# Essai RENATO

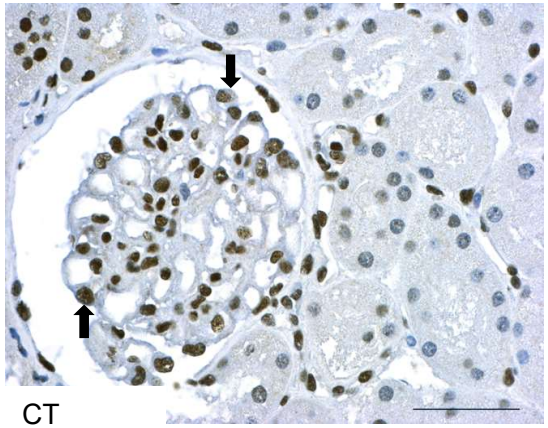
MULTICENTER **R**ANDOMIZED TRIAL TO **E**VALUATE THE EFFICACY OF PIOGLITAZONE TO PROMOTE RE**NA**L **TO**LERANCE IN ANCA-ASSOCIATED VASCULITIS

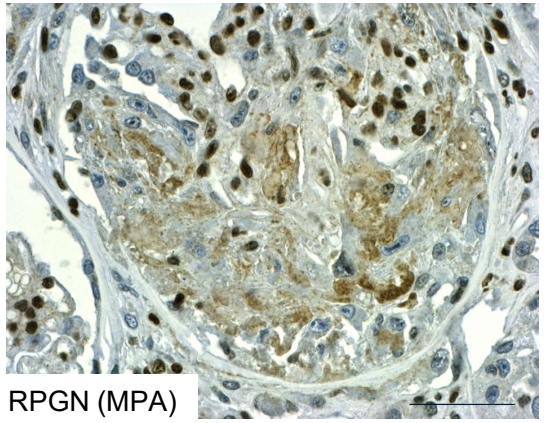
# Introduction

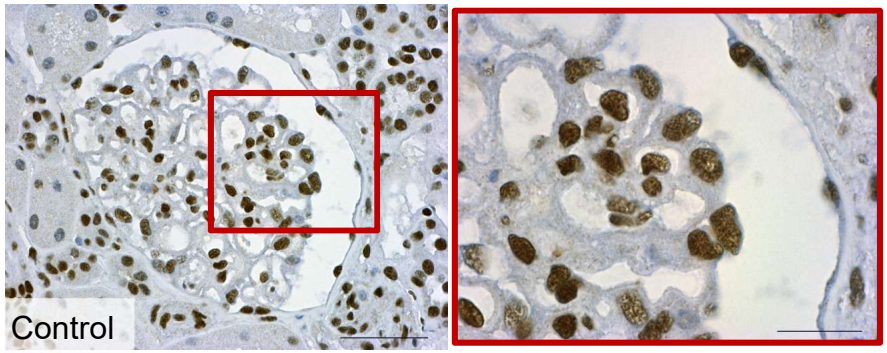
Comment limiter les séquelles rénales d'une poussée rénale de VAA ?

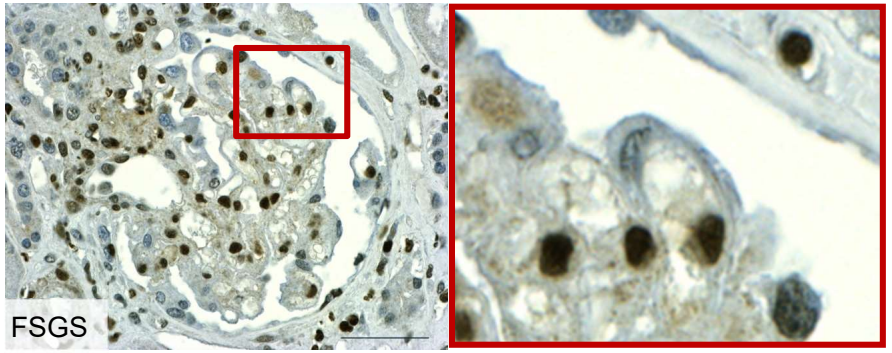
- Dépister et traiter précocément les poussées…
- Améliorer les schémas d'induction pour une efficacité plus rapide ?
- Epurer les ANCA circulants ?
- Améliorer la « cicatrisation » rénale ?

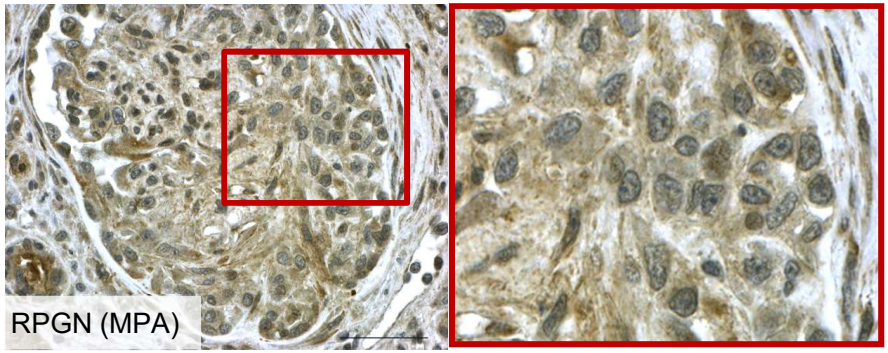
## Healthy Glomerular Epithelial Cells express PPARγ constitutively



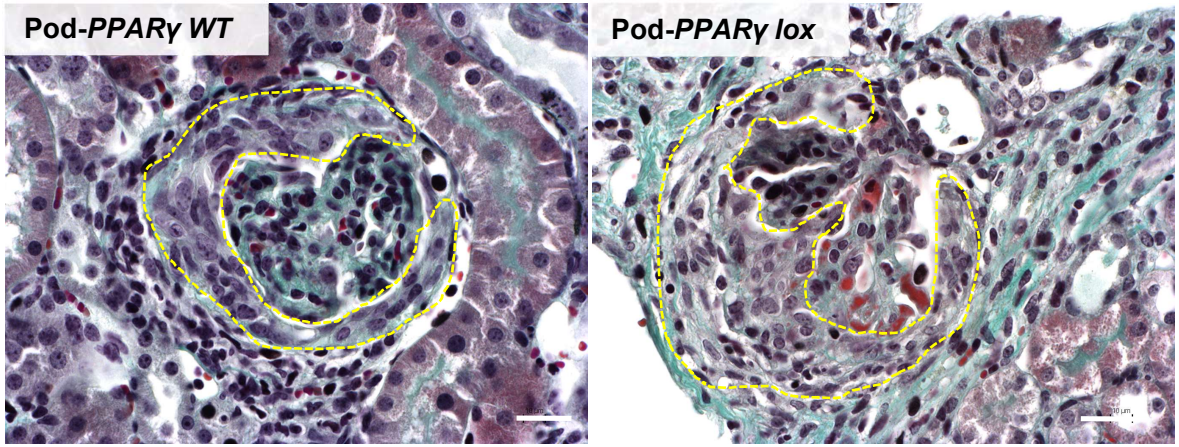



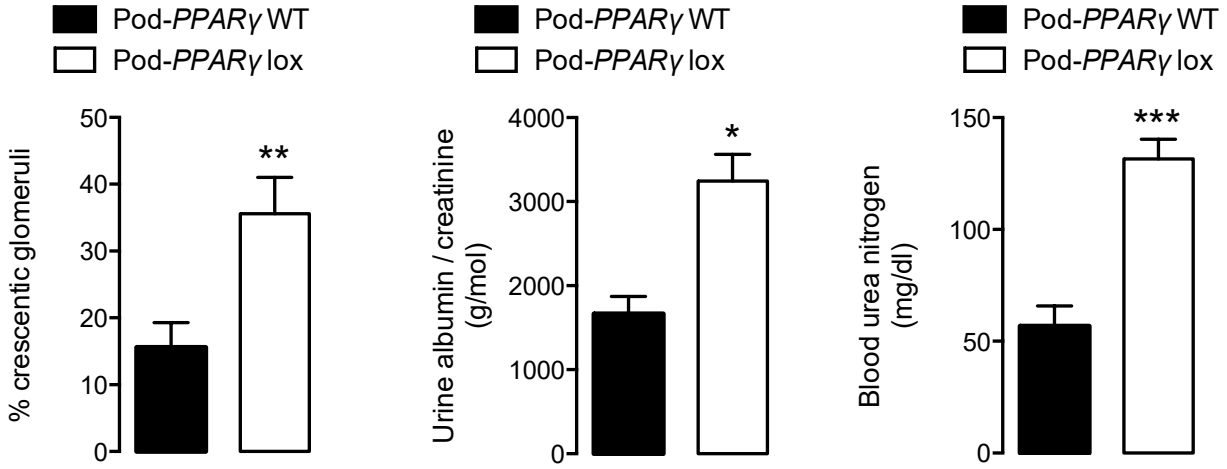




Henique et al.
J Am Soc Nephrol. 2016

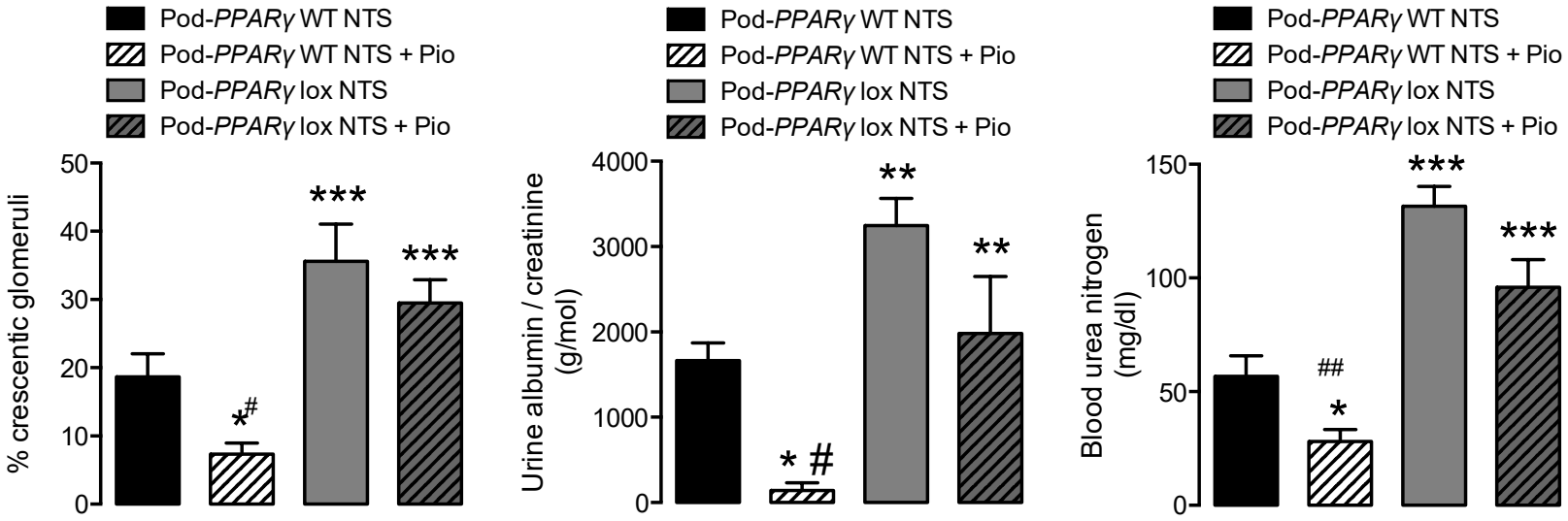
The nuclear PPARγ expression is lost in MPA- and GPA-associated crescentic RPGN

# Podocyte Selective PPARγ Deficiency Aggravates Crescentic RPGN



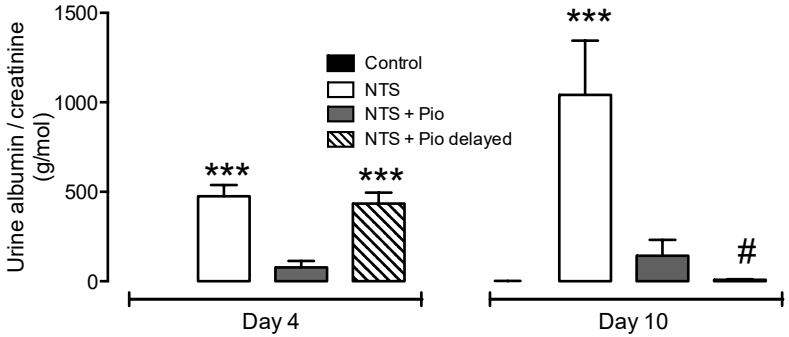



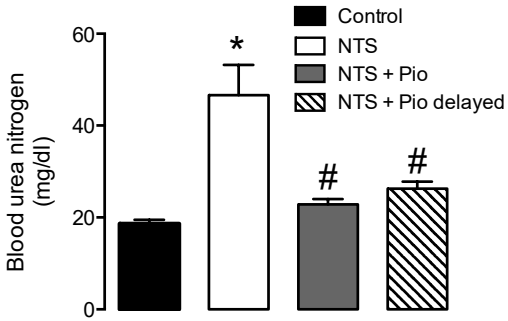
# Pioglitazone (PPARg agonist) Alleviates RPGN in WT mice

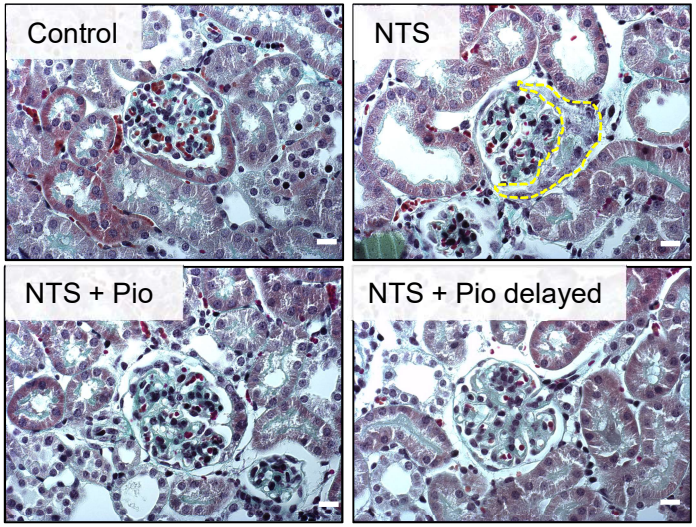


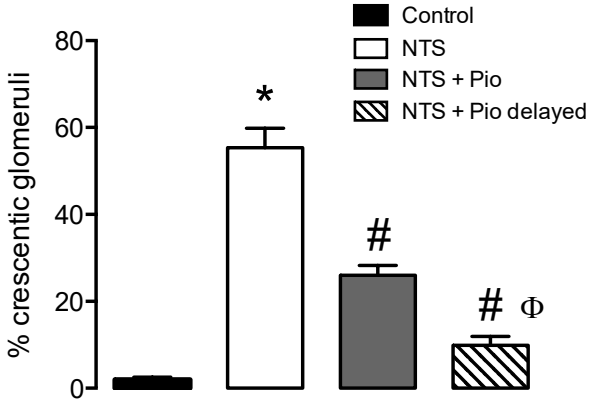

Henique et al. J Am Soc Nephrol. 2016;27(1):172-88

# Delayed PPARγ Agonism Halts Crescentic RPGN

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# Essai RENATO

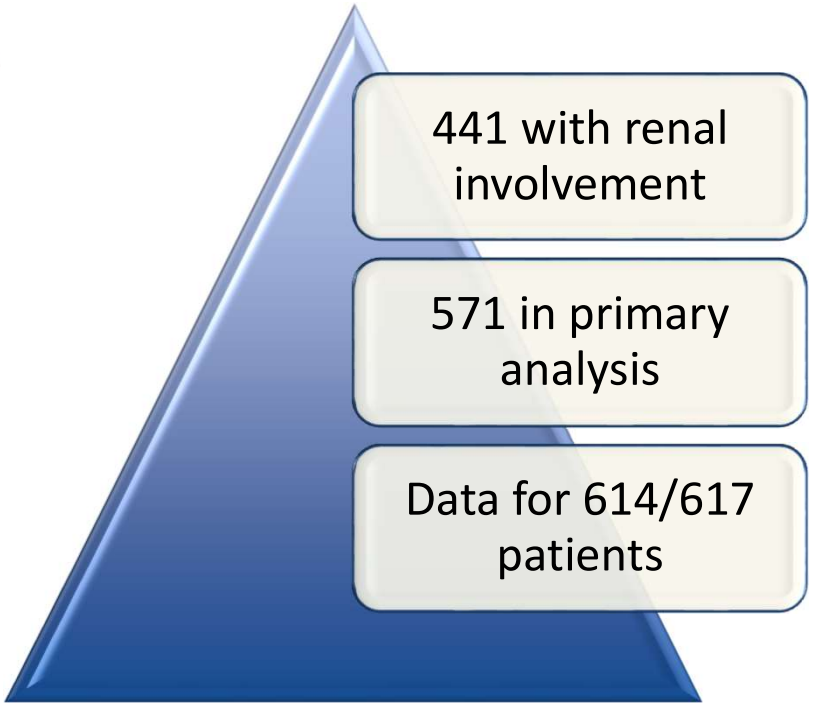
- Primary objective : to demonstrate a reduction of renal damage in ANCA-associated renal vasculitis, by pioglitazone add-on treatment on top of SOC standardized immunosuppressive regimen with glucocorticoids and rituximab.
- Secondary objectives :
  - To evaluate the efficacy of pioglitazone on long-term 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

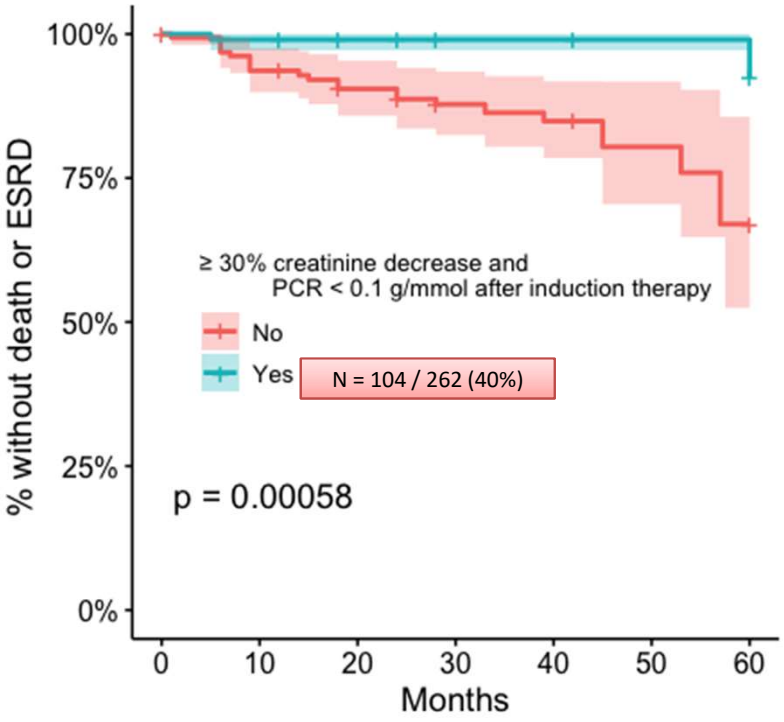
| | | | |
|---|---|---|---|
| IMPROVE (Hiemstra 2010) | 156 new AAV | Induction CYC | Maintenance AZA vs MMF |
| MYCYC (Jones 2019) | 140 new AAV | CYC vs MMF | AZA |
| RITUXVAS (Jones 2010) | 44 new AAV | CYC vs RTX | +/- AZA |
| MAINRITSAN (Guillevin 2014) | 115 new or relapsing AAV | CYC | RTX vs AZA |
| MAINRITSAN 2 (Charles 2018) | 162 new or relapsing AAV | CYC, RTX or MTX | Fixed vs tailored RTX |




Benichou N, Karras A, Kidney Int 2023

# Outcome : Death or ESRD

## Patients with sCreat > 130 umol/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 | **0.96** | **0.92 - 0.99** | **0.015** |
| Hematuria after induction therapy | 2.01 | 0.88 – 4.58 | 0.098 |
| Proposed surrogate endpoint (≥ 30% creatinine decrease and PCR < 0.1 g/mmol after induction) | **0.11** | **0.02 - 0.46** | **0.003** |

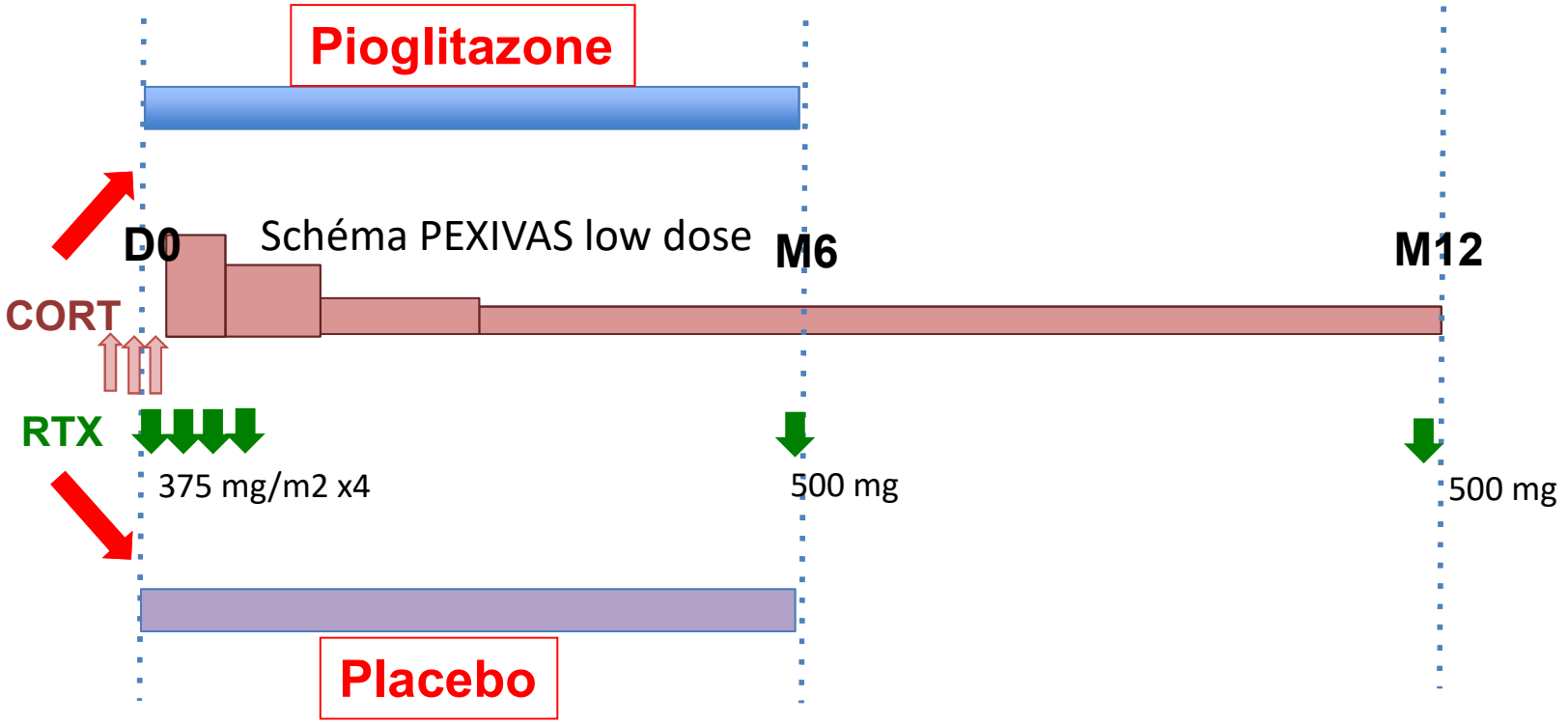
Benichou N, Karras A, ASN 2020

# 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.

- 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

# RENATO trial



# Essai RENATO

- Inclusion criteria :
  - Newly-diagnosed or relapsing AAV (GPA /MPA), with an active disease defined as a BVAS ≥ 3
  - Presence of proteinuria (UPCR >300 mg/g), haematuria (>10 RBC/hpf) and eGFR ≥15 mL/min/1.73 m2 at inclusion
  - Recent (<4 weeks) renal biopsy that confirms renal involvement of ANCA-associated vasculitis
  - Patients aged of 18 to 80 years

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- Non-inclusion criteria :
- Severe kidney injury with eGFR <15 ml/min/1.73m² 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

# EIG spécifiques

- Carcinomes urothéliaux
  - Pas de sur-risque confirmé sur multiples essais et métanalyses  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, œdème maculaire

# Traitements associés

- Traitements antihypertenseurs (ICa, diurétiques, bétabloquants, 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)**

- Utilisation libre des autres antidiabétiques
- Prophylaxies usuelles pneumocystose, ostéoporose cortisonique

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- 128 patients à inclure
- Durée de la période d'inclusion : 3 ans
- Durée du suivi : 1 an
- Nombre de centres prévus: 25 (10 centres ouverts à ce jour)
- Première inclusion : fin 2023 (8 patients inclus à ce jour)

## MERCI pour votre aide

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