Sclérodermie systémique: ulcères digitaux

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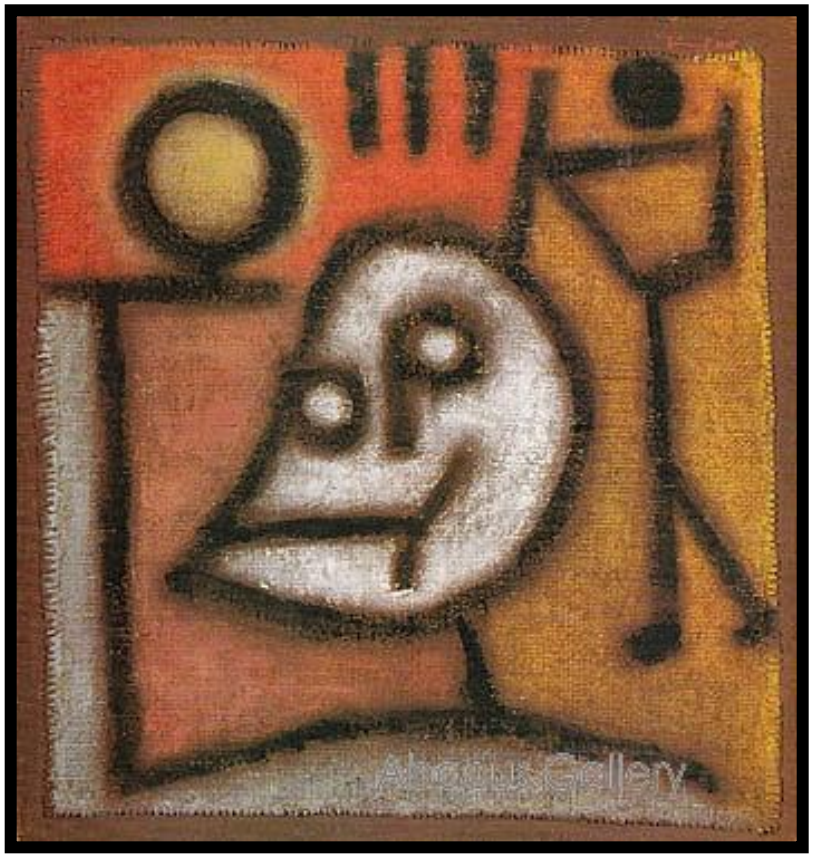
DU maladies systémiques – 13 octobre 2017

Conflicts of interest

- **Consultant**: Actelion, CSL Behring, LFB Biotechnologies, Lilly, Pfizer, Octapharma
  - Financial support to ARMIIC
- **Investigator**: Actelion, CSL Behring, Pfizer
- **Financial support (grants to ARMIIC)**: Actelion, CSL Behring, GSK, LFB Biotechnologies, Pfizer
- **Invited conference**: SOBI, Roche, Actelion, CSL Behring, Octapharma, GSK, LFB Biotechnologies, Pfizer, Lilly, UCB pharma

Paul Klee: 1879-1940 (II)

Mask – 1921



Death and Fire – 1940

Paul Klee **Polyphonies, Cité de la *musique*, Paris**
18 October 2011 – 15 January 2012

Digital ulcers: definition

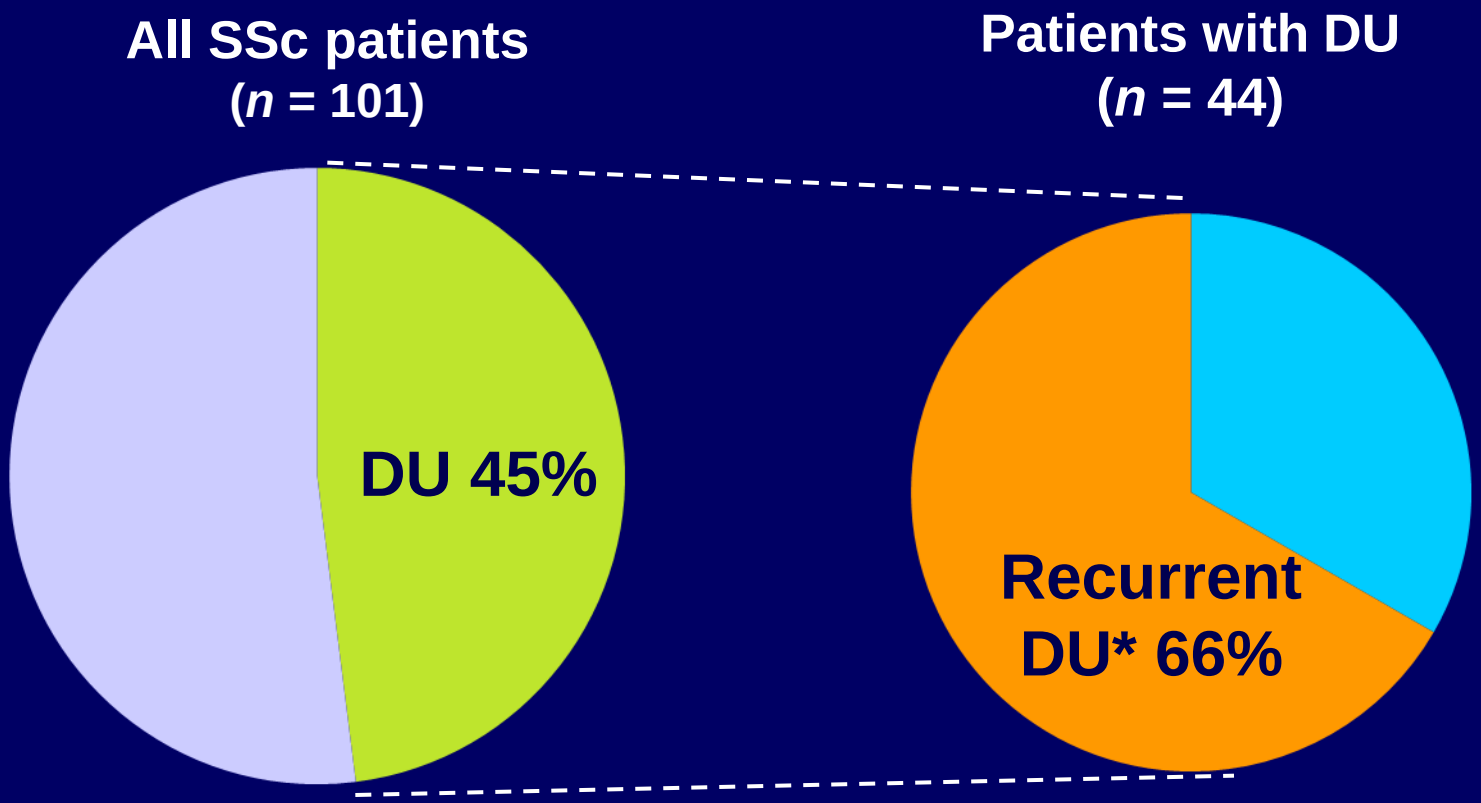
- **Well localised loss of dermis**, distal to the MCP joints
- **Does not include fissures** and **paronychias**
- Pathophysiology of DU in SSc
  - Ischaemic
  - Mechanical
  - Calcinosis
  - Infection

- **Fissure**

- **Paronychia**

Actelion France Brochure DU in SSc.

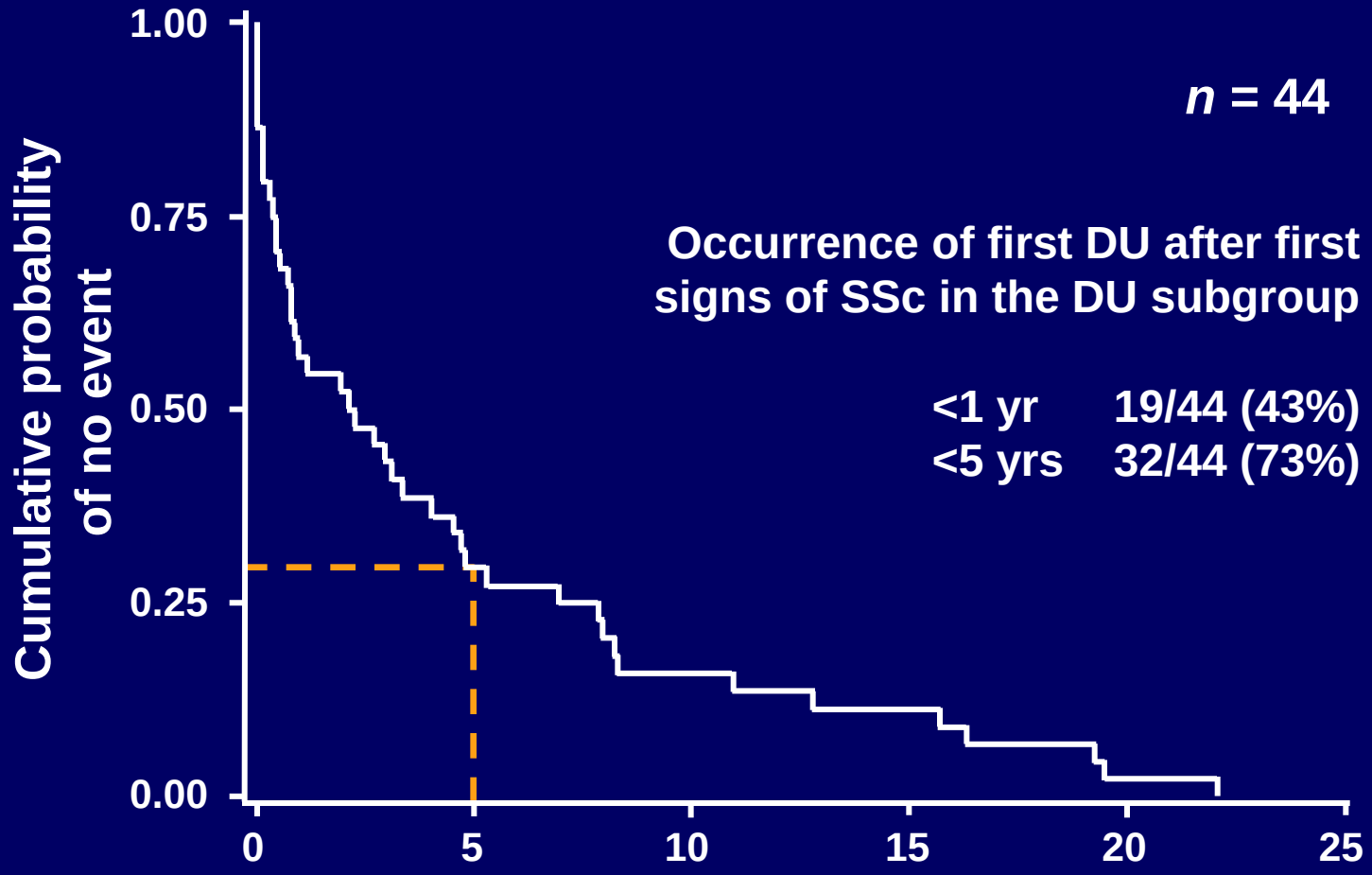
DU are a common and recurrent manifestation of SSc



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

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

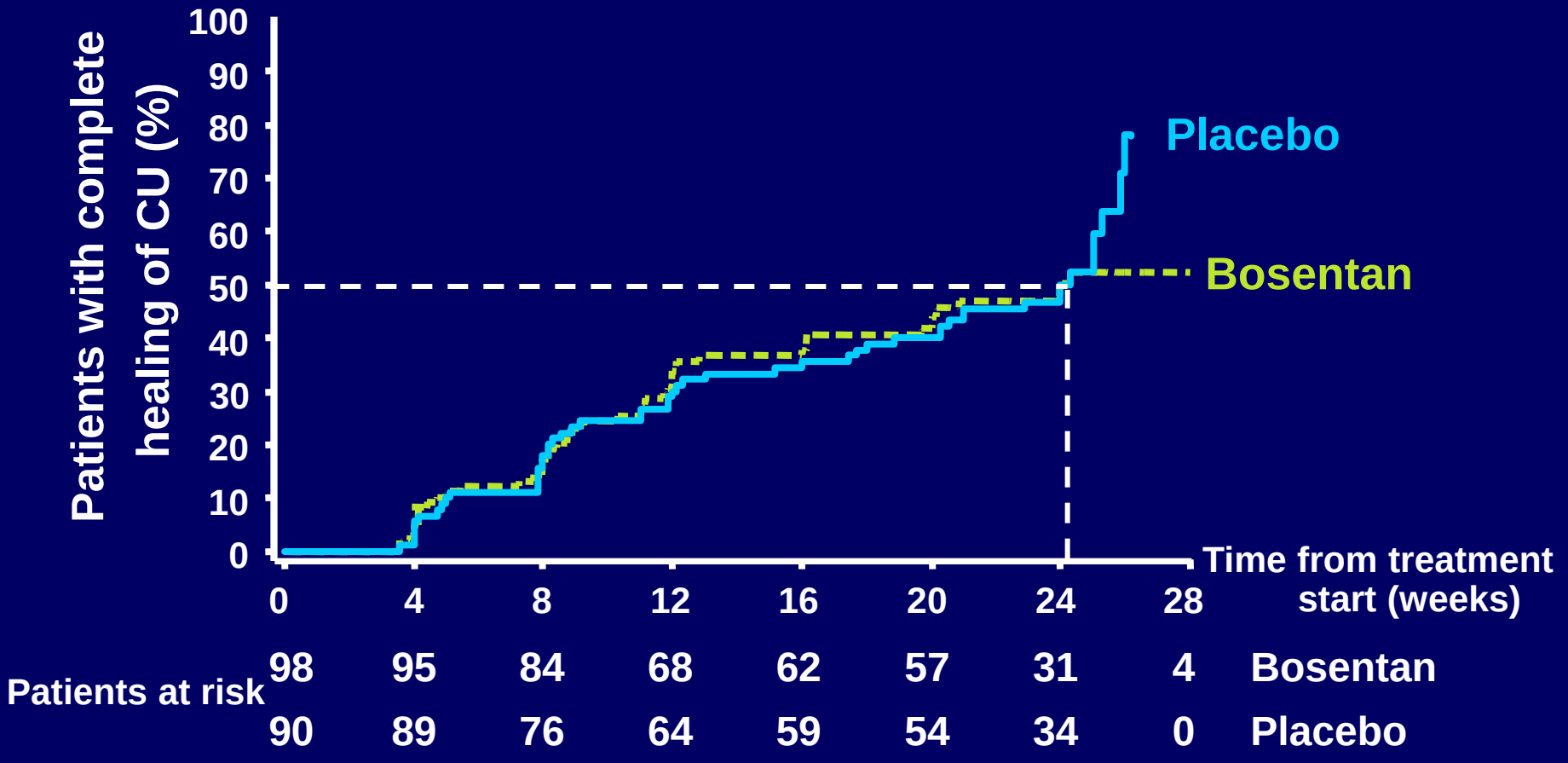
DU tend to occur early in the course of SSc



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

Persistence of DU in SSc

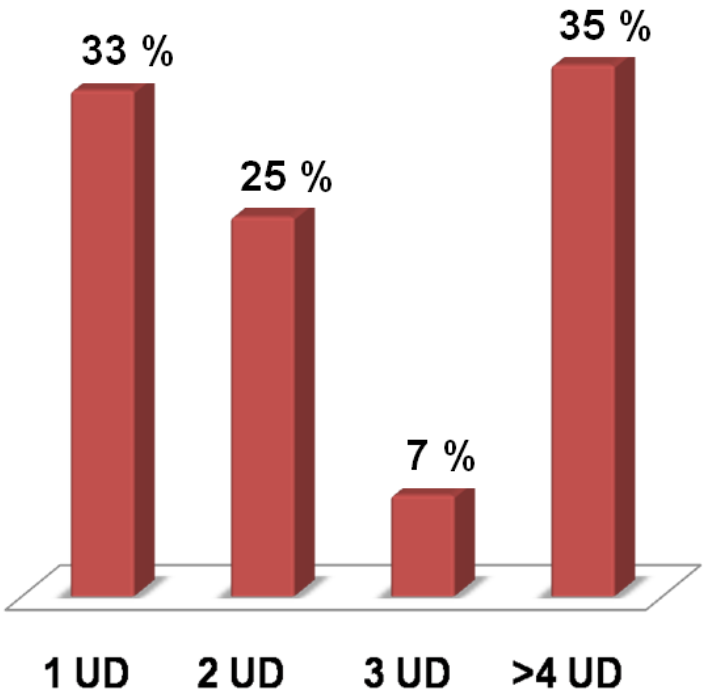
Persistence of cardinal ulcer (CU) is 50% at 6 months

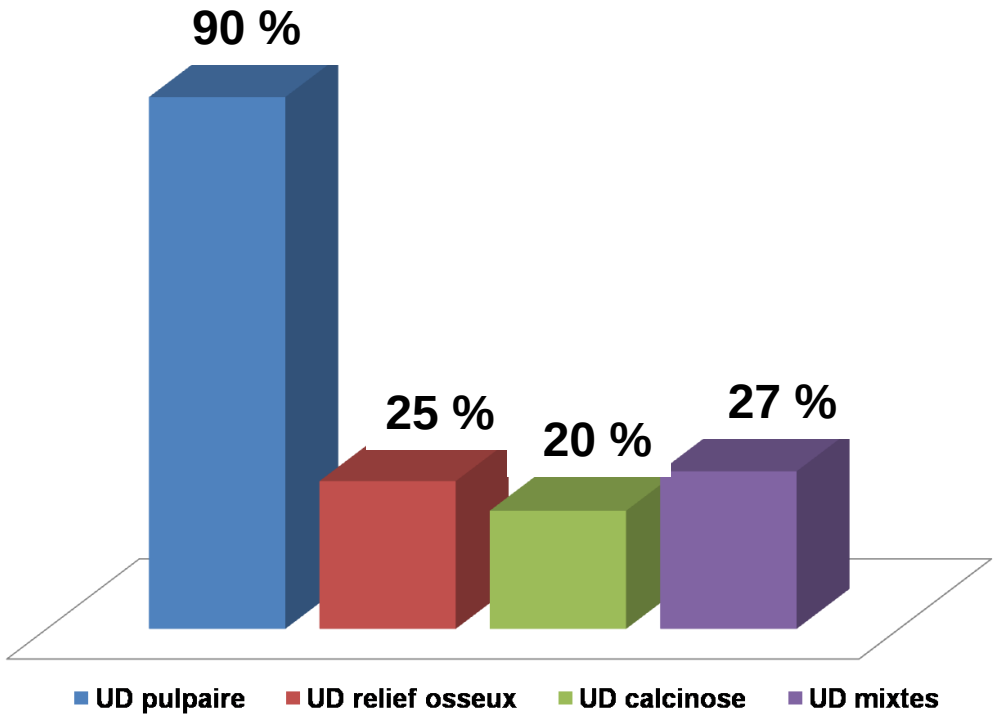


Matucci Cerinic M, *et al. Ann Rheum Dis* 2011; 70:32-8.

Description des UD

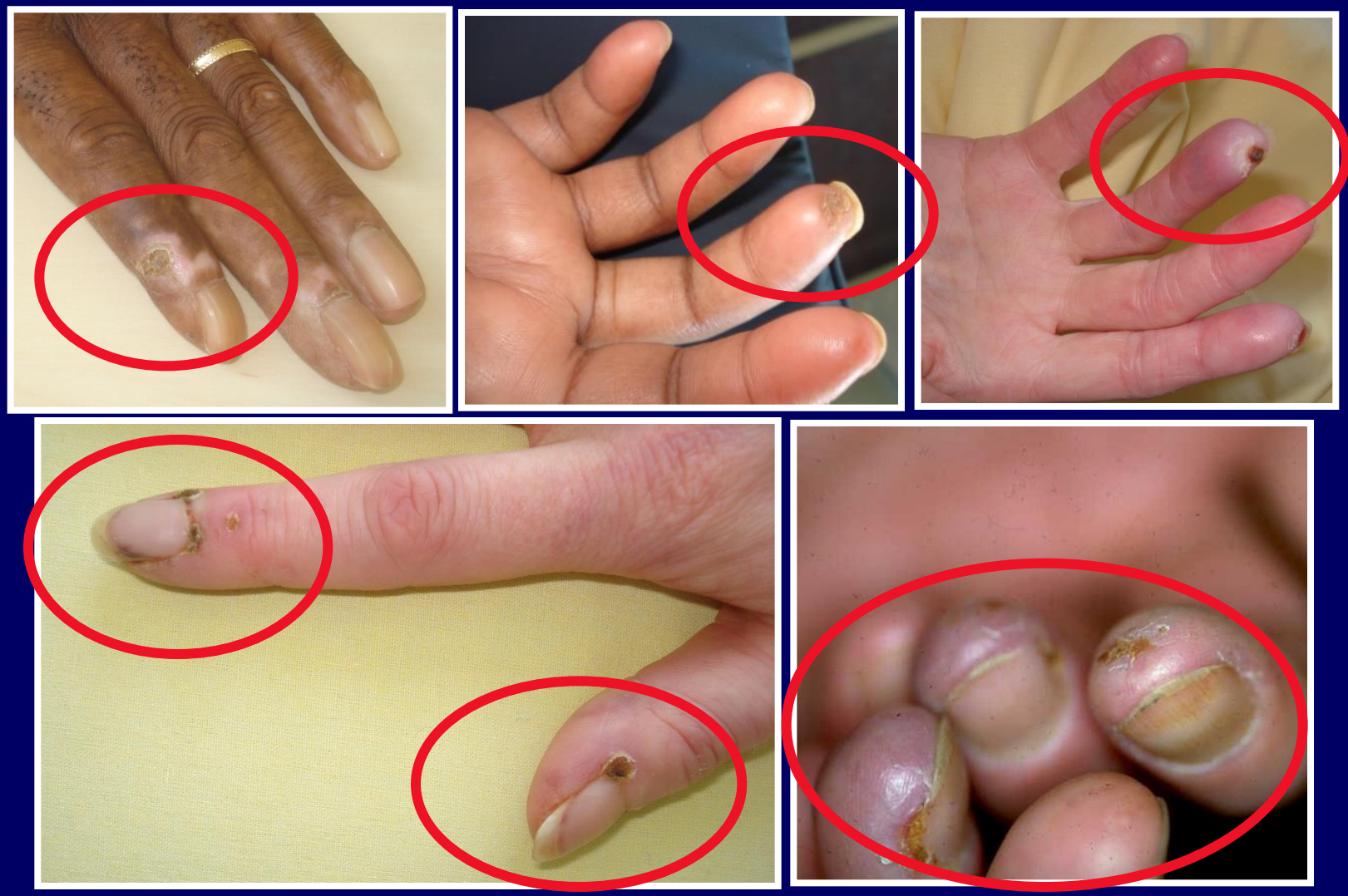
- UD actif(s) chez 60 patients (221 UD au total)
- UD unique pour 1/3 patients
- UD multiples pour 2/3 patients



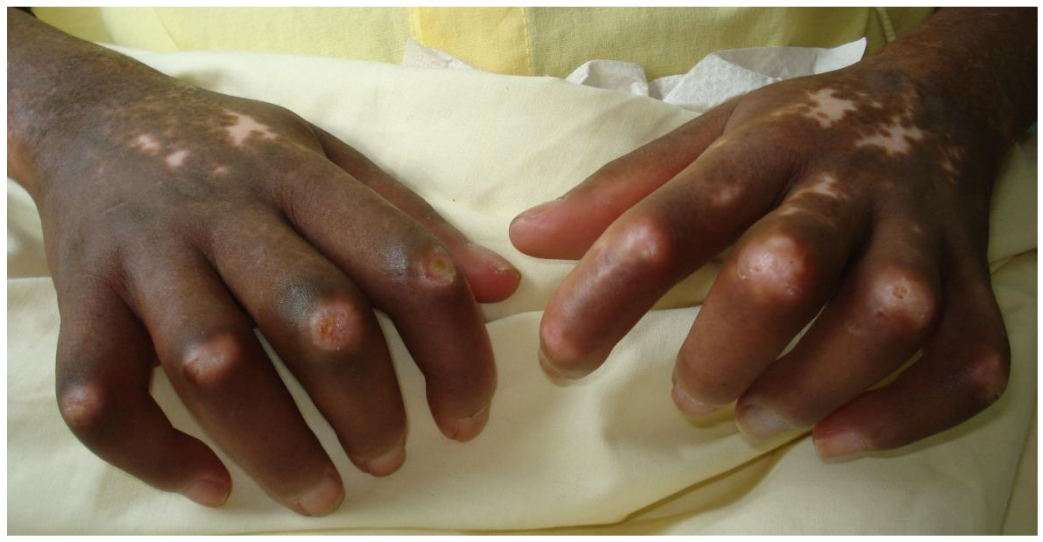


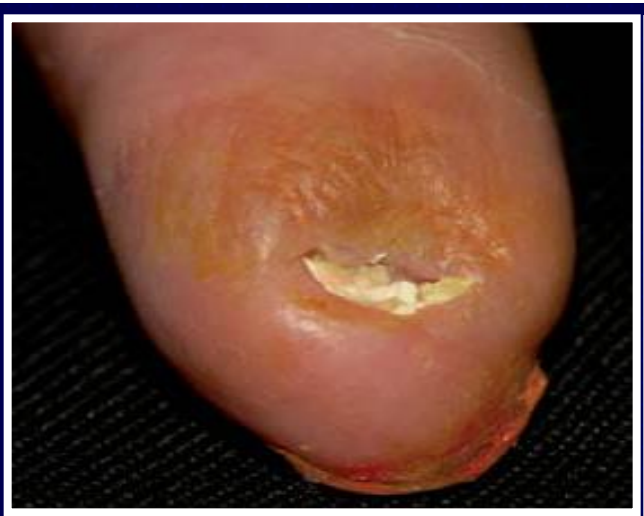
Bérezné *et al*. Arthritis Care Res 2011

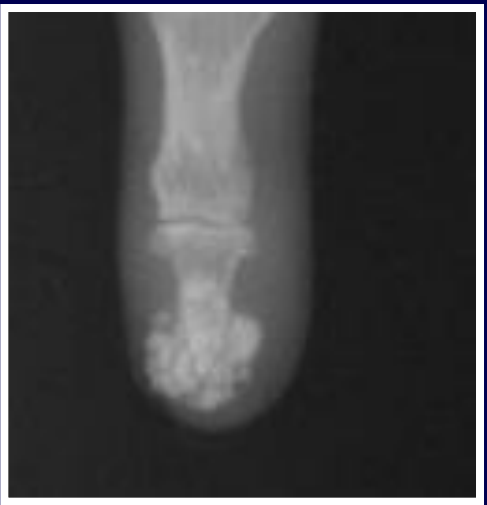
Digital ulcers: Vascular mechanisms

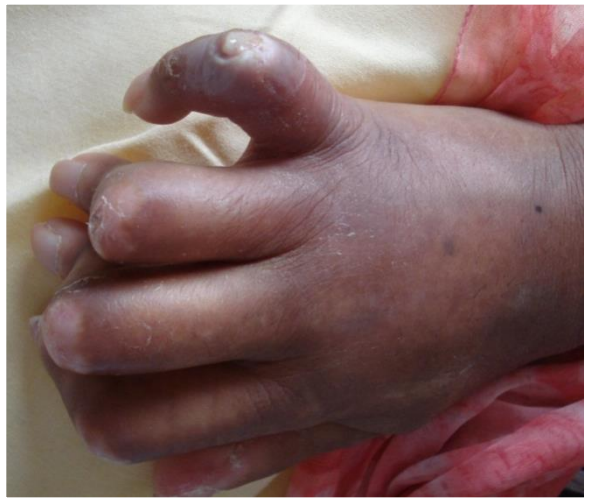


Calcinosis/mechanical



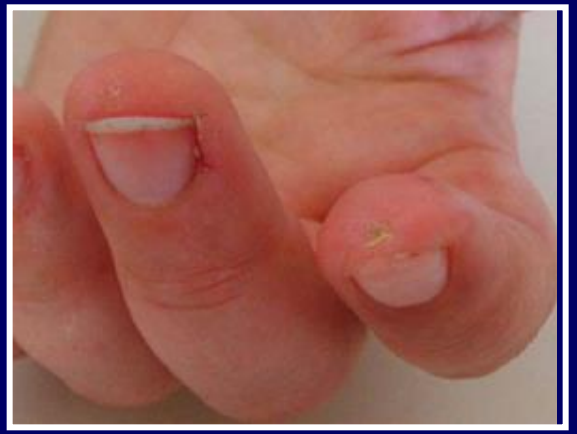


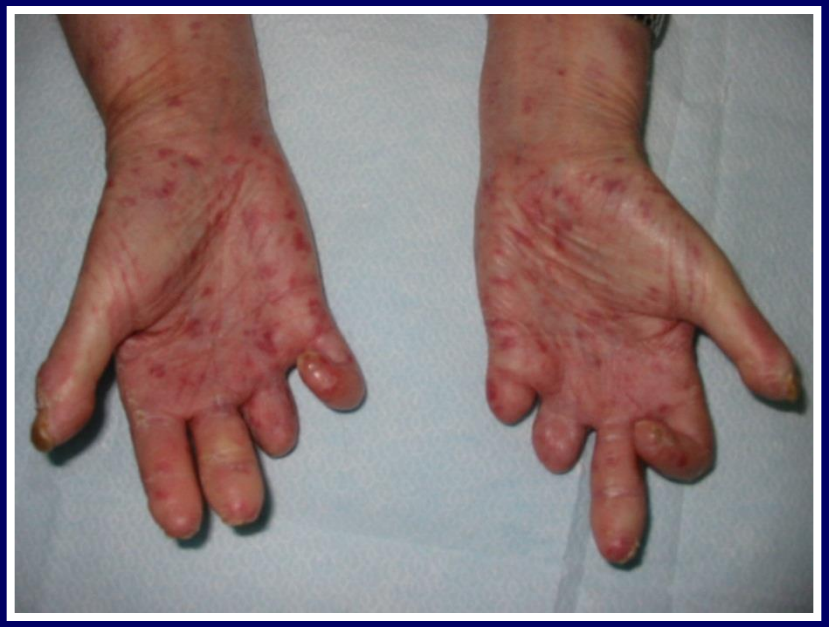




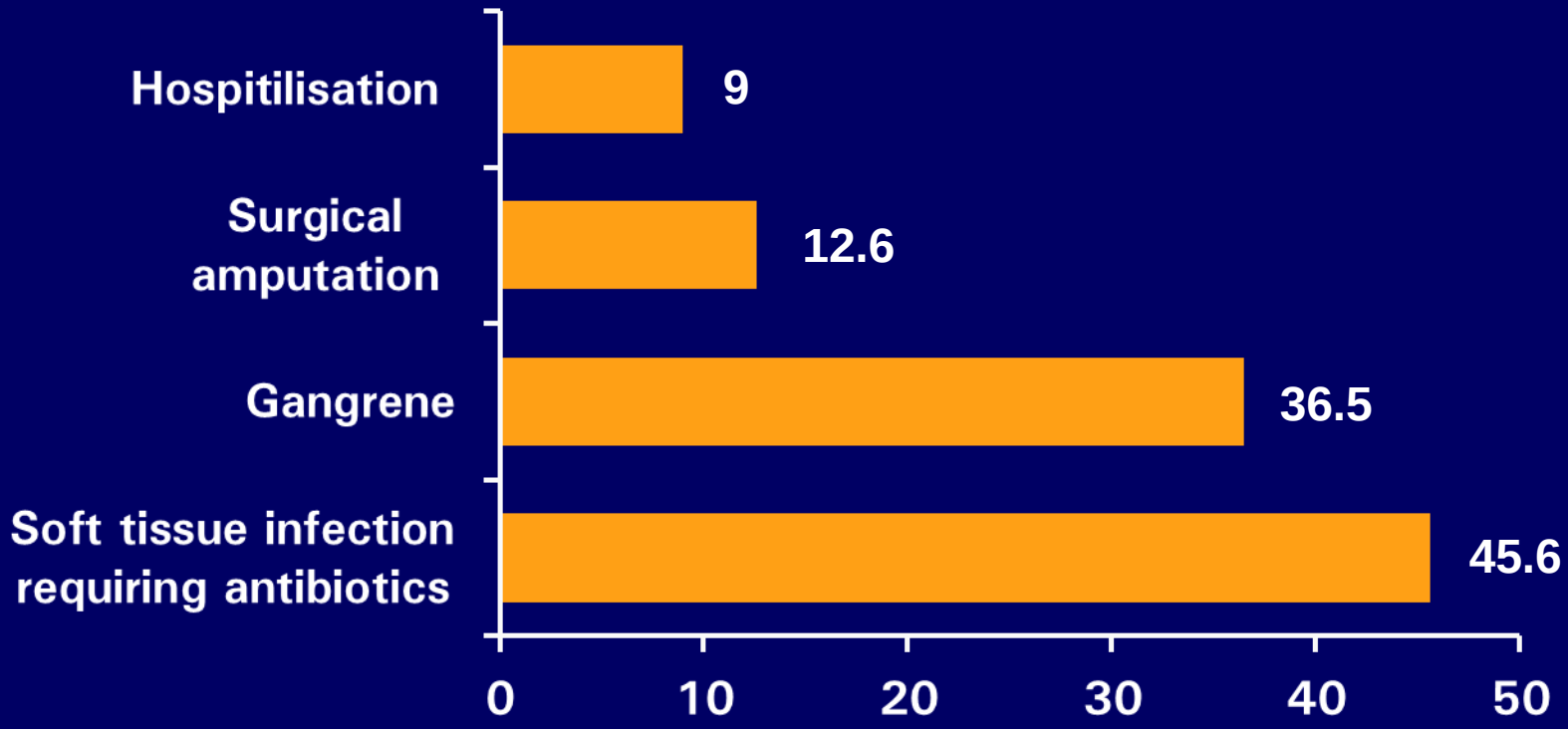
Digital ulcers: Healing

- Time to healing: Not well documented
- 30% sequelae
- Loss of substance
- Pitting scar
- Auto-amputation
- Surgical amputation





DU are a severe complication of SSc

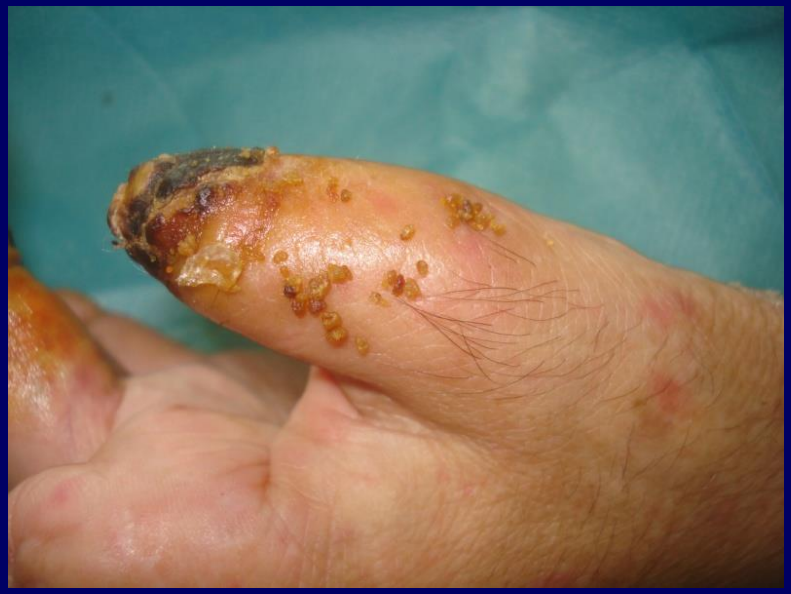


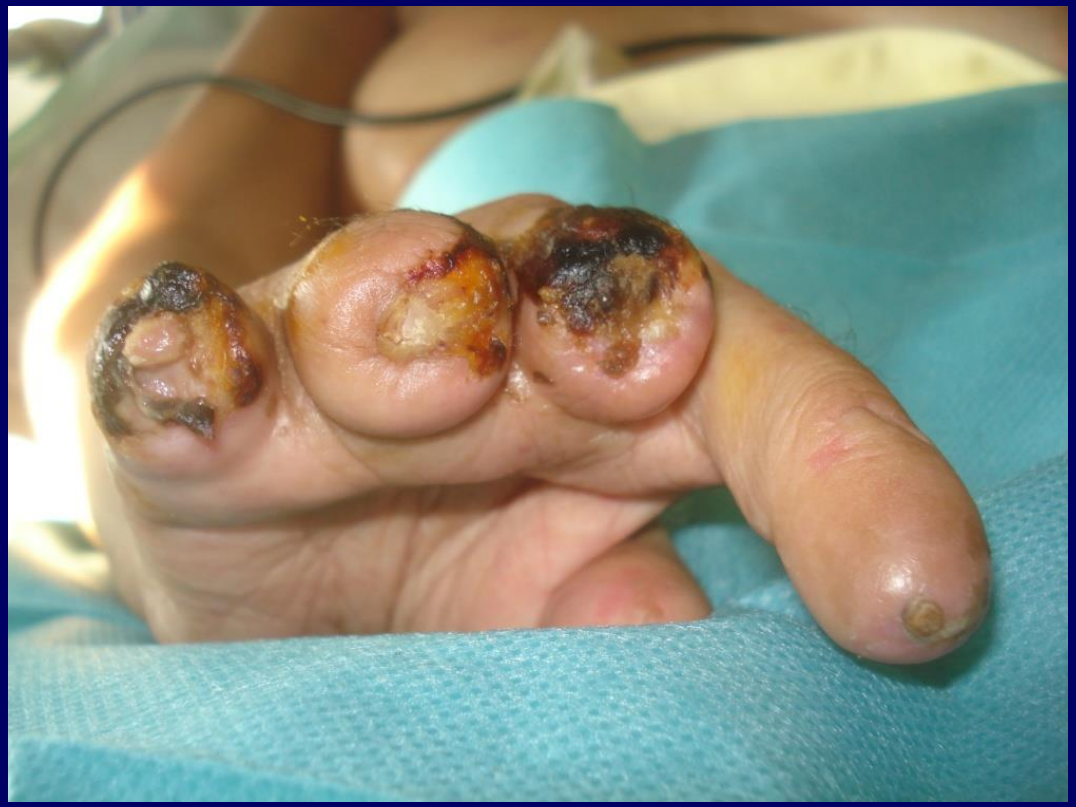
Patients with complications/interventions at enrolment (%)

Denton C, *et al. Ann Rheum Dis* 2009; 68:273.

Digital ulcers: Infection

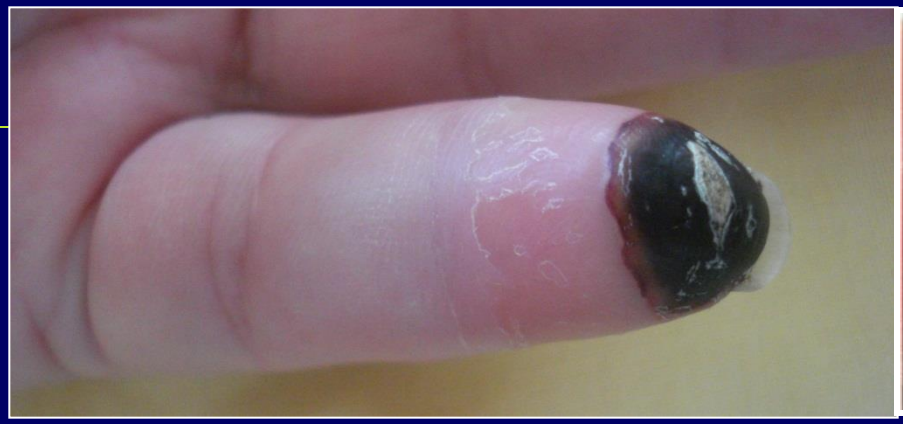
- 1/3 infections
- 10% osteomyelitis
- Delayed healing++++

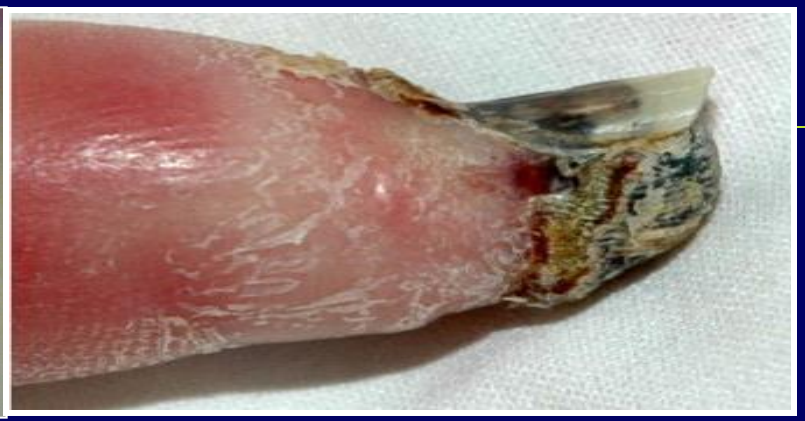


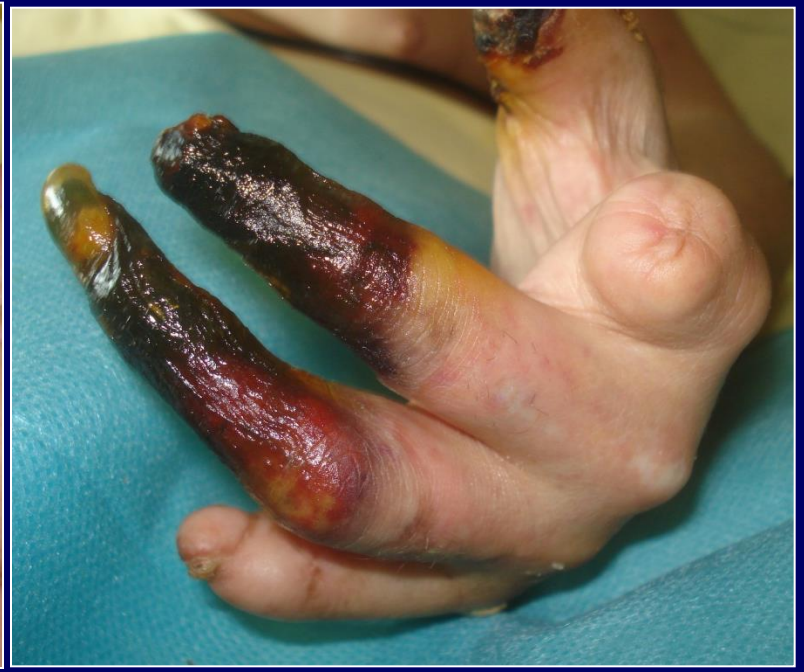


Hachulla E, *et al. J Rheum* 2007; 34:2423-30.
Nihtyanova SI, *et al. Ann Rheum Dis* 2008; 67:120-3.

Digital necrosis/gangrene

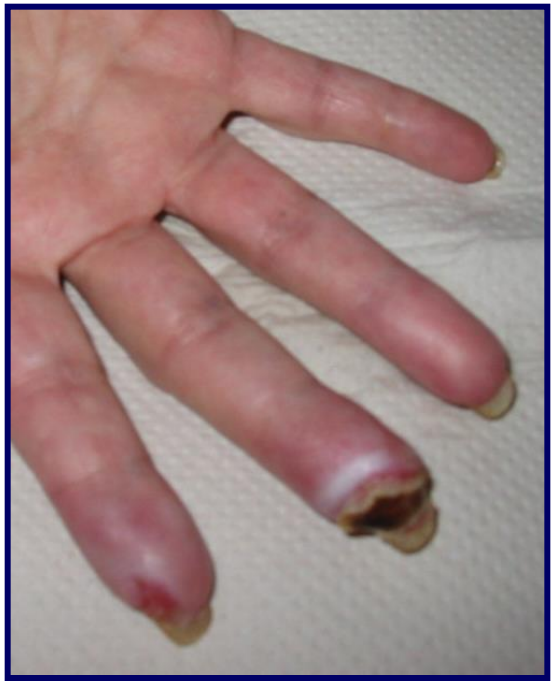


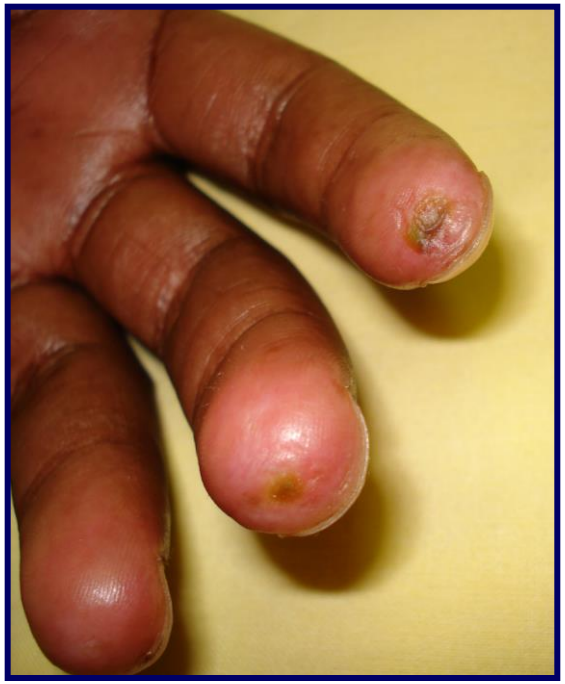


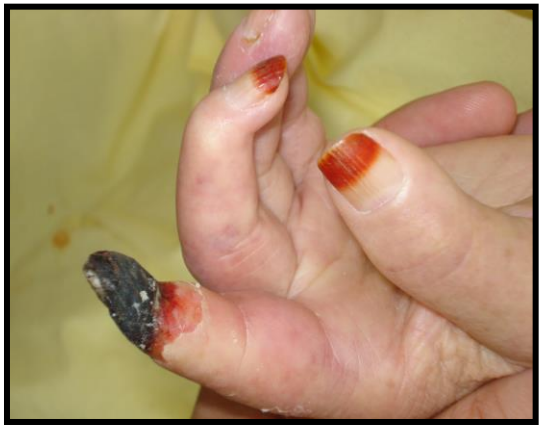


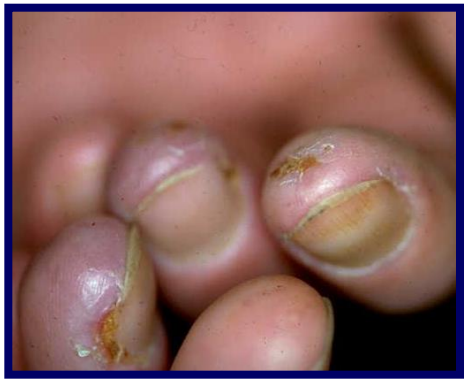
→ **Perform arterial doppler**

IMPACT OF DIGITAL ULCERS IN SYSTEMIC SCLEROSIS







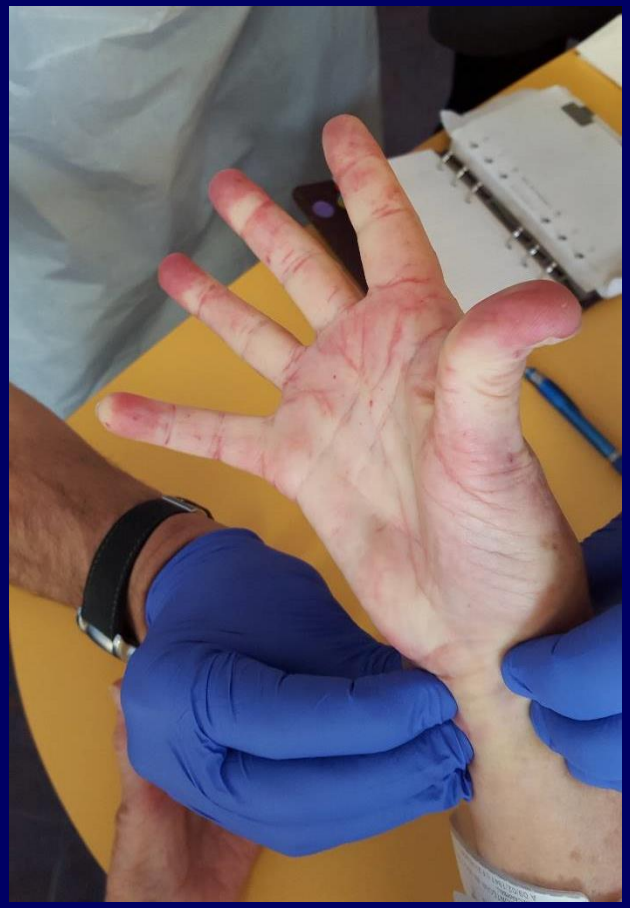


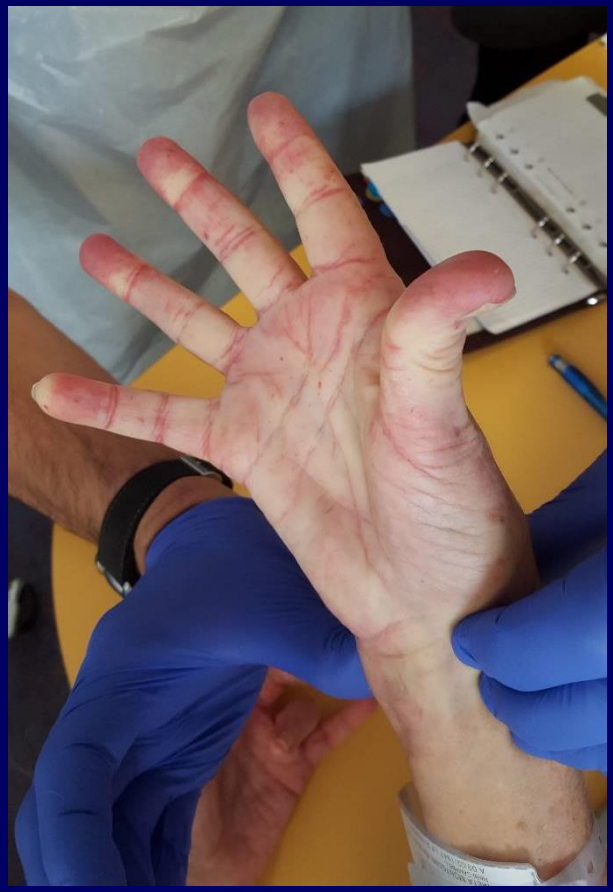
Infection
Gangrene
Amputation

→

Disability
Pain
Loss of function

Ulnar artery stenosis





Assessment of DU: Important details

- Site & dimensions
- Margins
- Bottom of the lesion (eschar, necrosis, fibrin)
- Exudate
- Perilesional skin
- Oedema
- Pain
- Infection

Decide on the most appropriate local treatment

Slide courtesy of Marco Matucci Cerinic.

Cochin hand function scale (CHFS)

Without the help of adapted instruments, in the past two weeks, did you:

- **Categories for assessment**

- **The scale is based on the following answer scores**

0 = Yes , without difficulty

1 = Yes, with a little difficulty

2 = Yes, with some difficulty

3 = Yes, with much difficulty

4 = Nearly impossible to do

5 = Impossible

Duruöz MT, *et al. J Rheumatol* 1996; 23:1167-72.

Impact of digital ulcers on disability and health-related quality of life in SSc (I)

Scores	DU group *n* = 67			No DU group *n* = 146			*p* value
	Mean ± SD	Min	Max	Mean ± SD	Min	Max	
HFI (range 4-42)	23.9 ± 12.0	2	40	18.7±26.2	4	40	0.048
Kapandji (range 0-100)	70.1 ± 22.6	13	100	81.5±17.8	36	100	0.001
CHFS (range 0-90) (*n*=209)	27.4 ± 20.6	2	86	16.7±18.2	0	87	0.0001
HAQ (range 0-3)	1.2 ± 0.7	0	2.75	0.9±0.7	0	3	0.008

Mouthon L, *et al*. *Ann Rheum Dis* 2010; 69:214-7.

Impact of digital ulcers on disability and health-related quality of life in SSc (II)

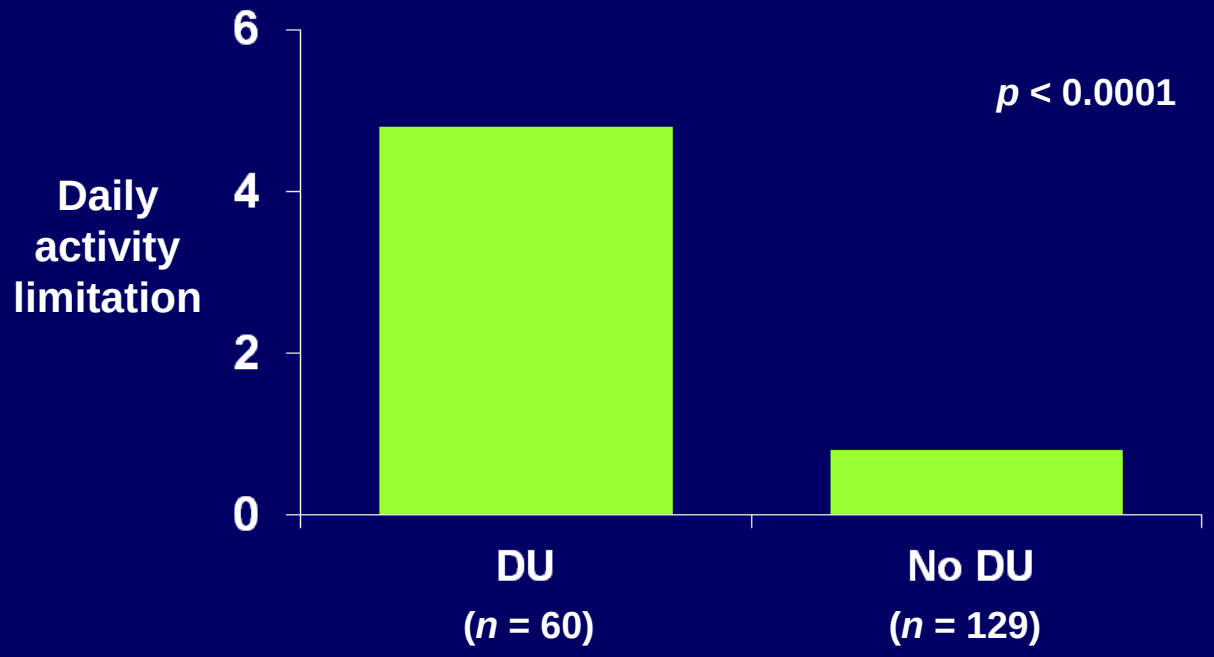
Scores	DU group *n* = 67			No DU group *n* = 146			*p* value
	Mean ± SD	Min	Max	Mean ± SD	Min	Max	
SF-36 PCS (range 0-100) (*n* = 179)	35.86 ± 9.39	15.41	63.23	37.7 ± 11.6	14	79.66	0.264
SF-36 MCS (range 0-100) (*n* = 179)	39.6 ± 9.5	15.64	60.32	43.4 ± 12.5	18.48	76.91	0.026
MHISS (range 0-48)	23.0 ± 10.8	2	48	17.5 ± 10.58	0	38	0.001
Aesthetic burden (range 0-10) (*n* = 148)	6.1 ± 2.2	0	10	3.9 ± 2.4	0	9	0.0001

QoL is impacted in many ways by DU

Mouthon L, *et al*. *Ann Rheum Dis* 2010; 69:214-7.

Digital ulcers influence daily living activities

- Daily activity is measured on a scale of 0-10, with 0 being no limitation and 10 being major limitations; *n* = 189

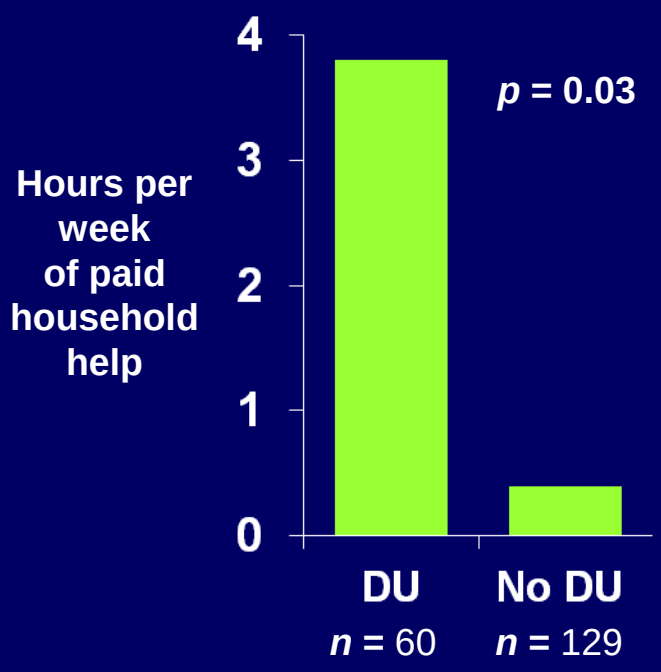


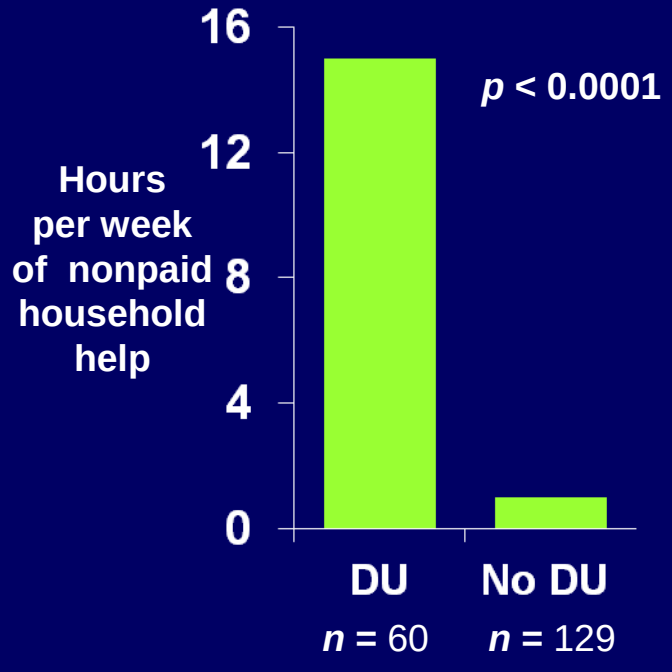
DU: digital ulcers

Bérezné A, *et al*. *Arthritis Care Res* 2011; 63:277-85.

Digital ulcers influence ability to perform household tasks

- Due to the inability to perform household tasks, patients with DU seek help in the form of paid or unpaid labour





DU: digital ulcers

Bérezné A, *et al*. *Arthritis Care Res* 2011; 63:277-85.

Management of DU: Multidisciplinary approach

Prevention of complications
Including patient education

Pharmacological treatment
Prevention of new DU
Healing pre-existing DU

Antibiotics

Pain relief

Non-pharmacological treatment: rehabilitation

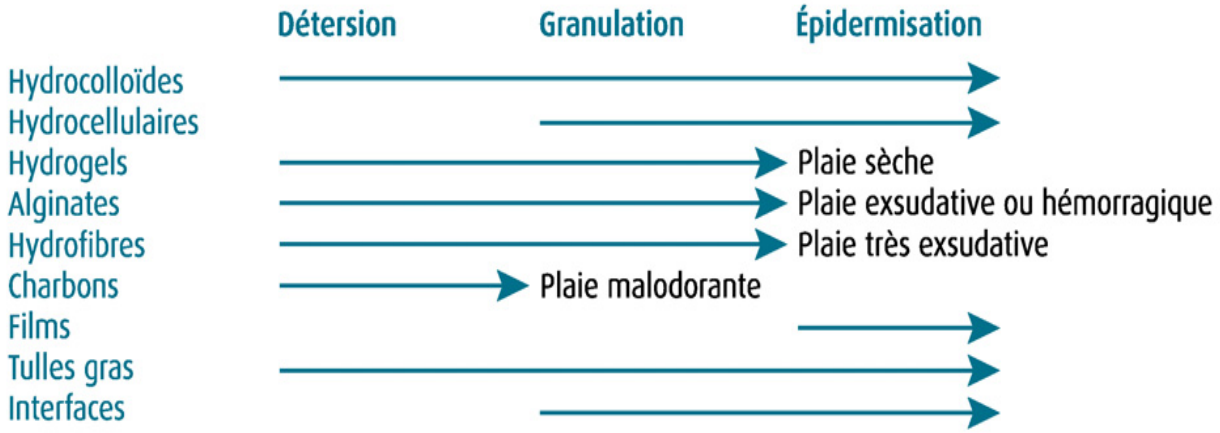
Local treatment & wound care

Surgery
only when necessary

Traitement local de l'ulcère

- diminuer les douleurs, de favoriser la cicatrisation, et de lutter contre le risque d'infection
- **Laver, Rincer, Sécher** +/- antiseptique
- **Détersion mécanique**:
  - éliminer la nécrose et la fibrine avec un grattoir, curette de Brocq, ou bistouri
  - Accélérer l'épidermisation
  - Antalgiques locaux (Emla® à 5% ou xylocaïne gel®)

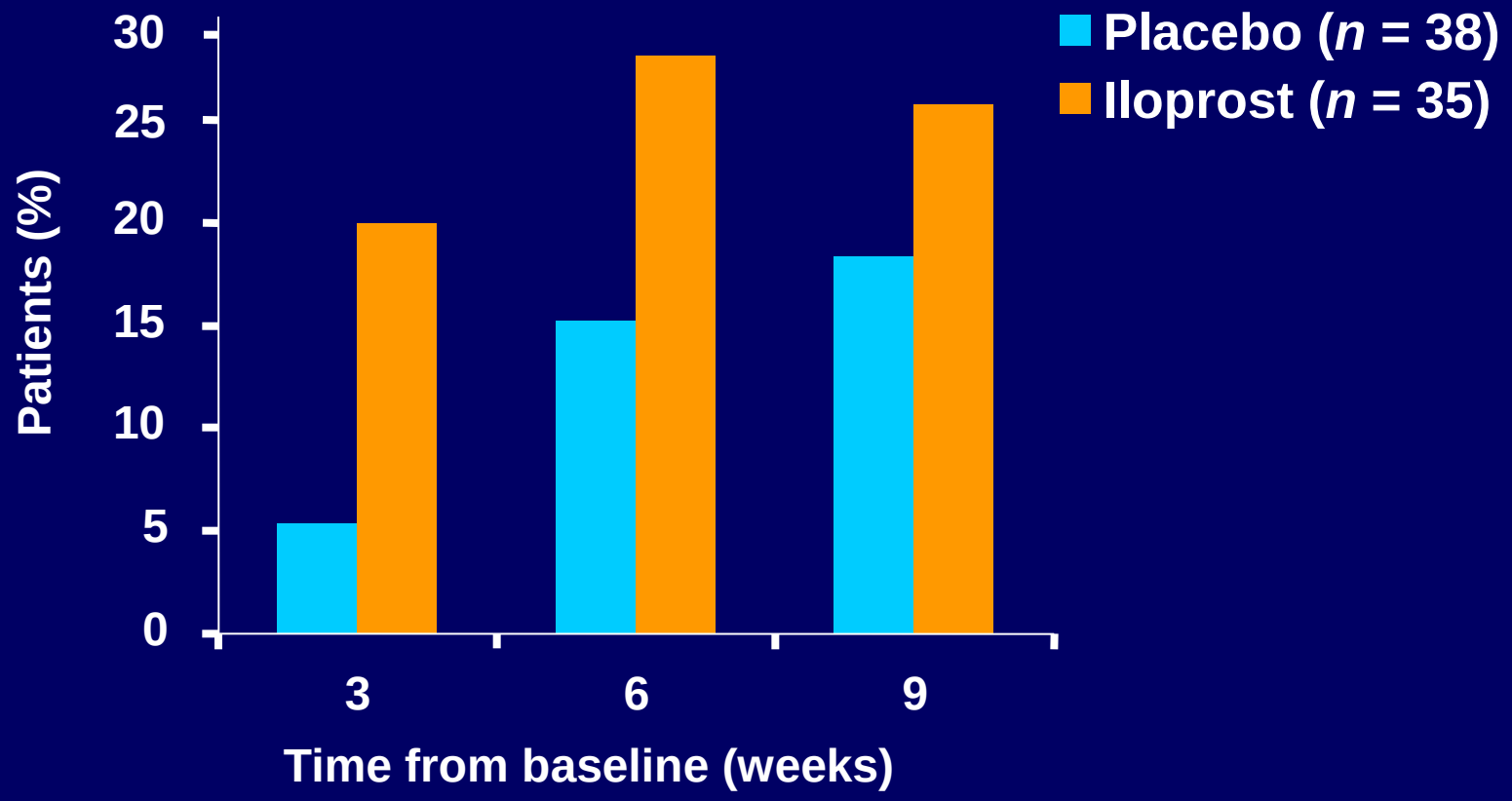
- **Pansement primaire au contact de la plaie:** Hydratent et favorisent la détersion de la fibrine et de la nécrose



Francès C et al, Presse Med. 2008

Effect of intravenous iloprost on DU healing

Proportion of SSc patients with RP who experience a reduction in the number of DU ≥ 50% following treatment with IV iloprost



Wigley FM, *et al. Ann Intern Med* 1994; 120:199-206.

EULAR/EUSTAR recommendations for healing of DU

- Two RCTs indicate that i.v. prostanoids (particularly i.v. iloprost) are efficacious in healing DU in patients with SSc
  - i.v. prostanoids (in particular iloprost) should be considered in the treatment of active DU in SSc patients
- Bosentan has no proven efficacy in the treatment of active DU in SSc patients

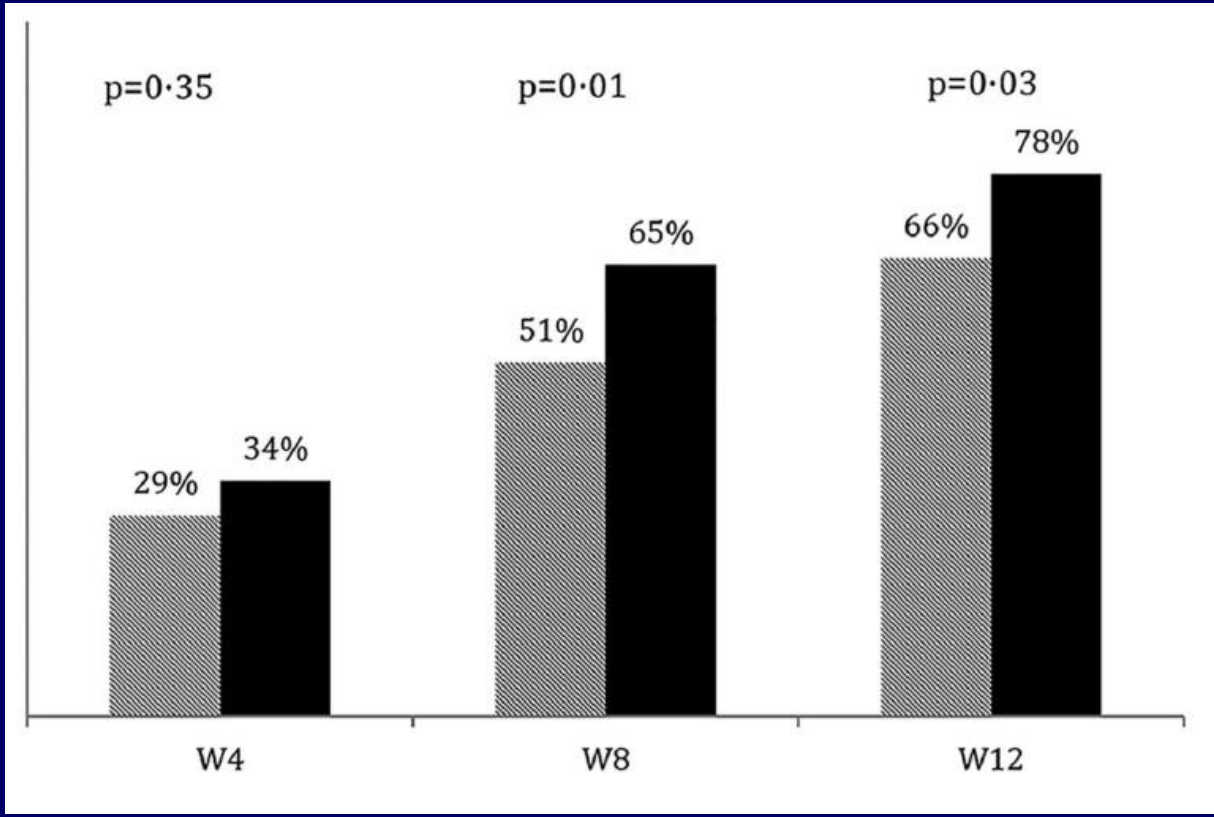
Kowal-Bielecka O, *et al. Ann Rheum Dis* 2009; 68:620-8.

Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

Efficacy of sildenafil on ischaemic digital ulcer healing in systemic sclerosis: the placebo-controlled SEDUCE study



The primary end point was not reached in intention-to-treat, partly because of an unexpectedly high healing rate in the placebo group. We found a significant decrease in the number of DUs in favour of sildenafil compared with placebo at W8 and W12, confirming a sildenafil benefit.

Hachulla et al. ARD 2016

Surgical treatment

Rarely proposed in SSc patients (2 to 4%)

1. **Debridement**
2. **Removal of calcinosis**
   - **Complete removal is rarely feasible; conventional surgery or laser**
3. **Surgery of ischaemia**
   - **Digital sympathectomy (transient improvement, absence of demonstrated beneficial effect)**

Prophylactic measures

A. Cold

- Reduce cold exposure by wearing long and warm clothes, mittens
- Reduce professional cold exposure

B. Drugs

C. Vasoconstrictive agents

- Withdrawal of tobacco, cannabis, cocaine

D. Injuries

- Avoid hand injury, avoid repeated microtrauma
- Work-related trauma
- Occlusion

Francès C, *et al. Presse Med* 2008; 37:271-85.

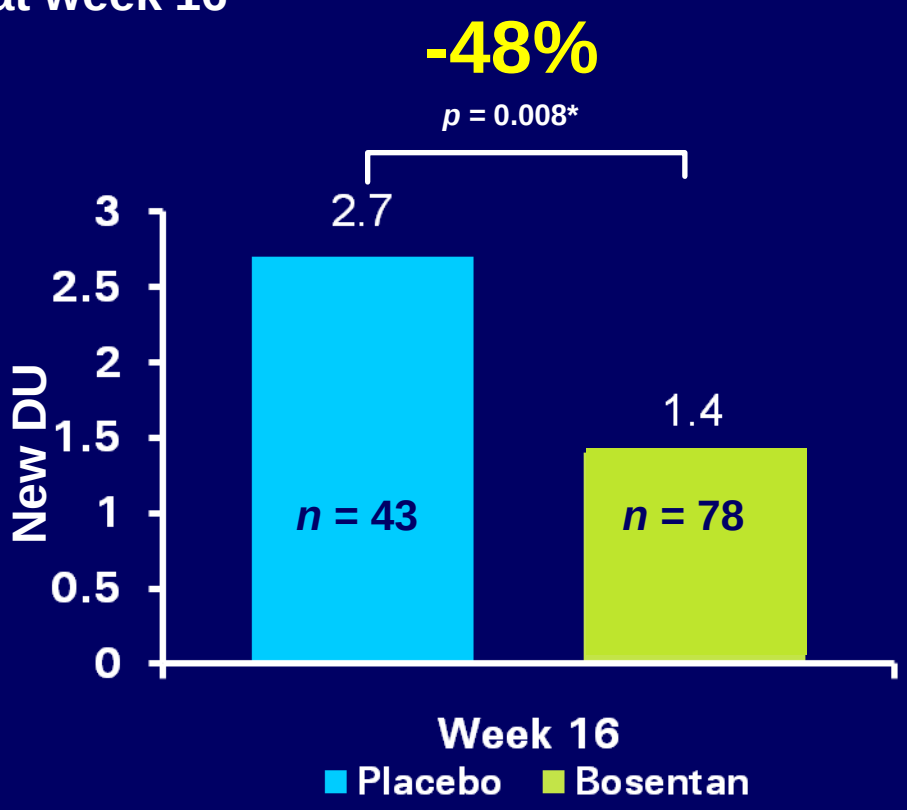
Prevention in the occurrence of new DU

- **Calcium channel blockers (CCBs)**
  - **The preventive role of CCBss has never been evaluated**
- **Prostacyclin**
  - **No evidence from literature that iloprost can prevent DU**
  - **Heterogeneity among clinicians regarding duration and frequency of infusions**
  - **Recommended dose: 0.5 to 2 ng/kg/mn for 6 to 8 h/d during 5 days; minimum six weeks between 2 infusions**
- **Bosentan[1,2]**
  - **Two prospective randomised studies demonstrated the efficacy of bosentan in preventing the occurrence of DU in SSc**
- **Atorvastatin[3]**
  - **84 pts double-blind RCT – 40 mg atorvastatin vs placebo**

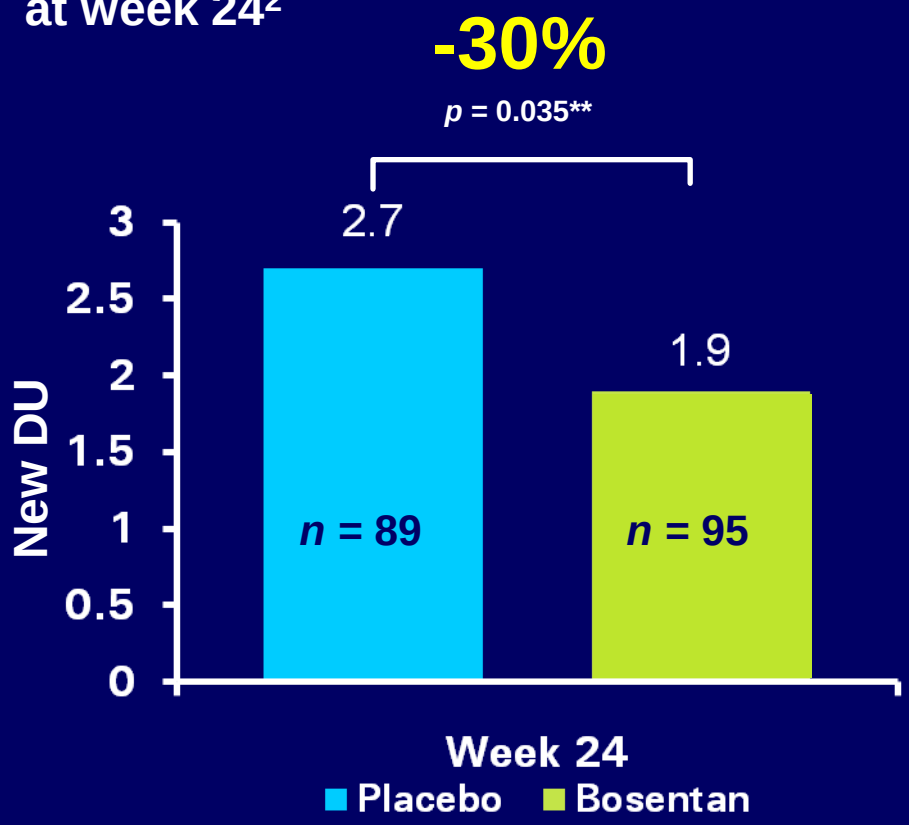
1. Korn JH, *et al*. *Arthritis Rheum* 2004; 50:3985-93.
2. Matucci Cerinic M, *et al. Ann Rheum Dis* 2011; 70:32-38.
3. Abou-Raya A, *et al*. *J Rheumatol* 2008; 35:1801-8..

Effect of bosentan in reducing the number of new DU

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



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



1. Korn JH, *et al*. *Arthritis Rheum* 2004; 50:3985-93.
2. Matucci Cerinic M, *et al. Ann Rheum Dis* 2011; 70:32-38.

Ongoing / recent studies in DU-SS

- Seduce: sildenafil vs placebo
- Dual: macitentan vs placebo
- Selexipag vs placebo

SELEXIPAG IN RAYNAUD'S PHENOMENON SECONDARY TO SYSTEMIC SCLEROSIS: A RANDOMISED, PLACEBO-CONTROLLED, PHASE II STUDY

- Objectives: To determine the activity of selexipag, an oral, selective, prostacyclin receptor agonist, on RP attack frequency in pts with SSc.
- Methods: placebo single-blind run-in phase of 2–4-weeks followed by an 8-week double-blind treatment phase. Pts (≥18 years) with definite SSc and ≥7 RP attacks on ≥5 days in the week before randomisation were assigned 1:1 to selexipag or placebo. Study drug was titrated to an individual highest tolerated dose (200–1600 µg BID).
- Results: Baseline (BL) characteristics were comparable between the groups (selexipag n=36, placebo n=38). No significant difference in effect was demonstrated for selexipag vs placebo (observed average number of RP attacks per week during the maintenance phase: 18.0 [vs 22.4 at BL, selexipag, n=27], 14.2 [vs 21.5 at BL, placebo, n=32]), adjusted mean treatment difference 3.43 in favour of placebo.
- Conclusions: The primary efficacy endpoint was not met (no reduction in number of RP attacks per week for selexipag vs placebo).

EULAR 2016; **FRI0265** C. Denton

Ulcères digitaux: conclusion

- Ulcères digitaux: un patient sclérodermique sur deux
- Maladie ulcéreuse digitale récidivante: très invalidante
- Traitement préventif : arrêt tabac, inhibiteurs calciques, bosentan si UD récidivants
- Traitement curatif….. Iloprost…..
- Nécessité de nouveaux traitements

French Vasculitis Study Group

GFRS Groupe Francophone de Recherche sur la Sclérodermie

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