Update in therapies for IgA Nephropathy

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Nephrology & Transplantation Update Course, ASM ANZSN 2017, Darwin

Disclosure

Honorarium from AstraZeneca, Amgen and Baxter.

The George Institute for Global Health, holds research contracts for trials in cardiovascular and/or kidney disease with a range of commercial organizations.

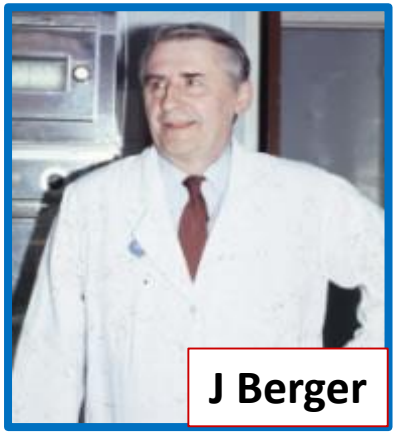
A member of the Executive Steering Committee for the TESTING study funded by the Australian NHMRC, Peking University and the Canadian Institutes of Health Research. Methylprednisolone was provide by Pfizer

Overview

Updates in therapies for IgA nephropathy

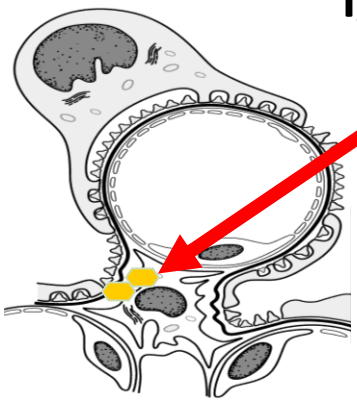
- Corticosteroid
- Mucosal steroid therapy
- Novel therapies in clinical trial

IgA Nephropathy

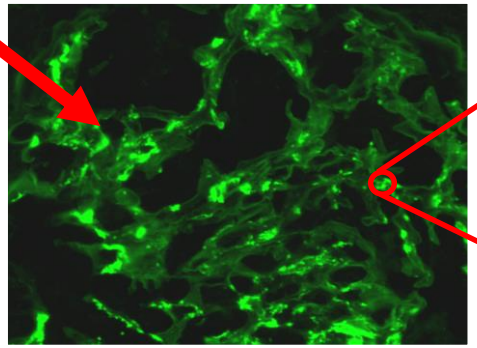


Jan Berger (1968): Berger's disease

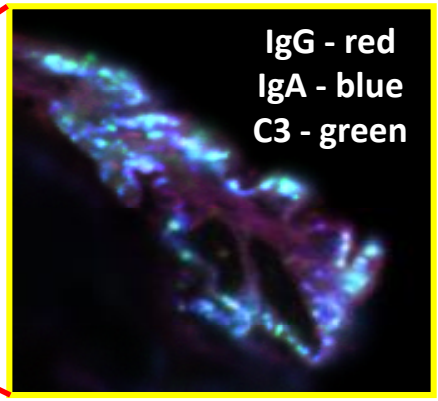
Def. mesangial deposition of IgA and IgG/IgM (IgA>IgG).



IgA1 deposition



Co-localization of IgG, IgA, and C3



Multi-Hit hypothesis

Hit 1

Increased circulating galactose-deficient IgA1

Hit 2

Production of unique anti-glycan antibodies

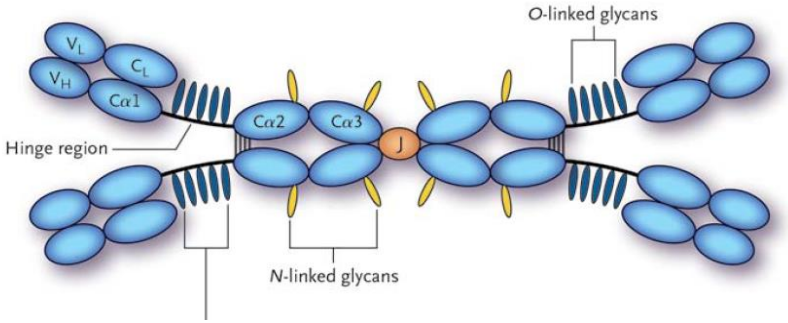
(IgG and IgA)

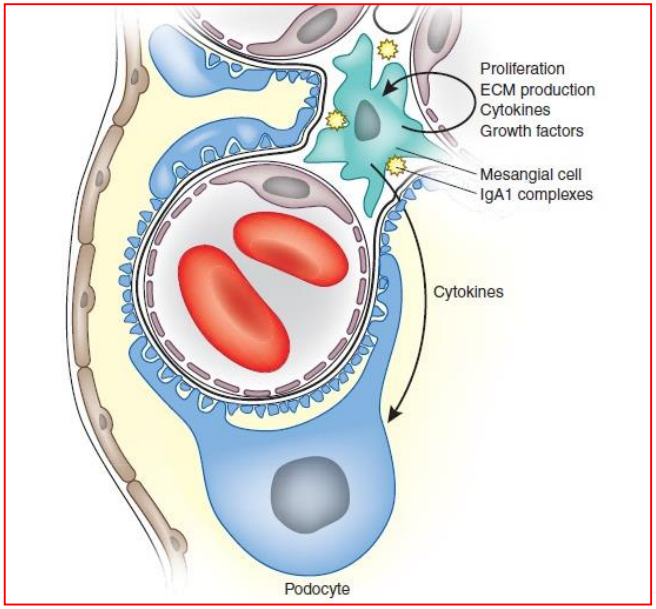
Hit 3

Formation of pathogenic IgA1-containing circulating immune complexes

Hit 4

Mesangial deposition and activation of mesangial cells resulting in glomerular injury





Suzuki H, et al: J Am Soc Nephrol 2011
Wyatt et al 2013 NEJM

Treatment for IgA nephropathy (KDIGO guidelines)

Recommendation

ACE inhibitor or ARB for urinary protein excretion of >1 g/day; increase dose depending on blood Pressure

Suggestions

ACE inhibitor or UPr 0.5 to 1.0 g/day; aim UPr <1 g/day

6-mo glucocorticoid therapy if UPr >1 g/day following 3 to 6 mo of supportive therapy (ACE inhibitor or ARB and BP control) and an eGFR of >50 ml/min/1.73 m^2 (Grade 2C)

Fish oil if UPr >1 g/day continues after 3 to 6 mo of supportive therapy

BP target: <130/80 mmHg if UPr is <1 g/day but <125/75 mm Hg if initial UPr is >1 g/day

Rapidly declining eGFR

Glucocorticoids and cyclophosphamide for crescentic IgA nephropathy (>50% glomeruli with crescents) with rapid deterioration in eGFR

Treatments without proven benefit

Glucocorticoids with cyclophosphamide or azathioprine unless crescentic IgA nephropathy with rapid deterioration in eGFR

Immunosuppressive therapy with an eGFR of <30 ml/ min/1.73 m^2, unless crescentic IgA nephropathy with rapid deterioration in eGFR (Grade 2C)

Mycophenolate mofetil

Antiplatelet agents

Tonsillectomy

Recent corticosteroid trials in IgA nephropathy

Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial

Bengt C Fellström, Jonathan Barratt, Heather Cook, Rosanna Coppo, John Feehally, Johan W de Fijter, Jürgen Floege, Gerd Hetzel, Alan G Jardine, Francesco Locatelli, Bart D Maes, Alex Mercer, Fernanda Ortiz, Manuel Praga, Søren S Sørensen, Vladimir Tesar, Lucia Del Vecchio, for the NEFIGAN Trial Investigators

JAMA | Original Investigation

Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy

The TESTING Randomized Clinical Trial

Jicheng Lv, MD; Hong Zhang, PhD; Muh Geot Wong, PhD; Meg J. Jardine, PhD; Michelle Hladunewich, MD; Vivek Jha, MD; Helen Monaghan, PhD; Minghui Zhao, MD; Sean Barbour, MD; Heather Reich, MD; Daniel Cattran, MD; Richard Glassock, MD; Adeera Levin, FRCPC; David Wheeler, FRCP; Mark Woodward, PhD; Laurent Billot, MSc; Tak Mao Chan, MD; Zhi-Hong Liu, MD; David W. Johnson, MD; Alan Cass, FRACP; John Feehally, MD; Jürgen Floege, MD; Giuseppe Remuzzi, MD; Yangfeng Wu, MD; Rajiv Agarwal, MD; Hai-Yan Wang, MD; Vlado Perkovic, PhD; for the TESTING Study Group

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

ıtensive Supportive Care plus ıosuppression in IgA Nephropathy

Rauen, M.D., Frank Eitner, M.D., Christina Fitzner, M.Sc., rer, M.D., Martin Zeier, M.D., Britta Otte, M.D., Ulf Panzer, M.D., Harm Peters, M.D., Urs Benck, M.D., Peter R. Mertens, M.D., Uwe Kuhlmann, M.D., Oliver Witzke, M.D., Oliver Gross, M.D., Volker Vielhauer, M.D., Johannes F.E. Mann, M.D., Ralf-Dieter Hilgers, Ph.D., and Jürgen Floege, M.D., for the STOP-IgAN Investigators*

Lv et al. JAMA 2017

Fellstrom et al Lancet 2017

Rauen et al. NEJM 2015

TESTING study

IgA nephropathy at high risk of progression

Biopsy proven IgA nephropathy

eGFR 20-120 mls/min/1.73 m^2

Proteinuria > 1g/day after at least 3 months of maximum labelled or tolerated RAS blockade

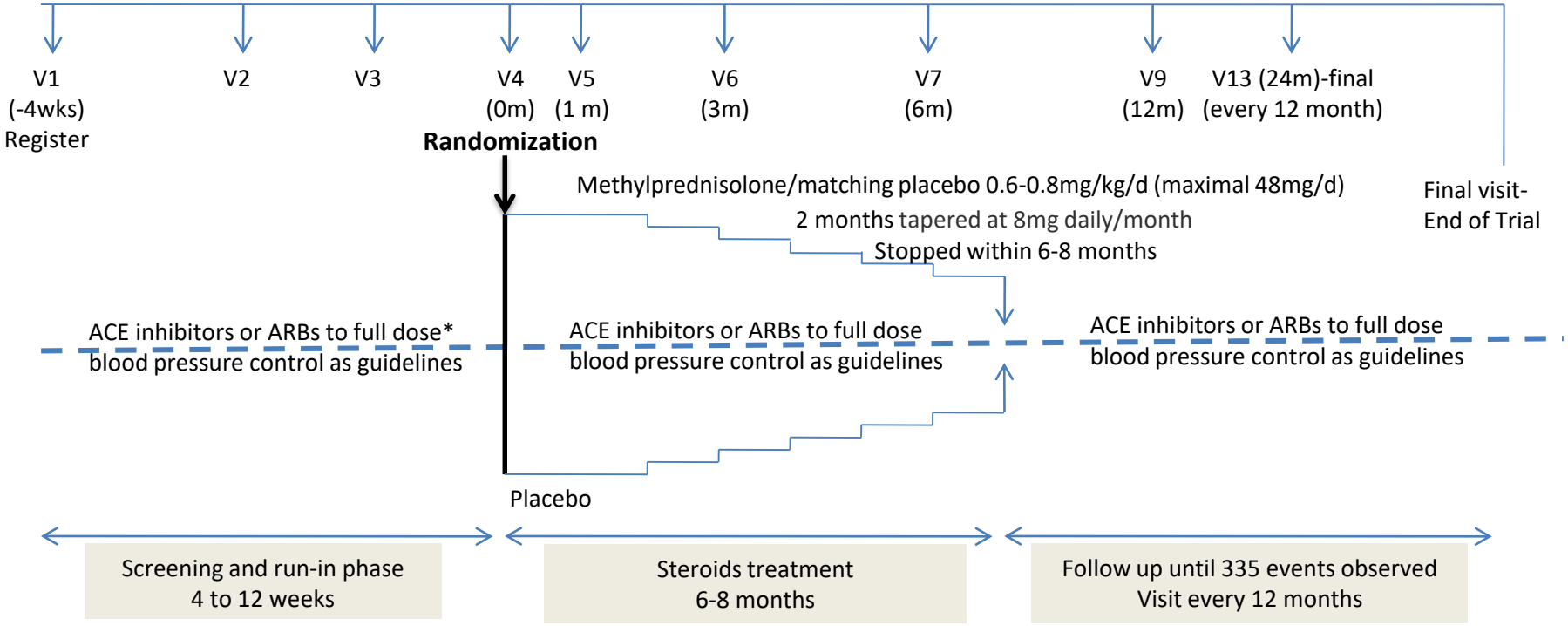
Background therapy

Optimal blood pressure control target <130/80mmHg

ACE inhibitors or ARBs adjusted to the maximum labeled or tolerated dose

Based on local guidelines and country practice.

TESTING-Trial design



Sample size: 750 participants, or total 335 primary outcome events
90% power to detect a 30% relative risk reduction for primary outcome
Follow-up : 4-6 years

Efficacy outcomes

Primary end points:

Composite of ESKD, death due to kidney disease, or a persistent 50% decrease in eGFR

Secondary end points:

50% decrease in eGFR, ESKD or all-cause death

Each of 50% decrease in eGFR, ESKD and all-cause death

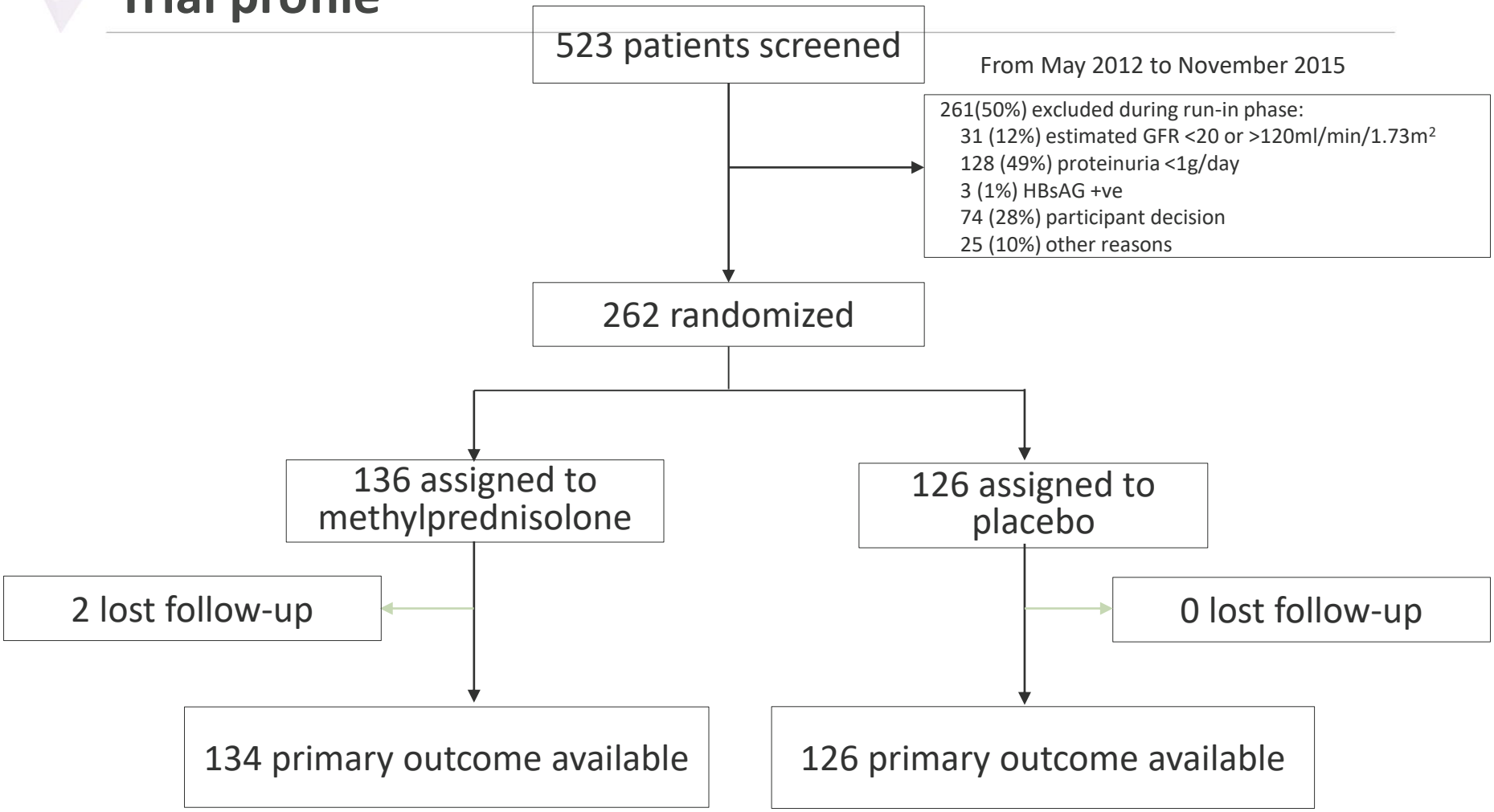
Annual rate of eGFR decline

Proteinuria reduction

Revised efficacy outcomes (November 15, 2014)

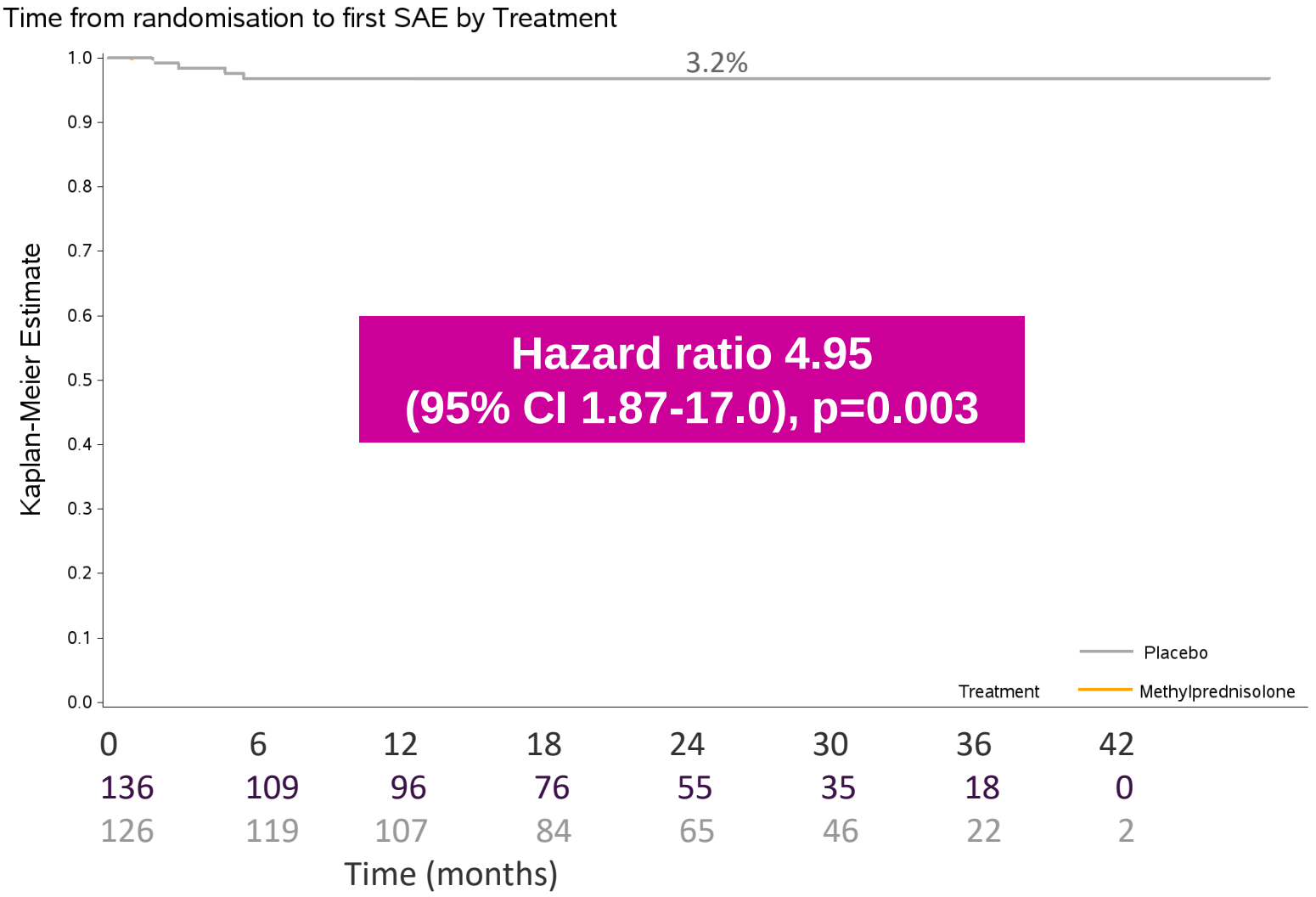
40% decrease in eGFR

Trial profile



Lv et al. JAMA 2017

Serious adverse events



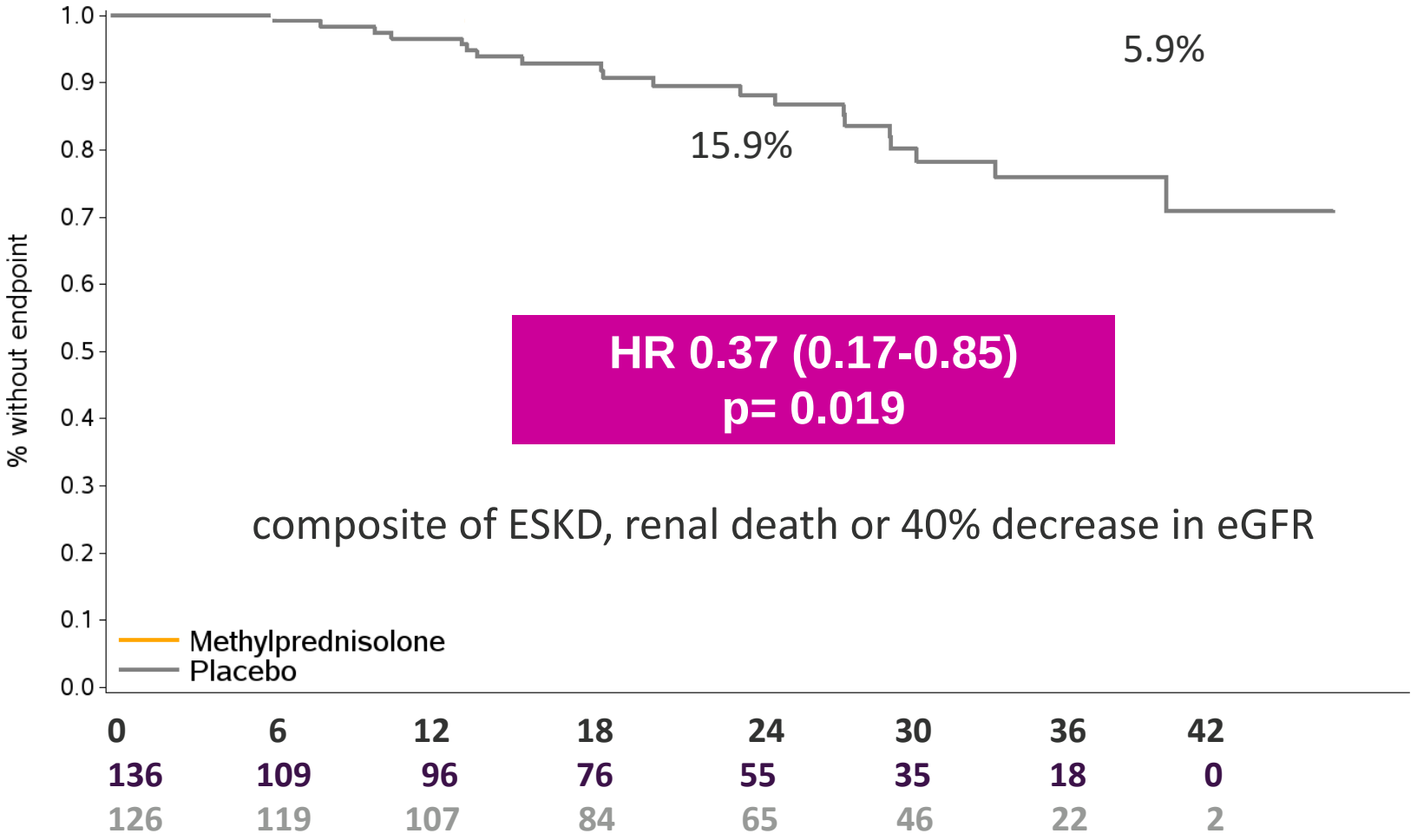
Lv et al. JAMA 2017

Safety outcomes

Outcome	Methylprednisolone group (N=136)	Placebo group (N=126)	P Value
Total patients with serious adverse events – no.	**20**	**4**	**0.001**
Serious adverse events of infection	**11**	**0**	**<.001**
Fatal infection	2	0	NS
Pneumocystis jirovecii pneumonia	3	0	NS
Other lung infection	2	0	NS
Septic arthritis	1	0	NS
Perianal infection	1	0	NS
Gastrointestinal serious adverse events	**3**	**1**	**NS**
Bone disorders			
Avascular necrosis	3	0	NS
Fracture	1	0	NS
New onset diabetes mellitus	**2**	**3**	**NS**

Lv et al. JAMA 2017

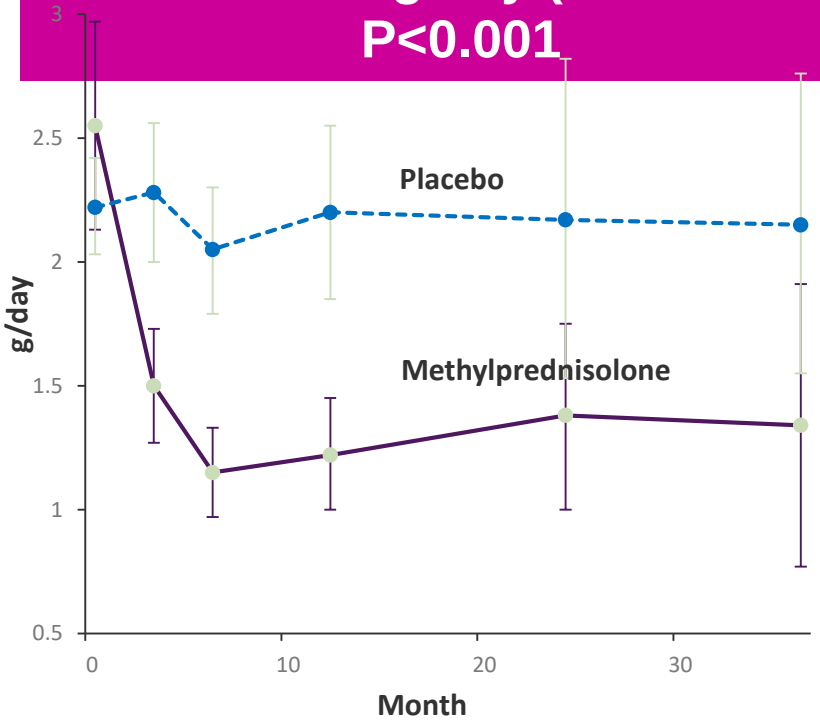
Primary outcome



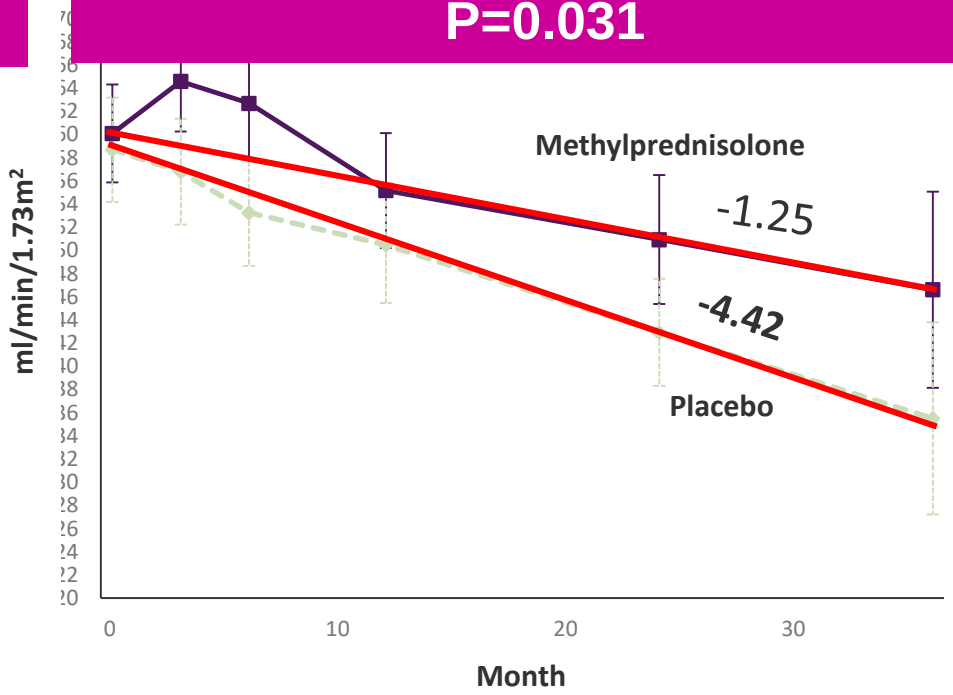
Lv et al. JAMA 2017

Effect on Proteinuria & eGFR

Time averaged proteinuria:
1.37 vs 2.36 g/day (42% lower)
P<0.001



Annual eGFR slope*:
-1.7 vs -6.8 mls/min/1.73m²/yr
P=0.031



*- defined for each individual patient using the slope from least squares linear regression of all eGFR estimates over time

Lv et al. JAMA 2017

Trial Design

Run-in phase (6 months)

Trial phase (3 years)

IgAN, 18-70 years, GFR ≥ 30 ml/min, proteinuria > 0,75 g/d
PLUS hypertension (> 140/90) or GFR < 90 ml/min

Optimized supportive therapy
(ACEi, ARB, target bp < 125/75 mmHg, statins, etc.)
Baseline (after 6 months): bp, proteinuria, eGFR

n=380

Responder
proteinuria < 0,75 g/d
optimized supp. therapy;
periodically proteinuria

Drop-Out
proteinuria > 3,5 g/d
GFR loss > 30%
GFR < 30 ml/min

proteinuria
≥ 0,75 g/d

Non-Responder
proteinuria ≥ 0,75 g/d

n=162

Randomization

n=80

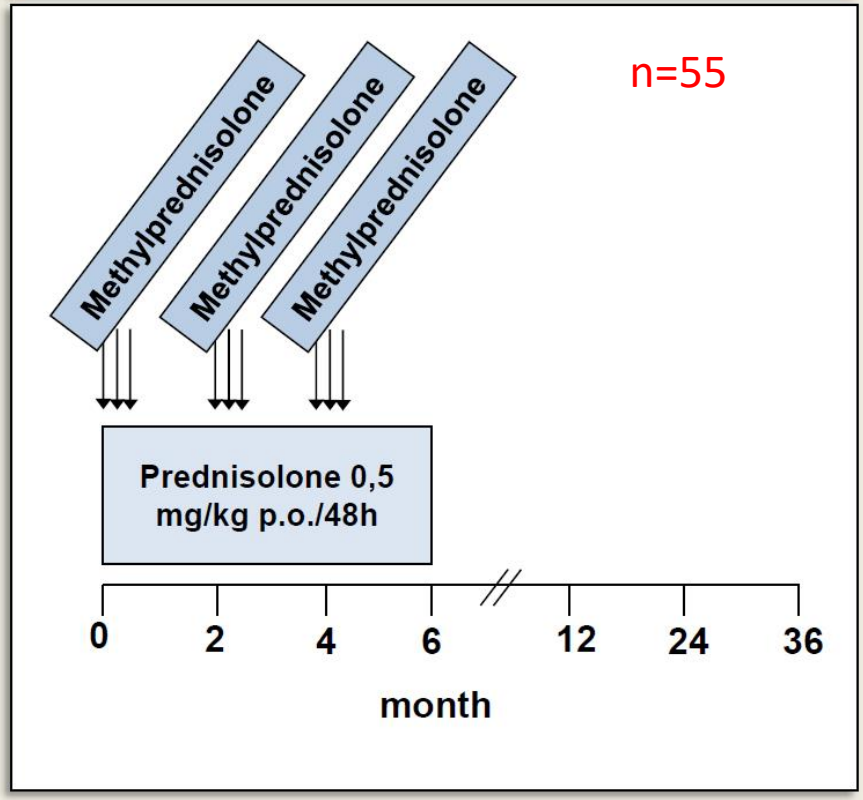
Optimized supportive therapy (SUP)

n=82

Optim. supp. therapy + immunosuppression (IMM)

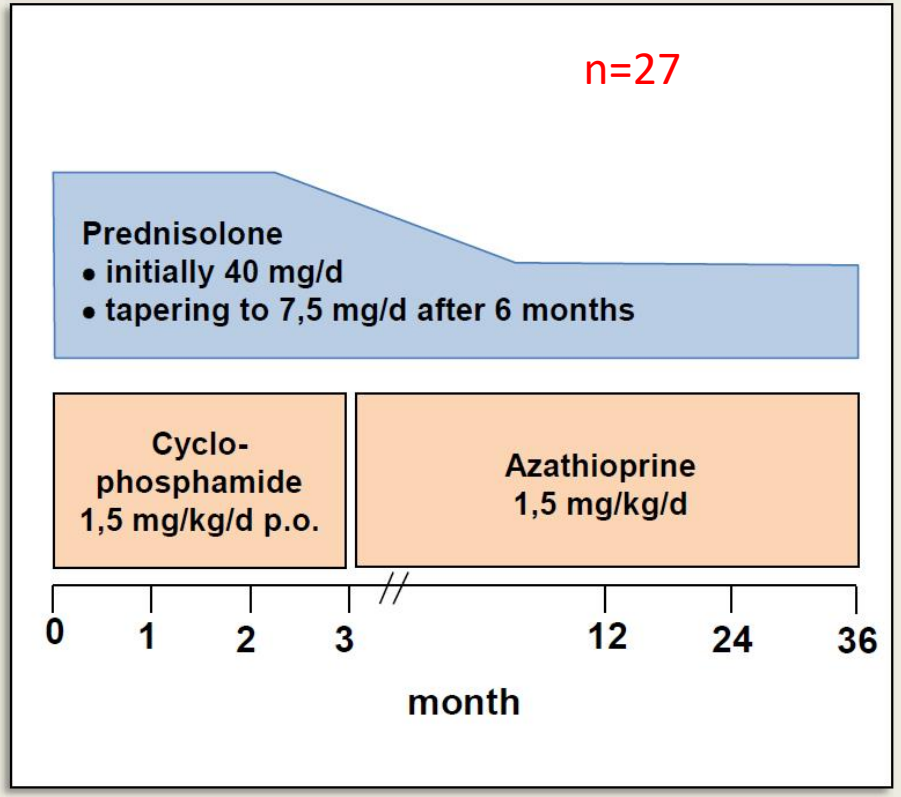
Immunosuppression

GFR ≥ 60 ml/min



Pozzi et al. Lancet 1999; 353: 883

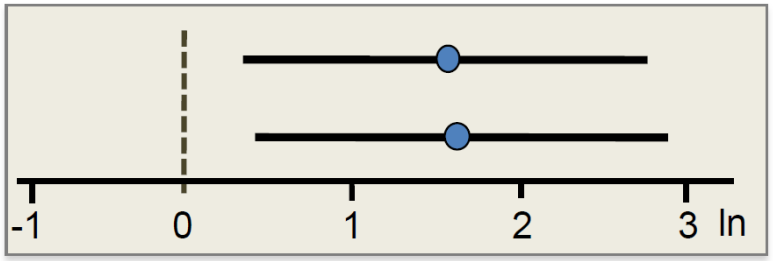
GFR 30-59 ml/min



Ballardie et al., J Am Soc Nephrol 2002; 13:142

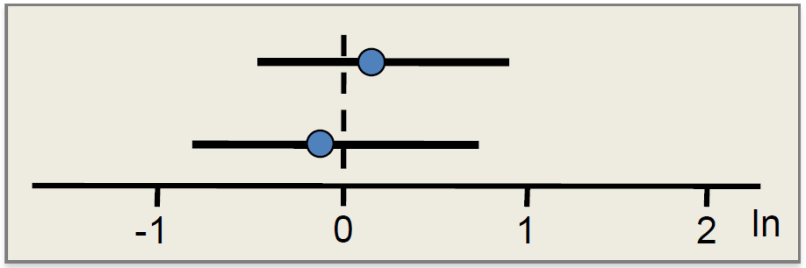
3-Year Trial Phase: Primary End Points

	SUP events/total	IMM events/total	OR (95%-CI)	*p*-value
In full clinical remission (prot. < 0.2 g/g plus eGFR loss < 5 ml/min/1.73 m²)				
WCS	4/80	14/82	4.82 (1.43-16.3)	**0.011**
ACA	4/68	14/66	5.33 (1.54-18.5)	**0.008**



favours SUP favours IMM

eGFR loss ≥ 15 ml/min/1.73 m²				
WCS	24/80	28/82	1.20 (0.61-2.33)	0.602
ACA	16/72	14/68	0.91 (0.40-2.05)	0.817



favours IMM favours SUP

Safety

Immunosuppression arm comparison

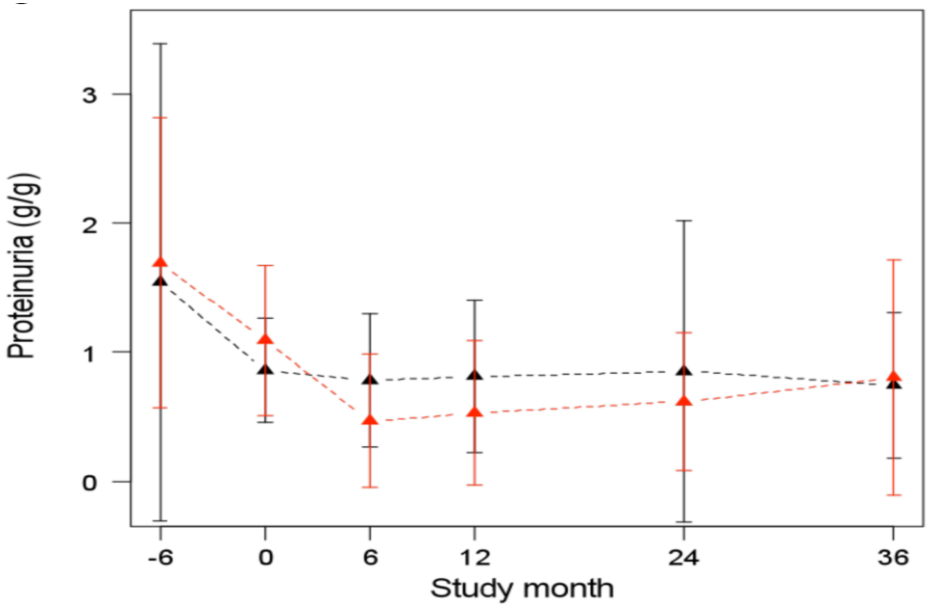
Outcome	STOP IgAN	TESTING
SAEs	29 (35%)	20 (14.7%)
Serious infections	8 (9.8%)	11 (8.1%)
Fatal infections	1 (1.2%)	2 (1.5%)

TESTING vs. STOP-IgAN

	TESTING study	STOP-IgAN study
Sample size	262	162
Follow up duration (yrs)	Up to 3 (Median 2.1)	3
Race	Asian 96.3% Caucasian 3.7%	Caucasian
Age (mean)(yr)	38.6	44.5
Female (%)	36.7%	21.5%
RAS blockers during f/up	100%	96%(c) 100%(Rx)
Blood pressure (mmHg)		
systolic	124.1	125.5
diastolic	79.5	77.5
Proteinuria (g/d)	2.4	1.7
eGFR (ml/min/1.73m^2)	59	59
Annual eGFR decline in supportive group	-4.4	-1.6
Annual eGFR decline in Steroid group	-1.3	-1.5

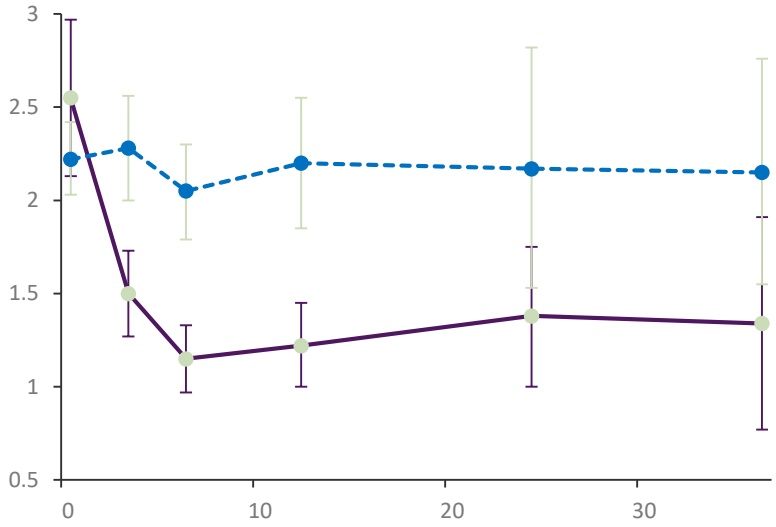
Proteinuria in STOP-IgA & TESTING

STOP-IgA study



STOP IgA study. NEJM 2015

TESTING



TESTING, JAMA 2017

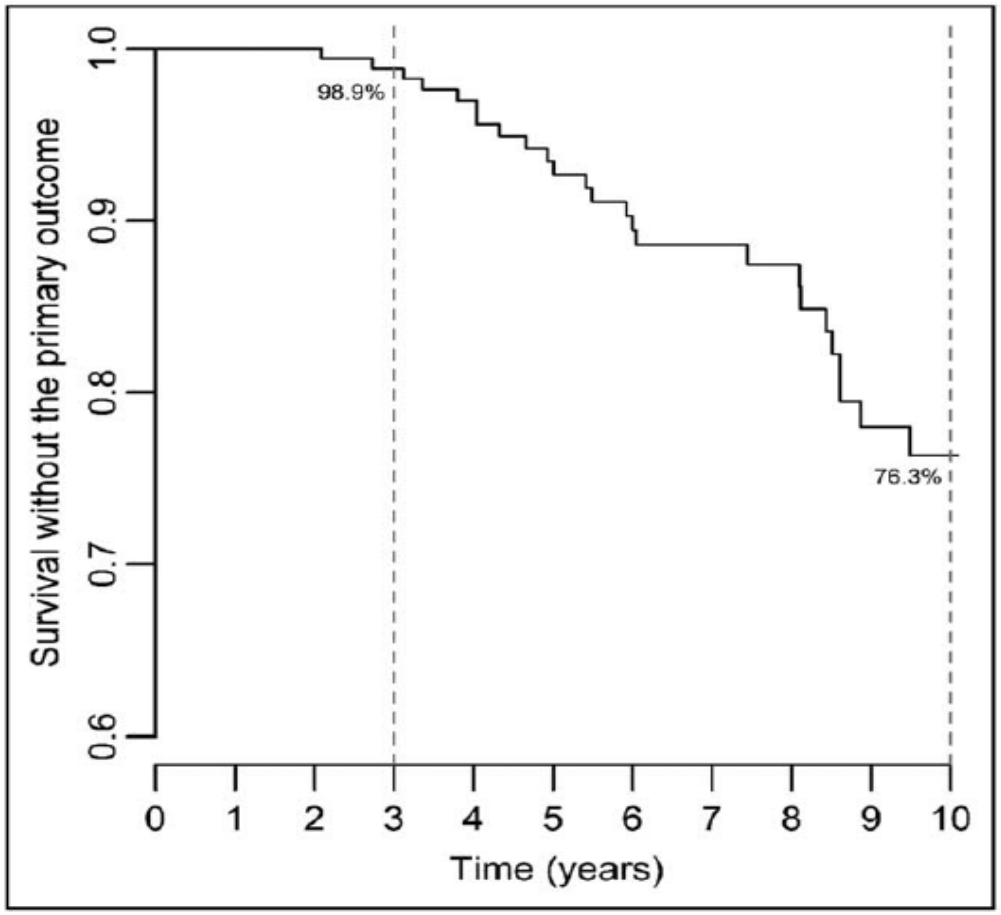
STOPIgA trial: Differential proteinuria response

Table 3. Proteinuria over time in the STOP-IgAN trial

	STOP-IgAN trial [13▪]			
	Control group	**Combined IS group**	**Steroid group**	**CYC+Aza group**
PCR (g/g):				
Baseline	1.0	1.1	0.98*	1.2[a]
12 months	0.80*	0.57*	0.50	0.74
36 months	0.85**	0.76**	0.57	1.27
PCR <0.2 g/g (%)	11.3%	24.4%	30.9%	11.1%

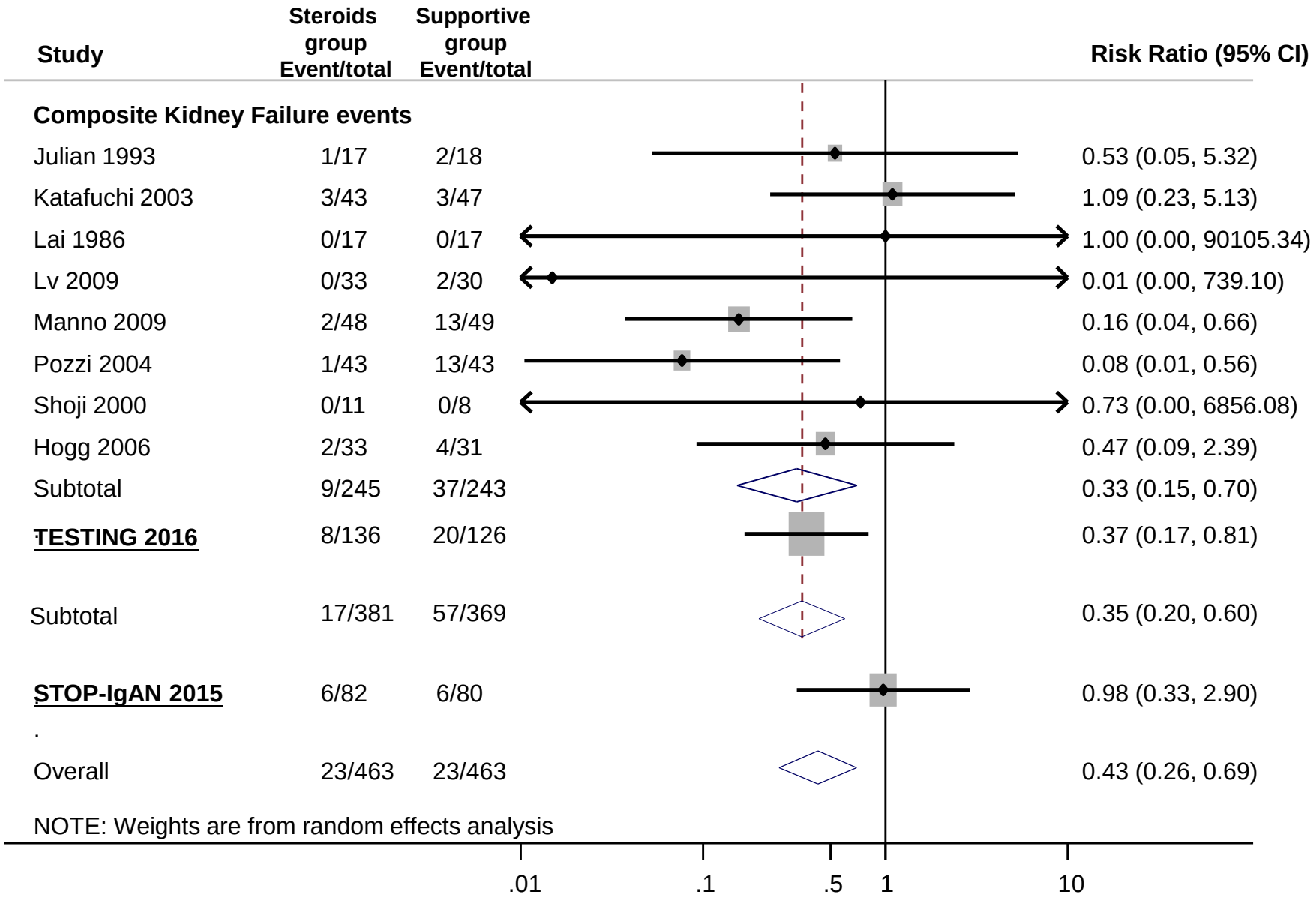
Barbour et al Curr Opinion in Nephro and hyperten 2017

Renal survival over time in IgAN patients with 1-2g/day proteinuria



Adapted from Barbour et al KI 2016

Meta-analysis



What did we learn?

Supportive therapy can retard progressive IgA nephropathy

Full dose steroid & immunosuppressive therapy was associated with significantly increased rates of SAE in patients with IgA nephropathy

TESTING results to date suggest renal benefit based on a modest number of events

The ongoing, long-term follow-up will help to further define the balance of risks and benefits

TESTING low dose

CLINICAL TRIAL PROTOCOL

TESTING low dose Study

Therapeutic Evaluation of STeroids in IgA Nephropathy Global low dose study

Protocol Number: GI-R-01-2011
Version Number: 6.0

Testing Study Amendment 5_Version 6.0_12 July 2016

"A collaboration between the Peking University Institute of Nephrology, the George Institute for Global Health and renal researchers around the world"

PRIVILEGED AND CONFIDENTIAL
Not for distribution beyond intended function

TESTING low dose study

This study will evaluate the long-term efficacy and safety of **low dose oral methylprednisolone** compared to matching placebo, on a background of routine RAS inhibitor therapy, in preventing kidney events in patients with IgA nephropathy and features suggesting a high risk of progression

A randomised, parallel-group, two-arm, double-blind, long-term study

Inclusion Criteria

IgA nephropathy proven on renal biopsy

Proteinuria: ≥ 1.0g/day while receiving maximum labeled dose of RAS blockade following the recommended treatment guidelines of each country where the trial is conducted

eGFR: **30 to 120ml/min** per 1.73m2(inclusive) while receiving maximum tolerated RAS blockade

Study intervention

Full-dose cohort: oral methylprednisolone 0.6-0.8 mg/kg/day, with a reducing dose regimen over 6-8 months.

Low-dose cohort: oral methylprednisolone **0.4mg/kg/day** initially, maximal dose of **32mg/day**, minimum dose of **24mg/day** and then reducing over 6-9 months

vs.

Placebo

Prophylactic trimethoprim/sulfamethoxazole (one single strength or half a double strength tablet daily or every other day) for the first 3 months

Primary outcome specifically for the low-dose cohort

Change in proteinuria from baseline at 6 and 12 months - > 90% power to detect reduction of 0.5 g/day

Mean change in eGFR at 6 and 12 months – 80% power to detect difference of 5 mls/min

Outcomes -combined cohort

Overall Primary outcomes

Progressive kidney failure: 40% decrease in eGFR, ESKD, and death due to kidney disease

Overall Secondary outcomes for combined cohorts

The composite of ESKD, 30% decrease in eGFR and all cause death

The composite of ESKD, 40% decrease in eGFR and all cause death

The composite of ESKD, 50% decrease in eGFR and all cause death

Each of ESKD, death due to kidney disease and all cause death

Annual eGFR decline rate

Time averaged proteinuria post-randomization

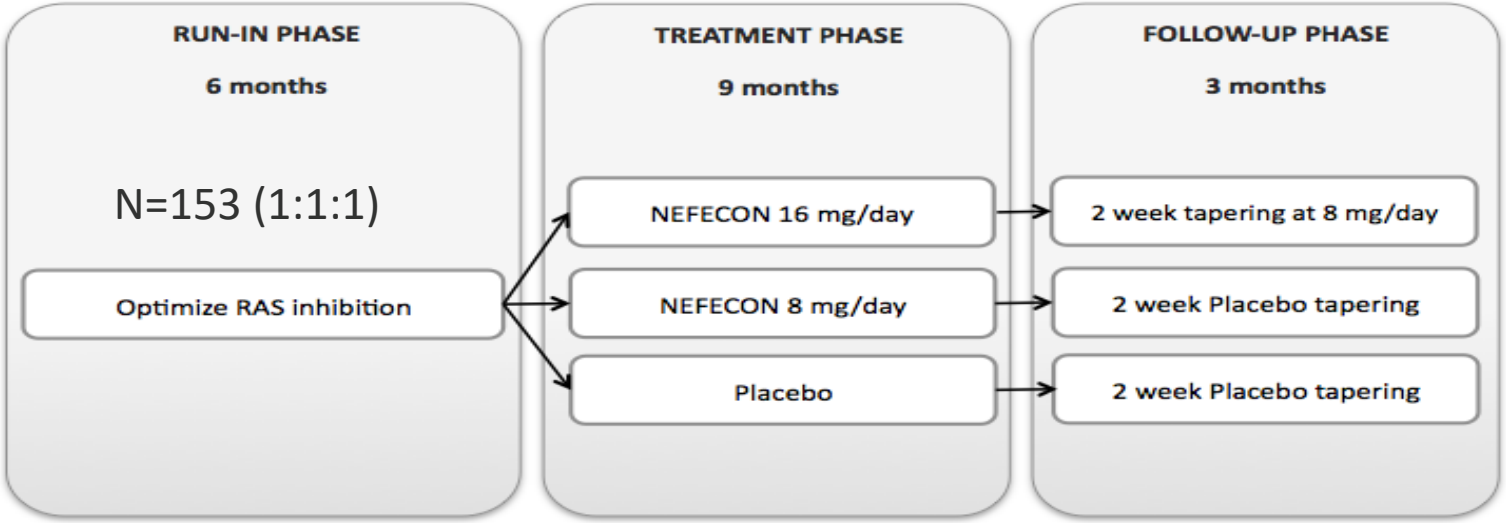
500 participants in total will provide 90% power (α=0.05) to detect a 40% risk reduction after an average follow-up of 4 years, and 80% power to detect a 35% RRR

Currently recruiting in Australia, China, Canada, India and Malaysia.

NEFIGAN trial

Phase 2b RCT

Aim to evaluate the Efficacy and Safety of Two Different Doses of Nefecon in Primary IgA Nephropathy Patients at Risk of End-stage Renal Disease



NEFECON, an oral targeted-release formulation budesonide, in the lower ileum and ascending colon of the gastrointestinal (GI) tract by Pharmalink AB

Fellstrom et al Lancet 2017

NEFIGAN trial

Inclusion:

All biopsy-proven IgAN patients, above 18 years of age will be considered if:

UPCR > 0.5 g/g or

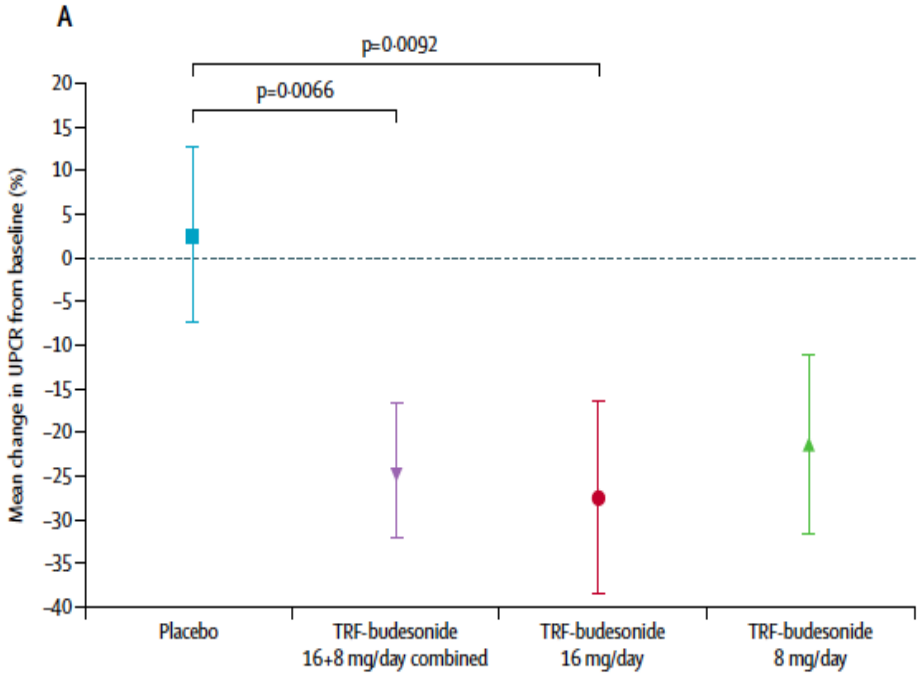
24-UTP > 0.75 g/day and GFR > 45 mL/min

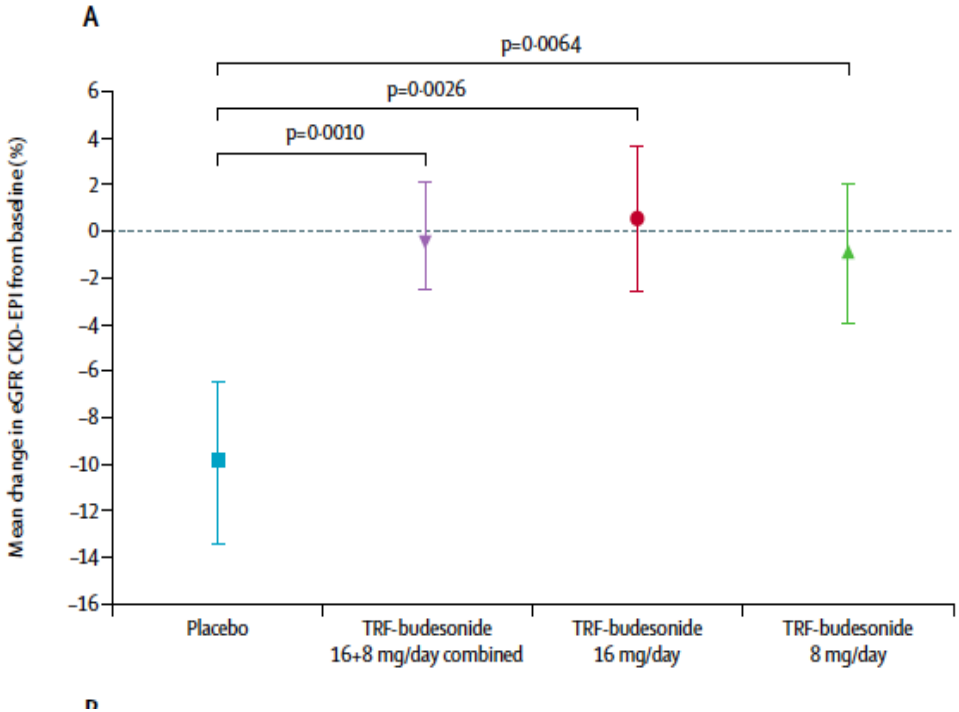
Exclusion:

Received immunosuppression in past 2 years

At the end of run-in phase, patients will be excluded if: Decrease in GFR > 30% (from baseline)

Effect on proteinuria and eGFR





Upto 27% reduction in UPCR in Budesonide vs. 3% rise in the placebo group

Mean changes in eGFR -4.7 mL/min/1.73m2 for the placebo group

0.32mL/min/1.73m2 for 8-mg group
1.95 mL/min/1.73m2 for the 16-mg group

Fellstrom et al Lancet 2017

NEFIGAN trial: Adverse events

AE is more in treatment group although not statistical significant.

Two serious events assessed as being possibly related to treatment included a case of deteriorated renal function (in follow-up) and deep-vein thrombosis.

22% of high dose Budesonide group ceased treatment.

Comparison of NEFIGAN to other RCT

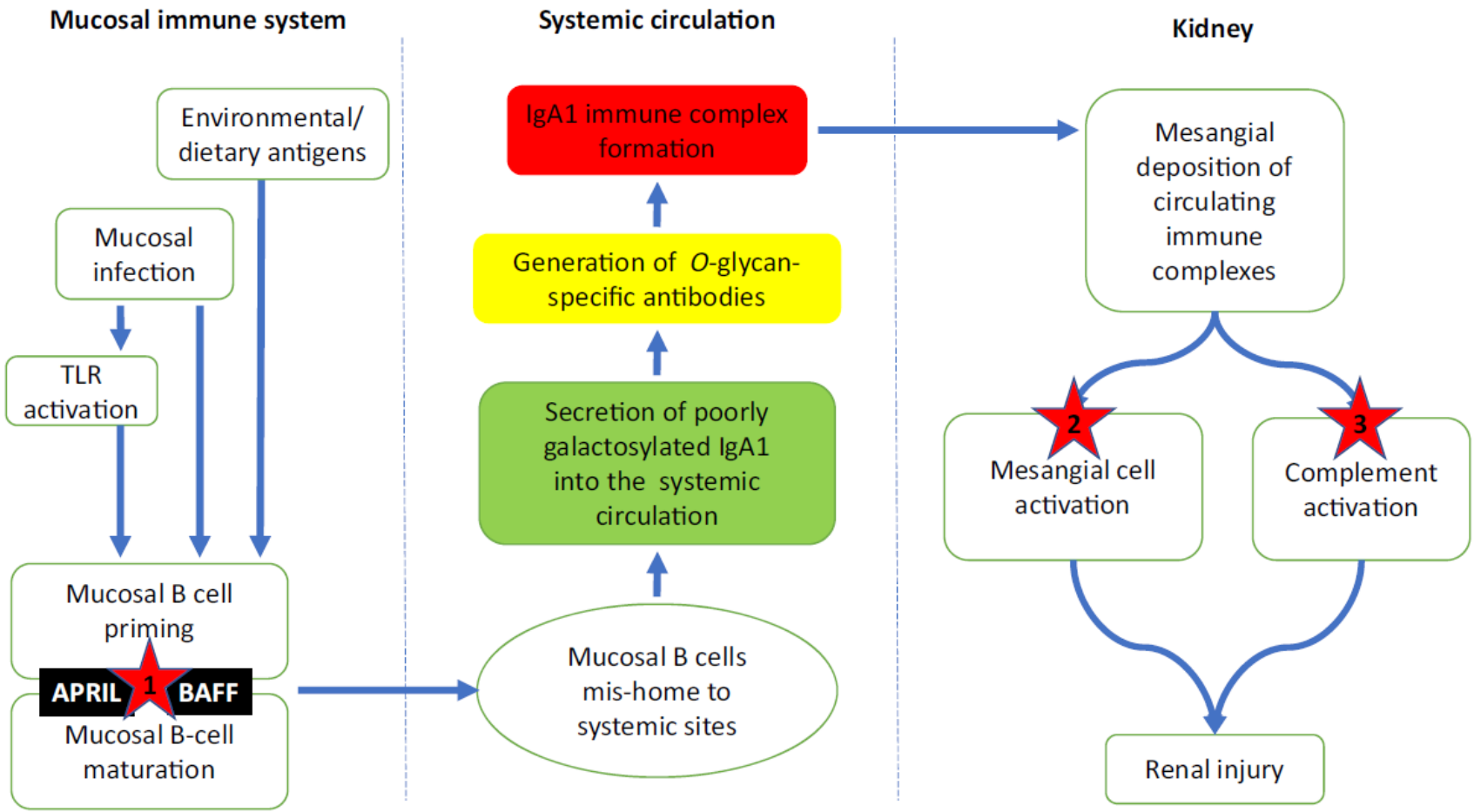
Table 1 | Comparison of selected recent randomized controlled trials in IgA nephropathy

RCT in IgAN patients	NEFIGAN[5]	STOP-IgAN[2]	TESTING[a]	Manno *et al.*[7]	Lv *et al.*[8]
Population	European	European	Chinese	European	Chinese
Patients randomized	149	162	262	97	63
Mean baseline age	39	45	39	33	29
Run-in phase	6 mo, uptitration of RAS blocker	6 mo, optimized supportive care[b]	1–3 mo, uptitration of RAS blocker	3 mo, at least 1 mo of RAS blocker withdrawal	1 mo, at least 1 mo of RAS blocker withdrawal
Mean baseline eGFR (ml/min)	78	59	59	99	101
Mean baseline proteinuria (g/d)	1.2[c]	1.7	2.4	1.6	2.3
Trial phase	0.75 yr	3 yr	1.5 yr[d]	3–9 yr	1–4 yr
Intervention	TRF budesonide 8 or 16 mg/d	High-dose i.v. + oral corticosteroid therapy or combined immunosuppression	High-dose oral corticosteroid therapy	High-dose oral corticosteroid therapy	High-dose oral corticosteroid therapy
Mean annual eGFR loss (ml/min/yr) in the intervention group	−3.4[e] (low dose) +0.2[e] (high dose)	−1.7	−1.5	−0.6	N/A (10% with >25 ml/min GFR loss)
Mean annual eGFR loss (ml/min/yr) in the control or placebo group	−5.9[e]	−1.6	−6.8	−6.2	Not reported (45% with >25 ml/min GFR loss)

[a]Reported by Lv *et al.*[6]
[b]Including blood pressure reduction, proteinuria reduction, and lifestyle modification (see Rauen *et al.*[2] for details).
[c]Median.
[d]Median follow-up at the time of termination of the trial.
[e]Course over 9 months.

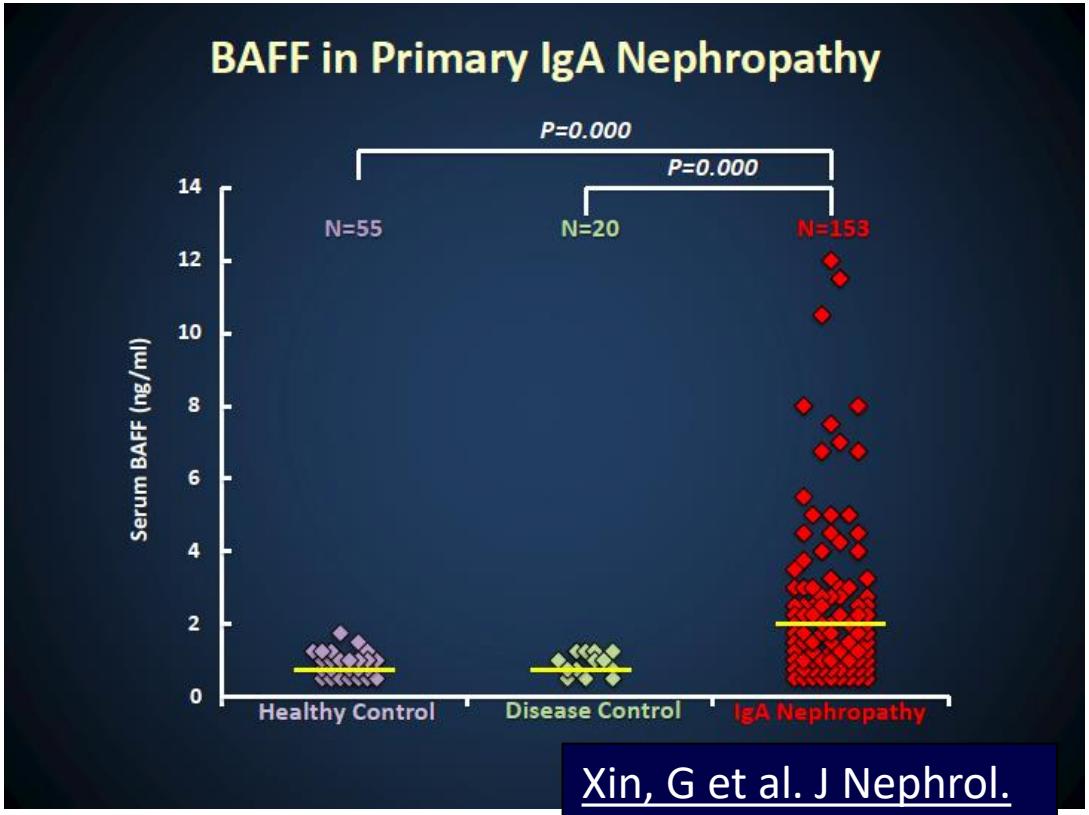
Jurgen Floege KI 2017

Novel therapeutic targets



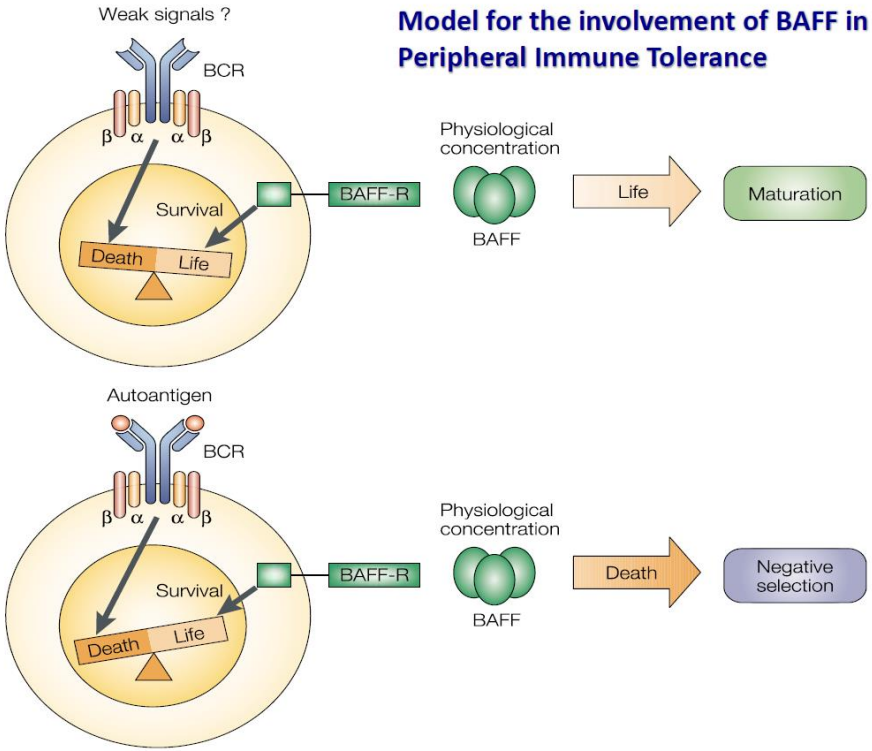
Yeo et al. Pediatr Nephrol 2017

BAFF and APRIL



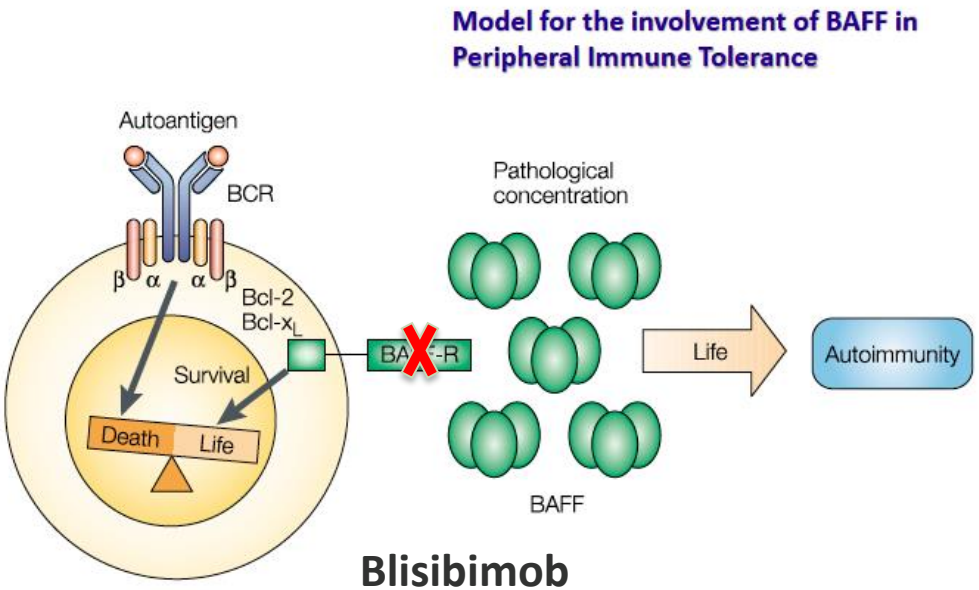
Xin, G et al. J Nephrol. 2013

Role of BAFF/ APRIL in peripheral immune tolerance



Courtesy of Dr. Adrian Liew

Role of BAFF/ APRIL in peripheral immune tolerance

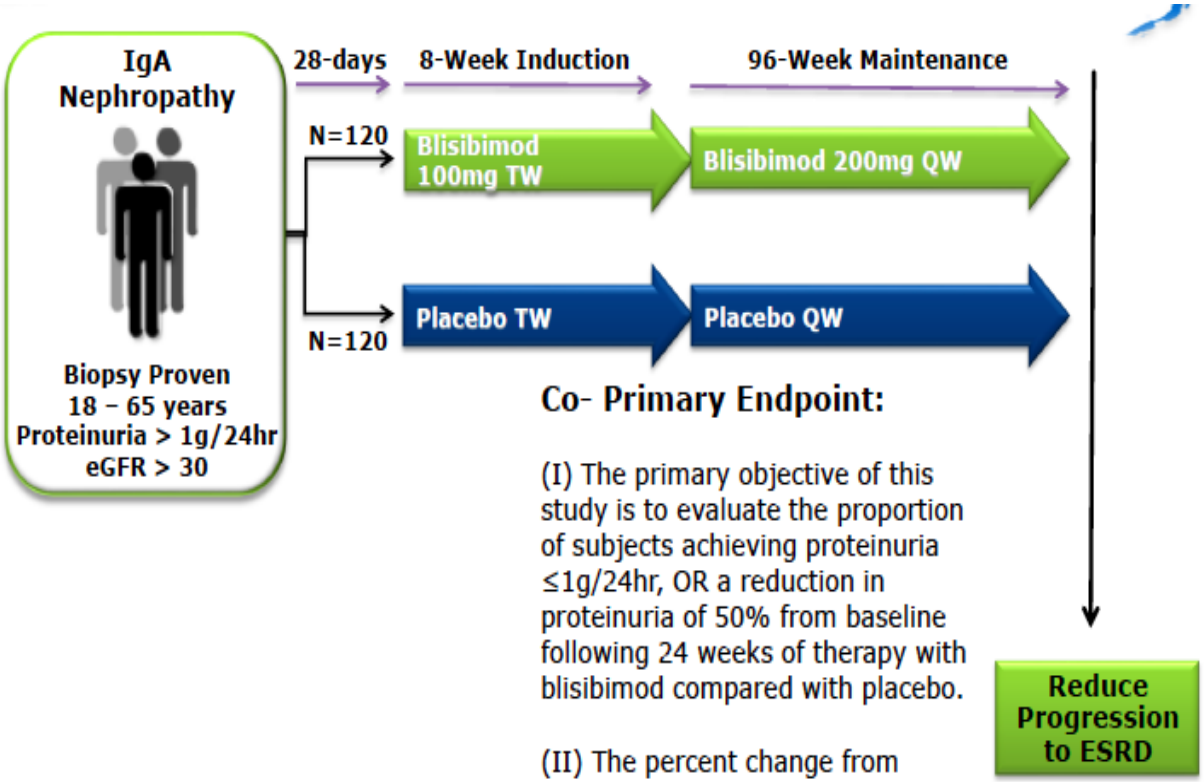


Blisibimob

Atacicept

Courtesy of Dr. Adrian Liew

BRIGHT-SC study



BRIGHT-SC study- N=58 (Placebo (28) Treatment (30)) -24w & 60w

Estimated 24 Hour Urine Protein Excretion

Study Week	0	24	48	60	96	120	144	168
Blisibimod - mean (grams)	2.02	2.17	1.86	1.86	1.88	2.12	2.19	1.18
Placebo - mean (grams)	2.26	2.16	2.01	2.42	2.89	3.35	3.22	4.68
N (blisibimod)	30	27	27	26	20	12	5	3
N (placebo)	28	23	17	17	11	9	4	2

Blisibimob eGFR +6.2mL/min/1.73 m^2 per year compared to -4.8 mL/min/1.73 m^2 with placebo.

AE: URTI, nasopharyngitis, and injection site reactions. Similar infection rate.

Press release by Anthera Pharmaceuticals, Inc (28 August 2017)

Novel therapy in Clinical trial

JANUS: Atacicept in IgA nephropathy (NCT02808429)- recruiting

Rituximab in IgA nephropathy* (NCT00498368)- Open label RCT Rituximab vs. standard therapy. No difference in proteinuria and renal function, effect on serum IgA1, Anti-IgA1 IgG antibody, over 12 mo. More AE.

Acthar gel- a purified adrenocorticotropic hormone in previously failed immunosuppressant therapy (NCT02382523)

SIGN: Fostamatinib (C-935788-050) oral Spleen tyrosine kinase (SYK) inhibitor, 24 weeks (NCT02112838)

Bortezomib in IgA nephropathy (NCT01103778)

Complement inhibition: OMS721 Monoclonal antibody targeting alternate lectin complement pathway.

** Lafayette at al. JASN 2017*

Conclusions

Better understanding of pathomechanistic of IgA nephropathy

Equipoise remains for corticosteroid use in IgA nephropathy

The current evidence suggest renal benefit in selected cohort but ongoing follow up or longer study duration will provide further clarity

Corticosteroid therapy is not without risk

The TESTING low dose study will assess the balance of efficacy and safety with low dose steroids

Emerging novel therapy for a safer treatment options for IgA nephropathy

Thank you

Baseline characteristics

Characteristics	Methylprednisolone (N=136)	Placebo (N=126)
Age - yr	38.6 ±11.5	38.6±10.7
Female sex – no. (%)	50 (36.8%)	46 (36.5)
Race – no. (%)		
Chinese	130 (95.6)	121(96.0)
Caucasian	5 (3.7)	3 (2.4)
South-East Asian	1 (0.7)	2(1.6)
Smoker - %	34 (25.0)	31 (24.6)
Body-mass index	24.4 ± 4.5	23.4 ± 3.7
Hypertension-no.(%)	71 (52.2)	52 (41.3)
Blood pressure - mmHg		
systolic	123.9 (14.7)	124.3 (11.6)
diastolic	79.3 (10.5)	79.8 (9.9)
Urine protein excretion – g/day	2.55 (2.45)	2.23 (1.11)
Serum creatinine – mg/dl	1.5 (0.6)	1.6 (0.6)
Estimated GFR – ml/min/1.73m2	59.6 (24.1)	58.5 (23.1)
Total Cholesterol – mg/dl	188.9 (39.0)	191.8 (51.1)
Oxford histological Score		
M1 lesion – no. (%)	76 (57.6)	75 (61.0)
E1 lesion – no. (%)	43 (31.6)	30 (23.8)
S1 lesion – no. (%)	94 (71.2)	89 (72.4)
T0/T1/T2 lesion – no. (%)	51(38.6%)/58(43.9)/23(17.4)	43(35.0)/60(48.8)/20(16.3)

*Plus–minus values are means ±SD

†The estimated glomerular filtration rate (GFR) was estimated with the use of the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation.

Baseline characteristics

Characteristics	Methylprednisolone (N=136)	Placebo (N=126)
Therapy - %		
ACE inhibitor	83 (61.0%)	74 (58.7%)
ARBs	56 (41.2%)	49(38.9%)
Maximum labelled dose of ACE inhibitor-no. (%)		
>80%	41 (49.4)	34 (45.9)
50-80%	33 (39.8)	29 (39.2)
<50%	9 (10.8%)	11 (14.9%)
Maximum labelled dose of ARB - no. (%)		
>80%	26 (46.4)	23 (46.9)
50-80%	27 (48.2)	23 (46.9)
<50%	3 (5.4)	3 (6.1%)

‡Patients received the maximum labelled dose according to the drug information.

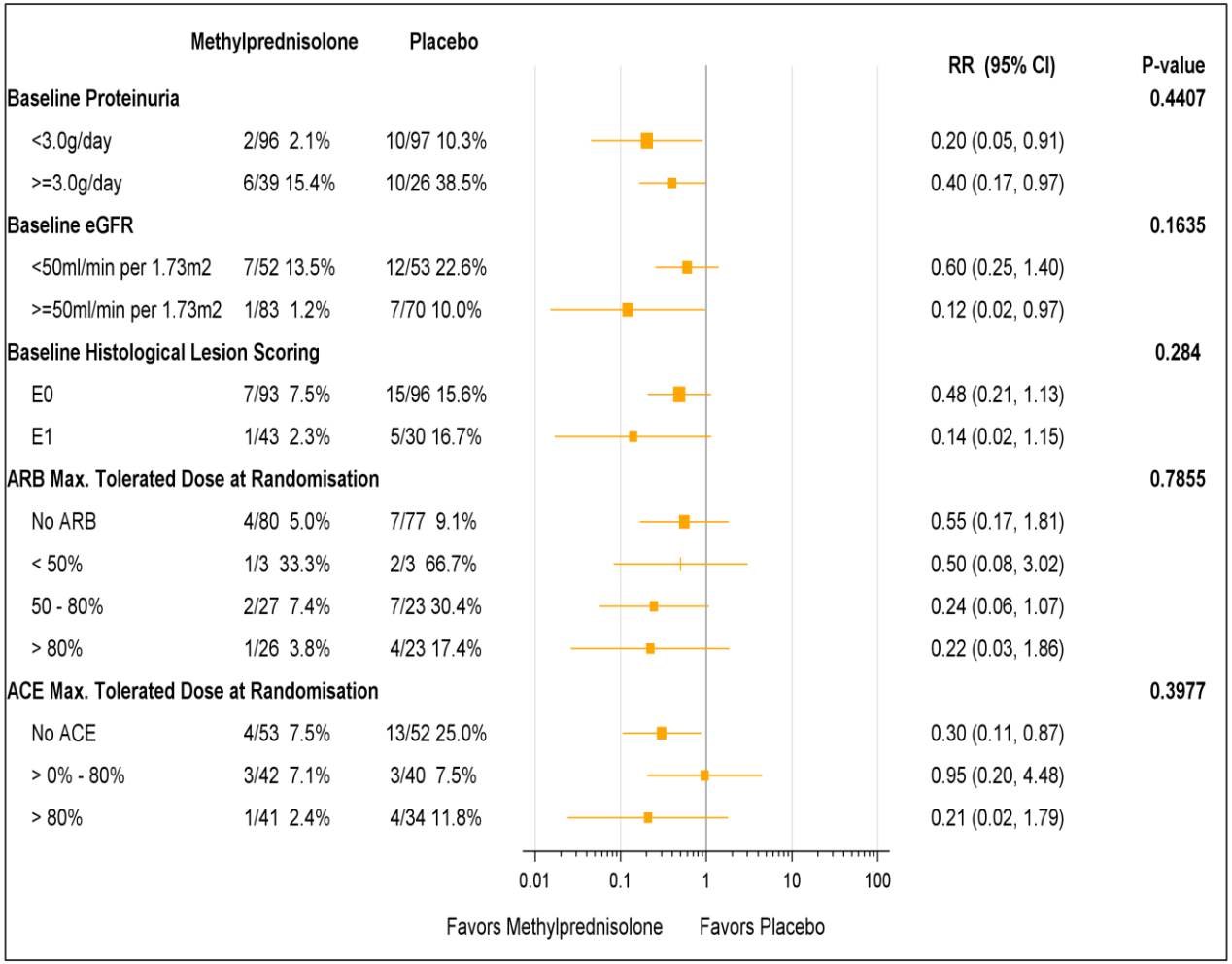
Relative effects of steroids on prespecified primary and secondary outcomes

Subgroup	Methylprednisolone group (N=136)	Placebo group (N=126)	P Value
Primary End Point			
40% estimated GFR decrease, ESKD or renal death – no.	8	20	**0.019**
Secondary End points			
40% estimated GFR decrease, ESKD or all death – no.	10	20	0.034
50% estimated GFR decrease, ESKD or all death – no.	10	15	0.293
40% estimated GFR decrease – no.	7	16	0.047
50% estimated GFR decrease – no.	7	11	0.330
ESKD or renal death – no.	4	9	0.156
Death – no.	2	1	1.000
[1]Rate of estimated GFR decline with method 1	-1.71	-6.78	0.031
[2]Rate of estimated GFR decline with method 2	-1.25	-4.42	0.005
time average proteinuria –g/day	1.37±1.08	2.36±1.67	p<0.001

[1] Method 1: defined for each individual patient using the slope from least squares linear regression of all eGFR estimates over time
[2] Method 2: defined as method 1, but excluding the treatment period with highest steroid exposure i.e. excluding eGFR values from month 1 and month 3

Lv et al. JAMA 2017

Predefined subgroup analyses
by baseline characteristics



Lv et al. JAMA 2017

Proteinuria during follow-up and GFR decline including TESTING and STOP-IgAN