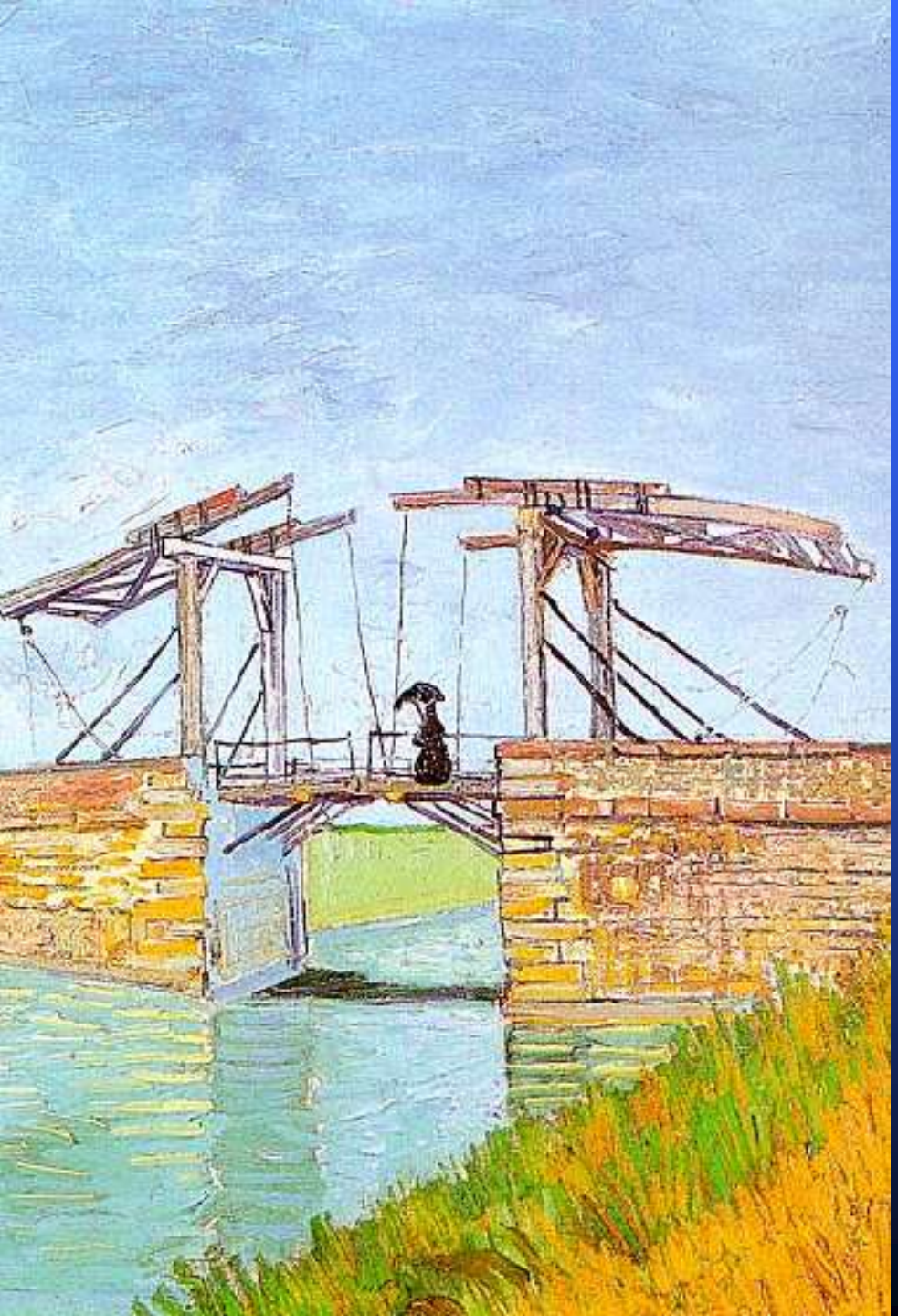


Pneumo-Reuma senza frontiere

La diagnosi precoce di ipertensione polmonare

XlIL Congresso Italiano della Società Italiana di Reumatologia
Milano 21-24 Novembre 2012

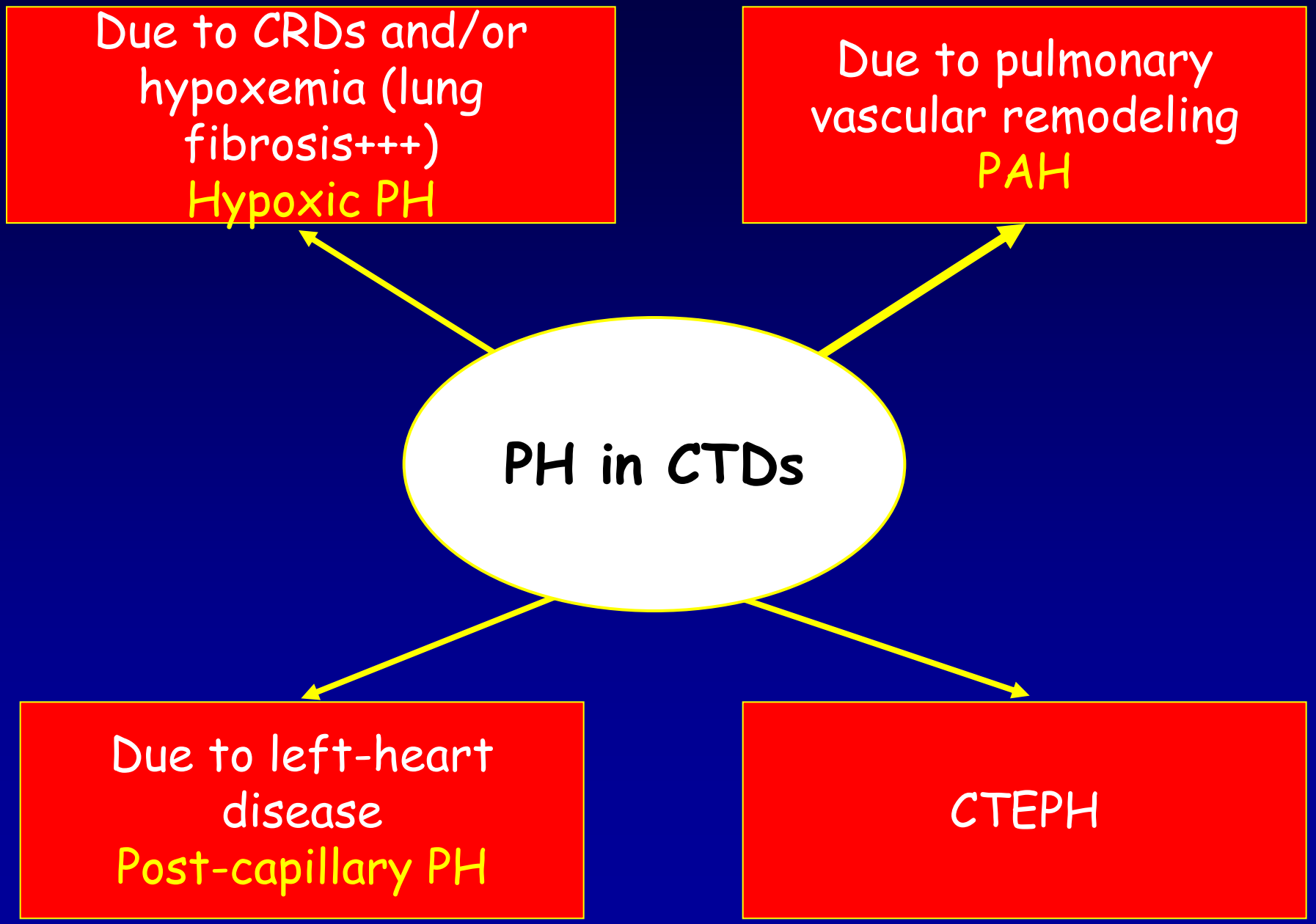
Sergio Harari

U.O. Pneumologia e UTIR
Servizio di Emodinamica e Fisiopatologia Respiratoria
Osp. San Giuseppe - Milano

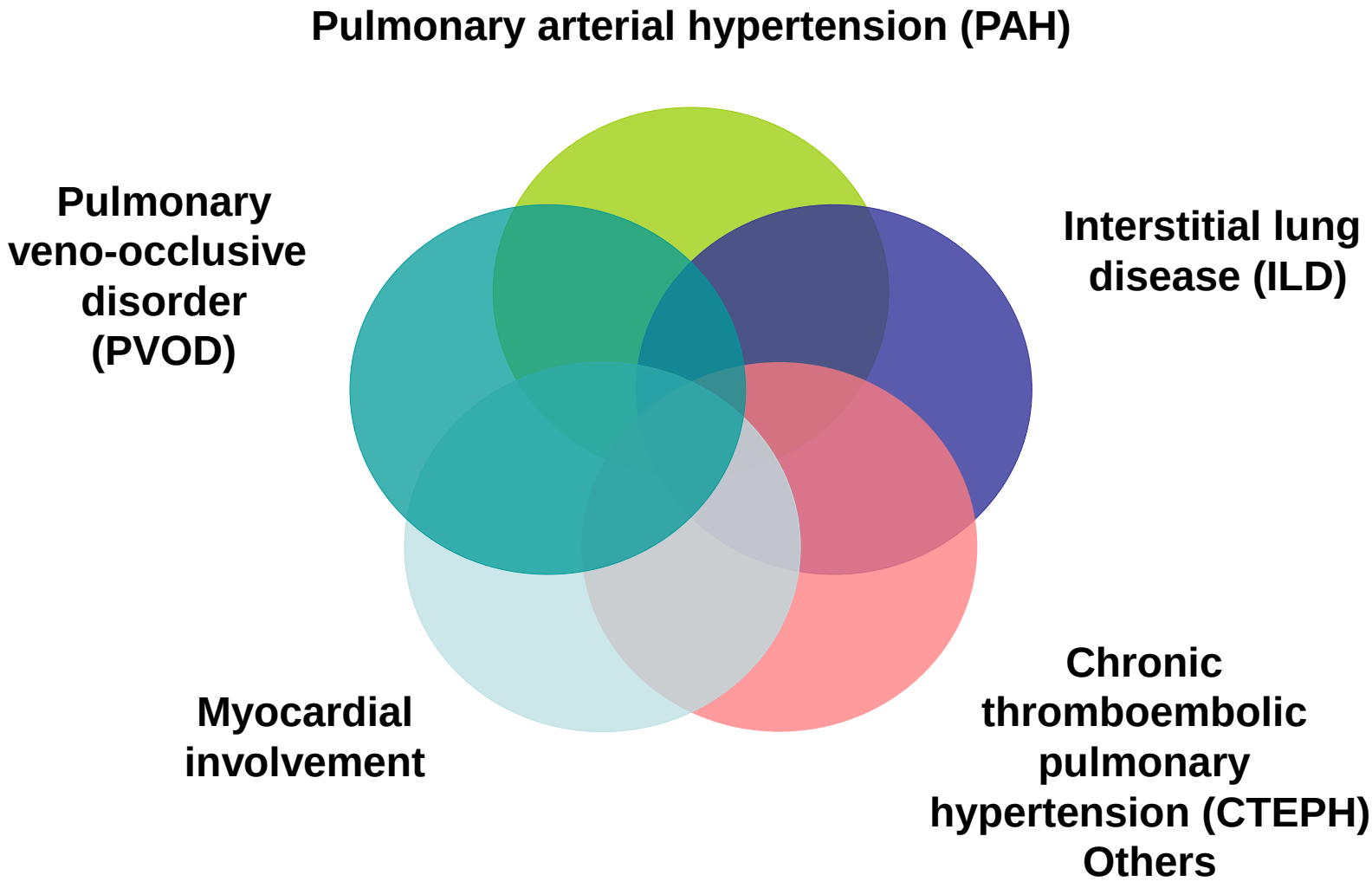
CTDs

- PAH may complicate a number of autoimmune diseases, such as
  - Systemic sclerosis
  - Systemic lupus erythematosus and anti-phospholipids syndrome
  - Mixed connective tissue disease
  - Rheumatoid arthritis
- Most data come from cohorts of SSc patients because PAH is a frequent occurrence in this disease

MULTIPLE MECHANISMS LEADING TO PH IN CTDs



Differential diagnosis of “PH” CTD



PH = pulmonary hypertension

Updated clinical classification of pulmonary hypertension

1 PAH
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK-1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2 Pulmonary hypertension due to left heart disease
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3 Pulmonary hypertension due to lung diseases and/or hypoxia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

4 Chronic thromboembolic pulmonary hypertension

5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

BMPR2: bone morphogenetic protein receptor, type 2; ALK-1: activin receptor-like kinase 1 gene; APAH: associated pulmonary arterial hypertension; PAH: pulmonary arterial hypertension. Reproduced from Dana Point [1], with permission from the publisher.

Galie' N, et al. Eur Respir J 2009

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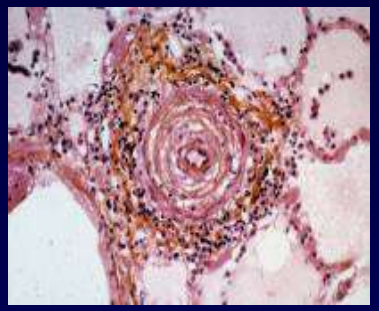
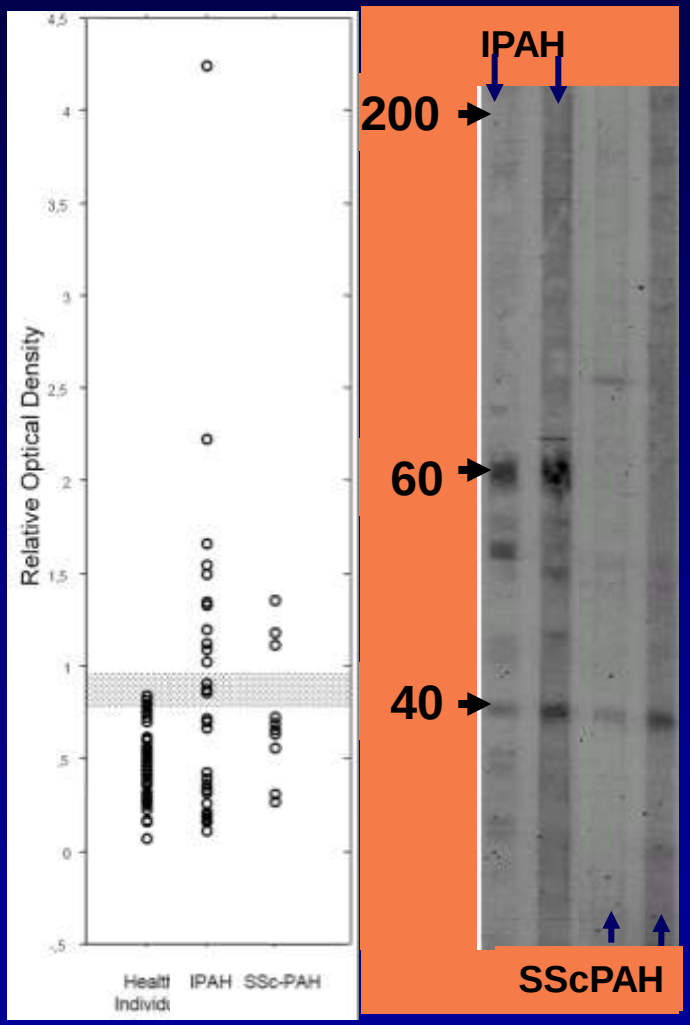
Galie' N, et al. Eur Respir J 2009



IDIOPATHIC AND SYSTEMIC SCLEROSIS ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

- Pathogenesis includes
  - Angiogenesis
  - Inflammation
  - Autoimmunity
    - ✓anti-endothelial cell antibodies
    - ✓anti-fibroblast antibodies
- Perspectives
  - Identification of target antigens
  - Characterisation of function



Tamby MC et al. Thorax 2005; 60 : 765-772.
Mouthon et al, Eur Resp J 2005;

SSc PAH

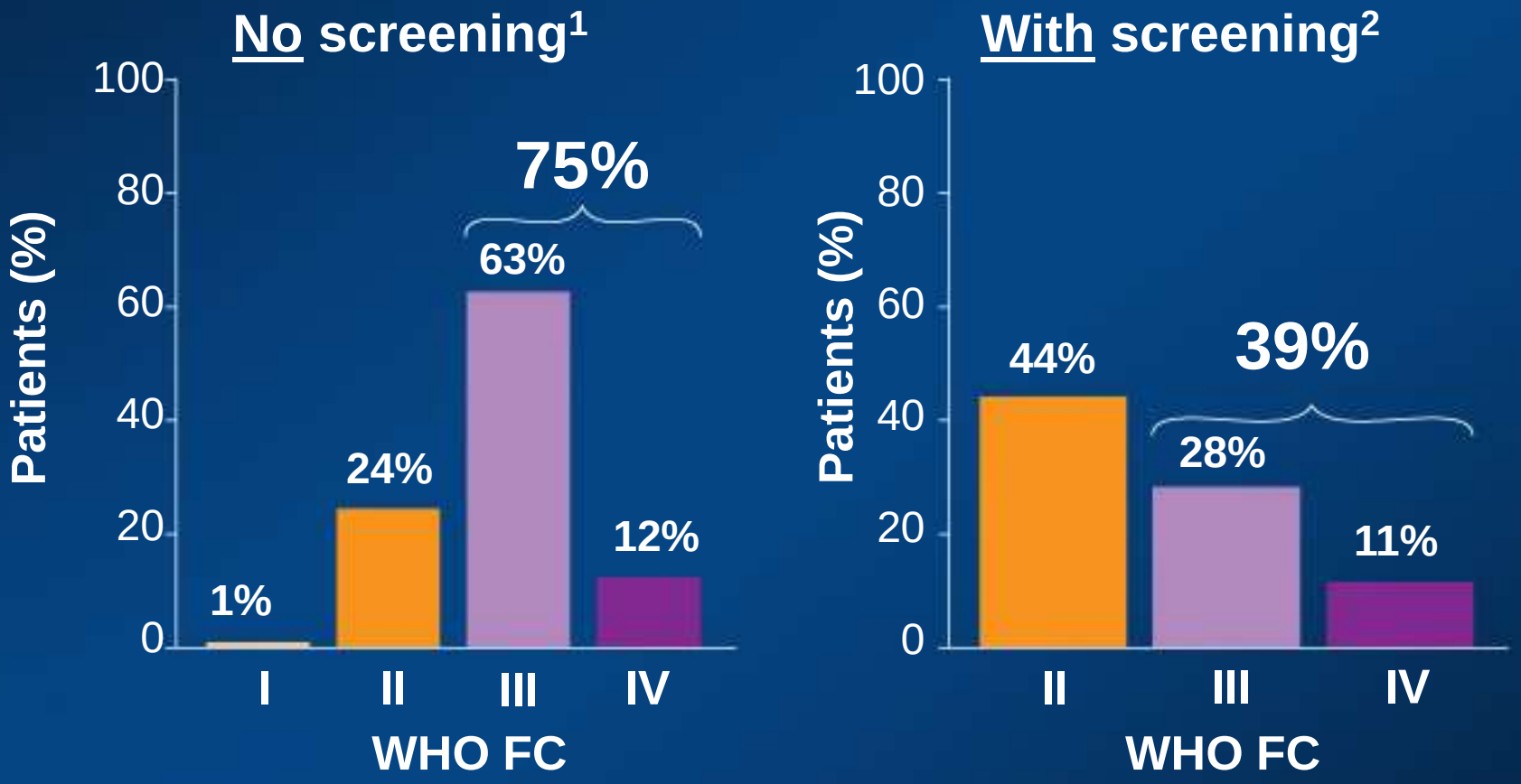
- In SSc frequency estimated between **7.5 and 12%** (variable between 4 and 38% depending on the study considered)

Table 2 Determination of survival in SScPAH: baseline demographic characteristics of 148 patients with SScPAH (89 from our own institution and 59 referred from other institutions) on cardiac catheterisation

Mean age (years)	66 (7)
Male:female	28:120
Mean duration of SSc (years)	14±5
Number with pulmonary fibrosis	40
Number of diffuse:lcSSc	37:111
Mean % predicted TLCO (mmol/min/kPa)*	56.7 (3.2)
Number with ACA+	78
Number with Scl70+	37
mRAP (mm Hg)	7.7 (4.8)
mPAP (mm Hg)	39.5 (13.5)
MAP (mm Hg)	93.9 (15.6)
PVR (dyne.s/cm^5)	687 (564)
SVR (dyne.s/cm^5)	1713 (606)
CI (l/min/m^2)	2.6 (1.4)
SVo_2 (ml/l)	659 (107)

Mukerjee D, et al. ARD 2003

Lo screening è efficace per diagnosticare la malattia



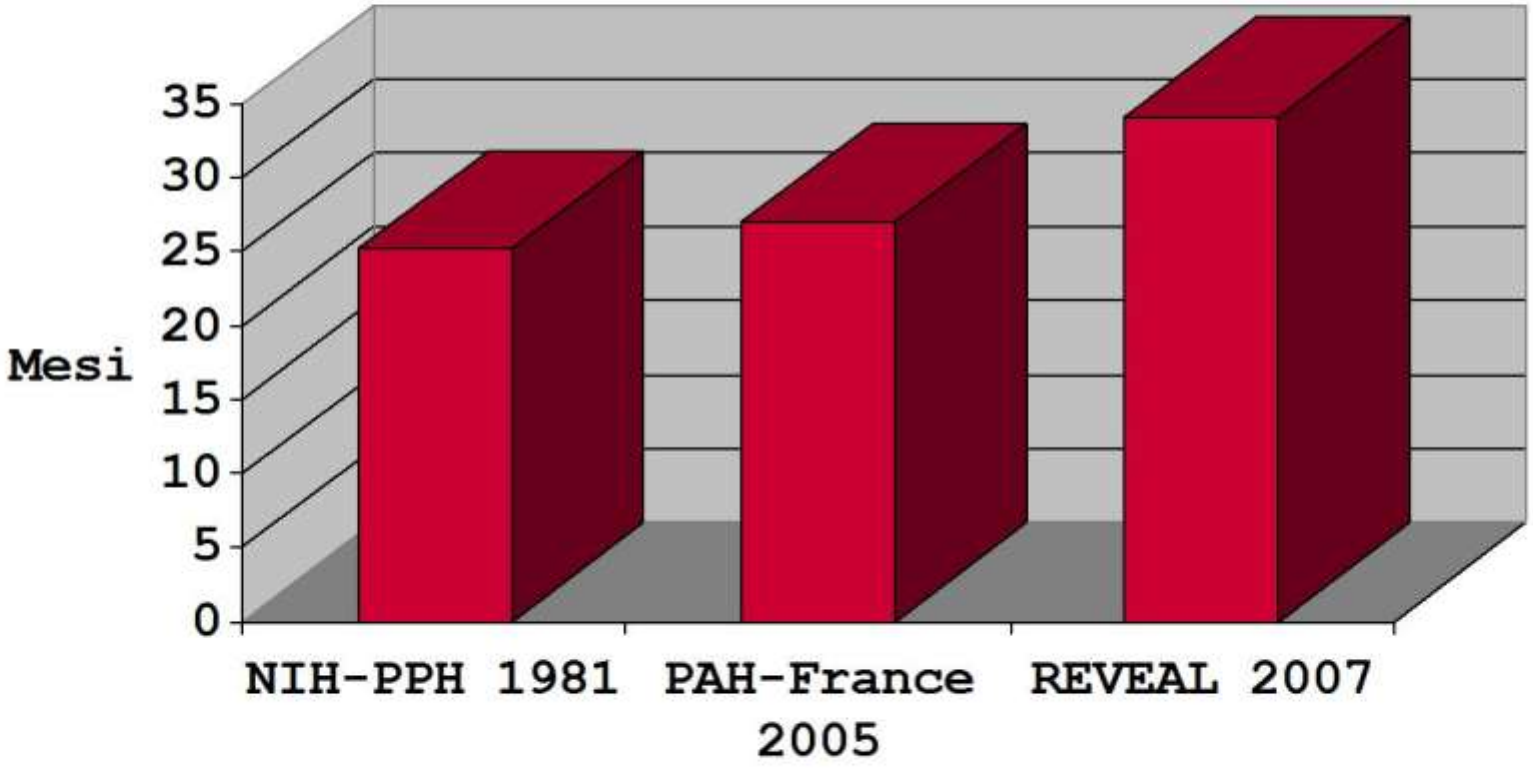
[1]Hachulla et al. *Arthritis Rheum* 2005; [2]Humbert et al. *Am J Respir Crit Care Med* 2006

Detection of milder disease with screening

	Systemic Sclerosis[1]		HIV infection[2]	
	Previously known PAH (n=29)	Newly diagnosed PAH (n=18)	Previously known PAH (n=30)	Newly diagnosed PAH (n=5)
mPAP (mmHg)	49 ± 17	30 ± 9	46 ± 13	30 ± 9
CI (L/min/m^2)	2.8 ± 0.7	3.2 ± 1.0	3.0 ± 0.8	3.6 ± 0.8
PVR (d.s.cm^{-5})	1007 ± 615	524 ± 382	800 ± 320	320 ± 240

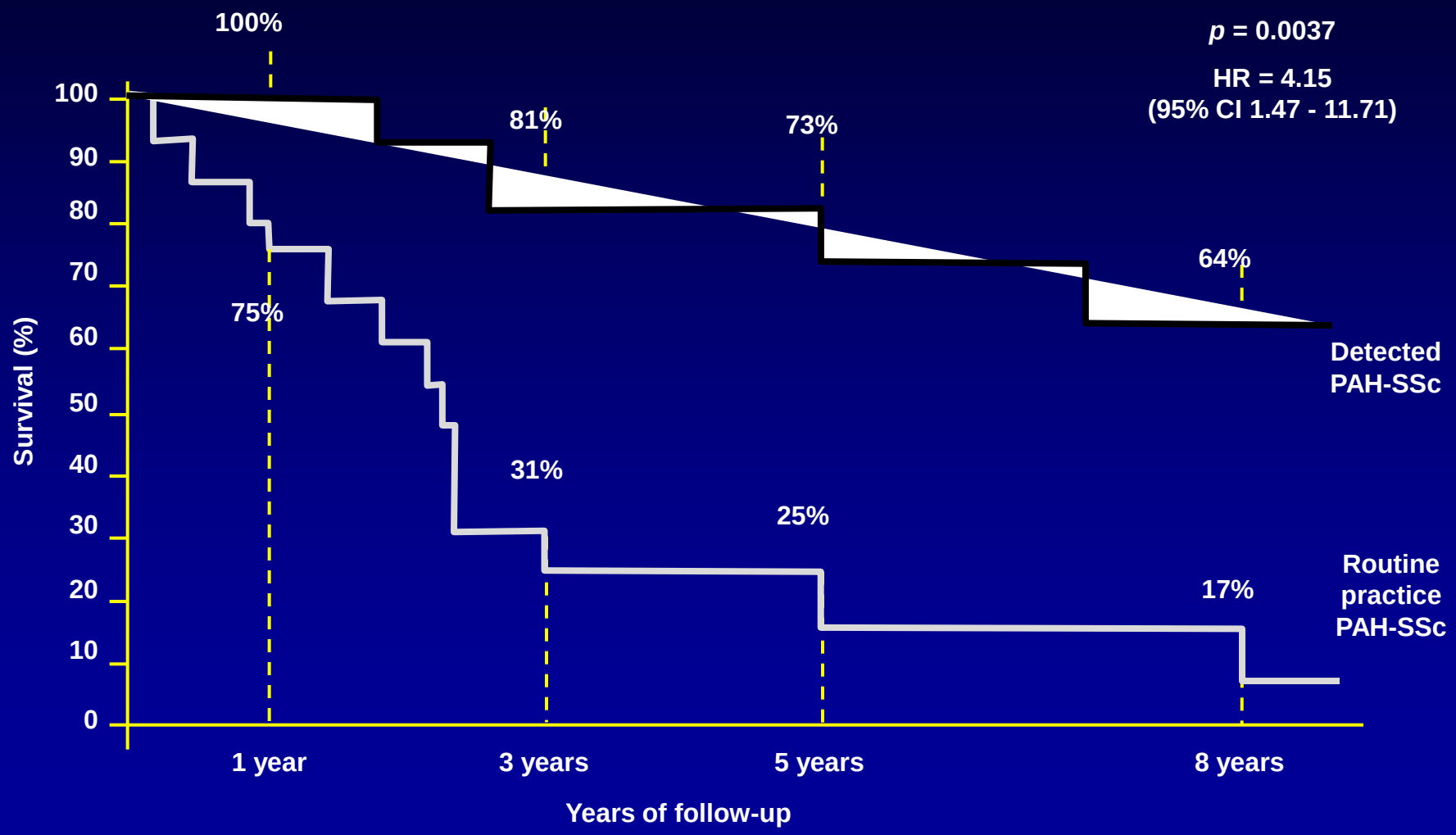
1. Hachulla E, et al. *Arthritis Rheum* 2005;52:3792-800.
2. Sitbon O, *et al*. *Am J Respir Crit Care Med* 2008;177:108-13.

Tempo fra valutazione iniziale e cateterismo



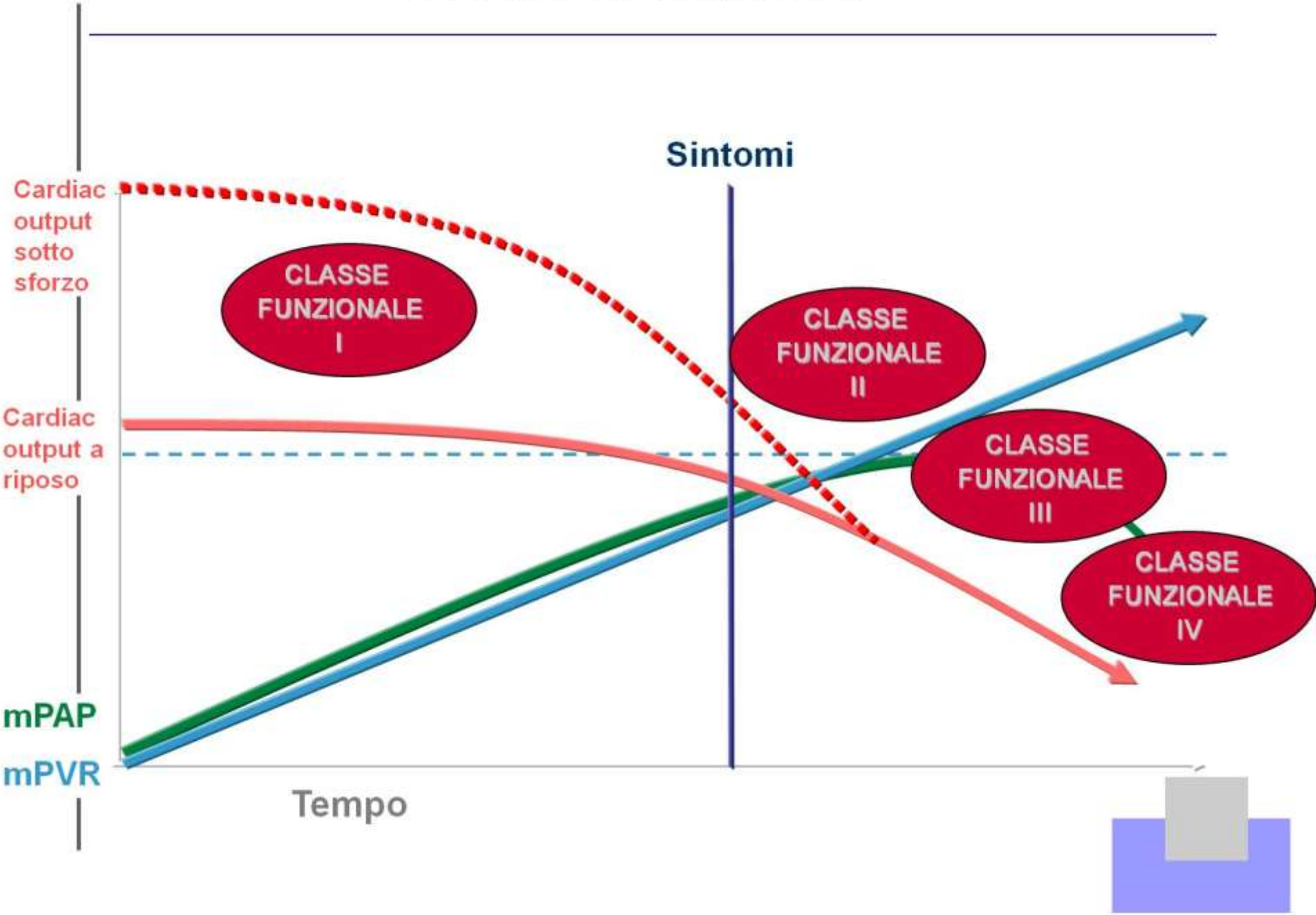
Palevsky H, Chest 2007

Prognosis of “routine practice” and “detected” PAH-SSc patients



Humbert M, *et al. Arthritis Rheum* 2011; Epub ahead of print.

PAH: malattia progressiva



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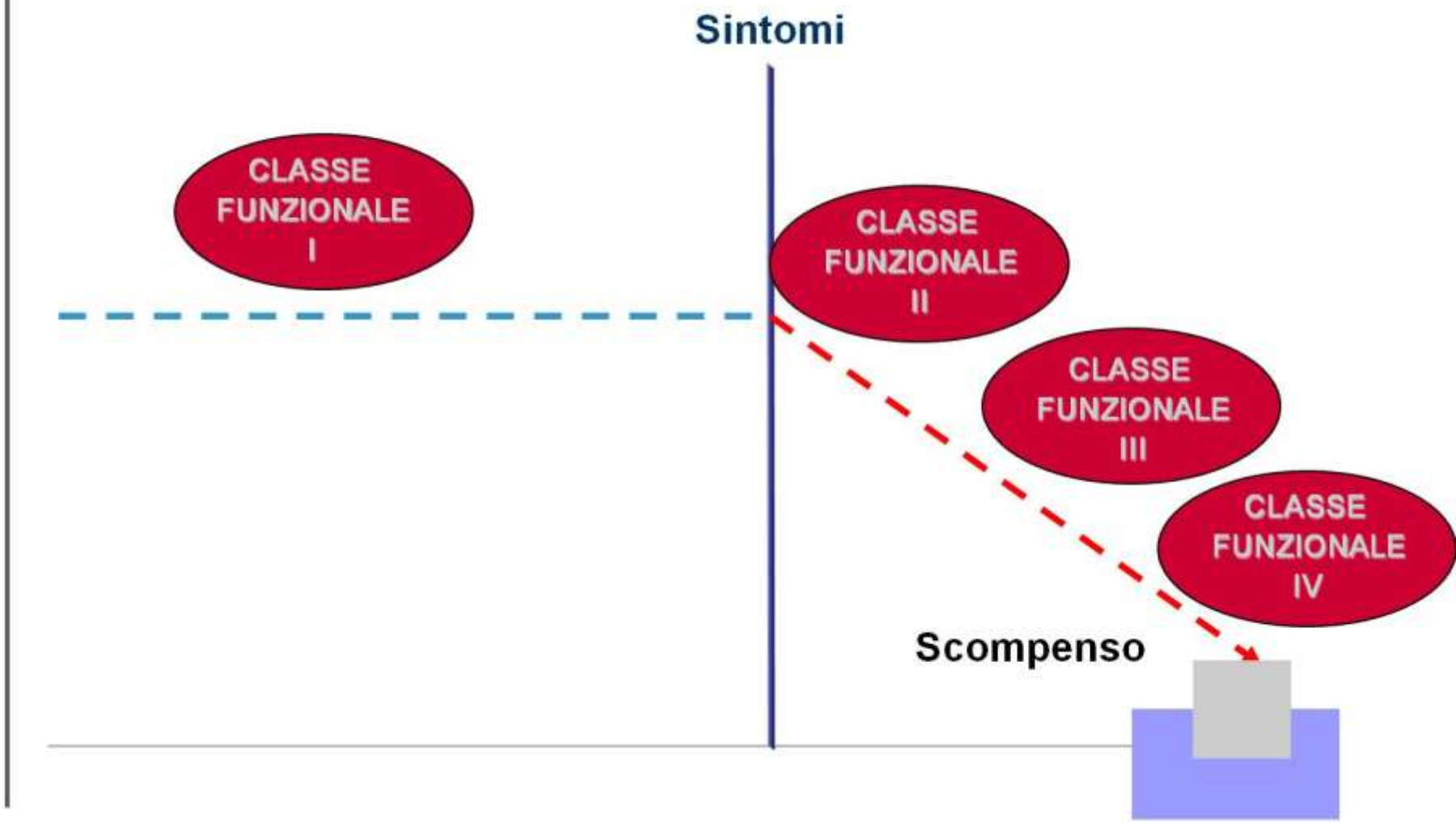
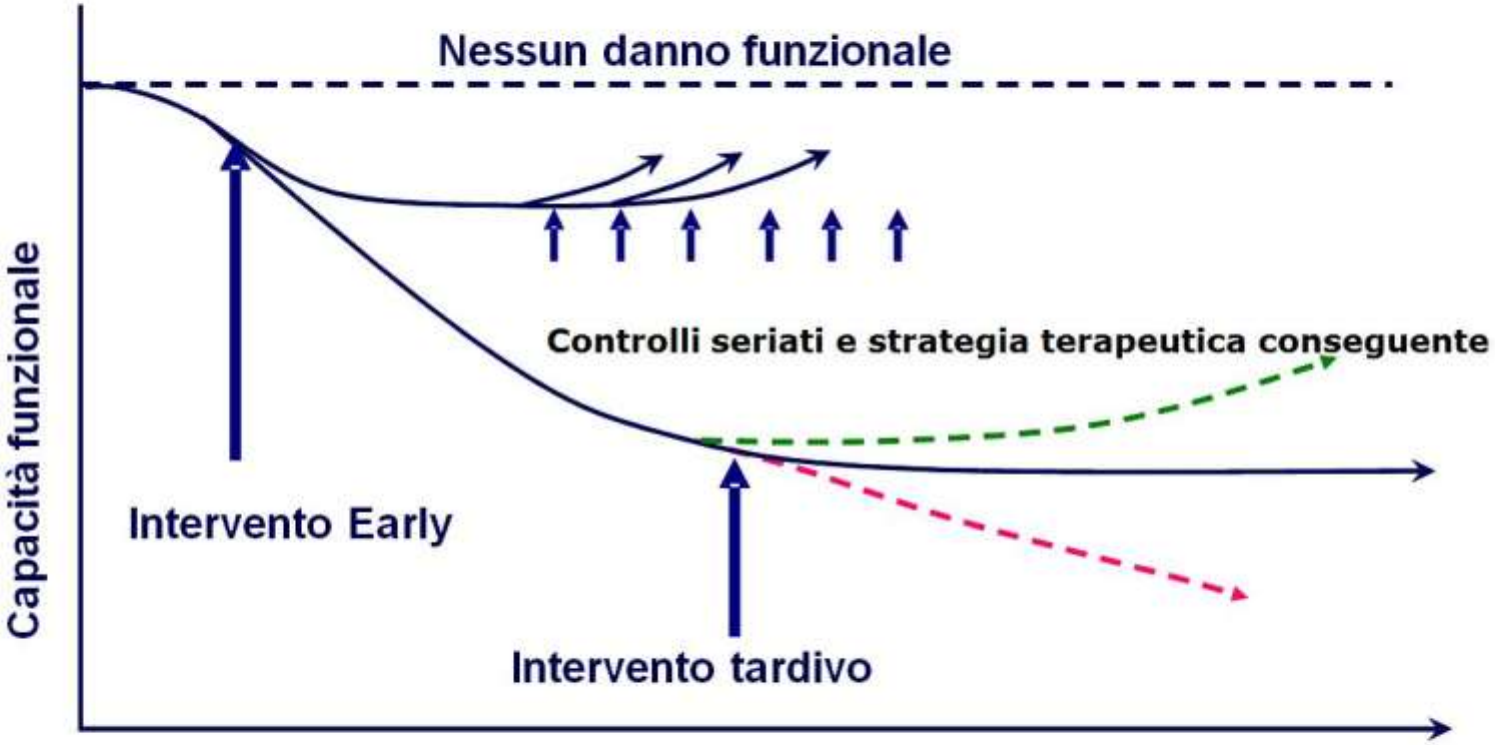


Classe funzionale II

Maggiore sopravvivenza per trattati in fase precoce



Sitbon et al. J Am Coll Cardiol 2002.

Pulmonary hypertension: clinical manifestations, classification and diagnosis

M.J. Hegewald, B Markewitz, CG. Elliott. Int J Clin Pract 2007;61 (Suppl. 156):5–14 5.

Table 1 Symptoms of patients with pulmonary arterial hypertension initially, and at the time of diagnosis (7)

	Initial symptom (%)	At diagnosis (%)
Dyspnoea	60	98
Fatigue	19	73
Chest pain	7	47
Near syncope	5	41
Syncope	8	36
Leg oedema	3	37
Palpitations	5	33

Primary pulmonary hypertension. A national prospective study. Rich S, Dantzker DR, Ayres SM et al. Ann Intern Med 1987; 107:216–23.

Pulmonary hypertension: clinical manifestations, classification and diagnosis

M.J. Hegewald, B Markewitz, CG. Elliott. Int J Clin Pract 2007;61 (Suppl. 156):5–14 5.

Table 3 Frequency of physical findings in patients with pulmonary arterial hypertension (7)

Findings	Per cent of patients
Accentuation of P2	93
Tricuspid regurgitation	40
Right-sided S4	38
Peripheral oedema	32
Right-sided S3	23
Cyanosis	20
Pulmonic insufficiency	13

P2, pulmonic component of the second heart sound; S3, right ventricular third heart sound; S4, right ventricular fourth heart sound.

Primary pulmonary hypertension. A national prospective study. Rich S, Dantzker DR, Ayres SM et al. Ann Intern Med 1987; 107:216–23.

Key problems for clinicians

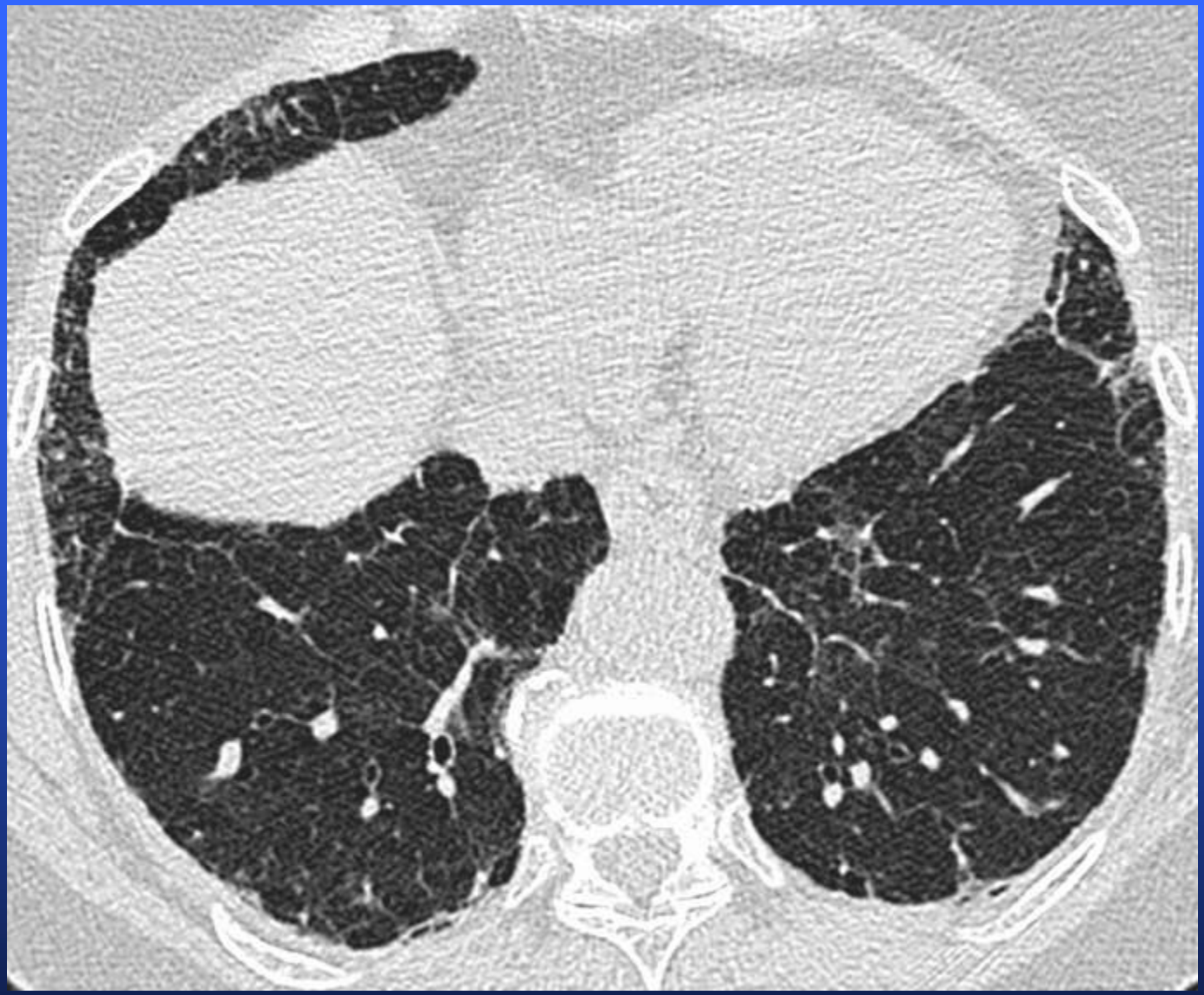
- Is interstitial lung disease present?
- Is pulmonary hypertension present?
- Is it clinically significant?

Is pulmonary hypertension or fibrosis present?

- Symptoms misleading
- Chest radiography insensitive
- Sensitive markers include pulmonary function tests, echocardiography, right heart catheterization

HRCT can sometimes creates its own problems

Is disease clinically significant?



When does a minor abnormality become "disease"?

SSc PAH: risk factors

Pulmonary Hypertension

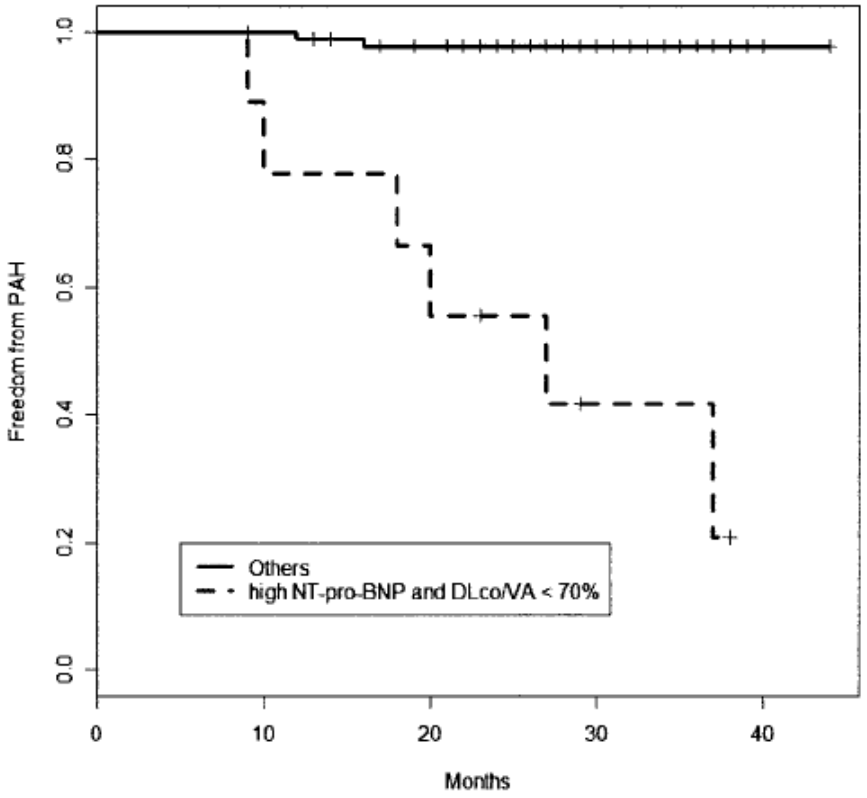
- Risk Factors
  - Longstanding (> 10 year), limited SSc
  - Anticentromere or antinuclear antibodies
  - DLCO < 65% predicted, FVC/DLCO ratio > 1.6
  - Mild to moderate fibrosis on CXR or HRCT
  - ? Increased resting PASP, ? Exercise PASP

  - SOB develops slowly. Patients not always aware

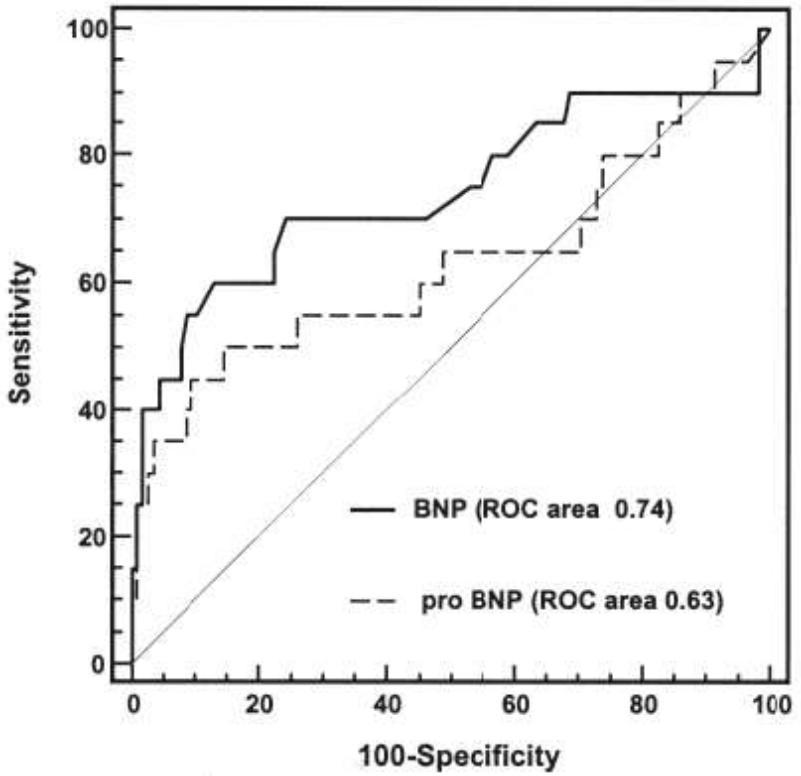
- Diagnosis of Pulmonary Hypertension
  - Suspect PHT:
    - Late limited, ACA, antinuclear AB, low DLCO, FVC/DLCO > 1.8
    - Echo PASP > 30 mm Hg
    - Right heart changes
  - Exclude:
    - Left heart failure
    - Pulmonary emboli
    - Severe pulmonary fibrosis
    - Right heart catheterization

Steen V. J Clin Rheumatol 2005

Predictors of PAH in SSc

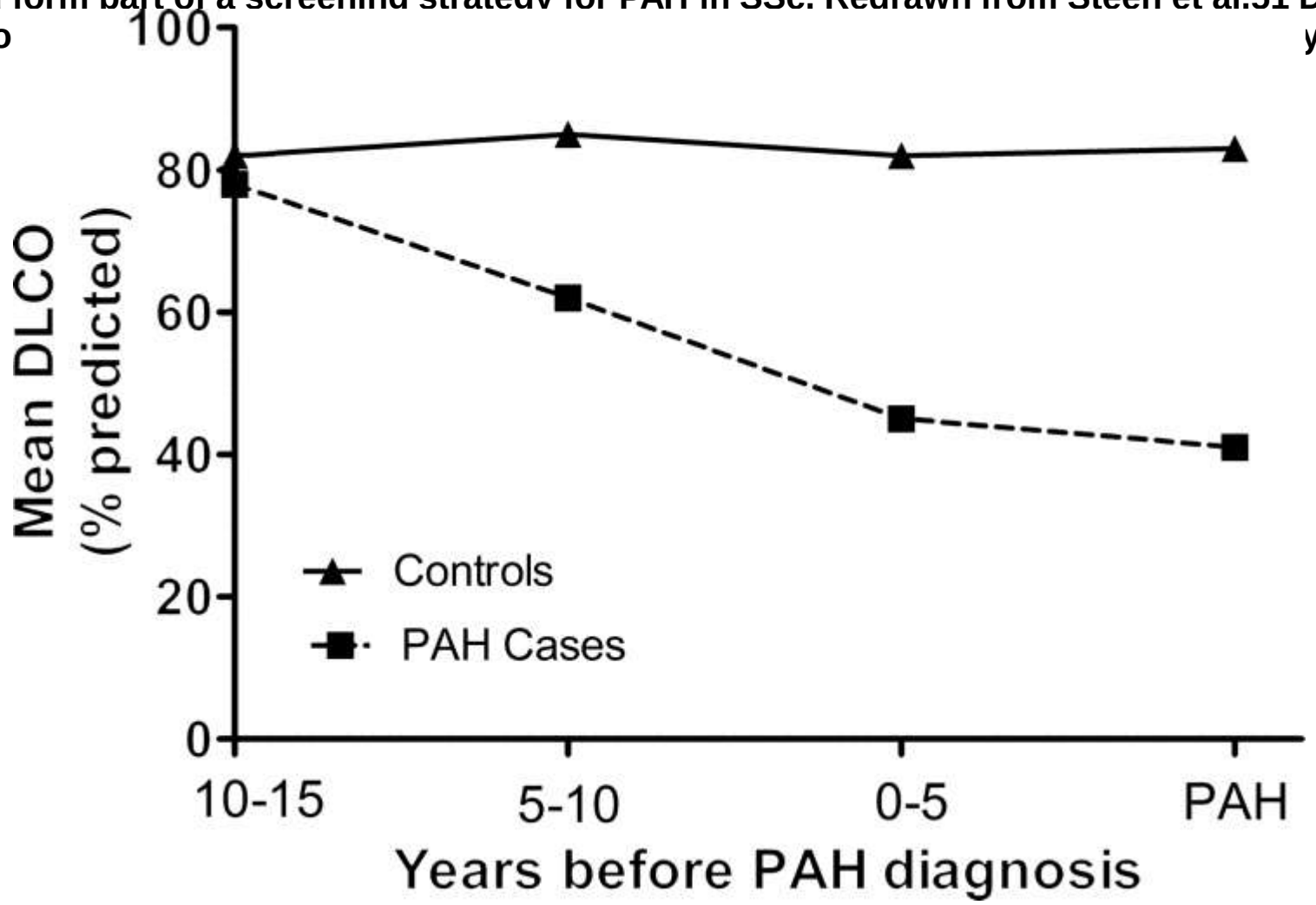


Allanore Y et al, A&R 2008



Cavagna L et al, J Rheumatol 2010

The relationship between DLCO and the development of SSc-associated PAH. Serial falls in DLCO are predictive of the development of future PAH, suggesting that DLCO monitoring could form part of a screening strategy for PAH in SSc. Redrawn from Steen et al.51 DLCO, diffusio ystemic



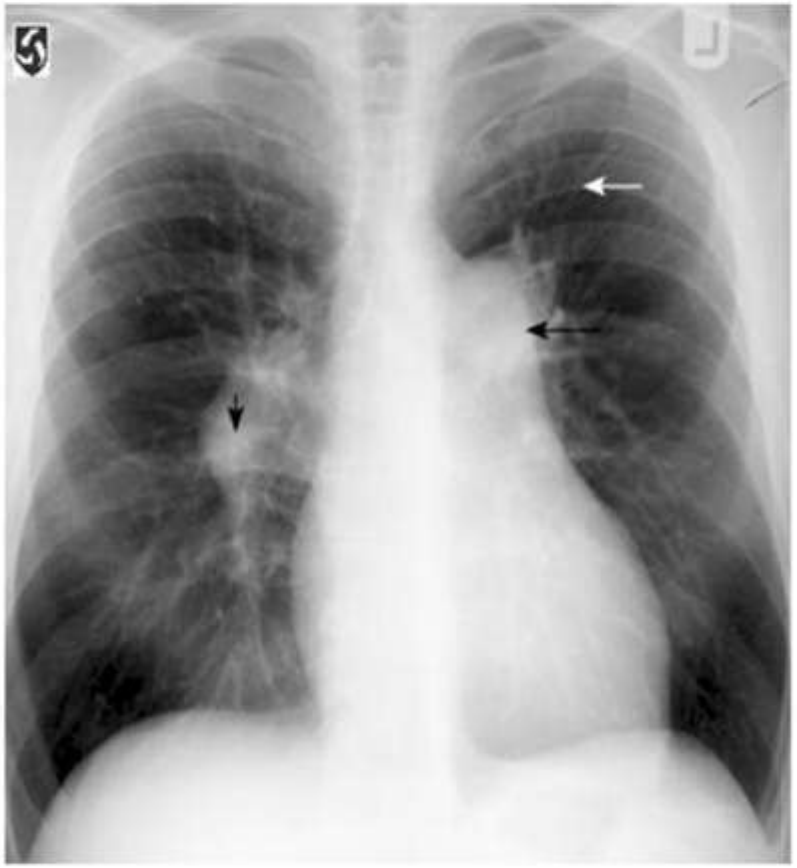
Lau E M et al. Eur Heart J 2011;32:2489-2498

European Heart Journal

Evaluation

Initial evaluation of the patient with dyspnea should include the following:

- Medical history and physical examination
- Chest x-ray
- Pulmonary function tests
- Computed tomography scan
- Electrocardiogram
- Ventilation/perfusion scan
- Echocardiogram



NON INVASIVE MARKERS OF PAH PROGNOSIS

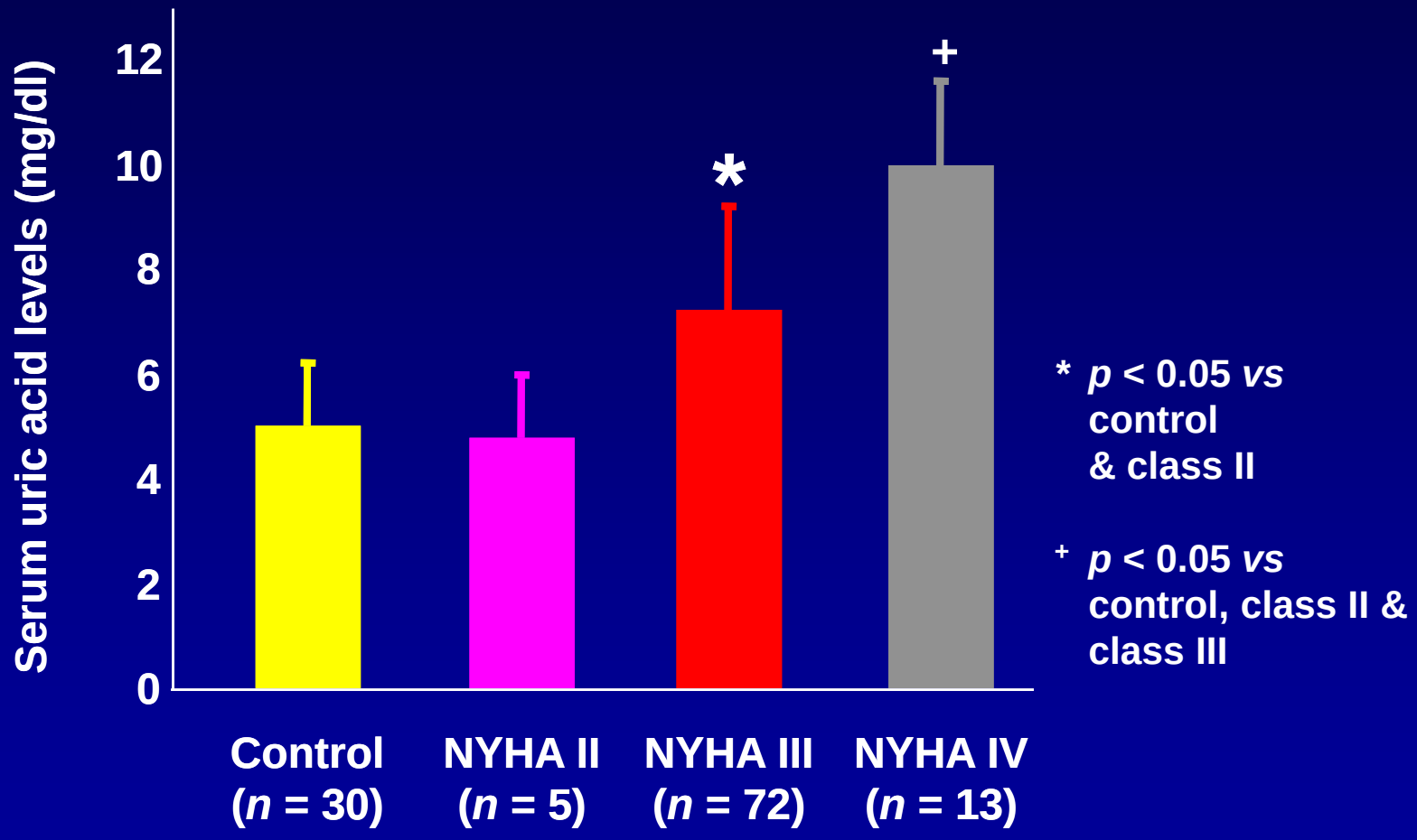
- Functional class (NYHA/WHO)
- Biochemical markers (uric acid, BNP, TnT/I)
- Echocardiography (PE, Tei index, RV-LV function)
- Exercise studies (6-min walk test, CPET)
- Hemodynamic variables (RAP, CO, SvO_2)

ASSESSMENT OF PAH SEVERITY
BIOLOGICAL MARKERS

Biological markers of disease severity

- ➔ Uric acid
- ➔ B-type naturetic peptide
- ➔ Cardiac troponin T

ASSESSMENT OF PAH SEVERITY
URIC ACID



Nagaya N, et al. *Am J Respir Crit Care Med* 1999; 160:478-492

ASSESSMENT OF PAH SEVERITY
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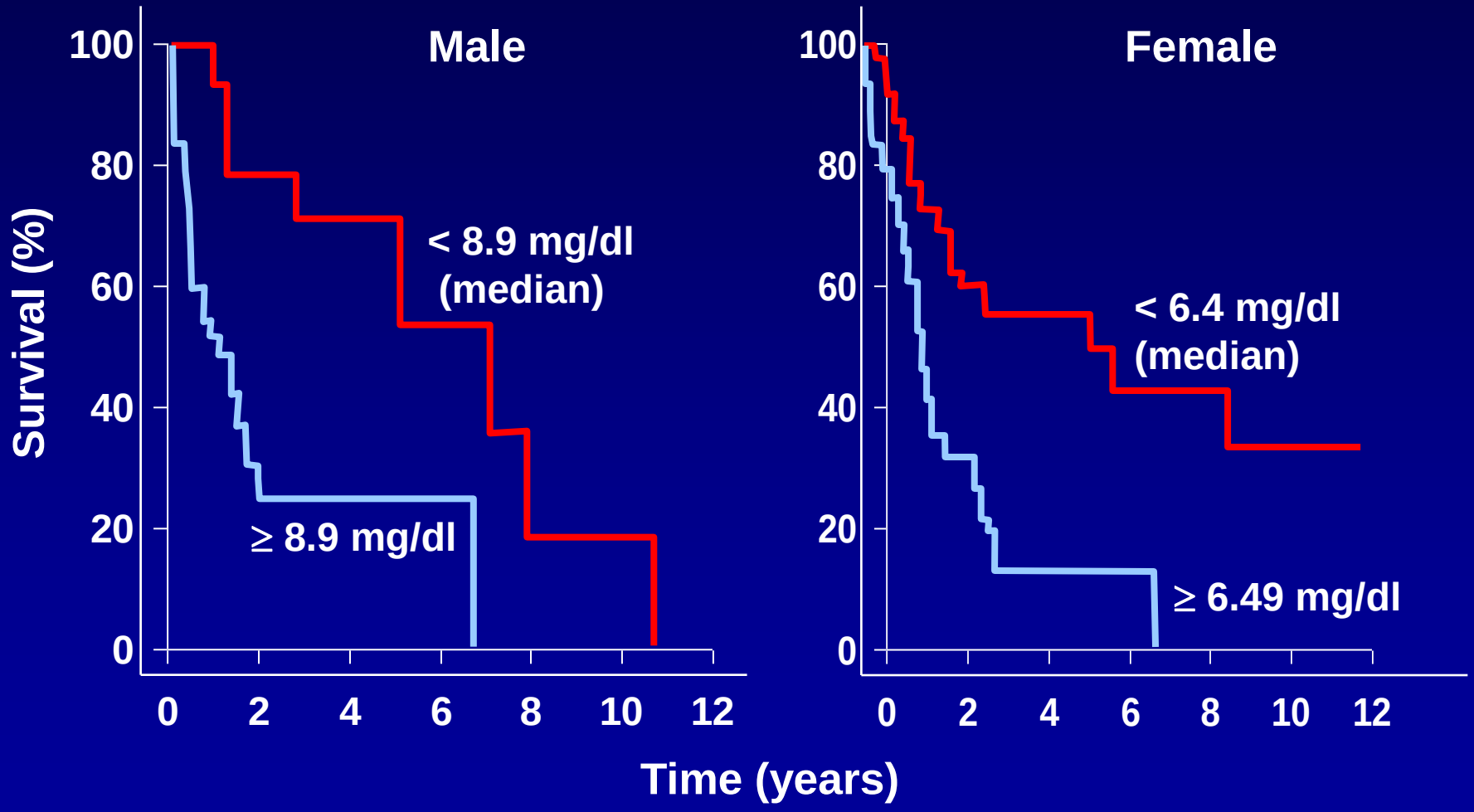

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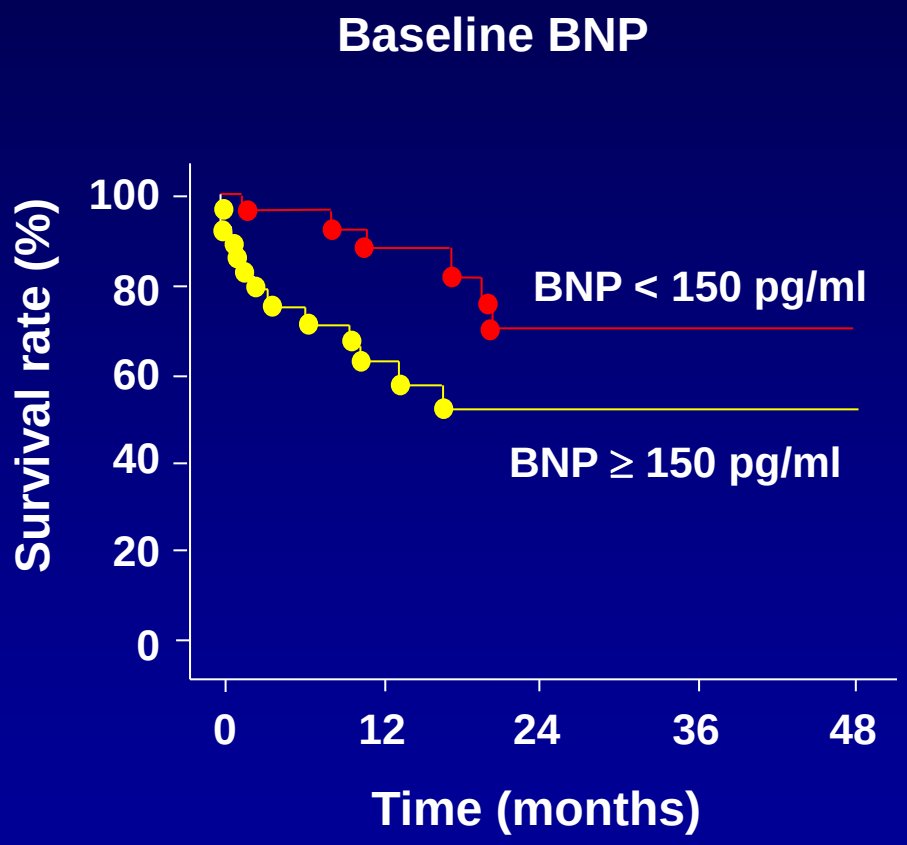
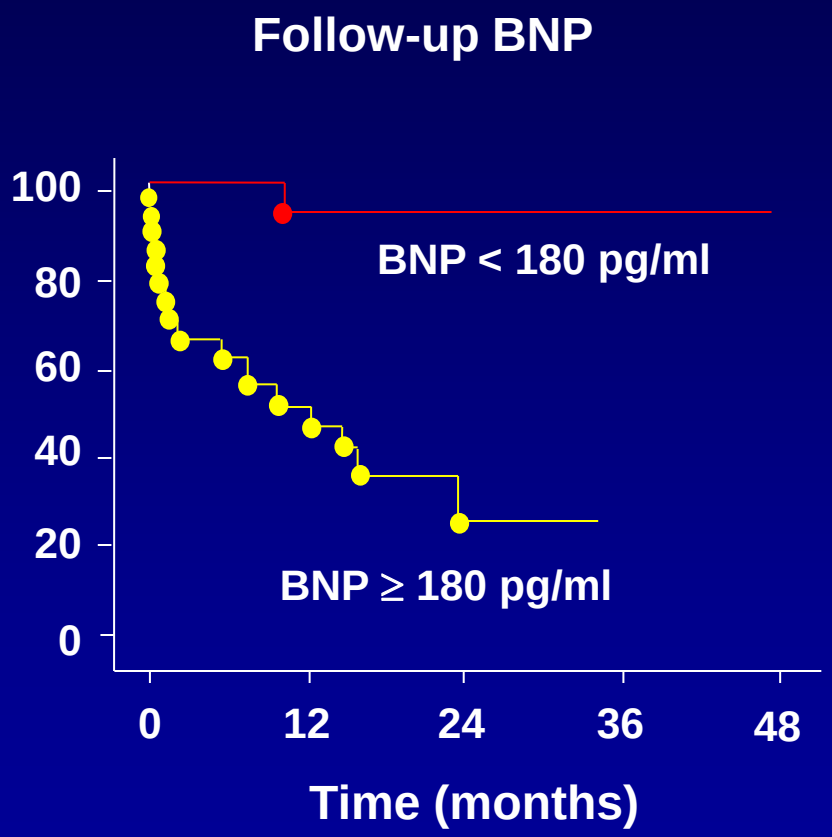
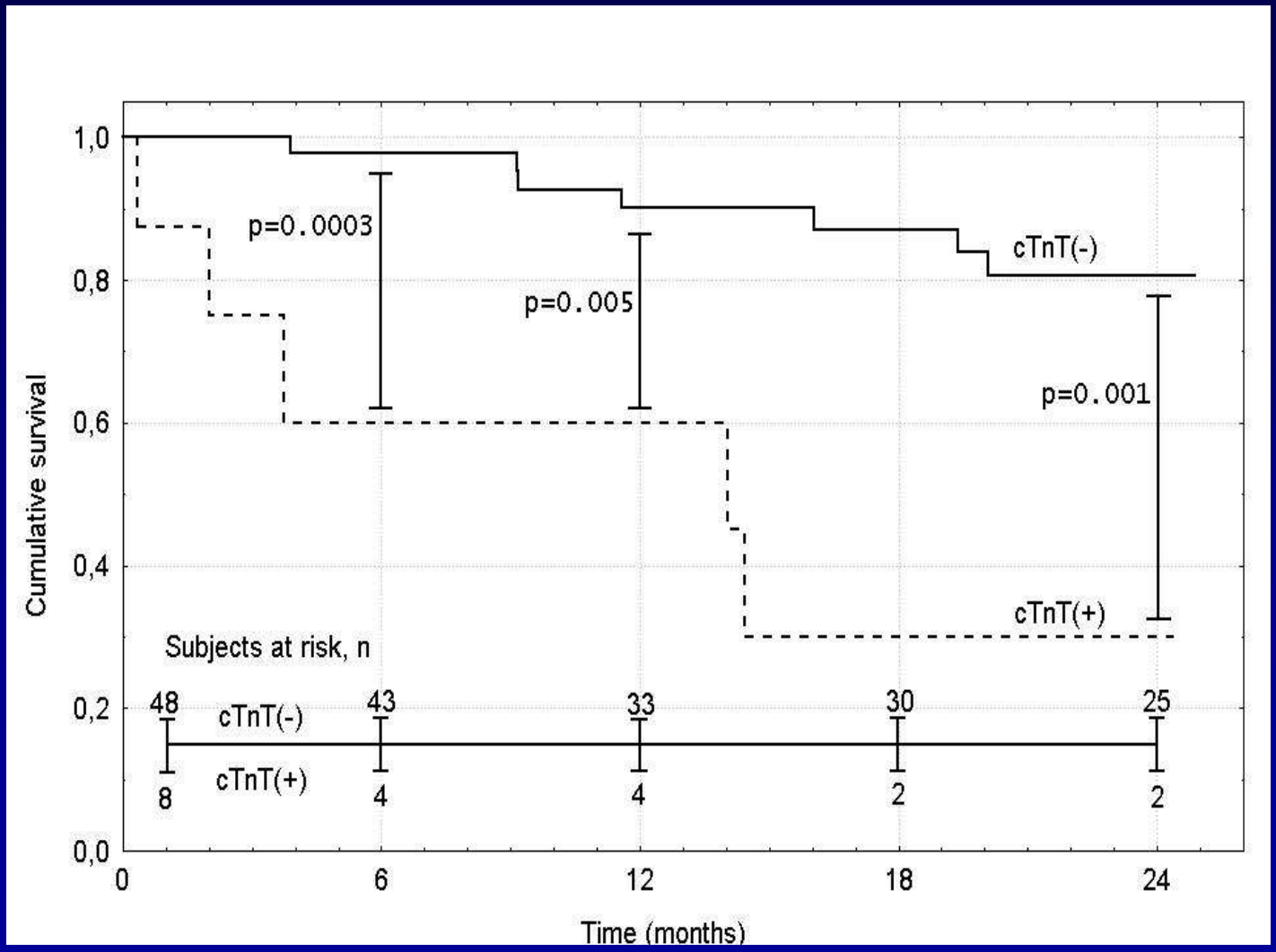
ASSESSMENT OF PAH SEVERITY
NATRIURETIC PEPTIDES





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

ASSESSMENT OF PAH SEVERITY
TROPONIN T



Torbicki A, et al. *Circulation* 2003

ASSESSMENT OF PAH SEVERITY
EXERCISE : 6-MIN WALK TEST

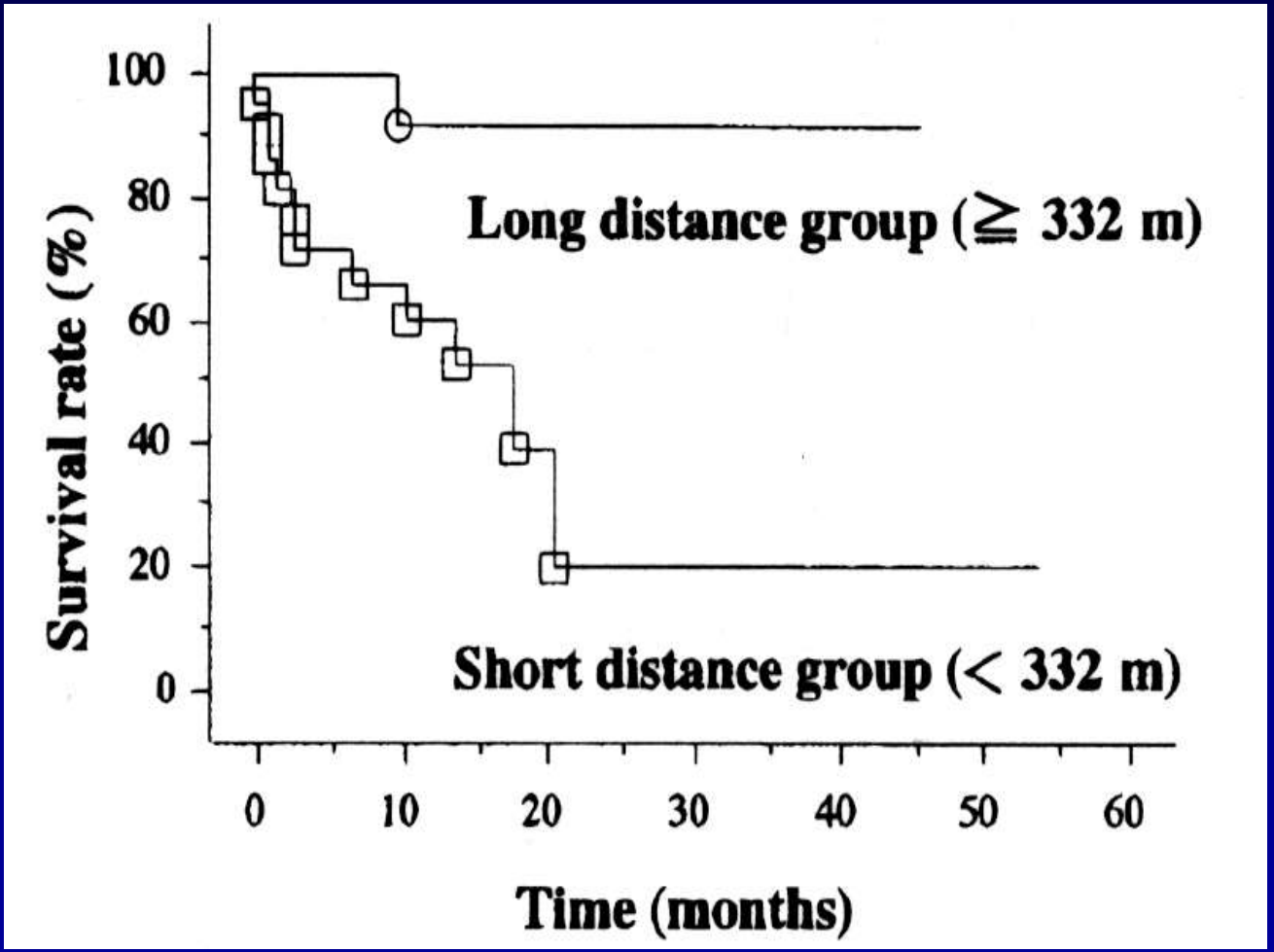
MULTIVARIATE ANALYSIS OF NONINVASIVE VARIABLES ASSOCIATED WITH MORTALITY IN PPH

Variable	Risk Ratio Estimate	95% CI	p Value
Age	1.024	0.940–1.115	0.5935
Sex	0.085	0.002–3.598	0.1970
Heart rate	1.044	0.917–1.189	0.5173
Sa_{O_2}	0.979	0.498–1.924	0.9503
Pericardial effusion	0.367	0.024–5.530	0.4687
LV deformity index	1.602	0.317–8.100	0.5689
Plasma NE	1.000	0.998–1.003	0.7467
Distance walked in 6 min	0.986	0.973–0.999	0.0381

Definition of abbreviatons: CI = confidence interval; LV = left ventricular; NE = norepinephrine; Sa_{O_2} = arterial oxygen saturation.

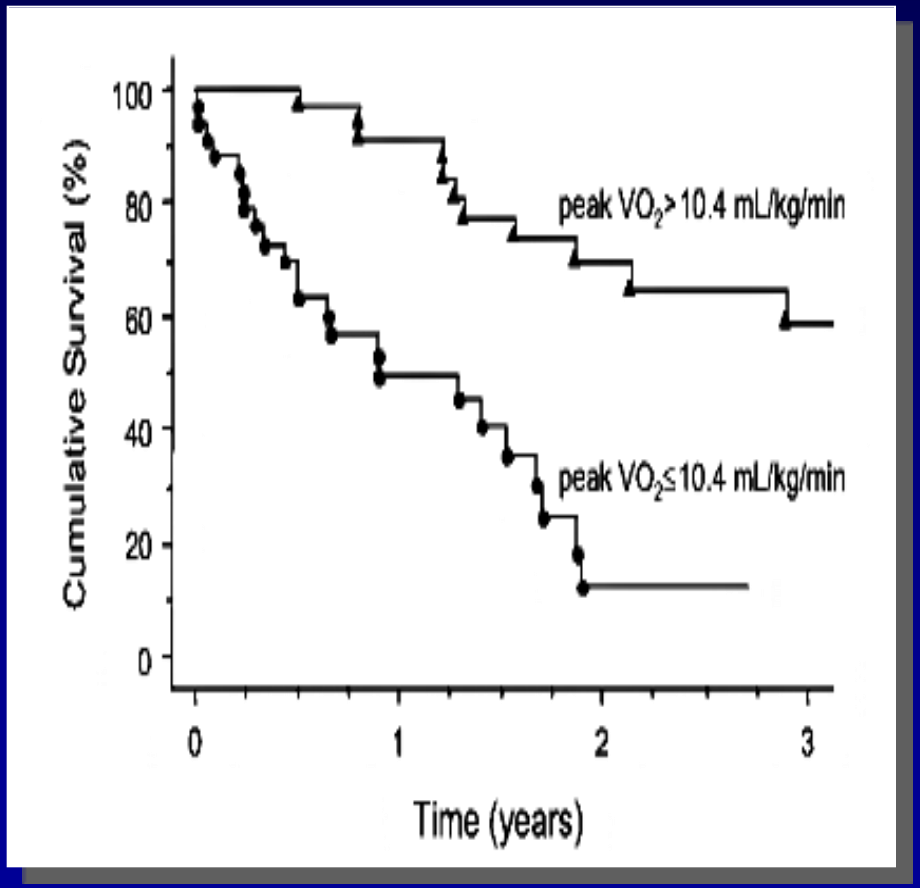
Miyamoto et al. *AJRCCM* 2000; 161:487-492

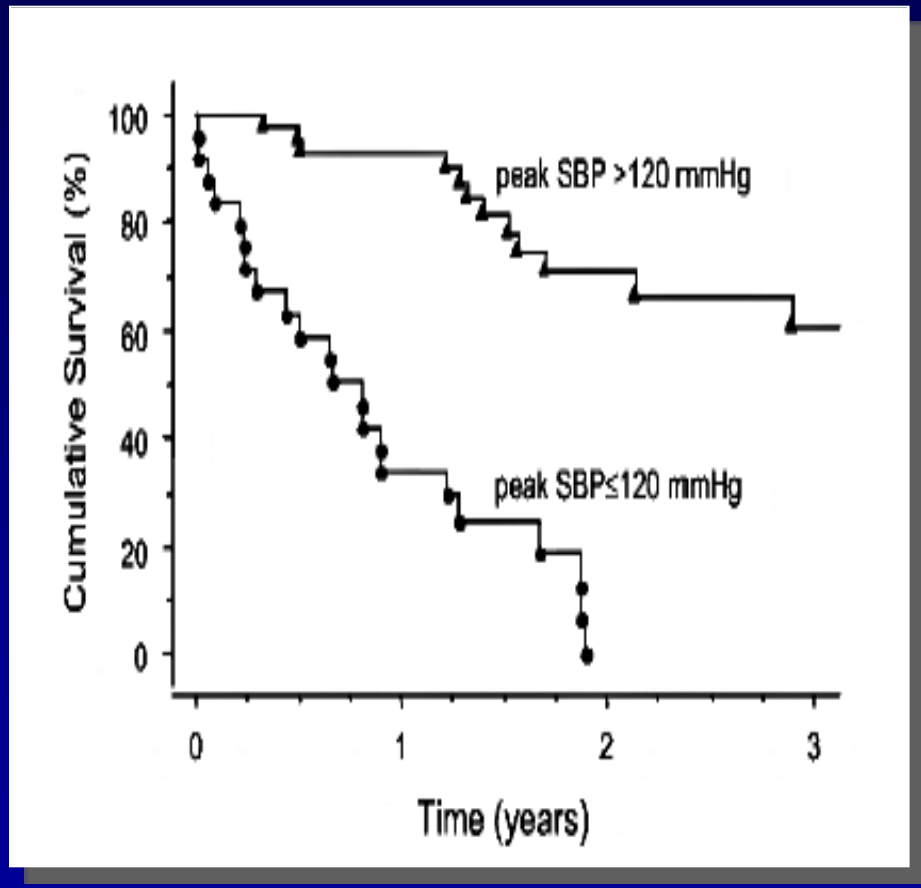
ASSESSMENT OF PAH SEVERITY
EXERCISE : 6-MIN WALK TEST



Miyamoto et al. *AJRCCM* 2000; 161:487-492

ASSESSMENT OF PAH SEVERITY
CARDIO-PULMONARY EXERCISE TESTING





Wensel et al. *Circulation* 2002; 106:319-324

Uses of exercise testing in lung disease

- Is exercise capacity impaired and is it consistent with symptoms?
- Is exercise impairment related to lung disease alone or do other conditions contribute?
- What physiological mechanisms contribute to exercise impairment?
- Prescription of exercise training program or oxygen during exercise

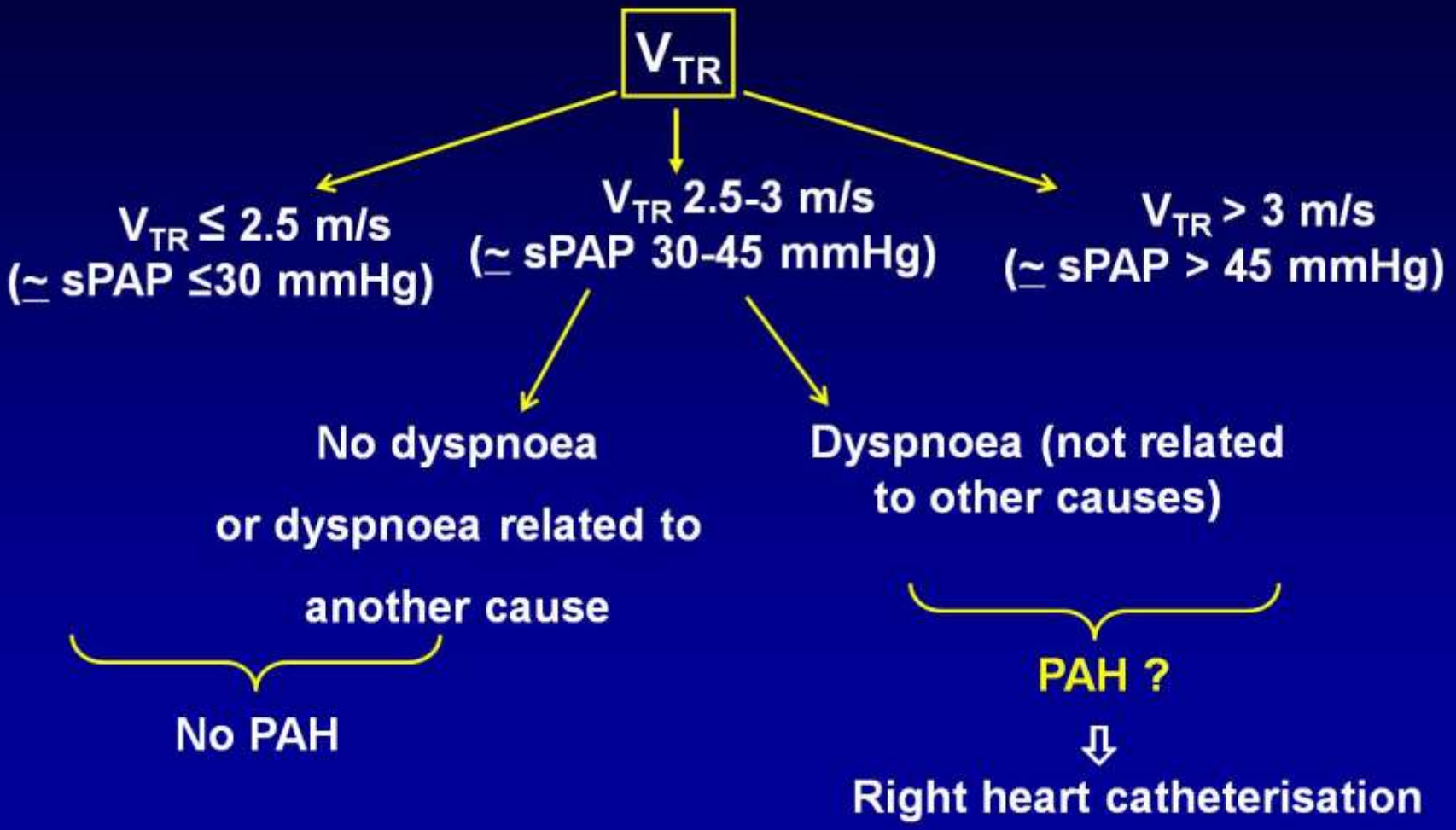
Med Clin N Am 1990; 4:634

Criteri per diagnosi di PH dalla misurazione della velocità di flusso del rigurgito tricuspidale

	Class[a]	Level[b]
Echocardiographic diagnosis: PH unlikely		
Tricuspid regurgitation velocity ≤2.8 m/s, PA systolic pressure ≤36 mmHg, and no additional echocardiographic variables suggestive of PH	I	B
Echocardiographic diagnosis: PH possible		
Tricuspid regurgitation velocity ≤2.8 m/s, PA systolic pressure ≤36 mmHg, but presence of additional echocardiographic variables suggestive of PH	IIa	C
Tricuspid regurgitation velocity 2.9–3.4 m/s, PA systolic pressure 37–50 mmHg with/without additional echocardiographic variables suggestive of PH	IIa	C
Echocardiographic diagnosis: PH likely		
Tricuspid regurgitation velocity >3.4 m/s, PA systolic pressure >50 mmHg, with/without additional echocardiographic variables suggestive of PH	I	B
Exercise Doppler echocardiography is not recommended for screening of PH	III	C

European Heart Journal (2009) **30**, 2493–2537

CARDIAC ECHO DOPPLER SCREENING FOR PAH IN SYSTEMIC SCLEROSIS

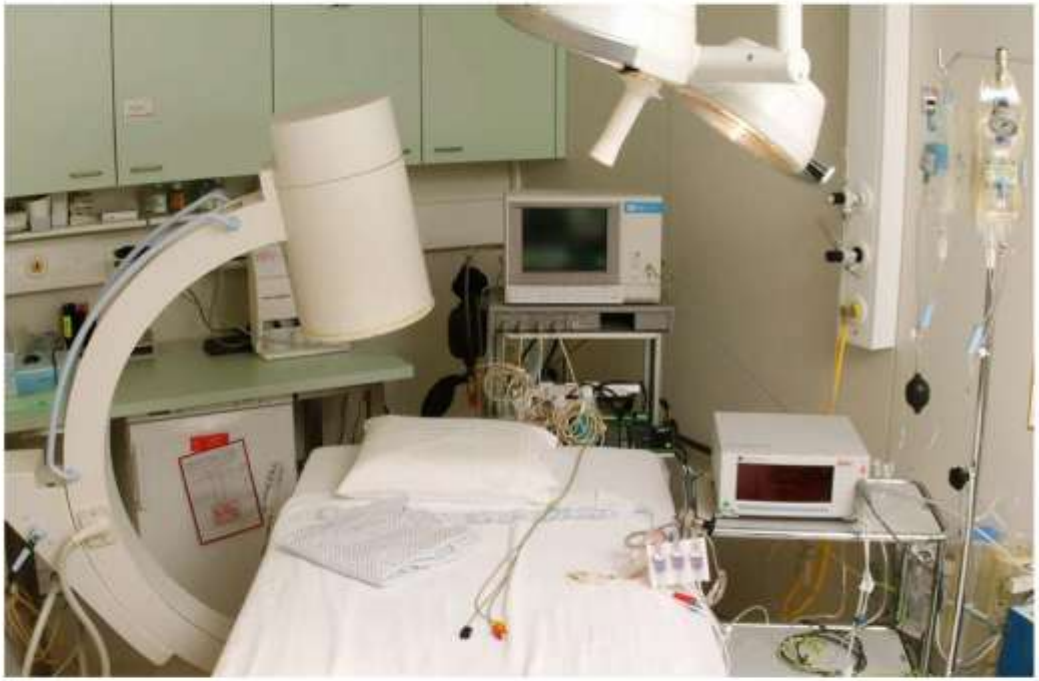


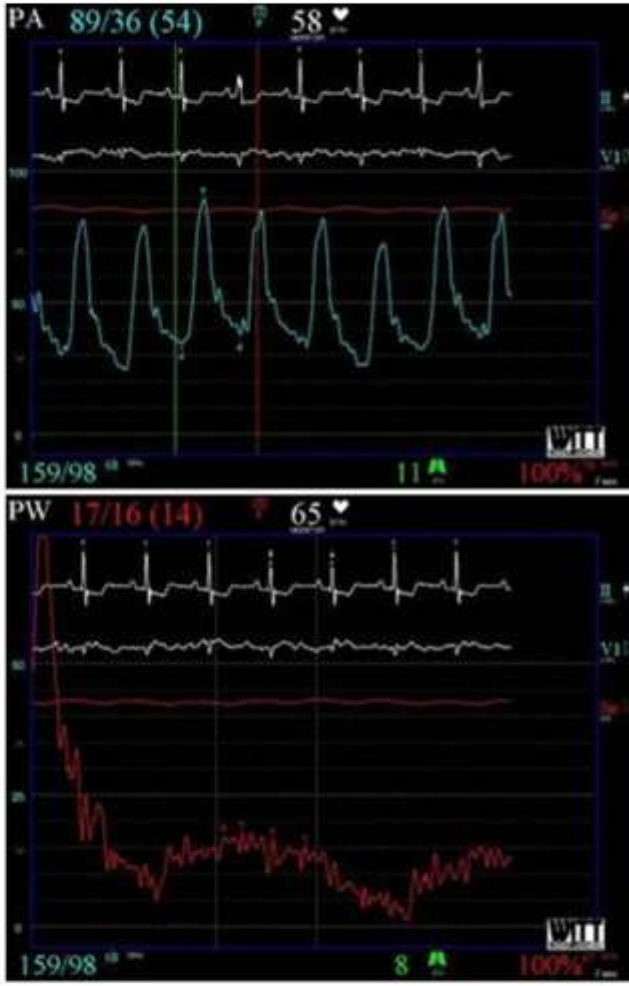
Hachulla et al. Arthritis Rheum 2005

- CTD-APAH patients have
  - better hemodynamics but higher prevalence of pericardial effusion
  - lower 6-MWD
  - Higher BNP levels
  - Lower DLCO

- SSc-APAH vs other CTDs have
  - Similar hemodynamics but
  - Higher BNP and lower DLCO

Cateterismo destro





Definizione di PAH
mPAP >25 mmHg a riposo o >30 mmHg durante esercizio fisico con PCWP normale

Why is PH/PAH-SSc so difficult to treat?

- Older patients
- Interstitial lung disease
- Left ventricular diastolic dysfunction
- Right ventricular diastolic dysfunction
- More severe structural vasculopathy
- Key outcome measures may differ
  (6 MWT-RHC ?)
- More inflammation

RHEUMATOLOGY

Concise report

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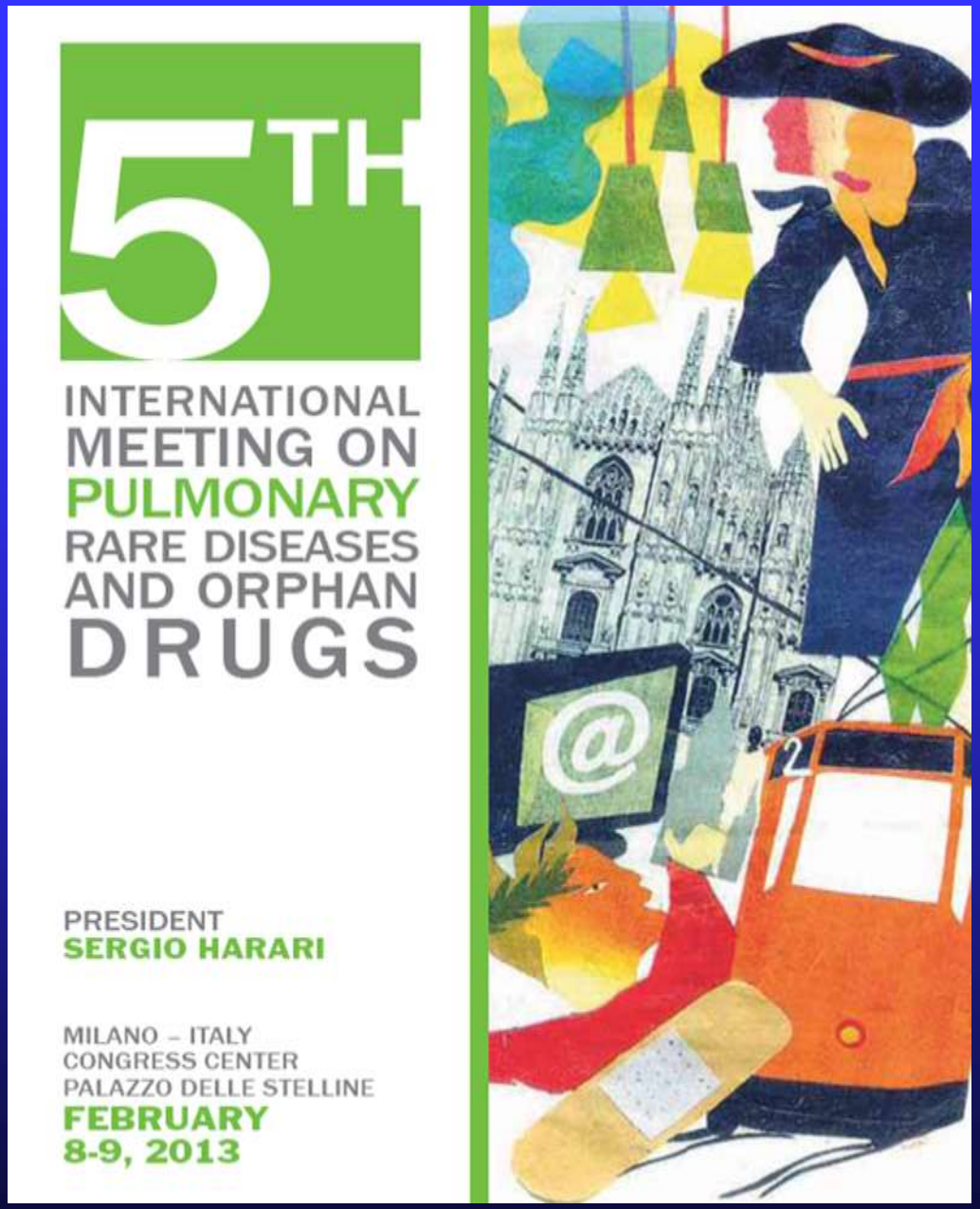
Pulmonary arterial hypertension associated with systemic sclerosis in patients with functional class II dyspnoea: mild symptoms but severe outcome

Eric Hachulla[1], David Launay[1], Azzedine Yaici[2,3,4], Alice Berezne[5], Pascal de Groote[4,6], Olivier Sitbon[2,3,4], Luc Mouthon[5], Loïc Guillevin[5], Pierre-Yves Hatron[1], Gérald Simonneau[2,3,4], Pierre Clerson[7] and Marc Humbert[2,3,4] , on behalf of the French PAH-SSc Network*

Take home messages

- PAH may frequently complicate CTDs
- Among CTDs, Systemic Sclerosis-associated PAH represents a unique phenotype for clinical presentation and outcome
- Screening of PAH is mandatory in SSc patients at any time of the disease course
- A big effort is needed in identifying the earliest predictors of this complication in order to make the most of the **new therapeutic armamentarium**
- A multidisciplinary management may improve diagnosis and outcome



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