Pulmonary Hypertension - Current Perspectives

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Pulmonary Hypertension –

- Characterized by
  - Restricted flow through the pulmonary arterial circulation
  - Result in increased pulmonary vascular resistance and raised pulmonary arterial pressure
  - Right heart failure – “endpoint”
- Life-threatening condition with a poor prognosis if untreated

Definitions:

- Mean PAP ≥25 mm Hg at rest or >30 mm Hg during exercise in the presence of a normal pulmonary capillary wedge pressure (≤15 mm Hg)

1st World Symposium on Pulmonary Hypertension, Geneva,1971

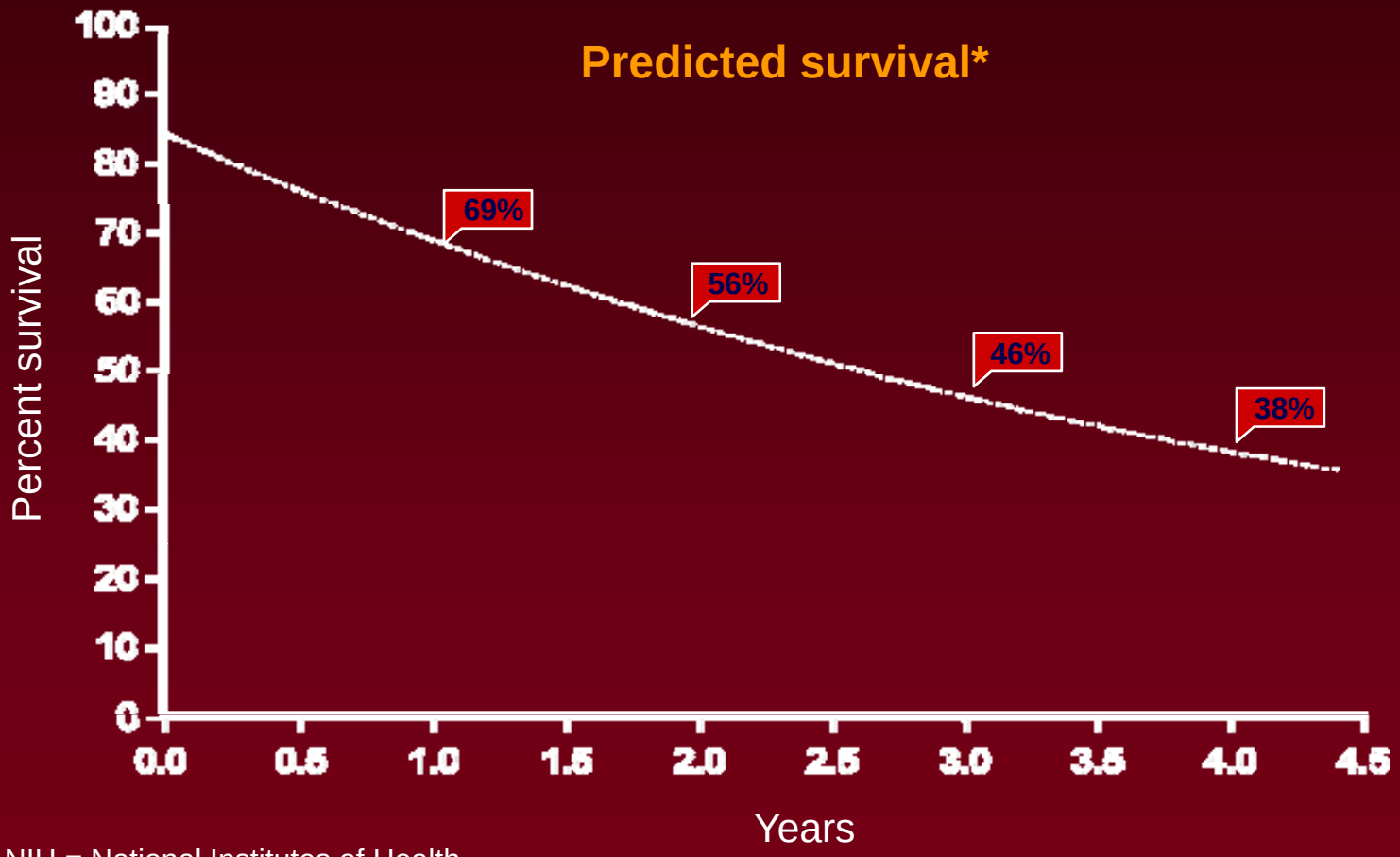
- Mean PAP ≥ 25 mm Hg at rest in the presence of a pulmonary capillary wedge pressure ≤ 15 mm Hg

4th World Symposium on Pulmonary Hypertension, Dana Point, CA, 2008

Pulmonary Hypertension

- Is a “Disease of Triggers”
  - Genetic mutation /high LA pressure/hypoxia/obstruction
- Endothelial dysfunction is an early feature
- “Double Hit” theory
  1. Genetic predisposition: loss of function mutation of BMPR II & AKL-1
  2. Environmental factors – drugs,viruses or toxins

Natural History of PAH: NIH Registry[1,2]



NIH = National Institutes of Health.

Predicted survival according to the NIH equation. Predicted survival rates were 69%, 56%, 46%, and 38% at 1, 2, 3, and 4 years, respectively. The numbers of patients at risk were 231, 149, 82, and 10 at 1, 2, 3, and 4 years, respectively. *Patients with primary pulmonary hypertension, now referred to as idiopathic pulmonary hypertension.

1. Rich et al. *Ann Intern Med*. 1987;107:216-223. **2.** D'Alonzo et al. *Ann Intern Med*. 1991;115:343-349.

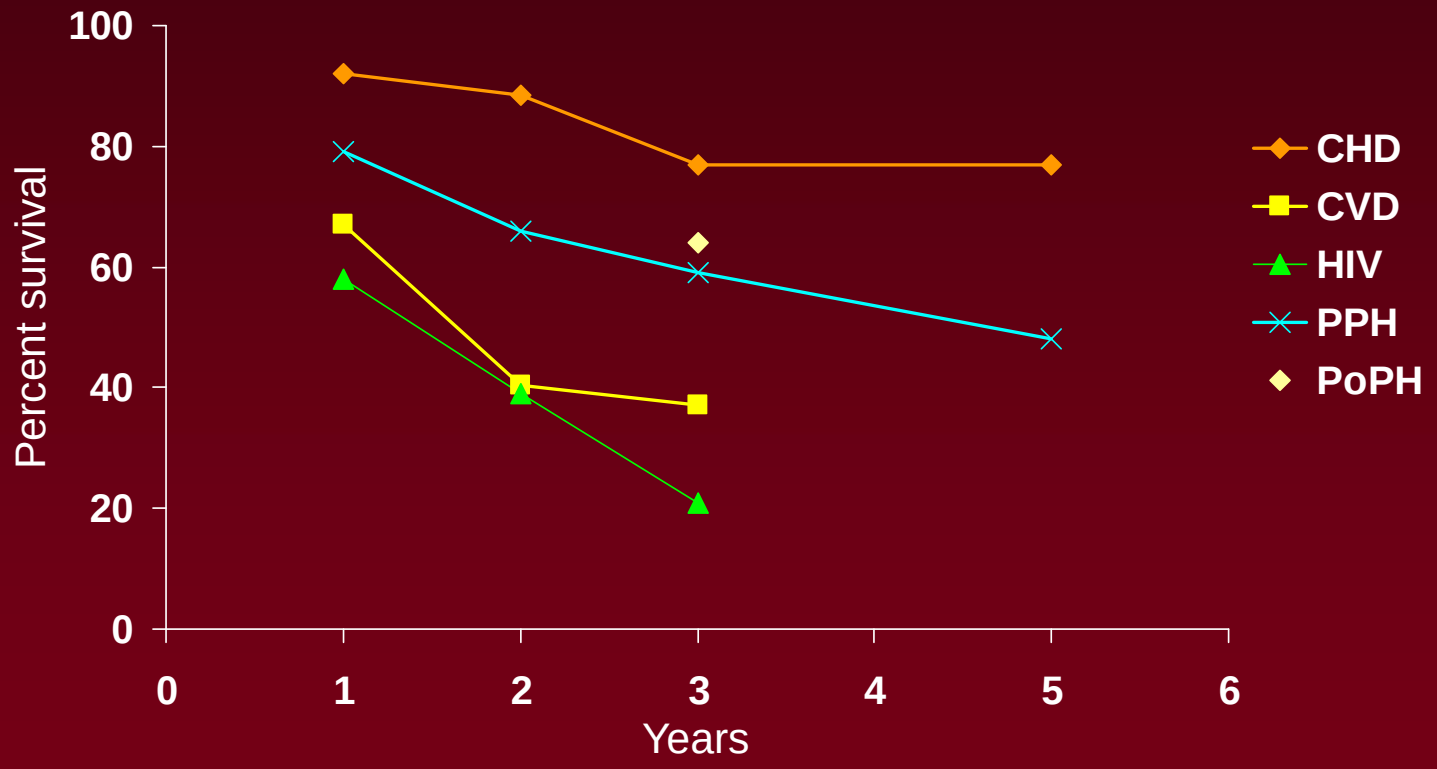
Hemodynamics

- ***In the NIH registry***, 3 hemodynamic variables were associated with an increased risk of death by univariate analysis:

  1. ***Increased mPAP*** (odds ratio [OR]: 1.16; 95% confidence interval: 1.05 to 1.28),
  2. ***Increased mean right atrial pressure (mRAP)*** (OR: 1.99; 95% confidence interval: 1.47 to 2.69), and
  3. ***Decreased cardiac index (CI)*** (OR: 0.62; 95% confidence interval: 0.46 to 0.82).

Survival by PAH Etiology

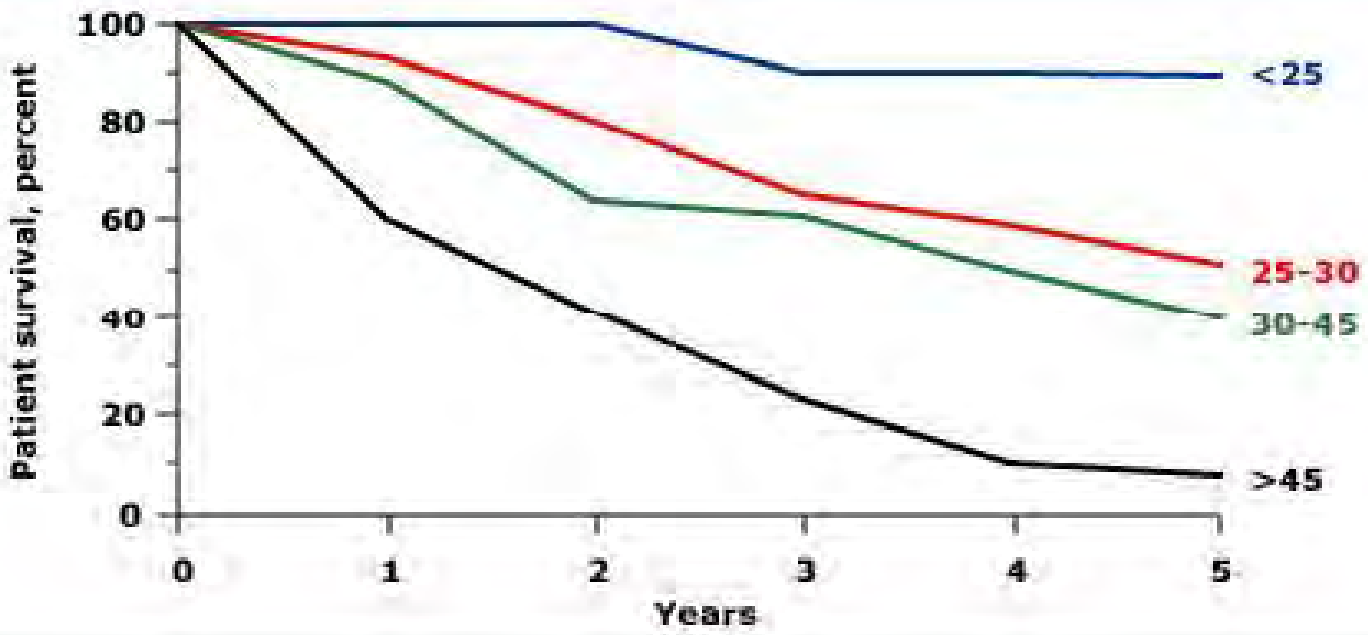
Prognosis in Mixed Treated/Untreated Cohorts



CHD = congenital heart disease; CVD = collagen vascular disease; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; PPH = primary pulmonary hypertension; PoPH = portopulmonary hypertension.

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

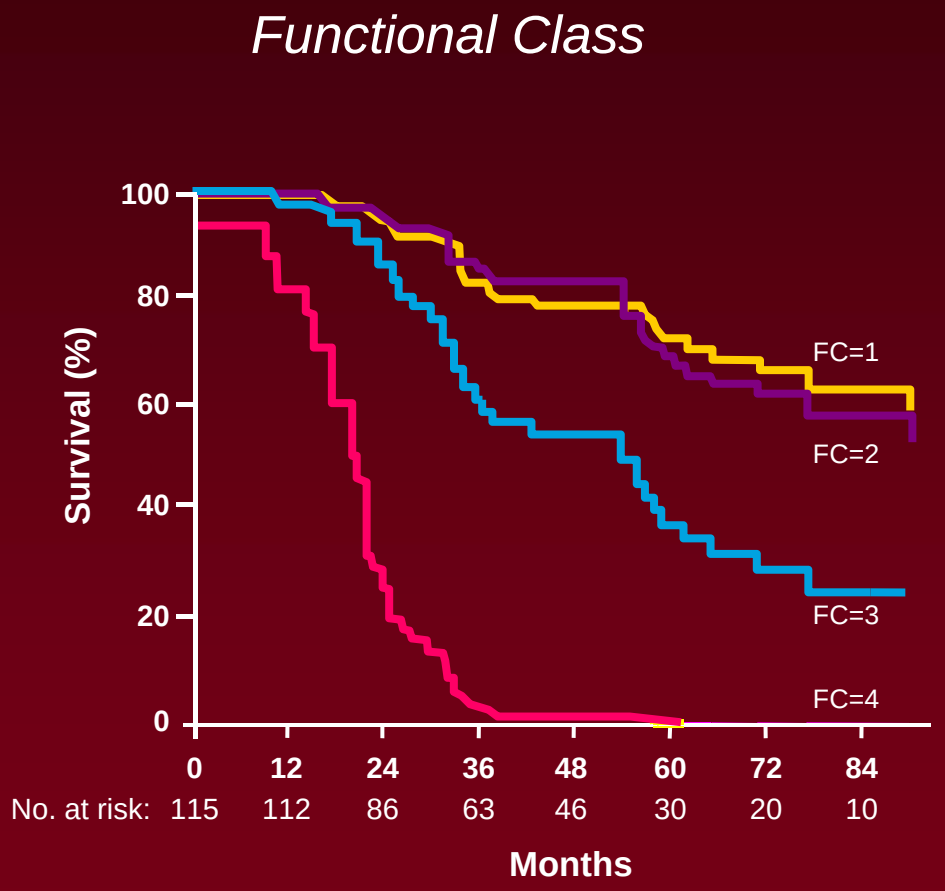
Pulmonary artery pressure and survival in COPD



The relationship between baseline mean pulmonary artery pressure (from less than 25 to more than 45 mmHg) and survival in patients with chronic obstructive pulmonary disease. Increasing pulmonary artery pressure was associated with a progressive decline in survival.

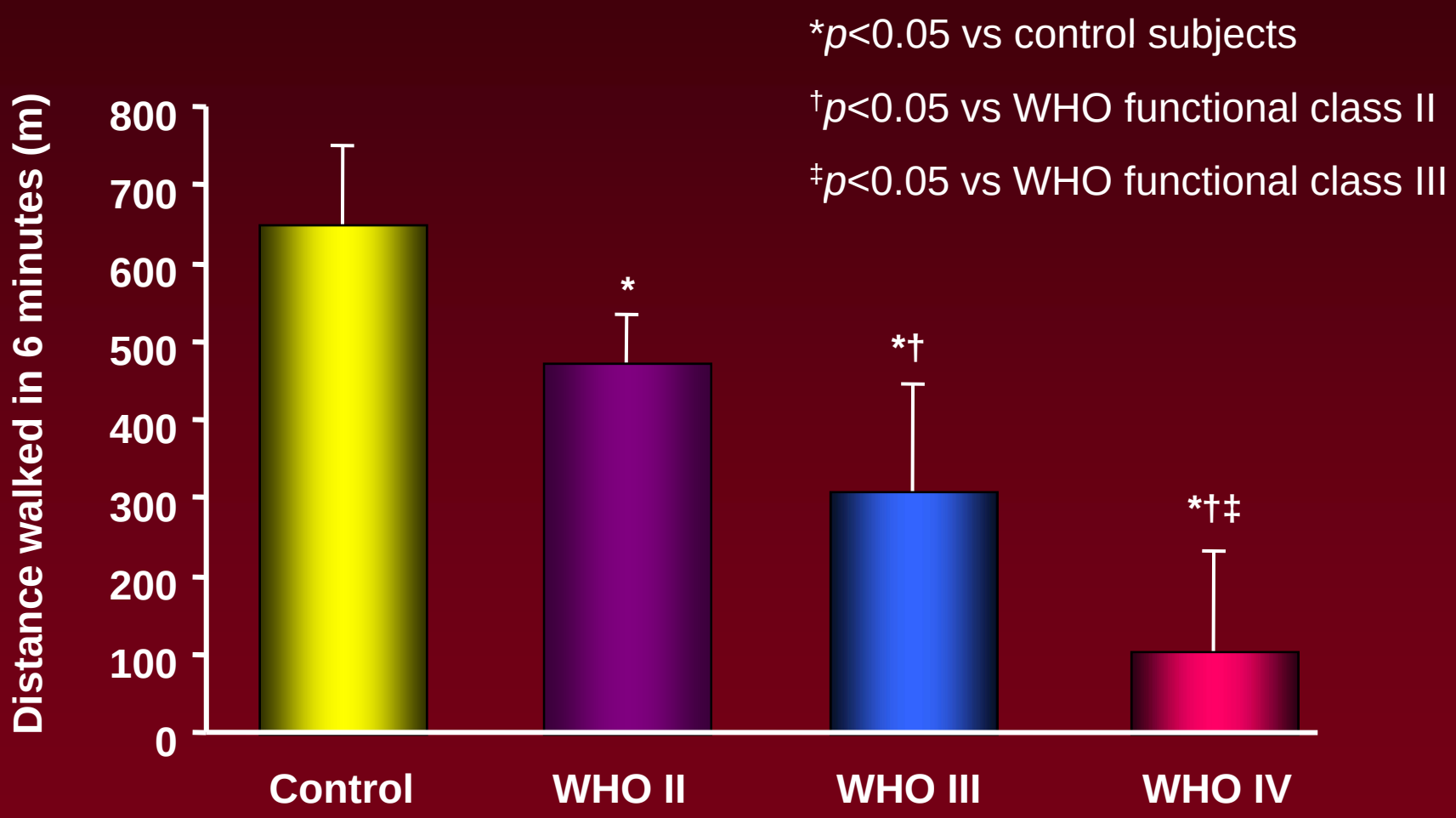
Bishop, JM, Prog Respir Res 1975; 5:9.

Impact of Functional Class on Survival



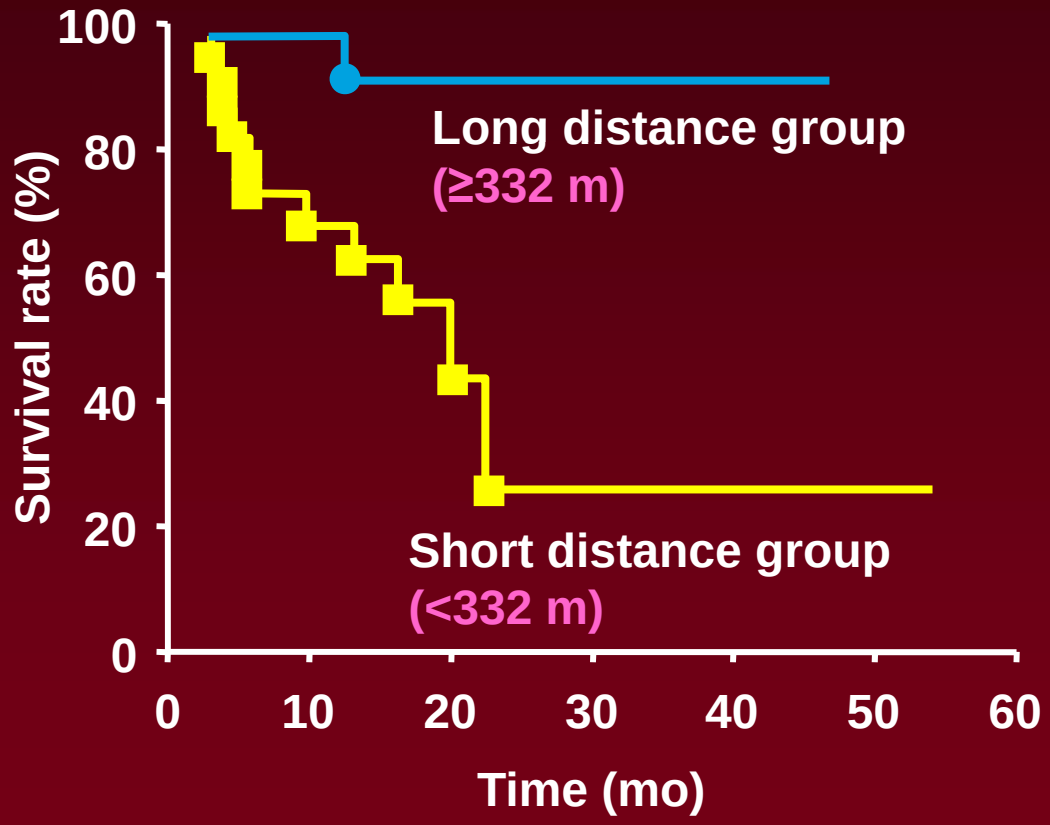
McLaughlin VV, et al. *Circulation.* 2002;106:1477-1482.

Correlation of Six-minute-walk Test and WHO Functional Class



Miyamoto S et al. *Am J Respir Crit Care Med.* 2000;161:487-492.

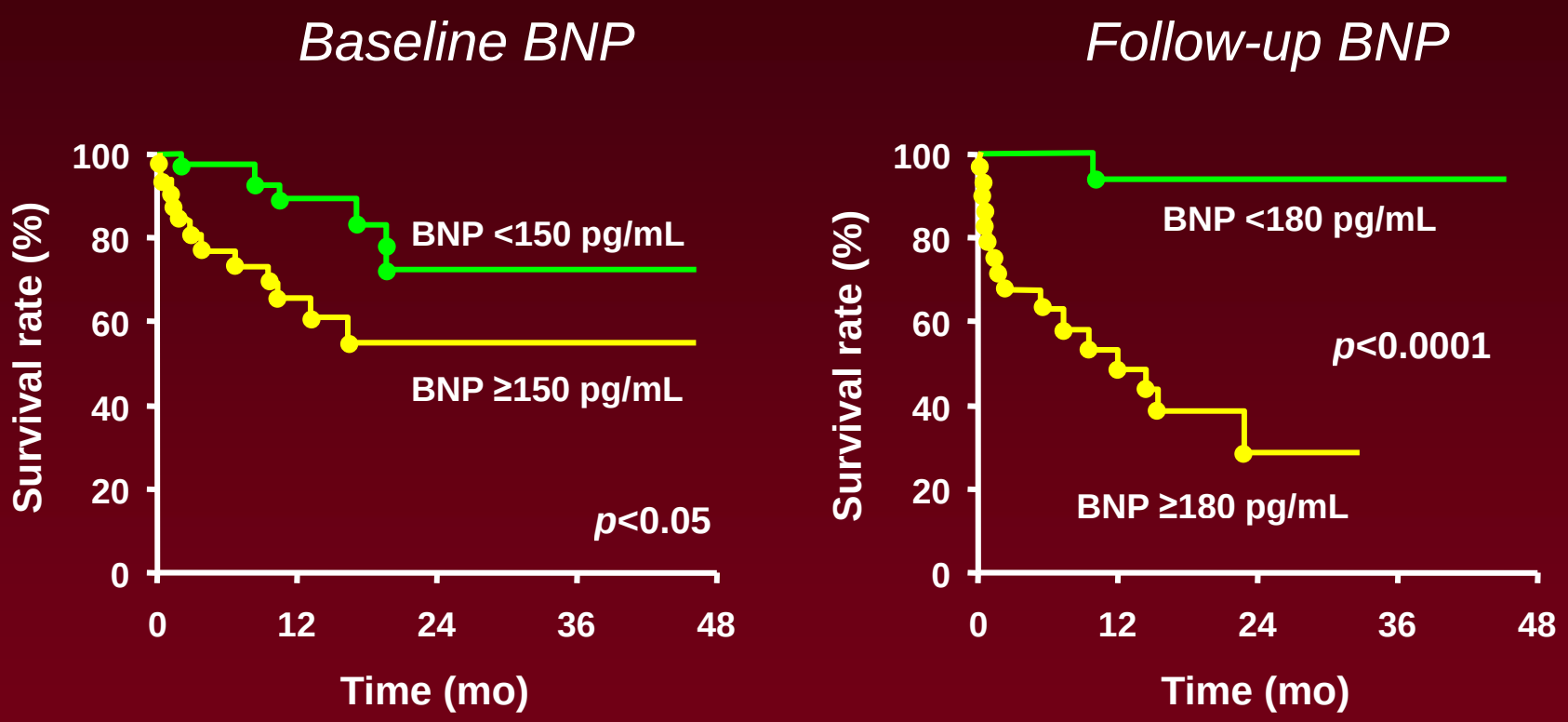
Correlation of Six-minute-walk Test With Survival in PPH



- 6-minute-walk distance strongly predictive of survival
  - <332 m: 20% 3-year survival
  - >332 m: 92% 3-year survival

Miyamoto S et al. *Am J Respir Crit Care Med.* 2000;161:487-492.

Plasma BNP as a Prognostic Indicator of Mortality in Patients With PPH



higher BNP at <u>baseline</u> (RR=11.971, *p*=0.0348) and at <u>follow-up</u> (RR=25.880, *p*=0.0243) were independent predictors of mortality

Nagaya N et al. *Circulation.* 2000;102:865-870.

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

Table 2. PAH*: Determinants of Prognosis

Determinants of Risk	Lower Risk (Good Prognosis)	Higher Risk (Poor Prognosis)
Clinical evidence of RV failure	No	Yes
Progression of symptoms	Gradual	Rapid
WHO class†	II, III	IV
6MW distance‡	Longer (greater than 400 m)	Shorter (less than 300 m)
CPET	Peak VO_2 greater than 10.4 mL/kg/min	Peak VO_2 less than 10.4 mL/kg/min
Echocardiography	Minimal RV dysfunction	Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement
Hemodynamics	RAP less than 10 mm Hg, CI greater than 2.5 L/min/m^2	RAP greater than 20 mm Hg, CI less than 2.0 L/min/m^2
BNP§	Minimally elevated	Significantly elevated

Reprinted from McLaughlin and McGoon (99). *Most data available pertains to IPAH. Little data is available for other forms of PAH. One should not rely on any single factor to make risk predictions. †WHO class is the functional classification for PAH and is a modification of the New York Heart Association functional class. ‡6MW distance is also influenced by age, gender, and height. §As there is currently limited data regarding the influence of BNP on prognosis, and many factors including renal function, weight, age, and gender may influence BNP, absolute numbers are not given for this variable.

6MW indicates 6-minute walk; BNP, brain natriuretic peptide. CI, cardiac index; CPET, cardiopulmonary exercise testing; peak VO_2, average peak oxygen uptake during exercise; RAP, right atrial pressure; RV, right ventricle; and WHO, World Health Organization.

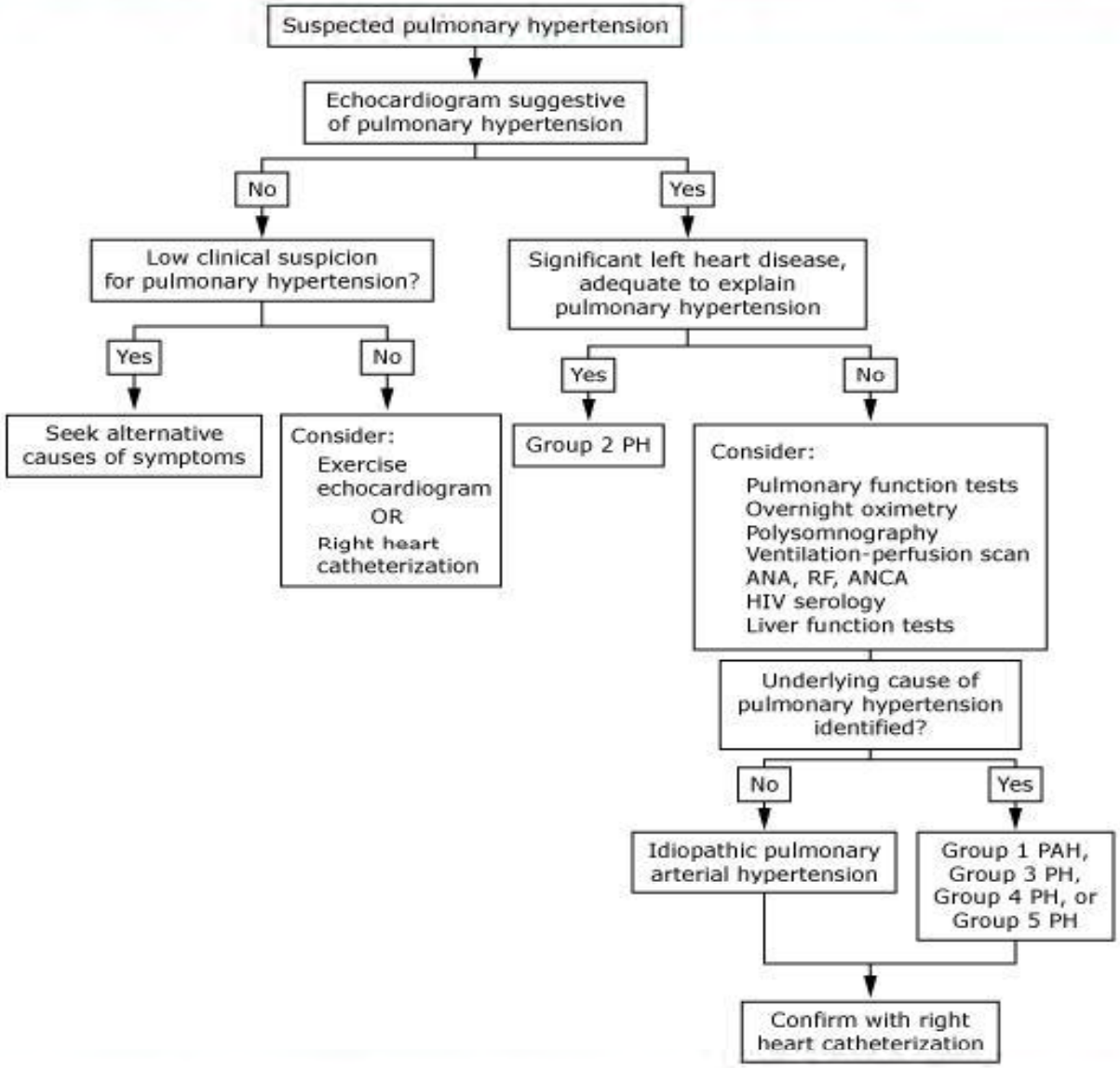
Predicting Survival and Following Therapy

- Clinical parameters
  - functional class
  - exercise capacity
  - neurohormones
- Hemodynamics
- Imaging
  - right ventricle: function and size
  - pulmonary artery remodeling (future)

Screening and Diagnostic and Hemodynamic Assessment

- The diagnostic strategy for PH depends on the context in which it is employed:
  - 1) detection of a substrate in which the likelihood of a pulmonary vasculopathy may be heightened;
  - 2) discovery of the presence of PH;
  - 3) classification of the type of PH;
  - 4) confirmation of the presence of suspected PH; and
  - 5) determination of an appropriate treatment category

Algorithm for investigation of suspected pulmonary hypertension



PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; ANA: anit-nuclear antibody; RF: rheumatoid factor; ANCA: anti-neutrophil cytoplasmic antibody.

Diagnosis PAH = RHC

Cardiac Catheterization to Assess Severity and Prognosis of PAH

- To measure wedge pressure or LVEDP
- To exclude or evaluate CHD
- To establish severity and prognosis
- To test vasodilator therapy

Catheterization is required for every patient with suspected pulmonary HTN.

LVEDP = left ventricular end diastolic pressure.

Treatment of Pulmonary Hypertension

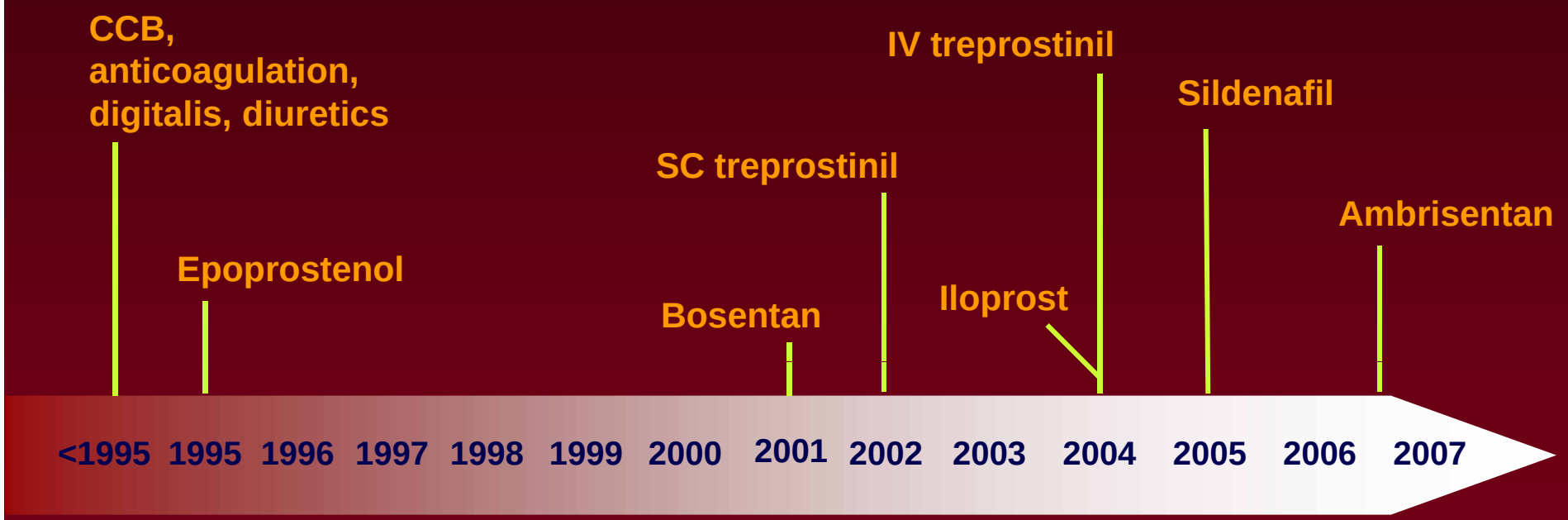
Goals of Therapy

- Improve symptoms
  - 6-minute walk (>380 m)
  - functional class (I or II)
  - CPET (VO_2 max >10.4)
  - quality of life
- Improve hemodynamics
- Improve survival

General Measures

- Low level graded aerobic exercise - walking
- Avoid heavy physical exertion or isometric exercise
- Avoid exposure to high altitudes
  - Preflight SpO2 <92% should receive supplemental oxygen
- A sodium restricted diet (< 2,400 mg / day)
- Routine immunizations - influenza and pneumococcal pneumonia
- Current guidelines recommend that pregnancy be avoided or terminated early in women with PAH (30-50 % mortality)

PAH Treatments—
a Historical Overview



CCB = calcium channel blocker.

Background Therapy

- ***Anticoagulants*** :
  - 3 non-controlled observational series in patients with primarily IPAH : improvement in survival

    NEJM 92,Chest 97,Circulation 84

  - ACCF/AHA recommend warfarin in IPAH
    - ***INR target of 1.5 - 2.5.***
  - Recommendations for patients with associated forms of PAH :
    - more advanced disease, such as those on continuous intravenous therapy, in the absence of contraindications.

Background Therapy

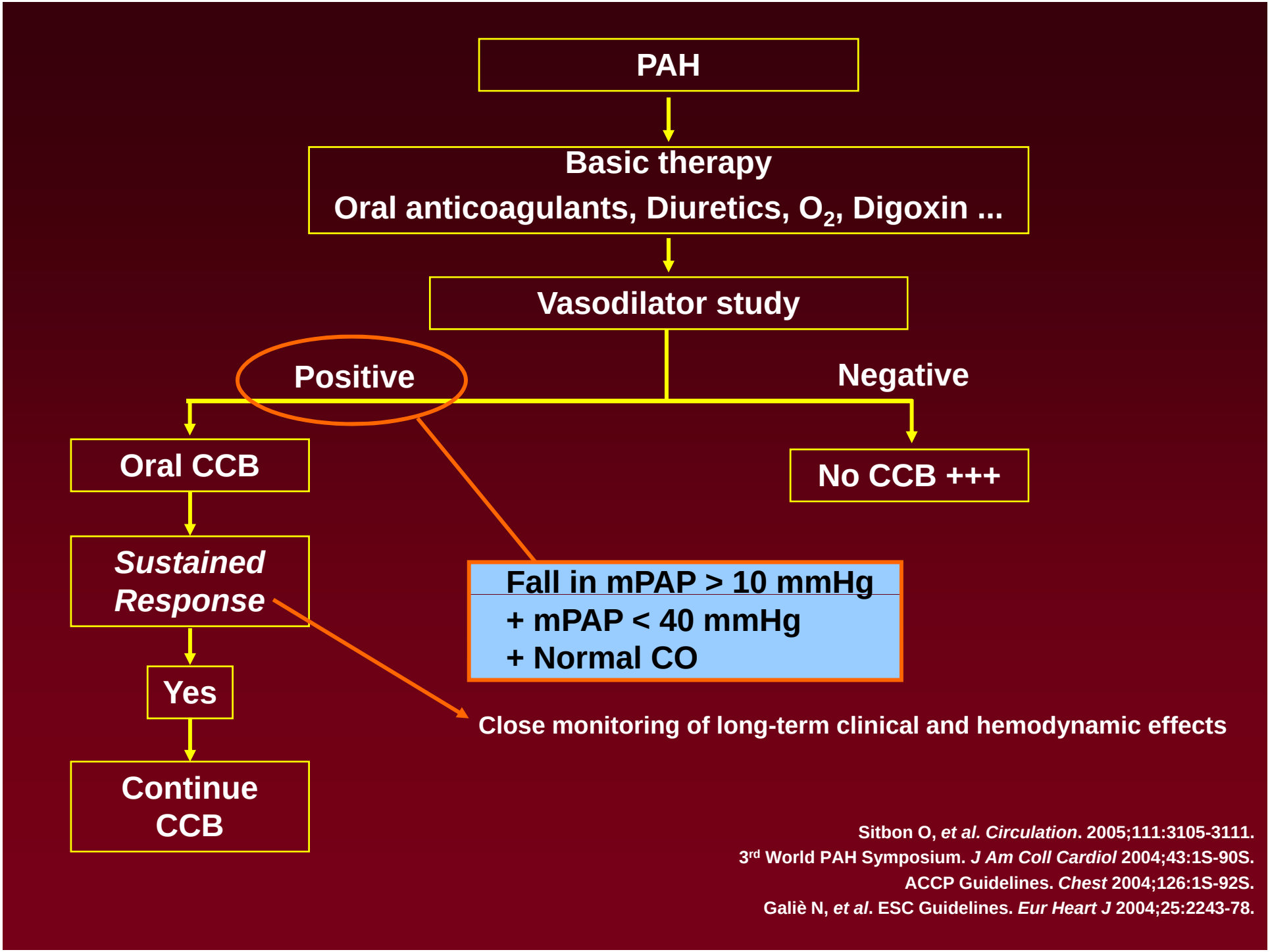
- ***Diuretics*** to manage RV volume overload
- ***O2 supplementation*** to maintain SpO2 >90%.
- ***Digoxin in PAH*** :
  - One study demonstrated that the administration of iv digoxin in IPAH patients produced a modest increase in cardiac output and a reduction in circulating norepinephrine levels, although longer-term data are not available

Chest 1998;114:787–92

  - Digoxin is used

1.Patients with RHF & low CO

2. Atrial arrhythmias



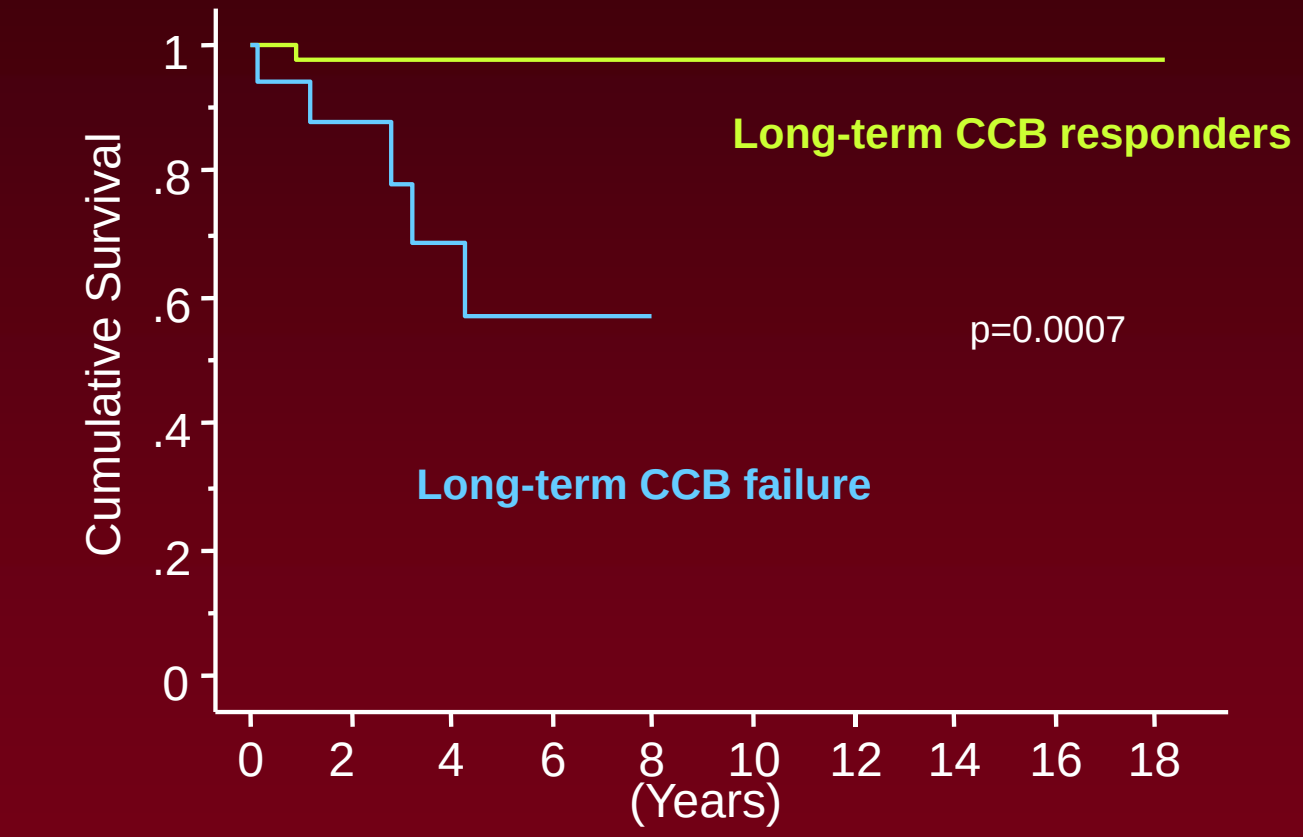
Sitbon O, *et al. Circulation*. 2005;111:3105-3111.

3rd World PAH Symposium. *J Am Coll Cardiol* 2004;43:1S-90S.

ACCP Guidelines. *Chest* 2004;126:1S-92S.

Galiè N, *et al*. ESC Guidelines. *Eur Heart J* 2004;25:2243-78.

Survival in IPAH
Long-term CCB responders



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

Use of calcium channel blockers in pulmonary arterial hypertension

Indications

- PAH patients with WHO group I and
- PAH diagnosis confirmed on right heart catheterization (ie, PVR above 3.0 wood units by Fick's method) and
- "Responder" on "acute vasoreactivity testing"

Contraindications

- Low cardiac output, cardiac index <2.0
- Severe RHF
- Hypotension, systolic BP below 90 mm Hg
- History of adverse reaction or intolerance to CCB

Cautions

- Empiric trial of CCB without acute vasoreactivity testing should not be performed. It is unsafe and may cause hypotension [125] and even death [124]
- Acute vasoreactivity testing should not be performed with CCB because it is unsafe and may cause profound hypotension, acute pulmonary edema, and potentially death
- Patients who are acutely decompensated with RHF are not candidates for CCB therapy. There is no real reason to perform acute vasoreactivity testing in such patients

Clin Chest Med 28 (2007) 91–115

Use of calcium channel blockers in pulmonary arterial hypertension

Practical use of CCBs

Choice and dose of calcium channel blockers

- Chose nifedipine if baseline resting heart rate <100/min and diltiazem if >100/min
- Amlodipine may be used if significant side effects from other agents (eg, worsening edema, significant tachycardia, bradycardia, or hypotension)
- Verapamil should not be used secondary to strong cardiodepressor effects
- Generally high doses are required (eg, nifedipine up to 240 mg/d and diltiazem 720 mg/d, both in three divided doses, amlodipine up to 5 mg twice a day
- Only oral administration is used

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Use of calcium channel blockers in pulmonary arterial hypertension

Initiation of CCB

CCB may be started in either inpatient setting or outpatient setting (there are no rigid recommendations, and approaches may vary among different centers)

A. Inpatient setting: rapid CCB dose escalation

- All rapid CCB dose escalations are generally performed with PA catheter in place
- Patients receive initial dose of nifedipine 10–20 mg orally or diltiazem 60 mg orally; hemodynamic measurements are obtained in 1 h
- The dose and hemodynamic measurements are repeated every hour until a "threshold" response (fall in PVR by 50% and, not or, fall in mPAP by 33%) is achieved or significant side effects are experienced (eg, hypotension [mBP <90 mm Hg], gastrointestinal upset [nausea, vomiting])
- Total daily dose is calculated by adding up total amount of drug administered during this testing. The goal is to achieve this in three divided doses (four to six divided doses if significant side effects)
- Patient is then given nifedipine 20 mg orally three times daily or diltiazem 60 mg orally three times daily next day and is discharged
- The dose is then gradually increased to the desired level (as estimated previously) over a period of 6–12 wk while frequently monitoring BP and heart rate

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Use of calcium channel blockers in pulmonary arterial hypertension

B. Outpatient setting: slow CCB dose escalation

- Patients are started on initial dose of nifedipine 10–20 mg orally three times daily or diltiazem 60 mg orally three times daily
- The dose is then gradually increased with a goal to ultimately achieve the maximum dose (nifedipine 240 mg/d or diltiazem 720 mg/d, both in three divided doses; amlodipine up to 5 mg twice daily) over a period of 6–12 wk, while frequently monitoring the BP and heart rate. If patient experiences limiting side effects (as mentioned previously) before the maximum dose is reached, either the dose is kept at that level or further increase is achieved by increasing the dose frequency to every 4–6 h

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Use of calcium channel blockers in pulmonary arterial hypertension

Follow-up, when to use additional therapies

- Only 6.8% of all patients who have PAH are long-term responders to CCB (ie, who will be in NYHA I or II on monotherapy with CCB for 1 y) [32]
- Approximately half of the patients who are responders at initial acute vasoreactivity testing and are placed on CCB require an additional PAH therapy within 1 y
- Secondary to this risk of failure of CCB monotherapy, such patients should be closely followed (every 3–6 mo) and should be started on an additional therapy if there is clinical worsening or worsening of 6-minute walking distance.
- Secondary to this risk of failure of CCB monotherapy, some experts consider adding a specific PAH agent at the beginning, especially in patients who have poor predictors of long-term response at baseline hemodynamics and vasoreactivity testing [32]

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PAH : Evidence-Based Treatment Algorithm

Table 1 Quality of Evidence, Net Benefit, and Strength of Recommendation

Variables	Description
Quality of the evidence	
Good	Evidence is based on good randomized controlled trials or meta-analyses.
Fair	Evidence is based on other controlled trials or randomized controlled trials with minor flaws.
Low	Evidence is based on nonrandomized, case-control, or other observational studies.
Expert opinion	Evidence is based on the consensus of the carefully selected panel of experts in the topic field.
	There are no studies that meet the criteria for inclusion in the published reports review.
Net benefit	
Substantial	
Intermediate	
Small/weak	
None	
Conflicting	
Negative	

Strength of recommendation

A	Strong recommendation
B	Moderate recommendation
C	Weak recommendation
D	Negative recommendation
I	No recommendation possible (inconclusive)
E/A	Strong recommendation on the basis of expert opinion only
E/B	Moderate recommendation on the basis of expert opinion only
E/C	Weak recommendation on the basis of expert opinion only
E/D	Negative recommendation on the basis of expert opinion only

Chest 2004;126;11-13

Table 2 Relationship of Strength of the Recommendations Scale to Quality of Evidence and Net Benefits

	Net Benefit					
Quality of Evidence	Substantial	Intermediate	Small/Weak	None	Conflicting	Negative
Good	A	A	B	D	I	D
Fair	A	B	C	D	I	D
Low	B	C	C	I	I	D
Expert opinion	E/A	E/B	E/C	I	I	E/D

Prostacyclins

- Intravenous (epoprostenol, treprostinil)*
- Subcutaneous (treprostinil*)
- Inhaled (iloprost*, treprostinil†)
- Oral (beraprost‡)

***FDA approved**
†Investigational/in development
‡Non-FDA approved

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

◄ Previous Volume 334:296-301 February 1, 1996 Number 5 Next ►

A Comparison of Continuous Intravenous Epoprostenol (Prostacyclin) with Conventional Therapy for Primary Pulmonary Hypertension

Robyn J. Barst, M.D., Lewis J. Rubin, M.D., Walker A. Long, M.D., Michael D. McGoon, M.D., Stuart Rich, M.D., David B. Badesch, M.D., Bertron M. Groves, M.D., Victor F. Tapson, M.D., Robert C. Bourge, M.D., Bru Brundage, M.D., Spencer K. Koerner, M.D., David Langleben, M.D., Cesar A. Keller, M.D., Srinivas Murali, M.D., Barry F. Uretsky, M.D., Linda M. Clayton, Pharm.D., Maria M. Jöbsis, B.A., Shelmer D. Blackburn, B.A. Shortino, M.S., James W. Crow, Ph.D., for The Primary Pulmonary Hypertension Study Group

Abstract *Background.* Primary pulmonary hypertension is a progressive disease for which no treatment has been shown in a prospective, randomized trial to improve survival.

Methods. We conducted a 12-week prospective, randomized, multicenter open trial comparing the effects of the continuous intravenous infusion of epoprostenol (formerly called prostacyclin) plus conventional therapy with those of conventional therapy alone in 81 patients with severe primary pulmonary hypertension (New York Heart Association functional class III or IV).

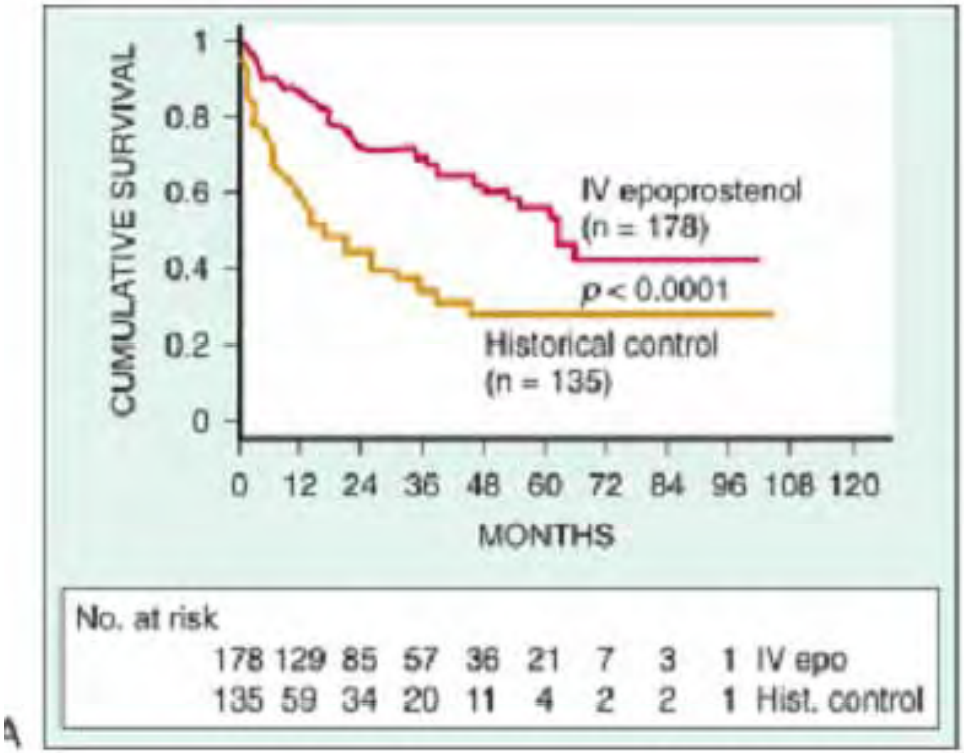
Results. Exercise capacity was improved in the 41 patients treated with epoprostenol (median distance walked in six minutes, 362 m at 12 weeks vs. 315 m at base line), but it decreased in the 40 patients treated with conventional therapy alone (204 m at 12 weeks vs. 270 m at base line; $P<0.002$ for the comparison of the treatment groups). Indexes of the quality of life were improved only in the epoprostenol group ($P<0.01$).

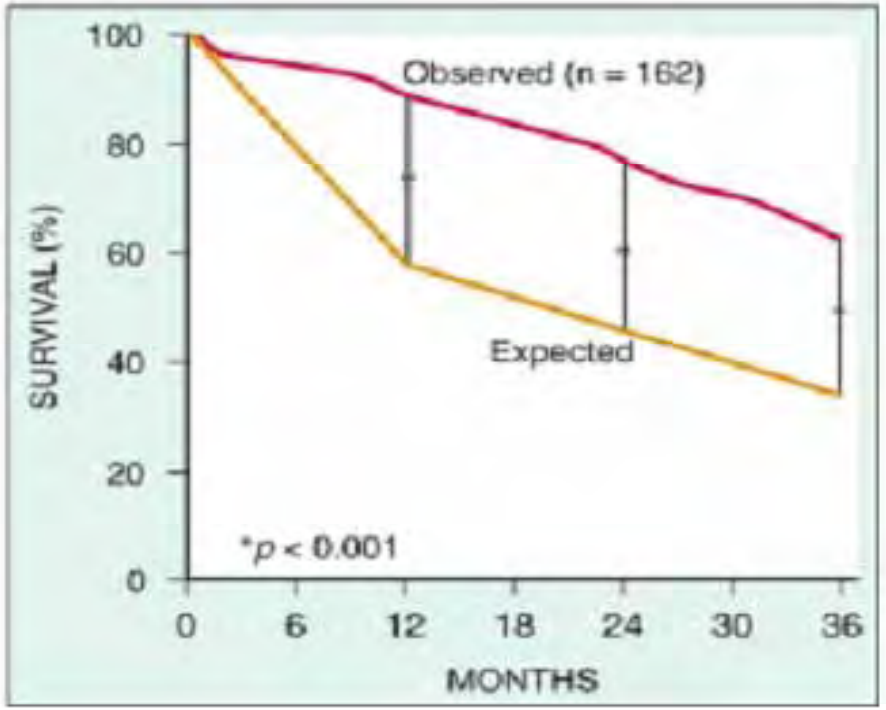
Hemodynamics improved at 12 weeks in the epoprostenol-treated patients. The changes in mean pulmonary-artery pressure for the epoprostenol and control groups were −8 percent and +3 percent, respectively (difference in mean change, −6.7 mm Hg; 95 percent confidence interval, −10.7 to −2.6 mm Hg; $P<0.002$), and the mean changes in pulmonary vascular resistance for the epoprostenol and control groups were −21 percent and +9 percent, respectively (difference in mean change, −4.9 mm Hg per liter per minute; 95 percent confidence interval, −7.6 to −2.3 mm Hg per liter per minute; $P<0.001$). Eight patients died during the study, all of whom had been randomly assigned to conventional therapy ($P=0.003$). Serious complications included four episodes of catheter-related sepsis and one thrombotic event.

Conclusions. As compared with conventional therapy, the continuous intravenous infusion of epoprostenol produced symptomatic and hemodynamic improvement, as well as improved survival in patients with severe primary pulmonary hypertension. (N Engl J Med 1996;334:296-301.)

©1996, Massachusetts Medical Society.

Long term outcome in IPAH





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

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

Epoprostenol

- Indications : NYHA Class III or IV PAH
- Contraindicated in severe LV systolic dysfunction (LVEF <30%) & in veno-occlusive disease
- Cost ~ $60,000 to $120,000/year depending on dose
- ***Continuous iv infusion*** : Initial dose of 2 ng/kg/min >>>> optimal dose between 25 and 40 ng/kg/min for most adult
- **Side effects**: high cardiac **output failure, headache, jaw pain, flushing, nausea, d**iarrhea, skin rash, and musculoskeletal pain. Infections and infusion interruptions can be life-threatening
- Half life 3-6 mts .Given as Continuous IV infusion via tunneled catheter . Unstable at room temp & acidic pH

Important Points: Epoprostenol

- Functional capacity, hemodynamics, and survival are improved
- Baseline NYHA functional class is predictor of survival
- Response after 12 to 18 months can predict subsequent outcomes
- Most benefit apparent in first 12 to 18 months
- Dosing: Outcomes with moderate dosing are the same as with aggressive dosing

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

IV epoprostenol in PAH associated with the scleroderma spectrum of diseases

- Multicenter, open label, randomized trial
- Marked improvements in exercise endurance and hemodynamics,
- No effect on mortality after 12 weeks of therapy.

Ann Intern Med. 2000;132:425–34

- Observational series have also reported favorable effects of intravenous epoprostenol in patients with numerous forms of associated PAH
  - PH with associated congenital heart defects.

    Circulation. 1999;99:1858–65.
  - HIV-associated pulmonary hypertension

    Am J Respir Crit Care Med. 2000;162:1846 –50.

    Am J Respir Crit Care Med. 2003;167:1433–9
  - Secondary pulmonary ***hypertension***

    Ann Intern Med. 1999;130: 740–3.
  - Portopulmonary hypertension.

    Transplantation. 1997;63:604–6.

SC Treprostinil

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Am. J. Respir. Crit. Care Med., Volume 165, Number 6, March 2002, 800-804

Continuous Subcutaneous Infusion of Treprostinil, a Prostacyclin Analogue, in Patients with Pulmonary Arterial Hypertension

A Double-blind, Randomized, Placebo-controlled Trial

GERALD SIMONNEAU, ROBYN J. BARST, NAZZARENO GALIE, ROBERT NAEIJE, STUART RICH, ROBERT C. BOURGE, ANNE KEOGH, RONALD OUDIZ, ADAANI FROST, SHELMER D. BLACKBURN, JAMES W. CROW, and LEWIS J. RUBIN, for the Treprostinil Study Group

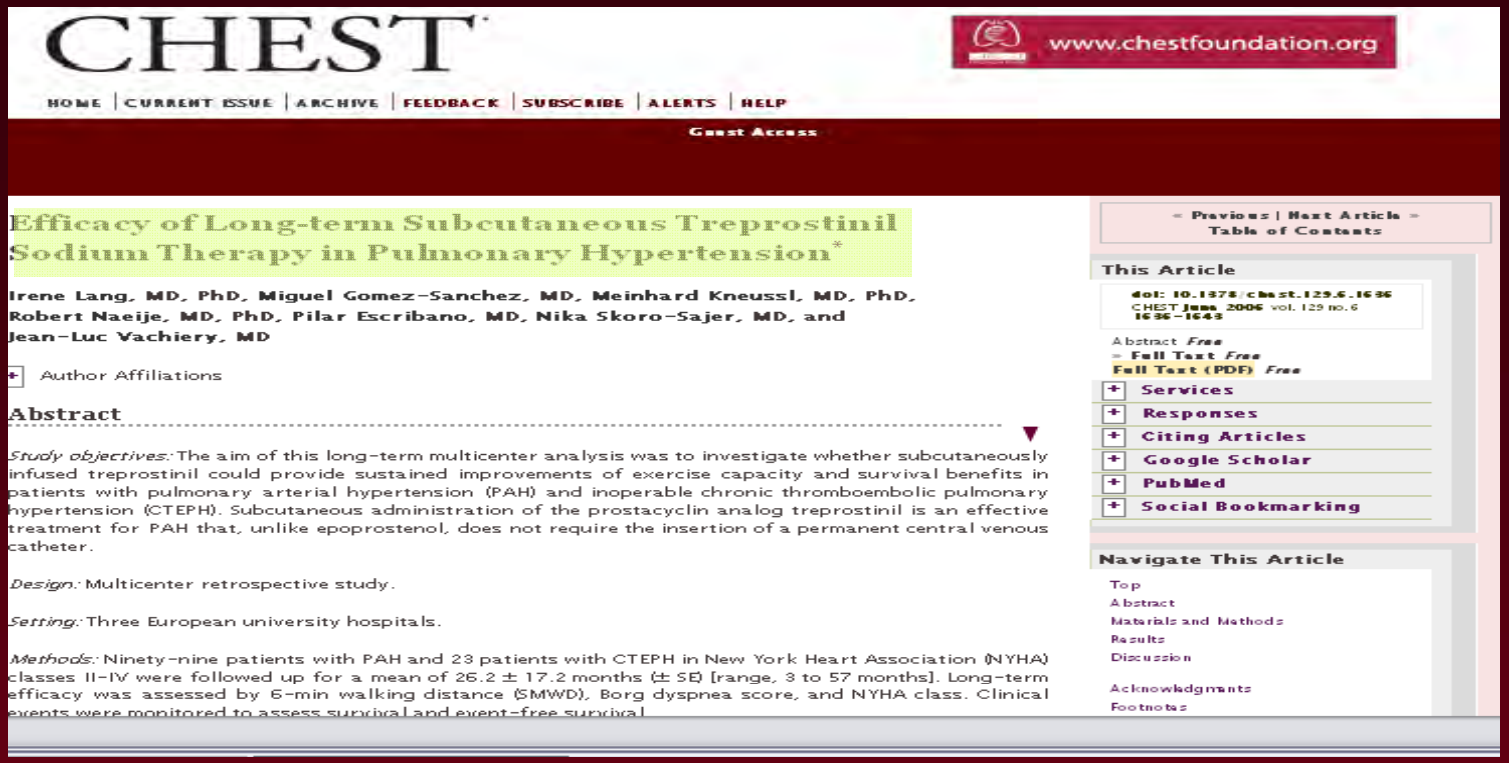
Division of Pulmonary and Critical Care Medicine, Antoine Béclère Hospital, Clamart, Paris-Sud University, Clamart, France; Department of Pediatrics, Columbia Presbyterian Medical Center, New York, New York; Division of Cardiology, University of Bologna, Bologna, Italy; Departments of Pathophysiology and Cardiac Surgery, Erasme University Hospital, Brussels, Belgium; Division of Cardiology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois; Division of Cardiology, University of Alabama, Birmingham, Alabama; Department of Medicine, St. Vincent's Hospital, Sydney, Australia; Division of Cardiology,

First studied in a 12-week, placebo controlled, multicenter, randomized trial of 470 patients with functional class II, III, or IV PAH (IPAH, connective tissue disease of CHD related)

modest but statistically significant increase of 16 m of the 6MW test, which was dose related.

FDA 2002

CONCLUSION: chronic subcutaneous infusion of treprostinil is an effective treatment with an acceptable safety profile in patients with pulmonary arterial hypertension



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Guest Access

Efficacy of Long-term Subcutaneous Treprostinil Sodium Therapy in Pulmonary Hypertension*

Irene Lang, MD, PhD, Miguel Gomez-Sanchez, MD, Meinhard Kneussl, MD, PhD, Robert Naeije, MD, PhD, Pilar Escribano, MD, Nika Skoro-Sajer, MD, and Jean-Luc Vachiery, MD

Author Affiliations

Abstract

Study objectives: The aim of this long-term multicenter analysis was to investigate whether subcutaneously infused treprostinil could provide sustained improvements of exercise capacity and survival benefits in patients with pulmonary arterial hypertension (PAH) and inoperable chronic thromboembolic pulmonary hypertension (CTEPH). Subcutaneous administration of the prostacyclin analog treprostinil is an effective treatment for PAH that, unlike epoprostenol, does not require the insertion of a permanent central venous catheter.

Design: Multicenter retrospective study.

Setting: Three European university hospitals.

Methods: Ninety-nine patients with PAH and 23 patients with CTEPH in New York Heart Association (NYHA) classes II-IV were followed up for a mean of 26.2 ± 17.2 months (± SE) [range, 3 to 57 months]. Long-term efficacy was assessed by 6-min walking distance (SMWD), Borg dyspnea score, and NYHA class. Clinical events were monitored to assess survival and event-free survival

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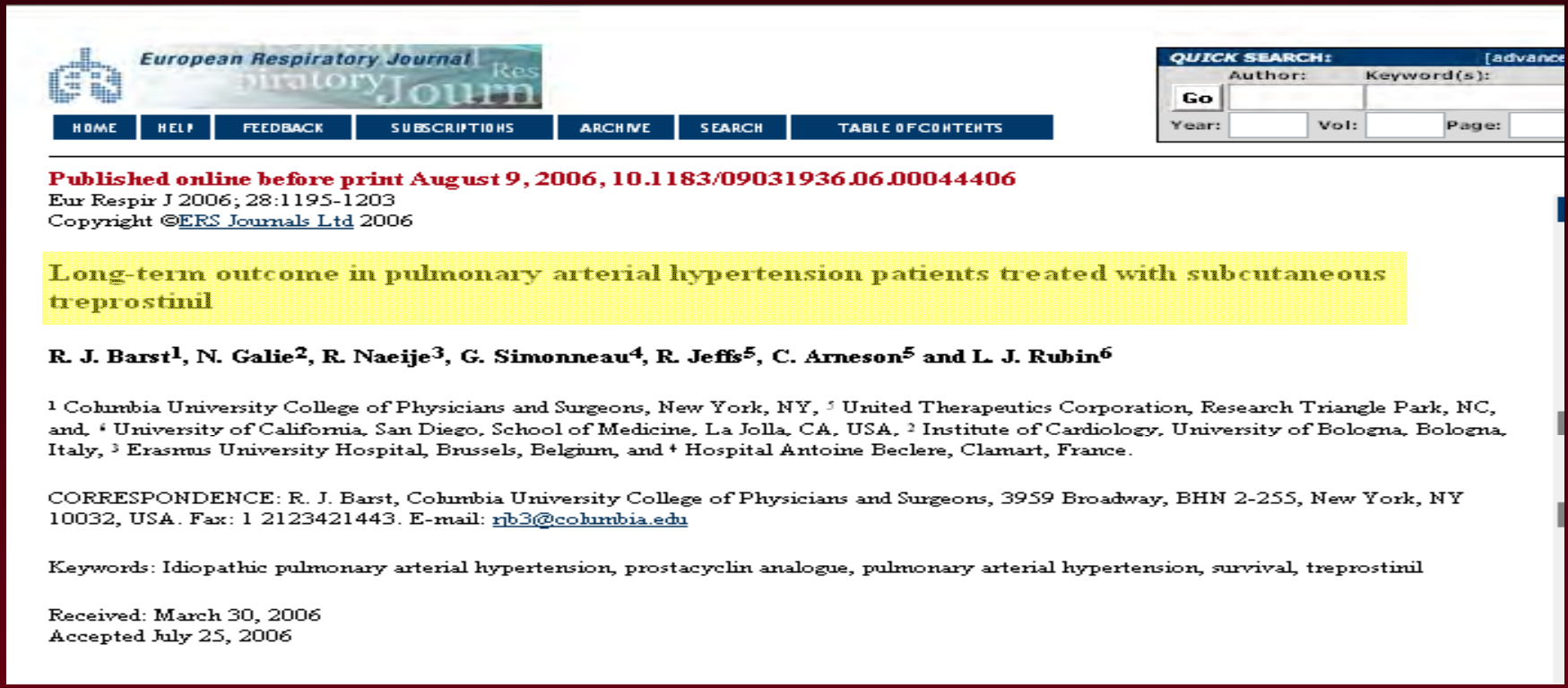
Footnotes

Conclusions:

Long-term subcutaneous therapy with treprostinil appears to continuously improve exercise tolerance and symptoms in patients with PAH and inoperable CTEPH.

Moreover, treatment may provide a significant survival benefit.



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Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil

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Keywords: Idiopathic pulmonary arterial hypertension, prostacyclin analogue, pulmonary arterial hypertension, survival, treprostinil

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Conclusion : Subcutaneous treprostinil as a therapeutic option may improve outcome in pulmonary arterial hypertension.
The safety profile for long-term subcutaneous treprostinil was consistent with previous short-term trials with no unexpected adverse events.

Treprostinil Sodium Injection

- Administered via continuous infusion using an ambulatory pump
- Given via self-inserted sc catheter
- Patients must have immediate access to backup infusion pump to prevent the risk of worsening of PAH symptoms due to interruption of therapy
- Dose 50-80 ng/kg/min
- Cost ~$60,000 to $120,000/year (exclusive of costs for administration/monitoring; IV more expensive)

- Requires capable patient
- Site pain is major impediment
  - Affects 85%
  - Local measures: ice, heat, lidocaine, capsaicin, collagenase ± effective
  - NSAIDs, narcotics, gabapentin ± effective
  - PLO gel topical; promising, but unconfirmed reports of benefit; not useful at active site
- ***Other common side effects*** include headache, diarrhea, rash, and nausea

IV Treprostinil

- Approved by FDA in January 2005
- Has safety (longer half-life : 4.5 hrs) and convenience advantages (no mixing or cold packs, smaller pump) over IV epoprostenol
- Can be used for de novo patients and transitions from epoprostenol
- Improvements in hemodynamics and functional status similar to epoprostenol
- Requires at least double the epoprostenol dose (may be more expensive)

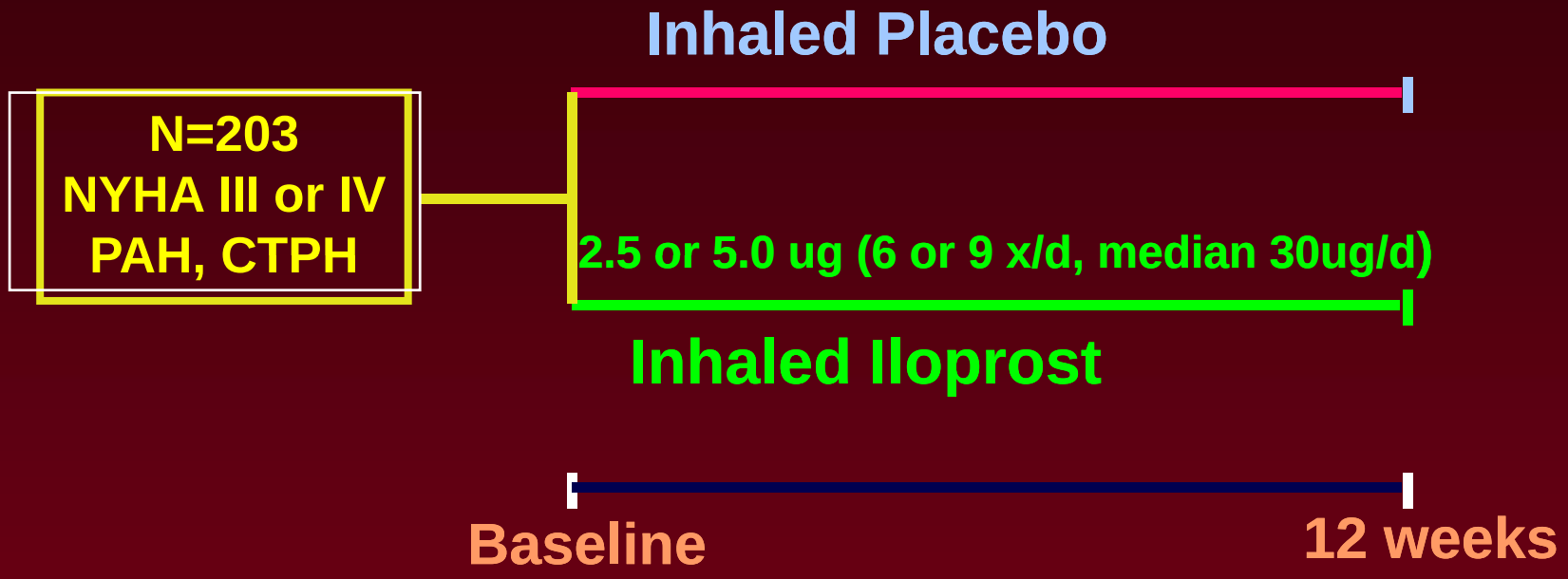
Inhaled Iloprost

- Approved for class III - IV PAH
- Duration of hemodynamic effect only 90 minutes
- Requires frequent administration
- Has favorable effects on gas exchange in pulmonary fibrosis
- Cost of ~ $60,000-$70,000/year

Olschewski H, et al. *N Engl J Med*. 2002;347:322-329.

Inhalational Iloprost

Olschewski et al, NEJM 2002, 347:322-9



Conclusion:

6-min walk distance improved (36 m, p=0.004)

NYHA class improved (p=0.03)

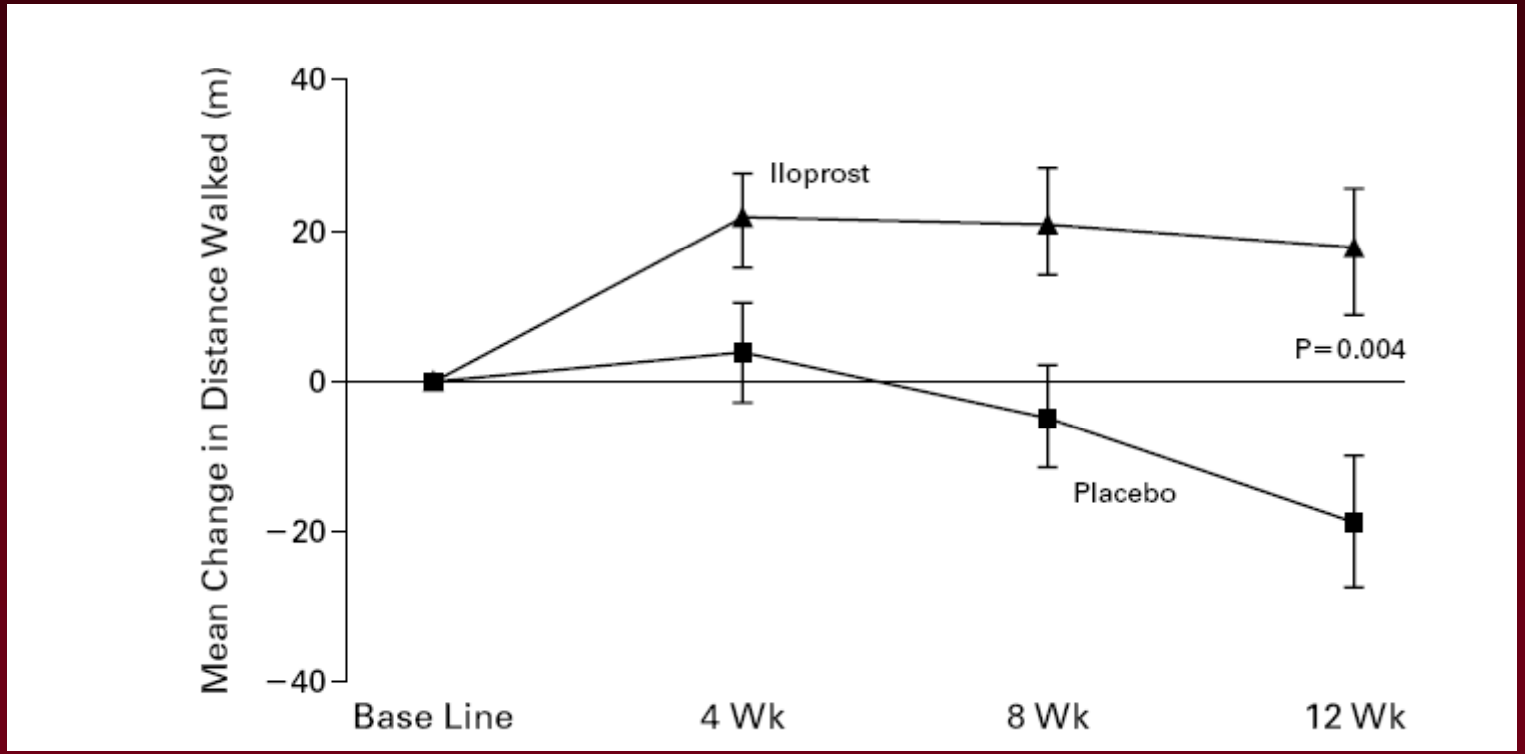
Dyspnoea improved (p=0.015)

Minimal improvement in hemodynamics

1° End-point

10% ↑6-min walk & improved NYHA Class w/o clinical deterioration or death

INHALED ILOPROST FOR SEVERE PULMONARY HYPERTENSION



Iloprost group mean baseline = 332 m
Placebo group mean baseline = 315 m

Placebo corrected mean difference at 12 weeks = 40 m (p=<0.01)

- In a study of 24 iloprost-treated IPAH patients, Hoeper et al. reported sustained benefits in exercise capacity and hemodynamics at 1 year.
- More recently, Opitz et al. reported event-free survival rates of 53%, 29%, and 20% at 1, 2, and 3 years, respectively, in IPAH patients treated with iloprost monotherapy.
- ***Common side effects*** of inhaled iloprost include cough, headache, flushing, and jaw pain. .
- Iloprost was approved by the FDA in 2004 for functional class III and IV PAH
- Dose 2.5-5.0 mcg ampules via nebulizer , upto 12 times a day

Beraprost

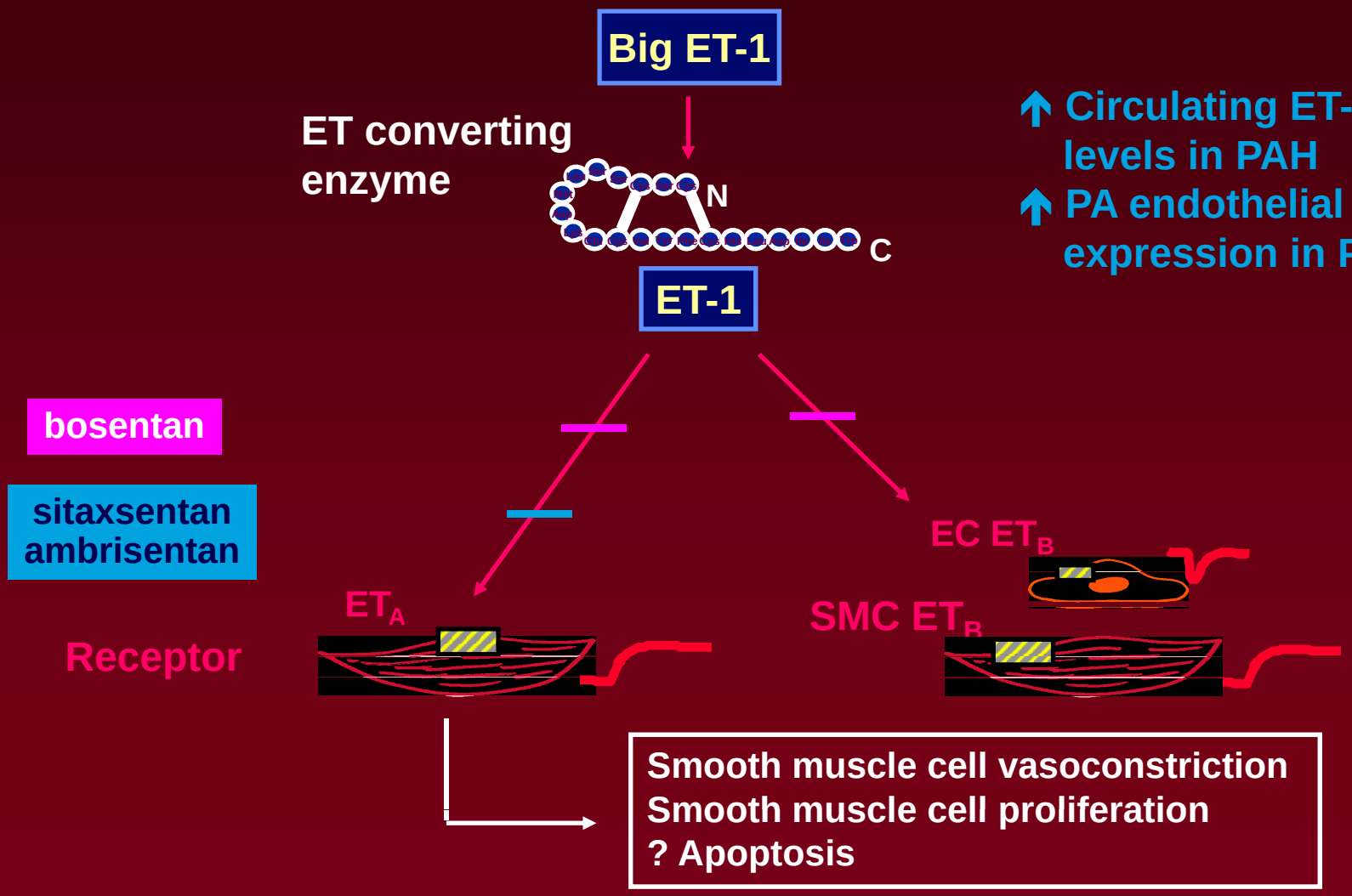
- Oral analogue : half life 30-45 min
- ***ALPHABET study*** (RCT,double blind,multicenter) : improved exercise capacity & symptoms but not the hemodynamics & functional class
- Approved in Japan only

Endothelin Antagonists (ERAs)

- Oral
  - "Nonselective" ERA/ERB
    - **Bosentan***
  - "Selective" ERA
    - **Ambrisentan***
    - **Sitaxsentan†**

***FDA approved**
†Investigational/in development

The Endothelin System

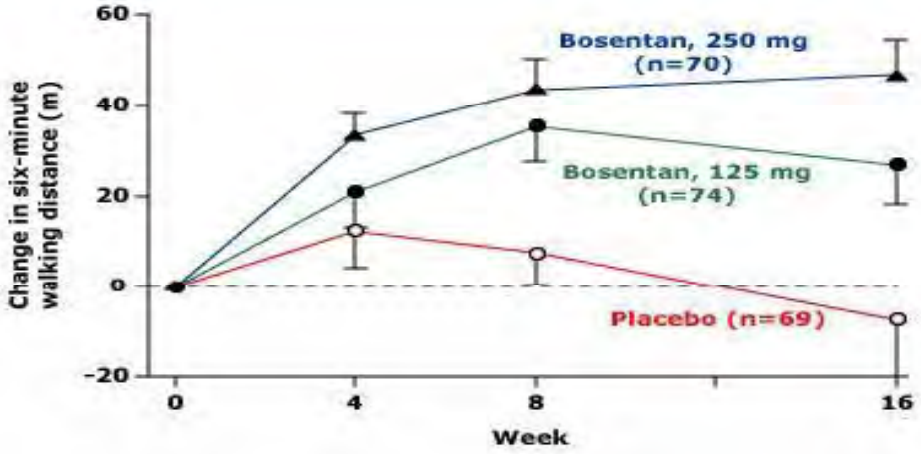


Bosentan (Tracleer) Indication

- PAH with WHO Class III (or II - IV) symptoms
  "to improve exercise capacity and decrease the rate of clinical worsening"
- Dose 62.5 mg BID oral for 4 weeks
- 125 mg BID oral thereafter if liver functions OK
- Costs ~$36,000/year
- Contraindicated with glyburide and cyclosporine

BREATHE-1
Randomized double-blind, placebo-controlled

Mean change (±SE) in six-minute walking distance from baseline to week 16 in the placebo and bosentan groups



P<0.01 for the comparison between the 125-mg dose of bosentan and placebo, and P<0.001 for the comparison between the 250-mg dose and placebo by the Mann-Whitney U test. There was no significant difference between the two bosentan groups (P=0.18 by the Mann-Whitney U test).

Data from: Rubin LJ, Badesch, DB, Barst, RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002; 346:896.

UpToDate

Bosentan Randomized trial of Endothelin receptor Antagonist THErapy of pulmonary hypertension

Longer-term Study

McLaughlin et al. reported that first-line therapy with bosentan, with the addition or transition to other therapy as needed, resulted in Kaplan-Meier survival estimates of 96% at 12 months and 89% at 24 months.

At the end of 12 and 24 months, 85% and 70% of patients, respectively, remained alive and on bosentan monotherapy.

Eur Respir J 2005; 25:244–9.

- Sitbon et al. compared survival in functional class III IPAH treated with bosentan with historical data from similar patients treated with epoprostenol..
  - Kaplan-Meier survival estimates after 1 and 2 years were 97% and 91%, respectively, in the bosentan-treated cohort and 91% and 84% in the epoprostenol cohort.

Thorax 2005;60:1025–30.

- ***BREATHE-5 (Tracleer (Bosentan)***: multicenter, double-blind, randomized, and placebo-controlled study in Fc III Eisenmenger syndrome PAH :
  - Bosentan did not worsen oxygen saturation, and compared with placebo, bosentan reduced PVRI, decreased mPAP, and increased exercise capacity.

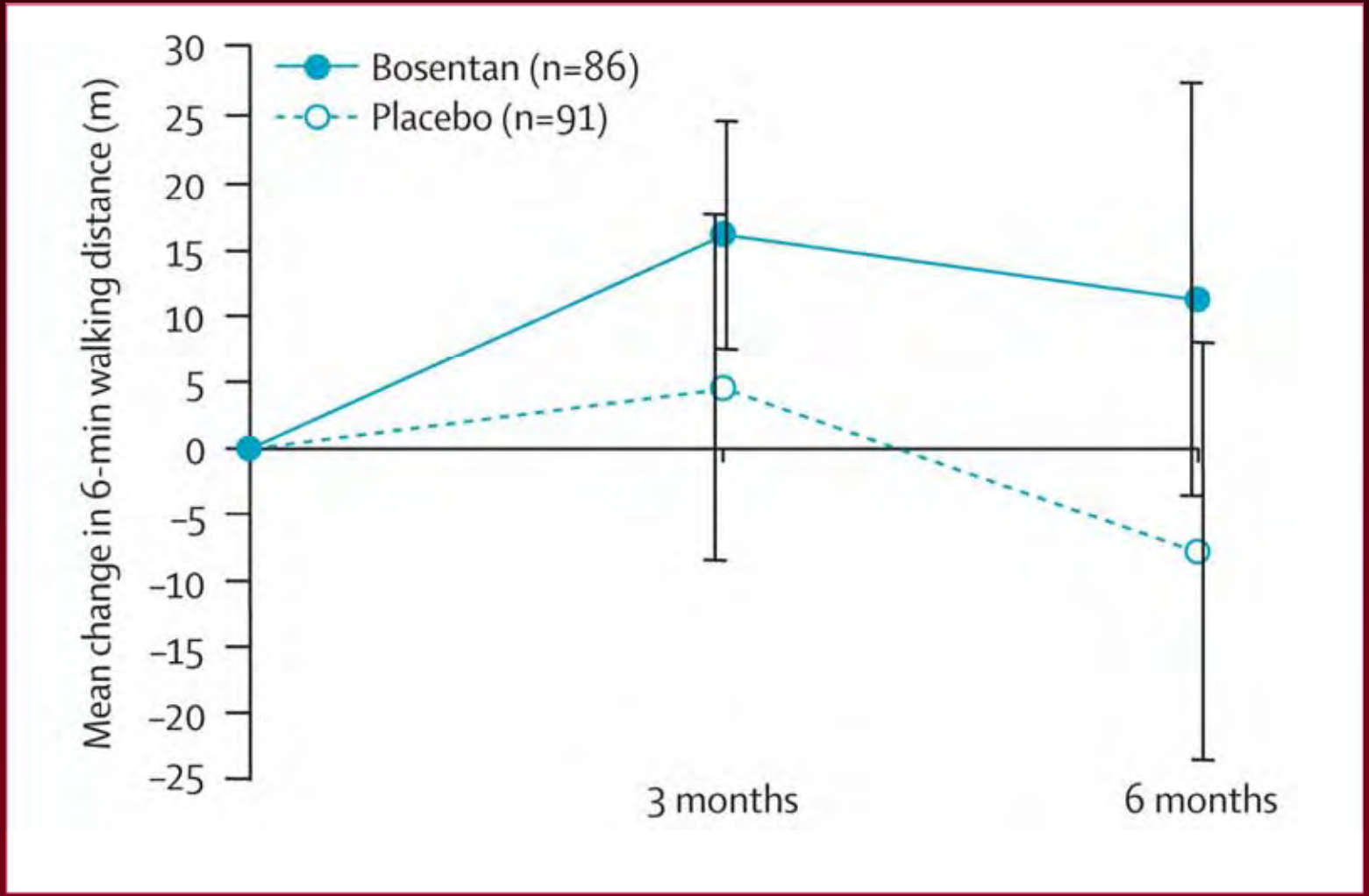
Galie N et al. Circulation 2006;114:48–54

- Data with bosentan suggest clinical improvements in HIV patients with PAH & benefits in those with inoperable CTEPH and early stage disease

EARLY STUDY

- Bosentan has also recently been evaluated in a mildly symptomatic or functional class II population
- 168 PAH patients (IPAH, FPAH, PAH associated with connective tissue disease, anorexigen use, HIV, CHD) with a mean baseline 6MW test of 435 m were randomized to receive bosentan or placebo for 26 weeks.
- There was a significant improvement in PVR, but not in 6MW test.
- There was an improvement in the secondary end point of time to clinical worsening.
- The adverse event profile with bosentan was similar to previous studies

EARLY trial: Bosentan in NYHA class II



Galie N et al. Lancet 2008; 371: 2093-2100

Bosentan Monitoring

- Liver enzymes: initial and monthly (stop if >5x elevation) reversible with cessation; can try rechallenge with lower dose
- Watch for leg edema/pulmonary edema/nasal congestion/testicular atrophy & male infertility
- Hemoglobin: initial, 1 and 3 months
- May interfere with hormonal birth control; barrier method advised
- Caveat: Response takes time (up to 2 to 3 months), should be used with caution in Class IV patients and not without right heart catheterization to document presence of PAH

Ambrisentan (Letairis) Indication

- PAH with WHO Class II - III symptoms
  "to improve exercise capacity and decrease the rate of clinical worsening"
- Dose 5 mg qD
- Consider increasing to 10 mg qD if tolerated
- Costs ~$36,000/year
- Contraindicated with cyclosporine

Ambrisentan

	ARIES-1	ARIES-2
Study	RCT, placebo-controlled phase III trials	
Place	North America	Europe
Study population	202	192
Doses	Placebo or 5 or 10 mg of ambrisentan daily	Placebo, 2.5 mg, and 5 mg
Duration	12 weeks	12 weeks
6MWD	44-m improvement for the 10-mg dose and 23-m improvement for the 5-mg dose ($p < 0.05$)	49 m and 22 m in the 5- and 2.5-mg daily dosage

ARIES-1 News Release, April 10, 2006.
Results of the ARIES-2 study. Proc Am Thorac Soc 2006; 3:A728.

- Ambrisentan was FDA approved in June 2007 for PAH patients with functional class II and III symptoms.
- The incidence of transaminases elevations at 1 year was 2.8% in the clinical trials.
- Monthly monitoring of liver function tests, a monthly pregnancy test in women of child-bearing potential, and periodic hemoglobin measurements are required.
- Other potential side effects include lower extremity edema, which is more frequent (29%) and severe in patients over 65 years of age, and nasal congestion .
- Precautions regarding contraception and testicular atrophy are similar to bosentan.

PDE 5 Inhibitors

- Indicated in Fn class II & III
  - Sildenafil (tid dosing)
  - Tadalafil (advantage of single daily dose)

FDA approved 2005 & 2009

Sildenafil

- FDA approved in June 2005 for PAH (WHO Group 1) “to improve exercise ability” regardless of functional class
- Must not be used with nitrates, but compatible with other drugs
- Metabolized by liver (CYP3A4 isoenzyme), slowed in cirrhotics, no effect of renal failure
- Oral and relatively inexpensive (~ $12,000/year)
- The FDA-approved dose of sildenafil in patients with PAH is 20 mg administered orally 3 times daily.
- Side effects include headache, flushing, dyspepsia, and epistaxis , Blue haze periphery of vision in up to 11%

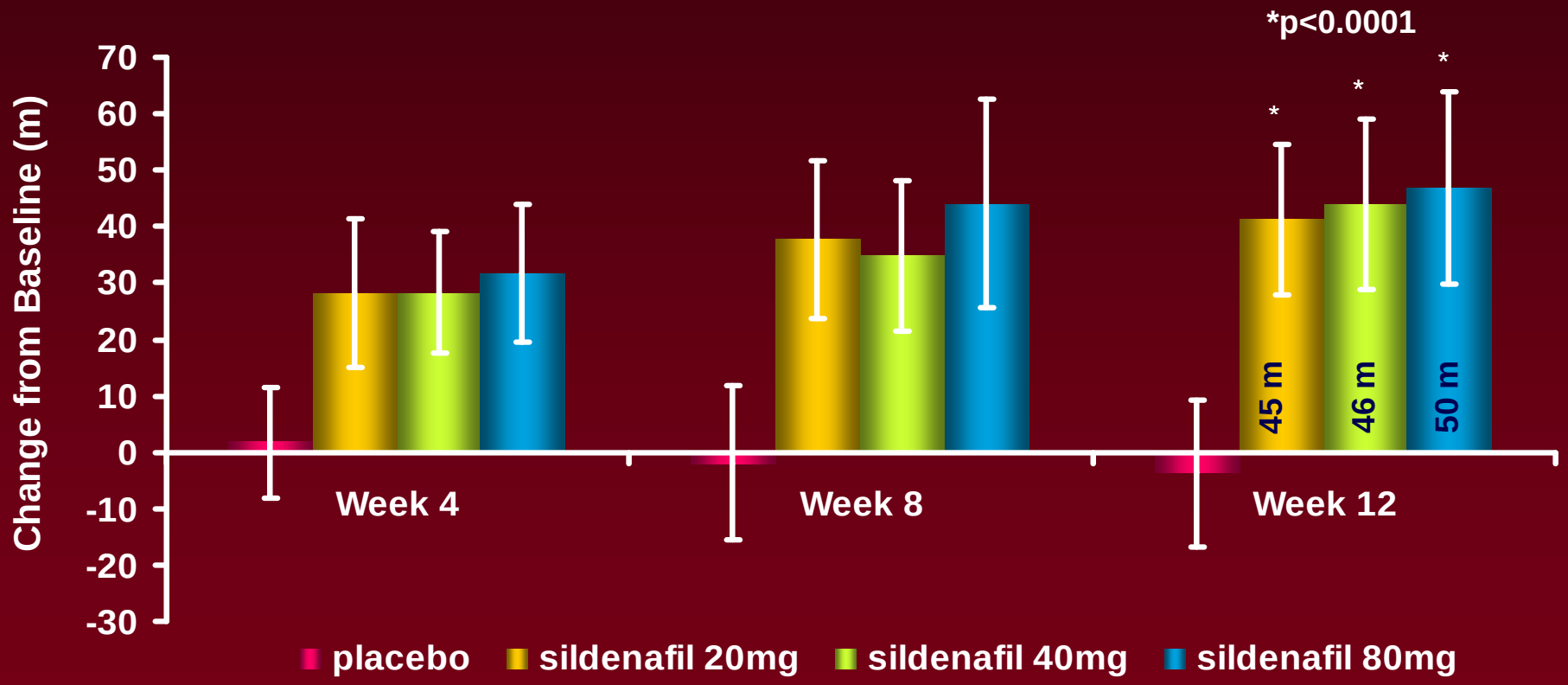
The SUPER-1 study

(Sildenafil Use in Pulmonary Arterial Hypertension)

- Randomized, double-blind, placebo controlled trial
- 278 patients with PAH (either IPAH or PAH associated with CTD or with congenital shunts) treated with placebo or sildenafil (20, 40, or 80 mg orally 3 times daily) for 12 weeks
- Mean placebo corrected increase in 6MD was 45,46,& 50m for 3 doses, respectively (p 0.001 for all comparisons)
- All sildenafil doses reduced the mPAP and improved Fn class
- Long-term data (available only at a dose of 80 mg 3 times daily) in 222 patients completing 1 year of treatment with sildenafil mono therapy showed sustained improvement from baseline at 1 year in the 6MW test (51 m).

N Engl J Med. 2005;353:2148–57

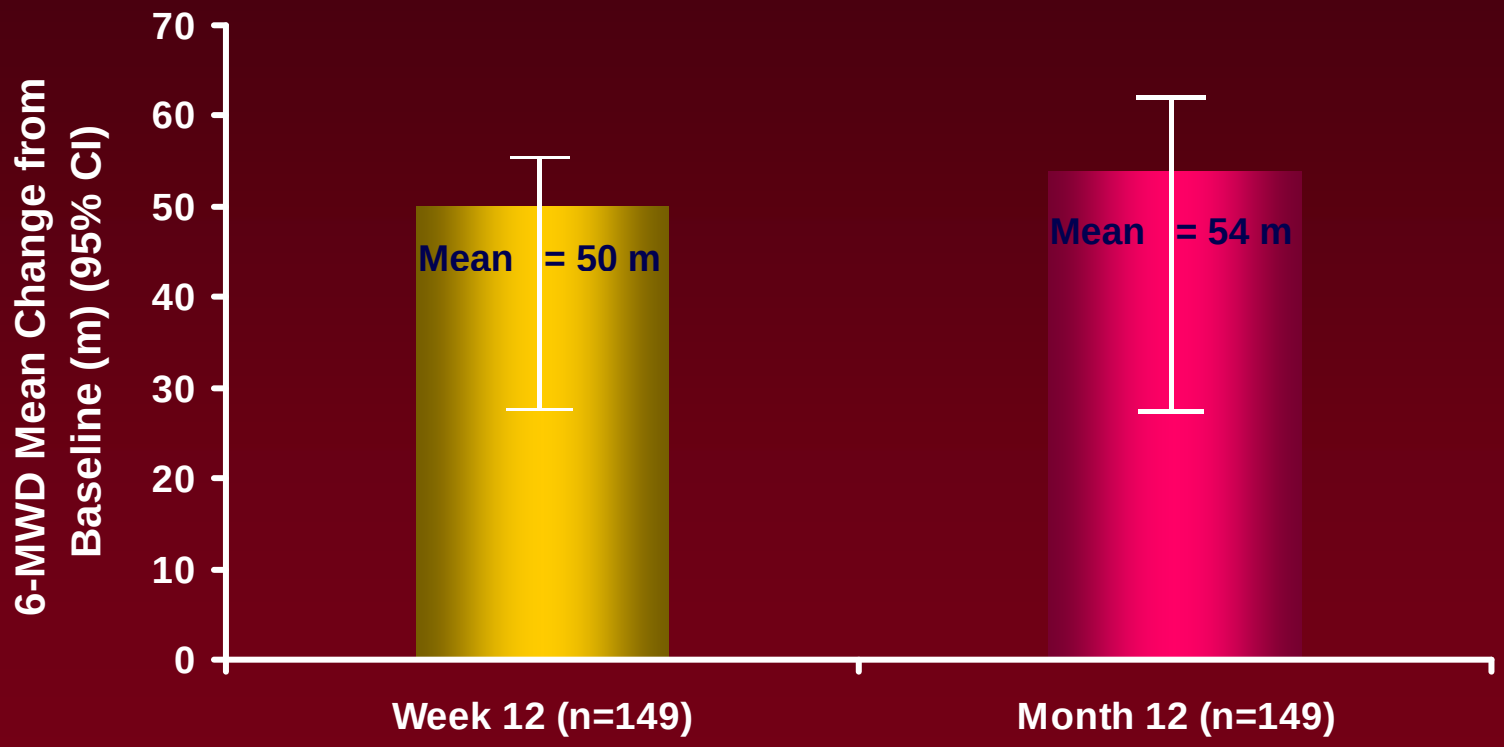
Sildenafil in PAH: SUPER-1, 6-Minute Walk Test Change from Baseline to Week 12



n=278

Ghofrani HA, et al. Presented at: the 20th Annual Meeting of the American College of Chest Physicians; October 23, 2004; Seattle, Washington.

Exercise Capacity at Week 12 and 1 Year



Rubin L, et al. Presented at: the Annual Meeting of the American Thoracic Society; May 20, 2005; San Diego, CA.

Tadalafil

- Approved in 2009 by FDA for PAH,40 mg OD
- ***PHIRST study*** : 16-week, randomized trial
- 405 patients (either not received bosentan or receiving bosentan, and almost all with Fn class II or III)
- Doses of 2.5, 10, 20, and 40 mg were compared with placebo.
- Only with 40-mg dose significant improvement in the primary end point, 6MWD was seen
- In the patients who had not received bosentan, the increase was greater than in patients who were receiving bosentan (44 vs. 23 m).
- Tadalafil did not alter the WHO functional class but slightly prolonged the time to clinical worsening.

Circulation 2009;119: 2894-903.

Rationale for Combination therapy

- Increase treatment efficacy
- Reversal of treatment failure
- Targeting complementary signaling pathway
- Amplification of vasodilatation
- Prolongation of vasodilatory effect
- Augmentation of vascular anti-remodelling

Prostanoid and PDE-5

- PACES-1 trial (Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil)
  - 267 patients with PAH who were being treated with a stable epoprostenol dose were randomized to receive either sildenafil or placebo.
  - Improvement in the 6MWT, hemodynamics and time to clinical worsening were demonstrated

Ann Intern Med 2008;149: 521–530

Prostanoid and PDE-5

- TRIUMPH-1 study (Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension)
  - Investigating inhaled treprostinil or placebo in combination with either bosentan or sildenafil or both.
  - Preliminary analysis results demonstrates improvement in 6MWT distance at 12 weeks in the treprostinil group; however, the results of combination remain to be published

Prostanoid and ETRA

- STEP trial (Safety and Pilot Efficacy Trial in Combination with Bosentan for Evaluation in Pulmonary Arterial Hypertension), a randomized, double blind, placebo-controlled trial looking at inhaled iloprost in combination with bosentan (n¼67), improvements were noted in 6MWT, NYHA functional status, and the time to clinical worsening
- COMBI trial (COMbination therapy of Bosentan and aerosolized Iloprost), a smaller (n¼40) open-label study of similar duration, no improvement was noted in the 6MWD and NYHA functional class

Limitations of Clinical Trials in PAH

- Many patients remain symptomatic, with a suboptimal quality of life and impaired hemodynamics despite treatment.
- With the exception of CCB in a robust responder, most therapies reduce PAP by 10% to 20%.
- ***A recent meta-analysis of 16 randomized trials in PAH found the following:***
- 1) a non significant reduction in all-cause mortality (relative risk 0.70, 95% confidence interval: 0.41 to 1.22);
- 2) a significant improvement in exercise capacity as assessed by the 6MW test of 42.6 m (95% confidence interval: 27.8 to 57.8 m); and
- 3) an improved dyspnea status by at least 1 functional class (relative risk 1.83, 95% confidence interval: 1.26 to 2.66) (161).

- These trials were all 8 to 16 weeks in duration.
- ***None were powered to detect a survival benefit***.
- **More recently**, a meta analysis performed on 21 RCT (3140 patients) in PAH patients published through October 2008 reported improvements in the 6MW distance and a 43% decrease in mortality in patients treated with PAH-specific therapies versus patients randomized to placebo

  (Eur Heart J. 2009;30:394– 403).

- A meta-analysis of the scleroderma spectrum of diseases related PAH patients included in 10 randomized controlled trials of oral therapy failed to demonstrate an improvement in exercise capacity in this subgroup ***(Ann Rheum Dis. 2008;67:808 –14.).***
- This is contrary to the study of epoprostenol performed specifically in the scleroderma population, which demonstrated the greatest improvement in 6MW test ever reported in a clinical trial in PAH

Cost Considerations

- Clinical trials in PAH have not included analysis regarding cost/benefit ratio, quality-adjusted life years saved, or number needed to treat.
- The PAH-specific therapies are expensive.
- The approx annual cost for sildenafil is $12761,
- bosentan is $55 890,
- ambrisentan is $56 736,
- iloprost is $92 146.
- epoprostenol is $33 153 and
- treprostinil is $97 615.
- These costs may be much higher for larger patients and at higher doses

Invasive Therapies

- Despite advances in the medical treatment for PAH, many patients experience progressive functional decline, largely related to worsening right heart failure.
- In these patients interventional and surgical therapeutic options should be considered, including atrial septostomy and lung or combined heart and lung transplantation.
- In patients with PH caused by chronic pulmonary thromboembolism, surgical thromboendarterectomy may be beneficial.
- Other surgical approaches, such as RV mechanical assistance, are under investigation.

Atrial Septostomy

- Atrial septostomy creates a right to left inter-atrial shunt, decreasing right heart filling pressures and improving right heart function and left heart filling.
- While the created shunt decreases systemic arterial oxygen saturation, it is anticipated that the improved cardiac output will result in overall augmentation of systemic oxygen delivery.
- Improved cardiac output appears to be the principal hemodynamic benefit; magnitude from 15% to nearly 60%.
- Reported success rates for bridging patients to transplantation with septostomy range from 30% to 40%
- Procedural mortality is :15% based on published series (ranged from 5% to 50% in the different centers).

- Currently, atrial septostomy is recommended for patients with severe PAH and intractable right heart failure despite maximal medical therapy, including optimized PAH-specific agents and inotropes.
- The goals of the procedure are palliation and restoration and maintenance of clinical stability until a transplant can be performed.

Lung and Combined Heart and Lung Transplantation

- There is no agreement on the optimal type of transplantation for patients with PAH.
- While acceptable outcomes have been demonstrated with SLTx, many centers prefer DLTx to limit the reperfusion injury that has been reported in the donor lung of PAH patients undergoing SLTx
- The combined procedure is generally reserved for patients
- 1. with intractable right heart failure, especially when a patient has become dependent on inotropic support.
- 2. also required in patients with PAH in complex CHD
- 3. Also with PH and concomitant advanced left heart disease

Pulmonary Thromboendarterectomy

- Patients with suspected PAH should undergo evaluation for CTEPH.
- Patients are considered to be candidates for pulmonary thromboendarterectomy (PTE) if they have surgically accessible disease and present acceptable surgical risk.
- The goal of PTE is to remove sufficient material from the pulmonary arteries to substantially lower PVR and improve cardiac output.

Right Ventricular Assist Device

- Preclinical studies have suggested the usefulness of right ventricular assist device (RVAD) support in a model of PH (***Biventricular support with the Jarvik 2000 ventricular assist device in a calf model of pulmonary hypertension. ASAIO J. 2004;50:444 –50***.).
- While a growing body of literature has emerged demonstrating the utility of RVAD support in patients with acute postoperative RV failure, often in the presence of PH, its utility in patients with PAH has not as yet been tested.

Other Investigational Therapies

- **Inhaled NO**
- **NO/nucleophile adducts** eg DETA/NO >>Release NO when in contact with aqueous solutions . Effective when given intra venously . When given as aerosol, prolonged release of NO with long half life of >20 hours
- Increasing supply of substrate and co factors involved in the reaction >>
    1. **L-arginine** supplementation- usually in excess of 10gm/d
    2. **Tetrahydrobiopterin**
- **NO donors**- nitroglycerin, sodium nitroprusside, long acting oral nitrates

Other Investigational Therapies

- Statins (HMG coreductase inhibitors):?anti VEGF action
- K+ channel openers
- Rho kinase inhibitors
- Imatinib >> ? anti PDGF action
- Angiogenesis factors
- Gene therapy
  - NOS, K+ channel openers
- Serotonin receptor antagonists
- Inhaled vasoactive intestinal peptide

Early, Risk-based and Combination Therapy:

Changing Paradigms for PAH?

Summary: Treatment

- Traditional therapies; diuretics, oxygen, phlebotomy still used as indicated; anticoagulants recommended
- Calcium Channel Blockers should be used in Class II or III acute responders but followed closely for safety & efficacy
- Newer agents are tailored to WHO class – ACCP Guidelines
  - Class IV – Infused prostacyclins
  - Class III – Oral endothelin receptor antagonists (ERAs), phosphodiesterase (PDE) 5 inhibitors, infused or inhaled prostacyclins
  - Class II – PDE 5 inhibitors, or ERAs
    - Consider therapy if evidence of Right Ventricular Dysfunction
- Combination therapies and an array of investigational therapies hold hope for the future
- Role of transplantation/septostomy now diminished because of new effective pharmacologic therapies

Indications for Referral to a Specialized Center for Rx of PAH

- Unexplained dyspnea on exertion with evidence of PH on Echo
- Evidence of moderate to severe PH
  - **Estimated PAS pressure > 45 mm Hg on Echo**
  - Symptoms consistent with NYHA functional class II or worse
  - **Near-syncope or syncope**
- Absence of substantial left sided cardiac disease or parenchymal lung disease
- Clinical or echocardiographic evidence of RV dysfunction
  - Lower- extremity edema
  - Ascites
  - **Right ventricular enlargement or systolic dysfunction on echocardiography**

Rubin, L. J. et. al. Ann Intern Med 2005;143:282- 292

Summary:

Use of Clinical Parameters, Hemodynamics, and Imaging Techniques to Predict Survival and Therapeutic Options

- High index of suspicion
- Thorough diagnostic evaluation, need RHC
- Exclude thromboembolic disease
- Vasodilator testing to eliminate inappropriate CCB use