

**ACTUALITÉS NÉPHROLOGIQUES  
JEAN HAMBURGER  
HÔPITAL NECKER**

***NECKER SEMINARS IN NEPHROLOGY***

# **Calciphylaxie : Nouvelles Approches Thérapeutiques**

**Dr Pablo Ureña Torres**  
[urena.pablo@wanadoo.fr](mailto:urena.pablo@wanadoo.fr)

**Chief of Dialysis Service AURA Nord Saint Ouen. 108 bis, avenue Gabriel Péri. 93400 Saint Ouen, France.  
Service des Explorations Fonctionnelles. Hôpital Necker-Enfant Malades, Assistance Publique-Hôpitaux de Paris.**

**Paris, France. May 10th, 2022**



# Conflicts of Interest

**Pablo A. Ureña Torres, MD**

**Grants/research support:** Abbvie, Amgen, Astellas, GSK, Hemotech

**Consultant:** Abbvie, Amgen, Sanofi, Vifor Pharma FMC

**Scientific advisor:** Astellas, GSK, Leo Pharma,

**Honoraria:** none

**Board position:** CKD-MBD Working Group ERA-EDTA

# Outline

- 1- Introduction, definition and epidemiology**
- 2- Factors associated**
- 3- Clinical aspects and evolution**
- 4- Diagnostic**
- 5- Treatments : Traditional and New**

# Outline

**1- Introduction, definition and epidemiology**

2- Factors associated

3- Clinical aspects and evolution

4- Diagnostic

5- Treatments : Traditional and New

# Calciphylaxis

## CUA: Late Stage Orphan Disease Program

High morbidity and mortality - no approved therapy

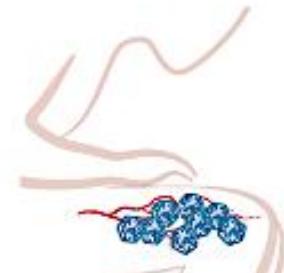
**Extreme form of CVC in skin arterioles affecting mostly ESKD patients**

No approved treatments; standard of care limited to palliative options

**Characterized by intensely painful ischemic/necrotic wounds**

Rapid disease progression leads to extreme pain, infection and death  
~55% 1-year mortality

**Nephrologists highly aware of CUA despite it being a rare condition**  
Believed to be underdiagnosed due to lack of approved treatments



~10K  
patients  
in US and Europe<sup>1</sup>

~55%  
1-year  
mortality<sup>2</sup>

94%  
Specialists  
familiar w/ CUA<sup>1</sup>

The image contains several components related to Calciphylaxis:

- Journal Article Cover:** A thumbnail of a New England Journal of Medicine article titled "Calciphylaxis" by John R. Ingelhart, M.D., et al. The abstract notes that calcification in skin arterioles can lead to intensely painful, necrotic wounds.
- Anatomical Diagrams:** Two detailed anatomical illustrations. One shows a cross-section of a blood vessel with labels for the tunica intima, tunica media, tunica adventitia, and afferent and efferent arterioles. The other is a larger circular diagram of a blood vessel showing calcification within the tunica intima, with labels for the internal elastic lamina, external elastic lamina, tunica media, tunica adventitia, and afferent/efferent arterioles.

# Epidemiology of Calciphylaxis

## Incidence and prevalence

Very rare disease (1 à 4 % of dialysis patients)  
(Levin AJN 13:448-453, 1993, Angelis Surgery 122:1083-1090, 1997)

Hayashi M., Japanese study NDT 27:1580-1584, 2012

3760 Questionnaires	100 %
1838 Positive answers	49 %
151 Centers with CUA	4 % (n = 249 cases – 100 %)
64 Centers willing to participate	1.7 % (n = 67 cases – 27 %)

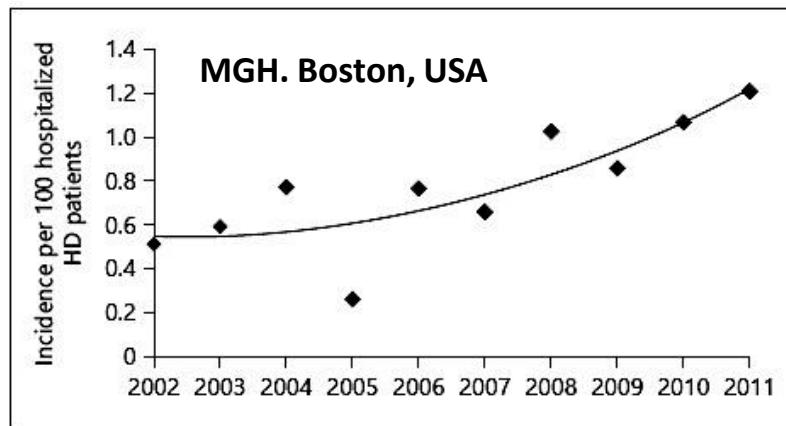


Fig. 1. Increasing trend in CUA cases over the study period.

Nigwekar S et al., Am J Nephrol 37:325-332, 2013

1 to 4 % in USA

1.7 % in Japan

0.4 to 1 % in Europe

German CUA Registry  
Brandenburg V. et al.

35 cas/year  
160 cases of calciphylaxis  
prospectively collected  
between 2006 and 2015

24 cas/year in France  
(2015-2017)

Gaisne R. et al. BMC Nephrol 2020  
89 cases over 10-year period  
Western France

# Epidemiology of Calciphylaxis

## Incidence and prevalence in French Polynesia (Tahiti)

Population : 275 918

Approximately 100 patients incidents in dialysis per year

An incidence 10 fold higher than in Europe

2018 : 15/1000 persons                    15/100 patients

2017: 17/1000                                17/100 patients

2016: 11.8/1000                                11/100 patients

2015: 11.8/1000                                11/100 patients



# Outline

1- Introduction, definition and epidemiology

**2- Factors associated**

3- Clinical aspects and evolution

4- Diagnostic

5- Treatments : Traditional and New

# Factors Associated with Calciphylaxis

General	CKD-Related
Woman	Dialysis ou renal transplantation
Obesity	Inflammation
Diabetes	Malnutrition (weight loss)
Caucasian	Hypo-albuminemia
Cancer (melanome, breast, myeloma, leukemia, etc.)	Hyperparathyroidism Treatments :
Liver fibrosis (cirrhosis)	Vitamin D
Immune disease (Lupus, rheumatoid polyarthritis, etc.)	Anti-vitamin K
Crohn disease	Steroids
Thrombophilia	
Coronary artery disease	

# Factors Associated with Calciphylaxis

## 6 Major Risk Factors

Factor	Odd Ratio	IC	p
Anti-vitamin K therapy	11.4	2.7-48.1	0.0009
Hypo-albuminemia (for each decrease of 1 g/L)	19.8	4.4-89.5	0.0001
Glycemia (for each increase of 1 g/L)	3.7	1.0-12.9	0.03
Calcemia (for each increase of 1 mg/dL)	3.2	1.6-6.3	0.0008
Hyperphosphatemia	3.5		0.008
Number of insulin injection (3)	1.8	1.3-3.4	<0.05

1- Rivet J, Lebbe C, Urena P., et al. Arch Dermatol 142:900-9006, 2006

2- Hayashi M. et al. NDT 27:1580-1584, 2012

3- Nigwekar S. et al. JASN 2016

4- Gaisne R. et el. BMC Nephrol 2020

# Diagnosis of Calciphylaxis

## Analysis of the EuCalNet Registry (2019)

N = 218 dialysis CUA 2006 – 2015. Dialysis Vintage

Parameter	All HD/HDF N= 193 (100%)	PD N = 25 (100%)	Men HD/HFD (n = 72)	Women HD/HDF (n = 121)
Age (year)	70 (62-76)	64 (55-74)	69 (61-76)	71 (64-77)
Caucasians (%)	All	All		
Females	121 (63%)	12 (48%)		
Time interval to diagnosis (days)	24 (11-50)	24 (12-42)	30 (14-60)	21 (10-46)
Time interval since start of dialysis to CUA diagnosis (months)	30 (7-56)	46 (29-69)	25 (4-50)	34 (7-64)

# Outline

1- Introduction, definition and epidemiology

2- Factors associated

**3- Clinical aspects and evolution**

4- Diagnostic

5- Treatments : Traditional and New

# Clinical Aspect of Calciphylaxis

## Initial Lesions

Livedo



Central necrotic lesion



# Clinical Aspect of Calciphylaxis

## Evolution



# Clinical Aspect of Calciphylaxis

## Evolution

Scars



Necrosis, Gangrene



# Clinical Aspect of Calciphylaxis

## Evolution

Ulceration, scarring and necrotic lesions (legs, breast...)



# Clinical Aspects of Calciphylaxis

## Evolution



Courtesy from Dr Arnaud LIONET

# Clinical Aspects of Calciphylaxis

## Evolution



Courtesy from Dr Arnaud LIONET

# Clinical Aspects of Calciphylaxis

## Evolution



Moe SM. et al., Kidney Int 61:638-647, 2002

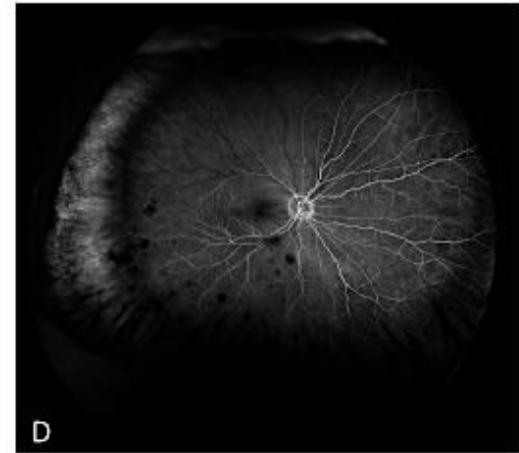
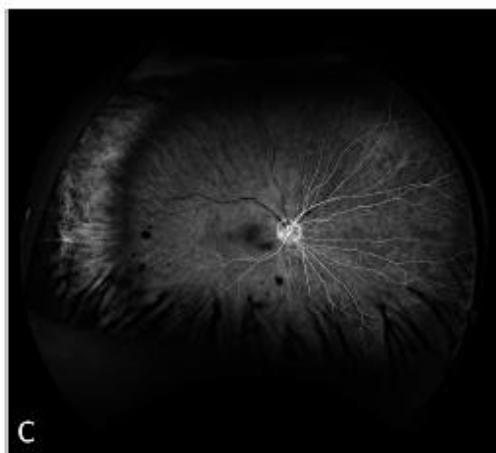
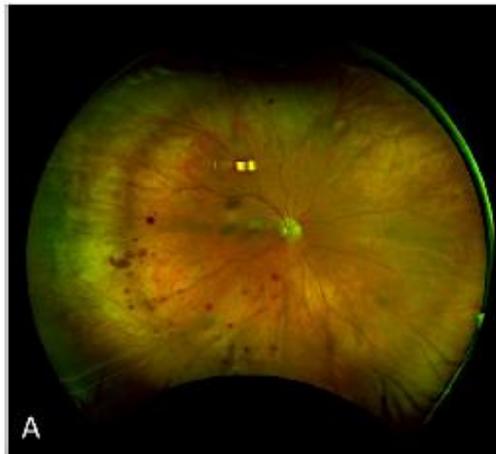
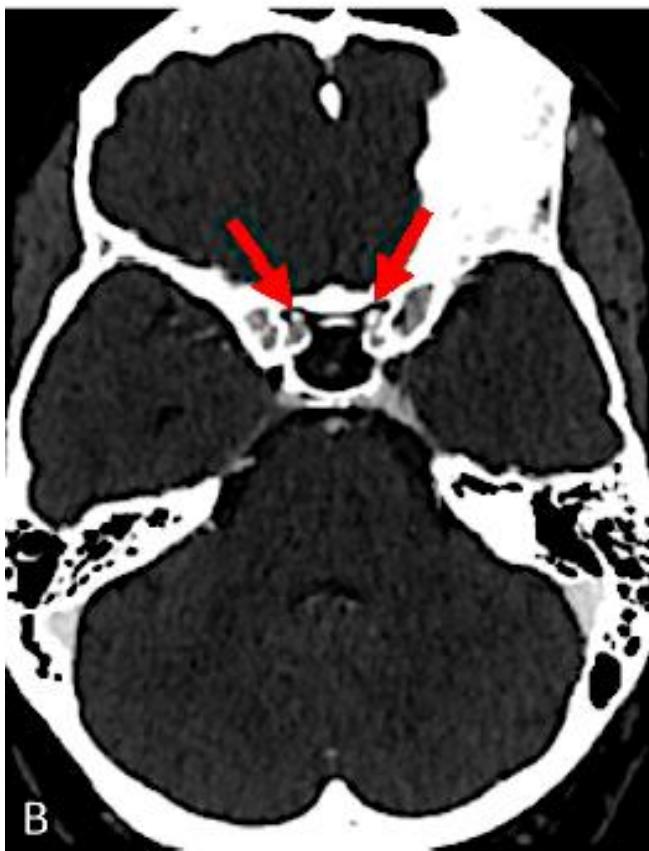
# Clinical Aspects of Calciphylaxis

## Evolution



# Clinical Aspects of Calciphylaxis

## Retinal arteria and vein occlusion



# Outline

1- Introduction, definition and epidemiology

2- Factors associated

3- Clinical aspects and evolution

4- Diagnostic

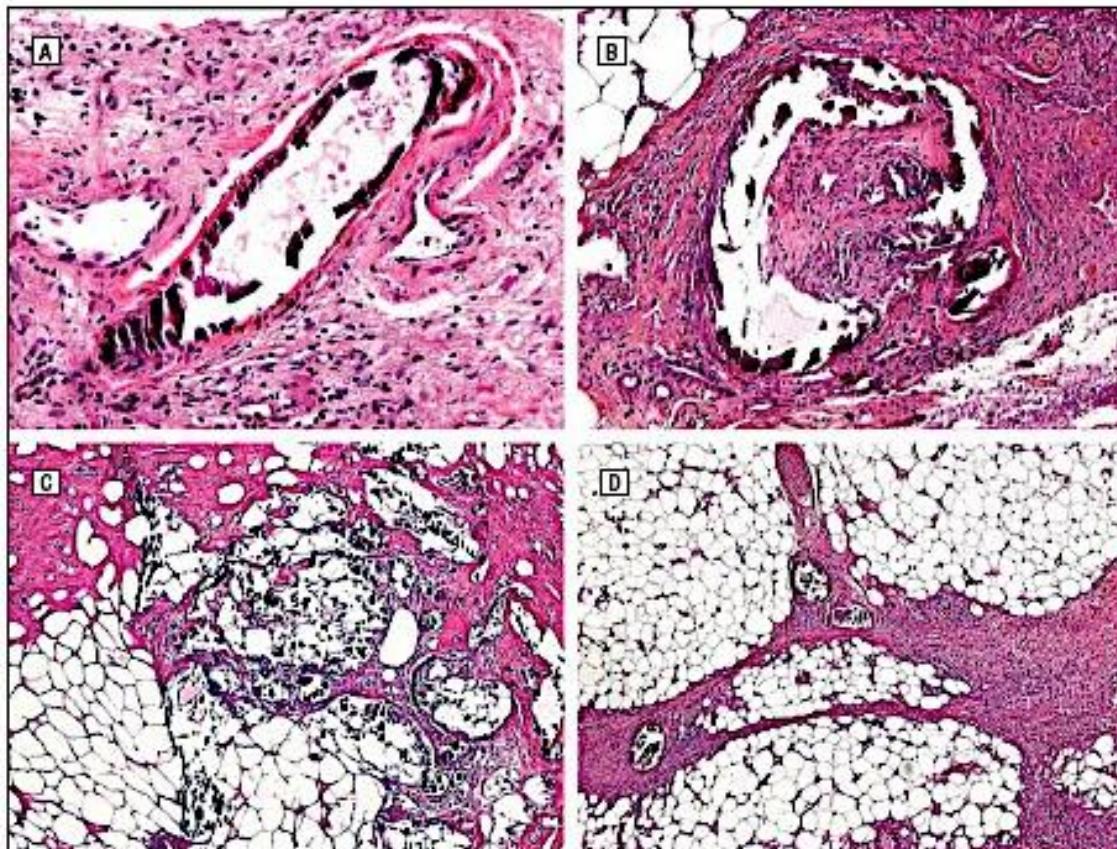
5- Treatments : Traditional and New

# Diagnosis of Calciphylaxis

## « Punch » Skin Biopsy

**Results:**

- Massive calcification of the intima layer
- Severe arterial stenosis, media calcification, and endovascular fibrosis
- Extra-vascular calcification around adipocytes
- Large calcification of sub-cutaneous capillar



**Figure 2.** Pathologic features of cutaneous calcifications (hematoxylin-eosin for all specimens).  
A, Massive calcification of the intima (original magnification  $\times 200$ ). B, Severe stenosis with nearly circumferential medial calcification and endovascular fibrosis (original magnification  $\times 200$ ). C, Extravascular calcification between lipocytes (original magnification  $\times 100$ ). D, Subcutaneous extensive calcifications of capillaries (original magnification  $\times 100$ ).

# Diagnosis of Calciphylaxis

clinical investigation

www.kidney-international.org

## Questionable specificity of histologic findings in calcific uremic arteriolopathy



see commentary on page 244

Carla L. Ellis<sup>1</sup> and W. Charles O'Neill<sup>2</sup>

<sup>1</sup>Department of Pathology, Emory University School of Medicine, Atlanta, Georgia, USA; and <sup>2</sup>Renal Division, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA

**Table 1 | Patient characteristics**

	Amputations	Skin biopsies	P Value
N	34	37	
Age (mean $\pm$ SEM)	62 $\pm$ 1.9	53 $\pm$ 2.5	0.006
Gender (% female)	29	81	<0.0001
Diabetes (%)	71	51	0.14
ESRD (%)	100	78	0.005
Dialysis	91	76	
Transplantation	9	3	
Warfarin use (%)	21	49	0.02

ESRD, end-stage renal disease.

Ellis L, et al. Kidney Int 94:390-395, 2018

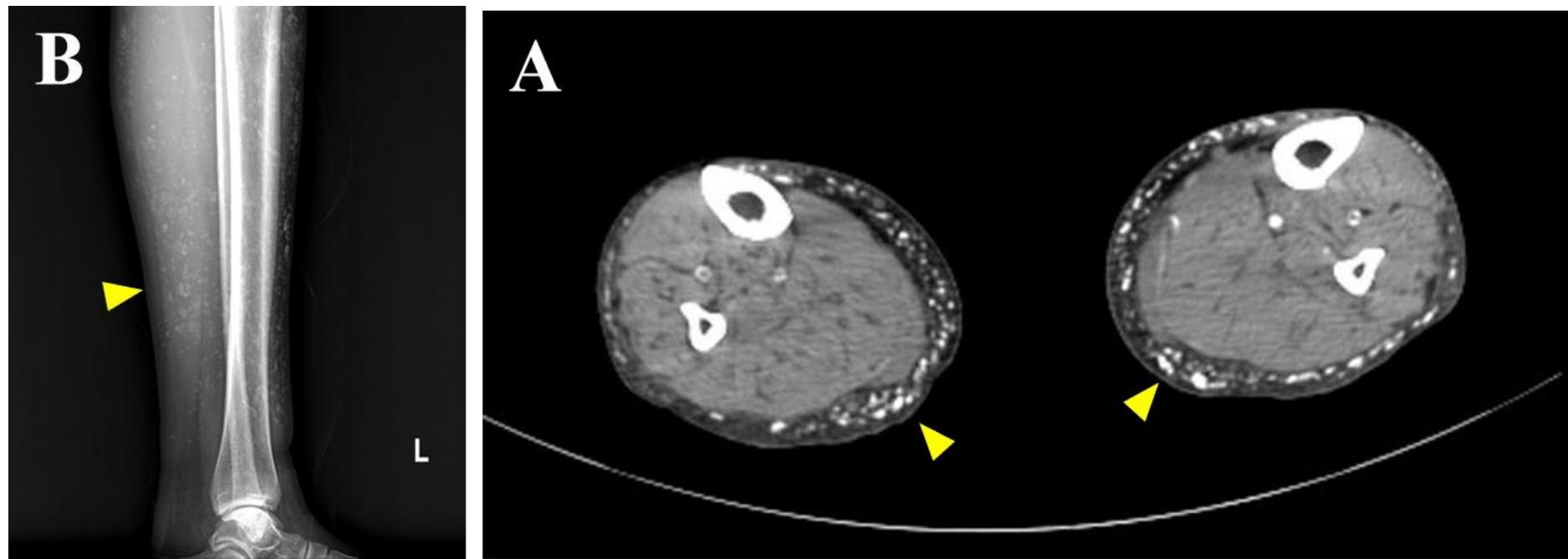
# Diagnosis of Calciphylaxis

**Table 2 | Histologic findings in skin biopsies and amputations**

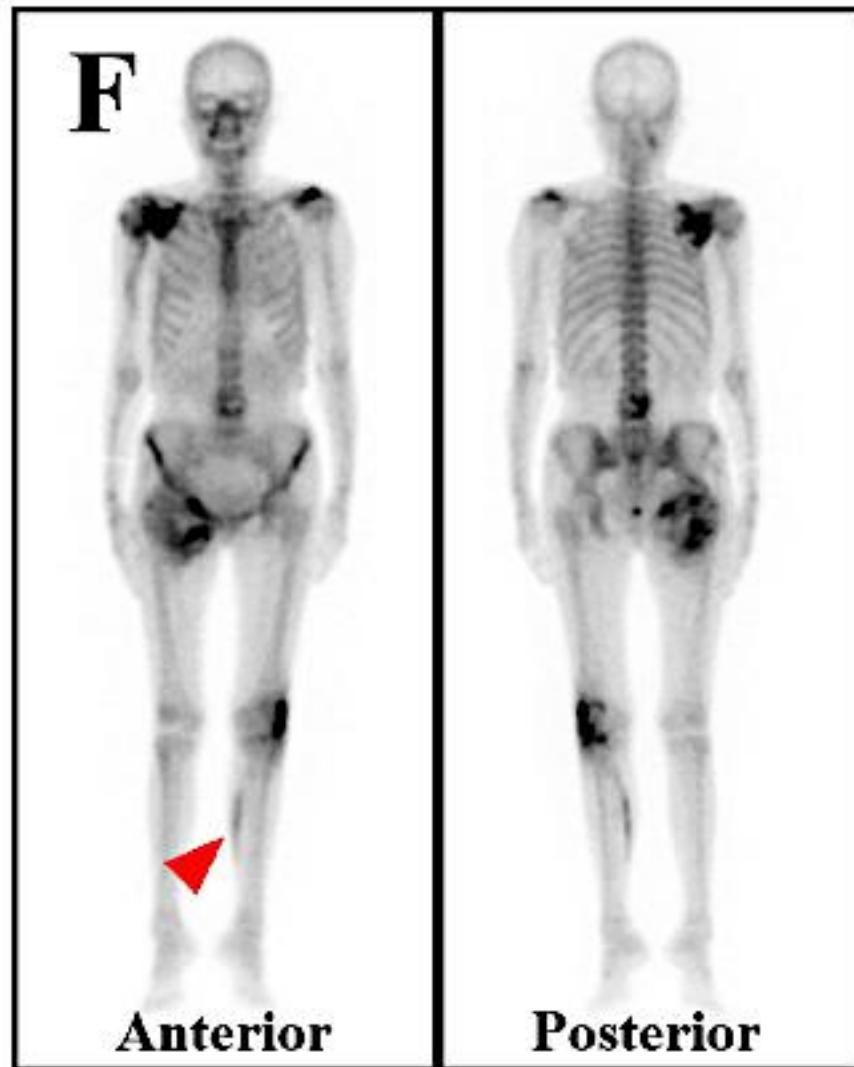
	Amputations	Skin biopsies	P Value
<u>Lesions in small arteries and arterioles (%)</u>	32	57	0.07
<u>Calcification</u>	19	38	0.08
<u>Thrombosis</u>	14	36	0.04
<u>Intimal hyperplasia</u>	12	5	0.44
<u>Calcification + thrombosis</u>	5	19	0.07
<u>Calcification + intimal hyperplasia</u>	5	0	0.5
<u>Extravascular soft tissue calcification (%)</u>	40	27	0.54
<u>Perieccrine</u>	2	5	0.59
<u>Vascular + extravascular calcification (%)</u>	9	8	1
<u>Vascular or extravascular calcification (%)</u>	49	46	0.83

# Diagnosis of Calciphylaxis

## Standard Radiography and CT



# Diagnosis of Calciphylaxis



# Outline

- 1- Introduction, definition and epidemiology
- 2- Clinical aspects and evolution
- 3- Diagnostic
- 4- Factors associated
- 5- Treatments : Traditional and New**

# Traditional Treatments

## Analysis of the German EuCalNet Registry (2019)

### GENERAL MEASURES

- Pain relief	
- Dialysis intensification	(16,9%)
- Surgical	(29,2%)
- Prevention of infection	(16,1%)
- Nutritional supplementation	
- Stop anti-vitamin K	(25,4%)
- Vitamin K supplementation	(17,7%)
- Limiting calcium prescription	(23,8%)
- Limiting active vitamin D use	(16,2%)

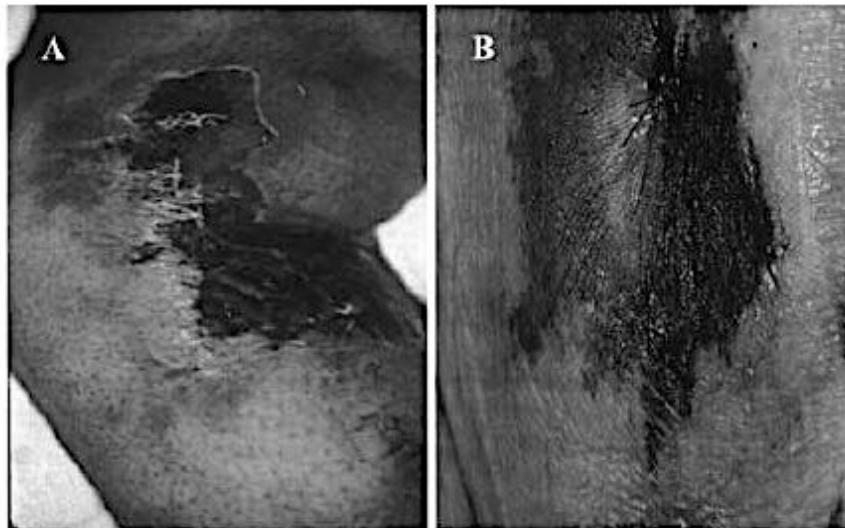
### SPECIFICS

- Parathyroidectomy	
- Calcimimetics	(10,8%)
- Sodium thiosulfate (STS)	(21,7%)
- Bisphosphonates	
- Hyperbaric oxygenation	
- Albumin	
- Statins	
- Antagonist of endothelin receptor	

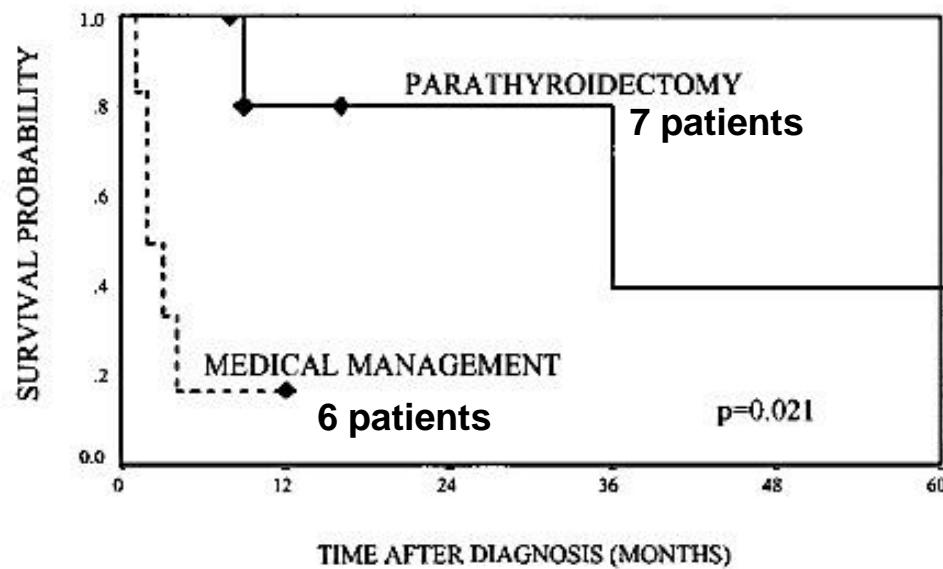
Paracetamol, gabapentine, pregabalin et amitriptyline  
opioids, fentanyl

# Parathyroidectomy for the Treatment of Calciphylaxis

# Parathyroidectomy Improves the Healing of Calciphylaxis Lesions and Survival Rate in Dialysis Patients with SHPT



**Fig 1.** Skin lesions in patients with calciphylaxis. **A**, Note purpuric areas with necrotic centers. **B**, Punch biopsy of the center of the lesion confirms the diagnosis.



**Fig 2.** Actuarial survival comparison of patients with secondary hyperparathyroidism and calciphylaxis treated by parathyroidectomy versus medical management alone.

# **Calcimimetics for the Treatment of Calciphylaxis**

# Cinacalcet HCl Induced the Regression of Calciphylaxis Lesions



	Before	3	6	month
PTH (pg/ml)	190	11	12	
Calcemia (mmol/L)	2.55	2.45	2.09	
Phosphatemia (mM)	3.19	1.55	1.55	

Sharma A, et al. Br J Dermatol 155 (6):1295-1297, 2006

# Calcimimetic in the Treatment of Calciphylaxis

Nephrol Dial Transplant (2007) 0: 1–3  
doi: 10.1093/ndt/gfm676  
Advance Access publication xx xx xxxx



## *Case Report*

### Proximal calciphylaxis treated with calcimimetic ‘Cinacalcet’

Ismail A. Mohammed<sup>1</sup>, Vashisht Sekar<sup>2</sup>, Abdullah J. Bubtana<sup>1</sup>, Sandip Mitra<sup>1</sup> and Alastair J. Hutchison<sup>1</sup>

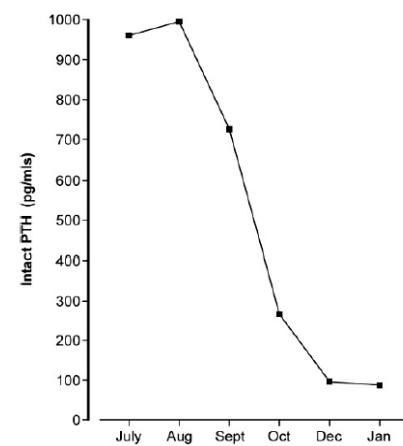
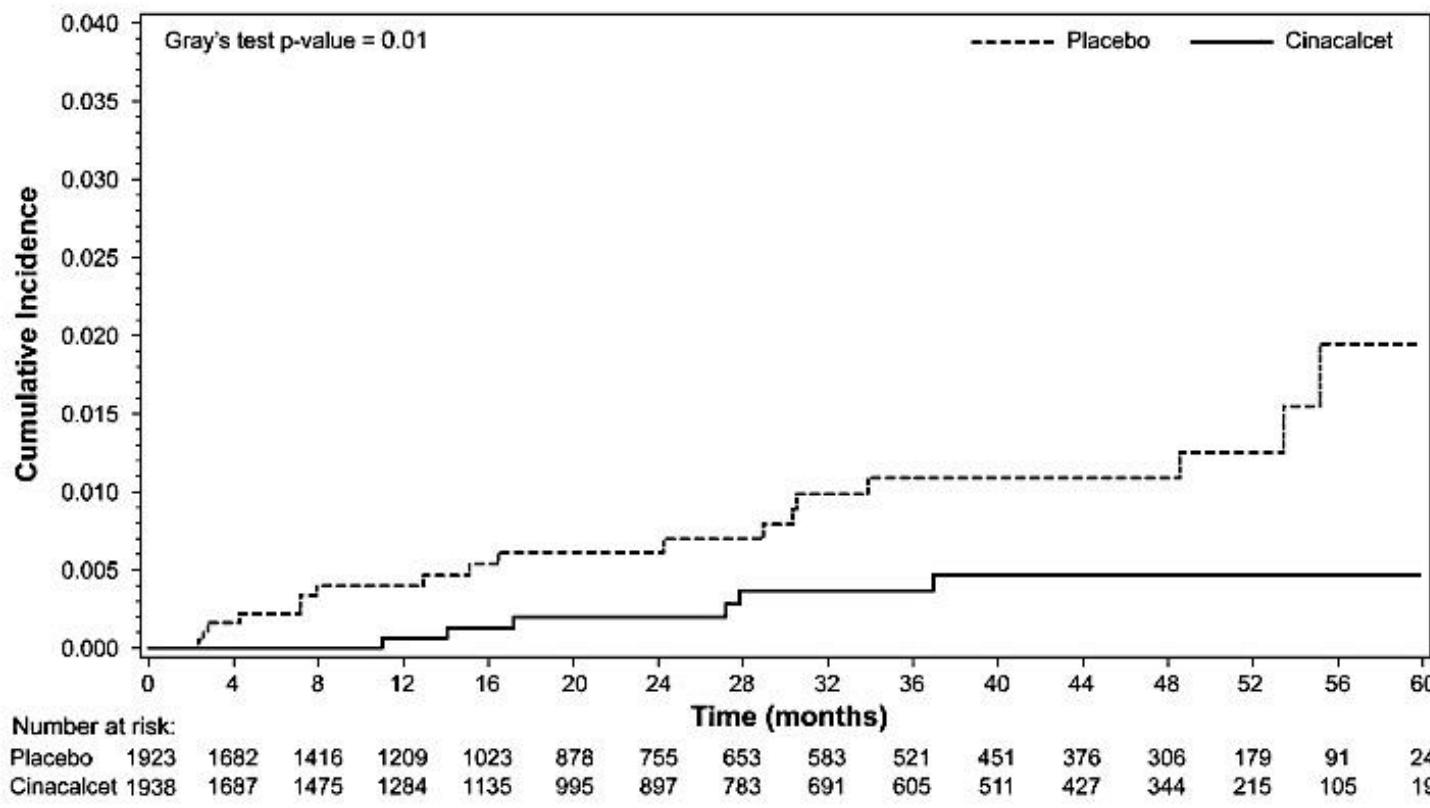


Fig. 2. Intact PTH levels during the course of treatment with Cinacalcet (treatment commenced in August 2005).

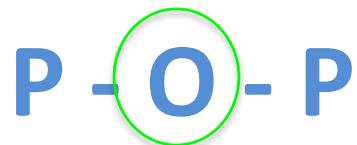
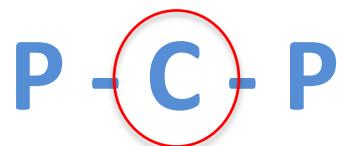
# Reduction of Calciphylaxis Incidence in the EVOLVE Study



Among the 3861 trial patients who received at least one dose of the study drug, 18 patients assigned to placebo and six assigned to cinacalcet developed CUA (unadjusted relative hazard, 0.31; 95% confidence interval [95%CI], 0.13 to 0.79; P=0.014).

Figure 1. | Cumulative incidence plot of time to calcific uremic arteriolopathy adverse event (safety analysis set).

# Bisphosphonates for the Treatment of Calciphylaxis



Bisphosphonate (P-C-P) bonds are biologic analogues of naturally produced pyrophosphate (P-O-P) bonds. Bisphosphonates are not metabolized.

# Bisphosphonates

## Successful treatment of calcific uraemic arteriolopathy with bisphosphonates

José V. Torregrosa, Carlos E Durán, Xoana Barros, Miquel Blasco, Marta Arias, Aleix Cases, Josep M. Campistol

Servicio de Nefrología. Hospital Clínic. Barcelona (Spain)

Nefrologia 2012;32(3):329-34

doi:10.3265/Nefrologia.pre2012.Jan.11137



**8 patients**

**5 on hemodialysis**

**3 kidney transplanted**

---

**Calciphylaxis lesions regressed in all patients  
4 to 24 weeks after treatment by**

**1 patient 70 mg/d oral alendronate**

**4 patients 35 mg/w oral residronate**

**3 patients 6 mg i.v. ibandronate**

**Or 60 mg i.v. pamidronate monthly**

# Bisphosphonates

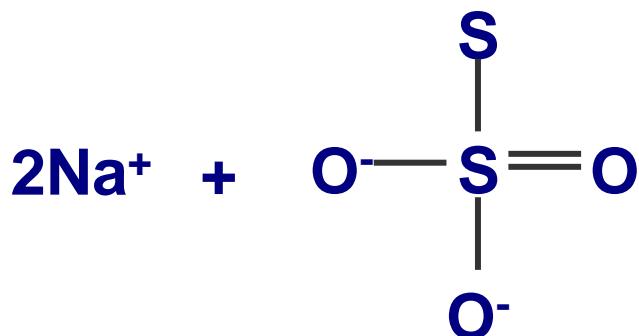
Table 1. Baseline characteristics of the study population and evolution post treatment.

	Group I (n = 12) (No bisphosphonates)	Group II (n = 11) (Bisphosphonates)	p-value
Age	54 ± 13	54 ± 9	ns
Gender (man)	41.7%	36.4%	ns
BMI	25.23 ± 6.34	24.04 ± 4.79	ns
DM	33.3% (4)	9.1% (1)	ns
Peripheral vascular disease	33.3%	36.4%	ns
Cause ESRD	Glomerulonephritis 20% Diabetes mellitus 20%	Glomerulonephritis 45.5% Diabetes mellitus 9.1%	ns
RRT	Hemodialysis 50% Renal Transplant 50%	Hemodialysis 45.5% Renal Transplant 54.5%	ns
Dicoumarin treatment	37.5%	54.5%	ns
Parathyroidectomy	55.6%	44.4%	ns
Vitamin D analogues treatment	12.5%	9.1%	ns
Calcium based binder treatment	0%	0%	ns
Steroids treatment	54.5%	63.6%	ns
Outcome	Amputation (7) 66.7% Recovery (3) 11.1% Exitus (2) 22.2%	Amputation 0% Recovery 100% Exitus 0%	< 0.01

BMI = body mass index, DM = diabetes mellitus, ESRD = end stage renal disease, RRT = renal replacement therapy, i-PTH = intact parathyroid hormone, Ca × PO<sub>4</sub>: calcium phosphate product, ns: no significative.

# **Sodium Thiosulfate for the Treatment of Calciphylaxis**

# Mode of Action of Sodium Thiosulfate



$\text{Na}_2\text{S}_2\text{O}_3$   
Donneur d'électron  
Capteur de cation



Glutathione

Anti-oxidants

- Selenium
- Vitamin E
- DMSO
- Catalase
- Glutathione transferase
- Glutathione peroxidase



Plus soluble

10 to 25 g during the last 30-60 min of the dialysis session.

Calcium binding effect

Antalgic

Anti-proliferative effect on vascular smooth muscle cells

Anti-thrombotic

Anti-oxidant

# Evolution of Calciphylaxis Lesions after Sodium Thiosulfate

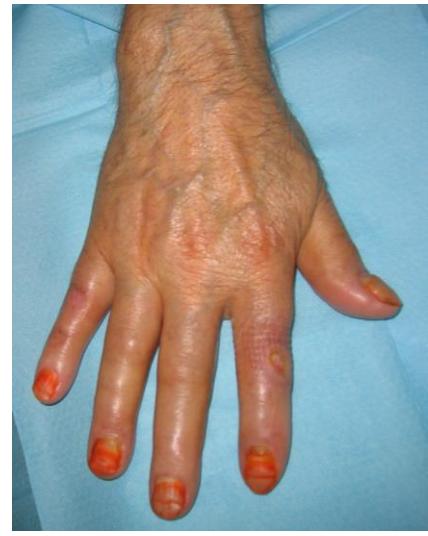
01 NOV 2007



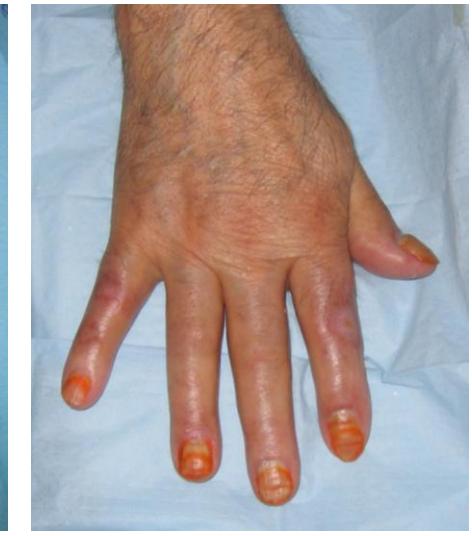
04 DEC 2007



10 JAN 2008



31 JAN 2008



# Effect of Sodium Thiosulfate on Calciphylaxis

T0



Figure 1. Ulcers of the right leg prior to treatment.

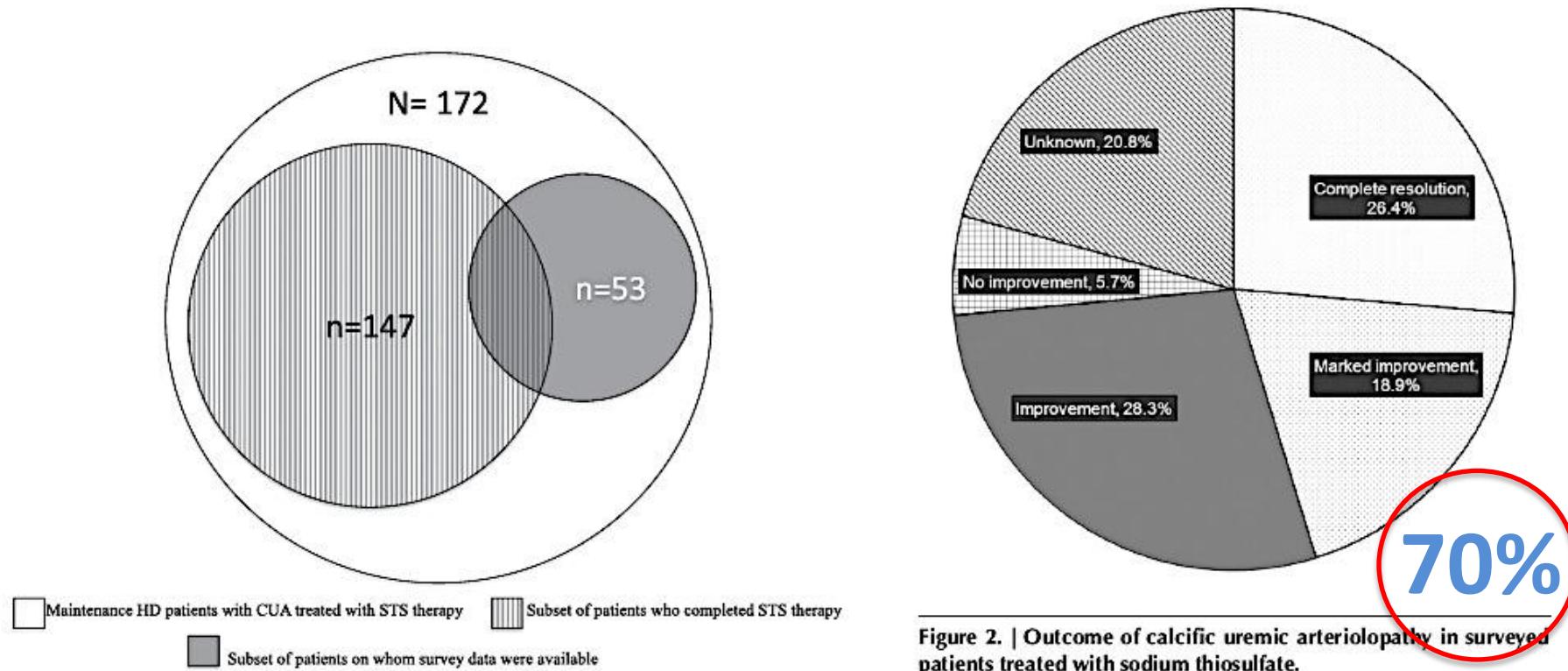
T3 months



Figure 2. Healed ulcers of the right leg 4 months after treatment.

# Sodium Thiosulfate Therapy for Calcific Uremic Arteriolopathy

Sagar U. Nigwekar,<sup>\*†</sup> Steven M. Brunelli,<sup>#§</sup> Debra Meade,<sup>||</sup> Weiling Wang,<sup>||</sup> Jeffrey Hymes,<sup>||</sup> and Eduardo Lacson Jr.<sup>||</sup>



# Sodium Thiosulfate Therapy for Calcific Uremic Arteriolopathy

Sagar U. Nigwekar,<sup>\*†</sup> Steven M. Brunelli,<sup>#§</sup> Debra Meade,<sup>||</sup> Weiling Wang,<sup>||</sup> Jeffrey Hymes,<sup>||</sup> and Eduardo Lacson Jr.<sup>||</sup>

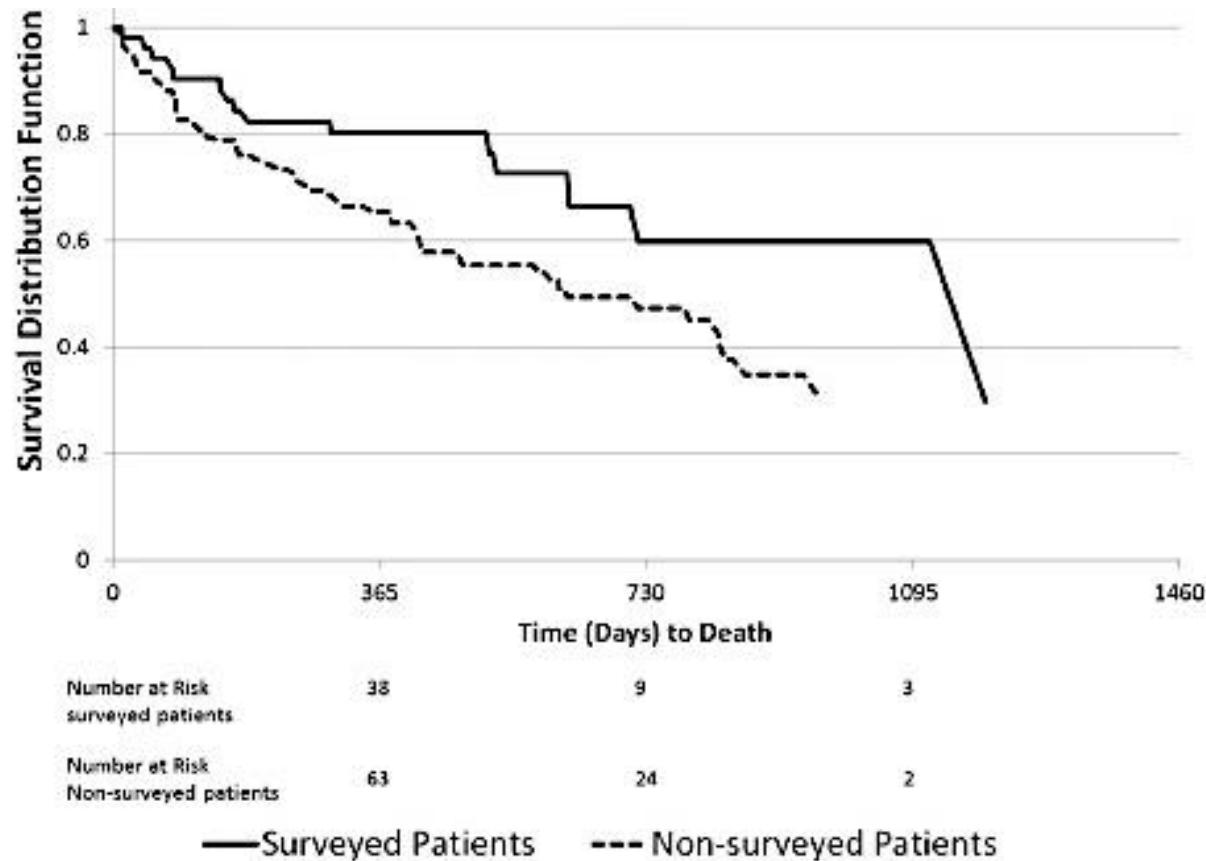


Figure 3 | Kaplan-Meier survival curves comparing surveyed and nonsurveyed patients treated with sodium thiosulfate.

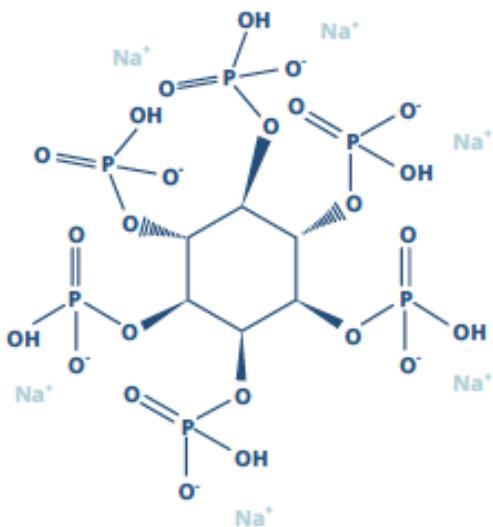
# New Treatments

**1- SNF-472**

**2- Rheopheresis**

# SNF-472 : First-In-Class Inhibitor of Cardiovascular Calcification

**SNF472**  
MW = 792 Da



**Novel mechanism: agent physiochemically blocks vascular HAP crystals, selectively inhibiting CVC**

**A naturally derived substance, present in serum (< 0.3  $\mu\text{M}$ )**

Anti-calcification effect at > 5  $\mu\text{M}$

GMP production in place, extracted from corn and purified

**3x/week IV dosing optimized for dialysis → patient convenience and compliance**

Compound is highly polar, with poor oral absorption

The dose of SNF472 : 400, 450, 700, or 900 mg, based on dry body weight.  
Average dose of 7 mg/kg (range, 5.6–8.6 mg/kg).  
Perfused during 2.5-4h of dialysis sessions.

# Improvements in Calciphylaxis Wound Healing During SNF-472 Treatment: Results of a Phase 2 Trial

## Positive Phase 2 Data in CUA

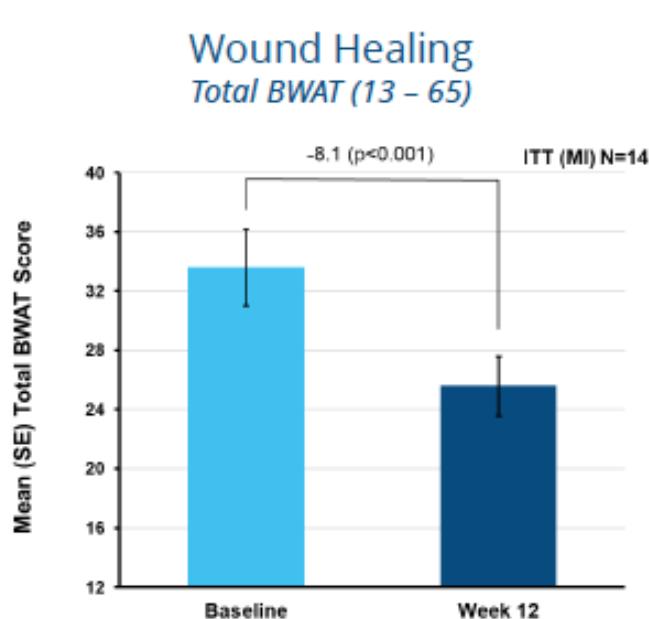
Significant improvement in wound healing and pain

14 HD Patients



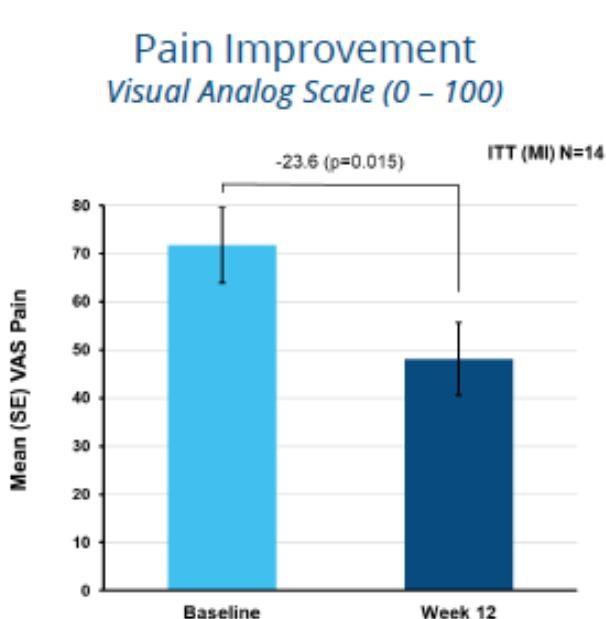
### Wound Healing Total BWAT (13 – 65)

Primary endpoint



### Pain Improvement Visual Analog Scale (0 – 100)

Secondary endpoint



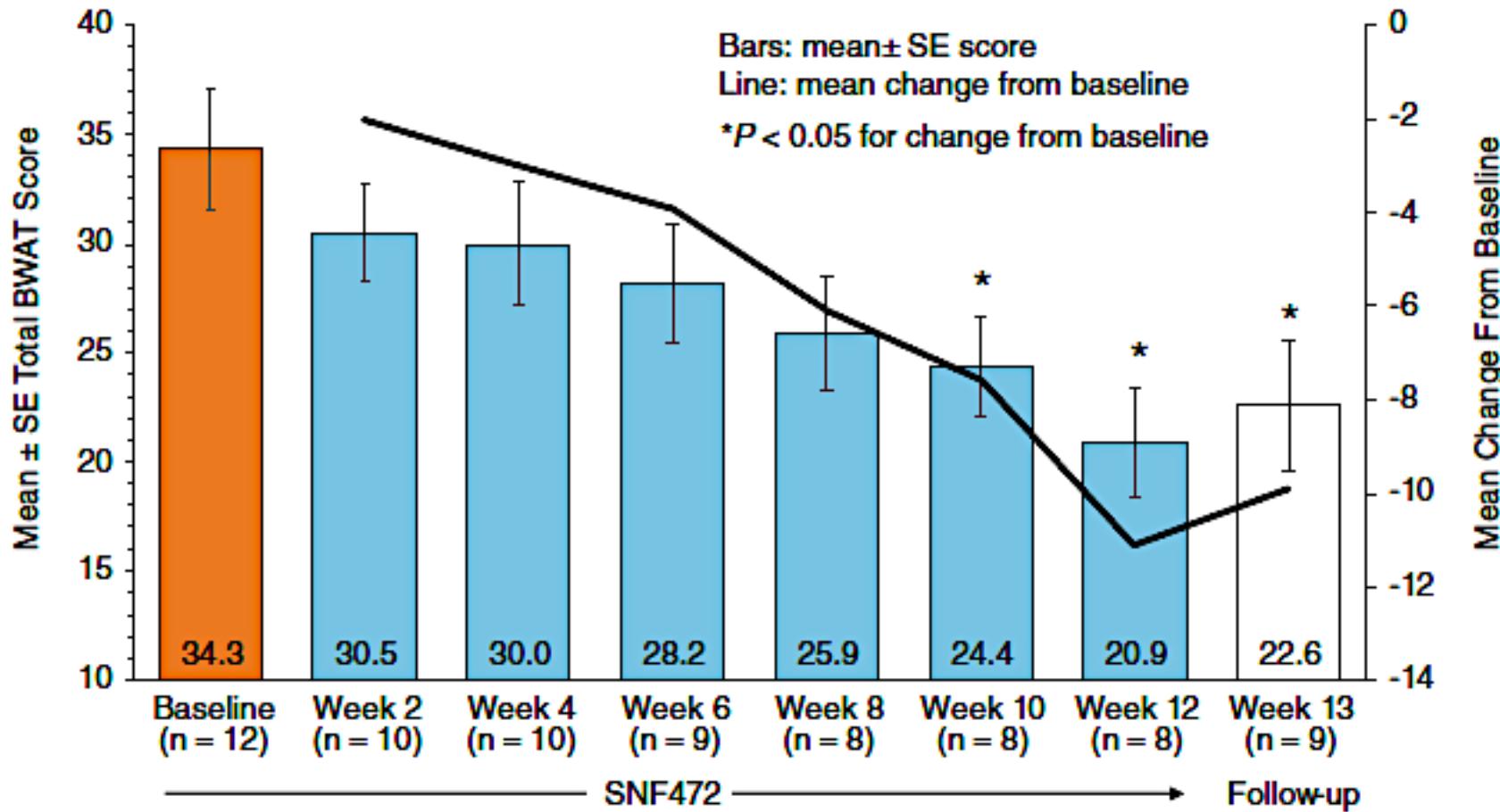
Brandenburg et al. J Nephrology 2019

SNF472 was well tolerated with no drug-related serious adverse events

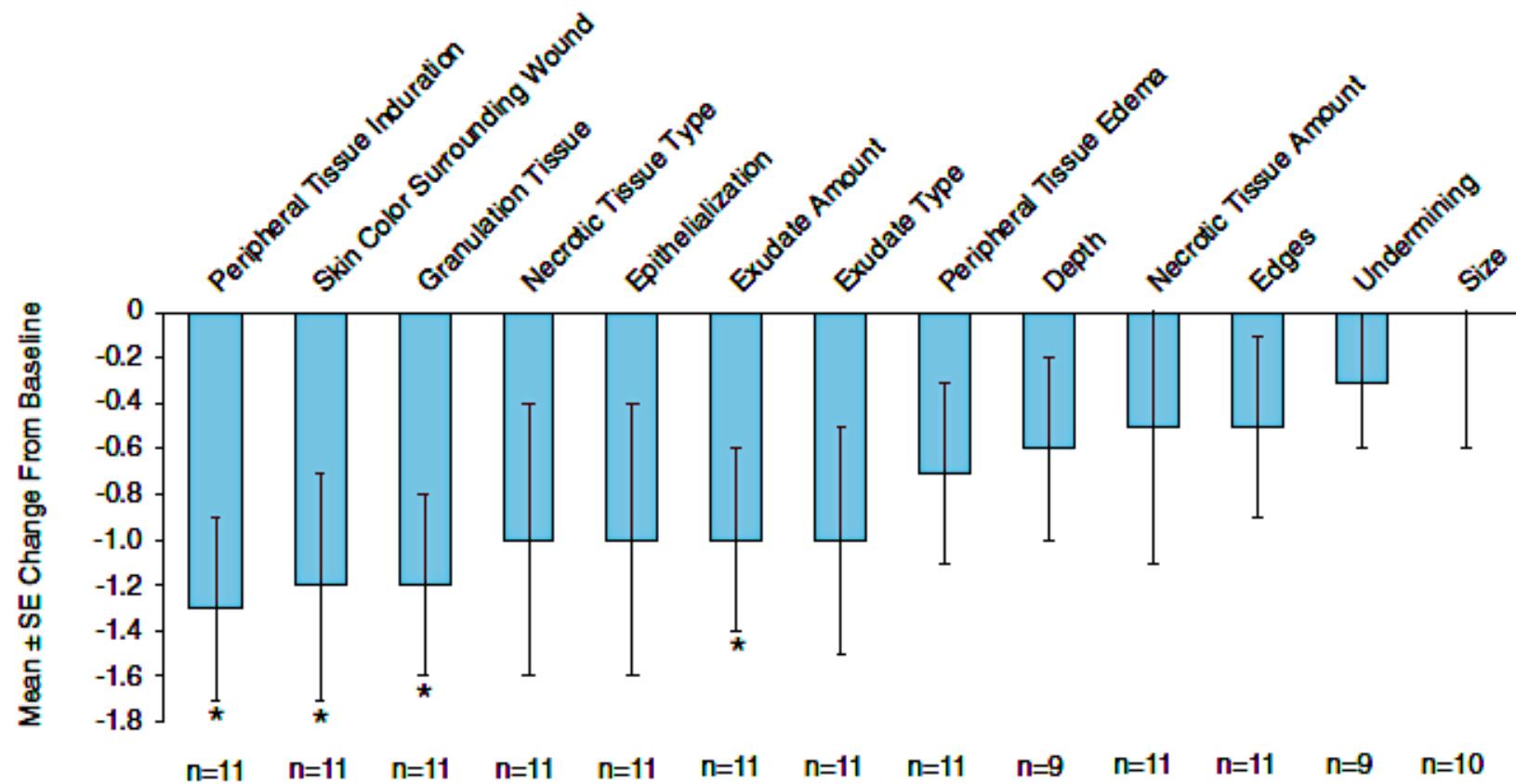
ITT (MI) = Intent-to-treat population with multiple imputation



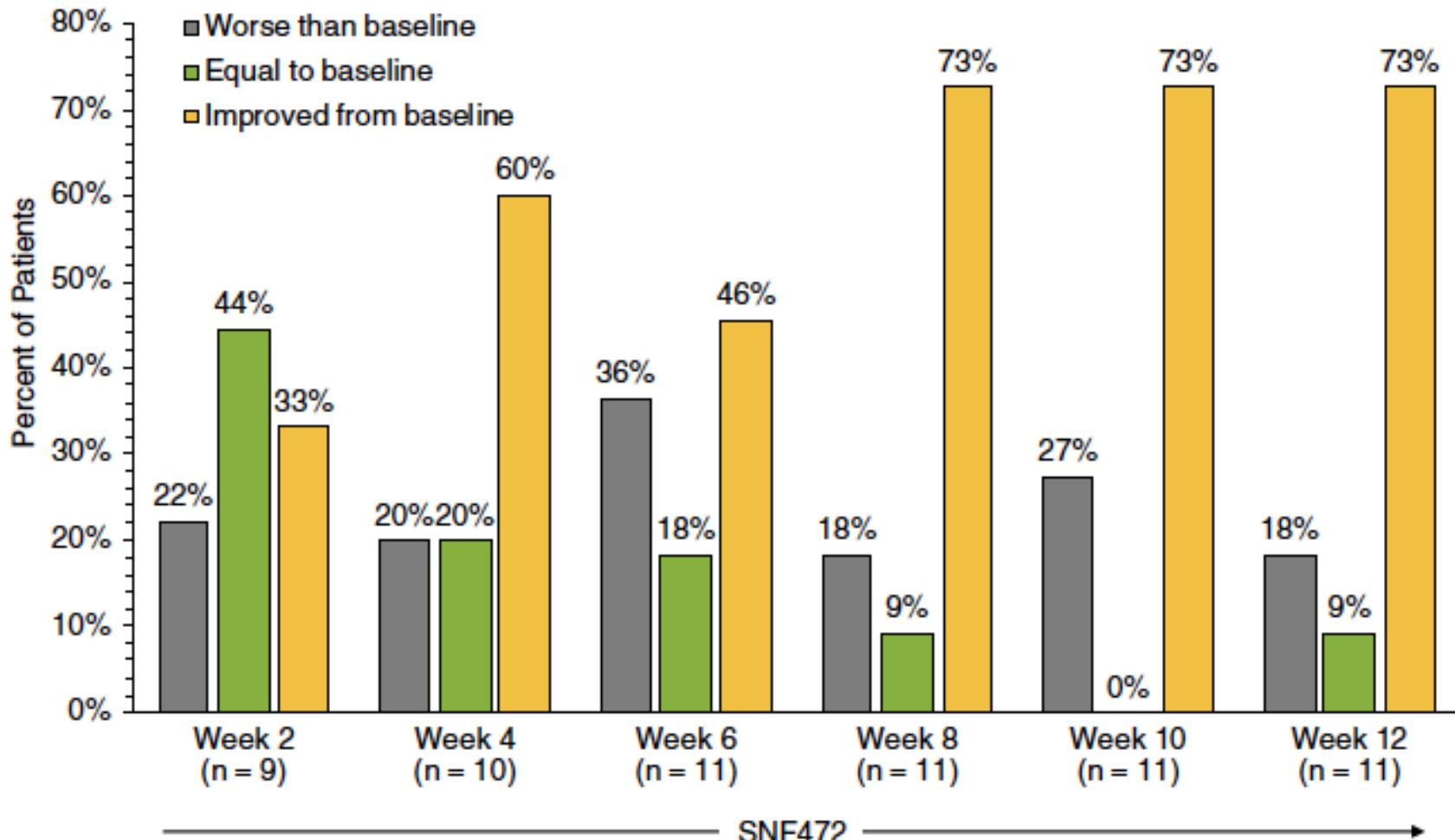
# Improvements in Calciphylaxis Wound Healing During SNF-472 Treatment: Results of a Phase 2 Trial



# Improvements in Calciphylaxis Wound Healing During SNF-472 Treatment: Results of a Phase 2 Trial



# Improvements in Calciphylaxis Wound Healing During SNF-472 Treatment: Results of a Phase 2 Trial



# New Treatments

## Rheopheresis

Double filtration rheopheresis

Eliminates LDL particles

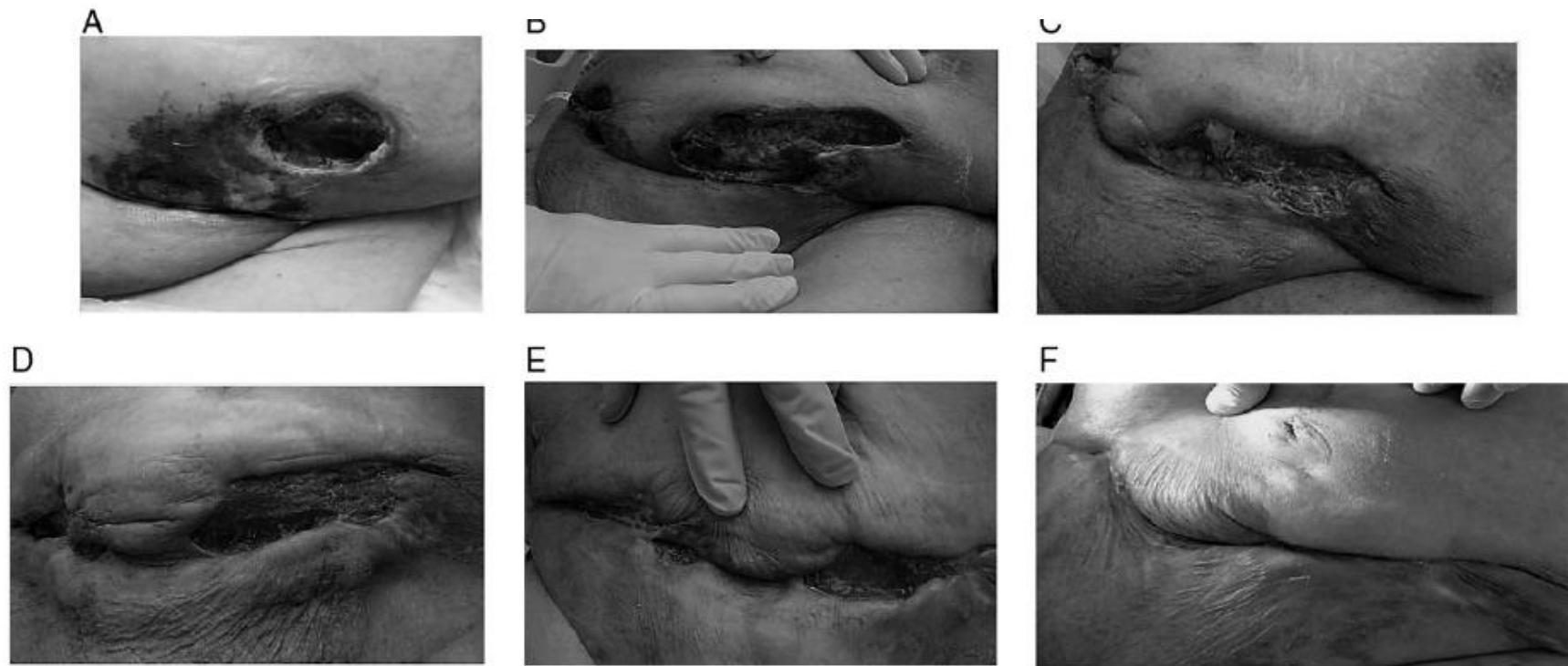
Decreases high m.w. proteins ( $\alpha_2$ - macroglobulin, IgM)

Decreases plasma viscosity

Improves hemorheology and microcirculation

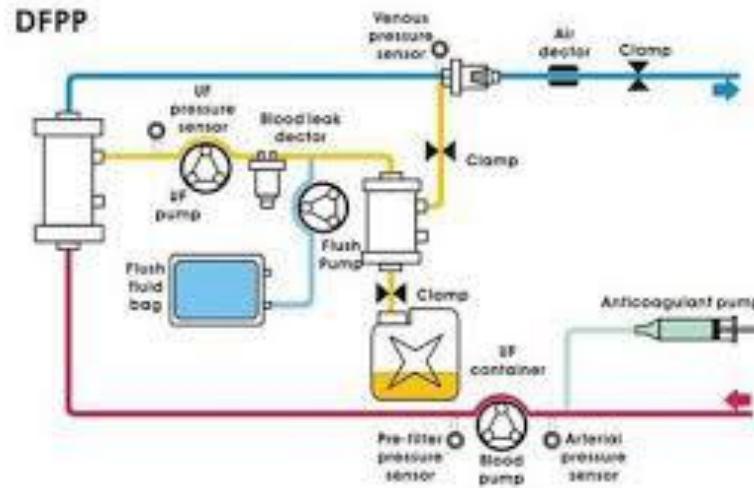
# Rheopheresis

## Rheopheresis for Adjuvant Treatment in Resistant Calciphylaxis



**FIG. 1.** Abdominal lesions of calciphylaxis, at admission (A). Rheopheresis initiation (B). 2–4–10 week treatment (C–E) and complete scarring (F).

# Rheopheresis

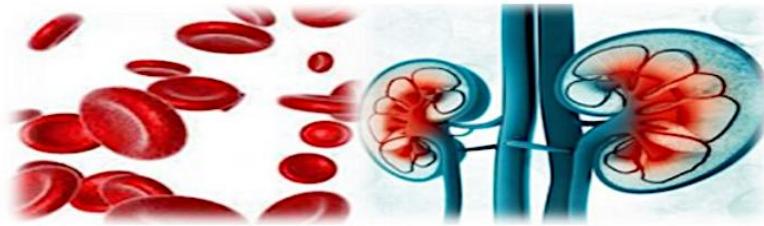


	Delay before Rheopheresis start (days)	Number of Rheopheresis sessions	Rheopheresis treatment (days)	Complete remission	Death	Relapse	Total follow-up (months)
Patient 1	1	15	84	Yes	No	No	2,8
Patient 2	1	19	114	Yes	No	Yes	3,8
Patient 3	77	25	119	Yes	No	No	6,5
Patient 4	39	27	128	No	Yes	No	5,6
Patient 5	13	10	59	No	Yes	No	2,4
Patient 6	65	55	196	Yes	No	Yes	8,7
Patient 7	158	39	274	Yes	No	No	14,4
Patient 8	4	8	25	No	Yes	No	1,0
Median	26,0	22,0	116,5				4,7
Ecart-type	51,4	14,8	73,7				4,0

# Rheopheresis

## RHEO-CUA

Étude rétrospective évaluant l'apport de la RHEOphérèse dans le traitement de la Calciphylaxie Urémique



### Etude rétrospective, multicentrique

Calciphylaxie urémique chez le patient hémodialysé.  
=> Traitement conventionnel vs conventionnel + rhéophérèse

Critère principal : Rémission complète 6 mois après le diagnostic de calciphylaxie.

Population étudiée : patients atteints de calciphylaxie en 2021 et qui ont commencé la rhéophérèse dans le mois qui suit le diagnostic.

#### Objectif :

- 55 patients traités par rhéophérèse
- 55 patients traités de manière conventionnelle. (Issus de la cohorte Calciwest)\*

\* Gaigne et Al - Calciphylaxis epidemiology, risk factors, treatment and survival among French chronic kidney disease patients: a case-control study - BMC Nephrology (2020) 21:63

### Etat des inclusions

Au 30 avril 2022



## Contacts

### Responsable scientifique

Dr Guillaume SERET  
[gseret@echo-sante.com](mailto:gseret@echo-sante.com)

### Coordinatrice Etude Clinique

Angélique COLIN  
Tél : 06 66 73 89 79  
[acolin@echo-sante.com](mailto:acolin@echo-sante.com)

# Conclusions

- 1- The calciphylaxis (CUA) is a rare disease (0.4 to 4%)**
- 2- The calciphylaxis results from an active mineralization process involving; a) the activation of osteogenic factors such as BMP-2, Cbfa1, ALP, others; b) the mineralization and ossification of an extracellular matrix with deposition of hydroxyapatite; and c) the extensive remodeling of the extracellular matrix**
- 3- No specific treatment exists for calciphylaxis. However, it requires the correction of bone and mineral disorders, improving nutritional status, when possible withdrawing anti-vitamin K, sodium thiosulfate, and soon SNF-472**
- 4- The calciphylaxis has a very bad prognosis (40-80 % mortality)**

**THANK YOU !**  
**MUCHAS GRACIAS !**  
**MERCI BEAUCOUP !**

