Sclérodermie systémique: introduction, quels examens réaliser

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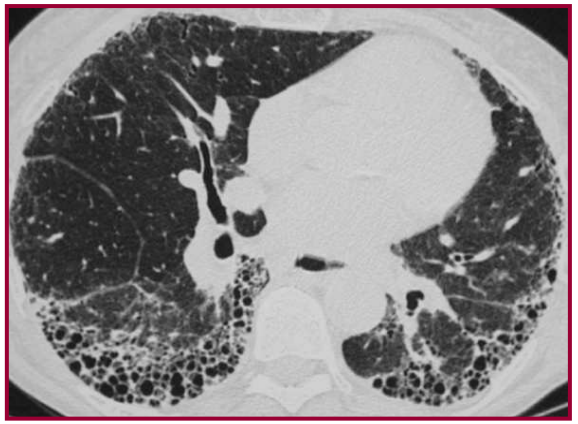
Conflicts of interest

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

SCLÉRODERMIE SYSTÉMIQUE

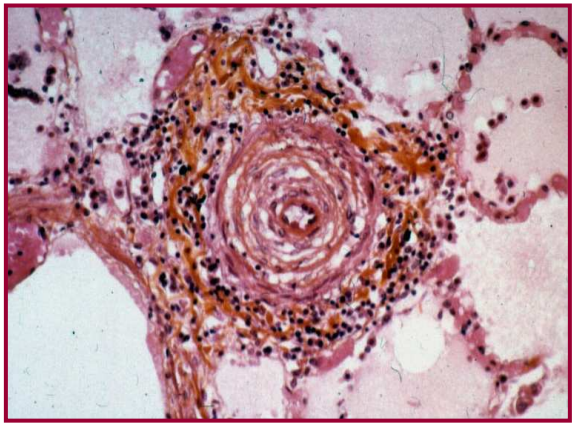
➢Fibrose

Peau
Poumon
Appareil digestif
Coeur



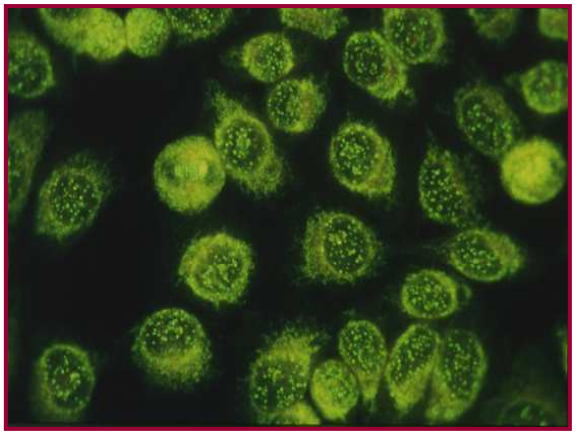
➢Hyperréactivité vasculaire

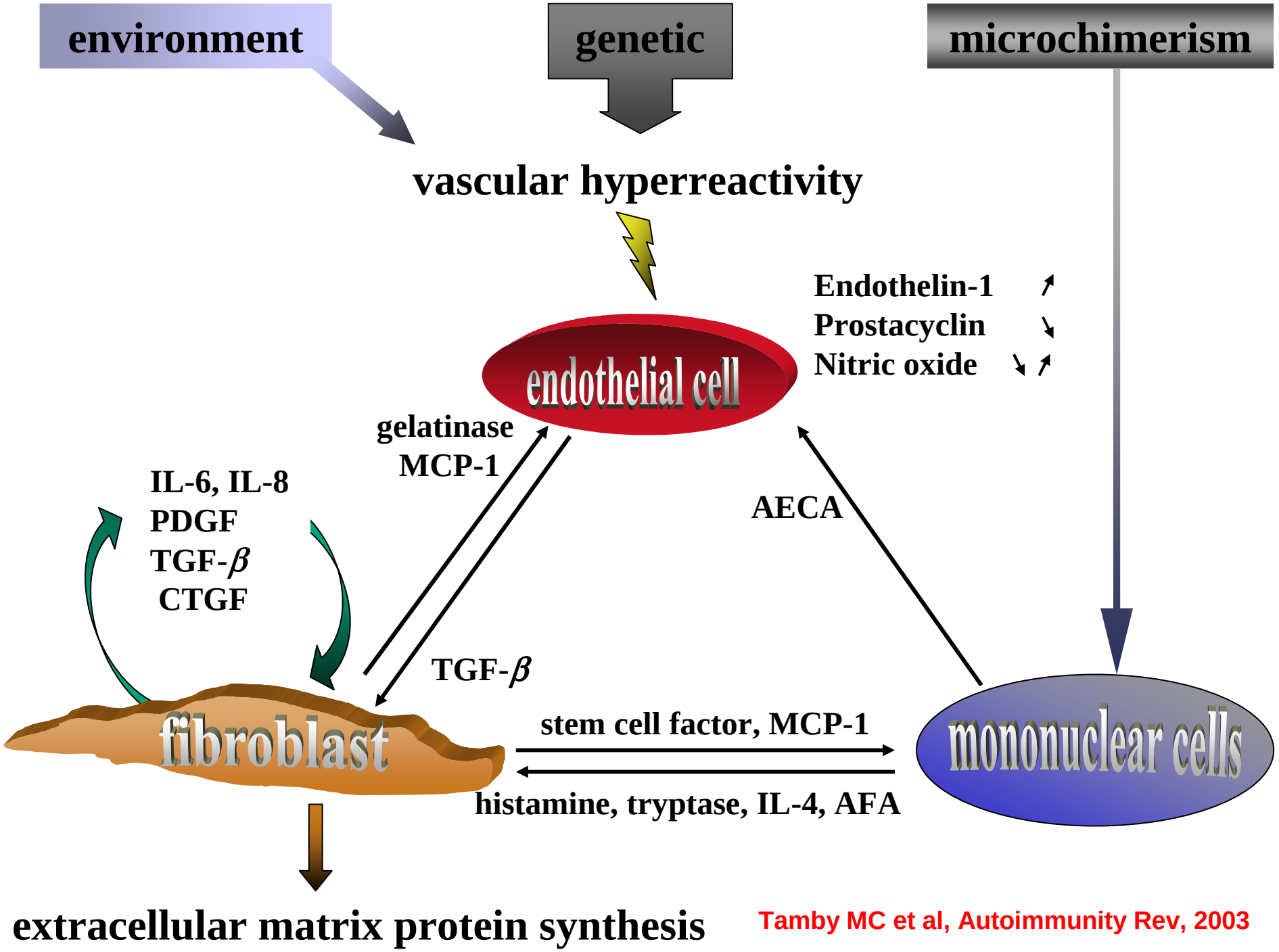
Syndrome de Raynaud
Crise Rénale
Hypertension artérielle pulmonaire



➢Autoimmunité

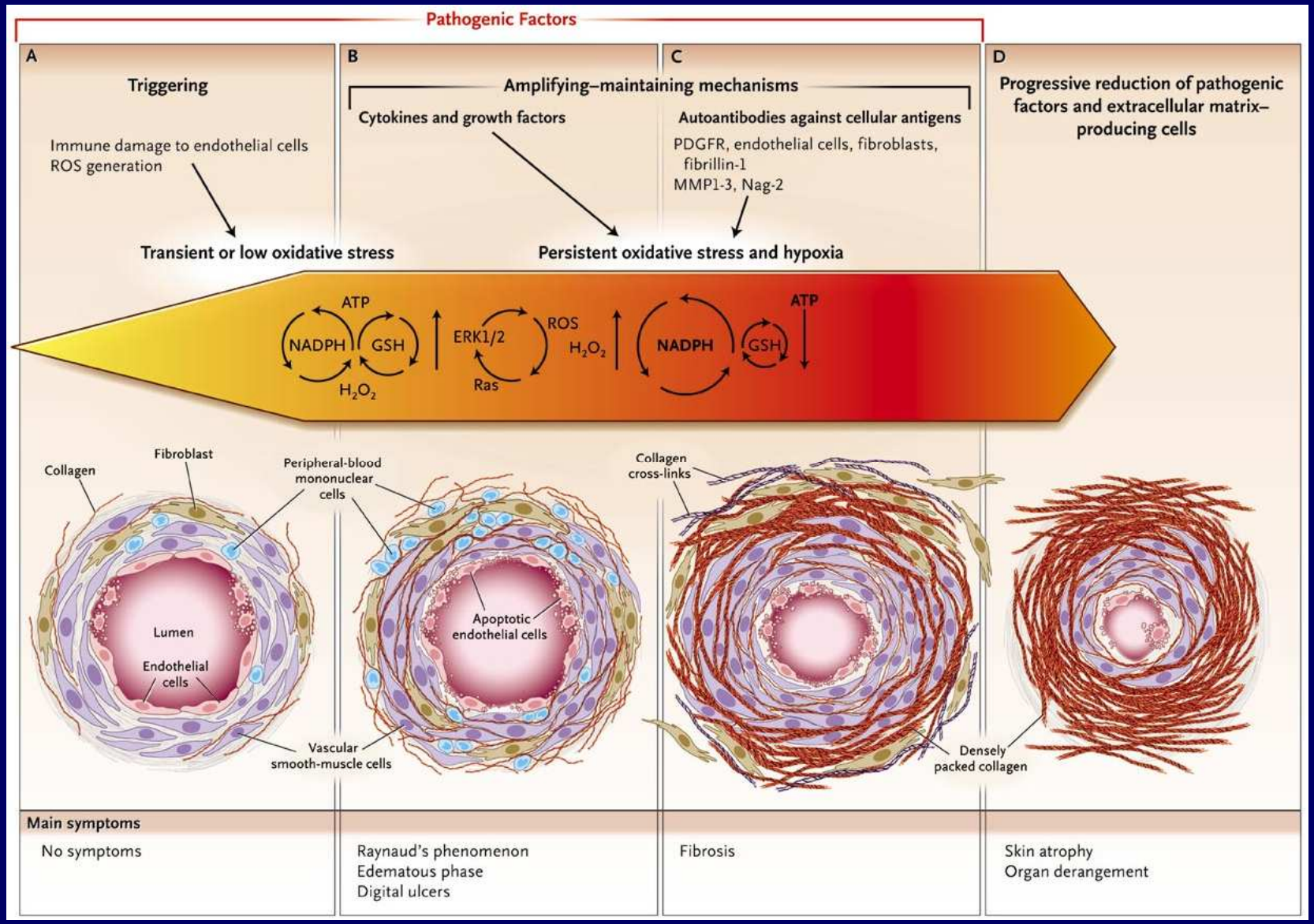
Autoanticorps
Anti-Scl70
Anti-centromère
Anti-ARNPolIII





Tamby MC et al, Autoimmunity Rev, 2003

Systemic sclerosis: lesions at different stages



Gabrielli A. *NEJM* 2009

Prévalence

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

Critères diagnostiques de sclérodermie systémique

Arthritis Rheum, 1980

Critère majeur

Sclérose cutanée proximale

Critères mineurs

Sclérodactylie

Cicatrices digitales, pertes de substance

Fibrose pulmonaire des bases

Sclérodermie systémique si un critère majeur ou deux critères mineurs

Criteres de classification des formes débutantes de SSc

Sclérodermie systémique limitée

- **Phénomène de Raynaud**

+

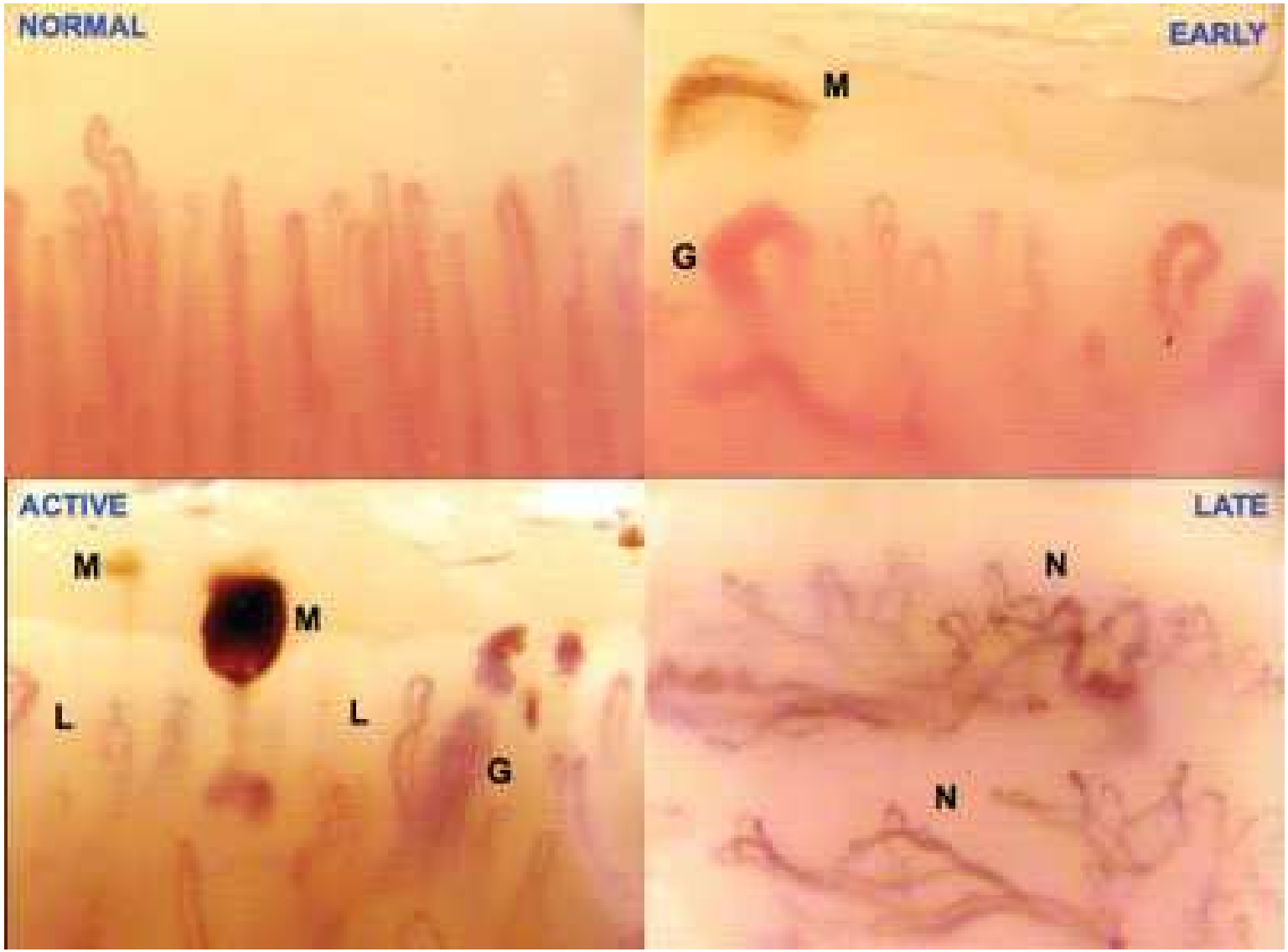
- **Soit anomalie capillaroscopique**
- **Soit Ac spécifique de la Sclérodermie systémique (anti-centromere, anti-topoisomérase 1, anti-fibrillarine, anti-PMScl, anti-fibrilline, anti-RNA pol I ou III à un titre 1/100)**

Sclérodermie systémique cutanée limitée

En plus des critères précédents, infiltration distale, en aval des coudes et des genoux

Leroy & Medsger, Rheumatology, 2001

Specific microvascular changes that characterize the different nailfold videocapillaroscopic SSc patterns



Herrick A & Cutolo M A&R 2010

Clinical classification of SSc

Diffuse cutaneous SSc

- Skin sclerosis proximal to elbows and knees
- Inflammatory features prominent in 1st 3 years
- Anti-Scl-70 or anti-RNA polymerase
- Increased frequency of interstitial lung disease, renal crisis, bowel & cardiac involvement

Limited cutaneous SSc

- No skin sclerosis proximal to elbows and knees
- Anti-centromere antibody (ACA)
- CREST subgroup
- Lung fibrosis, renal crisis & cardiac involvement less common than in dcSSc

Scleroderma sine Scleroderma

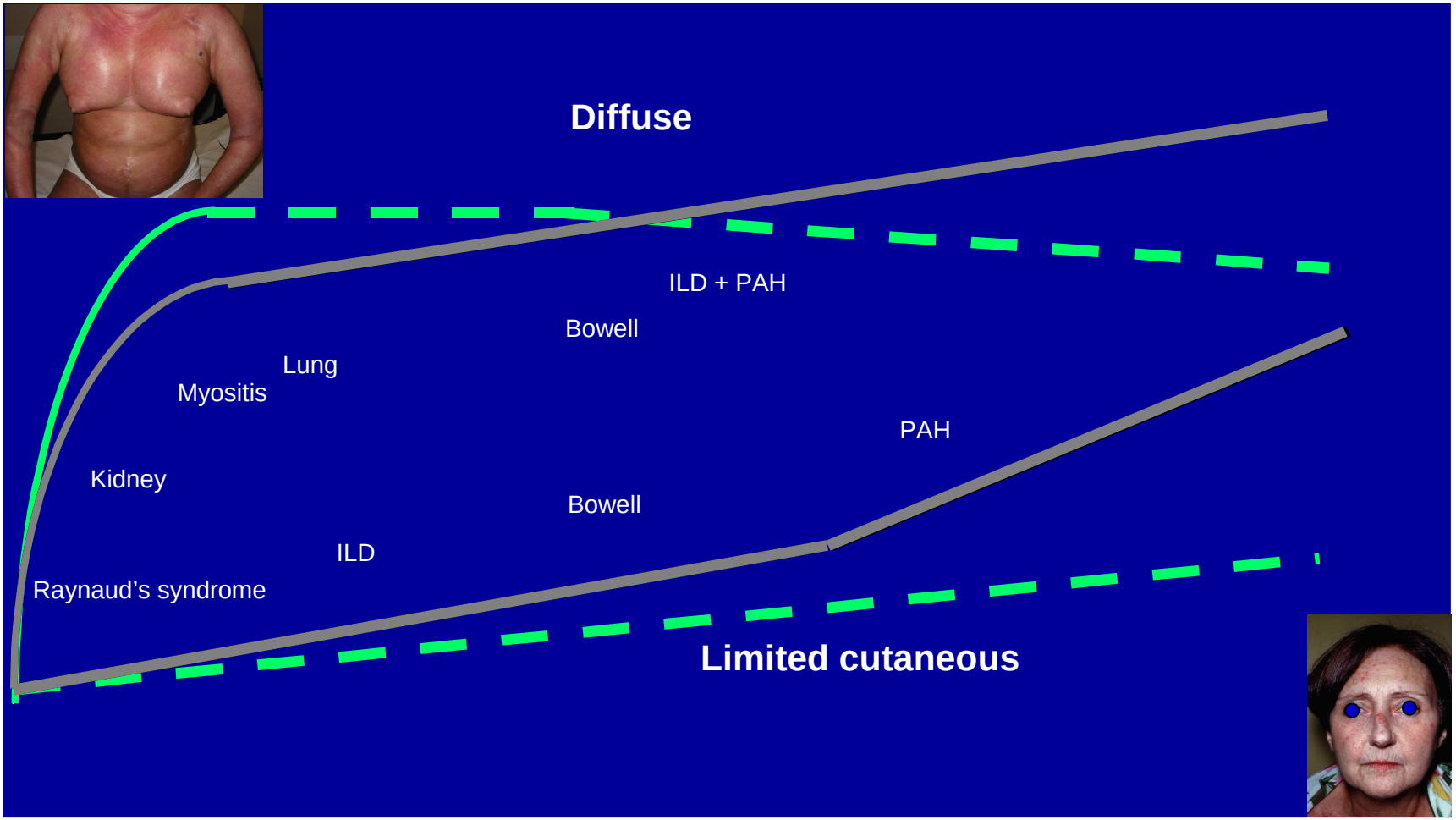
- No skin sclerosis

Overlap syndrome

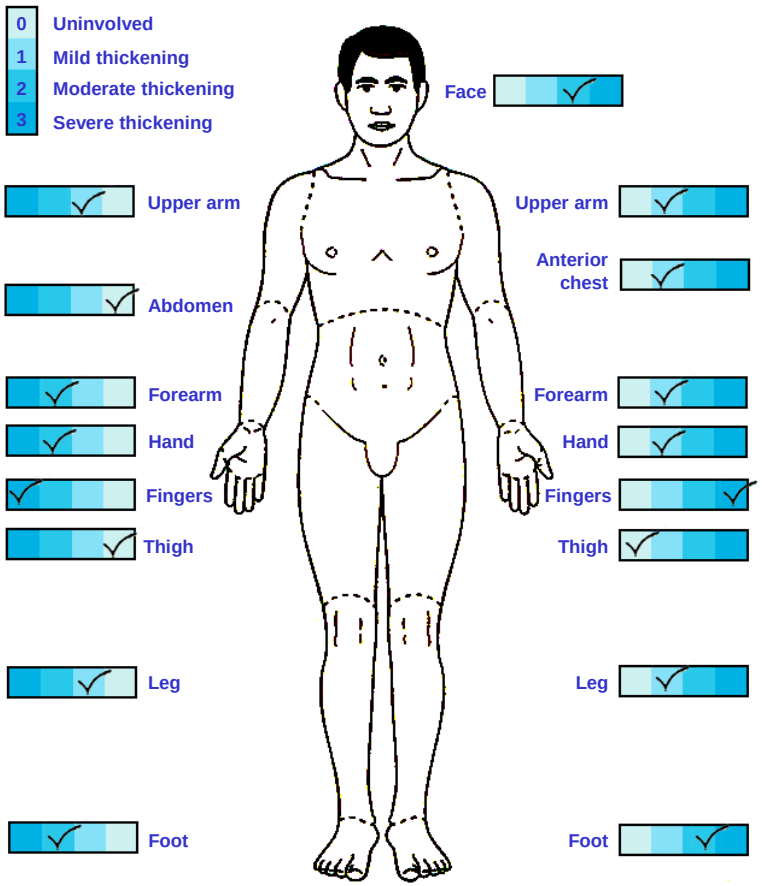
- Features include those of lcSSc or dcSSc with those of other autoimmune disease(s)

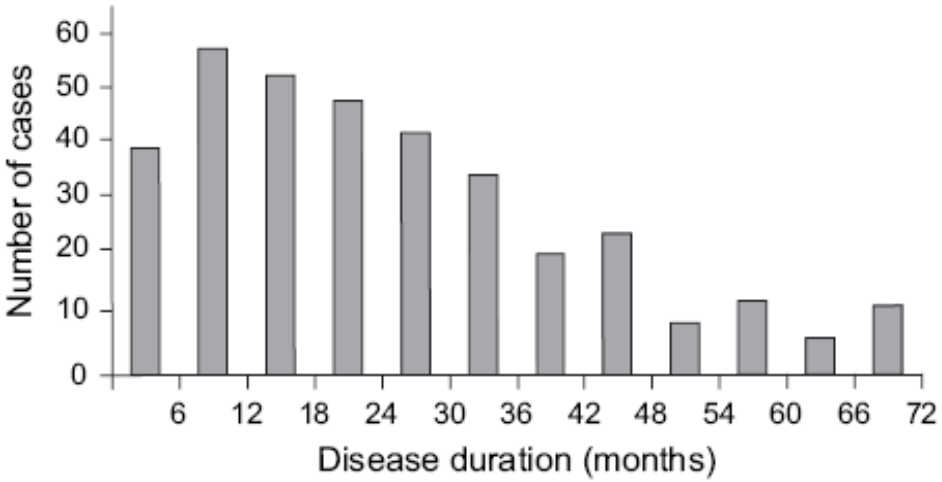
Poormoghim H, *et al. Arthritis Rheum* 2000; 43:444-51,
Denton CP and Black CM, *Trends Immunol* 2005; 26:596-602.

SYSTEMIC SCLEROSIS : EVOLUTION



The modified Rodnan skin score (MRSS)



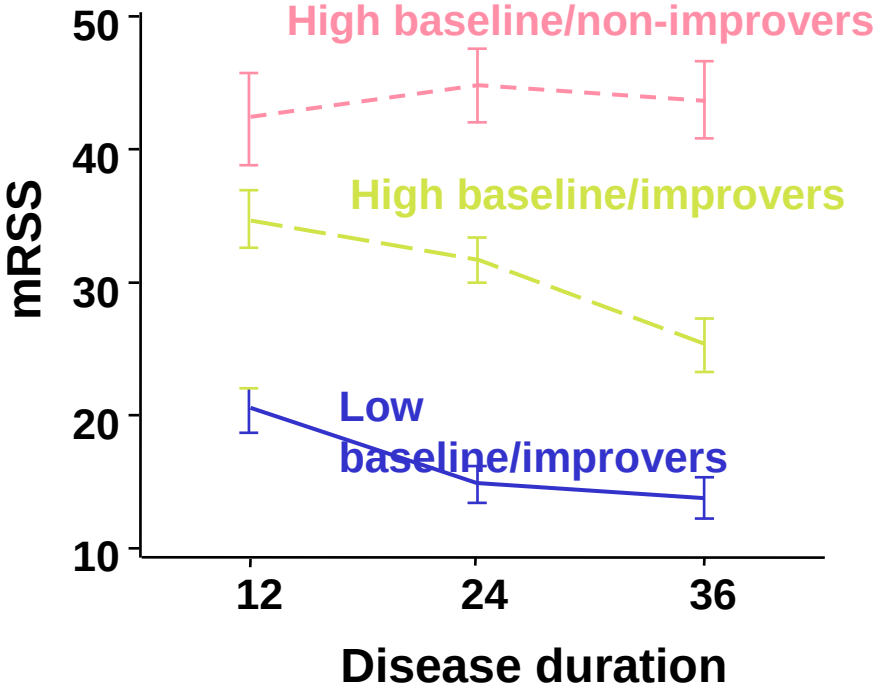


Disease duration at peak skin score of the patients who had dcSSc from the Royal Free Hospital scleroderma database.

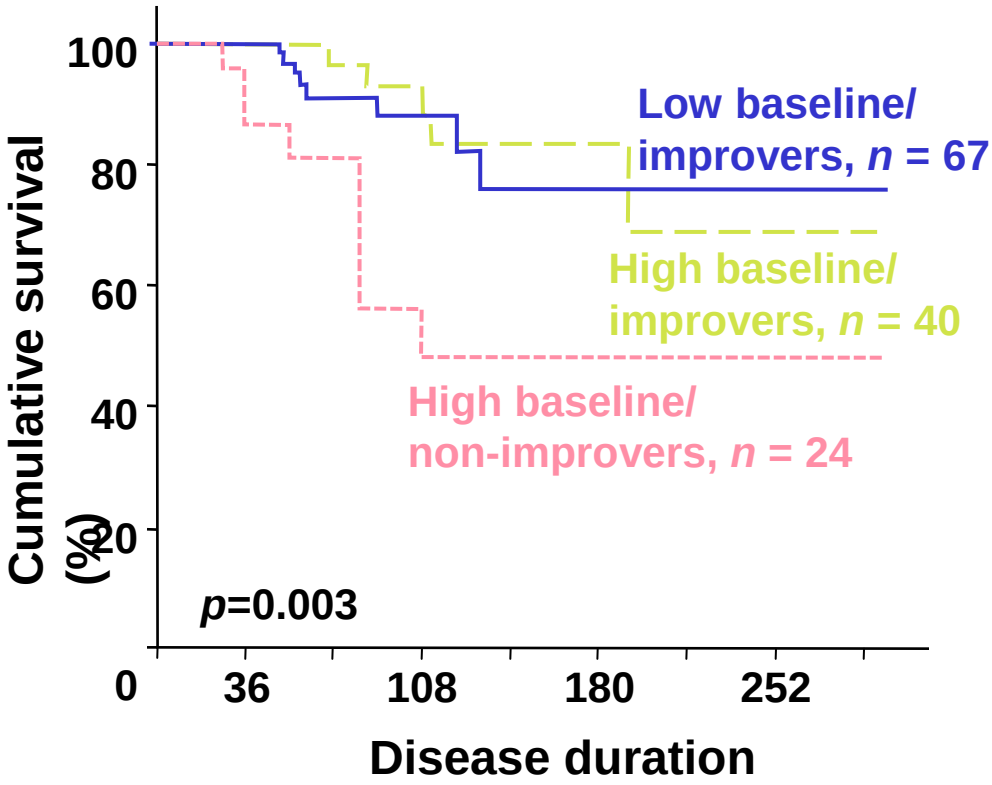
Nihtyanova SI, Denton CP. Rheum Dis Clin N Am 34 (2008) 161–179

Disease duration and skin score in dcSSc

Change in skin score over 3 years in the subgroups



Survival in the subgroups



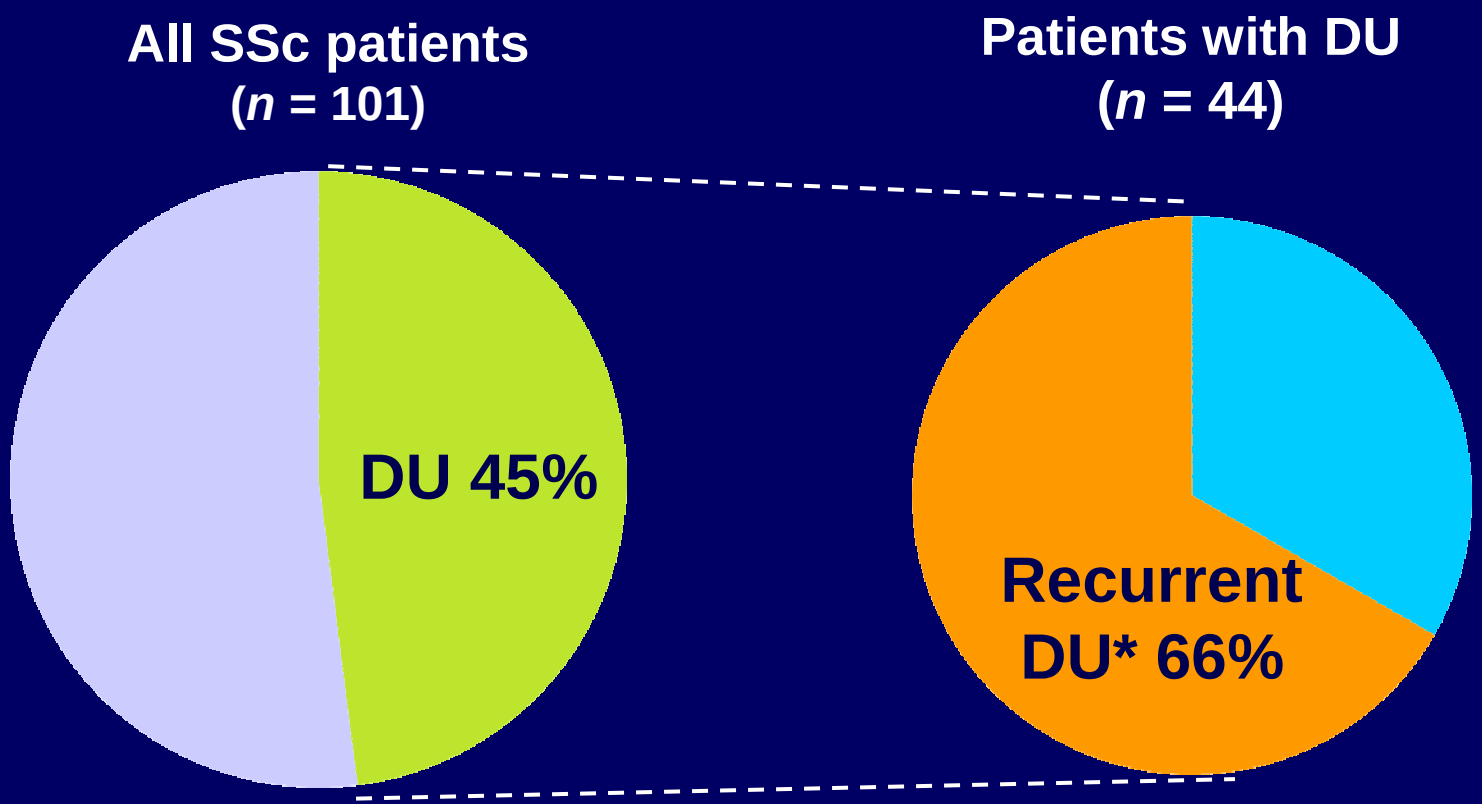
Shand L, *et al. Arthritis Rheum* 2007; 56:2422-31.

Prevalence of visceral involvement in SSc

	Total	Missing data	lcSSc	dcSSc
Number of patients, *n* (%)	1483 (100)	0 (0)	674 (45.5)	484 (32.7)
Percentage of organ involvement by SSc subsets				
RP	94.4	0.1	96.3	94.2
Skin involvement	87.8	0.3	91.5	97.6
PAH	15.8	0.1	14.9	18.5
Pulmonary fibrosis	34.5	0.1	20.8	56.1
Oesophagus	60	0.1	59.2	69.3
Stomach	14.2	0.2	15.3	15.6
Intestine	5.7	0.2	6.1	5.3
Kidney	10.5	0.2	9.1	15.9
Heart	14.6	0.2	12	23
Musculoskeletal system	47.5	1.4	44.9	56.6
Nervous system	6.4	2.2	4.1	7.1
Sicca-symptoms	39.5	2.5	43.5	39.7
Masticatory organ	24.1	7.2	23.7	34.1

Hunzelmann N, *et al.* *Rheumatology* 2008; 47:1185-92.

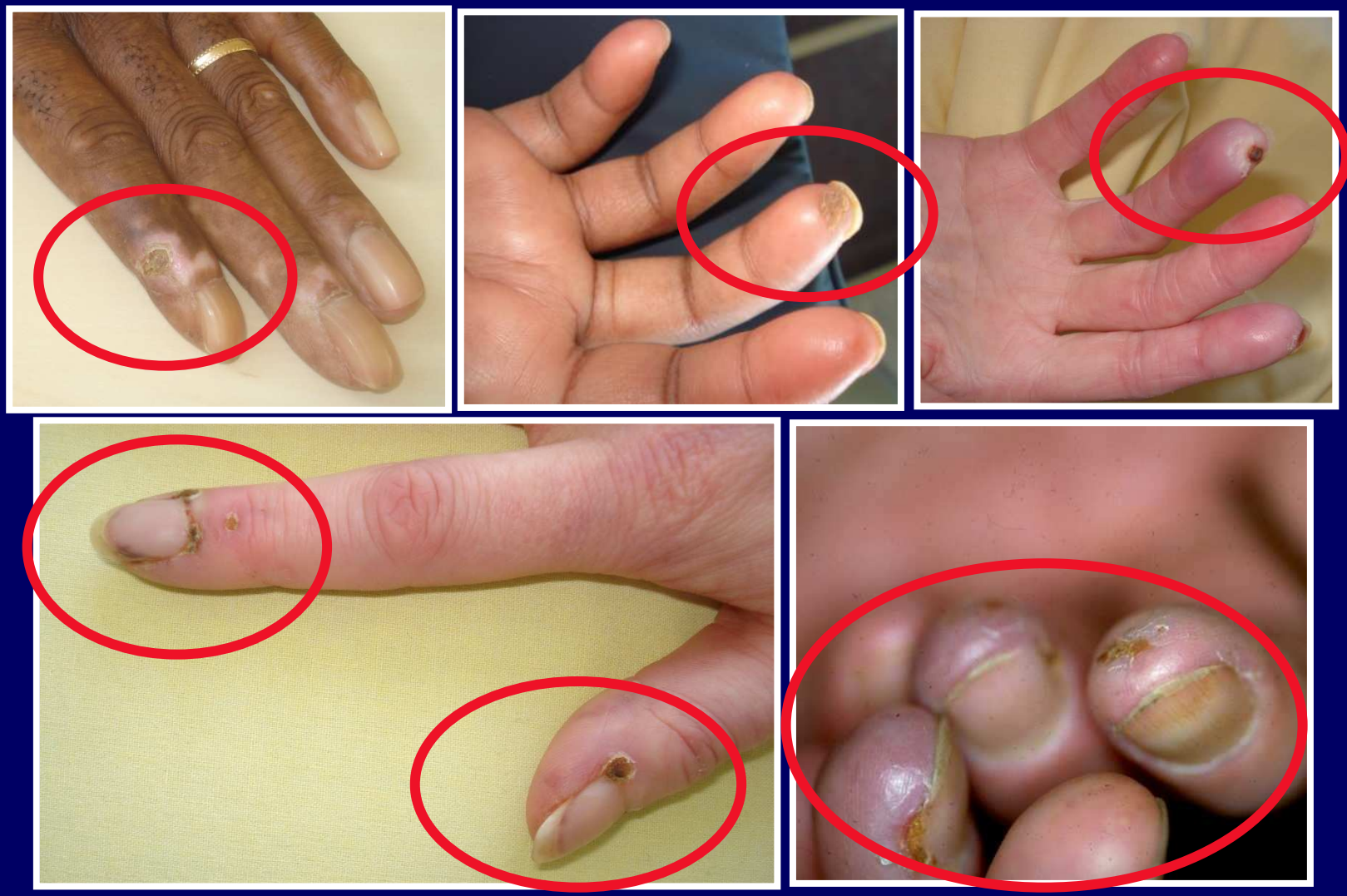
DU are a common and recurrent manifestation of SSc



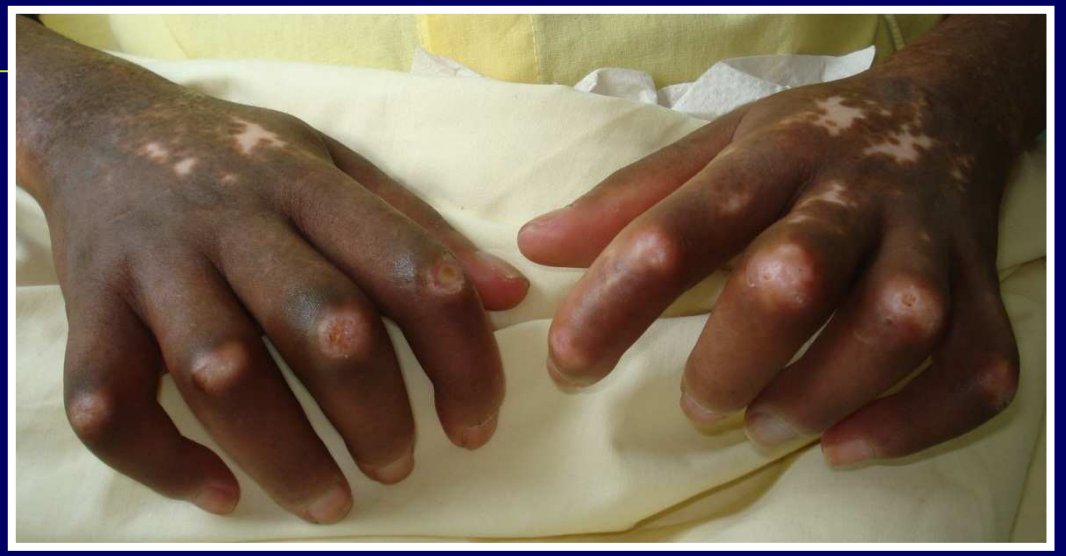
*Recurrent DU: Having more than one DU after the first DU

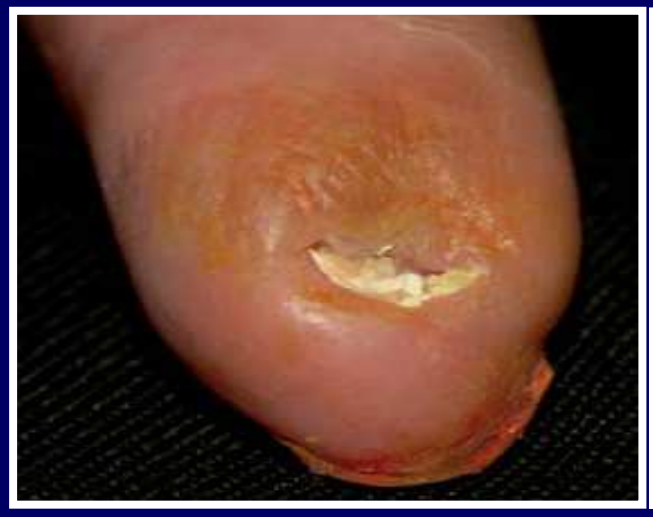
Hachulla E, *et al*. *J Rheumatol* 2007; 34:2423-30.

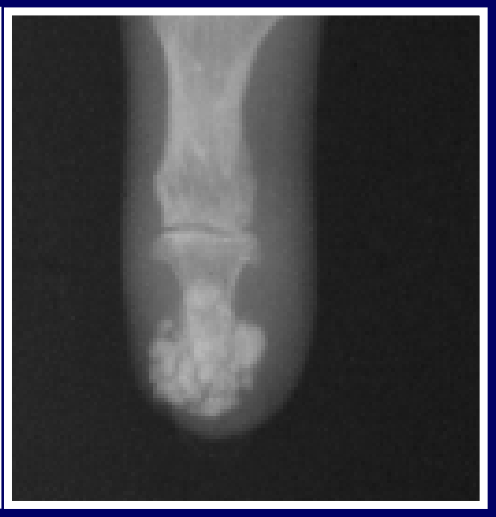
Digital ulcers: Vascular mechanisms



Calcinosis/mechanical

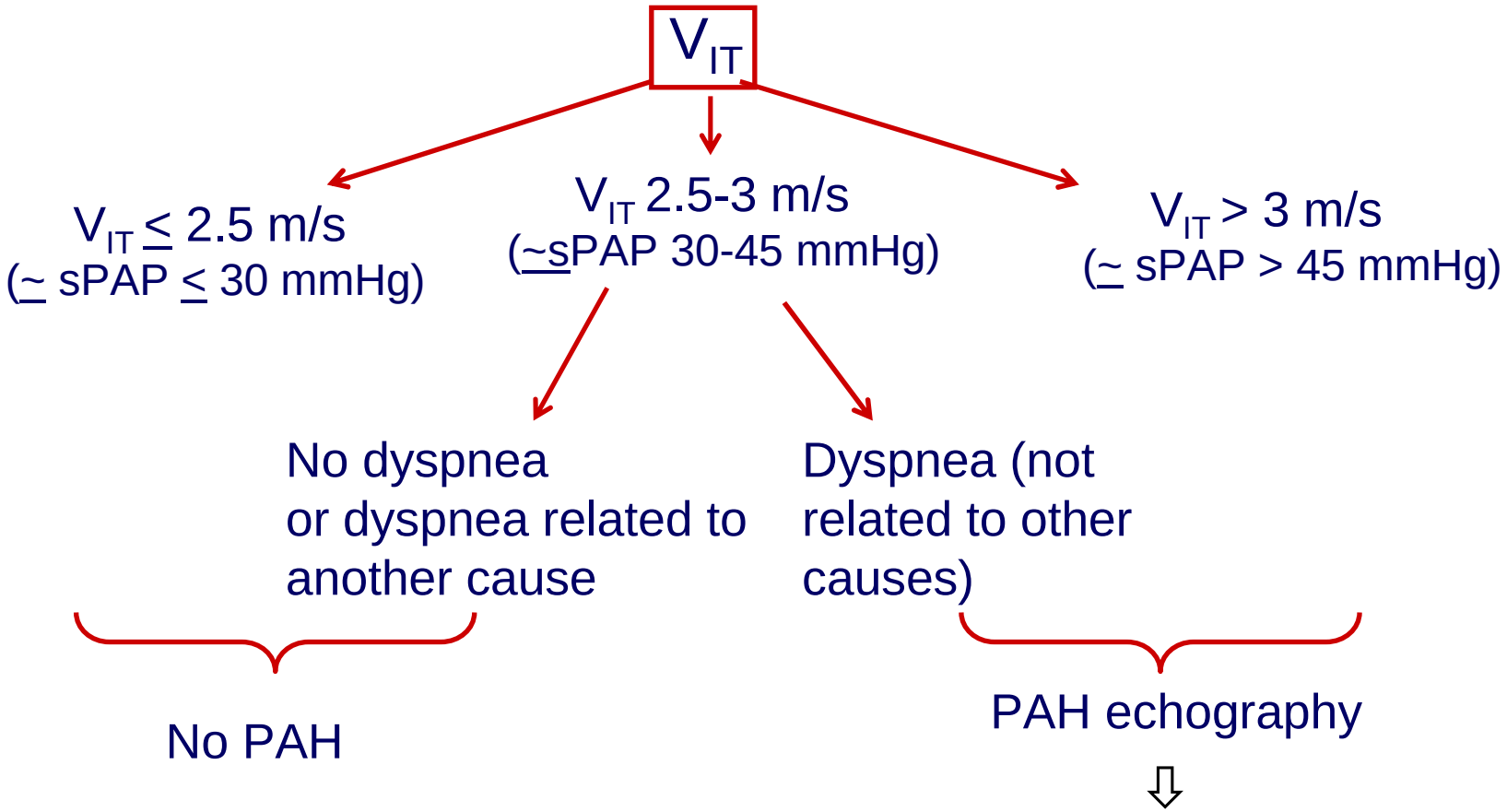






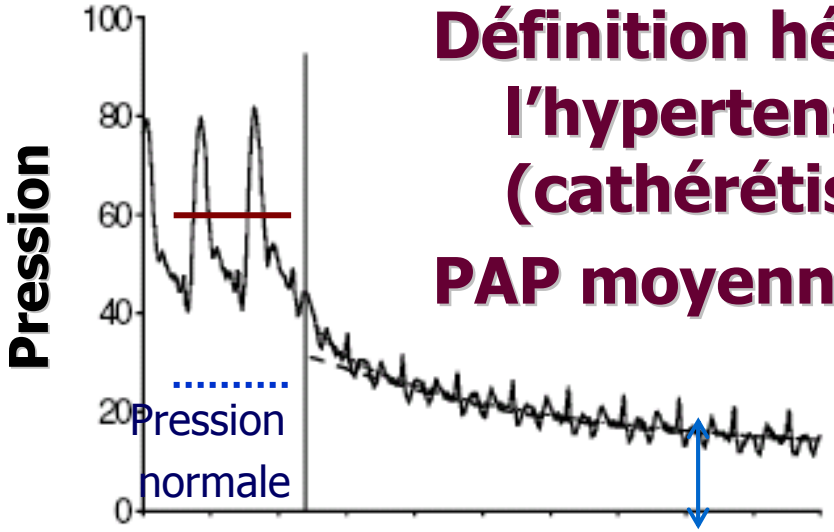
Actelion France Brochure DU in SSc.

Cardiac EchoDoppler
PAH definition



Hachulla et al. Arthritis Rheum 2005

HTAP: définition



Définition hémodynamique de l'hypertension pulmonaire (cathérétisme droit)

PAP moyenne > 25 mmHg au repos

Définition hémodynamique de l'hypertension artérielle pulmonaire (cathérétisme droit):

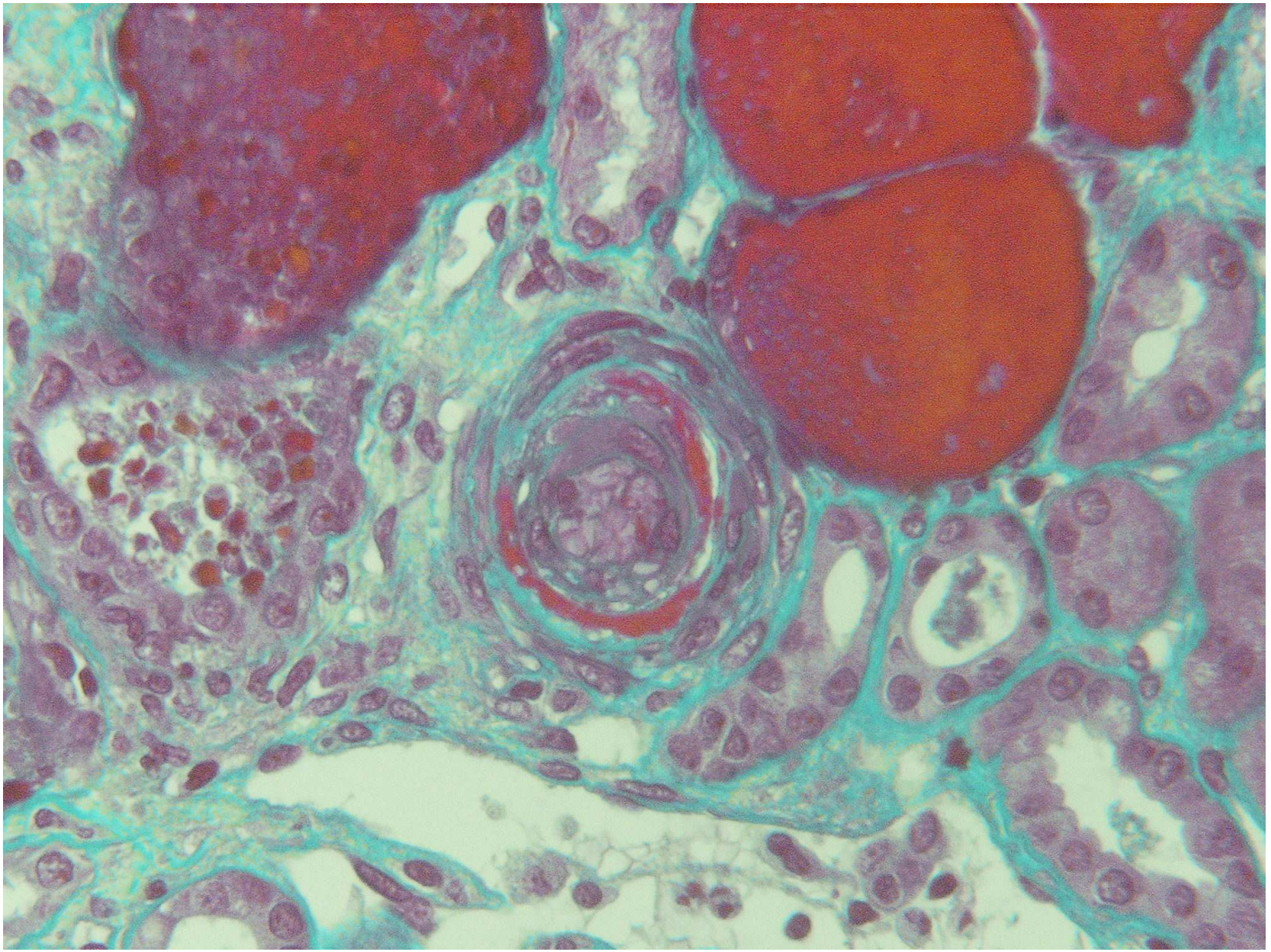
- PAP moyenne > 25 mmHg au repos
Et
- Pression capillaire pulmonaire < 15 mmHg au repos

Galiè N et coll. Eur Heart J. 2009 & Eur Resp J 2009

Scleroderma renal crisis

- Scleroderma renal crisis (SRC) occurs in 5% scleroderma patients :
  - 10-20% of patients with diffuse SSc
  - About 1% in limited cutaneous forms (Steen 2003).
- Two time periods :
  - Before ACEi : less than 10% survival at 1 year.
  - After ACEi: 65% survival at 5 years.
- In a recent work from the EUSTAR group data base, it is reported to have decreased to less than 5% (Walker UA et al. Ann Rheum Dis 2007) and less than 2% in patients with limited cutaneous SSc (lcSSc).

Interlobular artery with mucoid changes and concentric intimal fibroplasia with so-called « onion-skinning changes ».



Sclérodermie systémique: atteinte cardiaque

•Le plus souvent occulte

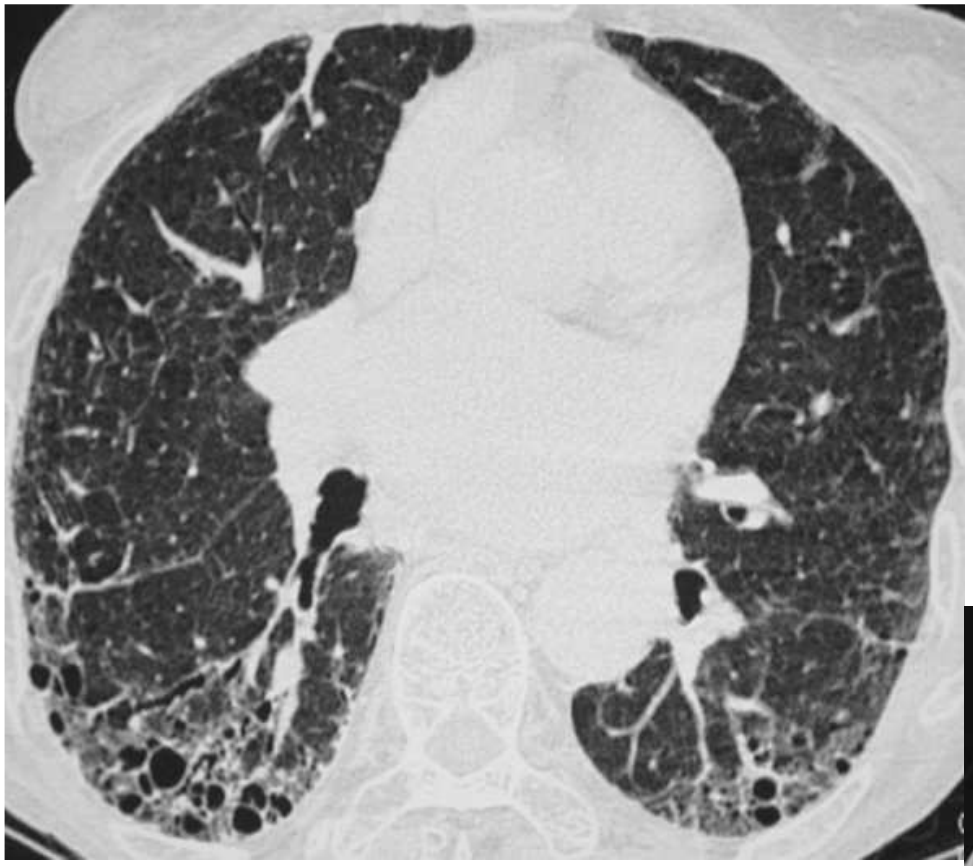
• Peut être secondaire à :
- une atteinte rénale (hypertrophie ventriculaire gauche)
- une fibrose pulmonaire ou une hypertension artérielle pulmonaire (hypertrophie ventriculaire droite)

• Une atteinte cardiaque symptomatique est de mauvais pronostic.

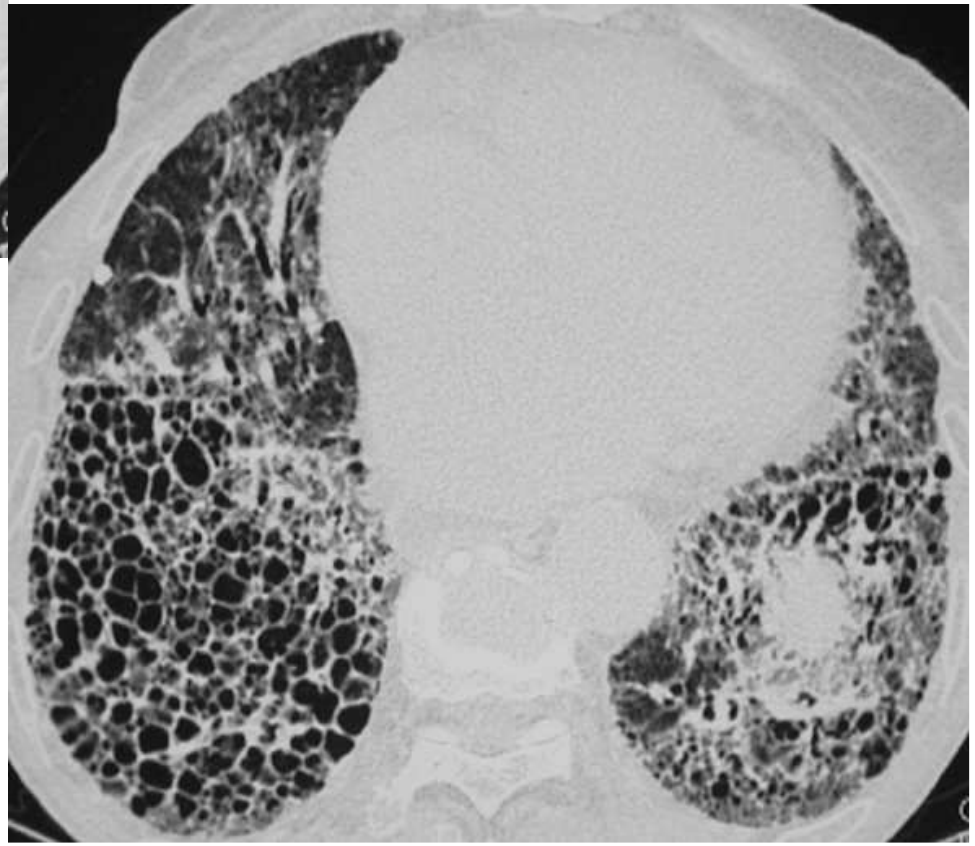
•Depistage: ECG, Echo cœur….
•IRM cardiaque

Examens complémentaires: PID

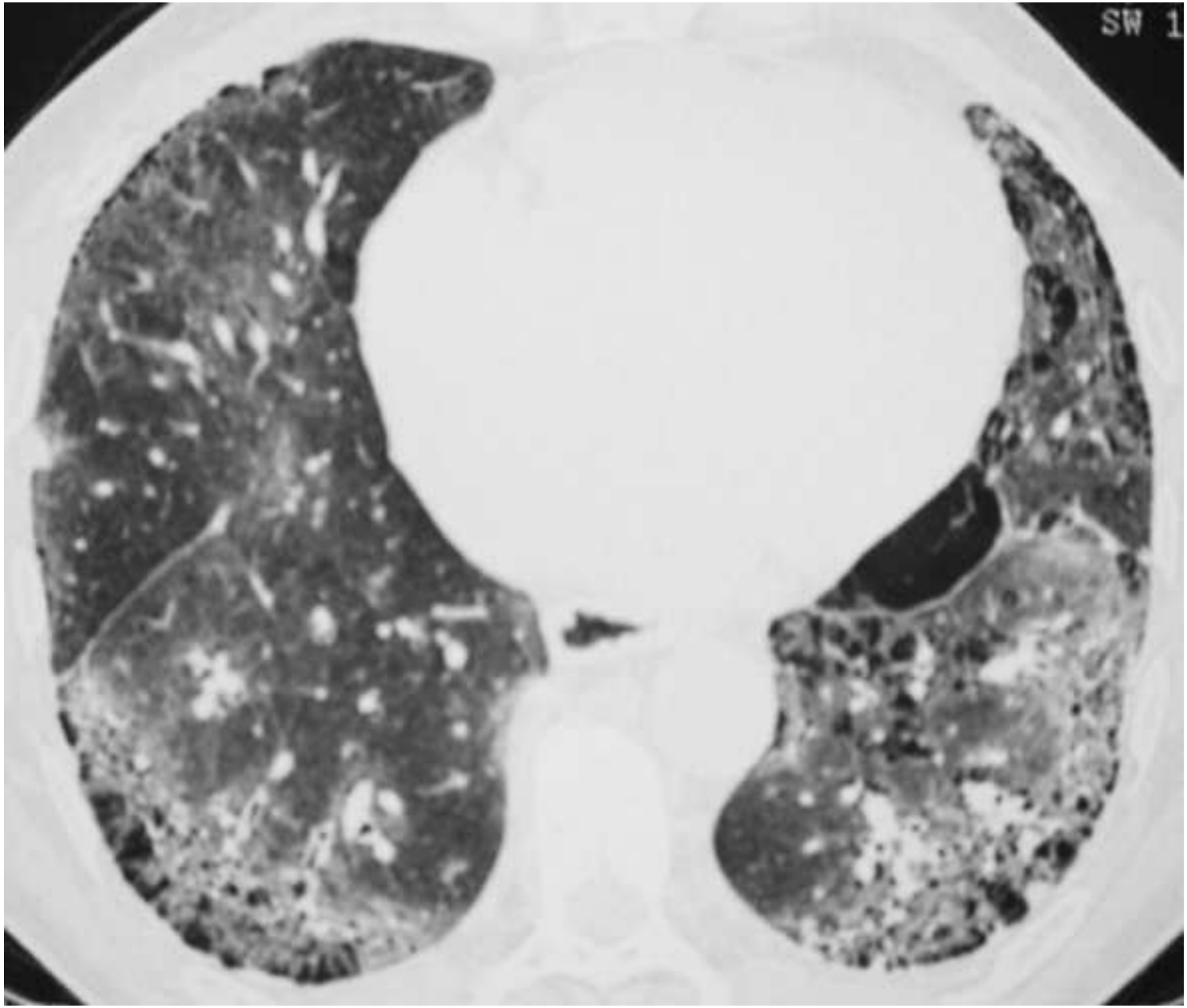
- Le mauvais pronostic de la PID au cours de la ScS impose son **dépistage systématique**.
- Pas de recommandations consensuelles sur les examens de dépistage et la fréquence à laquelle les renouveler.
- Le bilan doit comporter:
  - tomodensitométrie thoracique haute résolution (TDMHR)
  - épreuves fonctionnelles respiratoires (EFR) avec mesure du coefficient de transfert du monoxyde de carbone (DLCO)
  - test de marche de 6 min avec mesure de la saturation en oxygène et l'estimation de la dyspnée à l'aide de l'indice de Borg.



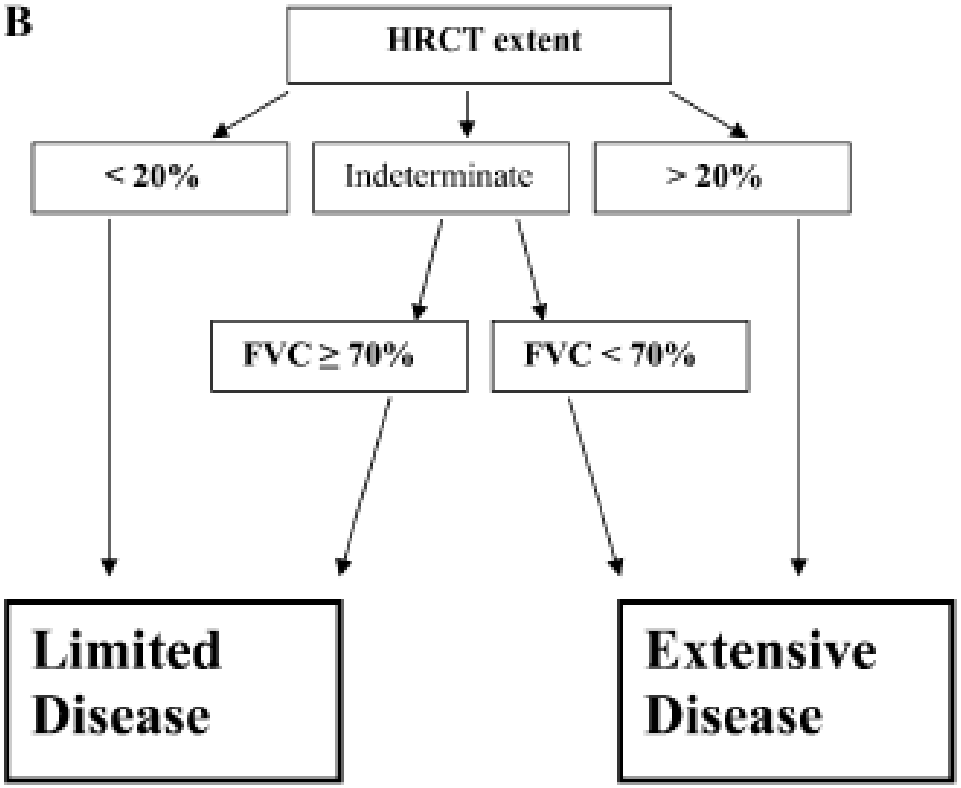
Usual interstitial pneumonia

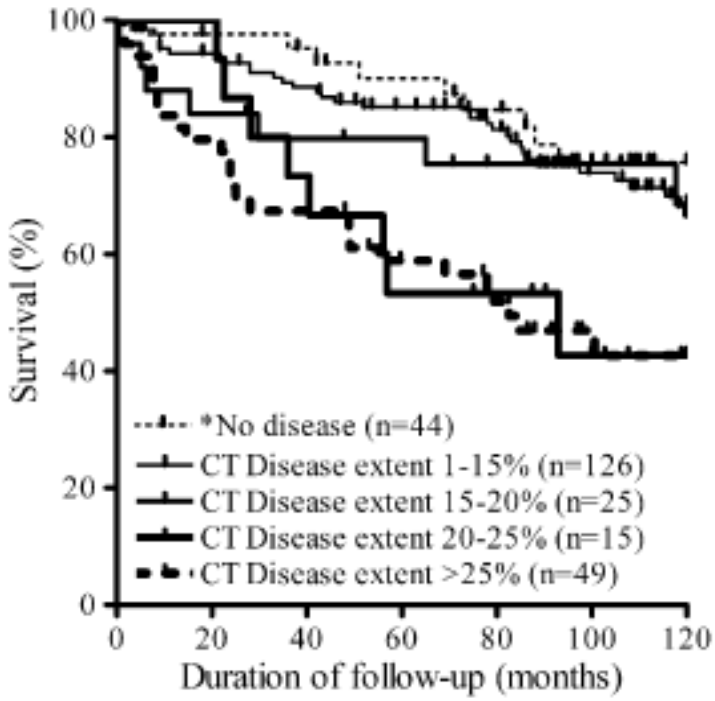


Non specific interstitial pneumonia



Interstitial Lung Disease in Systemic Sclerosis
A Simple Staging System
Goh NSL, AJRCCM 2008

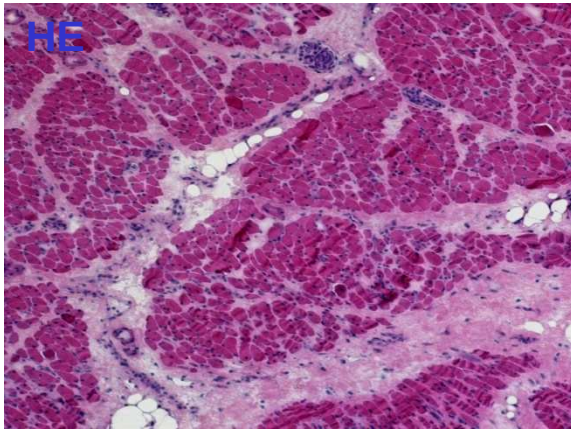


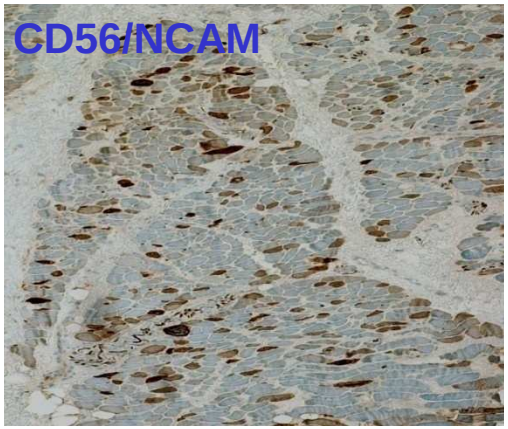


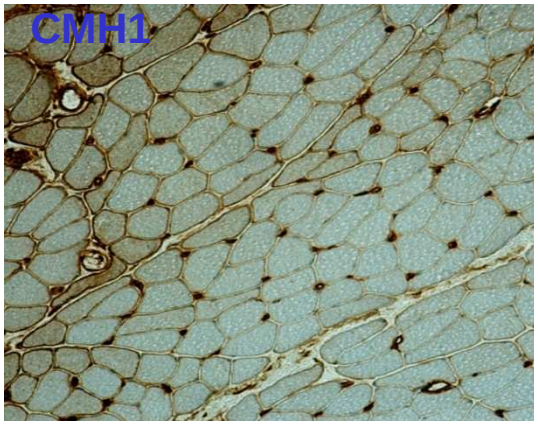
Atteintes digestives: quelles explorations

- Œsophage: FOGD, manométrie
- Estomac: FOGD, scintigraphie
- Grêle: recherche malabsoption, manométrie, TDM…. Transit du grêle
- Colon: TDM
- Anus-rectum: manométrie ano-rectale

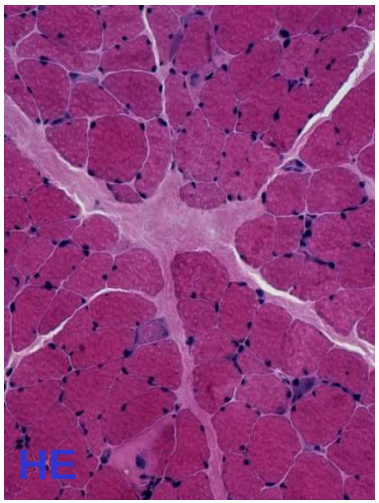
Myopathological features of SSc-related myopathy



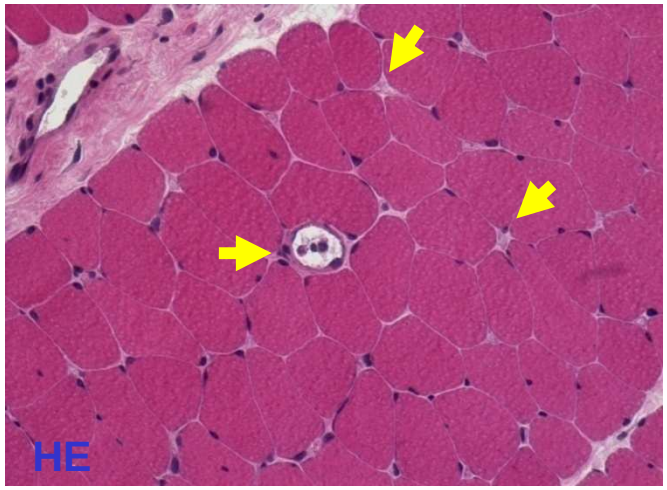


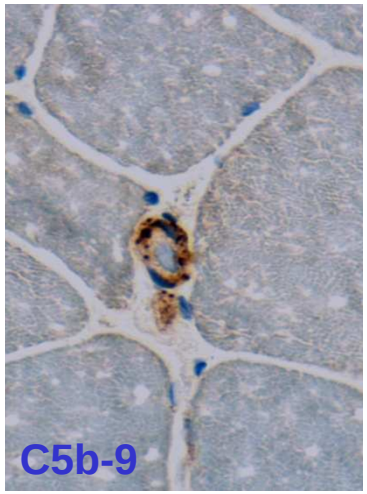


Myofiber injury



Interstitial fibrosis



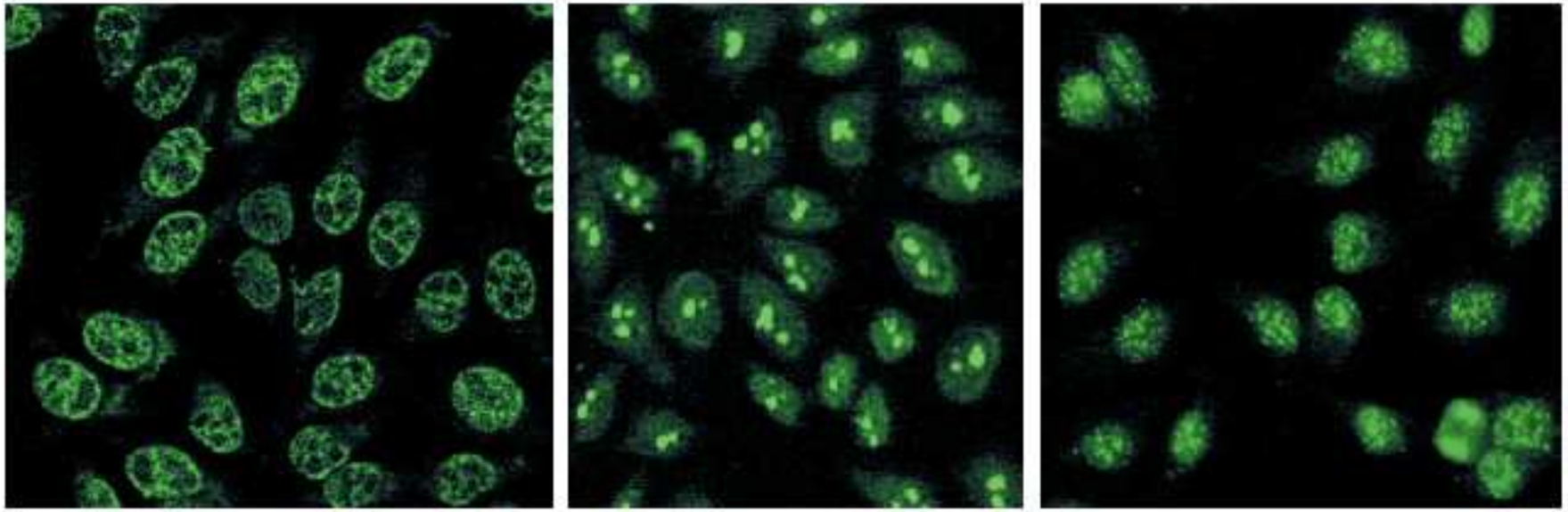


Microangiopathy

Ranque B, *et al*. *Ann N Y Acad Sci* 2007; 1108:268-82.

Autoantibodies in scleroderma

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		

Gabrielli A, *et al. N Engl J Med* 2009

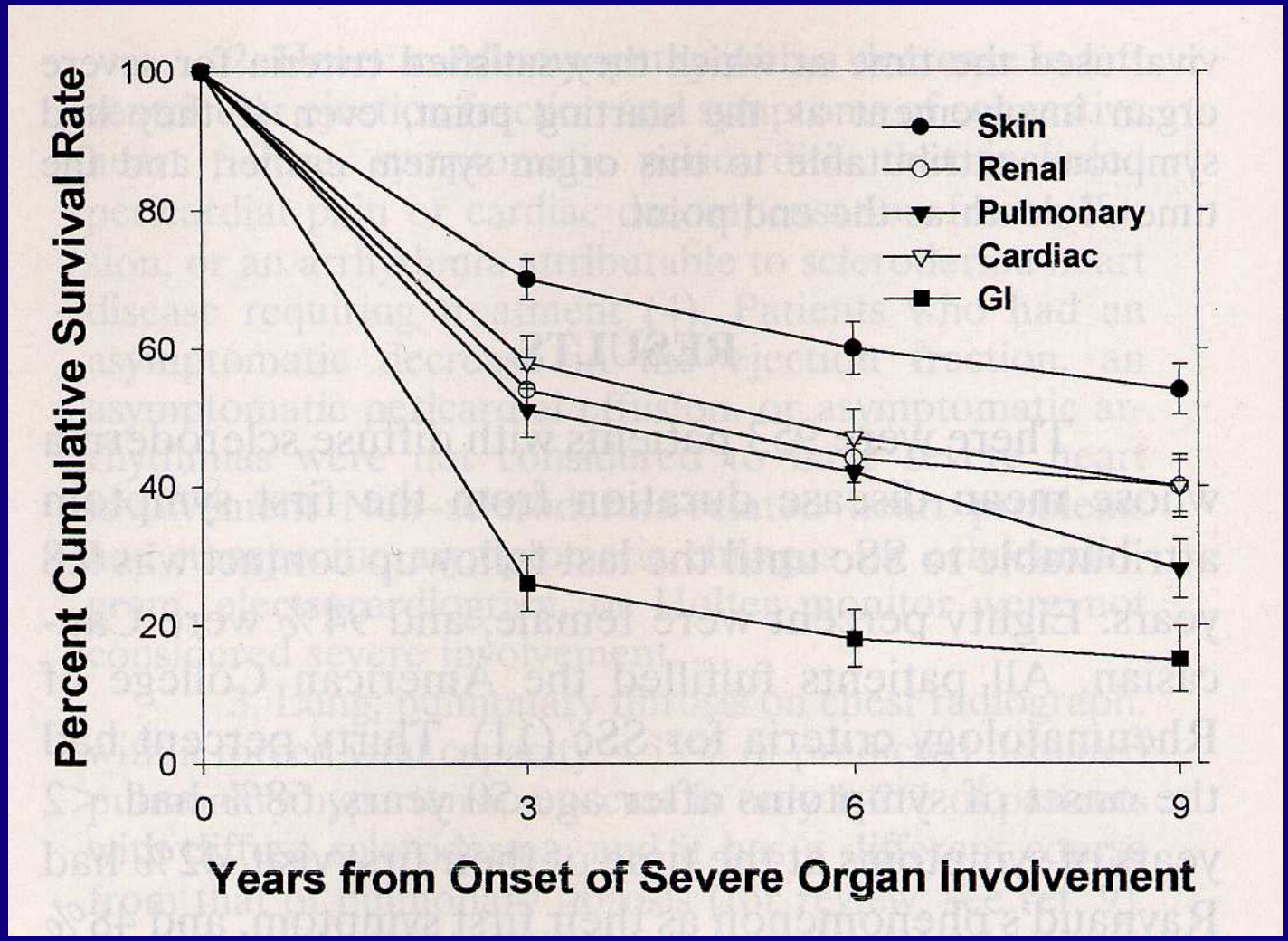
Autoanticorps

Survie à 10 ans des patients atteints de ScS

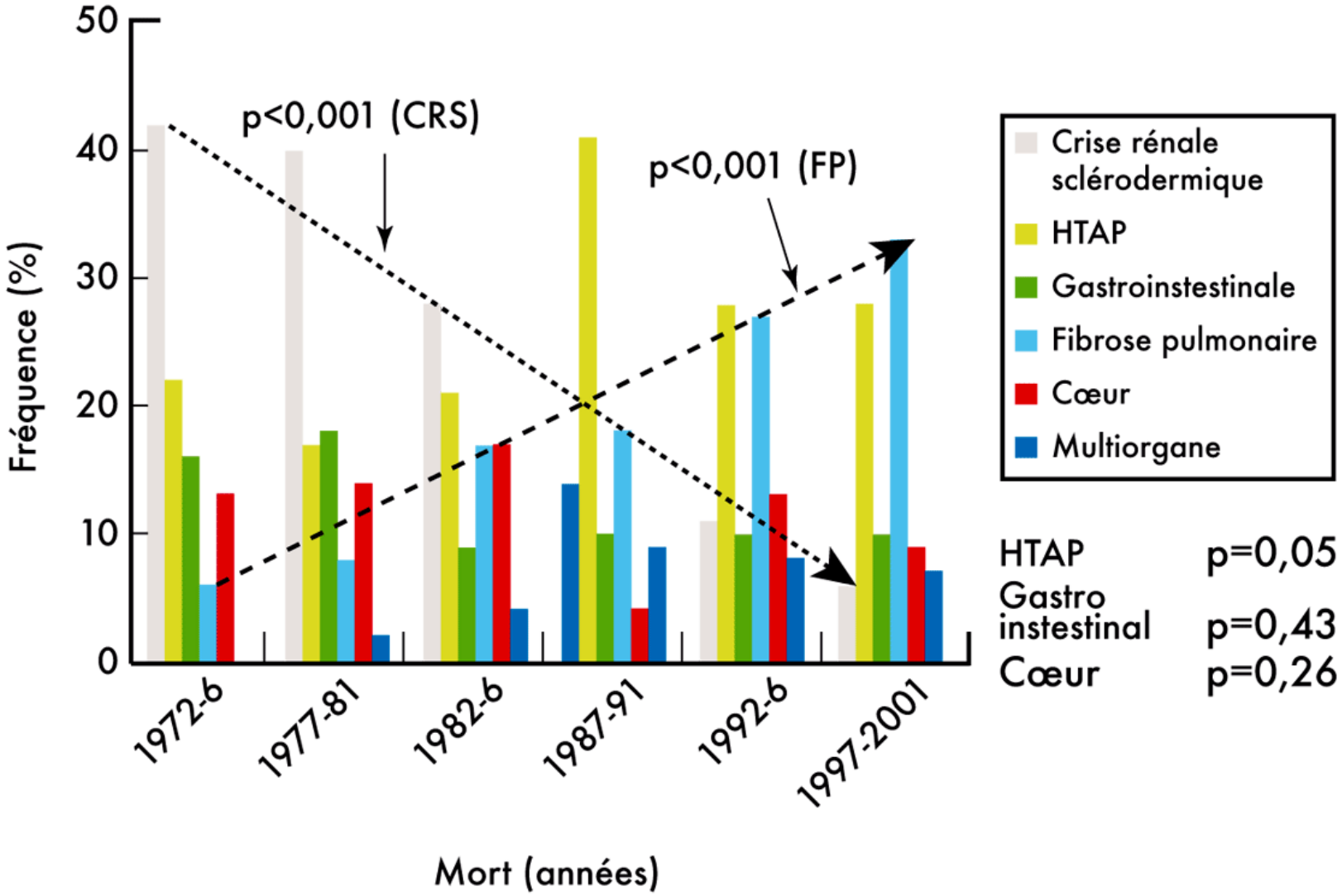
- **93 % avec anticorps anticentromère**
- **66 % avec Ac anti-Scl70**
- **30 % chez les patients ayant des anti-ARN polymérase.**

Kuwana M, Arthritis Rheum 1994; 37: 75-83

Severe organ involvement in SSc with diffuse scleroderma (Steen VD, Medsger T, Arthr Rheum 2000; 43: 2437-2444)



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



Steen et Medsger. Ann Rheum Dis 2007

Disease modifying agents in systemic sclerosis

(adapted from Mouthon L et al. Presse Med, 2006)

Immunosuppressants

- *Corticosteroids*
- *Methotrexate #*
- *Ciclosporine A #*
- *Cyclophosphamide #*
- *Azathioprine*
- *Mycophenolate mofetyl*
- *Stem cell transplantation*
- *Photochemotherapy #*

Anti-fibrotic agents

- *D-penicillamine #*
- *Colchicine*
- *Relaxine #*
- *Interferons #*
- *Calcitriol*
- *Pentoxifylline*
- *Factor XIII #*
- *Retinoids*

Vasodilators

- *Epoprostenol*
- *Prostacycline*
- *Bosentan #*
- *Ambrisentan*
- *Sildenafil*
- *Taladafil*

Other treatments

- *ACE inhibitors*
- *Octréotide*
- *Ketotifen #*
- *Plasmapheresis #*
- *Minocyclin*

Biologics

- *Anti-TNFα*
- *Rituximab*

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GFRS

Groupe Français de Recherche sur la Sclérodermie