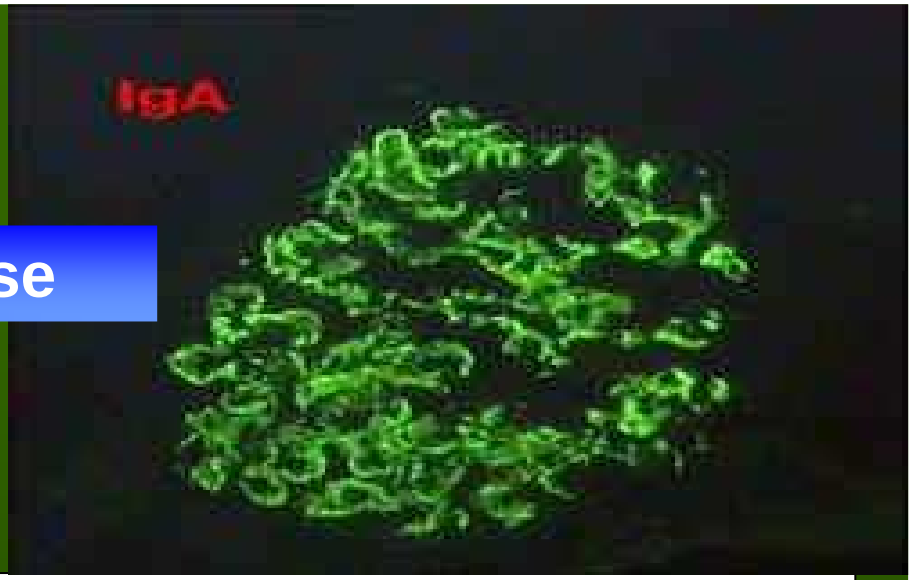
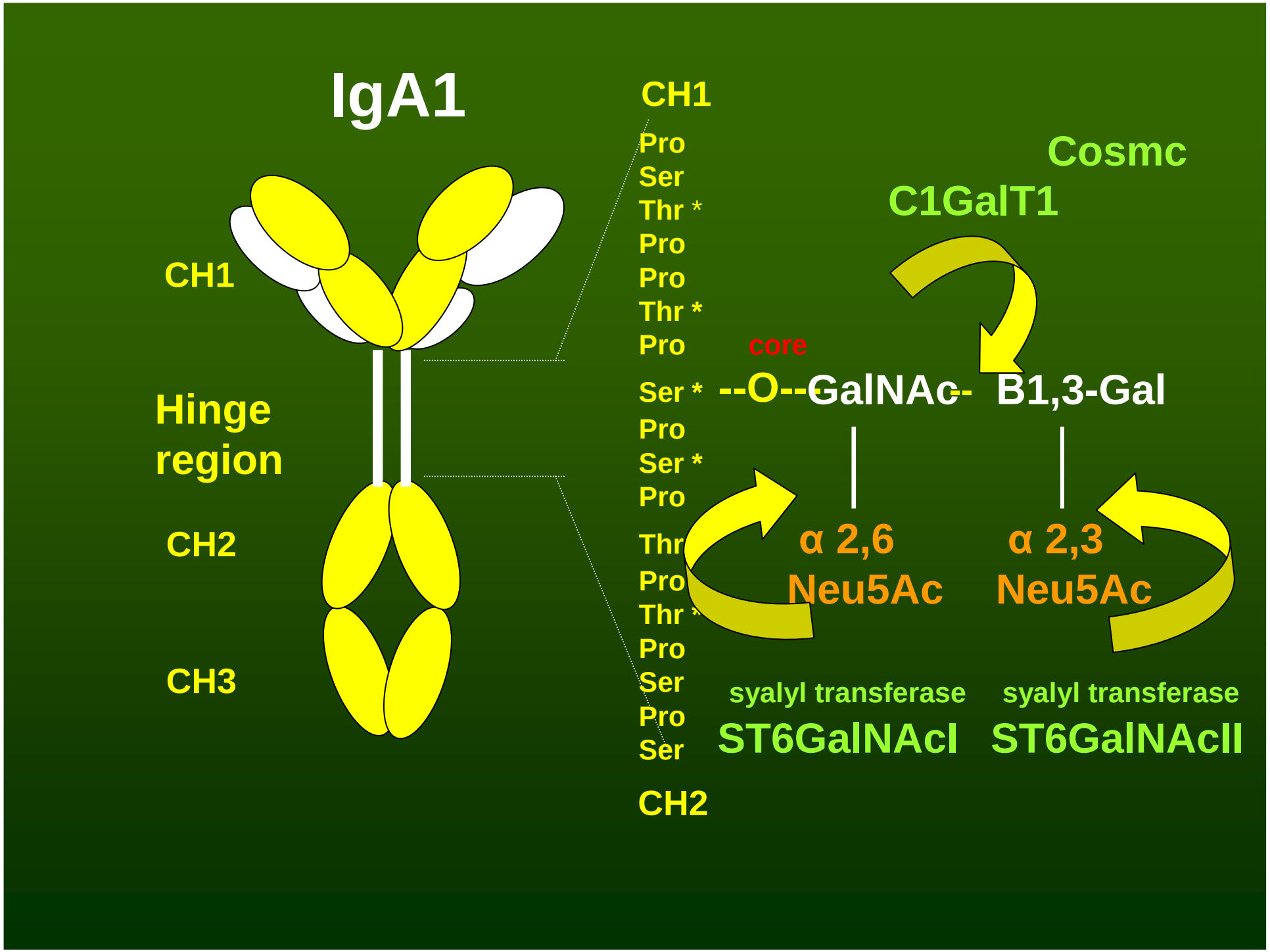
ERA-EDTA supported CME course

Budapest,
August 2008



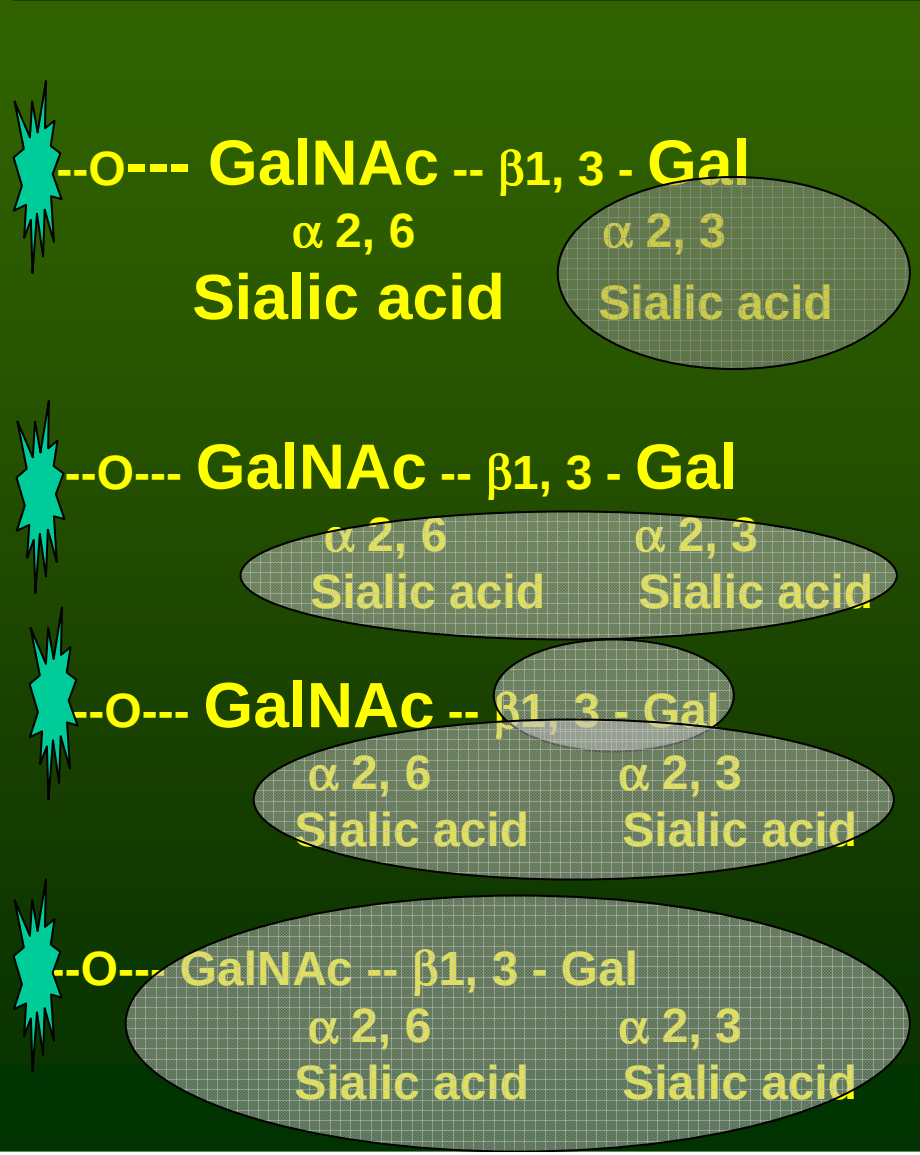
News in pathogenesis and treatment of IgA Nephropathy

Rosanna Coppo
Regina Margherita Children's University Hospital
Torino, Italy


IgA1
CH1
Hinge region
CH2
CH3
CH1
Pro
Ser
Thr *
Pro
Pro
Thr *
Pro
Ser *
Pro
Ser *
Pro
Thr
Pro
Thr *
Pro
Ser
Pro
Ser
CH2
Cosmc
C1GalT1
core
--O--GalNAc-
B1,3-Gal
α 2,6
Neu5Ac
α 2,3
Neu5Ac
syalyl transferase
ST6GalNAcI
syalyl transferase
ST6GalNAcII

Aberrant glycosylation of serum IgA1 in IgAN:

defective galactosylation and/or sialylation of O-linked glycans



1995-2000

Increased binding to GalNAc lectins (*Vicia Villosa and Helix Aspersa*)

Allen AC, Feehally J.

- Increased Asialo-GalNAc

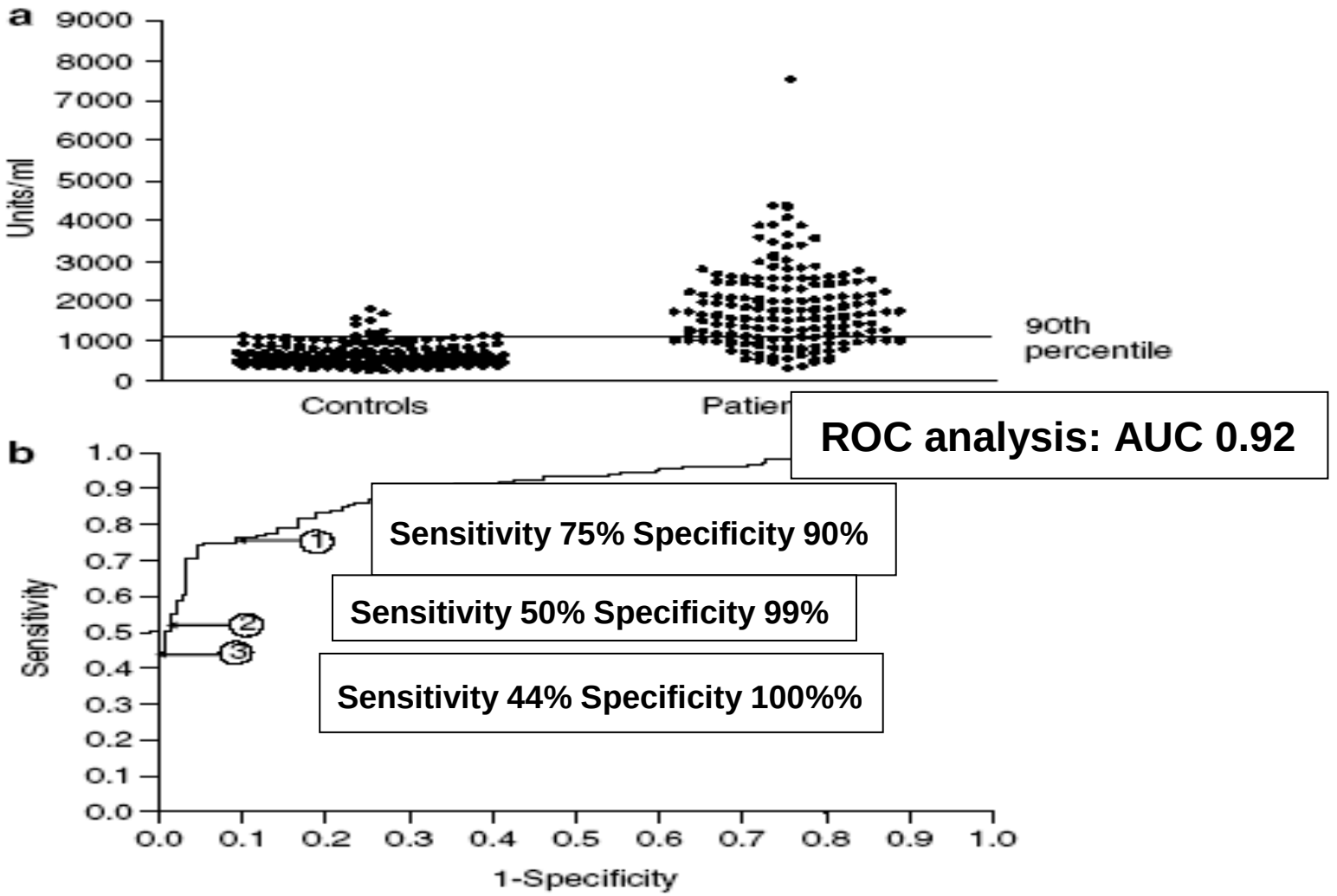
Hiki Y

- Galactose-deficient IgA1

Tomana M, Mestecky

- Increased exposure of GalNAc/Gal

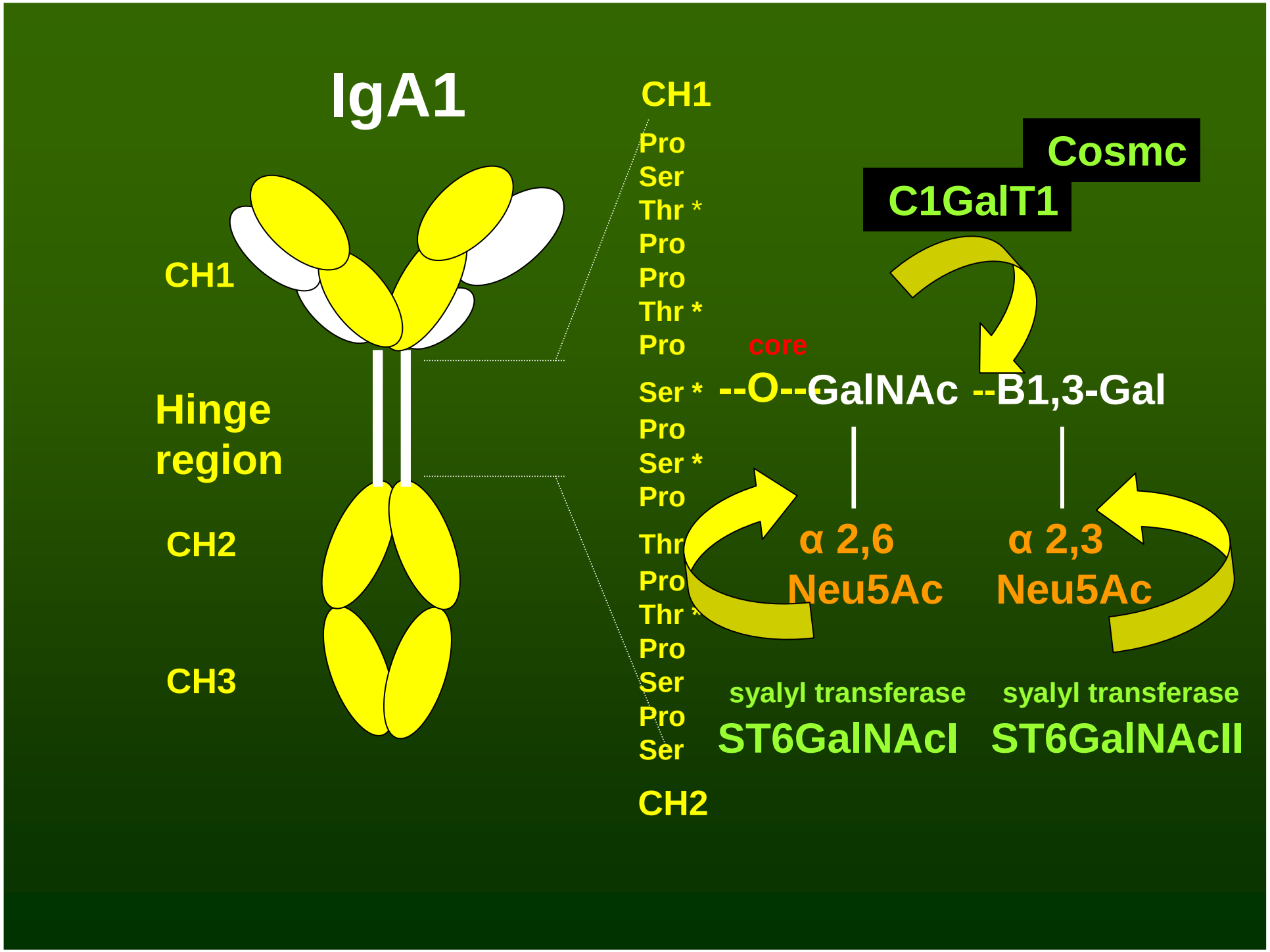
Amore and Coppo



Patients with IgA nephropathy have increased serum galactose-deficient IgA1 levels

Z Moldoveanu[1], RJ Wyatt[2], JY Lee[3], M Tomana[3], BA Julian[1,3], J Mestecky[1,3], W-Q Huang[1], SR Anreddy[1,5], S Hall[1], MC Hastings[2], KK Lau[2,6], WJ Cook[4] and J Novak[1]

Kidney International (2007) **71,** 1148–1154;


IgA1
CH1
Hinge region
CH2
CH3
CH1
Pro
Ser
Thr *
Pro
Pro
Thr *
Pro
Ser *
Pro
Ser *
Pro
Thr
Pro
Thr *
Pro
Ser
Pro
Ser
CH2
Cosmc
C1GalT1
core
--O--GalNAc --B1,3-Gal
α 2,6 Neu5Ac
α 2,3 Neu5Ac
syalyl transferase
ST6GalNAcI
syalyl transferase
ST6GalNAcII

Possible mechanisms leading to reduced glycosylation of IgA1 side chain glycans

β 1,3 Gal transferase (core 1 GALT) reduced activity

as proved in

-in B lymphocytes of IgAN patients (Allen 1997), but not confirmed by the same Authors in 2007

- **in tonsillar B lymphocytes of IgAN patients (Inoue 2007)**

Journal of Internal Medicine 2005; 258: 467–477 doi:10.1111/j.1365-2796.2005.01558.x

Peripheral B lymphocyte β1,3-galactosyltransferase and chaperone expression in immunoglobulin A nephropathy

W. QIN[1], Q. ZHOU[2], L.-C. YANG[1], Z. LI[1], B.-H. SU[1], H. LUO[1] & J.-M. FAN[1]

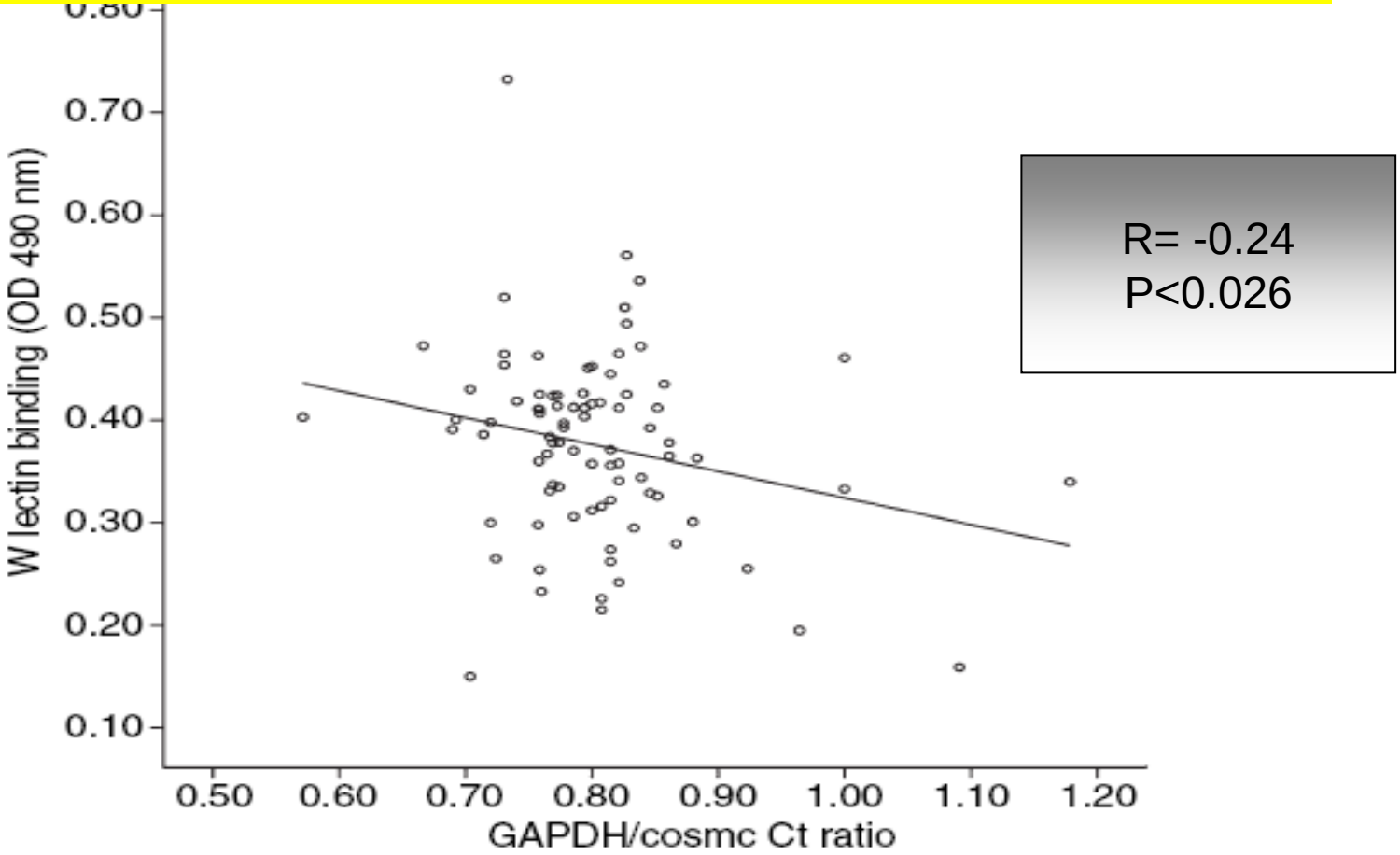
From the [1]Division of Nephrology, Department of Internal Medicine, Sichuan University West China Hospital, Chengdu, Sichuan; and [2]Division of Gene Engineered Mouse, State Key Laboratory of Biotherapy, Sichuan University, Chengdu; China

41 Patients wiht IgAN.

mRNA of circulating B lymphocytes (Rt-PCR:Taqman analysis)

β1,3 GT (C1GALT1) and its chaperone (Cosmc)

No difference between patients and controls
for Beta 1,3 GT (C1GALT1) mRNA
while
Cosmc mRNA was significantly lower in IgAN than in controls.



Week correlation between low Cosmc activity and levels of aberrantly glycosylated IgA1 (VV binding).

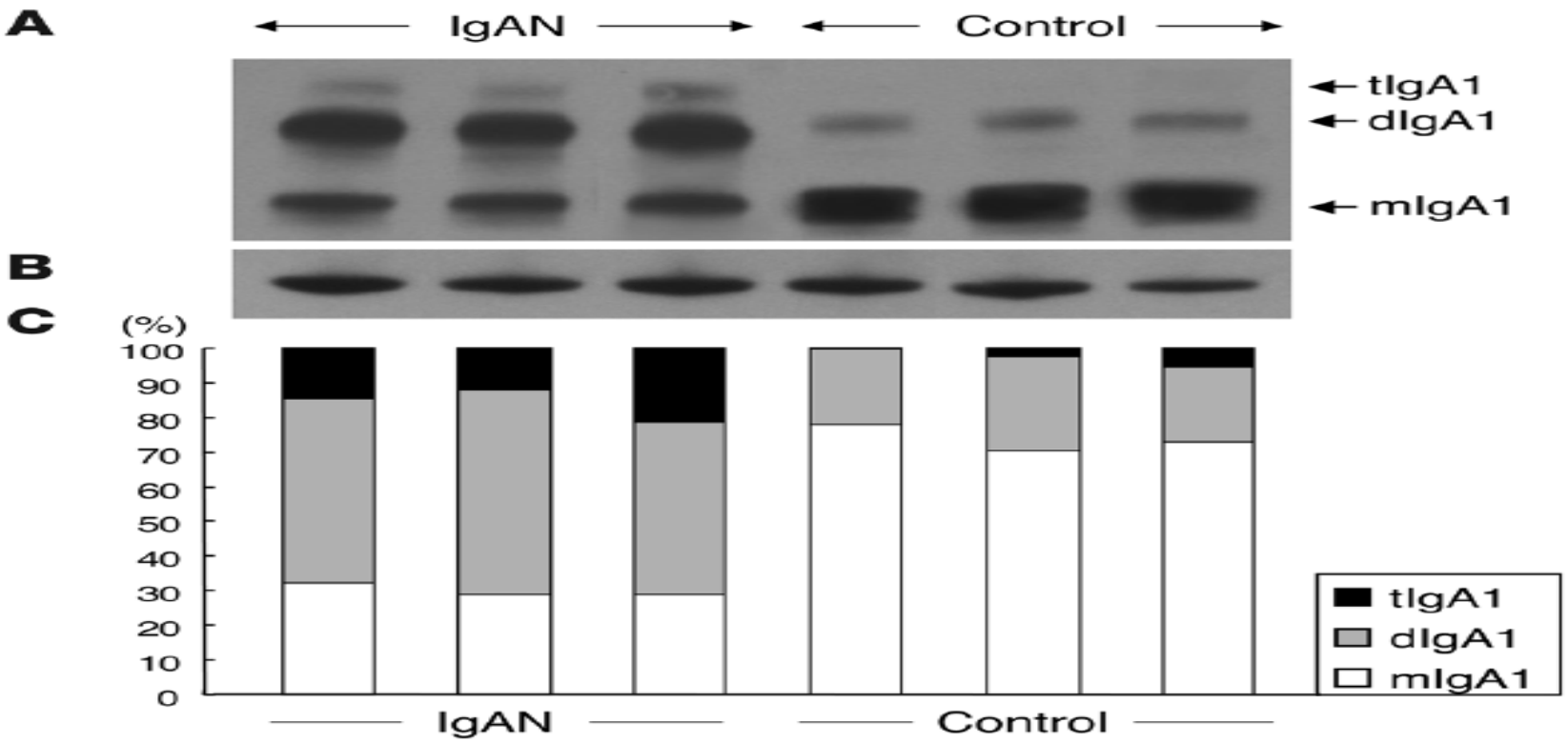
No correlations for C1GALT.

IgA1-secreting cell lines from patients with IgA nephropathy produce aberrantly glycosylated IgA1

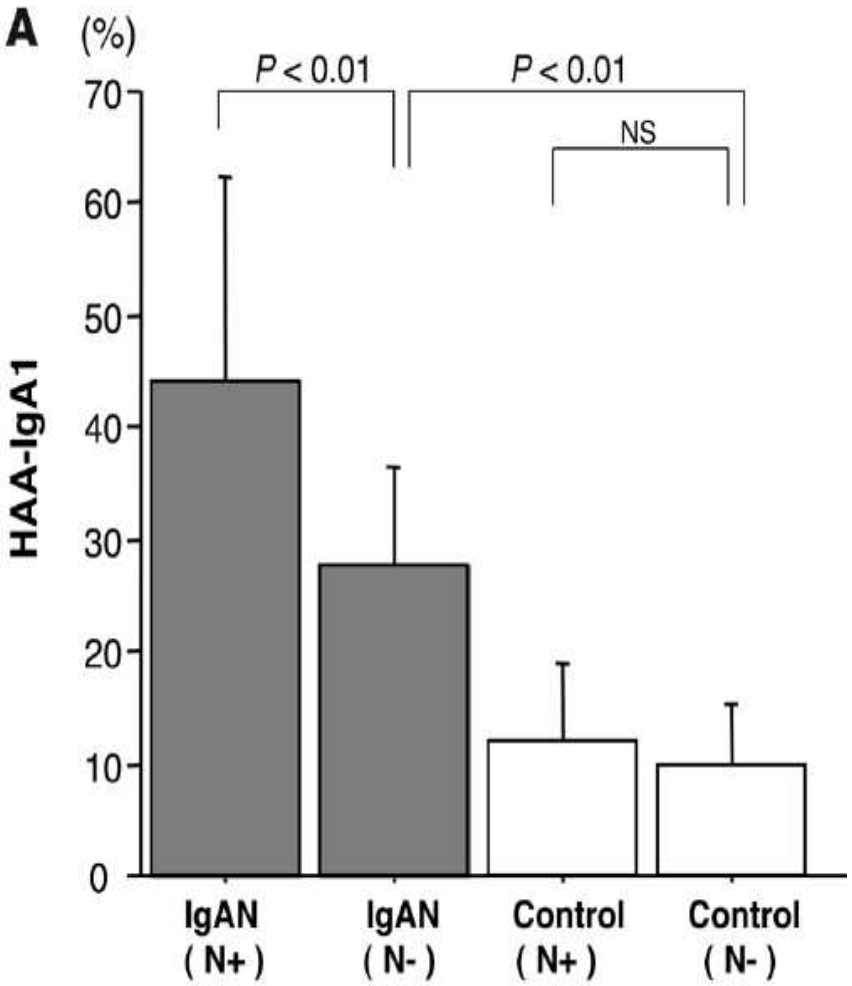
Hitoshi Suzuki,[1,2] Zina Moldoveanu,[1] Stacy Hall,[1] Rhubell Brown,[1] Huong L. Vu,[1] Lea Novak,[1] Bruce A. Julian,[1] Milan Tomana,[1] Robert J. Wyatt,[3] Jeffrey C. Edberg,[1] Graciela S. Alarcón,[1] Robert P. Kimberly,[1] Yasuhiko Tomino,[2] Jiri Mestecky,[1,4] and Jan Novak[1]

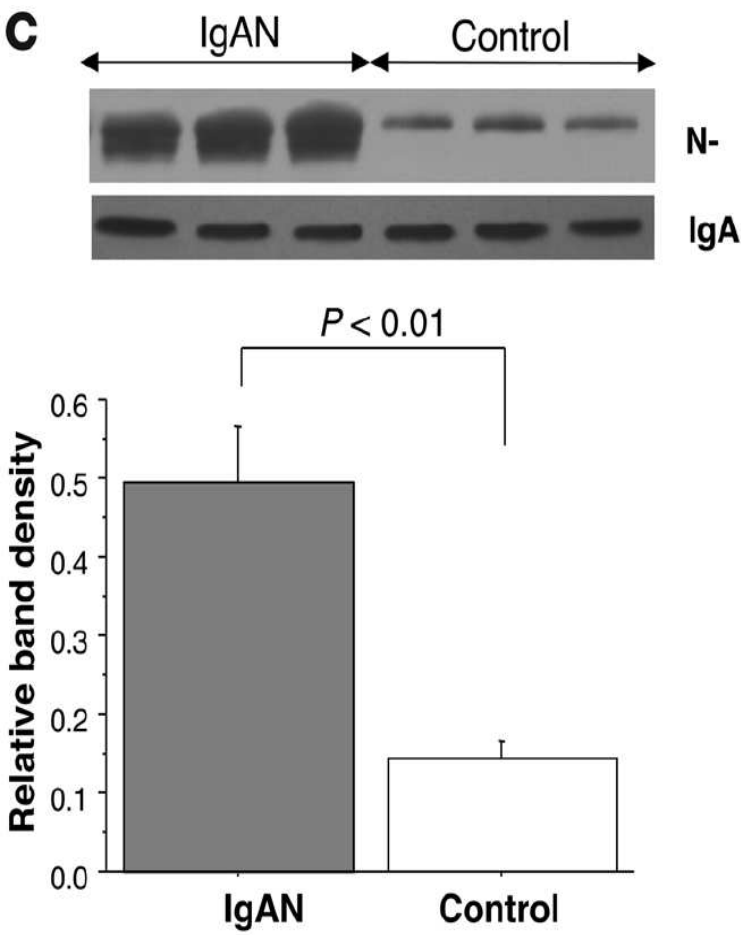
[1]University of Alabama at Birmingham, Birmingham, Alabama, USA. [2]Juntendo University School of Medicine, Tokyo, Japan. [3]University of Tennessee Health Science Center, Memphis, Tennessee, USA. [4]Charles University, School of Medicine, Prague, Czech Republic.

J Clin Invest 2008; 118:629-639

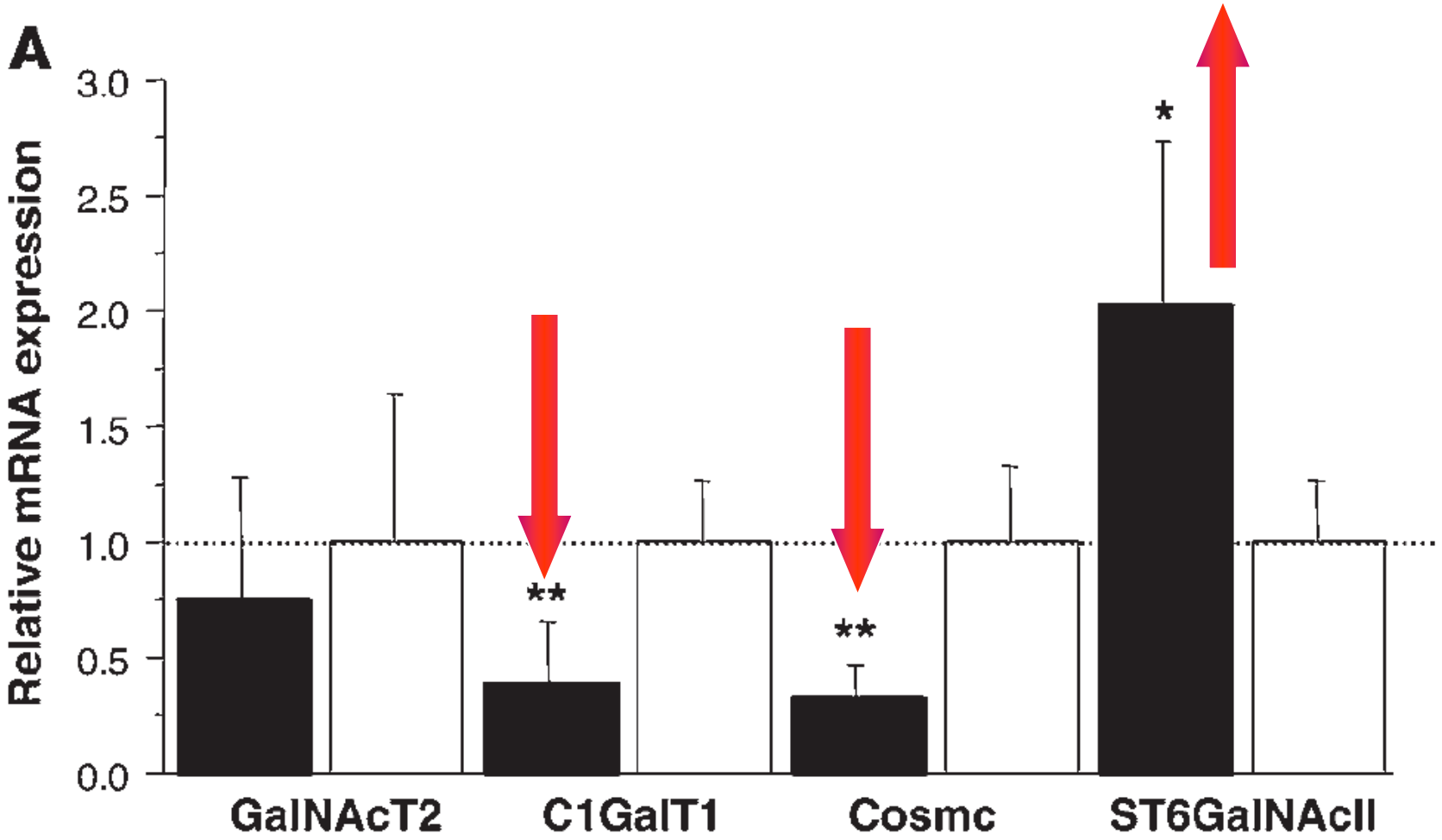


IgA1 secreted by cell lines from IgAN patients has Gal-deficient O-linked glycans with highly sialylated GalNAc





Gene transcriptional levels in IgA1-producing cell lines from IgAN patients ■ and controls □



Possible mechanisms leading to reduced glycosylation of IgA1 side chain glycans

β 1,3 Gal transferase (core 1 GALT) reduced activity

C1GALT1 enzyme is encoded

by C1GALT1, chromosome 7p14-p13

Cosmc (core 1 GALT specific molecular chaperone) is encoded by C1GALT1C1, chormosome Xq24

Variants of C1GALT1 gene are associated with the genetic susceptibility to IgA nephropathy

G-S Li[1,2], H Zhang[1], J-C Lv[1], Y Shen[2] and H-Y Wang[1]

Kidney International (2007) **71,** 448–453.

Table 1 | Polymorphisms of *C1GALT1* gene were detected in 24 subjects

Marker name	dbSNP name	Region	Position[a]	Alleles[b]	Minor allele frequency
SNP1	rs9639031	5′ Flanking[c]	−734	C/T	0.250
SNP2	Novel	5′ Flanking	−722	G/T	0.145
SNP3	Novel	5′ Flanking	−552	A/G	0.043
SNP4	Novel	5′ Flanking	−465	A/G	0.167
SNP5	rs1008897	5′ Flanking	−449	A/G	0.021
SNP6	rs1008898	5′ Flanking	−330	G/T	0.479
SNP7	rs5882115	5′ Flanking	−292	C/–	0.125
SNP8	rs1047763	3′ UTR	1365	G/A	0.438
SNP9	rs3807859	3′ UTR	1484	T/A	0.043

[a]The base immediately preceding the start of transcription numbered as −1.
[b]With major allele given first and minor allele given second.
[c]5′ Flanking means the upstream from the first transcribed nucleotide.

3 SNPs were significantly different in IgAN and healthy controls
YATIG was less frequent (OR 0.70)
YAGDA was more frequent (OR 1.77)
YATDG was more frequent (OR 3.03)

Possible mechanisms leading to reduced glycosylation of IgA1 side chain glycans

β 1,3 Gal transferase (core 1 GALT) genetic conditioning

Is still a debated issue

Gharavi A et al JASN 2008

Aberrant IgA1 glycosylation is inherited in familiar and sporadic IgAN.

In 45% of relatives of familial cases and

In 25% of relatives of sporadic cases.

Since they are healthy, additional co-factors should exist.

Nephrol Dial Transplant (2007) 22: 1518–1520
doi:10.1093/ndt/gfm003
Advance Access publication 19 March 2007

Translational Nephrology

NDT
Nephrology Dialysis Transplantation

Mutant mice provide new insight into the role of (mis-)glycation in IgA nephropathy and other glomerular diseases*

Jürgen Floege[1], Frank Eitner[1], Jonathan Barratt[2], Alice C Smith[2] and John Feehally[2]

[1]Department of Nephrology and Clinical Immunology, RWTH University Hospital Aachen, Germany and
[2]Department of Nephrology, Leicester General Hospital, Leicester, UK

mice KO C1GalT1 with < 5% of enzymatic activity do not develop IgAN

mice KO for beta 1-4 GALT develop IgAN
Nishie & Asano 2007

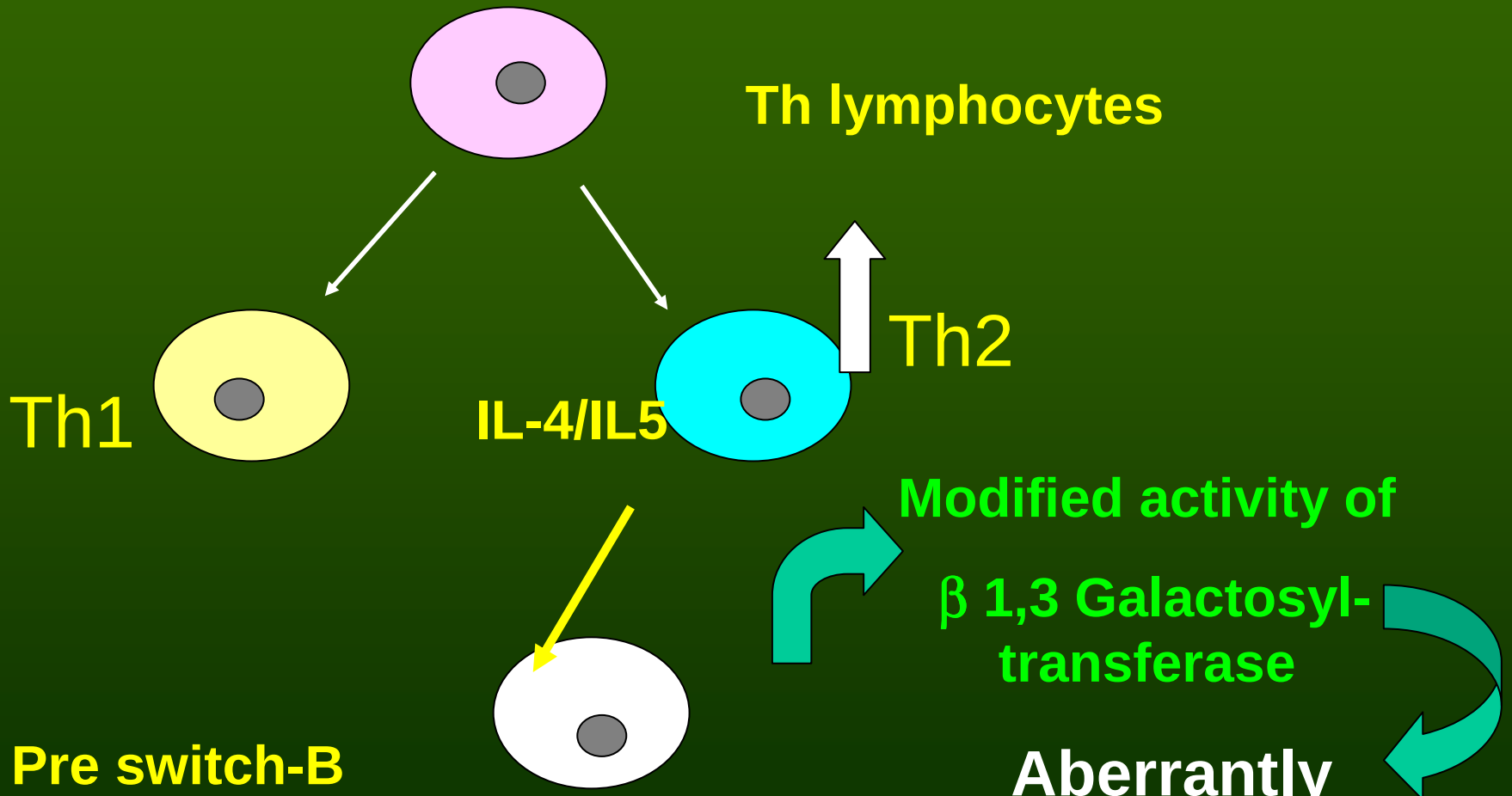
Possible mechanisms leading to reduced glycosylation of IgA1 side chain glycans

β 1,3 Gal transferase reduced activity

- **acquired mechanisms:**
  - **Th1/Th2 unbalance during infections (Emancipator,1998)**

Selective Th2 subset activation in IgAN

Emancipator SN

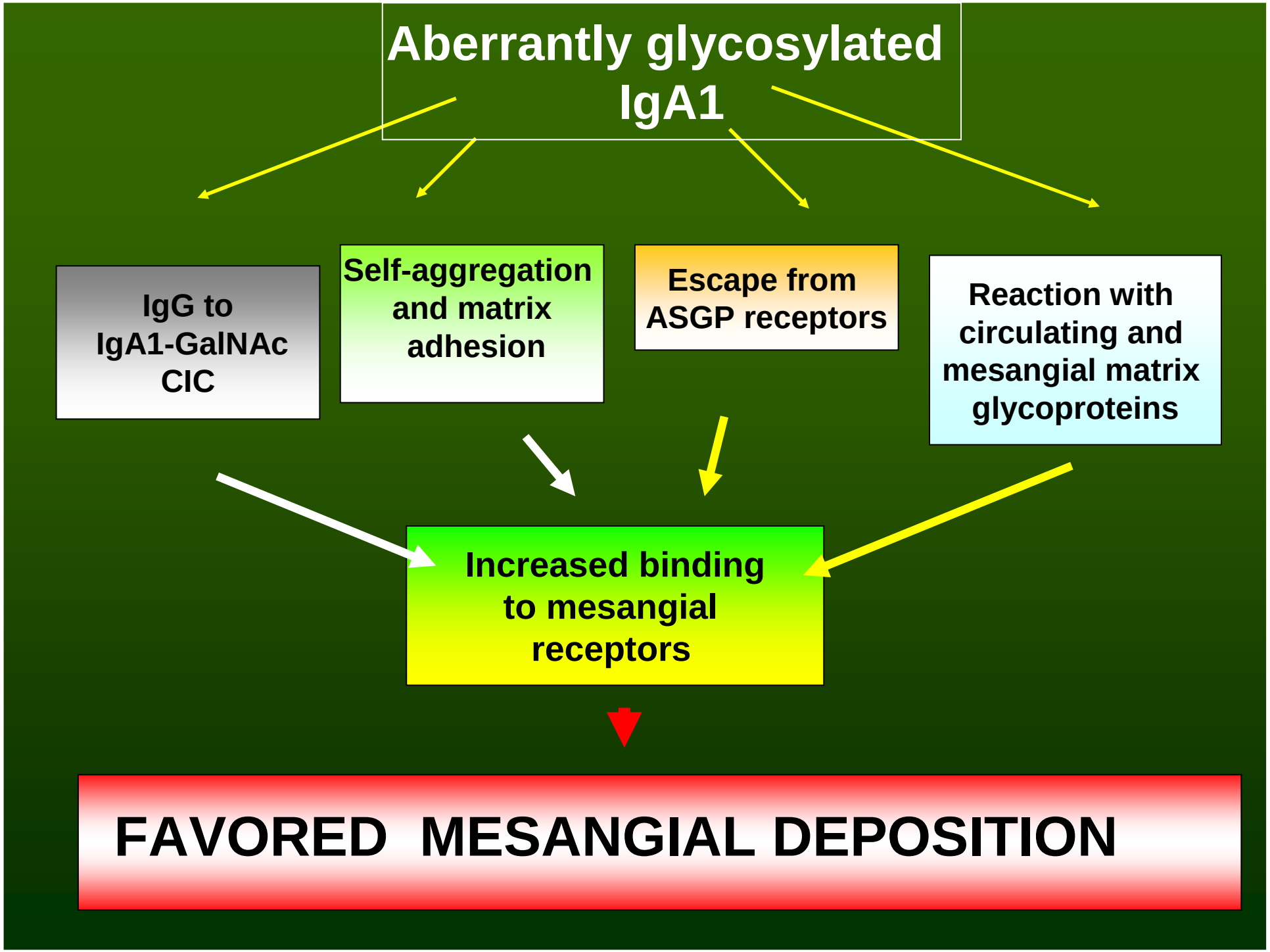


Aberrant glycosylation of IgA1 is likely to be secondary to aberrant immunoregulation

- **O-gycosylation of serum IgD is not altered**

(Smith , Feehally and Barratt, JASN 2006)

(IgD, produced early in B cell development and IgA1 , produced by mature B cells are O-glycosylated)


Aberrantly glycosylated IgA1
IgG to IgA1-GalNAc CIC
Self-aggregation and matrix adhesion
Escape from ASGP receptors
Reaction with circulating and mesangial matrix glycoproteins
Increased binding to mesangial receptors
FAVORED MESANGIAL DEPOSITION

Still unanswered observations & questions

- Why some patients have innocent IgA deposition, detected only at kidney donation?
- Why some IgAN progress to sclerosis and loss of renal function while others maintain microscopic hematuria but do not progress?
- Some 5-30% IgAN show remission of any clinical signs, but IgA deposits are stll present even in remission.

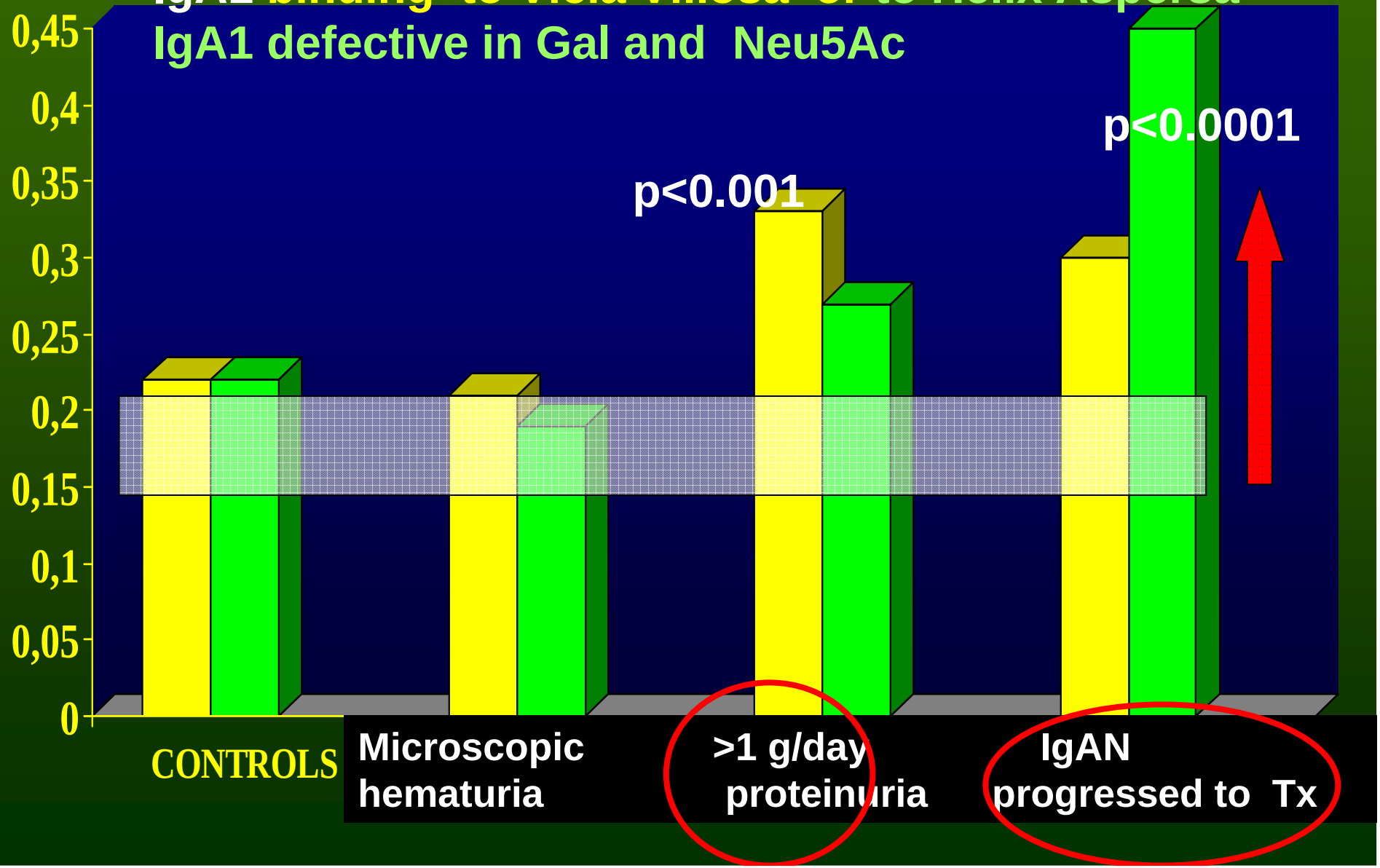
What regulates IgA deposition and "malignancy"?

May the glycosylation pattern of IgA1 molecules influence the clinical features of IgAN?

Aberrantly glycosylated IgA1 in IgAN patients with different risk factors for progression

IgA1 binding to Vicia Villosa or to Helix Aspersa

IgA1 defective in Gal and Neu5Ac



Serological and genetic factors in early recurrence of IgA nephropathy after renal transplantation.

(Coppo et al Clin Transplant. 2007; 21:728-37)

Variable	B	SE	Wald	P value	ODDS ratio	95% CI for ODDS Ratio	
						Lower	Upper
Aberrantly glycosylated IgA1: IgA1-VV	2.1	1.189	3.119	0.077	8.172	0.794	84.085
TNF α genotype GA	-2.0	0.991	4.391	0.036	0.125	0.018	0.874
IL-10 genotype ACC/ATA	-3.2	1.249	6.826	0.009	0.038	0.003	0.443

Serological and genetic factors in early recurrence of IgA nephropathy after renal transplantation.

(Coppo et al Clin Transplant. 2007; 21:728-37)

Aberrantly glycosylated IgA1 may have an influence in recurrence of IgAN when there is a cytokine milieu favouring the Th2 subset

hypothesis of
a systemic inflammatory milieu in IgAN

IgACE:A placebo-controlled, randomized trial of ACE-I in moderately proteinuric IgAN in the young

JASN 2007; 18:1880-1888

R Coppo, L Peruzzi, A Amore,
A Piccoli, P Cochat, R Stone,
M Kirschstein, T Linné on behalf the
EC Biomed Concerted Action
Project BMH4-97-2487(DG 12-SSMI)
IgACE European Collaborative Group.

IgACE:A placebo-controlled, randomized trial of ACE-I in moderately proteinuric IgAN in the young

JASN 2007; 18:1880-188

EC Biomed Concerted Action

Project BMH4-97-2487(DG 12-SSMI)

25 Centers from Italy, France, Germany, Sweden, Portugal

ACE-I (Benazepril 0.2 mg/Kg/day)

in children and young < 35 y.o. IgAN with proteinuria >1 and < 3.5 g/1.73 m2/day

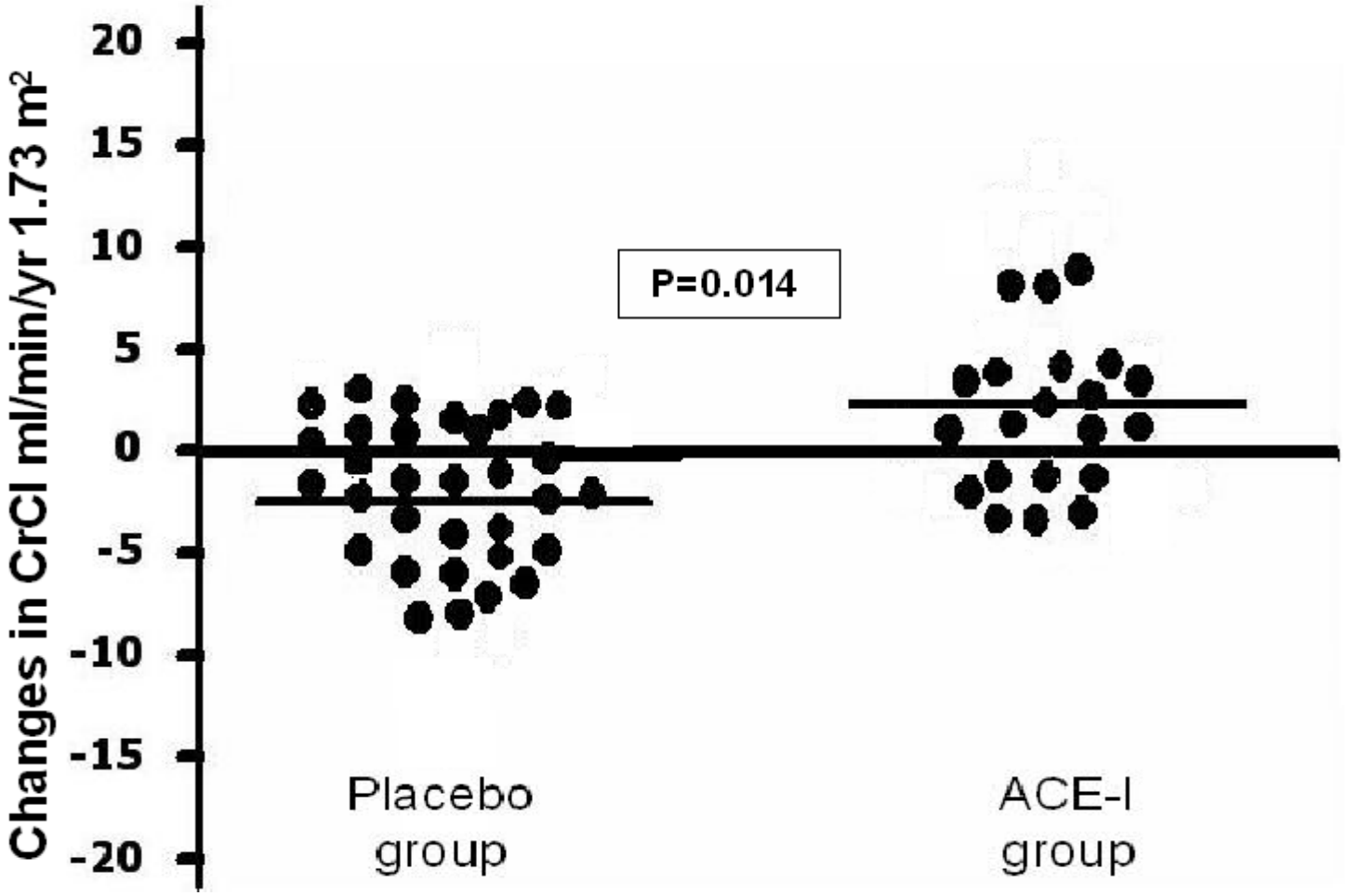
CrCl >50 ml/min/1.73m2

Effects on

- **risk of renal damage progression**
- **proteinuria remission**

IgACE trial

Changes in CrCl slopes over the follow-up



34 patients

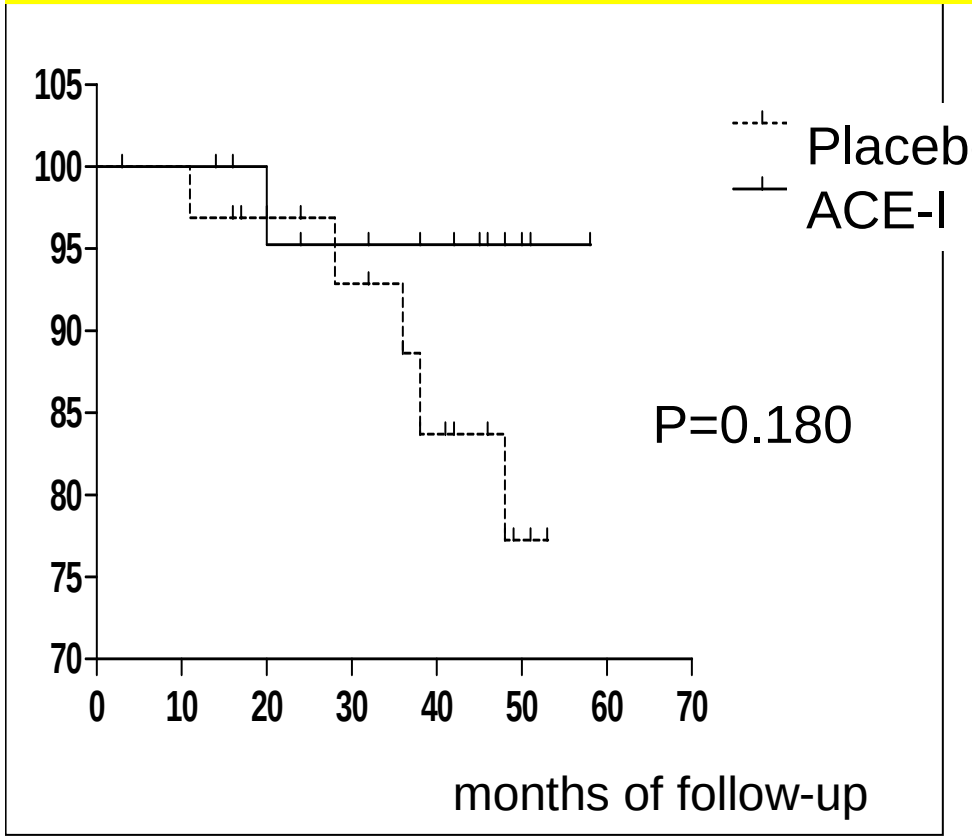
Median FU 38 months

23 patients

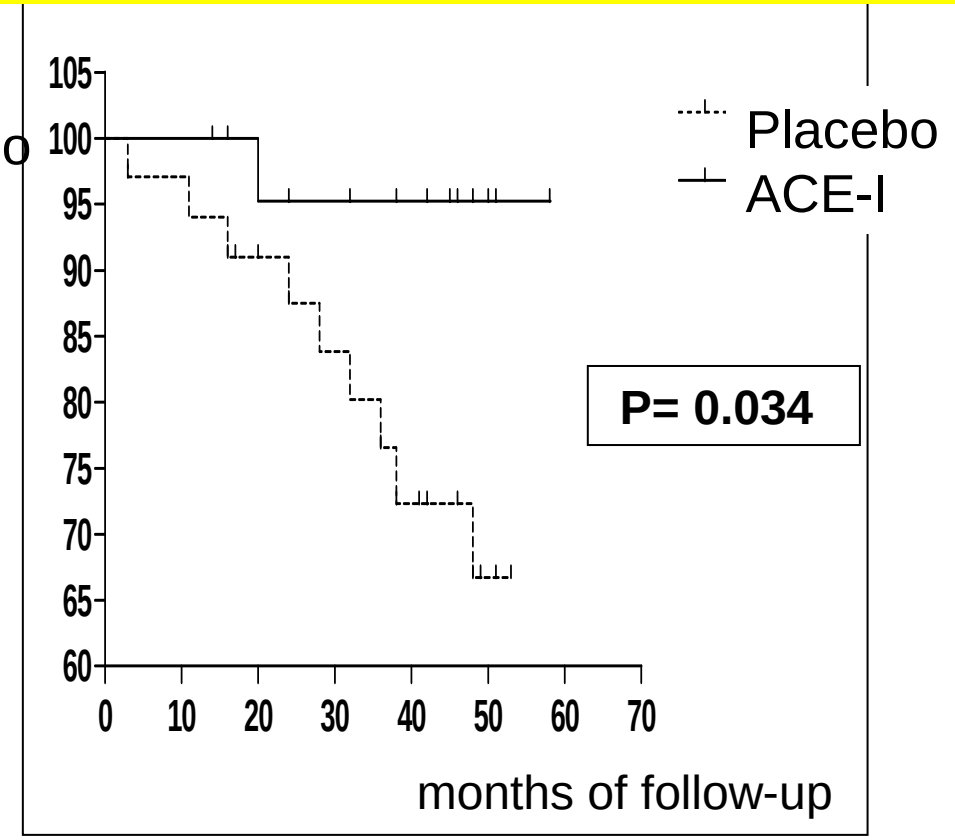
Median FU 46 months

Outcome: progression of renal damage

End-point
30% reduction of initial CrCl

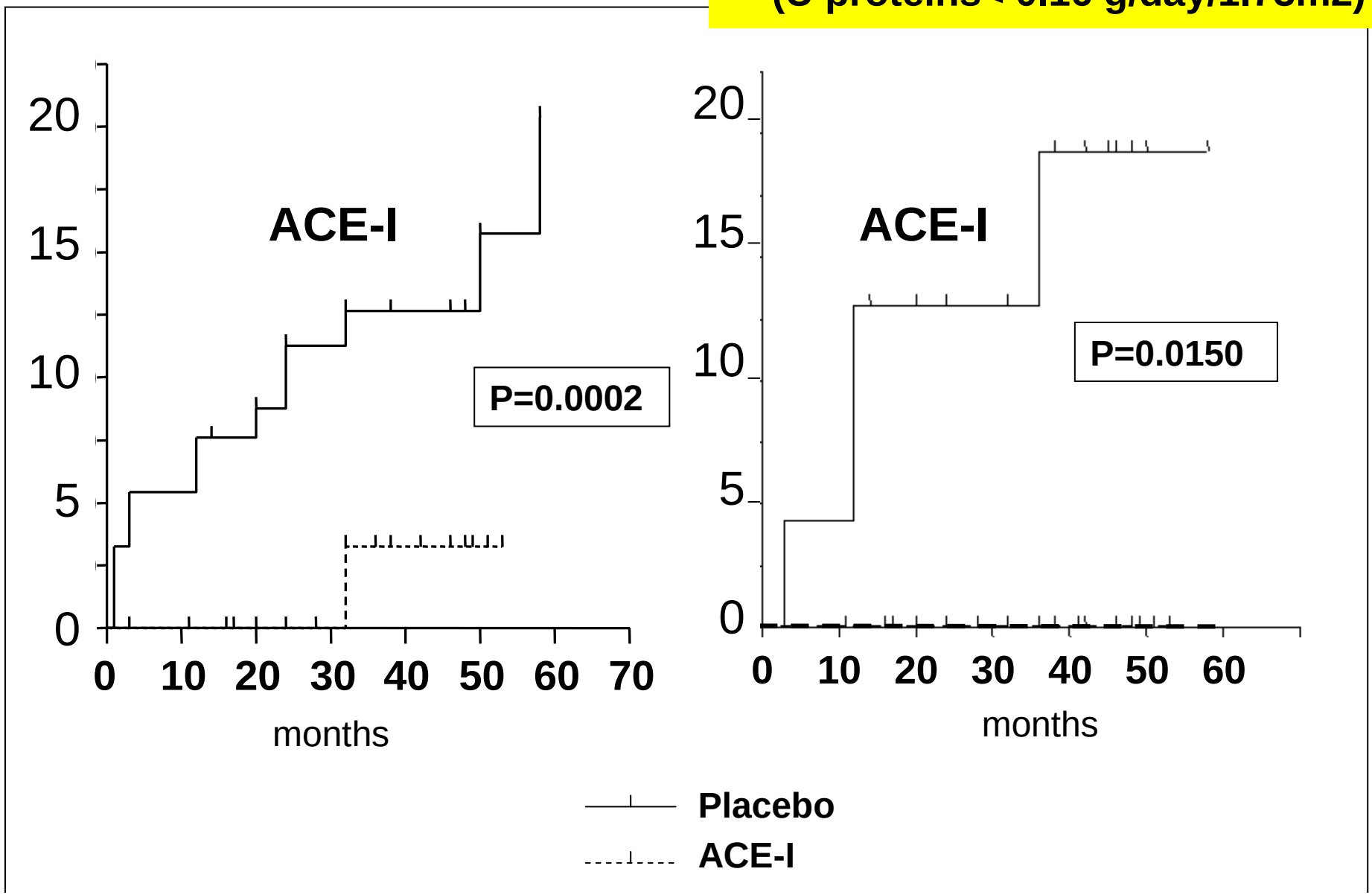


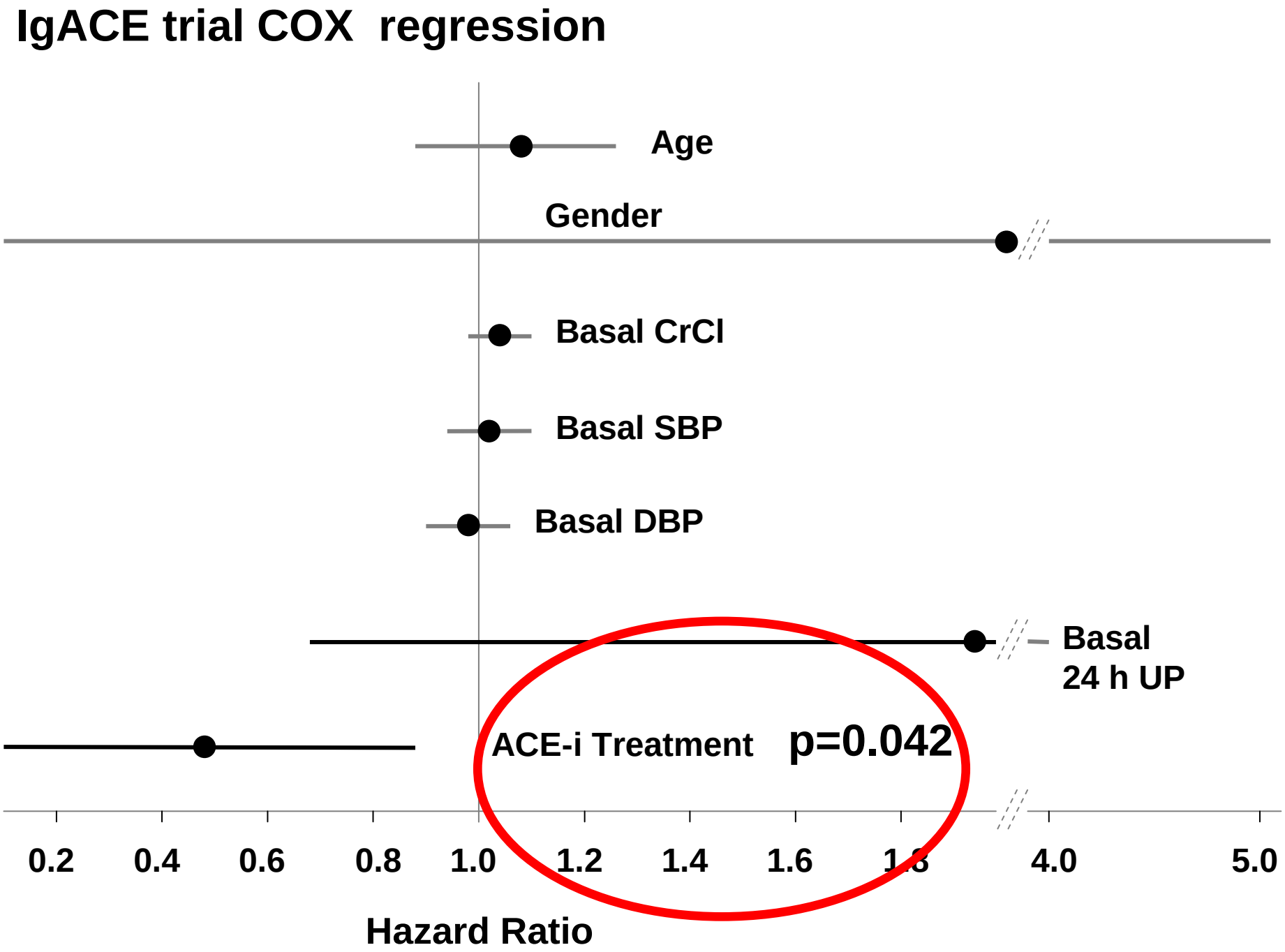
End-point
30% loss of initial CrCl and/or worsening of proteinuria to nephrotic range (>3.5 g/1.73m2/day)



Partial remission of proteinuria (U proteins< 0.50 g/day/1.73m2)

Total remission of proteinuria (U proteins< 0.16 g/day/1.73m2)




IgACE trial COX regression
Age
Gender
Basal CrCl
Basal SBP
Basal DBP
Basal
24 h UP
ACE-i Treatment
p=0.042
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
4.0
5.0
Hazard Ratio

AOPP

Advanced oxidation protein products as risk factors for atherosclerotic cardiovascular events in nondiabetic predialysis patients

Descamps-Latscha B, Witko-Sarsat V, London GM et al Am J Kidney Dis. 2005

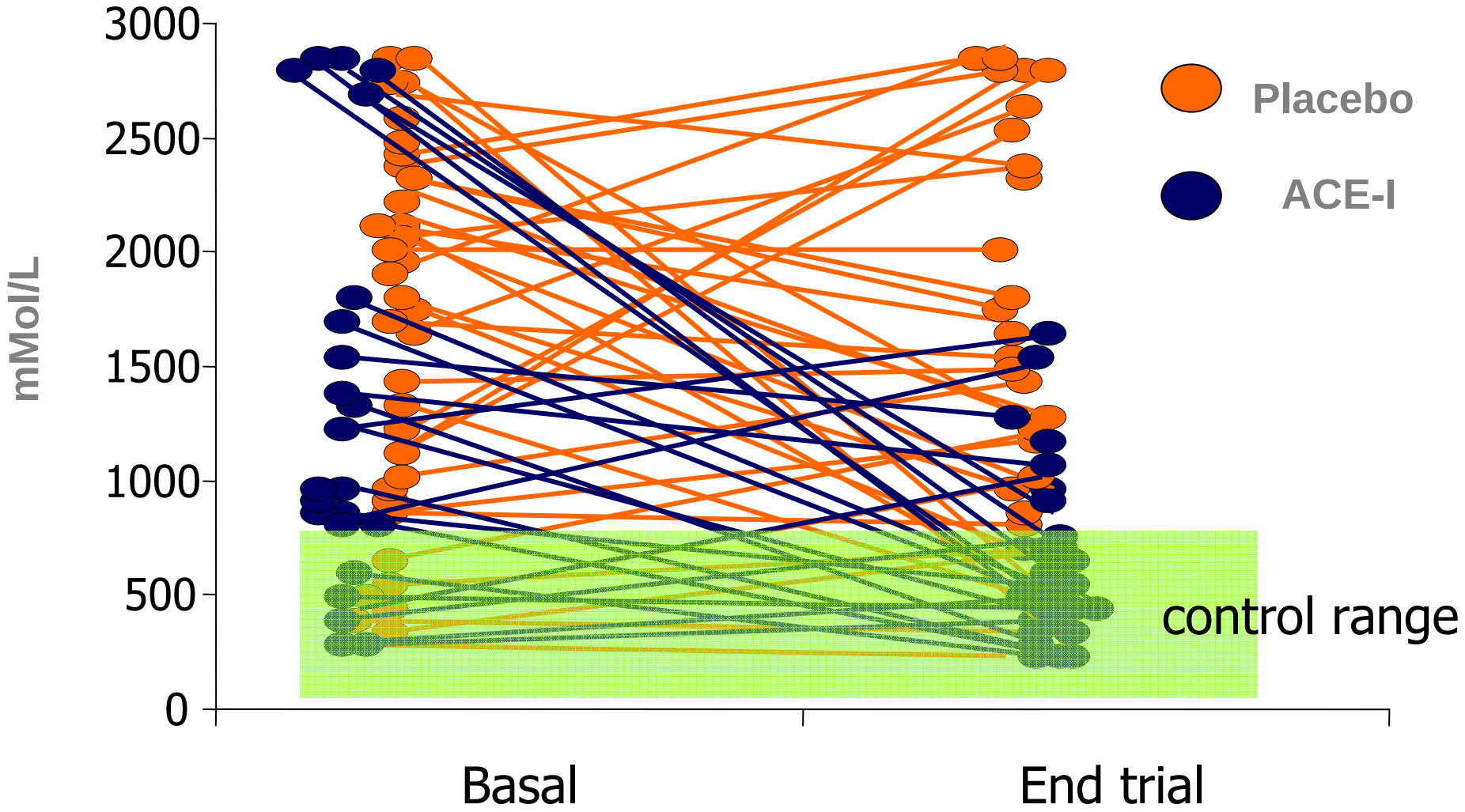
Advanced oxidation protein products

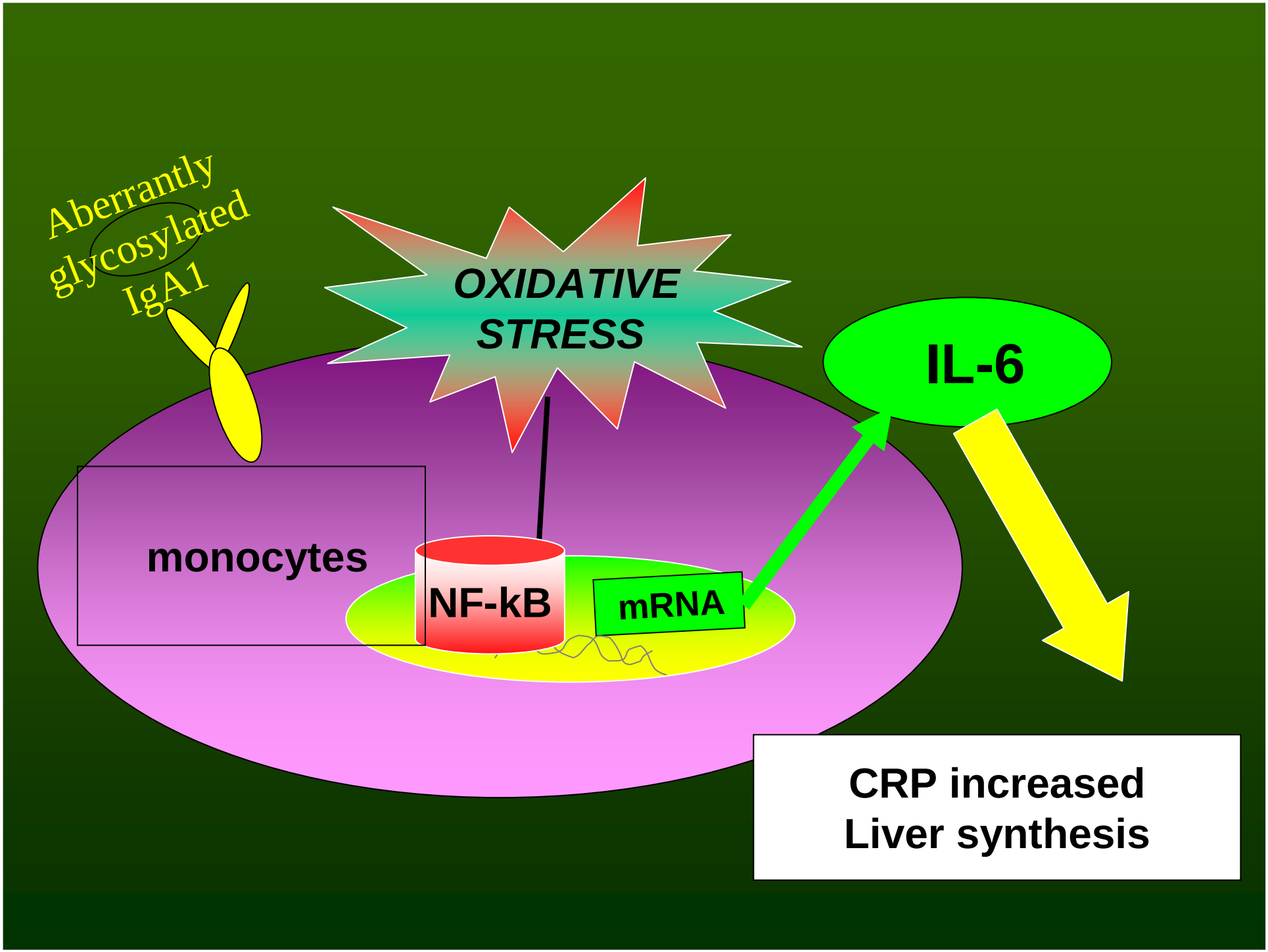
a new marker for progressive IgAN

Descamps-Latscha B, London GM et al KI 2004

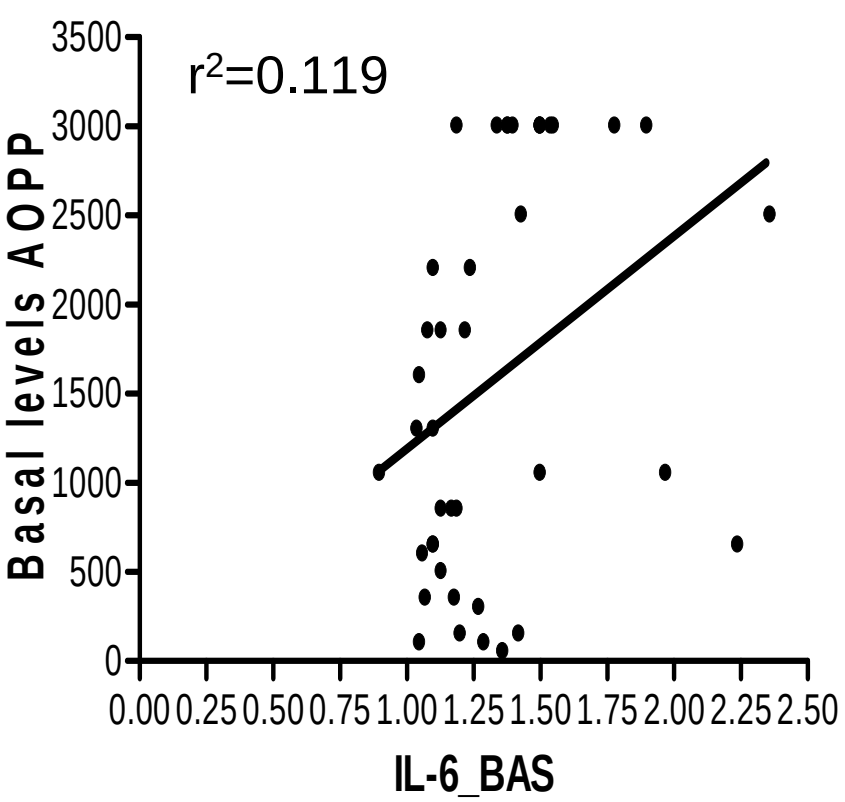
AOPP levels in IgAN patients enrolled in the IgACE BMH4-97-2487 trial Treated with ACE-Inhibitors (ACE-I) or placebo (PL)

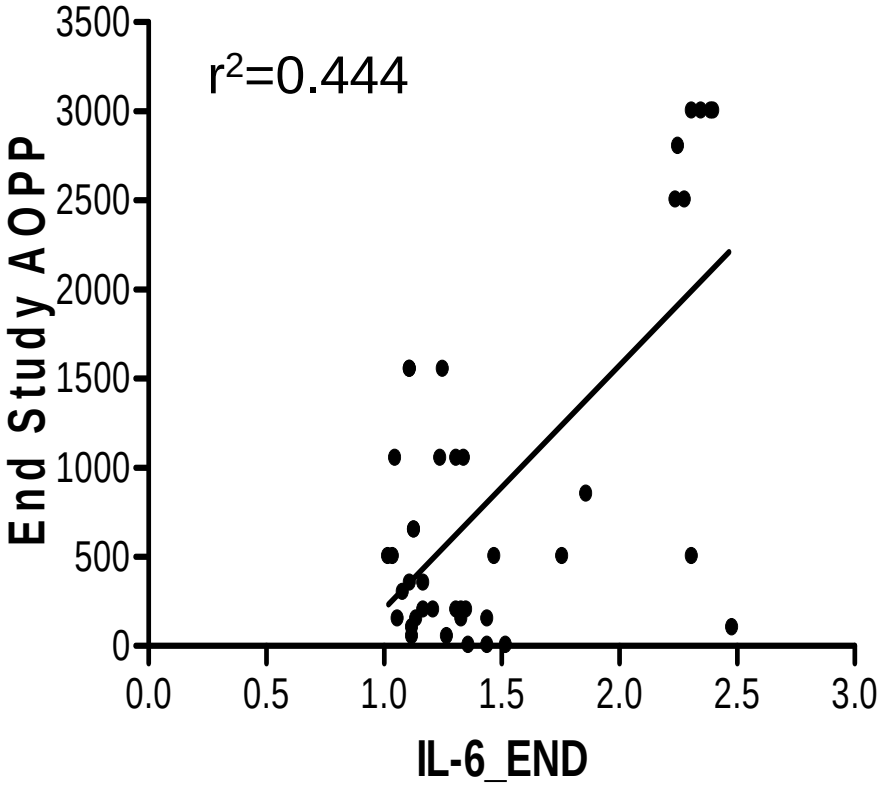
Coppo et in preparation




Aberrantly glycosylated IgA1
OXIDATIVE STRESS
IL-6
monocytes
NF-kB
mRNA
CRP increased
Liver synthesis

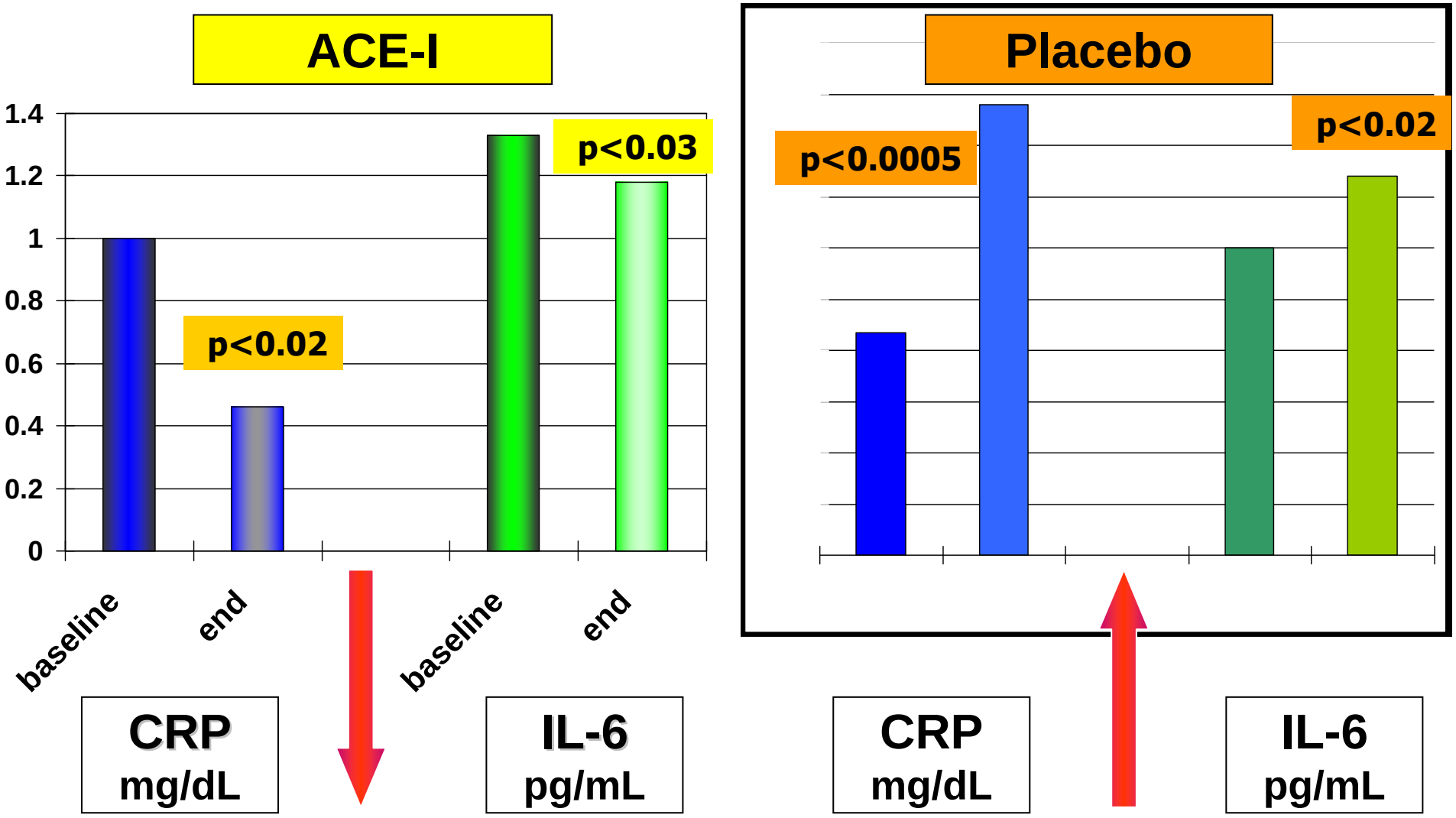
Significant linear correlation between
AOPP and IL-6 levels





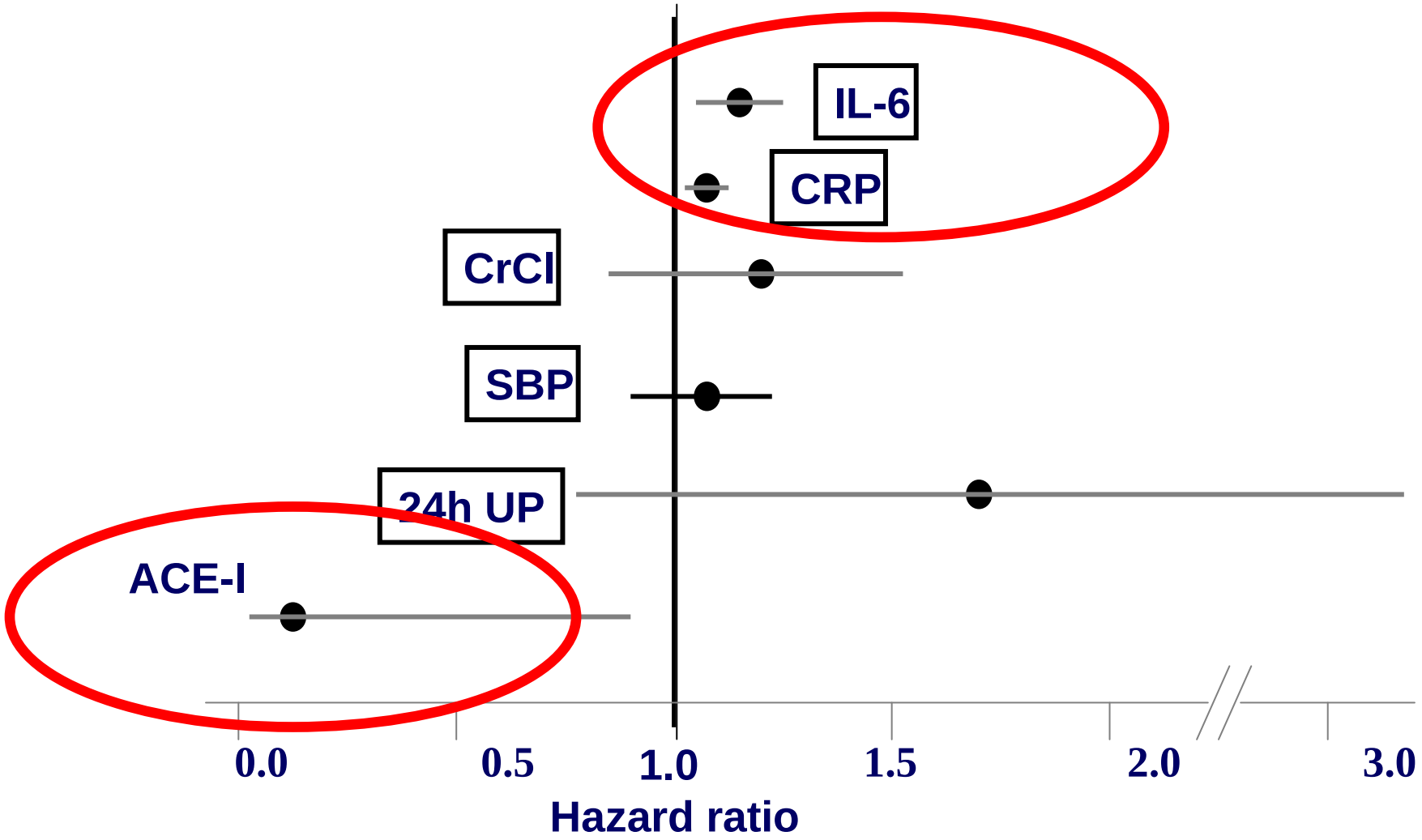
No significant linear correlation was found between AOPP and CRP serum levels.

CRP and IL-6 levels at the end of the IgACE trial were significantly reduced in ACE-I treated patients and significantly increased in the Placebo group



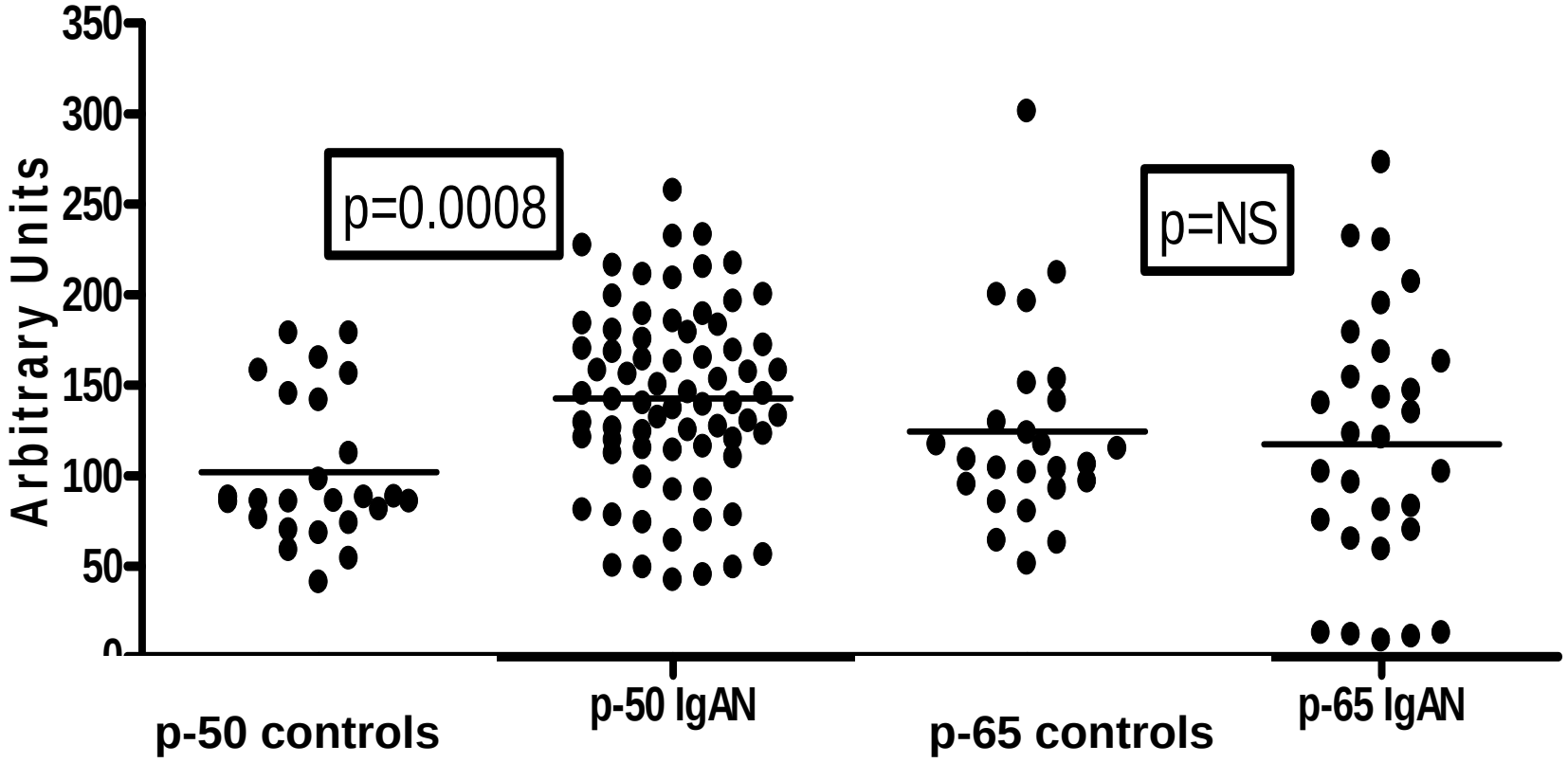
Survival predictive variables to progression end-point of renal damage (30% reduction of GFR and/or nephrotic proteinuria)

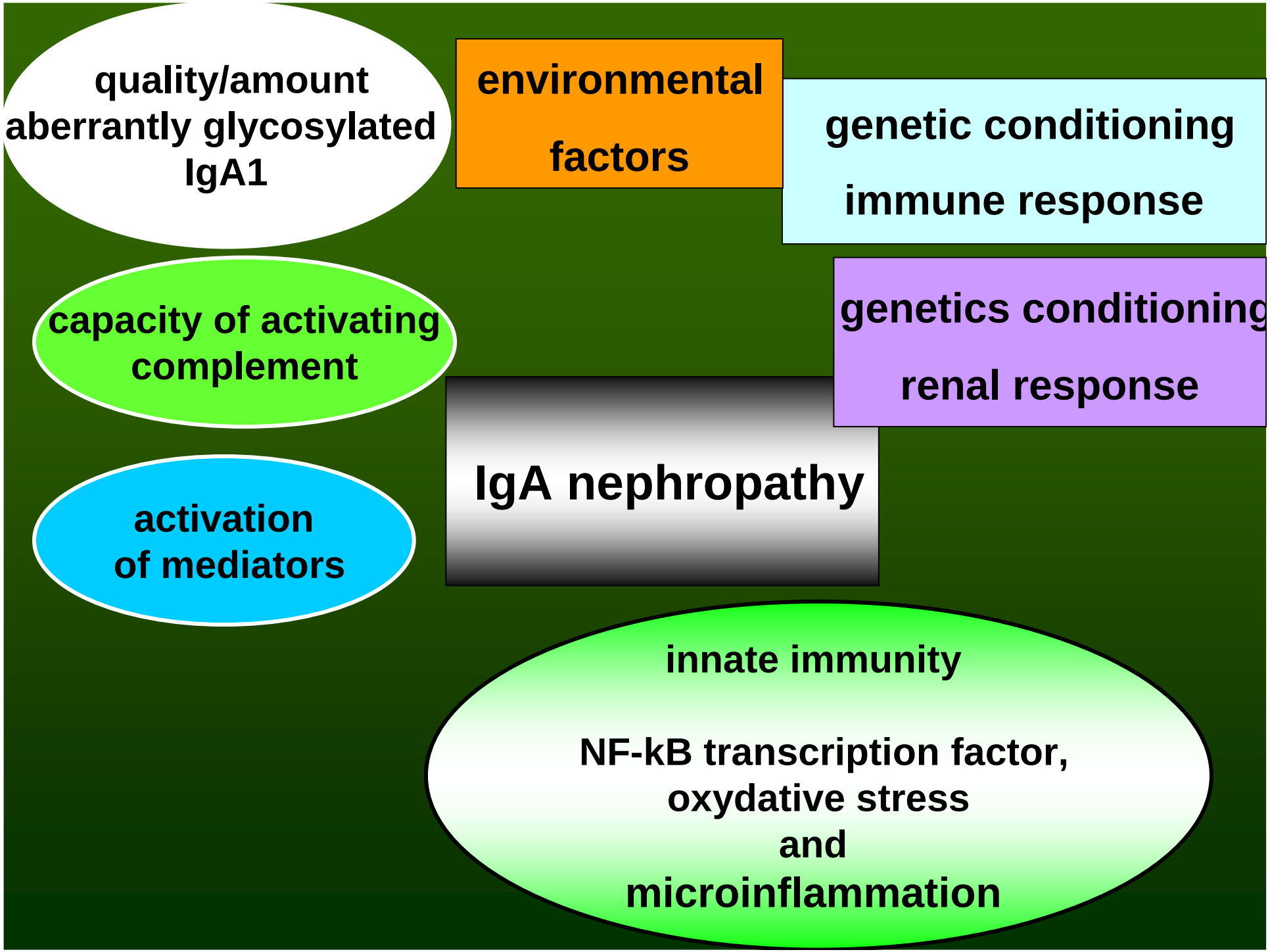
Cox Analysis



Systemic activation of the transcriptional factor NF-kB in IgAN: a condition of microinflammation

NF-kB DNA binding activity in lymphomonocytes (PBMC) in IgAN patients and controls




quality/amount
aberrantly glycosylated
IgA1
environmental
factors
genetic conditioning
immune response
capacity of activating
complement
genetics conditioning
renal response
IgA nephropathy
activation
of mediators
innate immunity
NF-kB transcription factor,
oxydative stress
and
microinflammation

Treatment of IgA nephropathy

Should we treat all the cases of IgAN ?

Asymptomatic deposition of IgA in 5-16%
of healthy subjects

Spontaneous remissions in 5-30%
of patients with IgAN

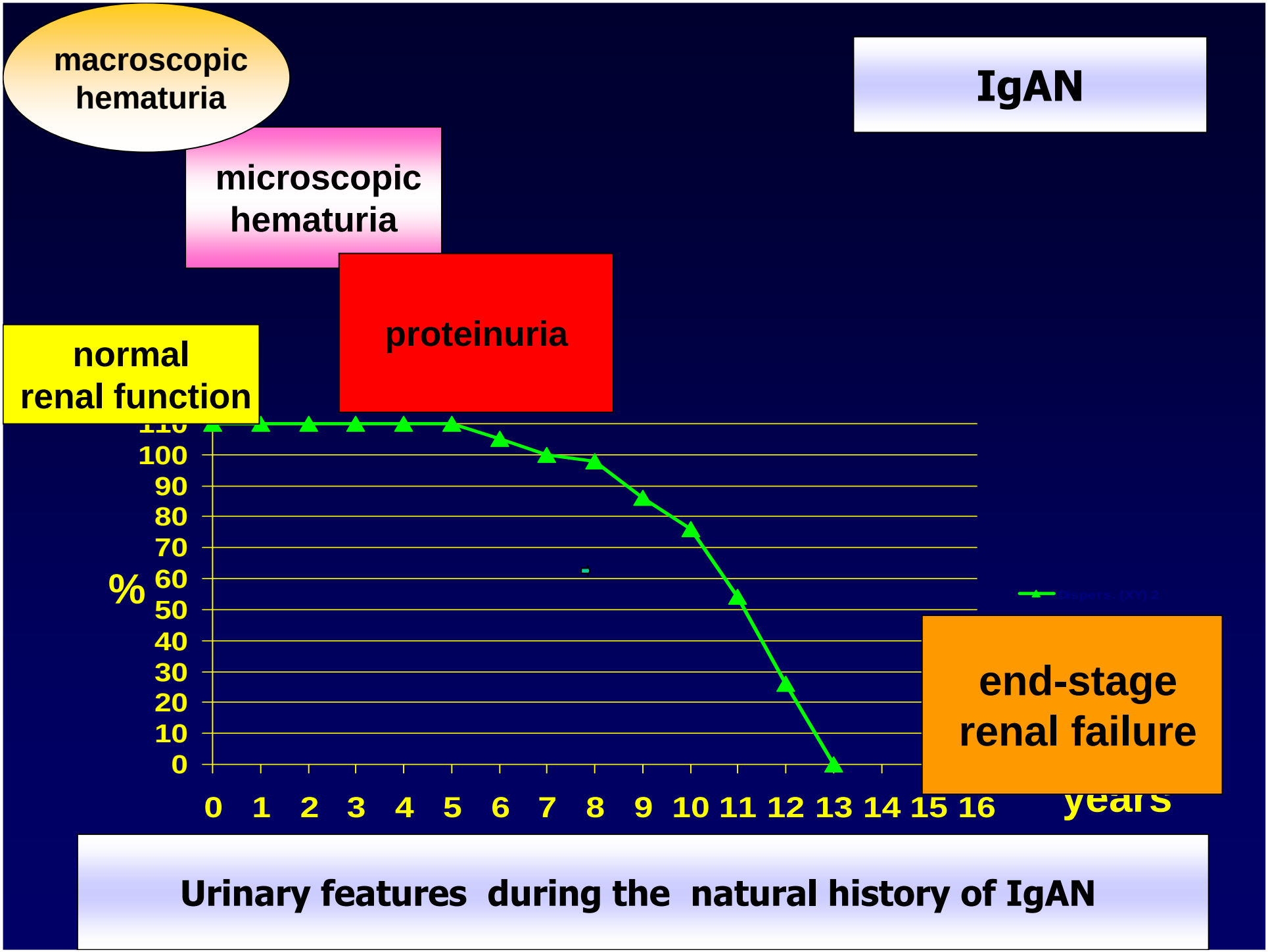
Renal survival at 10 years is variable from 57 to 96

Patients to be treated

Treatment with the highest probabilities of success

Cases of di IgAN with

- Isolated urinary abnormaties , early detected
- Microscopic hematuria persistent over years
- **Proteinuria of variable degree**
- **Associated Hypertension**
- **Lack of expected results at the first treatment**
- **Progressive features**
- CKD 4 or 5 with advanced sclerosis


macroscopic hematuria
IgAN
microscopic hematuria
proteinuria
normal renal function
100
90
80
70
60
%
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
years
end-stage renal failure
Urinary features during the natural history of IgAN

proteinuria at renal biopsy

Survival of IgAN patients with different level of proteinuria

Radford MG J Am Soc Nephrol 1997

in IgAN even proteinuria<0.4g/day may be associated with progression

proteinuria<1g/day

proteinuria 1-1.9

proteinuria 2-2.9

proteinuria >3

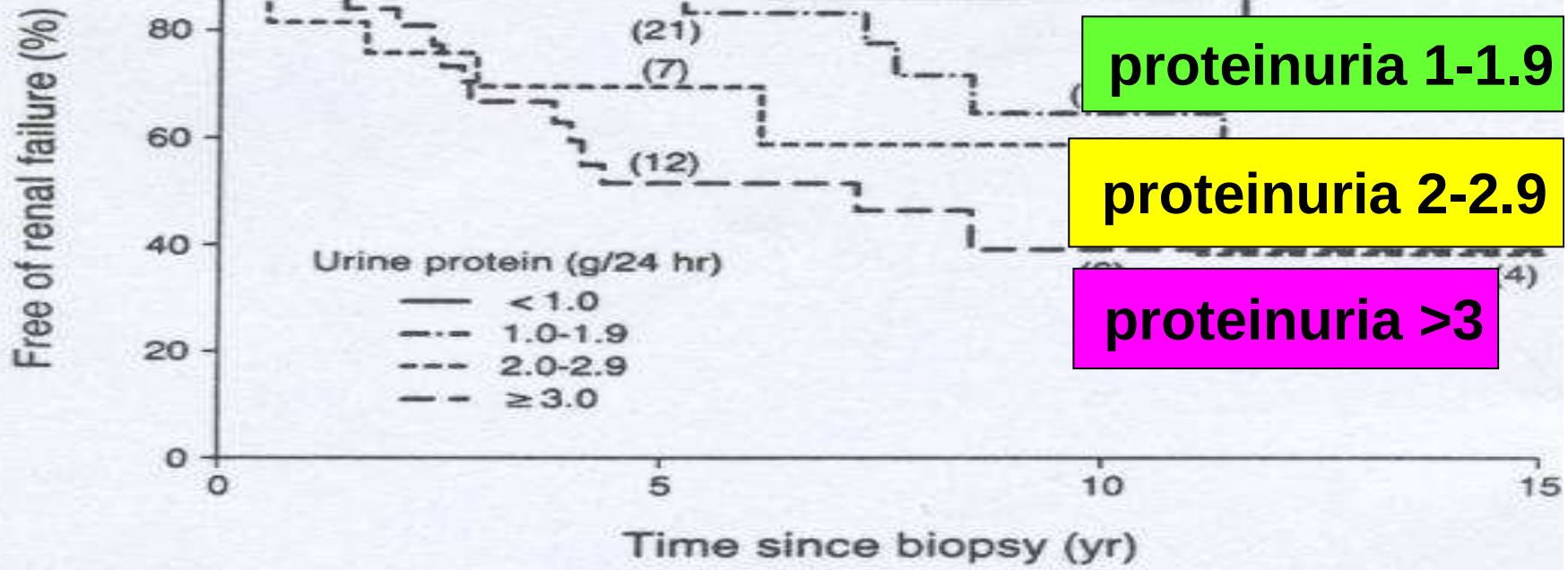
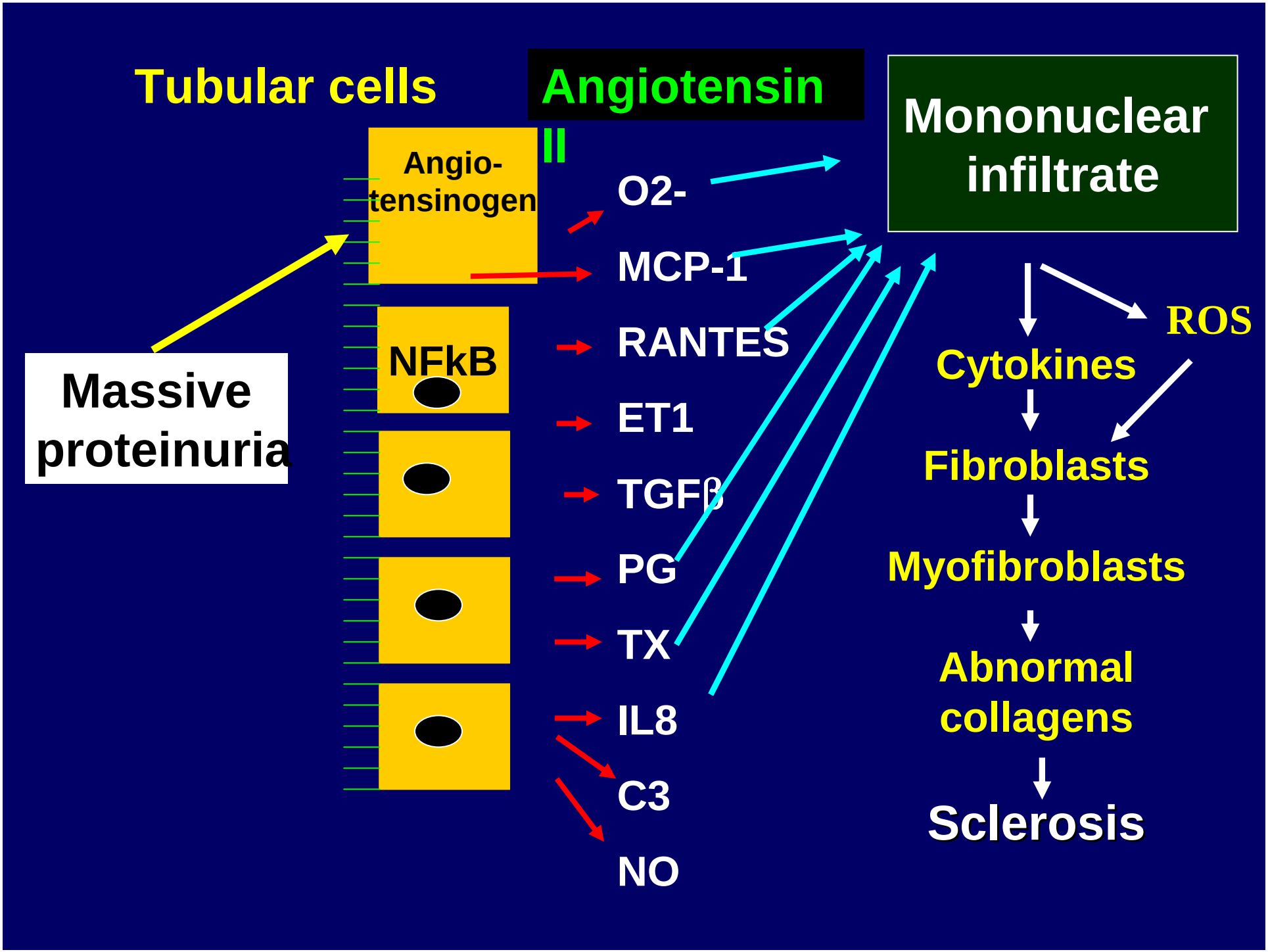


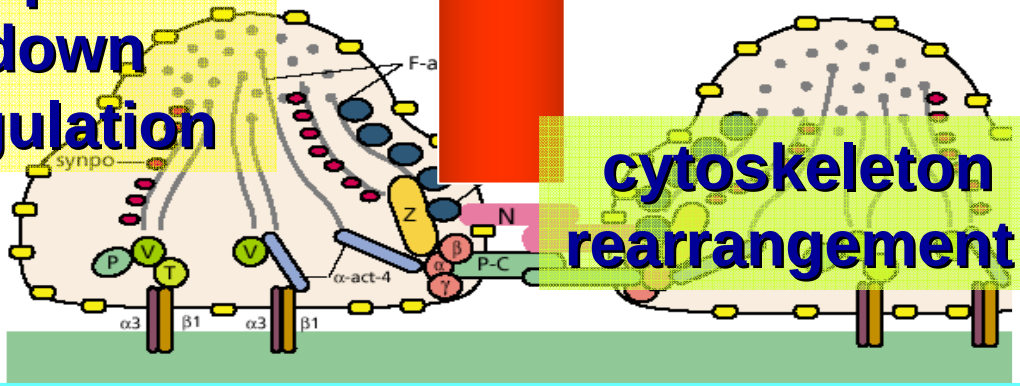
Figure 3. Survival free of renal failure by urine protein level measured at renal biopsy; $N = 128$ patients. Survival decreased progressively according to higher levels of baseline proteinuria ($P = 0.014$). Numbers in parentheses indicate the number of patients at risk at 5, 10, and 15 yr.


Tubular cells
Angiotensin II
Mononuclear infiltrate
Angio-tensinogen
NFkB
Massive proteinuria
O2-
MCP-1
RANTES
ET1
TGFβ
PG
TX
IL8
C3
NO
ROS
Cytokines
Fibroblasts
Myofibroblasts
Abnormal collagens
Sclerosis

Proteinuria

?

Nephrin down regulation



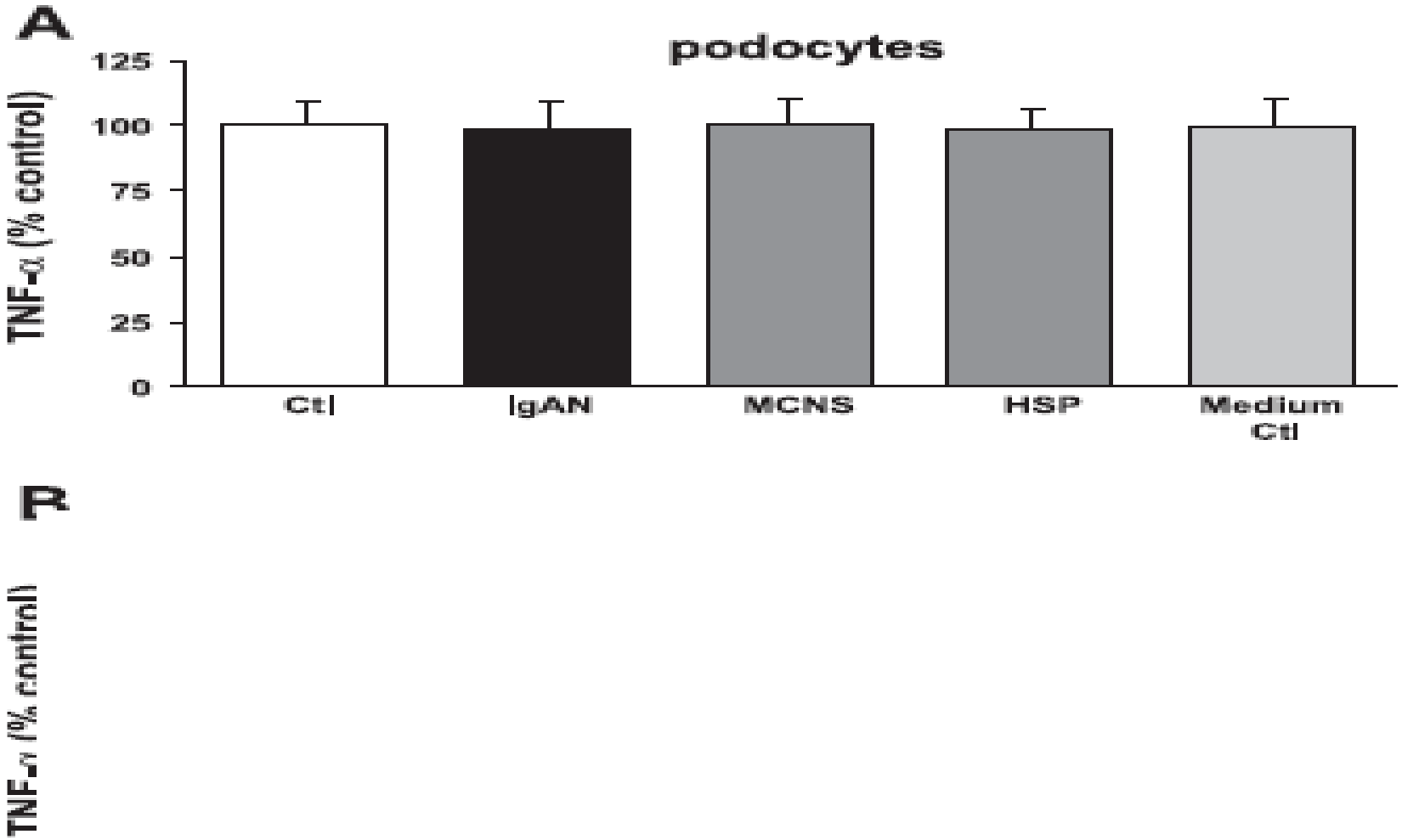
cytoskeleton rearrangement

glomerular basement membrane

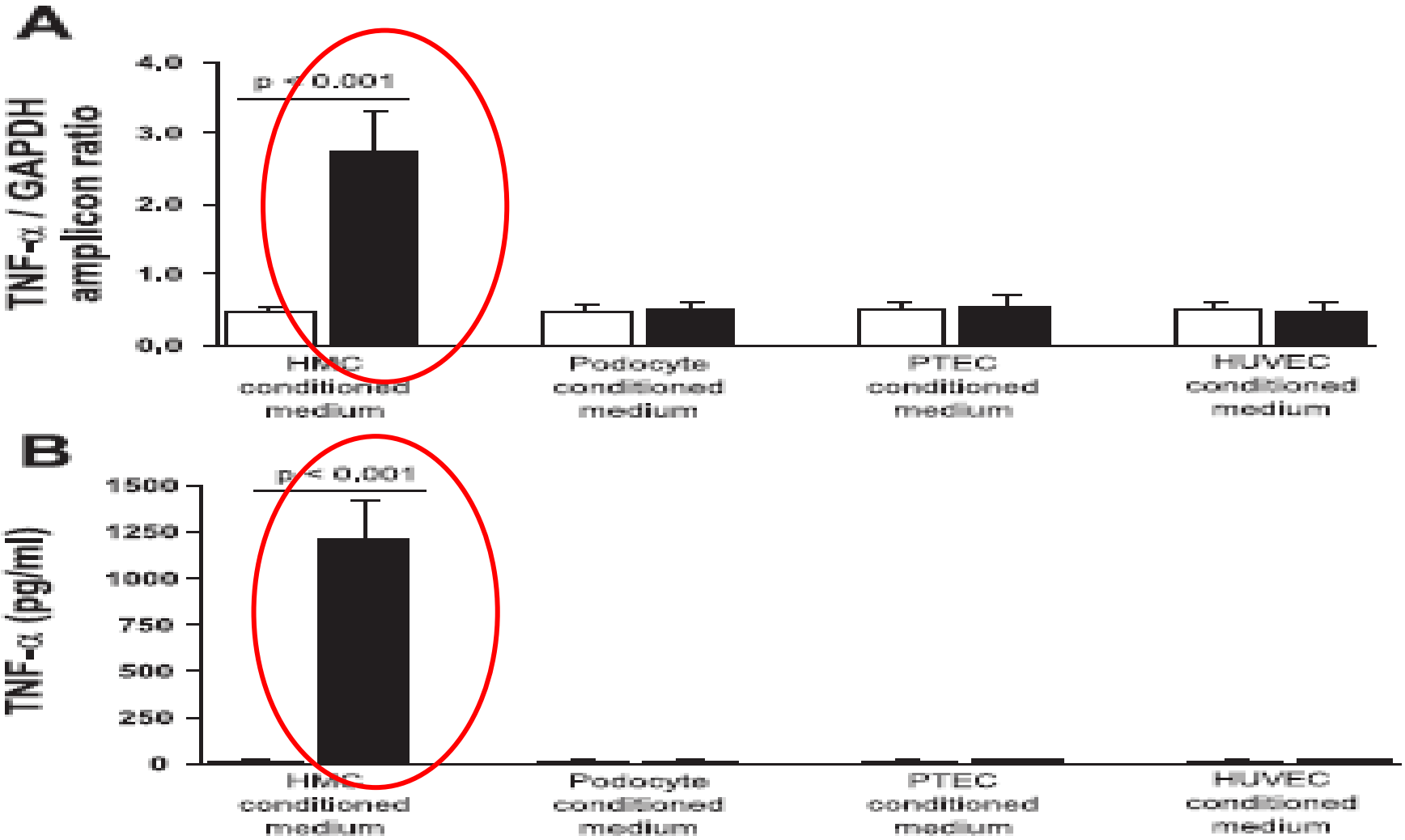
Activation of mesangial cells by deposited IgA

Kar Neng Lai, Joseph C. K. Leung, Loretta Y. Y. Chan, Moin A. Saleem, Peter W. Mathieson, Fernand M. Lai and Sydney C. W. Tang
Am J Physiol Renal Physiol 294:945-955, 2008. First published Feb 6, 2008;
doi:10.1152/ajprenal.00423.2007

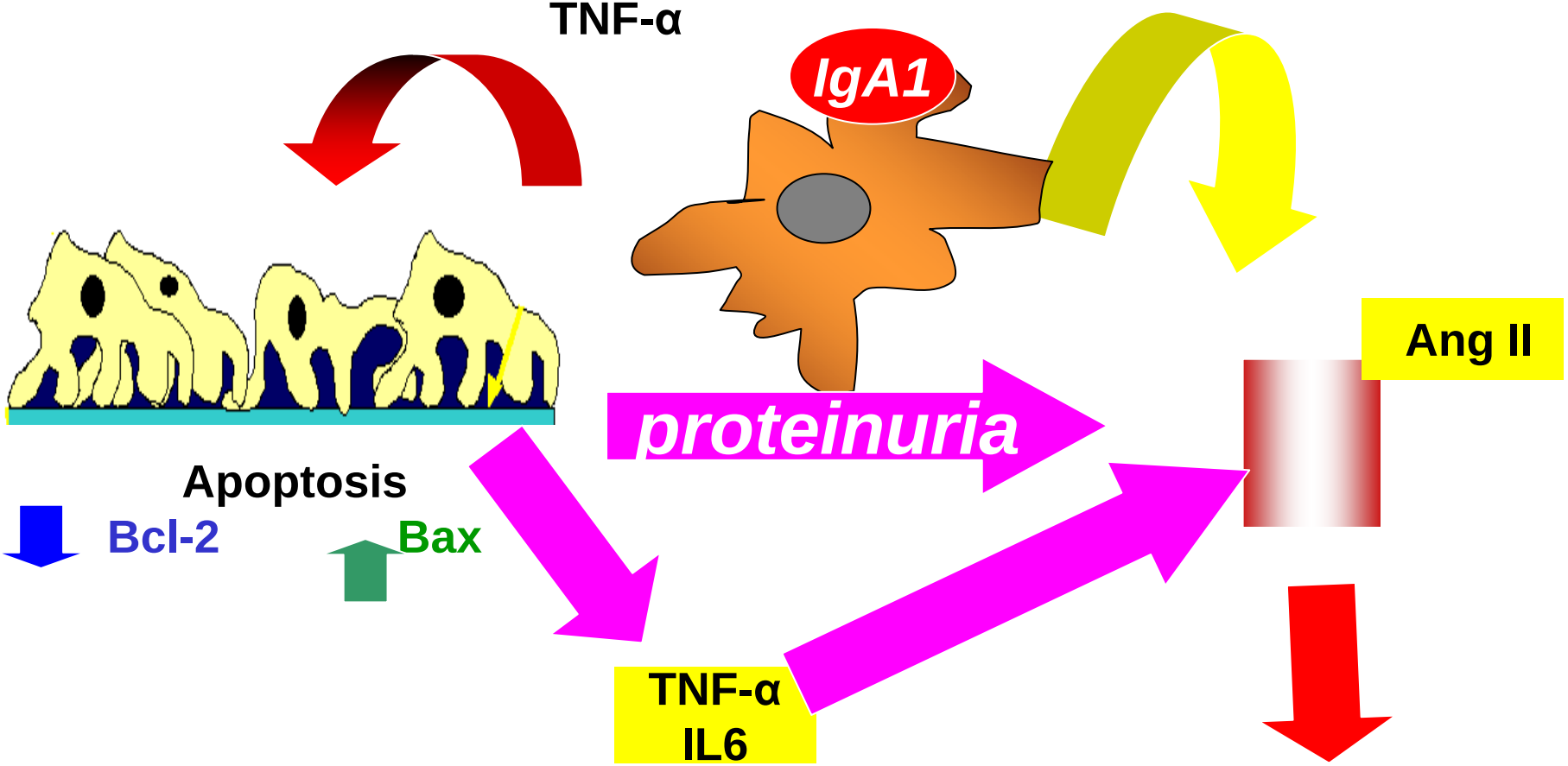
Synthesis of TNF-α in cells cultured with IgA from patients with IgAN and controls



Upregulation of TNF-α in podocytes cultured with medium obtained from mesangial cells cultured with IgA from IgAN patients



Glomerulo-tubular cross-talk via TNF-α, IL6 and Angio II

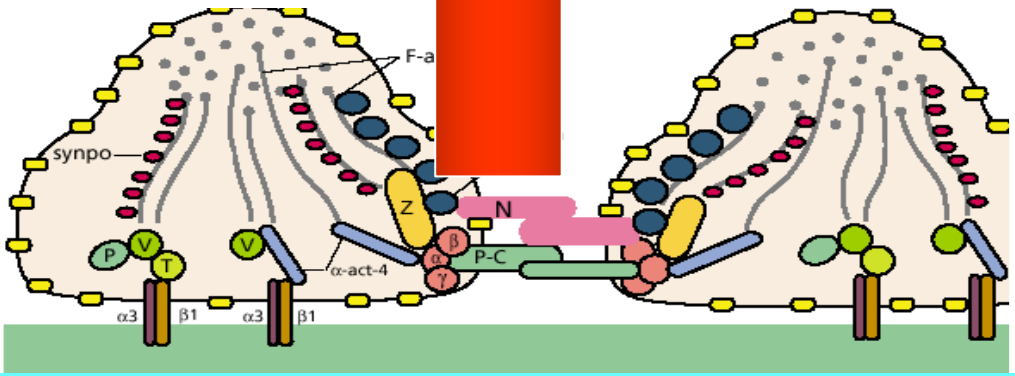


modified from Lai KN, et al
2008
Am J Phisiol Renal Physiol

SIGNALS FROM MESANGIAL CELLS ACTIVATED BY ABERRANTLY GLYCOSYLATED IgA TO PODOCYTES.

R.Coppo, G.Camussi
et al Torino, Italy
(Barcelona, 2007)

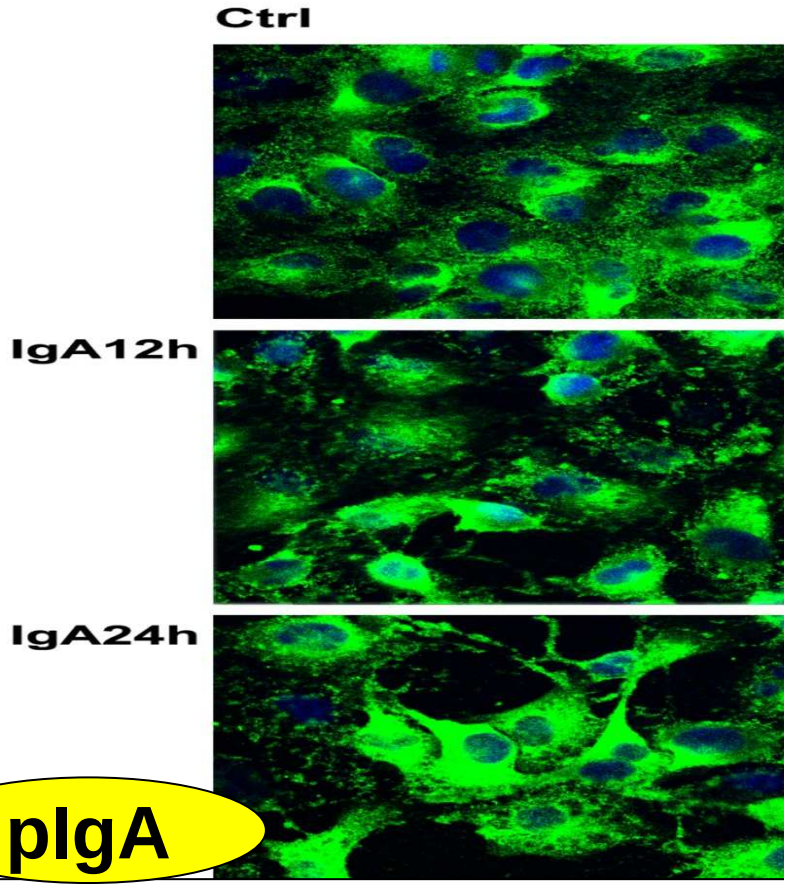
Podocytes **Proteinuria**



glomerular basement membrane

Activation of mesangial cells by deposited IgA

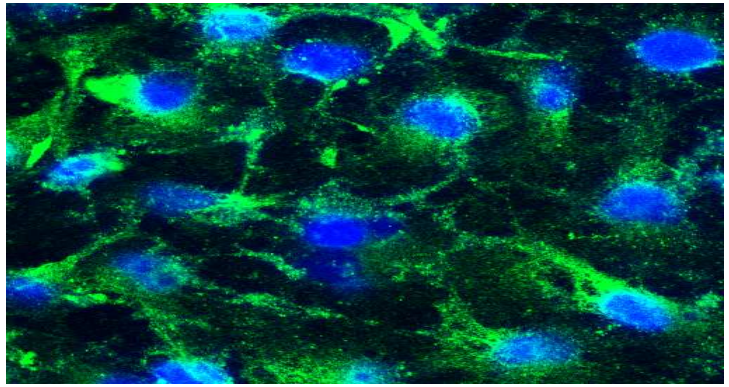
PODOCYTES EXPRESSION OF NEPHRIN

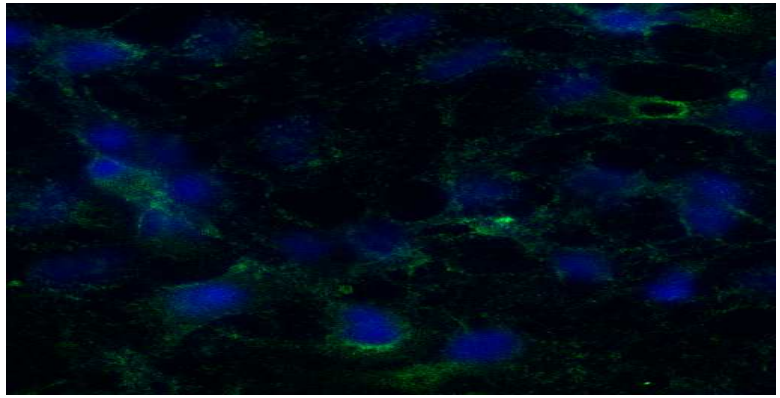


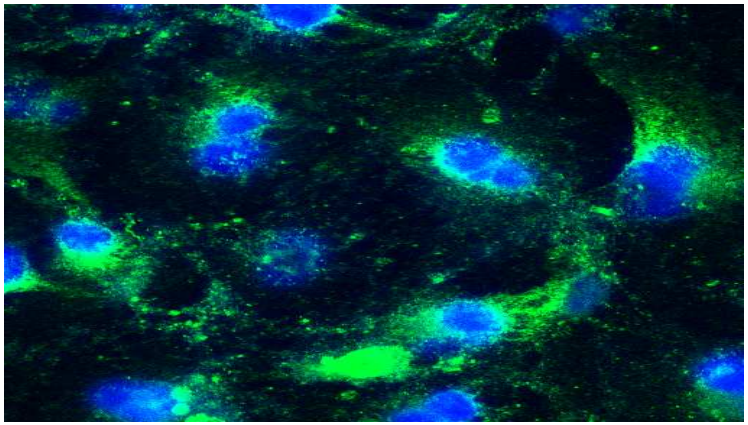
pIgA

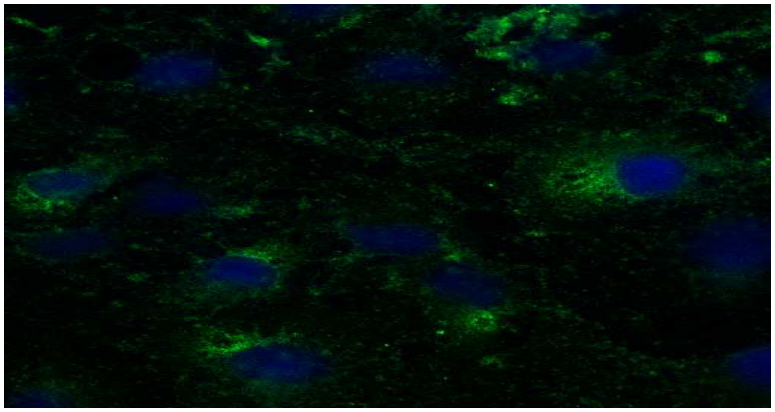
12 h-24 incubation with supernatants from mesangial cells cultured with

Nephrin staining on human podocytes before and after incubation with supernatants of mesangial cells cultured with IgA1 from IgAN patients









NDT Advance Access published August 6, 2008

Nephrol Dial Transplant (2008) 1–11
doi: 10.1093/ndt/gfn441

NDT
Nephrology Dialysis Transplantation

Original Article

Podocyte injury induced by mesangial-derived cytokines in IgA nephropathy

Kar Neng Lai[1], Joseph C. K. Leung[1], Loretta Y. Y. Chan[1], Moin A. Saleem[2], Peter W. Mathieson[2], Ka Ying Tam[1], Jing Xiao[1], Fernand M. Lai[3] and Sydney C. W. Tang[1]

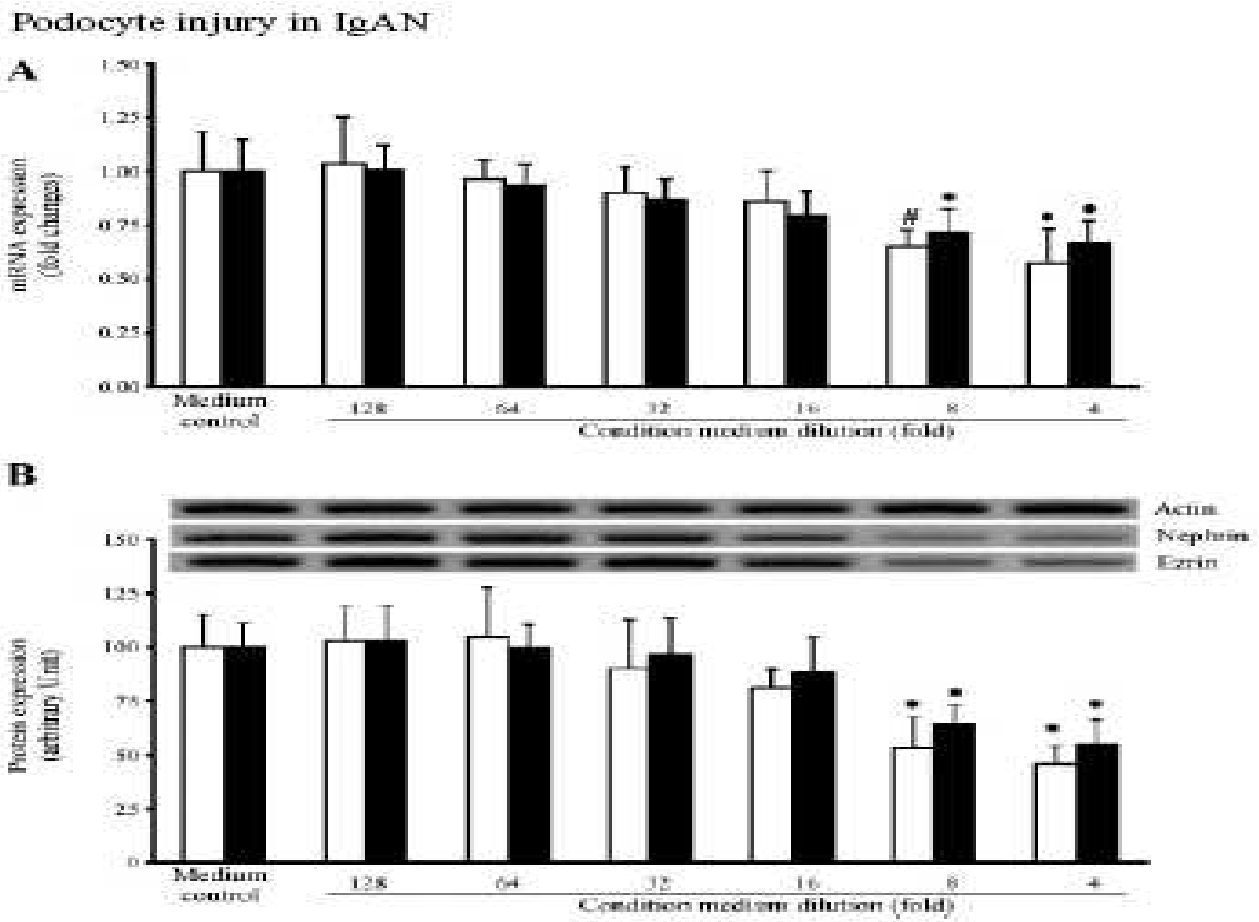


Fig. 6. Dose-related down-regulation of nephrin and ezrin expression by podocytes cultured with the IgA–HMC conditioned medium prepared from IgAN patients. Gene (A) and (B) protein expressions of nephrin (white bar) and ezrin (black bar) decreased significantly in podocytes following incubation with different doses (4- to 8-fold diluted medium) of the IgA–HMC conditioned medium prepared from IgAN. * signifies $P < 0.01$ when compared with data from podocytes cultured with medium control. The results represent the mean ± standard deviation from six individual experiments.

More than baseline proteinuria
persistence of proteinuria during follow-up
is the most relevant risk factor for progression

Risk factor for progression of IgAN:

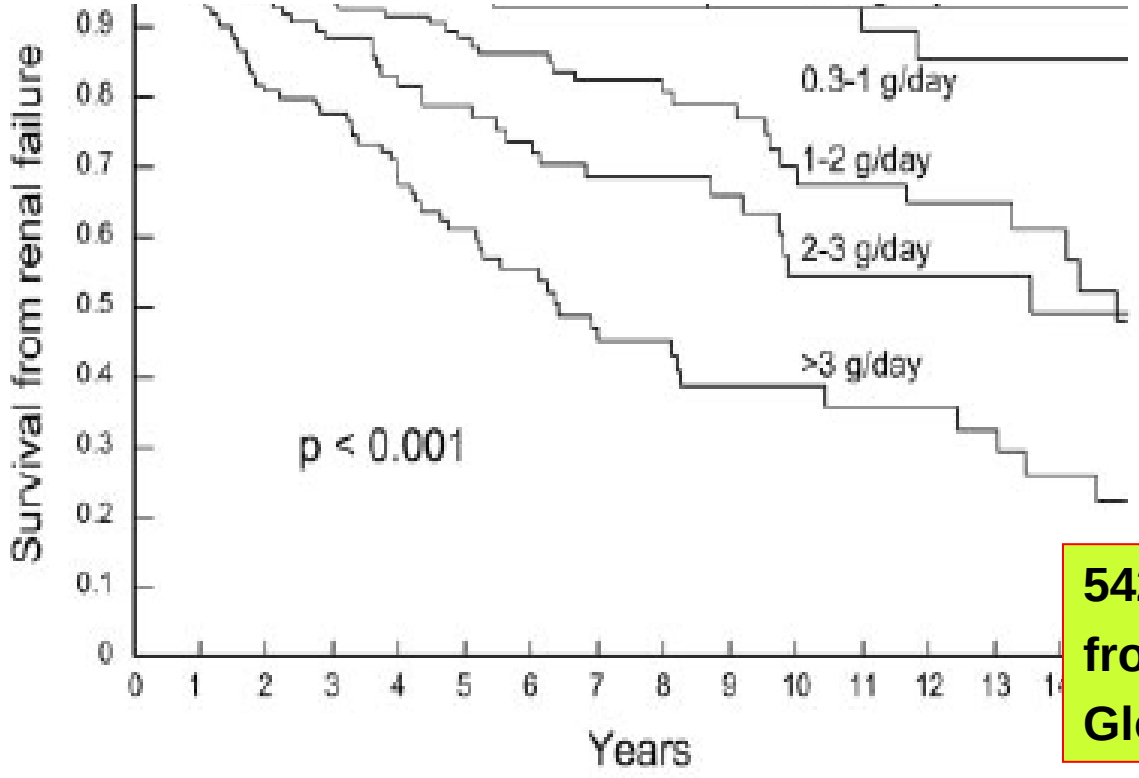
percent duration of massive proteinuria

- **proteinuria after 1 year of follow-up**
- **duration and amount of proteinuria in years**
  (time average proteinuria)

Remission of Proteinuria Improves Prognosis in IgA Nephropathy

Heather N. Reich,* Stéphan Troyanov,† James W. Scholey,* and Daniel C. Cattran,* for the Toronto Glomerulonephritis Registry

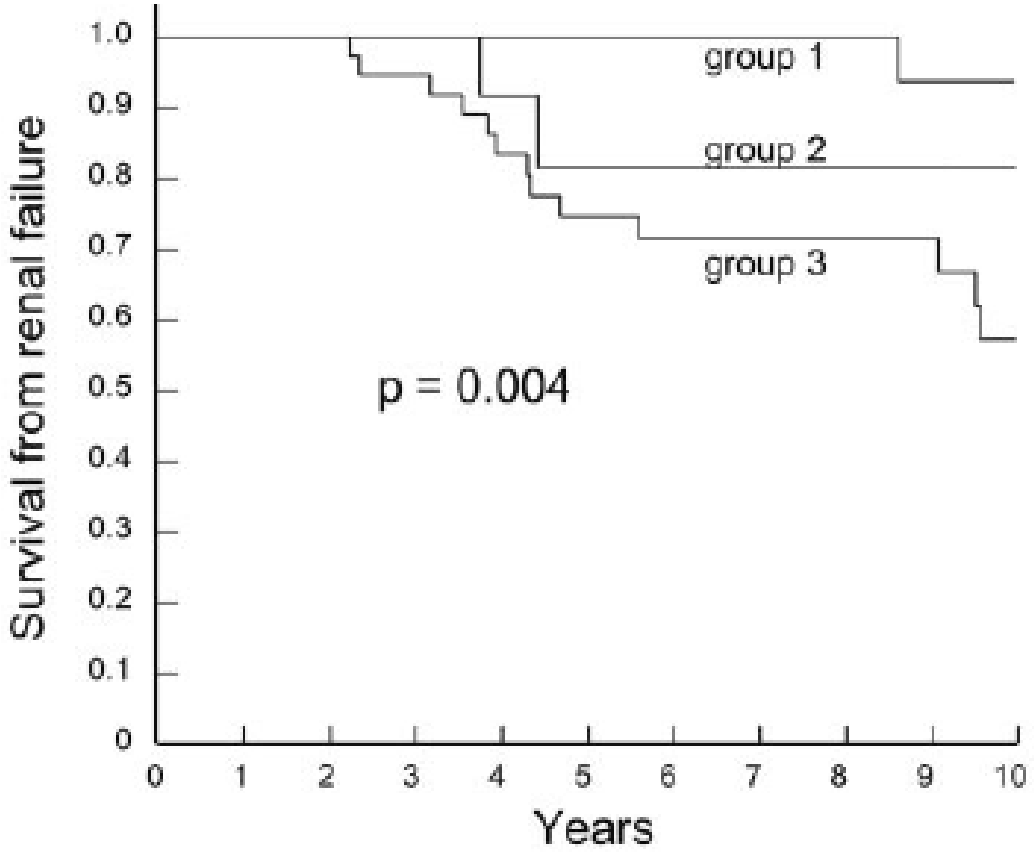
J Am Soc Nephrol 18: 3177–3183, 2007.



<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

542 patients with IgAN from Toronto Glomerulonephritis Registry

Renal survival of patients with IgAN by category of TIME AVERAGE PROTEINURIA.



Group 1	37	27	11
Group 2	16	8	2

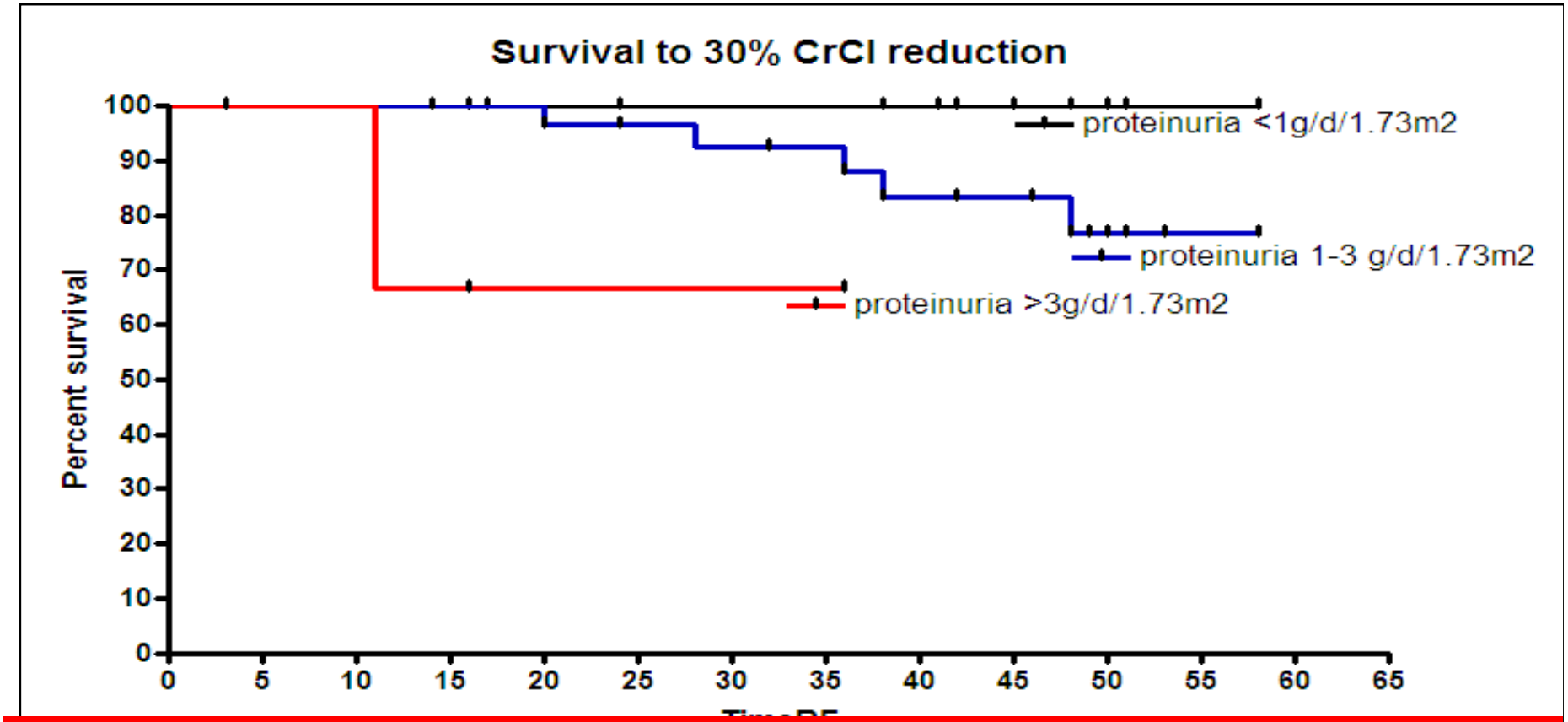
more than baseline proteinuria at presentation, the modifications of proteinuria levels from baseline (decrease, G1 or increase, G2 or G3) are relevant.

baseline. $P = 0.004$ by trend test.

IgACE: A Placebo-Controlled, Randomized Trial of Angiotensin-Converting Enzyme Inhibitors in Children and Young People with IgA Nephropathy and Moderate Proteinuria

Rosanna Coppo,* Licia Peruzzi,* Alessandro Amore,* Antonio Piccoli,† Pierre Cochat,‡ Rosario Stone,§ Martin Kirschstein,‖ and Tommy Linné;¶ on behalf of the EC Biomed Concerted Action Project BMH4-97-2487(DG 12-SSMI) and IgACE European Collaborative Group

J Am Soc Nephrol 18: 1880–1888, 2007.



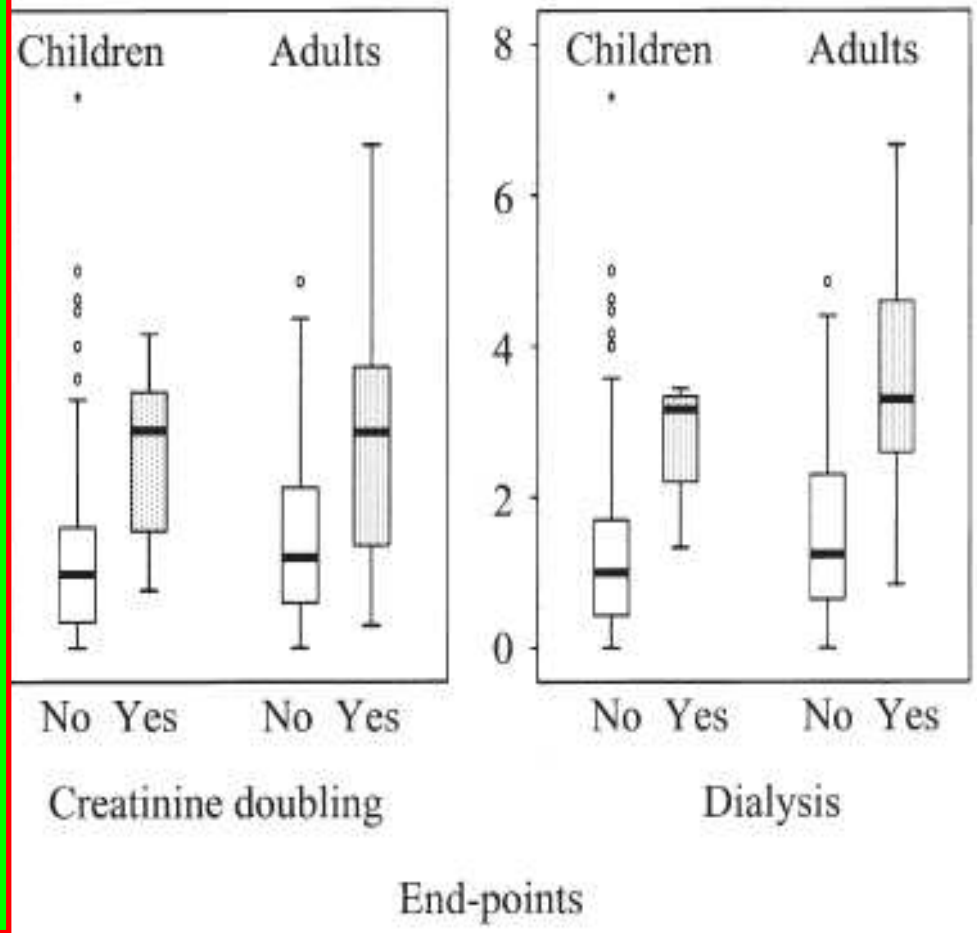
Survival to the end point 30% loss of CrCl by category of time-average proteinuria during follow-up (Peruzzi L et al ERA-EDTA 2008)

Predictors of Outcome in Henoch-Schönlein Nephritis in Children and Adults

Rosanna Coppo, MD, Simeone Andrulli, MD, Alessandro Amore, MD, Bruno Gianoglio, MD, Giovanni Conti, MD, Licia Peruzzi, MD, Francesco Locatelli, MD, and Leonardo Cagnoli, MD

American Journal of Kidney Diseases, Vol 47, No 6 (June), 2006: pp 993-1003

mean proteinuria over follow-upn (g/day)



219 patients

for each g/day

of proteinuria

over follow-up

relative risk for cr doubling

or for dialysis

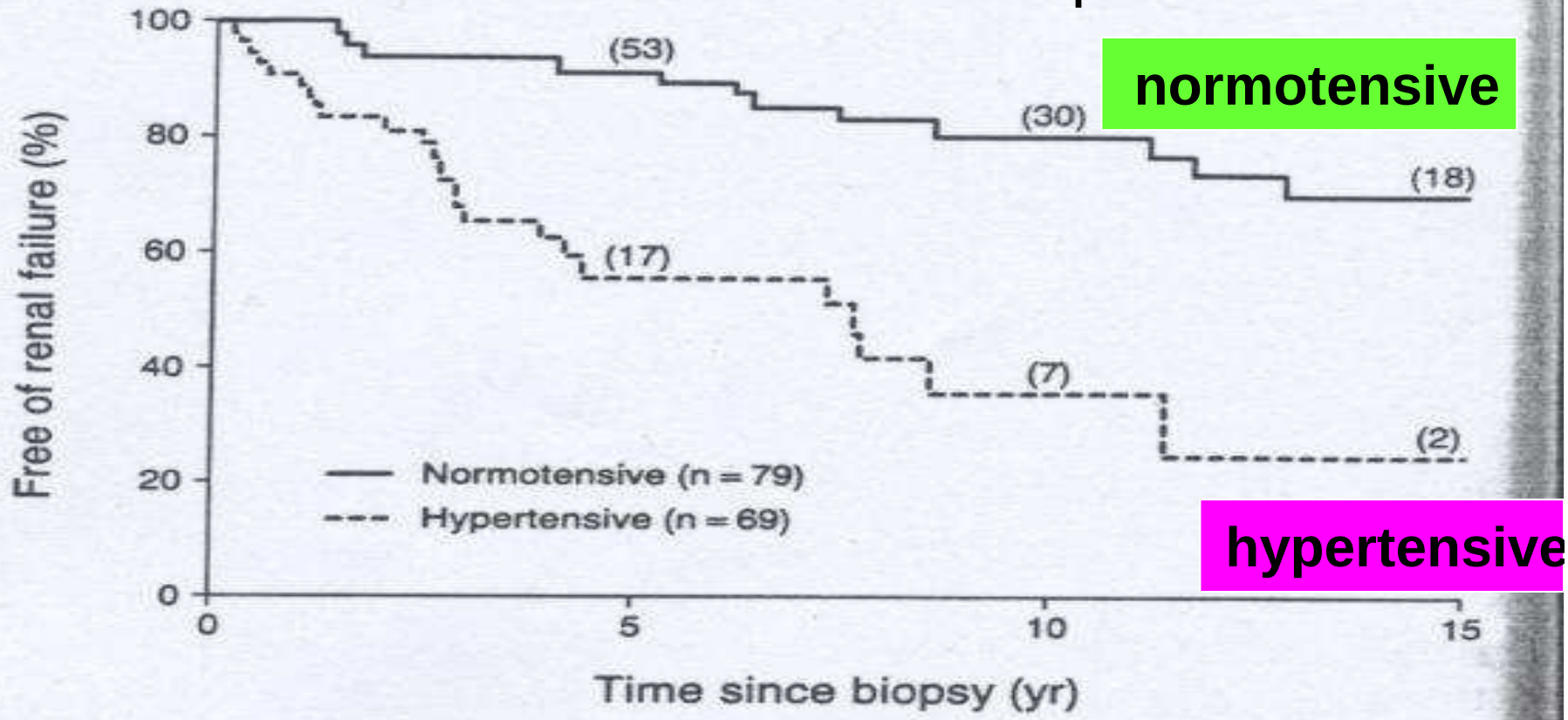
RR 1.44 p 0.04

(95% CI 1.01-2.06)

hypertension at renal biopsy

Survival of IgAN patients hypertensive and normotensive at renal biopsy

Radford MG J Am Soc Nephrol 1997



normotensive

hypertensive

Figure 1. Hypertension present at the time of renal biopsy was associated with decreased survival free of renal failure ($P < 0.001$; $N = 148$ patients). Numbers in parentheses indicate the number of patients at risk at 5, 10, and 15 yr.

Cases of IgAN with

- Proteinuria of various levels
- **Associated hypertension**
- Lack of expected results at the first treatment
- Progressive features

Hypertension and proteinuria: Risk factors in IgAN

(Bartosik and Cattran 2001)

298 patients, followed for 6 years

At multivariate analysis

2 independent factors were found:

Mean artherial blood pressure (MAP) and proteinuria during 1 year of follow-up

proteinuria < 1 g/day: PB < 135/85 mmHg (MAP 99 mmHg)
proteinuria >1 g/day : BP < 130/70 mmHg (MAP 92 mmHg)

IgAN with severe proteinuria

(if not treated the loss of GFR is 4-6 ml/min/year)

Author	Regimen	Patients (F-up)	Results (balanced difference of means)
Kobayashi (1996) UP >1 <2 g/day	Prednisone 40 mg/day x4 months + 18 months tapered doses	46 (120 m)	Decrease in UP (-0.50 g/day) Difference RR% ESRF - 46%
Pozzi (1999)	MP 3 pulses i.v every 2 months + P 0.5 mg/Kg/alt d. for 6 months	86 (60 months)	Decrease in UP (-0.70 g/day) Difference RR% ESRF - 7 %
Pozzi (2004)	Same as above	86 (120 m.)	Decrease in UP (-0.90 g/day) Difference RR% ESRF - 10 %

(EBM grade A)

IgAN with non nephrotic proteinuria >1 <3.5 g/day

Outcome ESRF at 10 years	steroids	controls
Kobayashi (1996)	20%	66%
Pozzi (2004)	2%	12%

significant steroids benefit

why the doubts on the efficacy of steroids in treating IgAN?

Author	Regimen	Patients (F-up)	Result (balanced difference of means)
Katafuchi (2003) (variabile UP, CKD1)	P 20-5 mg/Kg/day for 24 months + Dipyridamole vs Dipyridamole alone	103 (60 mo.)	Minimal UP decrease (-0.08g/day) No effect on GFR
2 studies have 3-12 months Fup			
Welch (1992)	P 2 mg/Kg for 2 w + 3months a.d.	20 (3 mo.)	Mild UP reduction (-0.50g/day)
Julian (1993)	60 mg/a.d. for 3 months	35 (12 mo.)	Difference in RR% ESRF (-7 %)

RENAL FUNCTION

IgAN with PROTEINURIA

Primary outcome

protection against GFR decline

THE EFFECT OF STEROIDS

IS DOSE AND TIME DEPENDENT

10 g in 6 months (Pozzi)
6 g in 2 years (Kobayashi)

→ **Maximal reno-protective effect**

Cochrane Database Syst Rev 2003: CD 003965

immunosuppressive agents for treating IgAN

(Samulels, Strippoli, Craig, Schena, Molony, 2004)

6 RCT on 341 cases of IgAN :

Steroids versus Placebo

- **Renoprotective effect** **RR 0.44 (IC 0.25-0.80)**
- **Decrease in proteinuria** **- 0.49 g/day (-0.25-0.72)** **(balanced difference of means)**

at meta-analysis

significany benefit of steroids in IgAN

NDT Advance Access published July 30, 2008

Nephrol Dial Transplant (2008) 1–6
doi: 10.1093/ndt/gfn394

Original Article

The improvement of renal survival with steroid pulse therapy in IgA nephropathy

Ritsuko Katafuchi[1], Toshiharu Ninomiya[2], Tohru Mizumasa[1], Kiyoshi Ikeda[1], Harumitsu Kumagai[1], Masaharu Nagata[2] and Hideki Hirakata[1]

702 patients with IgAN
Follow-up median: 62 months.

1) **Oral P: 60 mg for 4 weeks, tapered within 1 year or 20-30 mg for 4 weeks tapered within 2 years**
2) **MP pulses: 3 times 1g/day pulses, followed by 30 mg tapered within 2 years.**
3) **No steroid or antiplatelets**

Table 3. Crude or multivariate-adjusted hazard ratios for the development of end-stage renal failure

		Univariate analysis		Multivariate analysis (backward method)	
Risk factor	Scale	HR	95% CI	HR	95% CI
Age (years)	(every 10 years)	1.43	(1.23–1.66)**	1.03	(0.81–1.31)
Women	(versus men)	0.52	(0.34–0.80)**	1.29	(0.67–2.47)
UP-UCR	(every 1)	1.29	(1.22–1.35)**	1.16	(1.02–1.31)*
Serum creatinine	(every 1 mg/dl)	3.91	(3.26–4.69)**	3.95	(2.50–6.25)**
SBP	(every 10 mmHg)	1.34	(1.21–1.48)**	1.03	(0.87–1.20)
Serum albumin	(every 1 g/dl)	0.27	(0.19–0.37)**	0.49	(0.29–0.84)**
Serum total cholesterol	(every 10 mg/dl)	1.01	(1.04–1.13)**	–	–
Serum triglycerides	(every 10 mg/dl)	1.00	(1.03–1.06)**	1.03	(1.00–1.06)*
Serum uric acid	(every 1 mg/dl)	1.57	(1.40–1.75)**	1.3	(1.04–1.63)*
Histological grade					
Grade I+II (glomerular score 1–4)		1 (reference)		1 (reference)	
Grade III (glomerular score 5 or 6)		3.58	(1.40–9.14)**	3.56	(1.11–11.39)*
Grade IV (glomerular score 7 or 8)		16.5	(7.04–38.79)**	8.64	(2.66–28.05)**
Grade V (glomerular score ≥9)		73.9	(29.07–187.78)**	5.74	(1.31–25.08)*
Steroid therapy					
No steroid		1 (reference)		1 (reference)	
Oral steroid		0.88	(0.54–1.46)	0.61	(0.30–1.22)
Pulse steroid		2.6	(1.18–5.71)*	0.14	(0.05–0.44)**
Use of ACE-I or ARB	(versus no use)	1.09	(0.66–1.81)	0.39	(0.21–0.71)**
Tonsillectomy	(versus no tonsillectomy)	0.86	(0.27–2.74)		–

UP-UCR, urinary protein-creatinine ratio; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; SBP, systolic blood

Pulse therapy significantly improved survival of IgAN

Proteinuria target

- < 1g/day
- <0.5 g/day
- < 0.03 g/day

IgAN with proteinuria < 1 g/day

400 cases (Usui 2001)

20% serum Cr > 1.5 mg/dl

5% ended in dialysis

IgAN
with mild proteinuria
show signs of progression
at long follow-up

IgAN with proteinuria < 0.4 g/day

72 cases at diagnosis (Szeto 2001)

33% developed proteinuria >1 g/day
26% developed hypertension
7% had a decrease in GFR <70 ml/min

ACE-I Treatment of IgAN: RCT

Praga M, et al JASN 2003; 14. 1578—83

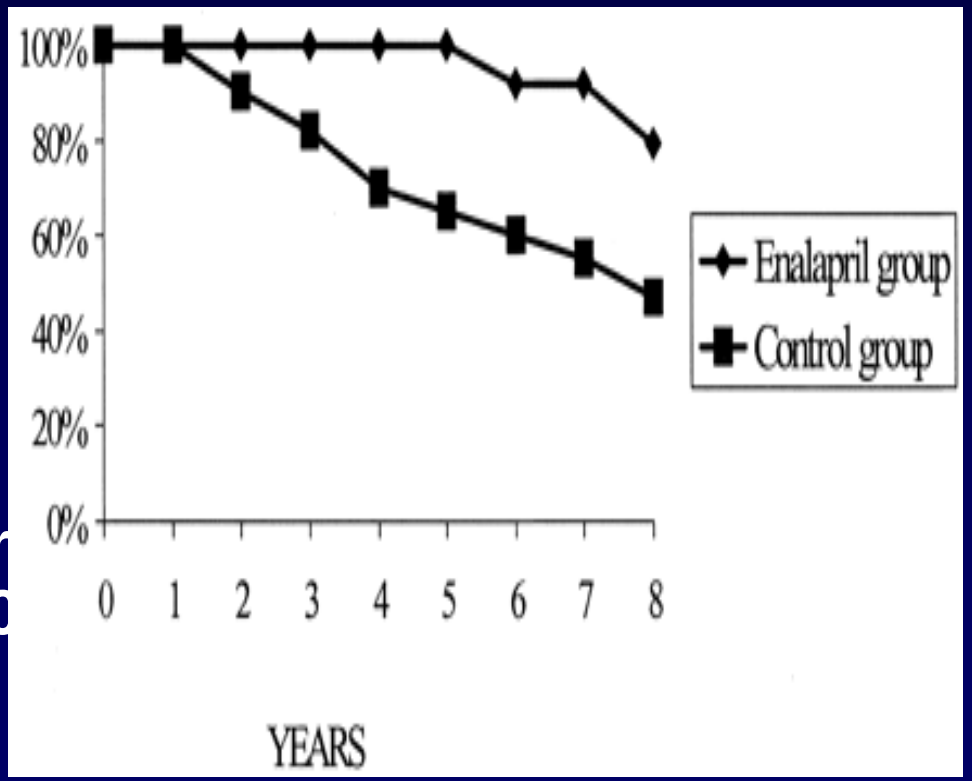
44 patients with IgAN (29± 12 y.o.)

Proteinuria >0.5- 5.3 g/day

Cr< 1.5 mg/dl.

Enalapril 5 mg- 40 mg

Titled on BP



3/23 treated and 12/21 contr
reached the end-point of 50
increase in Cr

at **4 years: p<0.05**

IgACE:A placebo-controlled, randomized trial of ACE-I in moderately proteinuric IgAN in the young

JASN 2007; 18:1880-1888

R Coppo, L Peruzzi, A Amore, A Piccoli, P Cochat, R Stone, M Kirschstein, T Linné

on behalf the EC Biomed Concerted Acti

Project BMH4-97-2487(DG 12-SSMI)

and IgACE European Collaborative Grou

Hong Kong Study Using Valsartan in IgA Nephropathy (HKVIN): A Double-Blind, Randomized, Placebo-Controlled Study

Philip Kam-Tao Li, MD, FRCP, Chi Bon Leung, FRCP, Kai Ming Chow, MRCP, Yuk Lun Cheng, MRCP, Samuel Ka-Shun Fung, FRCP, Siu Ka Mak, FRCP, Anthony Wing-Chung Tang, MRCP, Teresa Yuk-Hwa Wong, MRCP, Chun Yu Yung, MRCP, Jonathan Chee-Unn Yung, MRCP, Alex Wai-Yin Yu, FRCP, and Cheuk Chun Szeto, MD, FRCP, for the HKVIN Study Group

109 patients with IgAN
-proteinuria > 1g/day
- CKD 2

-Valsartan 80 mg/day (titrated up to 160 mg/day) Vs placebo for 2 years

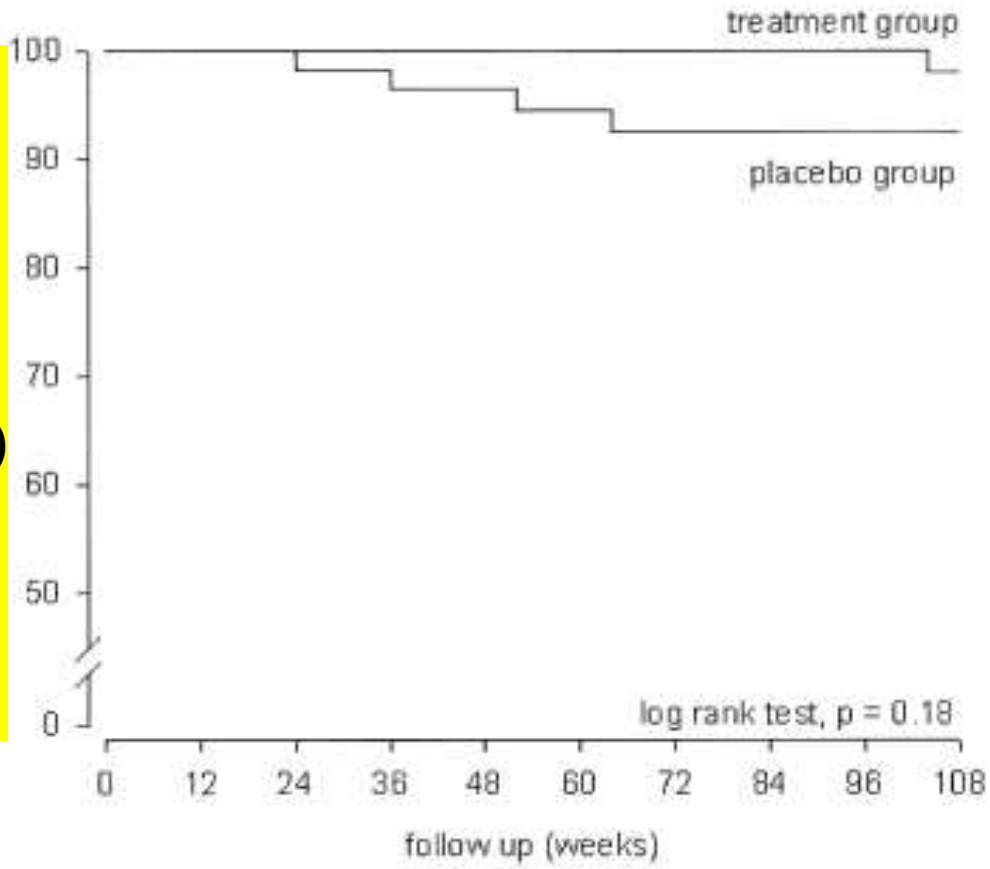


Fig 2. Kaplan-Meier plot of event-free survival.

Angiotensin antagonism therapy still debated points

The relative contribution of BP reduction and other in vivo additional effects (Casas J Lancet 2005)

ACE-I remains effective over years or there is an escape mechanism (Suissa S. Kidney Int 2006)

Any additional effect for anti-aldosterone drugs?

Aldo increases after long-term ACE-I

"aldosterone escape" (Fogo 2006)

Mildly proteinuric IgAN (Horita 2004)

UP < 0.35- 0.76 g/day; GFR >50 ml/min; BP normal

Combination therapy (Temocapril + Losartan) 31 cases / 6 months

Remission of proteinuria in

63% combination therapy vs 41% with ACE-I, p<0.04

vs 36% with ARB , p< 0.01

The same patients were given anti-aldosterone (Horita 2006)

43 cases of IgAN

Proteinuria 0.7- 0.3 g/day, CrCl > 50 ml/min

Anti aldosterone given for 12 months did not modify proteinuria.

Fish oil /Omega 3 Fatty Acids (3-PUFA)

EPA

DHA

Arachidonic acid

cyclooxygenase

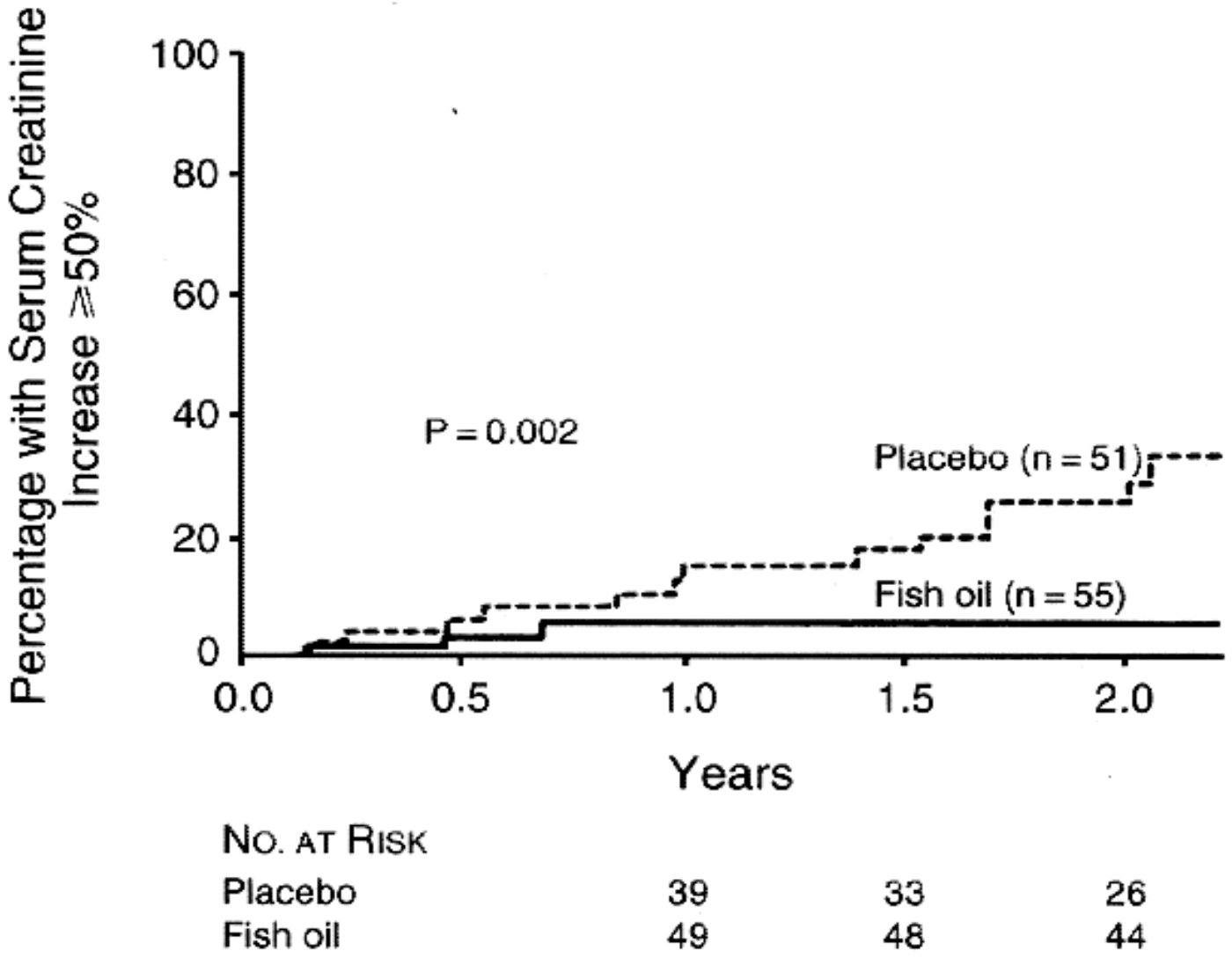
lipoxygenase

TxA3
PGI3

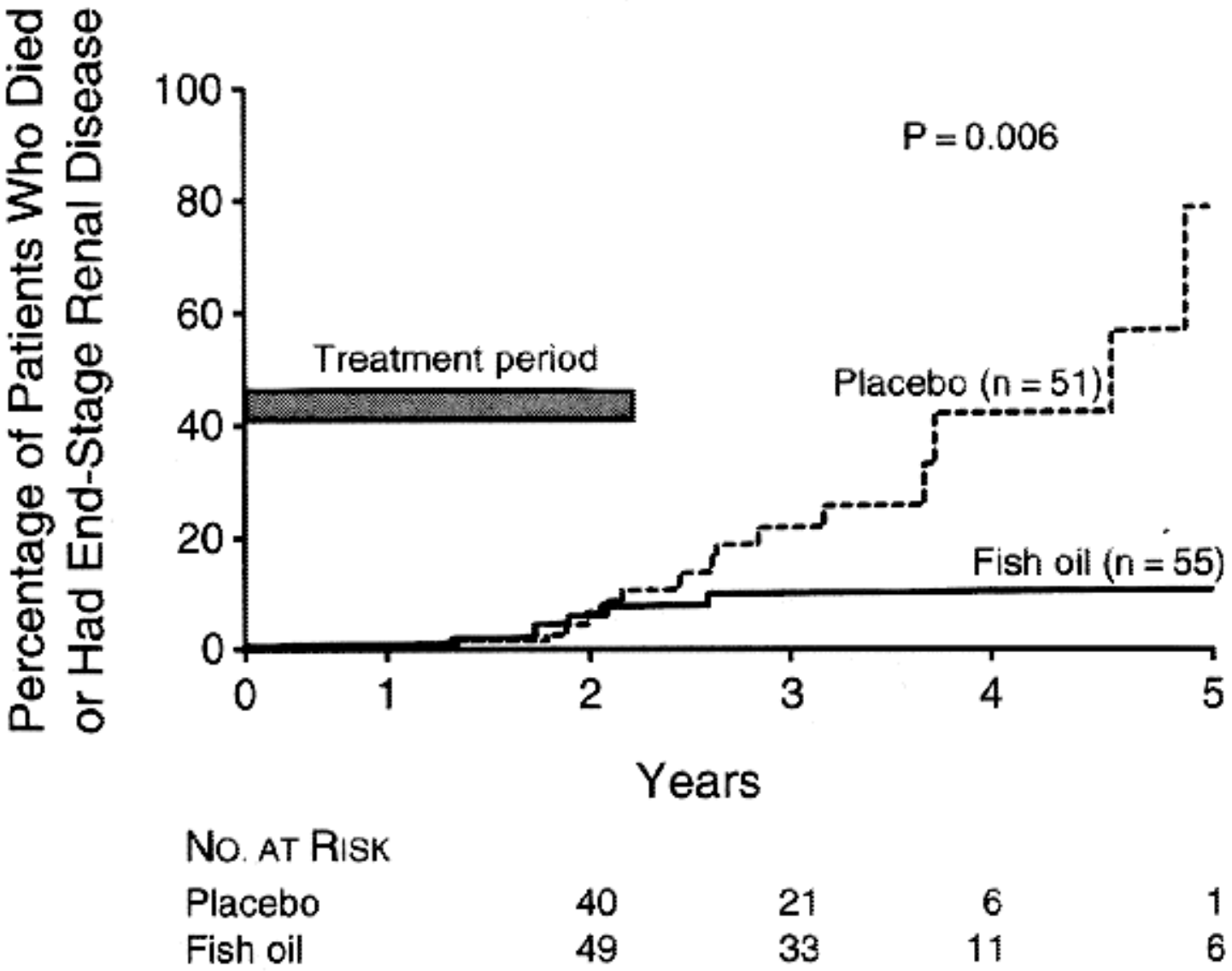
TxA2
PGI2

LTB4

LTB5

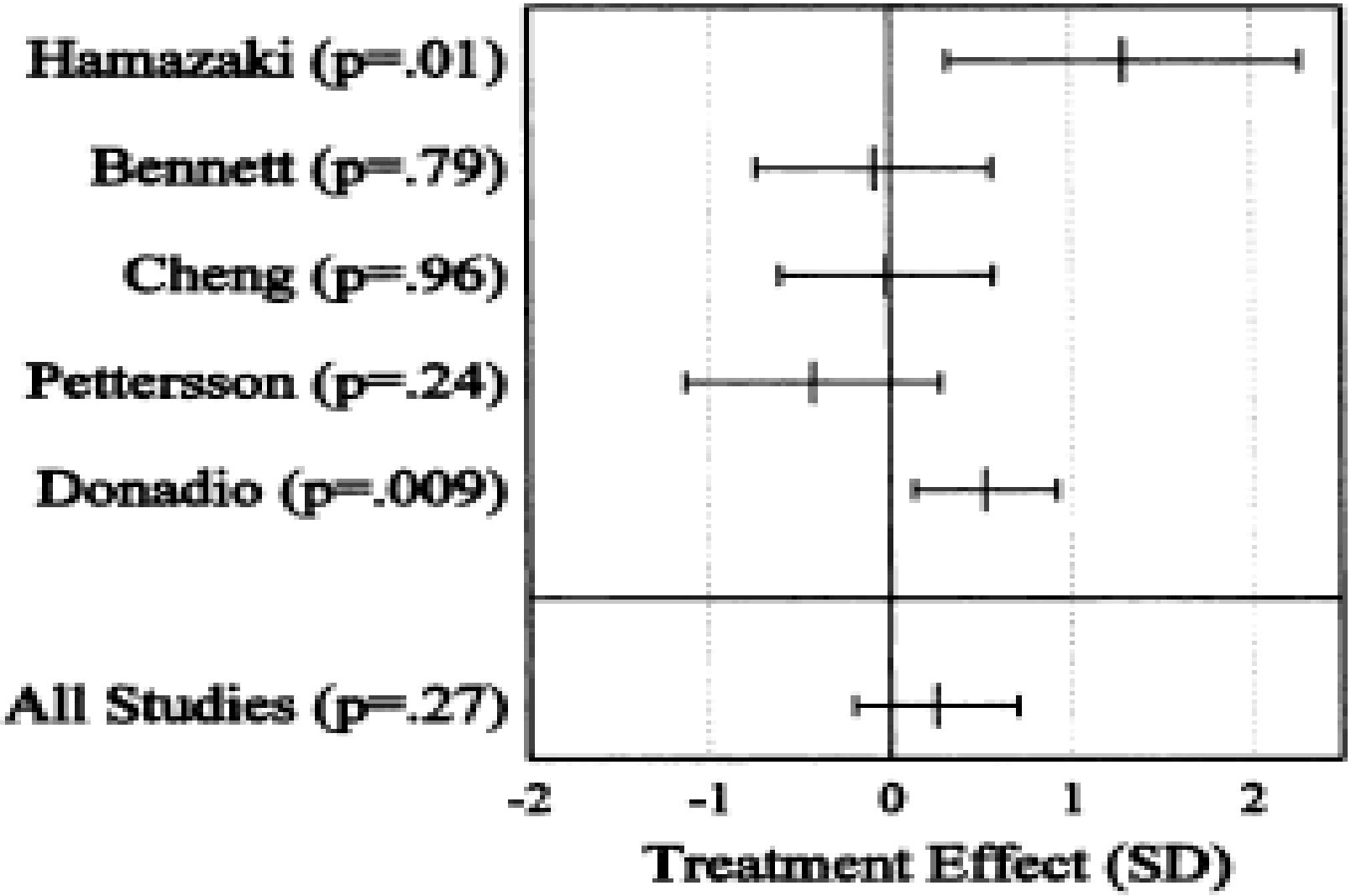


Donadio J, NEJM 1994



Donadio J, NEJM 1994

Outcome of studies treating IgAN with fish oil



Dillon JJ, JASN, 1997

Clinical Trial to Evaluate Omega-3 Fatty Acids and Alternate Day Prednisone in Patients with IgA Nephropathy: Report from the Southwest Pediatric Nephrology Study Group

Ronald J. Hogg,* Jeannette Lee,† Nancy Nardelli,‡ Bruce A. Julian,† Daniel Cattran,§ Bryson Waldo,† Robert Wyatt,‖ J. Charles Jennette,¶ Richard Sibley,** Keith Hyland,†† Lisa Fitzgibbons,‡ Gladys Hirschman,‡‡ James V. Donadio, Jr.,§§ and Bruce J. Holub‖‖

Clin J Am Soc Nephrol 1: 467–474, 2006.

Double-blind RCT

IgAN < 40 years old

CrCl> 50 ml/min, UP/Cr > 1 or >0.5 with glomerulosclerosis or important mesangial proliferation)

1) Prednisone (33 patients)

60 mg/m2/day 3 months ; 40 mg/m2/a.day for 9 months, 30 mg/m2/a.day for 12 months

2) Omega3FA 4g/day for 2 years (32 cases)

3) Placebo (31 cases)

End point: eGFR < 60 % baseline value

Results

No difference among treatments groups and placebo.
(end-points: 2 Prednisone; 8 Fish-oil, 4 Placebo)

The probability of reaching the end-point
(60% drop in eGFR) was
9% in P, 18% in omega 3, versus placebo 8.7 %

Even considering only the cases with UP/Cr > 1
the probability was
5% in P, 23% in omega 3, versus placebo 16 %

Cases of IgAN with

- **Proteinuria of variable degree**
- **Associated Hypertension**
- **Lack of expected results at the first treatment**
- **Progressive features**

Mycophenolate in IgAN

No clear conclusions

Author	Regimen	Patients (F-up)	Results
Maes (2004) (CrCl 20-70 and/or UP >1 g/day and/or HT	MMF 2g/d x36 months+ ACE-i in 21 cases vs ACE-I	34 (36 months)	UP increase GFR decrease Difference in RR% ESRF -46%
Frisch (2005) UO>1 g/day after ACE-i	MMF1 g/day vs placebo 1 year	32 (16 mo)	UP no effect RR % -3%
Tang (2005) >1 g/day after ACE-i	MMF1.5-2 g/day x 24 weeks + ACE-i vs ACE-I	40 (18 mo)	UP – 1.2 g/day: p< 0.02

Cases of IgAN with

- **Proteinuria of variable degree**
- **Associated Hypertension**
- **Lack of expected results at the first treatment**
- **Progressive features**

Progressive IgAN

Author	Regimen	Patients (F-up)	Result
Ballardie (2002) (Crs >1.5 mg/dl)	P 40-10 mg for 2 years then 10 mg/day 4 years + CYP 2 mg/Kg 2 months AZA1.5 mg/Kg for 2 years	38 (24-72 months)	Significant reduction of GFR loss at 3 years
Pozzi (2007 abst) (Cr>1 <2 and Cr >2	3MP pulses, 1g, on alt months 0.5 mg/kg P p.o. 6 months + AZA 1.5 mg/Kg/day for 6 months	251 (36 mo)	98% vs 84% in Crs<2 mg/dl 53% vs 53% in Crs > 2 mg/dl AZA does not significantly improve the nephro-protection (increase in adverse side effects)

Cochrane Database Syst Rev 2003: CD 003965

immunosuppressive agents for treating IgAN

(Samulels, Strippoli, Craig, Schena, Molony, 2004)

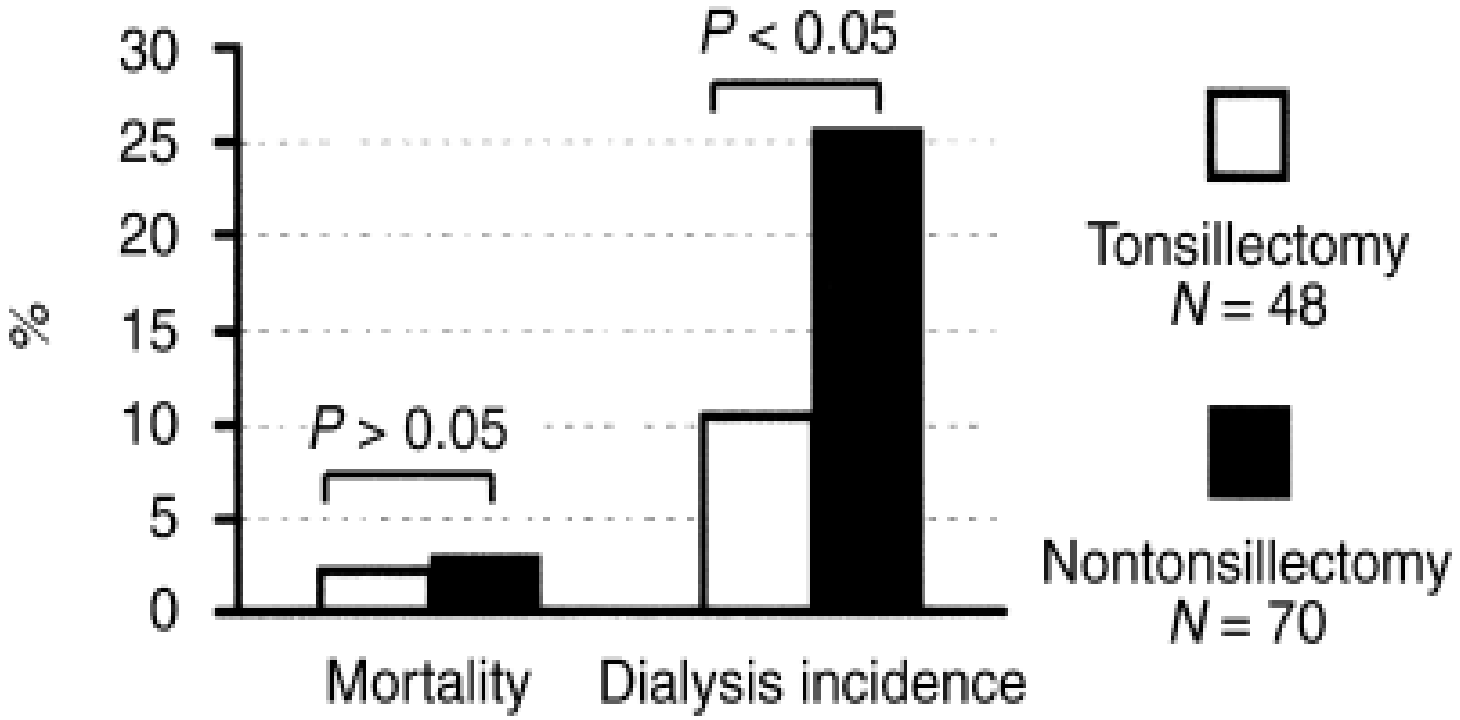
13 RCT on 623 cases of IgAN

7 Steroids in monotherapy

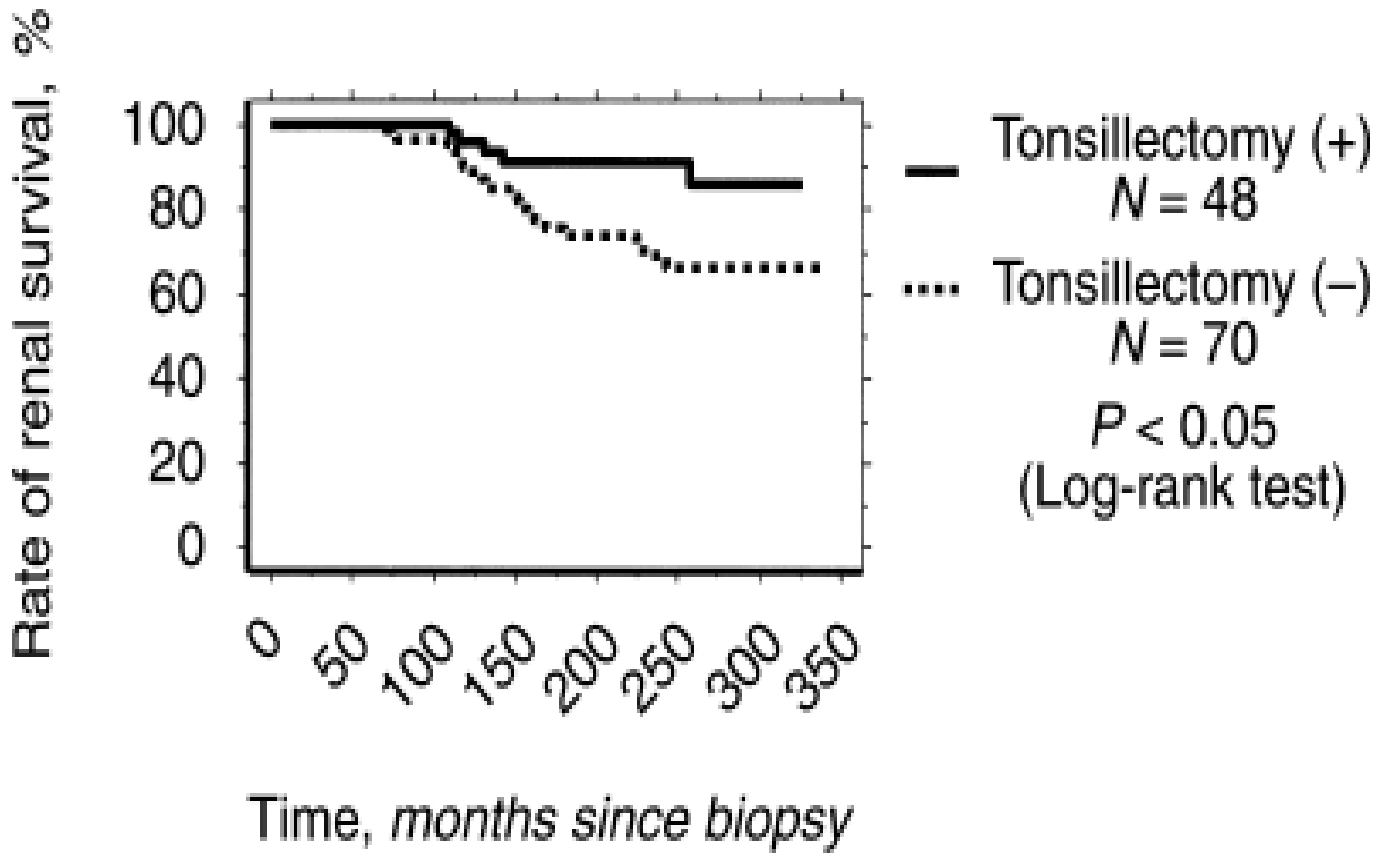
3 alkyating agents/ cyclosporin

3 steroids + alkylating agents/ cyclosporin UP – 0.94 g/24

No significant benetif of immuno suppressive drugs (alkylating agents and cyclosporin) in IgAN



Xie Y, Kidney Int 2003 63: 1861-1867



Xie Y, Kidney Int 2003 63: 1861-1867

CJASN ePress. Published on May 28, 2008 as doi: 10.2215/CJN.00310108

Effect of Tonsillectomy Plus Steroid Pulse Therapy on Clinical Remission of IgA Nephropathy: A Controlled Study

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Prospective RCT:
55 patients followed for 54 ± 21 months.
37 had tonsillectomy.
Both groups had
MP pulses 0.5 g/day for 3 days,
then oral P 0.5 mg/Kg/day for 12-18 months

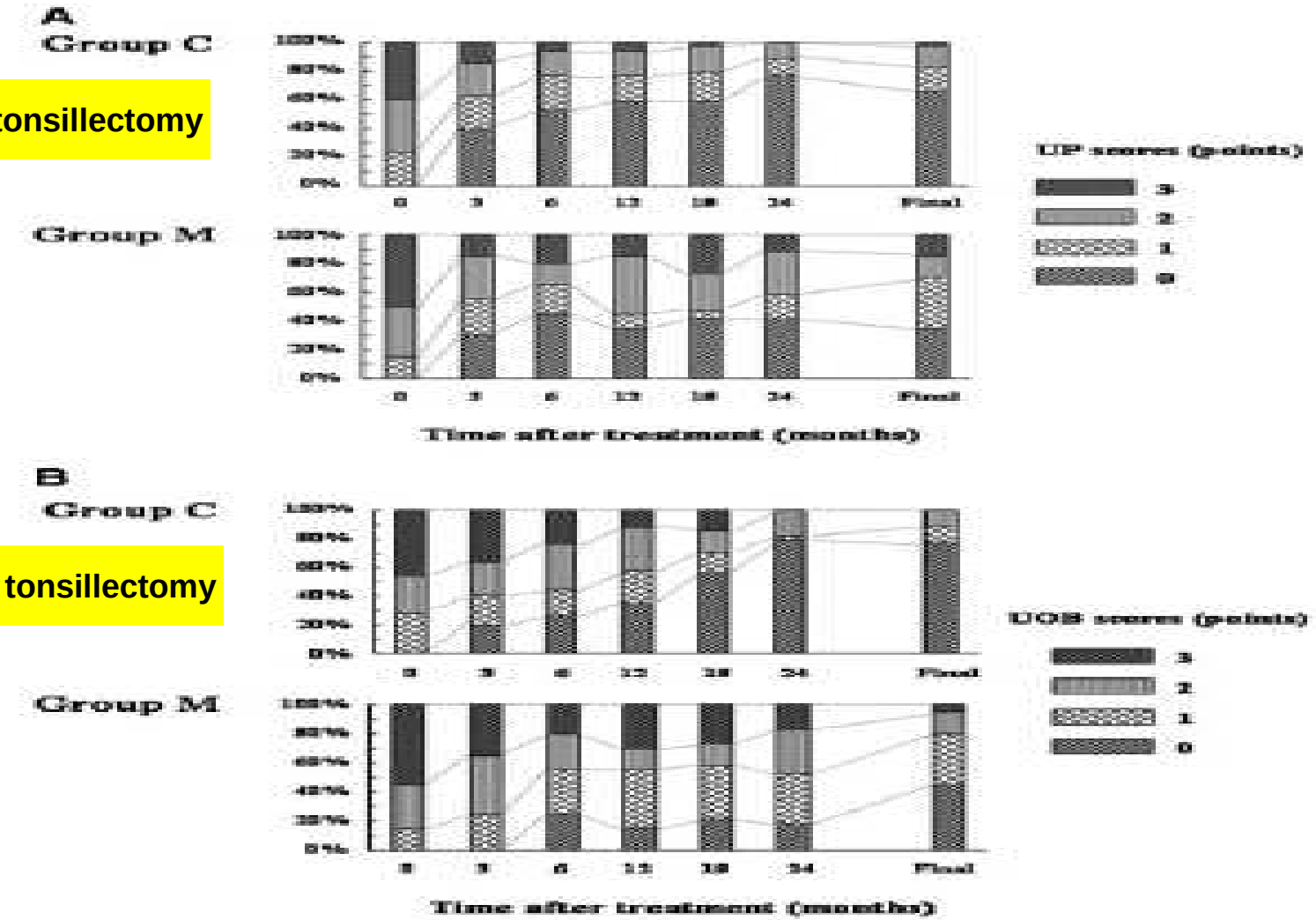

Figure 1. Change in urinary findings over time after treatment. (A) Urinary protein (UP) scores. (B) Urinary occult blood (UOB) scores. Group C, combined therapy (steroid pulse with tonsillectomy); group M, monotherapy (steroid pulse).

Table 2. Comparison of clinical findings at 24 mo after biopsy and at final observation

Parameter	24 Mo after Biopsy			Final Observation		
	tonsillectomy (*n* = 34)	Group M (*n* = 17)	*p*[a]	tonsillectomy	Group M (*n* = 20)	*p*[a]
Observation period (mo; mean ± SD)				49.3 ± 15.6	62.4 ± 27.0	0.060
SBP (mmHg; mean ± SD)	117.5 ± 12.8	120.9 ± 10.0	0.364	116.2 ± 13.7	116.4 ± 18.0	0.969
DBP (mmHg; mean ± SD)	73.0 ± 9.1	75.2 ± 8.3	0.438	70.5 ± 13.5	71.8 ± 12.9	0.721
Patients with BP >140/90 mmHg (*n* [%])	2 (5.9)	0 (0.0)	0.477	2 (5.7)	1 (5.0)	0.703
Serum creatinine (mg/dl; mean ± SD)	0.86 ± 0.22	1.01 ± 0.91	0.517	0.84 ± 0.28	1.24 ± 1.82	0.344
Patients with 100% increased sCr (*n* [%])	0 (0.0)	1 (6.7)	0.306	0 (0.0)	1 (5.0)	0.364
Disappearance of UP (*n* [%])	26 (76.5)	7 (41.2)	0.013[b]	23 (65.7)	7 (35.0)	0.028[b]
Disappearance of UOB (*n* [%])	27 (79.4)	3 (17.6)	<0.001[b]	27 (77.1)	9 (45.0)	0.016[b]
Remission of urinary abnormalities (*n* [%])	21 (61.8)	3 (17.6)	<0.001[b]	19 (54.3)	5 (25.0)	0.033[b]

[a]Data compared using unpaired *t* test, χ^2 test, and Fisher exact test.
[b]Statistically significant.

Table 4. Univariate and multivariate analysis of factors that contribute to UP remission in 55 patients with IgAN[a]

Variable	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (per 10 yr of age)	0.82	(0.58 to 1.17)	0.278	0.71	(0.46 to 1.10)	0.135
Male (*versus* female)	0.69	(0.32 to 1.49)	0.348	0.93	(0.32 to 2.68)	0.885
Macroscopic hematuria (*versus* no macrohematuria)	0.84	(0.41 to 1.74)	0.637	0.60	(0.26 to 1.38)	0.229
SBP (per 10 mmHg)	0.78	(0.60 to 1.03)	0.076	0.97	(0.70 to 1.33)	0.835
Urinary protein (per 0.5 g/d)	0.72	(0.55 to 0.95)	0.018[b]	0.74	(0.54 to 1.02)	0.063
Serum creatinine (per 0.5 mg/dl)	0.61	(0.36 to 1.04)	0.071	0.84	(0.43 to 1.64)	0.607
Histologic severity (per grade)	0.46	(0.23 to 0.90)	0.023[b]	0.98	(0.39 to 2.45)	0.969
Combined therapy (*versus* monotherapy)	5.19	(2.01 to 13.40)	0.001[b]	6.20	(1.98 to 19.50)	0.002[b]
RAS-I (*versus* absence of RAS-I)	0.52	(0.25 to 1.07)	0.076	0.80	(0.37 to 1.73)	0.571

[a]CI, confidence interval; HR, hazard ratio; RAS-I, renin-angiotensin system inhibitors.
[b]Statistically significant.

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Cardiovascular, Pulmonary and Renal Pathology

Microbial IgA Protease Removes IgA Immune Complexes from Mouse Glomeruli *In Vivo*: Potential Therapy for IgA Nephropathy

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From the Departments of Pathology and Pharmacology,† Case Western Reserve University, Cleveland, Ohio; and the Department of Medicine,‡ Tufts-New England Medical Center, Boston, Massachusetts*

Bacterial IgA proteases have specificity for hinge region of IgA1
Recombinant Hemophilus influenzae protease.
IgA1/IgG complexes prepared in vitro and injected in mice (IgA mesangial deposits)

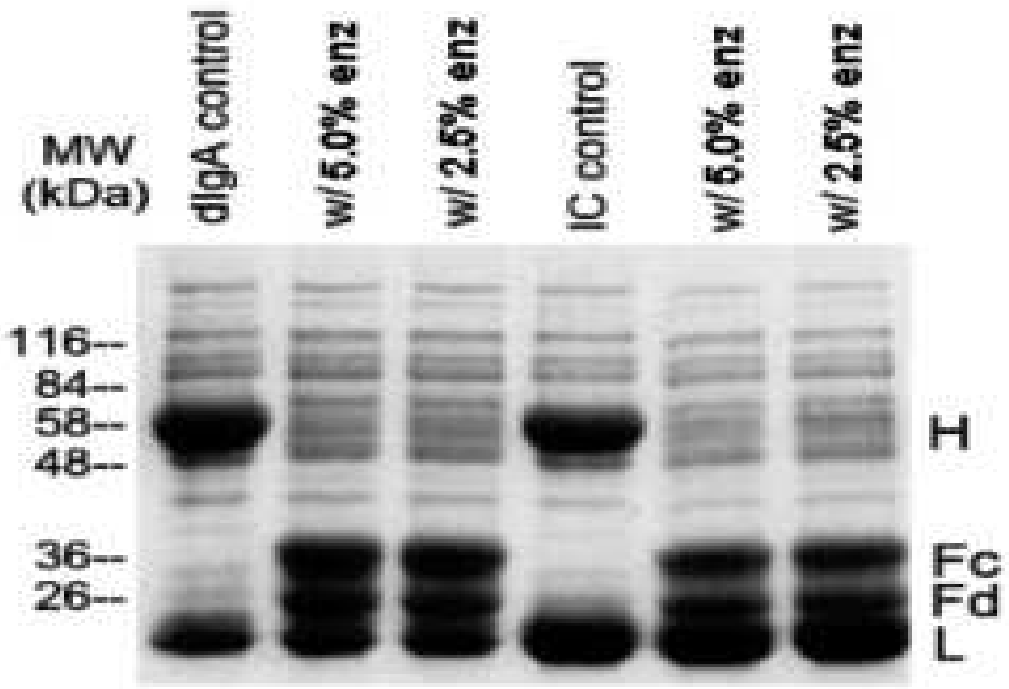

Figure 1. Cleavage of free and immune-complexed IgA by IgA protease *in vitro*. Human dIgA1 and IgA immune complexes (IC), the latter containing IgA1 antigen and goat $F(ab')_2$ anti-human $F(ab')_2$ antibody, were digested with two strengths of *H. influenzae* IgA protease (either 5% or 2.5% enzyme by weight of IgA), subjected under reducing conditions to SDS-PAGE, and stained with Coomassie Blue. H and L indicate intact H(α) and L polypeptide chains, and Fc and Fd indicate the H chain fragments after IgA protease cleavage at the IgA hinge. After 1 hour at 37°C at both enzyme/substrate weight ratios, the enzyme cleaved the IgA, whether free or complexed.

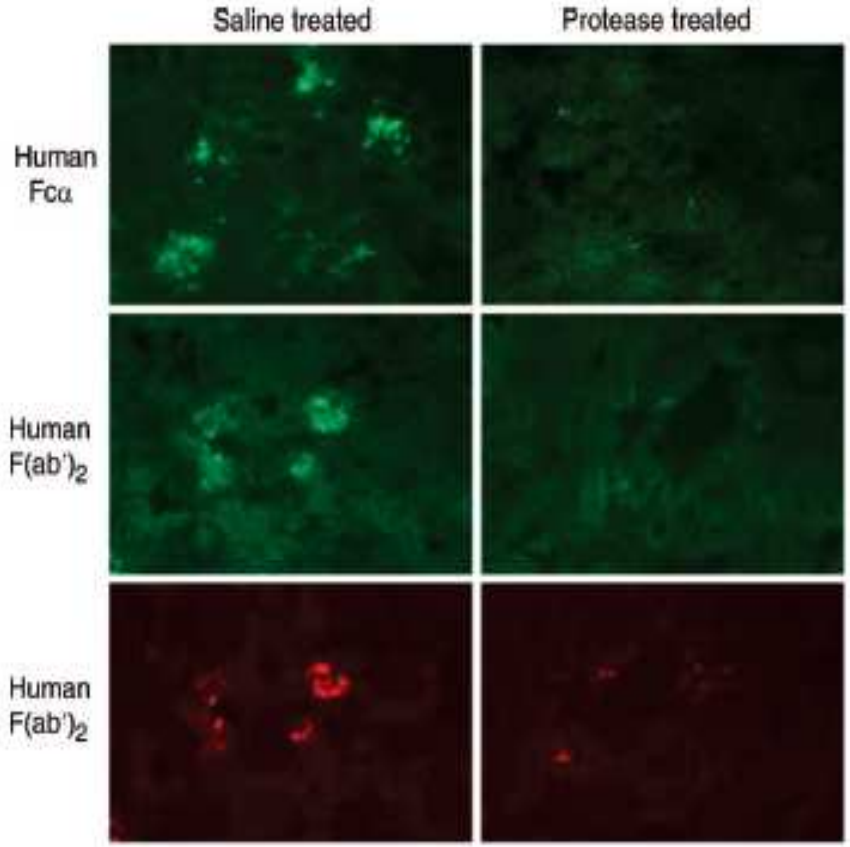

Figure 2. Immunofluorescence photomicrographs of kidney sections from mice injected i.v. 2 hours before sacrifice with immune complexes composed of human IgA1 and goat $F(ab')_2$ anti-human $F(ab')_2$ and 1 hour before sacrifice with IgA1 protease (right column) or saline (left column). The top and middle rows (fluorescein fluorescence) show the human IgA component of the complexes. The bottom row (rhodamine fluorescence) shows the goat immunoglobulin component. The IgA is detected with anti-human Fcα and anti-human $F(ab')_2$ in the top and middle rows, respectively. Note that the enzyme removed most of the deposited immune complexes, both the human IgA antigen and the goat antibody.

Table 2. Immunofluorescence Scores of Kidney Sections from Mice Injected with IgA Immune Complexes and 24 Hours Later with Enzyme (4 Mice) or Saline (4 Mice)

Human IgA		Goat $F(ab')_2$	
Enzyme	Saline	Enzyme	Saline
0	+	0	++
0	++	+	+++
0	+	+	++
0	++	0	+++

Immunofluorescence intensity is indicated on a scale of 0 to 4+.

Saline

IgA protease

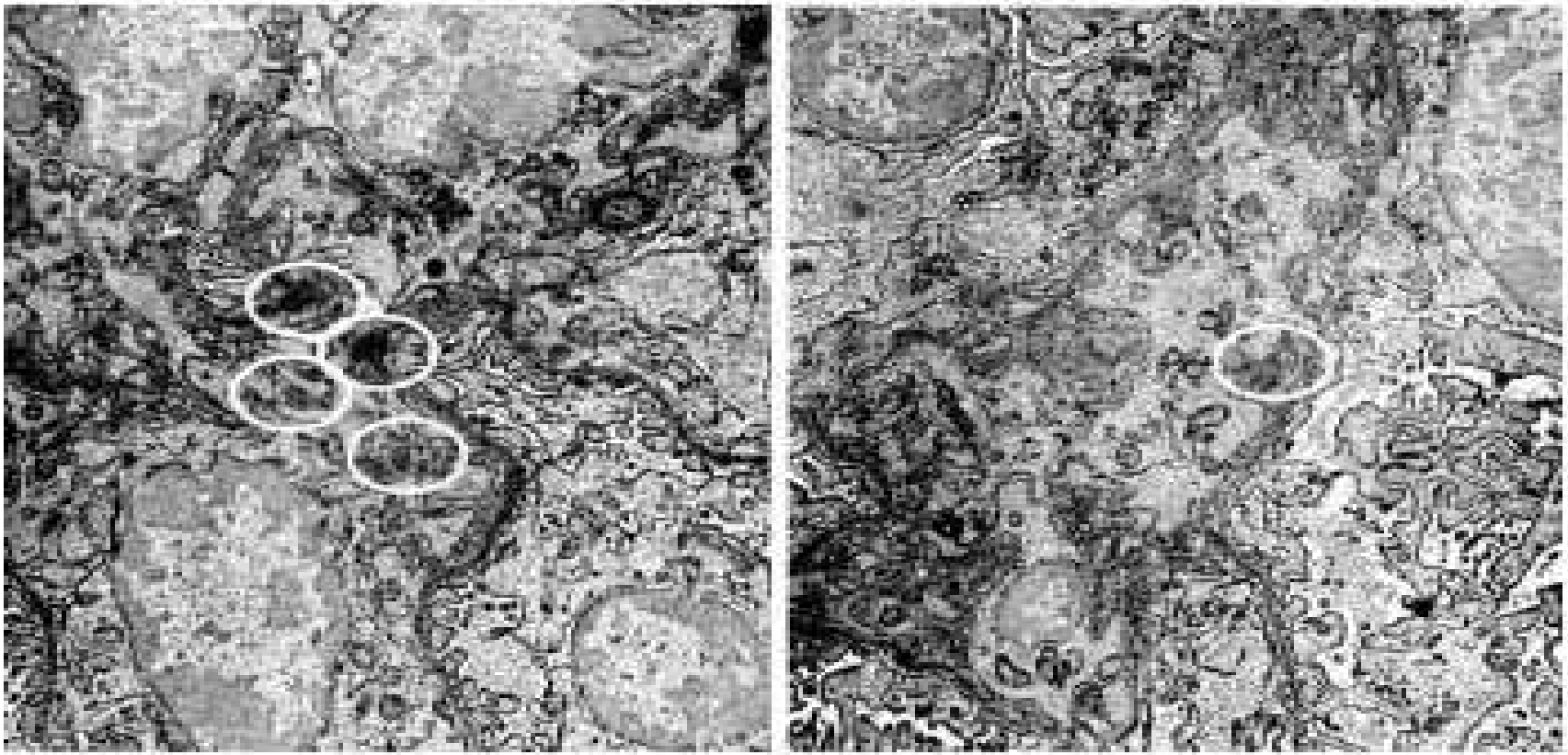

Figure 3. Electron micrographs of representative mesangial regions from mice injected i.v. with immune complexes (as detailed for Figure 2 and in Materials and Methods), followed by saline (left panel) or IgA1 protease (right panel). Amorphous electron-dense deposits (circled) are significantly less plentiful in mice given enzyme.

do you want to know

more about IgAN?

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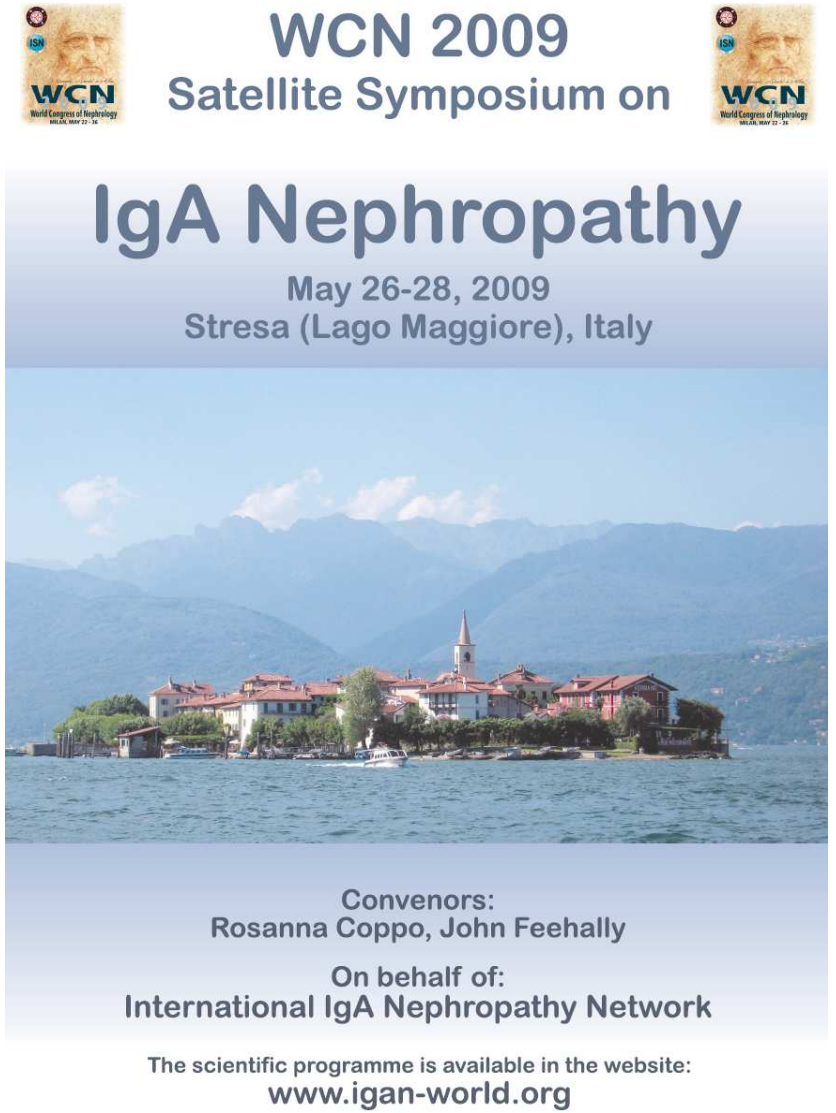



MICROFLOW
BIOLOGICAL SAFETY CABINET

IgACE: A Placebo-Controlled, Randomized Trial of Angiotensin-Converting Enzyme Inhibitors in Children and Young People with IgA Nephropathy and Moderate Proteinuria

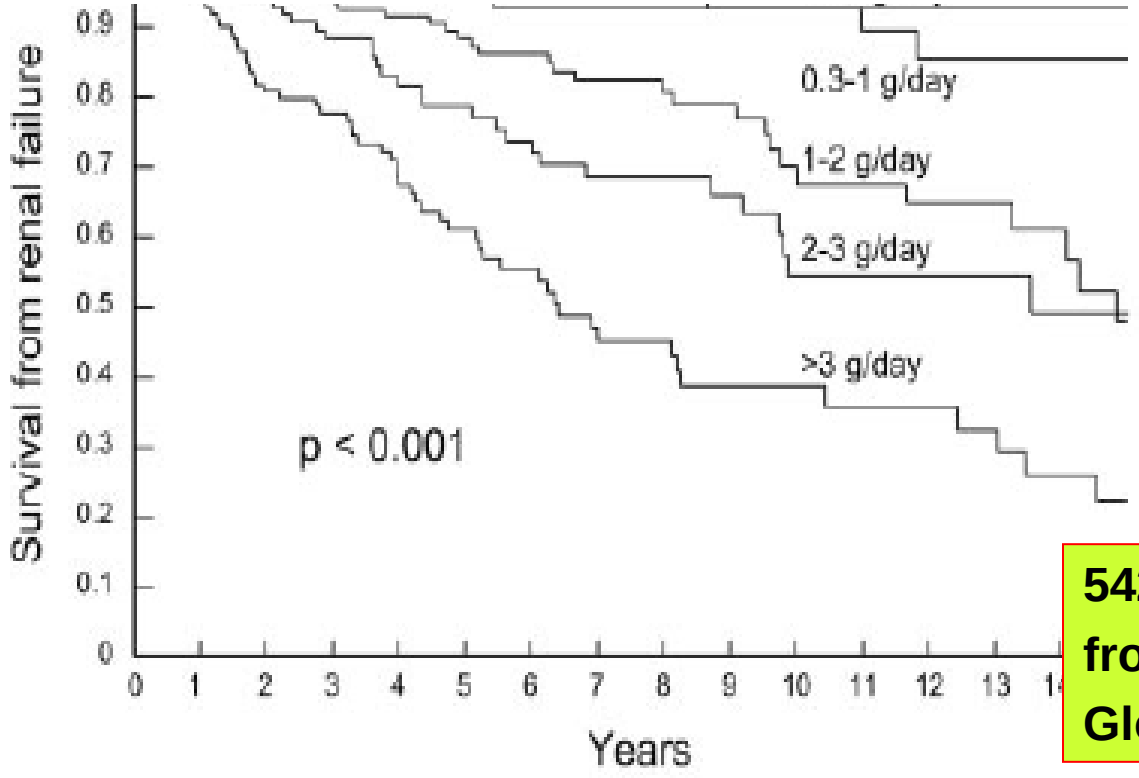
Rosanna Coppo,* Licia Peruzzi,* Alessandro Amore,* Antonio Piccoli,† Pierre Cochat,‡ Rosario Stone,§ Martin Kirschstein,‖ and Tommy Linné;¶ on behalf of the EC Biomed Concerted Action Project BMH4-97-2487(DG 12-SSMI) and IgACE European Collaborative Group

J Am Soc Nephrol 18: 1880–1888, 2007.

Remission of Proteinuria Improves Prognosis in IgA Nephropathy

Heather N. Reich,* Stéphan Troyanov,† James W. Scholey,* and Daniel C. Cattran,* for the Toronto Glomerulonephritis Registry

J Am Soc Nephrol 18: 3177–3183, 2007.



<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

542 patients with IgAN from Toronto Glomerulonephritis Registry

Renal survival of patients with IgAN by category of TIME AVERAGE PROTEINURIA.

Table 2. Factors at presentation and during follow-up influencing decline in renal function (slope in ml/min per 1.73 m^2/mo) by univariate and multivariate regression[a]

Parameter	Univariate		Multivariate	
	Mean/Standardized β	*P*	Mean/Standardized β	*P*
Presentation				
ln(24 h Upro)[b]	−0.145/−0.258	<0.01	–	NS
MAP	−0.005/−0.145	<0.01	–	NS
Follow-up				
ln(24 h Upro)[b]	−0.258/−0.403	<0.01	−0.302/−0.493	<0.01
MAP	−0.020/−0.337	<0.01	−0.013/−0.231	<0.01
BP med	−0.088/−0.105	0.02	–	NS
ACEi/ARB[c]	0.227/0.092	0.03	0.077/0.124	0.02

Upro, urine protein excretion; BP med, average number of BP medications during follow-up.

[b]Urine protein results were log transformed.

[c]ACEi/ARB e… …rtiles of medication exposure (see Concise Methods section).

TA: time average proteinuria.

Table 3. Outcome based on categorical grouping of TA 24-h urine protein excretion during follow-up[a]

Group (*n*)	TA-Proteinuria (g/24 h)	Slope (ml/min per 1.73 m^2/mo; Mean ± SD)	Renal Failure Risk (Hazard [95% CI])
1 (171)	0 to 1	−0.030 ± 0.46	Reference
2 (145)	1 to 2	−0.326 ± 0.53	3.48 (1.8 to 6.7)
3 (105)	2 to 3	−0.516 ± 0.66	5.17 (2.6 to 10.0)
4 (121)	>3	−0.719 ± 0.61	9.89 (5.3 to 18.4)

[a]CI, confidence interval.

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Rosanna Coppo,* Licia Peruzzi,* Alessandro Amore,* Antonio Piccoli,† Pierre Cochat,‡ Rosario Stone,§ Martin Kirschstein,‖ and Tommy Linné;¶ on behalf of the EC Biomed Concerted Action Project BMH4-97-2487(DG 12-SSMI) and IgACE European Collaborative Group

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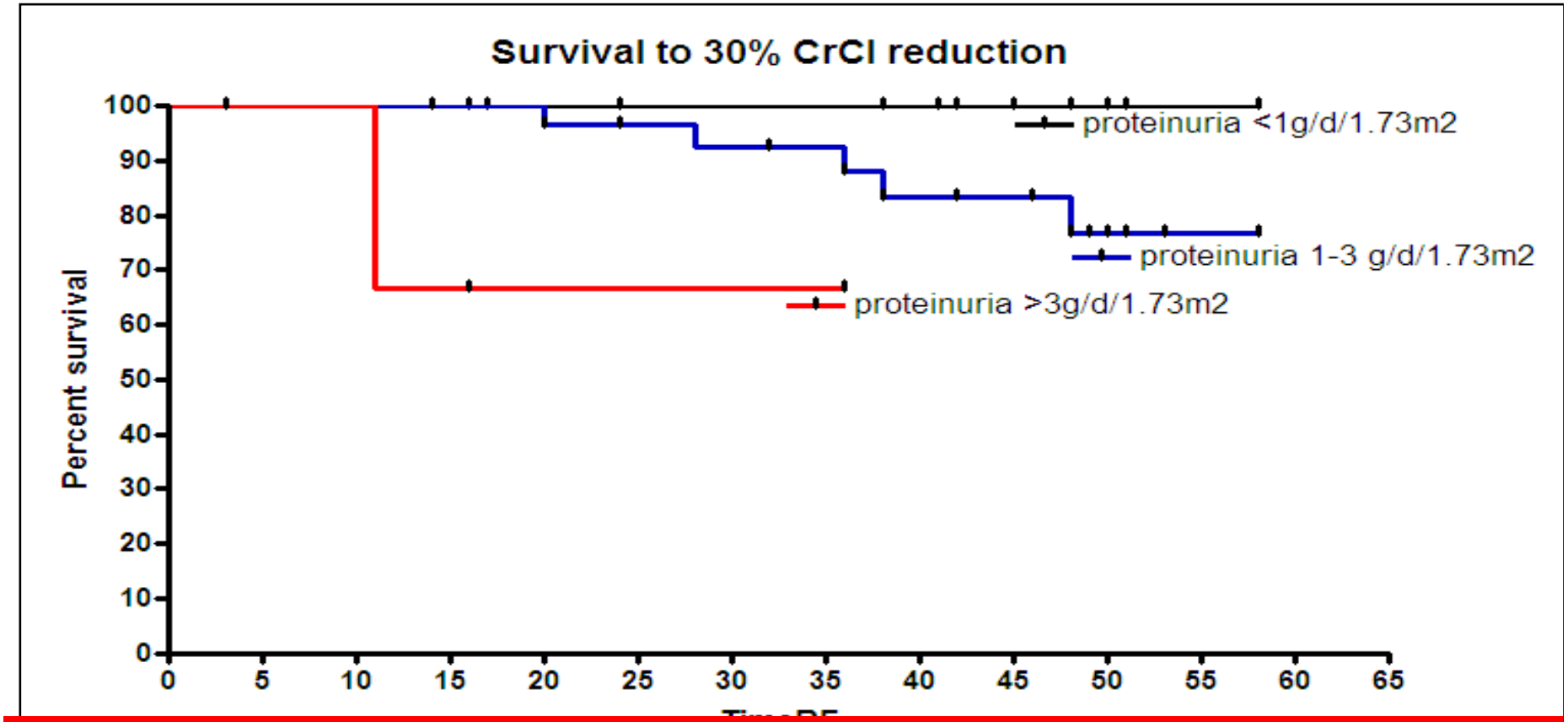

Survival to the end point 30% loss of CrCl by category of time-average proteinuria during follow-up (Peruzzi L et al ERA-EDTA 2008)

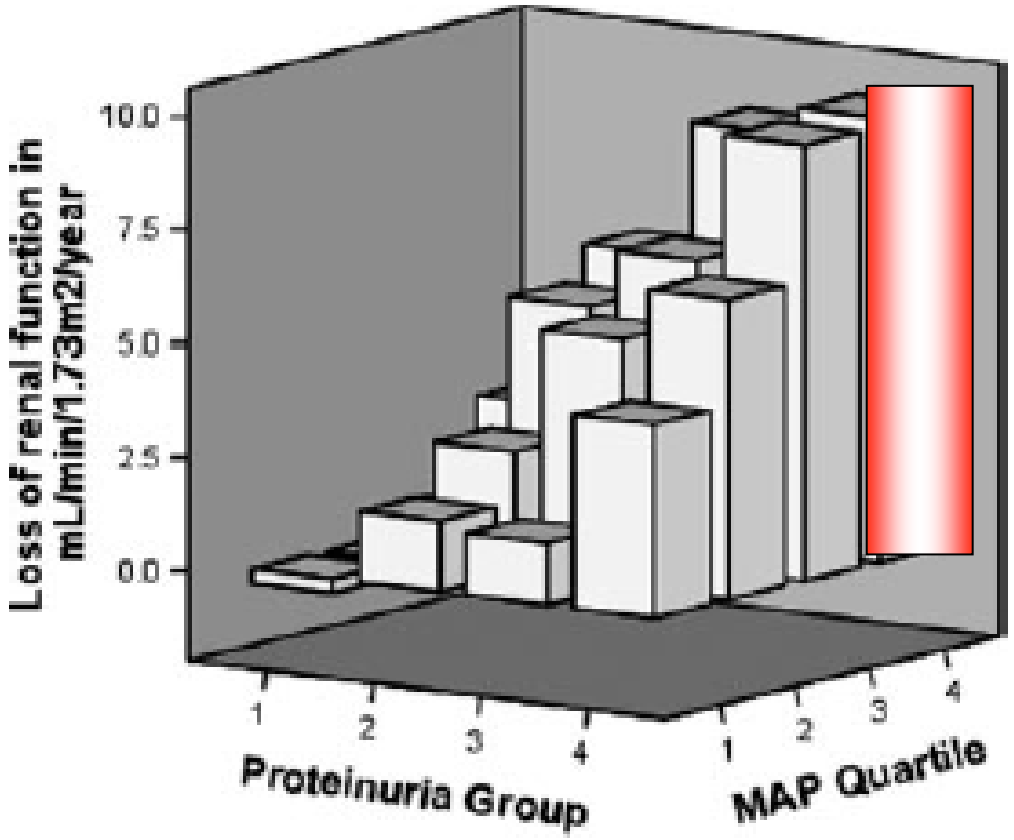

Figure 4. Relationship between TA-proteinuria group, quartile of MAP, and loss of CrCl. Group 1, TA-proteinuria <1 g/24 h; group 2, 1 to 2 g/24 h; group 3, 2 to 3 g/24 h; group 4, >3 g/24 h.