Νεφρική Ύφεση στην ANCA-σχετιζόμενη Σπειραματονεφρίτιδα

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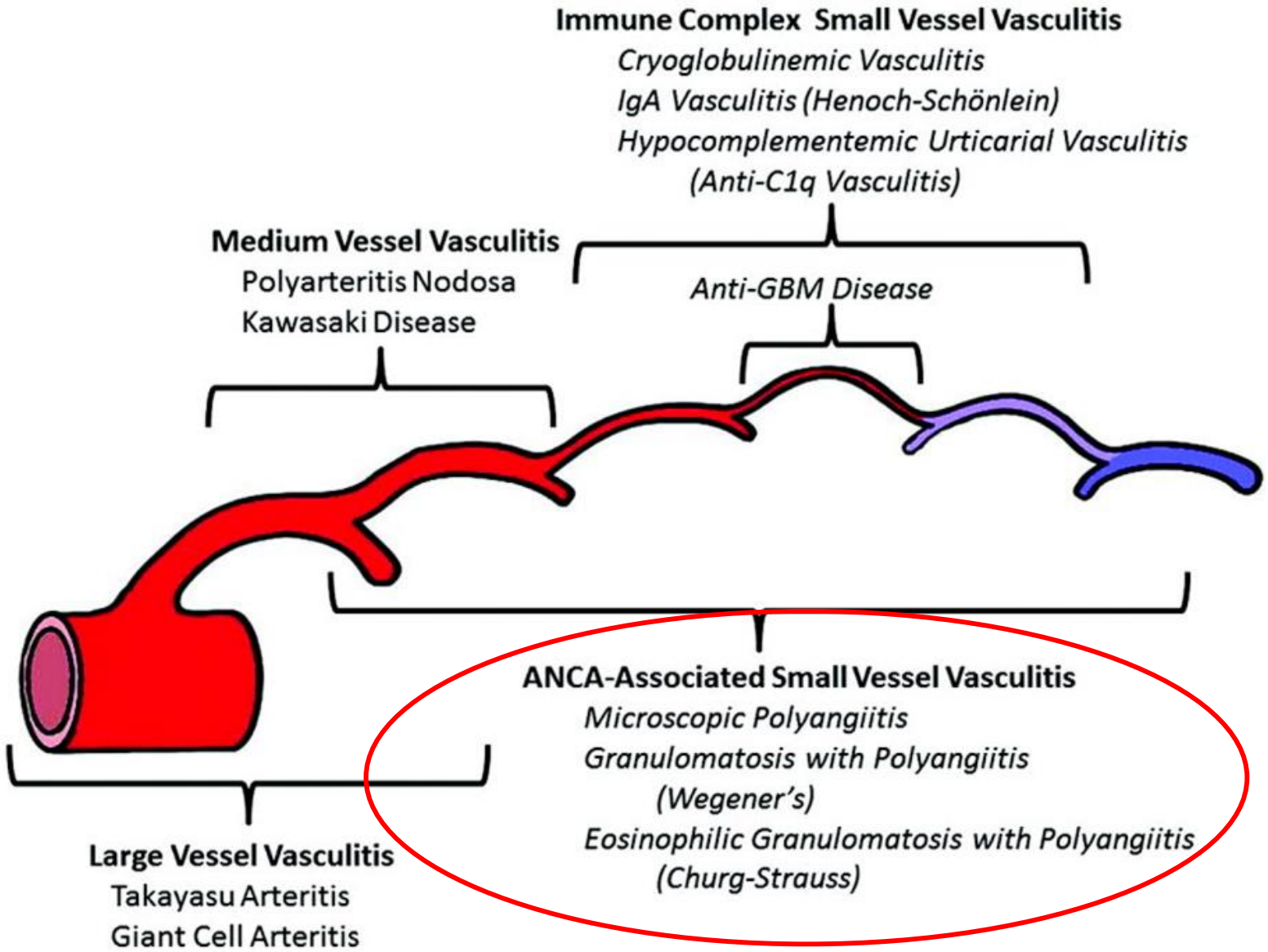
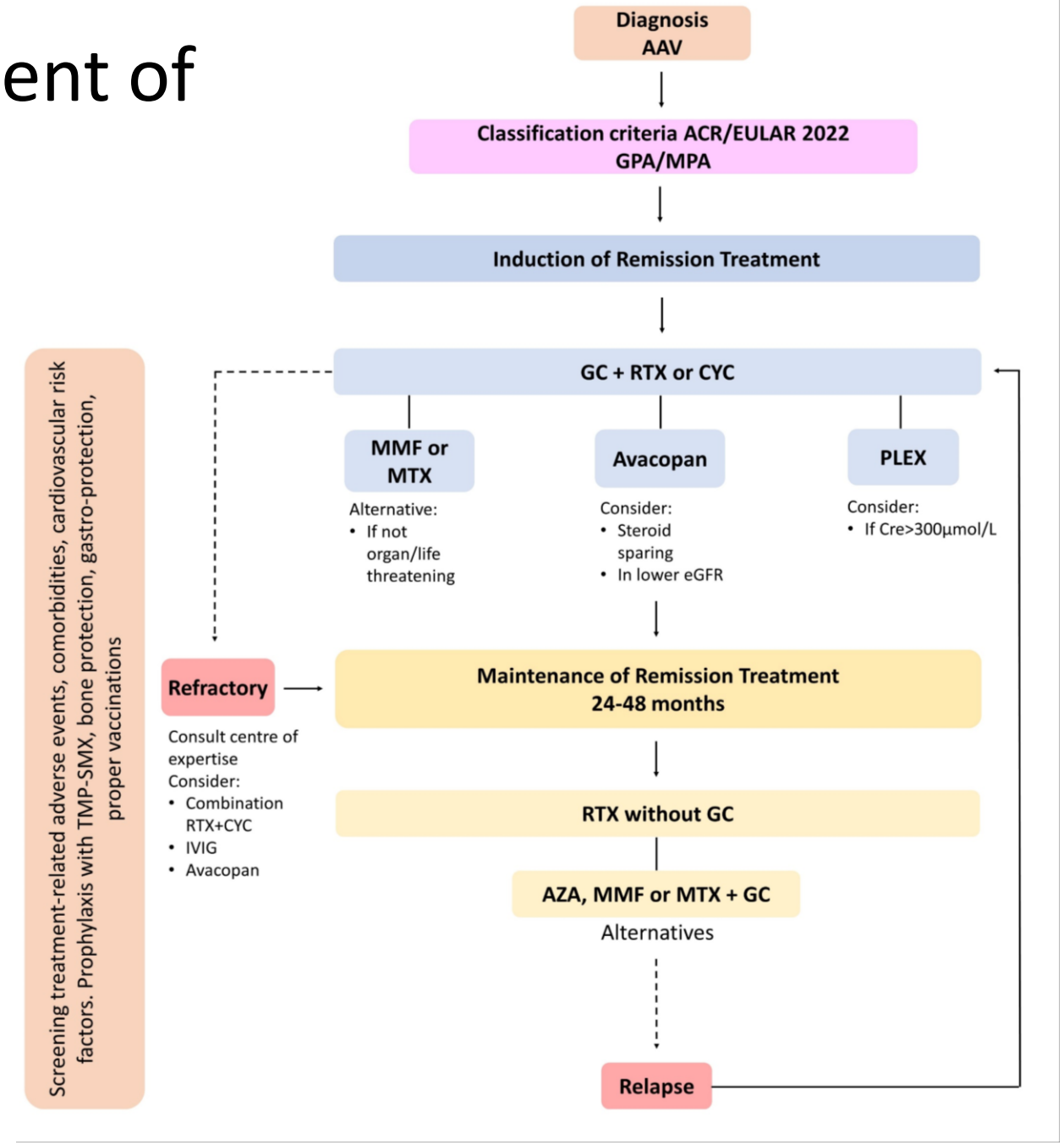


- Rare diseases
- High mortality
- Delayed diagnosis
- Multisystem involvement
- Treatment «aggressive»
- Comorbidities are common
- Relapses are common

Basic Principles of Treatment of Vasculitis

- Reduce inflammation → short-term/quick benefit
- Suppress immune system → longer-term benefit
- Goals of treatment:
  - -survival
  - -prevent permanent damage (CKD, ESKD)
  - -preserve/improve quality of life
  - -prevent relapses
- Avoid under-treatment or over-treatment



Chalkia A. Jayne D. Nephrol Dial Transplant. 2024

Granulomatosis with polyangiitis (GPA)	Microscopic polyangiitis (MPA)	Eosinophilic granulomatosis with polyangiitis (EGPA)
50-80%	90-100%	31–51% in ANCA (+) 4–16% in ANCA (-)

Renal Presentations of ANCA-associated Vasculitis

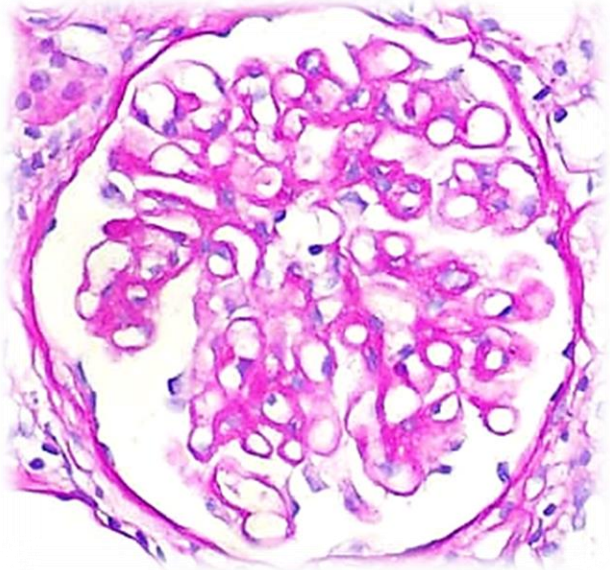
Easy

- **Rapidly progressive glomerulonephritis**
  - Acute kidney injury
  - Hematuria
  - Proteinuria
- Nephritis with normal eGFR
  - Hematuria and proteinuria

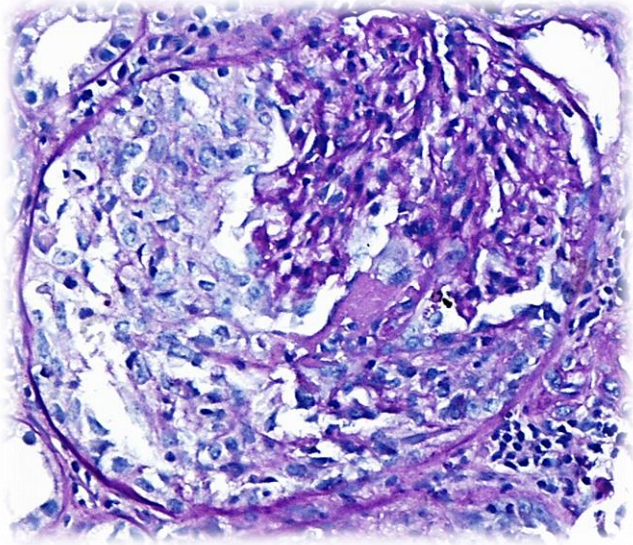
Harder

- **Slow progressive course**
  - Chronic kidney disease, abnormal/normal urine
  - Glomerulosclerosis on biopsy
- Delayed nephritis
- ANCA negative

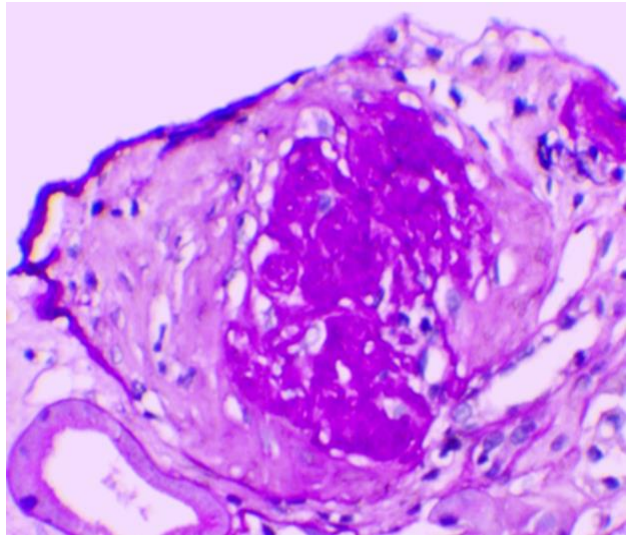
Normal



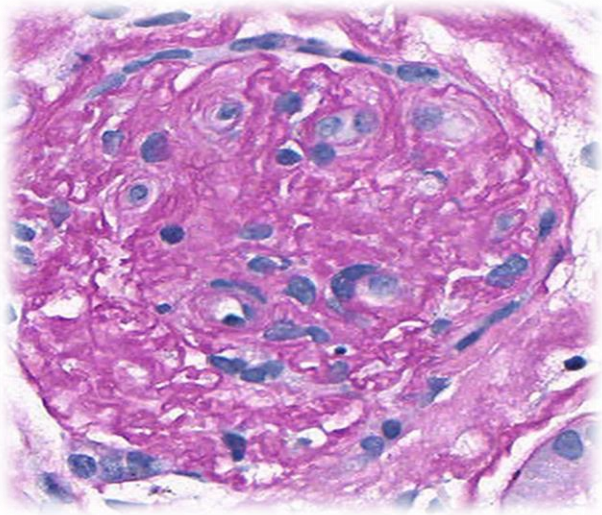
Cellular crescent



Fibrous crescent



Global sclerosis



Activity

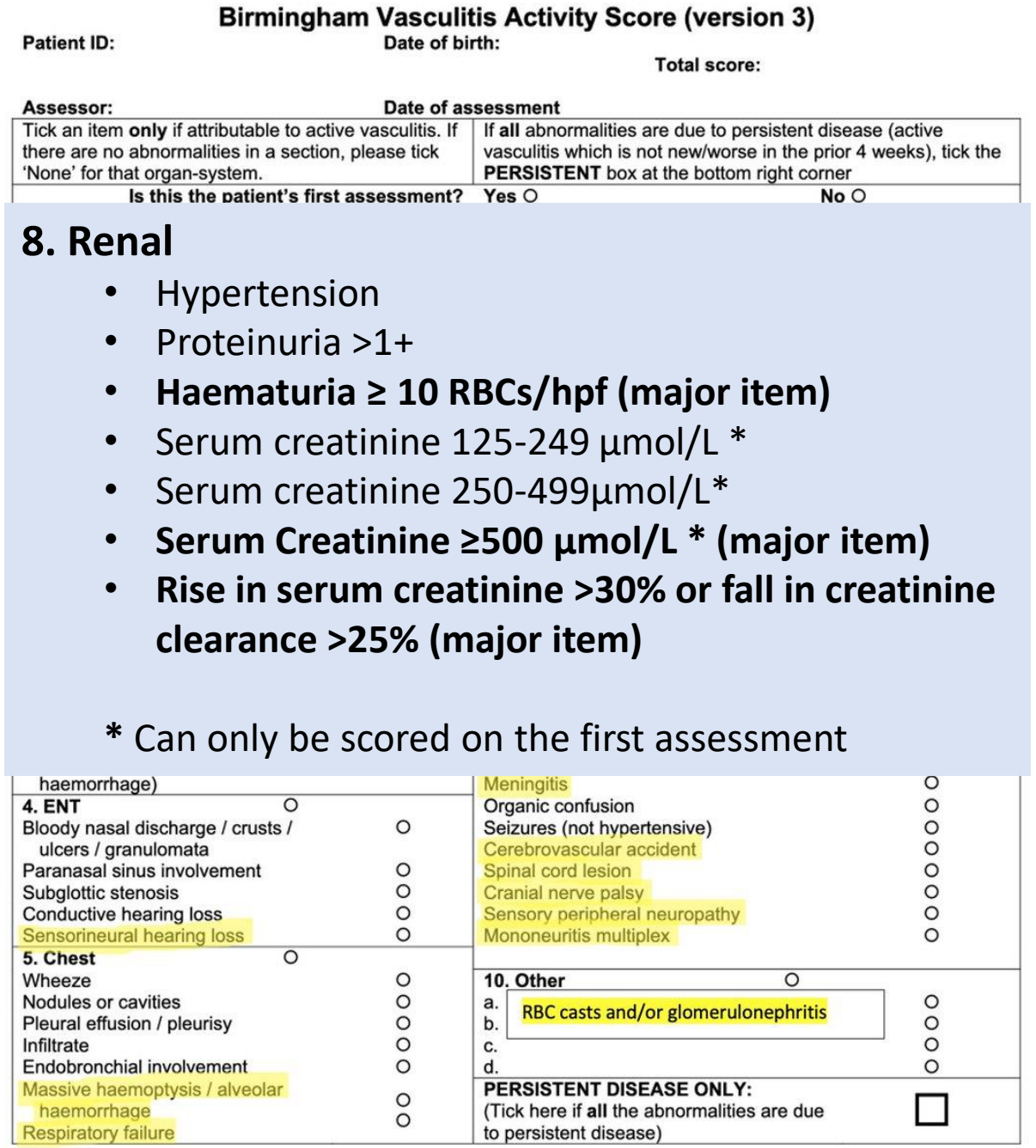
Birmingham Vasculitis Activity Score (BVAS)

- 9 organ systems
- Numerical score (0-63 active, 0-33 persistent)
- Used in RCTS (76%)
- Not linear

Activity (new disease or relapse)

- Active (BVAS>0) or remission (BVAS=0)

Mukhtyar C. et al. Ann Rheum Dis. 2009



Birmingham Vasculitis Activity Score (version 3)

Patient ID: Date of birth: Total score:

Assessor: Date of assessment

Tick an item **only** if attributable to active vasculitis. If there are no abnormalities in a section, please tick 'None' for that organ-system.	If **all** abnormalities are due to persistent disease (active vasculitis which is not new/worse in the prior 4 weeks), tick the **PERSISTENT** box at the bottom right corner
Is this the patient's first assessment?	**Yes** ○ **No** ○

8. Renal

- Hypertension
- Proteinuria >1+
- **Haematuria ≥ 10 RBCs/hpf (major item)**
- Serum creatinine 125-249 µmol/L *
- Serum creatinine 250-499µmol/L*
- **Serum Creatinine ≥500 µmol/L * (major item)**
- **Rise in serum creatinine >30% or fall in creatinine clearance >25% (major item)**

* Can only be scored on the first assessment

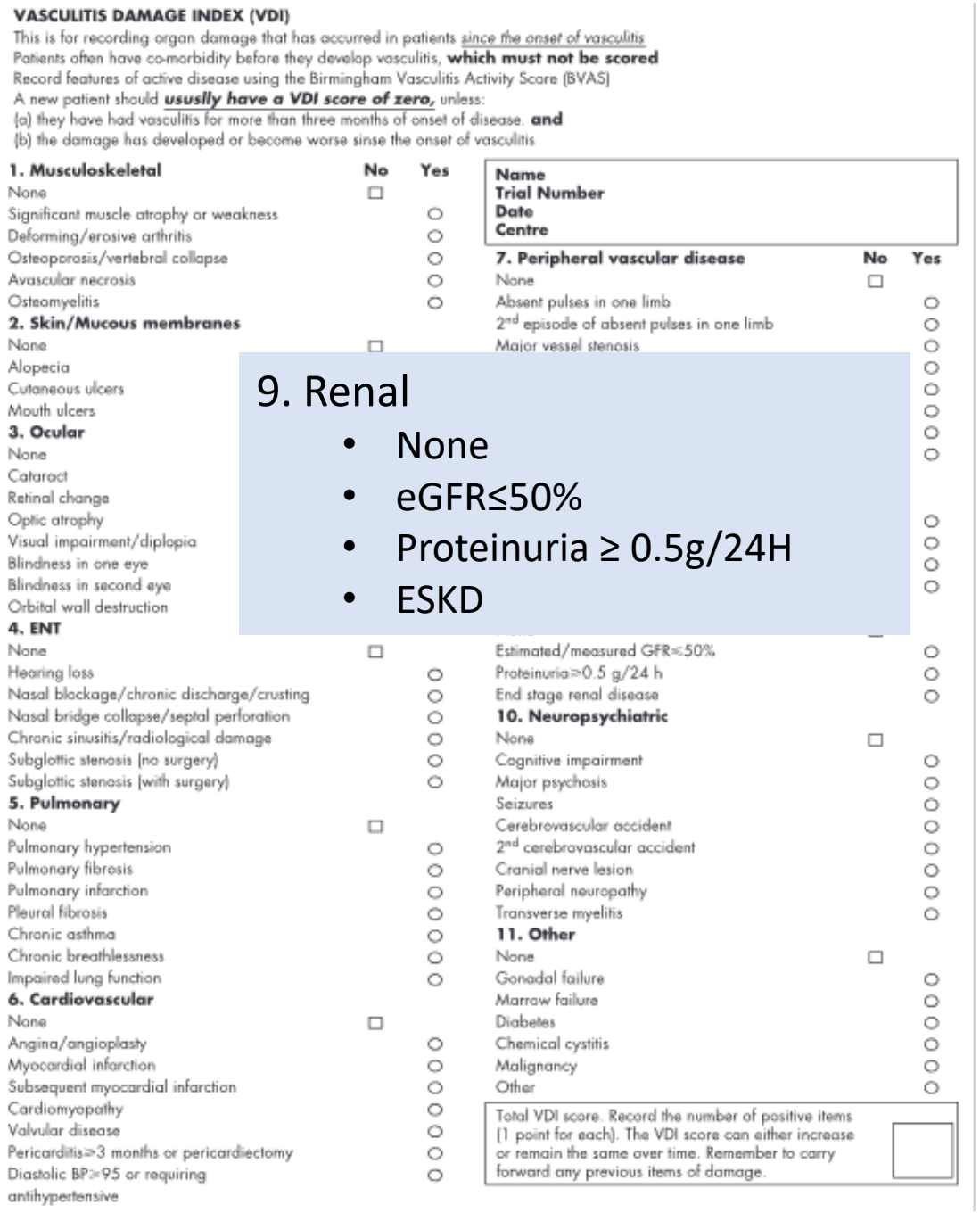
haemorrhage)		Meningitis	○
4. ENT	○	Organic confusion	○
Bloody nasal discharge / crusts / ulcers / granulomata	○	Seizures (not hypertensive)	○
Paranasal sinus involvement	○	Cerebrovascular accident	○
Subglottic stenosis	○	Spinal cord lesion	○
Conductive hearing loss	○	Cranial nerve palsy	○
Sensorineural hearing loss	○	Sensory peripheral neuropathy	○
5. Chest	○	Mononeuritis multiplex	○
Wheeze	○	**10. Other**	○
Nodules or cavities	○	a. RBC casts and/or glomerulonephritis	○
Pleural effusion / pleurisy	○	b.	○
Infiltrate	○	c.	○
Endobronchial involvement	○	d.	○
Massive haemoptysis / alveolar haemorrhage	○	**PERSISTENT DISEASE ONLY:** (Tick here if **all** the abnormalities are due to persistent disease)	☐
Respiratory failure	○		

Assessment Damage

Damage

- Disease activity
- Treatment toxicity
- Comorbidities

VDI≥5 ↑X6.4 folds mortality



VASCULITIS DAMAGE INDEX (VDI)

This is for recording organ damage that has occurred in patients *since the onset of vasculitis*
Patients often have co-morbidity before they develop vasculitis, **which must not be scored**
Record features of active disease using the Birmingham Vasculitis Activity Score (BVAS)
A new patient should ***ususlly have a VDI score of zero,*** unless:
(a) they have had vasculitis for more than three months of onset of disease. **and**
(b) the damage has developed or become worse sinse the onset of vasculitis

1. Musculoskeletal	**No**	**Yes**
None	☐	
Significant muscle atrophy or weakness		○
Deforming/erosive arthritis		○
Osteoporosis/vertebral collapse		○
Avascular necrosis		○
Osteomyelitis		○
2. Skin/Mucous membranes		
None	☐	
Alopecia		○
Cutaneous ulcers		○
Mouth ulcers		○
3. Ocular		○
None		○
Cataract		
Retinal change		
Optic atrophy		○
Visual impairment/diplopia		○
Blindness in one eye		○
Blindness in second eye		○
Orbital wall destruction		
4. ENT		
None	☐	
Hearing loss		○
Nasal blockage/chronic discharge/crusting		○
Nasal bridge collapse/septal perforation		○
Chronic sinusitis/radiological damage		○
Subglottic stenosis (no surgery)		○
Subglottic stenosis (with surgery)		○
5. Pulmonary		
None	☐	
Pulmonary hypertension		○
Pulmonary fibrosis		○
Pulmonary infarction		○
Pleural fibrosis		○
Chronic asthma		○
Chronic breathlessness		○
Impaired lung function		○
6. Cardiovascular		
None	☐	
Angina/angioplasty		○
Myocardial infarction		○
Subsequent myocardial infarction		○
Cardiomyopathy		○
Valvular disease		○
Pericarditis≥3 months or pericardiectomy		○
Diastolic BP≥95 or requiring antihypertensive		○

Name
Trial Number
Date
Centre

7. Peripheral vascular disease	**No**	**Yes**
None	☐	
Absent pulses in one limb		○
2nd episode of absent pulses in one limb		○
Major vessel stenosis		○

9. Renal
- None
- eGFR≤50%
- Proteinuria ≥ 0.5g/24H
- ESKD

Estimated/measured GFR≤50%		○
Proteinuria≥0.5 g/24 h		○
End stage renal disease		○
10. Neuropsychiatric		
None	☐	
Cognitive impairment		○
Major psychosis		○
Seizures		○
Cerebrovascular accident		○
2nd cerebrovascular accident		○
Cranial nerve lesion		○
Peripheral neuropathy		○
Transverse myelitis		○
11. Other		
None	☐	
Gonadal failure		○
Marrow failure		○
Diabetes		○
Chemical cystitis		○
Malignancy		○
Other		○

Total VDI score. Record the number of positive items (1 point for each). The VDI score can either increase or remain the same over time. Remember to carry forward any previous items of damage. ☐

Bhamra K. et al. Curr Rheumatol Rep 2012

Remission

After 3-6 months

EULAR 2022 recommendations

Absence of typical signs, symptoms, or other features of active AAV with or without immunosuppressive therapy

KDIGO 2024 guidelines

Absence of manifestations of vasculitis and GN (BVAS=0)
For GN, it is defined as a stable or improved GFR. While hematuria and proteinuria are present at times of active disease and can resolve completely, their persistence does not necessarily imply active disease

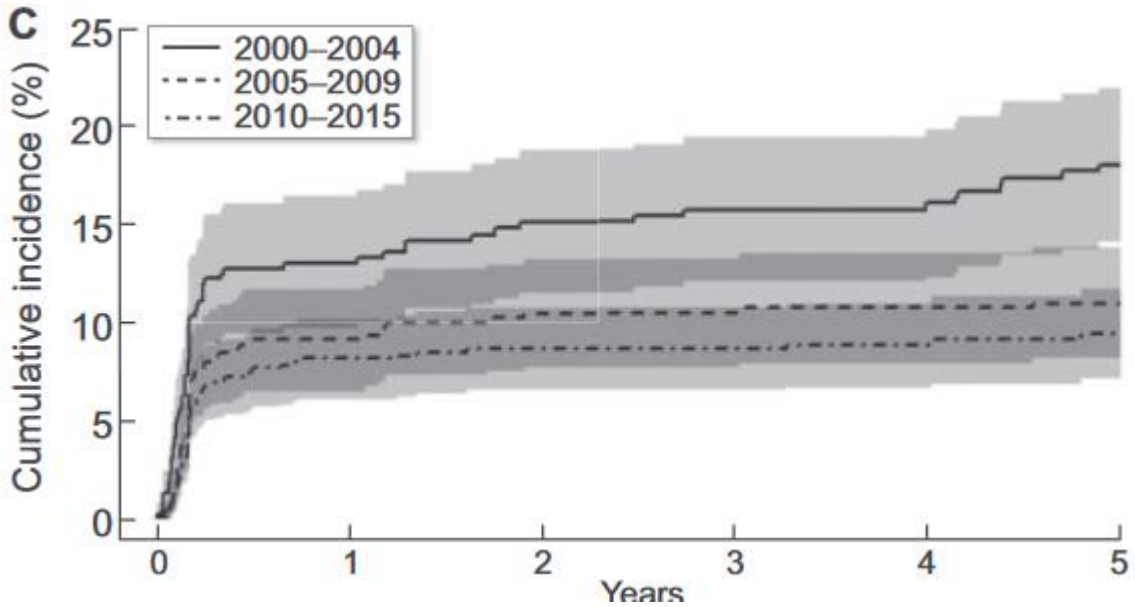
Hellmich B et al. Ann Rheum Dis 2024
Floege J. et al. Kidney Int. 2024

Renal Remission

- When inflammation has truly and completely resolved.
- Surrogate kidney markers associated with better long-term kidney and survival outcomes.

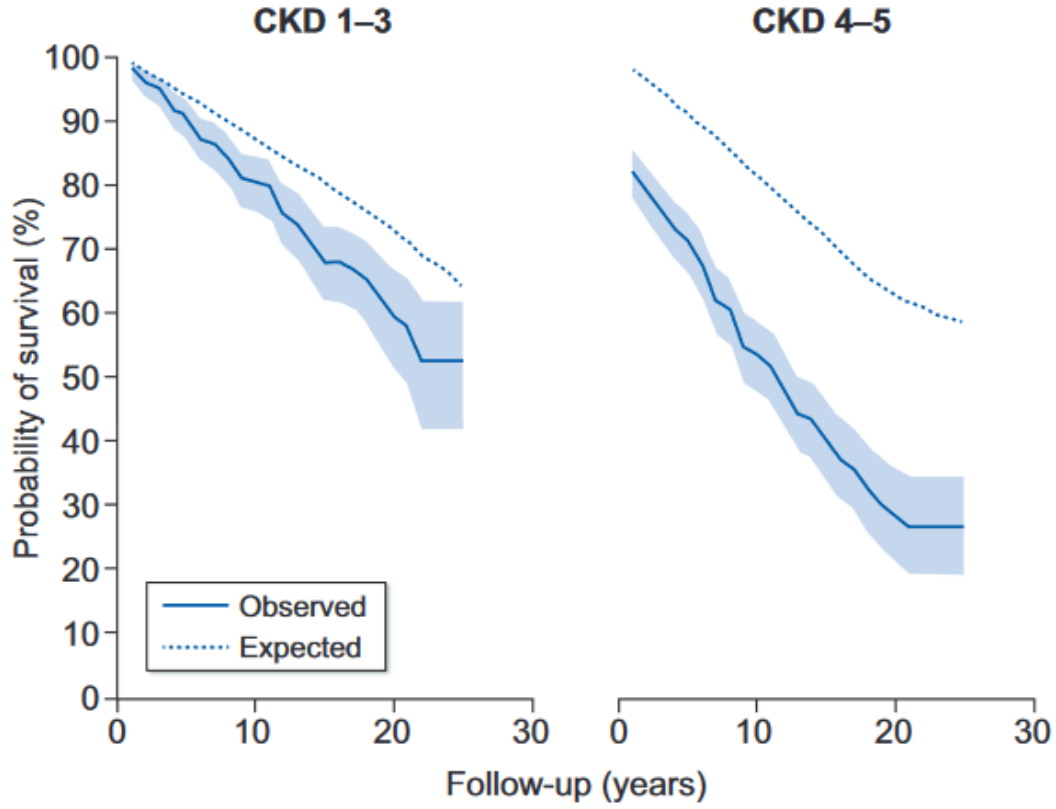
Importance of Renal Remission

Preventing end-stage kidney disease



Nelveg-Kristensen K. et al. Nephrol Dial Transplant 2021

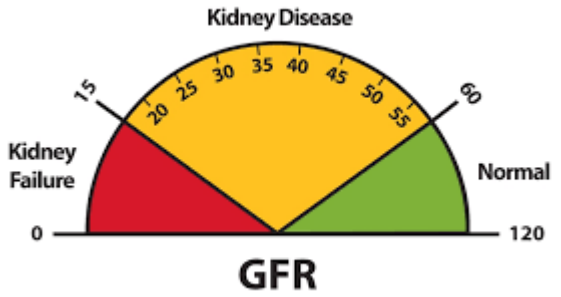
Improved Survival Rates



Alamo B. et al Nephrol Dial Transplant 2024

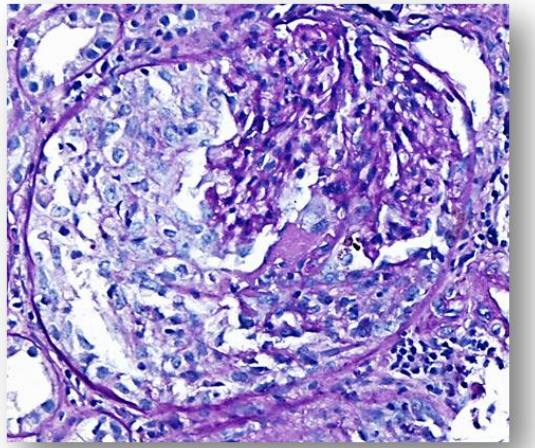
Defining Renal Remission is Challenging

Traditional surrogate markers



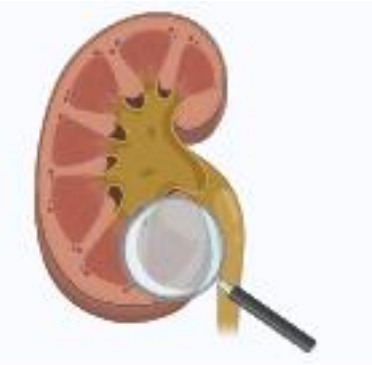
sCr
Proteinuria/Albuminuria
Haematuria

Tissue biopsy
invasive



Repeat biopsy

Novel biomarkers
non-invasive



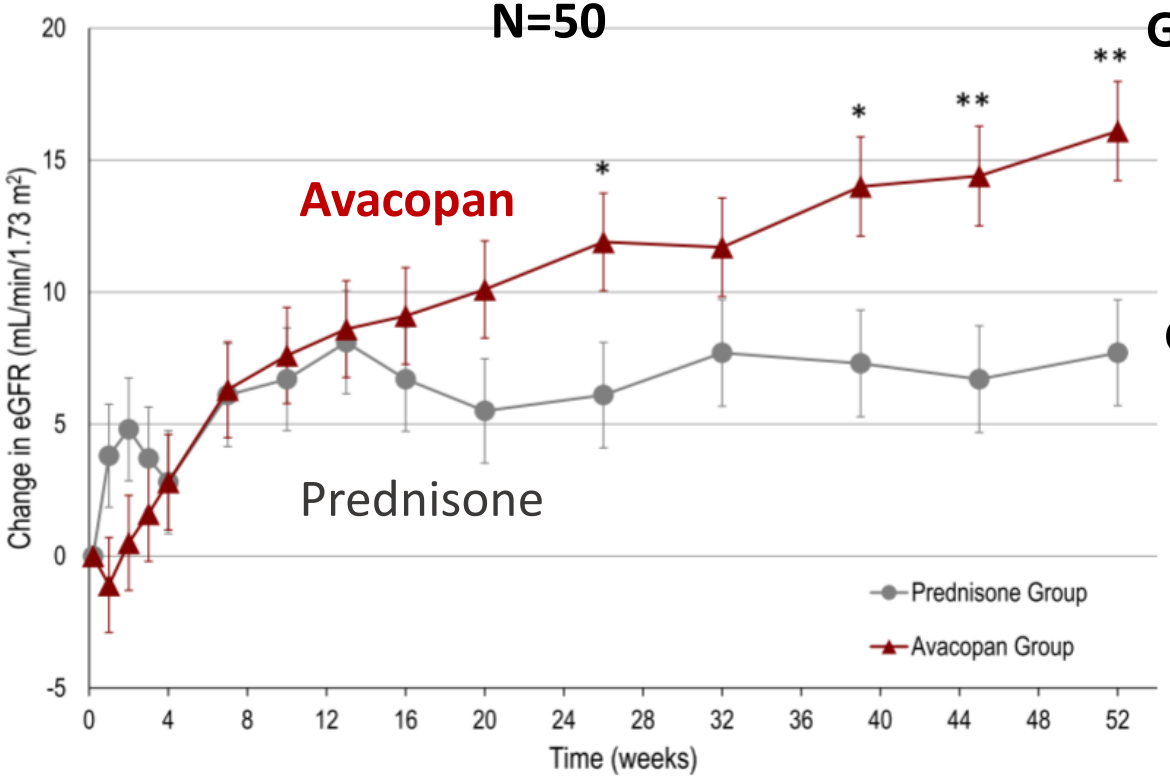
ANCA titers, sCD163, MCP-1,
T cells, complement

Landmark Induction Trials in AAV

Name	Design	End-point	Result	Renal parameters
NORAM 2005	MTX Vs oral CYC	Remission 6m	MTX non-inferior to CYC	sCr<150
MEPEX 2007	PLEX Vs iv methylpred	Dialysis independence 3m	Renal survival better with PLEX	sCr>500 or HDx, **sCR at 12 months**
CYCLOPS 2009	Iv CYC Vs oral CYC	Time to remission	Iv CYC non-inferior to oral CYC	150<sCr<500, **Change GFR, 3, 6 months**
RITUXVAS 2010	RTX+ iv CYC x2 Vs iv CYC	Sustained remission 12m	RTX non-inferior to CYC	All **Change GFR 12 months**
RAVE 2010	RTX Vs oral CYC	Remission without Pred 6m	RTX non-inferior to CYC	sCr<4mg/dL **Change GFR 18months**
MYCYC 2019	MMF Vs iv CYC	Remission at 6m (steroid-taper adherence)	MMF non-inferior to CYC	eGFR>15 **Change GFR at 18months**
PEXIVAS 2020	PEX Vs No PEX High Vs Low GC	ESKD-free survival	No benefit from PEX Low GC non-inferior to High	eGFR<50
RITAZAREM 2020	High Vs Low GC	Remission at 6m	Low GC non-inferior to High	sCR<500 4 months
LOVAS 2021	High Vs Low GC	Remission at 6m	Low GC non-inferior to High	eGFR>15
ADVOCATE 2021	Avacopan Vs GC	Remission at 26 and 52 weeks	Avacopan non-inferior to GC at 6m Avacopan superior to GC at 12 m	eGFR>15 **Change GFR, UACR, MCP-1 26 and 52 weeks**

Renal Recovery

Baseline
GFR≤20ml/min
N=50



M6

M12

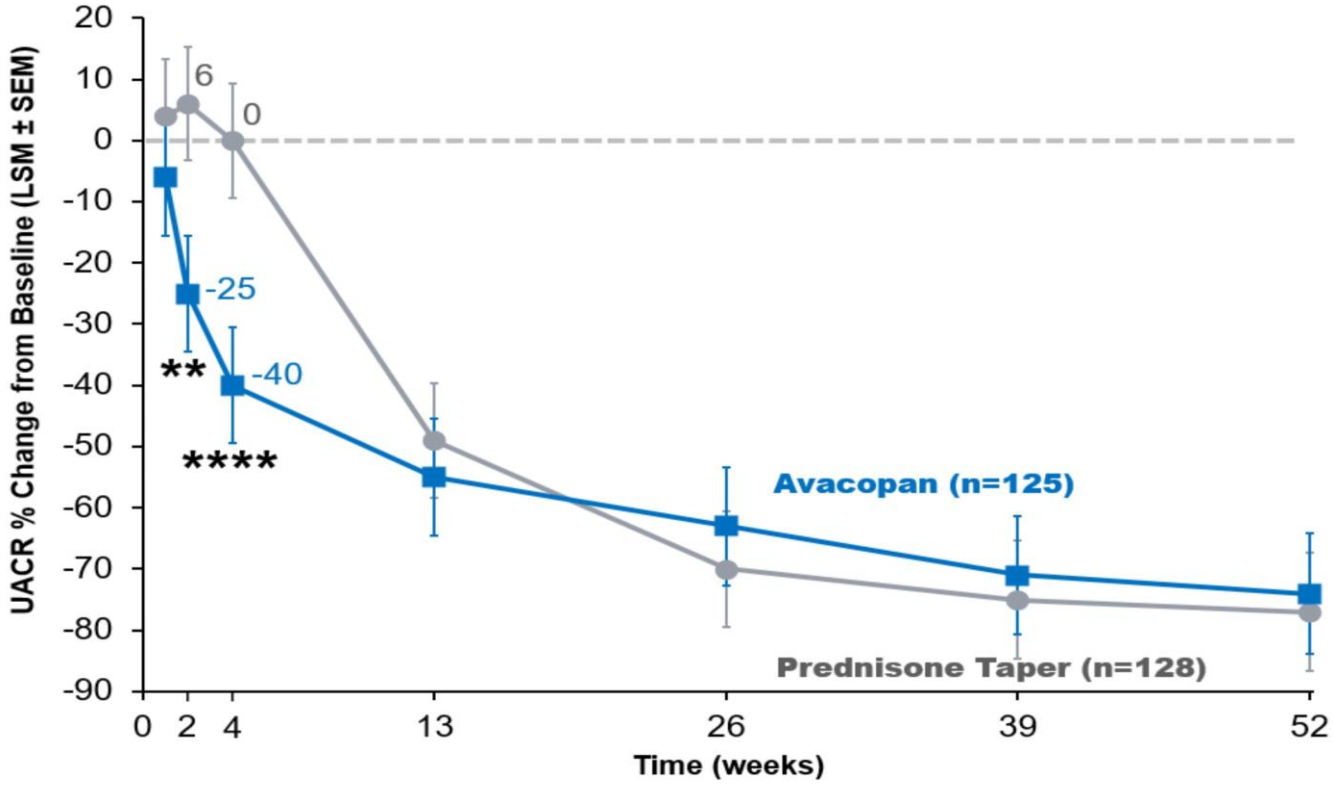
GFR +16.5ml/min

GFR+8.8ml/min

Renal remission may come later than vasculitis remission

Cortazar F et al. Kidney Int Rep. 2023
Jayne D et al. NEJM 2021

Albuminuria Reduction



LSM = least squares mean; SEM = standard error of mean; UACR = urinary albumin:creatinine ratio **p<0.01, ****p<0.0001 by mixed effects models for repeated measures (MMRM) with treatment group, visit, and treatment-by-visit interaction as factors and baseline as covariate. Percent changes from baseline are based on ratios of geometric means of visit over baseline.

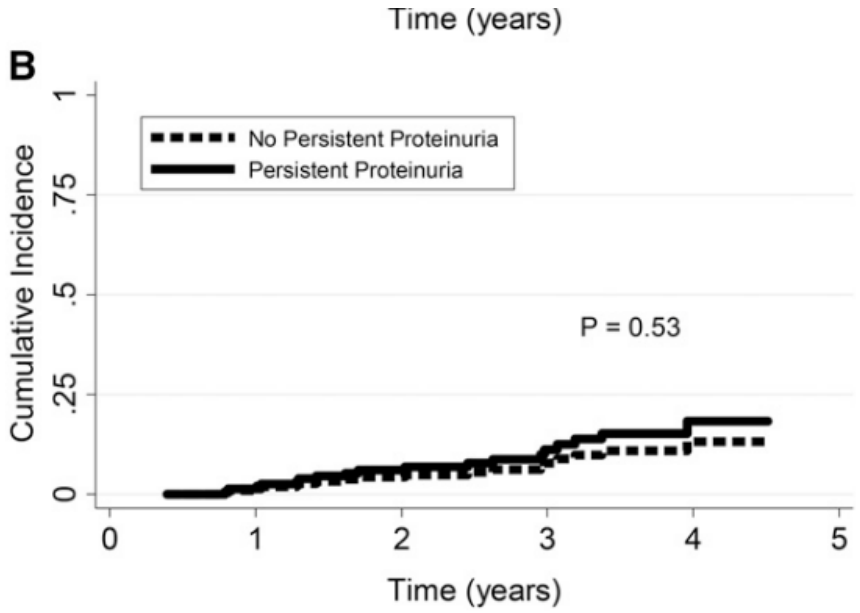
Rapid **reduction** of albuminuria suggests more rapid control of glomerular inflammation

Jayne D et al. NEJM 2021

Gueetha D et al. **#3236.** *Nephr Dial Transplant*, Issue Supplement_1, June 2023

Persistent Proteinuria

34.3% - 46%

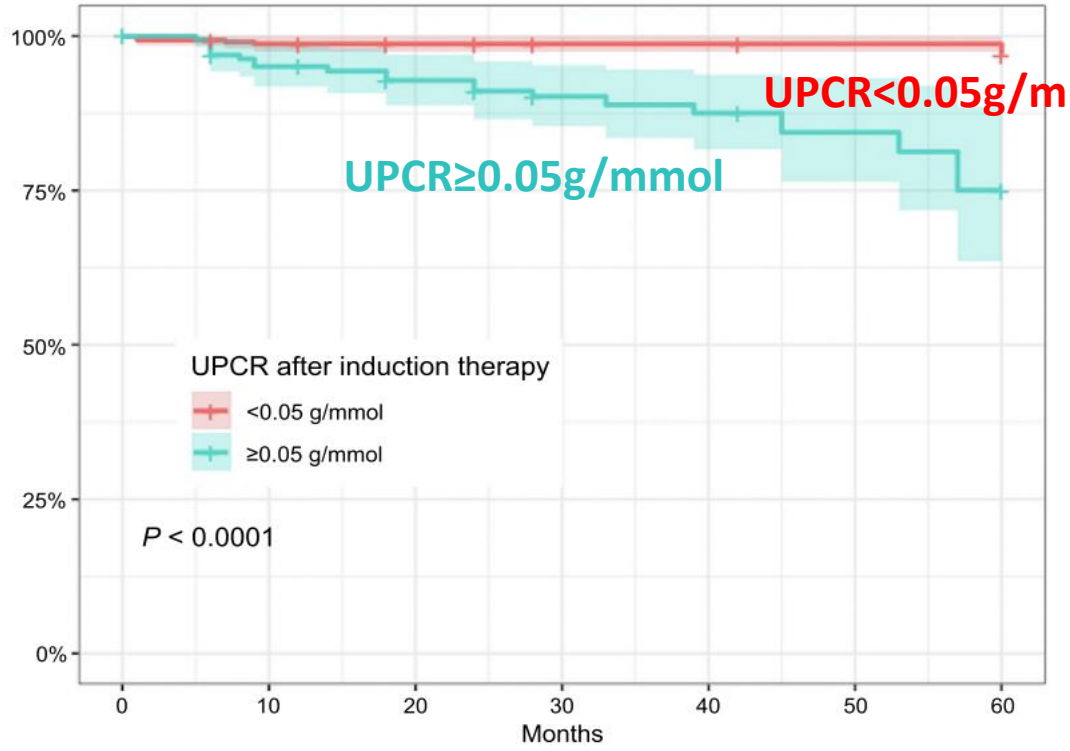


Association between persistent proteinuria and outcome

Outcome	Adjusted sHR (95% CI)	P value
Renal relapse	1.44 (o.47, 4.42)	0.53
Any relapse	0.78 (0.42, 1.45)	0.43
ESRD	3.61 (0.40, 32.3)	0.25
Slope of change in eGFR	--	0.75

Rhee R. CJASN.2018

End-Stage Kidney Disease



34.3% UPCR≥0.05g/mmol

Benichou N. et al. Kidney Int. 2023

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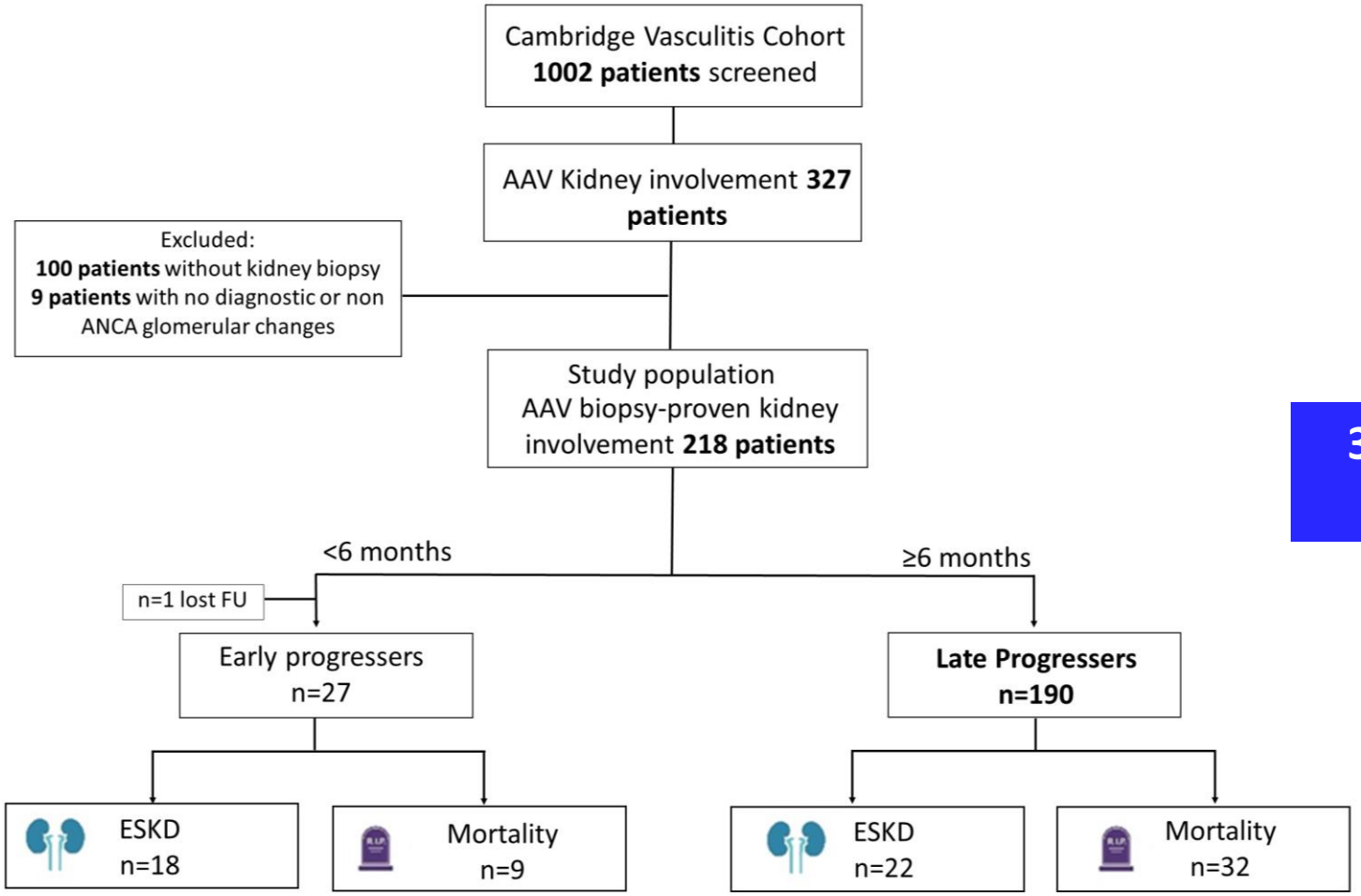
Persisting Albuminuria



37% albuminuria
UACR>300mg/g

End-stage kidney disease: GFR <15ml/min per 1.73m2 for more than 3 months or on haemodialysis or kidney transplantation

Chalkia A, Jayne D et al. under submission

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Persisting Albuminuria

	Univariate logistic regression		*Multivariate logistic regression	
	OR (95% CI)	p value	OR (95% CI)	p value
Gender (male vs female)	2 (1.05-3.83)	0.034	2.69 (1.13-6.41)	**0.025**
Age, years	0.97 (0.95-0.99)	0.02	0.96 (0.93-0.99)	**0.045**
Normal glomeruli (%)	0.95 (0.94-0.97)	<0.001	0.96 (0.93-0.99)	**0.013**

* Adjusted for GFR at diagnosis, ANCA type, haematuria, Berden classification, % crescents, % necrosis, % global sclerosis, % interstitial fibrosis

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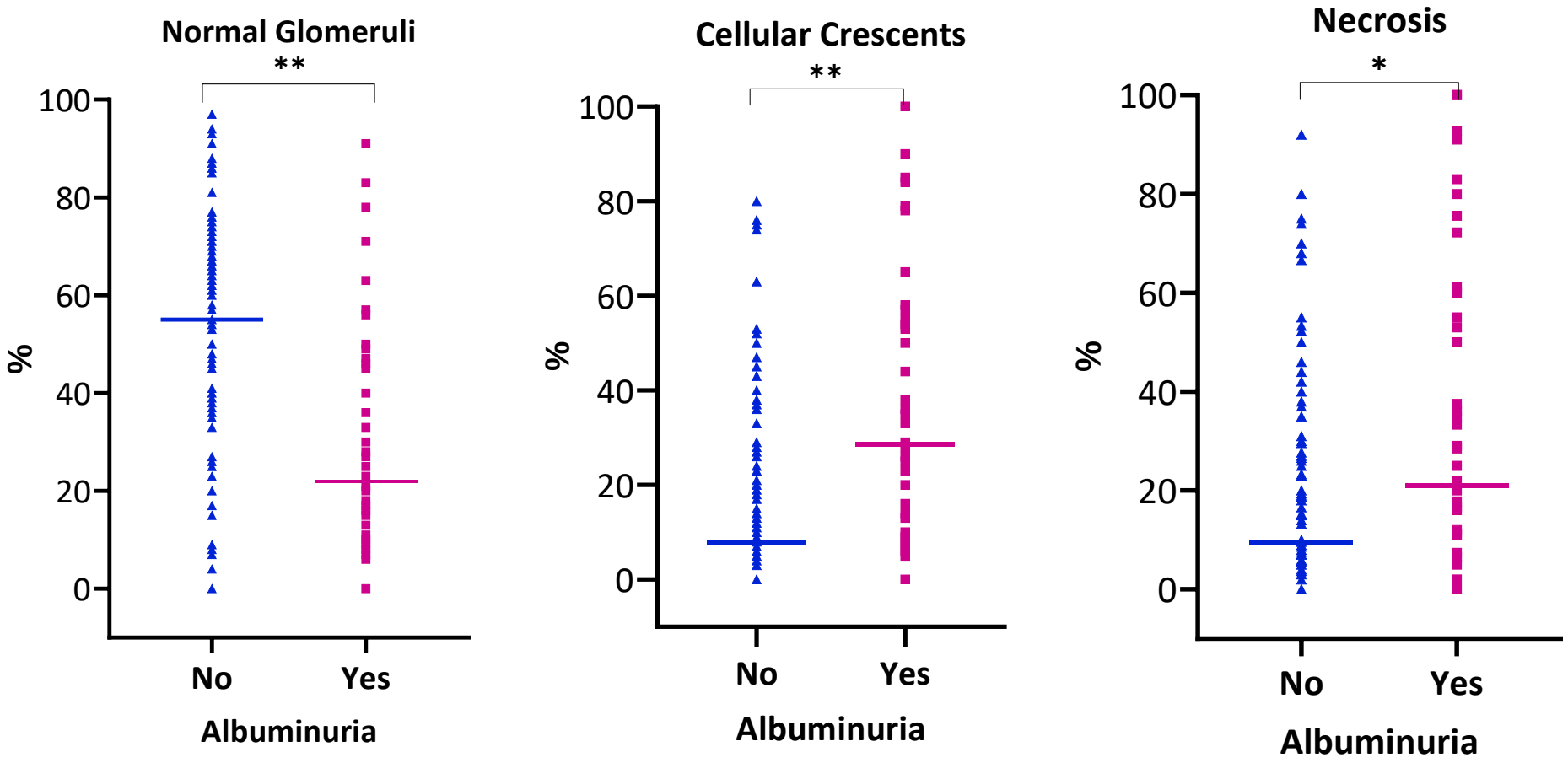
Persisting Albuminuria

Indicative of a higher baseline inflammatory burden



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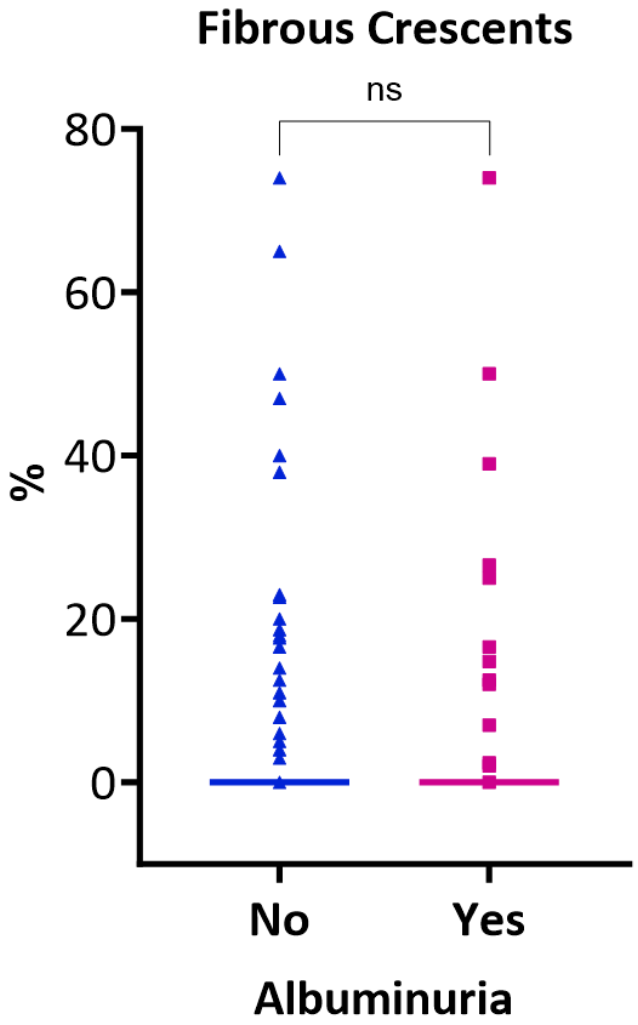
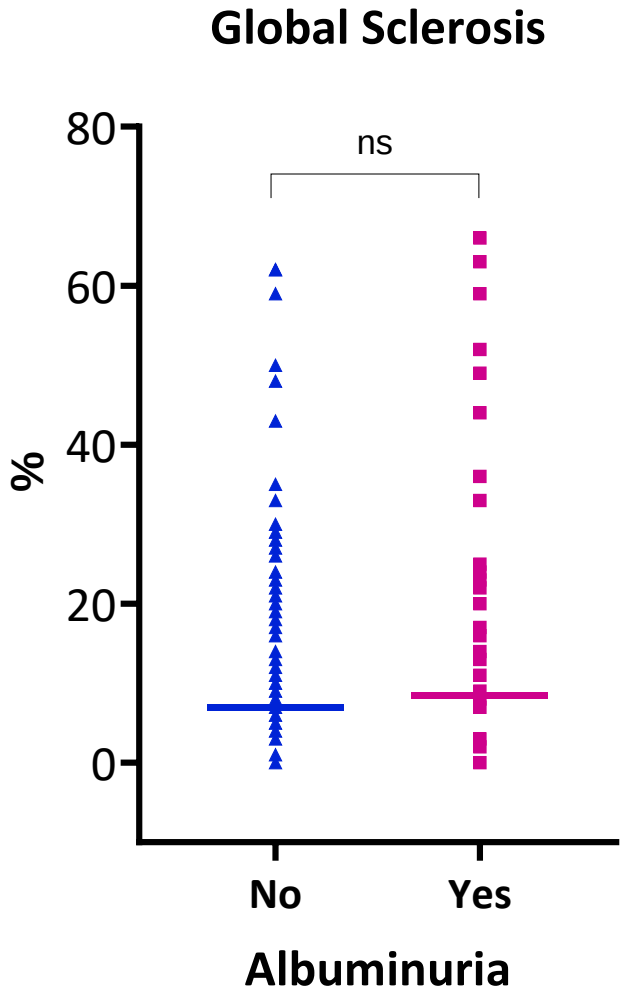
Persisting Albuminuria

No difference in **baseline fibrotic changes**





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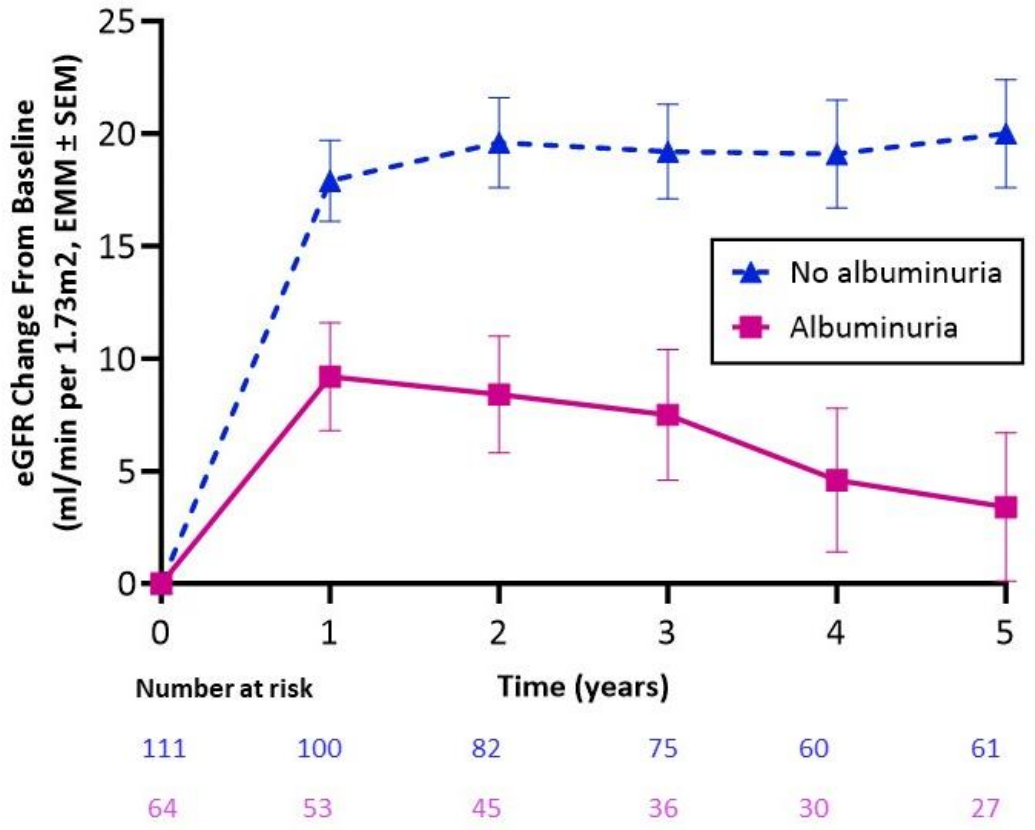
Persisting Albuminuria

Worst Renal Recovery

A.

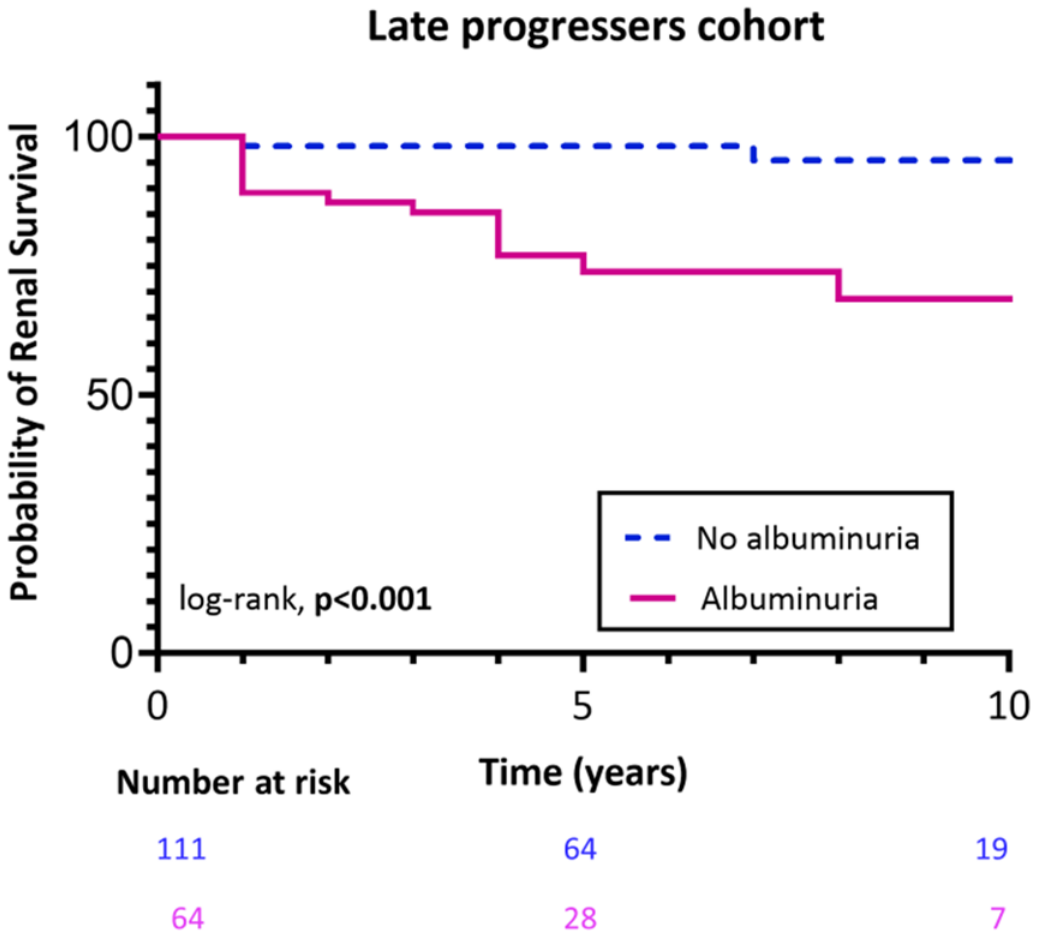


delta GFR per year over 5 years obtained by mixed effects model for repeated measures analysis with fixed effects albuminuria group, time, albuminuria and time interaction as factors, and baseline GFR and age as covariates.

Chalkia A, Jayne D et al. under submission

Persisting Albuminuria

Worst Renal Survival



	Adjusted Model 1[a]		Adjusted Model 2[b]	
	HR (95% CI)	P value	HR (95% CI)	P value
ACR> 300mg/g	7.25 (1.623-32.471)	0.010	4.39 (1.037-18.629)	0.045

[a] Model 1: adjusted for age, GFR at diagnosis, berden classification

[b] Model 2: adjusted for age, GFR at diagnosis, normal glomeruli, global sclerosis, cellular crescent

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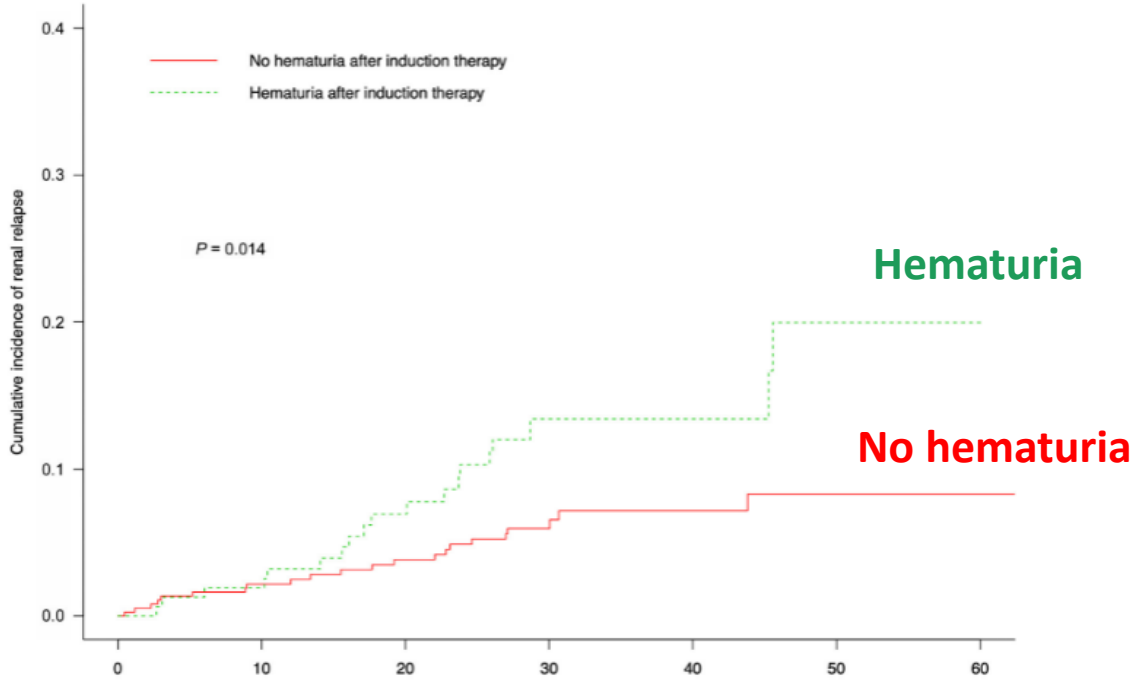
Persistent Haematuria

29.8% - 48%

Renal Relapse



Hematuria

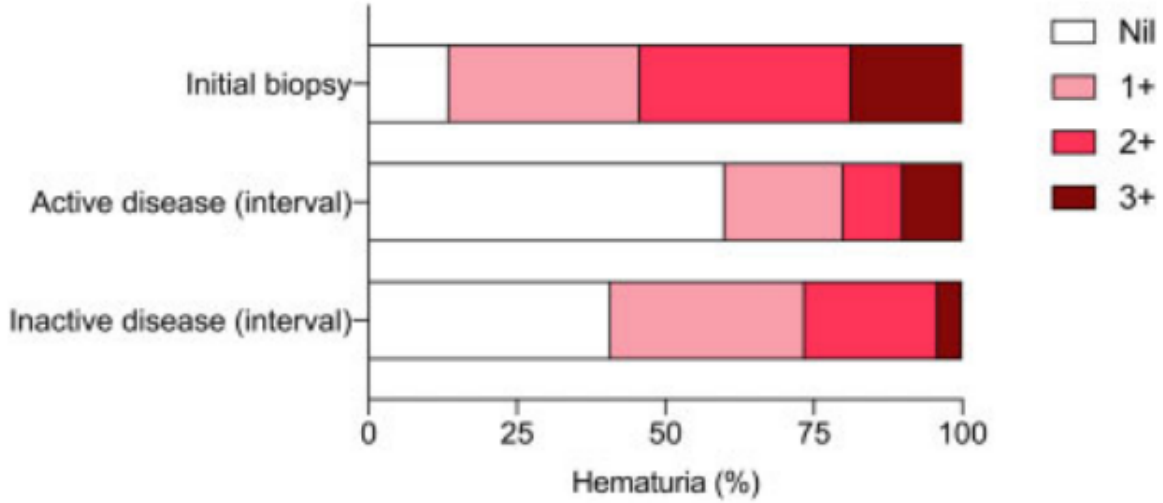
No hematuria

29.8% persistent hematuria

Benichou N. et al. Kidney Int. 2023

Internal Biopsy

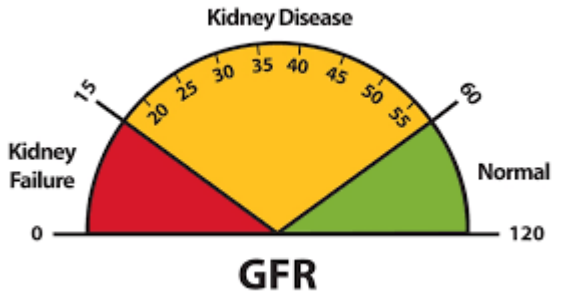
- 60% with active disease no haematuria
- 59% with inactive disease presented haematuria



Chapman G. et al. Rheumatology 2021

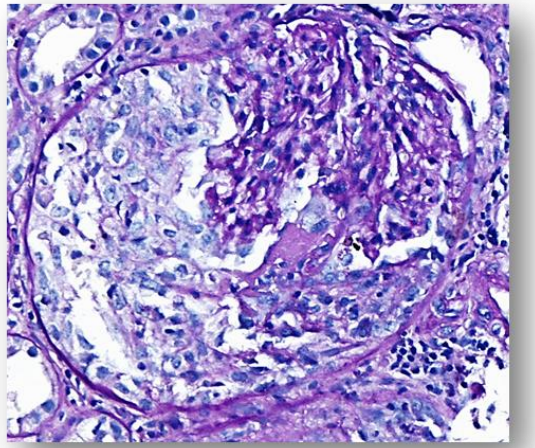
Defining Renal Remission is Challenging

Traditional surrogate markers



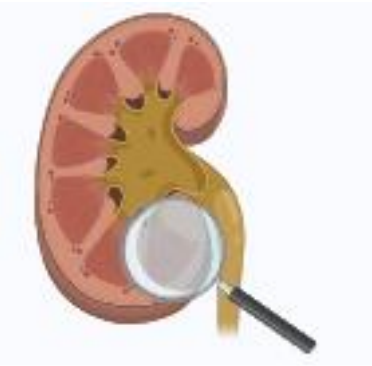
sCr
Proteinuria/Albuminuria
Haematuria

Tissue biopsy
invasive



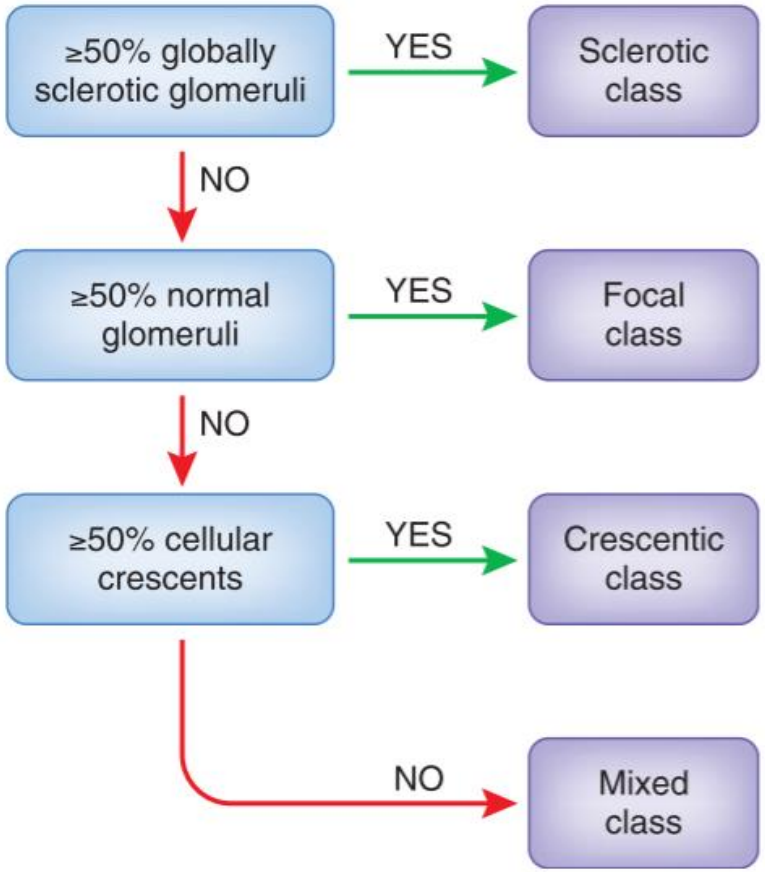
Repeat biopsy

Novel biomarkers
non-invasive



ANCA titers, sCD163, MCP-1,
T cells, complement

Baseline Kidney Biopsy



At 12 months

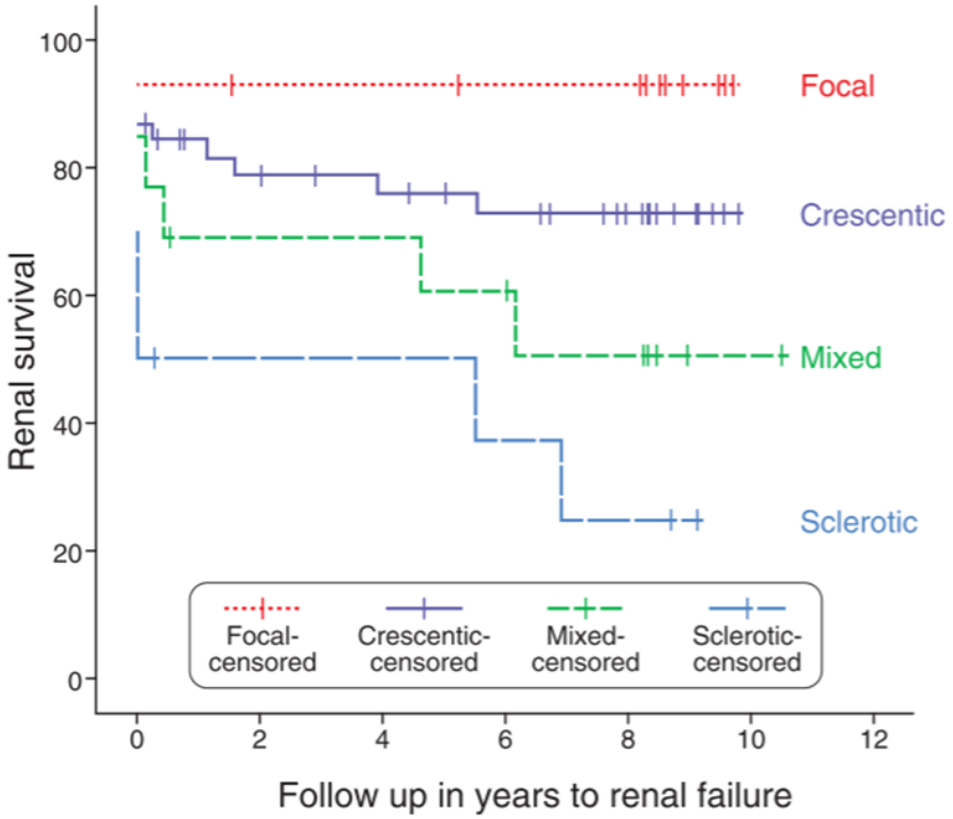
GFR +5.8 ml/min

GFR +11 ml/min

GFR +21.6 ml/min

GFR +9.1 ml/min

ESKD



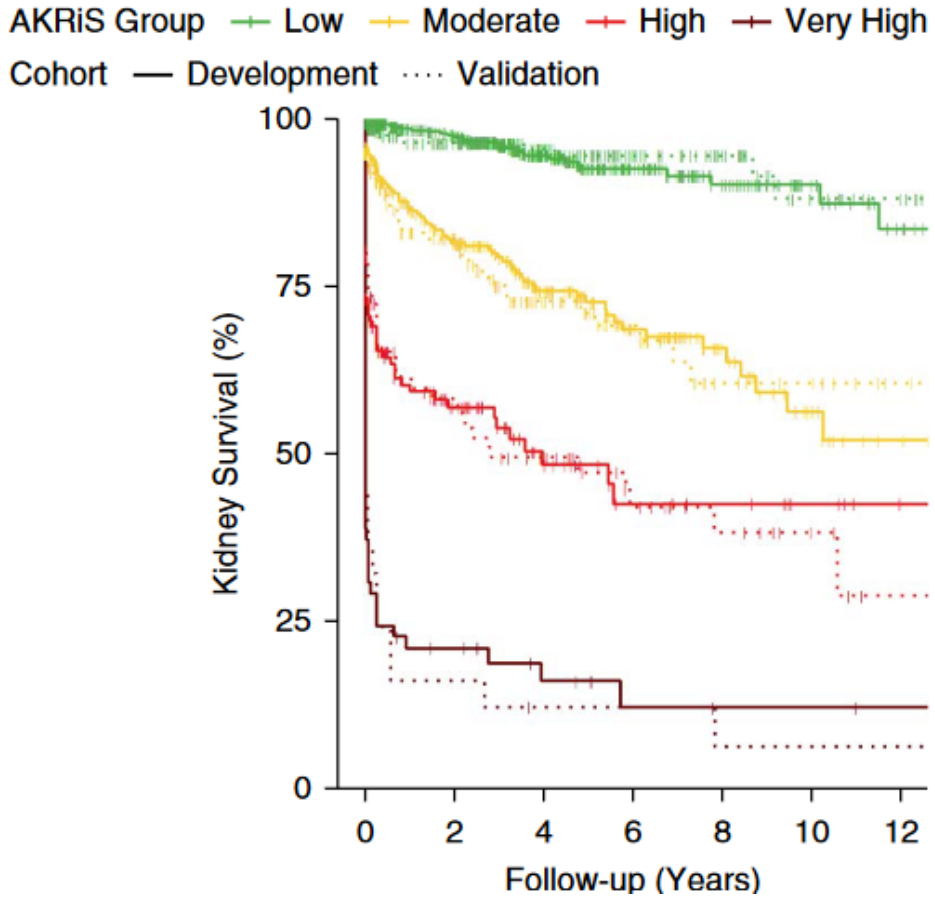
Berden A et al. JASN 2010

Baseline Kidney Biopsy

AKRiS
Percentage of normal glomeruli (N)
Tubular atrophy+interstitial fibrosis (T)
Serum creatinine at time of diagnosis

Risk Groups	ESKD at 3yrs
Low	4%
Moderate	11%
High	46%
Very High	81%

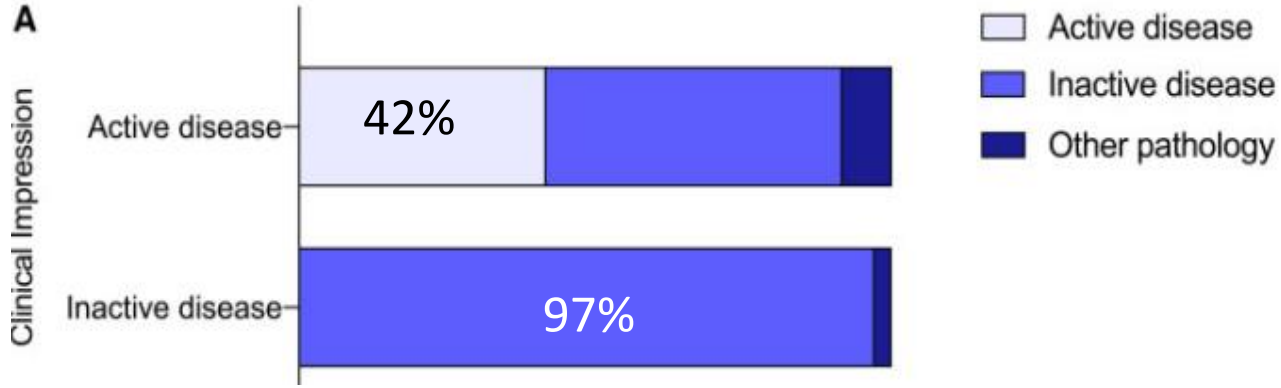
ESKD



Bate S et al. JASN 2024

Repeat Kidney Biopsies

N=59
~130 days



Active disease in repeat biopsy:

- ↓ increase GFR
- ↓decrease proteinuria
- ↓ Hb
- No difference in ANCA titers, CRP, Haematuria

Chapman G et al. Rheumatology 2021

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Repeat Kidney Biopsies

Persisting albuminuria

	Initial Biopsy N=11	Repeat biopsy N=11	p value
Glomeruli			
Normal Glomeruli (%), median (IQR)	18 (10-38)	25 (15-50)	0.386
Global Sclerosis (%), median (IQR)	3 (0-43)	36 (23-62)	**0.012**
Segmental Sclerosis (%), median (IQR)	0 (0-12)	19 (9-34)	**0.007**
Cellular Crescents (%), median (IQR)	38 (6-58)	0 (0-4)	**0.032**
Fibrinoid Necrosis (%), median (IQR)	18 (0-44)	0 (0-0)	**0.038**
Fibrous Crescents (%), median (IQR)	0 (0-20)	0 (0-0)	0.593
Interstitial Fibrosis			0.882
Absent % (n)	67 (6)	0 (0)	
Mild % (n)	22 (2)	22 (2)	
Moderate % (n)	11 (1)	33 (3)	
Severe % (n)	0 (0)	44 (4)	

Low activity
in a median 13% of the glomeruli accounting for about 36% of all repeat biopsies (4/11)

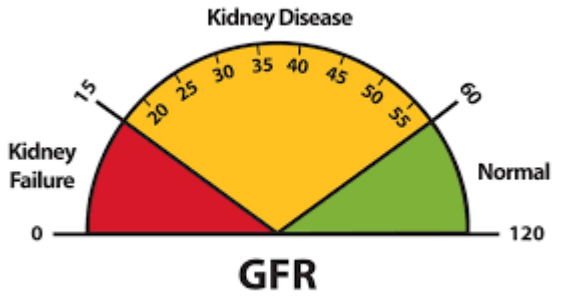
40% change Berden classification

Wilcoxon signed-rank test

Chalkia A, Jayne D. et al. under submission

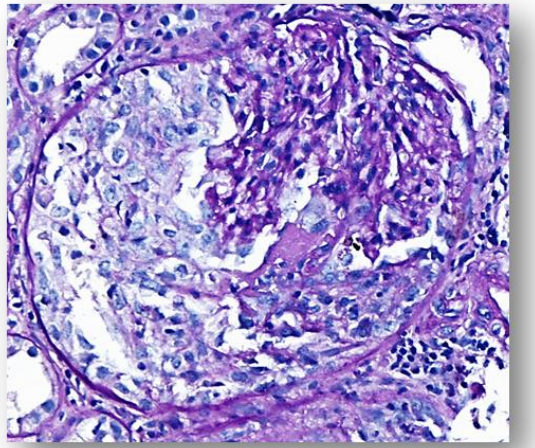
Defining Renal Remission is Challenging

Traditional surrogate markers



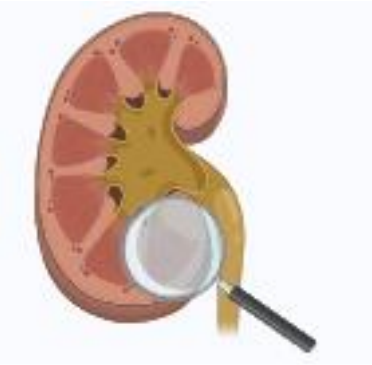
sCr
Proteinuria/Albuminuria
Haematuria

Tissue biopsy
invasive



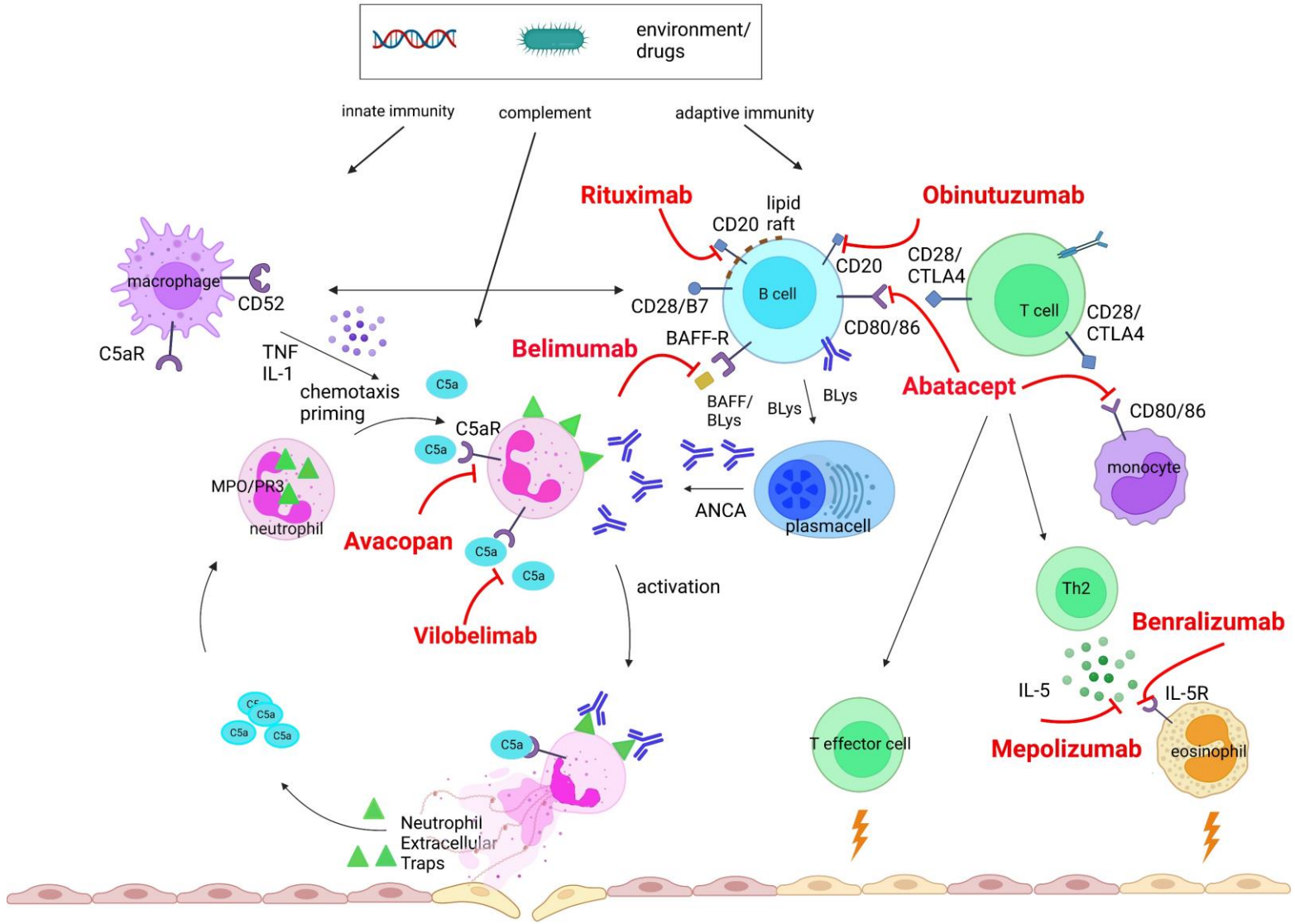
Repeat biopsy

Novel biomarkers
non-invasive



ANCA titers, sCD163, MCP-1, T cells, complement fragments

Pathogenesis- Novel markers

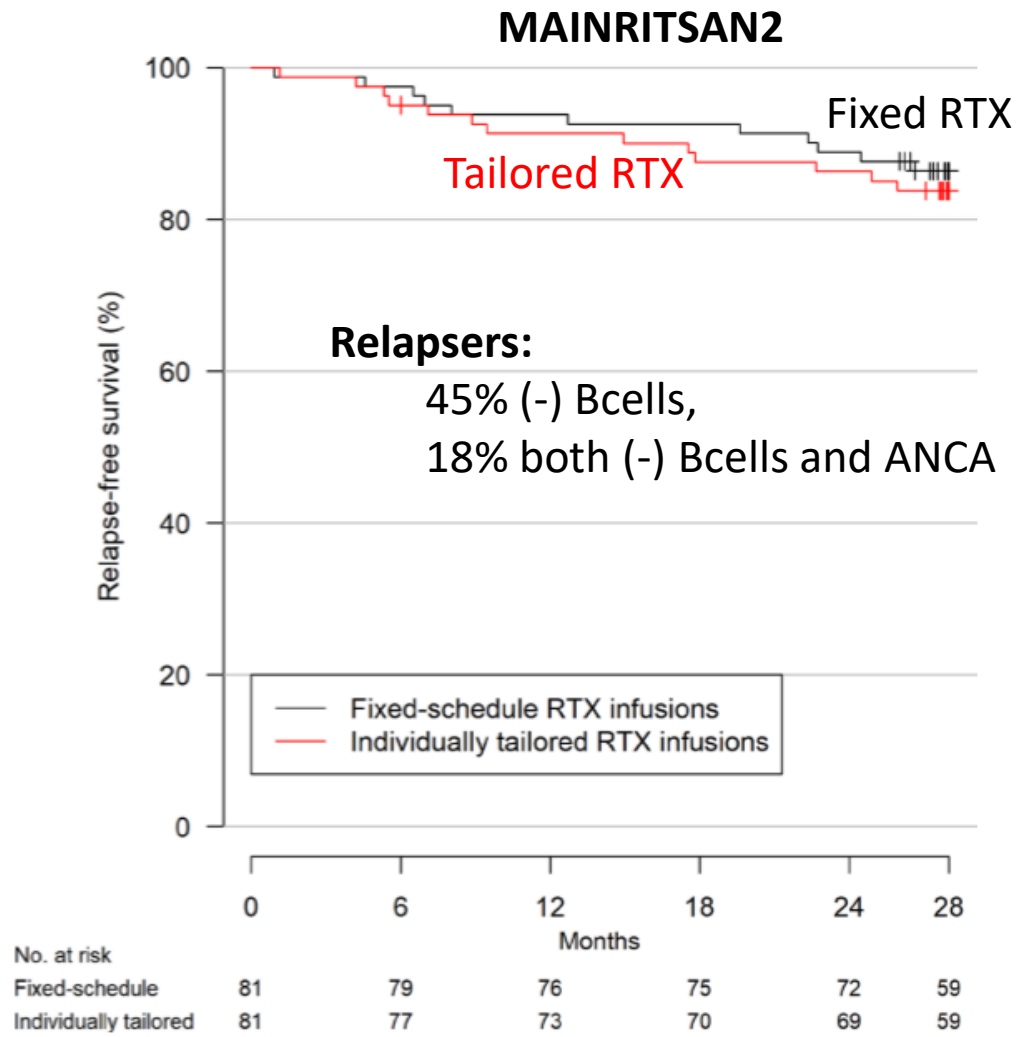


Chalkia A. Jayne D. Nephrol Dial Transplant. 2024

ANCA Titers and Remission

	RAVE n=180 45% new, 52% relapsing	
	CYC/AZA	RTX
Remission (6m)	53%	64%
ANCA negative (6m)	24%	47%

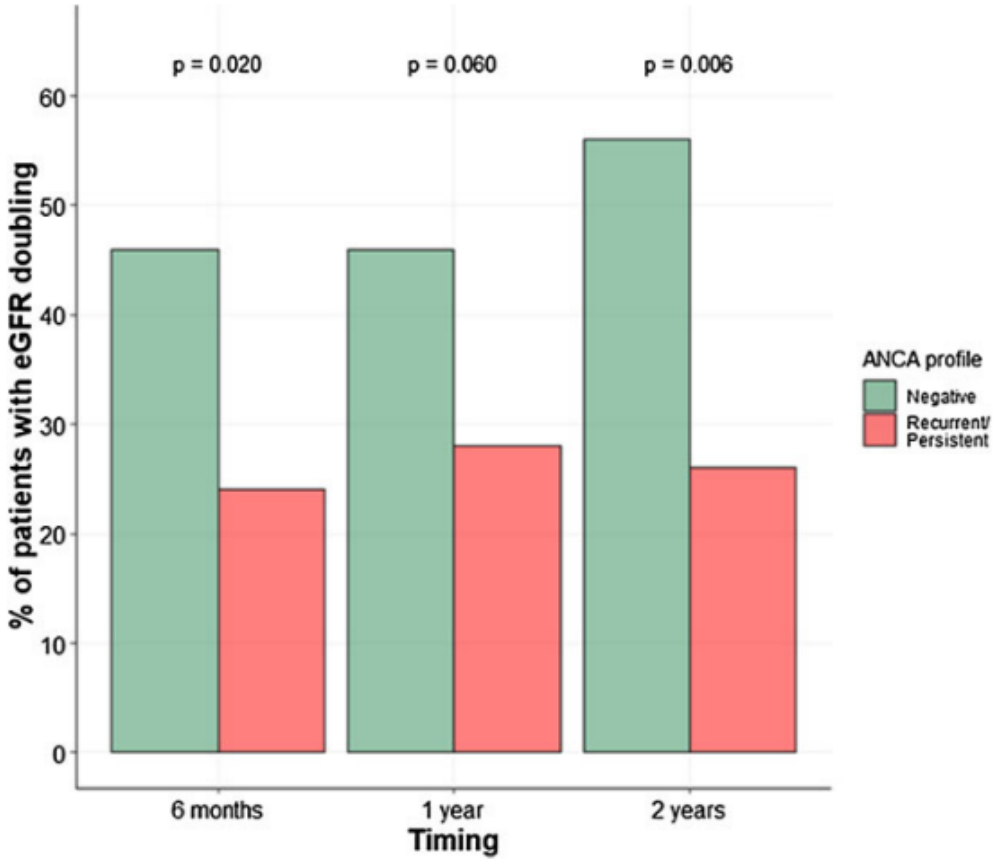
Stone J et al. NEJM 2010



Charles P. et al. Ann Rheum Dis 2018

ANCA Titers and Kidney Outcome

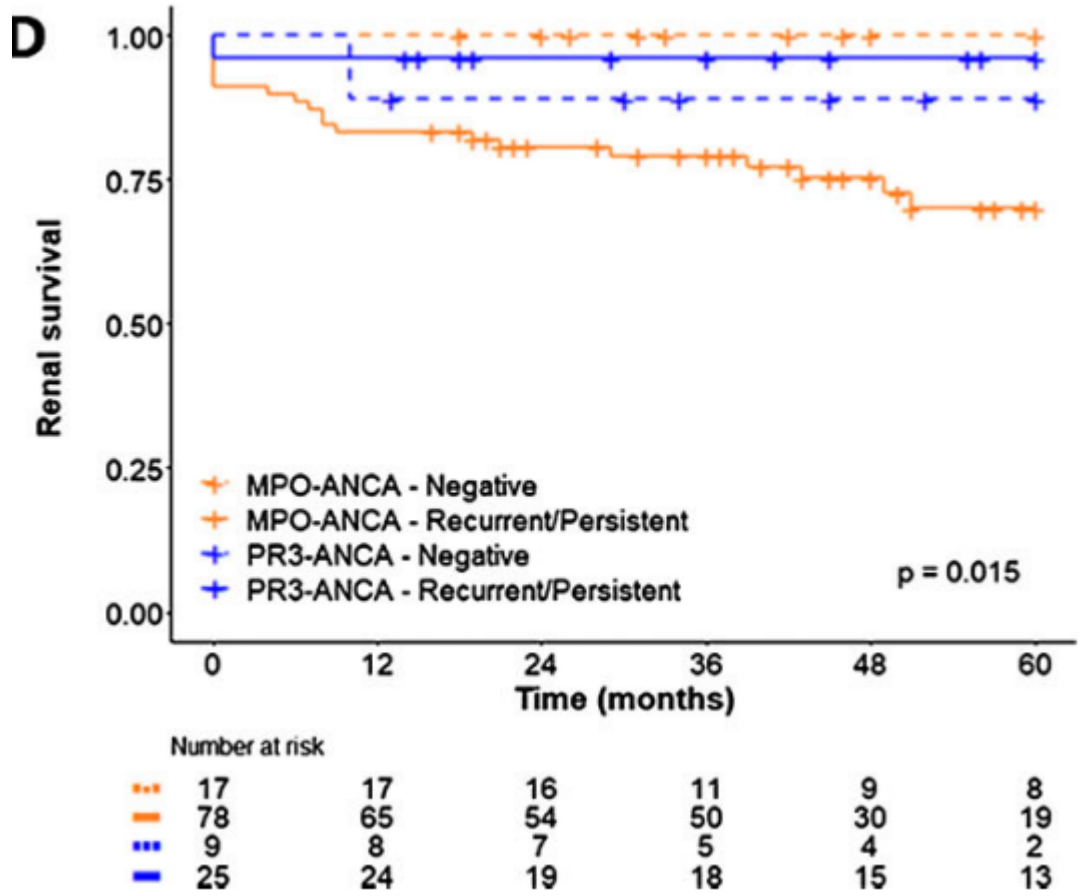
↓ Renal recovery in recurrent/persistent profile



N=134

Baseline GFR 18 vs 23 ml/min/1.73m2

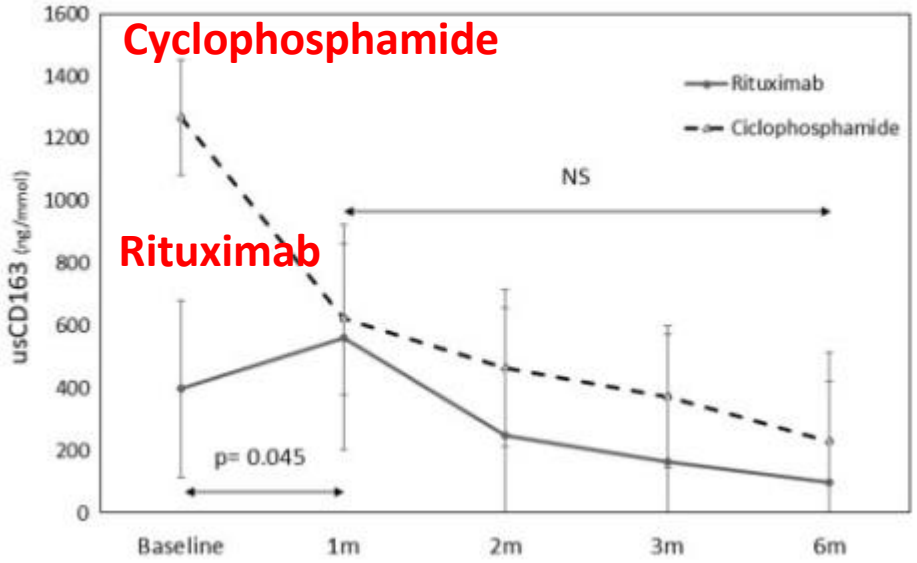
↓ Renal survival in recurrent/persistent profile

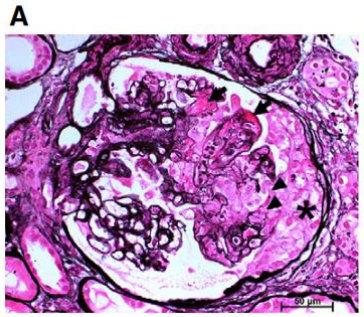


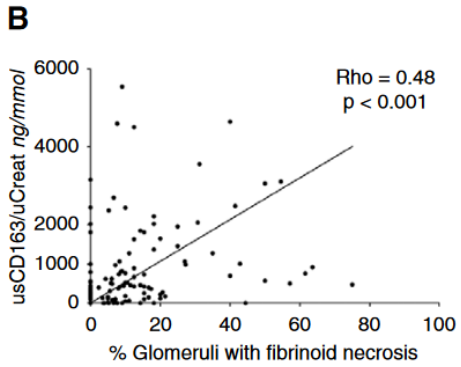
Samoreau C et al. Nephrol Dial Transplant. 2022

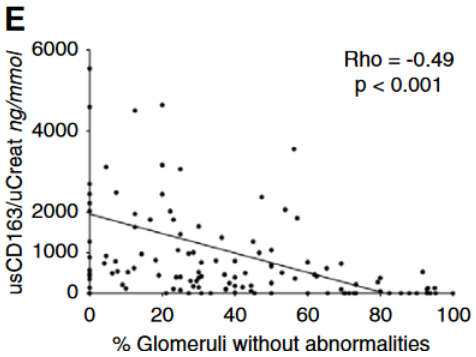
Novel Markers monocytes-macrophages

CD163 υποδοχέας
μονοκυττάρων-μακροφάγων
(M2)









10% with active disease normal levels CD163

Markers	Cutoff	AUC (95% CI)
AKI		0.66 (0.48 to0.83)
New-onset haematuria		0.58 (0.38 to 0.78)
Proteinuria	0.60 g/d	0.78 (0.64 to 0.91)
C-reactive protein	10 mg/L	0.62 (0.43 to 0.81)
Urinary soluble CD163	30 ng/mmol	0.94 (0.88 to 1.00)

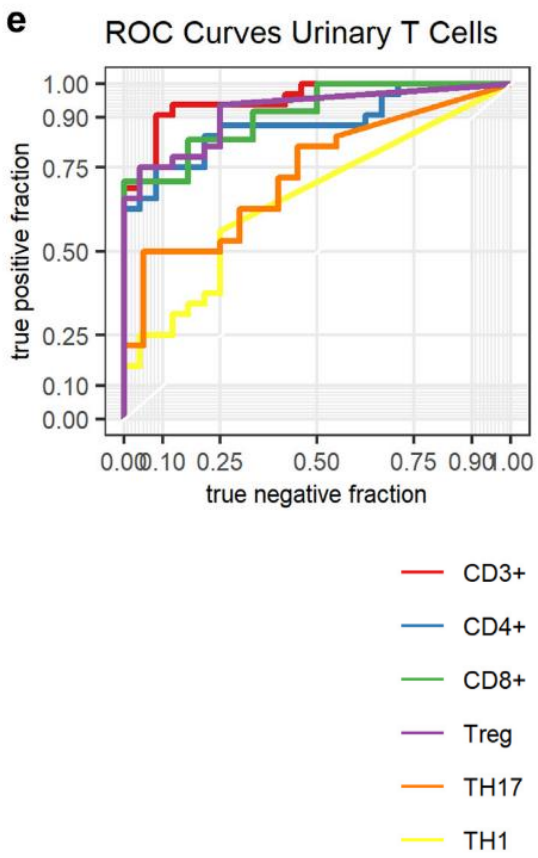
Villacorta J. et al. CKJ. 2021

Aendekerk J. et al. CJASN 2020

Novel Markers

T cells

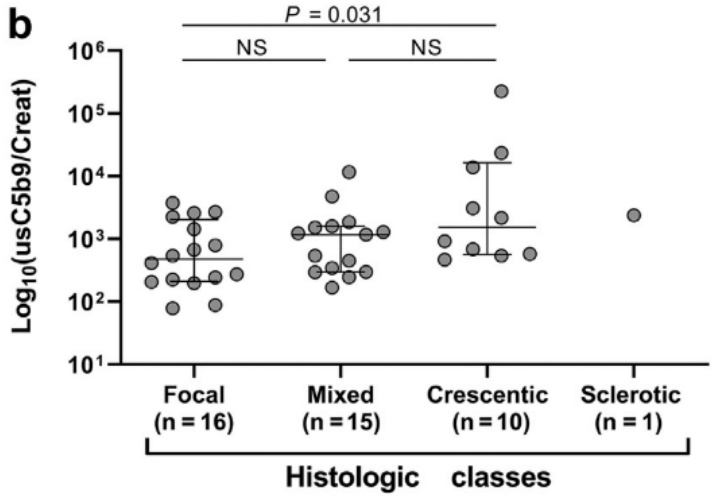
Inception cohort				
Urinary marker	**AUC**	**cut off**	**sens**	**spec**
$CD3^+$	0.95	3149	0.94	0.92
$CD4^+$	0.88	664	0.74	0.92
$CD8^+$	0.91	1321	0.71	1.00
T_{reg}	0.92	60	0.74	0.96
T_H17	0.73	103	0.48	0.95
T_H1	0.66	1	0.58	0.75
Erys dipstick	0.98	3+	0.88	1.00
Prot dipstick	0.81	1+	0.96	0.52
Active sediment[a]	0.89	y	0.79	1.00
sCD163/crea	0.78	40.88	0.72	0.83
MCP1/crea	0.82	0.44	0.72	0.92
sCD25/crea	0.54	0.52	0.42	0.77
C5a/crea	0.73	2.93	0.84	0.67

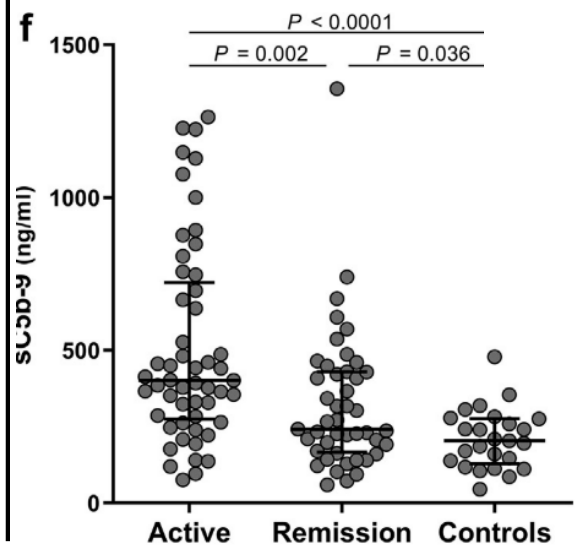


Sonnemann J. et al. KIReports. 2023

Complement

↓serum C3, FH, FB, properdin in active renal disease





urinary sC5b-9

Continente L. et al. Kidney Int. 2024

Take Home Messages

- **Renal response/remission** is a crucial measure and avoiding ESKD is one of the main goals in the therapy of AAV with kidney disease.
- The **BVAS tool** is the currently approved index for determining remission of AAV yet the kidney parameters are arbitrary and function poorly in determing severity, remission or relapse.
- **Persisting urine abnormalities** (haematuria/proteinuria/albuminuria) are associated with worst kidney outcomes.
- **Repeating a kidney biopsy** whenever uncertainty about full remission remains at the end of the induction phase of treatment (risk of providing a sampling error in focal disease).

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