Treatment guidelines and evidences for PAH associated with CHD

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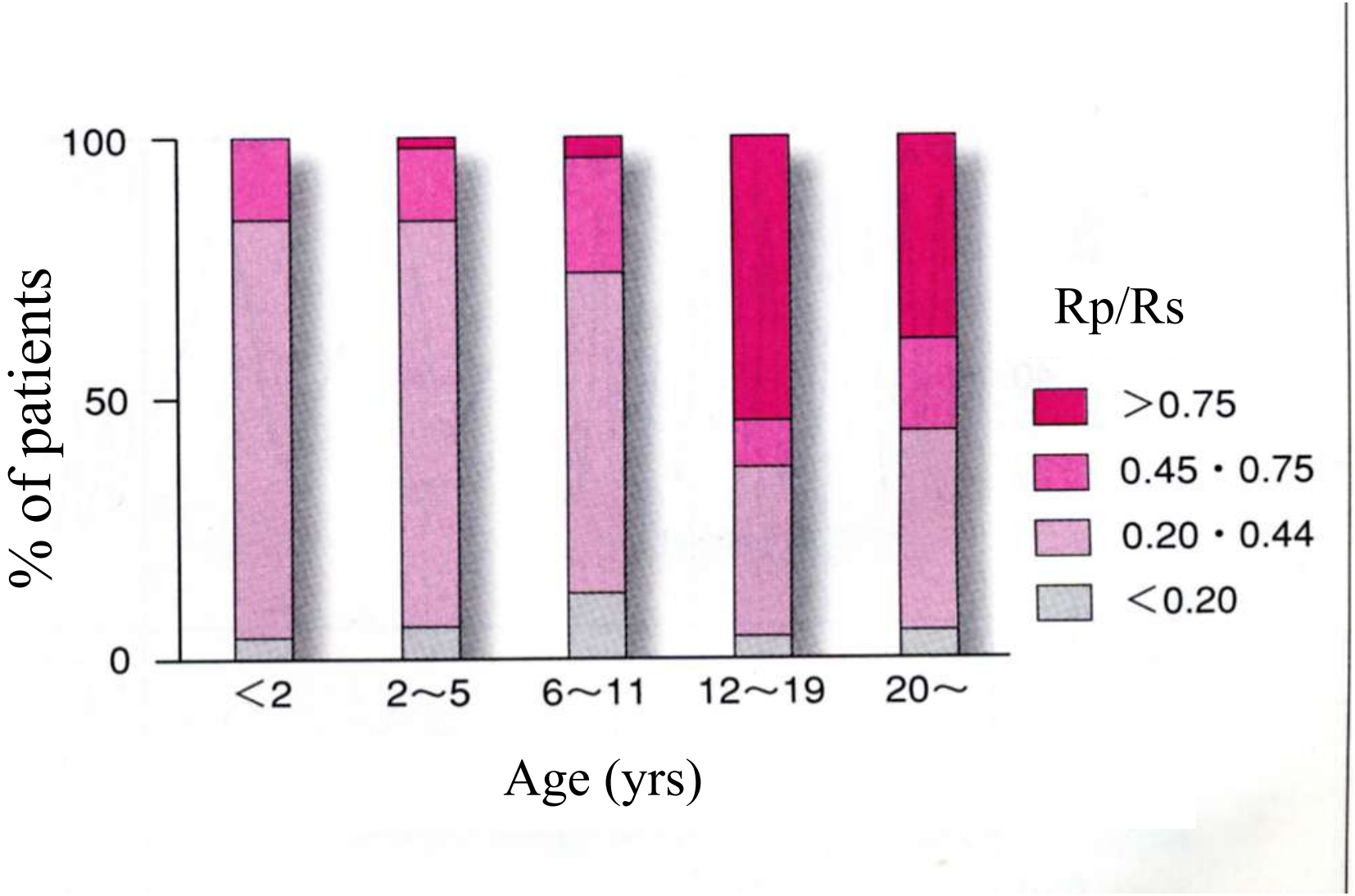
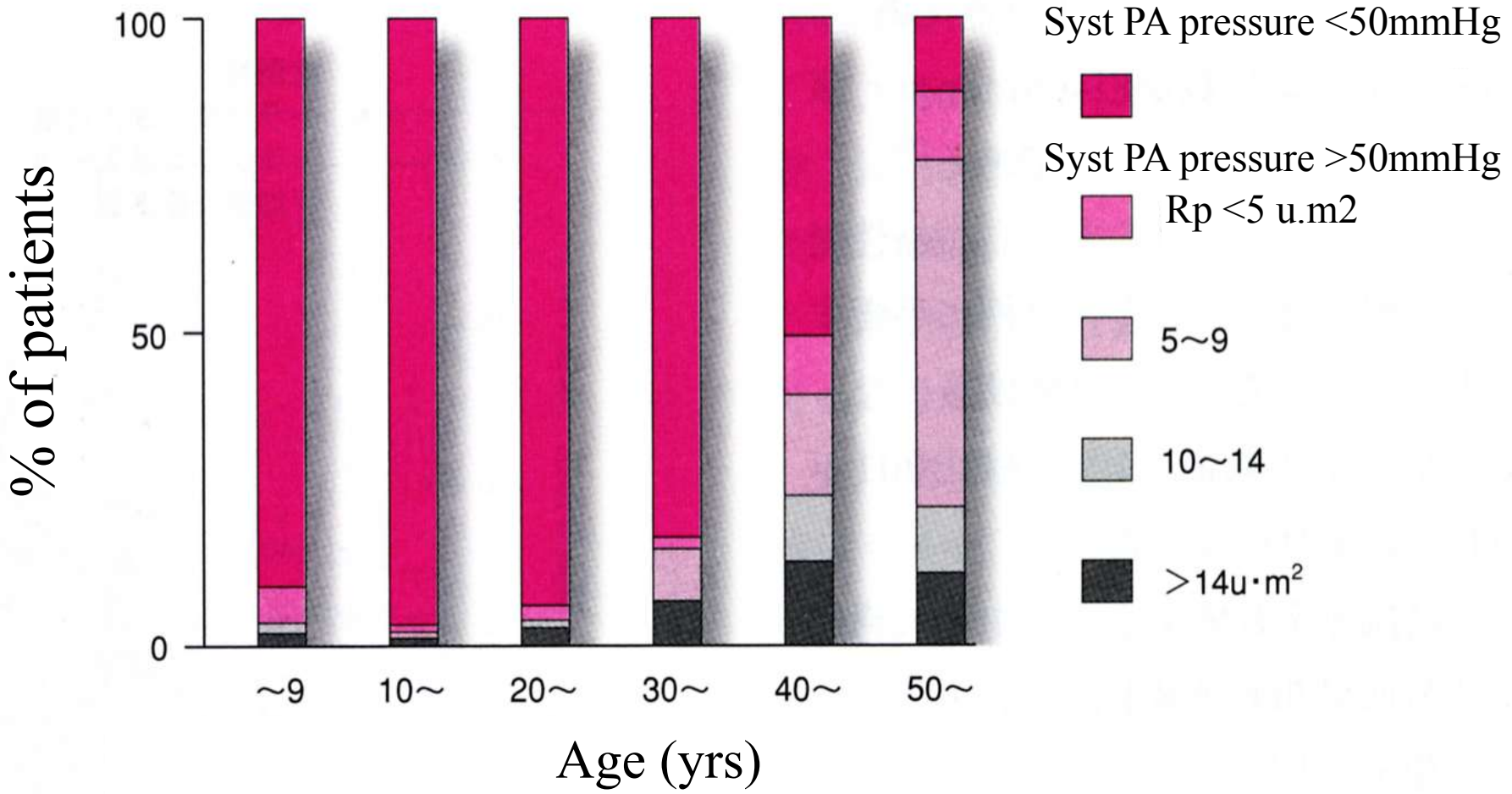
Pulmonary hypertension in patients with congenital heart disease

- Increased pulmonary flow
- Increased pulmonary pressure
- Vasoconstriction
- Intima- media hyperplasia
- Irreversible changes
- Genetic factors: unkown
- LV failure, MR

High Rp in pts with mod-large VSD



ASD

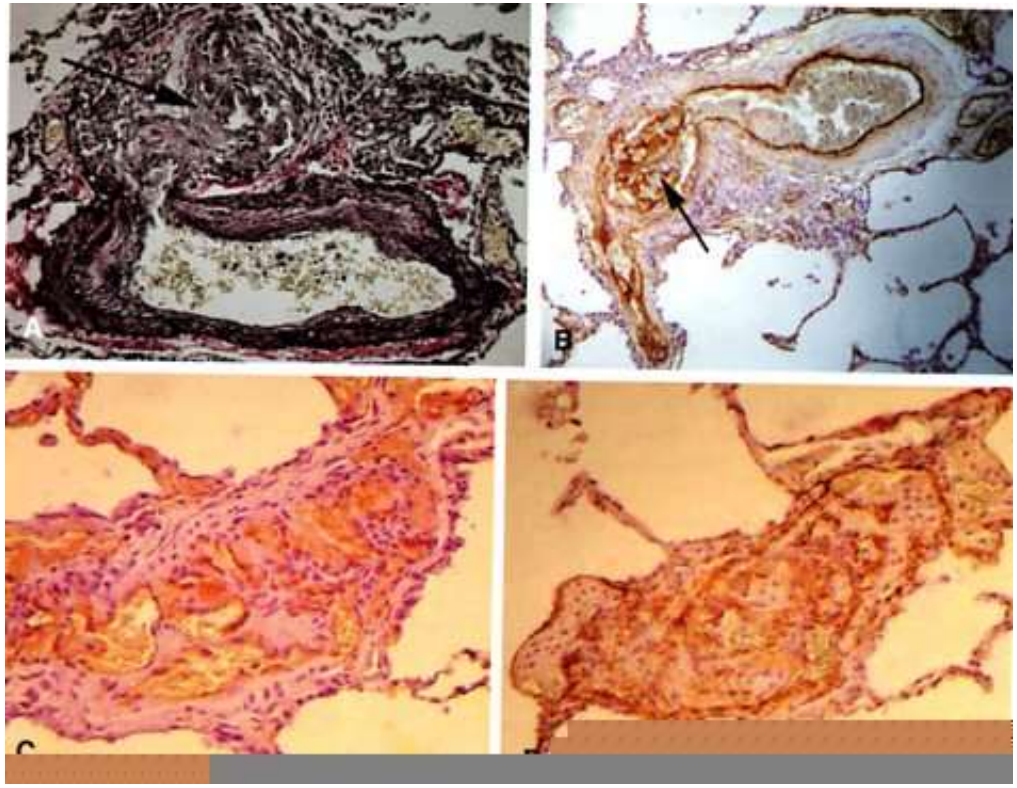

100
50
0
% of patients
~9
10~
20~
30~
40~
50~
Age (yrs)
Syst PA pressure <50mmHg
Syst PA pressure >50mmHg
Rp <5 u.m2
5~9
10~14
>14u·m²

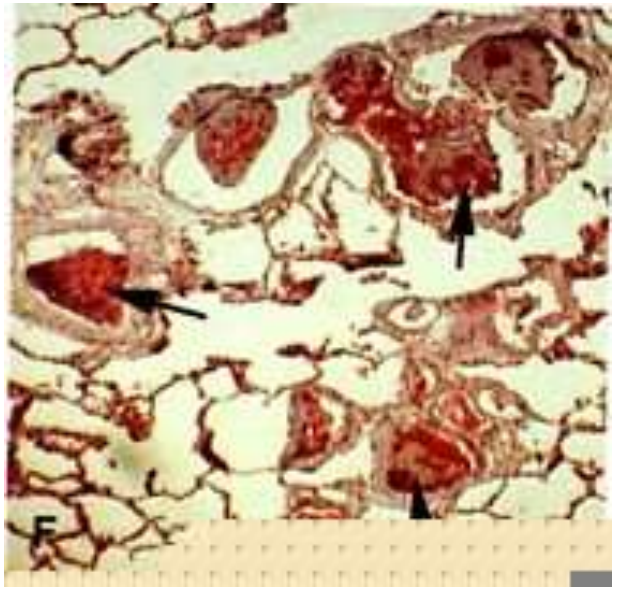
PH pathology: Heath-Edwards

	Media	Intima
I	hypertrophy	none
II		hyperplasia
III		fibrosis
IV	dilatation	plexiform
V		
VI	nectotizing	fibrinoid

Pathology of severe pulmonary hypertension

- Plexiform lesions
- Intimal thickening





Cardiac catheterization

- Pulmonary flow, Systemic flow
  - Fick mehod
- RAp, PAp, LA (PA wedge) pressure、AOp
- Reactivity test
  - 100% O2
  - Prostacyclin (Epoprostenol）2,4,8,10 ng/kg/min
  - NO　20 ppm (20-80 ppm)

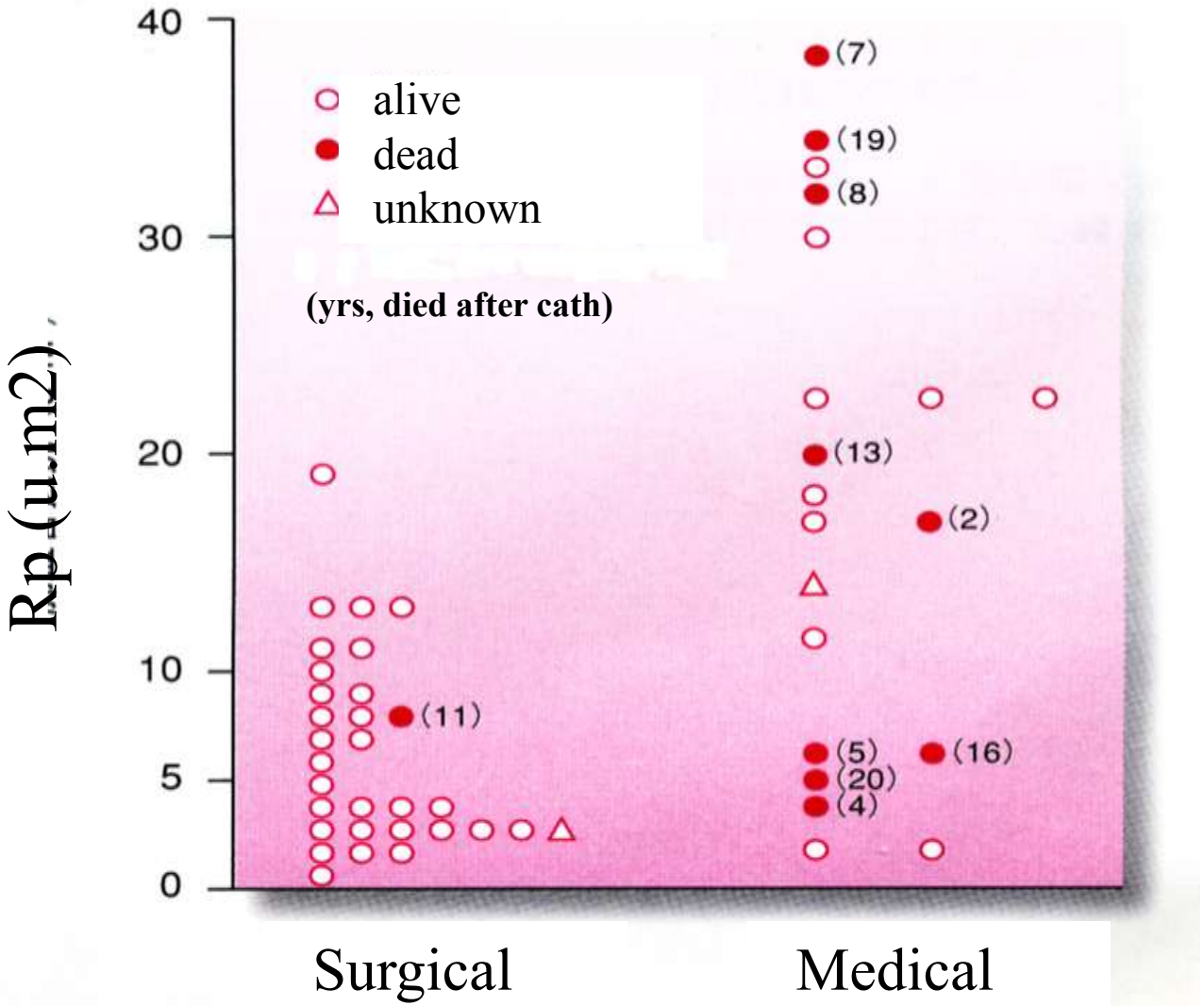
Pulmonary resistance

- Rule of Ohm: V=IR R=V / I
- Rp = (mean PA pressure – mean LA pressure) / Qp
- Example:

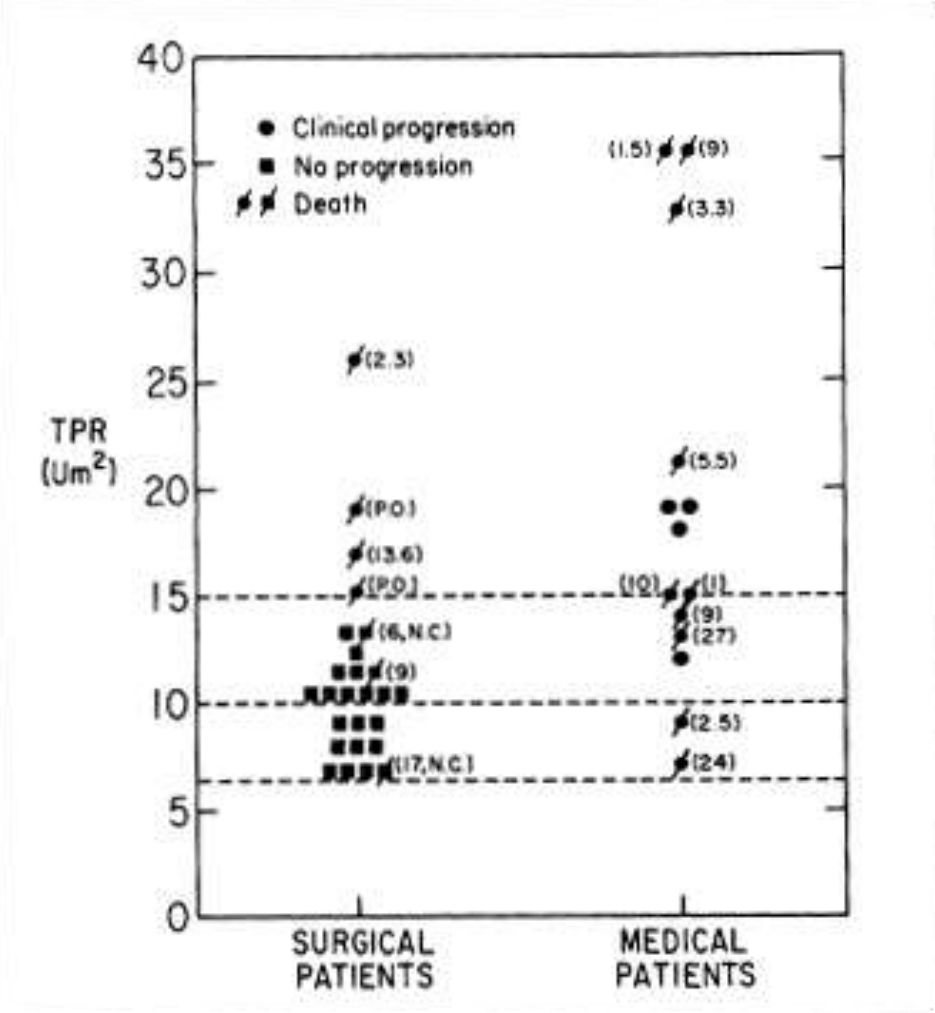
  Rp=(25 mmHg – 10 mmHg) / 3 L/min/m2

  = 5 Wood unit x m2
- Normal < 3 Wood unit x m2

Rp in patients with ASD



ASD with high total pulmonary resistance (>7 Um2)



Steele et al. Circulation 1987

Recommendations

- Pts with PAH associated with CHD should undergo pulmonary vasodilator testing
- Pts with PAH should undergo pulmonary vasodilator testing by experts

Criteria of responders: IPAH

- A decrease of mPAP > 10mmHg
- mPAP <40mmHg
- No decrease in CO

- A decrease in PVR> 20%

- A decrease in mPAP >20%, no decrease in CO

Operability

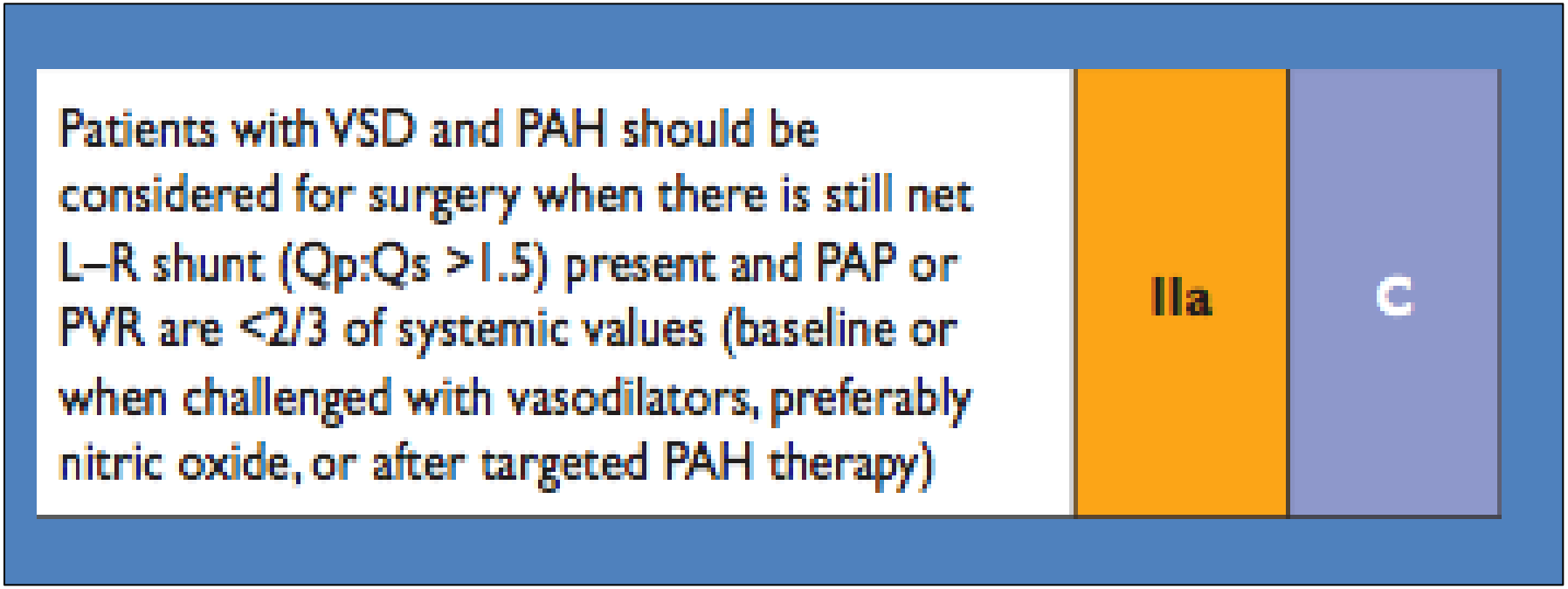
- PVR < 6 Wood units x m2, PVR:SVR <0.3
- If PVR between 6-9 and PVR:SVR between 0.3-0.5, do acute vasodilator test
  - A decrease of PVR > 20%
  - A decrease of ratio of PVR:SVR .>20%
  - Final PVR < 6
  - Final PVR:SVR <0.3

Lopes and O'Leary. Cardiology Young 2009

Indication of ASD closure

Patients with significant shunt (signs of RV volume overload) and PVR <5 WU should undergo ASD closure regardless of symptoms	I	B[26]
Patients with PVR ≥5 WU but <2/3 SVR or PAP <2/3 systemic pressure (baseline or when challenged with vasodilators, preferably nitric oxide, or after targeted PAH therapy) and evidence of net L–R shunt (Qp:Qs >1.5) may be considered for intervention	IIb	C

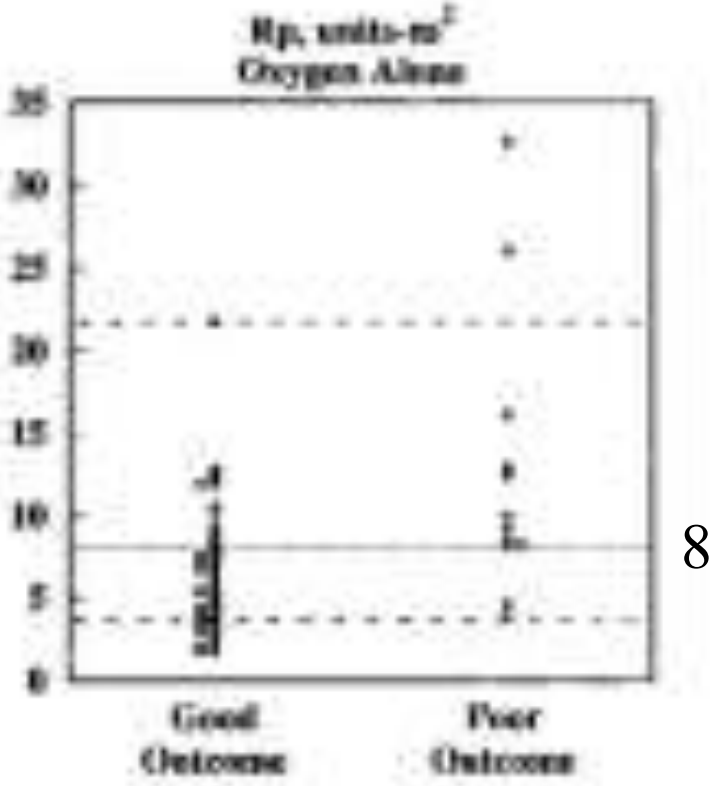
Indication of VSD closure



Indication of PDA closure

PDA should be closed in patients with PAH but PAP <2/3 of systemic pressure or PVR <2/3 of SVR	I	C
PDA closure should be considered in patients with PAH and PAP >2/3 of systemic pressure or PVR >2/3 of SVR but still net L–R shunt (Qp:Qs >1.5) or when testing (preferably with nitric oxide) or treatment demonstrates pulmonary vascular reactivity	IIa	C

Operability



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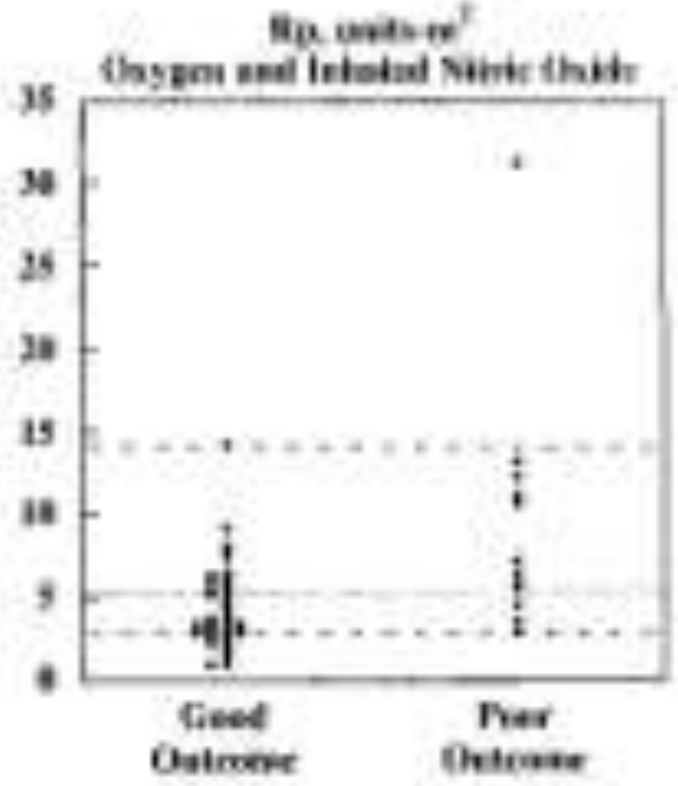

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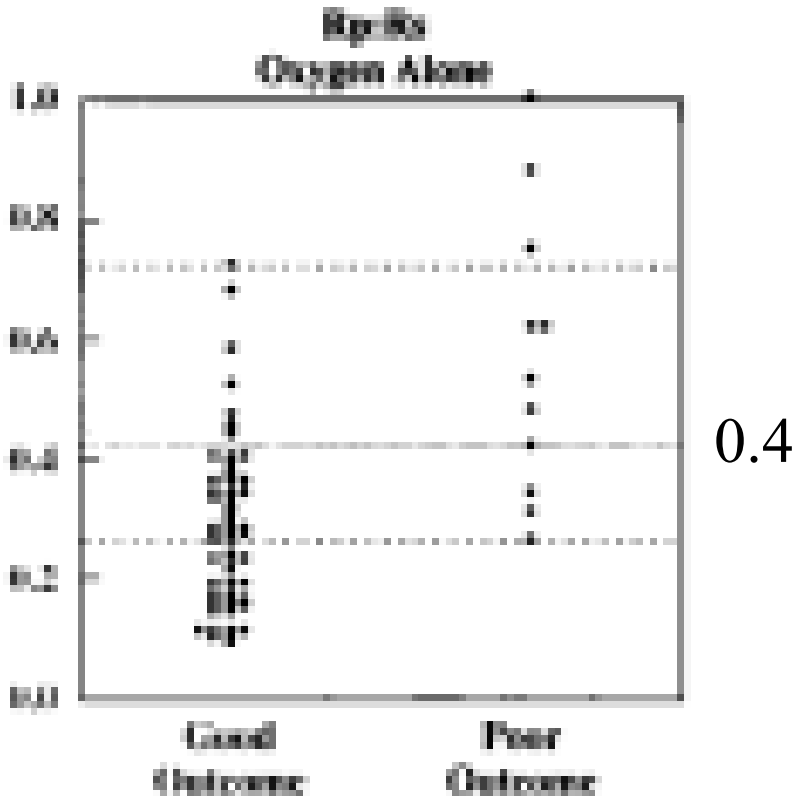
Balzer DT et al. Circulation 2002; 106: I76

Operability



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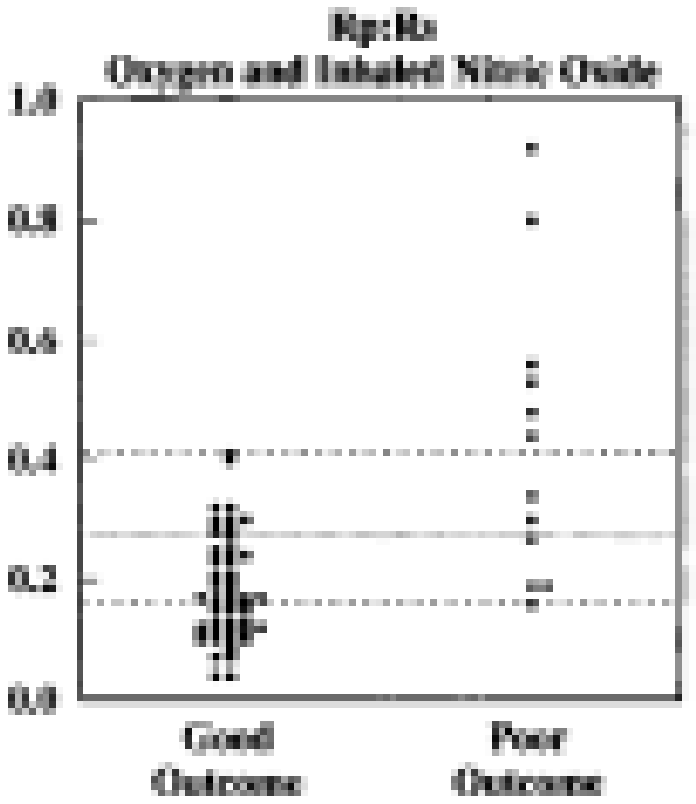


0.27

Acute vasodilator testing

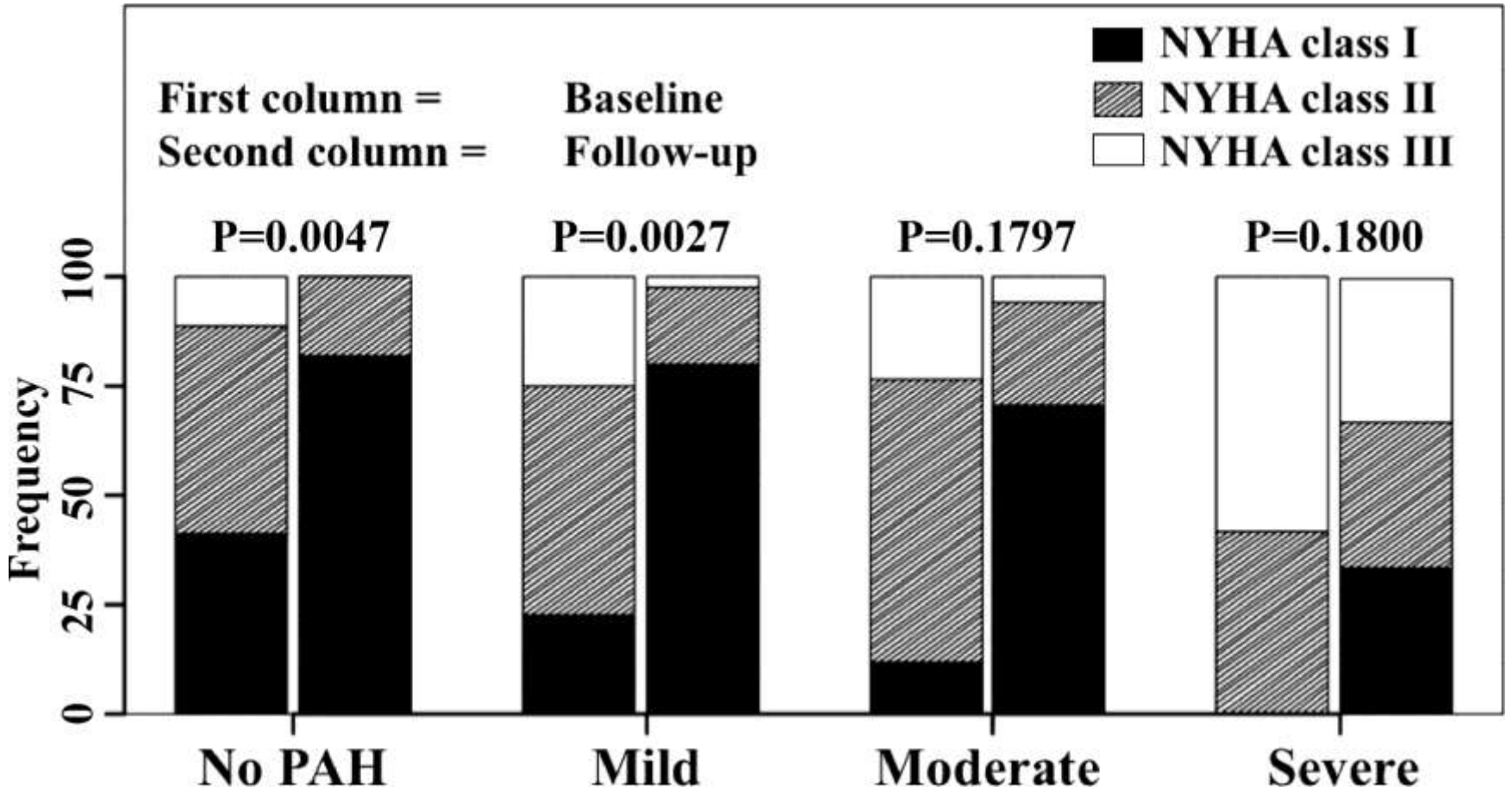
- There is no established protocol for acute vasodilator testing or proven criteria for assessing the response with respect to either operability or long term outcomes in CHD (level C).
- (2013, Nice)

Can treat-repair lower the threshold?

1) depends on the threshold,

2)we do not know a natural (unnatural) history of PH after repair under pulmonary vasodilators,

3)pulmonary vasodilators do not normalize PA pressure.



Yong G et al. Circ Cardiovasc Interv 2009;2:455-462

Indication of shunt closure in the era of advanced therapy

- Low Rp
- High Rp and acute responders
- High Rp and borderline pts
  - Treat-and-repair strategy, which has not been established
  - Appropriate selection of pts is important
  - A significant responses to chronic advanced therapy

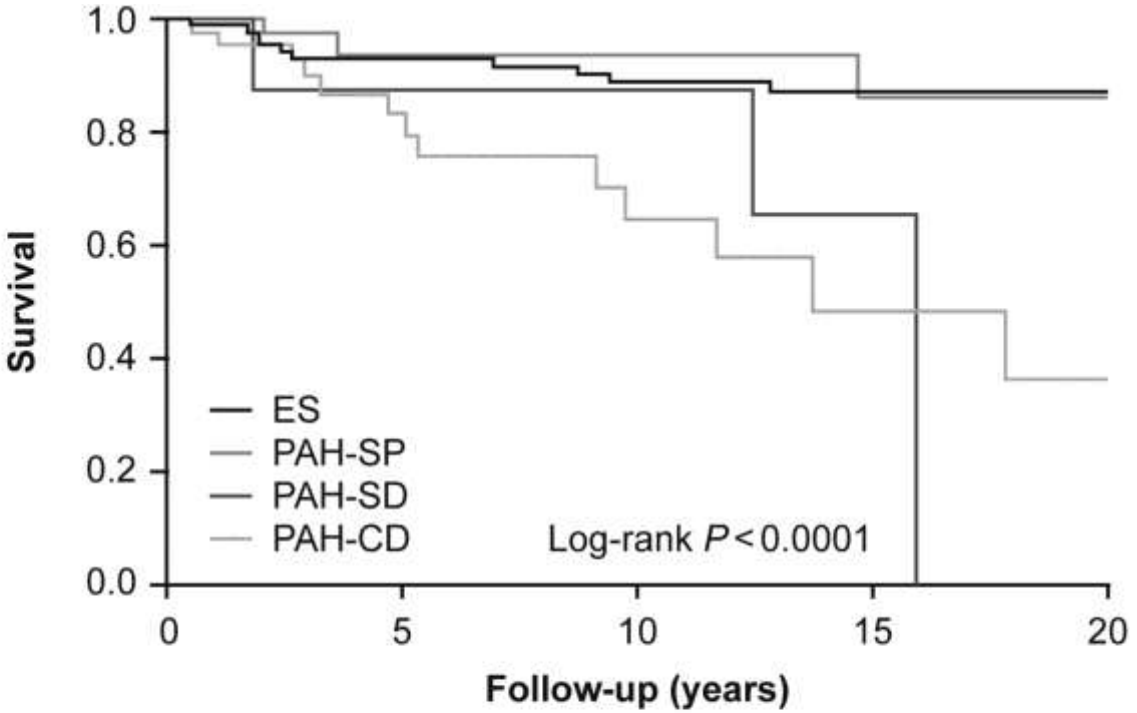
Repair of previously inoperable pts who respond to advanced therapy

For

- Abort R-L shunt
- Eliminates cerebrovascular events
- Prevent cyanosis
  - Increase Ex capacity
  - Decrease erythrocytosis
  - Decrease hemostatic problems
  - Decreasesystemic organ failure
- Protect pulmonary circulation

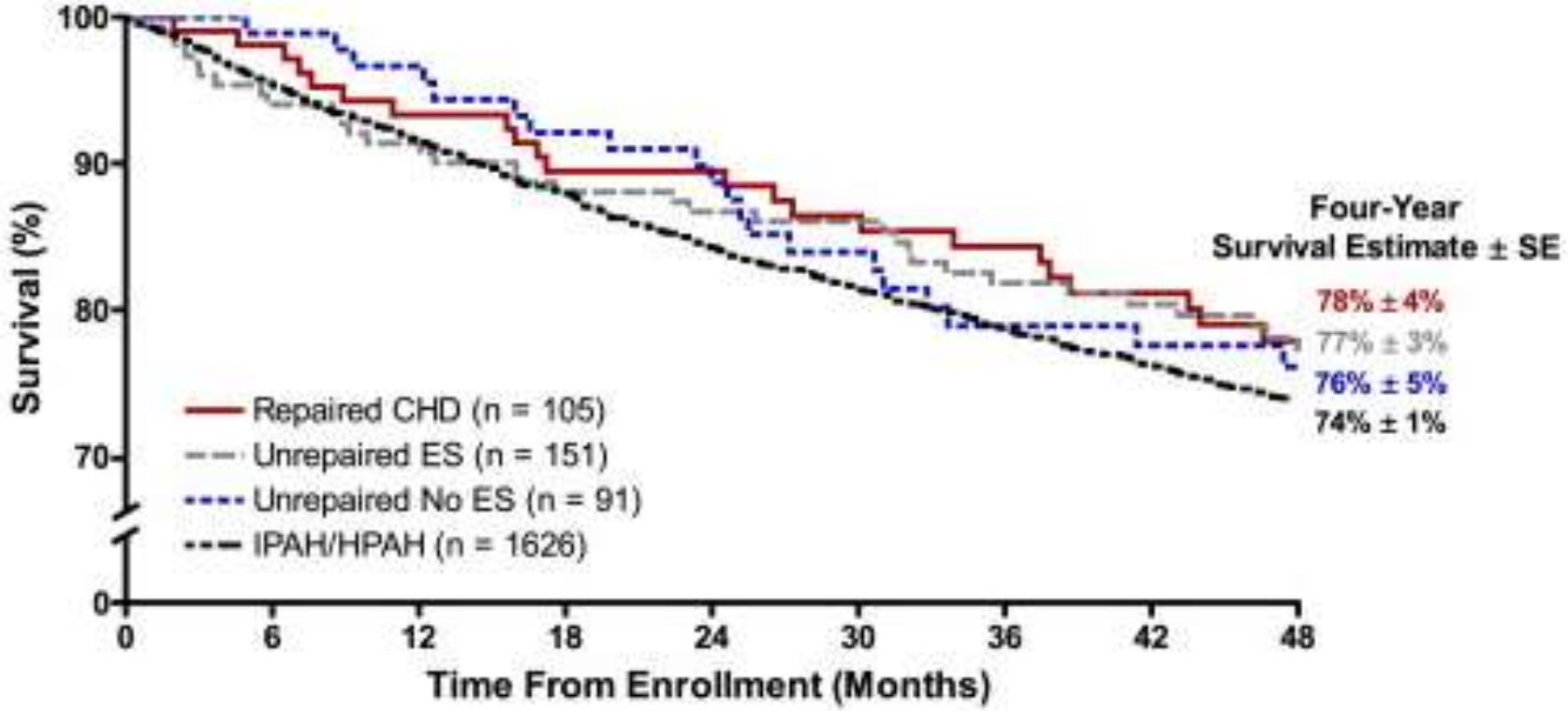
Against

- Potential conversion of Eisenmenger syndrome to IPAH (and thus worse long-term outcome)
- High perioperative risk
- Limited experience and no long term data



Patients at risk					
ES	90	71	59	52	48
PAH-SP	48	22	18	11	10
PAH-SD	10	4	4	2	0
PAH-CD	44	22	12	4	3

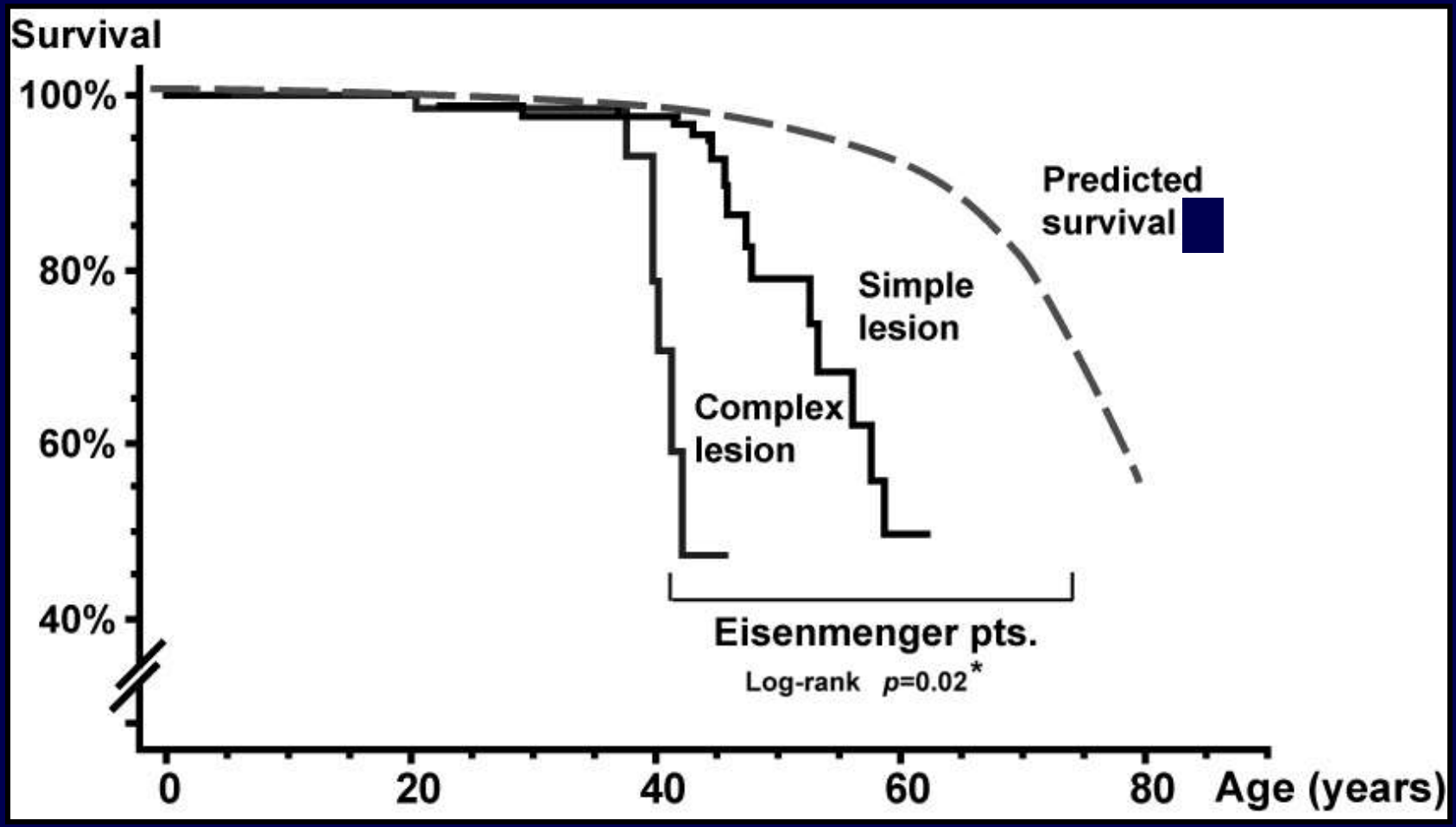
Manes A et al. Eur Heart J 2014;35:716-724



No. at Risk:									
Repaired CHD	105	103	98	93	88	83	80	76	70
Unrepaired ES	132	124	120	113	111	106	100	94	87
Unrepaired No ES	91	90	86	81	78	67	60	58	53
IPAH/HPAH	1626	1544	1470	1391	1303	1164	1086	999	912

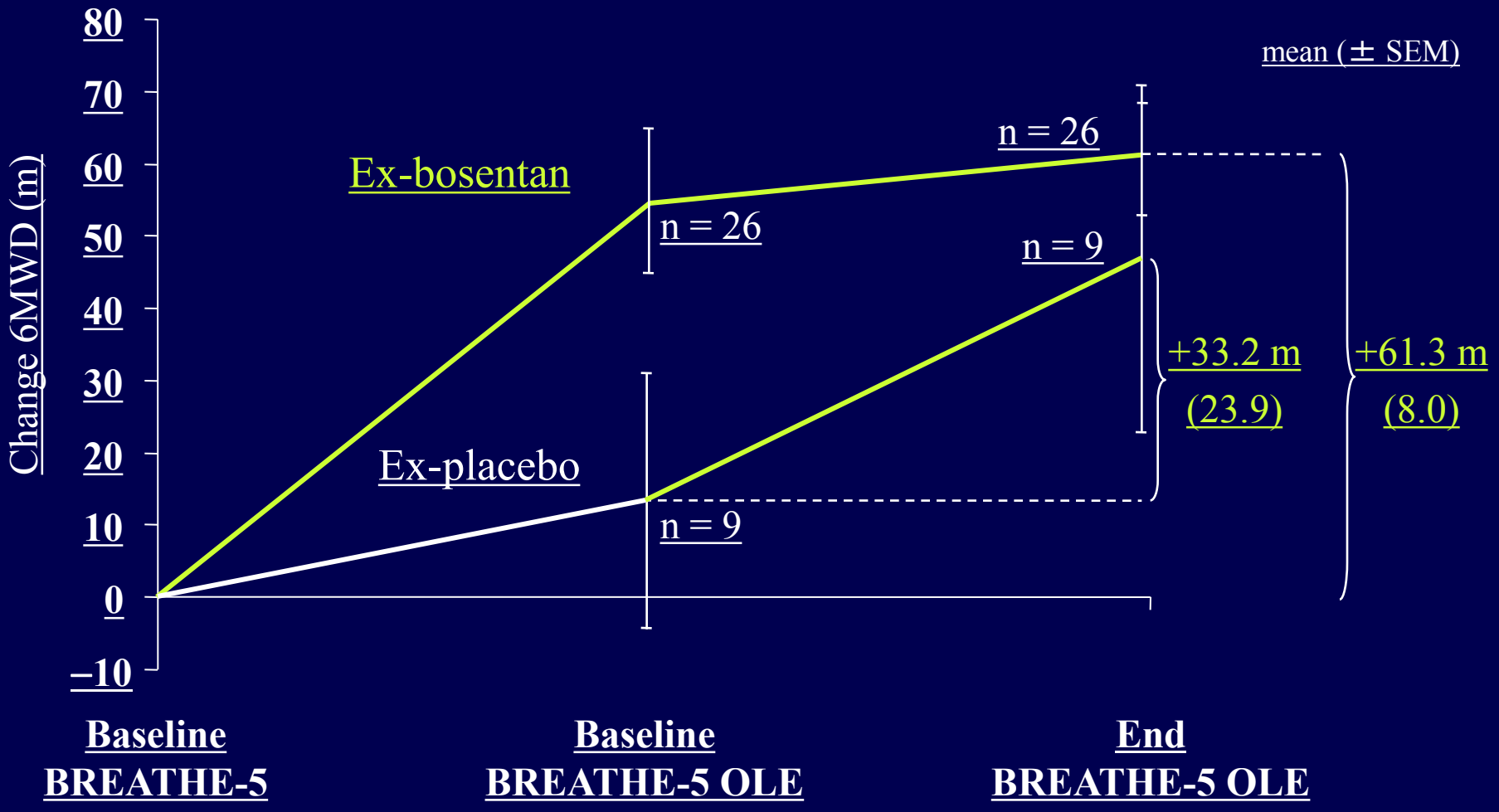
Adults with Eisenmenger Syndrome Survival

Diller *et al EHJ 2006*

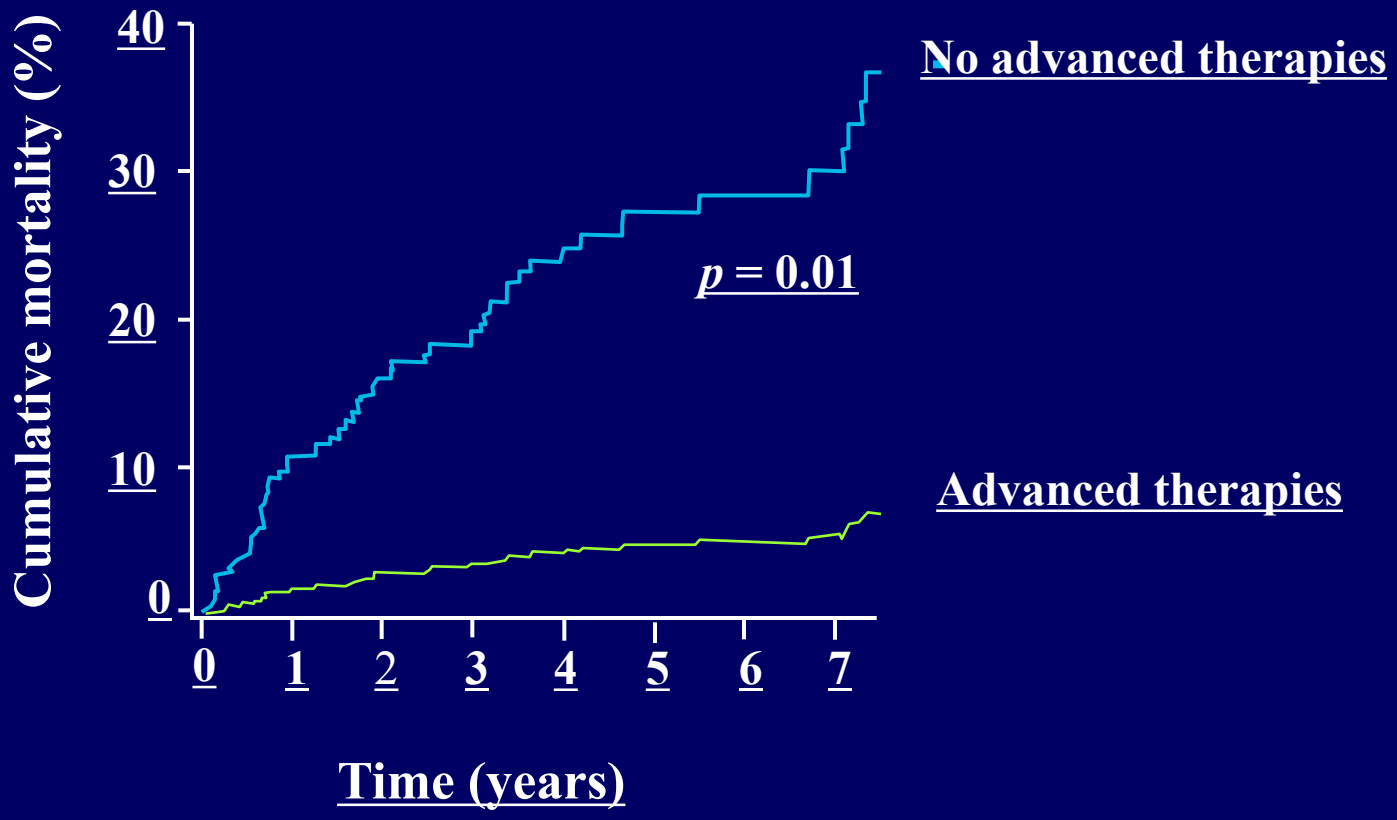


Standardised mortality ratio 3.8; 95% CI 2.0 – 7.0; p<0.0001

Bosentan increased exercise capacity



Cumulative mortality with advanced therapies



Dimopoulos et al Circulation 2010

European Heart Journal (2010) **31**, 1124–1131
doi:10.1093/eurheartj/ehq011

Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial†

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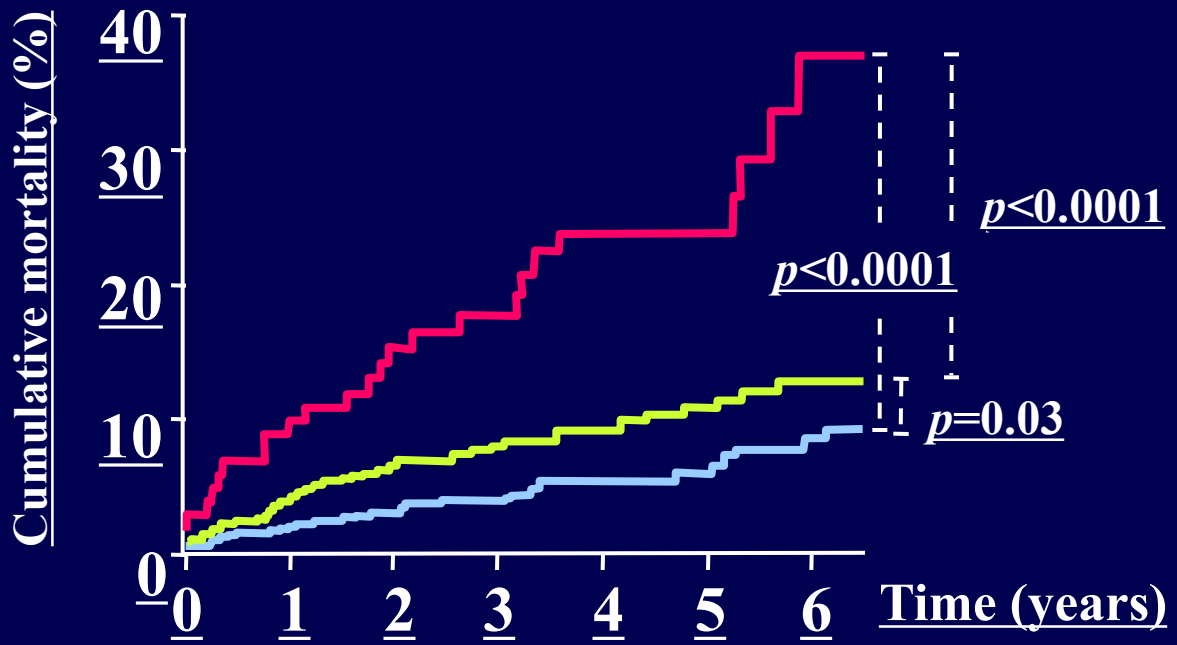
Aims To evaluate the efficacy of combining the dual endothelin receptor antagonist, bosentan, and the phosfodiesterase-5-inhibitor, sildenafil, in patients with Eisenmenger syndrome.

Methods and results The study was a randomized, placebo-controlled, double-blinded, cross-over design. Patients with Eisenmenger syndrome ($n = 21$) were treated open label with bosentan for 9 months. After 3 months, sildenafil/placebo was added for 3 months, and a cross-over was performed for the last 3 months. At baseline and after 3, 6, and 9 months, patients were examined with 6 min walk test, oxygen saturations, N-terminal pro-brain natriuretic peptide, New York Heart Association (NYHA) classification, cardiac catheterization, and magnetic resonance imaging. The primary endpoint was changed in 6 min walk distance (MWD). Bosentan improved the 6 MWD (377 vs. 414 m, $P = 0.001$), pulmonary vascular resistance (PVR) (28 vs. 22 wood, $P = 0.01$), and pulmonary blood flow (2.6 vs. 3.5 L/min, $P = 0.01$). 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%, $P < 0.01$).

Conclusion In Eisenmenger syndrome, treatment with bosentan significantly improved walking distance, pulmonary blood flow, and PVR. Adding sildenafil to bosentan did not significantly improve walking distance but did increase saturation at rest.

Renal failure in congenital heart disease

- GFR < 60 ml/min/1.73m^2 (moderate-severe GFR impairment)
- GFR = 60–80 ml/min/1.73m^2 (mild GFR impairment)
- GFR ≥ 90 ml/min/1.73m^2 (normal GFR)



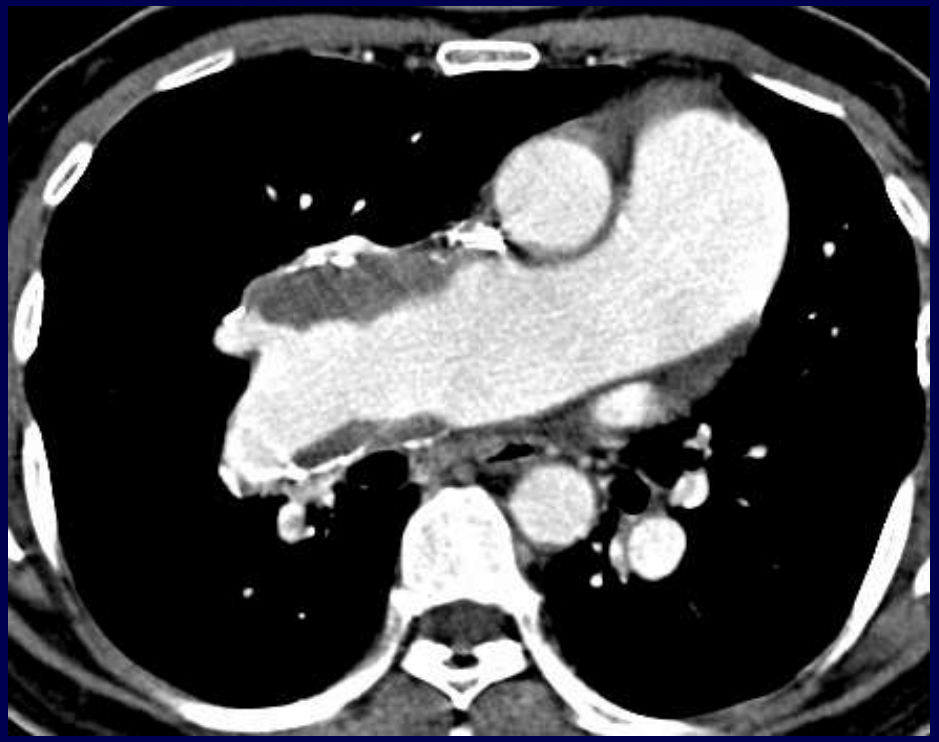
Dimopoulos K, *et al. Circulation* 2008; 117:2320-8.

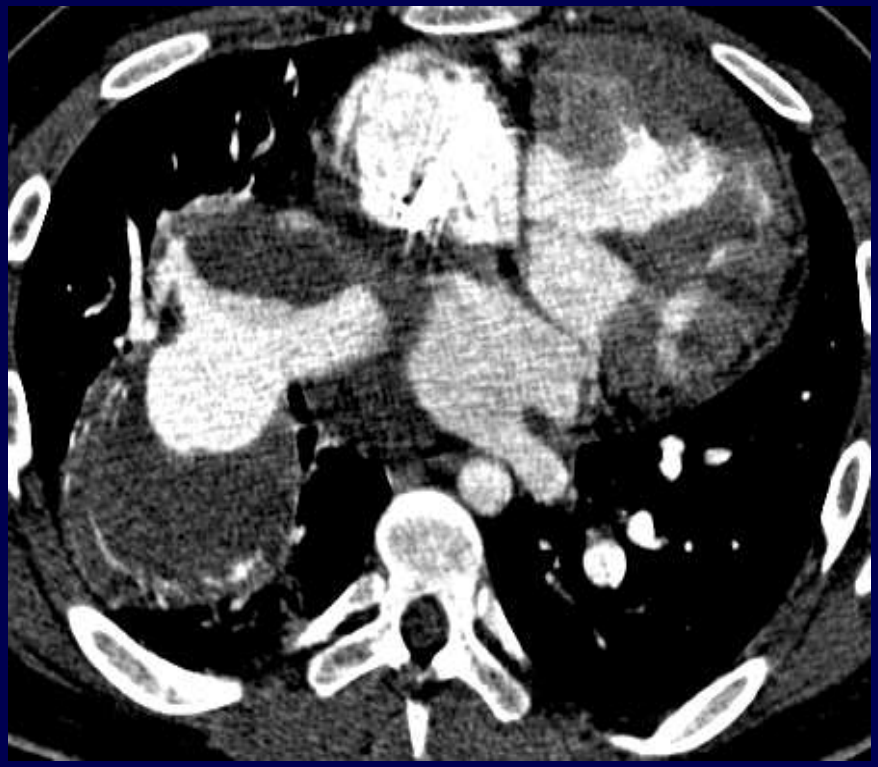
Pulmonary vasodilators

- Pulmonary vasodilators should be considered in patients with Eisenmenger syndrome, especially with low SPO2.
- Effect of reverse remodeling of bosentan remains to be clarified.

Anticoagulants, anti-platelets?

- Anti-coagulation is warranted (Paul Wood)
  - Thrombus in the large PA
  - microembilism
- Recommended in IPAH
- Not recommended in ES?
- In patients with AF, AFL?
- In patients with episodes of pulmonary embolism?





Broberg, *et al*. Heart 2004

Arrhythmias

- PSVT
  - DC
  - Verapamil?, Amiodarone?
    - Thyroid dysfunction with amiodarone
- AF, AFL
    - Anticoagulants?
- VT、Vf
    - Amiodarone
    - ICD?

Table 25 Recommendations for PAH associated with congenital cardiac shunts

Statement	Class[a]	Level[b]
The ERA bosentan is indicated in WHO-FC III patients with Eisenmenger's syndrome	I	B
Other ERAs, phosphodiesterase type-5 inhibitors, and prostanoids should be considered in patients with Eisenmenger's syndrome	IIa	C
In the absence of significant haemoptysis, oral anticoagulant treatment should be considered in patients with PA thrombosis or signs of heart failure	IIa	C
The use of supplemental O_2 therapy should be considered in cases in which it produces a consistent increase in arterial oxygen saturation and reduces symptoms	IIa	C
If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered usually when the haematocrit is > 65%	IIa	C
Combination therapy may be considered in patients with Eisenmenger's syndrome	IIb	C
The use of CCBs is not recommended in patients with Eisenmenger's syndrome	III	C

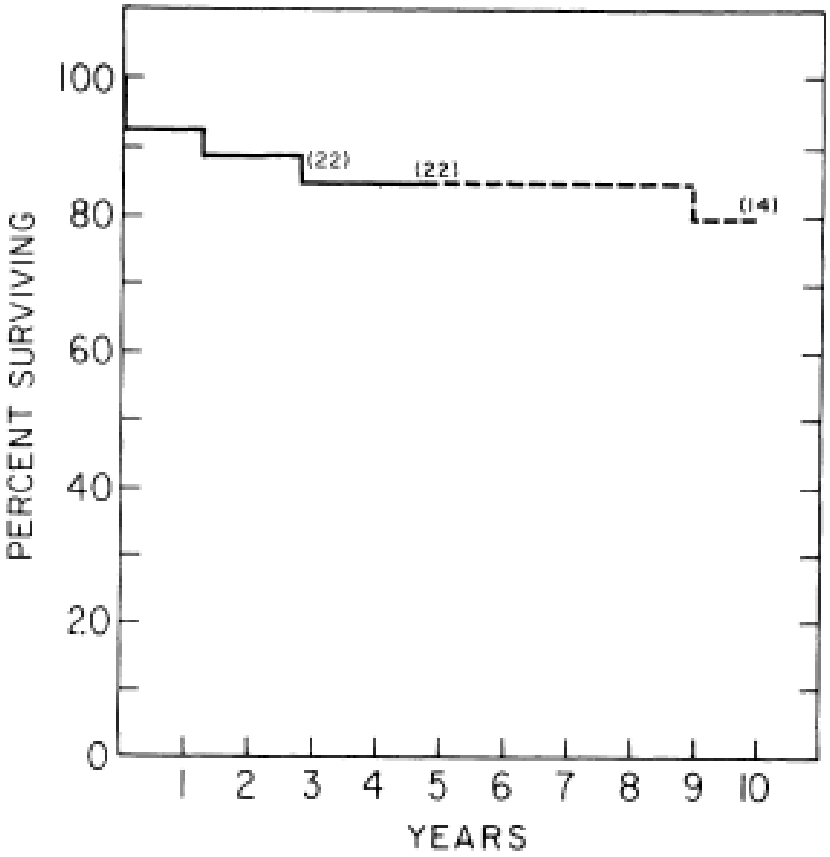
Conclusions

- There is no solid evidence for operability
- PH after repair
  - Management same as for IPAH?
  - Prognosis similar to or worse than in ES?
- There is no evidence for optimal treatment of morbidity of Eisenmenger syndrome, except for PH

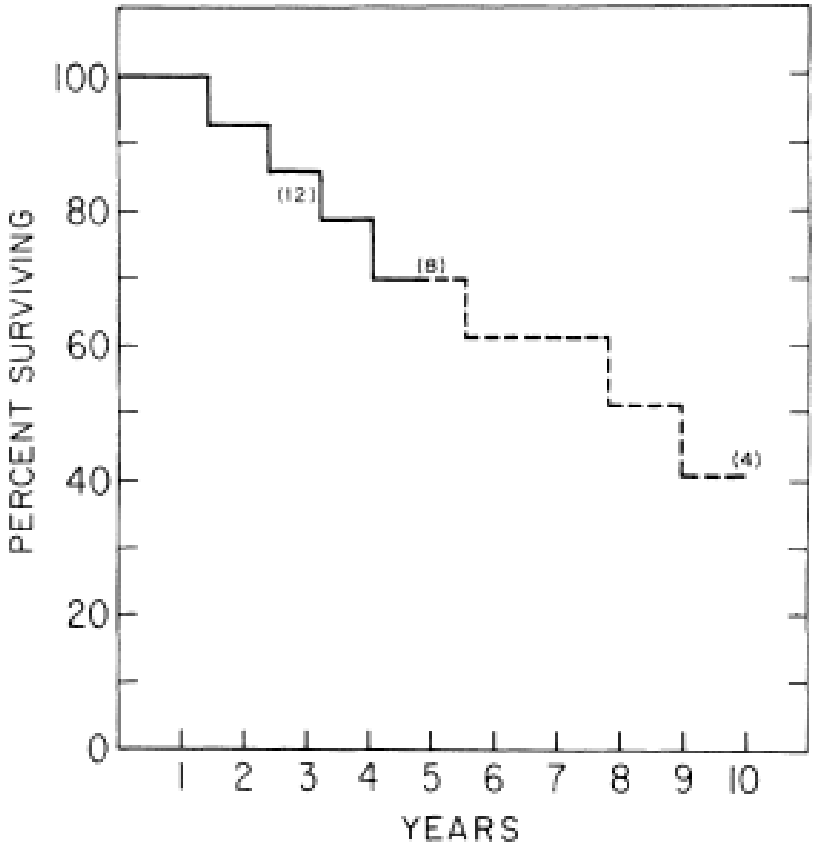
Conclusion

- Pulmonary hypertension should be evaluated carefully in patients with ASD and severe PH, and indication of intervention in patients with severe PH still remains to be clarified.
- The role of pulmonary vasodilators in the management ASD with moderate-severe PH also remains to be clarified.
- Pulmonary vasodilators should be considered in patients with Eisenmenger syndrome, especailly in patients with low SPO2.

Survival



Surgical patients

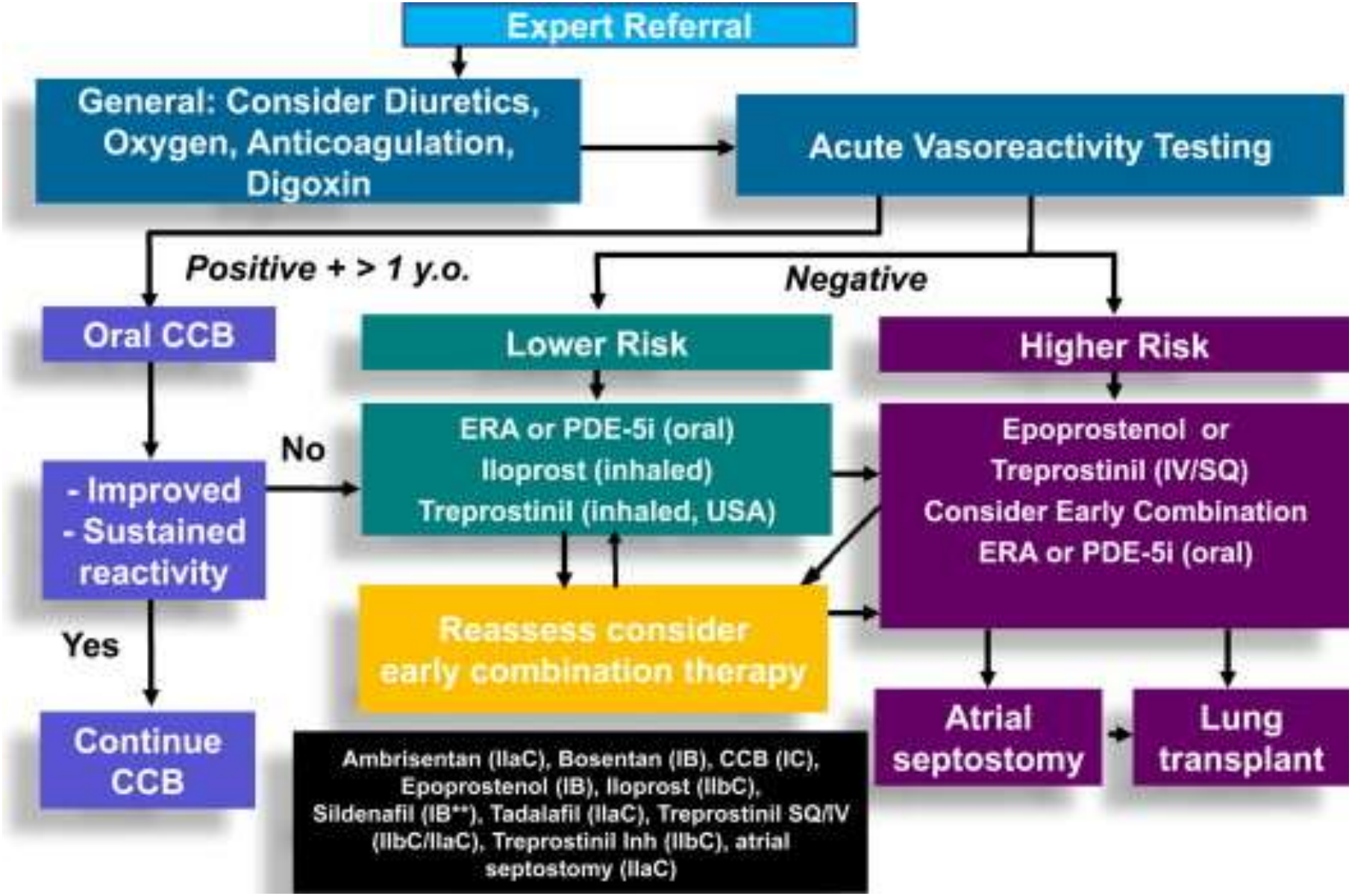


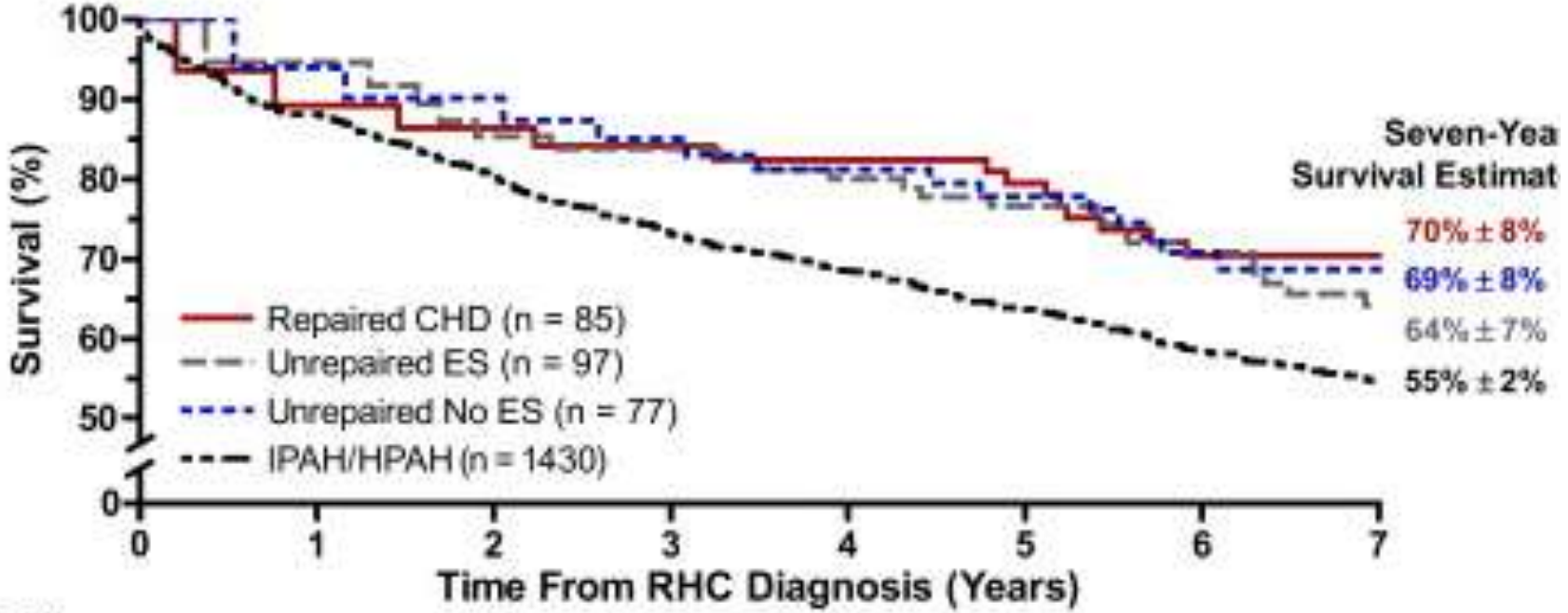
Medical patients

Steele et al. Circulation 1987

Recommendations

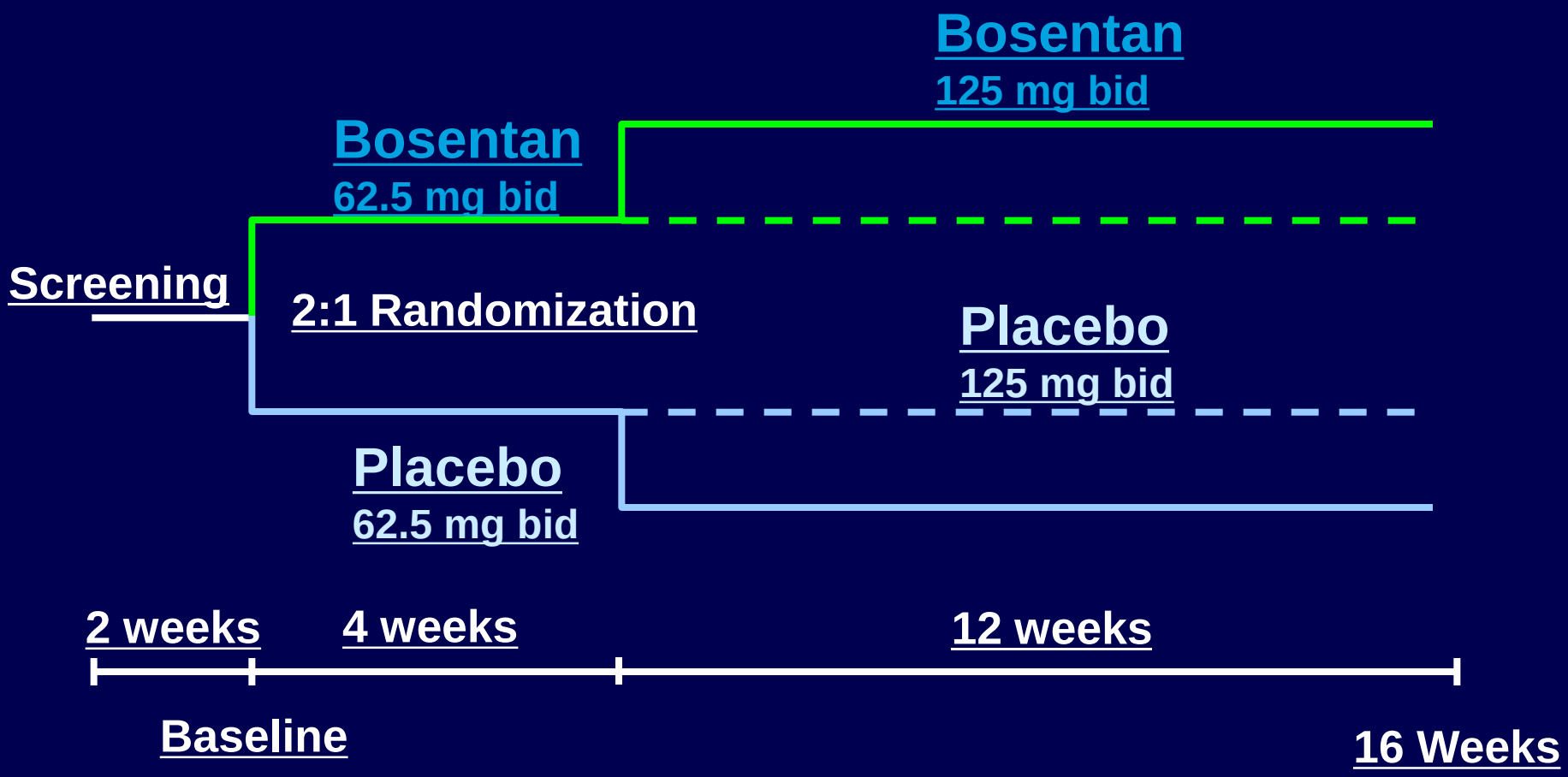
- CHD patients requiring PAH-specific therapy are managed in specialized centers


Expert Referral
General: Consider Diuretics, Oxygen, Anticoagulation, Digoxin
Acute Vasoreactivity Testing
Positive + > 1 y.o.
Negative
Oral CCB
Lower Risk
Higher Risk
ERA or PDE-5i (oral)
Iloprost (inhaled)
Treprostinil (inhaled, USA)
No
- Improved
- Sustained reactivity
Epoprostenol or Treprostinil (IV/SQ)
Consider Early Combination
ERA or PDE-5i (oral)
Yes
Reassess consider early combination therapy
Continue CCB
Atrial septostomy
Lung transplant
Ambrisentan (IIaC), Bosentan (IB), CCB (IC), Epoprostenol (IB), Iloprost (IIbC), Sildenafil (IB**), Tadalafil (IIaC), Treprostinil SQ/IV (IIbC/IIaC), Treprostinil Inh (IIbC), atrial septostomy (IIaC)



at Risk:								
ed CHD	15	24	38	46	56	55	40	33
ired ES	17	26	45	65	64	67	60	45
d No ES	12	22	32	41	49	47	35	26
H/HPAH	436	596	701	721	729	643	473	409

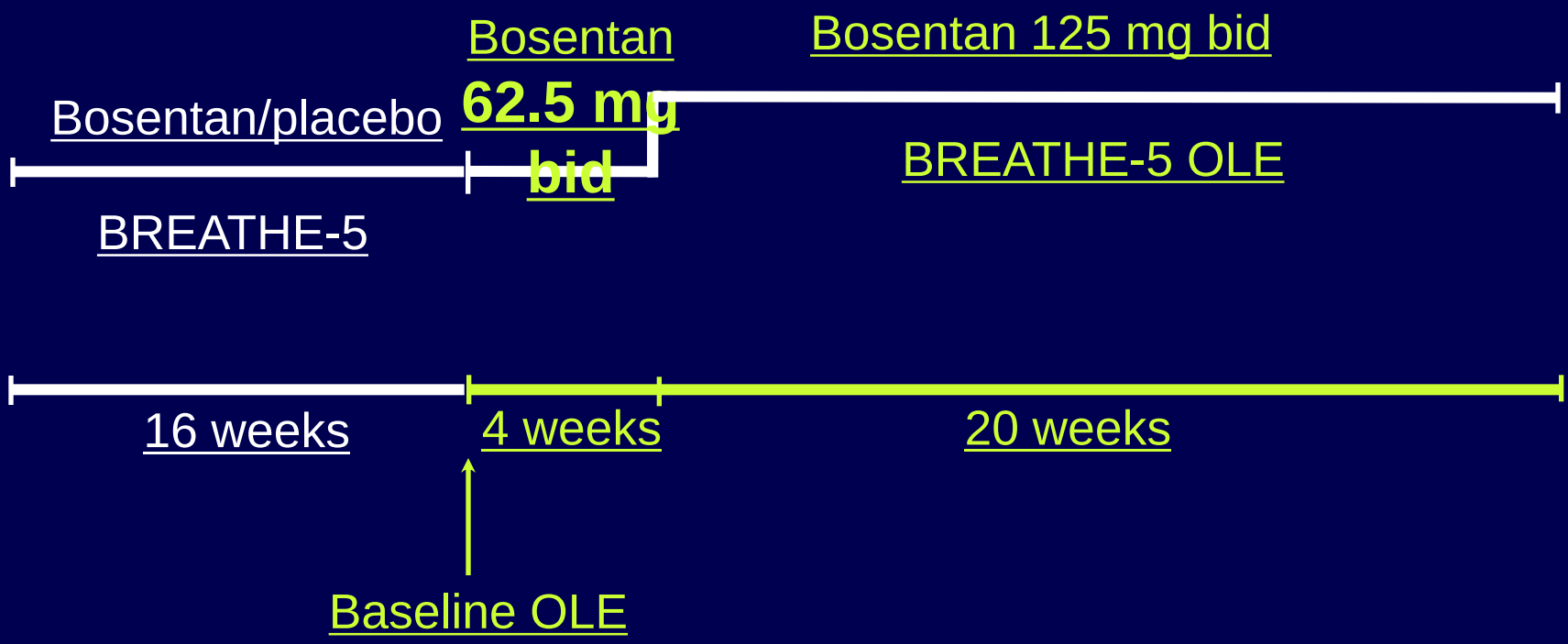
Endothelin Pathway
BREATHE-5: Study design



Galie et al for Breathe-5, *Circulation 2006*

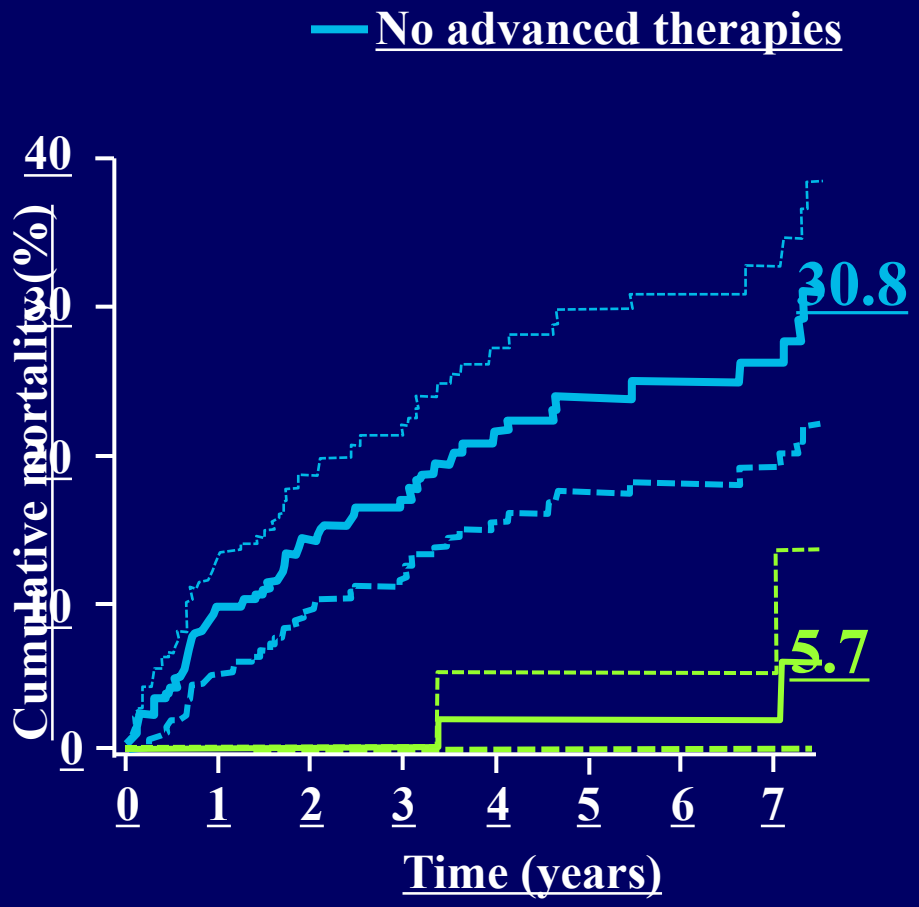
BREATHE-5 open label extension (OLE) study

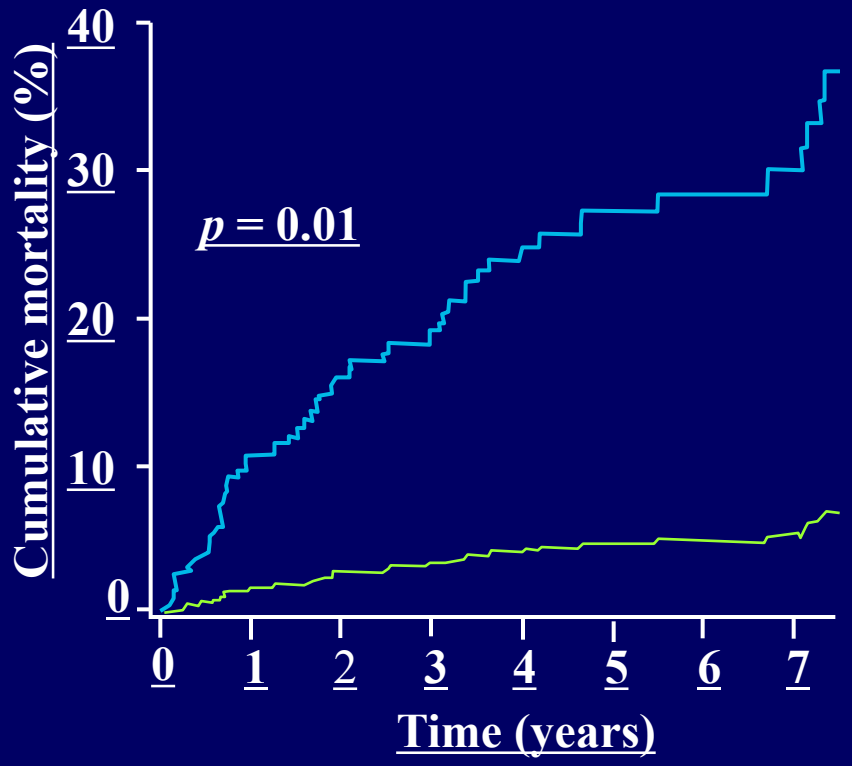
Study design



Gatzoulis *et al* for Breathe-5, *Int J Card 2007*

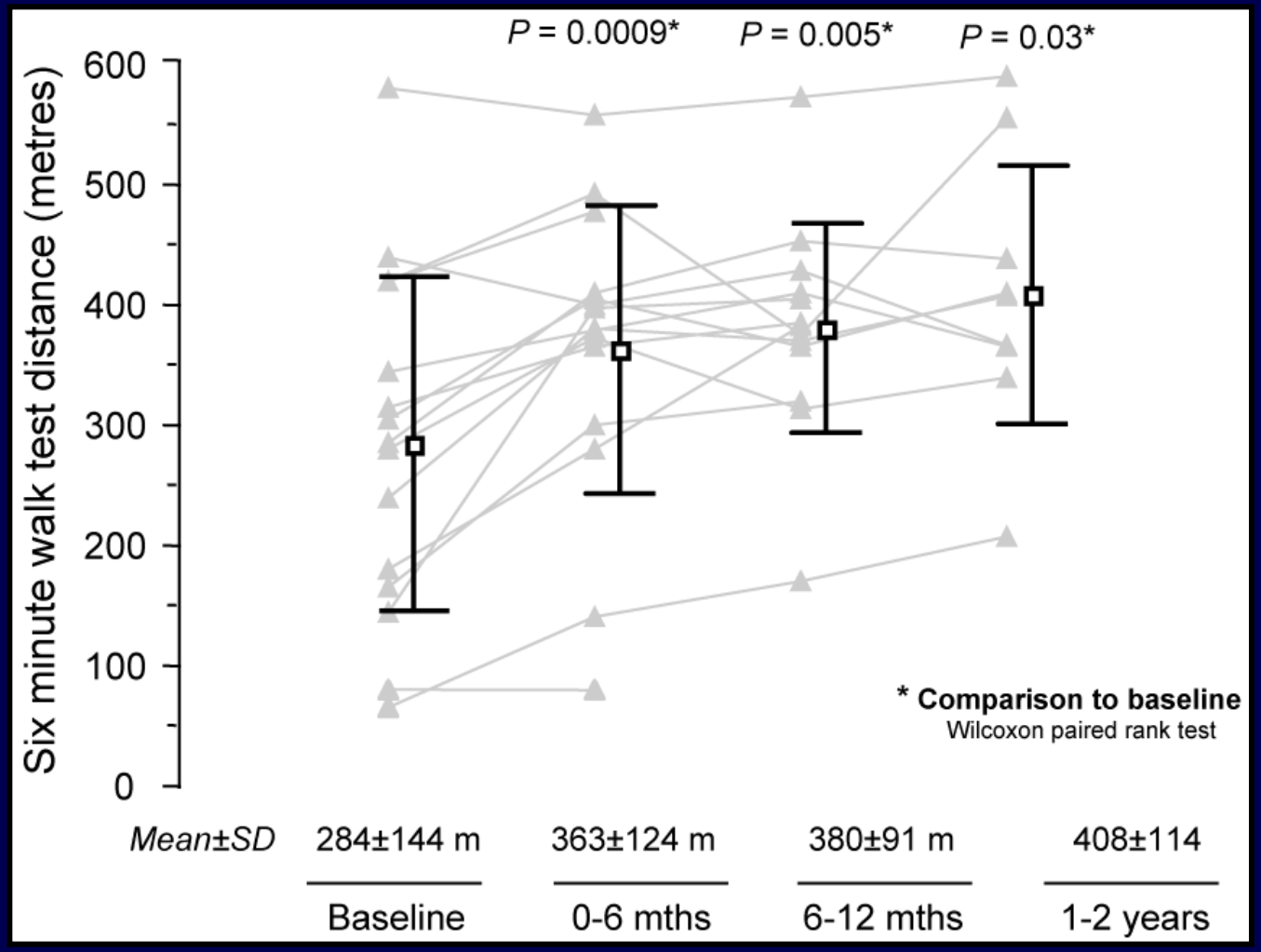
Cumulative mortality with advanced therapies





Dimopoulos et al Circulation 2010

Bosentan and Eisenmenger Syndrome
Longer-term 6 minute walk test



Diller *et al Heart 2007*

Eisenmenger syndrome
Multi-organ disease

- Heamatology (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)

Eisenmenger Syndrome: Management Algorithm

Diagnosis; referral to PAH/CHD centre

History and Examination. CXR and ECG

Non-invasive tests-ECHO, cardiac MRI, cardiac CT

Cardiac catheterisation for selected patients only

Functional class/other investigations

6MWT

Quality of life questionnaire

Biochemistry, Iron studies (transferrin saturation)

Education

Endocarditis prophylaxis, advice on exercise and other lifestyle issues

Effective contraception-risk of pregnancy very high

Therapy-general

Correct iron deficiency

Consider/Discuss thromboprophylaxis

Is there a role for reparative surgery/catheter based intervention ?

Therapy-advanced

Bosentan therapy for Class III patients

Consider other advanced therapies if evidence base widens

Therapy-other

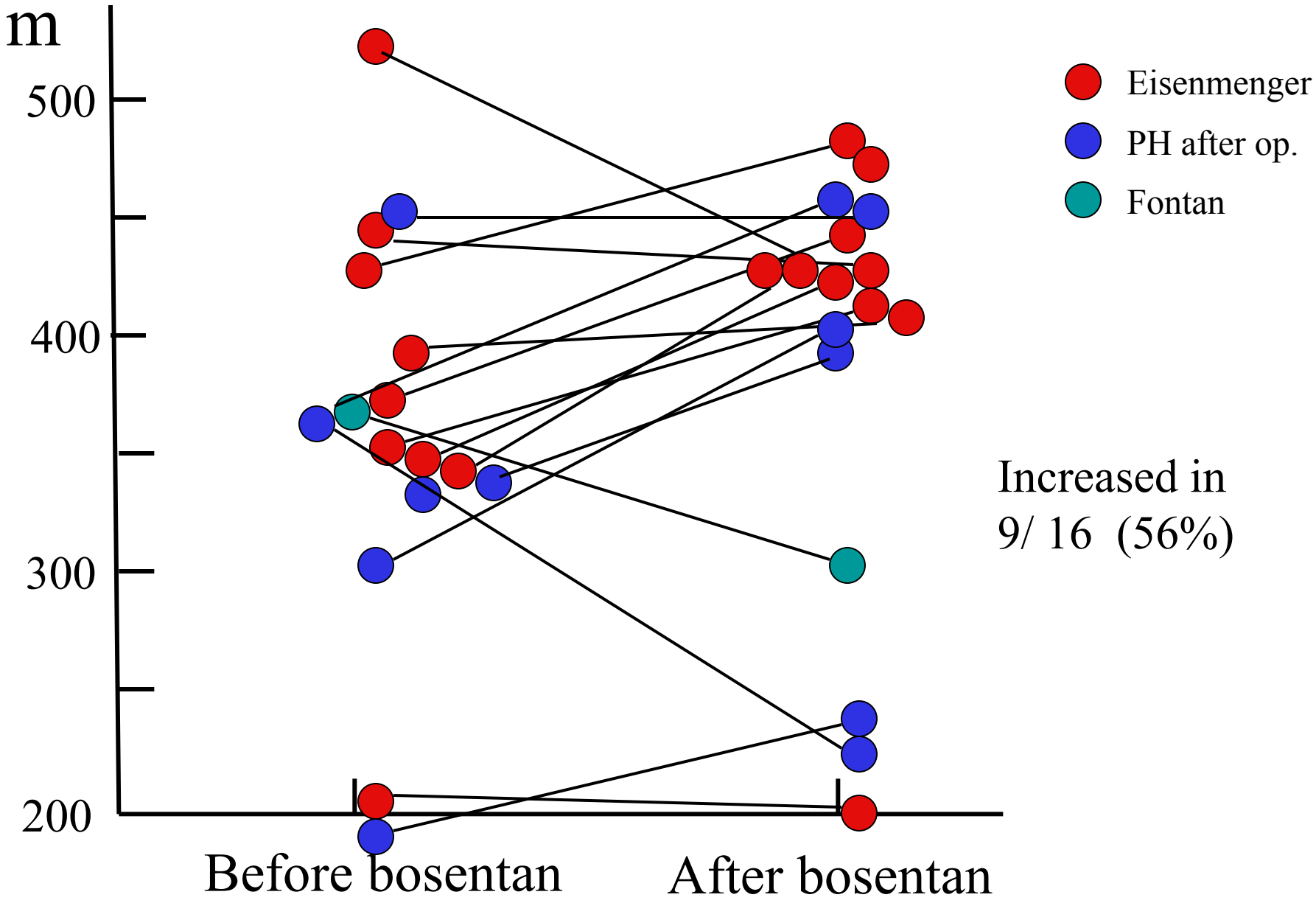
Lung or heart/lung transplantation for selected patients failing medical therapy

Prostanoids as a bridge to transplantation (or as destination therapy?)

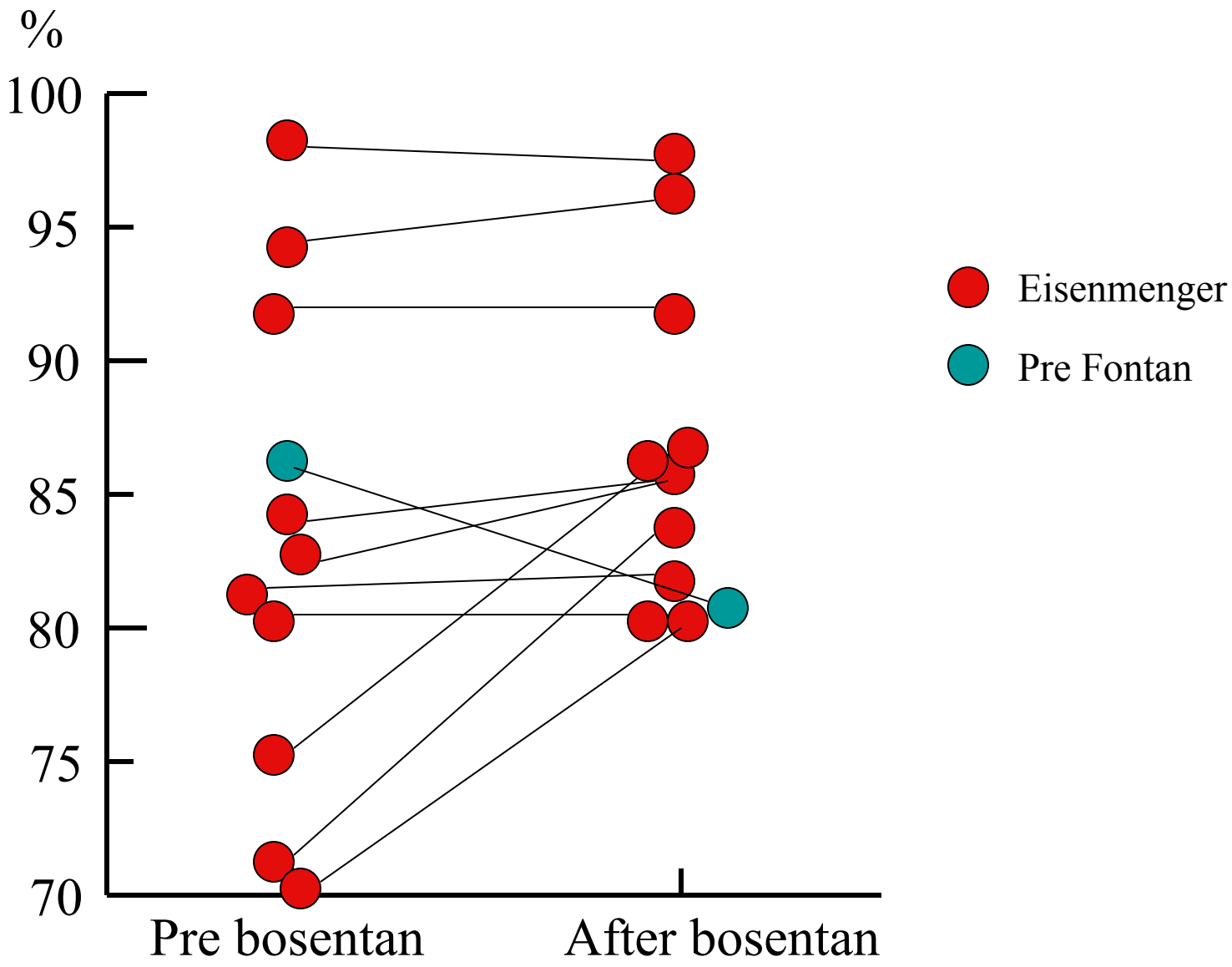
Inhaled NO or Iloprost may have a role for the pregnant patient with PAH

UK and Ireland PAH Physicians Committe, Heart & Thorax 2008

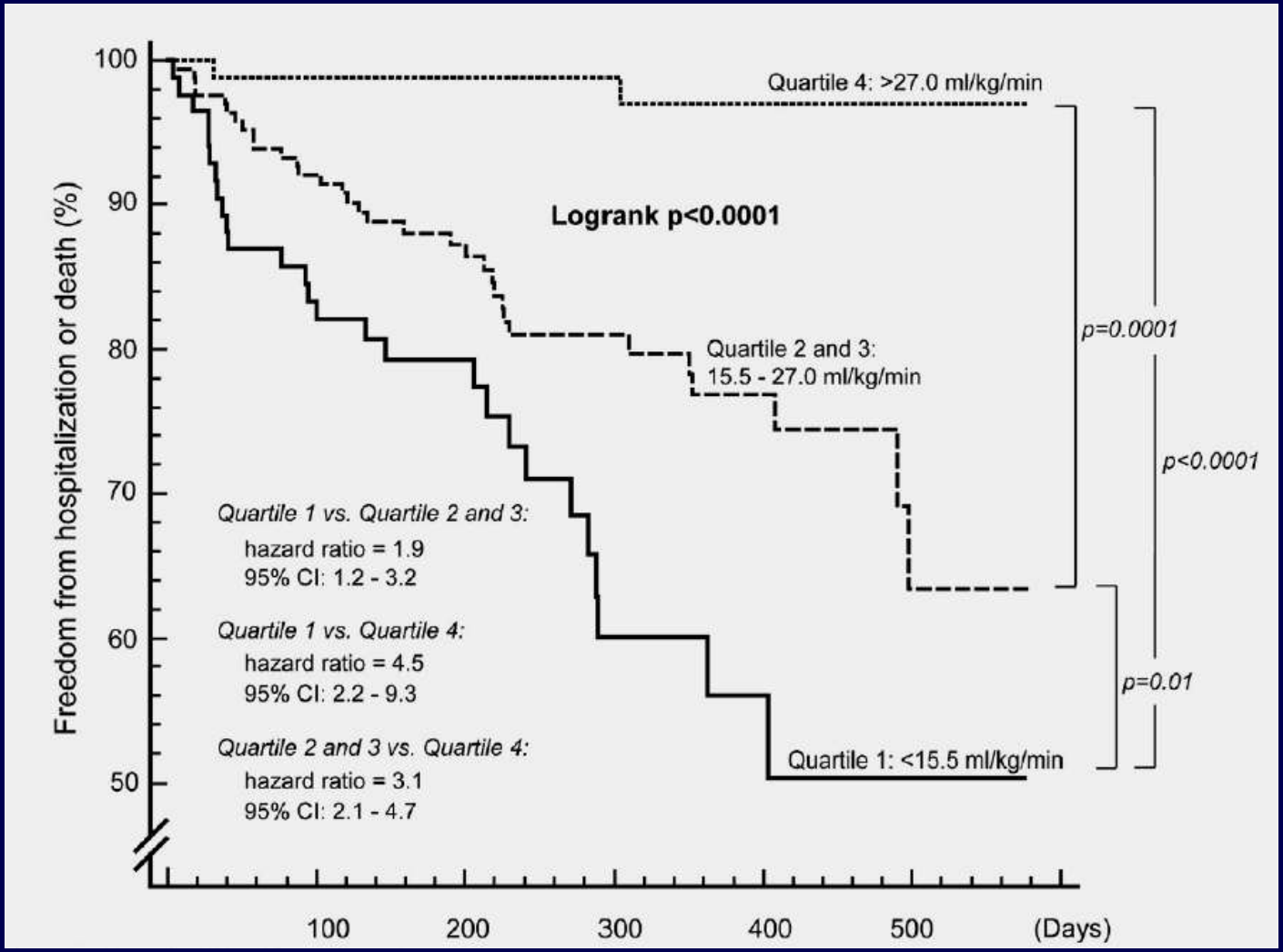
6-minute walk distance



Percutaneous O2 saturation



Peak VO2 Predicts Combined End-Point of Hospitalization or Death



Diller et al, Circulation 2005

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 (~ 1-2% 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)

全身の管理

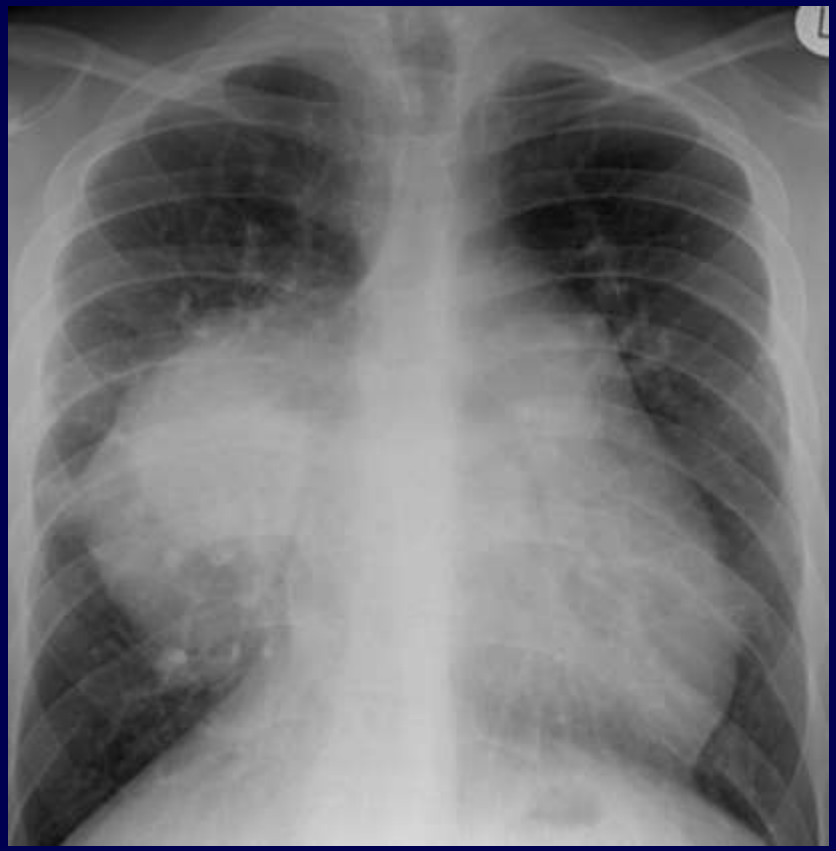
- 喀血
- 出産
- 不整脈
- 腎不全

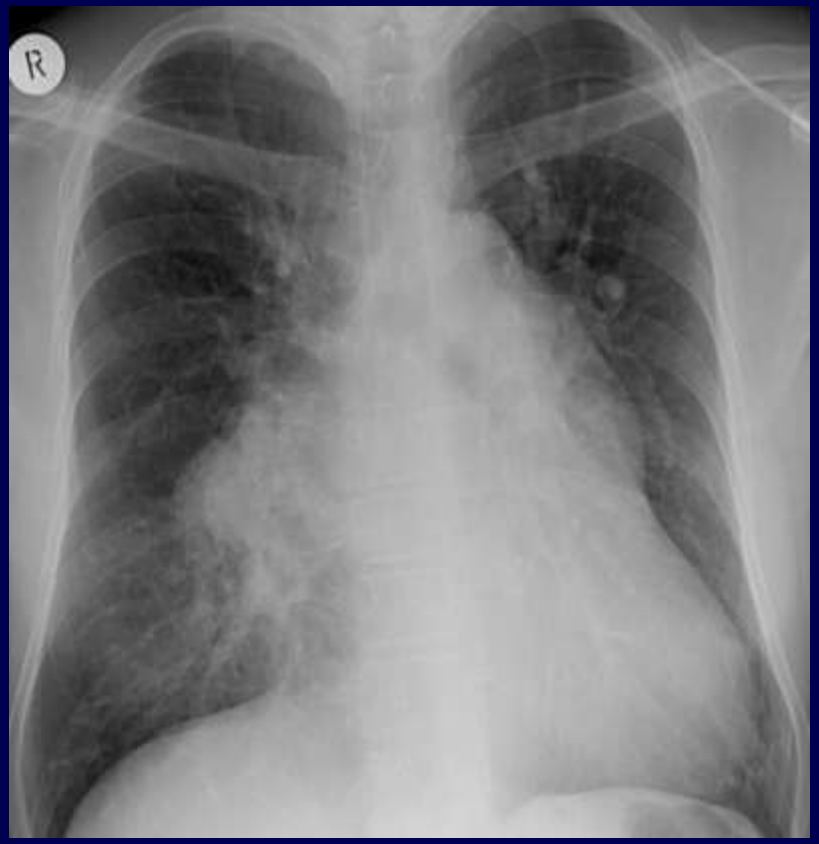
- 心不全ー肺高血圧

喀血と肺血栓

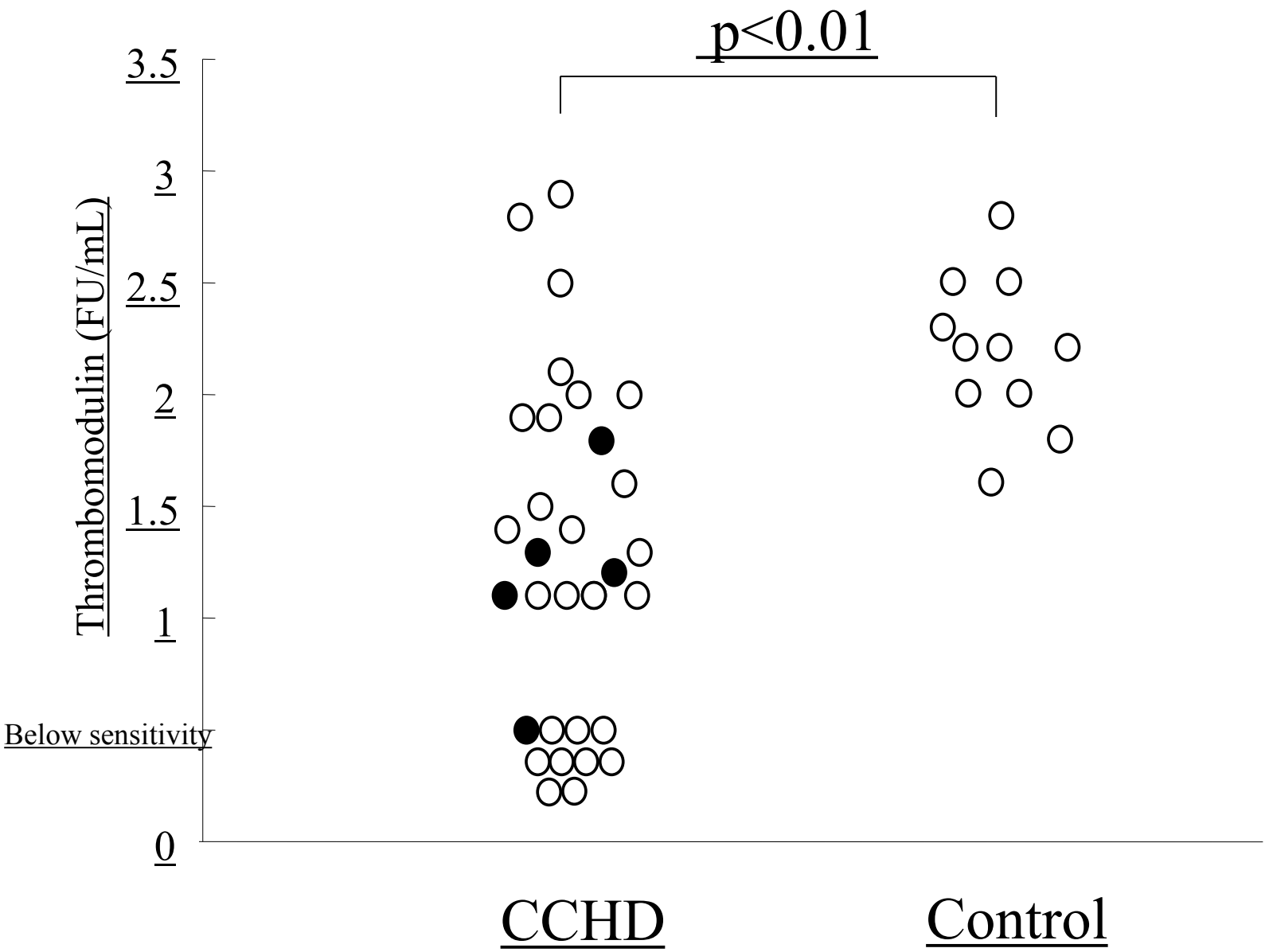
- Eisenmenger症候群では
  - 胸痛
  - 喀血　は鬼門
  - 入院させる
  - 入院の度に、突然死の可能性を　周囲（病棟）、家族に話す
  - アドナ、トランサミン？

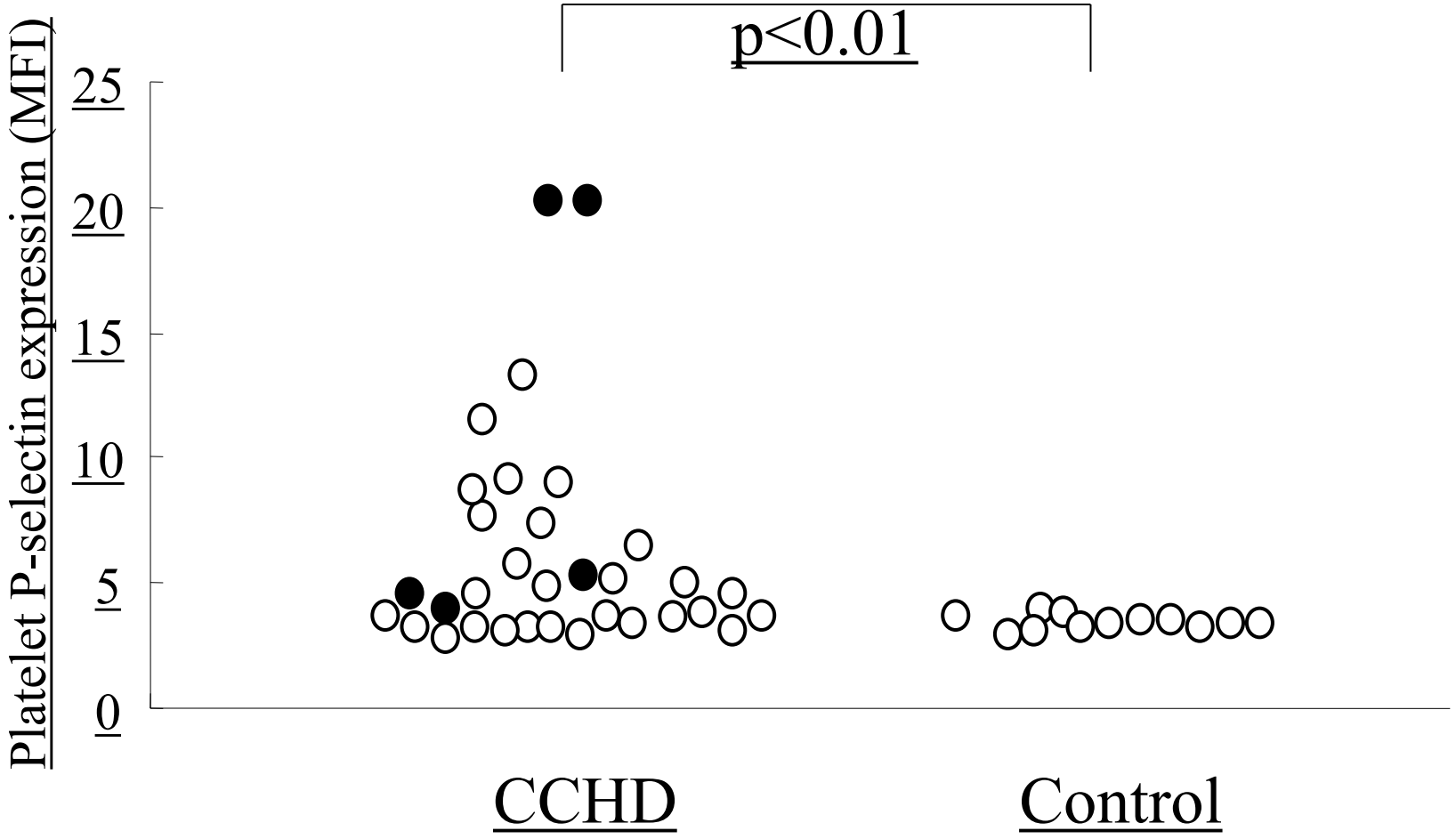
Eisenmenger Syndrome: *Thrombosis*

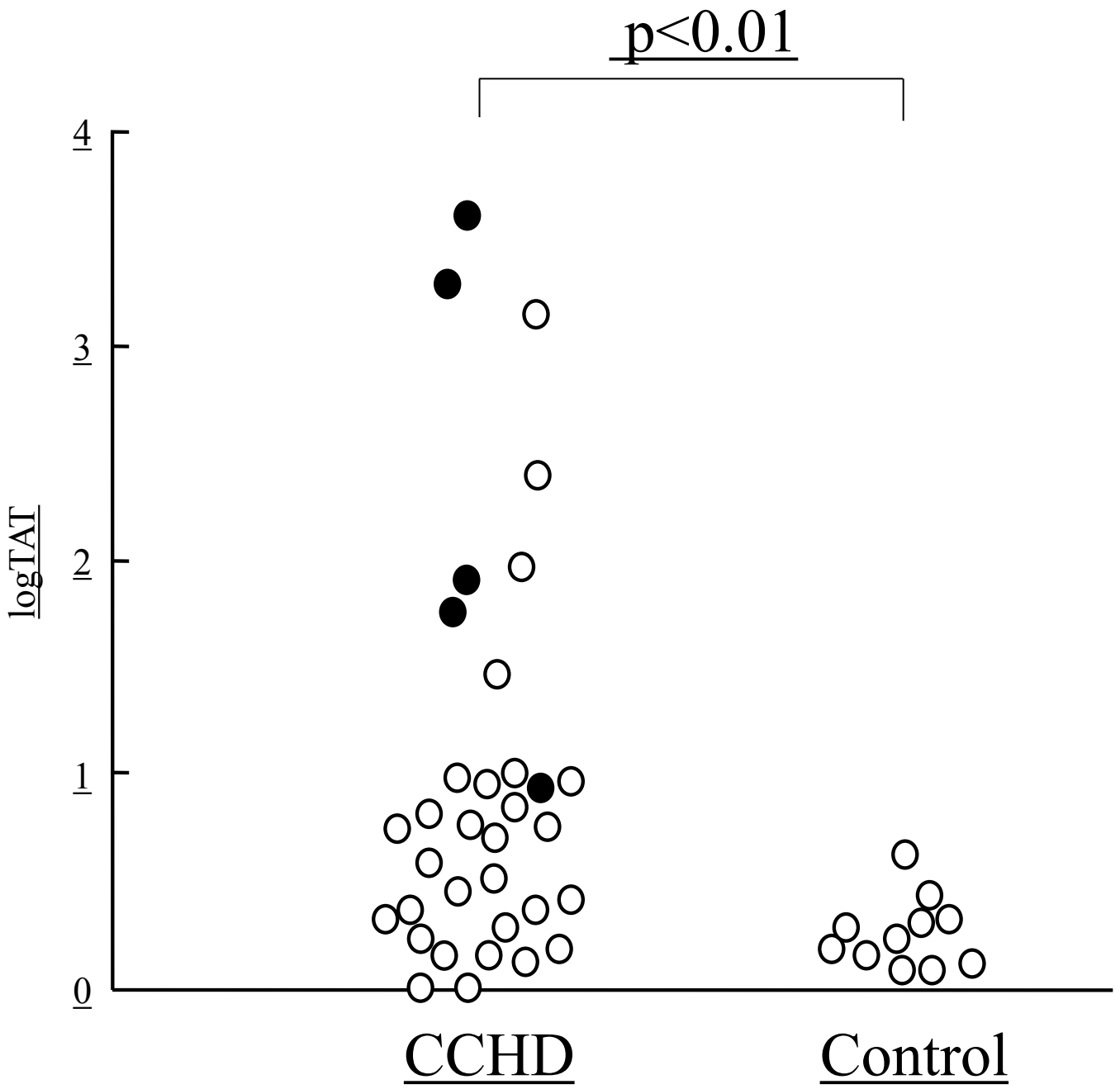




Broberg, *et al.* Heart 2004
Silversides et al, JACC 2003


p<0.01
Thrombomodulin (FU/mL)
3.5
3
2.5
2
1.5
1
Below sensitivity
0
CCHD
Control

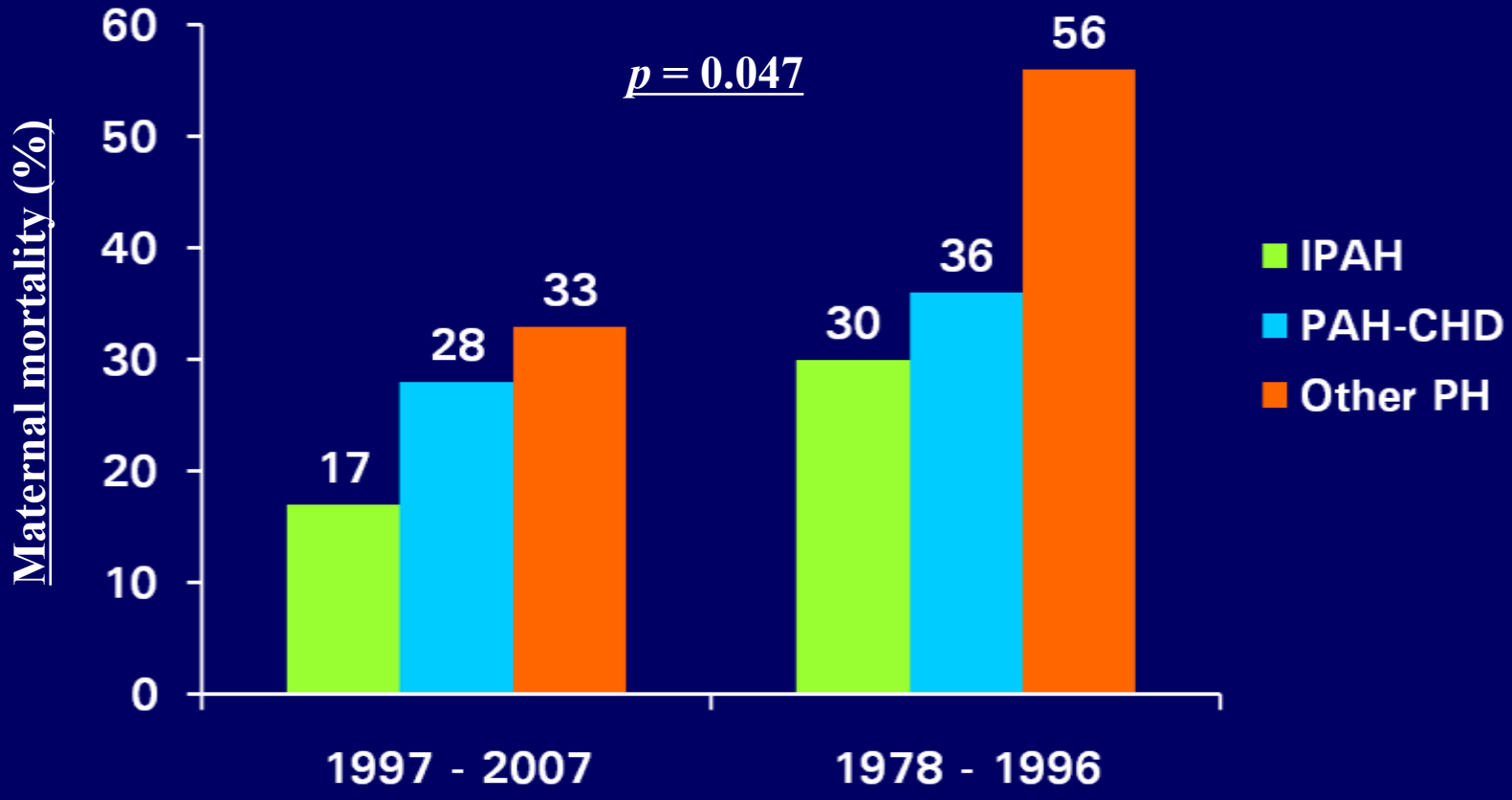

p<0.01
Platelet P-selectin expression (MFI)
25
20
15
10
5
0
CCHD
Control


p<0.01
4
3
2
1
0
logTAT
CCHD
Control

突然死

- 出産
  - 出産後、数日の突然死が多い
- カテーテル検査：　造影後
  - Volumeの変化
- 全身麻酔での手術
- 脱水

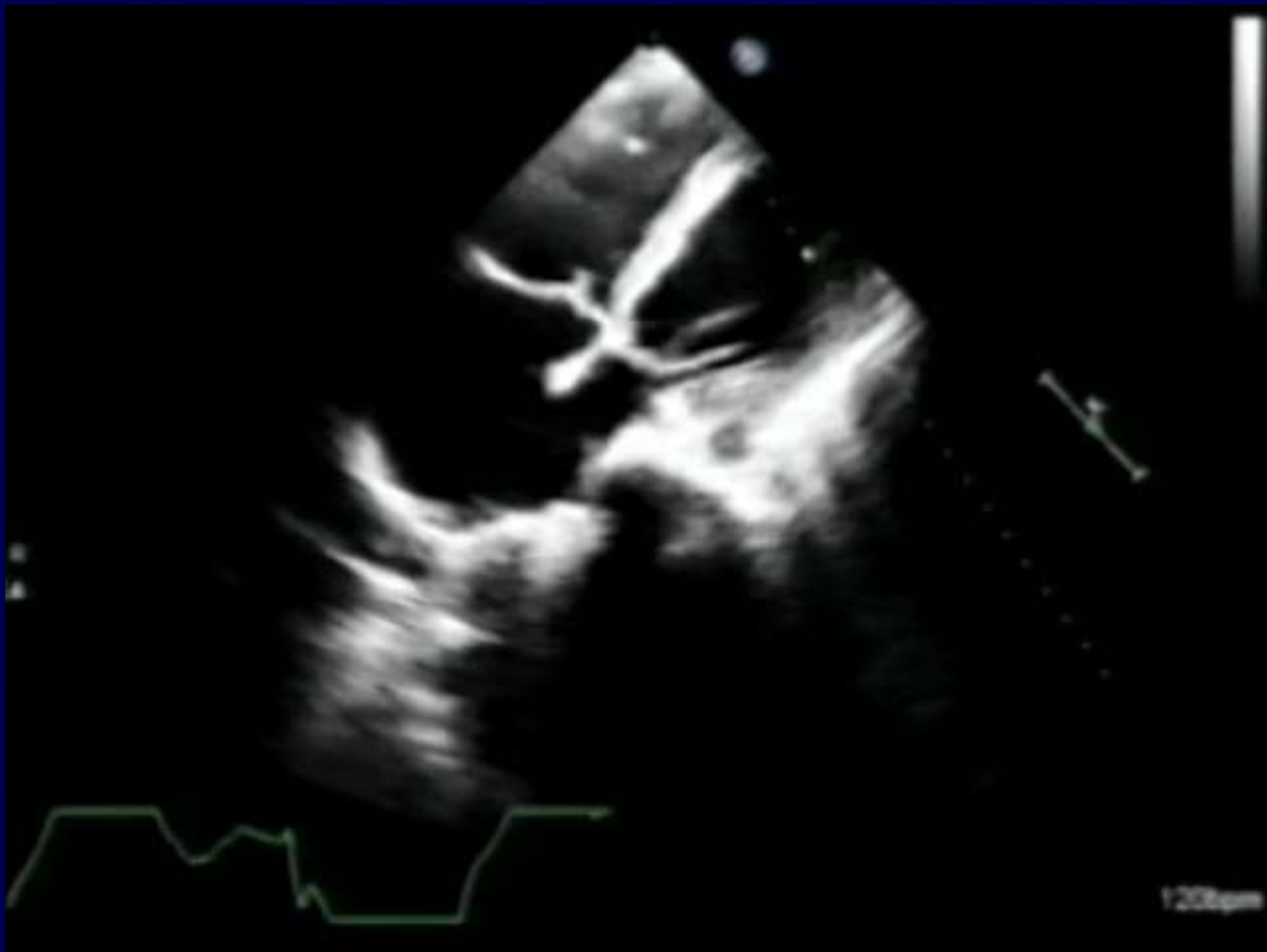
Pregnancy and PAH in association with CHD



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

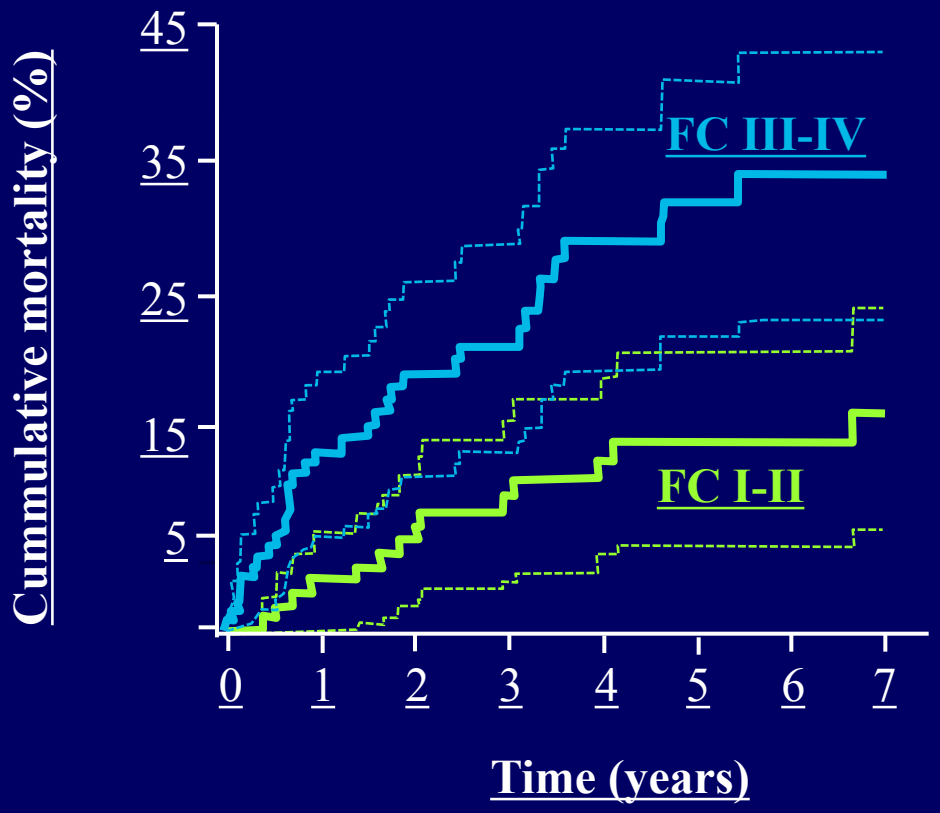
慢性腎不全

- チアノーゼ性心疾患に共通
- 低酸素血症による腎症
- ？高尿酸血症



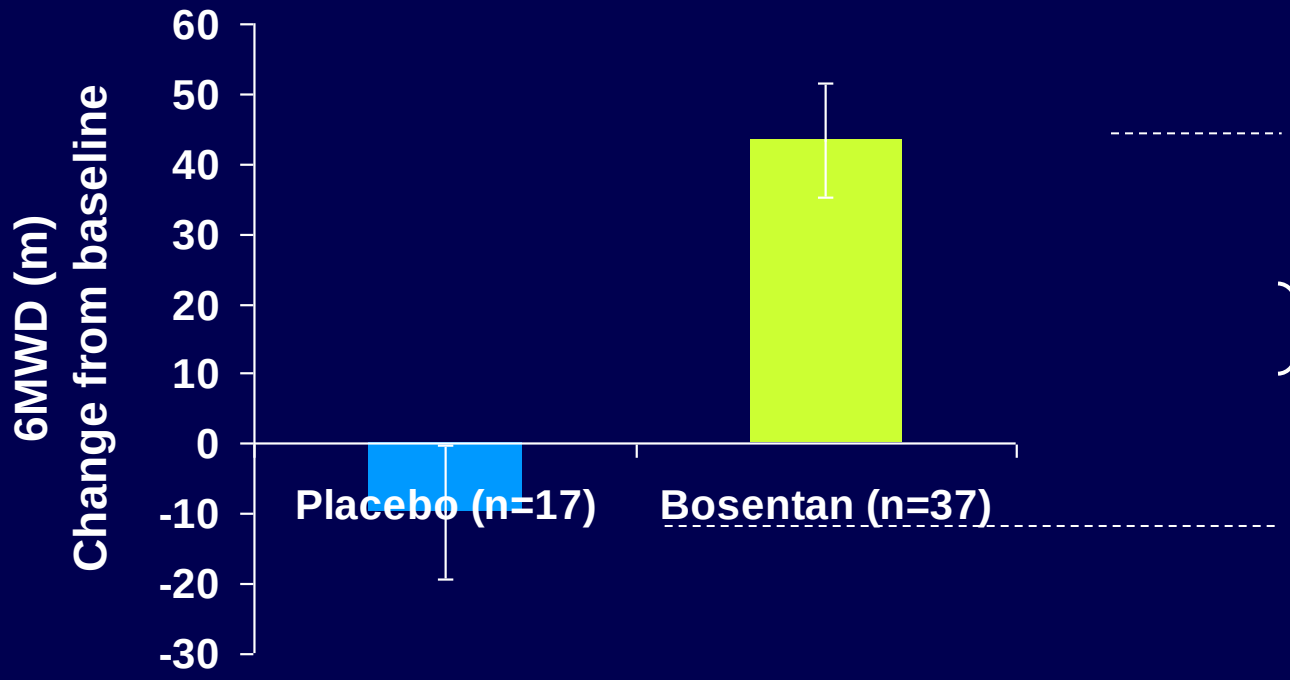
心不全、肺高血圧への治療

Contemporary survival in Eisenmenger syndrome: Relation to functional class



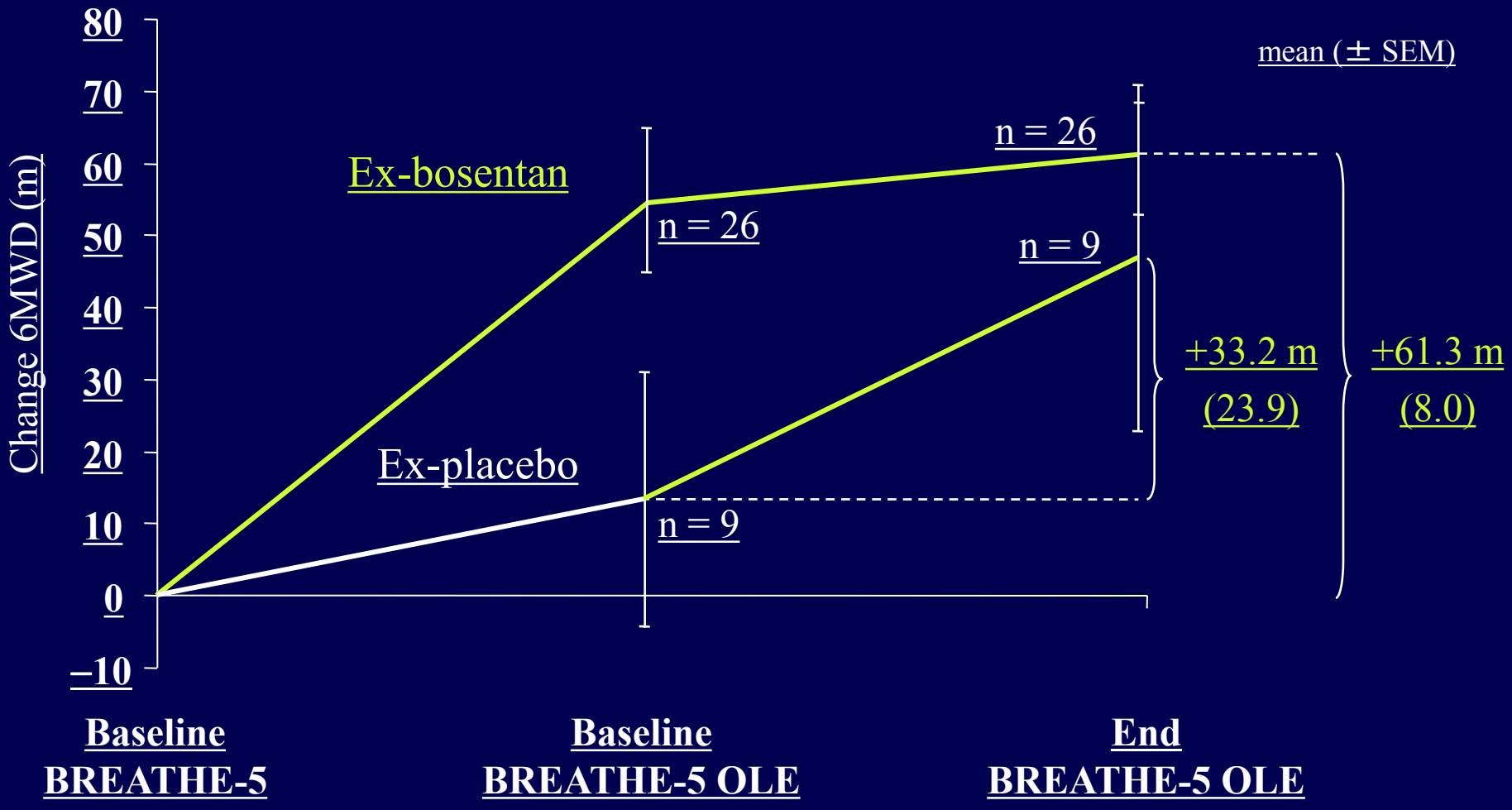
Dimopoulos et al Circulation 2010

Bosentan increases exercise capacity

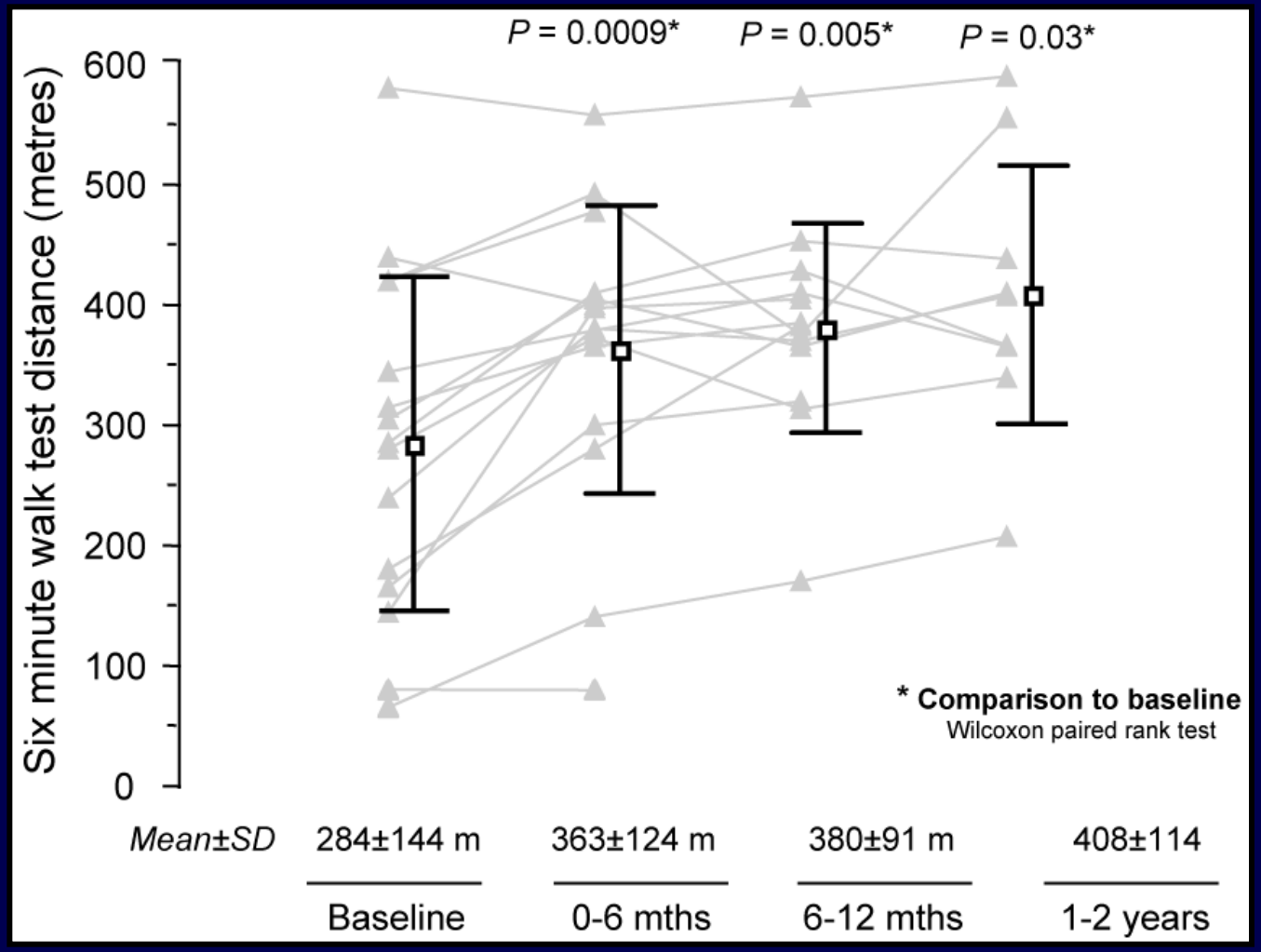


Galie et al for Breathe-5, *Circulation 2006*

Bosentan increased exercise capacity



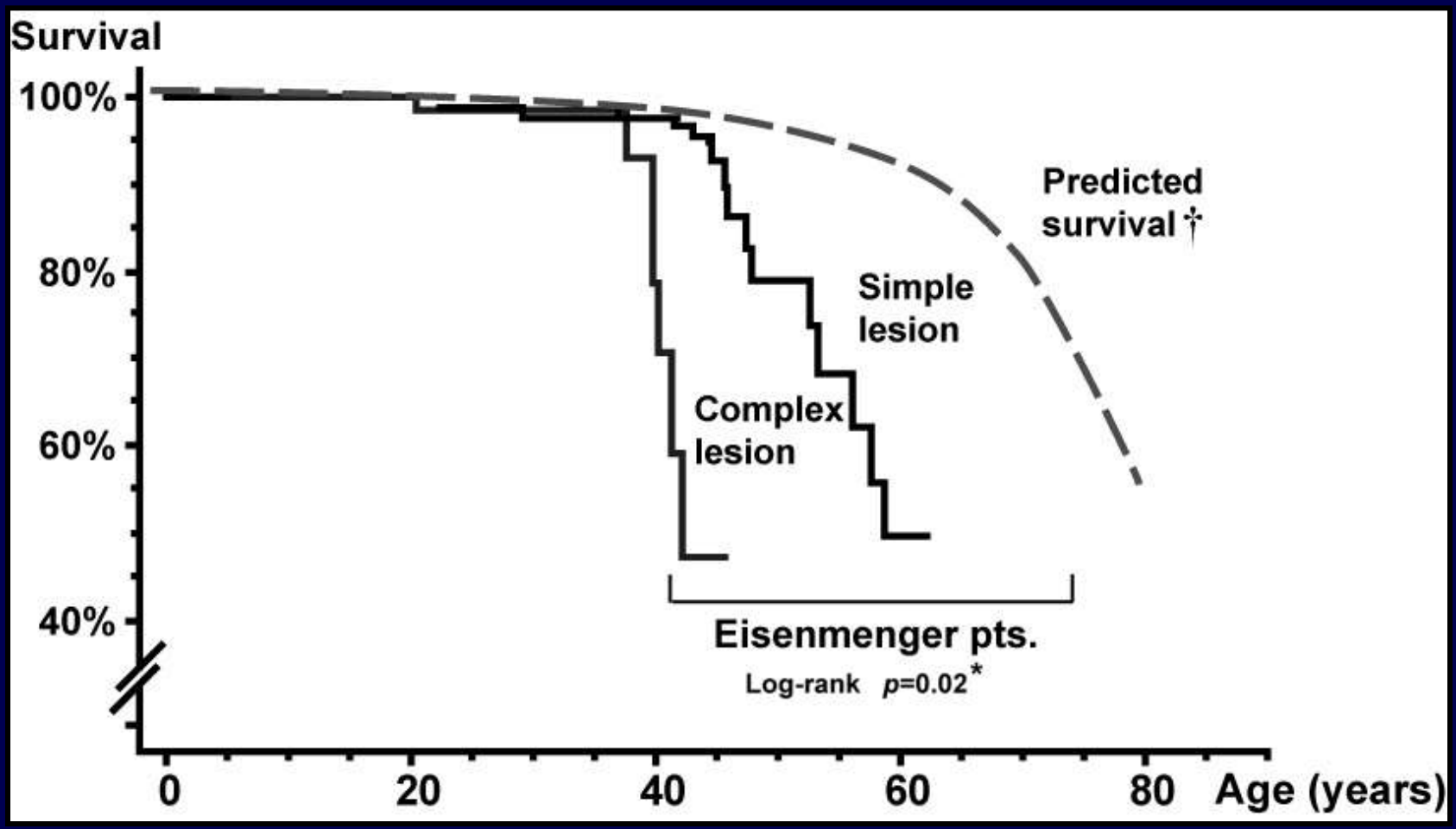
Bosentan and Eisenmenger Syndrome
Longer-term 6 minute walk test



Diller *et al Heart 2007*

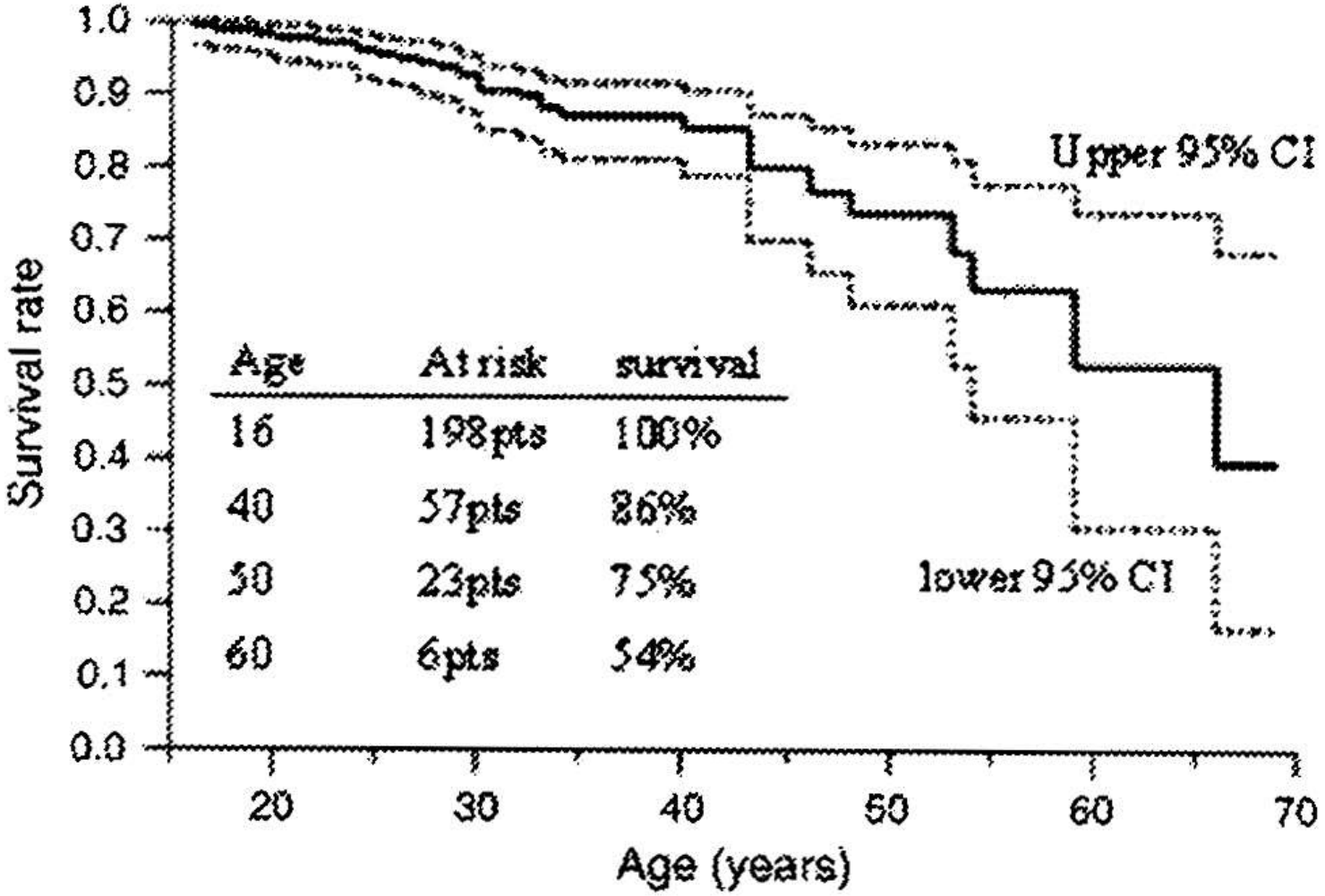
Adults with Eisenmenger Syndrome Survival

Diller *et al EHJ 2006*



Patient characteristics.

Total	198			
Female	127	(64%)		
Median age at the last clinic visit (years)	34	(range 16–69)		
Cardiac defects				
Simple	139	(70%)	VSD	72
			ASD	32
			PDA	27
			Combined	8
Complex	59	(30%)	AVSD	24
			Univentricular physiology	17
			TGA/DORV/cTGA	13
			AP window	4
			Truncus arteriosus	1

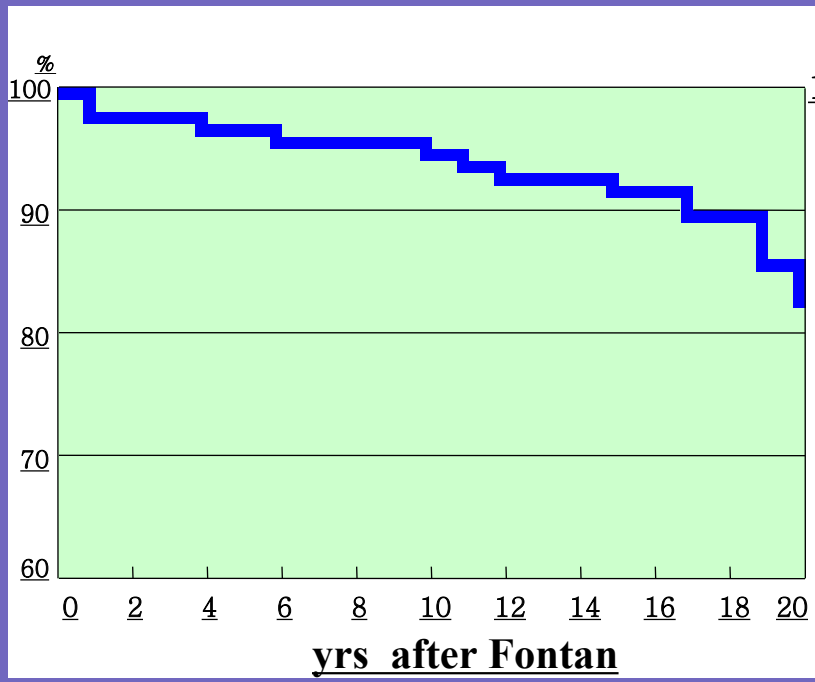

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Survival rate
Upper 95% CI
lower 95% CI
Age
At risk
survival
16
198pts
100%
40
57pts
86%
50
23pts
75%
60
6pts
54%
20
30
40
50
60
70
Age (years)

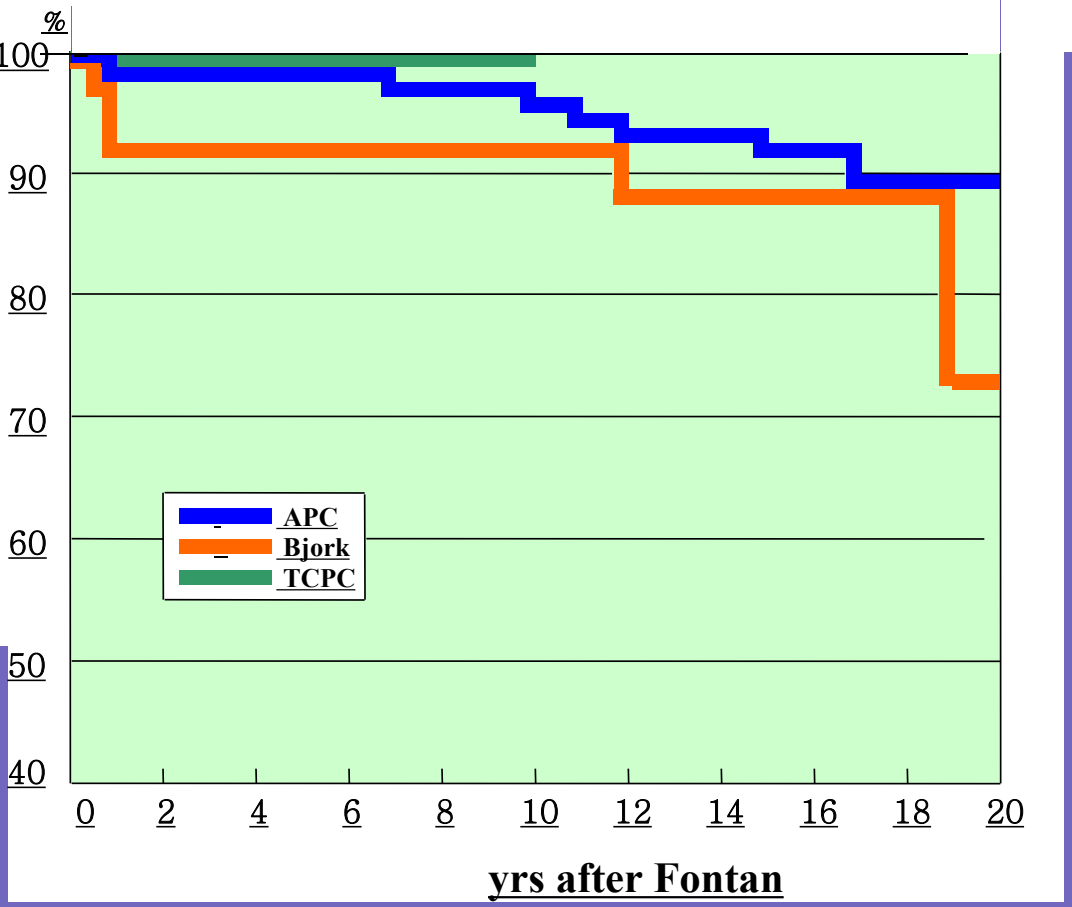
Problems of pulmonary (right side) circulation

- Branch PS
- Pulmonary arterio-venous malformation
- Systemic-to-pulmonary arterial collaterals
- Veno-left atrial shunt
- Baffle leak
- Pulmonary thromboembolism
- **Relative PH**

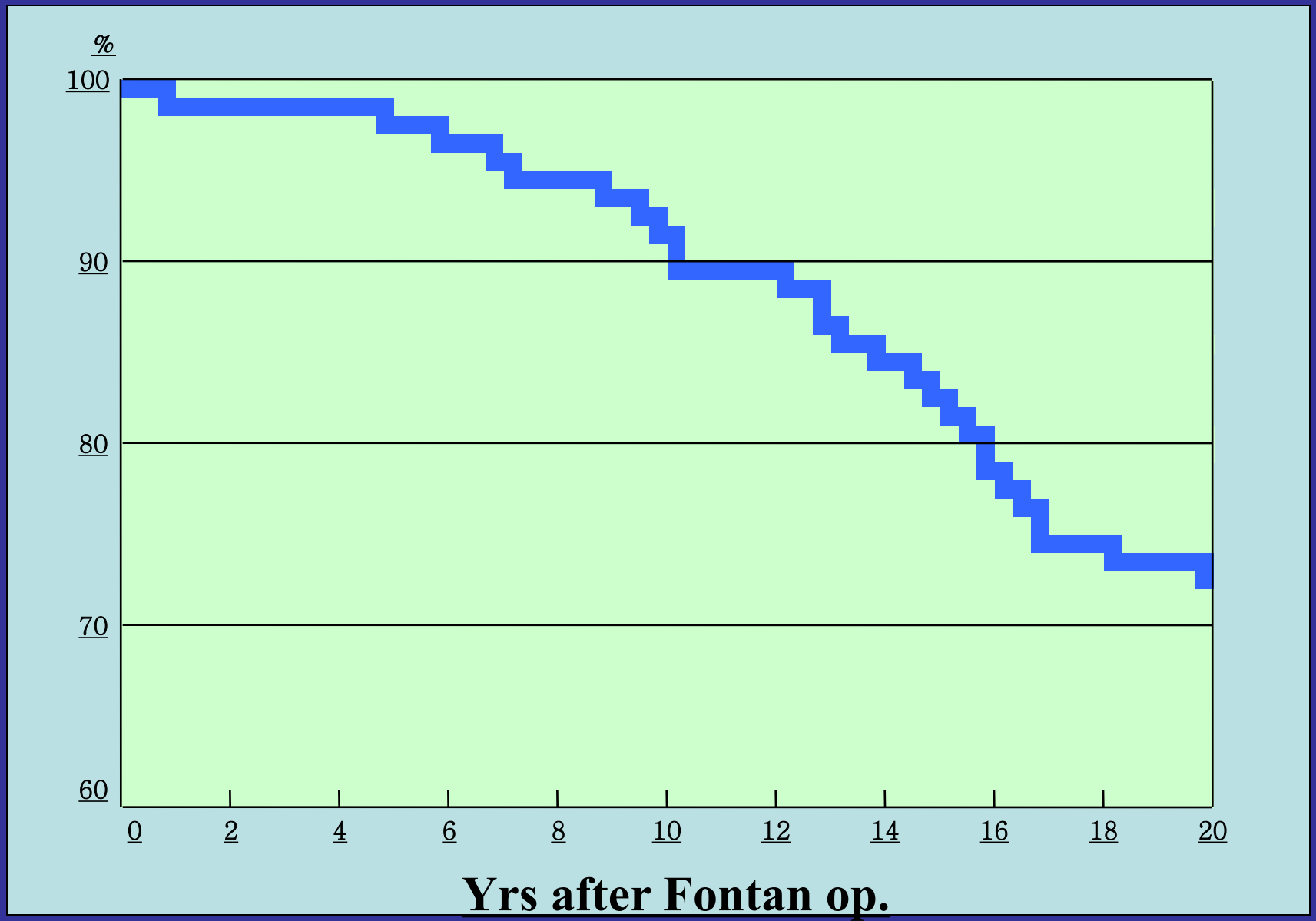
Actuarial survival curve after discharge

Fontan op (1974-2007) 605 pts





Freedom from failing Fontan



Failing Fontan: 46/180 pts (26%) > 10yrs after Fontan

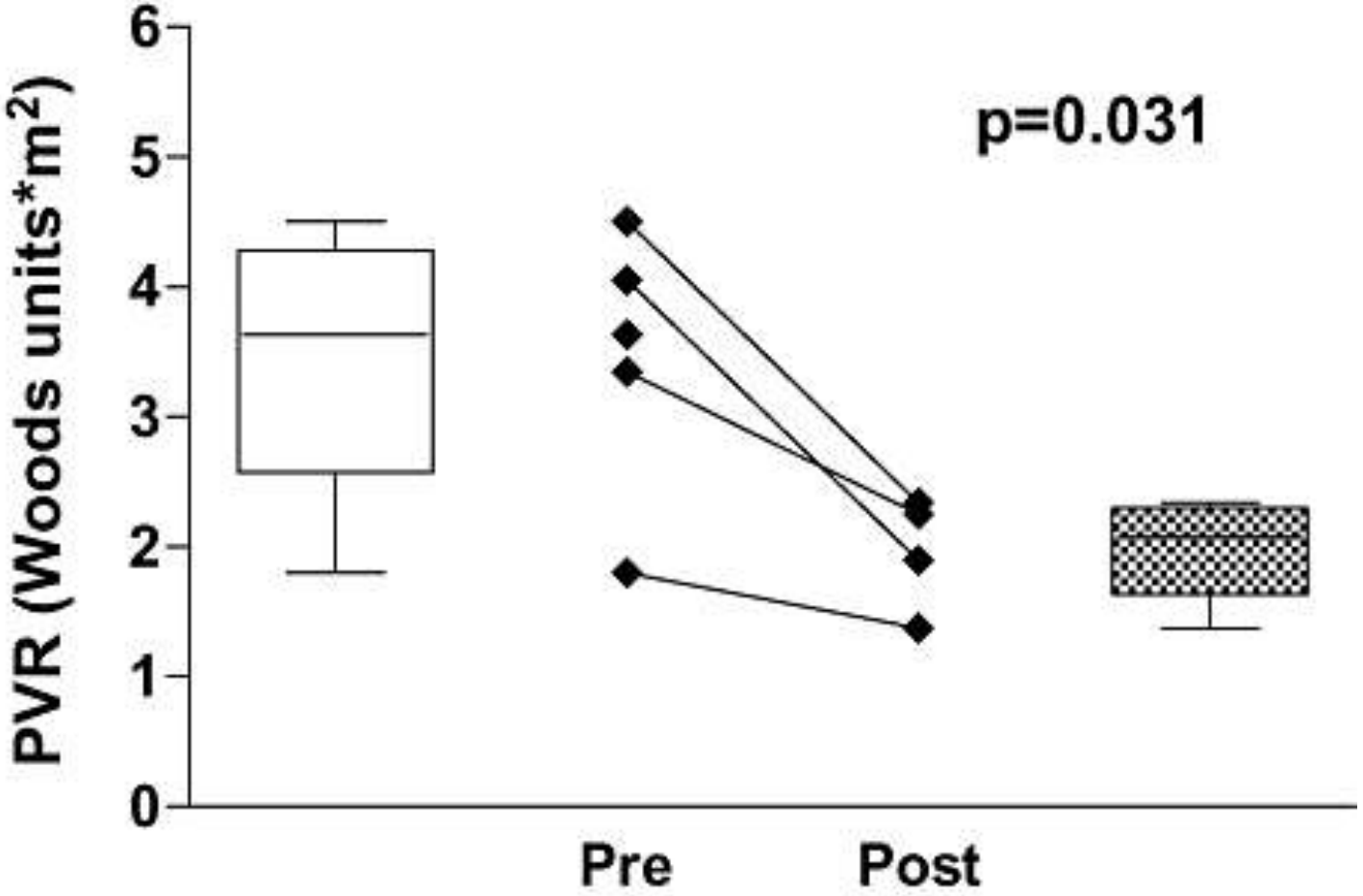
• Arrhythmia	50%
• Large thrombus/ embolism	35%
• CHF/ Ventricular dysfunction	28%
• Cyanosis	22%
• PLE	7%

Problems of pulmonary (right side) circulation

- may increase CVP and result in …..
  - arrhythmia
  - enlarged RA, and thrombus formation
  - veno-atrial shunt and cyanosis
  - PLE
  - liver cirrhosis
- may decrease cardiac output and cause CHF
- may cause pulmonary AVM and cyanosis

- Definition of relative PH?
  - CVP > 18 mmHg with low Lap
  - Rp >2.5 unit.m2
- Causes are unknown
  - Non-pulsatile flow
  - Endothelial dysfunction
  - Vasoconstriction due to increased EDP
- Can be reduced by pulmonary vasodilator?
  - Endothelin receptor antagonists
  - PDE inhibitors

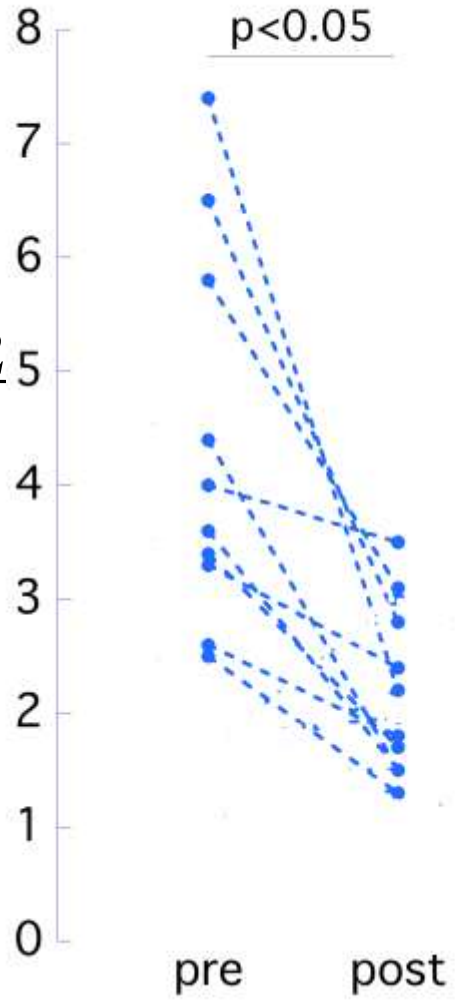
Effect of sildenafil in failing Fontan



Morchi et al. Congenital Heart Disease 2009; 4: 107

Effect of sildenafil in failing Fontan

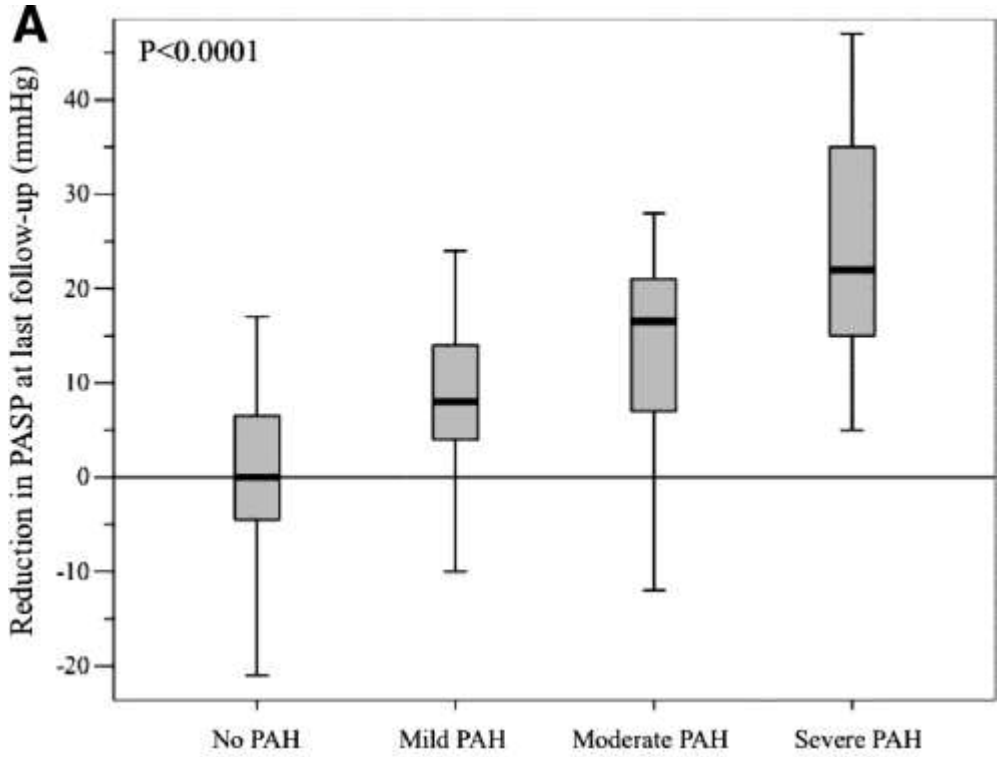
Rp
Wood unit.m2



これからの課題

- 肺血管拡張薬時代の手術適応は？
  - Borderline症例で適応を拡大できるか？
- 肺血管拡張薬時代の内科治療
  - 死亡例を生存せしめるか？
  - 延命できるか？
- 登録制度が必要

Long-term results of ASD closure in pts with PH and with reasonable indications

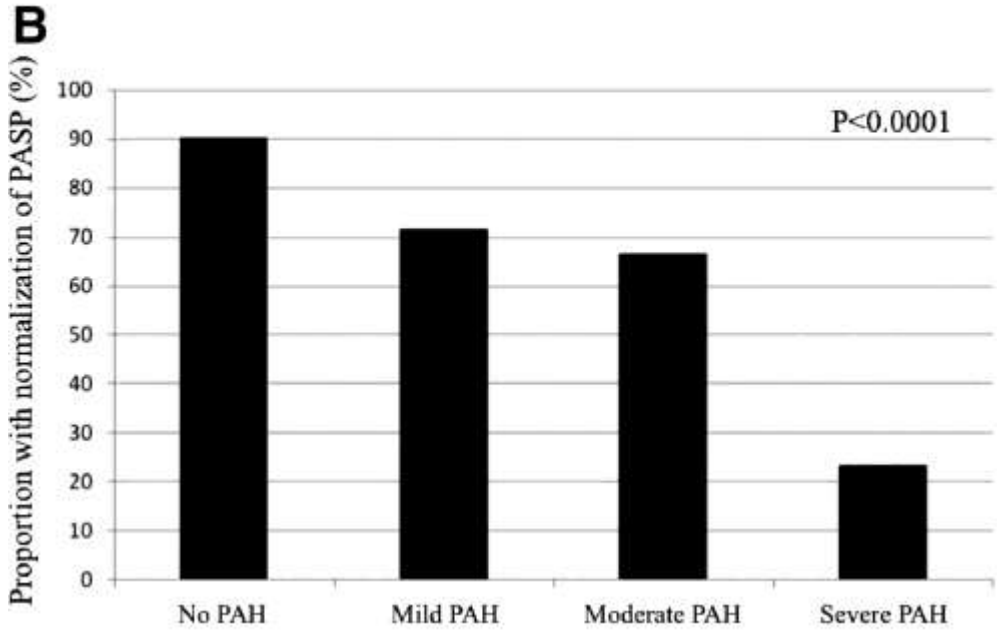


No PH : RVSP<40mmHG

Mild PH : RVSP 40-49mmHG

Moderate PH: RVSP 50-59mmHG

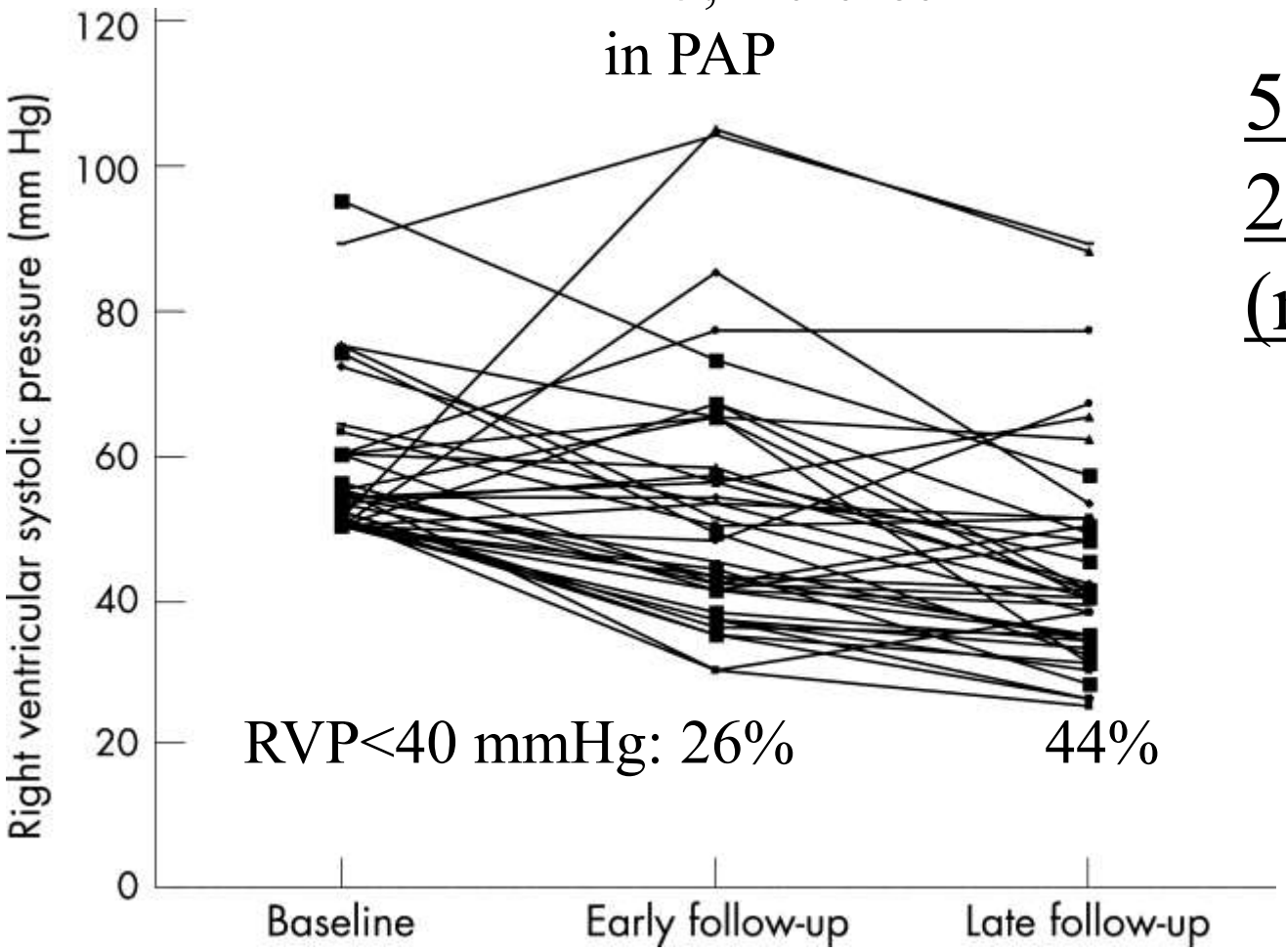
Severe PH : RVSP >60mmHG



Yong G et al. Circ Cardiovasc Interv 2009;2:455-462

RVP>50 mmHg before closure

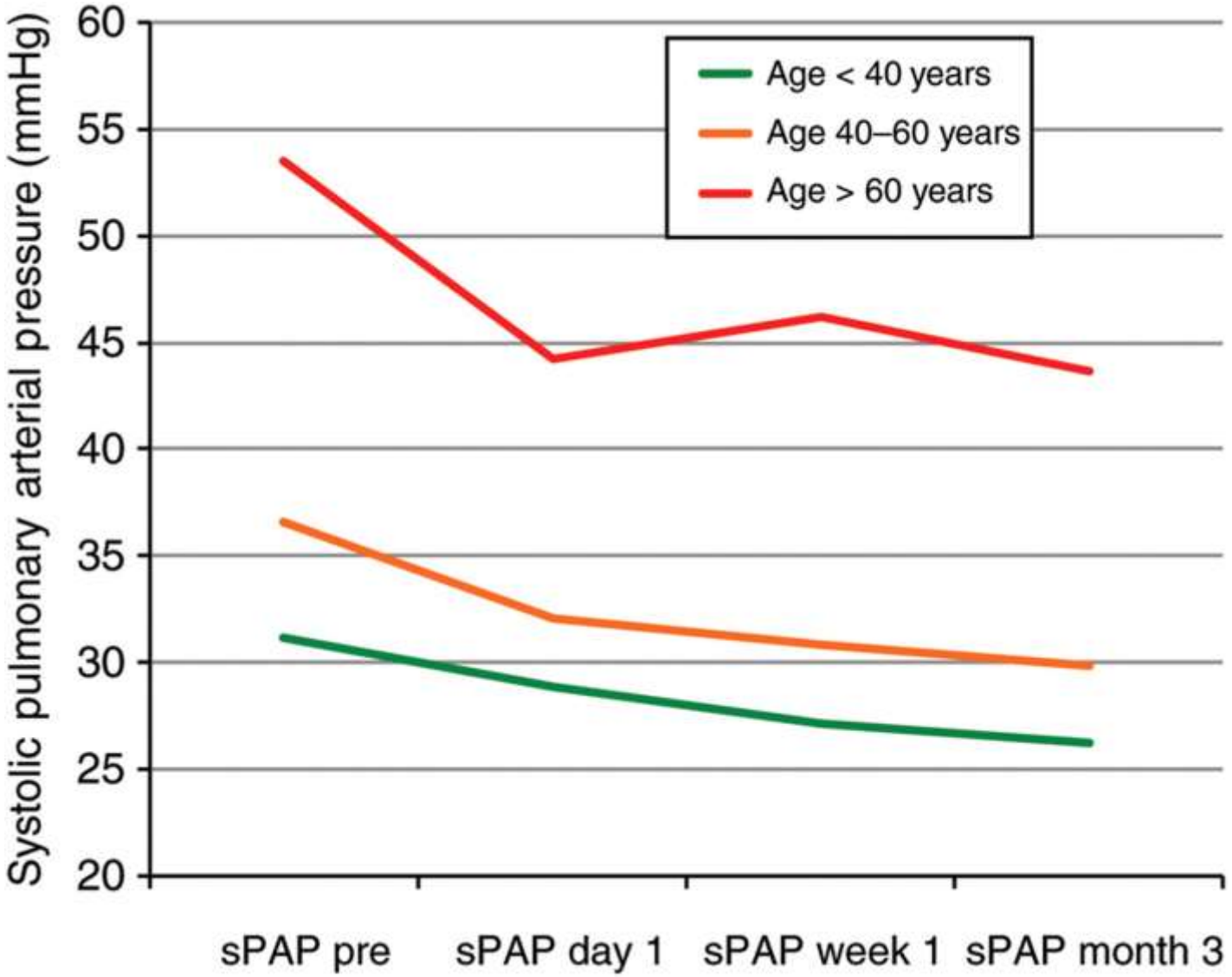
In 5, increase
in PAP



RVP<40 mmHg: 26% 44%

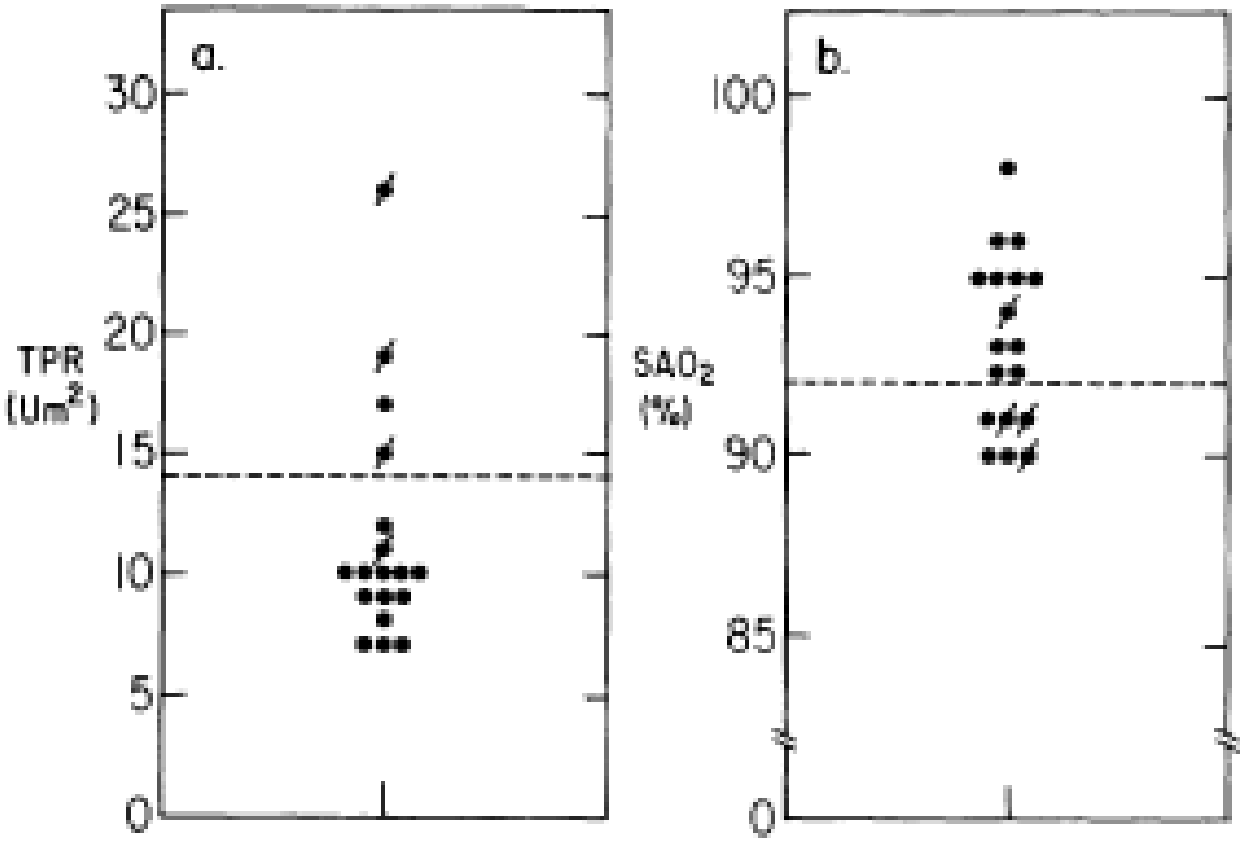
54 pts
20-79 yrs
(m 59)

Balint O H et al. Heart 2008;94:1189-1193



Humenberger M et al. Eur Heart J 2011;32:553-560

Operability



Acute test: Epoprostenol

- It activates prostaglandin I receptor and adenylate cyclase, increasing cAMP
- 2 ng/kg/min, 4, 6, 8, 10, 12
- Every 15 min
- Systemic hypotension can occur

Acute test: Inhaled NO

- NO activates soluble guanylate cyclase
- Soluble guanylate cyclase increases cGMP
- No is sacavengerd quickly by hemoglobin
- As a test, 20 ppm NO in 100% O2 is preferred
- Short time use of NO usually does not cause rebound
- Cost: controvertial; industrial gass, medical gass