Sclérodermie systémique
Hypertension artérielle pulmonaire (excepté la thérapeutique)

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DU maladies systémiques – 13 octobre 2017

Conflicts of interest

- **Consultant**: Actelion, CSL Behring, Cytheris, GSK, LFB Biotechnologies, Lilly, Pfizer
  - Financial support to ARMIIC
- **Investigator**: Actelion, CSL Behring, Pfizer
- **Financial support (grants)**: Actelion, CSL Behring, GSK, LFB Biotechnologies, Pfizer

Updated classification of pulmonary hypertension

Connective tissue diseases

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, ENG, **SMAD9**, **CAV1**, **KCNK3**
   - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
   - 1.4.1 Connective tissue disease
   - 1.4.2 HIV infection
   - 1.4.3 Portal hypertension
   - 1.4.4 Congenital heart diseases
   - 1.4.5 Schistosomiasis

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

1″. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease

2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

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 lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: **chronic hemolytic anemia**, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

*5th WSPH Nice 2013. Main modifications to the previous Dana Point classification are in **bold**.
BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

Simmoneau G et al. J Am Coll Cardiol 2013

Pulmonary Arterial Hypertension in France

Results from a National Registry

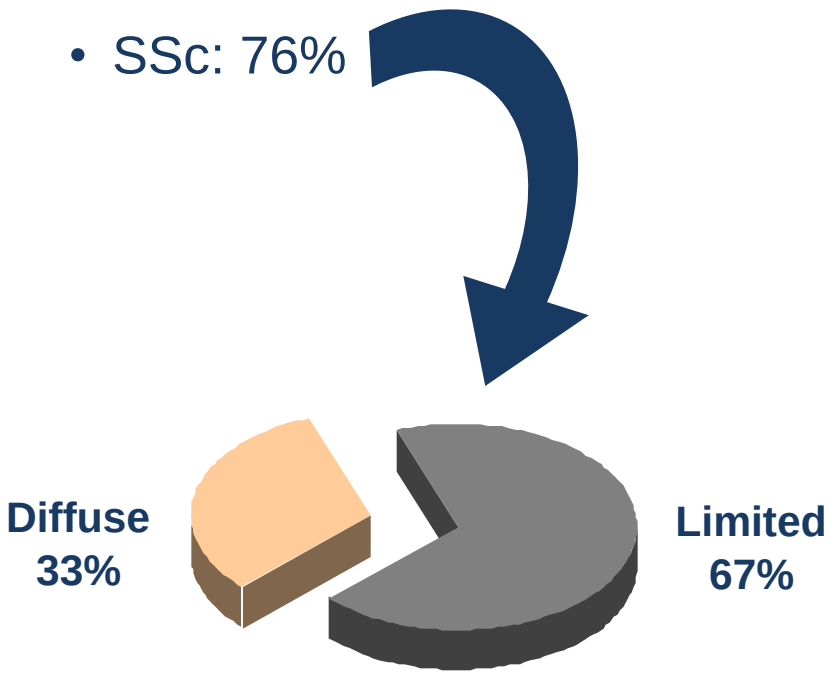
Marc Humbert, Olivier Sitbon, Ari Chaouat, Michèle Bertocchi, Gilbert Habib, Virginie Gressin, Azzedine Yaici, Emmanuel Weitzenblum, Jean-François Cordier, François Chabot, Claire Dromer, Christophe Pison, Martine Reynaud-Gaubert, Alain Haloun, Marcel Laurent, Eric Hachulla, and Gérald Simonneau

Service de Pneumologie, Centre des Maladies Vasculaires Pulmonaires, Hôpital Antoine Béclère, Assistance-Publique–Hôpitaux de Paris, Université Paris-Sud, Clamart, France; Service de Pneumologie, Hôpital Hautepierre, Strasbourg; Service de Pneumologie, Hôpital Louis-Pradel, Lyon; Service de Cardiologie, Hôpital de la Timone; Service de Pneumologie, Hôpital Sainte Marguerite, Marseille; Actelion Pharmaceuticals France, Paris; Service de Pneumologie, Hôpital de Brabois, Vandoeuvre-les-Nancy; Service de Chirurgie Thoracique, Hôpital du Haut Levesque, Bordeaux; Département Médecine Aiguë Spécialisée, Hôpital Michallon, Grenoble; Service de Pneumologie, Hôpital Laennec, Nantes; Service de Cardiologie, Hôpital Pontchaillou, Rennes; and Service de Médecine Interne, Hôpital Claude Huriez, Lille, France

15% of PAH have CTD

SSc is the leading cause of CTD-associated PAH

- SLE: 15%
- SSc: 76%
- Other ~ 10%
  - MCTD
  - Sjögren's syndrome
  - Polymyositis
  - (Rheumatoid arthritis?)

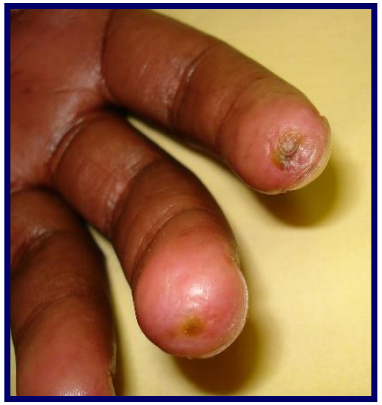


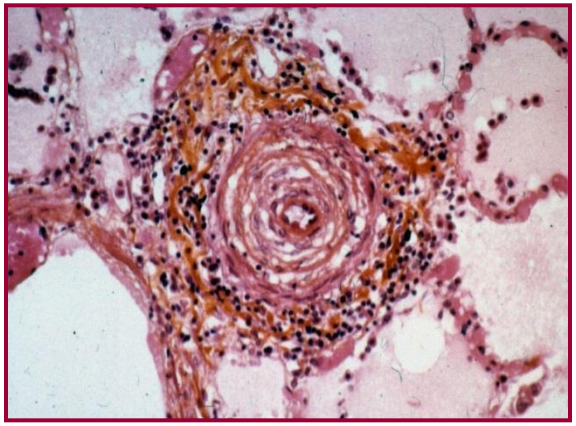
Humbert M, *et al. Am J Respir Crit Care Med* 2006;173:1023–30.

SYSTEMIC SCLEROSIS

➢Vascular hyperreactivity

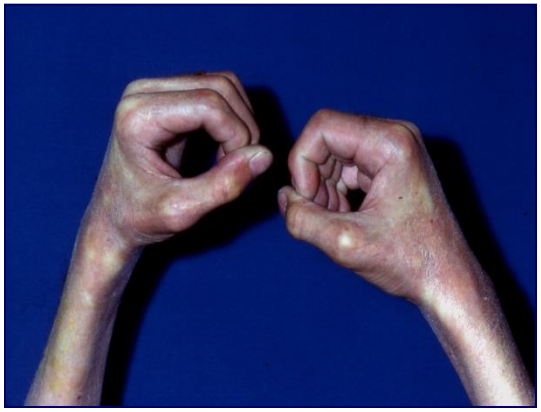
Raynaud's phenomenon
Renal crisis
Pulmonary arterial hypertension

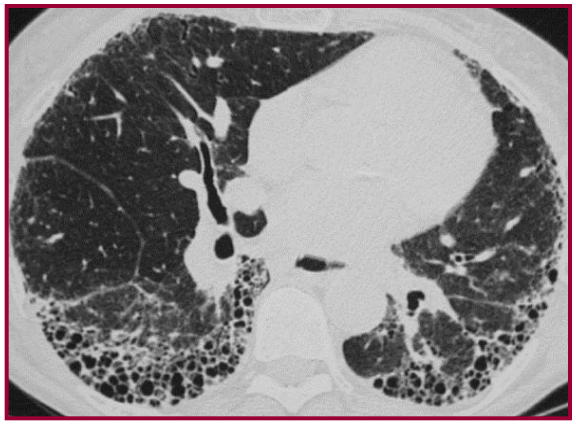




➢Fibrosis

Skin
Lung
Bowell
Heart

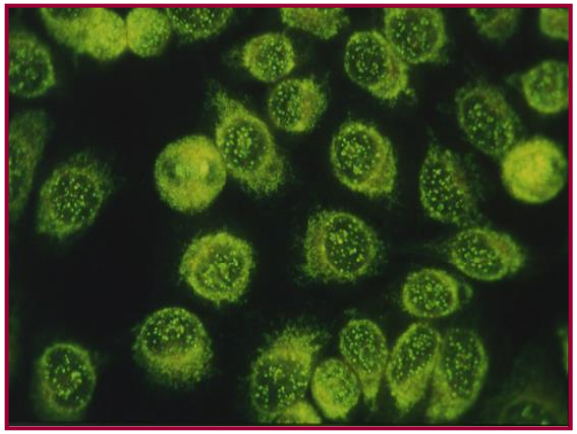


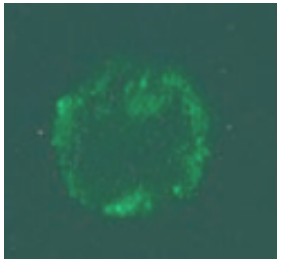


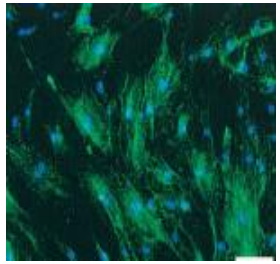
➢Autoimmunity

Autoantibodies
- Anti-Scl70
- Anti-centromere
- Anti-ARNPolIII

Ac anti-fibroblasts





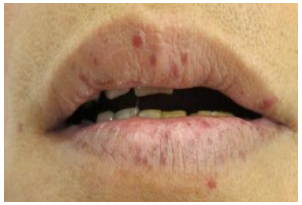


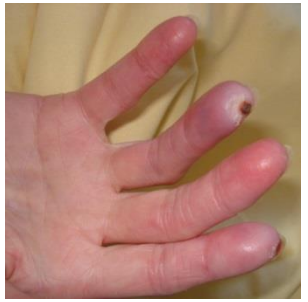
Prévalence

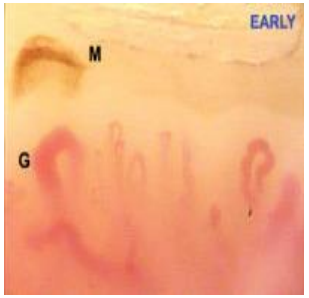
Auteurs	Régions	technique	Prévalence /million
Etats Unis			
Michet	Rochester	Hôpital	**138**
Mayes	Detroit	Sources multiples	**242**
Maricq	Caroline du sud	Population	**190-750**
Océanie			
Chandran	Australie du sud		**147-208**
Roberts-Thomson	Australie du sud	Sources multiples	**233**
Asie			
Shinkai	Japon	Santé publique	**7**
Tamaki	Tokyo	Santé publique	**21-53**
Europe			
Silman	West midland	Sources multiples	**31**
Asboe-Hansen	Danemark	Source hôpital	**126**
Le Guern	Seine Saint Denis	Sources multiples	**158**
El Adssi	Lorraine	Sources multiples	**132**

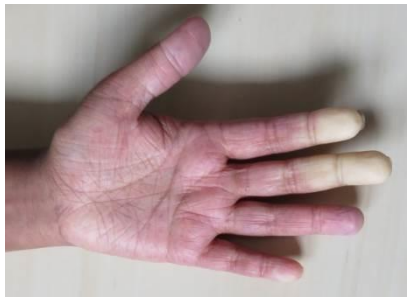
2013 classification criteria for SSc: an ACR/EULAR collaborative initiative (I)

- Skin thickening of the fingers extending proximal to the metacarpophalangeal joints: SSc;
- If that is not present, 7 additive items apply:
  - skin thickening of the fingers,
  - fingertip lesions,
  - telangiectasia,
  - abnormal nailfold capillaries,
  - interstitial lung disease or pulmonary arterial hypertension,
  - Raynaud's phenomenon,
  - SSc-related autoantibodies.





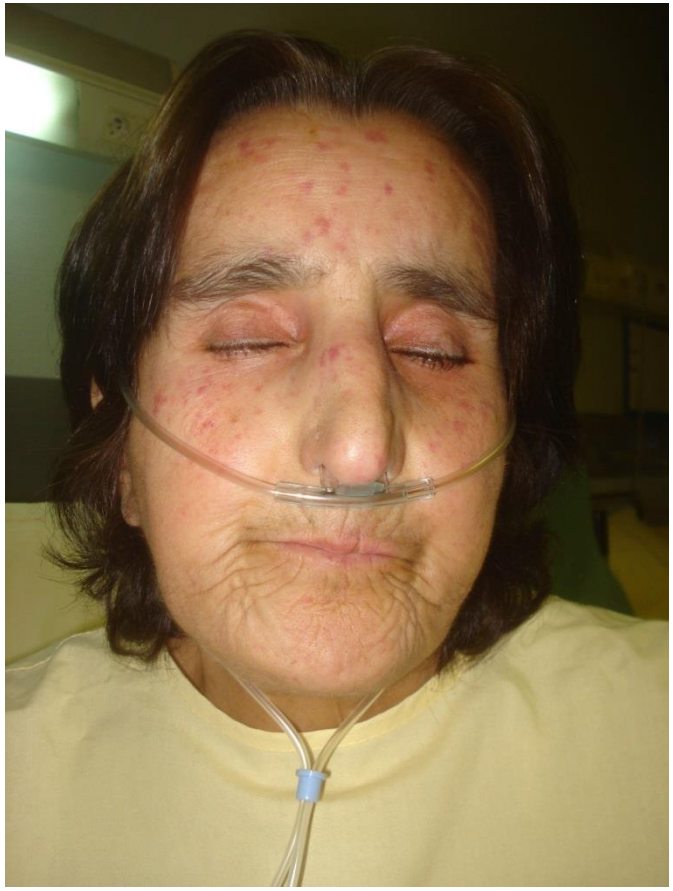


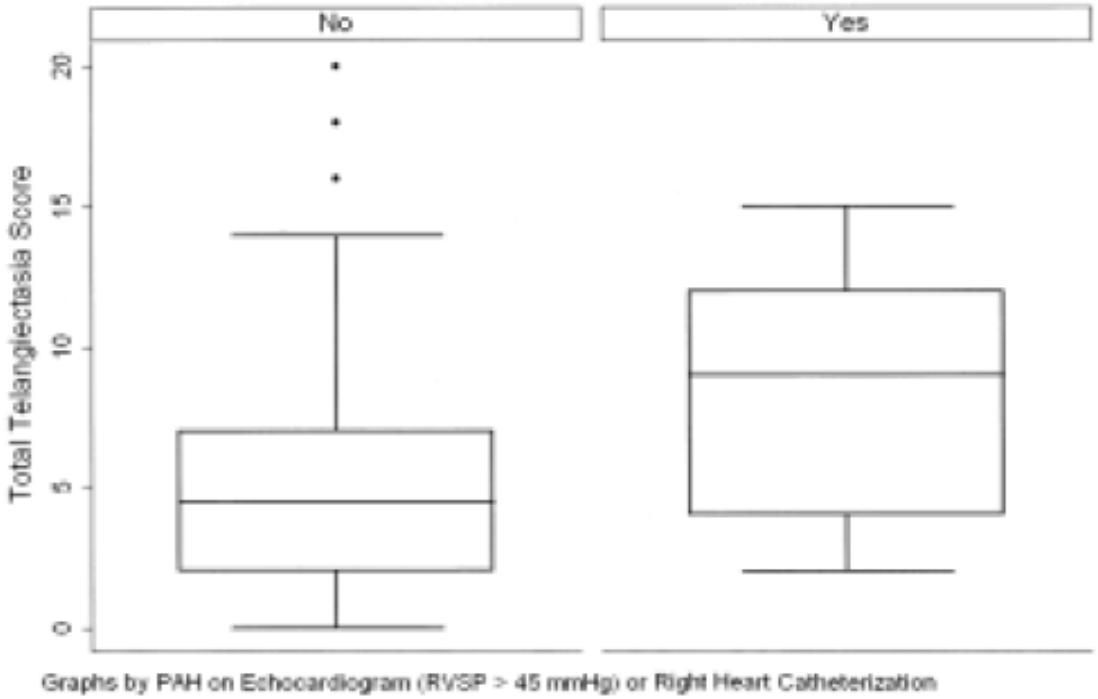


van den Hoogen F et al. Ann Rheum Dis 2013

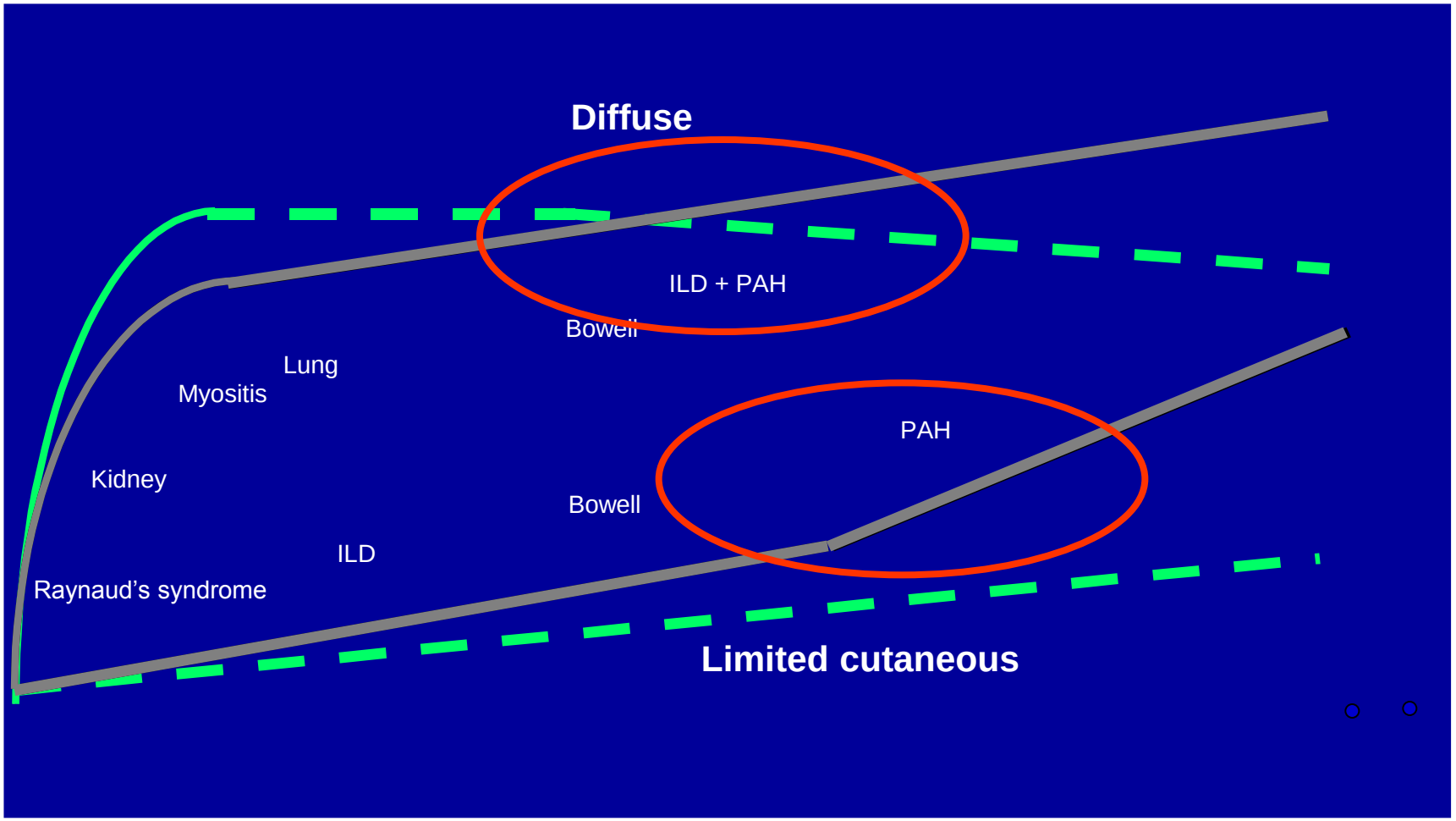
Telangiectases in Scleroderma: A Potential Clinical Marker of Pulmonary Arterial Hypertension

Shah et al. J Rheumatol 2010

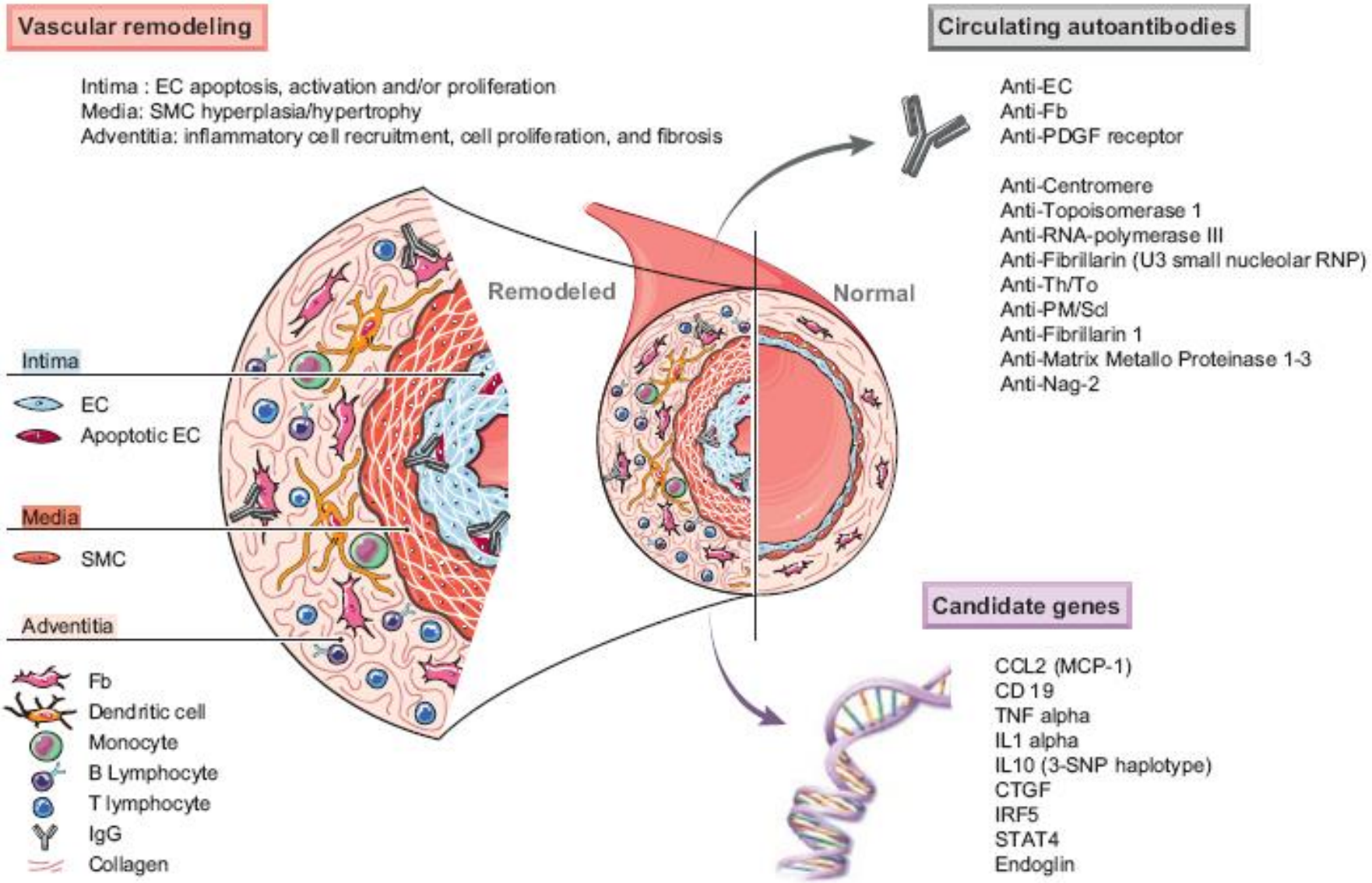




SYSTEMIC SCLEROSIS : EVOLUTION



Pulmonary vascular remodeling in SSc-PAH



Le Pavec J et al 2010 AJRCCM

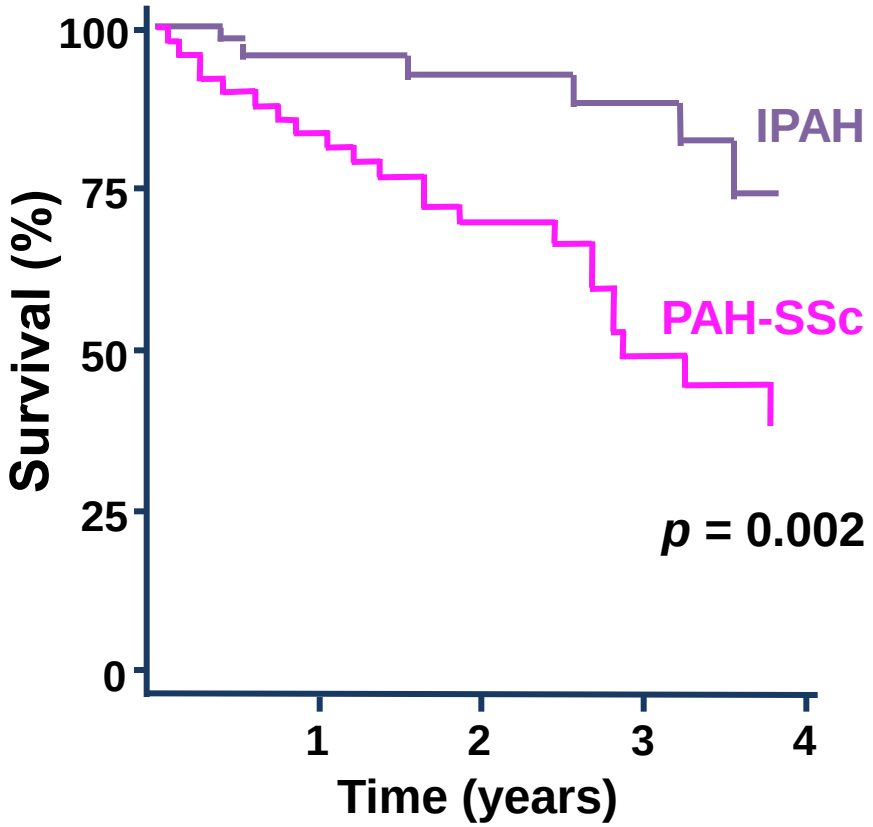
PAH-SSc: Prevalence

Author	Year of publication	Country	PAH definition (RHC)	PAH prevalence
Mukerjee et al.	2003	UK	mPAP > 25 mmHg at rest or > 30 at exercise pulmonary capillary < 14 mmHg	12% (86/722)
Hachulla E, et al.	2005	France	mPAP > 25 mmHg at rest or > 30 at exercise pulmonary capillary < 14 mmHg	7,85% (47/599)
Vonk, et al.	2009	Netherlands	PAPm ≥25mmHg at rest and normal pulmonary capillary pressure	9,9% (113/1,148)
Phung, et al.	2009	Australia	PAPm ≥25mmHg at rest, or ≥30mmHg at exercise pulmonary capillary < 15 mmHg and PVR> 240 dyn/s/cm^2	13% (24/184)
Avouac, et al.	2010	France and Italy	PAPm ≥25mmHg at rest, or ≥30mmHg at exercise pulmonary capillary < 15 mmHg absence of pulmonary fibrosis	3,6% (42/1,165)
Hsu et al.	2014	North America	PAPm ≥25mmHg au repos, ou ≥30mmHg à l'effort et PCP < 15mmHg	13,9% (35/251)

Legendre P, Mouthon L. Presse Med 2014

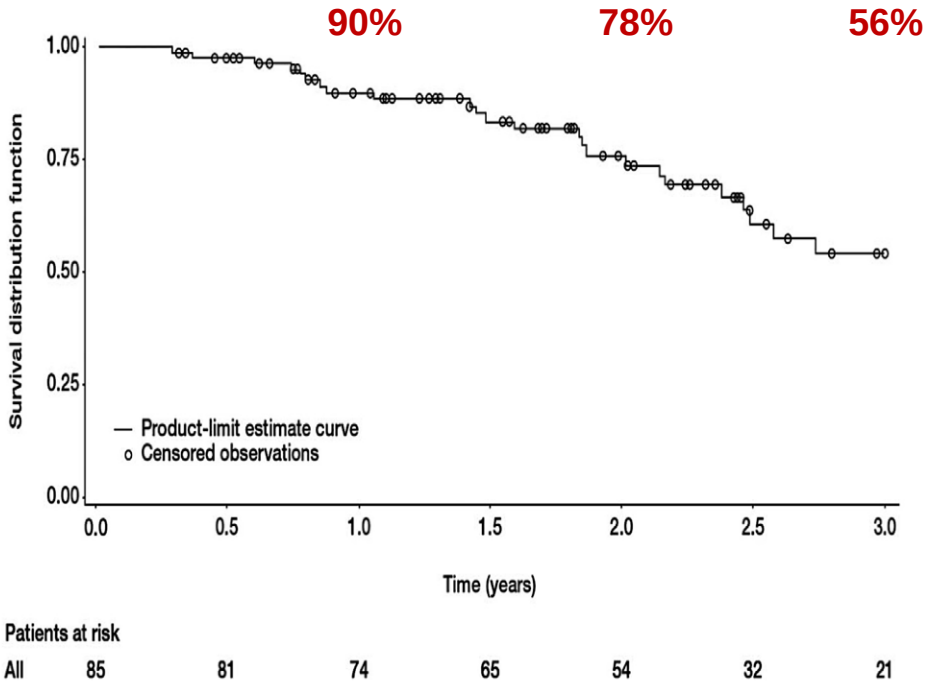
PAH-SSc has a poor prognosis…

PAH-SSc has a poorer prognosis than idiopathic PAH



Fisher MR, *et al. Arthritis Rheum* 2006; 54:3043-50.

In the modern treatment era PAH-SSc has still a poor prognosis…



Launay D, *et al. Ann Rheum Dis* 2013;72:1940–1946.

2015 ESC/ERS Guidelines

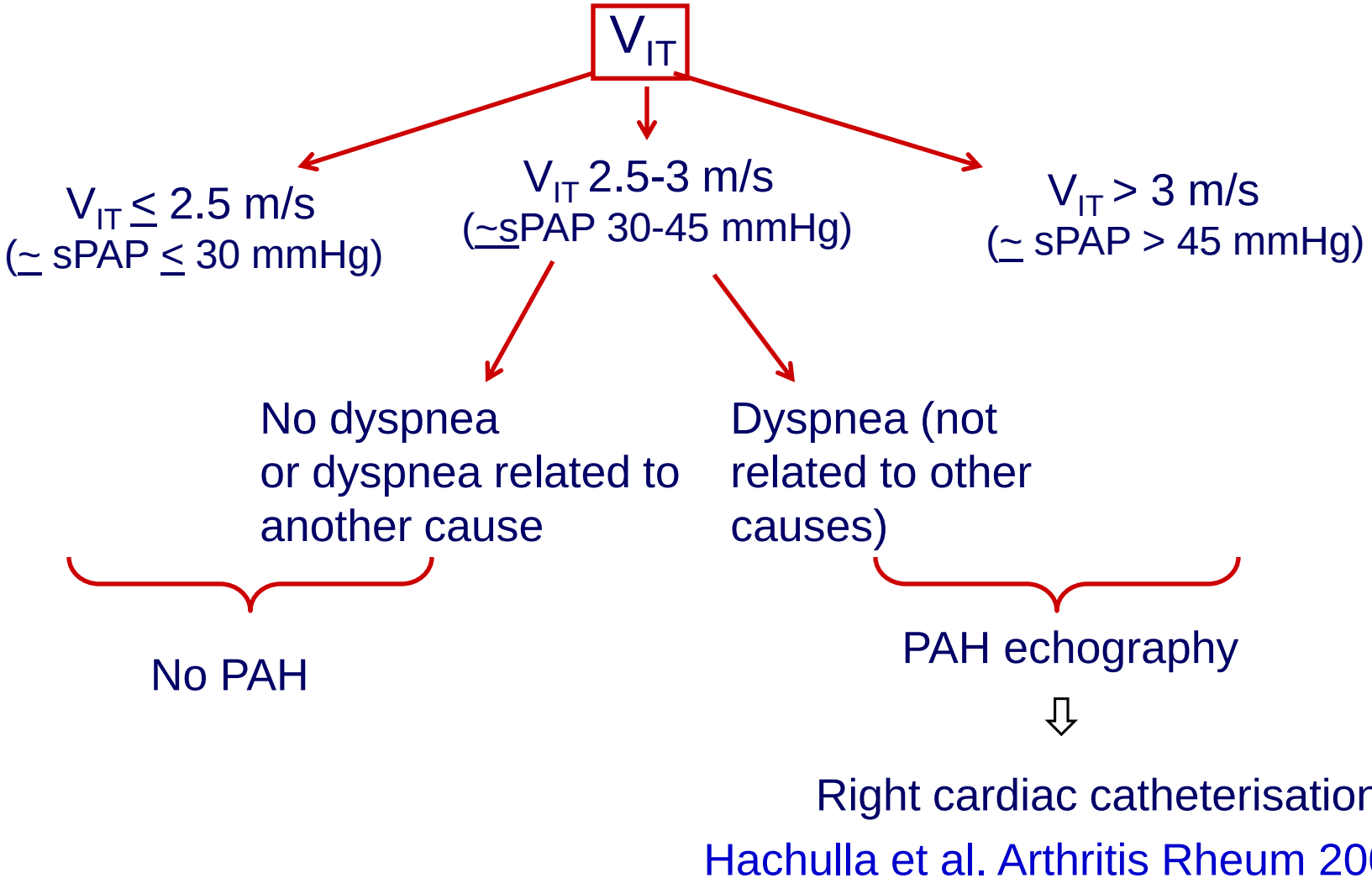
Table 26 **Recommendations for pulmonary arterial hypertension associated with connective tissue disease**

Recommendations	Class[a]	Level[b]	Ref.[c]
Resting echocardiography is recommended as a screening test in asymptomatic patients with SSc, followed by annual screening with echocardiography, DLCO and biomarkers	I	C	46
RHC is recommended in all cases of suspected PAH associated with CTD	I	C	46,327

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

Galiè N, *et al*. ESC/ERS Guidelines. *Eur Heart J* 2016 & *Eur Respir J* 2015.

Cardiac EchoDoppler
PAH definition



Hachulla et al. Arthritis Rheum 2005

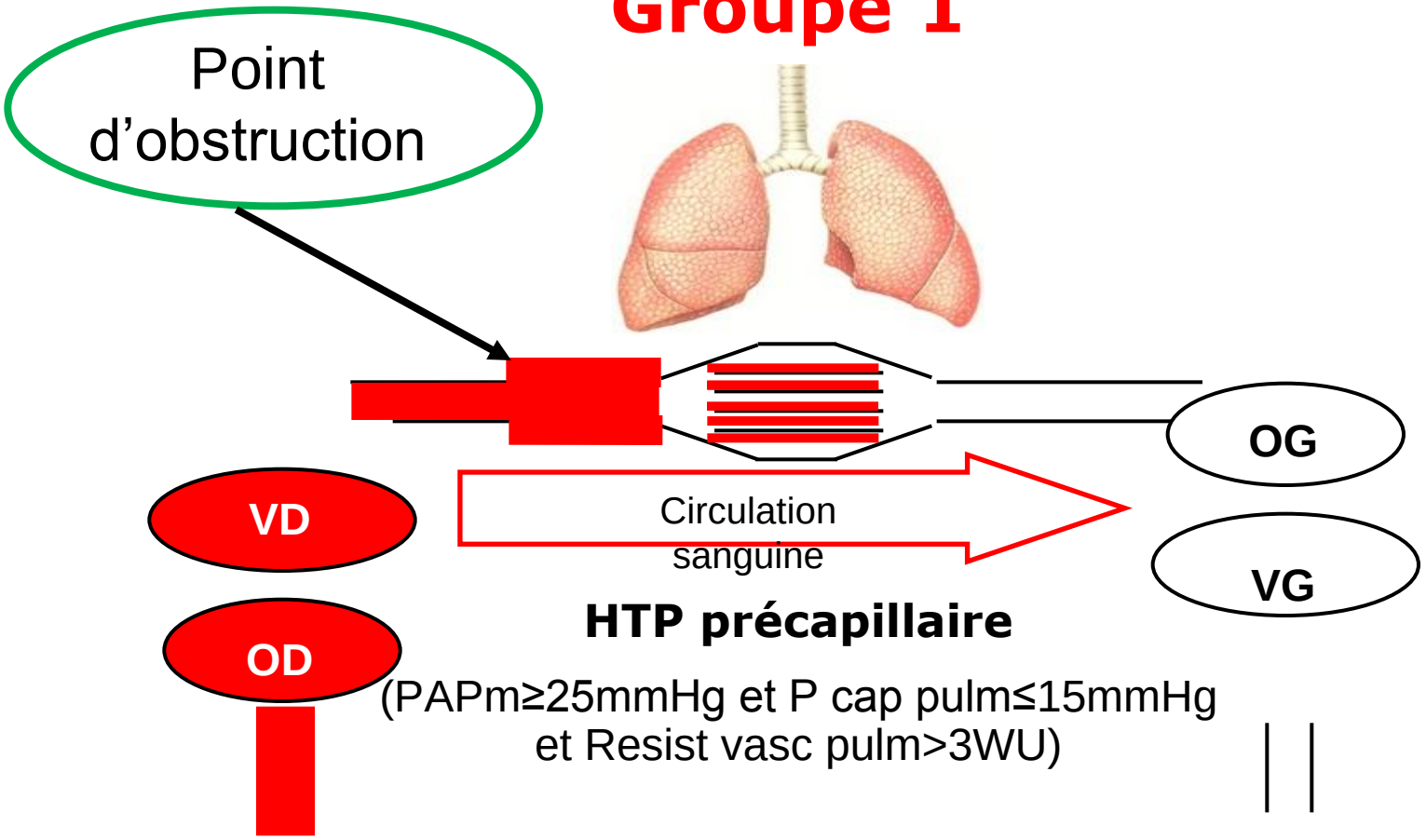
Cardiac catheterisation (n=33)

- PAH : 18
- [mPAP > 25 mmHg at rest or > 30 mmHg at exercise with PAwP < 15 mmHg]
  - 25-35 mmHg: 14
  - 35-45 mmHg: 3
  - 45 mmHg: 1
- Post-capillary “venous”pulmonary hypertension: 3 (10%)
- No PAH : 12 => 6 with mPAP > 20 mmHg

Hachulla et al. Arthritis Rheum 2005

HTP: quel est le bon diagnostic ?

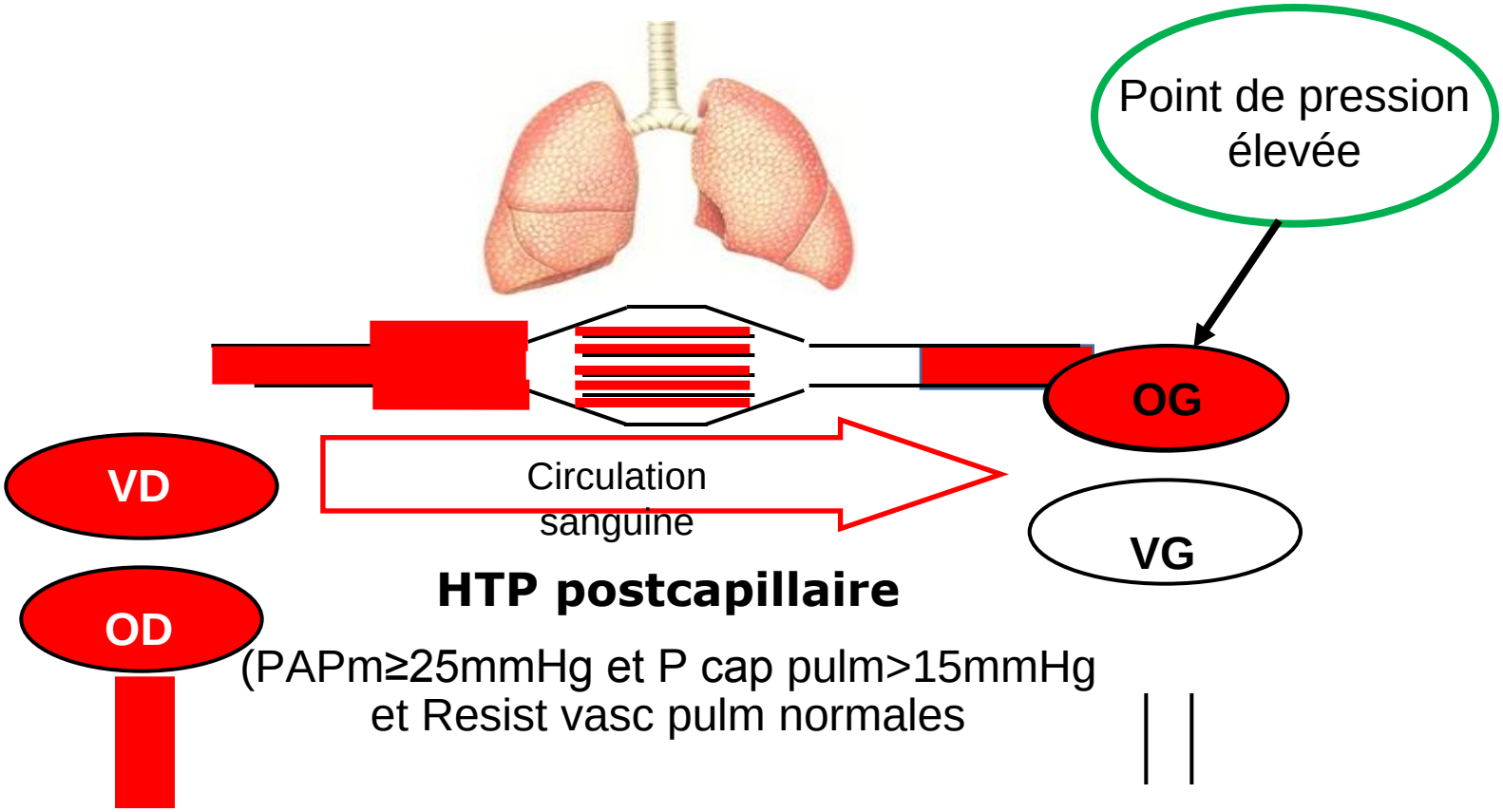
Groupe 1



- **Il s'agit bien d'une hypertension artérielle pulmonaire « pré-capillaire »**

HTP: quel est le bon diagnostic ?

Groupe 2: hypertension pulmonaire



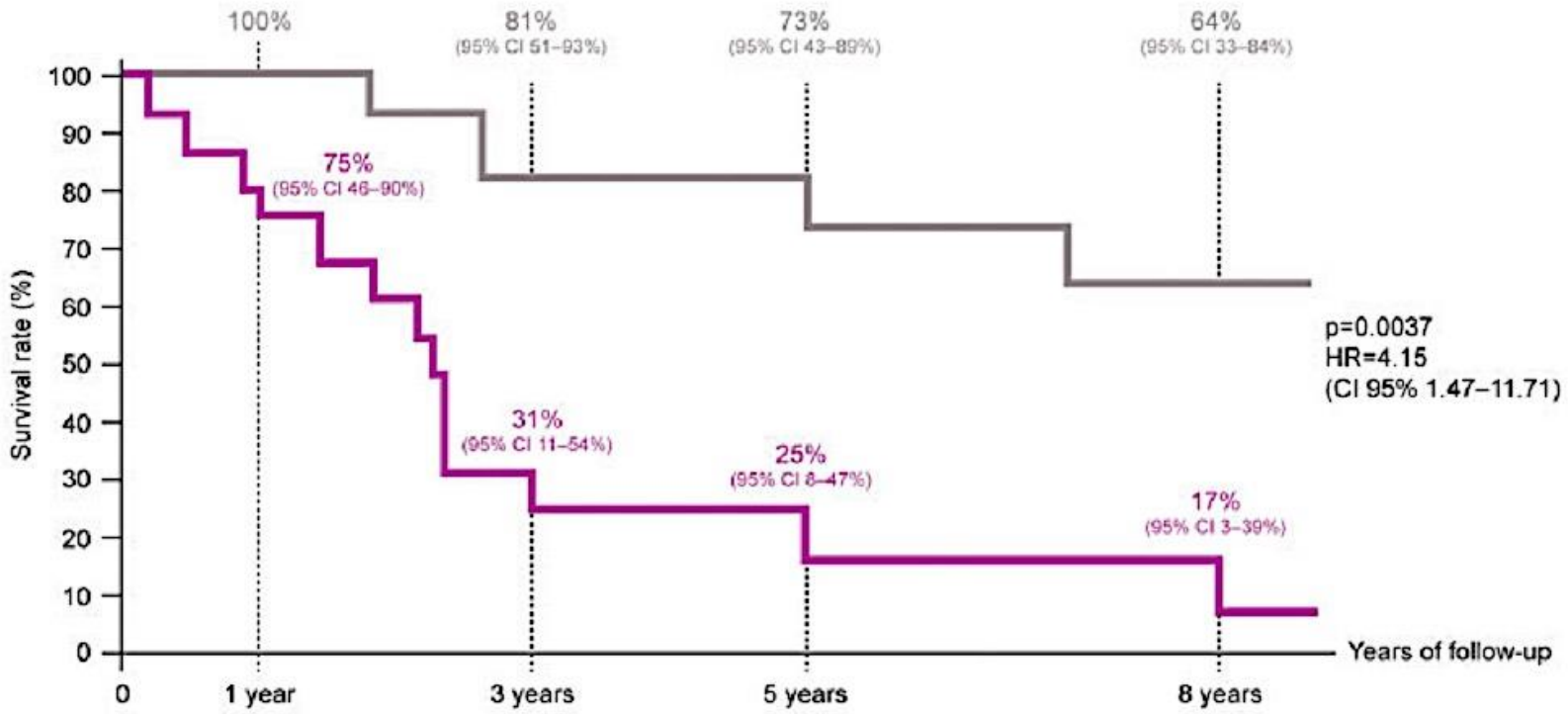
- **Il s'agit bien d'une hypertension pulmonaire « post-capillaire »**

Long-term outcomes in detected *vs* routine SSc-PAH

Screening for Pulmonary Arterial Hypertension in Patients With Systemic Sclerosis

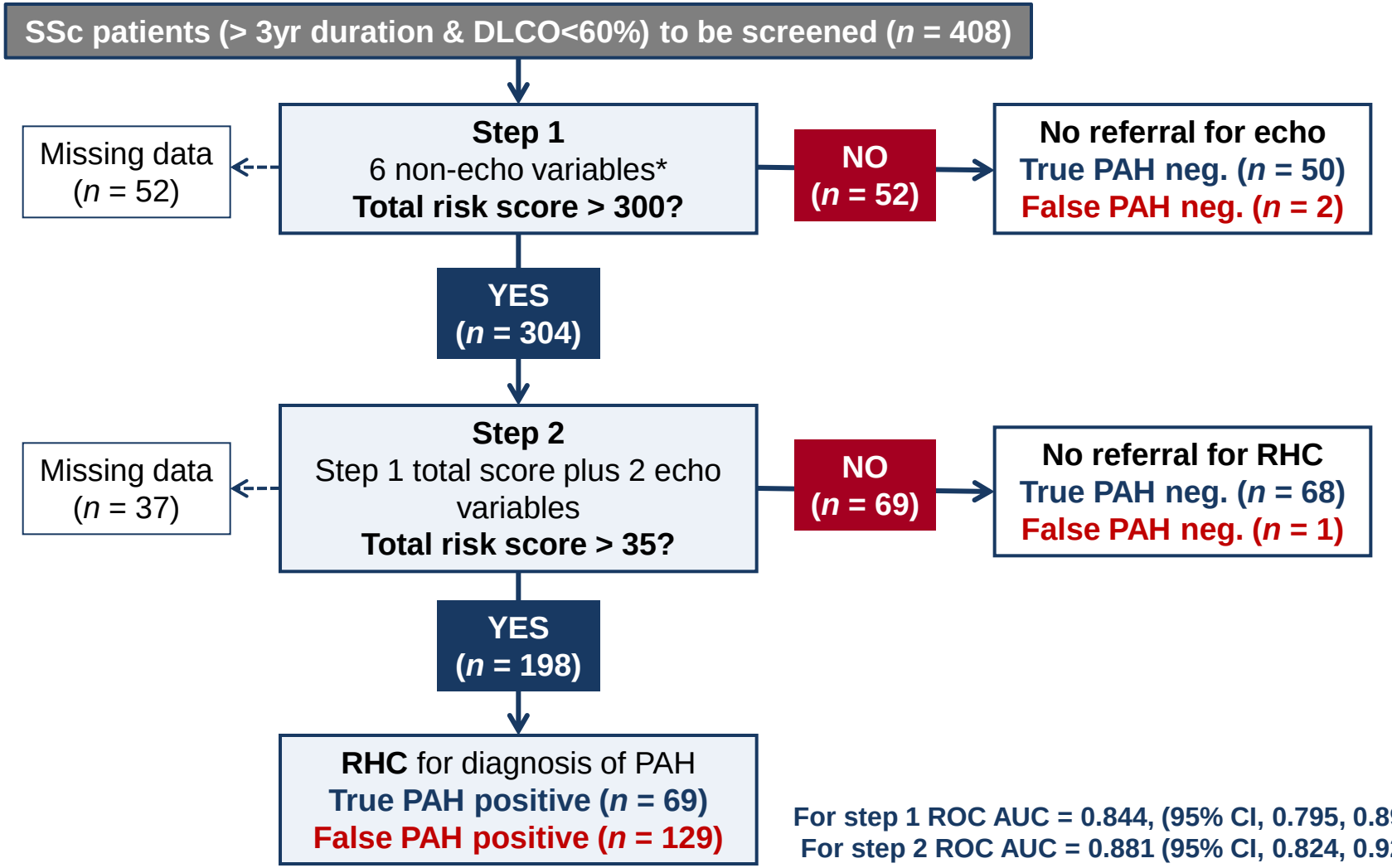
Clinical Characteristics at Diagnosis and Long-Term Survival

Marc Humbert,[1] Azzedine Yaici,[1] Pascal de Groote,[2] David Montani,[1] Olivier Sitbon,[1] David Launay,[3] Virginie Gressin,[4] Loïc Guillevin,[5] Pierre Clerson,[6] Gérald Simonneau,[1] and Eric Hachulla[3]



Humbert M, *et al. Arthritis Rheum* 2011; 63:3522-30.

DETECT algorithm



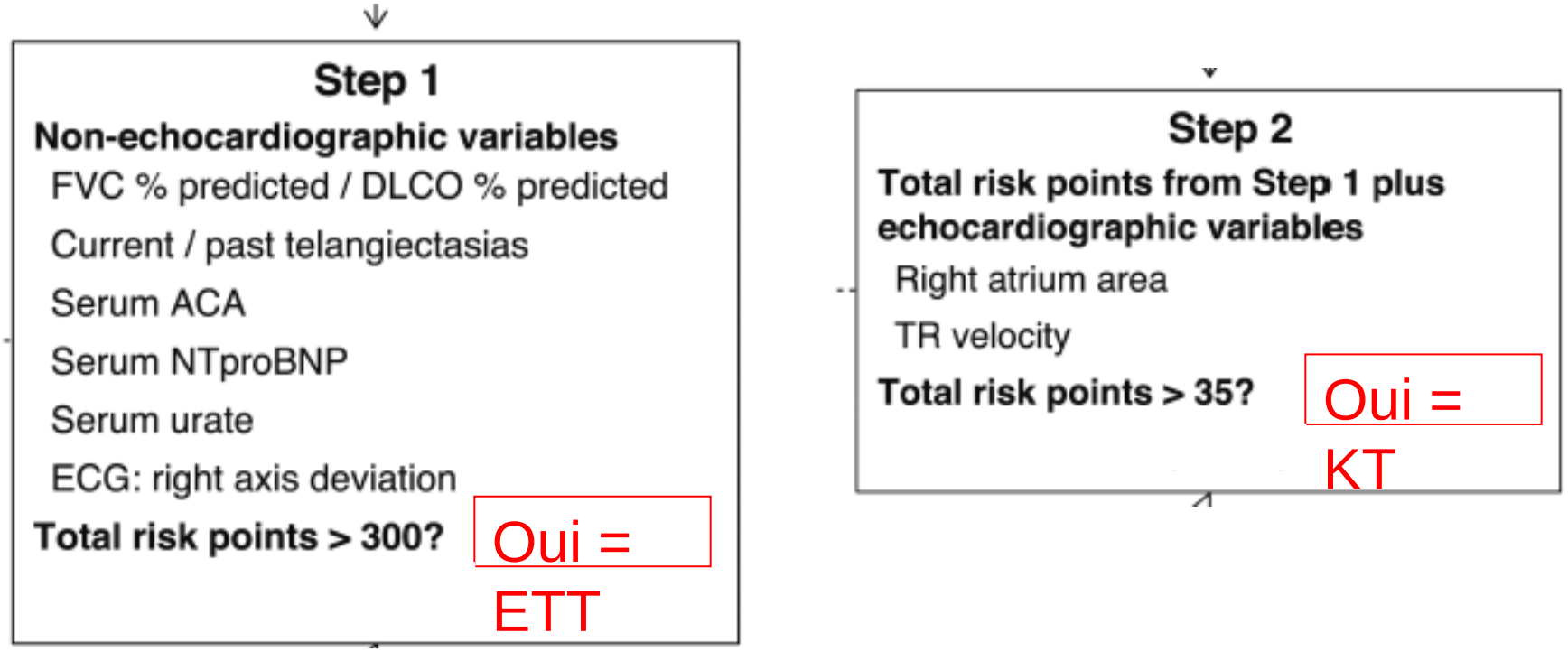
For step 1 ROC AUC = 0.844, (95% CI, 0.795, 0.898).
For step 2 ROC AUC = 0.881 (95% CI, 0.824, 0.923).

* telangiectasia, anti-centromere, PFT and DLCO, ECG and biomarkers (NT-proBNP and uric acid)

Coghlan JG, et al. Ann Rheum Dis. 2014.

PAH screening guidelinesESC/ERS Guidelines 2015

DETECT



Coghlan et al. ARD 2014

DETECT online PAH risk calculator

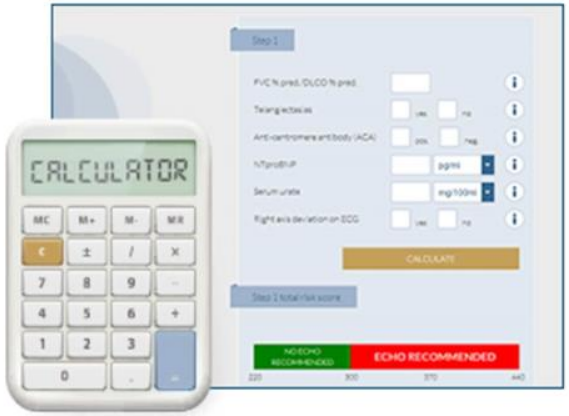
DETECT
DETECTion of PAH in SSc

HOME | WHAT IS DETECT? | PAH RISK CALCULATOR | ABOUT SSC AND PAH | SUPPORTING INFORMATION

WELCOME TO THE PAH RISK CALCULATOR

The PAH risk calculator is a tool for all physicians dealing with systemic sclerosis (SSc). The calculator was developed and validated in the DETECT study. The DETECT study was designed and carried out by a group of experts, all of whom are physicians practising in different countries, and was supported by Actelion Pharmaceuticals Ltd.

The calculator was developed for your daily clinical practise. It will help you to identify and diagnose SSc patients with pulmonary arterial hypertension (PAH), which is a serious condition that develops in 8-13% of SSc patients and is the leading cause of death in patients with this disease. The calculator is based on an algorithm with a high sensitivity and specificity and can help you to decide which of your SSc patients should be evaluated using echocardiography, and of those patients who should be referred for right heart catheterization.



START CALCULATOR

http://detect-pah.com

2015 ESC/ERS Guidelines

Table 26 Recommendations for pulmonary arterial hypertension associated with connective tissue disease

Recommendations	Class[a]	Level[b]	Ref.[c]
In patients with PAH associated with CTD, the same treatment algorithm as for patients with IPAH is recommended	I	C	46
Oral anticoagulation may be considered on an individual basis and in the presence of thrombophilic predisposition	IIb	C	175,339

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

Galiè N, *et al*. ESC/ERS Guidelines. *Eur Heart J* 2016 & *Eur Respir J* 2015.

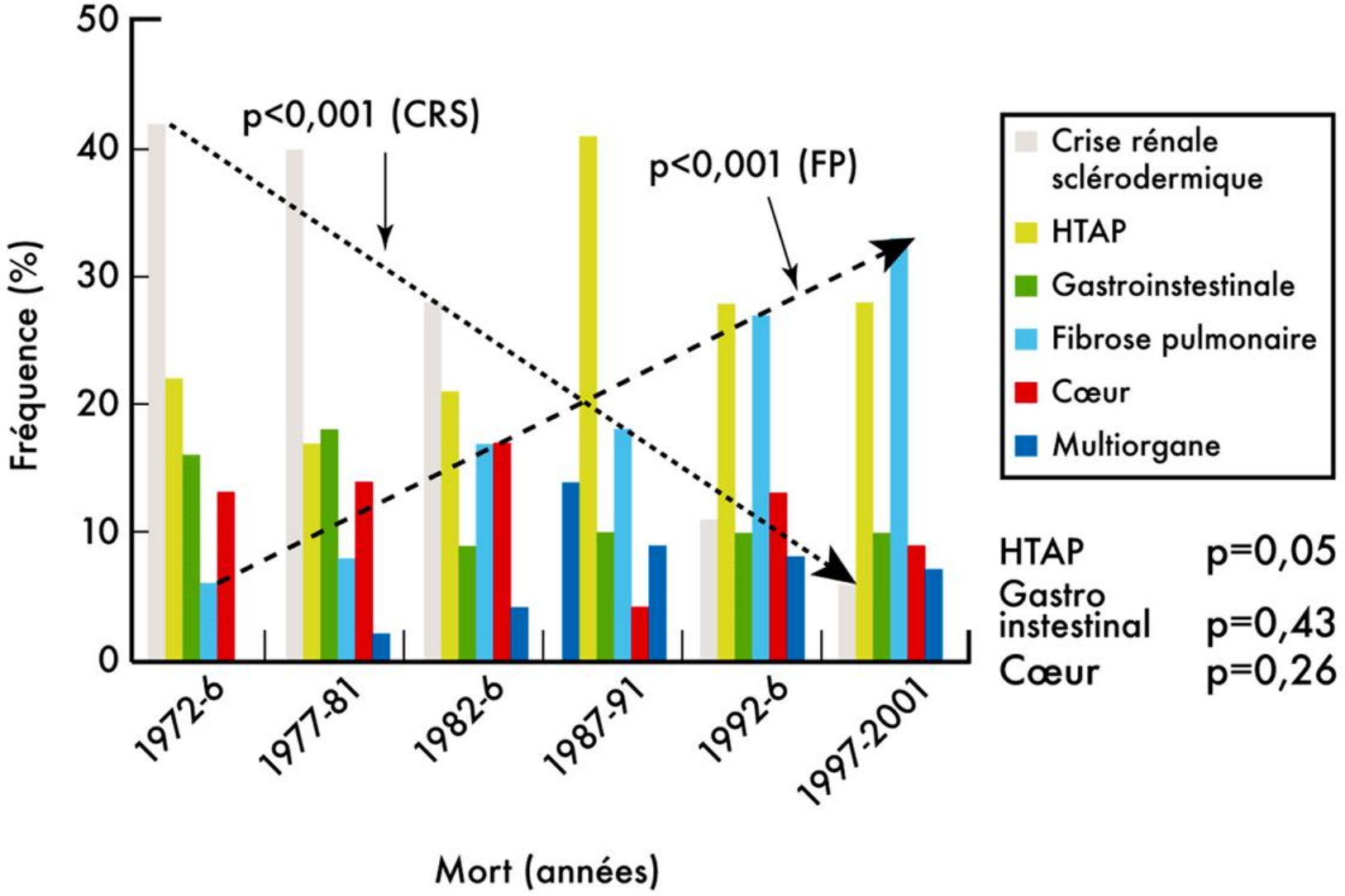
Estimated incidence of pulmonary hypertension during the 3-year followup period*

	Estimated incidence (no. of cases per 100 patient-years)	95% CI
All forms of pulmonary hypertension	1.37	0.74–2.00
Pulmonary arterial hypertension	0.61	0.26–1.20
Among patients with lcSSc	0.40	0.11–1.03
Among patients with dcSSc	1.25	0.34–3.20
Postcapillary pulmonary hypertension	0.61	0.26–1.20
Pulmonary hypertension secondary to pulmonary fibrosis	0.15	0.02–0.55

* 95% CI = 95% confidence interval; lcSSc = limited cutaneous systemic sclerosis; dcSSc = diffuse cutaneous systemic sclerosis.

Hachulla et al. Arthritis Rheum 2009

Changes in causes of Systemic Sclerosis related deaths between 1972 and 2001



Steen et Medsger. Ann Rheum Dis 2007

The impact of comorbidities

- Age
- Myocardial involvement
- Musculoskeletal involvement
- Pulmonary fibrosis
- Pulmonary Veno-Occlusive Disease

PAH complicating Pulmonary fibrosis

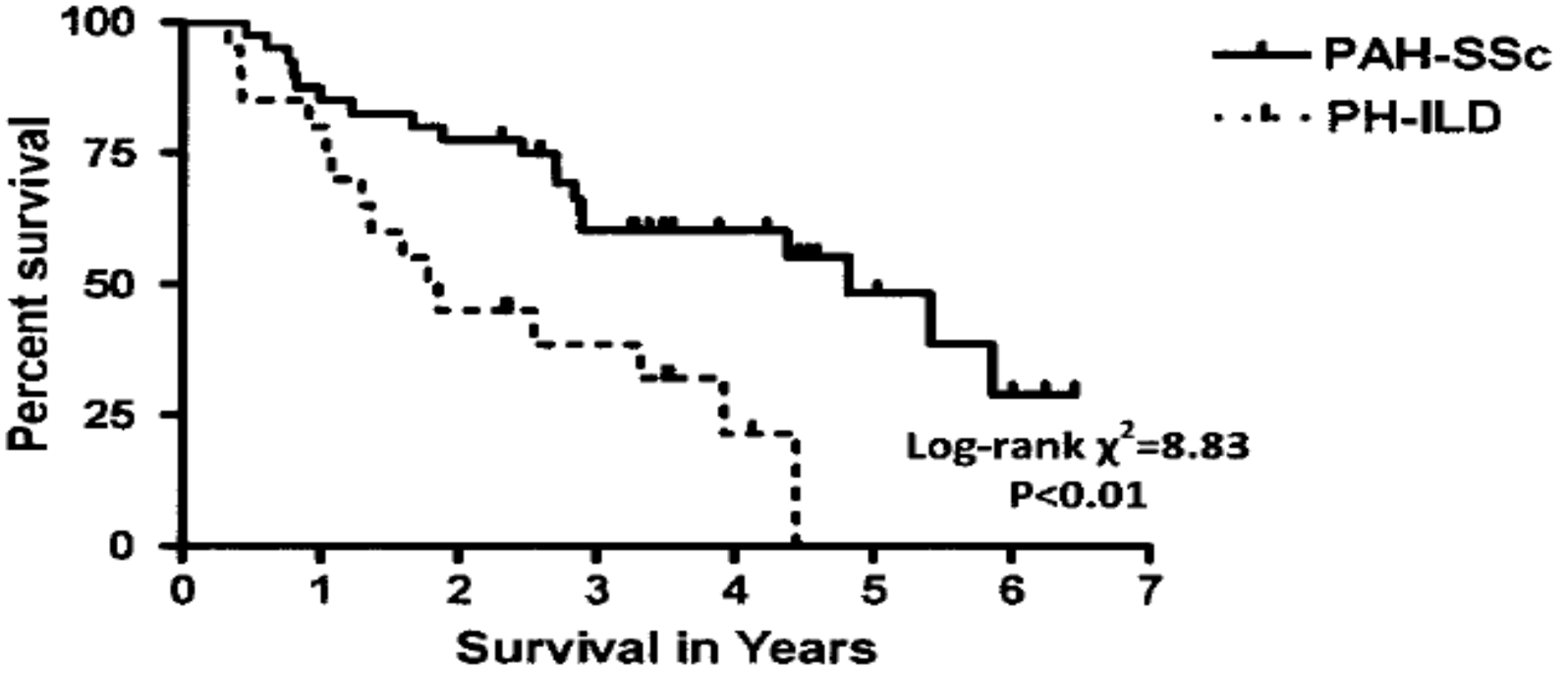


Figure 1. Kaplan-Meier survival graph comparing patients with systemic sclerosis (SSc) and pulmonary arterial hypertension (PAH) with those with SSc and interstitial lung disease (ILD)–associated pulmonary hypertension (PH). The x-axis shows years from diagnosis of PH by right heart catheterization.

Mathai et al,Arthritis Rheum. 2009;60:569---77

Combined Pulmonary Fibrosis and Emphysema Syndrome in Connective Tissue Disease

Table 1. Classification of connective tissue diseases in the 34 study patients*

Rheumatoid arthritis	18 (53)
Systemic sclerosis	10 (29)
Diffuse cutaneous	3 (9)
Limited cutaneous	7 (20)
Mixed connective tissue disease	2 (6)
Overlapping connective tissue disease	2 (6)
Sjögren's syndrome	1 (3)
Polymyositis	1 (3)

* Values are the number (%) of patients.

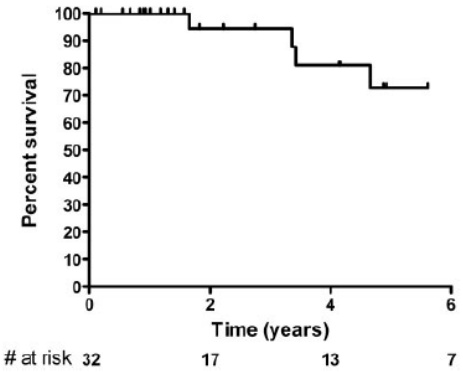
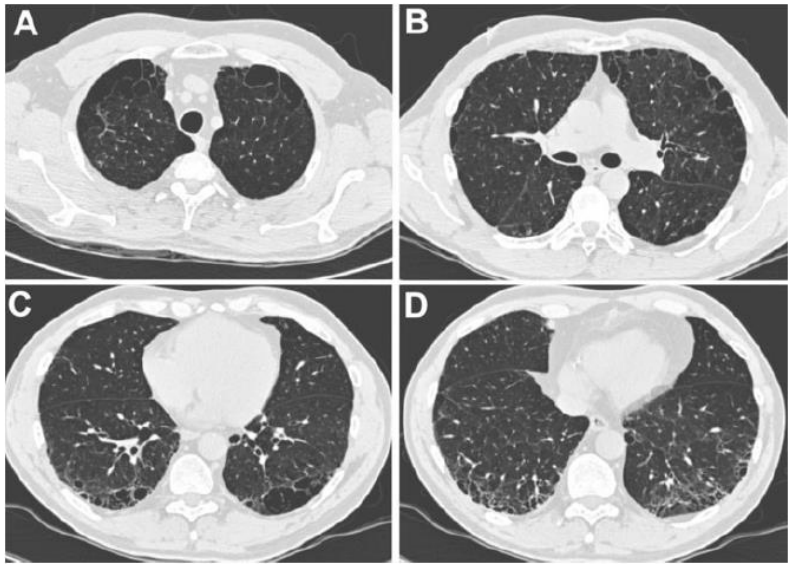
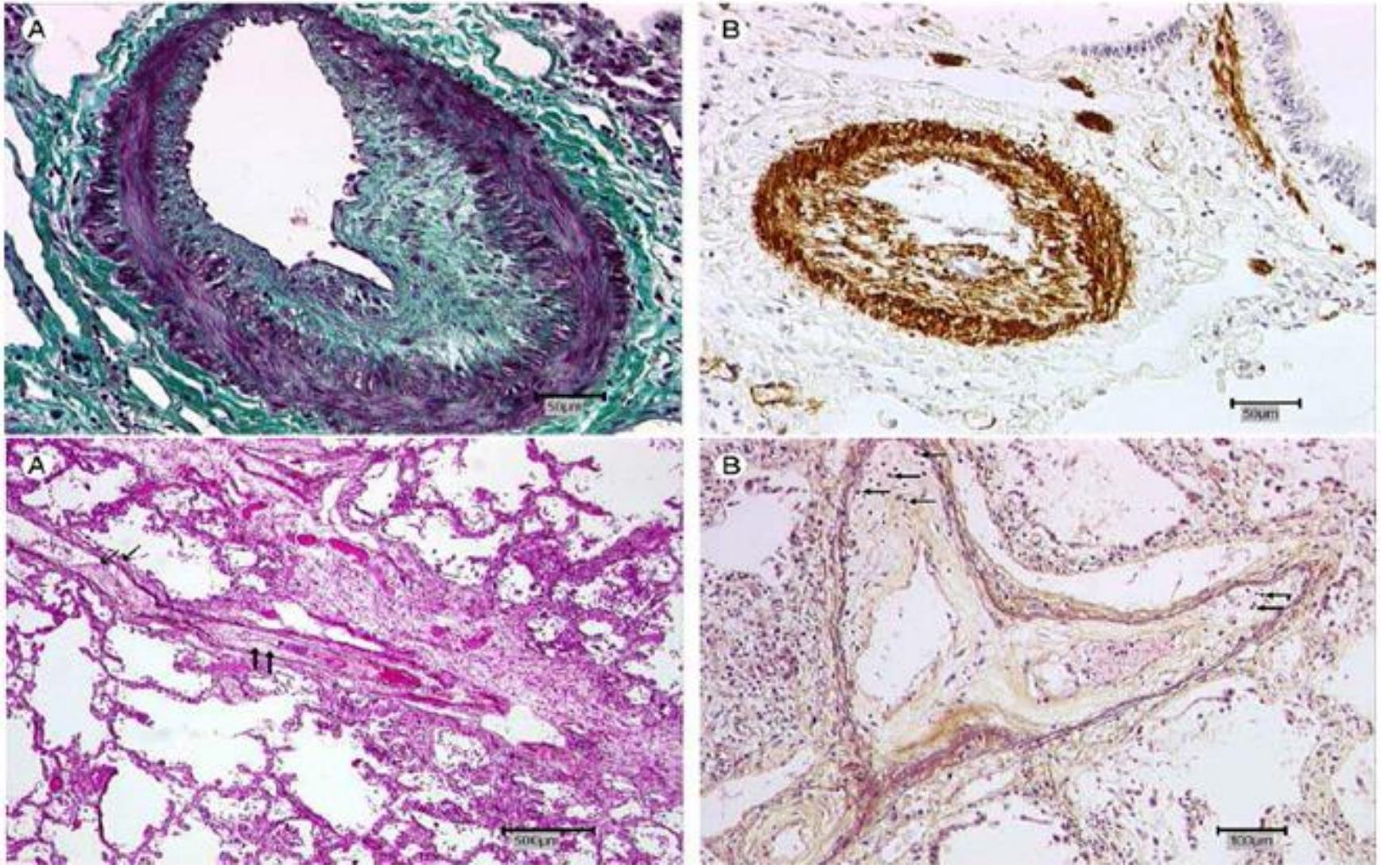


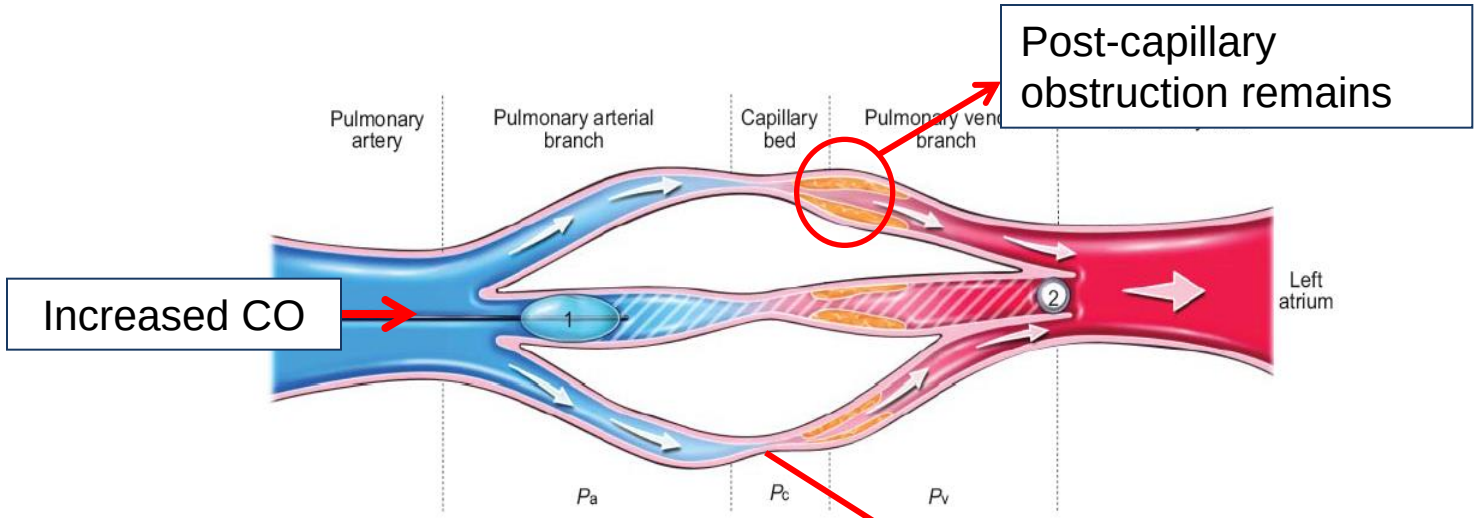
Figure 2. Kaplan-Meier estimates of survival in patients with combined pulmonary fibrosis and emphysema syndrome and connective tissue disease.

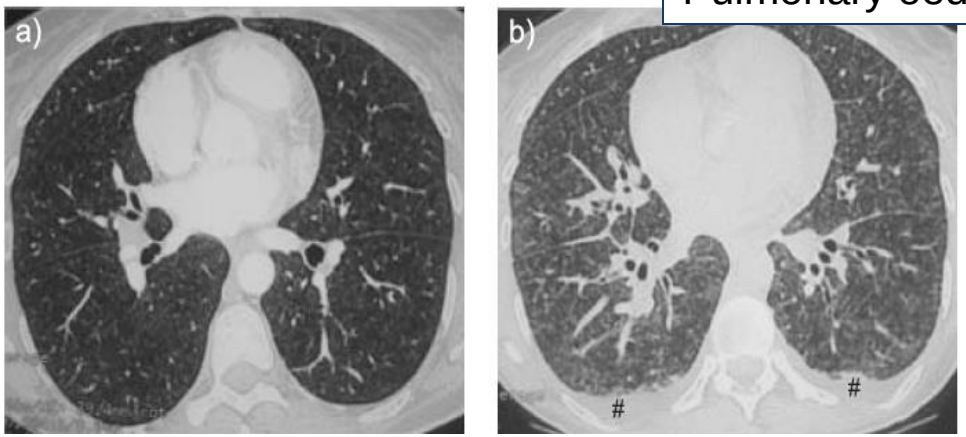


Fibrous remodeling of the pulmonary venous system in PAH associated with CTD



Pulmonary veno-occlusive disease (PVOD) is not uncommon in SSc





Pre-PAH therapy initiation

Post-PAH therapy

Günther S, *et al. Arthritis Rheum* 2012; 64:2995-3005.
Montani D, *et al. Eur Respir J* 2009; 33:189-200.

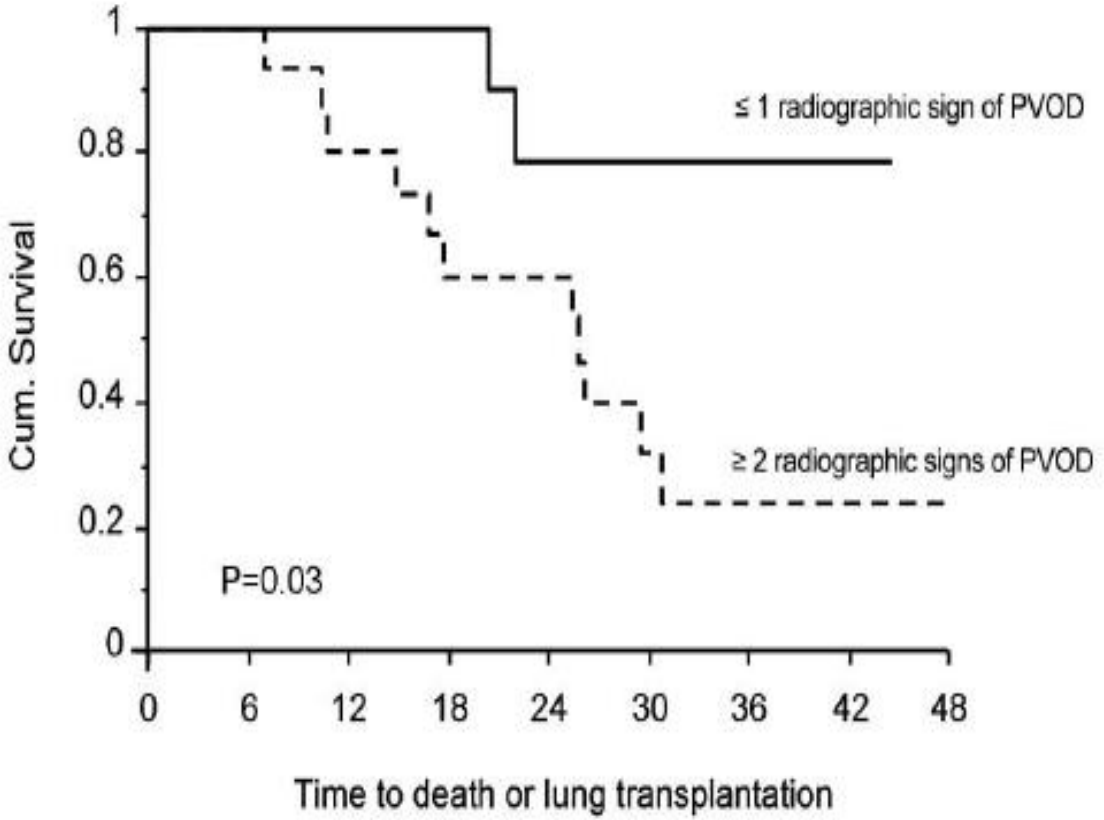
PVOD is not uncommon in SSc

Suggests PVOD in patients with severe PH & SSc

- Clinical
  - More severe (NYHA III-IV)
  - History of pulmonary oedema (on PAH therapy +++)
- HRCT
  - Lymph node enlargement
  - Centrilobular ground-glass opacities
  - Septal lines
- PFTs & ABG
  - Lower DLCO
  - Lower PaO_2
- BAL
  - Hemosiderin-laden macrophages

Günther S, *et al. Arthritis Rheum* 2012; 64:2995-3005.

Poor prognosis of PVOD-like disease in SSc



≥ 2 radiographic signs of PVOD	16	16	12	9	9	4	2	1	1
≤ 1 radiographic sign of PVOD	10	10	10	10	7	4	3	2	1

Günther S, *et al. Arthritis Rheum* 2012; 64:2995-3005.

Conclusions

- 8-12% of SSc patients develop PAH/Incidence 0.6%
- Detection: echocardiography
- Comfirmation: Right heart catheterization (treshold….)
- Detect algorithm: step 1 and step 2
- Prognosis: reserved
- Impact of comorbidities

French Vasculitis Study Group

GFRS Groupe Francophone de Recherche sur la Sclérodermie

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