ANCA-associated vasculitis

Vladimir Tesar

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Disclosure of Interests

Abbvie, Amgen, Baxter, Bayer, Boehringer-Ingelheim, Calliditas, Chemocentryx, Daichi-Sankyo Fresenius Medical Care

(consultancy, advisory board)

Outline of the lecture

- Anti-PR3 vs. anti-MPO disease, predictive value of renal biopsy?
- Initial therapy and relapse
- Plasma exchange
- Maintenance therapy
- Conclusions

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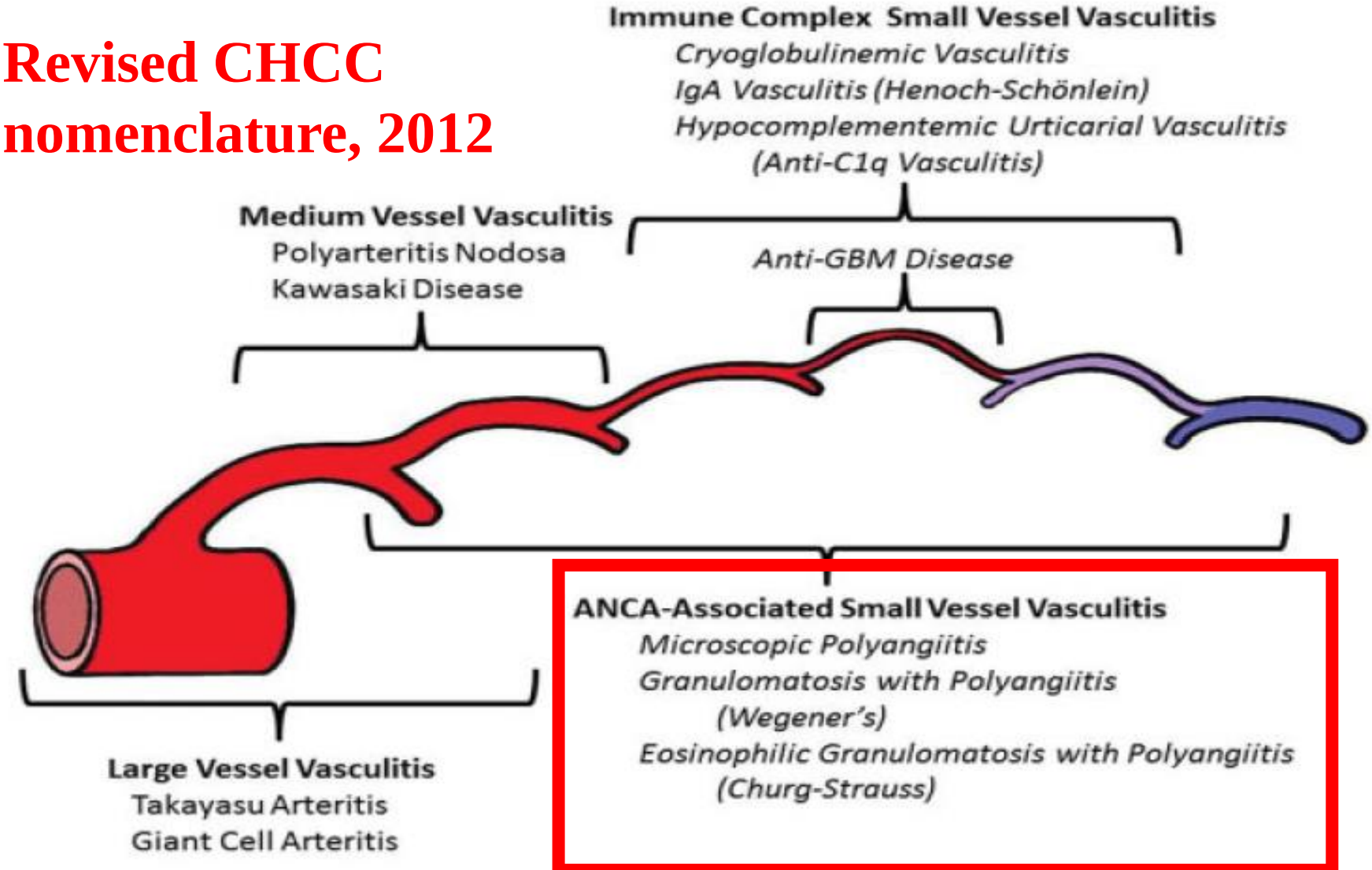
2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides

ARTHRITIS & RHEUMATISM
Vol. 65, No. 1, January 2013, pp 1–11

J. C. Jennette,[1] R. J. Falk,[1] P. A. Bacon,[2] N. Basu,[3] M. C. Cid,[4] F. Ferrario,[5] L. F. Flores-Suarez,[6] W. L. Gross,[7] L. Guillevin,[8] E. C. Hagen,[9] G. S. Hoffman,[10] D. R. Jayne,[11] C. G. M. Kallenberg,[12] P. Lamprecht,[13] C. A. Langford,[10] R. A. Luqmani,[14] A. D. Mahr,[15] E. L. Matteson,[16] P. A. Merkel,[17] S. Ozen,[18] C. D. Pusey,[19] N. Rasmussen,[20] A. J. Rees,[21] D. G. I. Scott,[22] U. Specks,[16] J. H. Stone,[23] K. Takahashi,[24] and R. A. Watts[25]

Revised CHCC nomenclature, 2012



Simplified clinicopathologic classification of AAV

Jennette a Falk, Arthritis Rheum, 1994, 37: 187-192

Granulomatosis with polyangiitis (GPA) *formerly Wegener granulomatosis*	**Vasculitis with granulomas without asthma**
Microscopic polyangiitis (MPA)	**Vasculitis without asthma and granulomas**
Eosinophilic granulomatosis with polyangiitis (EGPA) *formerly Churg-Strauss syndrome*	**Vasculitis with eosinophilia, astha and granulomas**

SMALL-VESSEL VASCULITIS

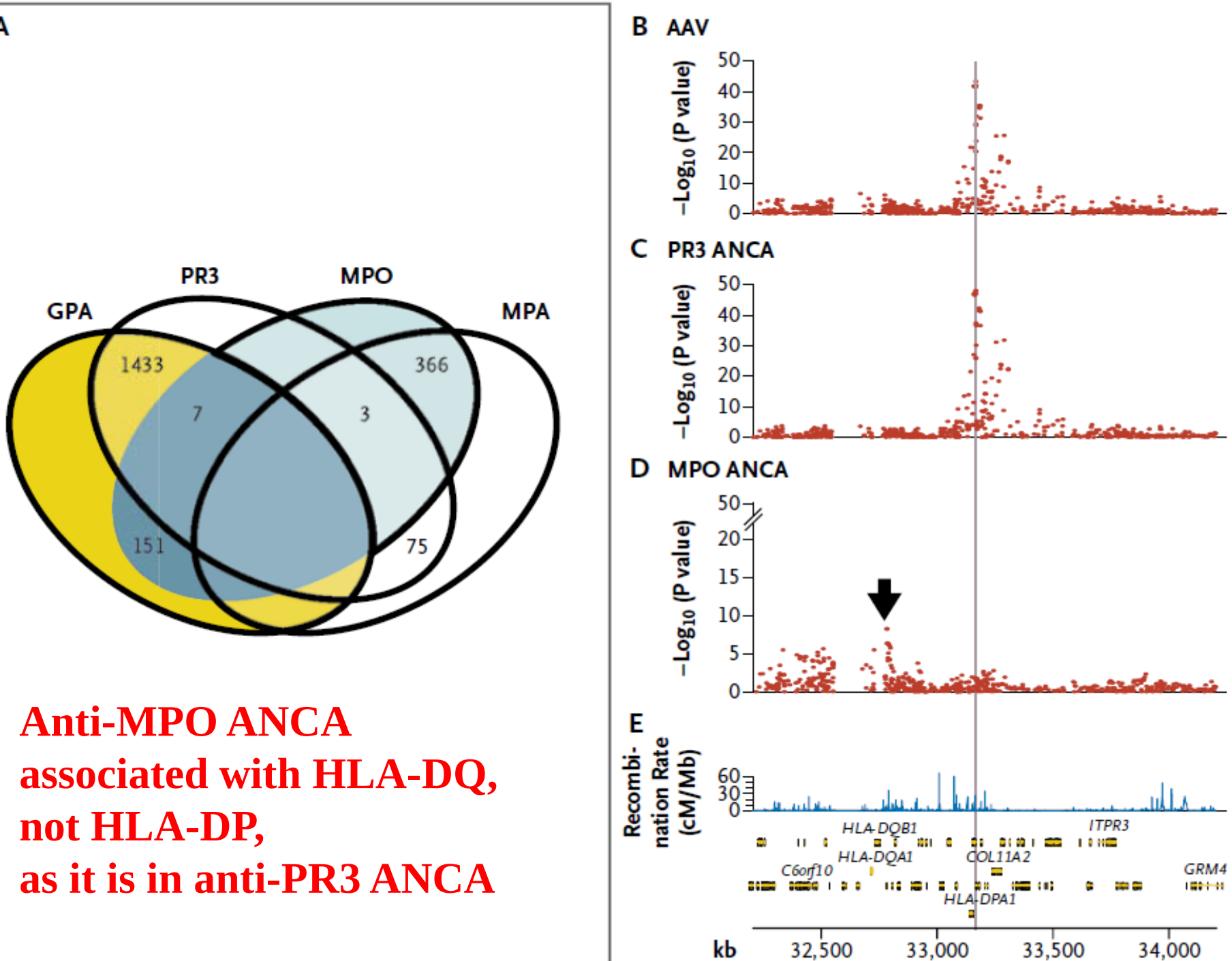
New England Journal of Medicine Volume 337 Number 21 1997

J. CHARLES JENNETTE, M.D., AND RONALD J. FALK, M.D.

Organ involvement in AAV

TABLE 4. APPROXIMATE FREQUENCY OF ORGAN-SYSTEM MANIFESTATIONS IN SEVERAL FORMS OF SMALL-VESSEL VASCULITIS.*

ORGAN SYSTEM	HENOCH–SCHÖNLEIN PURPURA	CRYOGLOBULINEMIC VASCULITIS	MICROSCOPIC POLYANGIITIS	WEGENER'S GRANULOMATOSIS	CHURG–STRAUSS SYNDROME
			percent		
Cutaneous	90	90	40	40	60
Renal	50	55	90	80	45
Pulmonary	<5	<5	50	90	70
Ear, nose, and throat	<5	<5	35	90	50
Musculoskeletal	75	70	60	60	50
Neurologic	10	40	30	50	70
Gastrointestinal	60	30	50	50	50



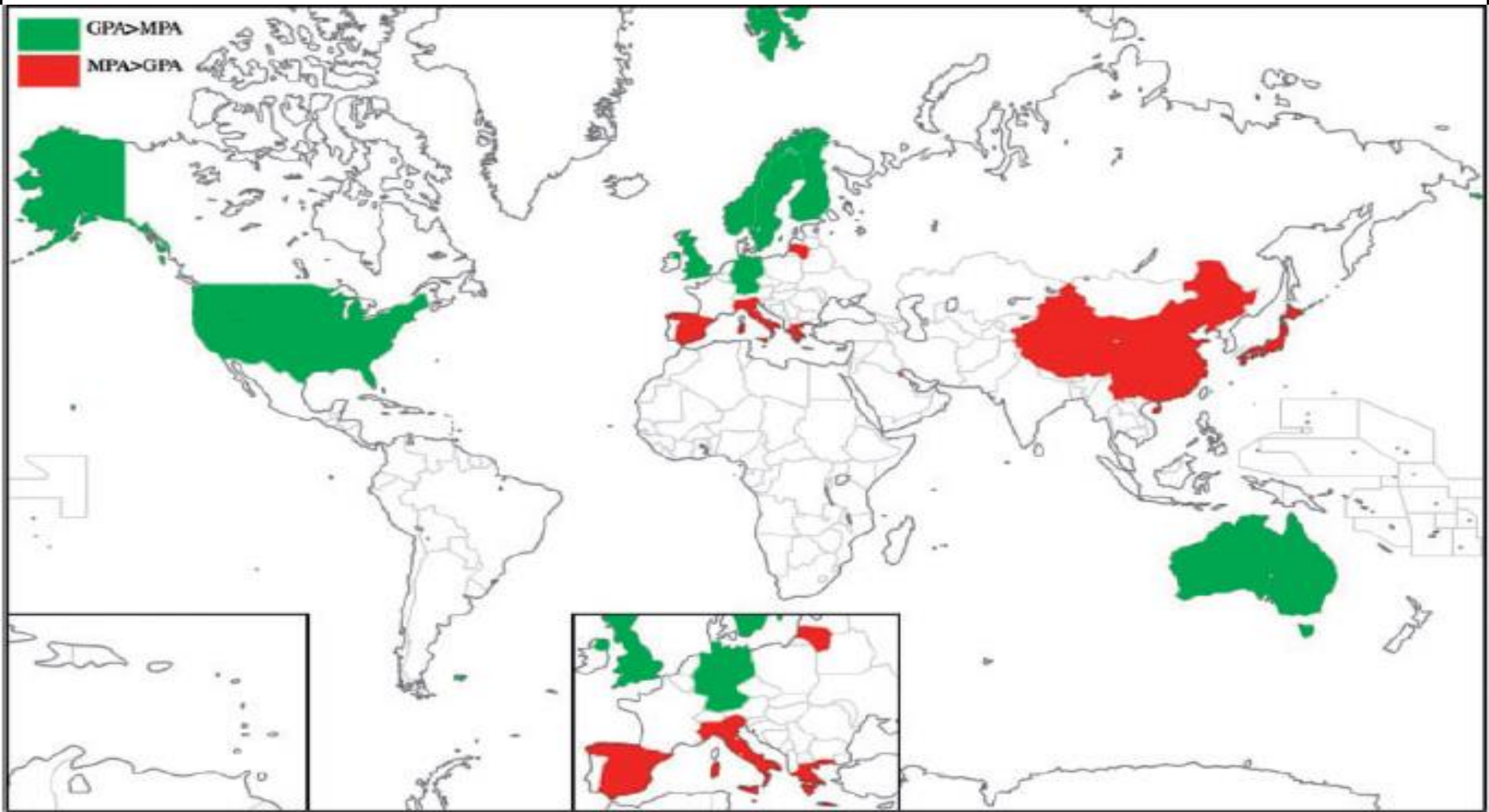
Anti-MPO ANCA associated with HLA-DQ, not HLA-DP, as it is in anti-PR3 ANCA

ANCA vasculitis: to lump or split?

Why we should study MPA and GPA separately

Rheumatology
August 25, 2012

Anti-PR3 and anti-MPO disease have different presentation and outcome



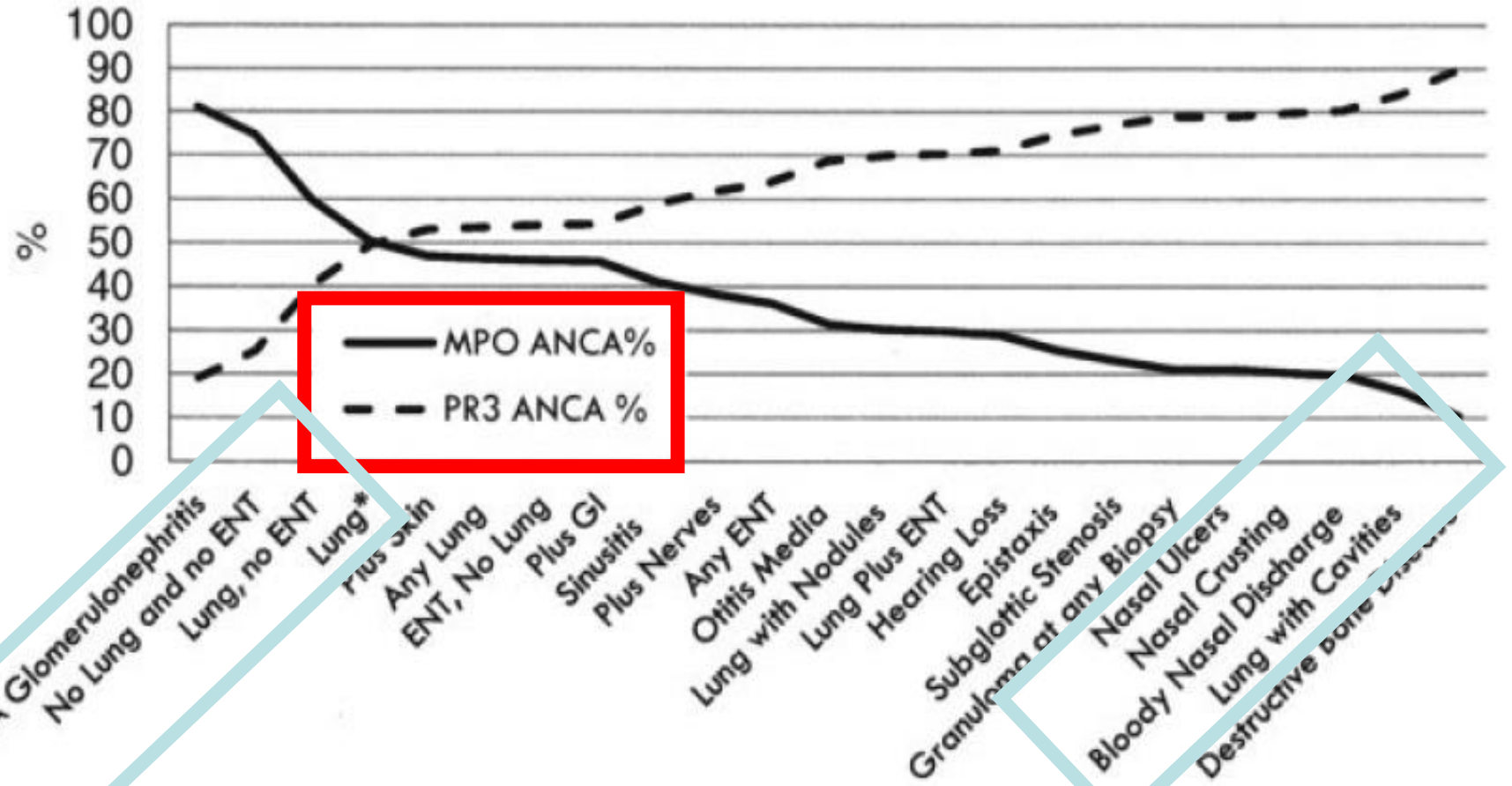
Classification of Antineutrophil Cytoplasmic Autoantibody Vasculitides

ARTHRITIS & RHEUMATISM
Vol. 64, No. 10, October 2012, pp 3452–3462

The Role of Antineutrophil Cytoplasmic Autoantibody Specificity for Myeloperoxidase or Proteinase 3 in Disease Recognition and Prognosis

Sophia Lionaki,[1] Elizabeth R. Blyth,[2] Susan L. Hogan,[2] Yichun Hu,[2] Brent A. Senior,[2] Caroline E. Jennette,[2] Patrick H. Nachman,[2] J. Charles Jennette,[2] and Ronald J. Falk[2]

Anti-PR3 and anti-MPO associated with different phenotypes (502 pts with AAV)



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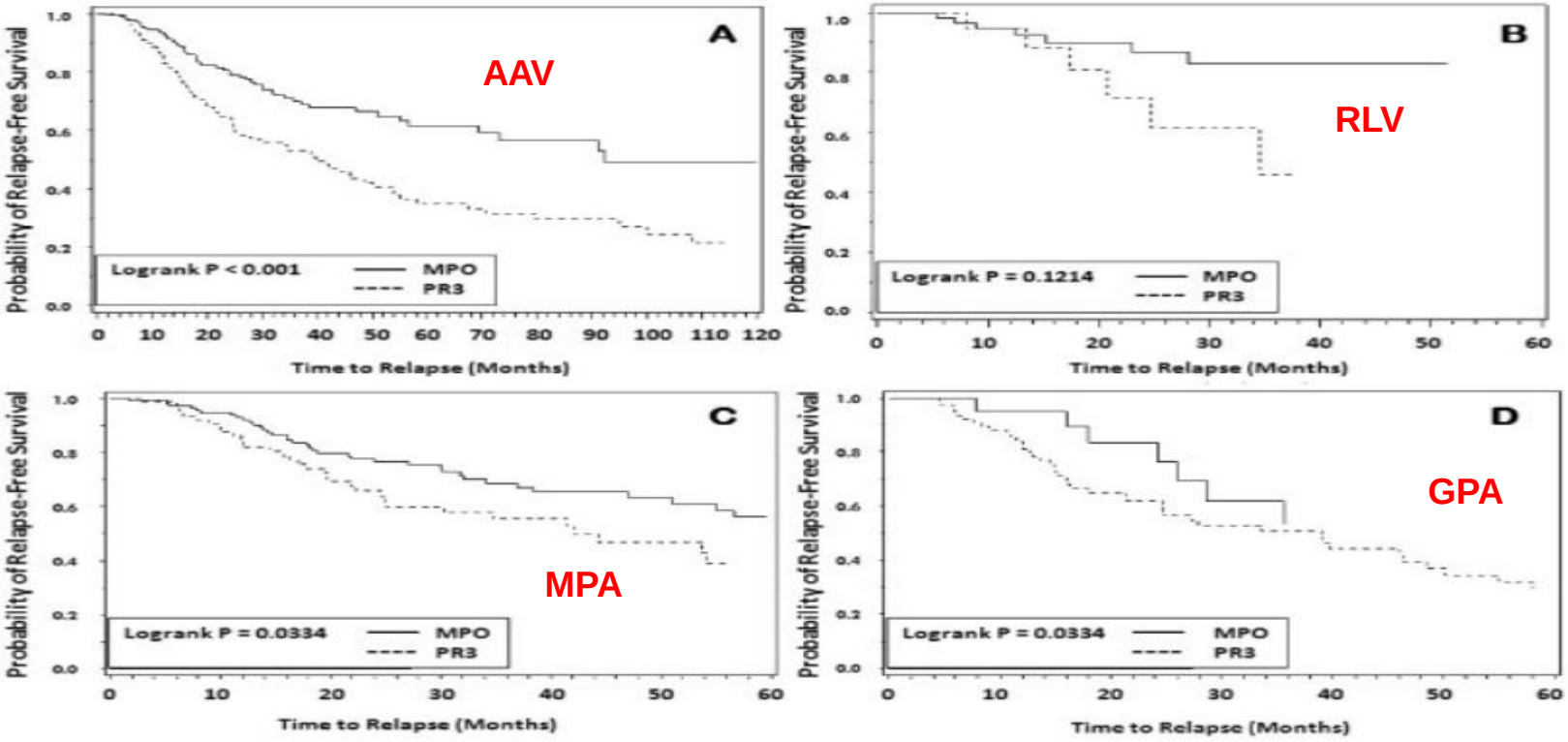
The Role of Antineutrophil Cytoplasmic Autoantibody Specificity for Myeloperoxidase or Proteinase 3 in Disease Recognition and Prognosis

In 502 AAV pts relapse predicted by ANCA specificity and not CHCC and EMA clinical diagnosis



Negative anti-neutrophil cytoplasm antibody at switch to maintenance therapy is associated with a reduced risk of relapse

Arthritis Research & Therapy (2017) 19:129

Matthew David Morgan[1,11*], Matthew Szeto[1], Michael Walsh[2,3], David Jayne[4], Kerstin Westman[5], Niels Rasmussen[6], Thomas F. Hiemstra[7], Oliver Flossmann[8], Annelies Berden[9], Peter Höglund[10], Lorraine Harper[1] and on behalf of the European Vasculitis Society

40% out of 252 pts from CYCLOPS and IMPROVE developed at least one relapse

Reduced risk of relapse - ANCA-negativity at switch to the maintenance therapy (anti-PR3, ↓ age, ↓SCr, pulsed CPH, MMF maintenance)

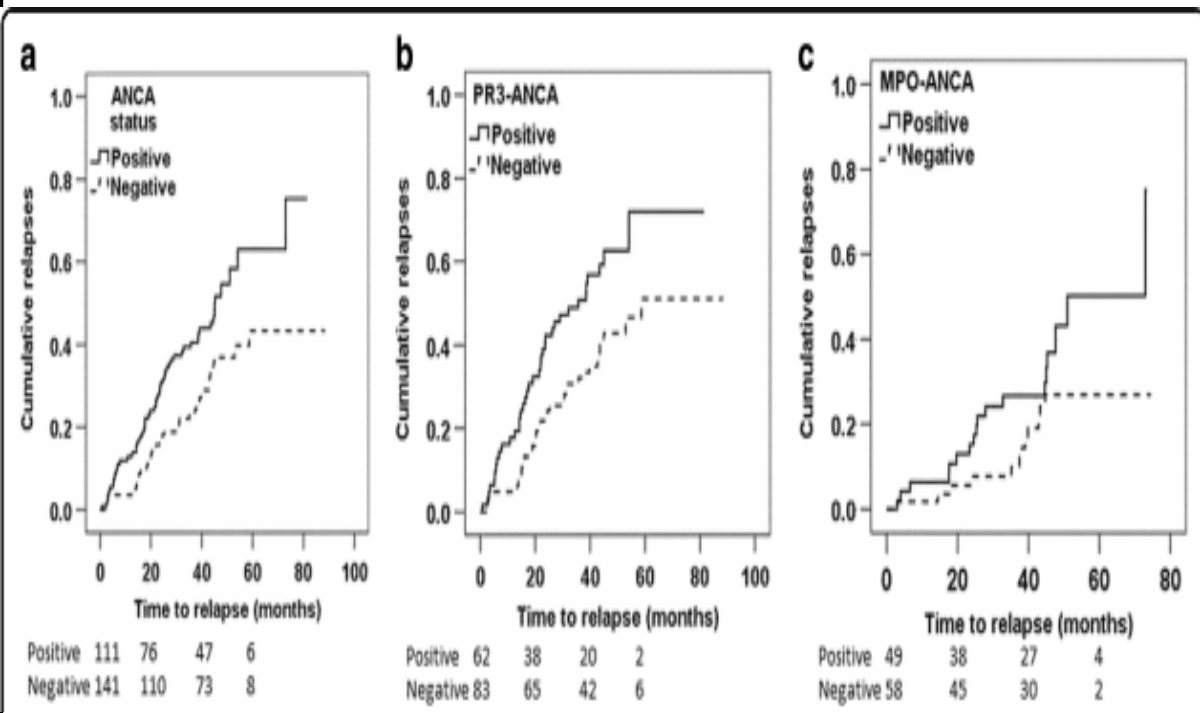


Table 4 Multivariable Cox regression survival analysis of factors associated with risk of relapse

Variable	Hazard ratio (95% CI)	*p*
ANCA status at switch to maintenance therapy		
ANCA-positive	1	0.026
ANCA-negative	0.63 (0.42–0.95)	
ANCA specificity at trial entry		
MPO-ANCA	1	0.005
PR3-ANCA	1.87 (1.21–2.89)	
Initial induction treatment		
Daily oral cyclophosphamide	1	0.045
Pulsed cyclophosphamide	1.52 (1.01–2.29)	
Creatinine at entry (per 50 μmol/L)	0.89 (0.83–0.97)	0.004
Initial maintenance therapy		
AZA	1	0.002
MMF	2.08 (1.38–3.13)	
Age (per decade)	0.88 (0.76–1.01)	0.065
Gender	0.98 (0.65–1.49)	0.93
Time to remission	1.0 (0.87–1.15)	0.97

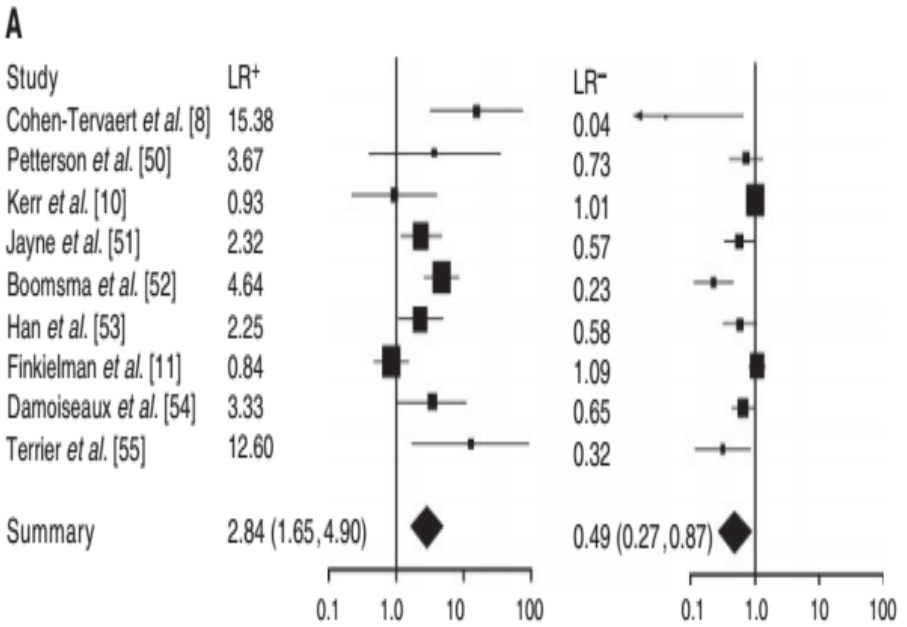
Value of ANCA measurements during remission to predict a relapse of ANCA-associated vasculitis—a meta-analysis

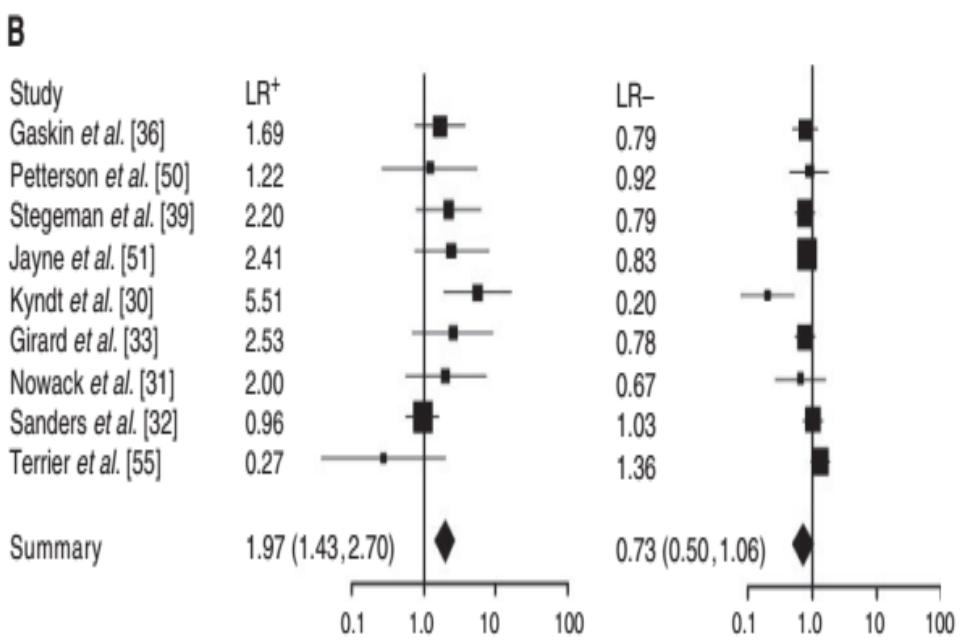
Rheumatology 2012;51:100–109

Gunnar Tomasson[1], Peter C. Grayson[1], Alfred D. Mahr[2], Michael LaValley[3] and Peter A. Merkel[1]

In 9 studies ↑ ANCA and ANCA persistence only modestly predict future relapses

Limited use to serial ANCA measurements during disease remission



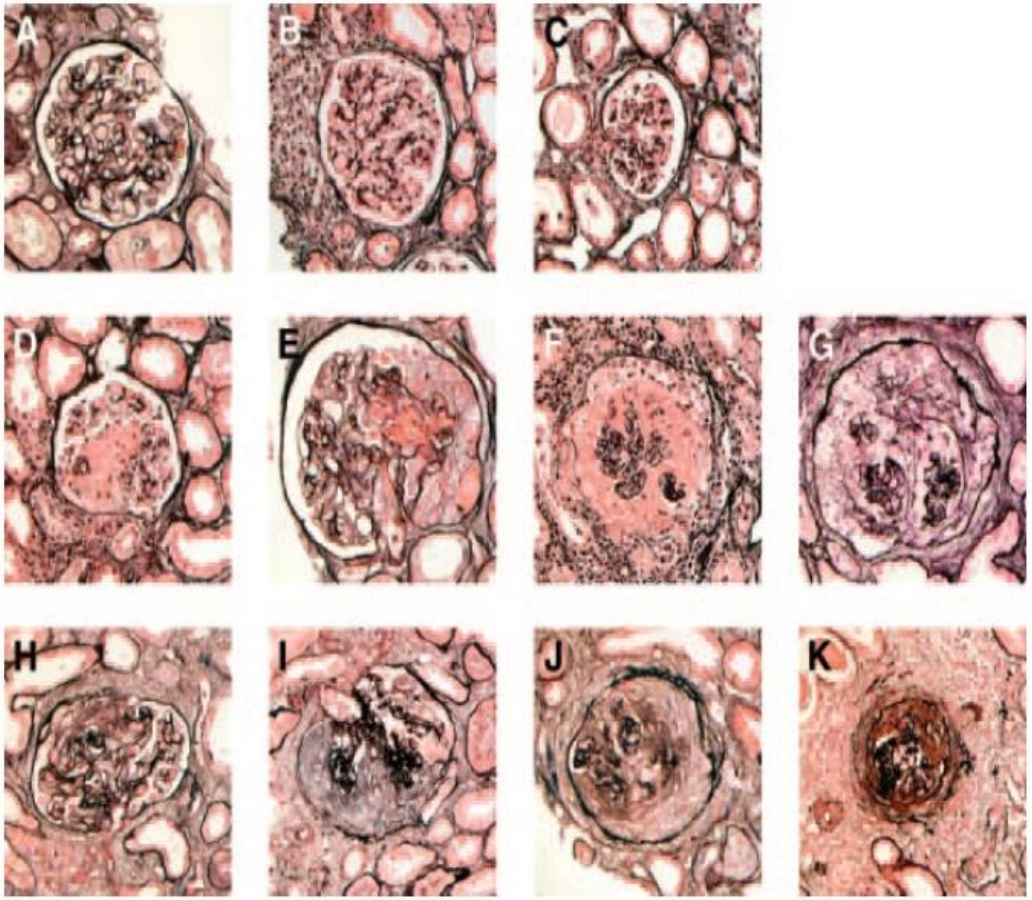


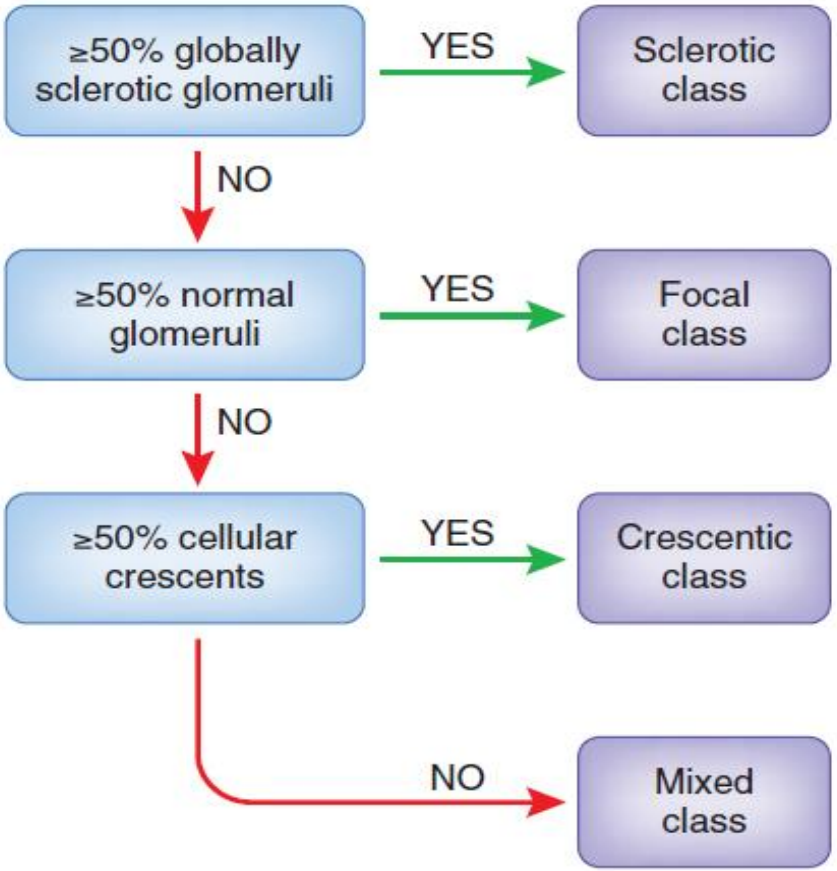
Histopathologic Classification of ANCA-Associated Glomerulonephritis

J Am Soc Nephrol 21: 1628–1636, 2010.

Annelies E. Berden,* Franco Ferrario,† E. Christiaan Hagen,‡ David R. Jayne,§ J. Charles Jennette,‖ Kensuke Joh,¶ Irmgard Neumann,** Laure-Hélène Noël,†† Charles D. Pusey,‡‡ Rüdiger Waldherr,§§ Jan A. Bruijn,* and Ingeborg M. Bajema*

New histologic classification of ANCA-associated glomerulonephritis





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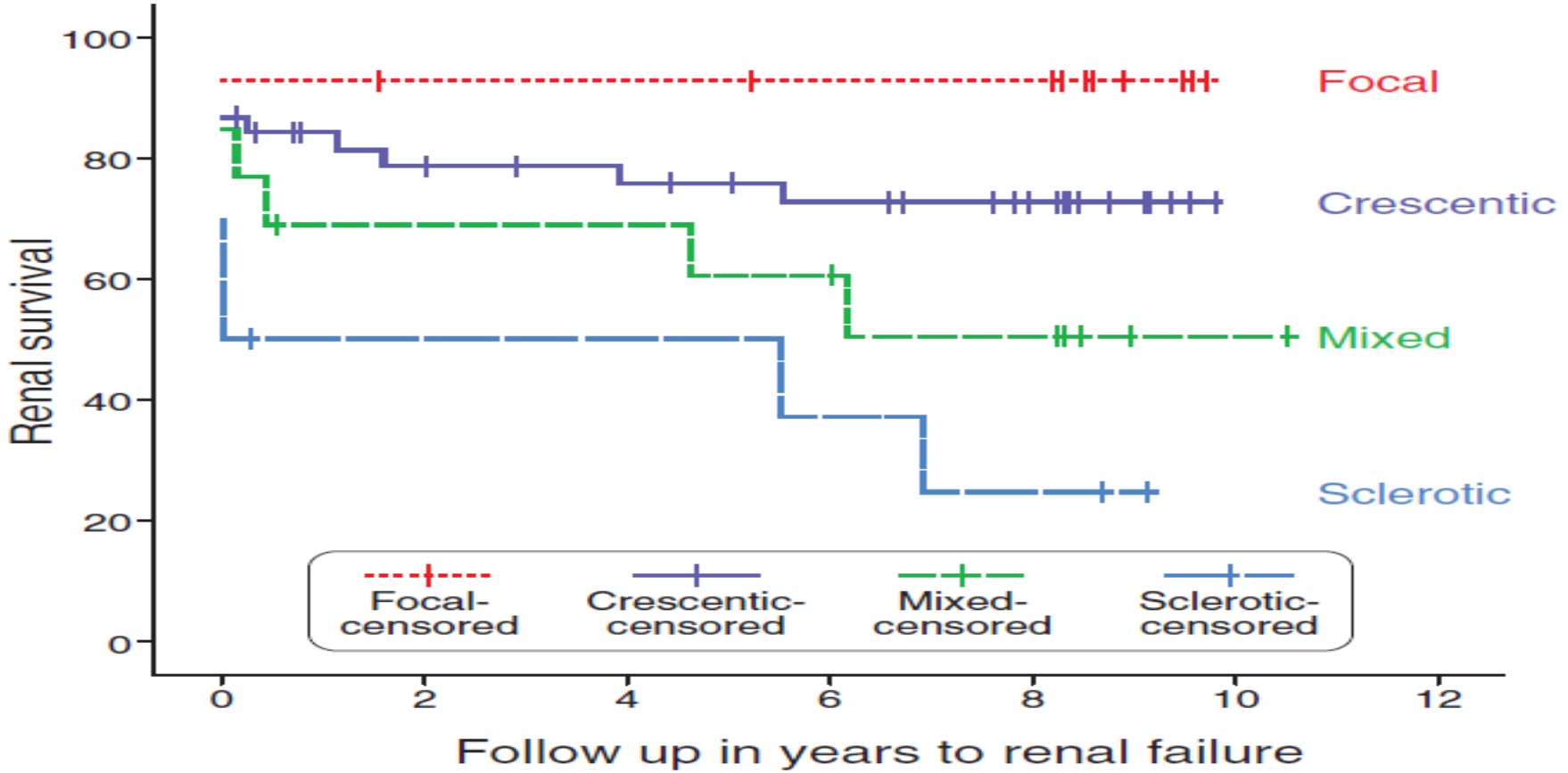
J Am Soc Nephrol 21: ●●●–●●●, 2010. doi: 10.1681/ASN.2010050477

GFR well preserved in focal and (relatively in) crescentic GN, deteriorating in mixed and sclerotic GN

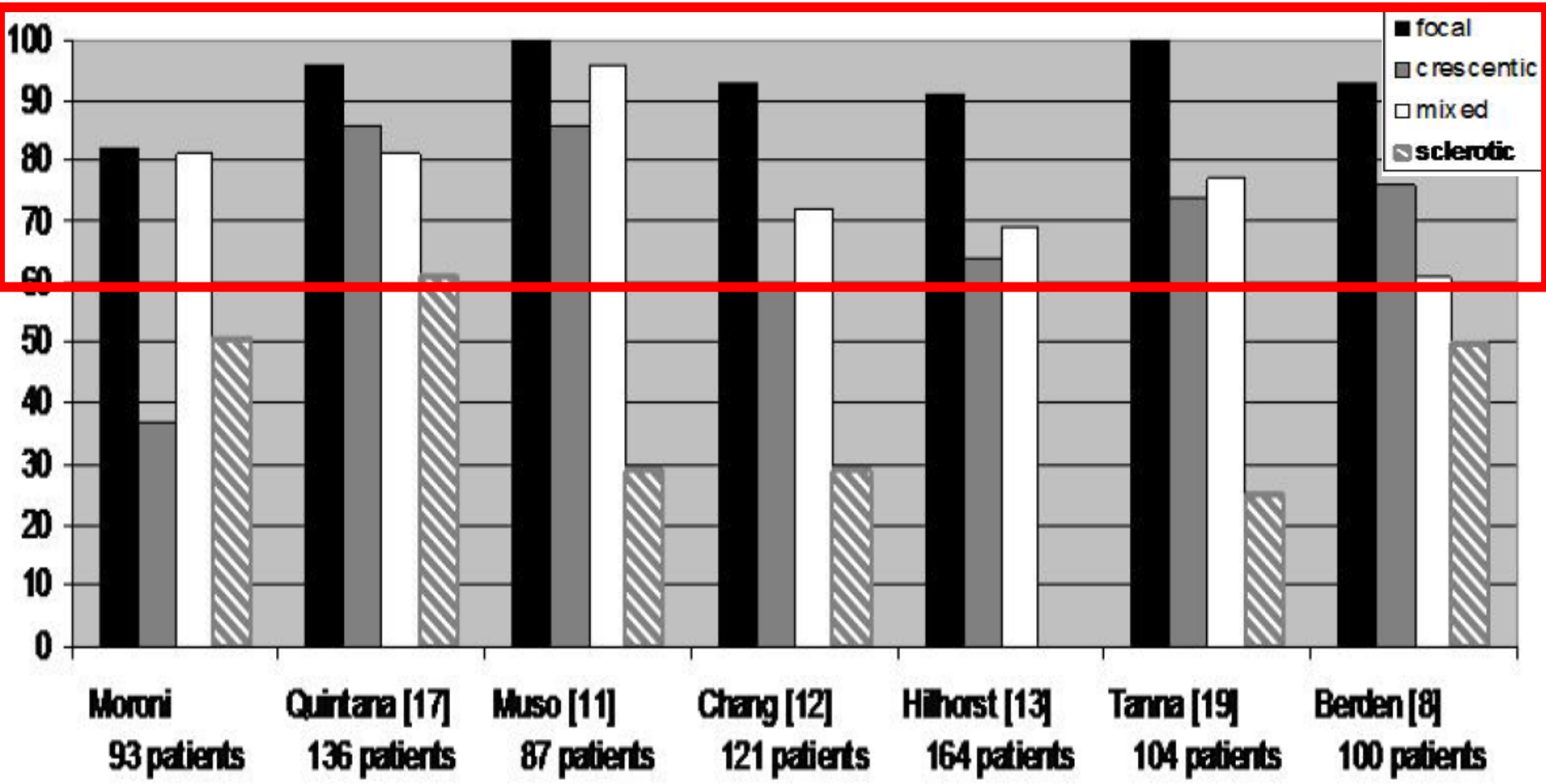


Predictors of renal survival in ANCA-associated vasculitis. Validation of a histopathological classification schema and review of the literature

Clin Exp Rheumatol 2015; 33 (Suppl. 89): S56-S63.

G. Moroni[1], V. Binda[1], A. Leoni[1], F. Raffiotta[1], S. Quaglini[2], G. Banfi[1], P. Messa[1]

5-year renal survival in mixed GN better in other studies than in original cohort of Berden et al.



Validation studies

Validation studies altogether in 1114 pts with AAV (784 Caucasian and 330 Asian)

Conclusions:

1. **classification generally validated (namely due to the difference between focal and sclerotic GN)**

2. **outcome in mixed GN generally better than in original study, no difference between crescentic and mixed GN**

3. **any difference driven namely by % of normal glomeruli, tubulointerstitial fibrosis and tubular atrophy (not part of classification) generally of importance**

4. **anti-MPO negative predictor, classification should be probably validated in anti-PR3 and anti-MPO disease separately**

5. **larger validation study warranted**

Repeat protocol renal biopsy in ANCA-associated renal vasculitis

Nephrol Dial Transplant (2014) 29: 1728–1732

Zdenka Hruskova[1], Eva Honsova[2], Annelies E. Berden[3], Ivan Rychlik[4], Vera Lanska[5], Jiri Zabka[6], Ingeborg M. Bajema[3] and Vladimir Tesar[1]

Protocol renal rebiopsy in 17 pts with AAV

Table 2. Comparison of clinical renal parameters at the time of first and reRB

Renal parameters	1st biopsy	Re-biopsy	P-value
S-creatinine (μmol/L)	281 (85–800)	142 (76–260)	<0.001
eGFR[a] (mL/min)	21 (6–95)	46 (23–107)	<0.001
HD (yes)	4 (23.5%)	0 (0%)	<0.05
PRU (g/24 h)	2.0 (0.5–6.3)	1.5 (0–6.7)	NS (0.055)
eryU (yes)	17 (100%)	4 (23.5%)	<0.05

Table 3. Comparison of histopathologic parameters between the first and reRB—significant differences

Histopathologic findings (in % of total gli)	1st biopsy	Re-biopsy	P-value
Normal glomeruli	25.0 (0–75)	26.8 (0–53.8)	NS (0.90)
Segm. cellular crescents	14.3 (4.7–71.4)	0 (0–6.5)	<0.001
Circumf. cellular crescents	15.8 (0–88.1)	0 (0–21.1)	<0.001
Total cellular crescents	52.2 (5.0–93.9)	2.0 (0–27.0)	<0.001
Fibrinoid necrosis	23.2 (7.8–47.1)	0 (0–15.1)	<0.001
Segm. fibrous crescents	2.6 (0–18.3)	13.9 (0–45.8)	0.01
Circumf. fibrous crescents	0 (0–25)	12.5 (0–34.3)	0.05
Total fibrous crescents	3.8 (0–38.8)	25.4 (0–51.3)	0.002
Global glomerulosclerosis	6.0 (0–46)	32.3 (0–59.5)	0.007
Segmental glomerulosclerosis	3.2 (0–25)	17.2 (0–28.6)	0.03
Total no. of sclerotic glomeruli	9.0 (0–64.5)	52.5 (0–70)	0.001
Oedema (yes)	12/15 (80%)	3/16 (18.8%)	0.01
Interstitial inflammation[a]	1.5 (0.5–3)	1 (0–2)	0.04
Interstitial fibrosis[b]	0.5 (0–2)	1.5 (0–2)	0.01

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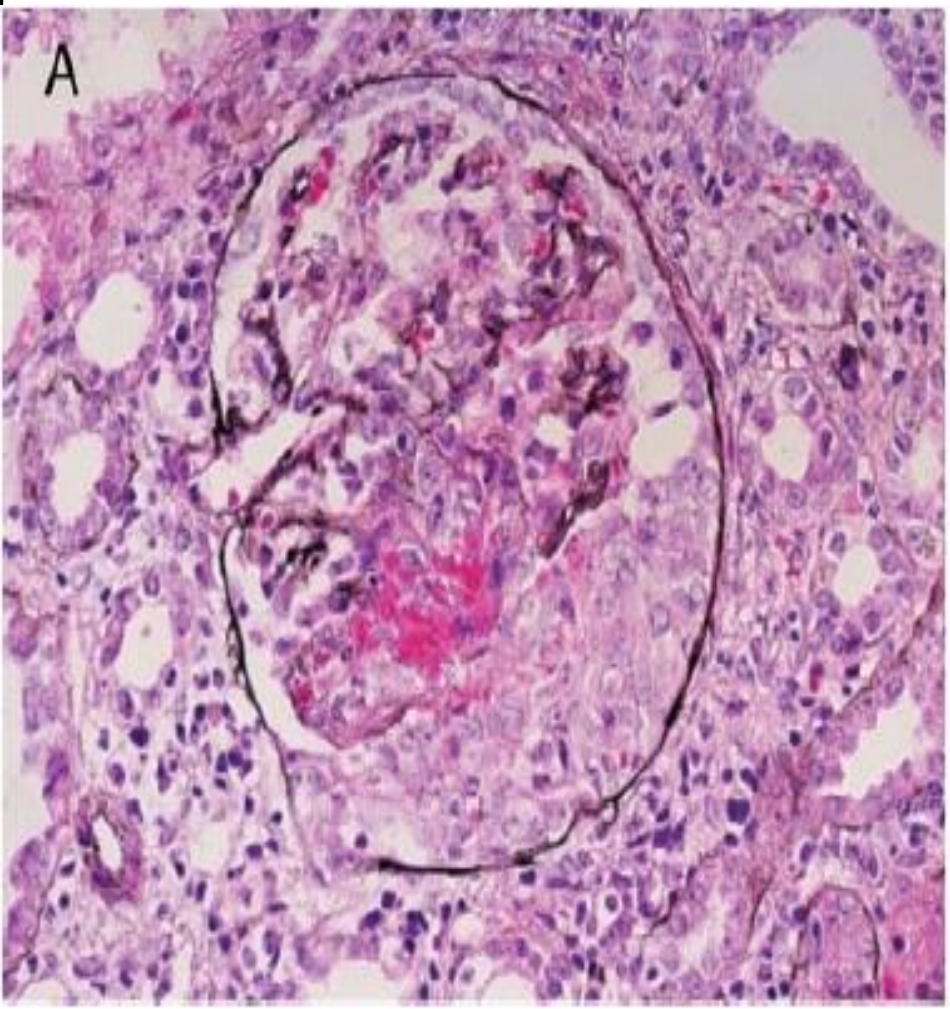
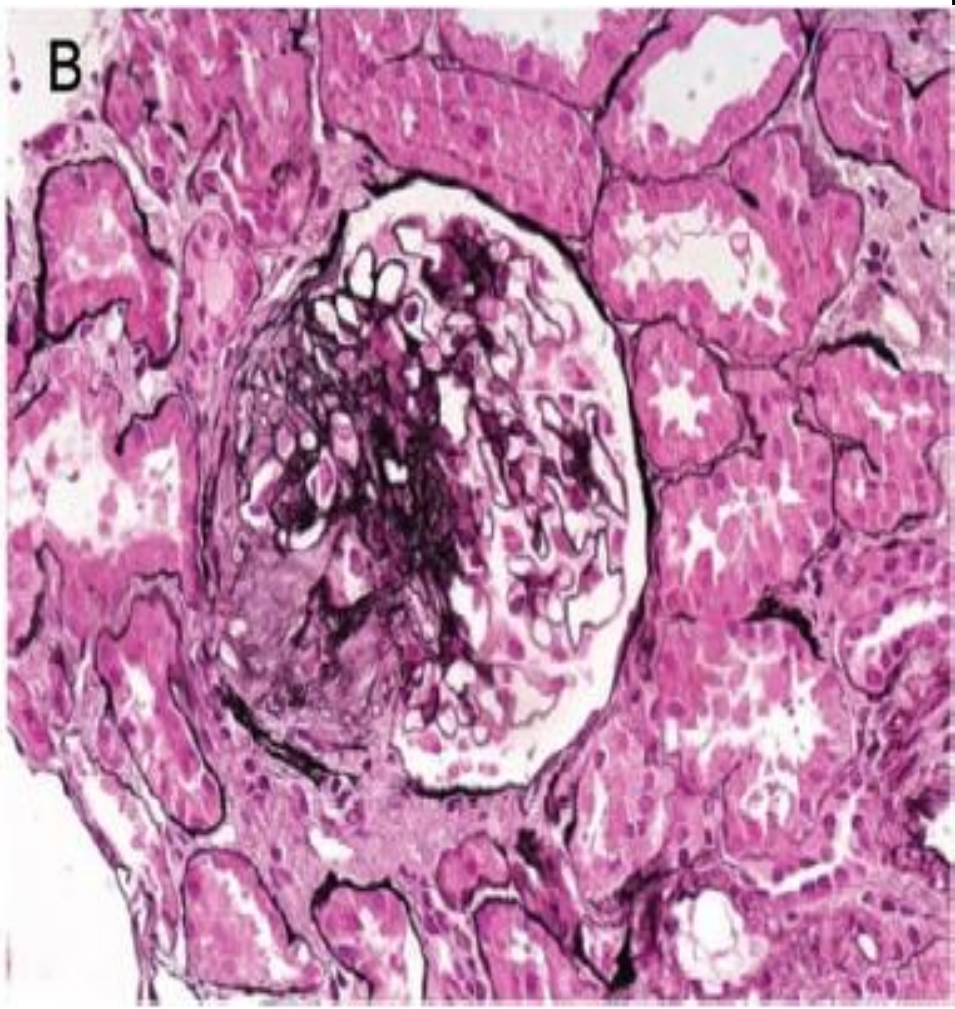
Necrosis and cellular crescents transform in fibrous crescents





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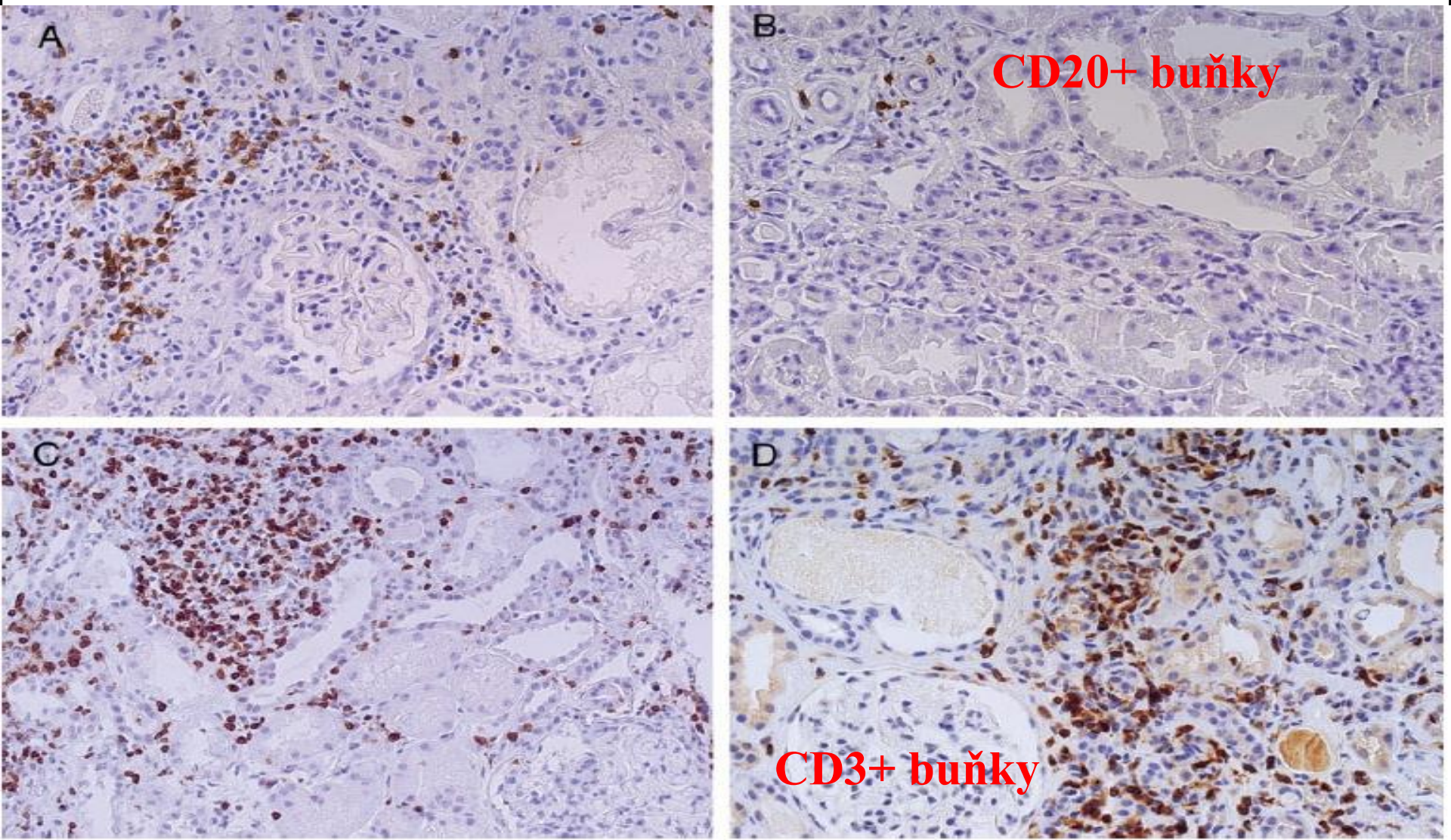
CD20+ cells disappeared, ale CD3+ cells persisted even in remission



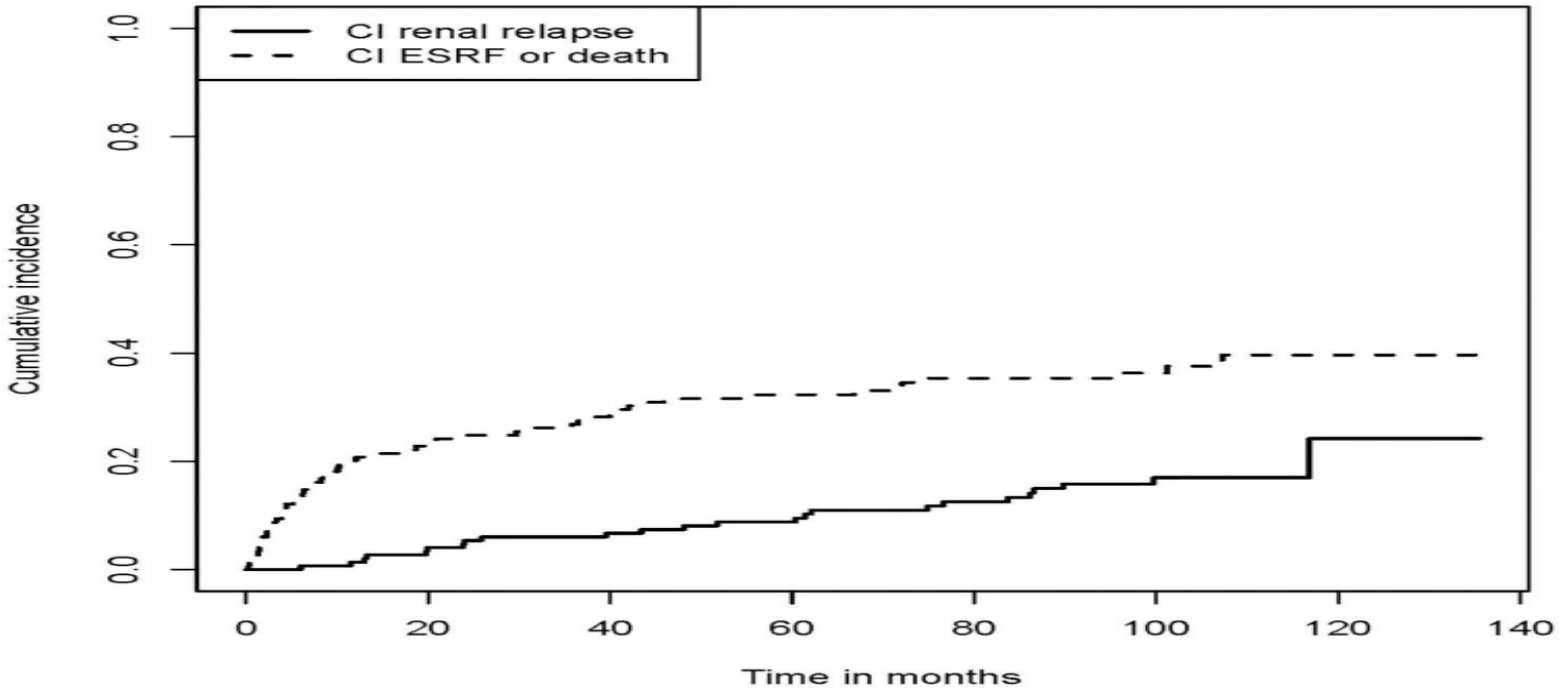
ANCA-Associated Glomerulonephritis: Risk Factors for Renal Relapse

PLOS ONE

December 14, 2016

Arda Göçeroğlu[1]*, Annelies E. Berden[1], Marta Fiocco[2,3], Oliver Floßmann[4], Kerstin W. Westman[5], Franco Ferrario[6], Gill Gaskin[7], Charles D. Pusey[7], E. Christiaan Hagen[8], Laure-Hélène Noël[9], Niels Rasmussen[10], Rüdiger Waldherr[11], Michael Walsh[12,13], Jan A. Bruijn[1], David R. W. Jayne[14], Ingeborg M. Bajema[1], on behalf of the European Vasculitis Society (EUVAS)[¶]

In 174 pts from MEPEX and CYCYZAREM cumulative incidence of renal relapse at 5 yrs was 9.5%, risk ↑in sclerotic class and with absence of interstitial infiltrates



Outline of the lecture

- Anti-PR3 vs. anti-MPO disease, predictive value of renal biopsy?
- **Initial therapy and relapse**
- Plasma exchange
- Maintenance therapy
- Conclusions

Wegener´s granulomatosis – outcome of untreated pts

1958 – Walton – outcome of untreated pts

Walton,E.W.: Giant-cell granuloma of the respiratory tract (Wegeners granulomatosis). British Medical Journal, 2: 265 – 269, 1958.

median survival: 5 months, majority of pts died of respiratory or renal failure

1983 – Fauci, NIH, Bethesda, survival of untreated pts

Fauci,A.S., et al.: Wegeners granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Annals of Internal Medicine, 98: 76 – 85, 1983.

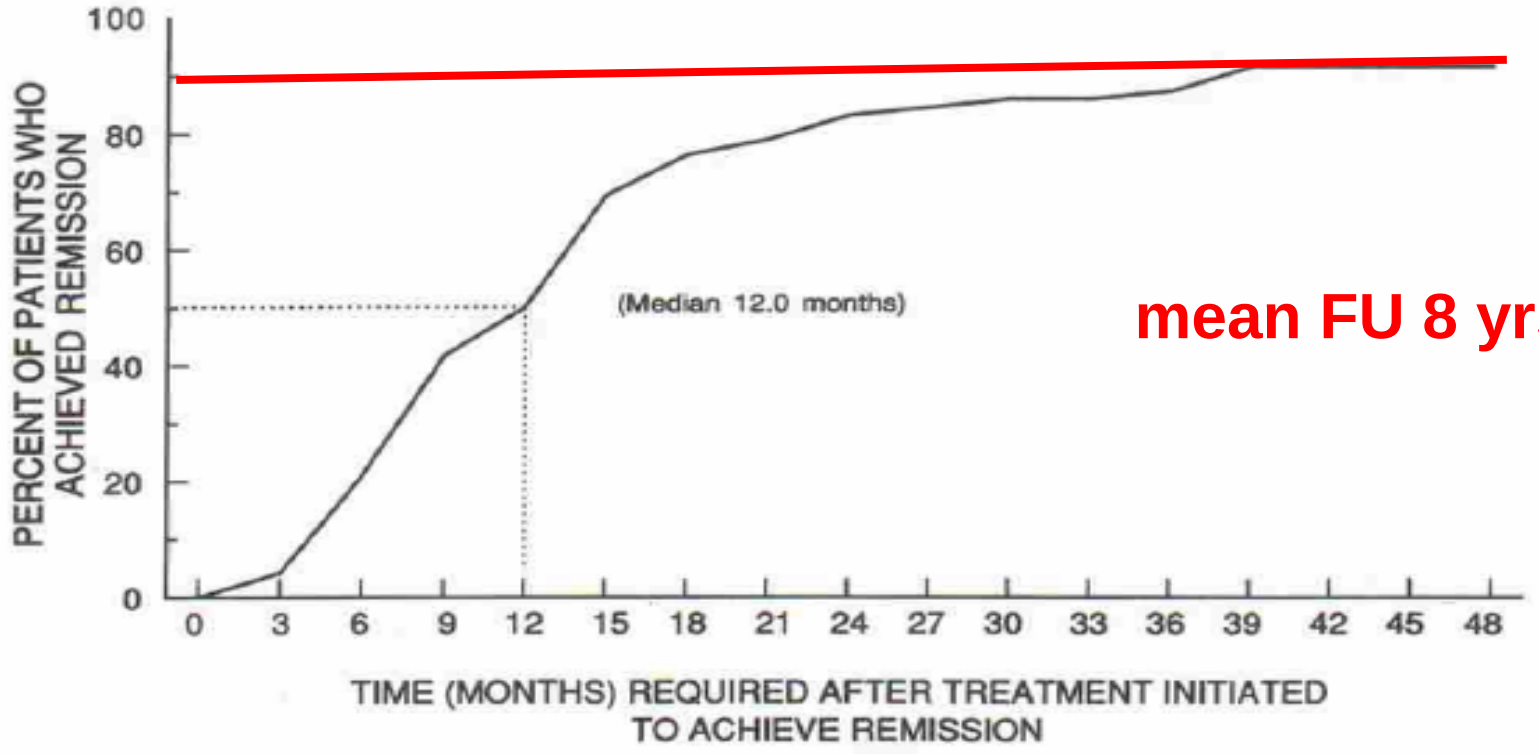
median survival – 5 months, 1-yr mortalita 82%, 2-yr mortalita 90%

Wegener Granulomatosis: An Analysis of 158 Patients

Gary S. Hoffman, MD; Gail S. Kerr, MD; Randi Y. Leavitt, MD, PhD; Claire W. Hallahan, MS; Robert S. Lebovics, MD; William D. Travis, MD; Menachem Rottem, MD; and Anthony S. Fauci, MD

Annals of Internal Medicine. 1992;**116**:488-498.

Cyclophosphamide – dramatic change of the outcome of patients



mean FU 8 yrs

91% marked improvement, 75% complete remission, 13% mortality, 50% remissions with at least one relapse, 15-yr risk of bladder cancer 16%

Long-term patient survival in ANCA-associated vasculitis

Ann Rheum Dis 2011;**70**:488–494.

Oliver Flossmann,[1] Annelies Berden,[2] Kirsten de Groot,[3] Chris Hagen,[4] Lorraine Harper,[5] Caroline Heijl,[6] Peter Höglund,[6] David Jayne,[7] Raashid Luqmani,[8] Alfred Mahr,[9] Chetan Mukhtyar,[10] Charles Pusey,[11] Niels Rasmussen,[12] Coen Stegeman,[13] Michael Walsh,[14] Kerstin Westman[6] for the European Vasculitis Study Group

Table 3 Causes of death within and after the first year of follow-up, respectively

Cause of death	<1 Year		>1 Year		Total (%)	
	Primary cause	Contributing factor	Primary cause	Contributing factor	Primary cause	Contributing factor
Active vasculitis	11 (18.6)	17 (28.8)	6 (8.1)	7 (9.5)	17 (12.8)	24 (18.0)
Pulmonary haemorrhage	6		2		8	
Infection	28 (47.5)	31 (52.5)	15 (20.3)	23 (31.1)	43 (32.3)	54 (40.6)
Pneumonia	15		8		23	
Sepsis	8		7		15	
CMV	2				2	
PCP	3				2	
Cardiovascular	9 (15.3)	11 (18.6)	19 (25.7)	21 (28.4)	28 (21.1)	32 (24.1)
Myocardial infarction	2		4		6	
Cerebrovascular accident	2		2		4	
Pulmonary embolus	2				2	
Sudden death	1		3		4	
Malignancy	0 (0)		16 (21.6)	18 (24.3)	16 (12.0)	18 (13.5)
Solid organ			12		12	
Haematological			4		4	
Miscellaneous	6 (10.2)		9 (12.2)		15 (11.3)	
Pulmonary fibrosis	3		3		6	
Unknown	5 (8.5)		9 (12.2)		14 (10.5)	
Total	59		74		133	

EUVAS studies to minimize CPH exposure

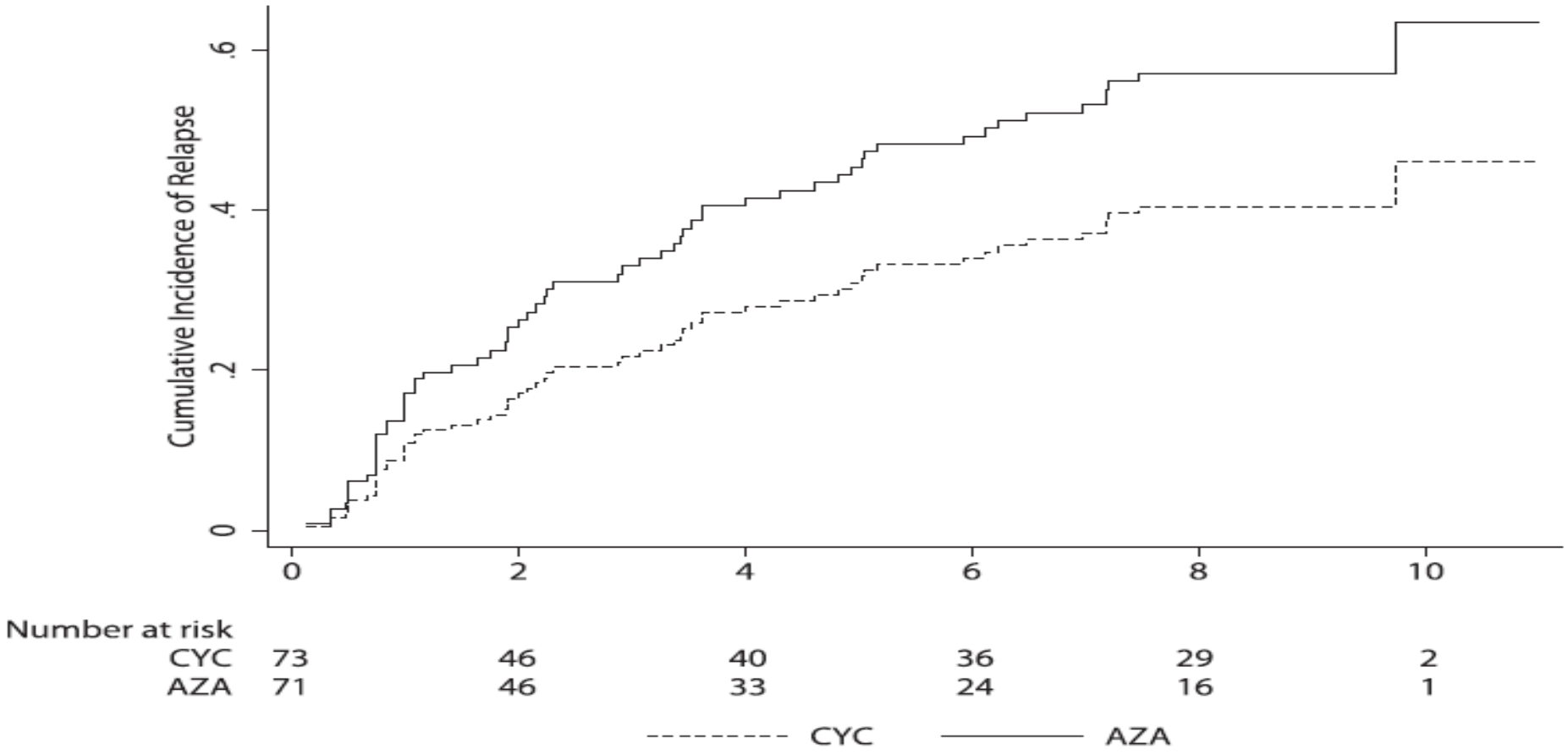
Early switch from CPH to AZA in generalized vasculitis does not increase the risk of relapses (*within relatively short follow-up* - CYCAZAREM)

CPH pulses (lower cumulative dose of CPH) are as effective as induction treatment in generalized vasculitis (CYCLOPS)

Long-Term Follow-Up of Cyclophosphamide Compared with Azathioprine for Initial Maintenance Therapy in ANCA-Associated Vasculitis

Michael Walsh, Mikkel Faurschou,† Annelies Berden,‡ Oliver Flossmann,§ Ingeborg Bajema,‡ Peter Hoglund,‖ Rona Smith,¶ Wladimir Szpirt,** Kerstin Westman,†† Charles D. Pusey,‡‡ and David R.W. Jayne,¶ for the European Vasculitis Study Group*

In CYCAZAREM after median FU of 8.5 yrs
there was a trend to ↑ relapse rate in pts switched early to AZA



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

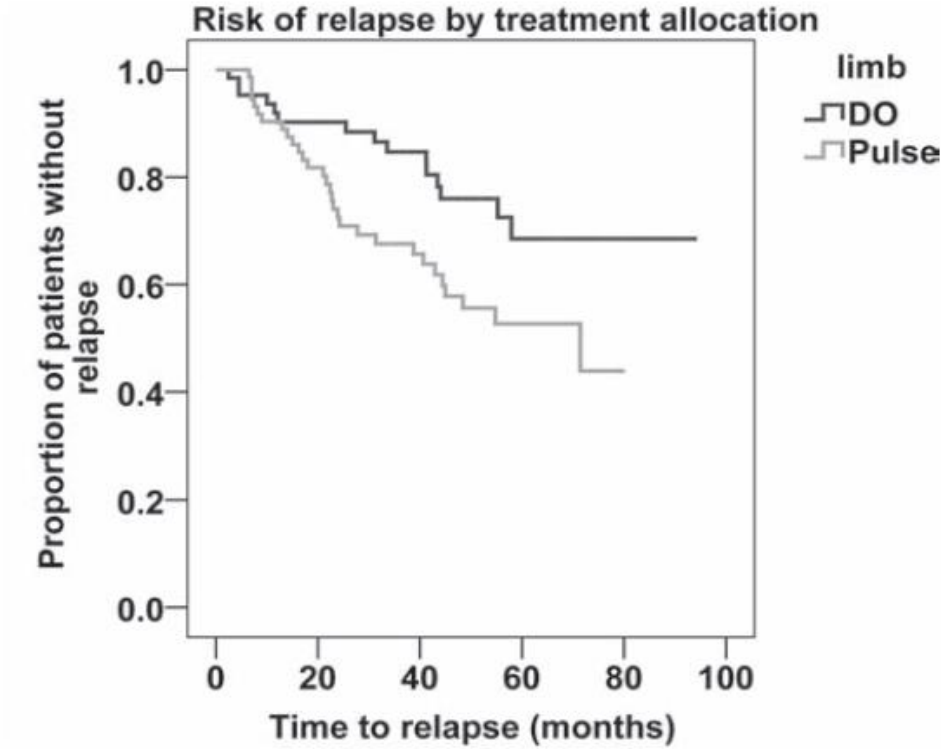
Ann Rheum Dis 2012;**71**:955–960.

Lorraine Harper,[1] Matthew D Morgan,[1] Michael Walsh,[2] Peter Hoglund,[3]

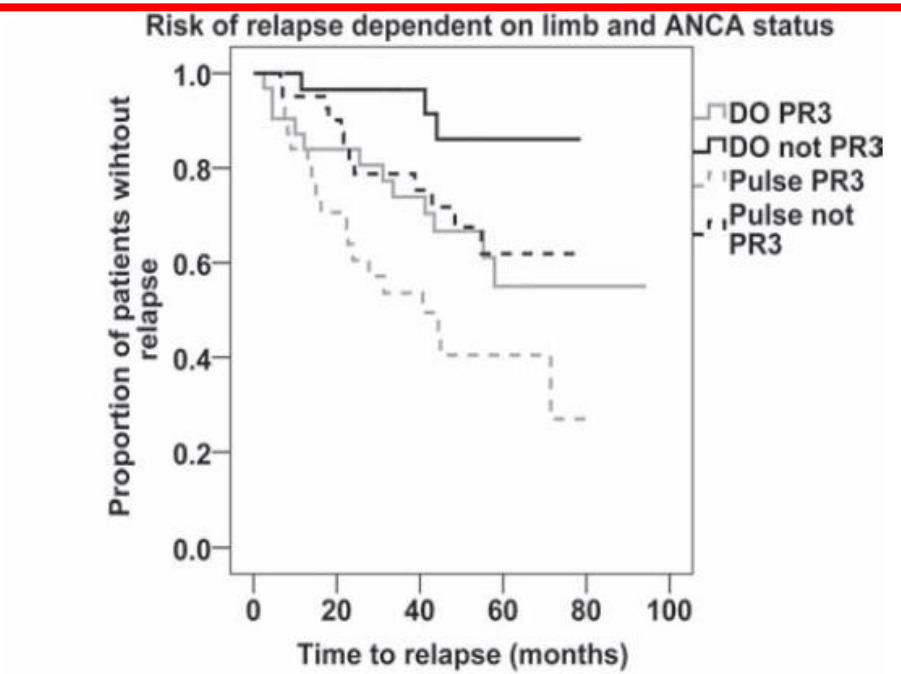
In CYCLOPS there was ↑ risk of relapse in pulse CPH limb

Table 1 Factors associated with relapse in the multivariable analysis

	HR	95.0% CI Lower	Upper	p Value
DO vs pulse	0.46	0.25	0.86	0.015
PR3-ANCA positive vs negative	2.47	1.32	4.59	0.004



Time (months)	0	20	40	60	80
DO (n)	72	55	46	26	2
Pulse (n)	76	64	54	24	3



Time (months)	0	20	40	60	80
DO not PR3-ANCA (n)	39	24	20	8	0
Pulse not PR3-ANCA (n)	43	32	22	9	0
DO PR3-ANCA (n)	33	25	21	9	2
Pulse PR3-ANCA (n)	33	21	13	5	1

ARD ONLINE

Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force

C Mukhtyar, O Flossmann, B Hellmich, P Bacon, M Cid, J W Cohen-Tervaert, W L Gross, L Guillevin, D Jayne, A Mahr, P A Merkel, H Raspe, D Scott, J Witter, H Yazici, R A Luqmani and on behalf of the European Vasculitis Study Group (EUVAS)

Ann Rheum Dis 2008;67;1004-1010; originally published online 2 Oct 2007; doi:10.1136/ard.2007.071936

Undertreatment shown to be one of the risk factors for relapses

Table 3 Factors associated with Wegener granulomatosis (WG) relapse with level of evidence

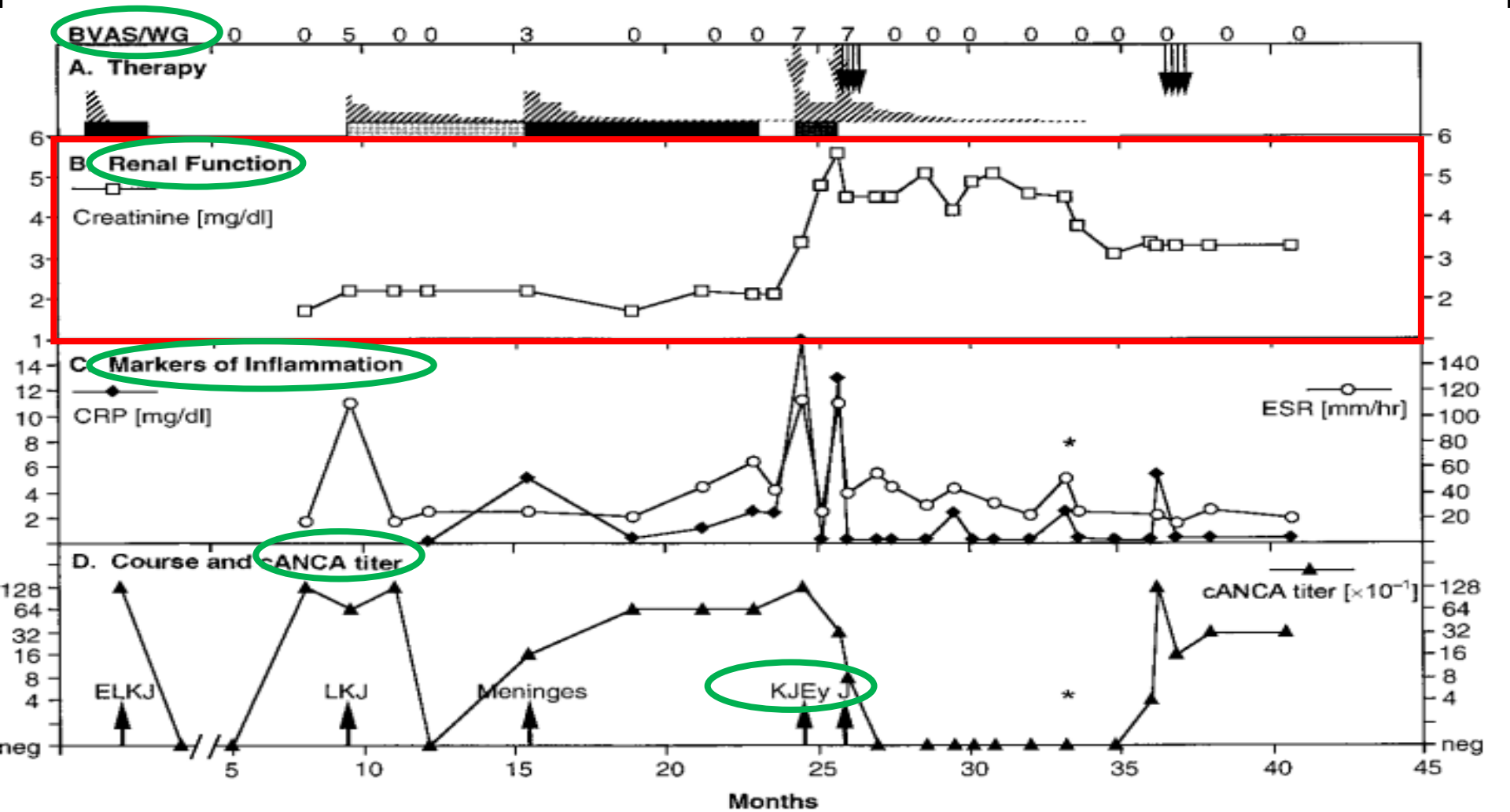
Risk factor	Risk of relapse	Level of evidence	Reference
A fourfold rise in C ANCA/PR3 ANCA titre	RR 42.5 (95% CI 9.48 to 180.8)	3	Boomsma *et al* 2000[23]
Chronic nasal carriage of *Staphylococcus aureus**	RR 7.16 (95% CI 1.63 to 31.50); p = 0.009	2B	Stegeman *et al* 1994[33]
Creatinine clearance >60 ml/min	RR 2.94 (95% CI 1.27 to 6.67); p = 0.01	3	Stegeman *et al* 1994[33]
The presence of ANCA at diagnosis	RR 2.89 (95% CI 1.12 to 7.45)	1B	Stegeman *et al* 1996[18]
Cardiac involvement at diagnosis	RH 2.87 (95% CI 1.09 to 7.58); p = 0.03	3	Koldingsnes and Nossent 2003[23]
Cumulative cyclophosphamide dose <10 g in the first 6 months	RH 2.83 (95% CI 1.33 to 6.02); p = 0.007	3	Koldingsnes and Nossent 2003[23]
Prednisolone ≥20 mg/day for <2.75 months	RH 2.41 (95% CI 1.12 to 5.21); p = 0.03	3	Koldingsnes and Nossent 2003[23]
Co-trimoxazole as adjuvant to remission maintenance therapy	RR 0.32 (95% CI 0.13 to 0.79)	1B	Stegeman *et al* 1996[18]

Response of Wegener's Granulomatosis to Anti-CD20 Chimeric Monoclonal Antibody Therapy

ARTHRITIS & RHEUMATISM
Vol. 44, No. 12, December 2001, pp 2836–2840

Ulrich Specks, Fernando C. Fervenza, Thomas J. McDonald, and Marie C. E. Hogan

First use of RTX in AAV - rapid response of BVAS, ANCA and CRP and stabilisation of renal function

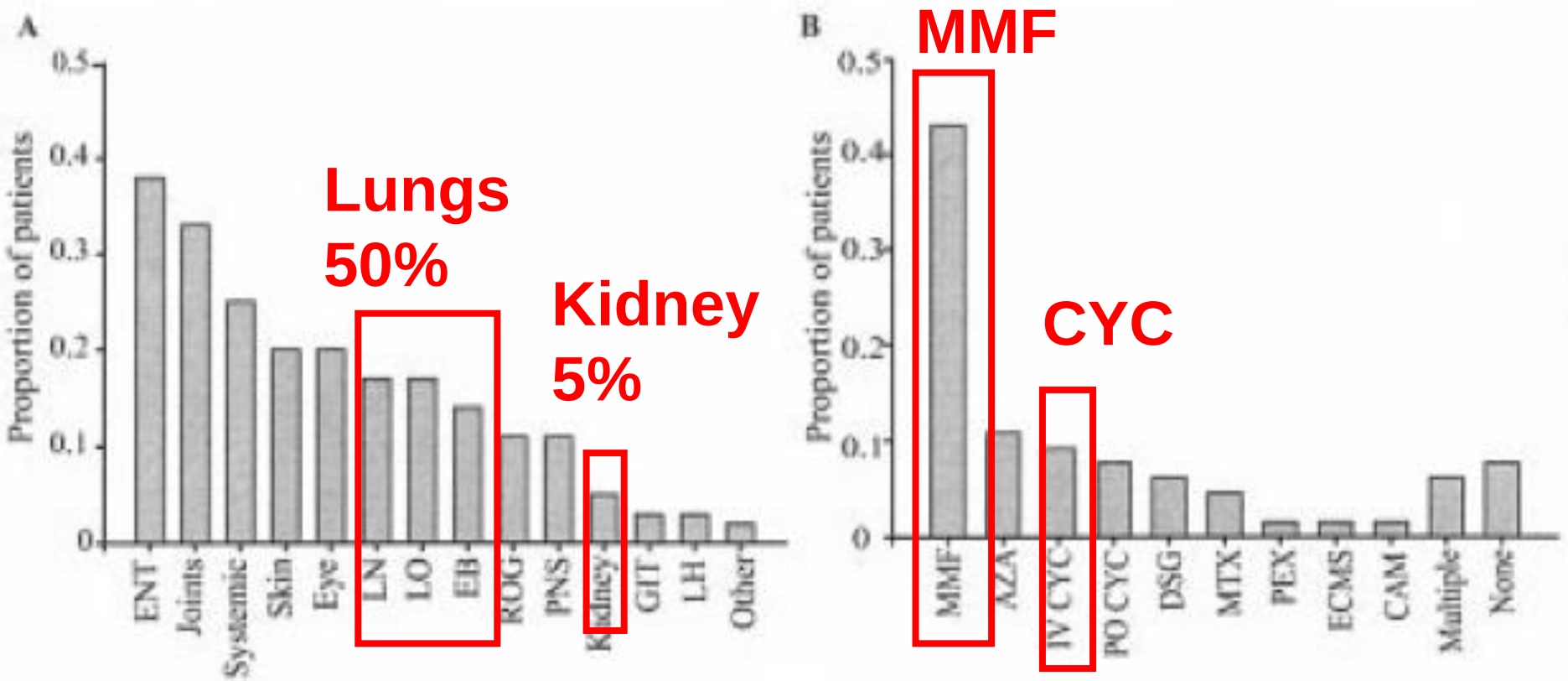


A Multicenter Survey of Rituximab Therapy for Refractory Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Rachel B. Jones,[1] Alastair J. Ferraro,[2] Afzal N. Chaudhry,[1] Paul Brogan,[3] Alan D. Salama,[4] Kenneth G. C. Smith,[5] Caroline O. S. Savage,[2] and David R. W. Jayne[1]

ARTHRITIS & RHEUMATISM
Vol. 60, No. 7, July 2009, pp 2156–2168

65 consecutive pts with refractory AAV, 4 British centres



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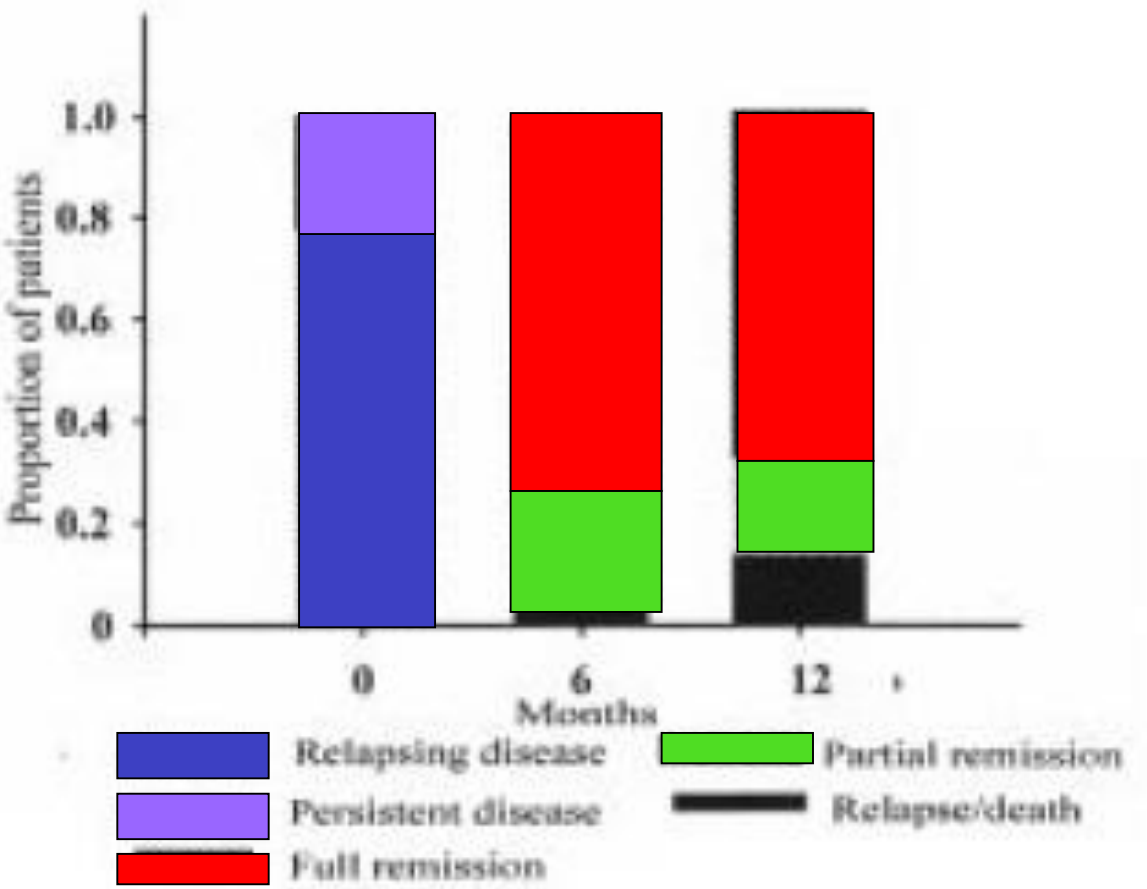
ARTHRITIS & RHEUMATISM
Vol. 60, No. 7, July 2009, pp 2156–2168



75% complete

remission

23% partial

remission

2% no response

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D., Philip Seo, M.D., M.H.S., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Anthony Turkiewicz, M.D., Nadia K. Tchao, M.D., Lisa Webber, R.N., Linna Ding, M.D., Ph.D., Lourdes P. Sejismundo, R.N., B.S.N., Kathleen Mieras, C.C.R.P., David Weitzenkamp, Ph.D., David Ikle, Ph.D., Vicki Seyfert-Margolis, Ph.D., Mark Mueller, B.S., C.C.R.P., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina A. Keogh, M.D., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., and Ulrich Specks, M.D., for the RAVE–ITN Research Group*

N ENGL J MED 363;3 NEJM.ORG JULY 15, 2010

RAVE study

194 pts with generalized AAV
(2/3 with renal involvement - mean GFR 61 ml/min)
randomized to either:

1) conventional treatment (CPH and CS, followed by AZA)
2) rituximab (plus CS, initially) for remission induction

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D., Philip Seo, M.D., M.H.S., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Anthony Turkiewicz, M.D., Nadia K. Tchao, M.D., Lisa Webber, R.N., Linna Ding, M.D., Ph.D., Lourdes P. Sejismundo, R.N., B.S.N., Kathleen Mieras, C.C.R.P., David Weitzenkamp, Ph.D., David Ikle, Ph.D., Vicki Seyfert-Margolis, Ph.D., Mark Mueller, B.S., C.C.R.P., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina A. Keogh, M.D., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., and Ulrich Specks, M.D., for the RAVE–ITN Research Group*

N ENGL J MED 363;3 NEJM.ORG JULY 15, 2010

RAVE study

64% of RTX pts vs. 53% of CPH pts reached the primary endpoint (non-inferiority)

RTX more effective than CPH in inducing remission in relapsing disease: 67% vs. 42% reached the primary endpoint

Rate of adverse events not different in both limbs

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 15, 2010 VOL. 363 NO. 3

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

Rachel B. Jones, M.R.C.P., M.D., Jan Willem Cohen Tervaert, M.D., Ph.D., Thomas Hauser, M.D., Raashid Luqmani, D.M., F.R.C.P., F.R.C.P.(E.), Matthew D. Morgan, M.R.C.P., Ph.D., Chen Au Peh, F.R.A.C.P., Ph.D., Caroline O. Savage, Ph.D., F.R.C.P., F.Med.Sci., Mårten Segelmark, M.D., Ph.D., Vladimir Tesar, M.D., Ph.D., Pieter van Paassen, M.D., Ph.D., Dorothy Walsh, B.S.C.N., Michael Walsh, M.D., F.R.C.P.(C.), Kerstin Westman, M.D., Ph.D., and David R.W. Jayne, M.D., F.R.C.P., for the European Vasculitis Study Group

RITUXVAS study

RTX vs. CPH in 44 pts with new AAV and renal involvement

Demographics	RTX N=33	CYC N=11
Age (years)	68 (56-75)	67 (58-76)
Male sex	17 (52)	6 (55)
Wegener's granulomatosis	18 (55)	4 (36)
Microscopic polyangiitis or renal-limited vasculitis	15 (45)	7 (64)
PR3/MPO ANCA (U/ml)	53 (14-100)	79 (28-163)
c-ANCA/ p-ANCA	20/13 (63/37)	5/6 (45/55)
Glomerular filtration rate (ml/min)#	20 (5-44)	12 (9-33)
Total number of organs involved	3 (2-4)	2 (2-3)
BVAS 2003	19 (14-24)	18 (12-25)
C-reactive protein	28 (12-87)	25 (7-87)
Erythrocyte sedimentation rate	52 (14-82)	64 (21-106)
Required dialysis at entry	8 (24)	1 (9)
Methyl prednisolone IV (grams)	1 (1-1)	1 (1-1)
Received any plasma exchange	8 (24)	3 (27)

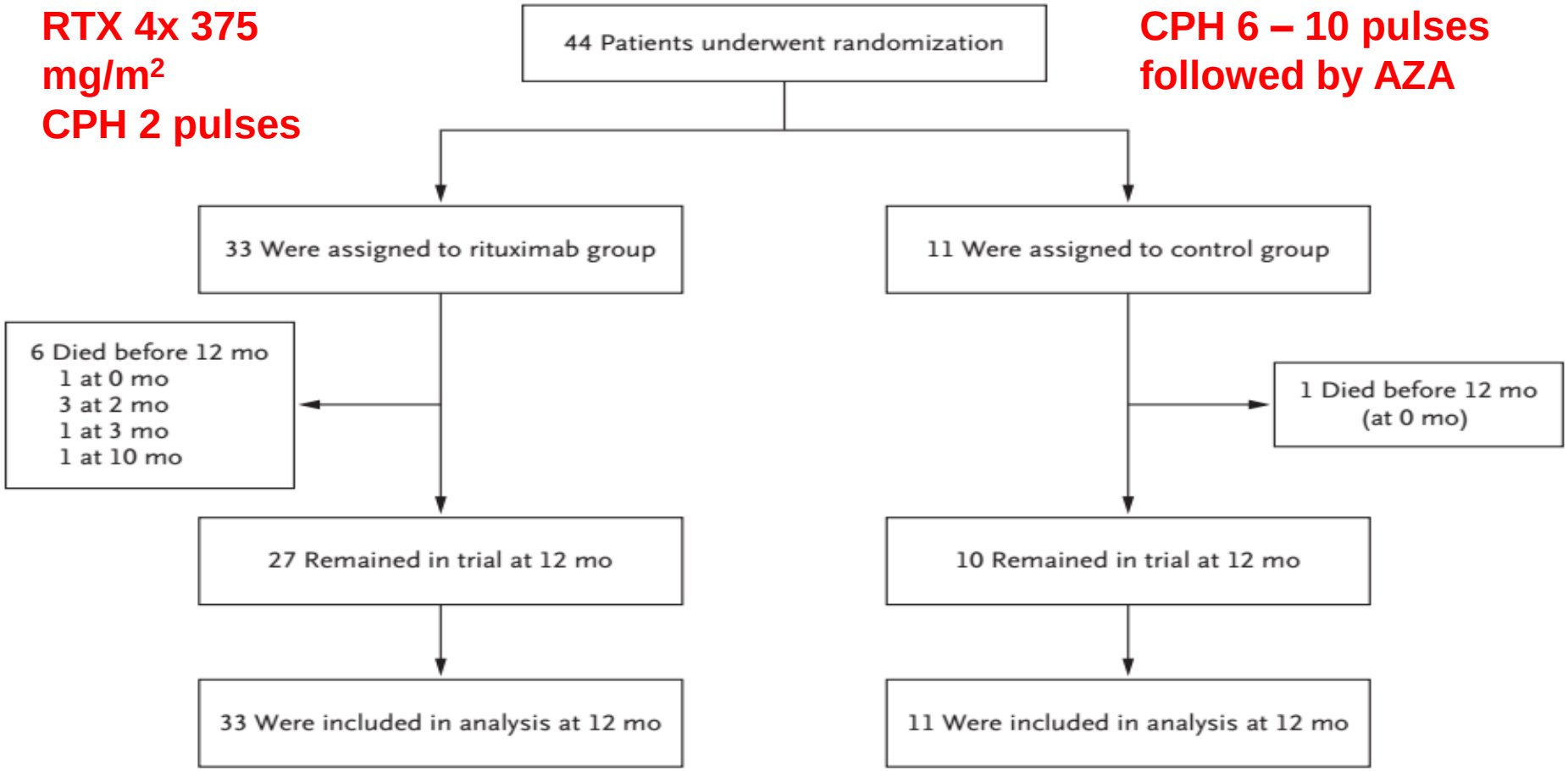
Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

RITUXVAS study

N ENGL J MED 363;3 NEJM.ORG JULY 15, 2010

RTX 4x 375 mg/m²
CPH 2 pulses

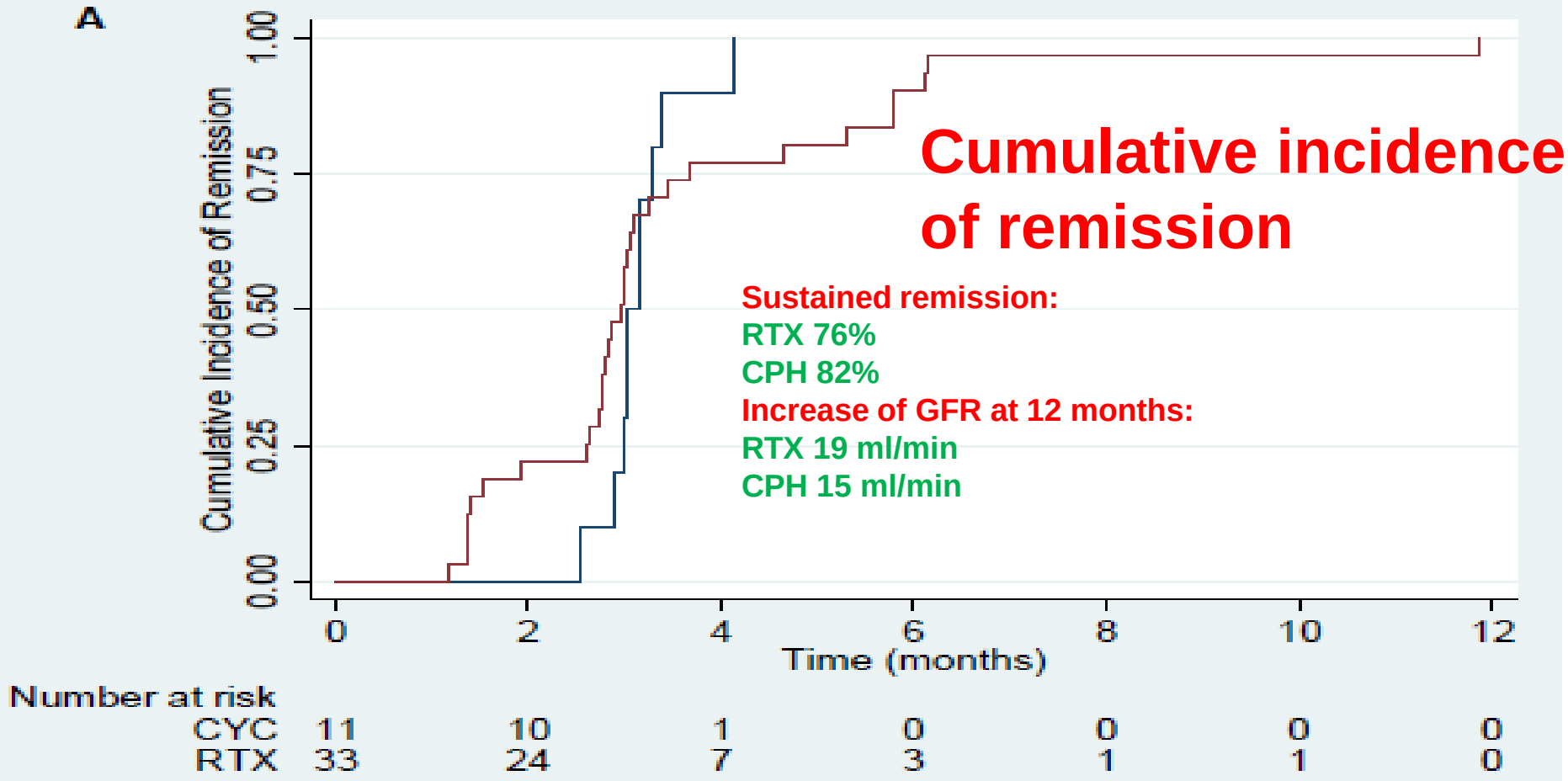
CPH 6 – 10 pulses followed by AZA



Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

RITUXVAS study

N ENGL J MED 363;3 NEJM.ORG JULY 15, 2010



Cumulative incidence of remission

Sustained remission:
RTX 76%
CPH 82%
Increase of GFR at 12 months:
RTX 19 ml/min
CPH 15 ml/min

KDIGO CLINICAL PRACTICE GUIDELINE FOR GLOMERULONEPHRITIS

CHAPTER 13: PAUCI-IMMUNE FOCAL AND SEGMENTAL NECROTIZING GLOMERULONEPHRITIS

VOLUME 2 | ISSUE 2 | JUNE 2012

13.1: *Initial treatment of pauci-immune focal and segmental necrotizing GN*

13.1.1: We recommend that cyclophosphamide and corticosteroids be used as initial treatment. (*1A*)

13.1.2: We recommend that rituximab and corticosteroids be used as an alternative initial treatment in patients without severe disease or in whom cyclophosphamide is contraindicated. (*1B*)

KDIGO CLINICAL PRACTICE GUIDELINE FOR GLOMERULONEPHRITIS

CHAPTER 13: PAUCI-IMMUNE FOCAL AND SEGMENTAL NECROTIZING GLOMERULONEPHRITIS

VOLUME 2 | ISSUE 2 | JUNE 2012

13.5: *Treatment of relapse*

13.5.1: We recommend treating patients with severe relapse of ANCA vasculitis (life- or organ-threatening) according to the same guidelines as for the initial therapy (see Section 13.1). (*1C*)

13.5.2: We suggest treating other relapses of ANCA vasculitis by reinstituting immunosuppressive therapy or increasing its intensity with agents other than cyclophosphamide, including instituting or increasing dose of corticosteroids, with or without azathioprine or MMF. (*2C*)

13.6: *Treatment of resistant disease*

13.6.1: In ANCA GN resistant to induction therapy with cyclophosphamide and corticosteroids, we suggest the addition of i.v. immunoglobulin (*2C*) or rituximab (*2D*), or plasmapheresis (*2D*).

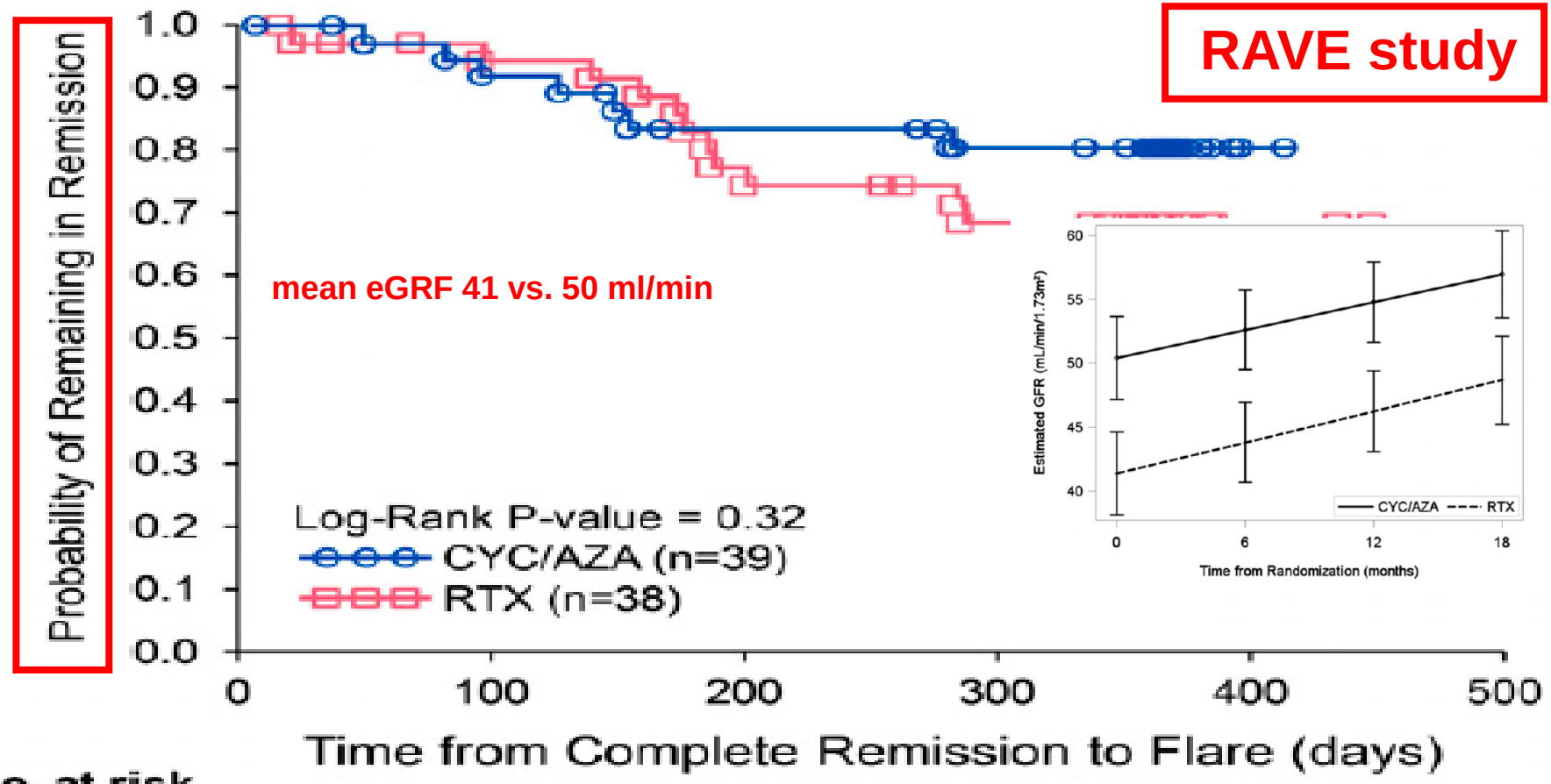
Rituximab Versus Cyclophosphamide for ANCA-Associated Vasculitis with Renal Involvement

J Am Soc Nephrol 26: ●●●–●●●, 2014.

Duvuru Geetha,* Ulrich Specks,† John H. Stone,‡ Peter A. Merkel,§‖ Philip Seo,*

Subanalysis of 102 pts from RAVE study with renal involvement, no difference in remaining in remission and improvement of eGFR

RAVE study



No. at risk

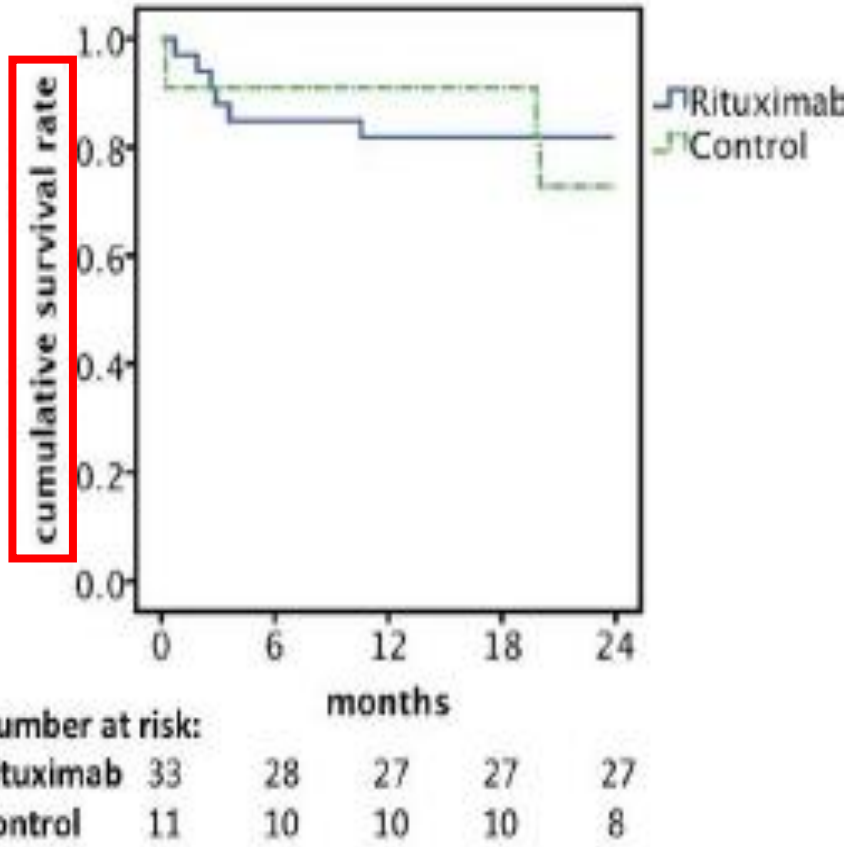
CYC/AZA	39	34	29	25	1
RTX	38	33	26	22	2

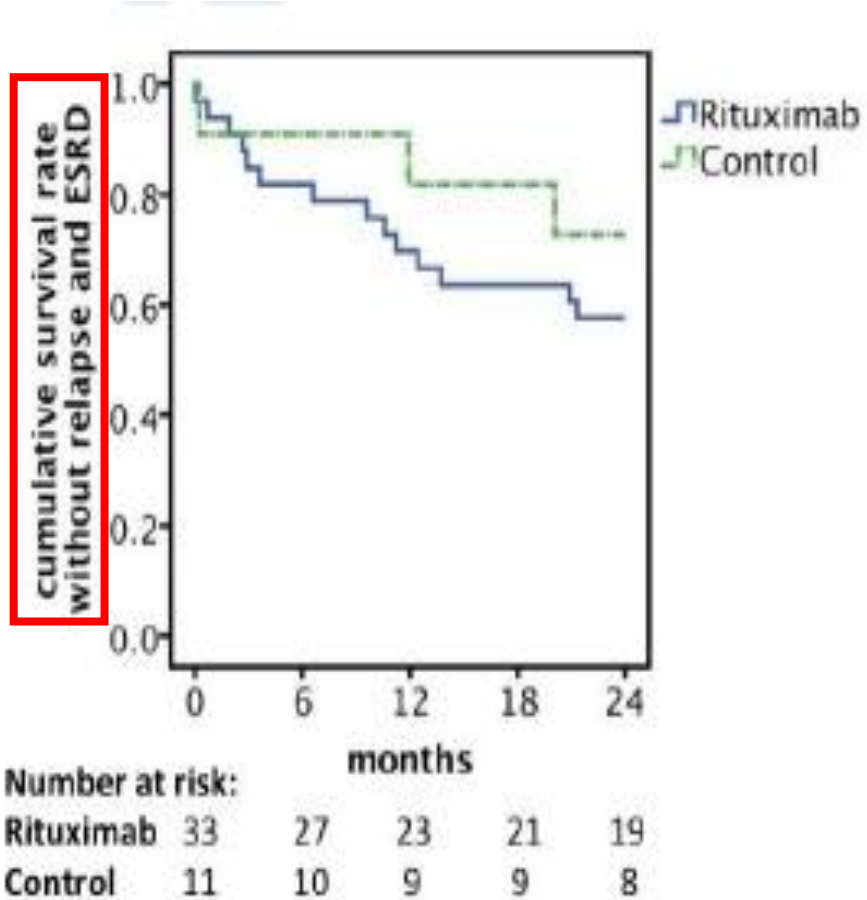
Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial

Ann Rheum Dis 2015;**74**:1178–1182

Rachel B Jones,[1] Shunsuke Furuta,[1] Jan Willem Cohen Tervaert,[2] Thomas Hauser,[3] Raashid Luqmani,[4] Matthew D Morgan,[5] Chen Au Peh,[6] Caroline O Savage,[5] Marten Segelmark,[7] Vladimir Tesar,[8] Pieter van Paassen,[2] Michael Walsh,[9] Kerstin Westman,[10] David RW Jayne,[1] for the European Vasculitis Society (EUVAS)

In RITUXVAS survival (and relapse-free and ESRD-free survival) not different between RTX and CPH limb





Rituximab for treatment of severe renal disease in ANCA associated vasculitis

Duvuru Geetha[1,11] · Zdenka Hruskova[2] · Marten Segelmark[3] · Jonathan Hogan[4] · Matthew D. Morgan[5] · Teresa Cavero[6] · Per Eriksson[7,8] · Philip Seo[1] · Rebecca L. Manno[1] · Jessica Dale[9] · Lorraine Harper[5] · Vladimir Tesar[2] · David RW Jayne[10]

J Nephrol (2016) 29:195–201

Retrospective analysis of 37 pts with AAV and eGFR < 20 ml/min demonstrated similar efficacy of RTX with or without CPH

Outcomes	Group A(n = 12)	Group B (n = 25)	p value
Remission n (%) (n = 34)	11 (100 %)	21 (95 %)	1.0
Median 6 month prednisone dose (mg) (range)	5 (0–6)	7.5 (5–10)	0.04
Mean GFR rise at 6 months (SD)	18 (20)	13 (24)	0.6
Renal recovery, n (%) (n = 15)	5 (71)	5 (62)	1.0
Infections, n (%)	2 (17)	8 (32)	0.44
Leukopenia, n (%)	2 (17)	2 (8)	0.58
ESRD, n (%)	4 (33)	8 (32)	1.0
Death in the first 6 months	0 (0)	3 (12)	0.54

Treatment of Severe Renal Disease in ANCA Positive and Negative Small Vessel Vasculitis with Rituximab

Shivani Shah[a] Zdenka Hruskova[c] Marten Segelmark[d] Matthew D. Morgan[e]
Jonathan Hogan[b] Steven K. Lee[a] Jessica Dale[f] Lorraine Harper[e]
Vladimir Tesar[c] David R.W. Jayne[g] Duvuru Geetha[a]

Am J Nephrol 2015;41:296–301

Analysis of 14 pts with severe renal AAV - good efficacy of RTX: all pts developed remission, eGFR improved, treatment well tolerated

Table 2. Outcomes of AAV/ANCA-negative small vessel vasculitis patients with severe renal disease treated with rituximab and glucocorticoids

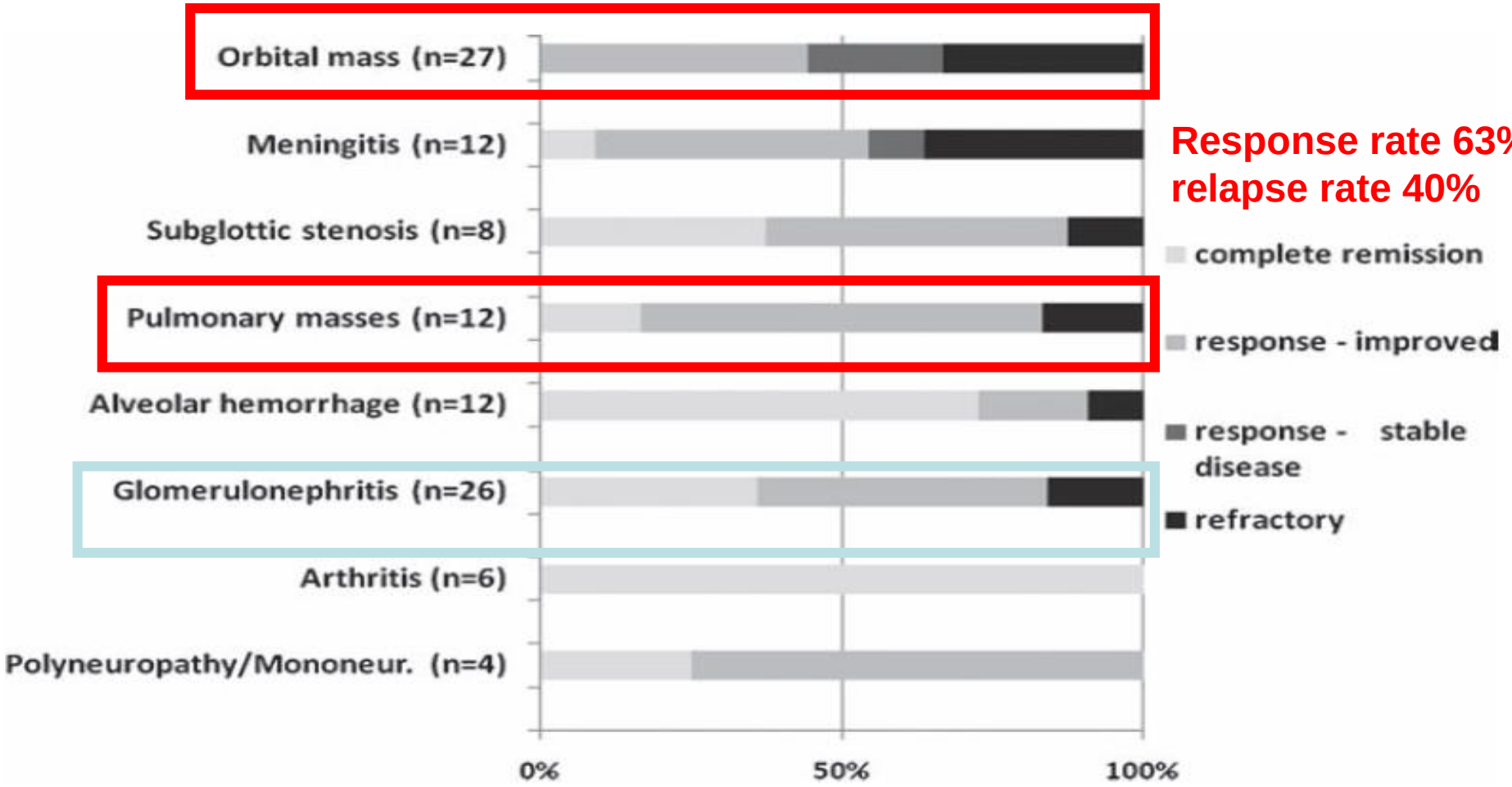
Patient	Vasculitis type	HD at presentation	Rituximab course completed	Remission	MDRD eGFR at 6 months	Dialysis independence at 6 months**	Prednisone dose (in mg) at 6 months	B-cell depletion at 6 months	Leukopenia	Infection causing hospitalization	ESRD	Cause of death (if applicable)
1	MPA	+	– (lost insurance coverage)	+	41	+	10	+	–		–	
2	MPA	–	+	+	22	n/a	0	Unknown	–		+	Clostridium difficile sepsis
3	MPA	+	+	+	25	+	5	Unknown	–	Herpes zoster	–	
4	MPA	–	+	+	23	n/a	5	+	–		–	
5	MPA	–	+	+	37	n/a	0	Unknown	–	Pneumonia, urinary tract infection	–	
6	GPA	–	+	+	35	n/a	8	Unknown	–		–	
7	MPA	+	+	+	ESRD	–	0	Unknown	+		+	
8	GPA	+	+	+	ESRD	–	10	+	–		+	
9	MPA	–	+	+	23	n/a	5	Unknown	–		–	
10	GPA	+	+	+	73	+	5	+	–		–	
11	GPA	+	+	+	49	+	5	+	+			
12	GPA	+	+	+	9	+	5	+	–		+	
13	MPA	–	+	+	n/a*	n/a	5	n/a	–		–	
14	GPA	–	+	+	31	n/a	10	+	–		–	

Rituximab for refractory granulomatosis with polyangiitis (Wegener's granulomatosis): comparison of efficacy in granulomatous versus vasculitic manifestations

Ann Rheum Dis 2012;**71**:327–333.

Julia U Holle,[1] Christin Dubrau,[1] Karen Herlyn,[1] Martin Heller,[2] Petra Ambrosch,[3] Bernhard Noelle,[4] Eva Reinhold-Keller,[1] Wolfgang L Gross[1]

Efficacy of RTX compared in 59 pts with refractory AAV with either granulomatous vs vasculitic lesions, RTX better in vasculitic vs. (some) granulomatous manifestations



Response rate 63%
relapse rate 40%

Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

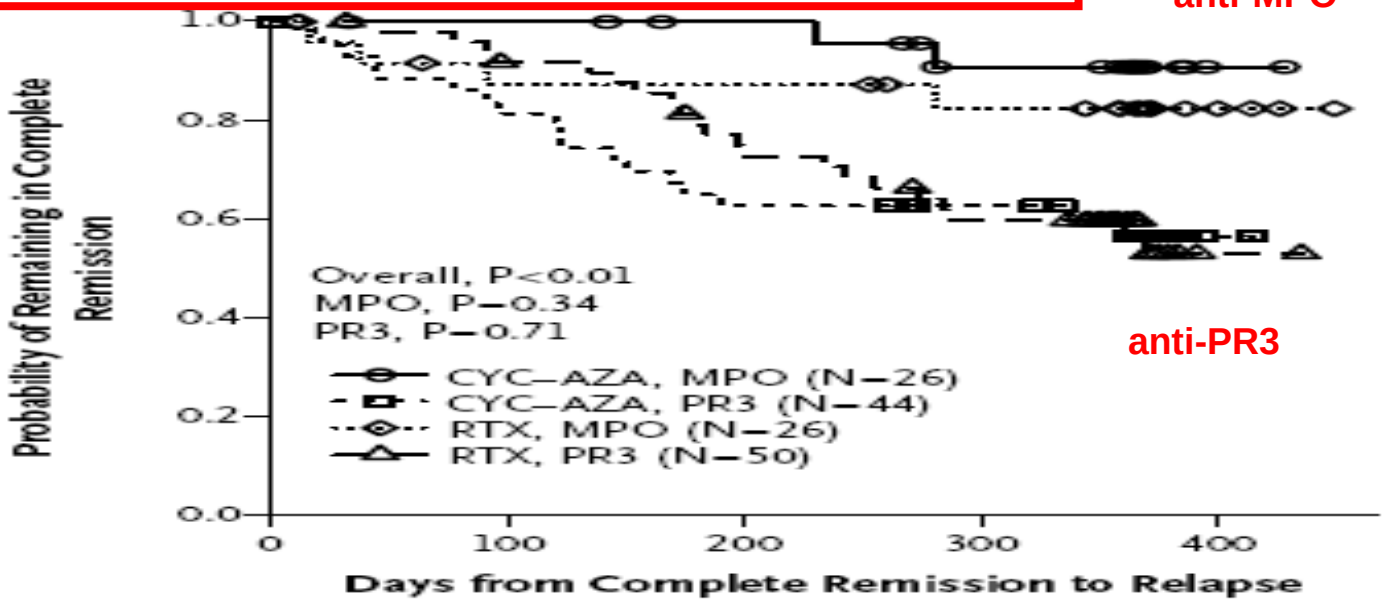
Ulrich Specks, M.D., Peter A. Merkel, M.D., M.P.H., Philip Seo, M.D., Robert Spiera, M.D.,

N ENGL J MED 369;5 NEJM.ORG AUGUST 1, 2013

RAVE study – 18-mo FU

The strongest determinant of relapse risk was anti-PR3 positivity

C **Time to First Relapse after Complete Remission, According to Treatment and Baseline Type of ANCA**



No. at Risk					
CYC–AZA, MPO	26	26	24	19	2
CYC–AZA, PR3	44	36	28	25	2
RTX, MPO	26	21	21	18	4
RTX, PR3	50	45	35	28	2

Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type

Sebastian Unizony,[1] Miguel Villarreal,[2] Eli M Miloslavsky,[1] Na Lu,[1] Peter A Merkel,[3] Robert Spiera,[4] Philip Seo,[5] Carol A Langford,[6] Gary S Hoffman,[6] CG M Kallenberg,[7] E William St. Clair,[8] David Ikle,[2] Nadia K Tchao,[9] Linna Ding,[10] Paul Brunetta,[11] Hyon K Choi,[1] Paul A Monach,[12] Fernando Fervenza,[13] John H Stone,[1] Ulrich Specks,[13] for the RAVE-ITN Research Group

Ann Rheum Dis 2016;**75**:1166–1169.

Pts with anti-PR3 relapsing disease achieved remission more often following RTX compared to CPH after 6, 12 and 18 mo

Table 3 Treatment response among patients with PR3-AAV who received RTX versus patients with PR3-AAV who received CYC/AZA

	OR*	95% CI	p Value
All patients with PR3-AAV (n=131)†			
CR at 6 months	2.11	1.04 to 4.30	0.04
CR at 12 months	1.96	0.95 to 4.05	0.07
CR at 18 months	1.44	0.68 to 3.05	0.34
Patients with PR3-AAV with relapsing disease at baseline (n=81)‡			
CR at 6 months	3.57	1.43 to 8.93	<0.01
CR at 12 months	4.32	1.53 to 12.15	<0.01
CR at 18 months	3.06	1.05 to 8.97	0.04

Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type

Sebastian Unizony,[1] Miguel Villarreal,[2] Eli M Miloslavsky,[1] Na Lu,[1] Peter A Merkel,[3] Robert Spiera,[4] Philip Seo,[5] Carol A Langford,[6] Gary S Hoffman,[6] CG M Kallenberg,[7] E William St. Clair,[8] David Ikle,[2] Nadia K Tchao,[9] Linna Ding,[10] Paul Brunetta,[11] Hyon K Choi,[1] Paul A Monach,[12] Fernando Fervenza,[13] John H Stone,[1] Ulrich Specks,[13] for the RAVE-ITN Research Group

Ann Rheum Dis 2016;**75**:1166–1169.

Pts with anti-PR3 disease achieved complete remission after 6 mo following RTX more often compared to CPH

Table 2 Treatment outcomes in patients with AAV according to serological and clinicopathological classifications*†

	PR3-AAV			MPO-AAV			GPA			MPA		
	RTX (n=66)	CYC/AZA (n=65)	p Value	RTX (n=33)	CYC/AZA (n=33)	p Value	RTX (n=74)	CYC/AZA (n=74)	p Value	RTX (n=24)	CYC/AZA (n=24)	p Value
CR at 6 months	43 (65)	31(48)	0.04	20 (61)	21 (64)	0.80	46 (63)	37 (50)	0.11	16 (67)	15 (63)	0.76
CR at 12 months	31 (47)	21 (32)	0.09	16 (49)	17 (52)	0.81	33 (45)	27 (37)	0.28	14 (58)	11 (46)	0.39
CR at 18 months	24 (36)	19 (29)	0.39	15 (46)	13 (39)	0.62	27 (37)	23 (31)	0.45	12 (50)	9 (38)	0.38

Different treatment of anti-PR3 and anti-MPO disease?

Long-Term Maintenance Therapy Using Rituximab-Induced Continuous B-Cell Depletion in Patients with ANCA Vasculitis

Clin J Am Soc Nephrol 9: 736–744, 2014.

William F. Pendergraft III,[*†‡] *Frank B. Cortazar,*[§] *Julia Wenger,*[†] *Andrew P. Murphy,*[†‡] *Eugene P. Rhee,*[†] *Karen A. Laliberte,*[†‡] *and John L. Niles*[†‡]

Adverse events in 172 pts treated with RTX maintenance for a median 2.1 year (up to 7 years)

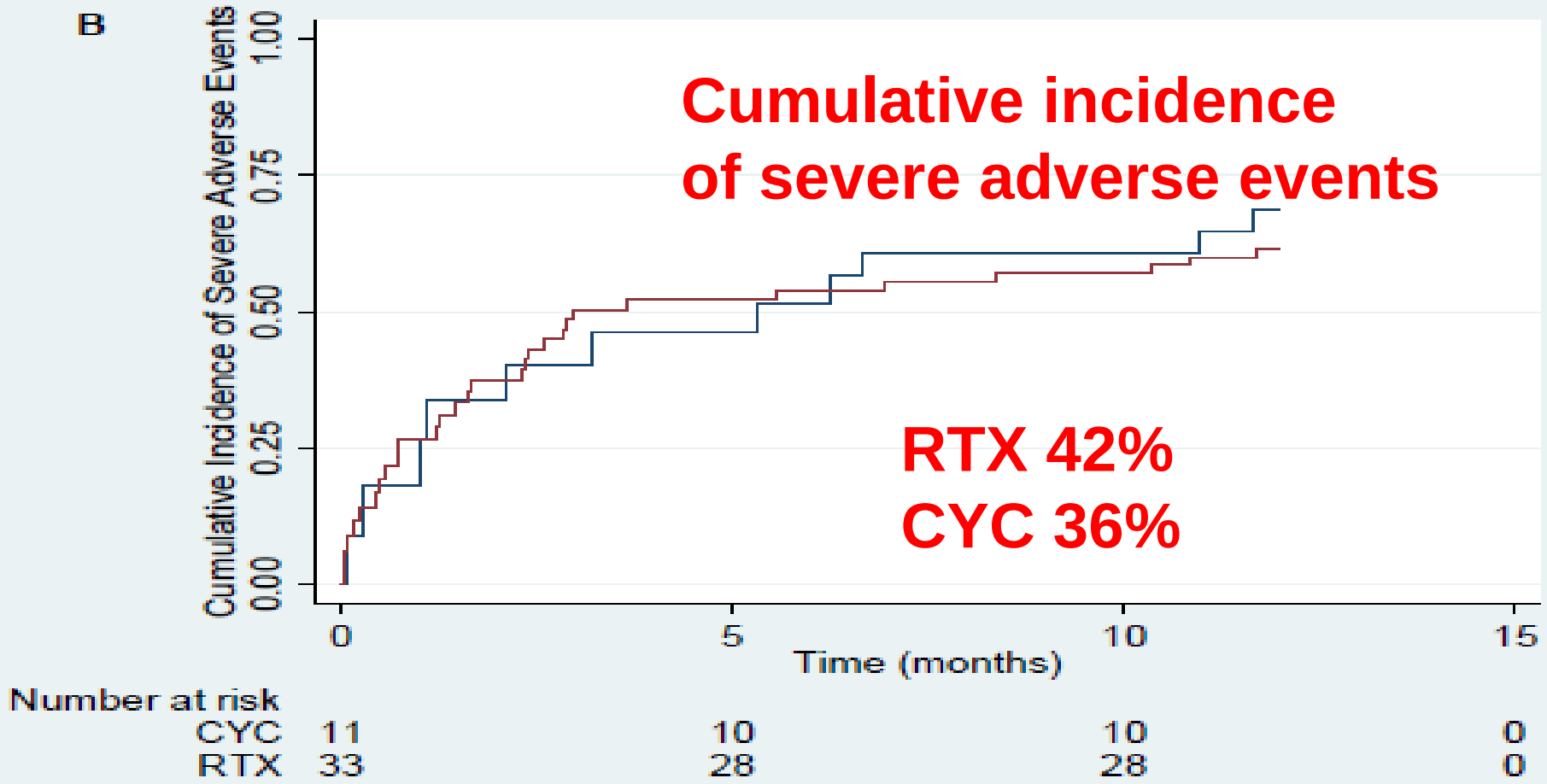
AEs mainly infections, hypogammaglobulinemia and LON

Adverse Events	*n*
Infections requiring hospitalization	25
Pulmonary	9
Disease-related hospitalizations	7
Flare	2
Tracheal/subglottic stenosis	5
Hypogammaglobulinemia (IgG<400 mg/dl) on RTX	17
Late-onset neutropenia[a]	17
Requiring hospitalization	4
Requiring GCSF (filgrastim)	13
Other events requiring hospitalization	52
Renal	6
Cardiac	12
Gastrointestinal	12
Orthopedic	7
Malignancy (bladder cancer)	1
Neuro	5
Miscellaneous	8
Malignancies	2
Melanoma	0
Nonmelanoma skin cancer	ND
Bladder cancer	1
Lung cancer	1
Major infusion reactions[b]	1
Delayed	1

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

RITUXVAS study

N ENGL J MED 363;3 NEJM.ORG JULY 15, 2010



Cumulative incidence of severe adverse events

RTX 42%
CYC 36%

Prolonged disease-free remission following rituximab and low-dose cyclophosphamide therapy for renal ANCA-associated vasculitis

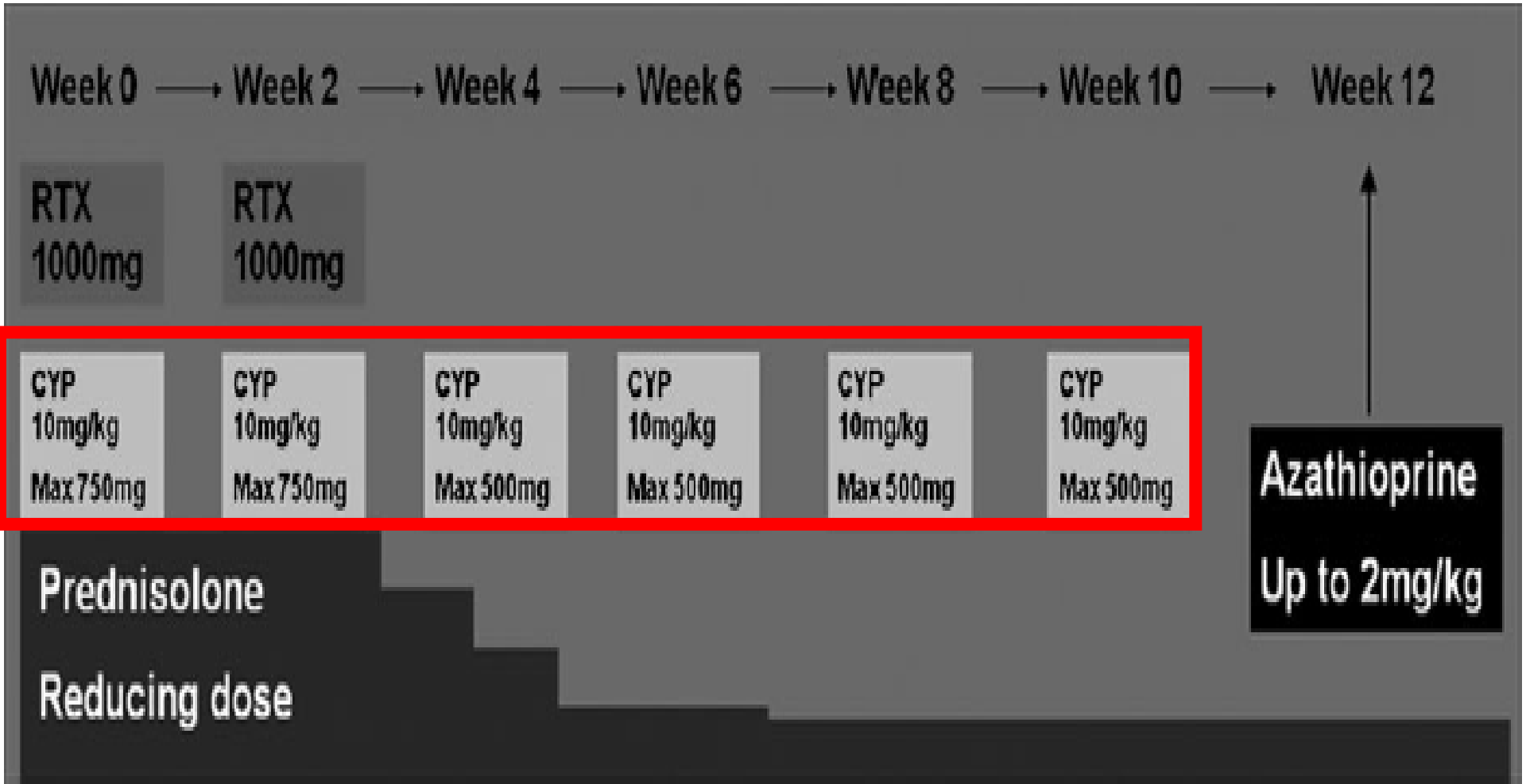
Nephrol Dial Transplant (2011) 26: 3280–3286

Nicholas Mansfield, Sally Hamour, Anne-Marie Habib, Ruth Tarzi, Jeremy Levy, Megan Griffith, Tom Cairns, H. Terence Cook, Charles D. Pusey and Alan D. Salama

RTX combined with low dose CPH

in 23 pts with renal AAV

Pts with SCr > 500 µmol/l, AH and RTX treatment excluded



Prolonged disease-free remission following rituximab and low-dose cyclophosphamide therapy for renal ANCA-associated vasculitis

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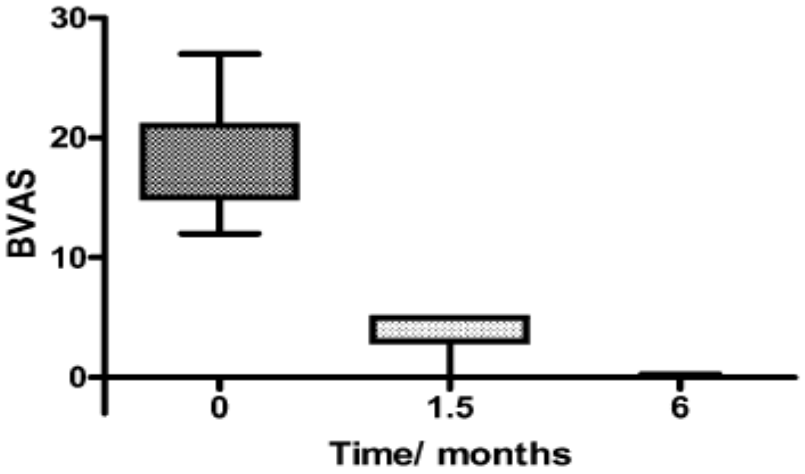
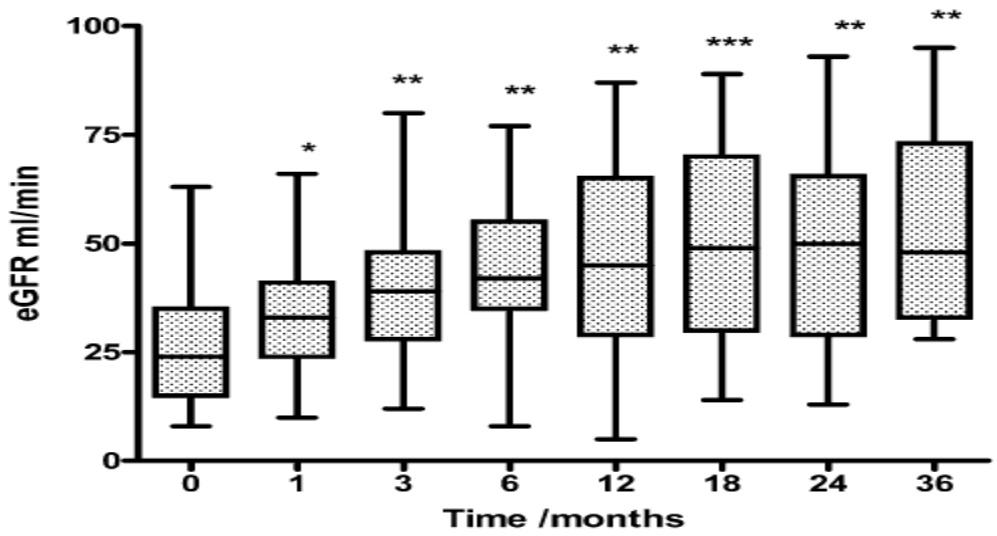
Nicholas Mansfield, Sally Hamour, Anne-Marie Habib, Ruth Tarzi, Jeremy Levy, Megan Griffith, Tom Cairns, H. Terence Cook, Charles D. Pusey and Alan D. Salama

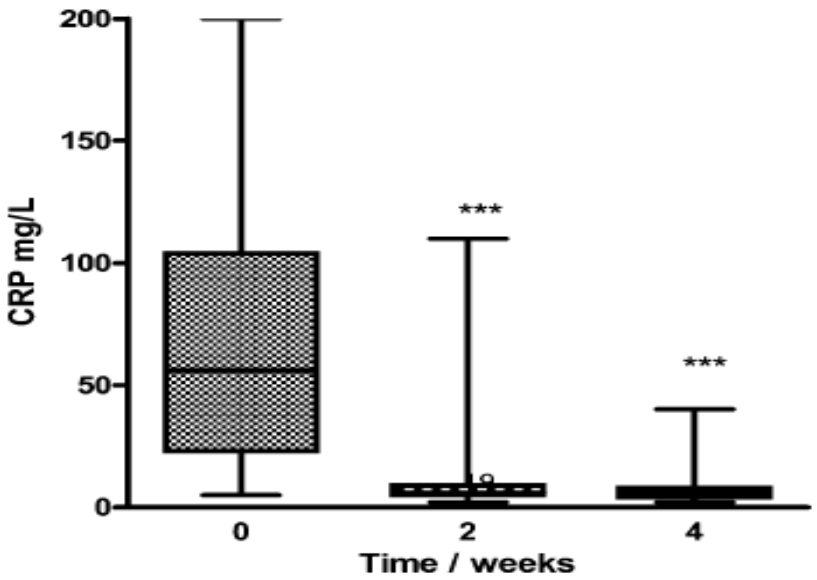
All pts achieved clinical remission within 6 weeks

3 major and 2 minor relapses occurred during a median FU of 39 mo (pts retreated with RTX for major relapses)

Long-term remission,
Putative steroid sparing platform







P2_139 LONG-TERM FOLLOW-UP OF A COMBINED RITUXIMAB AND LOW-DOSE CYCLOPHOSPHAMIDE REGIMEN FOR REMISSION INDUCTION IN RENAL ANCA-ASSOCIATED VASCULITIS

Stephen Paul McAdoo[1], Seerapani Gopaluni[2], Nicholas Medjeral-Thomas[1], Anisha Tanna[1], Megan Griffith[1], Jeremy Levy[1], Terence Cook[1], Thomas Cairns[1], Alan Salama[3], David Jayne[2] and Charles Pusey[1]
[1]*Imperial College Renal and Transplant Centre London, UK,* [2]*Lupus and Vasculitis Clinic, Addenbrookes Hospital Cambridge, UK,* [3]*University College Centre for Nephrology London, UK*

ABSTRACTS OF THE 18TH INTERNATIONAL VASCULITIS AND ANCA WORKSHOP

66 consecutive pts (AH, advanced CKD excluded) treated in one centre with RTX, low-dose CPH and CS

Outcomes compared with matched controls from EUVAS studies

At last FU (median 5 yrs)
patient and renal survival 94% and 84%, respectively,
major relapse rate 15%, median time to relapse 39 mo

In matched EUVAS patients:

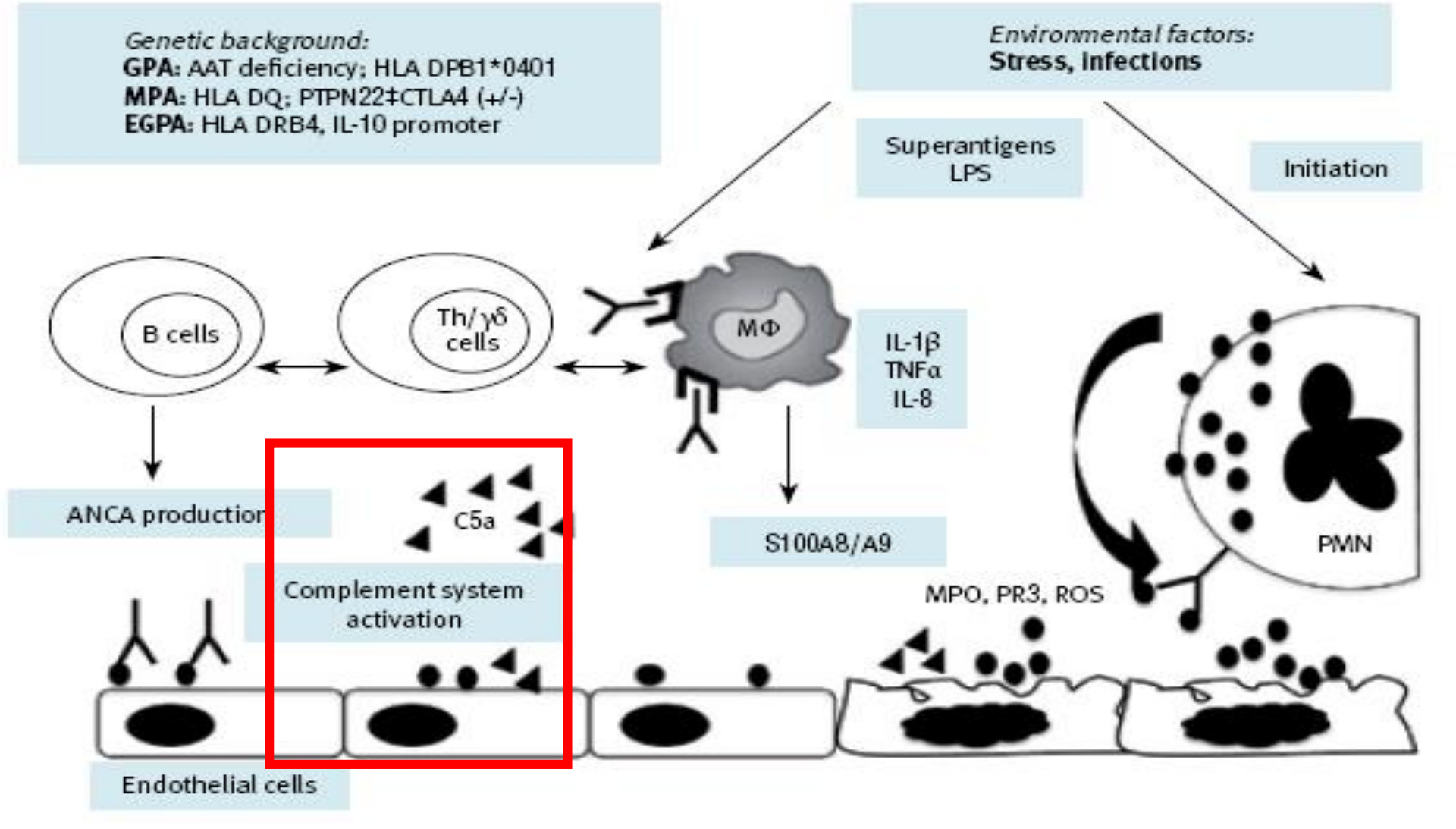
risk of relapse	**2.2 higher,**
ESRD	**4.8 higher,**
mortality	**3.5 higher**

Small-Medium Vessel Vasculitides: is the Complement System a Potential Forgotten Target?

IMAJ 2015; 17: 85–92

Eleonora Ballanti MD, Maria S. Chimenti MD PhD and Roberto Perricone MD

Activation of alternative complement pathway in AAV

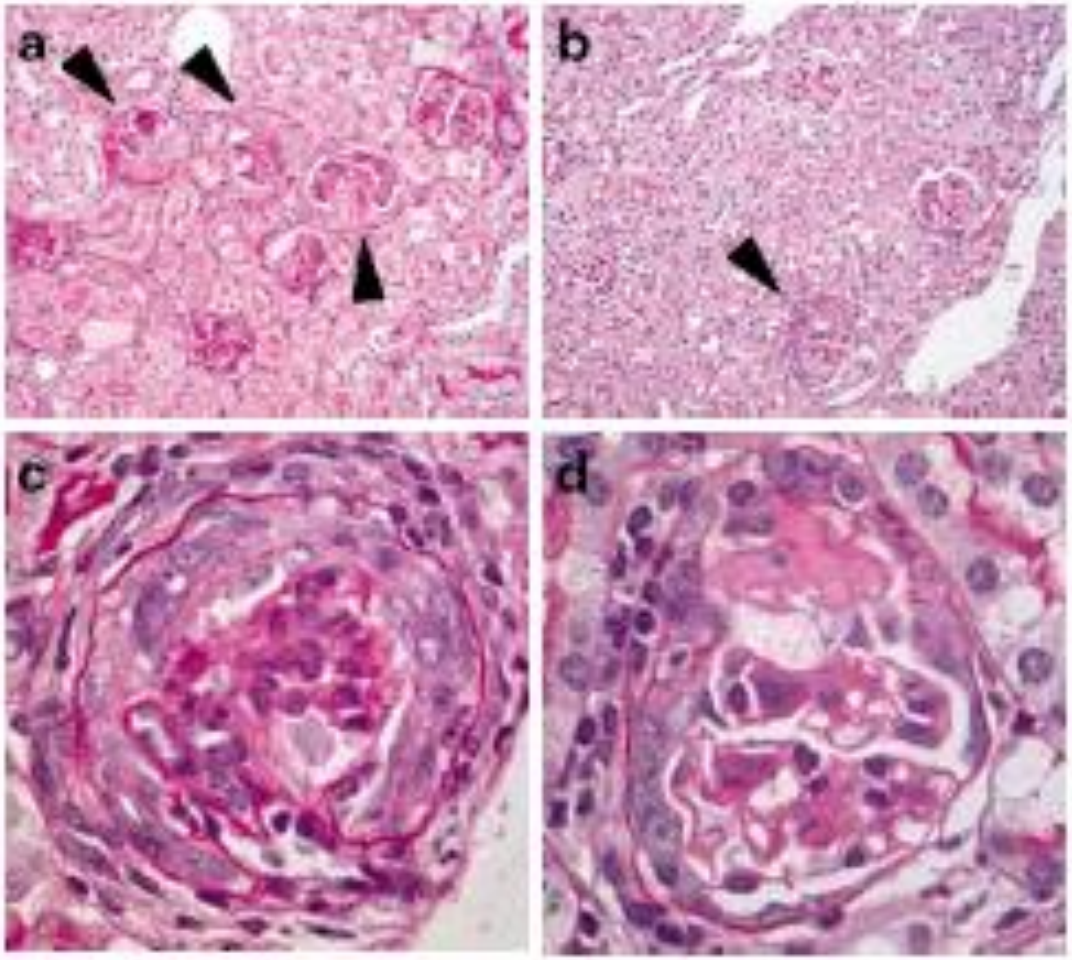


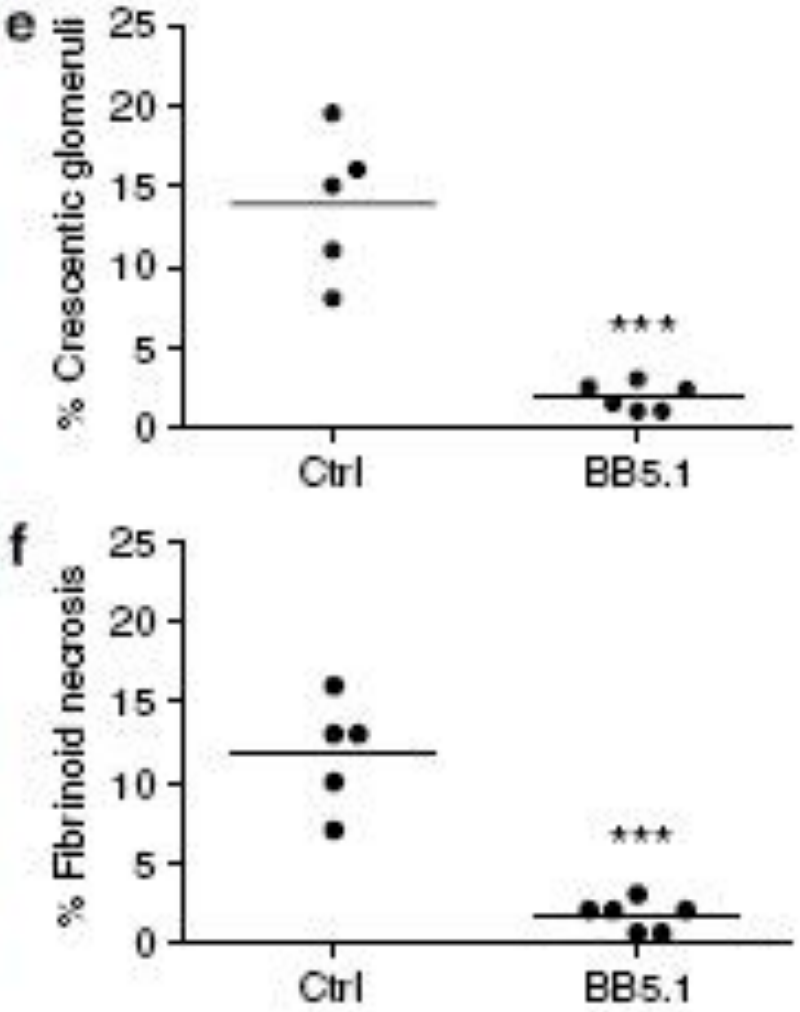
Inhibition of complement factor C5 protects against anti-myeloperoxidase antibody-mediated glomerulonephritis in mice

Kidney International (2007) **71**, 646–654

D Huugen[1], A van Esch[1], H Xiao[2], CJ Peutz-Kootstra[3], WA Buurman[4], JW Cohen Tervaert[1], JC Jennette[2] and P Heeringa[5]

Anti-C5 moAb prevented necroses and crescent formation





Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

J Am Soc Nephrol 28: 2756–2767, 2017

David R.W. Jayne,* Annette N. Bruchfeld,† Lorraine Harper,‡ Matthias Schaier,§ Michael C. Venning,‖ Patrick Hamilton,‖ Volker Burst,¶ Franziska Grundmann,¶ Michel Jadoul,** István Szombati,†† Vladimír Tesař,‡‡ Mårten Segelmark,§§ Antonia Potarca,‖‖ Thomas J. Schall,‖‖ and Pirow Bekker,‖‖ for the CLEAR Study Group

67 pts with AAV randomized to:

1) **Standard of care (SOC) control: Placebo + CYC or RTX + full starting dose of prednisone (60 mg),**
2) **CCX168 30 (avacopan) mg b.i.d. + CYC or RTX + reduced starting dose of prednisone (20 mg), or**
3) **CCX168 30 mg b.i.d. + CYC or RTX + no prednisone.**

Primary endpoint met:
BVAS response (decrease of BVAS for at least 50%) at week 12 numerically superior and statistically non-inferior to SOC control ($p = 0.005$ and $p = 0.02$) for each of the CCX168 groups vs. control

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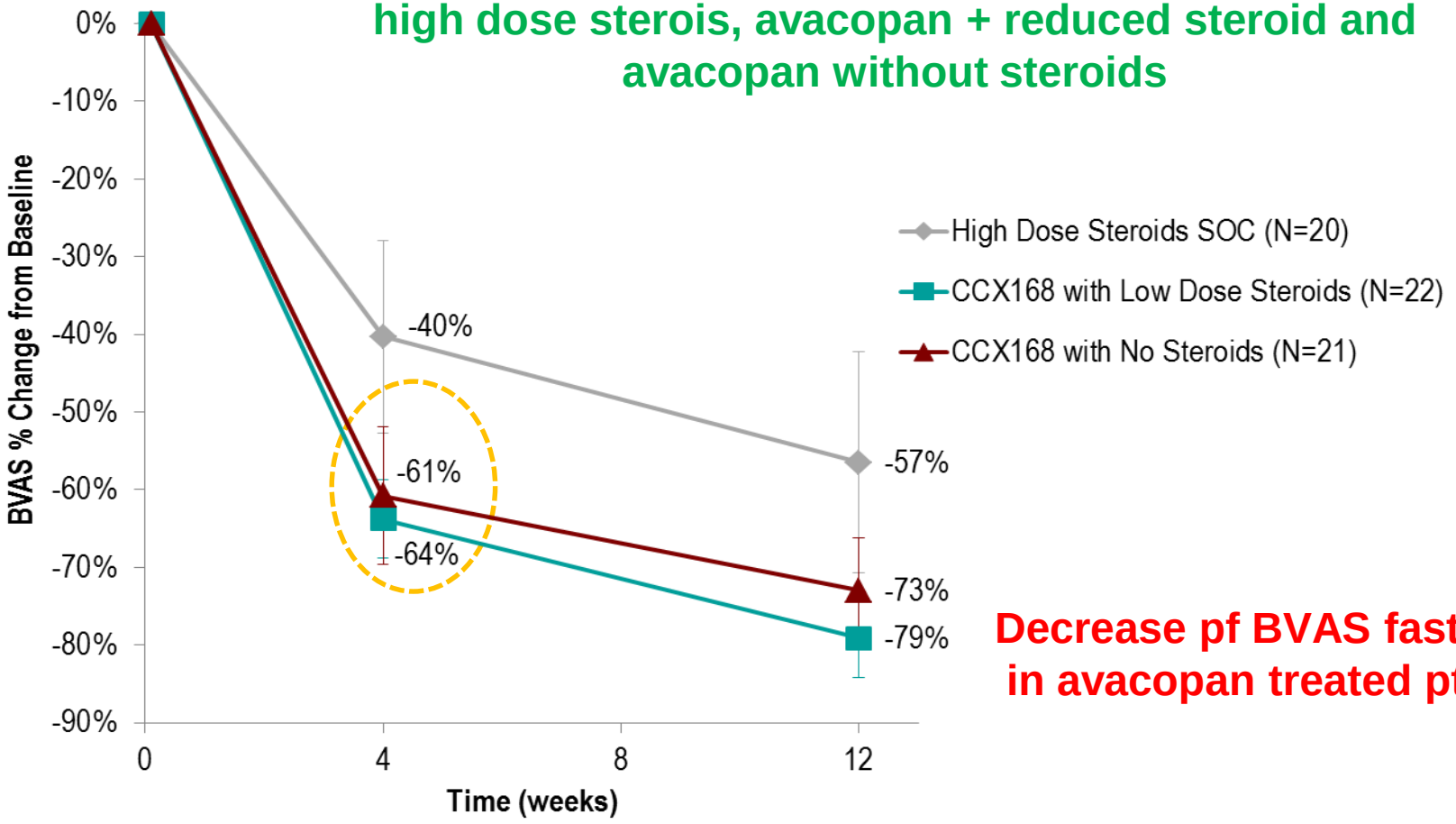
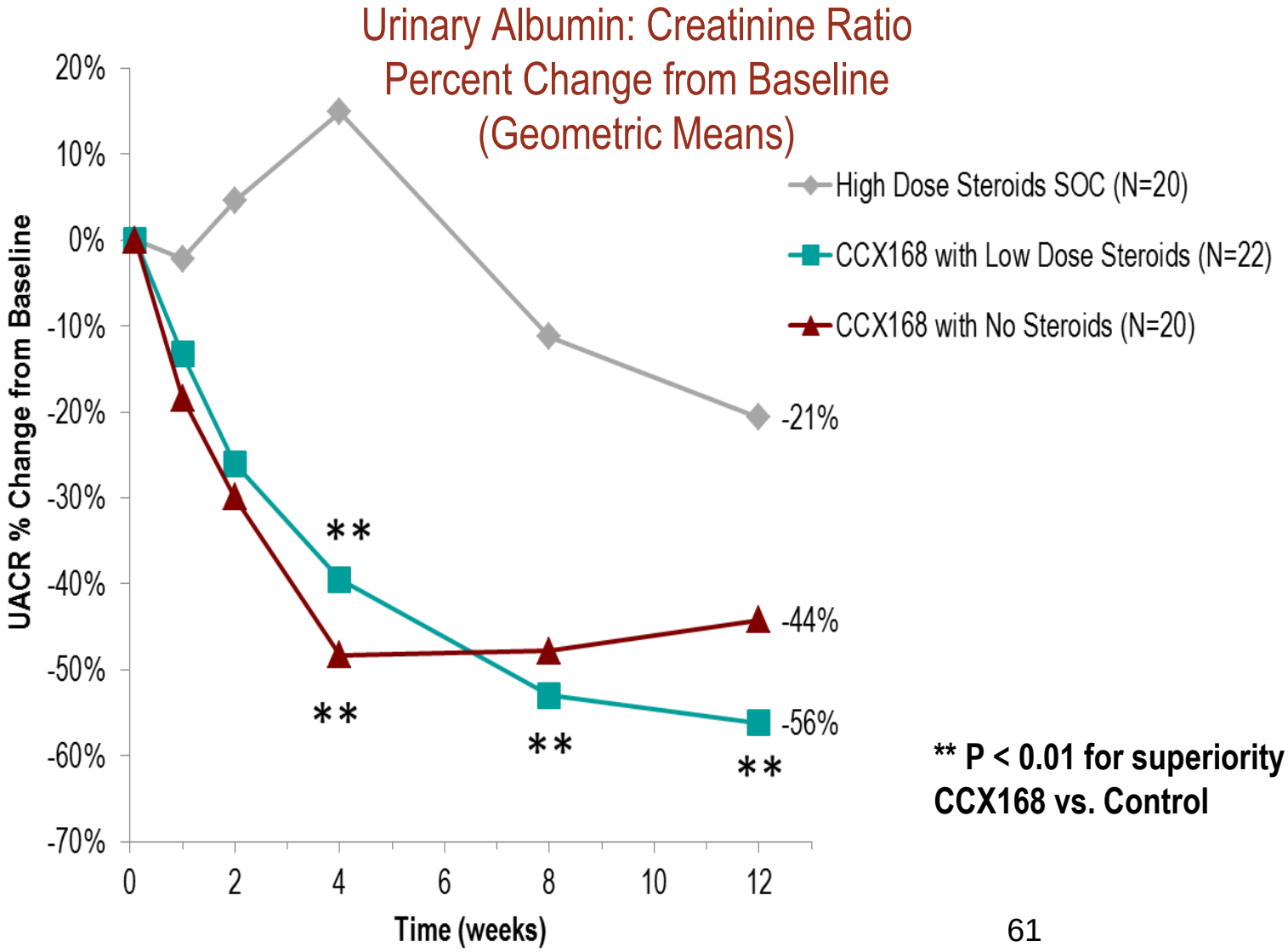
67 pts with AAV randomized to RTX or CPH and either high dose sterois, avacopan + reduced steroid and avacopan without steroids



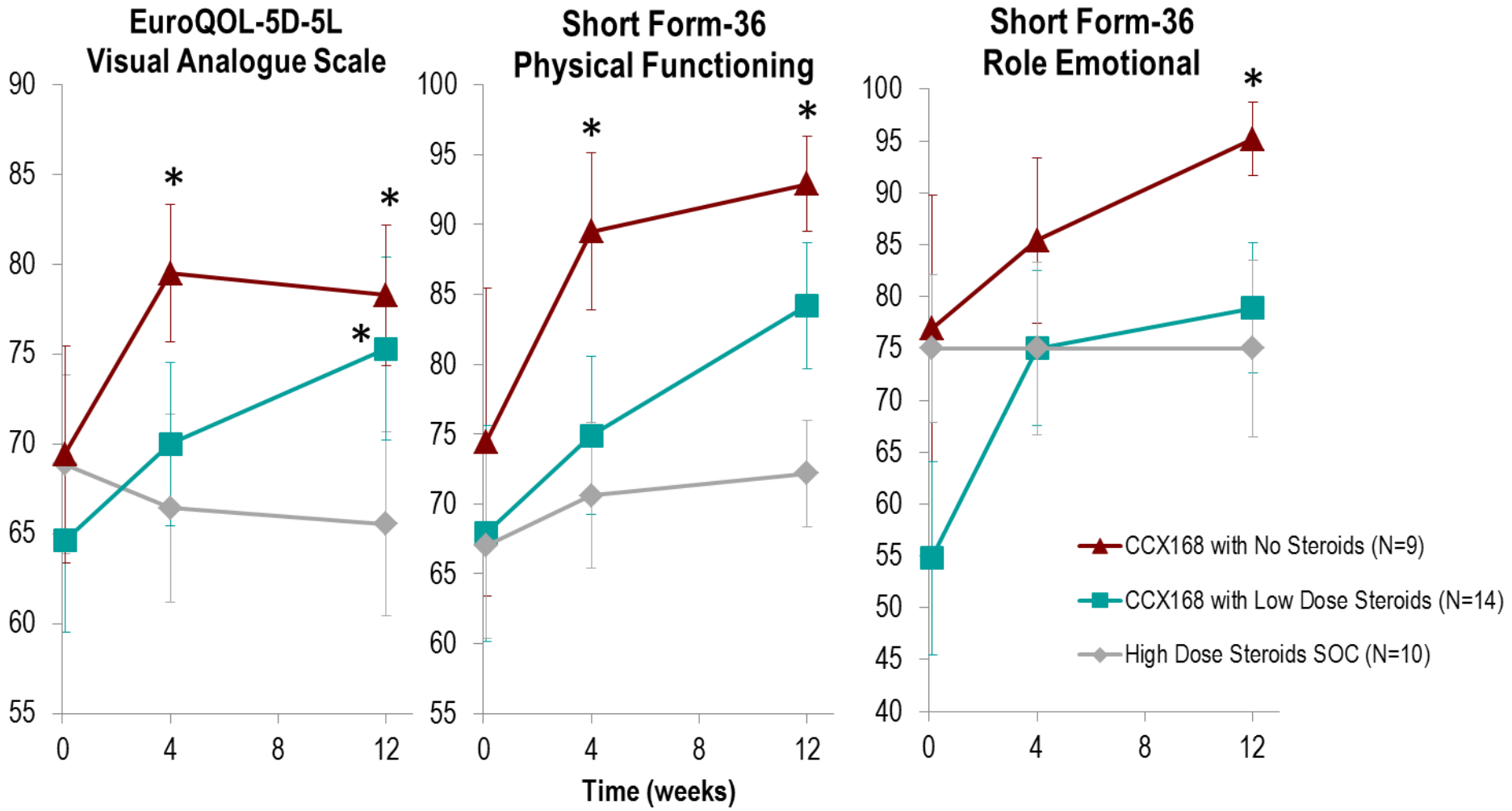
Decrease pf BVAS faster in avacopan treated pts

Decrease of albuminuria more expressed in pts treated with avacopan



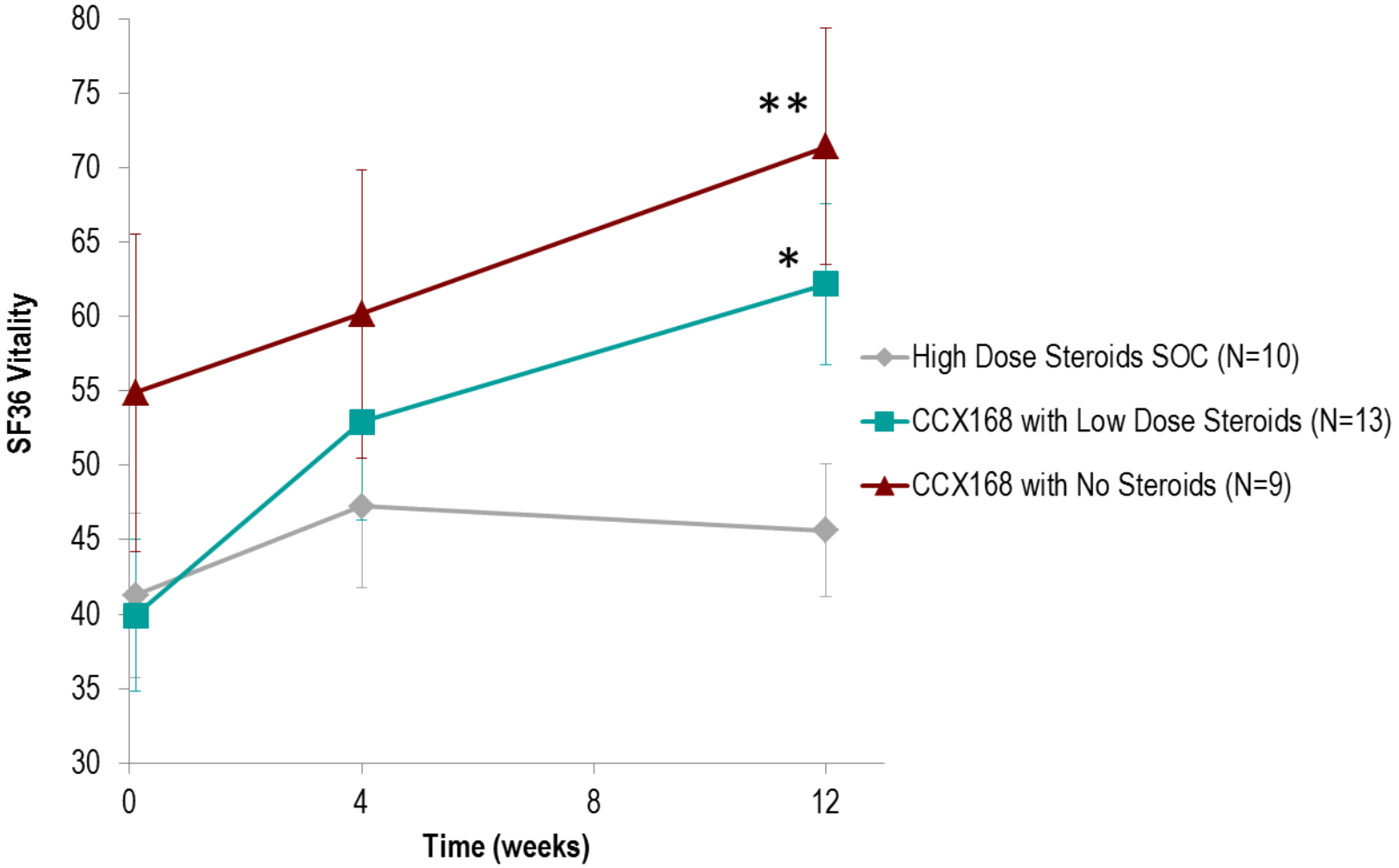
** P < 0.01 for superiority of CCX168 vs. Control

Rapid improvement of the quality of life in pts treated with avacopan (CCX168)



* P < 0.05 for CCX168 change or percent change from baseline vs. Control

Improvement of vitality (less fatigue) in pts on avacopan (CCX168)



** P < 0.01, * P < 0.05 for CCX168 vs. steroid control group

Adverse events possibly related to CS treatment

Adverse Effect	High Dose Steroids SOC (N=23)	CCX168 + Low Dose Steroids (N=22)	CCX168 + No Steroids (N=22)	CCX168 Combined (N=44)
Patients with Any Event	**15 (65.2%)**	4 (18.2%)	11 (50.0%)	**15 (34.1%) ***
Psychiatric disorders	6 (26.1%)	2	1	3 (6.8%)
Serious infections	1 (4.3%)	1	1	2 (4.5%)
New onset/worsening diabetes/hyperglycemia	4 (17.4%)	0	1	1 (2.3%)
New onset/worsening hypertension	5 (21.7%)	2	8	10 (22.7%)
Weight gain >10 kg	2 (8.7%)	1	0	1 (2.3%)
Bone fractures	1 (4.3%)	0	0	0 (0%)
Cataracts	1 (4.3%)	0	0	0 (0%)

*** P = 0.02 for CCX168 vs. SOC Control**

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

J Am Soc Nephrol 28: 2756–2767, 2017

David R.W. Jayne,* Annette N. Bruchfeld,† Lorraine Harper,‡ Matthias Schaier,§ Michael C. Venning,‖ Patrick Hamilton,‖ Volker Burst,¶ Franziska Grundmann,¶ Michel Jadoul,** István Szombati,†† Vladimír Tesař,‡‡ Mårten Segelmark,§§ Antonia Potarca,‖‖ Thomas J. Schall,‖‖ and Pirow Bekker,‖‖ for the CLEAR Study Group

Conclusions:

Avacopan (CCX168) successful as steroid sparing drug during the induction phase of AAV

ADVOCATE – phase 3 trial with avacopan is currently ongoing

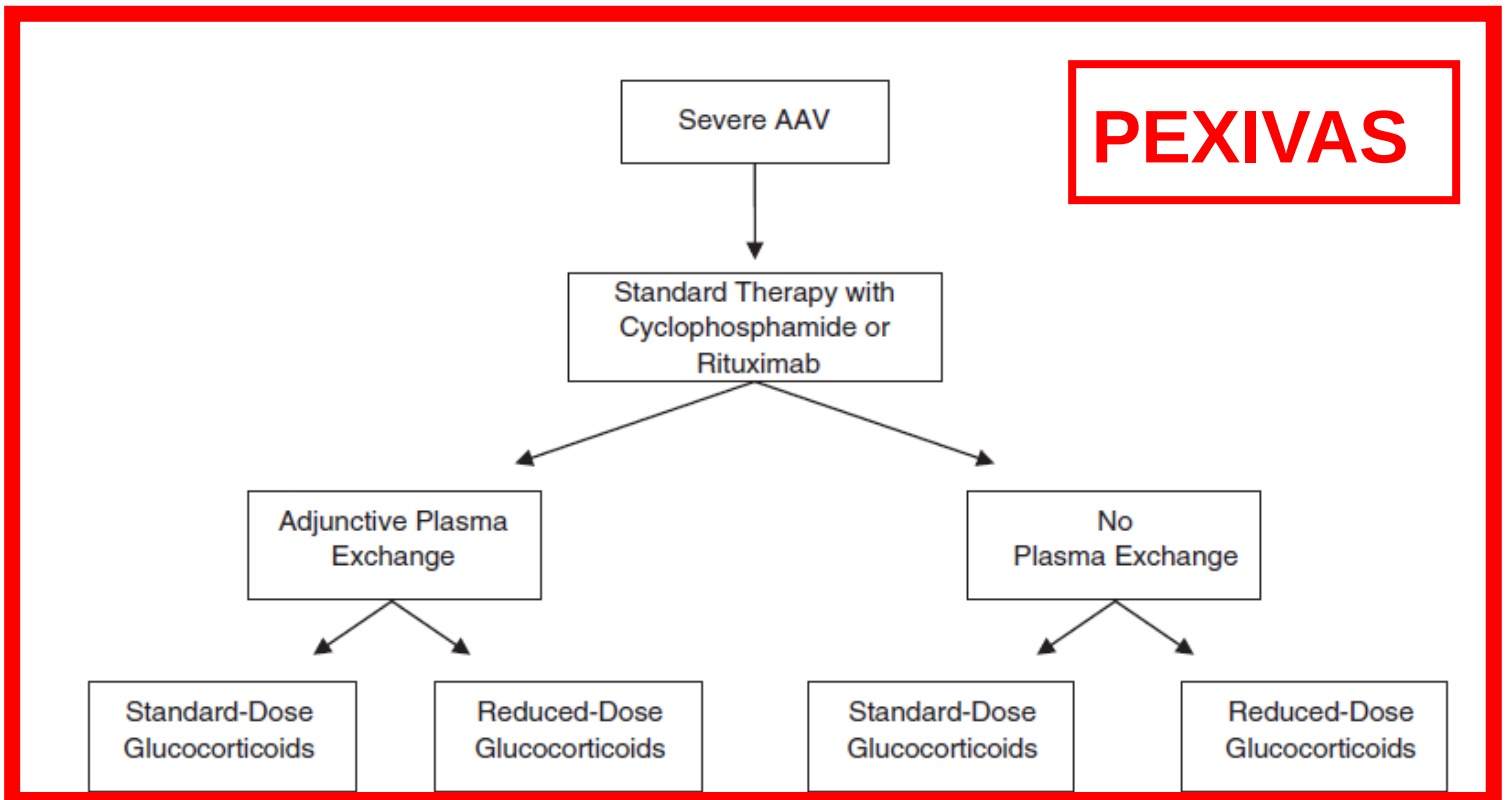
Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial

Trials 2013, 14:73

Michael Walsh[1*], Peter A Merkel[2], Chen Au Peh[3], Wladimir Szpirt[4], Loïc Guillevin[5], Charles D Pusey[6], Janak de Zoysa[7], Natalie Ives[8], William F Clark[9], Karen Quillen[10], Jeffrey L Winters[11], Keith Wheatley[12], David Jayne[13] and on behalf of the PEXIVAS Investigators

PEXIVAS recruited 700 pts with AAV a Scr > 200 µmol/l randomized also to standard-dose and reduced-dose corticosteroids (54% of the standard dose within 3 mo)

Reduced-dose CS non-inferior in terms of both primary outcome (composite of the death and ESRD) and secondary outcomes (death, ESRD) significantly lower risk of serious infections at 1 year (HR = 0.70, p = 0.02)



Malignancies in Wegener's Granulomatosis: Incidence and Relation to Cyclophosphamide Therapy in a Cohort of 293 Patients

J Rheumatol 2008;35:100–5

MIKKEL FAURSCHOU, INGE JUUL SORENSEN, LENE MELLEMKJAER, ANNE GITTE RASMUSSEN LOFT, BJARNE SVALGAARD THOMSEN, NIELS TVEDE, and BO BASLUND

High risk of late occurring (6.9 – 18.5 yrs after CPH) malignancies in pts with cumulative dose of CPH > 36 g

Site of Cancer (modified ICD-7 code[21])	Observed*	SIR	95% CI
All sites (140–205)	50	2.1	1.5–2.7
Buccal cavity and pharynx (140–148)	0	—	0.0–7.8
Digestive organs (150–159)	4	0.8	0.2–2.1
Colon (153)	2	1.1	0.1–3.9
Rectum (154)	1	1.0	0.0–5.8
Liver, not specified as primary (156)	1	3.8	0.1–21
Respiratory system (160–164)	5	1.5	0.5–3.4
Breast (170)	4	1.5	0.4–3.8
Female genital organs (171–176)	1	0.7	0.0–3.7
Male genital organs (177–179)	4	2.4	0.7–6.2
Kidney (180)	1	1.7	0.0–9.5
Bladder (181)	5	3.6	1.2–8.3
Malignant melanoma (190)	1	1.7	0.0–9.2
Non-melanoma skin (191)	19	4.7	2.8–7.3
Squamous cell carcinoma	6	11.5	4.2–25
Basal cell carcinoma	13	3.8	2.0–6.5
Brain and nervous system (193)	1	1.7	0.0–9.3
Non-Hodgkin's lymphomas (200, 202, 205)	0	—	0.0–6.8
Hodgkin's disease (201)	0	—	0.0–65
Leukemia (204)	3	5.9	1.2–17
Acute myeloid leukemia	3	19.6	4.0–57

Effect of rituximab on malignancy risk in patients with ANCA-associated vasculitis

Emma E van Daalen,[1] Raffaella Rizzo,[2,3] Andreas Kronbichler,[3,4] Ron Wolterbeek,[5] Jan A Bruijn,[1] David R Jayne,[3] Ingeborg M Bajema,[1] Chinar Rahmattulla[1,3]

Ann Rheum Dis 2016;**0**:1–6. doi:10.1136/annrheumdis-2016-209925

One-centre analysis of 323 pts with AAV
33 pts developed 45 malignancies
CPH associated with increased risk of cancer,
in RTX-treated pts similar risk of cancer as in general population

Table 3 SIR stratified according to treatment category*

Treatment†	Patients (n)	SIR (95% CI)‡	SIR p Value‡	Cyclophosphamide cumulative dose (g), mean (SD)§	Follow-up (years), mean (SD)¶	Organ involvement, mean**
Only cyclophosphamide	119	3.10 (2.06 to 4.48)	<0.001	7.26 (4.94)	4.92 (3.10)	2.11 (1.49)
Only rituximab	41	0.67 (0.08 to 2.43)	0.86	0.00	6.34 (3.56)	2.35 (1.09)
Both	114	1.01 (0.46 to 1.93)	1.00	11.05 (11.63)	6.60 (2.84)	2.56 (1.63)
None	48	2.10 (0.77 to 4.56)	0.14	0.00	4.20 (2.94)	1.96 (1.44)

EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis

M Yates,[1,2] R A Watts,[2,3] I M Bajema,[4] M C Cid,[5] B Crestani,[6] T Hauser,[7] B Hellmich,[8] J U Holle,[9] M Laudien,[10] M A Little,[11] R A Luqmani,[12] A Mahr,[13] P A Merkel,[14] J Mills,[15] J Mooney,[1] M Segelmark,[16,17] V Tesar,[18] K Westman,[19] A Vaglio,[20] N Yalçındağ,[21] D R Jayne,[22] C Mukhtyar[1]

Ann Rheum Dis 2016;**75**:1583–1594

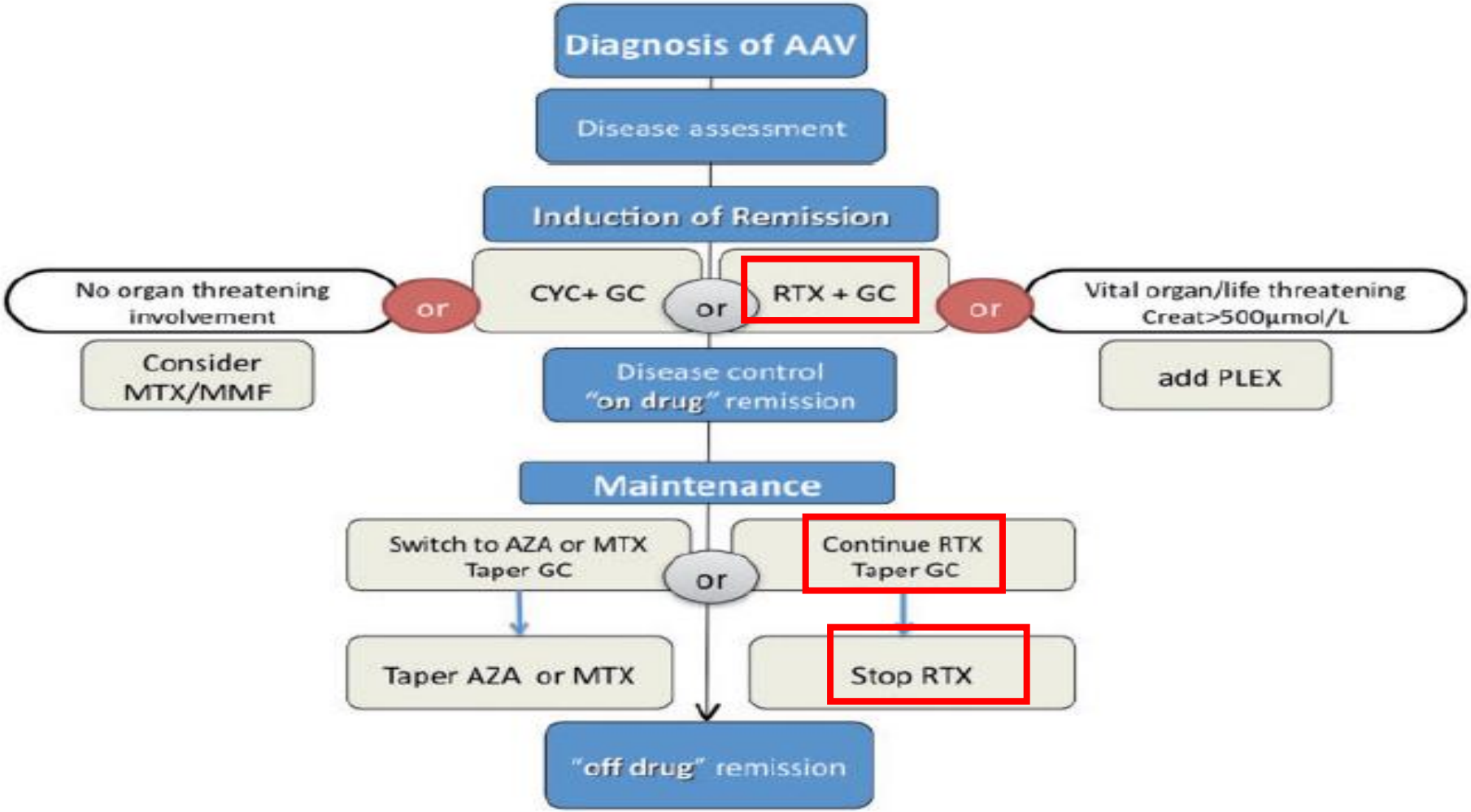
Table 1 Recommendation statements

Statement	Level of evidence	Grade of recommendation
1. We recommend that patients with AAV are managed in close collaboration with, or at, centres of expertise.	3	C
2. A positive biopsy is strongly supportive of a diagnosis of vasculitis and we recommend biopsies to assist in establishing a new diagnosis and for further evaluation for patients suspected of having relapsing vasculitis.	3	C
3. For remission-induction of new-onset organ-threatening or life-threatening AAV we recommend treatment with a combination of glucocorticoids and either cyclophosphamide **OR** rituximab.	1 for GPA/MPA, 3 for EGPA	A for GPA/MPA, C for EGPA
4. For remission-induction of non-organ-threatening AAV we recommend treatment with a combination of glucocorticoids and either methotrexate or mycophenolate mofetil*.	1B	B for MTX, C for MMF
5. For a major relapse of organ-threatening or life-threatening disease in AAV we recommend treatment as per new disease with a combination of glucocorticoids and either cyclophosphamide OR rituximab.	1 for GPA/MPA, 3 for EGPA and CYC, 4 for EGPA and RTX	A for GPA/MPA, C for EGPA and CYC, C for EGPA and RTX
6. (i) Plasma exchange should be considered for patients with AAV and a serum creatine level of ≥500 μmol/L (5.7 mg/dL) due to rapidly progressive glomerulonephritis in the setting of new or relapsing disease.	1B	B
6. (ii) Plasma exchange can also be considered for the treatment of severe diffuse alveolar haemorrhage.	3	C

BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis

Rheumatology 2014;53:2306–2309

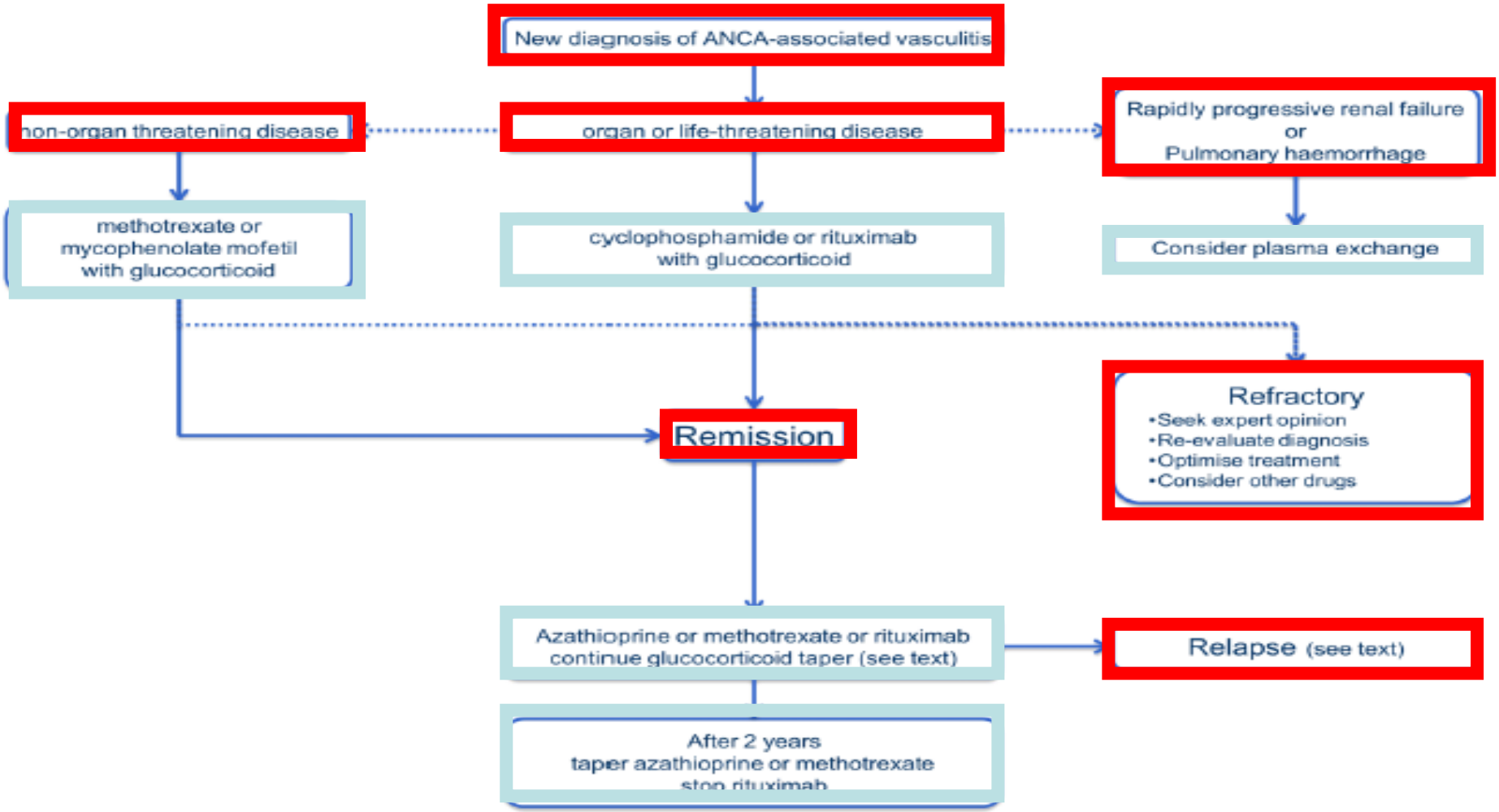
Eleana Ntatsaki[1,2], David Carruthers[3], Kuntal Chakravarty[4], David D'Cruz[5], Lorraine Harper[6], David Jayne[7], Raashid Luqmani[8], John Mills[9], Janice Mooney[10], Michael Venning[11] and Richard A. Watts[12,13], on behalf of the BSR and BHPR Standards, Guidelines and Audit Working Group



EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis

M Yates,[1,2] R A Watts,[2,3] I M Bajema,[4] M C Cid,[5] B Crestani,[6] T Hauser,[7] B Hellmich,[8] J U Holle,[9] M Laudien,[10] M A Little,[11] R A Luqmani,[12] A Mahr,[13] P A Merkel,[14] J Mills,[15] J Mooney,[1] M Segelmark,[16,17] V Tesar,[18] K Westman,[19] A Vaglio,[20] N Yalçındağ,[21] D R Jayne,[22] C Mukhtyar[1]

Ann Rheum Dis 2016;**75**:1583–1594



KDIGO CLINICAL PRACTICE GUIDELINE FOR GLOMERULONEPHRITIS

CHAPTER 13: PAUCI-IMMUNE FOCAL AND SEGMENTAL NECROTIZING GLOMERULONEPHRITIS

VOLUME 2 | ISSUE 2 | JUNE 2012

13.1: *Initial treatment of pauci-immune focal and segmental necrotizing GN*

13.1.1: We recommend that cyclophosphamide and corticosteroids be used as initial treatment. (*1A*)

13.1.2: We recommend that rituximab and corticosteroids be used as an alternative initial treatment in patients without severe disease or in whom cyclophosphamide is contraindicated. (*1B*)

We recommend rituximab be used as an alternative initial treatment in patients with ANCA-associated vasculitis (1B) and be preferred in anti-PR3 positive patients (1B). We suggest rituximab be used only in those patients with severe renal disease in whom cyclophosphamide is contraindicated (2B)

KDIGO CLINICAL PRACTICE GUIDELINE FOR GLOMERULONEPHRITIS

CHAPTER 13: PAUCI-IMMUNE FOCAL AND SEGMENTAL NECROTIZING GLOMERULONEPHRITIS

VOLUME 2 | ISSUE 2 | JUNE 2012

13.5: *Treatment of relapse*

13.5.1: We recommend treating patients with severe relapse of ANCA vasculitis (life- or organ-threatening) according to the same guidelines as for the initial therapy (see Section 13.1). (*1C*)

13.5.2: We suggest treating other relapses of ANCA vasculitis by reinstituting immunosuppressive therapy or increasing its intensity with agents other than cyclophosphamide, including instituting or increasing dose of corticosteroids, with or without azathioprine or MMF. (*2C*)

We recommend that rituximab and corticosteroids be used as a first line treatment in patients with severe (major) relapse of ANCA vasculitis (1C), especially in anti-PR3 positive patients; as an alternative we recommend cyclophosphamide and corticosteroids

Outline of the lecture

- Anti-PR3 vs. anti-MPO disease, predictive value of renal biopsy?
- Initial therapy and relapse
- **Plasma exchange**
- Maintenance therapy
- Conclusions

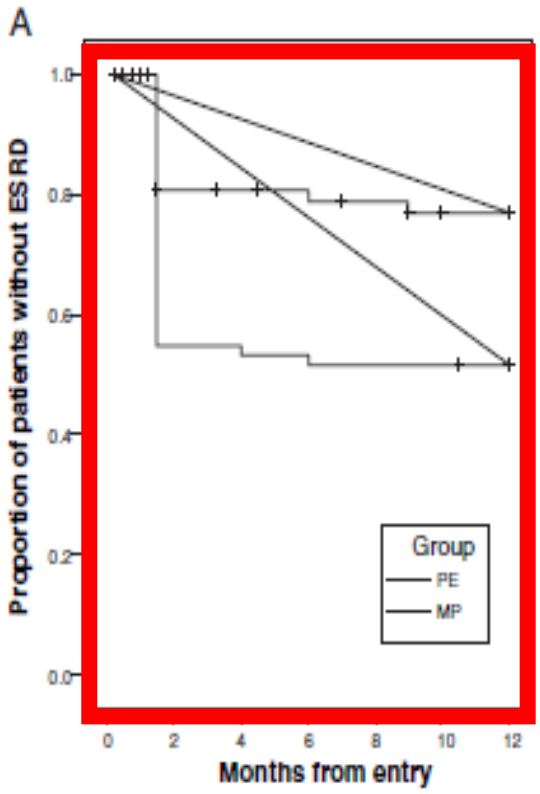
Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis

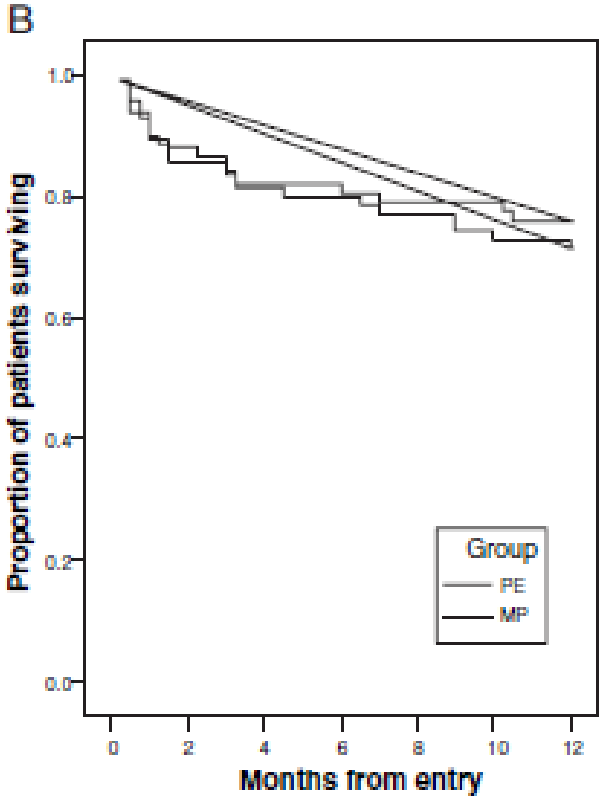
J Am Soc Nephrol 18: 2180–2188, 2007.

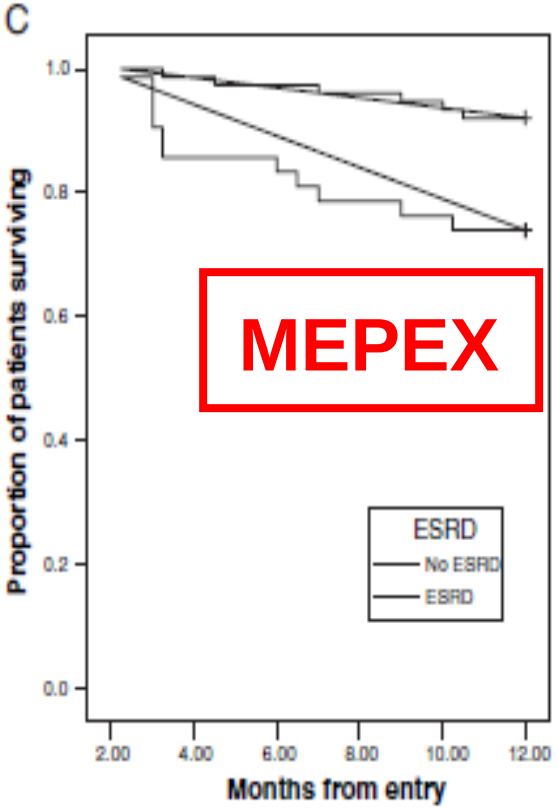
David R.W. Jayne,* Gill Gaskin,† Niels Rasmussen,‡ Daniel Abramowicz,§ Franco Ferrario,‖ Loic Guillevin,¶ Eduardo Mirapeix,** Caroline O.S. Savage,†† Renato A. Sinico,‖ Coen A. Stegeman,‡‡ Kerstin W. Westman,§§ Fokko J. van der Woude,‖‖ Robert A.F. de Lind van Wijngaarden,¶¶ and Charles D. Pusey; on behalf of the European Vasculitis Study Group†

In MEPEX trial 137 pts with AAV presenting with Scr > 500 µmol/l randomized either to PE or MP as an add-on treatment

At 3 months 69% treated with PE compared to 49% treated with MP were alive and with independent renal function







KDIGO CLINICAL PRACTICE GUIDELINE FOR GLOMERULONEPHRITIS

CHAPTER 13: PAUCI-IMMUNE FOCAL AND SEGMENTAL NECROTIZING GLOMERULONEPHRITIS

VOLUME 2 | ISSUE 2 | JUNE 2012

13.2: *Special patient populations*

13.2.1: We recommend the addition of plasmapheresis for patients requiring dialysis or with rapidly increasing SCr. (*1C*)

13.2.2: We suggest the addition of plasmapheresis for patients with diffuse pulmonary hemorrhage. (*2C*)

13.2.3: We suggest the addition of plasmapheresis for patients with overlap syndrome of ANCA vasculitis and anti-GBM GN, according to proposed criteria and regimen for anti-GBM GN (see Chapter 14). (*2D*)

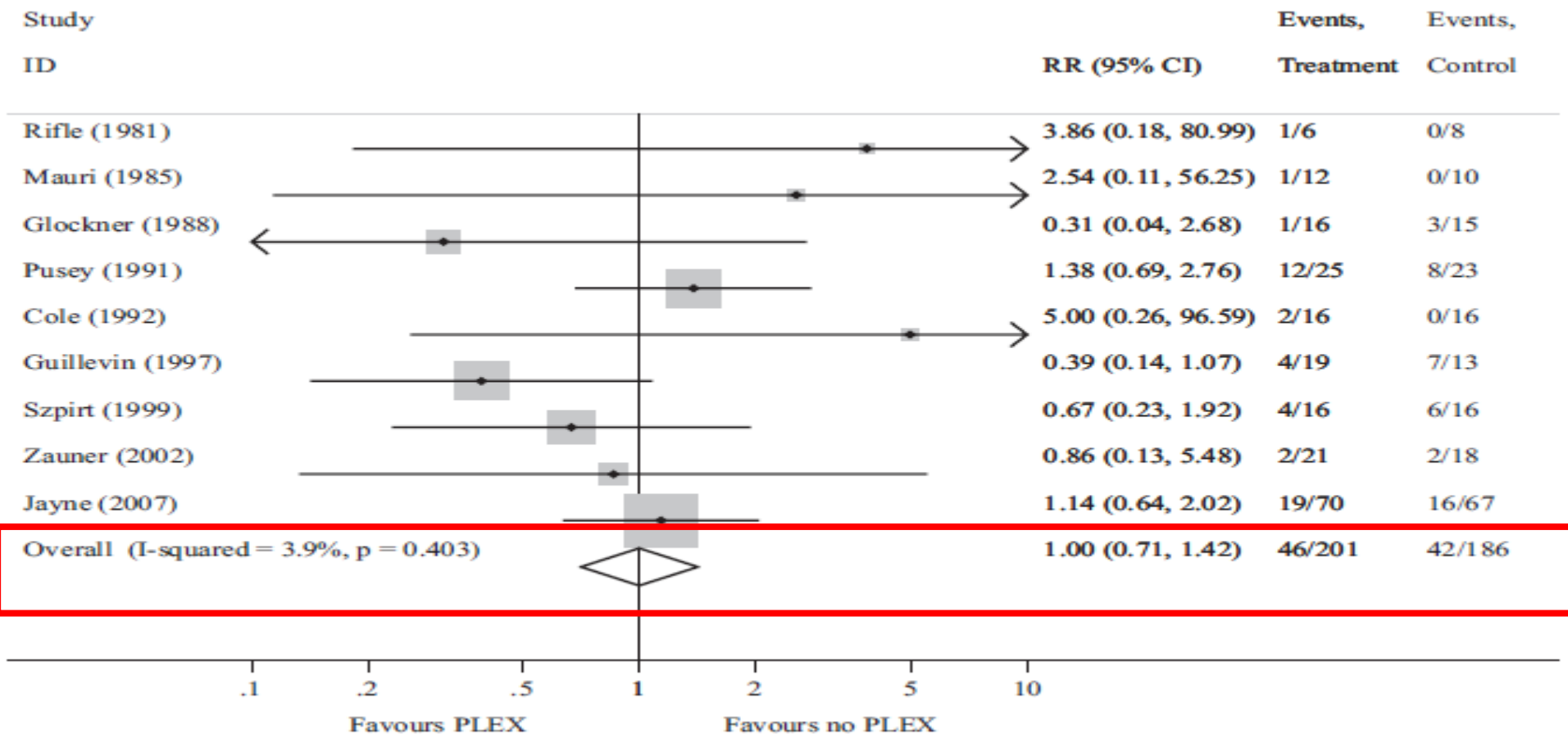
13.2.4: We suggest discontinuing cyclophosphamide therapy after 3 months in patients who remain dialysis-dependent and who do not have any extrarenal manifestations of disease. (*2C*)

Plasma Exchange for Renal Vasculitis and Idiopathic Rapidly Progressive Glomerulonephritis: A Meta-analysis

Am J Kidney Dis. 57(4):566-574. © 2011

Michael Walsh, MD, MSc,[1,2] Fausta Catapano, MD, PhD,[2] Wladimir Szpirt, MD,[3] Kristian Thorlund, MSc,[1] Annette Bruchfeld, MD, PhD,[4] Loic Guillevin, MD,[5] Marion Haubitz, MD,[6] Peter A. Merkel, MD, MPH,[7] Chen Au Peh, MD, PhD,[8] Charles Pusey, DSc,[9] and David Jayne, MD[2]

Metaanalysis - 9 studies, 387 pts, no impact on mortality in AAV



Plasma Exchange for Renal Vasculitis and Idiopathic Rapidly Progressive Glomerulonephritis: A Meta-analysis

Am J Kidney Dis. 57(4):566-574. © 2011

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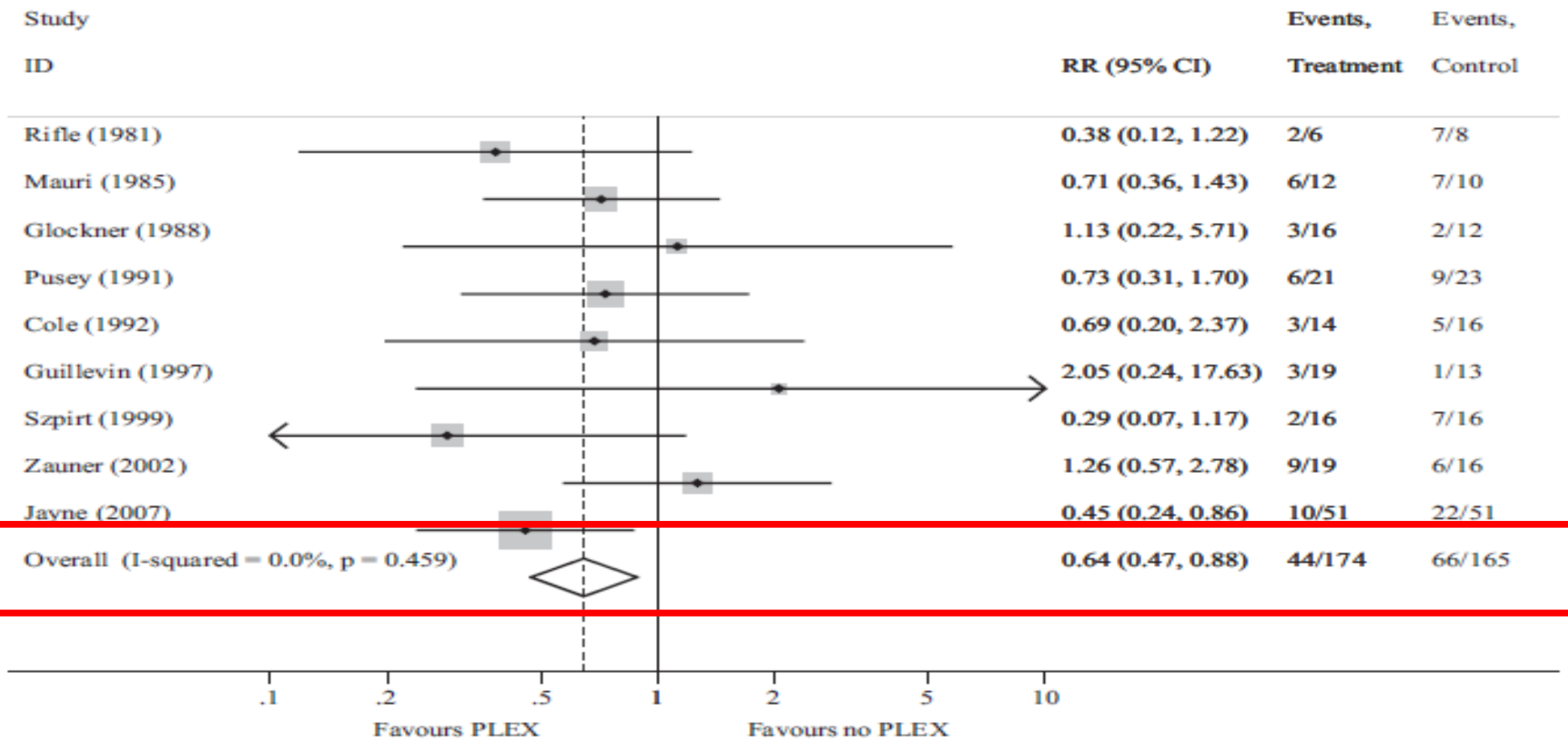
Plasma exchange had, however, significant impact on the rate of ESRD - decrease by 36%

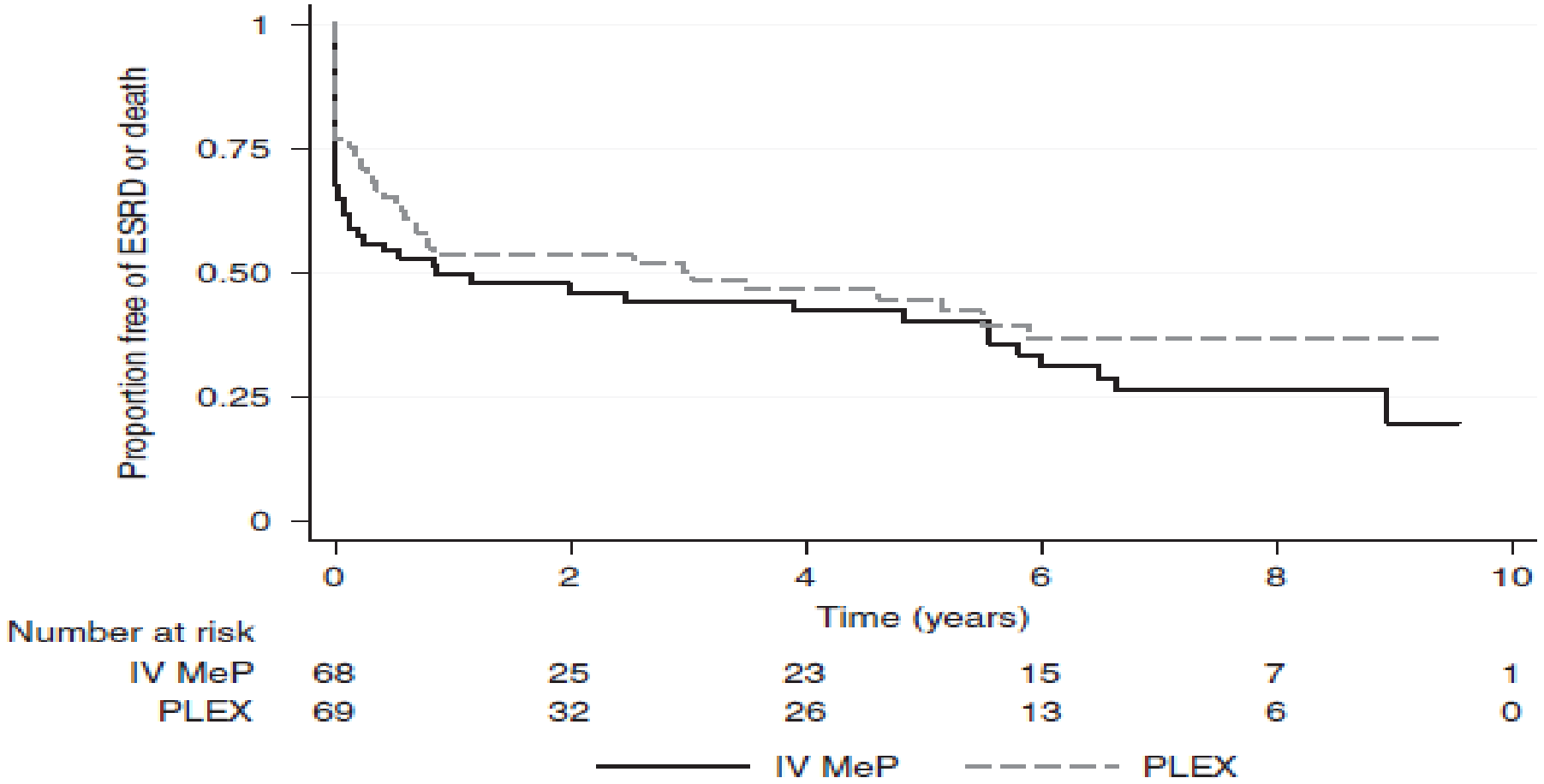


Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear

Michael Walsh[1], Alina Casian[2], Oliver Flossmann[3], Kerstin Westman[4], Peter Höglund[5], Charles Pusey[6] and David R.W. Jayne[2] on behalf of the European Vasculitis Study Group (EUVAS)

Kidney International (2013) **84,** 397–402

Long-term FU of MEPEX:
after a median FU of 3.95 yrs there was no difference in proportion of pts free of ESRD or death



Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear

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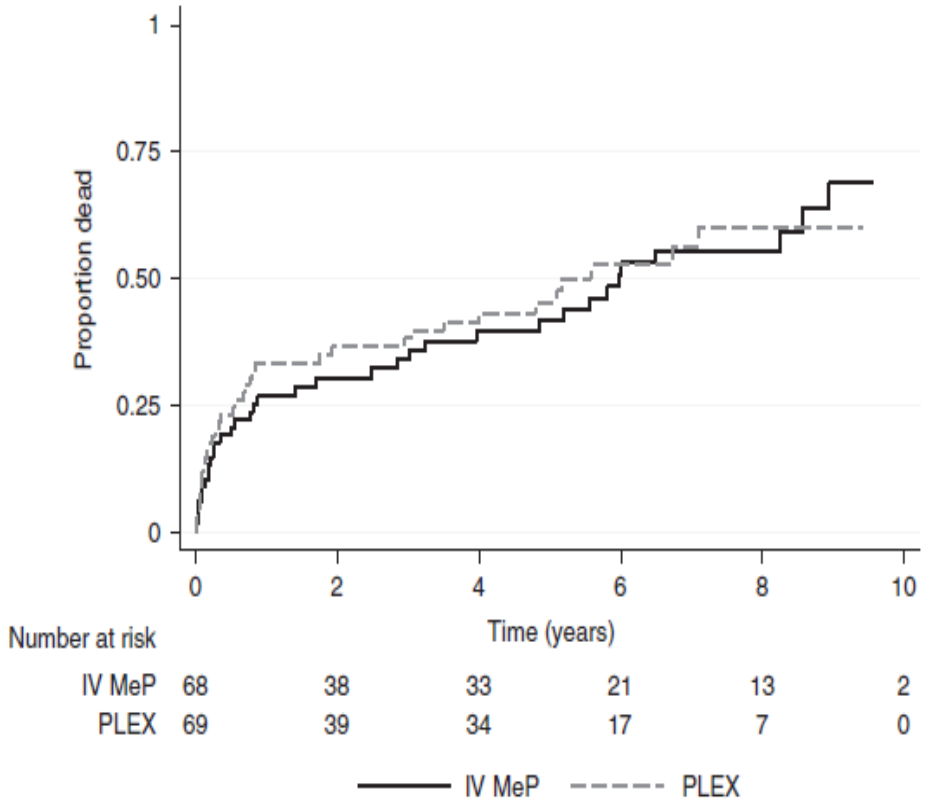
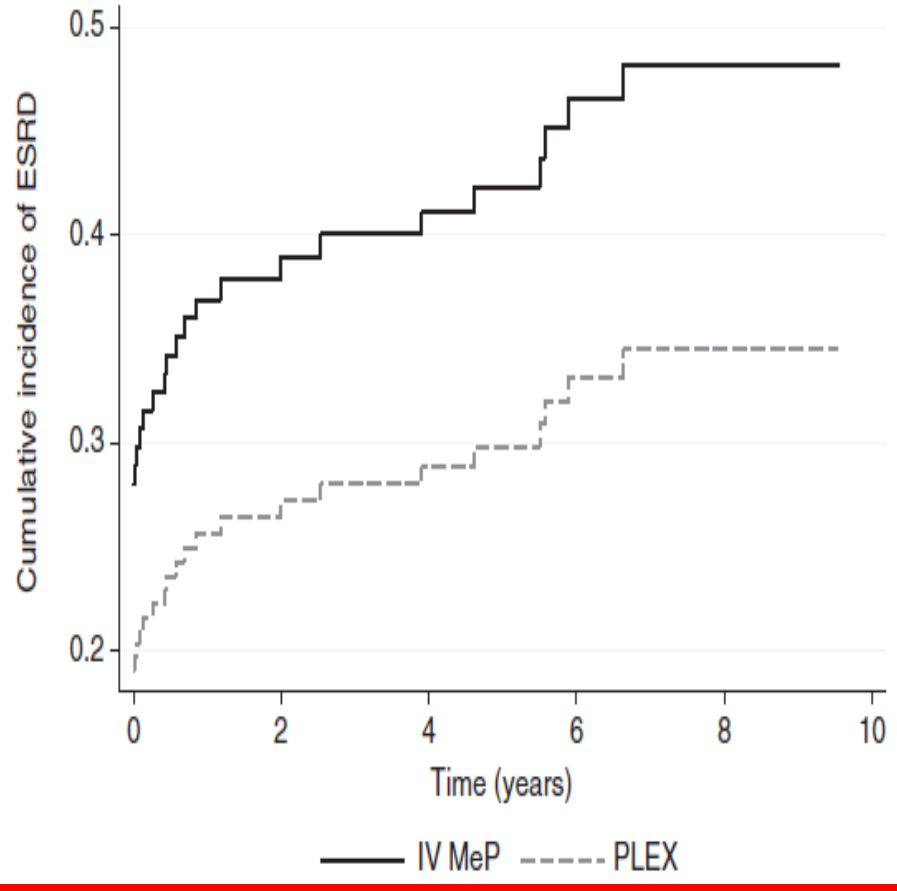
Kidney International (2013) **84,** 397–402

Reduction of the risk of ESRD
(0.64, confidence interval 0.40 – 1.05)
did not reach statistical significance





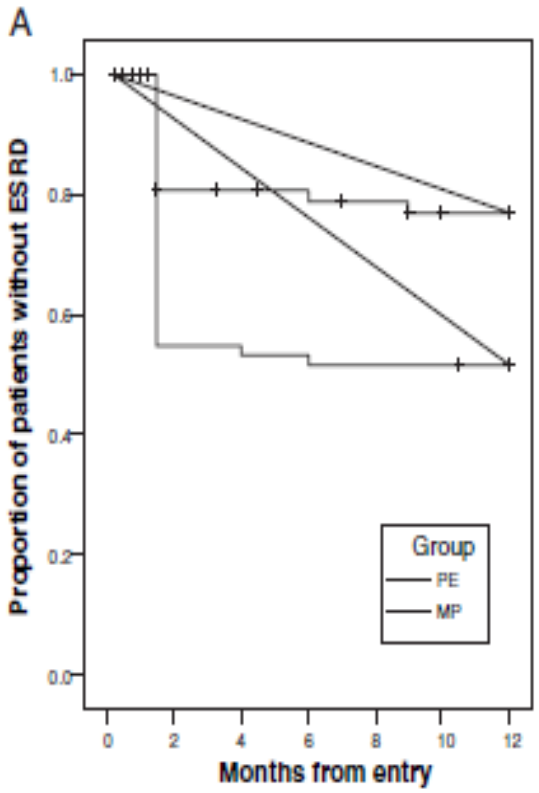
Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis

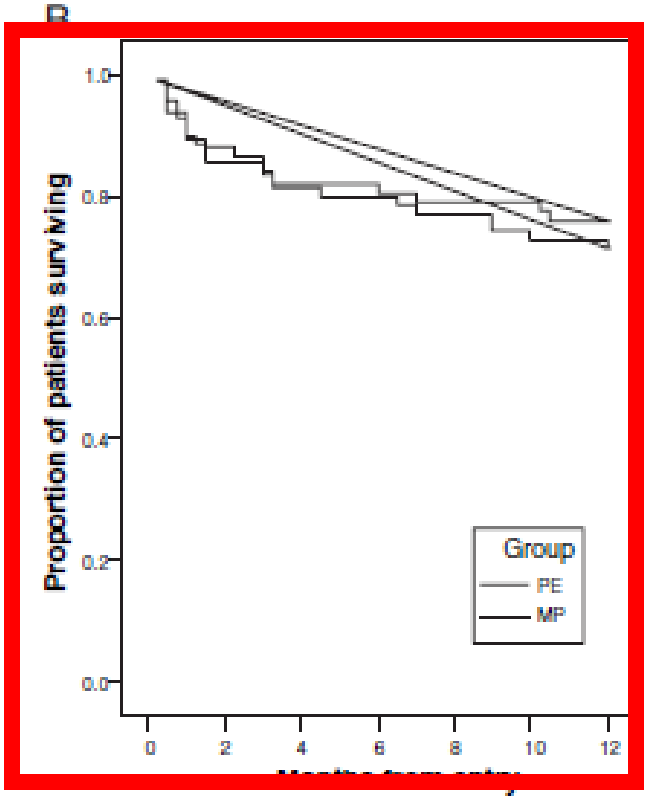
J Am Soc Nephrol 18: 2180–2188, 2007.

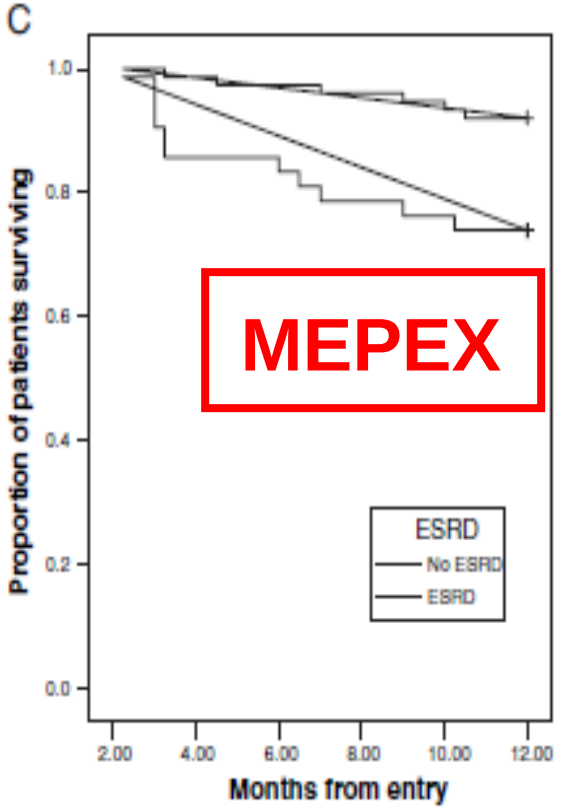
David R.W. Jayne,* Gill Gaskin,† Niels Rasmussen,‡ Daniel Abramowicz,§ Franco Ferrario,‖ Loic Guillevin,¶ Eduardo Mirapeix,** Caroline O.S. Savage,†† Renato A. Sinico,‖ Coen A. Stegeman,‡‡ Kerstin W. Westman,§§ Fokko J. van der Woude,‖‖ Robert A.F. de Lind van Wijngaarden,¶¶ and Charles D. Pusey; on behalf of the European Vasculitis Study Group†

In MEPEX trial 137 pts with AAV presenting with Scr > 500 µmol/l randomized either to PE or MP as an add-on treatment

At 3 months 69% treated with PE compared to 49% treated with MP were alive and with independent renal function







Intravenous Cyclophosphamide and Plasmapheresis in Dialysis-Dependent ANCA-Associated Vasculitis

Ruth J. Pepper,† Dimitrios Chanouzas,‡ Ruth Tarzi,† Mark A. Little,* Alina Casian,§ Michael Walsh,‖ Charles D. Pusey,† Lorraine Harper,‡ and Alan D. Salama,* European Vasculitis Study (FUVAS) investigators*

Clin J Am Soc Nephrol 8: 219–224, 2013

No difference in renal recovery in 41 pts treated with ivCYP and PLEX compared with 37 pts PLEX treated pts from MEPEX

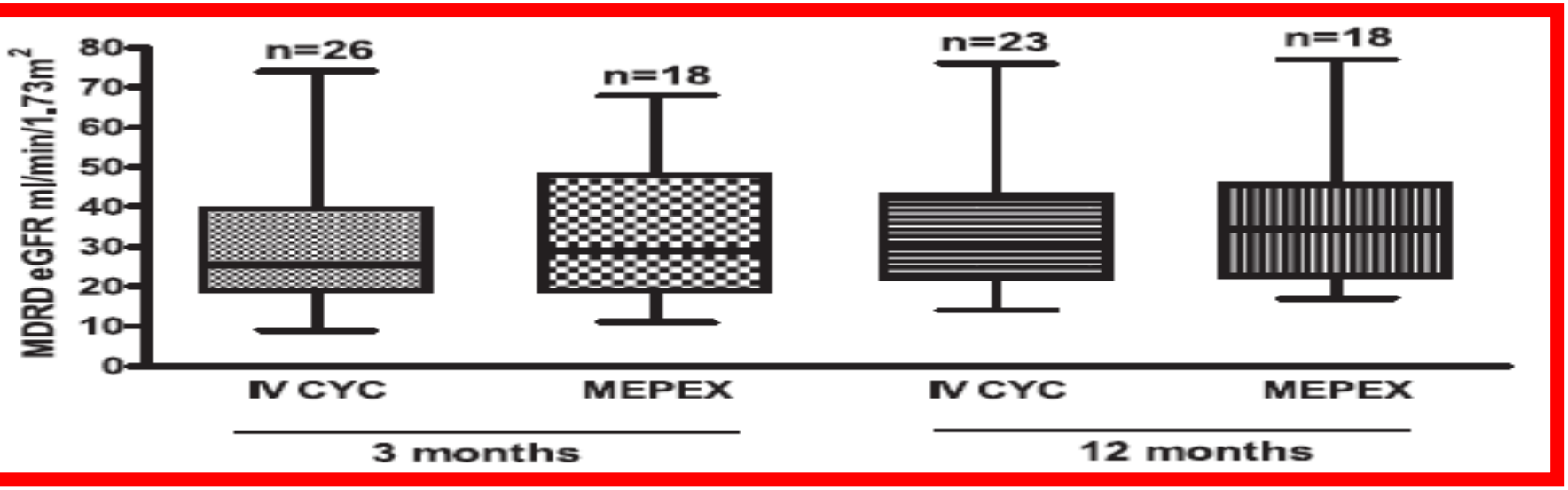


Table 2. Class of ANCA-associated GN according to Berden classification and renal recovery

Class of GN	Recovered Renal Function (*n*=16)	No Renal Recovery (*n*=11)
Crescentic	13 (81)	5 (45)
Focal	1 (6)	2 (18)
Mixed	1 (6)	1 (9)
Sclerotic	1 (6)	3 (27)

Intravenous Cyclophosphamide and Plasmapheresis in Dialysis-Dependent ANCA-Associated Vasculitis

Ruth J. Pepper,[*†] *Dimitrios Chanouzas,*[‡] *Ruth Tarzi,*[†] *Mark A. Little,*[*] *Alina Casian,*[§] *Michael Walsh,*[‖] *Charles D. Pusey,*[†] *Lorraine Harper,*[‡] *and Alan D. Salama,*[*] *European Vasculitis Study (EUVAS) investigators*

Clin J Am Soc Nephrol 8: 219–224, 2013

Much lower mortality in pts treated with ivCPH compared to MEPEX pts

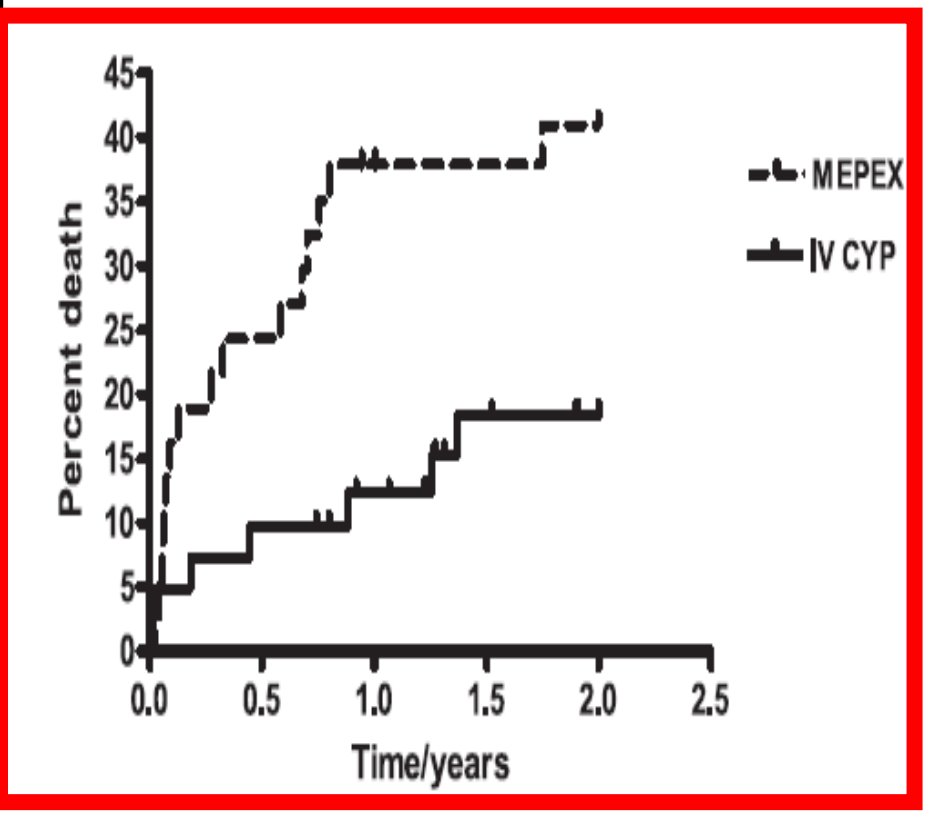


Table 4. Comparison of outcome between the intravenous CYP cohort and the MEPEX cohort

Characteristic	Intravenous CYP	MEPEX
Number of patients	41	37
Alive at 3 mo	38/41 (93%)	30/37 (81%)
On dialysis	12	6
Dialysis free	26	24
Alive at 12 mo	37/41 (90%)	23/37 (62%)
On dialysis	13	4
Dialysis free	24	19
Death in first 12 mo	4/41(10%)	14/37 (38%)
Death in first 12 mo presumed due to sepsis	1 (25%)	7 (50%)

CYP, cyclophosphamide; MEPEX, methylprednisolone versus plasma exchange (oral cyclophosphamide cohort).

Early plasma exchange improves outcome in PR3-ANCA-positive renal vasculitis

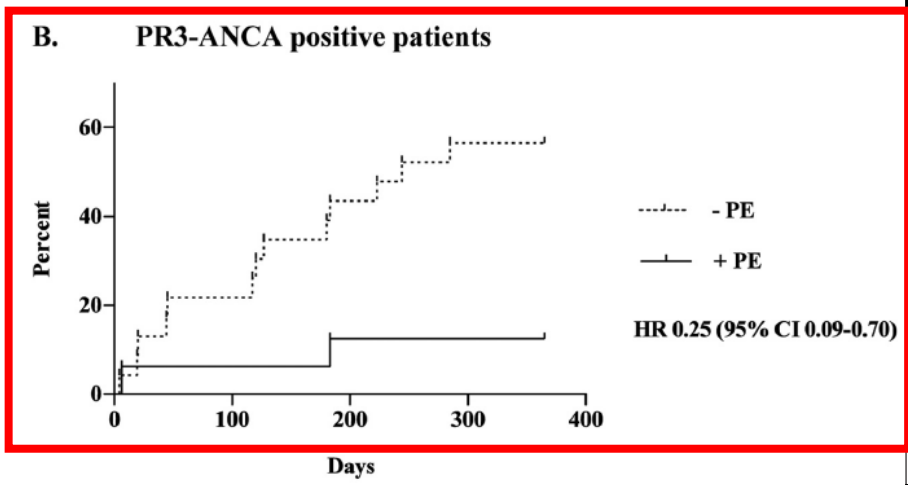
J.W. Gregersen[1], T. Kristensen[1], S.R.P. Krag[2], H. Birn[1], P. Ivarsen[1]

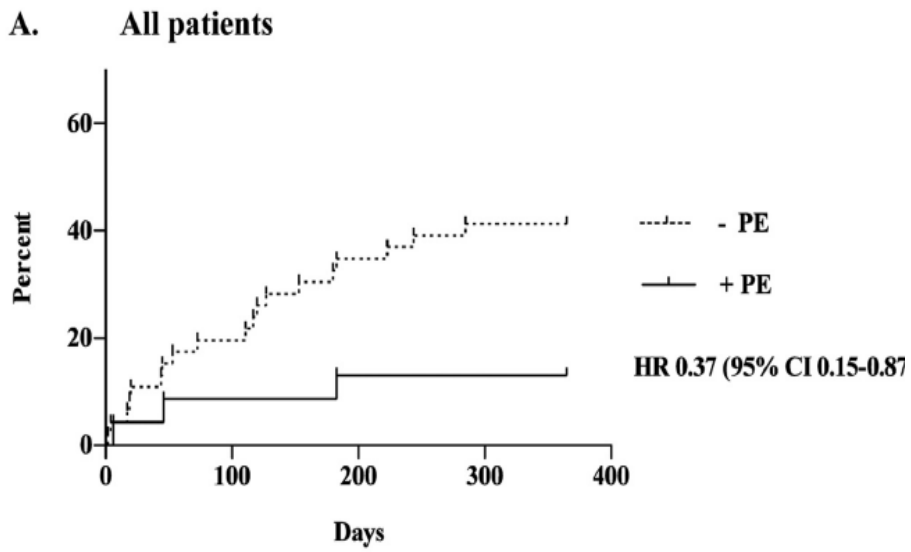
Clin Exp Rheumatol 2012; 30 (Suppl. 70): S39-S47.

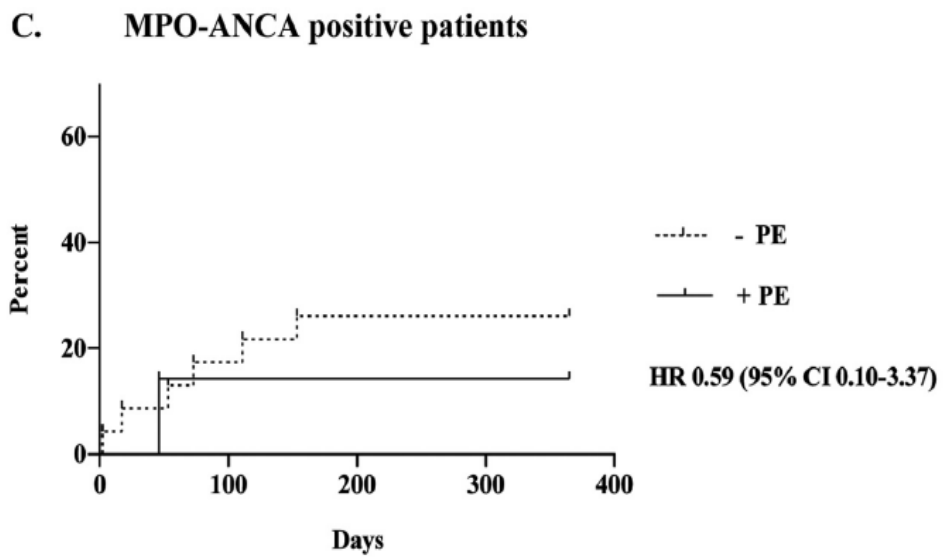
ESRD or death reduced only in PR3-ANCA positive pts

Table III. Clinical outcome according to treatment group and ANCA subtype.

		+ PE group	– PE group	*p*-value
Death/ESRD/relapses	All patients	5/25 (20%)	23/50 (46%)	**0.04**
	PR3-ANCA +	2/16 (13%)	15/25 (60%)	**0.004**
	MPO-ANCA +	3/9 (33%)	8/25 (32%)	1.0
Patients with p-creatinine <500 µM	All patients	1/15 (7%)	16/37 (43%)	**0.01**
	PR3-ANCA +	1/10 (10%)	11/20 (55%)	**0.02**
	MPO-ANCA +	0/5 (0%)	5/17 (29%)	0.29







ANCA-associated GN—to PLEX or not to PLEX?

Andrew S. Bomback and Gerald B. Appel

Nat. Rev. Nephrol. 9, 436–438 (2013);

Plasma exchange (PLEX) is often included in the initial therapy of patients with antineutrophil cytoplasmic autoantibody-associated glomerulonephritis who present with severe kidney failure. However, new long-term follow-up data from the MEPEX trial suggest that PLEX may not improve survival in these patients.

What we know from these trials is that PLEX reduces the risk of ESRD but does not seem to reduce the risk of mortality. What we do not yet know, but what the ongoing PEXIVAS trial[10] of 500 patients across four continents may tell us, is whether this reduced risk of ESRD translates to the reduced risk of death that can be logically expected in the modern era of treating ANCA-associated GN. Until such data emerge, continuing to offer PLEX to patients with ANCA-associated GN and severe renal failure is reasonable.

“...PLEX reduces the risk of ESRD but does not seem to reduce the risk of mortality”

Plasma exchange - open questions

Treatment of dialysis-dependent pts

Treatment of pts with preserved renal function

Treatment of pts with alveolar haemorrhage

Different treatment of anti-PR3 and anti-MPO disease?

Plasmapheresis Therapy in ANCA-Associated Vasculitides: A Single-Center Retrospective Analysis of Renal Outcome and Mortality

David Solar-Cafaggi,[1] Yemil Atisha-Fregoso,[1] and Andrea Hinojosa-Azaola[2]*

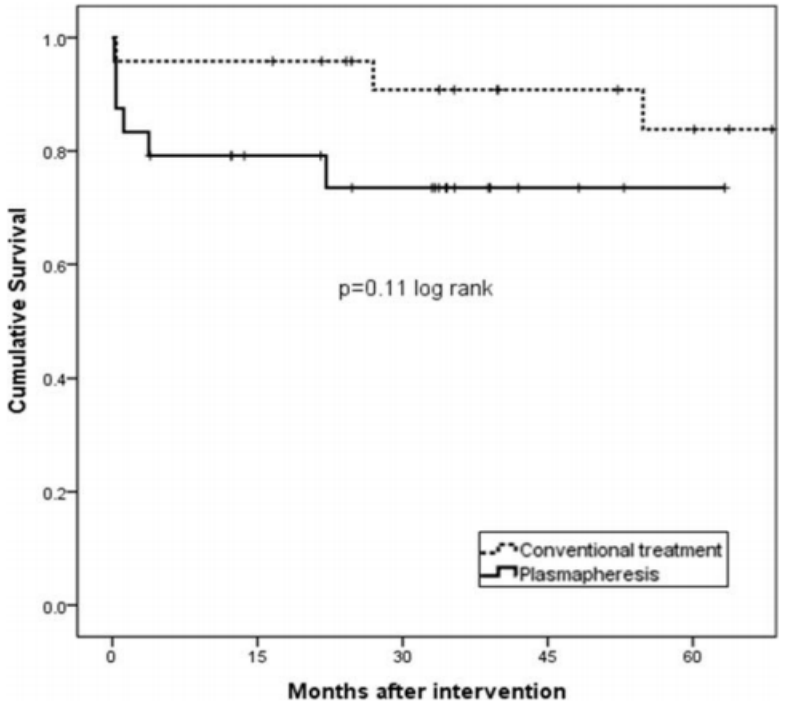
Journal of Clinical Apheresis 31:411–418 (2016)

Single-center retrospective comparison of 24 pts with AAV treated with adjunct PE and with 24 age-, eGFR- and disease activity- matched pts with standard treatment

No difference in survival and dialysis-free survival

TABLE IV. Outcomes at the End of Follow-up According to Treatment Group

Outcome	Plasma exchange $n = 24$	Conventional therapy $n = 24$	p
Alive, free of dialysis-n (%)	13 (54)	14 (58)	1.00
Alive, in dialysis-n (%)	5 (21)	5 (21)	1.00
Death, free of dialysis-n (%)	4 (17)	4 (17)	1.00
Death, in dialysis-n (%)	2 (8)	1 (4)	1.00

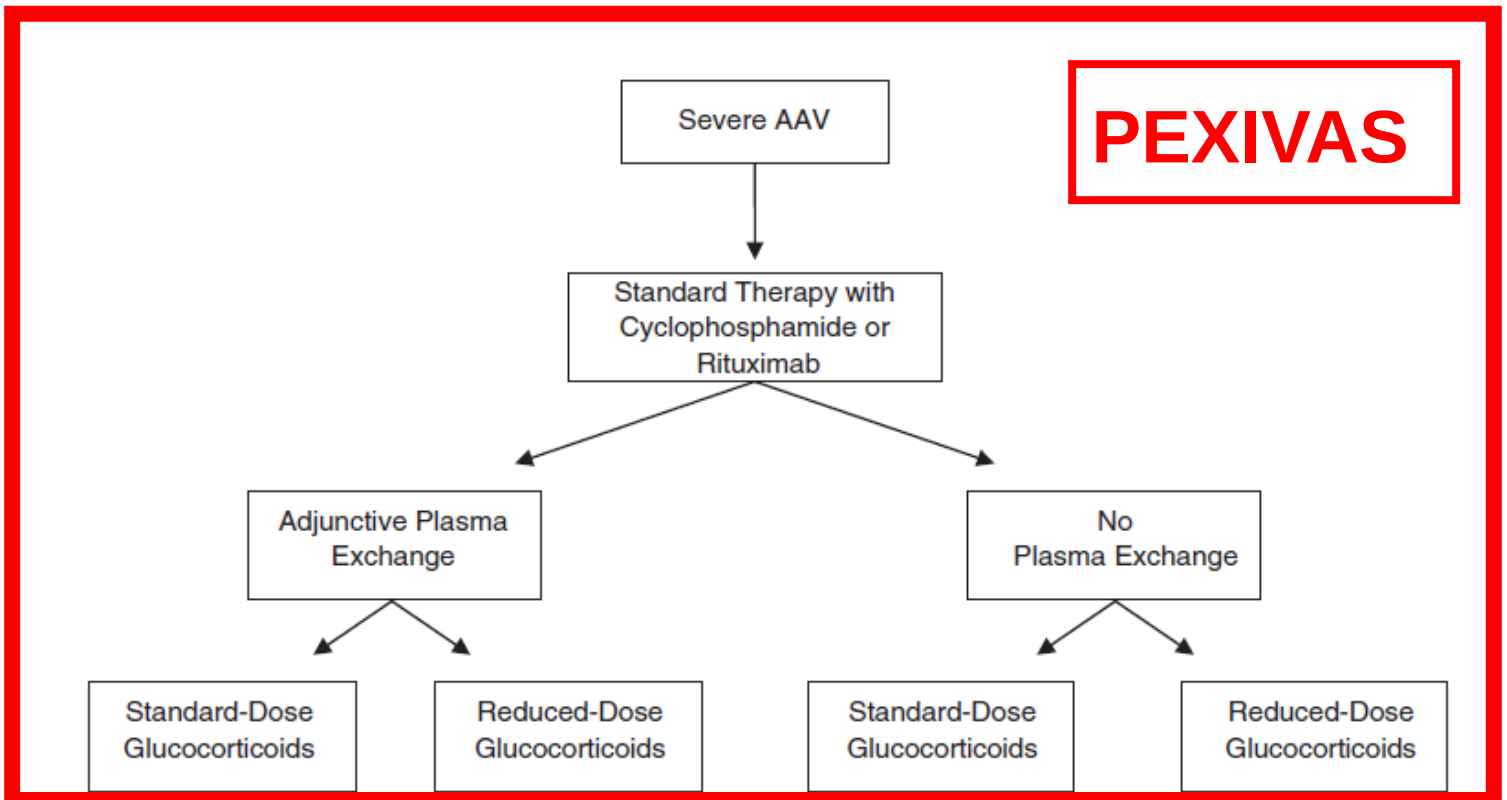


Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial

Trials 2013, 14:73

Michael Walsh[1*], Peter A Merkel[2], Chen Au Peh[3], Wladimir Szpirt[4], Loïc Guillevin[5], Charles D Pusey[6], Janak de Zoysa[7], Natalie Ives[8], William F Clark[9], Karen Quillen[10], Jeffrey L Winters[11], Keith Wheatley[12], David Jayne[13] and on behalf of the PEXIVAS Investigators

PEXIVAS recruited 700 pts with AAV a Scr > 200 µmol/l randomized to PE or no PE as an add-on treatment with a 2 yr FU, no effect on mortality and the risk of ESRD demonstrated in any of the studied subgroups



KDIGO CLINICAL PRACTICE GUIDELINE FOR GLOMERULONEPHRITIS

CHAPTER 13: PAUCI-IMMUNE FOCAL AND SEGMENTAL NECROTIZING GLOMERULONEPHRITIS

VOLUME 2 | ISSUE 2 | JUNE 2012

Data from PEXIVAS will definitely modify these statements

13.2: *Special patient populations*

13.2.1: We recommend the addition of plasmapheresis for patients requiring dialysis or with rapidly increasing SCr. (*1C*)

13.2.2: We suggest the addition of plasmapheresis for patients with diffuse pulmonary hemorrhage. (*2C*)

13.2.3: We suggest the addition of plasmapheresis for patients with overlap syndrome of ANCA vasculitis and anti-GBM GN, according to proposed criteria and regimen for anti-GBM GN (see Chapter 14). (*2D*)

13.2.4: We suggest discontinuing cyclophosphamide therapy after 3 months in patients who remain dialysis-dependent and who do not have any extrarenal manifestations of disease. (*2C*)

Outline of the lecture

- Anti-PR3 vs. anti-MPO disease, predictive value of renal biopsy?
- Initial therapy and relapse
- Plasma exchange
- **Maintenance therapy**
- Conclusions

Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis

Alexandre Karras,[1,2] Christian Pagnoux,[3] Marion Haubitz,[4] Kirsten de Groot,[5] Xavier Puechal,[6] Jan Willem Cohen Tervaert,[7] Mårten Segelmark,[8] Loic Guillevin,[2,6] David Jayne,[9] On behalf of the European Vasculitis Society

Ann Rheum Dis 2017;**0**:1–7. doi:10.1136/annrheumdis-2017-211123

110 pts with AAV 18 – 24 mo after diagnosis in stable remission randomized to continuation (up to 48 mo) or withdrawal (at 24 mo) of CS and AZA

Table 2 Demographics of randomised patients according to treatment arm, 18–24 months after diagnosis

Variable	Continuation group (n=59)	Withdrawal group (n=51)	p Value
Age (years)	57.7±14.1	57.4±14.3	0.89
Sex (%)			0.69
Male	49	53	
Female	51	47	
AAV type (%)			0.96
GPA	47	47	
MPA	53	53	
ANCA at diagnosis (%)			0.11
PR3	46	59	
MPO	47	41	
Negative	7	0	
Delay from diagnosis (months)	18.6±0.2	19.0±0.2	0.28
Serum creatinine (µmol/L)	140±67	129±54	0.34
eGFR (mL/min/1.73 m^2)	51.6±23.0	55.8±23.4	0.34
ANCA			0.59
Positive	51%	56%	
Negative	49%	44%	
Prednisolone dose (mg/day)	5.8±2.3	5.9±2.1	0.61
Azathioprine dose (mg/day)	102±35	95±39	0.27
VDI	1.8±0.2	1.8±0.2	0.98

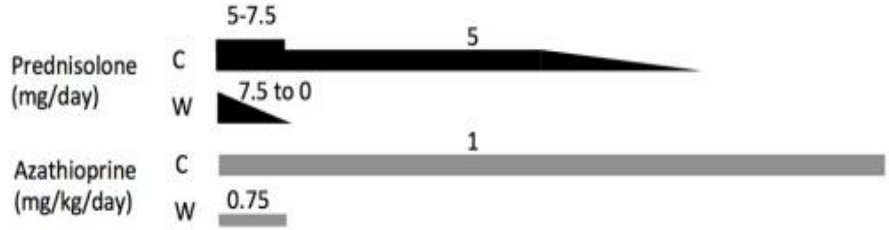
REMAIN

Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis

Alexandre Karras,[1,2] Christian Pagnoux,[3] Marion Haubitz,[4] Kirsten de Groot,[5] Xavier Puechal,[6] Jan Willem Cohen Tervaert,[7] Mårten Segelmark,[8] Loic Guillevin,[2,6] David Jayne,[9] On behalf of the European Vasculitis Society

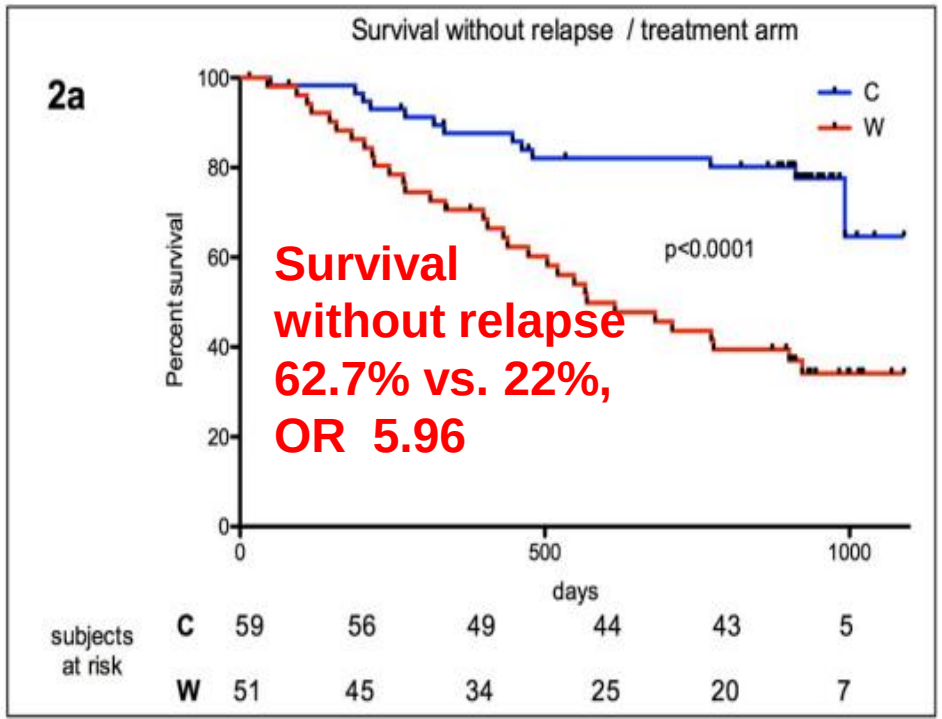
Ann Rheum Dis 2017;**0**:1–7. doi:10.1136/annrheumdis-2017-211123

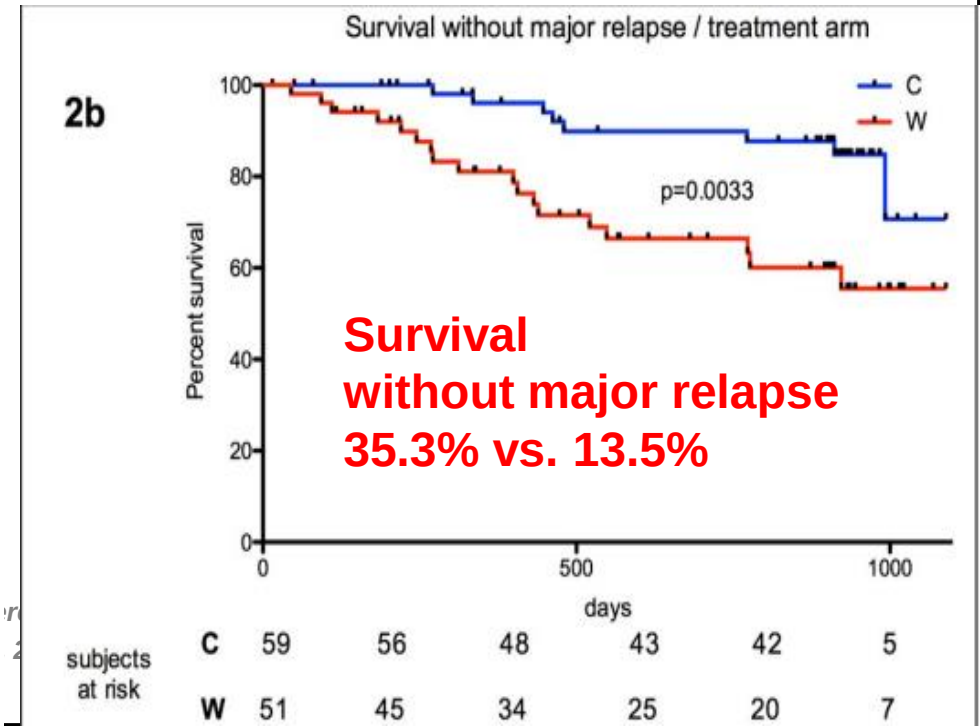
Primary endpoint (survival without relapse within 48 mo) reached in 62.7% of pts in continuation vs. in 22% withdrawal limb



REMAIN

ESRD 7.8% vs. 0%, p = 0.012





Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis

Alexandre Karras,[1,2] Christian Pagnoux,[3] Marion Haubitz,[4] Kirsten de Groot,[5] Xavier Puechal,[6] Jan Willem Cohen Tervaert,[7] Mårten Segelmark,[8] Loic Guillevin,[2,6] David Jayne,[9] On behalf of the European Vasculitis Society

Ann Rheum Dis 2017;**0**:1–7. doi:10.1136/annrheumdis-2017-211123

Relapse rate higher in patients ANCA positive at randomisation

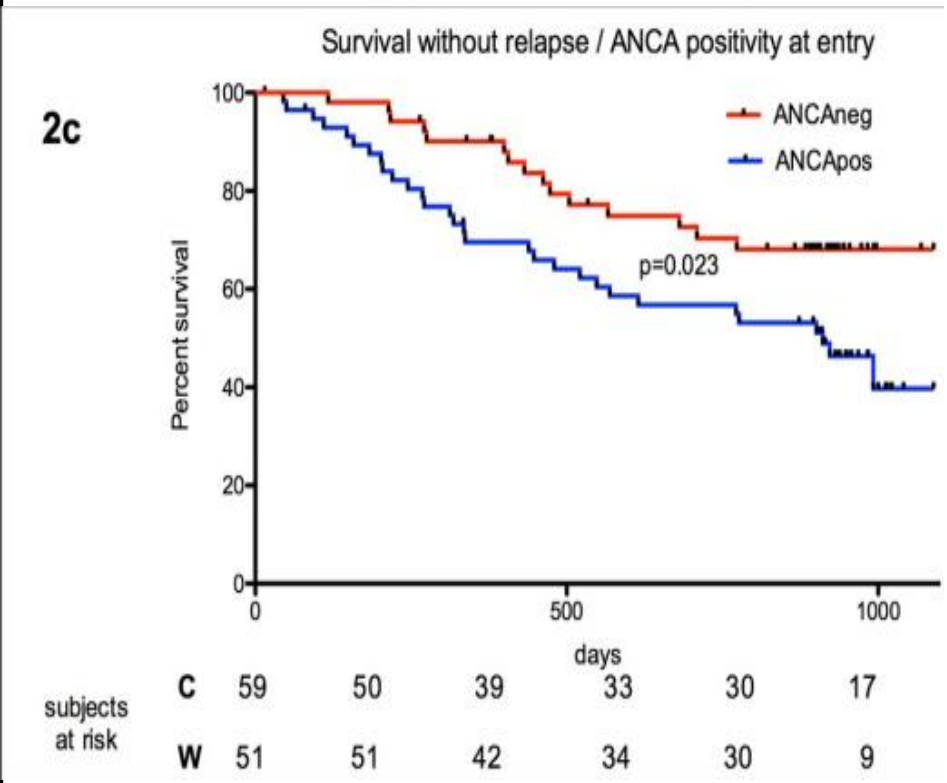


Table 3 Risk factors associated with AAV relapse

	Subgroup	Relapse risk	p Value	OR (95% CI)
Treatment arm	W	32/51 (63%)	<0.0001	5.96 (2.58 to 13.77)
	C	13/59 (22%)		
ANCA specificity at diagnosis	PR3	28/57 (49%)	0.13	1.82 (0.83 to 3.98)
	MPO	17/49 (35%)		
ANCA testing at randomisation	Positive	30/58 (51%)	0.017	2.57 (1.16 to 5.68)
	Negative	15/51 (29%)		
Disease	MPA	22/58 (38%)	0.5	0.77 (0.36 to 1.65)
	GPA	23/52 (44%)		

REMAIN

Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis

Alexandre Karras,[1,2] Christian Pagnoux,[3] Marion Haubitz,[4] Kirsten de Groot,[5] Xavier Puechal,[6] Jan Willem Cohen Tervaert,[7] Mårten Segelmark,[8] Loic Guillevin,[2,6] David Jayne,[9] On behalf of the European Vasculitis Society

Ann Rheum Dis 2017;**0**:1–7. doi:10.1136/annrheumdis-2017-211123

No significant difference in adverse event rate

Table 4 Adverse events (AEs)

Variable	Continuation group (n=59)	Withdrawal group (n=51)	p Value
Total number of AEs	43	28	0.07
Number (%) of patients with at least one AE	26 (44%)	20 (39%)	0.69
Number (%) of patients with ≥ grade 3 AE	9 (15%)	3 (6%)	0.13
Type of AE			
Cancer	7	4	0.54
Non-melanoma skin cancer	2	2	0.99
Infection	17	13	0.83
Cytopaenia	7	1	0.066
Hepatitis	2	2	0.99
Cardiovascular events	5	0	0.060

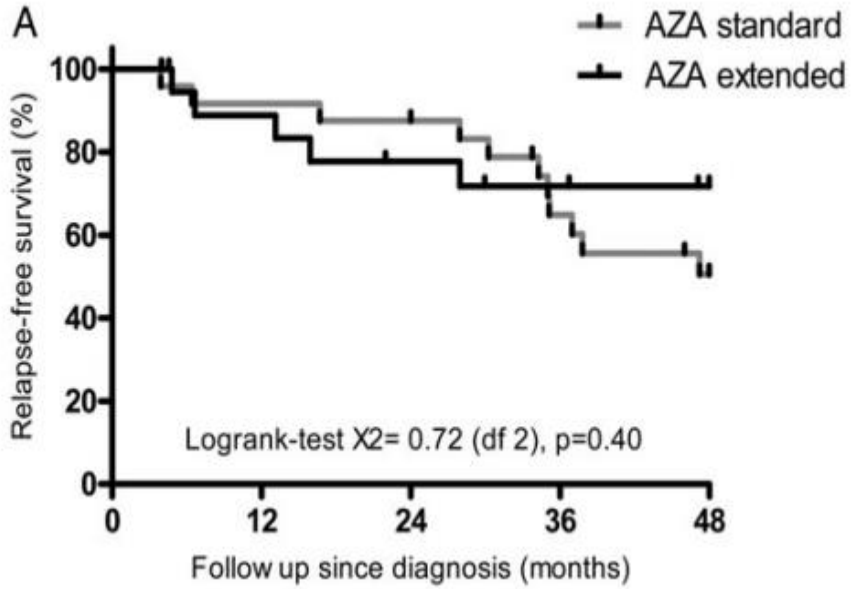
REMAIN

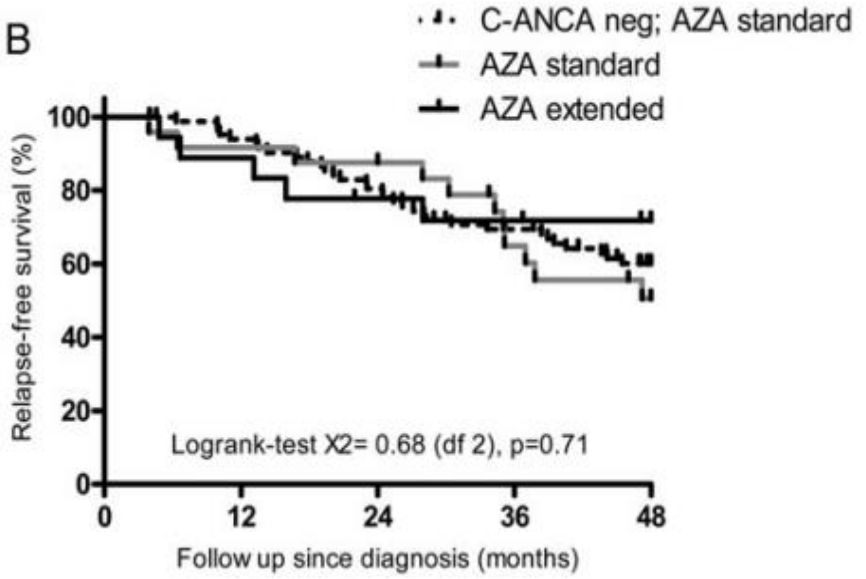
Extended versus standard azathioprine maintenance therapy

Jan-Stephan F. Sanders[1,†], Anoek A.E. de Joode[1,†], Ruud G. DeSevaux[2], Jan Broekroelofs[3], Alexandre E. Voskuyl[4], Pieter van Paassen[5], Cees G.M. Kallenberg[6], Jan Willem Cohen Tervaert[5] and Coen A. Stegeman[1,‡]

Nephrol Dial Transplant (2016) 31: 1453–1459

45 pts with c-ANCA positive AAV (75% with renal involvement)
in remission after oral CPH randomized to 1-yr vs 4 yr maintenance with AZA
No significant difference in relapse-free survival in both c-ANCA pos and neg pts





Extended versus standard azathioprine maintenance therapy

Jan-Stephan F. Sanders[1,†], Anoek A.E. de Joode[1,†], Ruud G. DeSevaux[2], Jan Broekroelofs[3], Alexandre E. Voskuyl[4], Pieter van Paassen[5], Cees G.M. Kallenberg[6], Jan Willem Cohen Tervaert[5] and Coen A. Stegeman[1,‡]

Nephrol Dial Transplant (2016) 31: 1453–1459

Study may have been underpowered to identify the difference, a trend to higher number of relapses in pts on standard vs extended AZA (46% vs. 25%)

Table 2. Relapse characteristics

	C-ANCA negative	C-ANCA positive, AZA standard	C-ANCA positive, AZA extended	P-value
Relapse, *n* (%)	33 (40)	11 (46)	5 (25)	0.28
Multiple relapses, *n*	4	2	2	
BVAS	12 (2–26)	14 (4–27))	9 (2–28)	0.30
CRP (mg/L)	46 (1–182)	70 (6–287)	95 (1–324)	0.62
Organ involvement, *n* (%)				
Renal	15 (45)	8 (73)	2 (40)	0.26
Pulmonary	5 (15)	3 (27)	1 (20)	0.66
ENT	15 (45)	7 (63)	1 (20)	0.26

Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis

Alexandre Karras,[1,2] Christian Pagnoux,[3] Marion Haubitz,[4] Kirsten de Groot,[5] Xavier Puechal,[6] Jan Willem Cohen Tervaert,[7] Mårten Segelmark,[8] Loic Guillevin,[2,6] David Jayne,[9] On behalf of the European Vasculitis Society

Ann Rheum Dis 2017;**0**:1–7. doi:10.1136/annrheumdis-2017-211123

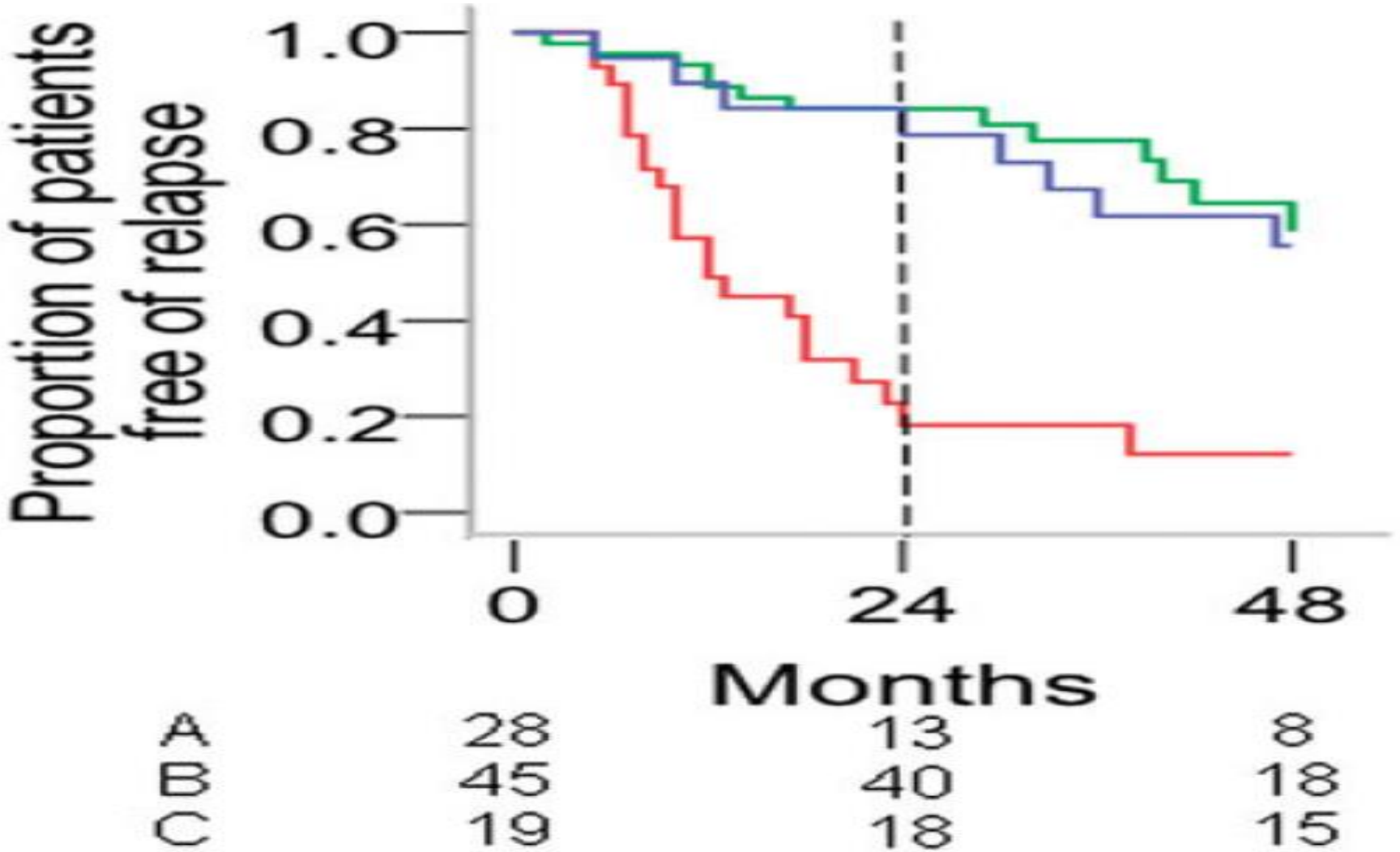
„…at least some of the pts who reached remission of AAV require long-term immunosuppressive therapy to prevent recurrence of the disease

Rituximab for Remission Maintenance in Relapsing Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

ARTHRITIS & RHEUMATISM7
Vol. 64, No. 11, November 2012, pp 3760–3769

Rona M. Smith,[1] Rachel B. Jones,[1] Mary-Jane Guerry,[1] Simona Laurino,[1] Fausta Catapano,[1] Afzal Chaudhry,[1] Kenneth G. C. Smith,[2] and David R. W. Jayne[1]

Outcome much better in pts treated with RTX preemptively



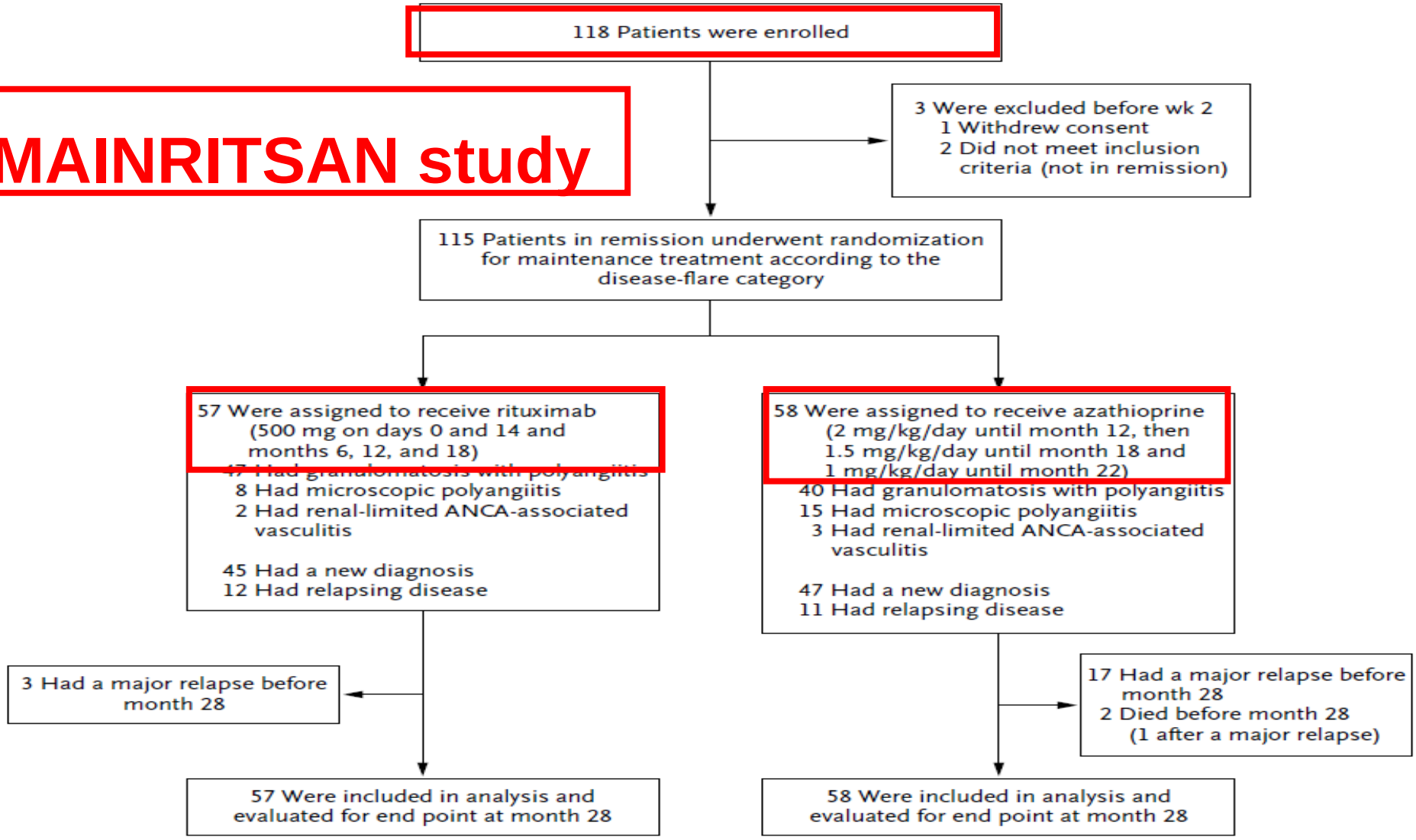
Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

L. Guillevin, C. Pagnoux, A. Karras, C. Khouatra, O. Aumaître, P. Cohen, F. Maurier, O. Decaux, J. Ninet, P. Gobert,

N ENGL J MED 371;19 NEJM.ORG NOVEMBER 6, 2014

115 pts with AAV in remission randomized to RTX or AZA maintenance

MAINRITSAN study



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MAINRITSAN study - renal involvement in 70% of pts

Table 1. Demographic, Clinical, and Biologic Characteristics of the Patients According to Treatment Group.*

Variable	Azathioprine Group (N=58)	Rituximab Group (N=57)	Total (N=115)	P Value
Age — yr	56±14	54±13	55±13	0.33
Female sex — no. (%)	30 (52)	20 (35)	50 (43)	0.07
ANCA-associated vasculitis type — no. (%)				0.22
Granulomatosis with polyangiitis (Wegener's)	40 (69)	47 (82)	87 (76)	
Microscopic polyangiitis	15 (26)	8 (14)	23 (20)	
Renal-limited ANCA-associated vasculitis	3 (5)	2 (4)	5 (4)	
Disease status — no. (%)				0.78
Newly diagnosed	47 (81)	45 (79)	92 (80)	
Relapsing	11 (19)	12 (21)	23 (20)	
Organ involvement at diagnosis or last flare — no. (%)				
Ear, nose, and throat	41 (71)	48 (84)	89 (77)	0.08
Pulmonary involvement	38 (66)	33 (58)	71 (62)	0.40
Alveolar hemorrhage	11 (19)†	9 (16)	20 (18)†	0.62
Renal involvement	41 (71)	40 (70)	81 (70)	0.95
GFR — ml/min/1.73 m²				
At disease flare	53.8±35.4	72.0±46.7	62.9±42.3	0.06
At inclusion	59.4±29.7	68.3±29.3	63.9±29.7	0.08
Induction treatment (until remission or randomization) — mg				
Cumulative cyclophosphamide dose	6901±2395	7291±2290†	7095±2341	0.38
Initial daily prednisone dose at diagnosis or flare	64.8±12.9	67.9±13.1	66.3±13.1	0.20
Daily prednisone dose at remission§	16.3±6.6	18.9±7.7	17.6±7.3	0.06

Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

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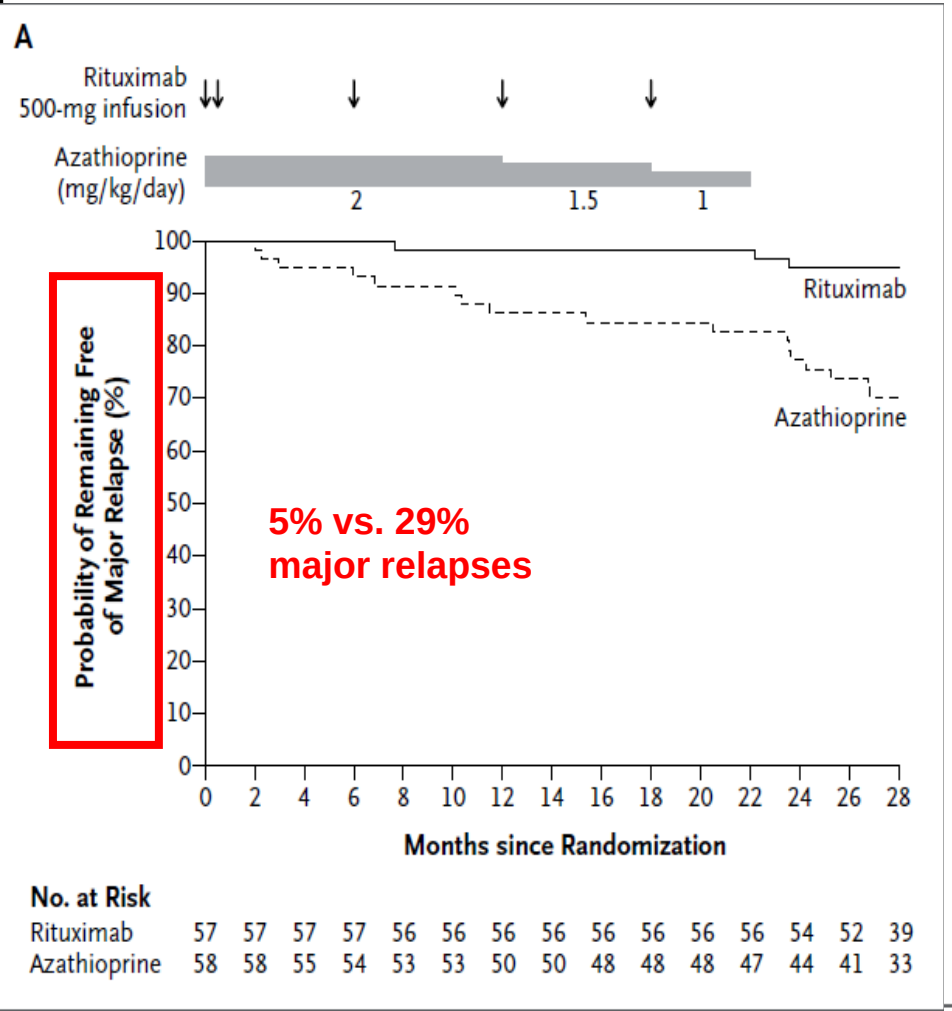
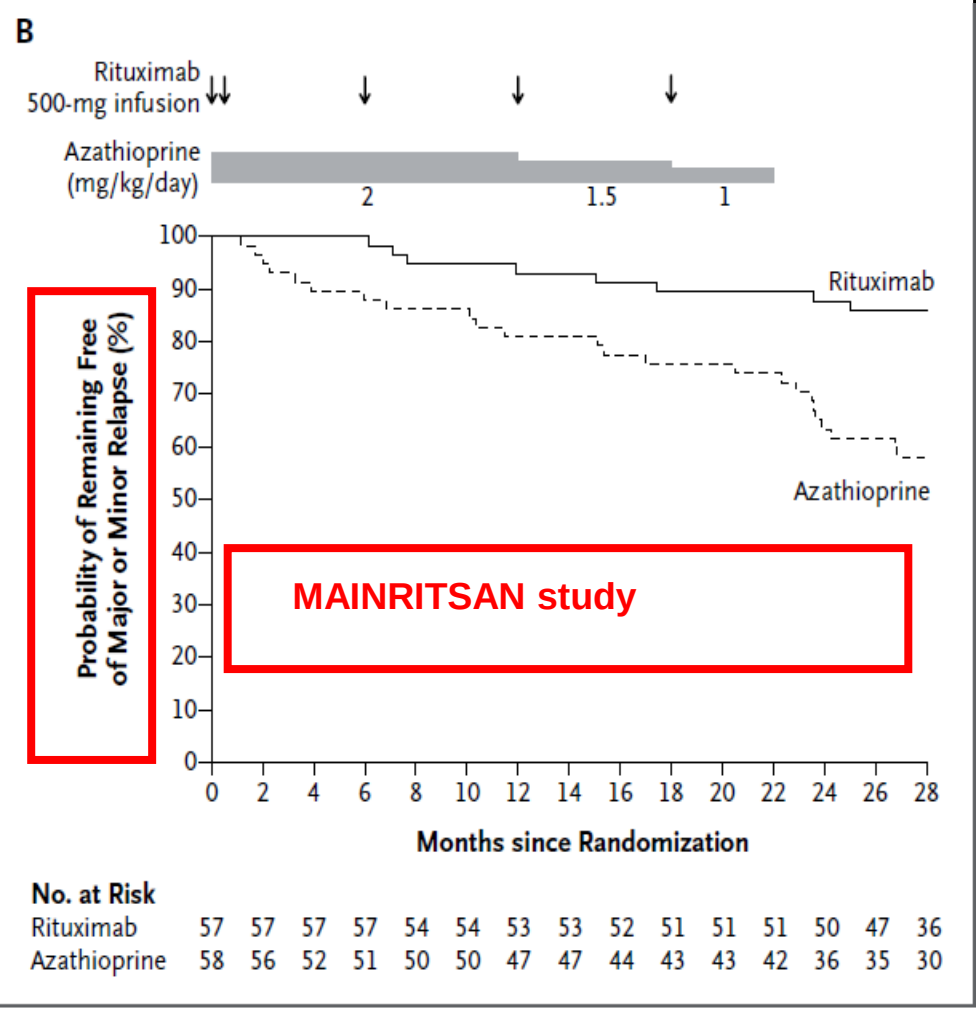
Significantly higher rate of (major) relapses in AZA limb





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MAINRITSAN study

no difference in SAE

Table 2. Severe Adverse Events According to Treatment Group.*

Severe Adverse Event	Azathioprine Group (N=58)	Rituximab Group (N=57)
	no. of events	
Infection	8	11
Bronchitis	0	3
Tuberculosis	0	1
Pneumonia with respiratory distress	1	2
Pneumocystis jiroveci pneumonia	0	1
Bacterial endocarditis	1	0
Atypical mycobacterial infection	1	0
Prostatitis	1	0
Herpes zoster infection	1	1
Cholecystitis	1†	0
Septicemia	1‡	0
Esophageal candidiasis	0	1
Infectious diarrhea	1§	2¶

Table 2. Severe Adverse Events According to Treatment Group.*

Severe Adverse Event	Azathioprine Group (N=58)	Rituximab Group (N=57)
	no. of events	
Cancer	2	1
Pancreas	1‡	0
Prostate	0	1
Basocellular carcinoma	1	0
Hematologic event	9	1
Anemia	1	0
Leukopenia	6	0
Lymphopenia	1	1
Thrombocytopenia	1	0
Other‖	25	26

SY6_4 RITUXIMAB VERSUS AZATHIOPRINE TO MAINTAIN REMISSION OF ANCA-ASSOCIATED VASCULITIDES (MAINRITSAN): FOLLOW-UP AT 60 MONTHS

Benjamin Terrier[1], Christian Pagnoux[1], Elodie Perrodeau[1], Alexandre Karras[1], Chahera Khouatra[1], Olivier Aumaitre[1], Pascal Cohen[1], Francois Maurier[1], Olivier Decaux[1], Philippe Ravaud[1] and Loic Ravaud[1]
[1]*French Vasculitis Study Group France*

ABSTRACTS OF THE 18TH INTERNATIONAL VASCULITIS AND ANCA WORKSHOP

60 mo FU of the MAINRITSAN study (RTX vs. AZA):

60-mo overall survival - 100 % vs. 93% (p = 0.045)
All relapse-free survival - 57.9% vs. 37.2% (p = 0.012)
Major relapse-free survival- 71.9% vs. 49.4% (p = 0.003)

No difference in AEs and corticosteroid doses

Maintenance therapy with RTX remains superior to AZA even after 60 months

ABSTRACTS OF THE 18TH INTERNATIONAL VASCULITIS AND ANCA WORKSHOP

WS7_3 ECONOMIC EVALUATION OF RITUXIMAB VERSUS AZATHIOPRINE FOR MAINTENANCE TREATMENT OF ANCA-ASSOCIATED VASCULITIS: THE MAINRITSAN TRIAL

Annalisa Montante[1], Alicia Le Bras[1], Benjamin Terrier[1], Pascal Cohen[1], Xavier Puechal[1], Alexandre Karras[1], Philippe Ravaud[1], Loic Guillevin[1] and Isabelle Durand-Zaleski[1]
[1]*French Vasculitis Study Group France*

Rituximab higher cost partly offset by fewer relapses, side effects and FU expenses

The cost of avoiding one relapse was 259 euros

	Azathioprine		Rituximab	
	Mean(SD)	Median[IQR]	Mean(SD)	Median[IQR]
Inpatient stays, n	1.9(2.6)	1[0–2]	1.7(2.9)	1[0–2]
Length of stay (days)	14.1(24.1)	7[1–16]	12.1(13.6)	7[5–14]
Outpatient visits, n	3.5(4.9)	1[0–5]	6.3(2.8)	6[5–7]
Cost (€/patient)				
Protocol drug	313(130)	337[(264–391]	6,035(165)	6,057[6,057–6,057]
Its administration	0	0[0–0]	2,467(1,076)	2,020[1,830–2,875]
Maintenance therapy	633(1,808)	0[0–0]	0(0)	0[0–0]
Relapses	2,547(4,748)	0[0–4,737]	724(3,537)	0[0–0]
Side effects	2,606(6,622)	0[0–2,523]	1,983(4,908)	0[0–2,531]
Follow-up	2,954(5,611)	636[0–3,254]	1,713(3,809)	0[0–2,426]
Outpatient visits	993(407)	1,069[770–1,314]	748(285)	615[614–669]
Total cost	10,046(10,558)	6,049[2,140–14,501]	13,67(7,946)	10,942[9,103–14,197]

Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis

Rheumatology Advance Access published December 3, 2014

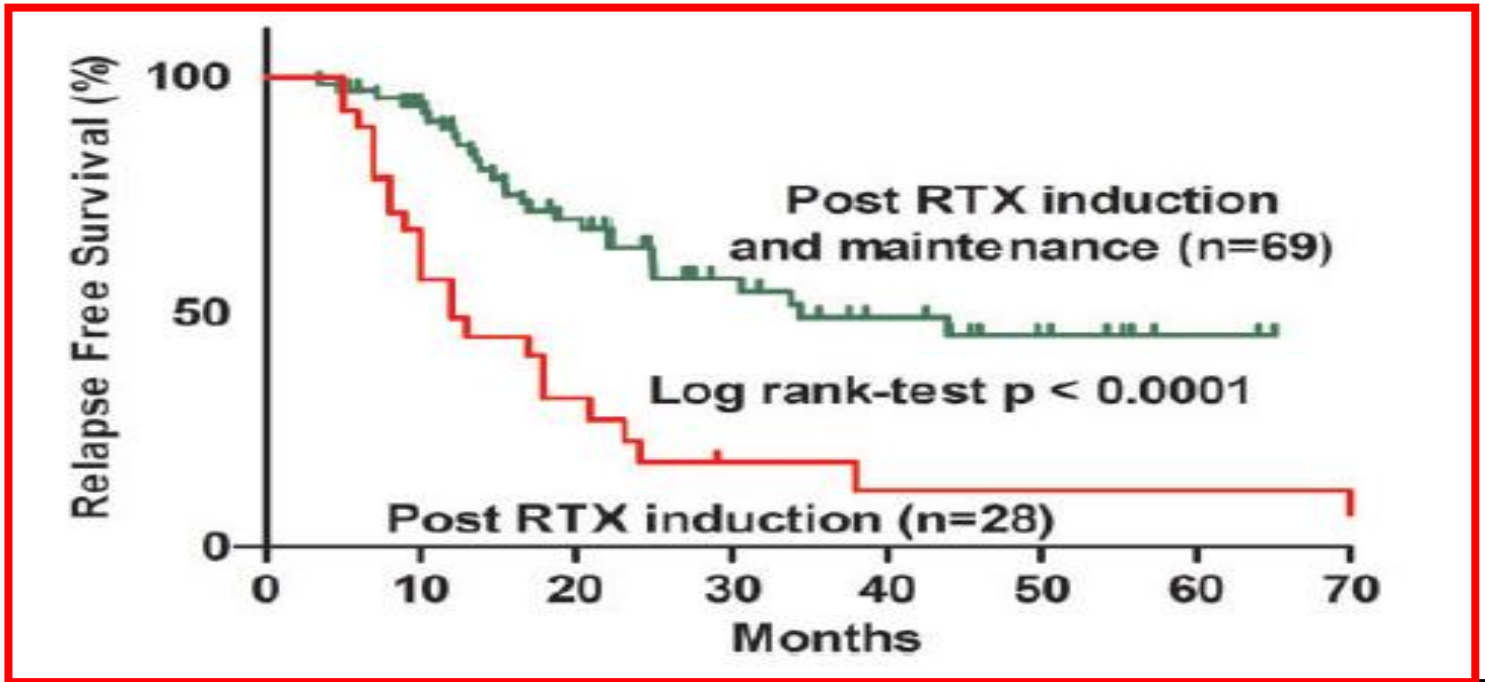
Federico Alberici[1,2,3], Rona M. Smith[1,2], Rachel B. Jones[1,2], Darren M. Roberts[1,2], Lisa C. Willcocks[1,2], Afzal Chaudhry[1,2], Kenneth G. C. Smith[1,2,4] and David R. W. Jayne[1,2]

69 pts treated with 2-yr RTX maintenance compared with 28 pts with RTX induction only

Relapses ↑ in pts with early B cell return and reappearance of ANCA

Relapse rate ↓ after RTX maintenance vs. after RTX induction only

FIG. 5 Relapse-free survival in two cohorts of relapsing ANCA-associated vasculitis patients



Further RCTs with RTX in AAV

MAINRITSAN 2

RTX maintenance given preemptively, or based on ANCA titre and reappearance of CD19 cells

MAINRITSAN 3

RTX maintenance given for 18 compared to 46 mo

RITAZAREM

RTX maintenance in relapsing pts treated with RTX induction

Comparison Study of Two Rituximab Regimens in the Remission of ANCA Associated Vasculitis

MAINRITSAN 2

NCT01731561

166 pts with ANCA-associated vasculitis (new or relapsing in remission after induction treatment)

RTX maintenance regimen based on the ANCA titre and CD19 lymphocytes compared to preemptive RTX

RTX given 1 g in the beginning, then 0.5 g each 6 months vs. based on ANCA titre and CD19 cells)

Primary outcome measure: number of relapses (major and minor) within 28 mo

P2 136 COMPARISON OF SYSTEMATIC VS INDIVIDUALLY TAILORED RITUXIMAB REGIMEN TO MAINTAIN ANCA ASSOCIATED VASCULITIS REMISSION

Pierre Charles[1], Benjamin Terrier[1], Pascal Cohen[1], Stanislas Faguer[2], Antoine Huart[2], Mohamed Hamidou[3], Christian Agard[3], Bernard Bonnotte[4], Maxime Samson[4], Alexandre Karras[5] and Loic Guillevin[1]

[1]Departement de Medecine Interne, Hopital Cochin Paris, [2]Service de Nephrologie et Immunologie Clinique Toulouse, [3]Departement de Medecine Interne, CHU Hotel-Dieu Nantes, [4]Service de Medecine Interne et d Immunologie Clinique Dijon, [5]Unite de Nephrologie, Hopital Europeen Georges-Pompidou Paris

ABSTRACTS OF THE 18TH INTERNATIONAL VASCULITIS AND ANCA WORKSHOP

VASCULITIS IN TOKYO 2017

Results of **MAINRITSAN2 study**

14 (7.3%) vs. 8 (9.9%) relapses in tailored vs preemptive treatment (p = 0.2, n.s.)

Median numbers of RTX infusion 3 vs. 5

Conclusion: both approaches similarly effective, fewer infusions and total RTX dose in tailored treatment limb

Rituximab Vasculitis Maintenance Study (RITAZAREM)

NCT01697267

Main investigator: D Jayne

190 pts with **relapsing AAV** treated with RTX and CS and after 4 mo randomized to either **RTX** (a single dose every 4 mo for 2 yrs) or **AZA** and followed for 4 yrs

Primary outcome measures: time to relapse (either minor or major relapse) from randomisation

Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis

Rheumatology Advance Access published December 3, 2014

Federico Alberici[1,2,3], Rona M. Smith[1,2], Rachel B. Jones[1,2], Darren M. Roberts[1,2], Lisa C. Willcocks[1,2], Afzal Chaudhry[1,2], Kenneth G. C. Smith[1,2,4] and David R. W. Jayne[1,2]

In 69 pts treated with 2-year RTX maintenance
Relapse rate ↓
after RTX withdrawal
than after RTX induction only

relapses ↑ in pts with early return of B cells and reappearance of ANCA

FIG. 4 Relapse-free survival stratified by B cell return within or after 12 months of the last rituximab dose

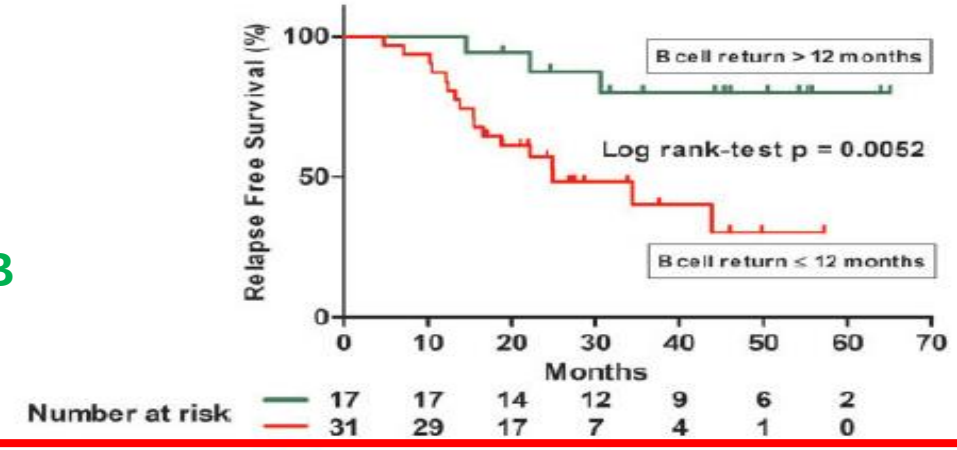


FIG. 3 Relapse-free survival after rituximab (RTX) maintenance treatment withdrawal

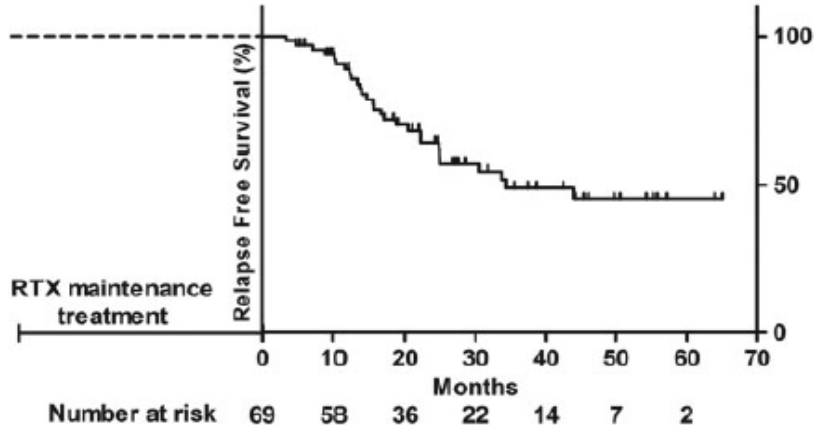
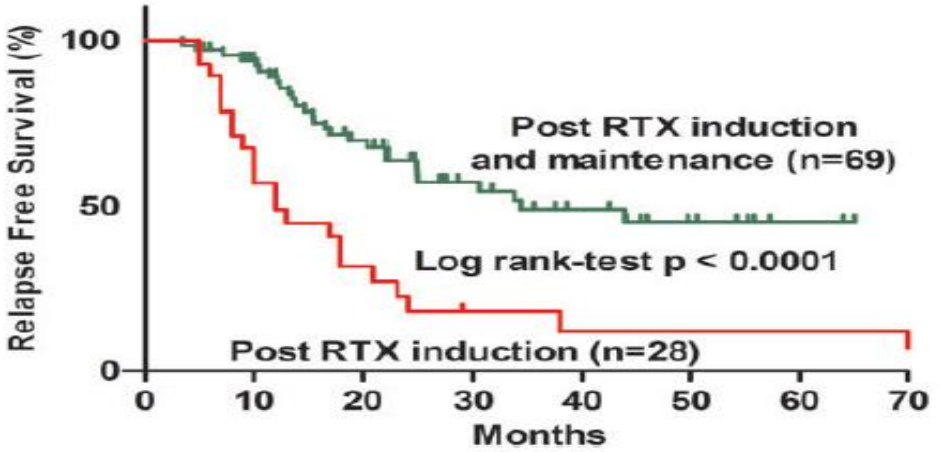


FIG. 5 Relapse-free survival in two cohorts of relapsing ANCA-associated vasculitis patients



Comparison Between a Long Term and a Conventional Maintenance Treatment With Rituximab (MAINRITSAN3)

NCT02433522

During FU of MAINRITSAN study, up to 30% of patients experienced a relapse 38 months after the last rituximab infusion (unpublished data) , duration of RTX maintenanc treatment to be defined

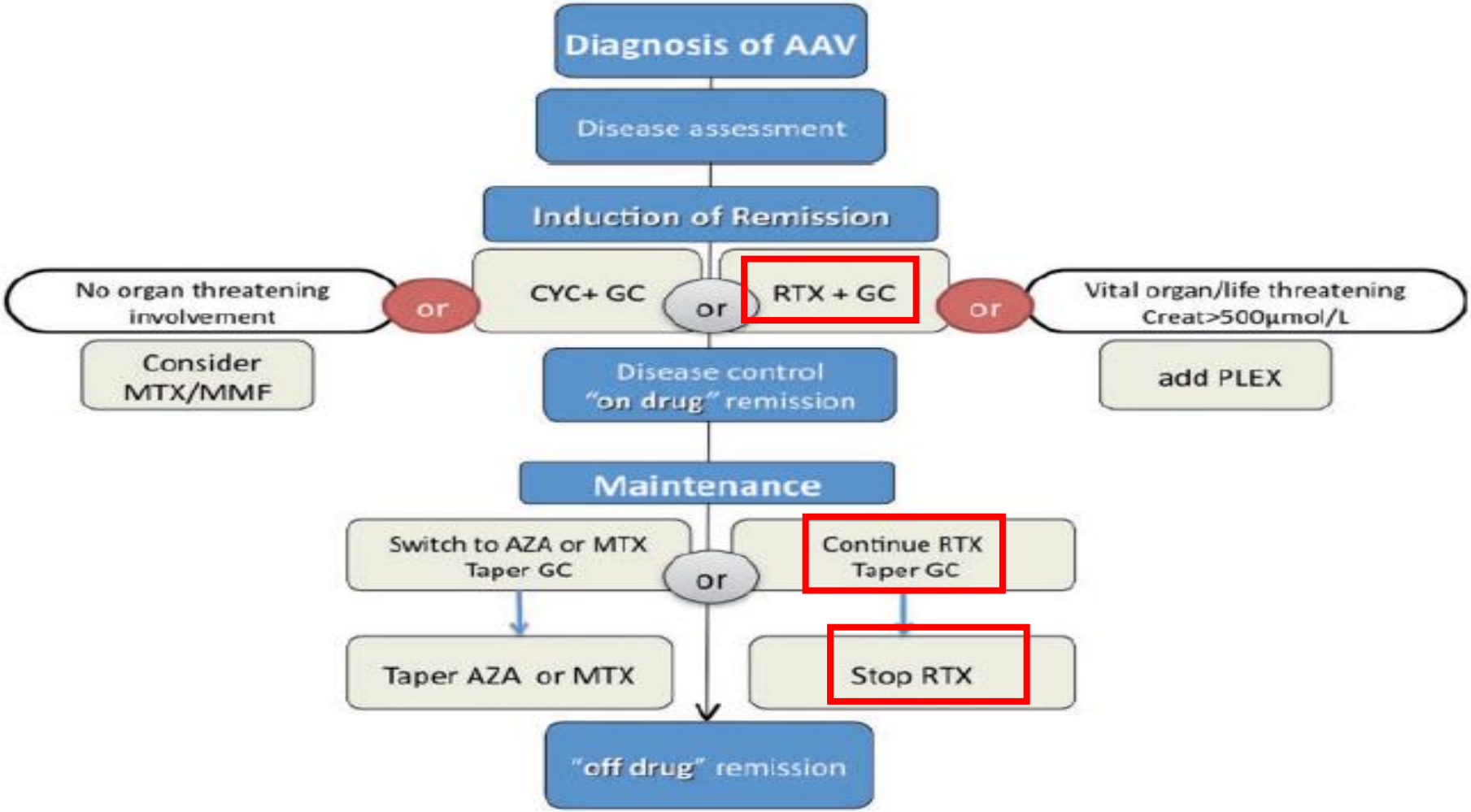
RTX maintenance of 18 mo will be compared with RTX maintenance of 46 mo in 116 pts with AAV in remission

Primary outcome measures: vasculitis score 2003 (BVAS 2003) and relapse free survival rates (BVAS > 0)

BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis

Rheumatology 2014;53:2306–2309

Eleana Ntatsaki[1,2], David Carruthers[3], Kuntal Chakravarty[4], David D'Cruz[5], Lorraine Harper[6], David Jayne[7], Raashid Luqmani[8], John Mills[9], Janice Mooney[10], Michael Venning[11] and Richard A. Watts[12,13], on behalf of the BSR and BHPR Standards, Guidelines and Audit Working Group



EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis

M Yates,[1,2] R A Watts,[2,3] I M Bajema,[4] M C Cid,[5] B Crestani,[6] T Hauser,[7] B Hellmich,[8] J U Holle,[9] M Laudien,[10] M A Little,[11] R A Luqmani,[12] A Mahr,[13] P A Merkel,[14] J Mills,[15] J Mooney,[1] M Segelmark,[16,17] V Tesar,[18] K Westman,[19] A Vaglio,[20] N Yalçındağ,[21] D R Jayne,[22] C Mukhtyar[1]

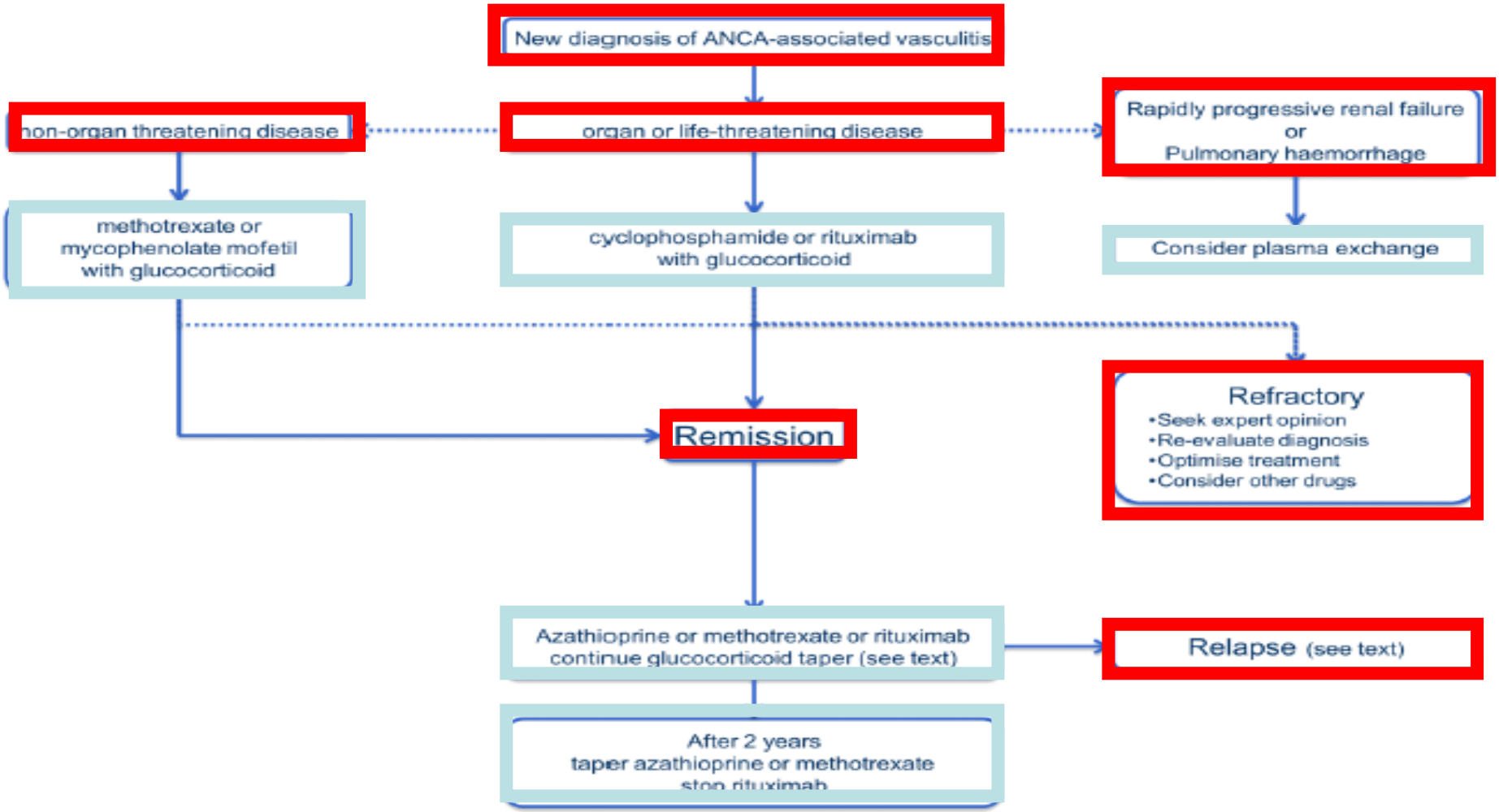
Table 1 Recommendation statements

Statement	Level of evidence	Grade of recommendation
7. For remission-maintenance of AAV we recommend treatment with a combination of low-dose glucocorticoids and either azathioprine, rituximab, methotrexate or mycophenolate mofetil*.	1B for GPA/MPA 3 for EGPA and AZA	A for GPA/MPA, C for EGPA and AZA
8. We recommend that remission-maintenance therapy for AAV be continued for at least 24 months following induction of sustained remission.	4	D
9. For patients with AAV refractory to remission-induction therapy we recommend switching from cyclophosphamide to rituximab or from rituximab to cyclophosphamide. These patients should be managed in close conjunction with, or referred to, an expert centre for further evaluation and potential enrolment in clinical trials.	3	C
10. We recommend that structured clinical assessment rather than ANCA testing should inform decisions on changes in treatment for AAV.	4	D
11. We recommend the investigation of persistent unexplained haematuria in patients with prior exposure to cyclophosphamide.	2B	C
12. Hypoimmunoglobulinaemia has been noted after treatment with rituximab. We recommend testing of serum immunoglobulin levels prior to each course of rituximab and in patients with recurrent infection.	3	C
13. We recommend periodic assessment of cardiovascular risk for patients with AAV.	2B	B
14. We recommend that patients with AAV should be given a clear verbal explanation of the nature of their disease, the treatment options, the side effects of treatment, and the short-term and long-term prognoses.	3	C
15. We recommend that following the remission-induction phase of treatment, patients with AAV be assessed for the extent and ongoing impact of comorbidities associated with their diagnosis. Patients should then be advised where they might find the necessary therapies or support for these conditions.	4	D

EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis

M Yates,[1,2] R A Watts,[2,3] I M Bajema,[4] M C Cid,[5] B Crestani,[6] T Hauser,[7] B Hellmich,[8] J U Holle,[9] M Laudien,[10] M A Little,[11] R A Luqmani,[12] A Mahr,[13] P A Merkel,[14] J Mills,[15] J Mooney,[1] M Segelmark,[16,17] V Tesar,[18] K Westman,[19] A Vaglio,[20] N Yalçındağ,[21] D R Jayne,[22] C Mukhtyar[1]

ARD Online First, published on June 23, 2016



KDIGO CLINICAL PRACTICE GUIDELINE FOR GLOMERULONEPHRITIS

CHAPTER 13: PAUCI-IMMUNE FOCAL AND SEGMENTAL NECROTIZING GLOMERULONEPHRITIS

VOLUME 2 | ISSUE 2 | JUNE 2012

13.3: Maintenance therapy

13.3.1: We recommend maintenance therapy in patients who have achieved remission. (*1B*)

13.3.2: We suggest continuing maintenance therapy for at least 18 months in patients who remain in complete remission. (*2D*)

13.3.3: We recommend no maintenance therapy in patients who are dialysis-dependent and have no extrarenal manifestations of disease. (*1C*)

Maintenance treatment should be prolonged up to 48 months in pts who remain ANCA-positive (1B).

13.4: Choice of agent for maintenance therapy

13.4.1: We recommend azathioprine 1-2 mg/kg/d orally as maintenance therapy. (*1B*)

13.4.2: We suggest that MMF, up to 1 g twice daily, be used for maintenance therapy in patients who are allergic to, or intolerant of, azathioprine. (*2C*)

13.4.3: We suggest trimethoprim-sulfamethoxazole as an adjunct to maintenance therapy in patients with upper respiratory tract disease. (*2B*)

We recommend rituximab or azathioprine as maintenance therapy, rituximab should be preferred in patients treated with rituximab induction (1B).

13.4.4: We suggest methotrexate (initially 0.3 mg/kg/wk, maximum 25 mg/wk) for maintenance therapy in patients intolerant of azathioprine and MMF, but not if GFR is <60 ml/min. (*1C*)

13.4.5: We recommend not using etanercept as adjunctive therapy. (*1A*)

Outline of the lecture

- Anti-PR3 vs. anti-MPO disease, predictive value of renal biopsy?
- Initial therapy and relapse
- Plasma exchange
- Maintenance therapy
- Conclusions

Conclusions

- Anti-PR3 and anti-MPO pts should be probably treated differently
- Rituximab becomes first-line treatment in pts with major relapses and also in new pts with anti-PR3 disease, more data on pts with advanced kidney disease needed
- Rituximab is probably the best maintenance treatment (anti-PR3 vs. anti-MPO pts, doses, intervals, length of treatment)
- Corticosteroids should be (and can be) reduced, or replaced
- Effect of plasma exchange on ESRD not confirmed in PEXIVAS trial