Rapidly Progressive Glomerulonephritis

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Asymptomatic

Isolated proteinuria 150 mg to 3 g/day

Hematuria > 2 red blood cells (RBC)/high-power field in spun urine (RBC usually dysmorphic)

Nephrotic syndrome

- Proteinuria
  - Adult >3.5 g/day
  - Child > 40 mg/h per m^2
- Edema
- Hypoalbuminemia <3.5 g/dl
- Hypercholesterolemia
- Lipiduria

Nephritic syndrome

- An abrupt onset of glomerular hematuria (RBC cast or dysmorphic RBCs)
- Proteinuria <3 g/day
- Azotemia
- Edema
- Oliguria
- Recent onset hypertension

Rapidly progressive glomerulonephritis

- Glomerular disease characterized by extensive crescents (usually >50%)
- A rapid loss of renal function (usually a 50% decline in GFR within 3 months)

Chronic glomerulonephritis

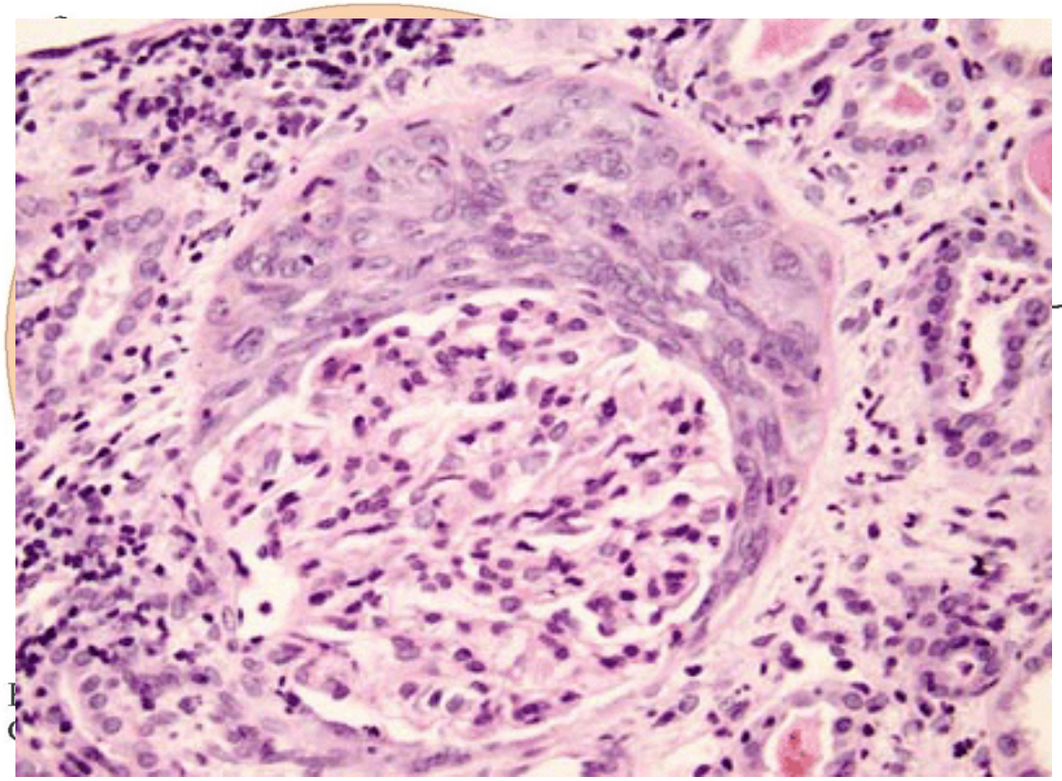
- Slowing developing renal insufficiency
- Proteinuria > 3 g/day and hematuria
- Hypertension
- Shrunken smooth kidneys

Satirapoj B. Common Problems in Internal Medicine. Bangkok 2010. p. 498-513.

Manifestation of glomerular diseases

Disease	Nephrotic features	Nephritic features
Minimal change glomerulopathy	++++	-
Membranous glomerulopathy	++++	+
Focal segmental glomerulosclerosis	+++	++
Fibrillary glomerulonephritis	+++	++
Mesangioproliferative glomerulopathy (IgAN, LN)	++	++
Membranoproliferative glomerulonephritis (MPGN)	++	+++
Proliferative glomerulonephritis (IgAN, LN)	++	+++
Acute diffuse proliferative glomerulonephritis (PSGN)	+	++++
Crescentic glomerulonephritis	+	++++

Adapted from Brenner & Rector's the kidney 10th edition, 2016



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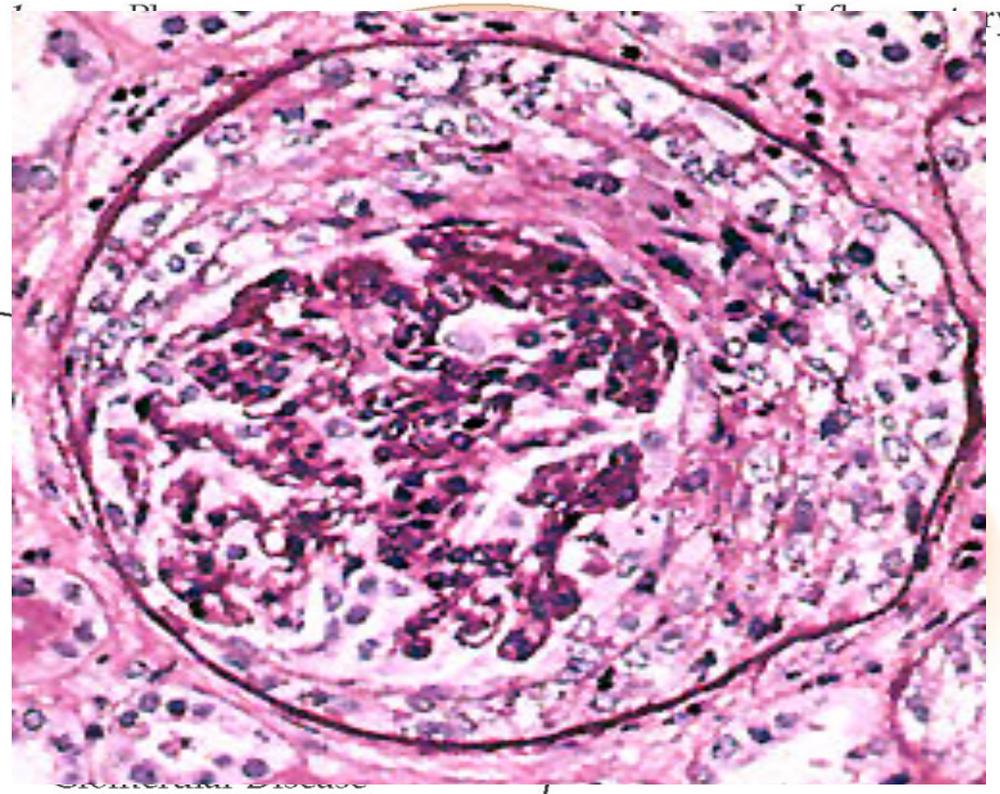

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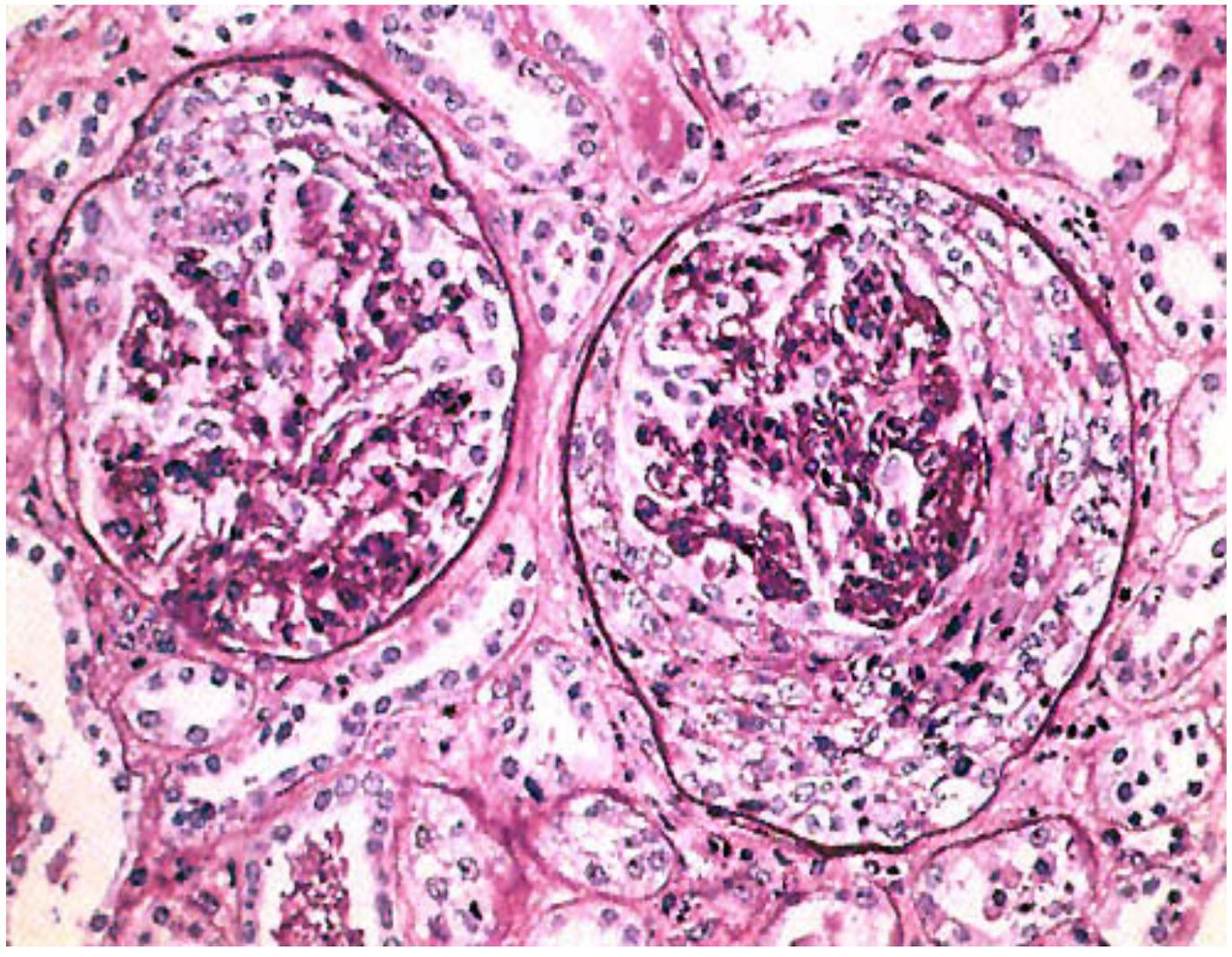
Infiltrating Macrophage

Interstitial Fibroblast

Fibrocellular Crescent

Proliferating Parietal Epithelial Cells

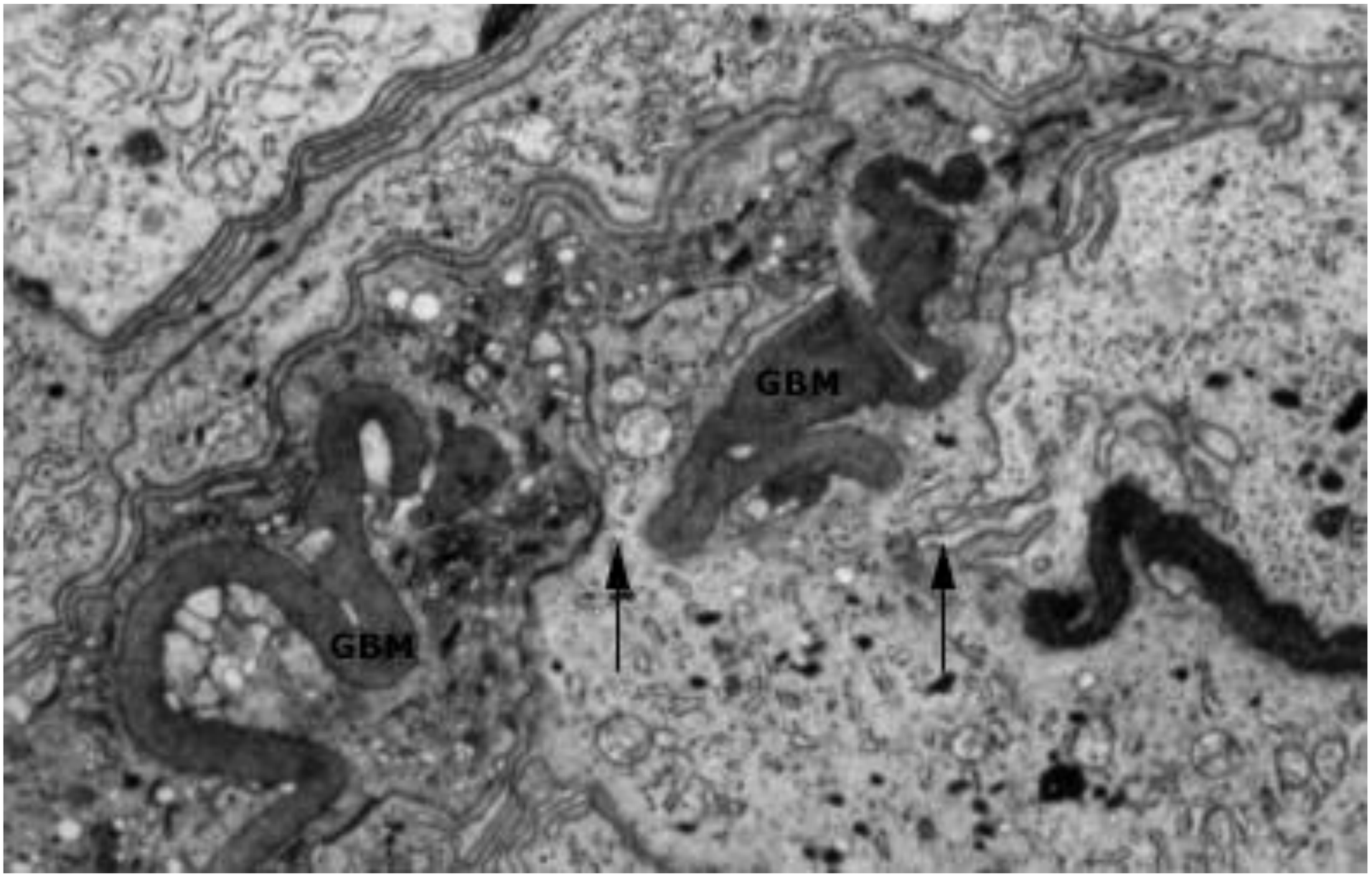
RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS



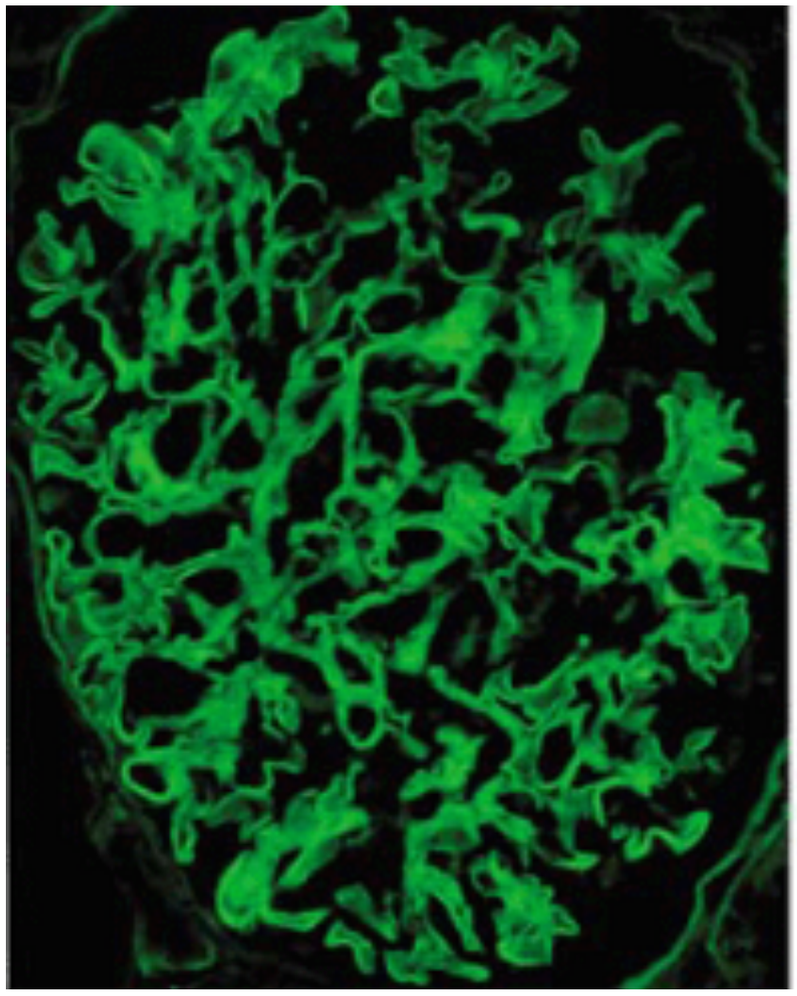
Crescentric glomerulonephritis

Collapsed glomerular tuft and crescent-shaped mass of proliferating parietal epithelial cells

Breaks in the glomerular basement membrane

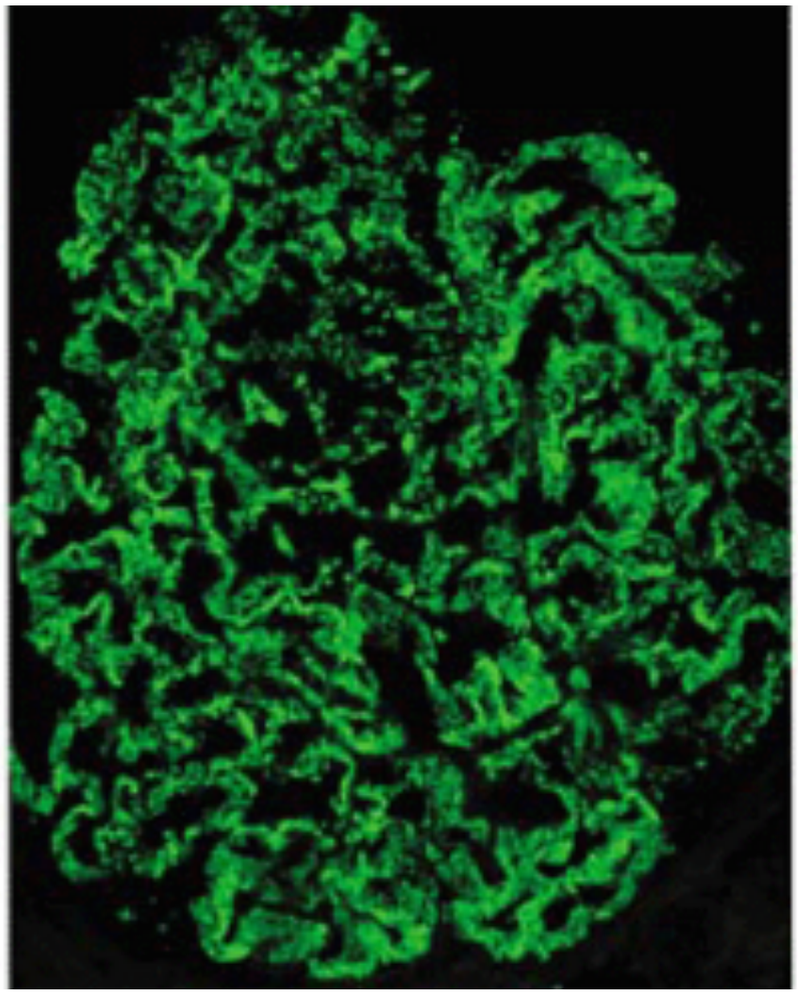


Type of RPGN



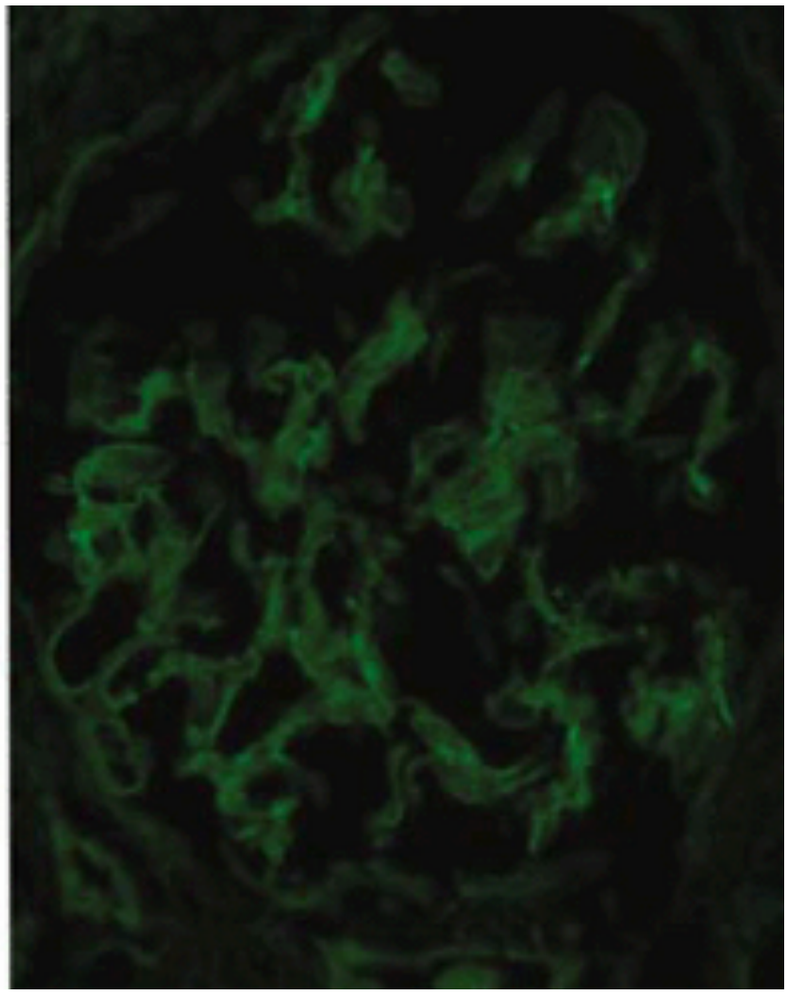
Linear staining for IgG

Anti-GBM GN



Granular staining

Immune complex GN



Pauci immune staining

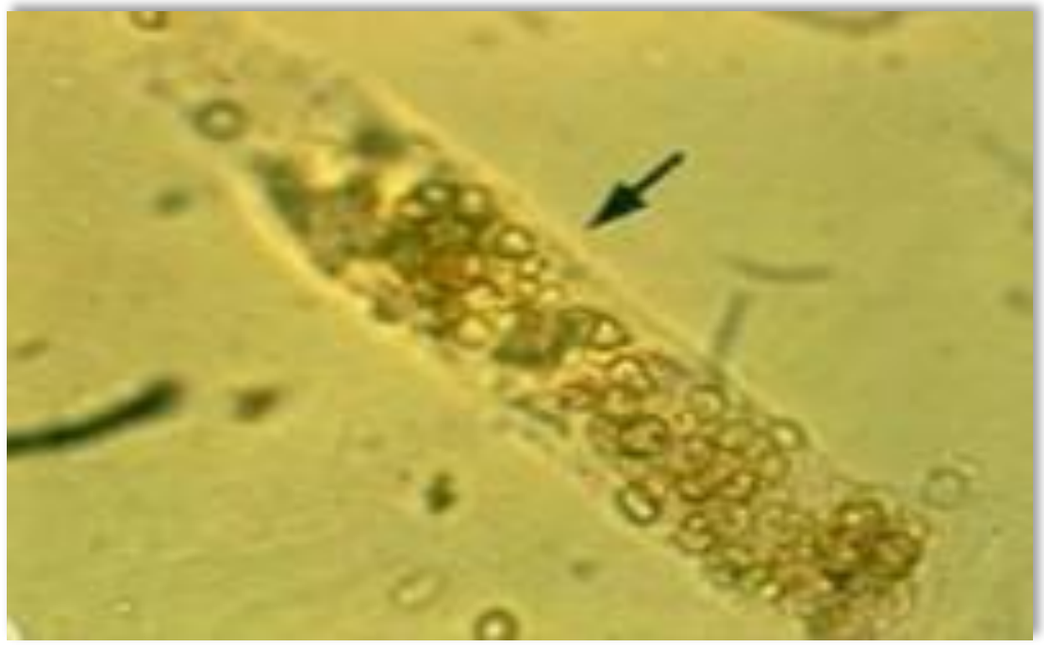
ANCA GN

Immunopathologic categories

- Type I: Anti- GBM crescentic glomerulonephritis
- Type 2: Immune-complex crescentic GN
- Type 3: Pauci-immune crescentic glomerulonephritis
- Type 4: Double-antibody positive disease: types 1+3
- Type 5: Pauci-immune crescentic glomerulonephritis with ANCA negative

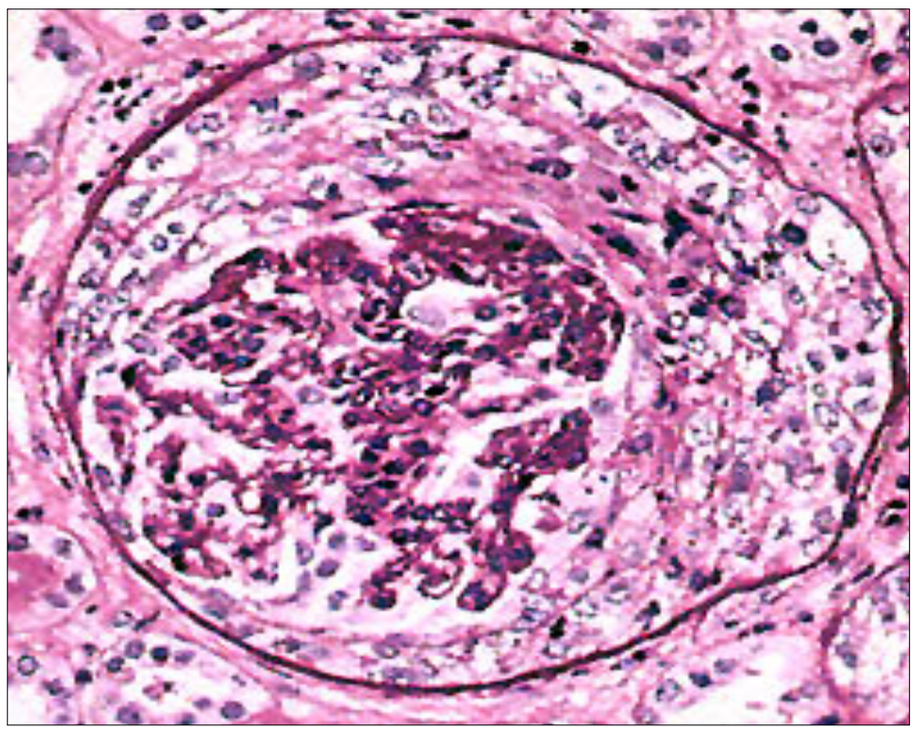
RPGN: Clinical features

- Acute nephritic picture
- Dysmorphic hematuria, red cell and other casts, and a variable degree of proteinuria
- Hypertension
- Hypervolemia, and edema
- Oliguria



RPGN: Clinical features

- Insidious onset with the initial symptoms being fatigue
- Almost all cases with serum Cr > 3 mg/dL
- Nephrotic syndrome is unusual



Frequency of different types of crescentic glomerulonephritis

Categories of RPGN	Age			
	10–19 (n=20)	20–39 (n=42)	40–64 (n=61)	>65 (n=66)
Anti-GBM mediated glomerulonephritis	15%	24%	2%	11%
Immune complex mediated glomerulonephritis	50%	48%	30%	8%
Pauci-immune glomerulonephritis	35%	28%	69%	82%

Jennette JC. Kidney Int 2003;63:1164–77.

Evaluation

- Serologic tests
- Anti-GBM antibodies
- Immune complex
  - Complement component assays
  - Antinuclear antibodies
  - Cryoglobulinemia
  - ASO titer
- ANCA antibodies

Serologic analysis of patients with RPGN

Positive anti-GBM antibodies		Positive immune complex		Positive ANCA	
Anti-GBM GN		**Immune complex GN**		**ANCA GN**	
Lung hemorrhage	Goodpasture syndrome	ANA	Lupus nephritis	No extra renal disease	ANCA associated GN
No lung hemorrhage	Anti-GBM GN	Antipathogen antibodies	Postinfectius GN	Systemic necrotizing vasculitis	Microscopic polyangiitis
		IgA	IgA nephropathy	Respiratory necrotizing granulomas	Granulomatosis with polyangiitis
		Cryoglobulin	Cryoglobulinemic GN	Asthma and eosinophilia	Eosinophilic granulomatosis with polyangiitis
		C3 nephritic factor	MPGN		

Serologic analysis of patients with RPGN

Positive anti-GBM antibodies

Positive immune complex

Positive ANCA

Anti-GBM GN

Immune complex GN

ANCA GN

Lung hemorrhage

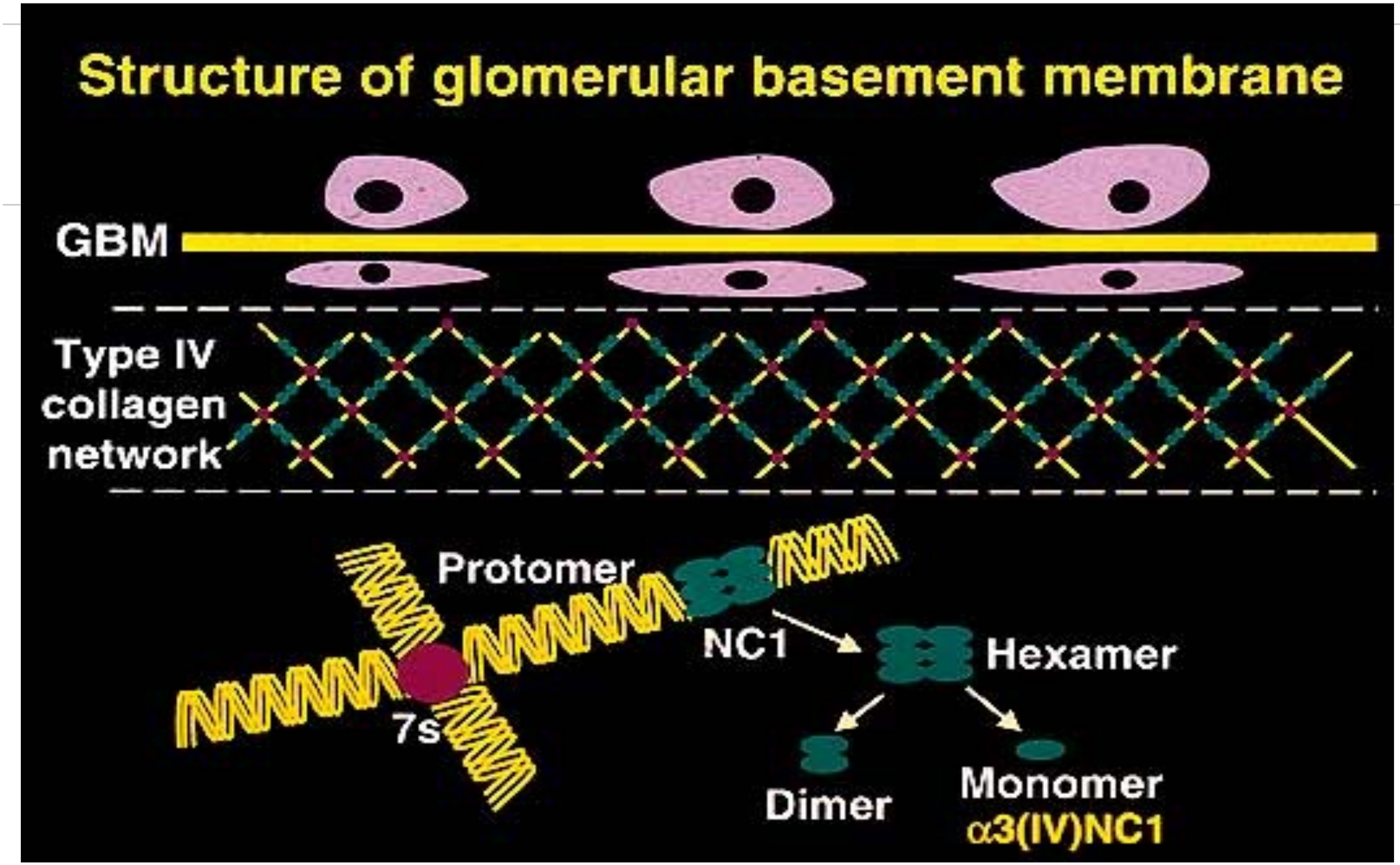
No lung hemorrhage

Goodpasture syndrome

Anti-GBM GN

Anti–GBM GN: Clinical features

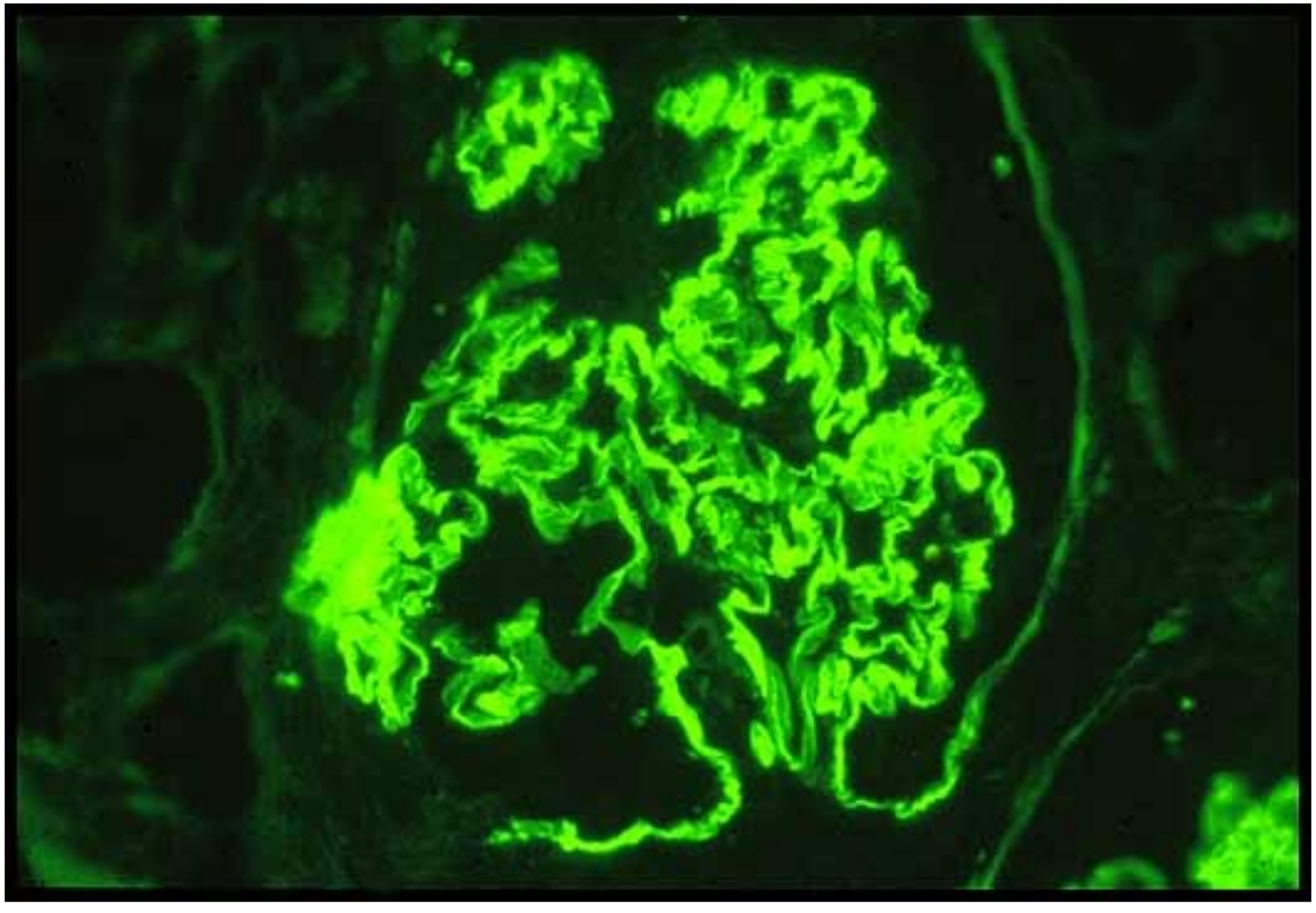
- Peak incidence in the third and sixth decades
- Malaise, fatigue, and weight loss, and anemia from pulmonary hemorrhage or to the effects of uremia
- Pulmonary hemorrhage and hemoptysis in anti–GBM disease
- Renal disease progresses rapidly and rarely resolves spontaneously



Main target of the autoantibodies is the noncollagenous domain (NC1) of the α 3 chain of type IV collagen.

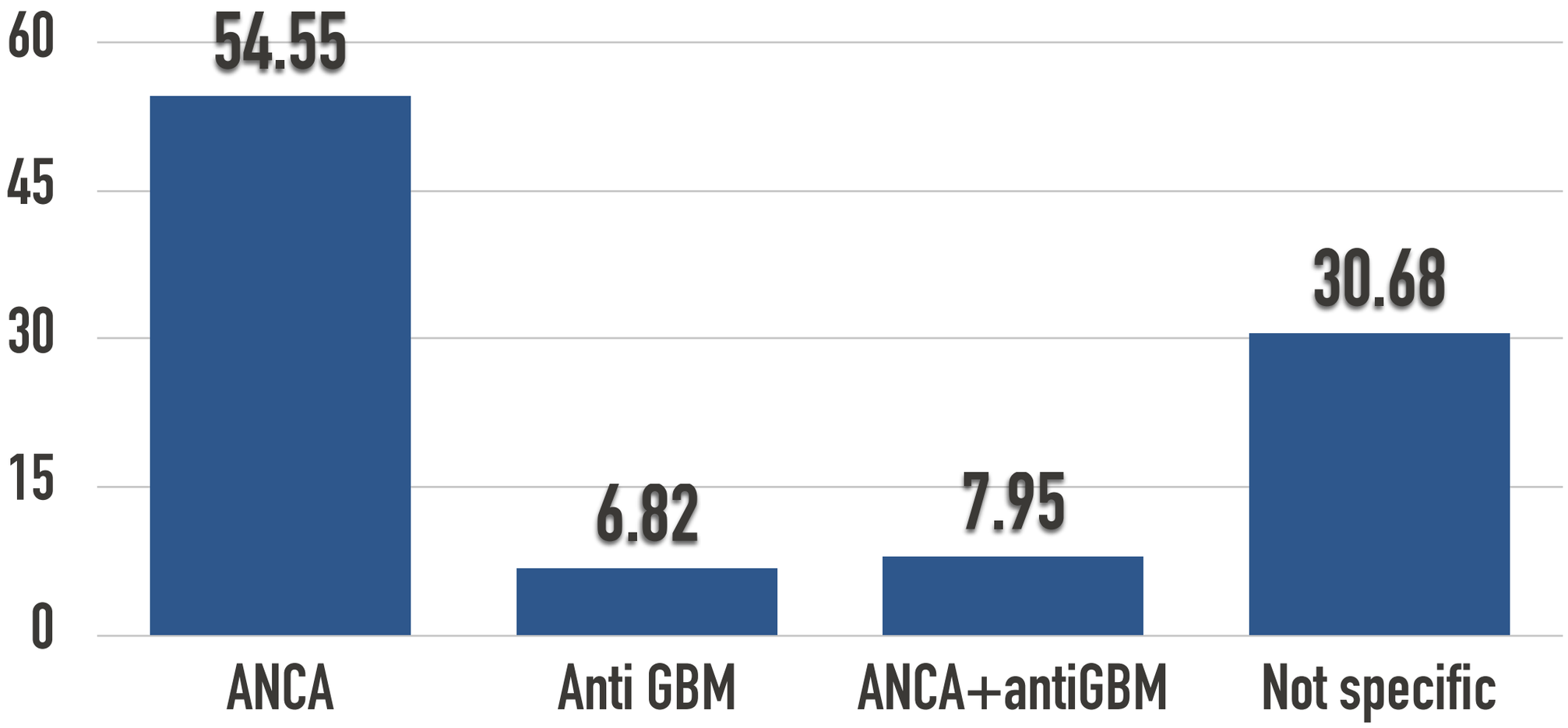
Hellmark T, et al. Kidney Int . 1999: 55:936–44.

Linear deposition of IgG/C3 along glomerular basement membrane



Pulmonary hemorrhage and nephritis

Pulmonary renal syndrome



Niles JL, et al. Arch Intern Med 1996; 26;156(4):440-5.

Initial treatment of RPGN

- Aggressive immunosuppressive agents
  - Intravenous methylprednisolone (IVMP) 500–1000 mg/day x 3 days
  - Cyclophosphamide (IVCY/Oral CY)

- Need to be confirm definite diagnosis for further Rx
  - Serology + kidney biopsy

Treatment of anti-GBM GN

- IV methylprednisolone 500-1000 mg/day x 3 days and then prednisoone 1 mg/kg/day for first week then reduce at weekly intervals to 45, 30, 25, 20, 15, 10 and 5 mg/day

- Cyclophosphamide: 2 mg/kg/day for 3 months

- Plasma exchange: 4 L exchanges daily with albumin as replacement solution x 14 days or no detection of anti-GBM ab

Outcome of patients with Goodpasture's disease

	Number of patients	1-year patient survival %	1-year renal survival %	Renal recovery if initial creatinine >600 μmol/L (6.6 mg/dL) % *treated patients*
Johnson et al [85]	17	94	45	0
Walker et al [86]	22	59	45	18
Savage et al [68]	59	75	8.5	NA[a]
	49	84	35	11
Bouget et al [87]	14	79	29	0
Herody et al [88]	29	93	41	0
Merkel et al [89]	35	89	40	6
Daly et al [90]	40	—	20	0

Pusey CD, et al. Kidney Int, 2003: 64: 1535–50.

Summary: Treatment of anti-GBM GN

- Initiating cyclophosphamide and corticosteroids plus plasmapheresis in all patients
- Except those who are dialysis-dependent at presentation, 100% crescents and no pulmonary hemorrhage (1B)
- No maintenance Rx for anti-GBM GN (1D)
- Defer kidney transplantation until undetected anti-GBM antibodies for a minimum of 6 months

KDIGO. Kidney International Supplements (2012)

Serologic analysis of patients with RPGN

Positive anti-GBM antibodies	Positive immune complex	Positive ANCA
Anti-GBM GN	Immune complex GN	ANCA GN

ANA	Lupus nephritis
Antipathogen antibodies	Postinfectius GN
IgA	IgA nephropathy
Cryoglobulin	Cryoglobulinemic GN
C3 nephritic factor	MPGN

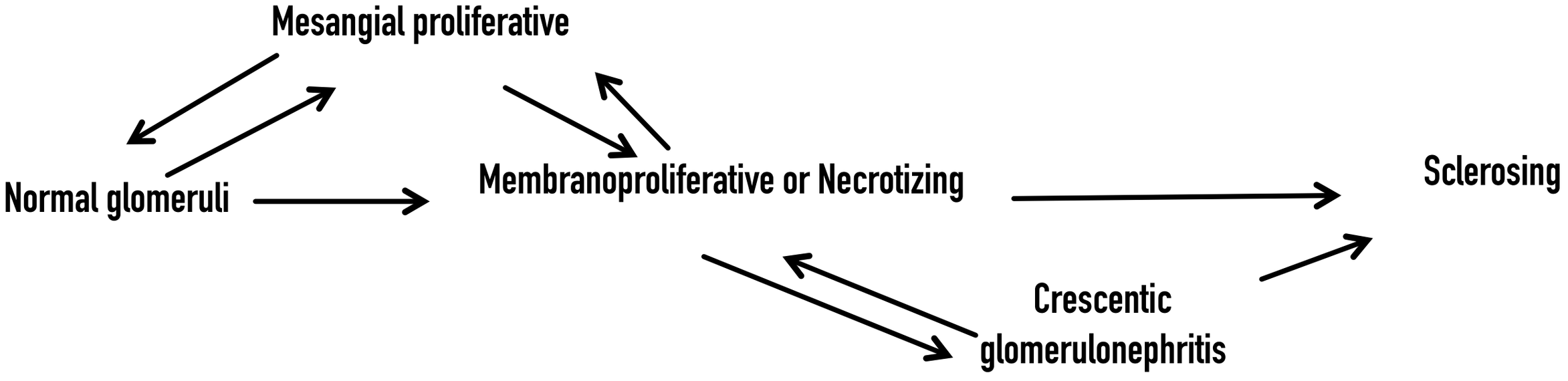
IgA nephropathy

Lupus nephritis

Clinical presentation

Asymptomatic hematuria/proteinuria	Acute nephritic/ Nephrotic syndrome	Rapidly progressive Glomerulonephritis	Chronic Glomerulonephritis

Renal pathology



IgA nephropathy: Clinical feature

- Wide spectrum of clinical presentations
- Recurrent macroscopic hematuria provoke by mucosal infection (synpharyngitis) (40–50%)
- Microscopic hematuria with or without proteinuria (30–40%)
- Nephrotic syndrome (5%)
- RPGN (<10%)

Variants of IgA nephropathy

- MCD with mesangial IgA deposits
  - Treatment as for MCD in nephrotic patients showing pathological findings of MCD with mesangial IgA deposits on kidney biopsy (2B)
- Crescentic IgA Nephropathy
  - Steroids and cyclophosphamide, analogous to the treatment of ANCA vasculitis (2D)

KDIGO. Kidney International Supplements (2012) 2, 143–153

Serologic analysis of patients with RPGN

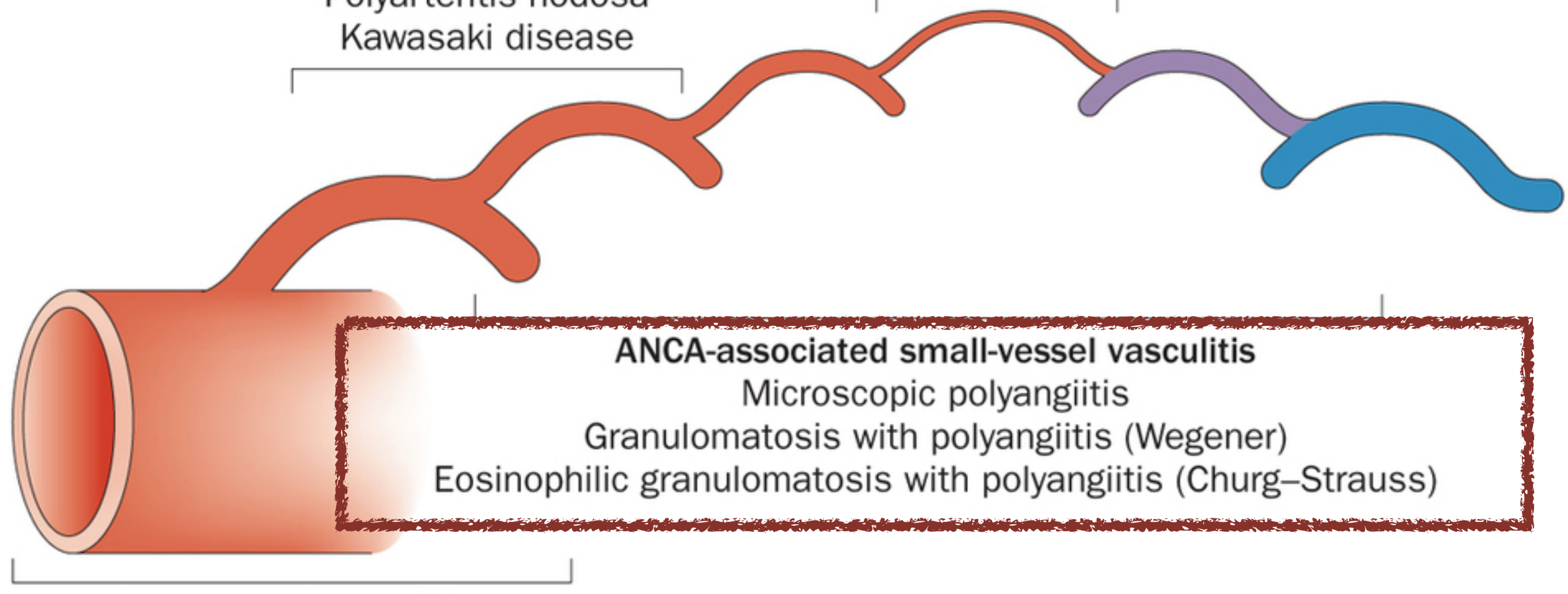
Positive anti-GBM antibodies	Positive immune complex	Positive ANCA
Anti-GBM GN	Immune complex GN	ANCA GN

No extra renal disease	ANCA associated GN
Systemic necrotizing vasculitis	Microscopic polyangiitis
Respiratory necrotizing granulomas	Granulomatosis with polyangiitis
Asthma and eosinophilia	Eosinophilic granulomatosis with polyangiitis

Immune complex small-vessel vasculitis
Cryoglobulinemic vasculitis
IgA vasculitis (Henoch–Schönlein)
Hypocomplementemic urticarial vasculitis
(Anti-C1q vasculitis)

Medium-vessel vasculitis
Polyarteritis nodosa
Kawasaki disease

Anti-GBM disease



ANCA-associated small-vessel vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegener)
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)

Large-vessel vasculitis
Takayasu arteritis
Giant cell arteritis

Jennette, J. C. et al. Arthritis Rheum. 2013: 65, 1–11.

Pauci-immune RPGN

- Systemic vasculitis
  - Systemic complaints
    - Constitutional symptoms, such as fever, myalgia, anorexia, weight loss, malaise, and night sweats
- Renal-limited vasculitis

Kain R; et al. Nat Med. 2008; 14:1088–96.
Salama AD. Kidney Int. 2009;76(1):15–7.

American College of Rheumatology: Wegener's granulomatosis

- Nasal or oral inflammation (painful or painless oral ulcers or purulent or bloody nasal discharge)
- Abnormal chest radiograph showing nodules, fixed infiltrates, or cavities
- Abnormal urinary sediment (microscopic hematuria with or without red cell casts)
- Granulomatous inflammation on biopsy of an artery or perivascular area

>2 criteria: a sensitivity of 88 % and a specificity of 92 %

Leavitt RY, et al. Arthritis Rheum 1990;33(8):1101–7.

Granulomatosis with polyangiitis (Wegener's): an alternative name for Wegener's granulomatosis

Falk RJ, et al. J Am Soc Nephrol. 2011;22(4):587.

Granulomatosis with polyangiitis (GPA)

Symptoms
(1) E symptoms
Nose (purulent rhinorrhea, epistaxis, and saddle nose)
Eyes (ophthalmic pain, visual disturbance, and exophthalmia
Ears (otalgia and otitis media)
Throat (pharyngeal ulcer, hoarseness, and laryngeal obstruction)
(2) L symptoms
Bloody sputum, cough and dyspnea
(3) K symptoms
Hematuria, proteinuria, rapidly progressive renal failure, edema and hypertension
(4) Others due to vasculitis:
General symptoms: fever (38c or higher, 2 weeks or longer), weight loss (6 kg or more for 6 months)
Local symptoms: purpura, polyarthritis, episcleritis, mononeuritis multiplex, ischemic heart disease, gastrointestinal bleeding and pleuritis

2. Histological findings
Necrotizing granulomatous vasculitis with giant cells at the sites of E, L and/or K
Necrotizing crescentic glomerulonephritis without immune deposits
Necrotizing granulomatous vasculitis of arterioles, capillaries, and venules
3. Laboratory findings
Positive PR3-ANCA or C-ANCA

Ozaki S. Allergol Int 2007;56:87–96.

Granulomatosis with polyangiitis (GPA)

Definite diagnosis
(1) Positive for 3 or more of the symptoms including E, L and K symptoms
(2) Positive for 2 or more of the symptoms and positive for ether of the histological findings
(3) Positive for 1 or more of the symptoms and positive for ether of the histological findings and positive PR3-ANCA/C-ANCA

Probable diagnosis
(1) Positive for 2 or more of the symptoms
(2) Positive for 1 or more of the symptoms and positive for ether of the histological findings
(3) Positive for 1 or more of the symptoms and positive PR3-ANCA/C-ANCA

Ozaki S. Allergol Int 2007;56:87-96.

Microscopic polyangiitis (MPA)

(1) Symptoms
(1) Rapidly progressive glomerulonephritis
(2) Pulmonary hemorrhage
(3) Symptoms due to vasculitis:
Purpura, subcutaneous hemorrhage, mononeuritis multiplex, and gastrointestinal bleeding
2. Histological findings
Necrotizing vasculitis of arterioles, capillaries, and venules and perivascular infiltration of inflammatory cells
3. Laboratory findings
(1) Positive MPO-ANCA
(2) Positive C-reactive protein
(3) Proteinuria, hematuria and rising BUN and serum creatinine

Ozaki S. Allergol Int 2007;56:87-96.

Microscopic polyangiitis (MPA)

Definite diagnosis

(1) Positive for 2 or more of the symptoms and positive histological findings

(2) Positive for 2 or more of the symptoms including the symptoms (1) and (2), and positive MPO-ANCA

Probable diagnosis

(1) Positive for 3 of the symptoms

(2) Positive for 1 of the symptoms and positive MPO-ANCA

Ozaki S. Allergol Int 2007;56:87-96.

ACR 1990 criteria of Churg–Strauss syndrome

Criteria	Remarks
1.Asthma	History of expiratory rales
2.Eosinophilia	More than 10 %
3.Mononeuropathy or polyneuropathy	Caused by systemic vasculitis
4.Pulmonary infiltrate, non-fixed	Migratory/ transitory infiltrate
5.Paranasal sinus abnormality	Clinical evidence of acute or chronic paranasal sinusitis
6.Extravascular eosinophils accumulation	

>4 criteria: sensitivity of 85 % and specificity of 99.7 %

Allergic granulomatous angiitis (AGA)

Symptoms
(1) Bronchial asthma and/or allergic rhinitis
(2) Eosinophilia
(3) Other organ symptoms:
General symptoms: fever (38c or higher, 2 weeks or longer), weight loss (6 kg or more for 6 months)
Local symptoms: purpura, polyarthritis, mononeuritis multiplex, gastrointestinal bleeding and myalgia
2. Characteristics clinical course
Symptoms (1) and (2) precede the development of (3)
3. Histological findings
(1) Granulomatous or necrotizing vasculitis of small vessels with marked infiltration of eosinophils
(2) Extravascular granulomas

Ozaki S. Allergol Int 2007;56:87–96.

Allergic granulomatous angiitis (AGA)

Definite diagnosis

(1) Positive for 1 or more of the symptoms and positive histological

(2) Positive for 3 or more of the symptoms and the characteristics clinical course

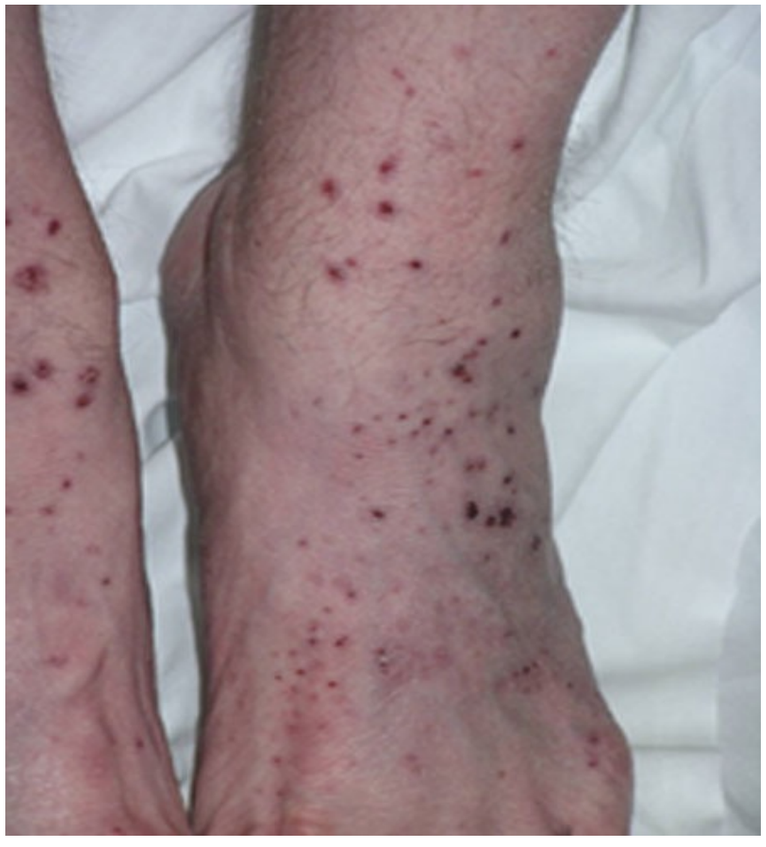
Probable diagnosis

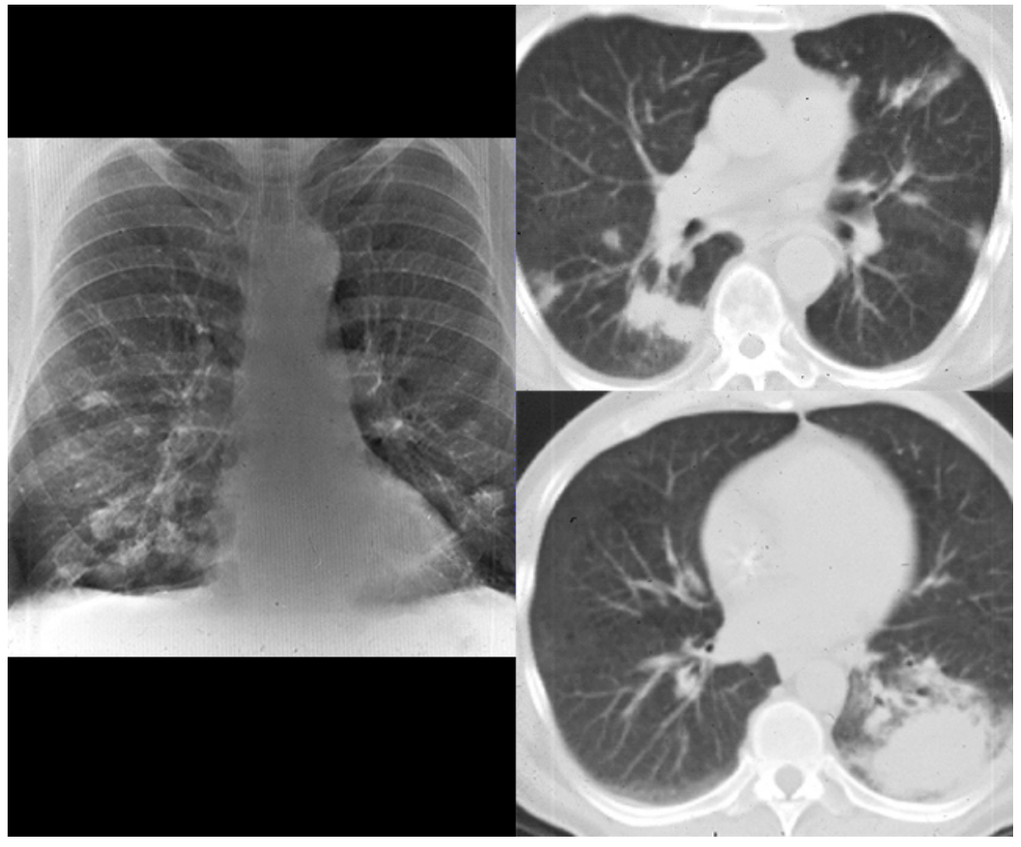
(1) Positive for 1 of the symptoms and positive histological findings

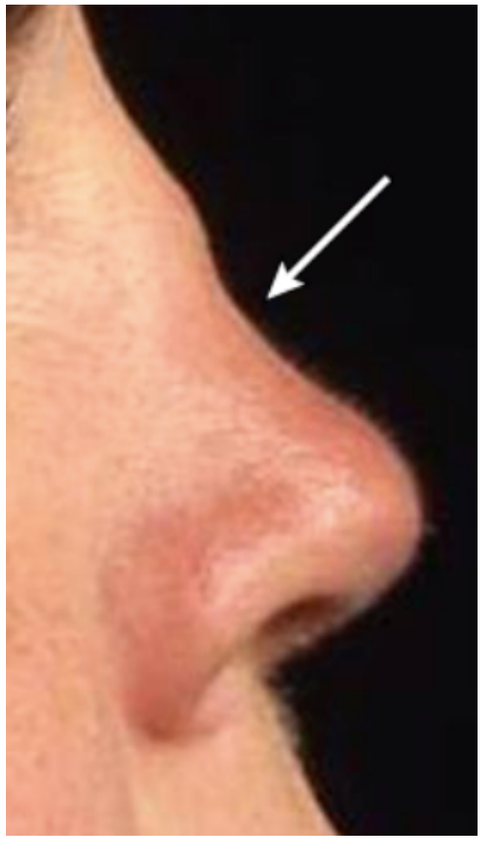
(2) Positive for 3 or more of the symptoms, but not the characteristics clinical course

Ozaki S. Allergol Int 2007;56:87–96.

Systemic vasculitis







ANCA associated Glomerulonephritis

- Pauci- immune focal and segmental necrotizing and crescentic GN
- Microscopic hematuria with dysmorphic red blood cells and red cell casts
- Proteinuria usually moderate (1–3 g/d)
- Rapidly declining GFR over days or weeks
- Few subjects: asymptomatic microscopic hematuria and minimal proteinria

Pauciimmune GN

Systemic vasculitis

Yes

- No asthma Or granulomas
  - Microscopic polyangiitis
- Granulomas and no asthma
  - Granulomatosis with polyangiitis (GPA)
- Eosinophilia asthma and granulomas
  - Allergic granulomatous angiitis (AGA)

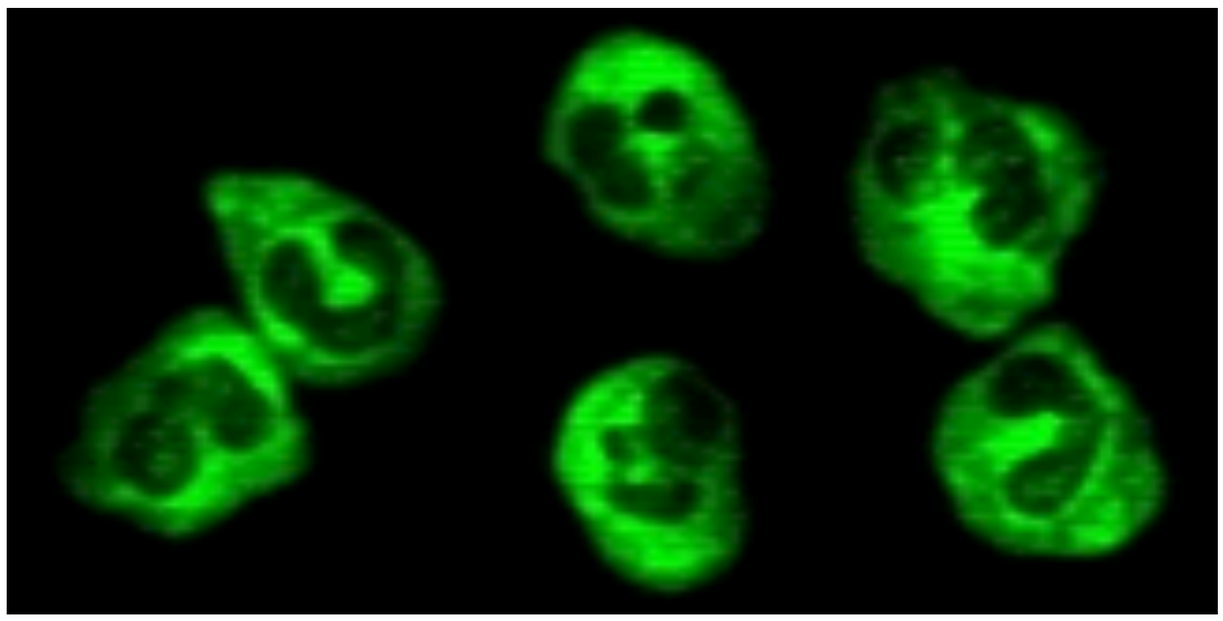
No

- PI-CGN

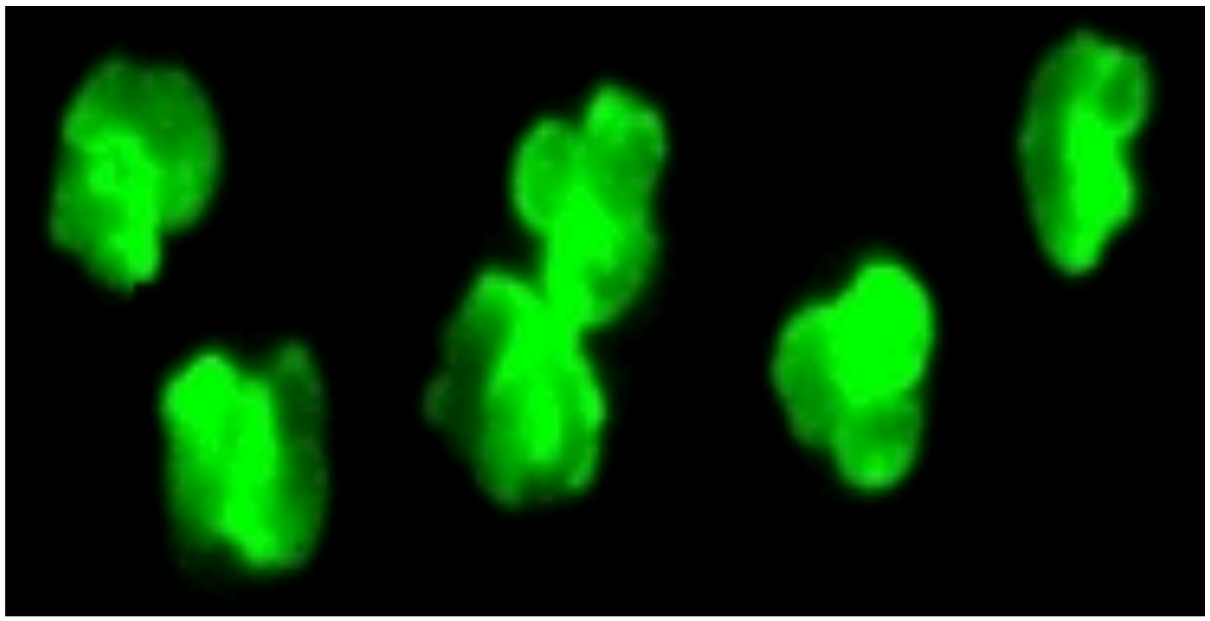
Indirect immunofluorescence

Antibodies directed against PR3	
PGA	80–90%

Antibodies directed against MPO	
Renal limited vasculitis	80%
MPA	70%
APA	70%



C-ANCA



P-ANCA

Indirect immunofluorescence assay : more sensitive

Enzyme-linked immunosorbent assay (ELISA): more specific

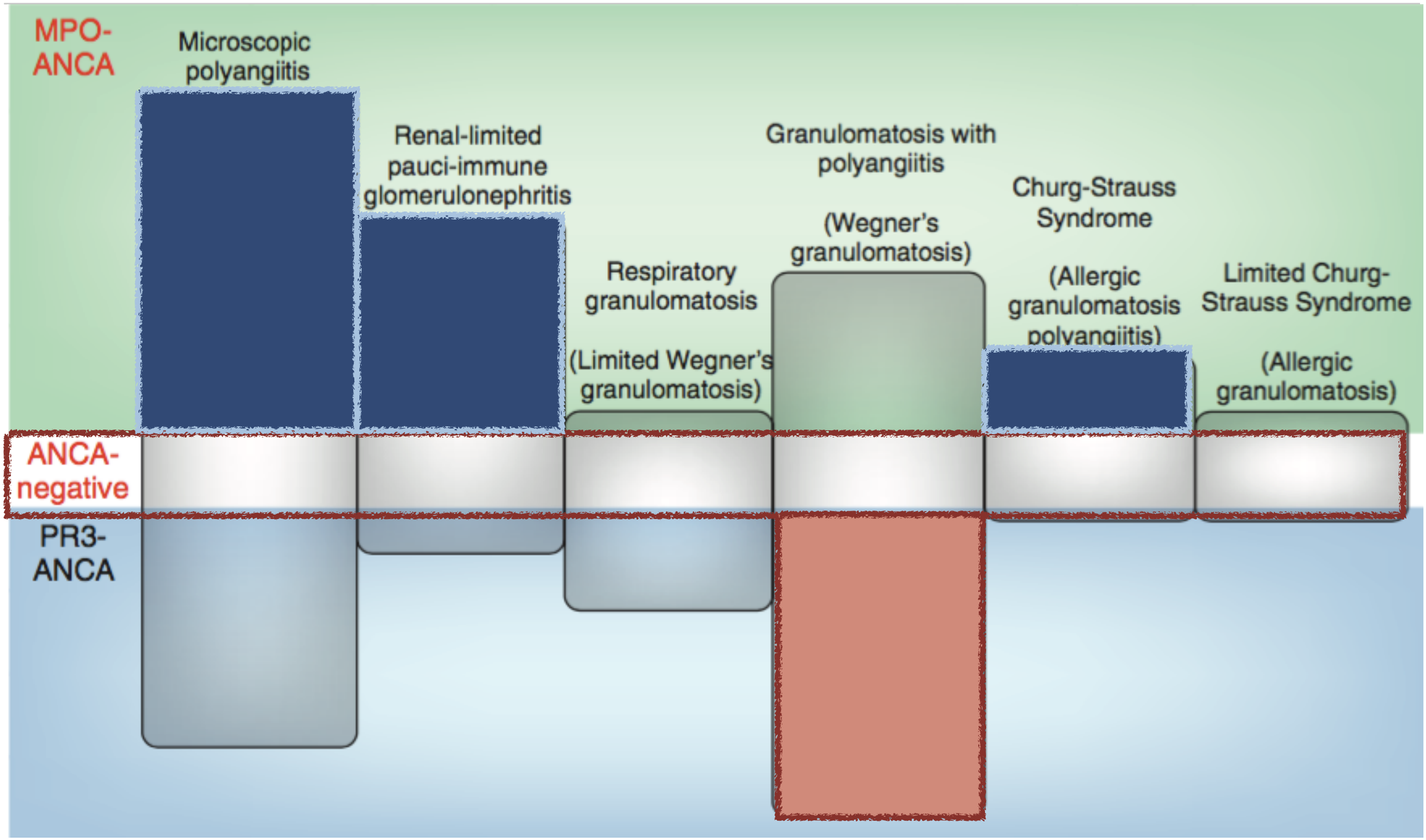
Indirect immunofluorescence

- C-ANCA pattern
  - C-ANCA high specificity > P-ANCA pattern for vasculitis
- P-ANCA
  - Variety of inflammatory illnesses, and low specificity for vasculitis.
  - Antibodies directed against lactoferrin, elastase, cathepsin G, bactericidal permeability inhibitor, catalase, lysozyme, beta-glucuronidase, etc……

ANCA in other diseases

- Autoimmune diseases
  - Systemic vasculitis : HSP, Kawasaki's disease
  - Other rheumatic disease: RA, SLE, Sjögren syndrome
  - Inflammatory bowel disease
- Infections
  - Endocarditis, respiratory tract infection, chromomycosis, HIV, amoebiasis
- Drugs
  - Propylthiouracil, hydralazine, minocycline

A proposed nomenclature for ANCA disease



Falk RJ, et al. J Am Soc Nephrol; 2010: 21: 745–752.

ANCA negative

- Up to 40 % of patients with limited PGA
- 30 % of all MPA patients
- 50 % of all APA patients
- 10 percent of patients with severe disease (RPGN)

Positive ANCA serology

Clinical presentation	Prevalence of pauci-immune GN (%)	Positive predictive value	Negative predictive value
Rapidly progressive glomerulonephritis	47	98	80
Hematuria, proteinuria, and creatinine >3 mg/dL	21	92	93
Hematuria, proteinuria, and creatinine 1.5–3 mg/dL	7	77	98
Hematuria, proteinuria, and creatinine <1.5 mg/dL	2	47	99

Jennette, JC, et al. . Kidney Int 1998; 53:796.

Positive ANCA serology

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Hematuria, proteinuria, and creatinine <1.5 mg/dL	2	47	99

Clinical presentation of RPGN: PPV at least 98 %.
Adults with hematuria, proteinuria, and a serum creatinine of less than 1.5 mg/dL: PPV only 47 %

Jennette, JC, et al. . Kidney Int 1998; 53:796.

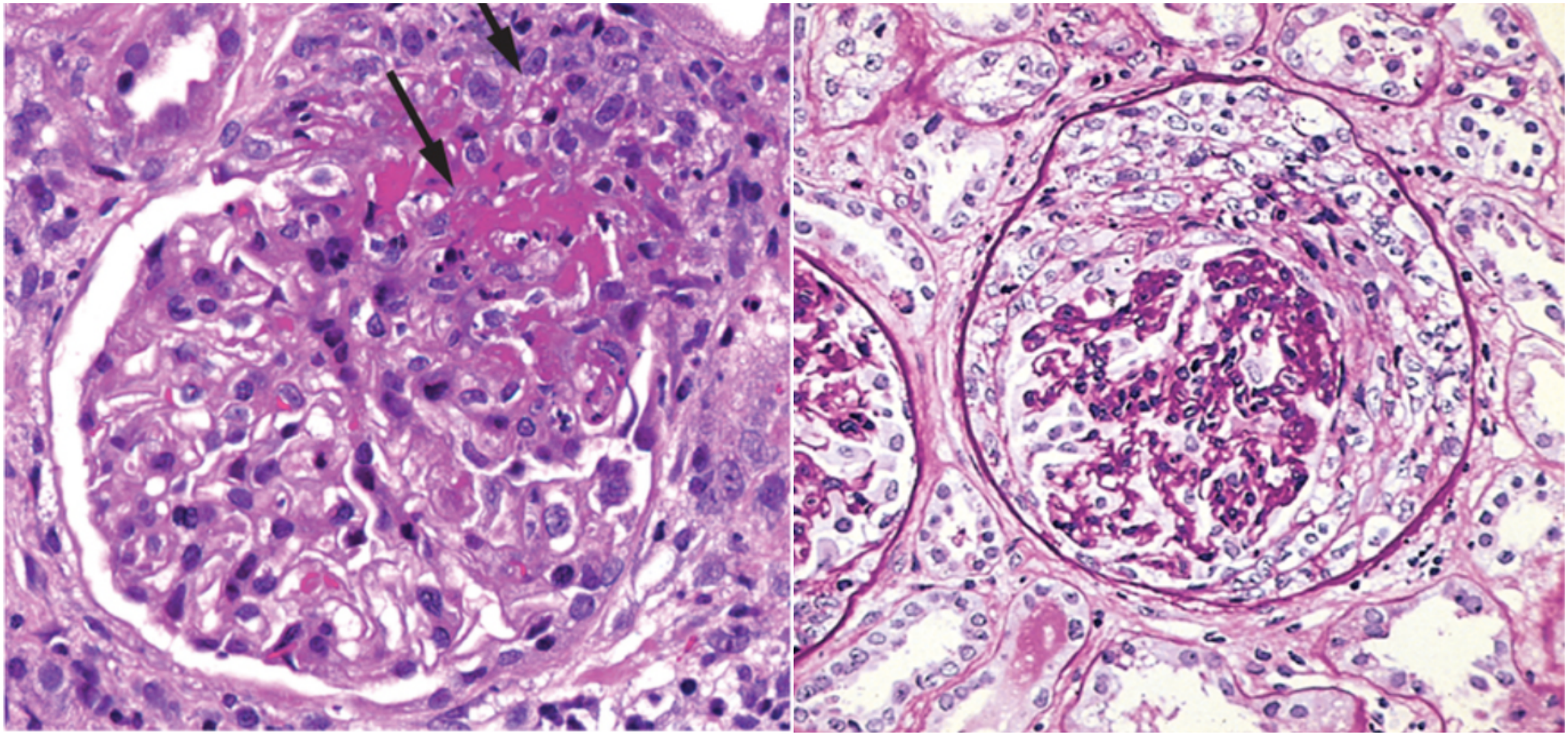
Does a rise in ANCA titers predict a disease flare?

- Closely follow patients with rising ANCA titers but not to alter their therapy unless there are clearcut clinical signs of active disease

Birck R; et al. Am J Kidney Dis. 2006;47(1):15–23.

KDIGO 2012 suggest not changing immunosuppression based on changes in ANCA titer alone. (2D)

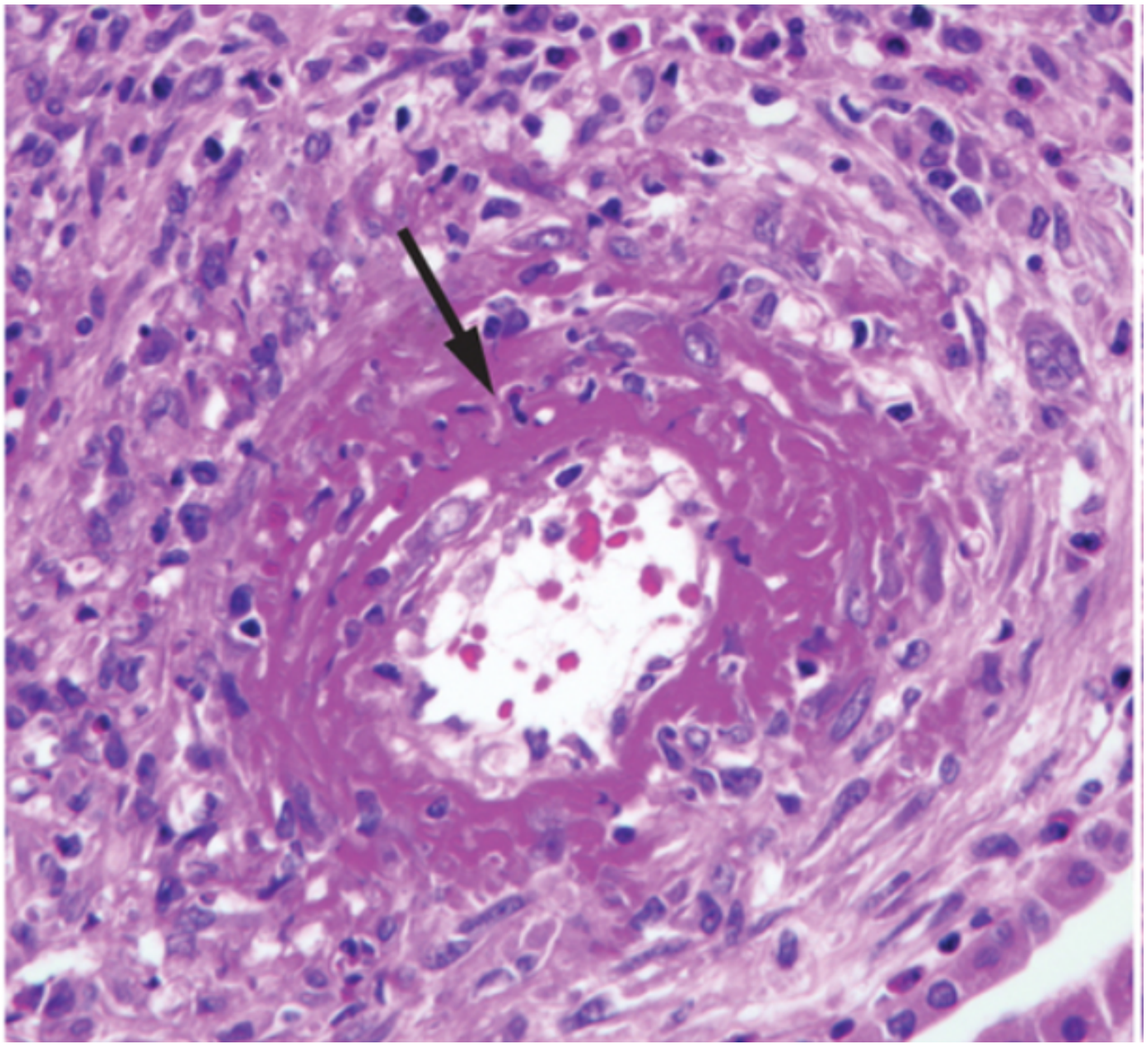
Cellular crescent composed of mononuclear leukocytes and epithelial cells



Segmental fibrinoid necrosis and cellular crescent

Jennette JC, et al. Nature Reviews Rheumatology: 2014: 10, 463–473.

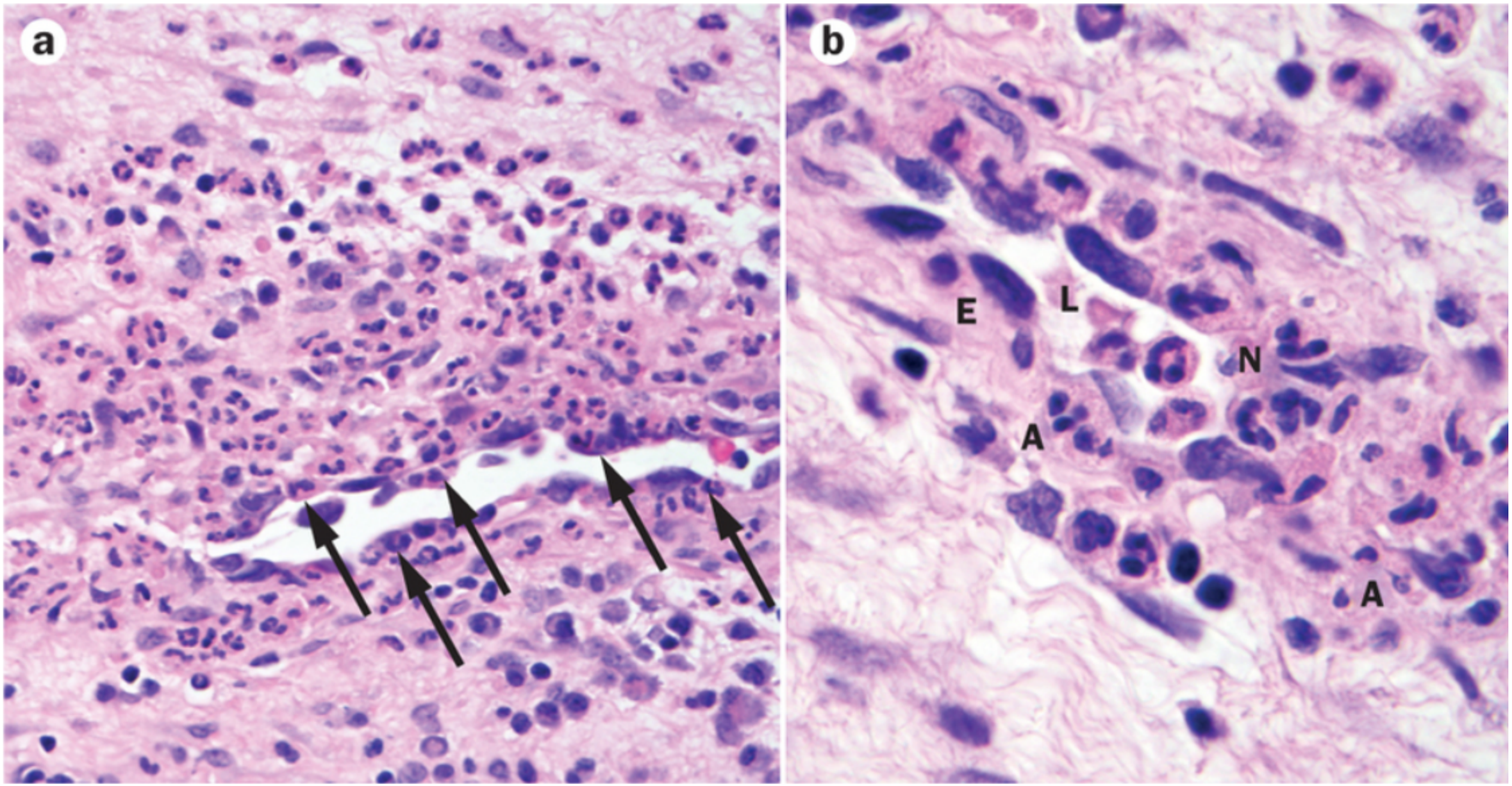
Necrotizing arteritis of a small artery in the kidney



A circumferential zone of fibrinoid necrosis (arrow) and perivascular leukocytes that, at this phase, contain predominantly mononuclear leukocytes

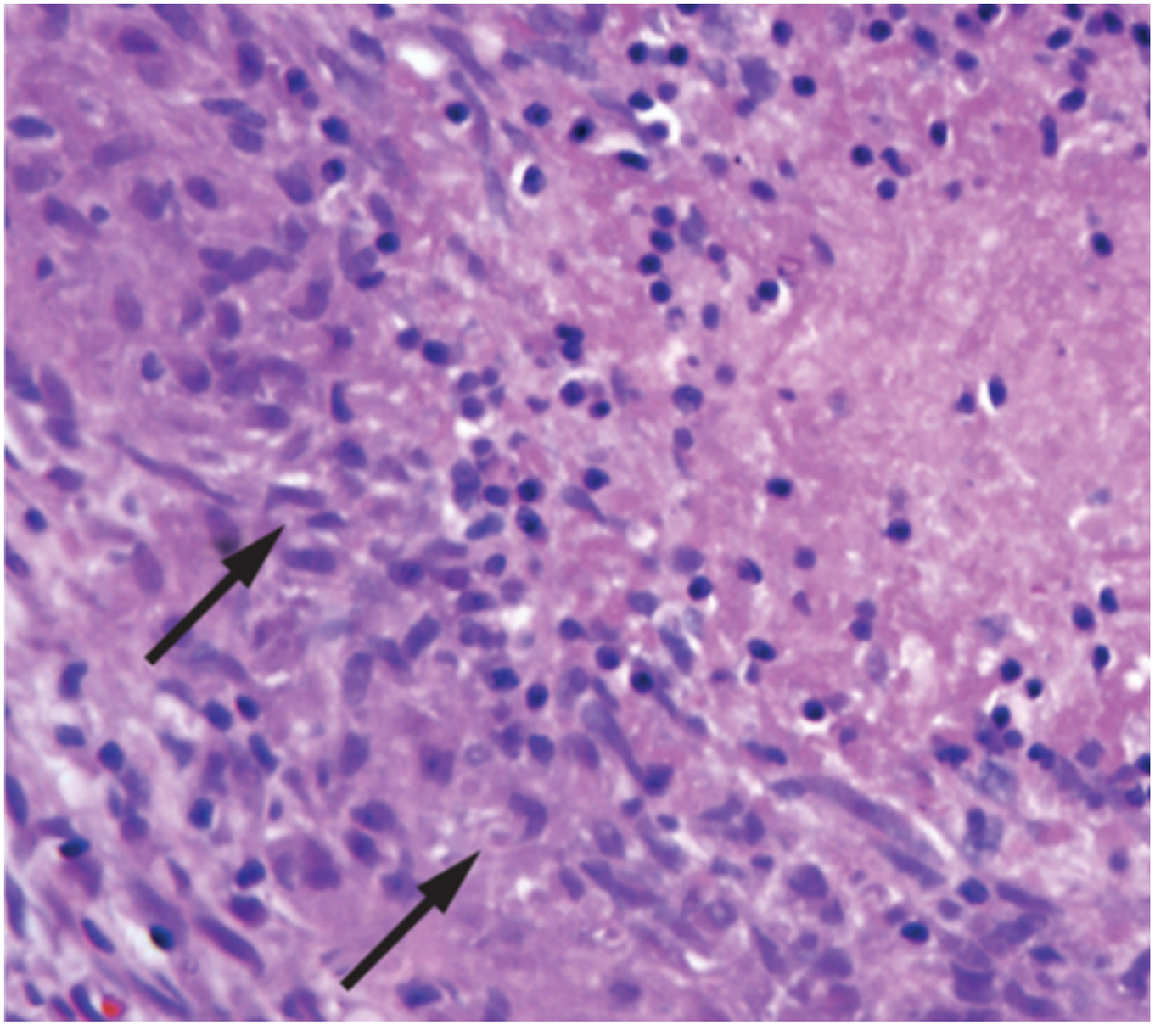
Jennette JC, et al. Nature Reviews Rheumatology: 2014: 10, 463–473.

Leukocytoclastic venulitis in the nasal septal mucosa of a patient with PR3-ANCA-associated disease



Jennette JC, et al. Nature Reviews Rheumatology: 2014: 10, 463–473.

Granulomatous inflammation



A central zone of amorphous necrotic debris containing a few pyknotic leukocytes and an adjacent marginal zone of epithelioid macrophages

Jennette JC, et al. Nature Reviews Rheumatology: 2014: 10, 463–473.

Classification of ANCA-associated vasculitis (EULAR)

Localized	Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms.
Early systemic	Any, without organ-threatening or life-threatening disease.
Generalized	Renal or other organ-threatening disease, serum creatinine ≤5.6 mg/dL (500 micromol/L).
Severe	Renal or other vital organ failure, serum creatinine ≥5.7 mg/dL (500 micromol/L)
Refractory	Progressive disease unresponsive to glucocorticoids and cyclophosphamide

Mukhtyar, C, et al. . Ann Rheum Dis 2008

Initial treatment of RPGN

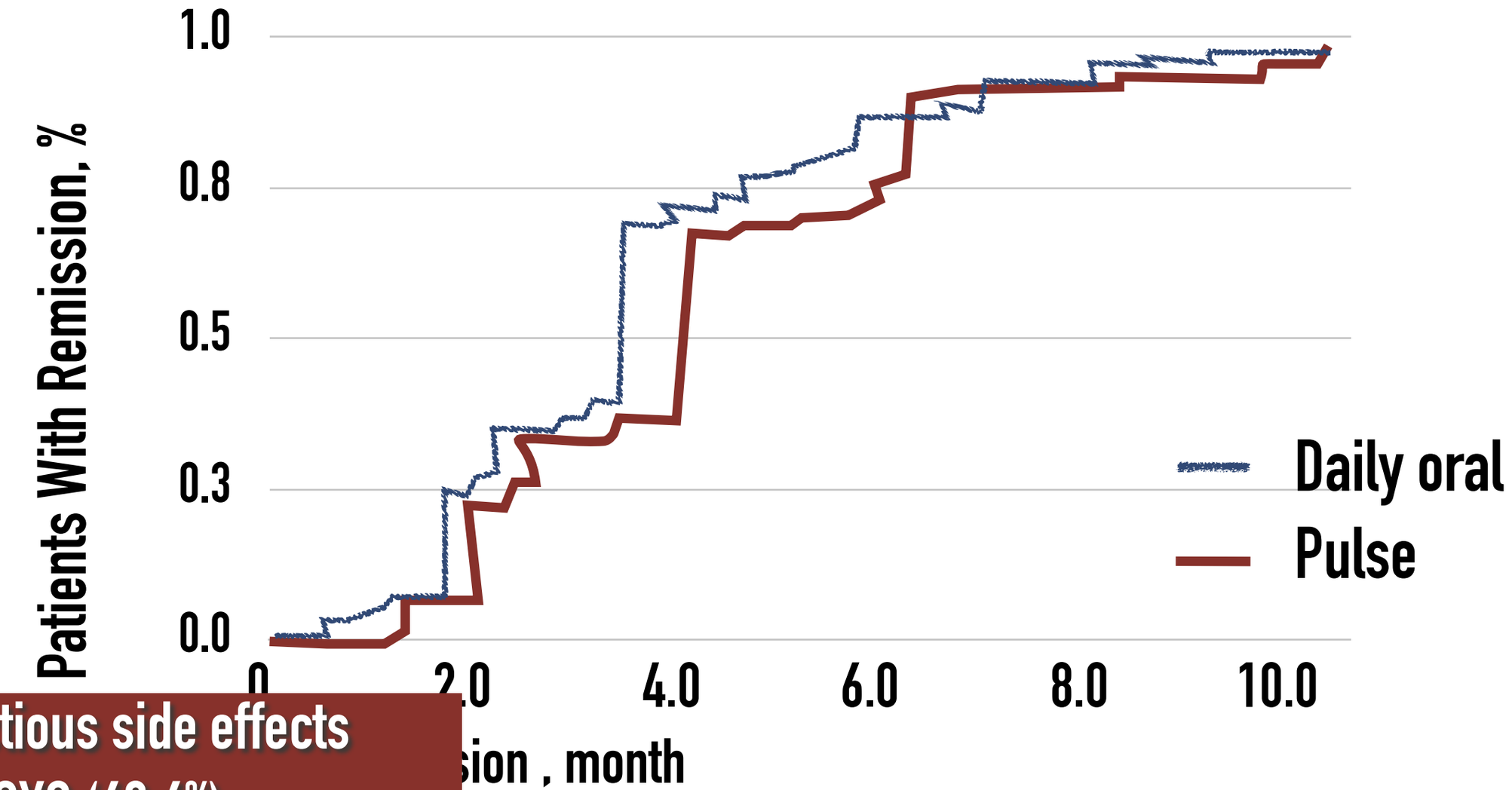
- Aggressive immunosuppressive agents
  - Intravenous methylprednisolone (IVMP) 500–1000 mg/day x 3 days
  - Cyclophosphamide (IVCY/Oral CY)

- Need to be confirm definite diagnosis for further Rx
  - Serology + kidney biopsy

CYCLOPS study

42 centers in 12 European countries: 149 patients

Pulse Versus Daily Oral Cyclophosphamide for Induction of Remission in ANCA associated vasculitis

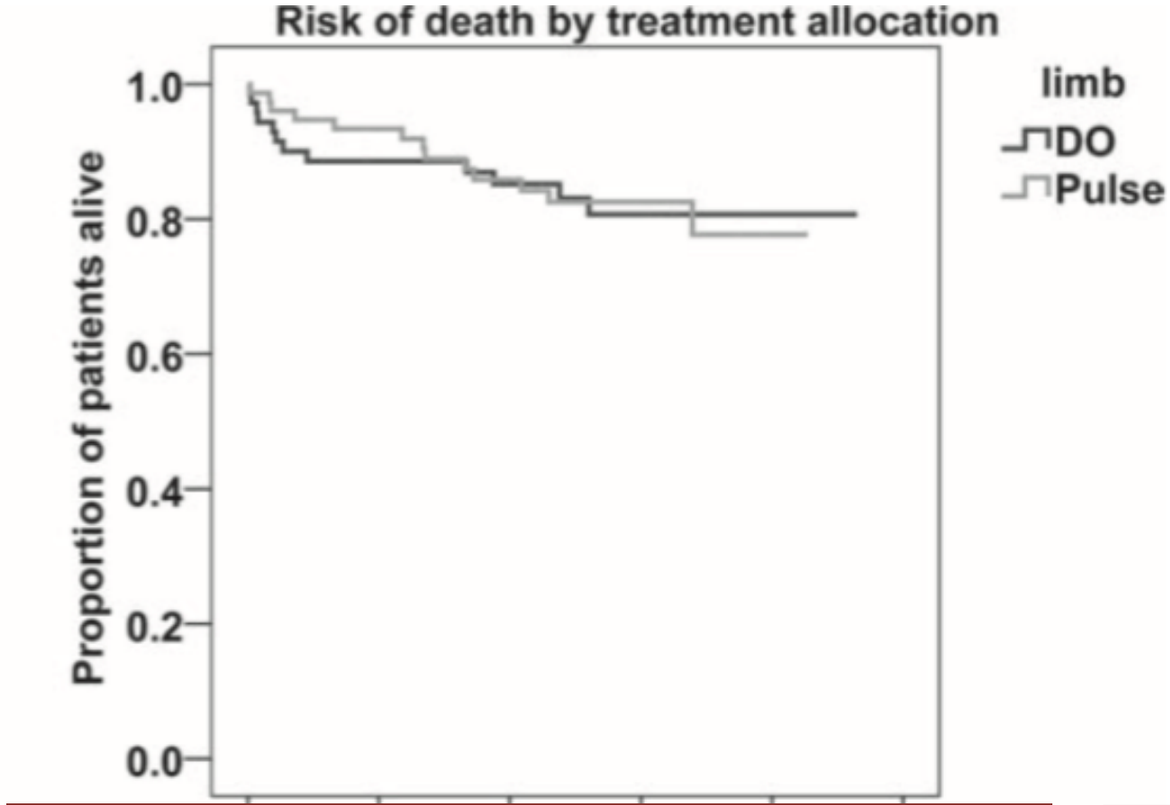


- Infectious side effects
- Oral CYC (69.6%)
- IV CYC (40.7%) ($P < 0.05$)

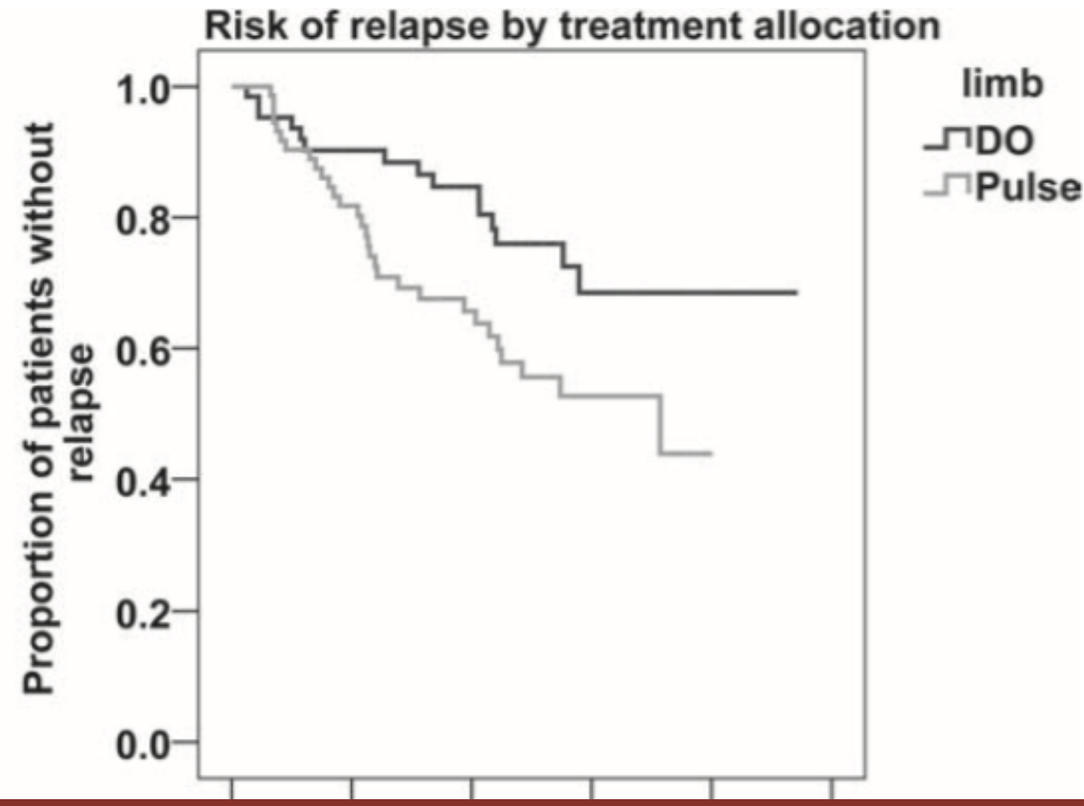
de Groot K; et al. Ann Intern Med. 2009;150(10):670–80.

Long-term outcomes in CYCLOPS study

- Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up: 4.3 years



No difference in survival, renal function and adverse events



Significantly lower relapse in the oral cyclophosphamide (HR=0.50, 95% CI 0.26 to 0.93; p=0.029)

Harber L, et al. Ann Rheum Dis 2012;71:955-960

Initial treatment of pauci-immune glomerulonephritis

- Cyclophosphamide and corticosteroids (1A)
- Discontinuing cyclophosphamide therapy after 3 months in patients who remain dialysis-dependent and who do not have any extrarenal manifestations of disease (2C)

Cyclophosphamide: Fertility, hair loss, the risk of malignancy

KDIGO. Kidney International Supplements (2012) 2, 143–153

Rituximab

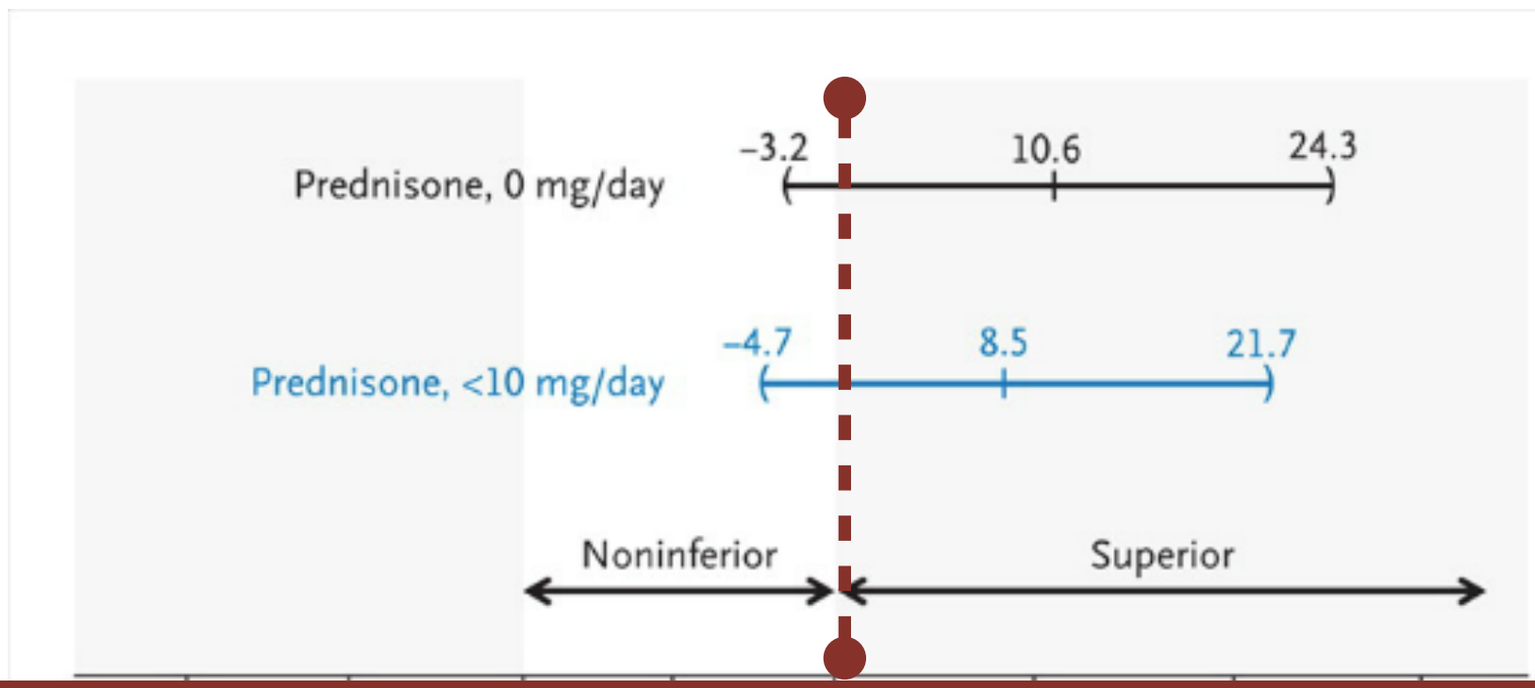
- RAVE–trial
- RITUXVAS trial

Jones RB, et al. N Engl J Med 2010;363:211–20.

Stone JH, et al. N Engl J Med 2010;363:221–32.

RAVE trial: Rituximab vs. Cyclophosphamide in ANCA–Associated Renal Vasculitis

- 197 ANCA–positive patients
- Rituximab 375 mg per m^2 per week for 4 weeks vs. Cyclophosphamide 2 MKD
- Remission of disease without the use of prednisone at 6 months



- 64% in the rituximab group
- 53% in the control group

Rituximab therapy was not inferior to daily cyclophosphamide treatment for induction of remission in severe ANCA–associated vasculitis and may be superior in relapsing disease

Stone JH, et al. N Engl J Med 2010;363:221–32.

RAVE trial: Rituximab vs. Cyclophosphamide in ANCA–Associated Renal Vasculitis

National Institutes of Health (NIH):

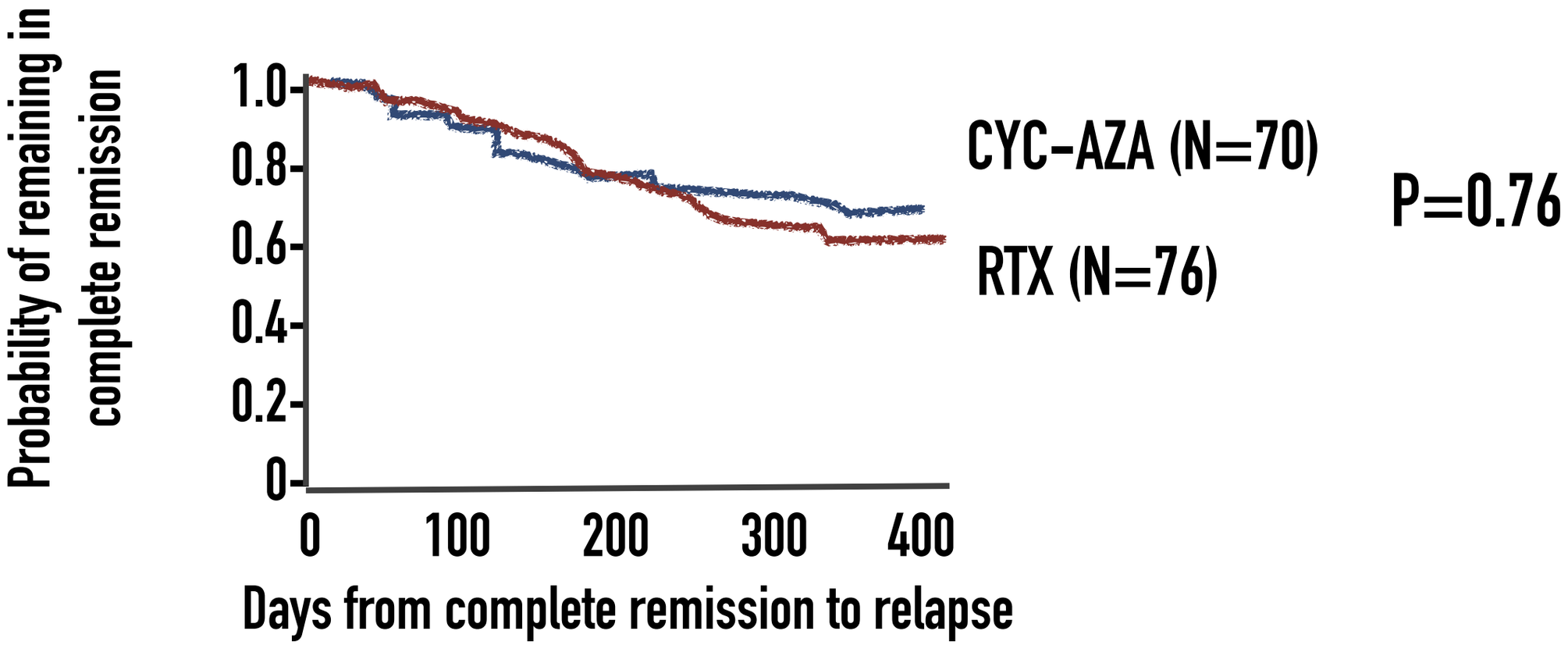
- 100 patients with relapsing disease
- Rituximab 375 mg per m^2 per week for 4 weeks vs. Cyclophosphamide 2 MKD
- Rituximab was superior to cyclophosphamide in inducing remission (67 versus 42 percent) at six months

The RAVE trial excluded patients with severe alveolar hemorrhage or severe kidney dysfunction (SCr >4 mg/dl, so the role of rituximab for such patients remains unknown.

Stone JH, et al. N Engl J Med 2010;363:221–32.

RAVE: Efficacy of remission–induction regimens for ANCA–associated vasculitis

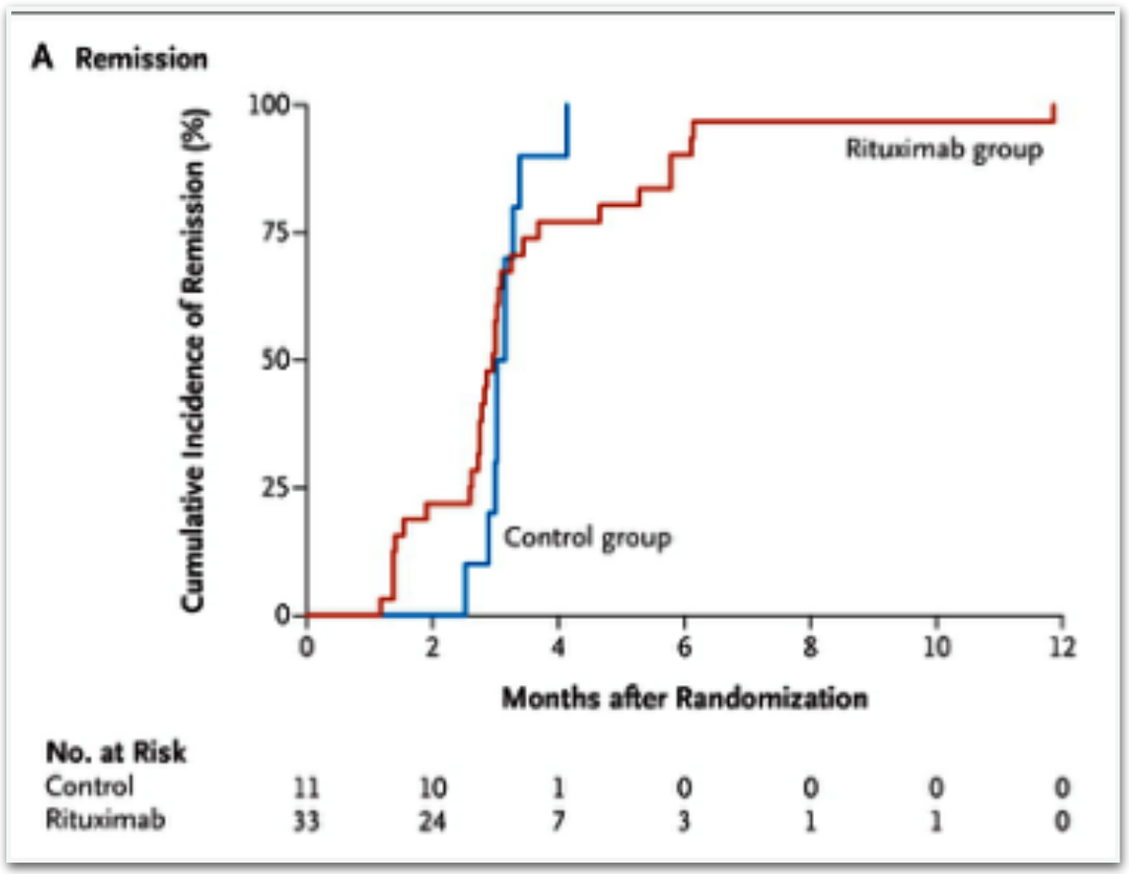
A single course of rituximab was as effective as continuous conventional immunosuppressive therapy for the induction and maintenance of remissions over the course of 18 months.

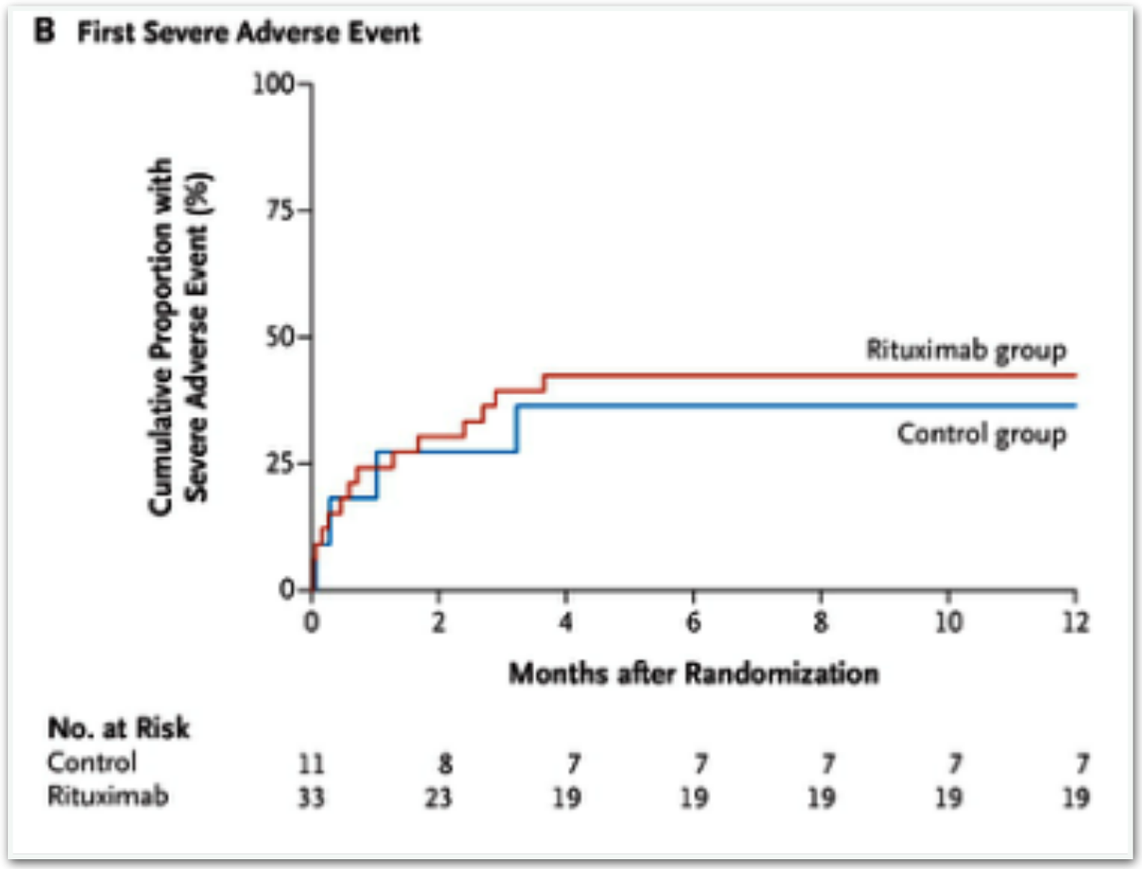


Specks U, et al. N Engl J Med 2013;369:417–27.

RITUXVAS: Rituximab versus cyclophosphamide in ANCA–associated renal vasculitis

- 44 patients with newly diagnosed antineutrophil cytoplasmic antibody (ANCA)–associated renal vasculitis





At 12 months, there was no difference in the rate of sustained remission between the rituximab– and cyclophosphamide–only groups (76 versus 82 percent).

Initial treatment of pauci-immune glomerulonephritis

- **Rituximab and corticosteroids: alternative initial treatment in patients without severe disease or in whom cyclophosphamide is contraindicated (1B)**

KDIGO. Kidney International Supplements (2012) 2, 143–153

Methotrexate

- NORAM trial
- Methotrexate effective as cyclophosphamide for the induction of remission in patients with mild disease, but was associated with a significantly higher relapse rate.

Methotrexate should not be used when the eGFR is below 50 mL/min.

Beck L, et al. Am J Kidney Dis 2013; 62:403.

Methotrexate

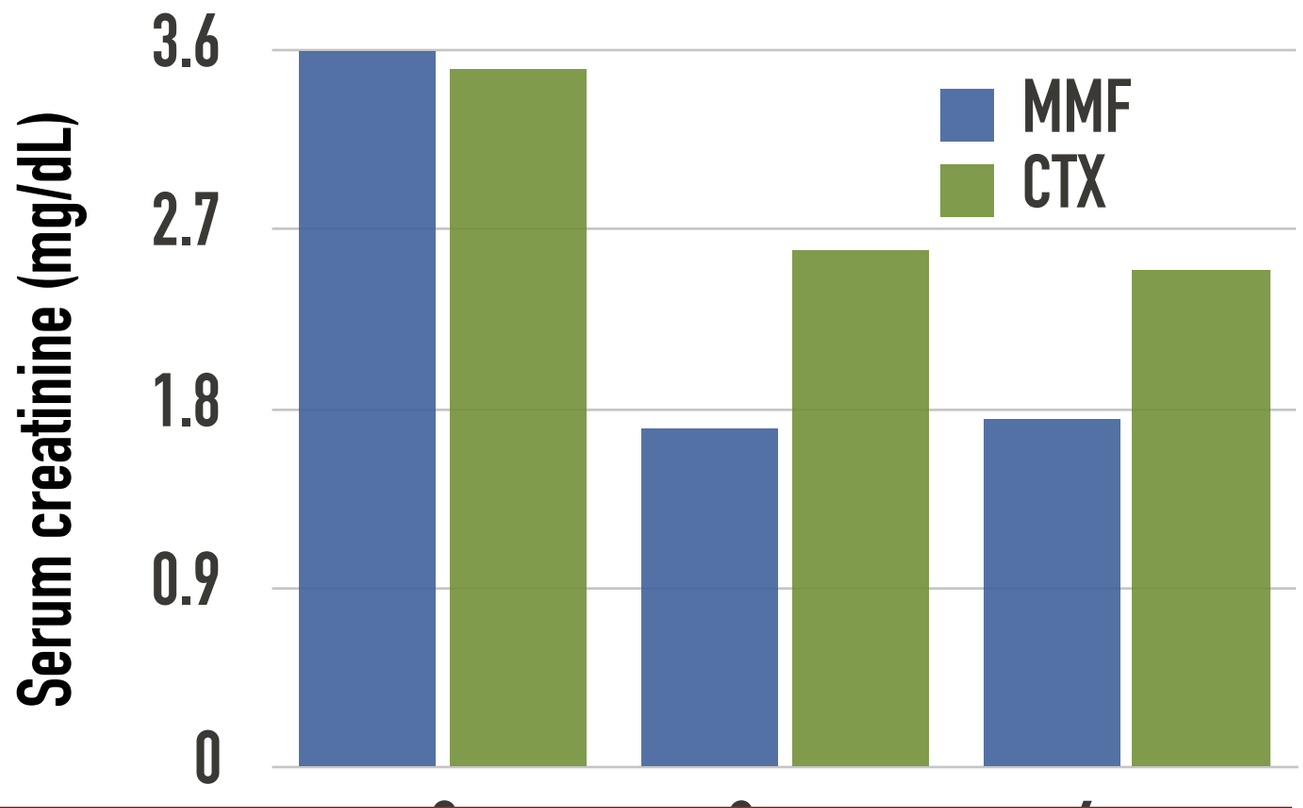
- The 2008 European League Against Rheumatism (EULAR) guidelines and the 2013 Kidney Disease Outcomes Quality Initiative (KDOQI)
  - Combination of methotrexate and glucocorticoids
  - Non–organ–threatening and non–life–threatening extrarenal ANCA–associated vasculitis

Beck L, et al. Am J Kidney Dis 2013; 62:403.

MMF

MMF versus cyclophosphamide for inducing remission of ANCA vasculitis with moderate renal involvement

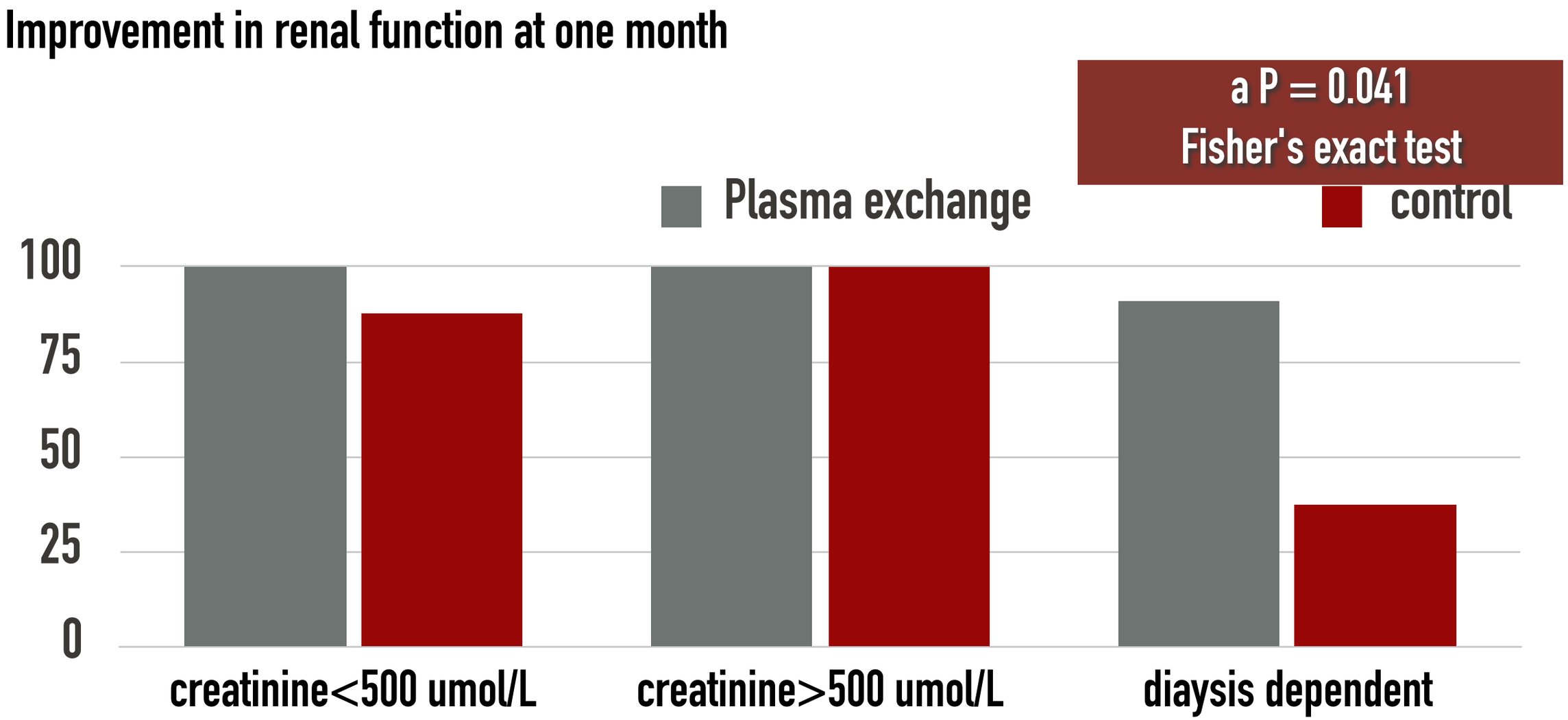
- 18 in the MMF group and 17 in the CTX group
- 77.8% treated with MMF
- 47.1% treated with CTX
- Complete remission with an absolute difference of 30.7%.



No data on follow-up beyond 6 months and insufficient data to support the use of MMF for induction therapy in ANCA vasculitis

Plasma exchange

Plasma exchange in focal necrotizing glomerulonephritis

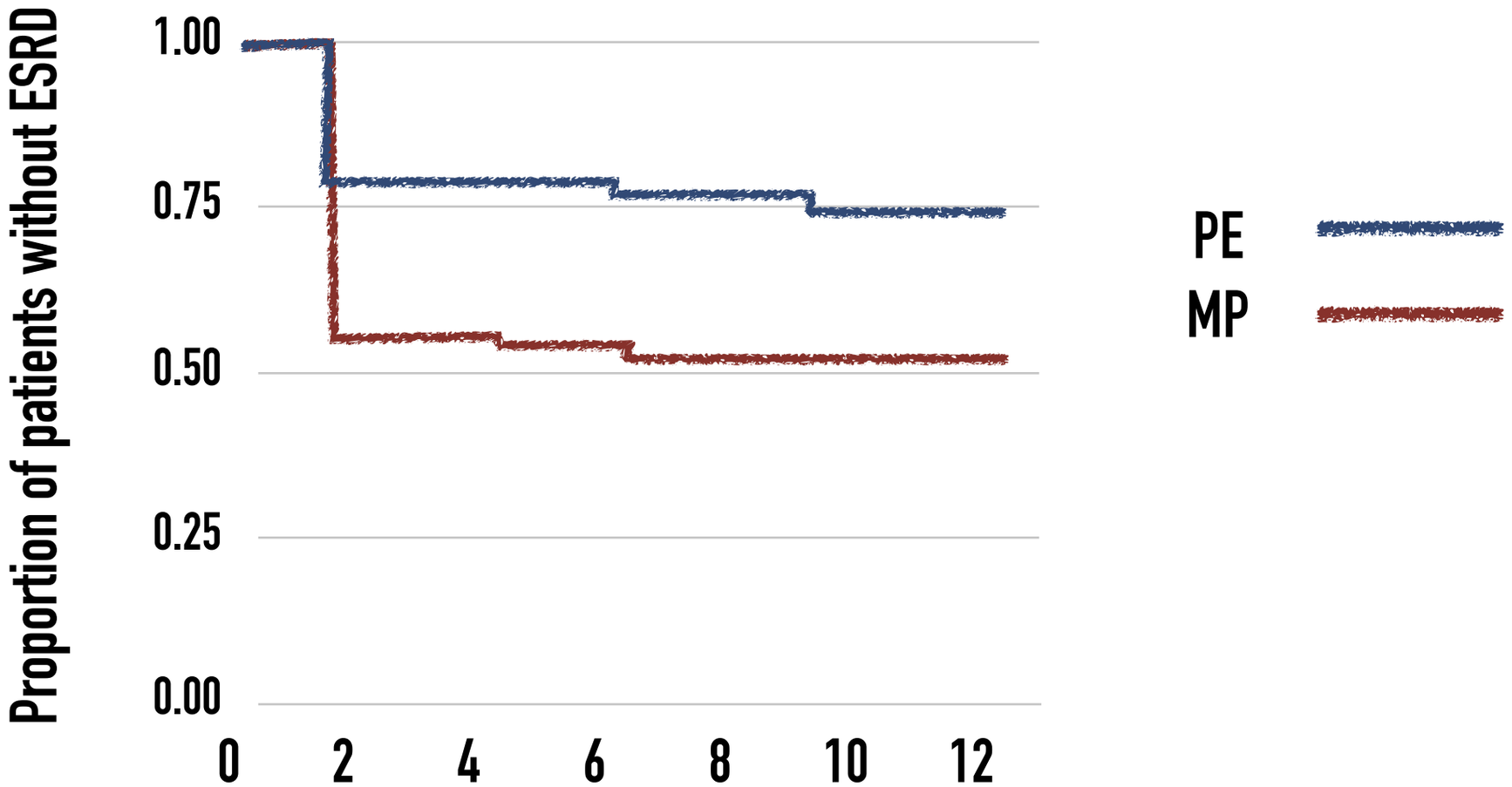


Treatment: plasma exchange, prednisolone, cyclophosphamide and azathioprine
Control: drug alone

Pusey CD, et al. Kidney Int 1991;40(4):757-63.

Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis

137 patients with pauci-immune glomerulonephritis, and serum creatinine >5.7 mg/dL. The mean serum creatinine at presentation was 8.3 mg/dL and 69 percent required dialysis,

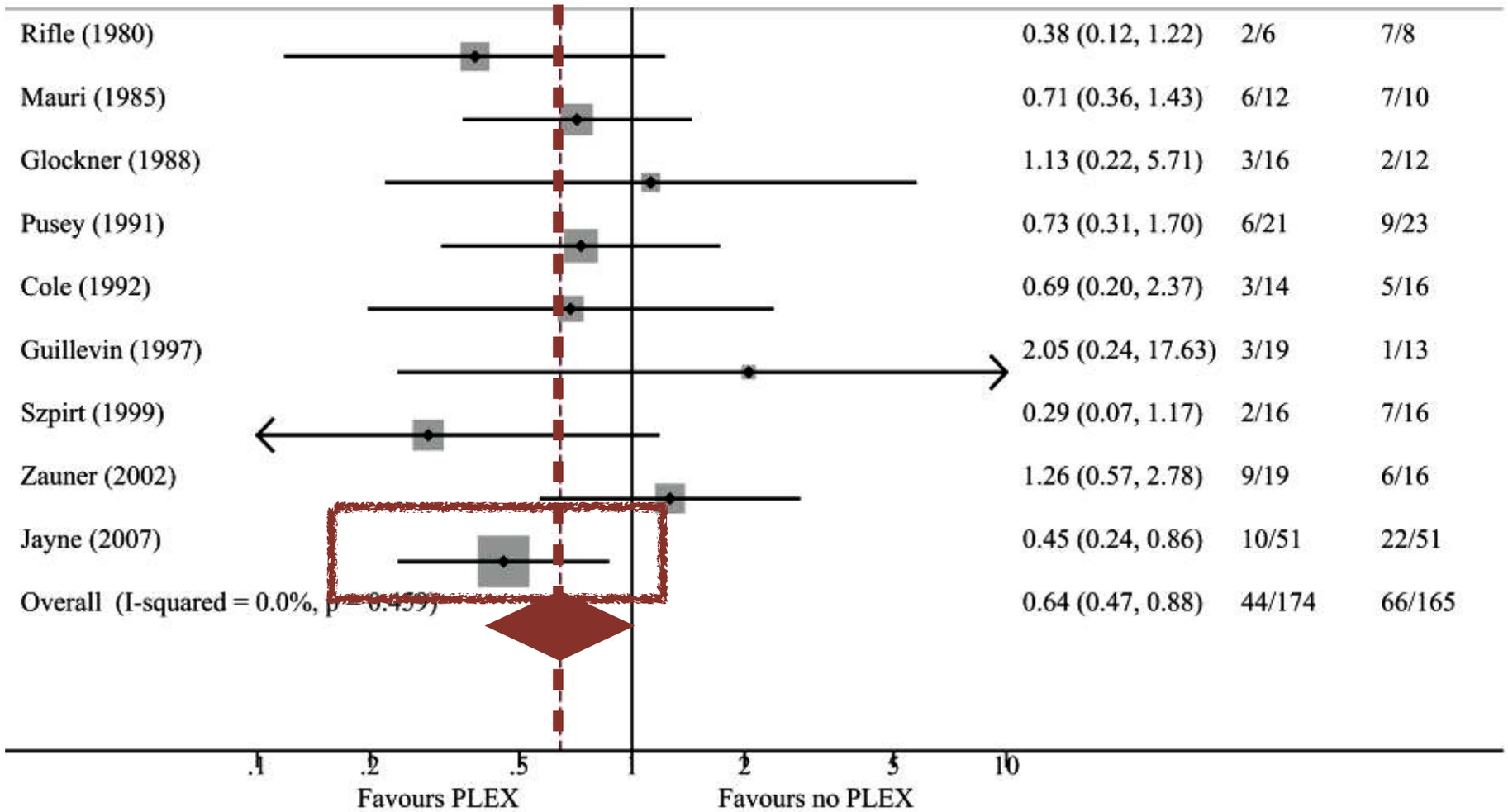


Plasma exchange was associated with a reduction in risk for progression to ESRD of 24% (95% CI 6.1 to 41%), from 43 to 19%, at 12 mo.

Jayne DR, et al. J Am Soc Nephrol. 2007;18(7):2180-8

Plasma exchange for renal vasculitis: a meta-analysis

The RR for ESRD was 0.64 (95% CI, 0.47–0.88; P = 0.006).
The RR for death was 1.01 (95% CI, 0.71–1.4; P = 0.9).



Forest plot of the effects of adjunctive plasma exchange on the endpoint of ESRD in patients with ANCA associated vasculitis.

Walsh M, et al. Am J Kidney Dis. 2011;57(4):566.

Initial treatment of pauci-immune glomerulonephritis

Addition of plasmapheresis

- Patients requiring dialysis or with rapidly increasing SCr (1C)
- Diffuse pulmonary hemorrhage (2C)
- Overlap syndrome of ANCA vasculitis and anti-GBM glomerulonephritis (2D)

KDIGO. Kidney International Supplements (2012) 2, 143–153

Recommended treatment regimens

Agent	Route	Initial dose
Cyclophosphamide[a]	i.v.	0.75 g/m^2 q 3–4 weeks. Decrease initial dose to 0.5 g/m^2 if age >60 years or GFR <20 ml/min per 1.73 m^2. Adjust subsequent doses to achieve a 2-week nadir leukocyte count >3000/mm^3.
Cyclophosphamide[b]	p.o.	1.5–2 mg/kg/d, reduce if age >60 years or GFR <20 ml/min per 1.73 m^2. Adjust the daily dose to keep leucocyte count >3000/mm^3.
Corticosteroids	i.v.	Pulse methylprednisolone: 500 mg i.v. daily × 3 days.
Corticosteroids	p.o.	Prednisone 1 mg/kg/d for 4 weeks, not exceeding 60 mg daily. Taper down over 3–4 months.
Rituximab[c]	i.v.	375 mg/m^2 weekly × 4.
Plasmapheresis[d]		60 ml/kg volume replacement. *Vasculitis*: Seven treatments over 14 days If diffuse pulmonary hemorrhage, daily until the bleeding stops, then every other day, total 7–10 treatments. *Vasculitis in association with anti-GBM antibodies*: Daily for 14 days or until anti-GBM antibodies are undetectable.

ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; GFR, glomerular filtration rate; GN, glomerulonephritis; i.v., intravenous; p.o., orally.
[a]Given with pulse and oral steroids. An alternative i.v. cyclophosphamide dosing schema is 15 mg/kg given every 2 weeks for three pulses, followed by 15 mg/kg given every 3 weeks for 3 months beyond remission, with reductions for age and estimated GFR.[705]
[b]Given with pulse and oral steroids.
[c]Given with pulse and oral steroids.
[d]Not given with pulse methylprednisolone. Replacement fluid is 5% albumin. Add 150–300 ml fresh frozen plasma at the end of each pheresis session if patients have pulmonary hemorrhage, or have had recent surgery, including kidney biopsy.

Maintenance immunosuppressive therapy

- Long-term cyclophosphamide has significant treatment-related toxicity
- Almost all patients with WG or MPA are switched to a less toxic non-cyclophosphamide maintenance regimen
- Azathioprine, MMF or methotrexate, to reduce the risk of relapse.

Azathioprine

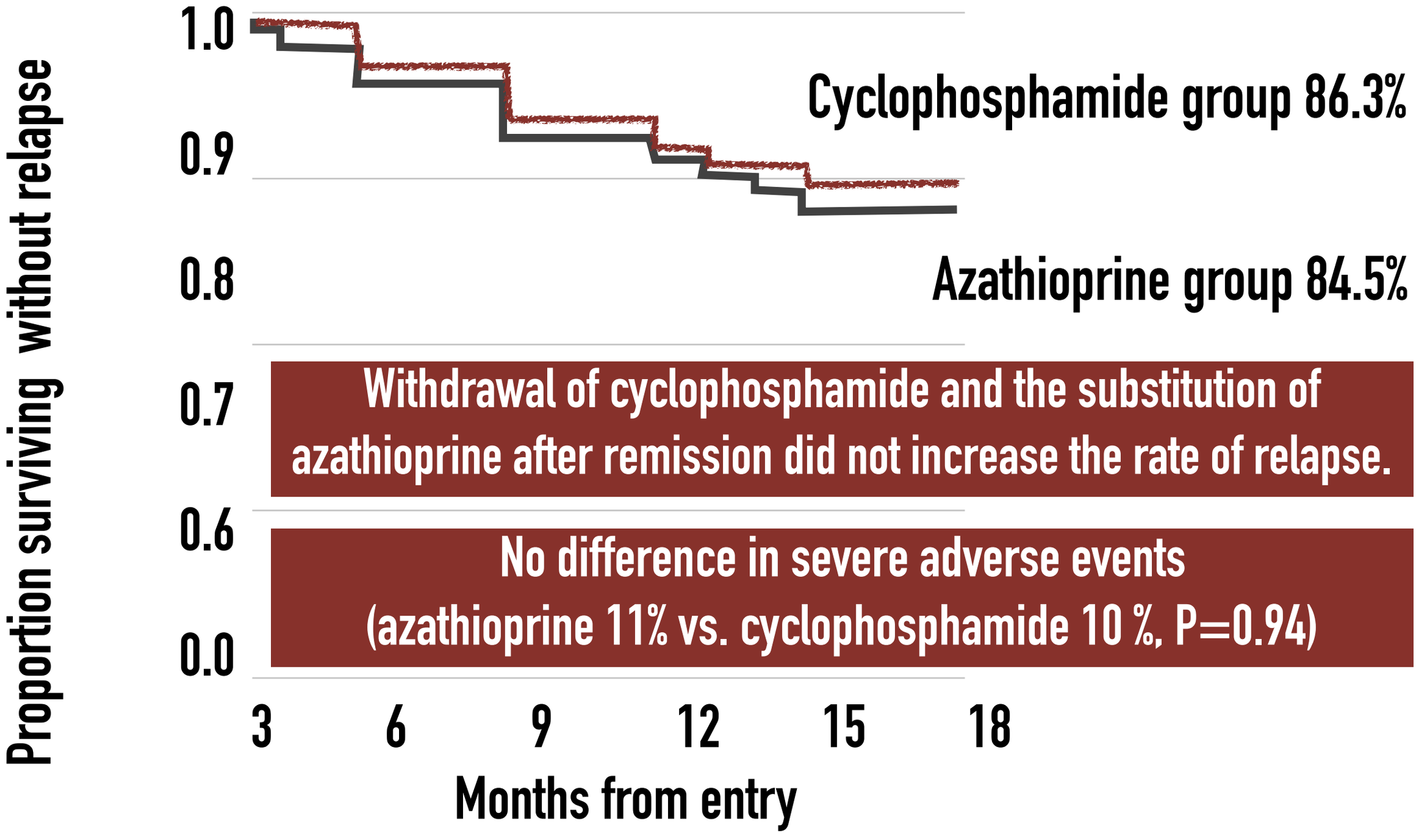
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Maintenance Therapy for Vasculitis Associated with Antineutrophil Cytoplasmic Autoantibodies

David Jayne, F.R.C.P., Niels Rasmussen, M.D., Konrad Andrassy, M.D., Paul Bacon, F.R.C.P., Jan Willem Cohen Tervaert, Ph.D., Jolanta Dadoniené, Ph.D., Agneta Ekstrand, M.D., Gill Gaskin, Ph.D., Gina Gregorini, M.D., Kirsten de Groot, M.D., Wolfgang Gross, M.D., E. Christiaan Hagen, M.D., Eduardo Mirapeix, M.D., Erna Pettersson, Ph.D., Carl Siegert, M.D., Alberto Sinico, Ph.D., Vladimir Tesar, Ph.D., Kerstin Westman, Ph.D., and Charles Pusey, F.R.C.P., for the European Vasculitis Study Group*

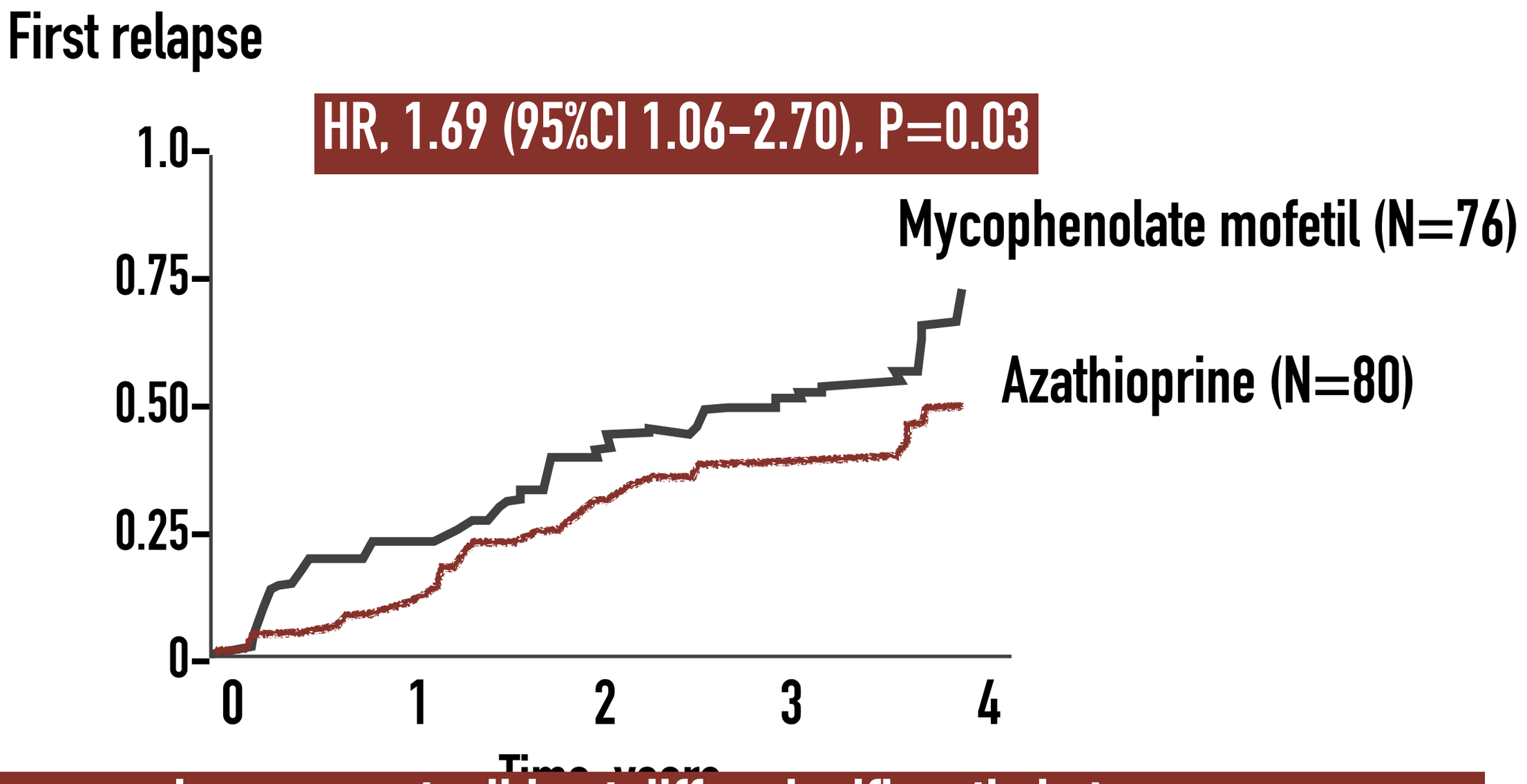
CYCAZAREM trial



N ENGL J MED 349;1 www.NEJM.ORG JULY 3, 2003

MMF

MMF vs Azathioprine for Remission Maintenance in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis: A Randomized Controlled Trial



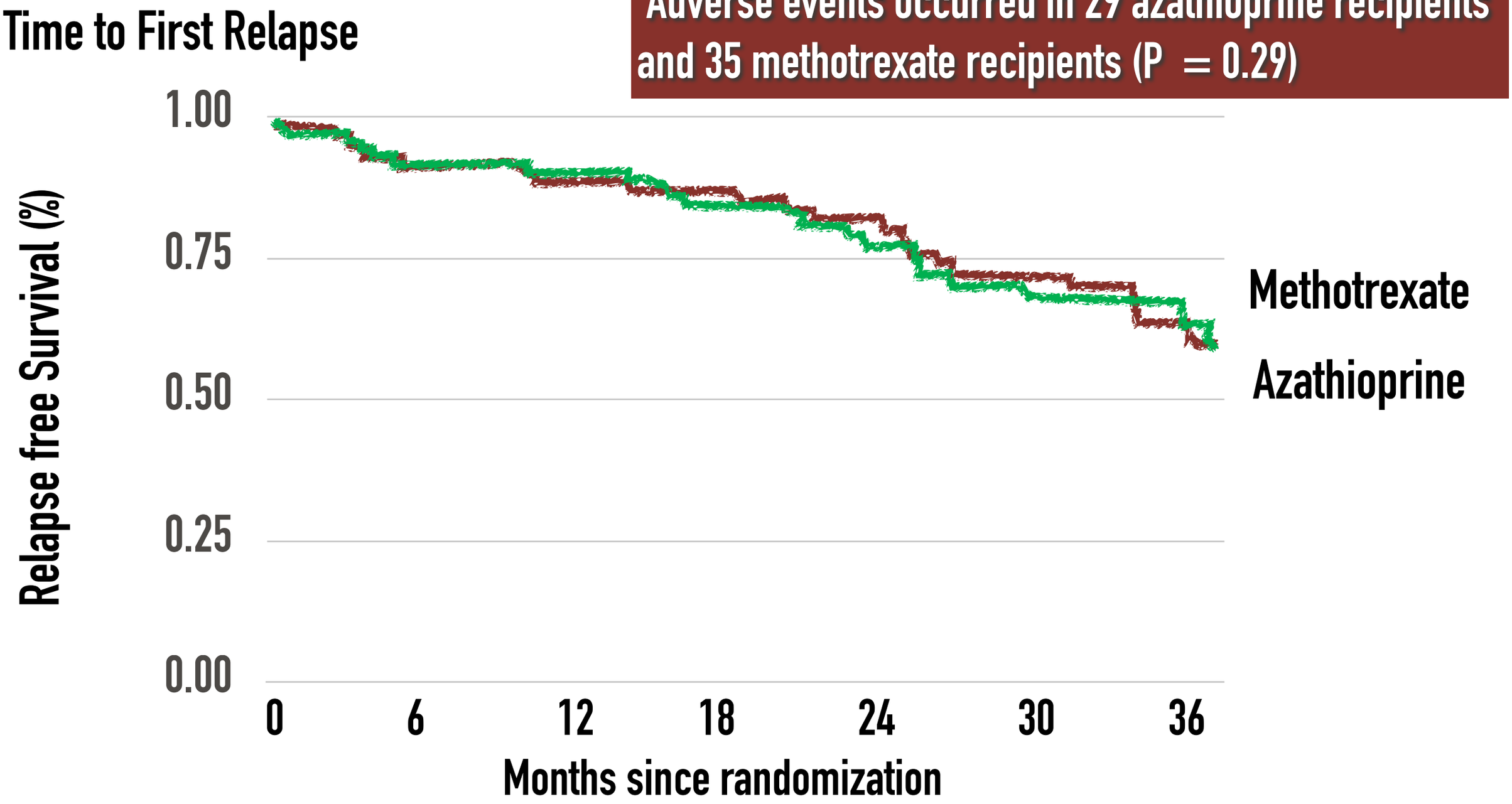
Severe adverse events did not differ significantly between groups

Hiemstra TF, et al. JAMA 2010;304:2381–8.

Methotrexate

Azathioprine or methotrexate maintenance for ANCA-associated vasculitis

Adverse events occurred in 29 azathioprine recipients and 35 methotrexate recipients (P = 0.29)



Pagnoux C; et al. N Engl J Med. 2008; 359(26):2790-803.

Choice of agent for maintenance therapy

- Azathioprine 1–2 mg/kg/d orally (1B)
- MMF, up to 1 g twice daily, in patients who are allergic or intolerant of azathioprine (2C)
- Methotrexate (initially 0.3 mg/kg/wk, maximum 25 mg/wk) for patients intolerant of azathioprine and MMF, but not if GFR <60 ml/min per 1.73 m^2 (1C)
- Trimethoprim–sulfamethoxazole as an adjunct to maintenance therapy in patients with upper respiratory tract disease (2B)

KDIGO. Kidney International Supplements (2012) 2, 143–153

Maintenance treatment

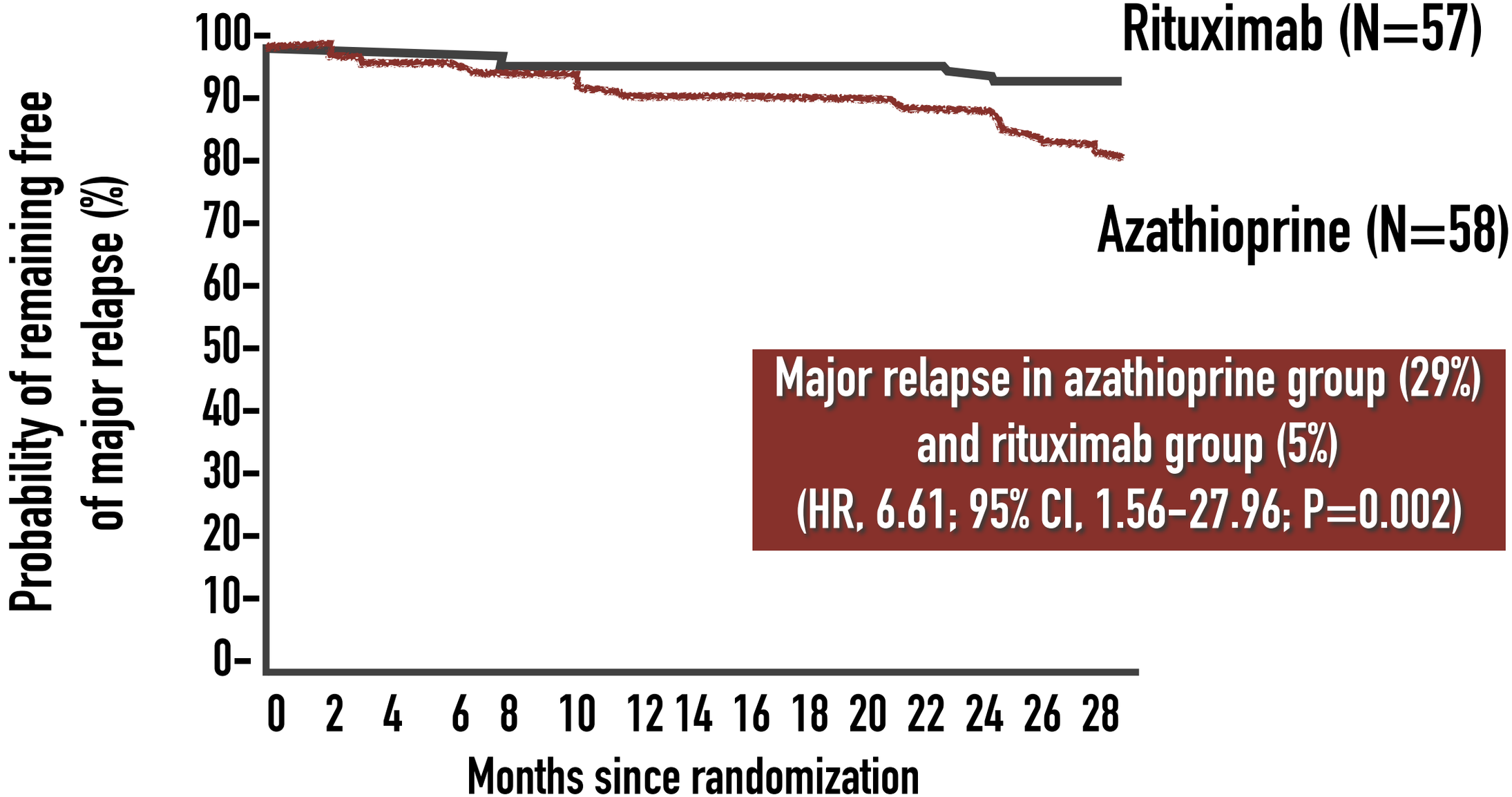
- Maintenance therapy for at least 18 months (2D)

- No maintenance therapy in patients who are dialysis-dependent and have no extrarenal manifestations of disease (1C)

KDIGO. Kidney International Supplements (2012) 2, 143–153

Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis

500 mg of rituximab on days 0 and 14 and at months 6, 12, and 18 after study



Guillevin L, et al. N Engl J Med 2014;371:1771–80.

Predictors of relapse in ANCA–associated small– vessel vasculitis

Predictor	Prediction of Relapse (n = 258)†	
	Hazard Ratio (95% CI)‡	*P* Value‡
Age per 10 years	0.94 (0.84–1.06)	0.31
Female versus male	1.05 (0.70–1.56)	0.97
Black versus nonblack	1.70 (0.83–3.90)	0.163
Antiproteinase-3 vs. antimyeloproteinase antibody status§	1.87 (1.11–3.14)	0.022
Wegener granulomatosis vs. kidney-limited	1.28 (0.53–3.11)	0.45
Microscopic polyangiitis vs. kidney-limited	1.08 (0.51–2.27)	0.87
Lung involvement	1.71 (1.04–2.81)	0.034
Upper respiratory involvement	1.73 (1.04–2.88)	0.030
Skin involvement	1.41 (0.85–2.32)	0.182
Serum creatinine level per μmol/L‖¶	1.01 (0.91–1.13)	0.82
Chronicity score per unit change (0 to 16)¶	0.99 (0.98–1.09)	0.98
Activity score per unit change (0 to 24)¶	1.00 (0.93–1.01)	0.97
Vascular sclerosis score per unit change (0 to 4)¶	1.00 (0.75–1.33)	0.97

Patients with all three risk factors have an 4.7-fold increased risk of relapse

Hogan SL, et al. Ann Intern Med 2005; 143: 621–631.

Treatment of relapse disease

- Treating patients with severe relapse of ANCA vasculitis (life- or organ- threatening) according to the same guidelines as for the initial therapy (1C)

- Treating other relapses of ANCA vasculitis by reinstitution immunosuppressive therapy or increasing its intensity with agents other than cyclophosphamide, including increasing dose of corticosteroids, with or without azathioprine or MMF (2C)

KDIGO. Kidney International Supplements (2012) 2, 143–153

Treatment of resistant disease

- ANCA GN resistant to induction therapy with cyclophosphamide and corticosteroids

- We recommend the addition of rituximab (1C), and suggest i.v. immunoglobulin (2C) or plasmapheresis (2D) as alternatives

KDIGO. Kidney International Supplements (2012) 2, 143–153

Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis

- 524 patients with newly diagnosed AAV
- 1-year mortality probability was 11.1%
- 59% therapy-associated adverse events
- 14% active vasculitis

Severe infection

Mark A Little, et al. Ann Rheum Dis 2010;69:1036-1043

RPGN: Prognosis

Factors	Poorer prognosis	Better prognosis
Urine output at presentation	Oliguric	Non-oliguric
Extent of crescent formation	>80%	50-80%
Glomerulus	Fibrinoid necrosis	Endocapillary cell proliferation
Glomerular immune deposits	Linear deposition (anti-GBM)	Granular deposition (immune complex) or no immune reactants
Interstitium	Interstitial fibrosis and tubular atrophy	

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Intelligence Dialysis Center
Nephrology Unit
Phramongkutklao Hospital and College of Medicine