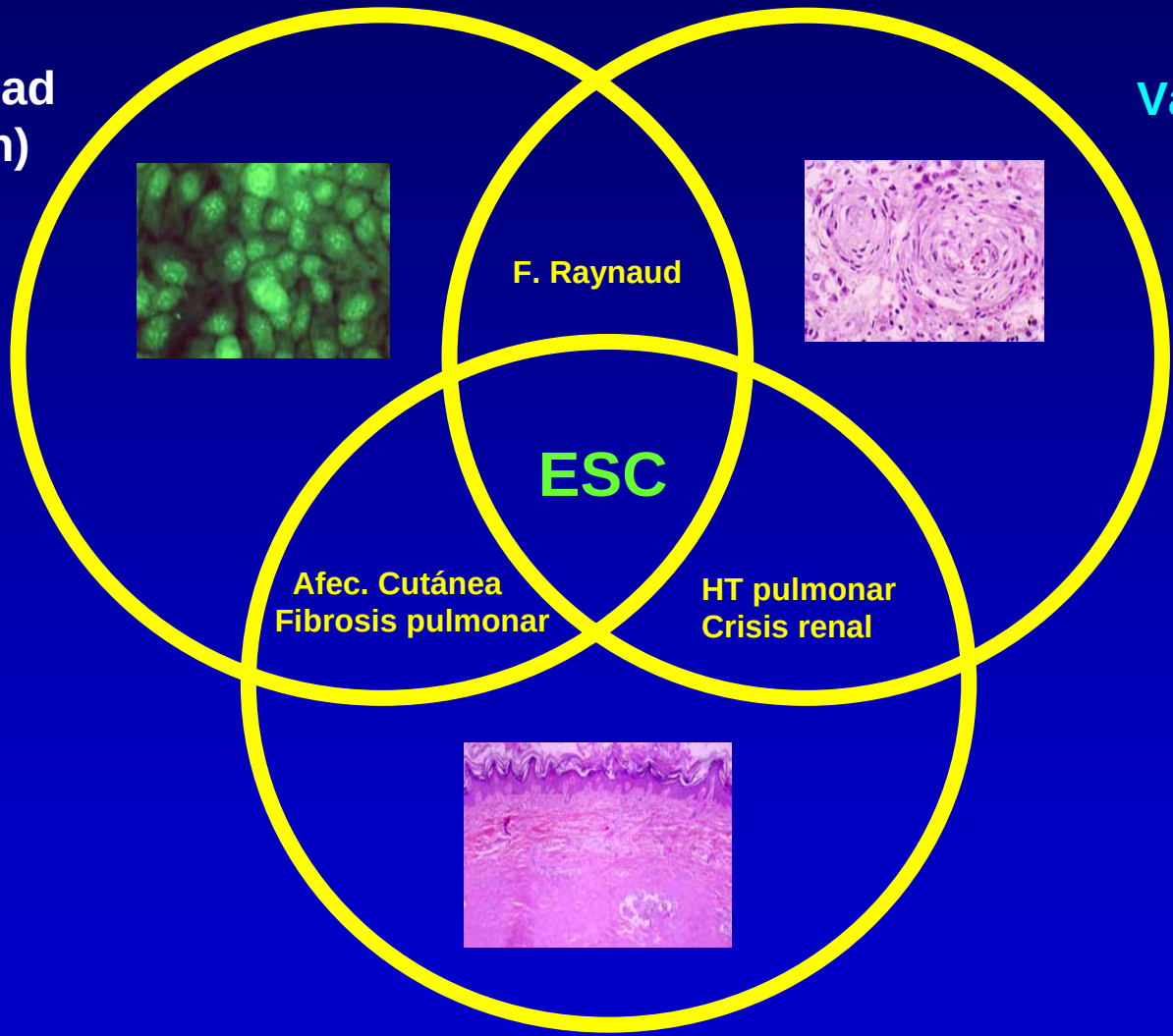
Esclerodermia

Principales novedades en enfermedades autoinmunes sistémicas

II Reunión en enfermedades autoinmunes sistémicas
Bilbao 25-26 de junio de 2009

Dr. Vicent Fonollosa Pla - Dra. Carmen Pilar Simeón Aznar
(Servicio de Medicina Interna – Prof. M. Vilardell)

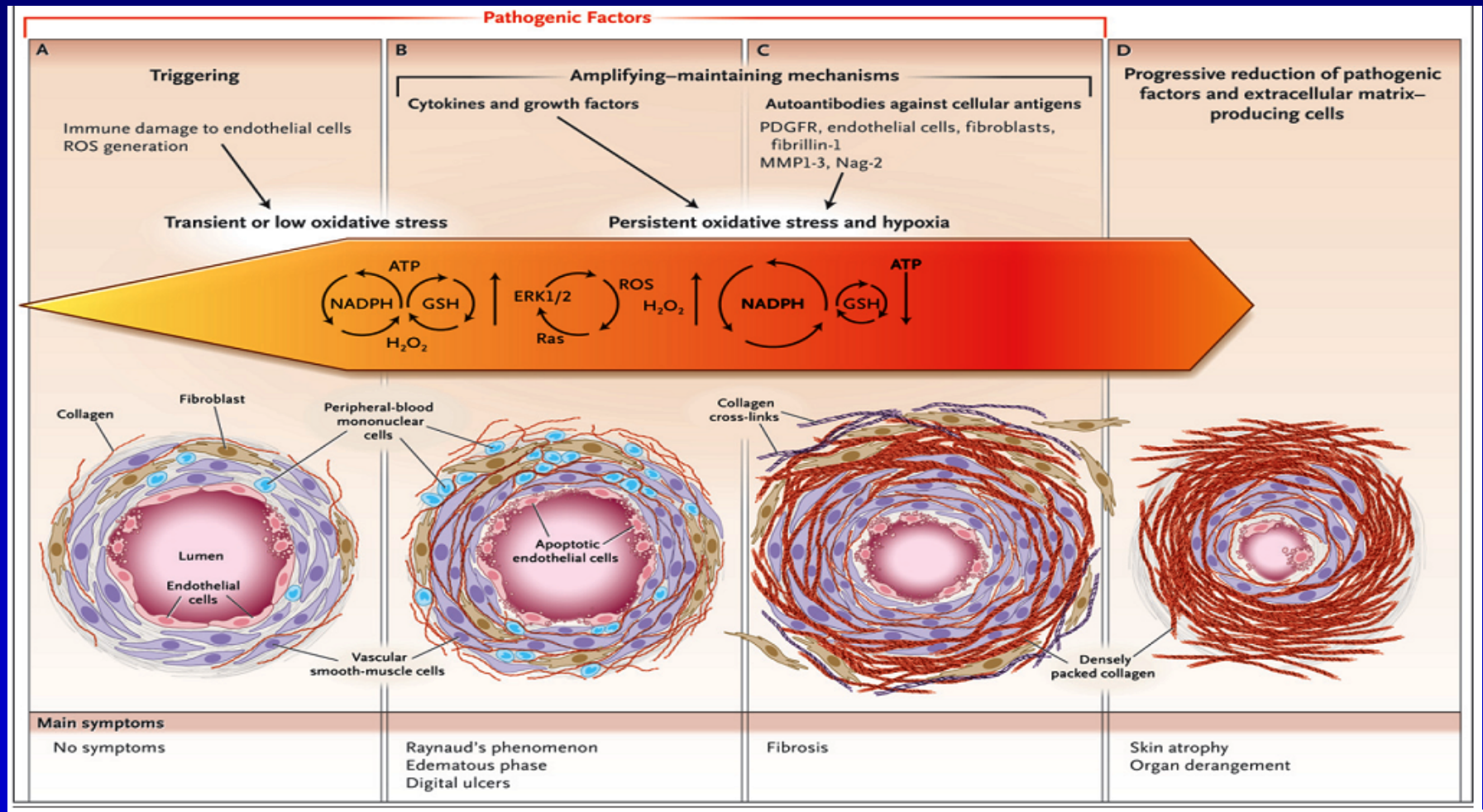
ESCLERODERMIA



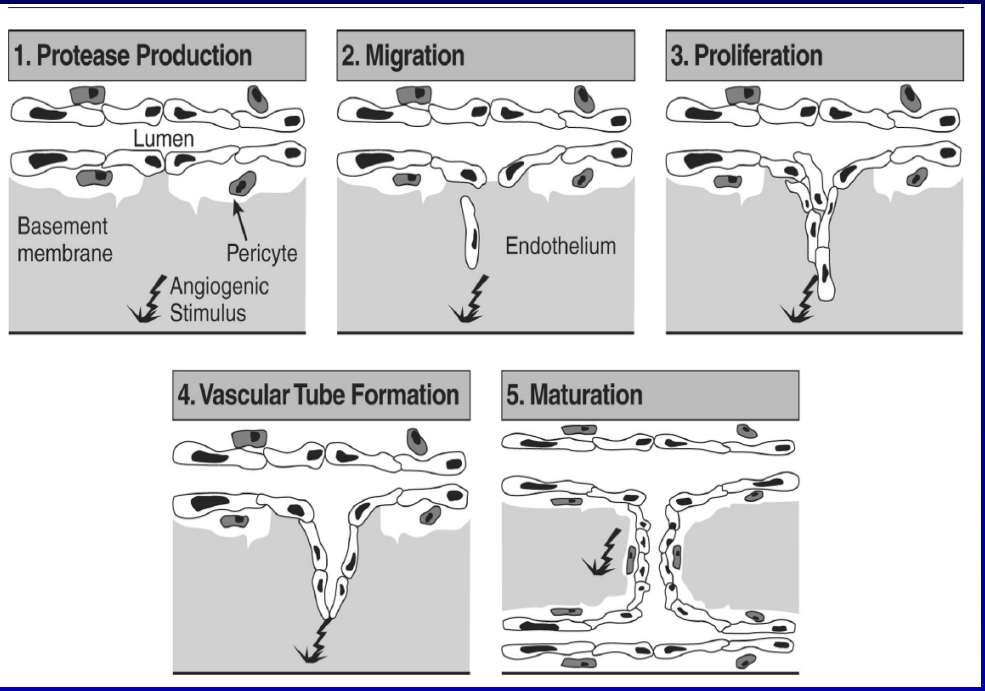
MECHANISMS OF DISEASE

Scleroderma

Armando Gabrielli, M.D., Enrico V. Avvedimento, M.D., and Thomas Krieg, M.D.

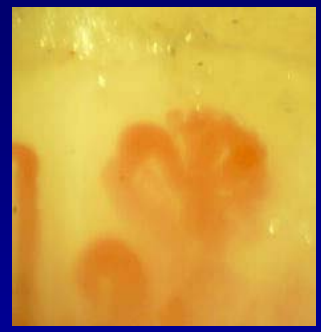


N Engl J Med 2009;360:1989-2003.



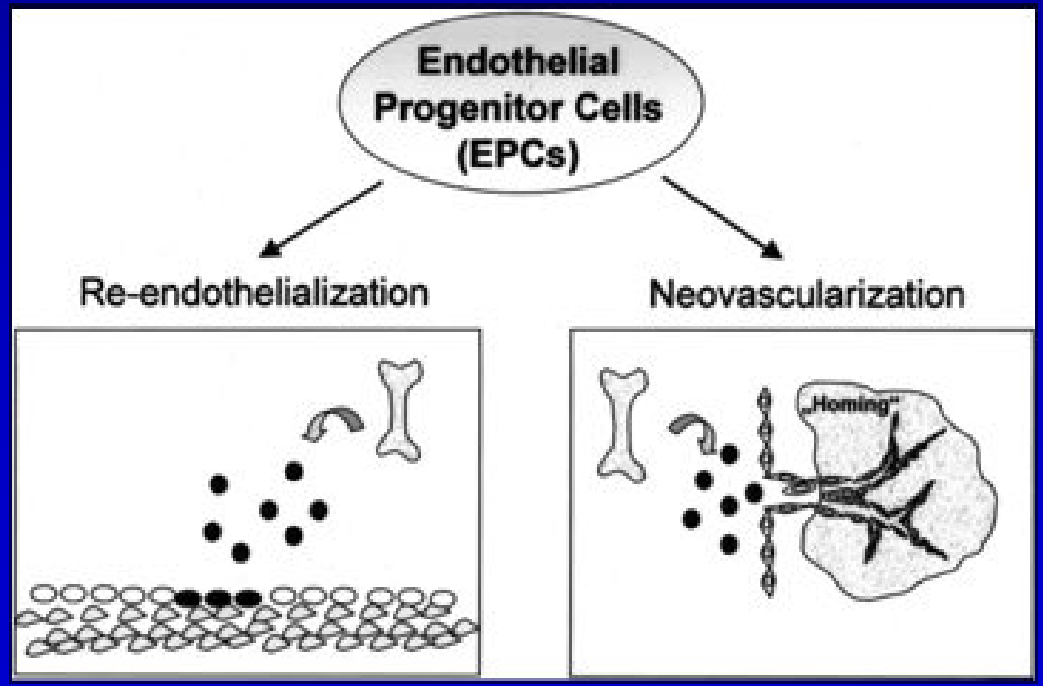
ANGIOGÉNESIS

DEFECTUOSA / INSUFICIENTE



VASCULOGÉNESIS

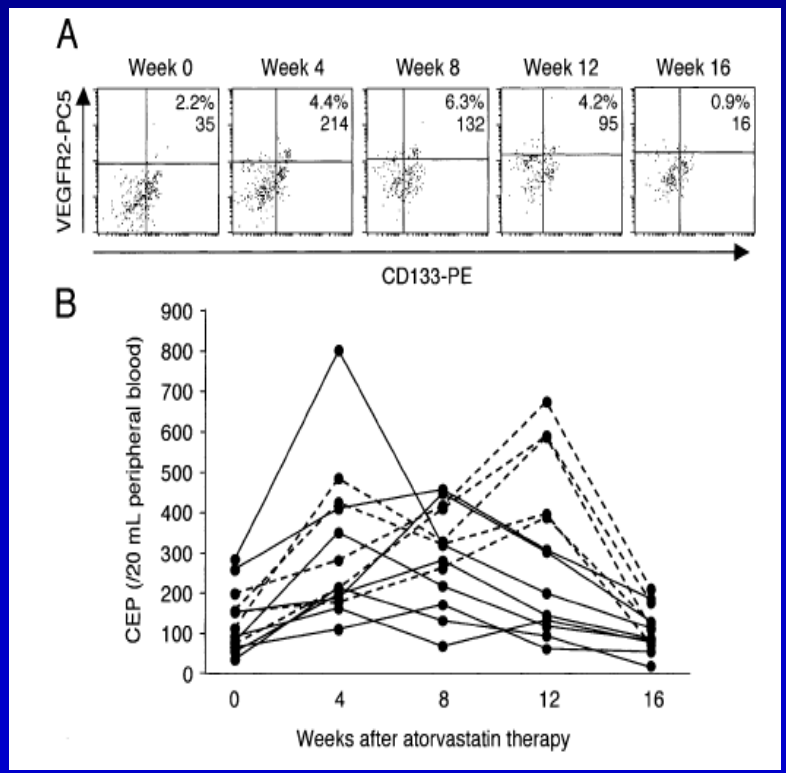
INSUFICIENTE / DEFECTUOSA

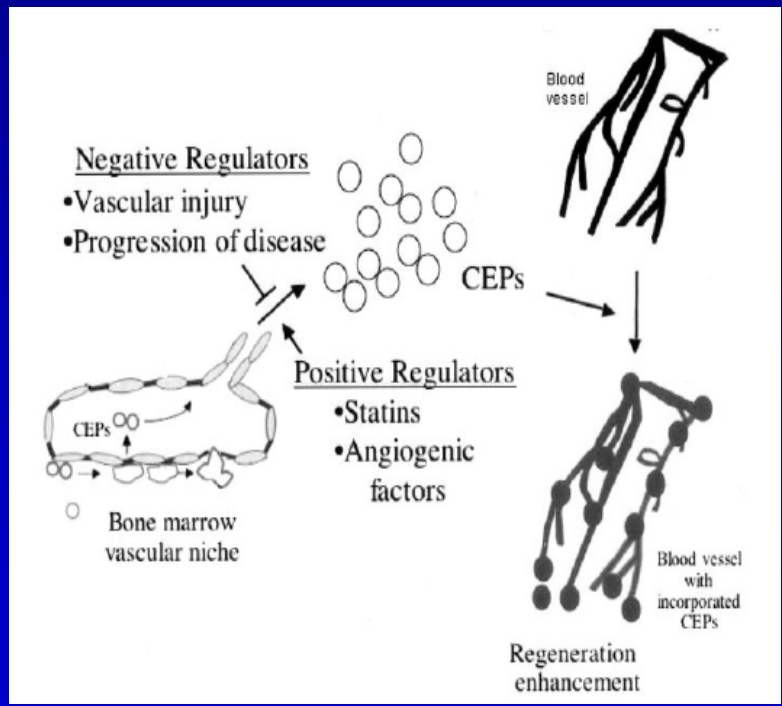


ARTHRITIS & RHEUMATISM
Vol. 54, No. 6, June 2006, pp 1946–1951
DOI 10.1002/art.21899

Increase in Circulating Endothelial Precursors by Atorvastatin in Patients With Systemic Sclerosis

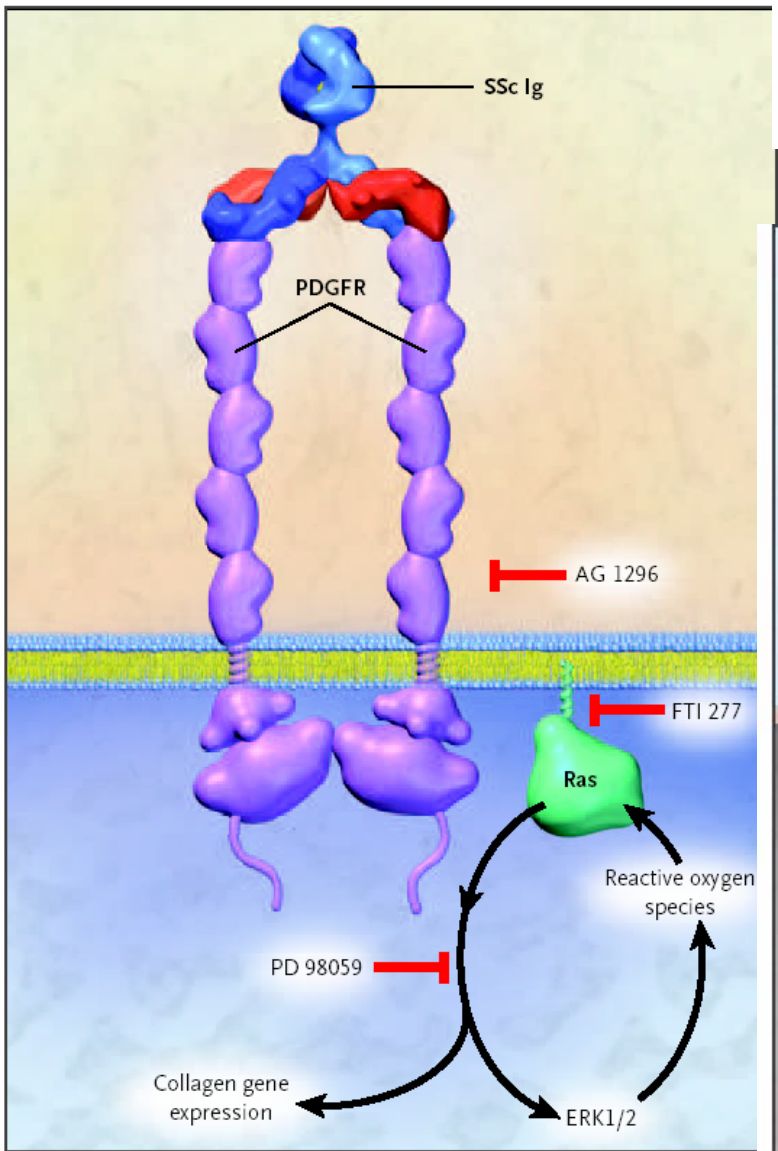
Masataka Kuwana,[1] Junichi Kaburaki,[2] Yuka Okazaki,[1] Hidekata Yasuoka,[1] Yutaka Kawakami,[1] and Yasuo Ikeda[1]

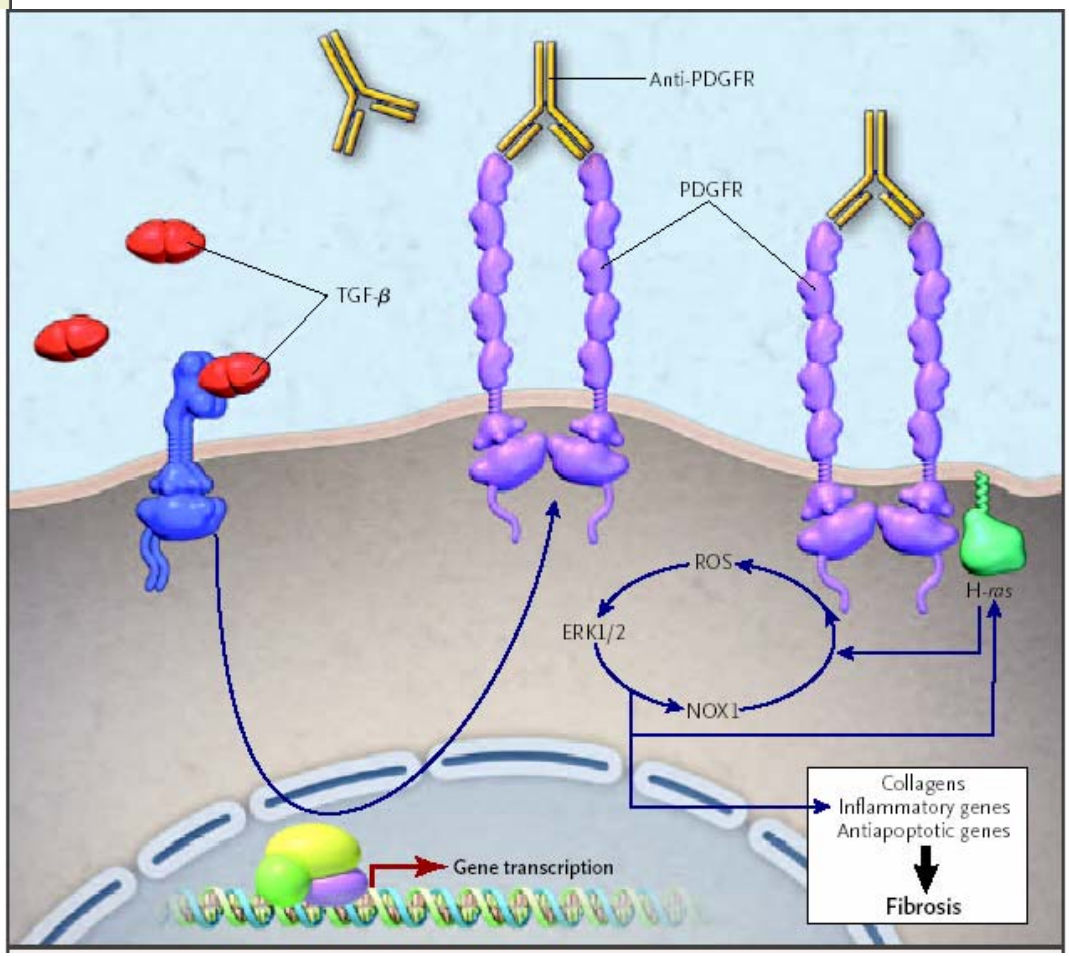




Clancy RM. *Arthritis Rheum 2006;54:1730-32*

Stimulatory Autoantibodies to the PDGF Receptor in Systemic Sclerosis

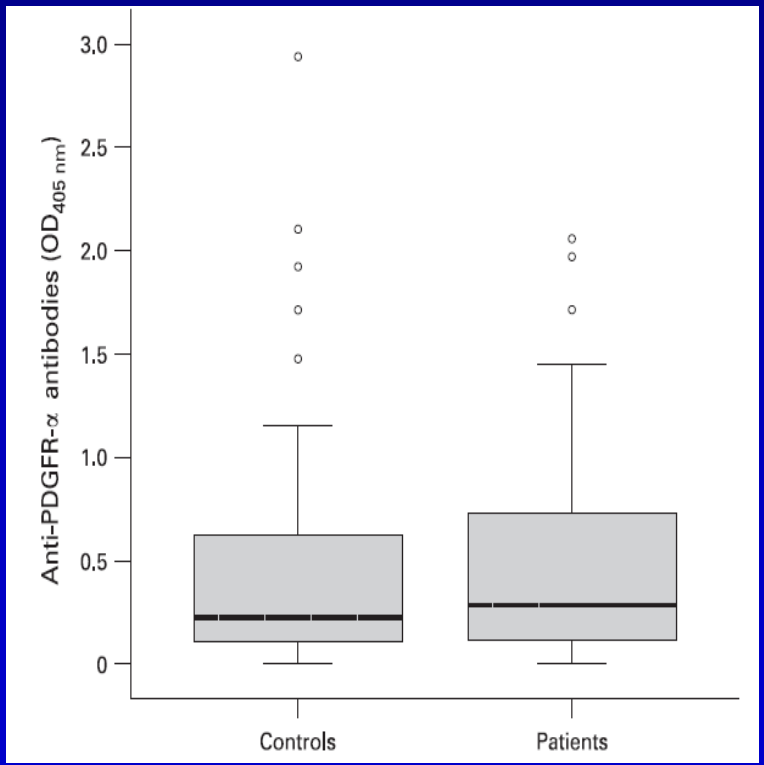




Anti-PDGFR-α antibodies measured by non-bioactivity assays are not specific for systemic sclerosis

Ann Rheum Dis 2008;**67**:1027–1029.

E Balada, C P Simeón-Aznar, J Ordi-Ros, M Rosa-Leyva, A Selva-O'Callaghan, J Pardos-Gea, V Fonollosa-Pla, M Vilardell-Tarrés



Conclusion: Although anti-PDGFR-α antibodies seem to be disease-specific when determined by bioactivity assays, these antibodies are also detected in normal subjects when immunological methods are used. Thus, anti-PDGFR-α antibodies may arise from natural auto-antibodies. Possibly, SSc autoantibodies recognise a different epitope on the PDGFR-α molecule which triggers its stimulatory effect when analysed by functional assays. Alternatively, naturally occurring autoantibodies may even become pathogenic after affinity maturation and class switching in genetically susceptible subjects.

ARTHRITIS & RHEUMATISM
Vol. 60, No. 4, April 2009, pp 1145–1151
DOI 10.1002/art.24365

Lack of Detection of Agonist Activity by Antibodies to Platelet-Derived Growth Factor Receptor α in a Subset of Normal and Systemic Sclerosis Patient Sera

Nick Loizos,[1] Leah LaRiccia,[1] Jami Weiner,[1] Heather Griffith,[1] Francesco Boin,[2] Laura Hummers,[2] Fredrick Wigley,[2] and Paul Kussie[1]

Conclusion. **Although approximately one-third of sera from scleroderma patients contained detectable autoantibodies to PDGFR, these antibodies were not specific to scleroderma, since they were also detected in a similar percentage of samples from normal subjects. PDGFRα agonist activity was not demonstrated when purified Ig from these sera was tested in cell-based assays.**

4. Conclusion

Available data establish a role for genetic factors in the pathophysiology of systemic sclerosis. As with many multifactorial diseases, the presence in a given individual of several polymorphisms probably contributes to the risk of developing the disease, whereas a single polymorphism probably has a limited impact. Additional genes or pathophysiological pathways involved in systemic sclerosis will probably be identified when association studies are conducted in larger populations, finer distinctions are made between the various phenotypes of the disease, and models that more closely replicate systemic sclerosis are developed.

in systemic sclerosis. Only then will it be possible to robustly compare patient subgroups and studies from distinct geographic or ethnic populations to fully understand the significance of genetic factors in determining the disease phenotype.

Lack of association of the PTN22 gene polimorphysm R620W with systemic sclerosis

Balada E. et al. *Clin Exp Rheumatol*. 2006

A large multicenter analysis of CTGF -945 promoter polymorphism does not confirm association with Systemic Sclerosis susceptibility or phenotype

Rueda B. et al. *Ann Rheum Dis*. 2008

The interleukin 23 receptor gene does not confer risk to systemic sclerosis and is not associated with systemic sclerosis disease phenotype

Rueda B. et al. Ann Rheum Dis. 2009

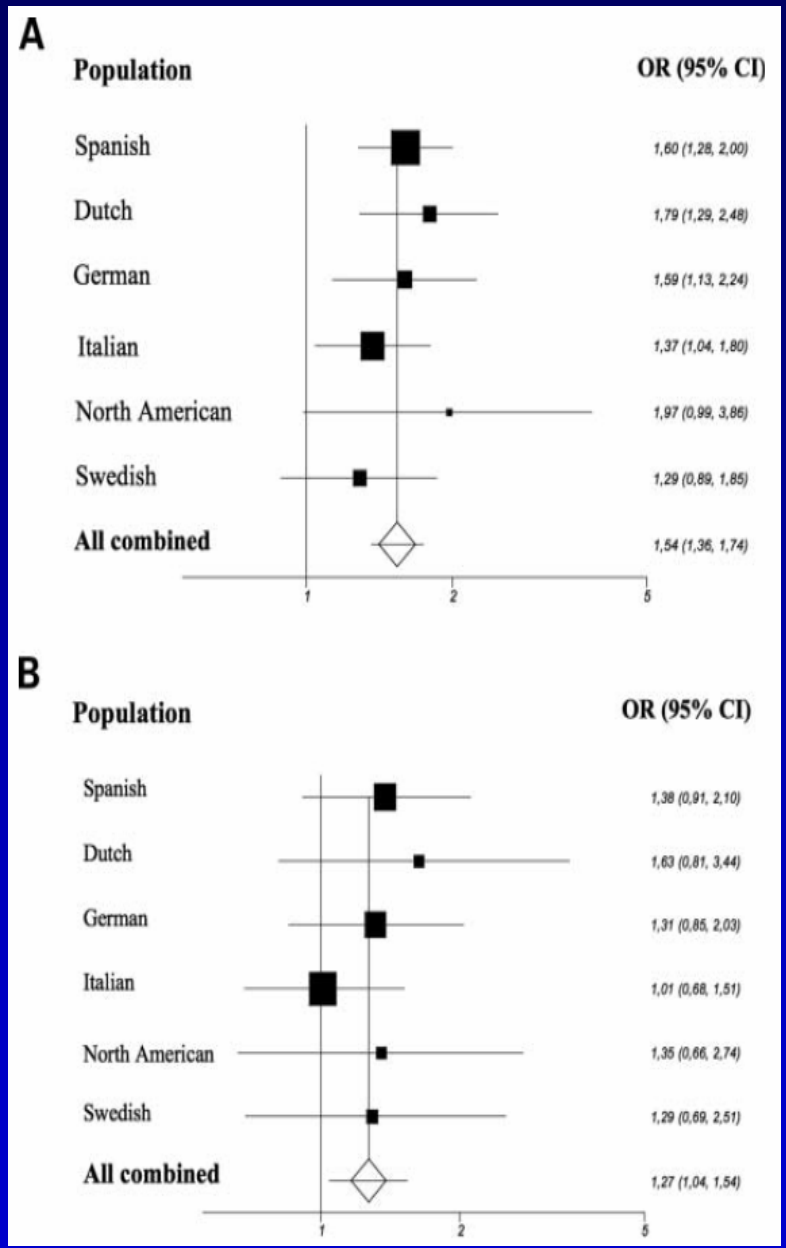
Human Molecular Genetics, 2009, Vol. 18, No. ? **1–7**
doi:10.1093/hmg/ddp119
Advance Access published on xxx

The *STAT4* gene influences the genetic predisposition to systemic sclerosis phenotype

B. Rueda[1], J. Broen[2], C. Simeon[4], R. Hesselstrand[5], B. Diaz[6], H. Sanchez[6], N. Ortego-Centeno[7], G. Riemekasten[8], V. Fonollosa[4], M.C. Vonk[2], F.H.J. van den Hoogen[9], J. Sanchez-Román[10], M.A. Aguirre-Zamorano[11], R. García-Portales[12], A. Pros[13], M.T. Camps[14], M.A. Gonzalez-Gay[15], M.J.H. Coenen[3], P. Airo[16], L. Beretta[17], R. Scorza[17], J. van Laar[18], M.F. Gonzalez-Escribano[19], J.L. Nelson[20], T.R.D.J. Radstake[2] and J. Martin[1,*]

RESULTS

STAT4 is associated with limited cutaneous SSc in the Spanish population



ESCLERODERMIA
Criterios de clasificación 1980

CRITERIO MAYOR

Esclerodermia proximal

CRITERIOS MENORES

Esclerodactilia
Cicatrices puntiformes en el pulpejo de los dedos
Fibrosis pulmonar bilateral

DIAGNÓSTICO

Criterio mayor
Dos o más de menores

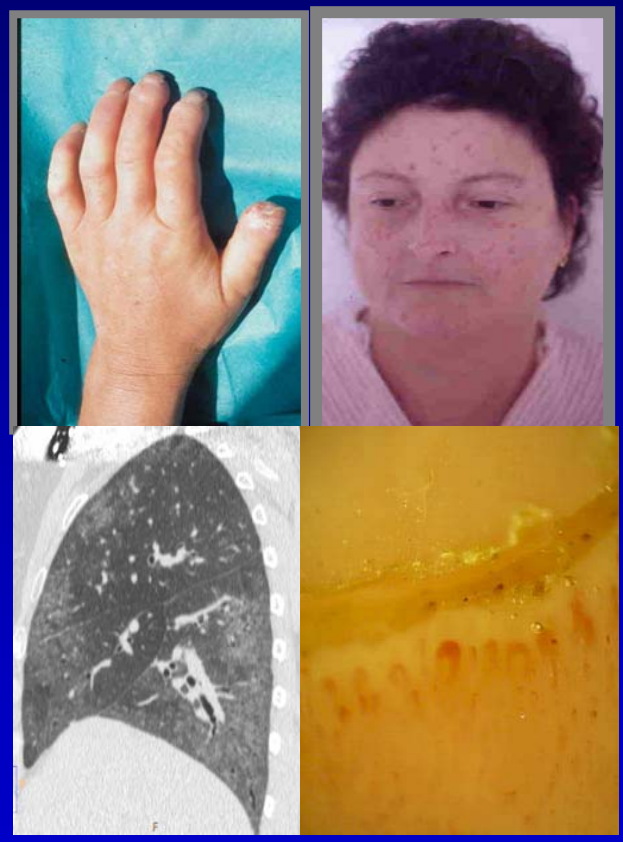
ESCLERODERMIA. Clasificación en subtipos

Forma difusa

F. Raynaud < 1 a.
Afec. cutánea troncal y acra
Roces tendinosos
Afección visceral temprana
Pérdida capilar
Anti-Scl 70 (25-30%)

Limitada

F. Raynaud > 5 a.
Afec. cutánea distal
Telangiectasias, a.diges.
Calcinosis,HTP
Dilatación capilar
AAcentrómero (60-80%)



ESC *sine* esclerodermia

F. Raynaud +/-
Sin afección cutánea
Afección visceral
AANs específicos

Pre-esclerodermia

Fenómeno de Raynaud
Alts. capilaroscópicas
Úlceras digitales
AANs específicos


ESCLERODERMIA DIFUSA
ANTICUERPOS
FENÓMENO DE RAYNAUD
Anti-Th/To
escleromiosistis
Reflujo gastroesofágico
FIBROSIS
CALCINOSIS
ANTIFIBRILARINA
ESCLERODERMIA LIMITADA
Anti-centrómers
PULMONAR
RENAL
CRISIS RENAL
CAPILAROSCOPIA
Pérdida capilar
ANTITOPOISOMERASA I
ANTIMIERASA
Anti-nucleolares
Acs PM Scl
Hipertensión arterial pulmonar aislada
Megacapilares+Hemorragias

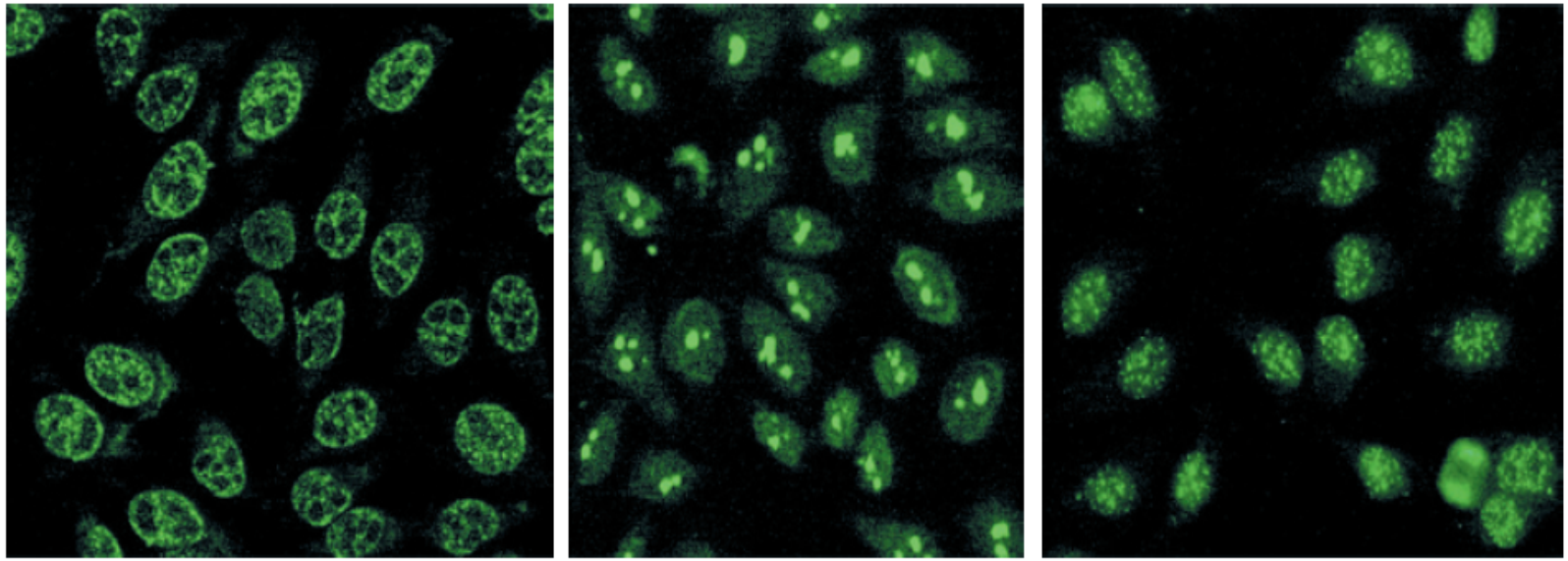
La esclerodermia: una enfermedad poliédrica

The Many Faces of Scleroderma

Virginia D. Steen, MD

Department of Medicine, Georgetown University, 3800 Reservoir Road, LL Gorman, Washington, DC 20007, USA

A



B

Classic Autoantibodies	Clinical Features	New Autoantibodies	Role
Anti–topoisomerase I	Diffuse cutaneous scleroderma	Anti–endothelial cell	Induce apoptosis of endothelial cells
Anticentromere proteins	Limited cutaneous scleroderma, pulmonary hypertension	Anti–FBN 1	Activate normal human fibroblasts
Anti–RNA polymerase I/II	Diffuse cutaneous scleroderma, renal involvement	Anti–MMP 1 and 3	Prevent degradation of ECM proteins
Antipolymyositis, sclerosis	Polymyositis, calcinosis	Anti-PDGFR	Stimulate normal human fibroblasts through Ha-Ras-ERK1/2-ROS
Antifibrillarin (U3RNP)	Diffuse cutaneous scleroderma, internal-organ involvement	Anti–Nag-2	Induce endothelial-cell apoptosis
Anti-Th/To	Limited cutaneous scleroderma, pulmonary fibrosis		

The Many Faces of Scleroderma

Virginia D. Steen, MD

Department of Medicine, Georgetown University, 3800 Reservoir Road, LL Gorman, Washington, DC 20007, USA

Features of patients with limited scleroderma-specific autoantibodies

Antibody	ACA	Th/To	Pm/Scl	U1-RNP
No. of patients	291	72	36	71
Male sex, %*	**8**	19	19	21
African African, %*	3	4	3	**13**
Age of onset*	42	40	38	**33**
Diffuse SSc, %*	5	7	22	20
Disease duration				
At diagnosis*	**8.7**	**7.9**	3.2	3.2
Joints, %*	60	60	75	**94**
Digital ulcers, %*	**61**	29	47	49
Gangrene, %*	**18**	5	5	11
Digital tuft	**27**	7	**32**	17
Resorption* (x-ray numbers actually performed)	(41/151)	(2/28)	(7/22)	(5/29)
Calcinosis, %*	**46**	**22**	**39**	14
Muscle inflammation, %*	1	6	**58**	**27**
Any GI, %	57	33	39	39
Severe GI, %*	8	**13**	0	14
Any lung, %	45	62	58	53
Number with PFTs	(184)	(49)	(22)	(49)
Severe fibrosis, %*	6	**16**	**27**	**22**
Lowest FVC,* % predicted	87	**70**	74	75
Isolated PAH*	**19**	**32**	3	14
Severe heart, %*	4	7	6	11
Renal crisis, %*	1	4	4	7
Survival, % cumulative survival from diagnosis				
5 y, 10 y	85,75	**78,65**	95,72	**78,65**

Features of patients with diffuse scleroderma specific autoantibodies present

Antibody	TOPO	POL 3	U3 RNP
No. of patients	318	120	55
Male sex, %*	27	**19**	29
African African, %*	**17**	3	**29**
Age of onset*	43	44	**35**
Diffuse SSc, %*	**71**	**85**	**64**
Disease duration			
At diagnosis	2.2	1.5	2.9
Joints, %	**86**	**88**	**89**
Carpal tunnel, %*	28	**43**	27
Tendon rubs, %	**50**	**61**	**42**
Digital ulcers, %*	**63**	42	**58**
Gangrene, %*	**13**	3	9
Digital tuft	**28**	5	9
Resorption* (x-ray numbers actually performed)	49/173	3/54	2/22
Calcinosis, %*	17	14	**22**
Muscle inflammation, %*	9	4	**18**
Any GI, %	56	37	59
Severe GI, %*	8	5	**25**
Any lung %	73	49	67
Number with PFTs	(235)	(74)	(37)
Severe fibrosis, %*	**23**	7	24
Lowest FVC,* % predicted	**67**	81	68
Isolated PAH	2	6	24
Severe heart, %*	**16**	**7**	**18**
Renal crisis, %*	**10**	**28**	7
Survival, % cumulative survival from diagnosis			
5 y, 10 y	78,65	**90,75**	80,61

ARTHRITIS & RHEUMATISM
Vol. 58, No. 7, July 2008, pp 2174–2182
DOI 10.1002/art.23555

Prognostic Model Based on Nailfold Capillaroscopy for Identifying Raynaud's Phenomenon Patients at High Risk for the Development of a Scleroderma Spectrum Disorder

PRINCE (Prognostic Index for Nailfold Capillaroscopic Examination)

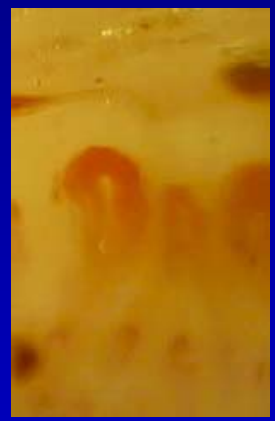
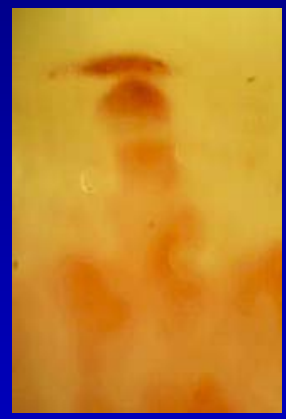
Francesca Ingegnoli, Patrizia Boracchi, Roberta Gualtierotti, Chiara Lubatti, Laura Meani, Lenka Zahalkova, Silvana Zeni, and Flavio Fantini

Table 2. Multivariate regression analysis of the 3 prognostically relevant capillaroscopy parameters*

Prognostic variable	HR	95% CI	χ^2	*P*
Giant loops	1.58	0.6–4.14	0.86	0.355
Microhemorrhages	1.77	0.79–3.95	1.93	0.164
No. of capillaries				
Linear	0.66	0.45–0.98	4.15	0.042
Nonlinear	1.66	1.01–2.70	4.06	0.044

* HR = hazard ratio; 95% CI = 95% confidence interval.

Conclusion. **Our prognostic capillaroscopic index identifies RP patients in whom the risk of developing SSDs is high. This model is a weighted combination of different capillaroscopy parameters that allows physicians to stratify RP patients easily, using a relatively simple diagram to deduce the prognosis. Our results suggest that this index could be used in clinical practice, and its further inclusion in prospective studies will undoubtedly help in exploring its potential in predicting treatment response.**

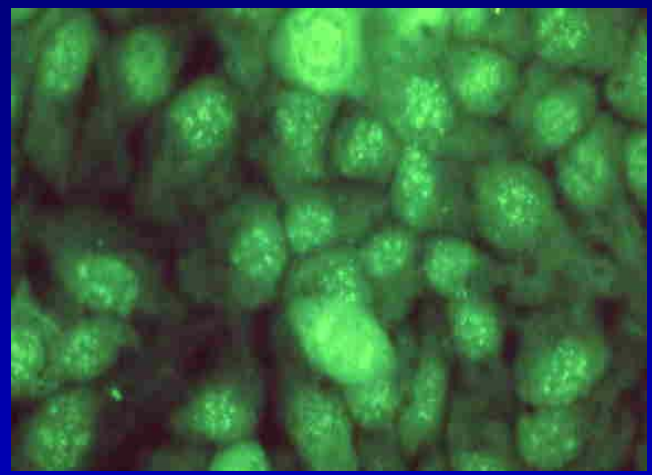



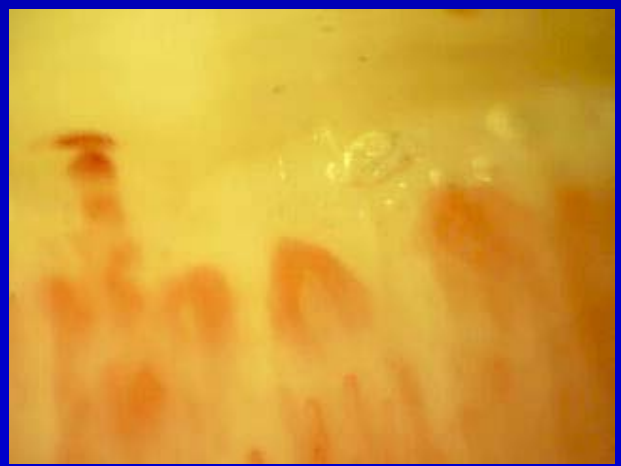

Autoantibodies and Microvascular Damage Are Independent Predictive Factors for the Progression of Raynaud's Phenomenon to Systemic Sclerosis

A Twenty-Year Prospective Study of 586 Patients, With Validation of Proposed Criteria for Early Systemic Sclerosis

Koenig M et al. *Arthritis and Rheumatism*. 2008;58:3.902-12

Last, this study is the first to validate the criteria for early SSc that were proposed by LeRoy and Medsger, but were not validated (21). According to these criteria, when the presence of RP is subjective only (i.e., by patient report only), as in the present study, early SSc may be diagnosed when *both* an SSc pattern on NCM and SSc-specific autoantibodies are observed (21). In our cohort, patients in whom both predictors were present at baseline were 60 times more likely to develop definite SSc than were patients without these predictors.



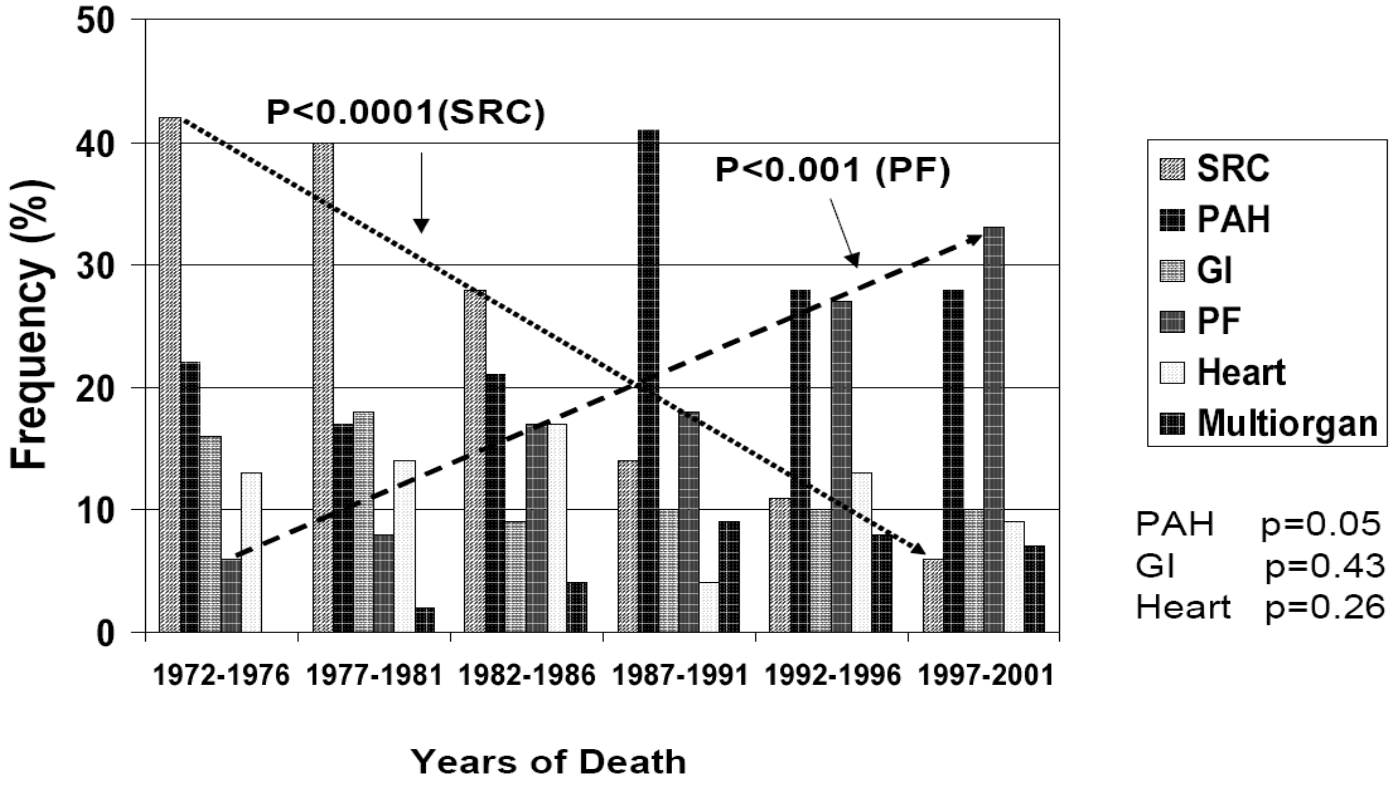


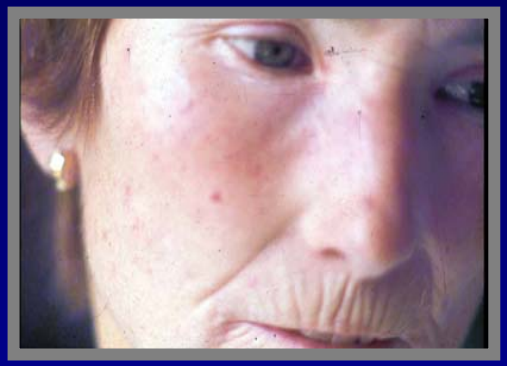
Conclusion. In RP evolving to definite SSc, microvascular damage is dynamic and sequential, while SSc-specific autoantibodies are associated with the course and type of capillary abnormalities. Abnormal findings on NCM at baseline together with an SSc-specific autoantibody indicate a very high probability of developing definite SSc, whereas their absence rules out this outcome.

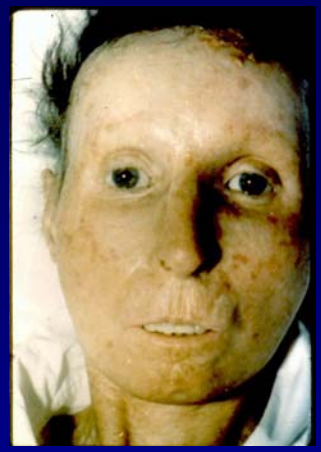
Changes in causes of death in systemic sclerosis, 1972- 2002

Virginia D. Steen and Thomas A Medsger, Jr

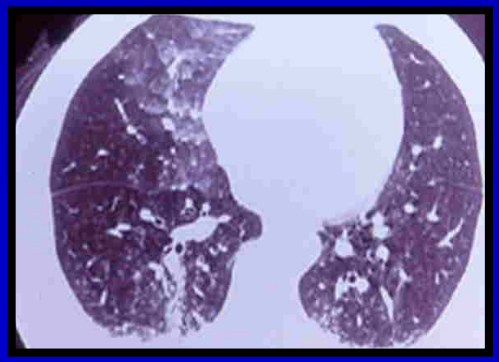
Ann Rheum Dis, 2007



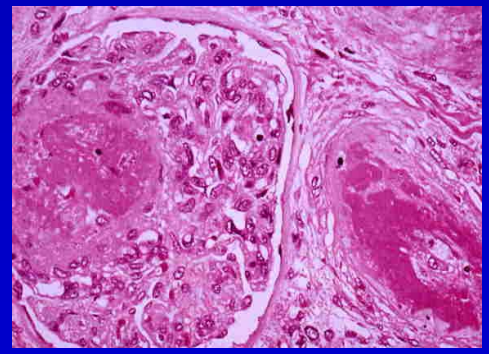




Factores pronósticos	RR	*p*
Esclerodermia difusa	2,730	0,001
Edad de comienzo	1,079	0,0001
Fibrosis pulmonar	2,463	0,003
HTAP	2,802	0,0001
Crisis renal	30,062	0,0001



Esclerodermia
Factores pronósticos



Long-Term Outcomes of Scleroderma Renal Crisis

Virginia D. Steen, MD, and Thomas A. Medsger Jr., MD

Conclusions: Renal crisis can be effectively managed when hypertension is aggressively controlled with ACE inhibitors. Patients should continue taking ACE inhibitors even after beginning dialysis in hopes of discontinuing dialysis.

Ann Intern Med. 2000;133:600-603. www.annals.org

Predictors and Outcomes of Scleroderma Renal Crisis

ARTHRITIS & RHEUMATISM
Vol. 46, No. 11, November 2002, pp 2983–2989

in the appropriate clinical setting. Although ACE inhibitors and dialysis are now readily available, SRC continues to be associated with poor survival (in this study, 50% of patients with SRC died).

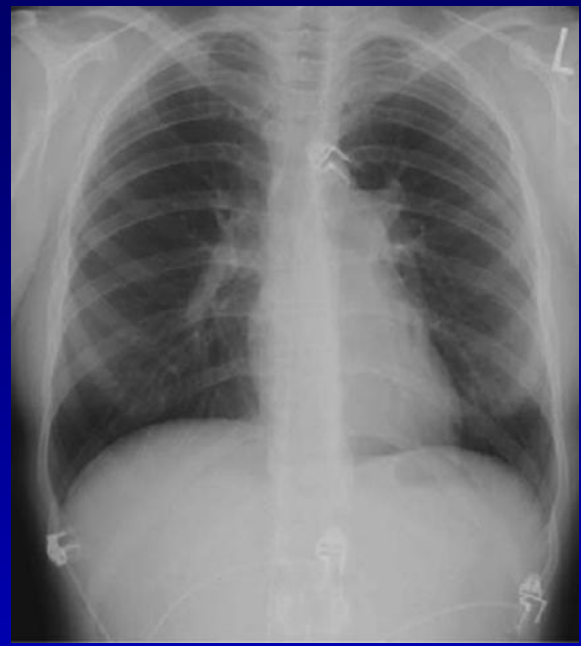
Q J Med 2007; **100**:485–494

Scleroderma renal crisis: patient characteristics and long-term outcomes

H. PENN[1], A.J. HOWIE[2], E.J. KINGDON[3], C.C. BUNN[4], R.J. STRA
A. BURNS[5] and C.P. DENTON[1]

Discussion: Despite the efficacy of ACEIs in managing SRC, the poor long-term outcome warrants evaluation for additional treatments for this devastating complication of systemic sclerosis.

ESCLERODERMIA
Manifestaciones clínicas



N: 348

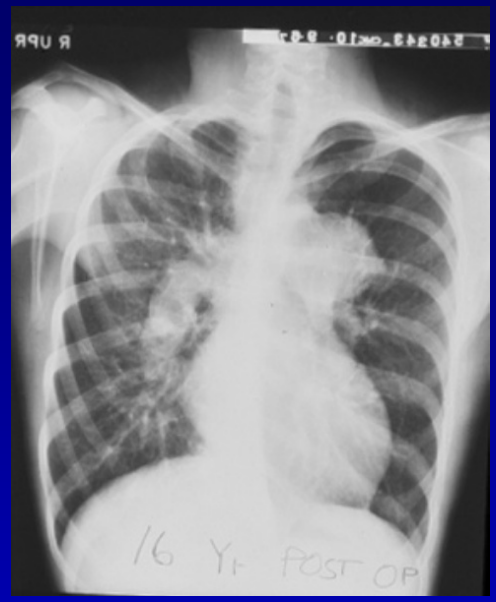
Fenómeno de Raynaud: 346 (99%)
Úlceras digitales: 171 (49%)
Afección osteomuscular: 245 (70%)
Afección digestiva: 249 (71%)

Afección respiratoria: 261 (75%)
EPID: 195 (56%) (CVF<70%: 84 (24%)
HTAP: 66 (19%) (HTAP (s> 55mmHg): 32 (9.7%)

Afección cardíaca: 164 (47%)
Afección renal (CRE): 14 (4%)

ESCLERODERMIA. Hipertensión pulmonar

N= 335 (Hospital Vall d'Hebron)

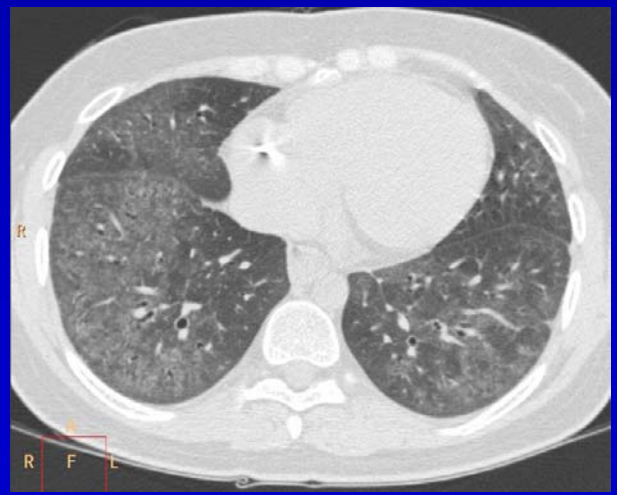


Causas de muerte

Afección pulmonar : 29 (40 %)

HTA pulmonar aislada: 15
Fibrosis pulmonar + HTAP: 8

Fibrosis pulmonar: 6

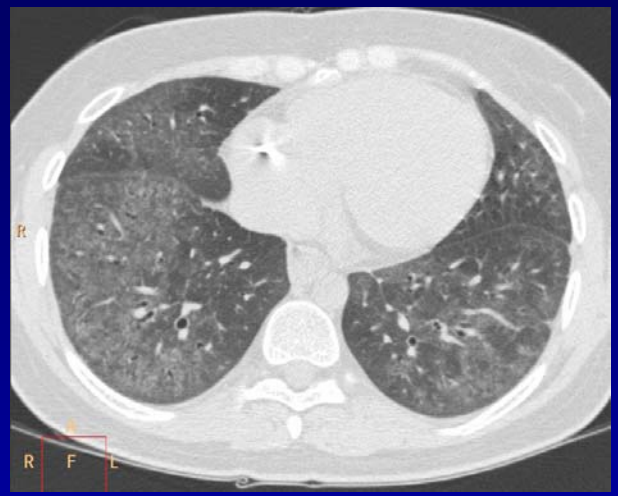


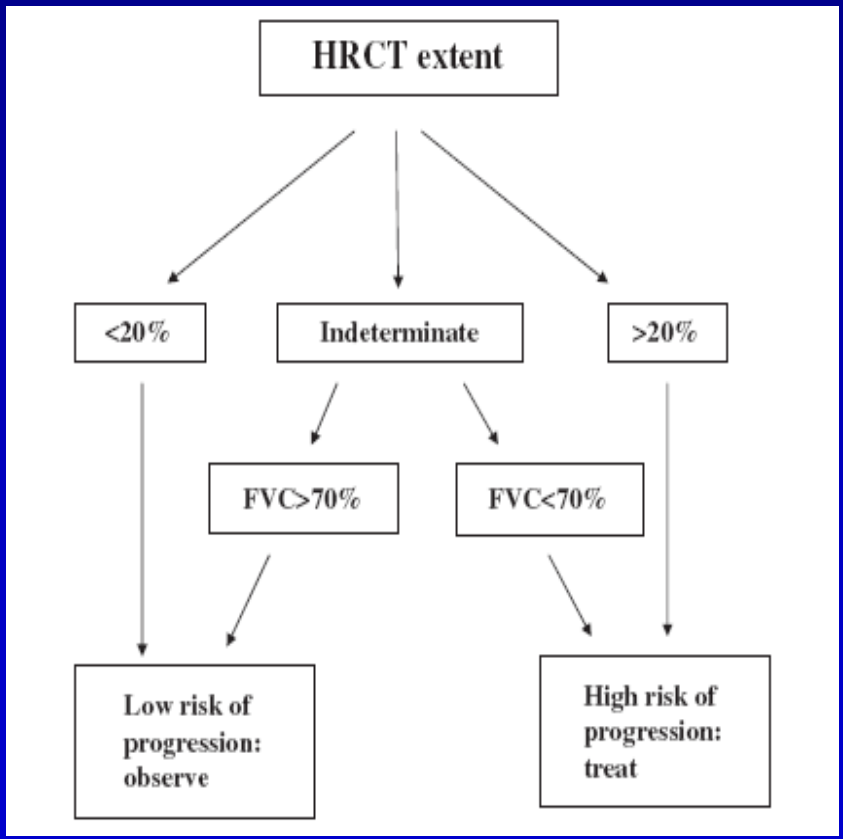
ESCLERODERMIA: EPI. Factores pronósticos

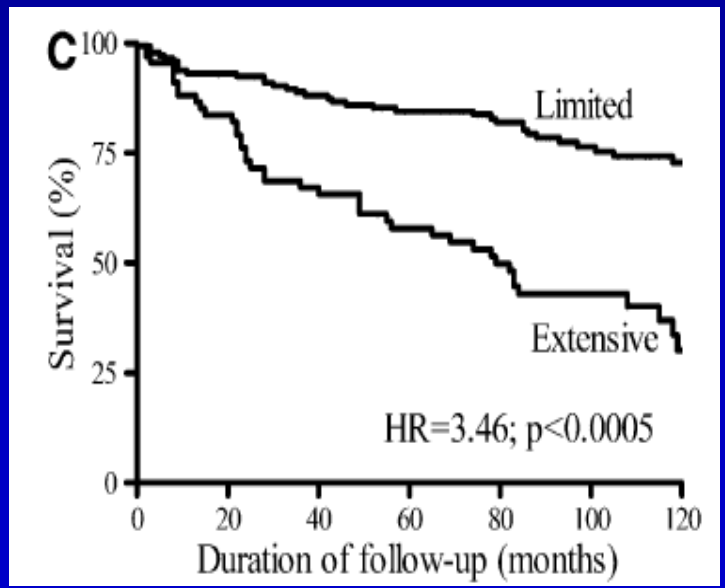
LBA. Dudosa utilidad clínica

PFRs. Diagnóstico y seguimiento

TACAR: Diagnóstico y factor pronóstico





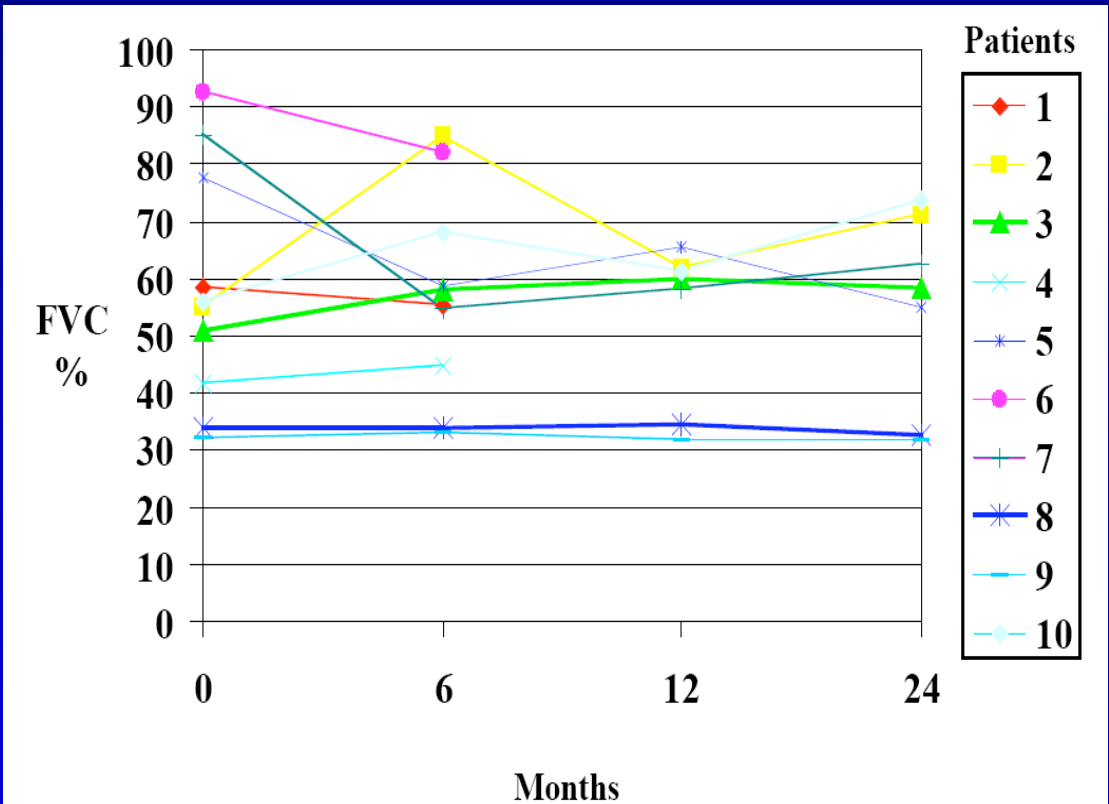


Goh NSL et al. Interstitial lung disease in systmic sclerosis: A simple staging system. *Am J Respir Crit Care Med. 2008*

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]



Rheumatology 2006; 1 of 4 doi:10.1093/rheumatology/kel244

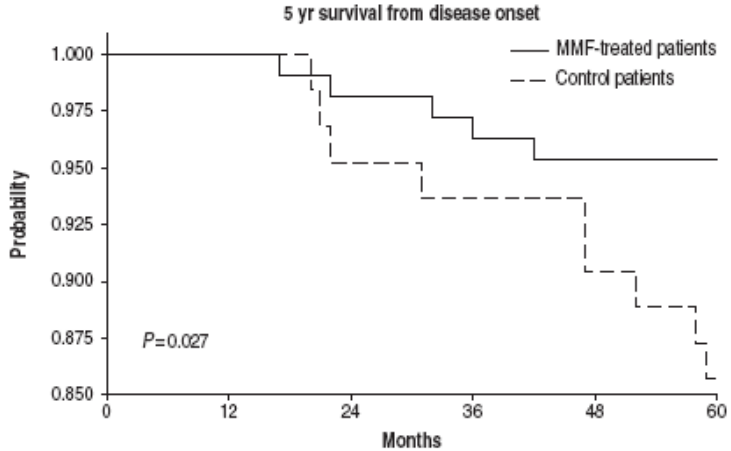
Concise Report

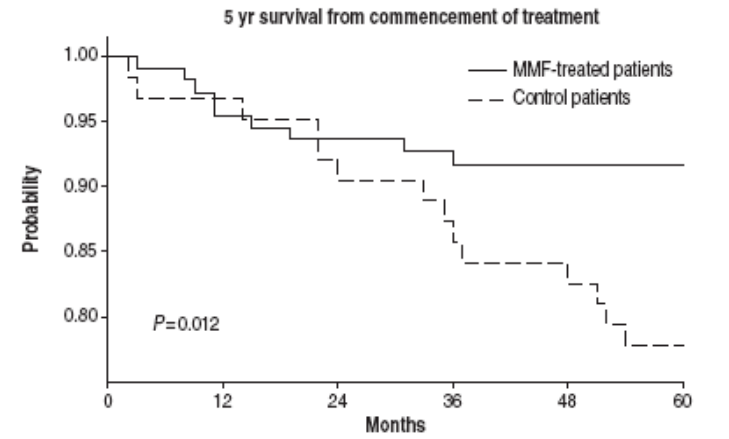
Mycophenolate mofetil in diffuse cutaneous systemic sclerosis—a retrospective analysis

Svetlana I. Nihtyanova, Geraldine M. Brough, Carol M. Black and Christopher P. Denton

	MMF patients % (No)	Controls % (No)
Patients	100 (109)	100 (63)
Female sex	82.6 (90)	81 (51)
Race		
Asian	9.2 (10)	9.5 (6)
Black	7.3 (8)	6.3 (4)
Caucasian	79.8 (87)	79.4 (50)
Other	3.7 (4)	4.8 (3)
Diffuse disease	92.7 (101)	98.4 (62)
Age at onset (yrs) mean ± s.d.	47 ± 13	45 ± 12
Overlap		
Total	23.9 (26)	22.2 (14)
>1 overlap	3.7 (4)	1.6 (1)
Polymyositis/dermatomyositis	11.9 (13)	14.3 (9)
Arthritis	8.3 (9)	7.9 (5)
Sjogren's	1.8 (2)	0 (0)
SLE	3.7 (4)	1.6 (1)
Vasculitis	3.7 (4)	1.6 (1)
Antibodies		
Scl 70	32.1 (35)	27 (17)
RNA polymerase	23.9 (26)	22.2 (14)
nRNP	4.6 (5)	3.2 (2)
U3RNP	4.6 (5)	6.3 (4)
ACA	1.8 (2)	1.6 (1)
PM/Scl	1.8 (2)	4.8 (3)
dsDNA	4.6 (5)	0 (0)
Ro	5.5 (6)	7.9 (5)
Sm	1.8 (2)	0 (0)
Non-defined Abs	30.3 (33)	30.2 (19)
Organ involvement		
Skin	100 (109)	100 (63)
Raynaud's	100 (109)	100 (63)
GIT[a]	78 (85)	87.3 (55)
Lung	56 (61)	63.5 (40)
Joint	19.3 (21)	14.3 (9)
Muscle	13.8 (15)	15.9 (10)
Heart	6.4 (7)	6.3 (4)
Kidney	22.9 (25)	4.8 (3)

[a]GIT, gastrointestinal tract.

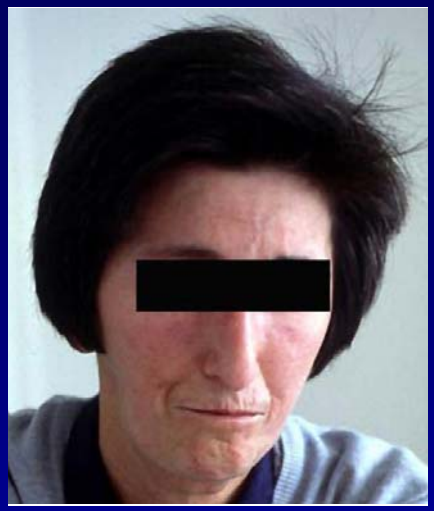




Tratamiento de la EPID asoc a ES: micofenolato sódico. N=14

Table 2: Differences in median of FVC (%) expected values prior, initiation and after treatment with MS

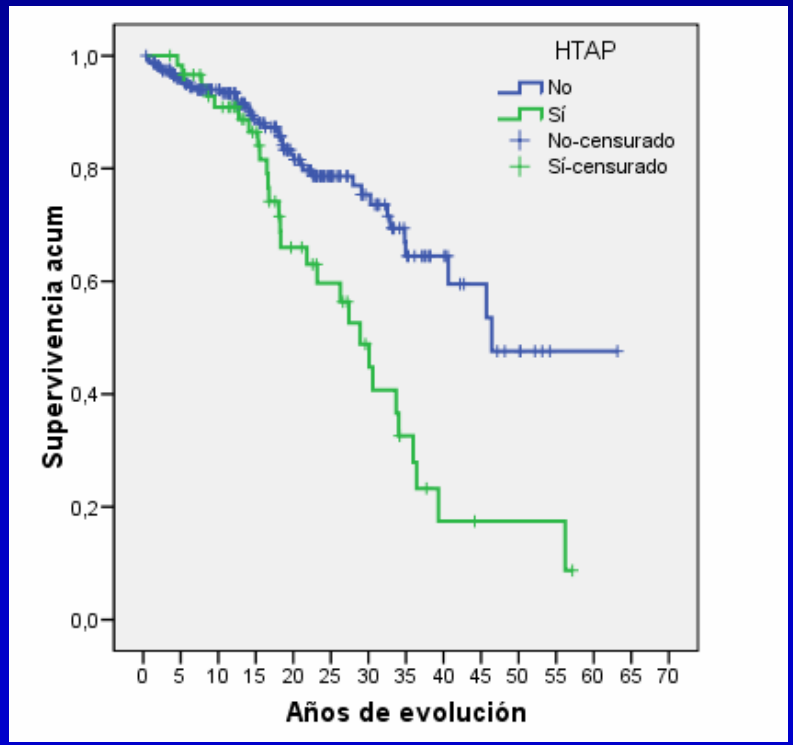
Variables	Prior to MS	Initiation MS	One year of MS
FVC(%)	59.80	55.5	59.00
Change (%)		-7.2	+ 6.3
p value		0.3115	0.951



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*



Early Detection of Pulmonary Arterial Hypertension in Systemic Sclerosis

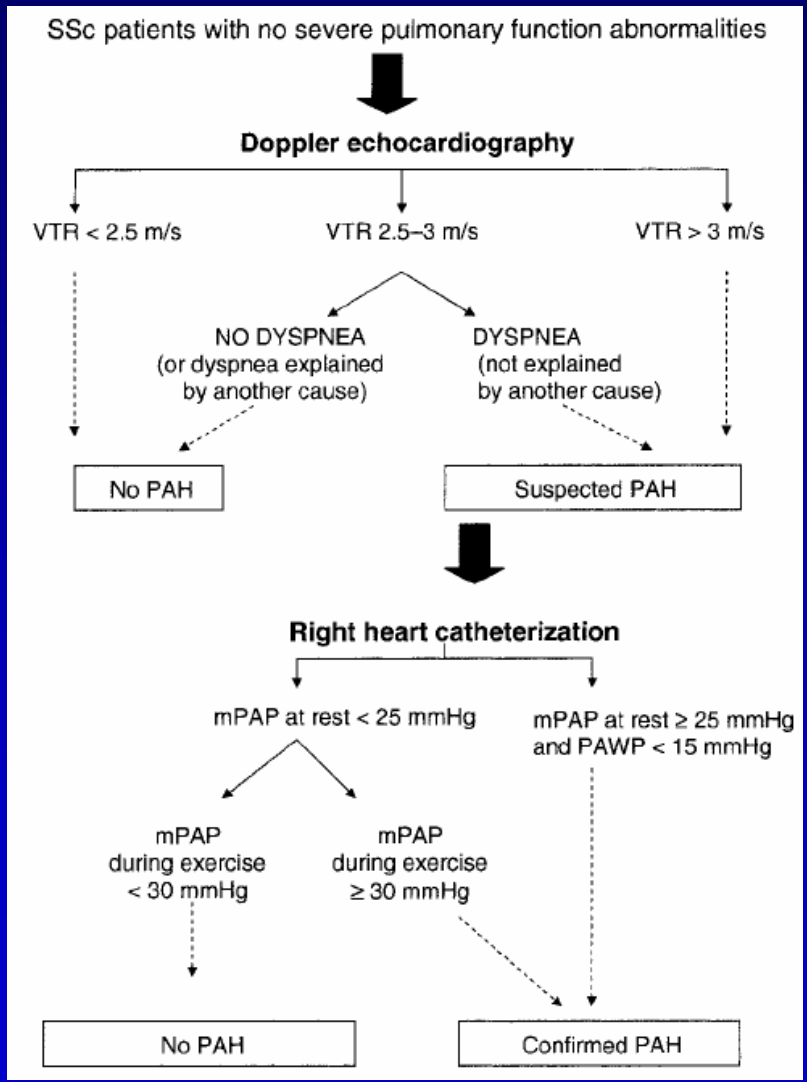


Table 3. Clinical characteristics, signs, symptoms, and pulmonary function test results in patients with newly diagnosed PAH versus those with no PAH (n = 566)*

Parameter	Newly diagnosed PAH (n = 18)	No PAH (n = 548)	*P*
Age, years	65.0 ± 11.7	54.1 ± 12.9	<0.001
Female, no. (%)	16 (88.9)	465 (84.9)	1.00
Body mass index, kg/m^2	26.6 ± 5.9	23.9 ± 4.5	0.014
SSc subtype, no. (%) limited	10 (55.6)	409 (74.6)	0.10
Age at first non-RP SSc symptom, years	52.0 ± 14.7	45.7 ± 13.8	0.07
Age at SSc diagnosis, years	57.4 ± 13.4	47.3 ± 13.6	0.003
Time since first non-RP symptom, years	11.9 ± 12.6	8.5 ± 7.8	0.29
Rodnan score	13.8 ± 8.6	13.0 ± 10.7	0.77
Dyspnea, no. (%)	15 (83.3)	147 (26.8)	<0.0001
Fatigue, no. (%)	11 (61.1)	182 (33.2)	0.014
Palpitations, no. (%)	6 (33.3)	78 (14.2)	0.037
Syncope or presyncope during exercise, no. (%)	3 (16.7)	15 (2.7)	0.016
Chest pain, no. (%)	1 (5.6)	17 (3.1)	0.45
Lower limb edema, no. (%)	6 (33.3)	37 (6.8)	<0.001
Hepatojugular reflux, no. (%)	4 (22.2)	4 (0.7)	<0.0001
Jugular venous distention, no. (%)	4 (22.2)	6 (1.1)	<0.0001
DLCO, % of predicted	56.2 ± 23.3	72.6 ± 18.0	<0.0004
Patients with DLCO <60%, no. (%)	13 (72.2)	149 (27.2)	<0.0001
PaO_2 + $PaCO_2$, mm Hg	111.3 ± 12.6	127.5 ± 15.1	<0.0001

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).

Hachulla E. *Arthritis Rheum*. 2005;52:3792

Risk factors for death and the 3-year survival of patients with systemic sclerosis: the French ItinérAIR-Sclérodermie study

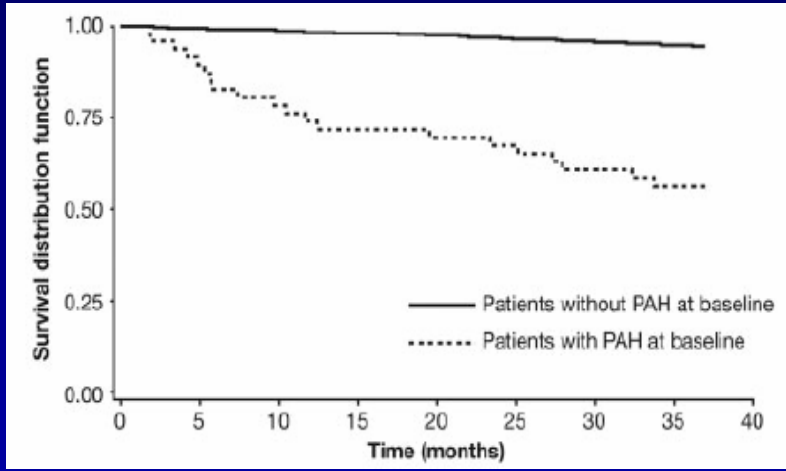


TABLE 2. Causes of death observed in the total population

Causes of death, *n* (%)	All patients (*n* = 546)
Total number of deaths	47 (8.6)
Scleroderma-related causes of death	24 (4.4)
PAH	17
Pulmonary fibrosis	2
Gastrointestinal	2
Renal crisis	3
Non-scleroderma-related causes of death	23 (4.2)
Cancer	8
Infection	4
Cardiovascular or cerebrovascular atherosclerosis	2
Other cause	2
Unknown cause	7

TABLE 3. Risk of death associated with baseline characteristics (univariate analysis)

Parameter	Univariate analysis HR (95% CI)	*p*
Male sex	2.60 (1.41, 4.81)	0.002
Age (per year)	1.06 (1.03, 1.09)	<0.0001
Age at first non-RP symptom (per year)	1.04 (1.02, 1.07)	0.0003
Time since first SSc sign (per year)	1.01 (0.98, 1.05)	0.39
dcSSc	2.21 (1.24, 3.92)	0.007
Rodnan skin score (per 1 point)	1.04 (0.94, 0.98)	<0.0001
Moderate dyspnoea (NYHA FC II)	2.45 (1.29, 4.67)	0.007
Severe dyspnoea (NYHA FC III-IV)	4.15 (1.93, 8.93)	0.0003
VTR ≥2.8 m/s	5.74 (2.81, 11.75)	<0.0001
PAH at baseline	10.41 (5.81, 18.52)	<0.0001
DL_{CO} <60% of predicted (per 1%)	1.05 (1.03, 1.08)	<0.0001
TLC (percentage of predicted)	95 (93, 98)	<0.0001
FVC (percentage of predicted)	96 (94, 98)	<0.0001
Anti-topoisomerase antibodies	0.58 (0.30, 1.14)	0.12
Anti-centromere antibodies	0.56 (0.28, 1.11)	0.10

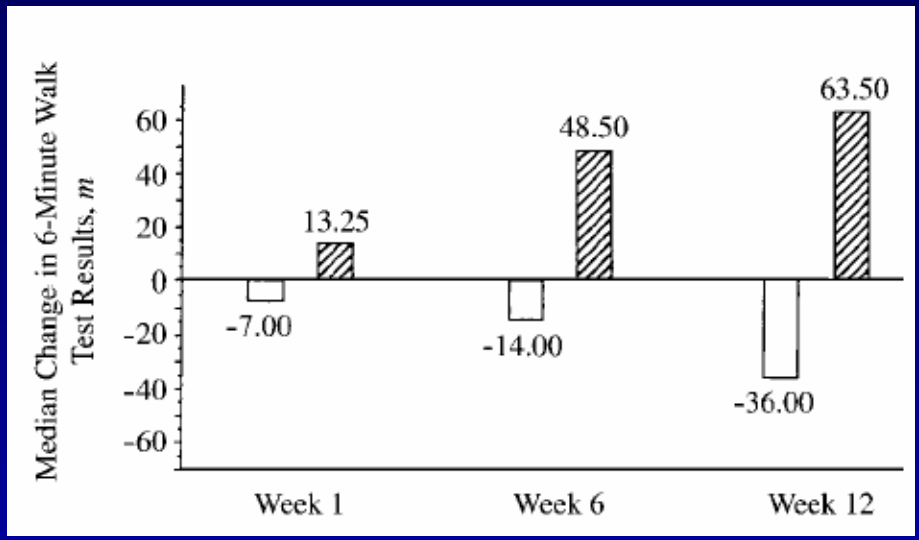
TABLE 4. Risk of mortality associated with baseline characteristics (multivariate analysis)

Parameter		S.E.	χ^2	*P*	HR (95% CI)
Age at first non-RP symptom, years	0.051	0.013	14.440	0.0001	1.052 (1.025, 1.080)
Duration of SSc	0.046	0.019	5.782	0.016	1.047 (1.008, 1.087)
PAH at baseline	1.979	0.302	42.909	<0.0001	7.246 (4.000, 13.158)
Rodnan skin score (per 1 point)	0.0436	0.0104	17.392	<0.0001	1.045 (1.023, 1.066)

- The 3-year Kaplan–Meier survival estimate of 91.1% in the ItinérAIR-Sclérodermie population is reduced to 56.3% among patients with baseline PAH.
- A Doppler echocardiographic VTR ⩾2.8 m/s is a strong predictor of death.

Hachulla E. *Rheumatology*. 2009

Esclerodermia. Hipertensión arterial pulmonar. Tratamiento



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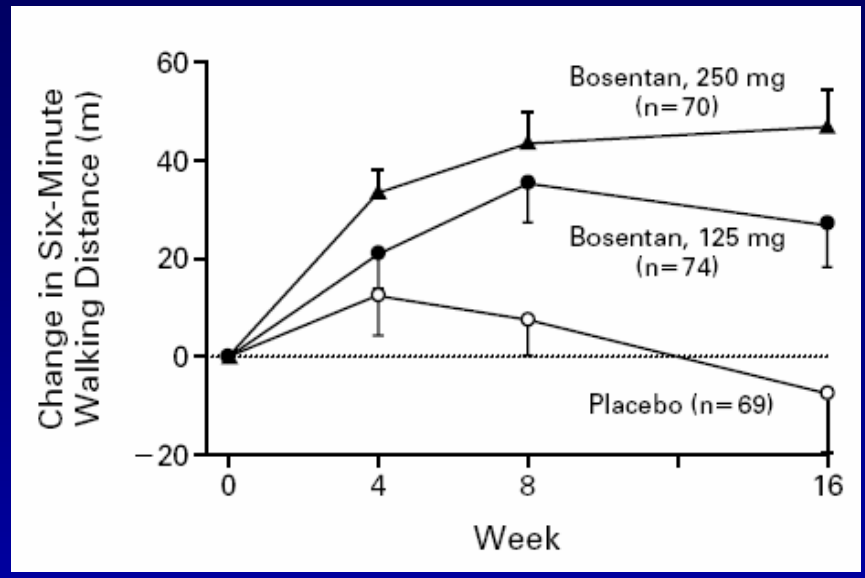

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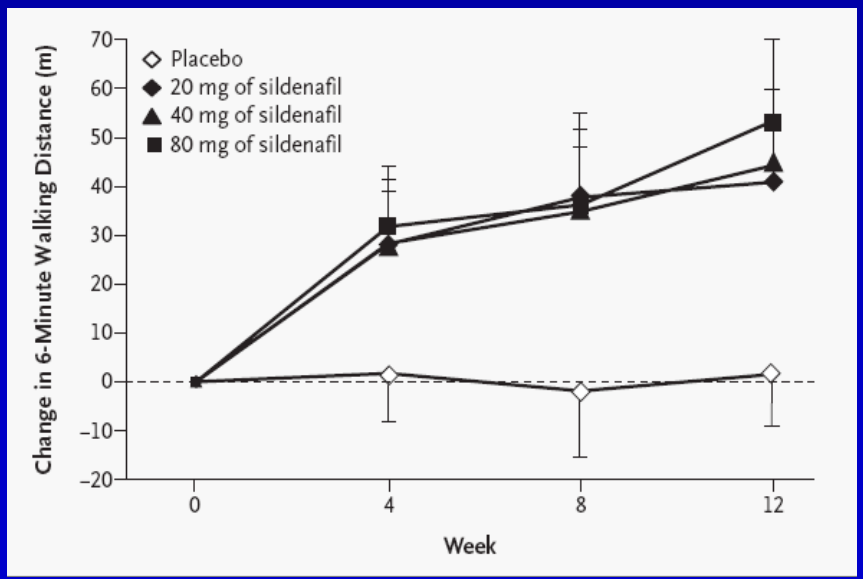
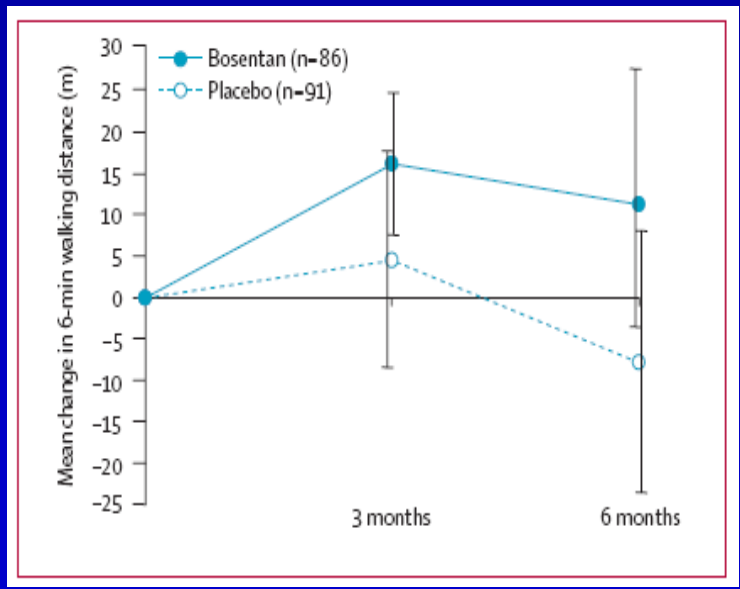


Galiè N et al. N Engl J Med 2005;353:2148

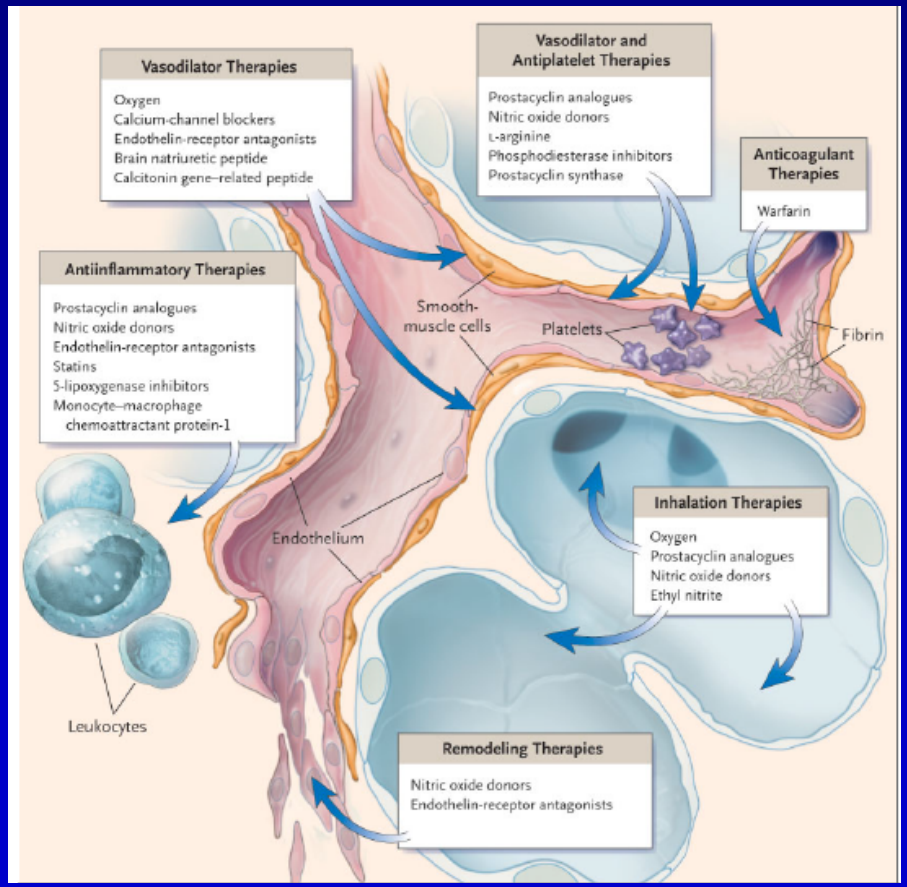


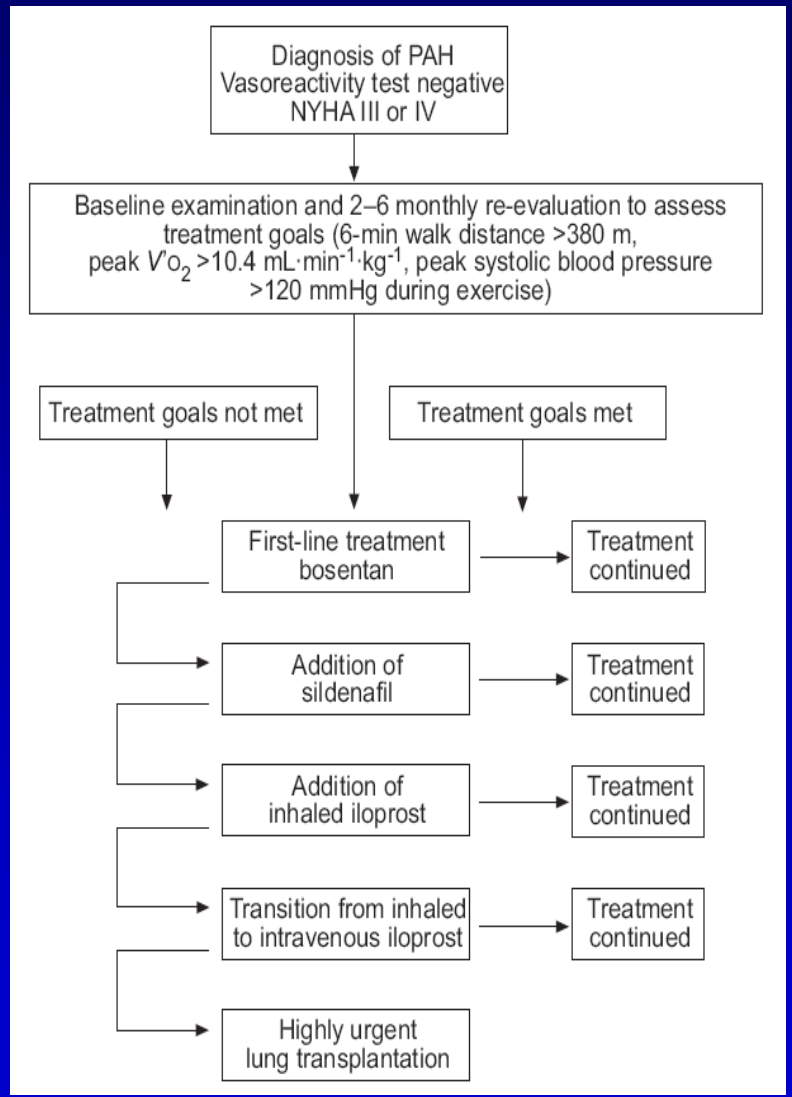
Galiè N et al.(EARLY study) Lancet 2008;371:2093-2100

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

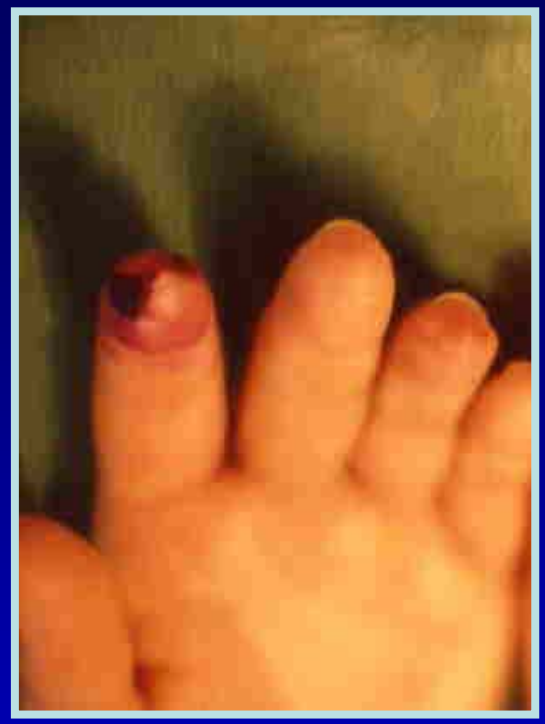
Goal-oriented treatment and combination therapy for pulmonary arterial hypertension

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





ESCLERODERMIA
Manifestaciones clínicas



N: 348

Fenómeno de Raynaud: 346 (99%)

Úlceras digitales: 171 (49%)

Afección osteomuscular: 245 (70%)

Afección digestiva: 249 (71%)

Afección respiratoria: 261 (75%)

EPID: 195 (56%) (CVF<70%: 84 (24%)

HTAP: 66 (19%) (HTAP (s> 55mmHg): 32 (9.7%)

Afección cardíaca: 164 (47%)

Afección renal (CRE): 14 (4%)

RAPIDS-1 AND RAPIDS-2

	RAPIDS-1		RAPIDS-2	
	16 weeks		24 weeks	
	Bos	Pbo	Bos	Pbo
Patients (n)	79	43	90	98
Ulcers at baseline (%)	1.9	2.2	3.7	3.6
New DUs (n)	1.4	2.7	1.9	2.7
	-48% (p=0.008)		-30% (p=0.035)	
Healing	NS		NS	

Kom JH et al. *Athritis Rheum*. 2004;50:3985-3993.
Seibold J, EULAR 2006.
Pope J. ACR 2006.

ESCLERODERMIA. Tratamiento

Terapia vascular

Bloqueadores Ca
Antiagregantes
IECAs
Ketanserina
Fluoxetina
ARA II
Prostaglandinas
Sildenafilo
Antioxidantes
Sitaxsentan
Ambrisentan
Bosentan

Terapia antifibrótica

D-penicilamina
Interferon-α
Interferon-γ
Relaxina
Imatinib
Halofuginona

Terapia inmunológica

Ciclofosfamida
Metotrexato
Azatioprina
Ciclosporina
G. Antimocítica
G. Antilinfocítica
Fotoféresis
Trasplante MO
Colágeno oral
Anti-citocinas
Micofenolato
Glucocorticoides

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