

# Pulmonary hypertension and COPD

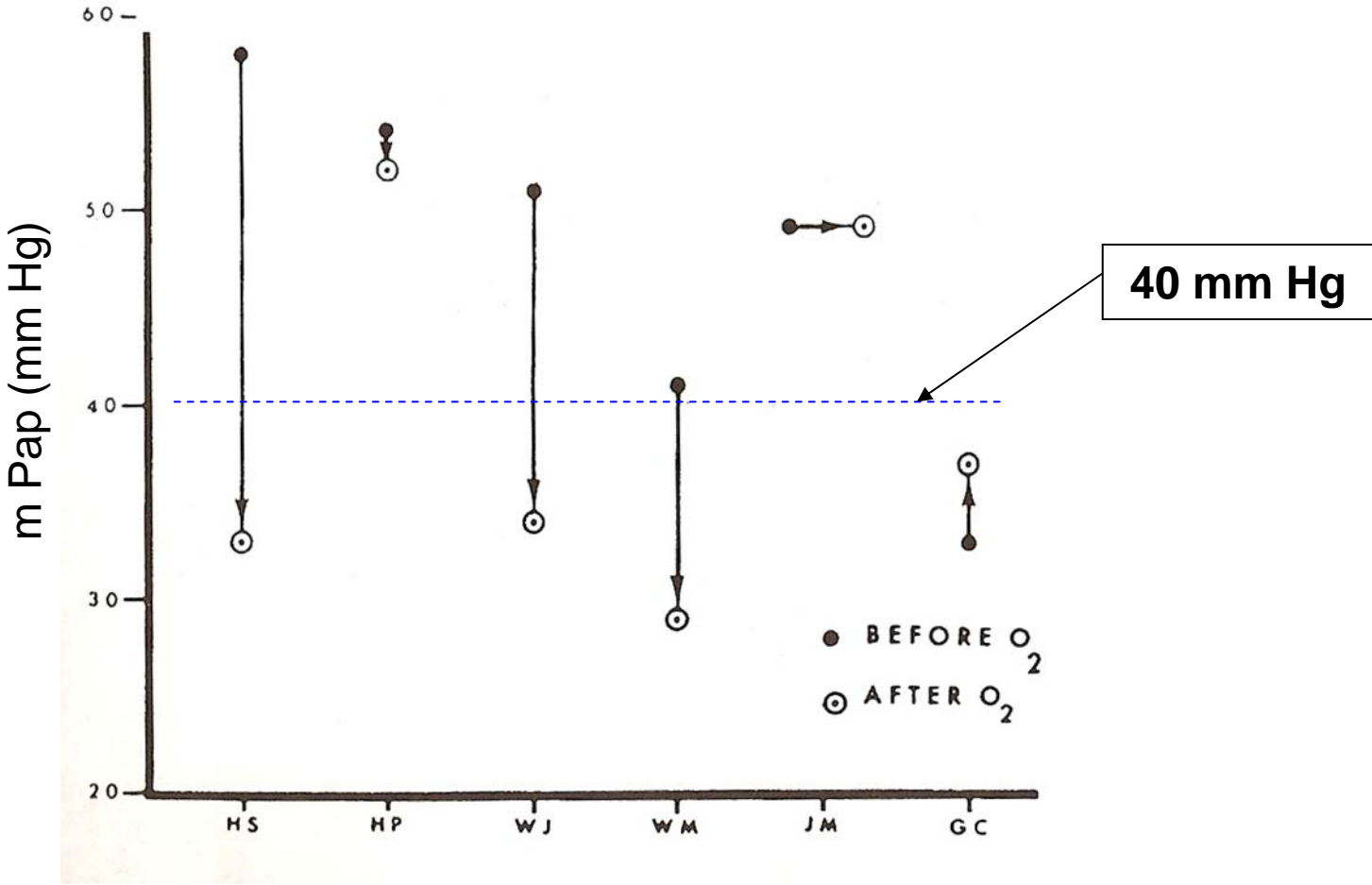
## Investigations and treatment

Rencontres Genevoises de Pneumologie  
17 février 2010

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| Definition                              | Characteristics  | Clinical group(s) <sup>b</sup>  |
|---|--|---|
| Pulmonary hypertension (PH)             | Mean PAP $\geq 25$ mmHg  | All   |
| Pre-capillary PH                        | Mean PAP $\geq 25$ mmHg<br>PWP $\leq 15$ mmHg<br>CO normal or reduced <sup>c</sup> | 1. Pulmonary arterial hypertension<br>3. PH due to lung diseases<br>4. Chronic thromboembolic PH<br>5. PH with unclear and/or multifactorial mechanisms |
| Post-capillary PH                       | Mean PAP $\geq 25$ mmHg<br>PWP $> 15$ mmHg<br>CO normal or reduced <sup>c</sup>    | 2. PH due to left heart disease   |
| Passive<br>Reactive (out of proportion) | TPG $\leq 12$ mmHg<br>TPG $> 12$ mmHg  |   |

# Pulmonary hypertension and COPD before LTOT

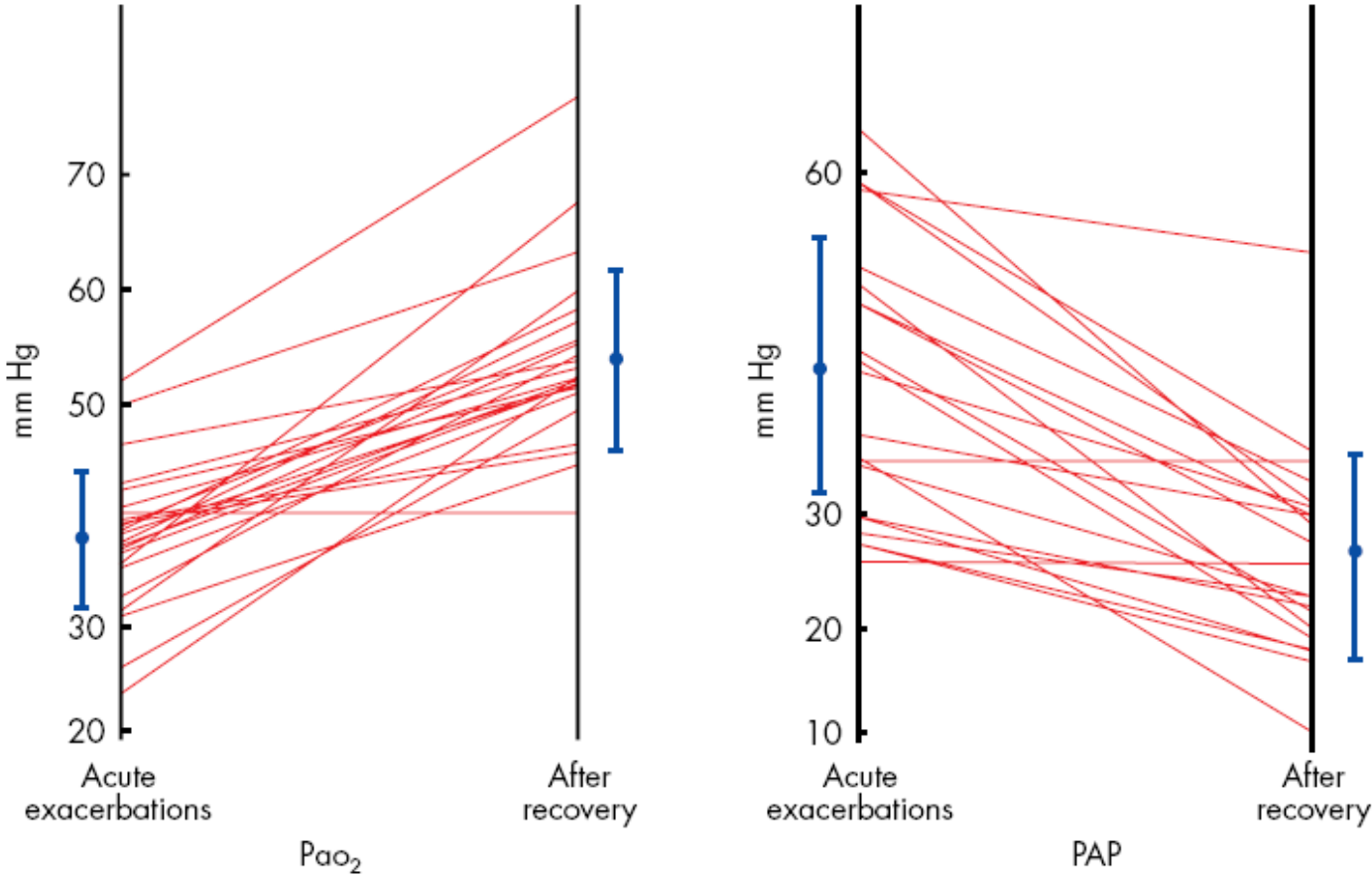


# Pulmonary haemodynamics during a period of disease stability

|   | COPD | COPD | iPAH | CTEPH |
|---|------|------|------|-------|
| <b>Reference</b>  | [19] | [6]  | [25] | [80]  |
| <b>Subjects n</b>                                       | 62   | 16   | 259  | 500   |
| <b>Age yrs</b>  | 55   | 66   | 50   |       |
| <b>FEV<sub>1</sub> mL</b>                               | 1170 |      |      |       |
| <b>FEV<sub>1</sub> % pred</b>                           |      | 27   | >70  |       |
| <b><i>P</i><sub>a,O<sub>2</sub></sub> mmHg</b>          | 60   | 56   |      |       |
| <b><i>P</i><sub>a,CO<sub>2</sub></sub> mmHg</b>         | 45   | 47   |      |       |
| <b><math>\bar{P}</math><sub>pa</sub> mmHg</b>           | 26   | 25   | 56   | 46    |
| <b><i>P</i><sub>pw</sub> mmHg</b>                       | 8.0  | 7.0  | 8.0  |       |
| <b>Cardiac output L·min<sup>-1</sup>·m<sup>-2</sup></b> | 3.8  | 2.8  | 2.3  | ~2.2  |

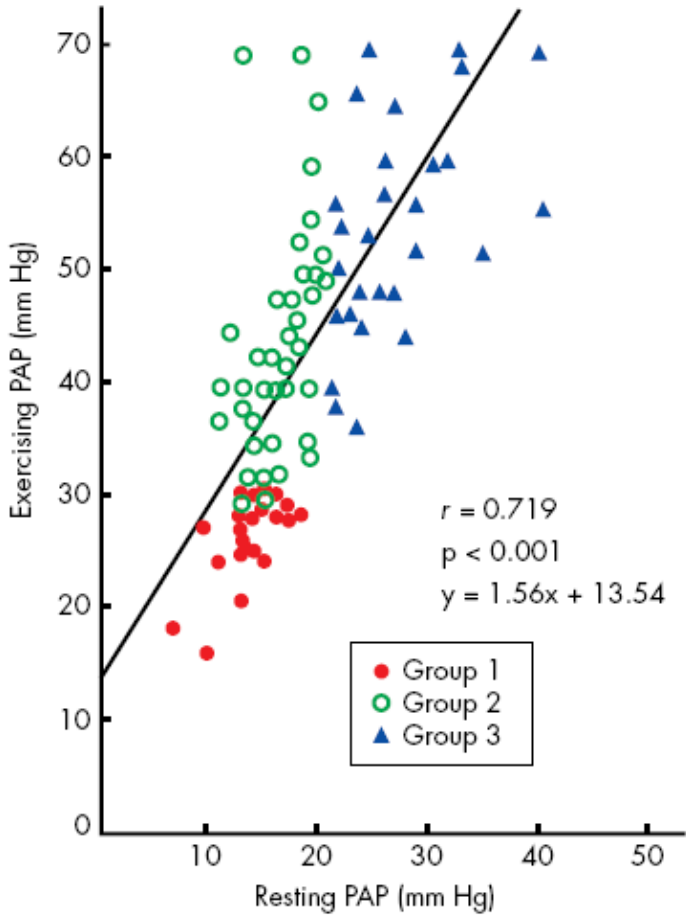
# Natural History of PH in COPD

## Rise of PAP during exacerbation

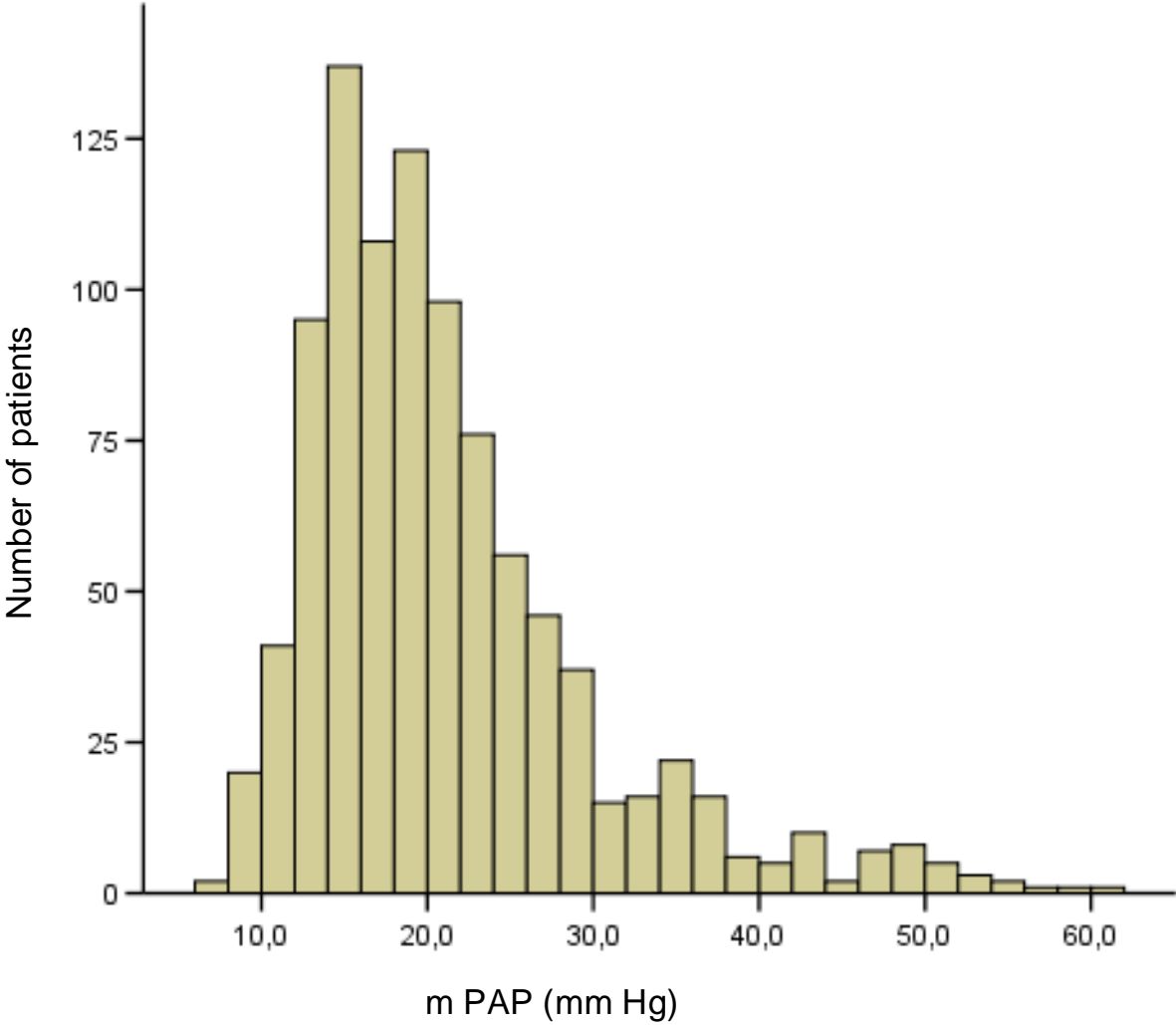


# Natural History of PH in COPD

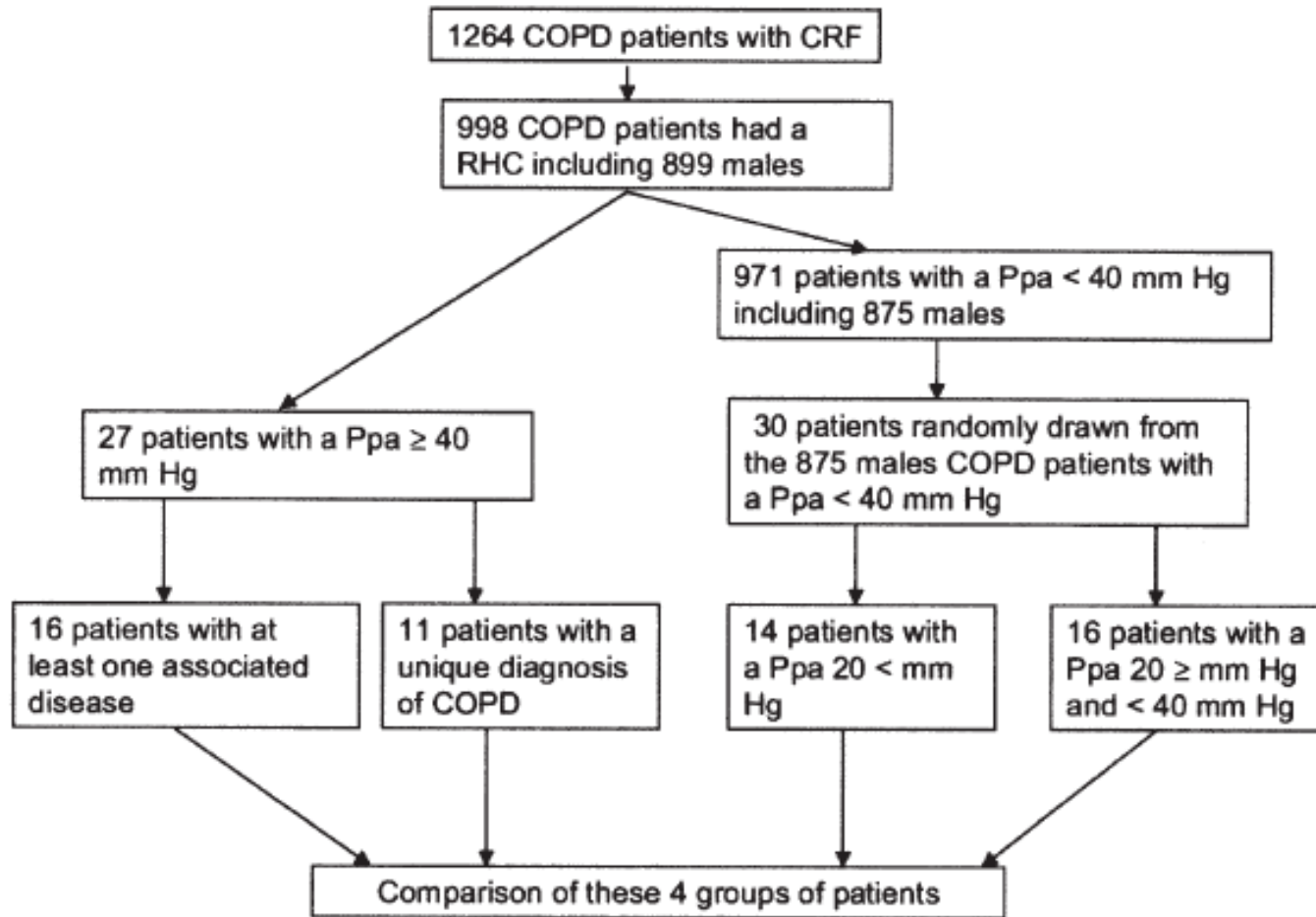
## “Exercising” pulmonary hypertension



# Severe pulmonary hypertension and COPD

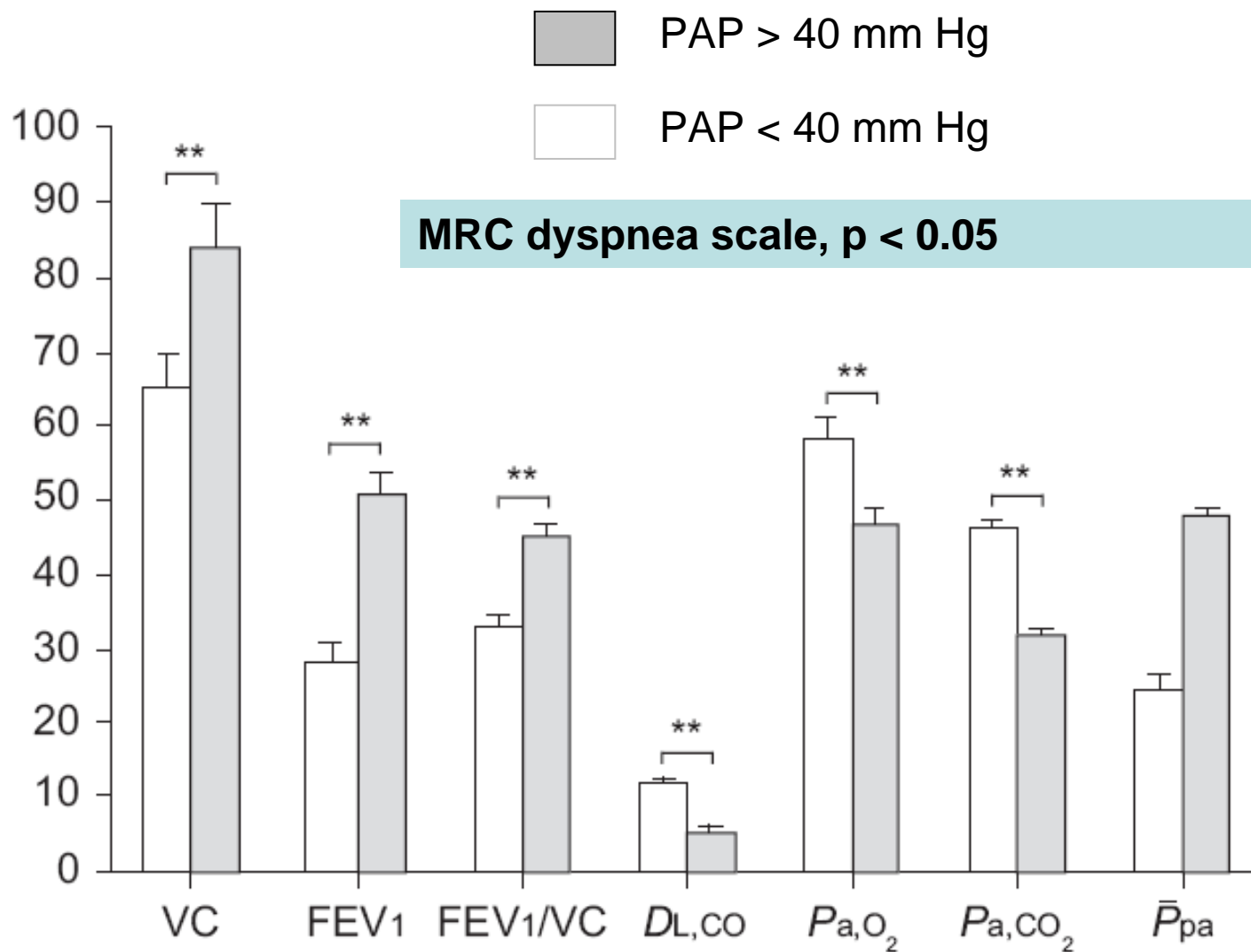


# Severe pulmonary hypertension and COPD





# Severe pulmonary hypertension and COPD

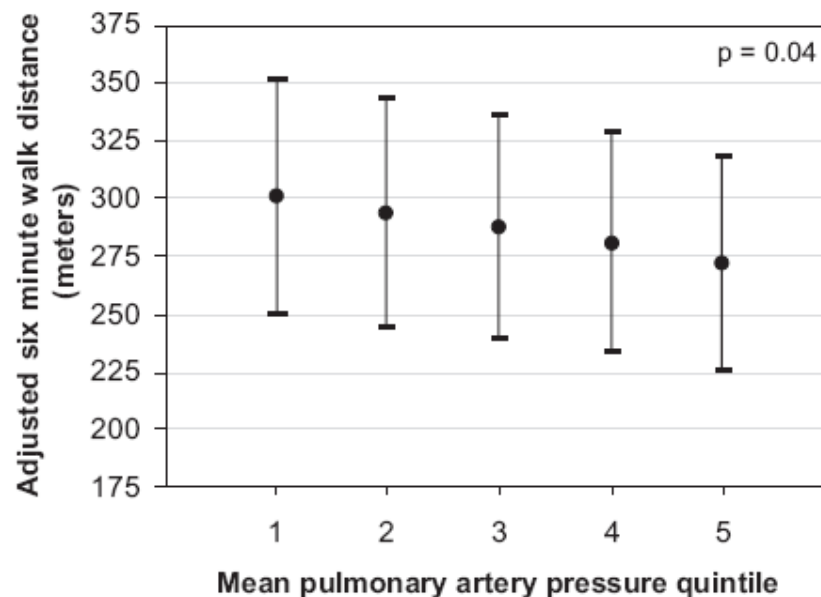
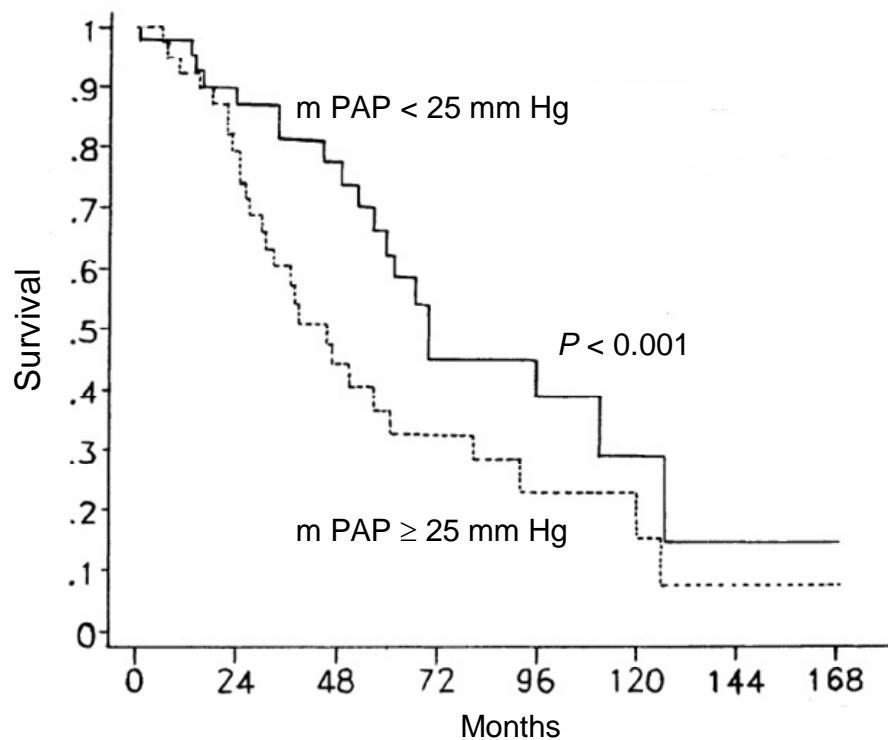


# Physiological consequences of PH in COPD

- Worsening of blood gas exchanges
- Right ventricular dysfunction
  - Usually RV systolic function is normal at rest in patients with COPD
- Peripheral edema
  - RV failure
  - CO<sub>2</sub> induces a decrease in renal blood flow

# Clinical consequences of PH in COPD

- Dyspnea on exertion
- Exercise limitation
- Survival



Sims M *et al. Chest* 2009; 136: 412

Oswald-Mammosser M *et al. Chest* 1995; 107: 1193

# Diagnosis strategy (1)

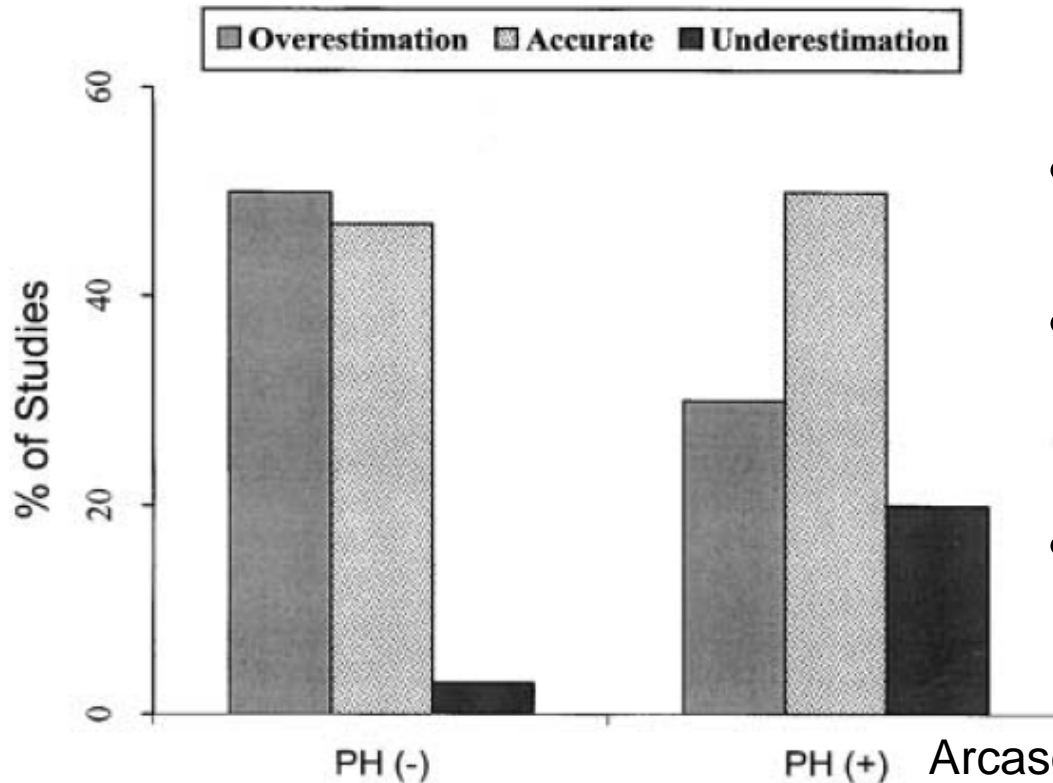
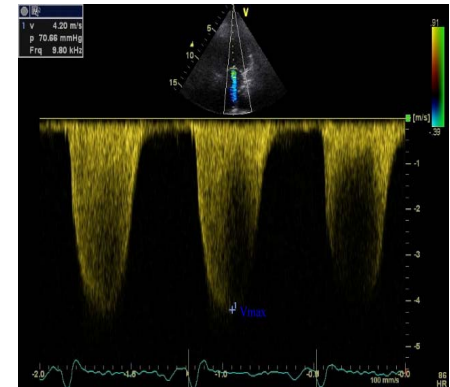
- Dyspnea on exertion
- Physical signs of PH
- Prediction of mean PAP from pulmonary function data
- 6-min walk distance
- B-type natriuretic peptide

Sims M *et al.* *Chest* 2009; 136: 412

Leuchte H *et al.* *AJRCCM* 2006; 173: 744

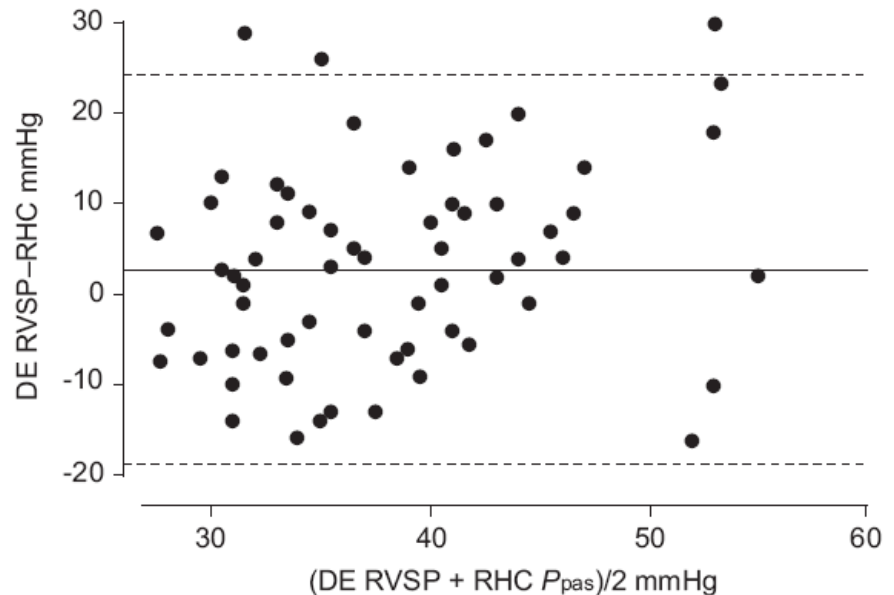
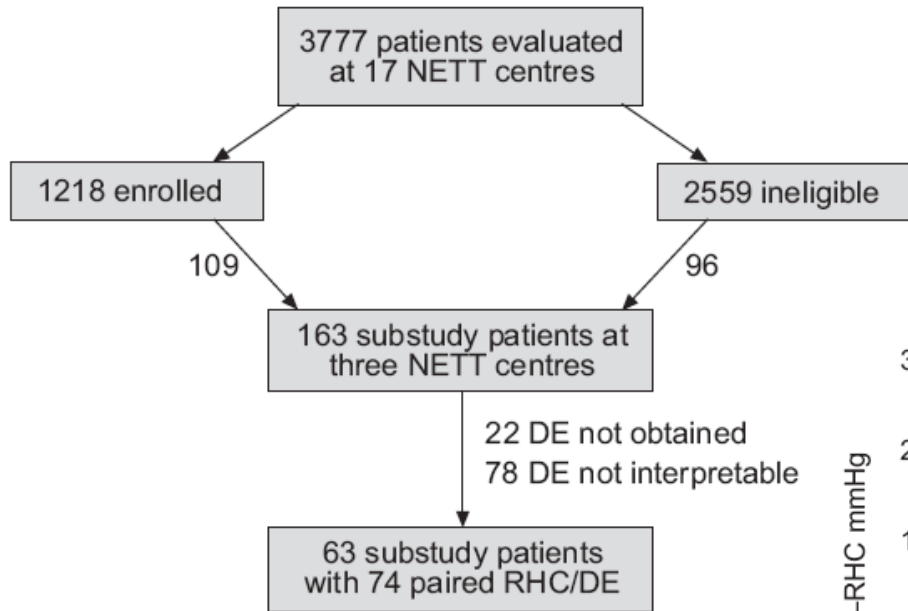
# Diagnosis strategy (2)

- Doppler echocardiography
  - Estimation of systolic Pap with continuous Doppler well correlated with catheterization measurement (0.60-0.85)



- 374 lung transplant candidates, 68 % COPD
- Prevalence of PH (systolic Pap > 45 mm Hg) was 25 %
- Inaccurate > 10 mm Hg difference

# Diagnosis strategy (3)



# Doppler echocardiography

- However
  - The goals are to exclude an associated left heart disease and to raise suspicion of PH
  - These objectives can be achieved with the combination of
    - Estimation of RV systolic pressure
    - Measurement of pulmonary blood flow velocity
    - Right-side chamber size
    - Indices of right ventricular dysfunction

**Chronic Lung Disease in stable state**  
Most commonly COPD  
History, Symptoms, Signs  
Chest radiograph  
Spirometry, ABG

Unexplained severity of CRF  
or signs of PH  
or signs of chronic heart failure

**Doppler echocardiography**

Technically adequate study

Technically inadequate study

**Evidence of CHF**

ACE inhibitor  
and other  
treatments of  
CHF if needed

**Severe increased systolic PAP depending of the airflow limitation**

No  
No PH or  
proportionate PH

Yes

Static lung volumes, DLCO  
HRCT, V/Q scan  
Sleep study  
Exercise testing

Treatments of an  
overlap of 2 lung  
diseases e.g. COPD  
and sleep apnea  
syndrome

**RHC**

Elevated PWP

Treatment of  
an associated  
DHF

Out of  
proportion  
PH

Send to a PAH  
referral centre



# Treatment: LTOT

- LTOT, MRC and NOT trials
  - LTOT improve survival in COPD patients with severe chronic hypoxemia
  - LTOT stabilises, or at least attenuates, and sometimes reverses, the progression of PH
- In one study mean PAP increases before the onset of LTOT and decreases after the initiation of LTOT

NOT trial group *Ann Intern Med* 1980; 93: 391

MRC working party *Lancet* 1981; 1: 681

Weitzenblum E *et al ARRD* 1985; 131: 493

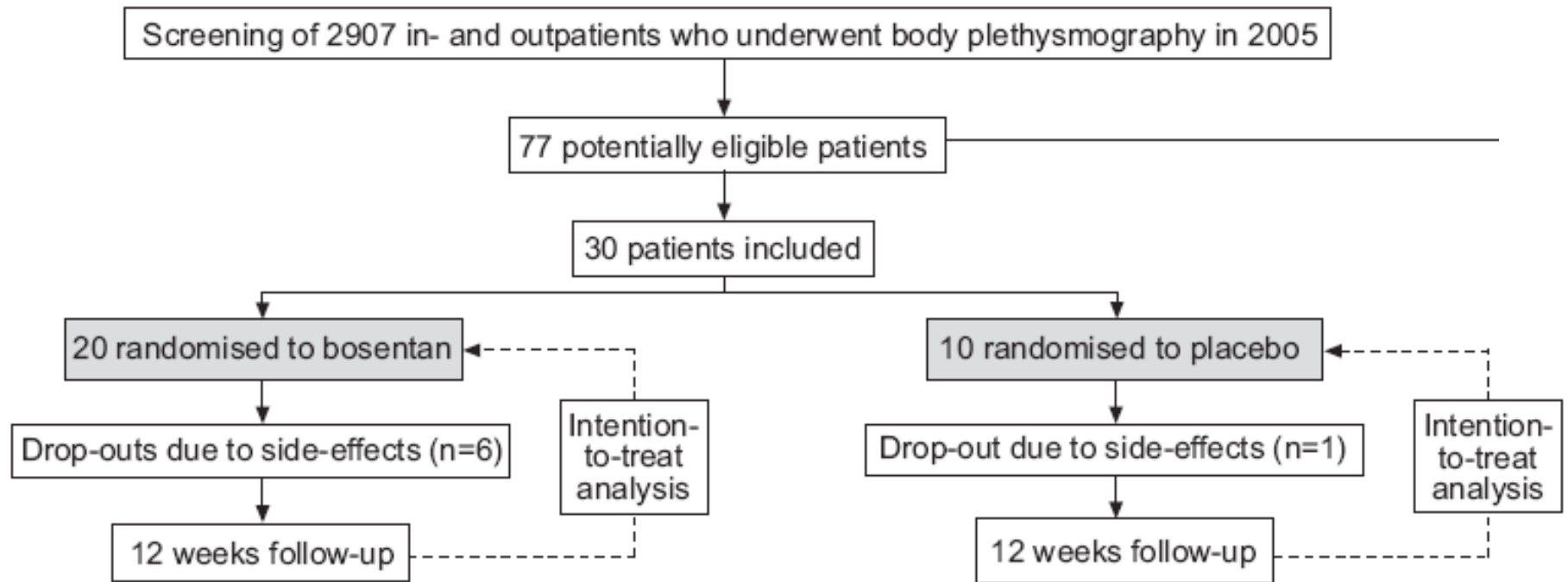
# Treatment: inhaled nitric oxide

|   | Oxygen alone (n= 17) |               | Oxygen + NO (n= 15) |               | p value |
|---|----------------------|---------------|---------------------|---------------|---------|
|   | Baseline             | 3 months      | Baseline            | 3 months      |         |
| PAPm (mm Hg)  | 24.6 (5.7)           | 25.2 (6.5)    | 27.6 (4.4)          | 20.6 (4.9)    | <0.001  |
| PVR ( $\text{dyne}\cdot\text{s}^{-1}\cdot\text{cm}^{-5}$ )                    | 259.5 (101.7)        | 264.0 (109.2) | 276.9 (96.6)        | 173.1 (87.9)  | 0.001   |
| PVRI ( $\text{dyne}\cdot\text{s}^{-1}\cdot\text{cm}^{-5}\cdot\text{m}^{-2}$ ) | 519.7 (209.5)        | 552.3 (238.1) | 569.7 (208.1)       | 351.3 (159.9) | <0.001  |
| HR (beats/min)  | 78.1 (14.6)          | 78.9 (11.9)   | 78.9 (14.6)         | 80.0 (15.0)   | 0.889   |
| CO (l/min)  | 5.5 (1.3)            | 5.3 (1.3)     | 5.6 (1.3)           | 6.1 (1.0)     | 0.025   |

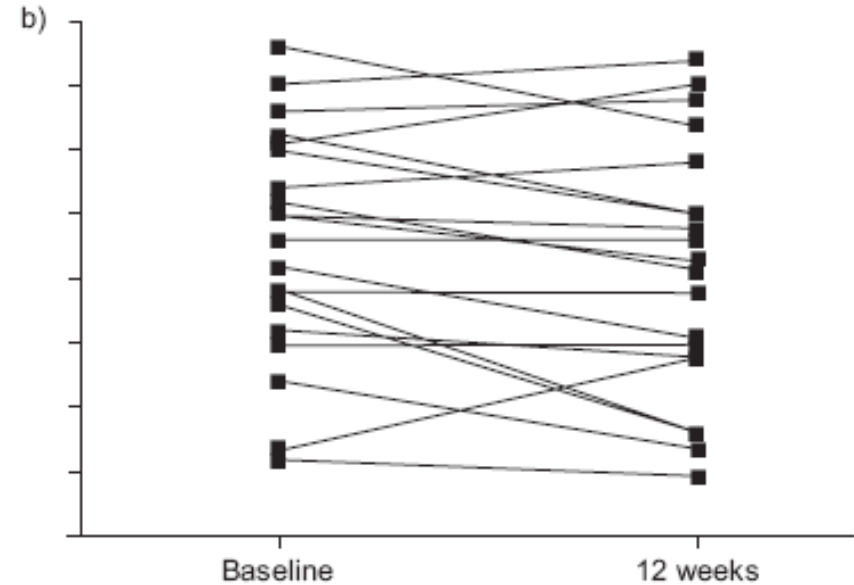
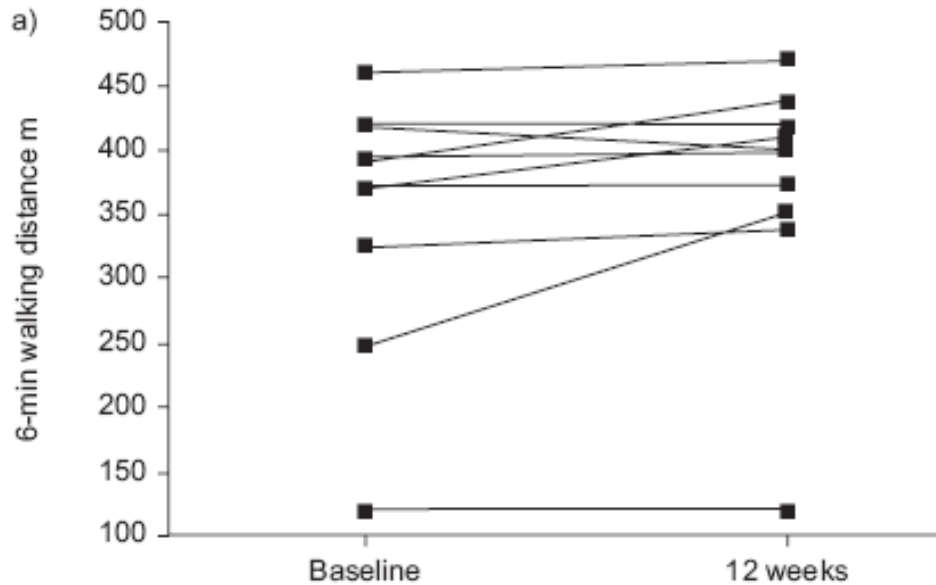
No change in arterial blood gases

Concerns about long-term safety and cumbersome device

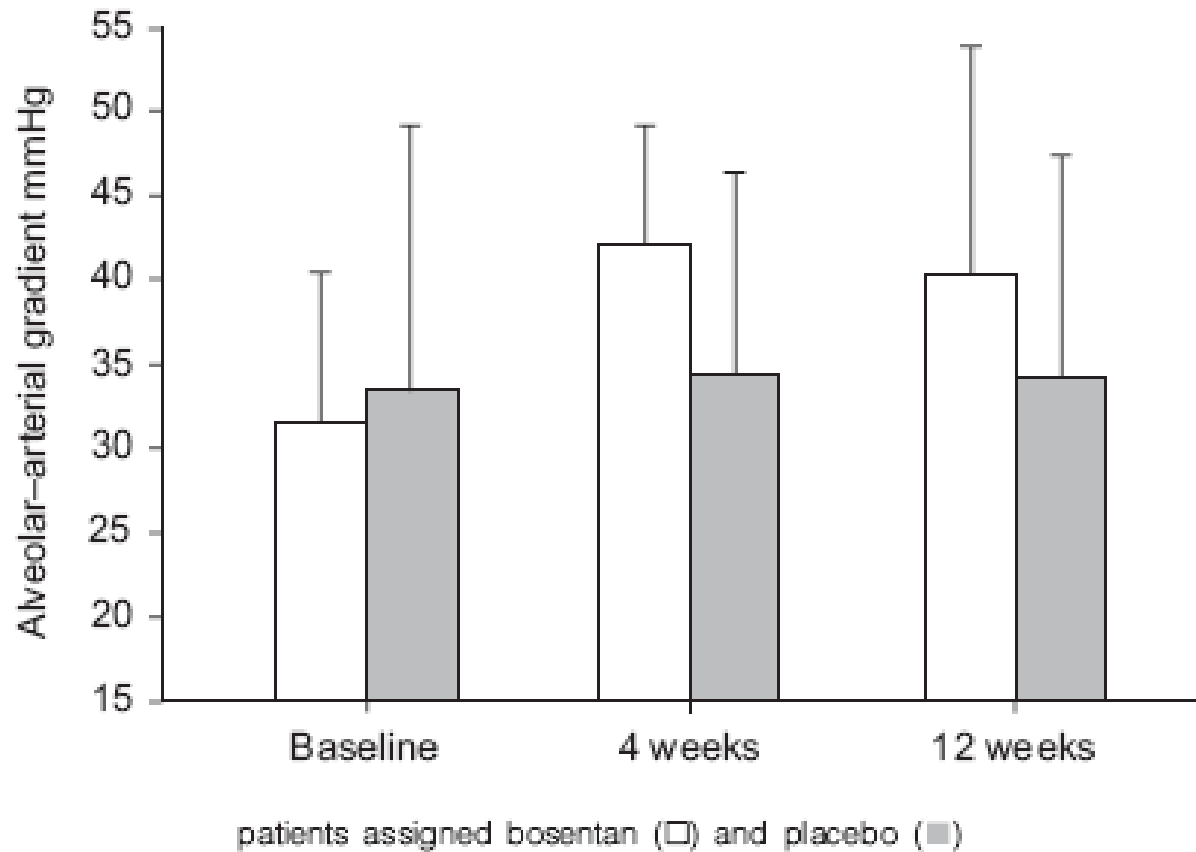
# Treatment: Endothelin Receptor Antagonist



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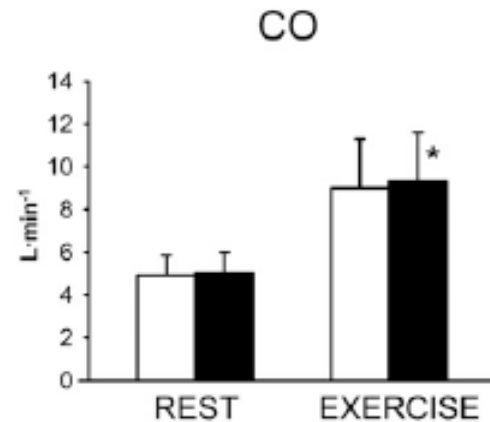
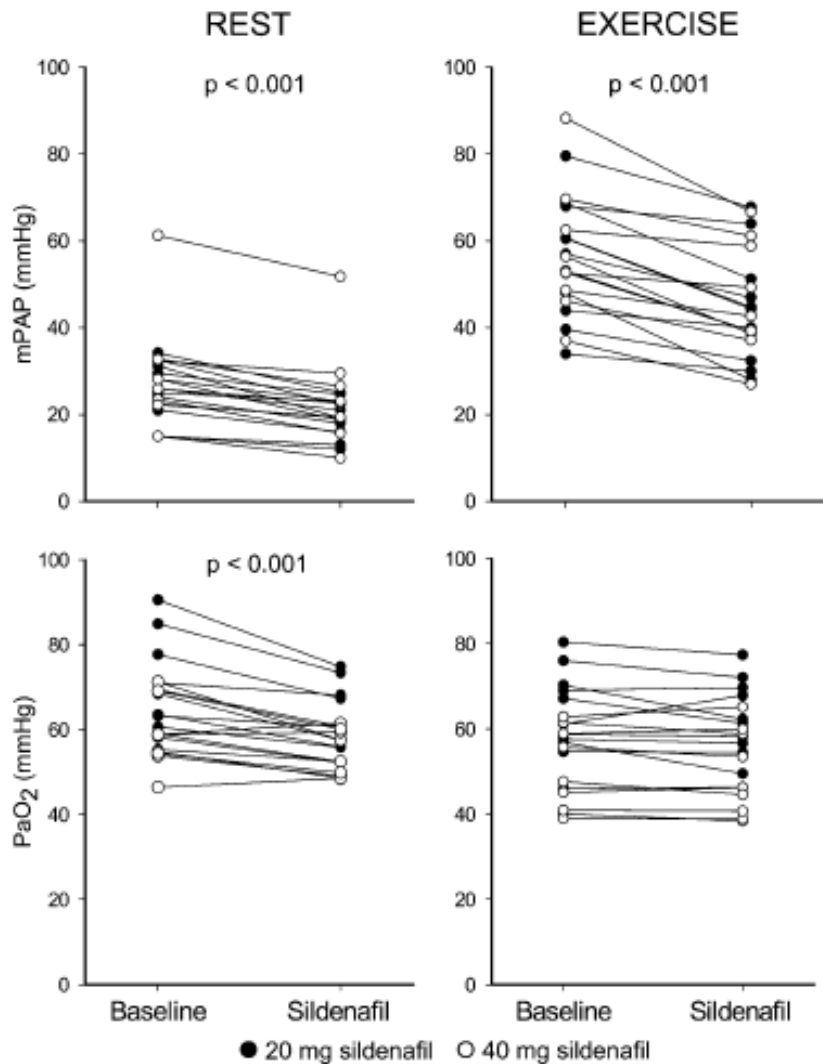
# Treatment: Endothelin Receptor Antagonist



# Treatment: PDE-5 inhibitors

|                                | All Patients | Patients Assigned<br>to 20 mg of<br>Sildenafil | Patients Assigned<br>to 40 mg of<br>Sildenafil |
|--------------------------------|--------------|--|--|
| N                              | 20           | 11   | 9  |
| Sex, men/women                 | 17/3         | 9/2  | 8/1  |
| Age, yr                        | 64 ± 7       | 66 ± 7   | 62 ± 6   |
| FVC, % predicted               | 65 ± 20      | 68 ± 23  | 62 ± 17  |
| FEV <sub>1</sub> , % predicted | 35 ± 11      | 35 ± 12  | 34 ± 11  |
| FEV <sub>1</sub> /FVC          | 0.39 ± 0.11  | 0.38 ± 0.11                                    | 0.42 ± 0.12                                    |
| PaO <sub>2</sub> , mm Hg       | 64 ± 11      | 69 ± 11  | 58 ± 8*  |
| PaCO <sub>2</sub> , mm Hg      | 42 ± 6       | 39 ± 5   | 46 ± 6*  |
| P(A-a)O <sub>2</sub> , mm Hg   | 32 ± 9       | 31 ± 9   | 35 ± 10  |
| mPAP, mm Hg                    | 27 ± 10      | 25 ± 6   | 30 ± 13  |

# Treatment: PDE-5 inhibitors



# Treatments

| Methods                                   | References | At least one randomised trial? |
|---|------------|--------------------------------|
| <b>LTOT</b>                               | [112–116]  | Yes                            |
| <b>Nocturnal oxygen therapy</b>           | [117, 118] | Yes                            |
| <b>Medical treatment dedicated to PAH</b> | [119, 120] | Yes                            |
| <b>Ca<sup>2+</sup> channel blockers</b>   | [121]      | No                             |
| <b>Urapidil</b>                           | [122]      | No                             |
| <b>Angiotensin inhibitors</b>             | [123, 124] | Yes                            |
| <b>Inhaled nitric oxide</b>               | [125]      | Yes                            |
| <b>Pulmonary rehabilitation</b>           | [126]      | No                             |
| <b>LVRS</b>                               | [127–130]  | Yes                            |
| <b>Lung transplantation</b>               | [131]      | No                             |



# Conclusions

- Diagnosis strategy
  - Determine the impact of the pulmonary vascular impairment in COPD patients on clinical end points
  - Search for an associated condition
- Treatment
  - Treat the underlying disease (s)
  - Correct severe hypoxemia
  - Pulmonary vasodilators are deleterious
  - Lung transplantation

Back