

# Essai RENATO

MULTICENTER **R**ANDOMIZED TRIAL TO **E**EVALUATE THE  
EFFICACY OF PIOGLITAZONE TO PROMOTE REN**AL**  
**T**OLERANCE IN ANCA-ASSOCIATED VASCULITIS

# Introduction

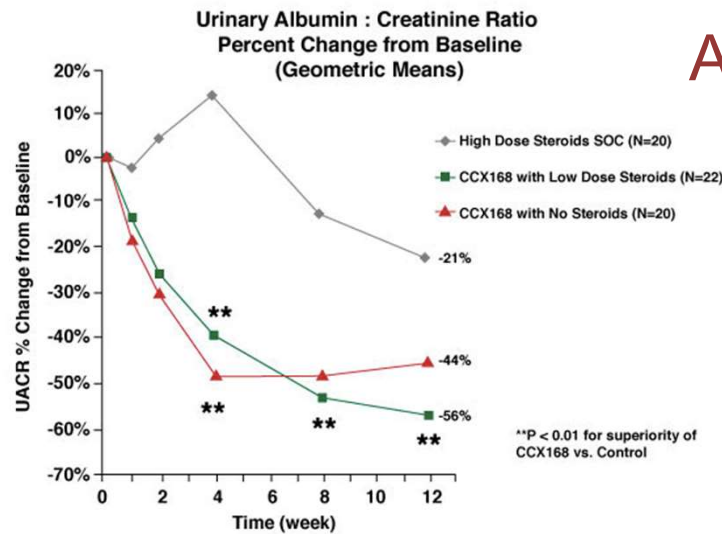
Comment limiter les séquelles rénales d'une poussée rénale de VAA ?

- Dépister et traiter précocément les poussées...

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- Améliorer les schémas d'induction pour une efficacité plus rapide

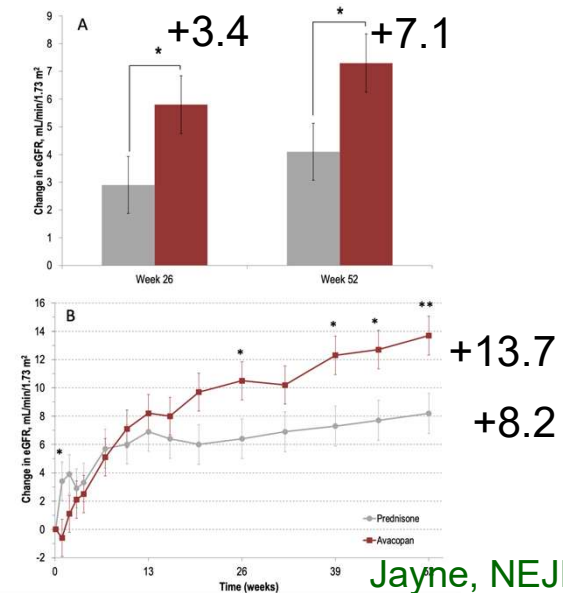


Jayne, JASN 2017

Avacopan ?

All patients

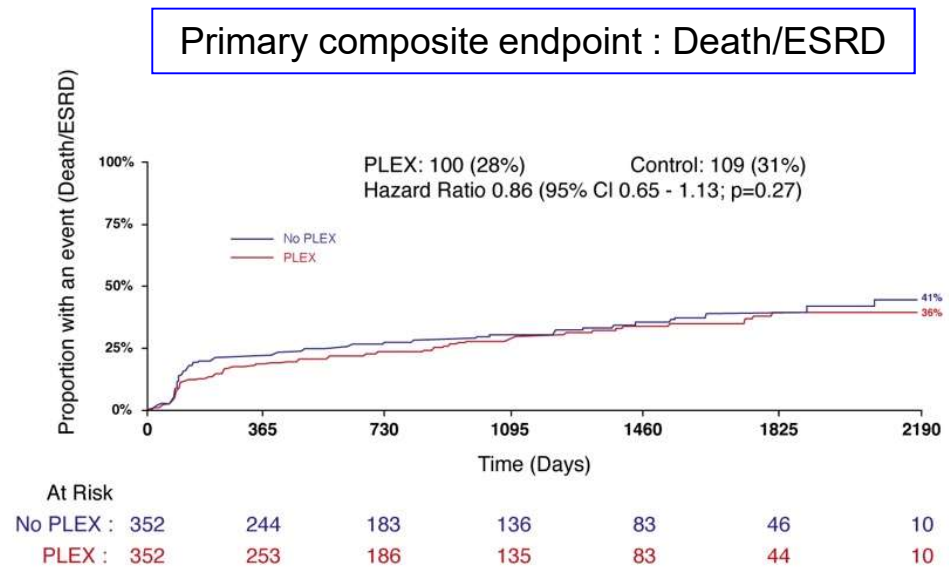
Patients with  
initial GFR<30



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- Epurer les ANCA circulants ?



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- Dépister et traiter précocément les poussées...
- Améliorer les schémas d'induction pour une efficacité plus rapide
- Epurer les ANCA circulants ?
- Améliorer la « cicatrisation » rénale ?

# Crescentic Rapidly Progressive Glomerulonephritis (RPGN)

## Pauci-immunes

ANCA  
Activated neutrophils



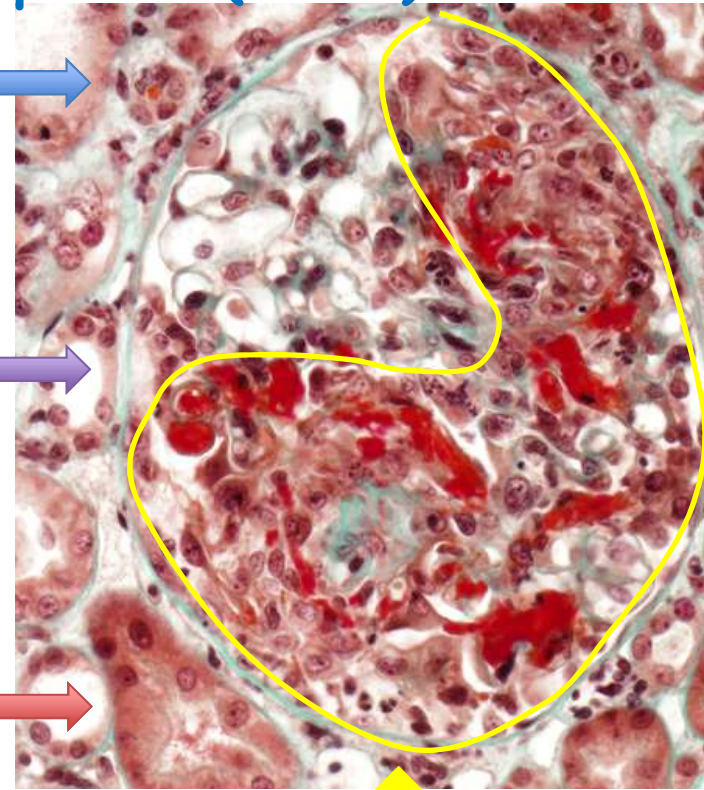
## anti-GBM Abs

anti- $\alpha$ 3NC1 /  $\alpha$ 5NC1  
Autoreactive T Lymphocytes



## Immune complexes

Auto-antibodies  
Complement activation  
Various Mechanisms (Lupus, IgA Nephropathy, infections...)



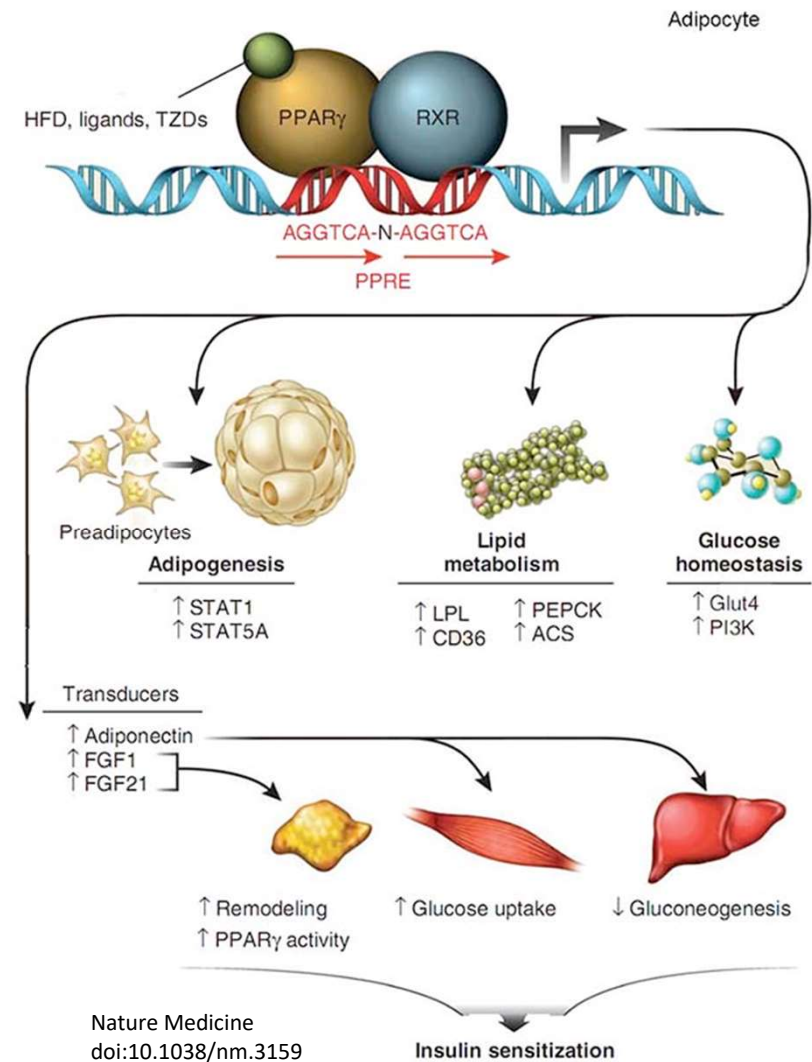
Common mechanisms causing  
loss of tolerance of glomerular epithelial cells to vasculitides?

## Quel est le métabolisme des podocytes normaux et pathologiques?

⇒ Les podocytes disposent des systèmes de métabolisation des acides gras libres, filtrés physiologiquement à travers le capillaire glomérulaire.

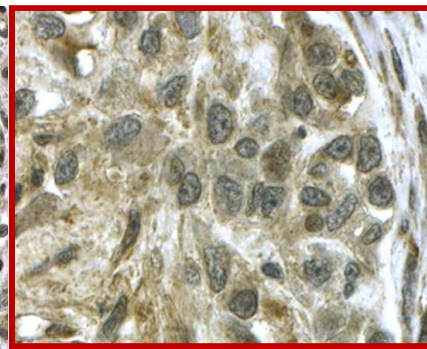
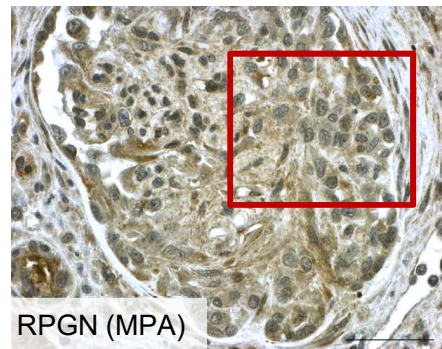
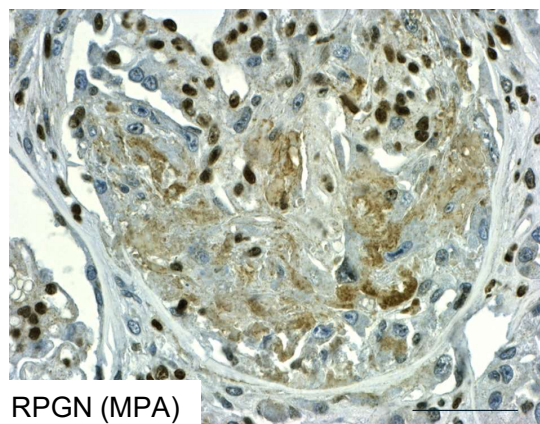
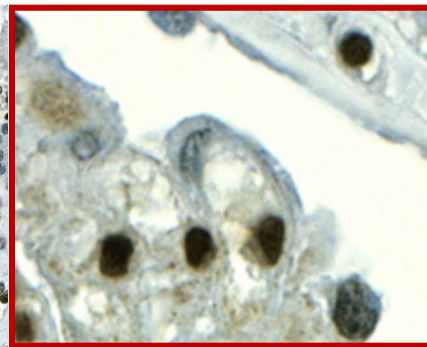
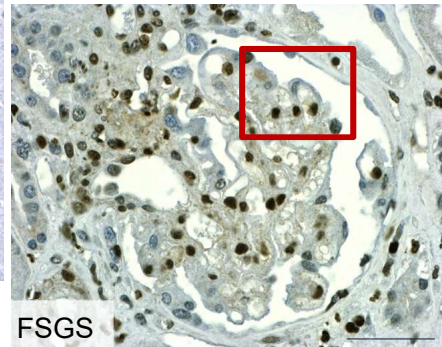
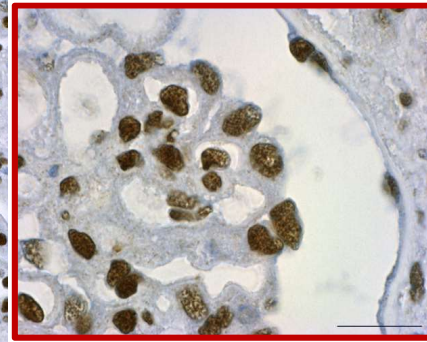
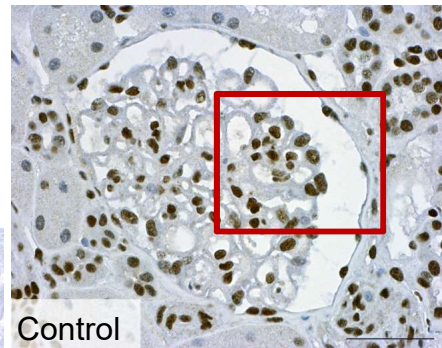
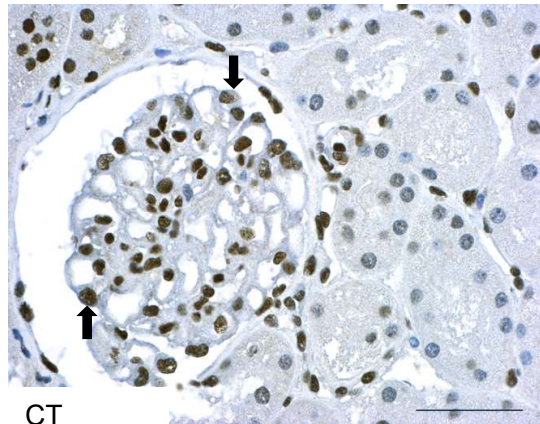
En particulier le récepteur nucléaire PPARgamma

=> Quel est le rôle de celui-ci?





Healthy Glomerular  
Epithelial Cells express  
PPAR $\gamma$  constitutively

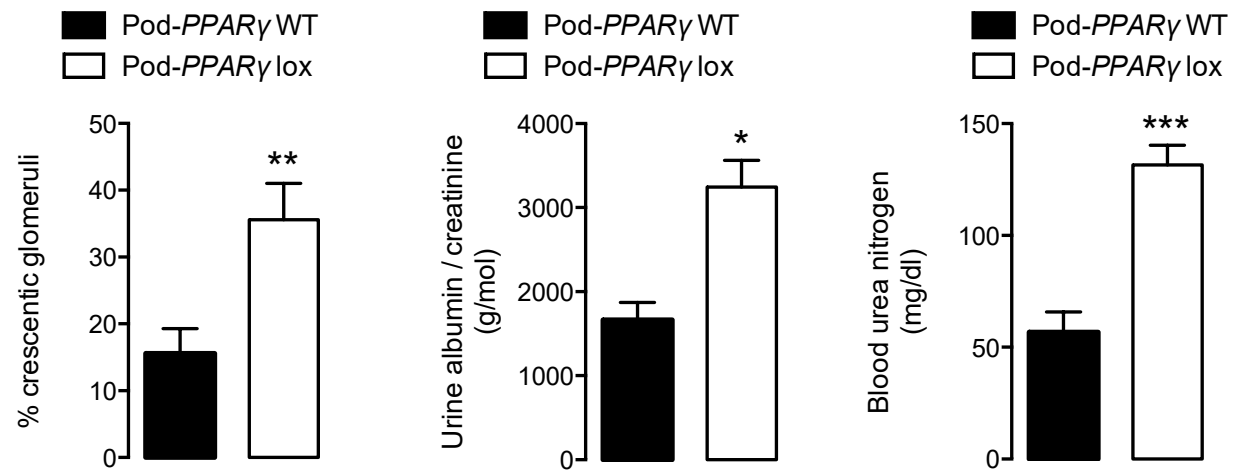
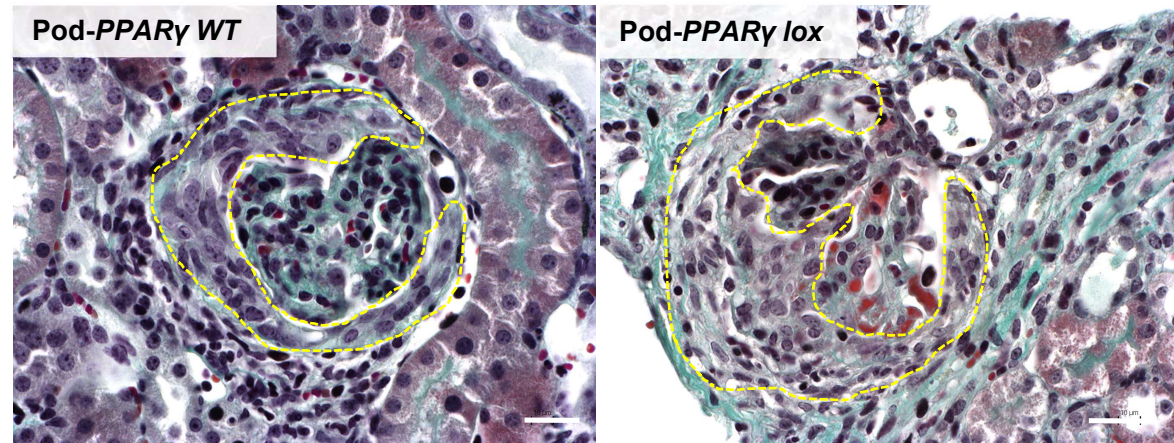


Henique et al.  
J Am Soc Nephrol. 2016

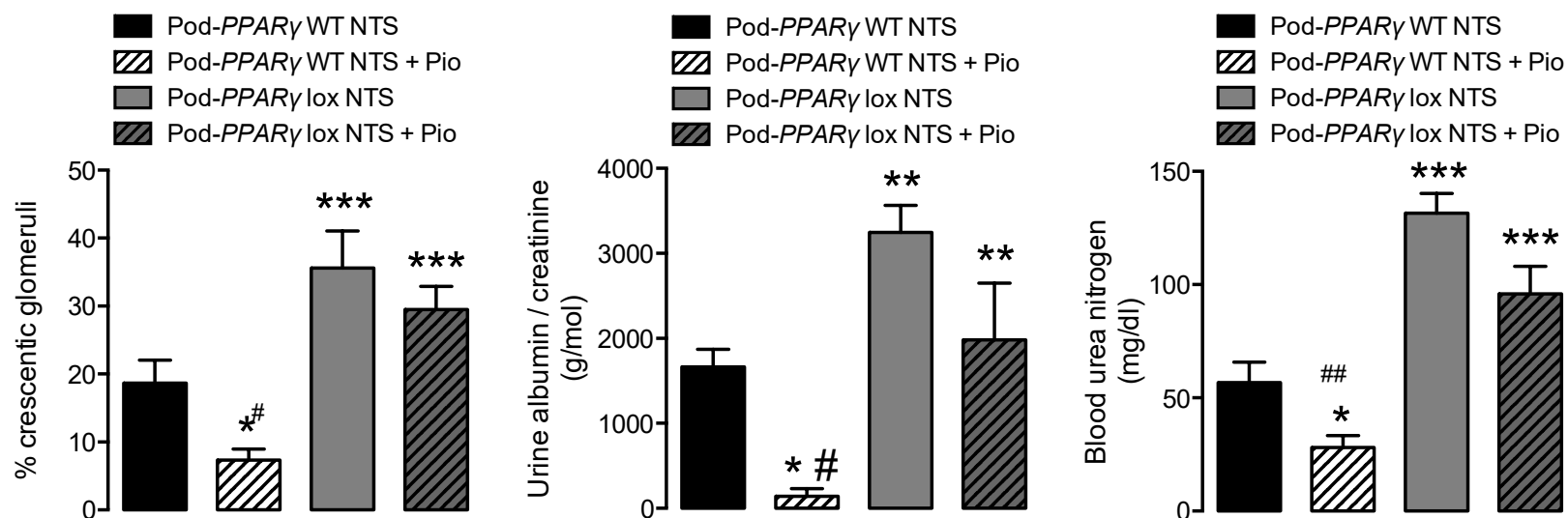
The nuclear PPAR $\gamma$   
expression is lost in  
MPA- and GPA-  
associated  
crescentic RPGN



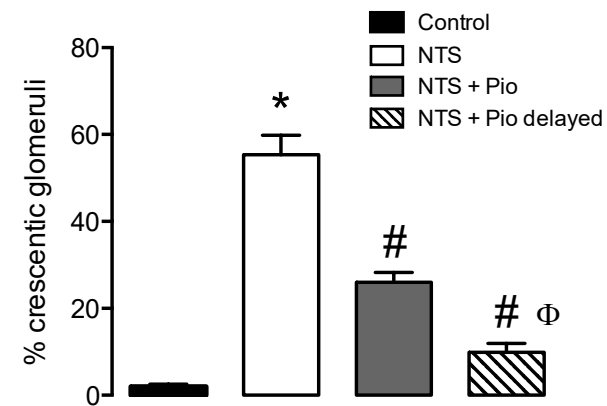
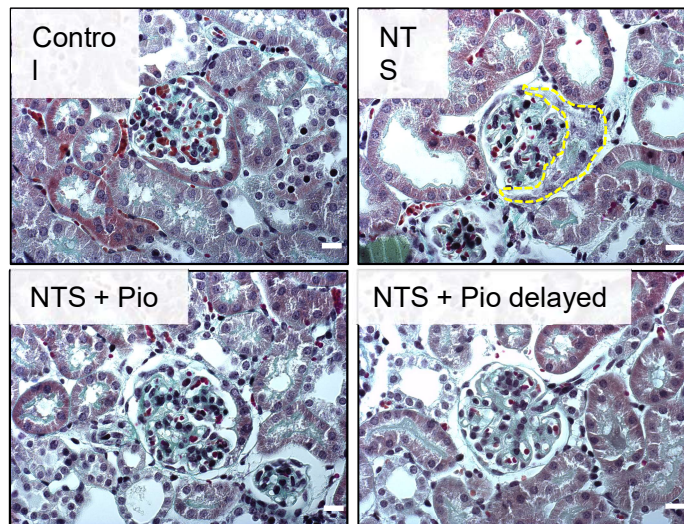
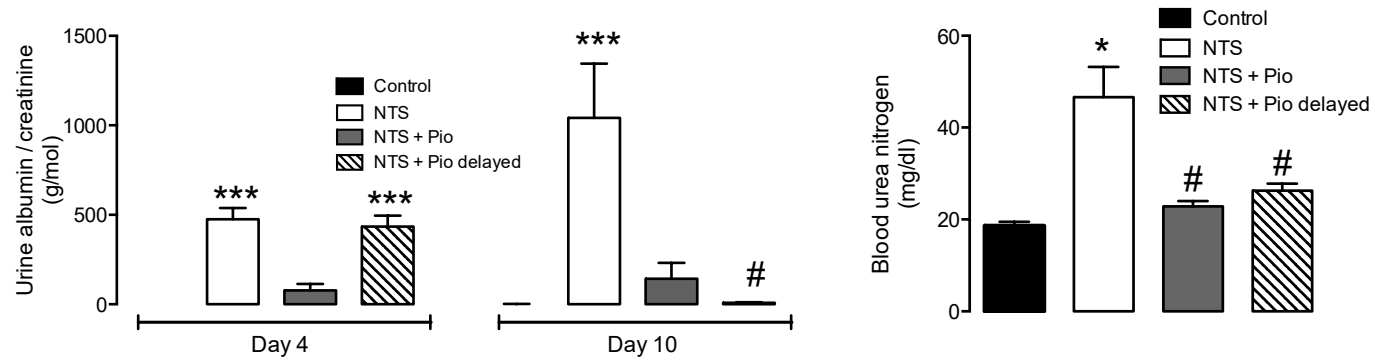
## Podocyte Selective PPAR $\gamma$ Deficiency Aggravates Crescentic RPGN



## Pioglitazone Alleviates RPGN in WT mice BUT NOT in Podocyte Selective PPAR $\gamma$ Deficiency



## Delayed PPAR $\gamma$ Agonism Halts Crescentic RPGN



Henique et al. J Am Soc Nephrol. 2016;27(1):172-88

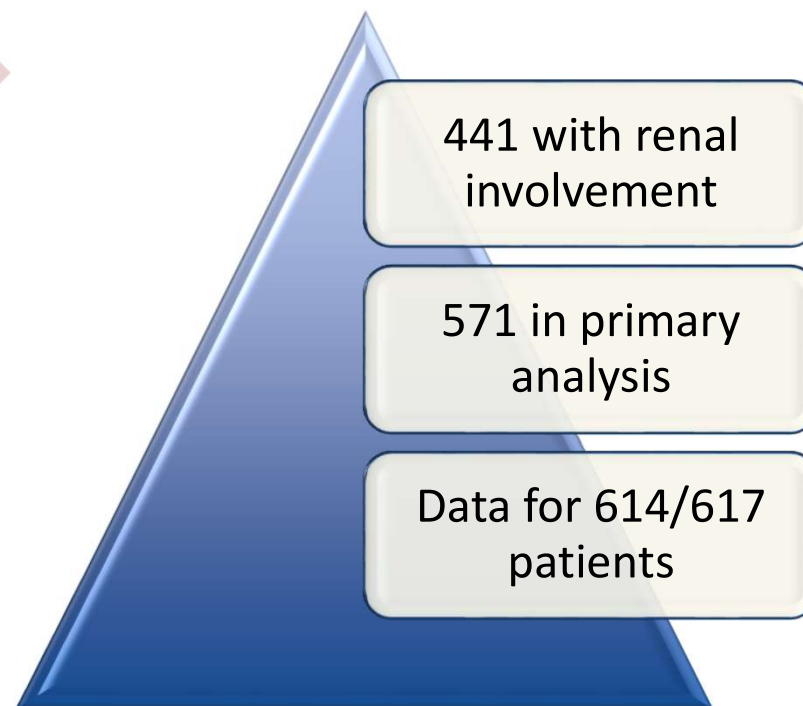
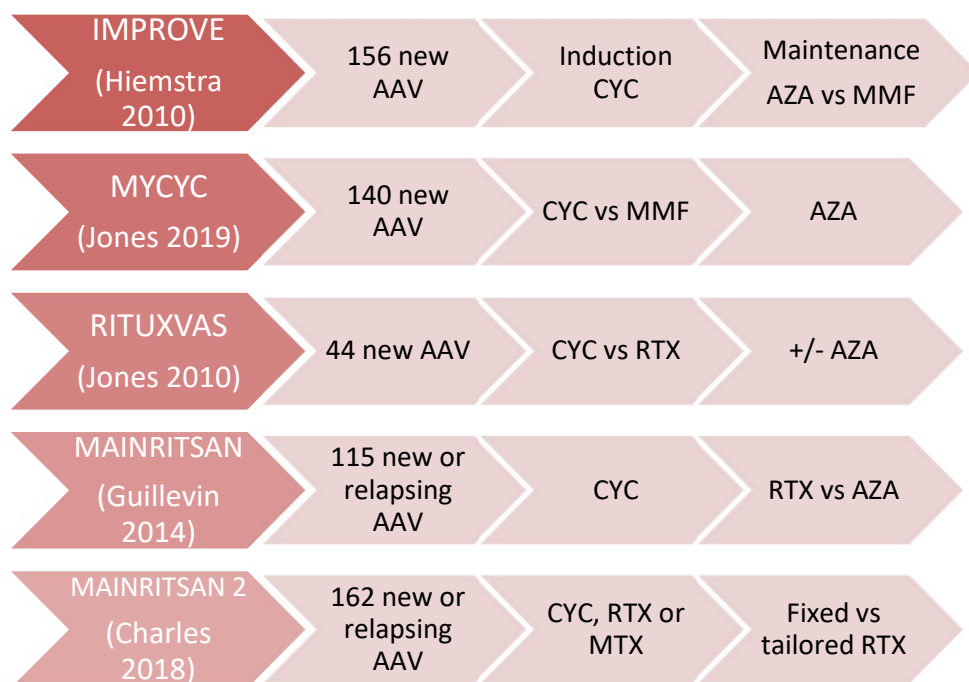
# Essai RENATO

- [Primary objective](#) : to demonstrate a reduction of renal damage in ANCA-associated renal vasculitis, by pioglitazone add-on treatment on top of SOC standardized immunosuppressive regimen with glucocorticoids and rituximab.
- [Secondary objectives](#) :
  - To evaluate the efficacy of pioglitazone on long-term preservation of renal function,
  - To assess the efficacy of pioglitazone on the reduction of hypertension and metabolic side effects of glucocorticoids.
  - To describe the clinical and biological tolerance of pioglitazone in this population,
  - To measure the impact of this drug on renal and systemic vasculitis activity,

# Essai RENATO

- Primary composite endpoint :
  - Improvement of serum creatinine (Delta sCreat) >30% of baseline value **AND** urine proteine-to-creatinine (uPCR) <1g/g at week 26.

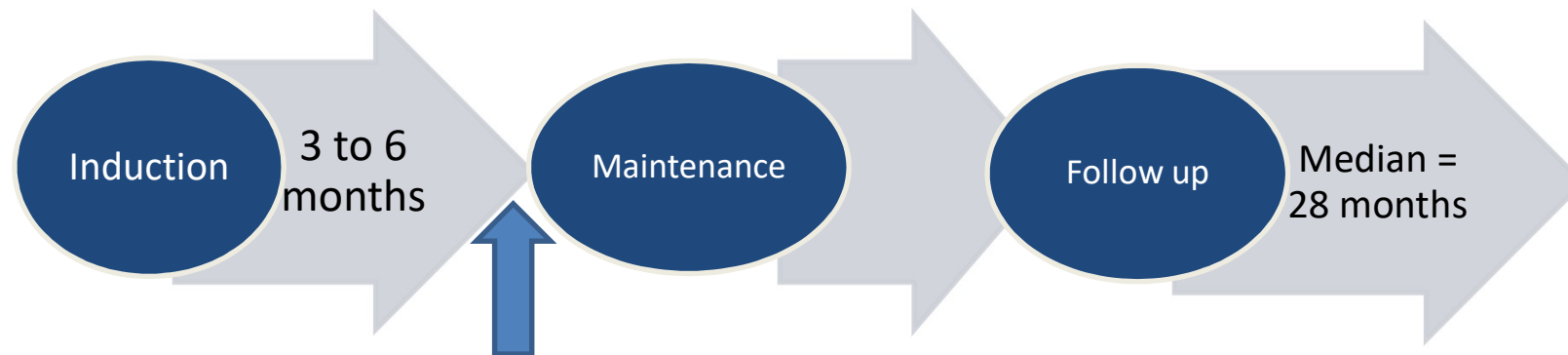
## Prognostic value of persistent proteinuria and hematuria after induction therapy in ANCA-associated vasculitis



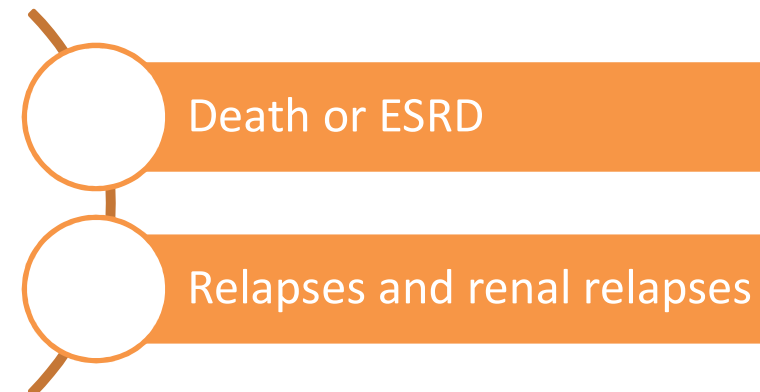
Benichou N, Karras A, ASN 2020



# Design – prospective assessment



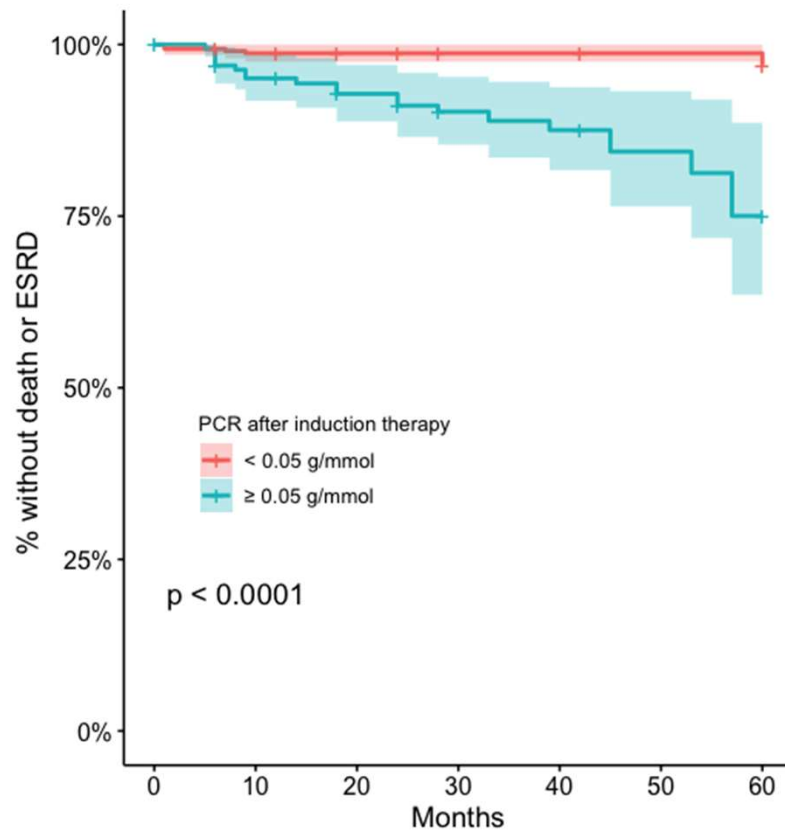
PROTEINURIA : 24h urine or protein/creatinine ratio on spot



Benichou N, Karras A, ASN 2020

# Outcome : Death or ESRD

5% of patients

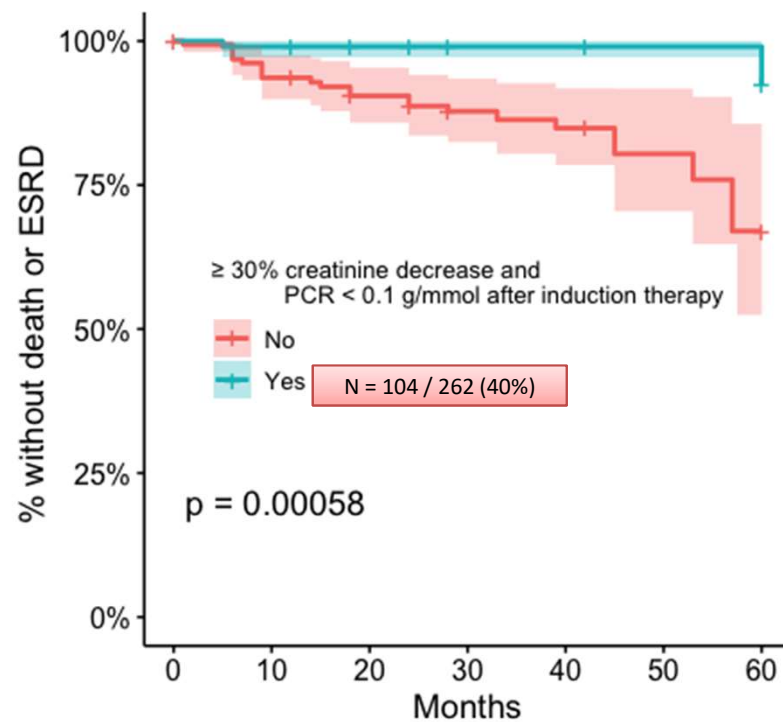


| Multivariate Cox analysis                 | Adjusted Hazard Ratio | 95% Confidence Interval | p value      |
|-------------------------------------------|-----------------------|-------------------------|--------------|
| Male sex                                  | 0.99                  | 0.43 - 2.28             | 0.974        |
| Age                                       | 1.03                  | 1.00 - 1.07             | 0.056        |
| ANCA type (ref: PR3)                      |                       |                         |              |
| Negative                                  | 0.69                  | 0.09 - 5.46             | 0.723        |
| MPO                                       | 2.06                  | 0.86 - 4.96             | 0.107        |
| eGFR at flare diagnosis                   | <b>0.97</b>           | <b>0.95 - 0.99</b>      | <b>0.016</b> |
| Hematuria after induction therapy         | 1.88                  | 0.83 - 4.29             | 0.132        |
| PCR after induction therapy ≥ 0.05 g/mmol | <b>4.08</b>           | <b>1.48 - 11.25</b>     | <b>0.006</b> |

Benichou N, Karras A, ASN 2020

## Outcome : Death or ESRD

Patients with sCreat > 130  $\mu\text{mol/L}$  at diagnosis



| Multivariate Cox Analysis                                                                       | Adjusted HR | 95% CI             | p value      |
|-------------------------------------------------------------------------------------------------|-------------|--------------------|--------------|
| Male sex                                                                                        | 1.03        | 0.42 - 2.50        | 0.955        |
| Age                                                                                             | 1.01        | 0.98 - 1.05        | 0.391        |
| ANCA type (ref: PR3)                                                                            |             |                    |              |
| Negative                                                                                        | 1.19        | 0.25 - 5.75        | 0.830        |
| MPO                                                                                             | 2.09        | 0.82 - 5.38        | 0.124        |
| eGFR at flare diagnosis                                                                         | <b>0.96</b> | <b>0.92 - 0.99</b> | <b>0.015</b> |
| Hematuria after induction therapy                                                               | 2.01        | 0.88 - 4.58        | 0.098        |
| Proposed surrogate endpoint<br>(≥ 30% creatinine decrease and PCR < 0.1 g/mmol after induction) | <b>0.11</b> | <b>0.02 - 0.46</b> | <b>0.003</b> |

Benichou N, Karras A, ASN 2020

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- Primary composite endpoint :
  - Improvement of serum creatinine (Delta sCreat) >30% of baseline value **AND** urine proteine-to-creatinine (uPCR) <1g/g at week 26.
- Secondary endpoints :
  - sCreat, Delta sCreat, eGFR, renal survival (off-dialysis) and proteinuria (UPCR) at W4, W12, W26, W52
  - BVAS and ANCA positivity at W4, W12, W26, W52, Relapse rate
  - Renal vasculitis activity (urinary MCP-1, KIM-1, Calprotectin, CD163 ) at W4, W12, W26, W52.
  - Damage score (VDI ) at W26, W52 and Glucocorticoid Toxicity Index (GTI) at W12, 26, 52
  - Blood pressure (ABPM and n of antihypertensive drugs), Diabetes (HbA1c), Lipid profile
  - Safety profile of pioglitazone

# Essai RENATO

- Inclusion criteria :
  - Newly-diagnosed or relapsing AAV (GPA /MPA), with an active disease defined as a BVAS  $\geq 3$
  - Presence of proteinuria (UPCR  $>300$  mg/g), haematuria ( $>10$  RBC/hpf) and eGFR  $\geq 15$  mL/min/1.73 m<sup>2</sup> at inclusion
  - Recent ( $<4$  weeks) renal biopsy that confirms renal involvement of ANCA-associated vasculitis
  - Patients aged of 18 to 80 years

# Essai RENATO

- Non-inclusion criteria :
  - Severe kidney injury with eGFR  $<15$  ml/min/1.73m<sup>2</sup> or dialysis therapy at inclusion
  - Alveolar haemorrhage requiring pulmonary ventilation support at inclusion
  - Active cancer (except non-melanoma skin cancer) within the past 24 months
  - Past history of bladder or urinary tract cancer
  - History of Class 3/4 congestive heart failure symptoms, Class 2 heart failure symptoms within the past 3 months and ejection fraction  $<40\%$  on recent echocardiography
  - Chronic liver disease
  - Positive serology for HIV, HBV (Ag HBs positivity), HCV at inclusion
  - Pregnant or breast-feeding women, or desire to become pregnant within 12 months
  - Severe neurologic or psychiatric disease (e.g., dementia or schizophrenia)
  - Kidney transplant recipients
  - Cyclophosphamide or rituximab use within 26 weeks prior to screening



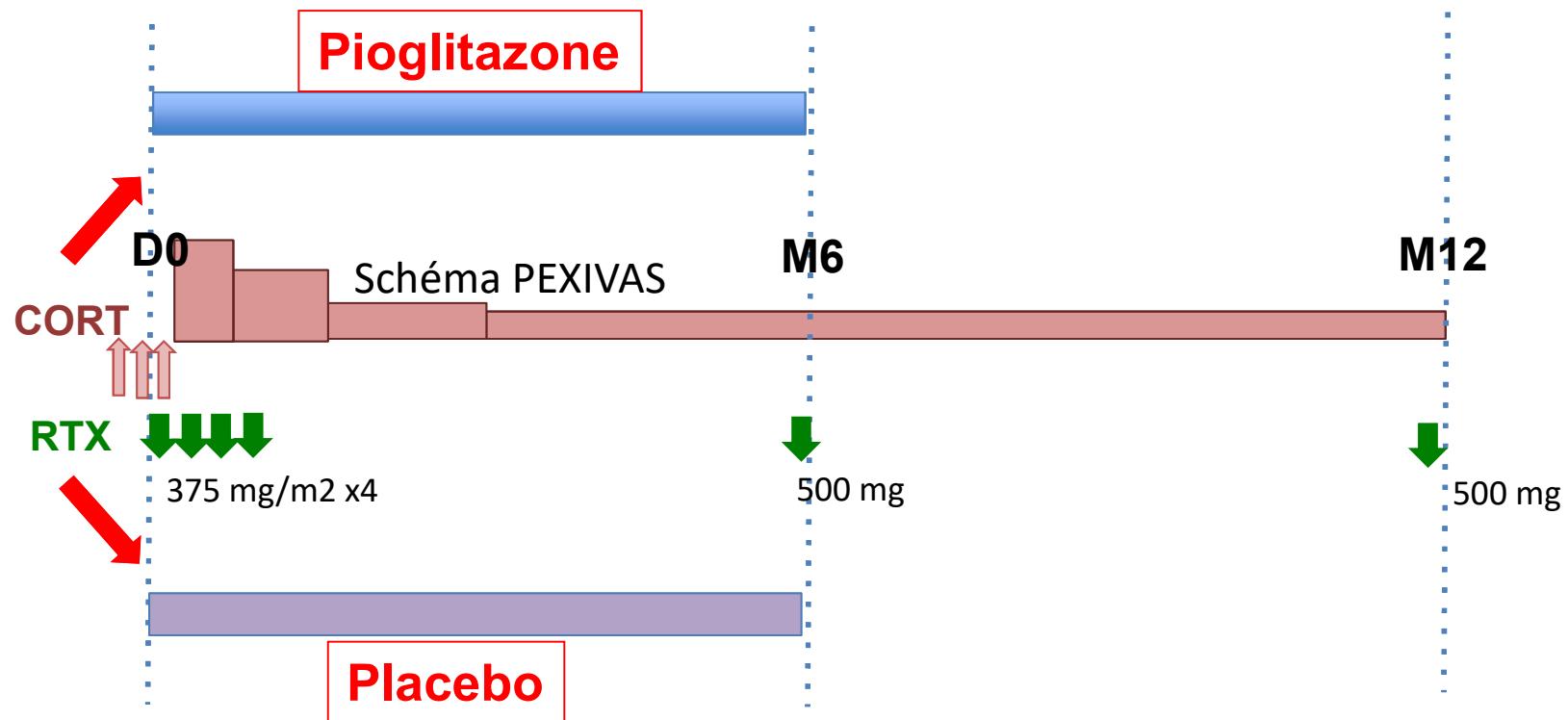
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# ElG spécifiques

- Carcinomes urothéliaux
  - Pas de sur-risque confirmé sur multiples essais et métaanalyses récentes
  - Par précaution : pas de cyclophosphamide, non inclusion si ATCD
- Insuffisance cardiaque :
  - Sur-risque d'OMI et décompensation cardiaque dans qq études chez diabétique
  - Par précaution : non inclusion si ATCD d'insuffisance cardiaque classe III/IV
  - Echo cardiaque à l'inclusion et exclusion si FEVG <40%
  - Surveillance poids et BNP à chaque visite pdt 6 mois et diurétique si besoin
- Hépatite, hypoglycémie, ostéoporose fracturaire

# RENATO trial



# Traitements associés

- Traitements antihypertenseurs (ICa, diurétiques, bêtabloquants, alphabloquants) en visant TA <140/90 (135/85 sur MAPA W4 et W12)
- Débuter diurétiques en priorité si prise de poids, OMI ou élévation BNP
  - suspension pioglit/placebo si >3 kg/1 sem, doublement de BNP)
  - arrêt du traitement de l'étude si poussée d'IC congestive
- Pas d'IEC, ARA2 ou iSGLT2 pdt les 6 premiers mois (sauf si HTA >160/95)  
(incitation à les utiliser au delà de M6 si PU >1g/g)
- Utilisation libre des autres antidiabétiques
- Prophylaxies usuelles pneumocystose, ostéoporose cortisonique

# Essai RENATO

- 128 patients à inclure
- Durée de la période d'inclusion : 3 ans
- Durée du suivi : 1 an
- Nombre de centres prévus: 25
- Date de début des inclusions : 4<sup>e</sup> trimestre 2022

MERCI pour votre aide

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