Treatment Updates in ANCA-associated vasculitis and glomerulonephritis

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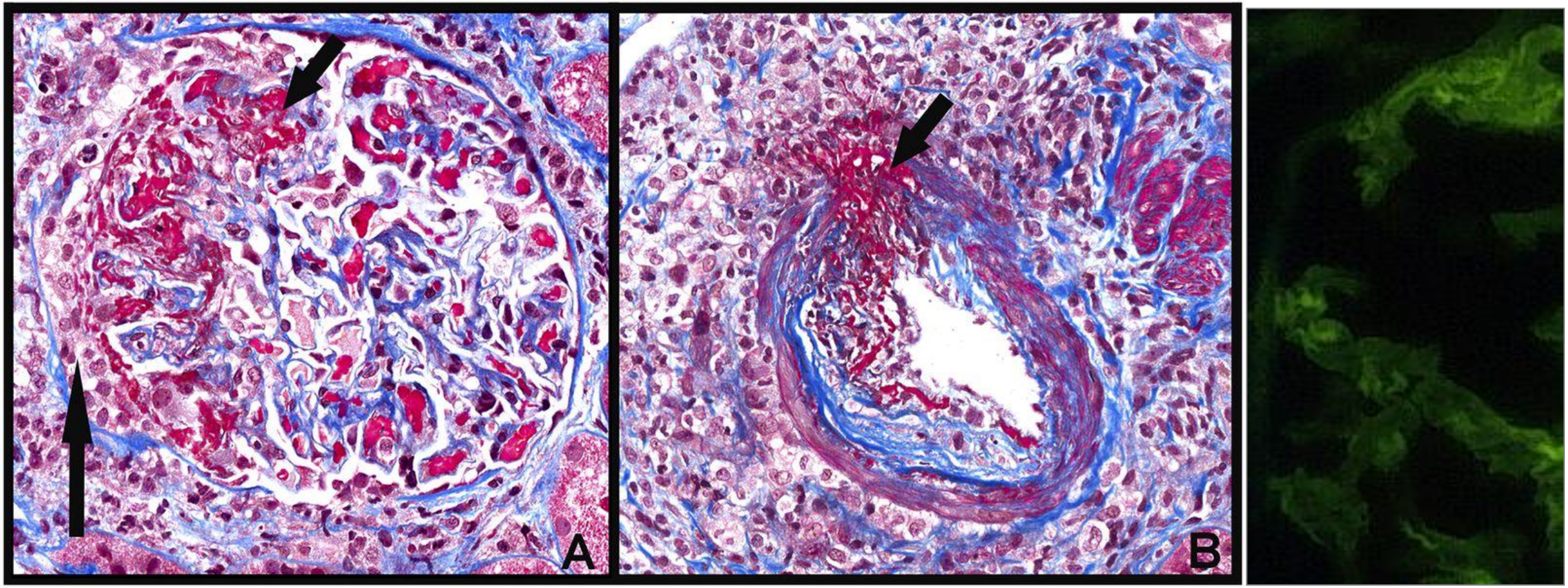
Kidney involvement in ANCA-vasculitis

- 77-85% within 2 years of diagnosis

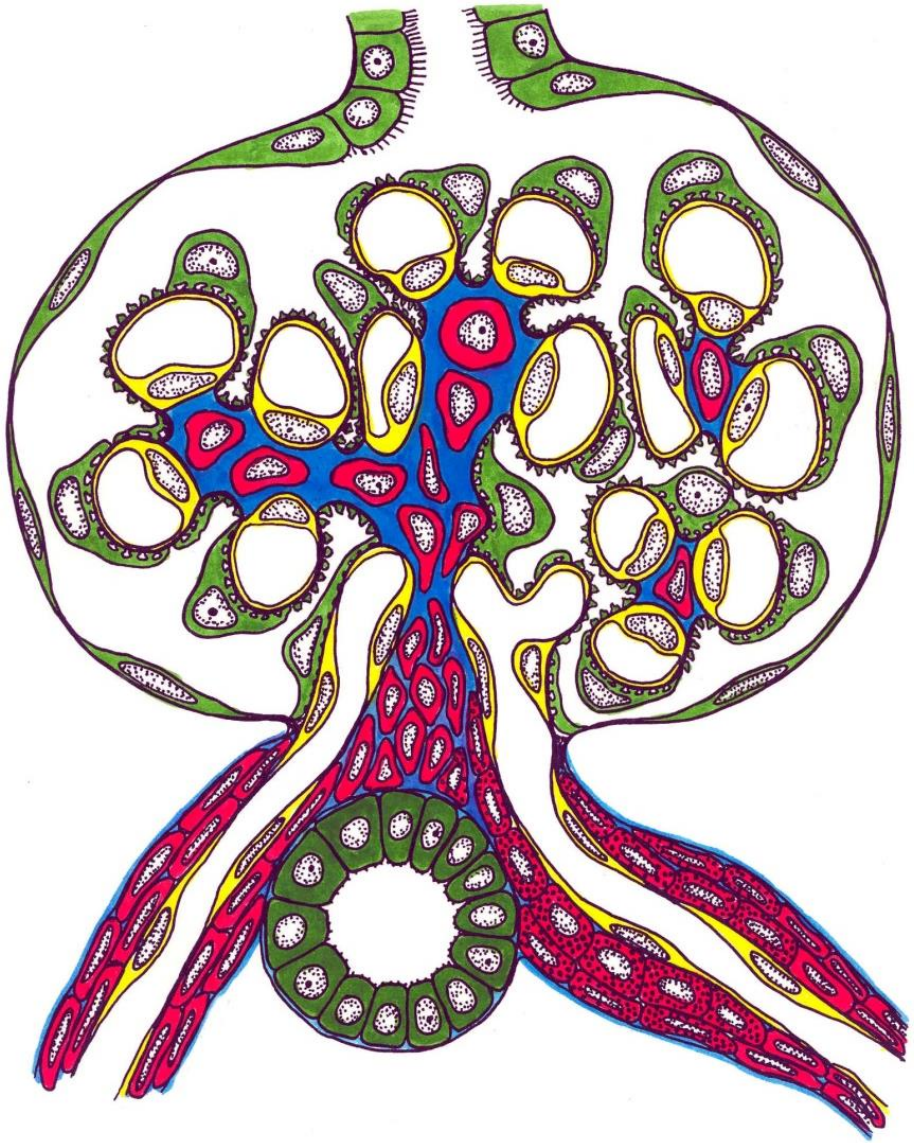
Hoffman GS. Et al. Ann Intern Med 1992

Pauci-immune glomerulonephritis

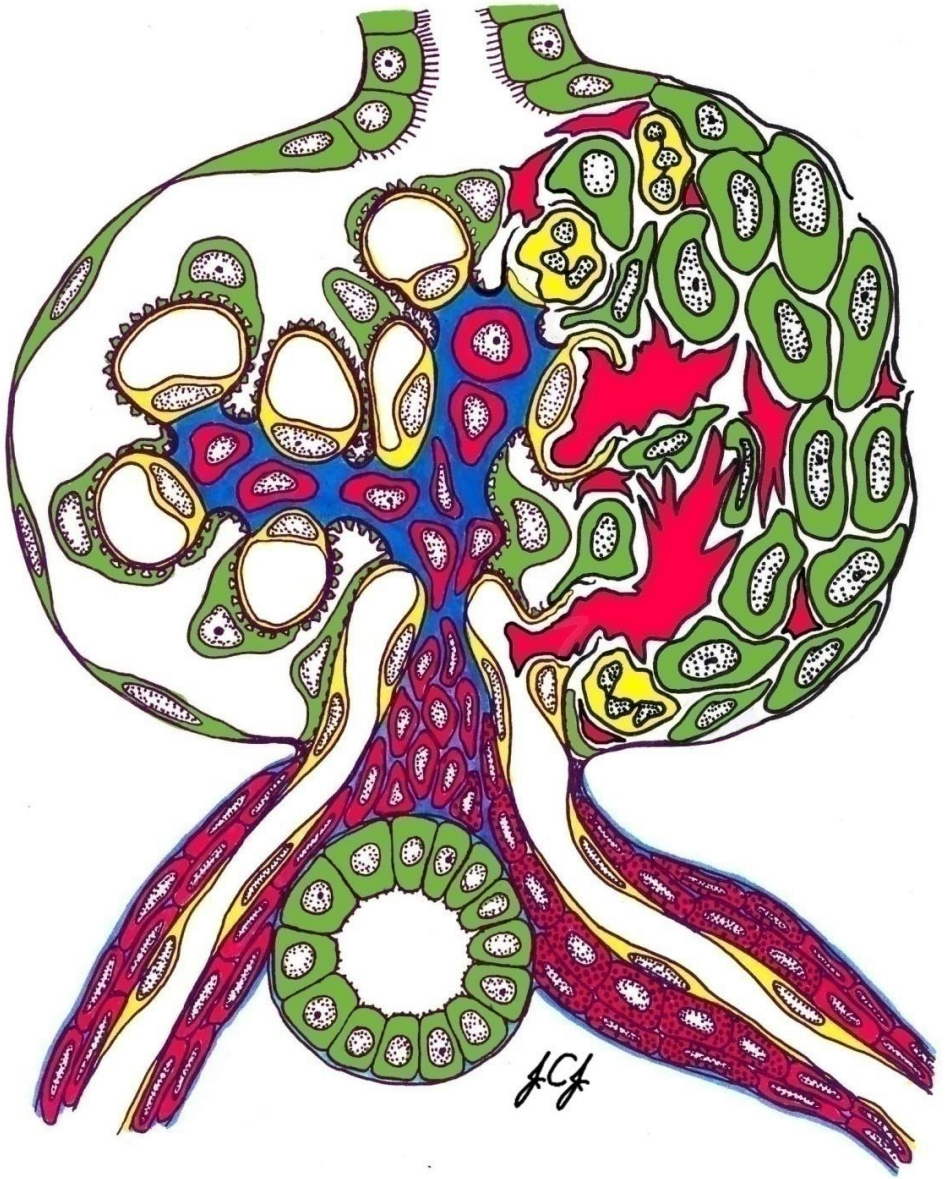


>85% of patients with pauci-immune GN are ANCA (+)

J. Charles Jennette, UNC Kidney Center



Normal glomeruli

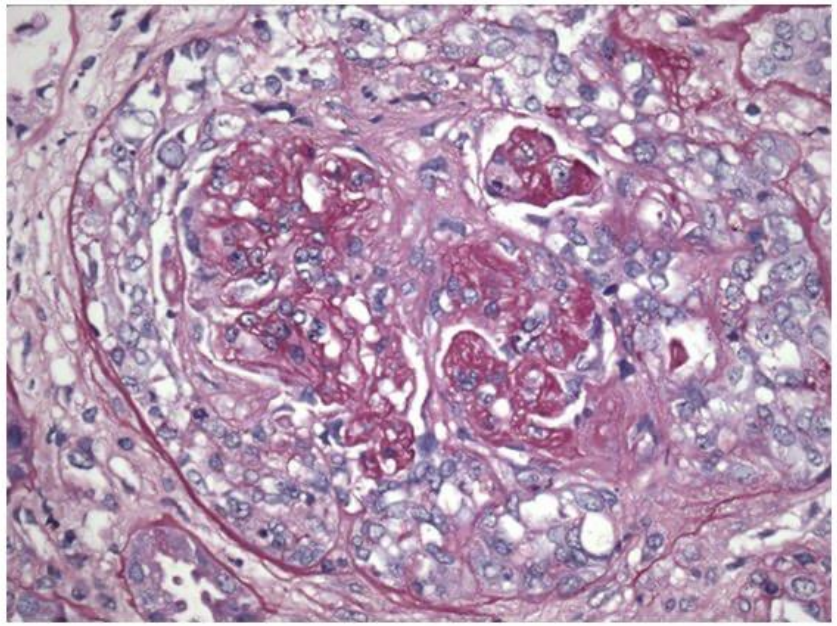


Crescent

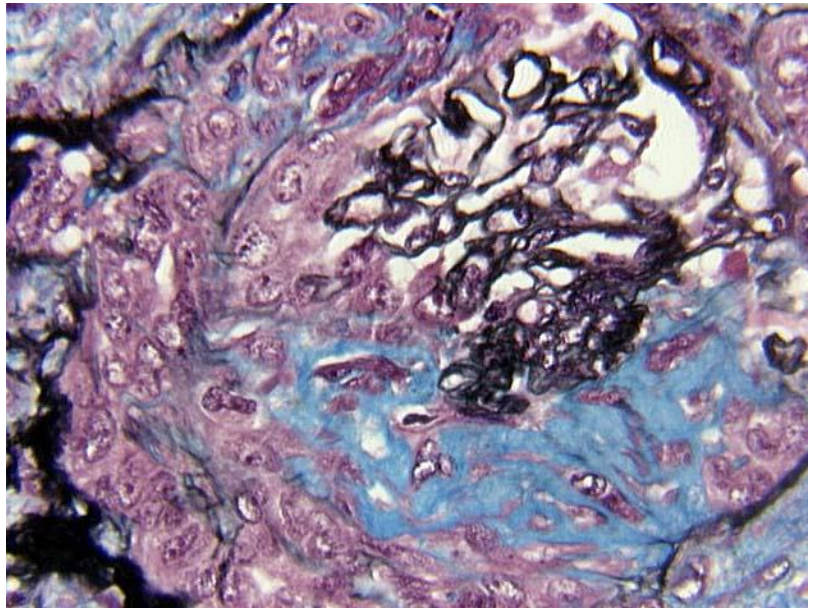
JC.Jennette

Aging crescent

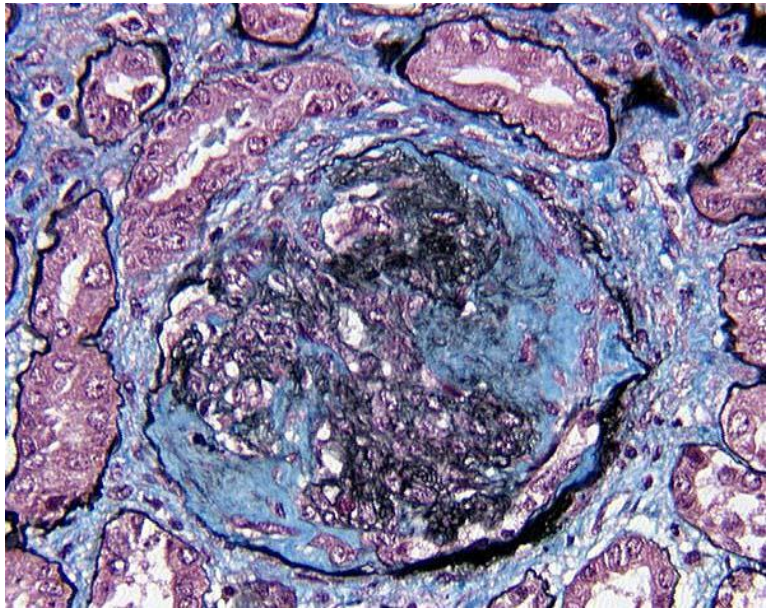
Cellular



Fibro-cellular

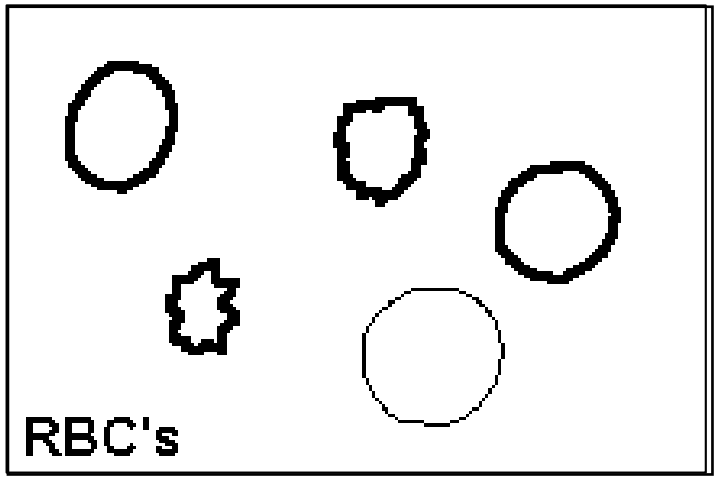


Fibrous



Time

Renal manifestations



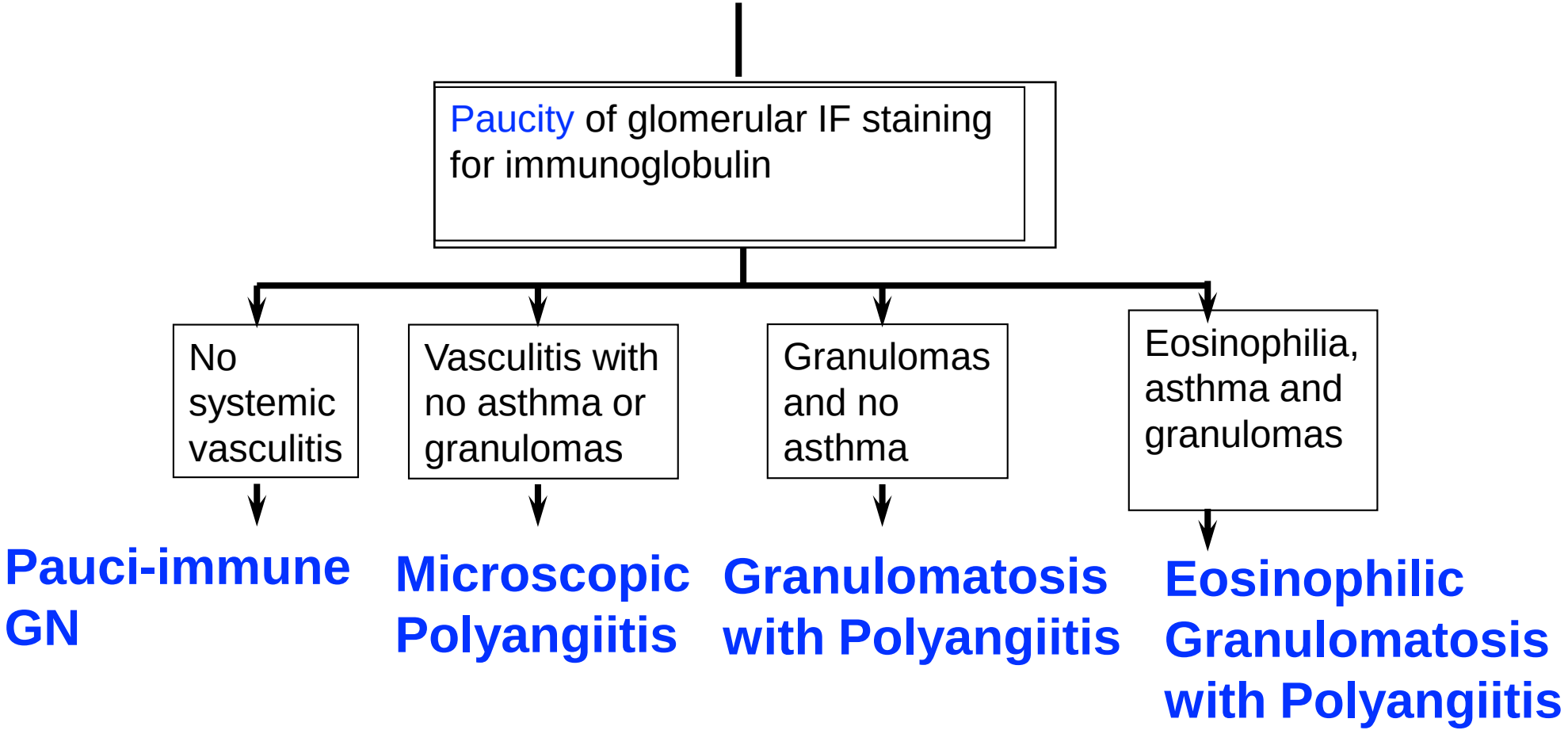
- Asymptomatic glomerular hematuria
- Glomerular hematuria and rise in serum creatinine with a variable degree of proteinuria
- Rapidly progressive glomerulonephritis

	Serum Creatinine (mg/dl)
Crescentic ANCA-GN	6.5±4 (0.8-22.1)

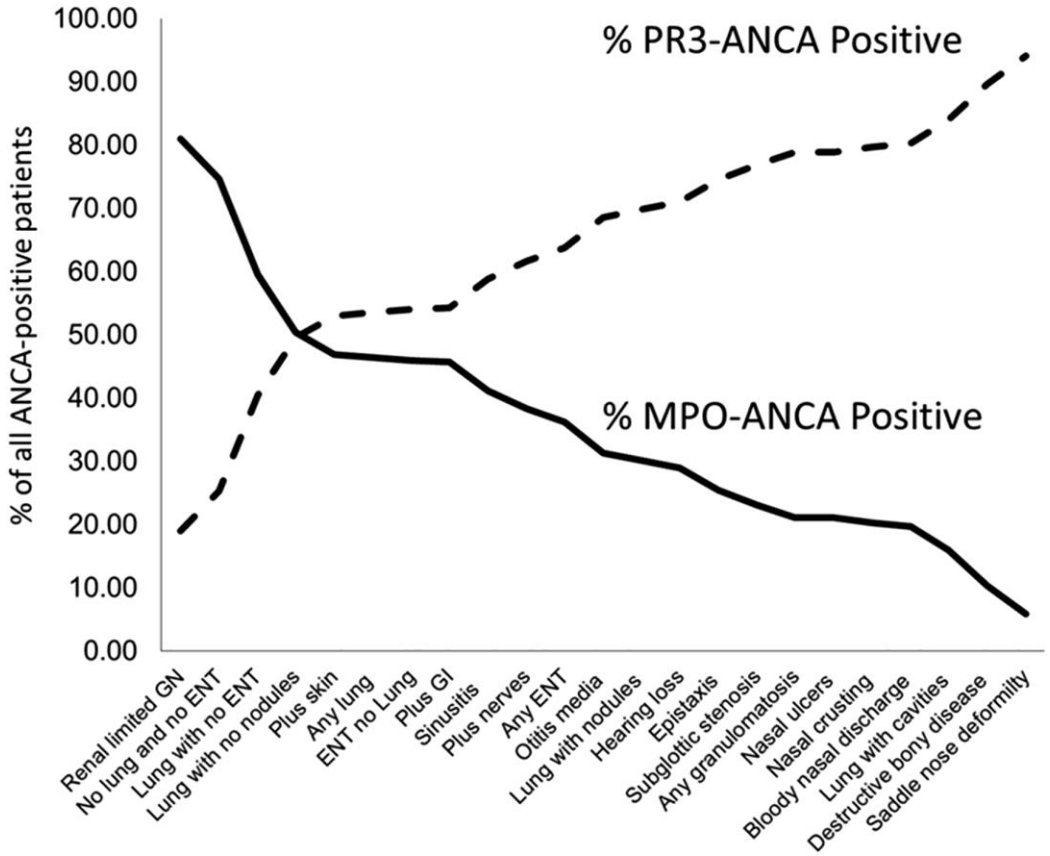
- Progressive loss of renal function within days or weeks
- >50% crescents

ANCA-GLOMERULONEPHRITIS

(usually with necrosis and crescents)



Serological classification



Lionaki S et al. Arthritis & Rheumatology 2012

PR3-ANCA vasculitis

- ↑ In northern Europe, north America, Australia
- HLA-DP genetic association
- ↑ Upper respiratory tract disease
- ↑ Granulomatous inflammation
- ↑ Necrosis at diagnosis

MPO-ANCA vasculitis

- ↑ In southern Europe, southern Unites States, Asia
- HLA-DQ genetic association
- ↑ Renal disease
- ↓ Granulomatous inflammation
- ↑ Sclerosis at diagnosis

5% of patients with ANCA vasculitis also have anti-GBM antibodies in their circulation

Pathogenesis: ANCA-GN mouse model

Injection anti-MPO IgG →  → **ANCA-GN**

Xiao H et al. J Clin Invest 2002

ANCA-glomerulonephritis diagnosis

- Active urine sediment
- Acute renal dysfunction
- 82-94% positive ANCA
- ↑ WBC, PLT
- ↓ Hb
- ↑ ESR
- ↑ C-reactive protein

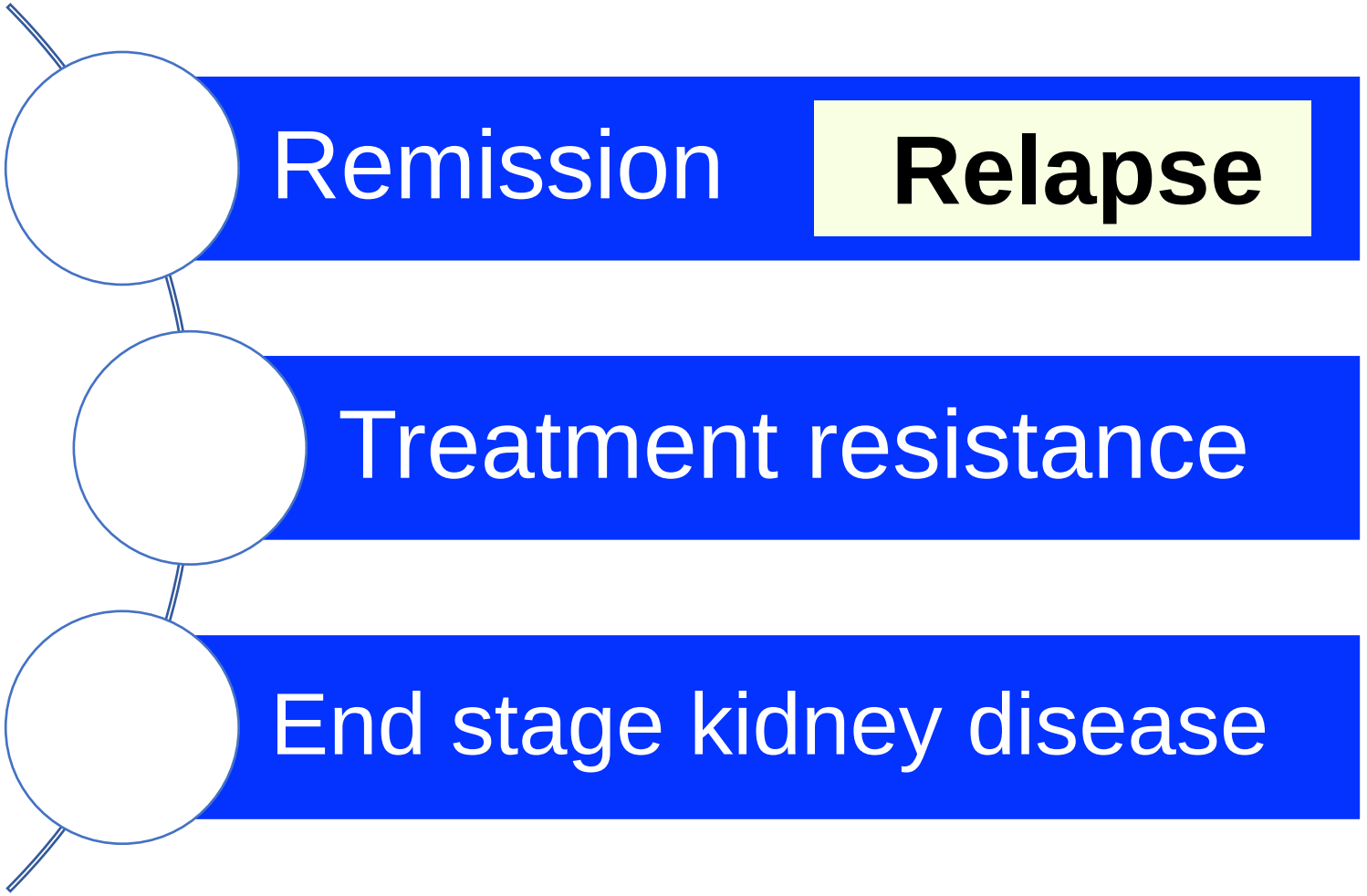
± Radiographic tests

± Bronchoalveolar lavage (+) for blood

Renal biopsy

- Establishment of diagnosis
- Prognostication
- Plan of therapy

Outcome of ANCA-glomerulonephritis



Induction of remission in ANCA-GN

- Cyclophosphamide + glucocorticoids
- Rituximab + glucocorticoids
- (±) IV pulses methylprednisolone
- (±) Plasma-exchange
- Combined therapies

Aggressive therapy is justified as mortality rate ~ 90% in 2 years due to:

- Respiratory failure
- Renal failure

Rate and time to remission

	Protocol	Response rate	Time to remission
Cycazarem	Cyclophosphamide p.o + GC	93%	3-6 months
CYCLOPS	Cyclophosphamide IV + GC	88%	2-6 months
WGET	Etarnecept	91%	3-6 months
RITUXVAS	Rituximab + CYC iv + GC	76%	6-12 months
RAVE	Rituximab + GC	64%	6 months

Cause of death within the first 12 months

All causes	56 (10.7%)
Infection	28 (50%)
Active vasculitis	8 (14%)
Cardio/cerebrovascular disease	7 (13%)
GI bleed/duodenal ulcer	3 (5%)
PE or complication of anticoagulation	3 (5%)
Malignancy	1 (2%)
Pulmonary fibrosis	2 (4%)
Other	4 (7%)

Little MA et al. Ann Rheum Dis. 2010 Jun

Factors associated with 1-year mortality

Multivariable analysis	Hazard Ratio (95% CI)	p value
Infection burden score	1.2 (1.1-1.23)	<0.001
Adverse event burden score	1.3 (1.1-1.4)	<0.001
Leucopenia burden score	1.2 (1.1-1.2)	<0.001
Cumulative Cyclophosphamide dose	1.2 (1.05-1.4)	0.04
GFR	0.7 (0.6-0.9)	0.002

Little MA et al . Ann Rheum Dis. 2010

Rituximab in ANCA disease

RAVE	RITUXVAS
N=197 • Rituximab + IV MP or • Cyclophosphamide po + GCs • Mean GFR at entry >50ml/min • Mean BVAS: 8.5	N=44 • Rituximab + Cyclophosphamide (2-3 pulses) + IV MP or • Cyclophosphamide (6-10 pulses) + IV MP • Mean GFR at entry: 18ml/min • Mean BVAS at entry: 19

Jones RB et al. N Engl J Med 2010

Stone JH et al. N Engl J Med 2010

Rituximab instead of Cyclophosphamide: RAVE

- **No difference in adverse events!**
- Total glucocorticoids exposure plays a major role in mediating adverse events.

New therapeutic targets in ANCA-SVV

Remission induction

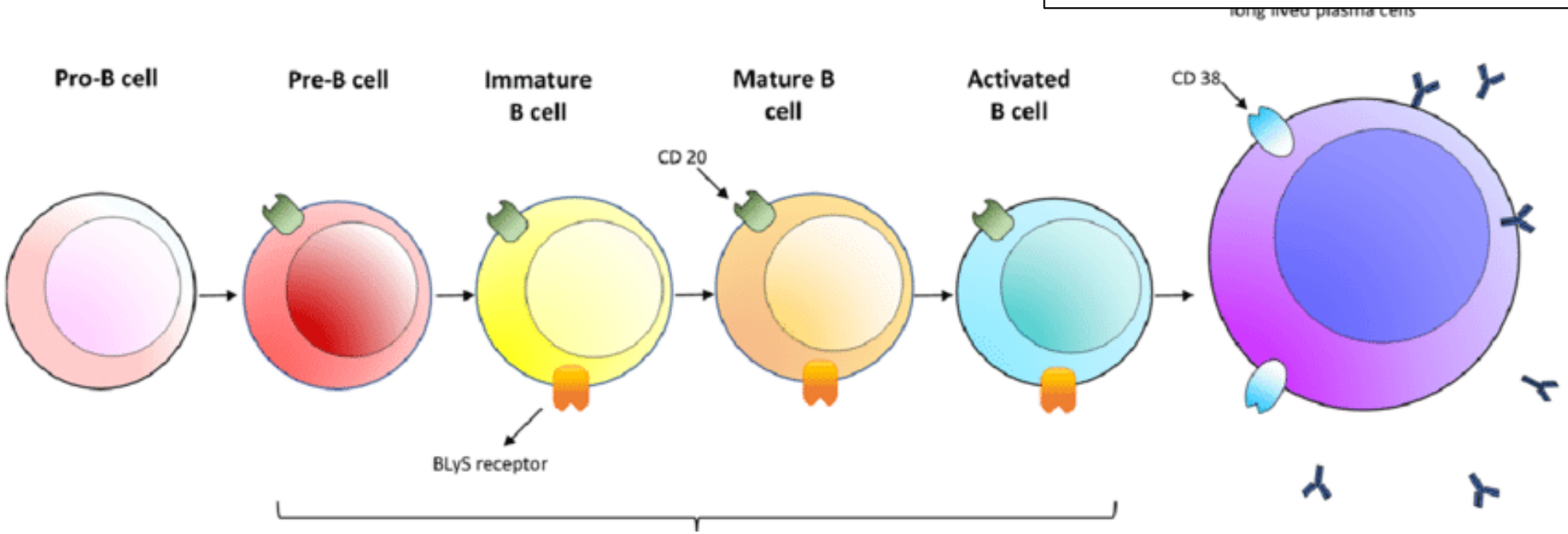
- **Faster response (**reduce non-reversible damage)
- **Increase response rates** (↓treatment resistance)
- **Reduce toxicity** (limitate dose and duration of GCs)

Combined therapies

- Cyclophosphamide + rituximab + GCs

Cyclophosphamide
Glucocorticoids

Antibody producing cells
- Plasmablasts
- Long lived plasma cells
- Plasma cells



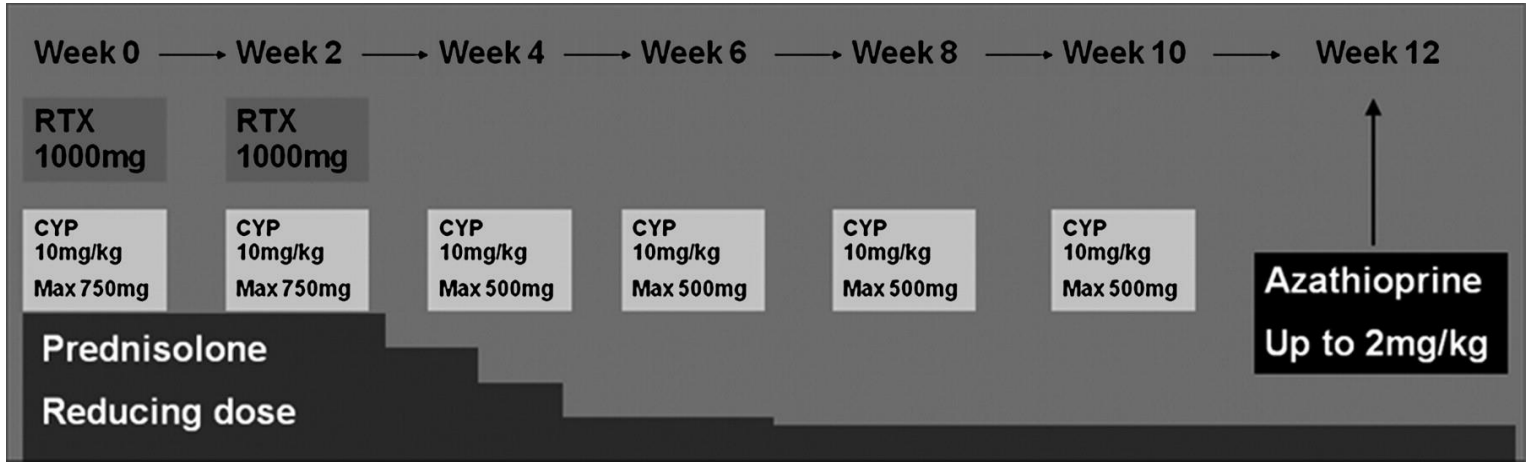
Target for anti-CD20 therapy (Rituximab)

Rituximab: Little direct effect on ANCA-producing plasmablasts and plasma cells not expressing CD20.

Rituximab alone necessitates prolonged courses of high-dose glucocorticoids to control disease activity.

Rituximab + low-dose cyclophosphamide for renal ANCA-vasculitis

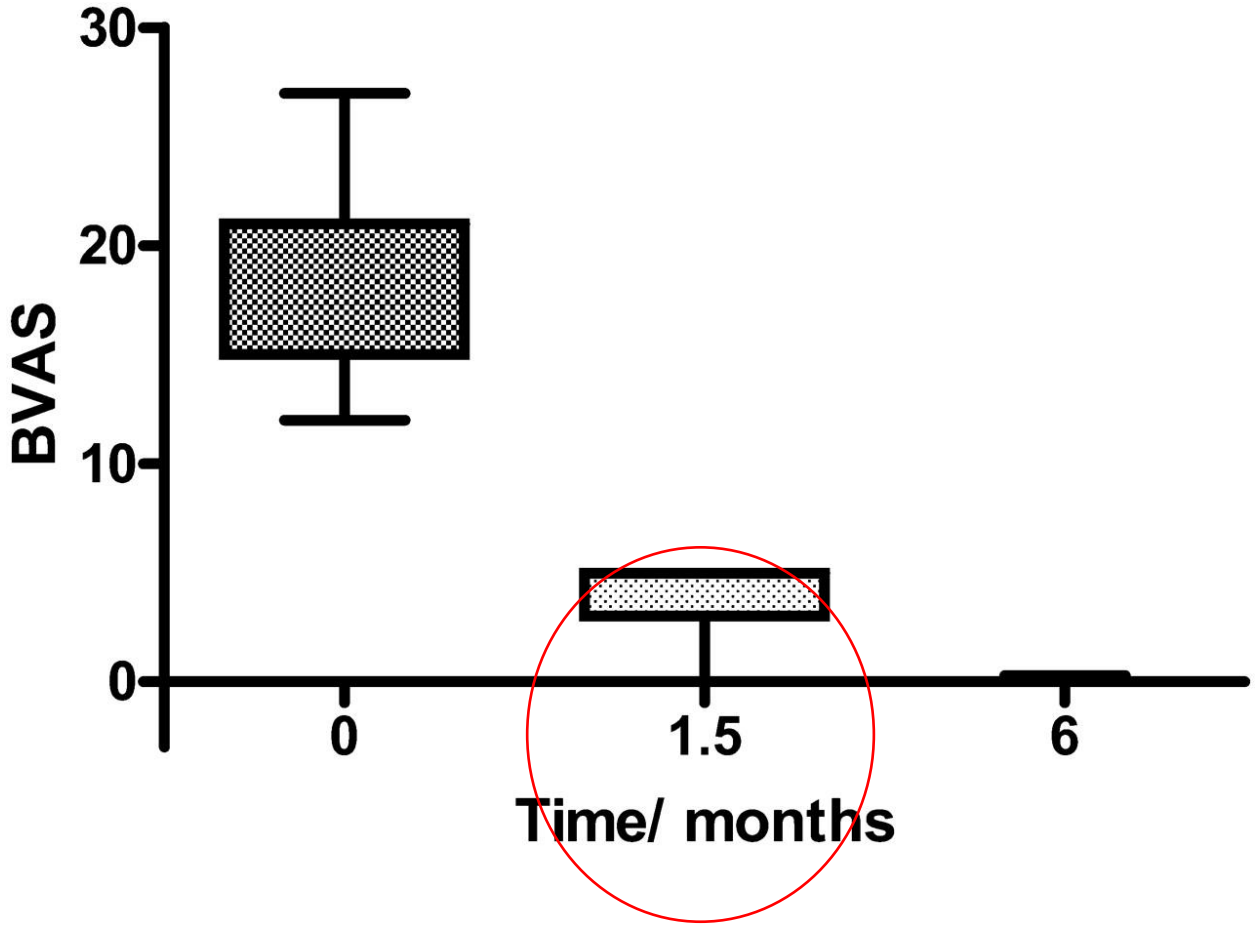
- **RTX 1 g**, at day 0 and 14.
- **IV CYC,** Day 0, every 14 days (6 doses), first 2 doses (max 750 mg), final 4 doses (max of 500 mg)
- **Oral prednisolone:** 1 mg/kg with (max dose 60 mg), reduced to 10 mg by Week 13.



Mansfield et al. Nephrol Dial Transplant, Volume 26, Issue 10, October 2011, Pages 3280–3286,

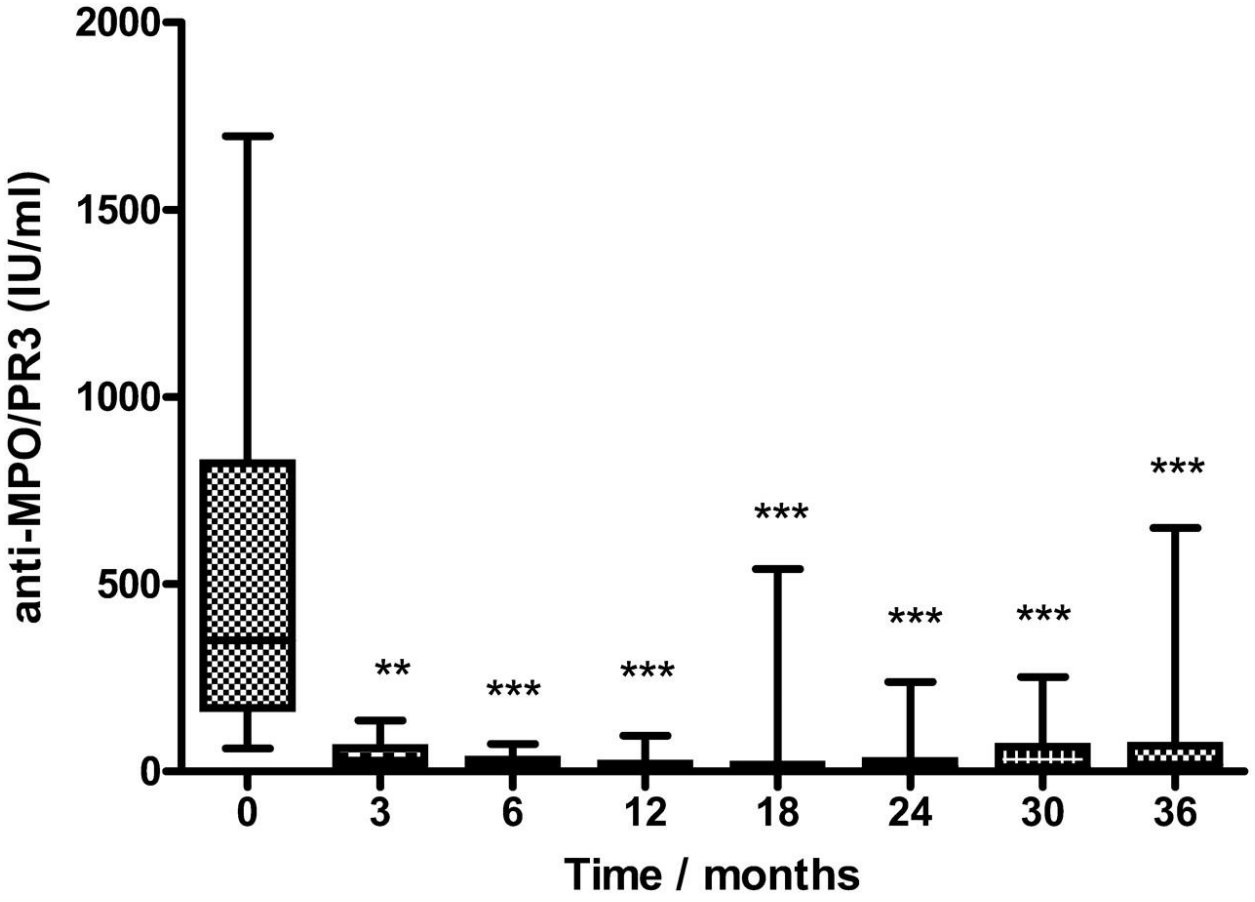
Rapid remission with combined therapy

Changes in BVAS over the first 6 months



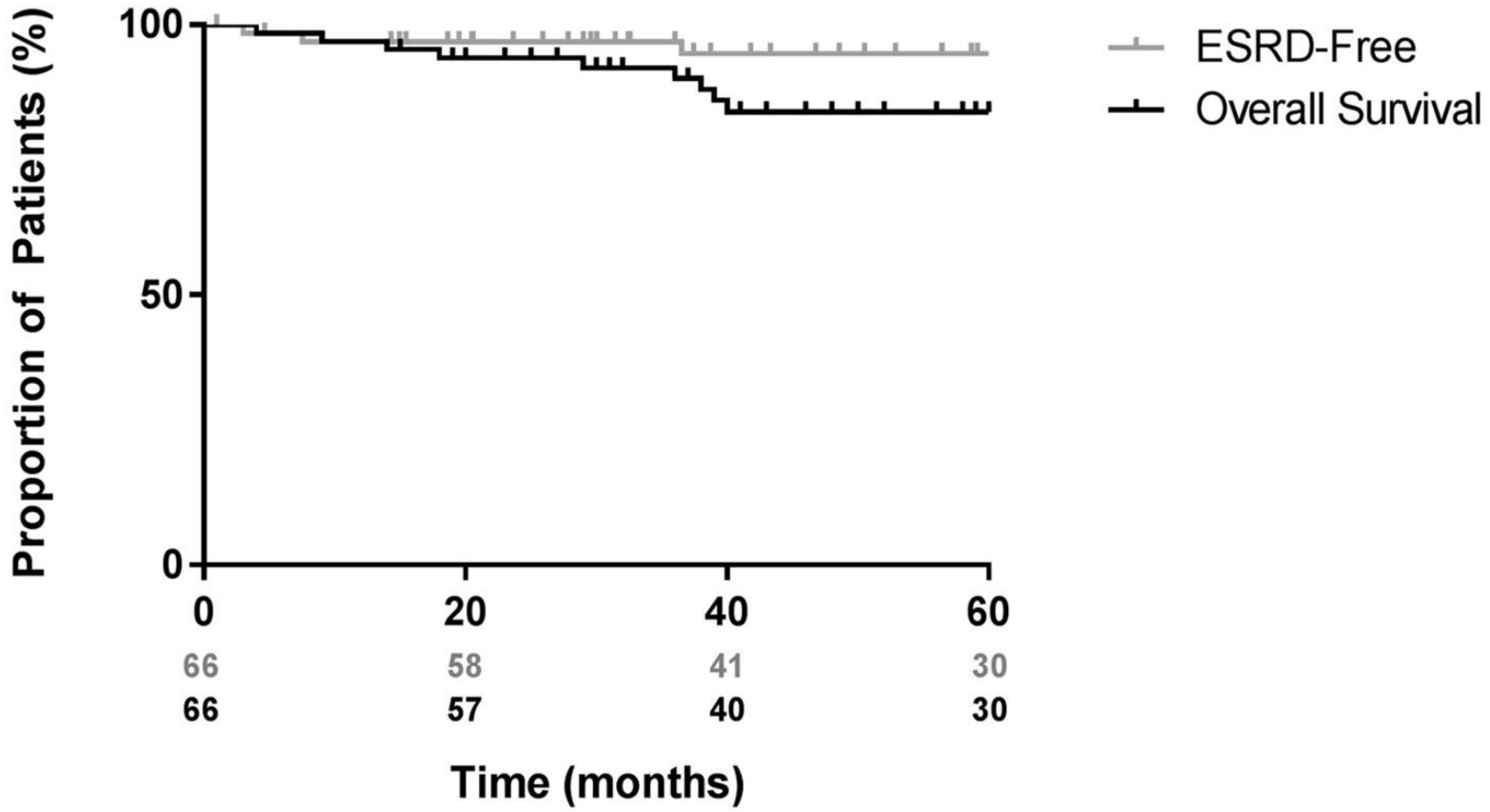
Mansfield et al. Nephrol Dial Transplant, Volume 26, Issue 10, October 2011, Pages 3280–3286,

Quick decline in anti-MPO or anti-PR3 antibodies titers



Mansfield et al. Nephrol Dial Transplant, Volume 26, Issue 10, October 2011, Pages 3280–3286,

End stage kidney disease during 5-year follo

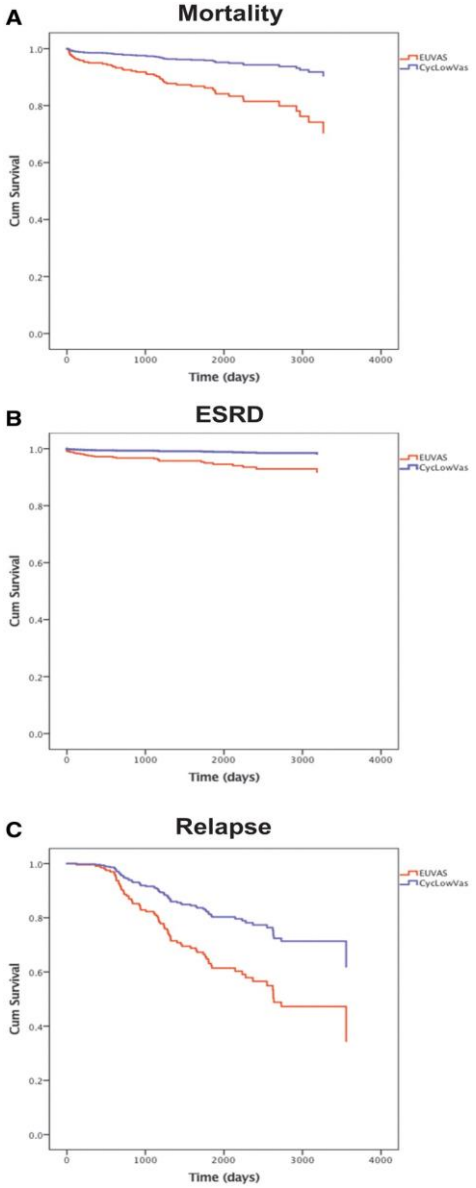


McAdoo S et al. Nephrol Dial Transplant, Volume 34, Issue 1, January 2019.

Case-control analysis with propensity-matched patients from EUVAS trials

CycLowVas:

- ↓ **Risk of death** {HR 0.29 [95% CI) 0.125–0.675], p= 0.004}
- ↓ **Progression to ESKD** [HR 0.20 (95% CI 0.06–0.65), p= 0.007]
- ↓ **Risk of relapse** [HR 0.49 (95% CI 0.25–0.97), p= 0.04].

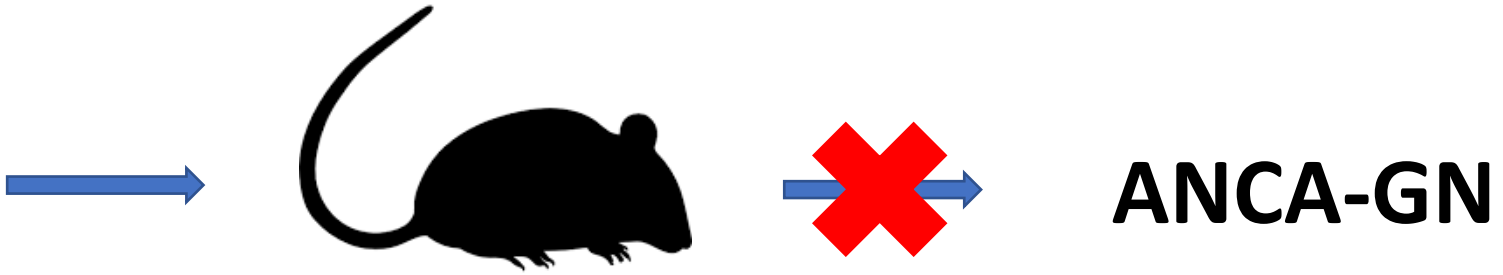


McAdoo S et al. Nephrol Dial Transplant, Volume 34, Issue 1, January 2019.

Complement inhibition

Complement deficient mice

Injection anti-MPO IgG



ANCA-GN

- In animal models complement depletion protects animals from developing ANCA-GN following injection of serum with anti-MPO IgG.

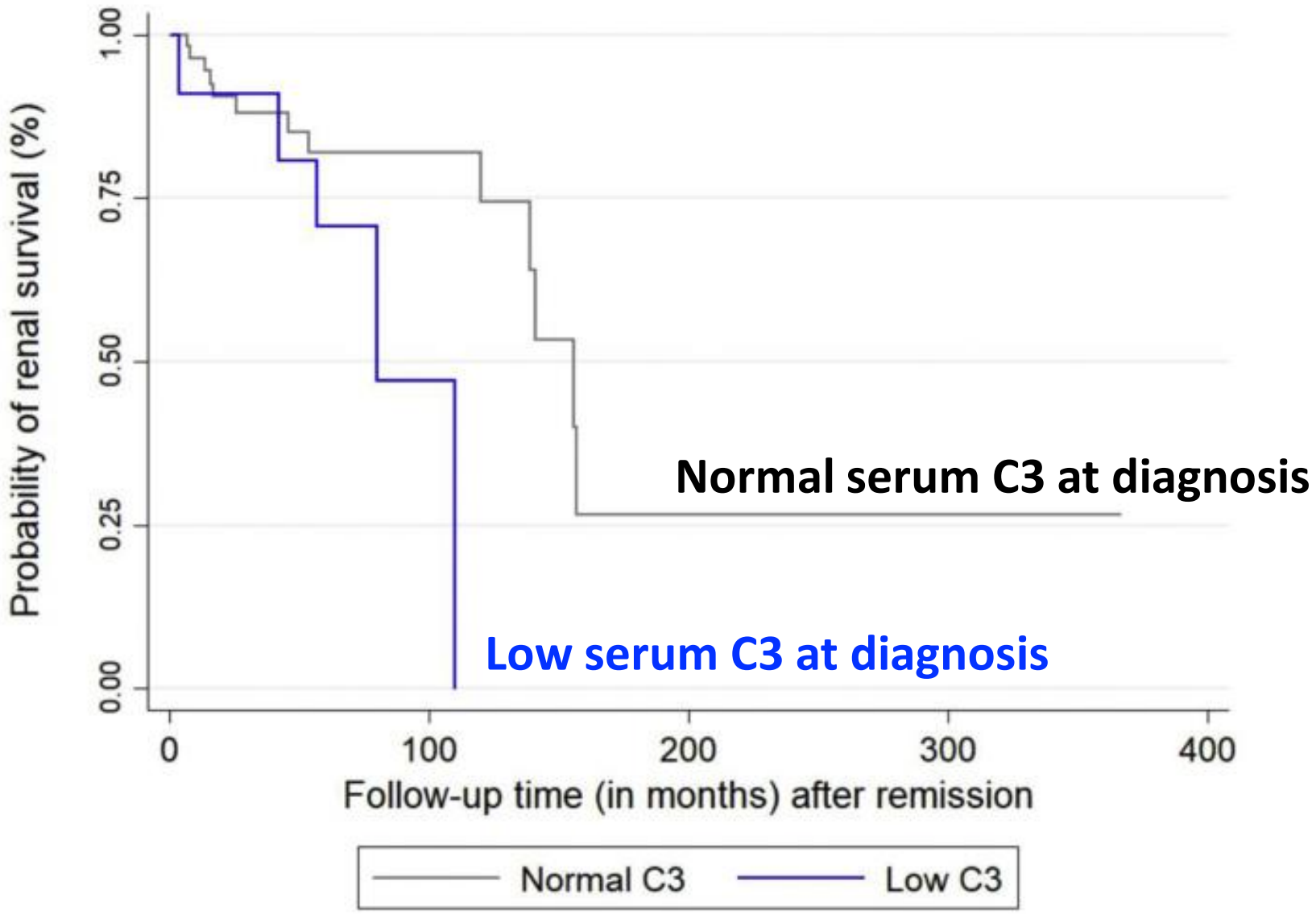
Xiao et al. AJP January 2007, Vol. 170.

Low C3 at diagnosis: major risk factor for ESKD or vasculitis-related death at 1st year

Parameter	Hazard ratio (95% CI)	p value
Low serum C3, mg/dl	6.47 (1.47–28.35)	0.013
Oliguria, present versus absent	29.57 (4.74–184)	<0.0001
Chronicity score	1.77 (1.23–2.54)	0.002
Serum creatinine, mg/dl	0.82 (0.57–1.19)	0.3
Estimated GFR >30 ml/min per 1.73 m^2	0.08 (0.0001–52.1)	0.44
Normal glomeruli >10%	1.22 (0.13–3.13)	0.59
Activity score	1.37 (0.85–2.24)	0.19
Acute dialysis requirement	0.85 (0.12–5.81)	0.87

Lionaki, S et al. *Kidney international reports* vol. 6,9 2425-2435. 12 Jun. 2021.

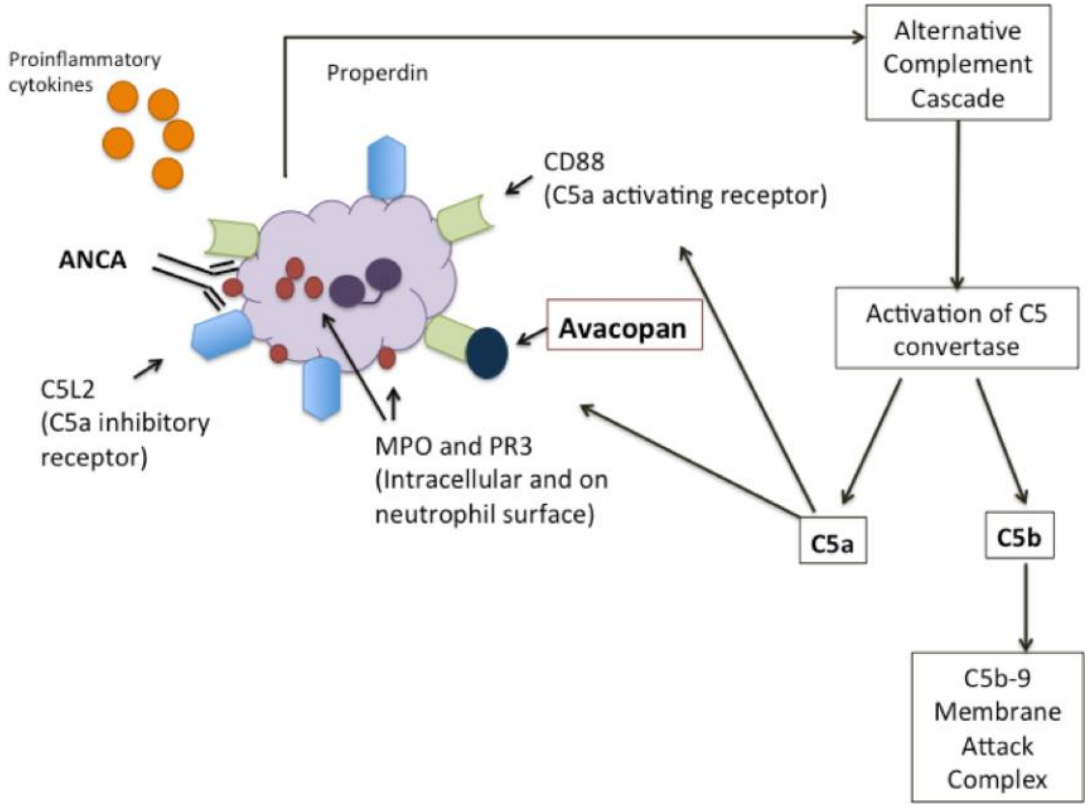
Renal survival of patients with ANCA-GN stratified by serum C3 at diagnosis



Lionaki, S et al. *Kidney international reports* vol. 6,9 2425-2435. 12 Jun. 2021.

CCX168 (Avacopan): Small molecule acting as antagonist of the human C5aR Receptor

- First given in an animal model which expressed the C5aR/CD88 receptor
- It resulted in significant improvement of the GN, which had developed as a result of anti-MPO-ANCA serum
- It is acting selectively in the C5a
- It does not alter MAC formation



Hong Xiao et al. JASN 2014;25:225-231

ADVOCATE trial: Avacopan vs. high-dose GCs in ANCA-vasculitis

- Double-blind, parallel-arm, randomized trial
- N=331, newly diagnosed or relapsing GPA/MPA patients
- eGFR>15 mL/min/1.73 m^2 , mean BVAS 16
- Oral avacopan, 30 mg, twice per day or oral prednisone taper
- With RTX or CYC , followed by AZA or MMF, for up to 1 year
- Primary trial endpoints:

➢ **% patients in remission at week 26** (BVAS=0), not taking GCs

➢ **% sustained remission** (week 26-week 52)

ADVOCATE study: Results

Remission at week 26:

- 72.3% in the avacopan group
- 70.1% in the prednisone group

(p<0.001 for the non-inferiority; p= 0.24 for superiority)

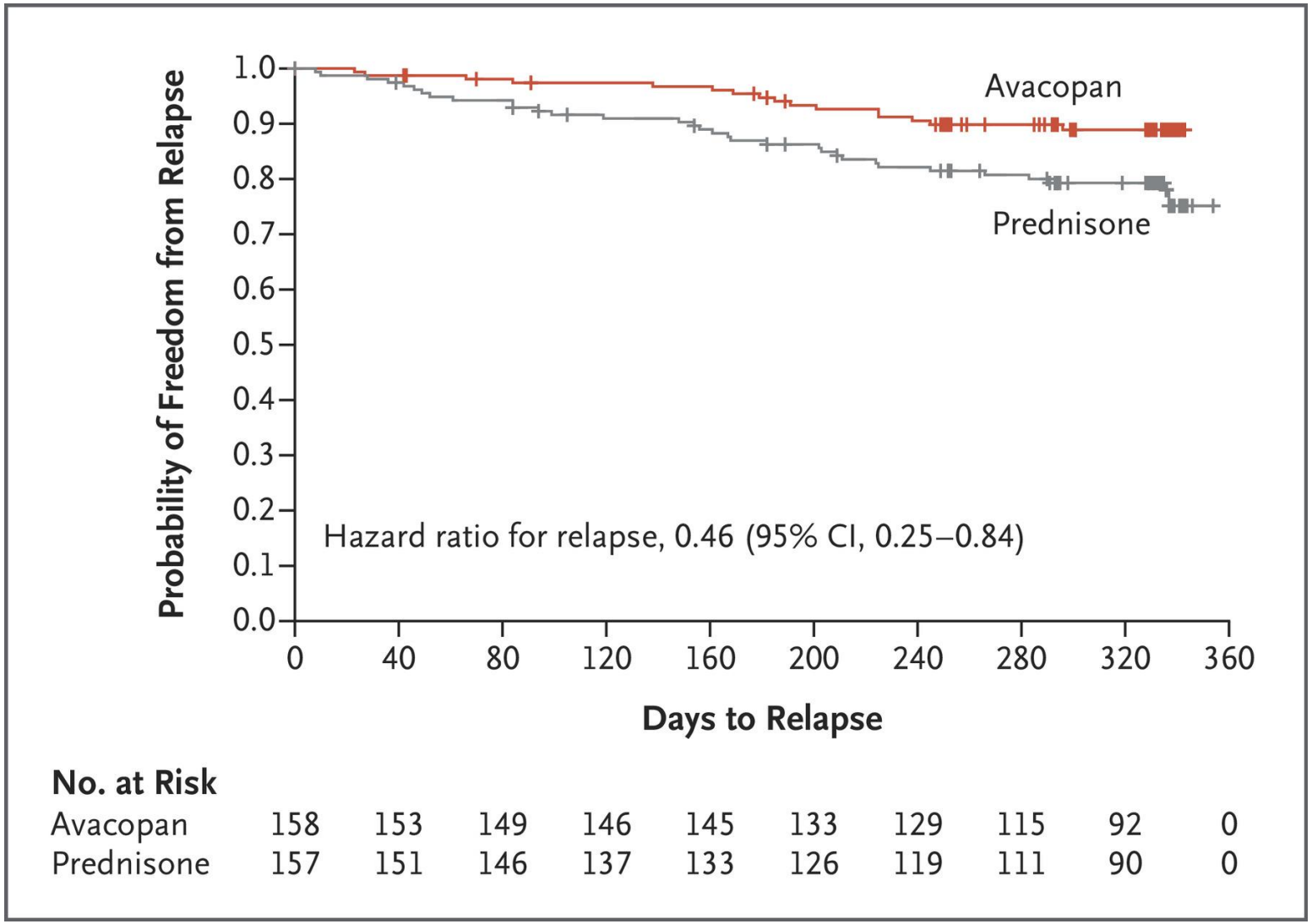
Sustained remission at week 52:

- 65.7% in the avacopan group
- 54.9%) in the prednisone group

(p<0.001 for non-inferiority; p= 0.007 for superiority)

Jayne DRW et al. ADVOCATE Study Group. N Engl J Med. 2021 Feb 18;384(7):599-609

ADVOCATE study: Probability of disease relapse



Relapses

- **10.1%, avacopan group**
- **21.%, prednisone group**
- HR for relapse

(avacopan vs prednisone):
HR: 0.46 (95% CI, 0.25-0.84)

Jayne DRW et al. ADVOCATE Study Group. N Engl J Med. 2021 Feb 18;384(7):599-609

Avacopan: Beneficial effect in renal function relative to GC

eGFR change from baseline:

81% of patients had renal involvement

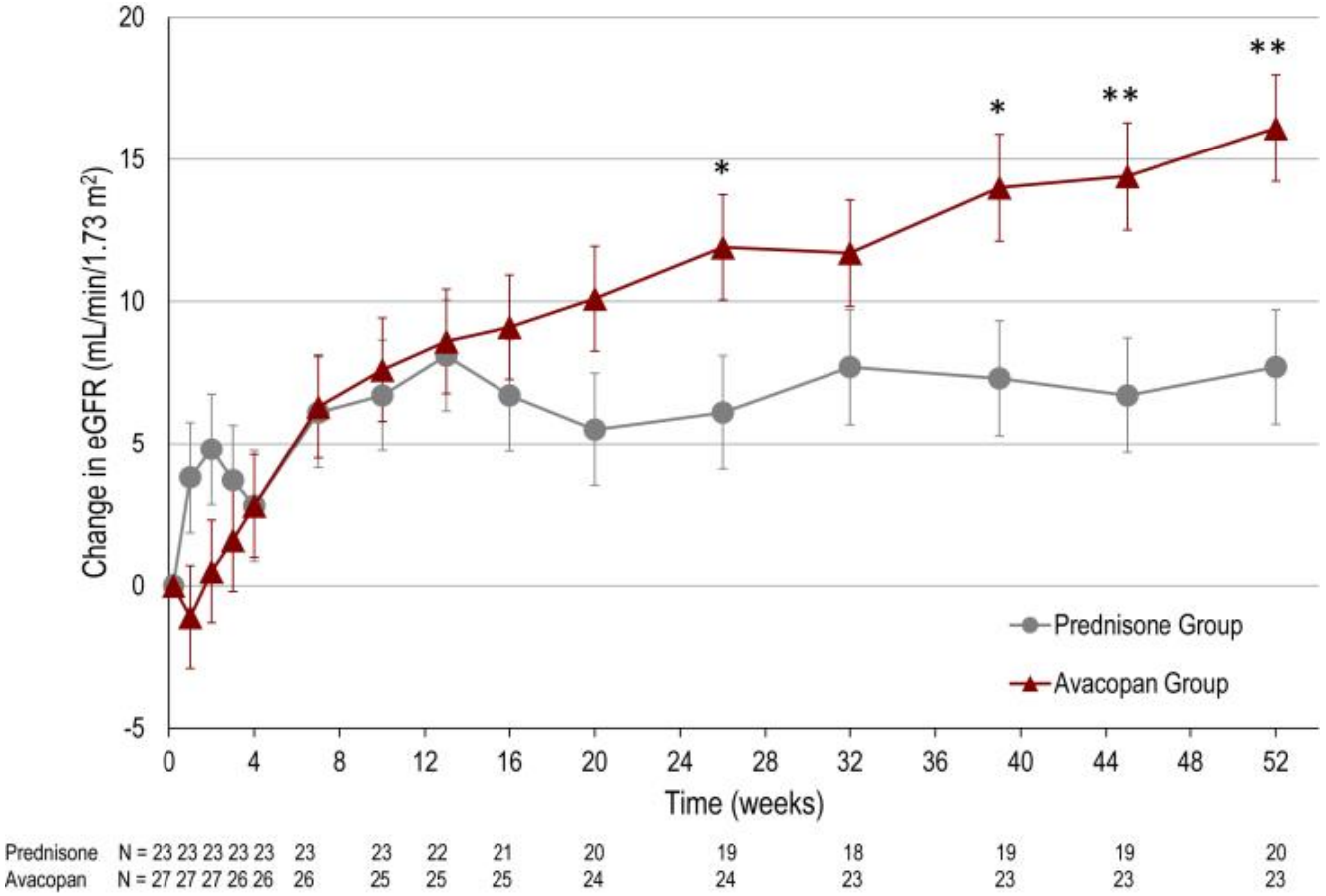
- **Avacopan group**: 7.3 mL/min/1.73 m^2
- **Prednisone group**: 4.1 mL/min/1.73 m^2
  (difference: 3.2 mL/min/1.73 m^2; 95% CI, 0.3-6.1)

Jayne DRW et al. ADVOCATE Study Group. N Engl J Med. 2021 Feb 18;384(7):599-609

ADVOCATE trial: Stage 4 CKD, change in kidney function at week 52:

Avacopan group: **13.7** mL/min/1.73 m^2

Prednisone group: **8.2** mL/min/1.73 m^2



Cortazar F et al. Kidney Int Rep. 2023 Apr; 8(4): 860–870.

Avacopan vs. prednisone

Serious infections

- **13.3%** of patients given **avacopan**
- **15.2%** of patients given **prednisone**

Incidence of AEs potentially related to GCs

➢**66.3%** in the **avacopan** group

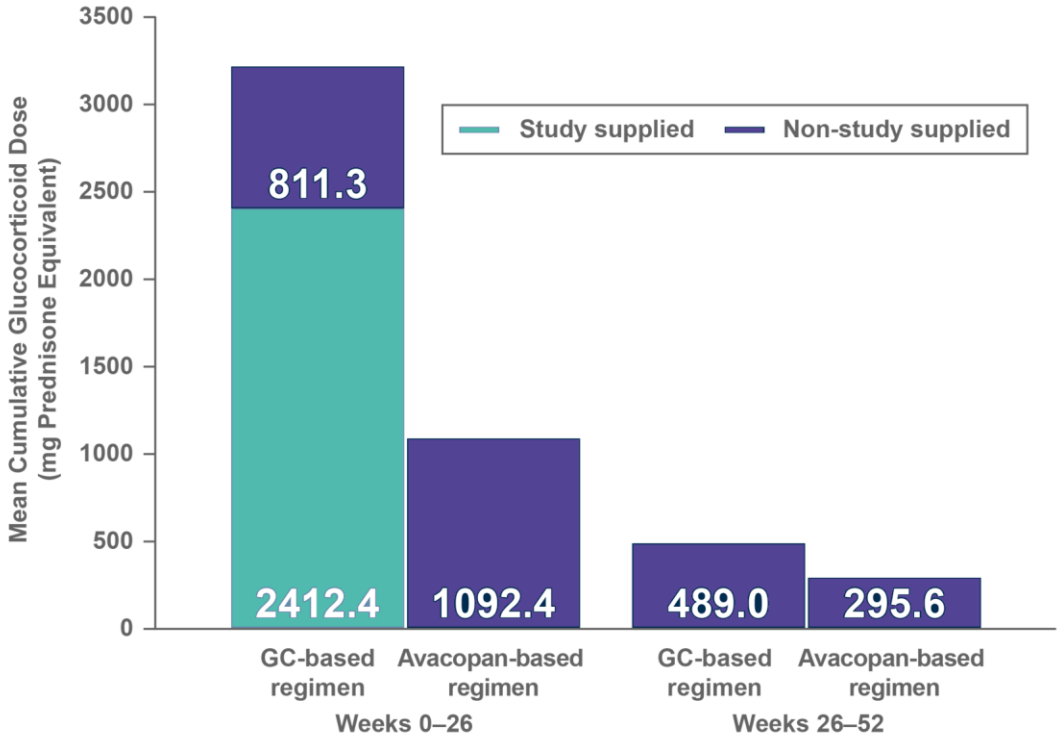
➢**80.5%** in the **prednisone** group

(difference: -14.2 % points; 95% CI, -23.7 to -3.8)

Jayne DRW et al. ADVOCATE Study Group. N Engl J Med. 2021 Feb 18;384(7):599-609

Avacopan based regimen lowers overall GC dose vs. GC-based regimen

Lower GC dosing with Avacopan-based regimen, including weeks 25-62



Mean total GC dose:

- **1,349 mg vs 3,655 mg**

GC, glucocorticoid.

1. Jayne D, et al. *N Engl J Med* 2021;384(7):599–609.
2. Jayne D, et al. *N Engl J Med* 2021;384(7):599–609 [Suppl Appendix].
3. Vifor Pharma. Clinical Study Report: CL010_168. Data on file.

In 2021 the US FDA avacopan was approved, for the treatment of ANCA-vasculitis

- Addition (30 mg twice daily) for induction of remission in new or relapsing ANCA-SVV treated with CYC or Rituximab
- After starting avacopan a faster GCs tapering protocol aiming to stop in week 4 can be considered
- Can be continued for 1 year

Indications of avacopan in ANCA-SVV to date

Patients with

- Serious contraindications for high dose steroids
- Severe kidney disease
- Low serum C3 level at onset

- Age
- Diabetes
- Obesity
- Osteoporosis
- Depression

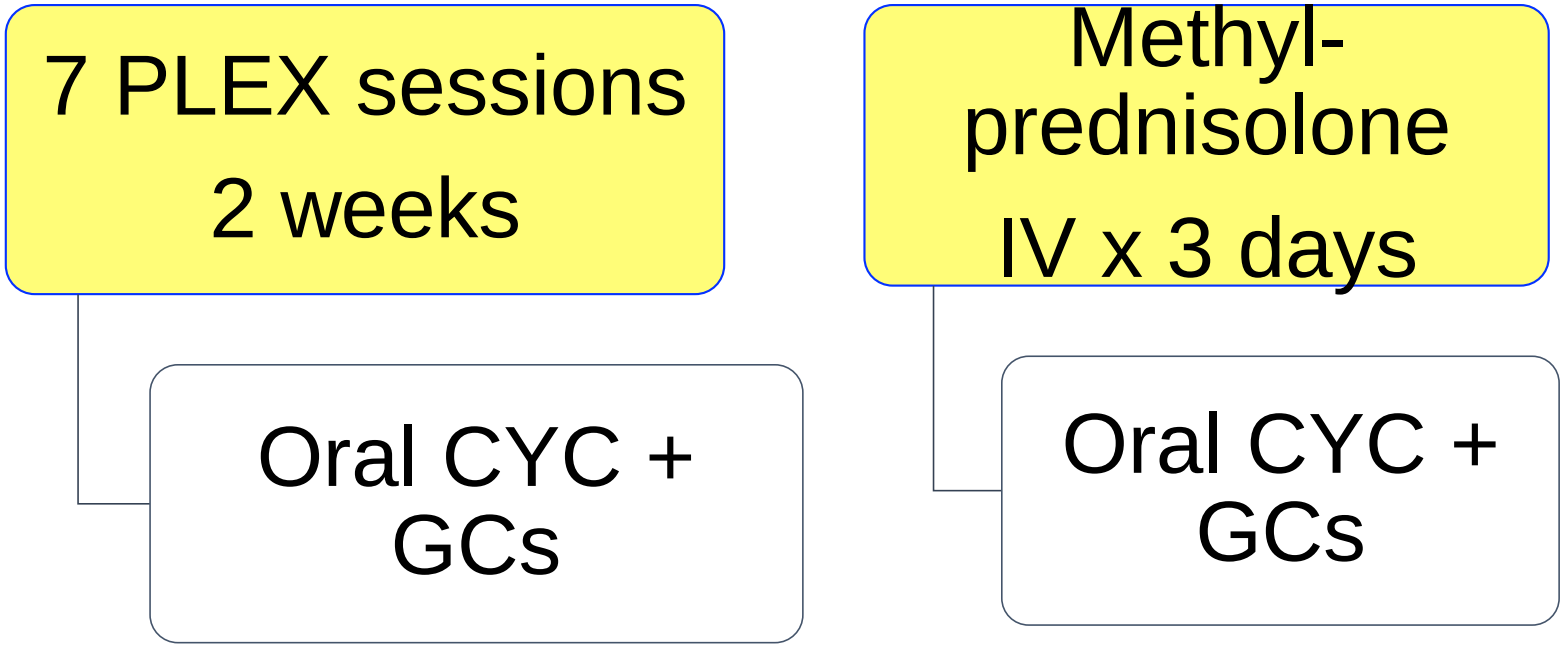
Plasma-exchange (PLEX)

MEPEX Trial:
PLEX ***or*** Methyl-prednisolone pulses

Adjunctive therapy in patients with initial serum creatinine > 5.8 mg/dl

N=137

69% required dialysis



Jayne D. et al. J Am Soc Nephrol 2007

MEPEX Trial:
PLEX (7 sessions) ***or*** Methyl-prednisolone pulses (3 days)

Plasma-exchange:

- Likelihood of being alive and dialysis independent by month 3 (69% vs. 49%)
- ⬇ Risk of progression to ESKD at 1st year (19% vs. 43%)
- ⬇ Risk of progression to ESKD at 4th year (33% vs. 49%)

Jayne D. et al. J Am Soc Nephrol 2007

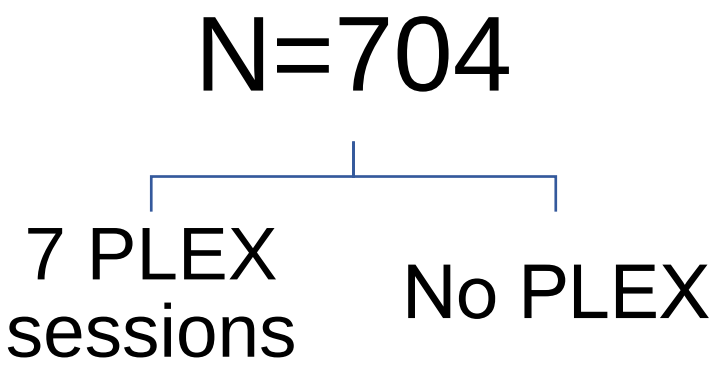
Predictors of dialysis independence at 1st year (N=67)

Compared outcomes	Variables	P value	Exp β	95% CI of Exp β
Dialysis independence (IVMeP) versus dialysis (PLEX)	Arm	0.008	0.08	0.01 to 0.52
	Tubular atrophy	0.005	17.2	2.4 to 122.7
	Normal glomeruli	0.025	0.91	0.84 to 0.99
Dialysis (IVMeP) versus death (PLEX)	Arm	0.056	4.1	0.97 to 17.4
	Glomerulosclerosis	0.061	0.03	0.001 to 1.2
Dialysis independence (IVMeP) versus death (PLEX)	Arteriosclerosis	0.042	4.7	1.1 to 20.5

de Lind van Wijngaarden RA et al. JASN 2007

PEXIVAS study: The effect of PLEX in remission induction, eGFR< 50 ml/min/1.73 m^2 or diffuse pulmonary hemorrhage

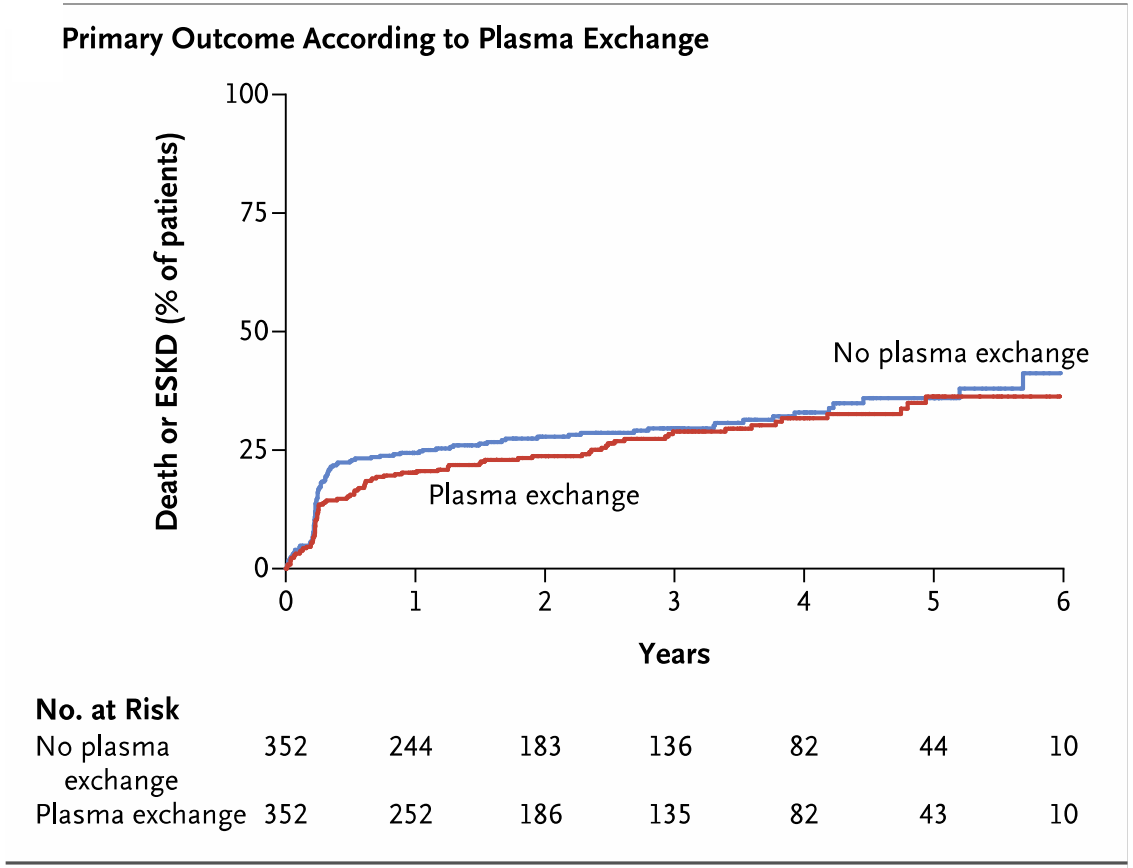
- 98 sites, 15 countries
- 41% PR3-ANCA, 59% MPO-ANCA
- 98% kidney involvement
- 27% alveolar hemorrhage
- 85% Cyclophosphamide (p.o or iv)
- 15% Rituximab
- Mean follow up time: 2.9 years



Replacement : 60 ml human albumin /kg BW or FFP

Walsh M et al. N Engl J Med 2020;382:622-31.

PEXIVAS study: PLEX in severe ANCA vasculitis



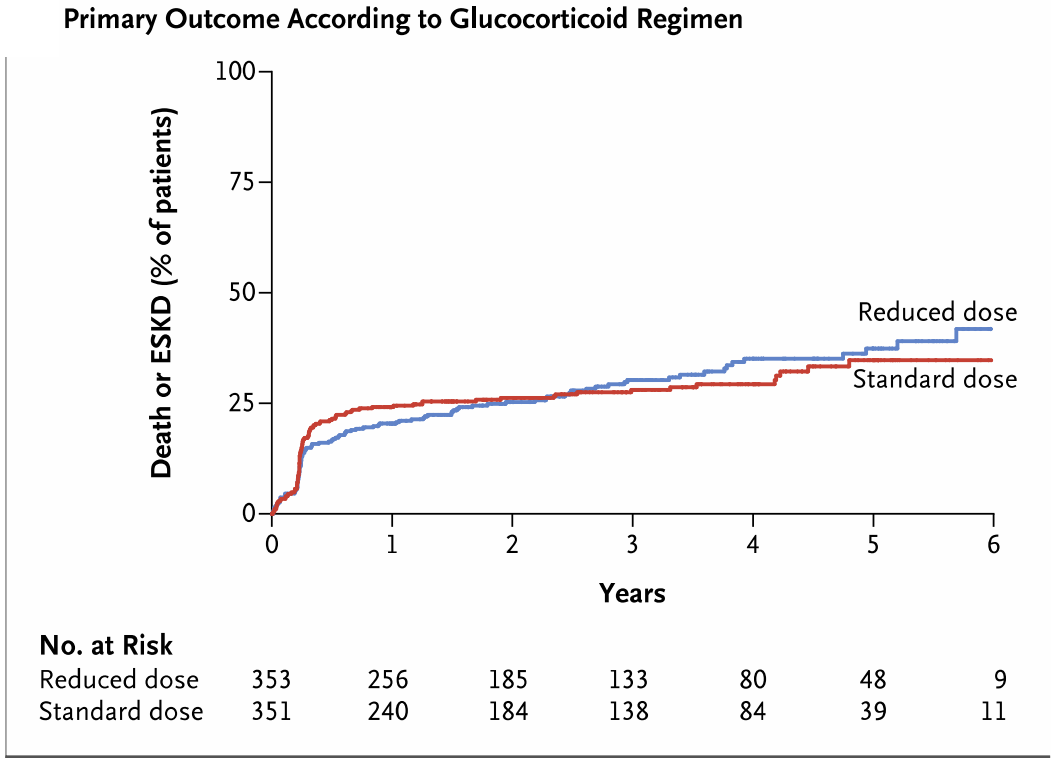
- **Death from any cause or ESKD was not different between groups**

(28% vs. 31%, HR: 0.86; 95% CI: 0.65-1.13, p=0.27)

A kidney biopsy was NOT required for inclusion in the study.

Walsh M et al. N Engl J Med 2020;382:622-31.

PEXIVAS: Glucocorticoids regimen and risk of death or ESKD



All patients received IV MP for 1-3 days, max 3 g

Standard dose of GCs

Reduced dose GCs

No difference

- Prednisone dose was determined by patient's weight.
- At 6 months the cumulative dose of oral GCs in the reduced group was 60% less.
- After 22 weeks both groups were on 5 mg prednisone per day.

Walsh M et al. N Engl J Med 2020;382:622-31.

PEXIVAS study

- No evaluation of the prognostic effect of kidney histopathology
- Just over 50% of patients had actually had a kidney biopsy
- In the patients who did, it is unclear when the kidney biopsy was performed relative to their presentation
- **AKI at presentation: Acute inflammation or advanced sclerosis?**

Kidney Histopathology to Predict PLEX benefit

- Multicenter, retrospective study, France
- Kidney biopsy data from patients with ANCA-SVV treated with PLEX
- Evaluate if **histopathologic findings** could predict kidney function and identify **which patients would most benefit from PLEX**
- **Primary outcome**: **Mortality or ESKD at 12 months (M12)**

Dorian Nezam et al. JASN 2022;33:628-637

Methods

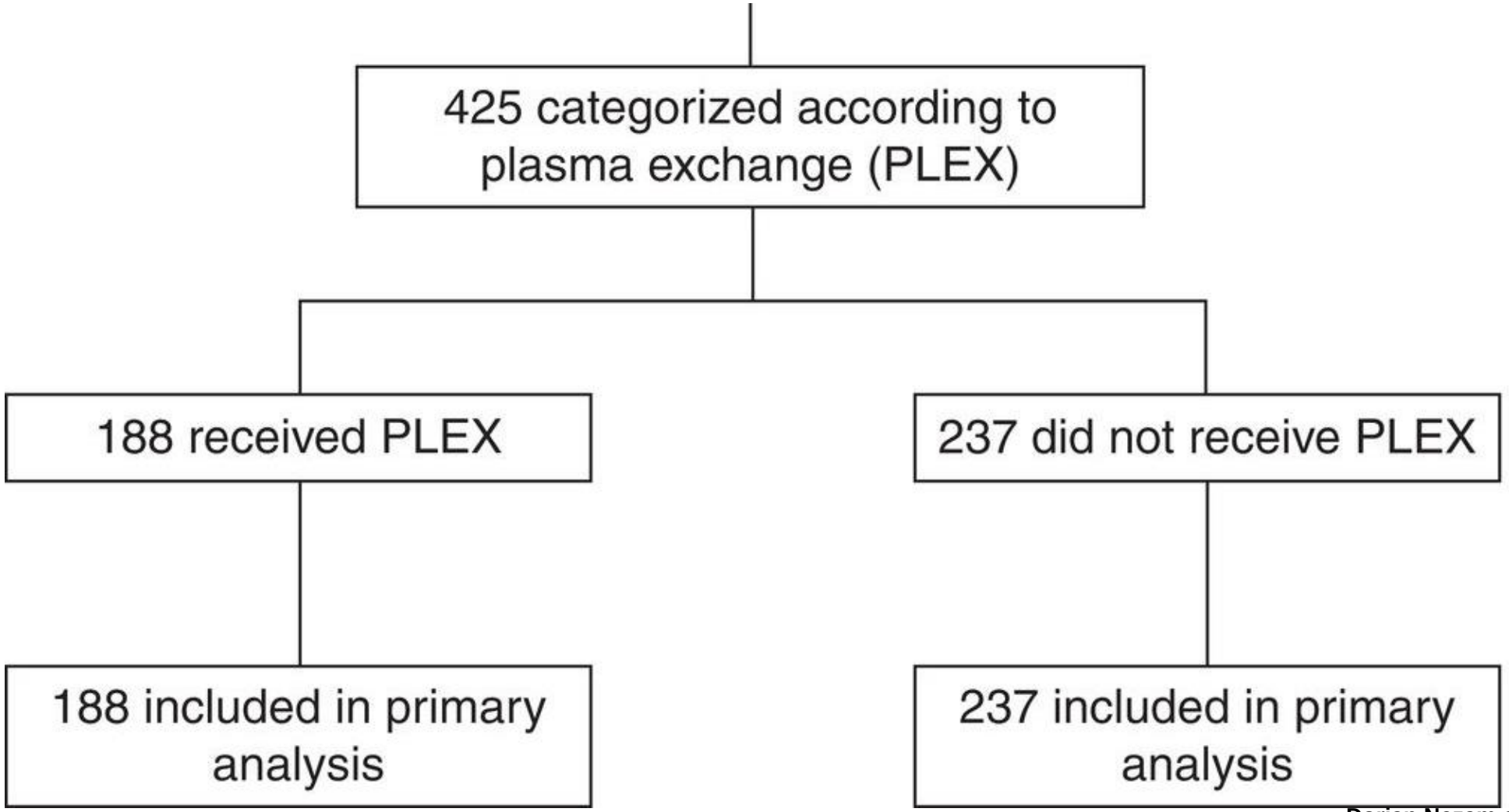
Eligibility Criteria

- Study participants were included retrospectively
- 31 French internal medicine and nephrology departments.
- MPA, GPA, renal-limited vasculitis
- Fulfilled ACR criteria or Chapel Hill consensus conference definitions
- Diagnosed 2004-2019
- Underwent a kidney biopsy at presentation
- Both patients receiving PLEX **(PLEX group)** and those who did not **(control group)**
- Patients with kidney biopsy was performed >1 month from the initiation of induction therapy were excluded

Dorian Nezam et al. JASN 2022;33:628-637

572 patients with AAV and severe renal flare

Study flow diagram



Dorian Nezam et al. JASN 2022;33:628-637

Prediction model:
Average treatment effect (ATE) estimation

- To identify patients who would benefit from PLEX
- **Berden Classification** (focal, crescentic, mixed, sclerotic)
- **Brix score** (low, medium, high)

Kidney biopsy: Score >7 ⇒

- Sensitivity 83.1%
- Specificity 96.0%
- Recommending PLEX

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Results

Total population: No significant benefit of PLEX for the primary outcome

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Results

Prediction model

- **42%** of the total population **had increased predicted probability with PLEX compared without PLEX of being alive and free from ESKD at M12.**
- **Risk difference for death or ESKD at M12**: **↓ 24.6%** with PLEX

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Conclusions

Large cohort of patients with ANCA-SVV and kidney involvement:

- PLEX was NOT associated with a better outcome for the whole population
- 42% of patients from this cohort could have benefitted from PLEX
- The **absolute risk reduction for death or ESKD at M12 of 24.6%**

Dorian Nezam et al. JASN 2022;33:628-637

Systematic review and meta-analysis: The effects of PLEX in patients with ANCA-vasculitis

When PLEX added to standard therapies:

- ↓ Risk of ESKD at 1st year, regardless of baseline kidney function
- ↑ Risk of serious infections, a previously unrecognized effect
- Did **not** change the risk of death

M. Walsh et al. BMJ 2022;376:bmj-2021-064604

ANCA glomerulonephritis

- Relapsing and remitting course
- Various kidney presentations at baseline
- Diffuse scarring can occur before the initial diagnosis
- **Baseline kidney biopsy**: **Required to distinguish between active inflammation or chronic sclerosis and predict outcome**
- **Individualization of therapy is crucial in order to reduce toxicity and increase therapeutic benefit**

Thank you for you attention!