LA HAP EN LAS ENFERMEDADES AUTOINMUNES SISTÉMICAS (ESCLERODERMIA, LUPUS) Y ABORDAJE TERAPÉUTICO ESPECÍFICO DE LAS MISMAS

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A Coruña 19-22 de Noviembre de 2008
PALEXCO. Palacio de Exposiciones y Congresos

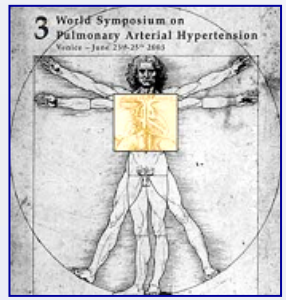
HTAP en las EAS. Reseña histórica

*"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".*
Salerni R et al., 1977

*"un tipo de afección vascular en los pulmones especialmente destructivo, que comienza bruscamente y tiene consecuencias letales" **Pulmonary hypertension: The Bête Noire** of the Connective Tissue Diseases.*
Le Roy CE, 1991

1980-2002 → 83 referencias
2002-2008 → 222 referencias

Clasificación de la hipertensión pulmonar

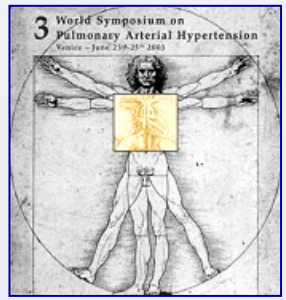


III Simposio Internacional sobre Hipertensión Pulmonar

Venecia 2003

1. **HAP: hipertensión arterial pulmonar**
2. **HP secundaria a patología cardiaca izquierda**
3. **HP asociada a neumopatías y/o hipoxemia**
4. **HP debida a enfermedad trombótica y/o embólica crónica**
5. **Miscelánea**

Clasificación de la hipertensión pulmonar



III Simposio Internacional sobre Hipertensión Pulmonar

Venecia 2003

1- HTAP:

- **Idiopática (HAPi)**
- **Familiar**
- **Relacionada con factores de riesgo u otras patologías:**
  - **Enfermedades del tejido conectivo**
  - **Cardiopatías congénitas**
  - **Hipertensión portal**
  - **VIH**
  - **Fármacos y tóxicos**
  - **Otros**
- **HAP asociada a afectación capilar y/o venosa significativa**

Pulmonary Arterial Hypertension in France
Results from a National Registry

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 173 2006

TABLE 1. CLINICAL AND HEMODYNAMIC DATA AT THE TIME OF DIAGNOSIS OF PULMONARY ARTERIAL HYPERTENSION

	All Cases (*n* = 674)	Incident Cases (*n* = 121)	Prevalent Cases (*n* = 553)	p Value*
Clinical data				
Female patients, %	65.3	57.0	67.1	0.035
Age, yr (range)	50 ± 15 (18–85)	53 ± 17 (19–85)	50 ± 14 (18–82)	0.06
NYHA III–IV, %	75	81	73	0.08
6-min walk distance, m	329 ± 109	312 ± 114	333 ± 108	0.09
Hemodynamic data				
RAP, mm Hg	8 ± 5	8 ± 5	8 ± 5	
mPAP, mm Hg	55 ± 15	49 ± 14	56 ± 15	< 0.0001
PAWP, mm Hg	8 ± 3	8 ± 3	8 ± 3	
Cardiac index, L/min/m²	2.5 ± 0.8	2.4 ± 0.9	2.5 ± 0.8	
Sv_{O_2}, %	63 ± 9	63 ± 8	63 ± 9	
PVRI, mm Hg/L/min/m²	20.5 ± 10.2	19.2 ± 9.3	20.7 ± 10.4	
Disease subtype, %				
Idiopathic (n = 264)	39.2	40.5	38.9	
Familial (n = 26)	3.9	2.5	4.2	
Connective tissue diseases (n = 103)	15.3	18.2	14.6	
Congenital heart diseases (n = 76)	11.3	4.1	12.8	
Portal hypertension (n = 70)	10.4	14.9	9.4	
Anorexigens (n = 64)	9.5	3.3	10.8	
HIV infection (n = 42)	6.2	9.9	5.4	
Two coexisting risk factors (n = 29)	4.3	6.6	3.8	

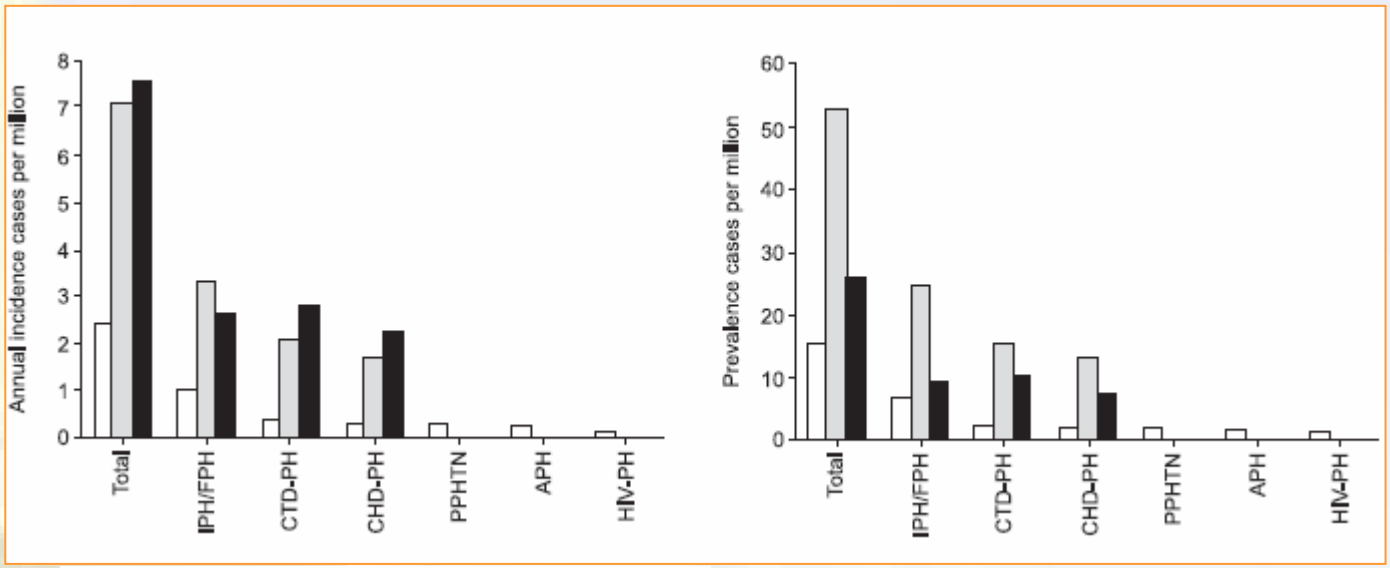
Eur Respir J 2007; 30: 104–109
DOI: 10.1183/09031936.00092306

An epidemiological study of pulmonary arterial hypertension

A.J. Peacock*, N.F. Murphy#, J.J.V. McMurray#, L. Caballero* and S. Stewart*

TABLE 2 Prevalence and incidence of pulmonary arterial hypertension and its subtypes from three sources#

	Total	IPH	CTD-PH	CHD-PH
Prevalence				
French	15	6.5	2.3	1.7
SMR	52	25	15	12
SPVU	26	9	10	7
Incidence				
French	2.4	1.0	0.4	0.3
SMR	7.1	3.3	2.1	1.7
SPVU	7.6	2.6	2.8	2.2



□: French national registry; ■: Scottish hospitalisation ■: Scottish Pulmonary Vascular Unit

Eur Respir J 2007; 30: 1103–1110
DOI: 10.1183/09031936.00042107

A USA-based registry for pulmonary arterial hypertension: 1982–2006

T. Thenappan, S.J. Shah, S. Rich and M. Gomberg-Maitland

	Year			p-value
	1982–1996	1996–2002	2002–2006	
Subjects n	103	328	147	
Age yr	41±12	49±14	52±14	<0.0001
Female	77 (75)	253 (77)	115 (78)	0.81
WHO functional class	3.2±0.9	2.9±0.8	3.2±0.8	0.003
Exercise capacity METs	3.6±3.05	3.6±3.05	3.4±2.9	0.81
Prostacyclins#	3 (2.9)	11 (3.4)	0	0.44
Endothelin antagonists#	0	1 (0.3)	17 (11.6)	<0.001
Phosphodiesterase inhibitors#	0	0	5 (3.4)	<0.001
Idiopathic/familial PAH	77 (75)	150 (46)	49 (33)	<0.0001
CTD	12 (11)	100 (30)	61 (42)	<0.0001
Congenital heart disease	10 (10)	34 (10)	18 (12)	0.78
Portal hypertension	4 (4)	25 (8)	14 (10)	0.241
Anorexigens	0	13 (4)	3 (2)	0.065
HIV	0	6 (2)	2 (1)	0.164

The Prevalence of Undiagnosed Pulmonary Arterial Hypertension in Subjects With Connective Tissue Disease at the Secondary Health Care Level of Community-Based Rheumatologists (the UNCOVER Study)

ARTHRITIS & RHEUMATISM
Vol. 52, No. 7, July 2005, pp 2125–2132
DOI 10.1002/art.21131

N 669: 604ES/89EMTC
HTAP 89
ES 82 (14%)
EMTC 7 (7.8%)

Table 1. Patients participating in the survey*

Patients	Unknown PAH status	PAH present	Total
Evaluable			
With SSc	604	111	715
With MCTD	89	11	100
Total	693	122	815
Final			
With SSc	586	111	697
With MCTD	83	11	94
Total	669	122	791

Table 2. ERVSP by Doppler echocardiography in 669 patients with unknown PAH status (the prospective group)*

ERVSP, mm Hg	No. (%) of patients
≥30	282 (42.2)
≥35	158 (23.6)
≥40	89 (13.3)
≥45	45 (6.7)
≥50	20 (3.0)
≥60	6 (0.9)

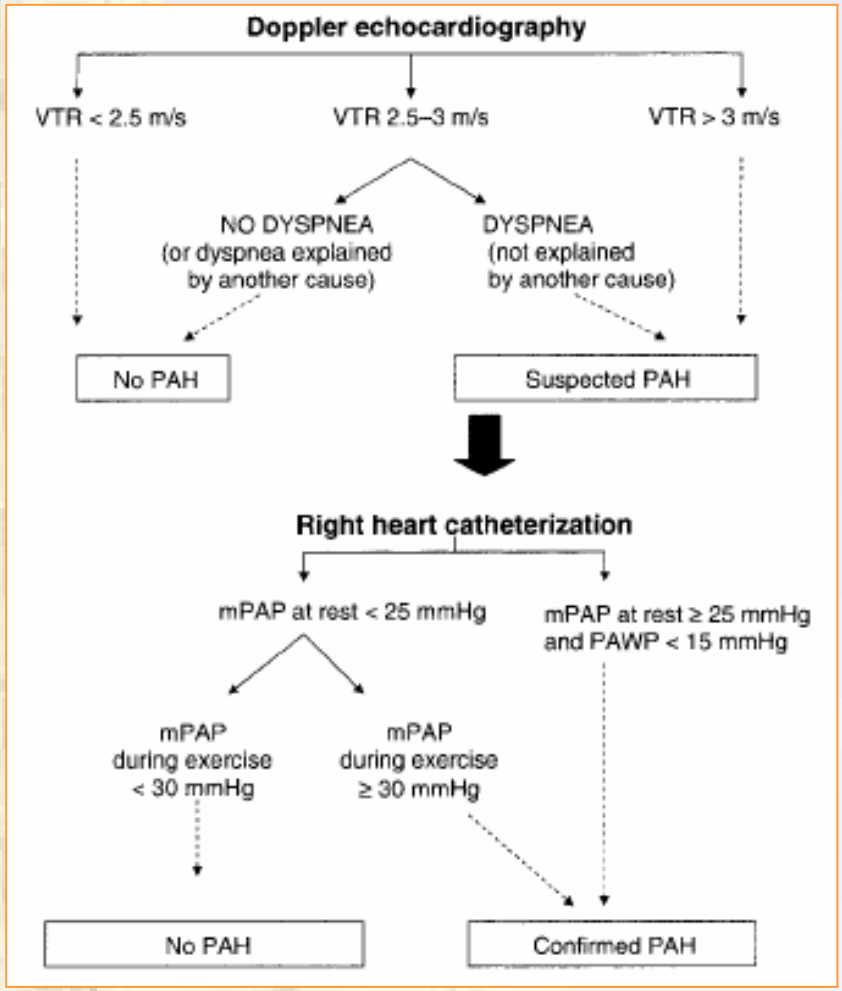
* ERVSP = estimated right ventricular systolic pressure; PAH =

Conclusion. **A significant number of patients with SSc or MCTD (13.3%) followed up in a community rheumatology practice setting have undiagnosed elevated ERVSP consistent with PAH.**

Early Detection of Pulmonary Arterial Hypertension in Systemic Sclerosis

A French Nationwide Prospective Multicenter Study

ARTHRITIS & RHEUMATISM
Vol. 52, No. 12, December 2005, pp 3792–3800
DOI 10.1002/art.21433

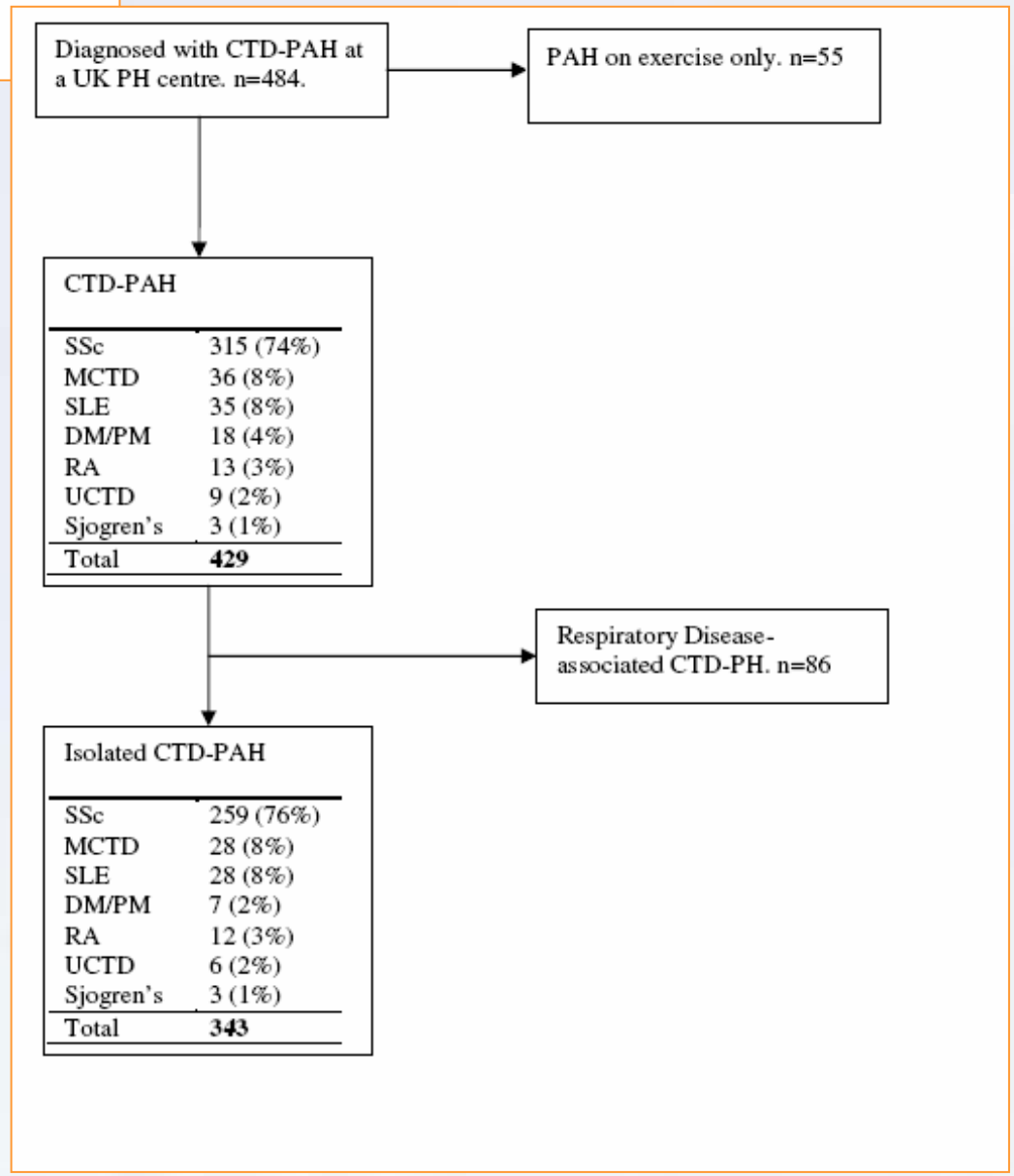


Results. **Of the 599 patients analyzed, 29 had known PAH and 33 had suspected PAH, based on Doppler echocardiography, and underwent RHC. Of these 33, 18 were found to have PAH, 3 had left ventricular dysfunction, and 12 had no PAH. Newly diagnosed cases of PAH were of mild severity (mean ± SD pulmonary artery pressure [mPAP] 30 ± 9 mm Hg, mean ± SD total pulmonary resistance [TPR] 524 ± 382 dynes × second/cm^5). Hemodynamic findings in patients with known PAH were mPAP 49 ± 17 mm Hg and TPR 1,007 ± 615 dynes × second/cm^5. The estimate of PAH prevalence was 7.85% (95% confidence interval 5.70–10.00).**

AJRCCM Articles in Press. Published on October 17, 2008 as doi:10.1164/rccm.200806-953OC

Connective tissue disease associated pulmonary arterial hypertension in the modern treatment era

Enero 2001-Junio 2006
Registro de HTAP en EAS
N= 484



HTAP en las EAS

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

HTAP en las EAS. Factor pronóstico.

	Factor mal pronóstico	Causa de muerte
Esclerodermia	+++++	1ª
DM/PM	+	rara
SS	-/+	rara
LES	+	rara
EMTC	++	3ª

HTAP en el Síndrome Sjögren primario.

TABLE 1. Demographic, Clinical, and Immunologic Features of 1010 Spanish Patients With Primary Sjögren Syndrome

Feature*	No. (%) (n = 1010)
Sex (female)	937 (93)
Age at onset (yr)†	53.0 ± 0.48
Age at protocol (yr)†	58.7 ± 0.46
Xerostomia	975 (96%)
Xerophthalmia	968 (96%)
Parotid enlargement	269 (27%)
Abnormal ocular tests	898/956 (94%)
Abnormal parotid scintigraphy/salivary flow	580/759 (76%)
Positive salivary gland biopsy	449/561 (79%)
Arthralgia	490 (48%)
Raynaud phenomenon	187 (18%)
Arthritis	150 (15%)
Pulmonary involvement	112 (11%)
Peripheral neuropathy	110 (11%)
Vasculitis	91 (9%)
Renal involvement	48 (5%)
CNS involvement	21 (2%)
Pancreatitis	5 (0.5%)
ANA	859/1005 (85%)
Anti-Ro/SS-A	518/1002 (52%)
RF	467/982 (48%)
Anti-La/SS-B	343/1000 (34%)
Low C3	67/753 (9%)
Low C4	66/747 (9%)
Cryoglobulins	62/628 (10%)

*GEMESS Study Group**

Medicine 2008;87:210–219

N= 32 casos

29 Datos completos

Pulmonary Arterial Hypertension: A Rare Complication of Primary Sjögren Syndrome

Report of 9 New Cases and Review of the Literature

David Launay, MD, Eric Hachulla, MD, PhD, Pierre-Yves Hatron, MD, Xavier Puéchal, MD, Gérald Simonneau, MD, and Marc Humbert, MD, PhD

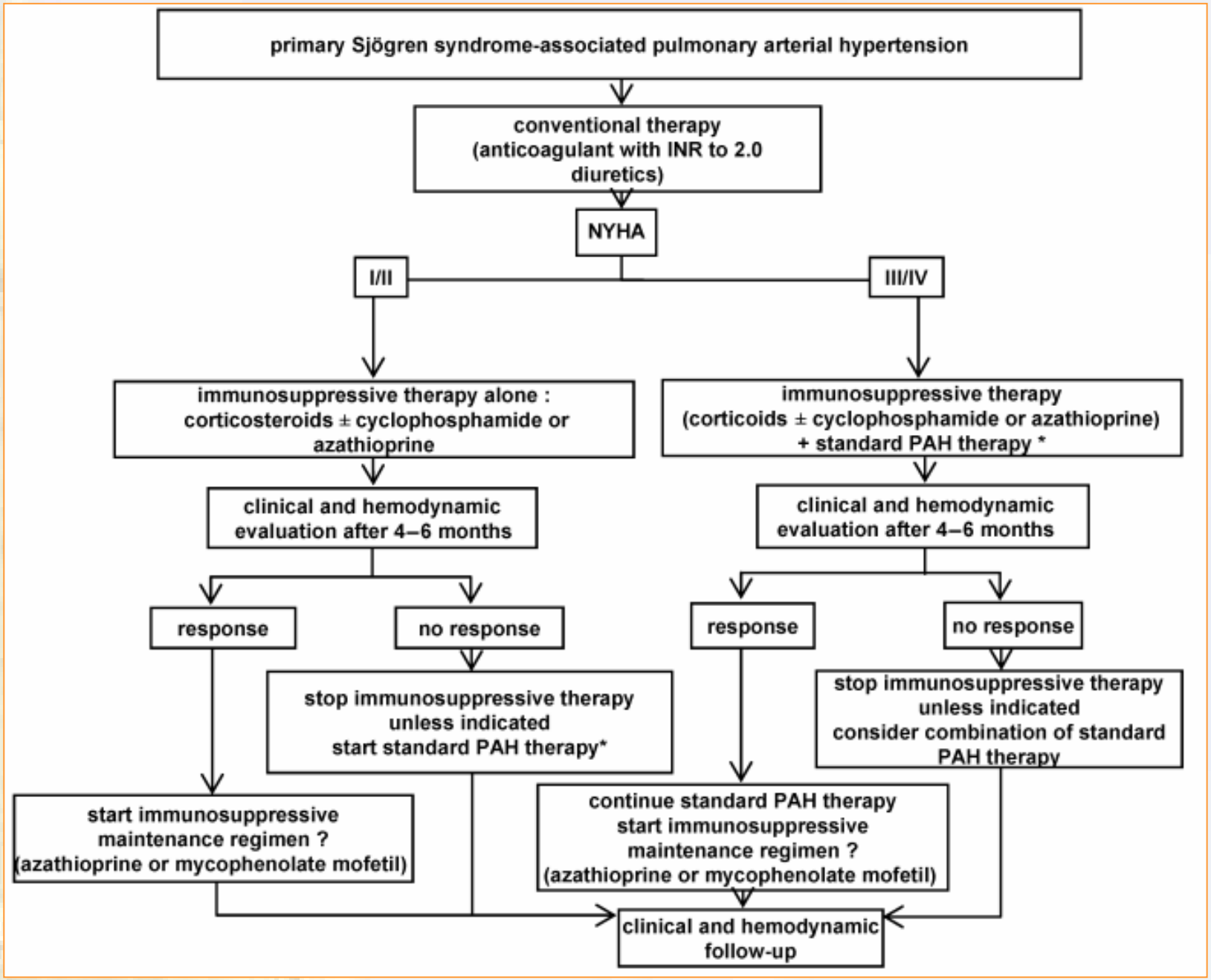
TABLE 6. Extraglandular Manifestations of our 9 Patients, the Whole Cohort of 28 Patients With pSS-Associated PAH, and the Cohort of 400 Patients With pSS Described by Garcia-Carrasco et al (28)

Manifestation*	9 Patients With pSS-Associated PAH	Whole Cohort of 28 Patients With pSS-Associated PAH	Cohort of 400 pSS Patients (Garcia-Carrasco et al [28])	p†
Articular involvement	2/9 (22)	6/18 (33)	147/400 (37)	NS
Raynaud phenomenon	6/9 (67)	15/25 (60)	62/400 (16)	<0.0001
Cutaneous vasculitis	3/9 (33)	5/13 (38)	47/400 (12)	0.02
Interstitial lung disease	4/9 (44)	6/23 (26)	37/400 (9)	0.03
Peripheral neuropathy	0/9 (0)	0/9 (0)	29/400 (7)	NS
Autoimmune thyroiditis	1/8 (12)	4/11 (36)	61/400 (15)	NS
Myositis	1/9 (11)	1/10 (10)	5/400 (1)	NS
Lymphoproliferative disease	0/9 (0)	0/9 (0)	8/400 (2)	NS

TABLE 8. Immunologic Features of our 9 Patients, the Whole Cohort of 28 Patients With pSS-Associated PAH, and the Cohort of 400 Patients With pSS Described by Garcia-Carrasco et al (28)

Feature*	9 Patients With pSS-Associated PAH	Whole Cohort of 28 Patients With pSS-Associated PAH	Cohort of 400 pSS Patients (Garcia-Carrasco et al [28])	p†
Antinuclear antibodies	9/9	27/28 (96)	288/392 (74)	0.01
Anti-Ro/SSA antibodies	7/9	20/25 (80)	153/385 (40)	0.002
Anti-La/SSB antibodies	6/9	8/18 (44)	102/385 (26)	NS
Rheumatoid factor	4/8	15/22 (68)	146/388 (38)	0.01
Low CH50	0/9	2/16 (12)	35/302 (12)	NS
Hypergammaglobulinemia‡	5/9	19/24 (79)	NK	NK
Total gammaglobulin level, g/L	23 ± 15	27 ± 12	NK	NK
Cryoglobulins	1/9	1/9 (11)	27/293 (9)	NS
Anti-RNP antibodies	1/9	5/21 (24)	4/312 (1)	<0.001
Anti-DNA antibodies	1/9	1/17 (6)	8/304 (3)	NS

Medicine • Volume 86, Number 5, September 2007


primary Sjögren syndrome-associated pulmonary arterial hypertension
conventional therapy (anticoagulant with INR to 2.0 diuretics)
NYHA
I/II
III/IV
immunosuppressive therapy alone : corticosteroids ± cyclophosphamide or azathioprine
immunosuppressive therapy (corticoids ± cyclophosphamide or azathioprine) + standard PAH therapy *
clinical and hemodynamic evaluation after 4–6 months
clinical and hemodynamic evaluation after 4–6 months
response
no response
response
no response
stop immunosuppressive therapy unless indicated start standard PAH therapy*
stop immunosuppressive therapy unless indicated consider combination of standard PAH therapy
start immunosuppressive maintenance regimen ? (azathioprine or mycophenolate mofetil)
continue standard PAH therapy start immunosuppressive maintenance regimen ? (azathioprine or mycophenolate mofetil)
clinical and hemodynamic follow-up

HTAP y DM/PM. Prevalencia. Mortalidad.

	Prevalencia	Mortalidad
Global	45%-65%	25%
EPID	20-40%	5-10%
NINE	40%	
NIU	30-40%	
Neumonia organizativa	20-60%	
Daño alveolar difuso	0-20%	90-100%
Neumonia por aspiración	15-20%	20%
Insuf.Resp. Debilidad musc.resp	15-45%	
HTAP	< 0.5%	90%

HTAP y DM/PM. Características

- Casos aislados.

- Prevalencia serie de Hospital Vall d´Hebron: 1 caso de 120 pacientes diagnosticados.

- La mayoría con patología intersticial pulmonar y Ac antisintetasa (Síndrome antisintetasa).

- Sospecha diagnóstica:

  CVF/DLCO > 1.8 → ecocardiograma-Doppler

- Tratamiento: vasodilatadores pulmonares.

HTAP en el LES. Prevalencia. Mortalidad.

	Prevalencia	Mortalidad
Afección respiratoria global	> 50%	
Clínica significativa	7%	
Pleuritis	30-70%	
Enfermedad pulmonar difusa		
Aguda (unidad alveolo-capilar):		
Neumonitis Lúpica	1-4%	50%
Hemorragia alveolar (capilaritis)	2%	50%
Subaguda		
Neumonia organizativa con BO	1%	
Crónica		
Neumonia Intersticial Usual	<2%	
Infecciones	40%	
Bacteriana		
Oportunistas *(Mycobacterias,* Nocardia, *Pneumocystis)*		
"Sindrome del pulmón encogido"	<1%	
HTA Pulmonar		**25-50%**
Aislada	**5-14%**	
Secundaria a TEP por SAF	**< 10%**	

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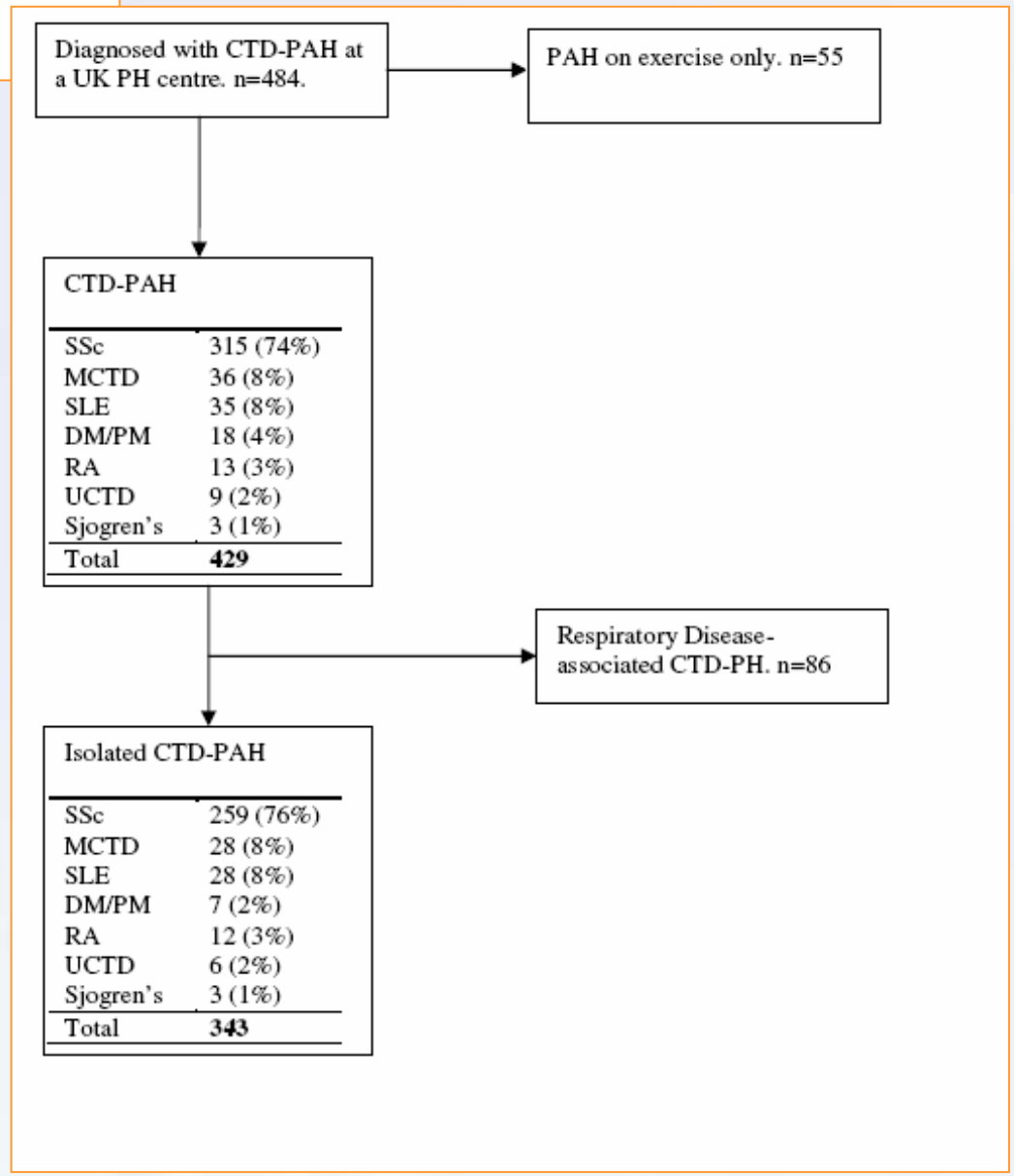
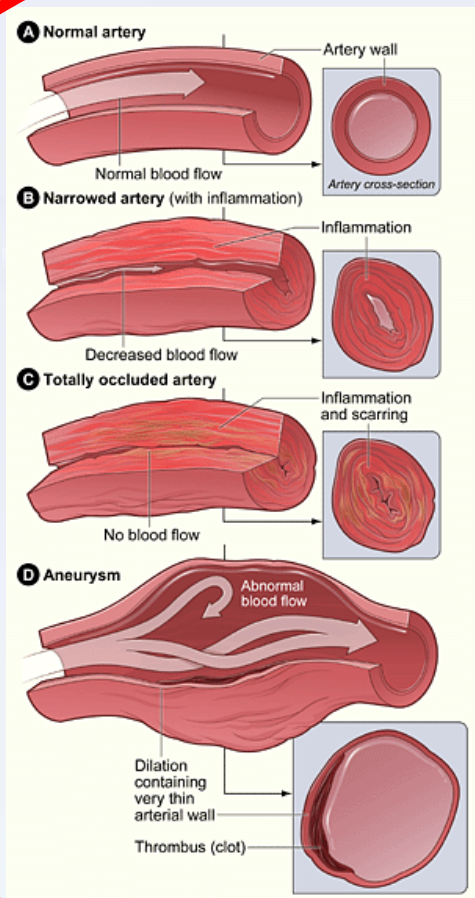
Connective tissue disease associated pulmonary arterial hypertension in the modern treatment era

Enero 2001-Junio 2006
Registro de HTAP en EAS
N= 484



HTAP en el LES/EMTC. Patogenia.



vasculopatía plexiforme

vasculopatía inflamatoria

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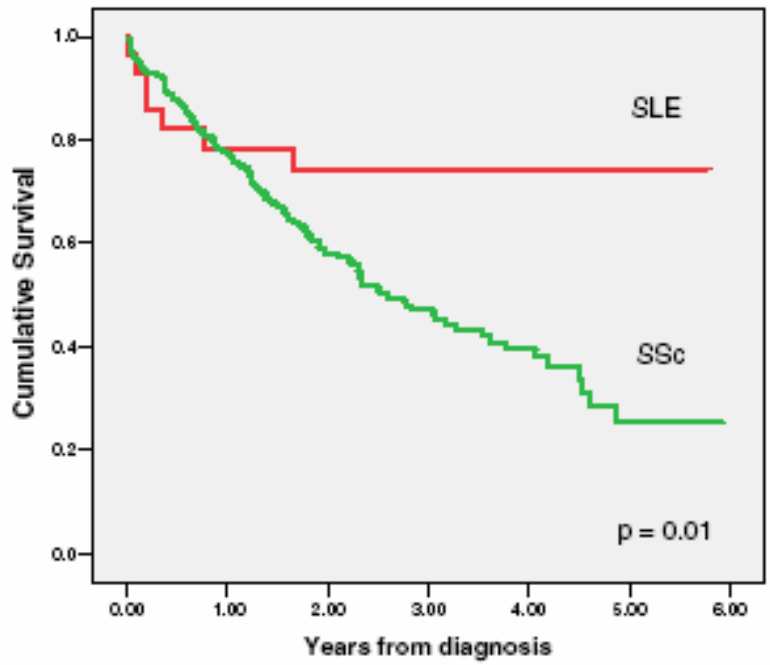
Connective tissue disease associated pulmonary arterial hypertension in the modern treatment era

Supervivencia

	1a	3a
LES	78%	74%
EMTC	89%	63%
ES	78%	47%



Immunosuppressive Therapy in Connective Tissue Diseases-Associated Pulmonary Arterial Hypertension*

Olivier Sanchez, MD; Olivier Sitbon, MD; Xavier Jaïs, MD; Gérald Simonneau, MD; and Marc Humbert, MD, PhD
(CHEST 2006; 130:182–189)

Table 3—*Comparison of Patients Who Responded and Did Not Respond to First-Line Immunosuppressive Therapy

Characteristics	Improved (n = 8)	p Value	Not Improved (n = 20)
Age, yr	32 ± 12		43 ± 18
Male/female gender, No.	1/7		4/16
SLE	5 (62)		8 (40)
MCTD	3 (38)		5 (25)
CREST	0 (0)		5 (25)
Other	0 (0)		2 (10)
NYHA functional class			
I	0 (0)	< 0.05	0 (0)
II	3 (38)	< 0.05	5 (25)
III	5 (62)	< 0.05	10 (50)
IV	0 (0)		5 (25)
6-min walk distance, m	294 ± 118†		240 ± 107‡
Mean right atrial pressure, mm Hg	5 ± 3		7 ± 5
mPAP, mm Hg	49 ± 16		51 ± 12
Cardiac index, L/min/m^2	3.1 ± 0.5	< 0.05	2.6 ± 0.7
PVR index, Wood U/m^2	15.6 ± 4	< 0.05	21.4 ± 8
Svo_2, %	68 ± 9		65 ± 8

Immunosuppressive Therapy in Lupus- and Mixed Connective Tissue Disease–Associated Pulmonary Arterial Hypertension

A Retrospective Analysis of Twenty-Three Cases

Xavier Jais,[1] David Launay,[2] Azzedine Yaici,[1] Jérôme Le Pavec,[1] Colas Tchérakian,[1] Olivier Sitbon,[1] Gérald Simonneau,[1] and Marc Humbert[1]

Table 1. Baseline clinical and hemodynamic characteristics of the patients according to first-line therapy of SLE- or MCTD-associated PAH*

	Patients treated with first-line immunosuppressants (n = 16)	Patients treated with first-line combination of immunosuppressants and PAH-specific therapy (n = 7)	*P*
Age, mean ± SD years	31 ± 10	38 ± 9	NS
Men/women	2/14	1/6	NS
SLE/MCTD	9/7	4/3	NS
Autoantibodies			
Anti-dsDNA	8	4	NS
Anti-RNP	11	3	NS
Anti-SSA/SSB	5	3	NS
Anti-Sm	6	2	NS
SLEDAI-2K score (range 0–105), mean ± SD	4.0 ± 4.8	5.0 ± 5.3	NS
NYHA functional class			
I	0	0	
II	7	0	<0.05
III	9	6	
IV	0	1	
Six-minute walking distance, mean ± SD meters	347 ± 80	381 ± 71	NS
Mean right atrial pressure, mean ± SD mm Hg	5 ± 4	7 ± 2	NS
mPAP, mean ± SD mm Hg	48 ± 12	58 ± 10	<0.05
CI, mean ± SD liters/minute/m^2	3.3 ± 1.0	2.2 ± 0.3	<0.001
PVR, mean ± SD mm Hg/liter/minute	8.6 ± 3.5	14.3 ± 1.3	<0.001
Svo_2, mean ± SD %	66 ± 8	60 ± 5	0.07

Tto: Todos ciclo ev 6 meses
CF III-IV vasodilatadores

ARTHRITIS & RHEUMATISM
Vol. 58, No. 2, February 2008, pp 521–531
DOI 10.1002/art.23303

Table 2. Comparison of clinical and hemodynamic characteristics before and after the cyclophosphamide pulses between patients who were responders and patients who were nonresponders to the immunosuppressive therapy alone*

	Baseline (before cyclophosphamide pulses)			After cyclophosphamide pulses		
	Responders (n = 8)	Nonresponders (n = 8)	*P*	Responders (n = 8)	Nonresponders (n = 8)	*P*
Age, mean ± SD years	29 ± 9	34 ± 11	NS	–	–	–
Men/women	0/8	2/6	NS	–	–	–
SLE/MCTD	4/4	5/3	NS	–	–	–
Time between diagnosis of SLE or MCTD and first cyclophosphamide pulse, mean ± SD months	72 ± 90	78 ± 80	NS	–	–	–
Autoantibodies						
Anti-dsDNA	6	2	0.07	–	–	–
Anti-RNP	7	4	NS	–	–	–
Anti-SSA/SSB	4	1	NS	–	–	–
Anti-Sm	5	1	0.07	–	–	–
SLEDAI-2K score (range 0–105), mean ± SD	6.0 ± 6.1	2.4 ± 3.4	NS	–	–	–
SLEDAI-2K score ≤3	2	4	NS	–	–	–
SLEDAI-2K score >3	2	1	NS	–	–	–
NYHA functional class			<0.05			<0.001
I	0	0		7†	0	
II	6	1		1	0	
III	2	7		0	8	
IV	0	0		0	0	
Six-minute walking distance, mean ± SD meters	331 ± 78	362 ± 84	NS	446 ± 43†	336 ± 94	<0.05
Mean right atrial pressure, mean ± SD mm Hg	5 ± 4	5 ± 3	NS	3 ± 2	9 ± 5‡	<0.01
mPAP, mean ± SD mm Hg	44 ± 15	51 ± 7	NS	35 ± 10‡	54 ± 11	<0.01
CI, mean ± SD liters/minute/m^2	3.8 ± 0.9	2.7 ± 0.3	<0.05	3.5 ± 0.6	2.5 ± 0.5	<0.01
PVR, mean ± SD mm Hg/liter/minute	6.6 ± 3.3	10.6 ± 2.5	<0.05	5.6 ± 2.3	13.6 ± 7.4	<0.01
SvO_2, mean ± SD %	67 ± 8	64 ± 7	NS	71 ± 5	59 ± 7	<0.01

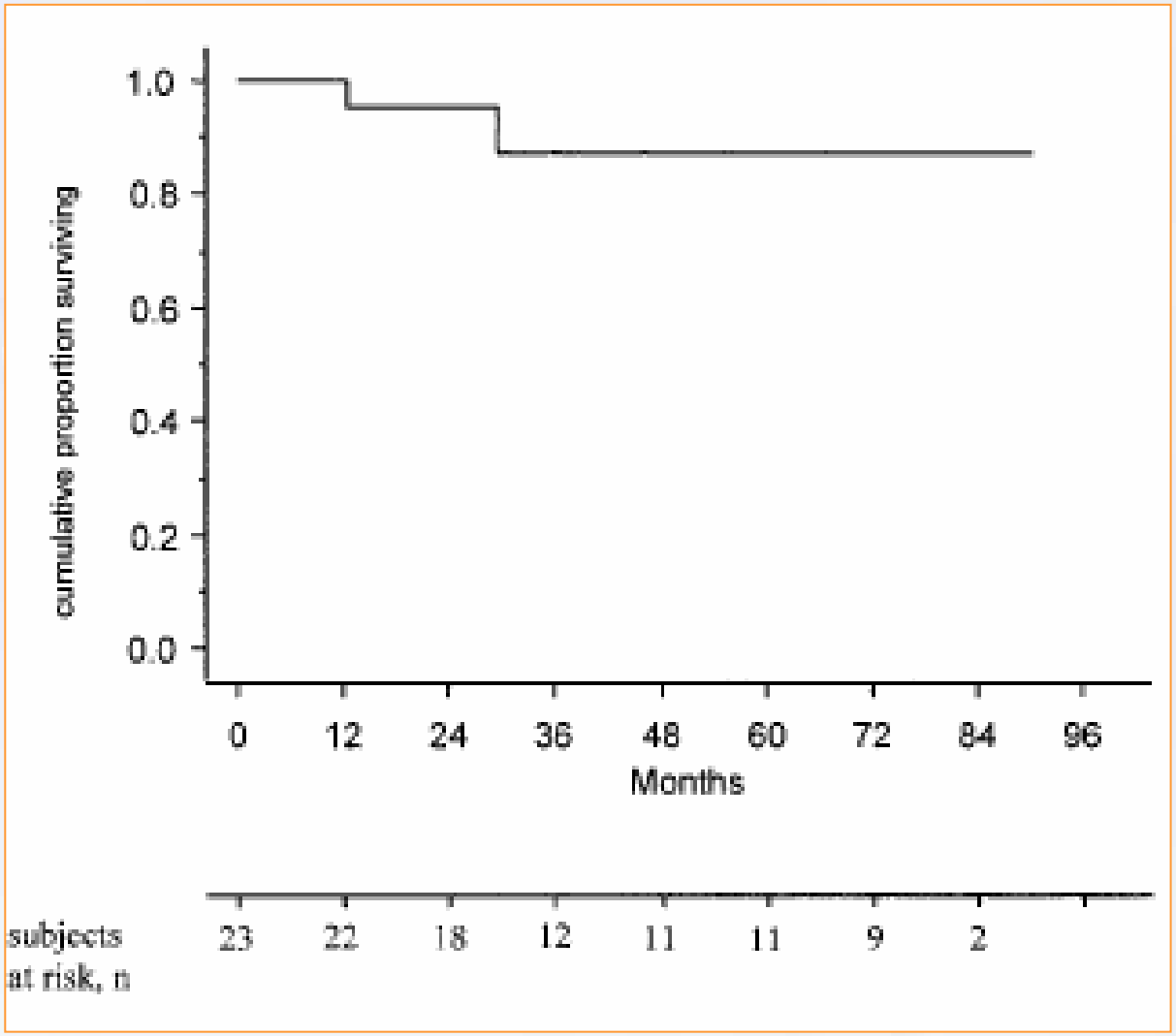
Respondedores: Mejoría CF
PAPm< 40mmHg
IC normal

ARTHRITIS & RHEUMATISM
Vol. 58, No. 2, February 2008, pp 521–531
DOI 10.1002/art.23303

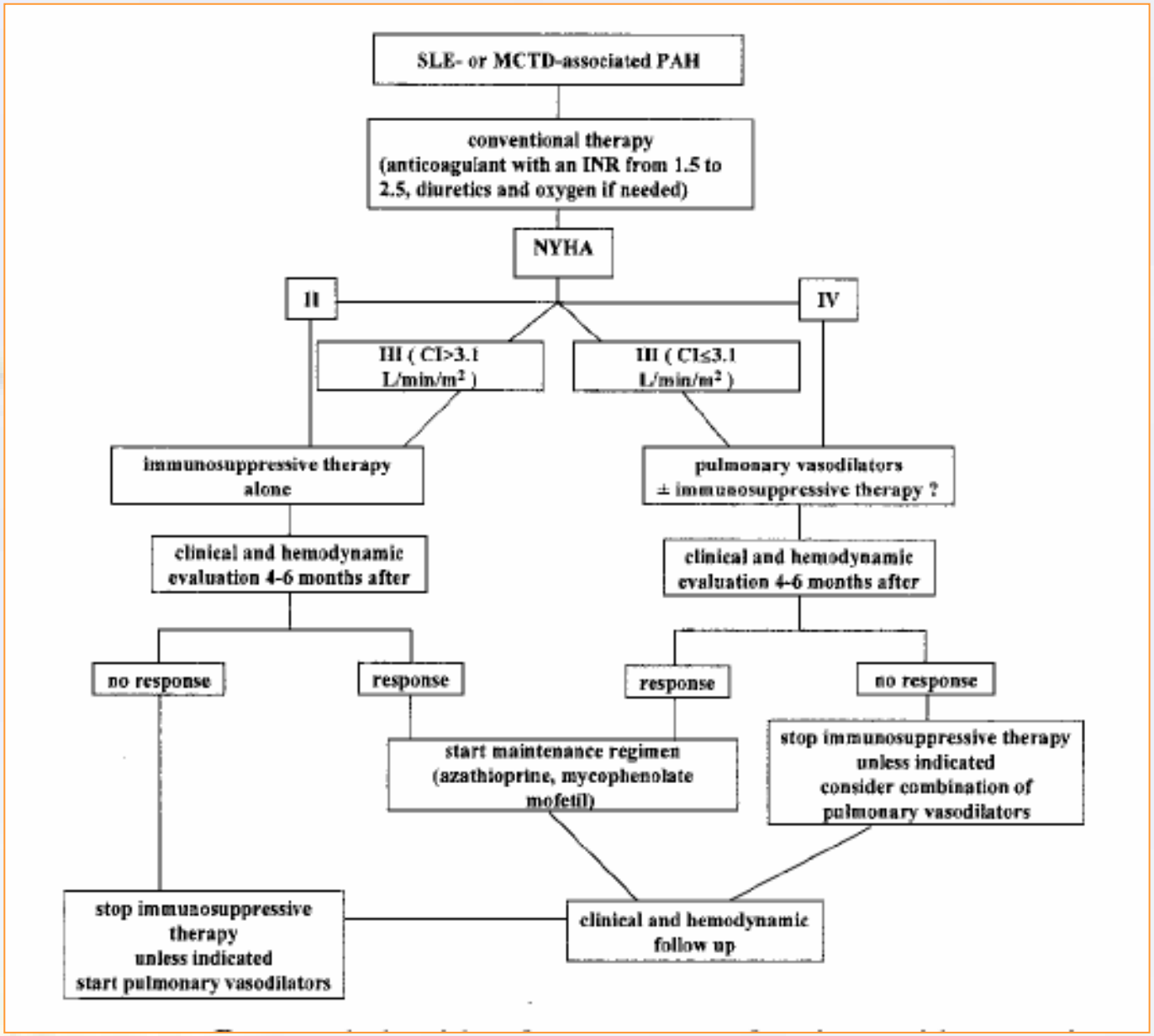
Table 3. Comparison of clinical and hemodynamic characteristics before and after the cyclophosphamide pulses between patients who were responders and patients who were nonresponders in the combination (immunosuppressants plus PAH-specific therapy) group*

	Baseline (before cyclophosphamide pulses)			After cyclophosphamide pulses		
	Responders (n = 4)	Nonresponders (n = 3)	*P*	Responders (n = 4)	Nonresponders (n = 3)	*P*
Age, mean ± SD years	30 ± 6	48 ± 5	NS	–	–	–
Men/women	1/3	0/3	NS	–	–	–
SLE/MCTD	2/2	2/1	NS	–	–	–
Time between diagnosis of SLE or MCTD and first cyclophosphamide pulse, mean ± SD months	131 ± 88	80 ± 57	NS	–	–	–
Autoantibodies						
Anti-dsDNA	3	1	NS	–	–	–
Anti-RNP	2	1	NS	–	–	–
Anti-SSA/SSB	2	1	NS	–	–	–
Anti-Sm	2	0	NS	–	–	–
SLEDAI-2K score (range 0–105), mean ± SD	6.0 ± 8.5	4.0 ± 2.8	NS	–	–	–
SLEDAI-2K score ≤3	1	2	NS	–	–	–
SLEDAI-2K score >3	1	0	NS	–	–	–
NYHA functional class			NS			<0.05
I	0	0		0	0	
II	0	0		4†	0	
III	4	2		0	3	
IV	0	1		0	0	
Six-minute walking distance, mean ± SD meters	345 ± 72	428 ± 39	NS	403 ± 120	454 ± 33	NS
Mean right atrial pressure, mean ± SD mm Hg	7 ± 3	7 ± 1	NS	3 ± 3‡	9 ± 2	<0.05
mPAP, mean ± SD mm Hg	58 ± 6	58 ± 15	NS	41 ± 9‡	56 ± 13	0.07
CI, mean ± SD liters/minute/m^2	2.2 ± 0.2	2.1 ± 0.3	NS	3.4 ± 0.3‡	2.1 ± 0.3	<0.05
PVR, mean ± SD mm Hg/liter/minute	13.6 ± 1.3	15.1 ± 0.5	NS	6.7 ± 3.1‡	14.4 ± 0.7	<0.05
Svo_2, mean ± SD %	59 ± 6	61 ± 5	NS	77 ± 16‡	54 ± 7	<0.05
Bosentan/epoprostenol/treprostinil	3/1/0	0/2/1	NS	–	–	–

ARTHRITIS & RHEUMATISM
Vol. 58, No. 2, February 2008, pp 521–531
DOI 10.1002/art.23303



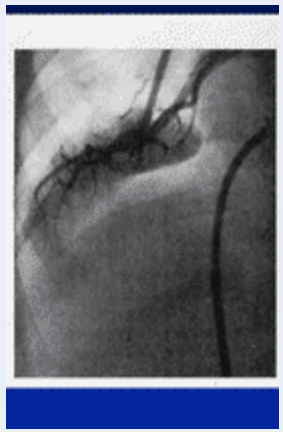
ARTHRITIS & RHEUMATISM
Vol. 58, No. 2, February 2008, pp 521–531
DOI 10.1002/art.23303

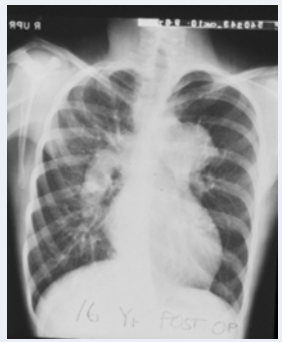


ARTHRITIS & RHEUMATISM
Vol. 58, No. 2, February 2008, pp 521–531
DOI 10.1002/art.23303

HTAP en la Esclerodermia. Prevalencia

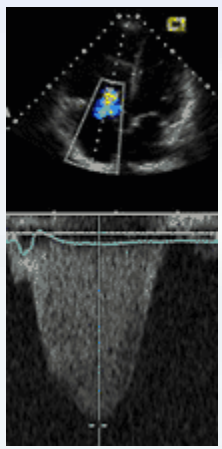
Salerni RM. 10 casos, 1977	
Ungerer RG.	**33%,**1983
Koh ET.	**4.9%,** 1996
Battle RW.	**35%,** 1996
Candell J.	**14%,** 1996
MacGregor AJ.	**13%,** 2001
Pope JE.	**21-26%,** 2005
Chang B.	**13,6%,** 2006

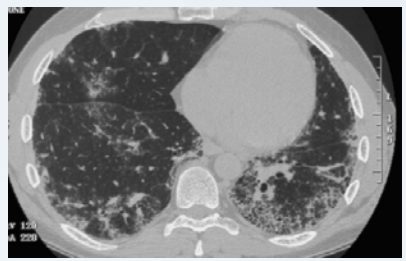




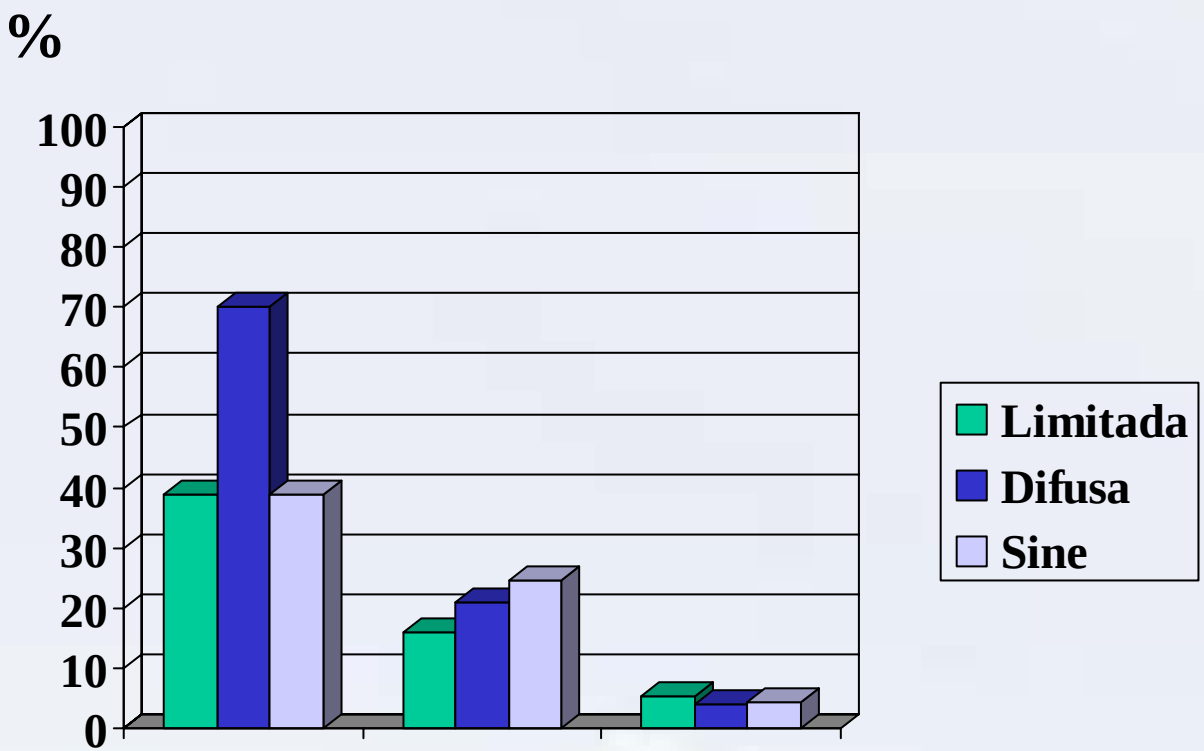
14 % – 19 %

Autopsia: 60%





HTAP en la Esclerodermia. Prevalencia



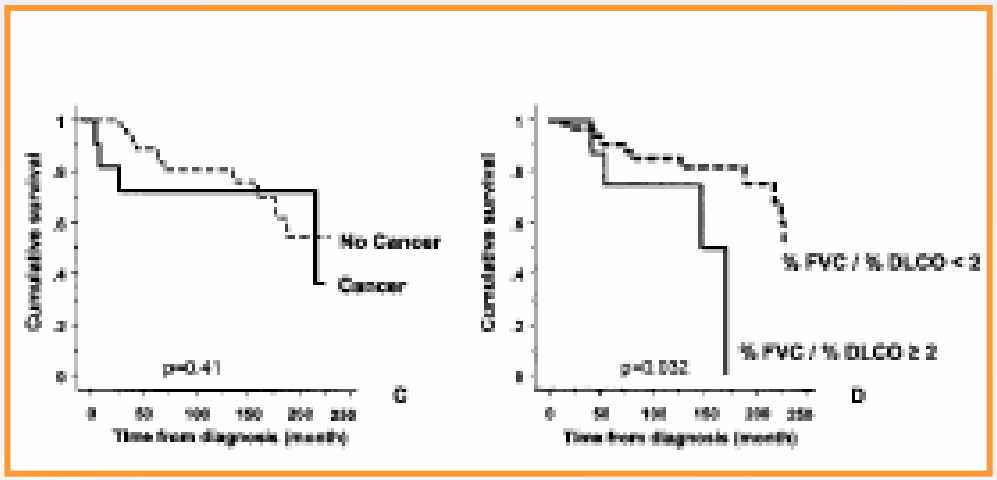
	EPID	HTAP	HTAP sin EPID
Global (%)	46	17.5	5

Características clínico-biológicas de una serie de 916 pacientes con Esclerosis Sistémica . ***Comunicación oral.***
XXIX Congreso SEMI. 19 Noviembre 2008

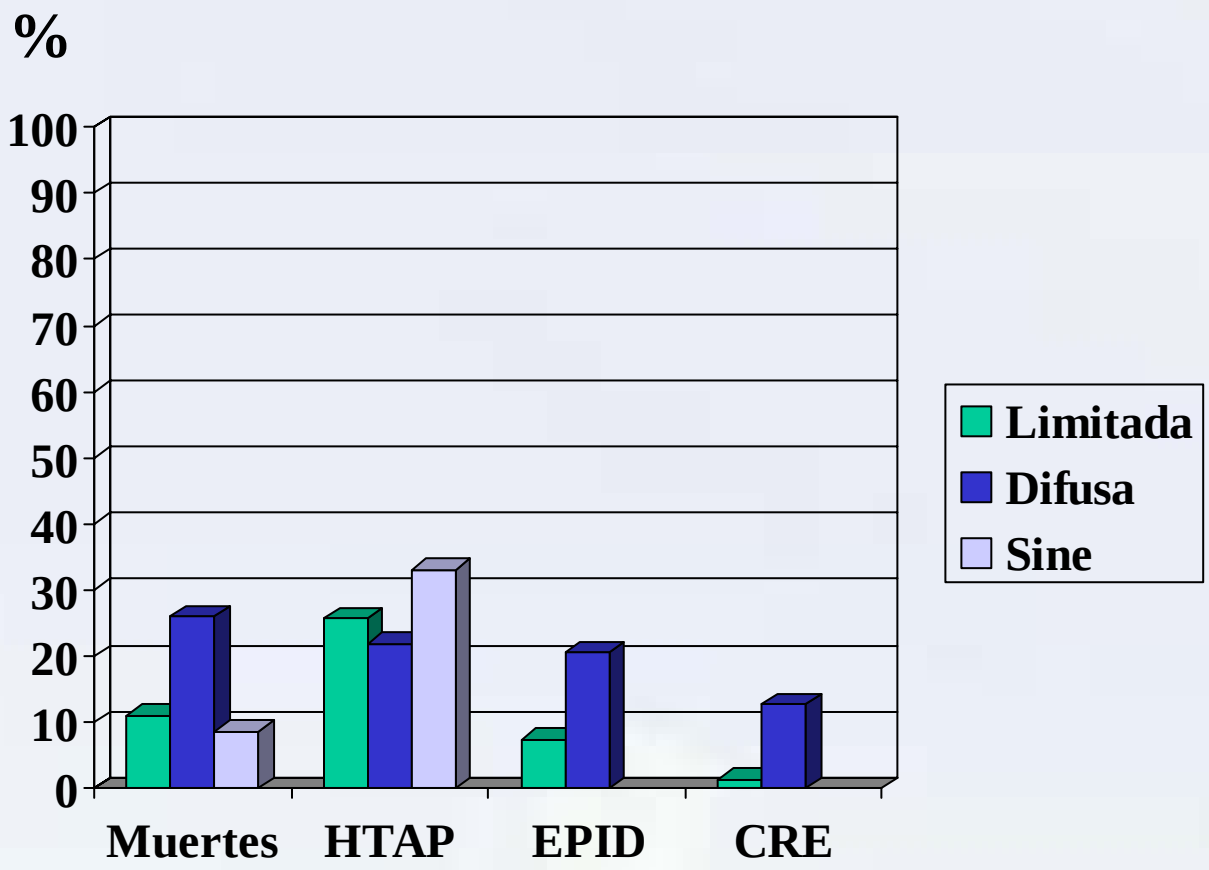
ARTHRITIS & RHEUMATISM
Vol. 54, No. 1, January 2006, pp 184–191
DOI 10.1002/art.21538

Pulmonary Arterial Hypertension Is a Major Mortality Factor in Diffuse Systemic Sclerosis, Independent of Interstitial Lung Disease

Salim Trad, Zahir Amoura, Catherine Beigelman, Julien Haroche, Nathalie Costedoat, Le Thi Huong Du Boutin, Patrice Cacoub, Camille Frances, Bertrand Wechsler, Philippe Grenier, and Jean-Charles Piette



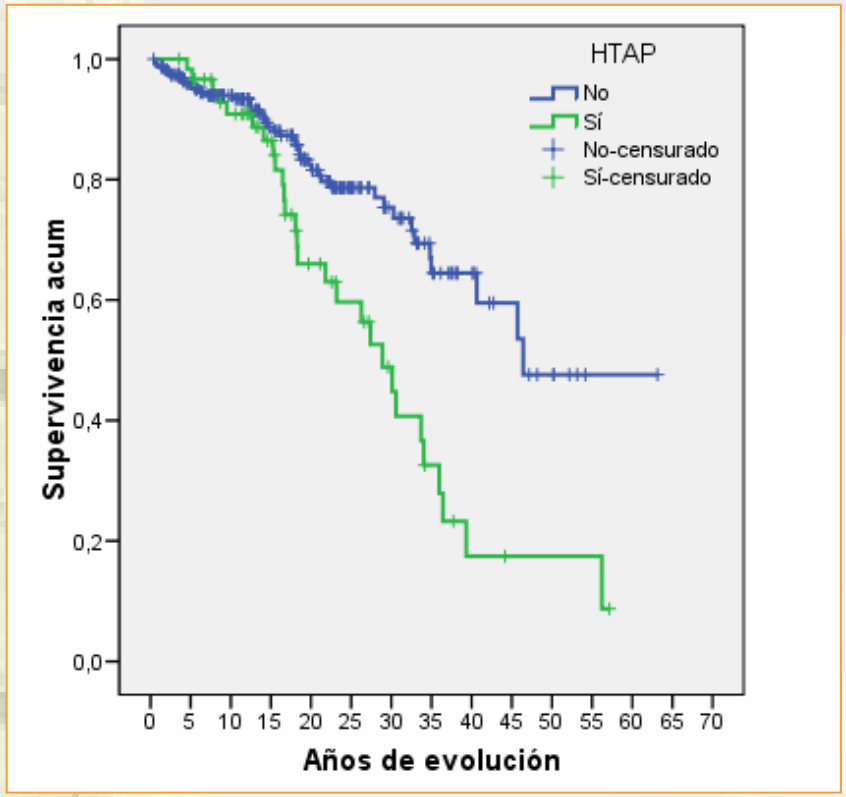
HTAP en la Esclerodermia. Factor pronóstico



	Muertes	HTAP	EPID	CRE
n (%)	138(15)	40(29)	18(13)	12(8.6)

Características clínico-biológicas de una serie de 916 pacientes con Esclerosis Sistémica . ***Comunicación oral.***
XXIX Congreso SEMI. 19 Noviembre 2008

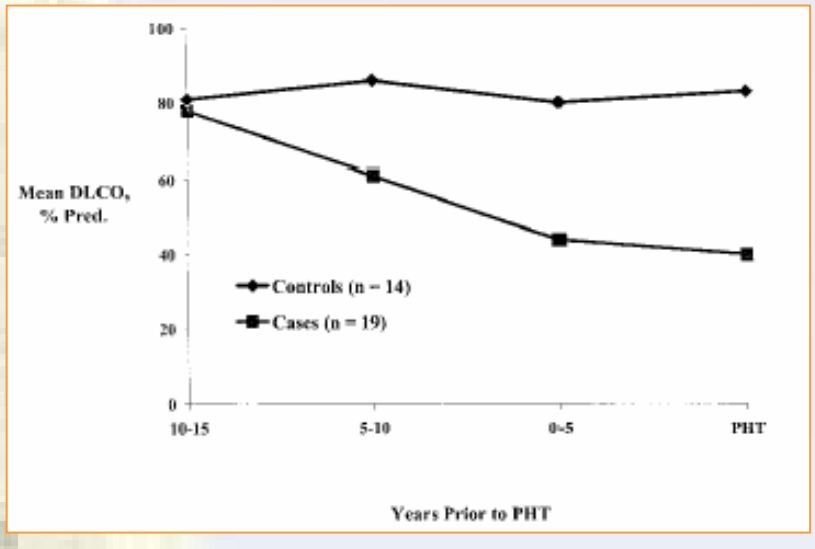
HTAP en la Esclerodermia. Factor pronóstico



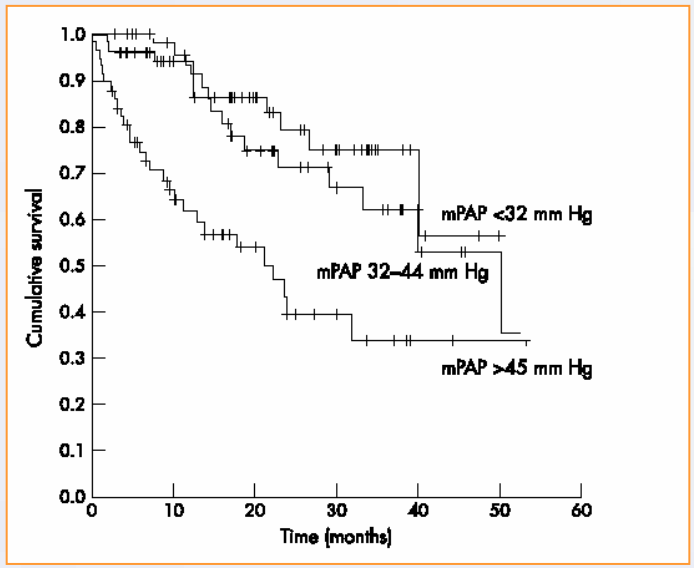
Factores pronósticos	RR	*p*
Esclerodermia difusa	2,730	0,001
Edad de comienzo	1,079	0,0001
Fibrosis pulmonar	2,463	0,003
HTAP	2,802	0,0001
Crisis renal	30,062	0,0001

Hospital Vall d´Hebron, n=317

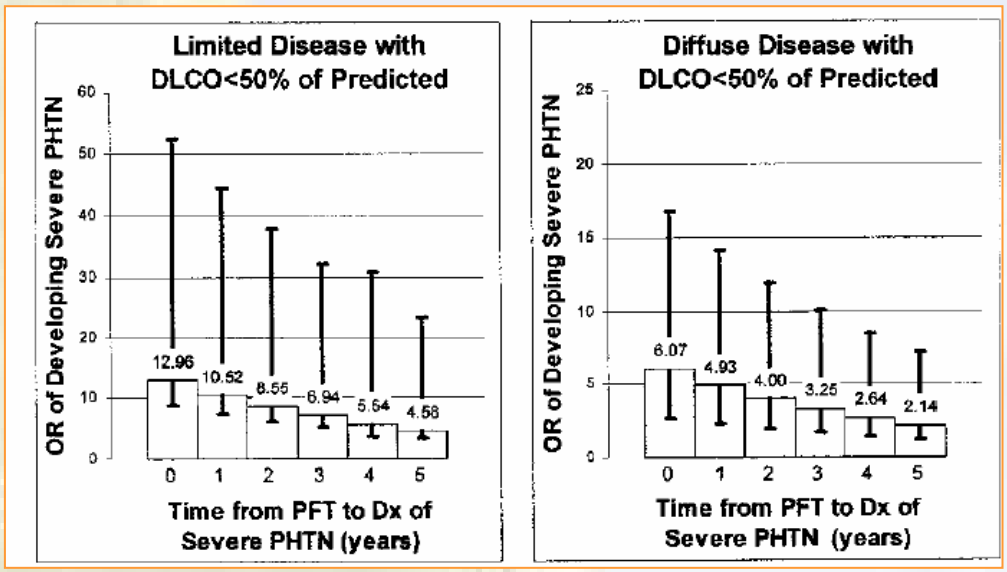
HTAP en la Esclerodermia. Factores pronósticos



Stenn V. et al. Arthritis Rheum. 2003;48:516



Mukerjee D. et al. Ann Rheum Dis. 2003;62:1088



Chang B. et al. J Rheumatol. 2006;33:269

- Forma limitada
- Edad ↑
- Evol > 15 años
- FR grave
- Úlceras digitales
- Acs. Anticentrómero
- DLco baja
- Relación CVF/DLco > 1.8
- PAPs: elevada
- BNP

Rheumatology 2008;47:v33–v35 doi:10.1093/rheumatology/ken306

Screening for PAH in patients with systemic sclerosis: focus on Doppler echocardiography

J. Sánchez-Román[1], C. F. Opitz[2], O. Kowal-Bielecka[3], F. J. García-Hernández[1], M. J. Castillo-Palma[1] and D. Pittrow[4] for the EPOSS-OMERACT Group

TABLE 1. Overview on echo Doppler parameters used for PAH screening in SSc patients

Author	Source	Setting	SSc patients *n*	Doppler parameter primarily used for screening
Murata	Jpn Circ J 1992;56:983	Univ. centre Japan	71	VTR
Battle	Chest 1996;110:1515	Univ. centre USA	34	sPAP ≥30 mmHg
Murata	Chest 1997:111:36	Univ. centre Japan	135	sPAP ≥40 mmHg
Denton	Br J Rheumatol 1997;36:239	Univ. centre UK	33	sPAP ≥30 mmHg
Mukerjee	Ann Rheum Dis 2003;62:1088	Univ. centre UK (mostly)	794	sPAP >35 mmHg (or DL_{CO} <50% predicted, or precipitous fall in DL_{CO} >20% over 1 yr)
Mukerjee	Rheumatology 2004;43:461	Univ. centre UK	137	Tricuspid gradient (range 30–40 mmHg); elevated sPAP
Hachulla	Arthritis Rheum 2005;52:3792	21 Univ. centres France ('ItinérAIR Sclérodermie')	599	VTR ≥3 m/s or VTR 2.5–3 m/s (plus unexplained dyspnoea)
Wigley	Arthritis Rheum 2005; 52:2125	50 Rheumatol. practices USA	669 *de novo*	(Estimated) RVSP ≥40 mmHg
Kiatchoosakun	J Med Assoc Thai 2007;90:2024	Univ. centre Thailand	129	RVSP >36 mmHg
Hsu	J Rheumatol 2008; online first	Univ. centre USA	49	RVSP >47 mmHg (optimal cutpoint compared with RHC)

RAP: right atrial pressure; sPAP: systolic pulmonary artery pressure; TL_{CO}: carbon monoxide transfer factor.

Rheumatology key messages

- SSc patients have a high incidence and prevalence of PAH.
- Despite important limitations, Doppler echocardiography currently represents the screening method of choice according to recent PAH guidelines.
- A RHC is mandatory to confirm the diagnosis.
- A number of predisposing factors may help to identify SSc patients at particularly high risk of developing PAH.

Assessment of Pulmonary Arterial Hypertension in Patients with Systemic Sclerosis: Comparison of Noninvasive Tests with Results of Right-Heart Catheterization

VIVIEN M. HSU, ABEL E. MOREYRA, ALAN C. WILSON, MEIR SHINNAR, DANIEL M. SHINDLER, JULIANNE E. WILSON, AMI DESAI, and JAMES R. SEIBOLD

The Journal of Rheumatology 2008; 35:3

Table 3. Performance statistics of noninvasive tests compared to pulmonary hypertension determined by right-heart catheterization criteria.

Test (Measure)	Cutpoint	ROC AUC (95% CI)	TP, FP FN, TN	PPV/NPV, %	Sensitivity, Specificity, %	+ LR/–LR
MRI, PA diameter	> 28 mm	0.78 (0.65–0.91)	17, 7 8,17	71/68	68/71	2.3/0.45
MRI, PA velocity	< 66 cm/s	0.70 (0.55–0.86)	12, 9 9, 12	57/57	57/57	1.3/0.75
Echo, estimated RVSP	> 47 mmHg	0.84 (0.72–0.95)	14, 1 10, 24	93/71	58/96	14.6/0.43
PFT, FVC/DLCO ratio	> 2.0	0.76 (0.62–0.90)	17, 7 7, 18	71/72	71/72	2.5/0.41

Conclusion. In evaluation of SSc with suspected PH, echo appeared to be the most useful among the noninvasive tests, mainly due to the high specificity, high positive predictive value, and highest AUC. However, due to the low sensitivity of noninvasive testing, RHC should remain the gold standard.

Prevalence of Exercise Pulmonary Arterial Hypertension in Scleroderma

JOSE LUIS CALLEJAS-RUBIO, EDUARDO MORENO-ESCOBAR, PILAR MARTÍN de la FUENTE, LOURDES LÓPEZ PÉREZ, RAQUEL RIOS FERNÁNDEZ, DANIEL SÁNCHEZ-CANO, JOSÉ POMARES MORA, and NORBERTO ORTEGO-CENTENO

The Journal of Rheumatology 2008; 35:9

N=41

PAPS > 55mmHg= 19. 5%

Correlación: DLCO bajas

BNP altos

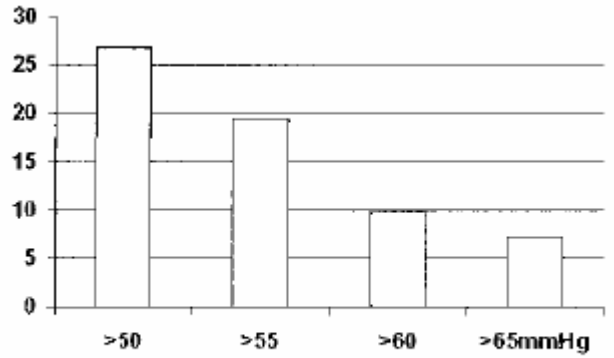


Figure 1. Prevalence of sPAP (mm Hg) during exercise using different cut-off.

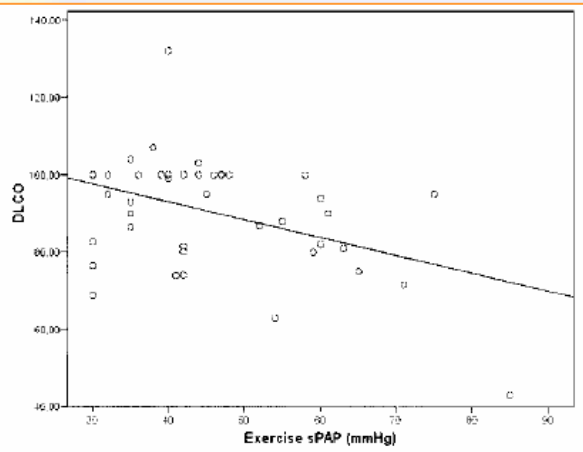


Figure 2. Correlation between sPAP (mm Hg) and DLCO (% predicted); r = –0.4, p = 0.008.

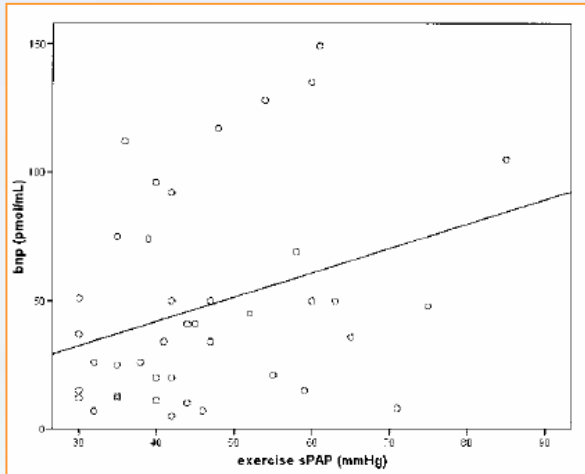
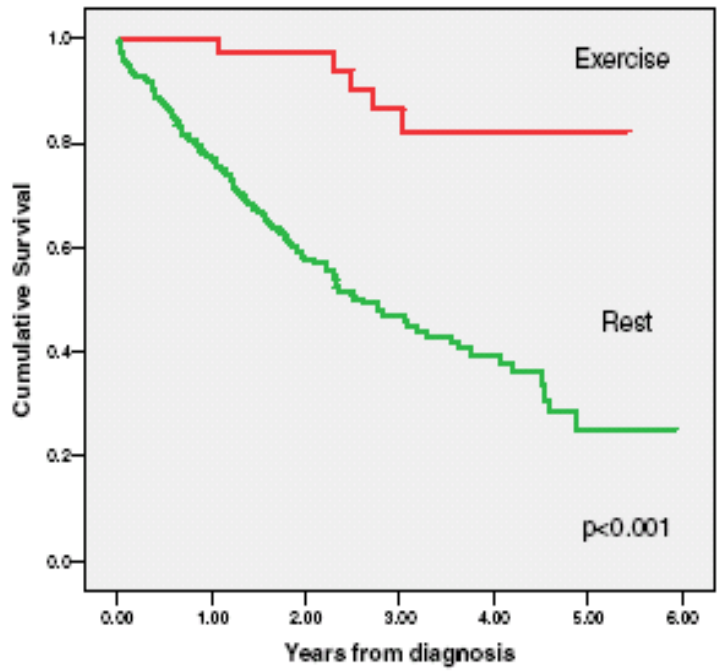


Figure 3. Correlation betwwen sPAP (mm Hg) and BNP (pmol/ml); r = 0.31, p = 0.04.

AJRCCM Articles in Press. Published on October 17, 2008 as doi:10.1164/rccm.200806-953OC

Connective tissue disease associated pulmonary arterial hypertension in the modern treatment era



Patients at risk

4	42	36	32	23	6	4	exercise
	259	179	94	53	27	6	rest

HTAP reposo= 19%

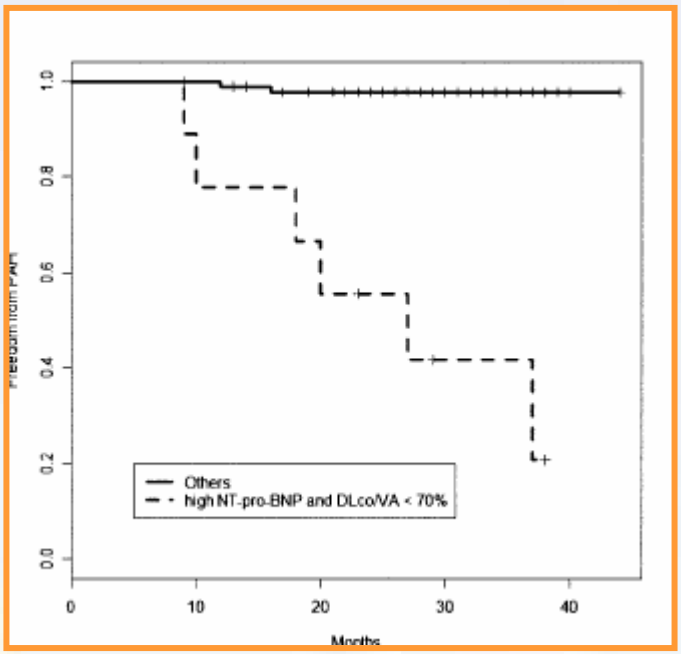
838±477

Muertes= 5

ARTHRITIS & RHEUMATISM
Vol. 58, No. 1, January 2008, pp 284–291
DOI 10.1002/art.23187

High N-Terminal Pro–Brain Natriuretic Peptide Levels and Low Diffusing Capacity for Carbon Monoxide as Independent Predictors of the Occurrence of Precapillary Pulmonary Arterial Hypertension in Patients with Systemic Sclerosis

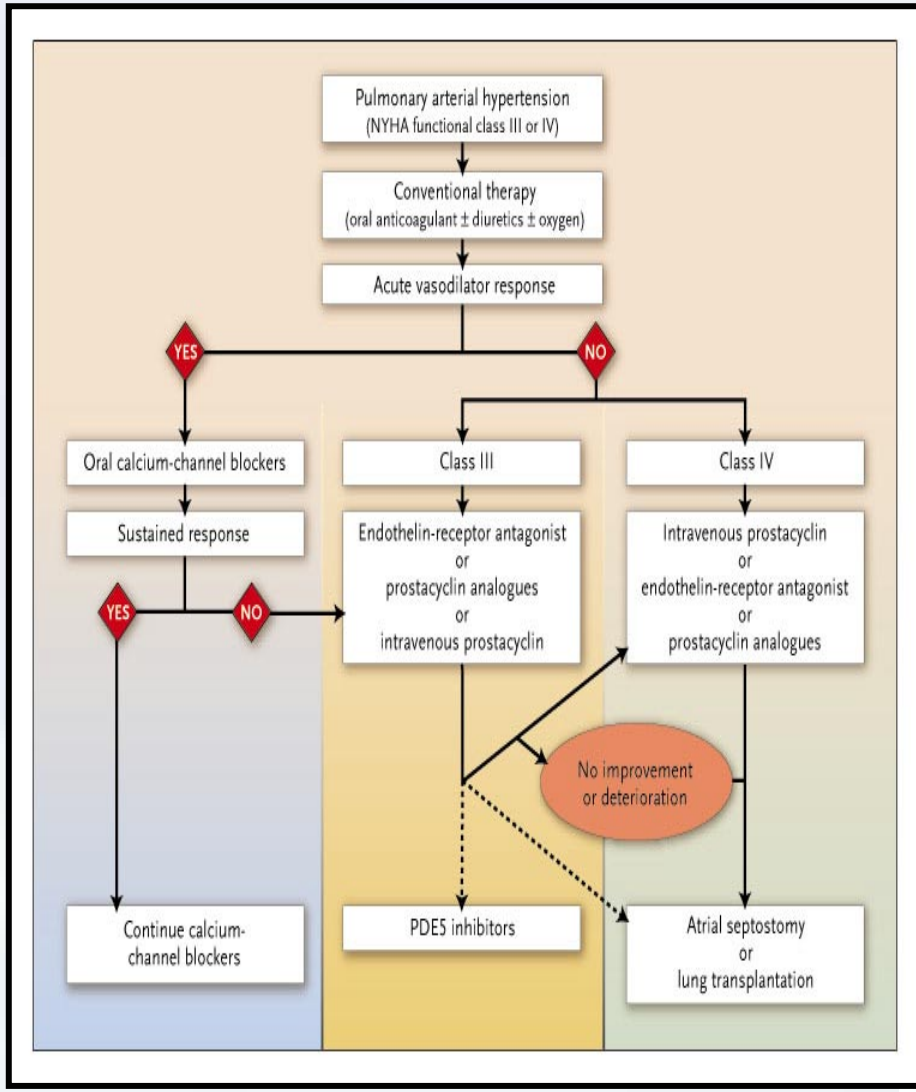
Y. Allanore,[1] D. Borderie,[1] J. Avouac,[1] D. Zerkak,[1] C. Meune,[1] E. Hachulla,[2] L. Mouthon,[1]



HTAP en la Esclerodermia. Tratamiento.

Análogos prostanoides:

Epoprostenol i.v.(20-40ng/kg/min) **(CF IV; A)**
Treprostinil s.c.(20-80ng/kg/min) **(CF III; A)**
Iloprost inh. (5µg/inh/4h) **(CF III; A)**



Hemodynamics and Survival in Patients With Pulmonary Arterial Hypertension Related to Systemic Sclerosis*

Steven M. Kawut, MD; Darren B. Taichman, MD, PhD; Christine L. Archer-Chicko, MSN, CRNP; Harold I. Palevsky, MD, FCCP; and Stephen E. Kimmel, MD, MSCE

(*CHEST 2003; 123:344–350*)

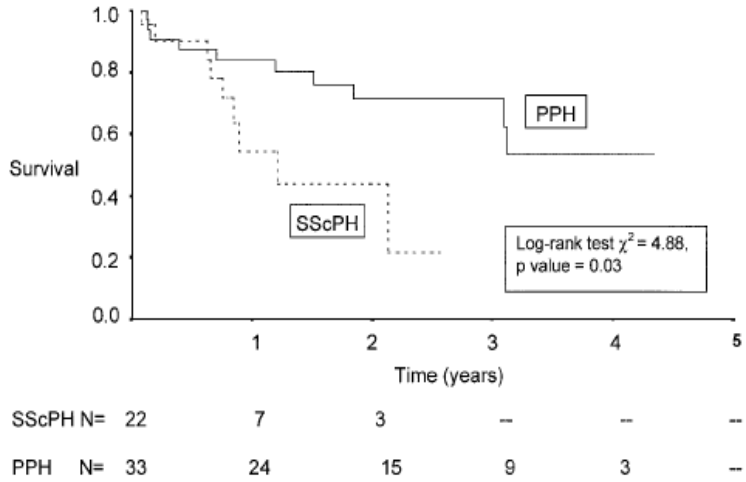


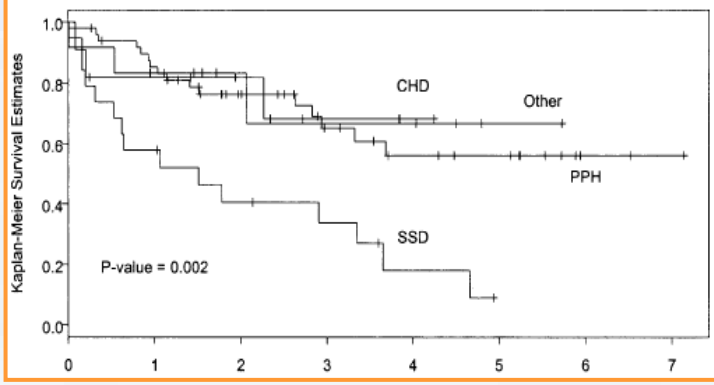
FIGURE 1. Kaplan-Meier survival estimates of patients with SScPH and PPH.

Outcome in 91 Consecutive Patients with Pulmonary Arterial Hypertension Receiving Epoprostenol

Karl P. Kuhn, Daniel W. Byrne, Patrick G. Arbogast, Thomas P. Doyle, James E. Loyd, and Ivan M. Robbins

Center for Lung Research, Division of Allergy, Pulmonary, and Critical Care Medicine; Department of Medicine, Division of General Internal Medicine, General Clinical Research Center; Department of Preventive Medicine, Division of Biostatistics; and Division of Pediatric Cardiology, Vanderbilt University School of Medicine, Nashville, Tennessee

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 167 2003



HTAP en la Esclerodermia. Tratamiento.

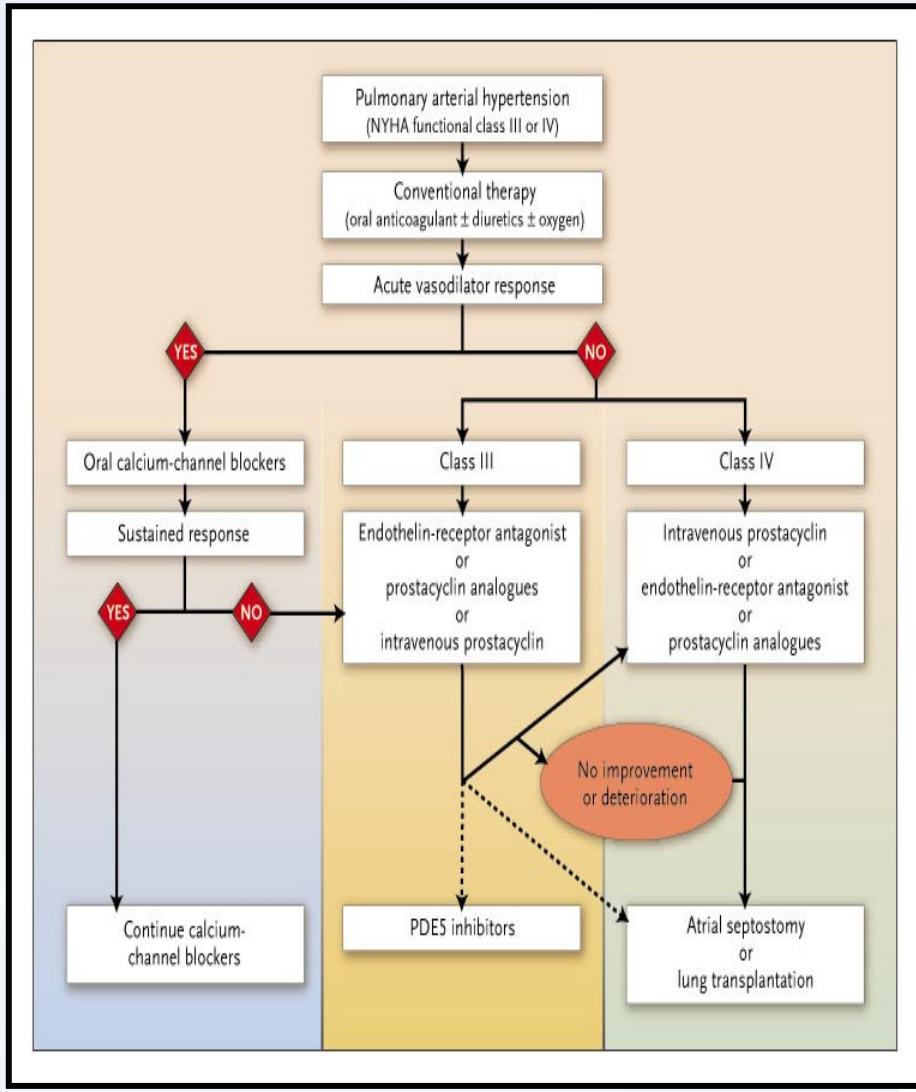
Antagonistas receptores endotelina: (CFIII; A)

Bosentan oral (125mg/12h) **(CFII;A)**

Sitaxsentan oral (100mg/d)

Inhibidores fosfodiesterasa: (CFII-III;A)

Sildenafilo oral (20-80mg/8h)



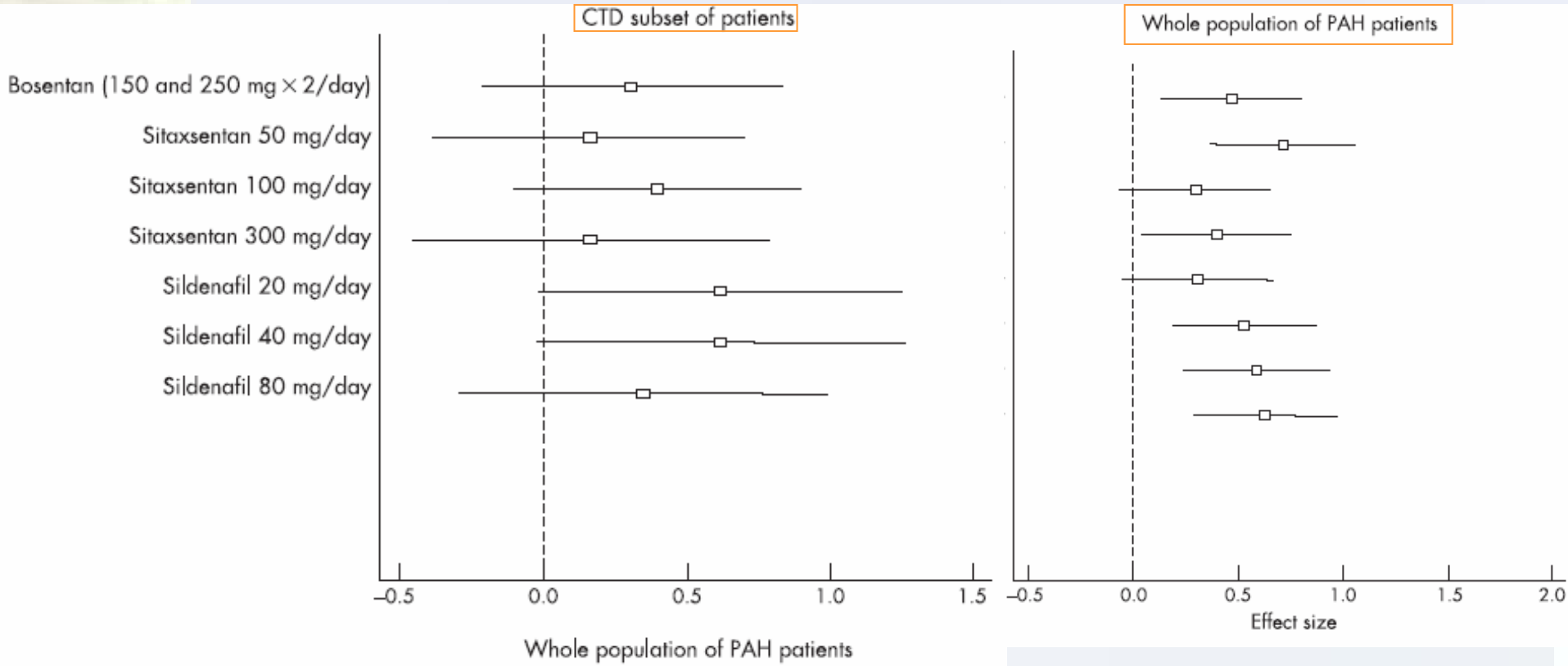
Effects of oral treatments on exercise capacity in systemic sclerosis related pulmonary arterial hypertension: a meta-analysis of randomised controlled trials

J Avouac, J Wipff, A Kahan and Y Allanore

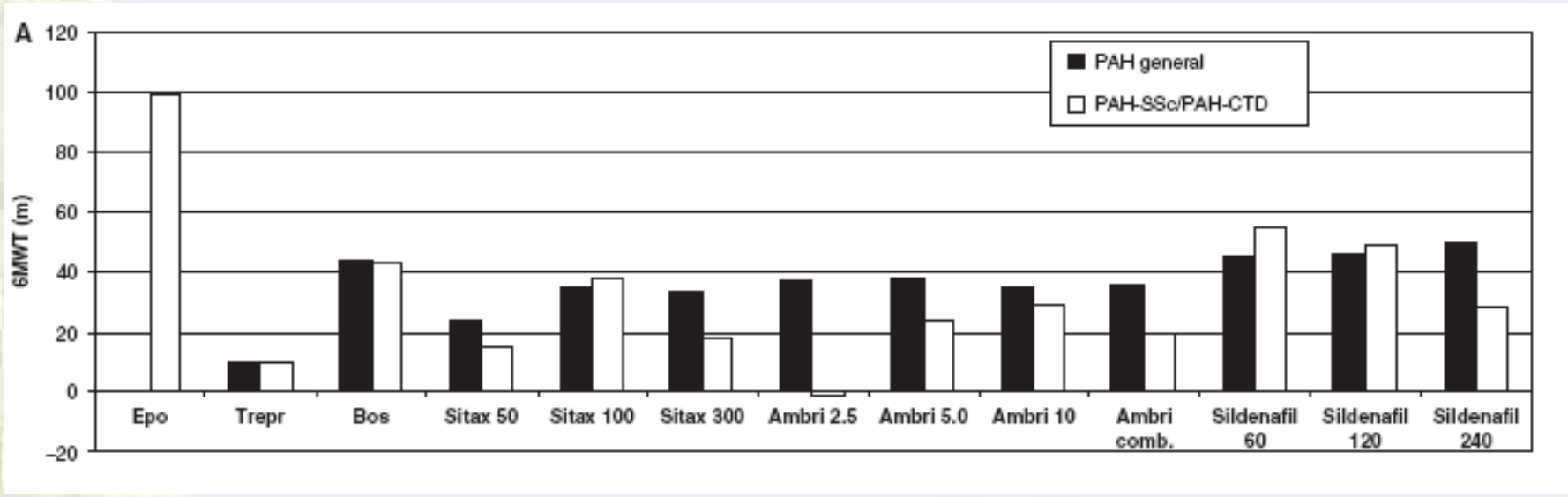
Ann Rheum Dis published online 27 Sep 2007;
doi:10.1136/ard.2007.077149

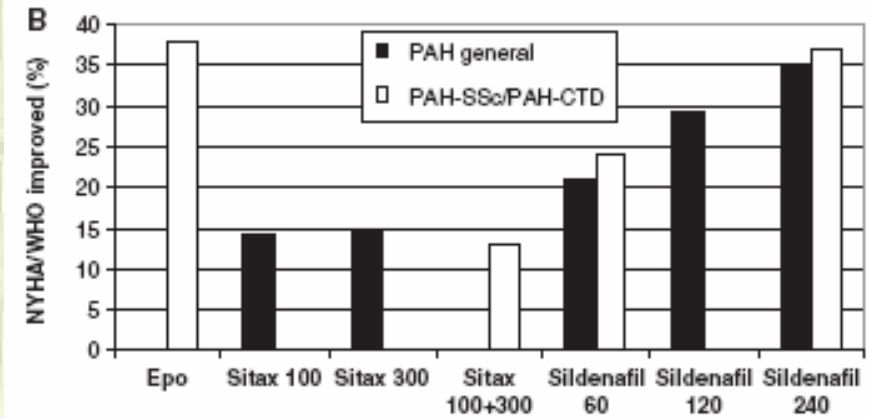
Number of articles selected for analysis: 11

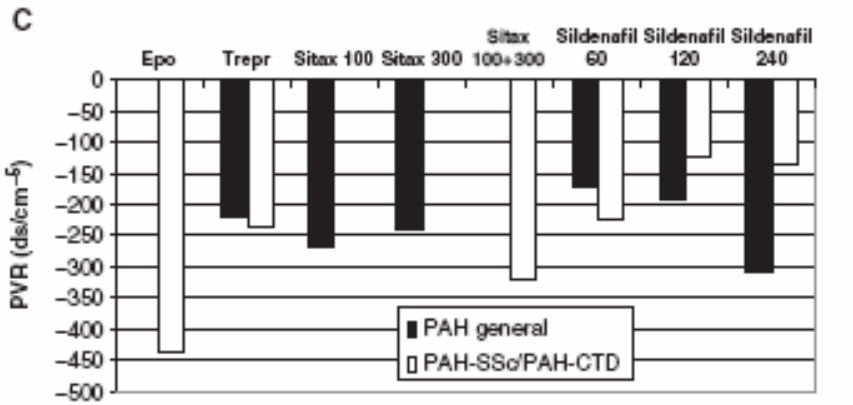
Pacientes= 613
ES-tto= 186
ES-pbo= 72



HTAP en la Esclerodermia. Respuesta al tratamiento.







Rheumatology 2008;47:v39–v41

Systemic sclerosis associated pulmonary hypertension: improved survival in the current era

M H Williams, C Das, C E Handler, M R Akram, J Davar, C P Denton, C J Smith, C M Black, J G Coghlan

Heart. doi: 10.1136/hrt.2005.069484

	Grupo histórico	ERA
	47	45
1a	68 %	81 %
2a	47 %	71 %

3

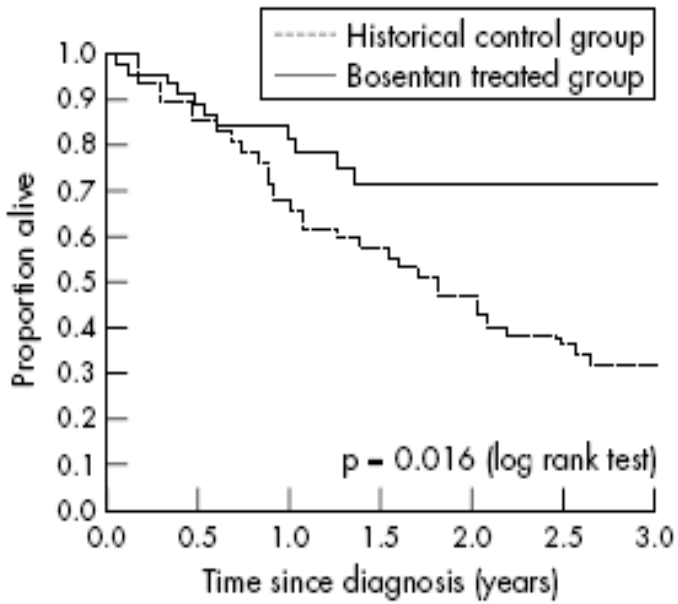


Figure 1 Kaplan–Meier analysis showing mortality among patients with systemic sclerosis associated pulmonary arterial hypertension (SSc-PAH). Historical group: one year survival 68%, two year survival 47%; current treatment era group: one year survival 81%, two year survival 71%.

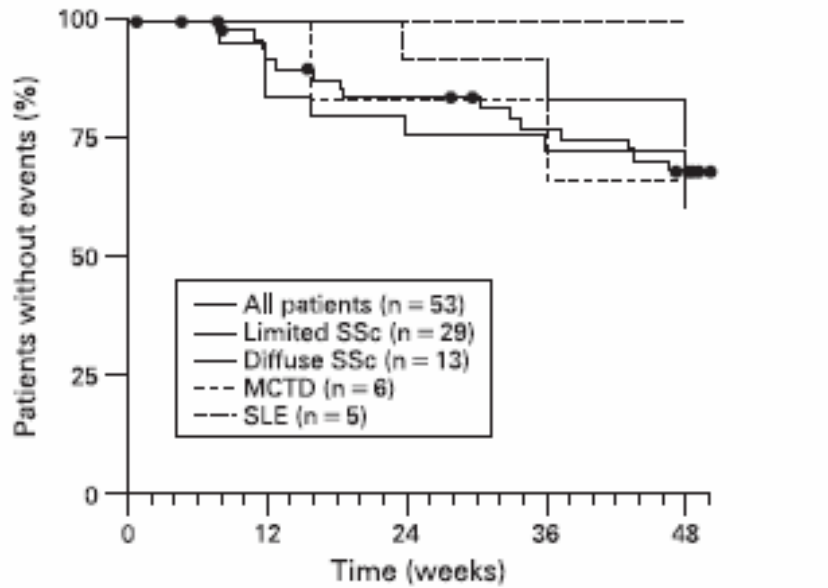
Long-term effects of bosentan on quality of life, survival, safety and tolerability in pulmonary arterial hypertension related to connective tissue diseases

C P Denton,[1] J E Pope,[2] H-H Peter,[3] A Gabrielli,[4] A Boonstra,[5] F H J van den Hoogen,[6] G Riemekasten,[7] S De Vita,[8] A Morganti,[9] M Dölberg,[9] O Berkani,[9] L Guillevin,[10] (on behalf of the TRacleer Use in PAH associated with Scleroderma and Connective Tissue Diseases (TRUST) Investigators)

Ann Rheum Dis 2008;**67**:1222–1228. doi:10.1136/ard.2007.079921

N=53

Aetiology, n (%):	
Limited systemic sclerosis	29 (55%)
Diffuse systemic sclerosis	13 (25%)
Mixed connective tissue disease	6 (11%)
Systemic lupus erythaematosus	5 (9%)



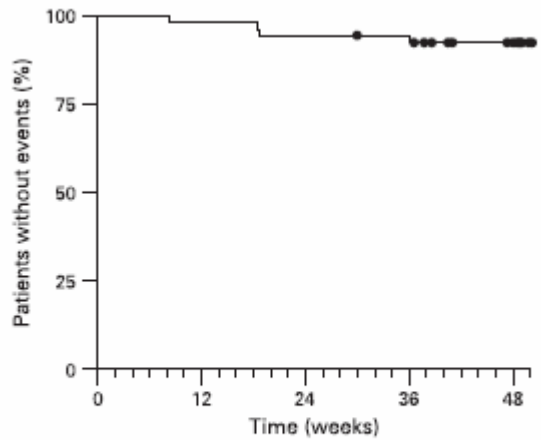
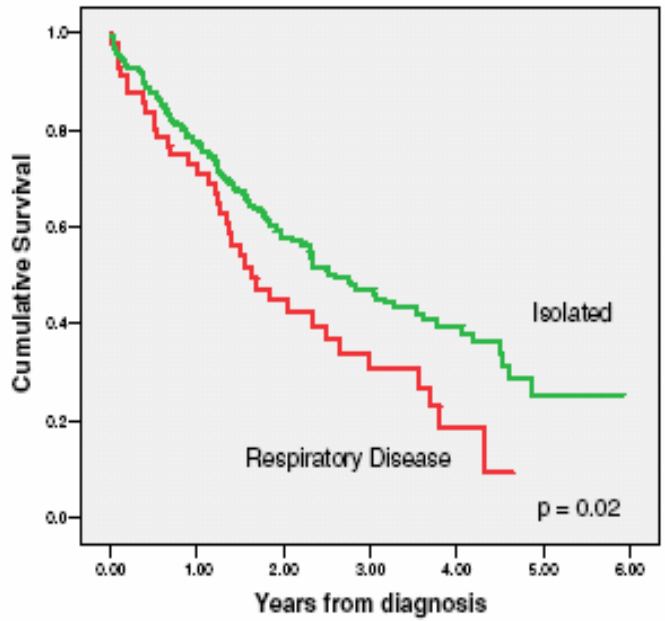


Figure 3 Kaplan–Meier estimates of survival (deaths occurring after treatment discontinuation for an adverse event were counted as an event). The Kaplan–Meier estimate was 92% (95% CI 85–100%) at week 48.

AJRCCM Articles in Press. Published on October 17, 2008 as doi:10.1164/rccm.200806-953OC

Connective tissue disease associated pulmonary arterial hypertension in the modern treatment era

Supervivencia	1	2	3
HTAP aislada (n=259)	78	58	47



Patients at risk

2	259	179	94	53	27	6	Isolated
	56	38	18	10	3		Respiratory disease

ARTHRITIS & RHEUMATISM
Vol. 54, No. 9, September 2006, pp 3043–3050
DOI 10.1002/art.22069

Clinical Differences Between Idiopathic and Scleroderma-Related Pulmonary Hypertension

Micah R. Fisher,[1] Stephen C. Mathai,[2] Hunter C. Champion,[2] Reda E. Girgis,[2] Traci Housten-Harris,[2] Laura Hummers,[2] Jerry A. Krishnan,[2] Fredrick Wigley,[2] and Paul M. Hassoun[2]

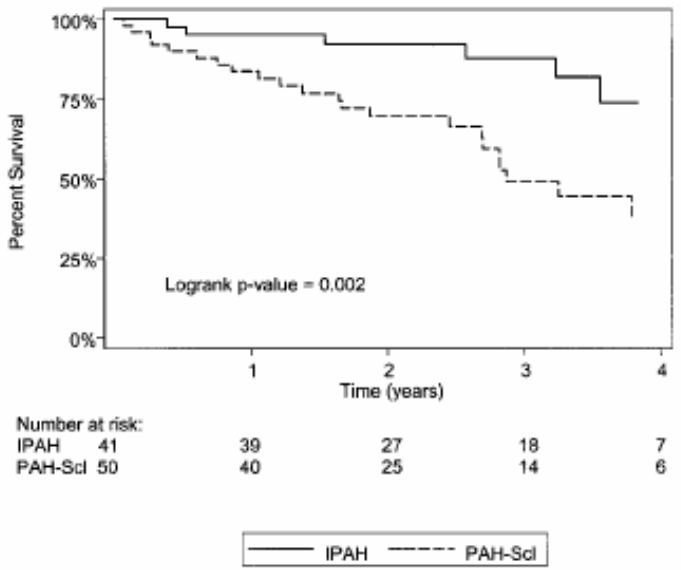


Table 3. Baseline echocardiographic findings*

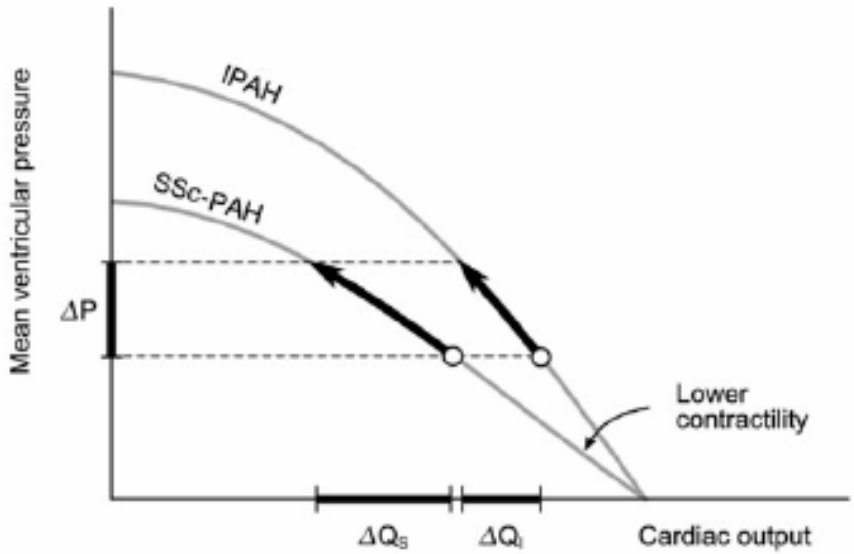
	IPAH (n = 38)	PAH-Scl (n = 49)	*P*
Right atrial dilation	31 (81.6)	36 (73.5)	0.37
Right ventricular dilation	34 (89.5)	39 (79.6)	0.21
Right ventricular hypertrophy	7 (18.4)	5 (10.2)	0.27
Left atrial diameter, mean ± SEM cm	3.3 ± 0.2	3.8 ± 0.1	0.004
Left atrial dilation	4 (10.5)	14 (28.6)	0.039
Left ventricular hypertrophy	5 (13.2)	17 (34.7)	0.022
Left ventricular ejection fraction, mean ± SEM	57.3 ± 1.6	55.7 ± 1.4	0.44
Diastolic dysfunction	5 (13.2)	16 (32.7)	0.035
Pericardial effusion	5 (13.2)	17 (34.7)	0.022

	SSc	HTAPi
PAPm:	**46**	**54**
Disf.VI	**++**	**+**
Super:		
1	**87**	**95**
3	**49**	**83**

Rheumatology 2008;47:v42–v43 doi:10.1093/rhe

Right ventricular function in scleroderma-related pulmonary hypertension

A. Vonk Noordegraaf[1] and R. Naeije[2]

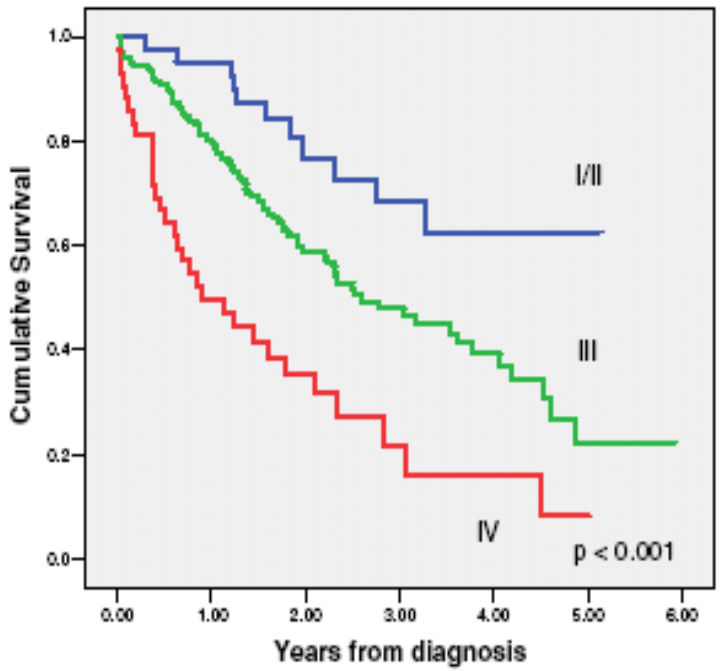


Rheumatology key messages

- SSc-PAH has a poorer exercise capacity and worse prognosis than those reported in most other types of PAH.
- This appears related to a relative RV failure, explained by altered contractility and maybe also decreased pulmonary arterial compliance.
- Further research is needed to understand the histopathology and pathobiology of RV failure in SSc-PAH.

AJRCCM Articles in Press. Published on October 17, 2008 as doi:10.1164/rccm.200806-953OC

Connective tissue disease associated pulmonary arterial hypertension in the modern treatment era



Patients at risk

3B	41	38	20	14	6	1	WHO I/II
	176	122	64	35	19	4	WHO III
	42	19	10	4	2	1	WHO IV

Empeoramiento: 39%
Muertes: 8
840±414 días

Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial

N Galiè, L J Rubin, M M Hoeper, P Jansa, H Al-Hiti, G M B Meyer, E Chiossi, A Kusic-Pajic, G Simonneau

Connective tissue disease	18 (19%)	15 (16%)
Systemic sclerosis	9 (10%)	6 (7%)
Lupus	7 (8%)	4 (4%)
Sarcoidosis	1 (1%)	0
Mixed connective tissue disease	0	3 (3%)
Sjögren's syndrome	0	1 (1%)
Takayasu's arteritis	0	1 (1%)
Other (not specified)	1 (1%)	0

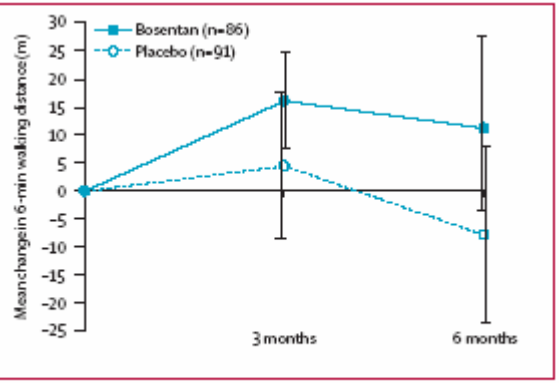


Figure 3: 6-min walking distance
Error bars are 95% CI.

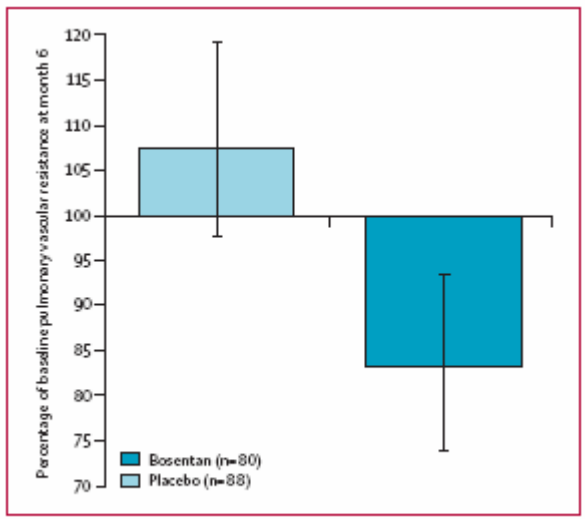


Figure 2: Percentage of baseline pulmonary vascular resistance at 6 months
Error bars are 95% CI.

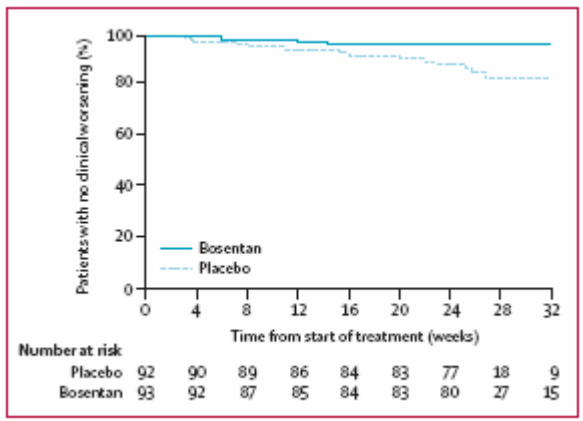
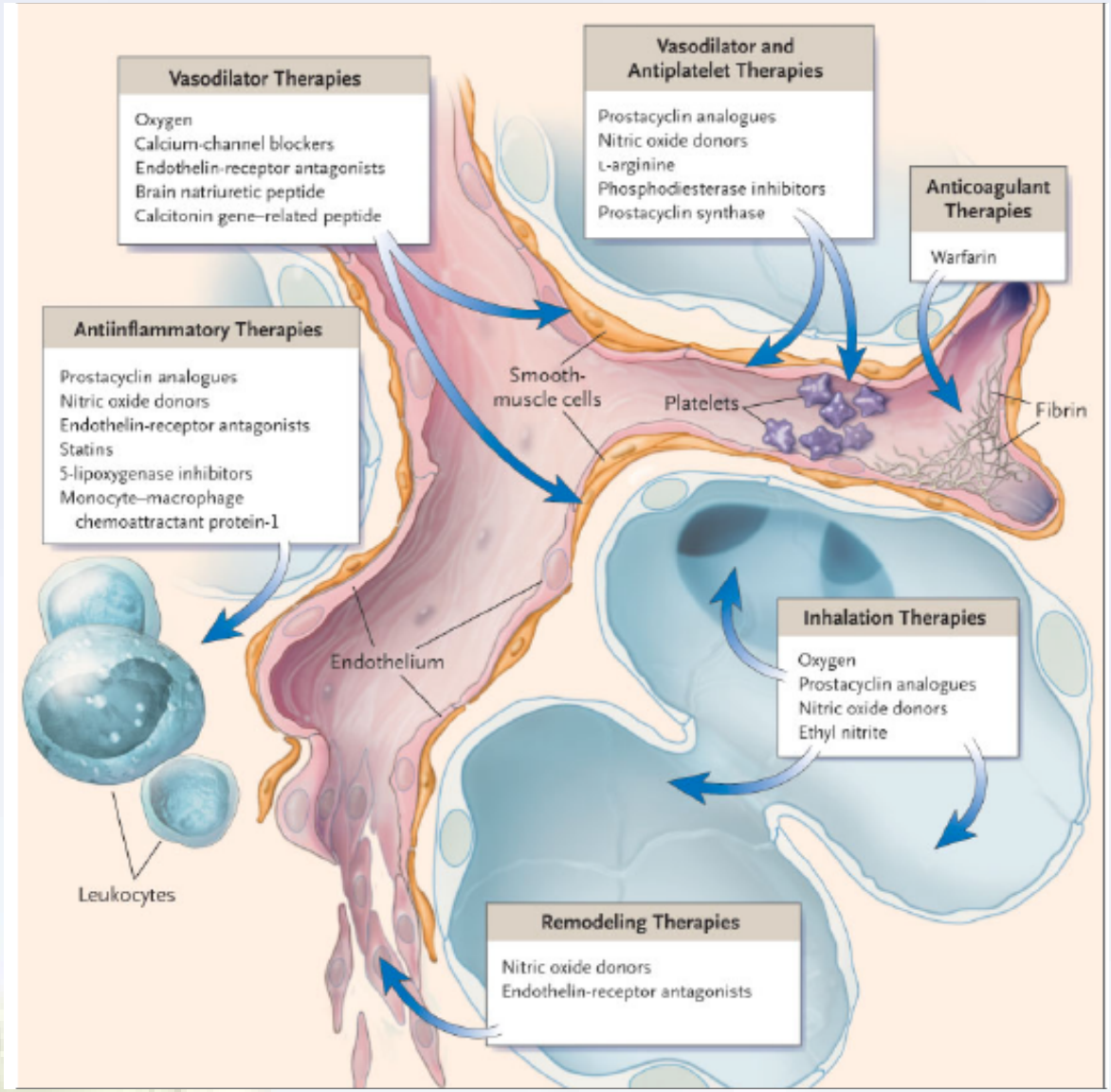


Figure 4: Time to clinical worsening

HTAP en la Esclerodermia. Tratamiento combinado.



Eur Respir J 2004; 24: 353–359
DOI: 10.1183/09031936.04.00028404
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European Respiratory Journal
ISSN 0903-1936

Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2

M. Humbert*, R.J. Barst#, I.M. Robbins¶, R.N. Channick+, N. Galiè§, A. Boonstraƒ, L.J. Rubin+, E.M. Horn#, A. Manes§, G. Simonneau*

Transition From Epoprostenol and Treprostinil to the Oral Endothelin Receptor Antagonist Bosentan in Patients With Pulmonary Hypertension*

Nizar Suleman, MD; and Adaani E. Frost, MD, FCCP

(*CHEST 2004; 126:808–815*)

Eur Respir J 2007; 29: 469–475
DOI: 10.1183/09031936.00081706

Addition of sildenafil to bosentan monotherapy in pulmonary arterial hypertension

S.C. Mathai*, R.E. Girgis*, M.R. Fisher#, H.C. Champion¶, T. Housten-Harris*, A. Zaiman* and P.M. Hassoun*

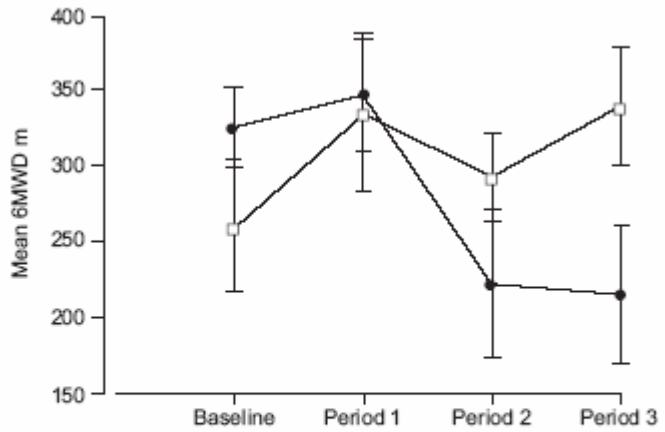


FIGURE 2. Mean 6-min walk distance (6MWD) at baseline, after 3 months of bosentan monotherapy (period 1), at bosentan monotherapy failure (period 2) and after 3 months of combination therapy with bosentan and sildenafil (period 3), for idiopathic pulmonary arterial hypertension (PAH) patients (□) and scleroderma-associated PAH patients (●). Error bars represent SE values.

N=25

HTAPi 13
SSc 12

Annals of Internal Medicine | ARTICLE

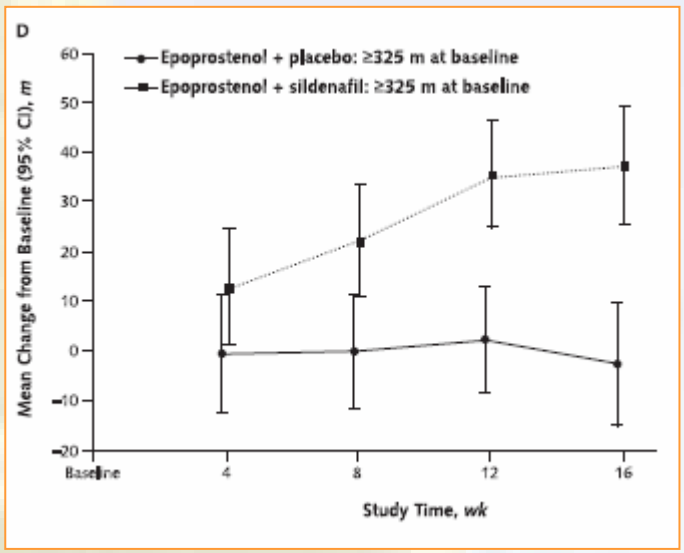
Addition of Sildenafil to Long-Term Intravenous Epoprostenol Therapy in Patients with Pulmonary Arterial Hypertension

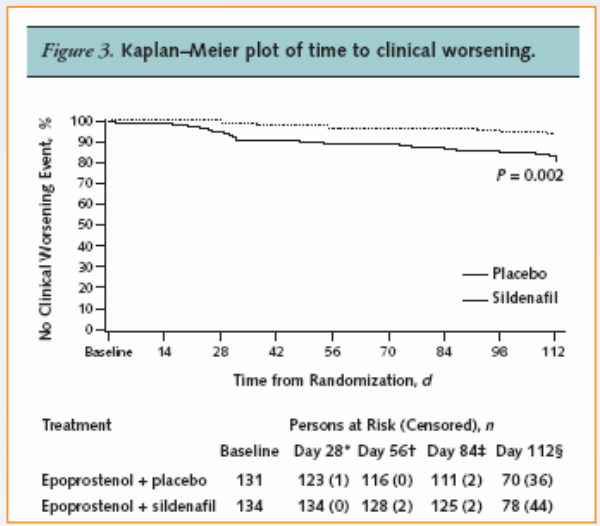
A Randomized Trial

Gérald Simonneau, MD; Lewis J. Rubin, MD; Nazzareno Galiè, MD; Robyn J. Barst, MD; Thomas R. Fleming, PhD; Adaani E. Frost, MD; Peter J. Engel, MD; Mordechai R. Kramer, MD; Gary Burgess, MD; Lorraine Collings, MSc; Nandini Cossons, MD, PhD; Olivier Sitbon, MD; and David B. Badesch, MD, for the PACES Study Group*

21 October 2008 | Annals of Internal Medicine | Volume 149 • Number 8

Primary diagnosis		
Idiopathic, *n (%)*	105 (78.9)	107 (79.9)
Mean duration (range), *y*	5.0 (0–37)	4.2 (0–36)
Associated with CTD		
Scleroderma, *n (%)*	15 (11.3)	16 (11.9)
Mean duration (range), *y*	4.2 (0–9)	3.0 (0–9)
SLE, *n (%)*	8 (6.0)	6 (4.4)
Mean duration (range), *y*	4.6 (2–10)	4.4 (2–7)
Other, *n (%)*	5 (3.8)	5 (3.7)
Mean duration (range), *y*	5.0 (1–13)	5.1 (3–7)

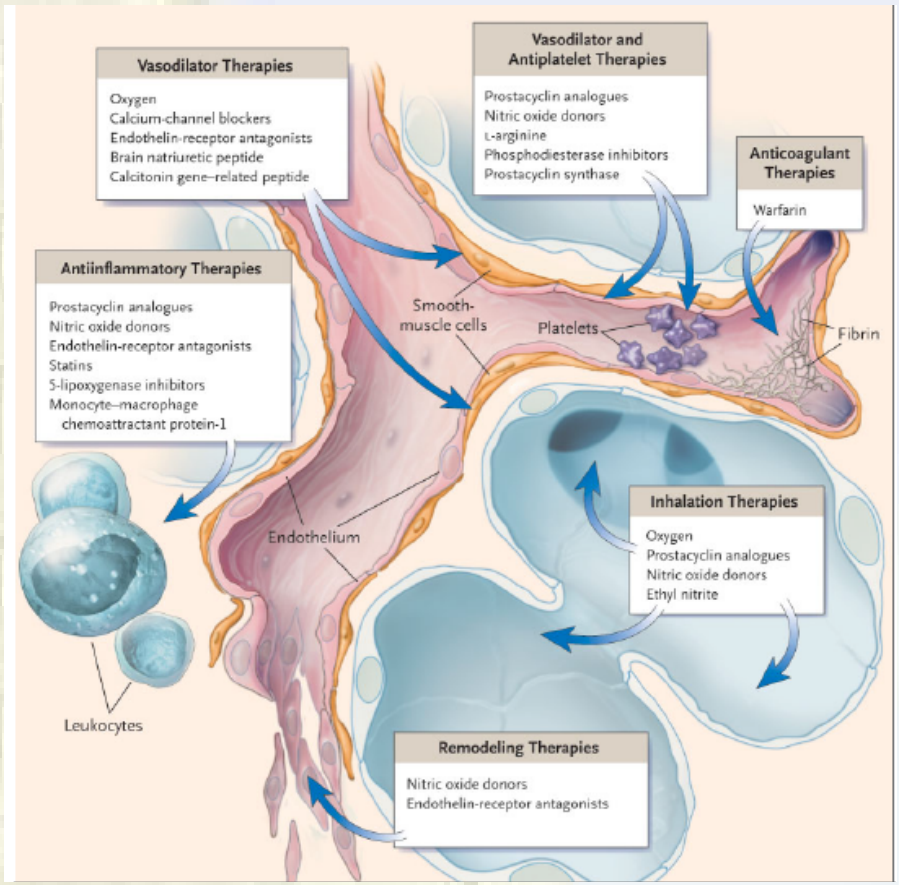


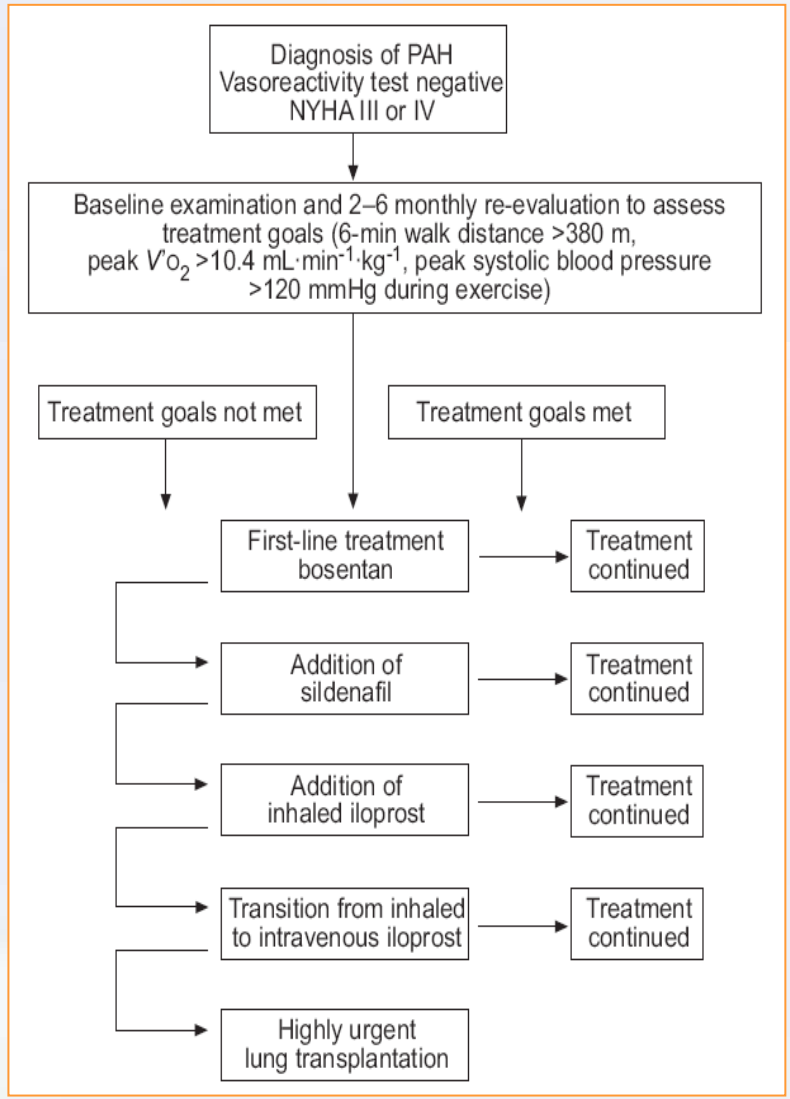


Eur Respir J 2005; 26: 858–863
DOI: 10.1183/09031936.05.00075305

Goal-oriented treatment and combination therapy for pulmonary arterial hypertension

M.M. Hoeper, I. Markevych, E. Spiekerkoetter, T. Welte and J. Niedermeyer



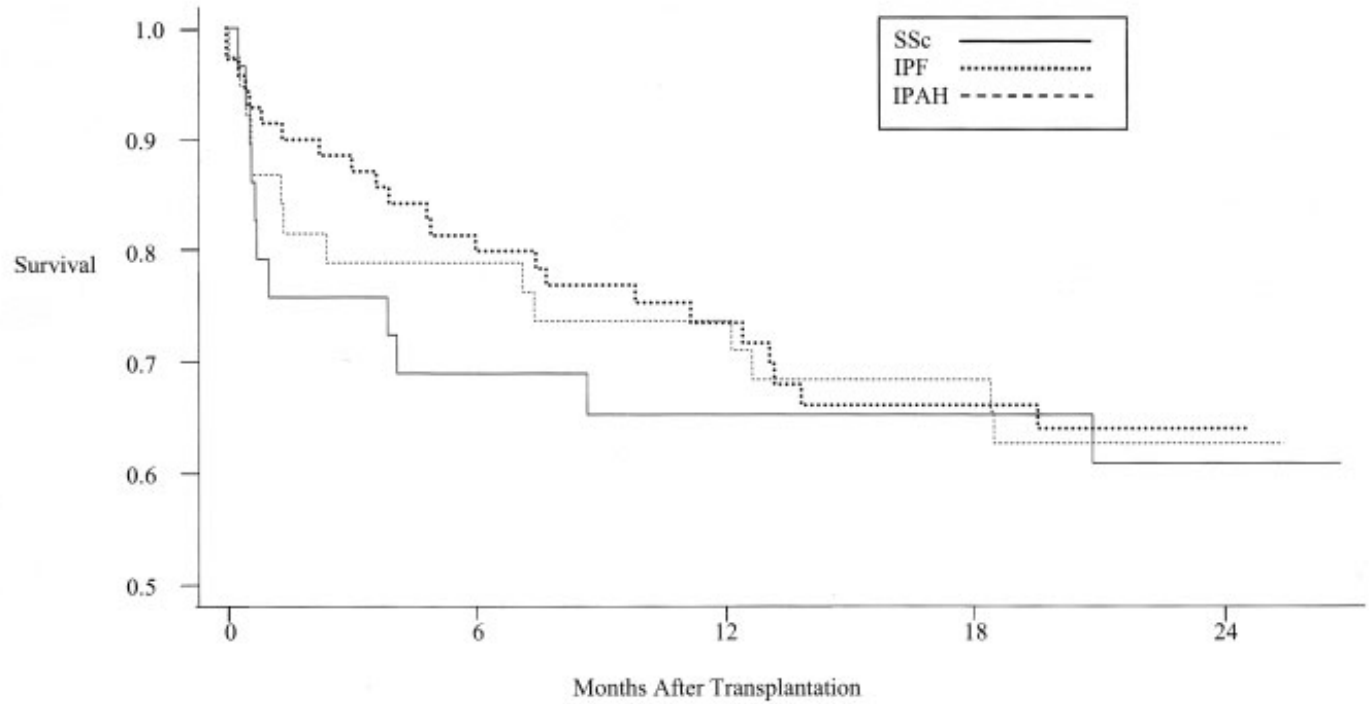


N= 123 (15 con ETC)

A los 2 años el 43% 2 fármacos

16% 3 fármacos

Lung Transplantation in Scleroderma Compared With Idiopathic Pulmonary Fibrosis and Idiopathic Pulmonary Arterial Hypertension



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

EPID: 15 HTAP: 11

EPID+HTAP: 3

Schachna L, Arthritis Rheum 2006;54;3956-61

Futuro de la HTAP asociada a esclerodermia

- Diagnóstico precoz
- Intervención terapéutica en clases funcionales I-II
- Combinación de fármacos.
- Nuevos tratamientos: imatinib, VIP, inhibidor de las roquinasas....
- Mejorar supervivencia de los enfermos trasplantados.

Pulmonary hypertension: The Bête Noire of the Diffuse Connective Tissue Diseases.

***E. Carwile LeRoy*, 1991**

"un tipo de afección vascular en los pulmones especialmente destructivo, que comienza bruscamente y tiene consecuencias letales"