LUNG IN SYSTEMIC SCLEROSIS
WHAT ARE THE ISSUES ?

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Conflict of interests

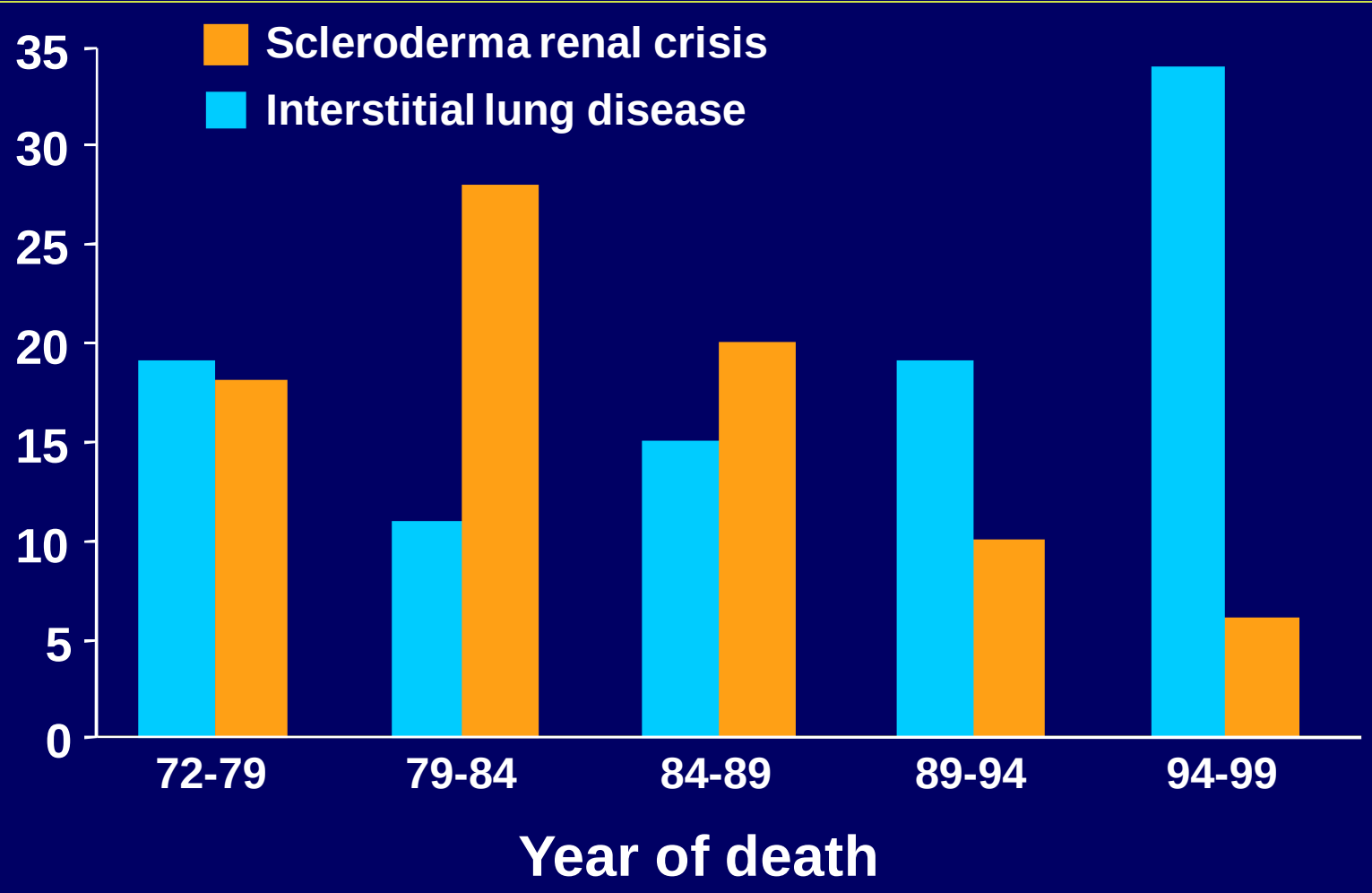
- Consultant for Actelion Pharma

Lung manifestations in Systemic Sclerosis

- **Infiltrative lung disease**
- **Pulmonary arterial hypertension**

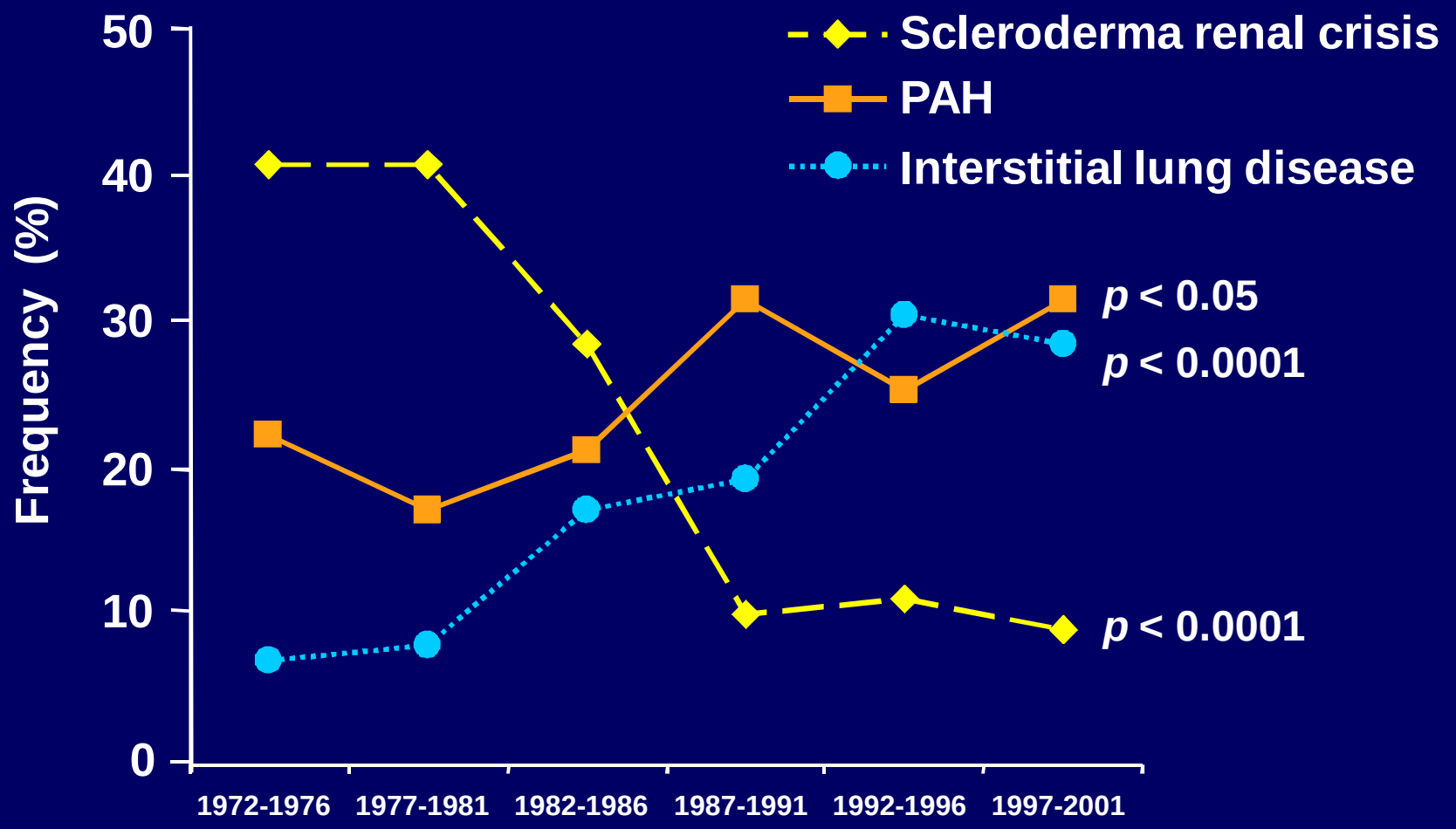
- Pneumonia due to inhalation
- Pleural effusion
- Pneumothorax
- Drug-induced pneumonia
- Pneumoconiosis
- Lung cancer

Causes of death have changed over time



Steen VD, *et al. Arthritis Rheum* 1994;37:1283-89.

Lung diseases are the first cause of death



Steen VD and Medsger TA. *Ann Rheum Dis* 2007; 66:940-4.

Lung manifestations in Systemic Sclerosis

- **Two different types of lung fibrosis**
- Usual interstitial pneumonia (UIP)
  - progressive impairment
  - Weak response to treatment
- Non specific interstitial pneumonia (NSIP)
  - Very slow impairment
  - Response to immunosuppressants

Lung fibrosis: frequent or rare ?

- ✓ 75 % when biopsies are systematically performed (or autopsies)
- ✓ 25 % according to clinical symptoms and CT scann
- ✓ 44% of deaths related to SSc

Epidemiology of lung fibrosis in SSc

- **EUSTAR registry (*EULAR Scleroderma Trials And Research*)**
  3 656 patients

	Diffuse	Limited	Scl-70	Centromère
Fibrosis	**53.4 %**	**34.7 % ***	**60.2 %**	**21.3 % ***
PAH	**22.3 %**	**20.5 % ***	**23.2 %**	**22.0 %**
PAH without ILD	5.9 %	9.2 % *	5.0 %	13 % *
PH with ILD	15.8 %	11.0 % *	17.2 %	8 % *

* $p < 0,05$

Walker *et al.* Ann Rheum Dis 2007

Lung fibrosis and auto-antibodies

Table 2. Frequency of pulmonary fibrosis (PF) in systemic sclerosis (SSc) patients followed at the University of Pittsburgh from 1982–2004, according to the presence of different SSc-associated serum autoantibodies, compared with SSc patients in this study*

SSc-associated autoantibody	PF frequency	*P* vs. U11/U12
U11/U12 RNP	23/33 (70)	
Centromere	59/436 (14)	< 0.0001
Ku	6/14 (43)	NS
PM-Scl	27/65 (42)	< 0.009
RNA polymerase III	63/343 (18)	< 0.0001
Th/To	47/121 (39)	< 0.002
Topoisomerase I	204/425 (48)	< 0.02
U1 RNP	36/123 (29)	< 0.0001
U3 RNP	16/84 (19)	< 0.0001

* Values are number/total number of antibody-positive patients (percentage). Overlap patients are excluded; no patient had more than 1 SSc-associated autoantibody. NS = not significant.

Fertig *et al.* Arthritis Rheum 2009

Progressive Systemic Sclerosis *Sine* Scleroderma

Gerald P. Rodnan, M.D., and Robert H. Fennell, Jr., M.D., Pittsburgh

Four patients, a man aged 51 and 3 women aged 59, 69, and 71, died of progressive systemic sclerosis and yet had minimal or no evidence of cutaneous disease (scleroderma). In addition to illus-

developed fatal, systemic sclerosis without clinical or pathological evidence of scleroderma, in whom the diagnosis of P.S.S. was established only after postmortem examination revealed a characteristic pattern of visceral lesions. The cutaneous disease in

Rodnan et Fennell. JAMA 1962

ILD in the context of undifferenciated CTD

- **Underdiagnosed CTD in patients with ILD**
  - **17 / 160 pts, including 1 SSc (Johns Hopkins, Baltimore) [1]**

- **CTD occuring during ILD follow up**
  - **8 / 83 with « idiopathic » NSIP, including 2 SSc [2]**

(1) Mittoo *et al. Respir Med* 2009
(3) Kinder *et al.* Am J Respir Crit Care Med 2007
(4) Kinder *et al. Lung* 2010
(2) Park *et al.* Am J Respir Crit Care Med 2009
(5) Fischer *et al. Chest* 2010

ILD in the context of undifferenciated CTD

- **28 patients with ILD and undifferientiated CTD :**
  - **Women > male,**
  - **Groud glass and NSIP *vs* UIP [3]**
- **Better outcome than idiopathic ILD [4]**

(1) Mittoo *et al. Respir Med* 2009
(3) Kinder *et al.* Am J Respir Crit Care Med 2007
(4) Kinder *et al. Lung* 2010
(2) Park *et al.* Am J Respir Crit Care Med 2009
(5) Fischer *et al. Chest* 2010

Characteristics of Scleroderma sine scleroderma

- Raynaud's or DU or megacapillaries
  1. Antinuclear antibodies
  2. One of the following : oesophagal symptoms, lung fibrosis, PAH, SRC, cardiac insufficiency
  3. No identification of another CTD
- Exertion dyspnea [1]

(1) Poormoghim *et al.* Arthritis Rheum 2000
(2) Hachulla et Launay. Clinic Rev Allerg Immunol 2010
(3) Fischer *et al.* Chest 2006
(4) Fischer *et al.* J Rheumatol 2006

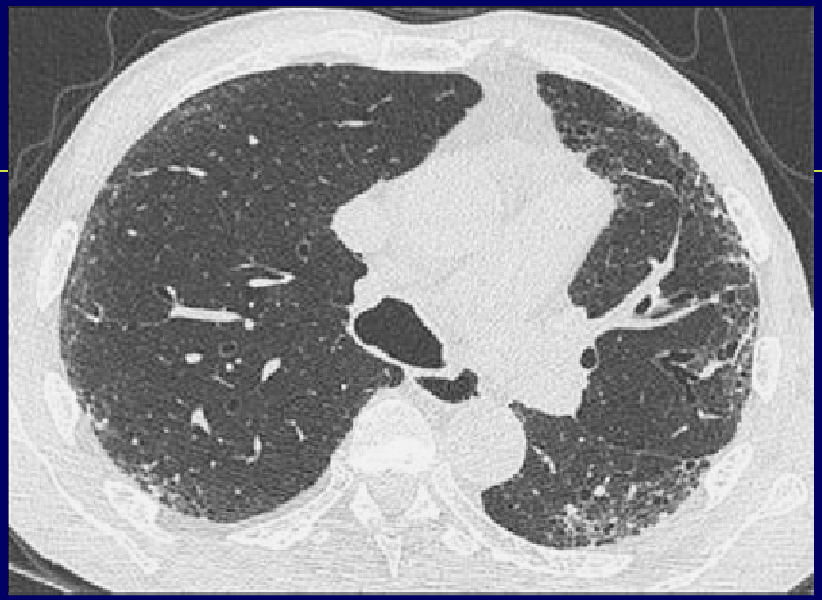
ILD, oesophagal reflux and inhalation

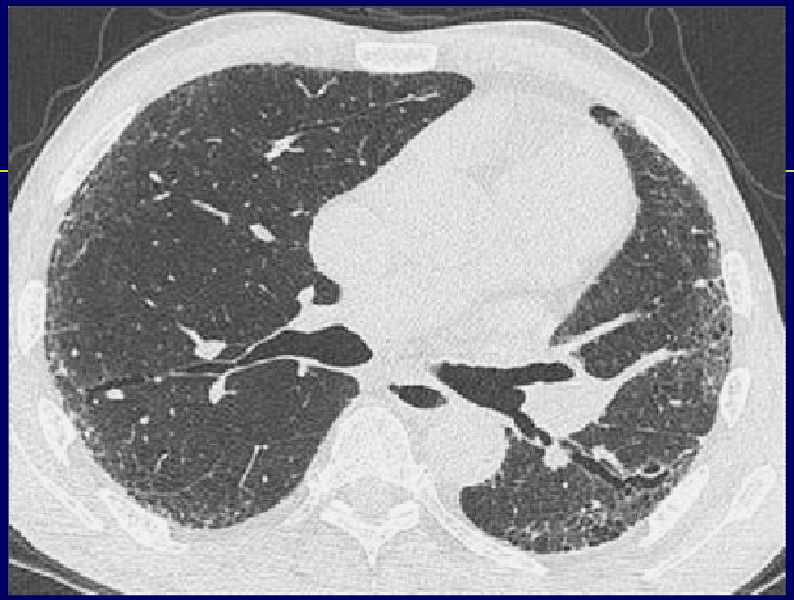
- **Autopsy findings and animal studies [2] [3]**
- **Lung function studies (3,4)**
- **Link between reflux severity and lung involvement [5] [6]**
- **Similar findings in idiopathic ILD [7]**
- **But reflux does not predict ILD outcome [8]**

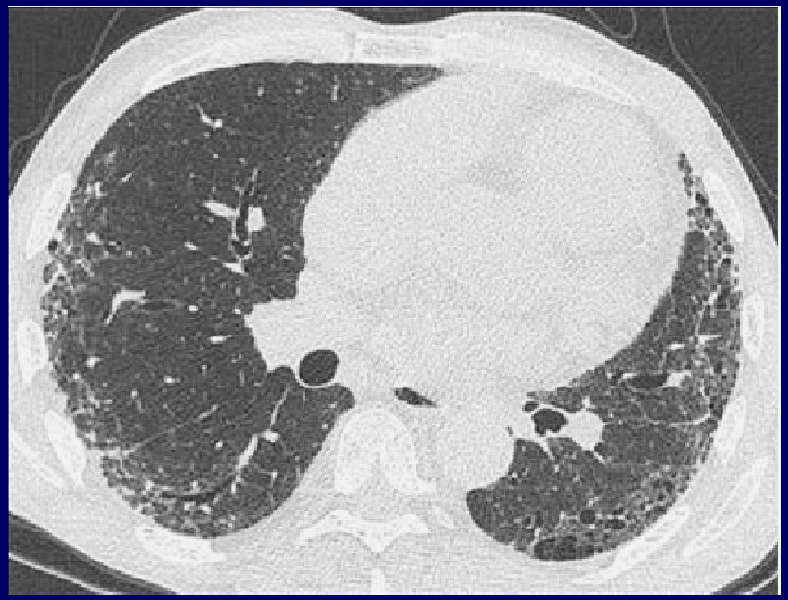
Corps étranger des voies aériennes distales [1]

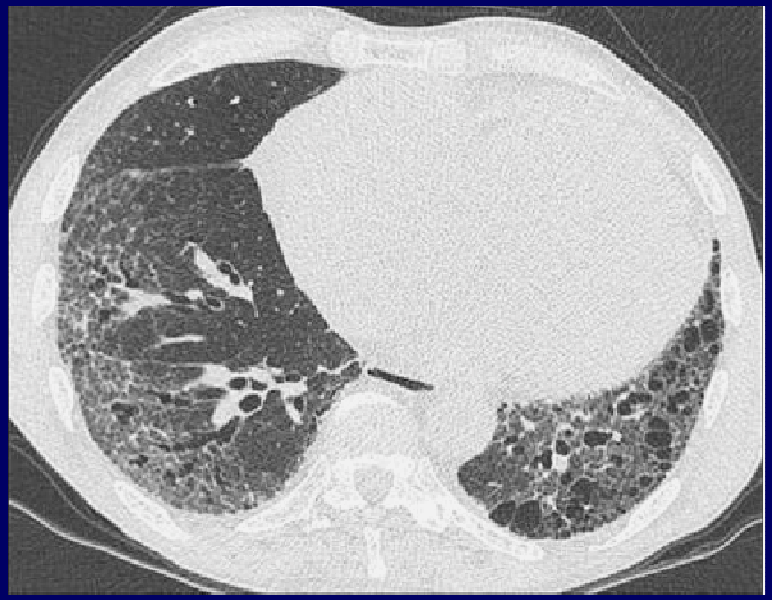
(1) de Souza *et al.* Respiration 2009 - (2) Matuse *et al.* Chest 1996 - (3) Moran *et al.* Arch Pathol 1955
(4) Marie *et al.* Arthritis Rheum 2001 - (5) Lock *et al.* Am J Gastroenterol 1998
(6) Christmann *et al.* Semin Arthritis Rheum 2010 (sous presse) - (7) Raghu *et al.* Chest 2006 - (8) Gilson *et al.* Eur Respir J 2010

Esophagus dilatation









Lung function: CO transfer

	pneumonectomy	fibrosis
VC	50%	70%
Dlco	**50%**	**50%**
Kco	100%	60%

- **DLco : to evaluate ILD or PAH**

Scleroderma lung study : caractéristiques à l'inclusion [1,2]

	Total	ScS limitée	ScS diffuse	P
Nombre	158	64 (40%)	94 (60%)	N/A
Femmes	70%	76%	65%	NS
Age moyen, ans	48	52	49	NS
Ancienneté ScS, ans	3,1	3,1	3,1	NS
Index Mahler (0-12)	5,7	5,7	5,7	NS
Index toux (0-4)	1,9	2,2	1,9	0,06
CVF, % th	66%	69%	67%	NS
CPT, % th	70%	70%	69%	NS
VEMS/CV, %	83%	84%	82%	NS
DLco, %	47%	46%	48%	NS

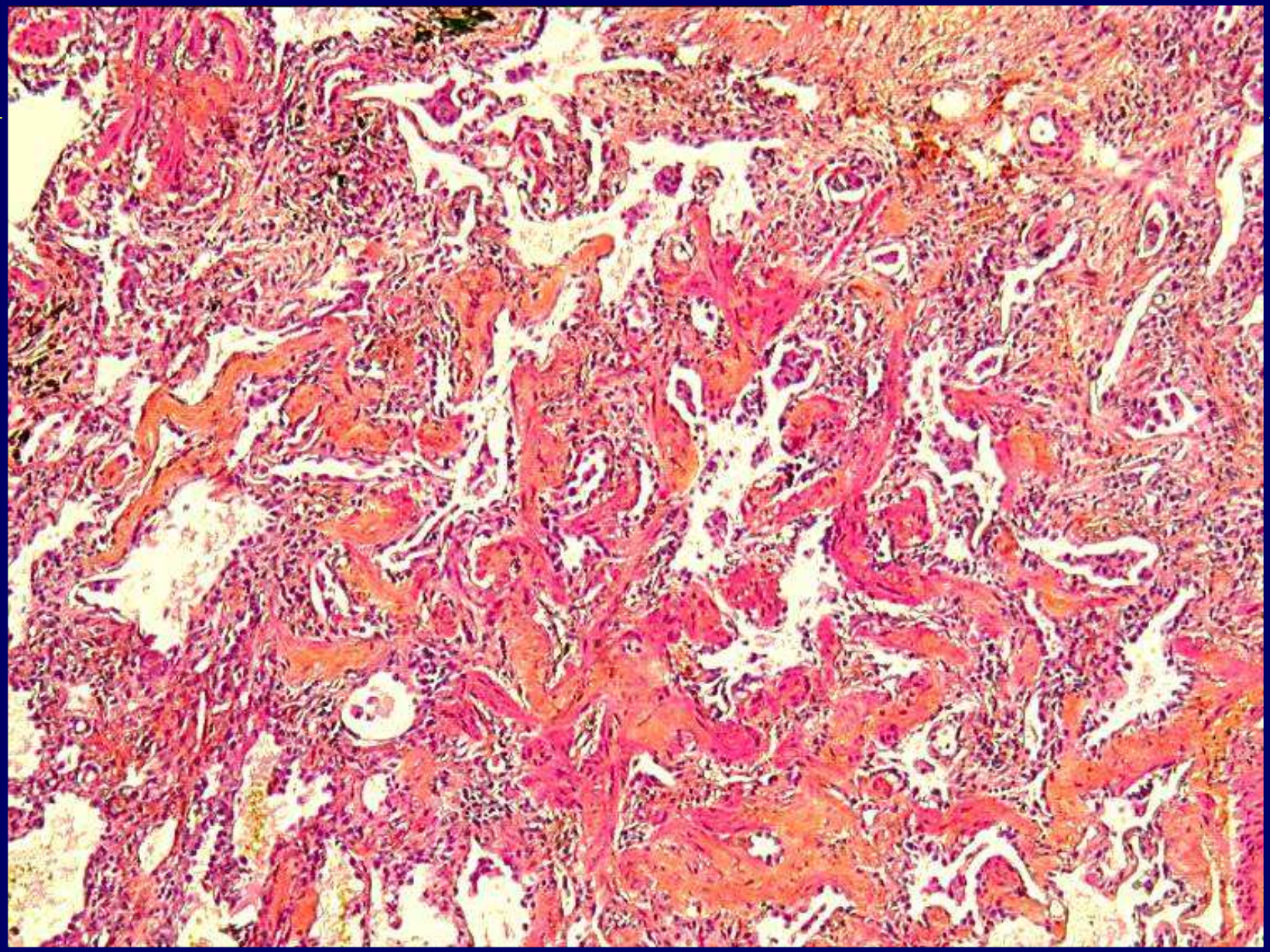
1. Clements et al, *Ann Rheum Dis* 2007;66:1641
2. Khanna et al, *Arthritis Rheum* 2005;2:592

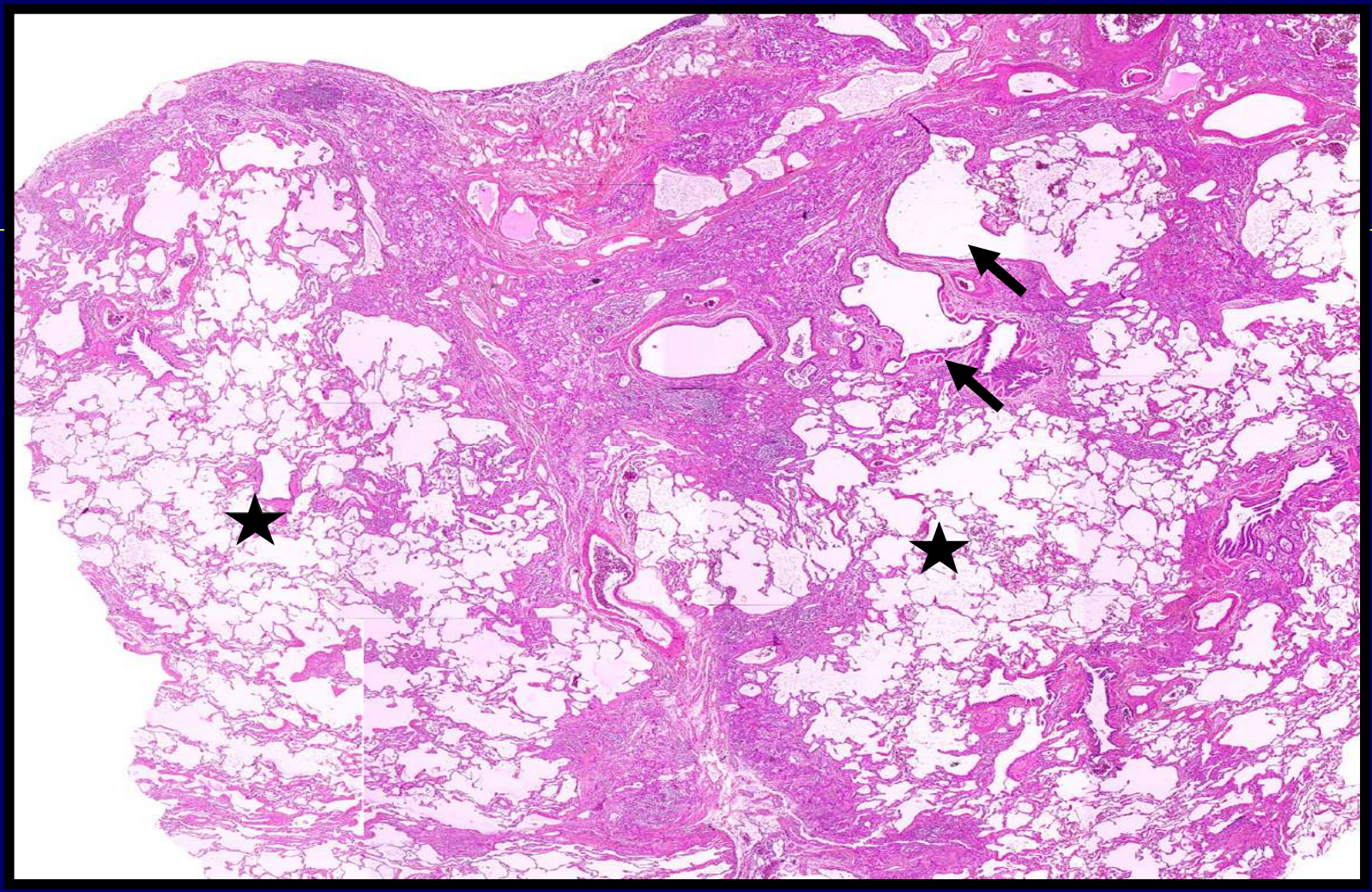
Classification of interstitial lung diseases

Classification of ILD (ATS/ERS 2002)

Interstitial lung disease	Main CT scann changes	Pathology	Outcome
UIP	Rayon de miel, DDB par traction	Remodelage dense, Hétérogène ; fibroblastique ; sous pleurale et para-septale	Aggravation progressive Peu sensible aux CS et IS
NSIP	Prédominance d'hyperdensités en verre dépoli, opacités en bandes et réticulées	Infiltration interstitielle lymphocytaire dominante, fibrose collagène modérée, lésions uniformes	Evolution variable, le plus souvent lente. Sensible aux CS et IS

Non specific interstitial pneumonia

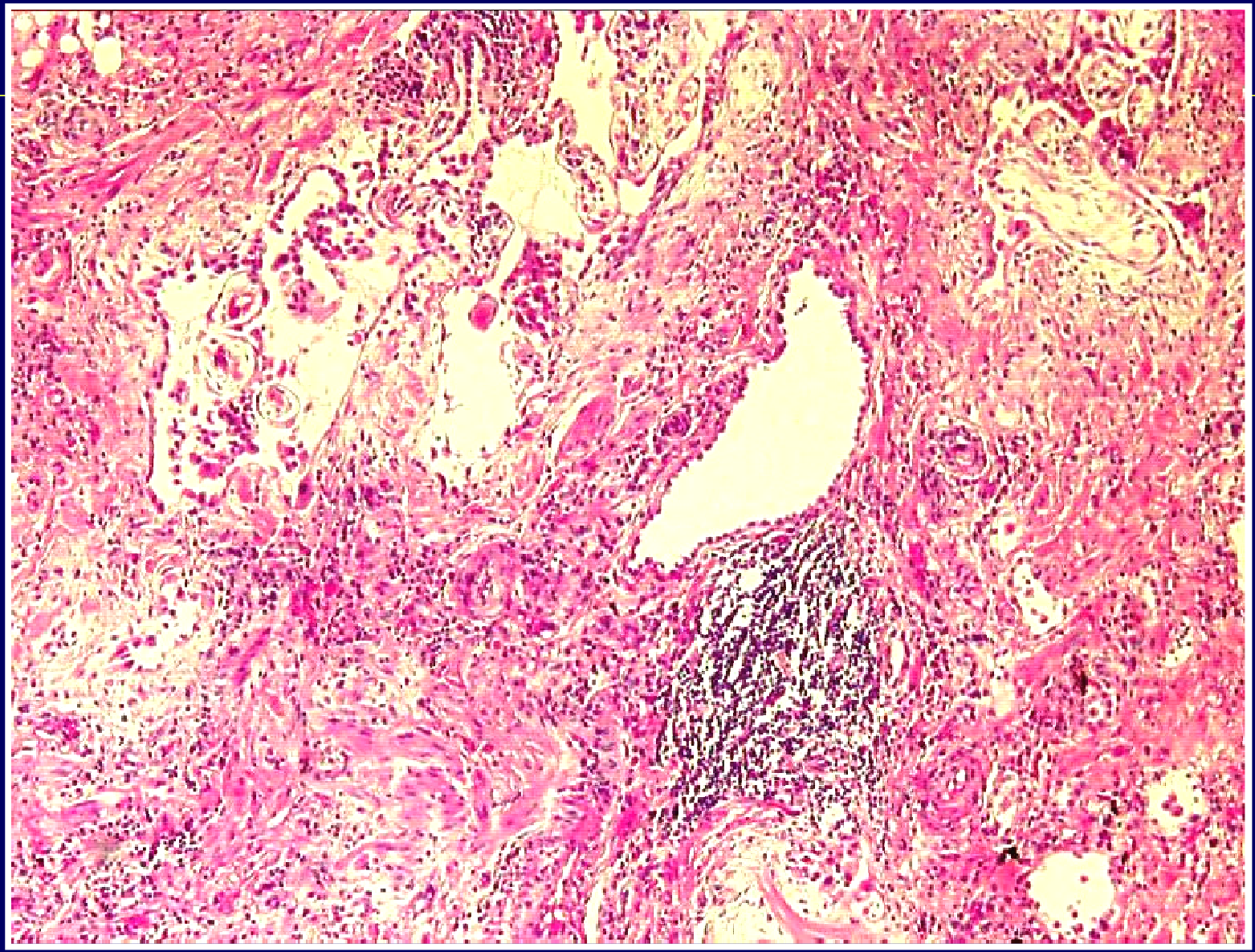


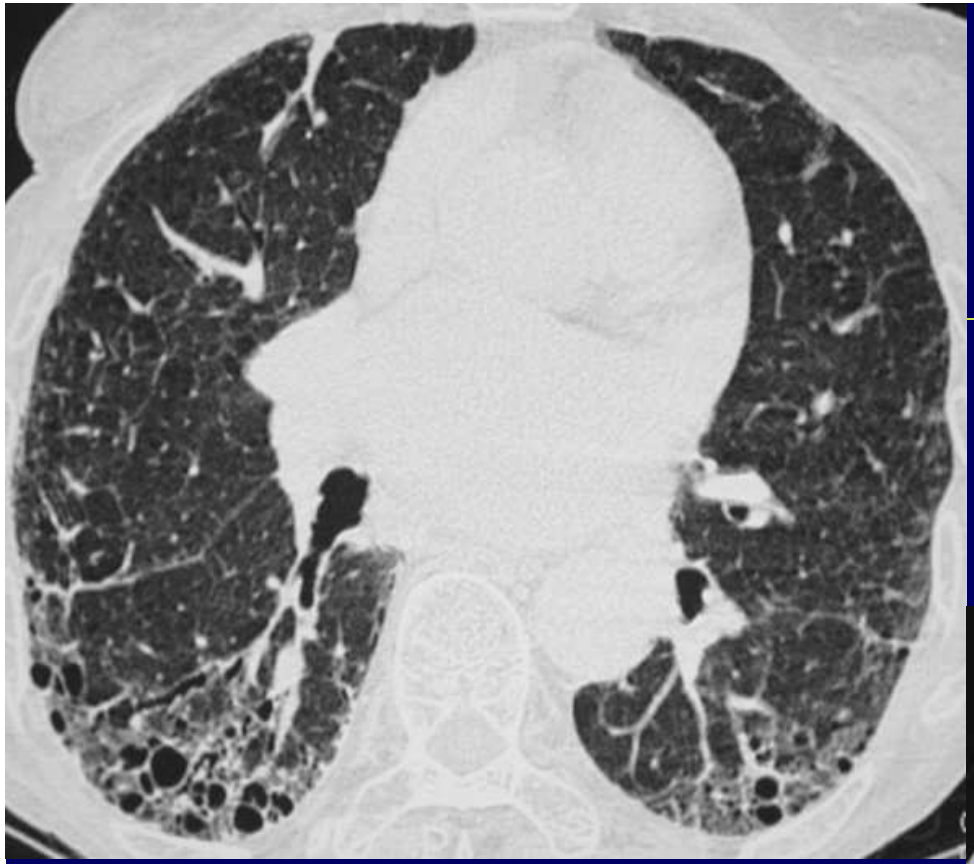


Usual interstitial pneumonia: fibrosis, Honey comb. (HES, x20).

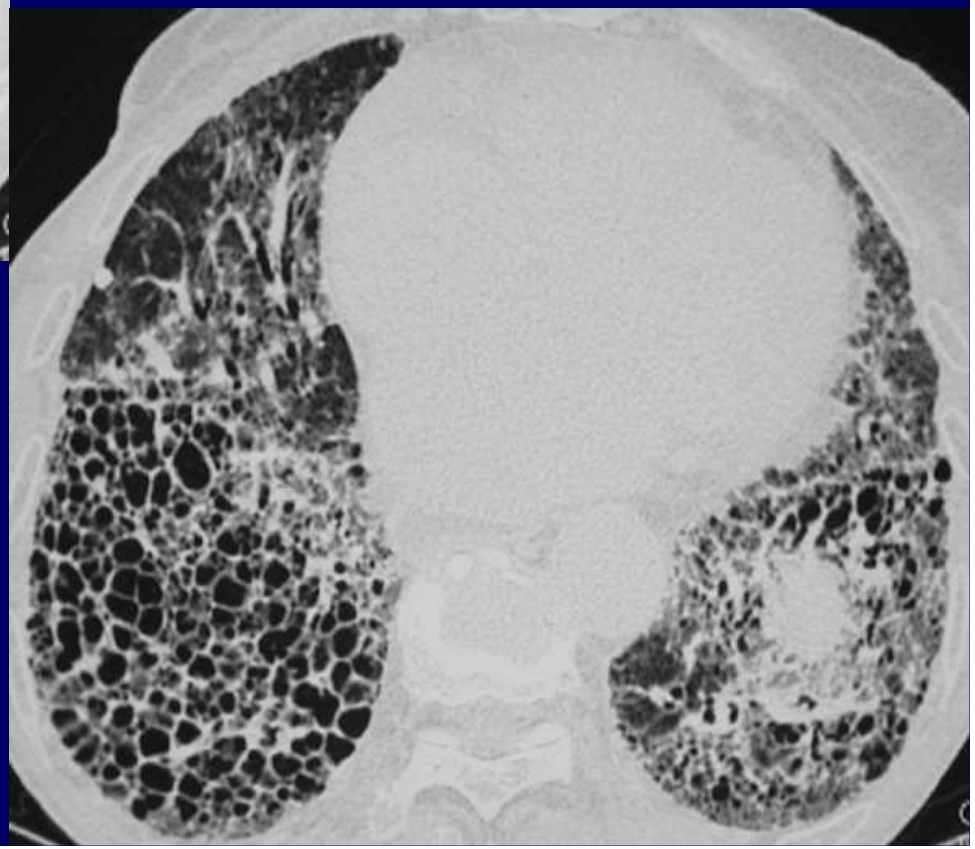
Mouthon et al. Rev Mal Resp. 2007

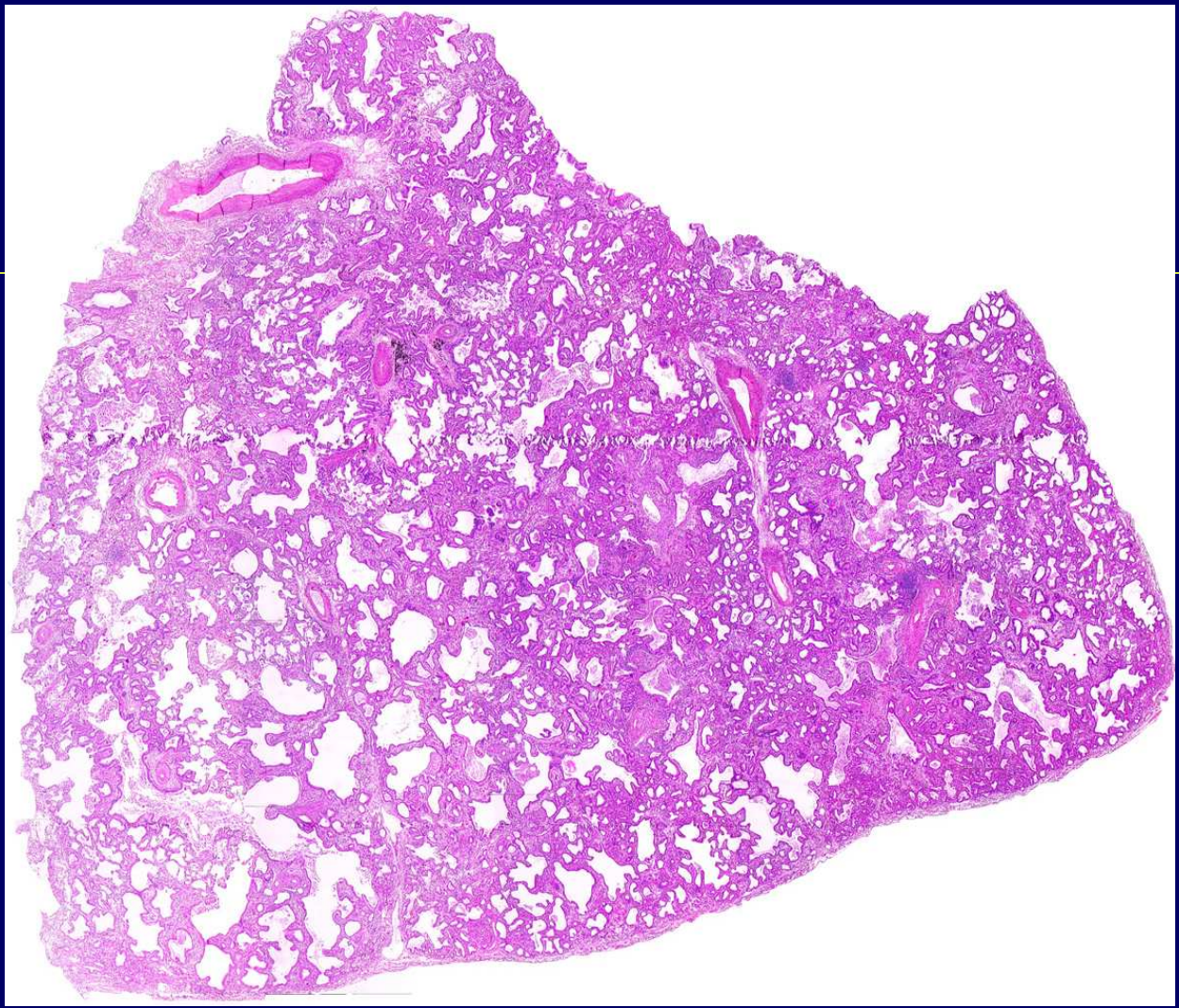
Usual intersititial pneumonia





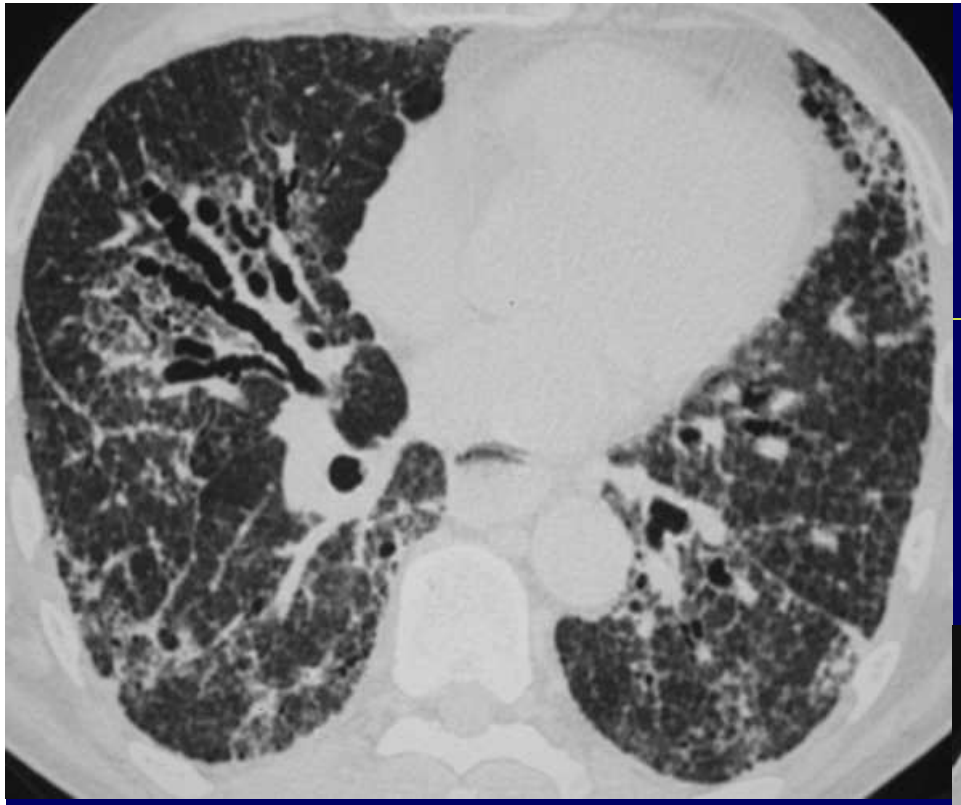
UIP





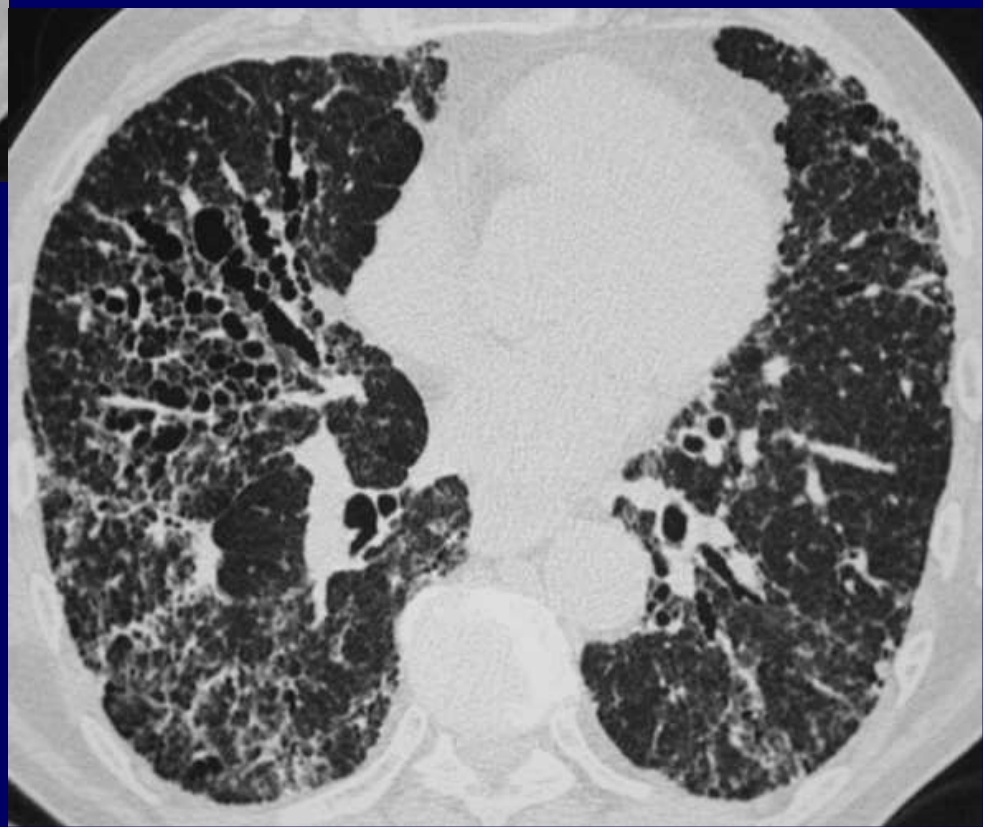
Non specific interstitial pneumonia: alveolar destruction is limited, inflammation is present (HES, x20).

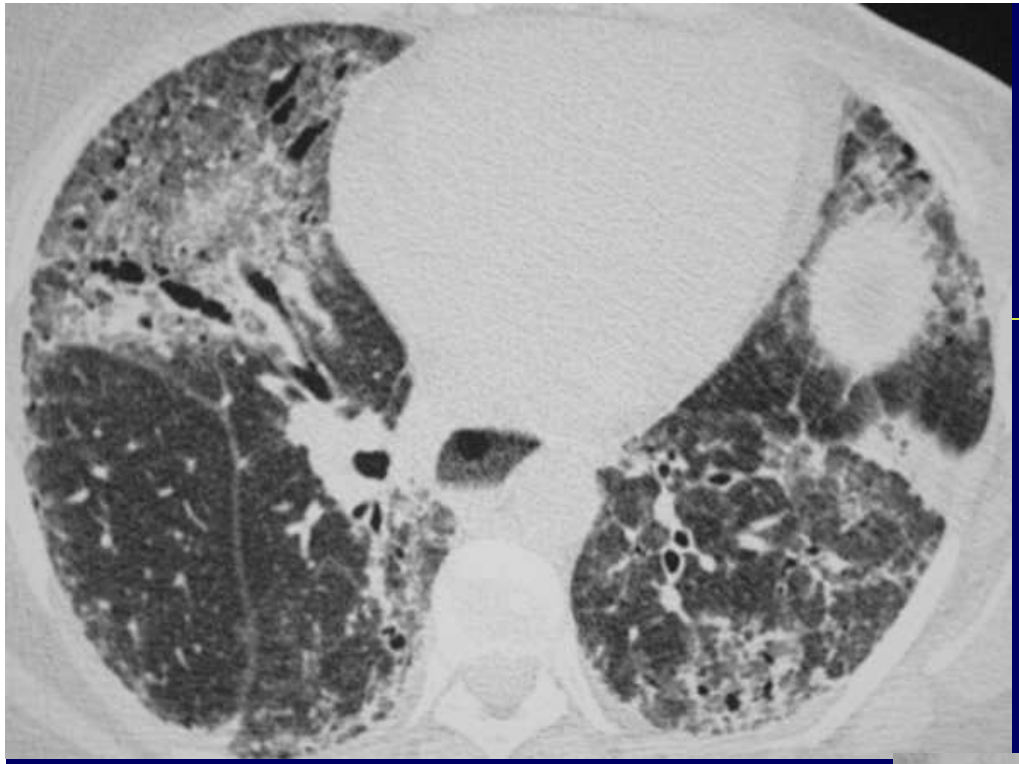
NSIP



February 2000

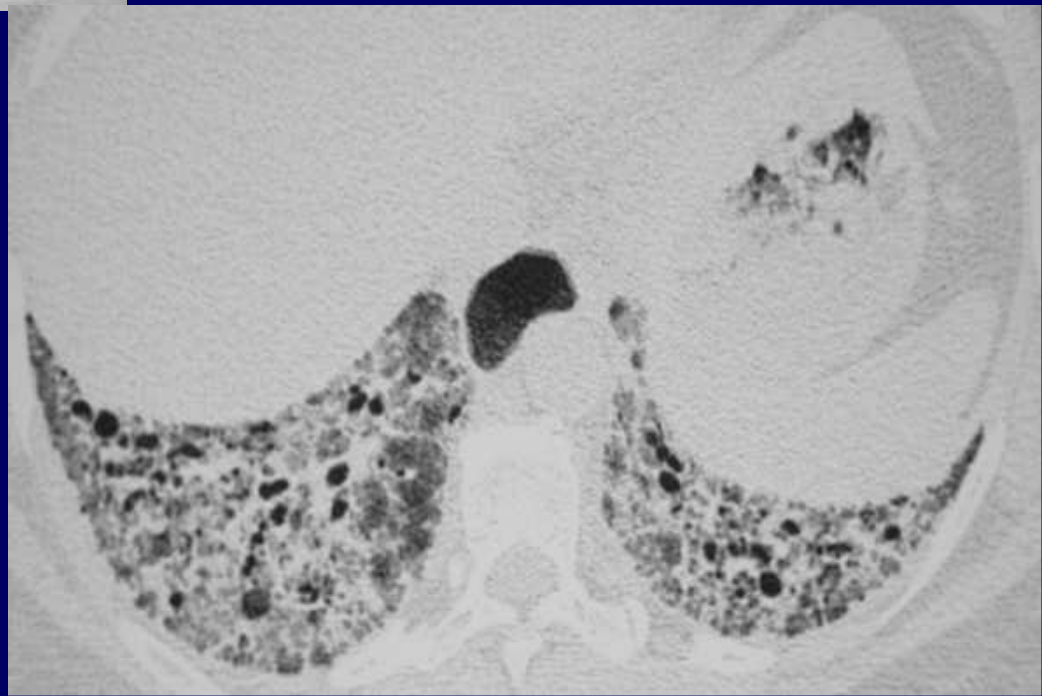
May 2001

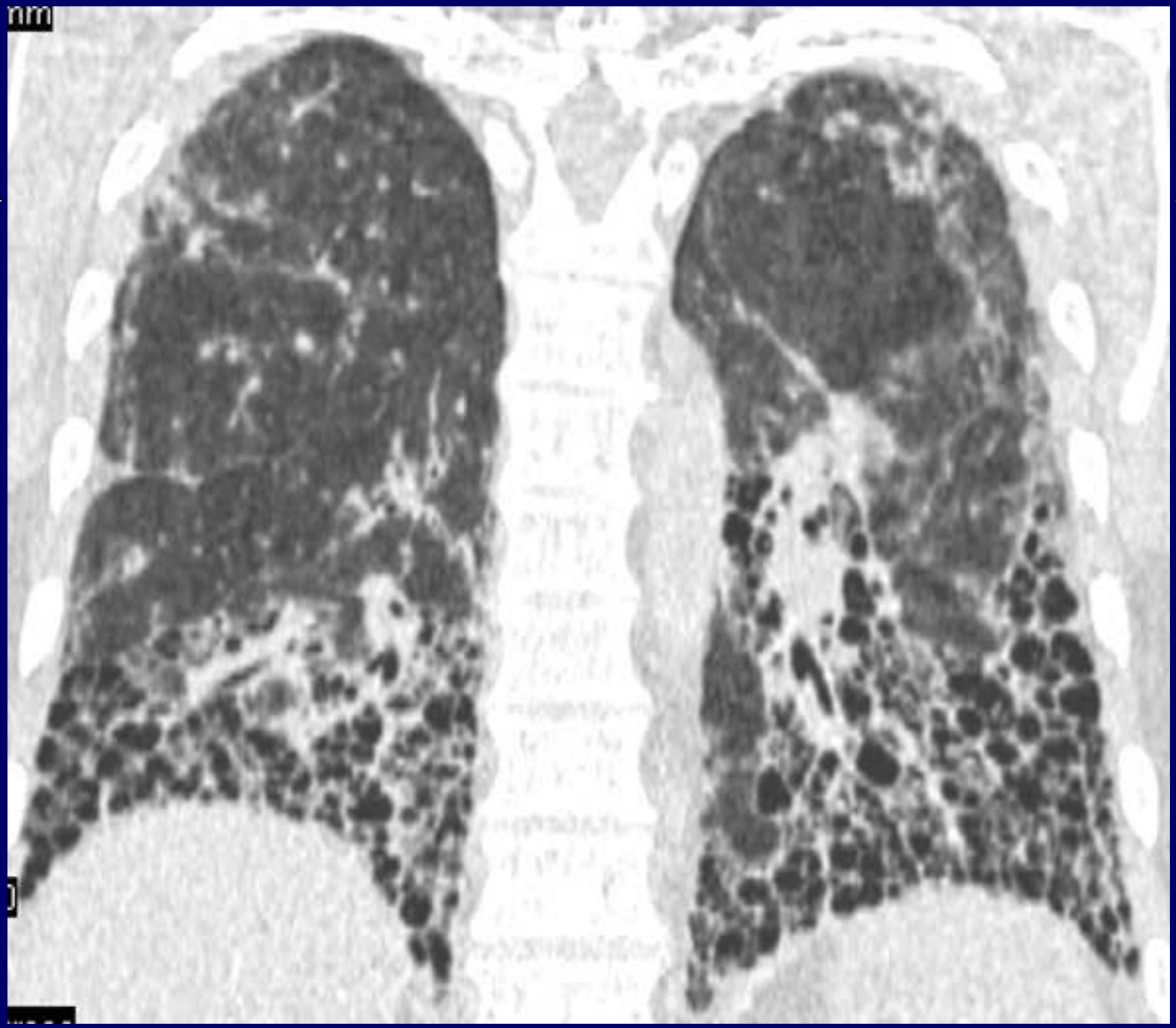




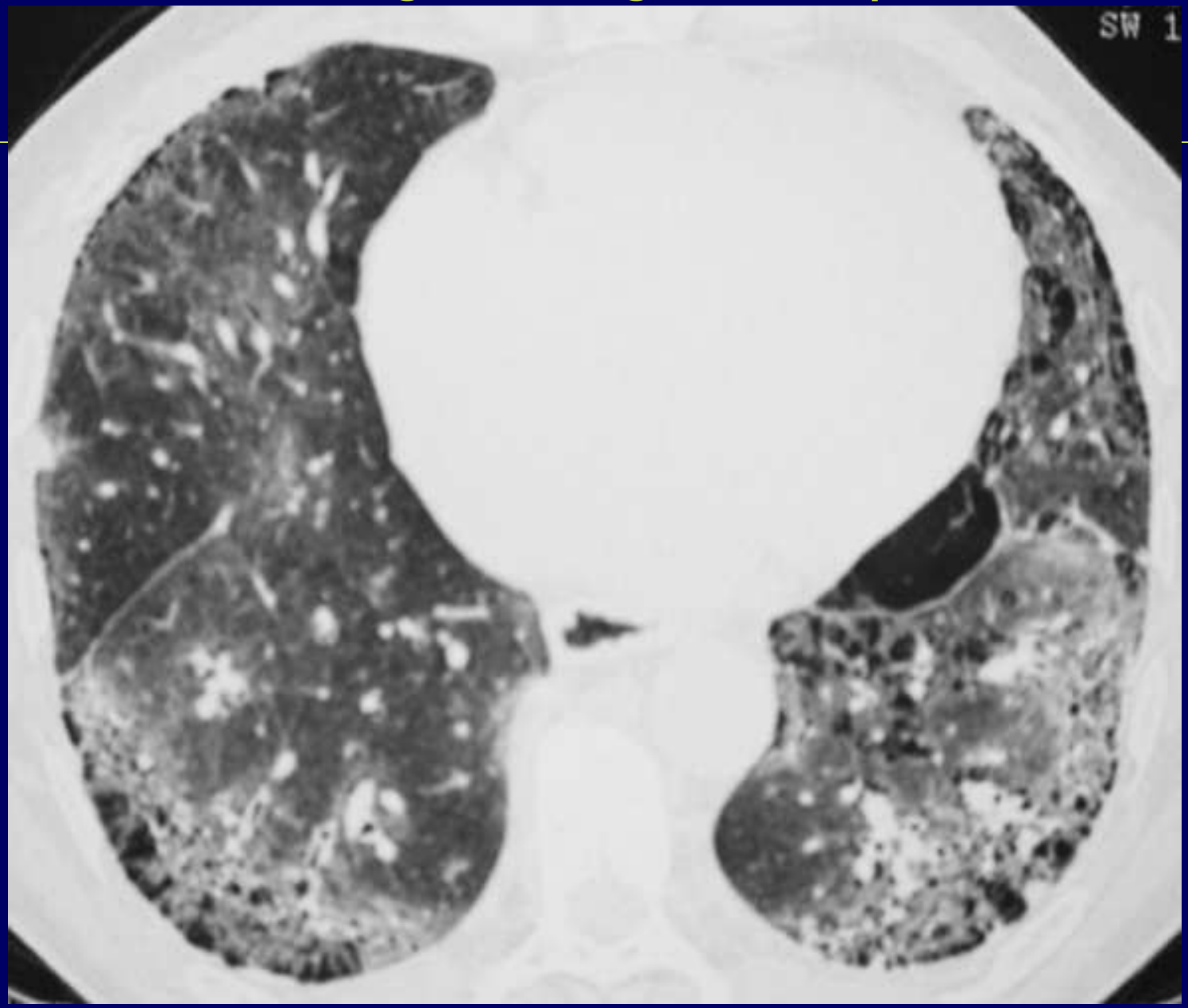
NSIP

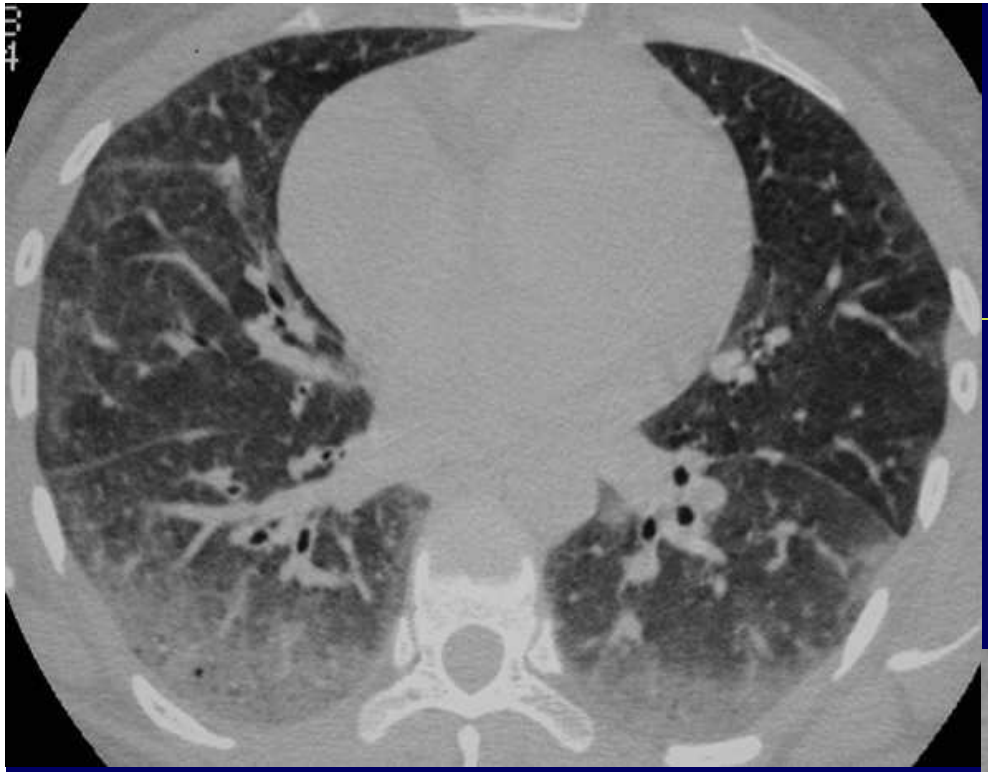
75 %
of patients





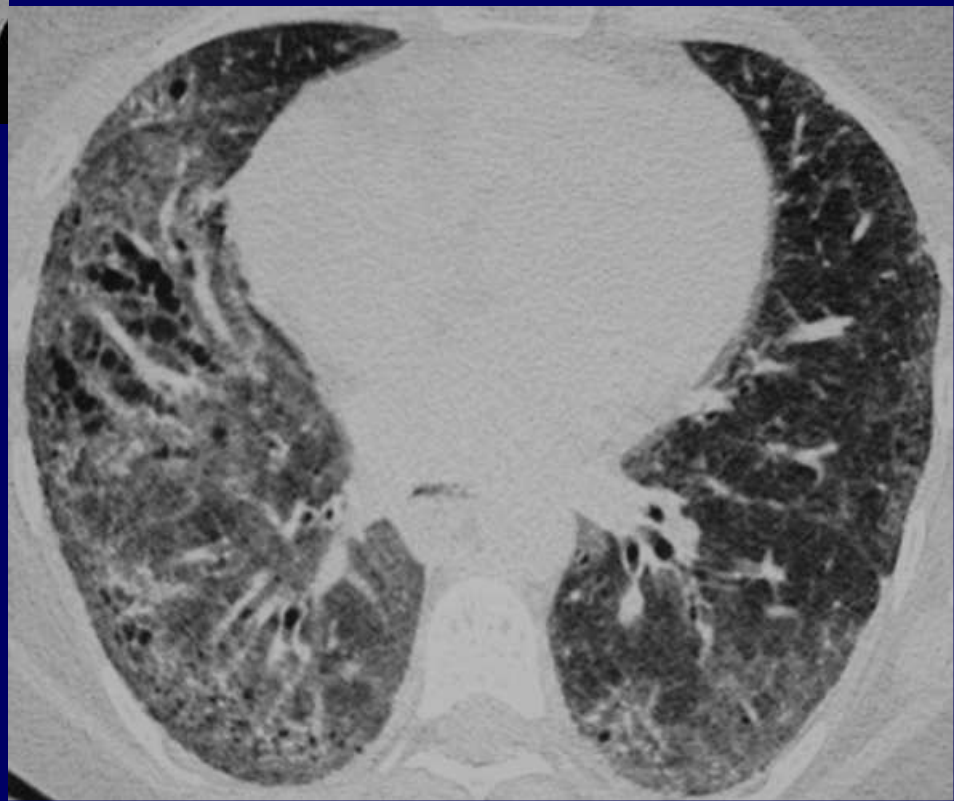
PINS/ ground glass aspect





1991

2001



Quelle est la place du LBA (I) ?

- Un des 4 critères diagnostiques en l'absence de biopsie pulmonaire (ATS/ERS. Am J Respir Crit Care Med 2002;165:277-304).
- Alvéolite inflammatoire: augmentation de la cellularité, avec polynucléaires neutrophiles > 3% ou d'éosinophiles > 2% (Silver RM, Am J Med 1990;88:470-75).
- Corrélation entre inflammation au LBA et dégradation des EFR (Silver RM, Am J Med 1990;88:470-75).

Quelle est la place du LBA (II) ?

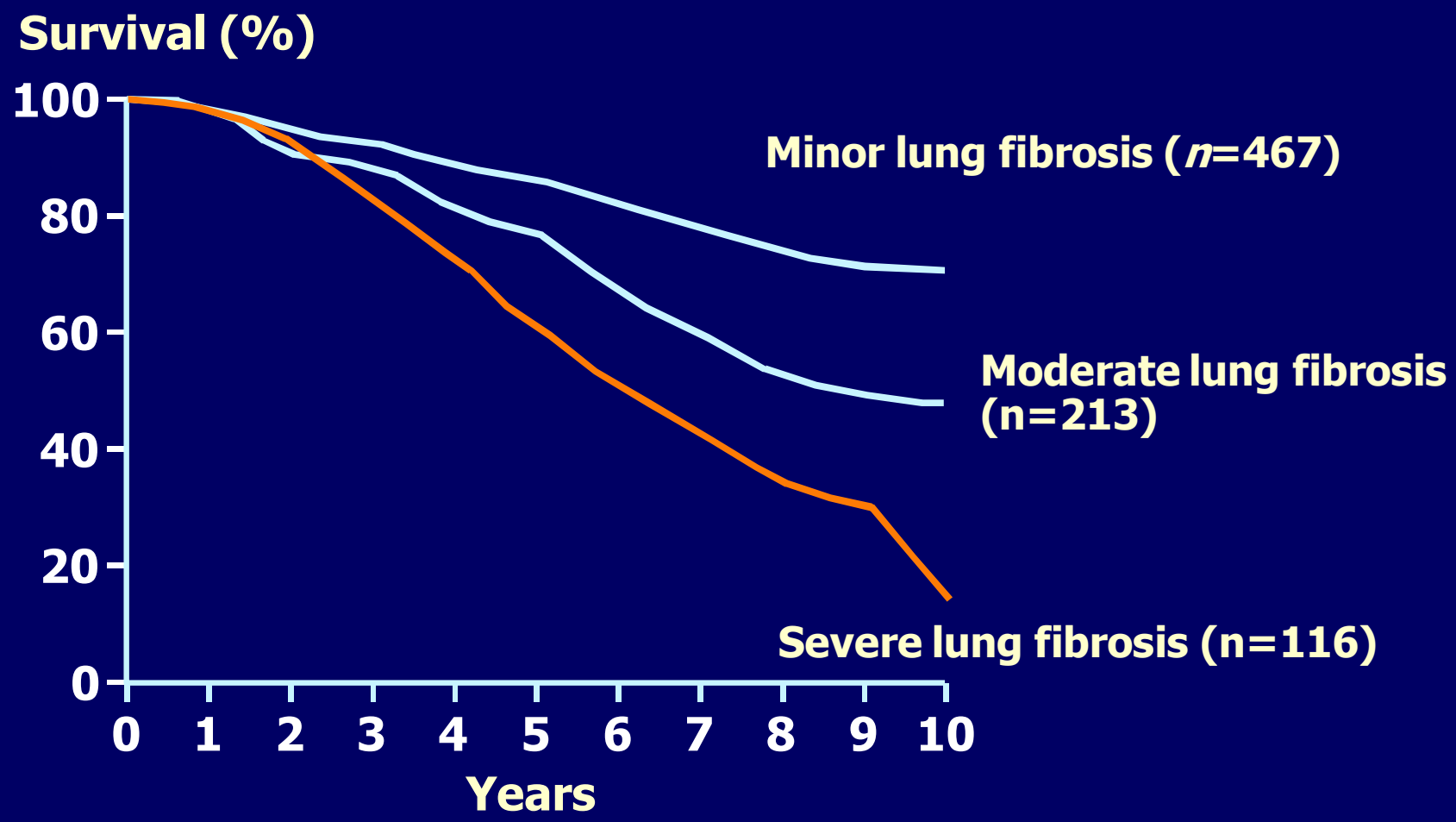
- Variabilité de l'alvéolite selon les lobes pulmonaires
- L'hyperéosinophilie alvéolaire est de mauvais pronostic car associée à une moins bonne survie.
- Le LBA permet, en cas d'aggravation rapide de la PID, d'éliminer une infection.

CLINICAL MANIFESTATIONS OF LUNG FIBROSIS

- No symptoms within months or years
- Dyspnea and cough
- Crackles
- Cardiac symptoms occur late
- Slerosis of lungs

Bouros *et al.* Am J Respir Crit Care Med 2002
Morgan *et al.* Ann Rheum Dis 2003

PROGNOSIS OF SCLERODERMA WITH LUNG FIBROSIS

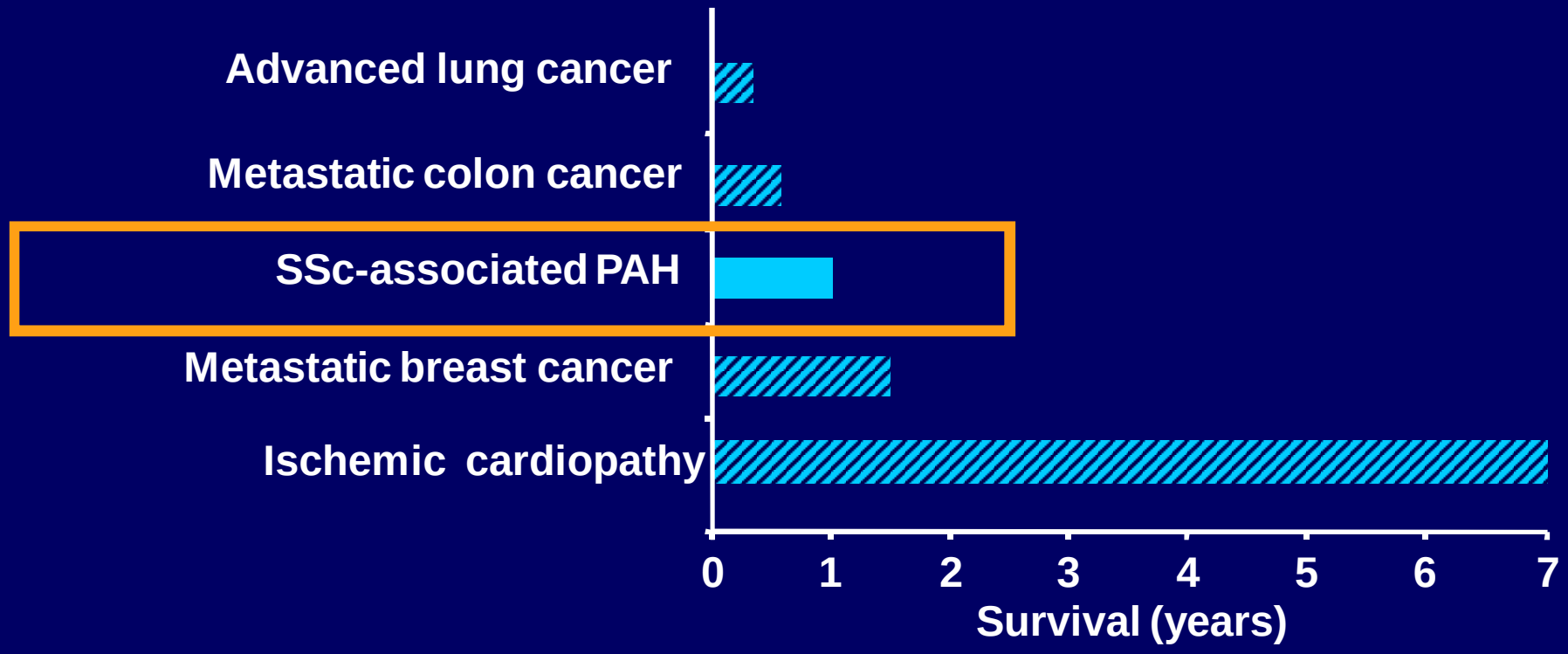


$p < 0.01$

Steen V, *Arthritis Rheum* 1994. 37:1283.

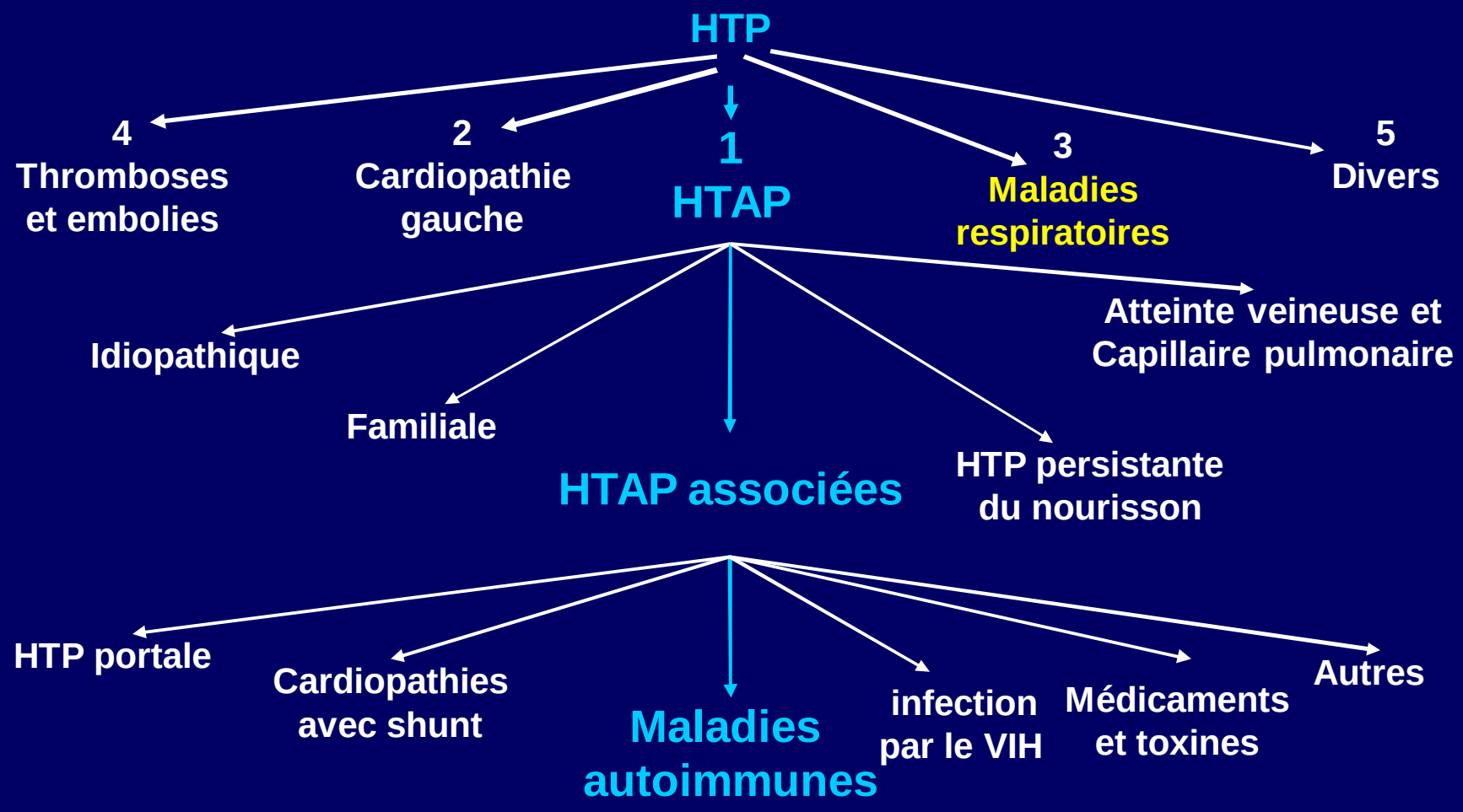
PAH: EPIDEMIOLOGY AND OUTCOME

Poor prognosis of PAH



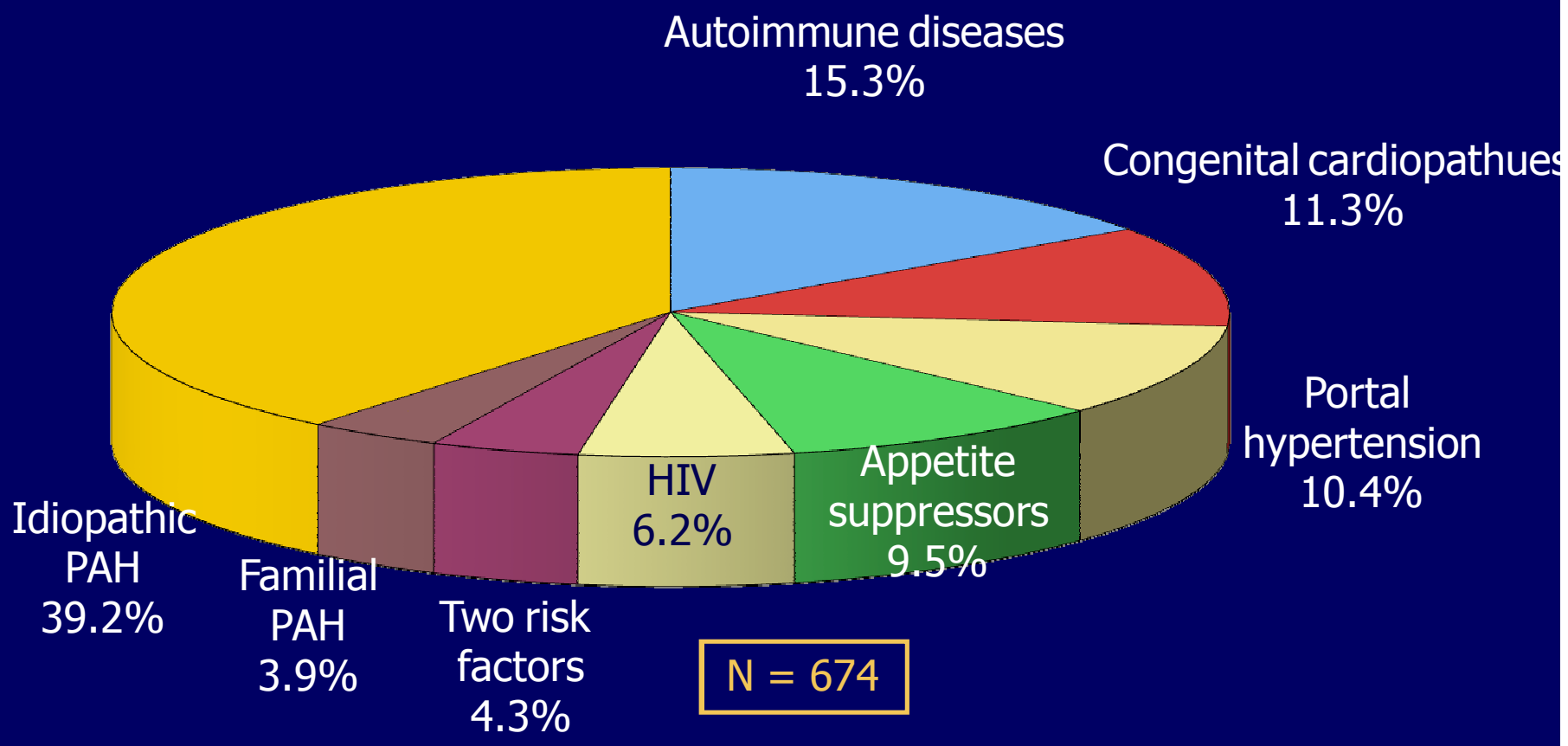
D'Alonzo GE, et al. *Ann Intern Med* 1991; 115:343-9.
Kato I, et al. *Cancer* 2001; 92:2211-9.
Felker GM, et al. *N Engl J Med* 2000; 342:1077-84.

Classification des hypertensions pulmonaires



Simonneau G, *et al. J Am Coll Cardiol* 2004; 43:5S-12S.

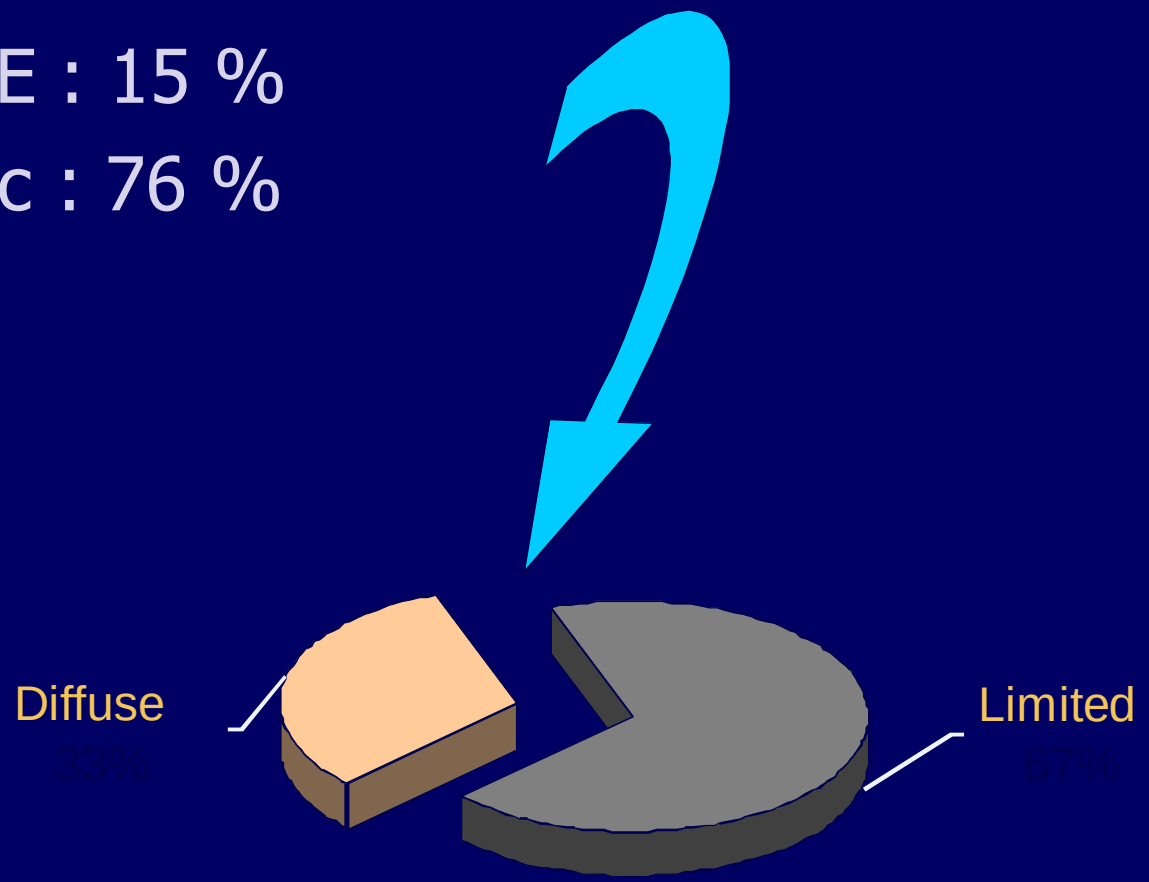
Etiologies of PAH



Humbert M et al. *Am J Respir Crit Care Med* 2006;173:1023

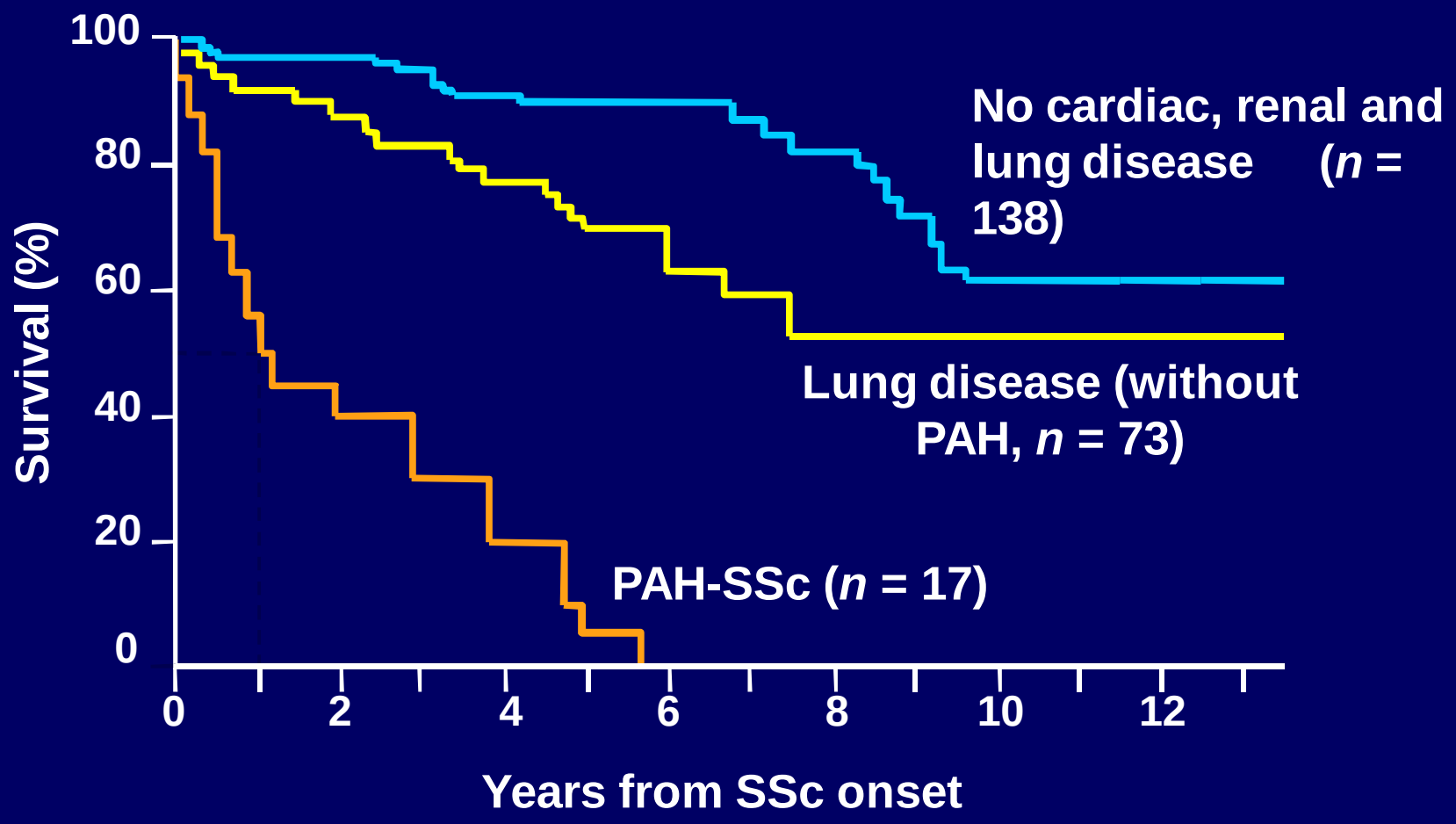
PAH-scleroderma

- SSc is the first AI disease responsible for PAH
  - SLE : 15 %
  - SSc : 76 %



Humbert M et al. *Am J Respir Crit Care Med* 2006;173:1023

Lung disease and prognosis of SSc



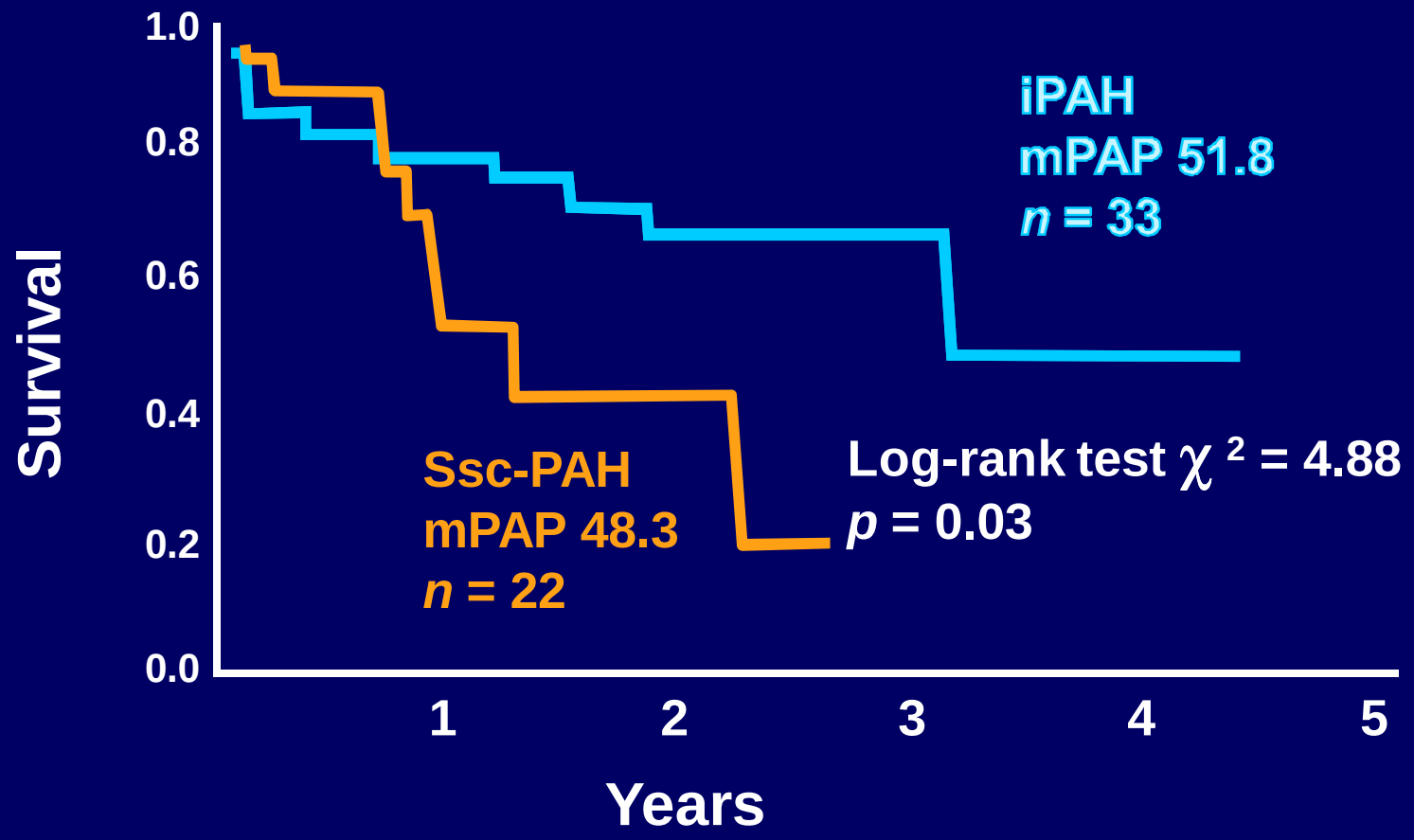
Koh ET, *et al. Br J Rheumatol* 1996; 35:989-93.

Idiopathic PAH vs SSc-PAH

- Prevalence of SSc-PAH : 8-16%[1,2]
- Poor prognosis of SSc-PAH
  - Mean survival = 2.8 years in idiopathic PAH[3]
  - One year for SSc-PAH[4,5]

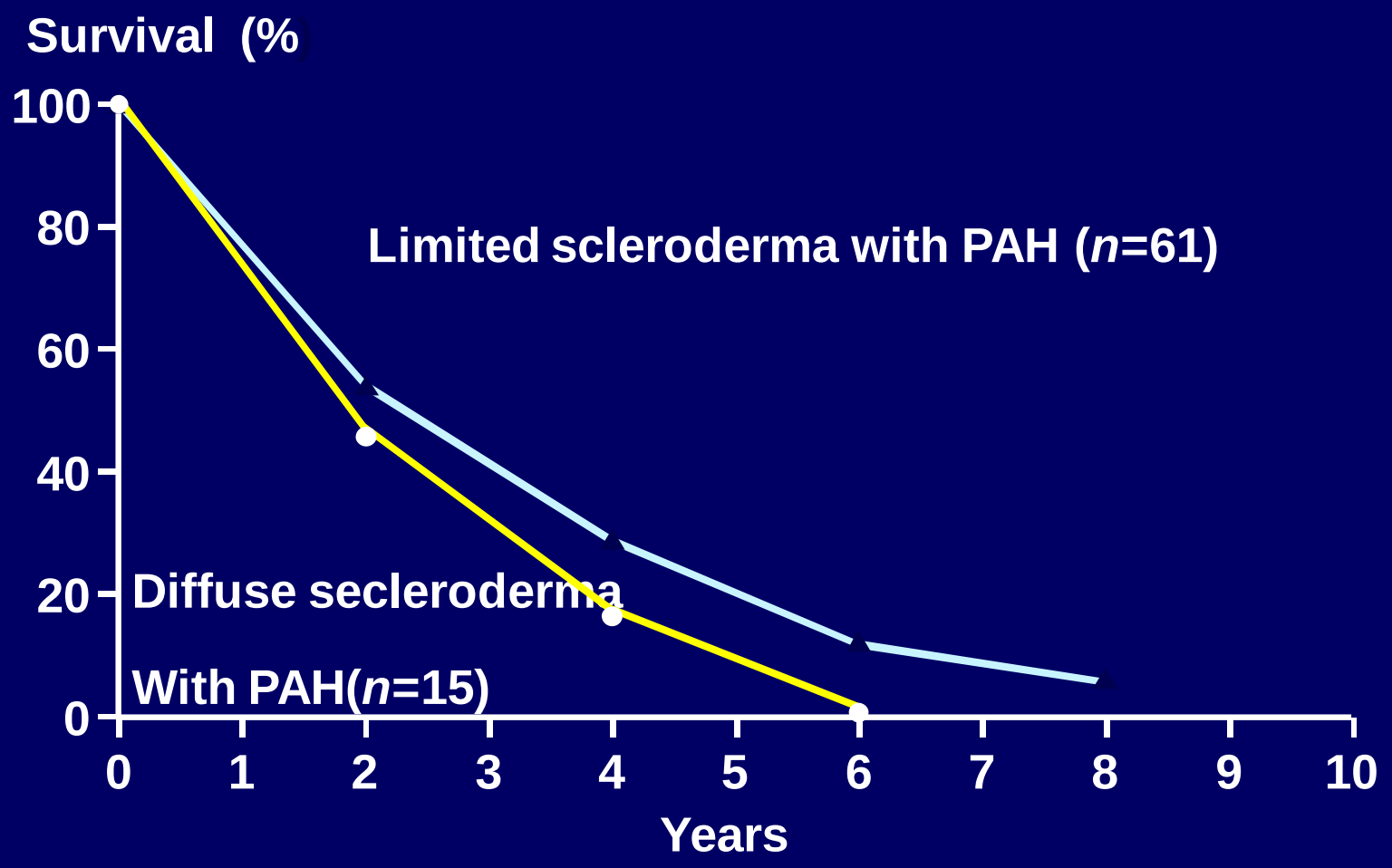
1. Humbert M, *et al. AJRCMM* 2006;173:1023-30. 2. McGoon M, *et al. Chest* 2004; 126:14S-34S. 3.D'Alonzo GE, *et al. Ann Intern Med* 1991; 115:343-9. 4. Kawut SM, *et al. Chest* 2003; 123:344-50. 5.Koh ET, *et al. Br J Rheumatol* 1996; 35:989-93.

SSc PAH vs idiopathic PAH



Kawut *et al. Chest* 2003;123:344.

Prognosis is related to PAH

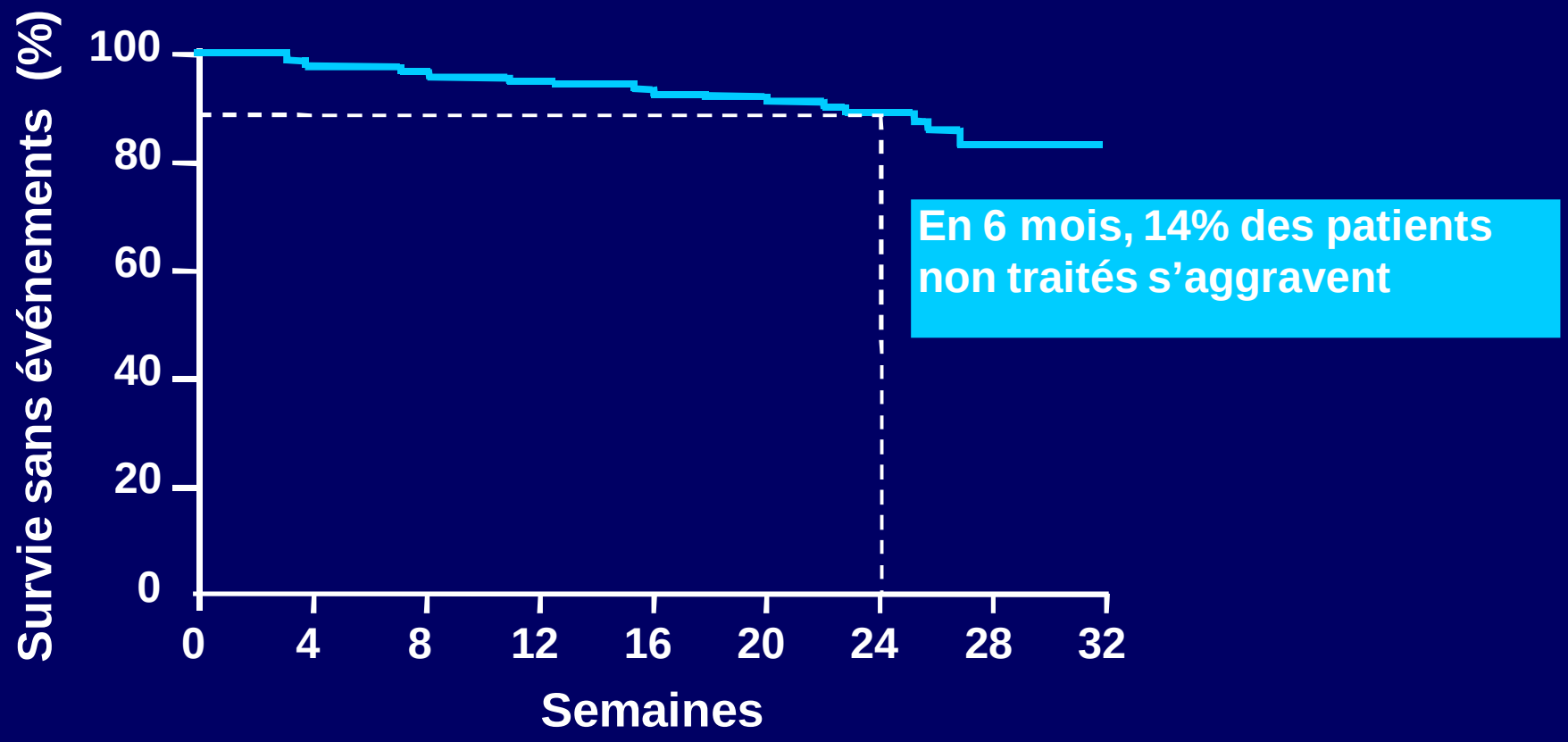


Medsger, *J Rheum* 1996; 23: 639-427

Peu de symptômes – Maladie grave

les patients en classe II de la classification de l'OMS peuvent s'aggraver rapidement en l'absence de traitement

Temps vers l'aggravation des malades en classe II non traités (EARLY)



N° patients exposés	92	90	89	86	84	83	77	18	9

Adapted from Galiè N, *et al. Lancet* 2008; 371:2093-100.

Progression de l'HTAP modérée

- **13.6%** patients sans HTAP à l'écho progressent vers une HTAP sévère
- **17.7%** avec une HTAP modérée progressent vers une forme sévère
- **15.6%** n'ont pas d'HTAP à l'écho cardiaque
- DLCO < 50% prédit le développement d'une hypertension pulmonaire dans les 5 ans suivant une échographie normale
- La prévalence cumulée de l'HTAP va de **8** à **13%**

Hachulla E, *et al*. *Arthritis Rheum* 2005; 52:3698-700
Chang *et al. J Rheumatol* 2006; 33;269-74.

TREATMENT

Prospective studies for ILD

- Prednisone
- Azathioprine
- Cyclophosphamide
- Mycophenolate mofetil
- Bosentan
- N-acetyl cystéine
- Imatinib

The NEW ENGLAND JOURNAL of MEDICINE

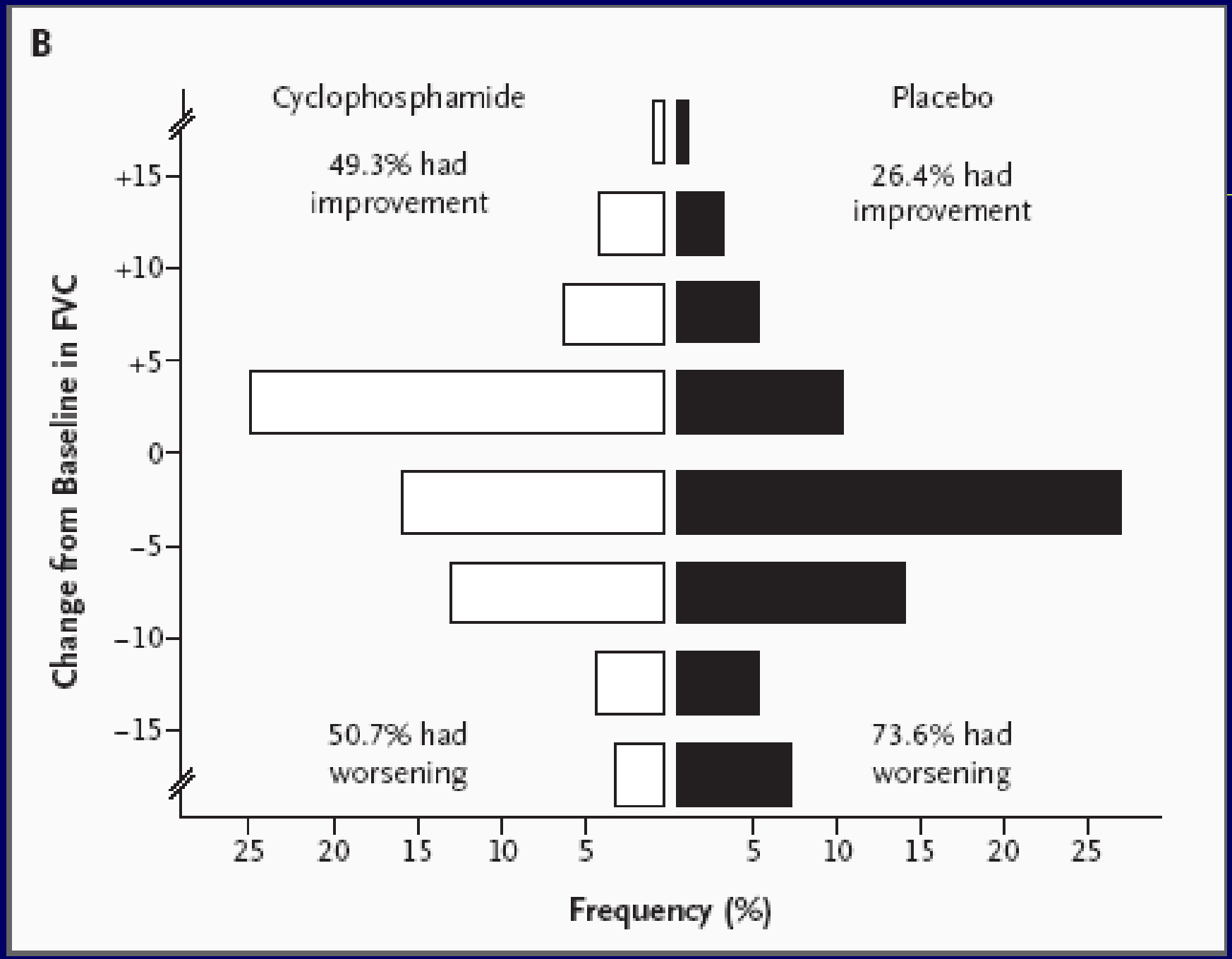
ORIGINAL ARTICLE

Cyclophosphamide versus Placebo in Scleroderma Lung Disease

Donald P. Tashkin, M.D., Robert Elashoff, Ph.D., Philip J. Clements, M.D., M.P.H., Jonathan Goldin, M.D., Ph.D., Michael D. Roth, M.D., Daniel E. Furst, M.D., Edgar Arriola, Pharm.D., Richard Silver, M.D., Charlie Strange, M.D., Marcy Bolster, M.D., James R. Seibold, M.D., David J. Riley, M.D., Vivien M. Hsu, M.D., John Varga, M.D., Dean E. Schraufnagel, M.D., Arthur Theodore, M.D., Robert Simms, M.D., Robert Wise, M.D., Fredrick Wigley, M.D., Barbara White, M.D., Virginia Steen, M.D., Charles Read, M.D., Maureen Mayes, M.D., Ed Parsley, D.O., Kamal Mubarak, M.D., M. Kari Connolly, M.D., Jeffrey Golden, M.D., Mitchell Olman, M.D., Barri Fessler, M.D., Naomi Rothfield, M.D., and Mark Metersky, M.D., for the Scleroderma Lung Study Research Group*

N ENGL J MED 354;25 WWW.NEJM.ORG JUNE 22, 2006

162 randomised patients; 142 were evaluated at 1 year.


B
Cyclophosphamide
Placebo
49.3% had improvement
26.4% had improvement
50.7% had worsening
73.6% had worsening
Change from Baseline in FVC
+15
+10
+5
0
−5
−10
−15
25
20
15
10
5
5
10
15
20
25
Frequency (%)

The Scleroderma Lung Study Cyclophosphamide vs placebo

	Forced vital capacity (FVC) % of predicted*	
	Cyclophosphamide *n* = 73	Placebo *n* = 72
Baseline value (mean ± SE)	67.6 ± 1.3	68.3 ± 1.5
Value at 12 months (mean ± SE)	66.6 ± 1.7	65.6 ± 1.6
Difference (mean ± SE)	−1.0 ± 0.92	−2.6 ± 0.9
p value	$p < 0.05$ after adjustment for baseline values in favour of cyclophosphamide	

- Patients with active alveolitis and SSc-ILD
- 145 patients completed at least 6 months of treatment

*Primary endpoint

Tashkin DP, *et al*. *N Engl J Med* 2006; 354:2655-66.

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A Multicenter, Prospective, Randomized, Double-Blind, Placebo-Controlled Trial of Corticosteroids and Intravenous Cyclophosphamide Followed by Oral Azathioprine for the Treatment of Pulmonary Fibrosis in Scleroderma

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Table 3. Efficacy end point variables*

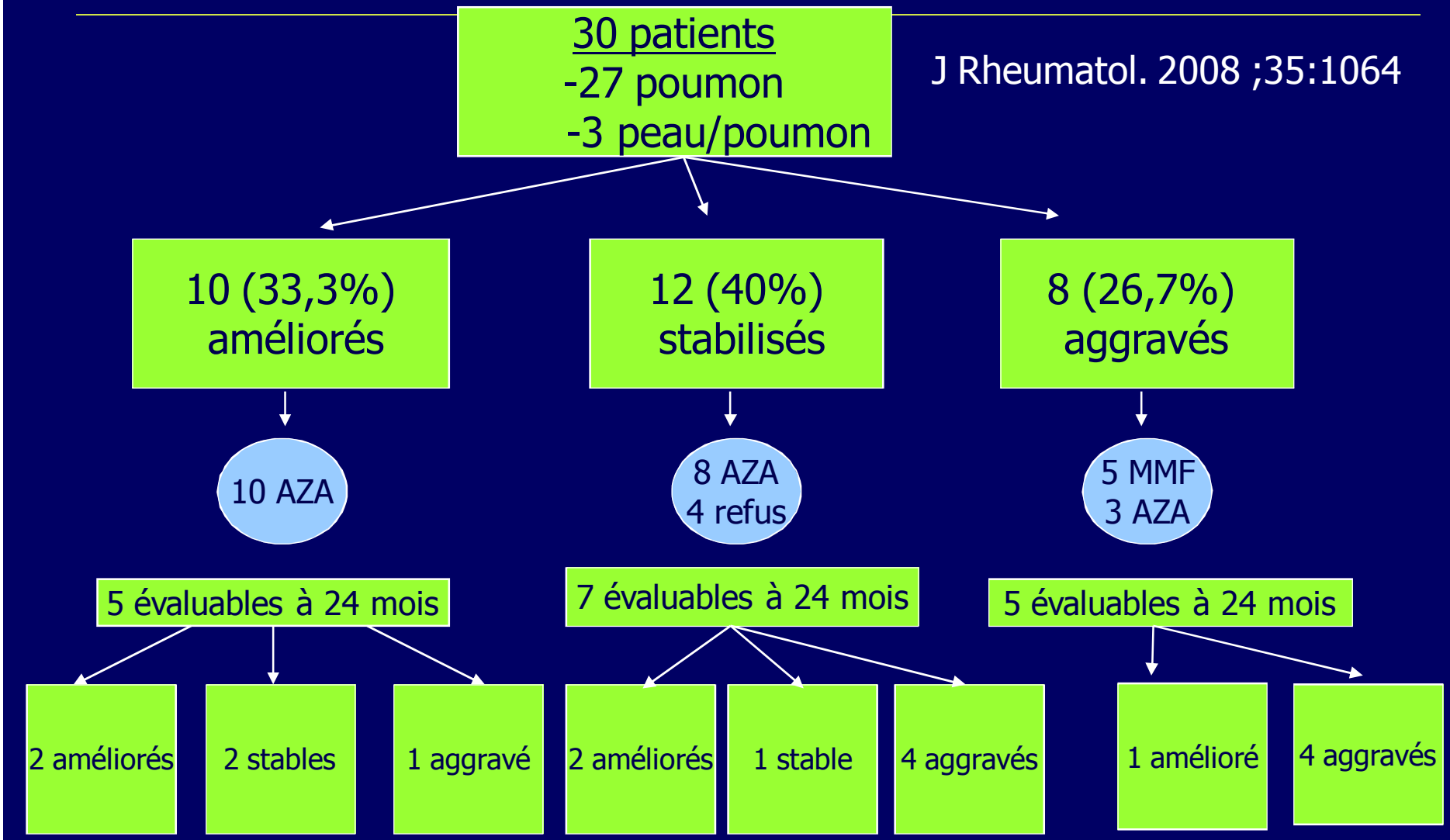
	Baseline		1-year followup		
	Treatment group (n = 22)	Placebo group (n = 23)	Treatment group (n = 19)	Placebo group (n = 18)	P†
Lung function, % predicted					
FVC	80.1 ± 10.3	81.0 ± 18.8	82.5 ± 11.3	78.0 ± 21.6	0.08
$DLCO_c$	52.9 ± 11.5	55.0 ± 12.9	49.6 ± 10.7	51.8 ± 14.9	0.64
TLC	81.8 ± 10.1	76.8 ± 16.9	80.2 ± 9.8	74.4 ± 16.7	0.61
FEV_1	79.6 ± 11.5	79.7 ± 19.1	81.3 ± 12.5	77.0 ± 21.3	0.16
Kco	71.3 ± 13.4	82.7 ± 19.1	71.5 ± 13.9	77.9 ± 23.3	0.32
Baseline HRCT‡					
Disease extent, mean (range) %	20 (6–40)	19 (5–40)	–	–	–
Ground-glass attenuation, mean (range) %	50 (15–91)	47 (0–95)	–	–	–
Improvement on serial HRCT, no (%)‡	–	–	6 (40)	3 (20)	0.39
Dyspnea score, mean (range)§	7.7 (2–14)	7.2 (0–18)	8.75 (0–14)	7.80 (2–14)	0.23

SSc-ILD: EULAR/EUSTAR Recommandations

- …Despite ist toxicity cyclophosphamide can be proposed to treat infiltrative lung disease in patients with SSc...

Kowal-Bielecka O, *et al. Ann Rheum Dis* 2009.

Résultats atteinte pulmonaire



J Rheumatol. 2008 ;35:1064

How and when to treat ILD ?

- Severe disease
- Recent impairment
- New diagnosis of ILD
- Anti-topoisomerase Ab
- Alvéolitis?
- Histology is a poor indicatior to treat patients

Latsi PI and Wells AU. *Curr Opin Rheumatol* 2003; 15:748-55.

Comparaison de l'évolutivité des EFR (augmentation ou diminution en % relatif par an) entre les différentes périodes de suivi:

Variable étudiée		Nombre d'individus évaluables	évolutivité durant la période1 (% par an)	évolutivité durant la période 2 (% par an)	Student apparié : p value
période1	période 2				
CVF					
avant	0-6 mois	26	-19.21	0.95	<.0001
avant	0-24 mois	14	-19.21	0.04	<.0001
0-6 mois	6-24 mois	12	0.95	-0.05	0.2123
CPT					
avant	0-6 mois	28	-18.15	0.60	0.0004
avant	0-24 mois	15	-18.15	0.01	0.0031
0-6 mois	6-24 mois	15	0.60	-0.03	0.4102
DLCO					
avant	0-6 mois	19	-24.08	0.48	0.0365
avant	0-24 mois	9	-24.08	0.26	0.0017
0-6 mois	6-24 mois	7	0.48	0.33	0.2255
DLCO/VA					
avant	0-6 mois	21	-12.57	-0.03	0,3160
avant	0-24 mois	10	-12.57	-0.10	0.0156
0-6 mois	6-24 mois	9	-0.03	-0.10	0.5200

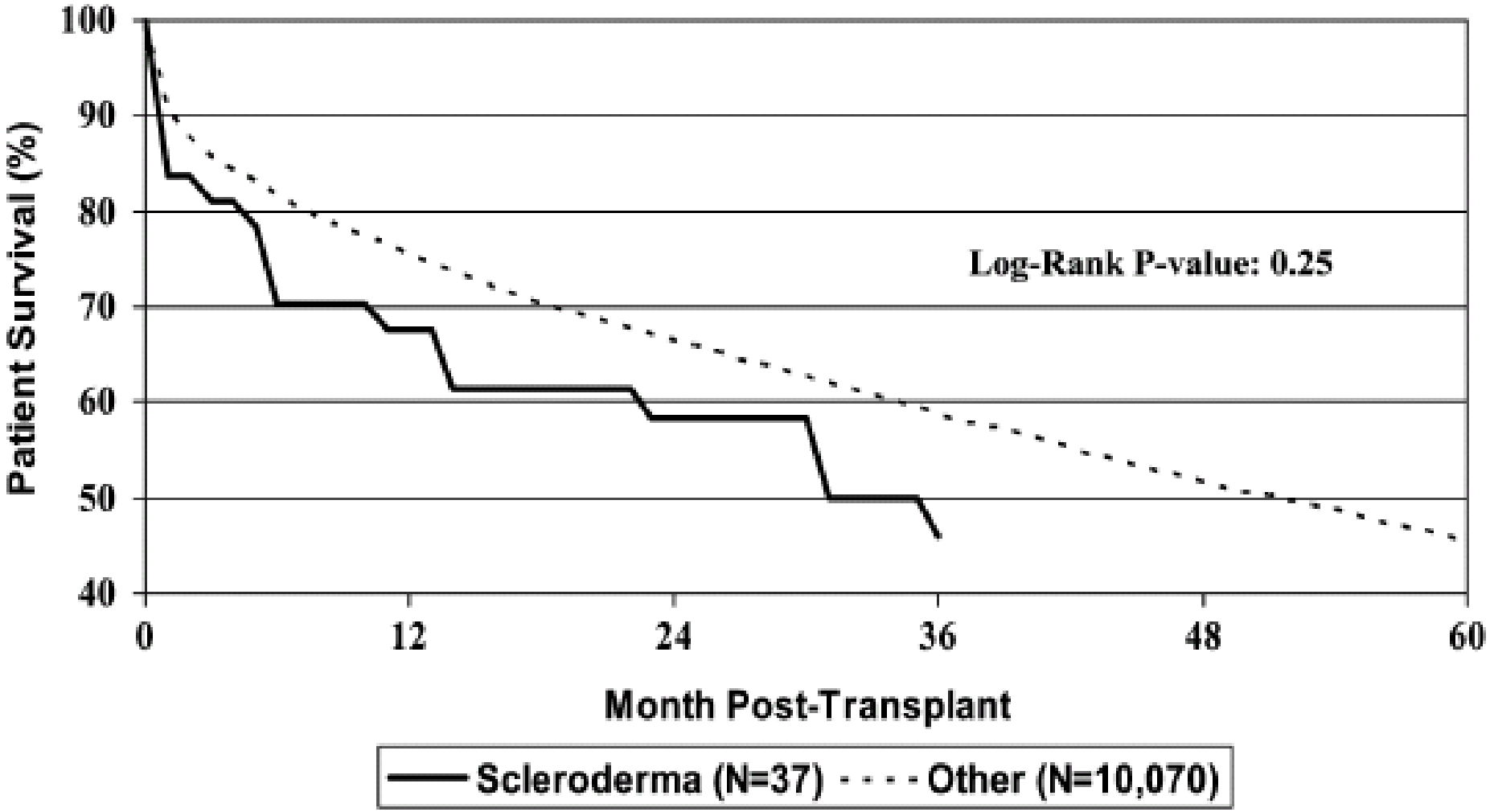
Test t de student apparié

J Rheumatol. 2008 Jun;35(6):1064-72.

Transplantation pulmonaire

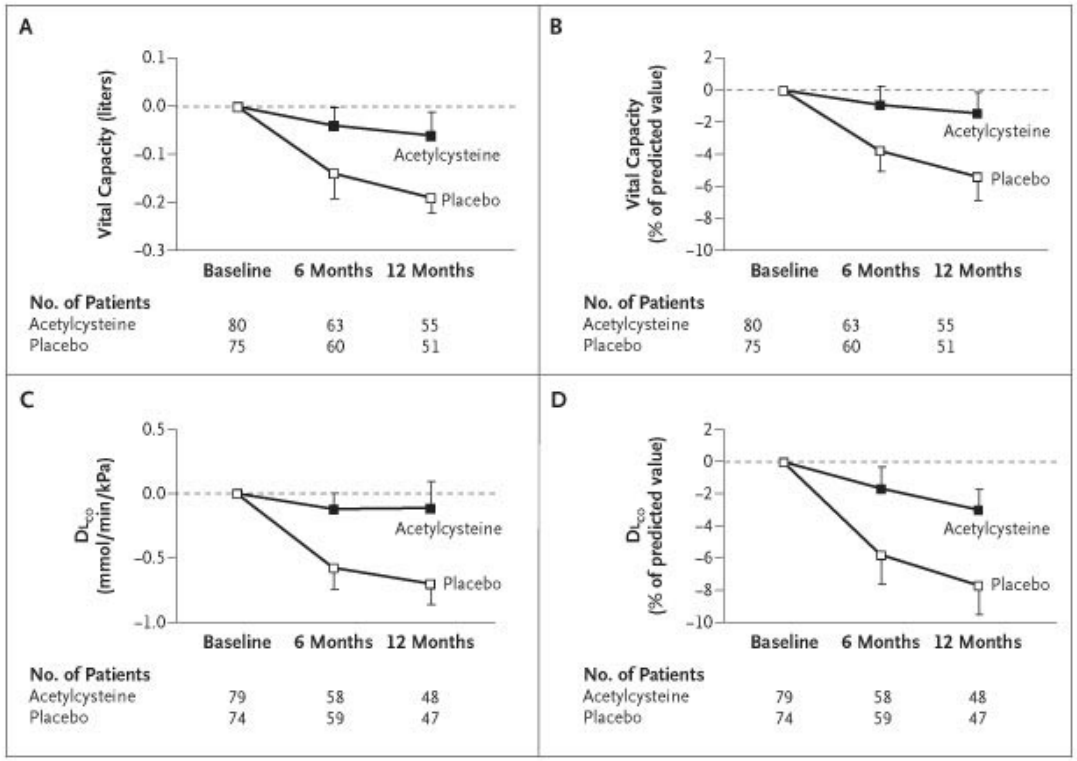
- 29 SS vs 70 patients avec PID et 38 avec HTAP idiopathique
- A 2 ans, 11 patients avec SS (38%), 23 avec PID (33%), et 14 avec HTAPi (37%) sont décédés.
- Survie à 6 mois:
  - Sclérodermie 69%
  - PID 80%
  - HTAP 79%
- Survie à 2 ans: 64% (dans chaque groupe)

Schachna L. et al. Arthritis Rheum 2006



Massad MG et al World Journal of Surgery 2005; 29: 1510-1515

La NAC ralentit la détérioration de la fonction respiratoire

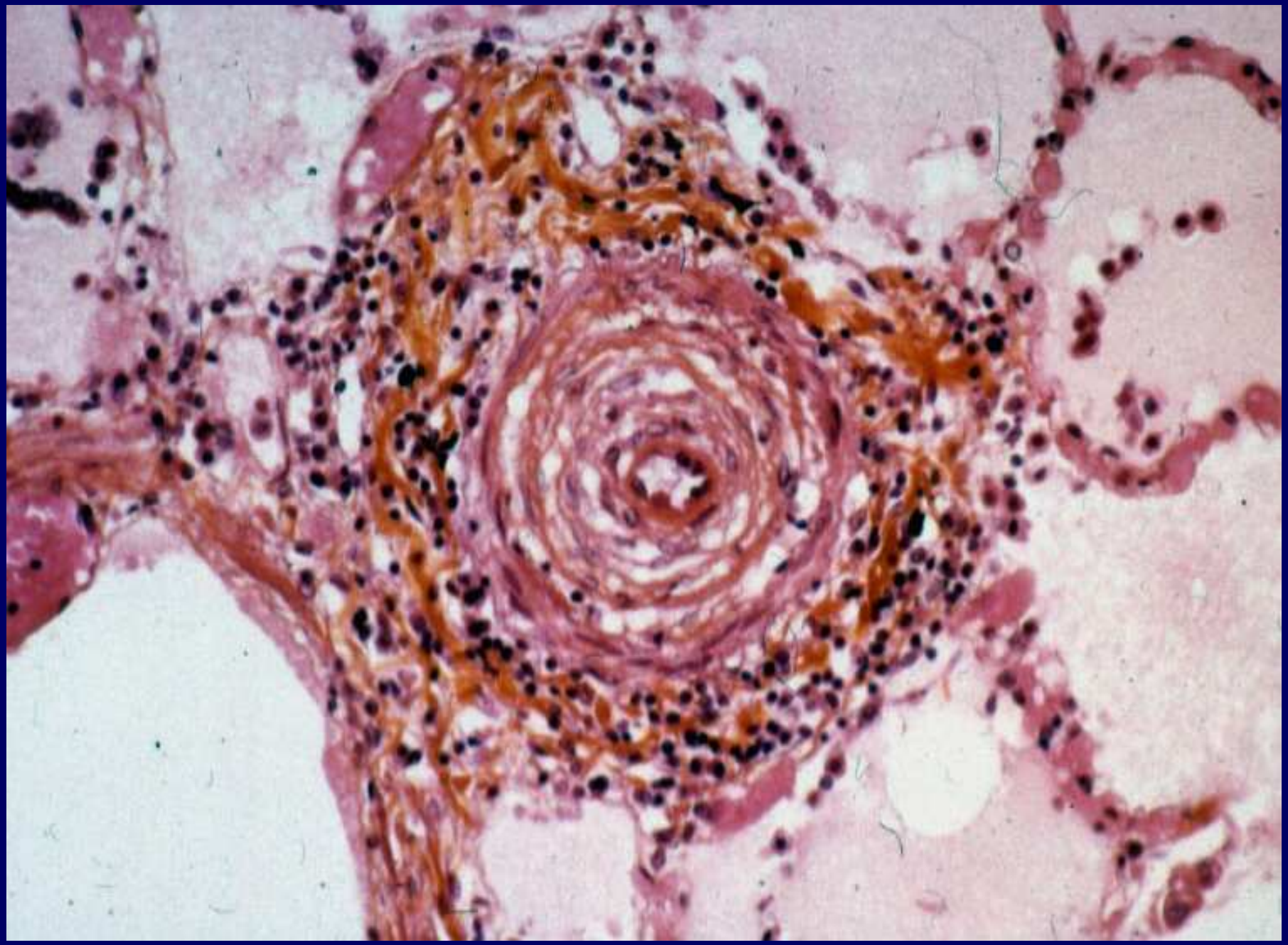


Δ CV: 180 ml *(4,8%)*
P = 0,017

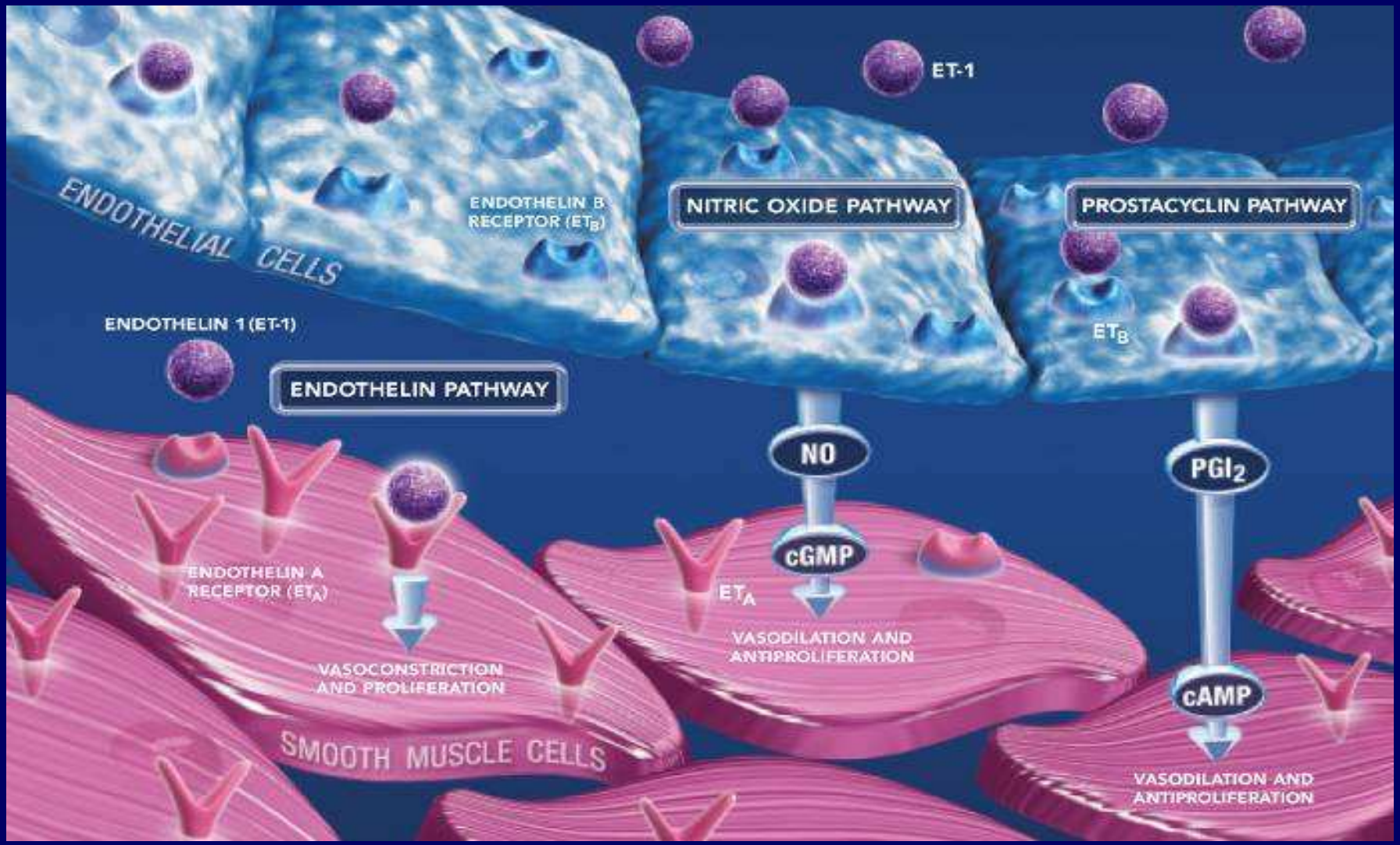
Δ DLCO : 0,75 *(5%)*
P = 0,003

Mortalité : 9% vs 11%
Dyspnée, score CRP,
Score TDM
QdV **NS**

Demedts, NEJM 2005

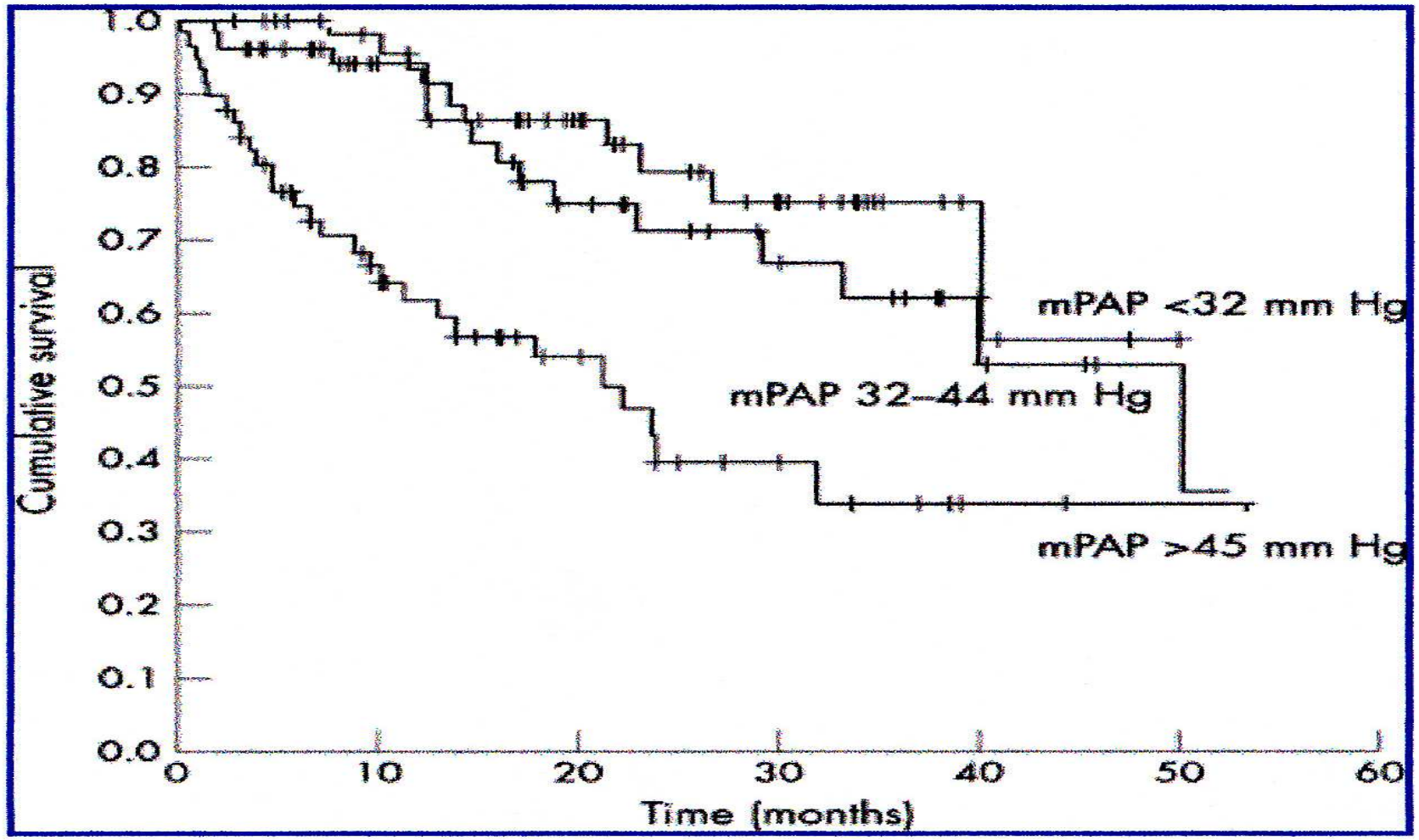


3 voies thérapeutiques dans la SS [1-3]



1.Peacock AJ *et al*, eds. *Pulmonary Circulation: Diseases and Their Treatment*. 2nd ed. Arnold; 2004. 2.Kaplan NM. In: Zipes DP *et al*. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 7th ed. Elsevier Saunders; 2005:959-987. 3.Spieker LE *et al*. *J Am Coll Cardiol*.2001;37:1493-505.

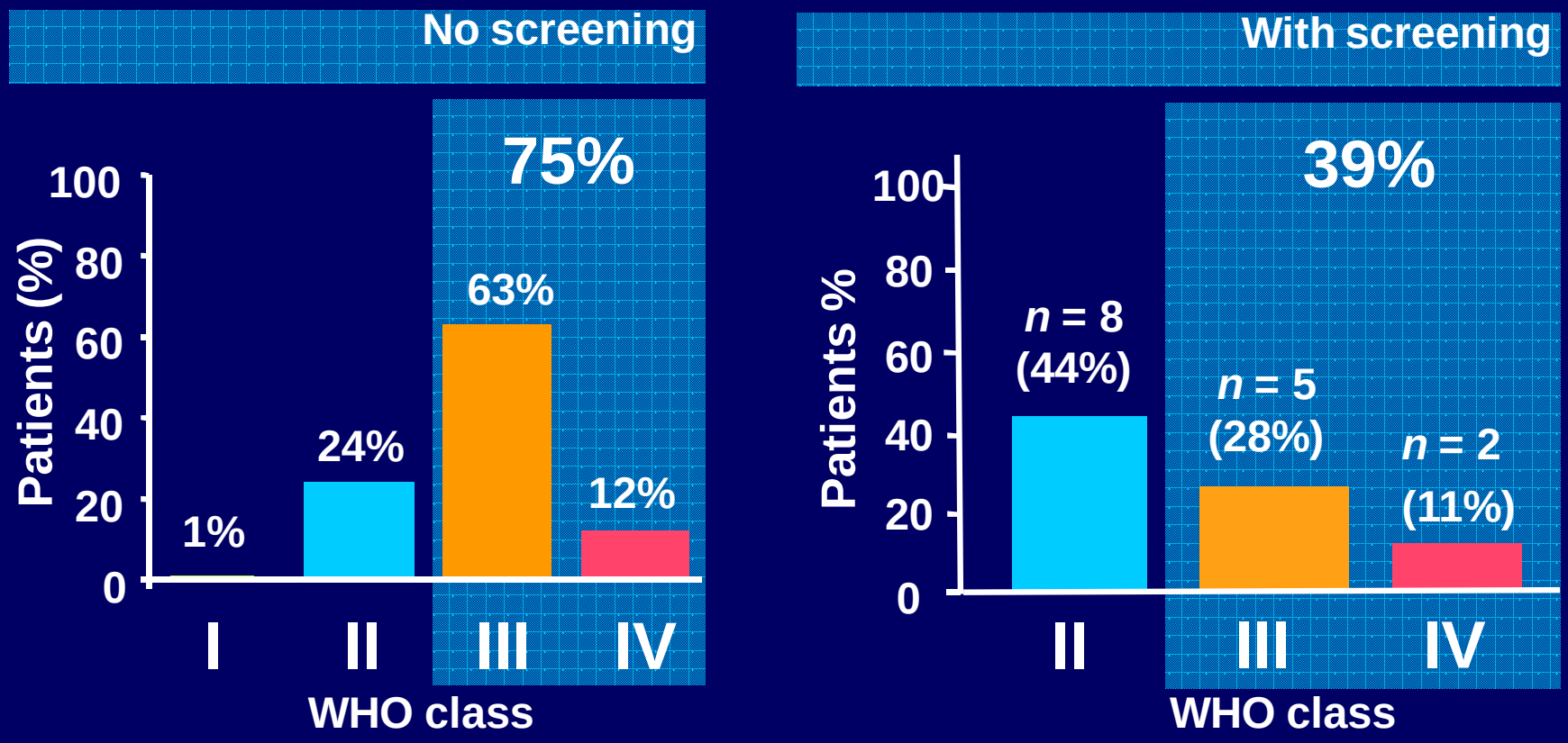
L''HTAP de la sclérodermie doit être traitéee précocément



Mukerjee D. Ann Rheum Dis 2003 ;62 :1088

Systematic detection is useful

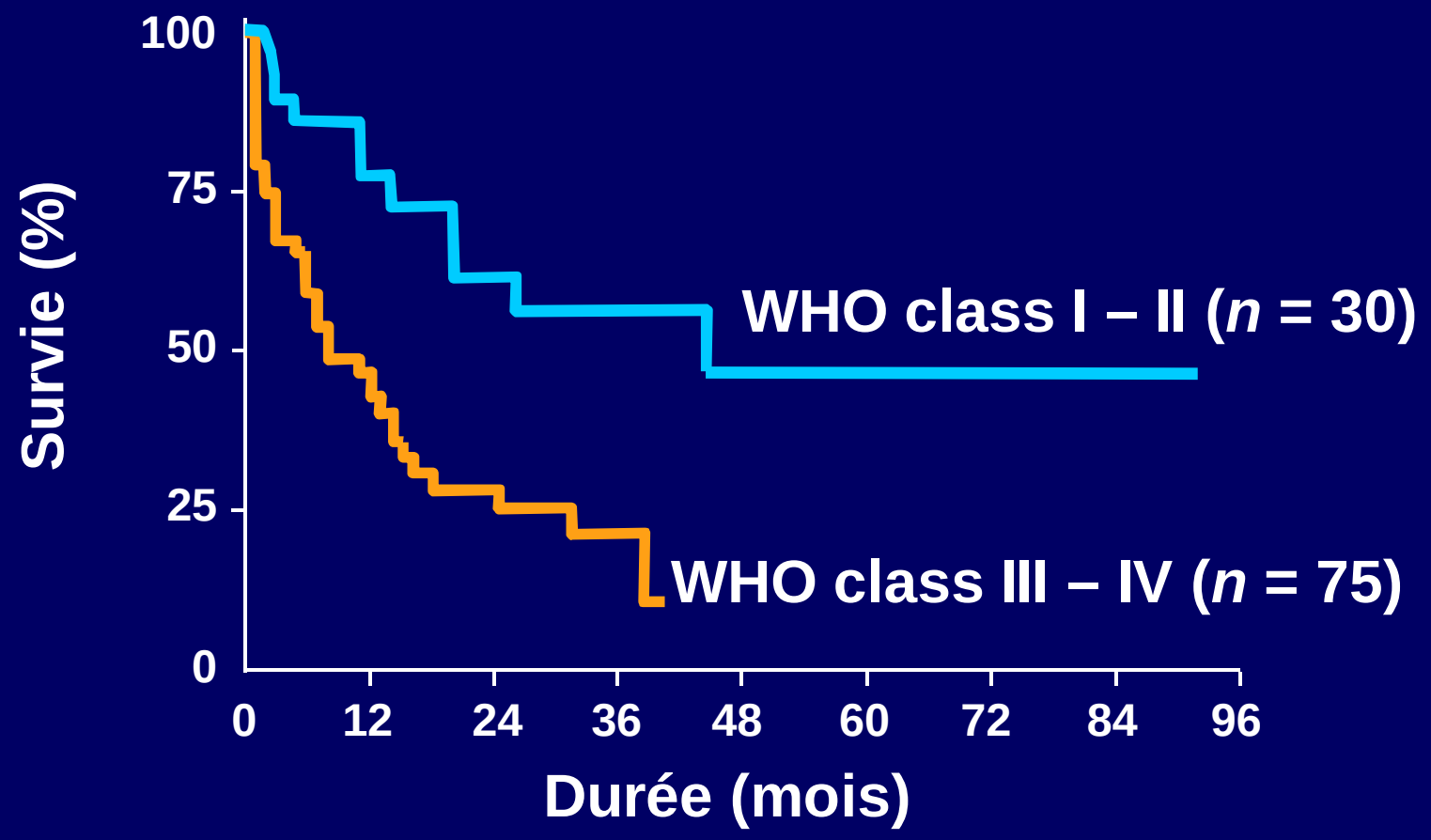
WHO functionnal class at diagnosis



Hachulla E, *et al*. *Arthritis Rheum* 2005; 52:3698-700.
Humbert M, *et al*. *Am J Respir Crit Care Med* 2006; 173:1023-30.

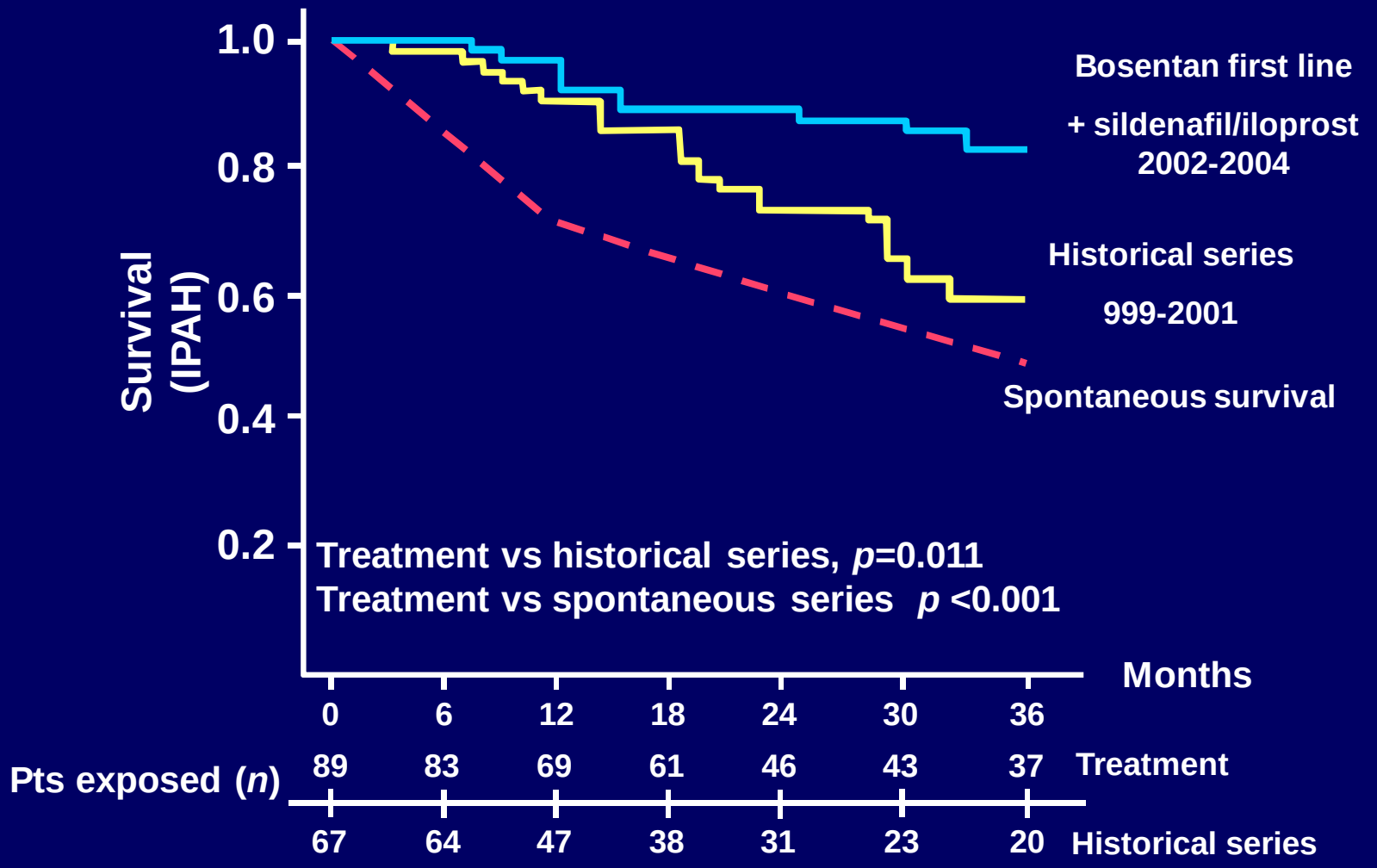
L'HTAP progresse rapidement en l'absence de traitement

... *Même si les symptômes sont mineurs*



Brenot F. *Chest* 1994; 105:33S-36S.

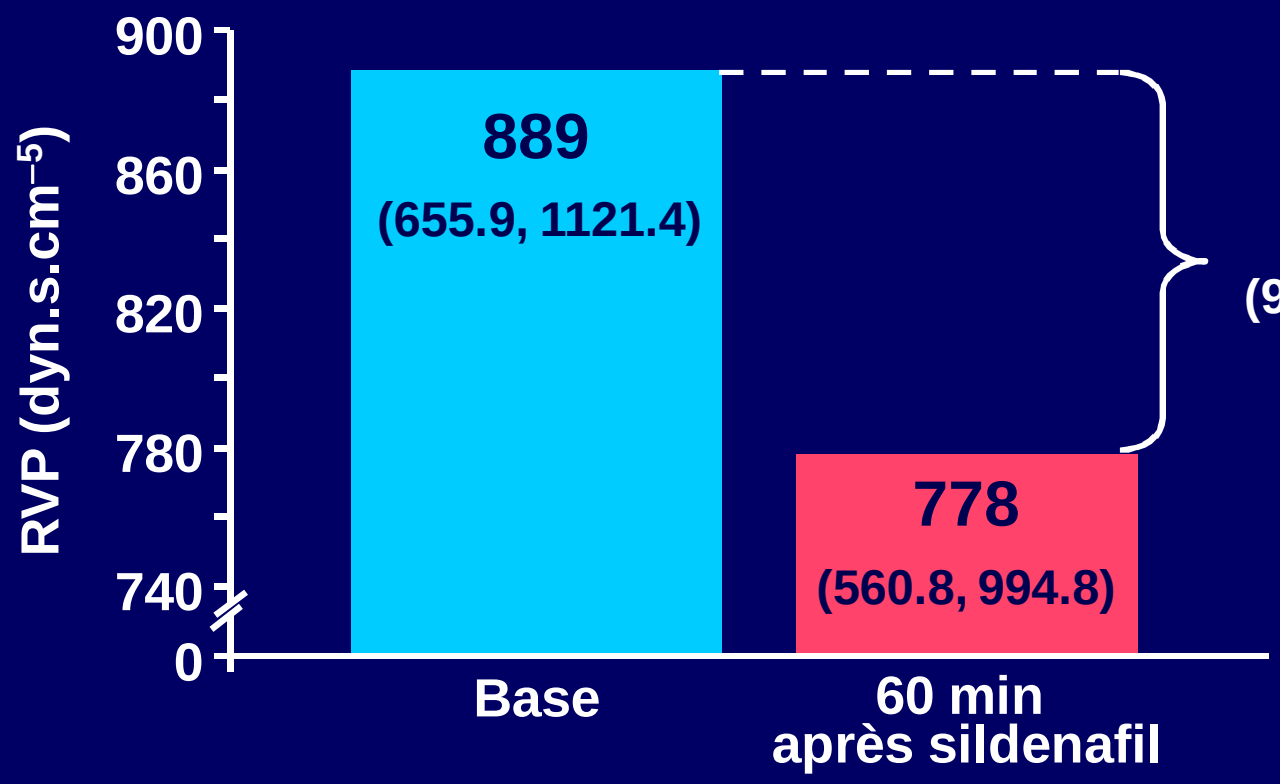
Treatment improves prognosis of PAH



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

COMPASS-1: Objectif primaire

Le sildenafil réduit les RVP des malades sous bosentan



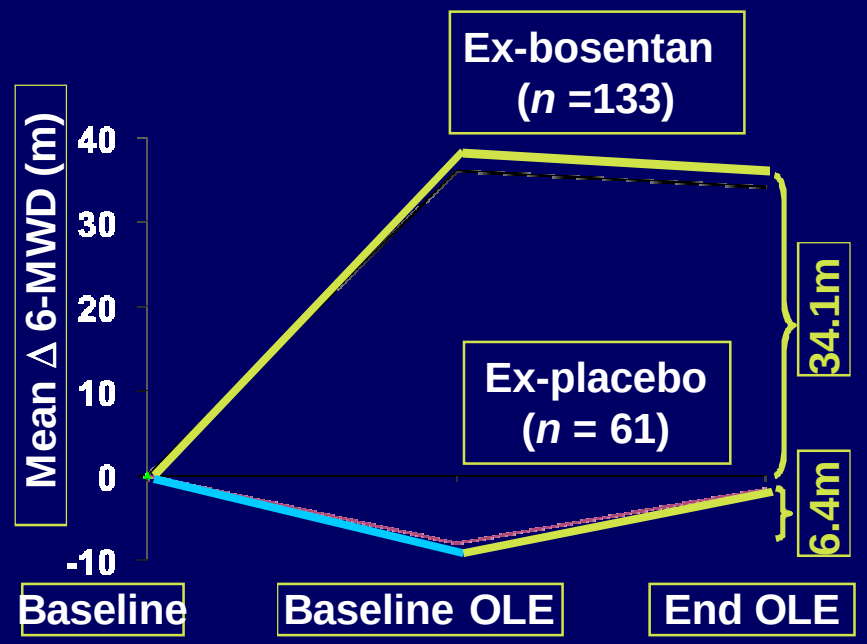
***n*=37**

–15.2%
(95% CI: –20.8, –9.6)
***p*<0.0001**

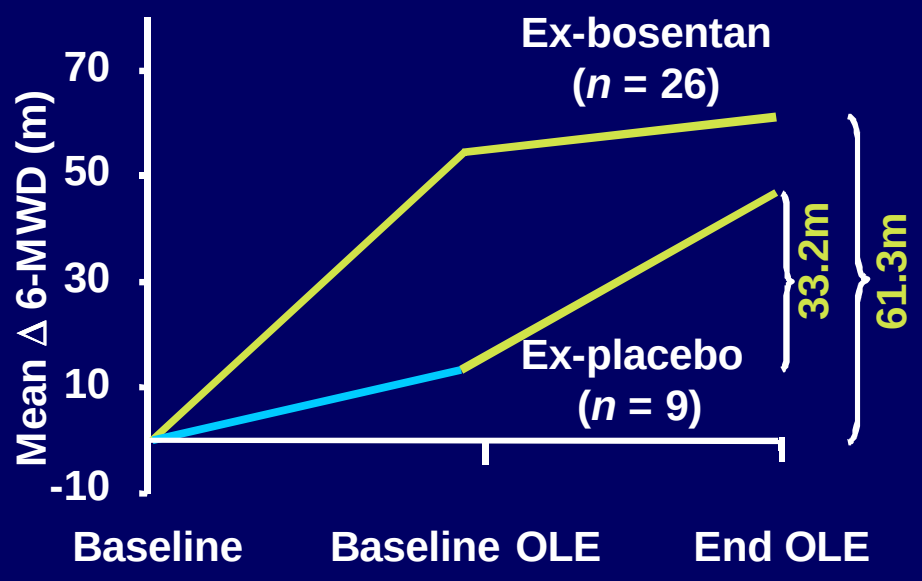
Gruenig E, *et al.* Presented at ESC 2007.

Time lost by delayed treatment cannot be made up

BREATHE-1[1] and 1 year OLE[2]



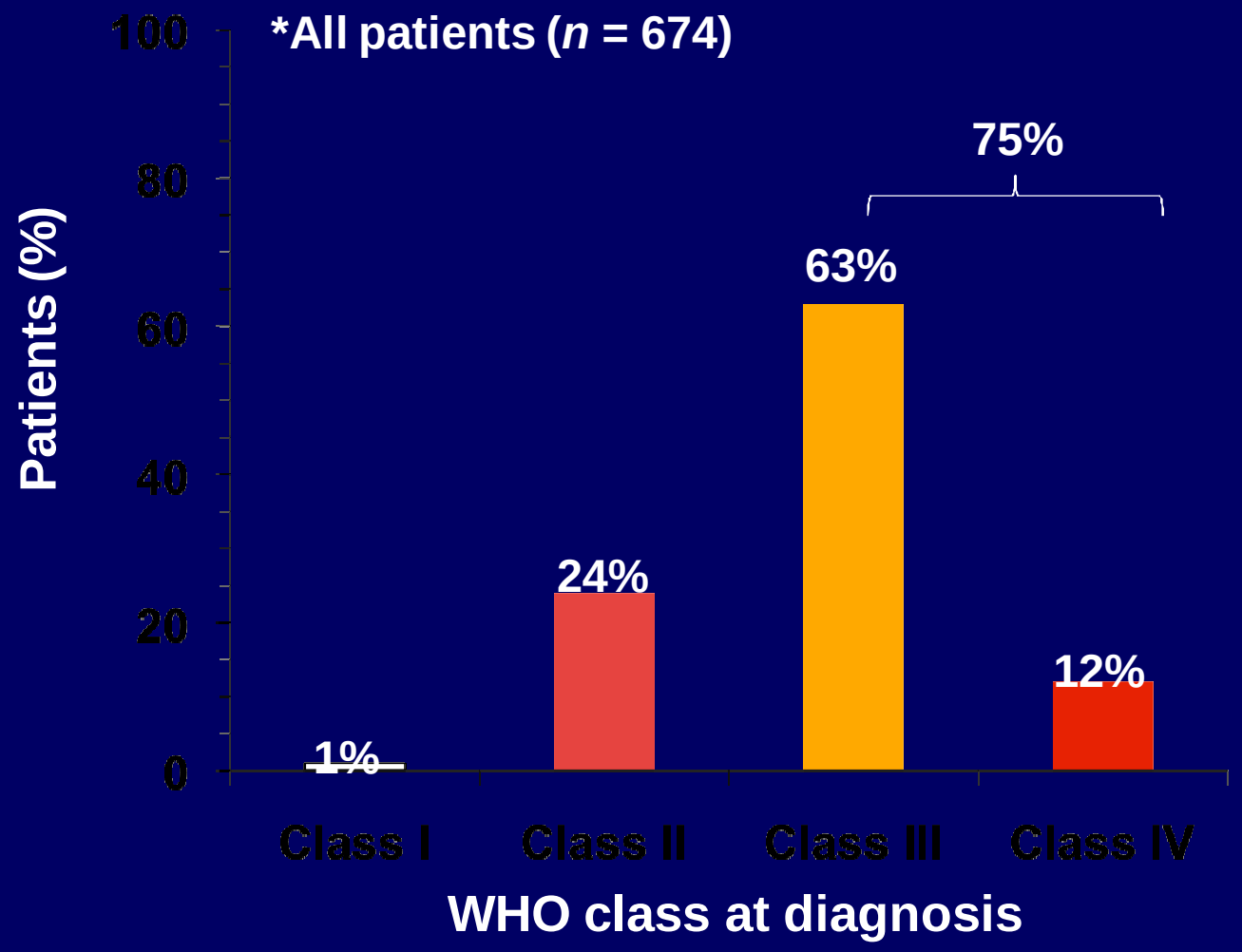
BREATHE-5 and 6 month OLE[3]



1. Rubin, *et al. New Engl J Med* 2002; 346:896-903.
2. Badesch DB, *et al. AHA* 2006.
3. Gatzoulis M, *et al. Int J Cardiol* 2008; 127:27-32.

OLE: Open label extension

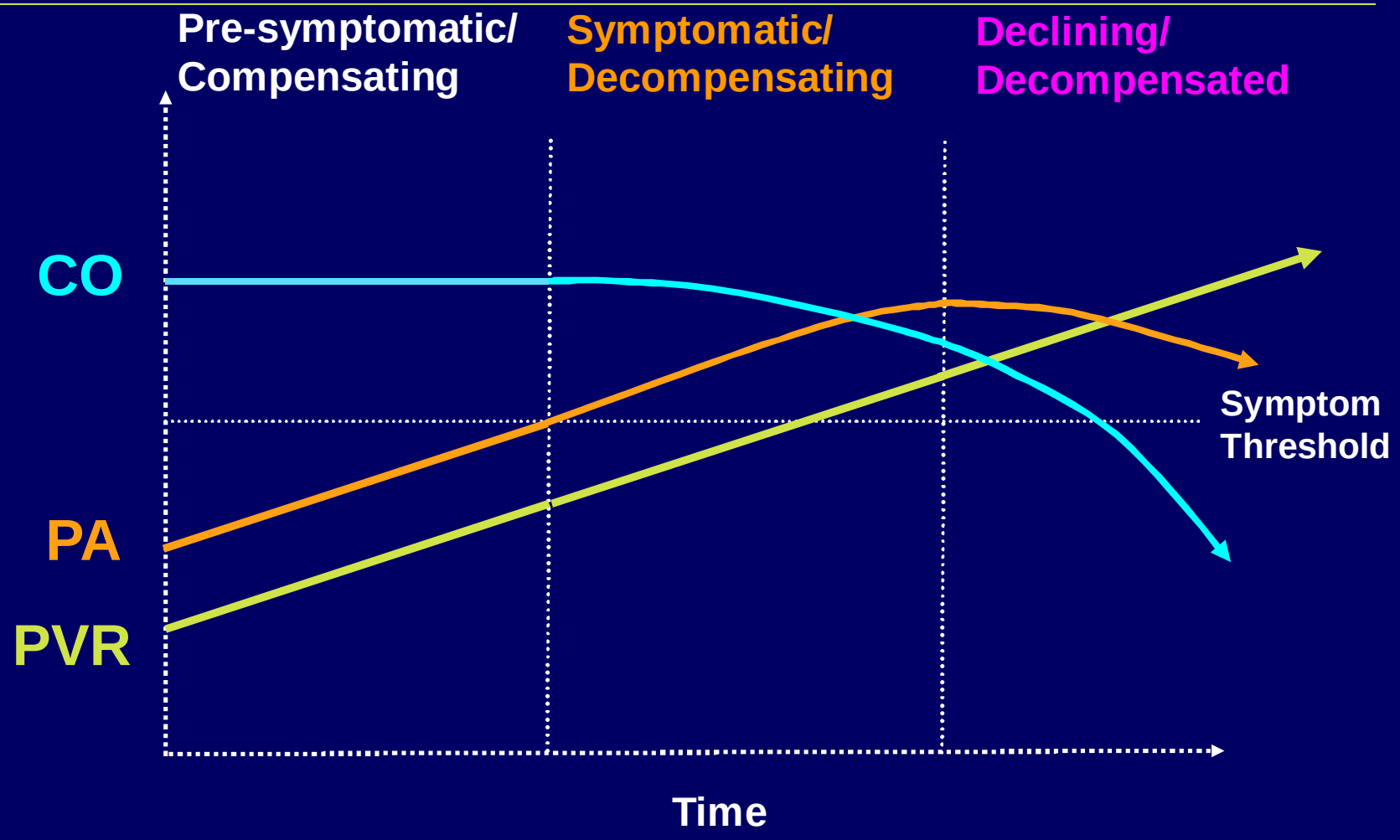
PAH is still diagnosed late in the course of the disease



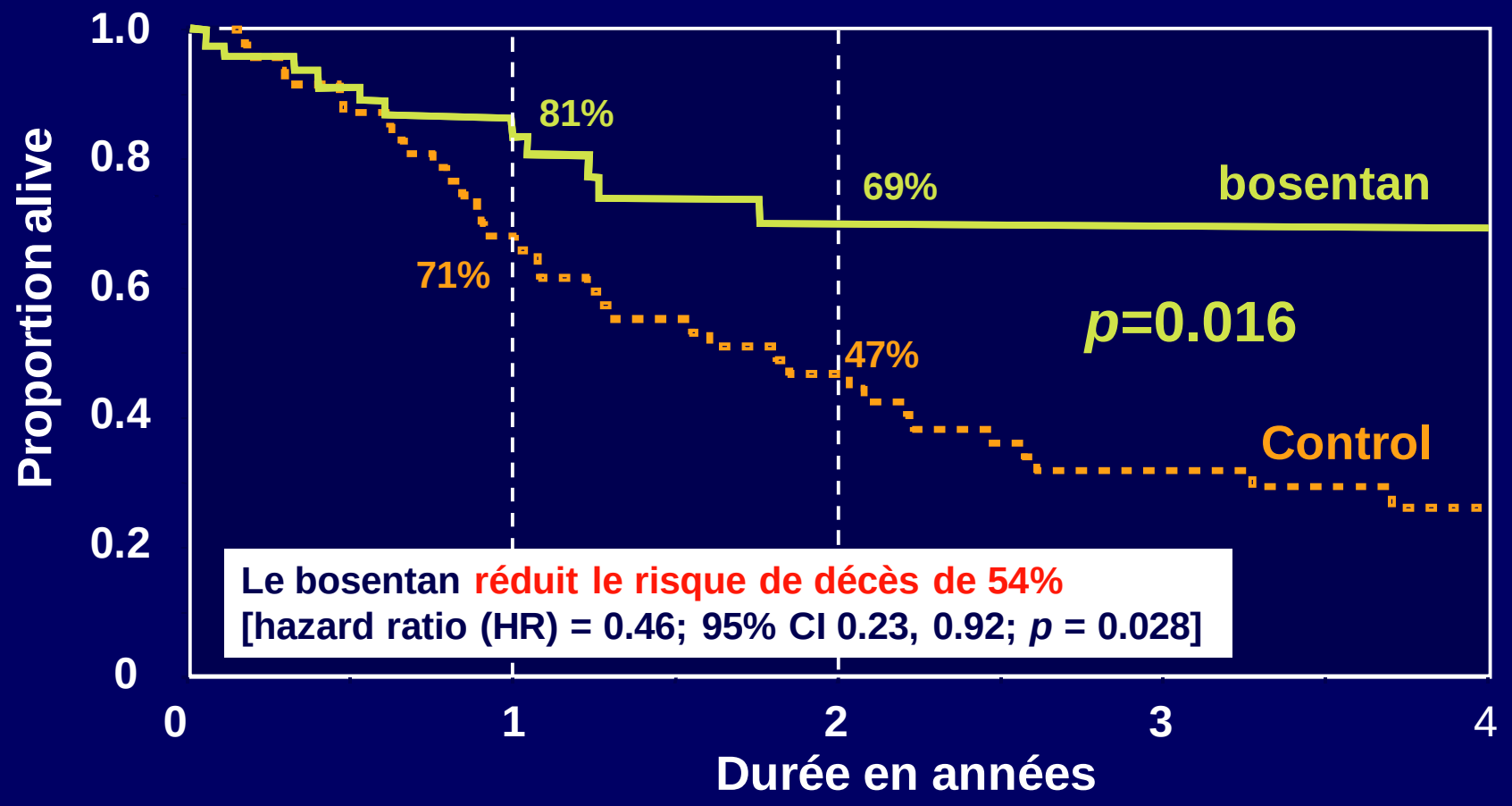
Humbert M, *et al. Am J Respir Crit Care Med* 2006;173:1023-30.

Pulmonary hypertension

A disease of pulmonary vascular resistance



Impact du bosentan en première ligne sur la survie des SSc avec HTAP

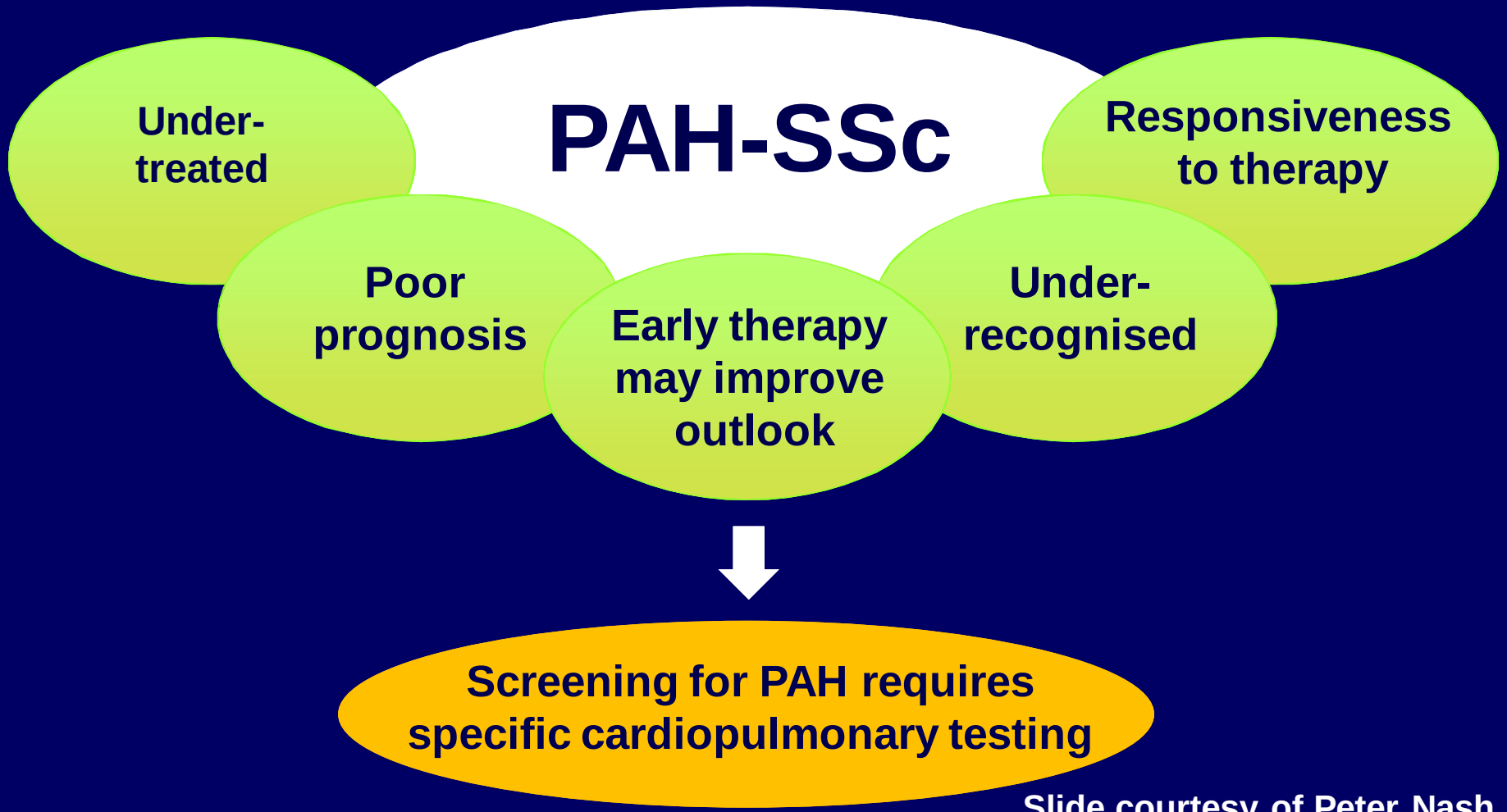


Le bosentan réduit le risque de décès de 54%
[hazard ratio (HR) = 0.46; 95% CI 0.23, 0.92; *p* = 0.028]

^Conventional therapy +/- prostanoids

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

Why screen SSc patients for PAH?



Slide courtesy of Peter Nash.

NEVER FORGET

- Prevention
  - vaccination (flu, pneumonia)
  - antibiotics
- Treat infections
  - antibiotics
- Oxygene
- rehabilitation
- etc….

CONCLUSIONS (1)

- ILD is the first cause of death in patients with SSc
- ILD occurs progressively
- NSIP is more frequent than UIP
- Lung function test and CT-scann are useful
- DLCO predicts outcome
- Cyclophosphamide is one of the treatment of ILD

CONCLUSIONS (2)

- PAH is a severe manifestation of SSc
- PAH is more frequent in limited SSc (10%)
- Early detection is the best guarantee for early treatment and better outcome
- Several drugs are available

CONCLUSIONS (3)

- In PAH, first line treatment comprises anti-endothelin phosphodiesterase inhibitor.
- Prostaglandins are proposed in secod or third line treatment.

French Vasculitis Study Group

Hôpital Cochin, Paris

www.vascularite.org

Centre de Référence Maladies Systémiques et Autoimmunes rares