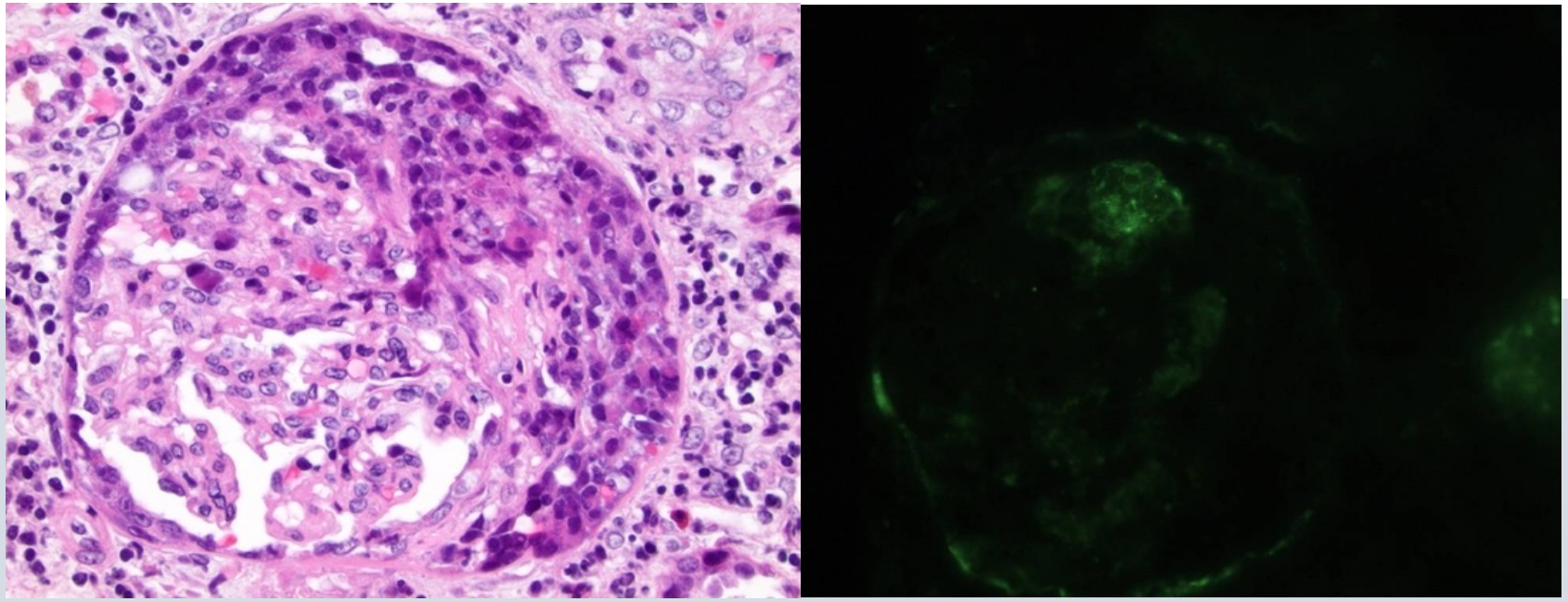
Zielgerichtete Therapie der ANCA-Vaskulitis – wieviel Steroid braucht es wirklich?



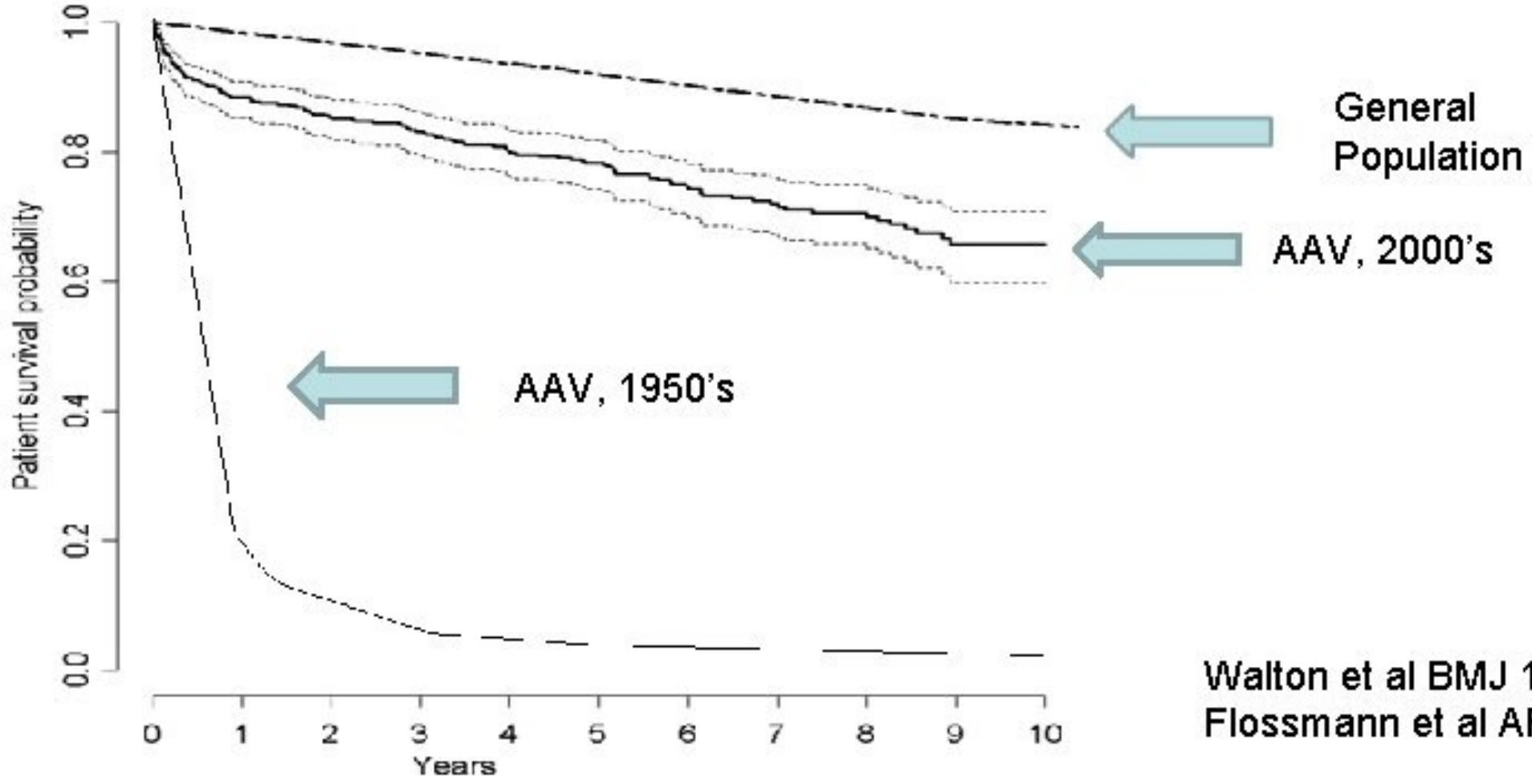
Andreas Kistler

Kantonsspital Frauenfeld

Conflict of interest

- Vortragshonorar von Vifor

Mortalität bei ANCA-Vaskulitis



Walton et al BMJ 1958;
Flossmann et al ARD 2011

Mortalität bei ANCA-Vaskulitis

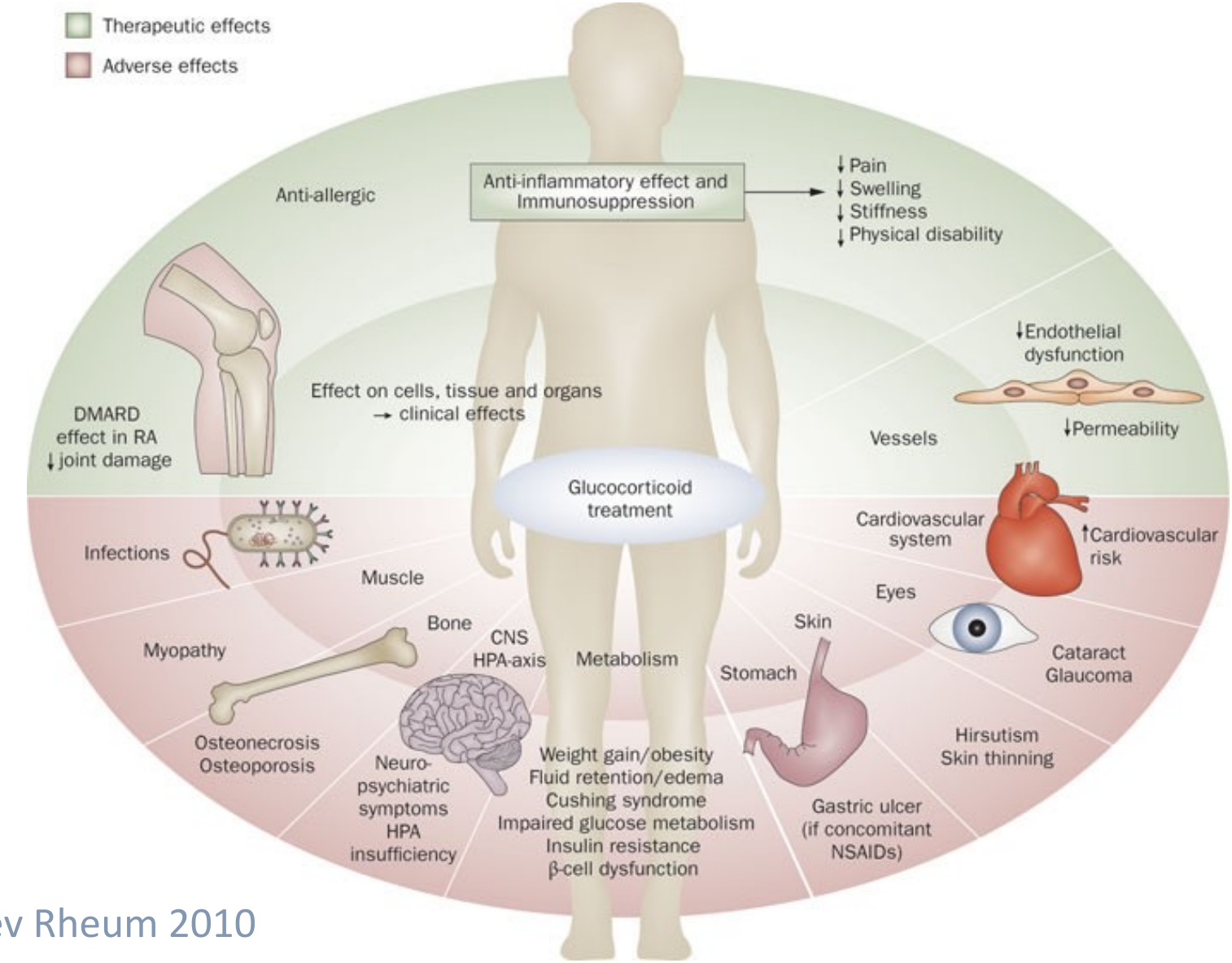
Table 3 Causes of death within and after the first year of follow-up, respectively

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	

EUVS-Studienpatienten
Einschluss 1995 - 2002

Flossmann, Ann Rheum Dis 2011

Glucocorticoide: Wirkungen und Nebenwirkungen

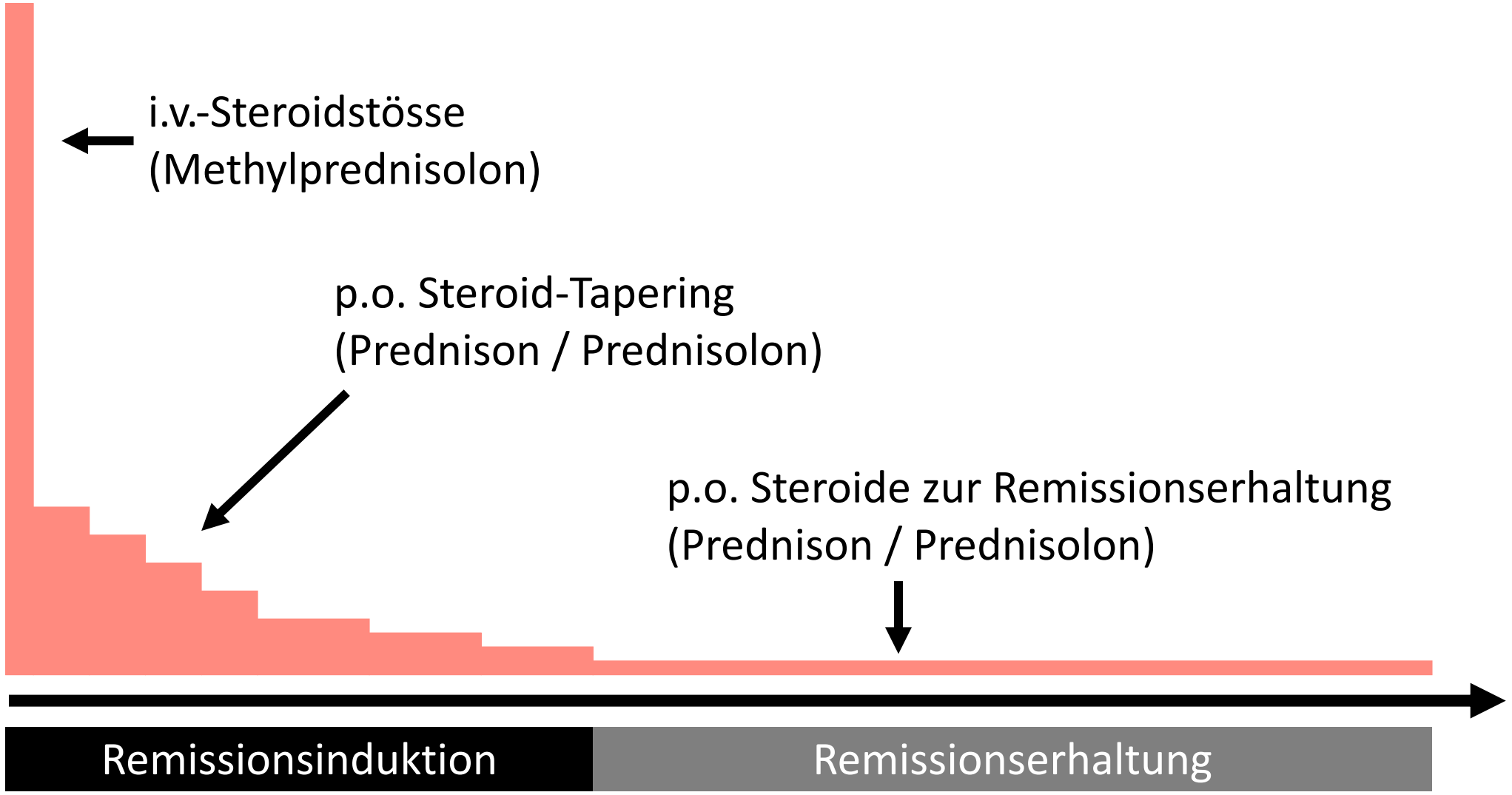


Hoes, Nat Rev Rheum 2010

Überblick

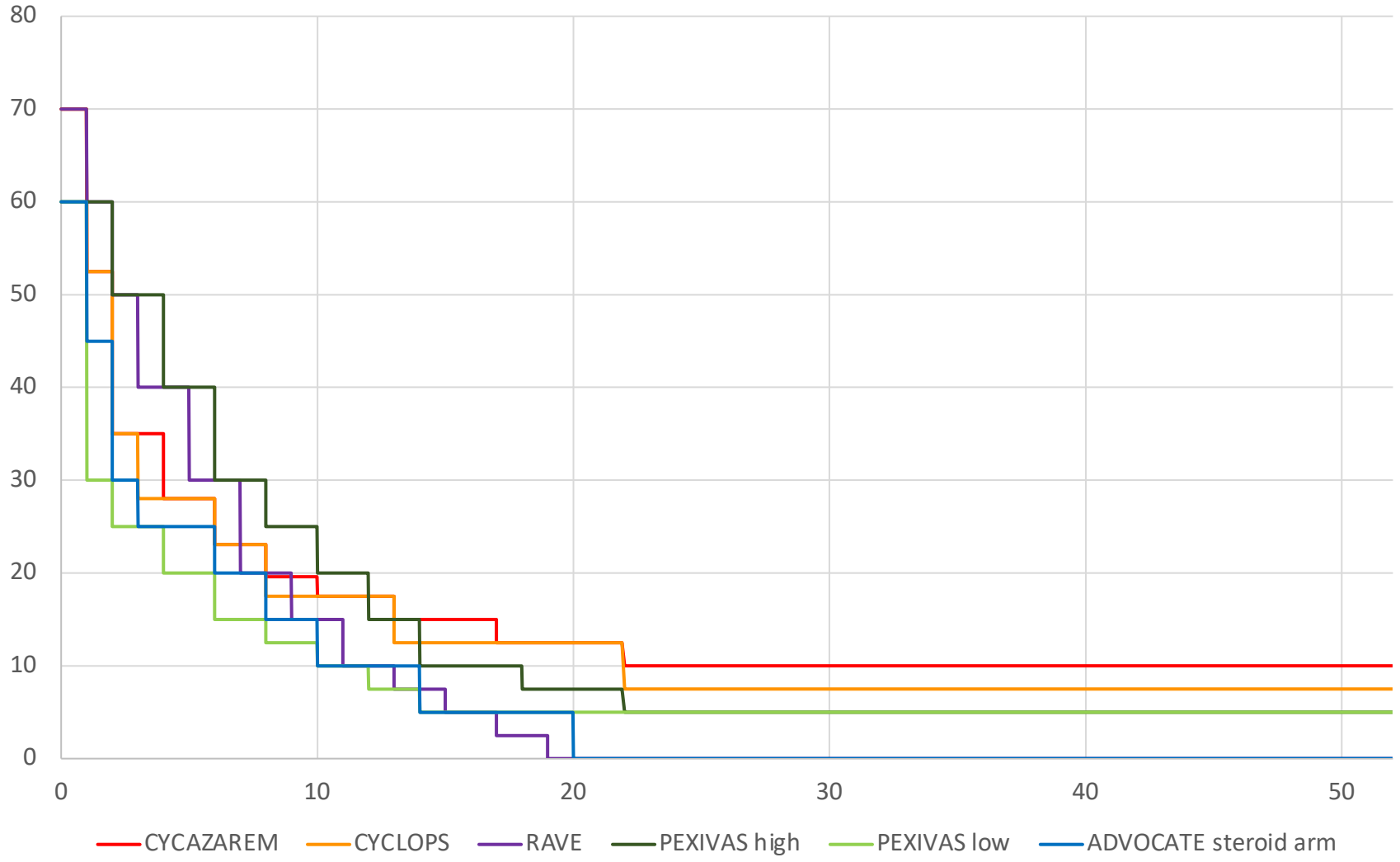
- Steroidschemata bei AAV
- Nutzen und Nebenwirkungen von Steroiden bei AAV
- Strategien zum Steroidsparen:
  - „reduce“
  - „replace“

Steroide in der Therapie der AAV



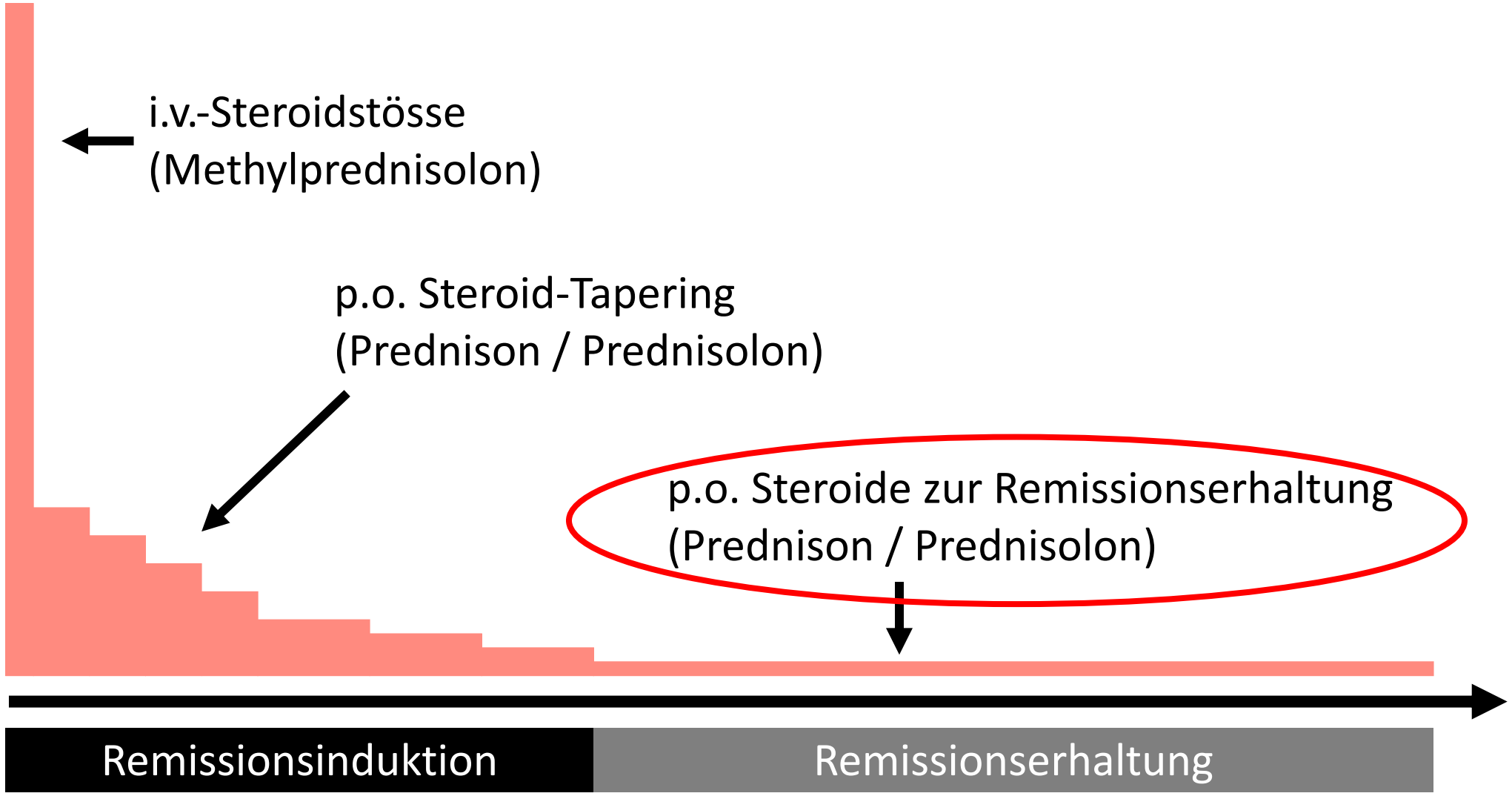
Steroidschemata in verschiedenen RCT

70 kg



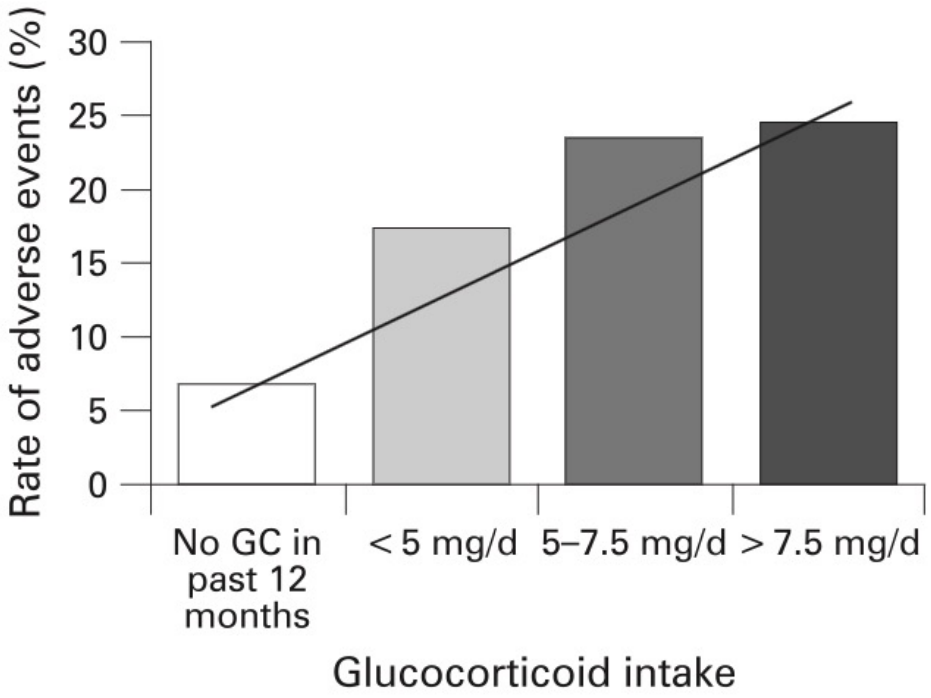
Kumulative Dosis (g) (ohne i.v.)	5.66	4.99	3.08	4.90	3.22	2.45

Steroide in der Therapie der AAV

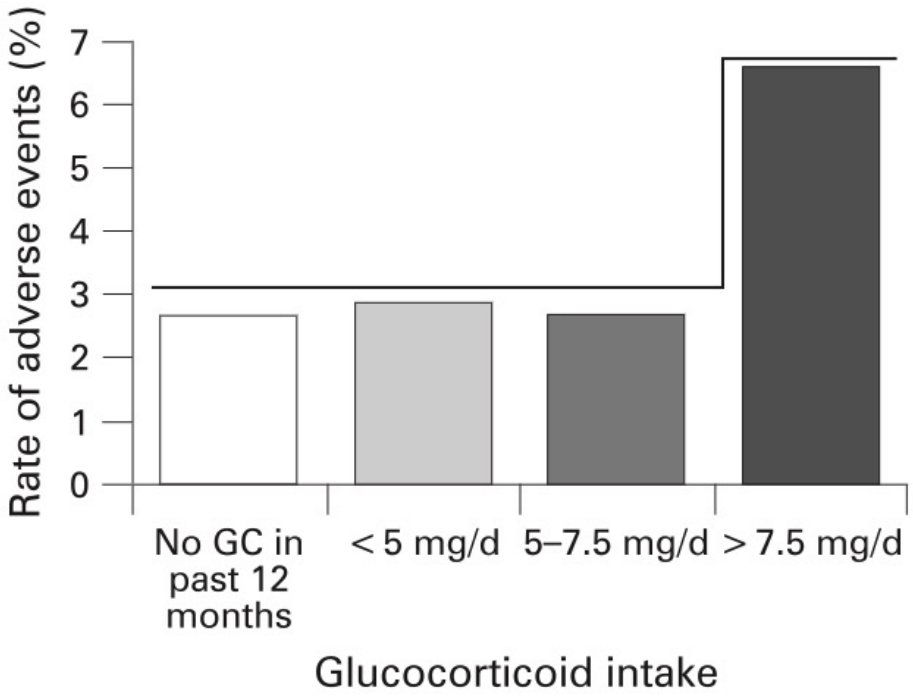


Dosis-Nebenwirkungs-Kurve bei Glukokortikoiden

Ecchymosen



Glaukom



n = 779 Patient*innen

„self reported“

Huscher, Ann Rheum Dis 2009

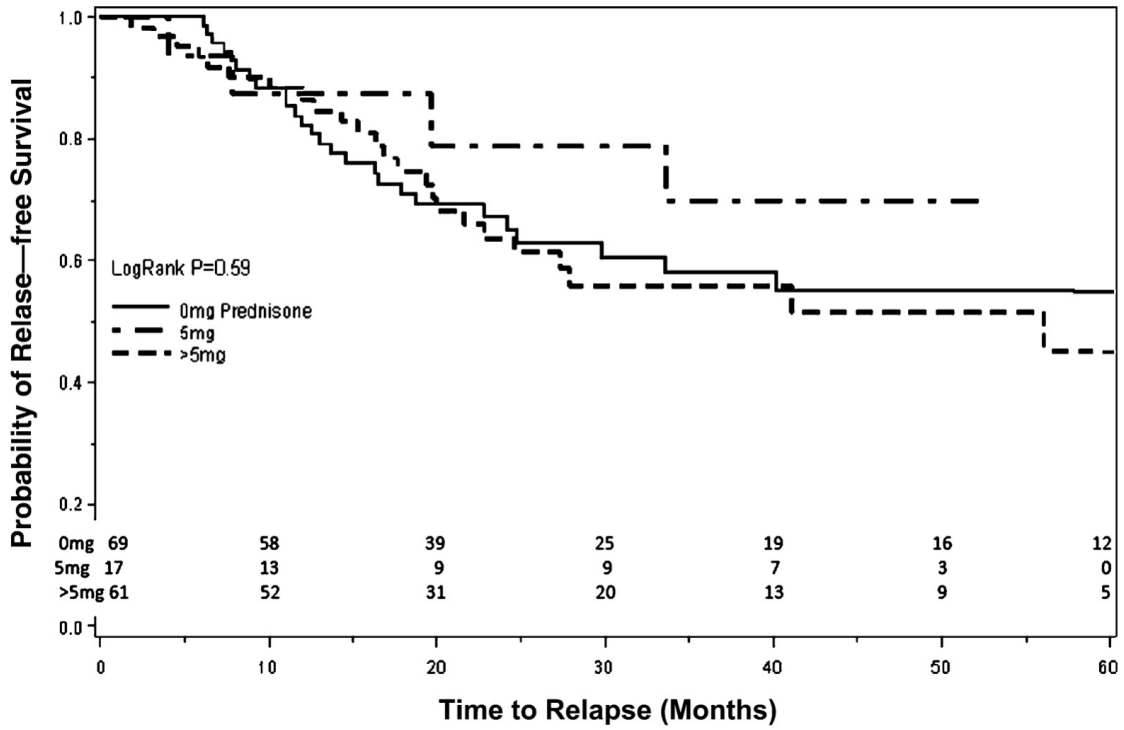
	No glucocorticoids in past 12 months	Patients with glucocorticoid intake for >6 months		
		<5 mg/day	5–7.5 mg/day	>7.5 mg/day
Patterns of adverse event rates (%) by dose of glucocorticoids				
"Linear" rising				
Cushingoid phenotype*	2.7	4.3	15.8	24.6
Ecchymosis*	6.8	17.4	23.5	24.6
Leg oedema*	9.5	11.6	20.2	26.2
Mycosis	4.5	5.8	6.6	8.2
Parchment-like skin*	3.2	10.1	15.8	21.3
Shortness of breath	9.5	10.1	12.6	16.4
Sleep disturbance*	20.7	33.3	37.2	44.3
Threshold at				
<5 mg/day				
Eye cataract	2.7	10.1	7.7	8.2
5–7.5 mg/day				
Epistaxis*	1.4	1.4	6.6	4.9
Weight gain*	9.5	8.7	22.4	21.3
>7.5 mg/day				
Depression, listlessness	12.6	10.1	13.7	19.7
Glaucoma	2.7	2.9	2.7	6.6
Increase in blood pressure	18.9	18.8	16.4	23.0

*The influence of the glucocorticoid dose on these adverse events was confirmed in a multivariate logistic regression model. OM, osteoporosis module.

Huscher, Ann Rheum Dis 2009

Steroide zur Remissionserhaltung

- 174 Pat, retrospektiv, CYC + PDN
- 0 / 5 / >5mg PDN nach 6 Monaten



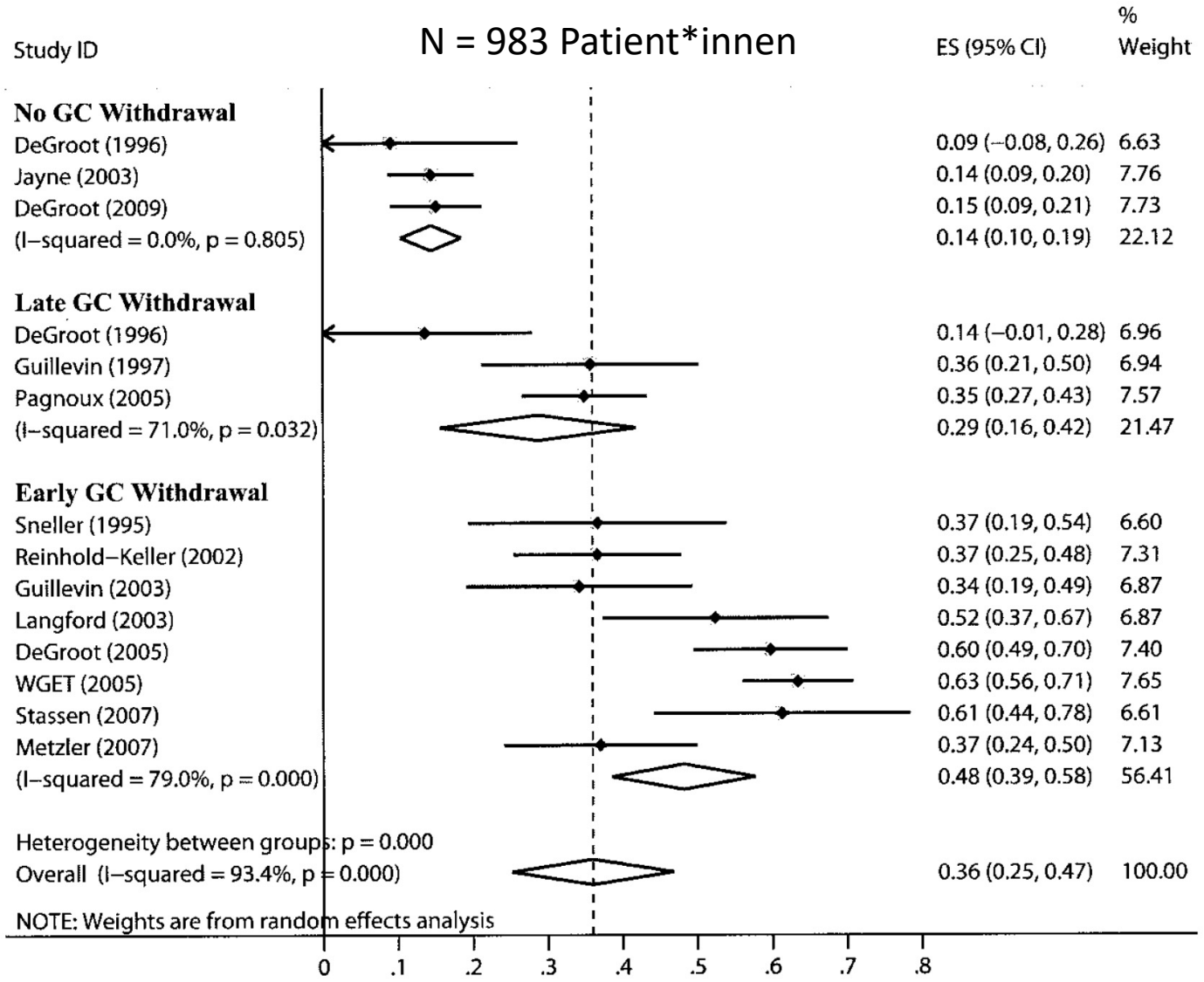
McGregor CJASN 2012
Chapel Hill

Table 4. Adverse events

	Adverse Event from Biopsy Date to the End of Follow-Up			Adverse Event from 6 mo to the End of Follow-Up		
	0 mg Prednisone 6 Mo (n=69)	Prednisone >6 Mo[a] (n=78)	P Value[b]	0 mg Prednisone 6 Mo (n=69)	Prednisone >6 Mo[a] (n=78)	P Value[b]
At least 1 infection	38 (55)	49 (63)	0.40	22 (32)	31 (40)	0.39
Absolute no. of infections/patient	1.25±1.62	1.56±2.42	0.46	0.82±1.38	1.15±2.29	0.47
Incidence of infection (per person-year) (95% CI)	0.39 (0.35–0.43)	0.64 (0.56–0.73)	<0.0001	0.23 (0.21–0.25)	0.42 (0.39–0.46)	<0.0001
New-onset DM	13 (19)	25 (32)	0.09	2 (3)	3 (4)	1.00
Osteoporosis	5 (7)	6 (8)	1.00	2 (3)	2 (3)	1.00
Cancer	7 (10)	6 (8)	0.77	5 (7)	4 (5)	0.73
Neuropsychiatric event	8 (12)	8 (10)	0.80	0	0	N/A
Cataracts	2 (3)	5 (6)	0.45	1 (1)	4 (5)	0.37
Myopathy	6 (9)	11 (14)	0.44	3 (4)	1 (1)	0.34
GI bleeding[c]	5 (7)	6 (8)	1.00	1 (1)	1 (1)	1.00
Acne	5 (7)	8 (10)	0.57	0	2 (3)	0.50

Data are expressed as n (%) or median (interquartile range). CI, confidence interval; DM, diabetes mellitus; GI, gastrointestinal.
[a]Includes patients taking ≥5 mg prednisone.
[b]P values were calculated by Fisher exact test.
[c]Gastrointestinal bleeding deemed not to be vasculitic in origin.

Steroide zur Remissionserhaltung



Vergleich der „relapse rate“ zwischen RCTs mit unterschiedlichem Zeitpunkt des Glucocorticoid-Stopps:
<12Mt
>12Mt
kein Stopp während Studie

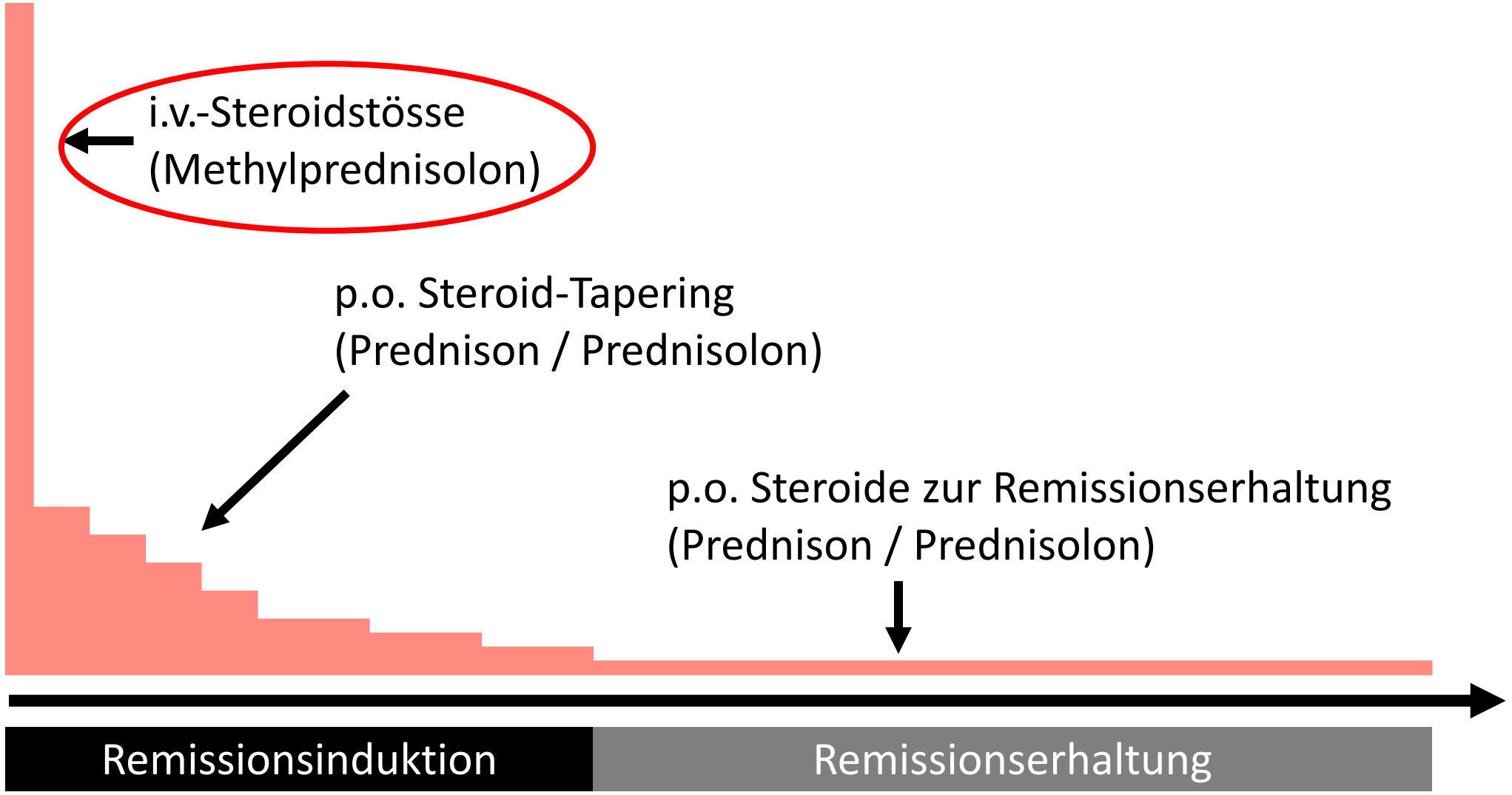
Cave: alle Daten prä-Rituximab

Walsh, Arthritis Care & Research 2010

Fazit low dose Steroide für Remissionserhaltung

- Rezidivrisiko wahrscheinlich etwas reduziert...
- ...aber zum Preis von (geringen) Nebenwirkungen
- Datenlage sehr dürftig
- Rituximab vs. CYC-AZA?

Steroide in der Therapie der AAV



Kumulative Steroiddosis: ein sinnvolles Mass? Oder: i.v. Puls vs. kontinuierlich oral

Kumulative Dosis: 4 g 4.5 g

	Oral prednisolone	Intravenous methylprednisolone	*P* value
Number of events	29	8	<0.001
Patients with events	18/35 (51%)	6/35 (17%)	0.005
Female with events	13/24 (54%)	4/25	0.007
Male with events	5/11 (45%)	2/10	0.361
Major events	2	0	
Weight gain (>3 kg)	9 (26%)	1	0.006
Gastrointestinal	6 (17%)	1	0.106
Sleeplessness	5 (14%)	2	0.428
Myalgias	3	0	
Hypertension	2	0	
Hirsutism	2	0	
Depression	1	0	
Palpitations	1	4	0.356

The exact test of Fisher (two-tailed) was performed.

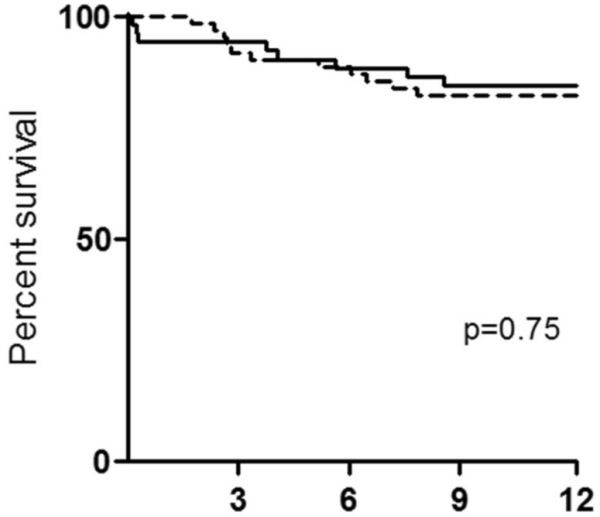
Methylprenisolon-Stosstherapie vs. Prednisolon p.o. bei endokriner Orbitopathie

Kahaly, J Clin Endocrinol Metab 2005

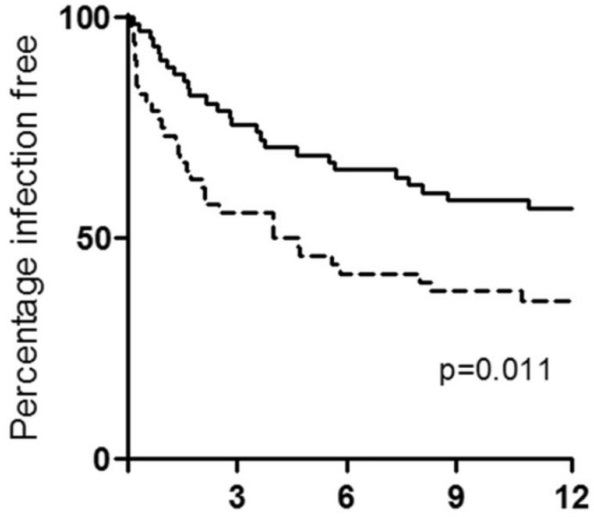
Sind Solumedrol-Stösse nötig?

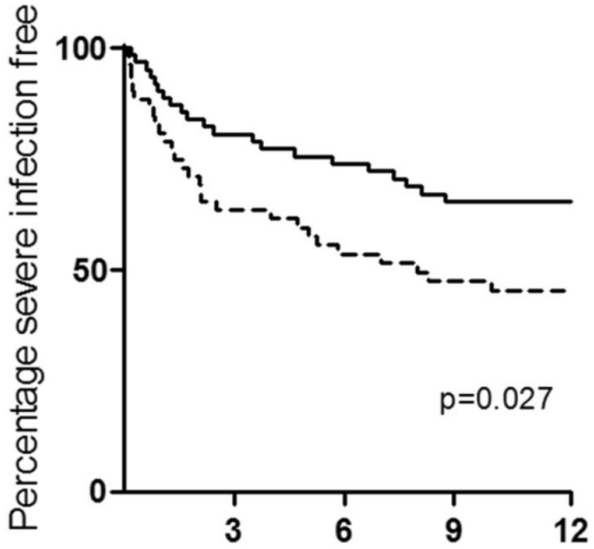
- Kein (!) RCT hat bisher den Nutzen von Methylprednisolon bei der Remissionsinduktion der AAV untersucht
- Retrospektive Analyse (Chanouzas, BMC Nephrol 2019):
  - 114 Patienten
  - Bei Diagnosestellung Krea >500 oder dialysepflichtig
  - 52 erhielten Methylprednisolon, 62 nicht
  - Baseline-Charakteristika vergleichbar ausser mehr alveoläre Hämorrhagien bei MP-Gruppe
  - MP-Gruppe erhielt weniger CYC (5.2 vs. 8.6 g) und orales PDN (4.0 vs. 6.8 g in 12 Monaten)

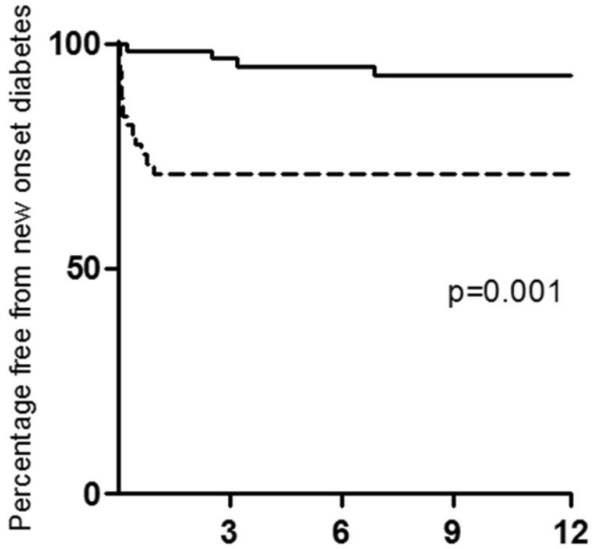
Sind Solumedrol-Stösse nötig?



- Renal recovery 58% (MP) vs. 66% (no MP)
- Creatinine 207µmol/L (MP) vs. 143 µmol/L (non-MP)
- Time to RRT independence 30 d (MP and non-MP)
- Relapse by 12 months 11.5% (MP) and 8.1% (non-MP)







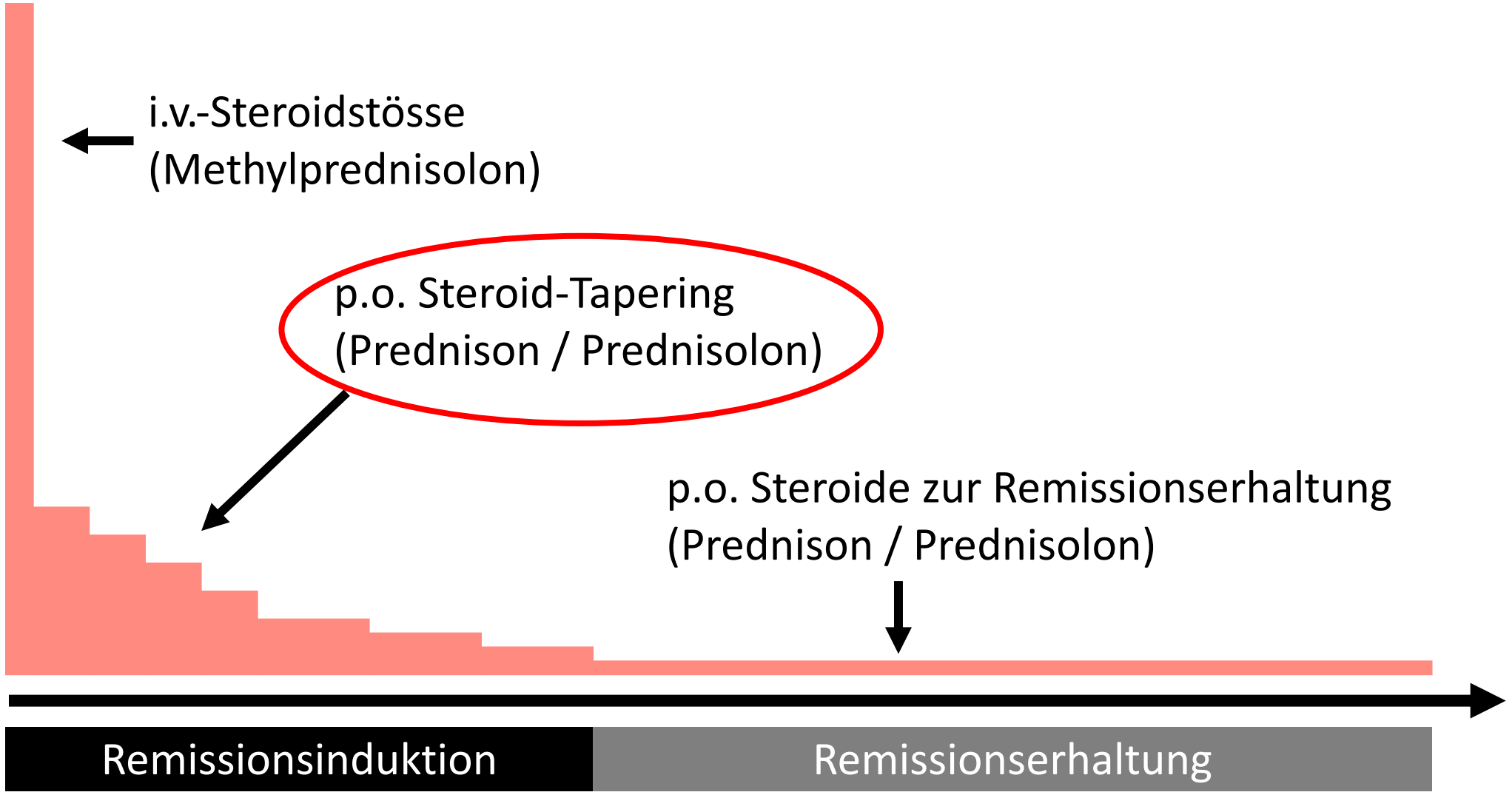
Cave: sehr hohe p.o. Steroiddosis in no MP-Gruppe!

Chanouzas, BMC Nephrol 2019
Birmingham UK

Fazit Solumedrolstösse

- Sehr kritisch zu hinterfragen
- Aber auch hier: ein RCT würde Not tun!

Steroide in der Therapie der AAV



PEXIVAS

- 704 Patienten mit AAV und Nierenbeteiligung oder alveolärer Hämorrhagie
- PEX vs. Kontrolle und reduced-dose vs. standard glucocorticoid regimen
- Endpunkt ESRD oder Tod

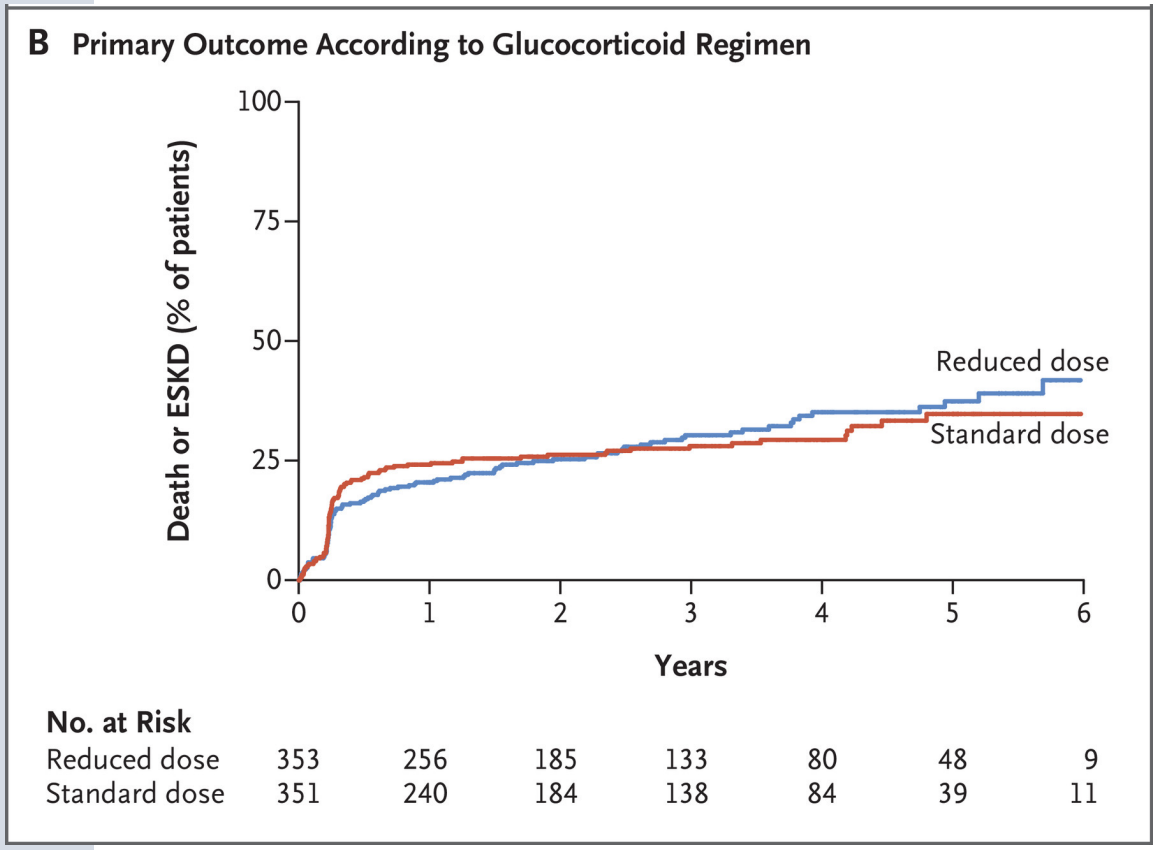


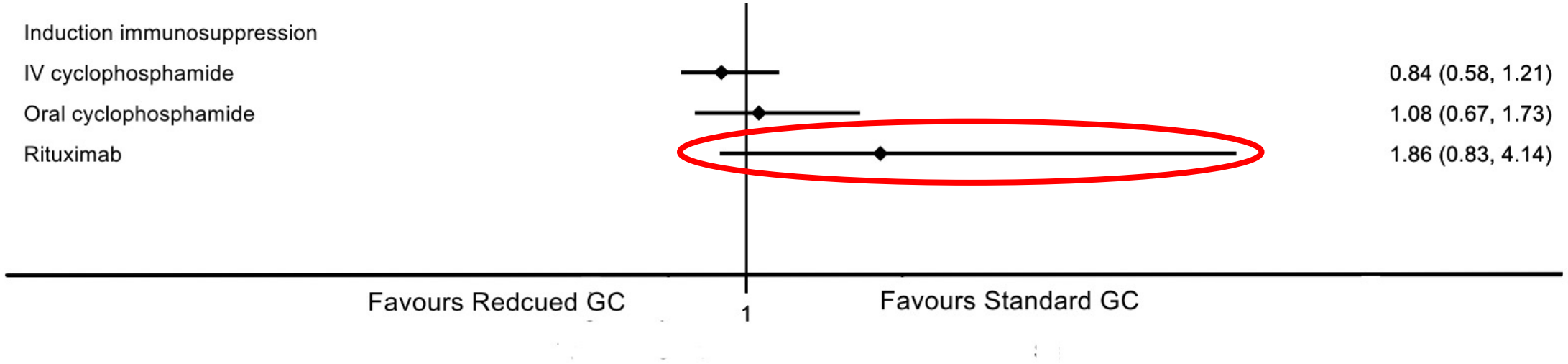
Table 3. Secondary Outcomes.*

Secondary Outcome	Reduced-Dose vs. Standard-Dose Glucocorticoid Regimen
	effect size (95% CI)
Death from any cause	0.78 (0.53–1.17)
End-stage kidney disease	0.96 (0.68–1.34)
Sustained remission	1.04 (0.92–1.19)
Serious adverse events	0.95 (0.75–1.20)
Serious infections at 1 year	0.69 (0.52–0.93)

Walsh, NEJM 2020

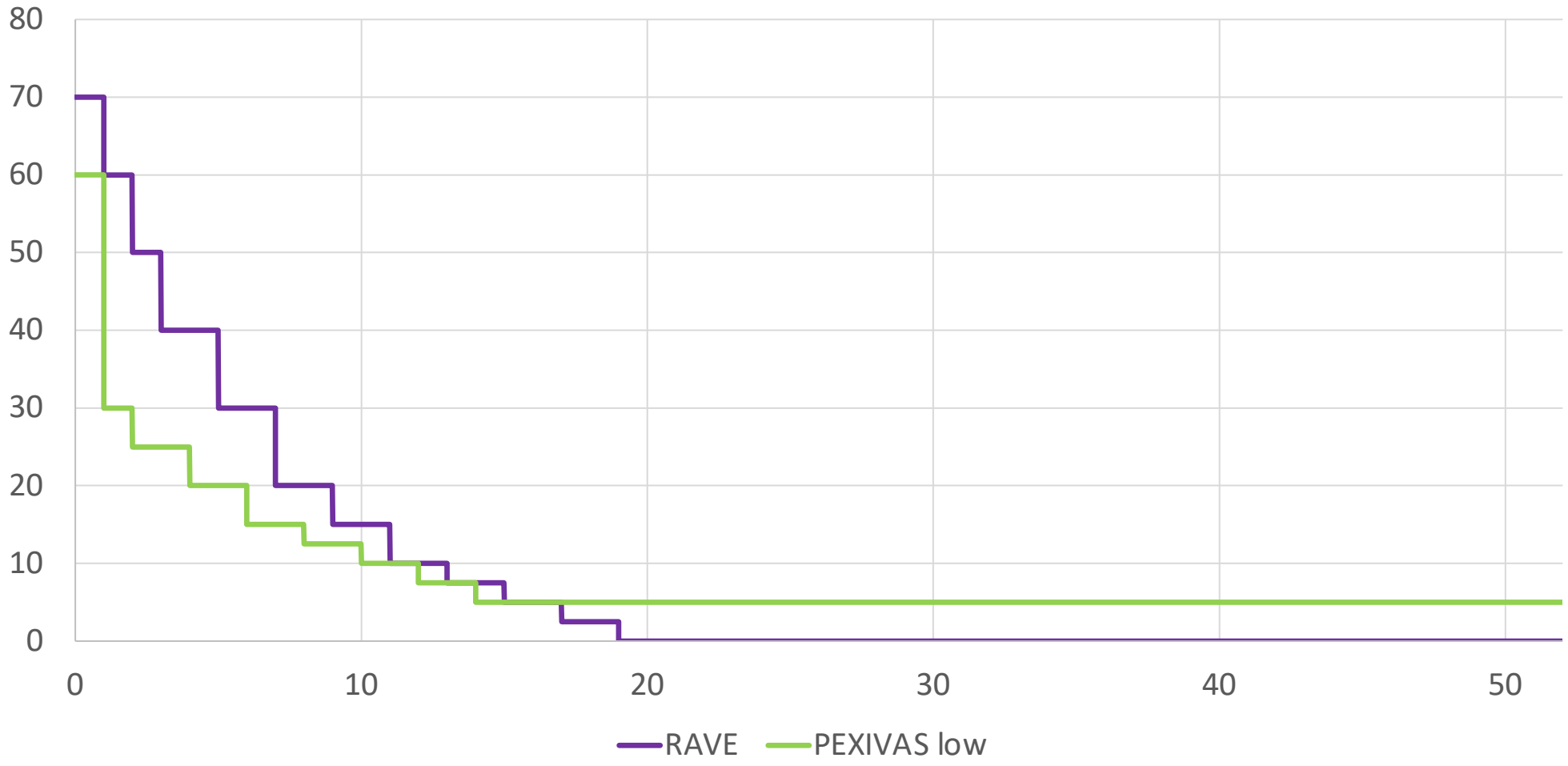
PEXIVAS

Planned immunosuppressive treatment — no. (%)	Reduced-Dose Glucocorticoid Regimen (N=353)	Standard-Dose Glucocorticoid Regimen (N=351)
Intravenous cyclophosphamide	179 (50.7)	175 (49.9)
Oral cyclophosphamide	120 (34.0)	121 (34.5)
Rituximab	54 (15.3)	55 (15.7)

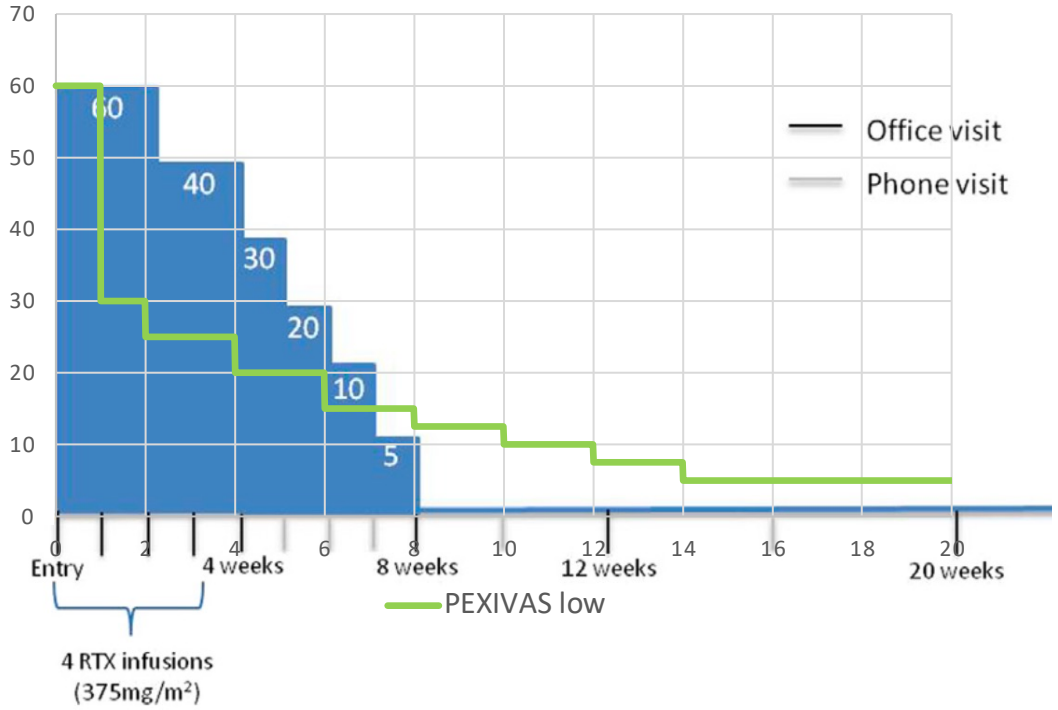


Walsh, NEJM 2020

PEXIVAS vs. RAVE



Frühes Steroidtapering: SCOUT



Primary outcome: CR (BWAS=0) at 12 weeks

Miloslavsky Sem Art Rheum 2018
Massachusetts General Hospital

Baseline patient characteristics

	SCOUT	RAVE cohort
Sample size	20	29
Age (median, IQR)	61.5 (48, 70)	58.0 (50, 69)
Sex (male, %)	7 (35%)	16 (55%)
BVAS (median, IQR)	5.0 (4, 6)	8.0 (6,9)
Disease group		
GPA	14 (70%)	23 (79%)
MPA	6 (30%)	4 (14%)
Indeterminate	0	2 (6.9%)
ANCA		
MPO	11 (55%)	9 (31%)
PR3	7 (35%)	20 (69%)
Negative	2 (10%)	0

Patient outcomes in SCOUT and RAVE controls

	SCOUT ($N = 20$)	RAVE ($N = 29$)	P value
Achieved primary outcome (%)	14 (70%)	18 (69%)	0.60
Relapses (%)	6 (30%, 5 severe)	2 (7%, 1 severe)	0.03
Adverse events (median, IQR)	2 (1, 5)	8 (3, 15)	< 0.01
Severe adverse events (median, IQR)	0 (0, 1)	0 (0, 1)	0.60
Baseline VDI (median, IQR)	0 (0, 1)	1 (0, 3)	0.08
VDI change (mean, SD)	+0.35 (0.8)	+0.31 (0.66)	0.90

Überblick

- Steroidschemata bei AAV
- Nutzen und Nebenwirkungen von Steroiden bei AAV
- Strategien zum Steroidsparen:
  - „reduce“
  - „replace“

Steroidsparen durch Tripeltherapie (RTX, CYC, PDN)

	Group 1 n = 23	Group 2 n = 26
Treatment protocol		
Induction therapy		
RTX	2 × 1 g Days 0 and 7	2 × 1 g Days 0 and 14
CYC	6 × pulses 500–750 mg Weeks 0, 2, 4, 6, 8 and 10	6 × pulses 500 mg Weeks 0, 2, 4, 6, 8 and 10
Corticosteroids		
Methylprednisolone	2 × 250–500 mg Days 0 and 7	250 mg–1 g (*n*=15)
Oral prednisolone	0.5 mg/kg (max 30 mg)/day Days 2–6 inclusive	60 mg/day 1 week 45 mg/day 1 week
Maintenance: from week 12		
First line	AZA 1–2 mg/kg/day	AZA 1–2 mg/kg/day
Alternatives	MMF, MTX, RTX	MMF, RTX

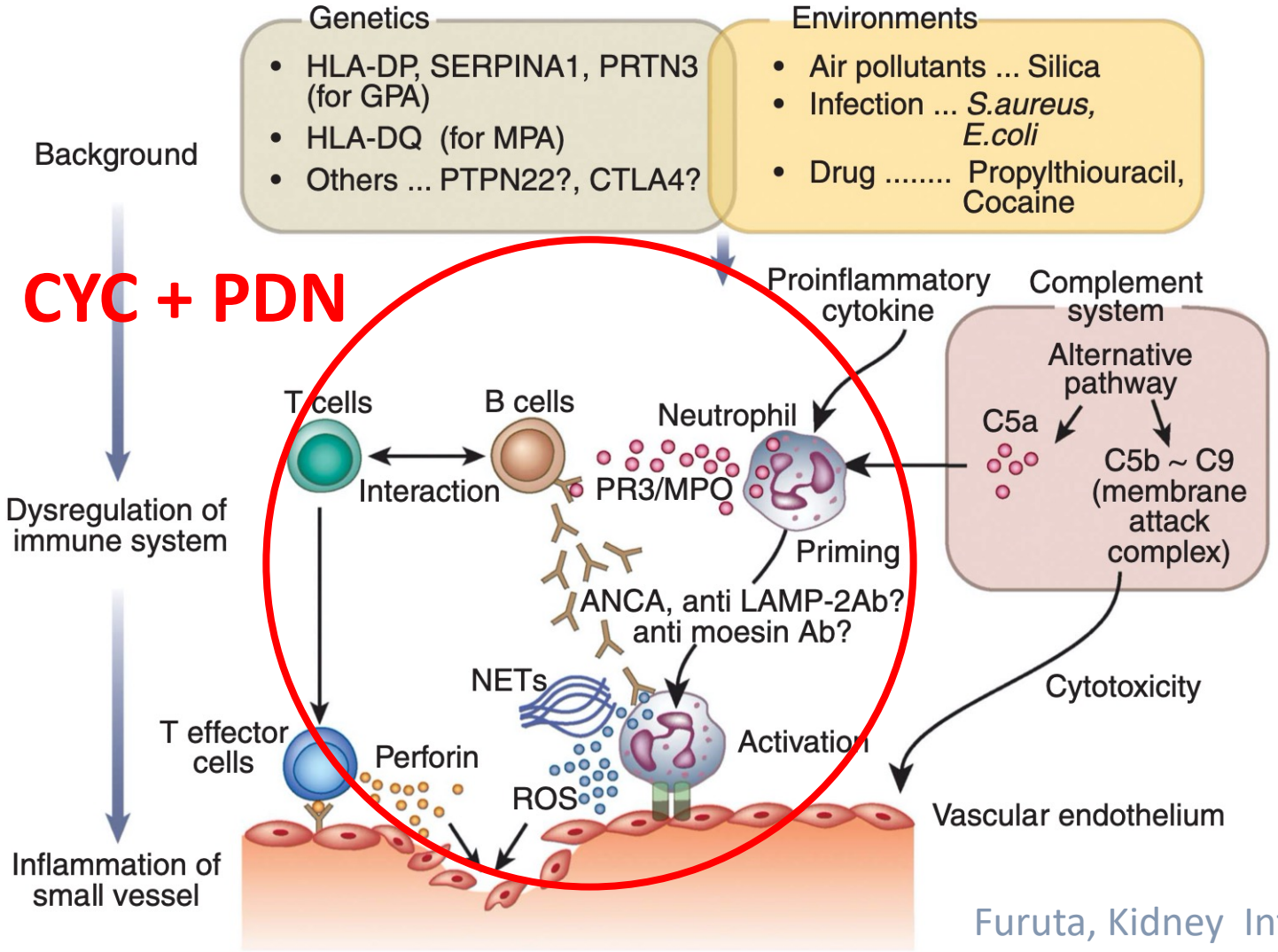
Pepper, Rheumatology 2019
London & Dublin

Steroidsparen durch Tripeltherapie (RTX, CYC, PDN)

	Cases ($n = 49$)	EUVAS trial patients (a) ($n = 139$)	*P*-value	RITUXIVAS patients (b) ($n = 33$)	*P*-value
eGFR at entry, median (IQR)	28.9 (14.6–46.9)	28.3 (12.7–44.3)	0.56	24.9 (12.2–55.3)	0.50[d]
eGFR at 12 months, median (IQR)	52.2 (34.9–71.4)	46.6 (32.5–62.2)	0.15	64.7 (24.5–71.9)	0.51[d]
ΔeGFR (mean)	16.9 (9.7–24.2)	10.3 (7.1–13.6)	0.10	21.3 (6.9–35.6)	0.67[a]
Urine proteinuria at entry, median (IQR)	146.5 (77–297)	103 (50–165)	0.003**		
BVAS at entry, median (IQR)	16 (12.3–20.8)	16 (11.5–23)	0.53	19 (14–24.5)	0.06[d]
BVAS at 12 months, median (IQR)	0 (0–0)	0 (0–0)	0.25	0 (0–0)	
In remission at 12 months, *n* (%) (BVAS=0)	45/46 (98%)	121/130 (93%)	0.46	24/27 (88%)	0.14[c]
Grade 3 infections: proportion of patients (⩾1 episodes), *n* (%)	5 (10.2)	11 (7.9)	0.36	10 (30)	0.02[b]
Mortality at 12 months, *n* (%)	3 (6.1)	16 (11.5)	0.41	6 (18.2)	0.15[c]
ESRF within 12 months, *n* (%)	1 (2)	5 (3.6)	0.99	1/27 (3.7)	0.99[c]

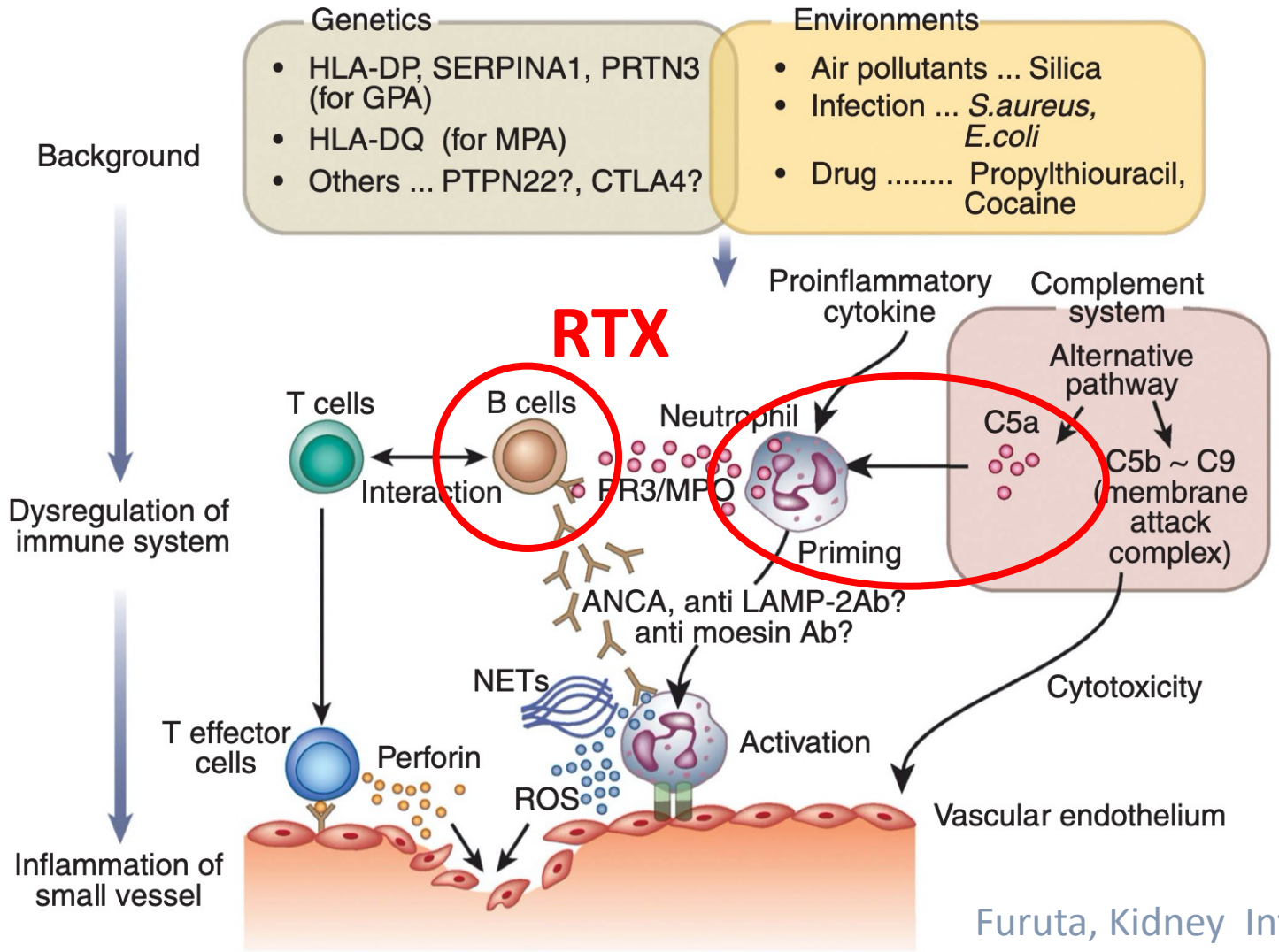
Pepper, Rheumatology 2019

Pathogenese der AAV und Ansätze für eine zielgerichtete Therapie

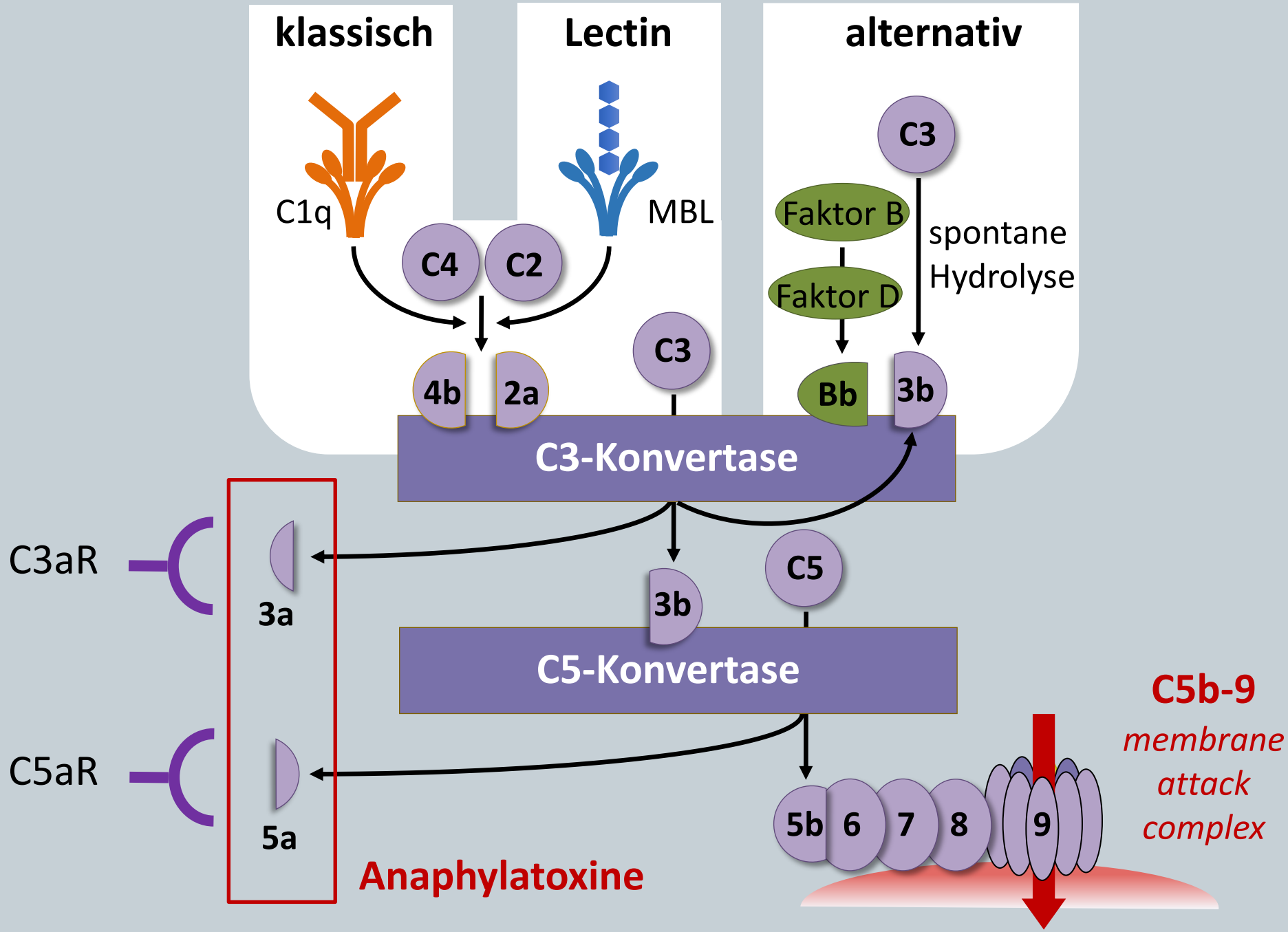


Furuta, Kidney International 2013:84;244–249

Pathogenese der AAV und Ansätze für eine zielgerichtete Therapie

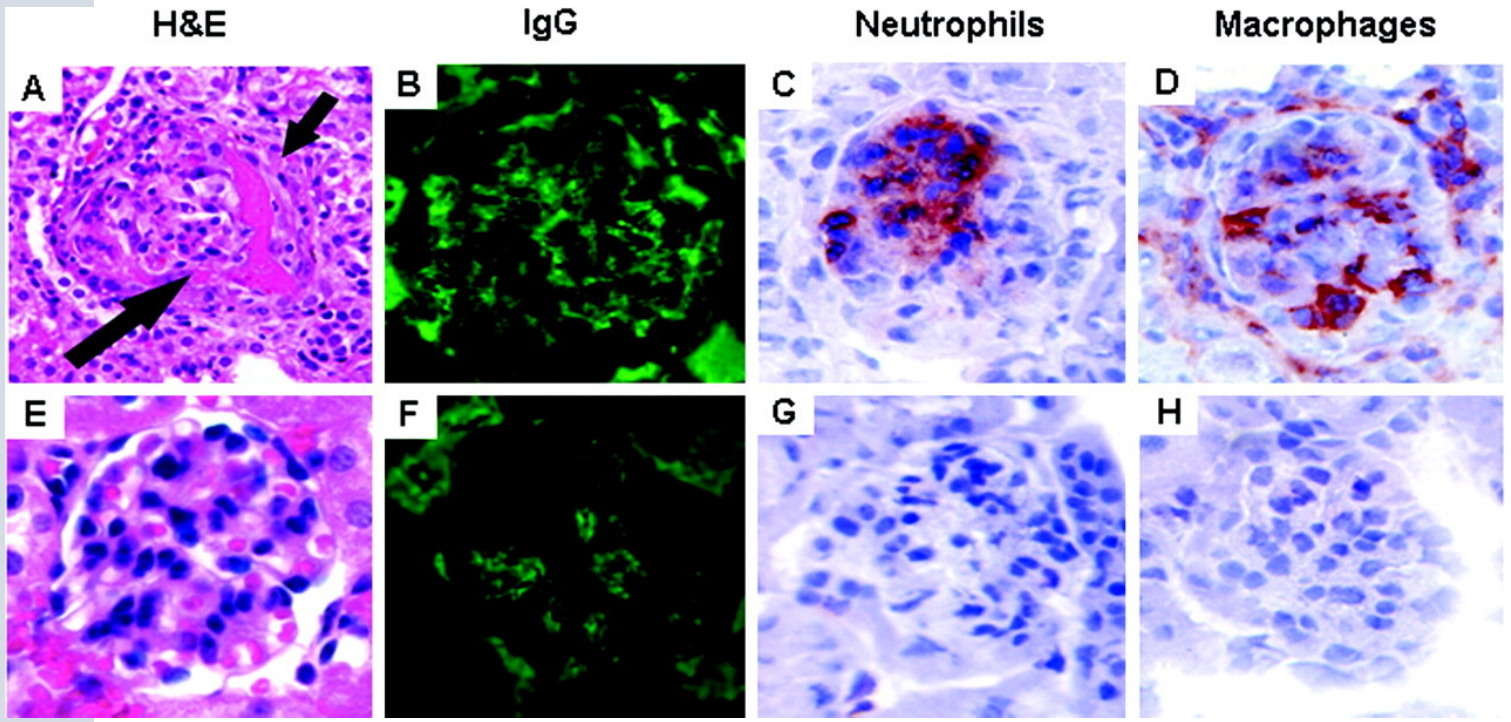


Furuta, Kidney International 2013:84;244–249

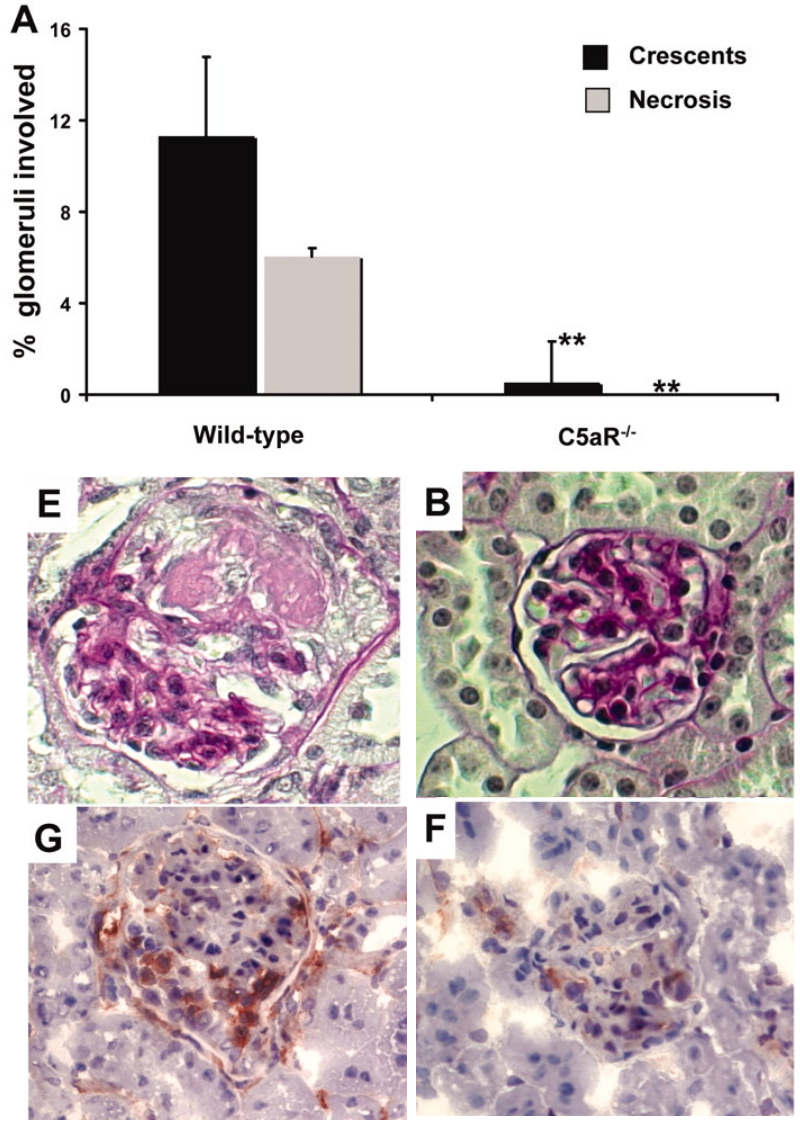

klassisch
Lectin
alternativ
C1q
MBL
C3
Faktor B
Faktor D
spontane
Hydrolyse
C4
C2
C3
4b
2a
Bb
3b
C3-Konvertase
C3aR
3a
C5
3b
C5-Konvertase
C5aR
5a
5b
6
7
8
9
C5b-9
membrane
attack
complex
Anaphylatoxine

Zielgerichtete Therapie: Komplement

Complement depletion

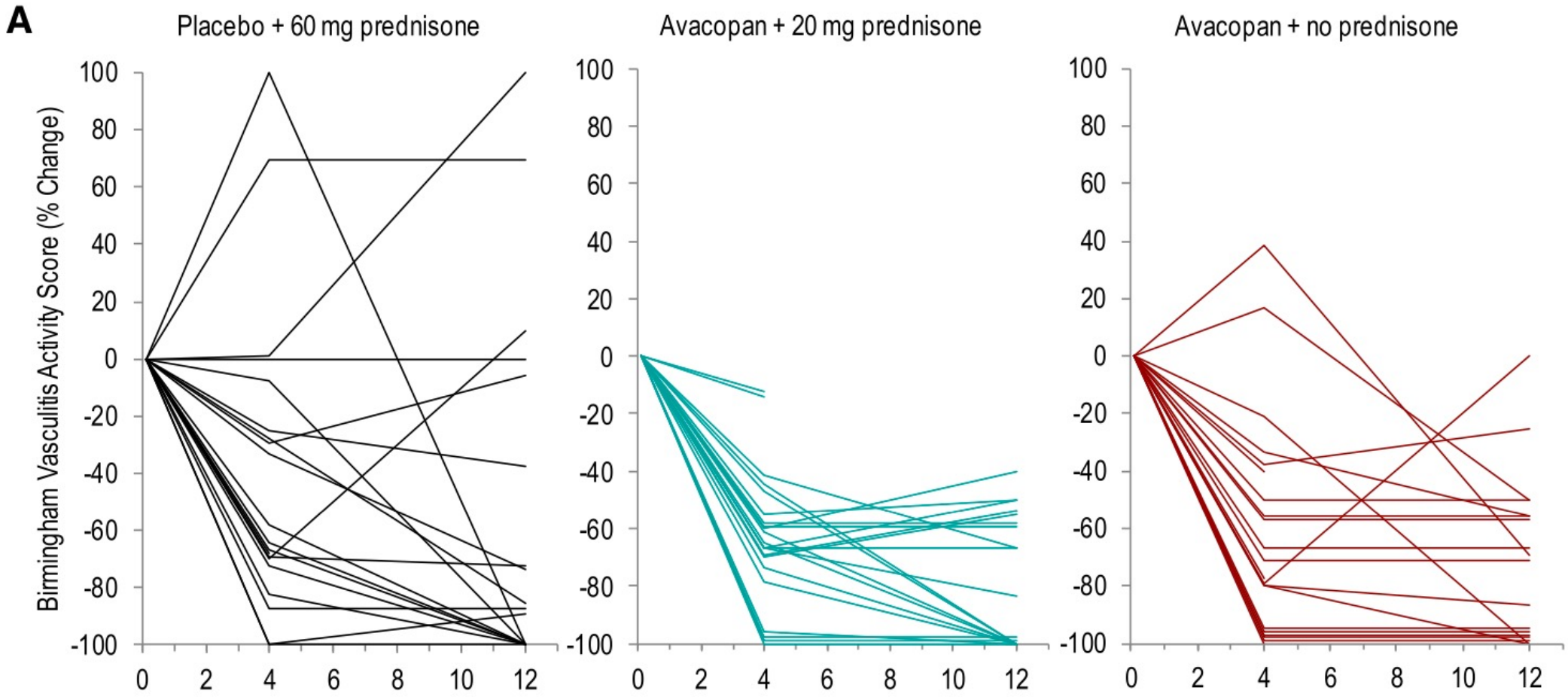


Xiao, Am J Pathol 2007



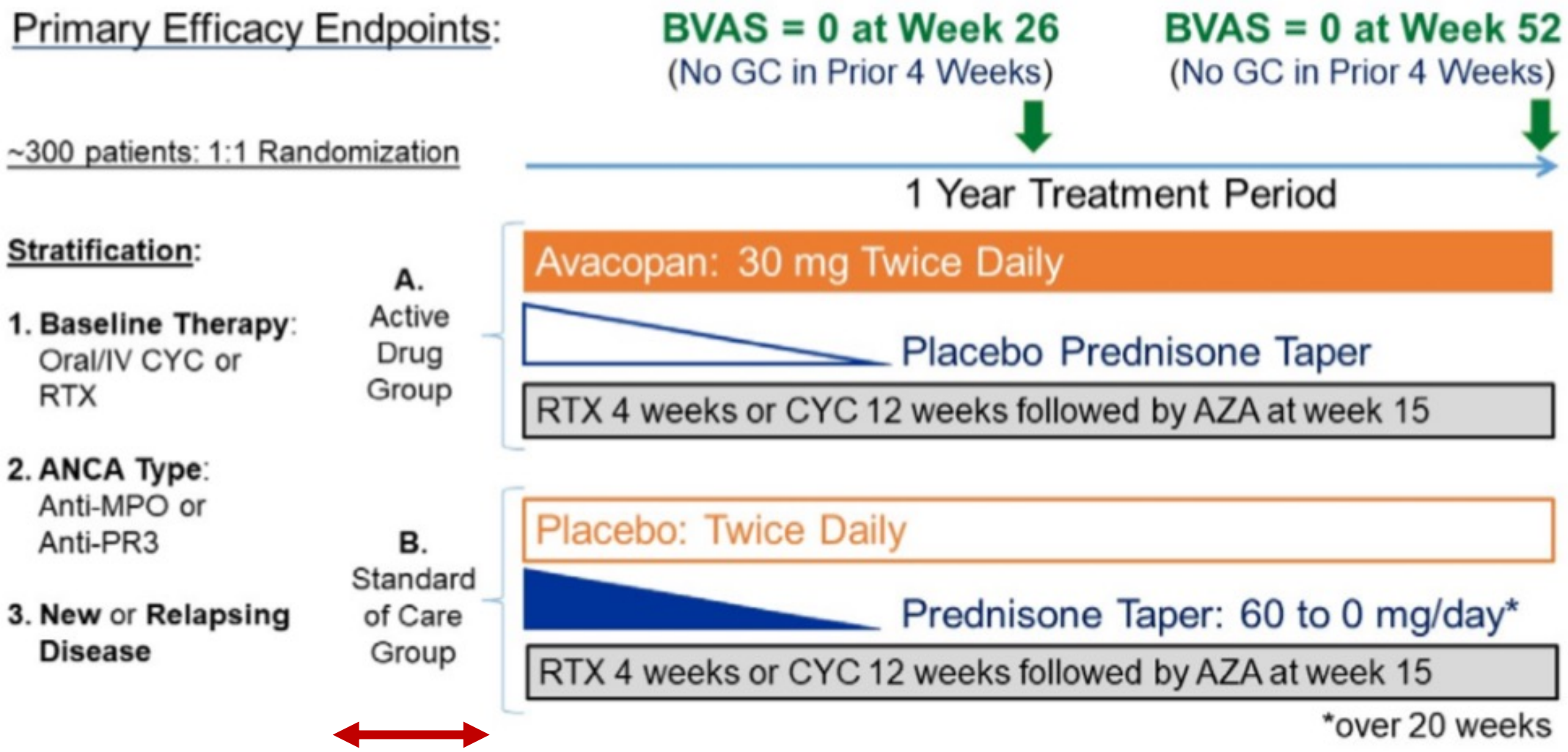
Schreiber, JASN 2009

C5a-Blockade bei AAV

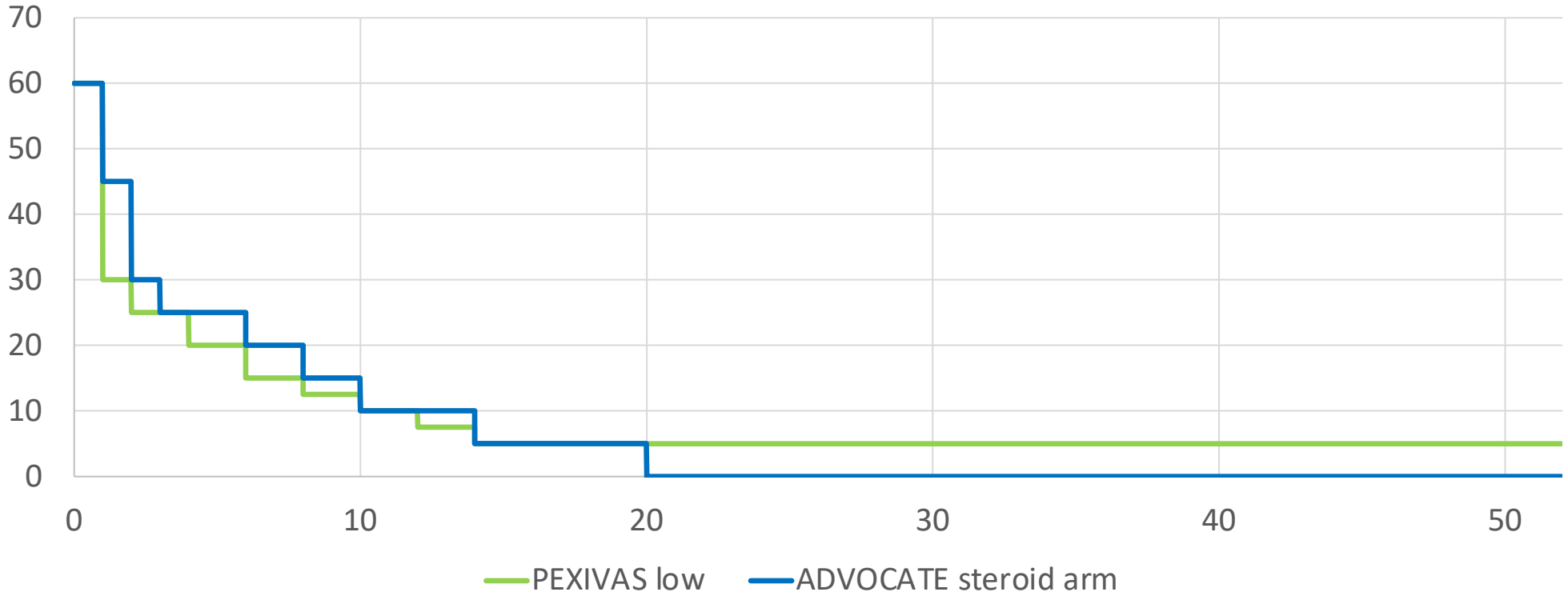


CLEAR study (Jayne, JASN 2017)

ADVOCATE: Studiendesign



ADVOCATE:
„background“ Therapie und Kontrollgruppe



Rituximab: 4 x 375 mg/m² (analog RAVE keine Remissionserhaltung)
CYC IV: 15mg/kg x 6 Gaben (13 Wochen) -> AZA 2mg/kg ab Woche 15
CYC PO: 2mg/kg x 14 Wochen -> AZA 2mg/kg ab Woche 15

ADVOCATE: „background“ Therapie

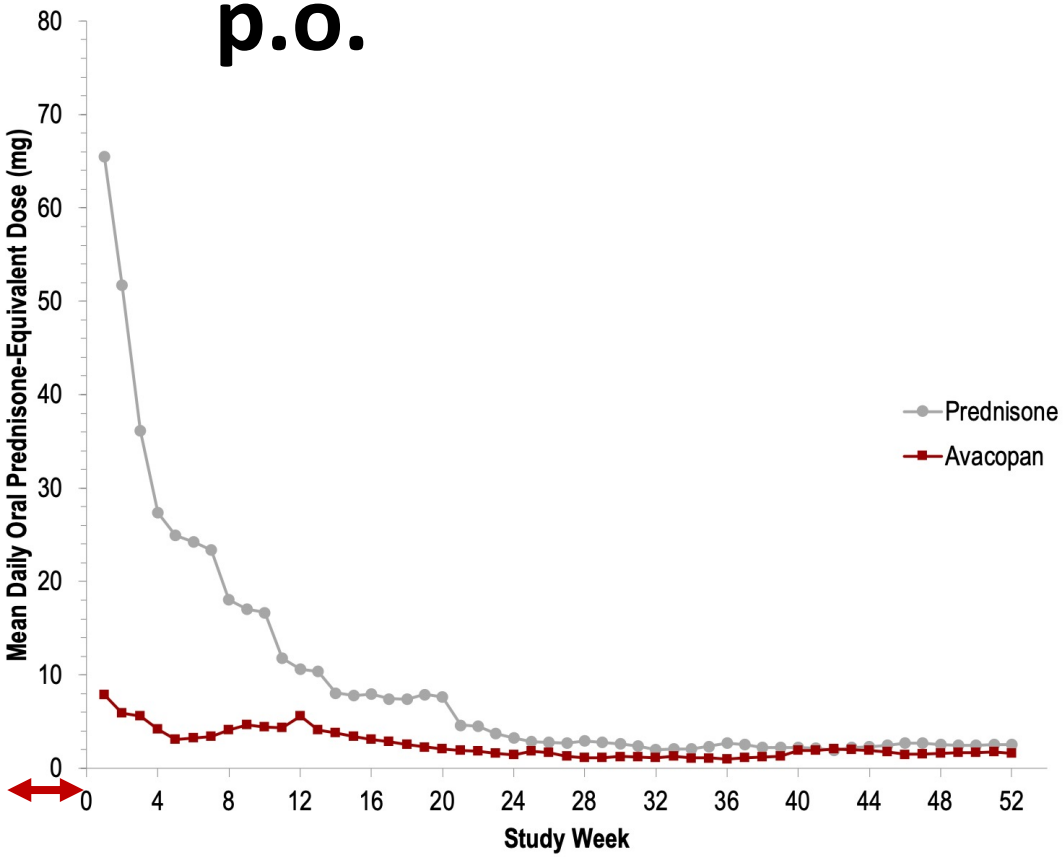
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Avacopan (N=166)	Prednisone (N=164)
Glucocorticoid use during screening period		
Use of any glucocorticoids — no. (%)	125 (75.3)	135 (82.3)
Intravenous use	63 (38.0)	73 (44.5)
Oral use	99 (59.6)	113 (68.9)
Total prednisone-equivalent dose — mg**	654.0±744.4	727.8±787.8
Daily prednisone-equivalent dose — mg**	46.7±53.2	52.0±56.3
Immunosuppressant induction treatment — no. (%)		
Intravenous rituximab	107 (64.5)	107 (65.2)
Intravenous cyclophosphamide	51 (30.7)	51 (31.1)
Oral cyclophosphamide	8 (4.8)	6 (3.7)

Jayne, NEJM 2021

ADVOCATE: tatsächliche Steroiddosis

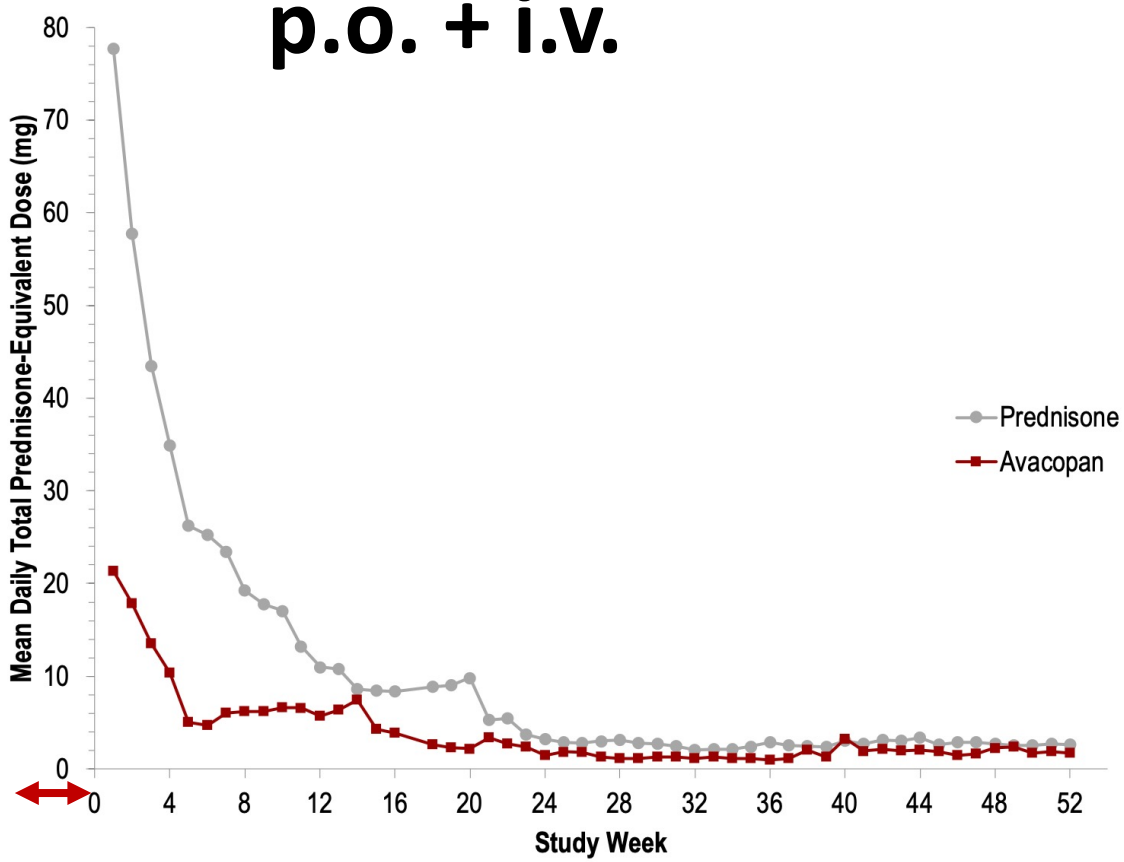
p.o.



+ 187 mg
+ 204 mg

} Während Screeningperiode

p.o. + i.v.



+ 654 mg
+ 728 mg

} Während Screeningperiode

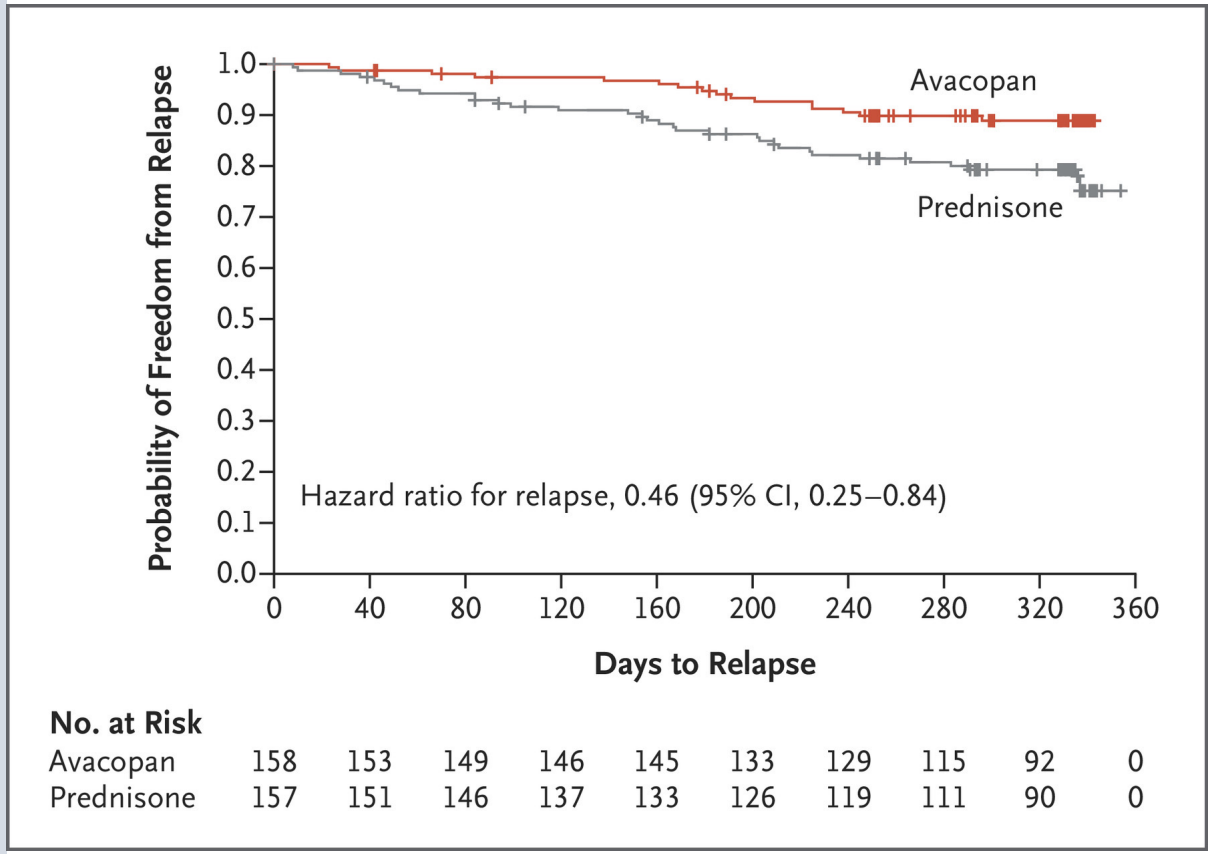
ADVOCATE: baseline Charakteristika

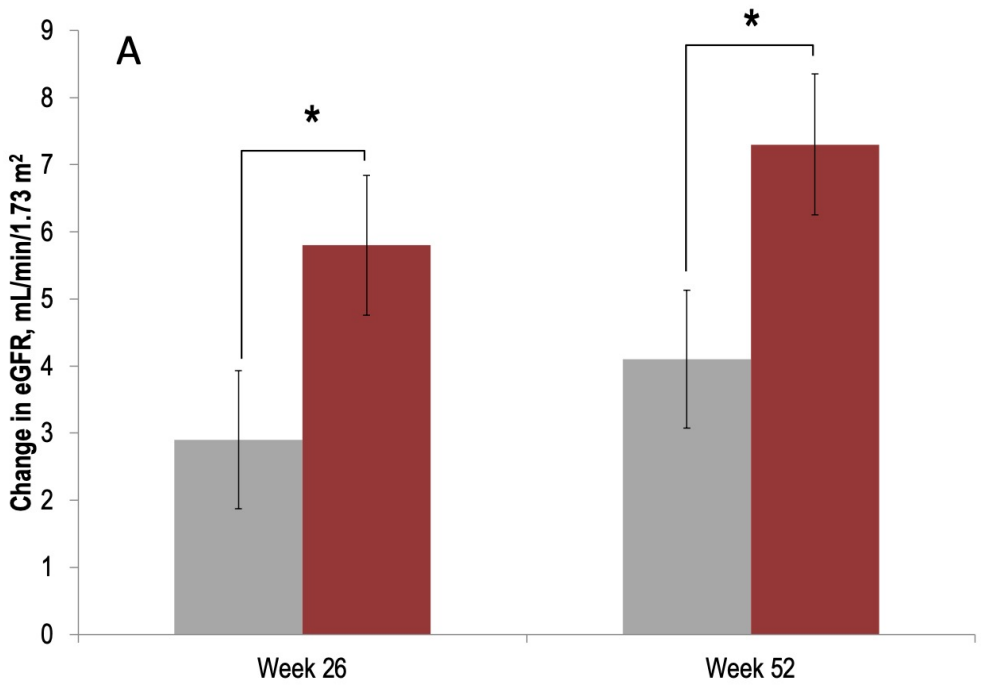
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Avacopan (N=166)	Prednisone (N=164)
Age — yr	61.2±14.6	60.5±14.5
Vasculitis disease status — no. (%)		
Newly diagnosed	115 (69.3)	114 (69.5)
Relapsed	51 (30.7)	50 (30.5)
ANCA status — no. (%)		
Antiproteinase 3 positive	72 (43.4)	70 (42.7)
Antimyeloperoxidase positive	94 (56.6)	94 (57.3)
Type of vasculitis — no. (%)		
Granulomatosis with polyangiitis	91 (54.8)	90 (54.9)
Microscopic polyangiitis	75 (45.2)	74 (45.1)
Organ involvement — no. (%)‖		
Renal	134 (80.7)	134 (81.7)
eGFR — ml/min/1.73 m^2‡‡		
Mean	44.6±2.4	45.6±2.4

ADVOCATE: Resultate Efficacy

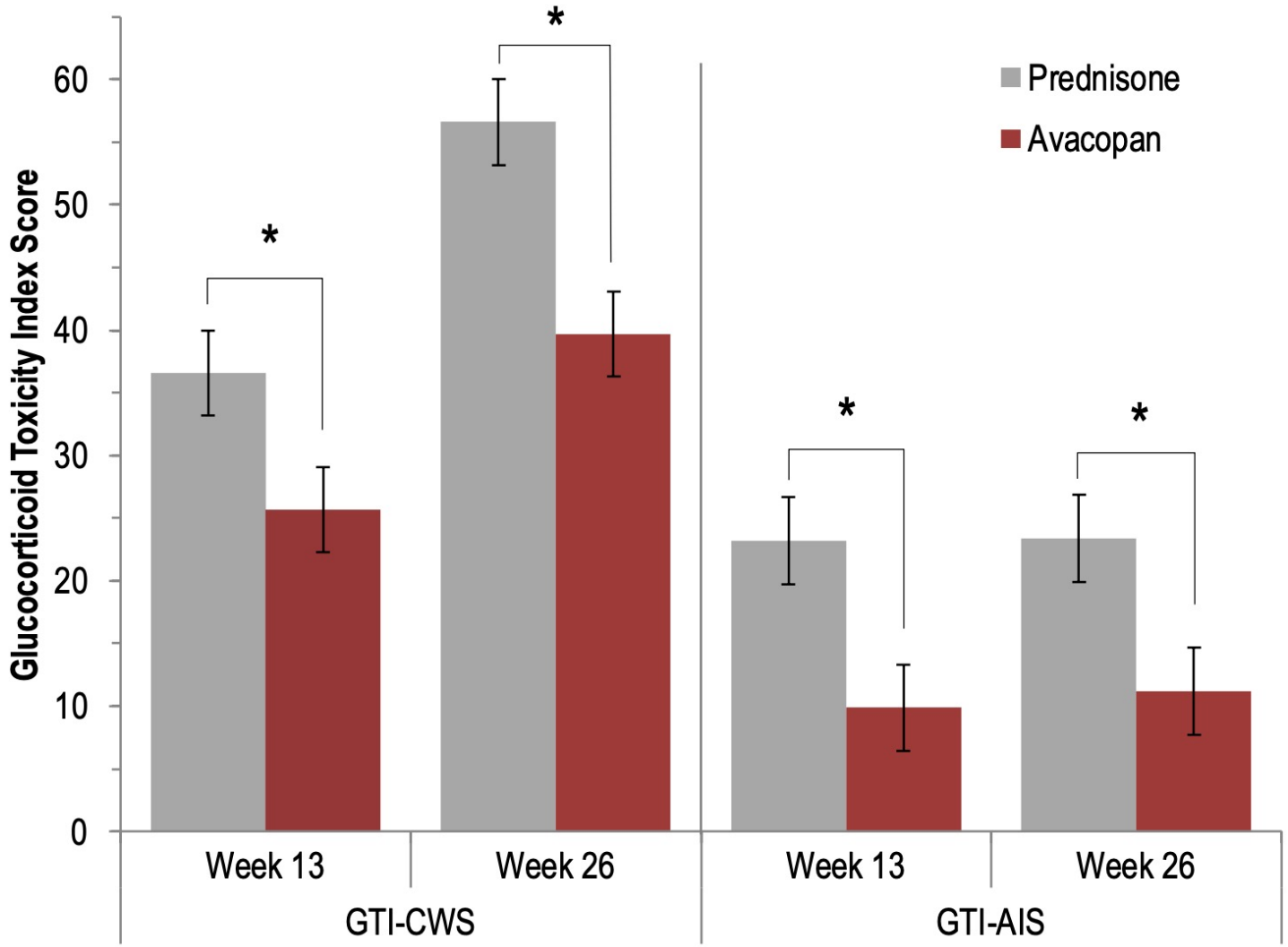
End Point	Avacopan (N=166)	Prednisone (N=164)	Difference (95% CI)
Primary end points			
Remission at wk 26 — no. (%)†	120 (72.3)	115 (70.1)	3.4 (–6.0 to 12.8)‡§
Sustained remission at wk 52 — no. (%)¶	109 (65.7)	90 (54.9)	12.5 (2.6 to 22.3)‡‖





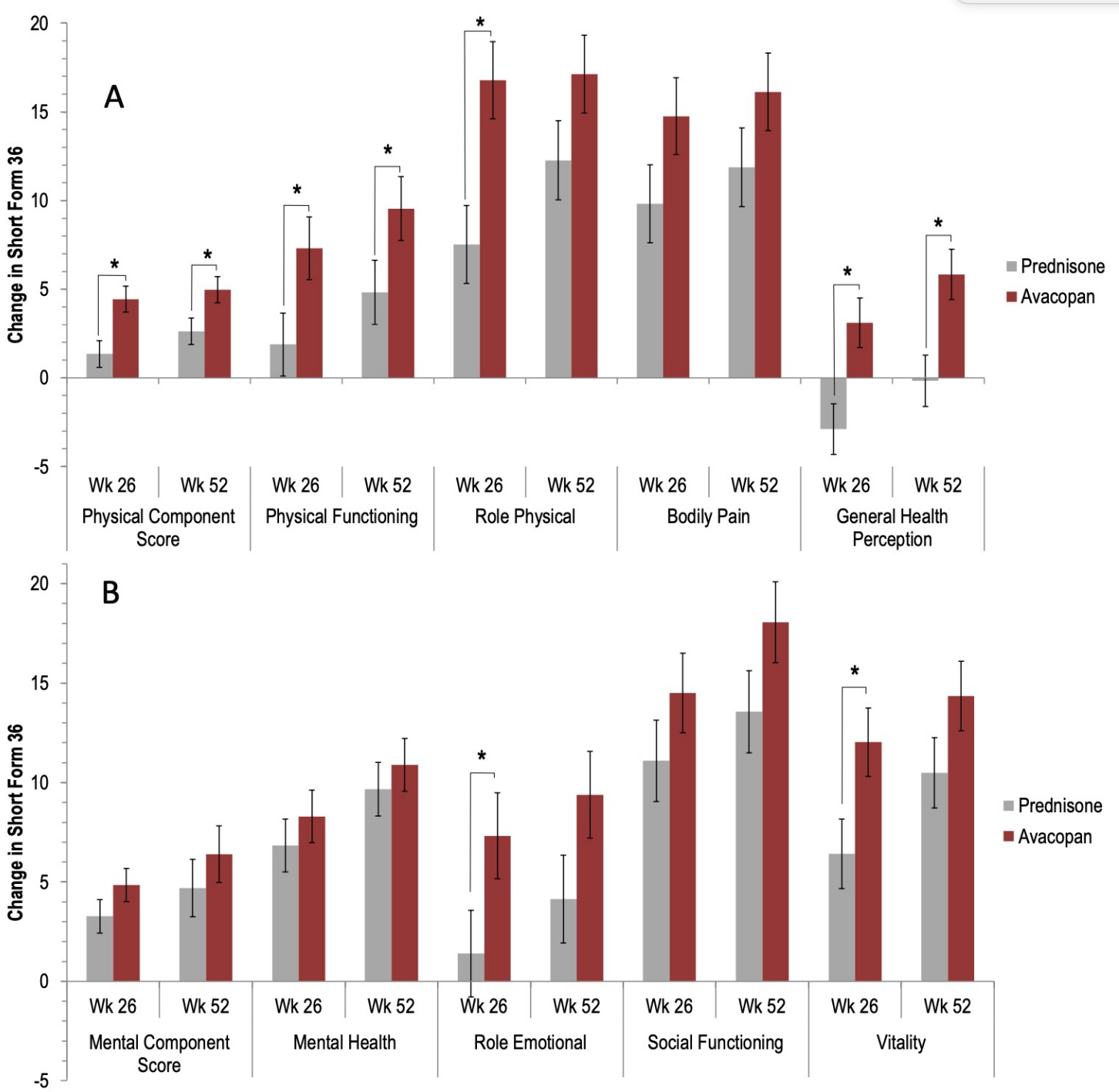
Walsh, NEJM 2020

ADVOCATE: Steroidnebenwirkungen



Walsh, NEJM 2020

ADVOCATE: Lebensqualität



Walsh, NEJM 2020

ADVOCATE: Adverse Events

Table 3. Safety Results.*

Event	Avacopan (N=166)	Prednisone (N=164)
Any adverse event		
No. of patients (%)	164 (98.8)	161 (98.2)
No. of events	1779	2139
Severe adverse event†		
No. of patients (%)	39 (23.5)	41 (25.0)
No. of events	71	94
Life-threatening adverse event		
No. of patients (%)	8 (4.8)	14 (8.5)
No. of events	8	22
Death — no. (%)	2 (1.2)	4 (2.4)
Any serious adverse event‡		
No. of patients (%)	70 (42.2)	74 (45.1)
No. of events	116	166

Walsh, NEJM 2020

ADVOCATE: Remission Woche 52 nach Subgruppen

	Prednisone (N=164)	**Avacopan (N=166)**
All Patients*	90 / 164 (54.9%)	109 / 166 (65.7%)
Disease Status		
Newly diagnosed patients	66 / 114 (57.9%)	70 / 115 (60.9%)
Relapsing disease	24 / 50 (48.0%)	39 / 51 (76.5%)
ANCA Type		
Anti-proteinase 3 positive	40 / 70 (57.1%)	43 / 72 (59.7%)
Anti-myeloperoxidase positive	50 / 94 (53.2%)	66 / 94 (70.2%)
Background Treatment		
Cyclophosphamide	30 / 57 (52.6%)	33 / 59 (55.9%)
Rituximab	60 / 107 (56.1%)	76 / 107 (71.0%)
Type of ANCA-Associated Vasculitis		
Granulomatosis with polyangiitis	52 / 90 (57.8%)	56 / 91 (61.5%)
Microscopic polyangiitis	38 / 74 (51.4%)	53 / 75 (70.7%)

Fazit Avacopan

- Äquivalente Remissionsinduktion, bessere Remissionserhaltung, weniger Nebenwirkungen
- Cave:
  - Relativ geringe „background“-Immunsuppression: rascher Steroidtaper in Kontrollgruppe, keine Erhaltungstherapie nach Rituximab
  - Wenige Pat mit schwerer Niereninsuffizienz
- Hat das Potential zum Game-Changer...
- ... wir sind gespannt auf den Preis!

Vielen Dank für die Aufmerksamkeit!

andreas.kistler@stgag.ch

www.nephrologie-thurgau.ch