

Royal Brompton & Harefield NHS Foundation Tr...

*Eisenmenger Syndrome:
A Call for Action*

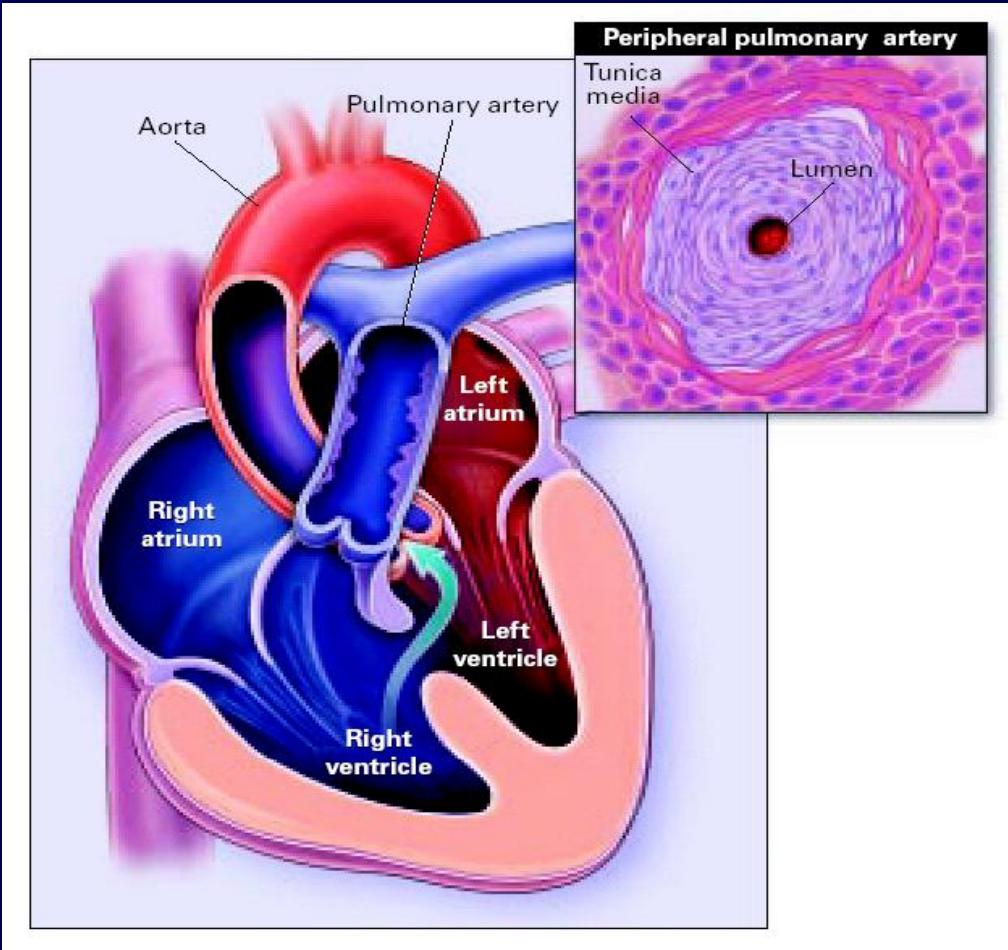


Adult Congenital Heart Centre & National Centre for Pulmonary Hypertension
Royal Brompton Hospital/National Heart & Lung Institute, Imperial College, London, UK

Pulmonary hypertension and congenital heart disease

- CHD is common (~ 1% of newborns)
- PAH is common amongst adults with CHD (~ 5-10%)
- Affects quality of life and outcome *Engelfriet et al Heart 2007*,
- *Eisenmenger patients extreme end of the spectrum (~ 2% of contemporary hospital cohorts)* *Duffels et al Int J Card 2007*
- Other CHD candidates for PAH targeted therapies
 - Class II patients
 - Patients with increased PVR aiming towards symptomatic improvement and potential repair ? *Dimopoulos et al Int J Card 2008*
 - Patients without a subpulmonary ventricle (Fontan)

Eisenmenger syndrome



Severe Pulmonary Arterial Hypertension associated with Congenital Heart Disease and a large intra- or extra- cardiac shunt.

The shunt with time leads to right to left shunting (shunt reversal), chronic cyanosis and multi-organ involvement.

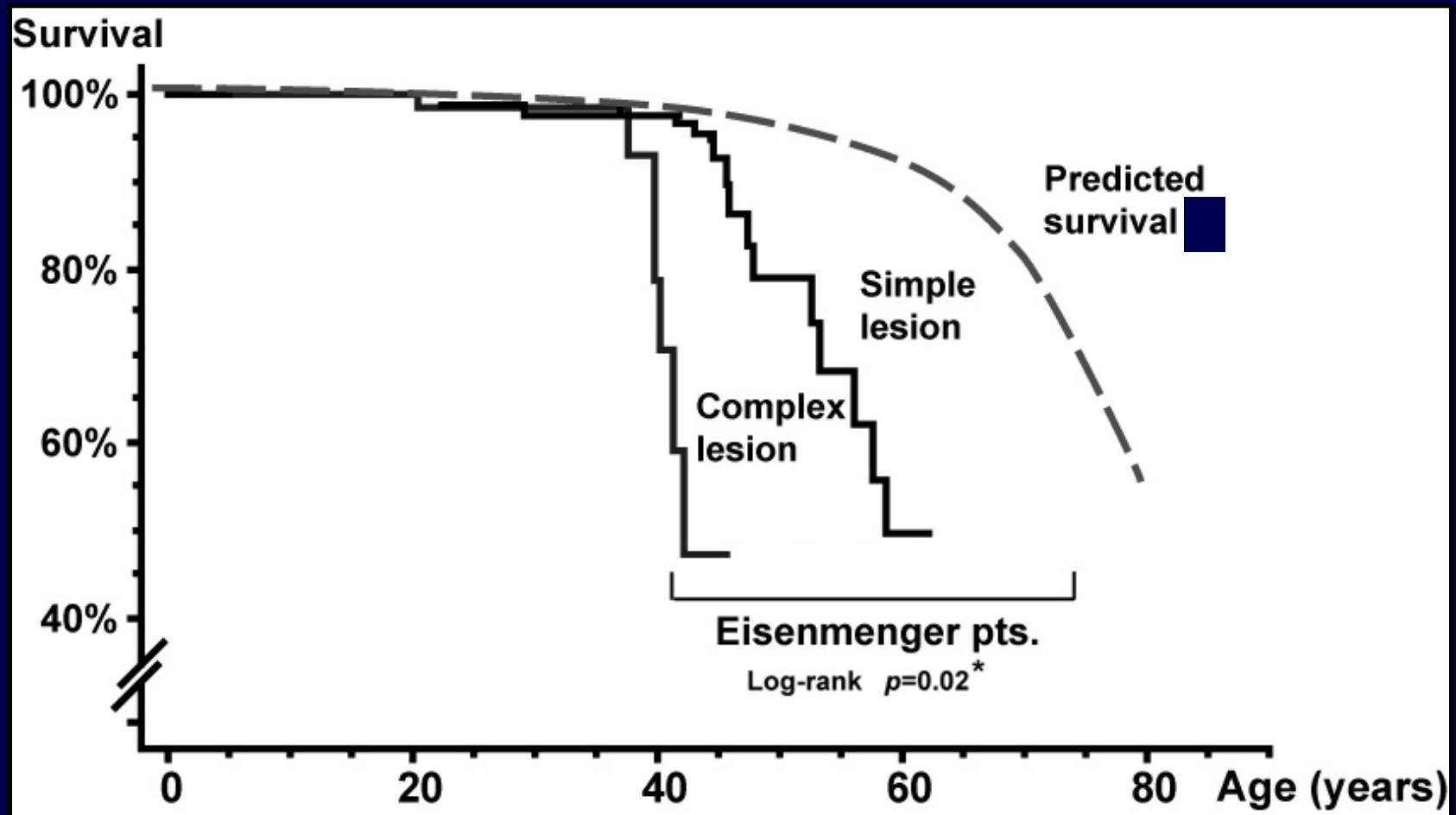
Eisenmenger syndrome

Multi-organ disease

- Haematology (secondary erythrocytosis/thrombocytopenia)
- Haemoptysis/thrombosis
- Menorrhagia
- Renal dysfunction
- Increased uric acid (less commonly gout)
- Cholelithiasis
- Scoliosis
- Arthropathy (osteochondrosis)
- Acne
- Systemic infection
 - Brain abscess (focal neurology not to be confused for hyperviscosity symptoms)
- Arrhythmias (atrial & ventricular)
- Syncope/Sudden cardiac death
- Right heart failure (late, often ominous sign)

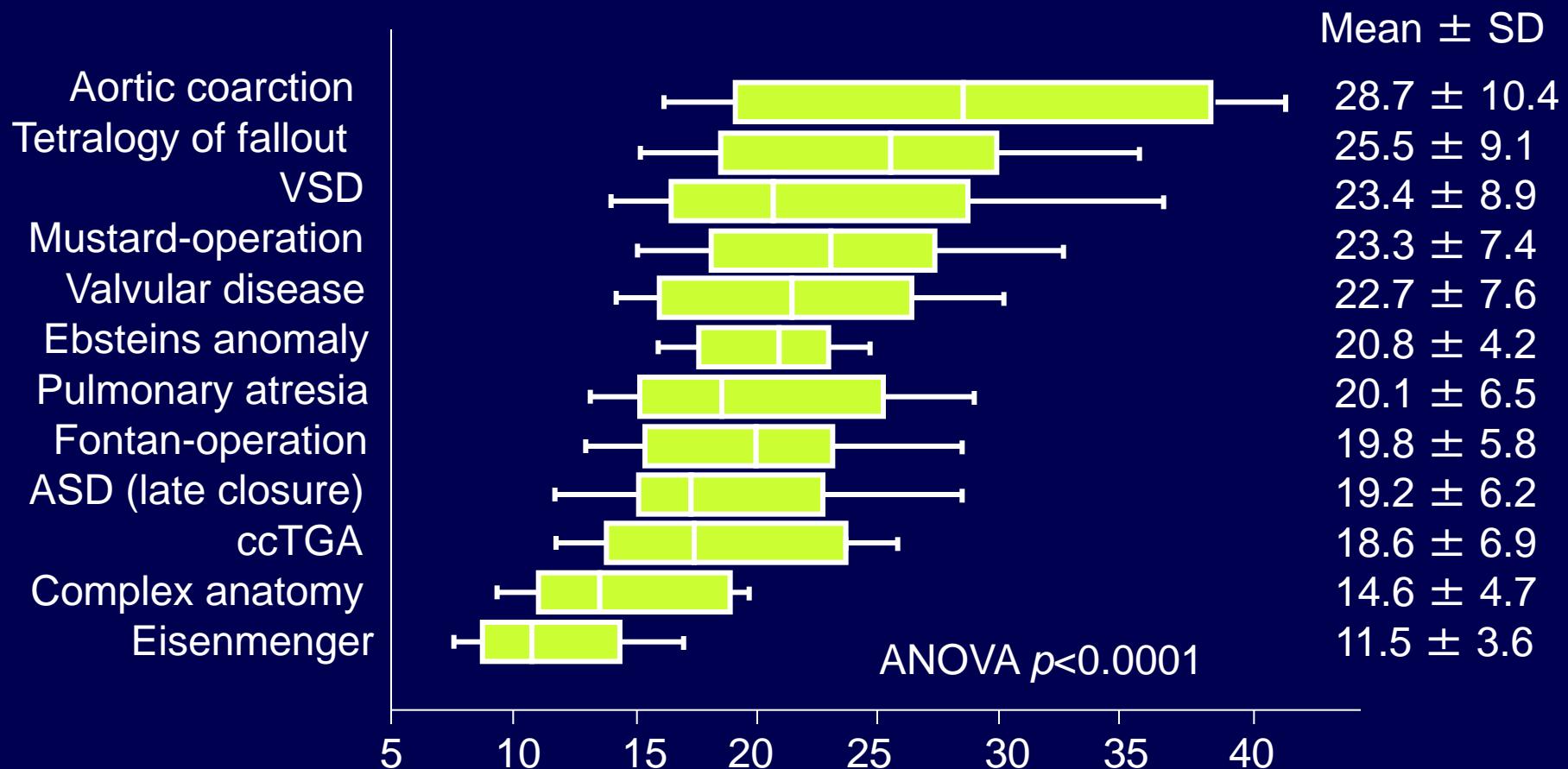
Adults with Eisenmenger Syndrome Survival

Diller et al EHJ 2006

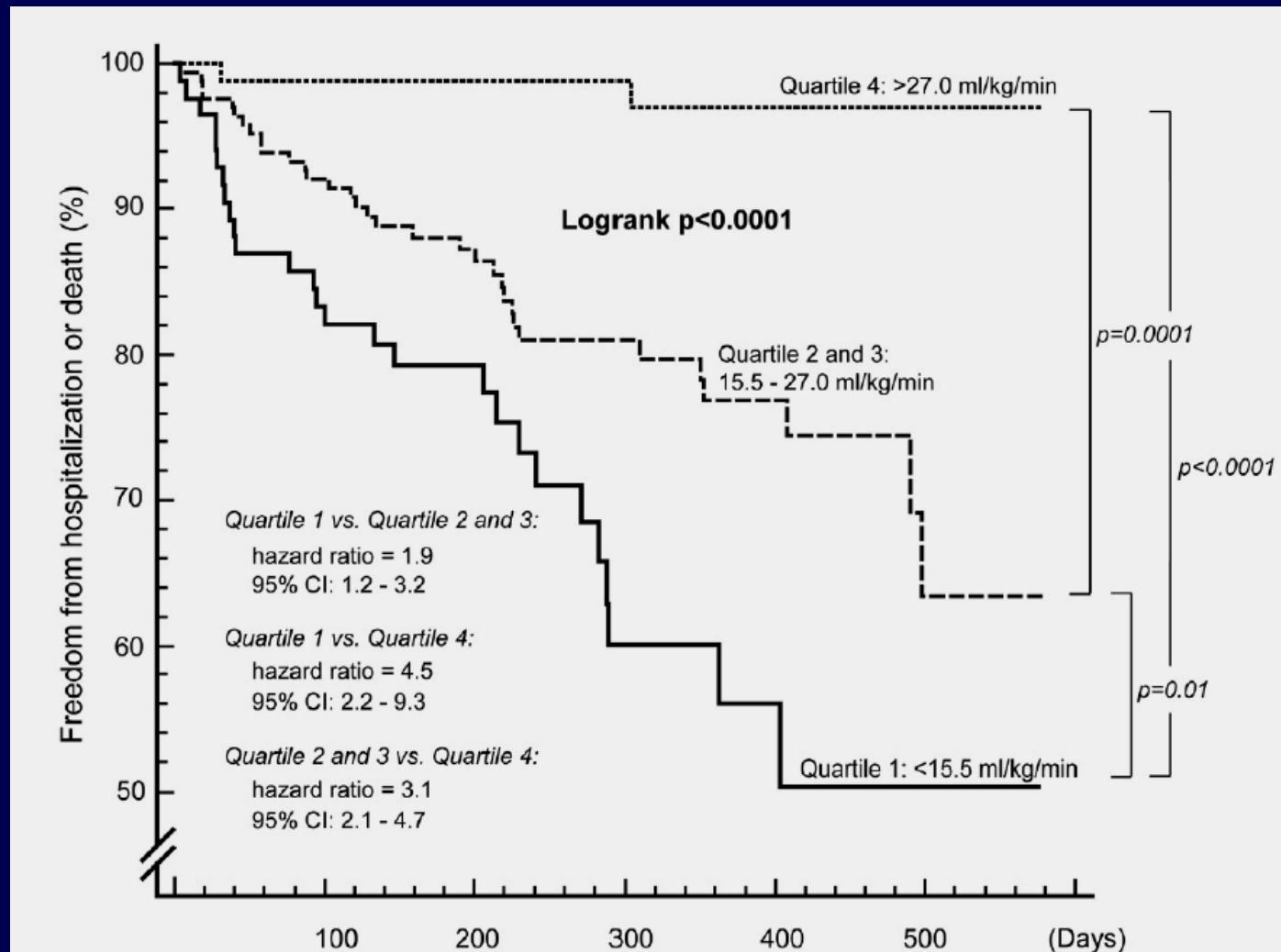


Standardised mortality ratio 3.8; 95% CI 2.0 – 7.0; $p<0.0001$

Exercise capacity in adults with CHD MVO₂ and underlying diagnosis



Peak VO₂ Predicts Combined End-Point of Hospitalization or Death



Diller et al, Circulation 2005

Eisenmenger syndrome

Therapy

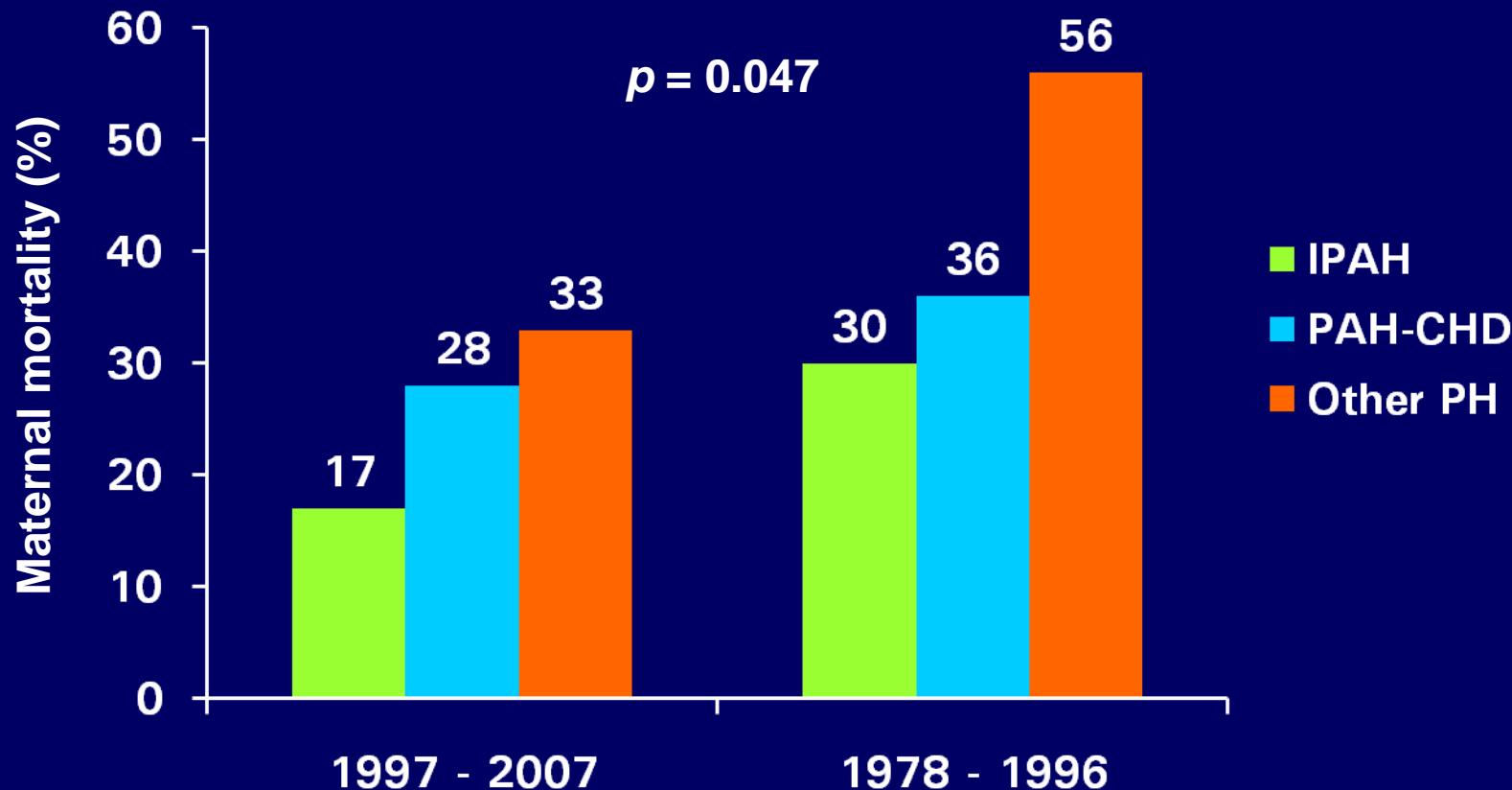
- Not standardised until recently
- Targeted towards avoiding complications

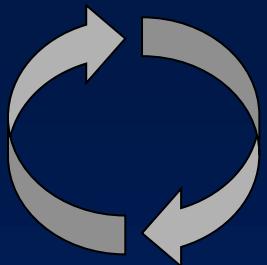
Eisenmenger syndrome

General management principles

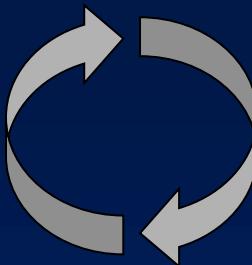
- **Avoid dehydration, extreme isometric exercise**
- **Avoid high altitude**
- **Air travel is safe** *Broberg et al Heart 2006*
- **Special anaesthetic management**
- **Special care around angiography and non-cardiac surgery**
- **Avoid pregnancy** *Bedard et al Eur Heart J 2009*
(≈ 30% maternal mortality)
- **Contraception issues**

Pregnancy and PAH in association with CHD





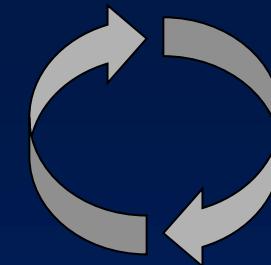
Ventilation



$Q_{p/s}$



O_2 carrying
capacity



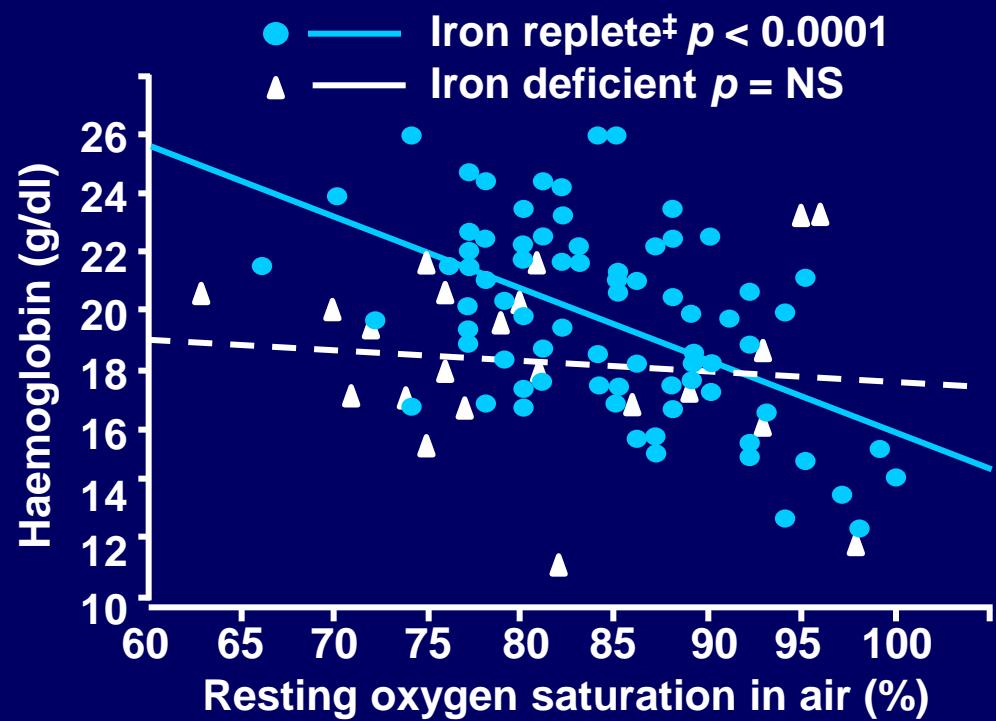
Muscle

..... the cyanotic CHD patient and the myth of "hyperviscosity" syndrome, therapeutic venesection and the risk of stroke.

Cyanosis and 2° erythrocytosis

Routine venesections:

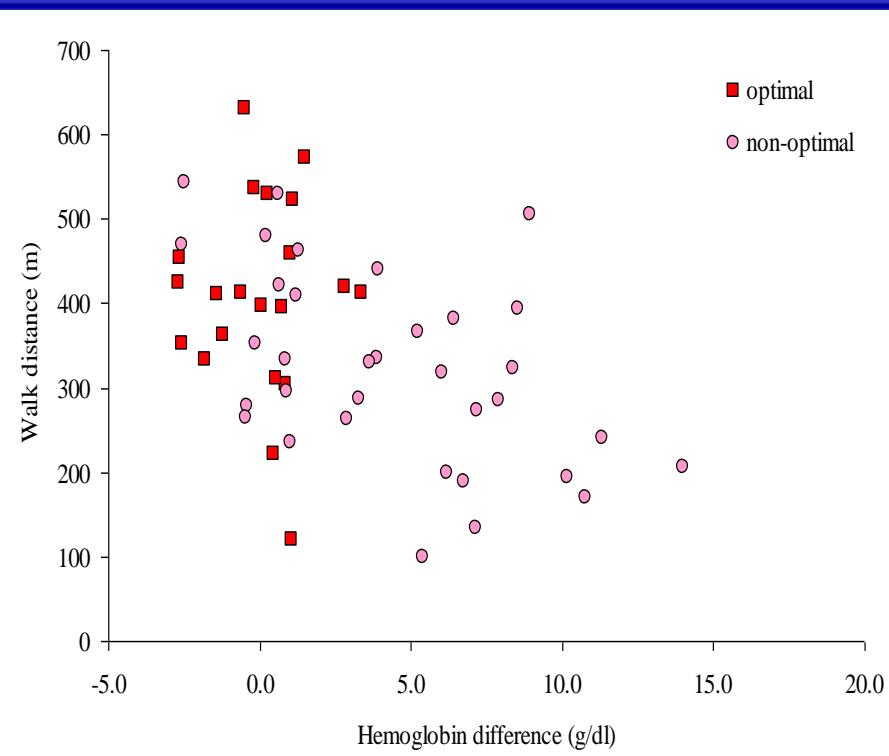
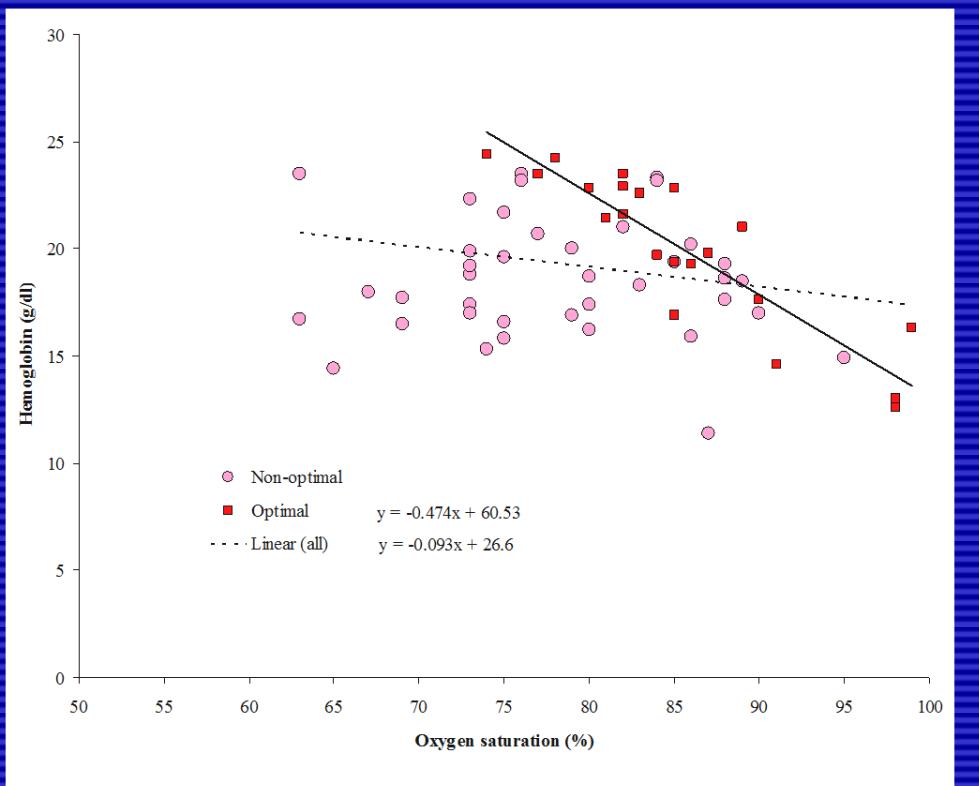
- ♦ Compromise O₂ carrying capacity
- ♦ Increase risk of stroke
- ♦ Reduce exercise capacity
- ♦ Induce/augment pre-existing iron deficiency*



*So-called symptoms of “hyperviscosity” syndrome mimic symptoms of iron deficiency...

Diller GP, et al. Eur Heart J 2006; 27:1737-42.

Optimal Hb* and its Relation with O₂Sats and Exercise

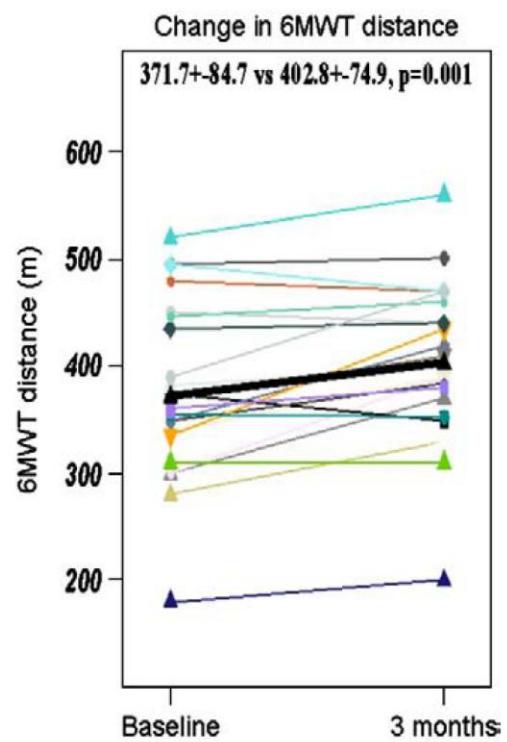
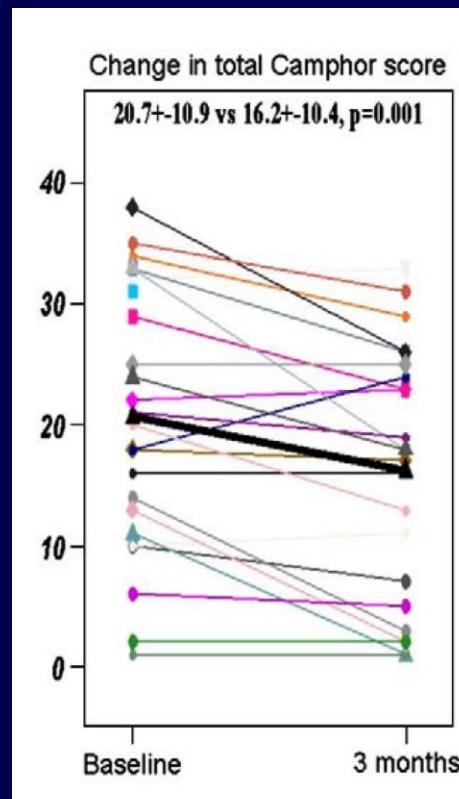
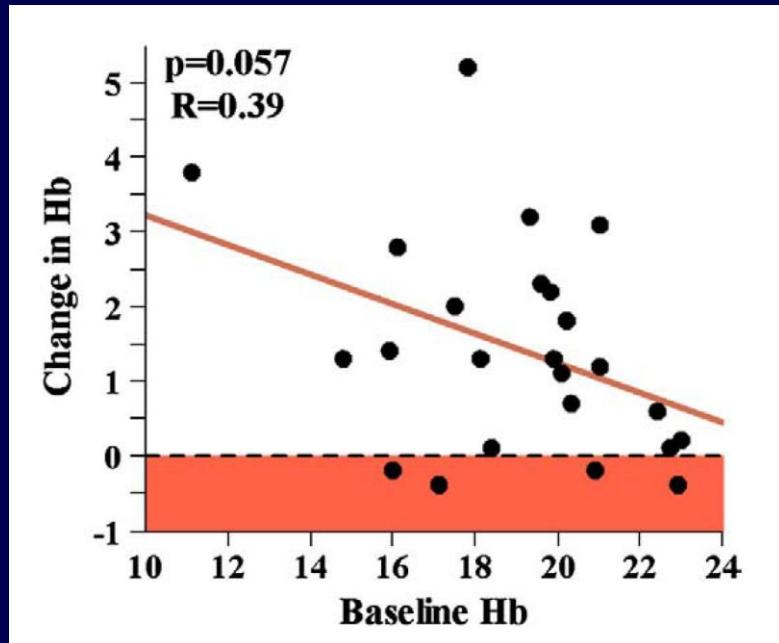


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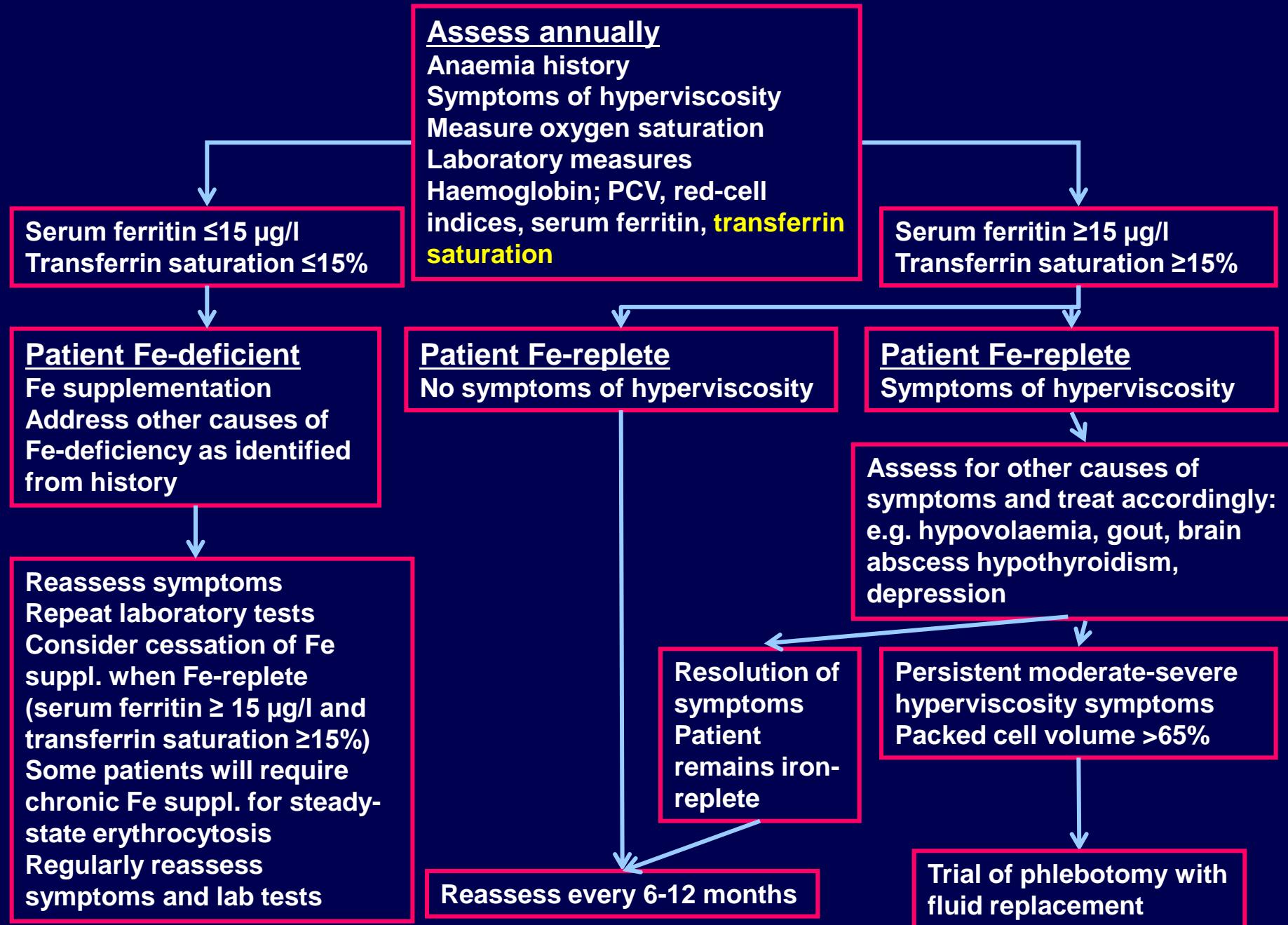
With adequate erythropoiesis, i.e. without iron/folate/B12 deficiency, raised erythropoietin/reticulocytosis, or right-shifted oxygen-Hb curve

Broberg et al Am J Card 2011

3 Months of Iron Replacement Therapy (Oral)



High CAMPHOR scores reflect worse QoL



Eisenmenger syndrome

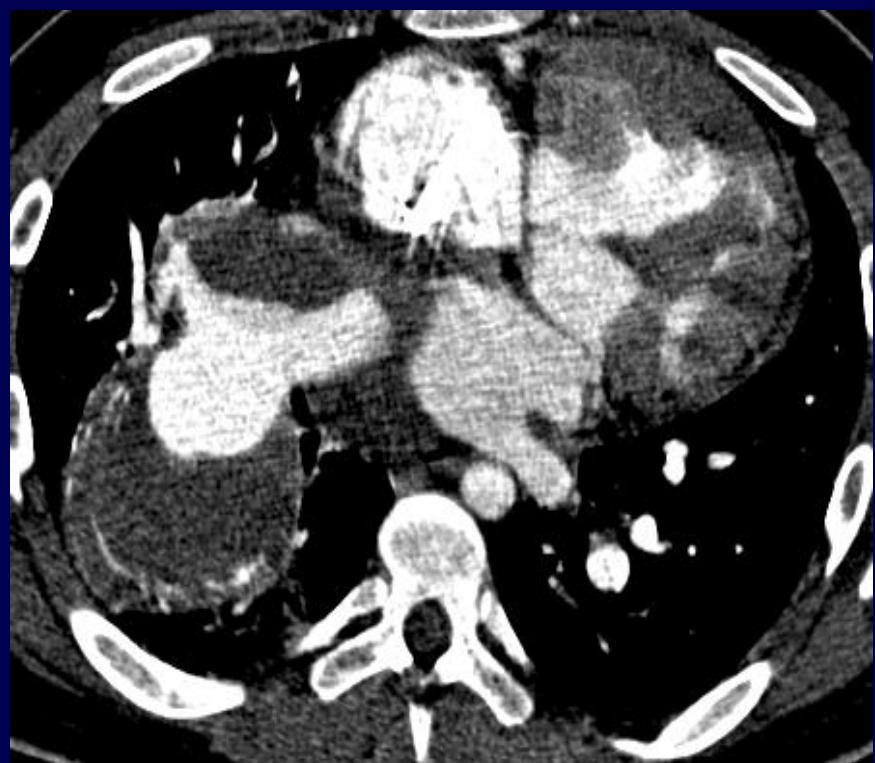
Therapy

- Not standardised until recently
- Targeted towards avoiding complications
 - Anticoagulation
 - Nocturnal oxygen
 - Chronic prostacyclin therapy
 - Nitric oxide
 - Transplantation
 - PDE-5 inhibitors
 - Endothelin antagonists

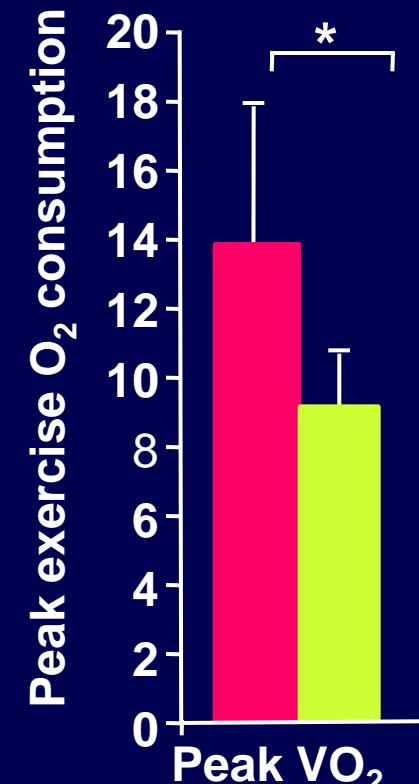
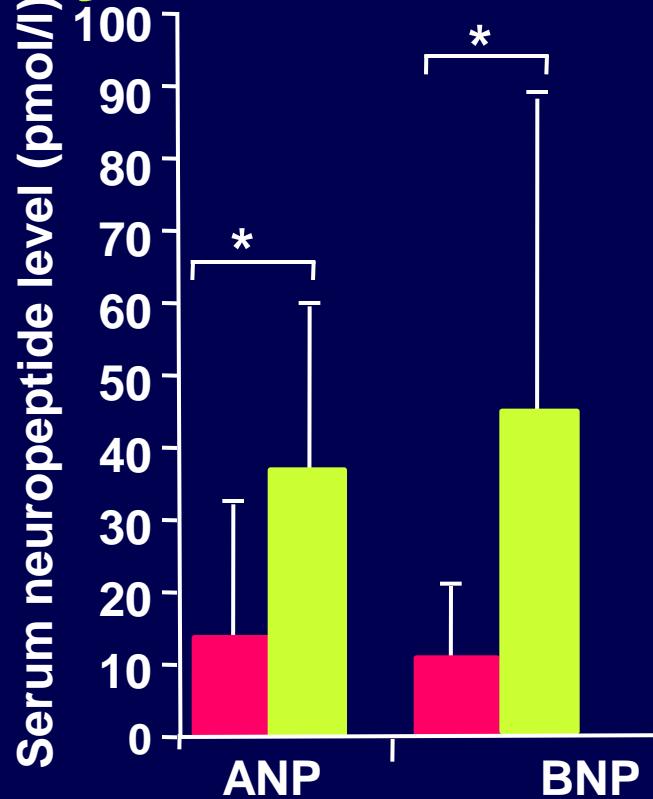
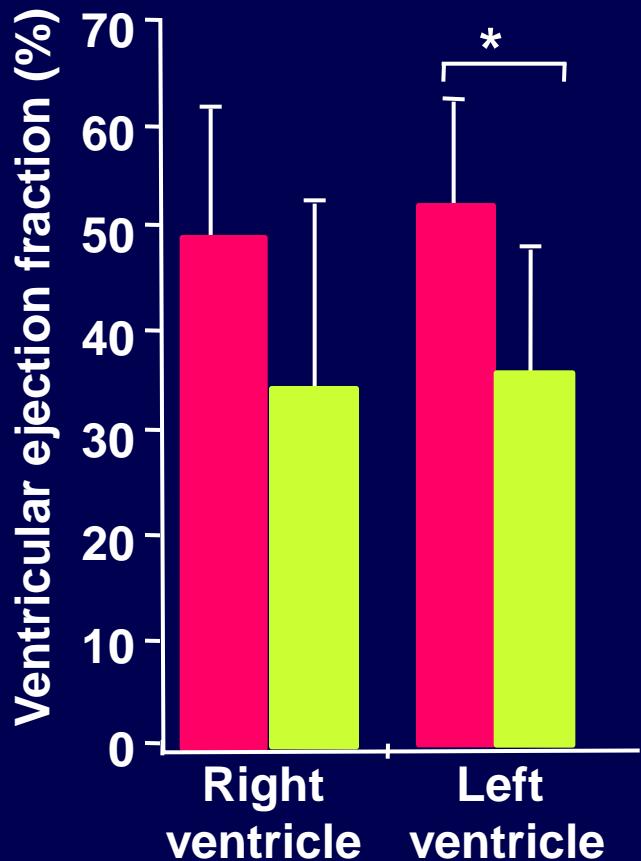
Eisenmenger Syndrome: *Thrombosis*



Broberg, et al. Heart 2004
Silversides et al, JACC 2003



Effect of pulmonary arterial thrombus formation in Eisenmenger syndrome



■ No thrombus ■ Thrombus * $p<0.05$

Broberg CS, et al. J Am Coll Cardiol 2007; 50:634-42.

Eisenmenger syndrome

Therapy

- Not standardised until recently
- Targeted towards avoiding complications
 - Anticoagulation
 - Nocturnal oxygen
 - Chronic prostacyclin therapy
 - Nitric oxide
 - Transplantation
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Eisenmenger syndrome

- Nocturnal oxygen
 - Survival benefits in children with PHT¹
 - 9/9 on O₂ alive vs 1/6 alive in controls (over 5 yrs)
 - No change in PA pressure or survival benefit in 23 adults with Eisenmenger complex after 2 years of nocturnal O₂ therapy²
 - Data limited, inconclusive
 - Use on empiric basis

¹Bowyer JJ, et al. *Br Heart J* 1986; 55:385-90.

²Sandoval J, et al. *Am J Respir Crit Care Med* 2001; 164:1682-7.

Eisenmenger syndrome

- Chronic prostacyclin therapy
 - 20 pts on IV prostacyclin¹ at 12 months
 - PA pressure ↓ 20% (no acute response)
 - 6 minute walk test ↑ (408 to 460 m)
 - Toxicity
 - Problems with IV lines
 - 15 children on aerosolized iloprost² at 12 months
 - Improved right sided haemodynamics
 - Improved 6 minute walk test
 - Short half life (inhalation every 3-4 hrs)
 - Similar side effects with IV (flushing and jaw pain)
 - May have a role in pregnancy

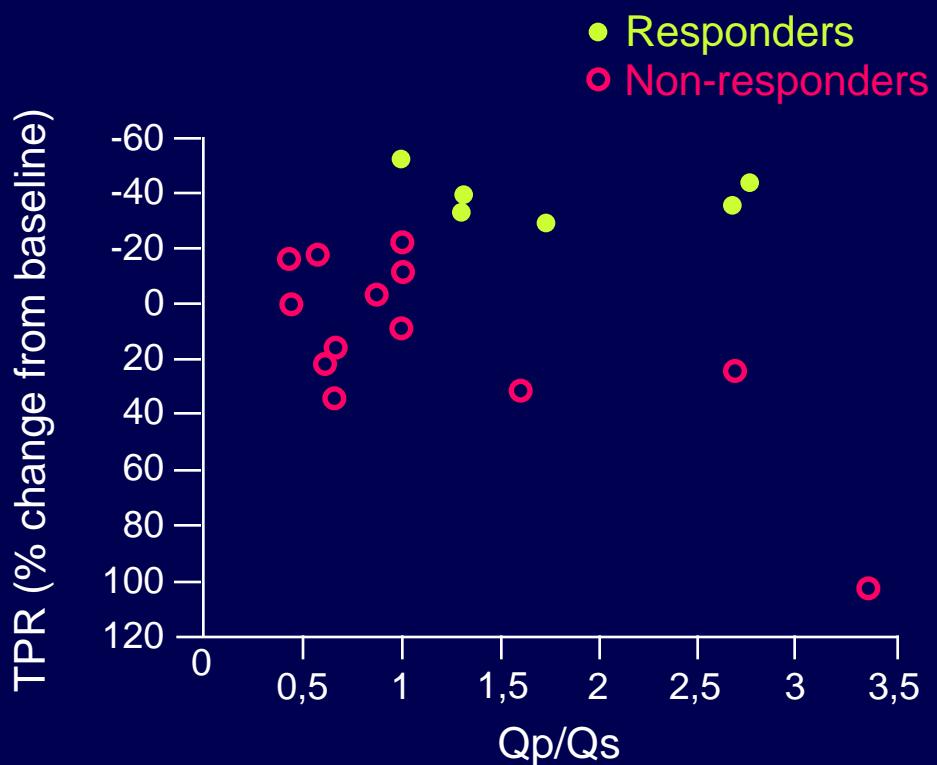
¹Berman Rosenzweig E, et al. *Circulation* 1999;99:1858-65.

²Hoeper MM, et al. *N Engl J Med* 2000;342:1866-70.

Eisenmenger syndrome

NO

- Selective pulmonary vasodilator
- No systemic disturbance



- 23 pts with Eisenmenger
- 30% responders (80ppm)
- All with L-to-R shunts
- Responders had improved survival
- *Administration challenges*

Establishing the Diagnosis of Eisenmenger Syndrome



Oechslin E. "Chapter on Eisenmenger Syndrome"
Gatzoulis, Webb and Daubenay. 2nd Edition Elsevier 2011

Eisenmenger syndrome

- Transplantation
 - H/LT superior to LT¹
 - 435/605 Tx in CHD pts period 1988-98 from the International Registry
 - 1 year survival 81% and 70% respectively
 - 5-year survival approximately 50%
 - Increased peri-operative risk²
 - 51 pts with Eisenmenger HLT
 - Similar long-term survival with non-Eisenmenger pts
- Selection criteria and timing ?

¹Waddell TK, et al. *J Heart Lung Transplant* 2002; 21:731-7.

²Stoica SC, et al. *Ann Thorac Surg* 2001; 72:1887-91.

Eisenmenger syndrome

- Phosphodiesterase inhibitors
 - Short-term randomized data at present in adult patients
 - *Sildenafil (high dose, 100mg tds)* ¹
 - 10 patients (age 15, 4- 35 years) , RC cross over study, 6 weeks
 - Non-invasive
 - 6MWT improved on sildenafil (269+/-99 to 358.9+/- 96.5 m)
 - *Tadalafil (40mg od)* ²
 - 28 patients (>30Kg in weight), RC cross over study, 6 weeks
 - 6MWT improved on tadalafil (358+/-73 to 404+/- 70)
 - PVR fell (-7.32+/-1.58, P<0.001)

¹Singh et al. Amer Heart J 2006

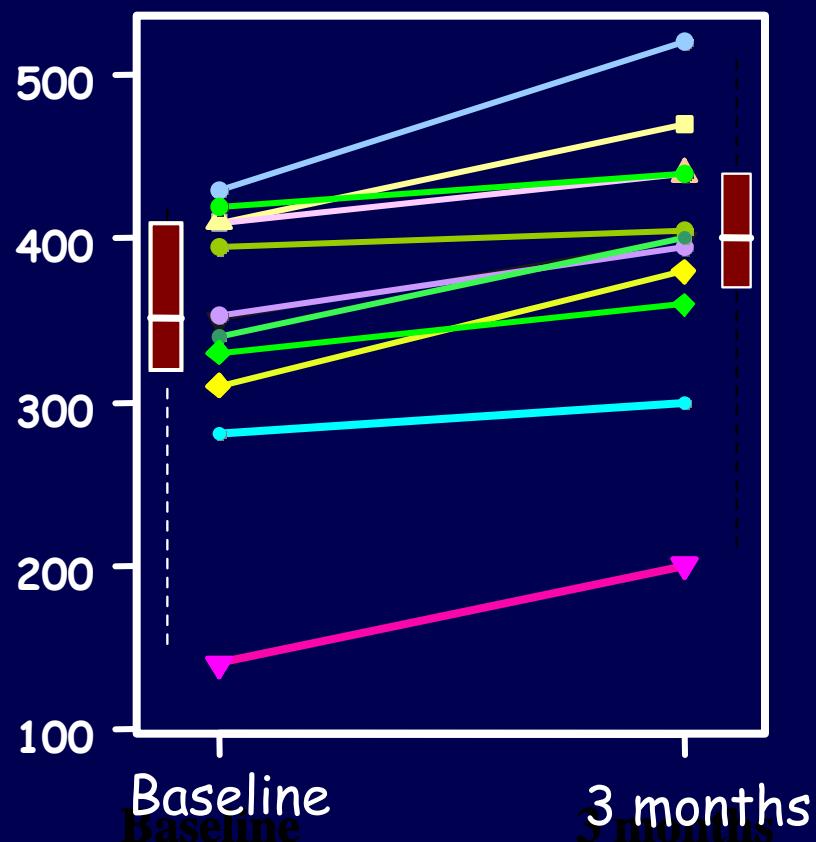
²Mukhopadyay et al. Cong Heart Dis 2011

Eisenmenger syndrome

Sildenafil

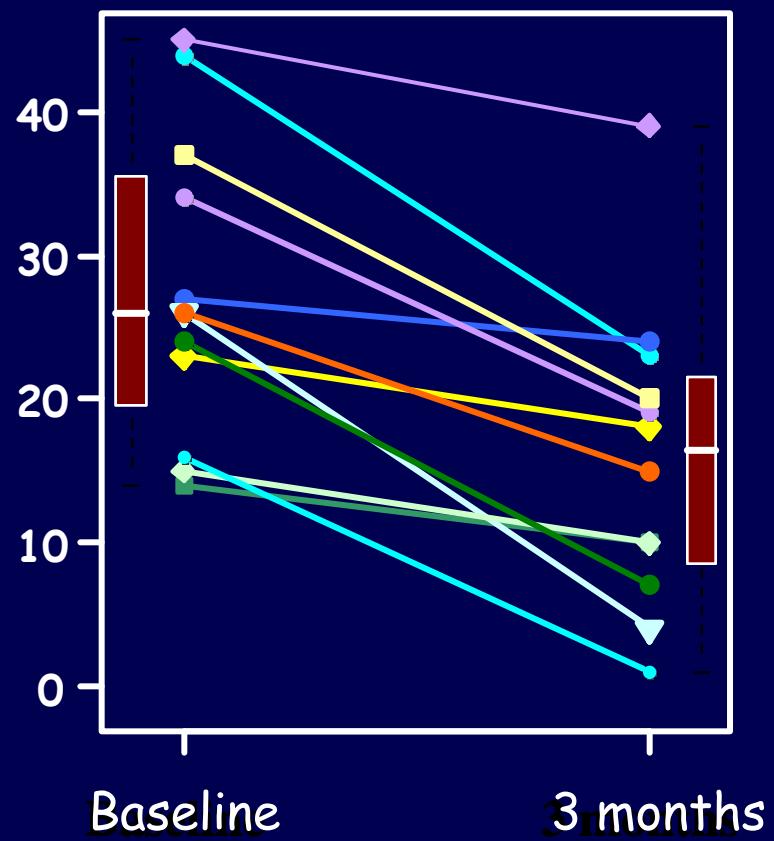
Change in 6MWD (m)

$p < 0.001$



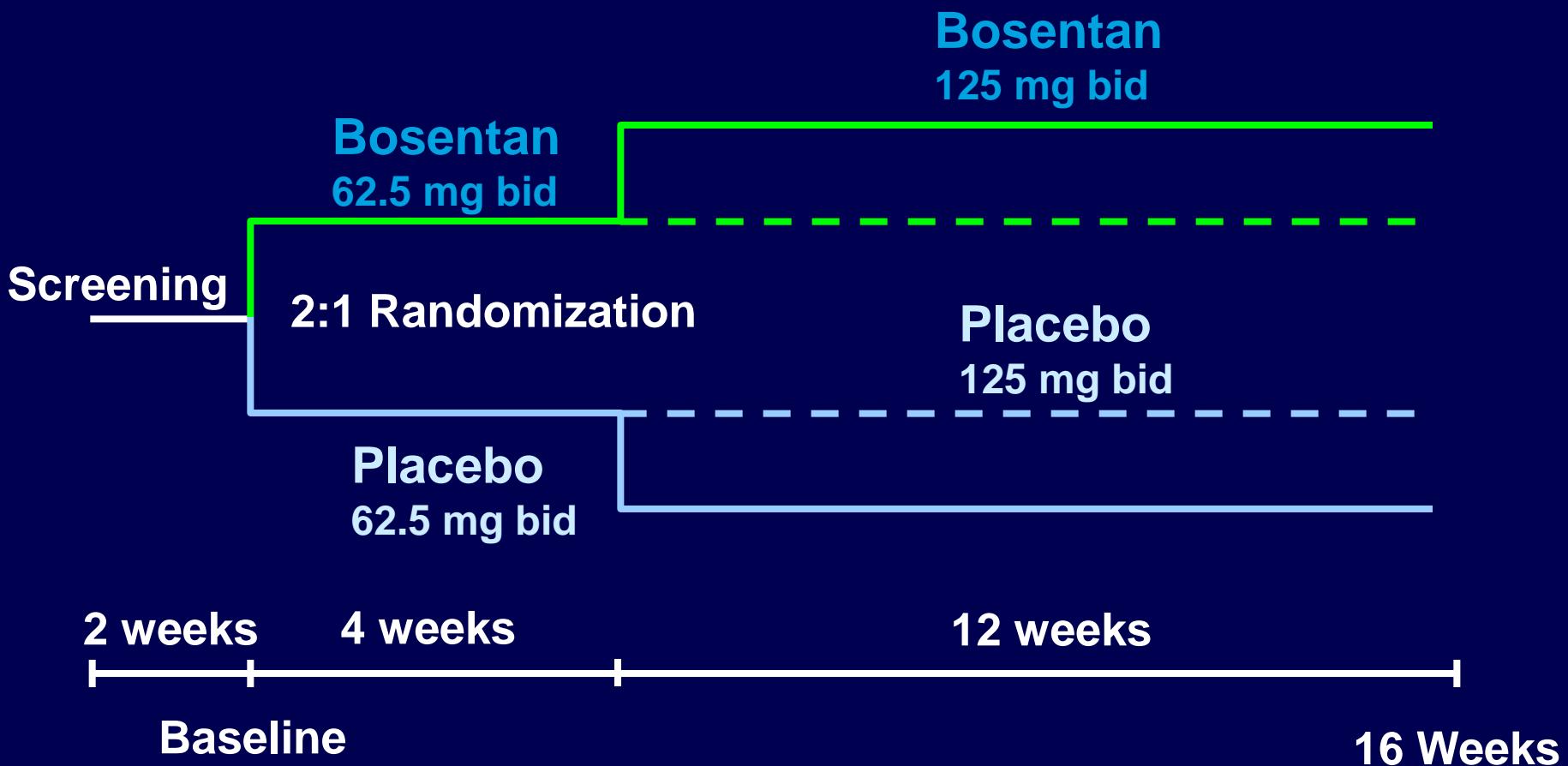
CAMPHOR score

$p < 0.001$

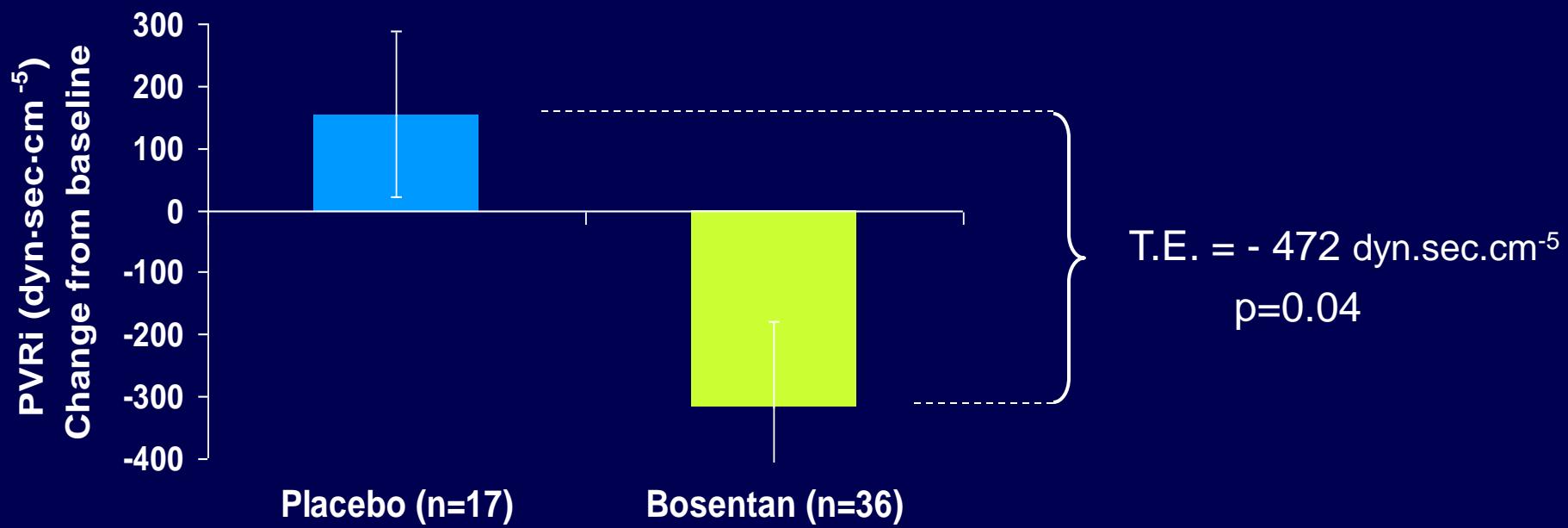


Endothelin Pathway

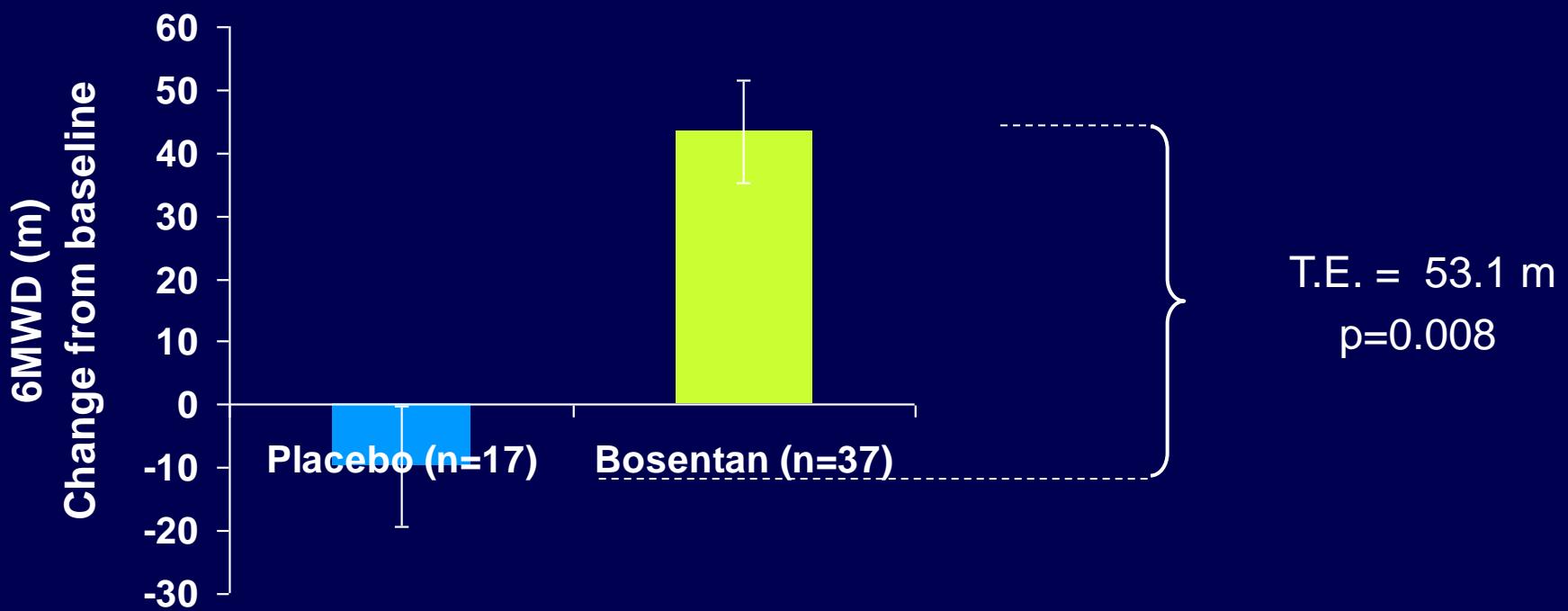
BREATHE-5: Study design



Bosentan reduces pulmonary vascular resistance indexed

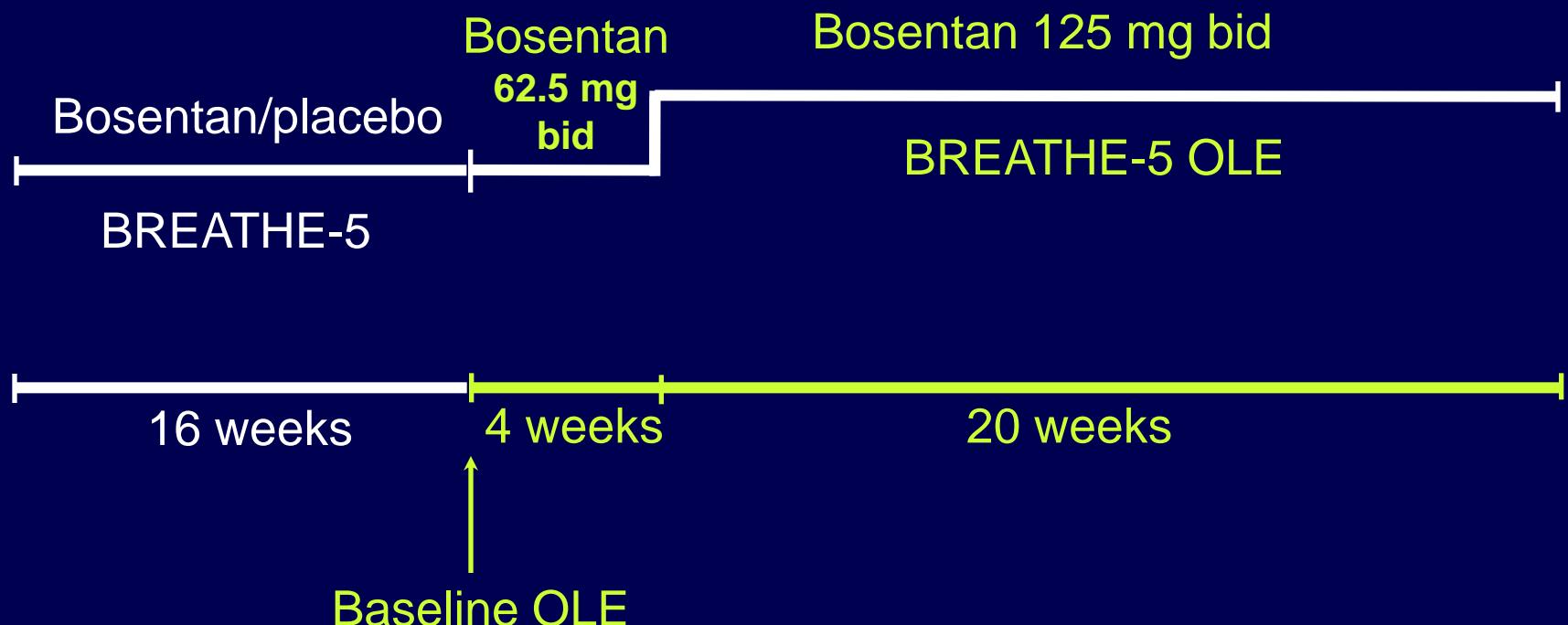


Bosentan increases exercise capacity

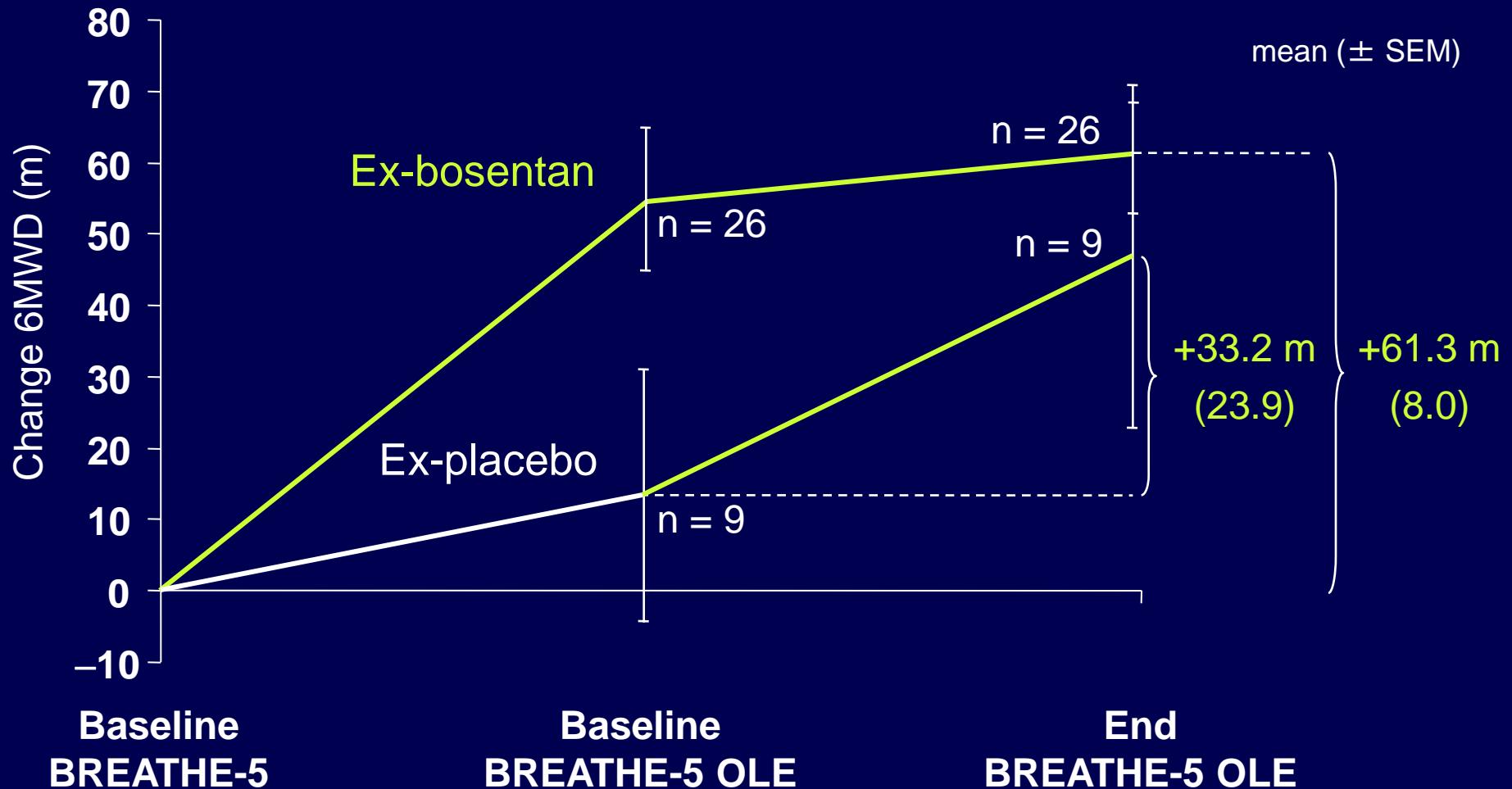


BREATHE-5 open label extension (OLE) study

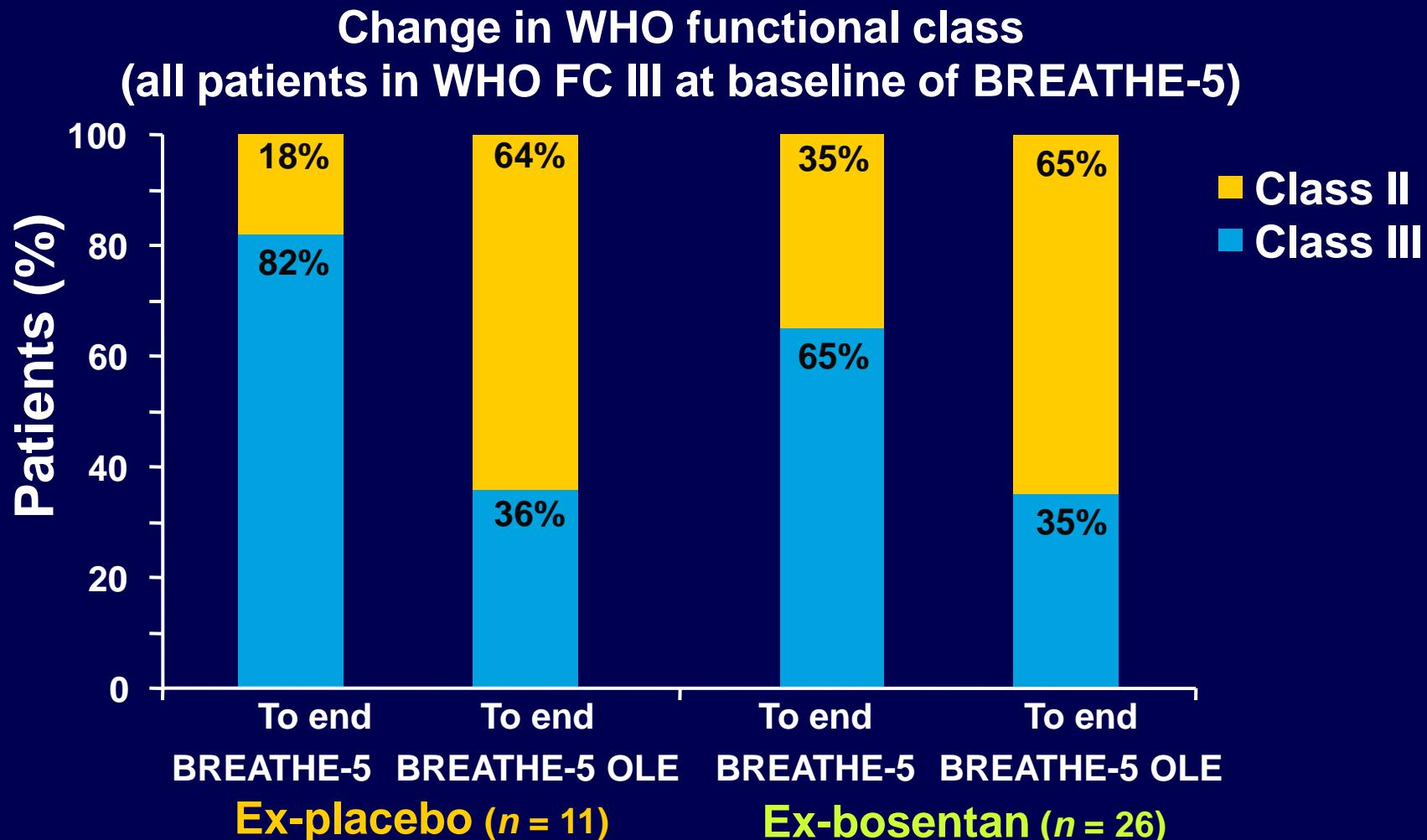
Study design



Bosentan increased exercise capacity

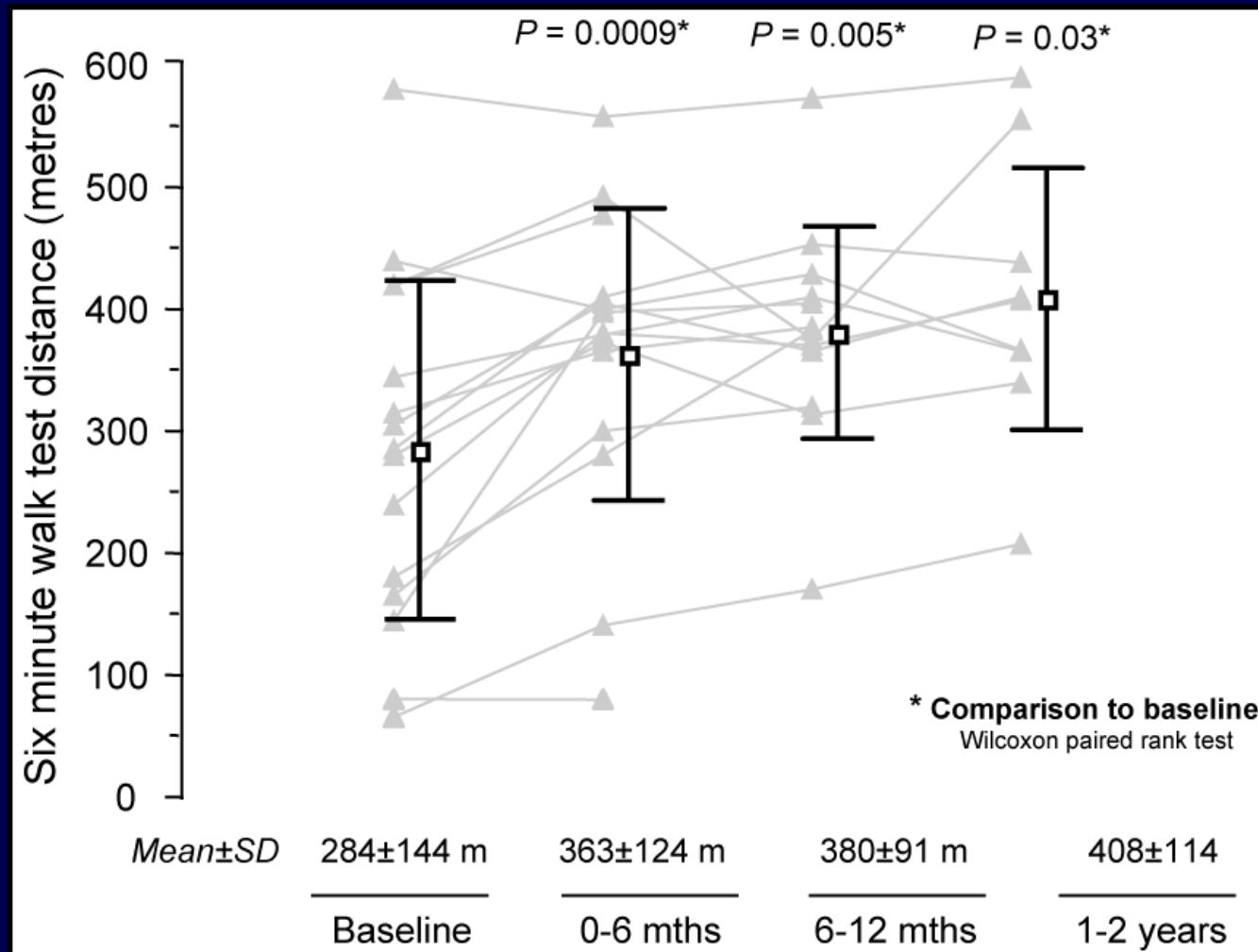


WHO functional class



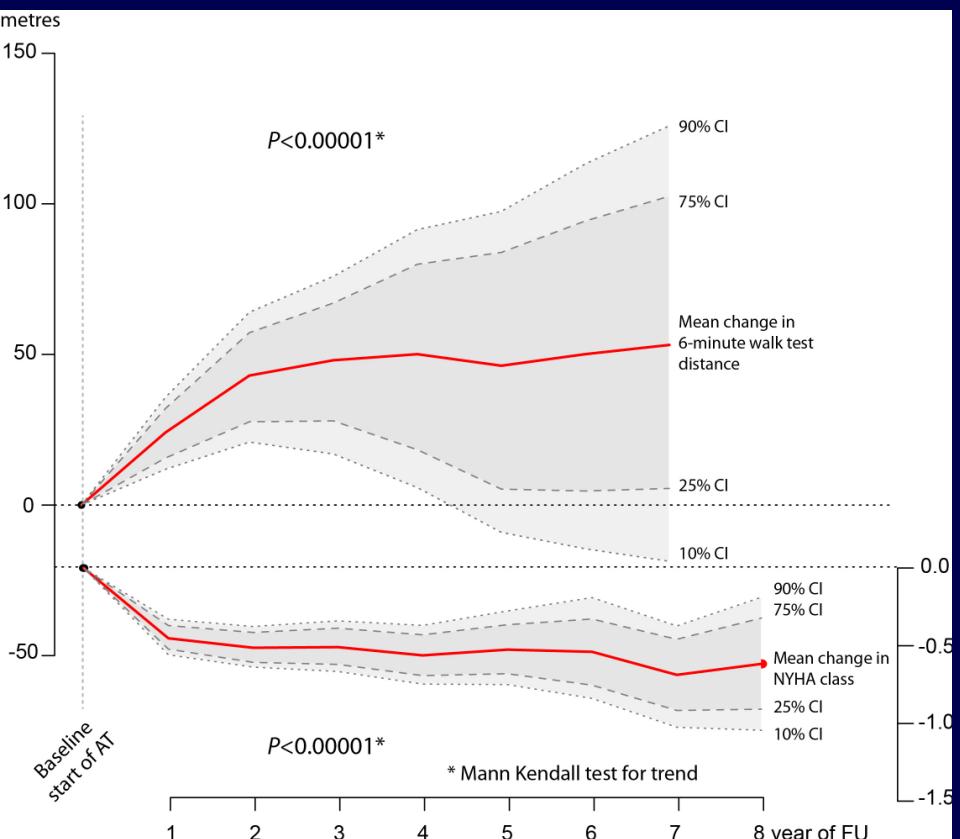
Bosentan and Eisenmenger Syndrome

Longer-term 6 minute walk test

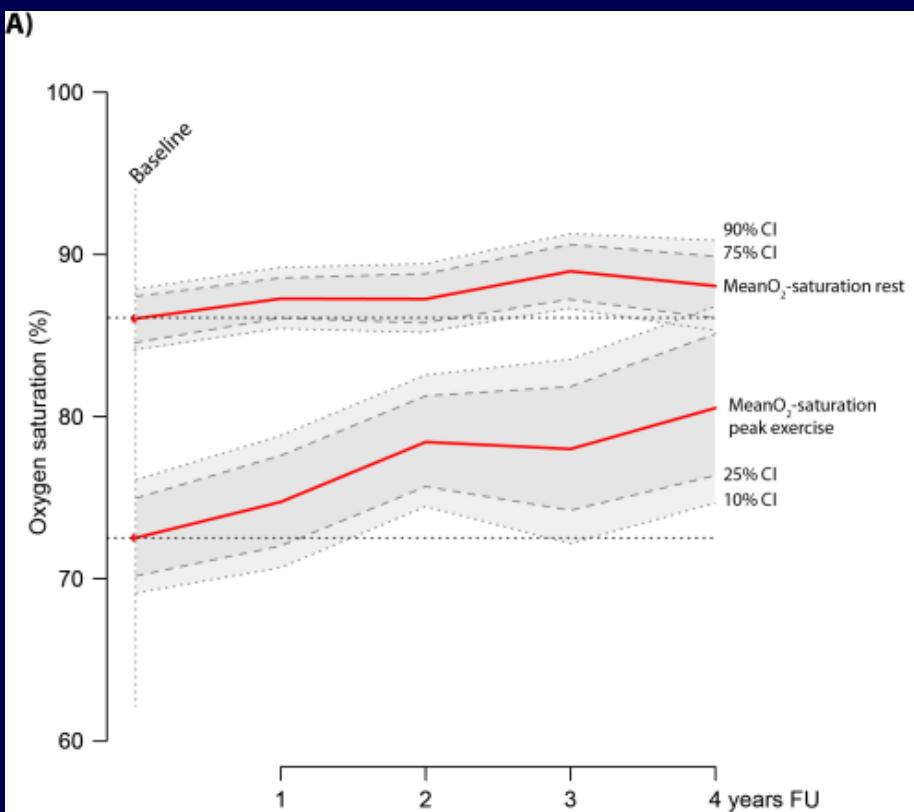


Changes with advanced therapy in PAH associated with CHD

The 6 Minute Walk Test and NYHA Class



O₂ Sats at rest and exercise



79 adults with Eisenmenger syndrome
Mean age 34+/-10 years
Follow-up of 3.3 years (on advanced therapy)
2 patients died

Diller et al *Int J Card* 2012

Hazard ratios for all cause mortality for changes in BNP within 1 year

181 pts with Eisenmenger S. (31% with Down S.)
Mean age 37 yrs, median FU 3.3 yrs, retrospective study

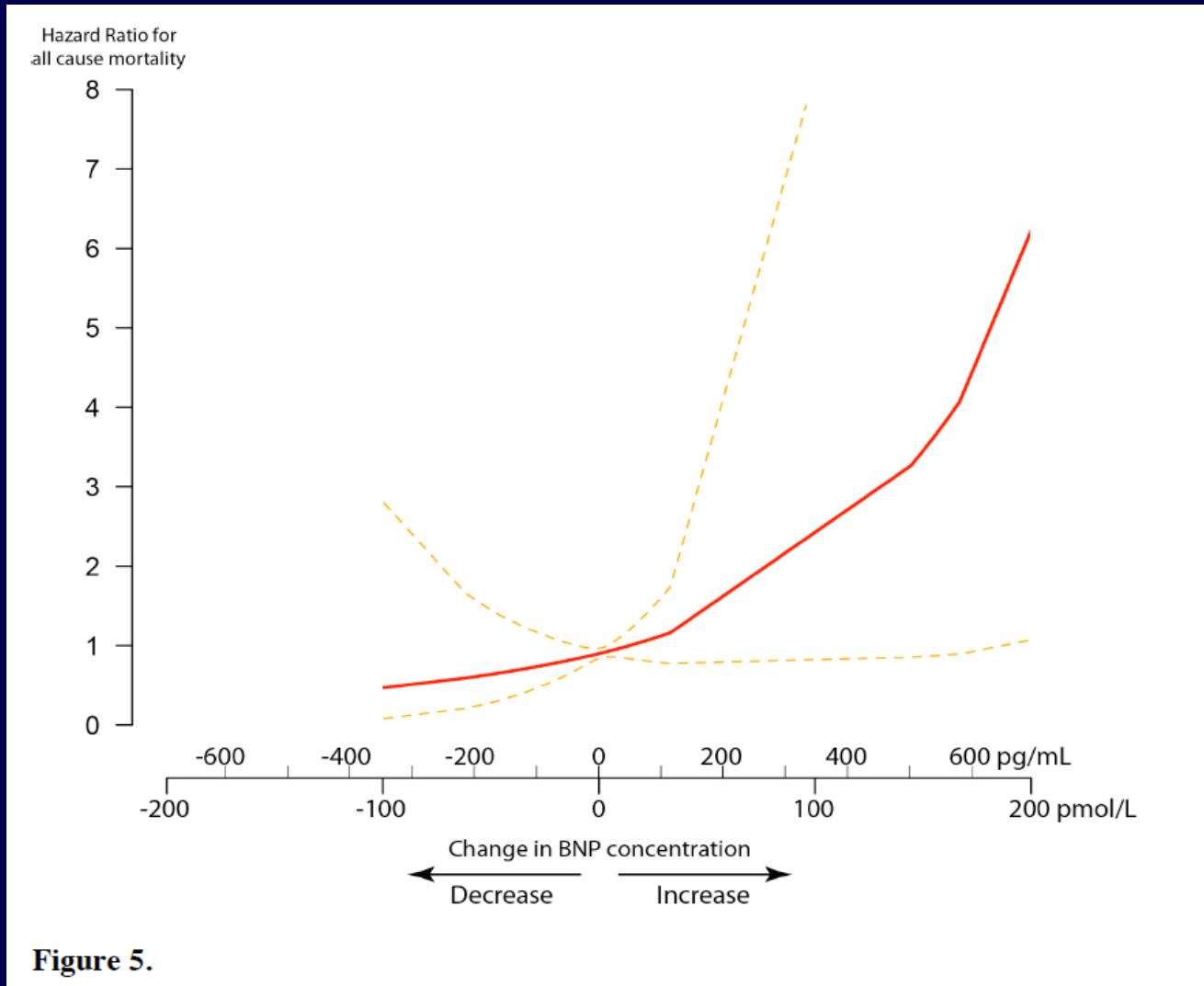
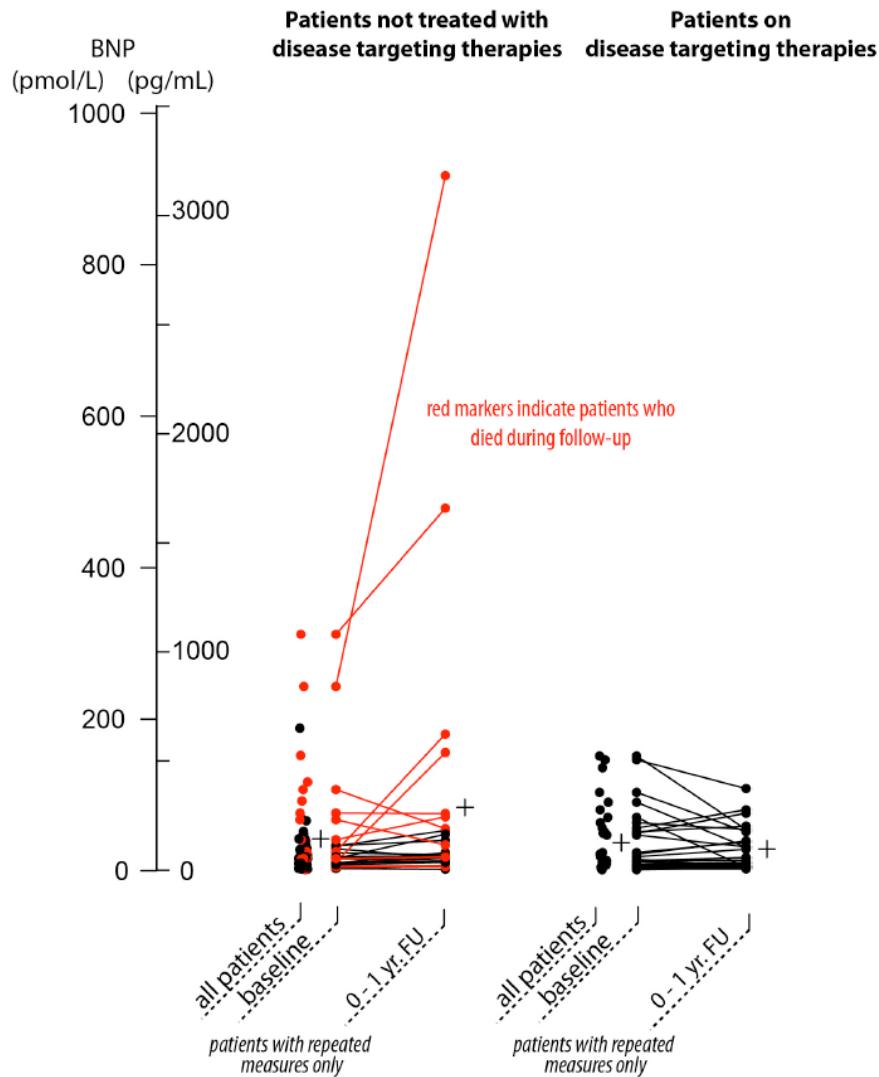


Figure 5.

Change in BNP within 1 year: Conventional vs Targeting PAH Therapy

181 pts with Eisenmenger S. (31% with Down S.)
Mean age 37 yrs, median FU 3.3 yrs, retrospective study

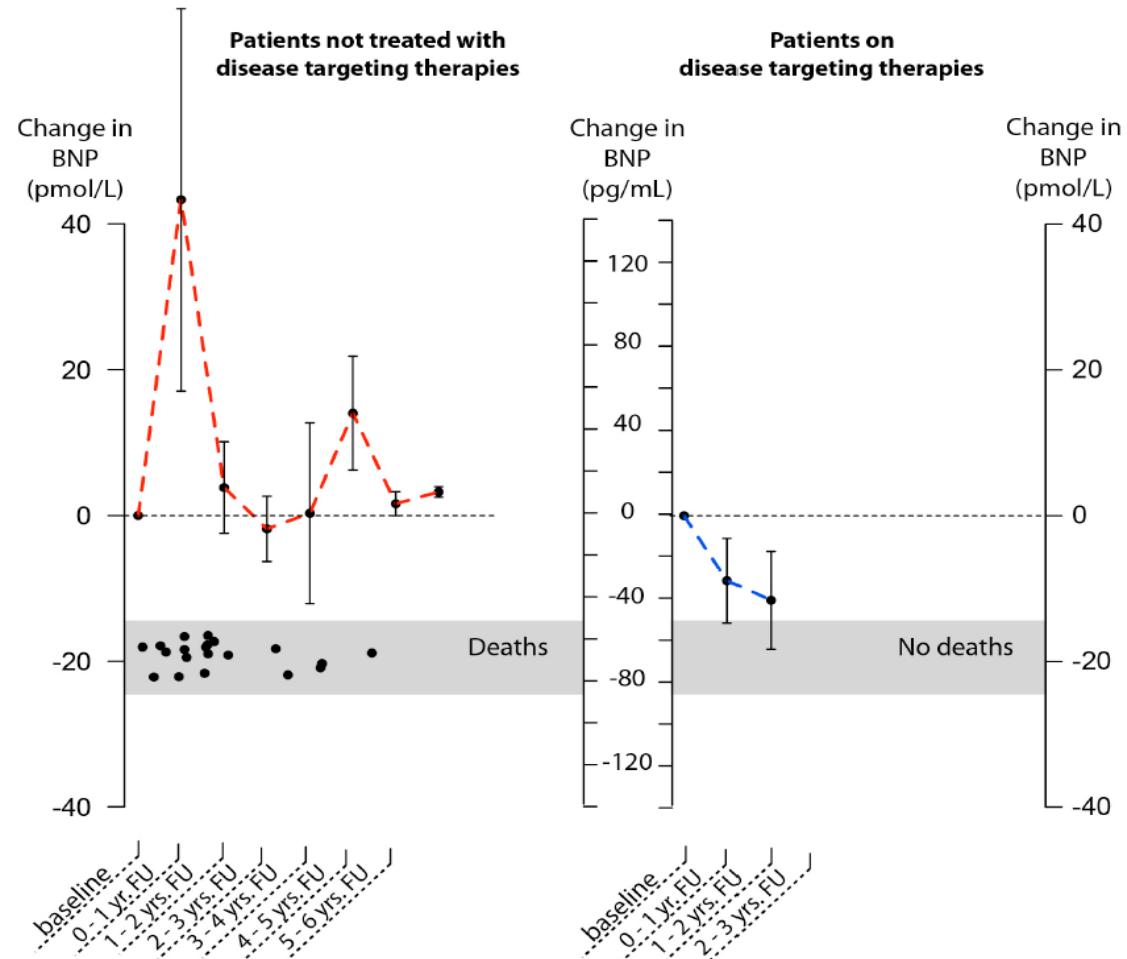
A)



Change in BNP from baseline: Conventional vs Targeting PAH Therapy

181 pts with Eisenmenger S. (31% with Down S.)
Mean age 37 yrs, median FU 3.3 yrs, retrospective study

B)

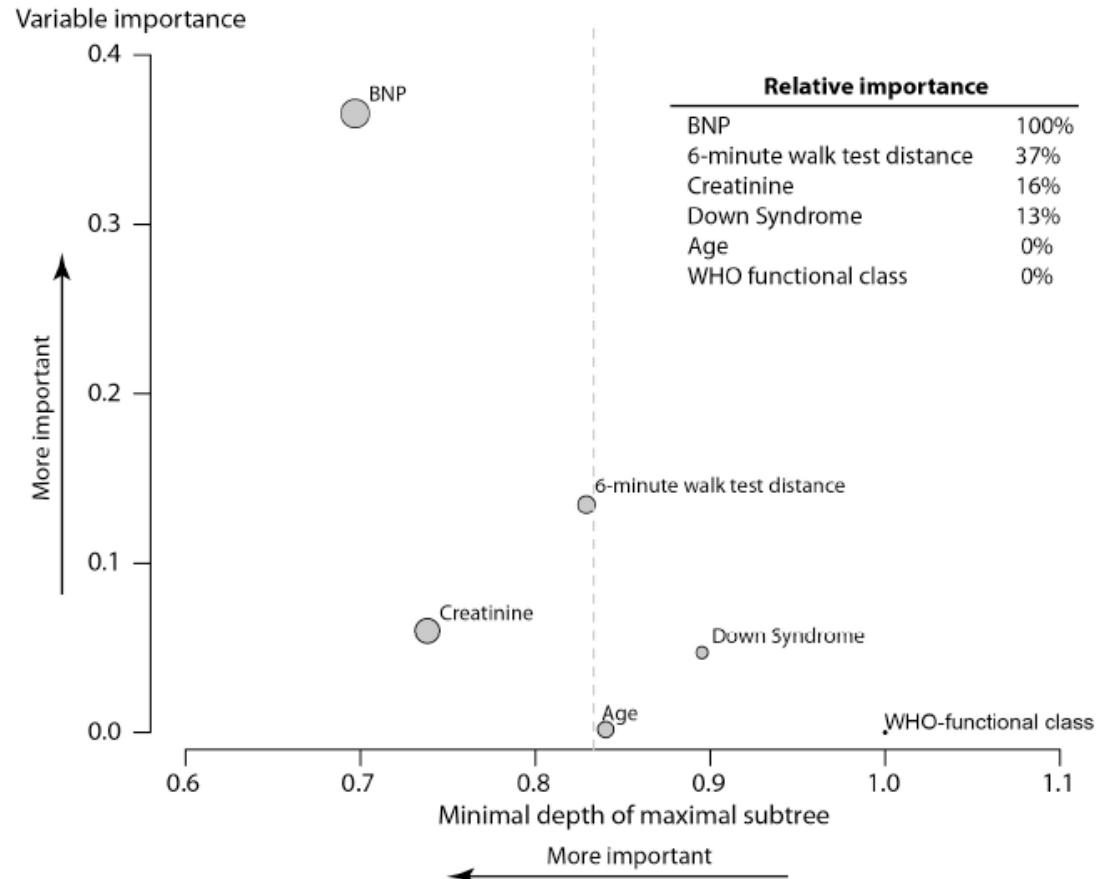


Random survival forest analysis

181 pts with Eisenmenger S. (31% with Down S.)

Mean age 37 yrs, median FU 3.3 yrs, retrospective study

A)



MI:1.7
Car RBH 2d 01

14 JAN 05
15:29:45

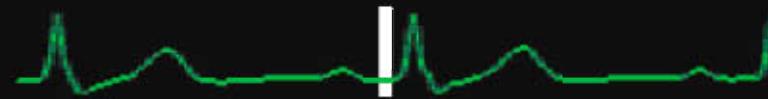
2/0/C/H3

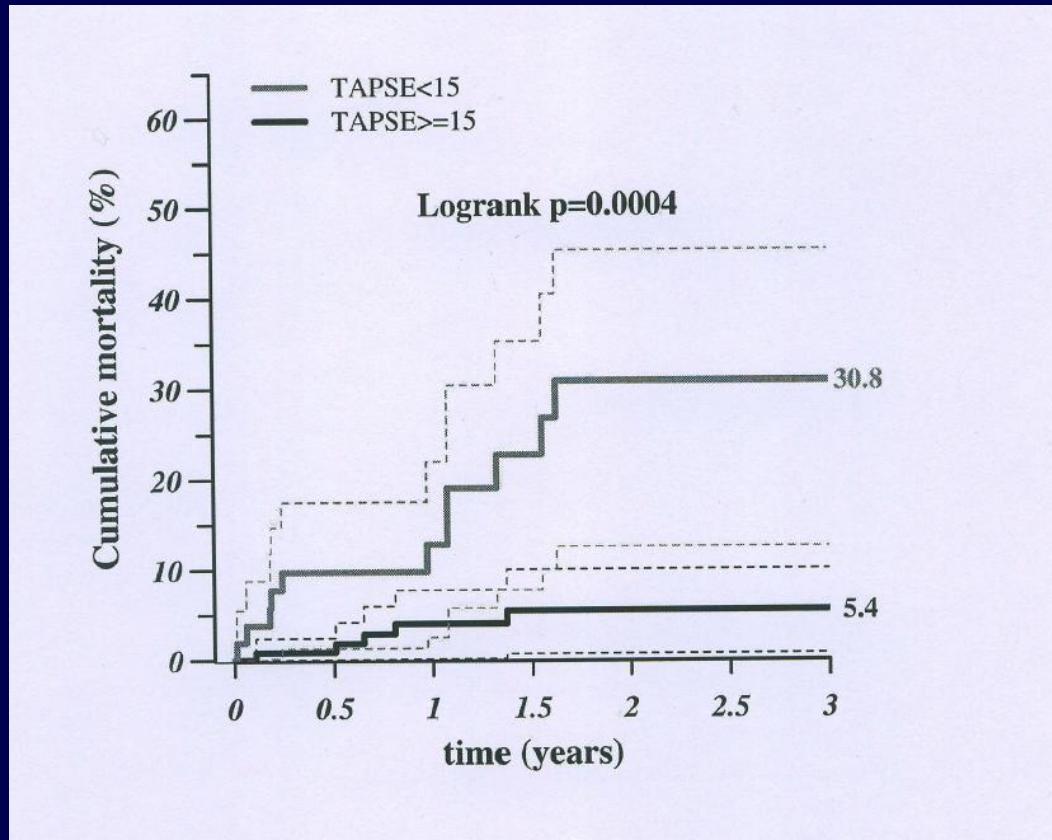
Royal Brompton
Hospital
RBH

03758.06
GAIN 51
COMP 70
66BPM

17CM
25HZ

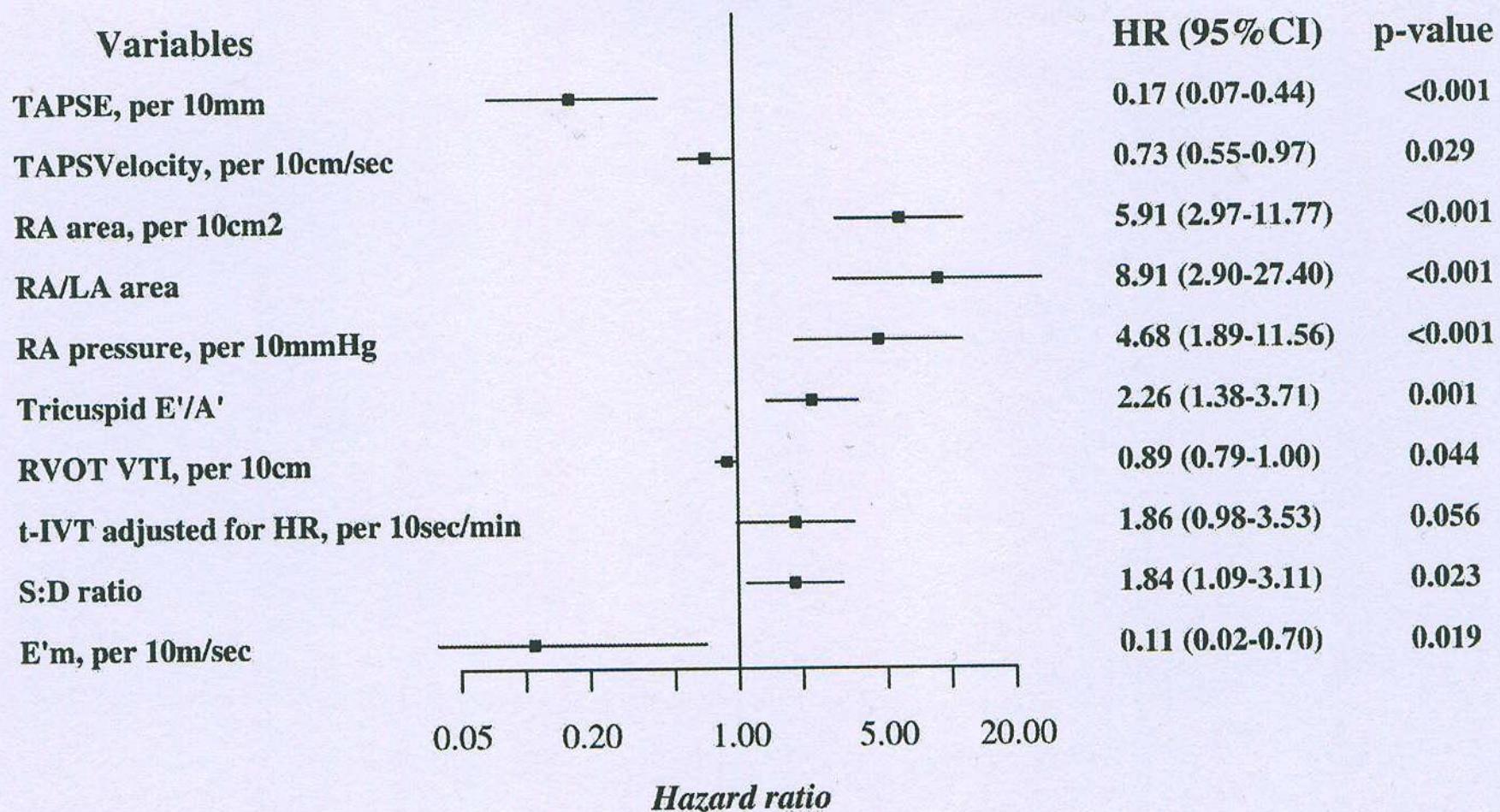
P T ®
2.1 4.2



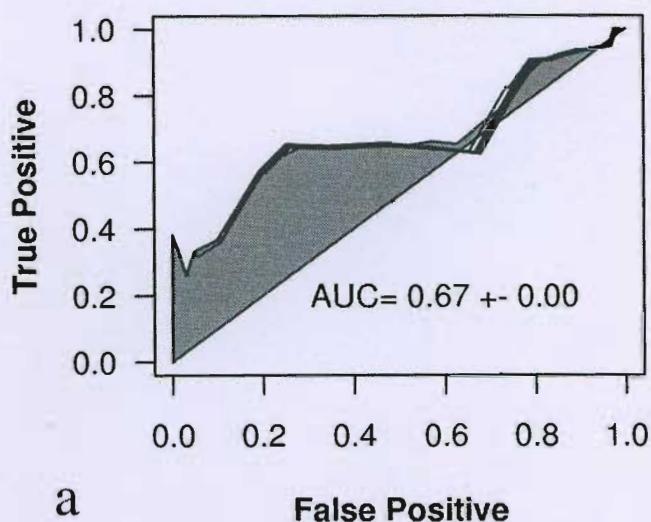


Moceri et al Circulation 2012

Predictors of death in model including ATs

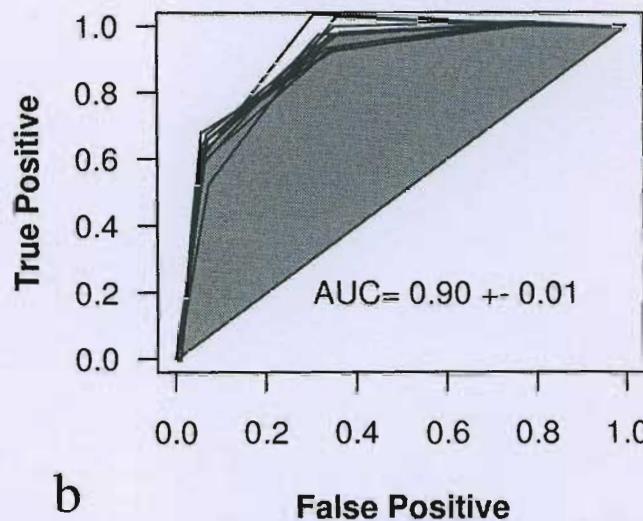


TAPSE



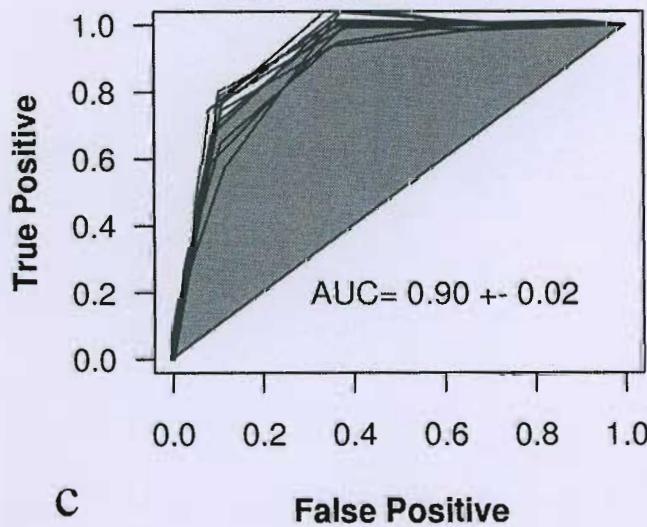
a

Echocardiographic Composite Score



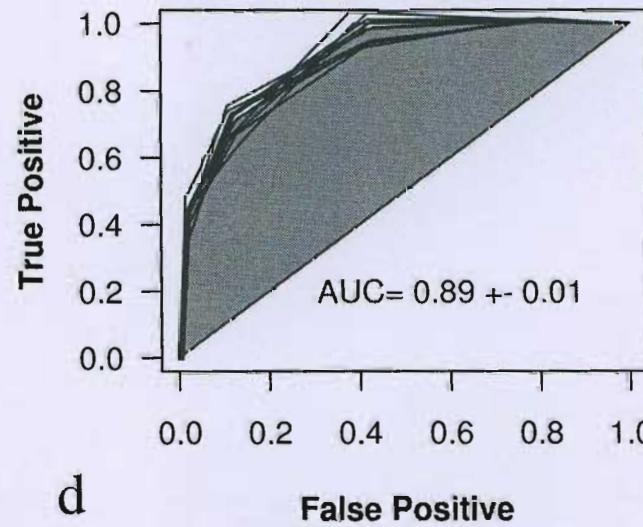
b

Echocardiographic Composite Score with E't/A't and E'm



c

Echocardiographic Composite Score with BNP and Saturations



d

Prognostication and monitoring of the adult with Eisenmenger Syndrome (ES): A roadmap towards a goal-oriented approach

Evolving markers for assessing prognosis, disease severity, disease progression and response to therapy in PAH-CHD @

Better Prognosis	Determinants of Prognosis	Worse Prognosis
Not applicable	RV failure: of limited value for early prognostication in ES*	Yes, guarded prognosis
Slow	Rate of progression of symptoms	Rapid
No	Syncope† ^{1a}	Uncertain
I, II	WHO FC ^{1b}	II, IV
Longer (> 400 m)	6MWD ²	Shorter (< 300 m)
Percentage predicted peak O ₂ consumption > 46%	Cardio-pulmonary exercise testing ³	Percentage predicted peak O ₂ consumption < 31%
Normal (<13.9 pmol/L) or near normal	BNP plasma levels ⁴	> 30 pmol/L
TAPSE ≥ 1.5 cm RA area < 25cm ² RA/LA < 1.5	Echocardiographic findings ⁵	TAPSE < 1.5 cm RA area ≥ 25cm ² RA/LA ≥ 1.5
RAP < 8 mmHg and CI ≥ 2.5 L/min/m ²	Haemodynamics‡ Not routinely examined	RAP > 15 mmHg and CI ≤ 2.0 L/min/m ²

PAH-CHD: pulmonary arterial hypertension in association with congenital heart disease.

@ (adapted from Galiè N et al. *Eur Heart J* 2009; 30:2493–537).

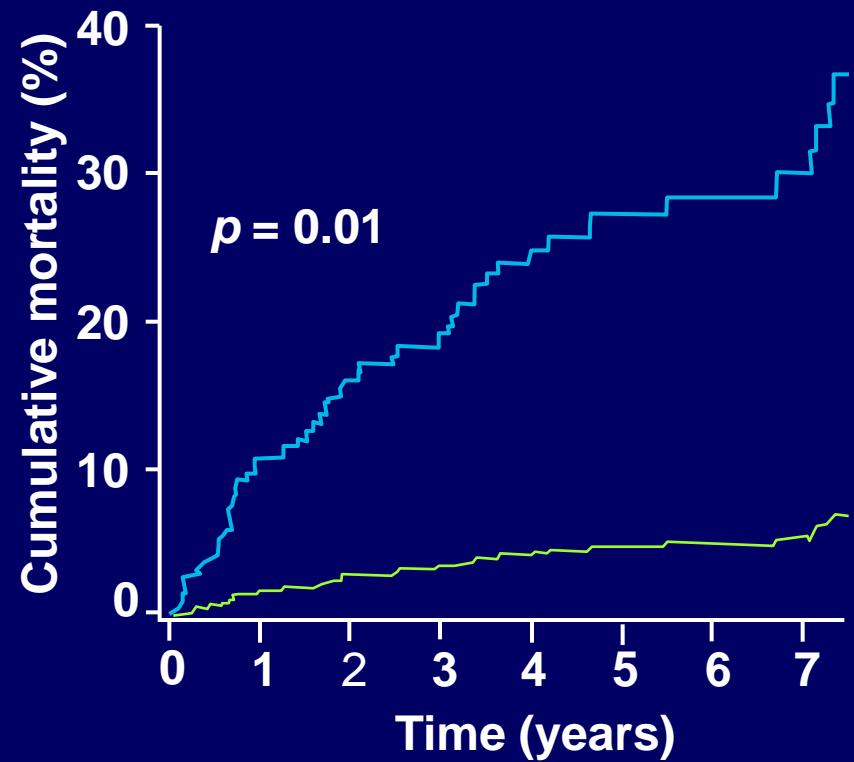
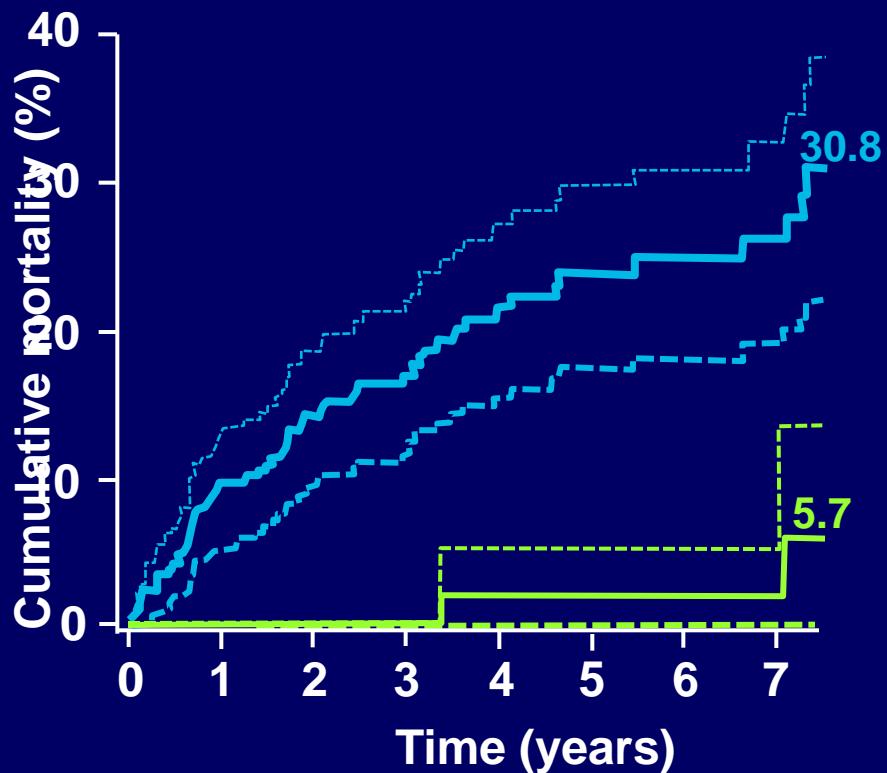
*RV failure in ES patients is an ominous sign and of limited value for early prognostication;

†Syncope in patients with ES and chronic cyanosis may also be vasovagal, due to autonomic nervous dysfunction; 1a syncope does not predict death; Diller et al EHJ 2006

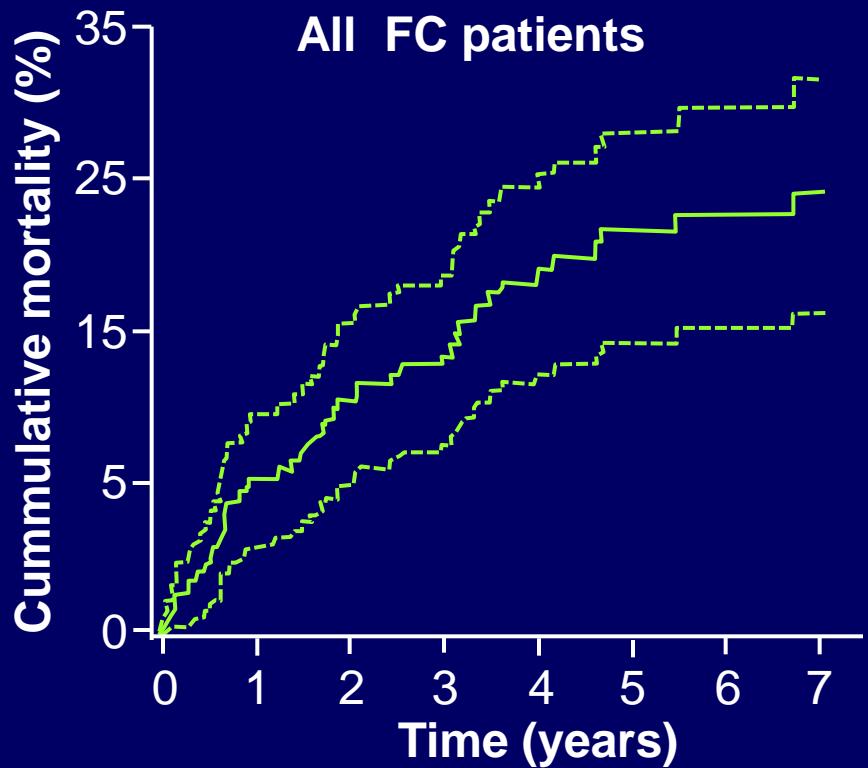
‡Baseline haemodynamics may be necessary in some ES patients. Repeat haemodynamics are not routinely recommended in ES

Survival benefits with advanced therapy

— No advanced therapies — Advanced therapies

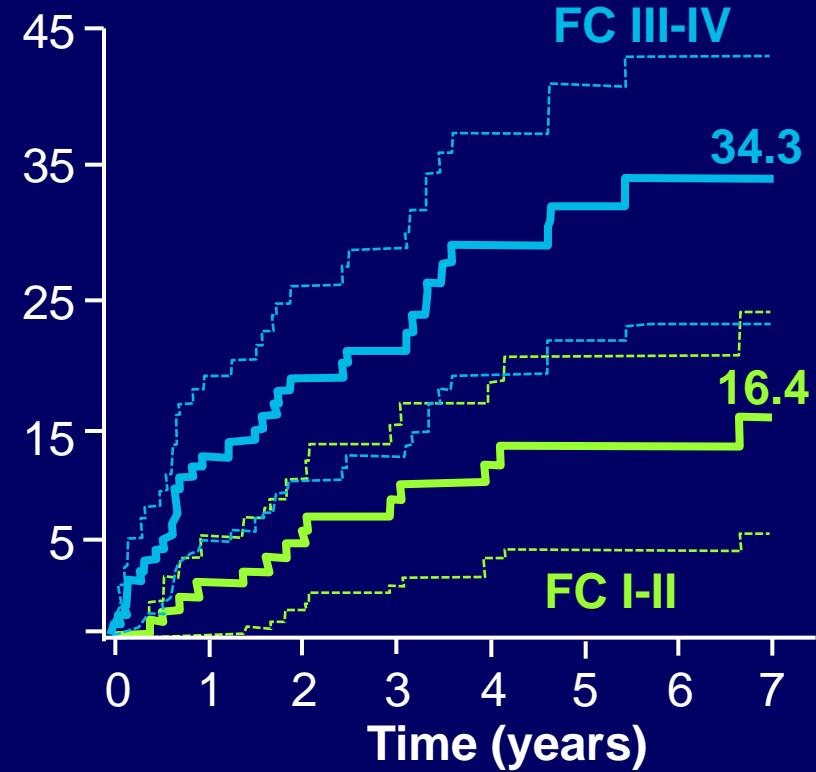


Contemporary survival in Eisenmenger syndrome: Relation to functional class



Patients at risk

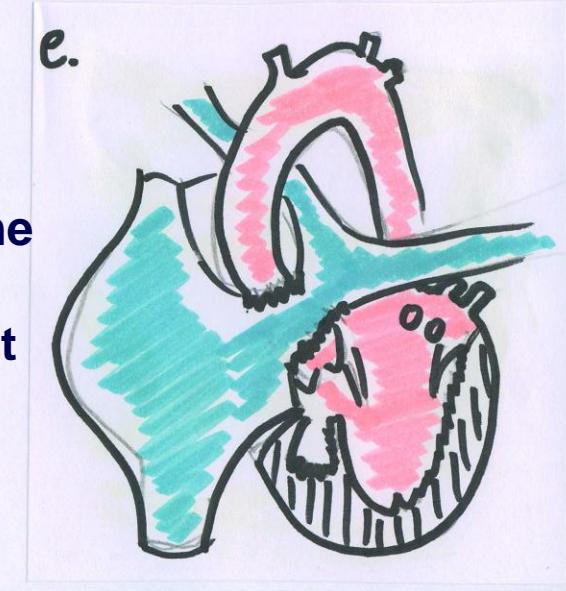
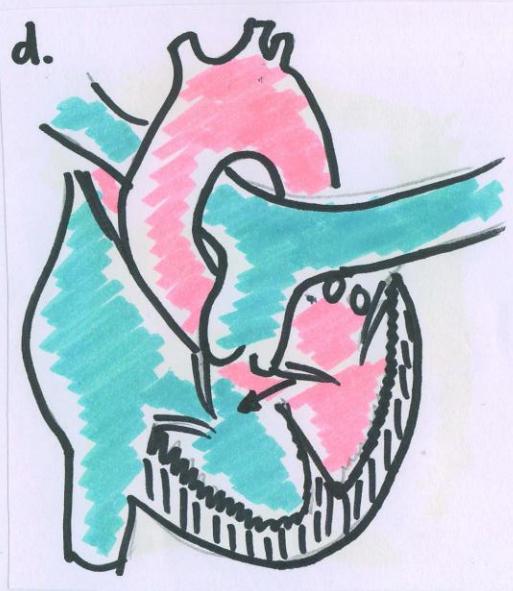
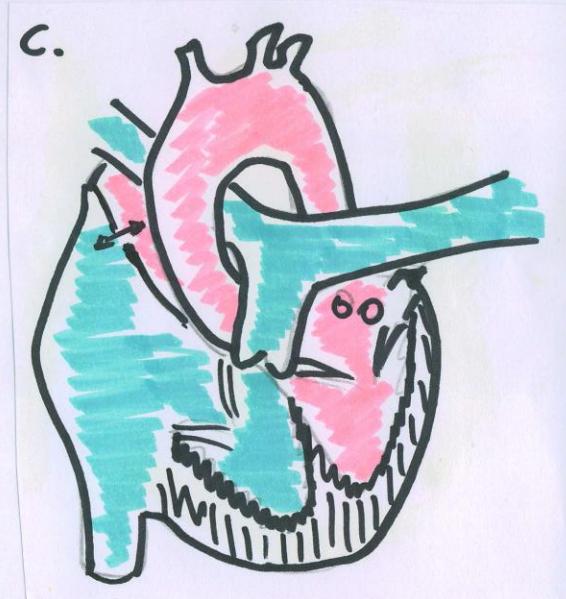
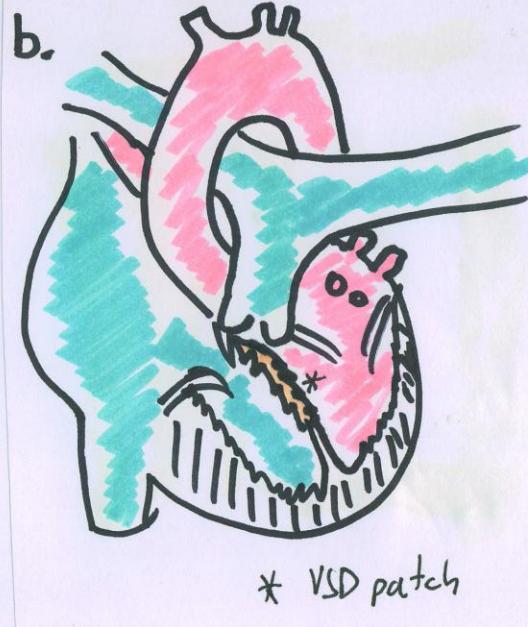
229 197 169 145 116 92 69 52



n 123 89 81 65 51 37 25 17

n 106 99 88 80 65 59 44 35

PAH-CHD Groups and Therapy



- a. Eisenmenger syndrome
- b. Operated shunt (VSD)
- c. PAH with a small shunt
- d. PAH with $L \rightarrow R$ shunt
- e. Fontan circulation

DISEASES OF THE HEART AND CIRCULATION

Second, revised and enlarged edition
Third impression

PAUL WOOD

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Physician, National Heart Hospital

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