HTAP associée à la Sclérodermie Systémique

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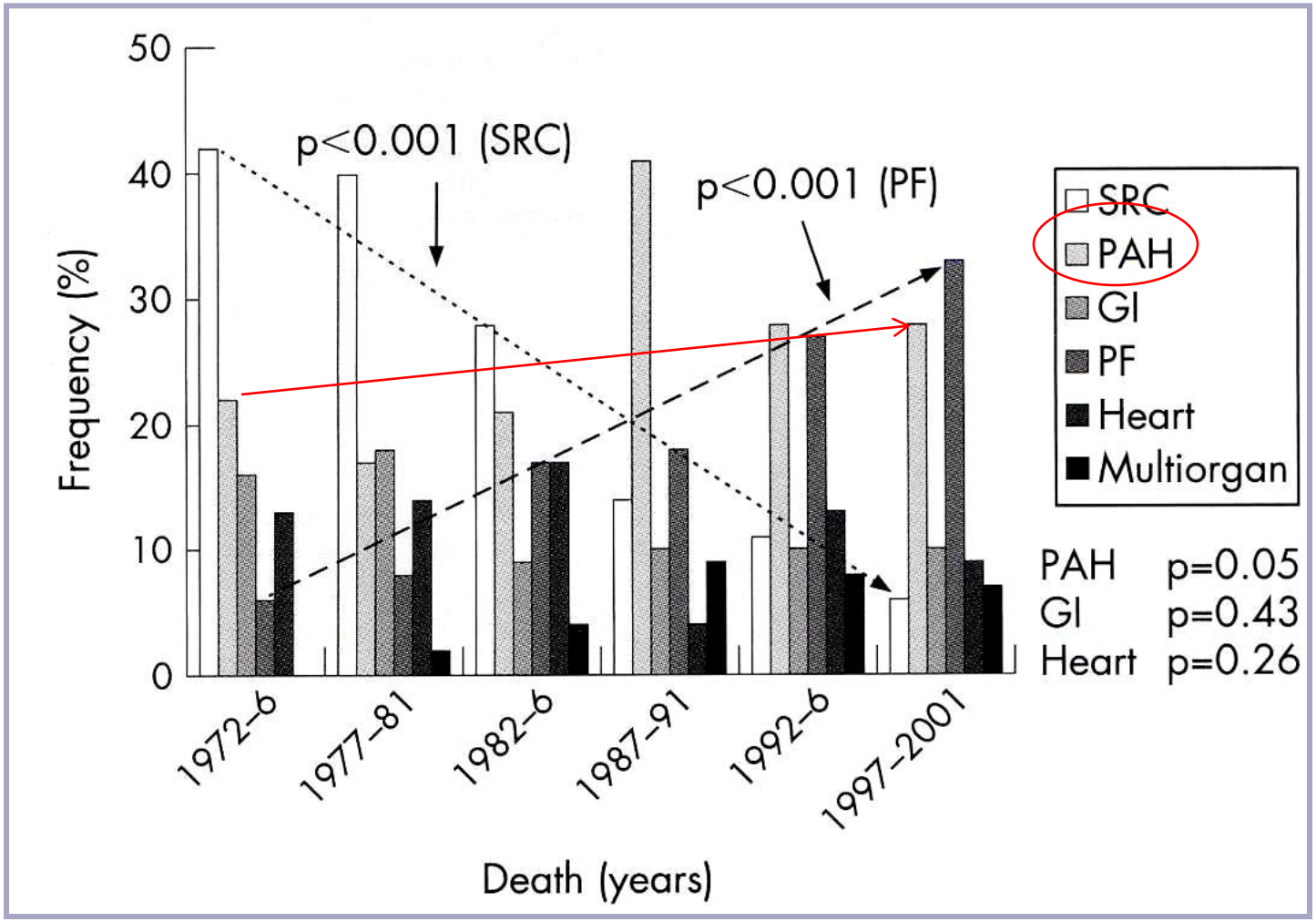
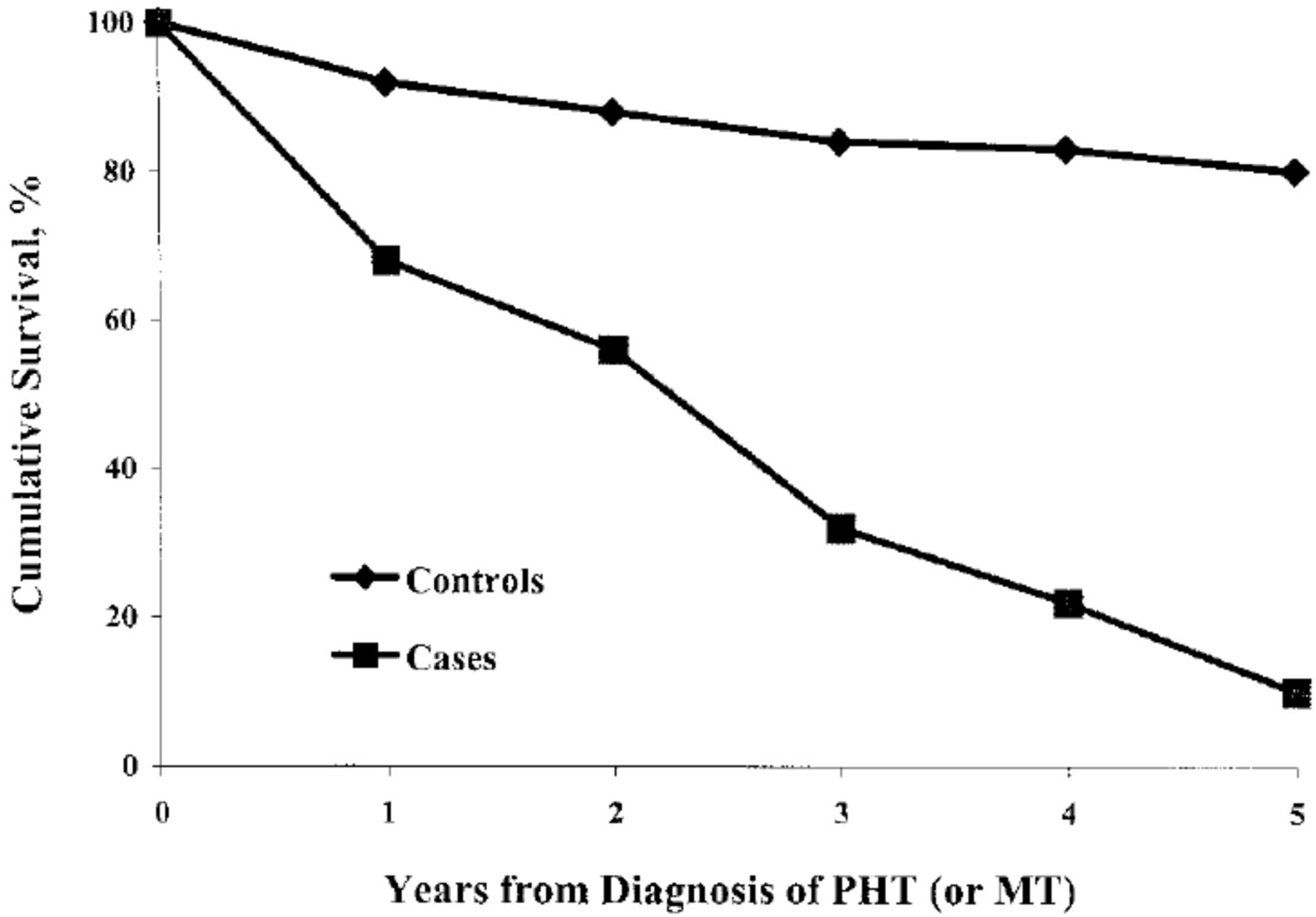
PAH: the bête noire of scleroderma



Steen V. Ann Rheum Dis 2007;66:940

PAH: the bête noire of scleroderma



Steen V, Medsger TA Jr. Arthritis Rheum 2003 ;48 :516

Prevalence of PAH in Scleroderma is high

Ref	Methodology	Diagnosis	PAH prevalence
Mukerjee 2003 UK	n=722, monocenter Prospective 1998-2002	RHC	12%
Hachulla 2005 France	599, multicenter Prospective, transsectionnal	RHC	8%
Phung 2009 Australia	184, monocenter Prospective, transsectionnal	RHC	13%

PH: classification

Table 2	Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic PAH
1.2. **Heritable**
1.2.1. **BMPR2**
1.2.2. **ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)**
1.2.3. **Unknown**
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. **Schistosomiasis**
1.4.6. **Chronic hemolytic anemia**
1.5 Persistent pulmonary hypertension of the newborn

1′. **Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)**

PH: classification

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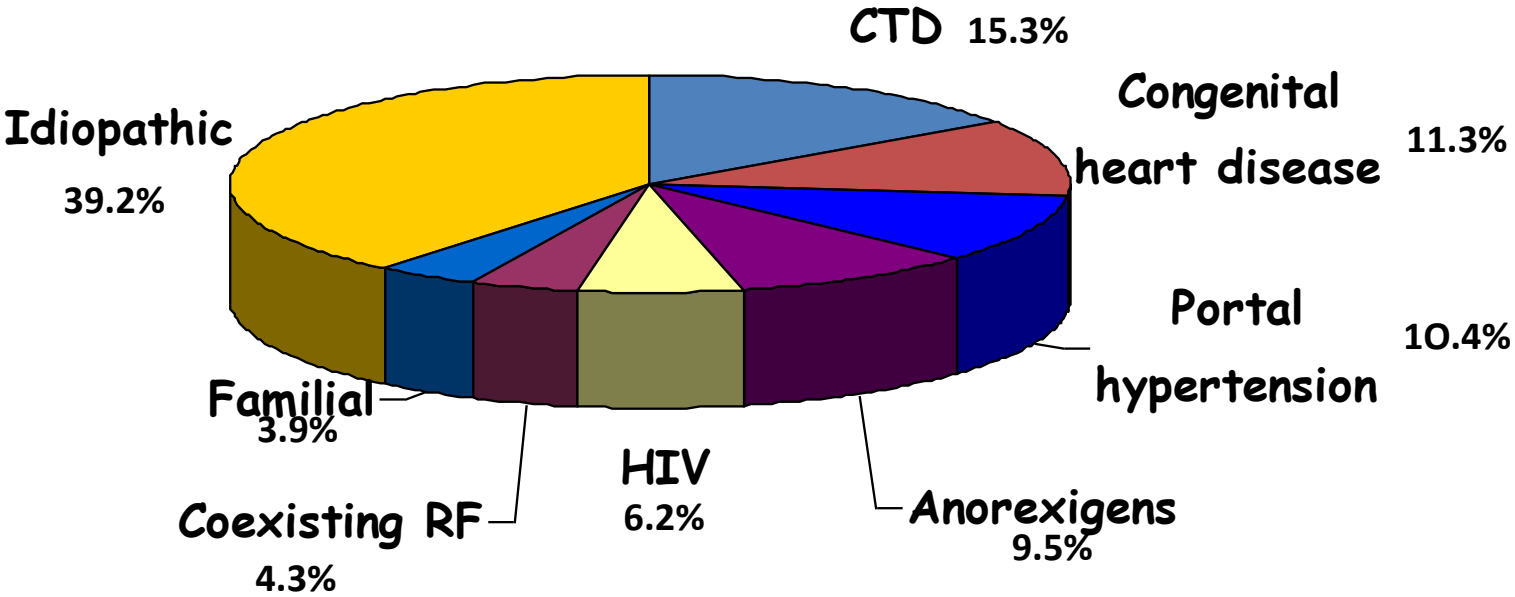
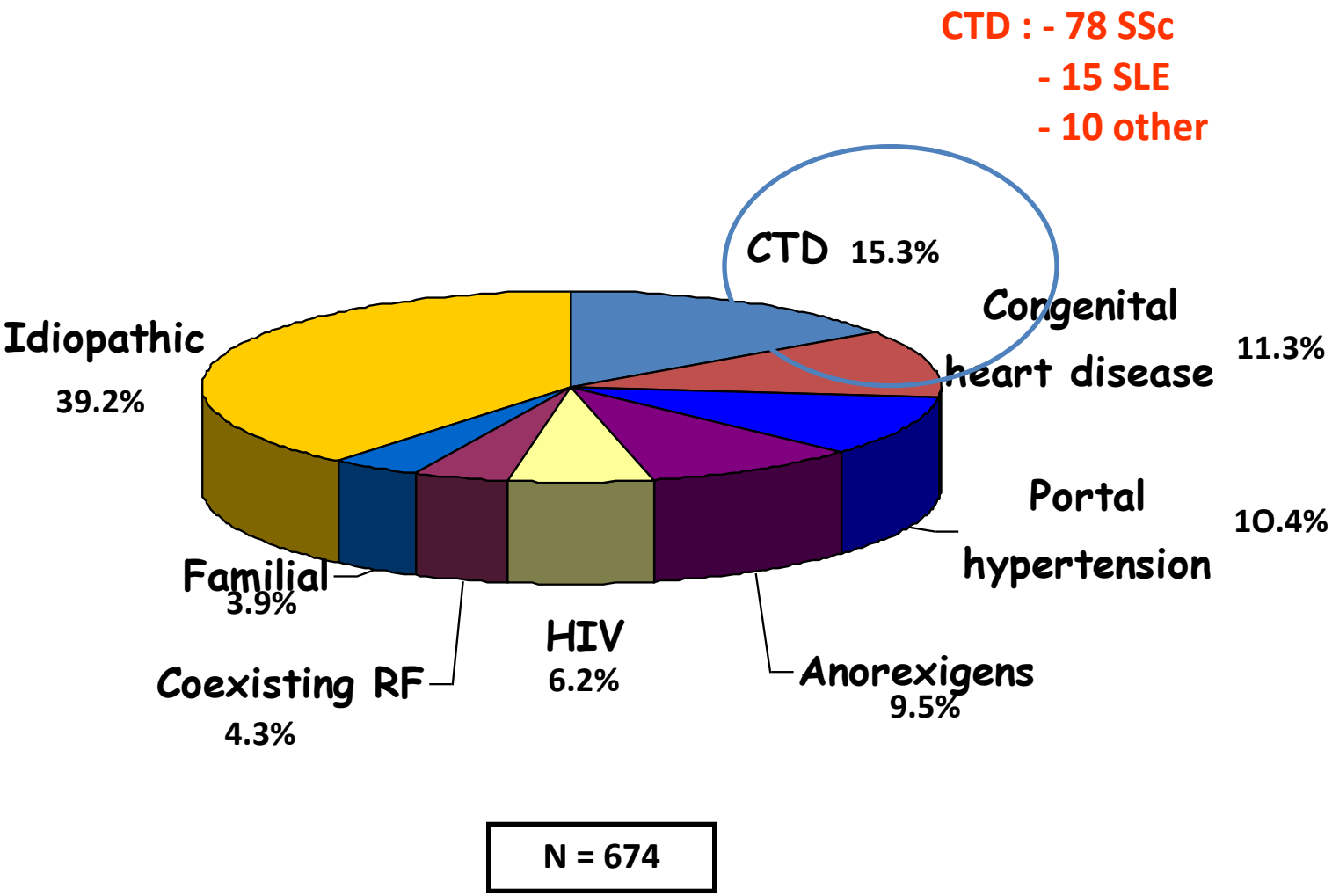
PAH in France: a national observatoire



N = 674

Humbert M. AJRCCM 2006; 173: 1023

PAH in France: a national observatoire



Humbert M. AJRCCM 2006; 173: 1023

PAH group 1 pathophysiology

PAH is characterized by dysfunctional

Pulmonary Artery Endothelial Cells

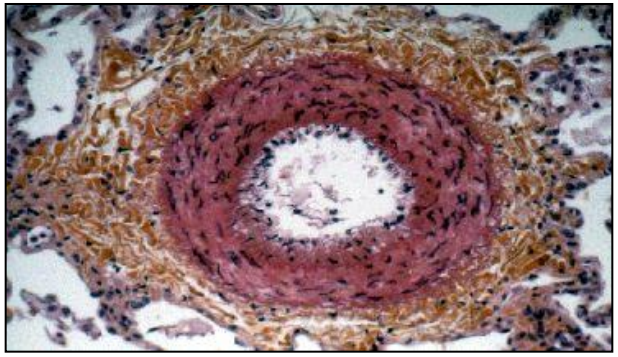
Pulmonary Artery Smooth Muscle Cells

Platelets

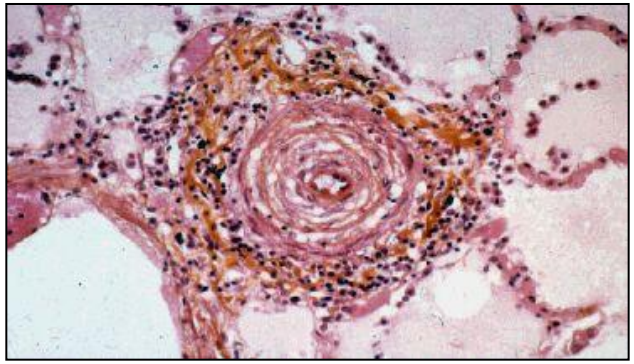
↓

Leading to pulmonary vasoconstriction, smooth muscle cell and endothelial cell proliferation and thombosis

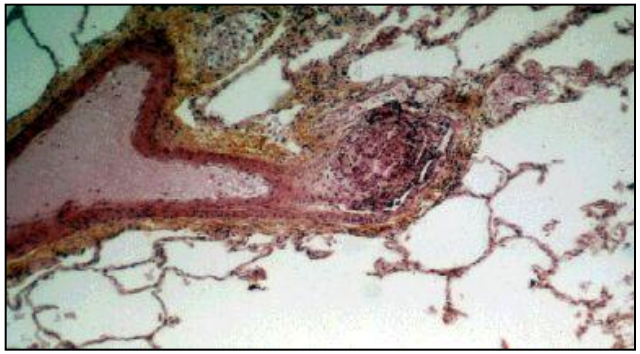
(pulmonary small vessels disease< 500 µm)



media hypertrophy



Intimal proliferation / thickening



Plexiform lesions

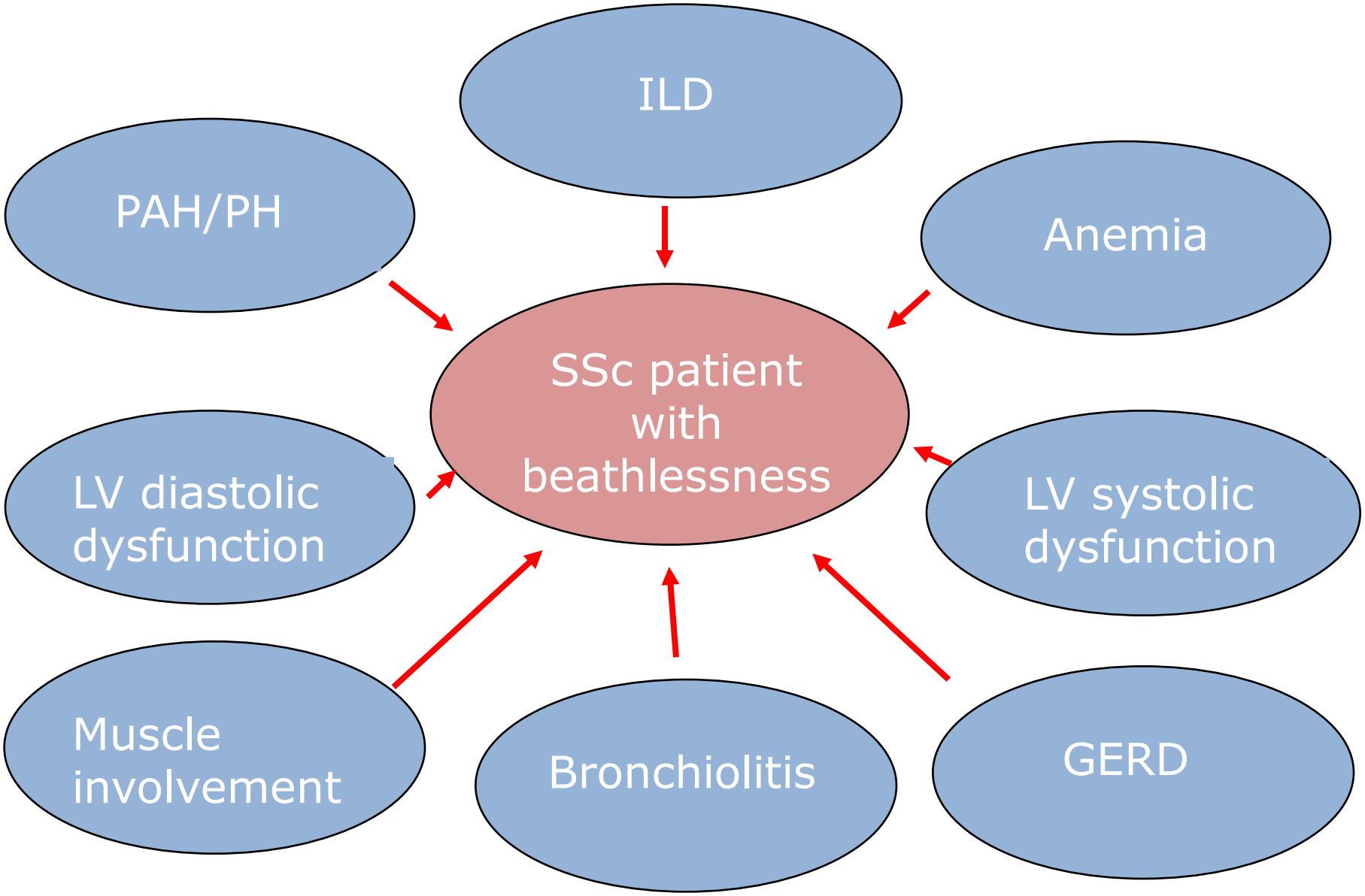
Courtesy Marc Humbert

PAH clinical symptoms are non specific

Most common initial presenting symptoms:

- breathlessness
- fatigue
- palpitations
- chest pain
- syncope
- edema

The multiple faces of dyspnea in SSc

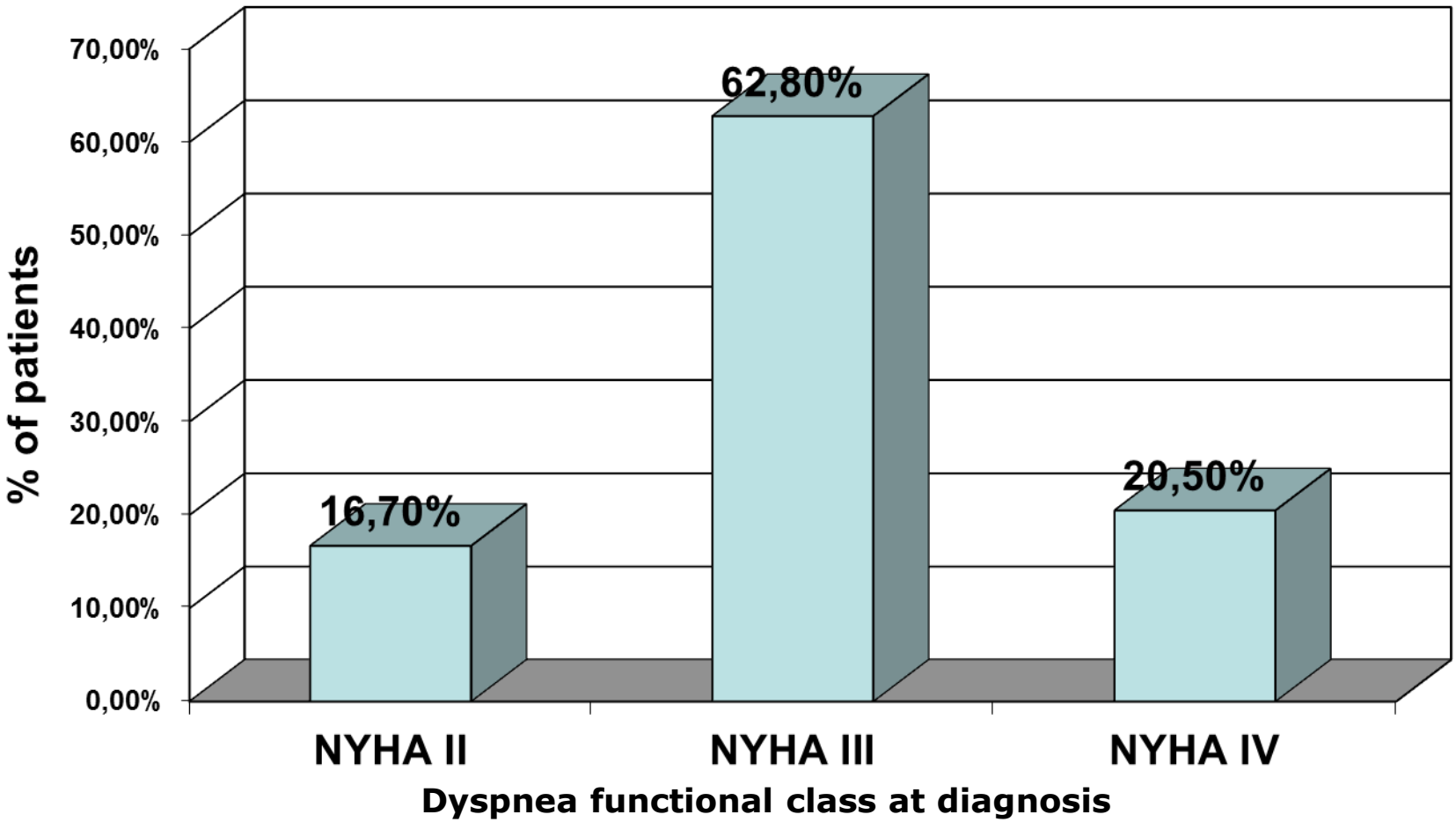


The multiple faces of dyspnea in SSc

	Classe fonctionnelle NYHA			
	II	III	IV	Total
SSc (*n* = 291)	49%	16%	4%	70%
PAH-SSc (*n* = 39)	33%	46%	18%	97%
PID-SSc (*n* = 117)	48%	26%	9%	82%
SSc sans HTAP ni PID extensive, avec CPT/CVF > 70% et FEVG normale (*n* = 74)	57%	5%	0%	62%

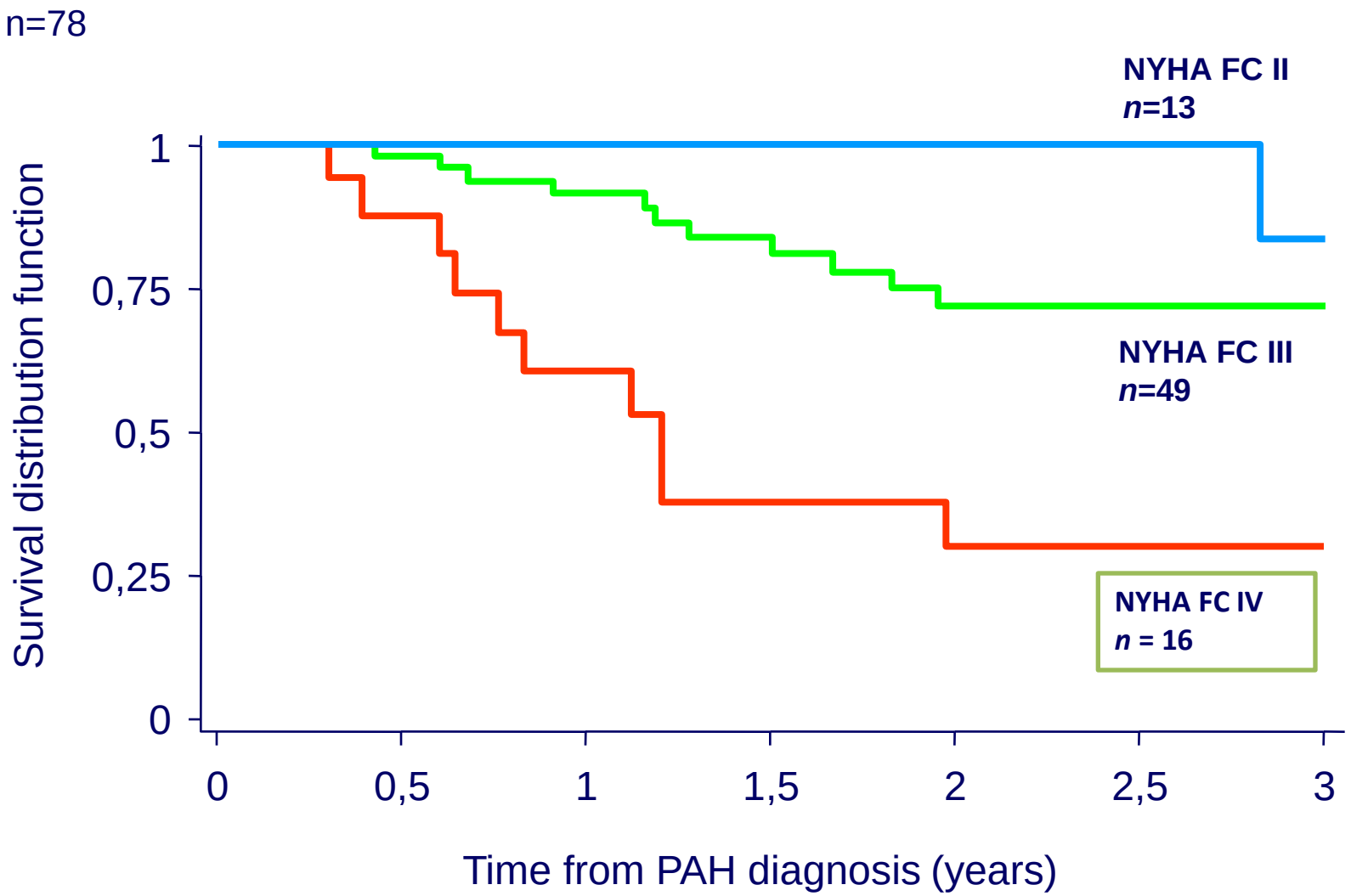
Dyspnea functional class at diagnosis

n=78



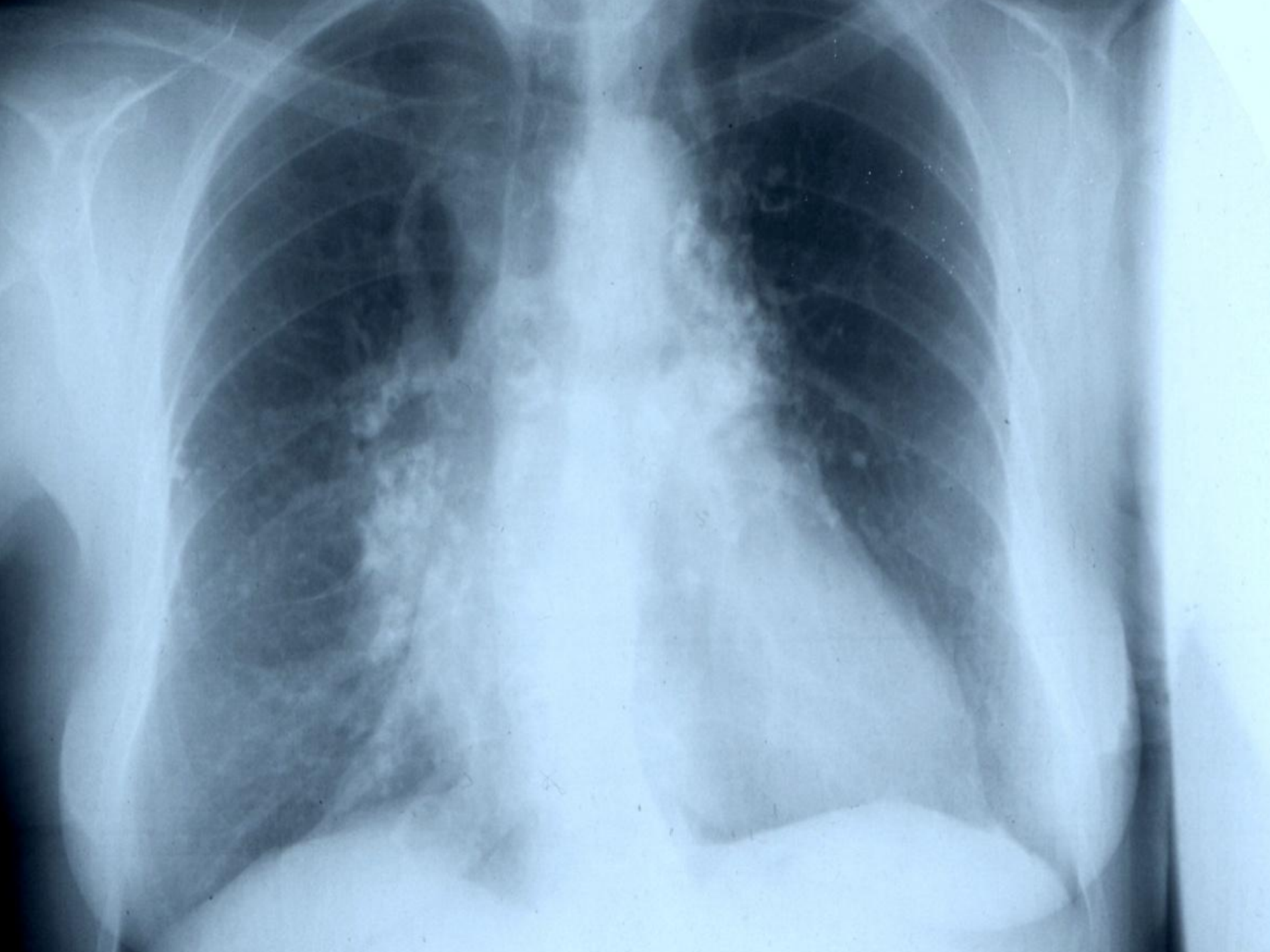
Hachulla E. Chest 2009; 136: 1211

Survival depends on dyspnea functional class at diagnosis



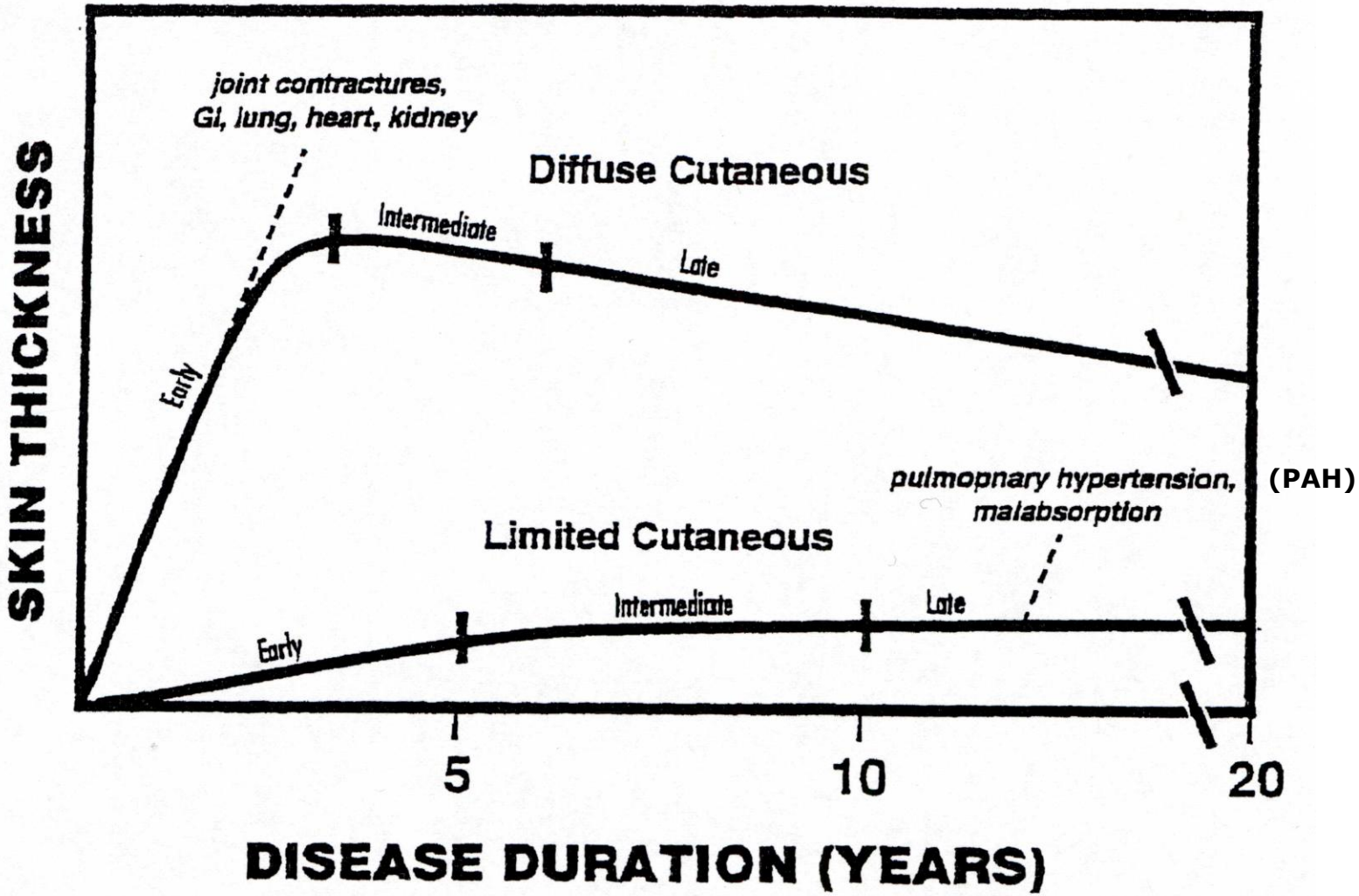
Log rank test p=0.002

Hachulla E. Chest 2009; 136: 1211



Which SSc-patients are at risk of PAH?

Only late onset in lcSSc patients?



Medsger TA. Rheum Dis Clin N AM 2003; 29: 255

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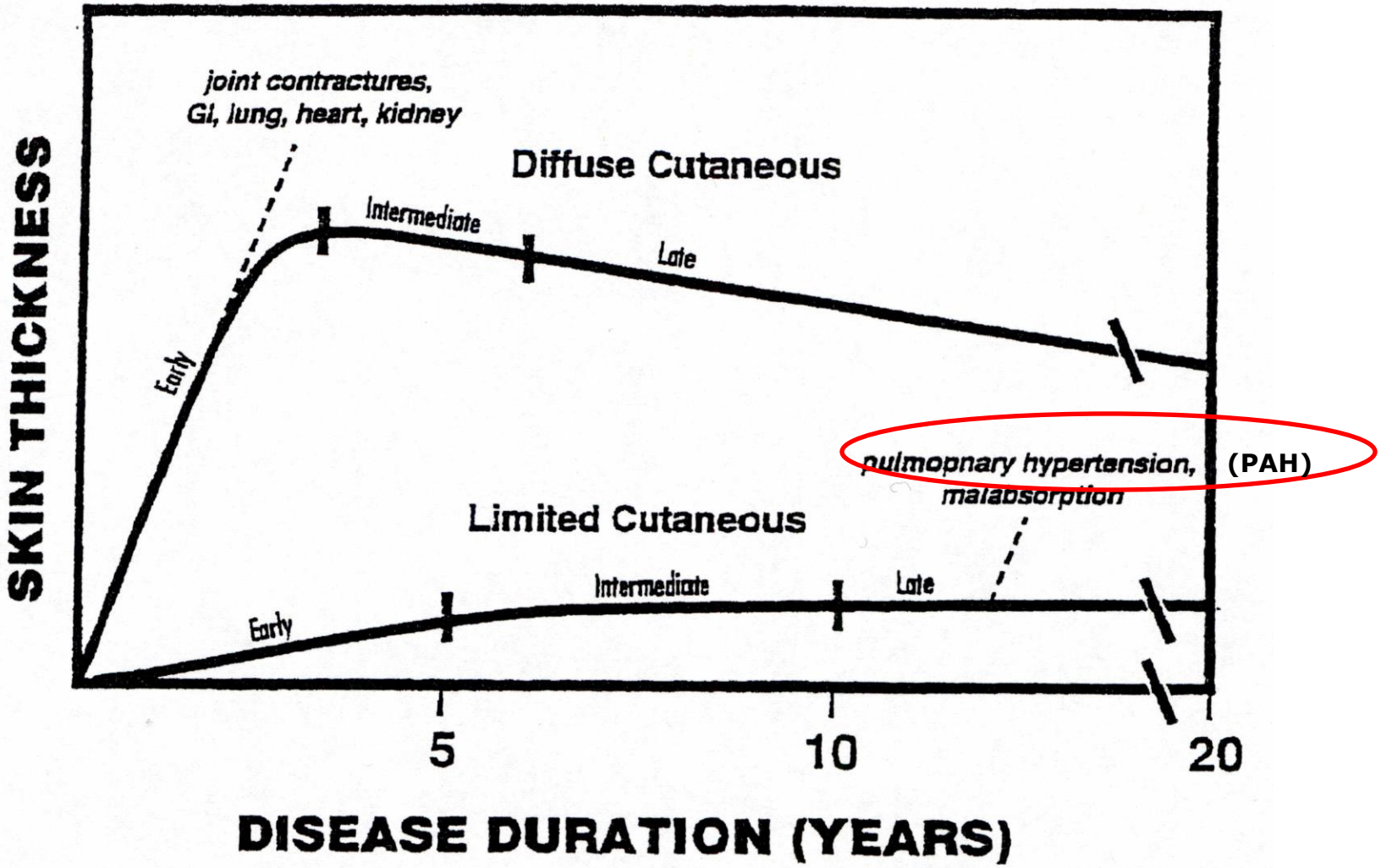

Medsger TA. Rheum Dis Clin N AM 2003; 29: 255

Which SSc-patients are at risk of PAH?

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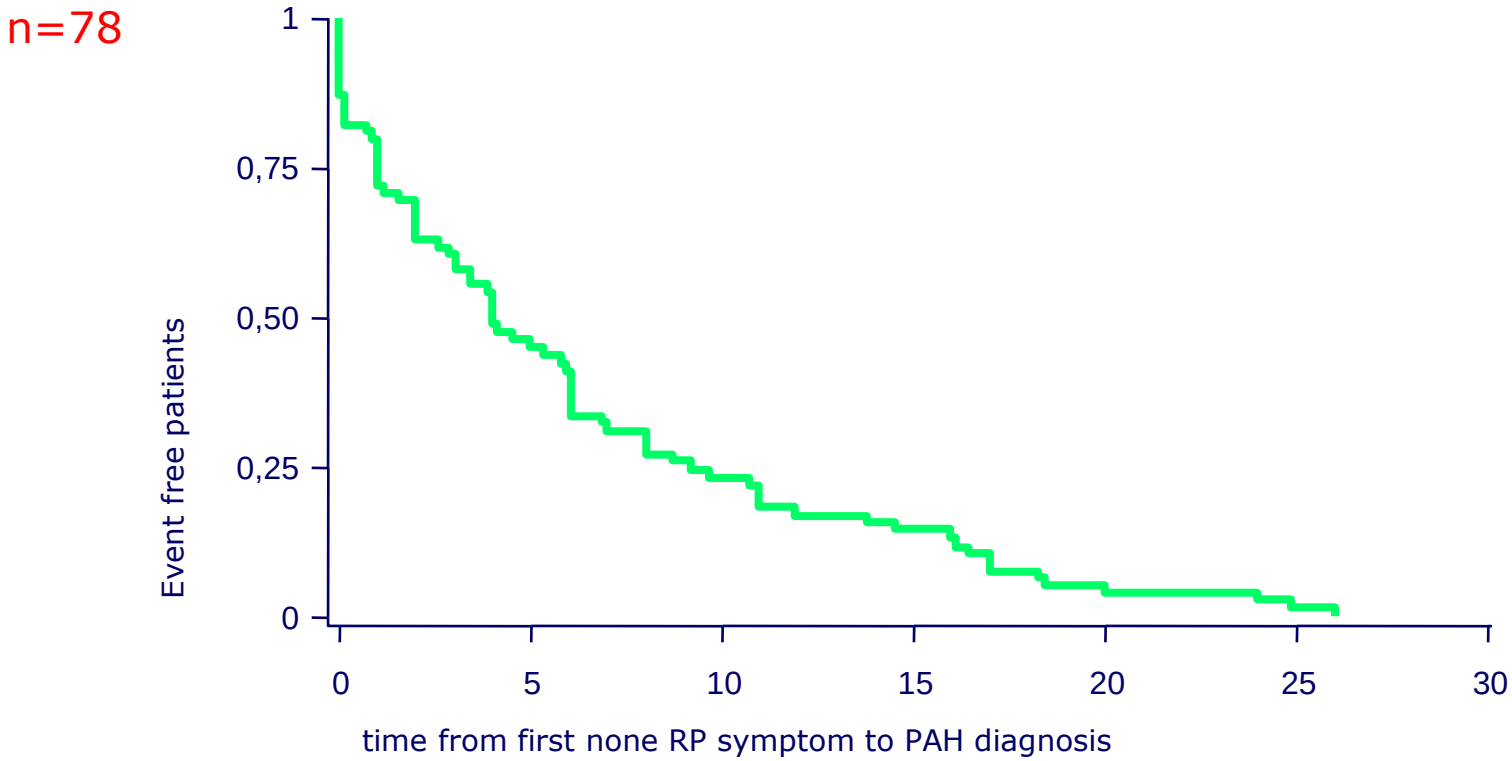


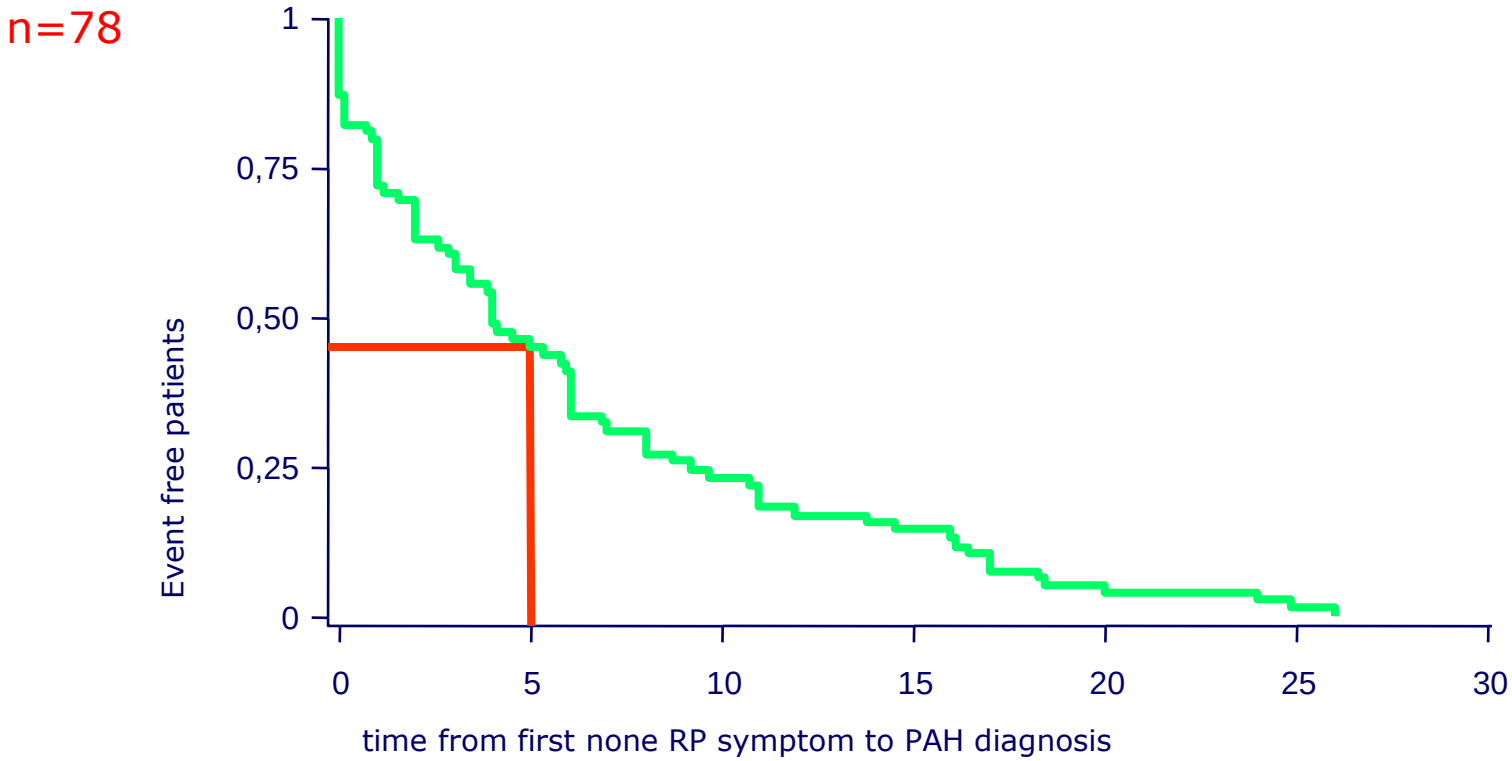
Time (years)	0	5	10	15	20	25	27,5
N at risk	28	36	18	11	4	1	0
events	-	13	6	2	2	2	1

→ 55.1% during the 5 first years
→ 22% dSSc and 78% lSSc

Hachulla E. Chest 2009; 136: 1211

Which SSc-patients are at risk of PAH?

Only late onset in lcSSc patients?



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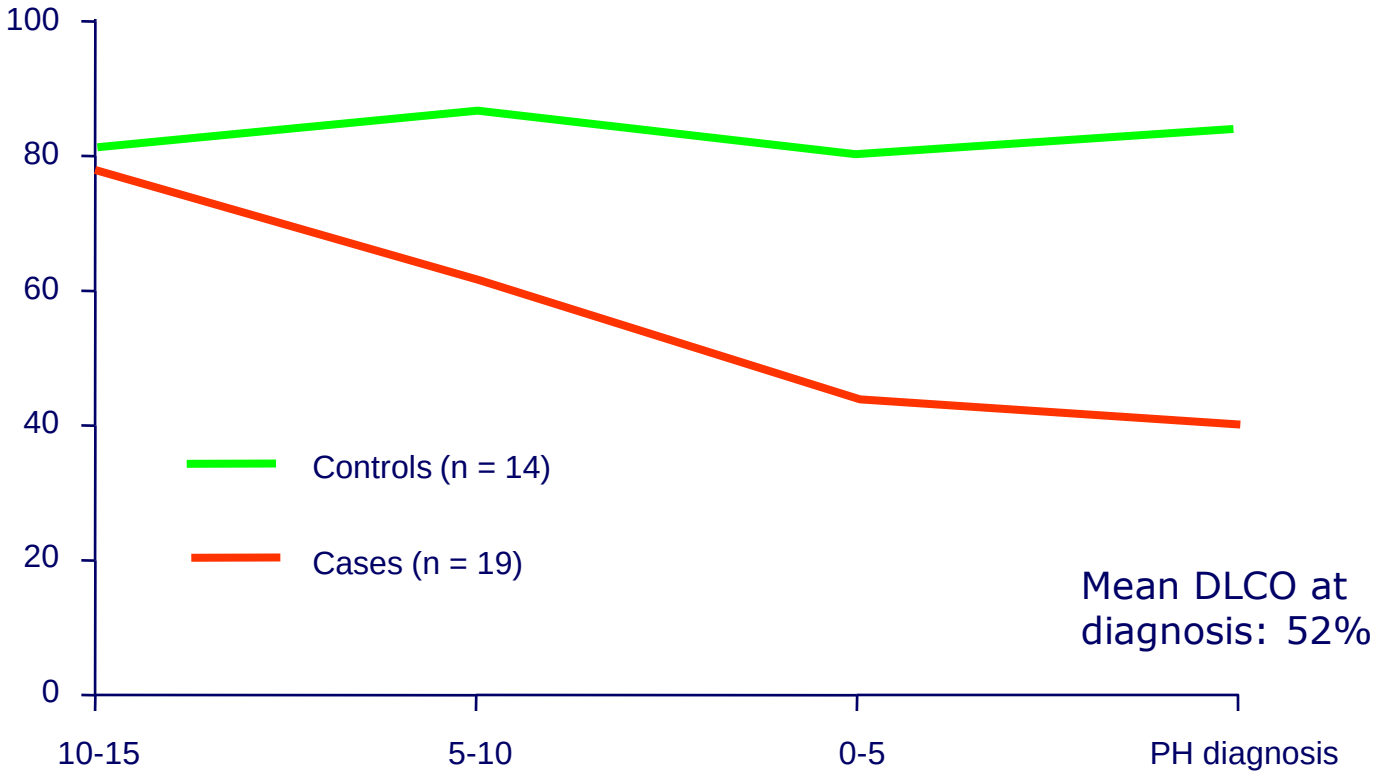
Hachulla E. Chest 2009; 136: 1211

Which SSc-patients are at risk of PAH?

Patients with low DLCO?



Steen V, Medsger TA Jr. Arthritis Rheum 2003 ;48 :516

Which SSc-patients are at risk of PAH?

Patienst with high NT-proBNP?

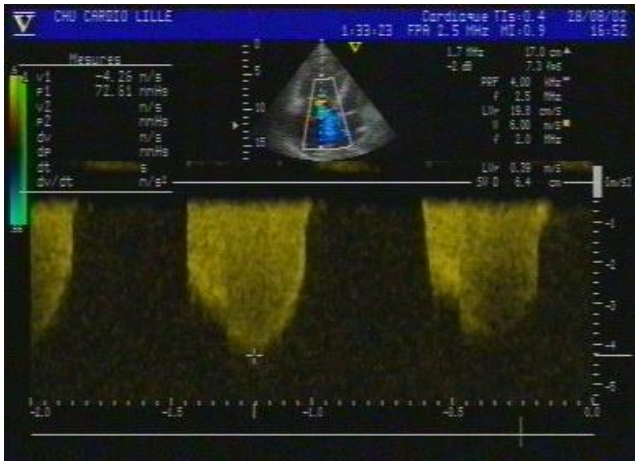
Table 2. Results of univariate and multivariate analyses of candidate predictors of PAH, by model analyzed*

Model, variable	Univariate analysis		Multivariate analysis	
	P	HR (95% CI)	*P*	HR (95% CI)
Main model				
DLCO/VA <70%	0.0043	21.3 (2.5–181.3)	0.014	18.81 (1.7–206.8)
High NT-proBNP	0.0048	10.1 (1.96–51.72)	0.053	6.35 (0.94–82.8)
Systolic PAP >40 mm Hg	0.0078	1.08 (1.63–30.87)	0.54	0.40 (0.02–7.79)
ESR >28 mm/hour	0.015	5.6 (1.35–23.01)	0.15	6.19 (0.49–76.9)

Allanore Y. Arthritis Rheum 2008;58 : 284

How patients should be screened?

Echocardiography: the best screening tool



tricuspid velocity jet (TVJ) = **4.26 m/s**

sPAP = **83** mm Hg

Bernoulli equation: tricuspid insufficiency peak gradient (TIPG) = $4 \times TVJ^2$

sPAP= TIPG + right atrial pressure (RAP) = **4 X 4.26 X 4.26 = 73 + 10 (**estimate **RAP)**

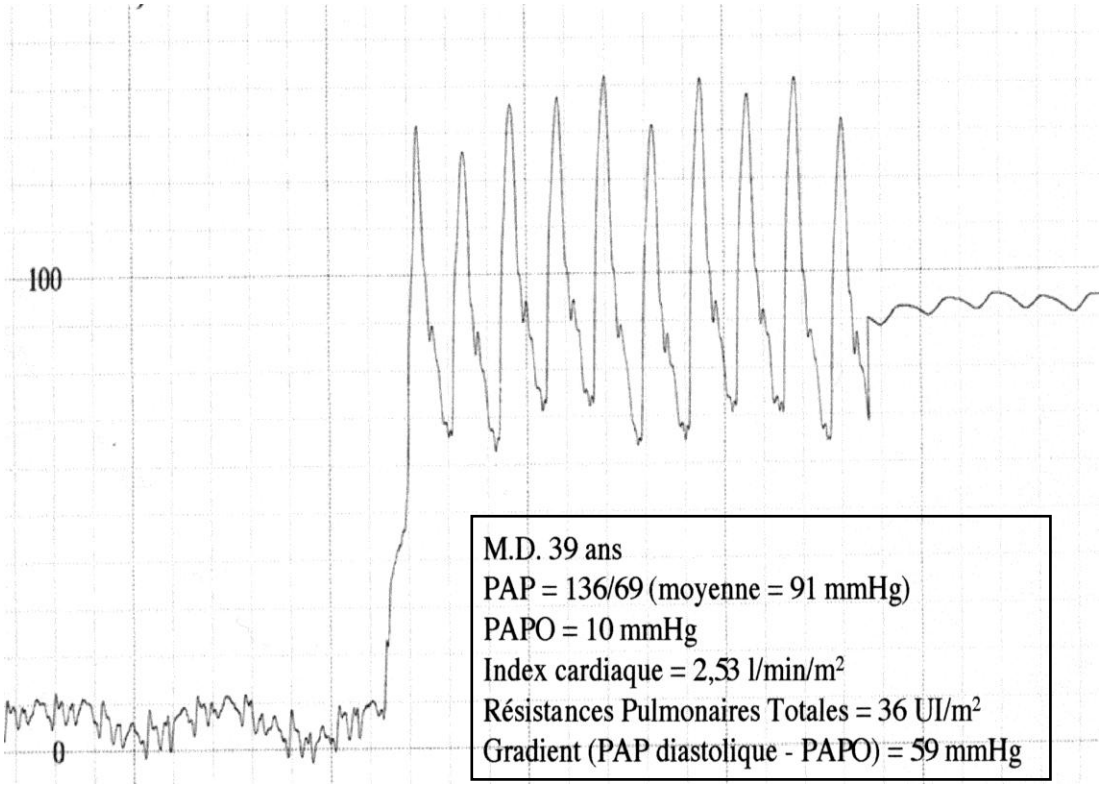
Courtesy P de Groote

Right heart catheterization = diagnostic tool

Hemodynamic definition

- Mean PAP > 25 mmHg at rest

- mPAWP < 15 mmHg



Courtesy Marc Humbert

Doppler echocardiography = screening tool

599 patients (165 dSSc and 434 lSSc)

29 known PAH

screening echocardiography

570 patients

VTR could not be measured: 114*

Not suspected PAH:419

LV diastolic dysfunc:4

Suspected PAH: 33

* no indirect evidence of pulmonary hypertension, since the size of their right heart chambers was comparable with that of the patients with a TJV 2.5 m/second

Hachulla E. Arthritis Rheum 2005; 52: 3792-3800

Right heart catheterization = diagnostic tool

33 with suspected PAH

↓

33 RHC done

Confirmed PAH
18 (54%)

Post capillary PH
(mPAWP > 15) : 3 (10%)

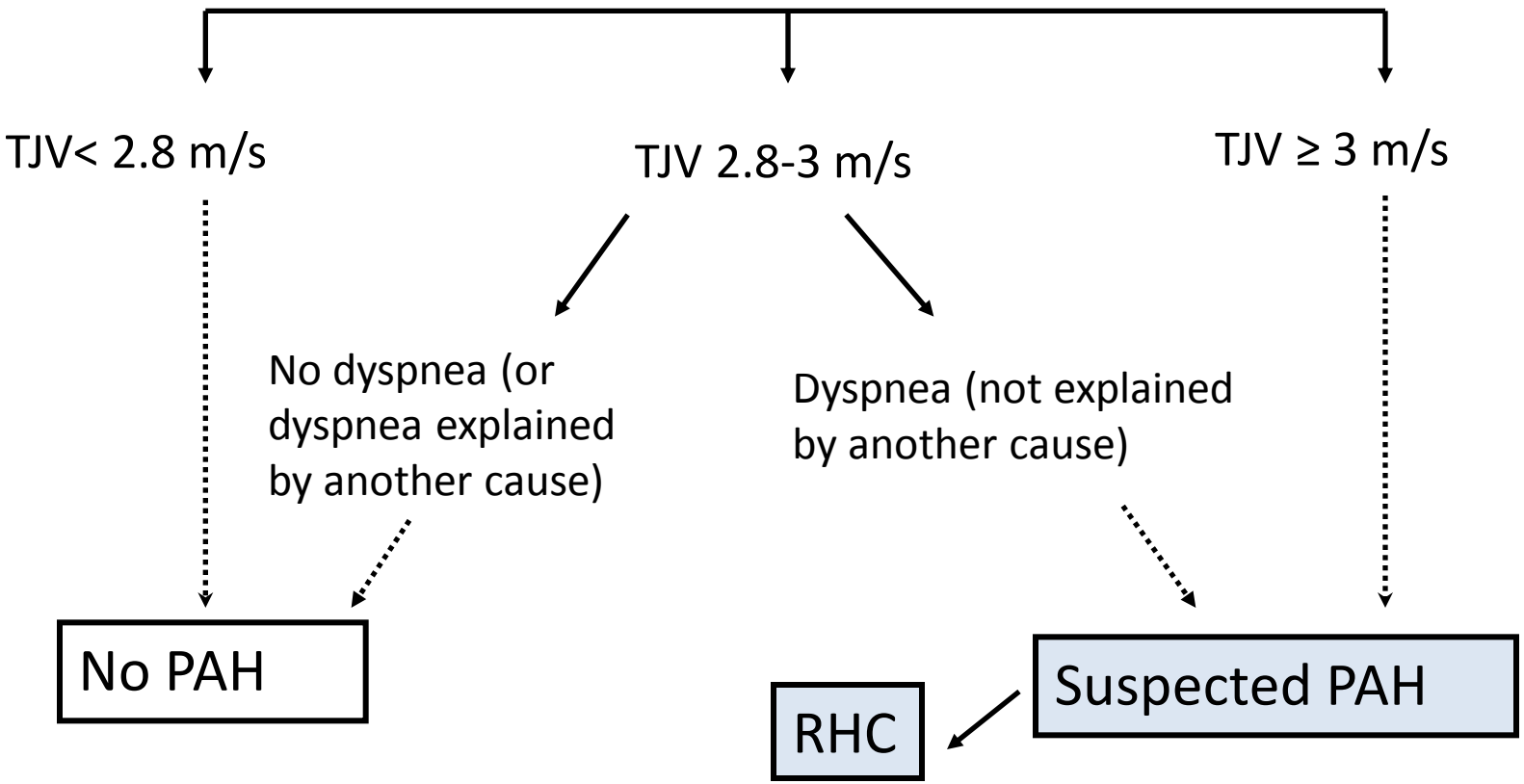
No PAH
12 (36%)

→ Total : 18 new PAH+ 29 known PAH: **prevalence 7.85 %**

Hachulla E. Arthritis Rheum 2005; 52: 3792-3800

Doppler echocardiography = screening tool

SSc patients with no severe pulmonary function abnormalities and no known severe cardiac disease



TJV= tricuspid jet velocity

Hachulla E. Arthritis Rheum 2009; 60: 1831

SSc-PAH incidence

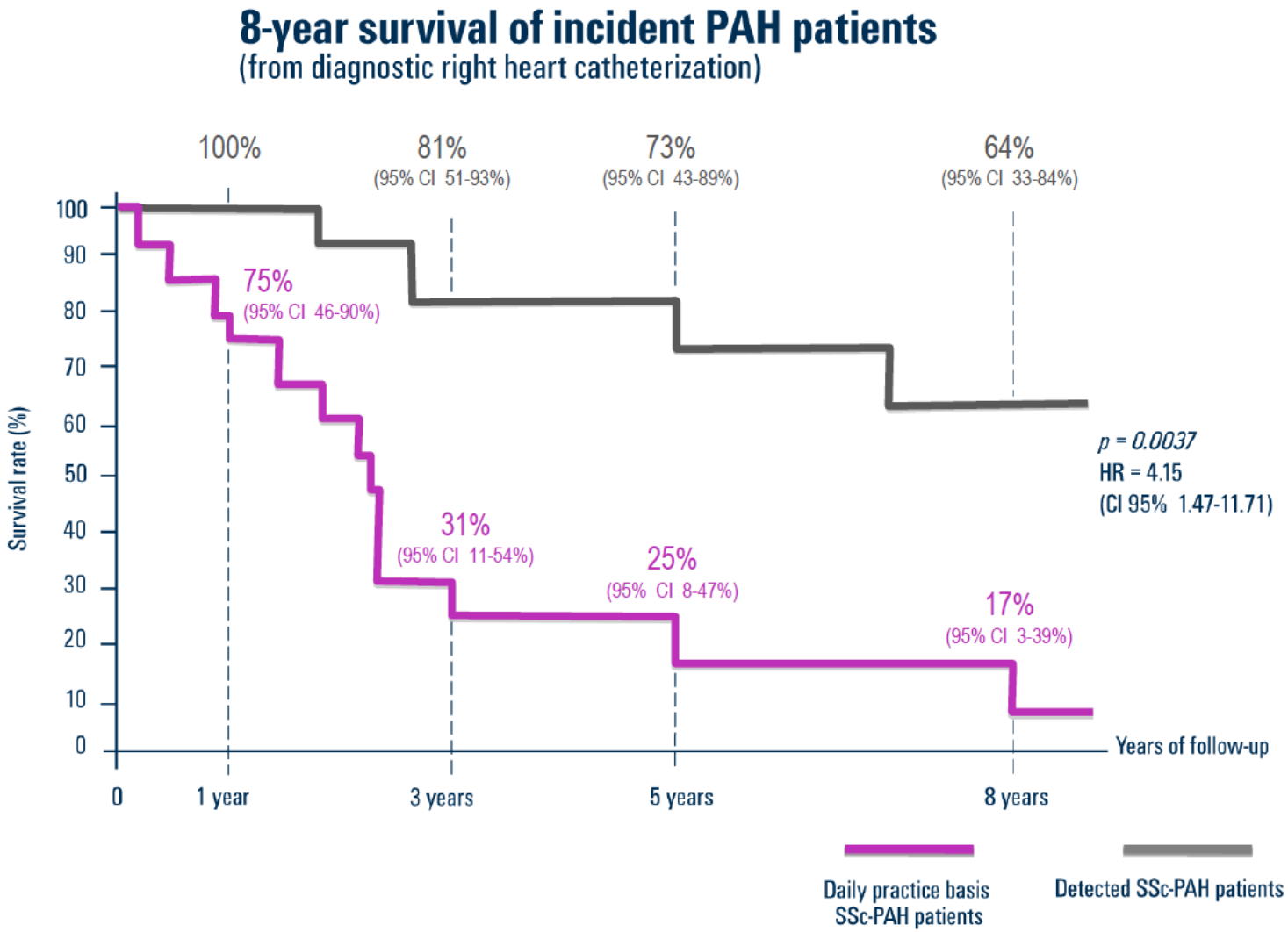
- Mean follow-up : 41.03 ± 5.66 months
- Corresponds to 1,313 patient-years

Forms of PH	Incidence per 100 patient-years [95% CI]
PAH	**0.61 [0.26 – 1.20]**
• Among patients with dSSc	1.25 [0.34 – 3.20]
• Among patients with lSSc	0.40 [0.11 – 1.03]
Postcapillary PH	0.61 [0.26 – 1.20]
PH associated with severe pulmonary fibrosis	0.15 [0.02 – 0.55]
All forms of PH	1.37 [0.74 – 2.00]

Hachulla E. Arthritis Rheum 2009; 60: 1831

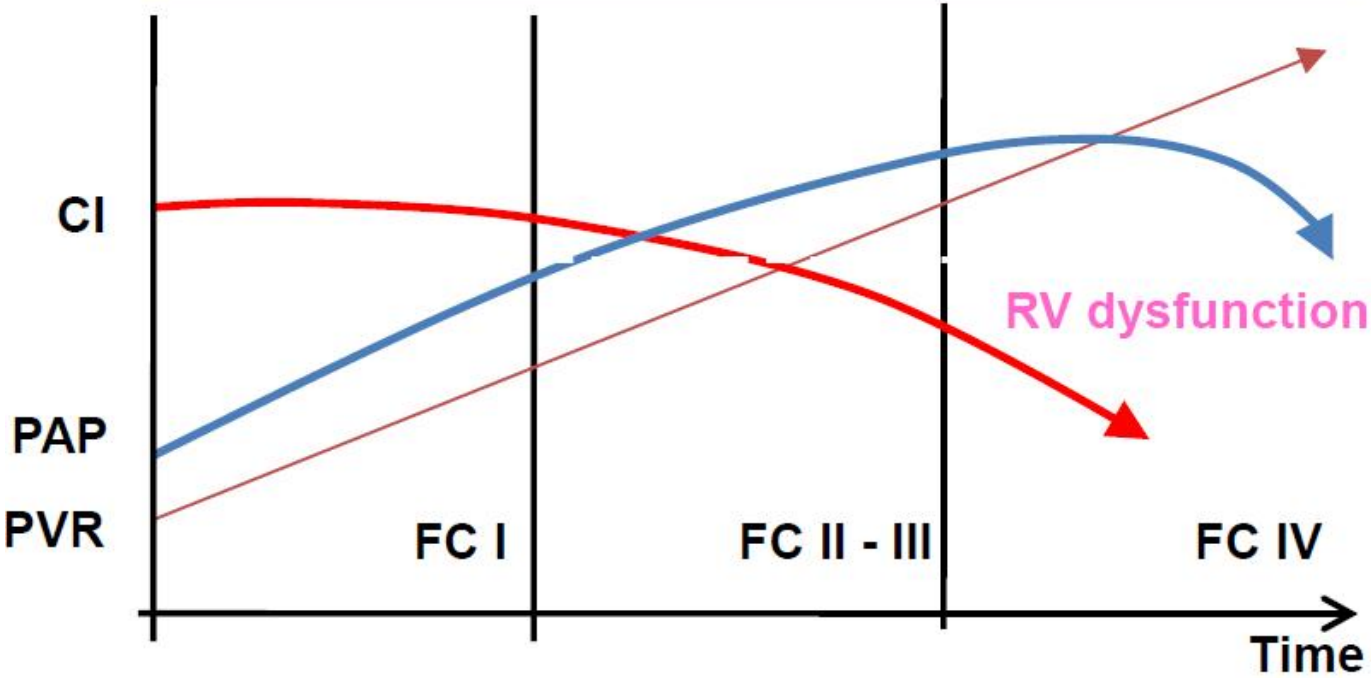
SSc-PAH survival

Detected versus daily practice diagnosed



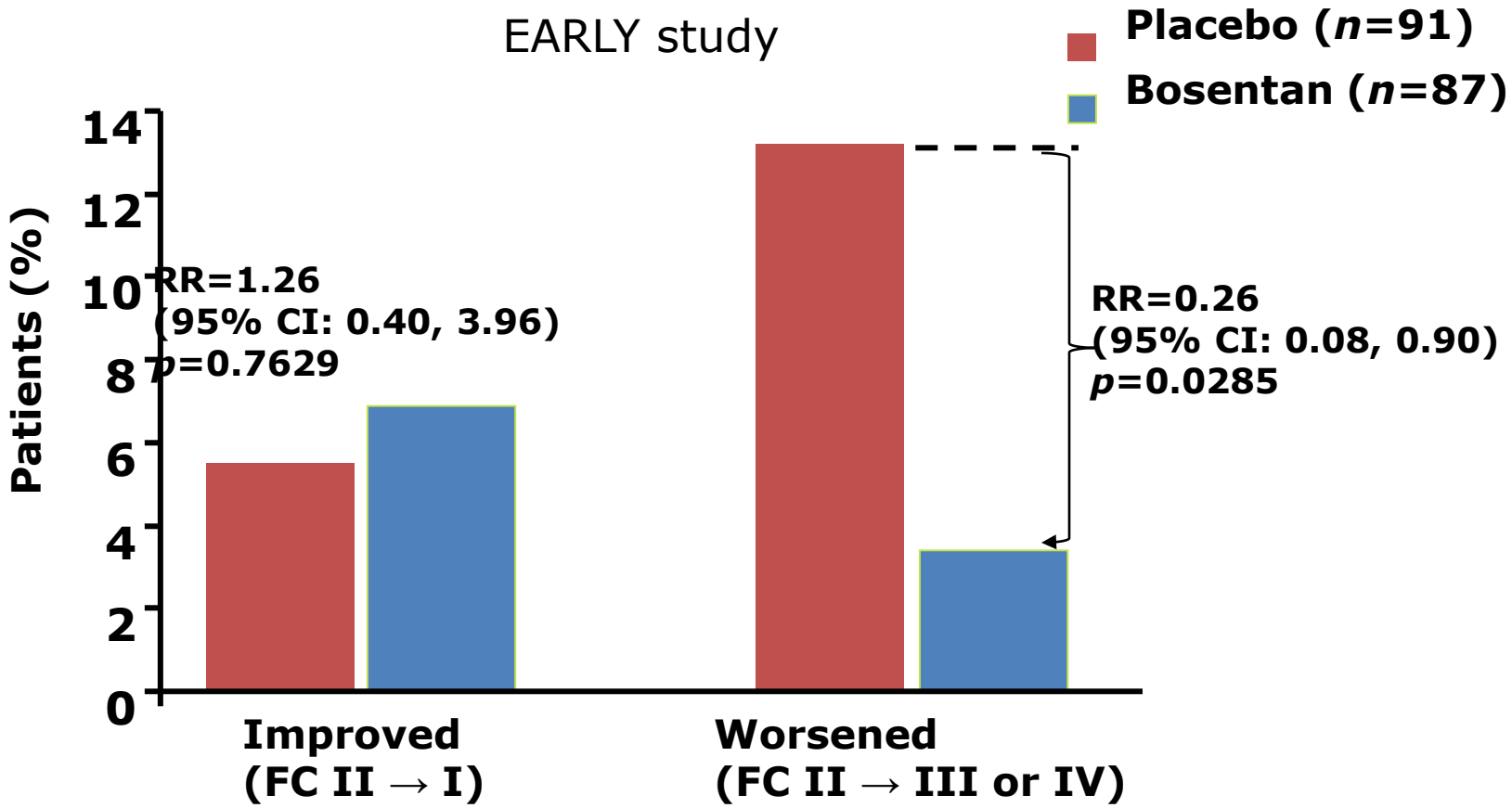
ItinerAIR study

SSC-PAH: natural history



Braunwald E, et al., eds. Harrison's Principles of Internal Medicine. Vol. 2. 15th ed
New York: McGraw-Hill; 2001:1506

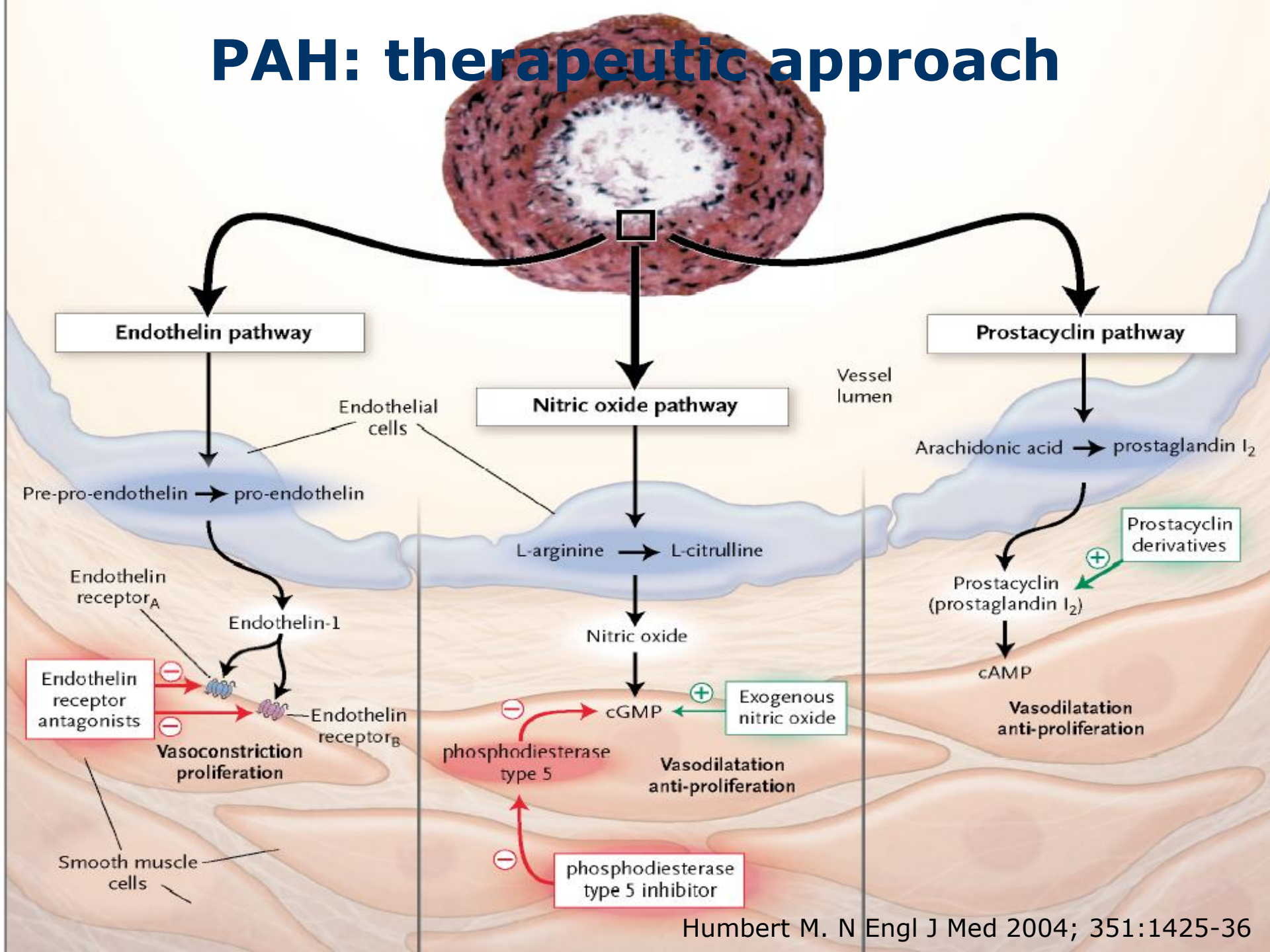
Early PAH diagnosis and early management may improve the prognosis



Effect on NYHA/WHO functional class

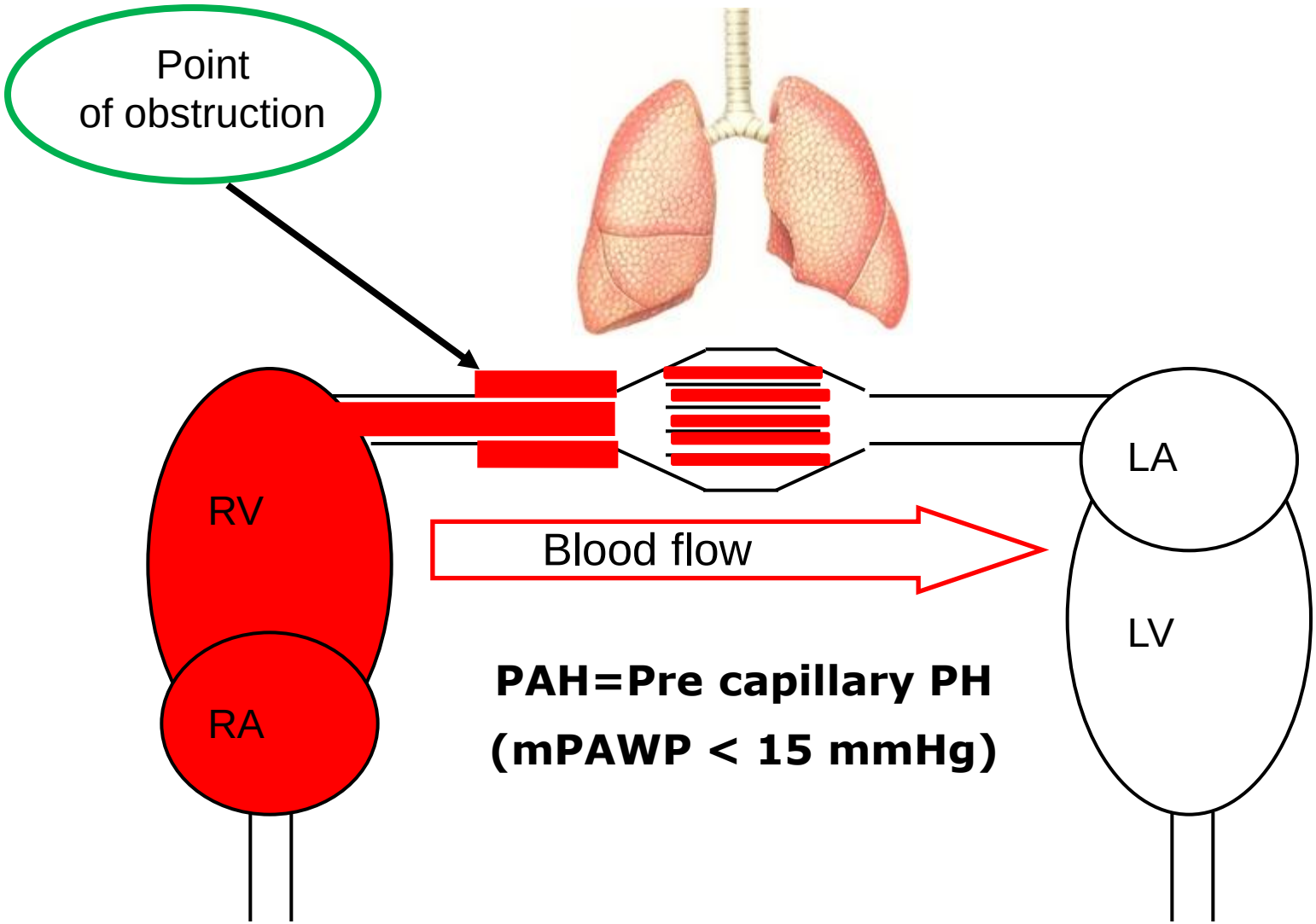
Galiè N et al. Presented at ESC 2007
Galiè N et al. Lancet 2008; 371:2093-100

PAH: therapeutic approach

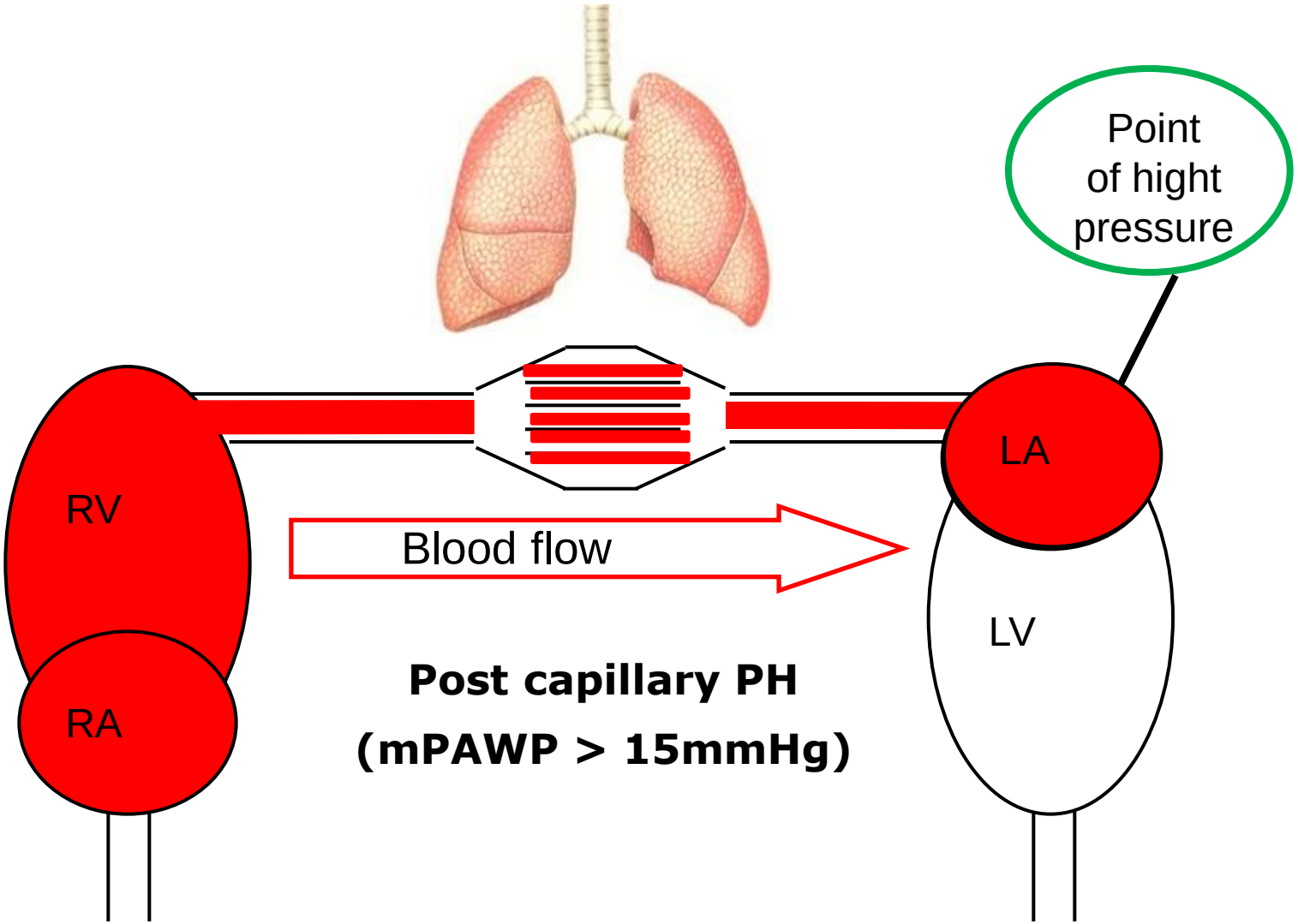


Humbert M. N Engl J Med 2004; 351:1425-36

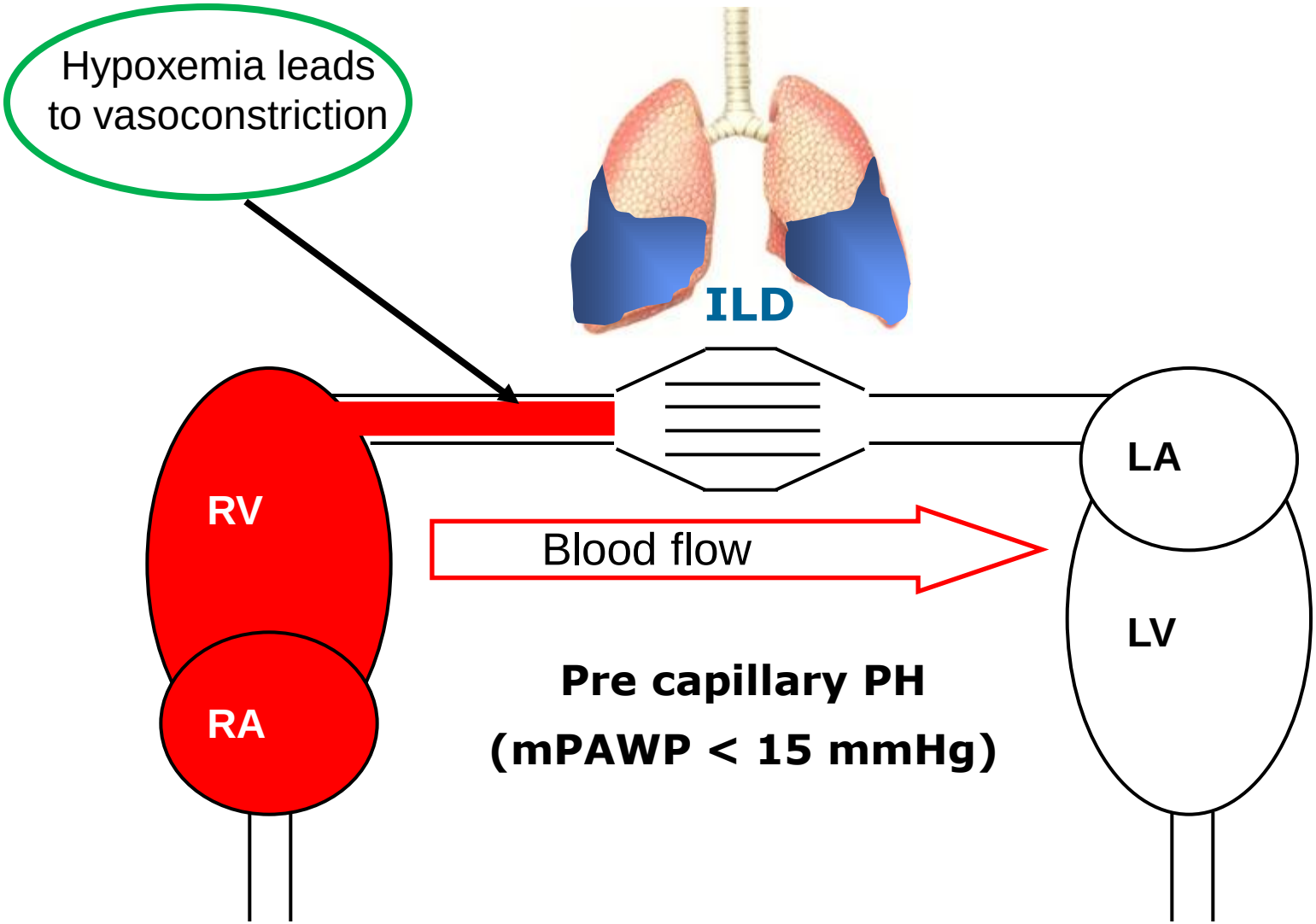
SSc-PAH: scenario 1



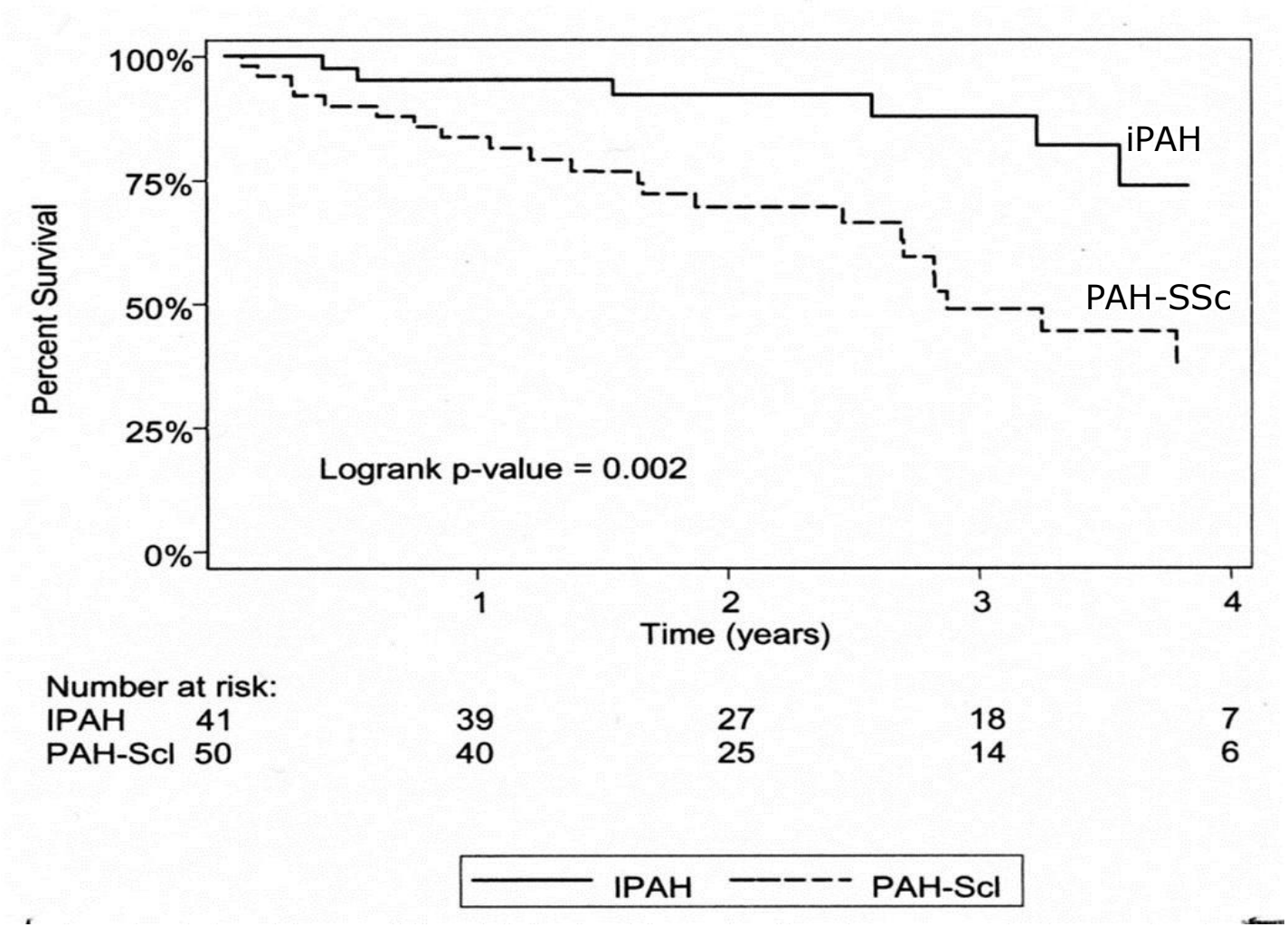
SSc-PH: scenario 2



SSc-PH: scenario 3



PAH-SSc: why such a bad prognosis?



Fisher MR et al. Arthritis Rheum 2006; 54: 3043

PAH-SSc: why such a bad prognosis?

Table 2. Baseline right heart catheterization findings*

	IPAH (n = 41)	PAH-Scl (n = 50)	*P*
Right atrial pressure, mm Hg	10.1 ± 0.9	11.2 ± 0.7	0.36
Pulmonary artery systolic pressure, mm Hg	86.4 ± 2.9	75.6 ± 2.4	0.004
Pulmonary artery pressure, mm Hg	54.4 ± 1.9	46.6 ± 1.5	0.002
Pulmonary capillary wedge pressure, mm Hg	12.0 ± 0.8	11.4 ± 0.7	0.59
Cardiac index, liters/minute/m^2	2.1 ± 0.1	2.2 ± 0.1	0.19
Pulmonary vascular resistance index, Wood units	22.8 ± 1.8	17.5 ± 1.5	0.026

* Values are the mean ± SEM. See Table 1 for definitions.

Fisher MR et al. Arthritis Rheum 2006; 54: 3043

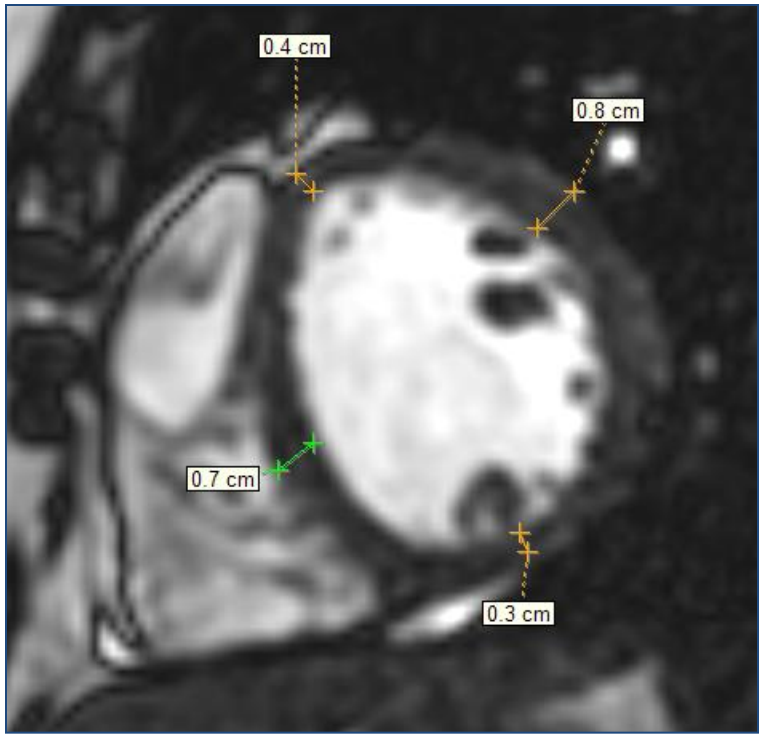
PAH-SSc: why such a bad prognosis?

Table 1. Patients' demographic characteristics and results of functional assessments*

	IPAH (n = 41)	PAH-Scl (n = 50)	*P*
Age, years	47.6 ± 2.4	58.7 ± 1.6	<0.001
Female, no. (%)	35 (85.4)	43 (86.0)	0.93†
Race, no. (%)			
White	32 (78.0)	42 (84.0)	0.67†
African American	7 (17.1)	7 (14.0)	–
Hispanic	2 (4.9)	1 (2.0)	–
Body mass index, kg/m^2	29.4 ± 1.4	27.2 ± 1.0	0.20
Limited scleroderma, no. (%)	–	46 (92.0)	–
History of systemic hypertension, no. (%)	14 (34.1)	20 (40.0)	0.57†

Fisher MR et al. Arthritis Rheum 2006; 54: 3043

PAH-SSc: why such a bad prognosis?

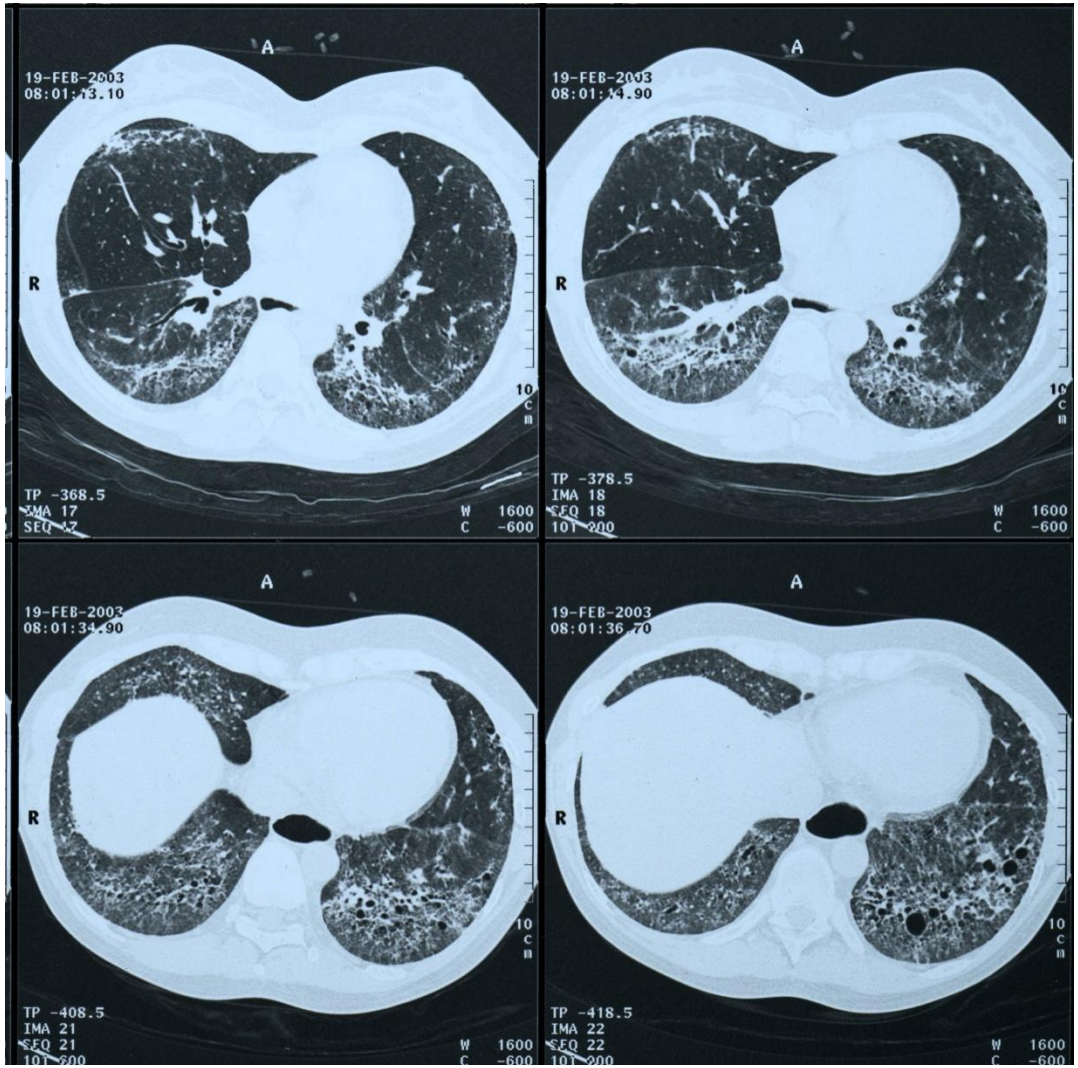


Localized thinning of LV in 29%

Increased signal intensity in T2 in 12%

Hachulla AL. Ann Rheum Dis 2009; 68: 1878

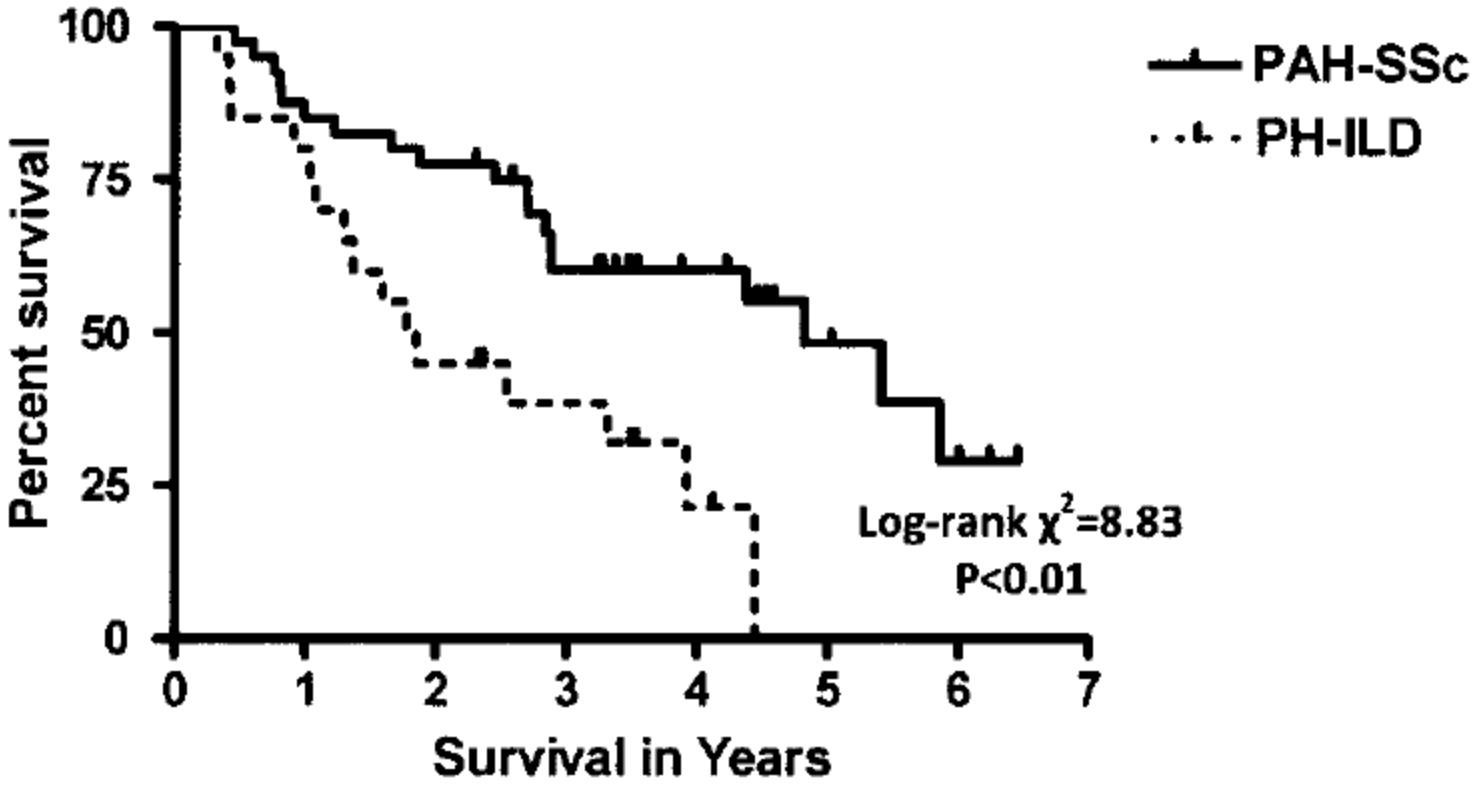
PAH-SSc: why such a bad prognosis?



- ILD: >60%
- TLC<70% risk of PH
- PH owing to ILD:

  - Generally mild =mPAP <35 mm Hg
  - Sometimes « out-of-proportion»

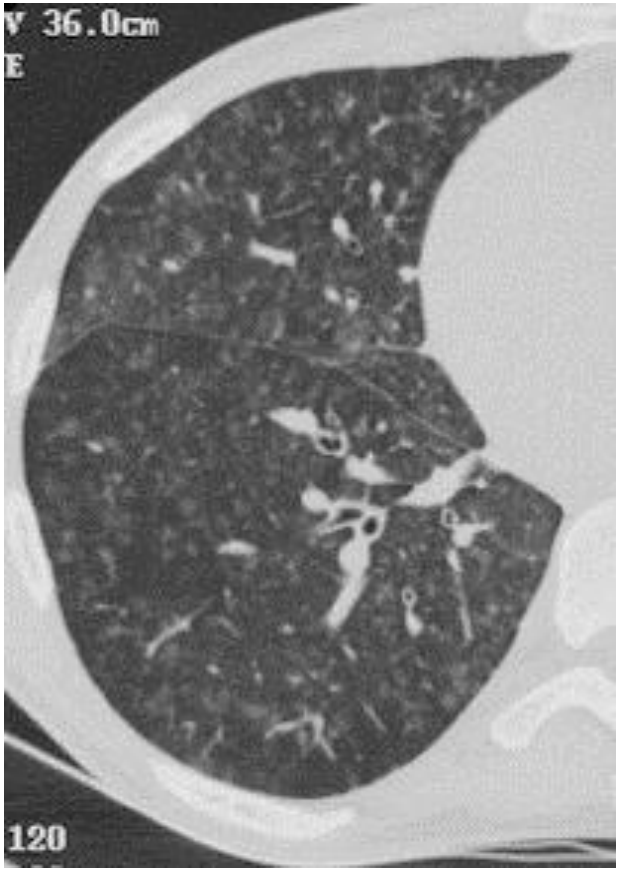
PAH-SSc: why such a bad prognosis?

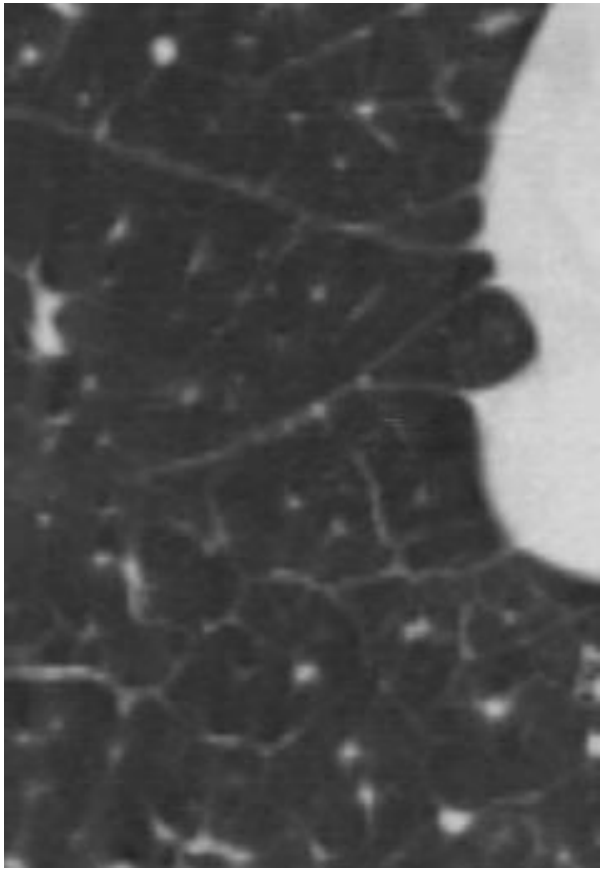


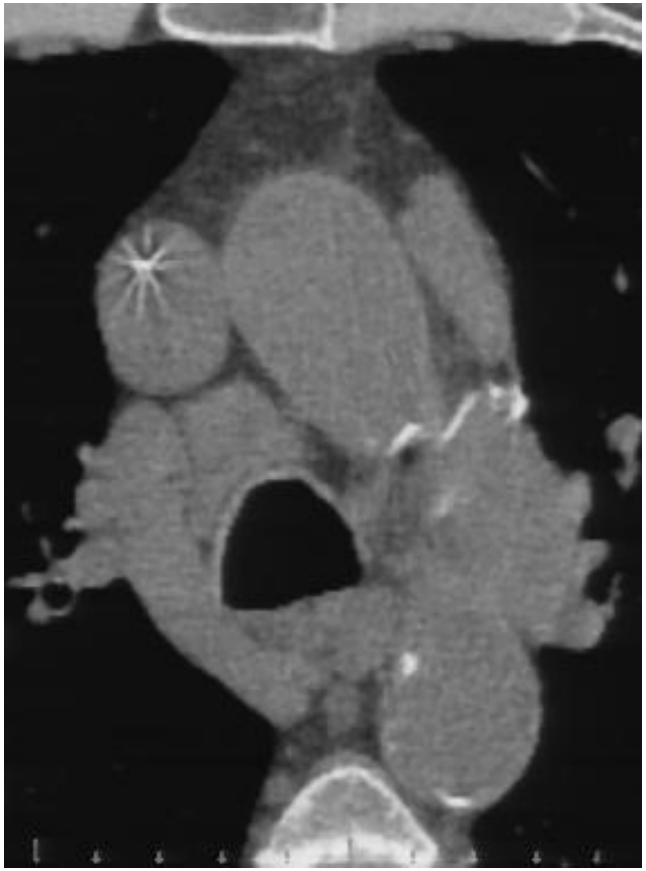
Mathai SC. Arthritis Rheum 2009; 60: 569

Veno-occlusive disease?

- HRCT scan: - septal thickening
  - intralobular ground glass opacities
  - pleural and pericardial effusion
  - Intrathoracic lymph nodes







Resten A. AJR 2004;183:65-70

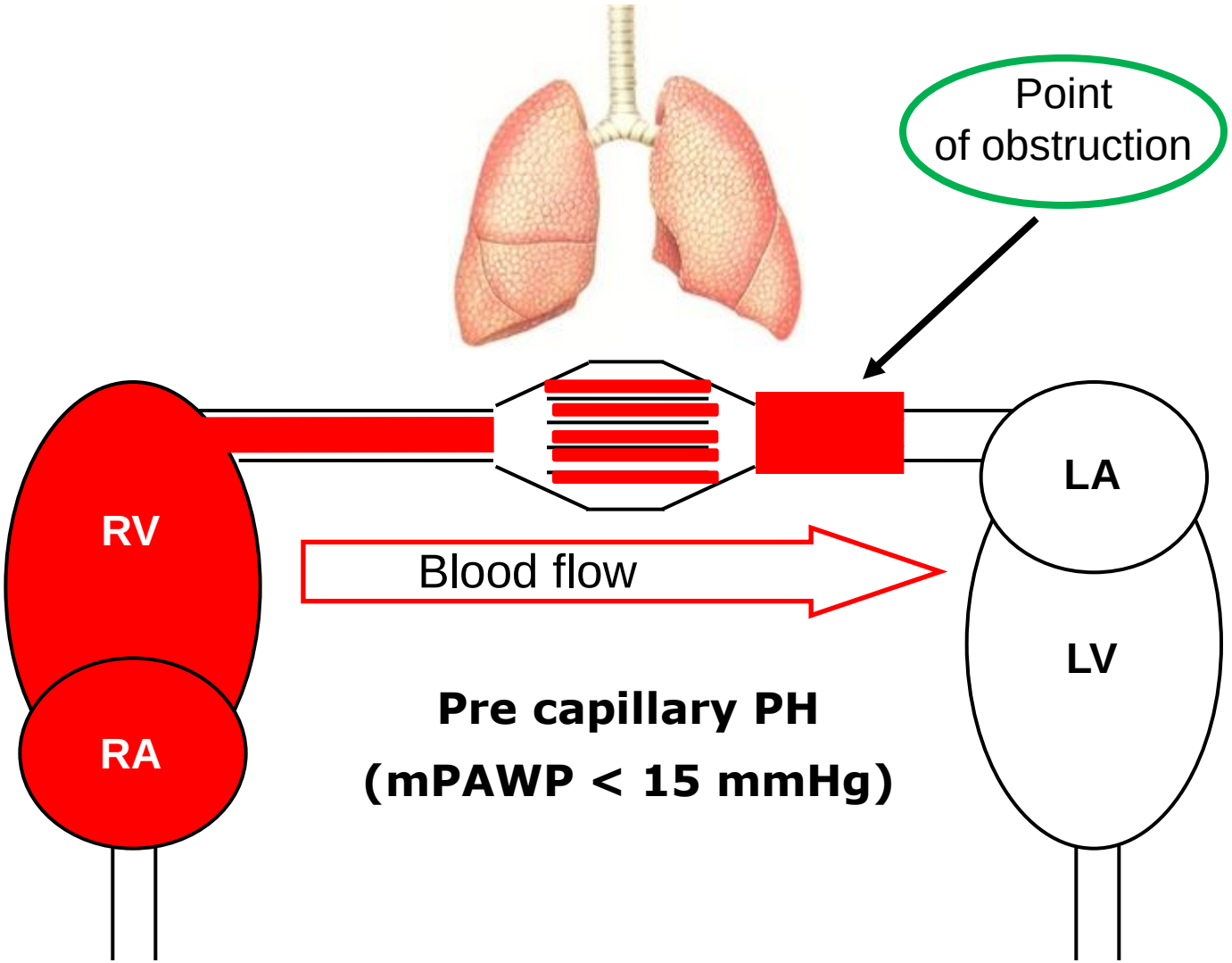
Veno-occlusive disease in PAH-SSc

Table 1 Overview of patients, disease, samples, and primary histologic findings

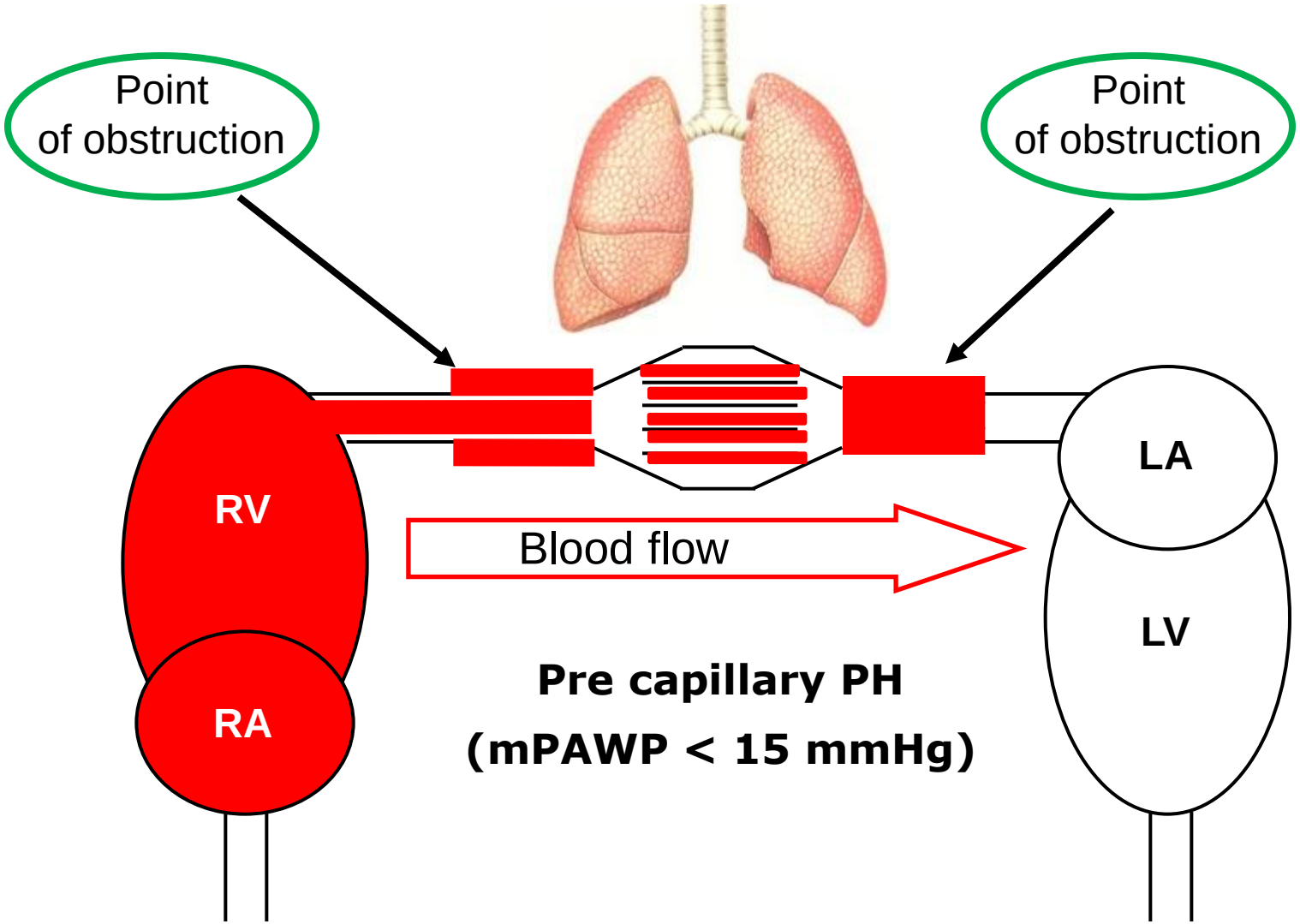
Patient	Sex/age (y)	CTD	Lung sample	Vascular lesions	Interstitial disease	Capillary congestion
1	Male/64	Limited SSc	Autopsy	Preseptal veins/ muscular arteries	Bronchiolitis	Edema/angiectasia
2	Female/51	Limited SSc	Lung transplantation	Preseptal veins/ muscular arteries	NSIP/bronchiolitis	Edema/angioproliferation
3	Female/69	Limited SSc	Autopsy	Preseptal veins/ muscular arteries	NSIP	Angioproliferation
4	Male/67	Limited SSc	Autopsy	Preseptal veins/ muscular arteries	UIP	Hemorrhagic edema/ angioproliferation
5	Female/46	SLE	Autopsy	Preseptal veins/ muscular arteries	No	Hemorrhagic edema/ angioproliferation
6	Female/24	SLE	Lung transplantation	Muscular arteries	No	No
7	Female/55	Mixed CTD	Lung transplantation	Muscular arteries	NSIP	Hemorrhagic edema/ angiectasia
8	Female/58	Rheumatoid arthritis	Autopsy	Preseptal veins/ muscular arteries	No	Hemorrhagic edema/ angioproliferation

Dorfmüller P. Hum Pathol 2007; 38: 983

SSc-PH: scenario 4



SSc-PH: scenario 4



PAH-SSc: how to improve the prognosis?

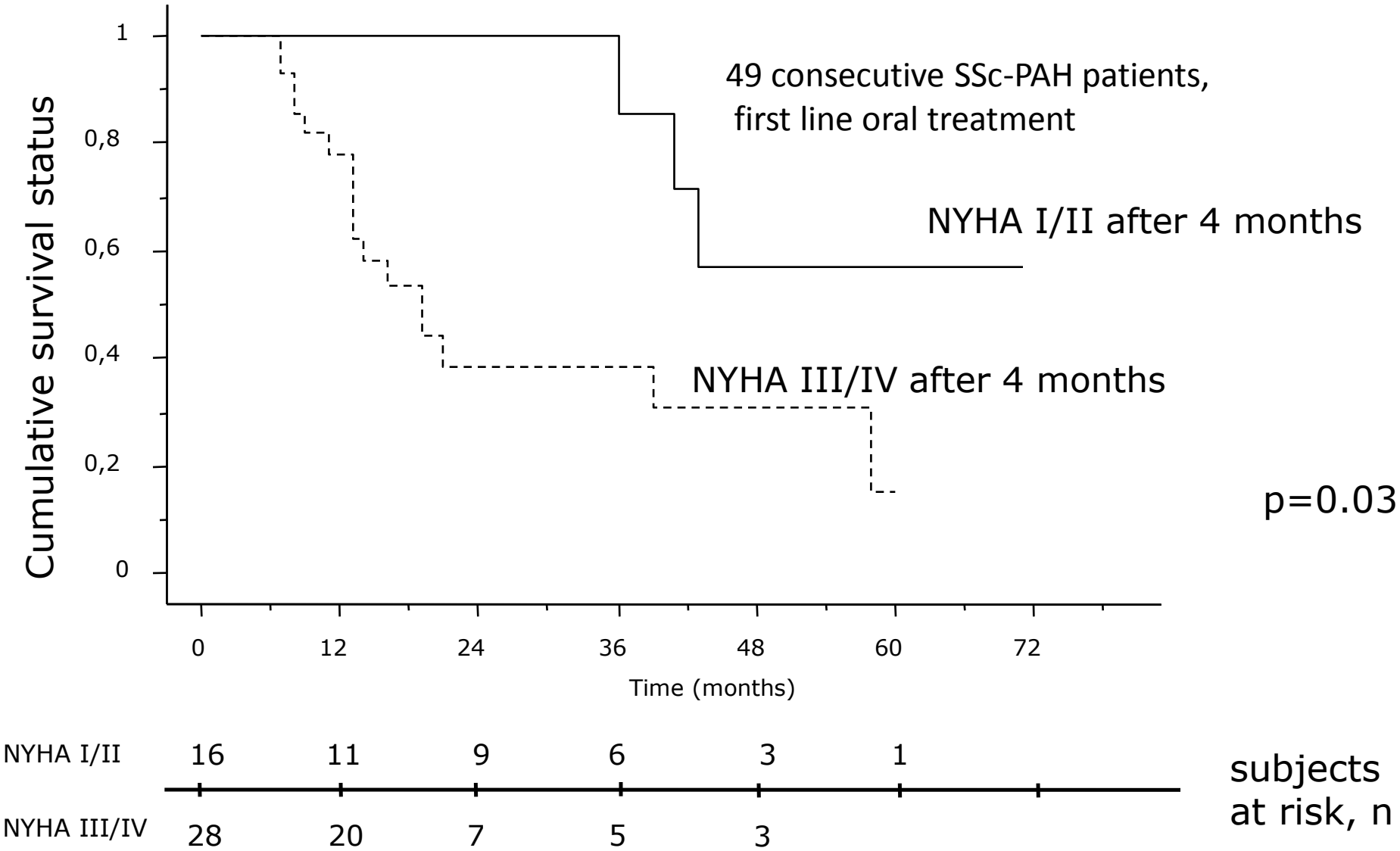
Goal-oriented therapy

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

→ Assessment should be performed at baseline and after 4 to 6 months of first-line treatment

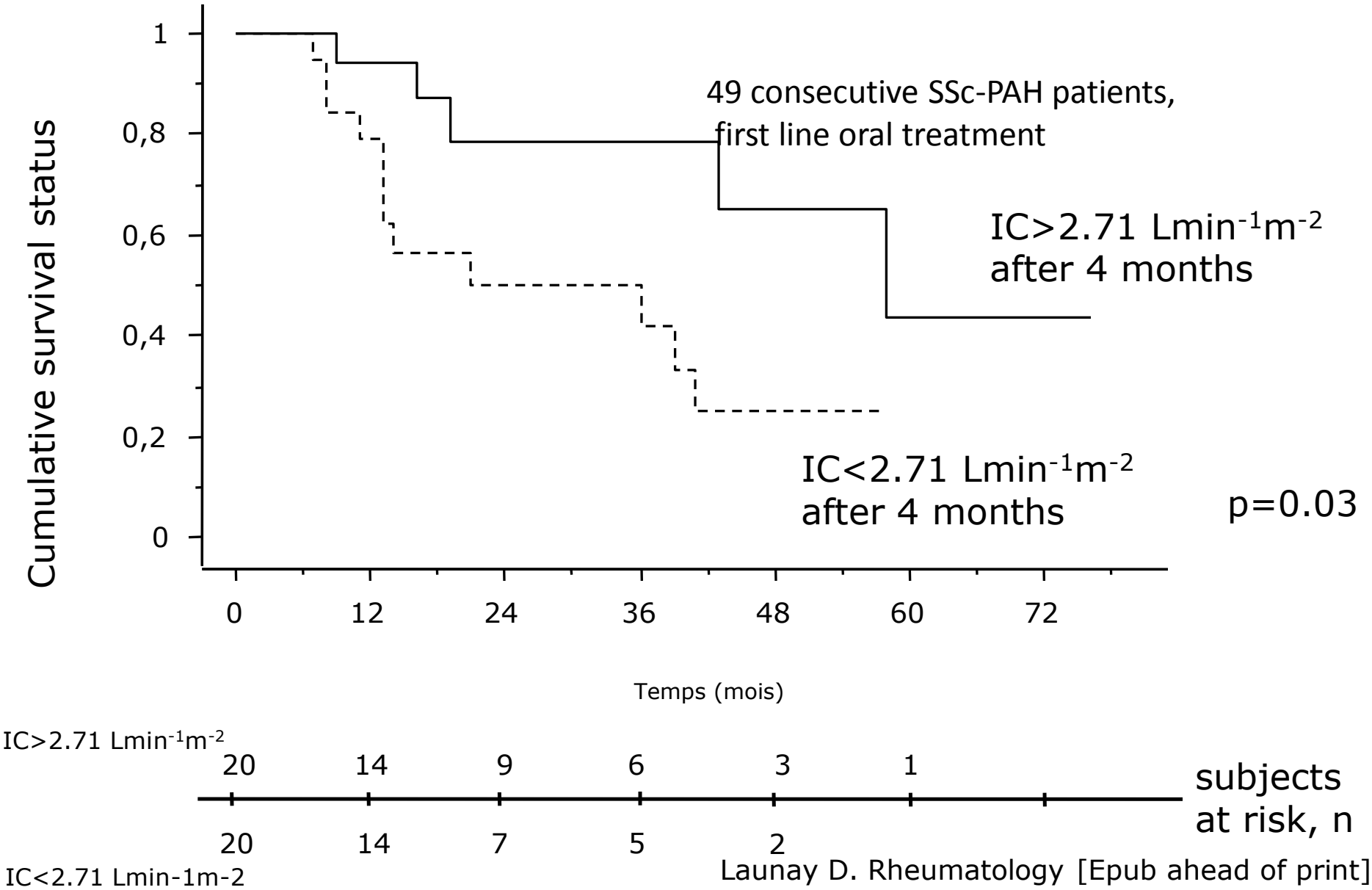
ESC-ERS guidelines ERJ 2009

PAH-SSc: a goal oriented therapy is needed



Launay D. Rheumatology [Epub ahead of print]

PAH-SSc: a goal oriented therapy is needed



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Take home messages

- ✓ **10% of SSc patients suffer from PAH**
- ✓ **DLCO is useful for identifying SSc patients at risk of PAH**
- ✓ **Echocardiography is the best screening tool**
- ✓ **RHC is mandatory for the diagnosis of PAH**
- ✓ **Keep in mind the different PH scenario**
- ✓ **Early detection and early intervention may improve survival**
- ✓ **A goal oriented therapy is needed**