Secondary Raynaud's Phenomenon

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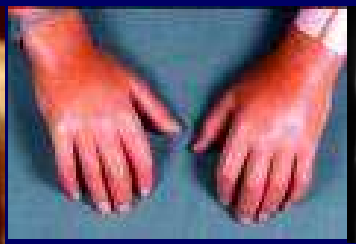
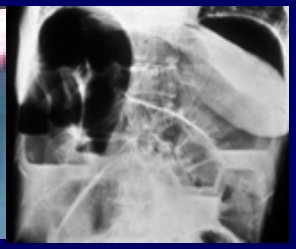
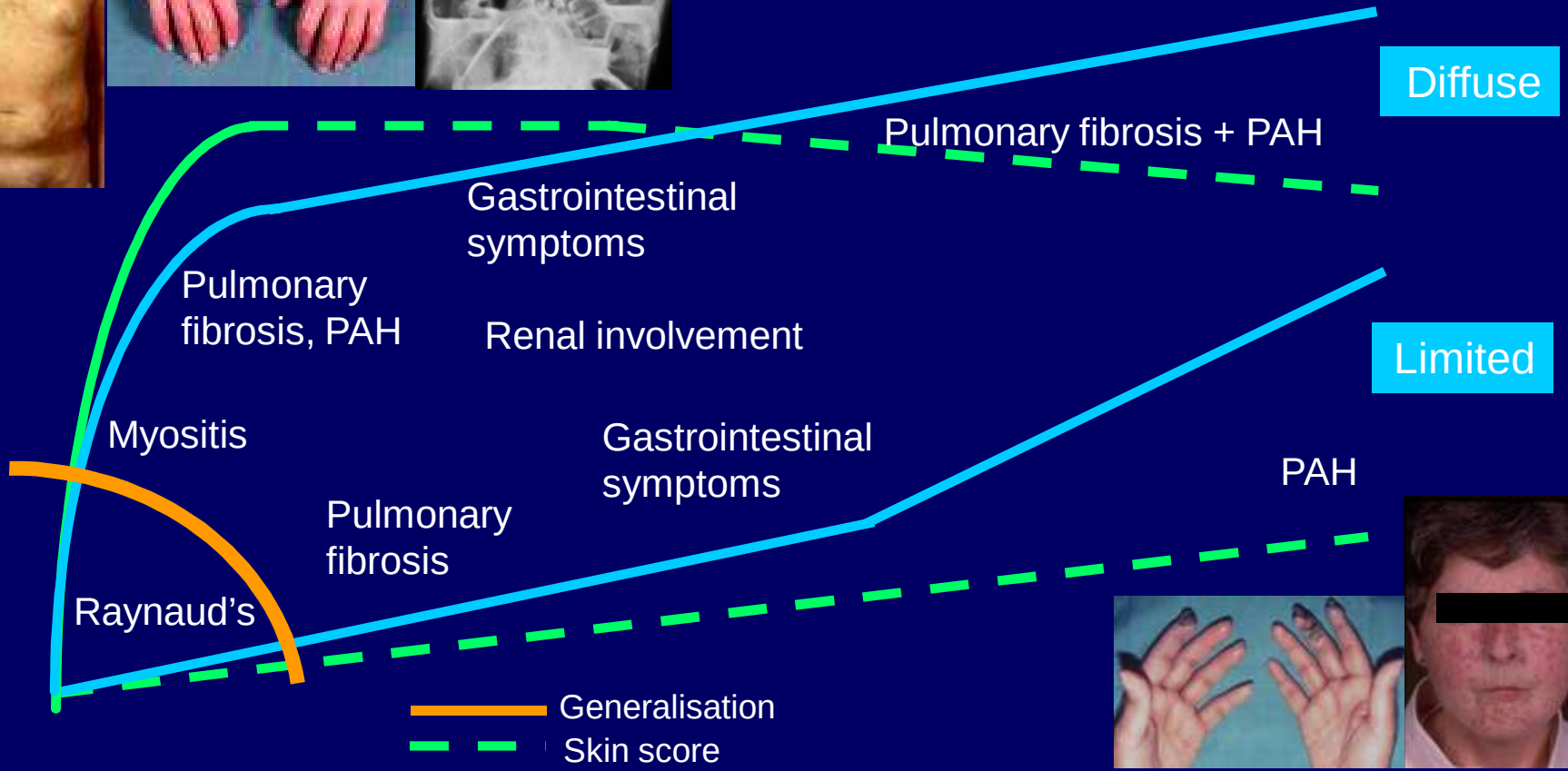
Clinical problems in SSc





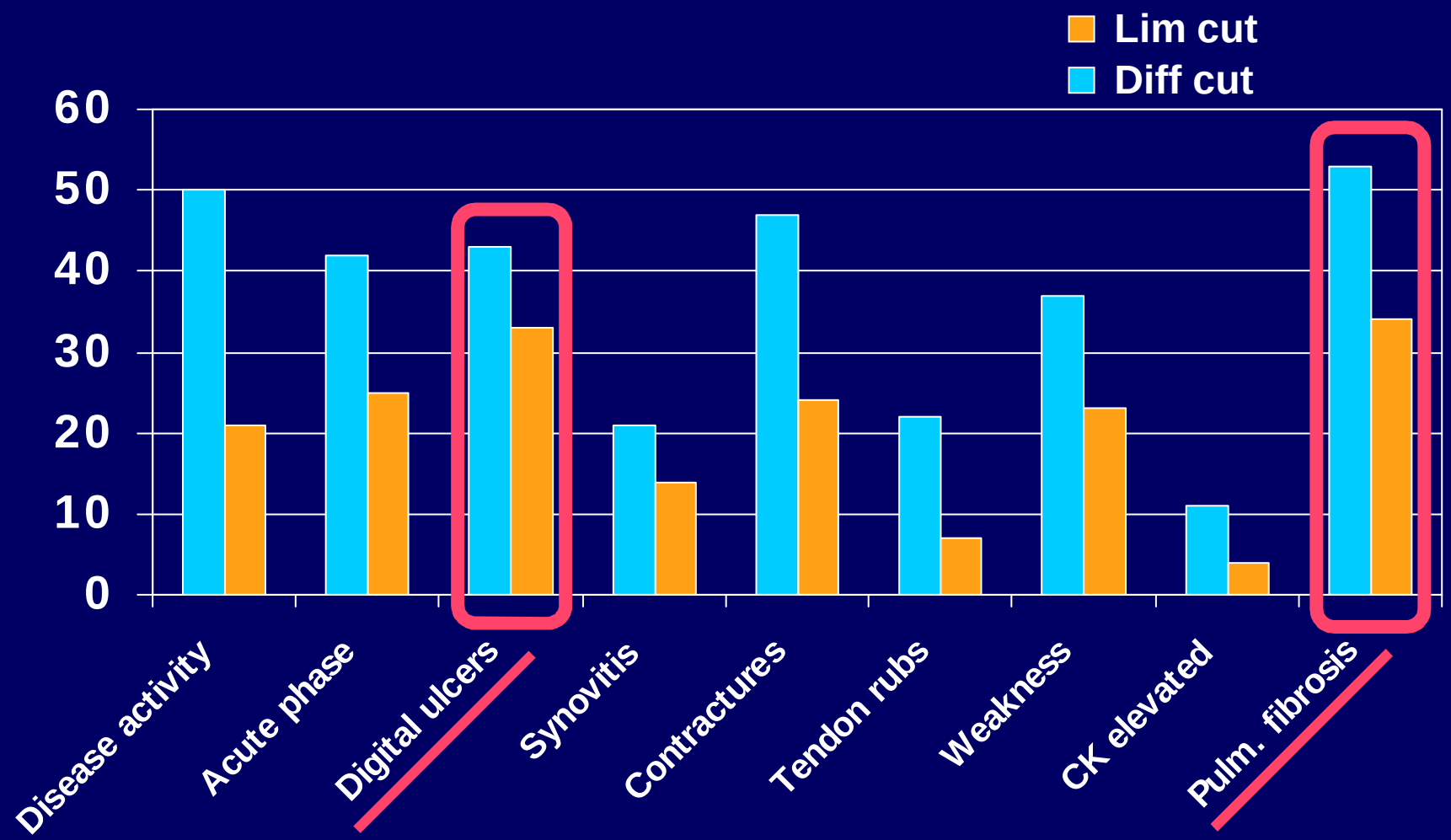
Therapeutic solutions?



Adapted from Black 2002.

EUSTAR patients

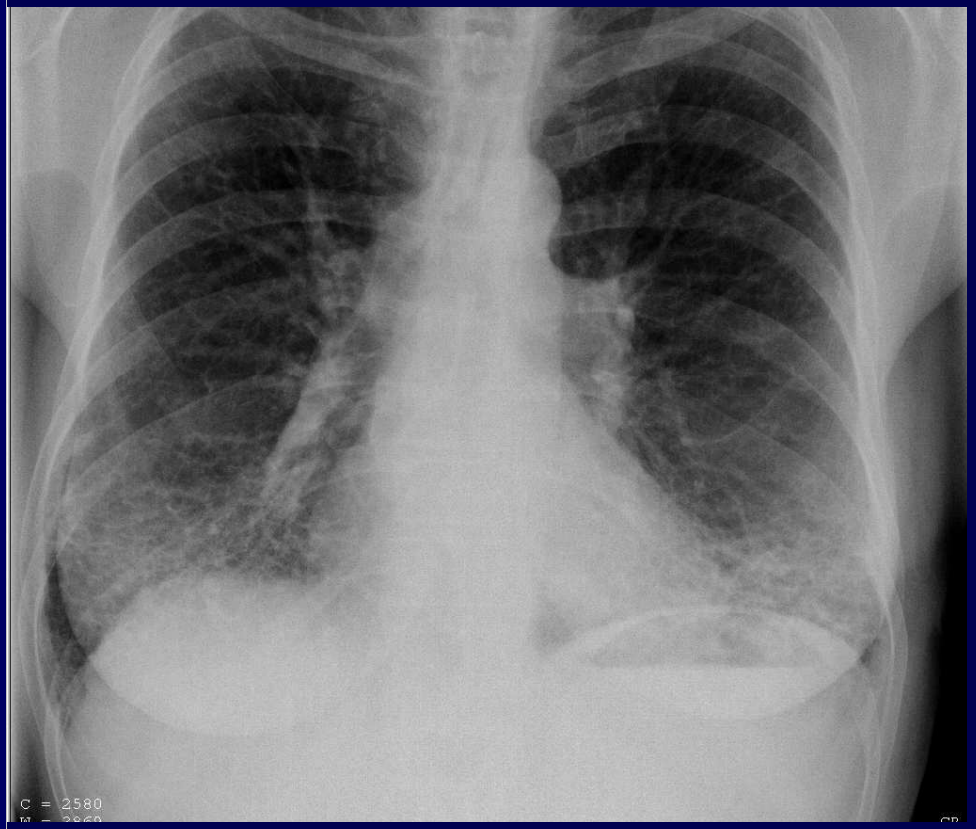
Organ involvement – Significant differences

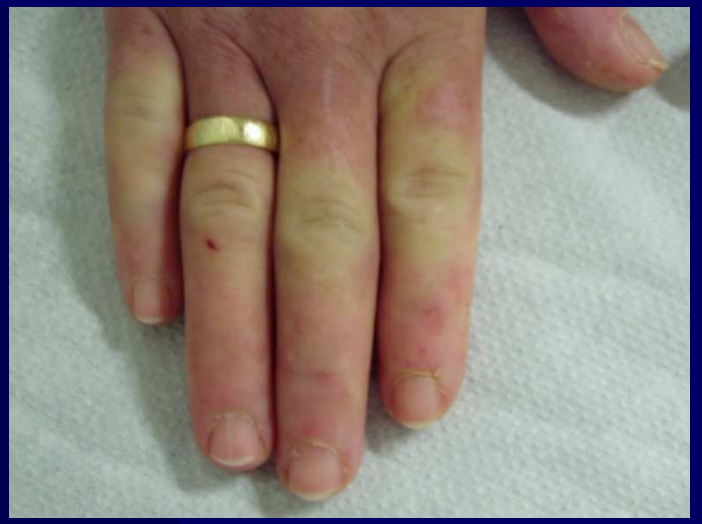


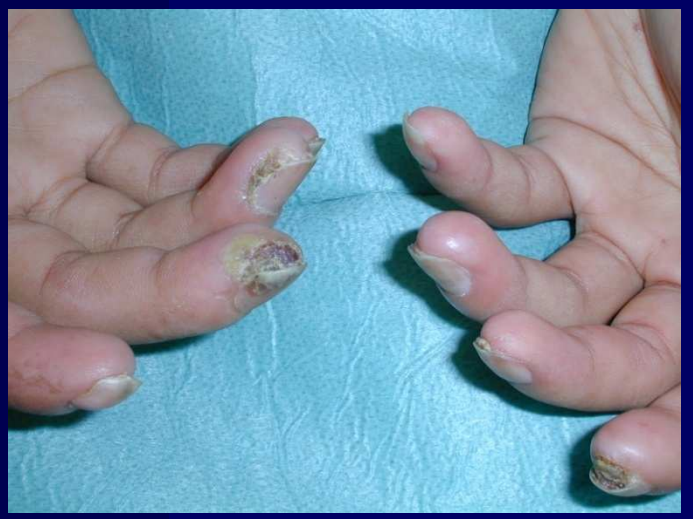
Walker UA, *et al*. *Ann Rheum Dis* 2007; 66:754-63.

From bench to bedside

Solutions to clinical problems

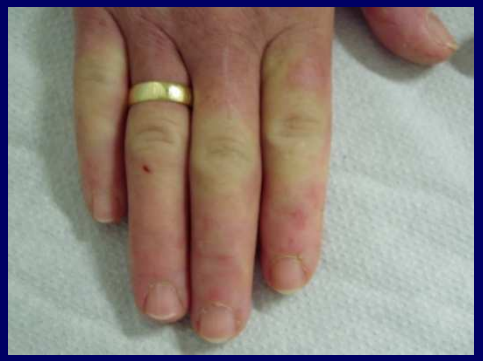




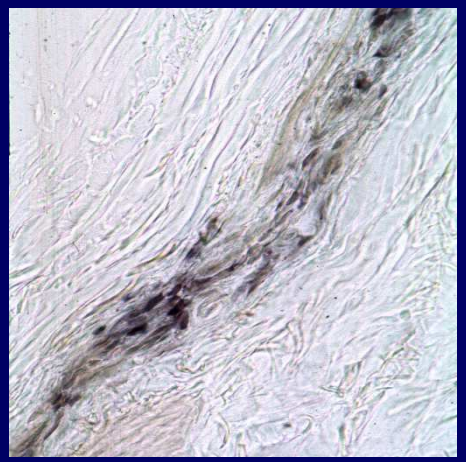


Pathogenesis of SSc

Vascular – Inflammation – Fibrosis



Vascular changes



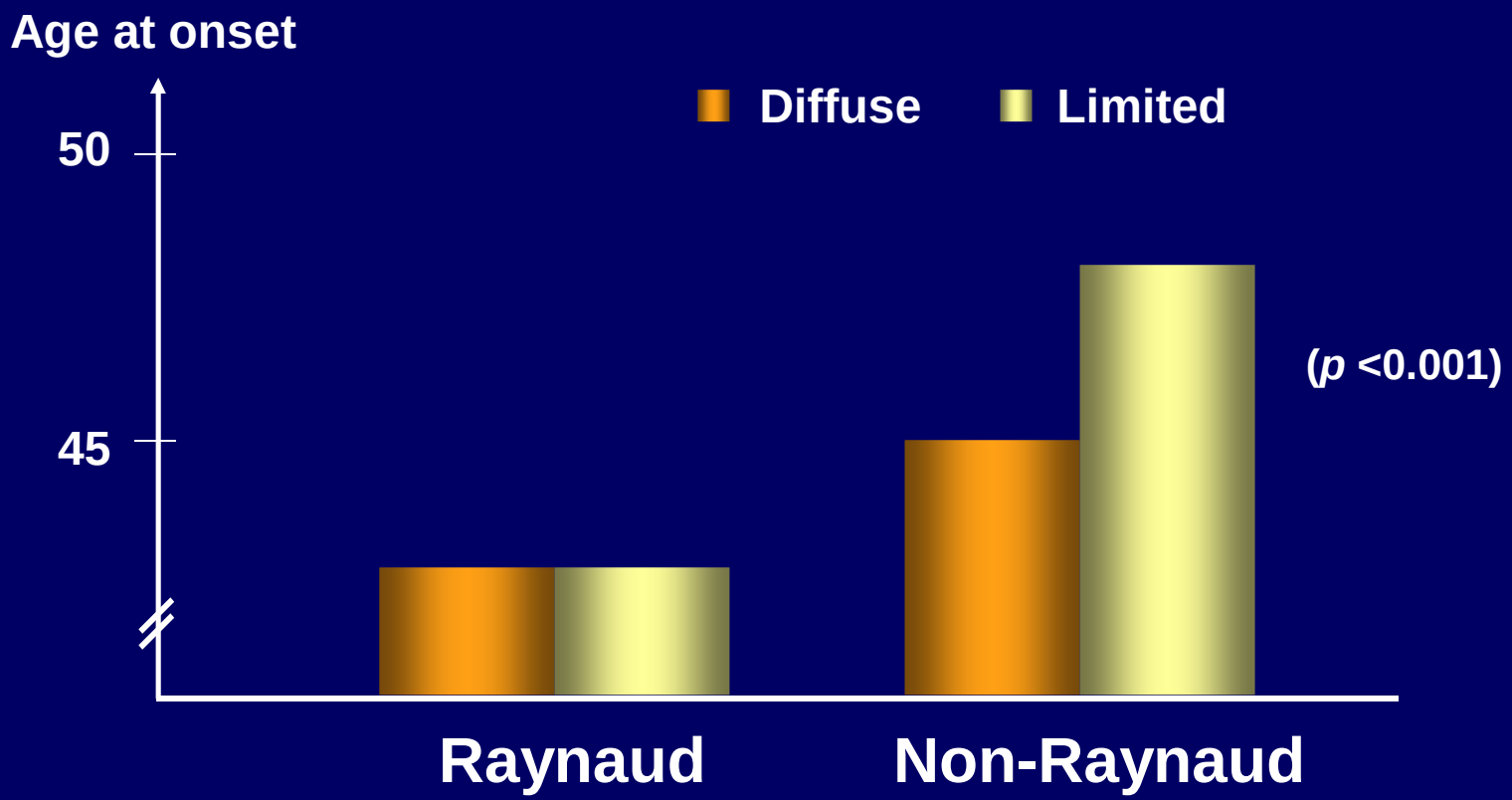
Inflammatory changes

Activation of fibroblasts

Accumulation of ECM

EUSTAR Patients

Early vascular alterations in SSc



Walker UA, *et al*. *Ann Rheum Dis* 2007; 66:754-63.

Diagnosis and Differential Diagnosis

Limitations of ACR criteria in early diagnosis of SSc

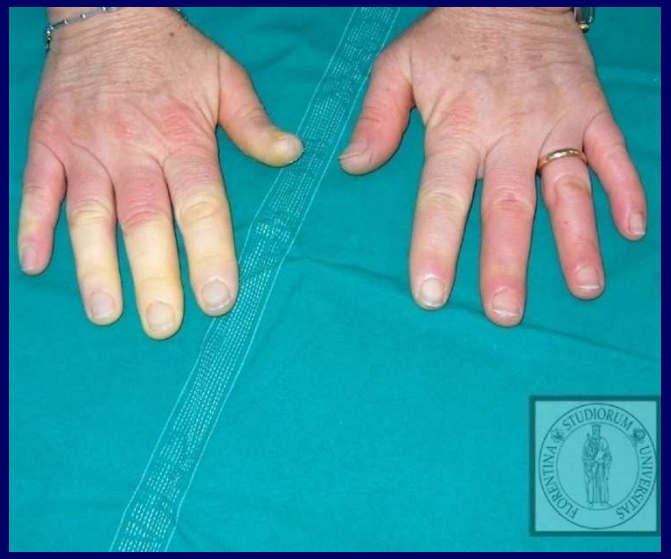
- Designed for classification, NOT diagnosis
- Do not take into account advances made in the last 30 years
  - Antibody associations (anticentromere, Scl 70)
  - Nailfold capillaroscopy
- Some patients with early SSc diagnosed by expert clinicians would be excluded based on ACR criteria
- In the Canadian Scleroderma Research Group, 20% of limited SSc patients do not meet the ACR criteria
- **Modifications / updates are required**

Lonzetti LS, *et al*. *Arthritis Rheum* 2001; 44:735-6.

VEDOSS
Very Early Diagnosis Of SSc

VEDOSS red flags

- **Raynaud's phenomenon**
- **Puffy fingers**
- **Positive antinuclear antibodies**



Avouac J, *et al. Ann Rheum Dis* 2010

VEDOSS
Very Early Diagnosis Of SSc

Presence of red flags raises suspicion of very early SSc

1st level: Suspicion

1. Capillaroscopy
2. Serology (TOPO-I, ACA)

If either one is positive, diagnosis of very early SSc & further investigations

2nd level: Diagnosis

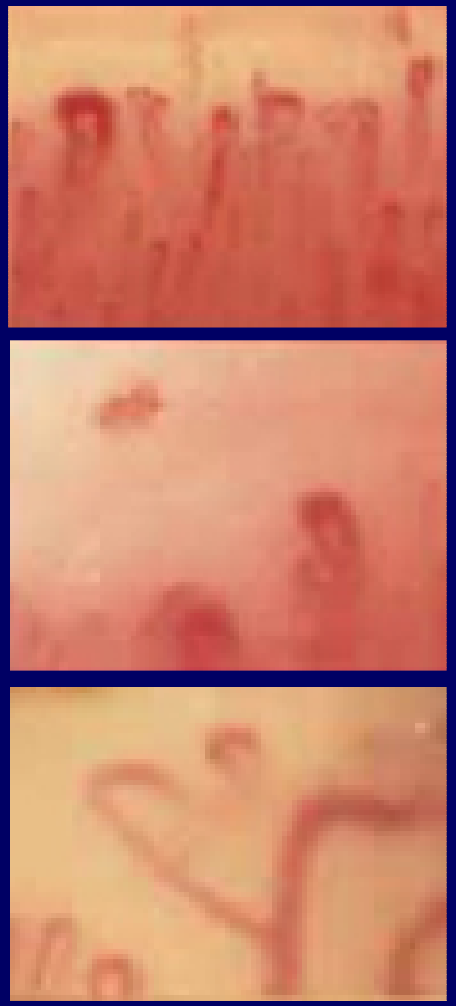
1. Oesophageal manometry
2. Chest HRCT
3. PFT

To contribute, visit www.eustar.org

Avouac J, *et al. Ann Rheum Dis* 2010

Capillaroscopic patterns in SSc

- **EARLY:**
  - Few enlarged/giant capillaries
  - Few capillary haemorrhages
  - No evident loss of capillaries
- **ACTIVE:**
  - Frequent giant capillaries and haemorrhages
  - Moderate loss of capillaries
  - Absent/mild ramified capillaries
- **LATE:**
  - Few/absent giant capillaries and haemorrhages
  - Severe loss of capillaries with extensive avascular areas
  - Disorganisation of the capillary arrays
  - Ramified/bushy capillaries



Cutolo M, et al. Rheumatology 2006

Differential Diagnosis: Primary vs. Secondary Raynaud's

Primary

- Symmetrical attacks
- Absence of tissue necrosis
- Absence of ulceration or gangrene
- Absence of secondary cause
- ANA negative
- Normal erythrocyte sedimentation rate
- ***Normal nailfold capillaries***

Secondary

- Age >30 years at onset
- Episodes that are intense, symmetrical, painful and/or associated with ischaemic skin lesions
- Clinical aspects suggestive of CTD
- Presence of specific autoantibodies
- ***Microvascular alterations of nailfold capillaries***

Cutolo M, *et al. Best Pract Res Clin Rheumatol* 2005

Treatment

EULAR/EUSTAR Recommendations for Treatment of SSc Complications

Task Force 2007

O Kowal Bielecka, J Avouac, I Miniati, S Chwiesko, R Landewé
B Garay, P Clements, L Czirijak, D Farge, C Denton, K Fligelstone,
I Földvari, D Furst, M Matucci-Cerinic, U Müller-Ladner, R Silver,
K Takehara, A Tyndall, G Valentini, F van den Hoogen,
F Wigley, F Zulian

Presented at EULAR 2007: Clinical Science Session on Scleroderma.

Key problems and complications

- **Raynauds phenomenon**
- **Digital ulcers**
- **Fibrosis of skin and internal organs**
- **Pulmonary arterial hypertension**
- **Gastrointestinal tract**
- **Scleroderma renal crisis**

General management of Raynauds and Digital Ulcers

Local therapy & wound care

Prevention of infection complications

Pharmacological intervention
prevention of new DU
healing pre-existing DU

Surgery

Last resort

Non-pharmacological intervention

Pain relief

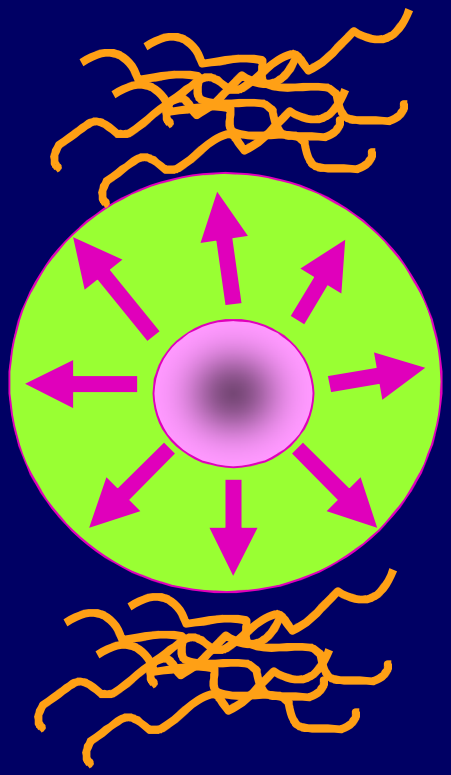
Multidisciplinary approach

Figure: Prof. Matucci-Cerinic

Potential therapeutic options

Endothelial protection

- Endothelin antagonists
- Antioxidants
- Termination of smoking
- Prostaglandins
- ACE inhibitors



Vasodilation

- Prostaglandins
- L-Arginine
- NO/Rho-kinase
- CO_2
- CGRP
- Calcium antagonists
- Nitro-derivatives
- PDE-5 inhibitors

Antifibrotics

- Endothelin antagonists
- Imatinib

Antithrombotics

- ASS, clopidogrel
- Heparin, cumarin

Reduction of vasoconstriction

- Endothelin antagonists
- ACE inhibitors
- Serotonin-reuptake inhibitors
- Selective α2-adrenoreceptorblockers

Local therapy

- **Prostaglandin PGE-1 ethylester patches[1]**
  - **Indication: Secondary Raynaud‘s in SSc**
    - **Increase of capillary blood flow 30 % after 14 days**
    - **Reduction of Raynaud‘s attacks from 21 to 15 per week**

- **CO_2-Immersion baths[2]**
  - **Indication: Primary and secondary Raynaud‘s**
    - **Increase of capillary blood flow > 40% after 18 days**
    - **Reduction of re-warming time of 25%, no change in Raynaud‘s**

1. Schlez A, *et al. VASA* 2003; 32:83-86.
2. Schmidt J, *et al. VASA* 2005; 34:93.

Systemic therapy

Calcium channel blockers

- **Indication:**
  primary and secondary Raynaud‘s
- **Cochrane analysis**
  - **18 controlled studies, 361 patients including 13 with nifedipine vs. placebo**
  - **Reduction by 3–5 Raynaud‘s attacks/week**
  - **Reduction of Raynaud‘s severity by 1/3**

Thompson AE, Pope JE. *Rheumatology* 2005; 44:145-50.

CCBs
Example 1

Nifedipine vs. losartan[1]

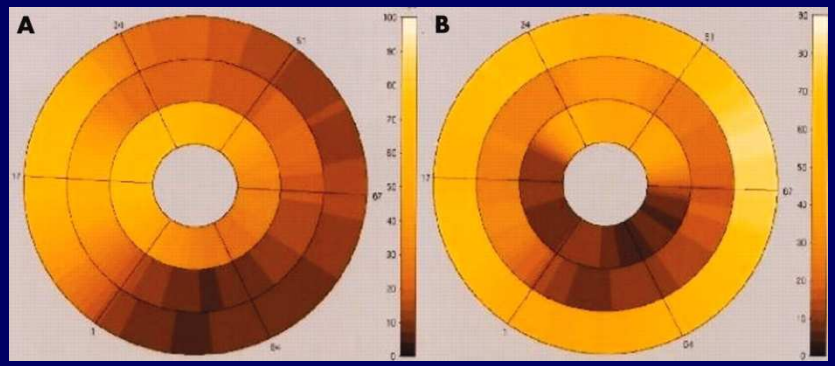
- **Indication: Primary and secondary Raynaud's in SSc**
- **40 mg nifedipine vs. 50 mg losartan for 12 weeks**
  - **Stronger effect of losartan on Raynaud's than nifedipine (especially on frequency)**
  - **Clinical benefit greater in primary than secondary Raynaud's**

1. Dziadzio M, et al. *Arthritis Rheum* 1999; 42:2646-55.

CCBs
Example 2

Effect of nifedipine on myocardial perfusion[1]

- **Long-term d/lSSc**
- **14 days nifedipine 60 mg/day**
- **Myocardial perfusion and function improved**



1. Vignaux O, *et al. Ann Rheum Dis* 2005; 64:1268-73.

CCBs
Example 3

Iloprost vs. nifedipine

- Indication: **Secondary Raynaud's in SSc**
- **5 days i.v. every 6 weeks for 12 months vs. 40 mg nifedipine p.o./die**
  - **Effectivity of iloprost on skin score higher with 13 → 9 vs. nifedipine 10 → 12**
  - **Effect on severity of Raynaud's comparable**
    2.2 → 1.2 iloprost vs. 2.1 → 1.3 nifedipine

Scorza R, et al. *Clin Exp Rheumatol* 2001; 19:503-8.

CCBs
Example 4

Nifedipine vs. fluoxetine

- Indication: Primary and secondary Raynaud‘s
- 40 mg nifedipine vs. 20 mg fluoxetine/day for 6 weeks
- Both effective for severity of Raynaud‘s
- Effect only for fluoxetine significant
- Serotonin-reuptake inhibitors most prominent effect in women with primary Raynaud‘s

Coleiro B, et al. *Rheumatology* 2001; 40:1038-43.

...and the other vasodilators ?

- **Prazosin 3 mg/day p.o. for 8 weeks[1]**
  - **Frequency and severity in secondary Raynaud's ⇓**
- **Diltiazem 360 mg/day p.o. for 2 weeks[2]**
  - **Frequency and severity only in primary Raynaud‘s ⇓**

1. Surwit RS*, et al. Arch Dermatol* 1984; 120:329-31.
2. Kahan A, Amor B, Menkes CJ. *Ann Rheum Dis* 1985; 44:30-3.

Systemic therapy

Iloprost vs. alprostadil:

- Indication: Secondary Raynaud‘s in CTD
- 5 days i.v. every 4 weeks
  - Effectivity of iloprost and alprostadil comparable (no improvement on skin score)
  - Alprostadil: Raynaud‘s in 90 vs. 45% improved
  - Iloprost: Digital ulcers in 60 vs. 40% improved

Marasini B, *et al. Scand J Rheumatol* 2004; 33:253-6.

Systemic therapy

Sildenafil: Numerous positive case reports

- **No peer-reviewed study available**

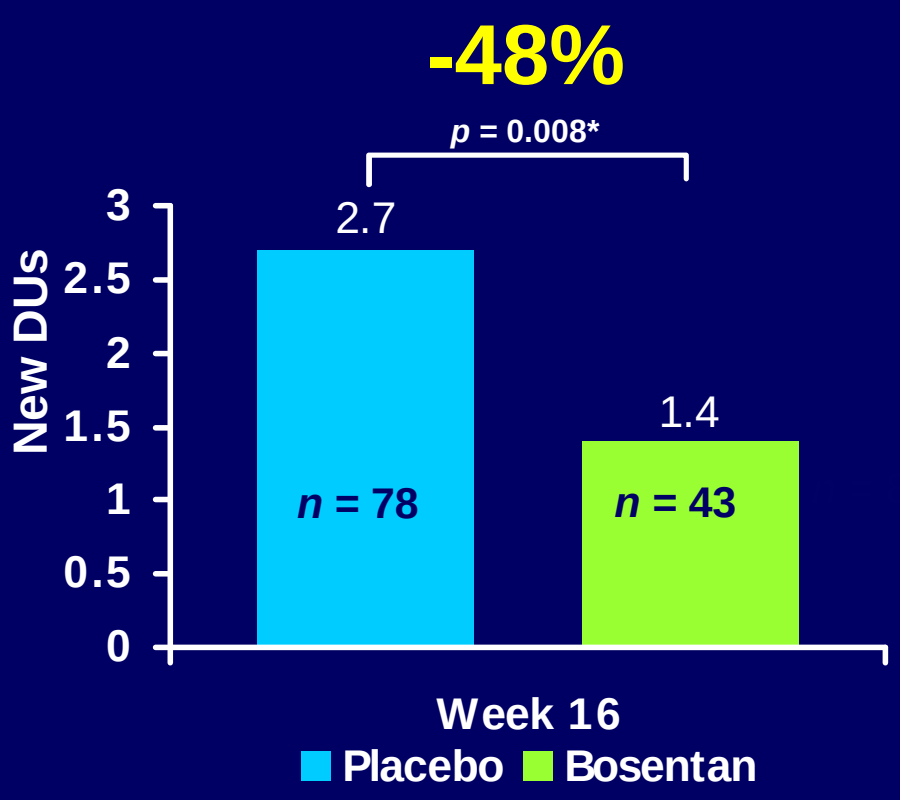
Tadalafil[1-3]:

- **Active secondary Raynaud's, 5-20 mg/eod**
- **Off-label study, 15 patients, 3 winter months**
- **Reduction of Raynaud's-Score (0-10) from 6.9 to 3.8**
- **Responder ca. 47% m, 66% w, DU 66%**

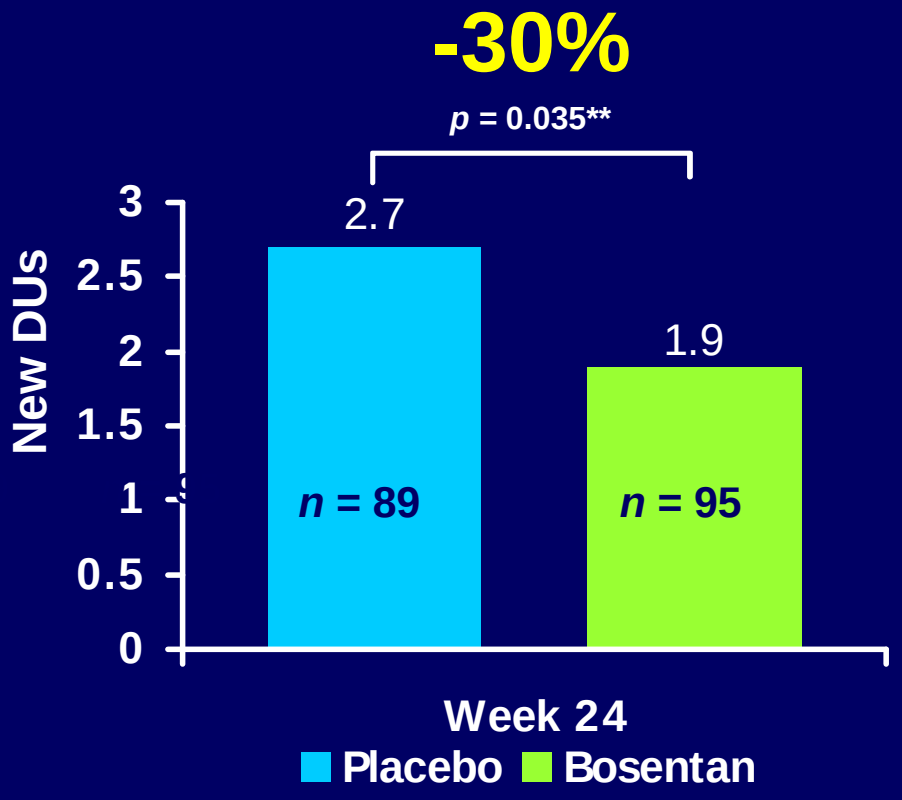
1. Baak SW, *Arthritis Rheum* 2005 (ACR Abstr).
2. Kumana CR, *et al. Ann Rheum Dis* 2004; 63:1522-4.
3. Rosenkranz S*, et al. Dtsch Med Wochenschr* 2004; 129:1736-40.

RAPIDS programme: Primary endpoint
Reducing the number of new DUs

RAPIDS-1: Occurrence of new DUs at week 16[1]



RAPIDS-2: Occurrence of new DUs at week 24[2]



*Poisson regression analysis
**Pitman permutation test

1. Korn JH, *et al*. *Arthritis Rheum* 2004
2. Matucci-Cerinic et al. Ann Rheum Dis 2011

SSc-digital vasculopathy

EULAR/EUSTAR Recommendations

- → Intravenous prostanoids (in particular **iloprost**) should be **considered** in the treatment of **active digital ulcers** in patients with SSc

- → **Bosentan** has no proven efficacy in the treatment of **active digital ulcers** in SSc patients. Bosentan **has proven efficacy** to **prevent digital ulcers** in diffuse SSc patients, in particular in those with multiple digital ulcers

- → **Bosentan** should be **considered** in diffuse SSc with multiple digital ulcers after failure of calcium channel blockers and, usually, prostanoid therapy

Presented at EULAR 2007: Clinical Science Session on Scleroderma.

Thank you very much
for your attention !