Gaps in evidence for risk stratification

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Gaps in evidence for risk stratification

- The evaluation of risk in patients with PAH takes place between the diagnostic process and the therapeutic decision making.
- This clinical assessment has a pivotal role in the choice of the initial treatment, the evaluation of response to therapy, and the possible escalation of therapy if needed.
- Regular evaluation of patients should focus on variables with established prognostic importance.
- Treatment decisions should be based on parameters that reflect symptoms and exercise capacity and that are relevant in terms of predicting outcome.

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

What is the evidence in risk stratification?

1. What are the tools and variables useful for risk stratification in PAH?

2. How these variables have been assessed?
   - Prospective or retrospective studies?
   - Patient population?
     - iPAH, aPAH, other PH…
     - Incident/prevalent cases

3. What is the evidence for multidimensional risk assessment?

4. What is the impact of risk assessment on current therapeutic strategy?

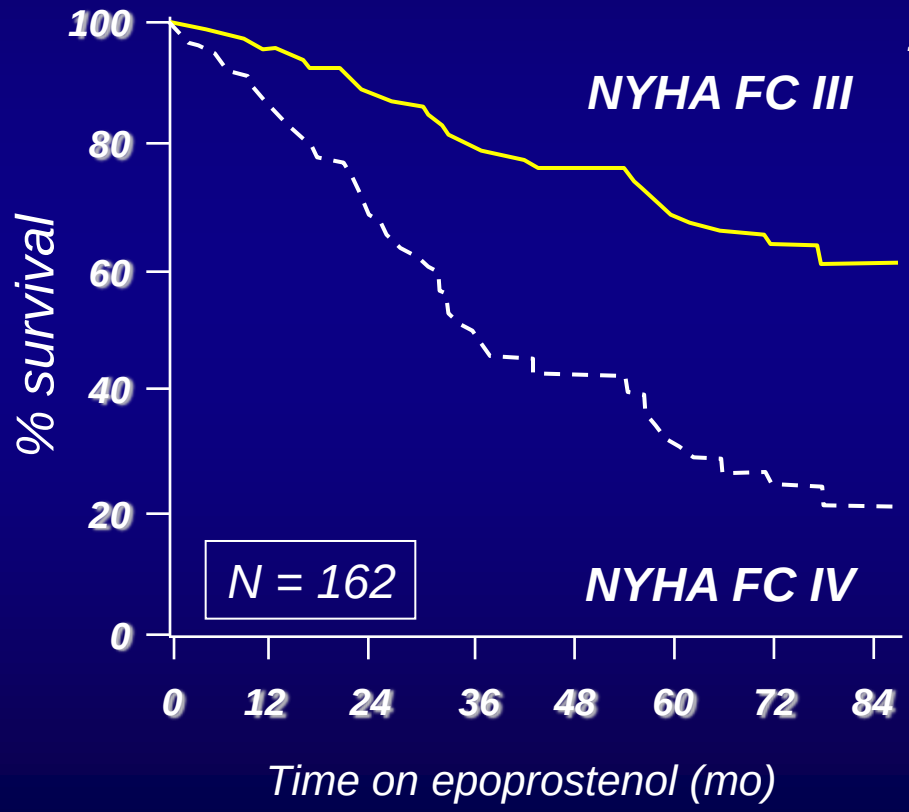
Assessment of risk in PAH
Which prognostic indicators?

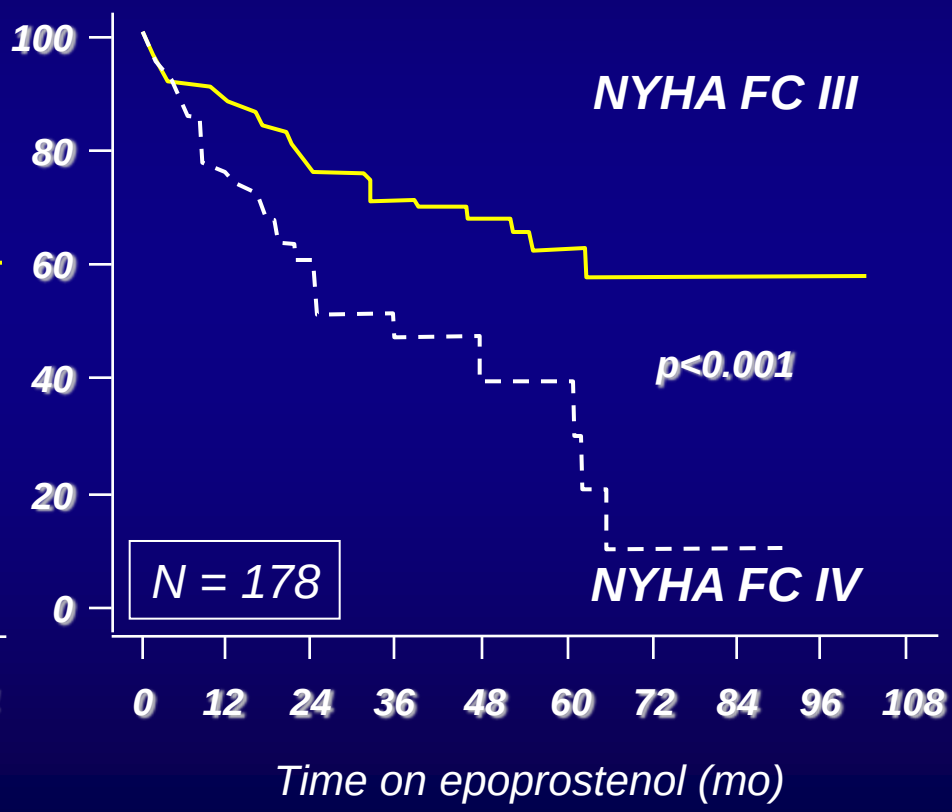
- Clinical assessment
  - Symptoms (NYHA/WHO functional class)
  - Clinical signs of RV failure
  - Rate of progression
- Exercise capacity
  - 6 minute walk test: distance, chronotropic response, O_2 desat.?
  - CPET: Peak VO2, Ve/VCO2 slope, change in sBP
- RV function
  - Echocardiographic variables: TAPSE, Tei index, PE
  - RH Cath: RAP, CO/CI
- Biomarkers
  - BNP/NT-proBNP, Troponin
  - Uric acid, Na^+

Properly evaluated at baseline…
More importantly at follow up…

Baseline NYHA / WHO Functional Class predicts Survival in PAH

Retrospective analysis of large cohorts of IPAH patients on epoprostenol therapy followed a2 expert centers

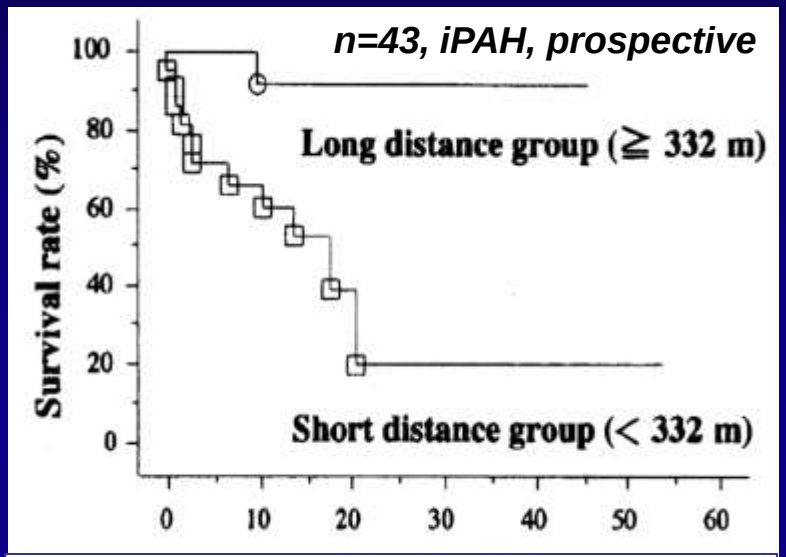


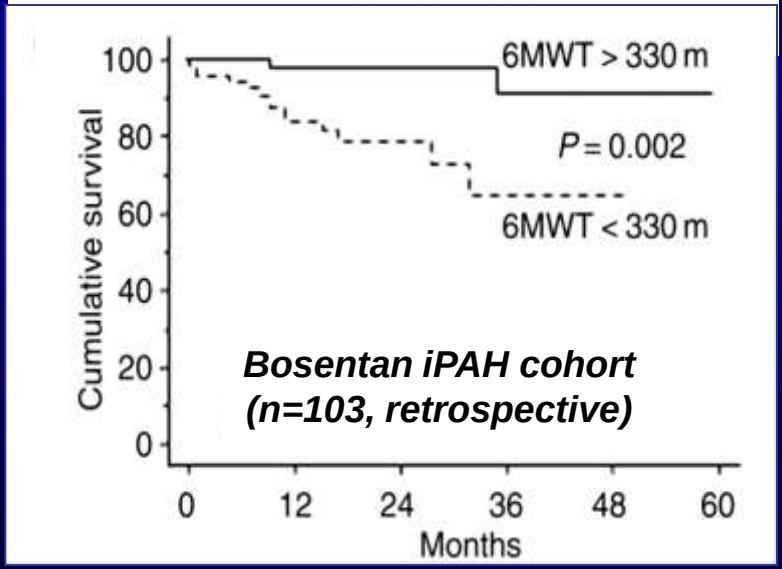


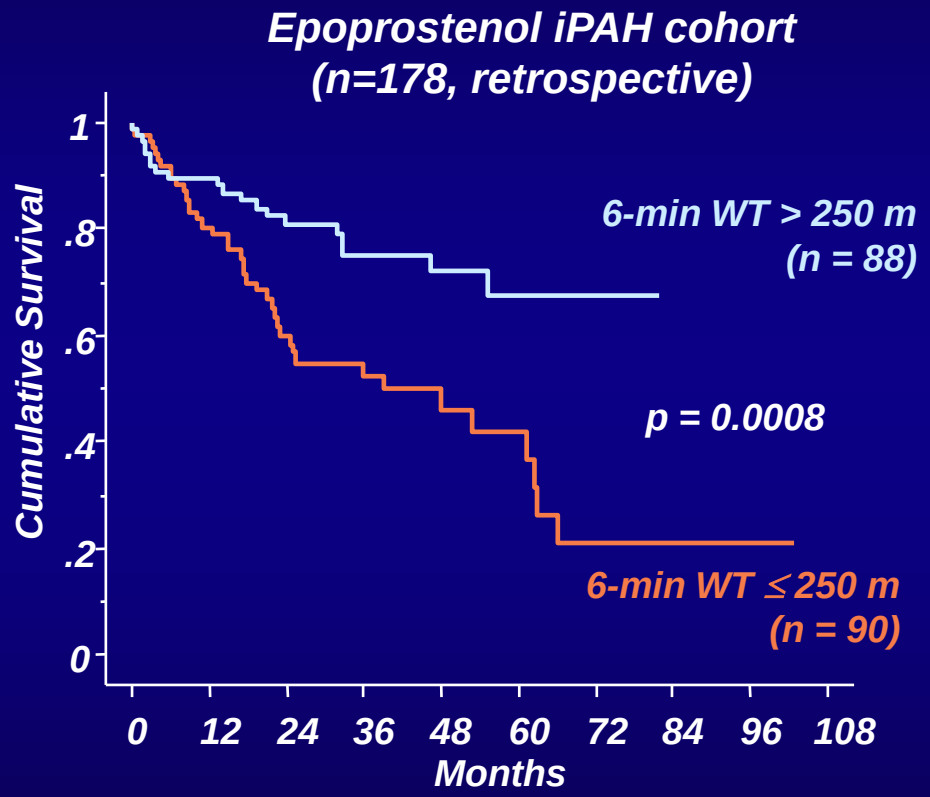
McLaughlin VV, et al. Circulation 2002; 106:1477-82.

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

Baseline 6-min walk distance correlates with survival



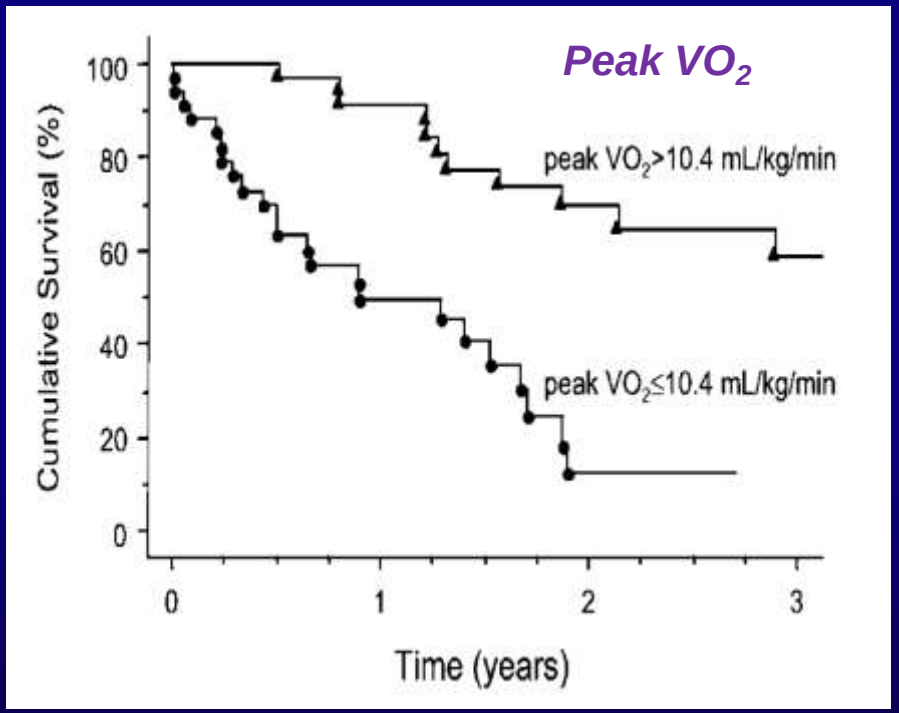


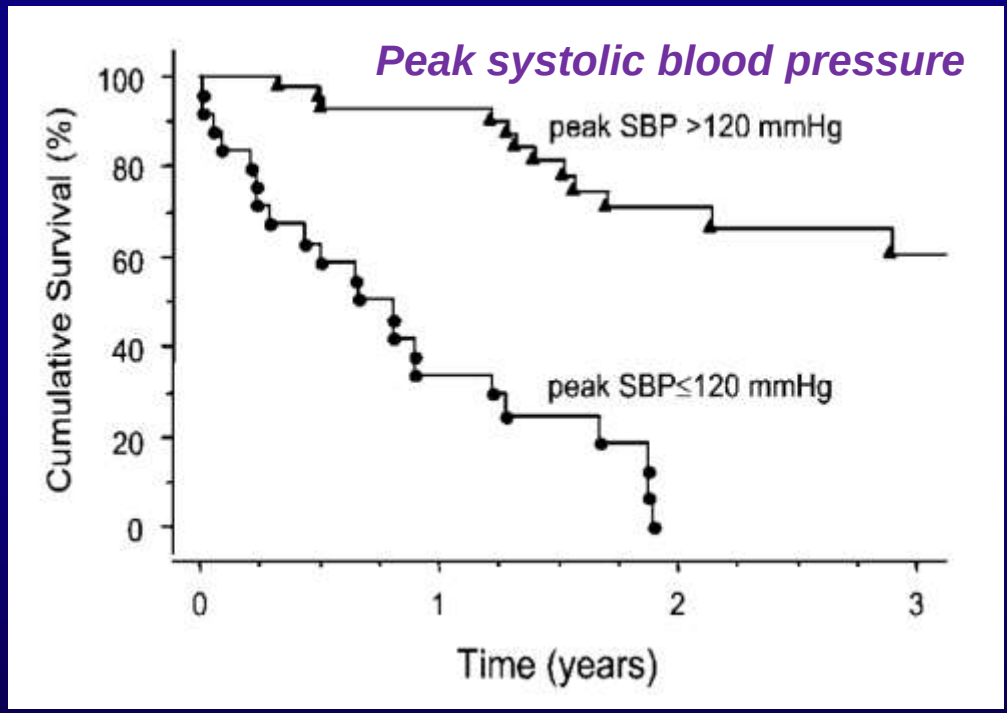


Miyamoto M, et al. Am J Respir Crit Care Med 2000; 161:487-92.
Sitbon O, et al. J Am Coll Cardiol 2002; 40: 780-8.
Provencher S, et al. Eur Heart J 2006; 27: 589–95.

CPET parameters assessed at baseline

Prospective analysis of 86 IPAH patients followed at expert centers



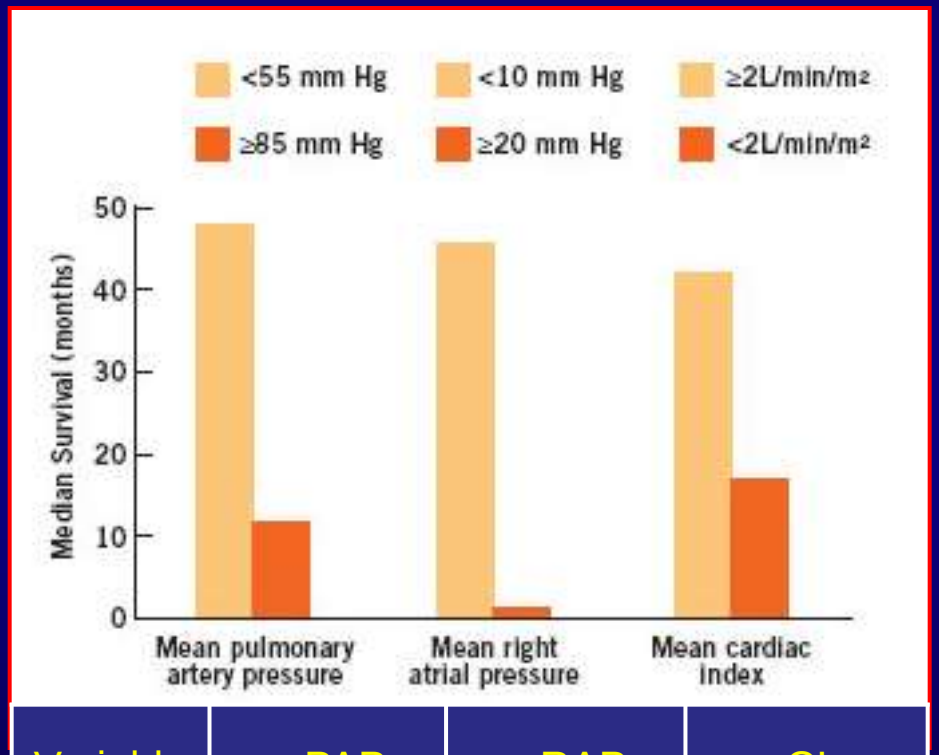


Wensel R, et al. Circulation 2002; 106: 319-24.

Baseline hemodynamics predicts survival

NIH Registry (80's)[1]

'Conventional' therapy (AC, diuretics, CCBs…)



Variable	mPAP	mRAP	CI
Odds ratio	**1.02** (1.01-1.03)	**1.07** (1.03-1.10)	**0.59** (0.42-0.84)

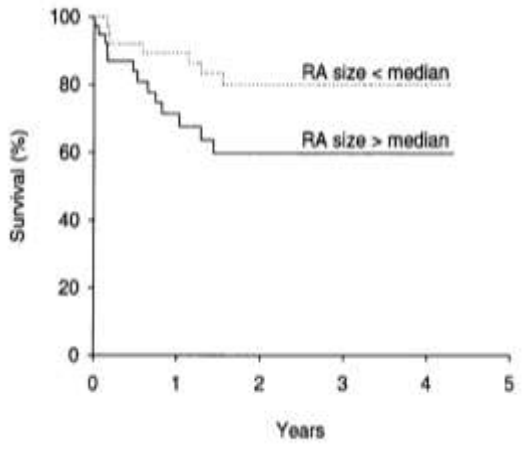
Epoprostenol cohort (90's) [n = 178][2]

Variable	HR (95% CI)	p value
RAP ≥ 12 mmHg	2.74 (1.58 – 4.75)	0.0003
mPAP < 65 mmHg	1.72 (1.04 - 2.86)	0.036

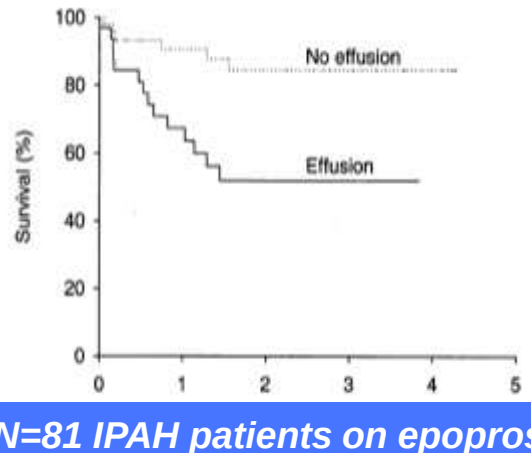
1. *D'Alonzo GE, et al. Ann Intern Med 1991;115:343-9.*
2. *Sitbon O, et al. J Am Coll Cardiol 2002;40:780-8.*

Baseline echocardiography

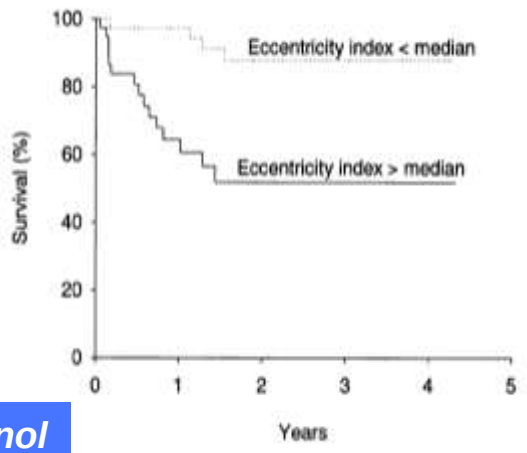
RA size[1]



Pericardial effusion[1]



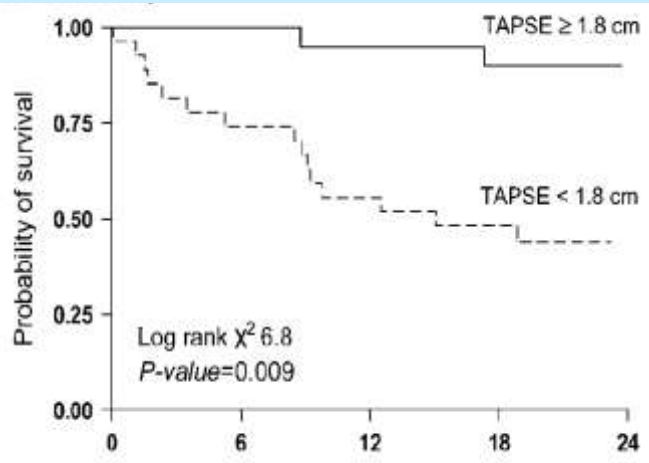
Eccentricity Index[1]



N=81 IPAH patients on epoprostenol

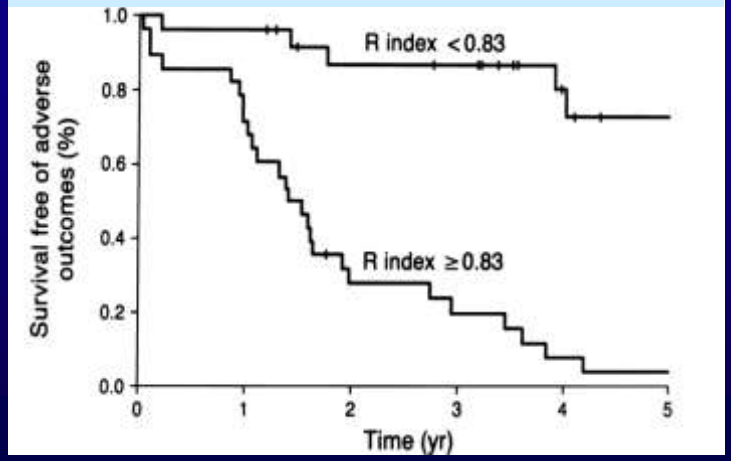
TAPSE[2]

(Tricuspid Annular Plane Systolic Excursion)



N=63, PAH, prospective

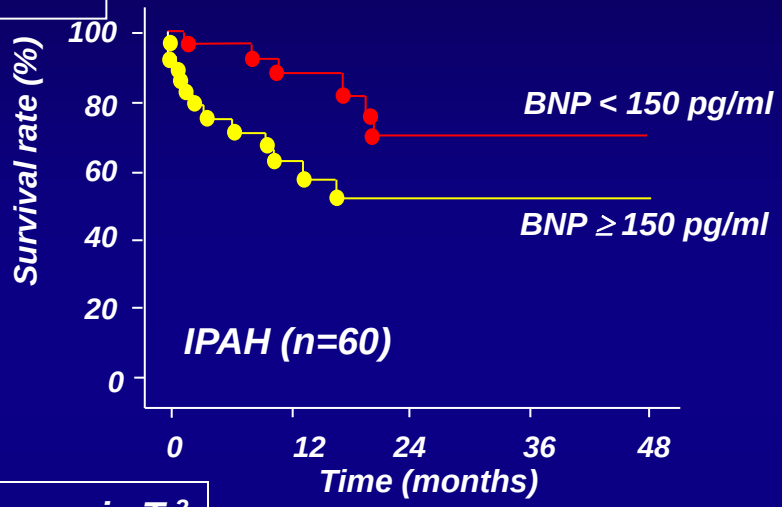
TEI index[3]



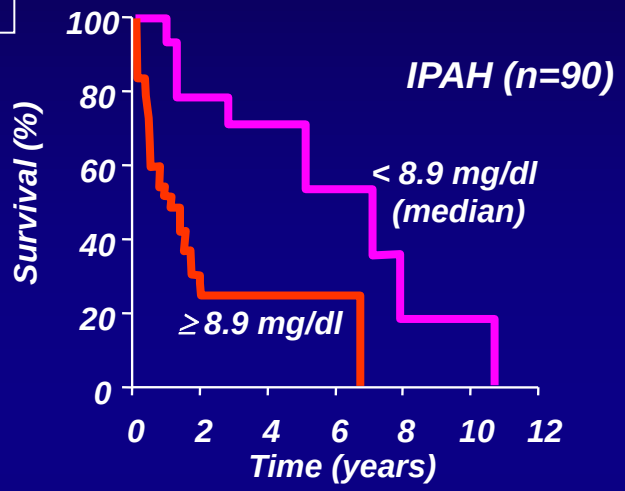
1. Raymond RJ, et al. J Am Coll Cardiol 2002;39:1214–9.
2. Forfia PR, et al. Am J Respir Crit Care Med 2006;174:1034–41.
3. Yeo TC, et al. Am J Cardiol 1998;81:1157–61.

Baseline biomarkers

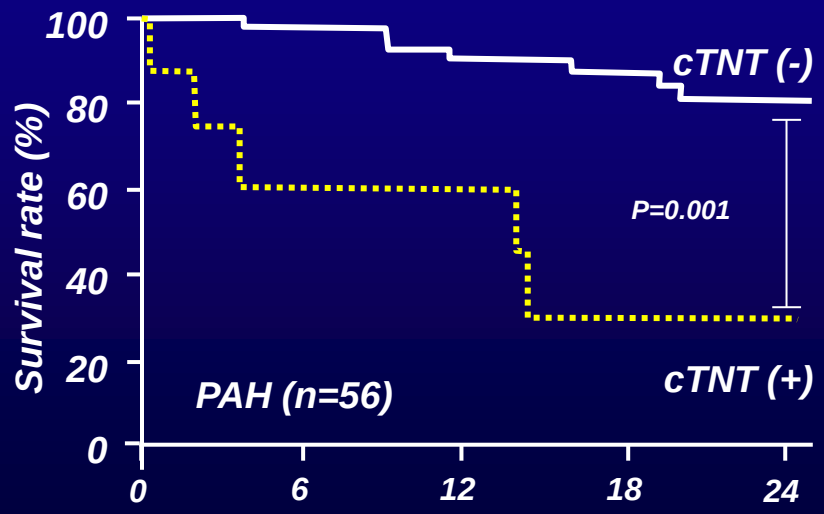
BNP [1]



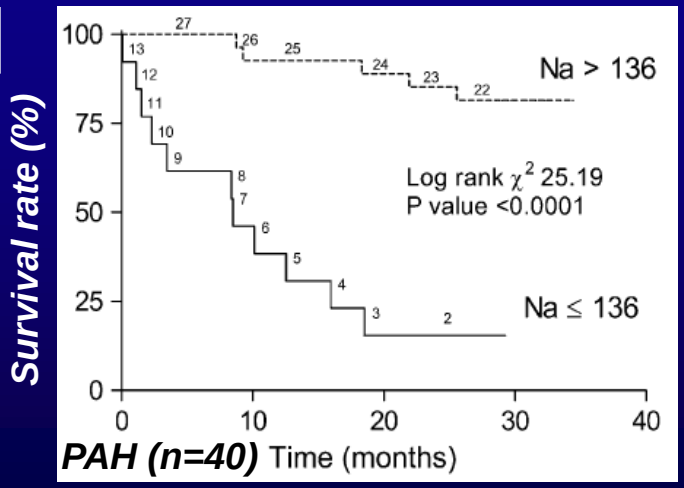
Uric acid [3]



Troponin T [2]



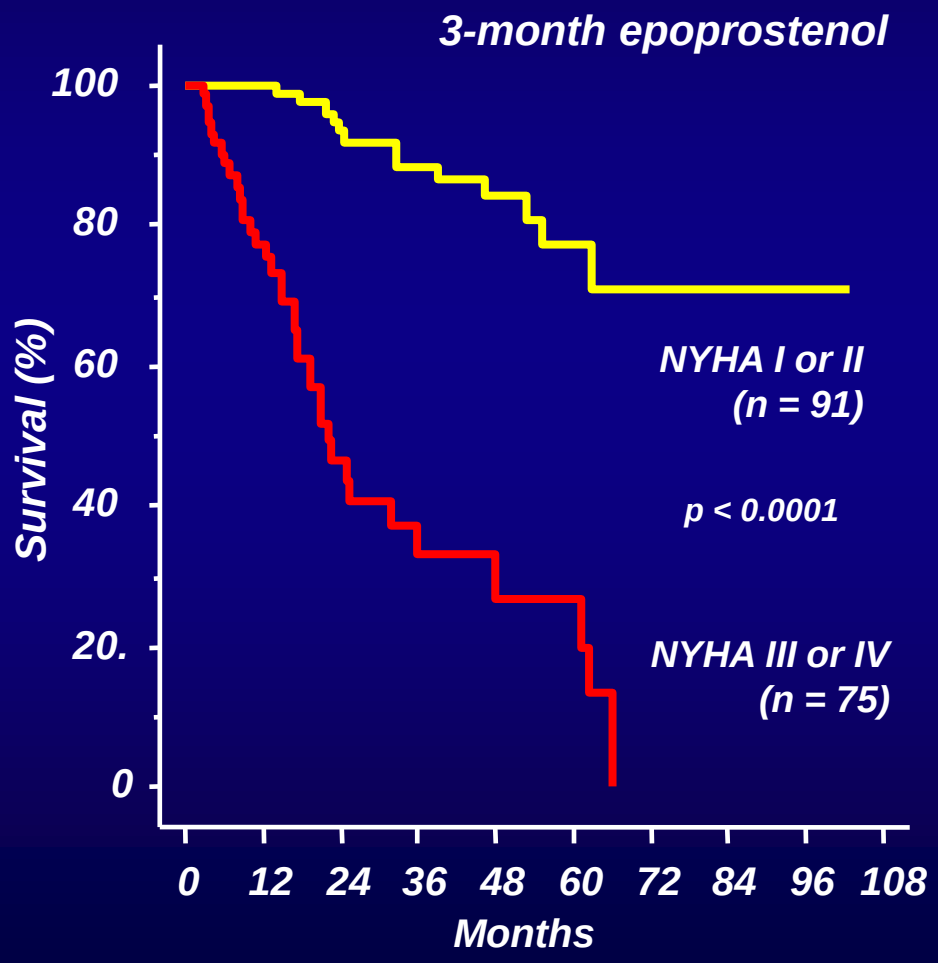
Na⁺ [4]

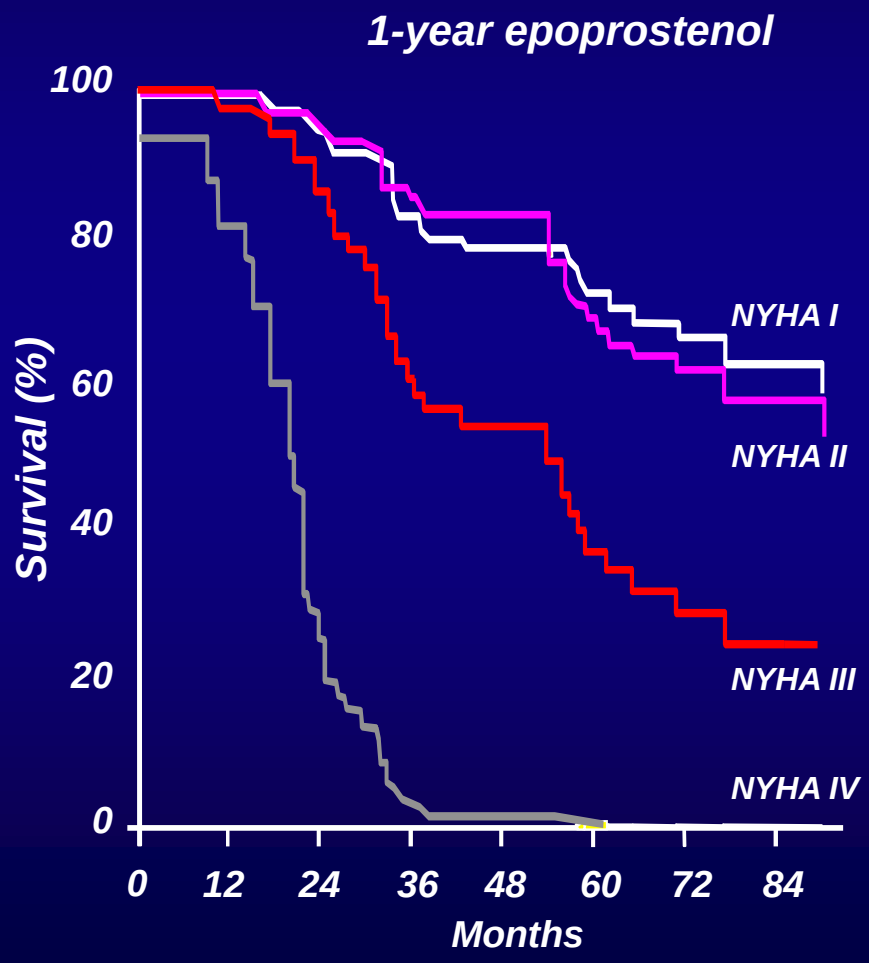


1. Nagaya N, et al. Circulation 2000;102:865-70.
2. Torbicki A, et al. Circulation 2003;108:844-8.
3. Nagaya N, et al. Am J Respir Crit Care Med 1999;160:478-92.
4. Forfia P et al. Am J Respir Crit Care Med 2008;177:1364–9.

Follow up – Impact of changes in functional class

NYHA class is the strongest prognostic factor in PAH…

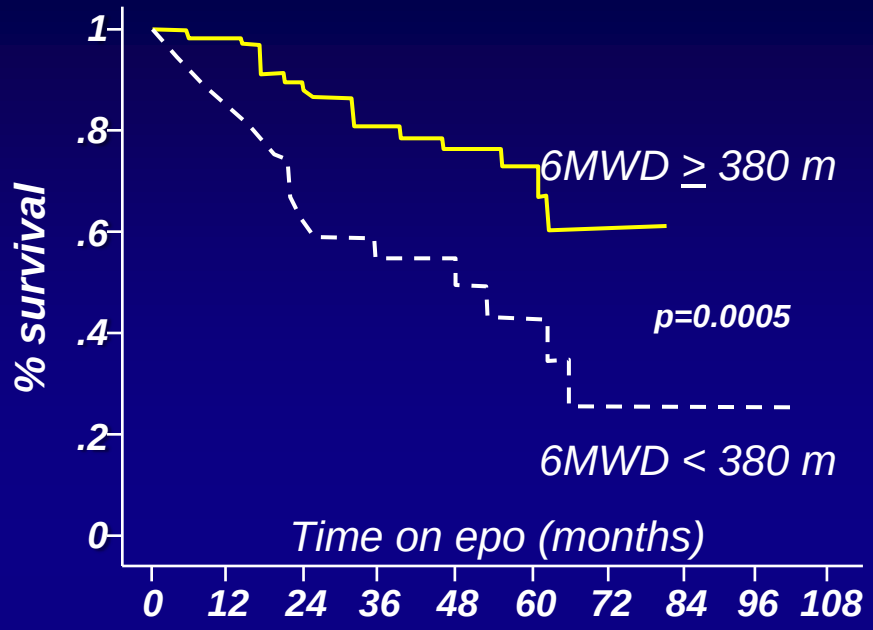


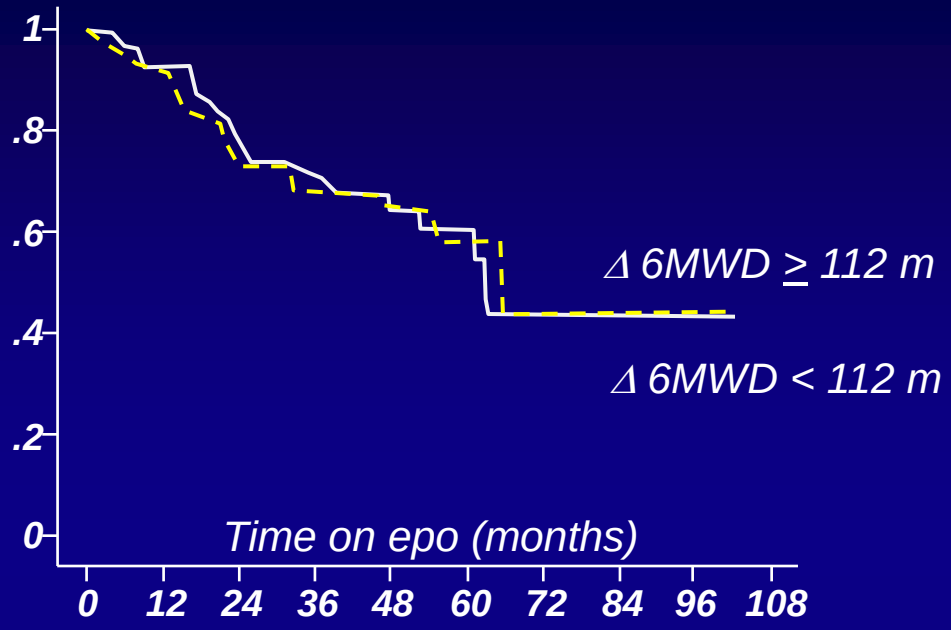


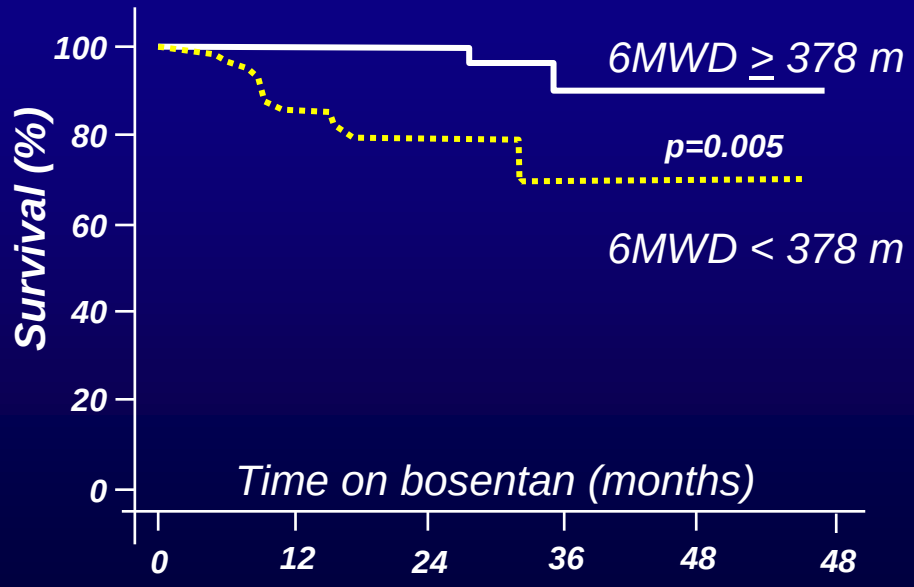
Sitbon O, et al. J Am Coll Cardiol 2002; 40: 780-8.

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

Follow up – Impact of changes in 6MWD







Importance of setting an absolute target *vs* relative change observed after 3-4 months of therapy

Sitbon O, et al. J Am Coll Cardiol 2002; 40: 780-8.
Provencher S, et al. Eur Heart J 2006; 27: 589–95.

Follow up – Impact of changes in haemodynamics

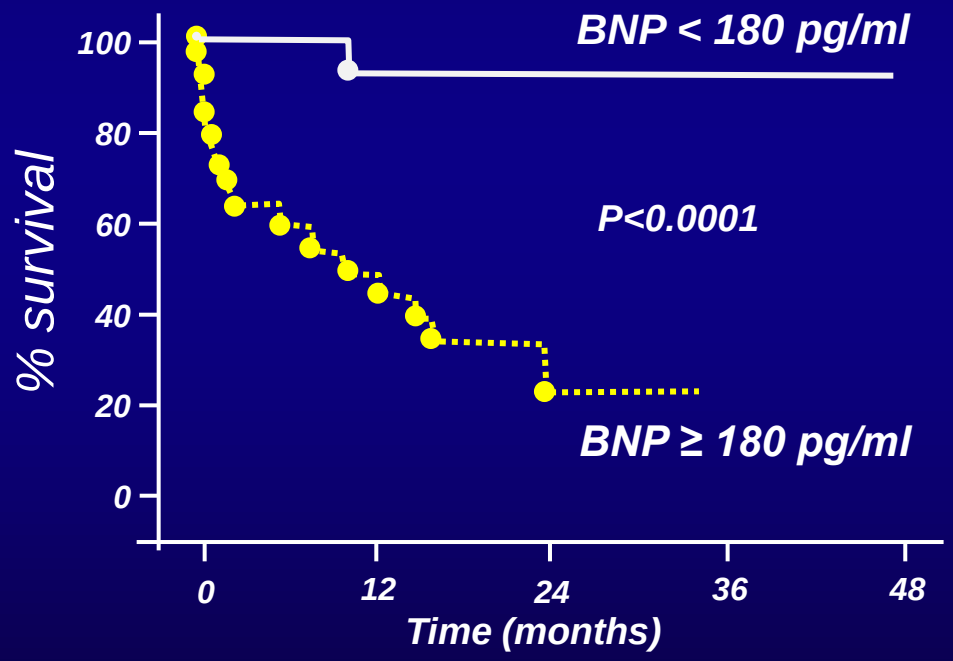
Variables measured after 3-month epoprostenol[1]		
Variable	**HR (95% CI)**	**p**
NYHA III-IV : I-II	**8.75 (4.58 – 16.7)**	**< 0.0001**
6MWD < 380 m	**2.62 (1.45 – 4.74)**	**0.001**
RAP > 10 mmHg	**3.57 (1.65 – 7.71)**	**0.001**
mPAP < 59 mmHg	**1.94 (1.06 – 3.55)**	**0.032**
Increase in CI < 0.5 L/min/m^2	**2.35 (1.23 – 4.52)**	**0.010**
Fall in TPR < 30%	**1.90 (1.02 – 3.54)**	**0.041**
SvO_2 < 62%	**2.64 (1.41 – 4.95)**	**0.002**

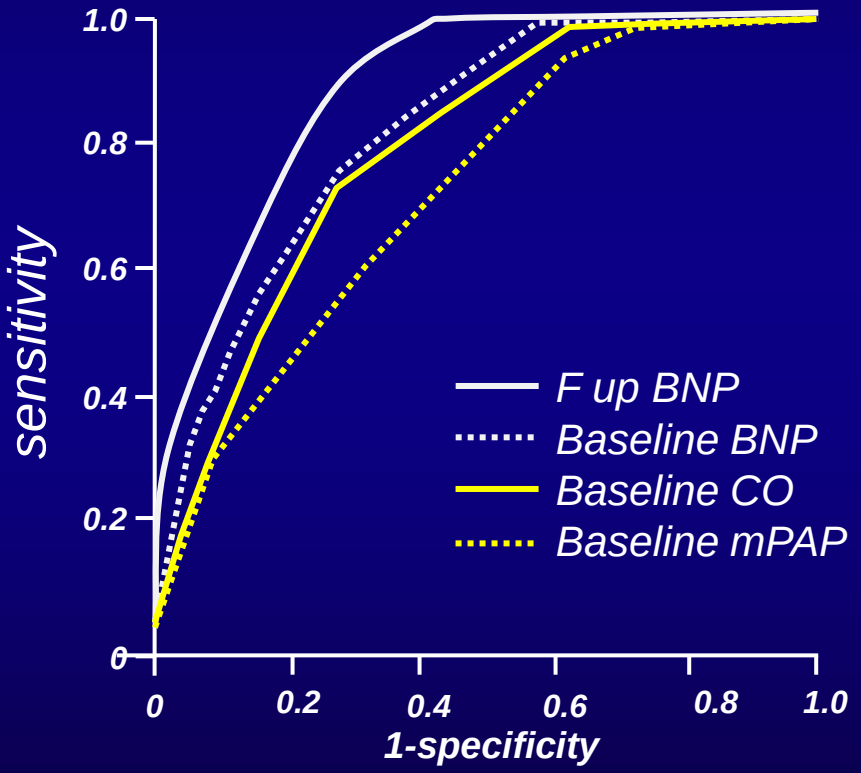
Variables measured after 4-month bosentan[2]		
Fall in TPR, per 10%	***0.79 (0.63–0.99)***	***0.044***

1. Sitbon O, et al. J Am Coll Cardiol 2002;40:780-8.
2. Provencher S, et al. Eur Heart J 2006; 27: 589–95.

Changes in BNP at follow up better predict outcome than baseline BNP or haemodynamics

N=53 IPAH, 3 months follow up





Nagaya et al. Circulation. 2000;102:865-870

Usefulness of prognostic indicators at baseline and follow up

Variable	Baseline	Follow up
NYHA FC	+++	+++
6MWD	+++	+++
BNP/NT-ProBNP	+++	++
Uric Acid	+	?
cTroponin-t	+	?
Pericardial effusion	++	+
TAPSE	++	?
Tei index	++	?
Mpap	-	-
RAP	++	++
CI	+++	+++

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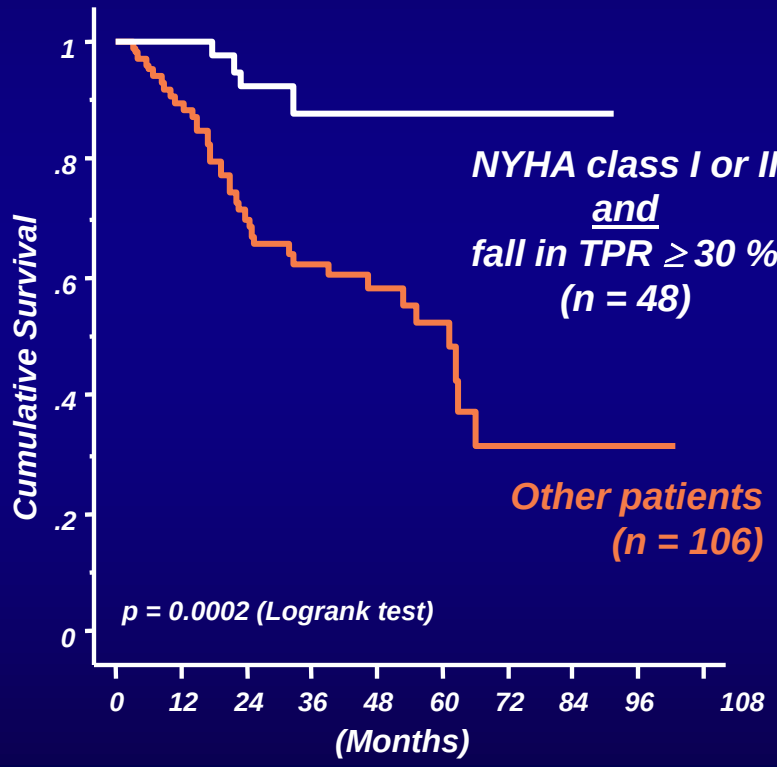
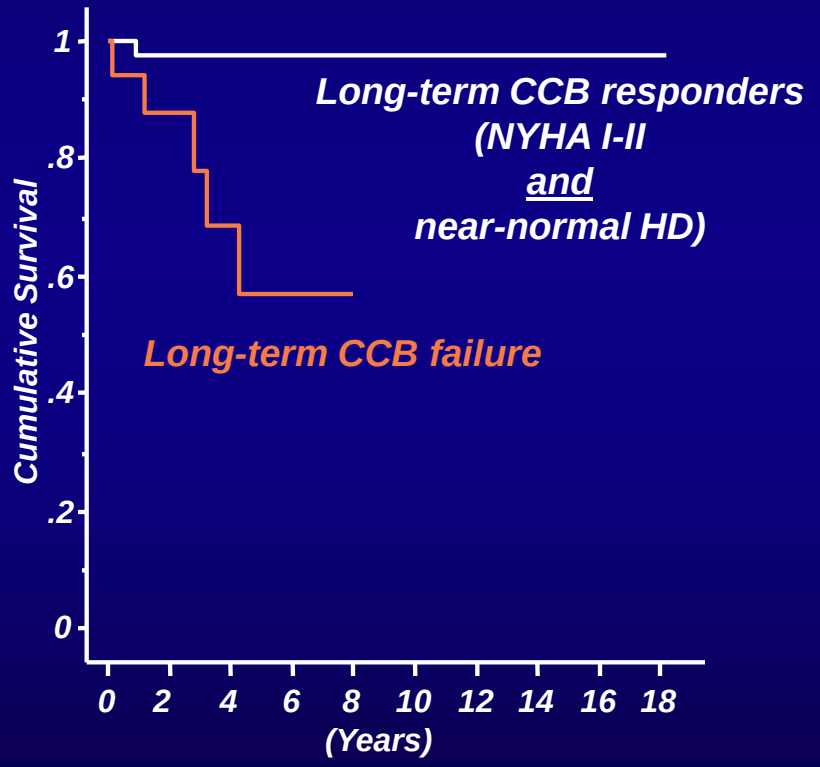
Multidimensional risk assessment

Combining NYHA/WHO FC and hemodynamic variables

After 3-month epoprostenol



After 1-year CCBs



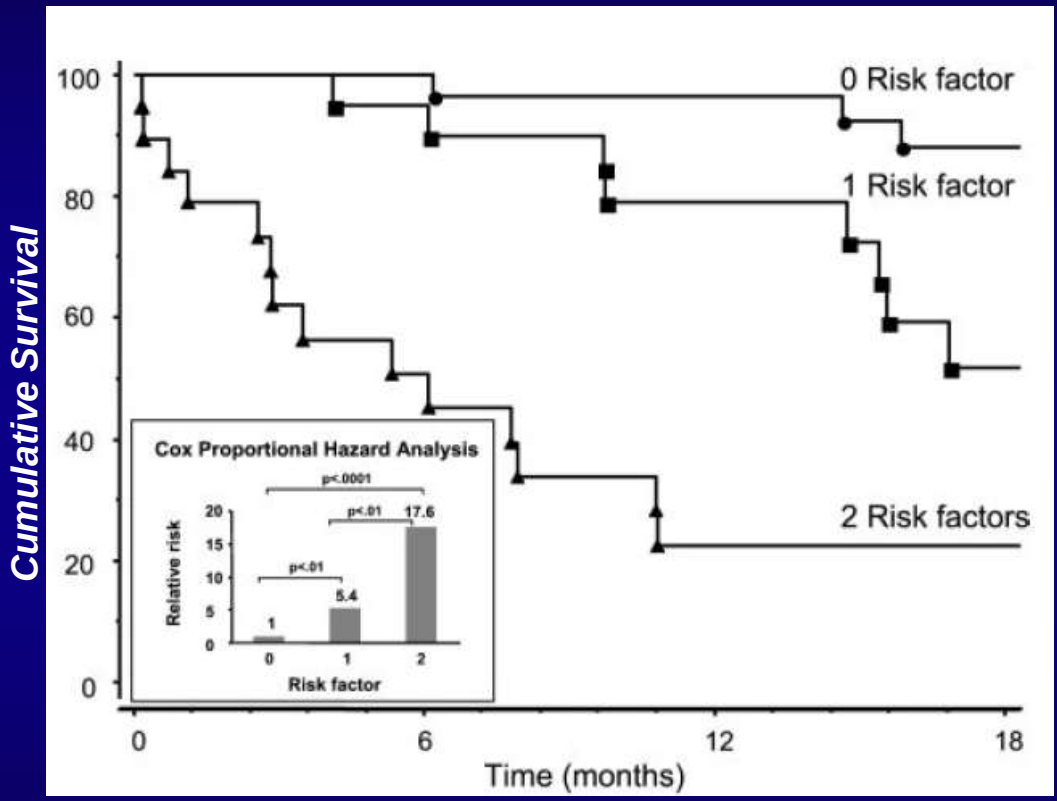
Sitbon O, et al. J Am Coll Cardiol 2002;40:780-8.

Sitbon O, et al. Circulation 2005;111:3105-11.

Multidimensional risk assessment

Combining variables assessed at CPET

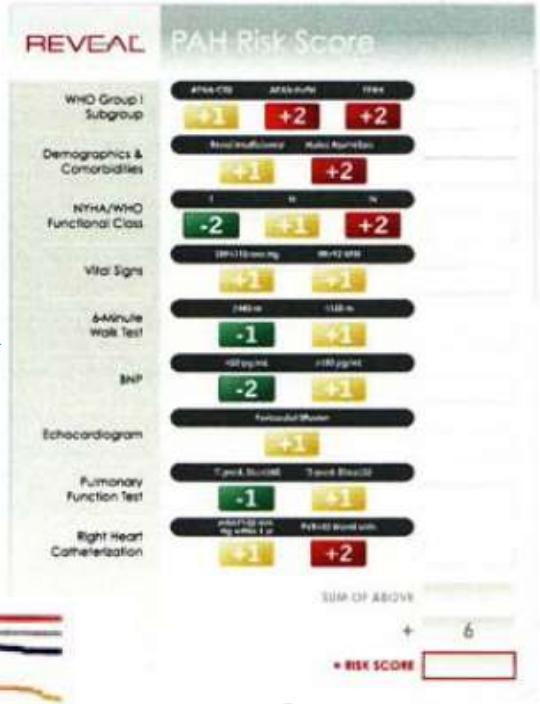
Variable	12-month AUC %	95% CI
Peak SBP	87.2	77.0–93.9
Peak DBP	70.0	57.9–80.4
Uric acid	54.1	42.3–65.5
Peak VO_2	76.9	65.3–86.1
RA	72.4	61.7–81.6
SvO_2	77.2	66.9–85.6

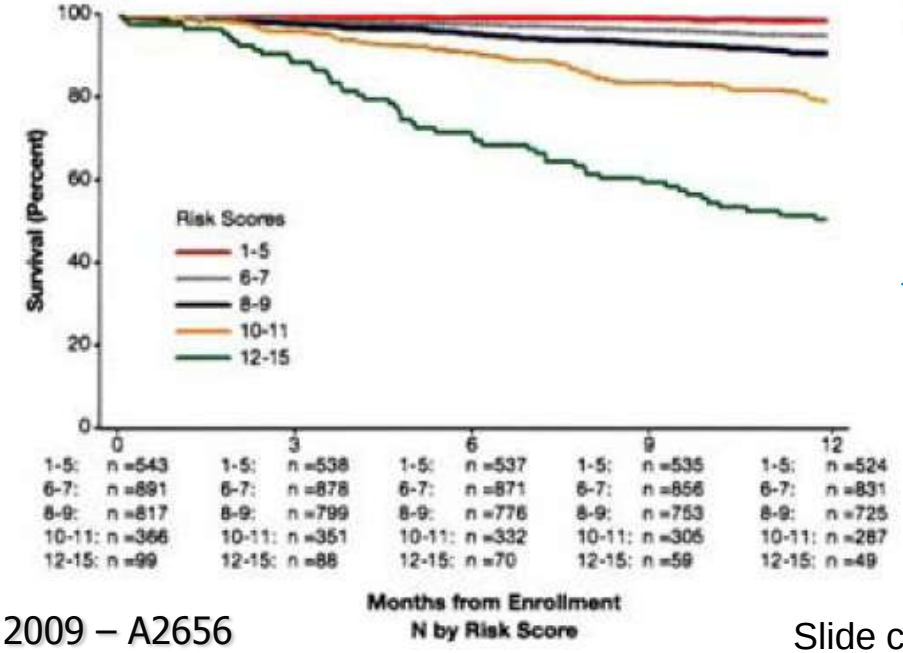


Wensel R, et al. Circulation 2002; 106: 319-24.

REVEAL registry – risk calculator

- PAH subgroup
- Demographics
- WHO FC
- Vital signs
- 6MWD
- BNP
- Echocardiography
- PFT's
- RHC





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REVEAL registry
Limitations of the risk calculator

- All cases, prevalent and incident
- Only tested retrospectively
- Prospective cohort needed
- Non dynamic model using only baseline values

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Slide courtesy of Jean-Luc Vachiery

What the Guidelines say?

EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal
doi:10.1093/eurheartj/ehp297

ESC/ERS GUIDELINES

Guidelines for the diagnosis and treatment of pulmonary hypertension

The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT)

Authors/Task Force Members: Nazzareno Galiè (Chairperson) (Italy)*; Marius M. Hoeper (Germany); Marc Humbert (France); Adam Torbicki (Poland); Jean-Luc Vachiery (France); Joan Albert Barbera (Spain); Maurice Beghetti (Switzerland); Paul Corris (UK); Sean Gaine (Ireland); J. Simon Gibbs (UK); Miguel Angel Gomez-Sanchez (Spain); Guillaume Jondeau (France); Walter Klepetko (Austria) Christian Opitz (Germany); Andrew Peacock (UK); Lewis Rubin (USA); Michael Zellweger (Switzerland); Gerald Simonneau (France)

Available on www.escardio.org/guidelines

Parameters with established importance for assessing disease severity, stability and prognosis in PAH

Better Prognosis	Determinants of Prognosis	Worse Prognosis
No	Clinical evidence of RV failure	Yes
Slow	Rate of Progression	Rapid
No	Syncope	Yes
I, II	WHO-FC	IV
Longer (> 500 m)	6MWT	Shorter (< 300 m)
Peak VO_2 > 15 ml/min/kg	CPET	Peak VO_2 < 12 ml/min/kg
Normal or near-normal	BNP/NT-proBNP plasma levels	Very elevated and rising
No pericardial effusion TAPSE > 2.0 cm	Echocardiographic findings	Pericardial effusion TAPSE < 1,5 cm
RAP < 8 mmHg and CI ≥ 2.5L/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.

Definition of patient status

Stable and satisfactory	**Patient in this condition should fulfill the majority of the findings listed in the 'better prognosis' column of the prognostic table**
Stable and not satisfactory	**This is a patient who although stable has not achieved the status which patient and treating physician would consider desirable. Some of the limits described in the first column of the prognostic table are not fulfilled. These patients require re-evaluation and consideration for additional or different treatment following full assessment in the expert centre.**
Unstable and deteriorating	**Patients in this condition fulfill the majority of the findings listed in the 'worse prognosis' column of the prognostic table.**

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

Suggested follow up strategies for patients with PAH

	Baseline (prior to therapy)	Every 3-6 months*	3 months after initiation or changes in Tx	Clinical worsening
Clinical assessment NYHA FC ECG	X	X	X	X
6MWT†	X	X	X	X
CPET†	X		X	X
BNP/NT-proBNP	X	X	X	X
Echocardiography	X		X	X
RHC	X‡		X§	X§

**Intervals need to be adjusted to individual needs of the patient*
†usually one of the two exercise tests is performed
‡ is recommended
§ should be performed

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

Recommendations for evaluation of severity and follow-up

Statement	Class[a]	Level[b]
It is recommended to evaluate the severity of PAH patients with a panel of data derived from clinical evaluation, exercise tests, biochemical markers, and echocardiographic and haemodynamic assessments (*Table 15*)	I	C
It is recommended to perform regular follow-up every 3–6 months (*Table 16*) also in stable patients with PAH	I	C
A goal-oriented treatment strategy is recommended in patients with PAH	I	C

[a]Class of recommendation.
[b]Level of evidence.

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Gaps in evidence for risk stratification

- Need for prospective validation of appropriate risk factors recorded at baseline and during follow up
- Need for a tool allowing multidimentional risk assessment
- Need to address different populations separately

→ How to fill these gaps?

Proposal of the French PAH Network
Project 2009-2010

- Cohort of incident patients only (idiopathic, heritable or anorexigen-associated PAH)
- Systematic assessment of combination of variables (NYHA, 6MWD, RHC, Echo and biomarkers)
- Timing at baseline, 3-4 months after treatment initiation and then once a year
- Duration: 3-year follow up
- Analysis of prognostic factors during follow up ("time-dependent covariates")

- Determination of treatment goals from combining variables associated with the longest survival time
- Comparison of monitoring tools