La crise rénal sclérodermique: mise à jour et perspectives en 2020

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Divulgations

- Subventions/soutien à la recherche : Bristol-Myers Squibb, Hoffmann-La Roche, Corbus, Sanofi, Grifols, Pfizer

- Bureau des conférenciers/honoraires : Janssen

- Honoraires de consultation : Boehringer Ingelheim, Alexion

Références

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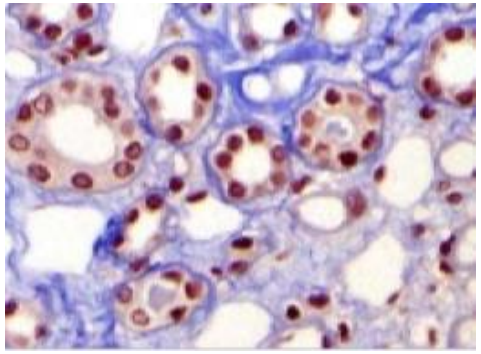
Objectifs

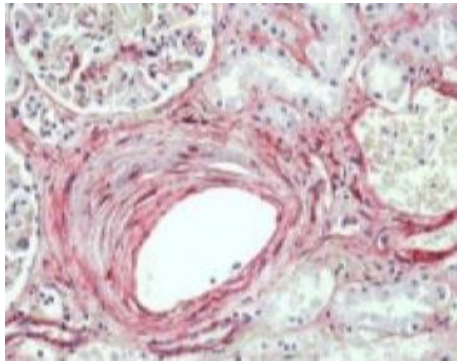
- Décrire les travaux en cours pour générer une definition standardisée de la crise rénale sclérodermique
- En rafale, discuter de :
  - quelques controverses épidémiologiques
  - l’association entre les corticoïdes et la crise rénale
  - la prévention de la crise rénale
  - les traitement de l’hypertension artérielle isolée
  - les nouveautés thérapeutiques
  - la greffe rénale post crise rénale

L’atteinte rénale dans la sclérodermie

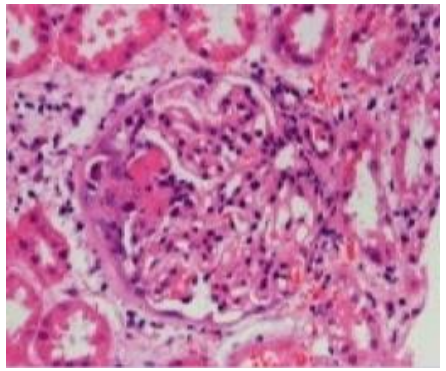
Fibrose interstitielle



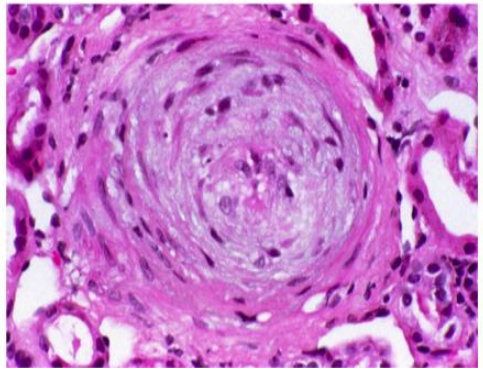
Vasculopathie chronique



Glomérulopathie



Crise rénale



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Définir la crise rénal

SCTC
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Scoping Review

Hoa et al. Autoimmun Rev 2017

Autoimmunity Reviews 16 (2017) 407–415

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Towards developing criteria for scleroderma renal crisis: A scoping review☆

Sabrina Hoa [a,b,*], Edward P. Stern [c], Christopher P. Denton [c], Marie Hudson [a,b,d],
Scleroderma Clinical Trials Consortium Scleroderma Renal Crisis Working Group
Investigators of the Scleroderma Clinical Trials Consortium Scleroderma Renal Crisis Working Group

M. Baron [1], T. Frech [2], C. Ghossein [3], S. Johnson [4], L. Mouthon [5], S. Proudman [6], V. Steen [7], J. Varga [3]

Figure 1. PRISMA flowchart of study selection process

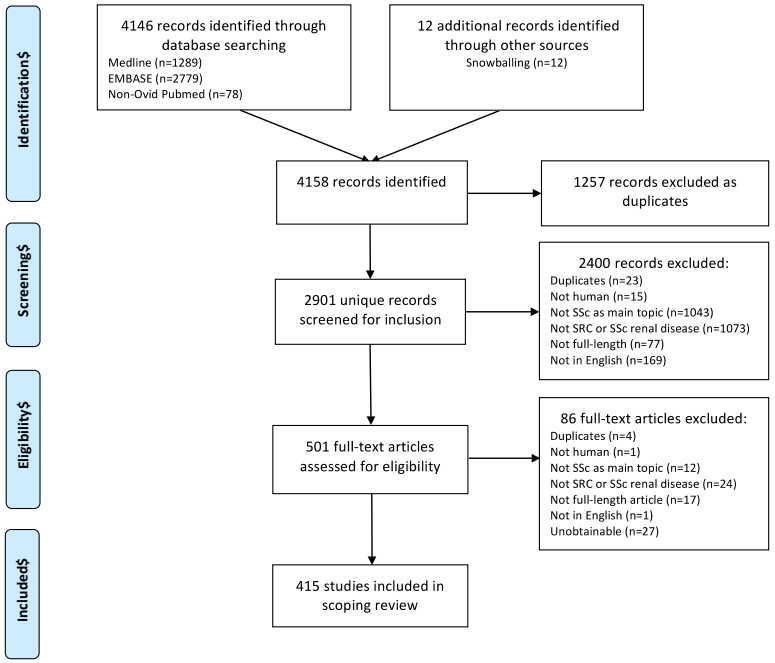

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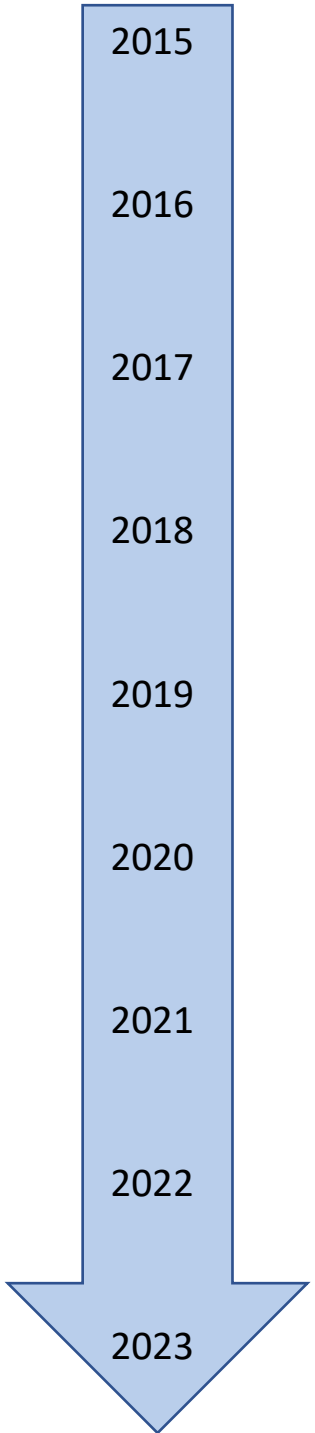
Table 3
Candidate items that could be used to define SRC.

Items from pre-existing definitions	Predictors of SRC
• Hypertension o Systolic blood pressure (>140, 150, 160 or 180 mm Hg) (new onset) o Diastolic blood pressure (>85, 90, 100, 110 or 120 mm Hg) (new onset) o Rise in systolic blood pressure > 30 mm Hg compared with baseline o Rise in diastolic blood pressure > 20 mm Hg compared with baseline o Abrupt onset or aggravation o Measured on at least 2 occasions ▪ Minimum of 12 h apart ▪ Over a 24-h period o Measured within 3 days of first event-associated observation o New onset of blood pressure > 150/85 mm Hg obtained at least twice over a 24-h period (i.e. significant hypertension as defined by the New York Health Association) o Independent of concomitant antihypertensive medication use o Responsive to ACE-inhibitors • Renal insufficiency (or Azotemia) o Serum creatinine > 120% of upper limit of normal for local laboratory o Serum creatinine ≥2.0 mg/day o Creatinine clearance ≤50 ml/min o Fall in creatinine clearance to <60 ml/min o Fall in estimated glomerular filtration rate (eGFR) by >30% o Increase in serum creatinine >50% over baseline o Increase in serum creatinine by ≥1.5 times baseline, known or presumed to have occurred within the prior 7 days, or increase in serum creatinine by ≥0.3 mg/dl (>26.5 μmol/l) within 48 h (i.e. acute kidney injury according to KDIGO definitions) o Doubling of serum creatinine above the value at baseline o Rapid increase in serum creatinine o When possible, a repeat serum creatinine and recalculation of eGFR should be obtained to corroborate the initial results o Rapid deterioration of renal function (within a period of < 1 month) o Rapidly progressive oliguric renal insufficiency o Oliguria or anuria o Absence of other defined cause • Proteinuria o ≥2 + by dipstick o ≥1 + by dipstick o Protein: creatinine ratio > upper limit of normal o >500 mg in 24 h • Hematuria o >2 + by dipstick o >10 RBCs/HPF o New onset of urinary RBCs (excluding other causes) o Without menstruation • Thrombocytopenia o < 100.000 platelets/mm^3 • Hemolysis (or Microangiopathic hemolytic anemia) o Schistocytes or other RBC fragments seen on blood smear o Increased reticulocyte count o Increase in LDH and indirect bilirubin o Haptoglobin consumption o Anemia not because of other causes • Hypertensive encephalopathy o Seizures • Hypertensive retinopathy o Grade III (flame-shaped hemorrhages and/or "cotton-wool" exudates) or IV (papilledema) retinopathy, according to Keith-Wagener classification o Retinopathy typical of acute hypertensive crisis • Hyperreninemia o Elevation of plasma renin activity to twice the upper limit of normal or higher • Abnormal kidney biopsy o Typical/characteristic changes of SRC (not further defined) o Findings consistent with SRC (microangiopathy) (not further defined) o Accumulation of mucin in interlobular arteries (indistinguishable from accelerated hypertension) and fibrinoid calcinosis of arteries • Flash pulmonary edema	• Patient-specific characteristics o Black race o Male sex • Clinical characteristics o Shorter disease duration o Diffuse cutaneous subset o Skin score (>14 or 20) o Large joint contractures o Tendon friction rubs o Digital pitting scars o Cardiopulmonary involvement ▪ Cardiac insufficiency ▪ Pericarditis ▪ FVC < 75% ▪ Lower DLCO o Muscle involvement ▪ Muscle wekaness ▪ High creatine kinase ▪ Myalgias and myopathy o Arthralgias • Medication history o Prednisone (prior or simultaneous use; higher dose; within prior 3 or 3 months; ≥15 mg/d in prior 6 months) o Absence of calcium channel blocker • Prednisone serologies, biomarkers and genetics o Anti-RNA polymerase III positivity o Anti-RNA polymerase I/II/III positivity o ELISA anti-RNA polymerase III ≥157 o Absence of anti-centromere o Anti-nRNP positivity o Speckled ANA o Anti-Scl70 positivity • Biomarkers and genetics o High lipocalin-2 levels o High sCD147 levels o High angiogenin levels o High endothelin-1 levels o HLA-DRB1*0407 o HLA-DRB1*1304 Differential diagnoses to exclude ANCA-associated glomerulonephritis Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome Membranous nephropathy Drug-induced nephropathies (e.g. cyclosporin A) Other vasculitides (e.g. polyarteritis nodosa, mixed cryoglobulinemia, Goodpasture syndrome) Oxalate nephropathy Renal artery stenosis Membranoproliferative nephropathy Pre-renal causes (e.g. sepsis, dehydration, cardiac or pulmonary vascular involvement) Isolated renal abnormalities Other considerations Hypertensive vs. normotensive SRC Definite vs. probable (or suspected or possible) SRC Classic vs. subacute presentation of SRC Restricted to SSc vs. expanded to SSc-spectrum of connective tissue diseases

- 40 définitions différentes
- >45 items
- Thèmes communs
  - Augmentation de la TA
  - Insuffisance rénale aigue
  - Microangiopathie hemolytique et thrombocytopénie
  - Dommage d'organe cible
    - Encephalopathie
    - Retinopathie
    - Dysfonction cardiaque
  - Changements à la biopsie rénale



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Scoping Review
Hoa et al. Autoimmun Rev 2017

Delphi 1 → Delphi 2 → Delphi 3

NGT meeting

Consensus on a core set

Consensus methods

Consensus core set

- 5 domains, 13 items
- input from content experts

Table 2. Final core set of items to develop classification criteria for SRC*

Blood pressure
Acute increase in blood pressure defined as any of the following:
Systolic blood pressure ≥140 mm Hg
Diastolic blood pressure ≥90 mm Hg
An increase in systolic blood pressure of ≥30 mm Hg above normal
An increase in diastolic blood pressure of ≥20 mm Hg above normal
Blood pressure measurement should be taken twice, separated by at least 5 minutes; if blood pressure readings are discordant, repeat readings should be taken until 2 consistent readings are obtained
Kidney injury†
Acute kidney injury defined as any of the following:
Increase in serum creatinine of ≥26.5 μmoles/liter (≥0.3 mg/dl) within 48 hours
Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days
Urine volume <0.5 ml/kg/hour for 6 hours
Microangiopathic hemolytic anemia and thrombocytopenia
New or worsening anemia not due to other causes
Schistocytes or other red blood cell fragments on blood smear
Thrombocytopenia ≤100,000 platelets/mm^3, confirmed by manual smear
Laboratory evidence of hemolysis, including elevated lactate dehydrogenase, reticulocytosis, and/or low or absent haptoglobin
A negative direct antiglobulin test
Target organ dysfunction
Hypertensive retinopathy (hemorrhages, hard and soft [cotton-wool] exudates, and/or disc edema, not attributable to other causes), confirmed by an ophthalmologist
Hypertensive encephalopathy, characterized by headache, altered mental status, seizures, visual disturbances, and/or other focal or diffuse neurologic signs not attributable to other causes
Acute heart failure, characterized by typical symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema)
Acute pericarditis, diagnosed with at least 2 of the 4 following criteria: 1) pericarditis chest pain; 2) pericardial rub; 3) new widespread ST segment elevation or PR segment depression on electrocardiography; 4) pericardial effusion (new or worsening) on cardiac echocardiography
Renal histopathology

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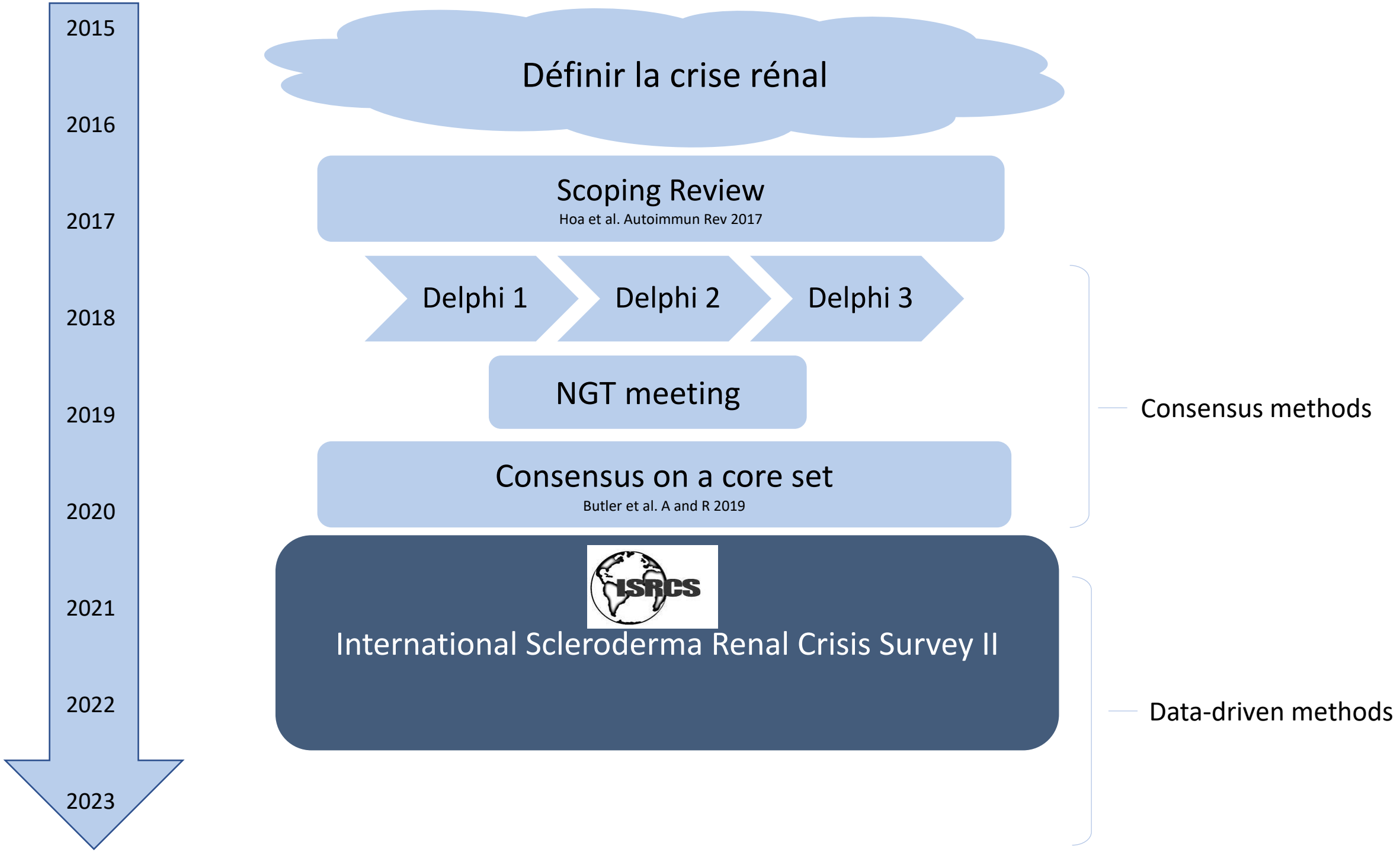
Butler et al. A and R 2019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Consensus on a core set
Butler et al. A and R 2019
ISRCS
International Scleroderma Renal Crisis Survey II
Consensus methods
Data-driven methods

Web-based survey

Resize font:

Development of classification criteria for Scleroderma Renal Crisis (SRC)

Did you diagnose a new case of Scleroderma Renal Crisis (SRC) in the past two weeks?

- Yes
- No

reset

Submit

Controls

Development of classification criteria for Scleroderma Renal Crisis (SRC): controls with thrombotic microangiopathy

Thank you for taking the time to complete the International Scleroderma Renal Crisis Survey II for control cases.

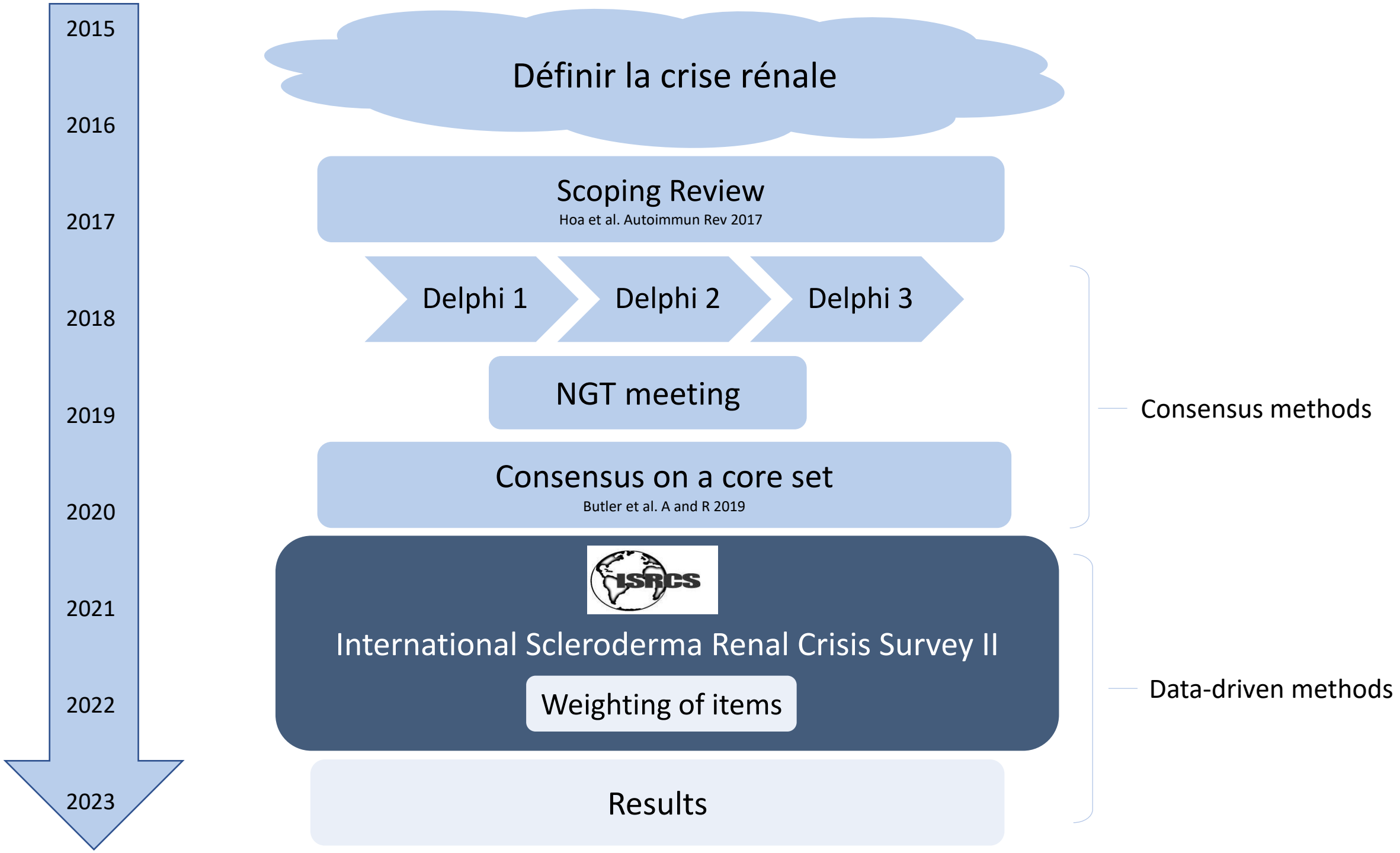
ISRCSII NEWSLETTER JULY 2020

A successful start for the International Scleroderma Renal Crisis Study II

Marie Hudson & Christopher Denton
Co-chairs of the SCTC SRC working group

The International Scleroderma Renal Crisis Study II (ISRCSII) started recruiting in January 2020. We have had a great response from 106 collaborators from 95 institutions around the world, including 28 countries: Argentina, Australia, Belgium, Brazil, Canada, Denmark, Egypt, France, Germany, Hungary, Iran, Israel, Italy, Japan, Mexico, The Netherlands, Norway, Pakistan, Poland, Portugal, Romania, Russia, Spain, Sweden, Switzerland, Turkey, United Kingdom, USA.

N=45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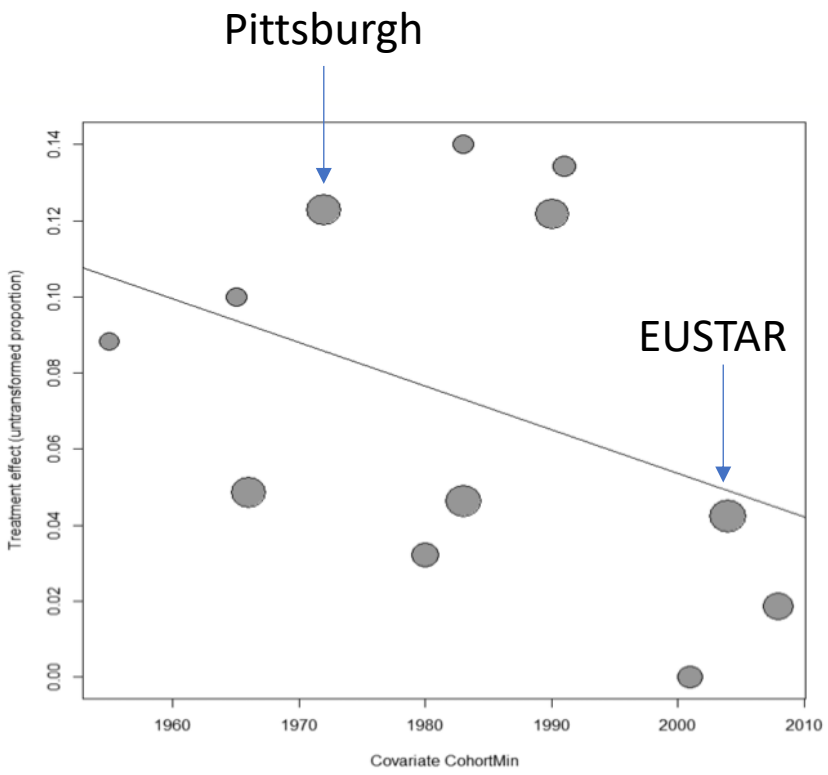
ISRCS
International Scleroderma Renal Crisis Survey II
Weighting of items
Results
Consensus methods
Data-driven methods

Controverses épidémiologiques

- Fréquence
  - Globale 4%
  - dcSSc 7%–9%
  - lcSSc 0.5%–0.6%



Temporal trends in dcSSc (p=0.16)

Turk, Pope. J Rheum 2016.

Controverses épidémiologiques

- Fréquence
  - Globale 4%
  - dcSSc 7%–9%
  - lcSSc 0.5%–0.6%

- Facteurs de risques connus
  - Atteinte cutanée diffuse (90%) et rapidement évolutive
  - Maladie debutante (<5 ans)
  - Anti-RNA polymerase III >> ATA

Table 2
Baseline characteristics of cohort ($n = 75$)

Mean (SD) age, years	52.5 (12.2)
Women, *n* (%)	50 (66.7)
Ethnic groups, *n* (%)	
White	58 (77.3)
Black	10 (13.3)
Asian	1 (1.3)
Hispanic	2 (2.7)
Native American	2 (2.7)
Other	2 (2.7)
Disease subsets, *n* (%)	
Diffuse	56 (74.7)
Limited	16 (21.3)
Sine scleroderma	3 (4.0)
Disease duration (since first non-Raynaud's symptom)	
Median disease duration, years (IQR)	1.5 (0.9, 3.7)
Number (%) with disease duration < 1 year	24 (32.0)

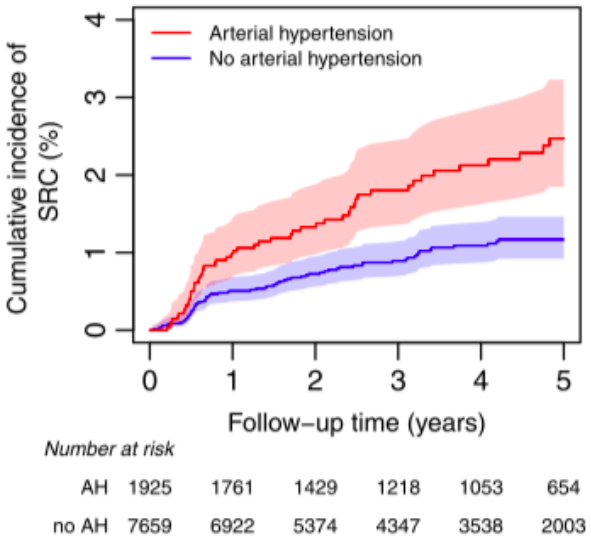
Hudson et al. SAR 2014.

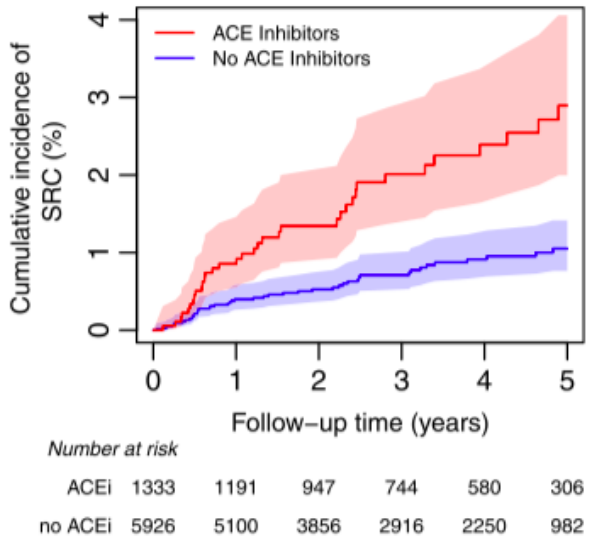
Controverses épidémiologiques

- Fréquence
  - Globale 4%
  - dcSSc 7%–9%
  - lcSSc 0.5%–0.6%

- Facteurs de risques connus
  - Atteinte cutanée diffuse (90%) et rapidement evolutive
  - Maladie debutante (<5 ans)
  - Anti-RNA polymerase III > ATA

- Nouveaux facteurs de risques?
  - Hypertension artérielle
  - Insuffisance rénal chronique
  - IECA





Bütikofer et al. ART 2020
Gordon et al. J Rheum 2019

Confounding by Indication Probably Distorts the Relationship between Steroid Use and Cardiovascular Disease in Rheumatoid Arthritis: Results from a Prospective Cohort Study

Alper M. van Sijl*, Maarten Boers, Alexandre E. Voskuyl, Michael T. Nurmohamed

Department of Rheumatology, VU University Medical Center, Amsterdam, the Netherlands

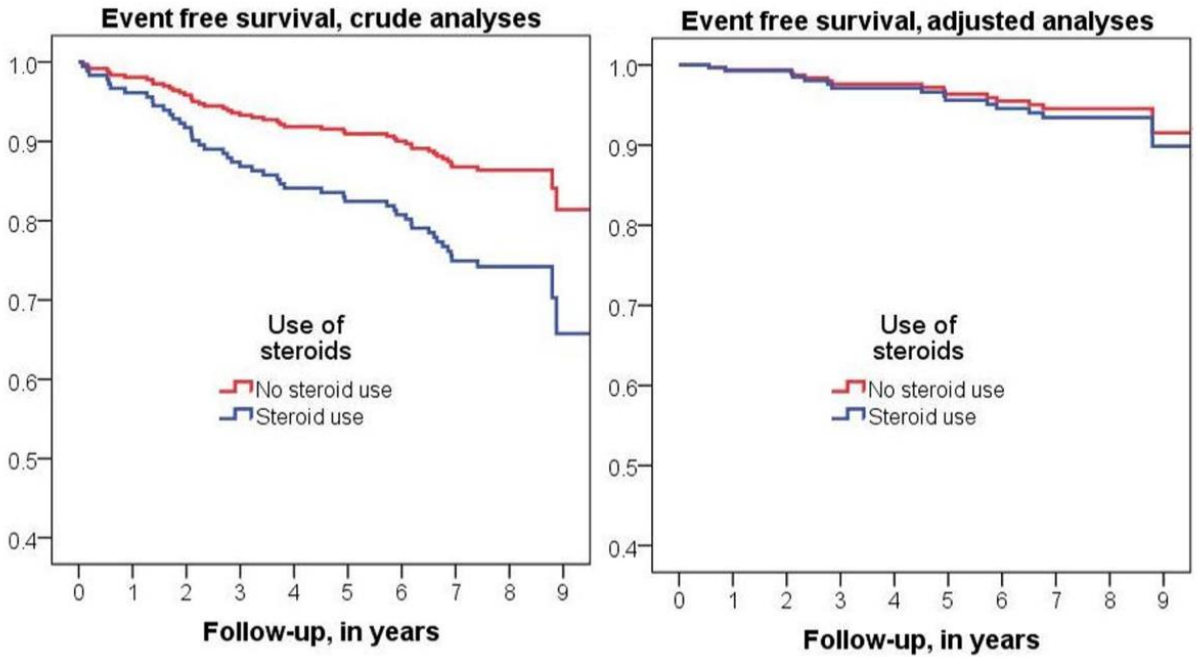


Figure 1. Kaplan-Meier survival curve of individuals who were using steroids at baseline vs. individuals who were not using steroids at baseline, both crude as well as fully adjusted for disease activity−/severity.
doi:10.1371/journal.pone.0087965.g001

Associations entre corticoïdes et crise rénale

Table 4. Frequency of corticosteroid use in the 6 months prior to new renal crisis in cases and prior to the initial visit in controls*

Corticosteroid regimen	Cases (+)/ controls (+)	Cases (+)/ controls (−)	Cases (−)/ controls (+)	Cases (−)/ controls (−)	McNemar's odds ratio (95% confidence interval)
New, high dose	5	35	8	62	4.37 (2.03–9.43)
New, low dose	3	15	8	84	1.87 (0.79–4.24)
Continuous dose	1	9	8	92	1.12 (0.43–2.9)
Any steroids	21	45	14	30	3.21 (1.76–5.85)

* Values are the no. of positive patients. High dose was defined as ≥15 mg/day of prednisone equivalent; low dose as <15 mg/day of prednisone equivalent. (+) = steroids present; (−) = no steroids.

Steen and Medsger. A&R 1998.

Associations entre corticoïdes et crise rénale

TABLE 1 Demographics, clinical symptoms and biologic findings of SSc patients with and without SRC

Clinical symptoms	SRC	No SRC	Total	Univariate analysis, *P*	Multivariate analysis *P*	Multivariate analysis aOR (95% CI)
Patients, *n*	91 (17.6)	427 (82.4)	518			
Male/female ratio	22/69	74/353	96/422			
Mean age at SSc diagnosis, mean (S.D.), years	50 (15)	55 (16)		0.14		
SSc onset-to-SRC interval, mean (S.D.), years	3.2 (8.1)	–	–			
Mean age at SRC onset, mean (S.D.), years	53 (15)	–	–			
Limited SSc	13 (14.2)	282 (66.0)	295 (56.9)			
Diffuse SSc	78 (85.7)	145 (34)	223 (43)	0.001	0.001	14.65 (4.12, 52.16)
CSs	64 (70.3)	156 (36.5)	220 (42.4)	<0.001	0.0079	4.98 (1.52, 16.30)
Oral CS at SRC onset	51 (56.0)	156 (36.5)	207 (40)	0.001		
Maximum CS dose,[a] mean (S.D.), mg	29.3 (28.4)	3.6 (9.9)		<0.001		

Guillevin et al. Rheumatology 2012.

L'utilisation des corticoïdes dans la sclérodermie

- Faibles doses
  - Atteinte cutanée inflammatoire
  - Frottements tendineux
  - (Pneumopathie interstielle)

- Hautes doses
  - Myosites sévères
  - Auto-greffe
  - *(Very early SSc* - ClinicalTrials.gov Identifier: NCT03059979)

Prévention

- Jay
- Homme de 55 ans de race noire
- SSc diffuse x 2 ans (anti-topoisomerase)
- MMF 2 gm die
- **TA 120/80**
- **Labos normaux**

- IECA en prévention?

Seminars in Arthritis and Rheumatism 43 (2014) 666–672

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Exposure to ACE inhibitors prior to the onset of scleroderma renal crisis—Results from the International Scleroderma Renal Crisis Survey

Marie Hudson, MD, MPH[a,b,*], Murray Baron, MD[a,b], Solène Tatibouet, MSc[a], Daniel E. Furst, MD[c], Dinesh Khanna, MD, MS[d], International Scleroderma Renal Crisis Study Investigators[1]

Table 5
Cox proportional hazard models to compare the risk of death of SRC patients exposed to ACE inhibitors prior to the onset of SRC compared to those unexposed. Model 1 is the crude analysis, model 2 is the pre-specified adjusted model, controlling for baseline differences significant at the $p < 0.05$ level, and model 3 is the post-hoc analysis also adjusting for pre-existing systemic hypertension

	Hazard ratio	95% Confidence intervals	*p* Values
Model 1			
ACE inhibitor prior to SRC	1.88	0.82, 4.30	0.14
Model 2			
ACE inhibitor prior to SRC	2.42	1.02, 5.75	< **0.05**
Prednisone (mg/day)	1.04	1.02, 1.07	< **0.01**
Model 3			
ACE inhibitor prior to SRC	2.17	0.88, 5.33	0.09
Prednisone (mg/day)	1.05	1.02, 1.08	< **0.01**
Hypertension	1.98	0.64, 6.13	0.24

Prévention

- Vigilance
  - Identifier les personnes à risque
  - Surveillance de la TA et de la fonction rénale
- Scleroderma Renal Crisis Prevention card

SCLERODERMA RENAL CRISIS PREVENTION

<< Please fill out this card and keep it with you. >>

- ► You have been identified as a person at risk of RENAL CRISIS, a preventable problem.
- ► Warning signs: New onset headaches, blurred vision, shortness of breath, confusion, abrupt elevation of blood pressure.
- ► Monitor your blood pressure and know and record your usual readings _____
- ► Call Dr. _____ if BP is greater than _____ or seek urgent care.

Show any treating physician this card.

SCLERODERMA RENAL CRISIS: PREVENTION AND TREATMENT

- ► This is a patient at risk of scleroderma renal crisis.
- ► If hypertensive or blood pressure is acutely increased, ACE INHIBITORS are the only drugs predictably effective at aborting renal crisis.
- ► If unable to administer orally, give I.V. enaprilat.
- ► Check creatinine as renal failure may occur abruptly.
- ► Please call this patient's rheumatologist,
  Dr. _____
  Phone # _____

Shapiro et al. ARD 2015;**74:**1136.

Hypertension artérielle isolée (sans atteinte rénale)

- Jay
- Homme de 55 ans de race noire
- SSc diffuse x 2 ans (anti-topoisomerase)
- MMF 2 gm die
- **TA 150/90**
- Labos normaux

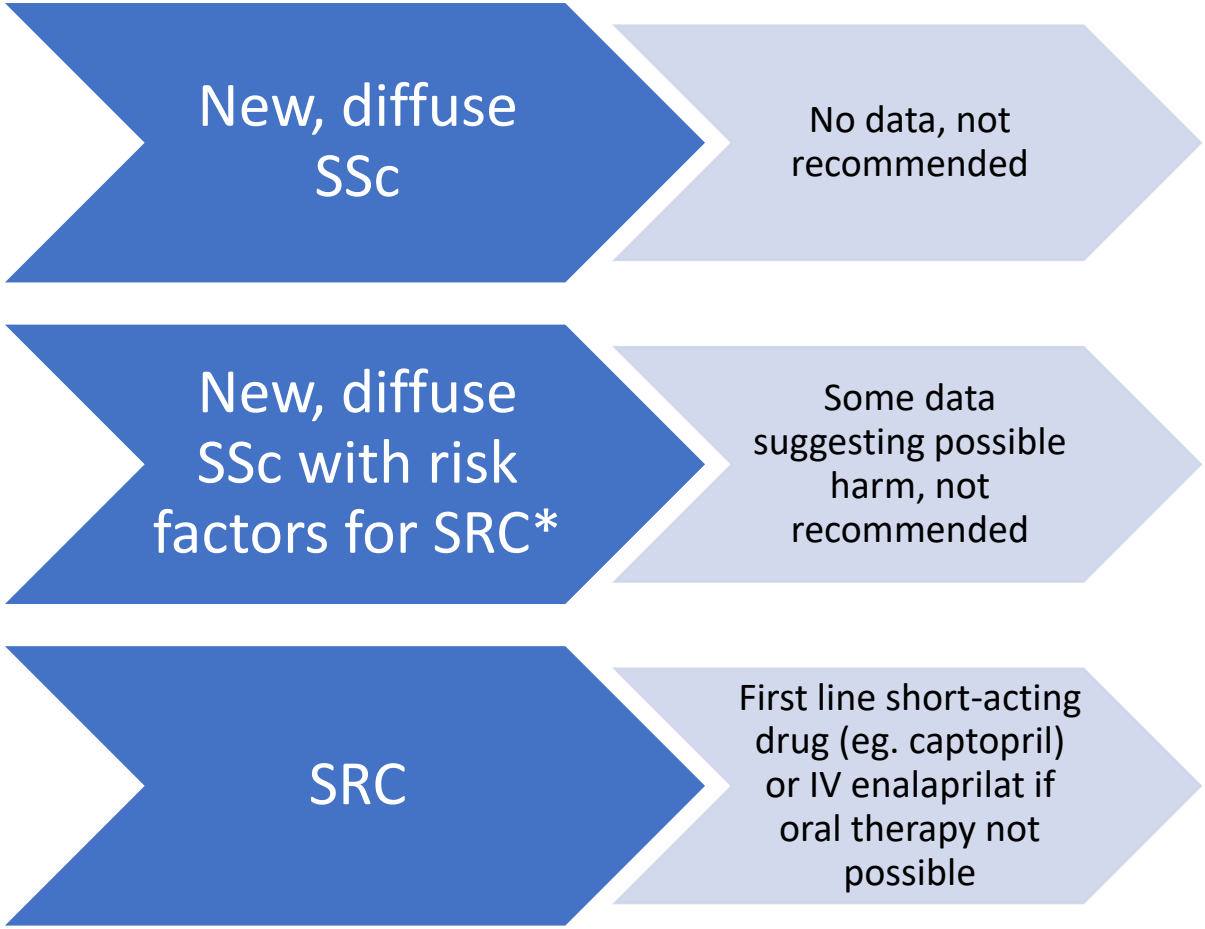
Hypertension artérielle isolée (sans atteinte rénale)

- Traitements?
  - IECA
  - B-bloquants
  - Diurétique
  - Bloqueur des récepteurs de l'angiotensine
  - Bloqueur des canaux calciques

Hypertension artérielle isolée (sans atteinte rénale)

- Traitements?
  - IECA
  - B-bloquants
  - Diurétique
  - Bloqueur des récepteurs de l'angiotensine
  - Bloqueur des canaux calciques

ACE inhibitors in systemic sclerosis



*eg. hypertension, proteinuria, exposure to glucocorticoids

Nouveautés thérapeutiques

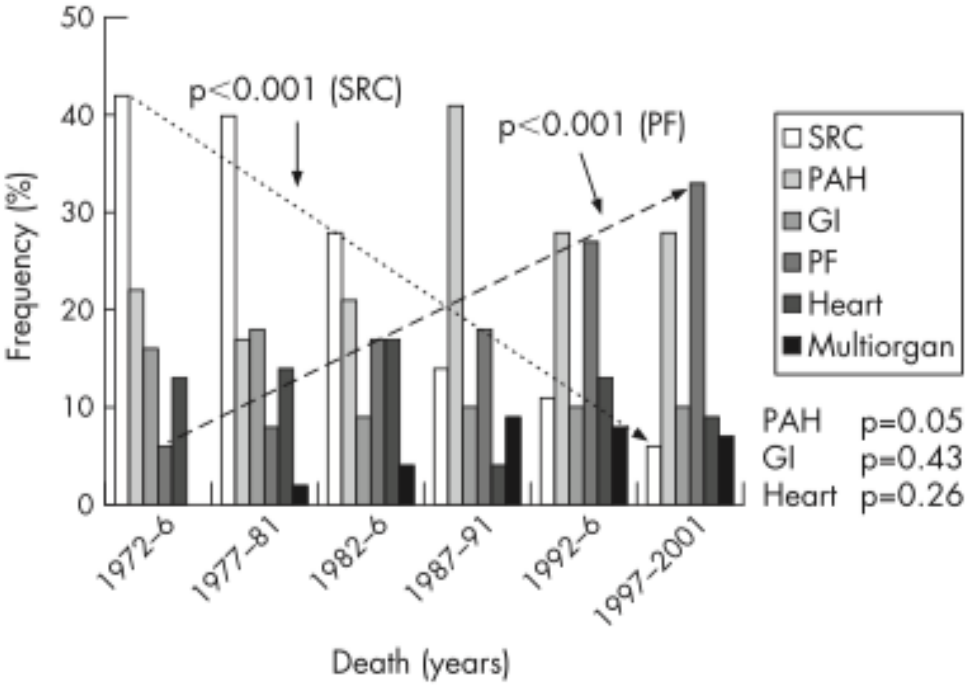


Figure 2 Changes in causes of systemic sclerosis-related deaths between 1972 and 2001. GI, gastrointestinal; PAH, pulmonary arterial hypertension; PF, pulmonary fibrosis; SRC, scleroderma renal crisis.

L’effet des inhibiteurs de l’enzyme de conversion de l'angiotensine (IECA)

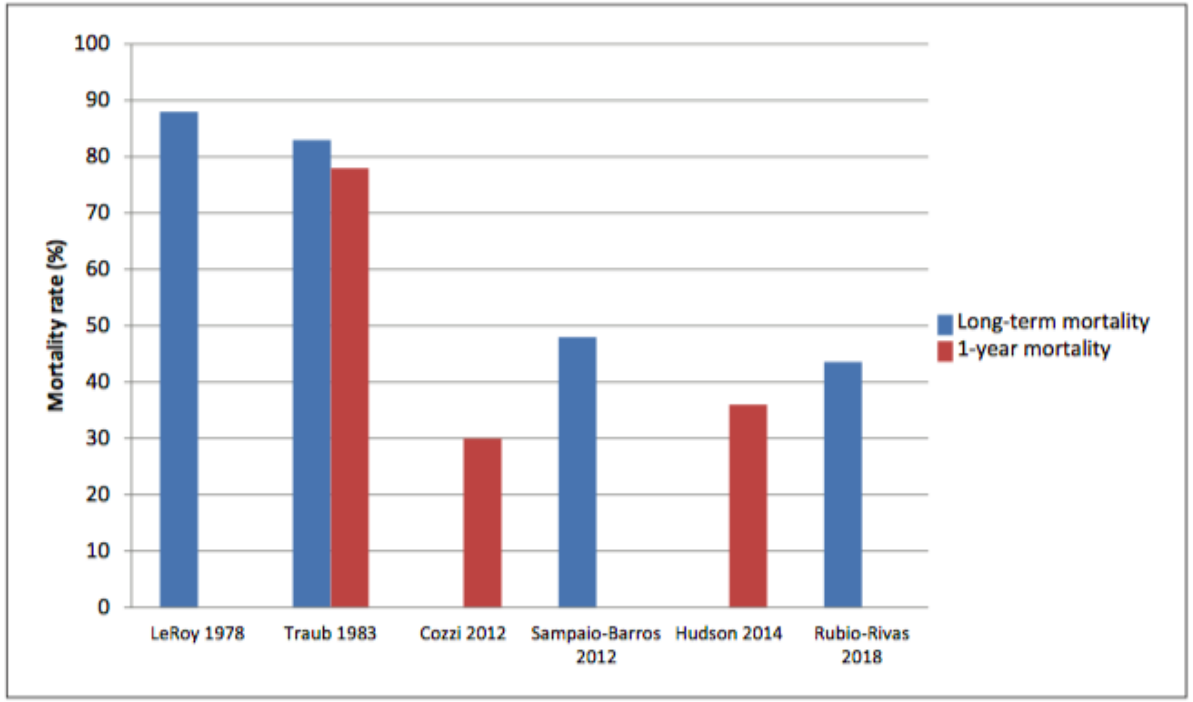
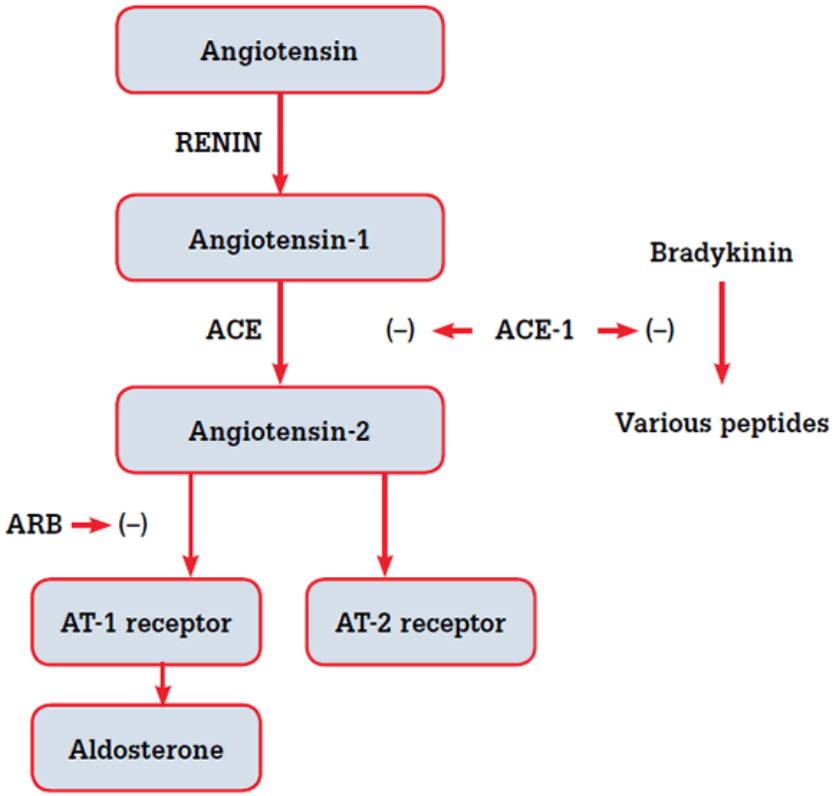


Figure 2. Mortality in scleroderma renal crisis and trends over time.

Kim, Lefebvre, Hoa, Hudson. JSRD 2020.

Nouvelles thérapies

- Bloqueur des récepteurs de l'angiotensine



Nouvelles thérapies

- **Les inhibiteurs de l'endothelin**
  - Augmentation de l'ET dans le sang de patients sclérodermiques
  - Augmentation de l'expression de l'ET-1 et des récepteurs de l'ET A et B dans les reins
  - Bosentan (double inhibiteur des récepteurs de l'endothéline)
  - Zibotentan (inhibiteur du récepteur A de l'endothéline)
    - ClinicalTrials.gov Identifier: NCT02047708

- **Les inhibiteurs de la cascade de complément**
  - Quelques cas de rapportés - avec IECA mais en presence de microangiopathie hémolytique

- **Plasmaphérèse** (avec IECA)

Penn et al. QJM, 106 (2013), pp. 839-848.

Mouthon et al. Hum Pathol, 42 (2011), pp. 95-102.

Bérezné A et al. Arthritis and Rheumatology. 2017;69 (suppl 10)

Thomas et al. Clin Kidney J, 8 (2015), pp. 698-701

Cozzi et al. Transfus Apher Sci, 25 (2001), pp. 25-31

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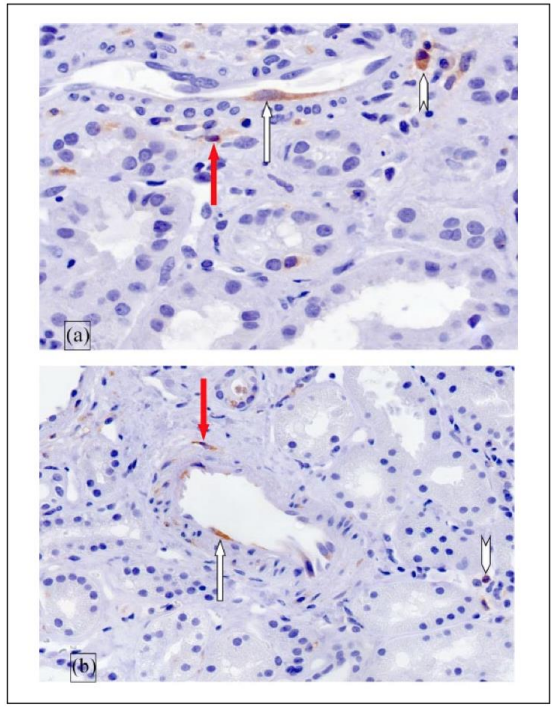


Figures 1. (a) Magnification at ×630 and (b) magnification at ×400: S6RP phosphorylation showing mTORC1 activation in arteriolar endothelial cells and arterial endothelial cells (white arrows), in arteriolar and arterial muscle cells (red arrows) and inflammatory cells (arrow head).

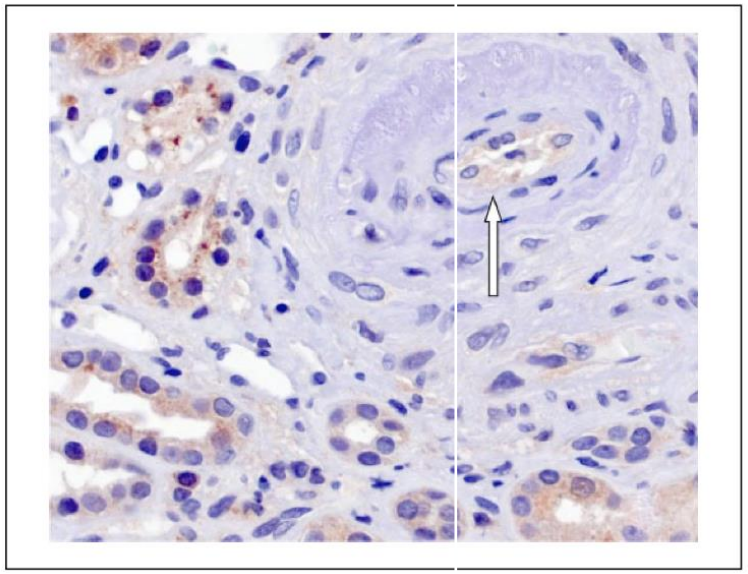


Figure 2. Anti-Rictor staining showing mTORC2 activation in arterial endothelial cells (arrow; magnification ×630).

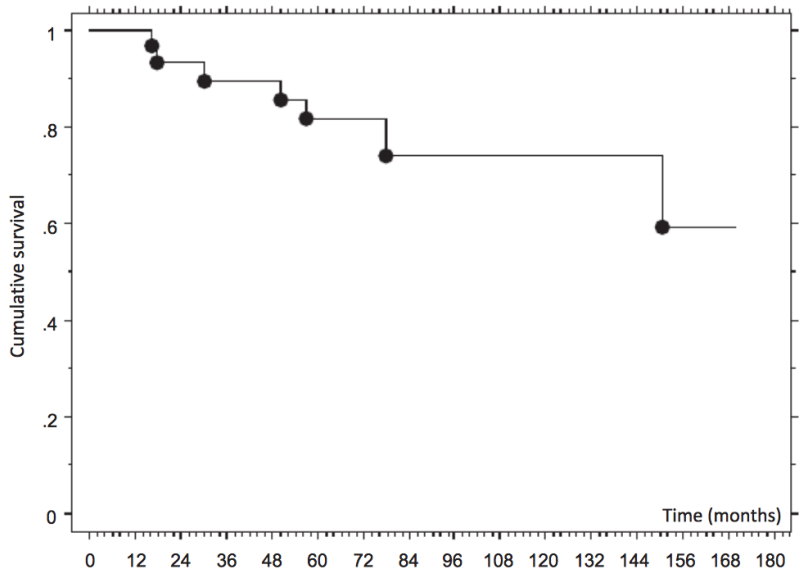
Salituri, Hudson. JSRD 2020.

Transplantation rénale

La fonction rénale peut s'améliorer jusqu'à 18 mois après la crise

La survie post-greffe est meilleure que celle sur la dialyse (bien que la survie parmi les sclerodermiques greffés est moins bonne que celle de patients avec d'autres indications)

La rechute après greffe est rare (~5%)



No at risk	**34**	**31**	**25**	**23**	**23**	**20**	**12**	**10**	**9**	**7**	**6**	**6**	**6**	**4**	**1**	**0**
Events	0	0	2	3	3	5	5	6	6	6	6	6	6	7	7	7

Figure 2 Patient survival. Patient survival was 100%, 93.8% and 82.5% at 1, 3, and 5 years post-transplant, respectively.

Bertrand et al. Transplant Int 2017

Conclusions

- Maladie rare, donc beaucoup d’inconnus
- Importance d’une definition standardisée
- Prévention via vigilance
  - Pas de données suffisantes pour justifier l’utilisation d’IECA en prévention
- Minimiser l’utilisation des corticoïdes surtout chez les patients à risques
- Risque de mortalité demeure très élevé
  - Grand besoin d’identifier de nouvelles cibles thérapeutiques

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