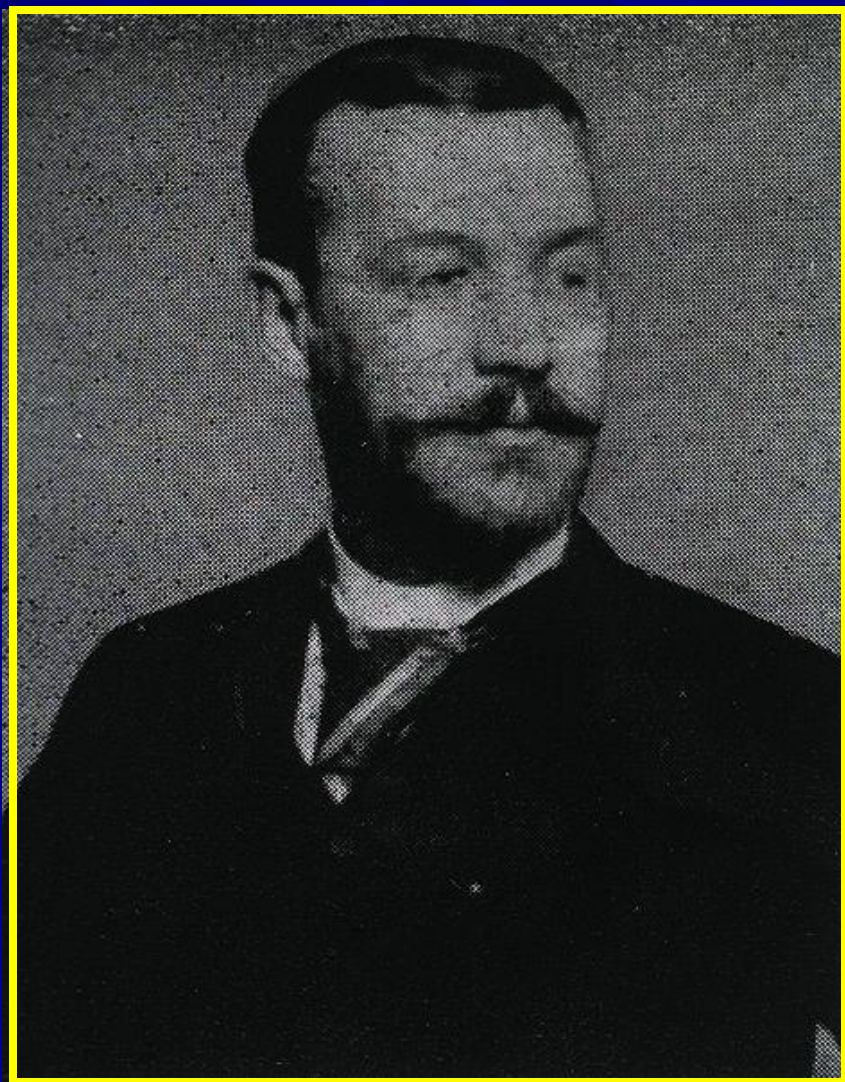
Eisenmenger Syndrome in Adults with Congenital Heart Disease

Amiram Nir, M.D.

Israel Association for Pediatric Cardiology Meeting
Ramot 2009

Victor Eisenmenger 1864-1932

- 1897 Victor Eisenmenger
- Irreversible pulmonary vascular disease in a 32 year old man with non-restrictive VSD



BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 27 1958

THE EISENMENGER SYNDROME

OR PULMONARY HYPERTENSION WITH REVERSED CENTRAL SHUNT*

BY

PAUL WOOD, O.B.E., M.D., F.R.C.P.

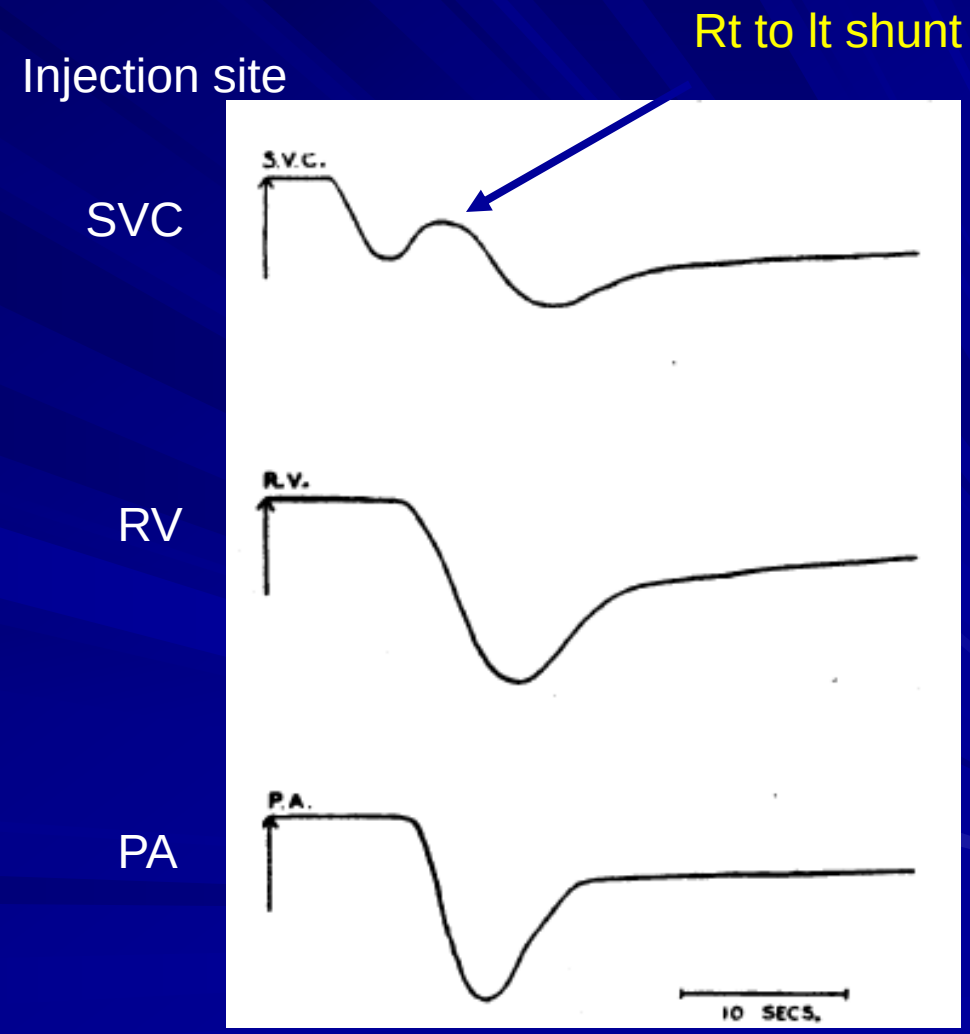
Director, Institute of Cardiology ; Physician, National Heart Hospital ; Physician-in-Charge, Cardiac Department, Brompton Hospital, London

- Paul Wood – 127 patients with Eisenmenger syndrome

BMJ 1958,ii:701-709

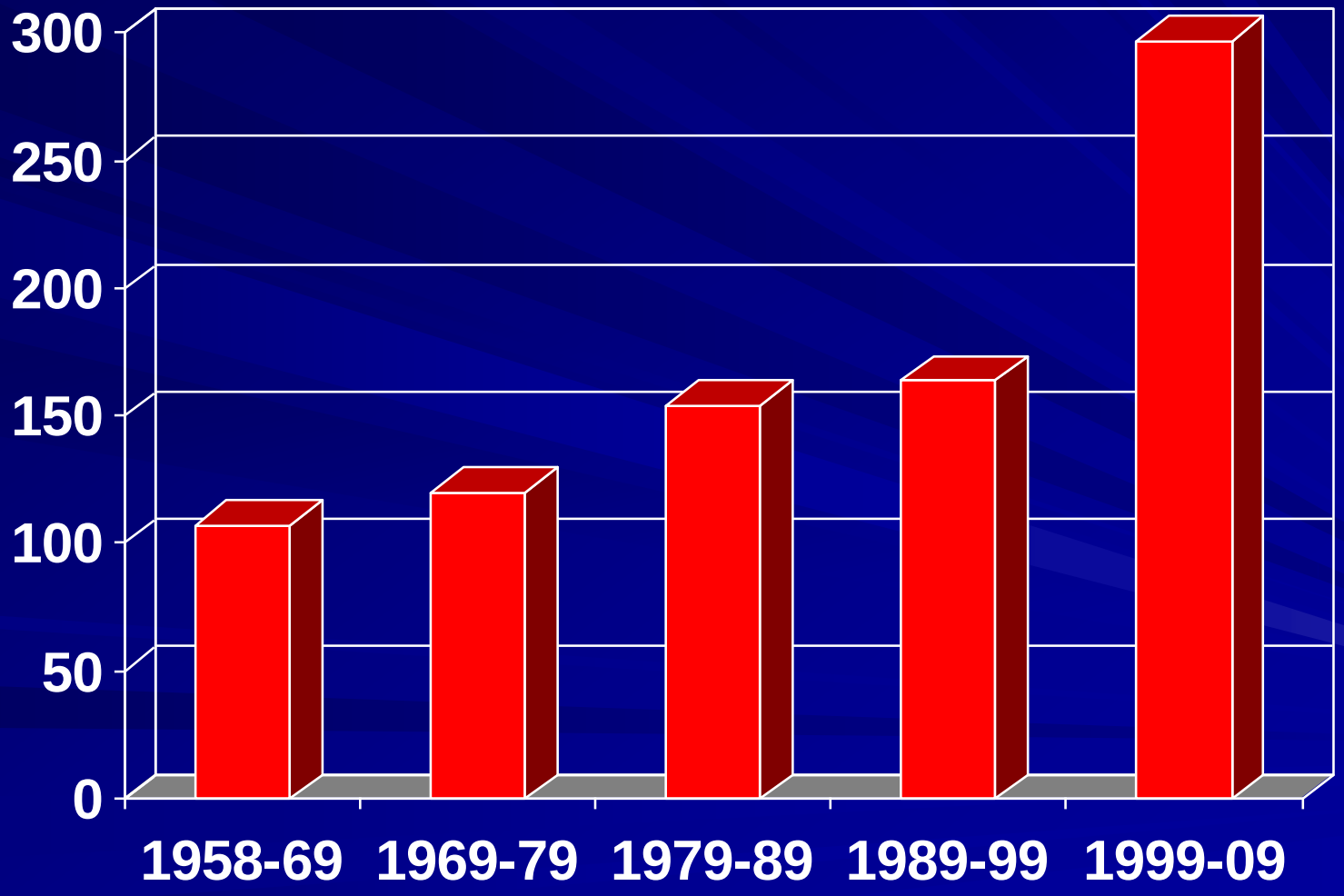
Eisenmenger syndrome cath

- 30 y old ASD
- Cardiogreen dye detection by modified ear detector as described by Swan et al. (1953)

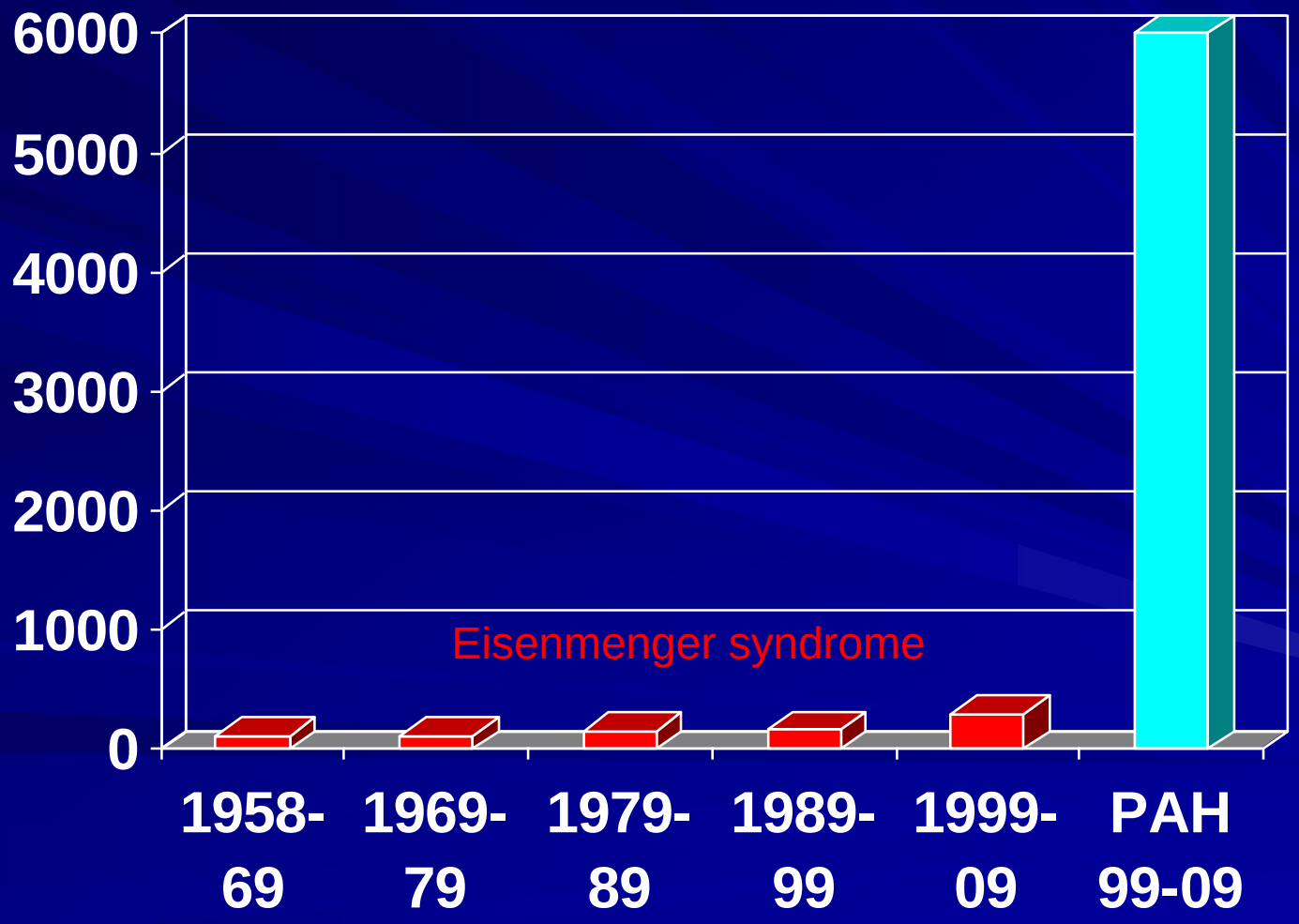


Wood P, BMJ 1958,ii:701-709

Eisenmenger syndrome publications



Eisenmenger syndrome and pulmonary hypertension publications



Risk for development of Eisenmenger syndrome

- 3% small-to-moderate VSDs (≤1.5 cm in diameter)
- Nearly 50% of large VSDs (>1.5 cm)

Kidd et al. second natural history study Circ 1993;87(suppl):138–151

Prevalence

- During the past 50 years, 50% less Eisenmenger syndrome in the Western world

Prevalence

- National Dutch registry of congenital heart disease (Dutch population 16M)
- 5970 registered adult with congenital heart disease
- 4.2% Pulmonary hypertension (n=250)
- 6.1% (n=112) of 1824 patients with septal defects
  - 65 pts - Eisenmenger syndrome
  - Estimated in Israel – 30 patients with Eisenmenger syndrome

Duffels Int J Cardiol. 2007;120:198

Eisenmenger syndrome by lesion

- n=171, 115 females 56 males
- Age 37±12 years (range 14–72 years)

- VSD 37%
- ASD 7%
- PDA 13%
- complex anatomy 44%
  - atrioventricular septal defects
  - Univentricular heart
  - TGA
  - Truncus arteriosus
- Down's syndrome 28%

Diller et al. European Heart Journal (2006) 27, 1737–1742

Eisenmenger Vs PAH

- Eisenmenger syndrome differs distinctly from other types of PAH
  - Cardiac anatomy
  - Physiology
  - Natural history

Dimopoulos et al. (Gazoulis) Current Opinion in Cardiology 2008, 23:545

Eisenmenger Vs PAH

- RV dysfunction is a major contributor to the adverse prognosis of patients PAH
- The RV in Eisenmenger syndrome is able to sustain an elevated afterload over a longer time
- In ASD the response of the RV resembles that of iPAH
  - Dilation
  - Progressive systolic dysfunction

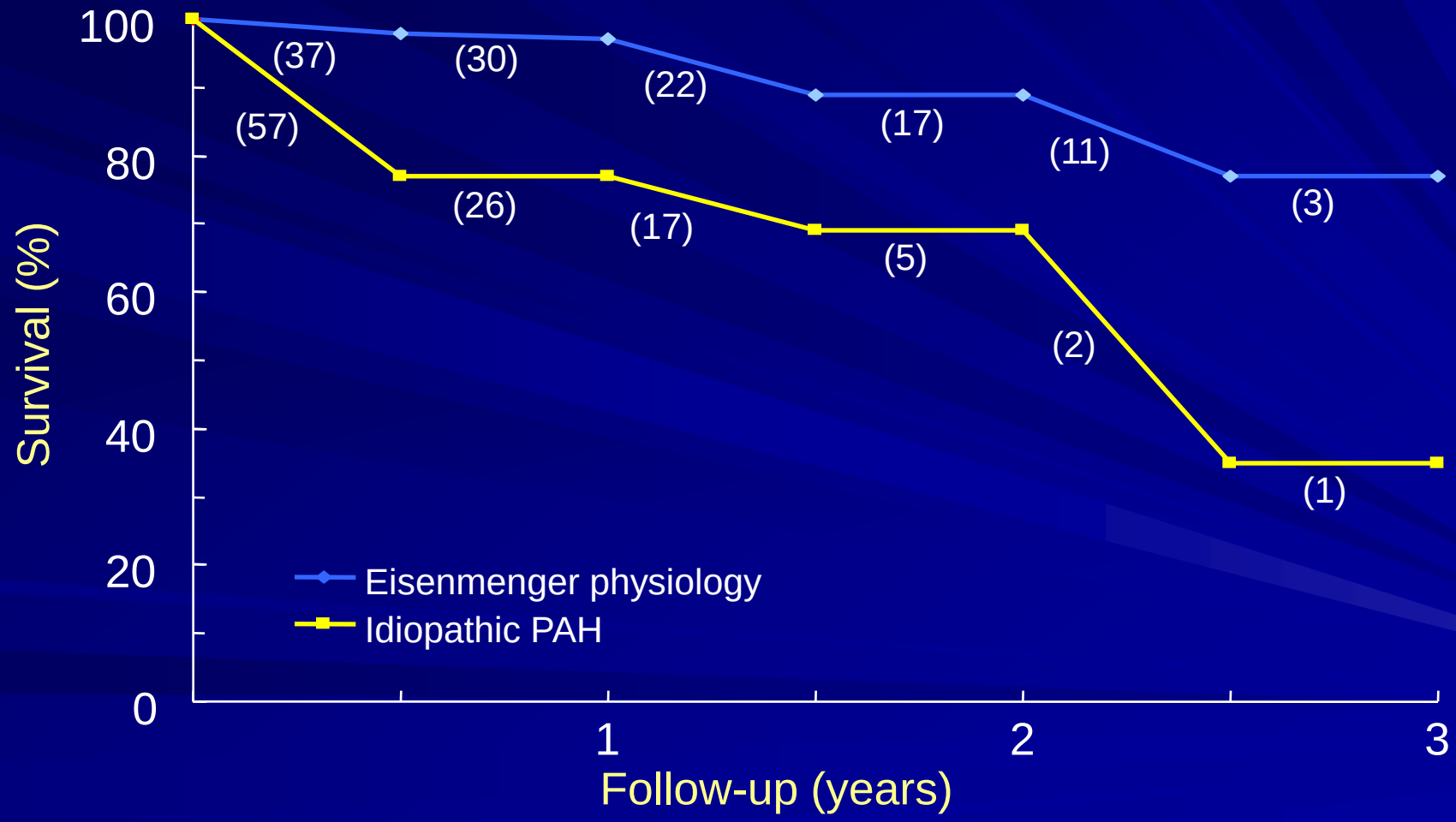
Dimopoulos et al. (Gazoulis) Current Opinion in Cardiology 2008, 23:545

Eisenmenger physiology

- Cyanosis rather than a drop in CO
- Shunting through the cardiac defect
  - Significant hypoxia
  - Increasing ventilation/perfusion (V/Q) mismatch
  - Exercise intolerance
  - Preservation of CO at rest and during mild–moderate exercise

Dimopoulos et al. (Gazoulis) Current Opinion in Cardiology 2008, 23:545

Survival: Eisenmenger syndrome vs. idiopathic PAH

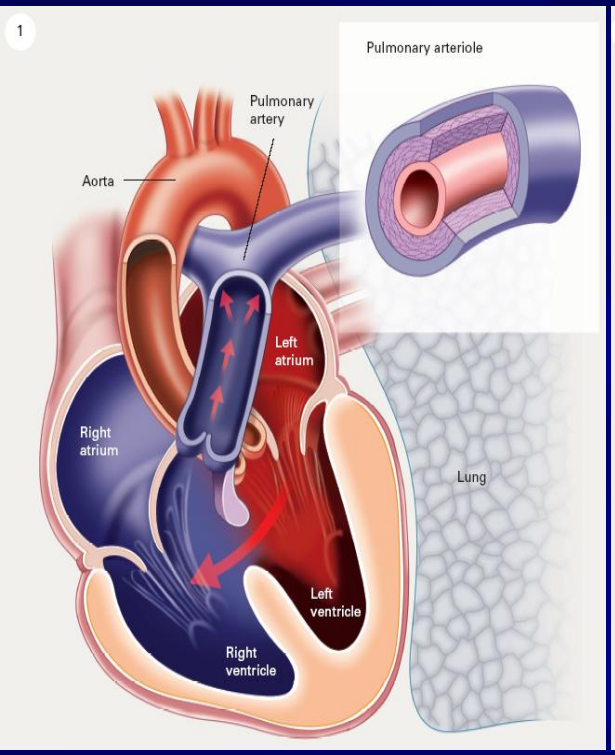


Hopkins WE, *et al. J Heart Lung Transplant* 1996;15:100

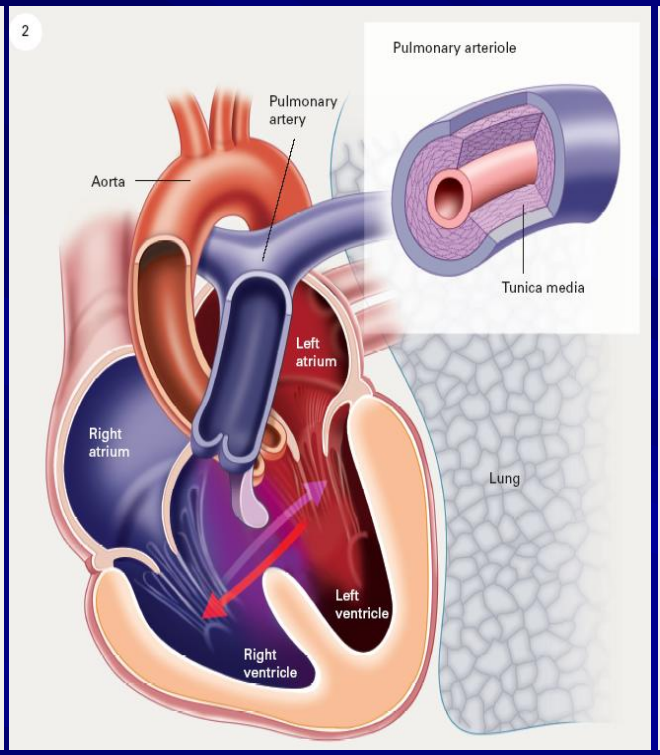
Stages in the development of Eisenmenger Synd

- Left to Right shunt
- Increased pulmonary blood flow
  - Shear stress
- Endothelial dysfunction and vascular remodeling
  - SMC proliferation
  - Increased extracellular matrix
  - Intravascular thrombi
- Increased PVR
- Inverted shunt
- Cyanosis – Eisenmenger syndrome

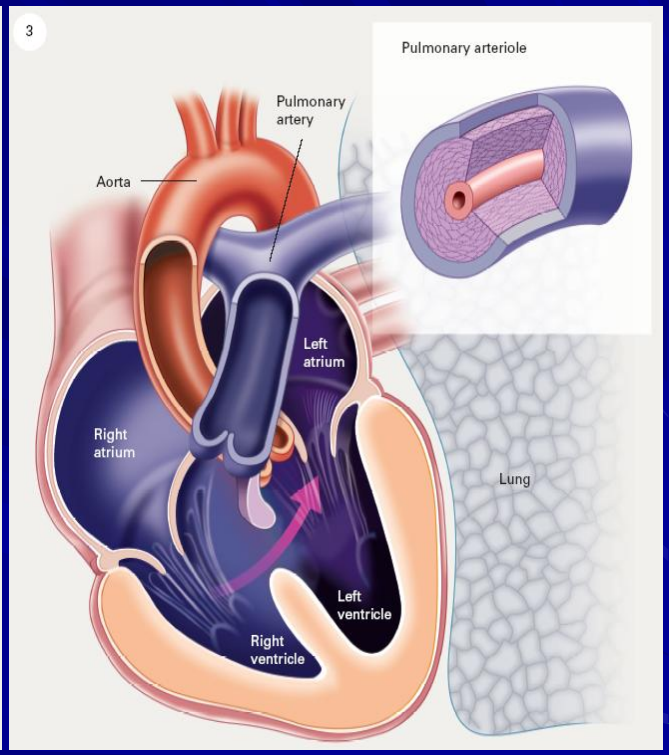
Evolution of Eisenmenger syndrome overview



ASD, VSD or complex defect increases pulmonary blood flow via left-to-right shunt



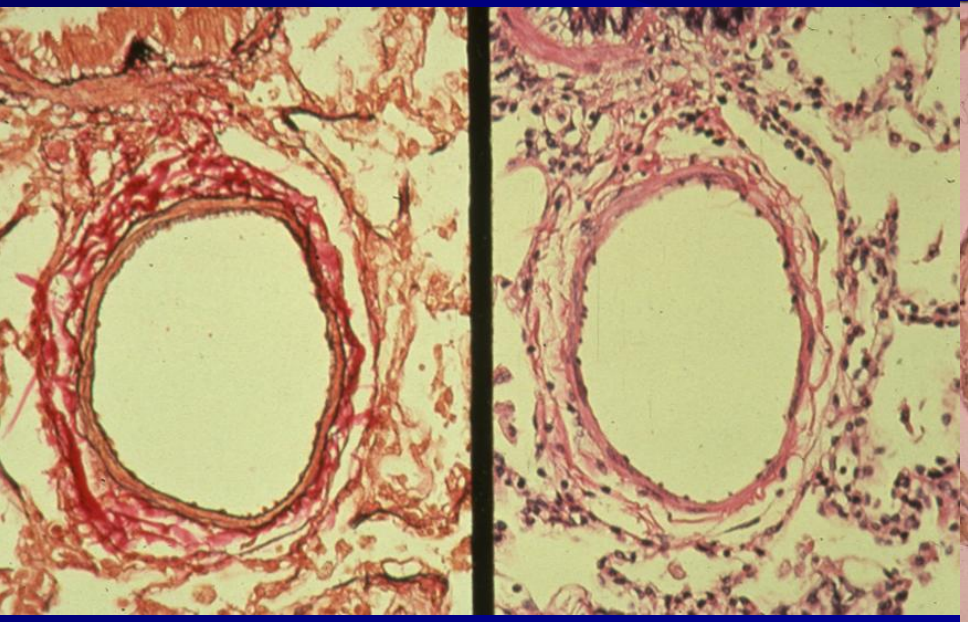
Pulmonary resistance rises and results in bi-directional flow



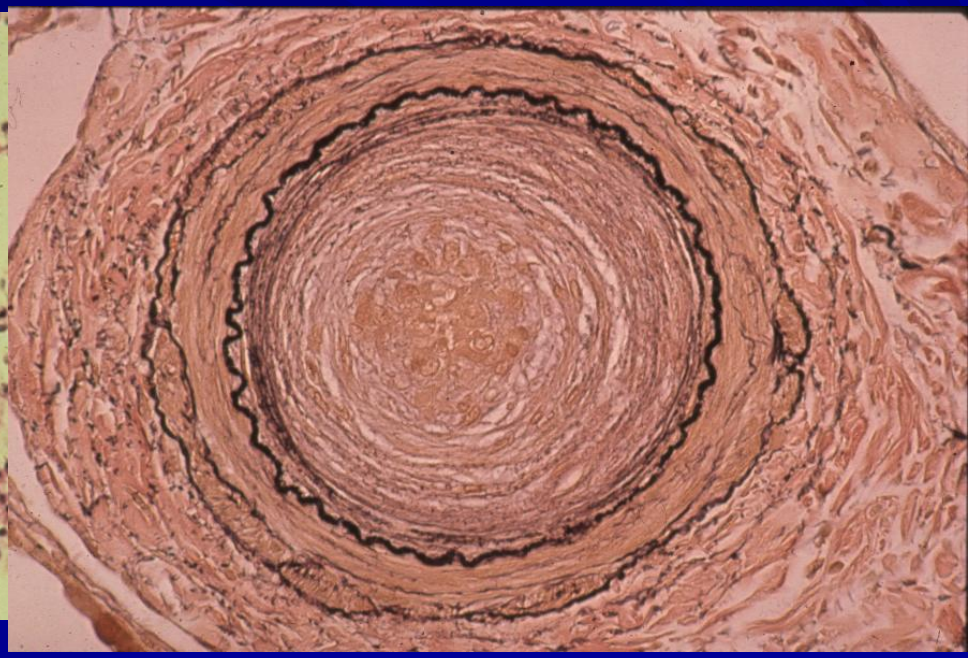
Reversal of shunt: right-to-left → Eisenmenger syndrome

Lung pathology

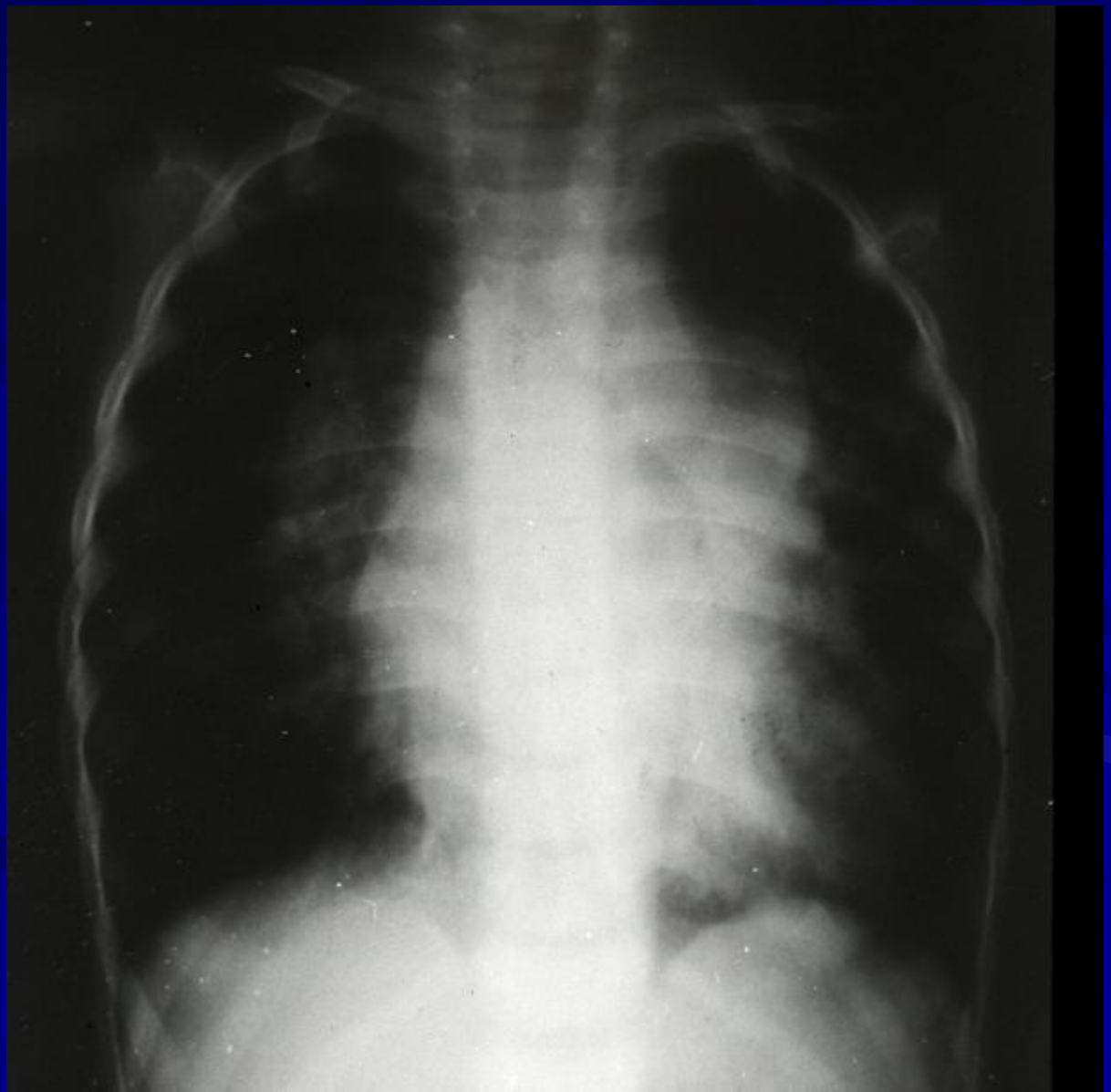
Normal pulmonary arteriols



Eisenmenger syndrome



Eisenmenger Syndrome

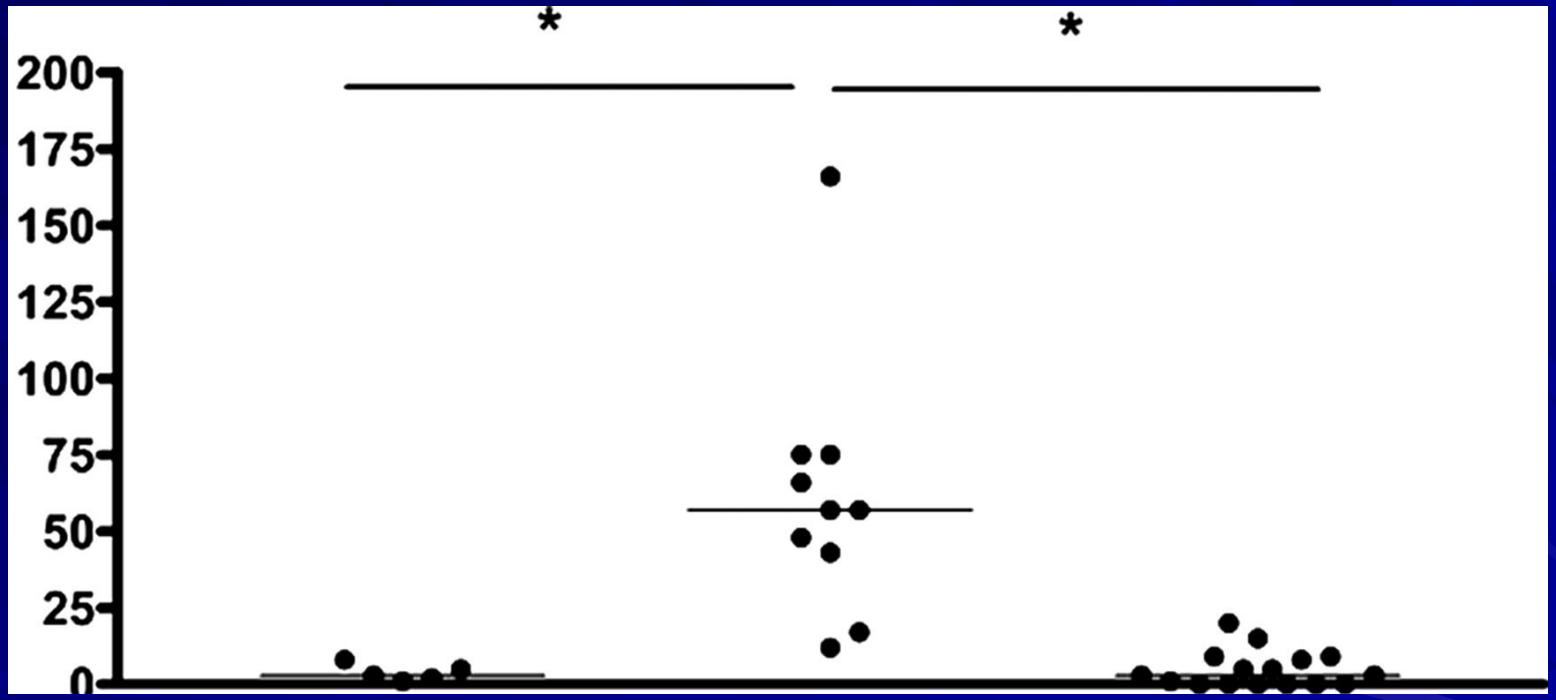


Possible mechanisms for pulmonary artery disease

- *Eisenmenger syndrome is likely* to be similar to iPAH
  - Loss of endothelial barrier function
  - Activation of the endothelin system
  - Decreased production of prostacyclin
  - Decreased production of nitric oxide
  - Increased inflammation mediators
  - Altered expression of potassium channels

Kumar and Sandoval, Cardiol Young 2009

Circulating endothelial cells in peripheral venous blood of CHD patients with PHT



Smadja, D. M. et al. Circulation 2009;119:374

Eisenmenger syndrome Clinical manifestations

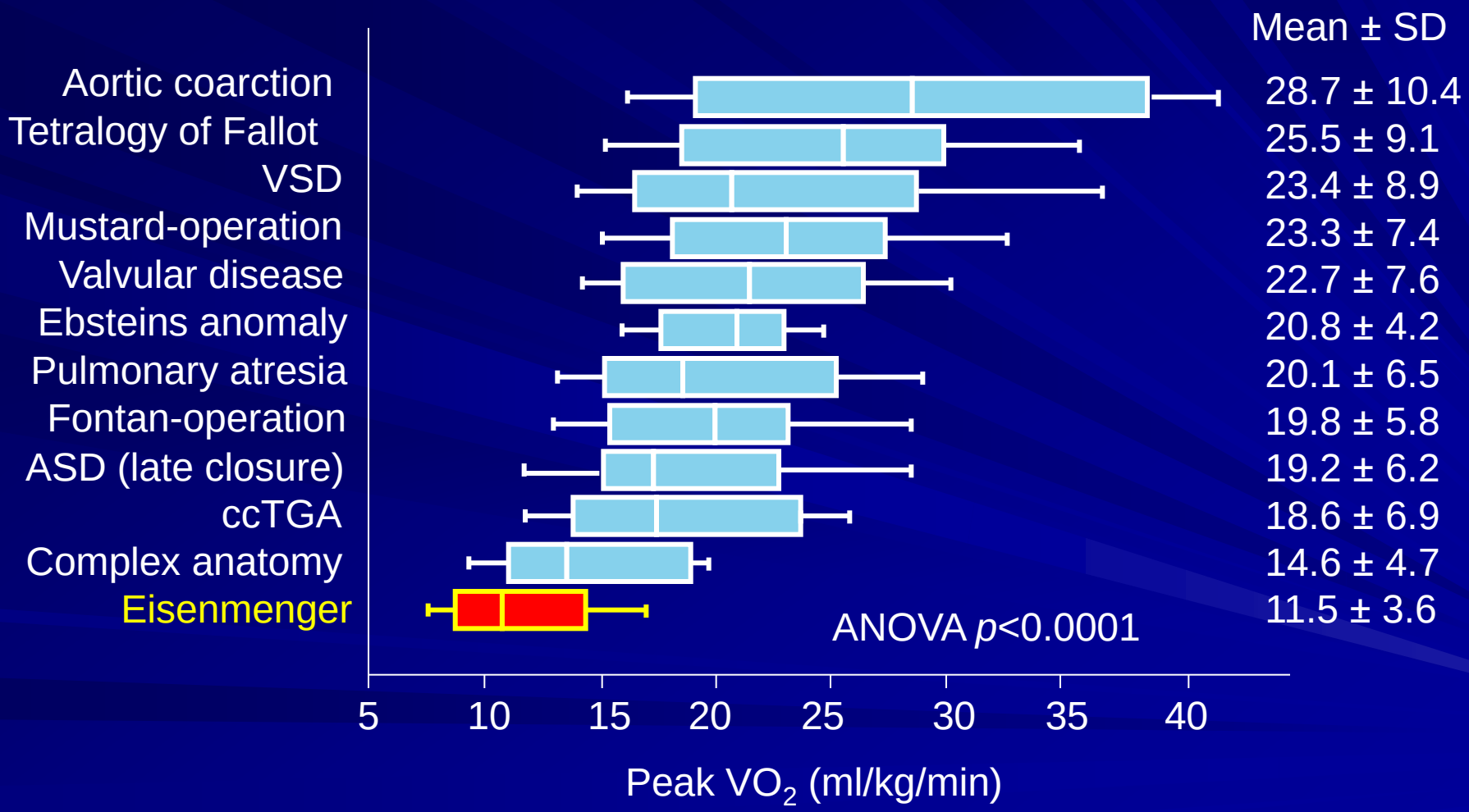
- Functional capacity
- Cyanosis
- Pulmonary vascular disease

Clinical manifestations

- Commonest: Exercise intolerance
- Other common symptoms
  - dyspnea
  - syncope
  - chest pain
  - Cyanosis
  - hemoptysis

Kumar and Sandoval Cardiol Young 2009; 19(E-Suppl. 1): 39–44

Exercise capacity in adults with CHD
Impact of underlying diagnosis



Diller GP, *et al. Circulation* 2005; 112:828-35.

Cyanosis
A multisystem Disorder

(Perloff's, CHD in the Adult, 2009)

Hyperviscosity symptoms

- Headache
- dizziness
- Slow mentation, irritability
- Blurred vision
- Parasthesias
- Tinnitus
- Fatigue
- Myalgias, Muscle weakness

Perloff's, CHD in the Adult, 2009

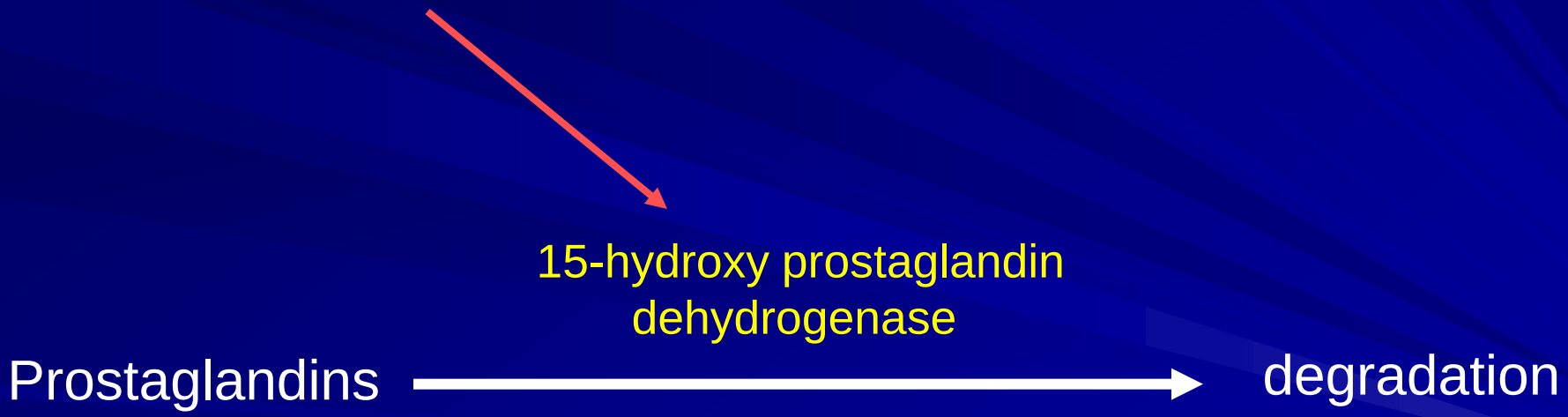
Hyperviscosity symptoms

- Bleeding tendency
- High bilirubin
  - Calcium bilirubinate gall stones
- Urate metabolism
  - Gouty arthritis
  - Osteoarthropathy – long bone pain and tenderness

Perloff's, CHD in the Adult, 2009

Clubbing and PGE_2

- Familial hypertrophic osteoarthropathy: mutation



Uppal et al. Nature Genetics, 2008;40:789

Clubbing and PGE_2

PG is taken down by the lung
right to left shunt results in less PG degradation

Cerebrovascular events in Eisenmenger syndrome

- 162 cyanotic adults
  - 45 Eisenmenger syndrome
- 8-year period
- 29 cerebrovascular events in 22 patients (13.6%)
- Risk factors for a cerebrovascular events
  - Hypertension
  - Atrial fibrillation
  - History of phlebotomy
  - Microcytosis (strongest predictor)

Mayo Clinic, JACC 1996;28:768

Renal changes with cyanosis

- Proteinuria (high hydraulic pressure)
- Dilated renal arteries and veins
- Enlarged, congested, hypercellular Glomeruli
- Renal failure is rare

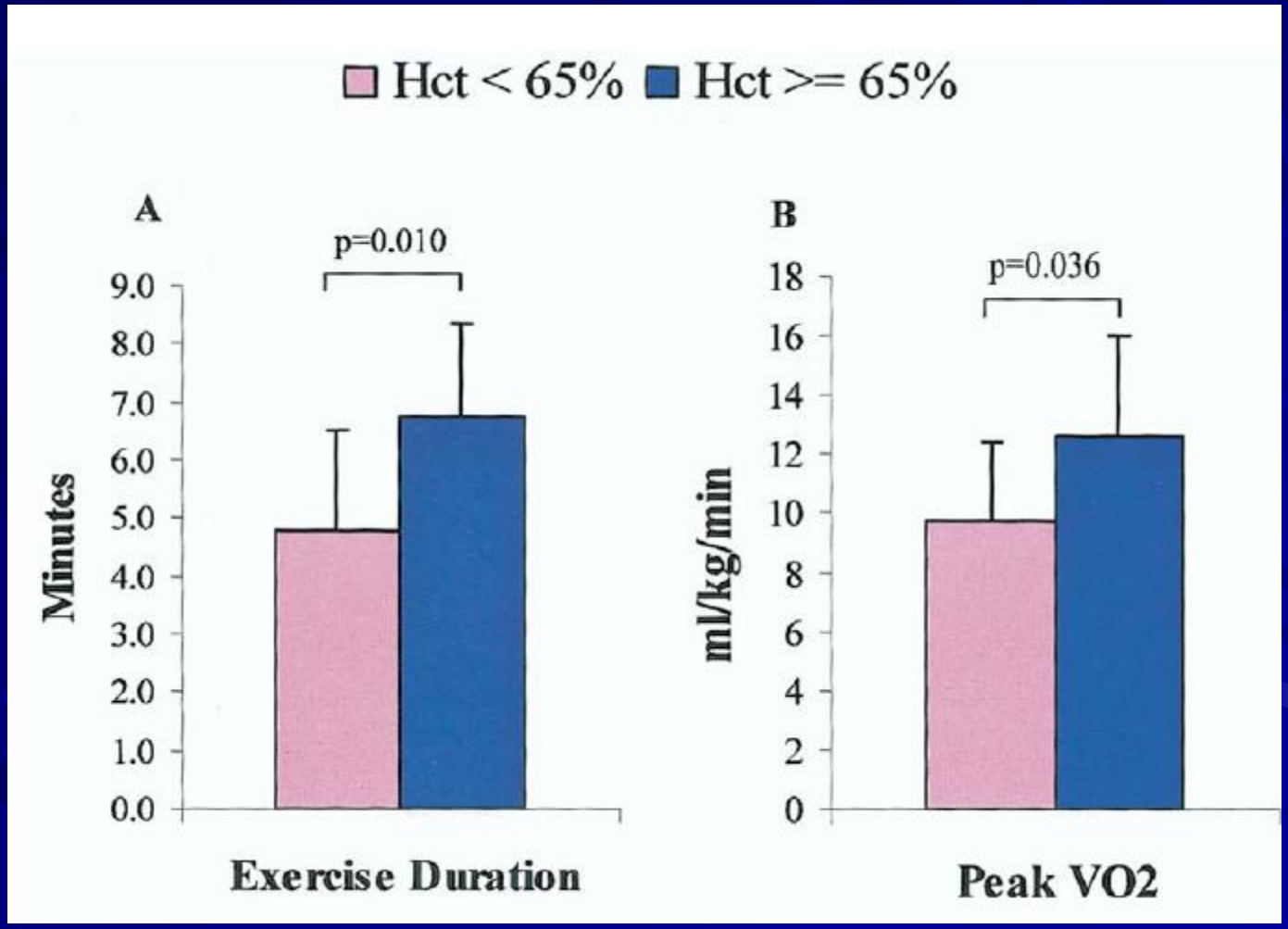
Perloff's, CHD in the Adult, 2009

Iron status

- >1/3 of adults with cyanotic CHD are iron-deficient
- Rarely sufficient to determine iron deficiency
  - Hemoglobin
  - Microcytosis
  - Hypochromia
- Measure serum ferritin and transferrin saturation

Perloff's, CHD in the Adult, 2009

Hct and exercise capacity



Broberg et al. JACC 2006;48:356–65

Patient assessment

Evaluation of patients with Eisenmenger Syndrome

- Every visit
  - O_2 sat
  - Echo
  - ECG
  - CBC
  - Serum ferritin and transferrin (if O_2 sat<90% or erythrocytosis)
  - Liver and renal fnxn, uric acid

Kumar and Sandoval Cardiol Young 2009

Evaluation of patients with Eisenmenger Syndrome

- First Visit
  - Chest X-ray
  - 6 min walk - 1st visit and as indicated

- Other tests
  - Pulmonary FT - if lung dis. Suspected
  - ABG – if lung dis. suspected
  - Exercise test + VO_2 - not routine
  - Catheterization (?)
  - CT/MRI (?)

Kumar and Sandoval Cardiol Young 2009

Treatment

Lifestyle

- Avoid dehydration
- Avoid frequent traveling or long commutes
- Avoid acute exposures to altitudes >2500 m
- Endocarditis prophylaxis
- Immunizations
- Avoid active or passive smoking

Kumar and Sandoval Cardiol Young 2009; 19(E-Suppl. 1): 39–44

Iron repletion

- Small dose (325 mg ferrous sulfate/d)
- Check after a week
- If Hct increases – stop
- Hydroxyurea – antitumor agent reduces cell proliferation – for iron repleted pts with high Hct (UCLA)
- Phlebotomy should be reserved for relief of symptoms of hyperviscosity

Perloff's, CHD in the Adult, 2009

Pregnancy

- pregnancy should be avoided
- Early termination of pregnancy is recommended
- Careful monitoring
- specialized follow-up of inevitable pregnancy

Class: I. Level of evidence: C.

Kumar and Sandoval Cardiol Young 2009; 19(E-Suppl. 1): 39–44

O_2 supplementation

- Routine use of long-term oxygen therapy cannot be recommended
- Selected patients with associated lung pathology may benefit from oxygen inhalation

Class: IIb. Level of evidence: B

Sandoval et al. Am J Respir Crit Care Med 2001;164:1682

Pulmonary hemorrhage and thrombosis

- Anticoagulation (warfarin) controversial
  - Boston yes Landzberg, Clin Chest Med 28 (2007) 243–253
  - UCLA no Perloff's, CHD in the Adult, 2009
- Possible reasons to anticoagulate
  - Marked blood hyperviscosity
  - Pulmonary arterial thrombosis
  - Chronic atrial flutter or fibrillation

Air Travel and Adults With Cyanotic Congenital Heart Disease

N=10	PO_2	pH	PCO_2
Sea level	44±12	7.39±0.21	35±2.6
Max altitude	45±7	7.35±0.25	36±2.3
Sea level	46±12	7.37±0.20	36±2.6

Harinck, et al. Circ. 1996;93:272-276

Air Travel and Adults With Cyanotic Congenital Heart Disease

- Cyanotic patients should not be discouraged from flying
- No need for O_2 during flight
- Drink – avoid dehydration
- Move – avoid deep vein thrombosis

Perloff's, CHD in the Adult, 2009

Heart failure Rx

- No data
- Digitalis and diuretics are often used in cases with cardiac failure
- It may have an effect on an individual patient basis

Dimopoulos et al. (Gazoulis) Current Opinion in Cardiology 2008, 23:545

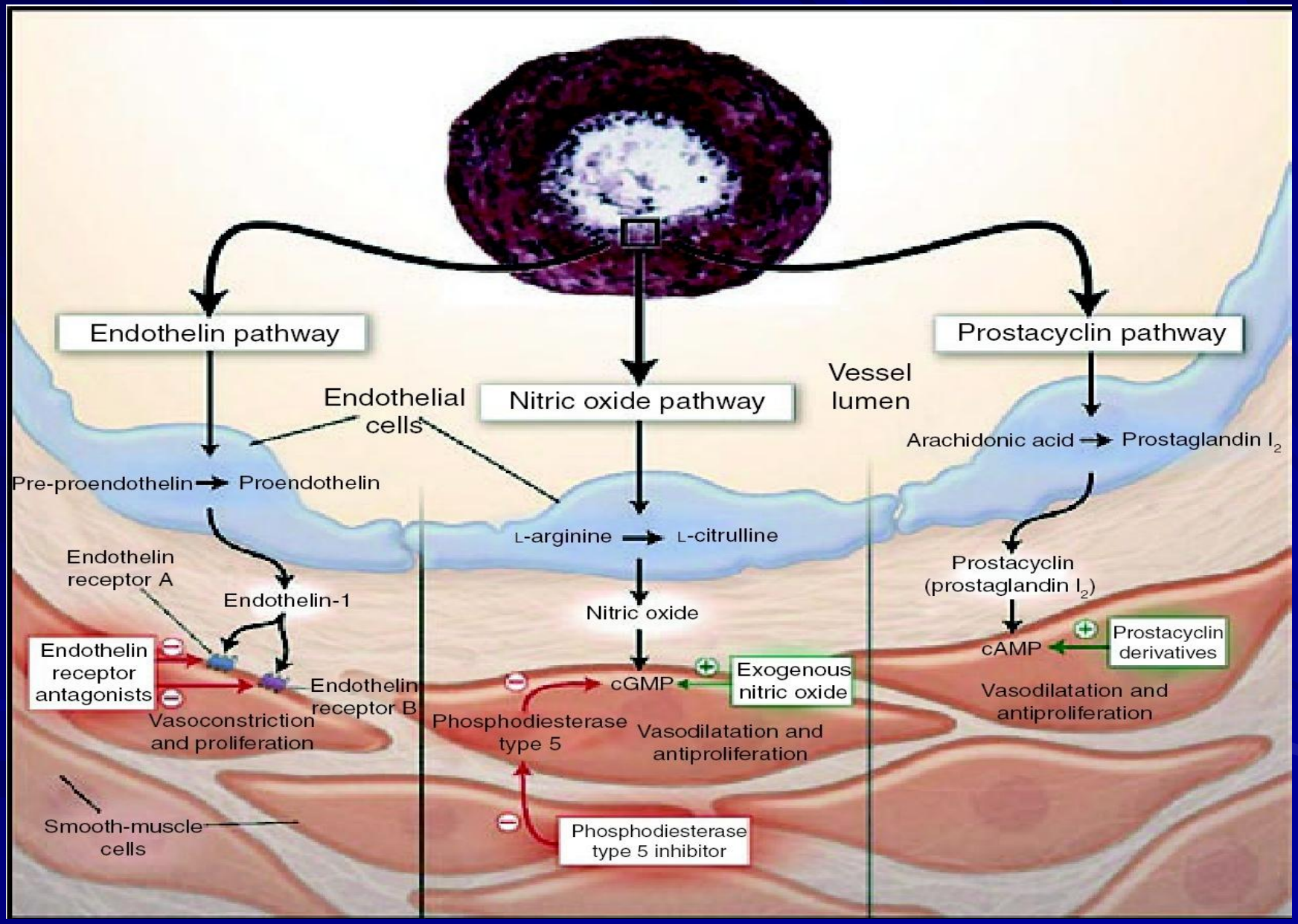
Targeted drug therapy

- The currently available therapies have been evaluated mainly in patients with the idiopathic or other forms of PHT
- Extrapolation to the Eisenmenger syndrome, should be made with caution

Class: I. Level of evidence: A

Kumar and Sandoval Cardiol Young 2009; 19(E-Suppl. 1): 39–44

Pathogenic Pathways and Treatment Targets in PAH



Humbert M et al: *N Eng J Med* 2004; 351: 1425-1436

Target drug therapy

- Prostanoids
  - Intravenous: Epoprostenol, Treprostinil
  - Subcutaneous: Treprostinil
  - Nebulised: Iloprost, *Treprostinil*
- Endothelin receptor antagonisnts
  - Bosentan (A+B)
  - Sitaxentan (A)
  - *Ambrisentan (A)*
- Phosphodiesterase 5 inhibitors
  - Sildenafil
  - Tadalafil

What is the evidence in Eisenmenger syndrome?

Epoprostenol

ref	n	Study population	Study design	Follow-up	6MWTD change	Hemodynamics
Fernandes 2003	8	ES	retro	3m	+299m	improved
Rosenzweig 1999	20	CHD-related	retro	1y	No change	improved

Dimopoulos et al. Current Opinion in Cardiology 2008, 23:545

Bosentan (12 studies)

ref	n	Study population	Study design	Follow-up	6MWTD change	Hemodynamics
Breathe 5 2006	54	ES	Multi cent,rand db, pc	4m	+43m	imp
Breathe 5 OL 2008	37	ES	Open label	40w	+61	NA
Schulze-Neick 2005	33	CHD-related	Multi op.label, pros	2.1y	+72	No change
D'Alto 2007	22	CHD-related	Op-label, sing arm, pros	12m	+67	imp
Christensen 2004	9	CHD-related	retro	9.5m	NA	NA
Gatzoulis 2005	10	ES	Pilot open label	3m	+99	imp

Dimopoulos et al. (Gazoulis) Current Opinion in Cardiology 2008, 23:545

Bosentan cont.

ref	n	Study population	Study design	Follow-up	6MWTD change	Hemodynamics
Apostolopoulou 2007	19	CHD-related	Pros, non-random	2y	No change	No change
Diller 2007	18	CHD-related	retro	29m	+79m	NA
Kotlyar 2006	23	ES	Retro, uncontr Observat.	15m	No change	NA
van Loon 2007	30	CHD-related	Retro, uncontr Observat	2.7y	No change	NA
Benza 2006	24	CHD-related	Open label	12m	+31	imp
Sitbon 2006	27	CHD-related	retro	15m	+66	Trend to imp

Dimopoulos et al. (Gazoulis) Current Opinion in Cardiology 2008, 23:545

Phosphodiesterase 5 inhibitors

ref	n	Study population	Study design	drug	Follo w-up	6MWTD change	Hemody namics
Mukhop adhyay 2006	16	ES	Pros, non-random, observ.	Tadalafil	3m	+43m	imp
Chau 2007	7	ES	Pro, op. label	Sildenafil	6 m	No change	imp
Singh 2006	10	ES	Rand, db Plac.contr crossover	Sildenafil	1.5 m	+98m	imp

Dimopoulos et al. (Gazoulis) Current Opinion in Cardiology 2008, 23:545

BREATHE-5

- Objectives
- To evaluate in a randomized controlled trial in patients with Eisenmenger syndrome the effects of bosentan on:
  - Overall shunting (SpO_2)
  - Cardiopulmonary hemodynamics (PVRi)
  - Exercise capacity (6MWD)

Galiè N, *et al. Circulation* 2006; 114:48-54

BREATHE-5

- PAH related to Eisenmenger syndrome
- Male or female ≥ 12 yrs
- WHO Class III
- 6MWD ≥ 150 m, ≤ 450 m
- Stable ≥ 3 months

- PDA excluded (for hemodynamic assessment difficulties)

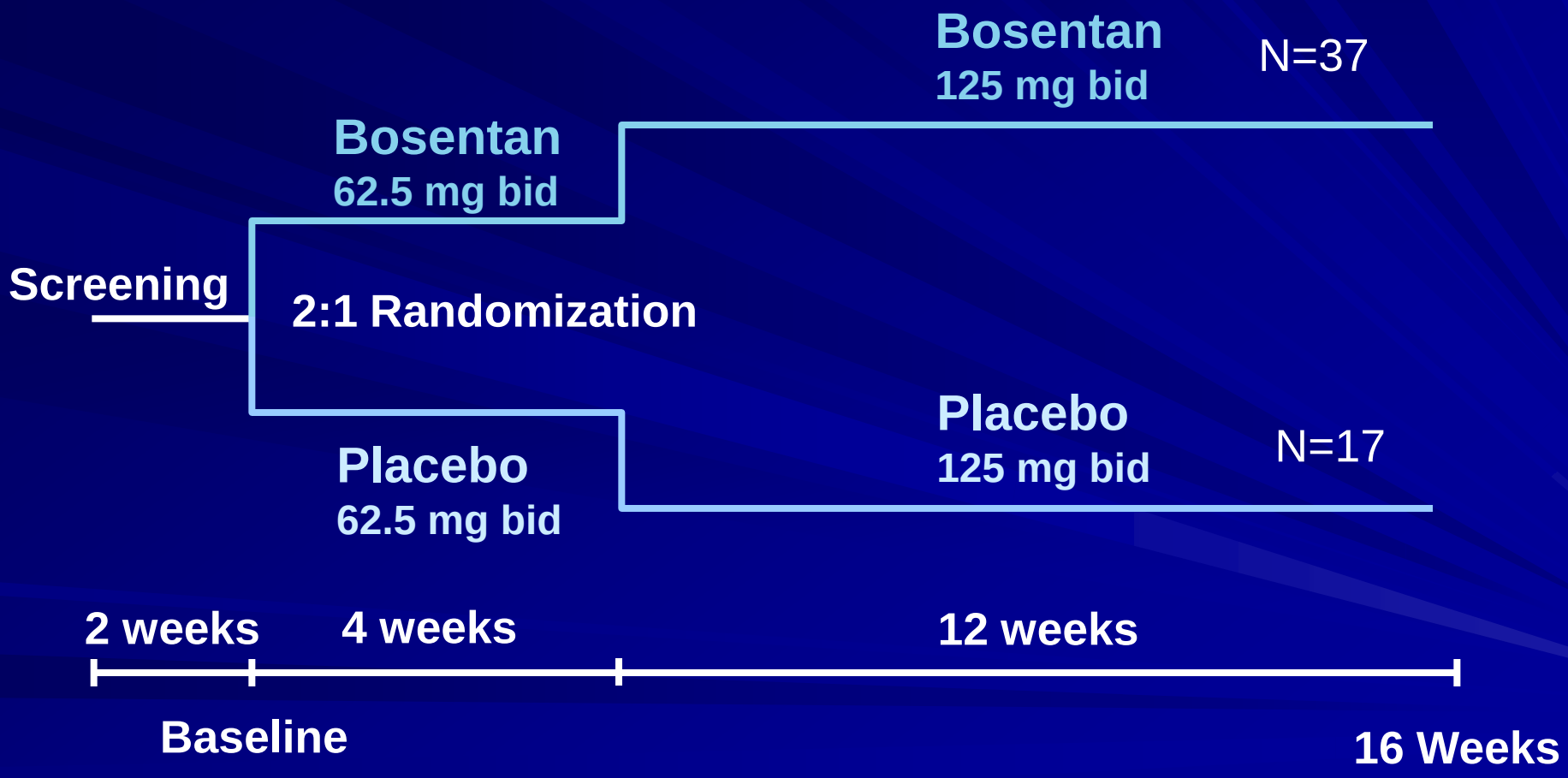
Galiè N, *et al. Circulation* 2006; 114:48-54

BREATHE-5 congenital heart disease

- **Placebo**
  - **ASD** **5**
  - **VSD** **15**
- **Bosentan**
  - **ASD** **8**
  - **VSD** **24**
  - **ASD + VSD** **5**

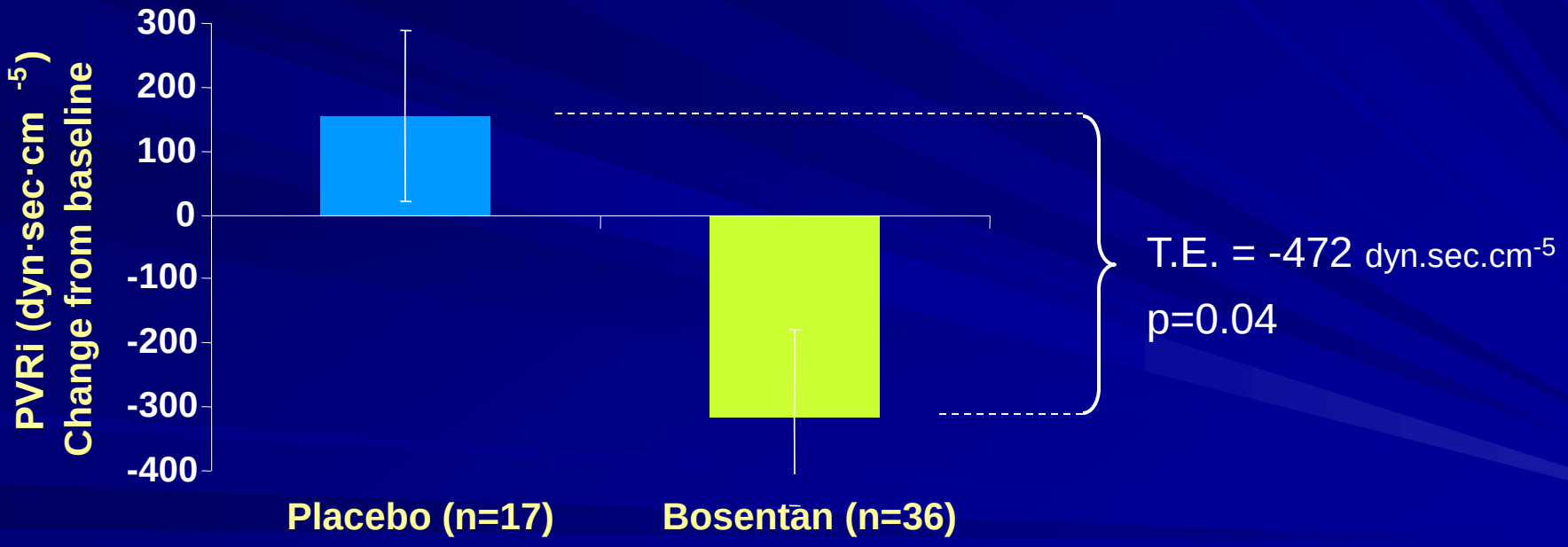
Galiè N, *et al. Circulation* 2006; 114:48-54

BREATHE-5 Study design



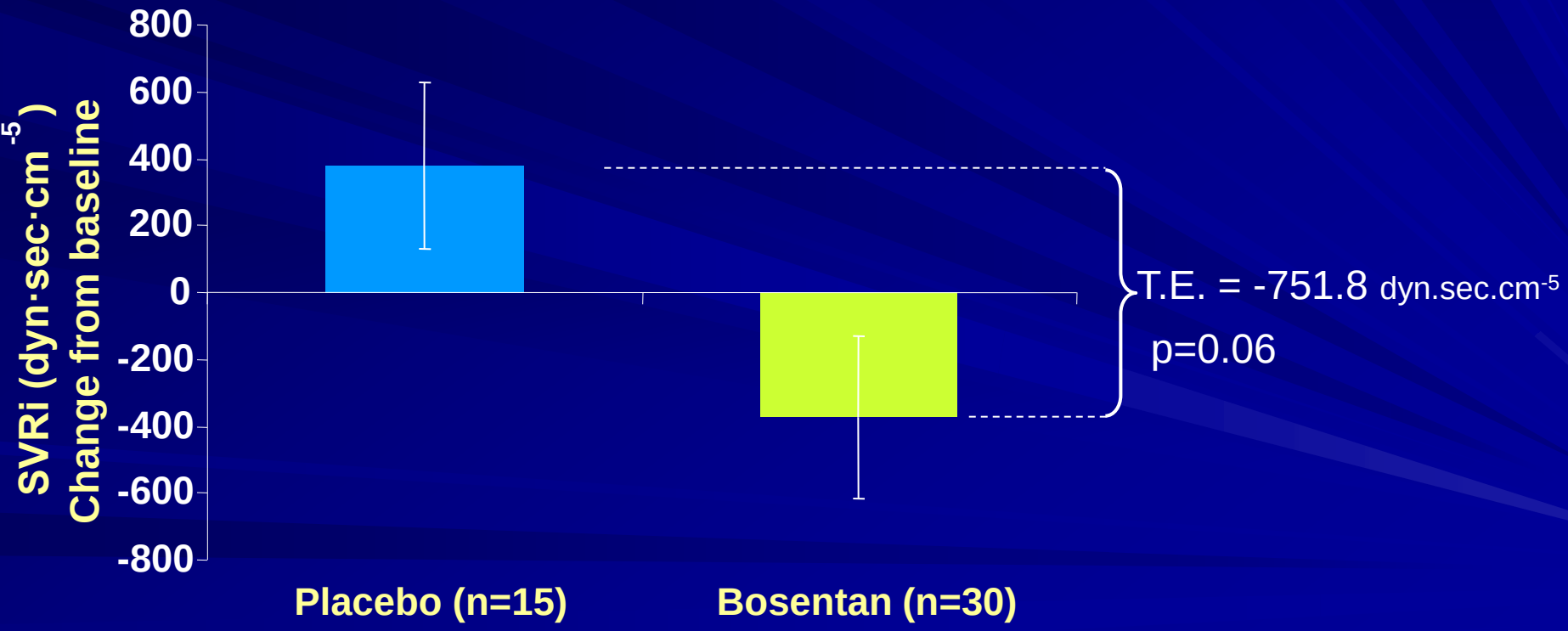
Galiè N, *et al. Circulation* 2006; 114:48-54

BREATHE-5 pulmonary vascular resistance index



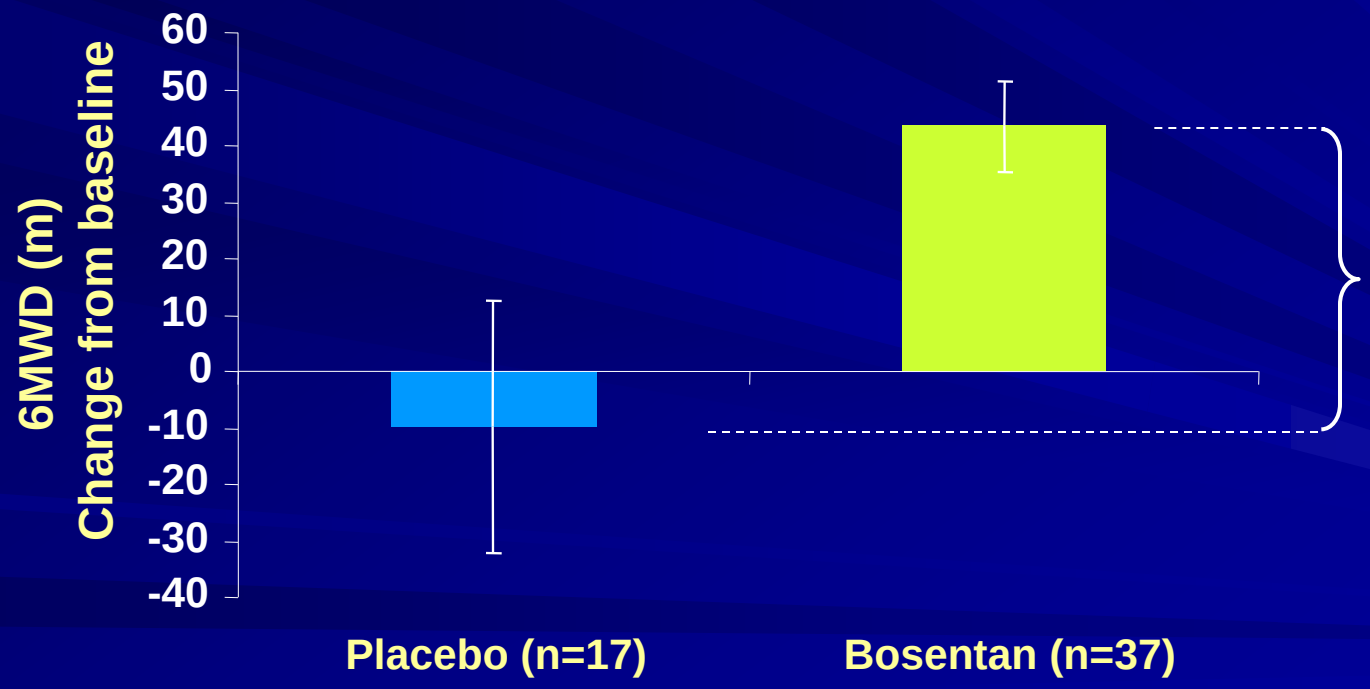
Galiè N, *et al. Circulation* 2006; 114:48-54

BREATHE-5 Systemic vascular resistance index - Change from baseline



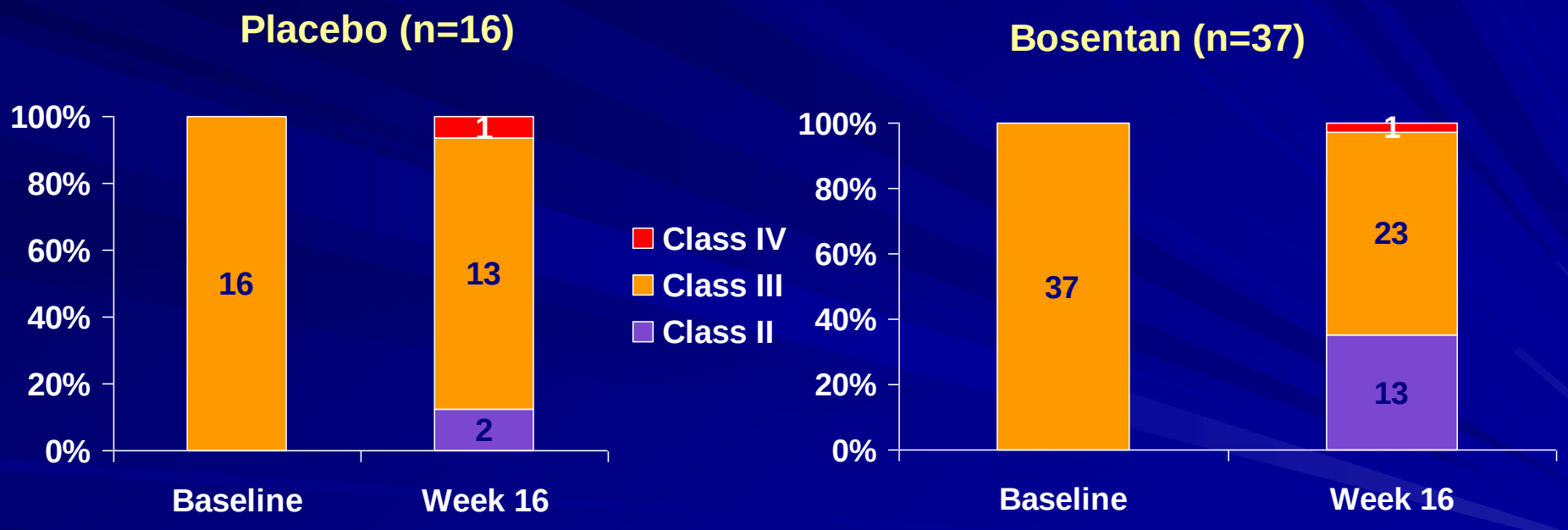
Galiè N, *et al. Circulation* 2006; 114:48-54

BREATHE-5
6 MIN WALK



Galiè N, *et al. Circulation* 2006; 114:48-54

BREATHE-5
WHO functional class



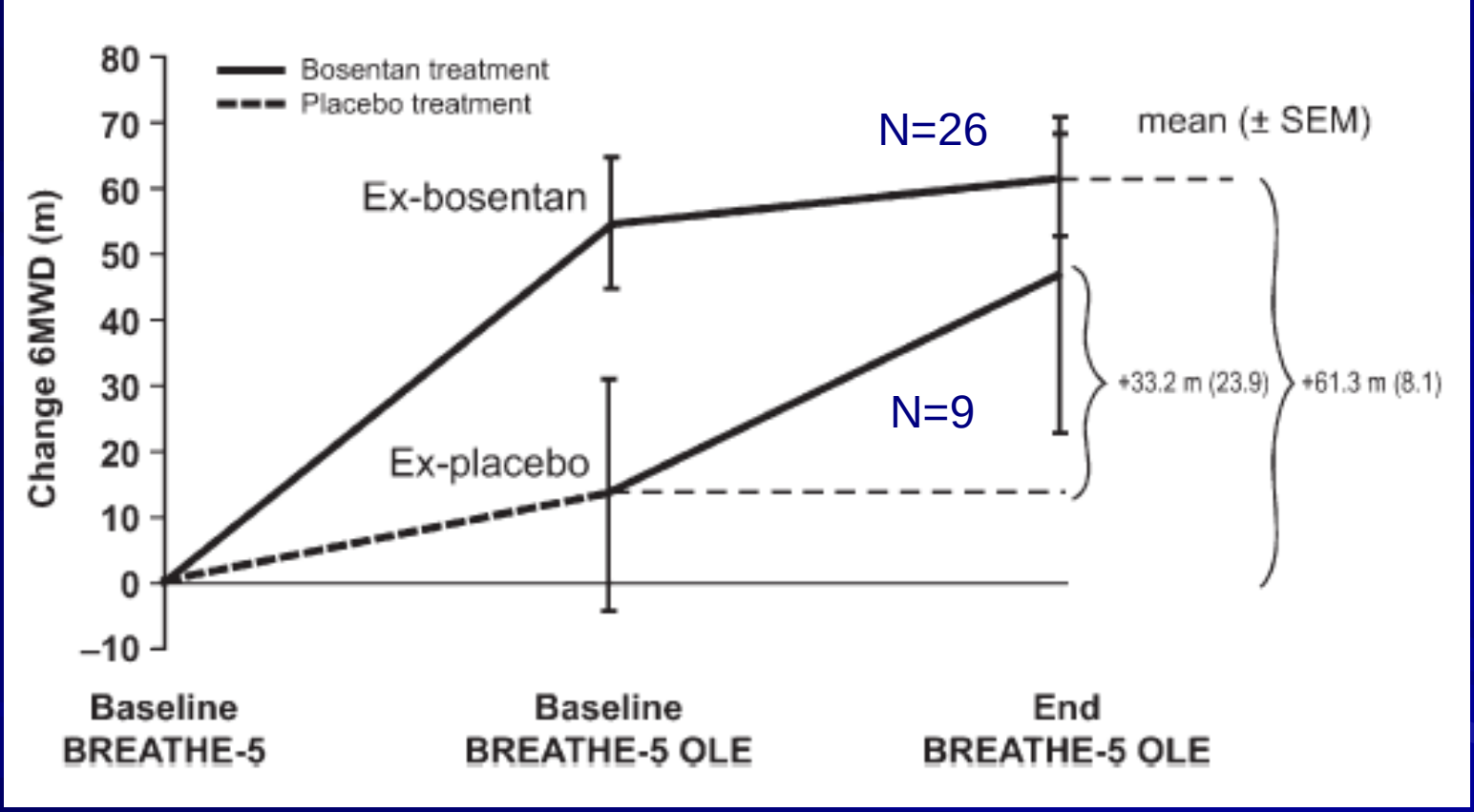
Galiè N, *et al. Circulation* 2006; 114:48-54

BREATHE-5 Summary

- Bosentan
  - Does not reduce systemic oxygen saturation
  - Significantly improved exercise capacity (6MWD)
  - Significantly reduced pulmonary vascular resistance (PVRi)
  - Safety profile consistent with previous prospective clinical trials in other forms of PAH

Galiè N, *et al. Circulation* 2006; 114:48-54

Breathe 5 open label



16w 40w

Gatzoulis et al. Int J Cardiol 2008;127: 27

Sildenafil

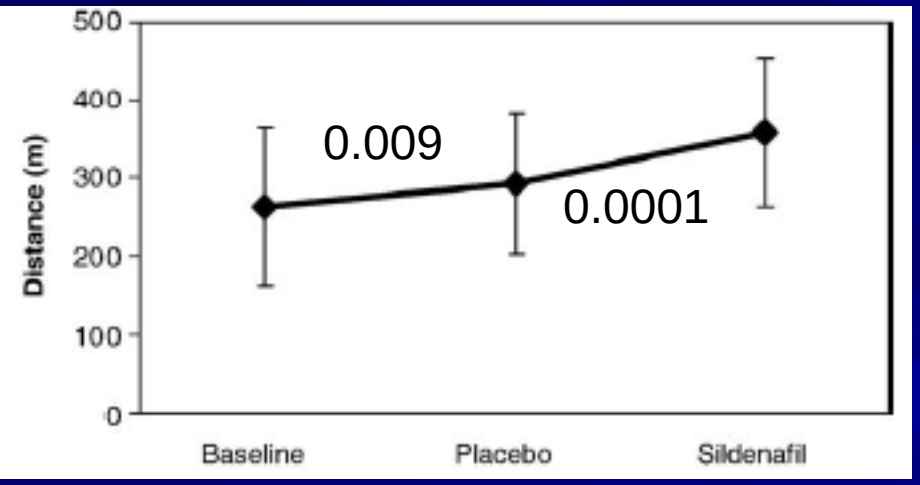
- Randomized placebo-controlled cross-over
- 10 Eisenmenger & 10 iPAH
- Dose: 100 mgx3/d
- Treatment for 6 weeks
- Washout for 2 weeks
- No difference between Eisenmenger and iPAH

Singh et al. Am Heart J 2006; 151:e85.

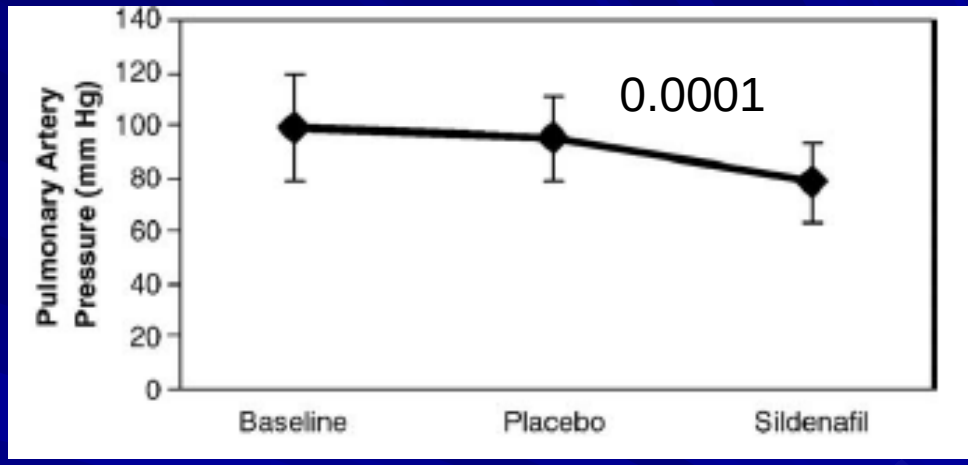
Sildenafil

Randomized placebo-controlled cross-over

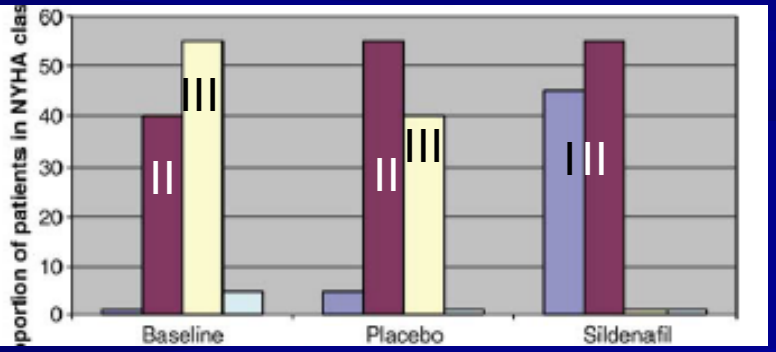
6MW



PAP



NYHA class



Singh et al. Am Heart J 2006; 151:e85.

Combination therapy

- Small studies of iPAH patients
  - Sildenafil on top of Bosentan (Grounig et al. J Clin Pharmacol. 2009)
  - Tadalafil on top of Bosentan – greater effect on bosentan-naive patients (Galiè et al. Circulation 2009)

Acute effect of sildenafil on top of Bosentan

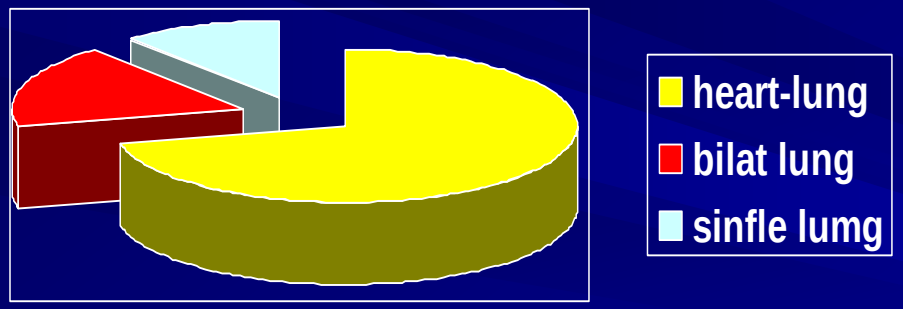
- 45 patients (>/=18 years) with stable PAH
  - Idiopathic
  - Familial
  - CHD
  - Drugs or toxins
- On bosentan treatment for at least 3 months
- A significant (-15%) decrease from baseline in mean PVR 60 minutes following sildenafil administration (cath)

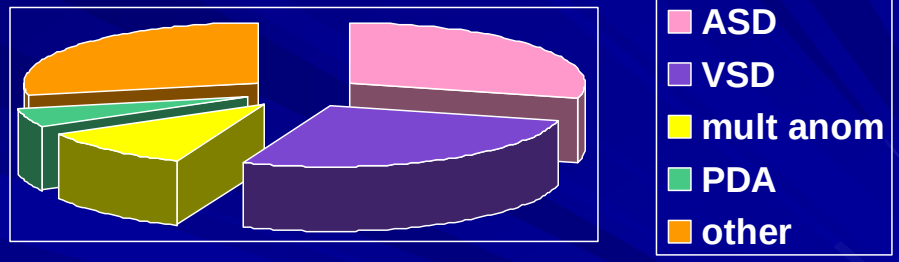
Bach et al. J Clin Pharmacol. 2009 Sep 15

No data on the effect of targeted therapy on survival

Transplantation

Transplantation for Eisenmenger syndrome

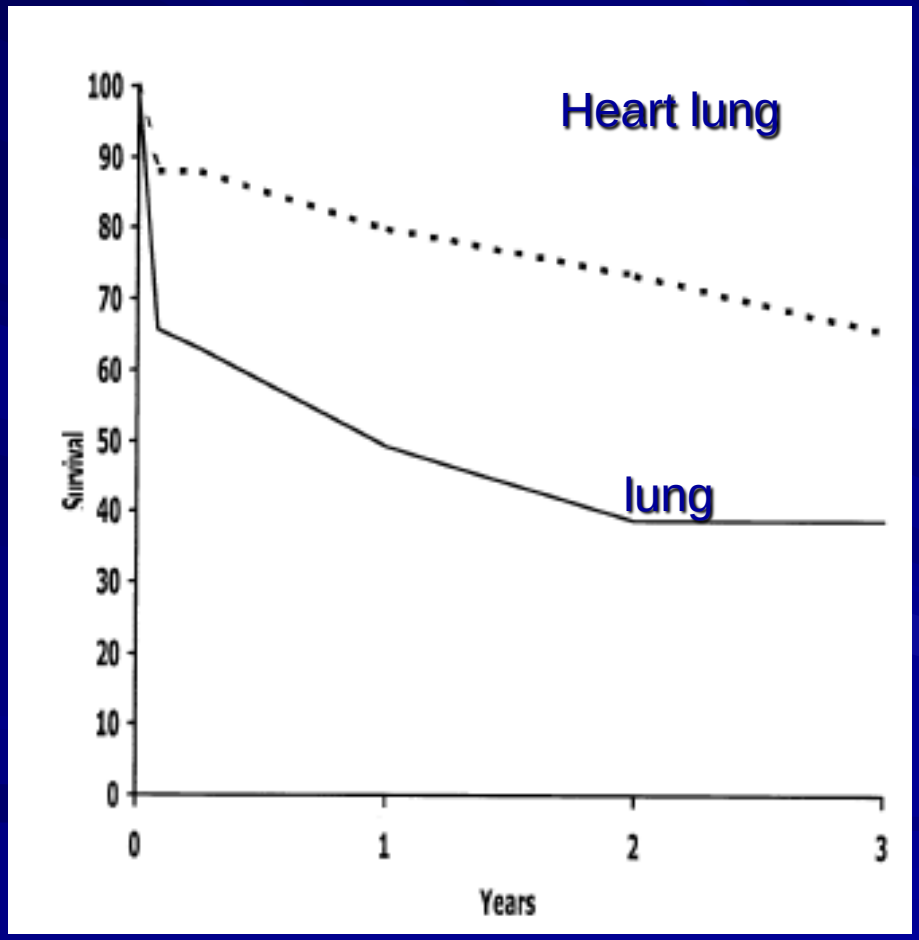




605 transplants between 1988 and 1998

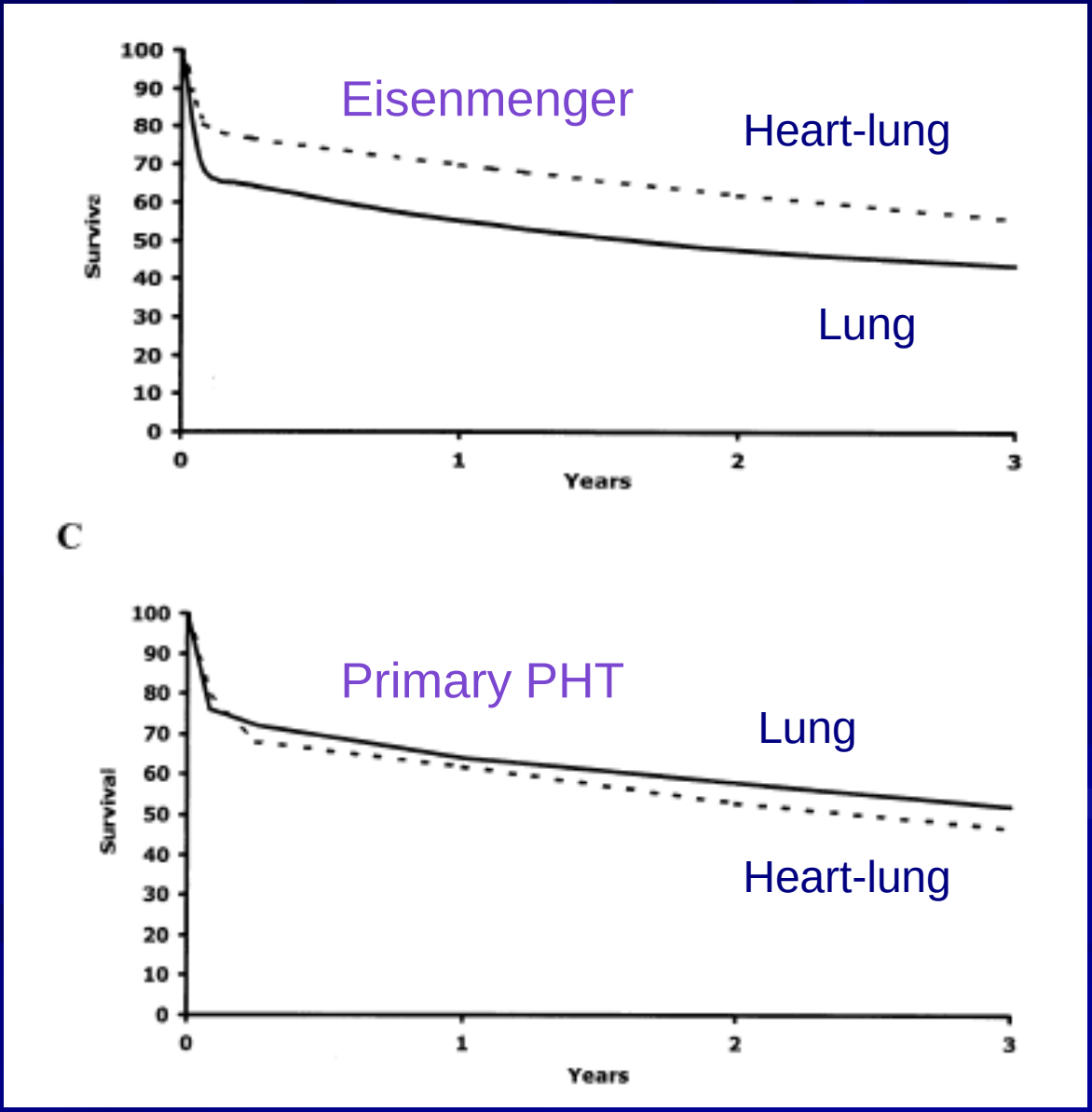
Waddell. Et al. J Heart Lung Transplant 2002;21:731-7..

Transplantation for Eisenmenger syndrome



Waddell. Et al. J Heart Lung Transplant 2002;21:731-7

Survival



Waddell. Et al. J Heart Lung Transplant 2002;21:731-7..

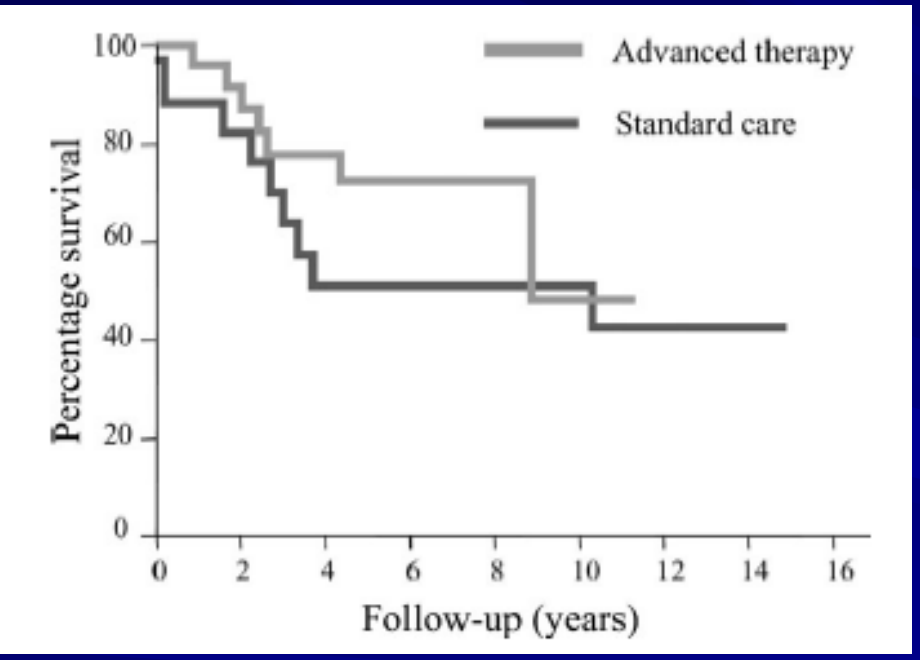
Advanced Rx for Eisenmenger Syndrome

- Retrospective study
- Standard care until 1996
- Advanced therapy 1996 on
- No clinical difference between the groups

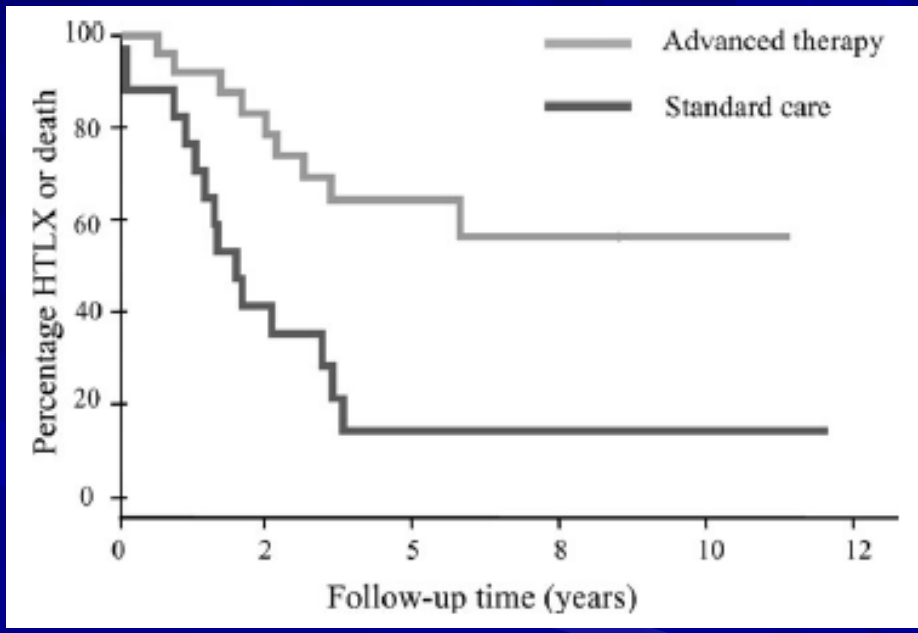
Adriaenssens et al. Eur Heart J 2006;27, 1472

Advanced Rx for Eisenmenger Syndrome

All cause mortality

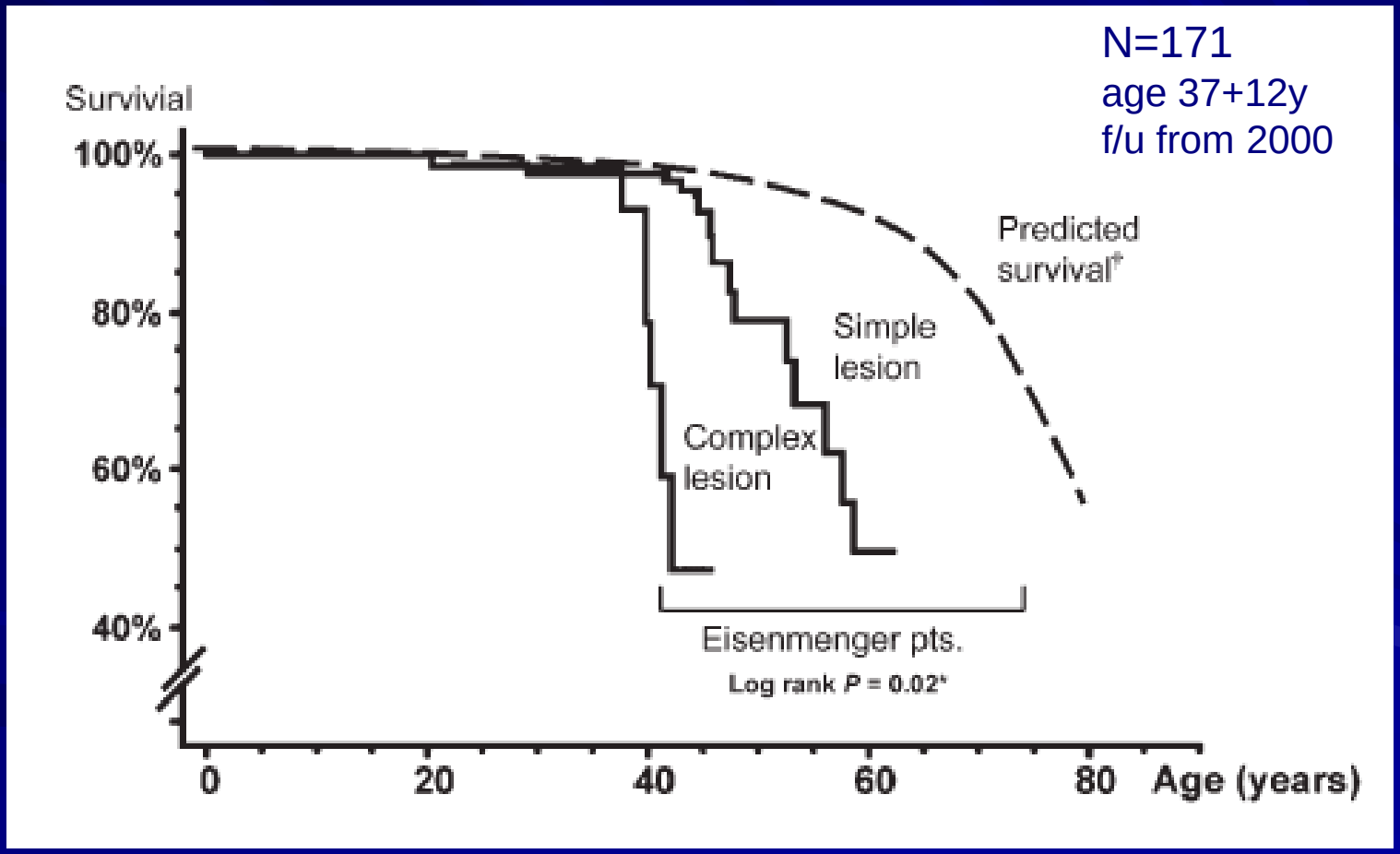


Death or Tx



Adriaenssens et al. Eur Heart J 2006;27, 1472

Survival with Eisenmenger syndrome



Diller et al. European Heart Journal (2006) 27, 1737–1742


Have a seat Kermit. What I'm about to tell you might come as big shock...
paisdelocos.com


Rise of Judah