Pulmonary Arterial Hypertension: Assessment of disease's severity

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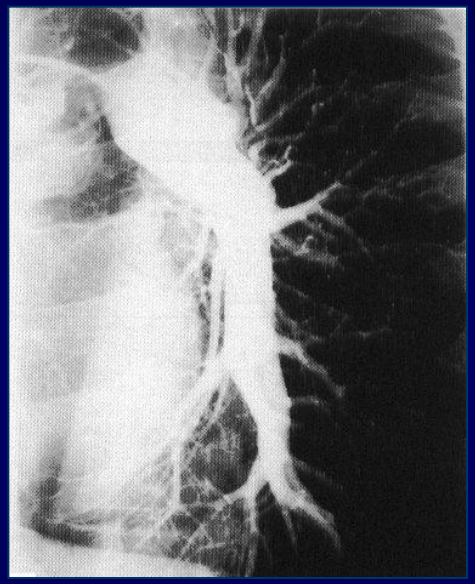
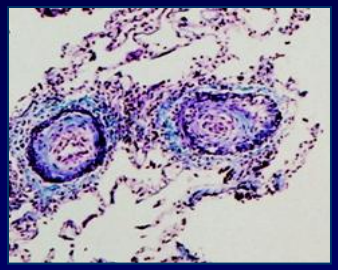
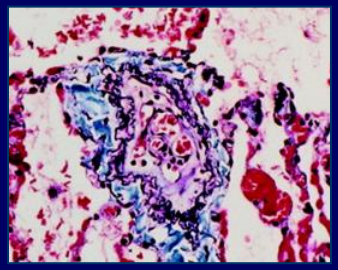
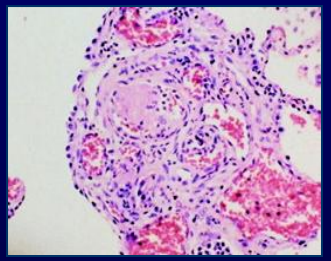
Pulmonary Arterial Hypertension: The disease

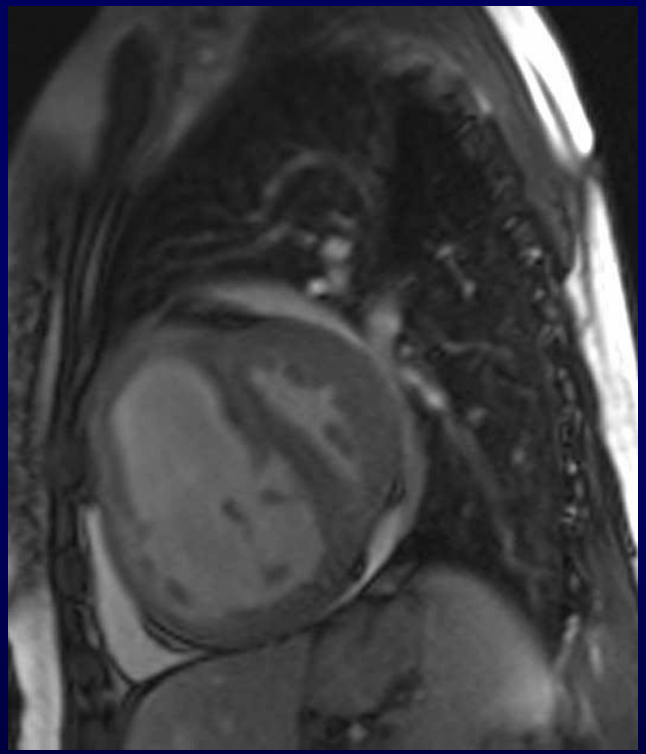






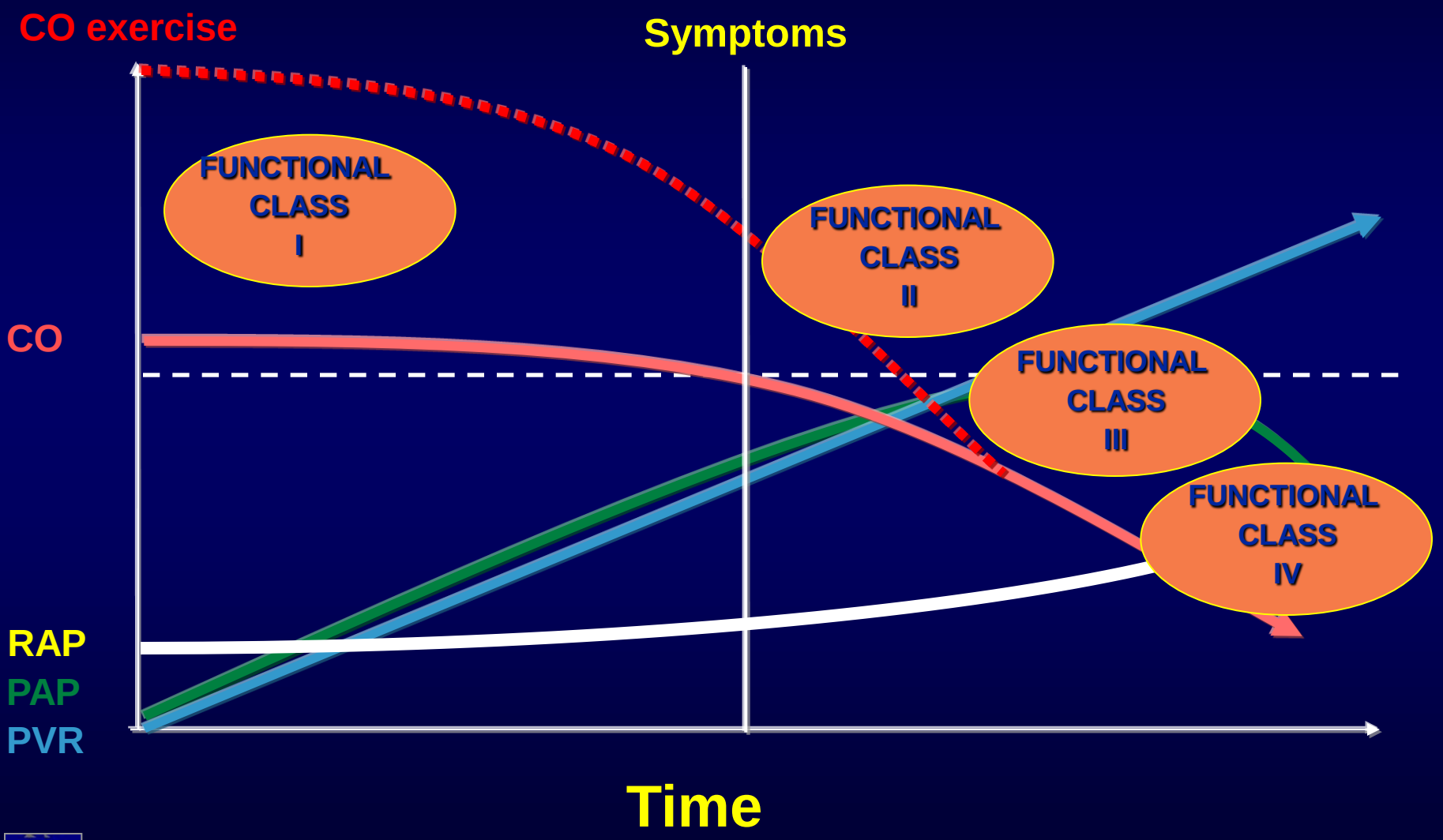


Female 40 yrs
PAP = 50 mmHg
CI = 2,3 l/m/m2

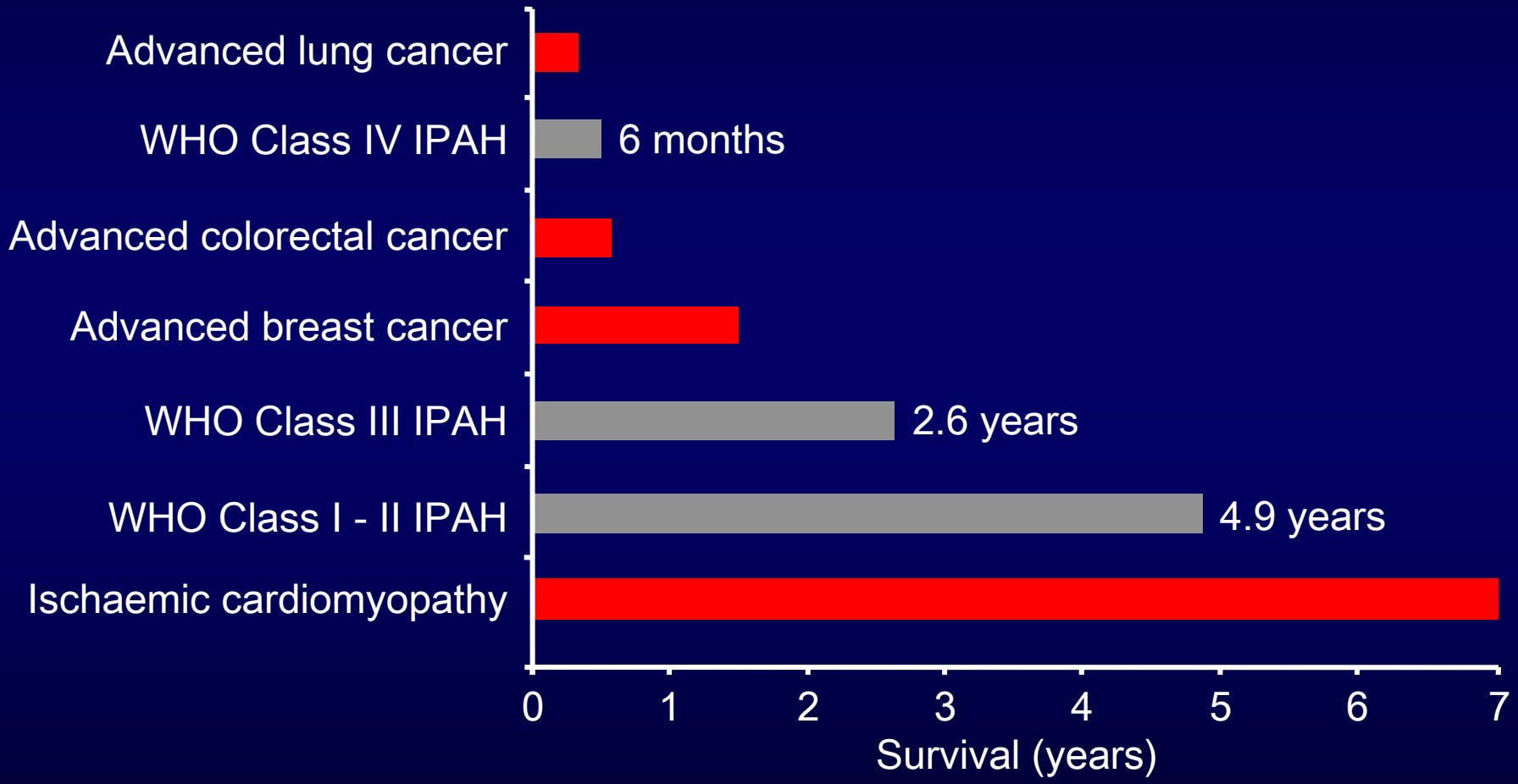


NYHA Class III
6MWD = 380 m

PAH: natural history



Prognosis of Idiopatic Pulmonary Arterial Hypertension (PAH) was poor



D'Alonzo GE, *et al. Ann Intern Med* 1991; 115:343-9.
Kato I, *et al. Cancer* 2001; 92:2211-9.
Felker GM, *et al. N Engl J Med* 2000; 342:1077-84.

Specific approved drugs in PAH

Prostacyclin Derivatives

- Epoprostenol: IV
- Iloprost: inhaled
- Treprostinil: subcutaneous or IV

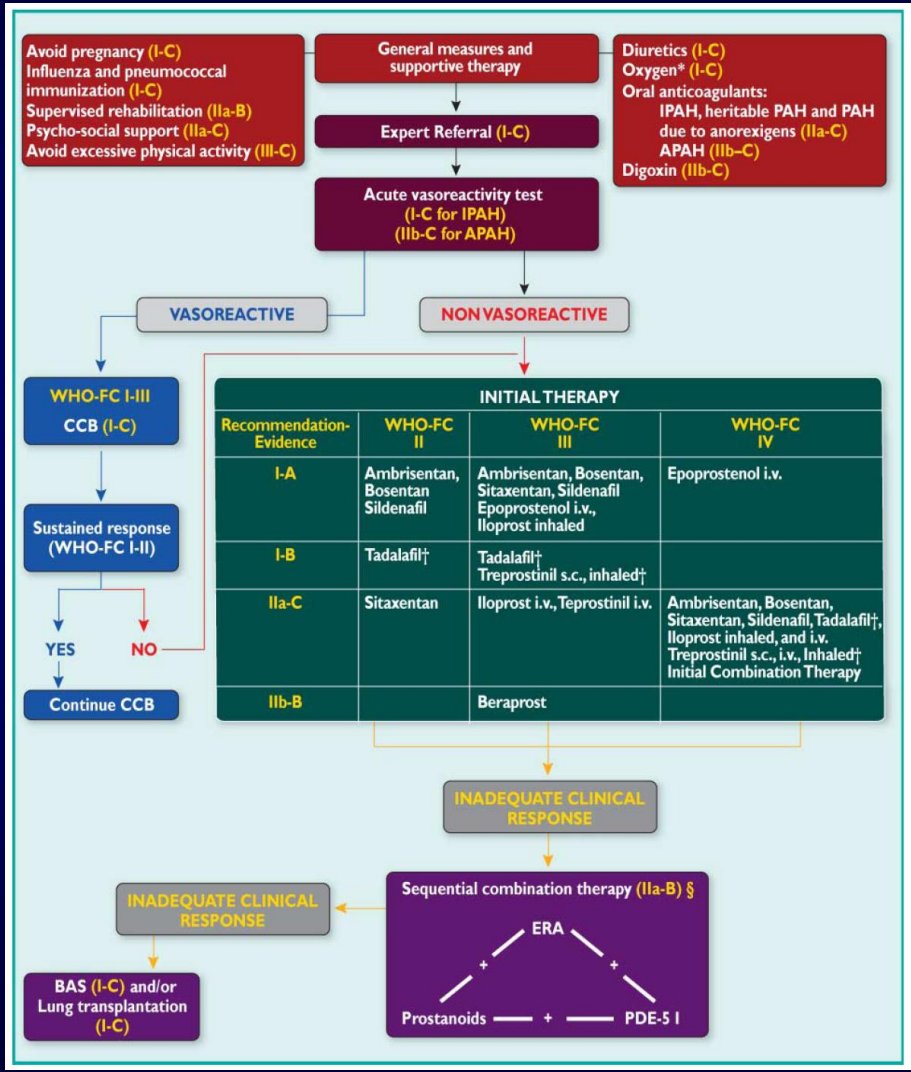
Endothelin Receptor Antagonists

- Bosentan: oral
- Ambrisentan: oral
- Sitaxsentan

Phosphodiesterase Type-5 Inhibitors

- Sildenafil: oral

The ESC/ERS 2010 therapeutic algorithm…

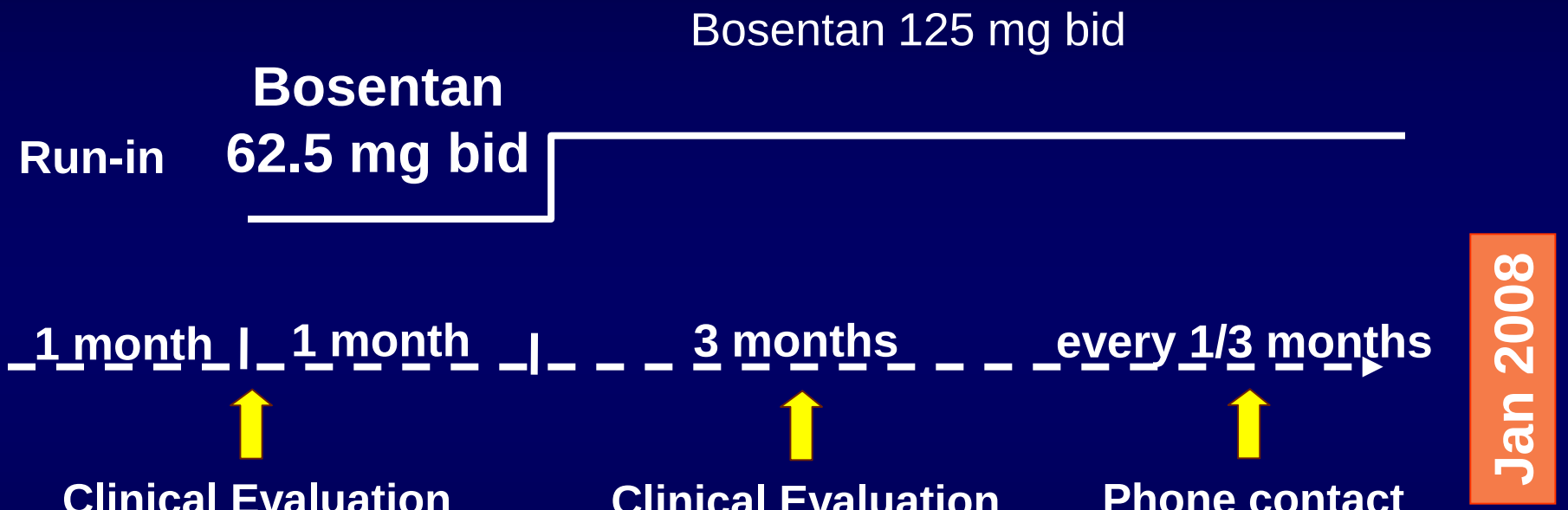


Treatment guided by Prognostic risk assessment ?

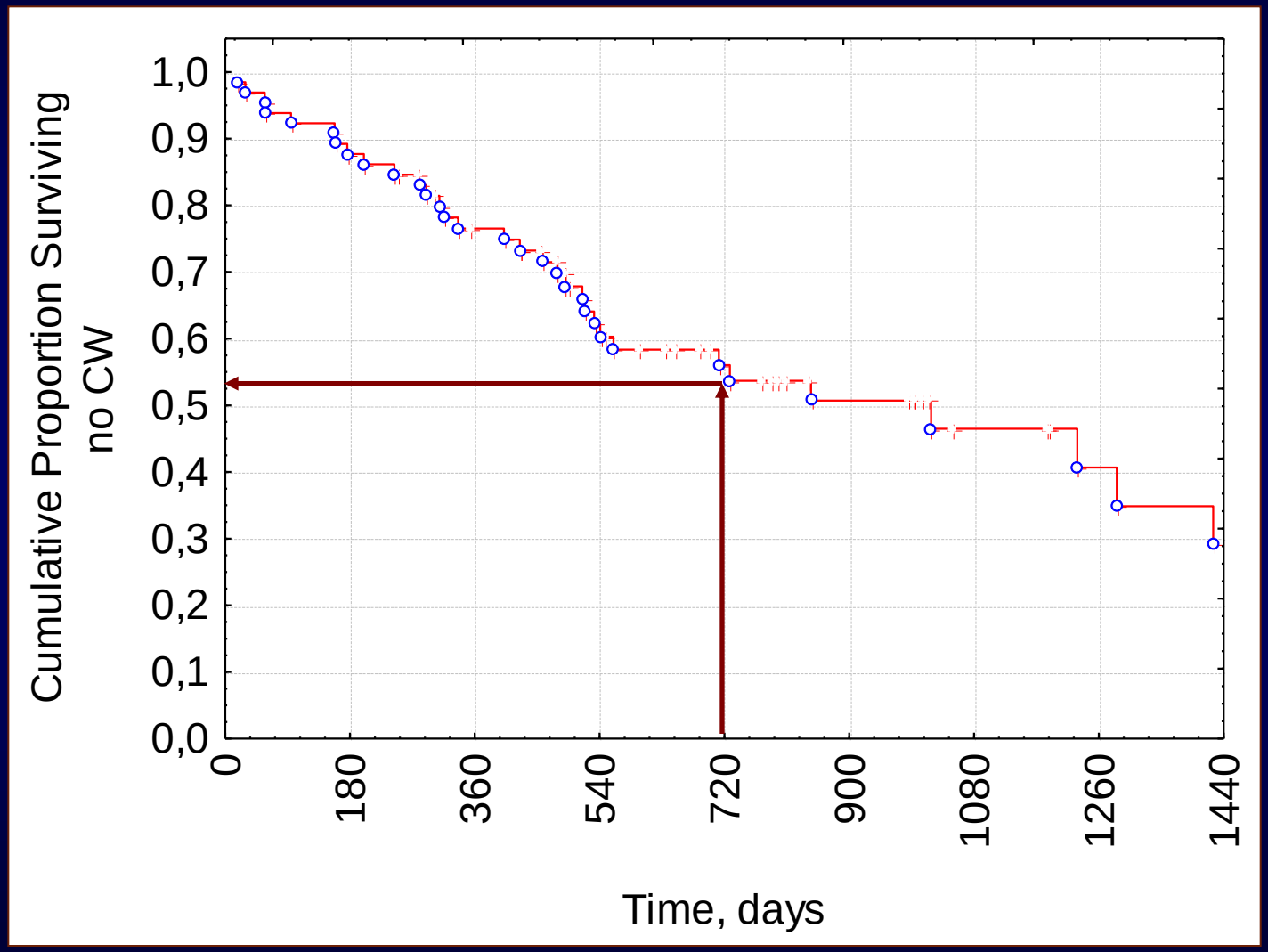
It introduces the concept of Inadequate clinical response

Need for assessment during Follow-up

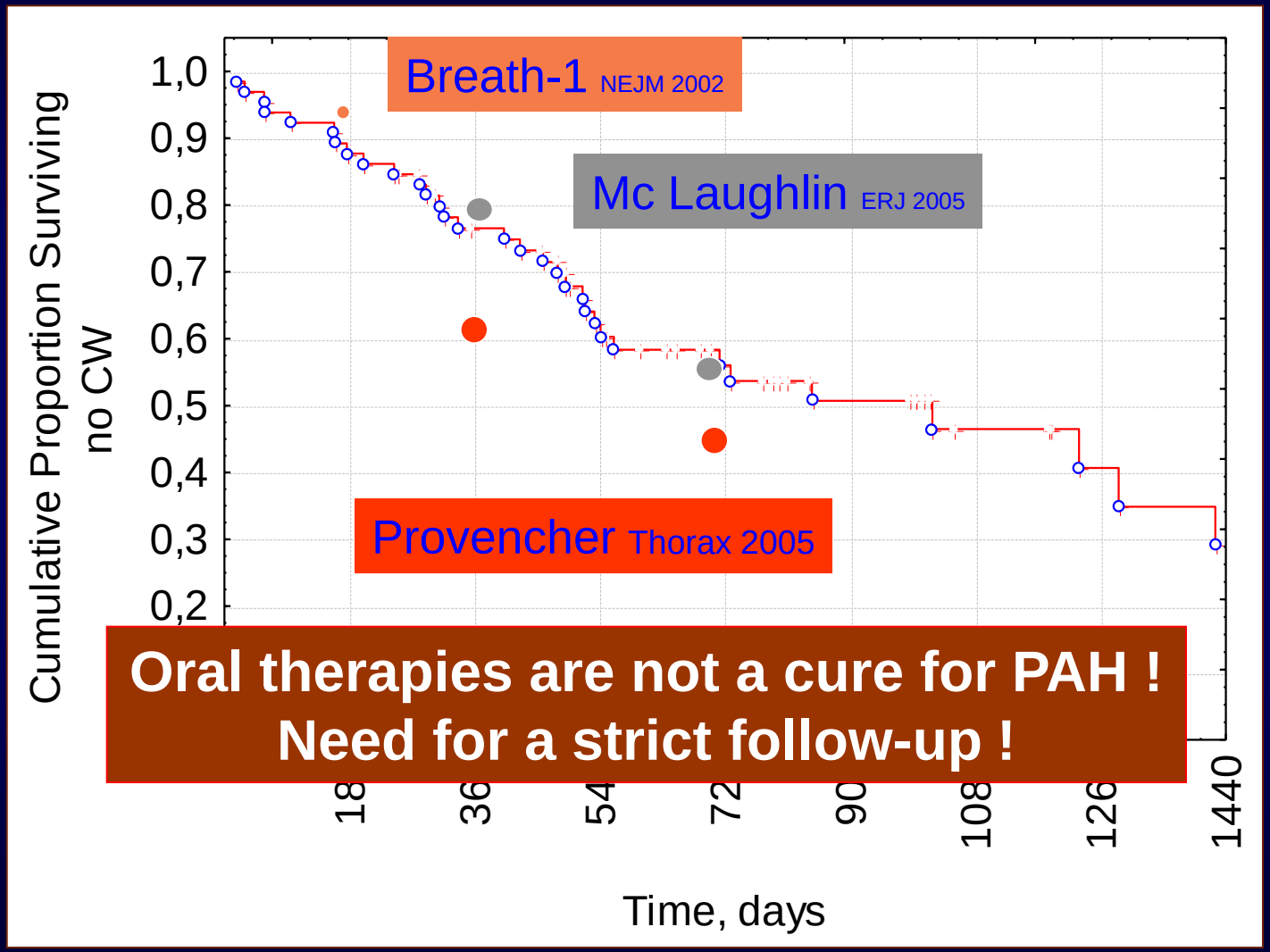
Our experience



KM plot: patients without CW



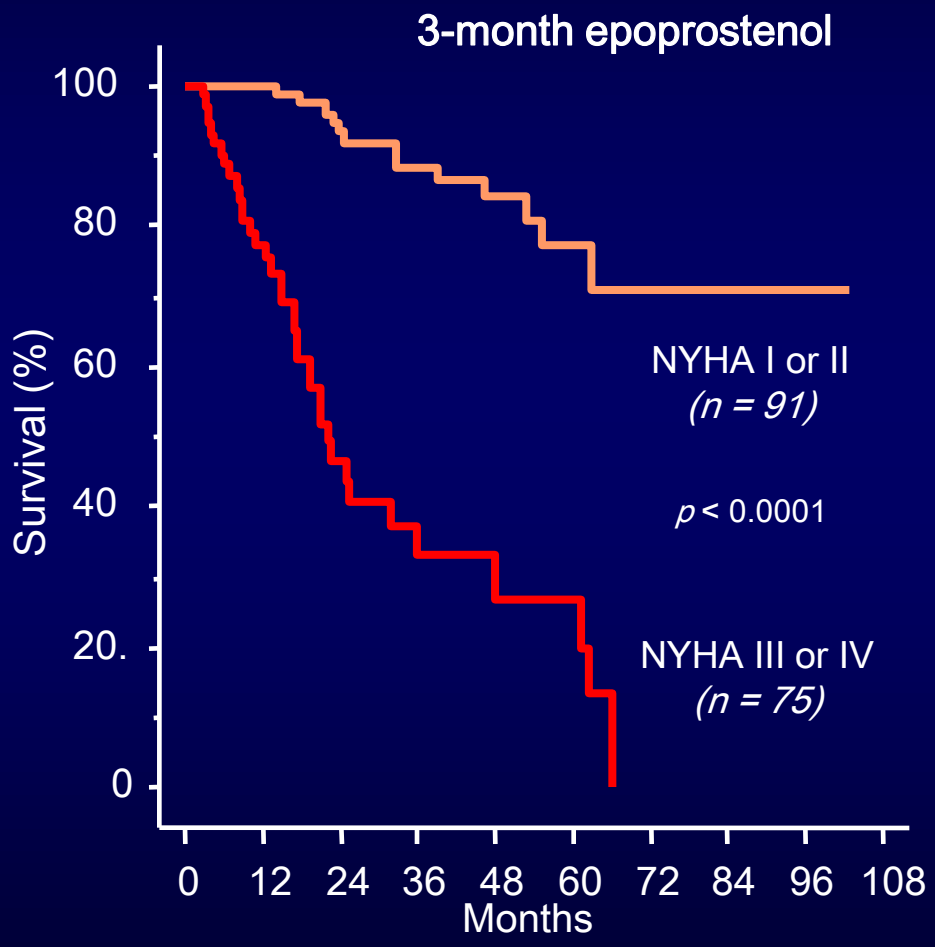
KM plot: patients without CW



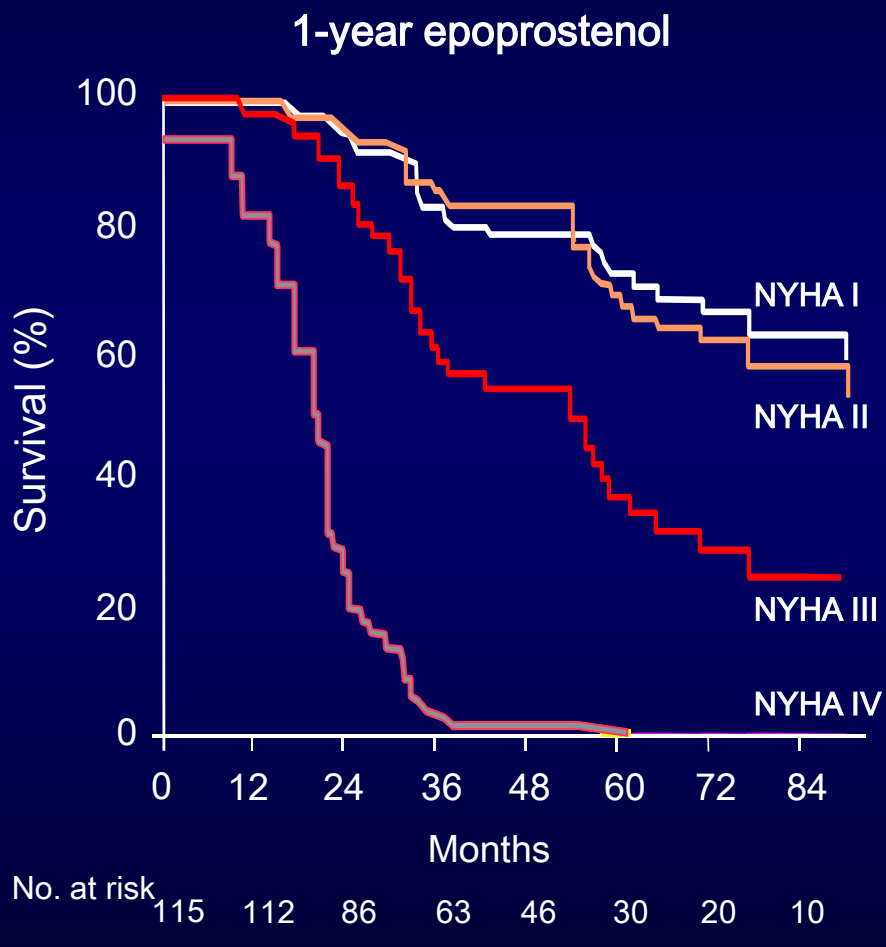
Prognostic indicators

- **Clinical assessment**
  - Symptoms
  - Clinical Signs
  - Rate of progression
- **Exercise capacity**
  - 6 minute walking test
  - CP exercise test
- **RV function**
  - Echo
  - MR heart
- **Hemodynamics**
  - Right Atrial Pressure
  - Cardiac Index
- **Biomarkers**
  - Troponin-T
  - BNP, Na, Creatinine
  - Uric Acid, PCR

Functional class & with survival

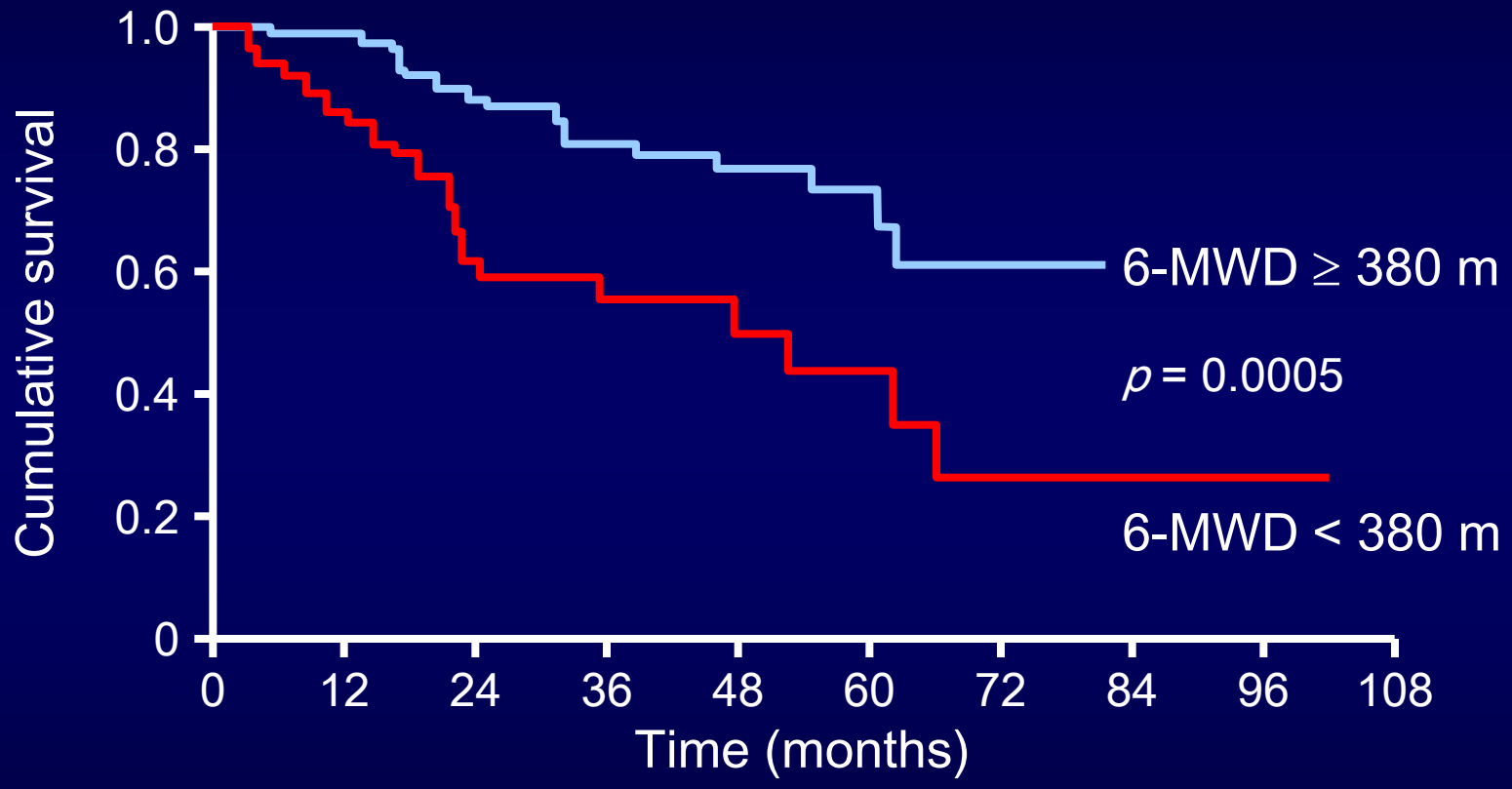


Sitbon O, *et al. J Am Coll Cardiol* 2002; 40:780-8.



McLaughlin VV, *et al. Circulation* 2002; 106:1477-82.

6-minute walk distance & survival



Subjects at risk (*n*)									
6-MWD ≥ 380 m	78	71	56	41	28	15	4		
6-MWD < 380 m	78	54	28	16	8	6	3	3	1

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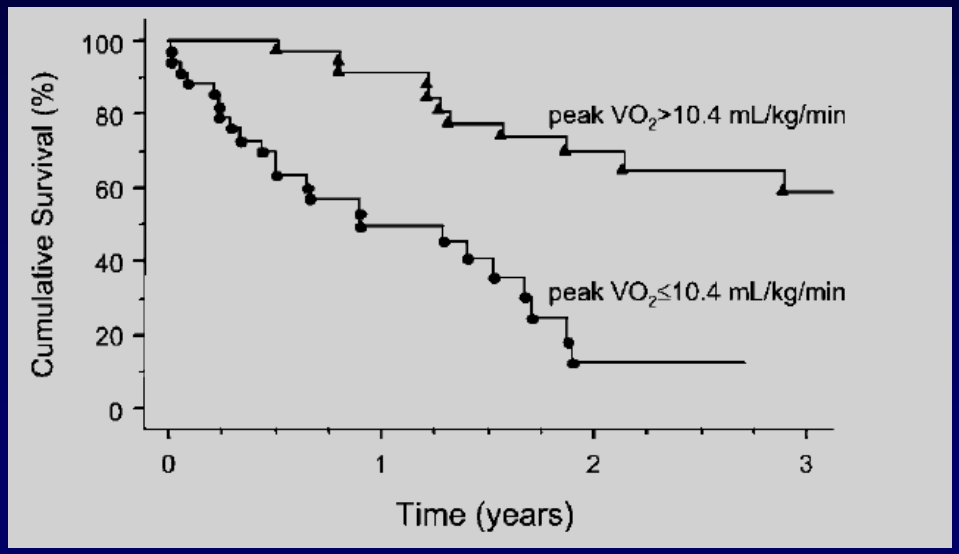
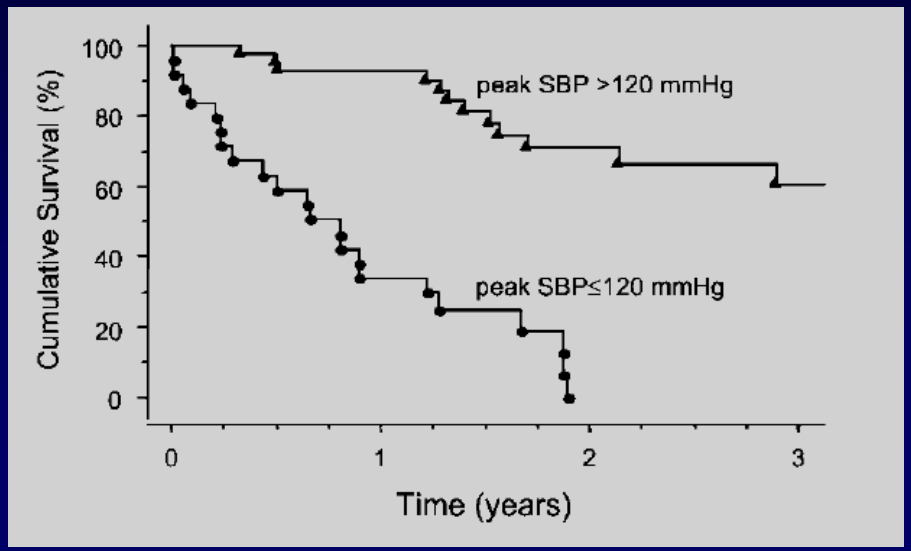
Sitbon O, *et al. J Am Coll Cardiol* 2002; 40:780-8.

Cardiopulmonary exercise test

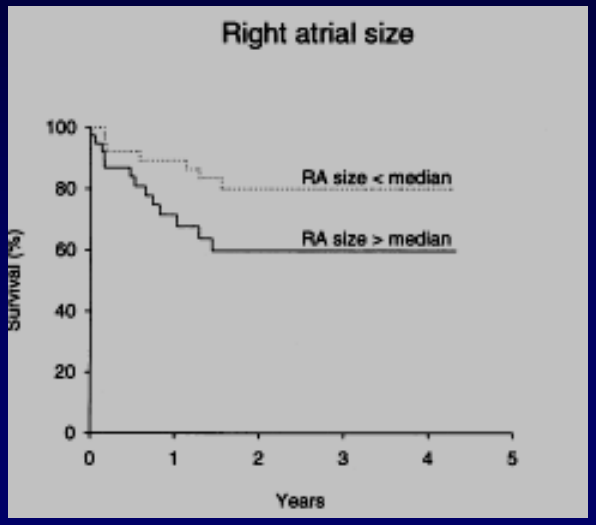


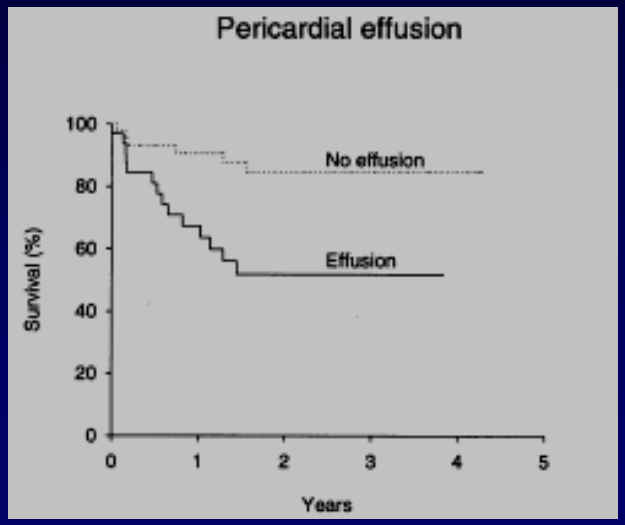


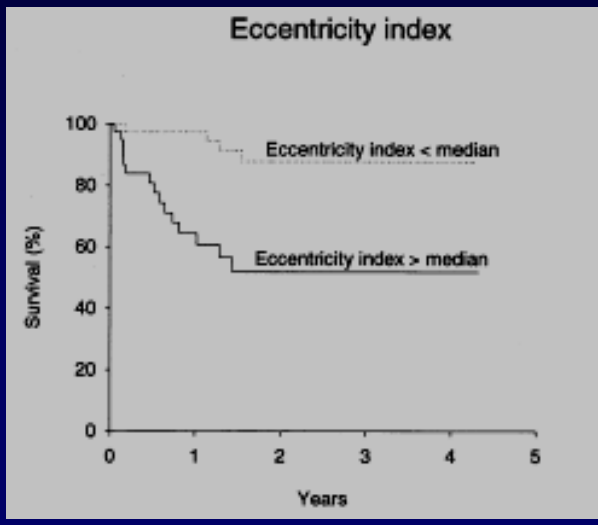
Step	Variable	RR	*P*	Cumulative χ^2
1	Peak SBP, mm Hg	0.955	0.0046	27.6
2	Peak DBP, mm Hg	0.961	0.0495	33.7
3	Peak $\dot{V}O_2$, mL · kg^{-1} · min^{-1}	0.814	0.0024	40.7
4	Uric acid, mg/dL	1.178	0.0037	44.7

Wessel R.Circulation. 2002;106:319-324

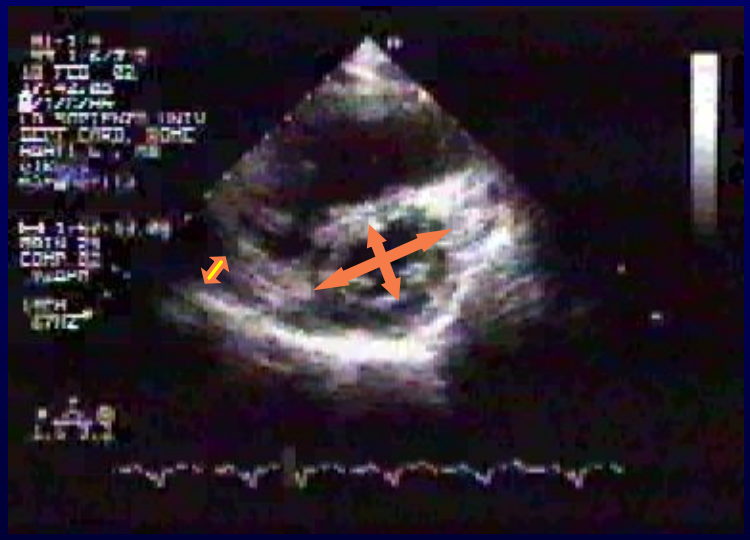
Prognostic Impact of Echocardigram





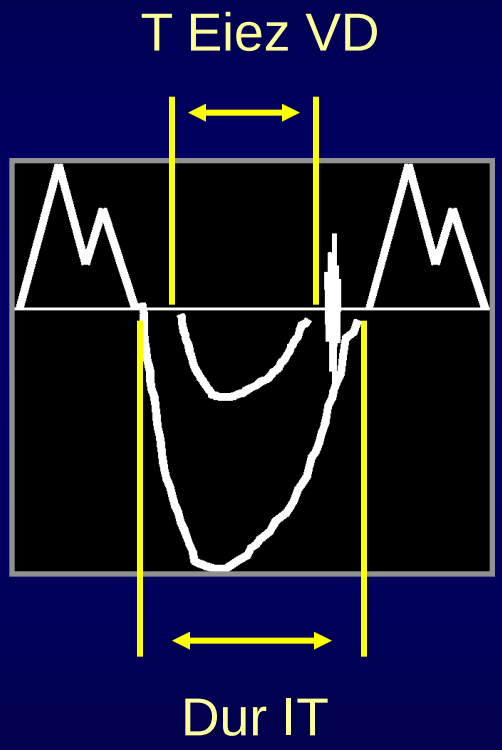


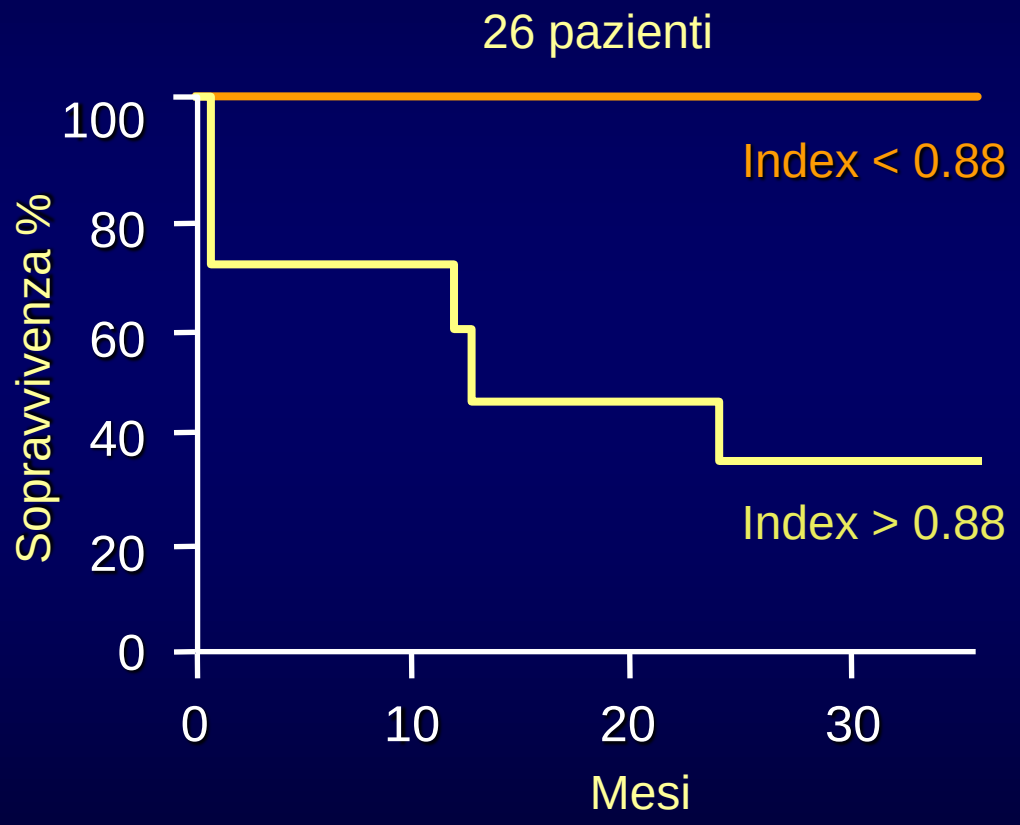
	HR (95% CI)	p Value
Significant multivariable predictors of death		
Pericardial effusion (Y/N)	4.38 (1.41–13.67)	0.011
Randomization to prostacyclin (Y/N)	0.25 (0.08–0.76)	0.014
6-min walk (500 ft)	0.56 (0.29–1.08)	0.082
Significant multivariable predictors of composite end point		
Mixed venous O_2 (10%)	0.73 (0.56–0.94)	0.016
RA area index (5 cm^2/m)	1.24 (0.96–1.61)	0.106



Raymond RJ. JACC 2002

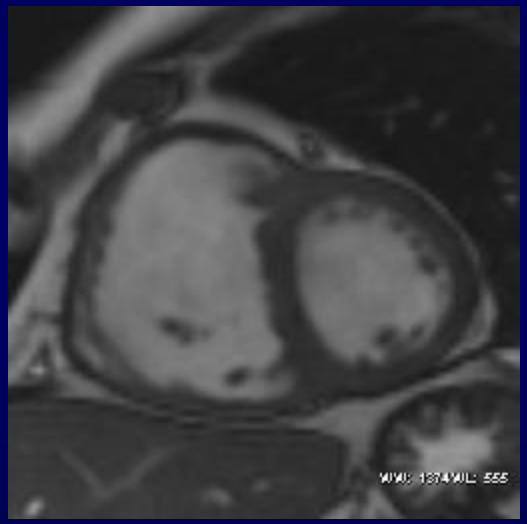
Tei Index = (Dur IT- T Eiez VD) / T Eiez VD





Tei C. J Am Soc Echocardiogr. 1996

Heart Magnetic Resonance & Survival



Variable	Hazard ratio	95% CI Lower	95% CI Upper	P
6MWT	0.28	0.09	1.18	0.087
Mean RA pressure	5.06	1.85	12.9	0.049
Mean PA pressure	0.81	0.21	3.08	0.745
PVRI	4.51	1.76	11.9	0.050
Cardiac index	0.34	0.10	1.44	0.158
Stroke volume index	0.14	0.06	0.85	0.027
Heart rate	0.98	0.26	3.68	0.974
Mixed venous O_2 saturation	0.23	0.08	1.36	0.126
Cardiac index (MRI)	0.16	0.07	1.00	0.051
Stroke volume index (MRI)	0.10	0.04	0.59	0.006
RV mass index	2.12	0.56	7.79	0.274
LV mass index	0.68	0.18	2.54	0.558
RV wall thickness	2.84	0.78	7.25	0.107
LV wall thickness	0.54	0.13	2.31	0.410
RVEF	0.12	0.05	0.73	0.015
LVEF	0.55	0.15	2.10	0.394
RVEDVI	6.69	1.91	15.4	0.037
LVEDVI	0.13	0.06	0.77	0.019

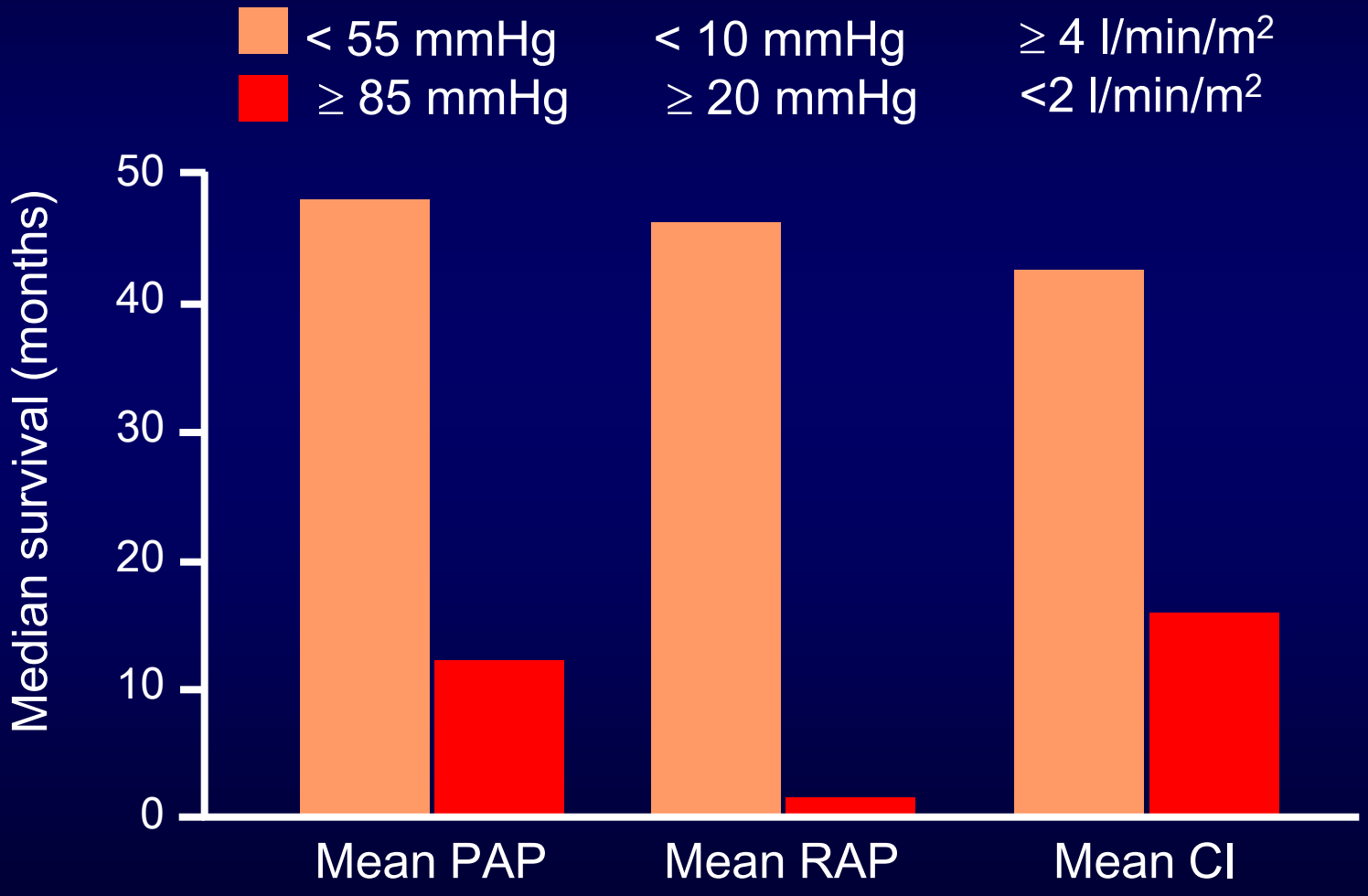
0 1 2 3 4 5 6 7 8 9 10

Hazard ratio

Univariate Analysis of the Change in Variables, Including Magnetic Resonance Imaging Data After 1-Year Follow-Up as a Potential Predictor of Mortality in IPAH

Badesch DB et al., J Am Coll Cardiol. 2009 Jun 30;54(1 Suppl):S55-66.

Haemodynamic abnormalities and prognosis



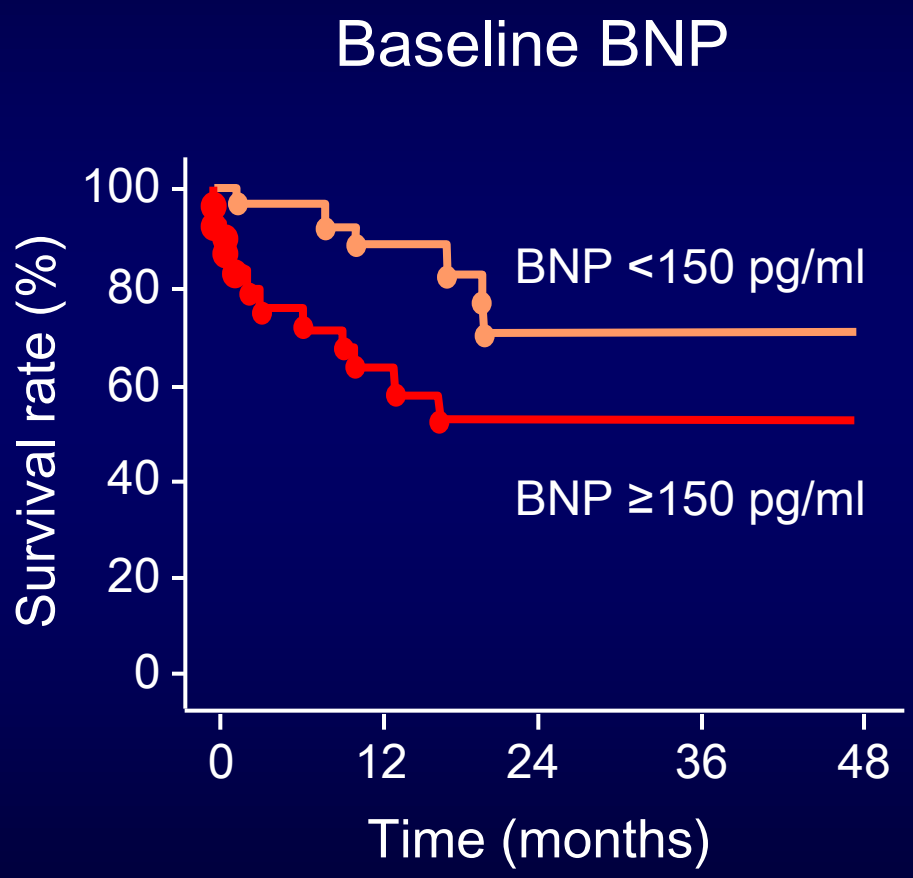
D'Alonzo, *et al. Ann Int Med* 1991; 115:343-9.

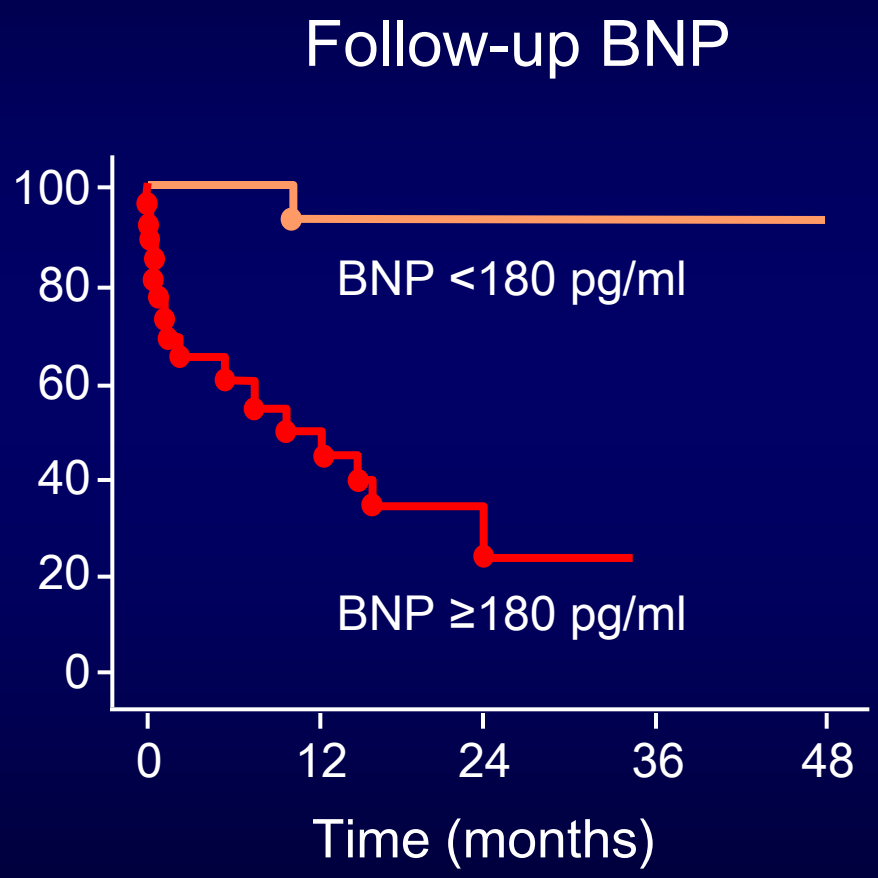
Biomarkers

Different mechanism:

- Marker of RV overload (BNP, NT-proBNP)
- Marker of myocardial injury (Troponin)
- Marker of Systemic inflammation (C-reactive protein)

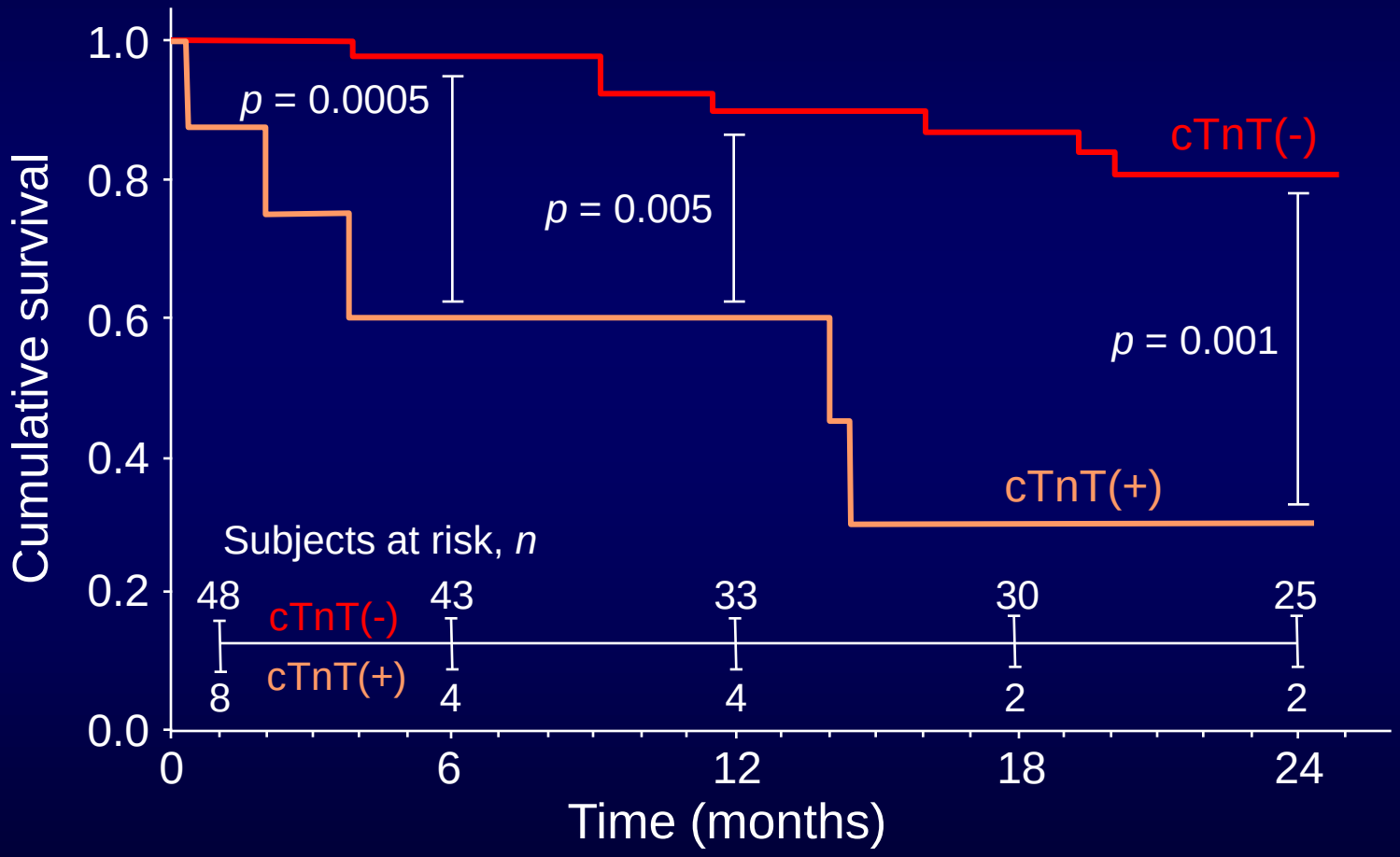
Brain natriuretic peptide (BNP)





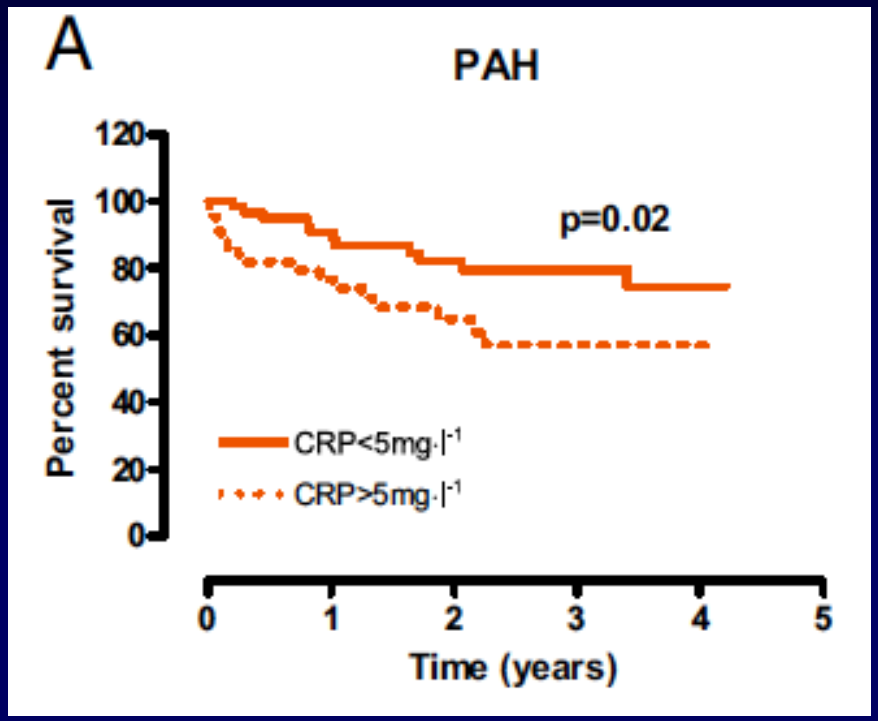
Nagaya N, *et al. Circulation* 2000; 102:865-70.

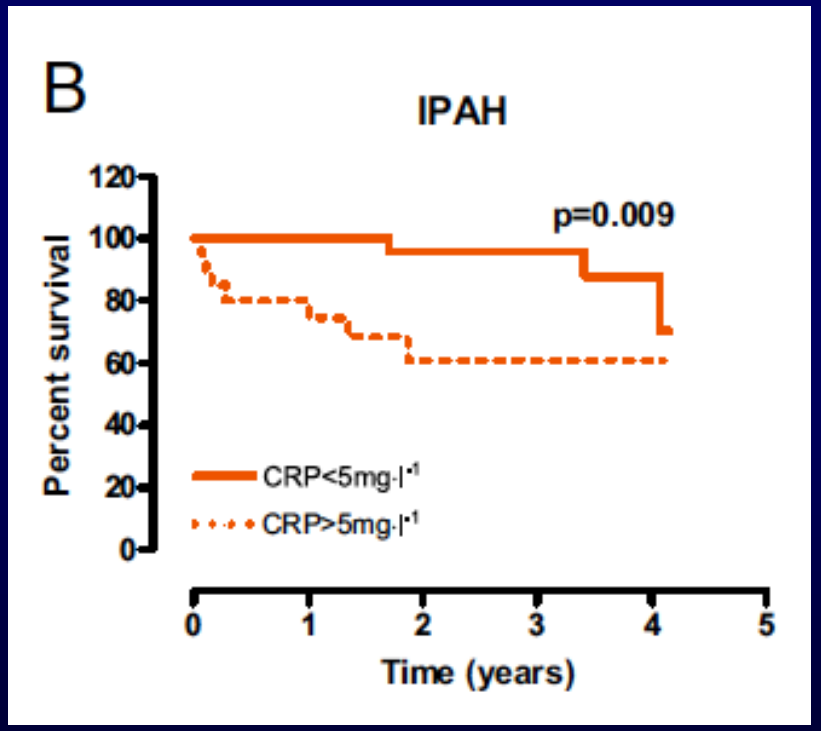
Troponin I and troponin T



Torbicki A, *et al. Circulation* 2003; 108:844-48.

C Reactive Protein





Quarck RA, *et al. JACC* 2009; 53:1211-8.

Follow-up

	Baseline	Montly	6 Months	Clinical judgement
Clinical evaluation	X	X		
ECG	X	X		
Walking test	X	X		
Blood gas analysis	X		X	
Pulmmonary Test	X		X	
Echo Doppler	X		X	X
Cardiopulm. test	X		X	X
Hemodynamic	X		X	X
BNP(?)	X			X

Goal-oriented treatment and combination therapy for pulmonary arterial hypertension

M.M. Hoeper, I. Markevych, E. Spiekerkoetter, T. Welte and J. Niedermeyer

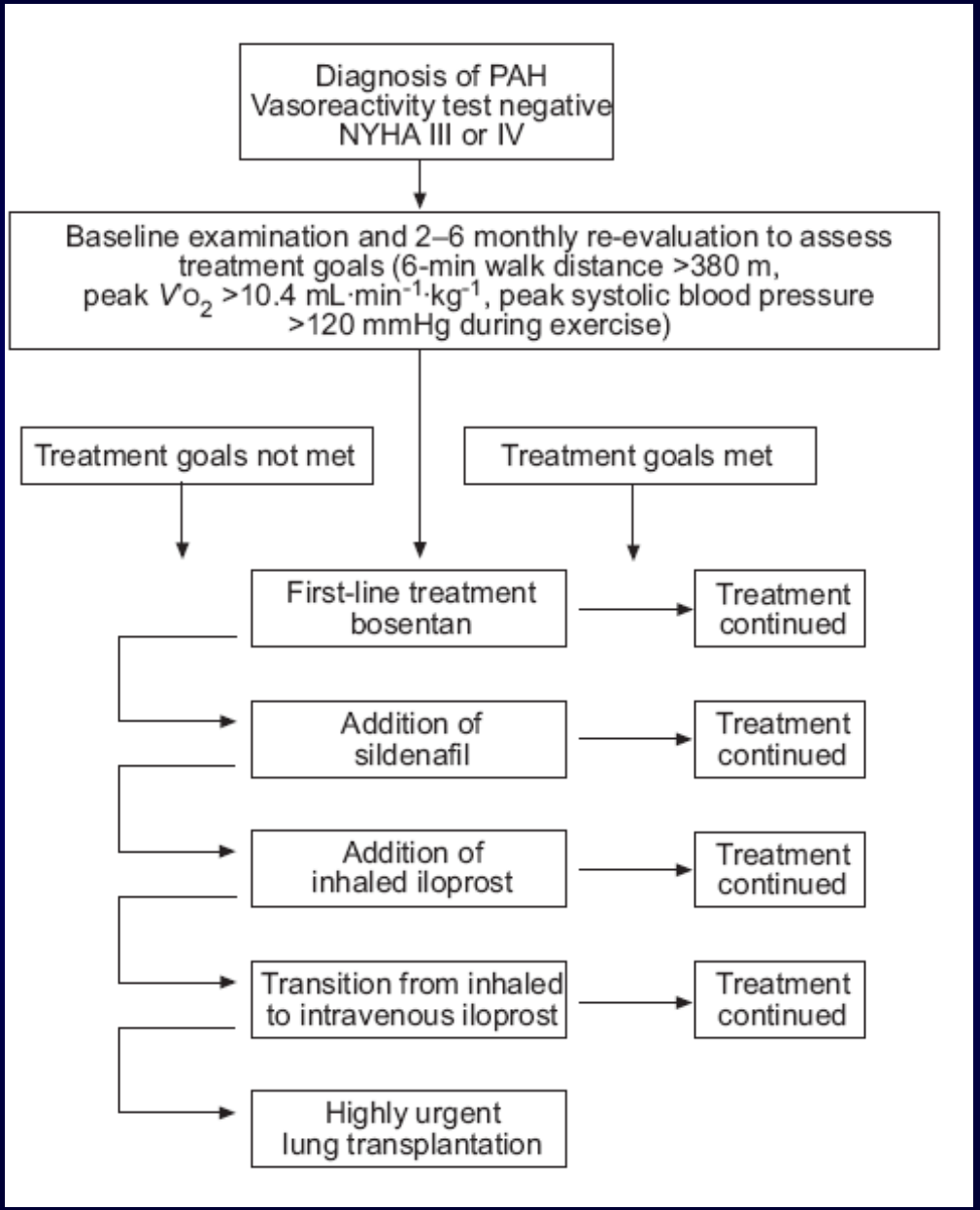
A shift of strategy !

We do not have to wait for deterioration,

but combine treatments if the patient does not reach clinical meaningful targets

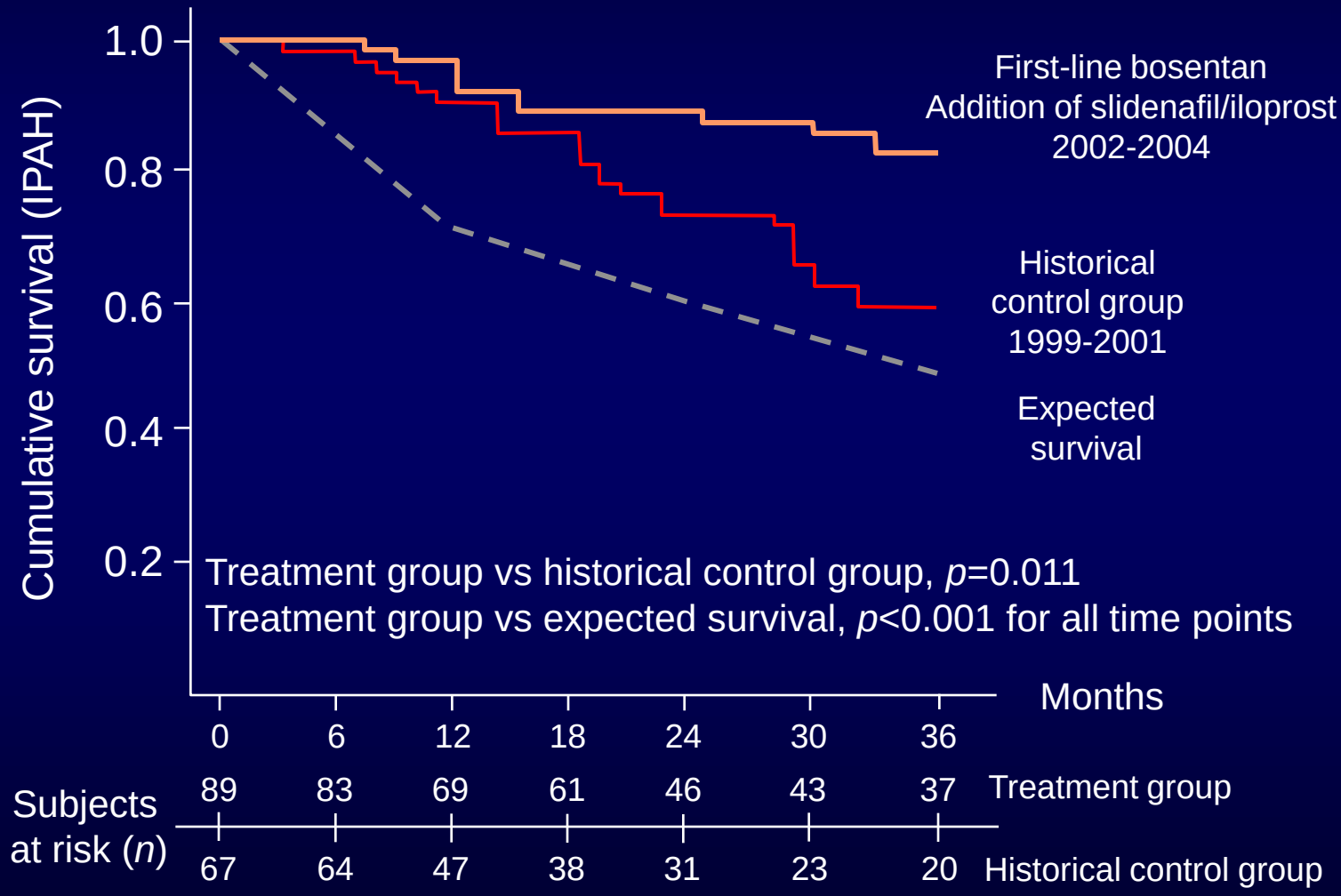
Treat to goals 2005

- **6MWT > 380 mt**
- **Peak VO2 10,4 ml/kg/m**
- **Exerc. BP > 120 mmHg**



Hoeper MM, *et al. Eur Respir J* 2005; 26:858-63.

Effect of “treatment to goals” on survival



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Hoeper MM, *et al. Eur Respir J* 2005; 26:858-63.

ESC/ERS 2009 PAH guidelines

Better prognosis	Determinants of prognosis	Worse prognosis
No	Clinical evidence of RV failure	Yes
Slow	Rate of progression of symptoms	Rapid
No	Syncope	Yes
I, II	WHO-FC	IV
Longer (>500 m)[a]	6MWT	Shorter (<300 m)
Peak O_2 consumption >15 mL/min/kg	Cardio-pulmonary exercise testing	Peak O_2 consumption <12 mL/min/kg
Normal or near-normal	BNP/NT-proBNP plasma levels	Very elevated and rising
No pericardial effusion TAPSE[b] >2.0 cm	Echocardiographic findings[b]	Pericardial effusion TAPSE[b] <1.5 cm
RAP <8 mmHg and CI ≥2.5 L/min/m^2	Haemodynamics	RAP >15 mmHg or CI ≤2.0 L/min/m^2

Galie N *et al, Eur Heart J* 2009;doi:10.1093/eurheartj/ehp297.

Are these criteria applicable to SSc-PAH ?

Registry data of bosentan therapy in PAH-SSc

- Royal Free Hospital registry-based evaluation of the impact of bosentan on exercise capacity, and survival in patients in class III and class IV PAH and SSc

- Patients with PAH-SSc treated with bosentan as per BREATHE-1 protocol were compared to PH-SSc BREATHE-1 eligible control patients

Williams MH *et al. Heart* 2006; 92:926-32.

Are these criteria applicable to SSc-PAH ?

	Current treatment era (n=45)	Hi co (n	
Mean age (years)	60 (11.3)	58	
Sex (men/women)	7/38	7/	
Time from diagnosis to start of bosentan or prostanoid (days)*	36 (0–512)	72	
SMWT distance (m)	207 (0–538)	179 (0–471)†	0.1
mRAP (mm Hg)	8 (6.1)	7 (4.4)	NS
mPAP (mm Hg)	40 (11.8)	40 (11.4)	NS
MAP (mm Hg)	102 (18)	95 (15)	NS
PVR (dyn·s·cm^{-5})	613 (345)	597 (359)	NS
Cardiac index (l/min/m^2)	2.6 (0.7)	2.7 (0.9)	NS
WHO functional class			
III	26 (58%)	36 (77%)	0.054
IV	19 (42%)	11 (23%)	
Scleroderma subset (%)			
Limited	43 (96%)	34 (72%)	0.0026
Diffuse	2 (4%)	13 (28%)	
Patients with pulmonary fibrosis	14 (31%)	22 (46%)	NS

SSc PAH patients have:
- **a worse effort capacity**
- **a better cardiac index**

compared to Idiopathic PAH

Williams MH *et al. Heart* 2006; 92:926-32.

Conclusions

- Assessment of PAH severity is important at every stage of the disease:
  - Baseline (decision making: which drug is indicated ?)
  - Response to treatment
  - Adjustment of treatment regimen

- A combination of end-points is recommended when evaluating disease severity and progression (NYHA, 6-minWT, echo, hemodynamics, biomarkers?)

PH Unit
La Sapienza, University of Rome

Head Carmine Dario Vizza

PH clinicians (Cardiology ward, CCU, consultation & outpatients management):

Senior Cardiologists	Dr Vizza, Dr Badagliacca Dr. Poscia
Fellows:	Dr. Nona, Dr. Crescenzi,
In Training:	Dr Gambardella, Dr. Pezzuto, Dr Papa, Dr Marcon

Echo Lab
Dr. Sciomer
Dr. Badagliacca

PFTs-CPX Lab
Prof. Palange
Dott.Valli

CT & RNM Lab
Dott. Carbone
Dott. Francone

Right Cath Lab
Dott. Mancone
Dott. Colantoni

Reumathologists
Prof Valesini
Prof.Riccieri

Liver Transplant Unit
Prof. Rossi
Prof. Corradini

HIV clinic
Prof.Vullo

Pulmonologists
Prof. Parola

Lung Transplant Program
Prof.Coloni
Prof.Venuta

Back-up slides