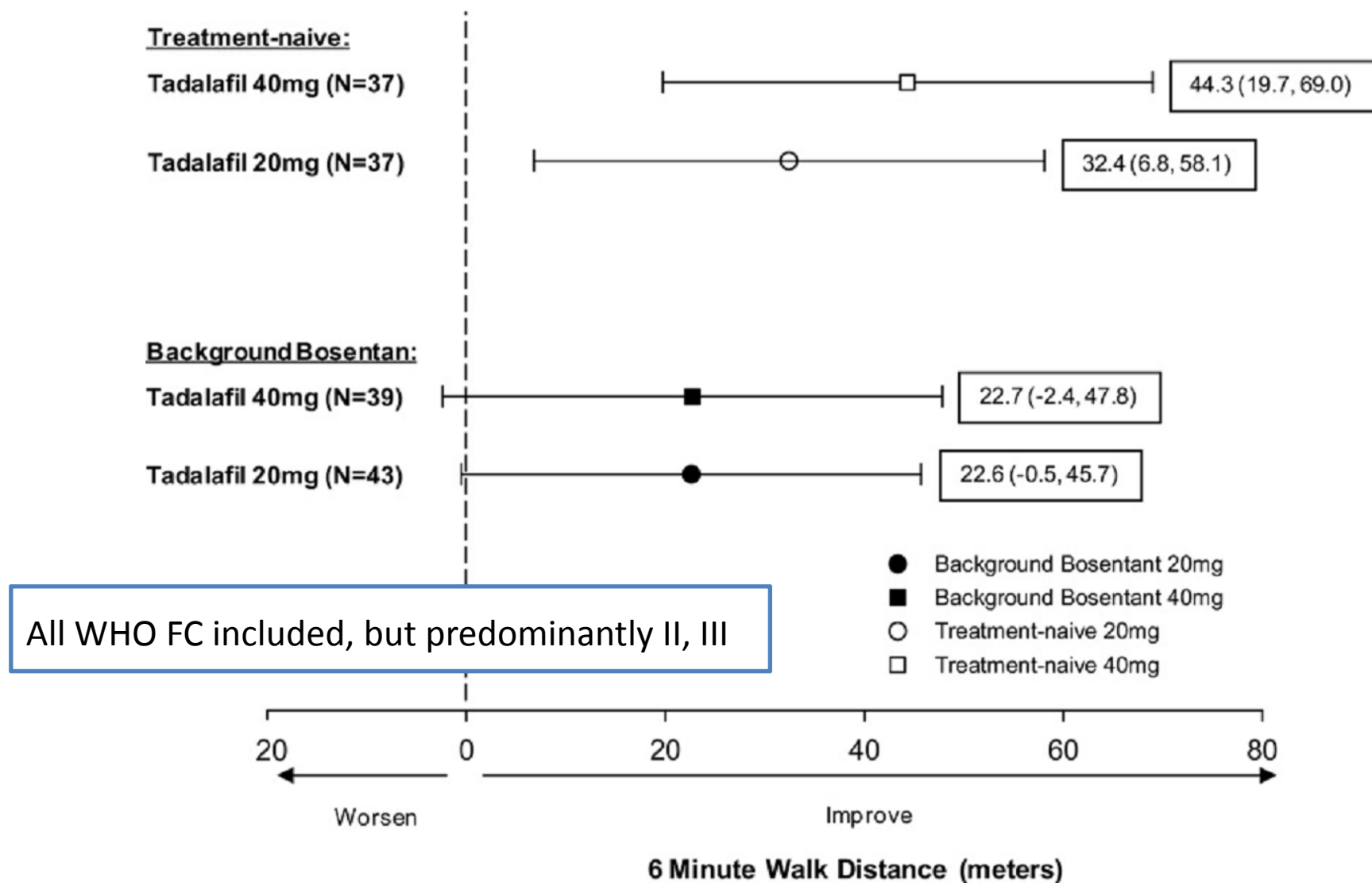


# TRIUMPH I: Addition of inhaled treprostinil to oral therapy

- Ⓢ Objectives: This study assessed the efficacy and safety of inhaled treprostinil in pulmonary arterial hypertension (PAH) patients receiving therapy with either bosentan or sildenafil.
- Ⓢ Methods: Two hundred thirty-five PAH patients with New York Heart Association (NYHA) functional class III (98%) or IV symptoms and a 6-min walk distance (6MWD) of 200 to 450 m while treated with bosentan (70%) or sildenafil were randomized to inhaled treprostinil (up to 54 µg) or inhaled placebo 4 times daily. The primary end point was peak 6MWD at 12 weeks. Secondary end points included time to clinical worsening, Borg Dyspnea Score, NYHA functional class, 12-week trough 6MWD, 6-week peak 6MWD, quality of life, and PAH signs and symptoms. The biomarker N-terminal pro-brain natriuretic peptide (NT-proBNP) was assessed.
- Ⓢ Results: Twenty-three patients withdrew from the study prematurely (13 treprostinil, 10 placebo). **The Hodges-Lehmann between-treatment median difference in change from baseline in peak 6MWD was 19 m at week 6 ( $p = 0.0001$ ) and 20 m at week 12 ( $p = 0.0004$ ).** Hodges-Lehmann between-treatment median difference in change from baseline in trough 6MWD at week 12 was 14 m ( $p = 0.0066$ ). Quality of life measures and NT-proBNP improved on active therapy. There were no improvements in other secondary end points, including time to clinical worsening, Borg Dyspnea Score, NYHA functional class, and PAH signs and symptoms. Inhaled treprostinil was safe and well-tolerated.
- Ⓢ Conclusions: This trial demonstrates that, among PAH patients who remain symptomatic on bosentan or sildenafil, inhaled treprostinil improves exercise capacity and quality of life and is safe and well-tolerated. (TRIUMPH I: Double Blind Placebo Controlled Clinical Investigation Into the Efficacy and Tolerability of Inhaled Treprostinil Sodium in Patients With Severe Pulmonary Arterial Hypertension; NCT00147199)

McLaughlin VV et al. J Am Coll Cardiol. 2010 May 4;55(18):1915-22.

# PHIRST-1: Addition of Tadalafil to Bosentan



# PHIRST-1: Addition of Tadalafil to Bosentan

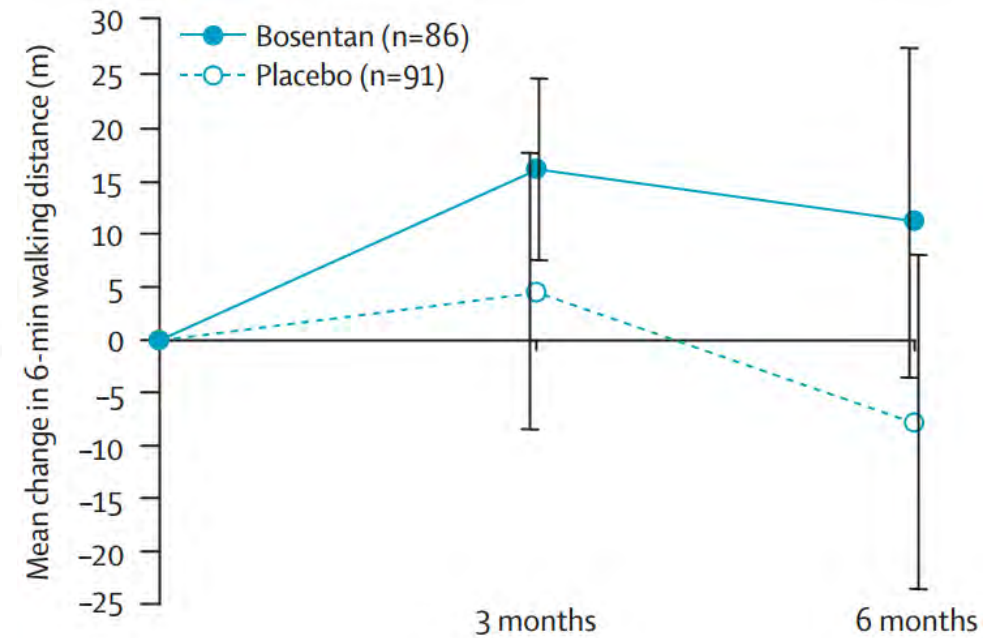
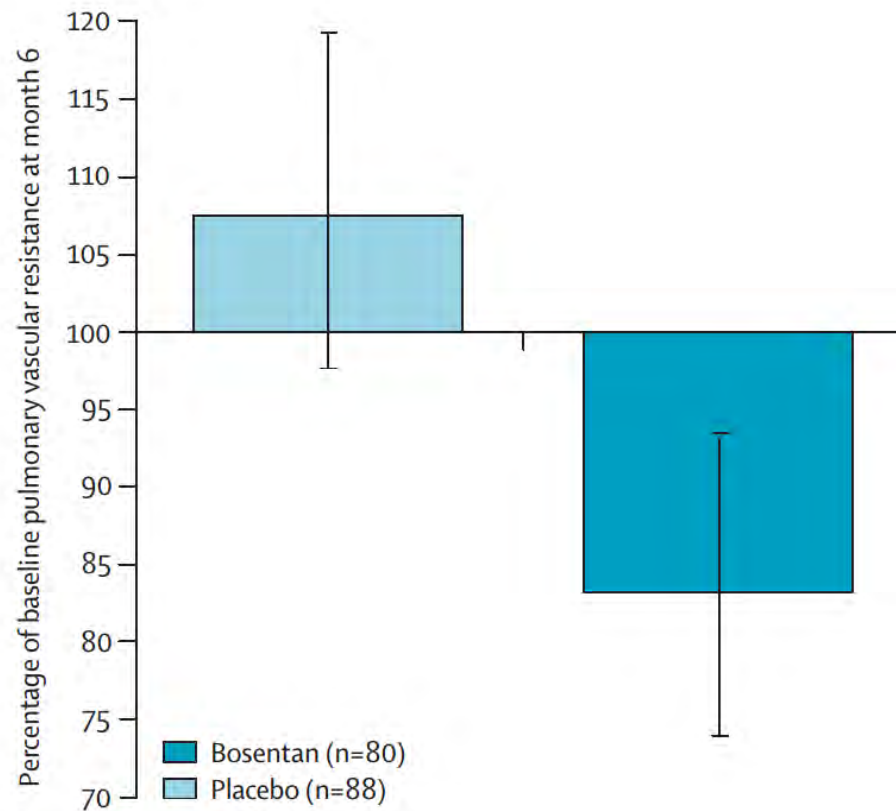
- Ⓒ Background: Tadalafil 40 mg orally once daily, was shown to be well-tolerated and efficacious for pulmonary arterial hypertension in a 16-week, double-blind, **placebo (PBO)**-controlled trial. Inclusion criteria included the option for background bosentan. Analyses of tadalafil in treatment-naive patients and as add-on to bosentan were pre-specified. Objectives were to provide safety and efficacy data for both groups.
- Ⓒ Methods: Groups analyzed included: treatment-naive + PBO; treatment-naive + tadalafil; background bosentan + PBO; and background bosentan + tadalafil. Patients randomized to tadalafil or PBO (N = 405) were analyzed by bosentan use (yes = 216, no = 189). Treatment differences in 6-minute walk distance (6MWD, PBO-adjusted), functional class (FC), clinical worsening (CW) and adverse events were assessed. Hazard ratios (HRs) with 95% confidence intervals (CIs) are presented for FC and CW.
- Ⓒ Results: **At Week 16, PBO-adjusted 6MWD increases were 44 m (CI: 20 to 69 m; n = 37) for tadalafil 40 mg in treatment-naive patients and 23 m (CI: -2 to 48 m; n = 42) for tadalafil 40 mg add-on to bosentan.** The 6MWD for treatment-naive and background bosentan PBO patients decreased by 3 m and increased by 19 m, respectively, at Week 16 compared with baseline. Two (5%) treatment-naive patients had CW with tadalafil 40 mg vs 8 (22%) with PBO (HR = 3.3, CI: 1.1 to 10.0). Two (5%) background bosentan patients had CW with tadalafil 40 mg add-on vs 5 (11%) for PBO add-on (HR = 1.9, CI: 0.4 to 10.2). Adverse events for tadalafil monotherapy and as add-on were similar.
- Ⓒ Conclusion: Tadalafil 40 mg was well-tolerated and provided clinical benefit in patients as monotherapy. It was also well-tolerated when added to background bosentan, but data are insufficient to conclude additional benefit.



**Is there any benefit in treating early  
PAH?**



# EARLY: WHO FC II



N = 185

# EARLY: WHO FC II

- Ⓢ Background: Treatments for pulmonary arterial hypertension have been mainly studied in patients with advanced disease (WHO functional class [FC] III and IV). This study was designed to assess the effect of the dual endothelin receptor antagonist bosentan in patients with WHO FC II pulmonary arterial hypertension.
- Ⓢ Methods: Patients with WHO FC II pulmonary arterial hypertension aged 12 years or over with 6-min walk distance of less than 80% of the normal predicted value or less than 500 m associated with a Borg dyspnoea index of 2 or greater were enrolled in this double-blind, placebo-controlled, multicentre trial. 185 patients were randomly assigned to receive bosentan (n=93) or placebo (n=92) for the 6-month double-blind treatment period via a centralised integrated voice recognition system. Primary endpoints were pulmonary vascular resistance at month 6 expressed as percentage of baseline and change from baseline to month 6 in 6-min walk distance. Analyses of the primary endpoints were done with all randomised patients who had a valid baseline assessment and an assessment or an imputed value for month 6.
- Ⓢ Findings: Analyses were done with 168 patients (80 in the bosentan group, 88 in the placebo group) for pulmonary vascular resistance and with 177 (86 and 91) for 6-min walking distance. **At month 6, geometric mean pulmonary vascular resistance was 83·2% (95% CI 73·8–93·7) of the baseline value in the bosentan group and 107·5% (97·6–118·4) of the baseline value in the placebo group (treatment effect –22·6%, 95% CI –33·5 to –10·0; p<0·0001). Mean 6-min walk distance increased from baseline in the bosentan group (11·2 m, 95% CI –4·6 to 27·0) and decreased in the placebo group (–7·9 m, –24·3 to 8·5), with a mean treatment effect of 19·1 m (95% CI 3·6–41·8; p=0·0758).** 12 (13%) patients in the bosentan group and eight (9%) in the placebo group reported serious adverse events, the most common of which were syncope in the bosentan group and right ventricular failure in the placebo group.
- Ⓢ Interpretation: Bosentan treatment could be beneficial for patients with WHO FC II pulmonary arterial hypertension.

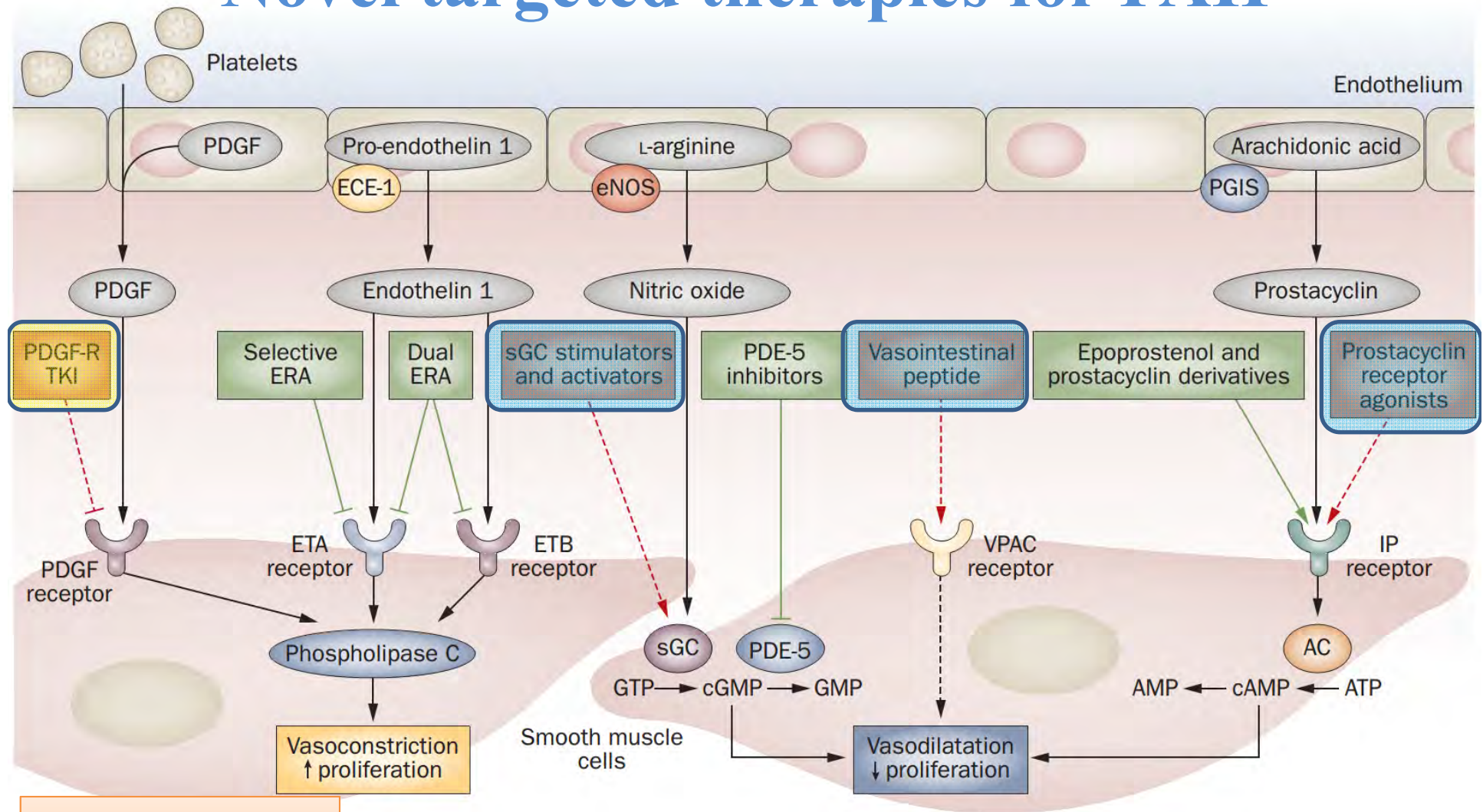
Galie N et al. Lancet 2008; 371: 2093–100.

# Emerging therapies in PAH

# Why are novel therapies needed?

- ⌚ These therapies (ERAs, PDE5-I, PGI2) can improve symptoms and exercise capacity. Although they have some anti-proliferative properties, they **do not reverse abnormal cell proliferation in vivo and, as such, do not represent a cure for PAH**. Thus, growth factors such as platelet-derived growth factor, epidermal growth factor and fibroblast growth factor, which are involved in abnormal proliferation, form targets for future novel therapies. (Source: PAH and CTEPH pathophysiology Humbert 2010)

# Novel targeted therapies for PAH



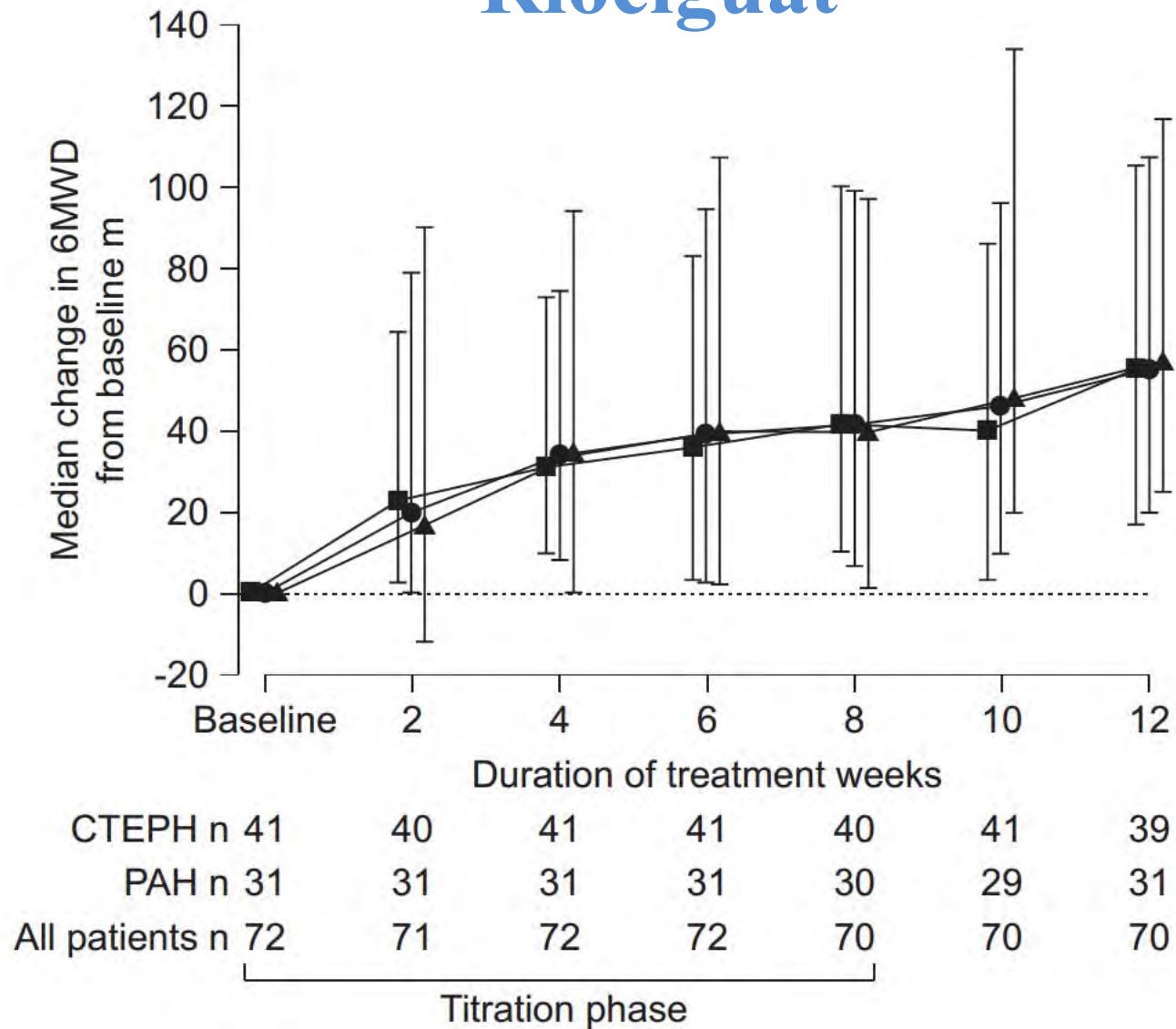
Inhibition of Rho and Ras family GTPases:  
**Statins**

O'Callaghan, D. S. et al. Nat. Rev. Cardiol. 8, 526–538 (2011)

# Novel targeted therapies

- ② PDGF-R tyrosine kinase inhibitors: Imatinib, Sorafenib, Nilotinib
- ② Soluble Guanylate cyclase (sGC) stimulators: Riociguat
- ② Vasointestinal peptide (VIP, or its analog aviptadil)
- ② Nonprostanoid prostacyclin receptor agonist: Selexipag (GRIPHON Phase III trial)

# Riociguat





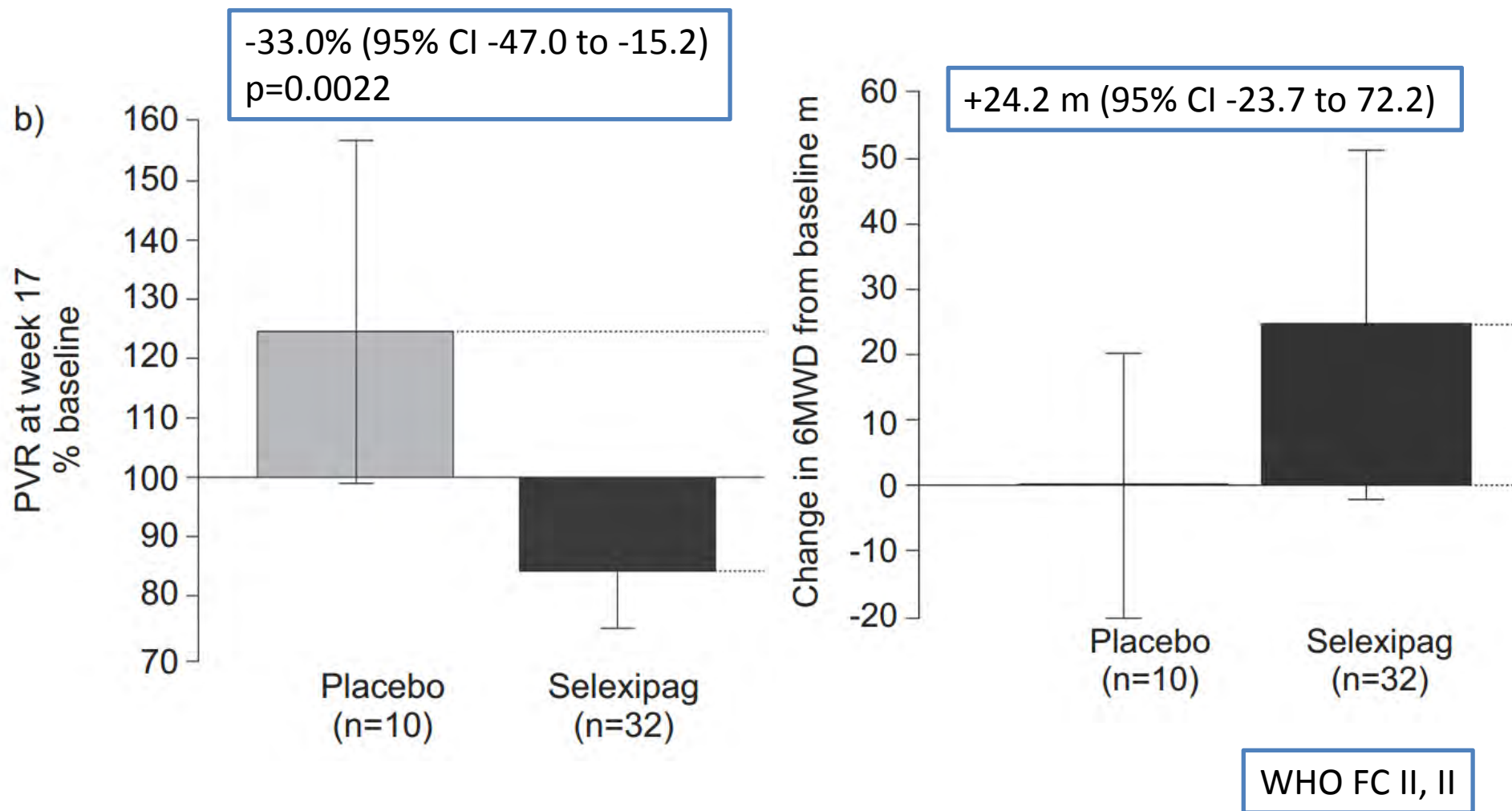
# Riociguat

- ⊙ We assessed the therapeutic potential of riociguat, **a novel soluble guanylate cyclase stimulator**, in adults with chronic thromboembolic pulmonary hypertension (CTEPH; n = 42) or pulmonary arterial hypertension (PAH; n = 33) in World Health Organization (WHO) functional class II/III. In this **12-week, multicentre, open-label, uncontrolled phase II study**, patients received oral riociguat 1.0-2.5 mg t.i.d. titrated according to systemic systolic blood pressure (SBP). Primary end-points were safety and tolerability; pharmacodynamic changes were secondary end-points. Riociguat was generally well tolerated. Asymptomatic hypotension (SBP <90 mmHg) occurred in 11 patients, but blood pressure normalised without dose alteration in nine and after dose reduction in two. Median 6-min walking distance increased in patients with CTEPH (55.0 m from baseline (390 m);  $p < 0.0001$ ) and PAH (57.0 m from baseline (337 m);  $p < 0.0001$ ); patients in functional class II or III and bosentan pre-treated patients showed similar improvements. Pulmonary vascular resistance was significantly reduced by 215 dyn·s·cm(-5) from baseline (709 dyn·s·cm(-5);  $p < 0.0001$ ). 42 (56%) patients were considered to have experienced drug-related adverse events (AEs; 96% mild or moderate). **Dyspepsia, headache and hypotension were the most frequent AEs.** Study discontinuation because of AEs was 4%. These preliminary data show that riociguat has a favourable safety profile and improves exercise capacity, symptoms and pulmonary haemodynamics in CTEPH and PAH. Randomised controlled trials are underway.

Ghofrani HA et al. Eur Respir J. 2010 Oct;36(4):792-9.



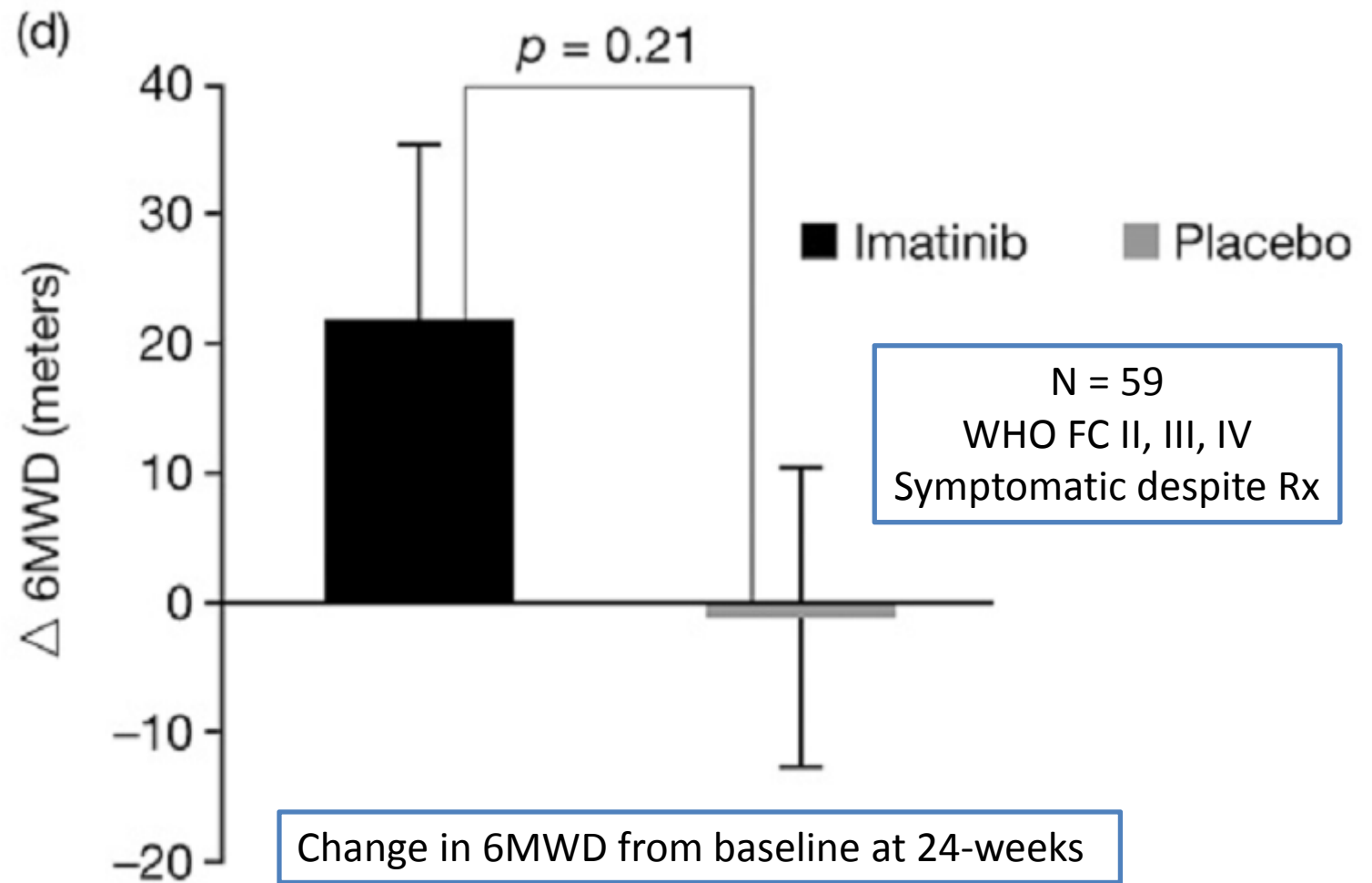
# Selexipag



# Selexipag

- ④ In this **phase 2 proof-of-concept study** we examined the safety and efficacy of selexipag, an orally available, **selective prostacyclin receptor (IP receptor) agonist**, as a treatment for pulmonary arterial hypertension (PAH). 43 adult patients with symptomatic PAH (receiving stable endothelin receptor antagonist and/or a phosphodiesterase type-5 inhibitor therapy) were randomised three to one to receive either selexipag or placebo. Dosage was up-titrated in 200-µg increments from 200 µg twice daily on day 1 to the maximum tolerated dose by day 35 (maximum allowed dose of 800 µg twice daily). Change in pulmonary vascular resistance at week 17 expressed as a percentage of the baseline value was the primary efficacy end-point, and was analysed in the per protocol set first and then in the all-treated set to assess robustness of results. A statistically significant 30.3% reduction in geometric mean pulmonary vascular resistance was observed after 17 weeks' treatment with selexipag compared with placebo (95% confidence limits -44.7- -12.2;  $p=0.0045$ , Wilcoxon rank sum test). This was supported by a similar result from the all-treated set. Selexipag was well tolerated with a safety profile in line with the expected pharmacological effect. Our results encourage the further investigation of selexipag for the treatment of PAH.

# Imatinib



# Imatinib

- Ⓢ RATIONALE: Pulmonary arterial hypertension (PAH) is a progressive condition with a poor prognosis. Platelet-derived growth factor receptor (PDGFR) signaling plays an important role in its pathobiology.
- Ⓢ OBJECTIVES: To assess safety, tolerability, and efficacy of the PDGFR inhibitor imatinib in patients with PAH.
- Ⓢ METHODS: Patients with PAH in functional classes II-IV were enrolled in a **24-week** randomized, double-blind, placebo-controlled **pilot study**. Patients received imatinib (an inhibitor of PDGFR activity) 200 mg orally once daily (or placebo), which was increased to 400 mg if the initial dose was well tolerated. The primary endpoints were safety and change from baseline in the 6-minute-walk distance (6MWD). Secondary endpoints included hemodynamics and functional classification.
- Ⓢ MEASUREMENTS AND MAIN RESULTS: Fifty-nine patients enrolled (imatinib [n = 28]; placebo [n = 31]); 42 completed the study. Dropouts were equally matched between the two groups. In the intention-to-treat (ITT) population there was no significant change in the 6MWD (mean  $\pm$  SD) in the imatinib versus placebo group ( $+22 \pm 63$  versus  $-1.0 \pm 53$  m). There was a significant decrease in pulmonary vascular resistance (imatinib  $-300 \pm 347$  versus placebo  $-78 \pm 269$  dynes  $\cdot$  s  $\cdot$  cm $^{-5}$ ,  $P < 0.01$ ) and increase in cardiac output (imatinib  $+0.6 \pm 1.2$  versus placebo  $-0.1 \pm 0.9$  L/min,  $P = 0.02$ ). Serious adverse events occurred in 11 imatinib recipients (39%) and 7 placebo recipients (23%). Three deaths occurred in each group. Post hoc subgroup analyses suggest that patients with greater hemodynamic impairment may respond better than patients with less impairment.
- Ⓢ CONCLUSIONS: These data from a **Phase II study** are consistent with imatinib being well tolerated in patients with PAH, and provide proof of concept for further studies evaluating its safety, tolerability, and efficacy in PAH.

Ghofrani HA et al. Am J Respir Crit Care Med. 2010 Nov 1;182(9):1171-7.



October 2011, Vol 140, No. 4\_MeetingAbstracts

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Slide Presentations | October 2011

## **Imatinib Improves Exercise Capacity and Hemodynamics at 24 Weeks as Add-on Therapy in Symptomatic Pulmonary Arterial Hypertension Patients: The IMPRES Study**

FREE TO VIEW

Marius Hoyer, MD; Robyn Barst, MD; Robert Bourge, MD; J. Feldman, MD; A. Frost, MD; Nazzareno Galie, MD; Miguel Angel Gomez Sanchez, MD; Ekkehard Gruenig, MD; Paul Hassoun, MD; Nicholas Morrell, MD; Andrew Peacock, MD; Toru Satoh, MD; Gérald Simonneau, MD; Victor Tapson, MD; F. Torres, MD; Keith Liu, PhD; Debbie Quinn, MD; Hossein Ghofrani, MD

[▶ Author and Funding Information](#)

N = 202

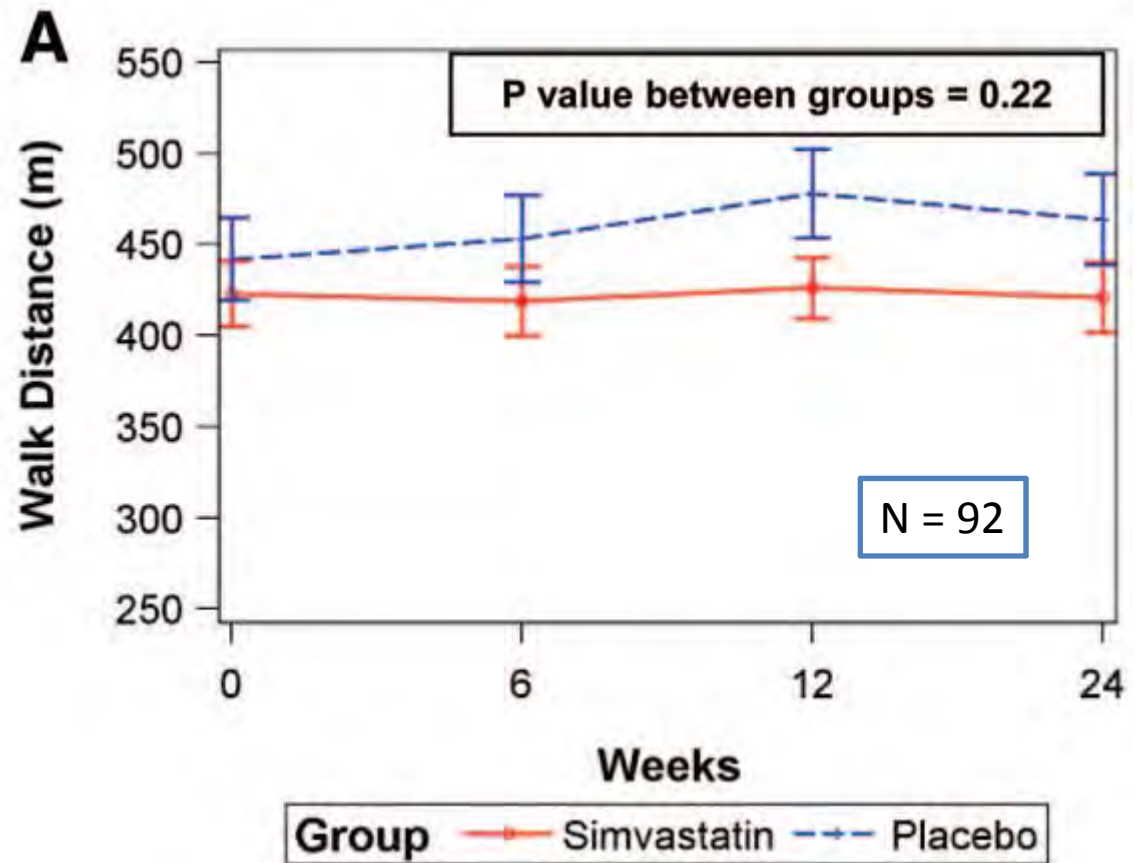
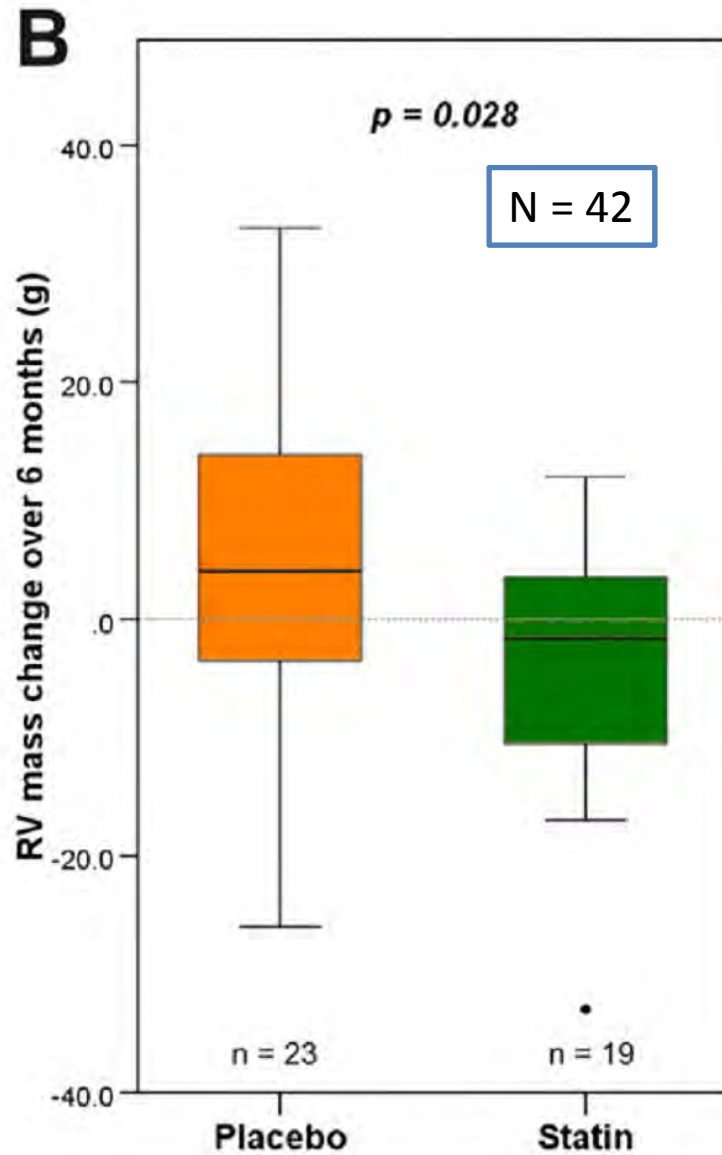
CHEST. 2011;140(4\_MeetingAbstracts):1045A-1045A. doi:10.1378/chest.1216523



# IMPRES: Imatinib

- Ⓢ PURPOSE: Pulmonary arterial hypertension (PAH) involves enhanced pulmonary vascular remodeling and proliferation. Currently approved therapies for PAH target the prostacyclin, endothelin and nitric oxide pathways. Imatinib is a novel orally-active anti-proliferative therapy in clinical development for PAH. The IMPRES study evaluated its efficacy, safety and tolerability over 24 weeks in patients with persistent PAH despite optimized therapy with established PAH therapies.
- Ⓢ METHODS: Double-blind, randomized, parallel-group study comparing oral imatinib (200 mg once daily, increased to 400 mg once daily after 2 weeks if well tolerated) with placebo in patients with pulmonary vascular resistance (PVR)  $\geq 800$  dynes/sec/cm-5 despite receiving at least two PAH-specific therapies. **Primary endpoint was change in 6-minute walk distance (6MWD), between baseline and Week 24.** Secondary endpoints included changes in hemodynamics, NT-pro-BNP, time to clinical worsening (TTCW) and safety and tolerability.
- Ⓢ RESULTS: 202 patients were randomized (103 imatinib; 99 placebo). Mean age 48 years (18-77), mean duration of PAH 5.3 years, 67.7% WHO Class III and mean 6MWD 344 m (337 vs 351 m for imatinib and placebo, respectively). 67.0% imatinib and 81.8% placebo patients completed and entered a separate extension study. Placebo-corrected treatment effects at Week 24 vs baseline included: improved 6MWD (32 m;  $p=0.002$ ), PVR (-379 dynes/sec/cm-5,  $p<0.001$ ), cardiac output (0.88 L/min,  $p<0.001$ ) and NT-pro-BNP values (-45.10 pmol/L,  $p=0.04$ ). The hazard ratio for TTCW was 1.16 (imatinib-placebo,  $p=0.563$ ). The overall incidence of adverse events (AEs) was similar for imatinib and placebo (97% vs 96% respectively). Serious AEs were more frequent with imatinib than placebo (44% vs 30%). There were three deaths in each group.
- Ⓢ CONCLUSIONS: Imatinib significantly improved 6MWD, CO, PVR and NT-pro-BNP. SAEs were higher in the imatinib group as expected for this population and class of drug. Long-term outcomes will be explored in extension studies.
- Ⓢ CLINICAL IMPLICATIONS: Imatinib may provide a new therapeutic option for selected PAH patients, symptomatic on two or more established PAH therapies.

# Simvastatin



**SiPHT.** Am J Respir Crit Care Med. 2010 May 15;181(10):1106-13

**ASA-STAT.** Circulation. 2011 Jun 28;123(25):2985-93

# Simvastatin MoA

- ② Statins offer a novel approach to the treatment of PAH. In addition to lowering cholesterol, statins have been shown to have antiproliferative, antithrombotic, antiinflammatory, and antioxidant effects. This spectrum of activity arises from **the inhibition of isoprenoids (geranylgeranylpyrophosphate and farnesylpyrophosphate), which are essential for the post-translational isoprenylation of Rho and Ras family GTPases.**
- ② Statins, in particular simvastatin, have been reported to attenuate the development of pulmonary hypertension in a number of experimental animal models and to regress established pulmonary hypertension and vascular remodeling induced by either pneumonectomy and monocrotaline treatment or chronic hypoxia. There is evidence that this is achieved through **increased apoptosis as well as reduced proliferation of smooth muscle cells in obstructive vascular lesions.** Of interest, not all studies report a reduction in pulmonary artery pressure, but a reduction in right ventricular (RV) hypertrophy appears to be a consistent finding



# Simvastatin

- ④ **SiPHT:** Forty-two patients with PAH were randomized to receive either simvastatin (80 mg/d) or placebo in addition to current care for 6 months, and thereafter offered open-label simvastatin. The primary outcome was change in RV mass, assessed by cardiac magnetic resonance (CMR). MEASUREMENTS AND MAIN RESULTS: At 6 months, RV mass decreased by  $5.2 \pm 11$  g in the statin group ( $P = 0.045$ ) and increased  $3.9 \pm 14$  g in the placebo group. The treatment effect was  $-9.1$  g ( $P = 0.028$ ). N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels decreased significantly in the statin group ( $-75 \pm 167$  fmol/ml;  $P = 0.02$ ) but not the placebo group ( $49 \pm 224$  fmol/ml;  $P = 0.43$ ; overall treatment effect  $-124$  fmol/ml;  $P = 0.041$ ). There were no significant changes in other outcome measures (including 6-minute walk test, cardiac index, and circulating cytokines). From 6 to 12 months, both RV mass and NT-proBNP increased toward baseline values in 16 patients on active treatment who continued with simvastatin but remained stable in 18 patients who switched from placebo to simvastatin. Two patients required a reduction in dose but not cessation of simvastatin. CONCLUSIONS: Simvastatin added to conventional therapy produces a small and transient early reduction in RV mass and NT-proBNP levels in patients with PAH, but this is not sustained over 12 months.

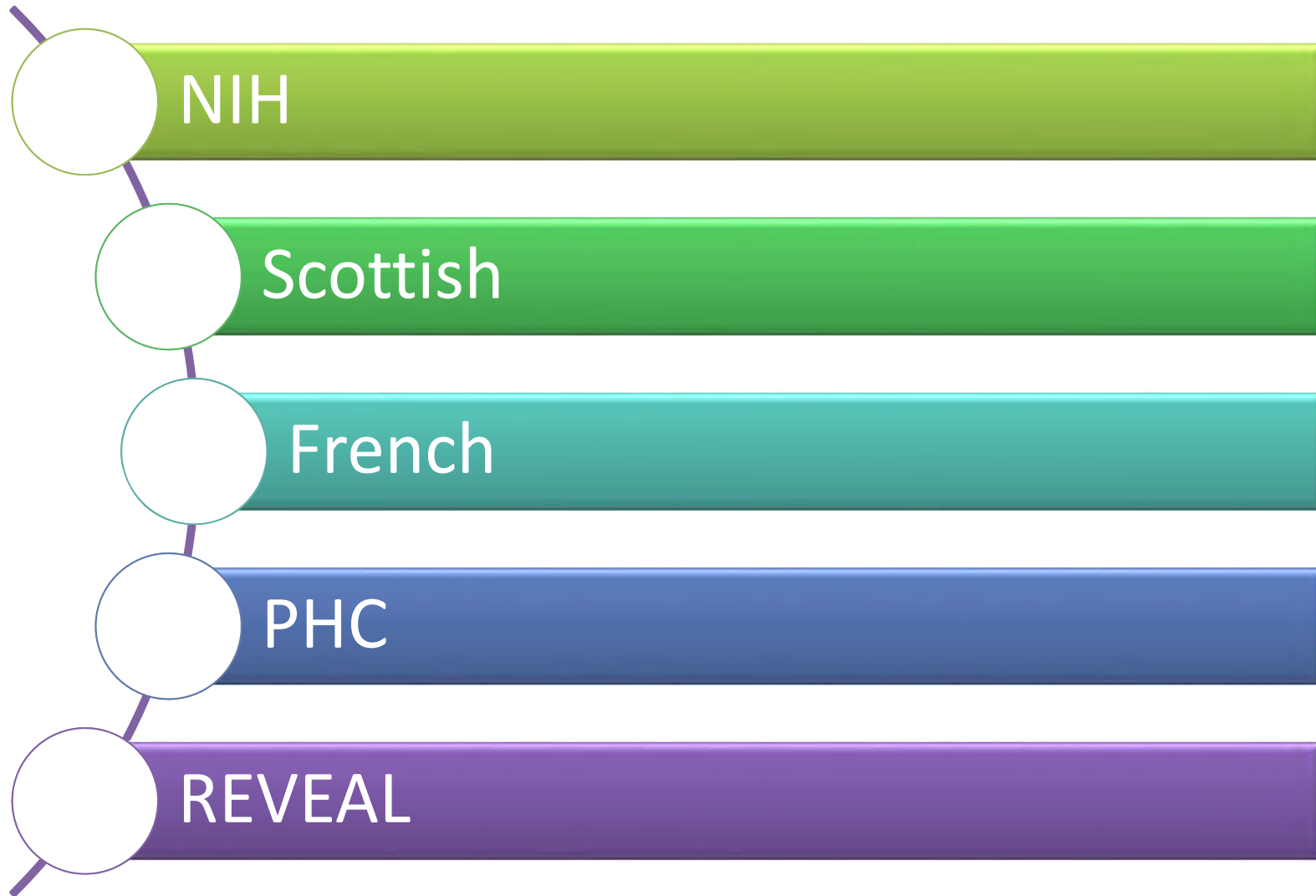
- ④ **ASA-STAT:** We performed a randomized, double-blind, placebo-controlled  $2 \times 2$  factorial clinical trial of aspirin and simvastatin in patients with PAH receiving background therapy at 4 centers. A total of 92 patients with PAH were to be randomized to aspirin 81 mg or matching placebo and simvastatin 40 mg or matching placebo. The primary outcome was 6-minute walk distance at 6 months. Sixty-five subjects had been randomized when the trial was terminated by the Data Safety and Monitoring Board after an interim analysis showed futility in reaching the primary end point for simvastatin. After adjustment for baseline 6-minute walk distance, there was no significant difference in the 6-minute walk distance at 6 months between aspirin ( $n=32$ ) and placebo ( $n=33$ ; placebo-corrected difference  $-0.5$  m, 95% confidence interval  $-28.4$  to  $27.4$  m;  $P=0.97$ ) or between simvastatin ( $n=32$ ) and placebo ( $n=33$ ; placebo-corrected difference  $-27.6$  m, 95% confidence interval  $-59.6$  to  $4.3$  m;  $P=0.09$ ). There tended to be more major bleeding episodes with aspirin than with placebo (4 events versus 1 event, respectively;  $P=0.17$ ). CONCLUSIONS: Neither aspirin nor simvastatin had a significant effect on the 6-minute walk distance, although patients randomized to simvastatin tended to have a lower 6-minute walk distance at 6 months. These results do not support the routine treatment of patients with PAH with these medications.

Wilkins MR et al. Am J Respir Crit Care Med. 2010 May 15;181(10):1106-13.

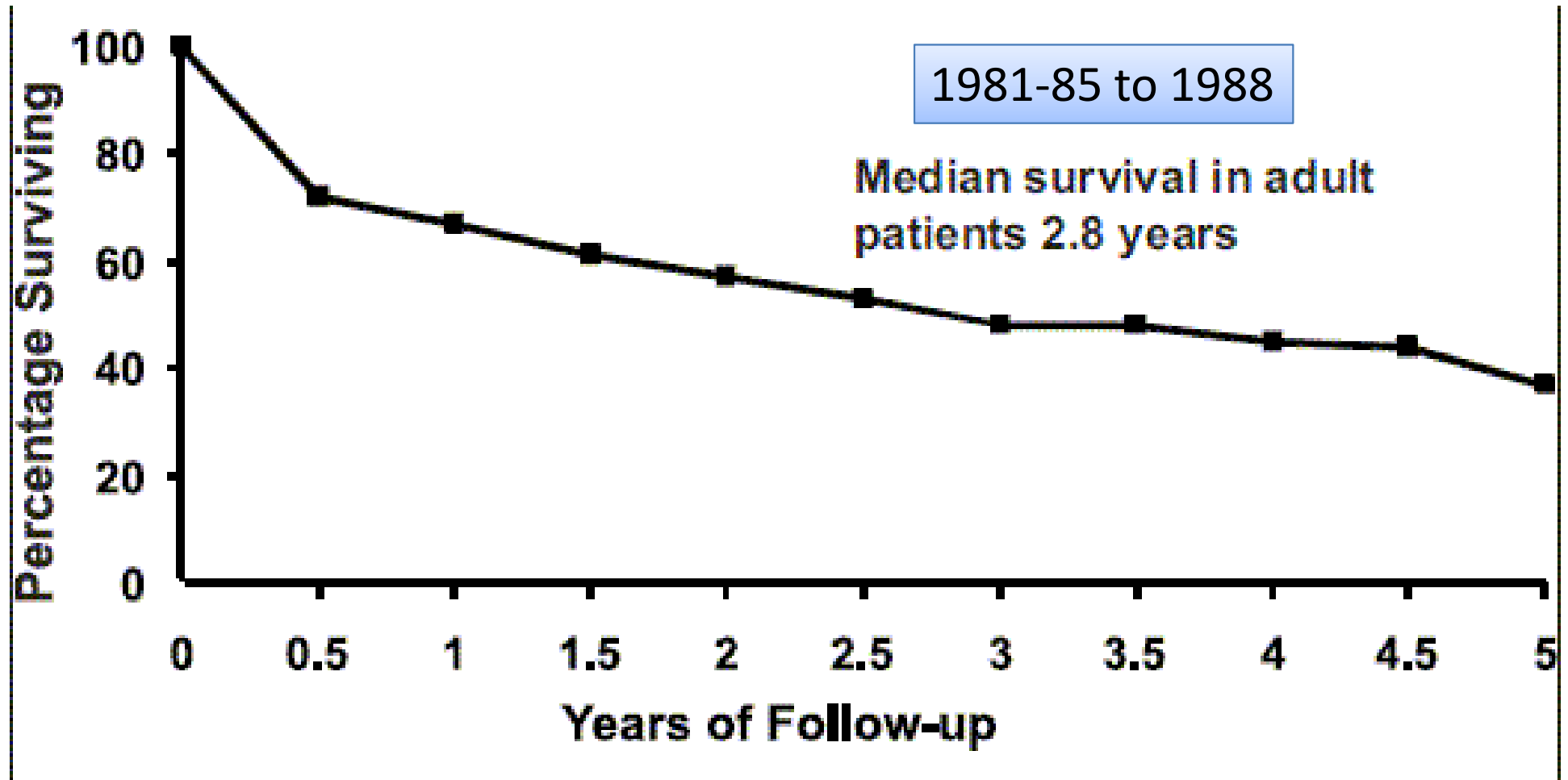
Kawut SM et al. Circulation. 2011 Jun 28;123(25):2985-93.

# Prognosis in PAH

# PAH registries



## Survival: CCB era



NIH registry. D'Alonzo GE et al. Ann Intern Med. 1991 Sep 1;115(5):343-9

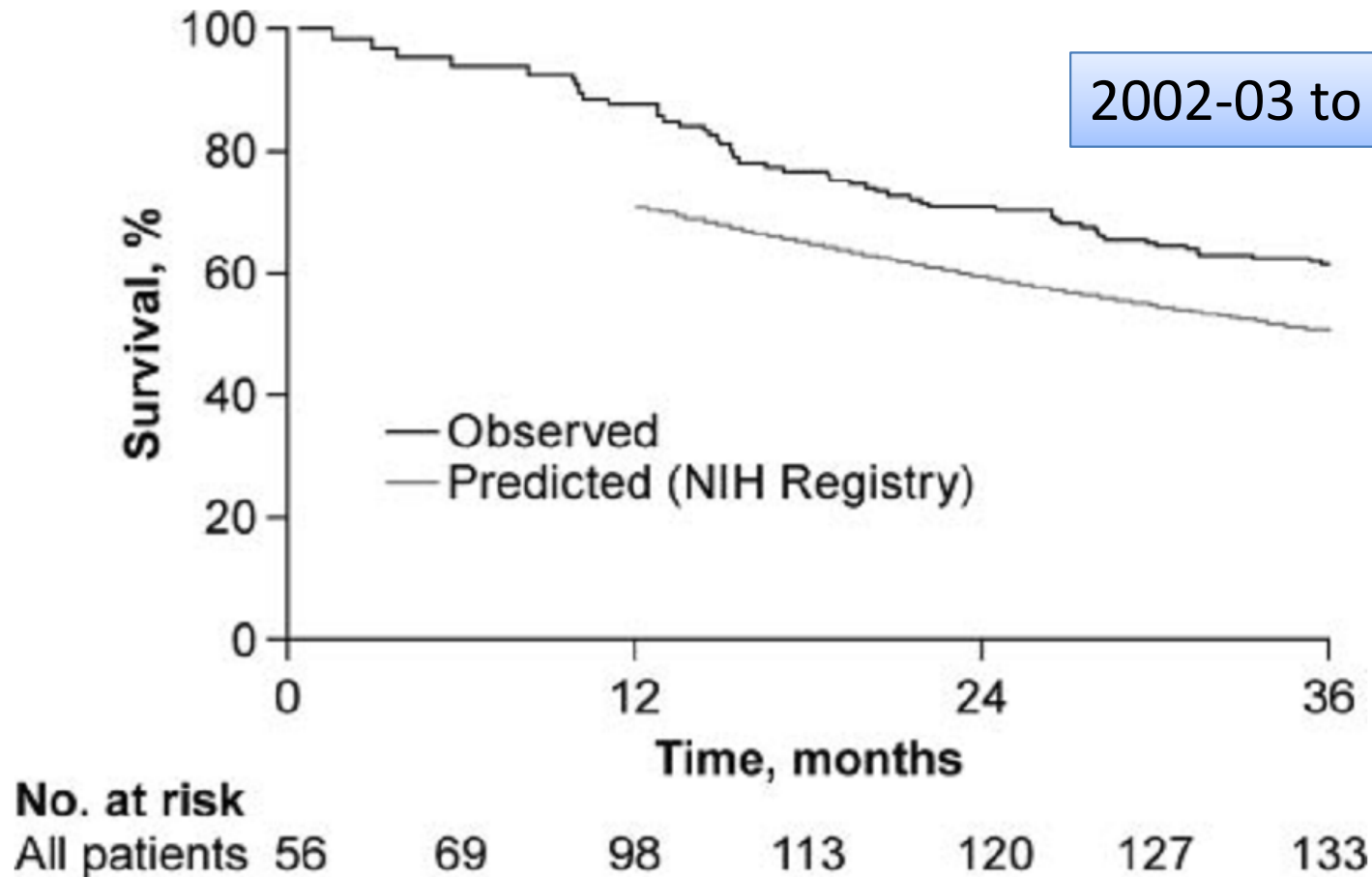
## NIH registry

- ② **Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. D'Alonzo GE et al. Ann Intern Med. 1991 Sep 1;115(5):343-9.**
- ② Thirty-two clinical centers in the United States participating in the Patient Registry for the Characterization of Primary Pulmonary Hypertension supported by the National Heart, Lung, and Blood Institute. **Patients (194) diagnosed at clinical centers between 1 July 1981 and 31 December 1985 and followed through 8 August 1988.** The estimated median survival of these patients was 2.8 years (95% CI, 1.9 to 3.7 years). Estimated single-year survival rates were as follows: at 1 year, 68% (CI, 61% to 75%); at 3 years, 48% (CI, 41% to 55%); and at 5 years, 34% (CI, 24% to 44%).

# NIH registry: Criticism

- ⊙ The **US PH registry** was established in the early 1980s with the support of the National Institutes of Health (NIH; Bethesda, MA, USA). Data from this resource, most commonly referred to simply as the “**NIH registry**”, not only highlighted the burden of this orphan disease in North America but also provided important information regarding its natural history prior to the introduction of targeted therapy. Clinical information and outcome data were collected across US specialised centres on patients diagnosed with “**primary**” PH, now referred to as **idiopathic or familial PAH** according to the updated classification system.
- ⊙ The majority of the 187 patients identified across the country were considered **incident cases**, based on the fact that their inclusion followed initial diagnostic right heart catheterisation. The remaining 36% of patients were considered **prevalent cases (or “survivors”)** since the diagnosis had been made prior to the establishment of the registry. As subsequently highlighted by the French registry data, this distinction between incident and prevalent cases is important because survival rates for incident PAH populations are worse than for corresponding prevalent populations. This is explained by the fact that **the sickest patients who are diagnosed at the same time as the surviving patients from a prevalent population (i.e. survivors that are included in registries) would be expected to have a high early mortality rate**. This high mortality rate subsequently stabilises over time and would then compare favourably to corresponding incident population survival rates (such as those included in registries), since the latter population will include patients that have severe disease and increased risk of early death. This bias is now well recognised and underscores the importance of separately studying incident and prevalent cases when analysing survival data. **Indeed, in the NIH registry, the overall survival for IPAH patients was 2.8 yrs, but was shorter in incident compared with prevalent cases (2.6 versus 3.2 yrs, respectively).**

## Survival: Modern era



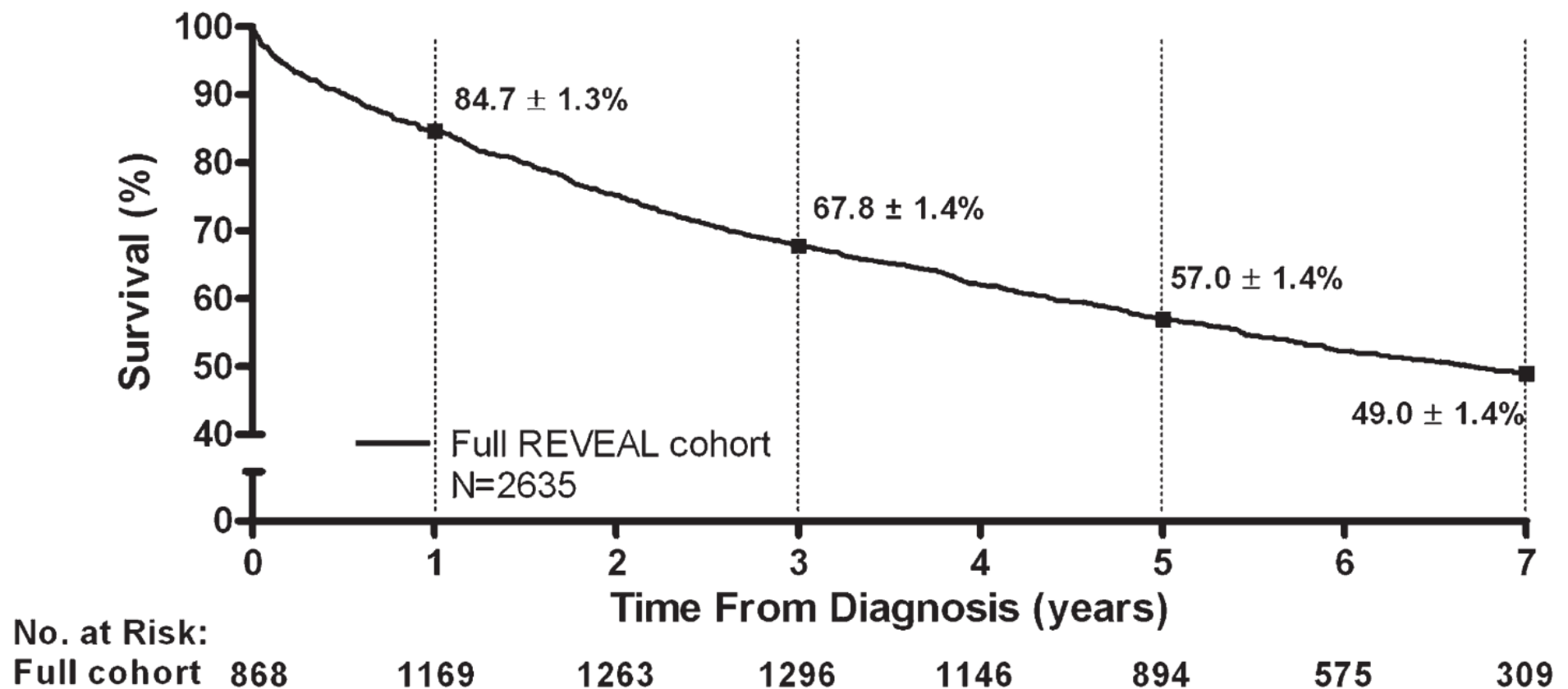
French registry vs. NIH registry: 1-year survival 83% vs 68%; 3-year survival 58% vs 48%

## Survival: French registry (Modern management era)

- ② **Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Humbert M et al. Circulation. 2010 Jul 13;122(2):156-63.**
- ② Between October 2002 and October 2003, 354 consecutive adult patients with idiopathic, familial, or anorexigen-associated pulmonary arterial hypertension (56 incident and 298 prevalent cases) were prospectively enrolled. Patients were followed up for 3 years, and survival rates were analyzed. For incident cases, estimated survival (95% confidence intervals [CIs]) at 1, 2, and 3 years was 85.7% (95% CI, 76.5 to 94.9), 69.6% (95% CI, 57.6 to 81.6), and 54.9% (95% CI, 41.8 to 68.0), respectively. In a combined analysis population (incident patients and prevalent patients diagnosed within 3 years before study entry; n=190), 1-, 2-, and 3-year survival estimates were 82.9% (95% CI, 72.4 to 95.0), 67.1% (95% CI, 57.1 to 78.8), and 58.2% (95% CI, 49.0 to 69.3), respectively.
- ② In France, epoprostenol, bosentan, iloprost, and sildenafil were approved for PAH in March 1998, May 2002, September 2003, and October 2005, respectively



# Survival: Getting better!



# Survival: Comparison across registries

	Enrolment	1-year	3-year	5-year	7-year
NIH registry	1981-85 (R + P)	68%	48%	34%	-
French registry	2002-03 (P)	82.9%	58.2	-	-
PHC registry	2004-07 (R + P)	86%	69%	61%	-
REVEAL registry	2006-09 (R + P)	85%	68%	57%	49%

P: Prospective

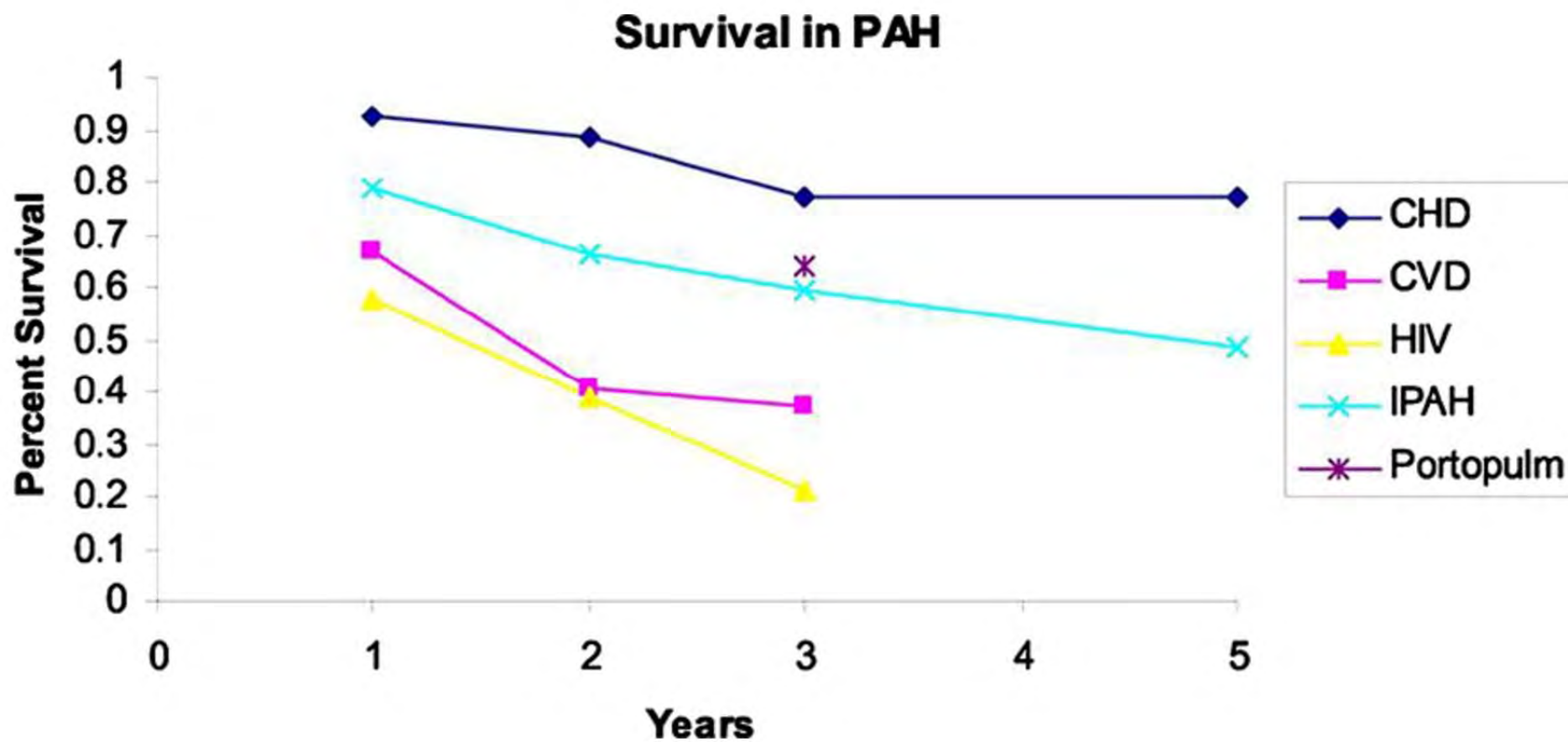
R: Retrospective

NIH registry. D'Alonzo GE et al. Ann Intern Med. 1991 Sep 1;115(5):343-9

French registry. Humbert M et al. Circulation. 2010 Jul 13;122(2):156-63

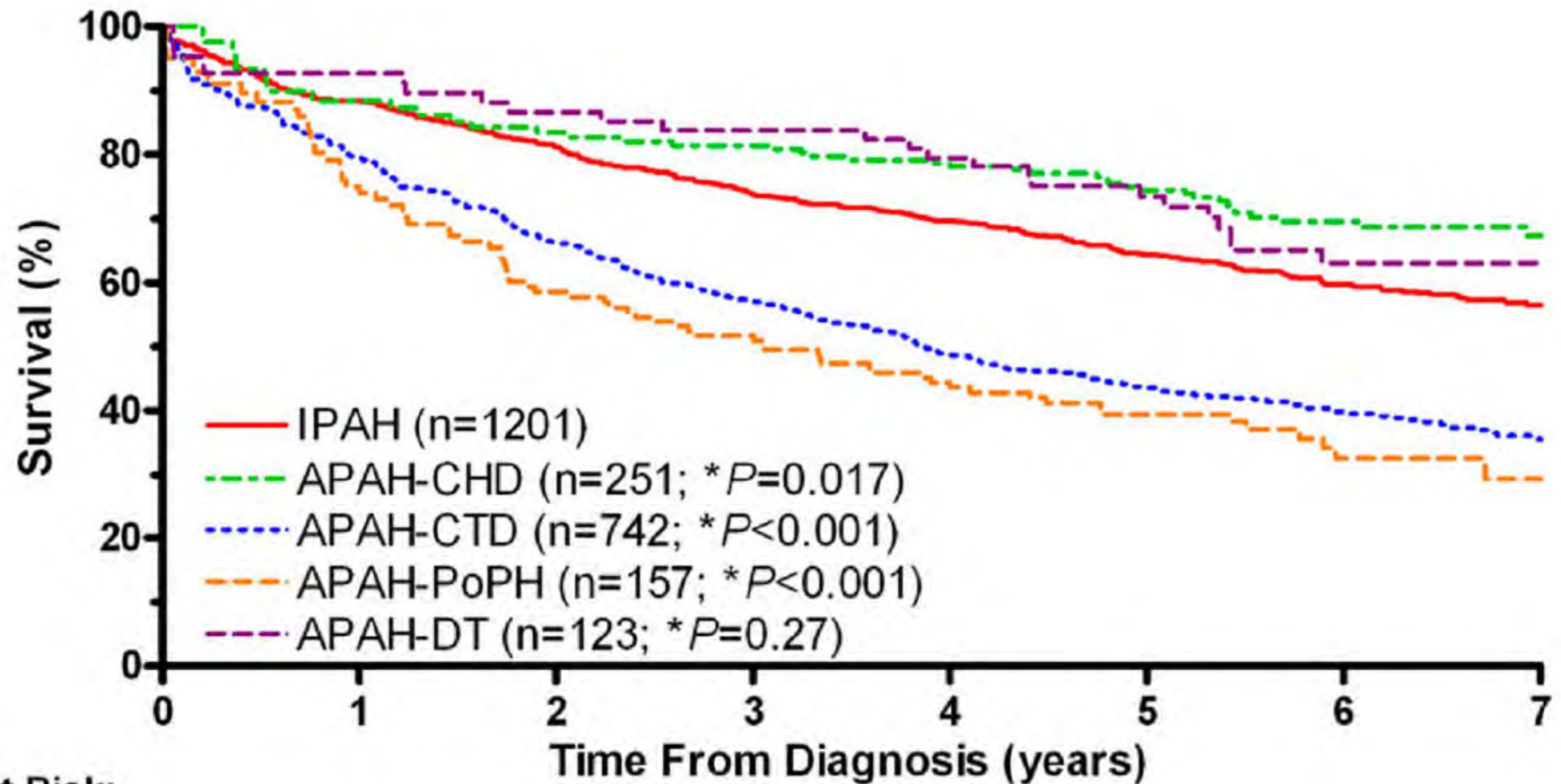
PHC registry. Thenappan T et al. Eur Respir J 2010; 35: 1079–1087

REVEAL Registry. Benza RL et al. Chest. 2012 Aug;142(2):448-56



ACCP guidelines. McLaughlin VV et al. Chest 2004; 126:78S–92S

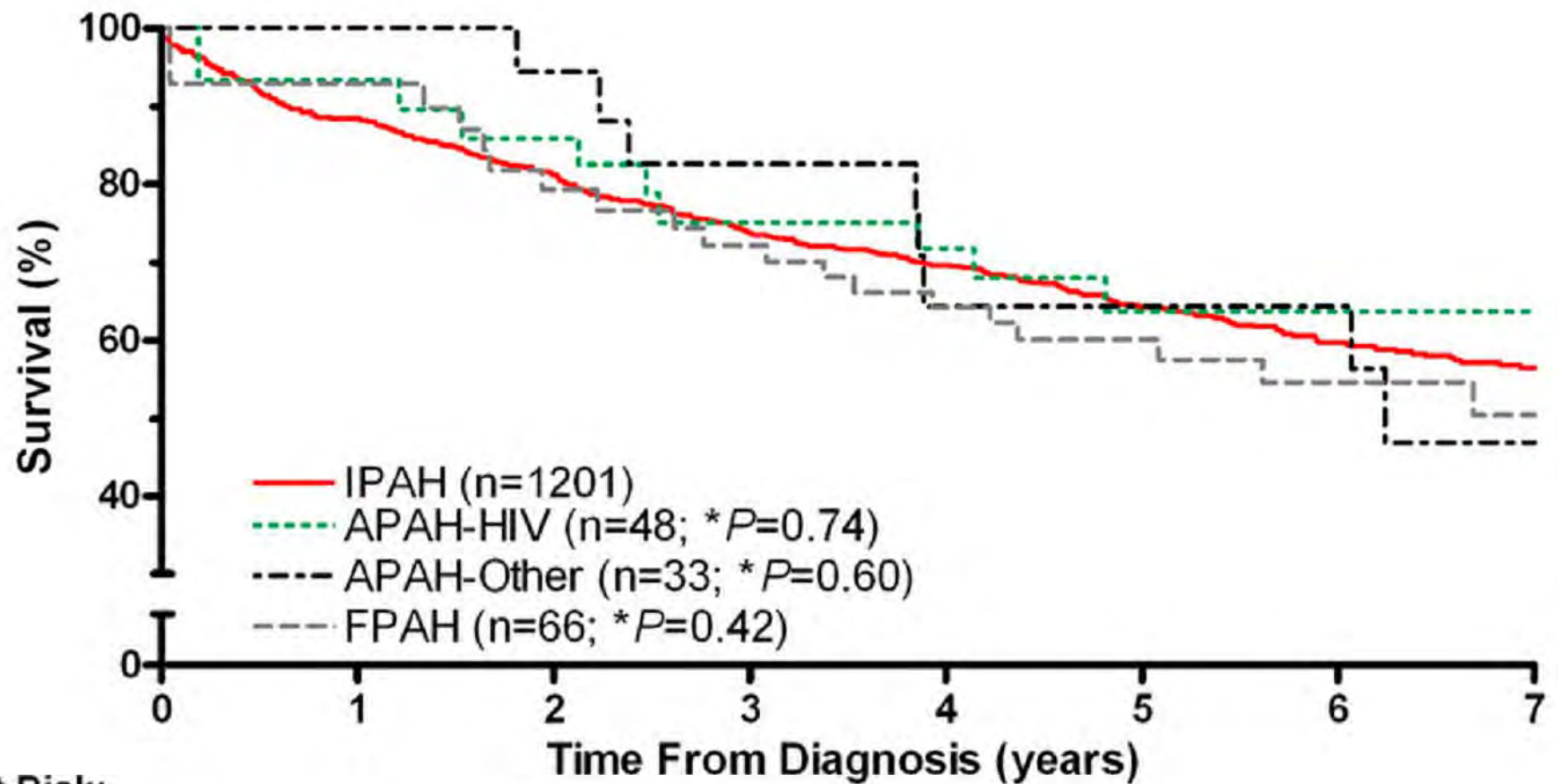
A



No. at Risk:

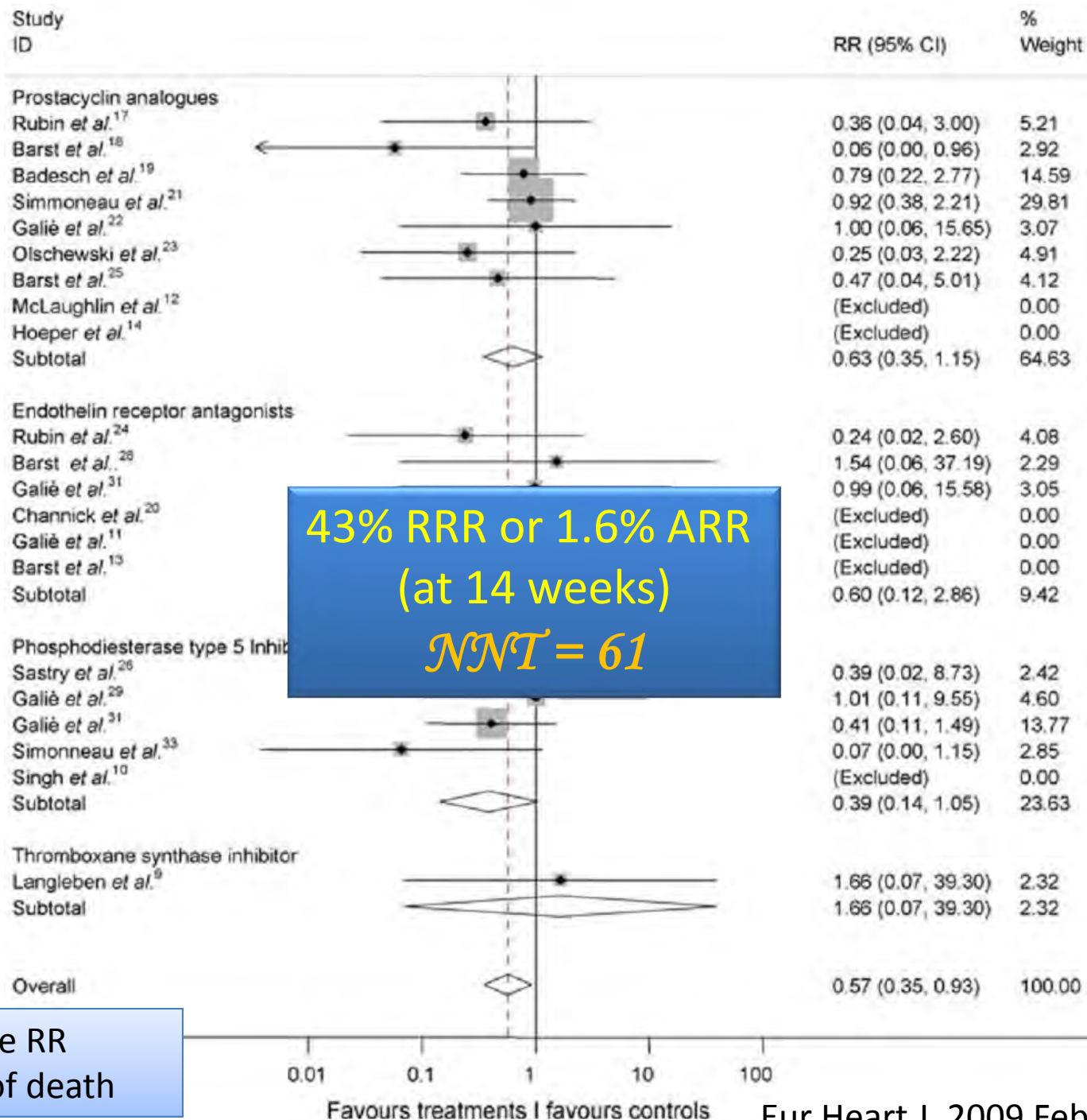
IPAH	415	553	600	609	538	415	268	143
APAH-CHD	46	70	107	144	150	138	85	49
APAH-CTD	257	342	344	329	276	203	138	67
APAH-PoPH	56	74	70	72	59	42	20	8
APAH-DT	40	57	62	60	55	45	29	21

B



No. at Risk:

IPAH	415	553	600	609	538	415	268	143
APAH-HIV	15	22	26	25	20	14	10	5
APAH-Other	9	15	15	14	10	12	8	5
FPAH	21	29	32	36	34	23	16	11





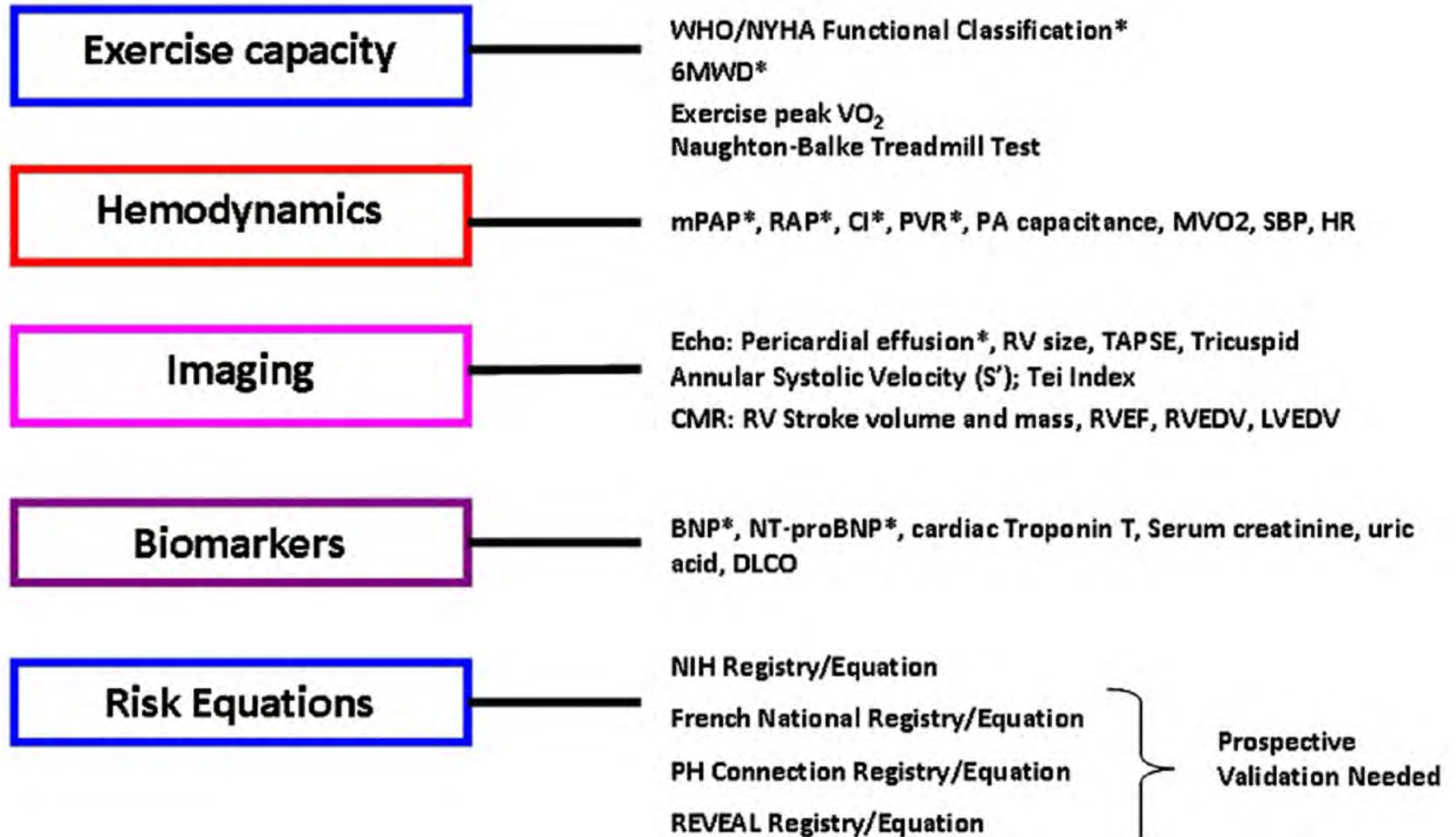
## Survival: Indian data

- ② Primary pulmonary hypertension: natural history and prognostic factors. Rajasekhar D et al. Indian Heart J. 1994 May-Jun;46(3):165-70
- ② Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Trivandrum, India.
- ② A retrospective cohort study was carried out in 61 patients (30 males, 31 females, age  $24.6 \pm 11.8$  years) with primary pulmonary hypertension diagnosed by strict clinical and hemodynamic criteria, to obtain an understanding of the natural history and prognostic markers. While 15 patients were alive, 46 patients (76%) had expired during the follow up period. Two, five and ten years survivals were 48%, 32% and 12% respectively. Median survival duration from time of diagnosis was 22 months.

# Assessment of prognosis

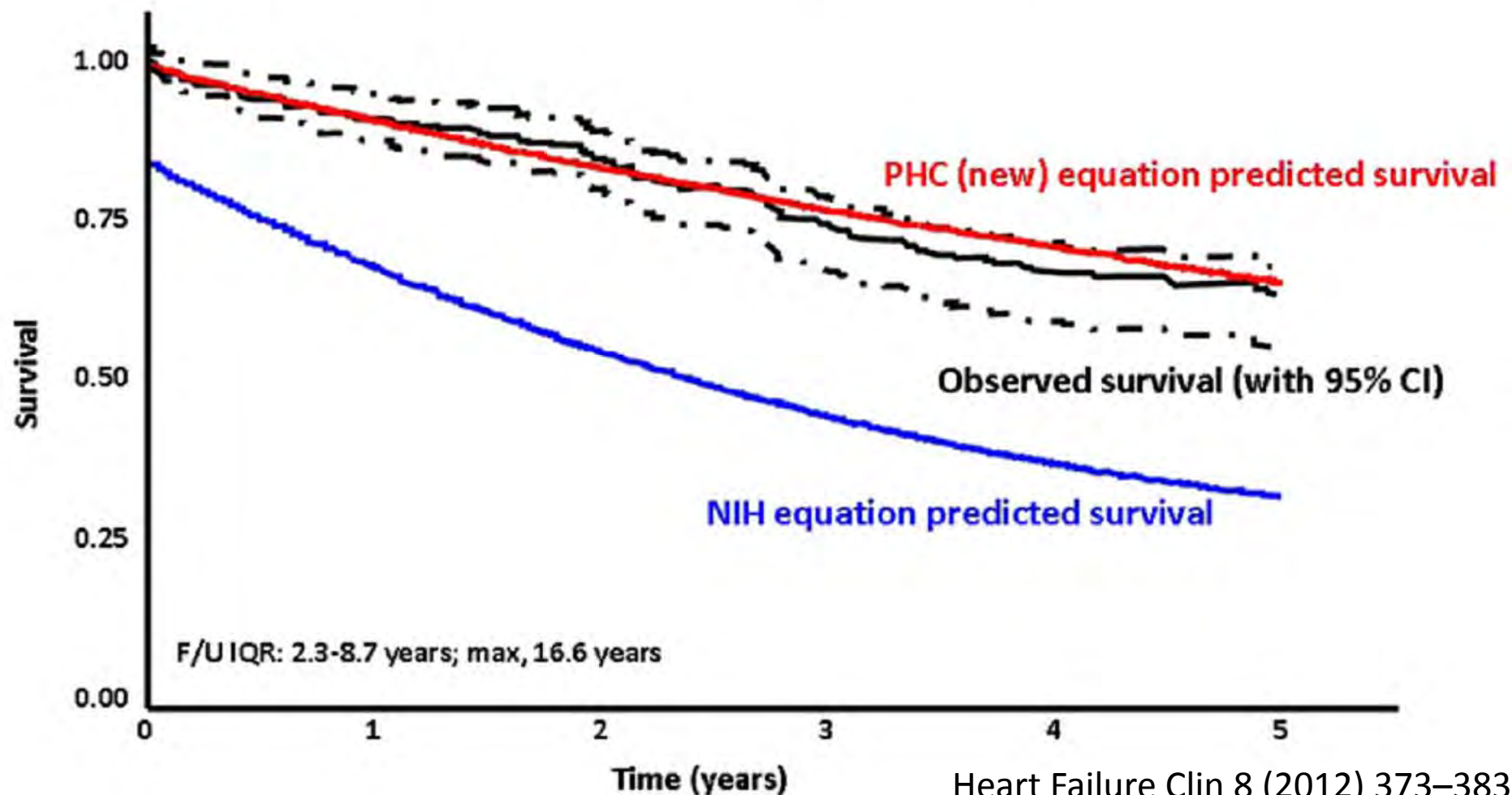


# Prognostic surrogates in PAH



# Predicting survival: PHC equation

1-, 3-, and 5-year survival rates of 91%, 75%, and 65% in PHC cohort



# PHC registry

- ② Pulmonary Hypertension Connection (PHC) registry, Chicago. Patients were entered into the database retrospectively from 1982 to February 2004 and prospectively from March 2004 onwards.
- ② In 576 patients with PAH referred during 1991-2007, observed survival was described using the Kaplan-Meier method. **In patients with idiopathic, familial and anorexigen-associated PAH (n = 247), observed versus NIH equation predicted survival was compared.** A new survival prediction equation was developed using exponential regression analysis.
- ② The observed 1-, 3- and 5-yr survival in the total cohort were 86, 69 and 61%, respectively. In patients with idiopathic, familial and anorexigen-associated PAH, the observed 1-, 3- and 5-yr survival (92, 75 and 66%, respectively) were significantly higher than the predicted survival (65, 43 and 32%, respectively). Contemporary survival in the PAH cohort was better than that predicted by the NIH registry equation. The NIH equation underestimated survival in idiopathic, familial and anorexigen-associated PAH.
- ② KTP: 476 cases were retrospective (before 2004) and 100 cases were prospective (from 2004). So it was a mix of old era and modern treatment era.

REVEAL™

# PAH Risk Score

WHO Group I  
Subgroup

APAH-CTD

+1

APAH-PoPH

+2

FPAH

+2

Demographics &  
Comorbidities

Renal Insufficiency

+1

Males Age>60yrs

+2

NYHA/WHO  
Functional Class

I

III

IV

-2

+1

+2

Vital Signs

SBP<110 mm Hg

+1

HR>92 BPM

+1

6-Minute  
Walk Test

≥440 m

-1

<165 m

+1

BNP

<50 pg/mL

-2

>180 pg/mL

+1

Echocardiogram

Pericardial Effusion

+1

Pulmonary  
Function Test

% pred. DLco≥80

-1

% pred. DLco≤32

+1

Right Heart  
Catheterization

mRAP>20 mm  
Hg within 1 yr

+1

PVR>32 Wood units

+2

SUM OF ABOVE

+

6

= RISK SCORE

## REVEAL score

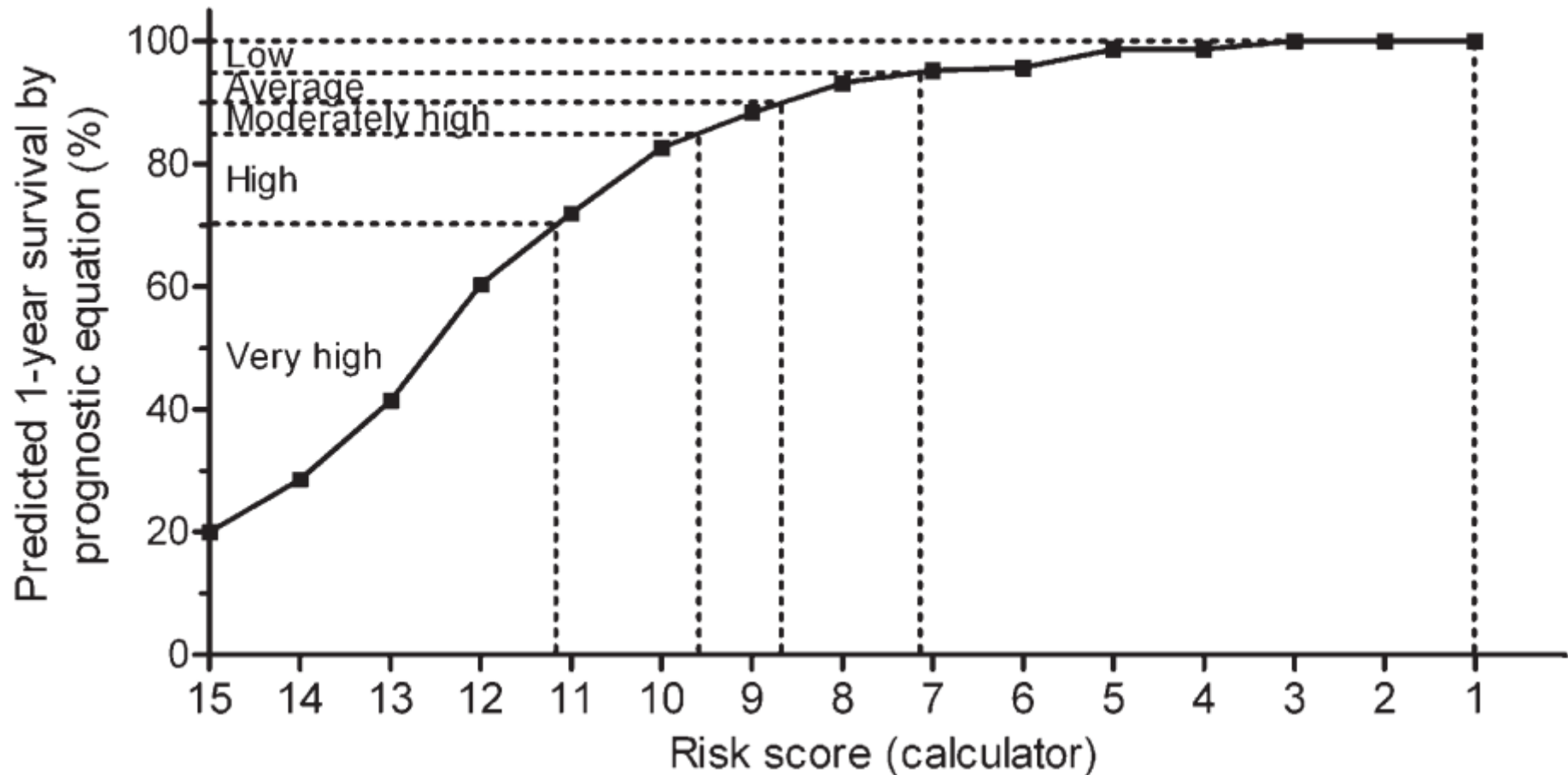
0 (lowest risk) to 22 (highest risk)

REVEAL Registry risk score calculator

Benza RL et al.

Chest. 2012 Feb;141(2):354-62

# REVEAL score: 1-year survival



REVEAL Registry risk score calculator

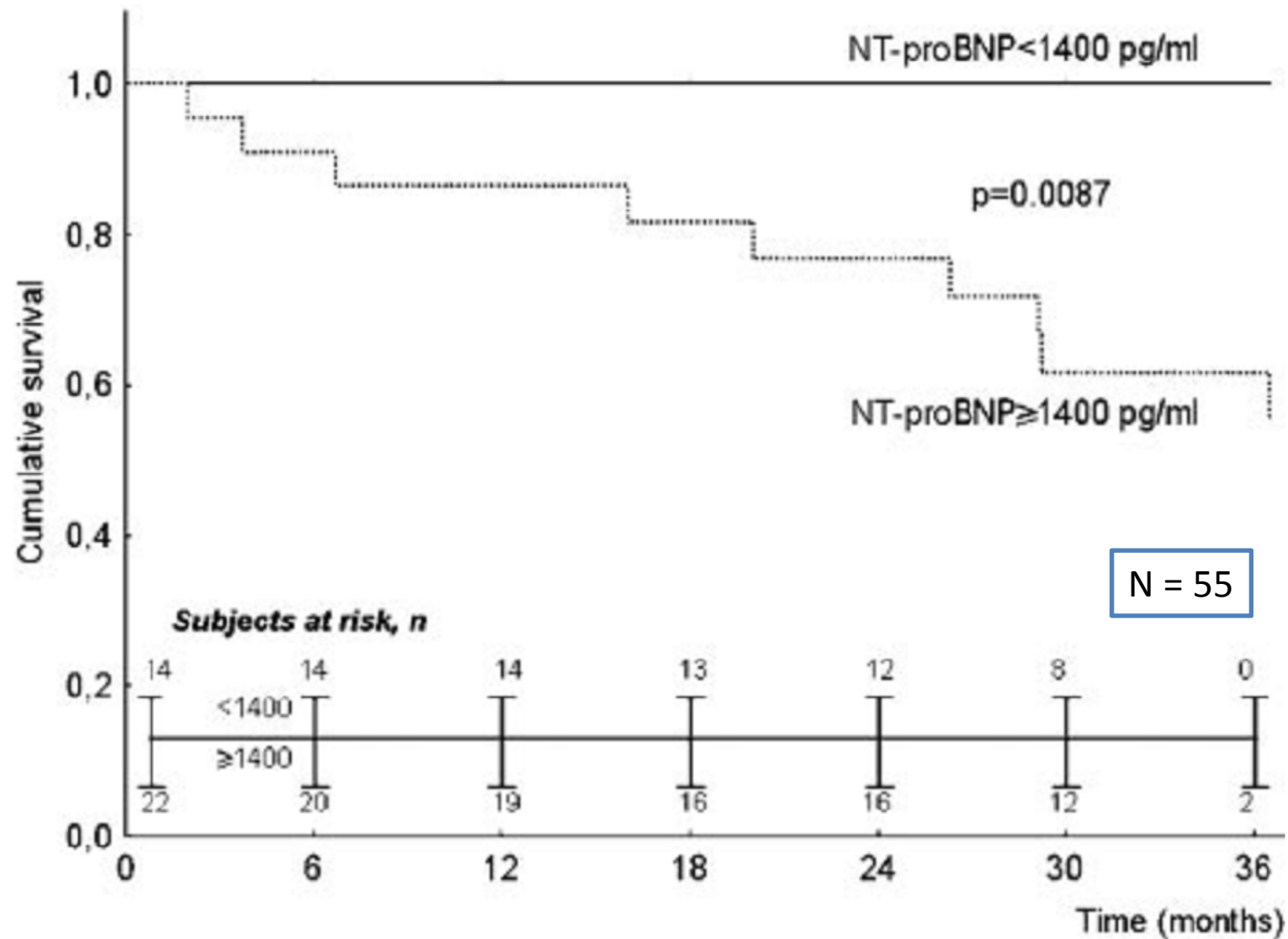
Benza RL et al. Chest. 2012 Feb;141(2):354-62



# REVEAL registry risk score

- ② **Prospectively collected data from patients with newly diagnosed (< 3 months) World Health Organization group I pulmonary hypertension** enrolled in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry) were used to validate a predictive algorithm for 1-year survival.
- ② The validation cohort comprised 504 individuals with mean  $\pm$  SD 6-min walk distance  $308 \pm 128$  m, and 61.5% were functional class III. The proportion of patients surviving 1 year fell within the range predicted by the model (95.1%, 91.5%, 84.6%, 76.3%, and 58.2%, respectively) among patients in the low (predicted survival  $\geq 95\%$ ), average (90% to  $< 95\%$ ), moderate (85% to  $< 90\%$ ), high (70% to  $< 85\%$ ), and very high ( $< 70\%$ ) risk strata. Predicted and observed 1-year survival were similar across risk stratum, and the c-index indicated good discrimination for both the full equation (0.726) and the simplified risk calculator (0.724).

# NT-proBNP



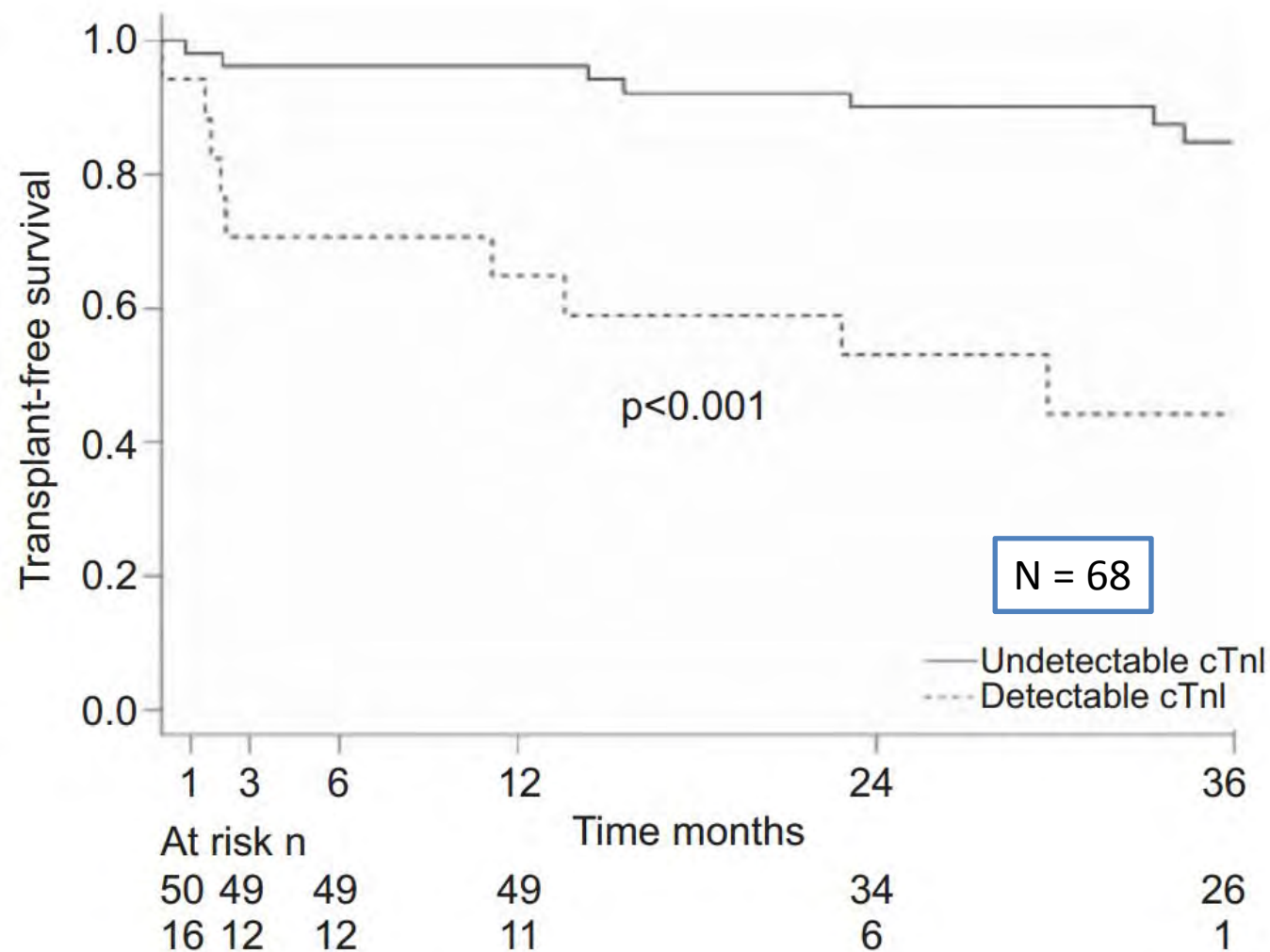
# ESC/ERS Guidelines: NT-proBNP

“BNP/NT-proBNP plasma levels should be recommended for **initial risk stratification** and may be considered for monitoring the effects of treatment, in view of their prognostic implications.”

“Low and stable or decreasing BNP/NT-proBNP may be a useful **marker of successful disease control** in PAH.”

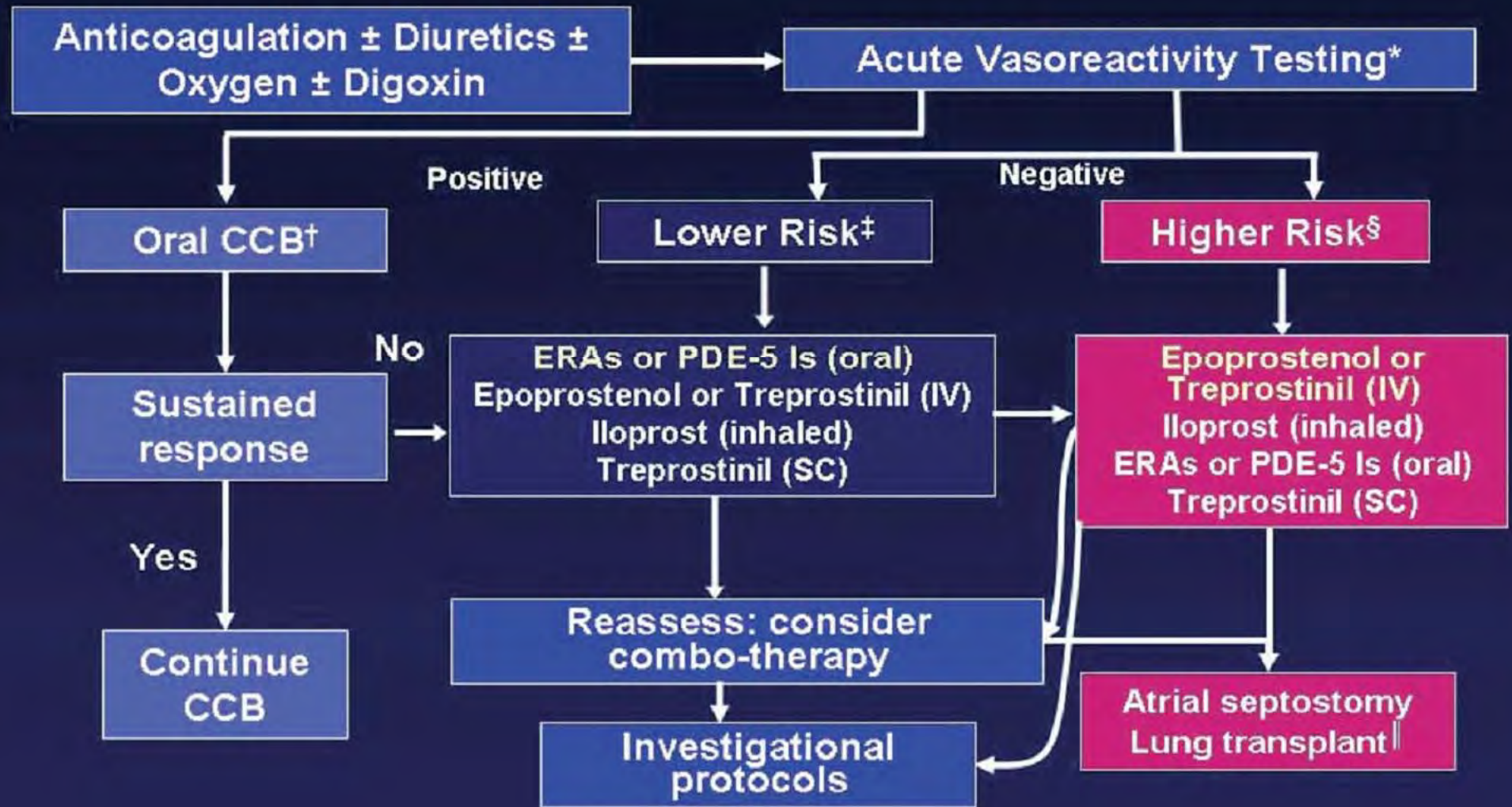


# Cardiac Troponin I

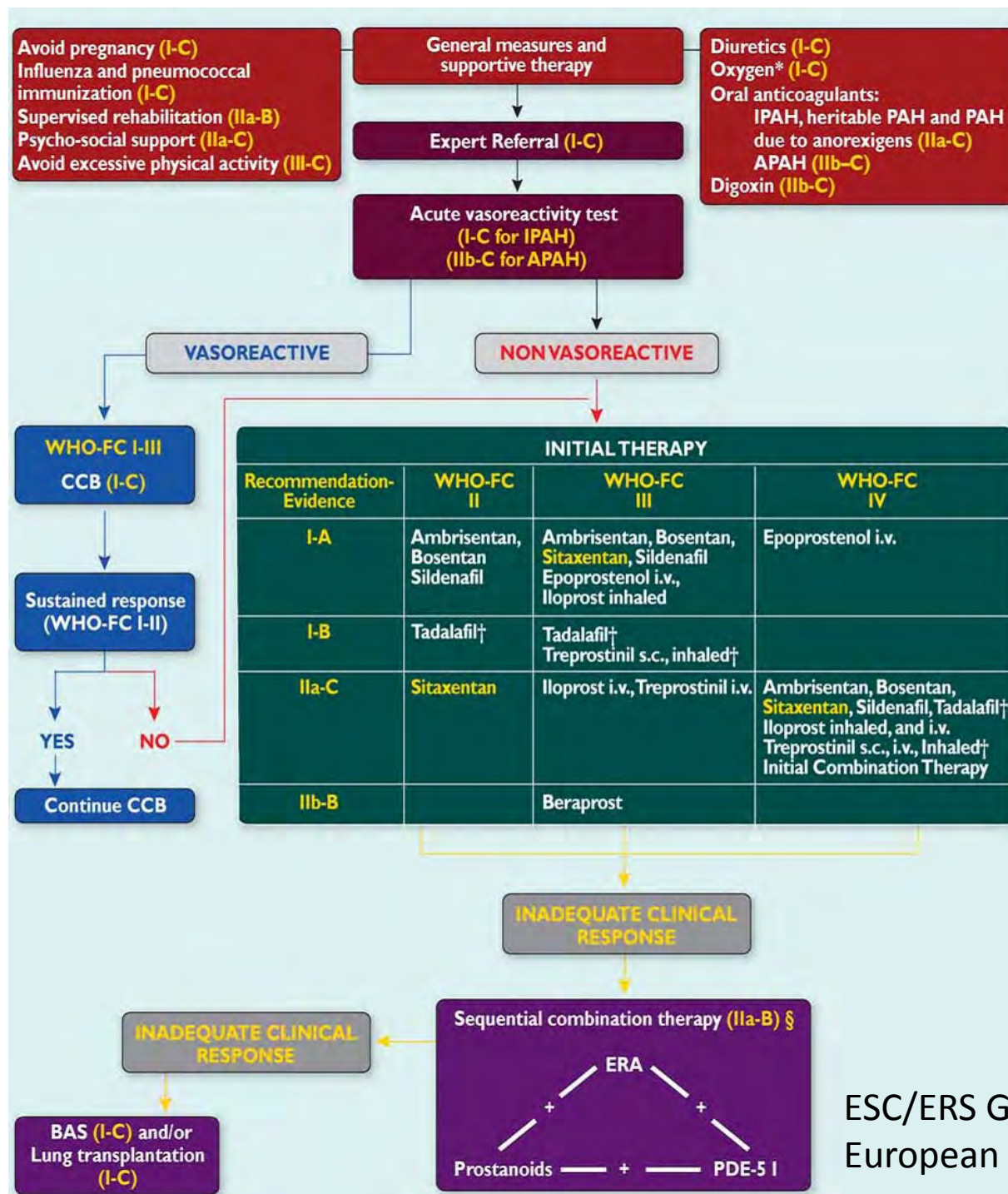


## **Current treatment algorithms**

# PAH Treatment Algorithm



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



# Summary

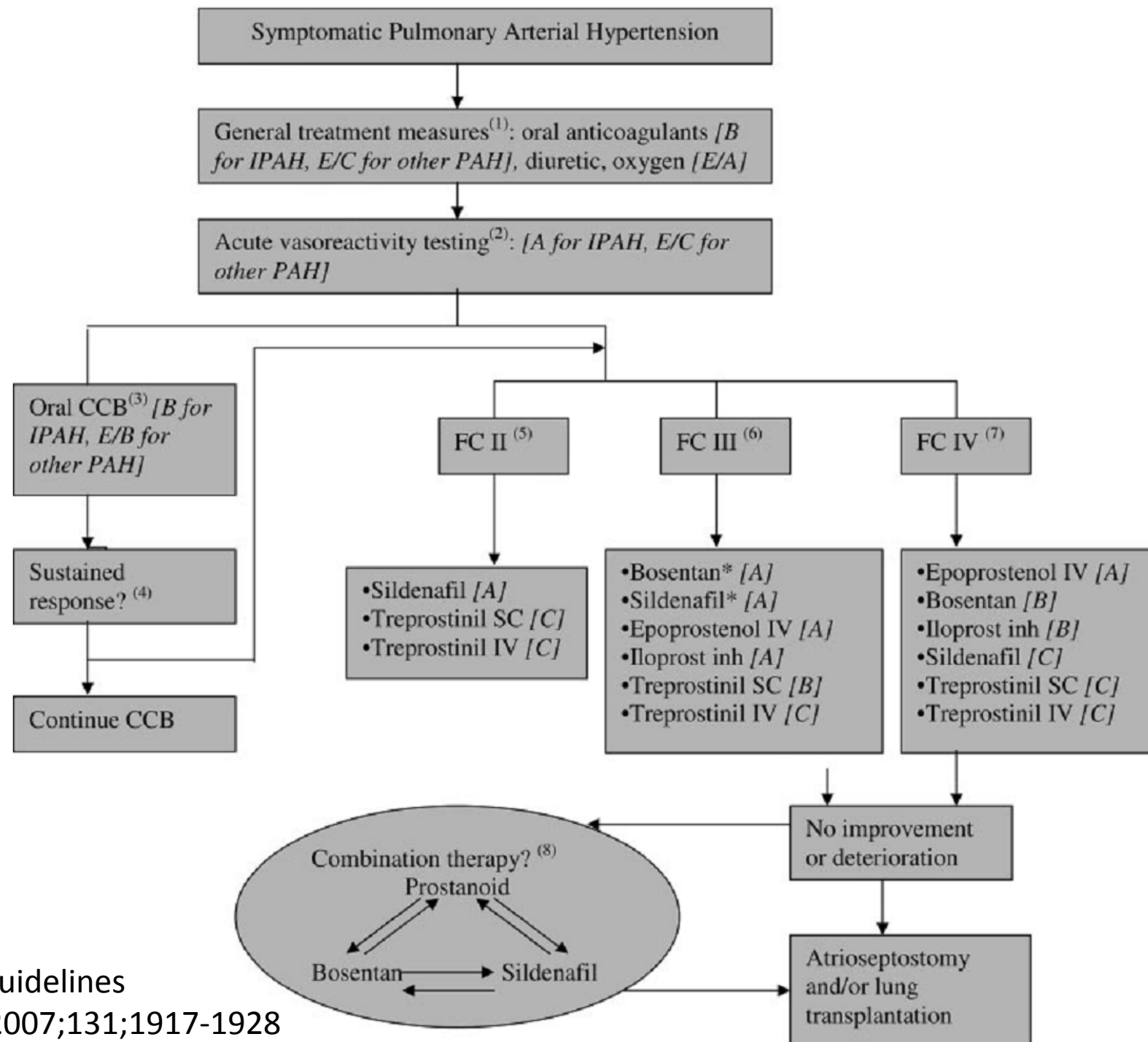
- ② Various registries have improved our understanding of PAH.
- ② Survival has improved significantly over the last two decades.
- ② Echo is not a good substitute to RHC for diagnosing PAH. CMR seems to be the best candidate at present.
- ② Targeted therapy has become the standard of care for PAH.
- ② Early therapy and combination therapy may produce better results.

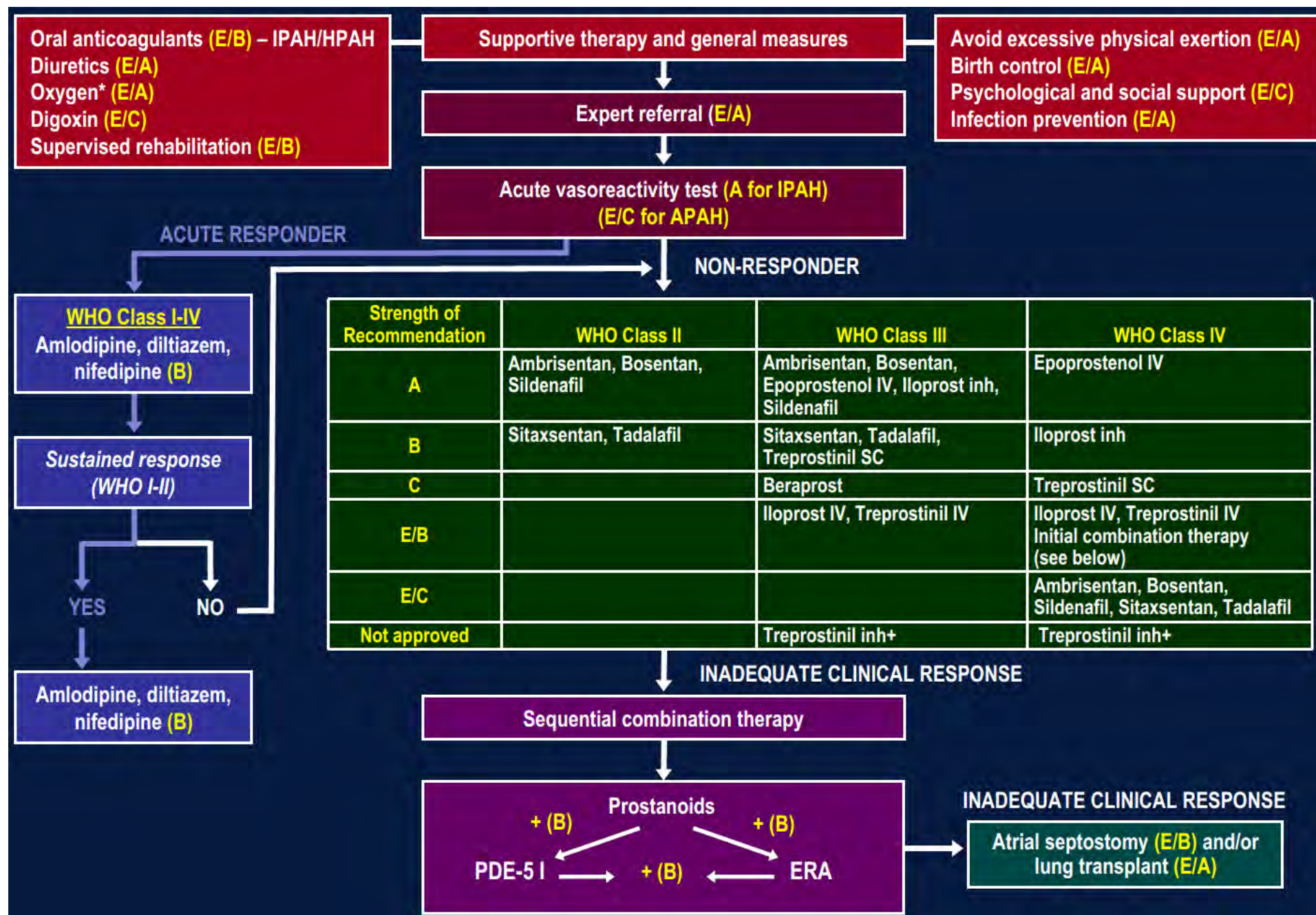


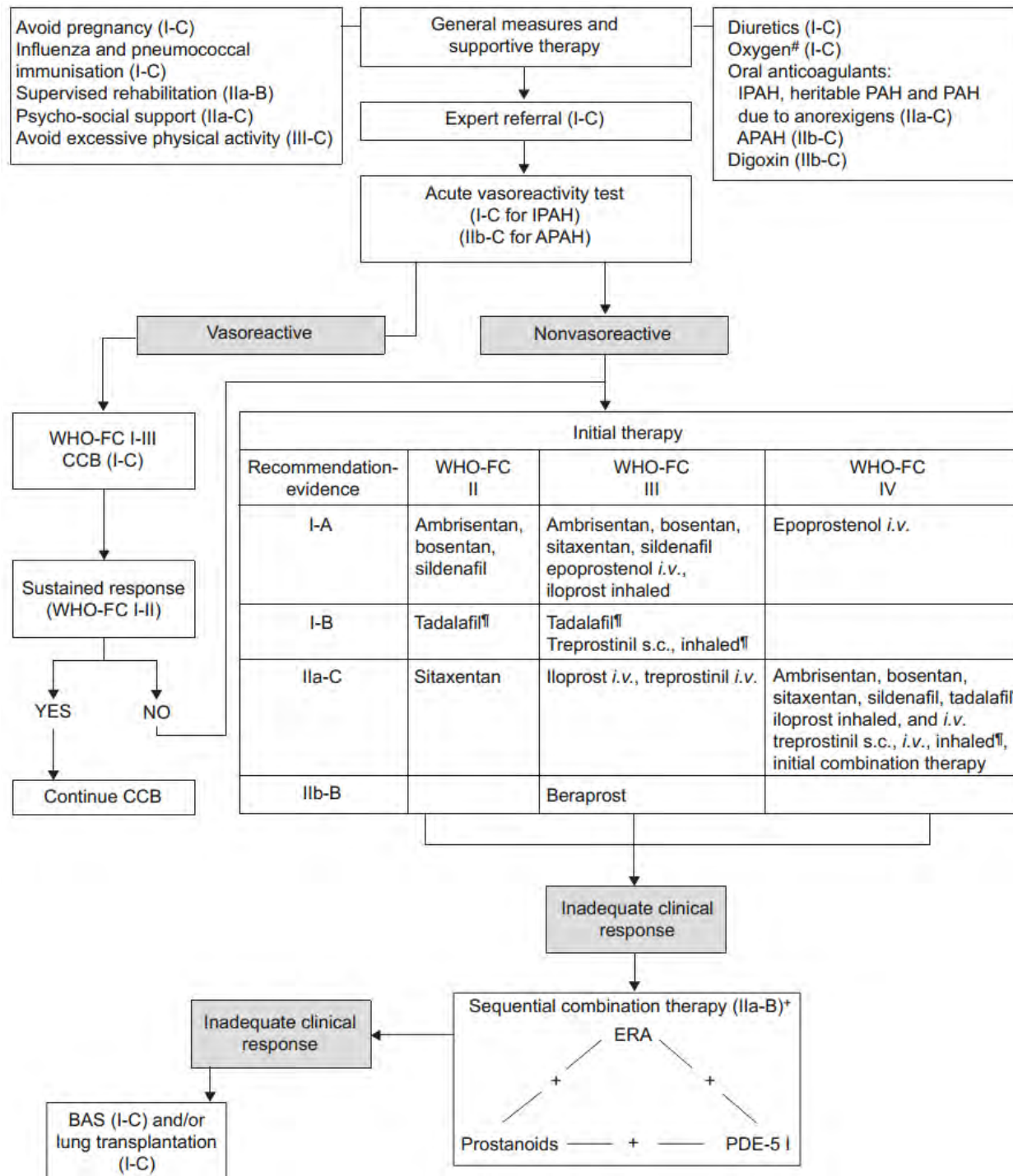
# WHO classification of functional status in PH

Class	Description
I	Patients with PH in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.
II	Patients with PH who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
III	Patients with PH who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.
IV	Patients with PH who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest, and symptoms are increased by almost any physical activity.





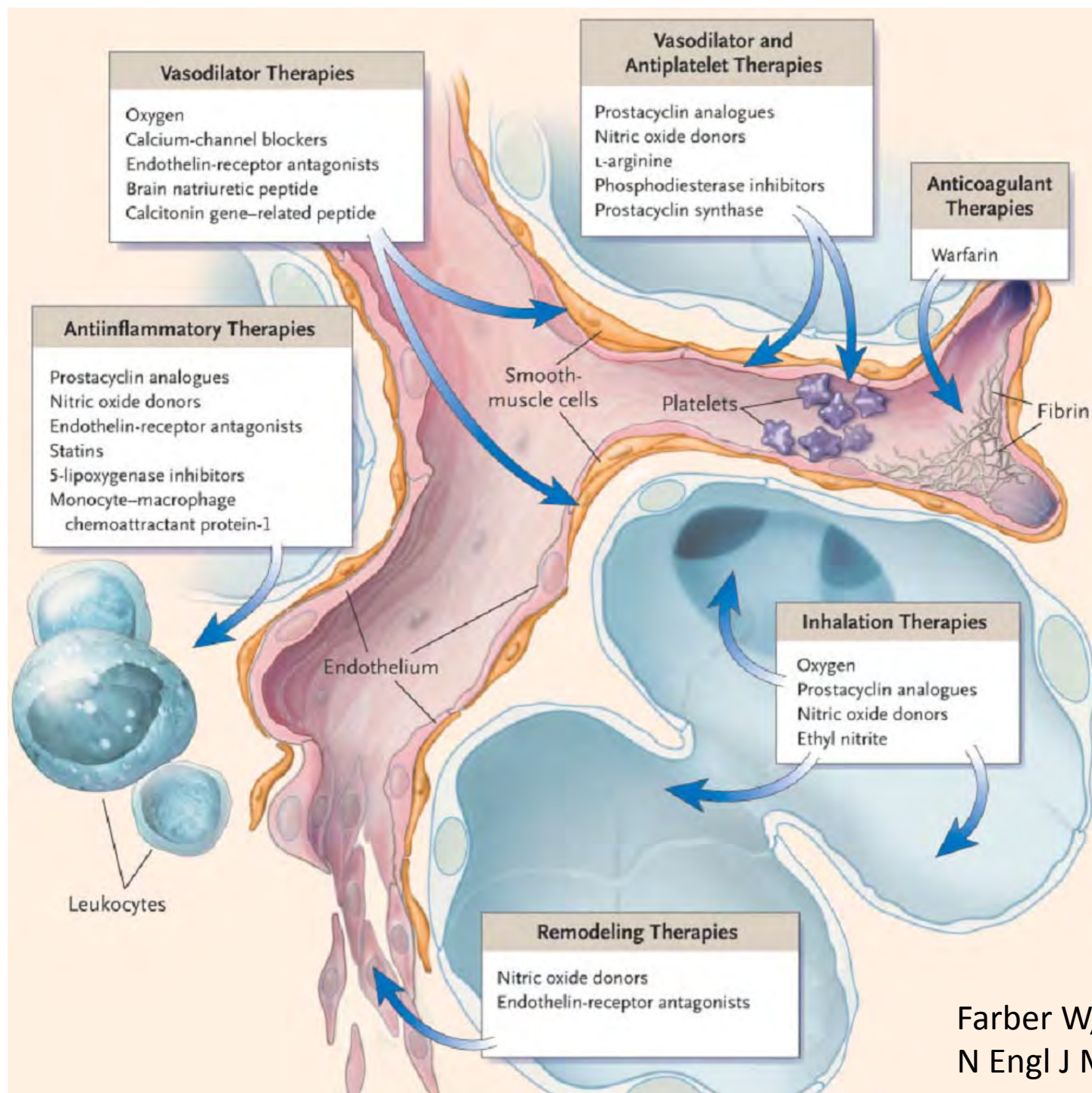




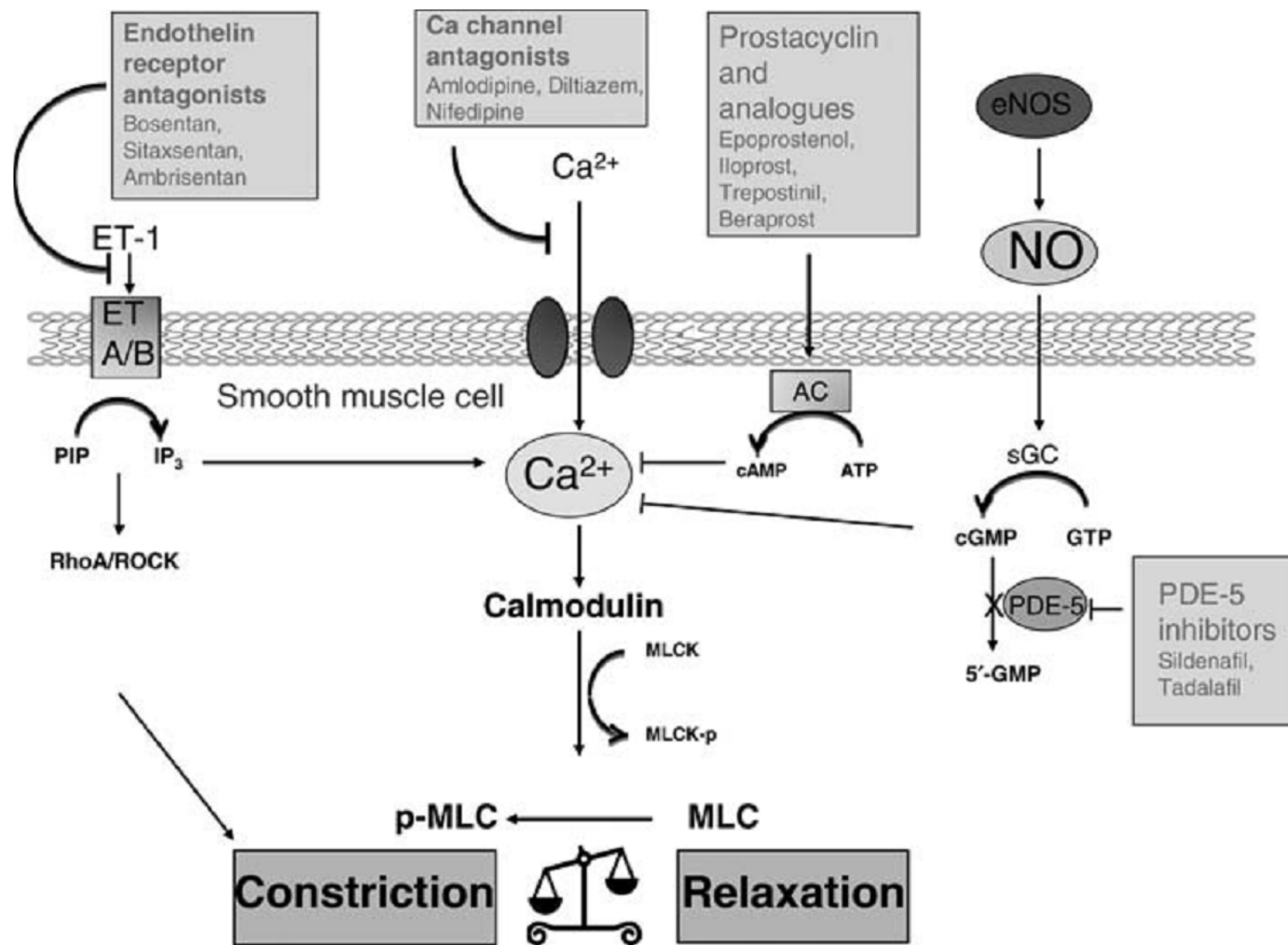


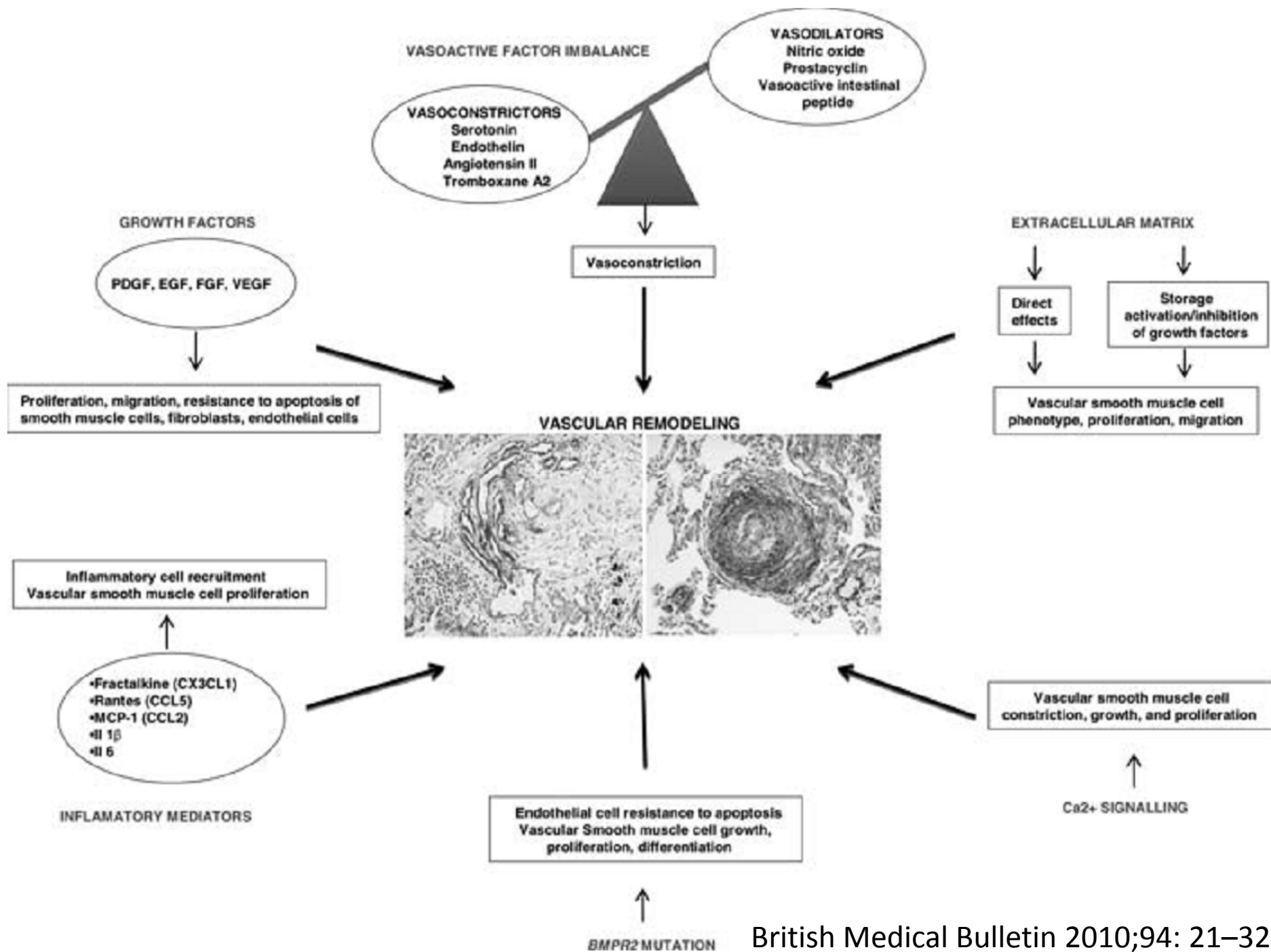
# Follow-up

	At baseline (prior to therapy)	Every 3–6 months <sup>a</sup>	3–4 months after initiation or changes in therapy	In case of clinical worsening
Clinical assessment WHO-FC ECG	✓	✓	✓	✓
6MWT <sup>b</sup>	✓	✓	✓	✓
Cardio-pulmonary exercise testing <sup>b</sup>	✓		✓	✓
BNP/NT-proBNP	✓	✓	✓	✓
Echocardiography	✓		✓	✓
RHC	✓ <sup>c</sup>		✓ <sup>d</sup>	✓ <sup>d</sup>



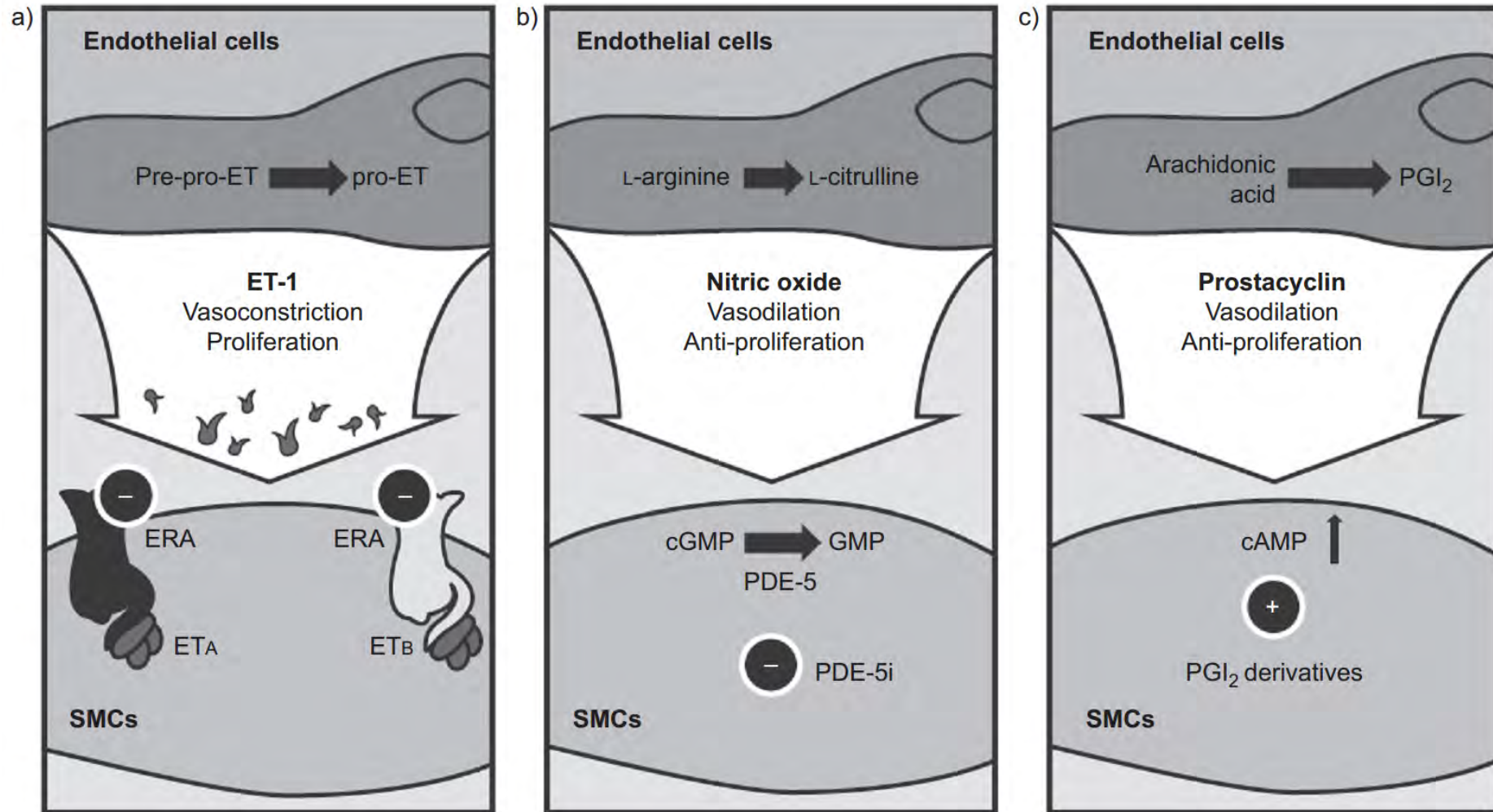
Farber W, Loscalzo J.  
N Engl J Med 2004;351:1655-65







# Key pathways in PAH





# Trial Endpoints

- ② Hemodynamics
  - RA pressure, PA pressure, RVEDP
  - Cardiac output (CO), Pulmonary vascular resistance (PVR)
- ② Exercise Capacity
  - 6MWT
  - CPET
- ② Disease Progression
  - Time to clinical worsening
  - WHO Functional Class
  - Biomarkers
- ② Survival
- ② Cost considerations