Should We Use Steroids and How for Treating IgA Nephropathy?

Francesco Locatelli MD,FRCPC (London),FNKF,FERA, Dr h.c.

Department of Nephrology, Dialysis and Renal Transplant
"Alessandro Manzoni" Hospital, Lecco – Italy

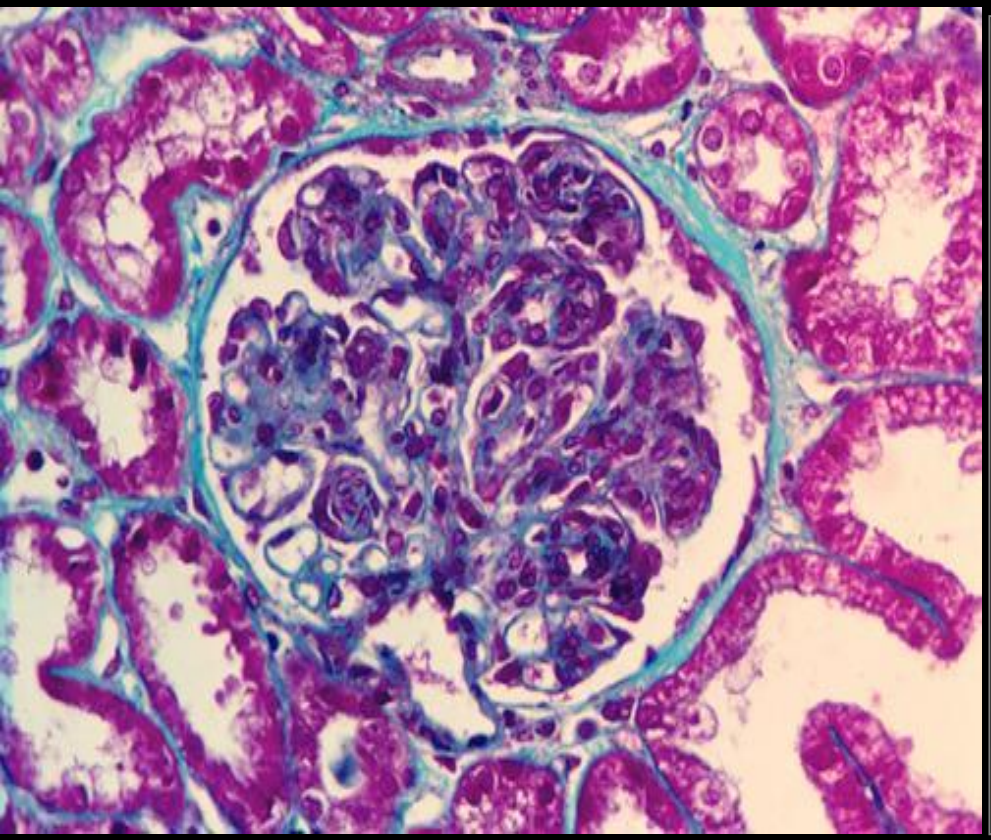
Prof Locatelli is or was a member of an advisory board of Akebia, Amgen, Astellas,GSK,Roche and Vifor Fresenius Medical Care Pharma and speaker at meetings supported by unrestricted grants from Abbvie,Amgen, Astra Zeneca, Roche and Vifor-Fresenius Medical Care Pharma.

IgA Nephropathy

IgA +++

C3 ++

IgG +



IgA Nephropathy
Prognosis

IgA Nephropathy usually develops during the infantry or the young age

In Europe, half of the patients who start dialysis due to IgAN are younger than 40 years

IgA Nephropathy
Prognosis

- Chronic renal failure requiring dialysis is observed

  - in 5-25% of cases at 10 years
  - in 25-50% of cases at 20 years

- Spontaneous recovery is observed in nearly 30% of cases

1968

1980

1990

2000

From 1968, when the disease was recognized, to the end of the 80s, IgAN was not treated, being regarded as a benign nephropathy

During the second half of the 80s, several therapeutic approaches, with many types of drugs, were begun

From 2000, attention was mainly focused on: Ace inhibitors/ARB, steroids, fish-oil, immunosuppressants

Therapeutic approaches in IgAN

- Tonsillectomy
- Low-antigen diets - sodium cromoglycate
- Phenytoin, dapsone, danazole
- ACE-inhibitors and AT1RA
- Fish oil
- Endothelin receptor antagonists - NO - Vitamine E
- Cyclosporin
- Immunoglobulin therapy
- Cytotoxic, antiplatelet and anticoagulant agents
- Steroids
- Immunosuppressants
- New Drugs

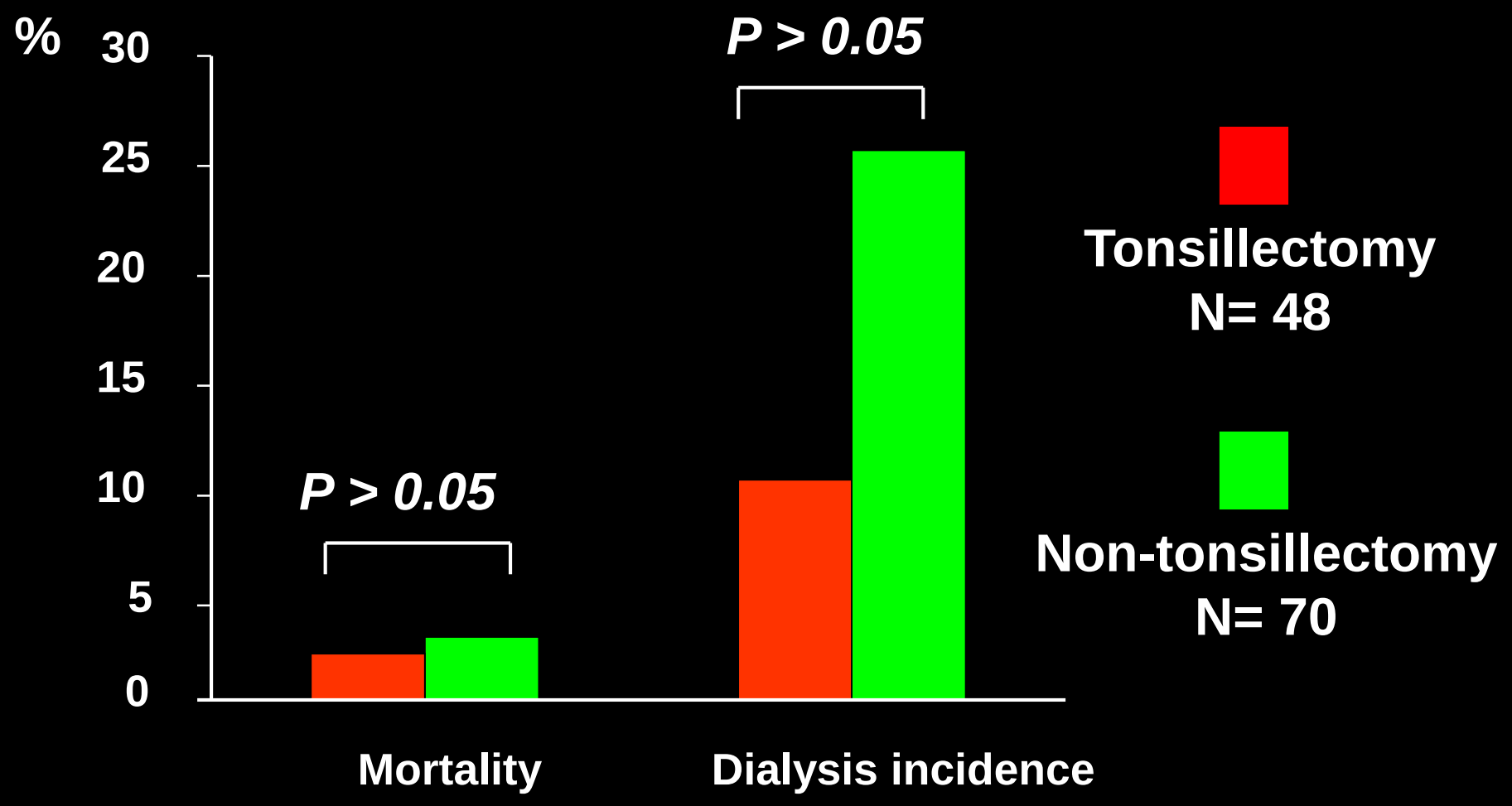
Therapeutic approaches in IgAN

- Tonsillectomy
- Low-antigen diets - sodium cromoglycate
- Phenytoin, dapsone, danazole
- ACE-inhibitors and AT1RA
- Fish oil
- Endothelin receptor antagonists - NO - Vitamine E
- Cyclosporin
- Immunoglobulin therapy
- Cytotoxic, antiplatelet and anticoagulant agents
- Steroids
- Immunosuppressants

Tonsillectomy in IgAN
Still controversial

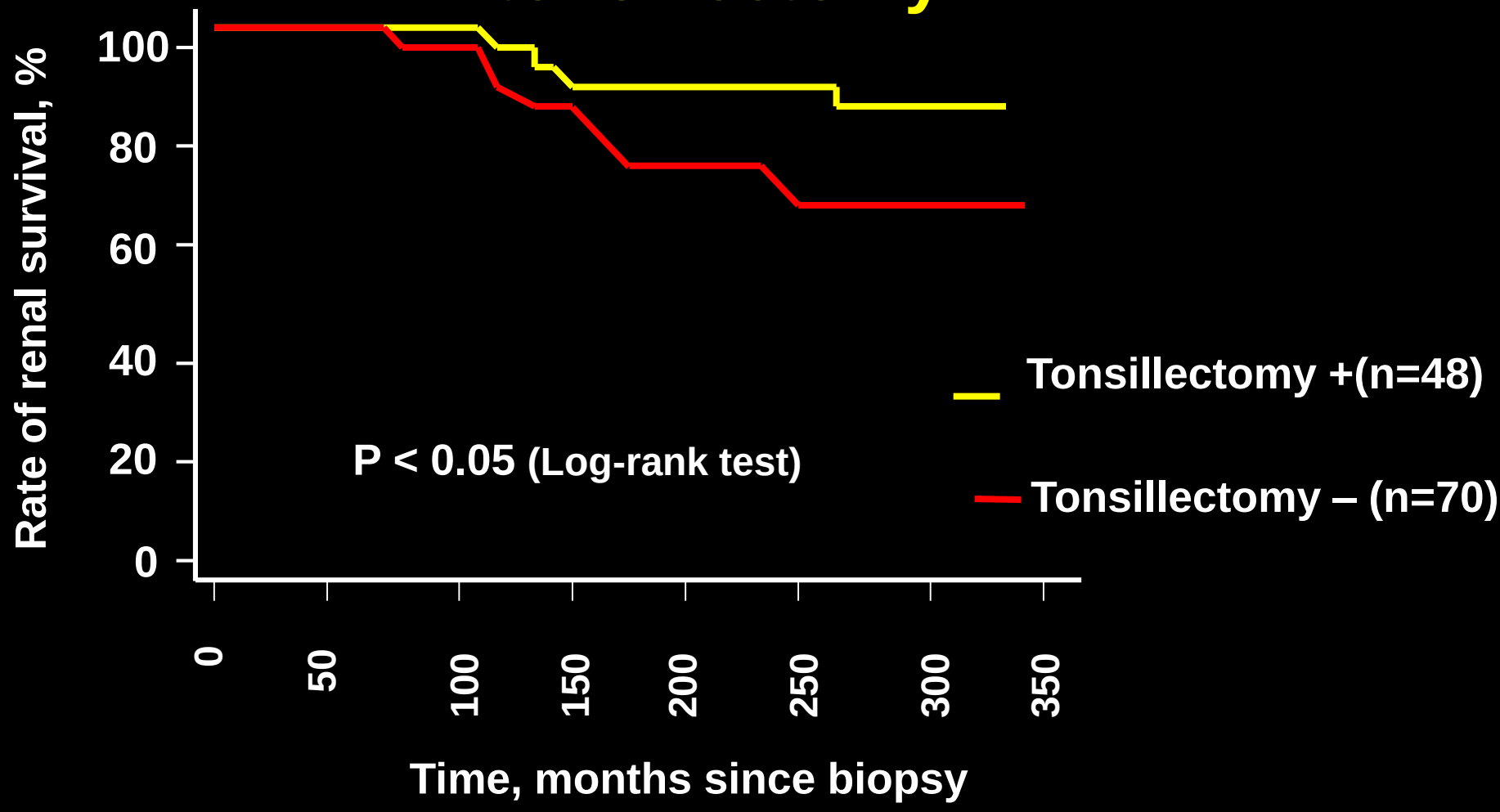
- The predominant mesangial IgA deposition in the glomeruli suggests the role of mucosal immunity in the pathogenesis of the disease
- Tonsillitis and upper respiratory tract infections often precede macrohematuria or deterioration of urinary findings

Comparison of mortality before renal failure and incidence of dialysis in tonsillectomy and non-tonsillectomy groups



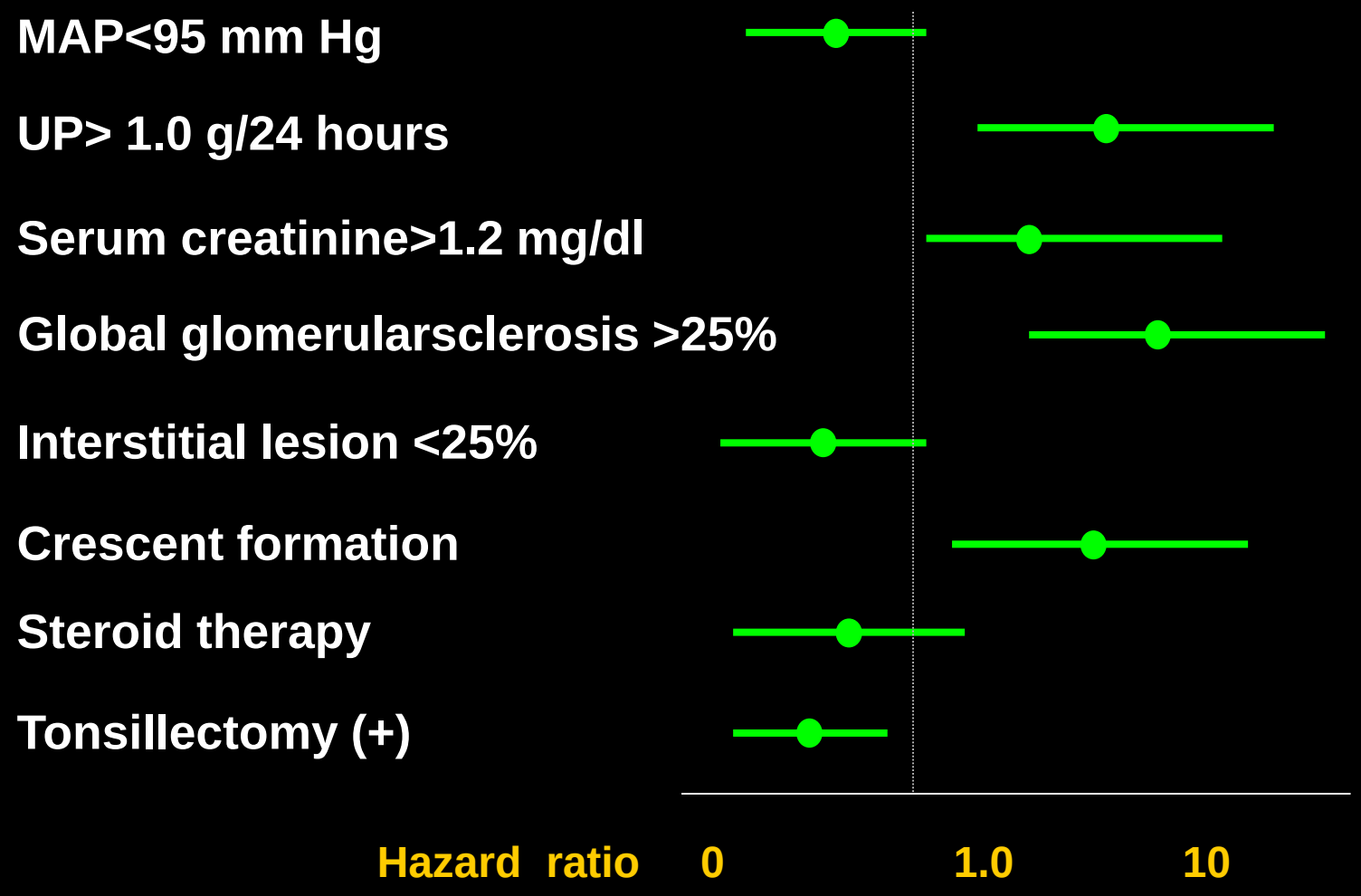
Xie Y et al. Kidney Int 2003; 63 (5): 1861-1867

Kaplan-Meier analysis of renal survival in IgAN patients with and without tonsillectomy



Xie Y et al. Kidney Int 2003; 63 (5): 1861-1867

Hazard ratios for the Cox regression model in IgAN



Xie Y et al. Kidney Int 2003; 63 (5): 1861-1867

Effect of Tonsillectomy on Longterm Renal Outcome of IgA Nephropathy

ClinicalTrials.gov Identifier: NCT02471599

Recruitment Status : Suspended (This study was suspended because that few participants were enrolled.)

First Posted : June 15, 2015

Last Update Posted : June 15, 2015

Sponsor: Sun Yat-sen University **Information provided by (Responsible Party):** Xue Qing Yu, Sun Yat-sen University

Is tonsillectomy useful?

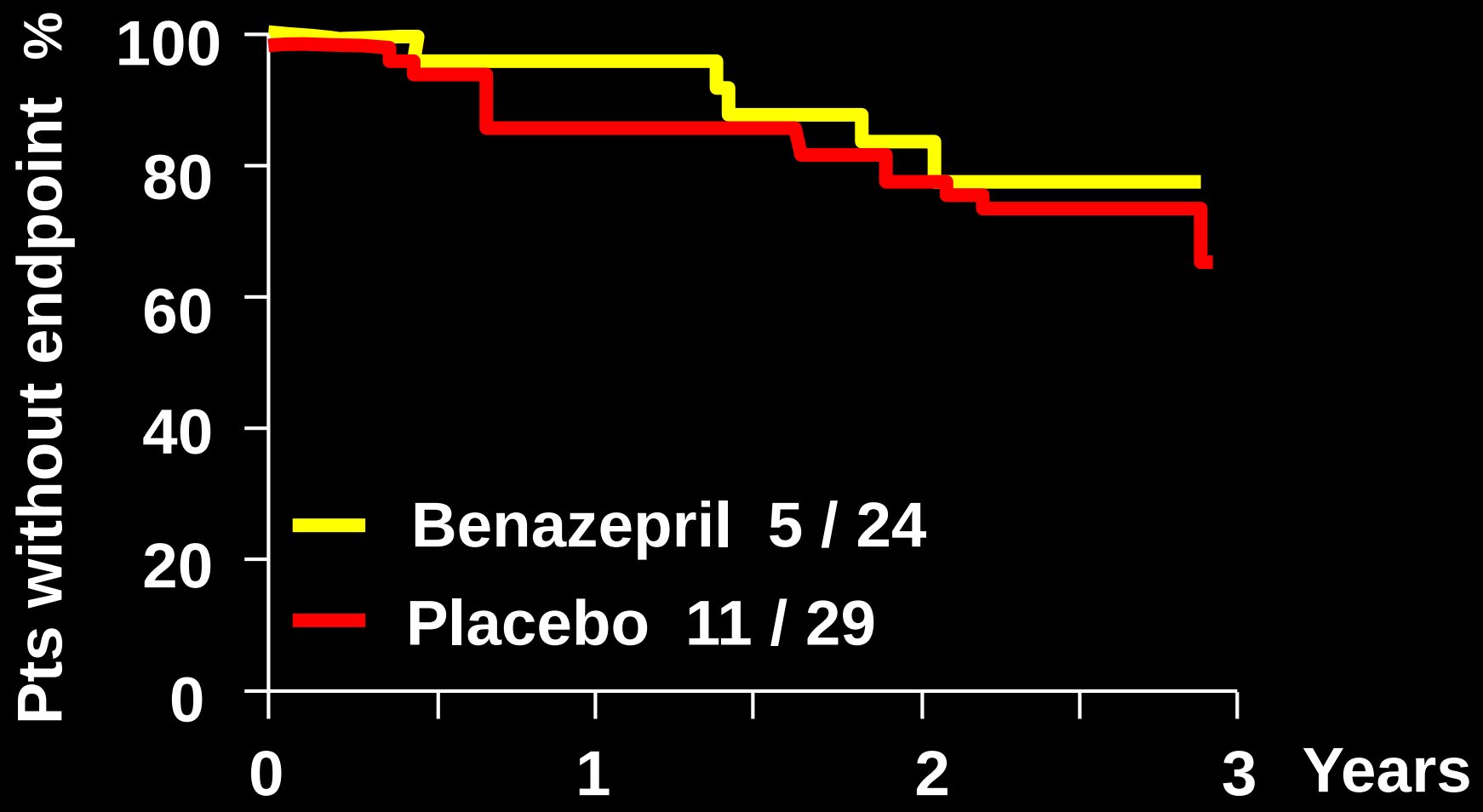
The results of tonsillectomy are still controversial and it can be recommended only in selected cases

Therapeutic approaches in IgAN

- Tonsillectomy
- Low-antigen diets - sodium cromoglycate
- Phenytoin, dapsone, danazole
- ACE-inhibitors and AT1RA
- Fish oil
- Endothelin receptor antagonists - NO - Vitamine E
- Cyclosporin
- Immunoglobulin therapy
- Cytotoxic, antiplatelet and anticoagulant agents
- Steroids
- Immunosuppressants

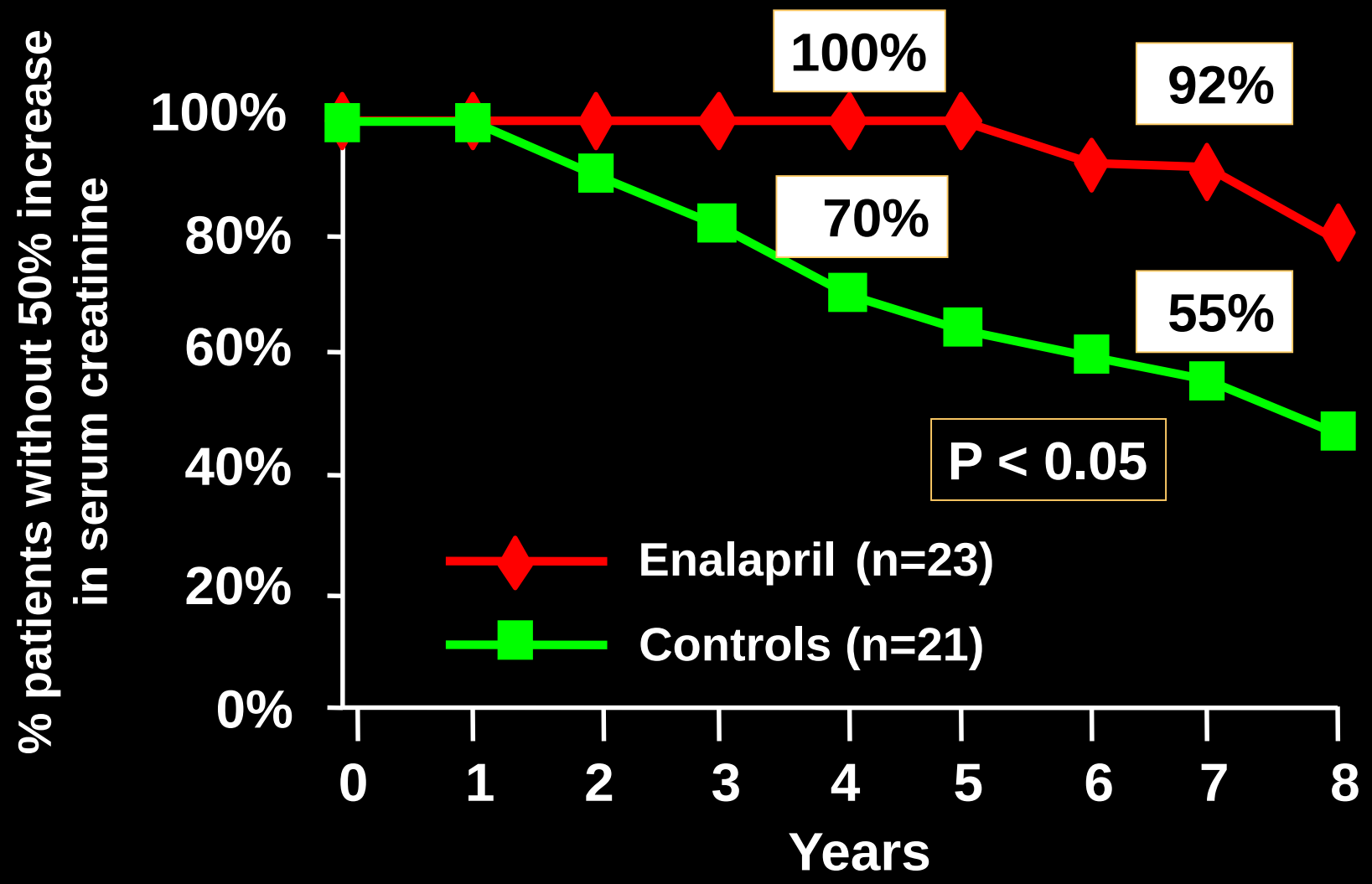
Renal Survival in the AIPRI Study

53 patients with IgA Nephropathy



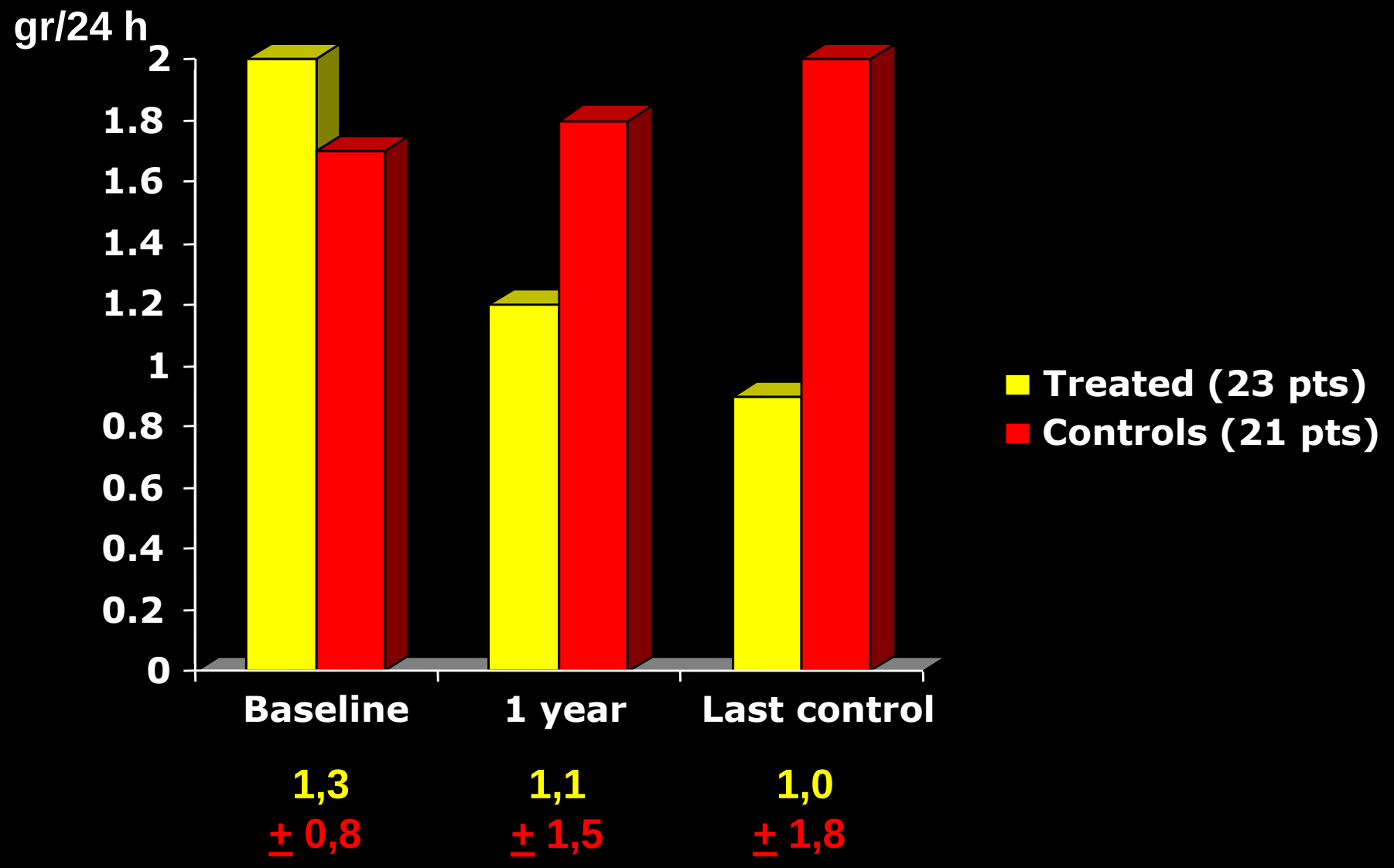
From Maschio G….Locatelli F. et al N Engl J Med 1996; 334: 939-945

Probability of renal survival in patients treated or not with enalapril



Praga M et al. J Am Soc Nephrol 2003; 14: 1578-1583

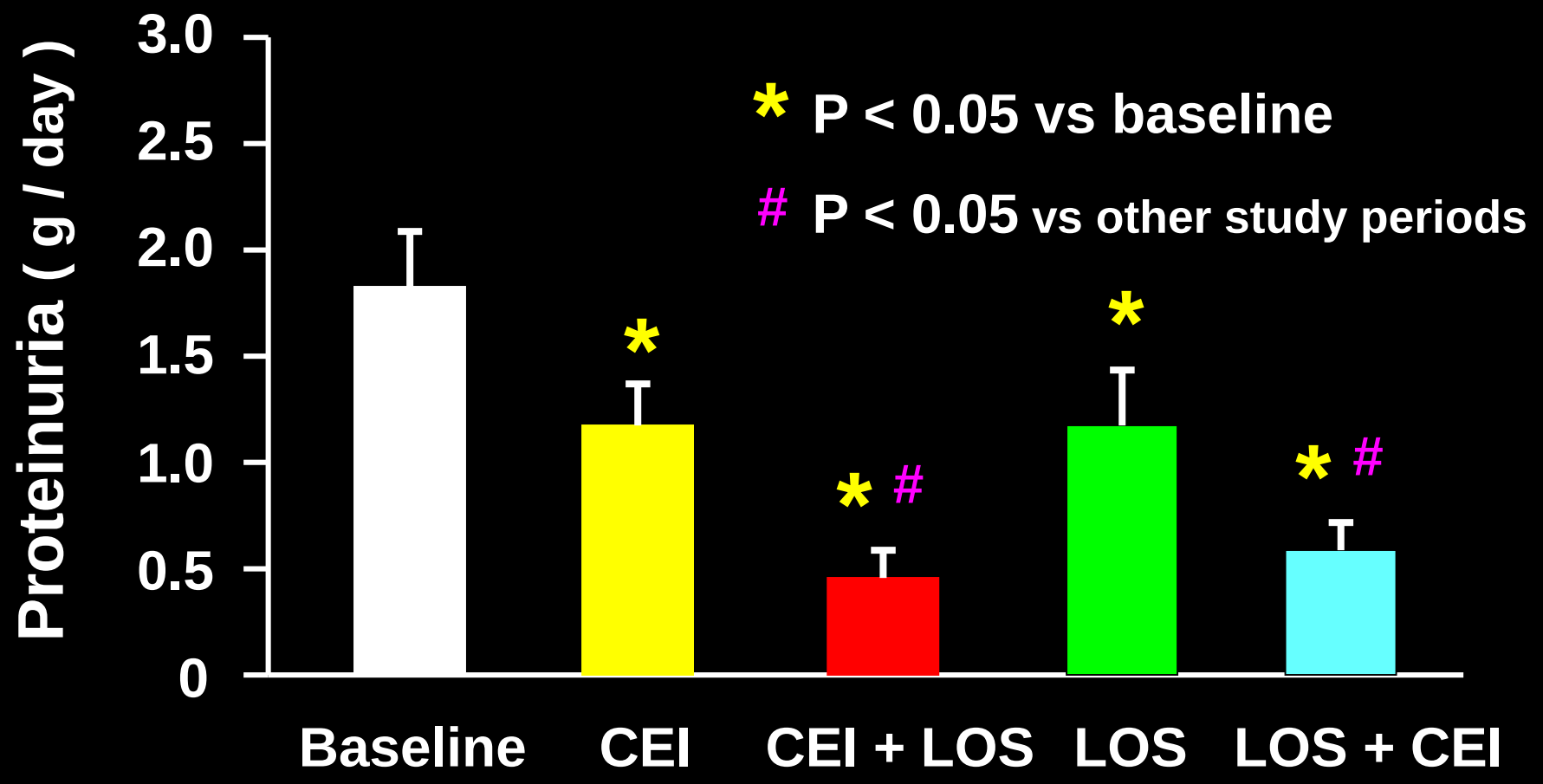
IgAN: changes in proteinuria with ACEi



Praga M et al. J Am Soc Nephrol 2003; 14: 1578-1583

Combination therapy with ACE inhibitors and losartan in IgAN

Antiproteinuric effect in 8 normotensive patients



Russo D et al. Am J Kidney Dis 1999; 33: 851-856

Are treatments with ACEi or AT1RA useful?

Available data suggests that ACEi and/or AT1RA

- may reduce protein excretion
- may slow disease progression

in patients with normal renal function

Therapeutic approaches in IgAN

- Tonsillectomy
- Low-antigen diets - sodium cromoglycate
- Phenytoin, dapsone, danazole
- ACE-inhibitors and AT1RA
- Fish oil
- Endothelin receptor antagonists - NO - Vitamine E
- Cyclosporin
- Immunoglobulin therapy
- Cytotoxic, antiplatelet and anticoagulant agents
- Steroids
- Immunosuppressants

Fish oil therapy in IgAN

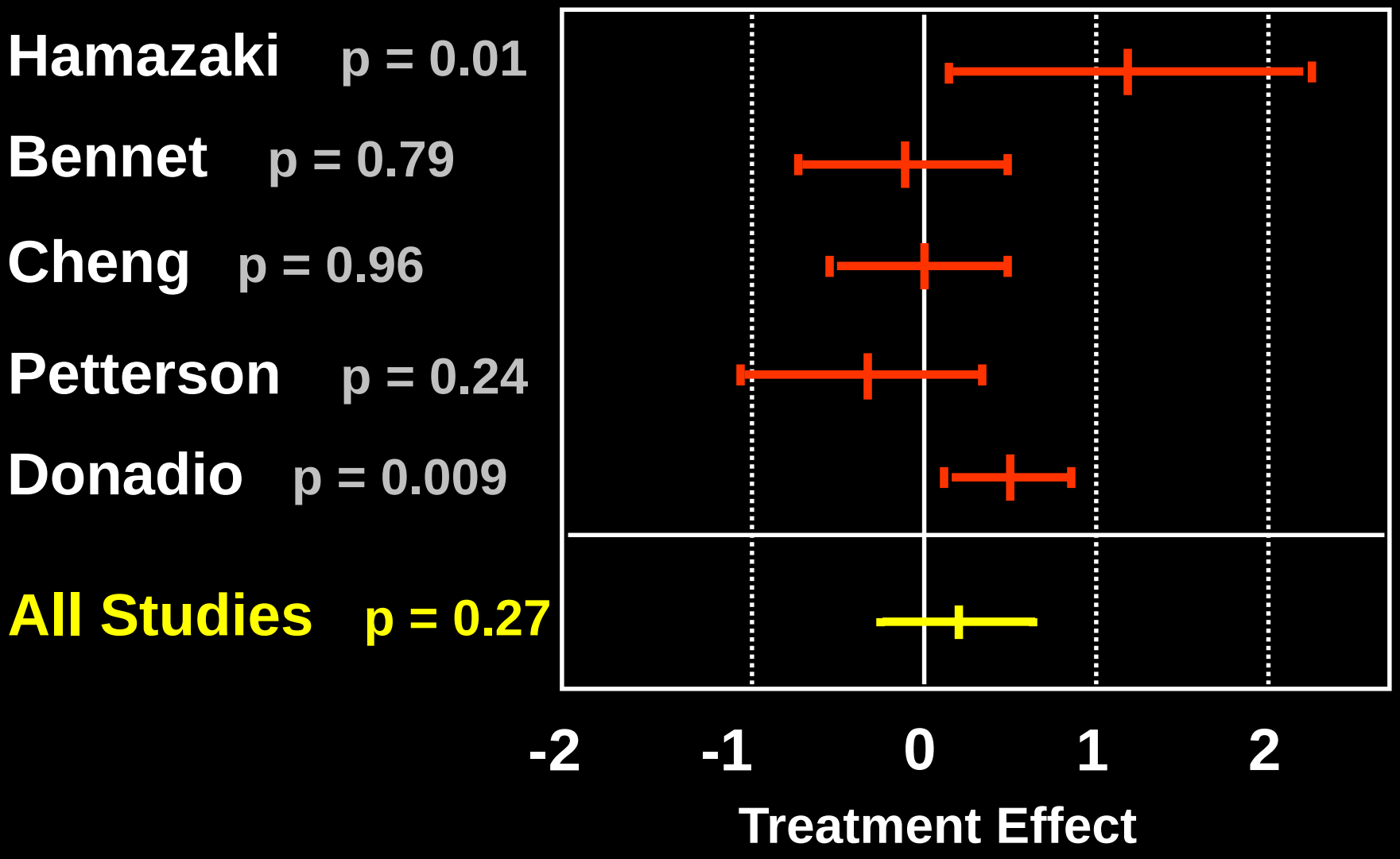
In 1984 Hamazaki published the results about fish oil administration in patients with IgAN.

Patients enrolled were 20.

Renal function was stable in 9 patients treated with fish-oil, declined in 11 patients without fish-oil therapy.

Hamazaki T et al. Lancet 1984; 1: 1017-1018

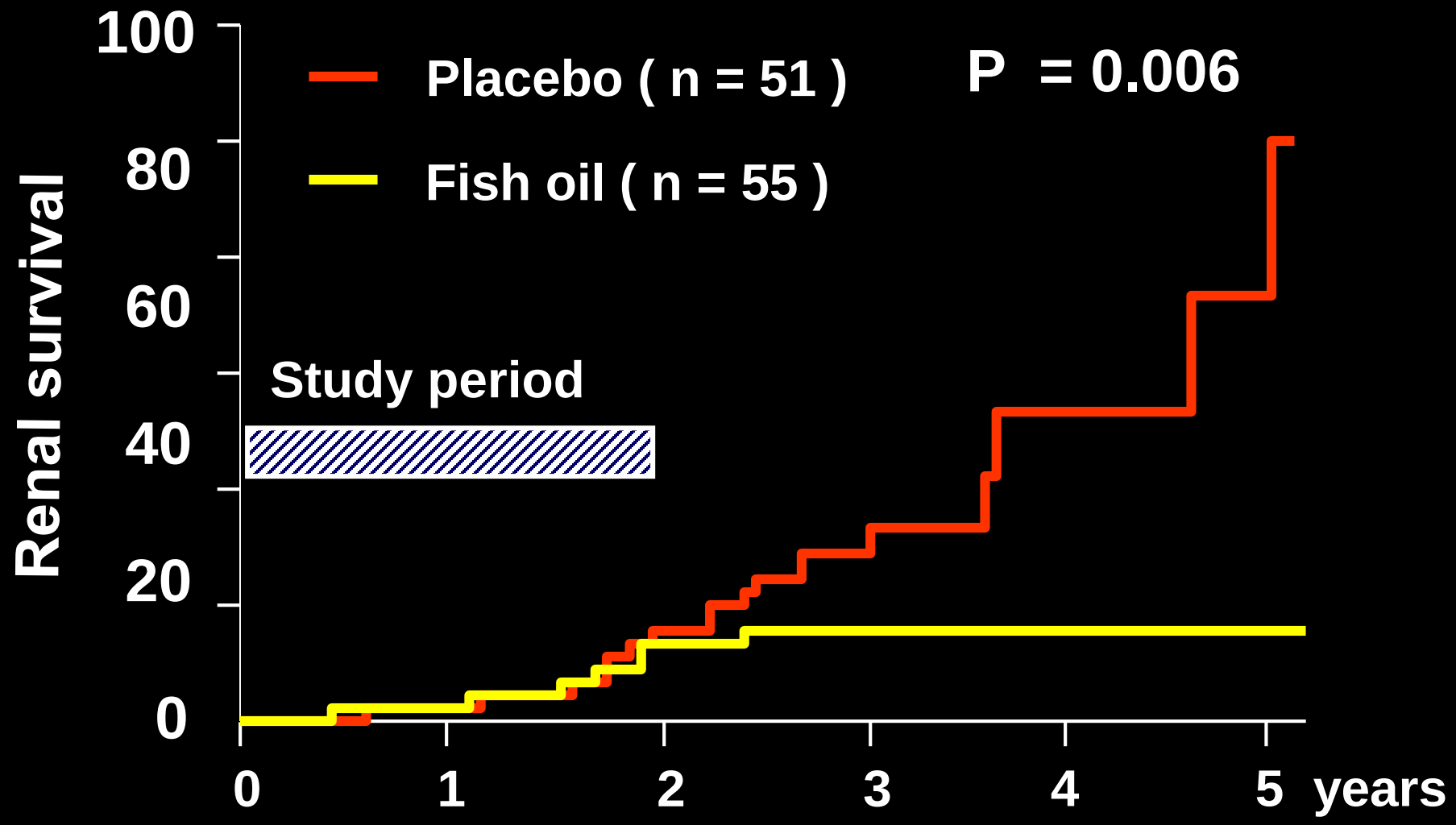
A meta-analysis of Fish oil in IgAN



Dillon JJ et al. J Am Soc Nephrol 1997; 8: 1739-1744

Fish oil in IgA Nephropathy

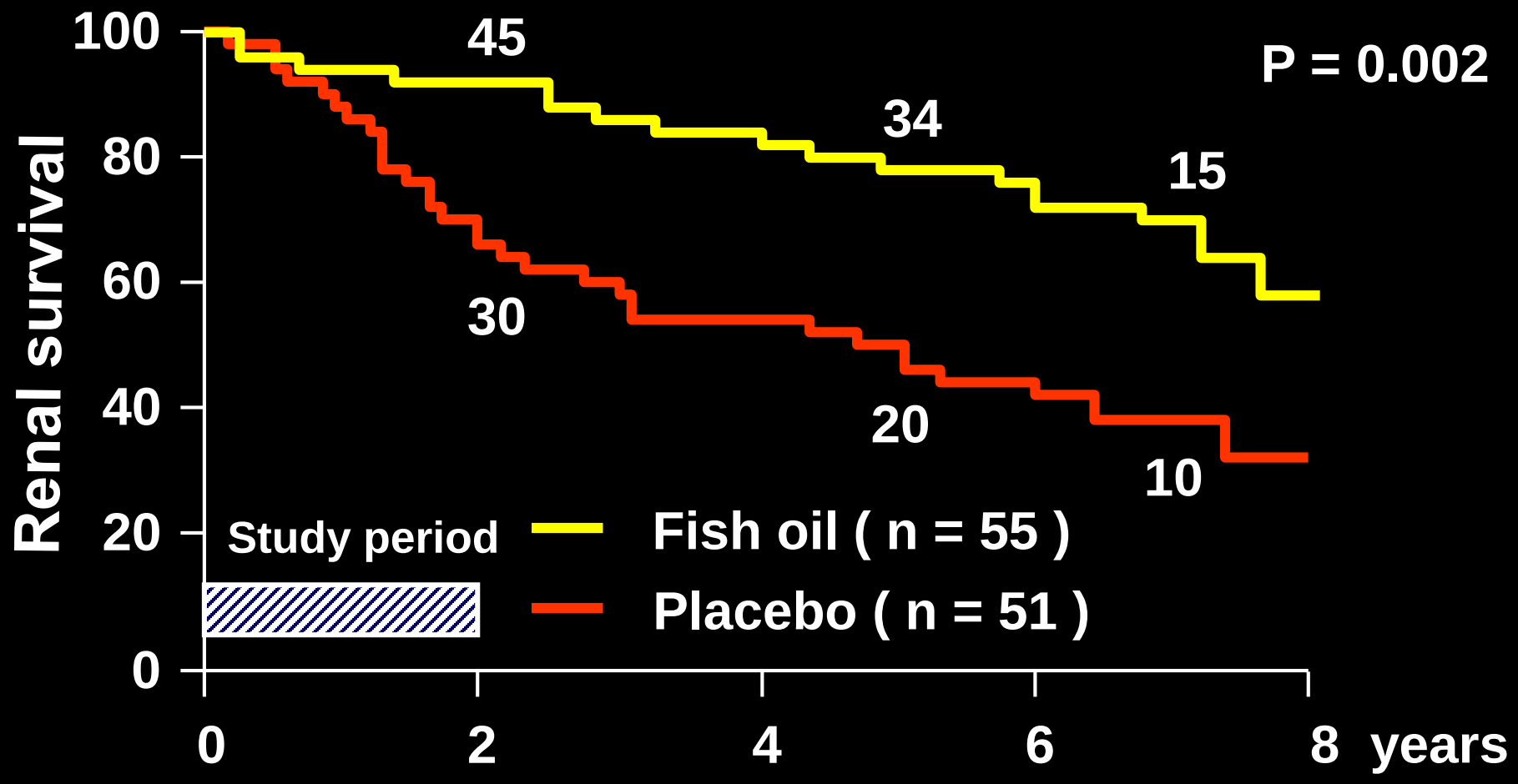
End-stage renal disease or death



Donadio JV et al. N Engl J Med 1994; 331: 1194-1199

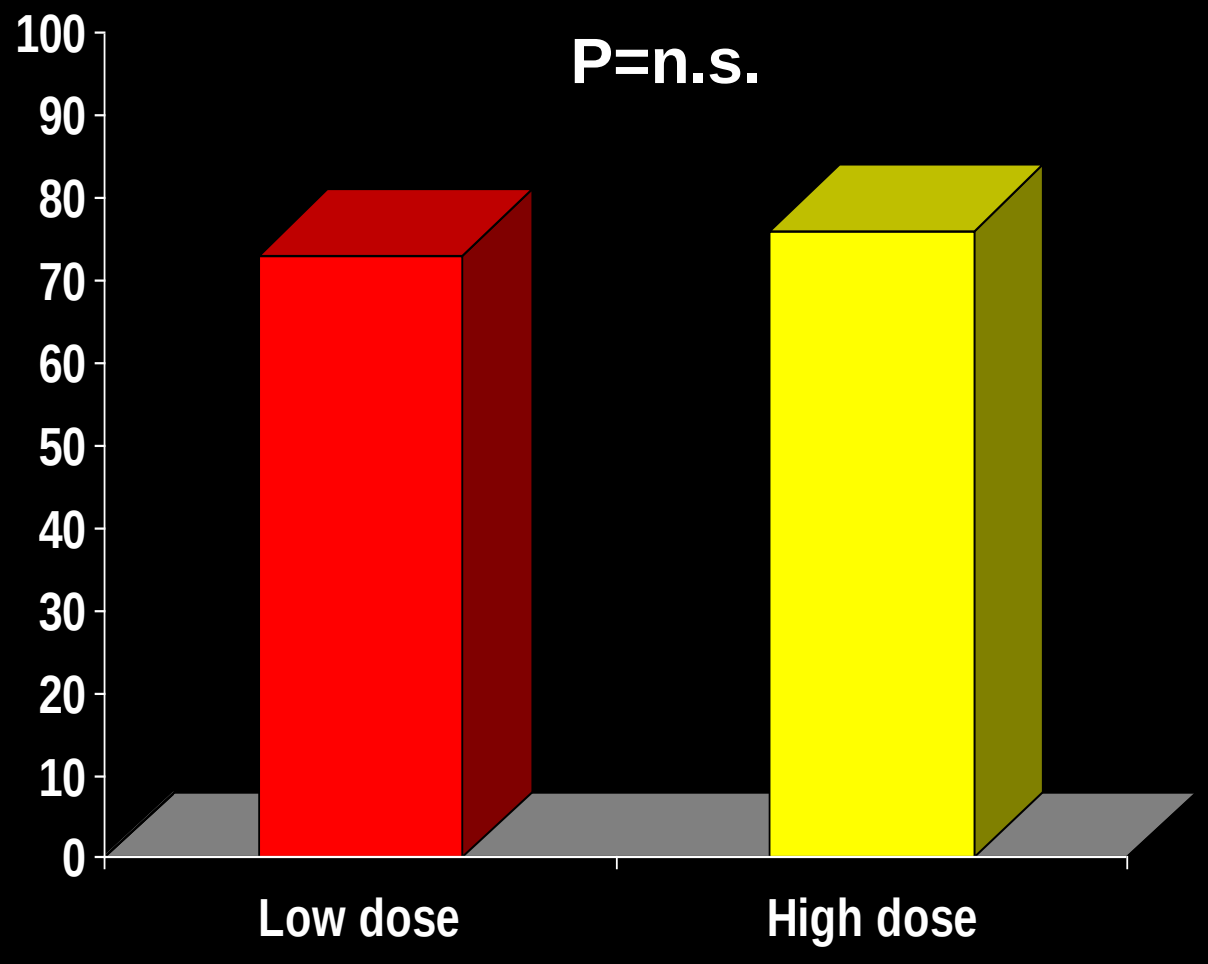
Long-term outcome in IgAN patients treated with Fish Oil

50% increase in serum creatinine



Donadio JV *et al*. J Am Soc Nephrol 1999; 10: 1772-1777

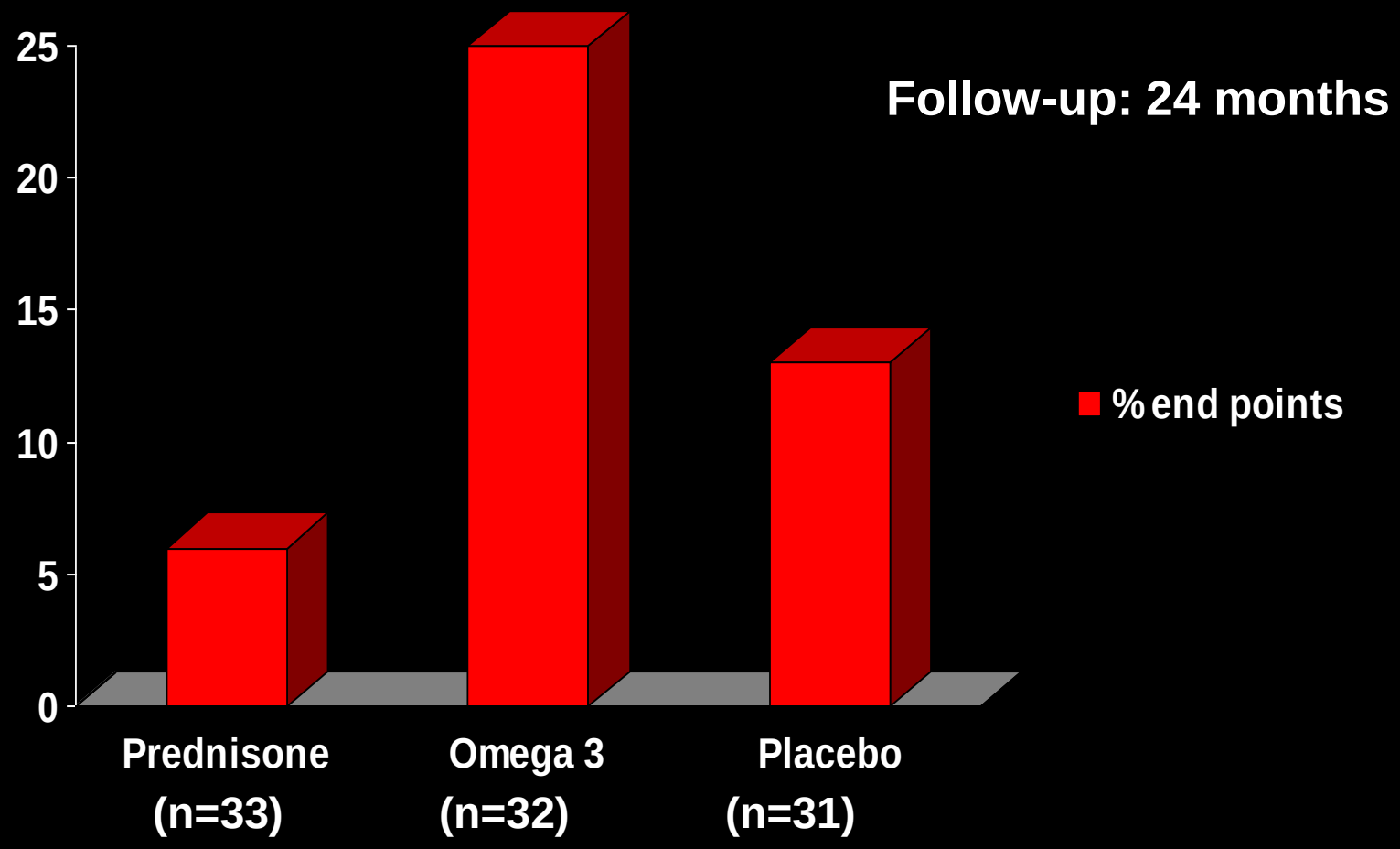
Renal survival after 3 years



Donadio JV et al. J Am Soc Nephrol 2001; 12: 791-799

Prednisone, omega 3 or placebo in IgAN percentage of end points (-60% GFR)

Age <40 yrs, GFR >50 ml/min and mild proteinuria (UPr/Cr >0.5)



Hogg RJ et al. ASN 2003

Is Fish oil therapy useful?

Available data are conflicting and do not show a clear benefit of fish oil therapy in IgAN

Therapeutic approaches in IgAN

- Tonsillectomy
- Low-antigen diets - sodium cromoglycate
- Phenytoin, dapsone, danazole
- ACE-inhibitors and AT1RA
- Fish oil
- Endothelin receptor antagonists - NO - Vitamine E
- Cyclosporin
- Immunoglobulin therapy
- Cytotoxic, antiplatelet and anticoagulant agents
- Steroids
- Immunosuppressants

THE LANCET

Corticosteroids in IgA nephropathy: a randomised controlled trial

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

Lancet 1999;353(9156):883–7

Therapeutic protocol

Serum Creatinine <1.6 mg/dl
Proteinuria 1 to 3.5 g/day

Group A:

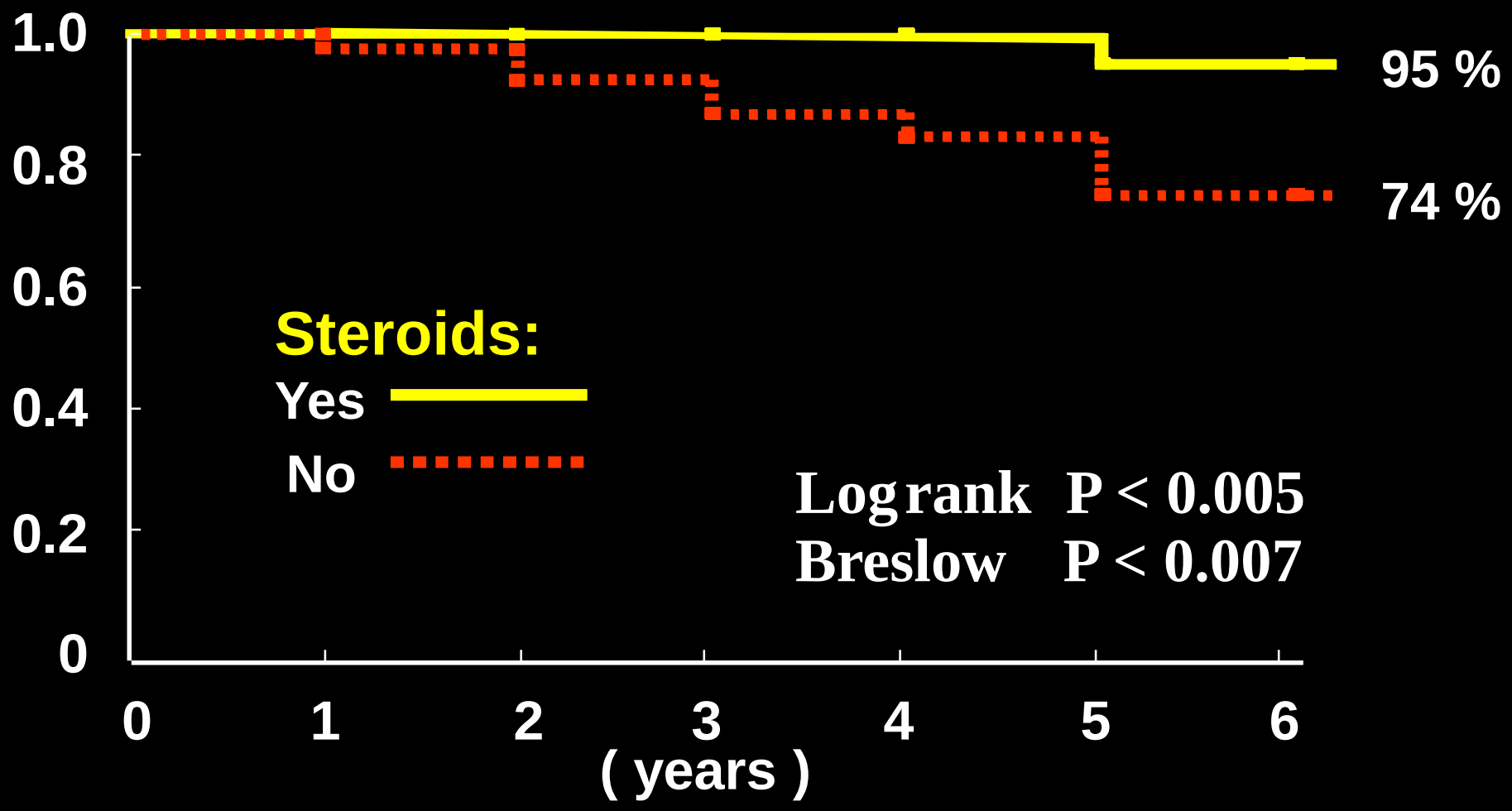
1 g of i.v. methylprednisolone for 3 days at the beginning of months 1, 3 and 5 combined with 0.5 mg/kg of oral prednisone given on alternative days for 6 months

Group B:

Supportive therapy

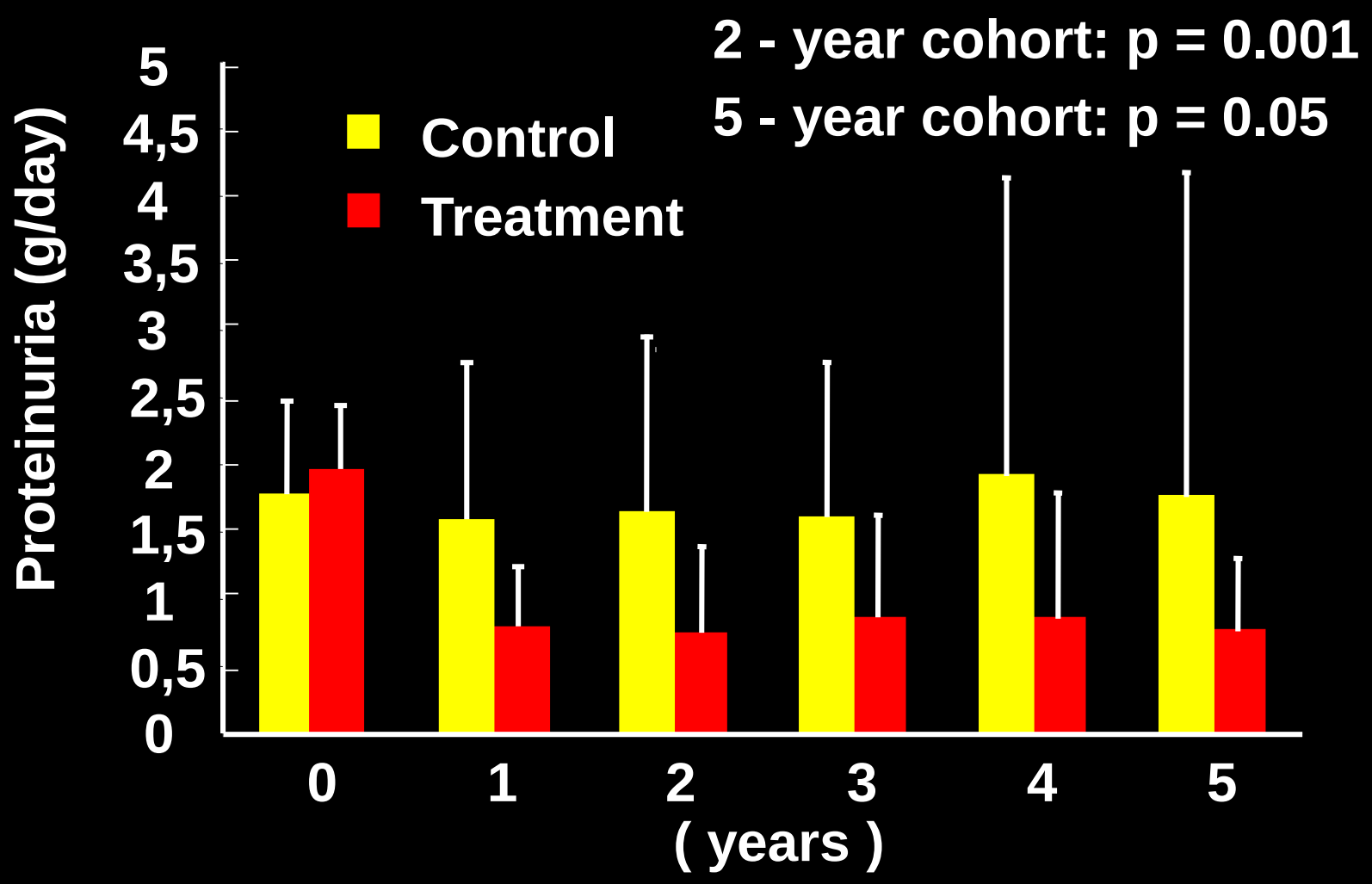
Renal survival without endpoint

100 % increase in plasma creatinine



Pozzi C….and Locatelli F. Lancet 1999; 353 (9156): 883-887

Proteinuria in the Italian Trial of Steroids



Locatelli F et al. Adv Nephrol Necker Hosp 1999; 29: 73-91

Journal of the American Society of Nephrology

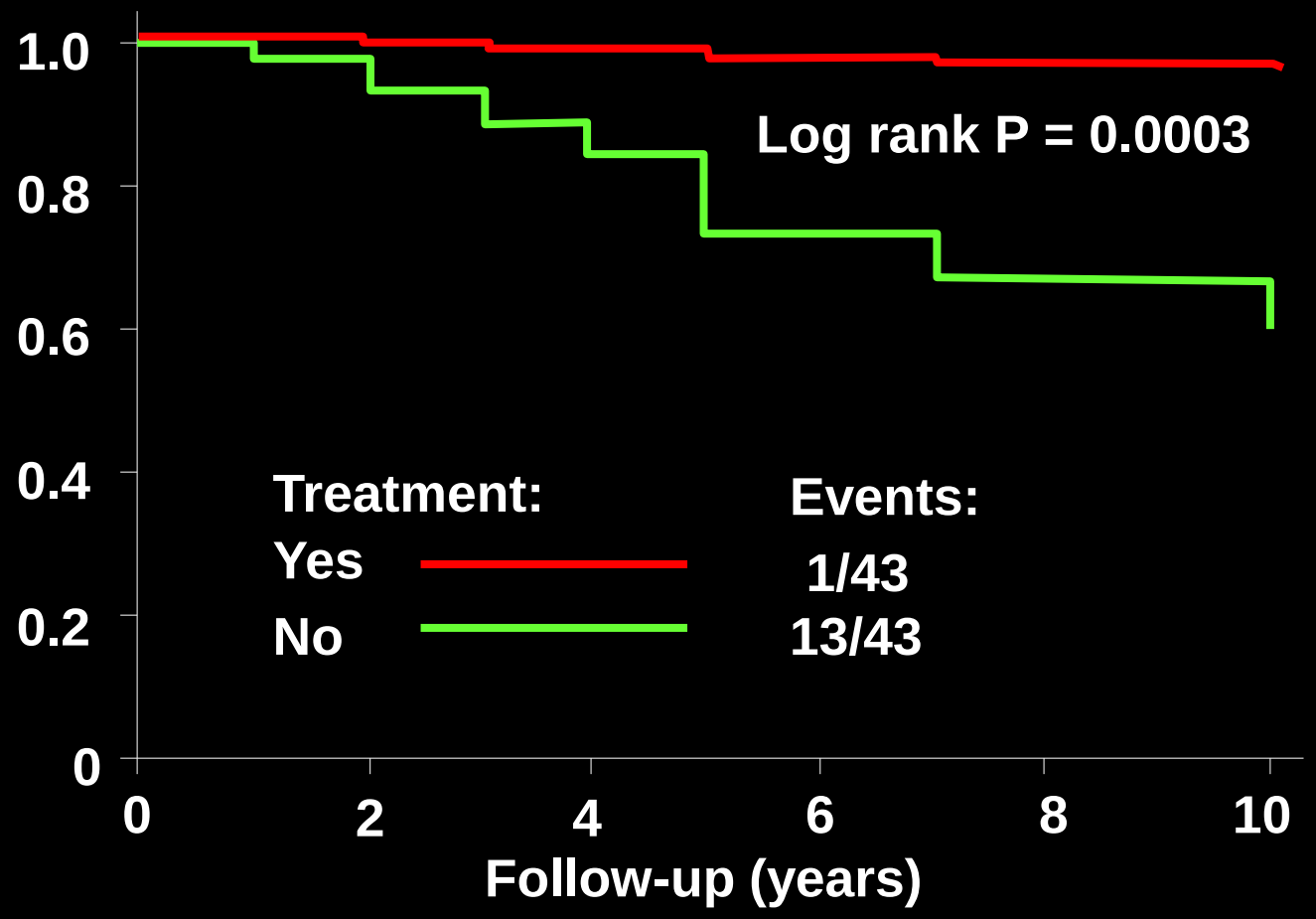
Corticosteroid Effectiveness in IgA Nephropathy: Long-Term Results of a Randomized, Controlled Trial

Claudio Pozzi, Simeone Andrulli, Lucia Del Vecchio, Patrizia Melis, Giovanni B. Fogazzi, Paolo Altieri, Claudio Ponticelli and Francesco Locatelli

J Am Soc Nephrol 2004; 15: 157-163

Corticosteroid effectiveness in IgA Nephropathy: long-term results

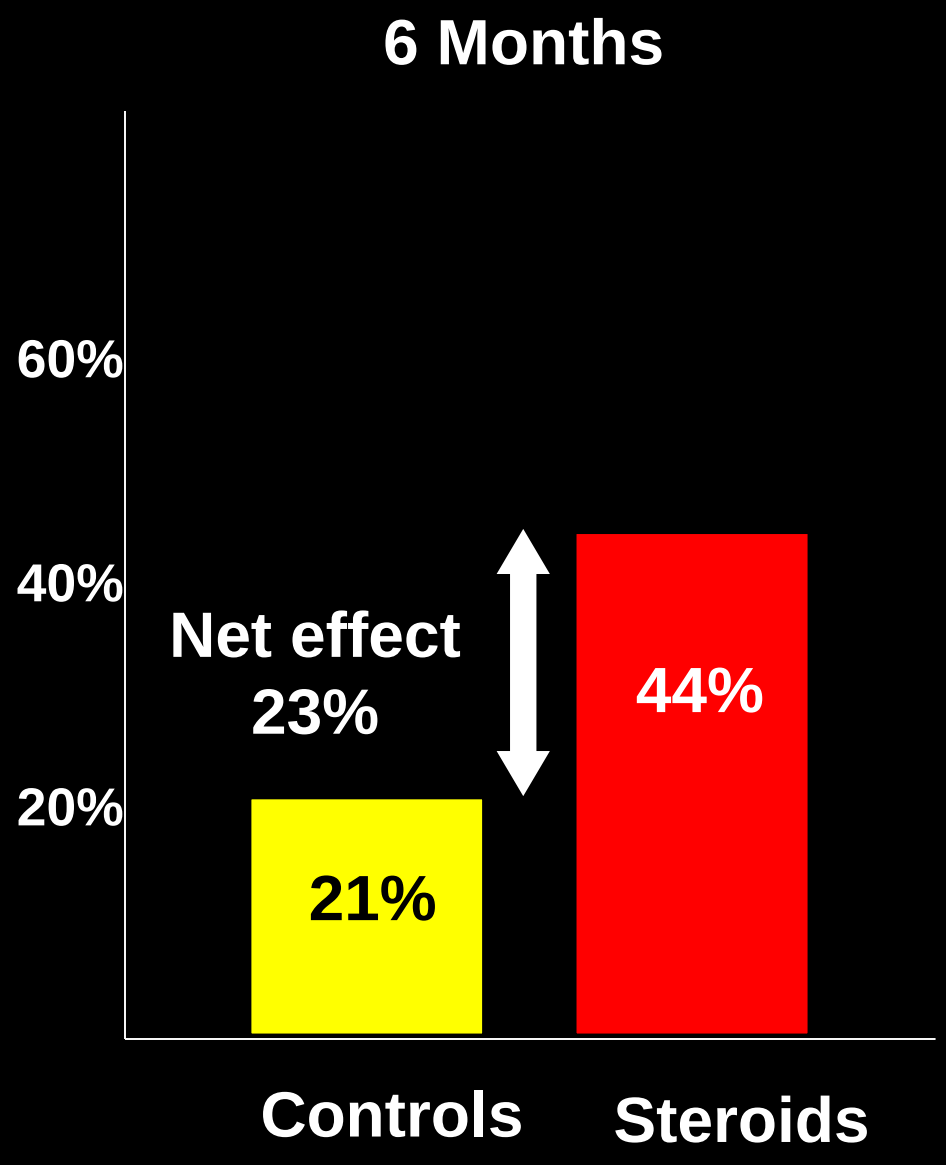
Survival without endpoint (creatinine doubling from baseline)

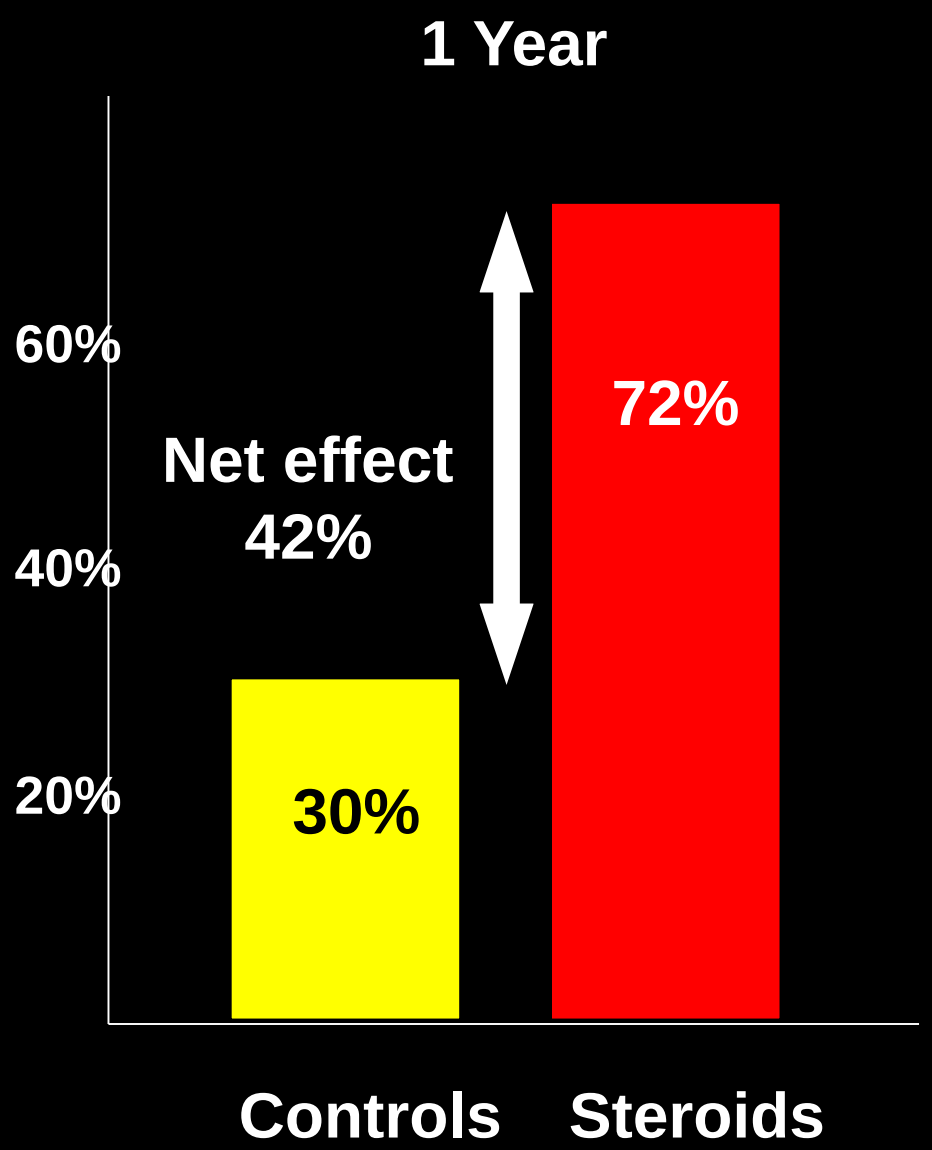


Pozzi C…and Locatelli F, J Am Soc Nephrol 2004; 15: 157-163

Minimal response: PROTEINURIA < 1 g/day

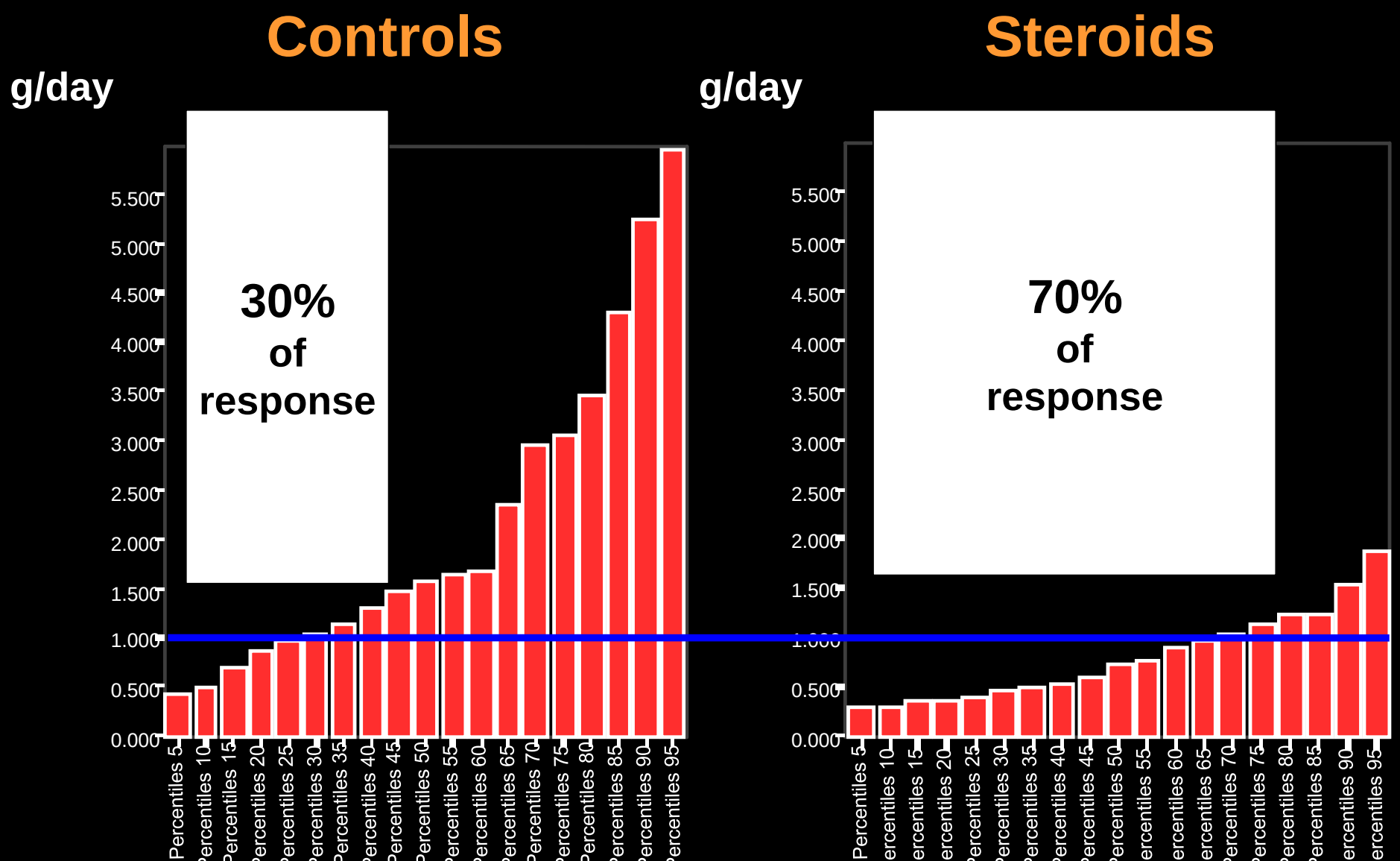
Pozzi C… and Locatelli F, J Am Soc Nephrol 2004; 15: 157-163





Median proteinuria over follow-up (7 years)

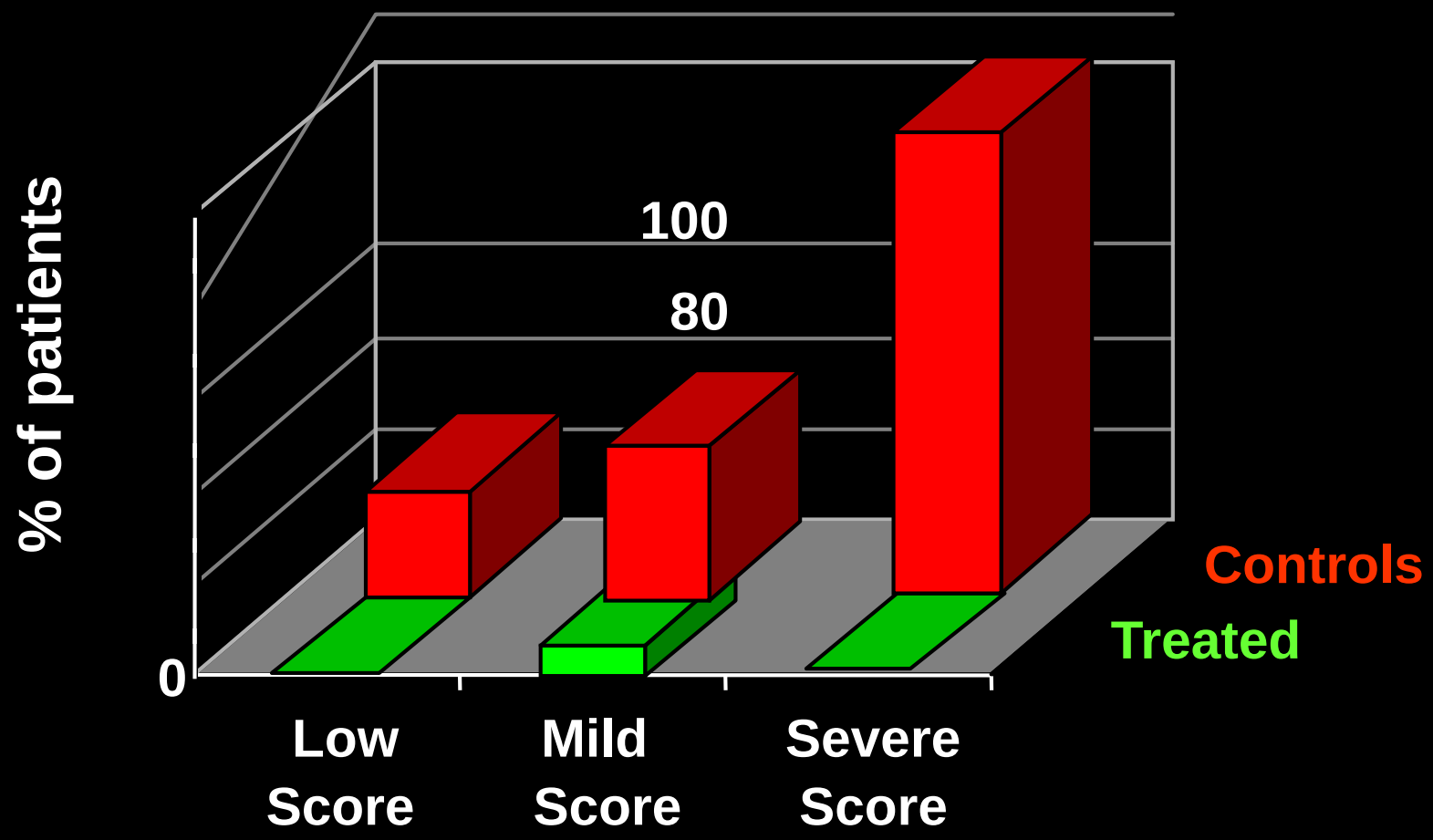
Pozzi C…and Locatelli F, J Am Soc Nephrol 2004; 15: 157-163



Development of endpoint in different classes of histologic score

Pozzi C…and Locatelli F, J Am Soc Nephrol 2004; 15: 157-163

% of patients who developed endpoint: doubling in serum creatinine



Side Effects / Adverse events

Weight increase: no difference between two groups (1.3 vs 1.0 kg of weight increase after 6 months)

Hypertension: no patient developed hypertension during 6 months of therapy.

Diabetes mellitus: 1 patient developed diabetes after 2 years of treatment.

No case of **gastroenterological/digestive haemorrhage**, **severe infection**, **glaucoma**, **pathological fracture**.

Mild side effects have not been evaluated: **acne**, **sleeplessness**, **hydrosaline retention**.

Pozzi C….and Locatelli F. Lancet 1999; 353 (9156): 883-887

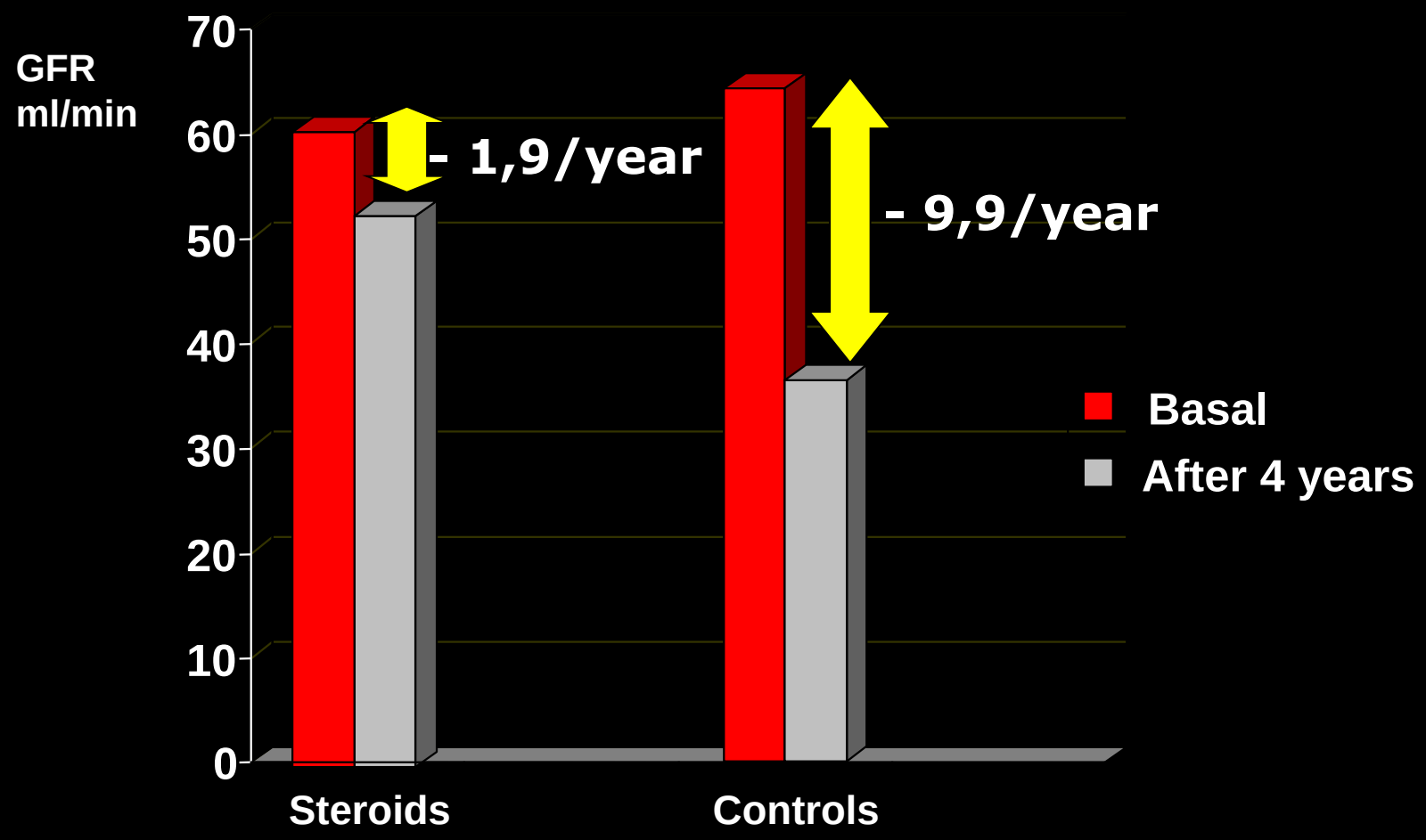
Effectiveness of steroid therapy in IgAN with impaired renal function

86 patients were enrolled and ramdomly assigned to treatment
18 of these patient had GFR <70 ml/min (mean: 60.7 ml/min)

Treatments:
- 10 pts treated (steroids for 6 months)
- 8 not treated

Pozzi C… and Locatelli F., Nephron 2002; 92: 699-701

Effectiveness of steroid therapy in IgAN with impaired renal function



Pozzi C…and Locatelli F., Nephron 2002; 92: 699-701

IgA Nephropathy with Severe Chronic Renal Failure a randomized controlled trial of Corticosteroids and Azathioprine

Pozzi, C., Andrulli, S., Pani, A., Scaini, P., Roccatello, D., Fogazzi, G., Pecchini, P., Rustichelli, R., Finocchiaro, P., Del Vecchio, L., and Locatelli, F.

Department of Nephrology and Dialysis, A. Manzoni Hospital, Lecco, Italy
Department of Nephrology and Dialysis, E. Bassini Hospital, Cinisello Balsamo, Milan, Italy
Department of Nephrology and Dialysis, G. Brotzu Hospital, Cagliari, Italy

Journal of Nephrology 26, 1, 2013, 86-93

Are steroids useful?

Available data indicate that
Steroids are effective
on proteinuria and renal survival,
especially in patients with normal renal function, but also in patients with mild renal insufficiency and severe histologic damage.

Therapeutic approaches in IgAN

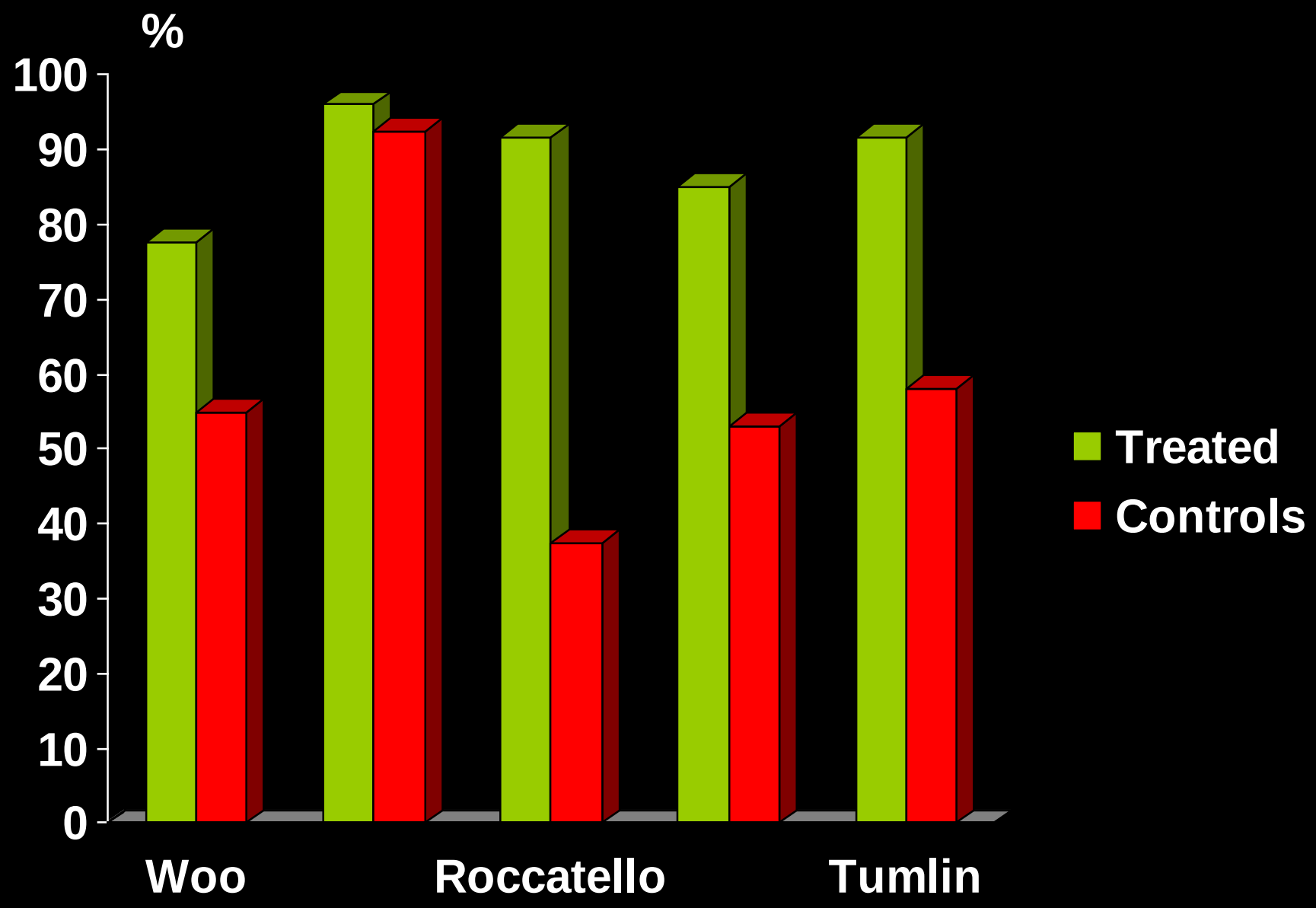
- Tonsillectomy
- Low-antigen diets - sodium cromoglycate
- Phenytoin, dapsone, danazole
- ACE-inhibitors and AT1RA
- Fish oil
- Endothelin receptor antagonists - NO - Vitamine E
- Cyclosporin
- Immunoglobulin therapy
- Cytotoxic, antiplatelet and anticoagulant agents
- Steroids
- Immunosuppressants

Immunosuppressants in IgAN

- Corticosteroids ↑↑
- Cyclophosphamide ↑
- Cyclosporine ↓
- Mycophenolate ↑?
- Azathioprine ↓
- Mizoribine ?
- Tacrolimus ?
- Rituximab ↓

Controlled studies on cyclophosphamide

Renal survival



CYCLOSPORINE

Autor	pts n	Protocol	GFR ml/min	Dose	Proteinuria	Renal function
Lai 1987	24	Not Rnd	> 50	5 mg/kg x 3 months	↓	↓
Chabova 1997	6	Not Rnd	70	5 mg/kg > 12 months	↓	↑

There are no randomized studies on cyclosporine

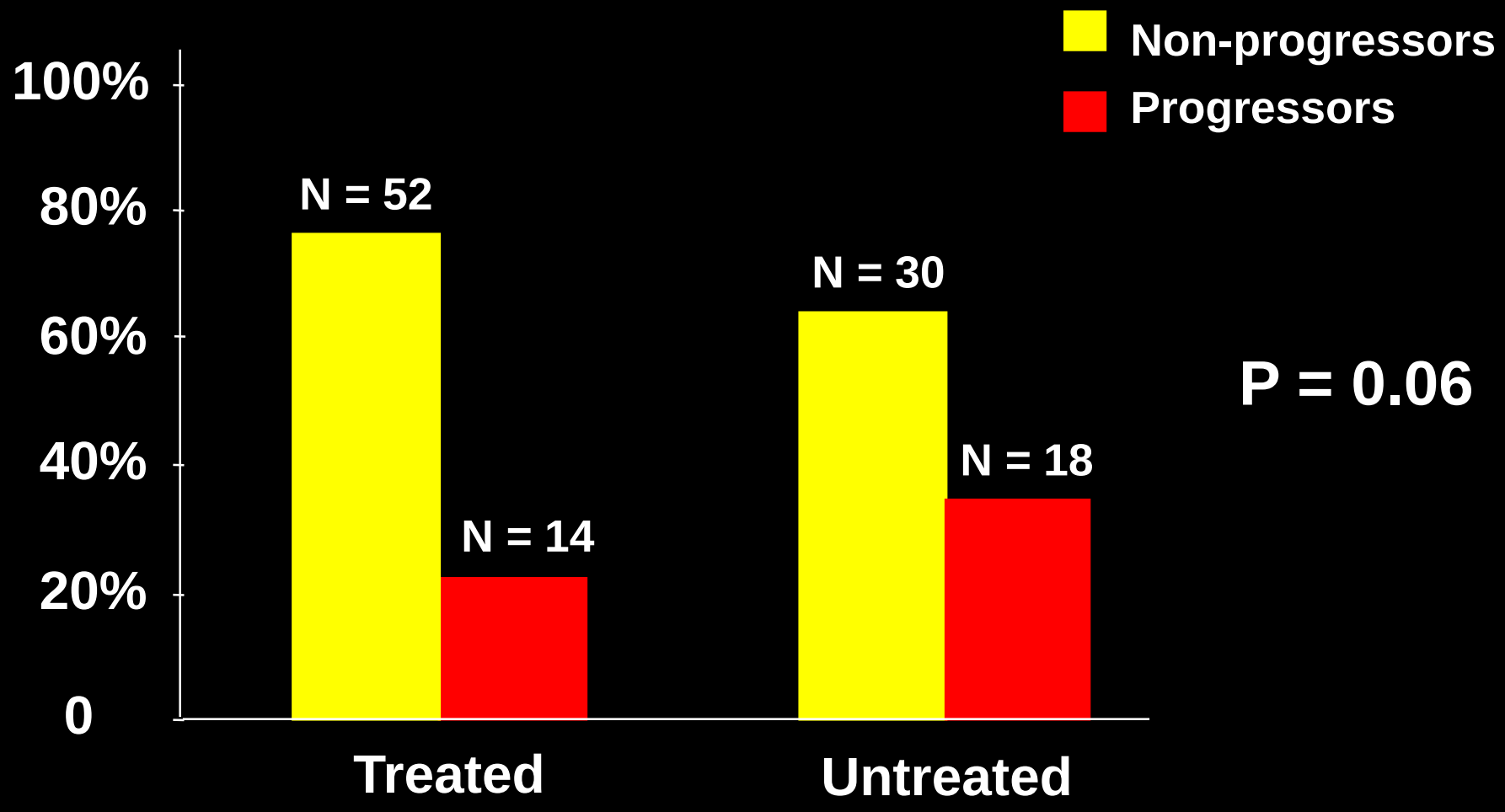
Cyclosporine is not actually used in therapy of IgAN

MIZORIBINE

Autor	pts n	Protocol	GFR	Time	Proteinuria
Nagaoka 2002	10	Not Rnd	normal	20 months	↓
Yagi 2003	30	Cont. Not Rnd	normal	6 months	↓ Cx↓↓
Kawasaki 2004	34	Not Cont	normal	6 months	↓

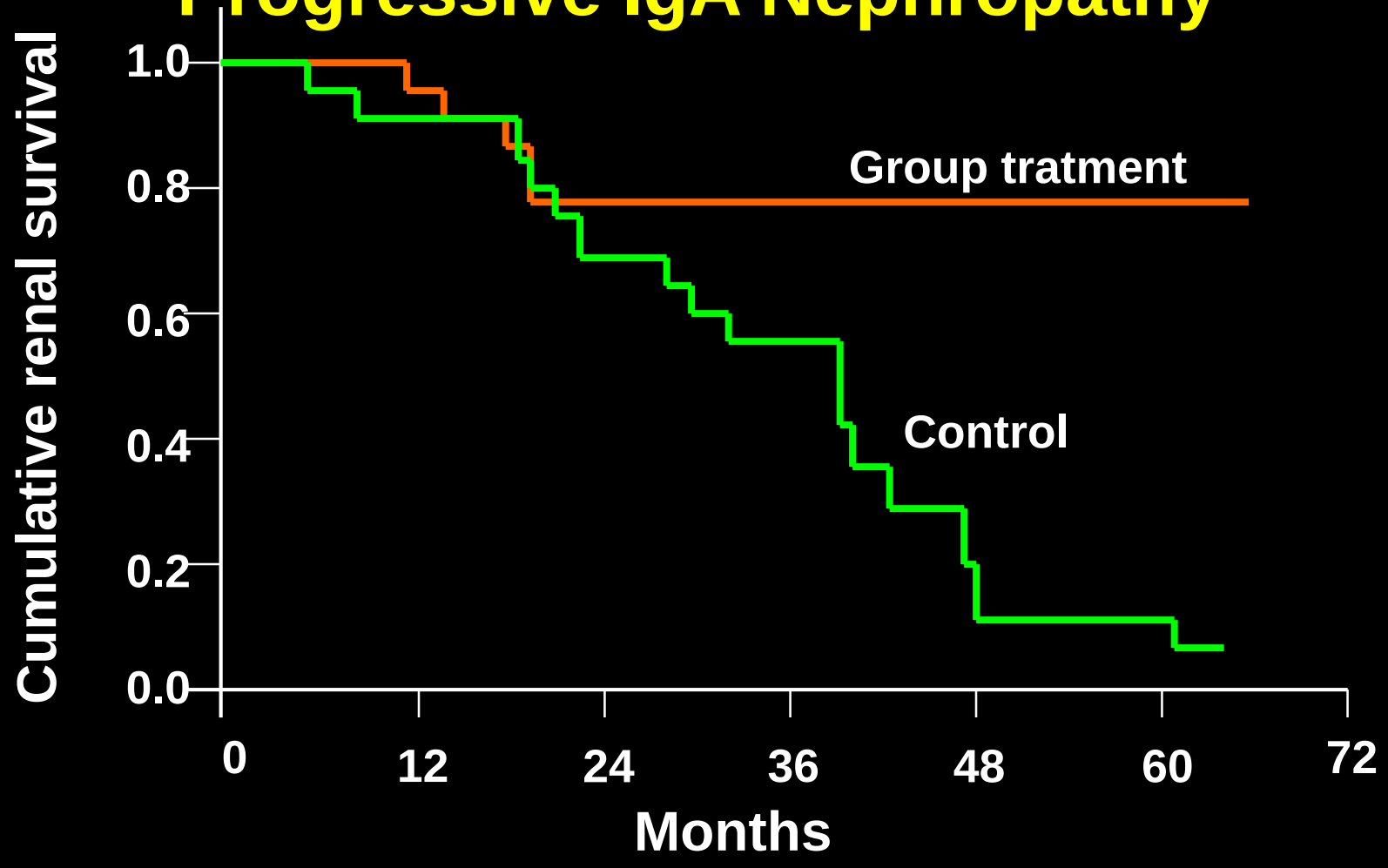
Corticosteroids were used in all protocols. Available data are not sufficient

Steroids & Azathioprine in IgAN



Goumenos D et al. Nephrol Dial Transplant 1995; 10: 1173-81

Controlled Prospective Trial of Prednisolone and Cytotoxics in Progressive IgA Nephropathy



Ballardie FW et al. J Am Soc Nephrol 2002; 13: 142-148

Steroids & Azathioprine in IgAN

	Goumenos (1995)	Ballardie (2002)
Trial design	Retrosp	Rnd-Prosp
Drugs	Ster-aza	Ster-cyclo-aza
Patients	114	38
Therapy (months)	18	24
Follow-up (months)	46	24-72
Proteinuria	=	⬇
Renal survival	⬆	⬆

Side effects

Goumenos: 15% of treated patients

Non-Hodgkin's lynphoma (1), epidermal carcinoma (1), infection (3), diabetes mellitus (1), Cushingoid feature (6), gastrointestinal disease (3), acne (3), transaminase's increase (1).

Ballardie: 16% of treated patients

Medullary inhibition (1), pulmonary tuberculosis (1), diabetes mellitus (1).

Yoshikawa: 25% of treated patients

alopecia (1), anemia (1), leukopenia (3), glaucoma (1), cataract (1), peptic ulcer (1), depression (1), transaminase's increase (1).

Journal of Nephrology

Combined treatment with steroids and azathioprine in IgA nephropathy: design of a prospective randomised multicentre trial

Locatelli F, Pozzi C, Del Vecchio L, Andrulli S, Pani A, Fogazzi G, Altieri P, Ponticelli C.

J Nephrol 1999 ;12 (5): 308-11

The New Italian Trial in IgAN

Study design: Multicentric, non-blinded, randomized

RECRUITMENT

Between 1998 and 2001

Stratum I
creatinine ≤ 1.3 mg/dl

Stratum II
creatinine >1.3 and ≤ 2.0 mg/dl

Randomization (Lecco Hospital)

Steroids

Steroids & Azathioprine

5-year follow-up

CLINICAL RESEARCH www.jasn.org

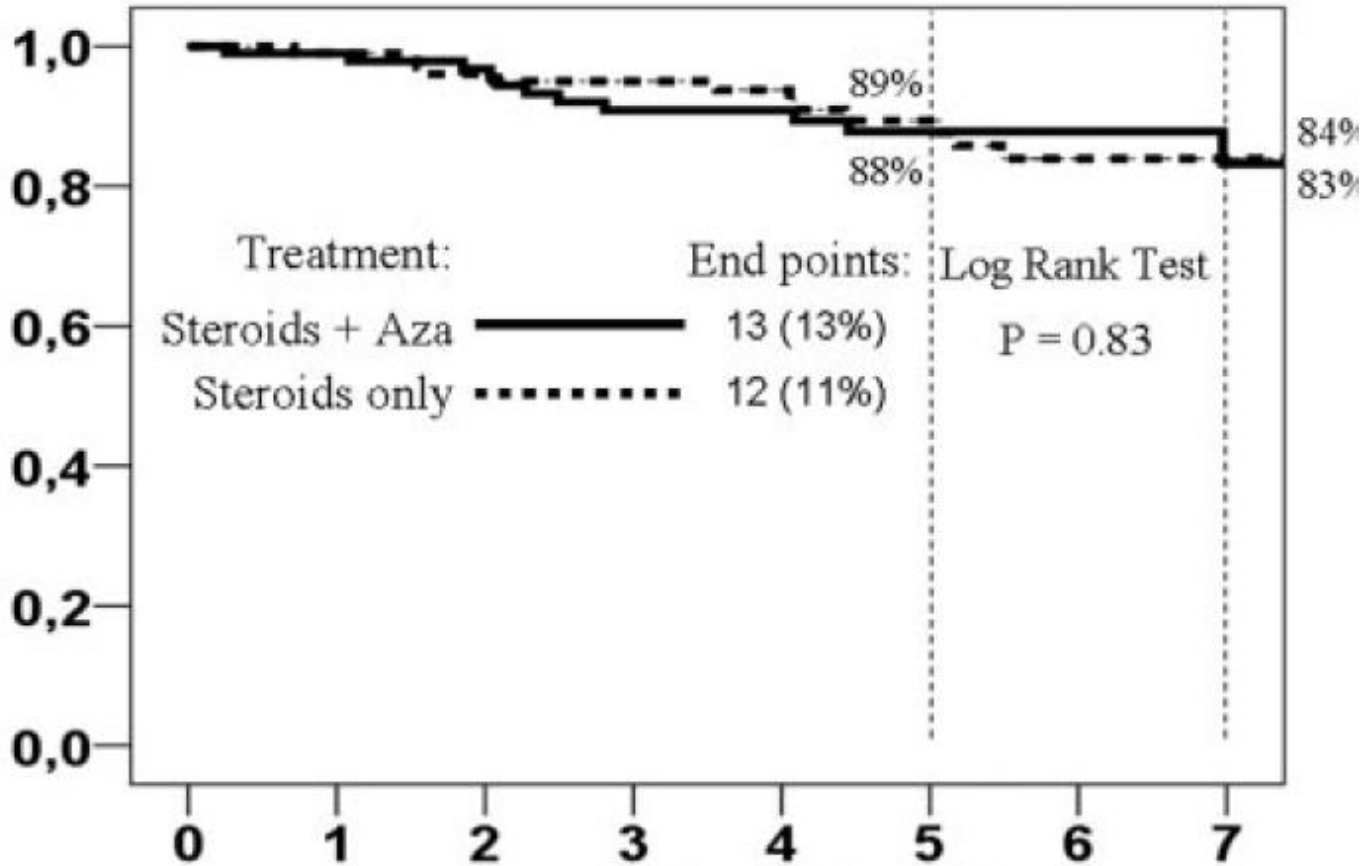
Addition of Azathioprine to Corticosteroids Does Not Benefit Patients with IgA Nephropathy

Claudio Pozzi,*† Simeone Andrulli,* Antonello Pani,‡ Patrizia Scaini,§ Lucia Del Vecchio,* Giambattista Fogazzi,‖ Bruno Vogt,¶ Vincenzo De Cristofaro,** Landino Allegri,†† Lino Cirami,‡‡ Aldo Deni Procaccini,§§ and Francesco Locatelli*

*Departments of Nephrology and Dialysis, Ospedale A. Manzoni, Lecco, Italy; †Ospedale E. Bassini, Cinisello Balsamo, Milan, Italy; ‡Ospedale G. Brotzu, Cagliari, Italy; §Spedali Civili, Brescia, Italy; ‖Ospedale Maggiore IRCCS, Milan, Italy; ¶University Hospital of Vaudois, Lausanne, Switzerland; **Ospedale di Sondrio, Sondrio, Italy; ††Ospedale Universitario, Parma, Italy; ‡‡Ospedale Careggi, Florence, Italy; and §§Ospedale Universitario, Foggia, Italy

J Am Soc Nephrol 21: 1783–1790, 2010. doi: 10.1681/ASN.2010010117

Addition of Azathioprine to Corticoids
No benefits

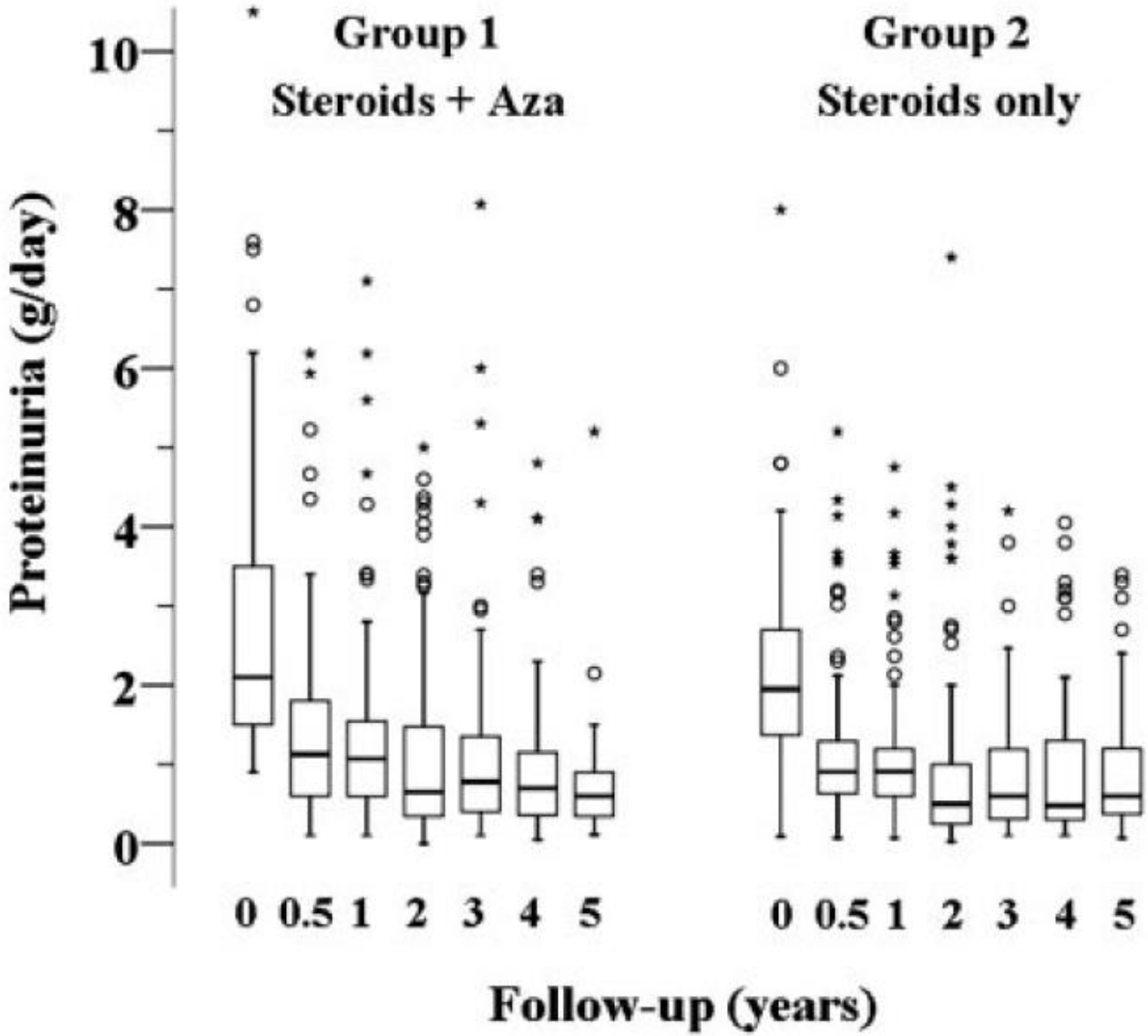


Patients at risk by treatment:

Steroids+Aza	101	90	84	74	65	47	35	17
Steroids	106	101	93	82	67	53	31	19

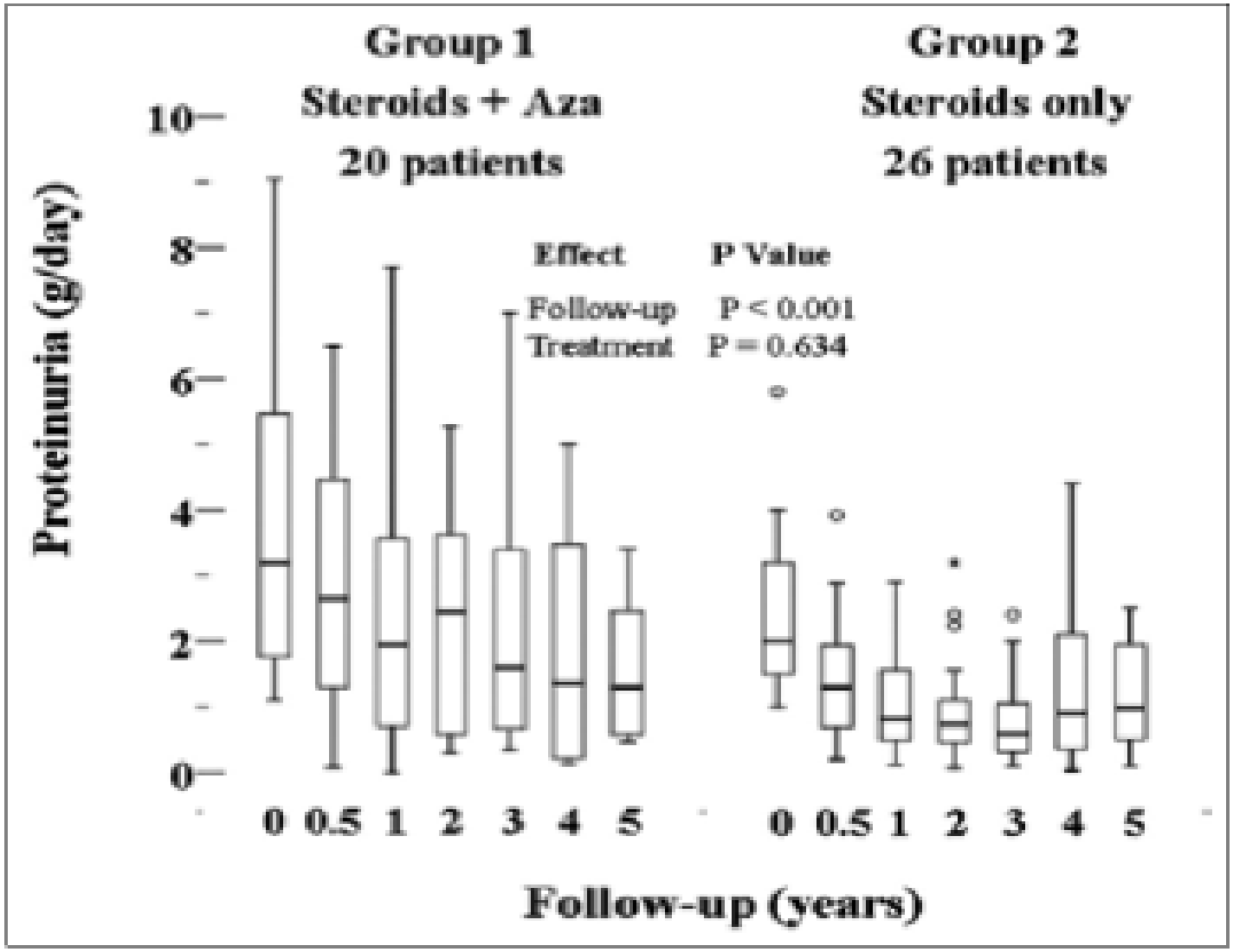
Pozzi C.... and Locatelli F. *J Am Soc Nephrol* 21: 1783–1790, 2010. doi: 10.1681/ASN.2010010117

Addition of Azathioprine to Corticoids : No benefits



Pozzi C…and Locatelli F. *J Am Soc Nephrol* 21: 1783–1790, 2010. doi: 10.1681/ASN.2010010117

IgA nephropathy with severe chronic renal failure
Behaviour of Proteinuria during the trial follow -up



Pozzi C.,…and Locatelli F. Journal of Nephrology 26, 1, 2013, 86-93

Addition of Azathioprine to Corticoids
No benefits

In conclusion, a 6-month course of corticosteroids plus low-dose azathioprine seems to produce no additional benefit over steroids alone in reducing the risk of progression to ESRD in patients with IgAN, and it may increase the number of adverse events.

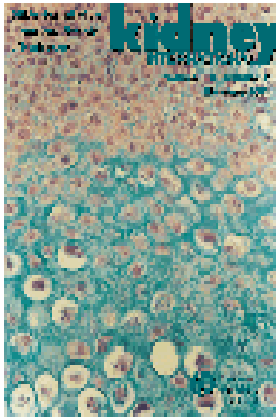
Pozzi C….and Locatelli F. *J Am Soc Nephrol* 21: 1783–1790, 2010. doi: 10.1681/ASN.2010010117

Are Immunosuppressants useful?

Available data do not show a clear benefit of immunosoppressive therapy in IgAN.

Nevertheless, some studies suggest that cyclophosphamide administration may be useful in patients with mild renal insufficiency and severe histologic damage.

Kidney International
Volume 68 Issue 2 Page 802 - August 2005
doi:10.1111/j.1523-1755.2005.00460.x



Mycophenolate mofetil alleviates persistent proteinuria in IgA nephropathy

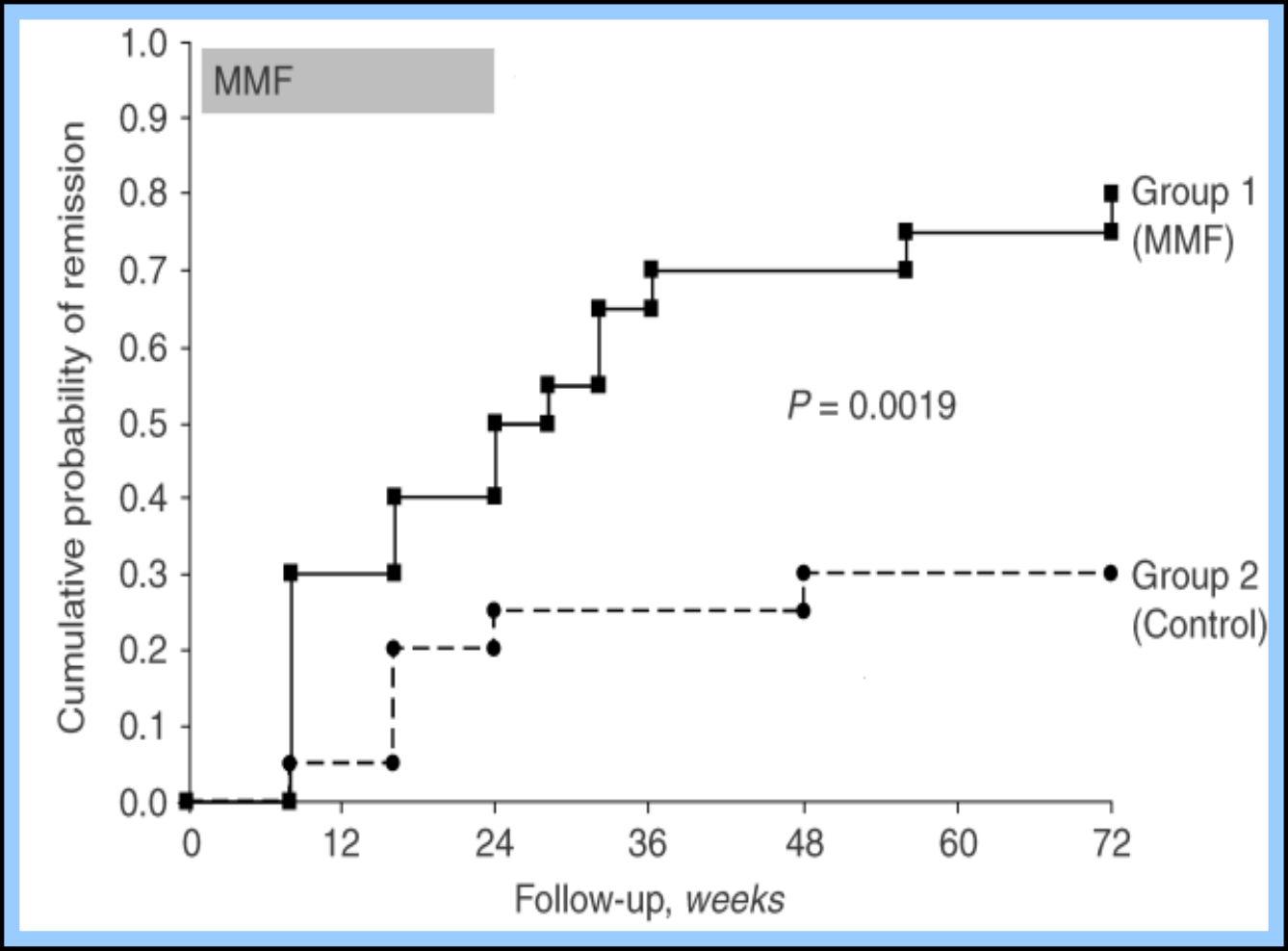
SYDNEY TANG, JOSEPH C.K. LEUNG*, LORETTA Y.Y. CHAN*, YUN HOI LUI*, COLIN S.O. TANG*, CHI HANG KAN*, YIU WING HO*, and KAR NENG LAI**

- **Prospective, randomised study**
- **40 IgAN patients with persistent proteinuria**
- **Treatment: MMF for 24 wks or convent. therapy**
- **72 weeks of follow up**

Primary end - point: Proteinuria reduction > 50% from baseline

Mycophenolate mofetil in IgA nephropathy

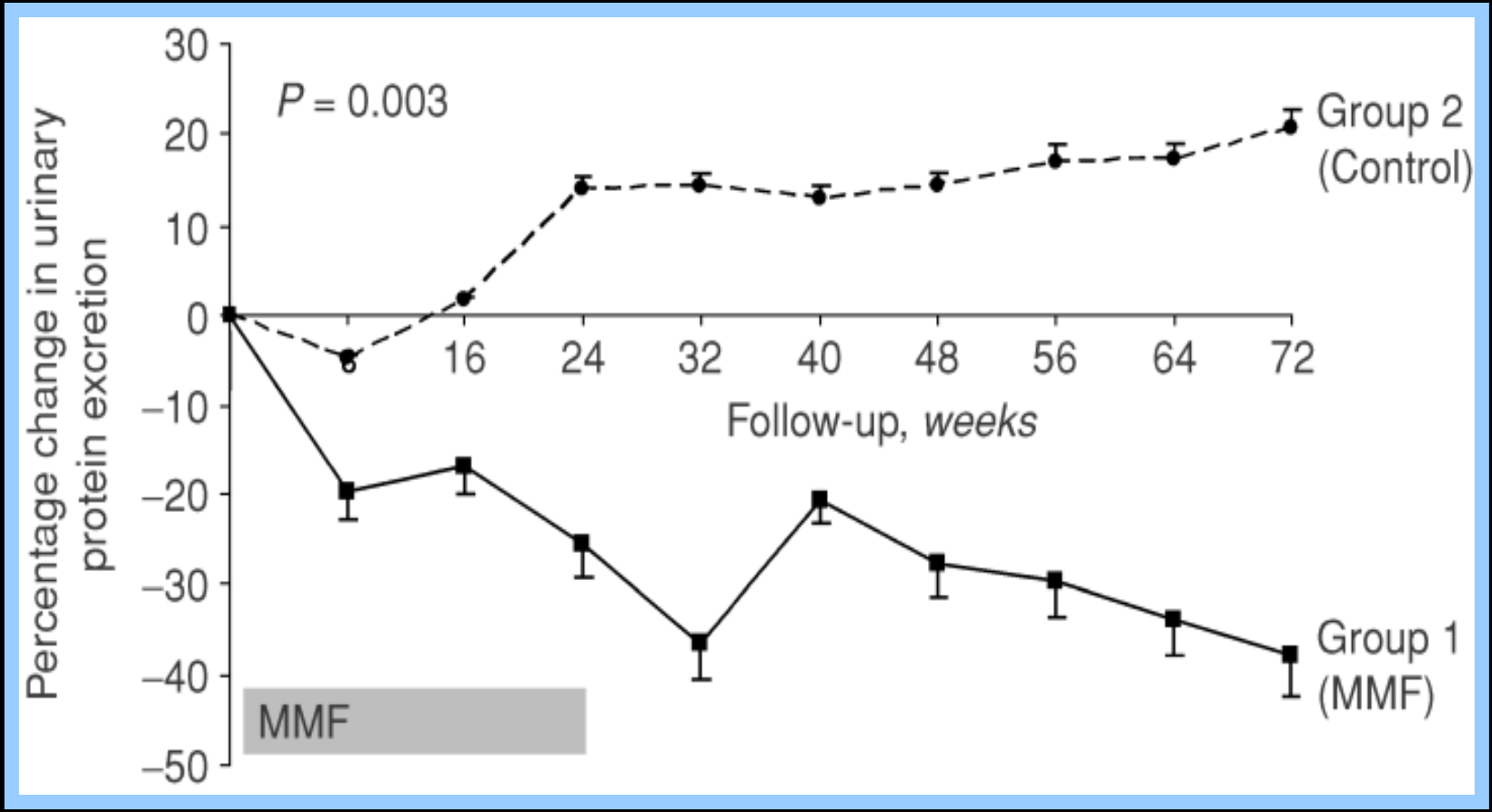
Probability of achieving remission of proteinuria



Tang S et al. Kidney Int 2005; 68: 802-812

Mycophenolate mofetil in IgA nephropathy

Percentage change in protenuria



Tang S et al. Kidney Int 2005; 68: 802-812

Nephrology Dialysis Transplantation

Original Article

Mycophenolate mofetil (MMF) *vs* placebo in patients with moderately advanced IgA nephropathy: a double-blind randomized controlled trial

Gershon Frisch, Julie Lin, Jordan Rosenstock, Glen Markowitz, Vivette D'Agati, Jai Radhakrishnan, Dean Preddie, John Crew, Anthony Valeri and Gerald Appel

Nephrol Dial Transplant 2005 20(10): 2139 - 45

MMF and IgAN: study design

Inclusion criteria N = 32

- Proteinuria > 1g/24h
- Creatinine clearance, <80 and >20 ml/min
- Hypertension
- Glomerulosclerosis or tubulointerstitial atrophy and fibrosis on renal biopsy

Treatment

- MMF (1000 mg BID) for 1 year OR Placebo

Frisch G et al. Nephrol Dial Transplant 2005 20(10): 2139 - 45

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

N ENGL J MED 373;23 NEJM.ORG DECEMBER 3, 2015

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*

Aim of the Study

in patients with IgA nephropathy

- **We tested the hypothesis that**

  Immunosuppressive therapy plus supportive care

  Would be superior to

  Supportive care alone

- **With the use of two primary end points:**

  full clinical remission

  and

  a decrease in the eGFR of at least 15 ml per minute per 1.73 m2

  of body surface area after 3 years of follow-up.

Aim of the Study

We conducted a multicenter, open-label, randomized, controlled trial with a two-group, parallel group-sequential design

During a 6-month run-in phase, supportive care (in particular, blockade of the renin–angiotensin system) was adjusted on the basis of proteinuria

Randomization

Patients that, after 6 months of run-in, have a proteinuria between 0.75 and 3.5 gr/die entered the study phase (3 years) and randomized to

- **Mantain the supportive therapy (supportive-care group)**
- **Add to the supportive and immunosoppressive therapy (immunosuppression group)**

Primary end Points
In hierarchical order

- **Full clinical remission at the end of the trial**
  (protein-to-creatinine ratio <0.2 : measured in grams]

  and

- **a decrease in the estimated glomerular filtration rate [eGFR]**
  of <5 ml per minute per 1.73 m2 of body-surface area from baseline
  and
  a decrease in the eGFR of at least 15 ml per minute per 1.73 m2
  at the end of the trial

Run-in-phase: 6 months

- During a 6-month run-in phase, all the patients received comprehensive supportive care that included blockers of the renin–angiotensin system to lower blood pressure to a target below 125/75 mm Hg

- If proteinuria remained above the target of 0.75 g per day ,despite blood-pressure control, the dose of renin–angiotensin system blocker was increased to the maximum approved daily dose or to the highest dose at which the patient did not have unacceptable side effects

Run-in-phase: 6 months

- **Patients received dietary counseling and were advised to quit smoking and to avoid nonsteroidal antiinflammatory drugs and other nephrotoxins**

- **Total cholesterol levels were lowered to less than 200 mg per deciliter (5.2 mmol per liter) with the use of statins, if necessary**

Therapy

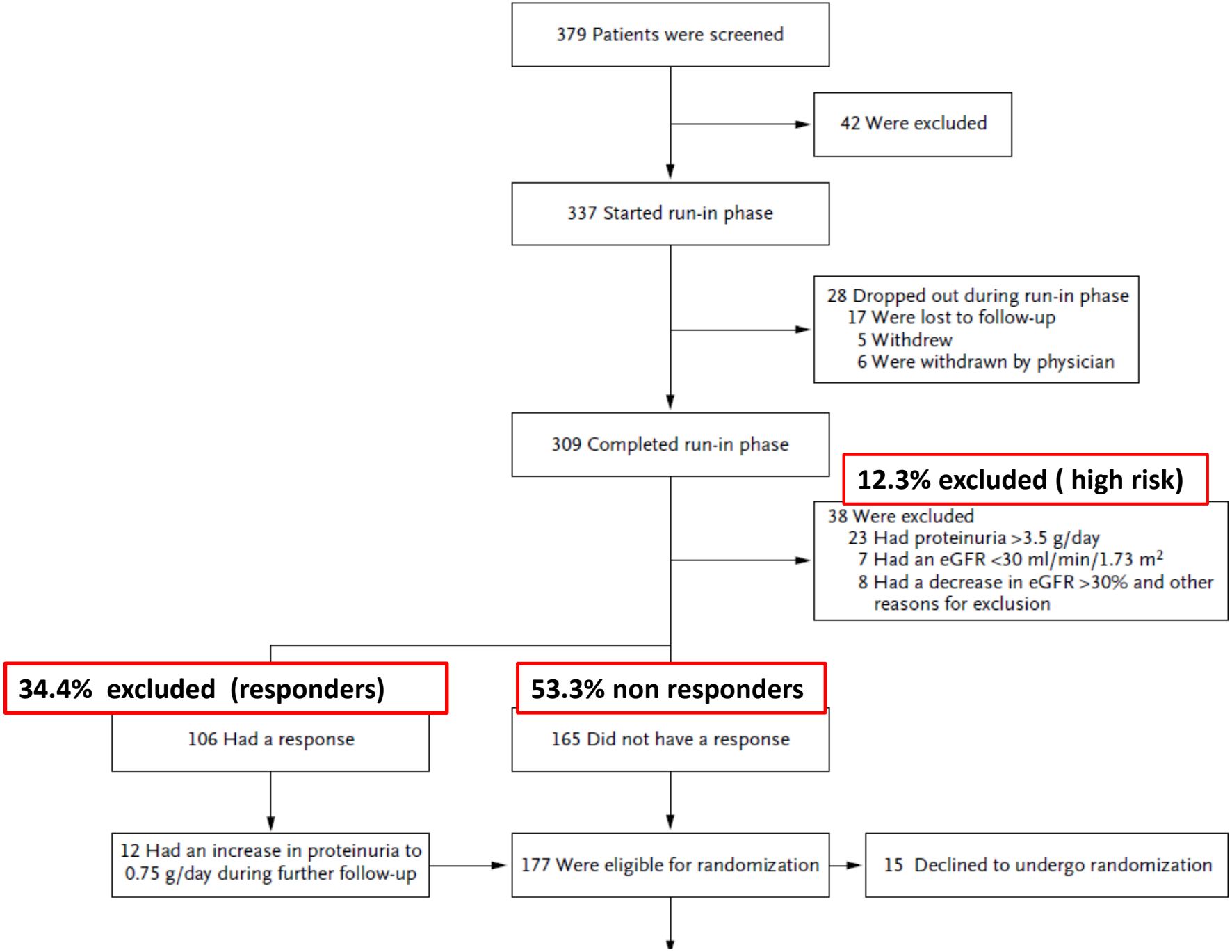
Immunosuppression group (2 schemes)

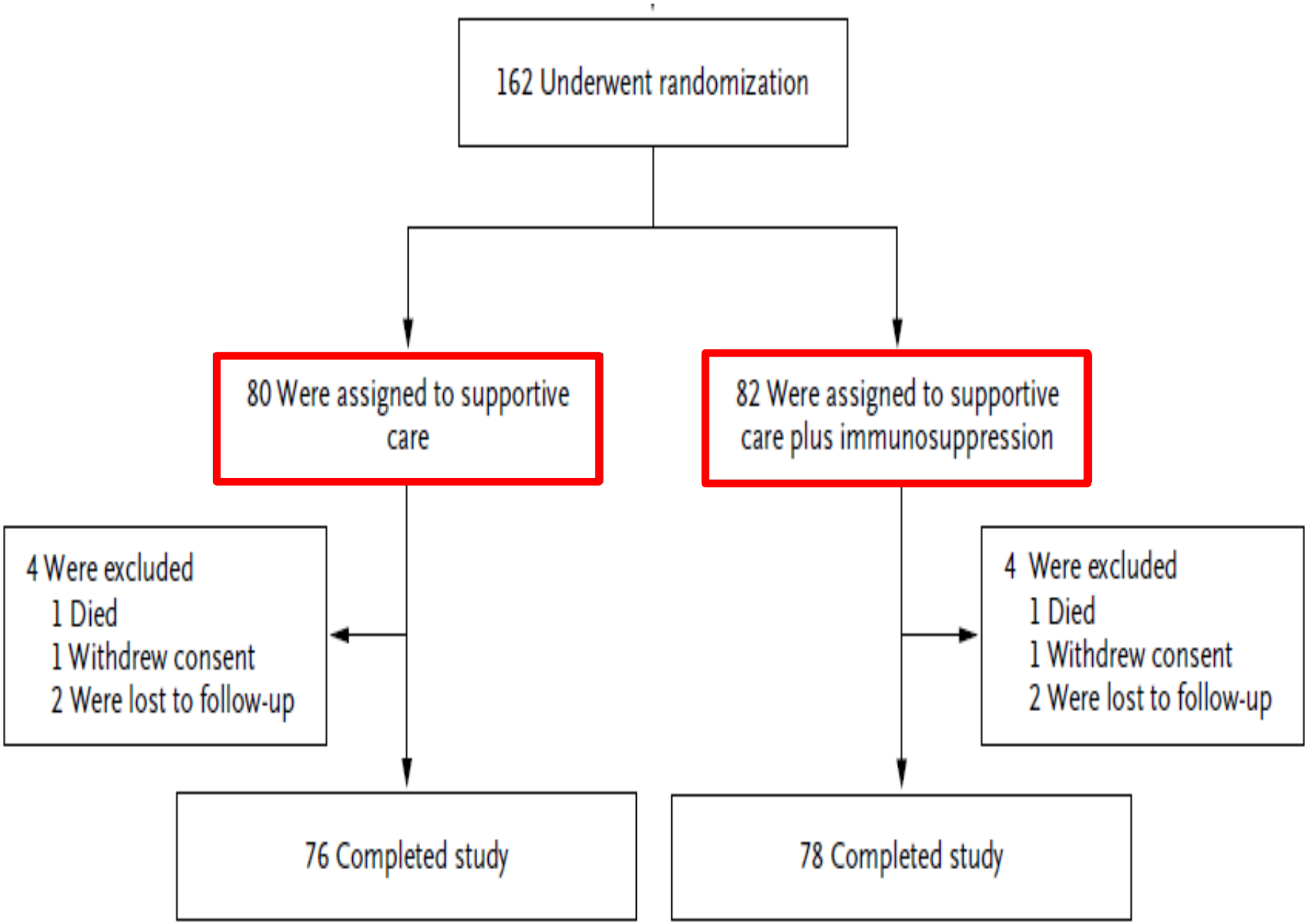
Patients with eGFR ≥ 60 ml/min:

- 1 gr iv of metilprednisolone for 3 days months 1, 3, 5 then prednisone 0.5 gr/kg every other day for 6 months

Patients with eGFR 59-30 ml/min:

- Ciclofosfamide 1.5 mg/kg/die for 3 months, then azatioprine 1.5 mg/kg/die for 32 months, associated with prednisolone 40 mg/die progressively tapered to withdrawal after 36 months.


379 Patients were screened
42 Were excluded
337 Started run-in phase
28 Dropped out during run-in phase
17 Were lost to follow-up
5 Withdrew
6 Were withdrawn by physician
309 Completed run-in phase
12.3% excluded (high risk)
38 Were excluded
23 Had proteinuria >3.5 g/day
7 Had an eGFR <30 ml/min/1.73 m2
8 Had a decrease in eGFR >30% and other reasons for exclusion
34.4% excluded (responders)
53.3% non responders
106 Had a response
165 Did not have a response
12 Had an increase in proteinuria to 0.75 g/day during further follow-up
177 Were eligible for randomization
15 Declined to undergo randomization


162 Underwent randomization
80 Were assigned to supportive care
82 Were assigned to supportive care plus immunosuppression
4 Were excluded
1 Died
1 Withdrew consent
2 Were lost to follow-up
4 Were excluded
1 Died
1 Withdrew consent
2 Were lost to follow-up
76 Completed study
78 Completed study

Results at 36 months

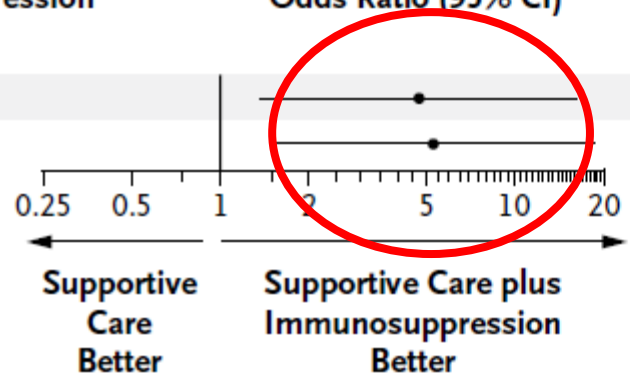
Primary end points

A. Complete Remission (proteinuria/creatininuria < 0.2)

stable renal function (eGFR reduction < 5 ml/min)

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	14/82	4.82 (1.43–16.30)	0.01
Available-case analysis	4/72	14/71	5.38 (1.55–18.66)	0.008



Complete Remission : **Supportive 4 (5%) Immunosuppression 14 (17%)**

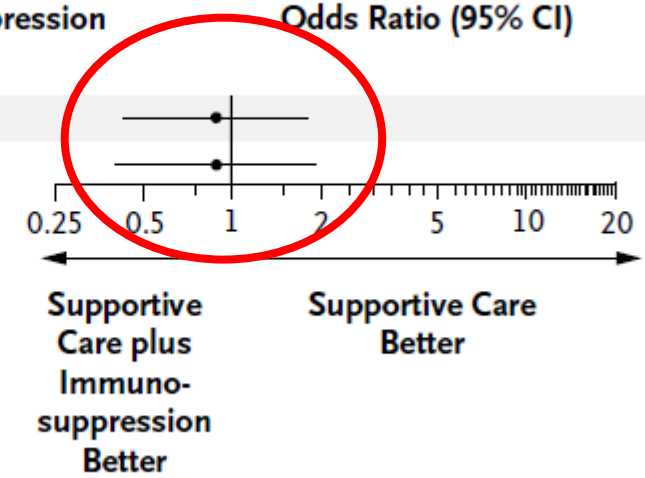
Results at 36 months

Primary end points

B. eGFR reduction of 15 ml/min versus baseline

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	21/82	0.89 (0.44–1.81)	0.75
Available-case analysis	18/76	17/78	0.89 (0.41–1.90)	0.76



Progression: Immunosuppression 21 (26%) Supportive 22 (28%)

Secondary end points

Secondary End Point	Supportive Care (N=80)		Supportive Care plus Immunosuppression (N=82)		Odds Ratio (95% CI)	P Value
	Patients with Available Data	End-Point Value	Patients with Available Data	End-Point Value		
	no.	*mean ±SD or no. (%)*	*no.*	*mean ±SD or no. (%)*		
Absolute eGFR change at 36 mo — ml/min/1.73 m^2	71	−4.7±12.3	72	−4.2±14.1	Not determined	0.32
Mean annual change in the slope of the reciprocal of serum creatinine concentration — mg/dl	77	−0.02±0.06	74	−0.01±0.06	Not determined	0.60
At 12 mo	67	0.80±0.67	59	0.57±0.53	Not determined	0.01
At 36 mo	64	0.85±0.66	59	0.76±0.90	Not determined	0.66
eGFR decrease ≥30 ml/min/1.73 m^2	76	7 (9)	78	10 (13)	1.45 (0.51–4.10)	0.49
Onset of end-stage renal disease	76	6 (8)	78	6 (8)	0.97 (0.29–3.22)	0.96
Disappearance of microhematuria	55†	9 (16)	57†	24 (42)	3.73 (1.52–9.14)	0.004

Microematuria disappeared

No other significant difference between the two treatment groups

Adverse Events

Variable	Supportive Care (N=80)	Supportive Care plus Immunosuppression (N=82)	P Value
Patients with ≥1 serious adverse event — no.	21	29	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 amino-transferase >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

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*

N ENGL J MED 373;23 NEJM.ORG DECEMBER 3, 2015

In conclusion, our trial showed that the addition of immunosuppression to ongoing comprehensive supportive care was not beneficial in patients with IgA nephropathy that was characterized by moderate proteinuria and chronic kidney disease stages 1 through 3.

Authors' CONCLUSIONS

- **The addition of immunosuppressive therapy to intensive supportive care in patients with high-risk IgA nephropathy did not significantly improve the outcome**

- **During the 3-year study phase, more adverse effects were observed among the patients who received immunosuppressive therapy, with no change in the rate of decrease in the eGFR.**

Authors' Conclusions

In conclusion, our trial showed that the addition of immunosuppression to ongoing comprehensive supportive care was not beneficial in patients with IgA nephropathy that was characterized by moderate proteinuria and chronic kidney disease stages 1 through 3.

Can we agree with these conclusions?

Critical aspects

1. Lack of hystological evaluation

RESEARCH PROTOCOL

JNEPHROL 2008; 21: 284-289

www.sin-italy.org/jnonline – www.jnephrol.com

Supportive Versus Immunosuppressive Therapy of Progressive IgA Nephropathy (STOP) IgAN trial: rationale and study protocol

Frank Eitner[1], Diana Ackermann[2], Ralf-Dieter Hilgers[2], Jürgen Floege[1]

[1] Division of Nephrology and Immunology, RWTH University of Aachen, Aachen - Germany
[2] Institute of Medical Statistics, RWTH University of Aachen, Aachen - Germany

Inclusion criteria

Patients with the following criteria can be included in the trial:

- Male or female patients aged from 18 to 70 years with histologically proven primary IgAN with typical mesangioproliferative features diagnosed within the last 3 years. Diagnosis has to have been made by a nephropathologist.

Critical Aspects

1. Lack of hystological evaluation

2. **Immunosuppression group includes two very different patient groups**

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Rauen T, Eitner F, Fitzner C, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. N Engl J Med 2015;373:2225-36. DOI: 10.1056/NEJMoa1415463

Patient Characteristics at Baseline Within the Immunosuppressive treatment Group Divided by Immunosuppressive Regimen

	Trial Phase	
	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)
	Steroids 6 months	Ster, Ciclof, Aza 36 months

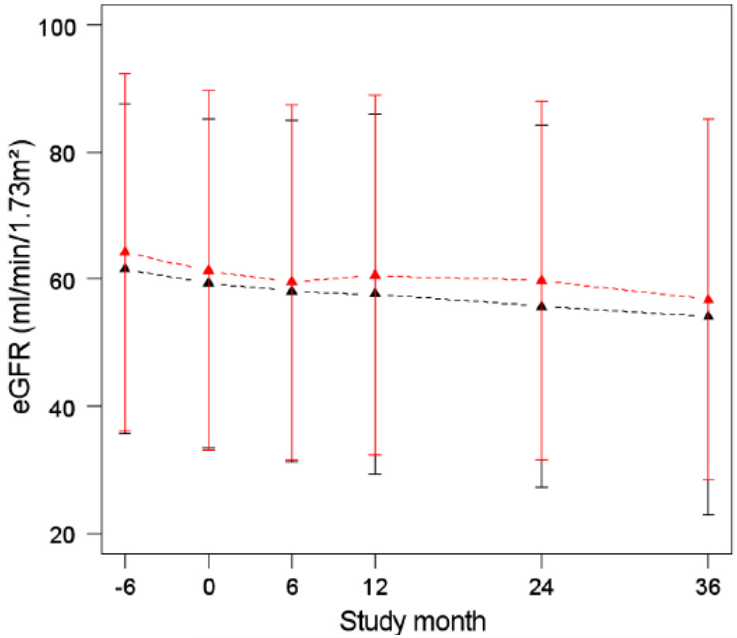
Critical aspects

1. Lack of hystological evaluation

2. The immunosuppression group includes two very different patient groups

3. The prognostic value of proteinuria on renal survival is not confermed

Despite the significant, though moderate, effects on proteinuria, we did not observe a significant effect of immunosuppressive therapy on a decrease in the eGFR over the 3-year study pe-



Supplementary Appendix

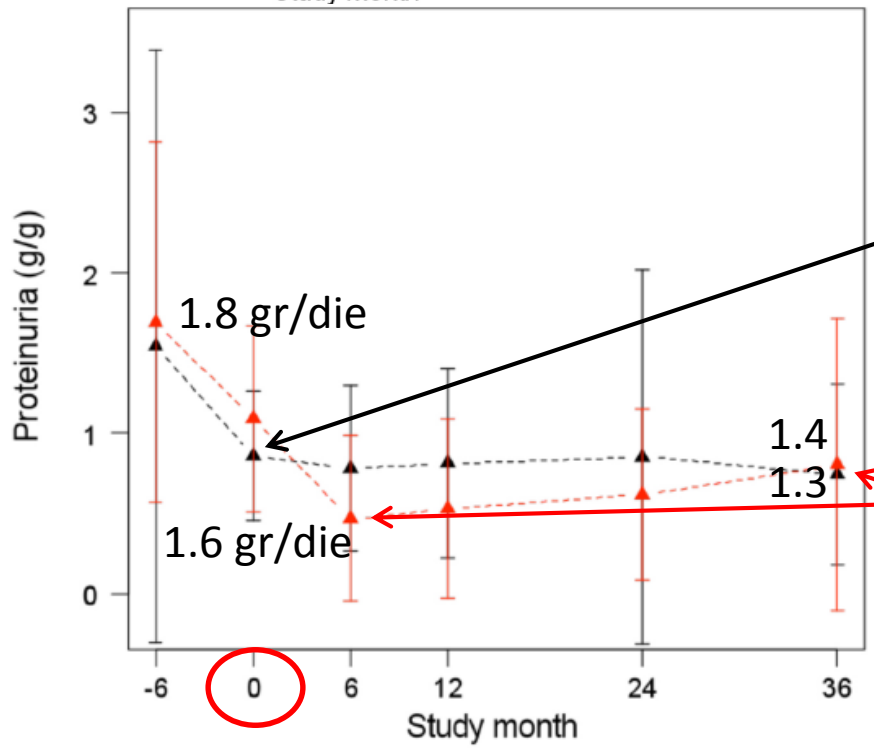
This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Rauen T, Eitner F, Fitzner C, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. N Engl J Med 2015;373:2225-36. DOI: 10.1056/NEJMoa1415463

Supportive therapy: .....

Immunosoppressive therapy : .....

6 months of RAS block reduced proteinuria only in 34% of the patients



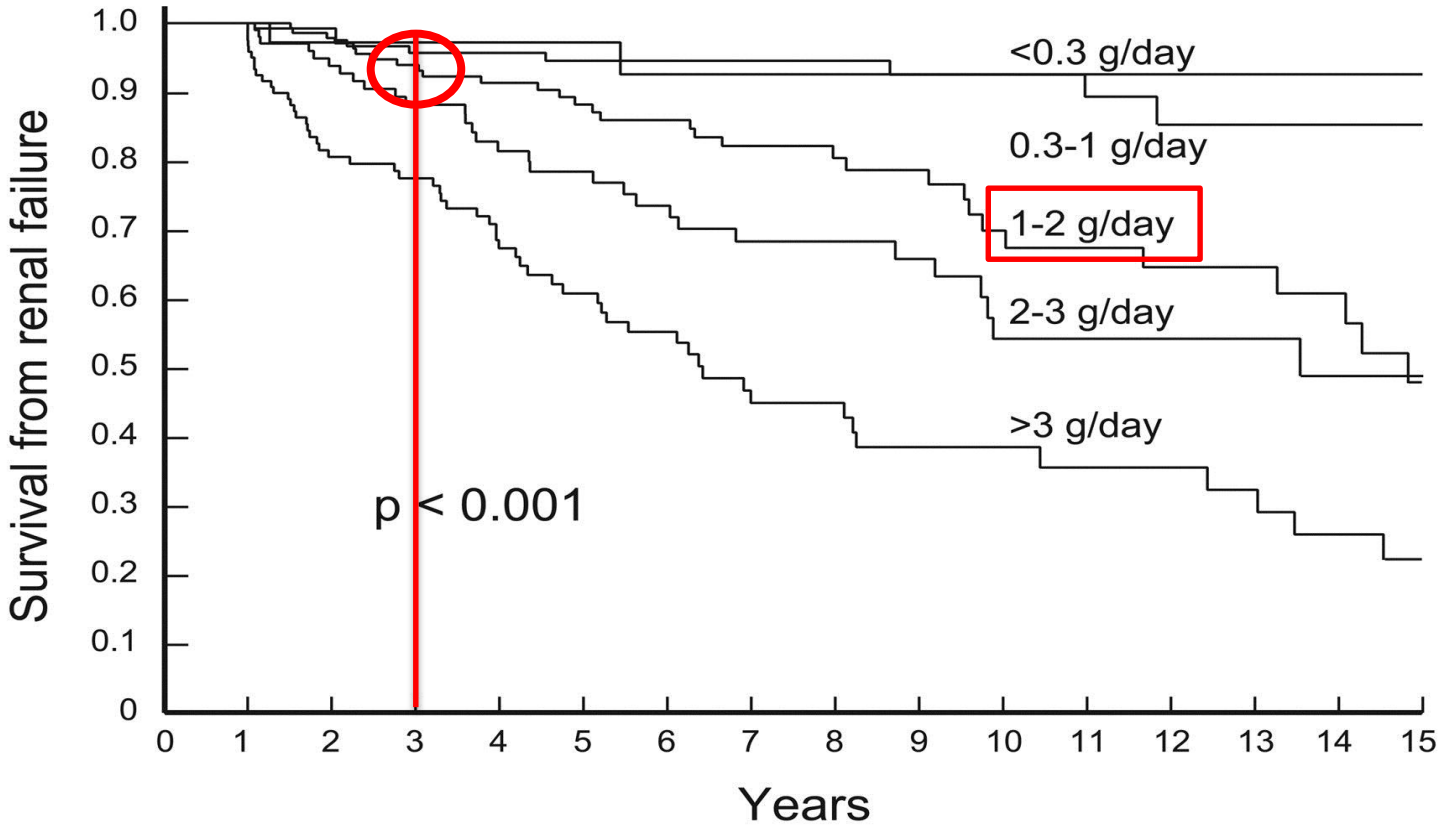
After Run-in RAS blockers seem to vanish their antiproteinuric effect (proteinuria during FU between 1.6 and 1.3 gr/die)

Adding immunosoppressors further reduced proteinuria, that increses again after 6 months

Rauen T et al, NEJM 2015

Time-Average Proteinuria and Renal Survival

541 canadian patients (caucasian and asian)



<0.3 g/day	37	22	8	1
0.3-1 g/day	134	79	35	11
1-2 g/day	145	79	28	10
2-3 g/day	105	50	18	4
>3 g/day	120	44	13	6

Reich HN et al, JASN 2007

Immunosuppression Group

Patients of"immunosuppression" group were evaluated as a whole

- **Patients with eGFR ≥ 60 ml/min**

  1 gr iv of metilprednisolone for3 days months 1, 3 e 5 then prednisone 0.5 gr/kg every other day for 6 months

- **Patients with eGFR 59-30 ml/min**

  Ciclofosfamide 1.5 mg/kg/die for 3 months, then azatioprine 1.5 mg/kg/die for 32 months, associated with prednisolone 40 mg/die with progressively tapered till to withdrawal after 36 months.

Was the proteinuria behaviour similar between the 2 groups?

Proteinuria/Hematuria Outcome Parameters in the Two Immunosuppressive Treatment Arms

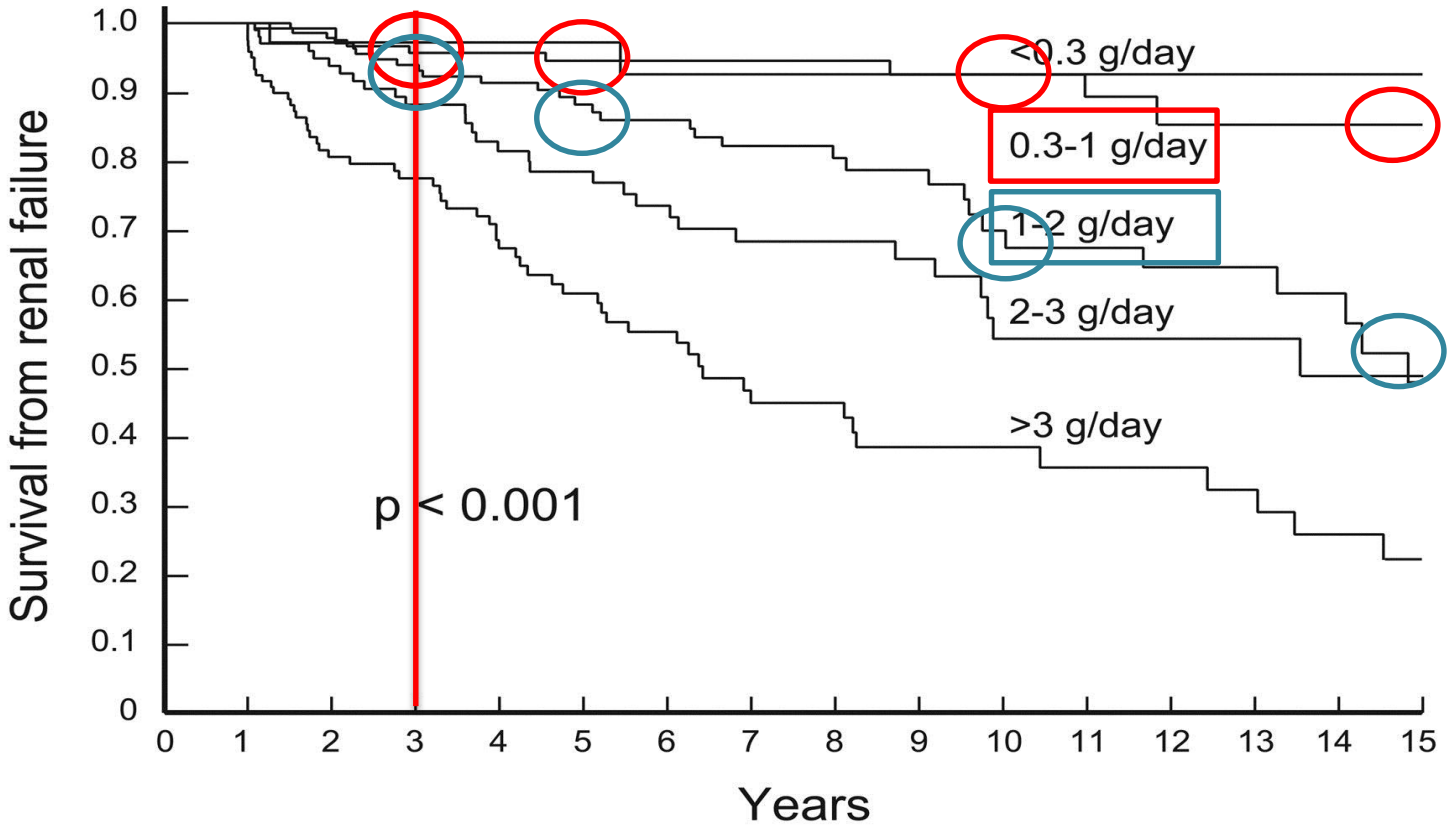
	Immunosuppressive monotherapy (N=55)			Immunosuppressive combination therapy (N=27)		
	available	mean	SD	available	mean	SD
Protein/creatinine ratio at 12 months (g/g)	41	0.50	0.52	18	0.74	0.52
Protein/creatinine ratio at 36 months (g/g)	43	0.57	0.53	16	1.27	1.40
Patients with proteinuria < 0.2 g/g at 36 months (n, %)	55	17 (30.9)		27	3 (11.1)	
Disappearance of microhematuria (n, %)	40*	19 (47.5)		17*	5 (29.4)	

eGFR	90-60 ml/min	60-30 ml/min
Proteinuria	1.6 g/day	2.0 g/day

The behaviour of proteinuria seems to show patients with different respons and prognosis

Time-Average Proteinuria and Renal Survival

541 Canadian Patients (caucasian and asian)

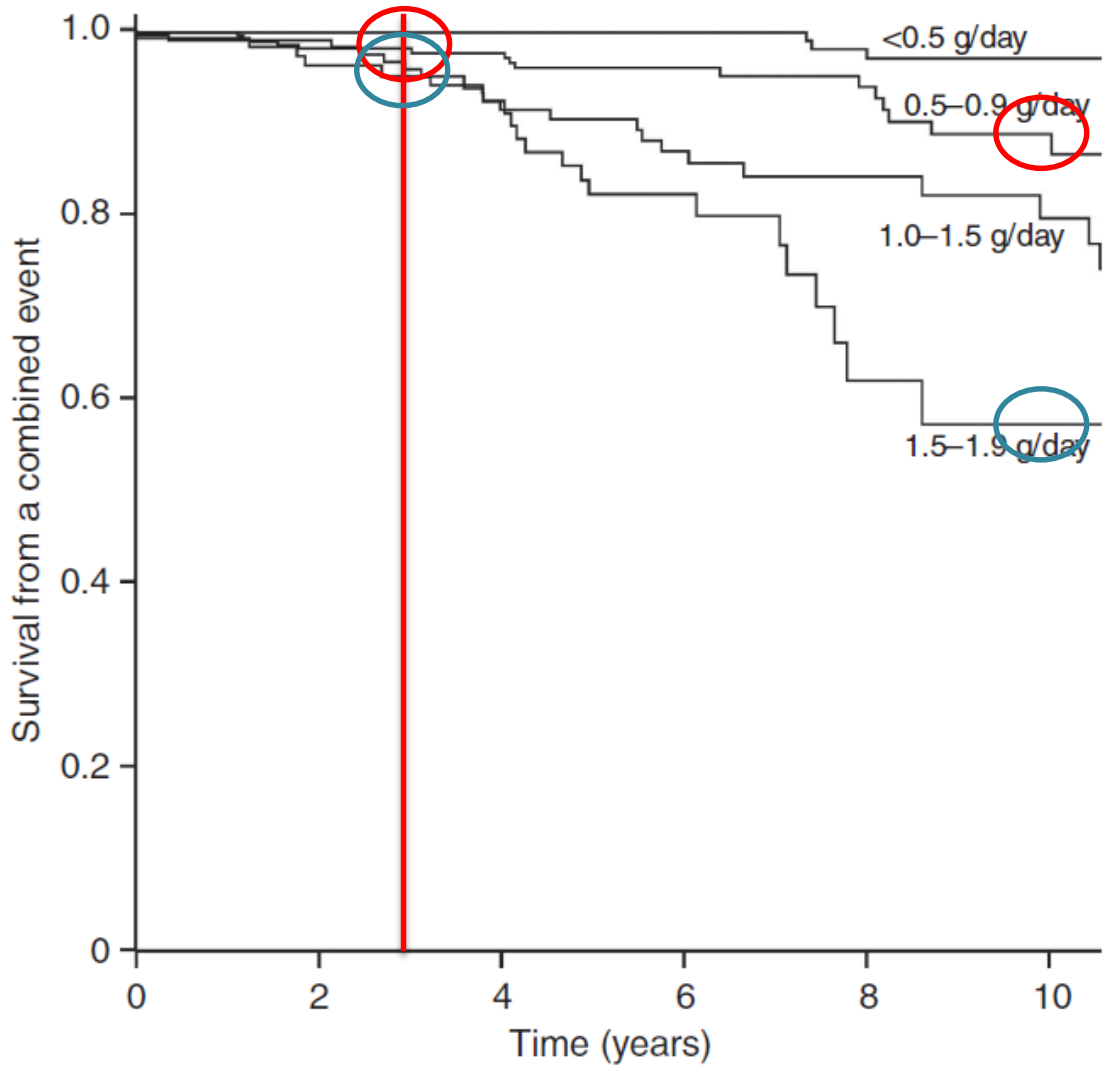


<0.3 g/day	37	22	8	1
0.3-1 g/day	134	79	35	11
1-2 g/day	145	79	28	10
2-3 g/day	105	50	18	4
>3 g/day	120	44	13	6

Reich HN et al, JASN 2007

Time-Average Proteinuria and Renal Survival

928 Patients of VALIGA Study



Coppo R et al, Kidney Int 2014

AJKD

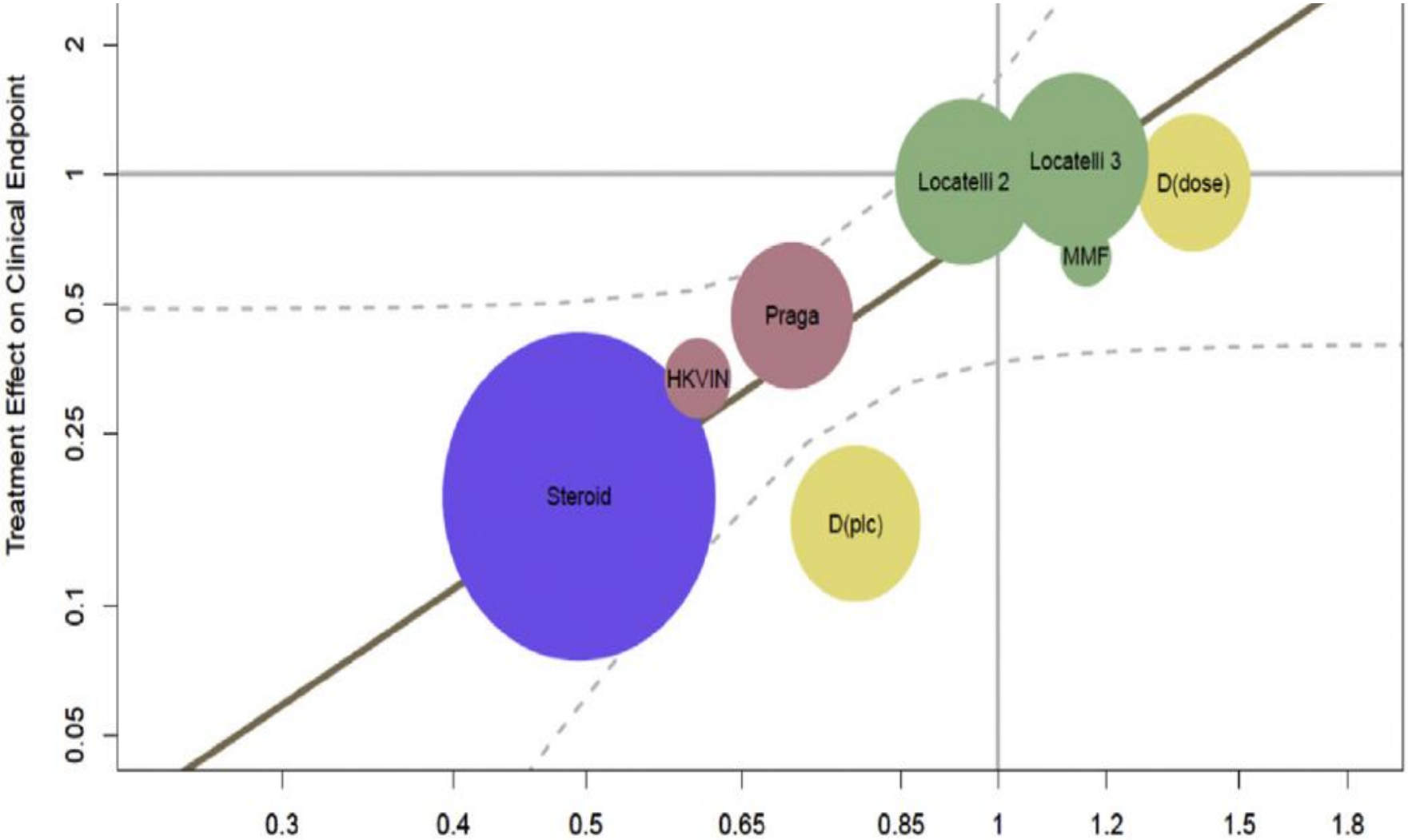
Original Investigation

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]

Am.J.Kidney Dis 2016

Treatment Effect on Proteinuria in IGA Nephropathy



Inker L. ….Locatelli F. e t al.. Am.J.Kidney Dis 2016

Only the patients treated for 6 months with corticosteroids show a TAP < 1 gr/die at 36 evaluation months

- **If the Time-Average proteinuria is a prognostic factor, the patients treated only with steroids (CKD stage2) will have a good renal survival on the medium-long term**
- **The patients treated with steroids,ciclofosfamide and azatioprine (CKD stage3) or only with supportive therapy will have a low renal survival**

Side effects

Total Number of Serious Adverse Events and Relation to Treatment

	Supportive only (n=80)	Additional immunosuppressive monotherapy (n=55)	Additional Immunosuppressive combination therapy (n=27)
SAE not or unlikely related	27	8	12
SAE possibly related	1 (rhabdomyolysis due to statin)	2 (perforated sigma-diverticulitis, pleuritis)	6 (sigma-diverticulitis, macrocytic anemia, scrotal tumor, repiratory infection, dyspnea, diabetes mellitus)
SAE probably related	1 (increased serum creatinine and potassium due to RAS-blockade)	3 (impaired glucose tolerance, herpes zoster, knee empyema)	-
SAE definitely related	-	-	2 (transaminase + creatinine increase, pneumogenic sepsis (SUSAR))

Total Number of Infectious Events and Relation to Treatment

	Supportive only (n=80)	Additional immunosuppressive monotherapy (n=55)	Additional Immunosuppressive combination therapy (n=27)
infectious event not or unlikely related	111	95	35
infectious event possibly related	-	13	22
infectious event probably related	-	5	1
infectious event definitely related	-	2	1

Critical aspects

1. Lack of hystological evaluation
2. The immunosuppression group includes two very different patient groups
3. The prognostic value of proteinuria on renal survival is not confermed
4. **It is difficult to explain why the supportive therapy was able to slow down the eGFR decrease (at least in the short term) without to reduce proteinuria**

Annual GFR decrease in patients without immunosoppressors

Rauen et al (2015) **-1.6 ml/min (FU 36 months)**

80 pz age 45.8 eGFR 57.4 ml/min Proteinuria 1.6 gr/die

Manno et al. (2009) **-6.2 ml/min (FU 57 months)**

49 pz age 34.9 eGFR 95.5 ml/min Proteinuria 1.5 gr/die

Lv et al (2009) **-25% in 72.5% pz (FU 28 months)**

30 pz age 30.4 eGFR 101.5 ml/min Proteinuria 2.0 gr/die

Pozzi et al (1999) **-6.3 ml/min (FU 60 months)**

43 pz age 40.0 eGFR 95.3 ml/min Proteinuria 1.9 gr/die

Which is the reason of this different effect?

Differences on supportive therapies

Rauen 2015 RAS blockers 100%, BP 126/78 mmHg, dietetic conseils (salt and protein restriction), stop smoking, no FANS and other nefrotoxic drugs, colesterol < 200 mg/dl.

Manno 2009 RAS blockers 100%, BP 122/77 mmHg, dietetic conseils (salt and protein restriction), no FANS, statins allowed

Lv 2009 RAS blockers 100%, mean BP < 92 mmHg, statins allowed

Pozzi 1999 RAS blockers 53% (at FU end), PA 133/83 mmHg, no FANS, statins allowed

Why this different effect?

(no suggestions from the authors)

Conclusions of Rauen Study

1. **Supportive therapy with a 36 months FU slowed down renal function deterioration,wthout reducing proteinuria < 1 gr/die.**

2. **Combined immunosoppressive therapy, in patients with eGFR 30-60 ml/min, was unable to reduce TAP < 1 gr/die, nor to preserve renal funtion**
3. **Steroid therapy for 6 months mantained TAp < 1 gr/die in patients with eGFR > 60 ml/min**
4. **Hystological evaluation (effect on prognosis and respons to the therapy) is not available**
5. **A longer FU is mandatory for reliable conclusions**

.

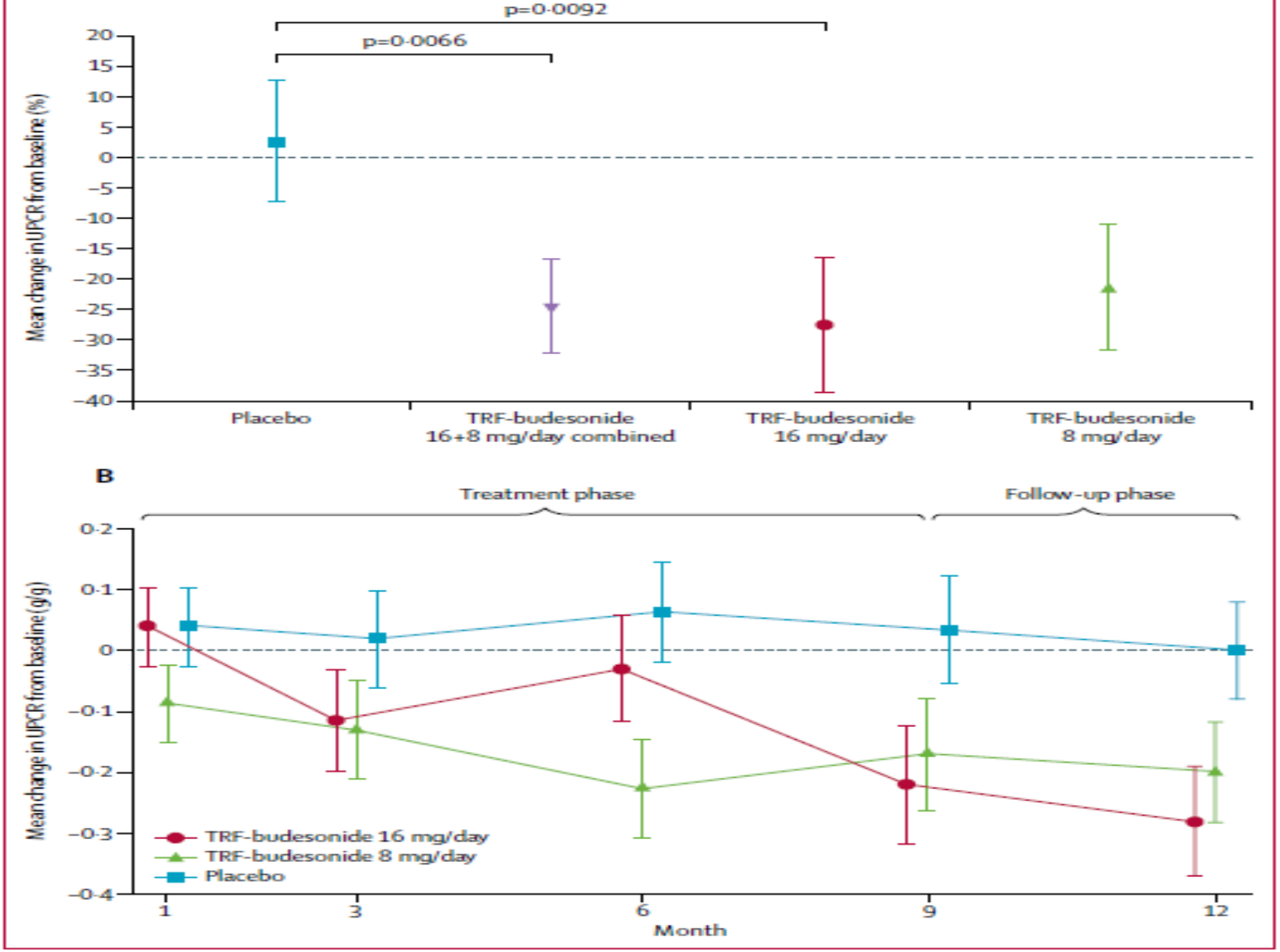
Authors' conclusions of the STOP:IGA-N trial

In conclusion, our trial showed that the addition of immunosuppression to ongoing comprehensive supportive care was not beneficial in patients with IgA nephropathy that was characterized by moderate proteinuria and chronic kidney disease stages 1 through 3.

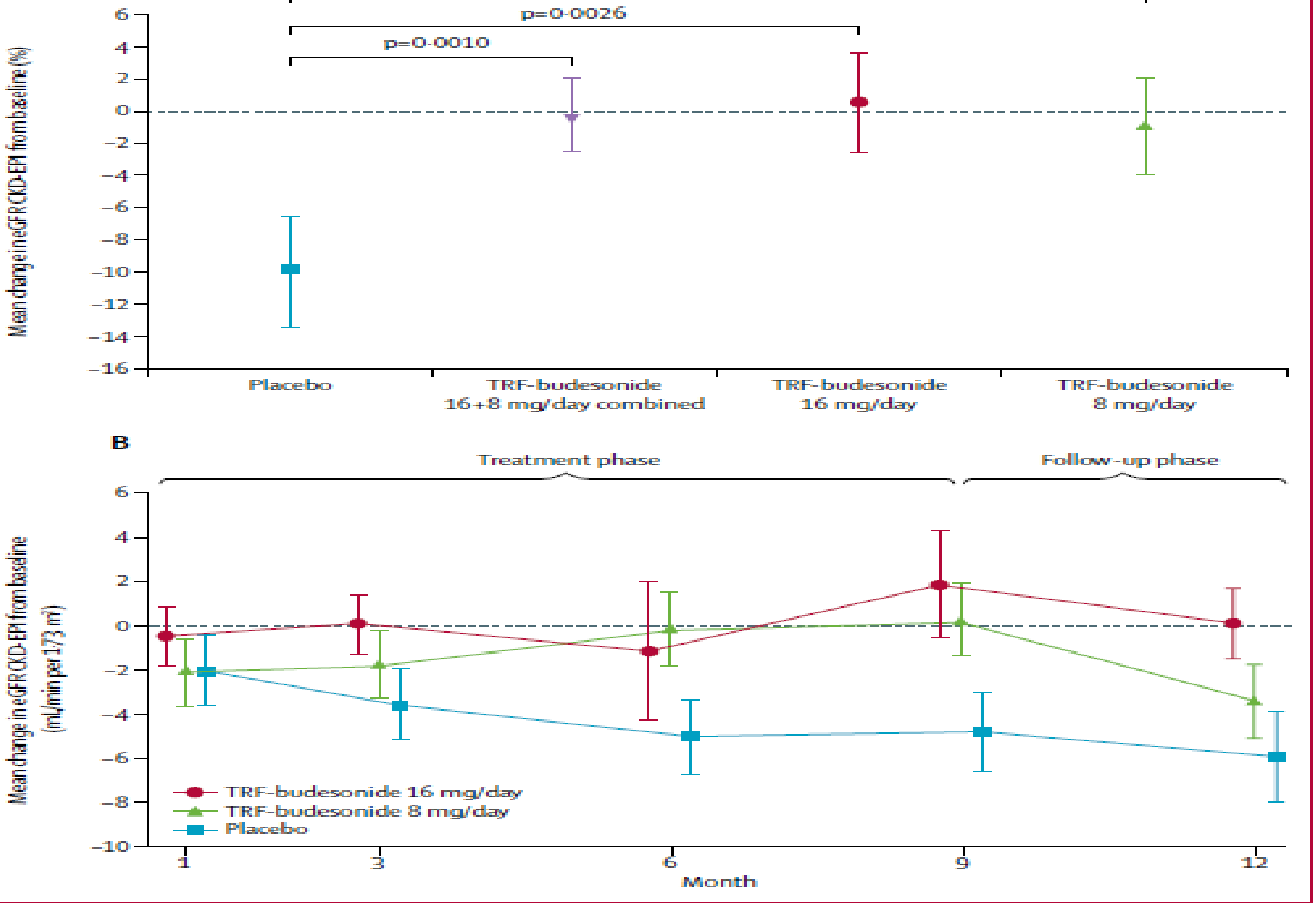
The Lancet 2017

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



Nefigan Trial: B.Felstrom,…F. Locatelli,…L. Del Vecchio, The Lancet 2017



Nefigan Trial: B.Felstrom,…F. Locatelli,…L. Del Vecchio, The Lancet 2017

Nefigan Trial Conclusions

B.Felstrom,…F. Locatelli,…L. Del Vecchio, The Lancet 2017

This trial showed that 9 months' treatment with TRF-budesonide resulted in reduced proteinuria and stabilised eGFR in patients with IgA nephropathy at risk of progression to end-stage renal disease. The observed effect was additive to optimised RAS blockade and supports the use of TRF-budesonide as adjunct therapy in patients with IgA nephropathy with persistent proteinuria. TRF-budesonide has the potential to become the first disease-specific treatment for IgA nephropathy, with a risk-benefit profile supportive of its use early in the course of disease.

Original Investigation
August 1, 2017

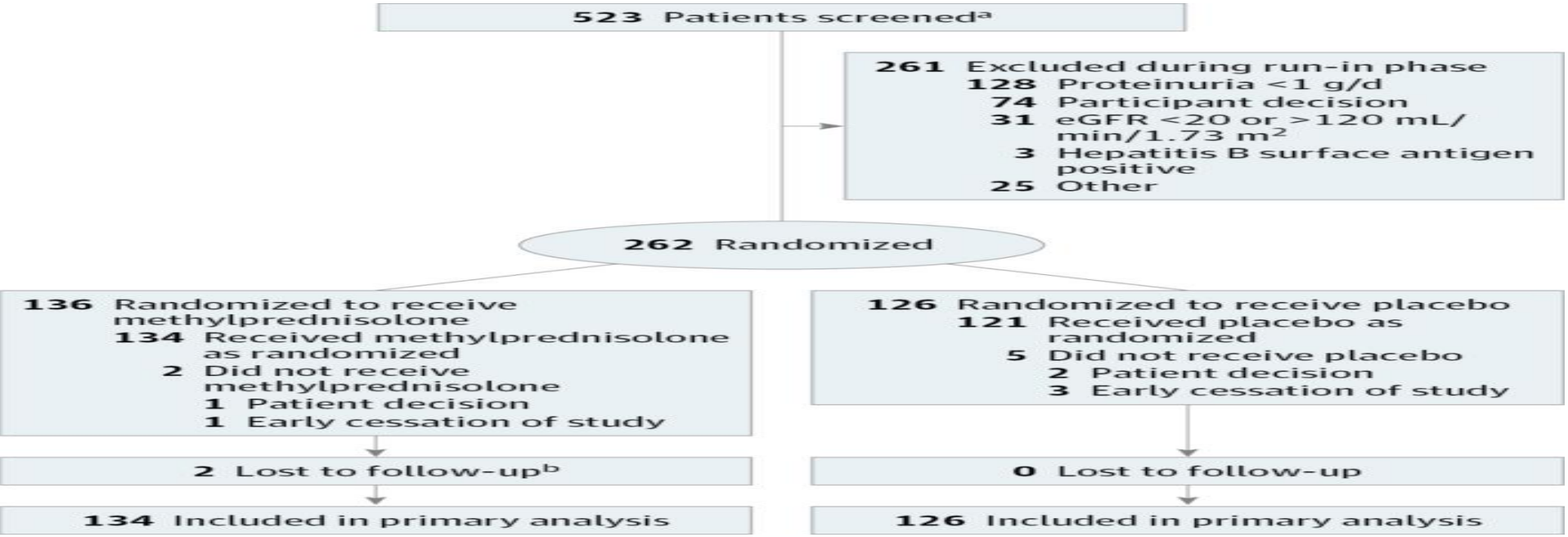
Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA NephropathyThe TESTING Randomized Clinical Trial

Jicheng Lv, MD[1,2];

JAMA. 2017;318(5):432-442.
doi:10.1001/jama.2017.9362

From: **Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA NephropathyThe TESTING Randomized Clinical Trial**

JAMA. 2017;318(5):432-442. doi:10.1001/jama.2017.9362



:

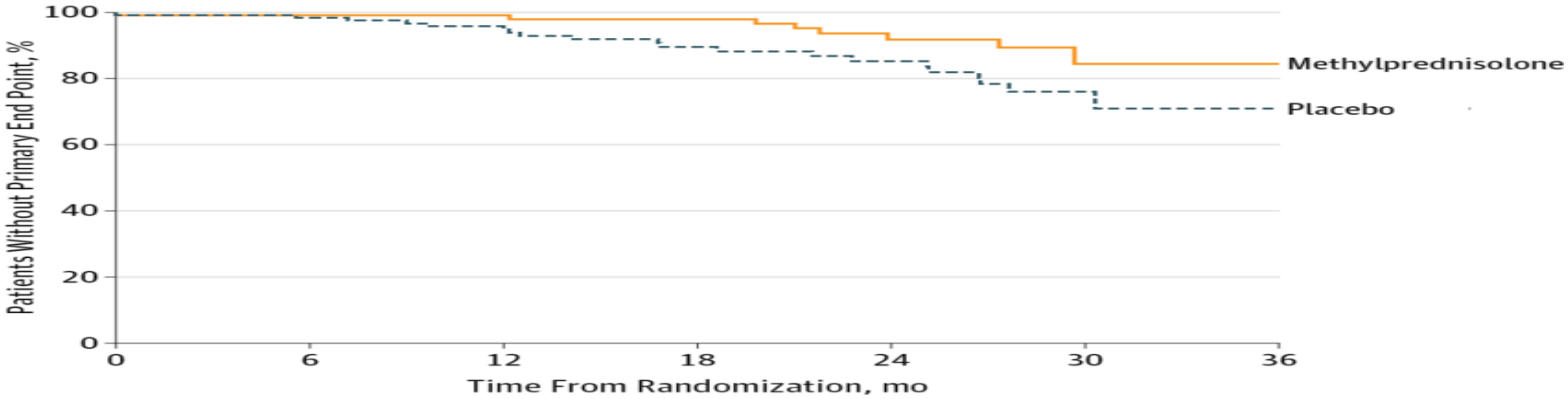
Enrollment, Randomization, and Follow-up of Study ParticipantseGFR indicates estimated glomerular filtration rate.

[a]Patients were prescreened by the local investigator for eligibility, and 523 patients signed consent and entered the run-in phase; prescreening data were not collected.

[b]One participant moved overseas and could not be contacted; a second could not be contacted despite many attempts.

From: **Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA NephropathyThe TESTING Randomized Clinical Trial**

JAMA. 2017;318(5):432-442. doi:10.1001/jama.2017.9362



No. at risk

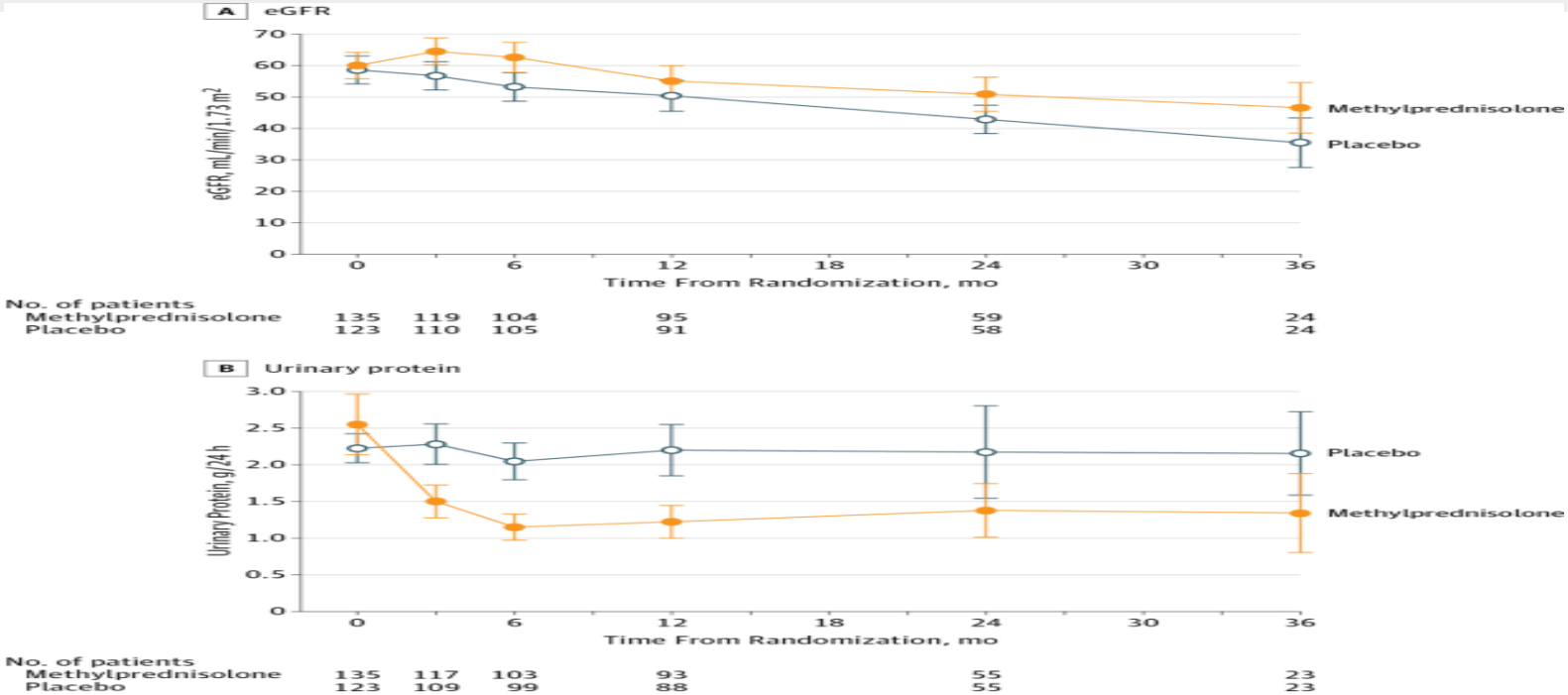
Methylprednisolone	136	129	111	89	60	34	16
Placebo	126	122	107	78	57	36	18

Time From Randomization to First Primary Composite Outcome of 40% eGFR Decrease, ESKD, or Death Due to Kidney Failure, by Treatment Group.

Hazard ratio, 0.37 [95% CI, 0.17-0.85]; P = .02. Median at-risk duration of follow-up was 22.2 (interquartile range, 14.9-30.4) months for methylprednisolone and 22.4 (interquartile range, 14.3 to 30.9) months for placebo. eGFR indicates estimated glomerular filtration rate; ESKD, end-stage kidney disease.

From: **Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA NephropathyThe TESTING Randomized Clinical Trial**

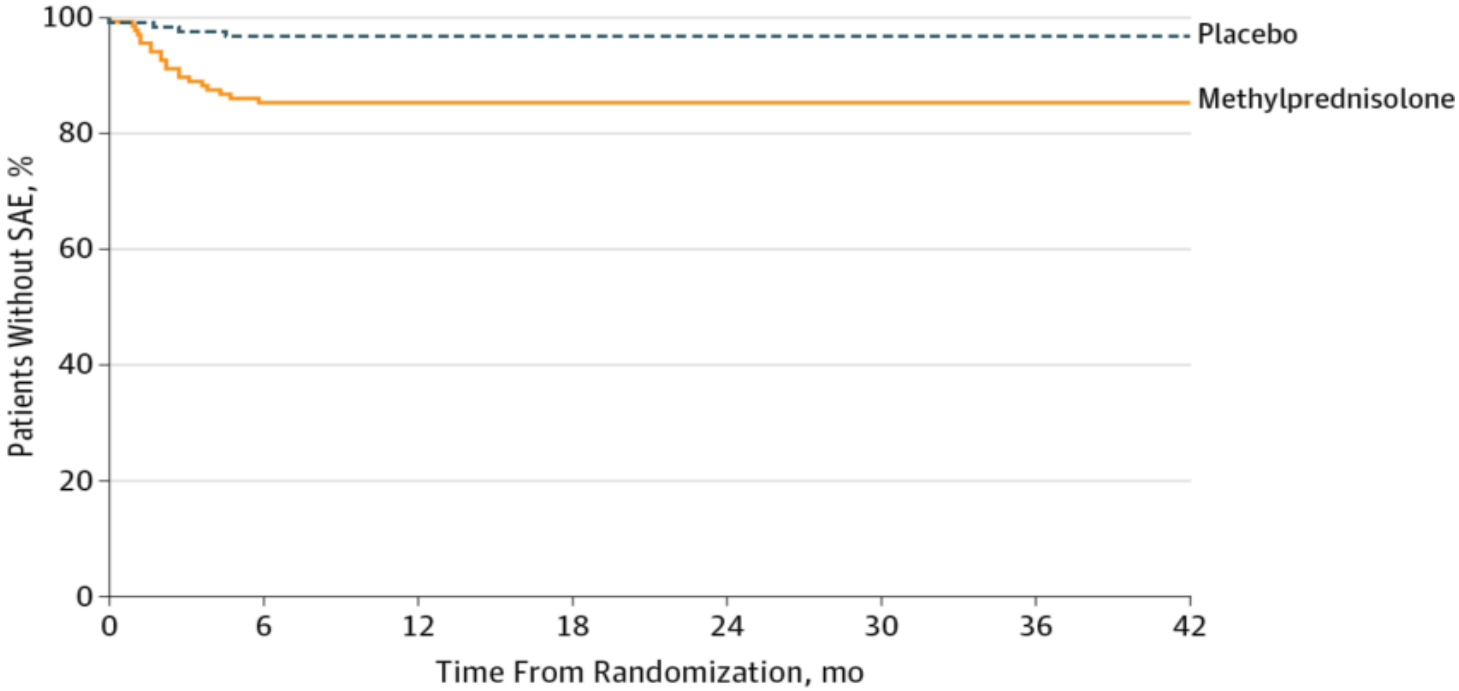
JAMA. 2017;318(5):432-442. doi:10.1001/jama.2017.9362



Effect of Methylprednisolone Therapy on eGFR and Proteinuria During Follow-upRandomization proteinuria and estimated glomerular filtration rate (eGFR) data are not available for 4 participants who were therefore excluded from this analysis. Error bars indicate 95% confidence intervals. A, Mean difference in eGFR was 5.14 (95% CI, 1.90 to 8.37) mL/min/1.73 m^2 at month 3; 6.74 (95% CI, 3.40 to 10.09) mL/min/1.73 m^2 at month 6; 4.62 (95% CI, 1.16 to 8.09) mL/min/1.73 m^2 at month 12; 5.43 (95% CI, 1.37 to 9.48) mL/min/1.73 m^2 at month 24; and 7.67 (95% CI, 1.91 to 13.43) mL/min/1.73 m^2 at month 36 ($P < .01$ for all). The annual rate of eGFR decline was lower in the methylprednisolone group (−1.79 vs −6.95 mL/min/1.73 m^2 per year; mean difference, 5.15 [95% CI, 0.42 to 9.89]; $P = .03$). B, Mean difference in proteinuria was −0.83 (95% CI, −1.18 to −0.47) g/d at month 3; −1.00 (95% CI, −1.37 to −0.63) g/d at month 6; −1.20 (95% CI, −1.59 to −0.81) g/d at month 12; −1.03 (95% CI, −1.49 to −0.56) g/d at month 24; and −0.93 (95% CI, −1.60 to −0.25) g/d at month 36 ($P < .01$ for all). Time-averaged proteinuria was significantly lower in the methylprednisolone group than in the placebo group (1.37 vs 2.36 g/d; mean difference, −0.99 [95% CI, −1.34 to −0.64]; $P < .001$).

From: **Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA NephropathyThe TESTING Randomized Clinical Trial**

JAMA. 2017;318(5):432-442. doi:10.1001/jama.2017.9362



No. at risk								
Methylprednisolone	136	116	115	106	94	71	51	33
Placebo	126	122	122	118	107	83	64	42

:

Time From Randomization to First Serious Adverse Event, by Treatment GroupMedian at-risk duration of follow-up was 19.7 (interquartile range, 9.2-30.1) months for methylprednisolone and 25.2 (interquartile range, 14.8-32.7) months for placebo. Relative risk, 4.63 (95% CI, 1.63-13.2); P = .001 by Fisher exact test. SAE indicates serious adverse event.

TESTING Trial Conclusions

- ***Among patients with IgA nephropathy and proteinuria greater than 1 g/d, oral methylprednisolone was associated with an increased risk of serious adverse events, primarily infections.***
- ***Although the results are consistent with potential benefit, definitive conclusions about treatment benefit cannot be made, owing to early termination of the trial.***

TESTING Corticosteroids in IgA Nephropathy

A Continuing Challenge

Frederick W.K. Tam and Charles D. Pusey

Clin J Am Soc Nephrol 13: 158–160, 2018. doi: https://doi.org/10.2215/CJN.10560917

In conclusion, the recent report of the TESTING Randomized Clinical Trial in IgAN demonstrates that development of safe and effective therapy is still a major challenge. This study provides encouraging evidence that large-scale clinical trials for IgAN are achievable. It is important that future trials should

AJKD

Corticosteroids in IgA Nephropathy

Claudio Ponticelli and Francesco Locatelli

Commentary on Lv J, Zhang H, Wong MG, et al; TESTING Study Group. Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: the TESTING randomized clinical trial. JAMA. 2017;318(5):432-442.

AJKD

Corticosteroids in IgA Nephropathy

Claudio Ponticelli and Francesco Locatelli

We believe that patients with eGFRs > 30 mL/min/1.73 m^2 and proteinuria with protein excretion > 1 g/d merit treatment with corticosteroids.

CJASN ePress. Published on February 23, 2018 as doi: 10.2215/CJN.12991117

Article

Glucocorticoids in the Treatment of Glomerular Diseases

Pitfalls and Pearls

Claudio Ponticelli[1] *and Francesco Locatelli*[2]

Glucocorticoids: Most frequent side effects

Table 1. Some of the most frequent side effects of glucocorticoids

Side Effects of Glucocorticoids
Infection
Diabetes mellitus
Arterial hypertension
Cardiovascular disease
Severe psychiatric reaction
Peptic ulcer
Hyperlipidemia
Obesity-metabolic syndrome
Osteoporosis
Aseptic necrosis
Myopathy
Adrenal insufficiency
Cataract
Hypercoagulability
Growth retardation in children
Skin changes (atrophy, friableness, acne, hirsutism, striae, Cushingoid facies)

Ponticelli C and Locatelli F., CJASN: 02,2018

Glucocorticoid Resistance

Table 3. Gucocorticoid resistance

Resistance categories
Generalized steroid resistance
Generalized genetic or familial glucocorticoid resistance.
Partial steroid resistance
Hyperacetylation of heat shock proteins causes poor nuclear translocation of glucocorticoid receptor.
Mutation or polymorphism of genes encoding multidrug resistance.
Low expression or low affinity of glucocorticoid receptors.
Polymorphism of glucocorticoid receptors (isoform β).
False steroid resistance
Insufficient dosage.
Short duration of treatment.
Poor gastrointestinal absorption due to mucosal edema or use of gastric protectors.
Accelerated catabolism caused by drugs that increase the activity of cytochrome P450 (anticonvulsants, rifampin, *etc.*).

Ponticelli C and Locatelli F., CJASN: 02,2018

Suggested Measures to Reduce the Side Effects of Glucocorticoids

Table 2. Suggested measures to reduce the side effects of glucocorticoids

Variable	Details
Type of drugs	For chronic treatment short-acting glucocorticoids should be preferred.
Time of administration	The daily dose of glucocorticoid should be given in a single morning administration between 7 and 9 AM to mimic the circadian cycle of cortisol.
Concomitant drugs	Glucocorticoids are metabolized by cytochrome P450 enzymes. Simultaneous use of drugs that inhibit the activity of cytochrome P450 enzymes increase the blood and tissue levels of glucocorticoids (ketoconazole, itraconazole, clarithromycin). On the other hand, drugs that activate cytochrome P450 (phenobarbital, phenytoin, and rifampin) reduce the blood levels of glucocorticoids. The prolonged use of proton pump inhibitors may cause interstitial nephritis, magnesuria, and osteoporosis.
Hygienic measures	Good personal hygiene, low-calorie diet, limited salt intake, physical activity, smoking cessation, mild alcohol intake, and strict control of BP are recommended.
Monitoring	Patients should be instructed to promptly report side effects and physicians should not disregard apparently trivial adverse events.
Gradual discontinuation	To avoid acute hypoadrenalism episodes glucocorticoids should be withdrawn gradually, tapering the doses over weeks or months to allow the atrophied cortex to regain functional status.
Selection of patients	Glucocorticoids should be used with caution in patients with chronic infection, severe hypertension, diabetes, obesity, psychiatric disease, and in those with eGFR<30 ml/min per 1.73 m^2.

Ponticelli C and Locatelli F., CJASN: 02,2018

Authors' conclusions of the STOP:IGA-N trial

In conclusion, our trial showed that the addition of immunosuppression to ongoing comprehensive supportive care was not beneficial in patients with IgA nephropathy that was characterized by moderate proteinuria and chronic kidney disease stages 1 through 3.

Locatelli's conclusions of the STOP:IGA-N trial

Do no STOP but GO with Steroids!

(Pozzi-Del Vecchio and Locatelli course)

PROTECT in Immunoglobulin A Nephropathy: Study Design of a Phase 3 Randomized, Double-blind, International Active-controlled Study of the Efficacy and Safety of Sparsentan

Jonathan Barratt[1], Brad Rovin[2], Kevin Carroll[3], Rosanna Coppo[4], Ulysses Diva[5], Richard Lafayette[6], Francesco Locatelli[7], Bart Maes[8], Alex Mercer[5], Vlado Perkovic[9], Manuel Praga[10], Pierre-Louis Tharaux[11], James Tumlin[12], Radko Komers[5]

PROTECT STUDY

- Sparsentan is a first-in-class, orally active, dual-acting: selective antagonist of angiotensin II Type 1 (AT_1) endothelin type A (ET_A) receptors

In development for the treatment of glomerular diseases

- The phase 3 PROTECT in IgAN study will evaluate long-term effects of sparsentan versus the AT_1 antagonist irbesartan on proteinuria and kidney function, and assess safety and tolerability.