COPD School 2014
17 : 15 ~ 17 : 35

Treatment of comorbid conditions

2nd Pulmonary Hypertension

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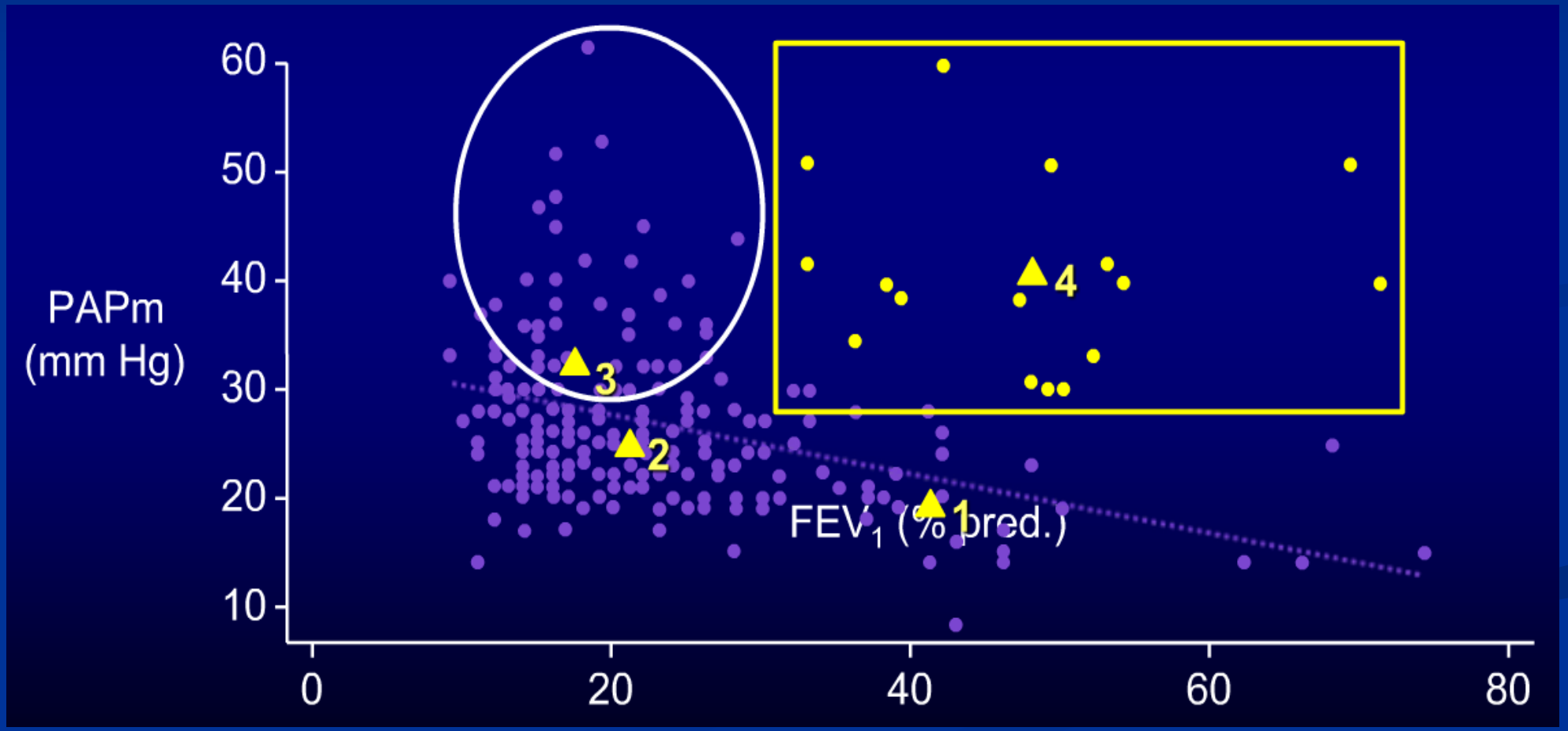
"Out-of-proportion" PH in COPD

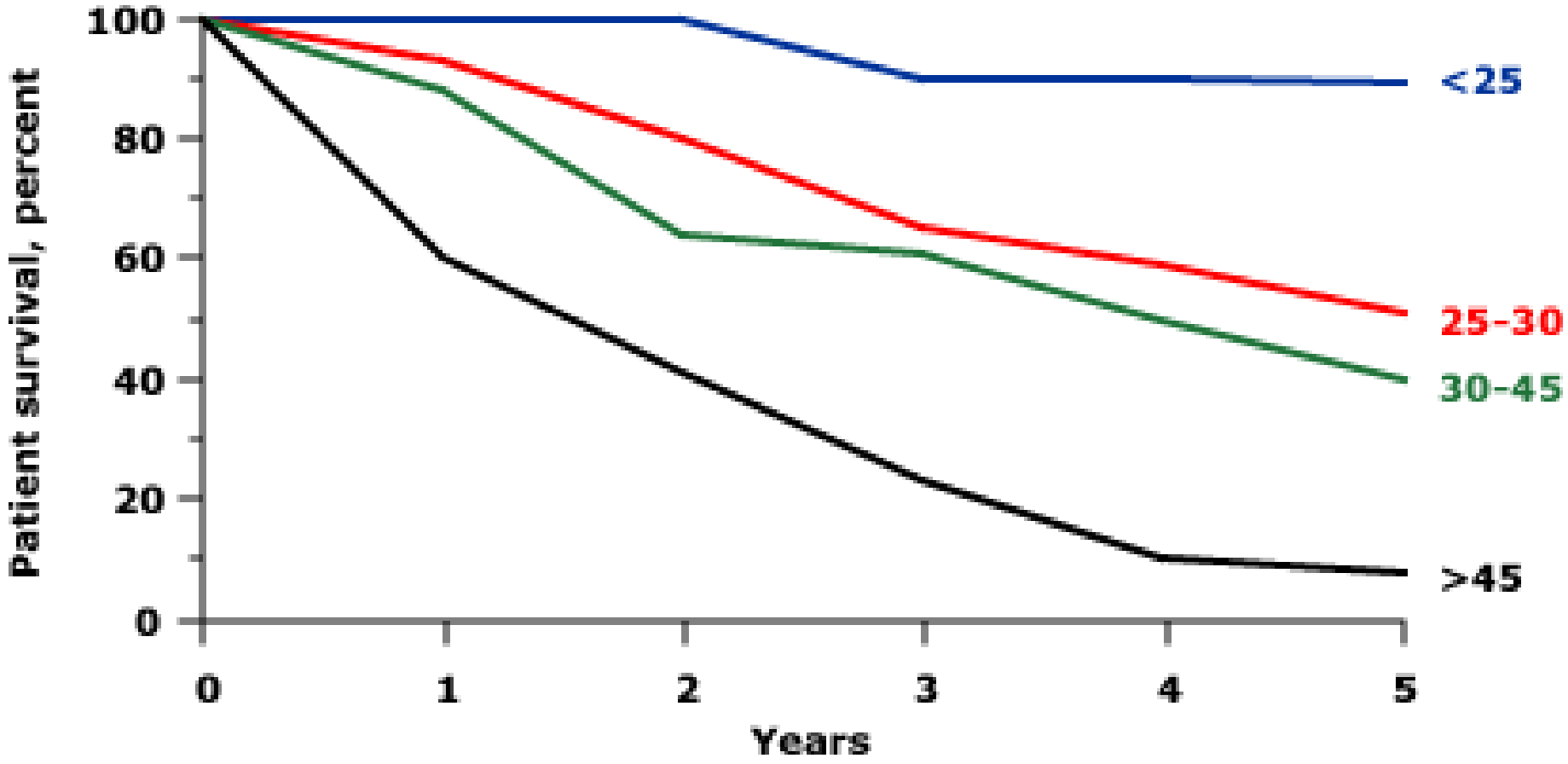
- Retrospectively study of 215 COPD patients
- 7.4% of patients with "out of proportion" PH (Severe PH without airflow limitation)



Thabut G et al. Chest 2005;127:1531

PH and survival in COPD

• Increasing pulmonary artery pressure was associated with a progressive decline in survival.



Prog Respir Res 1975; 5:9

Contents

- Classification
- Prevalence
- Pathogenesis
- Treatment

Conclusion

- WHO classification of PH
  - 5 groups based upon etiology
  - COPD is a frequent cause of group 3 PH
- Two mechanisms of COPD-related PH
  - Hypoxia induced vasoconstriction & obliteration of the vascular bed
- Tx of PH in COPD
  - Smoking cessation & oxygen therapy
  - Pulmonary vasodilators
    : have a therapeutic role in disproportionate subgroup
    : may worsen gas exchange, have no proven benefit
  - Lung transplantation

WHO Classification

3rd World Congress on Pulmonary Hypertension
Venice, Italy 2003

I	Pulmonary arterial hypertension
II	Pulmonary venous hypertension (Heart ds)
III	**Pulmonary hypertension associated with chronic lung ds/hypoxemia**
IV	Pulmonary hypertension due to thromboembolic disease
V	Miscellaneous

Updated Classification

5th World Congress on Pulmonary Hypertension
Nice, France 2013

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
   - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
   - 1.4.1 Connective tissue disease
   - 1.4.2 HIV infection
   - 1.4.3 Portal hypertension
   - 1.4.4 Congenital heart diseases
   - 1.4.5 Schistosomiasis

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

1″. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

*5th WSPH Nice 2013. Main modifications to the previous Dana Point classification are in bold.
BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

Lung/Respiratory Diseases Associated with PH

Obstructive Lung Diseases

- COPD
- Asthma
- Cystic fibrosis
- Bronchiectasis
- Bronchiolitis obliterans

Respiratory Insufficiency of "central" origin

- Central alveolar hypoventilation
- Obesity-hypoventilation syndrome
- Obstructive sleep apnea

Restrictive Lung Diseases

- Neuromuscular disease
- Kyphoscoliosis
- Thoracoplasty
- Sequelae of pulmonary tuberculosis
- Sarcoidosis
- Pneumoconiosis
- Drug-related lung diseases
- Extrinsic allergic alveolitis
- Connective tissue diseases
- Idiopathic interstitial pulmonary fibrosis
- Interstitial pulmonary fibrosis of known origin

Functional classification(WHO)

Class	WHO functional classification
I	Patients with pulmonary hypertension but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain, or heart syncope.
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in undue fatigue or dyspnea, chest pain, or heart syncope.
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue fatigue or dyspnea, chest pain, or heart syncope.
IV	Patients with pulmonary hypertension resulting in inability to carry on any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by physical activity.

-Rich, S. Primary pulmonary hypertension: executive summary. Evian, France. WHO, 1998.

Prevalence of PH in COPD

- 175 patients with mean FEV_1/FVC 40%,
  prevalence of PH (defined as Ppa>20 mm Hg) of 35%

Weitzenblum E et al. Thorax 1981; 36: 752

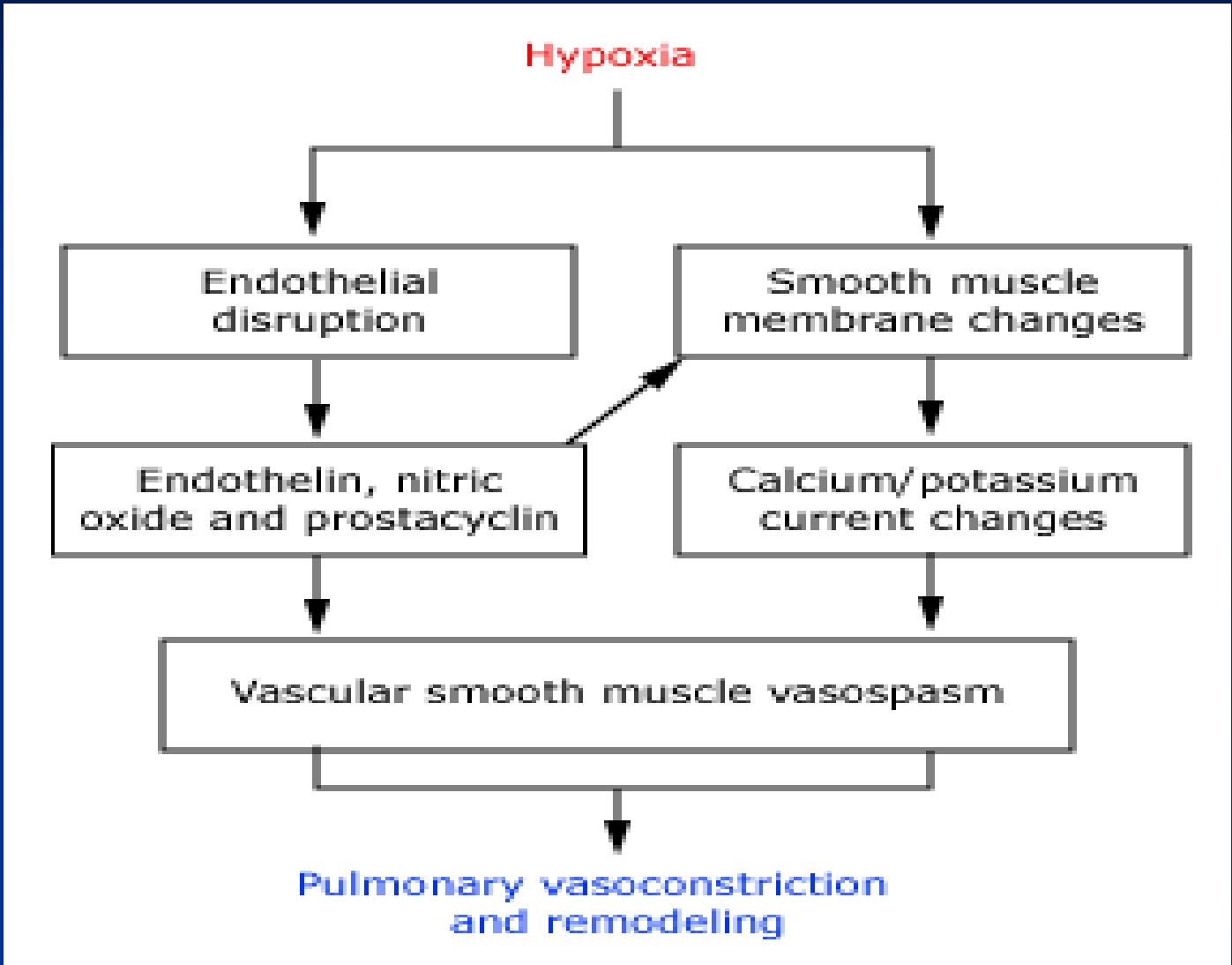
- 120 patients with severe emphysema in NETT

Mean PAP	%
Mild (≤ 20 mm Hg)	9.2
Moderate (21-35 mm Hg)	85.8
Severe (>35 mm Hg)	5.0

Scharf SM et al. Am J Respir Crit Care Med 2002; 166: 314

- Unclear
  - Definition is differ
  - Differ condition under which PH was reported(rest, exercise, exacerbation)
  - Right heart catheterization can not performed on large scale

Pathogenesis



Adapted from Fishman, AP, in: Pulmonary Disease, Fishman, AP (Ed), McGraw Hill, New York, 1989

Treatment of COPD-Associated PH

Technique	Description
Optimize COPD management	Smoking cessation, bronchodilator therapy, pulmonary rehabilitation
Workup for comorbidities contributing to PH (*eg,* PE, CAD, CCF, valvular disease)	
Oxygen therapy	LTOT, Nocturnal oxygen therapy
Non-specific vasodilators	Calcium channel antagonists, angiotensin-converting enzyme inhibitors, urapidil
PH-specific therapy	Inhaled nitric oxide, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, prostacyclin analogs
Surgical options	LVRS, LT

Treatment: LTOT

- Aims of LTOT is the improvement of PH induced by chronic alveolar hypoxia

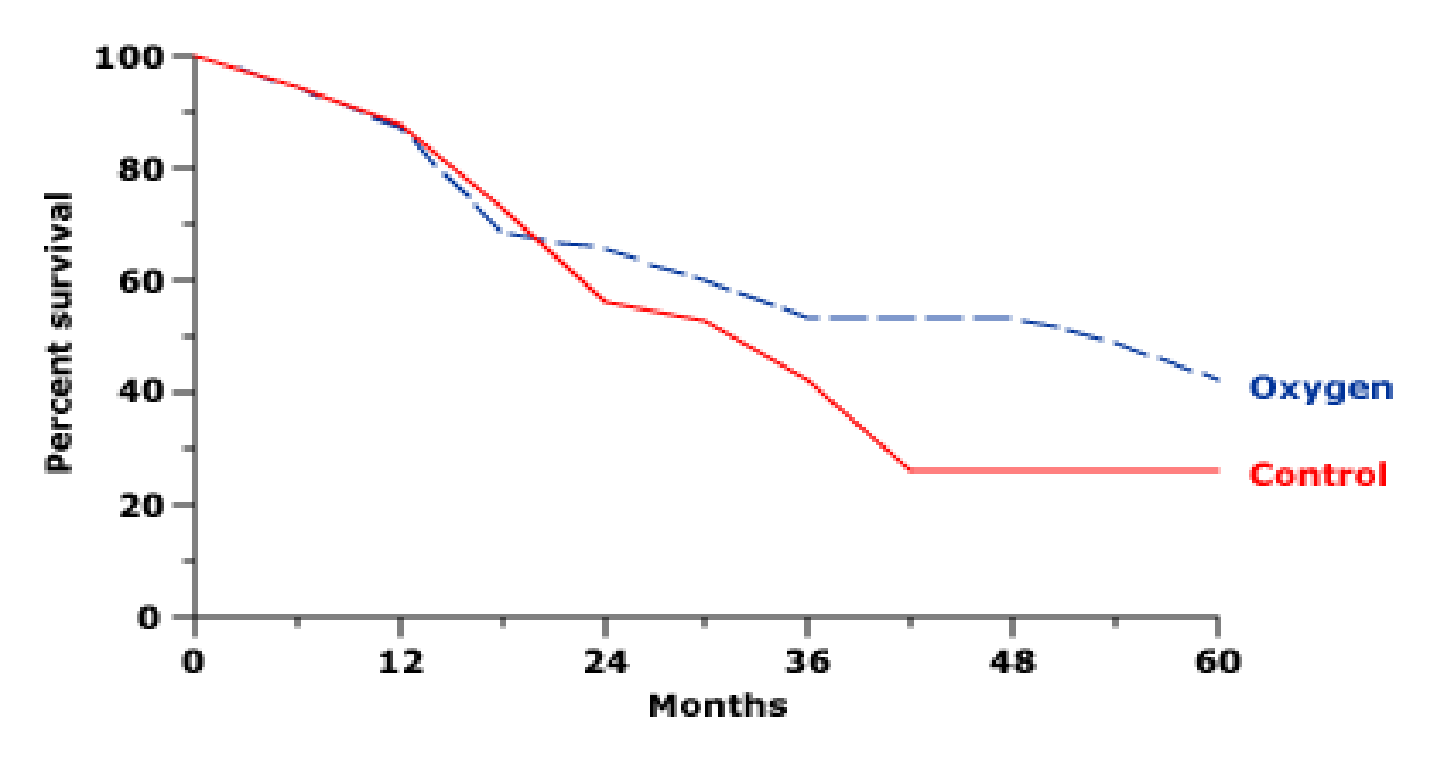
- **Medical Research Council (MRC) trial**
  - LTOT group: significant decreased in PAP
  - Control group : PAP was increased significantly (2.8 mm Hg/yr)
  - Survival benefit after 500 days of oxygen use

Lancet 1981; 1: 681–686

- **Nocturnal Oxygen Treatment Trial (NOTT) study**
  - Continuous (≥18 h/day) LTOT decreased slightly but significantly resting and exercising mean Ppa and PVR
  - Nocturnal oxygen therapy (10-12 h/day) did not

Timms RM et al. Ann Intern Med 1985; 102: 29

Survival benefit of LTOT in COPD

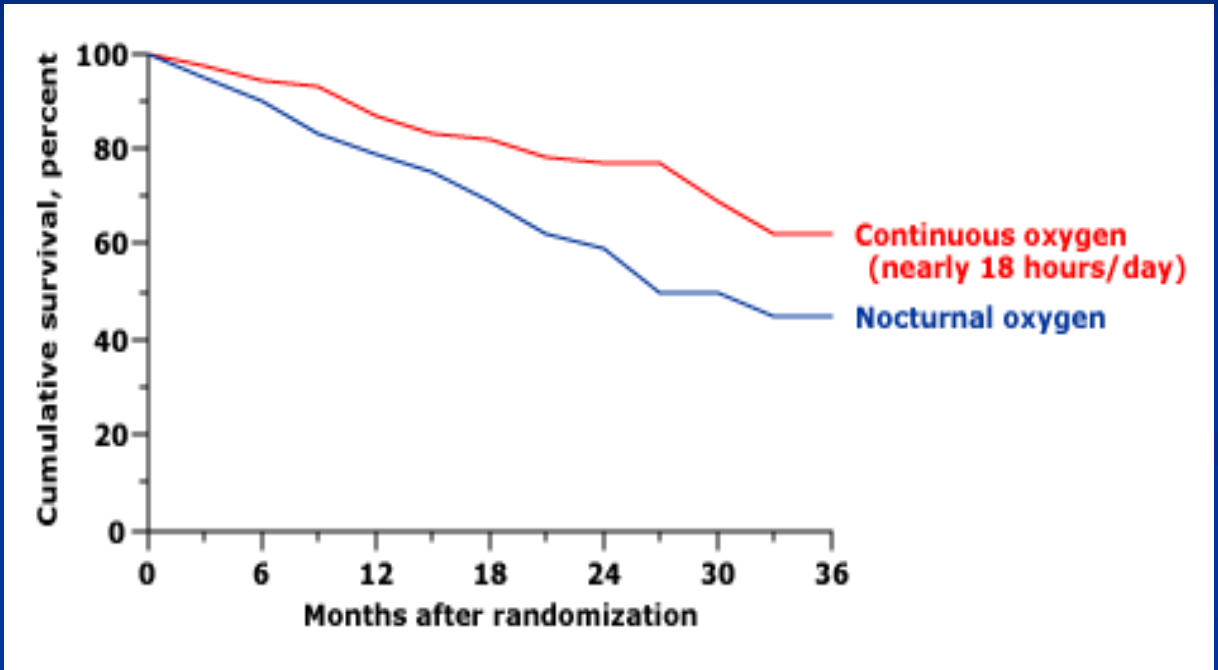


- **O2 Tx > 15 h/day (blue dashed line)**
- **no oxygen (red line)**

Continuous oxygen therapy led to a significant survival benefit.

- Report of the Medical Research Council Working Party, Lancet 1981; 1:681.

Survival benefit of continuous LTOT in COPD



- **nearly continuous oxygen therapy (red line)**
- **nocturnal oxygen alone (blue line)**

- **Continuous oxygen therapy was associated with a significant survival benefit (p = 0.01).**

-Nocturnal Oxygen Trial Therapy Group, Ann Intern Med 1980; 93:391.

Treatment: Nocturnal oxygen therapy

- In most COPD patients, hypoxemia does, in fact, worsen during sleep and especially during REM sleep

- FLETCHER et al. group
  - Mean Ppa increased by 3.9 mm Hg in the control group
  - Mean Ppa decreased by 3.7 mm Hg with nocturnal oxygen ($p<0.02$)
  - Nocturnal oxygen therapy had favorable effects on pulmonary hemodynamic

Fletcher EC et al. Am Rev Respir Dis 1992; 145: 1070

- European multicenter study
  - Study duration : 2 years
  - Nocturnal oxygen therapy did not modify the evolution of pulmonary hemodynamics

Chaouat A et al. Eur Respir J 1999; 14: 1002

Treatment: Vasodilator

Typical costs of pulmonary arterial vasodilators

	ROUTE	DOSE	COST ($)
• Endothelin receptor antagonist			
Ambrisentan	Oral	5–10 mg qD	4728
Bosentan	Oral	125 mg BID	4658
• Phosphodiesterase-5 inhibitors			
Sildenafil	Oral	20 mg TID	1063
• Prostacyclin			
Epoprostenol	IV	20 ng/kg/min	2763
Treprostinil	IV or SQ	40 ng/kg/min	8135
Iloprost	Inhaled	5 mcg/inhalation, 6 inhales/day	7679

Treatment: Calcium channel blockers

- Decrease in PAP
  - very few long-term study
  - deleterious effects on gas exchanges
  - associated systemic hypotension
  - ventilation/perfusion mismatch

- Should not be used to treat PH in COPD

Treatment: Prostacyclin (Iloprost)

- **Archer et al.** *Chest 1996; 109:750*
  - Prostacyclin infusion for 48 hours in mechanically ventilated COPD with PH
  - No significant benefit
    : PVR and SVR fell initially
    but response was unsustained despite optimization of prostacyclin dosage
  - PaO_2 dropped in patients receiving prostacyclin
  - Not beneficial in treating PH in COPD

- **Saadjian et al.** *J Cardiovasc Pharmacol. 1998;31:364*
  - Cicletanine (50 mg daily) for 12 months to COPD patients with PH
  - Reduction of mean PAP and PVR after three and 12 months of treatment
  - No significant reduction of PaO_2

Further studies are needed to evaluate the role of this agent in PH due to COPD

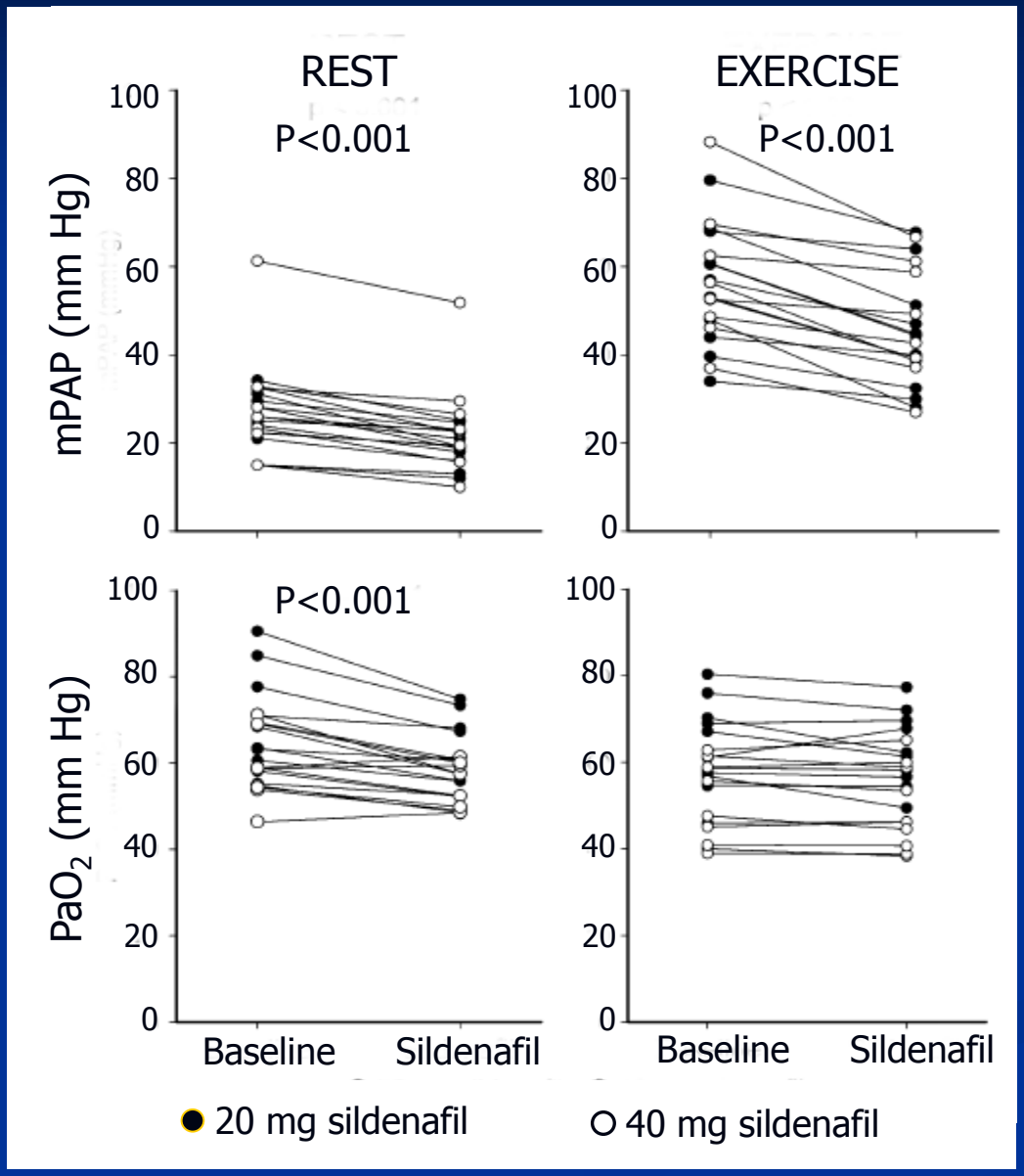
Treatment: PDE-5 inhibitors

- Blocks the degradation of cGMP and enhances the vasodilatory action of cGMP

	All Patients	20 mg of Sildenafil	40 mg of Sildenafil
N	20	11	9
Sex, M/F	17/3	9/2	8/1
Age, yr	64 ± 7	66 ± 7	62 ± 6
FVC, % pred	65 ± 20	68 ± 23	62 ± 17
FEV_1, % pred	35 ± 11	35 ± 12	34 ± 11
FEV_1/FVC	0.39 ± 0.11	0.38 ± 0.11	0.42 ± 0.12
PaO_2, mm Hg	64 ± 11	69 ± 11	58 ± 8
$PaCO_2$, mm Hg	42 ± 6	39 ± 5	46 ± 6
$P(A\text{-}a)O_2$, mm Hg	32 ± 9	31 ± 9	35 ± 10
mPAP, mm Hg	27 ± 10	25 ± 6	30 ± 13

Blanco I et al AJRCCM 2010; 181: 270

Treatment: PDE-5 inhibitors



Blanco I et al AJRCCM 2010; 181: 270

Treatment: PDE-5 inhibitors

- Sildenafil improves PAP, PVR

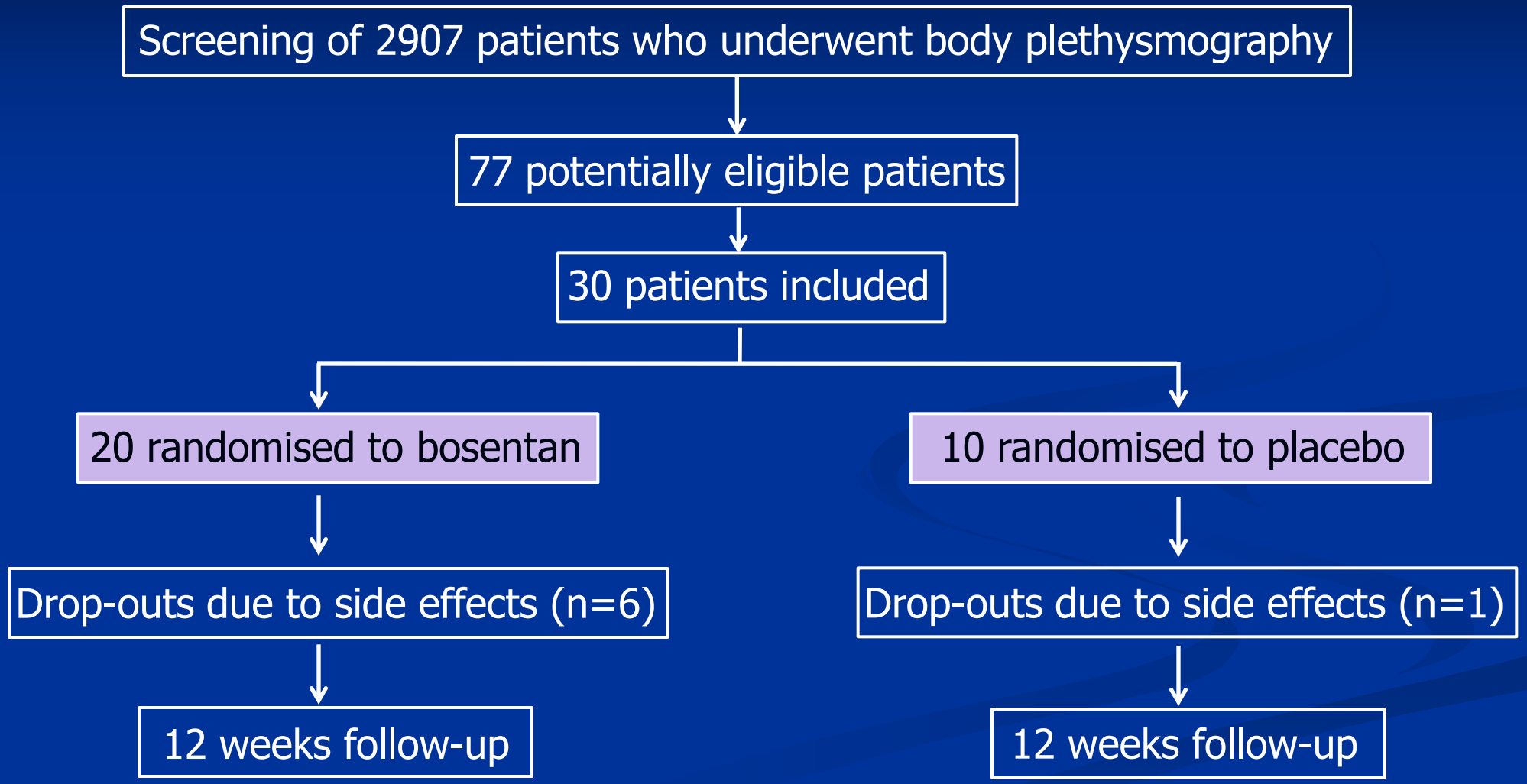
Blanco I et al AJRCCM 2010; 181: 270

- Sildenafil improved six-minute walk distance over long term follow up (range 12-51 months)

Madden BP et al. Vascul Pharmacol 2007; 47: 184

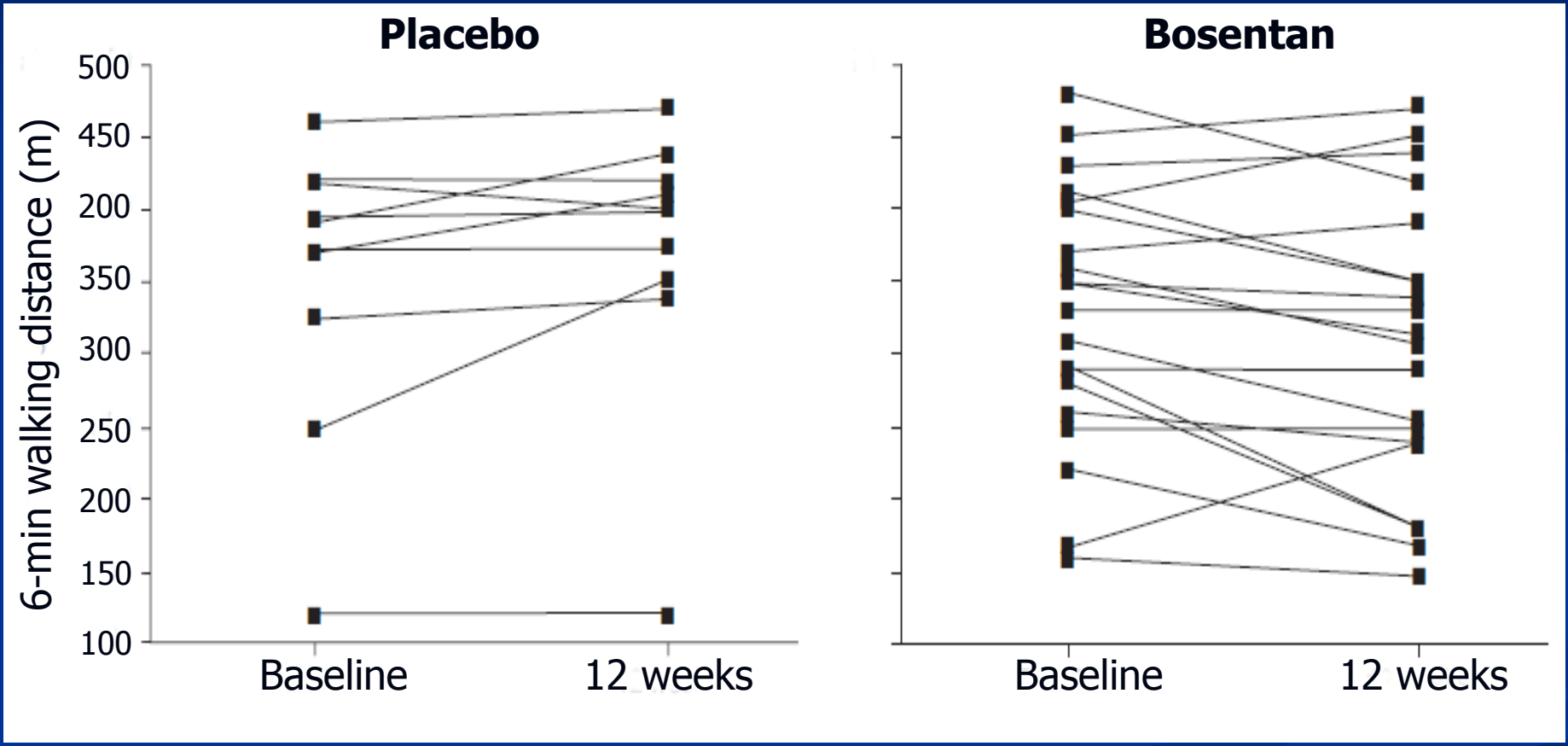
- Limited by the small number
- Confirmation of these results in larger studies in COPD-related PH is pending
- The use of sildenafil in COPD should be done cautiously and under close monitoring of blood gases

Treatment: Endothelin receptor antagonist



Stolz D et al . ERJ 2008; 32: 619

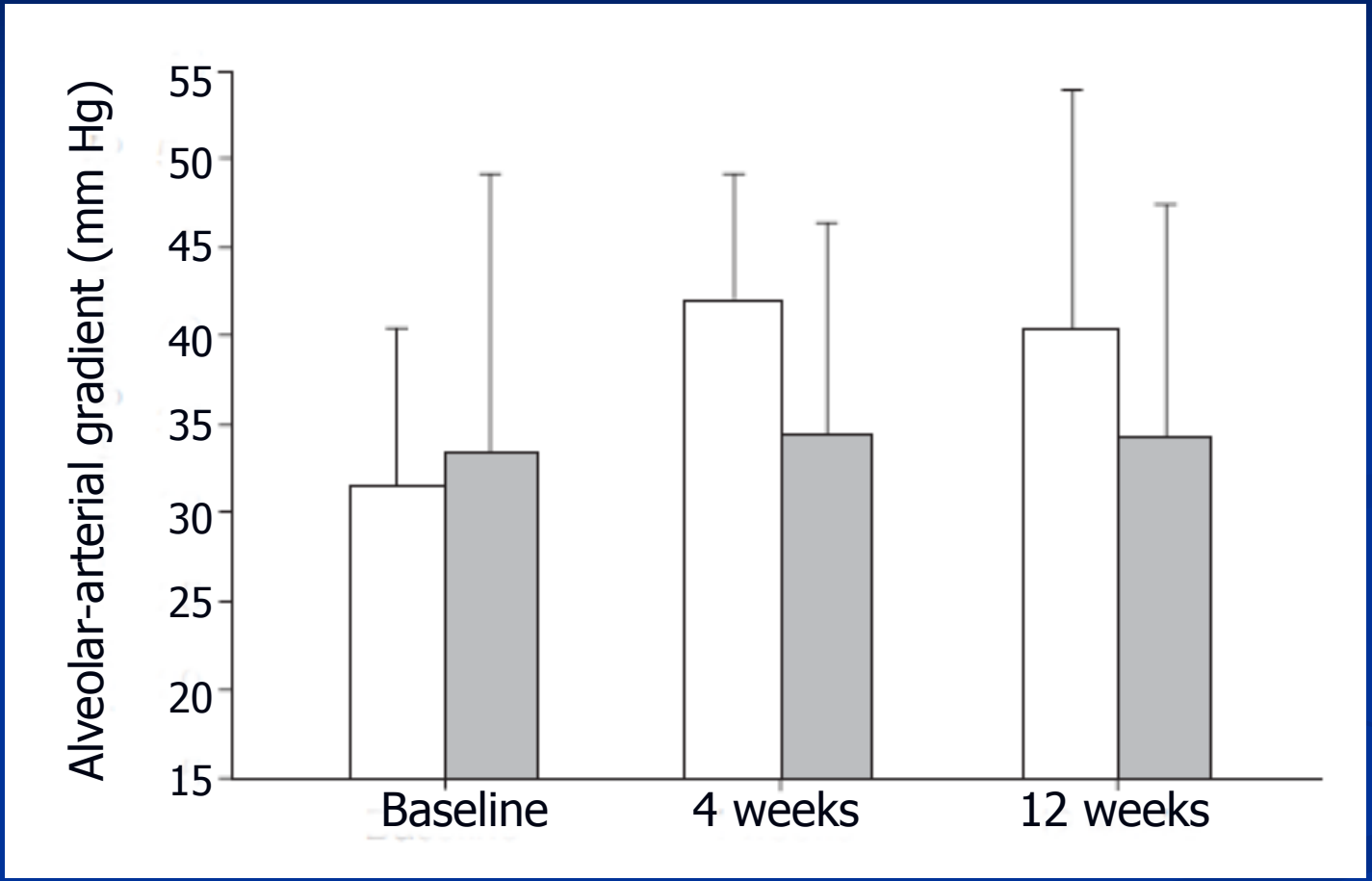
Treatment: Endothelin receptor antagonist



Compared with placebo, patients treated with bosentan during 12 weeks showed **no significant improvement** in the 6-min walking distance

Stolz D et al . ERJ 2008; 32: 619

Treatment: Endothelin receptor antagonist



Arterial oxygen pressure dropped, alveolar-arterial gradient increased in patients assigned bosentan

Stolz D et al . ERJ 2008; 32: 619

Treatment: Endothelin receptor antagonist

Eur Respir J 2008; 32: 619–628
DOI: 10.1183/09031936.00011308

A randomised, controlled trial of bosentan in severe COPD

D. Stolz*,#, H. Rasch¶, A. Linka+, M. Di Valentino§, A. Meyer*, M. Brutsche* and M. Tamm*

Oral administration of the endothelin receptor antagonist bosentan not only failed to improve exercise capacity but also deteriorated hypoxemia and functional status in severe COPD

Treatment: Endothelin receptor antagonist

Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease

Giuseppe Valerio, Pierluigi Bracciale and Anna Grazia D'Agostino

Ther Adv Respir Dis
(2009) 3(1) 15–21
DOI: 10.1177/1753465808103499

- 18 months F/U
- Bosentan (n=16) 125 mg bid
- Control group (n=16)

- Pulmonary function test, hemodynamics, effort performance
- dyspnea
- quality of life

Valerio G et al . Ther Adv Respir Dis 2009;3: 15

Treatment: Endothelin receptor antagonist

Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease

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Ther Adv Respir Dis
(2009) 3(1) 15–21
DOI: 10.1177/1753465808103499

Bosentan treatment group

- pulmonary arterial pressure from 37±5 to 31±6 mm Hg
- pulmonary vascular resistance from 442±192 to 392±180 dynes cm^2
- 6MWD from 256±118 to 321±122 m
- BODE index from 6.6±2.8 to 5.5±3 U

Valerio G et al . Ther Adv Respir Dis 2009;3: 15

Treatment: Endothelin receptor antagonist

- Small subject population of 16 patients

Valerio G et al . Ther Adv Respir Dis 2009;3: 15

- Conflicting results need to be reconciled in a large randomized clinical trial that is currently underway

- However, given the lack of convincing evidence, the use of bosentan in COPD-related PH is **not recommended**

Treatment: Nitric oxide

	Oxygen alone (n=17)		Oxygen + NO (n=15)		
	Baseline	3 months	Baseline	3 months	P value
Mean PAP	24.6	25.2	27.6	20.6	**<0.001**
PVR	259.5	264.0	276.9	173.1	**0.001**
PVRI	519.7	552.3	569.7	351.2	**<0.001**
HR	78.1	78.9	78.9	80.0	0.889
CO	5.5	5.3	5.6	6.1	**0.025**

- No change in arterial blood gases
- Concerns about long-term safety and cumbersome device

Vonbank K et al Thorax 2003; 58: 289

Treatment: LVRS (lung volume reduction surgery)

- LVRS may have adverse effects on pulmonary hemodynamics
  (increased PAP after LVRS)
  : due to the increased PVR associated with the decrease in cross sectional area by LVRS

Weg IL et al. Am J Respir Crit Care Med 1999; 159: 552

- National Emphysema Treatment Trial
  : **No significant differences** in terms of Ppa and PVR, 6 months after medical treatment or LVRS

Criner GJ et al. Am J Respir Crit Care Med 2007; 176: 253

- Generally, COPD with severe PH (Ppa ≥35 mm Hg) are not candidates for LVRS

Treatment: Lung Transplantation

- Single lung transplantation with 19 COPD

- Mean PAP and PVR were significantly decreased after transplantation
  (28±2 to 18±1 mmHg and 288 to 161±11 dyne·sec·cm^{-5}/m^2)
  → These results were maintained after 2 yrs of follow-up

Bjortuft O et al. Eur Respir J. 1996; 9: 2007

Lung transplantation may be considered in all patients with severe PH aged < 65 yrs and without comorbidities

Conclusion

- WHO classification of PH
  - 5 groups based upon etiology
  - COPD is a frequent cause of group 3 PH
- Two mechanisms of COPD-related PH
  - Hypoxia induced vasoconstriction & obliteration of the vascular bed
- Tx of PH in COPD
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