ACTUALIZACIÓN EN ENFERMEDADES RESPIRATORIAS: NOVEDADES EN LA PRÁCTICA CLÍNICA

El pulmón en las enfermedades autoinmunes sistémicas

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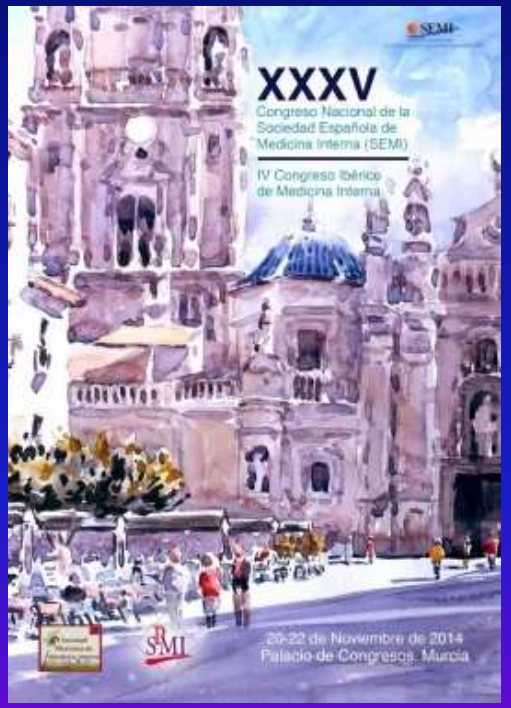
Servicio de Medicina Interna
Hospital Universitario Vall d'Hebron . Barcelona



Afección pulmonar en las enfermedades del tejido conjuntivo

	Esclerodermia	PM/DM	S Sjögren	LES	EMTC
NINE	++++	+++	+	+	+++
NIU	+	+	+	+	+
NIL			++		+
NOC	+/-	++	+	+	+
DAD		+++		++	+
Hemorragia alveolar				+++	

NINE: Neumonía intersticial no específica
NIU : Neumonía intersticial usual
DAD : Daño alveolar difuso

NIL : Neumonía intersticial linfocitaria
NOC: Neumonía organizativa criptogenética

Afección pulmonar en las enfermedades del tejido conjuntivo

	Esclerodermia	PM/DM	S Sjögren	LES	EMTC
Bronquitis/HRB			+++		
Bronquiolitis			++		
Afec.Pleural	+			++++	++
N. por aspiración	+	++			++
Infección oportun.				++	
Afec.muscular		++		+	
HTAP	+++	+/-		+	++
Neoplasia	+	+	+		
Toxicidad por fármacos		+		++	

ESCLERODERMIA. Afección pulmonar

Afección visceral frecuente: (70%-80%)

Tipos de afección

Enfermedad pulmonar intersticial difusa
Hipertensión pulmonar: 1ª - 2ª

Otras: Cáncer, bronquiolitis, hemorragia alveolar, neumotórax, enfermedad pleural

ESCLERODERMIA. Manifestaciones clínicas

N: 430

Fenómeno de Raynaud: 416 (97 %)

Úlceras digitales: 211 (49 %)

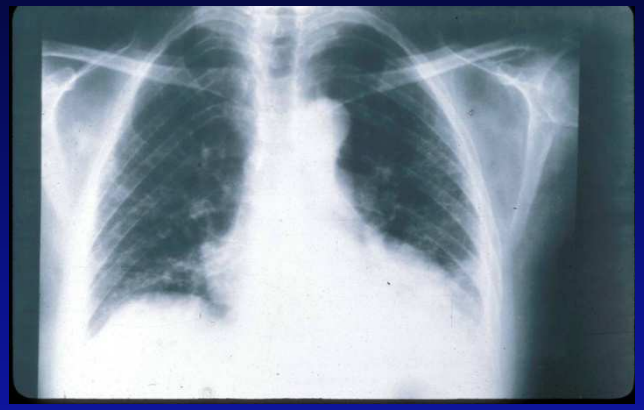
Afección osteomuscular: 320 (74 %)

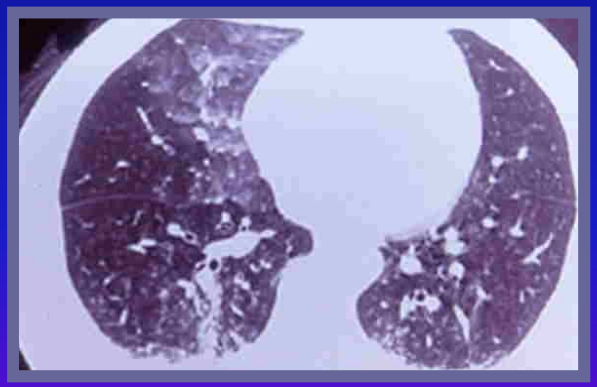
Afección digestiva: 361 (84 %)

Afección respiratoria: 199 (46 %)
EPID: 142 (33 %)
HTAP: 57 (13 %)

Afección cardíaca: 290 (67%)

Afección renal (CRE): 18 (4%)





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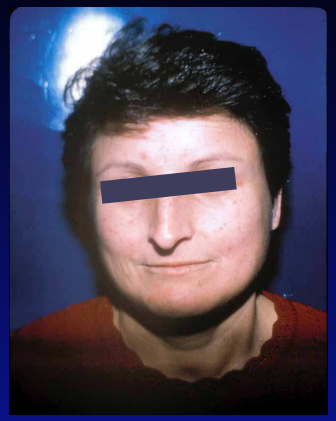
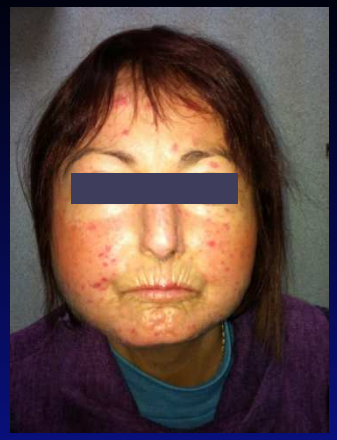
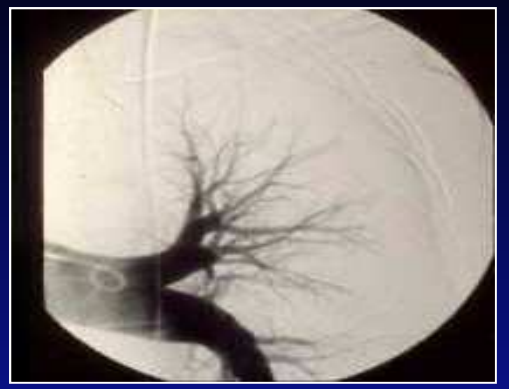
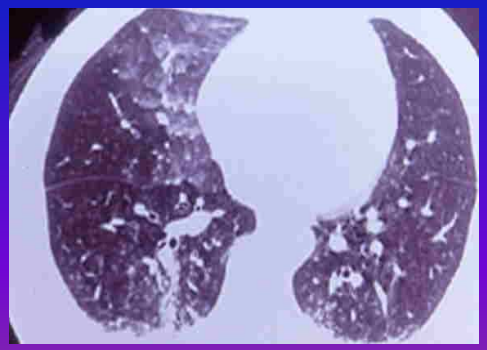
Factor de mal pronóstico. *(Peters Golden 1984, Bryan1999, Scussel-Lonzetti 2002, Ferri 2002, Simeón 1997, 2003)*





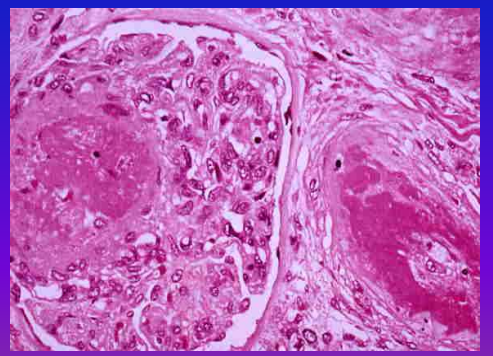


Factores pronósticos	RR	*p*
Esclerodermia difusa	2,730	0,001
Edad de comienzo	1,079	0,0001
Fibrosis pulmonar	2,463	0,003
HTAP	2,802	0,0001
Crisis renal	30,062	0,0001



Esclerodermia
Factores pronósticos

Simeón CP, ***Ann Rheum Dis, 1997***
Simeón CP, ***Rheumatology, 2003***



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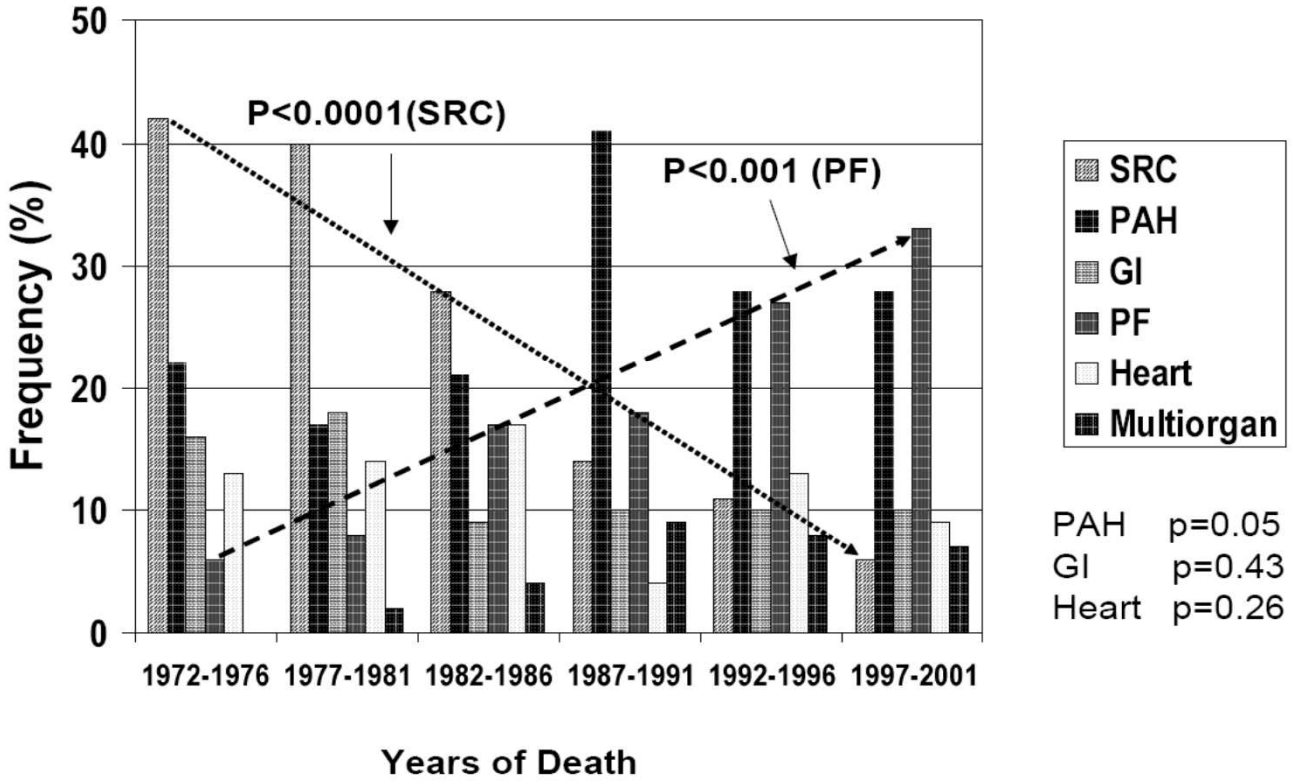
1ª causa de muerte

Changes in causes of death in systemic sclerosis, 1972- 2002

Virginia D. Steen and Thomas A Medsger, Jr

Ann Rheum Dis, 2007

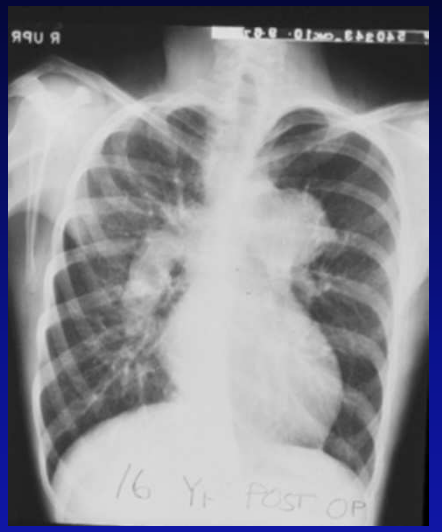


ESCLERODERMIA. Afección pulmonar

N= 430

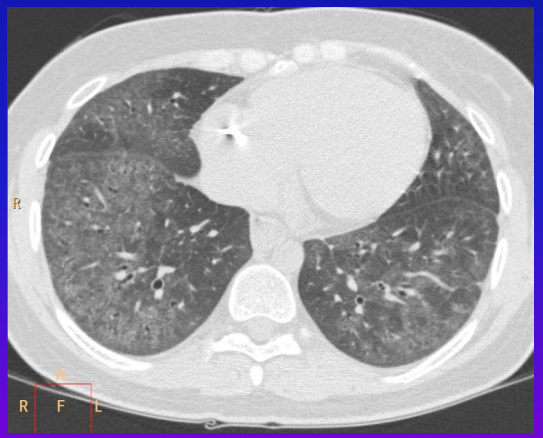
Causas de muerte: 128 (29,7%)

Afección pulmonar : 47 (36,7%)



HTA pulmonar aislada: 23 (18 %)
Fibrosis pulmonar + HTAP: 11 (8,5%)

Fibrosis pulmonar: 13 (10 %)



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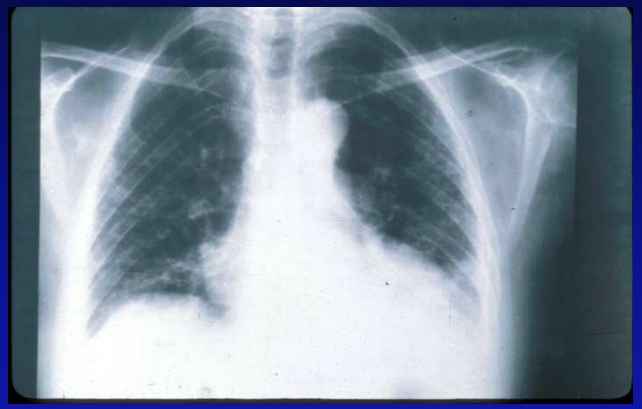

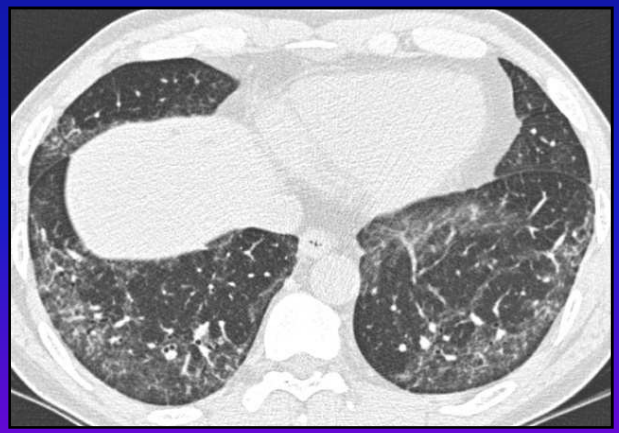

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Esclerodermia. Evolución

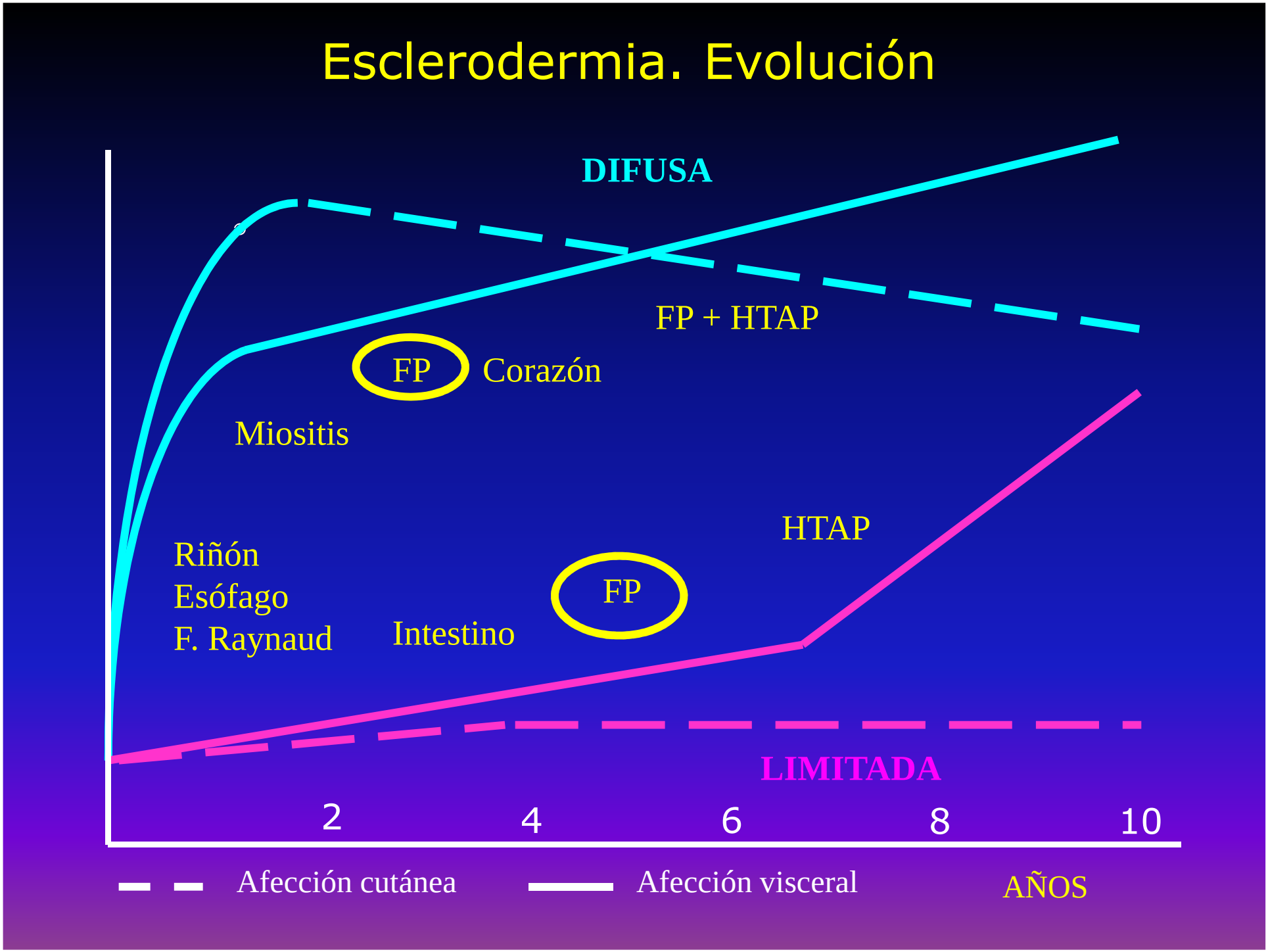


Table 2 Cumulative Clinical Manifestations Among Patients with SSc Patients According to Their Cutaneous Subsets

	a lcSSc (%)	b dcSSc (%)	c ssSSc (%)	*P* Value a vs b	*P* Value a vs c	*P* Value b vs c
Osteomuscular	318 (56.6)	154 (63.4)	36 (52.2)	ns	ns	ns
Arthritis	81 (14.4)	66 (27.2)	9 (13)	<0.0001	ns	0.016
Myositis	25 (4.4)	34 (14)	2 (2.9)	<0.0001	ns	ns
Tendon friction rubs	14 (2.5)	28 (11.5)	1 (1.4)	<0.0001	ns	0.008
Acrosteolysis	46 (8.2)	37 (15.2)	1 (1.4)	0.0004	0.049	0.001
Digestive involvement	392 (69.8)	195 (80.2)	49 (71)	0.002	ns	ns
Esophagus	322 (57.3)					
Gastric	60 (10.7)					
Malabsortion	9 (1.6)					
PBC	24 (4.2)					
Lung involvement	315 (56)					

	lsSSc	dcSSc	ssSSc
Lung involvement	315 (56)	197 (81.1)	49 (71)
Dyspnea	169 (30.1)	136 (56)	28 (40.6)
ILD	221 (39.3)	170 (70)	27 (39.1)
FVC ≤70%	70 (12.5)	87 (35.8)	15 (21.7)
FVC (%) (mean ± SD)	90.7 ± 22.7	74.9 ± 22	83.1 ± 21.7
DLCO/VA (%) (mean ± SD)	76.5 ± 23.2	74.8 ± 22.5	70.1 ± 18.3
Ground-glass pattern	62 (11)	77 (31.7)	9 (13)
Reticular pattern	84 (14.9)	92 (37.9)	10 (14.5)

Conduction alteration	67 (11.9)	25 (10.3)	10 (14.5)	ns	ns	ns
SRC	4 (0.7)	19 (7.8)	1 (1.4)	<0.0001	ns	ns
Sicca syndrome	211 (37.5)	80 (32.9)	10 (14.5)	ns	<0.0001	0.003
Capillaroscopy (n = 600)	383 (68.1)	131 (53.9)	54 (78.3)			
Slow pattern	231 (61.6)	50 (38.2)	37 (68.5)	<0.0001	<0.002	<0.0001
Active pattern	114 (30.4)	78 (59.5)	4 (7.4)	<0.0001	<0.002	<0.0001
Death	66 (11.7)	63 (25.9)	6 (8.7)	<0.0001	ns	0.002

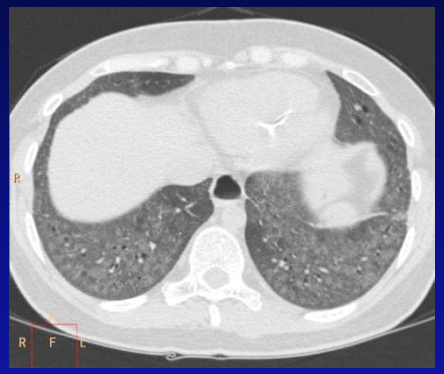
lcSSc, limited cutaneous systemic sclerosis; dcSSc, diffuse cutaneous systemic sclerosis; ssSSc, systemic sclerosis sine scleroderma; PBC, primary biliary cirrhosis; ILD, interstitial lung disease; FVC, forced vital capacity; DLCO/VA, diffusing capacity for carbon monoxide corrected by alveolar volume; PAH, pulmonary arterial hypertension; PAPs, systolic pulmonary arterial pressure, measured by echocardiography; PAPm, mean pulmonary arterial pressure, measured by right-sided heart catheterization; VTR, peak velocity of tricuspid regurgitation in meters/s; SCR, scleroderma renal crisis. #Results in patients without ILD.

Simeón-Aznar CP et al. Semin Arthritis Rheum. 2011

Esclerodermia: enfermedad pulmonar intersticial

Clínica
Asintomático
Inespecíficos:
Disnea de esfuerzo
tos irritativa
crujidos *(“velcro”)*

Laboratorio
Anti-Scl 70
Anti-U3 RNP
Anti-Th/To
Anti-U11/U12RNP
Anti-histona



2013 Classification Criteria for Systemic Sclerosis

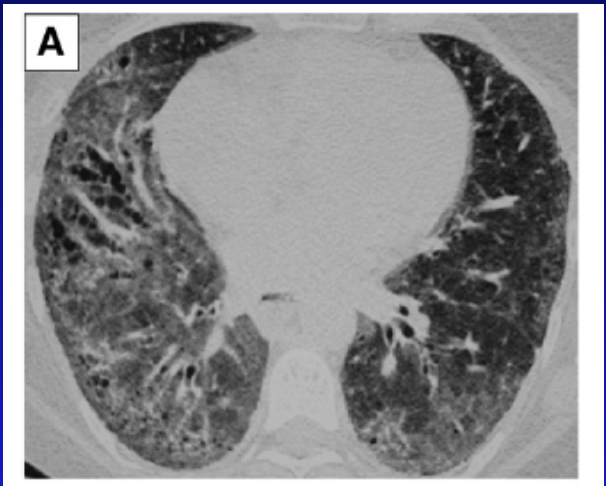
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right-sided heart catheterization according to standard definitions.
Interstitial lung disease	Pulmonary fibrosis seen on high-resolution computed tomography or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of “Velcro” crackles on auscultation, not due to another cause such as congestive heart failure.

Pulmonary fibrosis seen on high-resolution computed tomography or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of “Velcro” crackles on auscultation, not due to another cause such as congestive heart failure.

ESCLERODERMIA. Afección pulmonar intersticial

Diagnóstico y factores pronósticos

TACAR

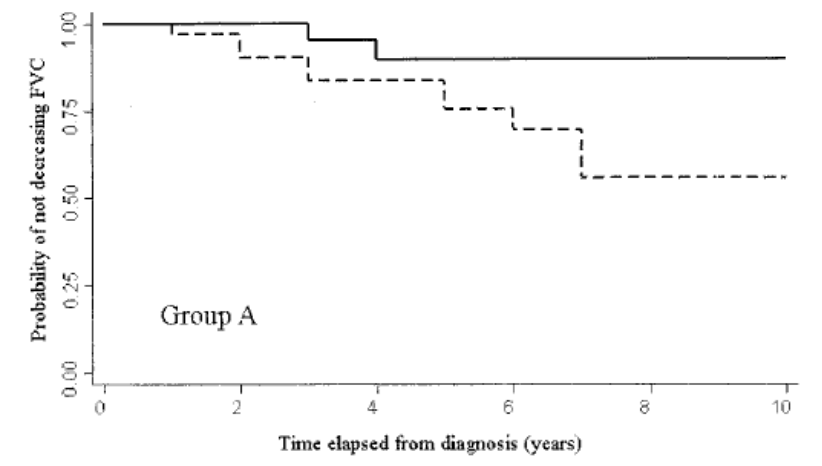


Prueba de referencia
Extensión: pronóstico
Seguimiento: 2 – 5 a.

Lavado broncoalveolar
Biopsia pulmonar

Pruebas funcionales respiratorias

Plastiras SC. ,2006

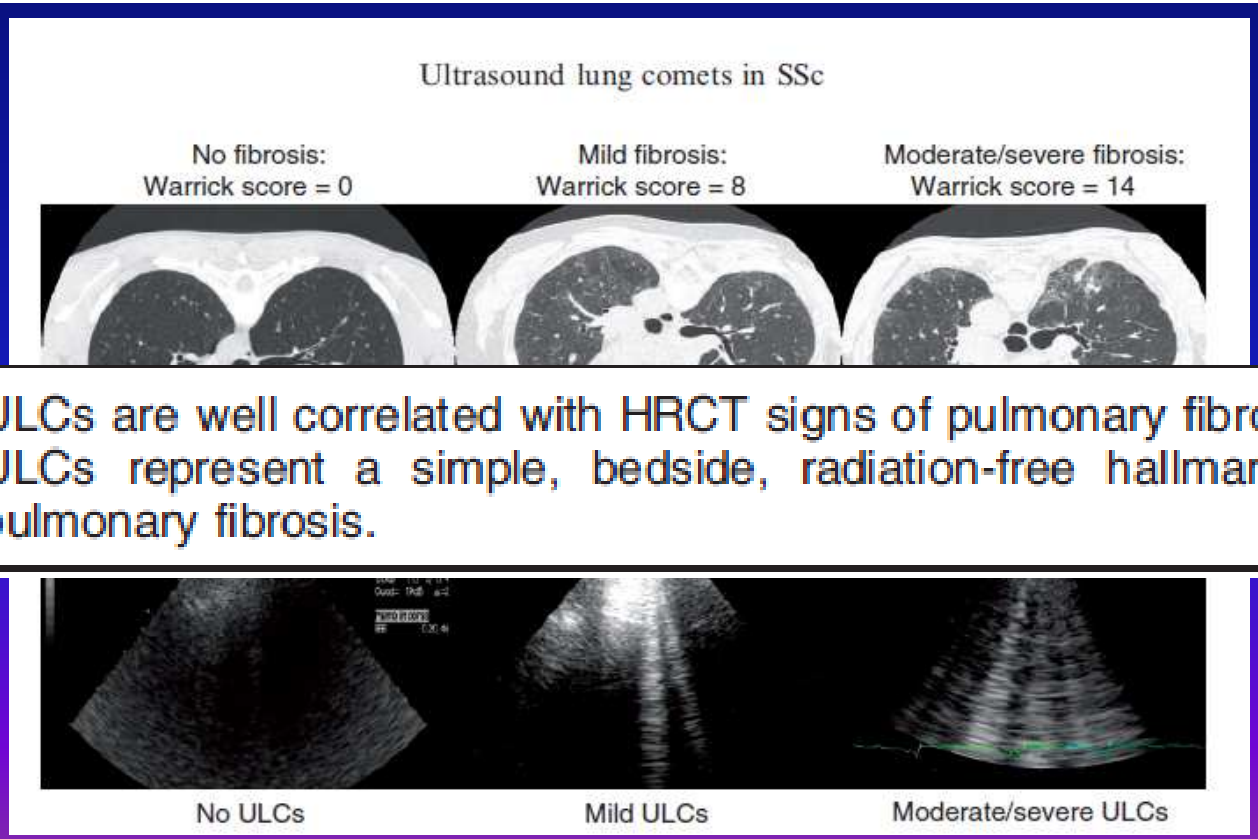


Patrón restrictivo
CVF: factor predictivo
Índice de gravedad
Respuesta al tratamiento
Seguimiento: 6 – 12 meses

Rheumatology 2009;48:1382–1387
Advance Access publication 28 August 2009
doi:10.1093/rheumatology/kep263

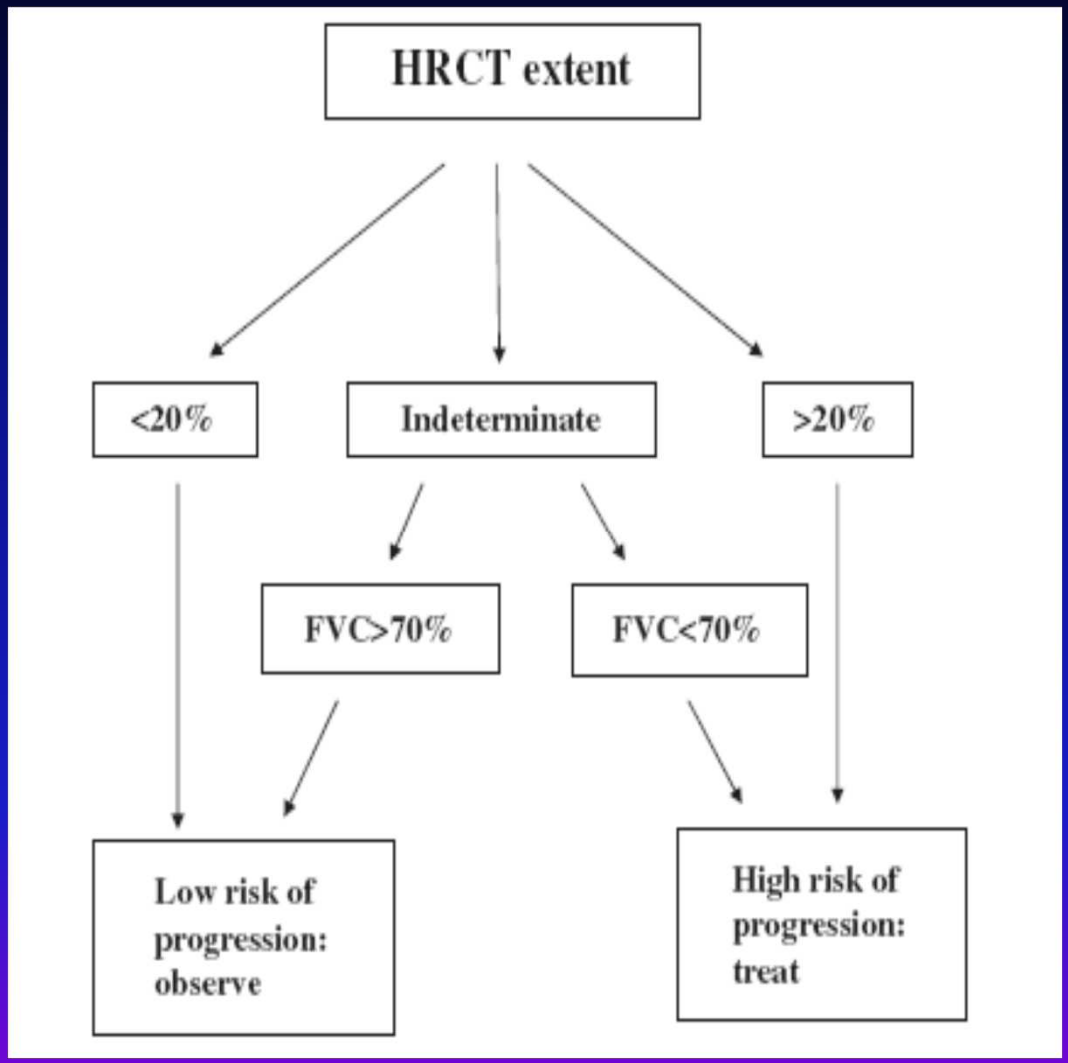
Ultrasound lung comets in systemic sclerosis: a chest sonography hallmark of pulmonary interstitial fibrosis

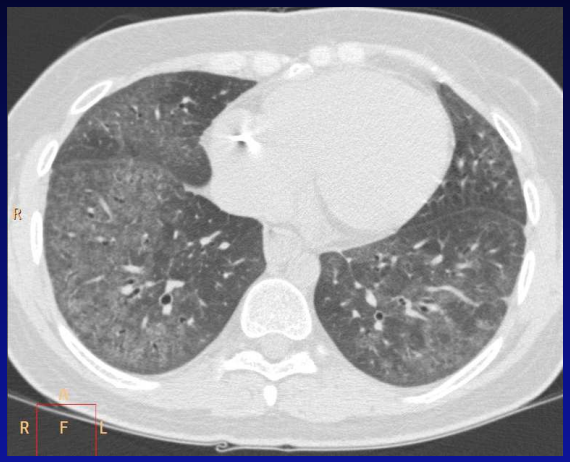
Luna Gargani[1], Marica Doveri[2], Luigia D'Errico[3], Francesca Frassi[1], Maria L. Bazzichi[2], Andrea Delle Sedie[2], Maria C. Scali[4], Simonetta Monti[1], Sergio Mondillo[4], Stefano Bombardieri[2], Davide Caramella[3] and Eugenio Picano[1]

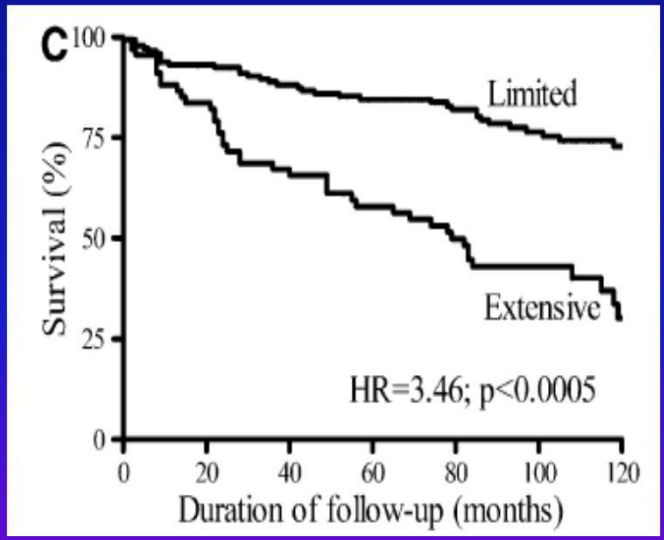


- ULCs are well correlated with HRCT signs of pulmonary fibrosis.
- ULCs represent a simple, bedside, radiation-free hallmark of pulmonary fibrosis.

ESCLERODERMIA: EPI. Factores pronósticos - Indicación terapéutica







Goh NSL et al.
A simple staging system., *2008*

Esclerodermia. Afección pulmonar intersticial Tratamiento con ciclofosfamida en *bolus*

- **White. *Ann Intern Med 2000; 132: 947***

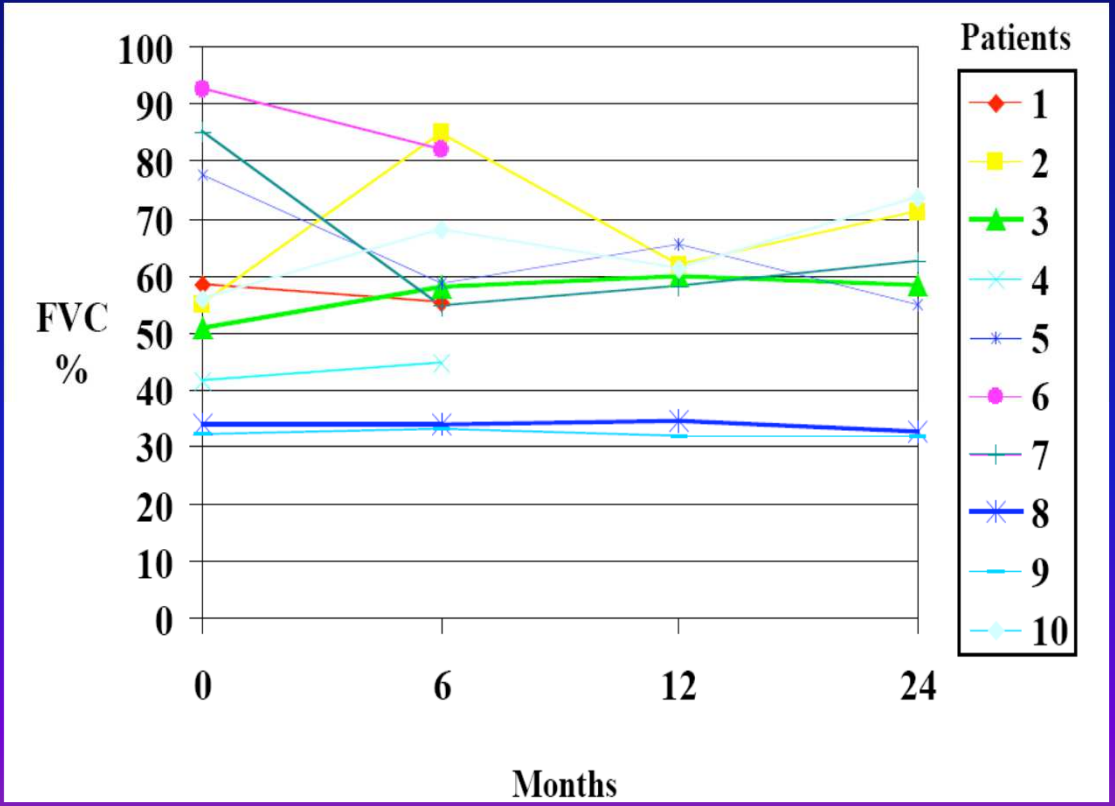
Estudio retrospectivo, no aleatorizado
N=103. Alveolitis en 69 (BAL o Biopsia)
Grupo 1(n=39) con CF y afección pulmonar grave
Grupo 2(n=30) sin CF
16 meses: DLCO mejoró en el 50% del G1 – 27% del G2

Supervivencia a los 5 años 89% Grupo 1 - 71% Grupo 2

The Open Respiratory Medicine Journal, 2008, *2*, 39-45

Intravenous Cyclophosphamide Pulse Therapy in the Treatment of Systemic Sclerosis-Related Interstitial Lung Disease: A Long Term Study

C.P. Simeón-Aznar[1], V. Fonollosa-Plá[1], C. Tolosa-Vilella[2], A. Selva-O´Callaghan[1], R. Solans-Laqué[1], E. Palliza[3], X. Muñoz[4] and M. Vilardell-Tarrés[1]



Effect of mycophenolate sodium in scleroderma-related interstitial lung disease

Carmen Pilar Simeón-Aznar · Vicent Fonollosa-Plá · Carles Tolosa-Vilella · Albert Selva-O'Callaghan · Roser Solans-Laqué · Miquel Vilardell-Tarrés

Clin Rheumatol. 2011;30:1393-8

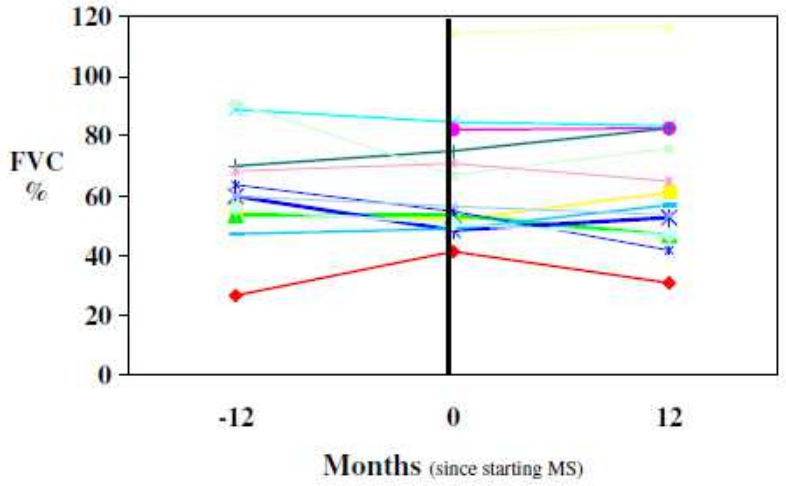


Fig. 1 FVC (percentage of predicted) over time in SSc-ILD patients. Each *line* represents measurements made in each single subject. A time of 0 month indicates when MS was started

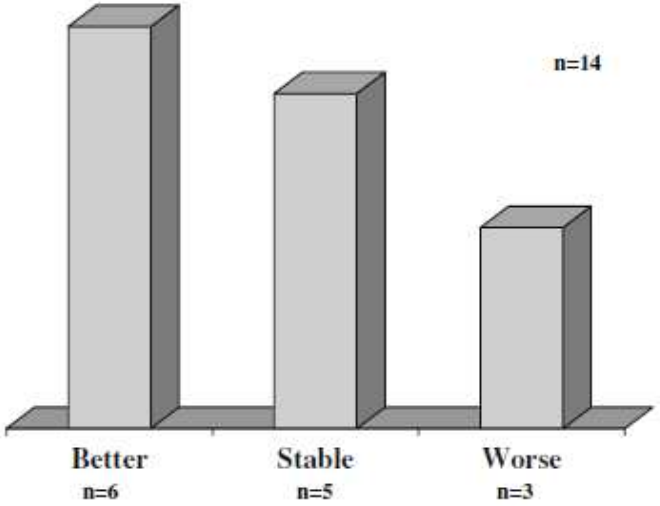


Fig. 2 Summary of the outcome of patients who had either improved, stable or worse FVC over 12 months of treatment

Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis

D. Daoussis[1], S.C. Liossis[1], A.C. Tsamandas[2], C. Kalogeropoulou[3], F. Paliogianni[4], C. Sirinian[2], G. Yiannopoulos[1], A.P. Andonopoulos[1]

Clin Exp Rheumatol 2011

Table I. Demographics, clinical characteristics and medications of study subjects.

Patient n./ sex/age	Disease duration (years)	Organ involvement at baseline other	Number of RTX	Follow-up (months)	Previous immune based pies§	Concurrent medications¶
1/F/47	6				en	Pred, Bos
2/M/72	5				C	Pred, MMF
3/F/56	6				C	Pred, Bos
4/M/39	13				CYC	Pred, Bos, MMF
5/F/33	15				MTX	Pred, MMF
6/F/56	7					MMF
7/F/70	1	GI	4	24	–	-
8/F/50	2	Musc	4	24	–	Pred

Treatment

Patients received 4 weekly pulses of rituximab (375 mg/m^2) at baseline, at 6 months, at 12 months and at 18 months, on top of the already administered treatment (details in Table I).

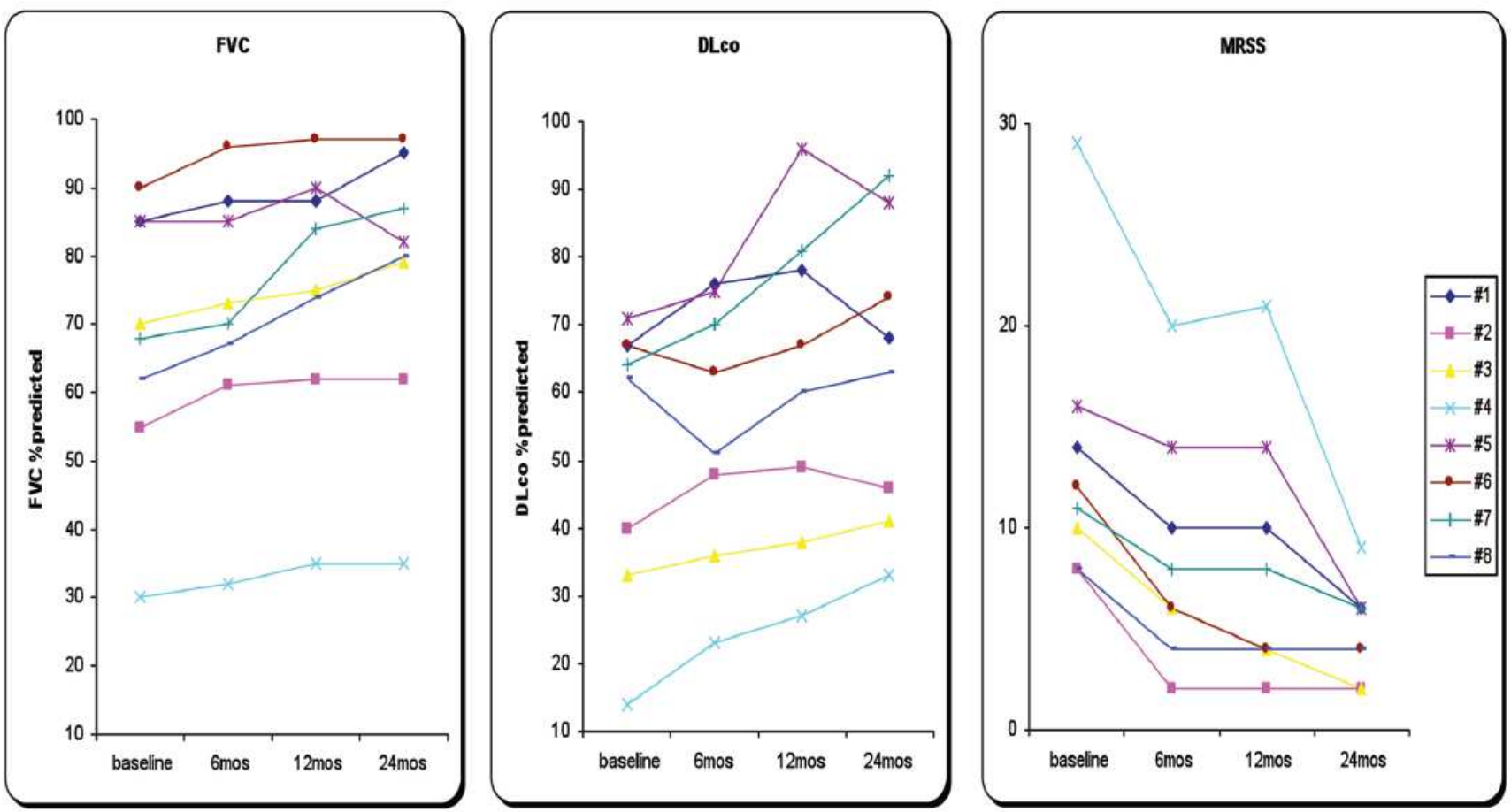
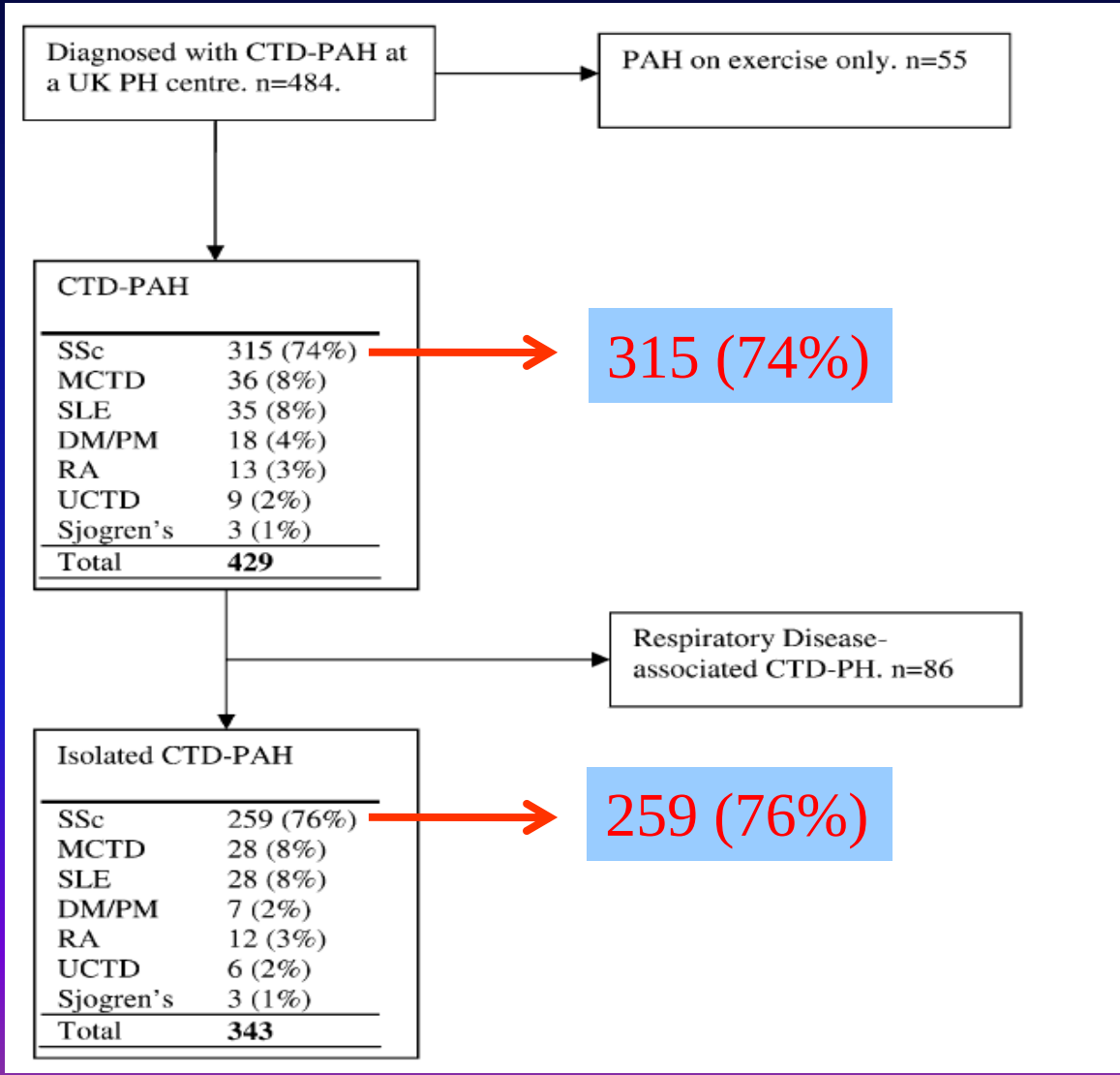


Fig. 1. Beneficial effect of long term RTX treatment on lung function and skin thickening in patients with SSc. RTX mediates a significant linear improvement of FVC ($p<0.0001$) and DLco ($p=0.0003$) during a 2-year follow-up (**A** and **B**, respectively). Similarly, skin thickening improved as indicated by a significant decline ($p<0.0001$) in MRSS (C).

Daoussis D et al. Clin Exp Rheumatol 2011

Connective Tissue Disease–associated Pulmonary Arterial Hypertension in the Modern Treatment Era

Condliffe R, *Am J Respir Crit Care Med*. 2009;179:151-157



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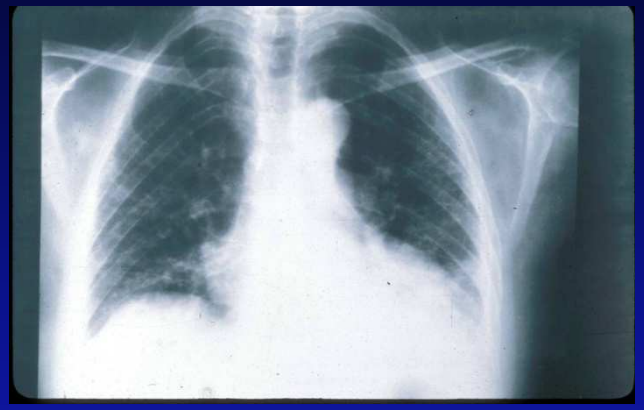
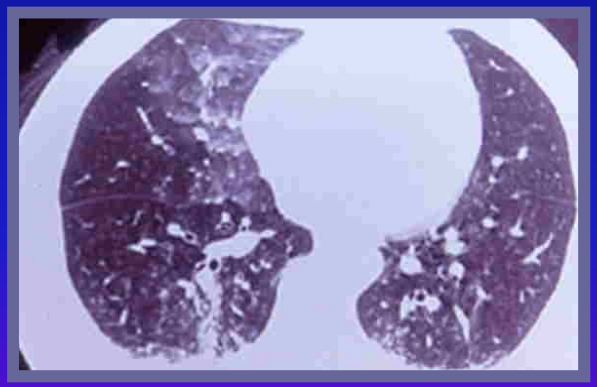
Afección renal (CRE): 18 (4%)





Hospital Universitario Vall d'Hebron 2014

Table 1 Updated Classification of Pulmonary Hypertension*

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

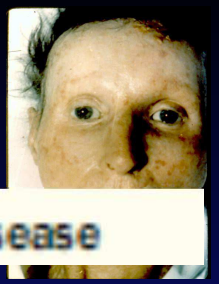
1″. **Persistent pulmonary hypertension of the newborn (PPHN)**

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**

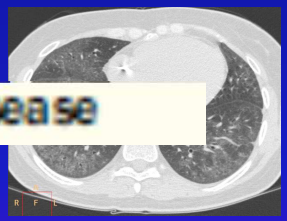


1.4.1 Connective tissue disease

1′ Pulmonary veno-occlusive disease

2.1 Left ventricular systolic dysfunction

2.2 Left ventricular diastolic dysfunction

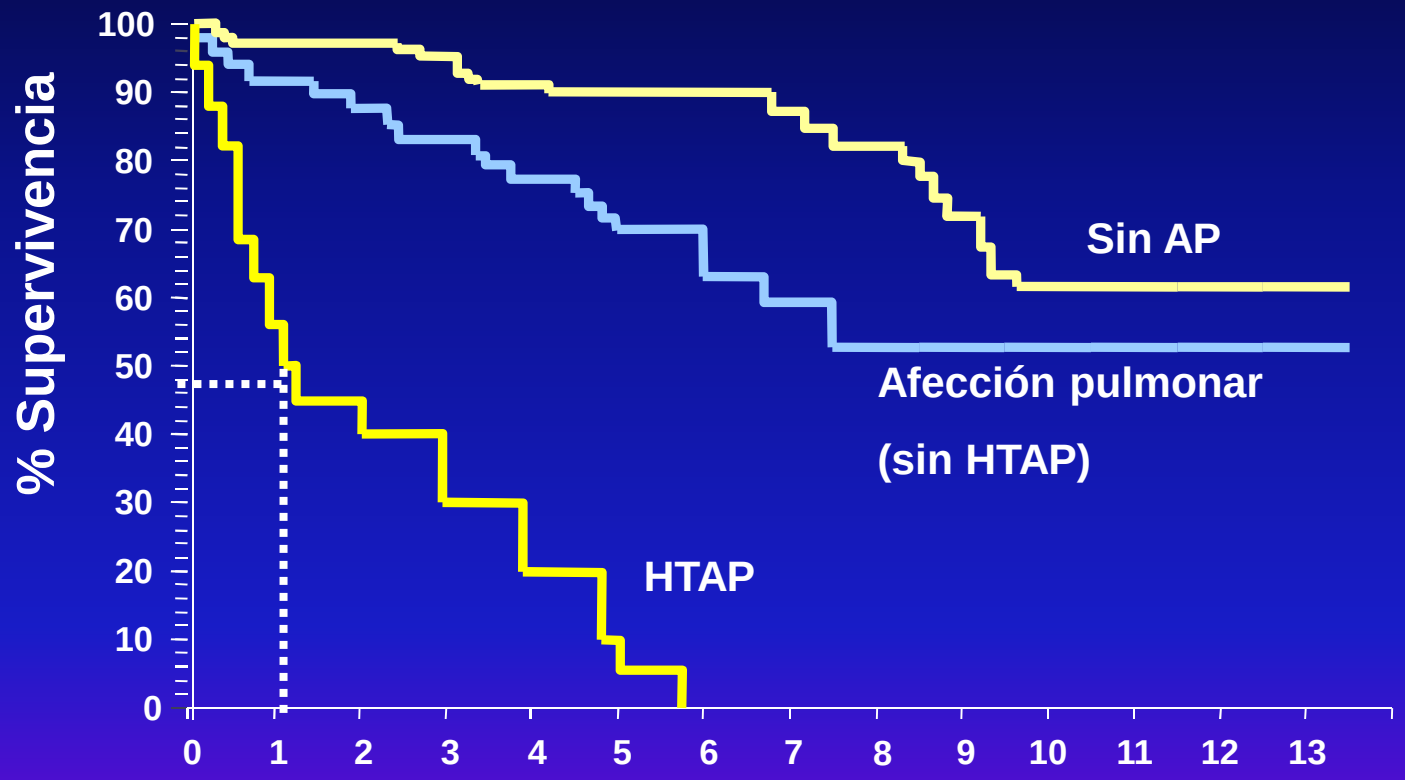


3.2 Interstitial lung disease

4. Chronic thromboembolic pulmonary hypertension

NIZA, 2013

HTAP y supervivencia en la ESC

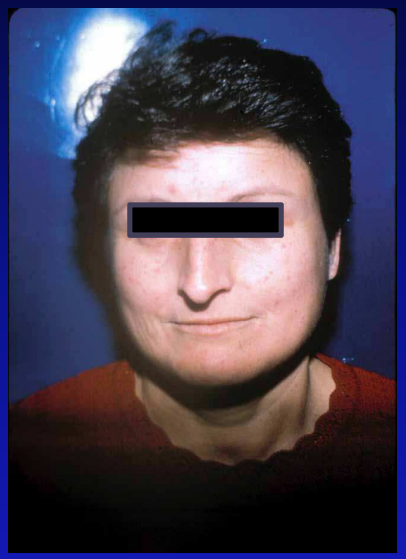


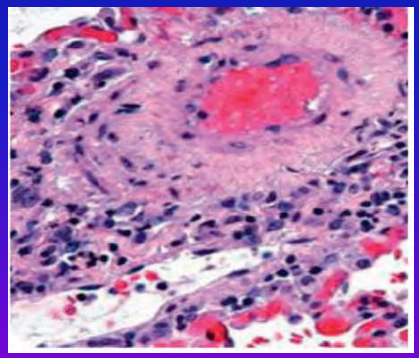
Koh ET, et al. *Brit J Rheumatol*. 1996;35:989.

Esclerodermia. Hipertensión arterial pulmonar

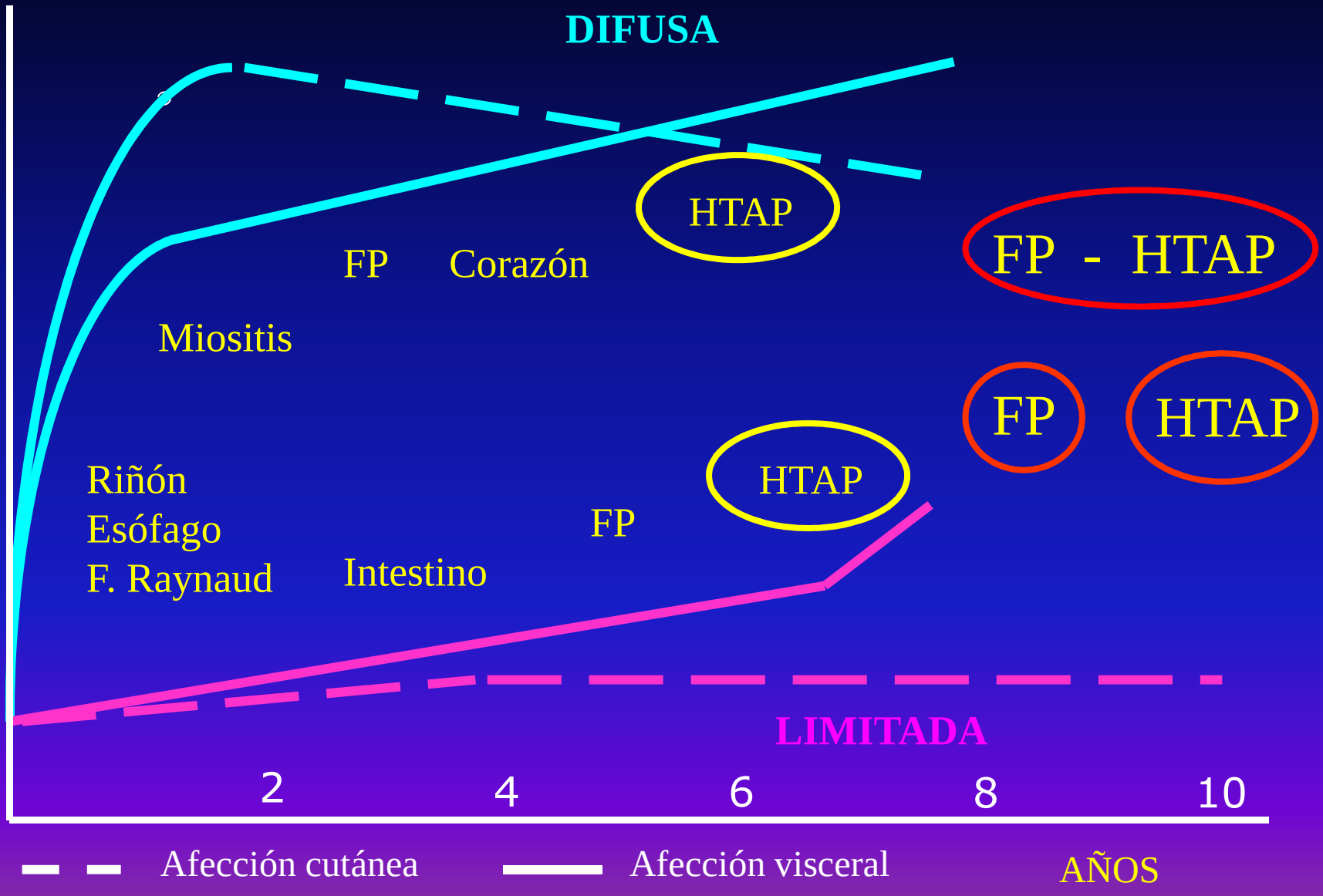
Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (Scleroderma). *Salerni et al*, 1977

"El síndrome CREST ***no siempre es benigno*** *ya que después de un curso clínico prolongado puede presentar una progresiva obliteración vascular pulmonar,* ***hipertensión pulmonar y muerte****, en ausencia de fibrosis pulmonar significativa"*

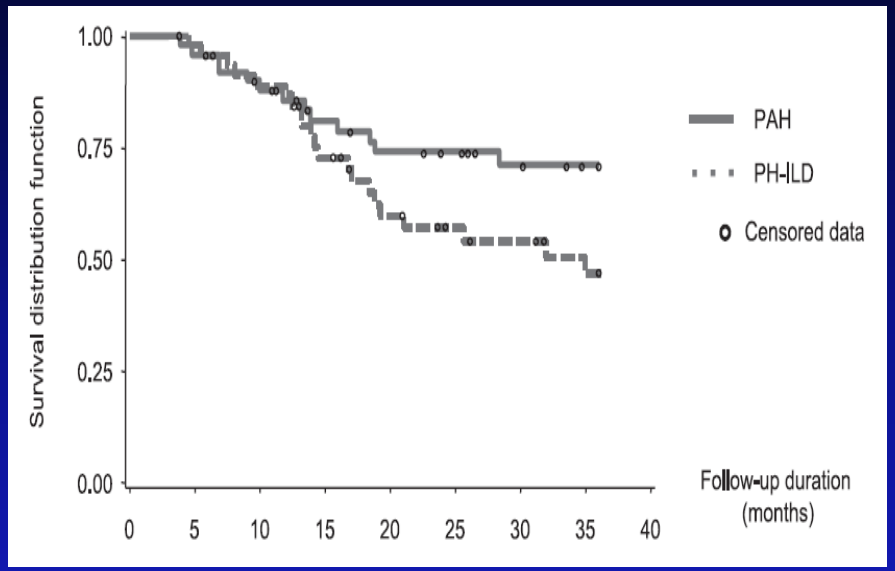


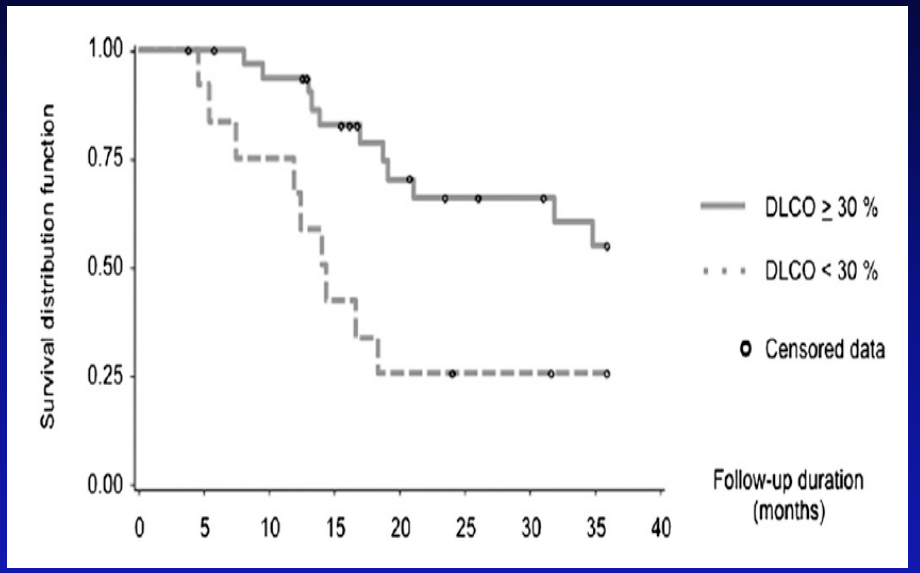


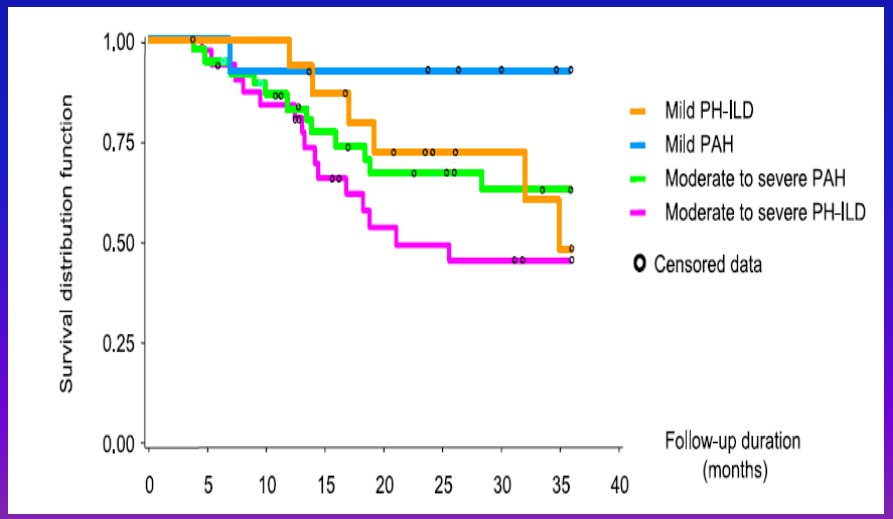
Esclerodermia. Evolución

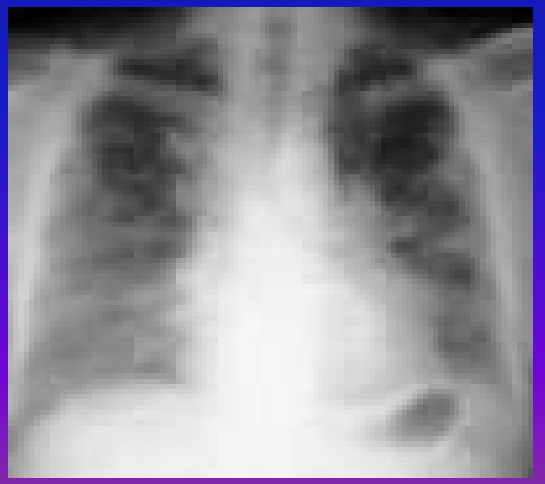


Esclerodermia. Hipertensión arterial pulmonar y neumopatía intersticial









Launay D et al. *Chest*. 2011

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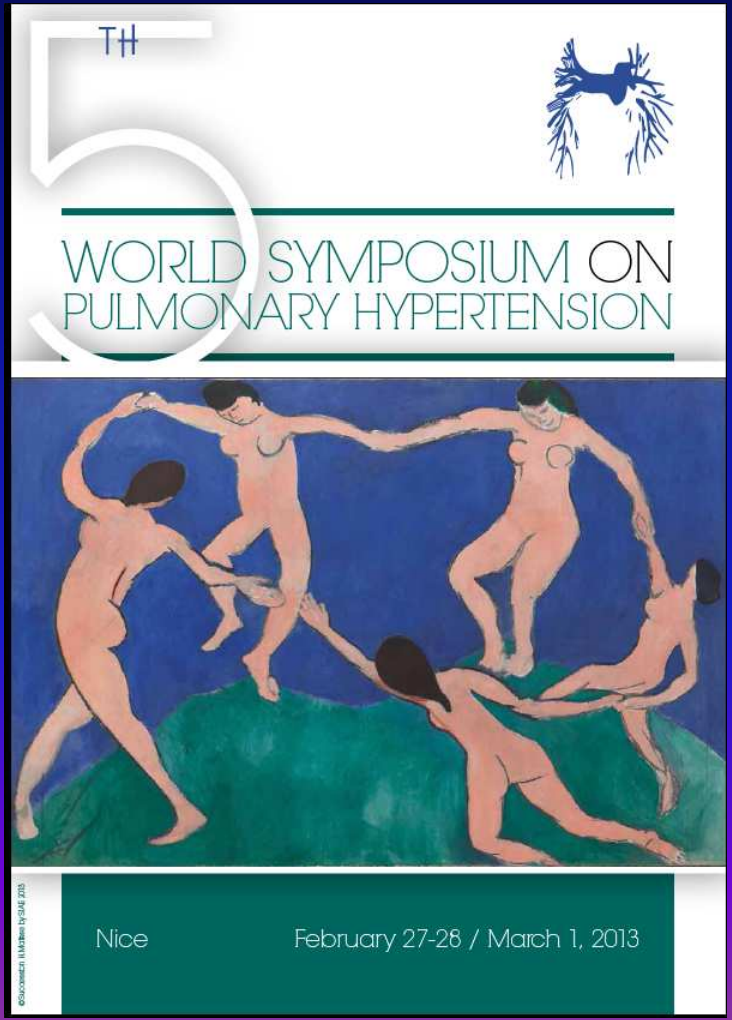
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.10.032

Definitions and Diagnosis of Pulmonary Hypertension

RECOMMENDATIONS.

- The general definition of PH should remain unchanged. PH is defined by PAPm ≥25 mm Hg at rest measured by right heart catheterization (RHC).
- There are still insufficient data to introduce the term "borderline PH" for patients with PAPm levels between 21 and 24 mm Hg, especially because the prognostic and therapeutic implications remain unknown.
- Patients with PAPm values between 21 and 24 mm Hg should be carefully followed, in particular when they are at risk for developing PAH (e.g., patients with CTD, family members of patients with idiopathic pulmonary arterial hypertension [IPAH] or heritable pulmonary arterial hypertension [HPAH]).



HTAP en la esclerodermia: aspectos clínicos

Forma clínica limitada /difusa

Disnea de causa no manifiesta (tos, dolor torácico, síncope, ICD)

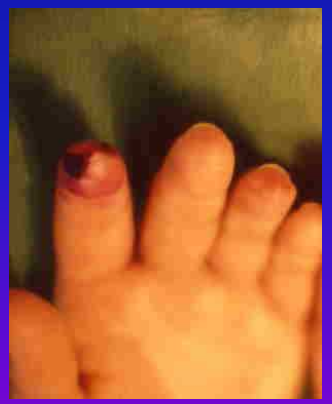
Diagnóstico de la enfermedad en edad tardía (>60 a.)

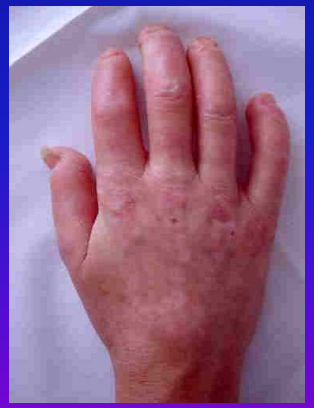
Fenómeno de Raynaud grave y de curso prolongado

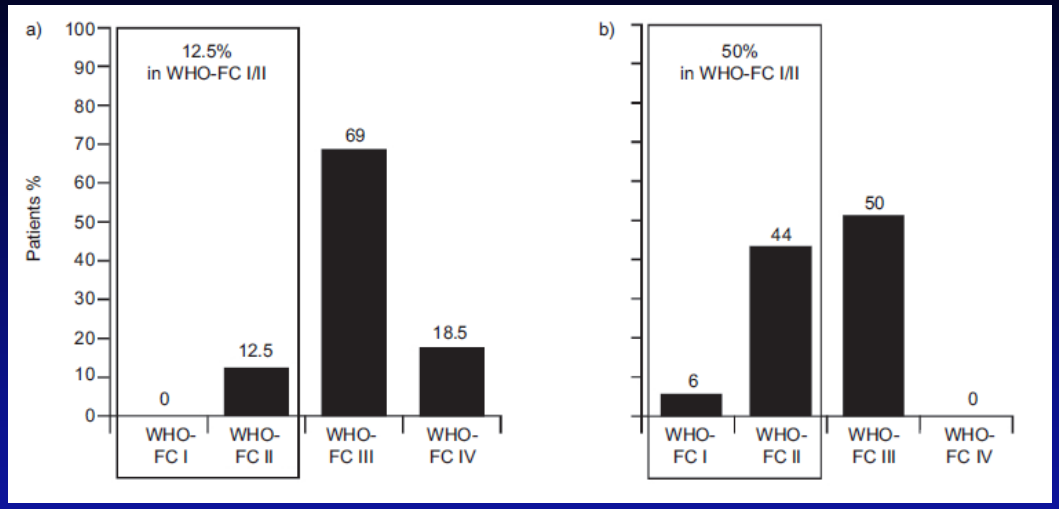
Pérdida capilar en la capilaroscopia

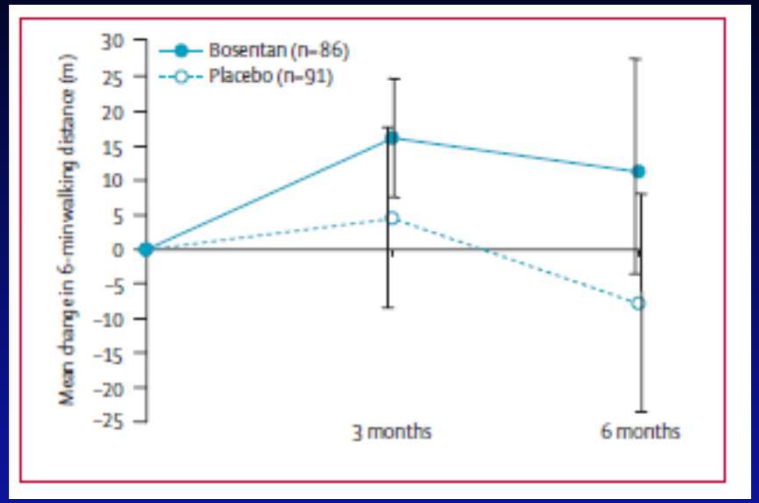
Anticuerpos anticentrómero
(anti-U3-RNP, anti-B23, anti-U1-RNP)

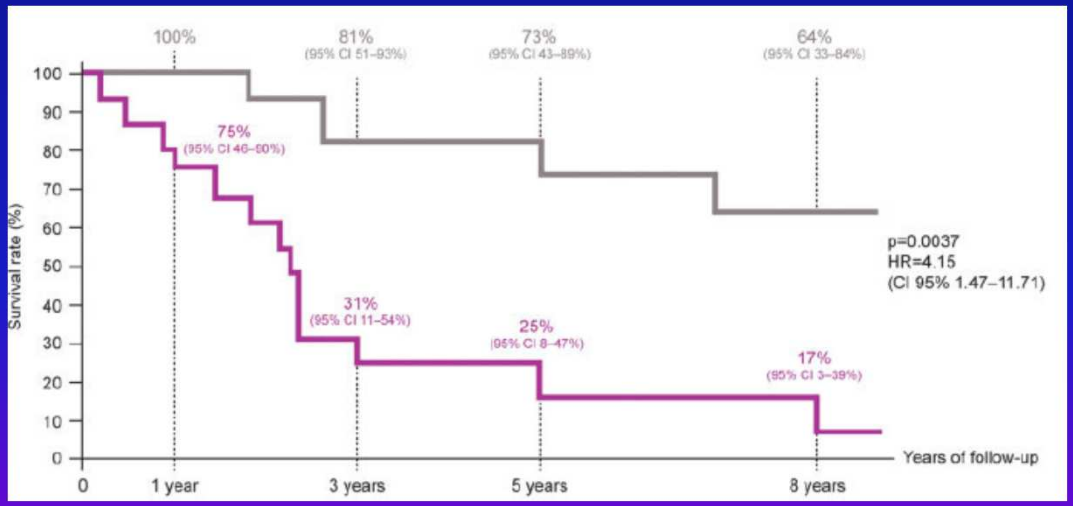
Telangiectasias

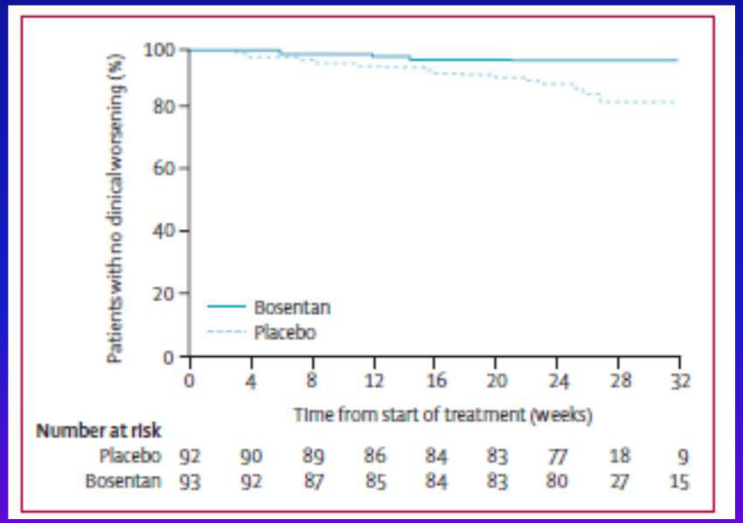












Humbert M. et al. *Eu Respir Rev* 2012

Galie N. et al. *Lancet* 2008


Expert
right heart
Delphi
Early
Prediction
Pulmonary Hypertension
Systemic Sclerosis by an
Clinical
Index
Development of pulmonary hypertension in a high-risk population
with systemic sclerosis in the Pulmonary Hypertension Assessment
and Recognition of Outcomes in Scleroderma (PHAROS) cohort study
Screening patients with scleroderma for
pulmonary arterial hypertension and
implications for other at-risk populations
Pulmonary hypertension
in scleroderma
Function Test Measures Improves Sensitiv
Diagnosis of Systemic Sclerosis-associated Pu
Arterial Hypertension: Analysis of 2 Cohorts

Prediction of Pulmonary Hypertension Related to Systemic Sclerosis by an Index Based on Simple Clinical Observations

Meune C et al. *Arthriris & Rheum*. 2011

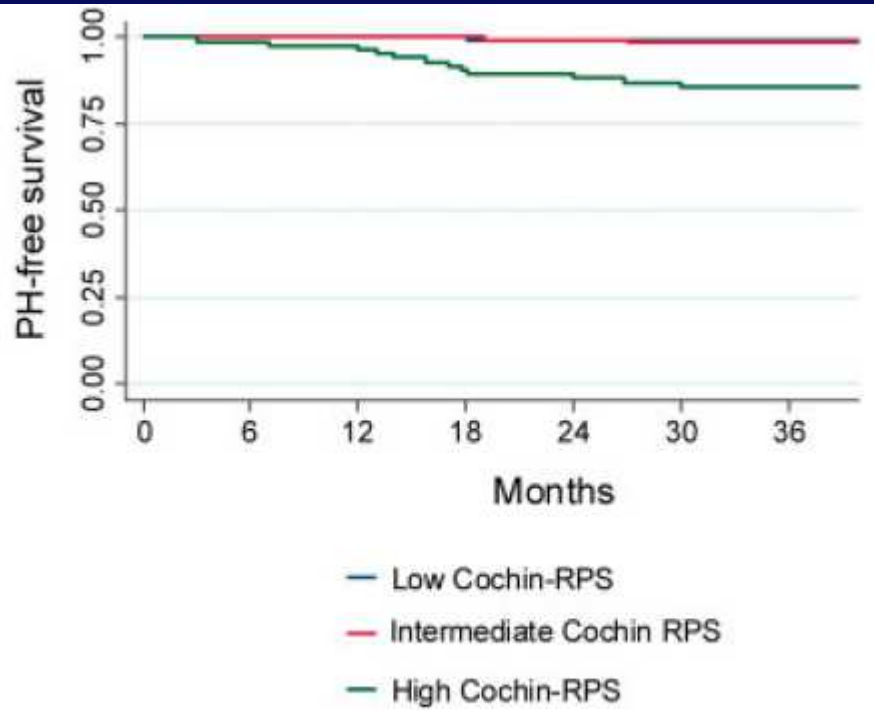
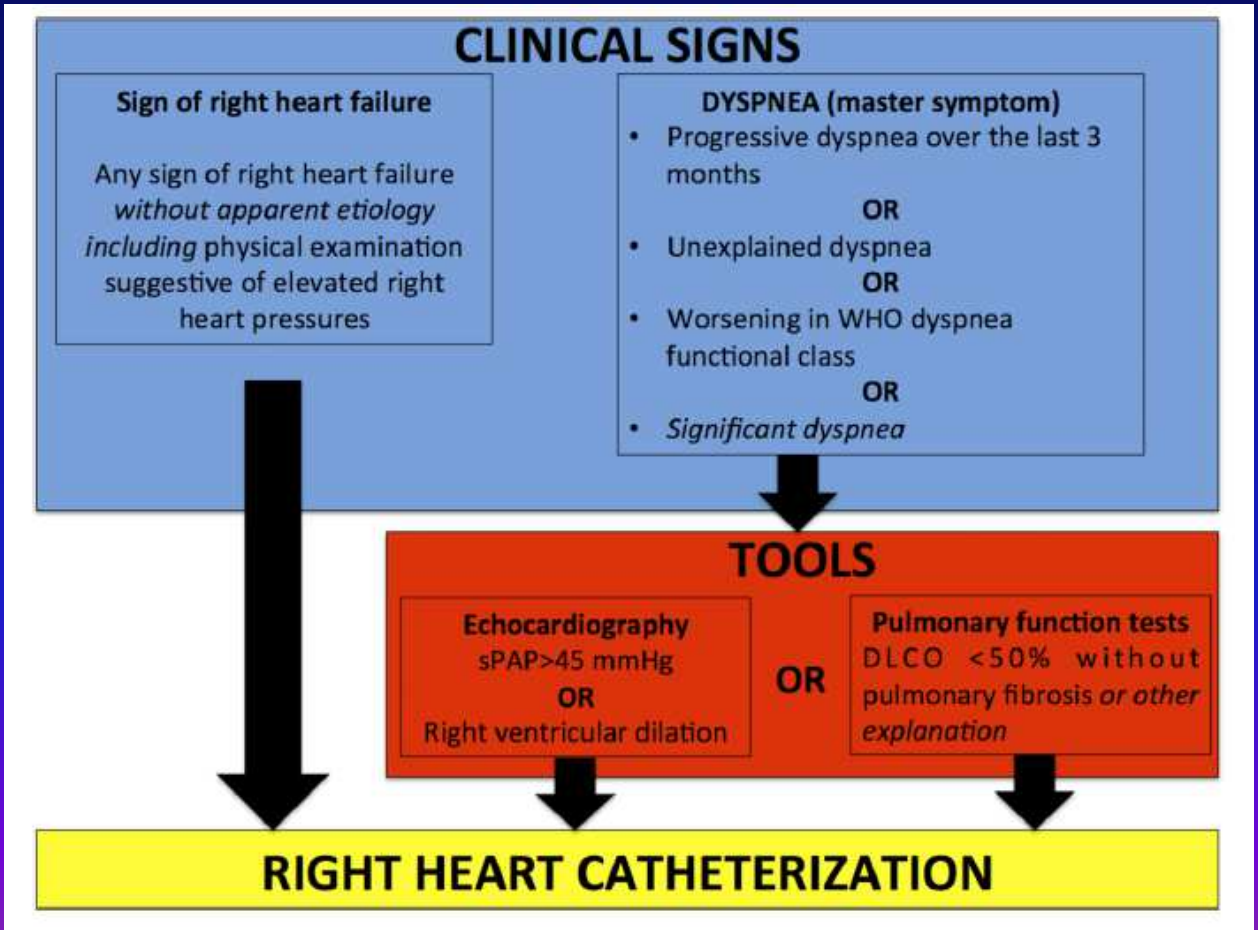


Figure 2. Kaplan-Meier cumulative pulmonary hypertension (PH)–free survival rates in patients with low, intermediate, and high Cochin risk prediction scores (RPS).

"COCHIN RPS" = 0,000117(edad) + 0,0207818(150 – CVF) + 0,04095(100-Dl_{co}/VA)

Expert consensus for performing right heart catheterisation for suspected pulmonary arterial hypertension in systemic sclerosis: a Delphi consensus study with cluster analysis



Avouac J. *Ann Rheum Dis*. 2013

Combination of Echocardiographic and Pulmonary Function Test Measures Improves Sensitivity for Diagnosis of Systemic Sclerosis-associated Pulmonary Arterial Hypertension: Analysis of 2 Cohorts

Glaude H et al. *J Rheumatol.* 2013

Table 5. Univariate logistic regression for association with pulmonary arterial hypertension (PAH).

	n	OR (95% CI)	p
Age	247	1.08 (1.05, 1.1)	< 0.001
Female	247	0.8 (0.4, 1.7)	0.58
SSc disease duration	244	1.06 (1.0, 1.1)	0.001
ACA	236	2.78 (1.5, 5.2)	0.001
ATA	235	0.41 (0.2, 0.9)	0.03
TTE (continuous)	241	1.17 (1.1, 1.2)	< 0.001
FVC%/DLCO% (continuous)	246	4.93 (2.8, 8.6)	< 0.001
eRVSP > 40 mm Hg	241	40.28 (17.7, 91.8)	< 0.001
FVC%/DLCO% ≥ 1.6	246	8.19 (4.2, 16.1)	< 0.001

ACA: anti-centromere antibody; ATA: anti-topoisomerase antibody; TTE: transthoracic echocardiogram in mm Hg; eRVSP: estimated right ventricular systolic pressure; FVC%/DLCO%: forced vital capacity/DLCO percent predicted ratio.

Table 6. Multivariate logistic regression for association with pulmonary arterial hypertension (PAH).

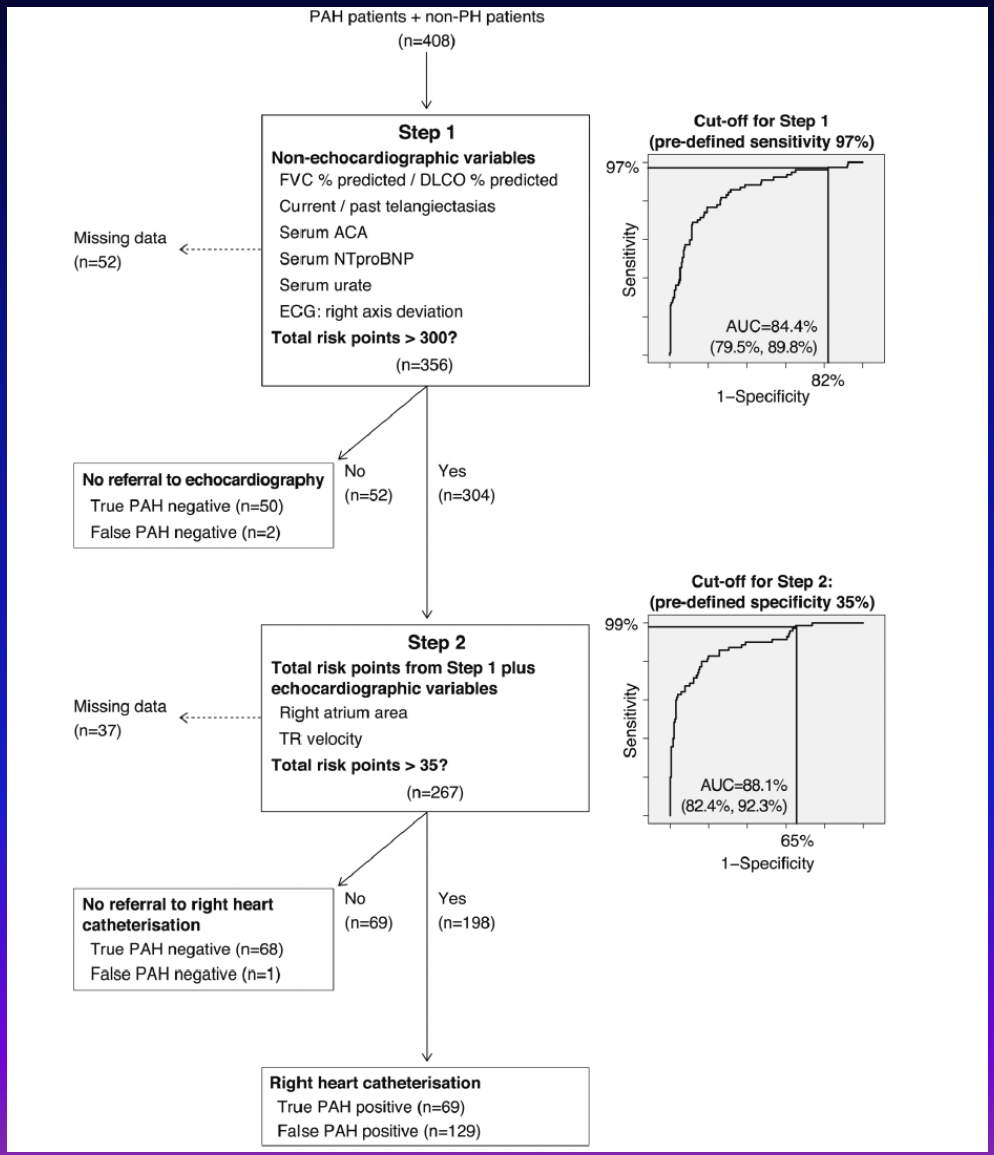
	OR (95% CI)	p
Age	1.04 (0.996, 1.09)	0.07
SSc disease duration	0.99 (0.93, 1.05)	0.78
ACA	1.54 (0.53, 4.42)	0.43
ATA	0.53 (0.16, 1.79)	0.31
eRVSP > 40 mm Hg	29.34 (11.26, 76.41)	< 0.001
FVC%/DLCO% ≥ 1.6	2.98 (1.16, 7.66)	0.02

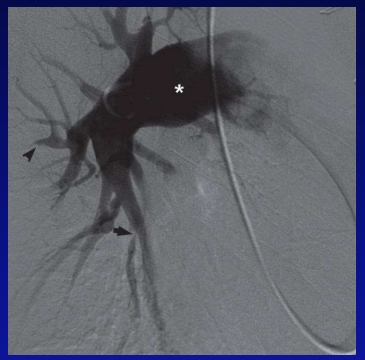
ACA: anti-centromere antibody; ATA: anti-topoisomerase antibody; eRVSP: estimated right ventricular systolic pressure; FVC%/DLCO%: forced vital capacity/DLCO percent predicted ratio.

Conclusion. In 2 large SSc cohorts, screening with TTE and PFT captured a majority of patients with PAH. TTE and PFT complement each other for the diagnosis of PAH. (J Rheumatol First Release Aug 15 2013 2013; doi:10.3899/jrheum.130400)

Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study

Coghlan JG et al. ARD. 2013





Riesgo elevado de HTAP:
- Evolución >3 años
- Dlco < 60%

HAP: 19%
HTAP no detectada: 4% (3)
Sensibilidad: 96%
Especificidad: 48%

HTAP en la esclerodermia: factores de riesgo

Descenso de la DLCO (<50-55%): CVF normal/mínima fibrosis

CVF/DLCO: > 1,6 – 1,8

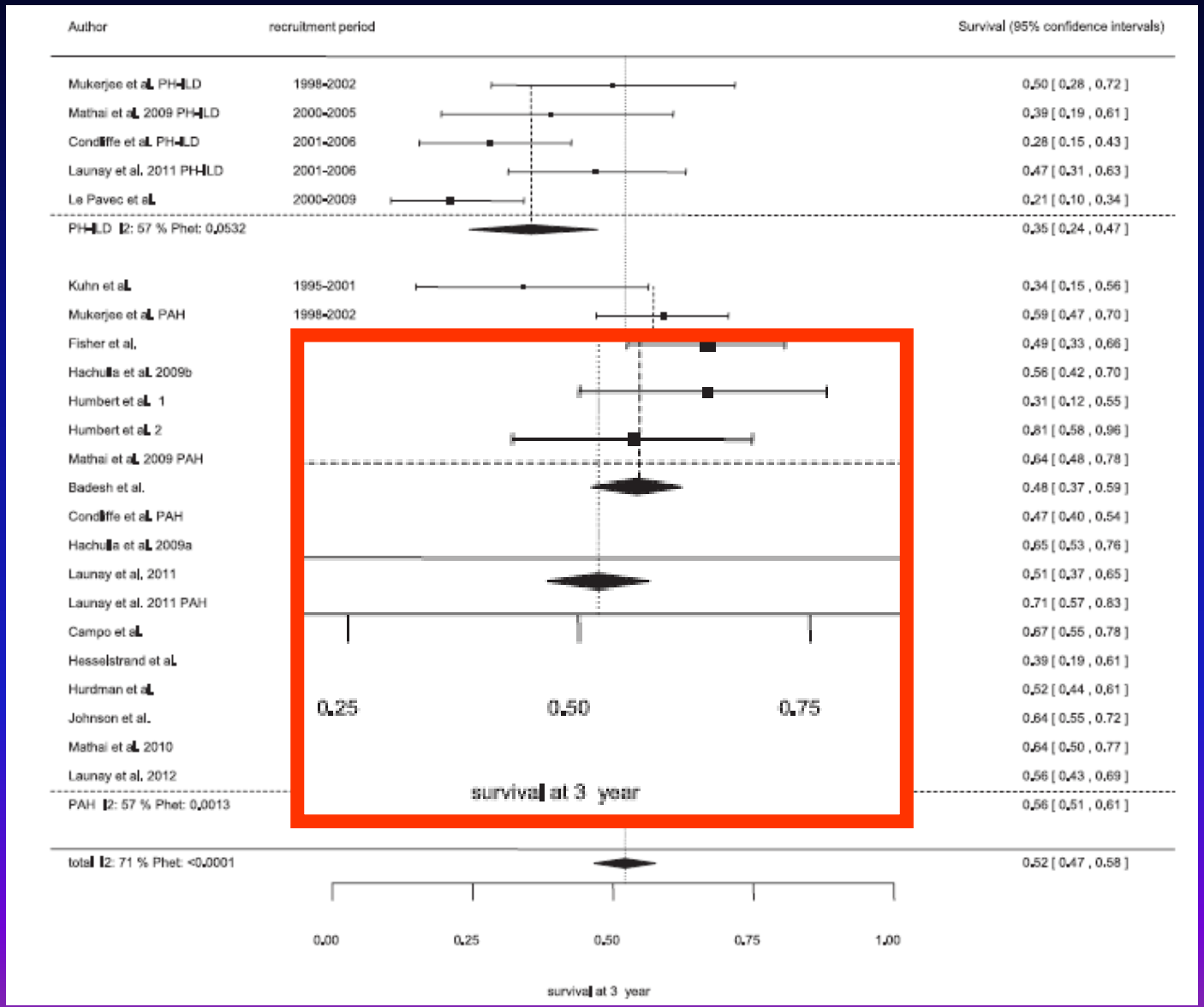
Por Ecocardiografía Doppler:

- Velocidad de regurgitación tricuspídea > 3 m/sec
- PAPs > 40 – 50 mm Hg
- Dilatación de cavidades derechas

Aumento de NT-proBNP

Controles: 6 m – 1 año: Ecocardiograma; PFRs; NT-proBNP
RNM

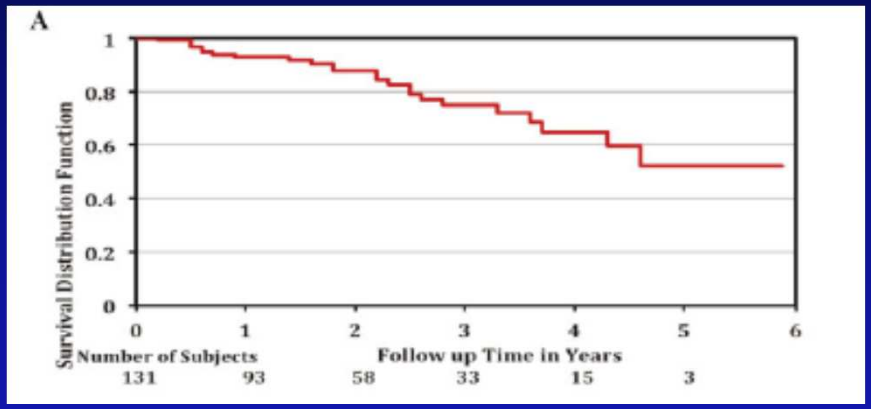
ESC: Hipertensión pulmonar y supervivencia



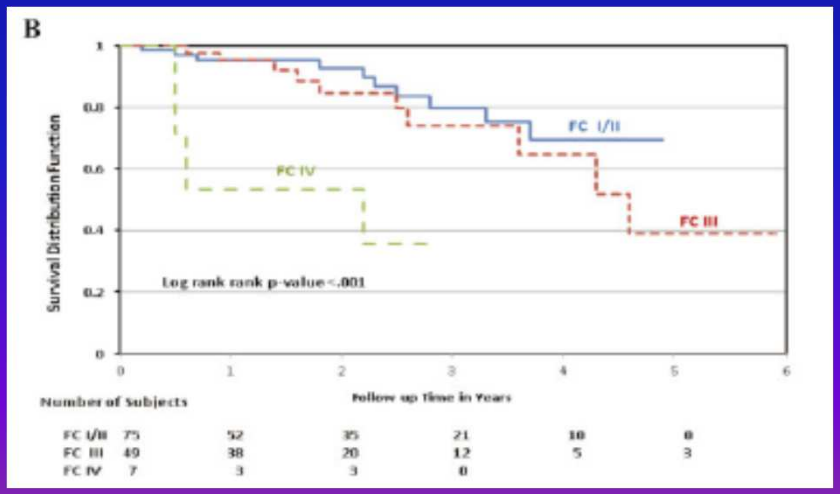
Lefèvre G et al. *Arthritis & Rheum*. 2013

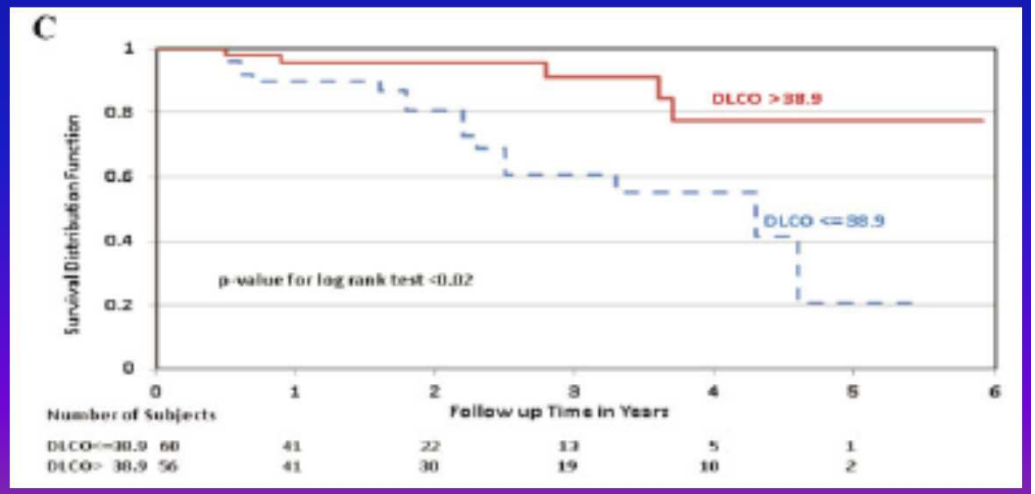
Survival and Predictors of Mortality in Systemic Sclerosis–Associated Pulmonary Arterial Hypertension: Outcomes From the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Registry

Chung L. et al. 2014



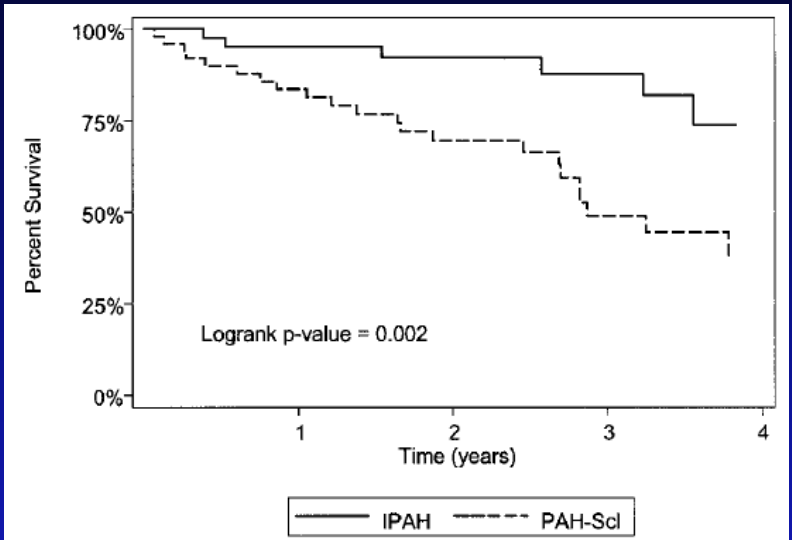
1 año	2 años	3 años
93%	88%	75%





HTAP: Diferencias entre HTAP- ESC e HTPA idiopática

Fisher MR et al. *Arthritis Rheum, 2006*



Clements PJ. *ARD*. 2012

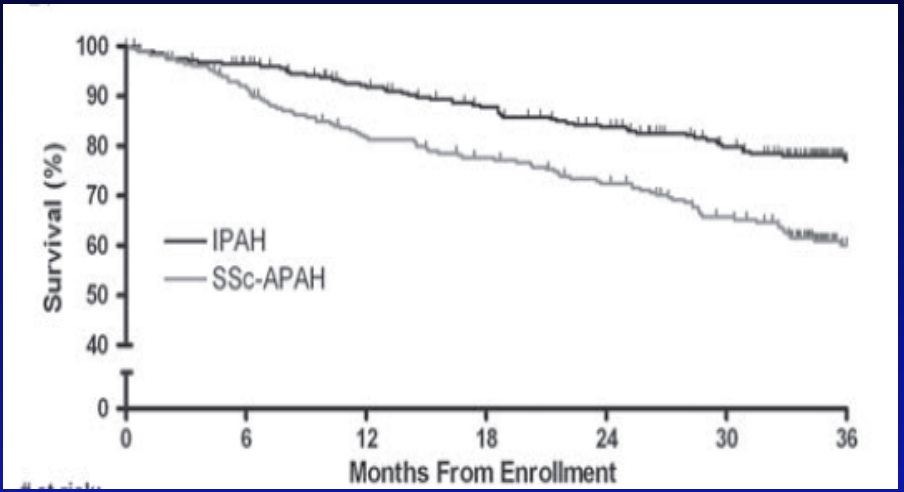
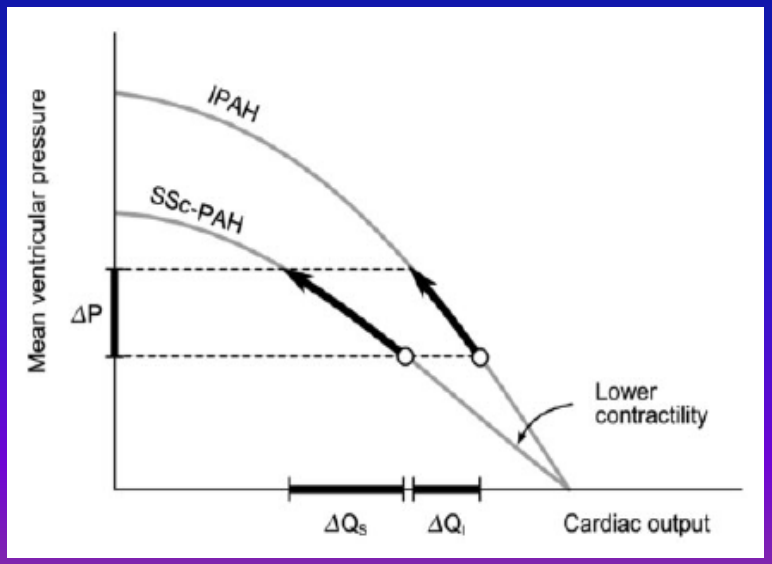
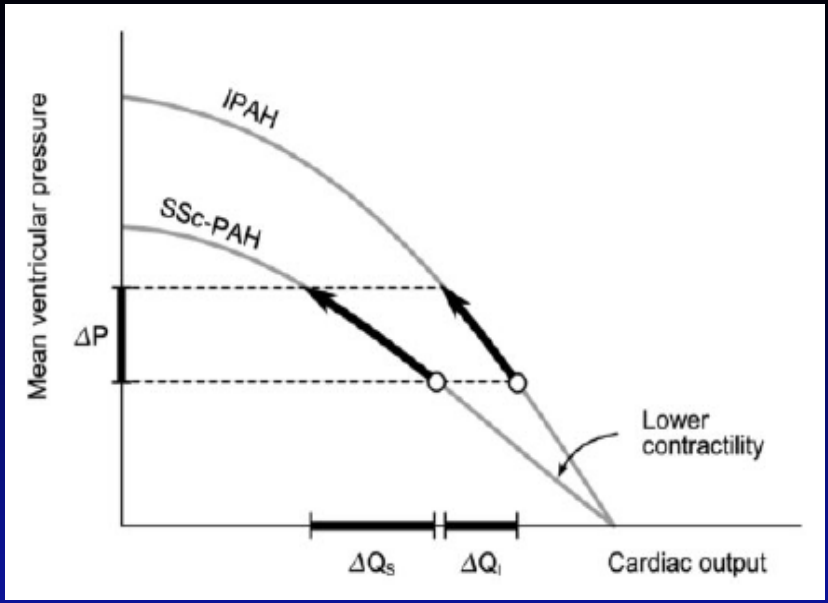


Table 2. Baseline right heart catheterization findings*

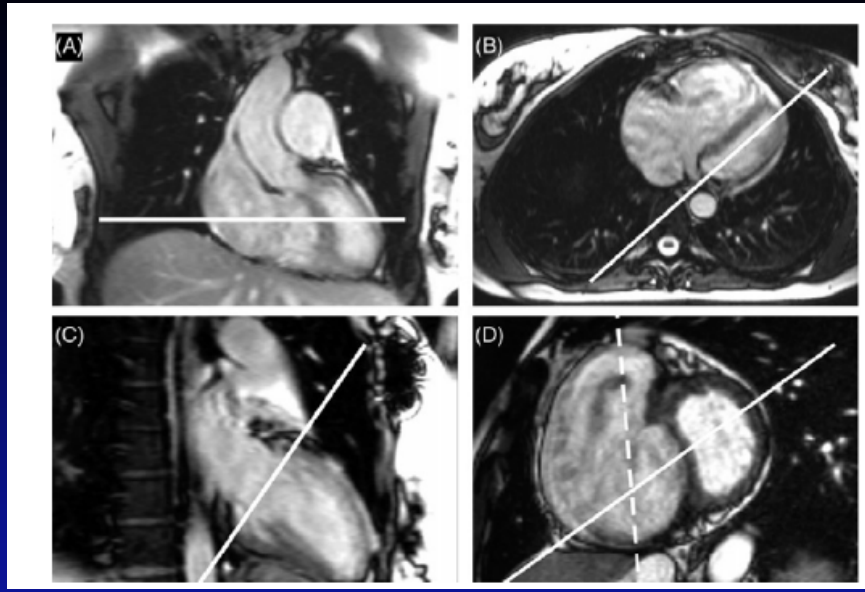
	IPAH (n = 41)	PAH-Scl (n = 50)	*P*
Right atrial pressure, mm Hg	10.1 ± 0.9	11.2 ± 0.7	0.36
Pulmonary artery systolic pressure, mm Hg	86.4 ± 2.9	75.6 ± 2.4	0.004
Pulmonary artery pressure, mm Hg	54.4 ± 1.9	46.6 ± 1.5	0.002
Pulmonary capillary wedge pressure, mm Hg	12.0 ± 0.8	11.4 ± 0.7	0.59
Cardiac index, 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



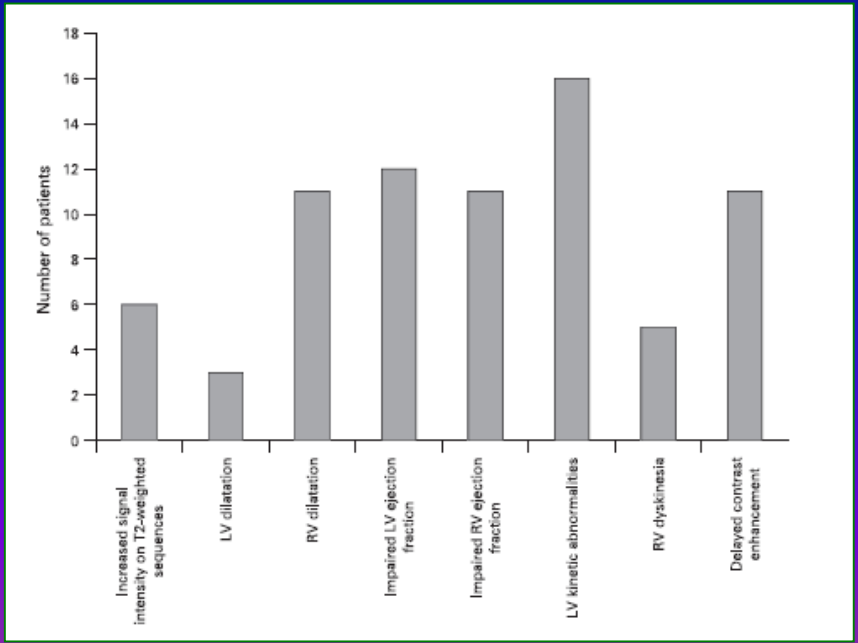
A Vonk Noordegraaf et al. *Rheumatology*, 2008



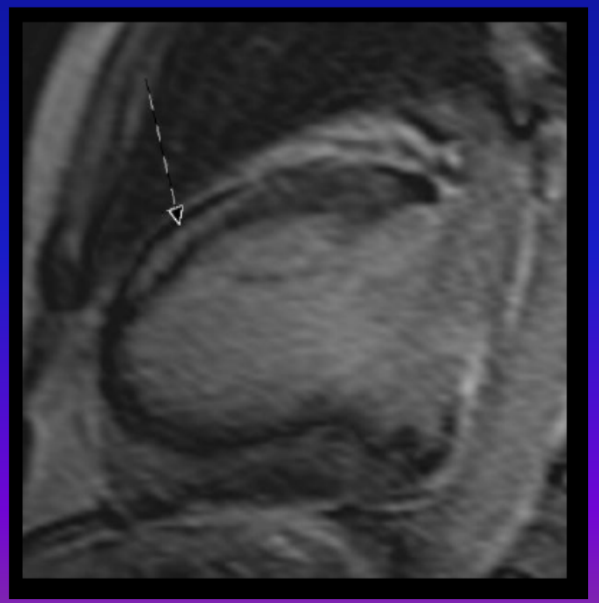
A Vonk Noordegraaf et al.*Rheumatology*, 2008



A Vonk Noordegraaf et al. *Am J Cardiol* 2012



Hachulla AL et al. *ARD*. 2009



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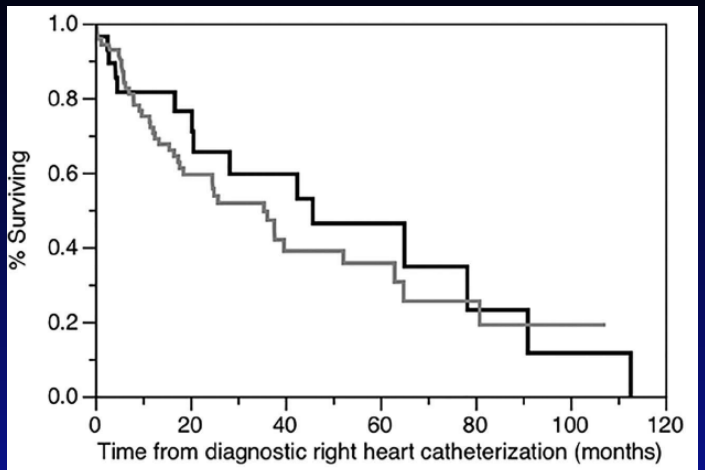
http://dx.doi.org/10.1016/j.jacc.2013.10.031

Updated Treatment Algorithm of Pulmonary Arterial Hypertension

YELLOW: M… cause morta… n all-
*Level of ev…
†Approved …); in Japan and S…
‡ Positive opinion for approval of the CHMP of EMA

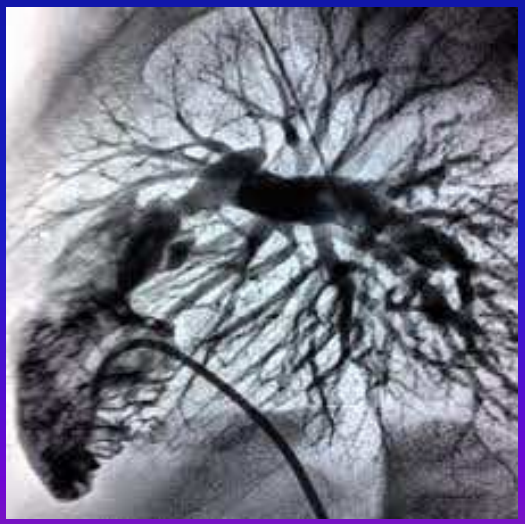
Recommendation	Evidence*	WHO-FC II	WHO-FC III	WHO-FC IV
I	A or B	Ambrisentan Bosentan Macitentan†‡ Riociguat† Sildenafil Tadalafil	Ambrisentan Bosentan Epoprostenol i.v. Iloprost inhaled Macitentan†‡ Riociguat† Sildenafil Tadalafil Treprostinil s.c., inhaled†	Epoprostenol i.v.
IIa	C		Iloprost i.v. † Treprostinil i.v.	Ambrisentan, Bosentan Iloprost inhaled and i.v† Macitentan†‡ Riociguat† Sildenafil, Tadalafil Treprostinil s.c., i.v., inhaled†
IIb	B		Beraprost†	
	C		Initial Combination Therapy	Initial Combination Therapy

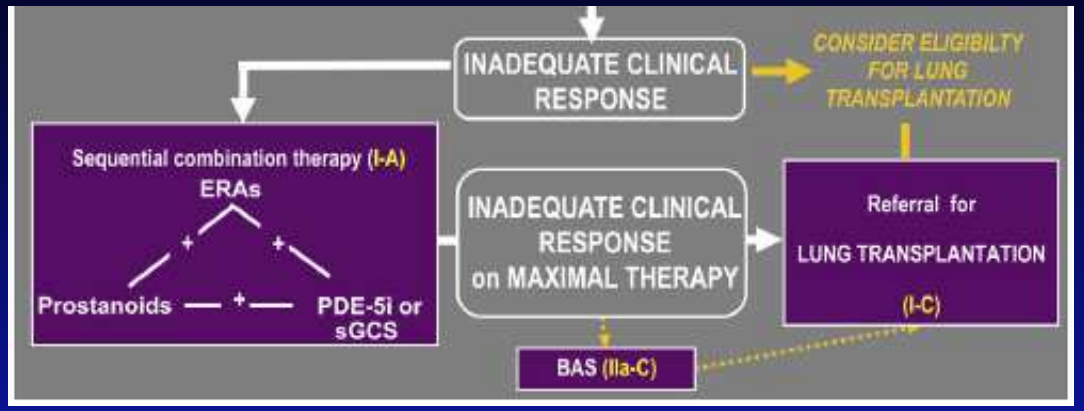


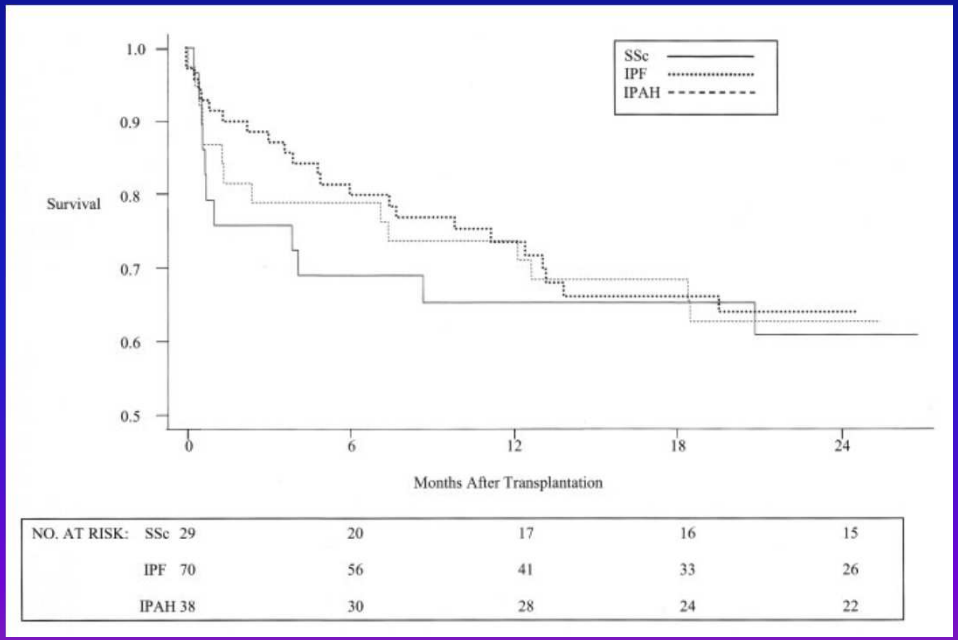
Number at risk

	0	1 year	2 years	3 years
SSc-PAH	28	20	13	10
SSc-PH-ILD	71	68	45	32

Volkmann ER., 2014





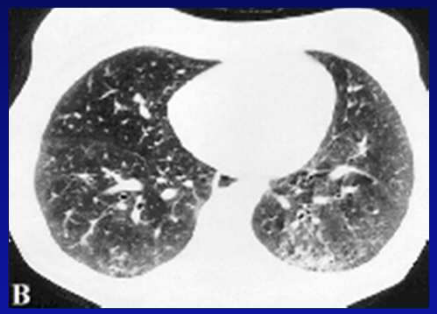


NO. AT RISK:					
SSc	29	20	17	16	15
IPF	70	56	41	33	26
IPAH	38	30	28	24	22

Schachma L., 2006

ESCLERODERMIA. Afección pulmonar
Conclusiones

Manifestación clínica frecuente: EPID > HTP



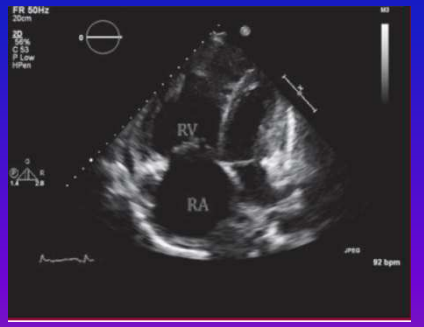
Complicación grave

Causa de muerte

EPID: TACAR y PFRs: diagnóstico, pronóstico y evolución

HTP cribaje: Ecocardiograma y PFRs (NT-ProBNP) anuales

EPID tratamiento: inmunosupresores



HTP tratamiento: monoterapia/terapia combinada

Esclerodermia. Afección pulmonar