IgA Nephropathy: An update on clinical trials

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Disclosures

- Relationships with commercial interests:
  - Grants: Roche
  - Honorarium/consulting: None

Outline

1. Introduction to IgAN
2. Review evidence for steroids in IgAN
3. Review evidence for cyclophosphamide in non-crescentic IgAN
4. New clinical trials:
    - STOP-IgAN trial
    - TESTING trial
5. Integrate the evidence into clinical practice

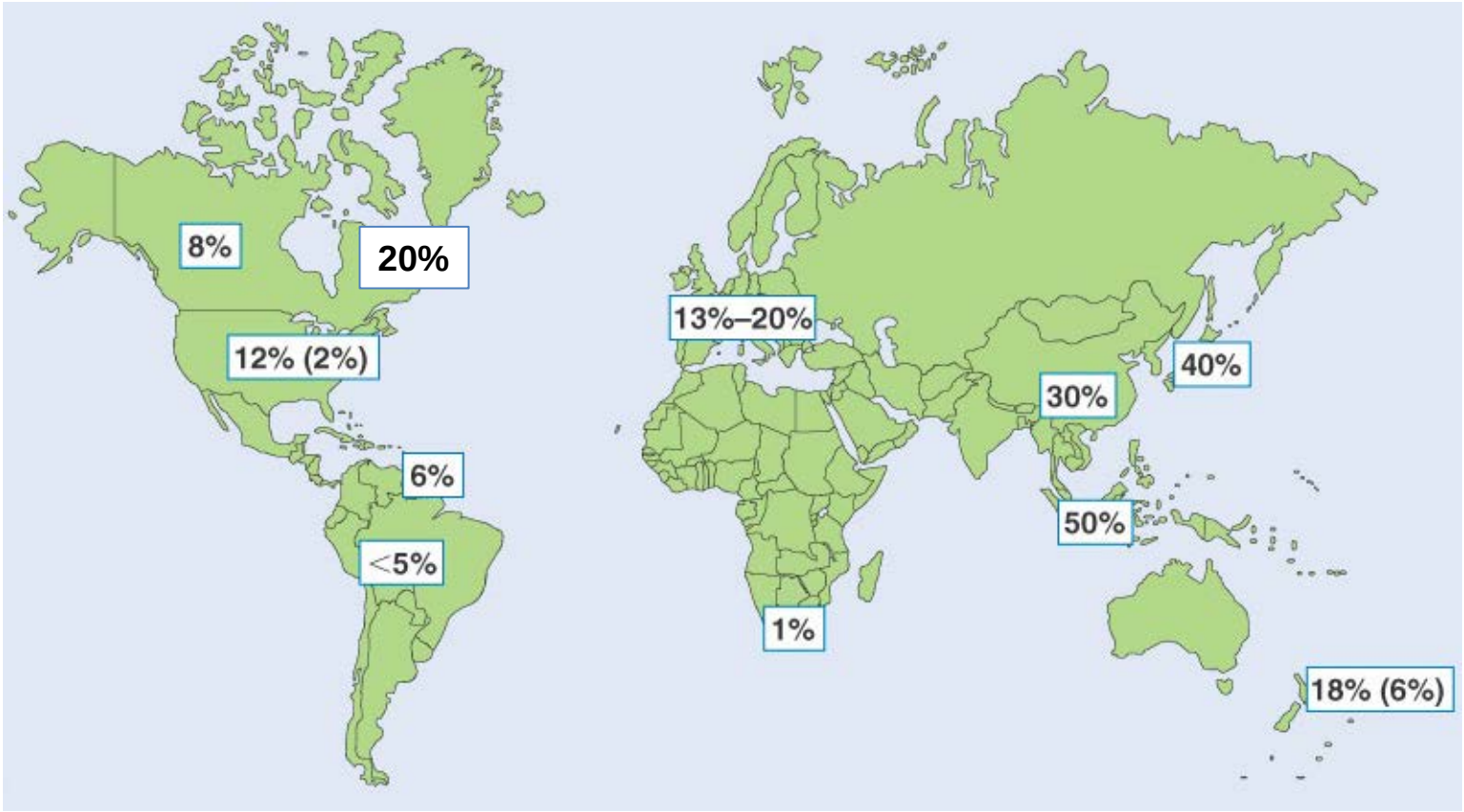
Review of IgAN

IgAN

- Worldwide is the most common type of GN
    - More common in Asia than Europe or N. America
    - Uncommon in Blacks
- Very important cause of ESRD in Asian countries
    - Childhood urine screening programs
- Typically presents in 20-30’s, equal male/female
- In Canada, may be increasing in prevalence
    - Due to demographic changes from immigration

IgAN prevalence world-wide

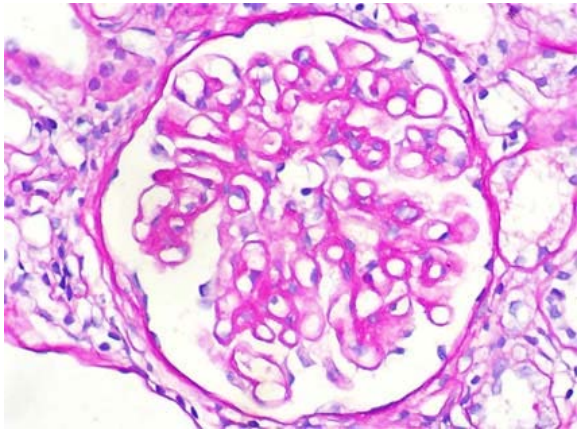
- Proportion of biopsy-proven GN cases due to IgAN:



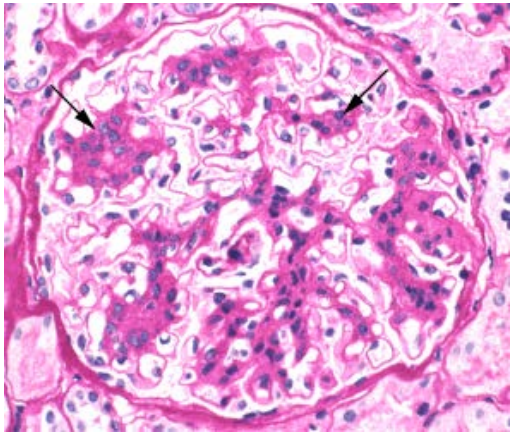
The percentage of biopsy-proven GN cases that are IgAN: Comprehensive clinical nephrology 3rd edition, Feehally

IgAN

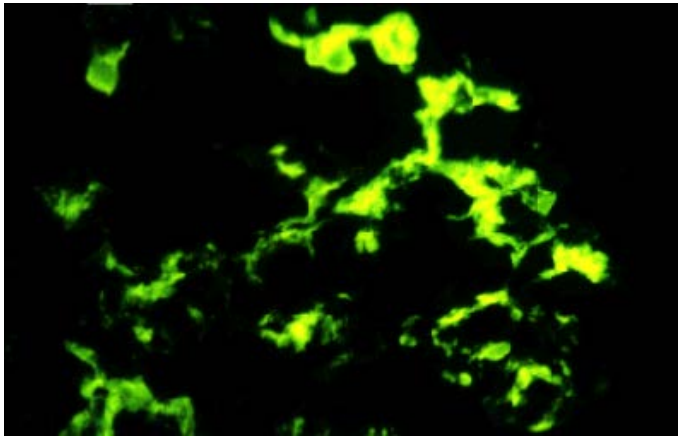
- Characterized by IgA deposits on the kidney biopsy
- Most commonly mild proliferative features



Normal glomerulus



Mesangial hypercellularity
Mesangial expansion



Mesangial IgA deposits

IgAN: clinical presentation

- Disease severity in IgAN is highly variable:

Asymptomatic hematuria

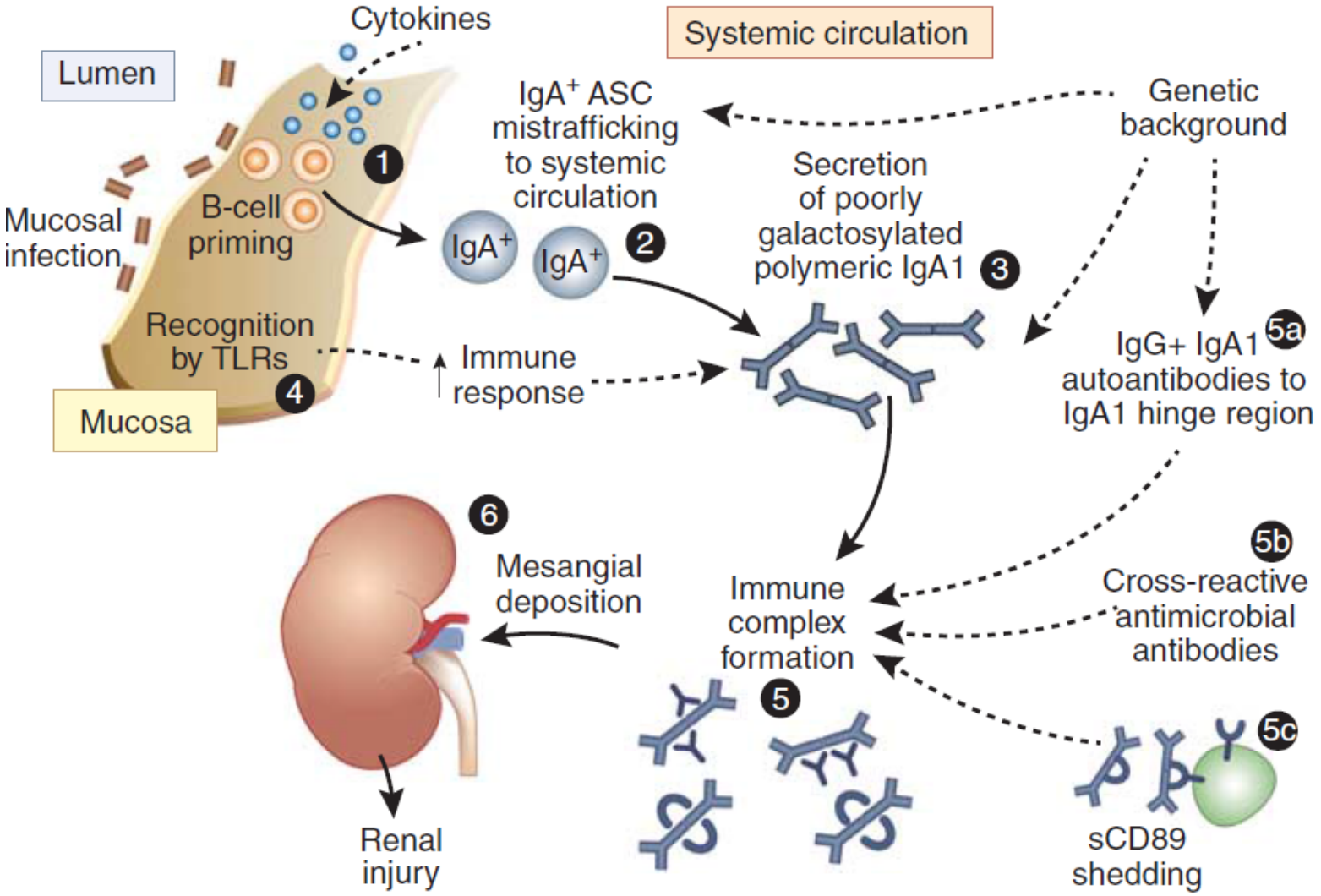
Slowly progressive proteinuric renal disease

Rapidly progressive glomerulonephritis

Severe nephrotic syndrome

- 40% have recurrent gross hematuria in context of viral infections (“synpharyngitic”)
- Most have asymptomatic slowly progressive proteinuric renal disease
- <10% have severe presentations:
    - RPGN or severe NS

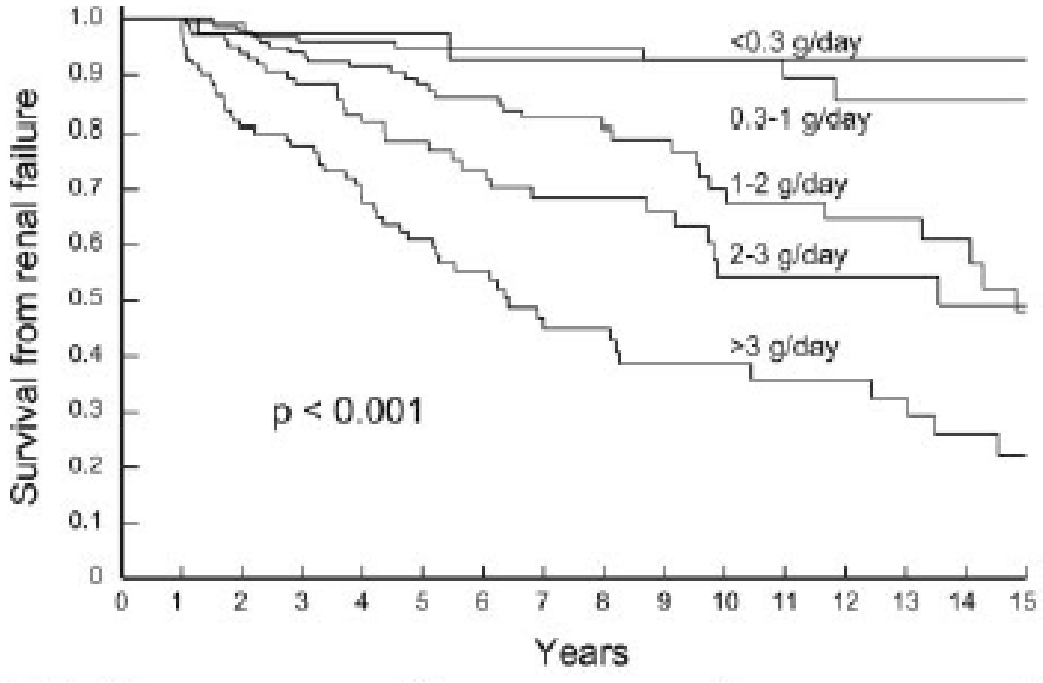
IgAN: pathogenesis



Boyd, KI 2012

IgAN: risk stratification

- Clinical problem:
  - Slowly progressive disease, largely asymptomatic
  - How do you identify IgAN patients at high enough risk of renal progression that they would benefit from IS?



Good prognosis with proteinuria <1g/day

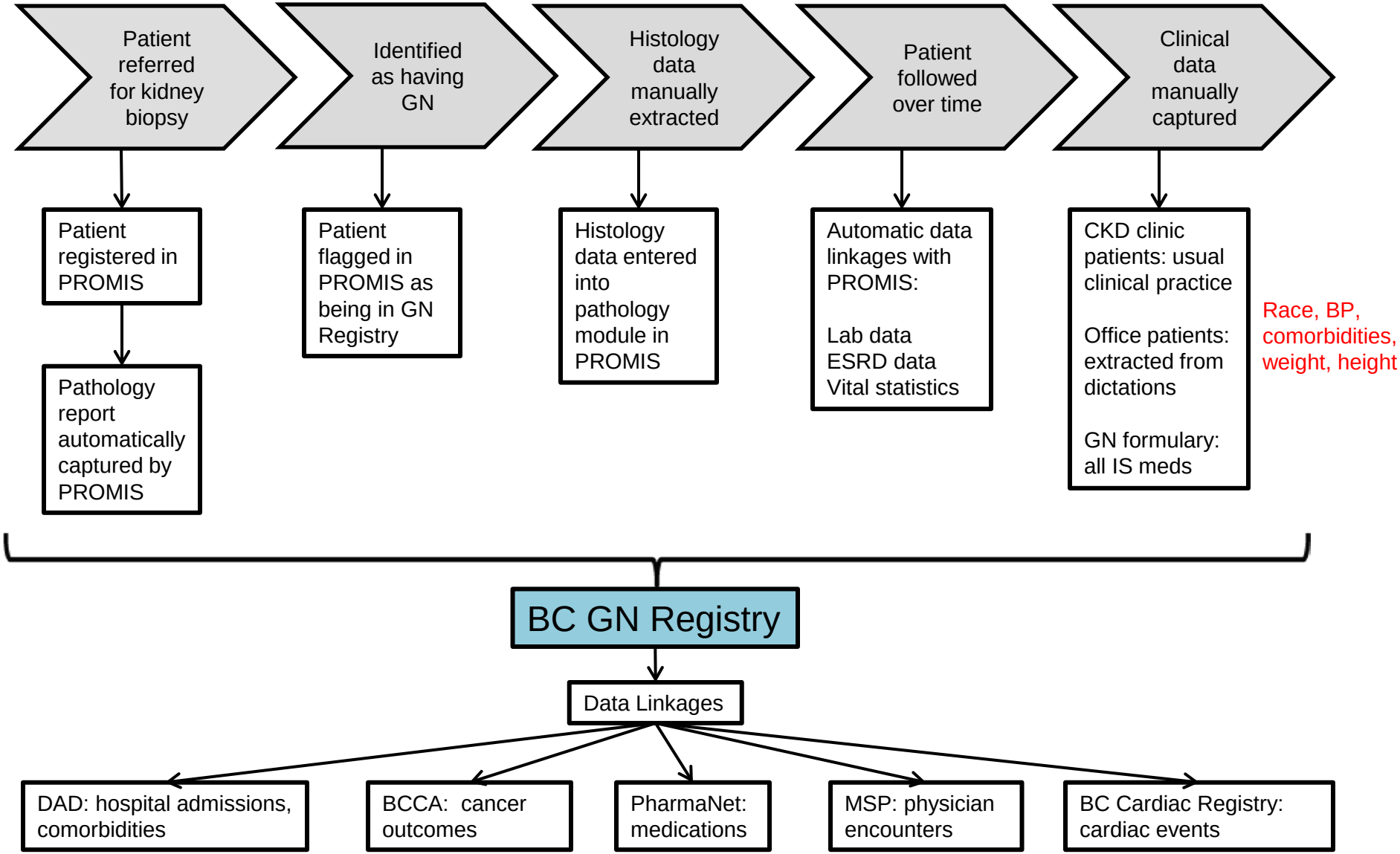
Reich, JASN 2007

IgAN: treatment approach

- According to 2012 KDIGO guidelines:
  1. Maximize conservative therapy
     - RASB
     - BP control
  2. Consider steroid IS only patients at highest risk most likely to benefit
     - Proteinuria >1g/d
     - eGFR>50
  3. Avoid steroid IS in those with advanced disease
     - eGFR<30
  4. Consider rare variants of IgAN separately
     - Crescentic IgAN
     - MCD variant IgAN

IgAN in BC

BC GN Registry: started in 2013



IgAN is the most common type of GN in Canada

BC GN Registry data: March 2013 – March 2016:

	Total Number	Number per Year	Percent of yearly GN	Incidence per 100000/yr
All types of GN (N)	954	318	100%	8.24
IgA Nephropathy	186	62	19.5%	1.61
MCD	52	17	5.5%	0.44
Pauci-immune GN	134	45	14.0%	1.16
Membranous N.	100	33	10.5%	0.86
Lupus Nephritis	99	33	10.4%	0.86
FSGS (all)	148	49	15.5%	1.28
FSGS (idiopathic)	32	11	3.4%	0.27

Incidence based on population estimates from BC Stats

GN as a cause of prevalent ESRD in Canada in 2010: CORR Report

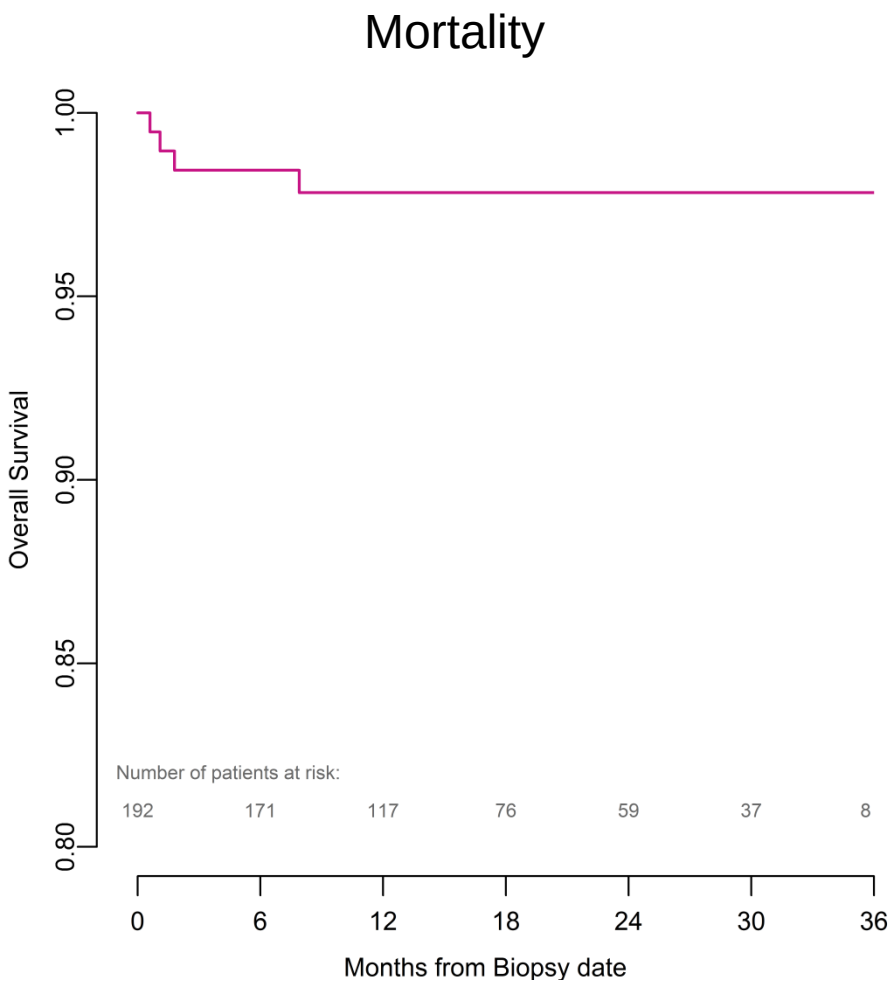
		HD	PD	TX	Total
Total	**N**	**19,076**	**4,110**	**16,164**	**39,350**
	RPMP	**559.3**	**120.5**	**473.9**	**1,153.7**
Diagnosis					
Diabetes	N	6,550	1,240	2,577	**10,367**
	RPMP	192.0	36.4	75.6	**303.9**
	%	34.3	30.2	15.9	**26.3**
Glomerulonephritis	N	2,627	745	5,236	**8,608**
	RPMP	77.0	21.8	153.5	**252.4**
	%	13.8	18.1	32.4	**21.9**
Renal Vascular Disease	N	3,294	743	1,046	**5,083**
	RPMP	96.6	21.8	30.7	**149.0**
	%	17.3	18.1	6.5	**12.9**
Pyelonephritis	N	867	167	1,352	**2,386**
	RPMP	25.4	4.9	39.6	**70.0**
	%	4.5	4.1	8.4	**6.1**
Polycystic Kidney Disease	N	858	221	1,860	**2,939**
	RPMP	25.2	6.5	54.5	**86.2**
	%	4.5	5.4	11.5	**7.5**
Drug Induced	N	337	67	209	**613**
	RPMP	9.9	2.0	6.1	**18.0**
	%	1.8	1.6	1.3	**1.6**
Other	N	1,966	393	2,454	**4,813**
	RPMP	57.6	11.5	71.9	**141.1**
	%	10.3	9.6	15.2	**12.2**
Unknown	N	2,577	534	1,430	**4,541**
	RPMP	75.6	15.7	41.9	**133.1**
	%	13.5	13.0	8.8	**11.5**

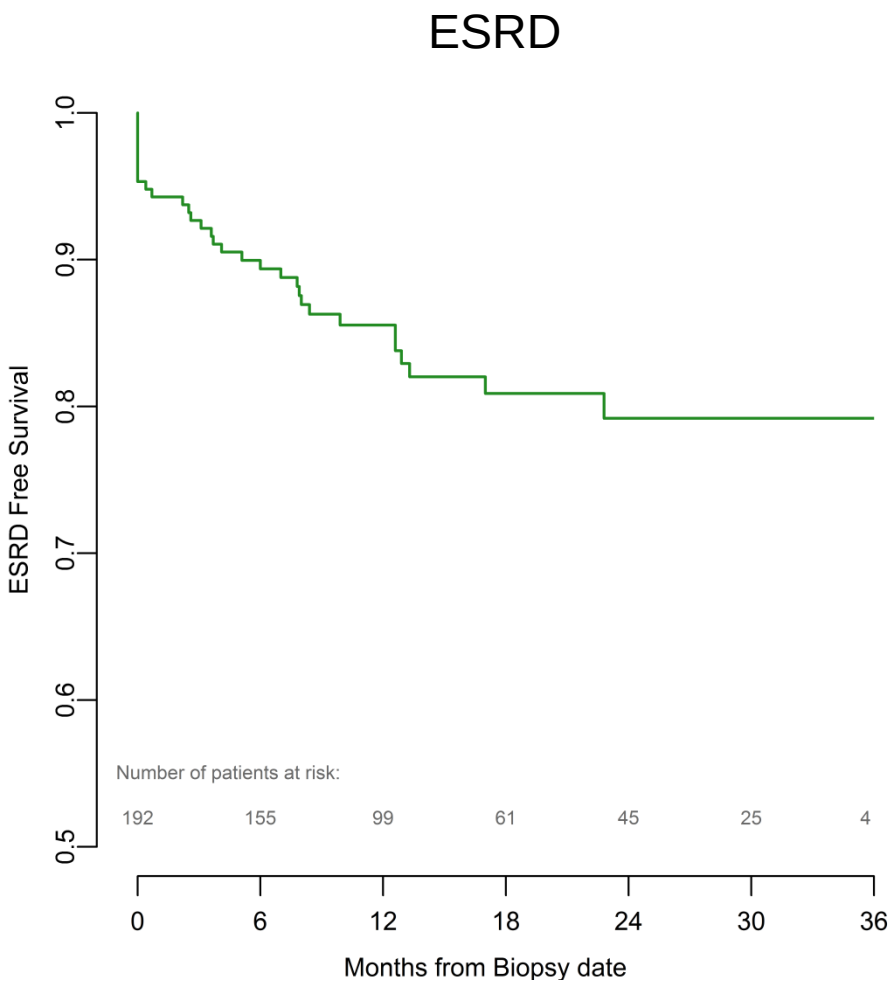
IgAN in BC: characteristics at biopsy

	IgAN	MN	FSGS (idiopathic)
Age (years)	44 [35 , 59]	61 [52 , 67]	52 [32 , 70]
Sex (% male)	66.2%	54.5%	56.5%
Creatinine (µmol/L)	154 [106 , 253]	95 [73 , 128]	83 [60 , 166]
eGFR (ml/min/1.73m^2)	38 [20 , 66]	64 [43 , 94]	81 [36 , 111]
Proteinuria (g/day)	1.3 [0.6 , 2.2]	3.8 [2.2 , 6]	4.3 [1.6 , 9.2]
<1g/d	37.8%	11.9%	14.3%
1-4g/d	50.4%	40.3%	28.6%
4-8g/d	9.2%	31.3%	28.6%
>8g/d	2.5%	16.4%	28.6%

BC GN Registry data: March 2013 – March 2016

IgAN in BC: outcomes





Steroids in IgAN

Major steroid trials in IgAN

Corticosteroids in IgA nephropathy: a randomised controlled trial

Claudio Pozzi, PierGiorgio Bolasco, GianBattista Fogazzi, Simeone Andrulli, Paolo Altieri, Claudio Ponticelli, Francesco Locatelli

Lancet, 1999, vol 353, March 13

Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy

Carlo Manno, Diletta Domenica Torres, Michele Rossini, Francesco Pesce and Francesco Paolo Schena

NDT, 2009, vol 24, 3694-3701

Combination Therapy of Prednisone and ACE Inhibitor Versus ACE-Inhibitor Therapy Alone in Patients With IgA Nephropathy: A Randomized Controlled Trial

Jicheng Lv, MD,[1,2] Hong Zhang, MD, PhD,[1,2] Yuqing Chen, MD,[1,2] Guangtao Li, MD,[1,2] Lei Jiang, MD,[1,2] Ajay K. Singh, MB, FRCP,[3] and Haiyan Wang, MD[1,2]

AJKD, 53(1), 2009, p26-32

Pozzi trial

- Italian RCT of 86 patients from 1987-1995 with:
  - IgAN on biopsy
  - Age 15-69 years
  - Cr≤ 133µmol/L
  - Proteinuria 1-3.5g/d
- Open-label, non-blinded, randomized to:
  - Steroids: IV methylprednisolone 1g daily x 3 days months 1, 3 and 5, prednisone 0.5mg/kg EOD for 6 months
  - Supportive care
- Median follow-up 4 years

Lancet, 1999, vol 353, March 13

Pozzi trial: baseline characteristics

Characteristic	Control group (n=43)	Steroid group (n=43)
Clinical		
Duration of IgA nephropathy (months)	24 (4–48)	24 (8–52)
Age (years)	40 (29–51)	38 (26–45)
Urine protein excretion (g/day)	1·8 (1·4–2·4)	2·0 (1·6–2·4)
Plasma creatinine (μmol/L)	88·4 (79·6–114·9)	97·2 (79·6–114·9)
Creatinine clearance (mL/min)*	87 (72–112)	93 (70–111)
Male/female	31/12	30/13
Hypertension	15	14
Treatment with ACE inhibitors	6	6
Macrohaematuria	17	8

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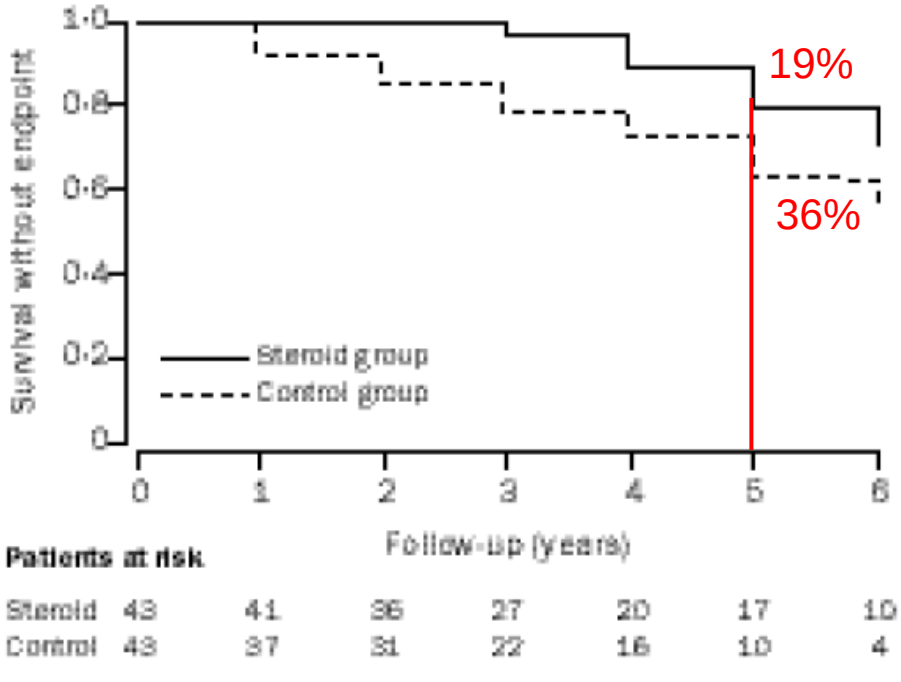
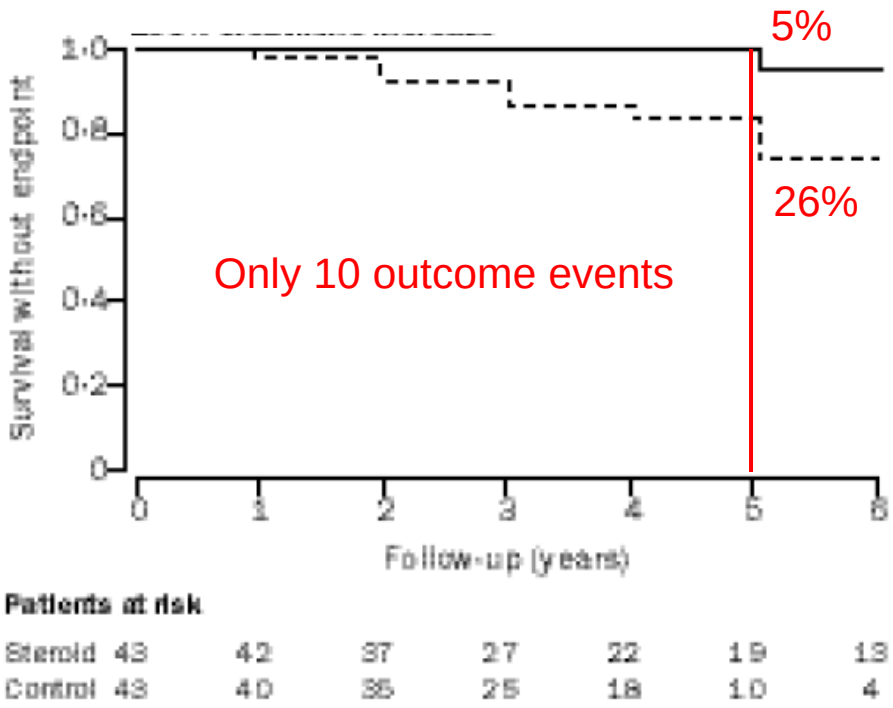
ACEi:
Baseline: 12 pts
Follow-up: 36 pts
Equal b/w groups

Pozzi trial: renal outcomes

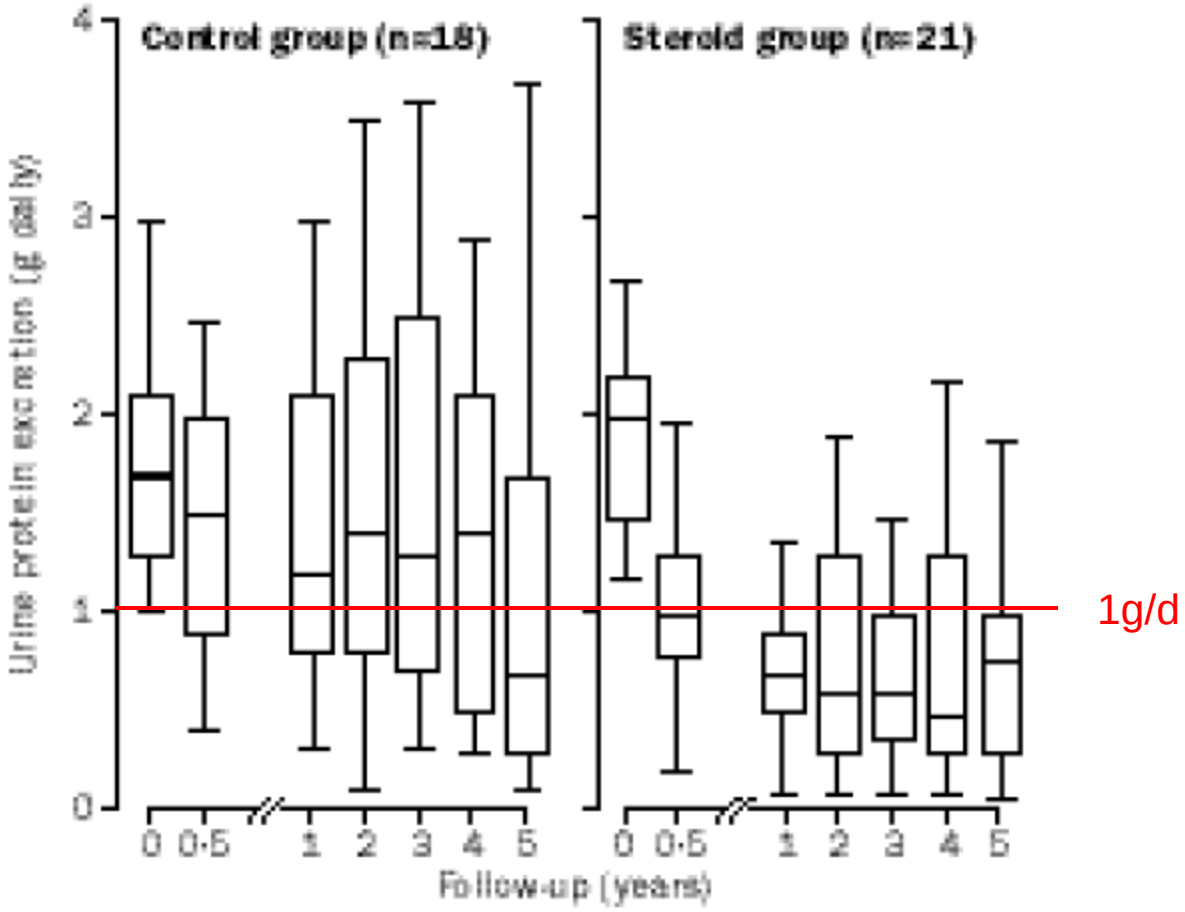
50% increase creatinine



100% increase creatinine



Pozzi trial: proteinuria

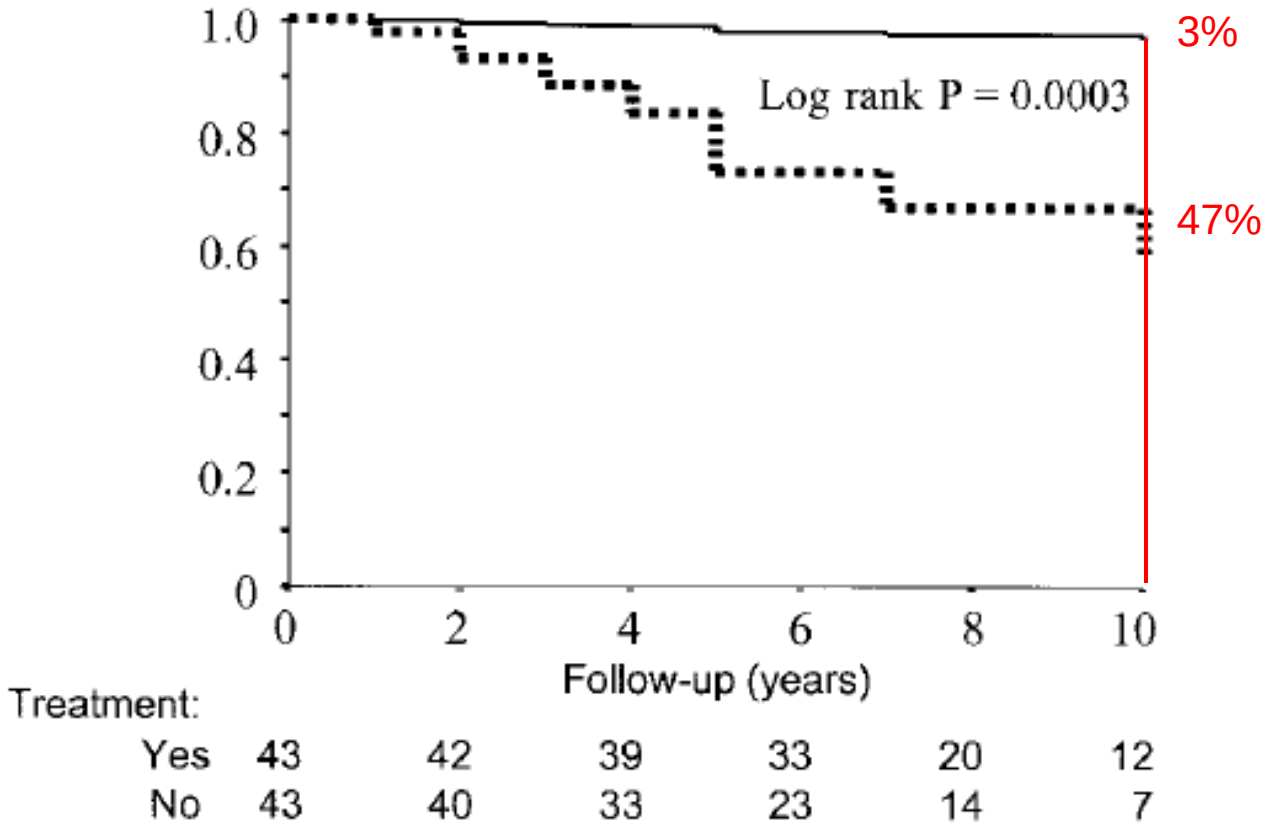


Pozzi trial: adverse events

- Not well captured or reported
- Describe “no major side-effects” in the 6 months of steroid treatment

Pozzi trial: long-term follow-up

100% increase creatinine



J Am Soc Nephrol 15: 157–163, 2004

Manno trial

- Italian RCT of 97 patients from 2000-2004 with:
  - IgAN on biopsy within 1 year
  - Manno grade G2
  - Age 15-70 years
  - eGFR ≥ 50ml/min/1.73m^2
  - Proteinuria ≥ 1g/d
- Open-label, non-blinded, randomized to:
  - Prednisone + ramipril: prednisone 1mg/kg/d x 2 months then tapered 0.2mg/kg per month, ramipril goal BP<120/80 and proteinuria <1g/d
  - Ramipril alone
- All patients had ACEi/ARB withdrawn prior to entering trial

NDT, 2009, vol 24, 3694-3701

Manno histologic grading system

- G1: minor or minimal lesions
- G2 any of:
  - Focal or diffuse mesangial proliferative lesions (>6 cells/mesangial region)
  - Endocapillary proliferation
  - Crescents in <50% of glomeruli
  - Segmental sclerosis only
  - IFTA in <1/3 of the cortical area
- G3 any of:
  - Crescents in >50% of glomeruli
  - Global sclerosis in >1/3 of glomeruli
  - Segmental sclerosis in >50% of glomeruli
  - IFTA in >1/3 of the cortical area
- Reproducibility and validity are not well studied

Manno trial: baseline characteristics

Characteristics	Ramipril alone ($n = 49$)	Prednisone plus ramipril ($n = 48$)
Mean age (years)	34.9 ± 11.2	31.8 ± 11.3
Gender (M:F)	35:14	33:15
Onset type (microhaematuria) (n)	16	14
Body weight (kg)	67.2 ± 8.9	68.1 ± 7.6
Body mass index (kg/m^2)	23.2 ± 2.1	23.5 ± 1.9
Current smokers (%)	12	14
Previous smokers (%)	18	21
Systolic blood pressure (mmHg)	123.4 ± 8.2	123.5 ± 10.3
Diastolic blood pressure (mmHg)	81.5 ± 6.7	81.3 ± 6.9
Serum creatinine (mg/dl)	1.07 ± 0.26	1.08 ± 0.32
eGFR (ml/min/1.73 m^2)	97.5 ± 27.7	100.4 ± 26.1
Proteinuria (g/24 h)	1.5 (1.4–2.3)	1.7 (1.2–2.5)
Follow-up (months)	57.2 (31.4–77.2)	63.0 (45.3–83.4)

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Off RASB

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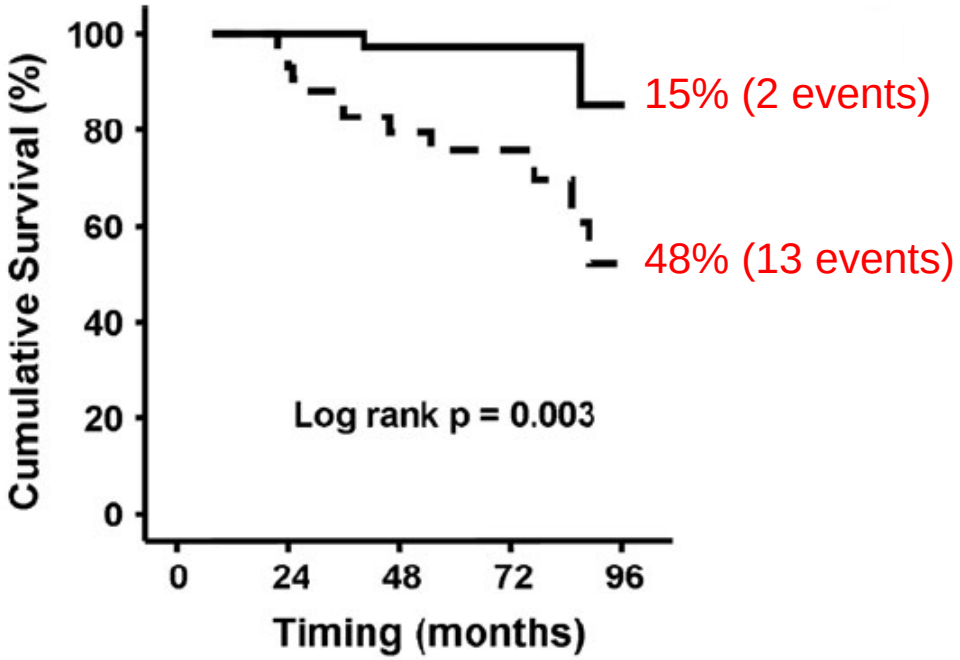
Median follow-up 5 years, trial stopped after early after 97/120 patients enrolled

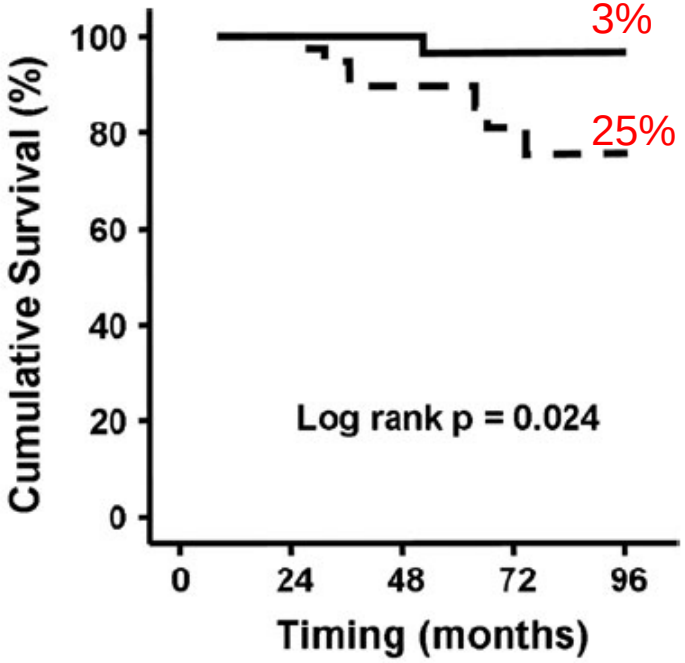
Manno trial: 8-year renal outcomes

Doubling creatinine or ESRD



Patients at risk					
Prednisone + Ramipril	48	37	32	19	4
Ramipril	49	40	24	13	6

ESRD



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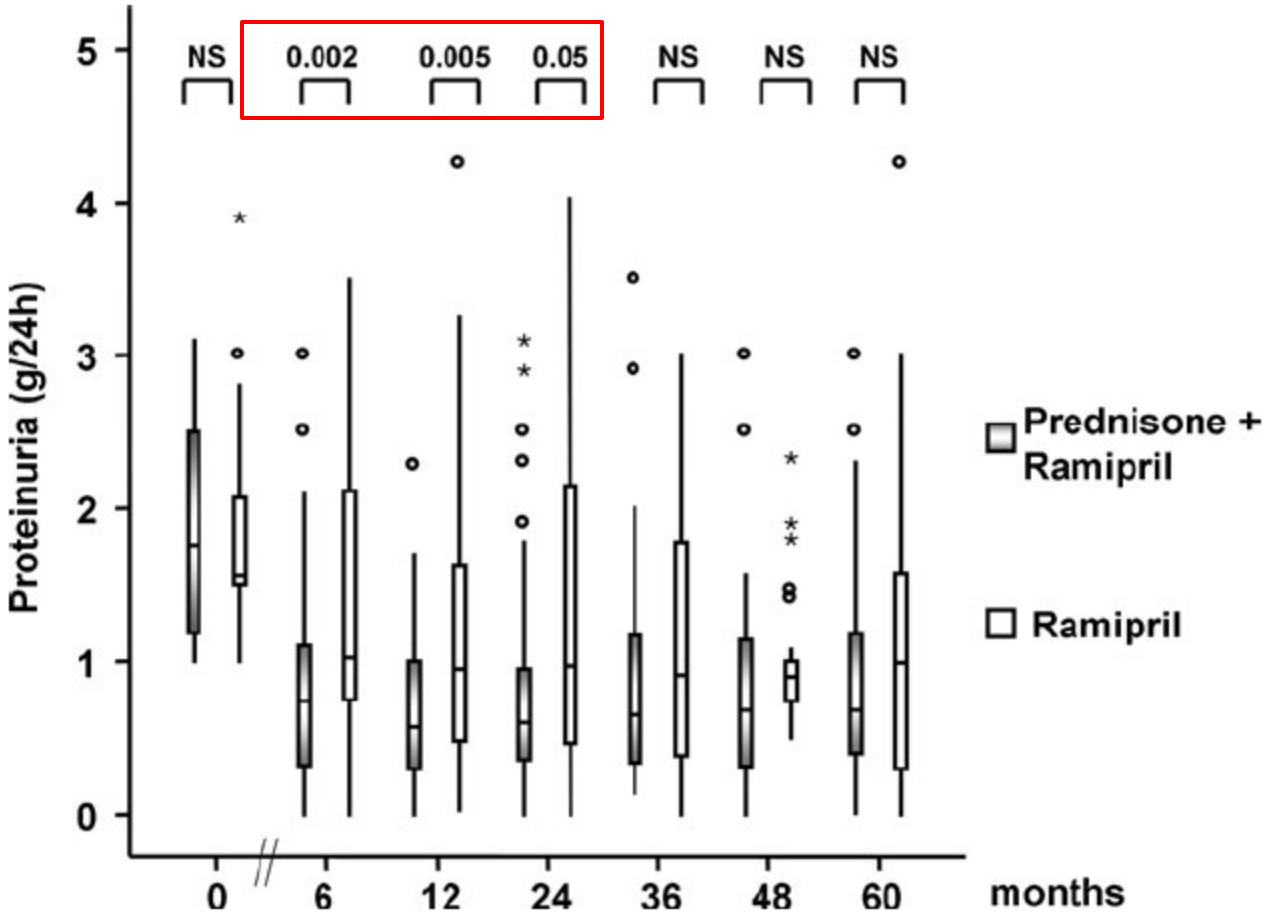
Manno trial: proteinuria



Manno trial: adverse events

- Not well captured or reported
- Describe no serious adverse events
- 3/48 patients in the steroid group had striaie or glucose intolerance

Lv trial

- Chinese RCT of 63 patients from 2004-2006 with:
  - IgAN on biopsy within 1 year
  - Age 18-65 years
  - GFR ≥ 30ml/min/1.73m^2
  - Proteinuria 1-5g/d
- Open-label, non-blinded, randomized to:
  - Prednisone + cilazipril: prednisone 1mg/kg/d x 8 weeks, then tapered over total 6-8 months, cilazipril goal BP <125/75
  - Cilazpril alone
- All patients had ACEi/ARB withdrawn prior to entering trial

AJKD, 53(1), 2009, p26-32

Lv trial: baseline characteristics

Characteristics	ACE-Inhibitor Group (n = 30)	Combination Group (n = 33)
Clinical		
Age (y)	30.43 ± 8.8	27.8 ± 8.9
Men/women	19/11	20/13
Systolic blood pressure (mm Hg)	119.1 ± 2.5	123.3 ± 2.3
Diastolic blood pressure (mm Hg)	75 ± 2.2	78.3 ± 2.4
Serum creatinine (mg/dL)	1.1 ± 0.3	1.1 ± 0.3
Patients with serum creatinine > 1.5 mg/dL	3 (10)	4 (12.1)
eGFR (mL/min.1.73 m^2)	101.5	101.2
Distribution of eGFR (>90/60-89/40-59 mL/min/1.73 m^2)	19/9/2	20/12/1
Urine protein excretion (g/d)	2.0 ± 0.8	2.5 ± 0.9
Follow-up (mo)	28 ± 7	26 ± 8

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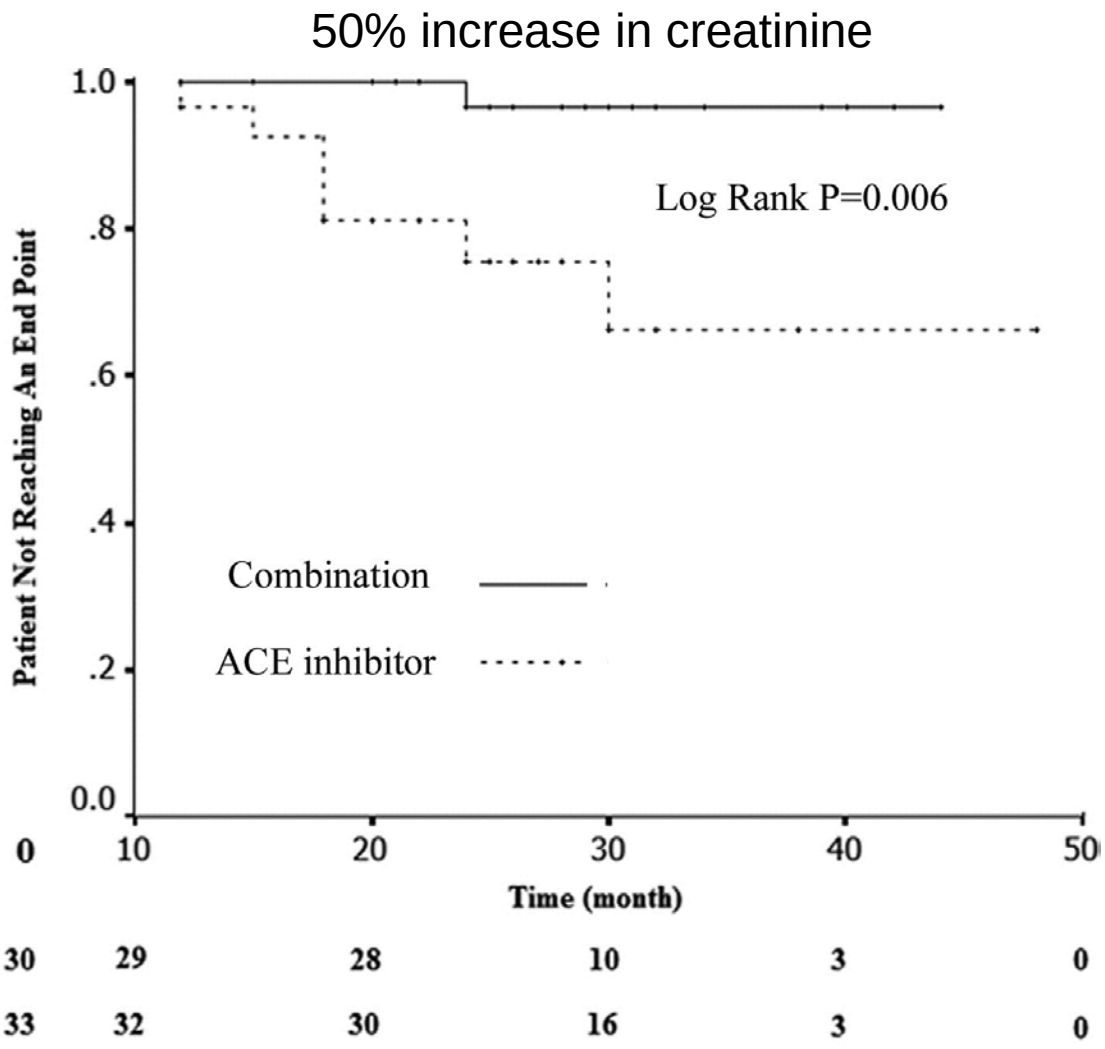
Median follow-up 27 months, trial stopped early after 2 years

Lv trial: renal outcome



3-year risk

3.4%

33.8%

Only 8 outcome events

Lv trial: adverse events

- Not well captured or reported
- Describe no serious adverse events

Summary of 3 major steroid trials

- All suggest benefit of steroids in those with preserved eGFR and proteinuria≥1g/d
- All used a surrogate renal endpoint based on Δ renal function
    - CKD surrogate outcome analyses support 57% and 40% decline in eGFR (less for 30%)
        - » Inker AJKD 2014, Levey, AJKD 2014, NKF and FDA workshop
    - Pozzi/Manno: doubling creatinine ~ 57% decline in eGFR
    - Lv: 50% increase creatinine ~38% decline eGFR less clear

Summary of 3 major steroid trials

- All have limitations:
  - Single ethnic groups: Caucasian (Italian), Chinese
  - RASB: none (Pozzi), not maximized prior (Manno/Lv)
  - Non-blinded, open label
  - Small studies, short term: very few outcome events, Lv/Manno stopped early
  - Inconsistent capture of AE with side-effect profile not seen in clinical practice
  - Generalizability: lower eGFR, other histology groups

CLINICAL RESEARCH www.jasn.org

Corticosteroid Therapy in IgA Nephropathy

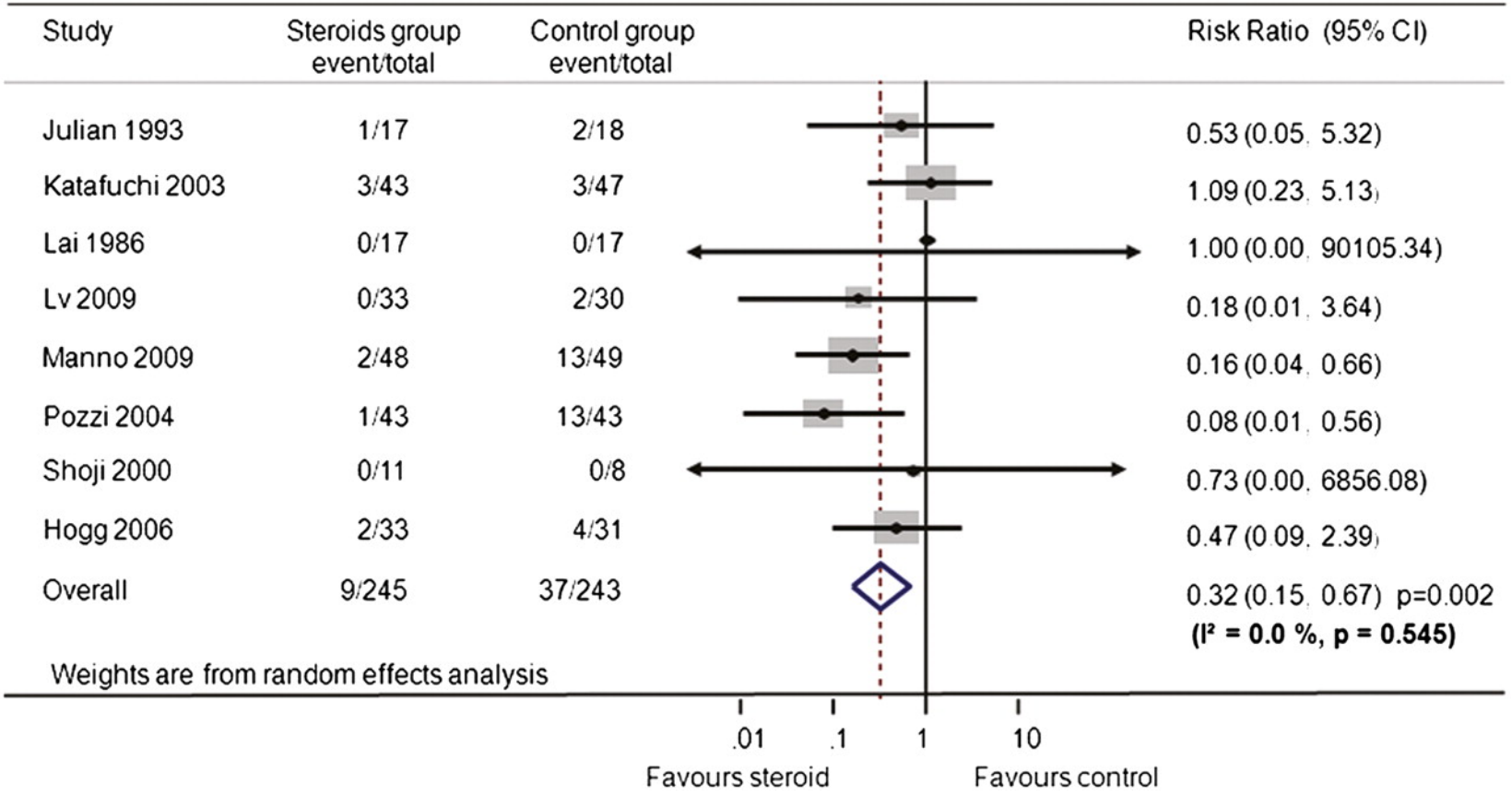
Jicheng Lv,* Damin Xu,* Vlado Perkovic,† Xinxin Ma,* David W. Johnson,‡§ Mark Woodward,†‖ Adeera Levin,¶ Hong Zhang,* and Haiyan Wang,* for the TESTING Study Group

JASN

Study quality: potential for bias

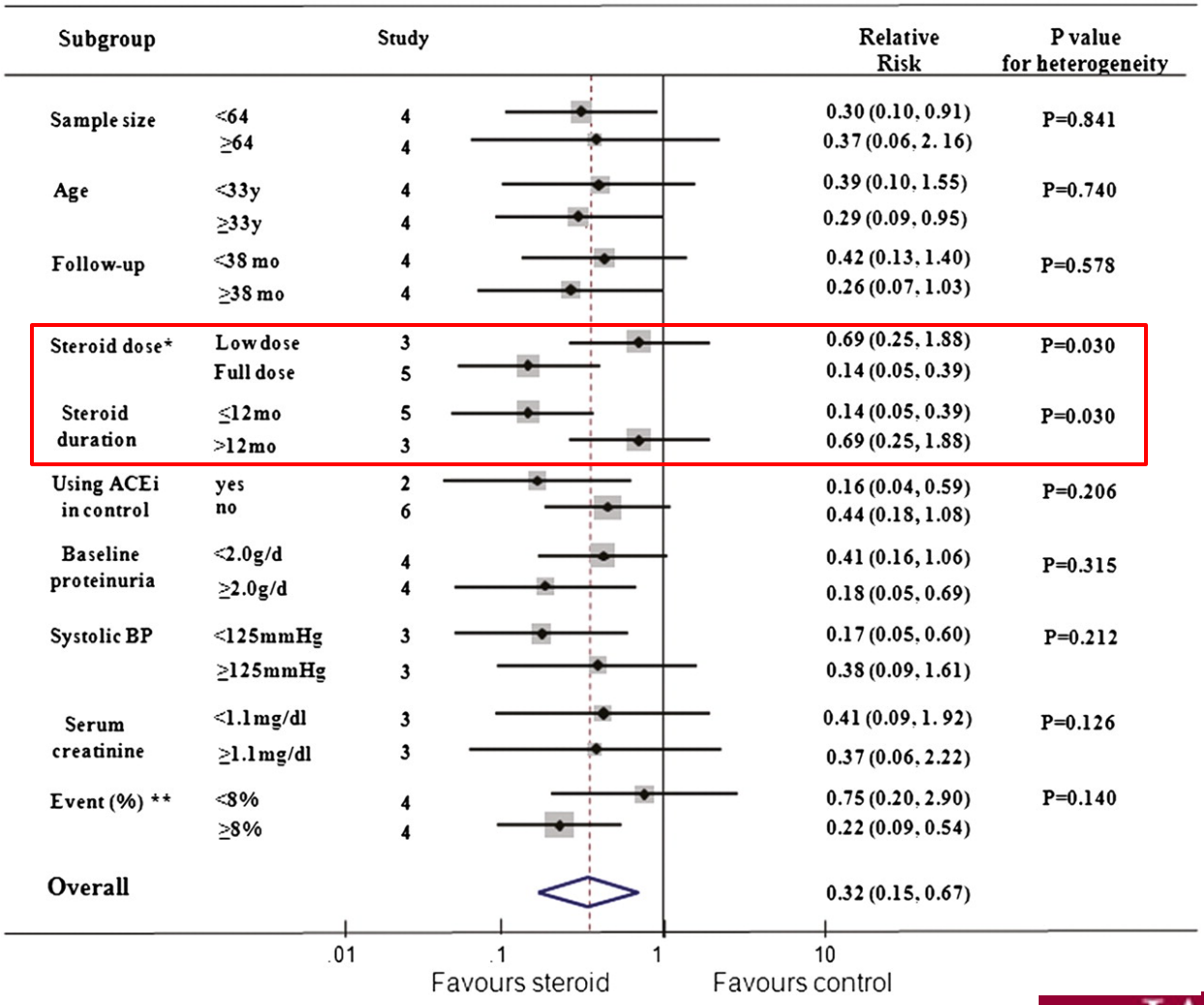
	Lai 1986	Julian 1993	Shoji 2000	Katafushi 2003	Pozzi 2004	Hogg 2006	Koike 2008	Lv 2009	Manno 2009
Allocation concealment*	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes
Blinding of patients†	No	No	No	No	No	Yes	No	No	No
Blinding of investigators†	No	No	No	No	No	Yes	No	No	No
Blinding of outcome assessors†	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear
Blinding of data analysts†	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear
Analysis by intention-to-treat principle‡	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Incomplete outcome data <10%§	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes

Effect of steroids on composite renal endpoint (ESRD or doubling of serum creatinine or halving of GFR) in patients with IgA nephropathy.



Jicheng Lv et al. JASN 2012;23:1108-1116

Subgroup analysis for the effect of corticosteroid on composite renal endpoint (ESRD or doubling in serum creatinine or halving of GFR)



Jicheng Lv et al. JASN 2012;23:1108-1116

Cyclophosphamide in non-crescentic IgAN

Ballardie trial

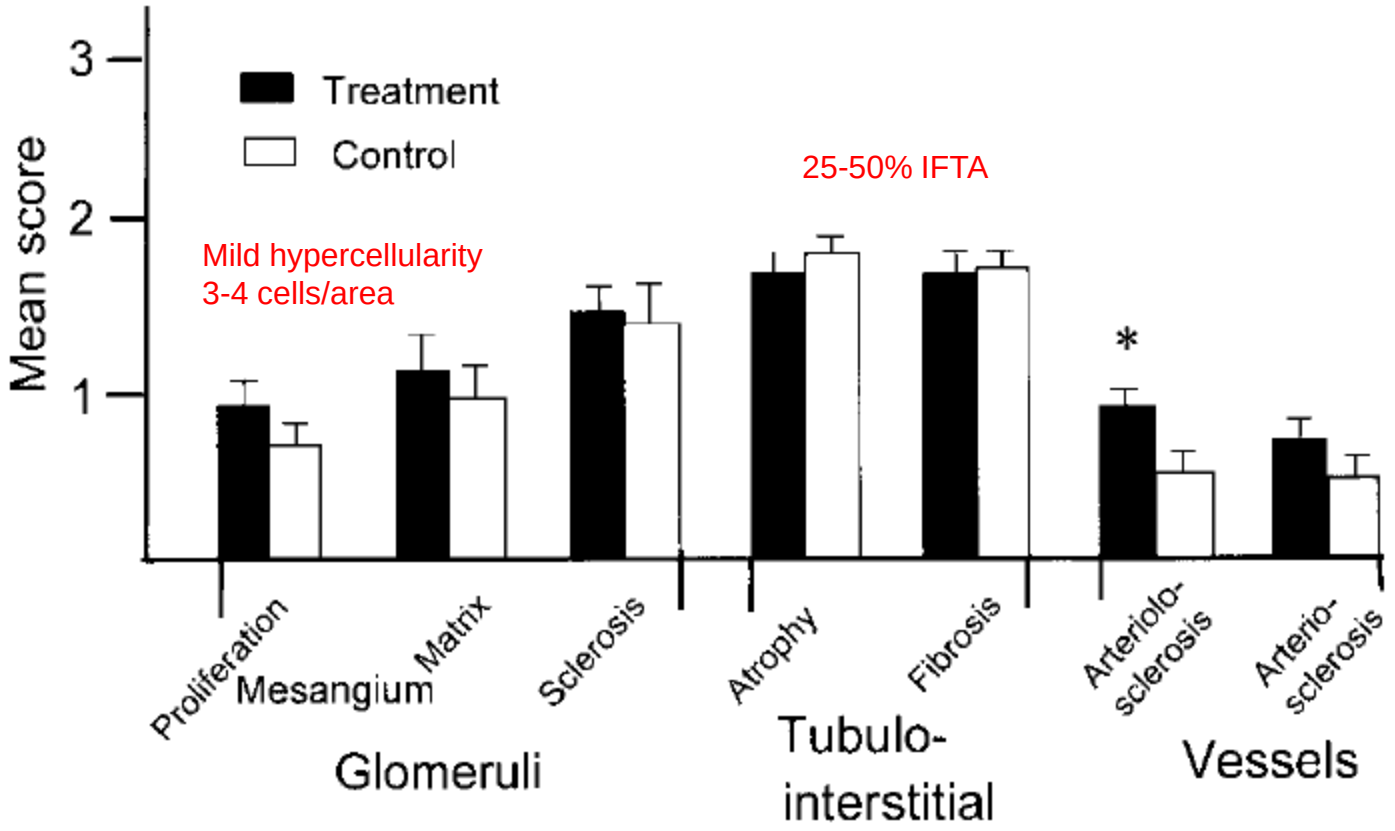
- Single centre UK RCT of 38 patients from 1991-1996 with:
    - IgAN on biopsy
    - Cr>130µmol/L (but <250µmol/L)
    - Documented increase in Cr by ≥15% in prior 12 months thought due to active IgAN
- Open-label, non-blinded, randomized to:
    - Prednisolone 40mg/d tapered to 10mg/d, cyclophosphamide 1.5mg/kg/d for 3 months then azathioprine 1.5mg/kg/d, continued indefinitely, with supportive care
    - Supportive care: goal BP <160/90
- RASB not universally used, dose could not be changed

J Am Soc Nephrol 13: 142–148, 2002

Ballardie trial

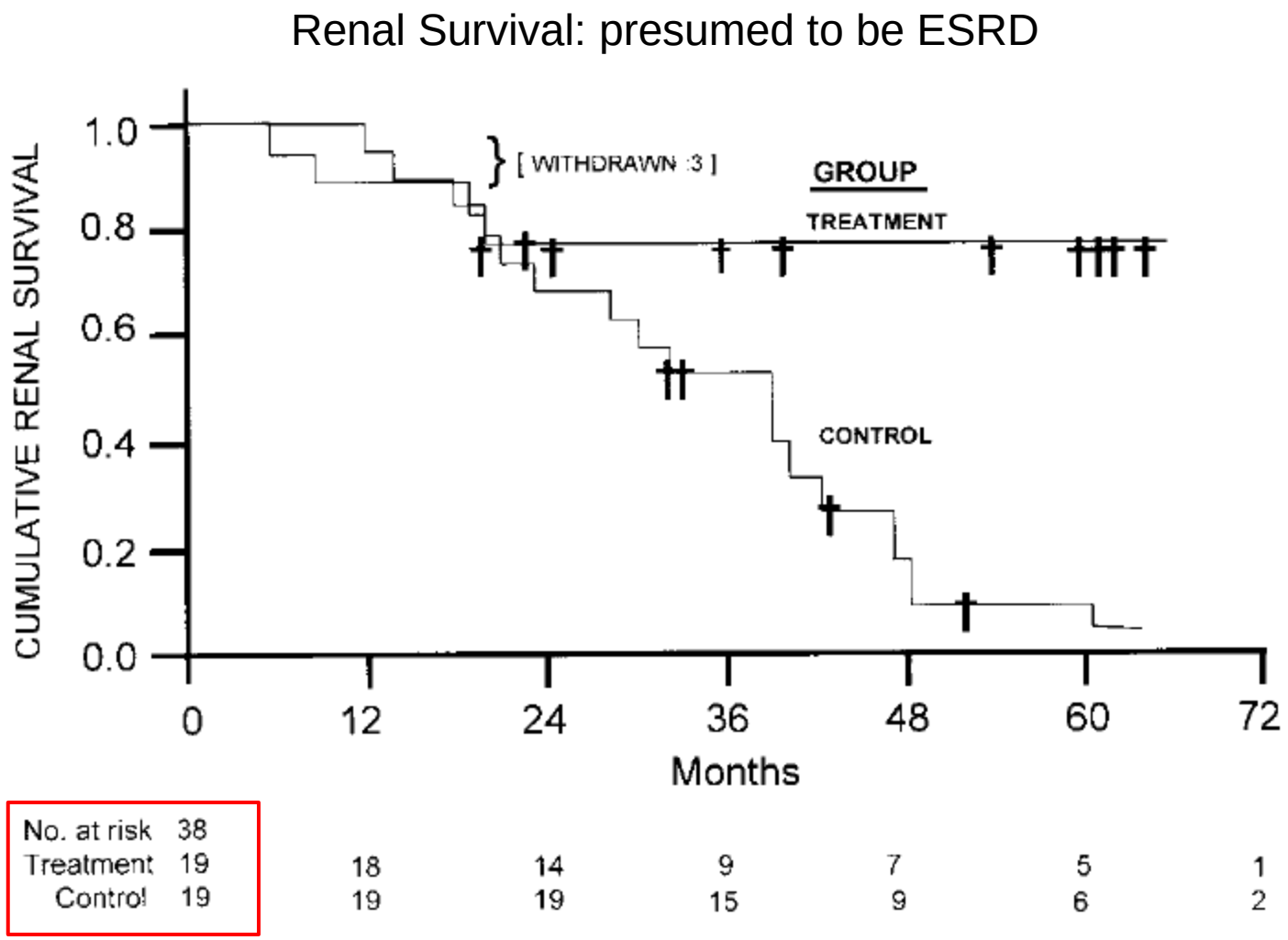
- Multiple methodologic issues that increase the risk of bias:
  - No primary outcome described (presumed to be ESRD)
  - No sample size calculation, small trial (N=38)
  - Randomization, allocation concealment not described
  - Un-blinded, open-label
  - No “Table 1” baseline description of two treatment groups
  - Not clear if intension-to-treat analysis

Ballardie trial: baseline histology



No patients had crescents
Focal endocapillary hypercellularity

Ballardie trial: renal outcome

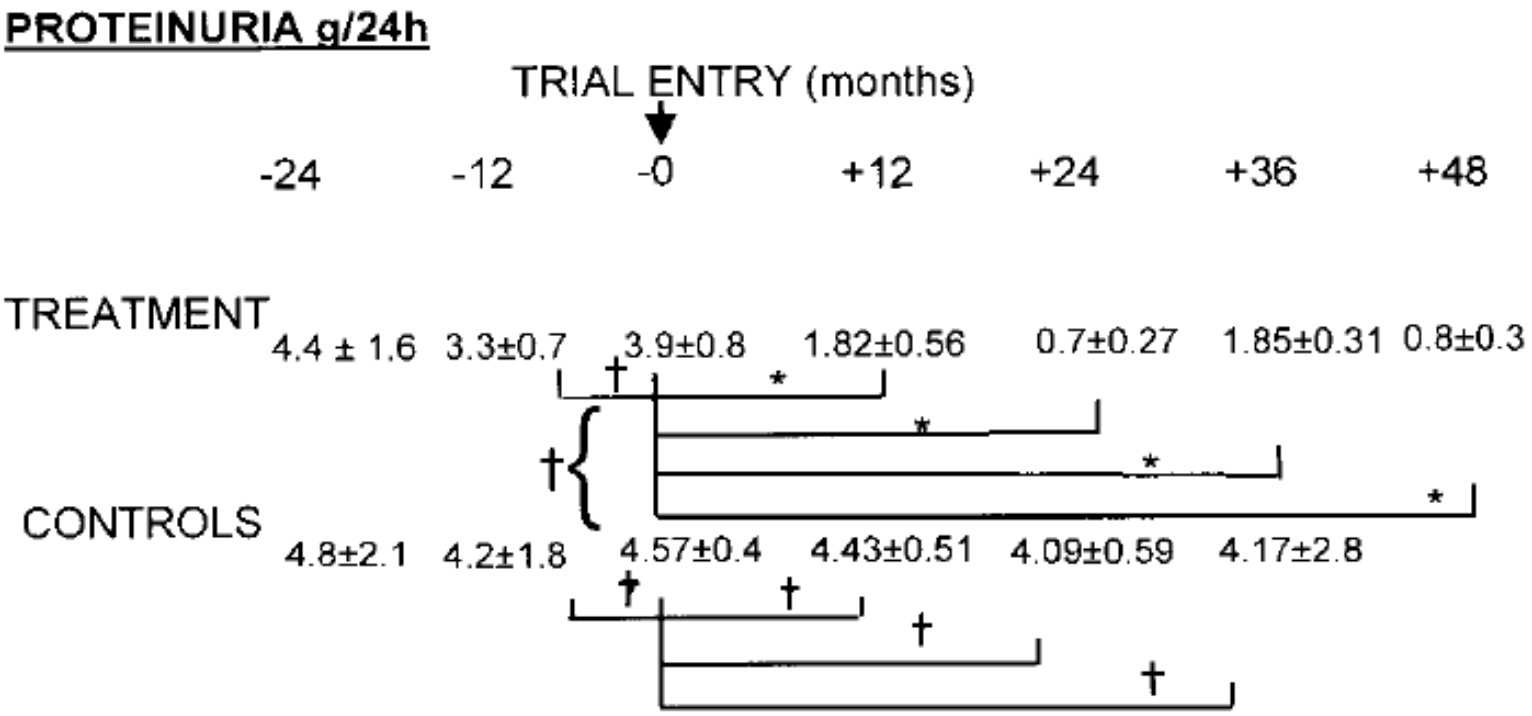


5-year risk

28%

95%

Ballardie trial: renal outcome



Ballardie trial: adverse events

- Not reported
- Treated group:
    - 3/19: stopped treatment early
    - 1/19: developed pulmonary TB
    - Total ~21%

Ballardie trial: summary

- High risk of bias
- Unclear how to generalize the results to overall population with IgAN
- No background use of RASB, goal BP<160/90
- Adverse events not reported, likely to be significant
- Not clear how long to continue azathioprine/steroids

Current KDIGO guideline recommendations

10.3.1: We suggest that patients with persistent proteinuria ≥ 1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR > 50 ml/min per 1.73 m^2, receive a 6-month course of corticosteroid therapy. (*2C*)

10.4.1: We suggest not treating with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients (unless there is crescentic IgAN with rapidly deteriorating kidney function; see Recommendation 10.6.3). (*2D*)

10.4.2: We suggest not using immunosuppressive therapy in patients with GFR < 30 ml/min per 1.73 m^2 unless there is crescentic IgAN with rapidly deteriorating kidney function (see Section 10.6). (*2C*)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

Thomas Rauen, M.D., Frank Eitner, M.D., Christina Fitzner, M.Sc., Claudia Sommerer, 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*

NEJM, Dec 2015, 373(23)

STOP-IgAN trial

- Multi-centre German RCT of 162 patients from 2008-2011 with:
    - IgAN on biopsy (no time-frame)
    - Proteinuria ≥ 0.75g/d
    - Age 18-70 years
    - eGFR <90ml/min/1.73m^2, or history of hypertension, or both
- Entered 6-month run-in phase:
    - Maximize RASB targeting <0.75g/d and BP <125/75
    - Smoking cessation, cholesterol with statin, diet

STOP-IgAN trial

- Eligible for randomization if at end of run-in:
  - Proteinuria 0.75g/d – 3.5g/d
  - eGFR did not decline to <30ml/min/1.73m^2, and did not decrease by >30% from baseline
- Open-label, un-blinded, randomized to:
  - IS group:
    - eGFR>60: Pozzi steroid protocol IV MP pulse months 1, 3, 5 and prednisolone 0.5mg/kg EOD for 6 months
    - eGFR<60: Ballardie regimen CYC 1.5mg/kg/d for 3 months then azathioprine 1.5mg/kg/d thereafter, prednisolone 40mg tapered
  - Control group: continue supportive care

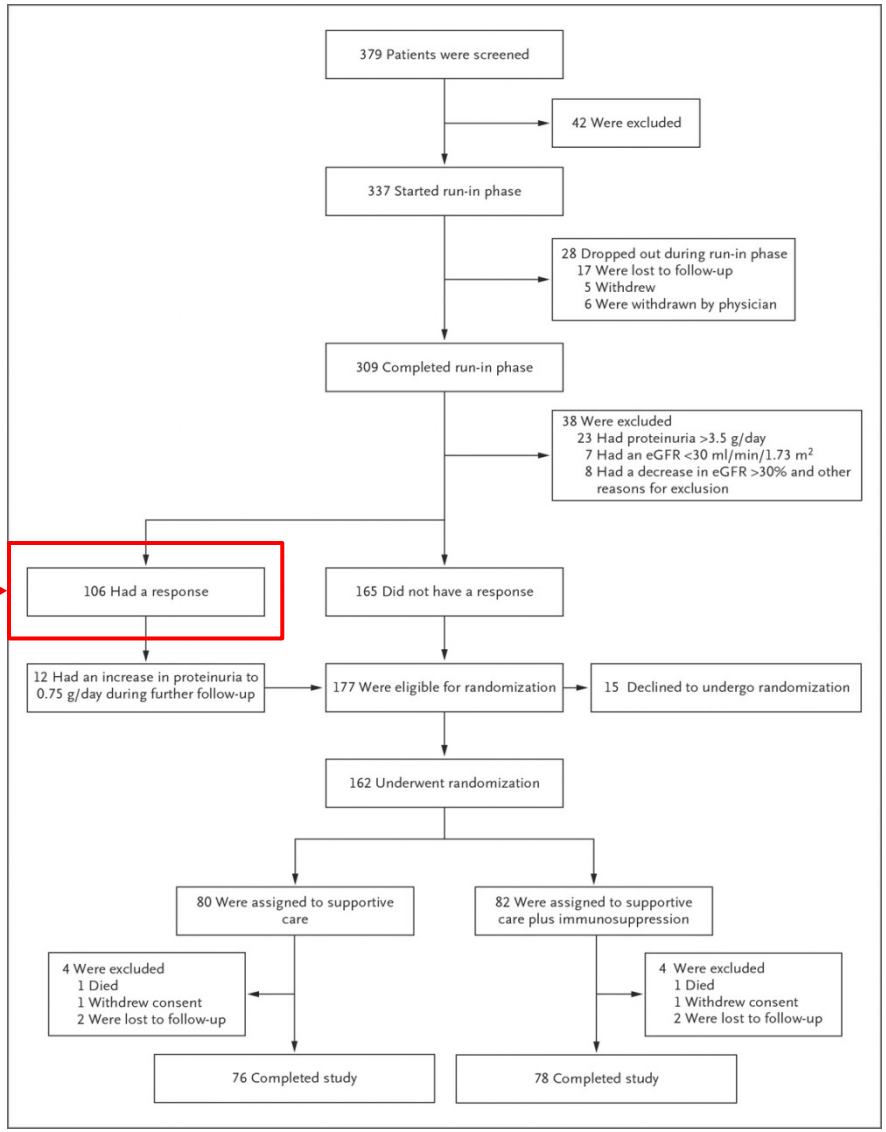
STOP-IgAN trial

- Two primary outcomes evaluated at 3 years
    1. Clinical remission: PCR <0.2g/g and eGFR decrease <5ml/min/1.73m^2 from baseline
    2. eGFR decline ≥15ml/min/1.73m^2 from baseline

- Study power:
    - N=74 per group required to detect 25% vs 5% clinical remission in IS vs control group (80% power, 5% significance, 10% drop-out)

Eligibility, Enrollment, and Randomization

Responded to supportive care



Rauen T et al. N Engl J Med 2015;373:2225-2236.

The NEW ENGLAND JOURNAL of MEDICINE

STOP-IgAN trial: baseline characteristics

Table 1. Patient Characteristics at the Start of the Run-in Phase and at the Start of the Trial Phase.*

Characteristic	Run-in Phase (N=337)	Trial Phase (N=162)	
		Supportive Care (N=80)	Supportive Care plus Immunosuppression (N=82)
Female sex — %	24	19	24
Smoker — %	18	16	17
Age — yr	43.7±12.8	45.8±12.5	42.8±13.1
Body-mass index†	27.9±5.3	28.6±5.3	27.0±5.0
Blood pressure — mm Hg			
Systolic	131±14.0	127±8.5	124±9.7
Diastolic	81±9.9	78±7.0	77±7.0
Serum creatinine — mg/dl	1.5±0.6	1.6±0.6	1.6±0.7
eGFR — ml/min/1.73 m^2‡	61.5±27.3	57.4±24.9	61.1±29.0
Creatinine clearance — ml/min	76.0±34.7	76.2±31.0	76.3±36.4
Urinary protein excretion rate — g/day	2.2±1.8	1.6±0.7	1.8±0.8
Protein-to-creatinine ratio§	1.4±1.4	1.0±0.5	1.1±0.6
Cholesterol — mg/dl	210.1±48.3	191.6±40.7	193.6±45.7
Antihypertensive drugs — no./patient	2.3±1.4	3.0±1.6	2.8±1.3
Therapy with RAS-blocking agents — % of patients	95	96	100
ACE inhibitor without ARB	51	34	49
ARB without ACE inhibitor	19	30	15
ACE inhibitor plus ARB	25	32	36
Maximum daily ACE inhibitor dose¶	32	37	48
Maximum daily ARB dose¶	18	33	17
Maximum ACE inhibitor and ARB dose¶	14	6	6
Aldosterone antagonist therapy — % of patients	1	0	4
Statin therapy — % of patients	57	73	81

STOP-IgAN trial: baseline characteristics

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ACE inhibitor plus ARB	25	32	36
Maximum daily ACE inhibitor dose¶	32	37	48
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Maximum ACE inhibitor and ARB dose¶	14	6	6
Aldosterone antagonist therapy — % of patients	1	0	4
Statin therapy — % of patients	57	73	81

STOP-IgAN trial: baseline characteristics

	Immunosuppressive monotherapy (N=55)	Immunosuppressive combination therapy (N=27)
Female sex (%)	24	26
Smoker (%)	20	11
Age (years)	41.7 (13.3)	45.1 (12.8)
Body mass index (kg/m^2)	27.3 (5.0)	26.6 (5.2)
Blood pressure (mm Hg)		
Systolic	123.6 (10.2)	126.1 (8.7)
Diastolic	76.5 (6.7)	77.7 (7.6)
Serum creatinine (mg/dl)	1.3 (0.4)	2.2 (0.7)
Estimated GFR (CKD-Epi; ml/min/1.73 m^2)	73.4 (27.2)	36.0 (10.7)
Creatinine clearance (ml/min)	94.2 (32.2)	42.4 (11.4)
Proteinuria (g/d)	1.6 (0.8)	2.0 (0.8)
Cholesterol (mg/dl)	193.9 (41.6)	192.9 (53.4)
No. of antihypertensive drugs	2.4 (1.3)	3.5 (1.2)
Patients treated with any RAS-blocking agent (%)	100	100

Similar to Lv, Manno, Pozzi populations

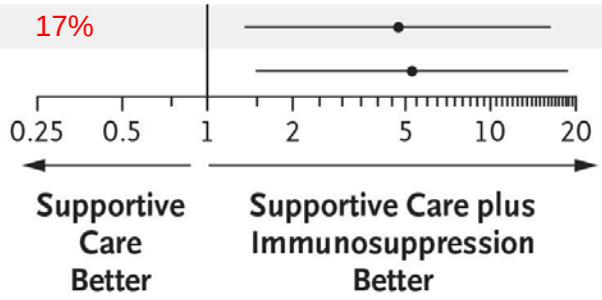
Not Ballardie Trial population

Supplementary Table 1

Primary outcome: full clinical remission

A In Full Clinical Remission

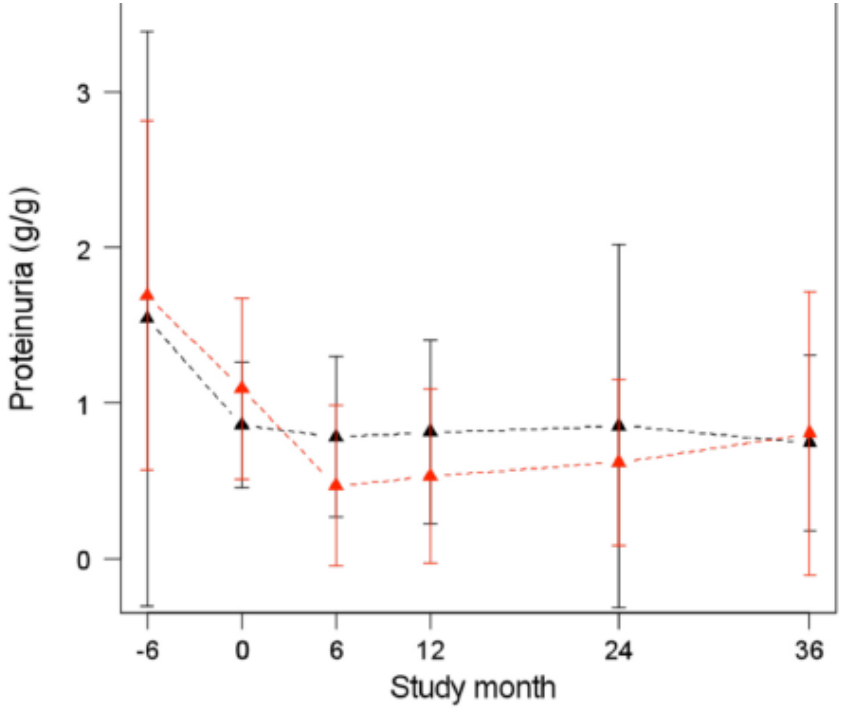
Subgroup	Supportive Care		Supportive Care plus Immunosuppression		Odds Ratio (95% CI)	P Value
	no. of events/total no.					
Full-analysis set	4/80	5%	14/82	17%	4.82 (1.43–16.30)	0.01
Available-case analysis	4/72		14/71		5.38 (1.55–18.66)	0.008



Proteinuria remission PCR<0.2g/g: 11.2% vs 24.3%

Stable eGFR <5ml/min/1.73m2 decline: 47.5% vs 46.3%

Proteinuria over time



	Supportive therapy	IS therapy	P-value
PCR at 12 months (g/g)	0.80±0.67	0.57±0.53	0.01
PCR at 36 months (g/g)	0.85±0.66	0.76±0.90	0.66

From Table 2

	Steroid therapy	Ballardie therapy
PCR at 12 months	0.50 g/g	0.75 g/g
PCT at 36 months	0.57 g/g	1.27 g/g
PCR<0.2 g/g	30.9%	11.1%

From Supplementary Table 2

AJKD

Original Investigation

Early Change in Urine Protein as a Surrogate End Point in Studies of IgA Nephropathy: An Individual-Patient Meta-analysis

Lesley A. Inker, MD, MS,[1] Hasi Mondal, MPH,[1] Tom Greene, PhD,[2] Taylor Masaschi, BA,[1] Francesco Locatelli, MD,[3] Francesco P. Schena, MD,[4] Ritsuko Katafuchi, MD,[5] Gerald B. Appel, MD, PhD,[6] Bart D. Maes, MD,[7] Philip K. Li, MD,[8] Manuel Praga, MD,[9] Lucia Del Vecchio, MD,[3] Simeone Andrulli, MD,[3] Carlo Manno, MD,[4] Eduardo Gutierrez, MD,[9] Alex Mercer, PhD,[10] Kevin J. Carroll, PhD,[11] Christopher H. Schmid, PhD,[12] and Andrew S. Levey, MD[1]

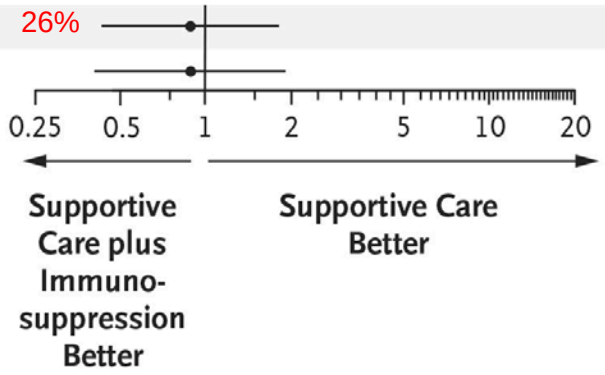
AJKD, epub, 2016

- Meta-analysis 830 patients from 11 RCTs in IgAN
- Conclusion: early (9-month) reduction in proteinuria is a valid surrogate outcome in IgAN treatment trials
    - Strongest evidence in steroid and RASB interventions

Primary outcome: eGFR decline ≥15

B eGFR Decrease ≥15 ml/min/1.73 m²

Subgroup	Supportive Care		Supportive Care plus Immunosuppression		Odds Ratio (95% CI)	P Value
	no. of events/total no.					
Full-analysis set	22/80	28%	21/82	26%	0.89 (0.44–1.81)	0.75
Available-case analysis	18/76		17/78		0.89 (0.41–1.90)	0.76



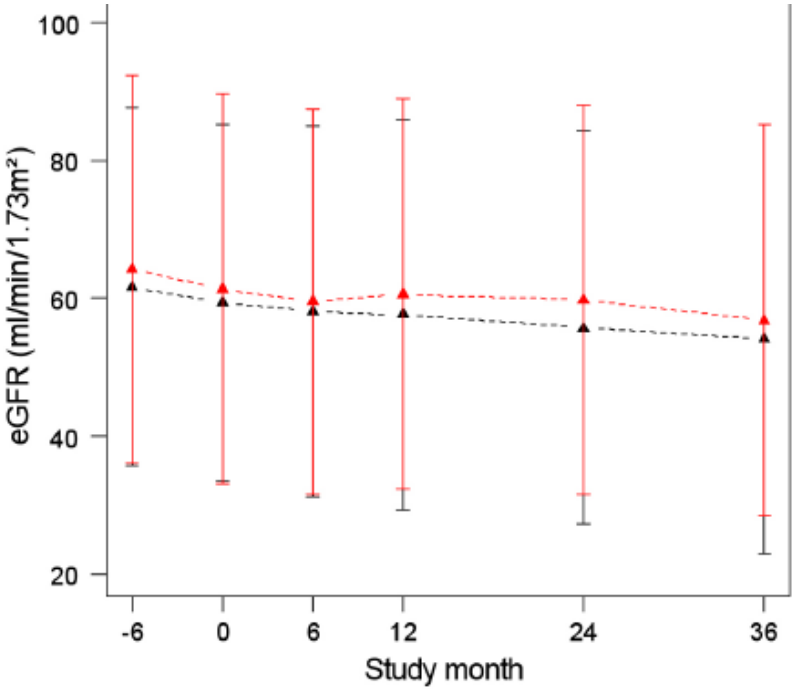
Study was not powered for this outcome event

eGFR decline ≥ 15 is not an established surrogate outcome

- Equivalent to ~ 24-26% relative decline in eGFR, relevance unclear
- NKF/FDA workshop established 57% or 40% decline eGFR as valid surrogates (less evidence to support 30%)

eGFR decline ≥ 30 (~50% decline) was far less common: 9-13%

eGFR over time



IS group: -1.56ml/min/1.73m^2 per year

Control group: -1.4ml/min/1.73m^2 per year

P-value = 0.32

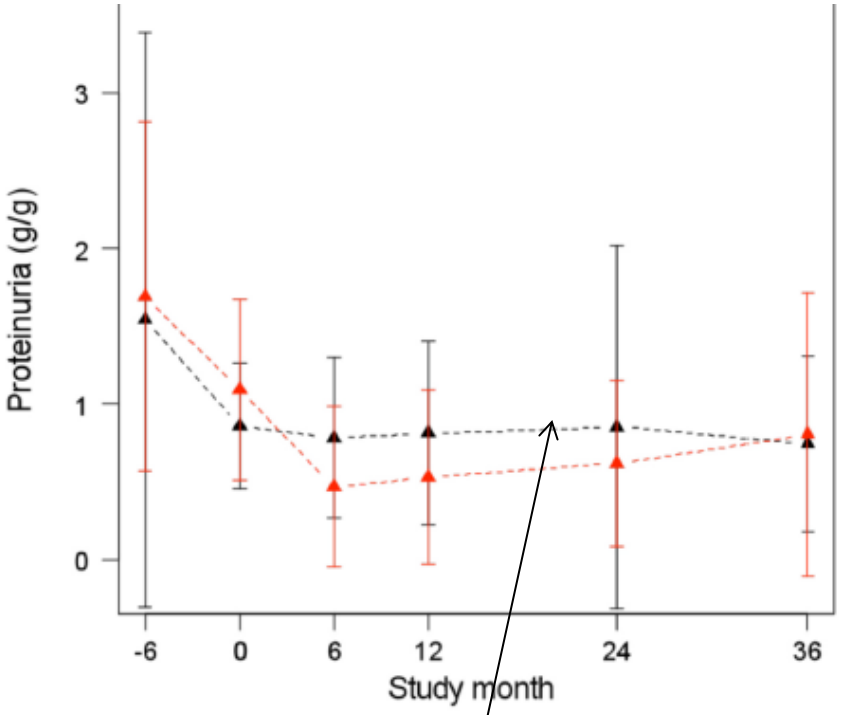
Very slow rate of eGFR decline

- VALIGA PS study control group: -3.2ml/min/1.73m^2
- Manno trial control group: -6.17ml/min/1.73m^2

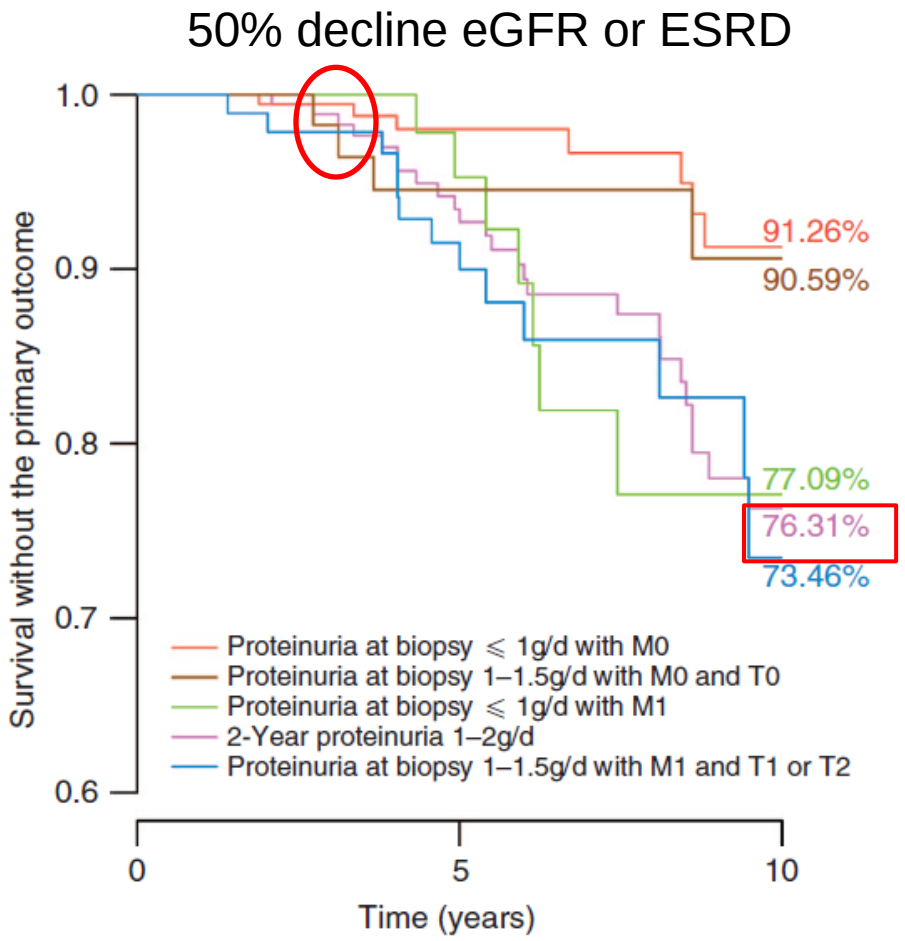
Study inadvertently recruited low risk patients

- Underpowered for renal outcome events over a short 3-year follow-up

Low-risk for renal outcome events



Control group PCR 1-2 years ~1g/g
Equivalent ~ 1.6g/day



Barbour et al, KI, 2016

Adverse events

Table 3. Adverse Events during the Trial.

Variable	Supportive Care (N=80)	Supportive Care plus Immunosuppression (N=82)	P Value
Patients with ≥1 serious adverse event — no.	21 26%	29 35%	0.24
Total no. of serious adverse events	29	33	0.18
Total no. of events of infection	111	174	0.07
Total no. of serious adverse events of infection	3	8	0.21
Diverticulitis or appendicitis	1	3	0.62
Pneumonia or respiratory tract infection	1	3	0.62
Viral exanthema	1	1	1.00
Knee empyema	0	1	1.00
Death — no.*	1	1	1.00
Additional adverse events of interest — no. of patients			
≥1 incidence of increase in liver-enzyme level (i.e., alanine aminotransferase >50 IU/ml)	12	13	1.00
≥1 incidence of observed leukopenia (i.e., leukocyte count <4000/μl)	3	2	1.00
Malignant neoplasm	0	2	0.50
Impaired glucose tolerance or diabetes mellitus	1	9	0.02
Gastrointestinal bleeding	0	0	Not determined
Fracture	0	1	1.00
Osteonecrosis — no. of patients	0	0	Not determined
Weight gain (≥5 kg within the first year)	5	14	0.049

* One patient who received supportive care alone died in a motor vehicle accident, and one patient who received additional immunosuppression died of pneumogenic sepsis, which corresponds to a "suspected unexpected serious adverse reaction" in clinical trials.

STOP-IgAN: summary

- Authors conclude trial failed to show a benefit of IS
  - BUT: primary outcome (clinical remission) was positive in favour of IS (17% vs 5%, NNT = 8.3)
- Clinical remission driven mostly by proteinuria
  - Recently validated as surrogate outcome
- Underpowered and too short to detect renal outcome events
  - Validity of eGFR decline ≥15 is not clear
- Inadvertently recruited low-risk patients
  - Highlights need for more accurate risk stratification in IgAN
  - Ex:
    - Manno trial: used G2 pathology grade to identify a high-risk group
    - STOP-IgAN: proteinuria threshold low 0.75g/d versus usual 1g/d

STOP-IgAN: summary

- Supportive therapy can be very effective at reducing proteinuria and slowing progression
    - ~30% screened patients achieved remission during run-in
- There were two interventions: steroids and Ballardie
    - May not be justified pooling the groups: interaction effect suggested (not formally tested)
    - Proteinuria remission was seen mostly in the steroid group
    - Ballardie regimen was applied to a different population from original study
- First trial to systematically record AE data
    - Demonstrates the toxicity of IS therapy in IgAN (35% SAE)
- Are the risks of IS worth the benefits in IgAN?

Presented by:

Hong Zhang and Vlado Perkovic

on behalf of the TESTING study group

Late Breaking Clinical Trials

ERA-EDTA Meeting, Vienna 2016

Slides courtesy of Vlado Perkovic

TESTING trial

- Aim:
  - Long-term efficacy and safety of oral methylprednisolone on a background of RAS inhibitor therapy, in patients with IgA nephropathy at a high risk of progression

- Design:
  - Investigator-initiated, international, randomized, double-blind, placebo-controlled trial

Study population

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

Intervention

- **Methylprednisolone or Placebo (double blind)**
  - 0.6-0.8 mg/kg/day (maximal 48mg/day) for 2 months
  - Tapered at 8mg daily/month and stopped within 6-8 months

- **Background therapy**
  - Optimal blood pressure control target <130/80mmHg
  - ACE inhibitors or ARBs adjusted to the maximum labeled or tolerated dose

Efficacy outcomes

- **Primary end points:**
  - Composite of ESKD, death due to kidney disease, or a persistent 40% decrease in eGFR

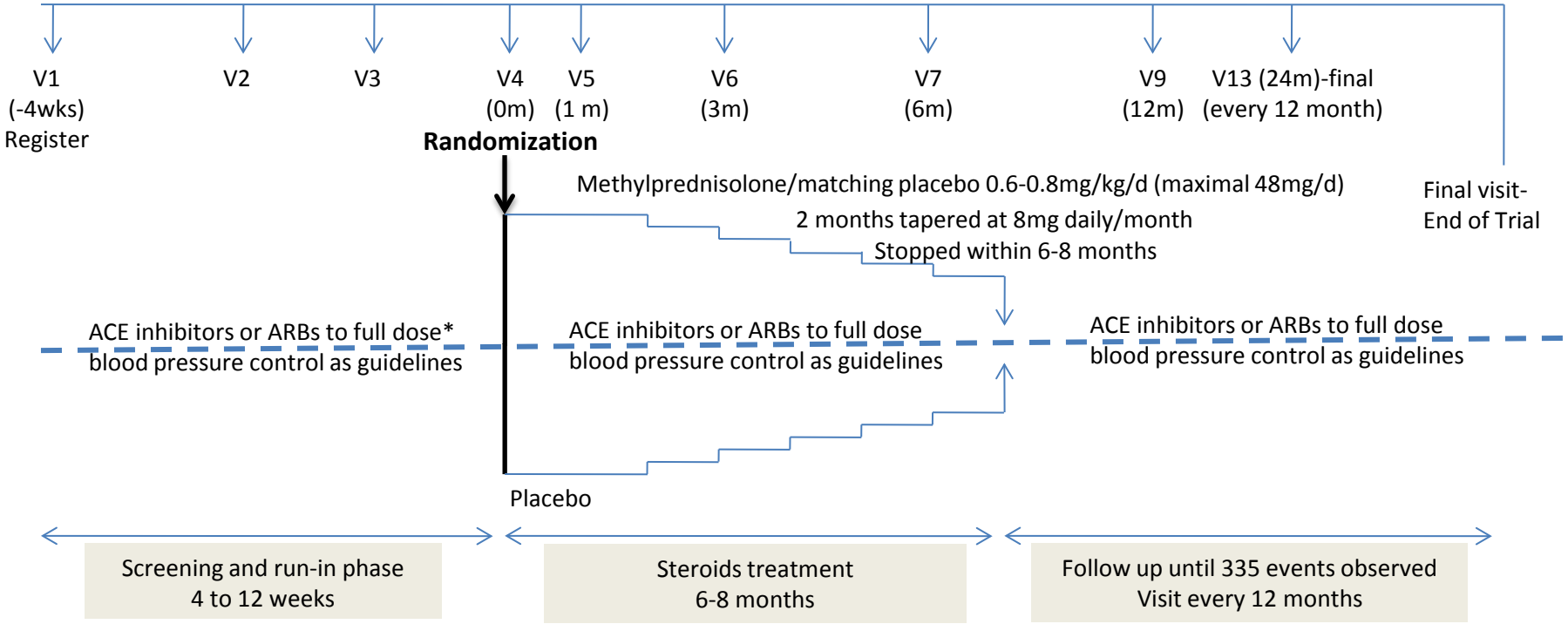
- **Secondary end points:**
  - 40% decrease in eGFR, ESKD or all-cause death
  - 50% decrease in eGFR, ESKD or all-cause death
  - Each of 40% decrease in eGFR, ESKD and all-cause death
  - Annual rate of eGFR decline
  - Proteinuria reduction

Safety outcomes

Pre-specified

- Serious infections requiring hospitalization
- New onset diabetes mellitus
- Clinically apparent gastrointestinal haemorrhage requiring hospitalisation
- Clinically evident fracture or osteonecrosis
- Cardiovascular events, defined as a composite of myocardial infarction, stroke , heart failure requiring hospitalization or death due to cardiovascular disease

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

RESULTS

IDMC communication

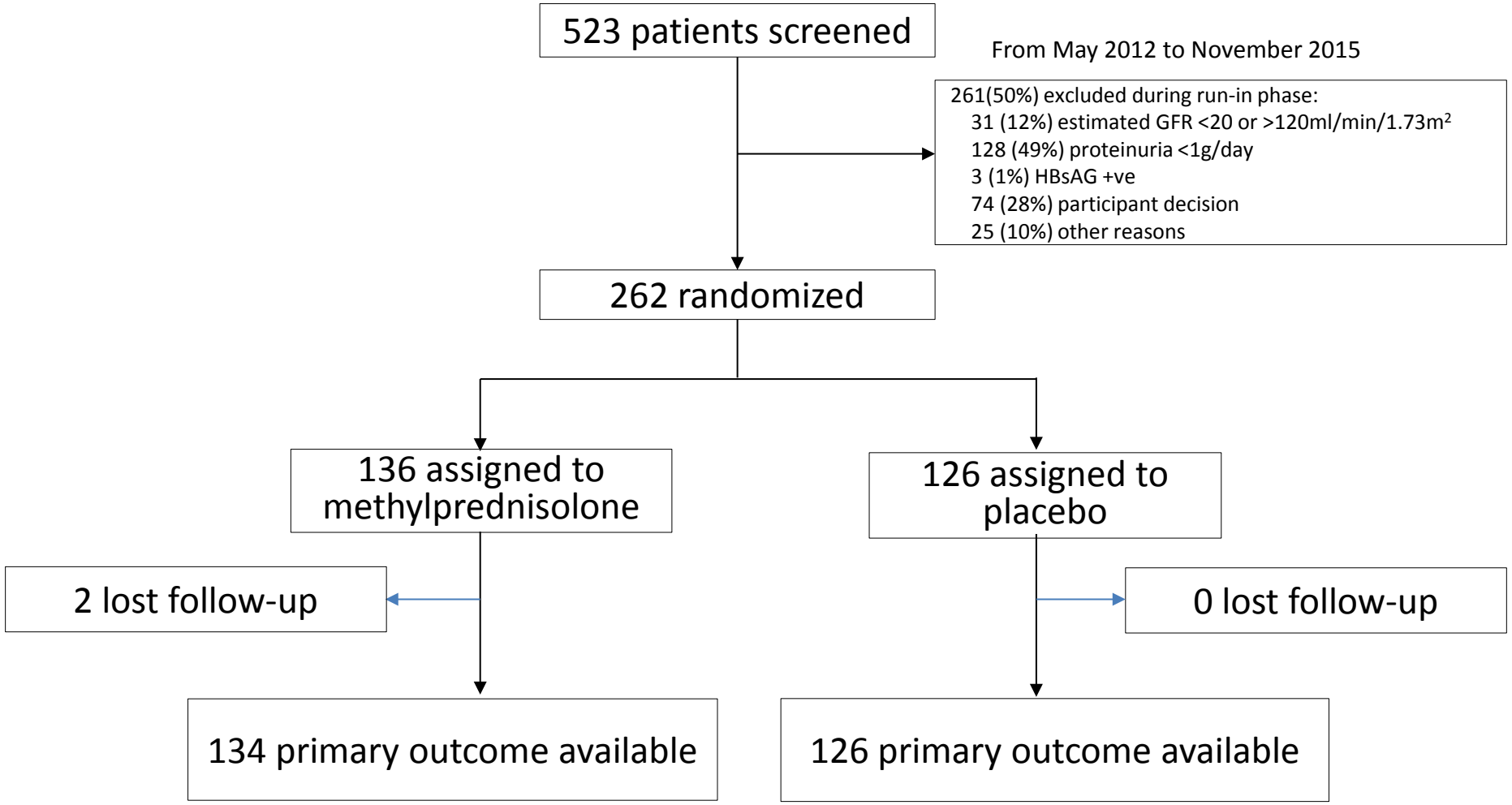
November, 2015

‘…….Concern over an imbalance in severe adverse events between the test and control treatment groups and attribution of the majority of the severe adverse events to the test medication, methylprednisolone, has led the DSMB to conclude that the trial should not continue in its current form…….’

SC decision in response

- Discontinue study treatment
- Continue follow-up of all participants off treatment
- Analyse and report results to date
  - All participants recalled for a study visit
  - Transitional study analysis

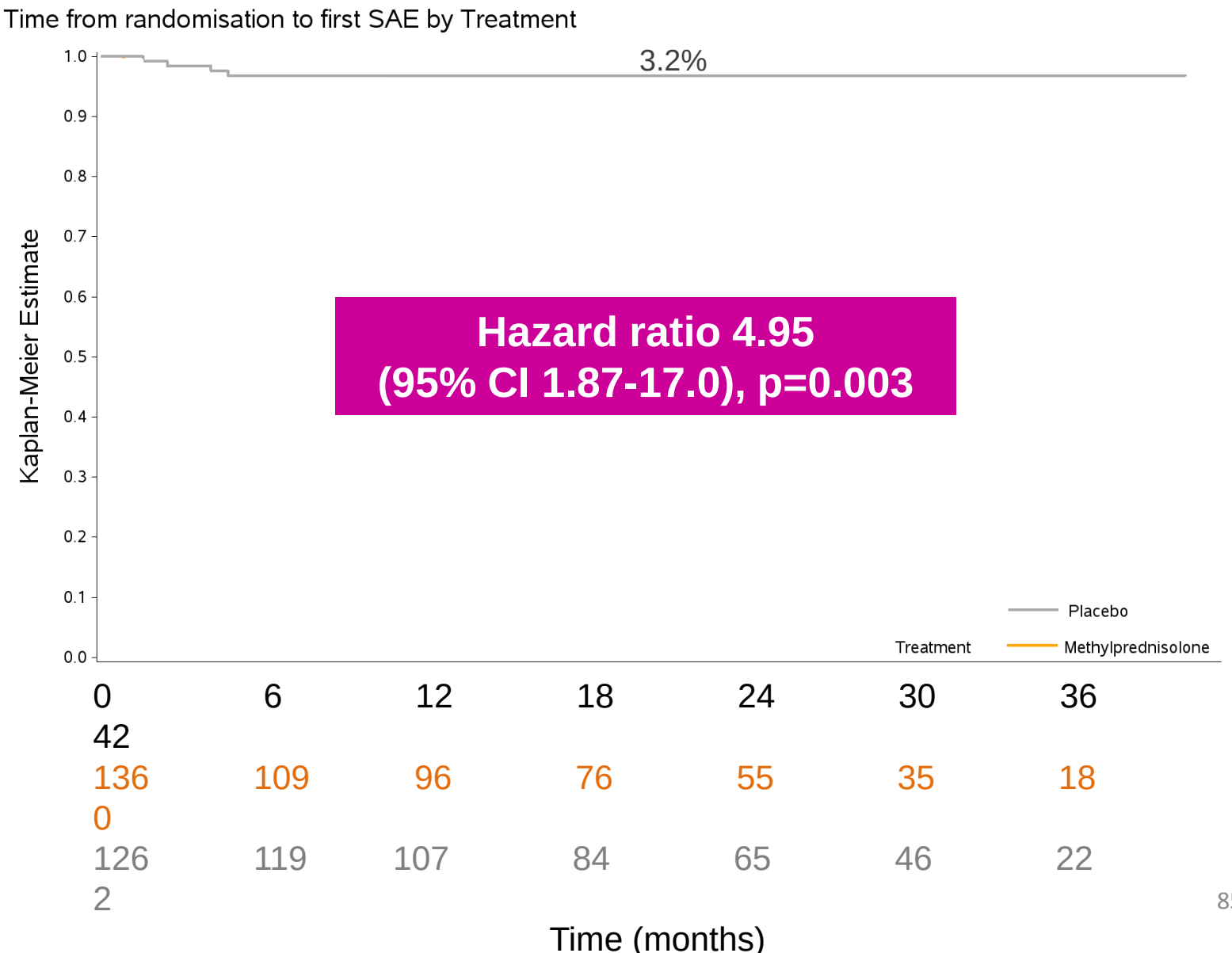
Trial profile



Baseline characteristics

Characteristics	Methylprednisolone group (N=136)	Placebo group (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)	12(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/1.73m^2	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)
Therapy with RAS-blocking agents - %		
ACE inhibitor	83 (61.0%)	77 (61.1%)
ARB	55 (40.4%)	49(38.9%)

Serious adverse events

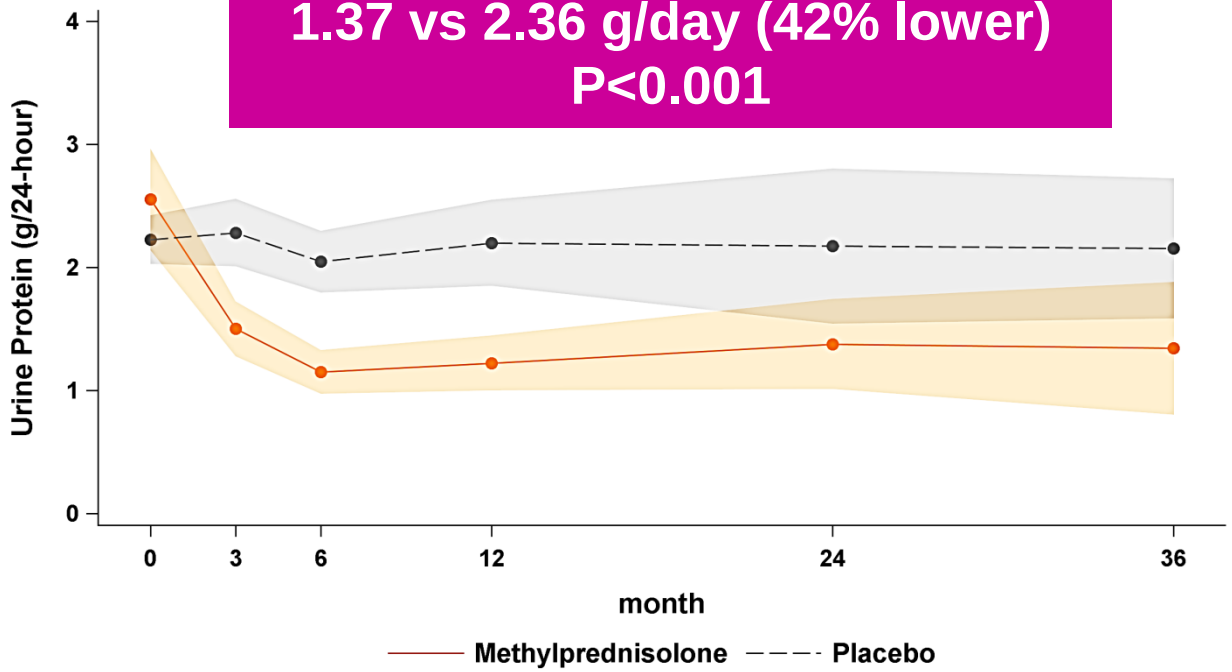


Safety outcomes

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**

Effect on Proteinuria

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



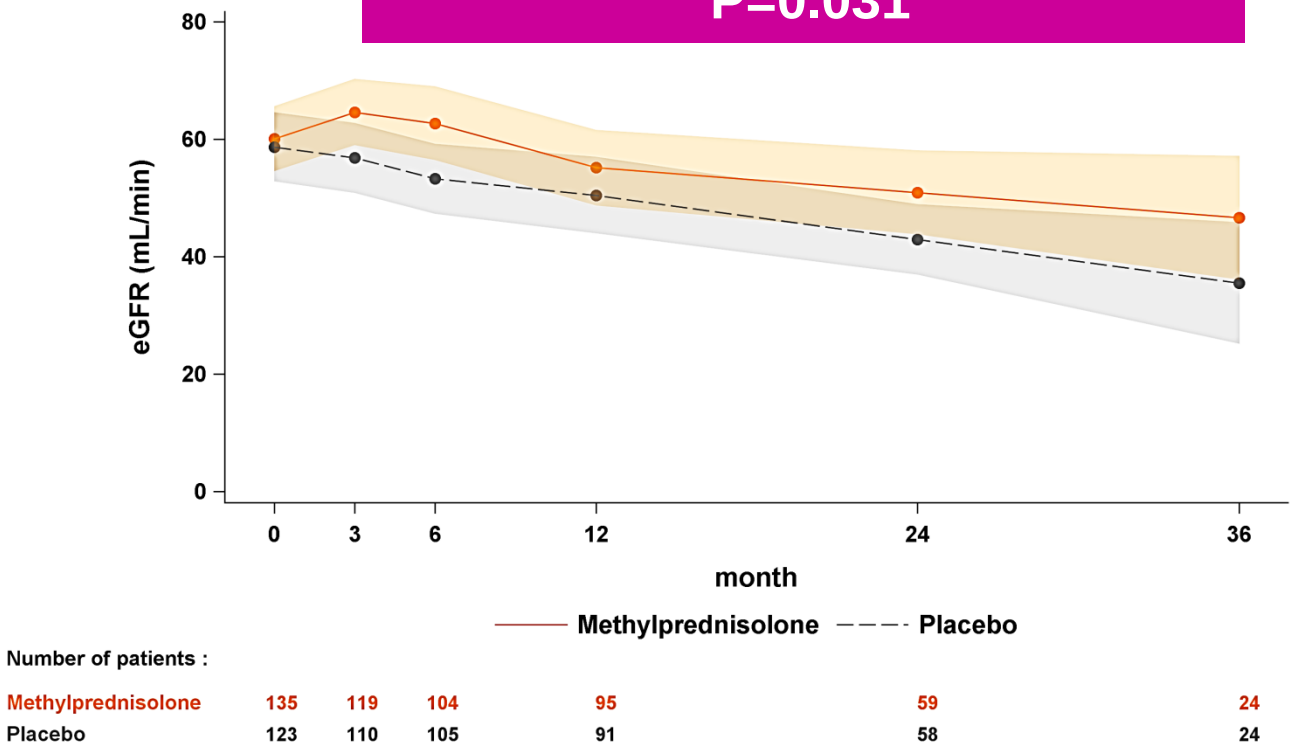
Number of patients :

Methylprednisolone	135	117	103	93	55	23
Placebo	123	109	99	88	55	23

Month	Mean Δ	p value
3	-0.83	<.0001
6	-1.00	<.0001
12	-1.20	<.0001
24	-1.03	<.0001
36	-0.93	0.0077

Effect on eGFR

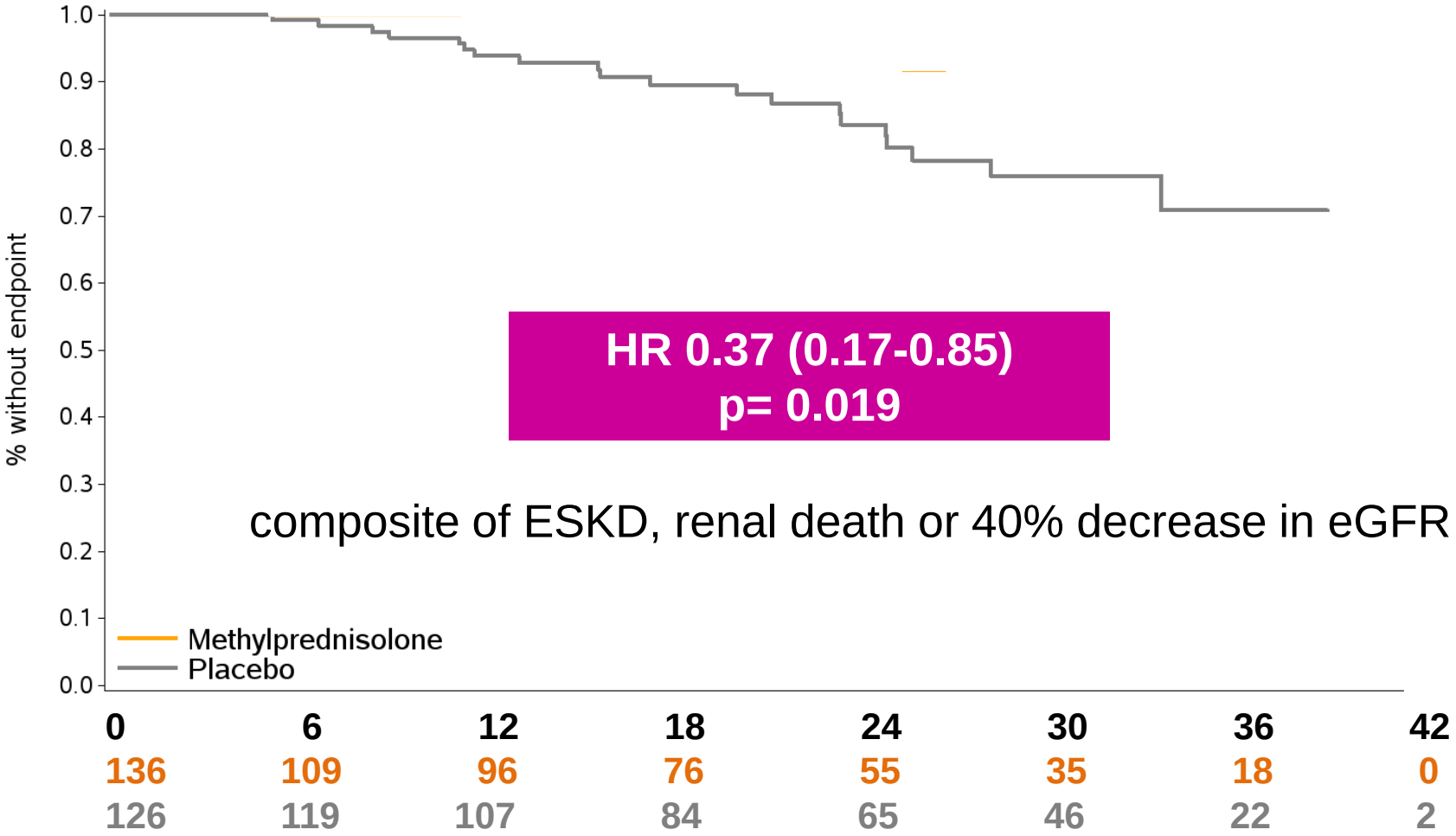
Annual eGFR slope*:
-1.7 vs -6.8 mls/min/1.73m^2/yr
P=0.031



Month	Mean Δ	p value
3	5.14	0.0019
6	6.74	<.0001
12	4.62	0.0091
24	5.43	0.0088
36	7.67	0.0092

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

Primary outcome



Efficacy outcomes

Outcome	Methylprednisolone group (N=136)	Placebo group (N=126)	P Value
Primary End Point			
40% eGFR decrease, ESKD or renal death	8	20	0.019
Secondary End points			
40% eGFR decrease, ESKD or all death	10	20	0.034
50% eGFR decrease, ESKD or all death	10	15	0.293
40% eGFR decrease	7	16	0.047
50% eGFR decrease	7	11	0.330
ESKD or renal death	4	9	0.156
Death	2	1	1.000

TESTING Trial: Conclusions

- Full dose steroid therapy was associated with significantly increased rates of serious adverse outcomes in patients with IgA nephropathy
- The 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
- Safer treatment options for IgA nephropathy are required
- Plan based on DSMB report: modified TESTING protocol to continue recruitment with lower steroid dose

What to do?

Summarizing the evidence

- Historical controversies in IgAN:
  - Are the risks of steroids accurately known and worth the benefits?
  - Are steroids beneficial after optimal RASB?
  - What about lower eGFR?
- STOP-IgAN and TESTING trials attempt to address these uncertainties
- What can we learn from STOP-IgAN?
  - Aggressive supportive care and RASB can be very effective
  - Immunosuppression (mostly steroids) can reduce proteinuria
  - Effects on renal function unclear
  - Serious adverse events are common

Summarizing the evidence

- What can we learn from TESTING?
  - Steroids might reduce the risk of renal outcomes
  - Possible benefit in those with lower eGFR
  - Serious adverse events are common
  - Need longer-term follow-up to understand risks vs benefits
- None of the available studies are definitively conclusive, all have flaws, significant equipoise remains
  - Further steroid trials are unlikely
  - Long-term follow-up of TESTING may help
- What we really need is less toxic therapy:
  - TESTING second phase with lower steroids
  - Other agents

Is there a role for steroids in IgAN in the current era?

- Appreciate the toxicity of steroids
- Acknowledge:
  - The limitations in the literature
  - Our own biases when discussing treatment with patients
- Always maximize RASB and supportive care
- Then consider steroids in patients:
  - Highest risk of progression
  - Lowest risk of AE
  - Understand the risk vs benefit

TESTING-2: recruitment in BC

- Continuation of TESTING randomizing patients to:
  - Lower dose steroids: methylprednisolone 0.4mg/kg/day (max 32mg) x2 months then tapered over ~6 months
  - Placebo
- Inclusion criteria:
  - IgAN on biopsy
  - Proteinuria >1g/d after maximal RASB, BP control
  - eGFR 30-120
  - No IS in prior year
- Goal: determine if a lower dose of steroids is effective and less toxic
- Recruitment to start soon in BC
  - International: Asia, Australia, Canada, India, Germany

Thank You