ΚΑΡΔΙΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ ΒΟΡΕΙΟΥ ΕΛΛΑΔΟΣ

Σύνδρομο Eisenmenger
Νεότερα δεδομένα

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 20 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

[WITH SPECIAL PLATE]

Pulmonary hypertension with Cyanosis

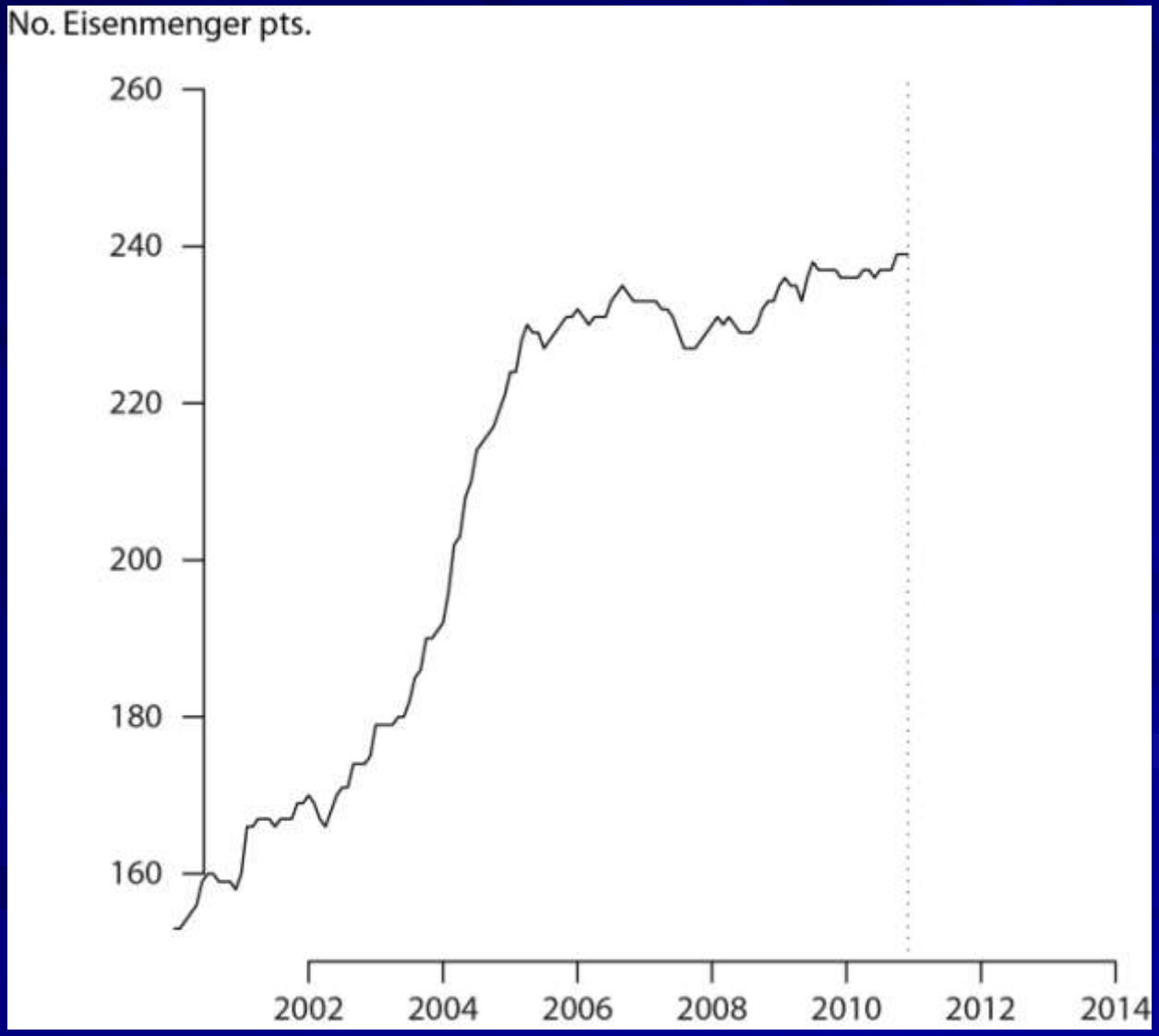
”Pulmonary hypertension at systemic level due to high pulmonary vascular resistance with reversed bi-directional shunt" - "...it matters very little where the shunt happens to be. The distinguishing feature is not anatomy, but the physiological behaviour of the pulmonary circulation."

Eisenmenger's syndrome (ES): A frequent complication of CHD

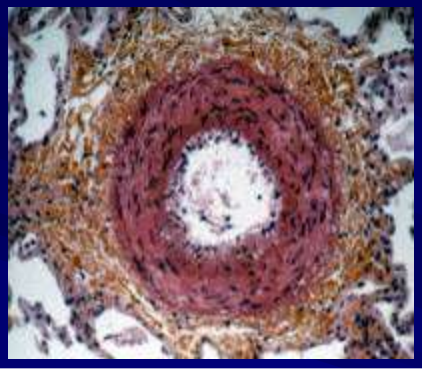
- Patients at risk of developing ES
  - 1-4% of patients with CHD[1,3] (8% in 1950s, P. Wood)
  - ~50% of patients with large unrepaired VSDs/PDAs[2]
  - ~10% of patients with large unrepaired ASDs[2]
  - Almost all patients with unrepaired truncus arteriosus[2]

1. **Mulder BJ.** ***Eur Respir Rev*** **2010; 19:308-13.**
2. **Beghetti M and Galiè N.** ***J Am Coll Cardiol*** **2009; 53:733-40.**
3. **Diller GP and Gatzoulis.** ***Circulation*** **2007;115:1039-50.**

The number of Eisenmenger Patients under FU at the Royal Brompton Hospital is Increasing at 5%/year



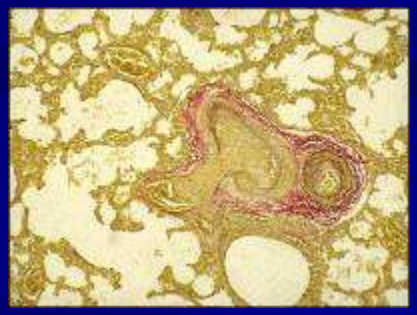
PAH-CHD pathophysiology



Proliferation of smooth muscle cells

Increase in extracellular matrix

Intravascular thrombosis



Left-to-right shunt

Increased pulmonary blood flow (shear stress)

Endothelial dysfunction

Increase in pulmonary vascular resistance

Inverted shunt: right-to-left

Cyanosis (Eisenmenger's)

Beghetti M. JACC 2009

Clinical classification of PAH-CHD

A. Eisenmenger's syndrome (ES)

ES includes all left-to-right shunts due to large defects leading to a severe increase in PVR and resulting in a reversed right-to-left or bidirectional shunt. Cyanosis, erythrocytosis, and multiple organ involvement are present.

B. PAH associated with systemic-to-pulmonary shunts

In these patients with moderate to large defects, the increase in PVR is mild to moderate, left-to-right shunt is still largely present, and no cyanosis is present at rest.

C. PAH with small defects

In cases with small defects (usually VSD < 1 cm and ASD < 2 cm of effective diameter assessed by echocardiography) the clinical picture is very similar to IPAH.

D. PAH after corrective cardiac surgery

CHD has been corrected but PAH is either still present immediately after surgery or has recurred several months or years after surgery in the absence of significant post-operative residual congenital lesions or defects that originate as a sequela to previous surgery.

Galiè N, *et al. Eur Heart J* 2009; 30:2493-537.

Differences between IPAH and Eisenmenger syndrome (I)

Parameters	IPAH	Eisenmenger syndrome
RV response		
Dimensions	Dilation	Typically hypertrophy in post-tricuspid defects
Function	Rapid deterioration	Often preserved (VSD), quite stable
Cardiac output	Reduced	Sustained by R-L shunting
Prognosis	Poor, survival limited to few years after diagnosis	Not as poor, patients survive decades after diagnosis
Cyanosis		
Prevalence	When low-cardiac output ± presence of PFO/ASD	The rule in ES
Severity	Rarely severe at rest	Often severe at rest
Haematologic	Rare unstudied manifestations	Secondary erythrocytosis common

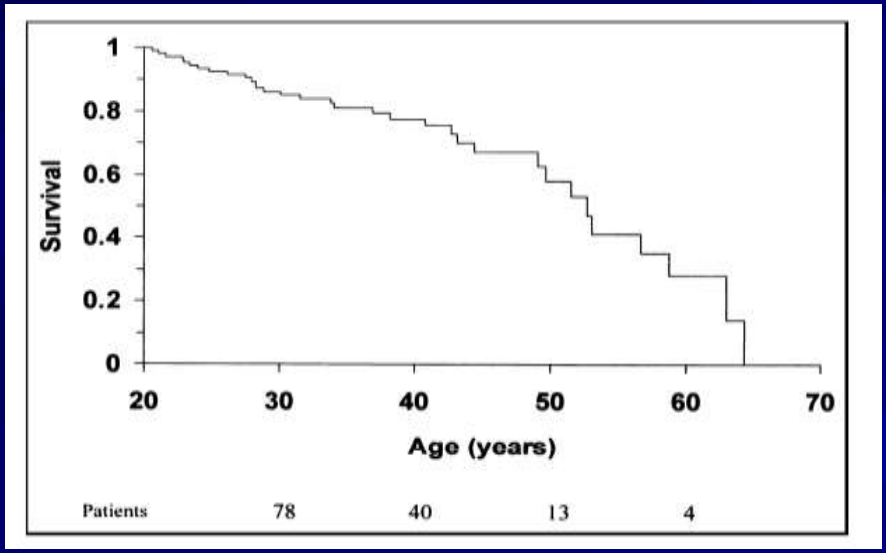
Dimopoulos, Giannakoulas *et al*. *Curr Opin Cardiol* 2008

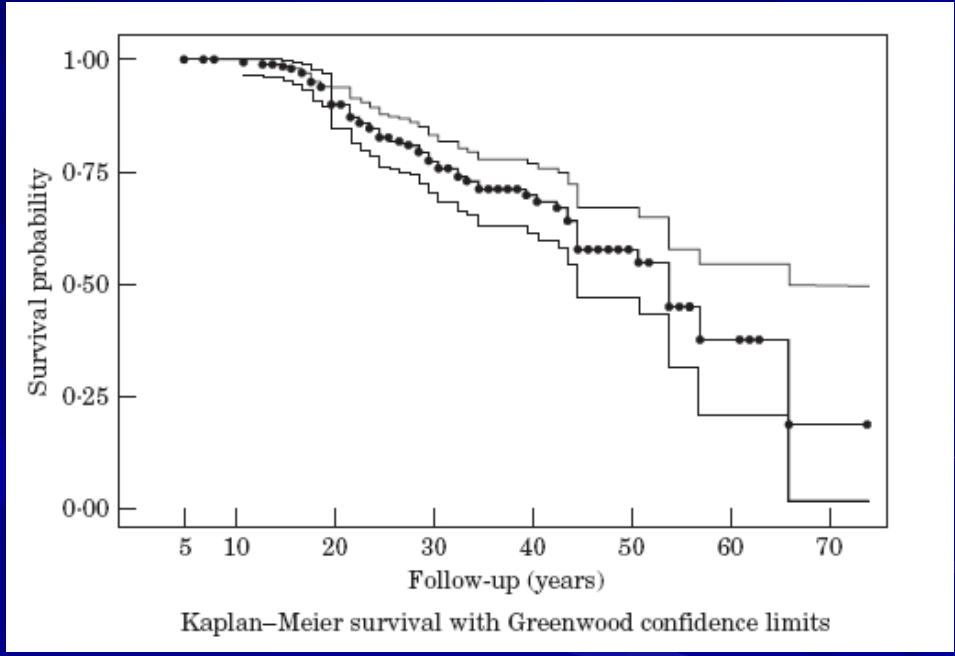
Differences between IPAH and Eisenmenger syndrome (II)

Parameters	IPAH	Eisenmenger syndrome
Systemic complications	Not common	Common (renal dysfunction)
Associated genetic/ chromosomal disorder	No	Common (Down's syndrome)
Perception of limitation	Normal	Underestimated
Coexisting left-sided/ valve disease	Rare until functional TR develops	Common (e.g. AVSD, univentricular circulation)
Transplantation	Rapid progression: Likely to benefit	Slow progression, common syst. complications, complex cardiac disease: not ideal
RA pressures	Increased with decompensation	May rise due to causes independent of PAH

Dimopoulos, Giannakoulas *et al*. *Curr Opin Cardiol* 2008

"… life expectancy of patients with this syndrome is 20 to 50 years …"

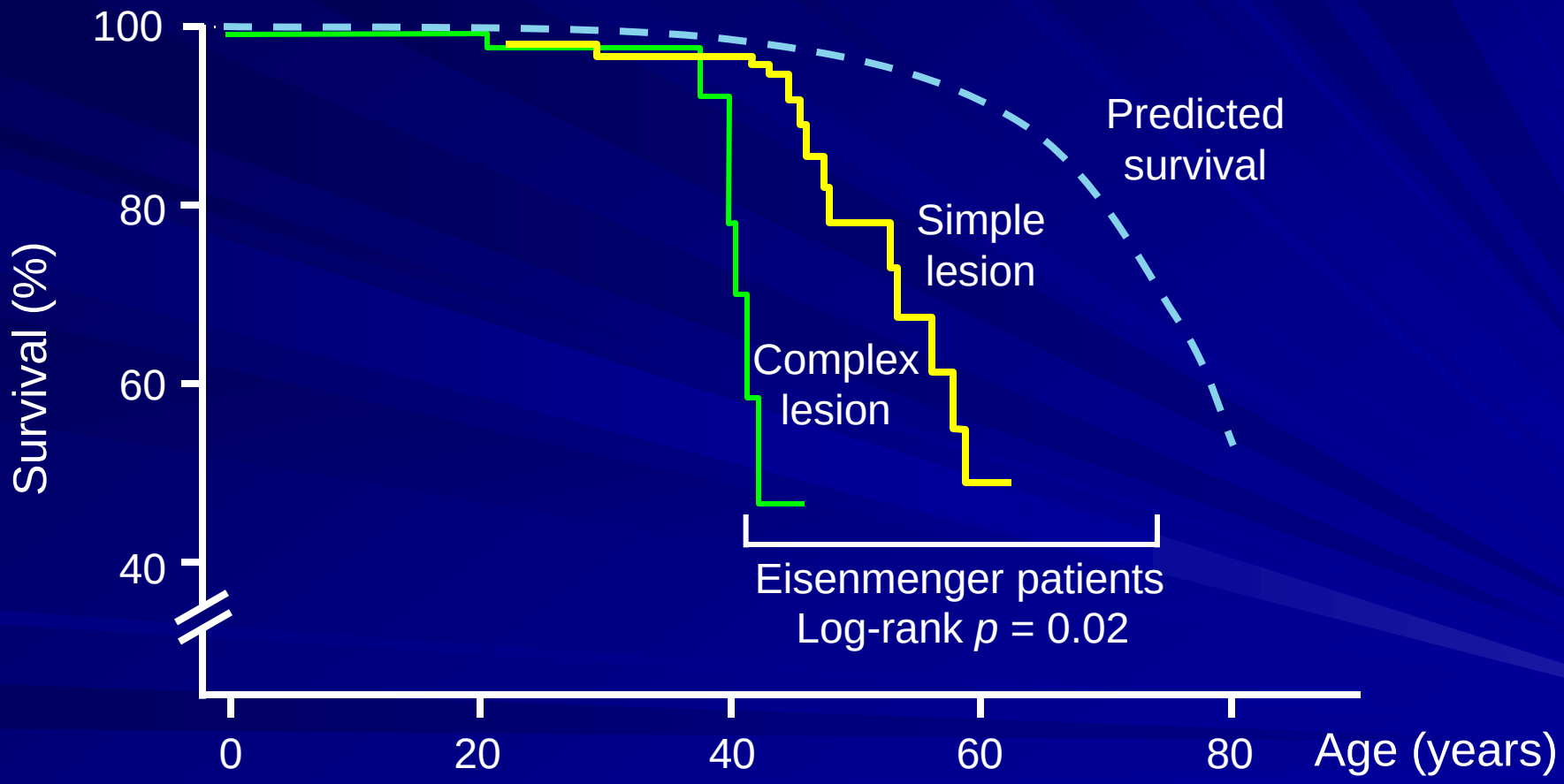




Kaplan–Meier survival with Greenwood confidence limits

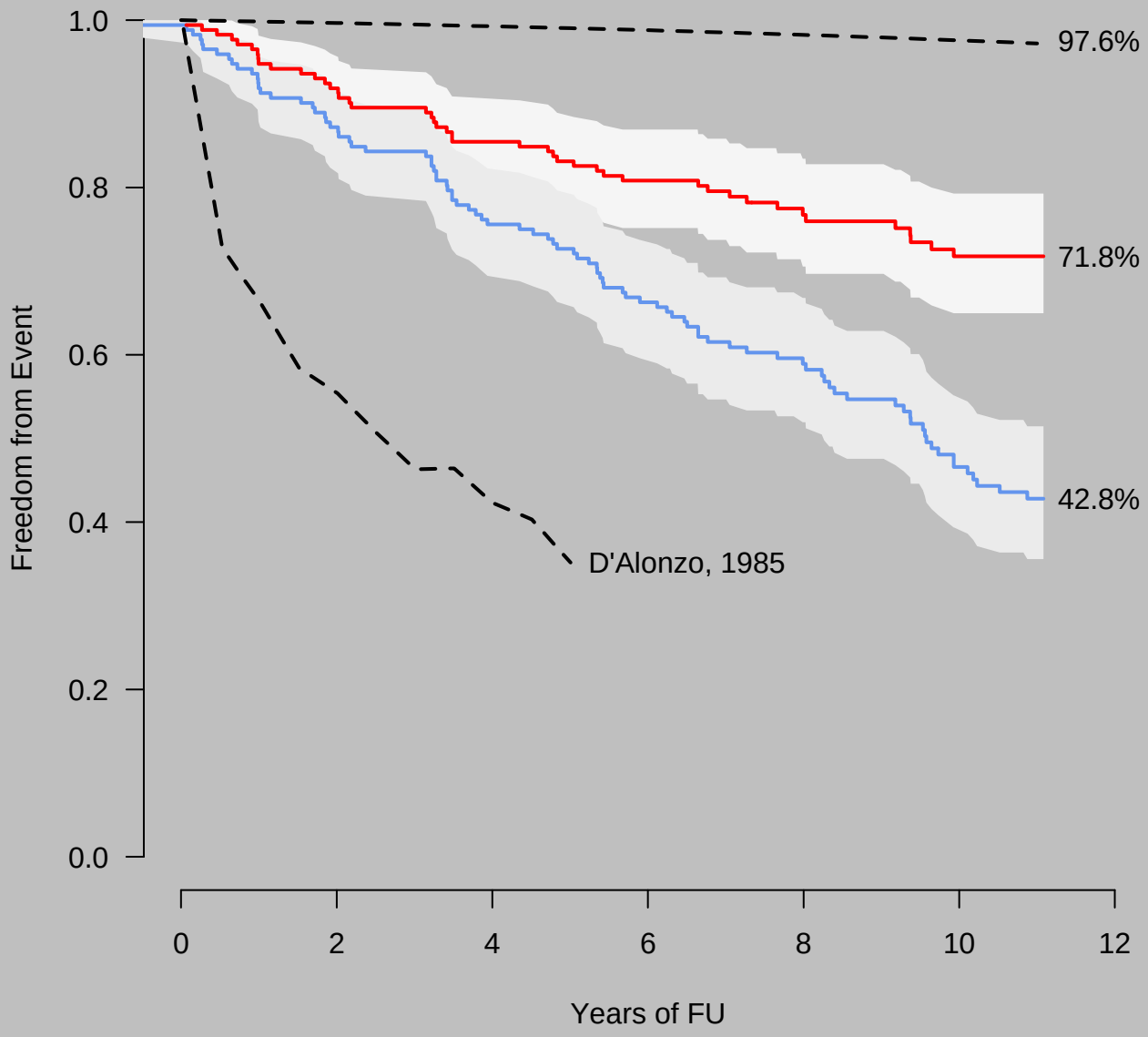
Oya H, *Am Heart J.* 2002
Daliento L, *Eur Heart J.* 1998
Cantor WJ, *Am J Cardiol.* 1999

Eisenmenger physiology: Survival in adults



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

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



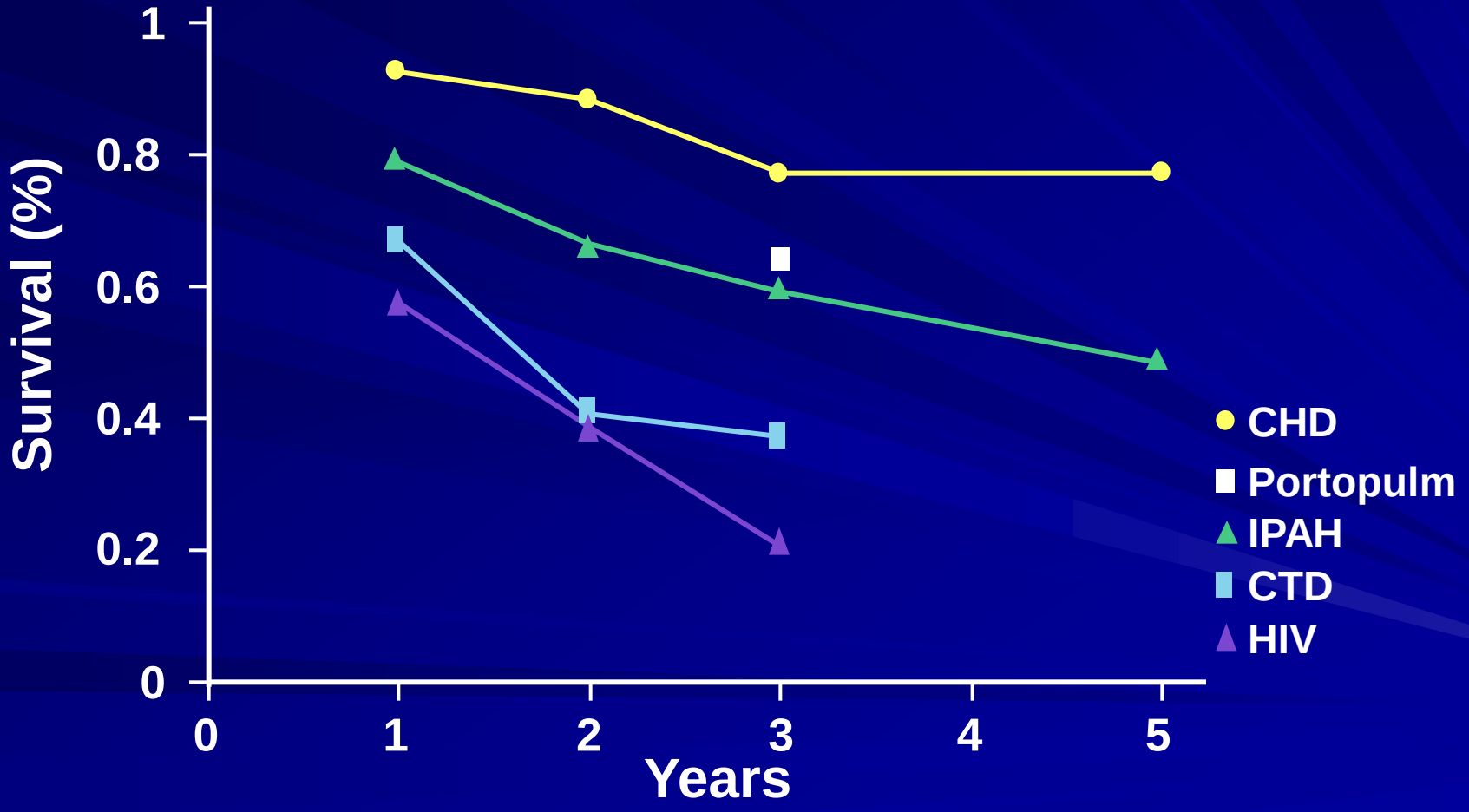
Survival
= approx. 3.2% annual risk of death

Survival or need for advanced therapies

35 y.o UK male approx. 0.1%; female 0.06% annual risk of death

Diller GP, *unpublished*

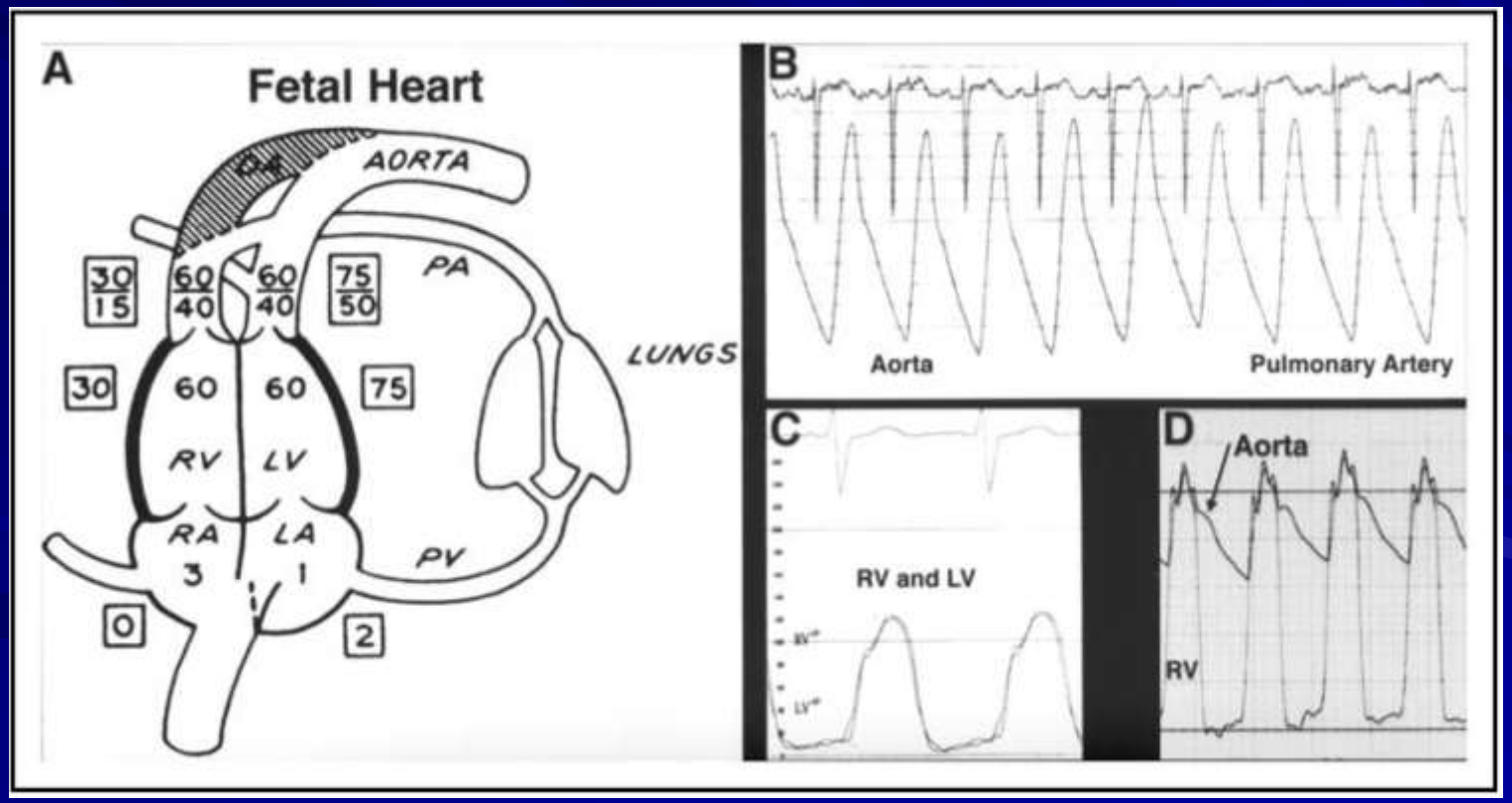
Natural history of adult PAH

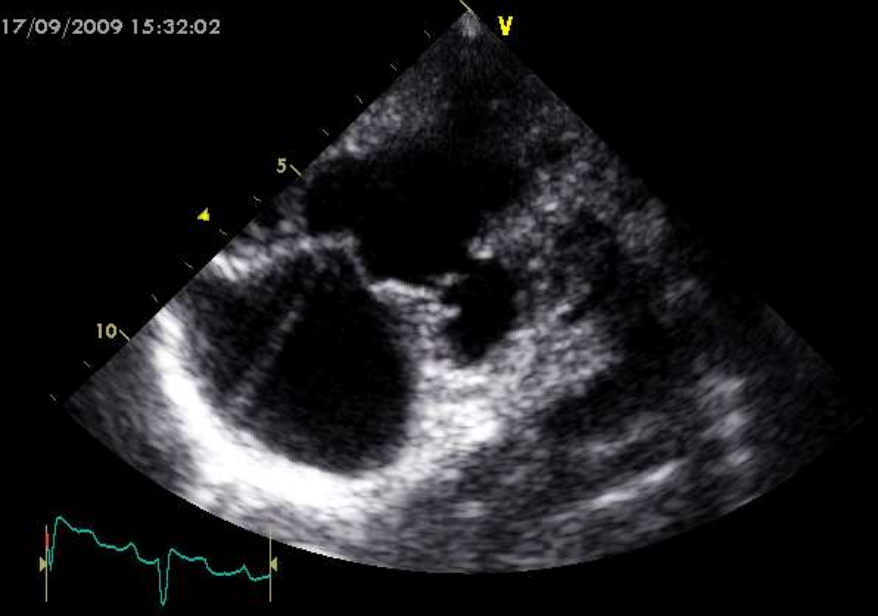


McLaughlin VV, *et al*. *Chest* 2004; 126:78S-92S.

Severe Pulmonary Hypertension Without Right Ventricular Failure: The Unique Hearts of Patients With Eisenmenger Syndrome

William E. Hopkins, MD, and Alan D. Waggoner, MHS, RDCS

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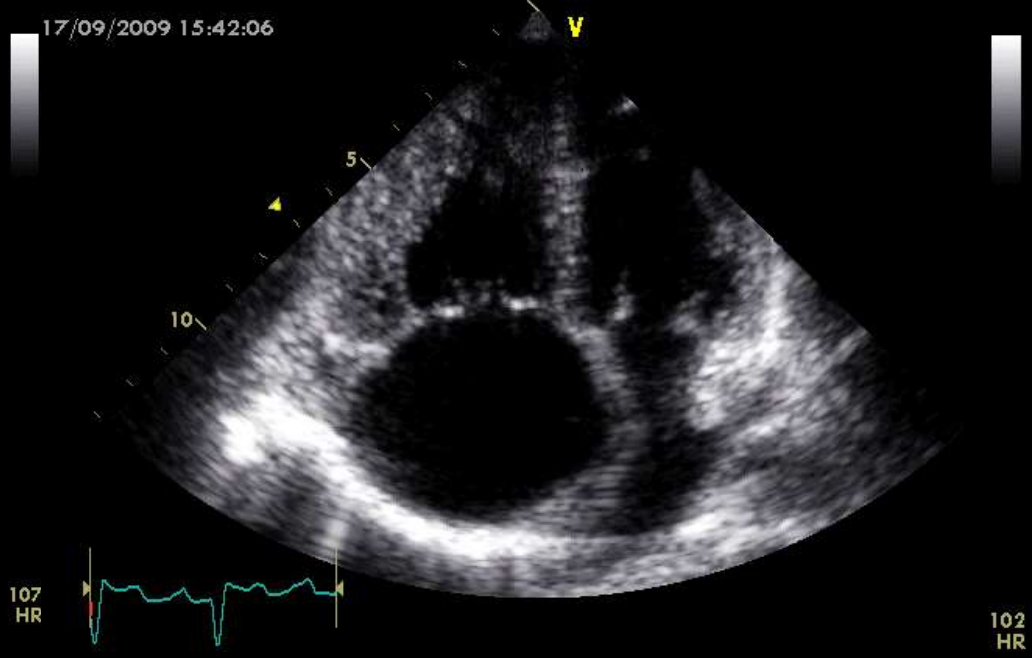
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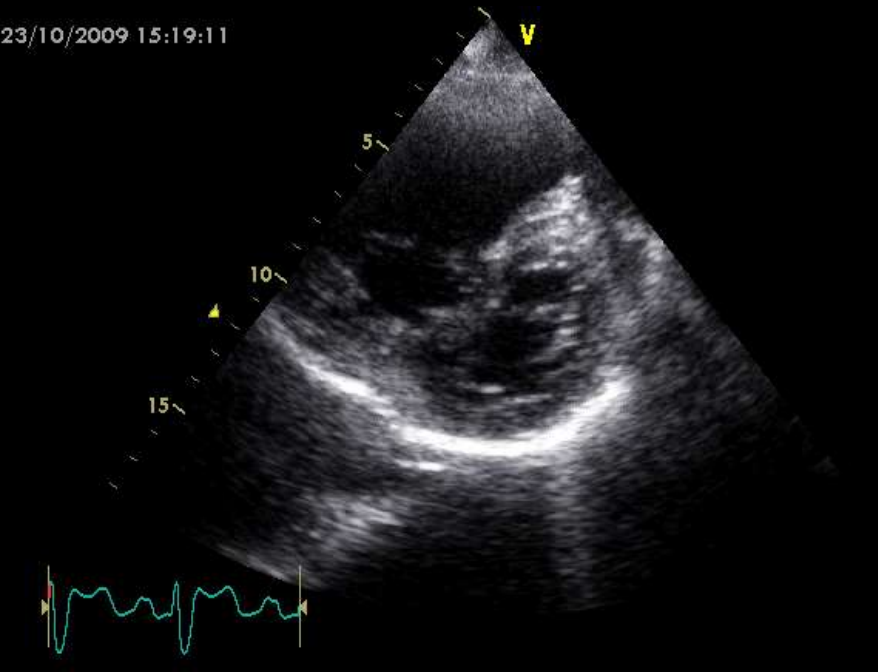
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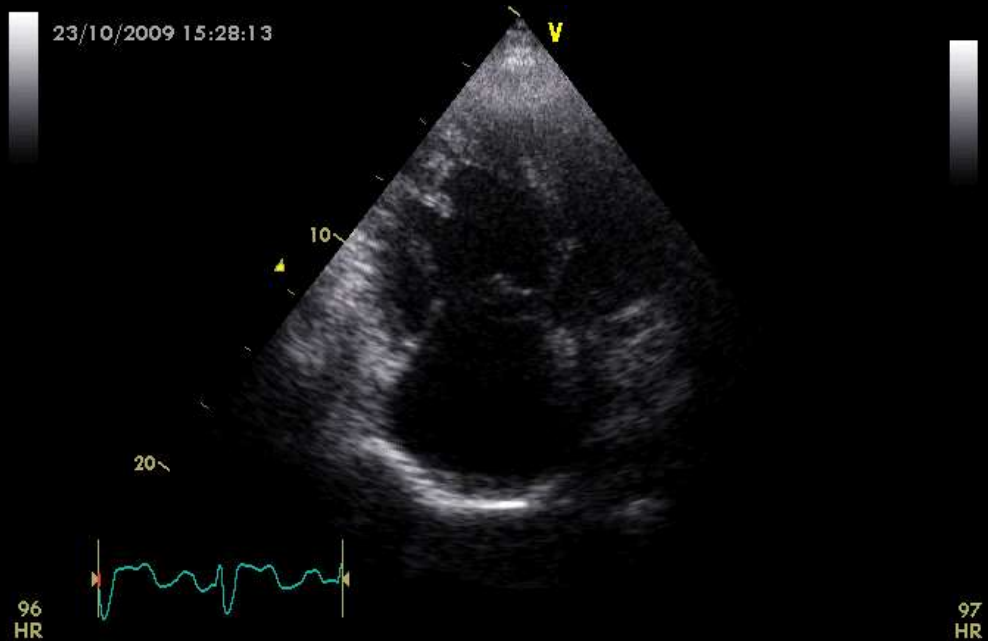
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Cyanosis

Dick Ket (1902 – 1940)

Eisenmenger syndrome
Multi-organ disease

Exercise intolerance, dyspnoea, fatigue, dizziness

Hyperviscosity symptoms
- **Headache, dizziness, visual disturbances, paresthesias**

Severe cyanosis

Renal dysfunction

Haematologic involvement
- **Secondary erythrocytosis**
- **Thrombocytopenia**
- **Iron deficiency**

Thrombotic and bleeding diathesis
- **Dilation of the pulmonary arteries, in situ thrombosis**
- **Haemoptysis, pulmonary haemorrhage**
- **Neoangiogenesis (GI, pulmonary, other bleeding)**
- **Cerebrovascular events**

Arrhythmias
- **Supraventricular tachycardias**
- **Ventricular tachycardia, sudden cardiac death**

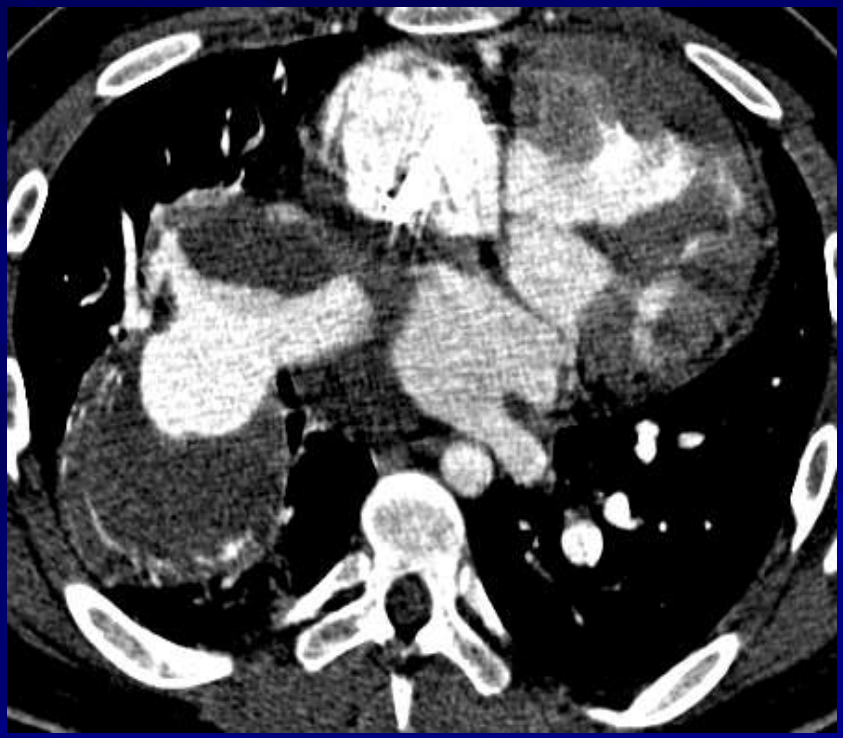
Rheumatologic complications
- **Hyperuricemia and gout**
- **Hypertrophic osteoarthropathy, clubbing**

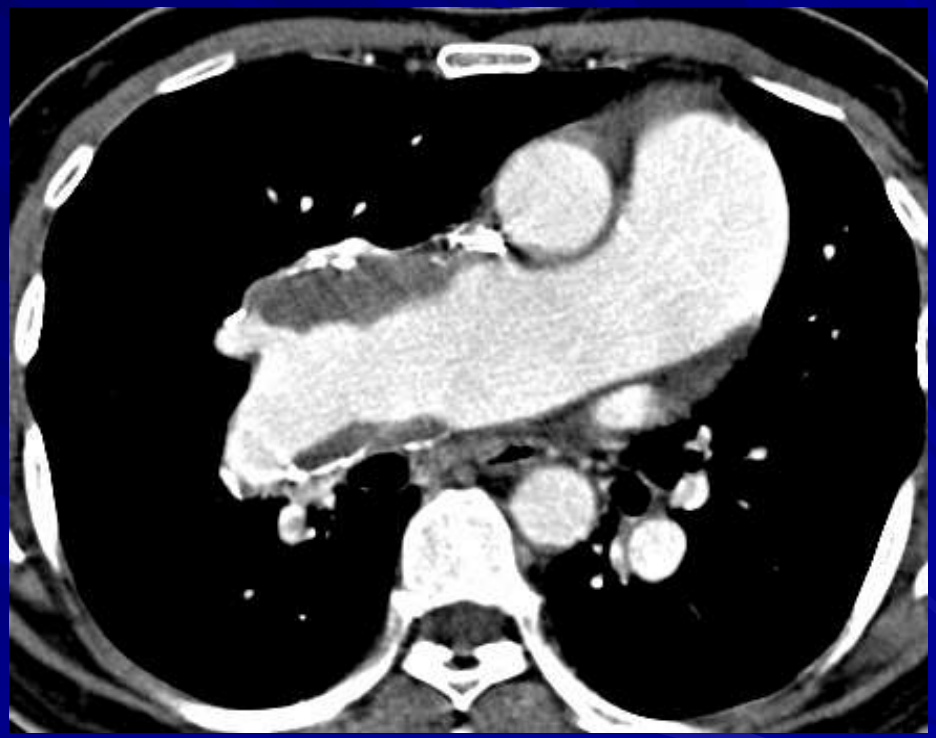
Gastrointestinal complications
- **Gallstones, cholecystitis**

Bacterial infectious diseases
- **Endocarditis**
- **Cerebral abscess**
- **Respiratory tract infection**

Dimopoulos K, Giannakoulas G. ***Eisenmenger Complex. In: Pulmonary Arterial Hypertension: Oxford Cardiology Library***

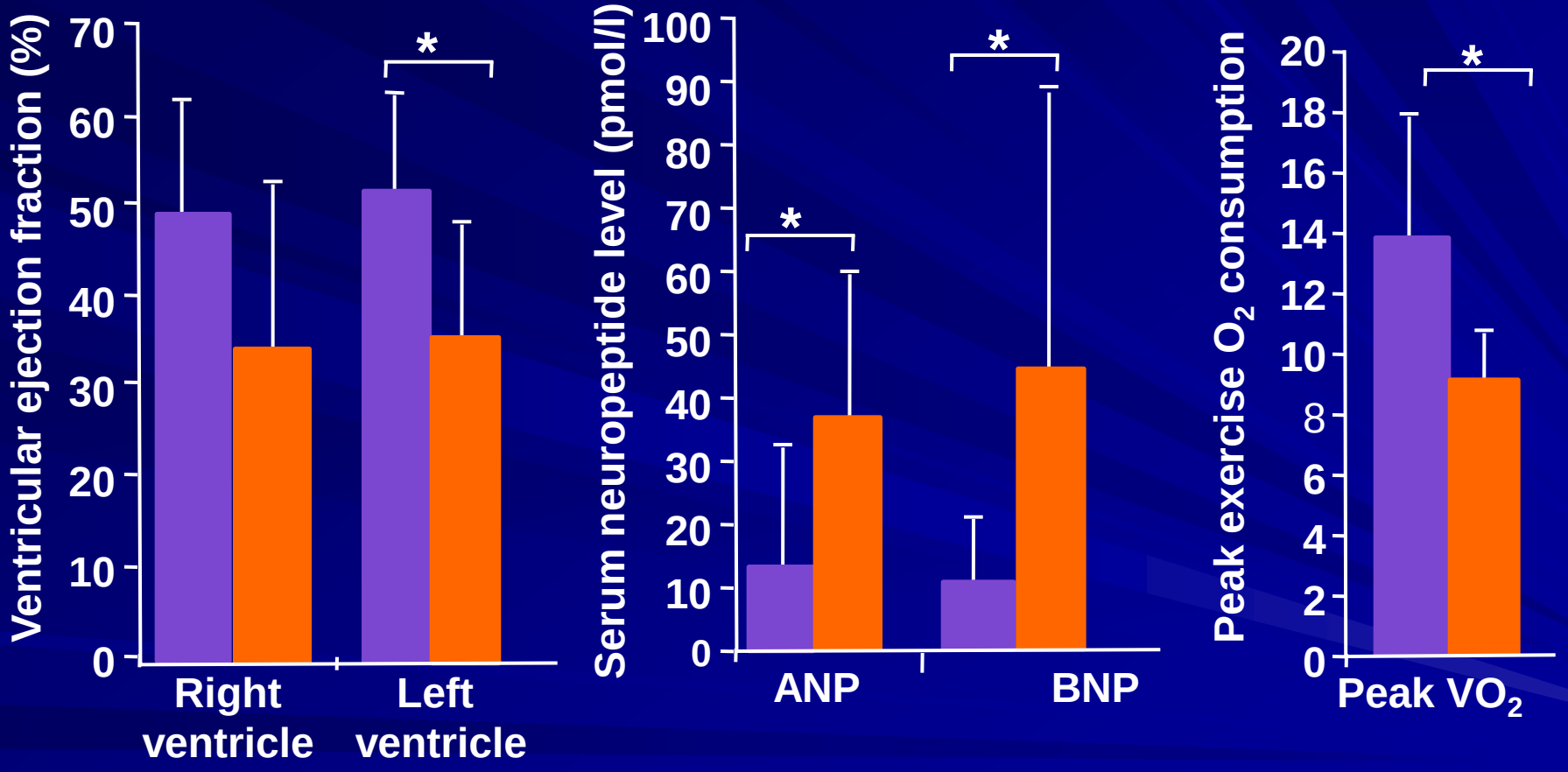
Pulmonary thrombosis in Eisenmenger syndrome





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

Risk of pulmonary arterial thrombosis



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

Complications / Stroke

Risk of Stroke in Adults With Cyanotic Congenital Heart Disease

Joseph K. Perloff, MD; Ariane J. Marelli, MD; and Pamela D. Miner, RN, MN

Background. **Adults with cyanotic congenital heart disease and elevated hematocrit levels are often phlebotomized because of an assumed risk of cerebral arterial thrombotic stroke. Whether a relation exists between hematocrit level, symptomatic erythrocytosis (hyperviscosity), and stroke remains to be established in this patient population.**

Methods and Results. **Accordingly, 112 cyanotic patients 19–74 years old (mean, 36±11.7 years) in the UCLA Adult Congenital Heart Disease Center Registry were selected for study by virtue of continuous observation for 1–12 years (total, 748 patient-years). Patients with independent risk factors for embolic or vasospastic stroke were excluded. The study patients were then divided into two groups: 1) compensated erythrocytosis (stable hematocrit levels of 46.0–72.7% [mean, 57.5±7.2%], iron replete, absent or mild hyperviscosity symptoms), and 2) decompensated erythrocytosis (unstable rising hematocrit levels of 61.5–75.0% [mean, 69.5±10.6%], iron deficiency, marked-to-severe hyperviscosity symptoms). No patient with either compensated or decompensated erythrocytosis, irrespective of hematocrit level, iron stores, or the presence, degree, or recurrence of cerebral hyperviscosity symptoms, progressed to clinical evidence of a completed stroke (cerebral arterial thrombosis with brain infarction).**

Conclusions. **Because a risk of stroke caused by cerebral arterial thrombosis was not demonstrated, because the circulatory effects of phlebotomy are transient, and because of the untoward sequelae of phlebotomy-induced iron deficiency, we recommend phlebotomy for the temporary relief of significant, intrusive hyperviscosity symptoms but not for the hematocrit level per se. According to our data, phlebotomy is not warranted to reduce an assumed risk of stroke because that risk did not materialize. (*Circulation* 1993;87:1954–1959)**

KEY WORDS • congenital heart disease • stroke • blood cells • hemodynamics

Iron deficiency and stroke

Table 2. Hemodynamic and Hematologic Variables

	Group I (no CVE) (n = 140)	Group II (CVE) (n = 22)	p Value
Continuous variable			
EF (%)			
Range	20–70	34–65	0.707
Mean ± SD	53 ± 9.8	52 ± 8.9	
Hemoglobin			
Range	14.5–23.5	14.5–23.1	0.081
Mean ± SD	17.7 ± 1.86	18.4 ± 2.2	
Hematocrit			
Range	41.7–70.1	41.3–63.1	0.11
Mean ± SD	53.3 ± 6.0	54.4 ± 6.7	
MCV			
Range	57.4–104.5	68.6–89.7	0.345
Mean ± SD	87.8 ± 9.7	85.7 ± 9.8	
Discrete variable			
Hypertension			
Yes	4	3	0.021
No	136	19	
Atrial fibrillation			
Yes	13	6	0.015
No	127	16	
Smoking			
Yes	17	2	0.68
No	123	20	
Phlebotomy			
Yes	35	11	0.016
No	105	11	
Iron deficiency anemia/ microcytosis			
Yes	30	11	0.004
No	110	11	
Antiplatelet intake			
Yes	17	2	0.68
No	123	20	
Warfarin intake			
Yes	17	1	0.29
No	123	21	

Ammash et al. JACC 1996

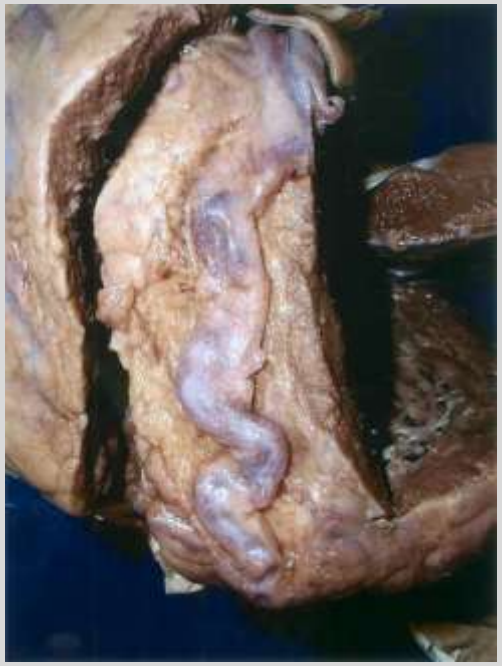


Fig. 2. Striking gross appearance of an ectatic, tortuous left anterior descending coronary artery in a 45 year old woman with an Eisenmenger ventricular septal defect.

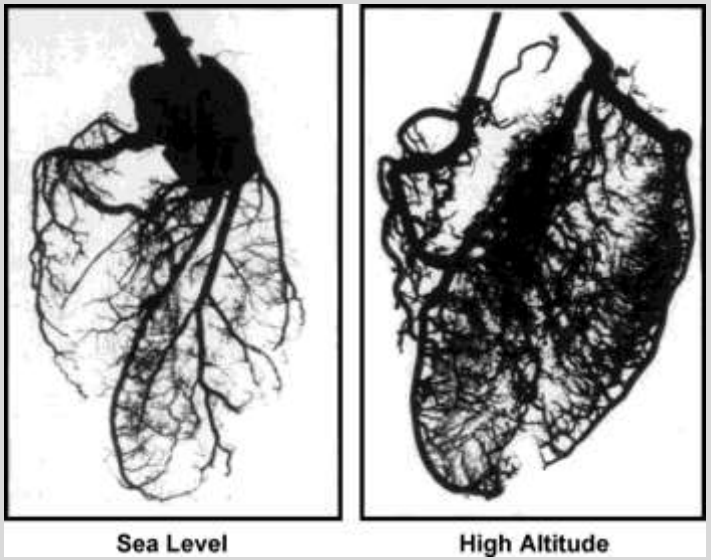


Fig. 8. Casts of the coronary vascular bed derived from acrylic resin injections in sea level residents and in age-matched acclimatized residents of high altitude. The casts from high altitude residents disclosed a much greater density of the coronary microcirculation. From Ref. [3].

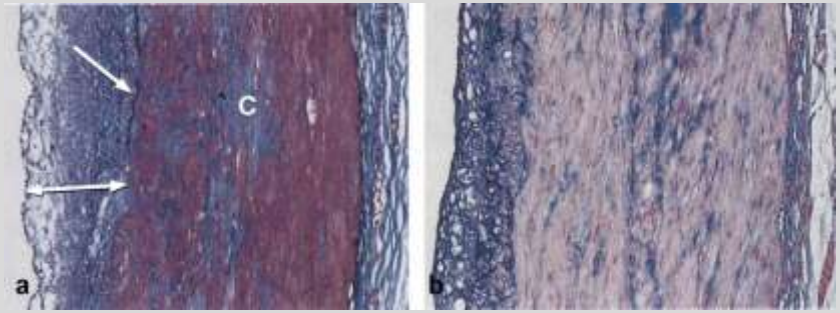


Fig. 3. Histologic appearance of the ectatic coronary artery shown in Fig. 2. (a) Trichrome stain showing disruption of the internal elastic lamina (left upper arrow), increased medial collagen (C) that stains blue, and fibrointimal hyperplasia (paired arrows). (b) Alcian blue stain showing increased extracellular matrix (blue) scattered throughout the media. Medial smooth muscle cells are pink. There was no atherosclerosis.

Perloff JK. *Int. J. Cardiol* 2004;97:79-86.

Burden of Coronary Artery Disease in Adults With Congenital Heart Disease and Its Relation to Congenital and Traditional Heart Risk Factors

Georgios Giannakoulas, MD, PhD[a,*], Konstantinos Dimopoulos, MD, PhD[a,b], Reto Engel, MD[a], Omer Goktekin, MD[a], Zekeriya Kucukdurmaz, MD[a], Mehmet Akif Vatankulu, MD[a], Elisabeth Bedard, MD[a], Gerhard Paul Diller, MD[a,b], Maria Papaphylactou, MD[a], Darrel P. Francis, MD[c], Carlo Di Mario, MD, PhD[b], and Michael A. Gatzoulis, MD, PhD[a,b]

As adult patients with congenital heart disease (CHD) grow older, the risk of developing coronary artery disease (CAD) increases. We sought to estimate the prevalence of CAD in adult patients with CHD, the safety of coronary angiography in this setting, and the potential relation of CAD to clinical and hemodynamic parameters. Two hundred fifty adult patients with CHD (mean age 51 ± 15 years; 53% men) underwent selective coronary angiography in our center for reasons other than suspected CAD. Clinical and hemodynamic data were retrieved retrospectively from medical records and echocardiographic and angiographic databases, respectively. Significant CAD using quantitative coronary angiography was found in 9.2% of adult patients with CHD. No patient with cyanosis or age <40 years had significant CAD. Systolic and diastolic systemic ventricular dimensions were significantly higher in patients with CAD, even after adjustment for age (odds ratio [OR] for 10-mm increase 2.59, 95% confidence interval [CI] 1.29 to 5.21, p = 0.007; OR 2.31, 95% CI 1.24 to 4.31, p = 0.008, respectively). Systemic arterial hypertension and hyperlipidemia were strong predictors of CAD (OR 4.54, 95% CI 1.82 to 12.0, p = 0.001; OR 9.08, 95% CI 3.56 to 24.54, p <0.0001, respectively), whereas no relation to chest pain was found. Only 1 major adverse event was recorded during coronary angiography. In conclusion, the prevalence of significant CAD in a hospital adult CHD cohort was similar to that in the general population. This study supported the performance of selective coronary angiography in patients >40 years referred for cardiac surgery, with low risk of major complications. Traditional cardiovascular risk factors for CAD also applied to adult patients with CHD, in whom primary prevention of CAD was as important as in the general population. (Am J Cardiol 2009;103:1445–1450)

No patient with cyanosis developed significant CAD

Eisenmenger syndrome

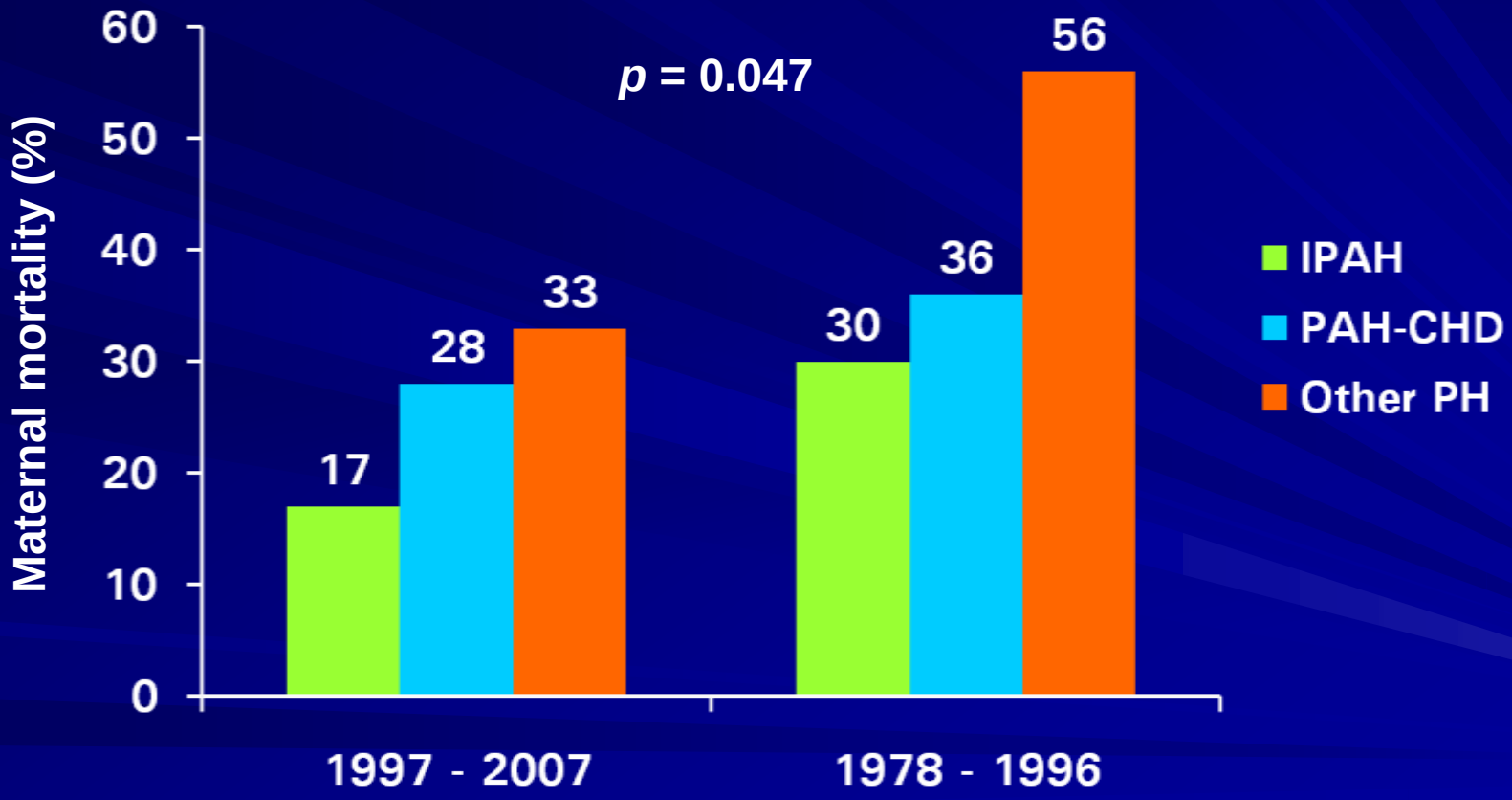
Therapy

- Not standardised until recently
- Targeted towards avoiding complications

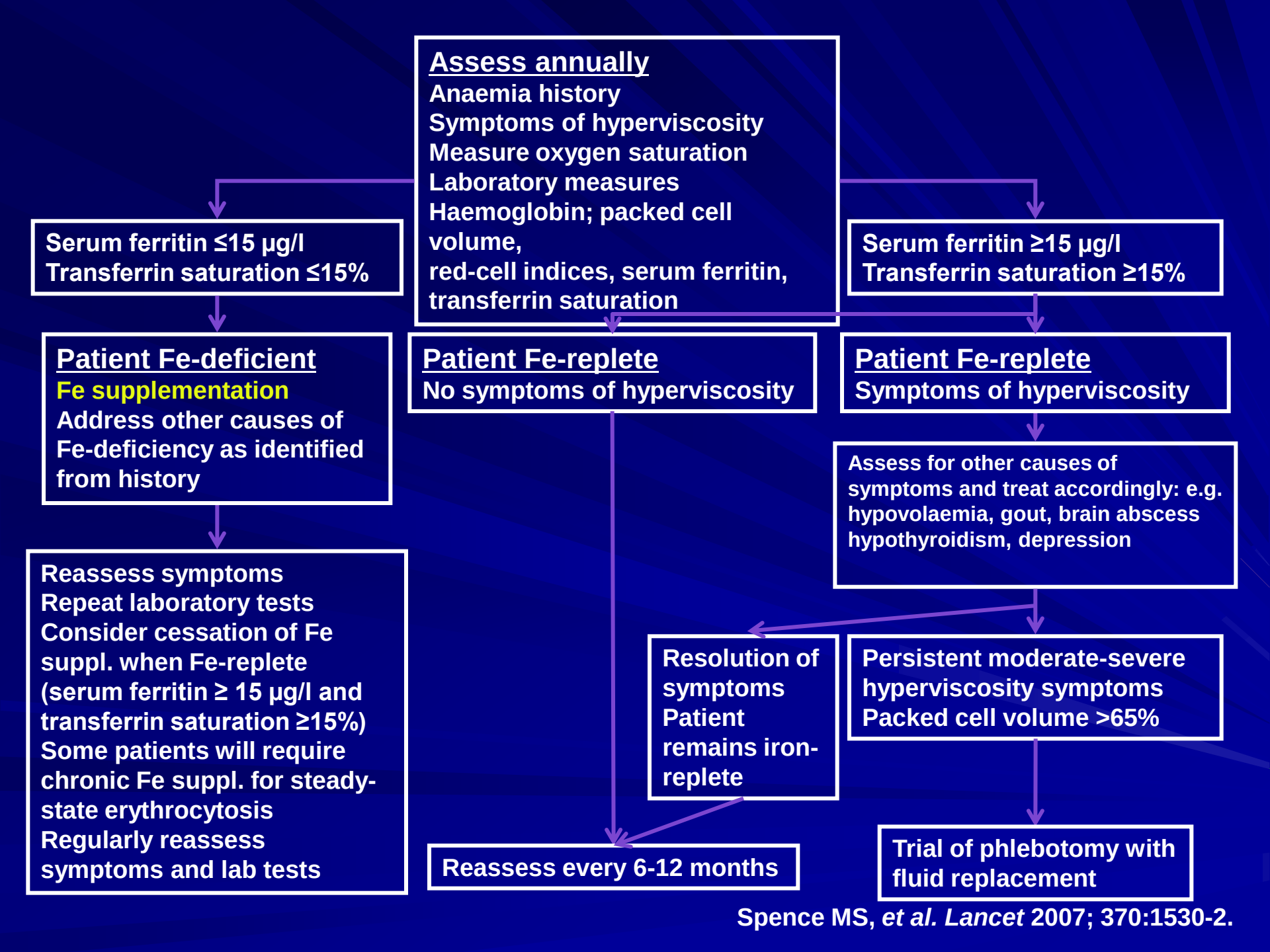
General management principles

- Avoid dehydration, extreme isometric exercise
- Avoid high altitude
- Air travel is safe in commercial airlines
- Special anaesthetic management
- Special care around angiography and non-cardiac surgery
- Avoid pregnancy (30-50% maternal mortality)
- Contraception issues

Pregnancy and PAH in association with CHD



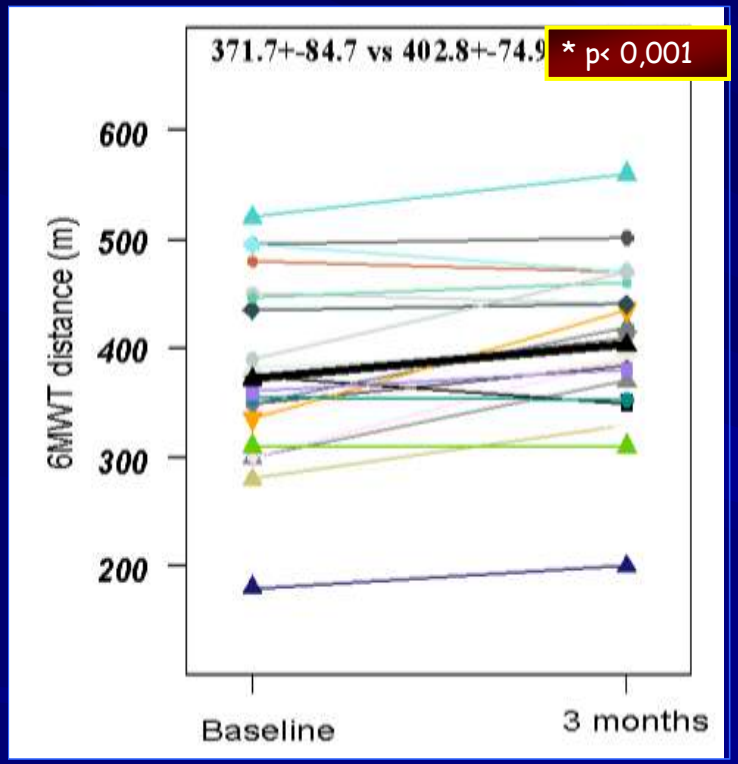
1. Bedard E, *et al. Eur Heart* J 2009; 30:256-65.

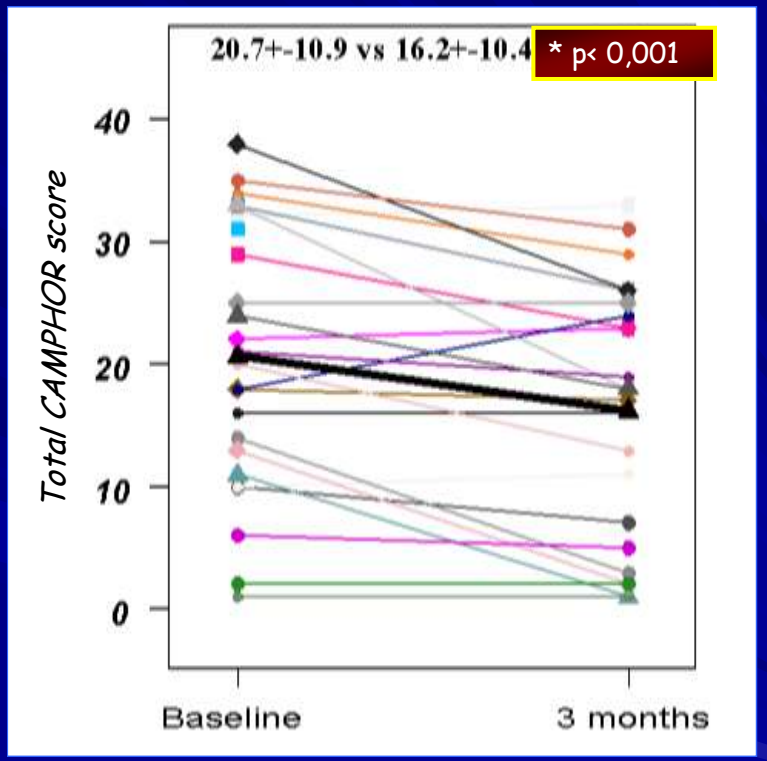


Spence MS, *et al. Lancet* 2007; 370:1530-2.

Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with cyanotic congenital heart disease and/or the Eisenmenger syndrome

Edgar L.W. Tay [a,*], Ana Peset [a], Maria Papaphylactou [a], Ryo Inuzuka [a], Rafael Alonso-Gonzalez [a], Georgios Giannakoulas [a], Aphrodite Tzifa [a], Sara Goletto [a], Craig Broberg [a], Konstantinos Dimopoulos [a,b], Michael A. Gatzoulis [a,b]



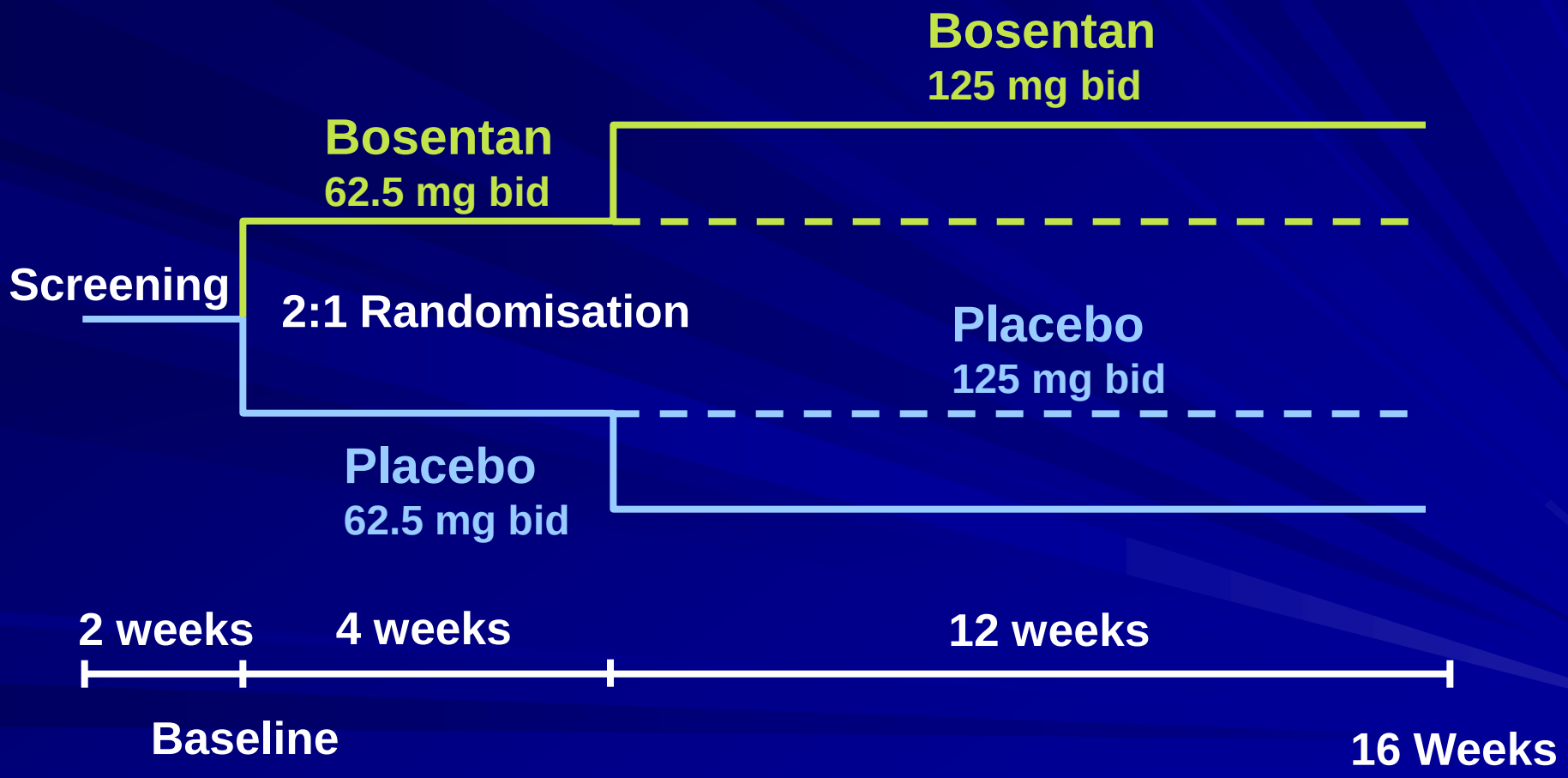


Prospective, single center, non-randomized study.

N= 25 cyanotic ACHD with iron deficiency

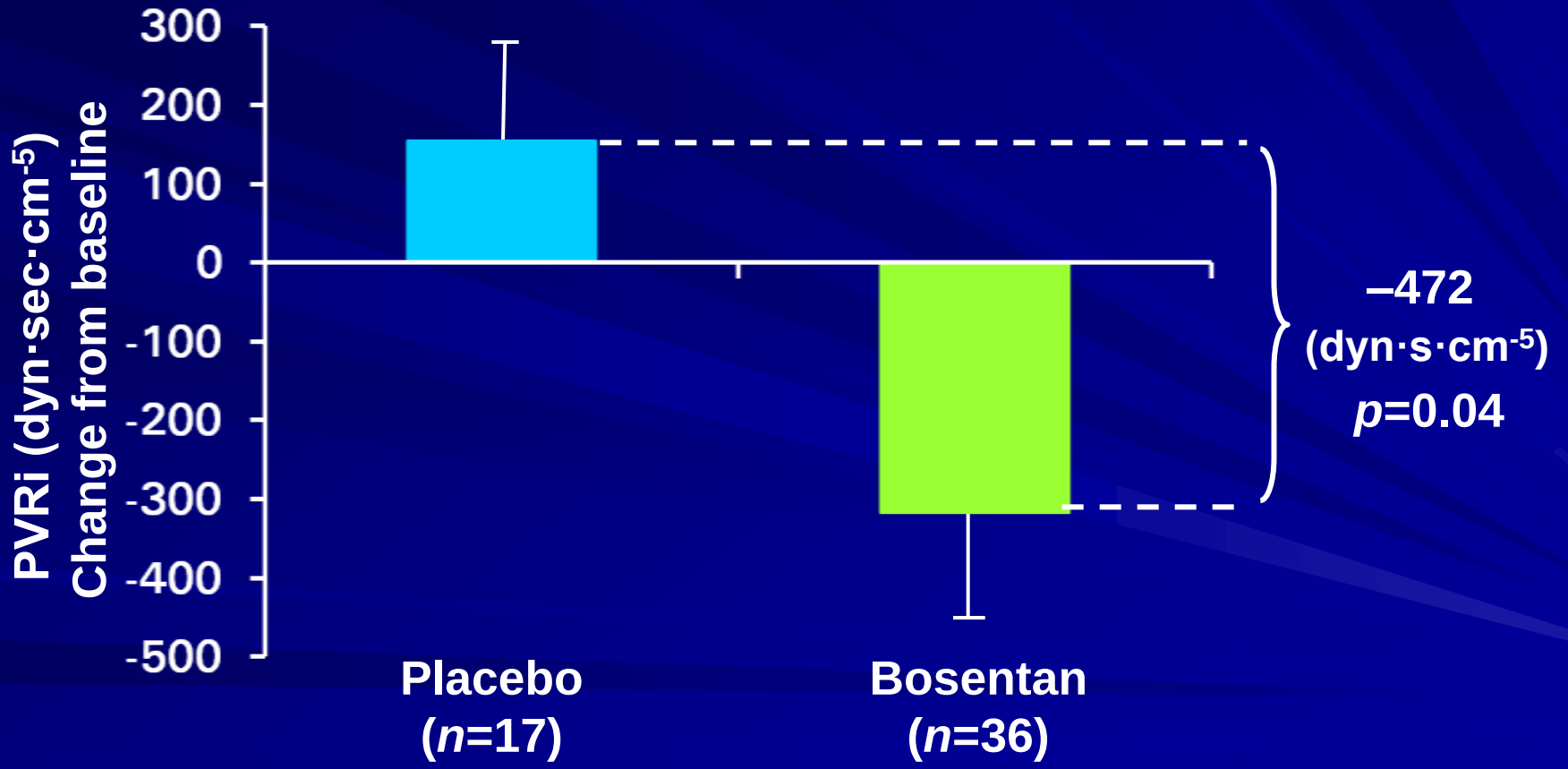
Int J Cardiol 2011

BREATHE-5: Study design



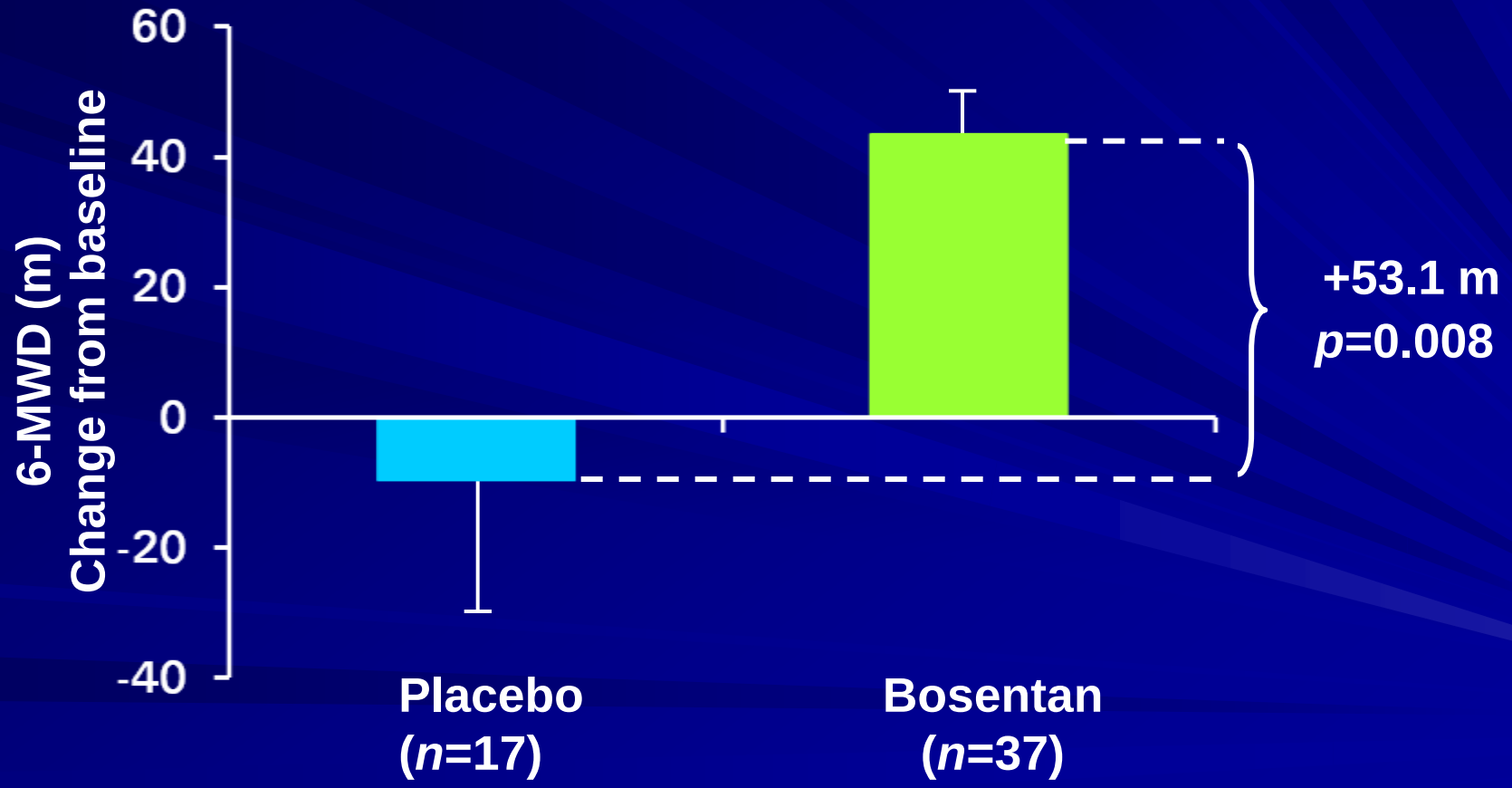
Galiè N, *et al*. *Circulation* 2006; 114:48-54.

Bosentan significantly reduced PVR: BREATHE-5



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

Bosentan significantly increased exercise capacity: BREATHE-5



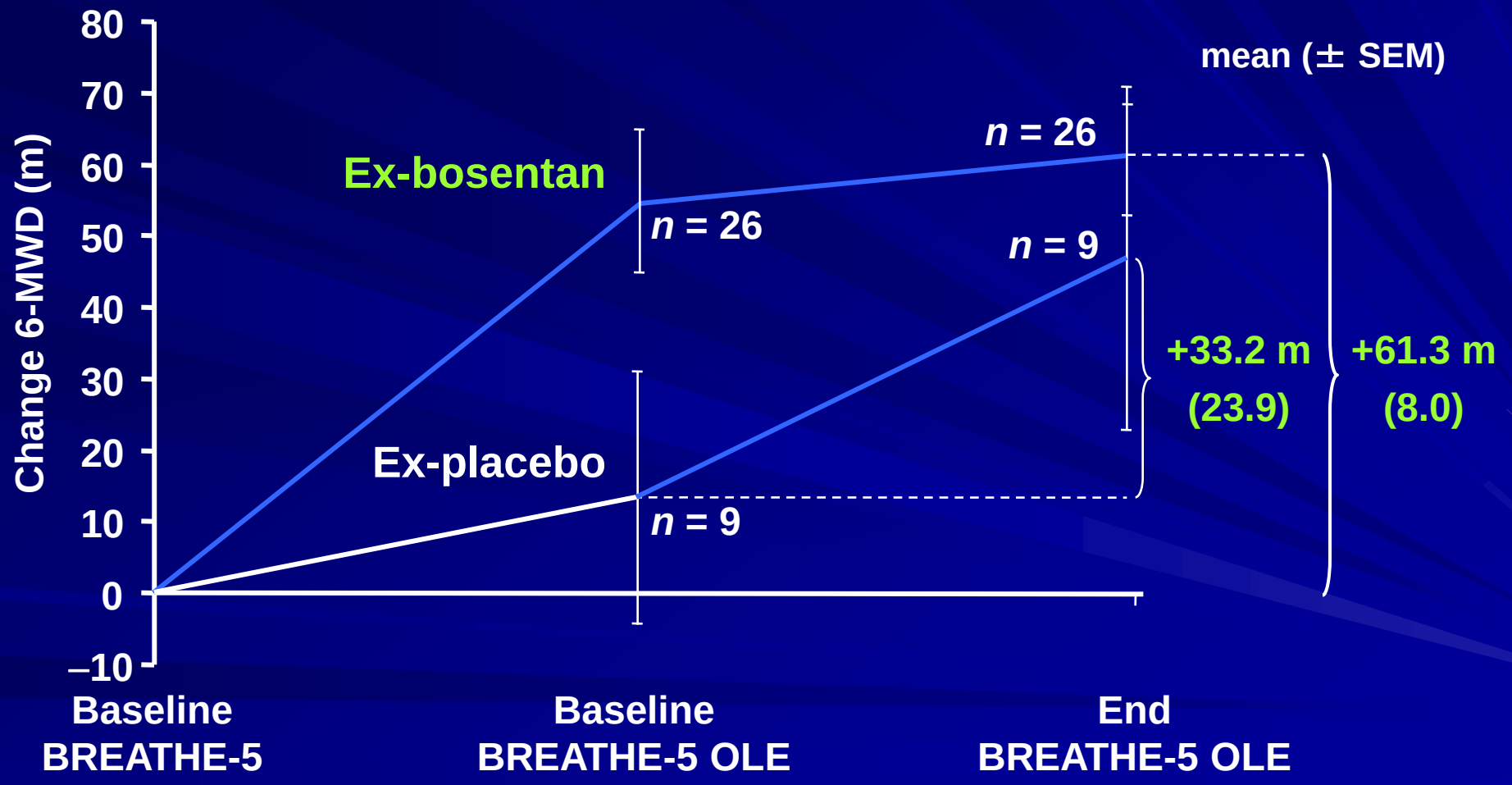
Galiè N, *et al. Circulation* 2006; 114:48-54.

BREATHE-5 OLE: Study design

OLE = Open label extension

Gatzoulis MA, *et al. Int J Cardiol* 2008; 127:27-32.

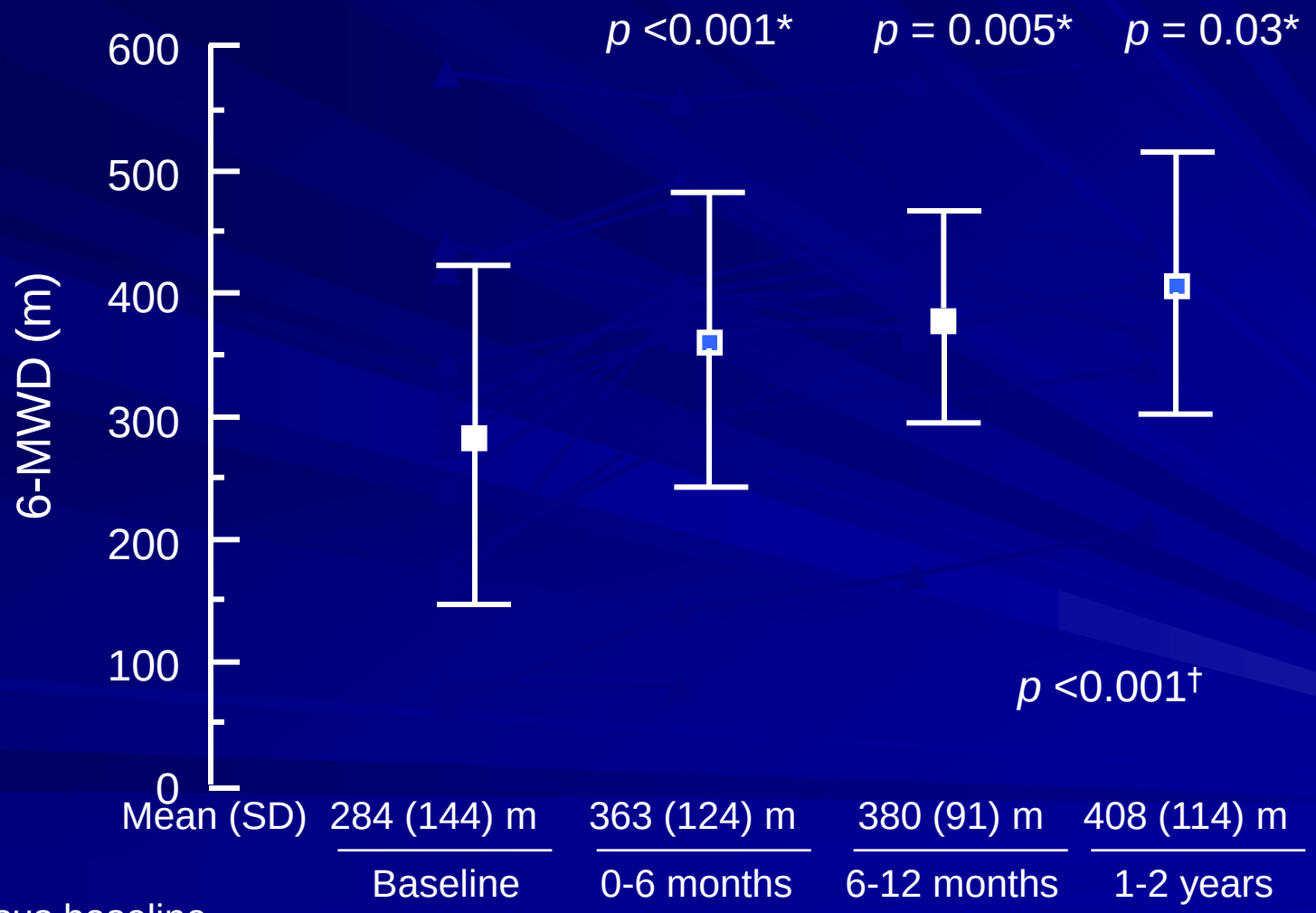
Bosentan increased exercise capacity



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

Gatzoulis MA, *et al*. *Int J Cardiol* 2008; 127:27-32.

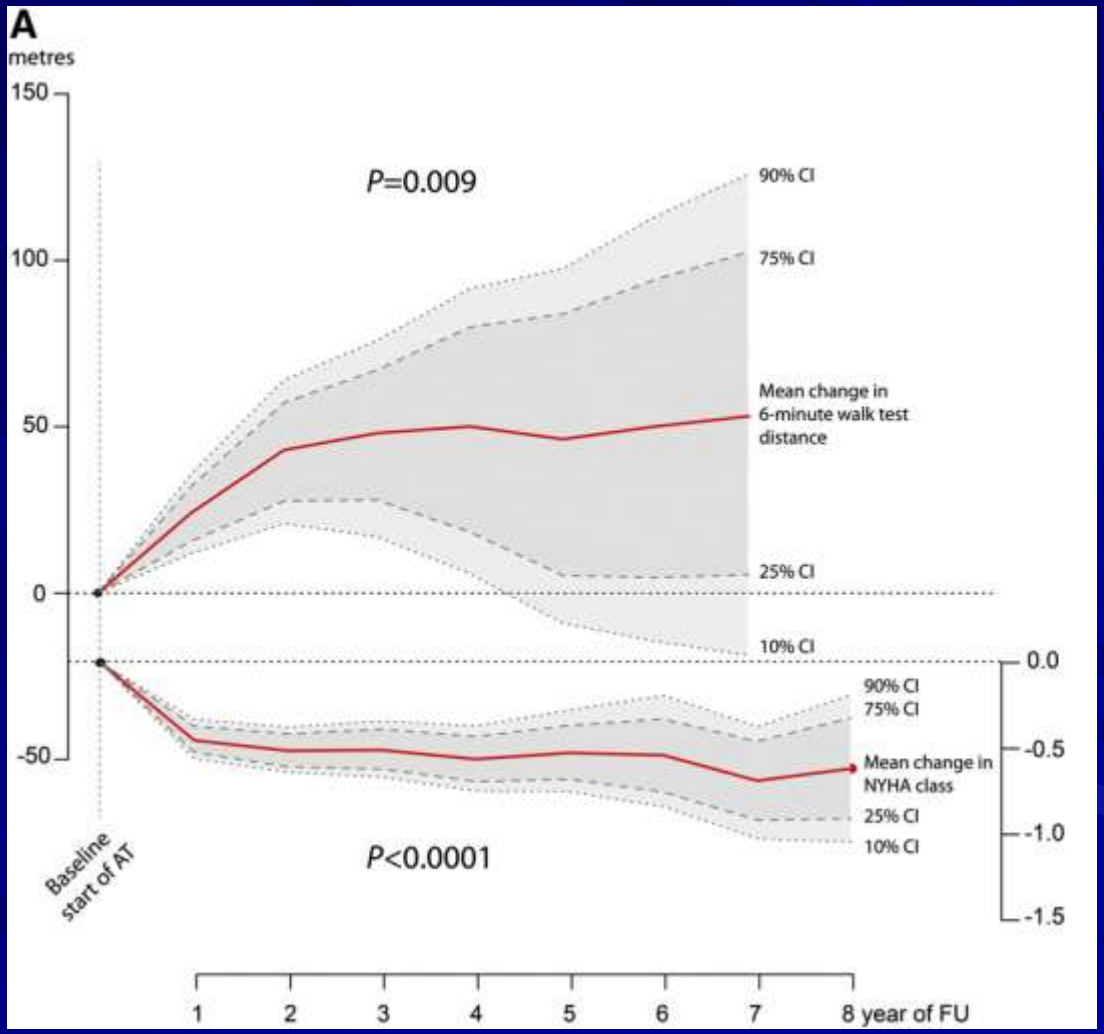
Long-term Brompton experience with bosentan in adults with PAH-CHD



*Versus baseline
†Analysis of covariance

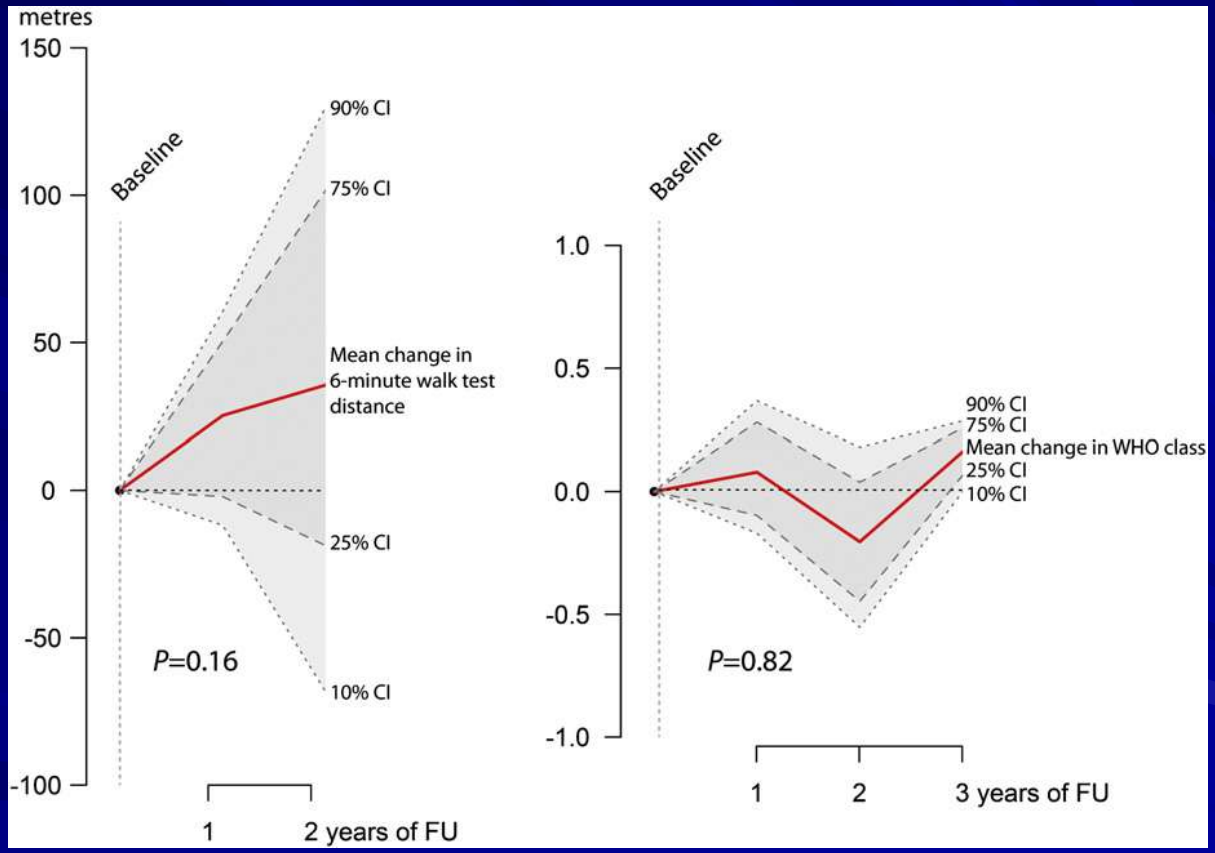
Diller GP, *et al. Heart* 2007; 93:974-6.

Long term efficacy of disease targeting therapies in Eisenmenger syndrome



Diller G et al. IJC 2012

Escalation of therapy



Diller G et al. IJC 2012

Sildenafil and quality of life

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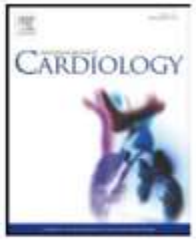


Quality of life and functional capacity can be improved in patients with Eisenmenger syndrome with oral sildenafil therapy

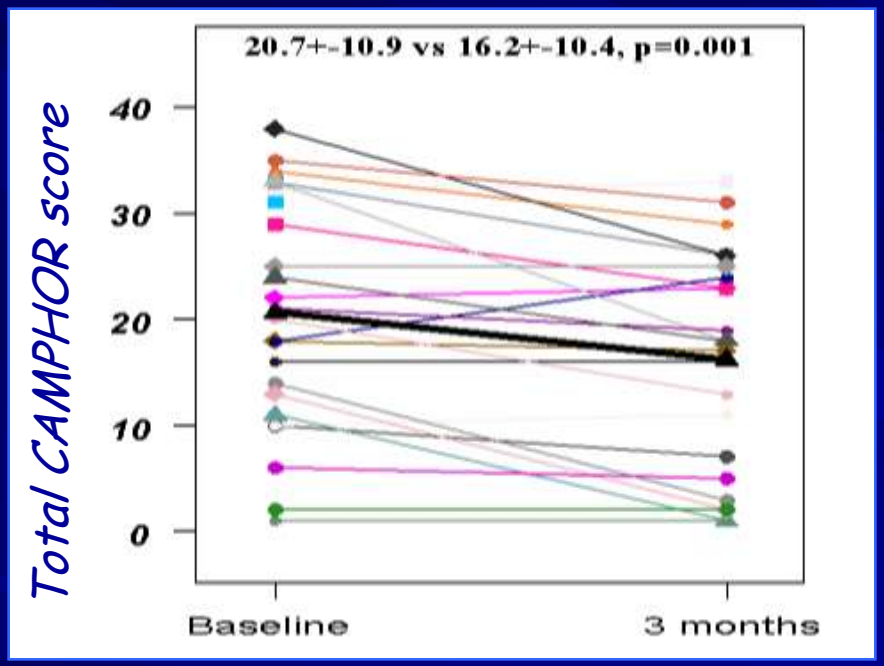
Edgar L.W. Tay [a], Maria Papaphylactou [a], Gerhard Paul Diller [a], Rafael Alonso-Gonzalez [a], Ryo Inuzuka [a], Georgios Giannakoulas [a], Carl Harries [a], Stephen John Wort [a], Lorna Swan [a], Konstantinos Dimopoulos [a,b,*], Michael A. Gatzoulis [a,b]

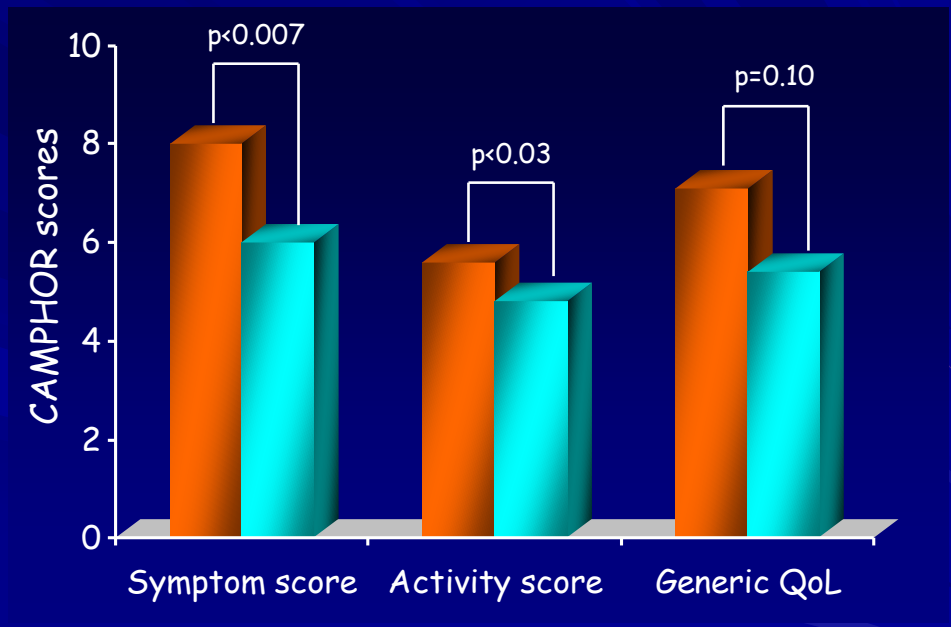
[a] *Adult Congenital Heart Centre and Centre for Pulmonary Hypertension, Royal Brompton Hospital, London, UK*
[b] *National Heart Lung Institute, Imperial College of Science and Medicine, London, UK*

Prospective study, n=12 patients with Eisenmenger syndrome,

NYHA class III, sildenafil for 3 months

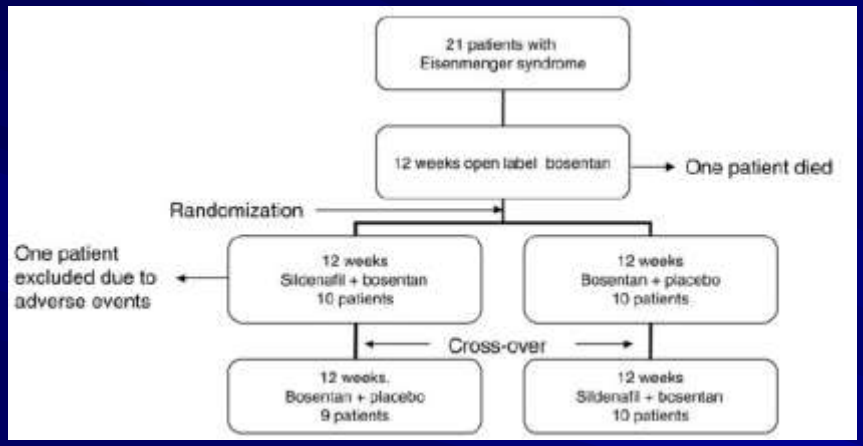
Effect on quality of life

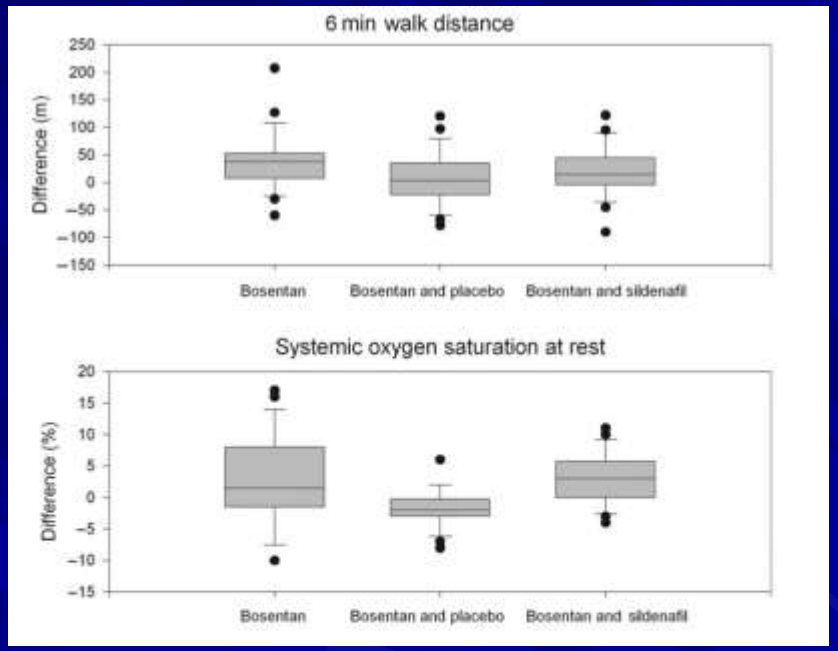




Tay ELT, *et al*. *Int J Cardiol 2010*

Combination therapy





Adding sildenafil to bosentan did not improve the 6 MWD significantly (21 vs. 8 m, P = 0.48), but increased saturation at rest (2.9 vs. –1.8%, P<0.01)

Iversen et al. EHJ 2010

Have we improved survival?

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®
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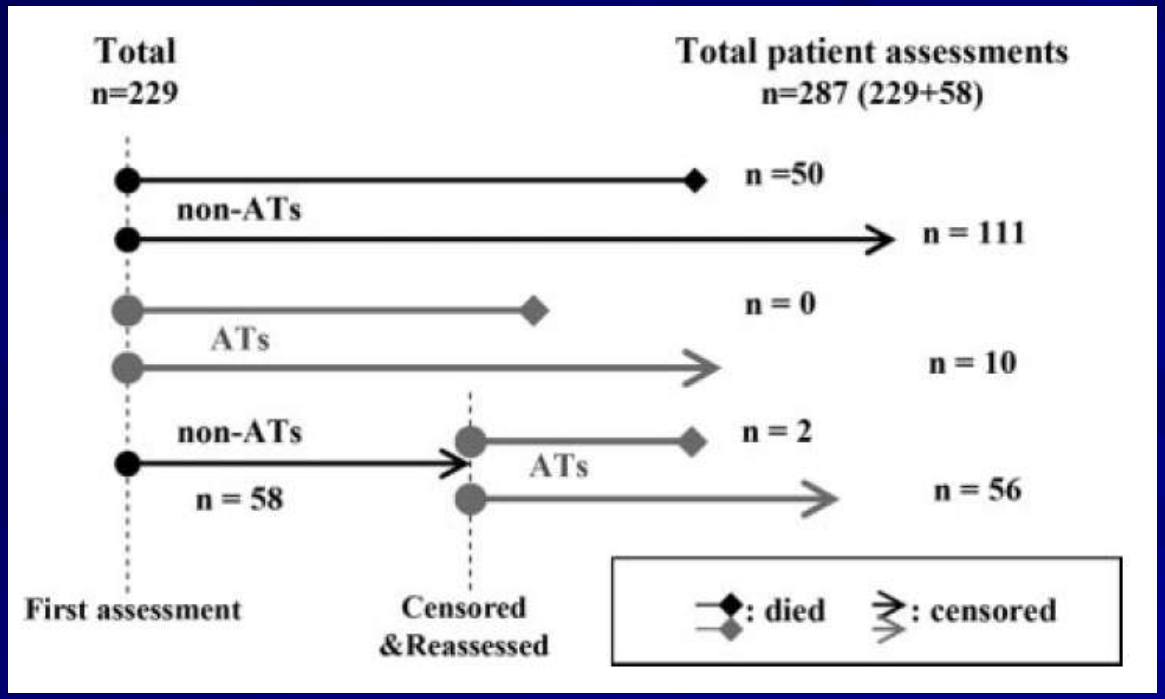
Improved Survival Among Patients With Eisenmenger Syndrome Receiving Advanced Therapy for Pulmonary Arterial Hypertension

Konstantinos Dimopoulos, Ryo Inuzuka, Sara Goletto, Georgios Giannakoulas, Lorna Swan, Stephen J. Wort and Michael A. Gatzoulis

Circulation published online Dec 21, 2009;
DOI: 10.1161/CIRCULATIONAHA.109.883876
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

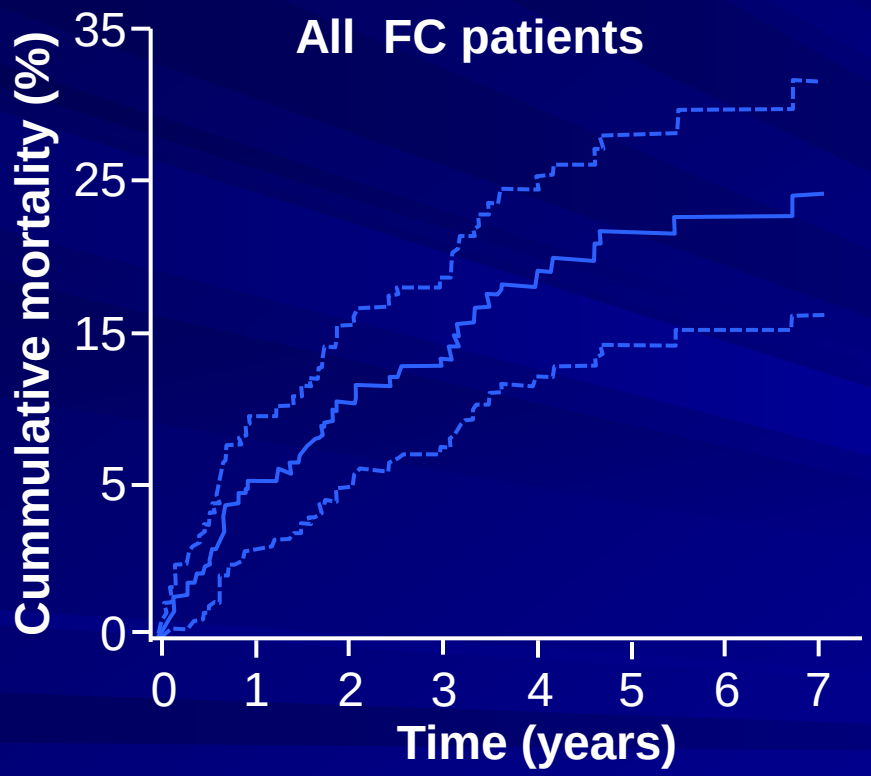
Study design



- 229 patients (34.5±12.6 years; 35% male)
- 54% NYHA class >III
- 30% Down syndrome
- Mean resting saturations 84%
- 68 patients (30%) either were on AT or had AT initiated during follow-up
- 73.5% bosentan, 25% sildenafil, 1.5% epoprostenol

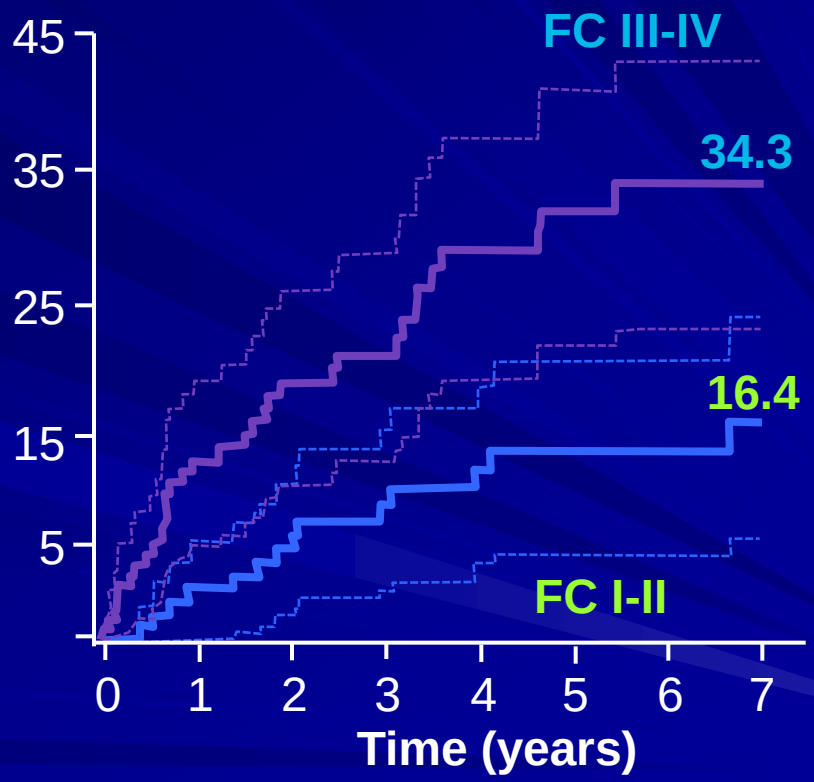
Dimopoulos et al. Circulation 2010

Contemporary survival in Eisenmenger syndrome: Relation to functional class



Patients at risk

229 197 169 145 116 92 69 52

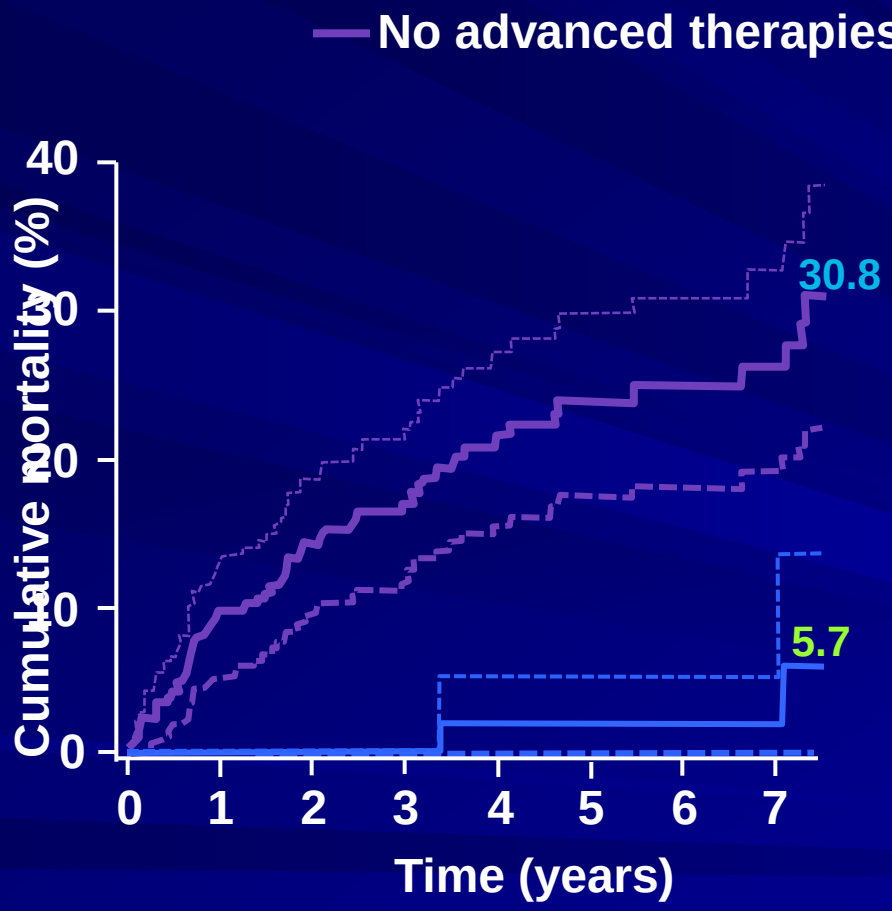


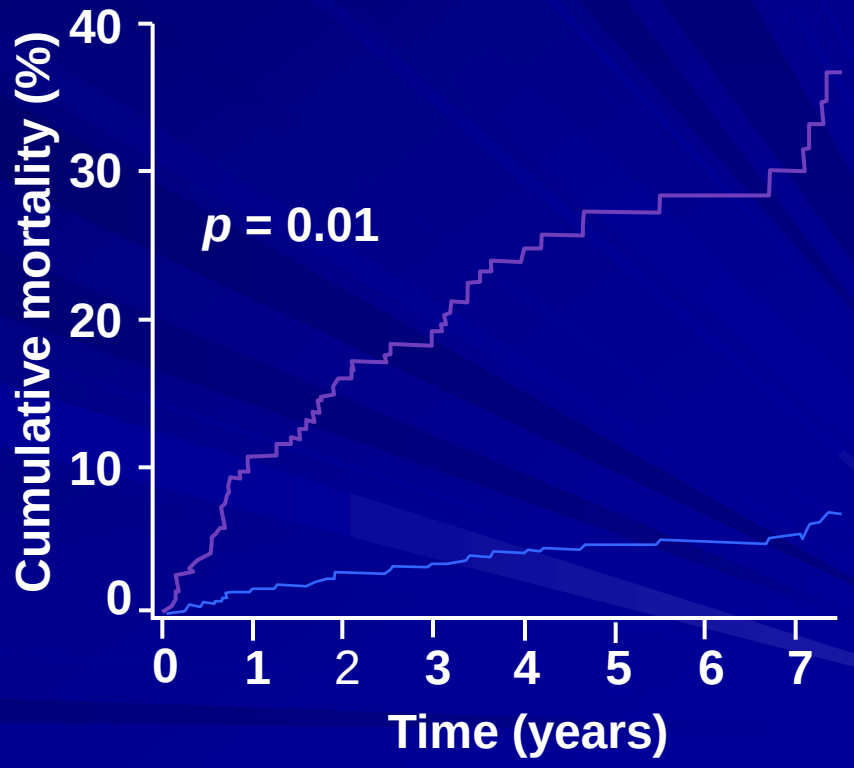
n 123 89 81 65 51 37 25 17

n 106 99 88 80 65 59 44 35

Dimopoulos et al Circulation 2010

Cumulative mortality with advanced therapies





Dimopoulos et al Circulation 2010

Goal-oriented treatment strategy

Congenital heart disease

ORIGINAL ARTICLE

B-type natriuretic peptide concentrations in contemporary Eisenmenger syndrome patients: predictive value and response to disease targeting therapy

Gerhard-Paul Diller,[1,2] Rafael Alonso-Gonzalez,[1] Aleksander Kempny,[1] Konstantinos Dimopoulos,[1,2] Ryo Inuzuka,[1] Georgios Giannakoulas,[1] Lianne Castle,[1] Astrid E Lammers,[1] James Hooper,[3] Anselm Uebing,[1] Lorna Swan,[1] Michael Gatzoulis,[1,2] Stephen J Wort[1,2]

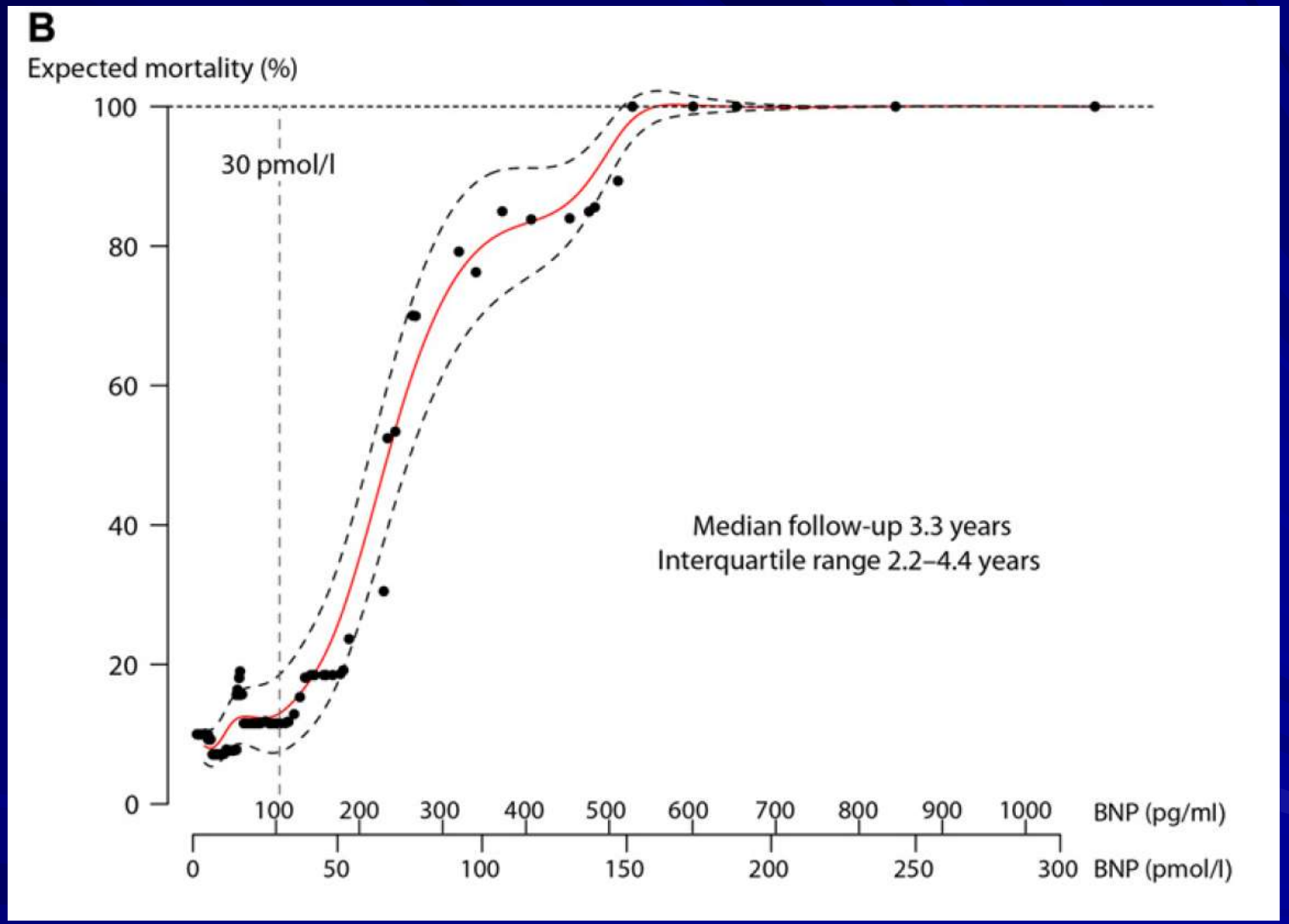
Predictors of outcome

Table 3 Multivariable predictors of mortality on Cox proportional hazards analysis

Variables	HR (95% CI)	p Value
Multivariable analysis		
BNP (per 100 pg/ml)	1.71 (1.07 to 2.73)	**0.02**
Creatinine (per 10 µm/l)	0.70 (0.50 to 0.97)	**0.03**
6 min walk test distance (per 10 m)	0.93 (0.87 to 0.99)	**0.02**
Down syndrome	2.11 (0.47 to 9.39)	0.33

BNP, B-type natriuretic peptide, WHO, World Health Organization functional class.
Significant variables are printed in bold.

Diller G et al. Heart 2012



Diller G et al. Heart 2012

Conclusions

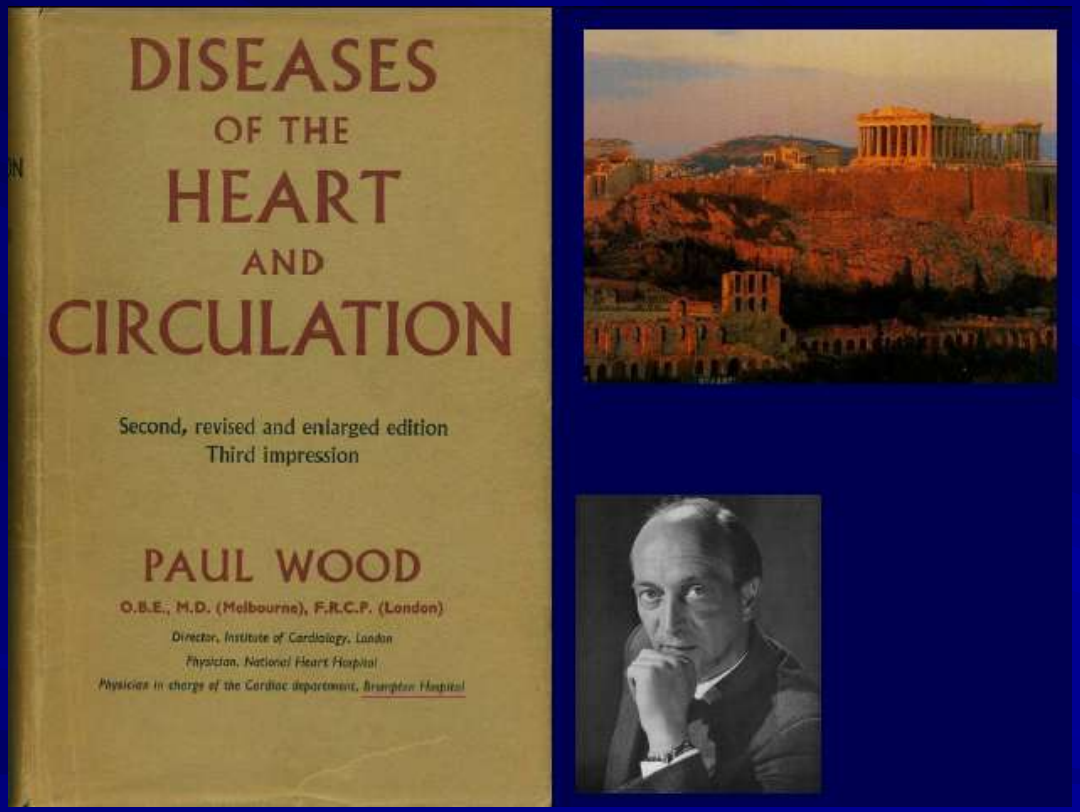
- Eisenmenger syndrome differs significantly from other types of pulmonary arterial hypertension in terms of pathophysiology and natural history.
- Eisenmenger syndrome is associated with multiple systemic complications and multiorgan failure
- Advanced therapies have been shown to improve haemodynamics, exercise capacity and survival in Eisenmenger population. Their efficacy appears to be long-lasting
- A goal oriented treatment strategy based on BNP and 6MWT might be beneficial in patients with Eisenmenger syndrome

Challenge

ΜΗΤΡΩΟ ΚΑΤΑΓΡΑΦΗΣ ΑΣΘΕΝΩΝ
ΜΕ ΣΥΓΓΕΝΕΙΣ ΚΑΡΔΙΟΠΑΘΕΙΕΣ

Hospital	Number of Patients
Achilopouleion' General Hospital of Volos	5
Ahepa Hospital Thessaloniki	15
Mediterraneo Hospital Athens	1
General Hospital of Kavala	2
Saint Luke's Clinic	8
University General Hospital ATTIKON	4
Thessaloniki General Hospital ' Papanikolaou'	2
Total	**37**

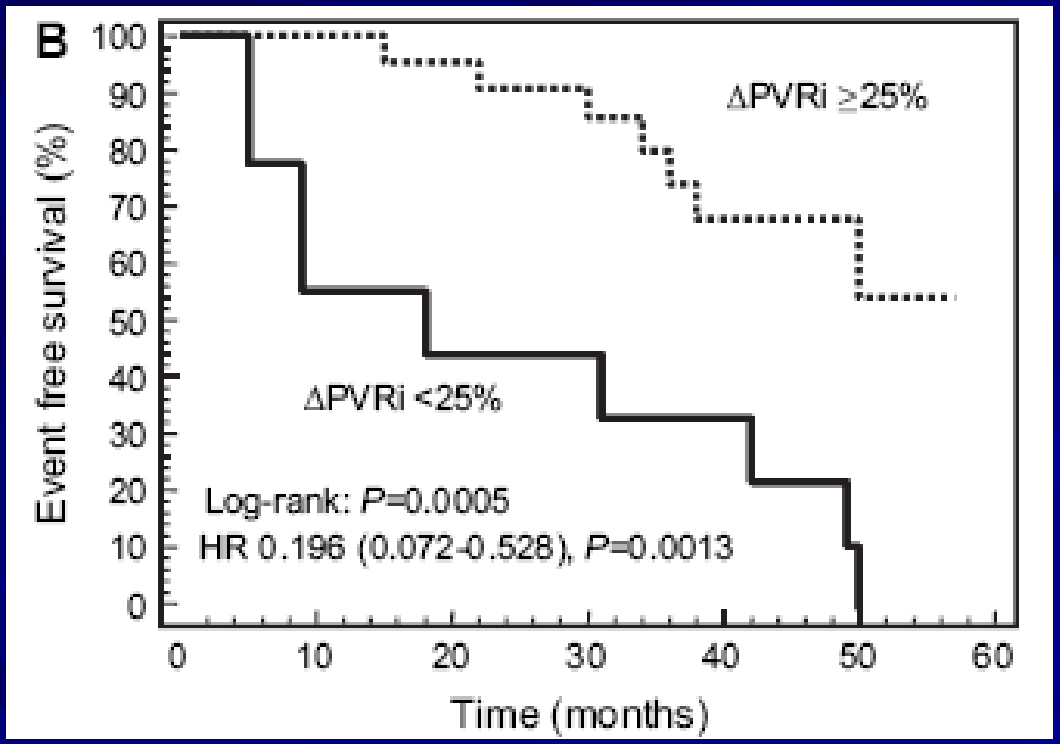
Thanks for your attention



giannak@med.auth.gr

Pulmonary vasoreactivity predicts long-term outcome in patients with Eisenmenger syndrome receiving bosentan therapy

Michele D'Alto,[1] Emanuele Romeo,[1] Paola Argiento,[1] Giuseppe Santoro,[1] Berardo Sarubbi,[1] Giampiero Gaio,[1] Christian Mélot,[2] Maria Giovanna Russo,[1] Robert Naeije,[3] Raffaele Calabrò[1]



N=38 consecutive patients with CHD-PAH and Eisenmenger syndrome under bosentan treatment

Heart 2010