Immunosuppressive treatment for IgA nephropathy - when and how?

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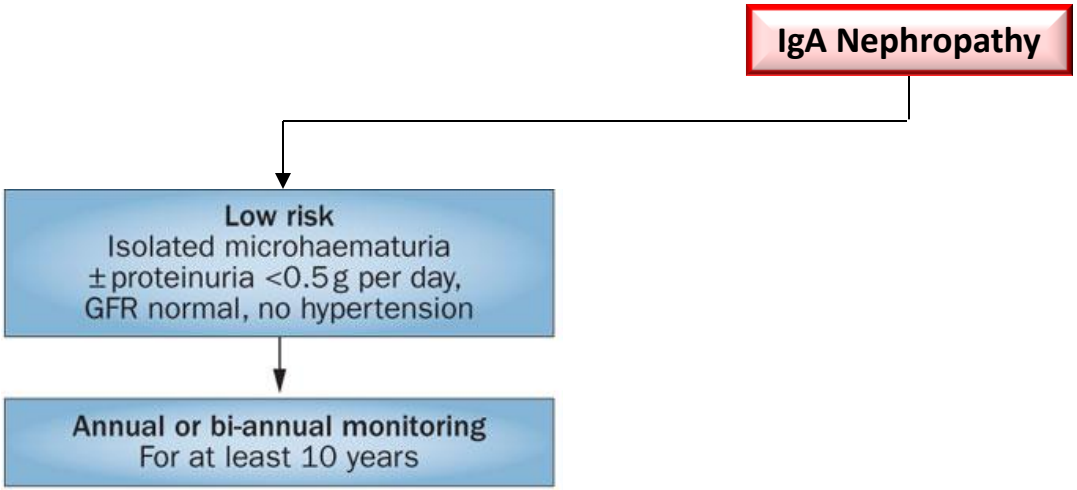
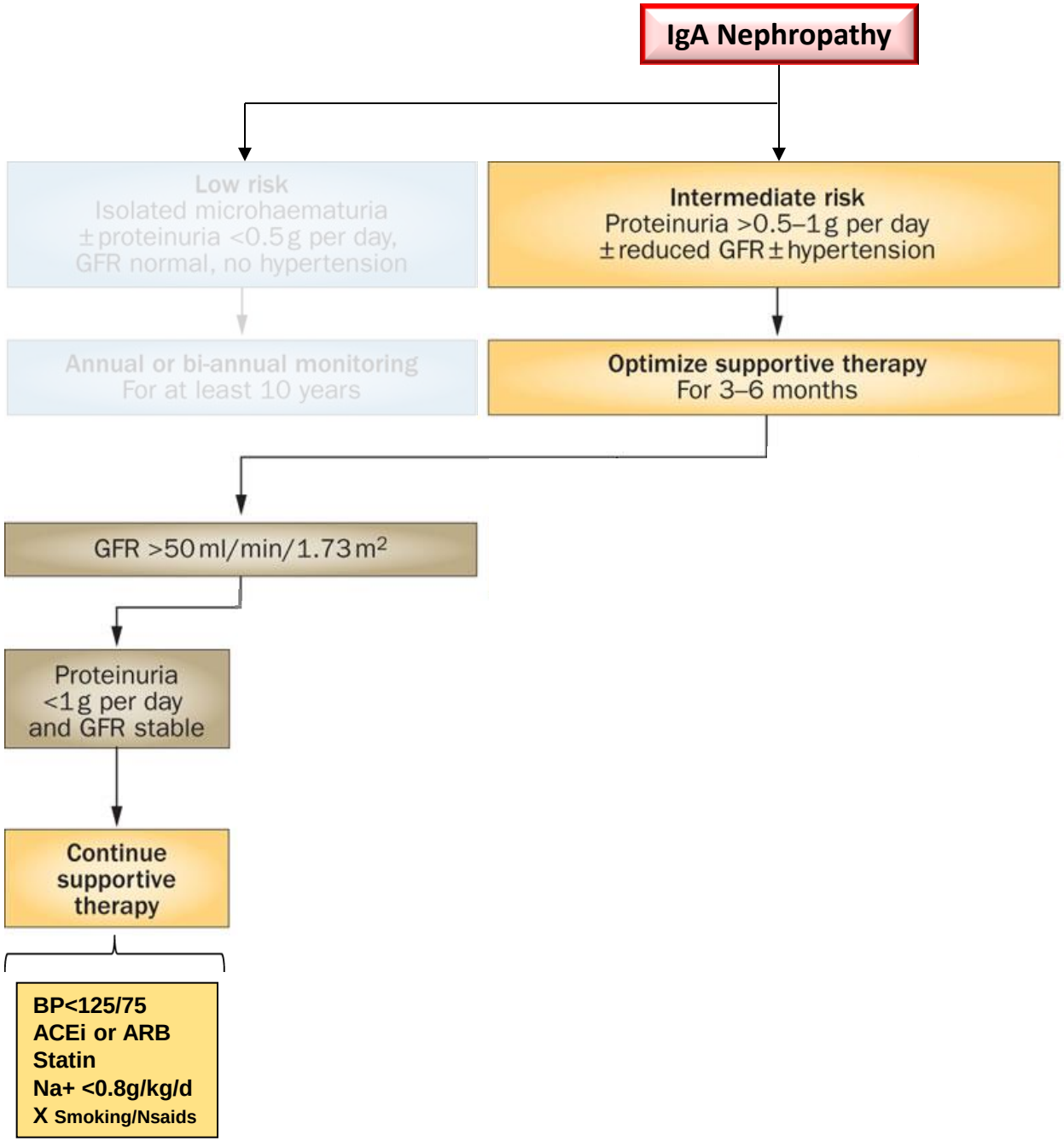
1st International Congress of Chinese Nephrologists - Scientific Congress on Nephropathies

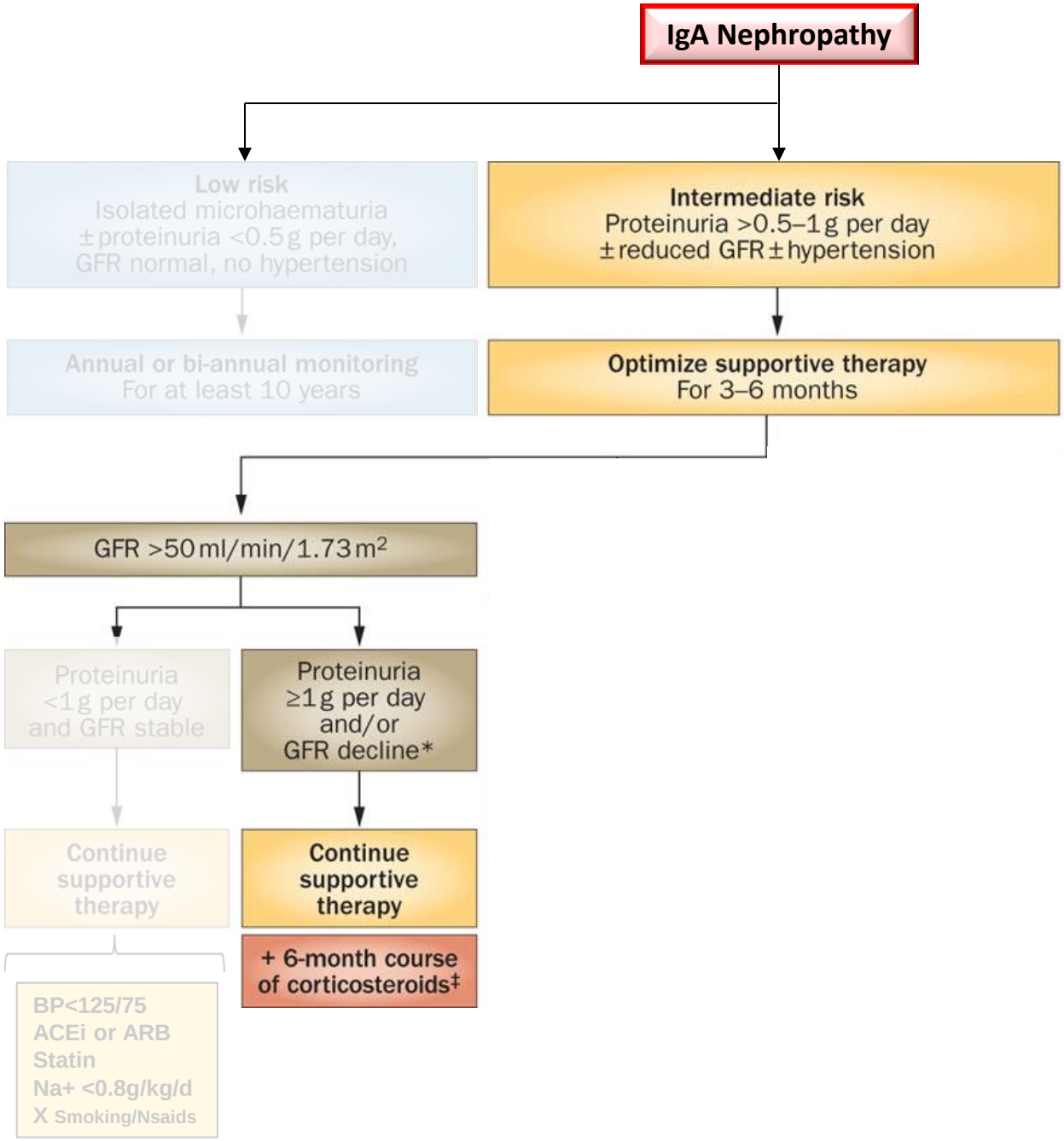
11 – 13 /12 / 2015



Floege & Feehally. Nat Rev Nephrol 2013



Floege & Feehally. Nat Rev Nephrol 2013



Floege & Feehally. Nat Rev Nephrol 2013

Corticosteroid treatment in IgAN

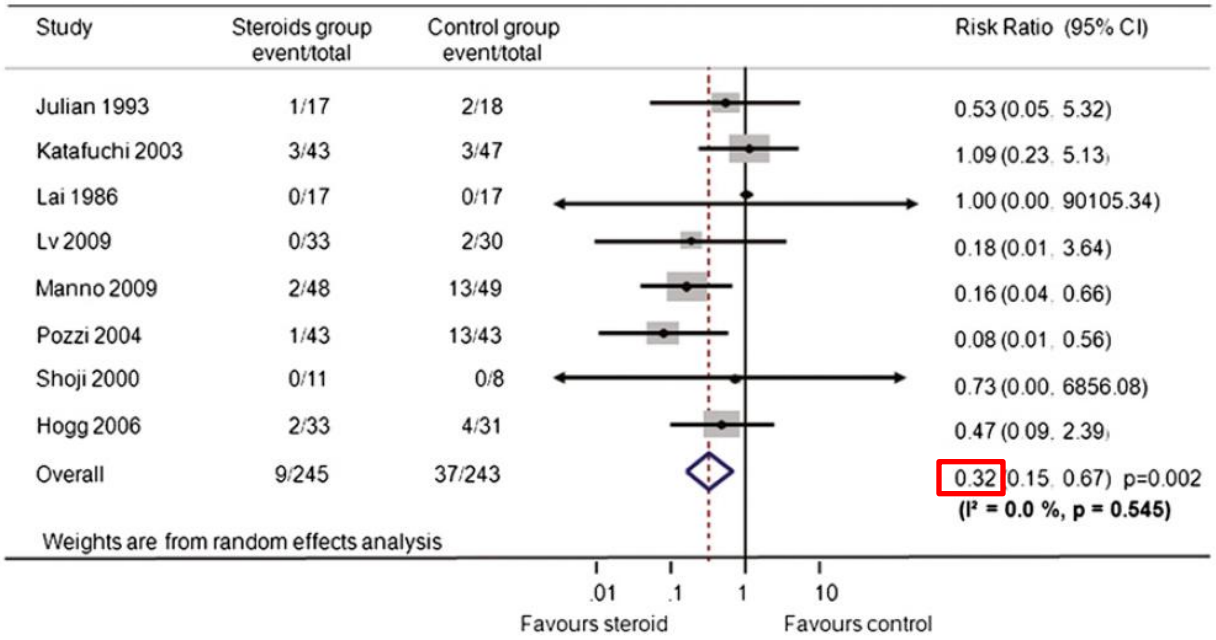
- A large contribution by Japanese researchers in early years
- Kobayashi et al. *Q J Med* 1986
  - *Nonrandomized prospective study, UP 1-2 g/d N=14 (steroids) vs N=29 (controls)*
  - *After 19 m, steroid group had lower proteinuria and better GFR, esp among those with baseline GFR > 70 ml/min*
  - *At 10 yrs, renal survival 80% vs 34% (Nephron 1996)*

Corticosteroid treatment in IgAN

- 6-month course of steroid treatment protected against renal function deterioration (UP>1-3.5g/d and sCr < 133uM)
  - Pozzi C, et al. Corticosteroids in IgA nephropathy: a randomised controlled trial. Lancet 1999
- invalidated in Chinese patients (randomized study)
  - Lai KN, et al. Corticosteroid therapy in IgA nephropathy with nephrotic syndrome: a long-term controlled trial. Clin Nephrol 1986

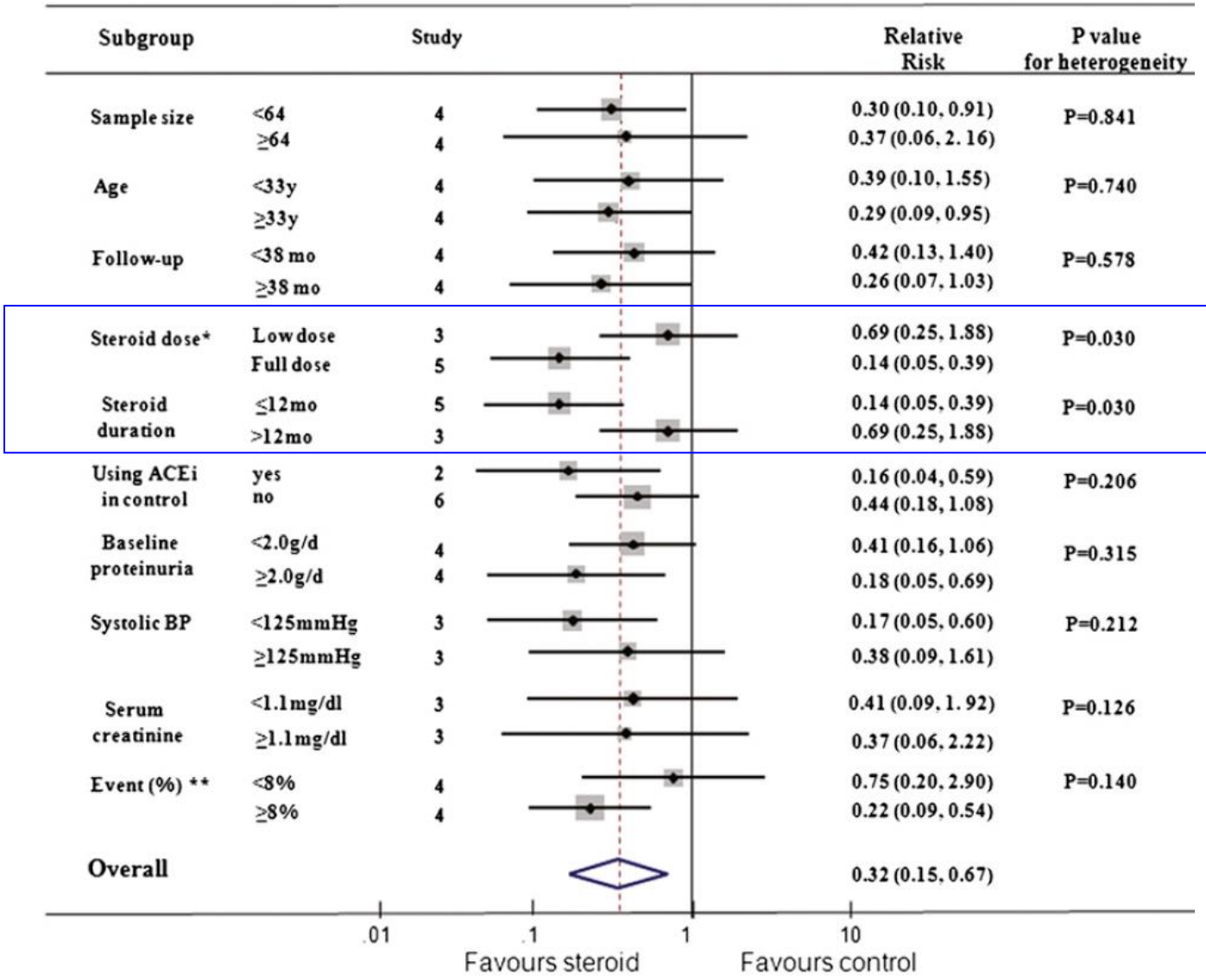
Corticosteroid Therapy in IgA Nephropathy

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



Steroid therapy was associated with a lower risk for kidney failure

High-dose / short-term* better than low-dose / long-term steroid



*prednisone >30 mg/d or high-dose pulse intravenous methylprednisolone with duration ≤1 year

STOP IgAN

Supportive Versus Immunosuppressive Therapy for the Treatment Of Progressive IgA Nephropathy

Inclusion:

Proteinuria > 0.75 g/day despite 6 m of intensive supportive care

Presence of at least one further risk factor for ESRD:

a) arterial hypertension (ambulatory BP>140/90 or use of antihypertensive) or

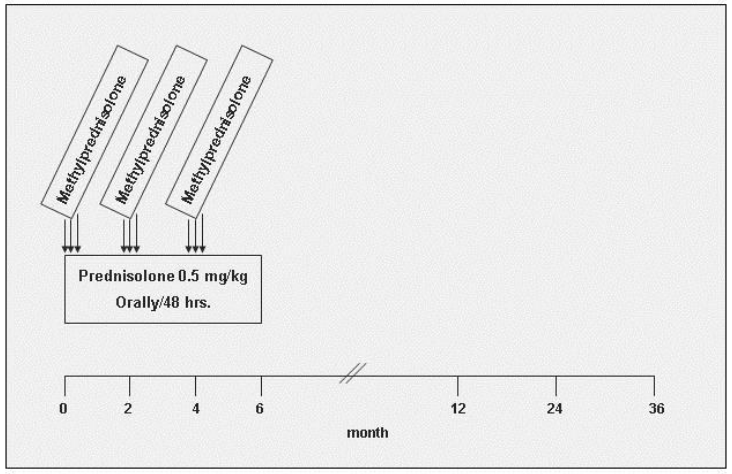
b) impaired renal function (creatinine clearance or estimated GFR <90 ml/min)

148 patients:

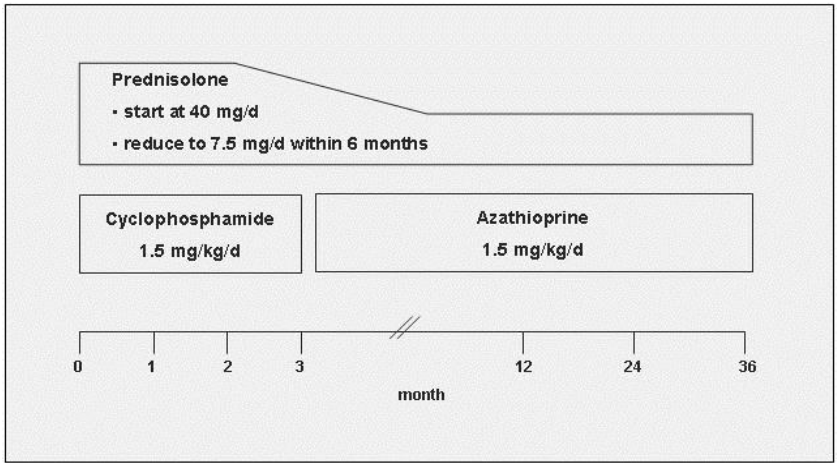
A: Support care (n=74)

B: Support care + (n=74, depending on eGFR):

GFR 60 – 89 ml/min

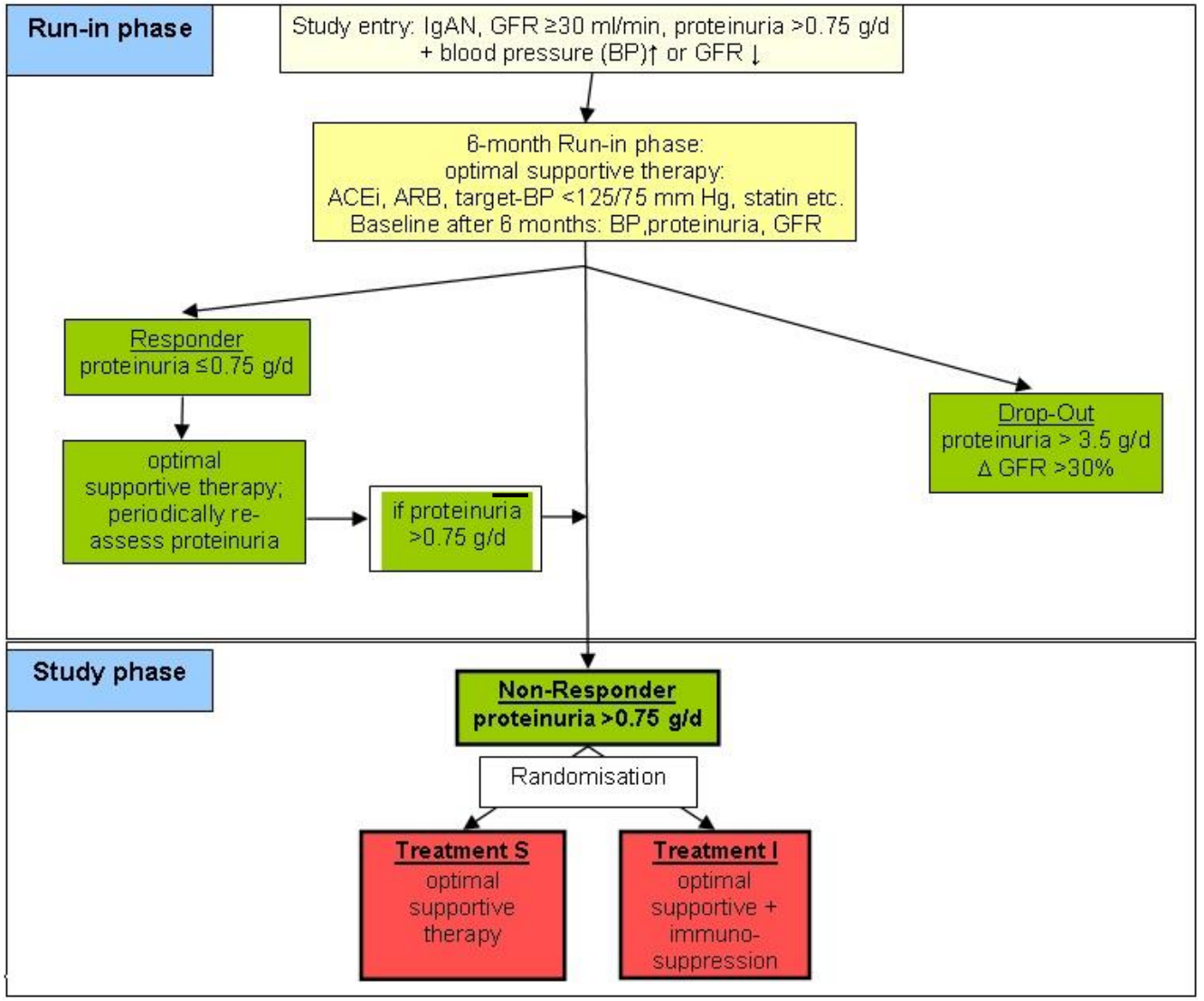


GFR 30 – 59 ml/min



STOP IgAN

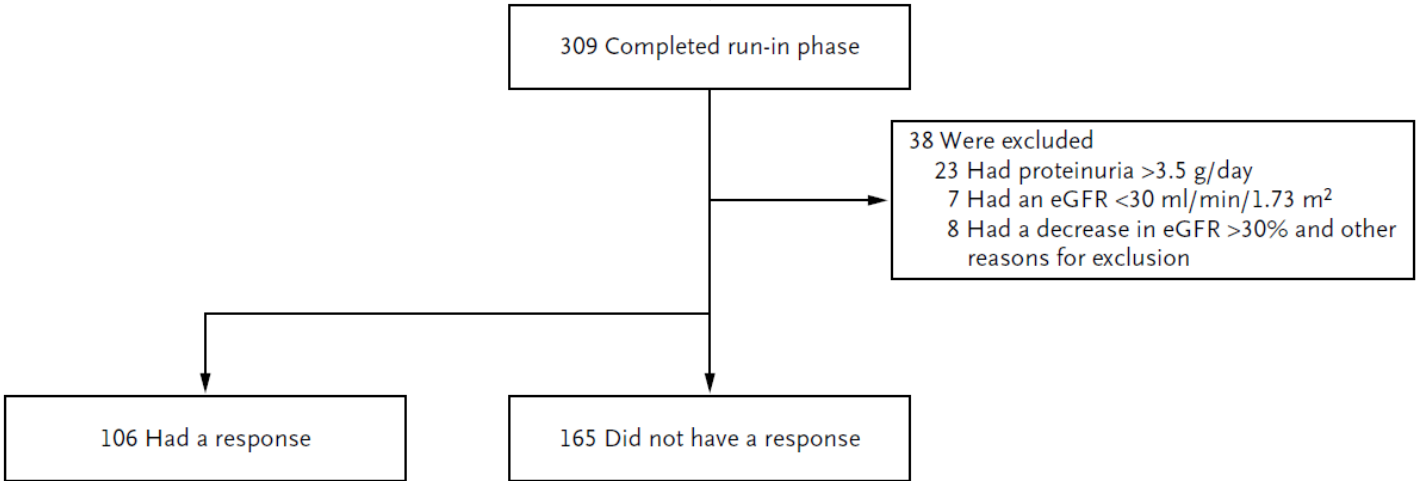
Supportive Versus Immunosuppressive Therapy for the Treatment Of Progressive IgA Nephropathy



Primary endpoints:
Patients reaching full clinical remission at 3 years, defined as proteinuria < 0.2 g/d and stable renal function (GFR loss of < 5 ml/min from baseline GFR at the end of the 3 year study period)
GFR loss of 15 ml/min or higher from baseline GFR at the end of the 3 year study period

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*

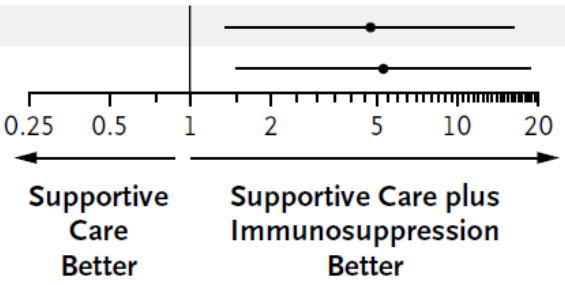


	Supportive Care (N=80)	Supportive Care plus Immunosuppression (N=82)
Serum creatinine — mg/dl	1.6±0.6	1.6±0.7
eGFR — ml/min/1.73 m²‡	57.4±24.9	61.1±29.0
Creatinine clearance — ml/min	76.2±31.0	76.3±36.4
Urinary protein excretion rate — g/day	1.6±0.7	1.8±0.8
Protein-to-creatinine ratio§	1.0±0.5	1.1±0.6

Primary end points

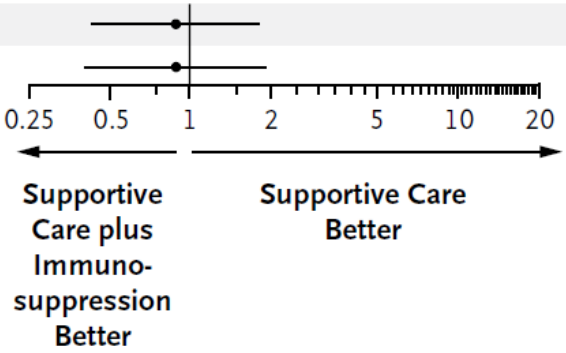
A **In Full Clinical Remission** (protein-to-creatinine ratio <0.2 g/g and a decrease in eGFR <5 ml /min from baseline)

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



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



Rauen T, et al. NEJM 2015

Secondary endpoints

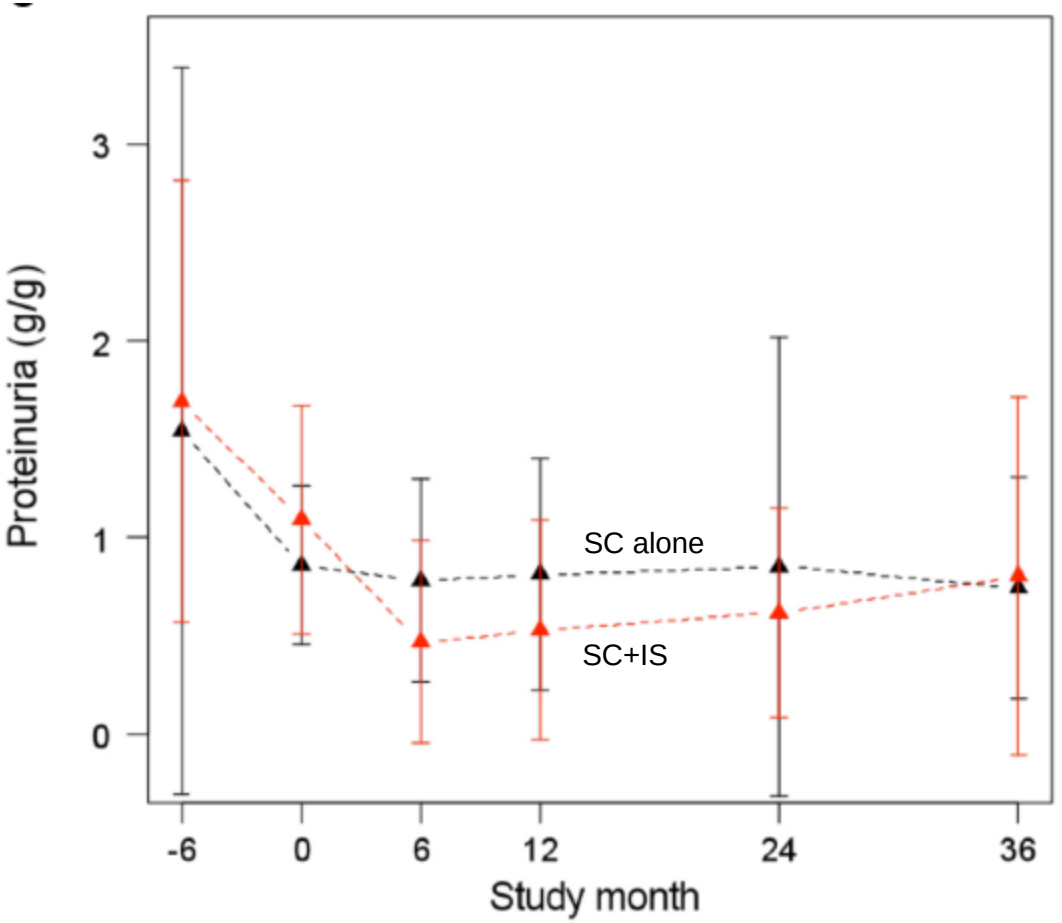
Secondary End Point	Supportive Care (N=80)		Supportive Care plus Immunosuppression (N=82)		Odds Ratio (95% CI)	P Value
	Patients with Available Data	End-Point Value	Patients with Available Data	End-Point Value		
	no.	*mean ±SD or no. (%)*	*no.*	*mean ±SD or no. (%)*		
Absolute eGFR change at 36 mo — 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

Rauen T, et al. NEJM 2015

Proteinuria reduction

At 12 months, immunosuppression group had a significantly lower mean proteinuria.

At month 36, the difference was no longer significant



Rauen T, et al. NEJM 2015
Supplementary data

Table 3. Adverse Events during the Trial.

Variable	Supportive Care (N=80)	Supportive Care plus Immunosuppression (N=82)	P Value
Patients with ≥1 serious adverse event — no.	21	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 aminotransferase >50 IU/ml)	12	13	1.00
≥1 incidence of observed leukopenia (i.e., leukocyte count <4000/μl)	3	2	1.00
Malignant neoplasm	0	2	0.50
Impaired glucose tolerance or diabetes mellitus	1	9	0.02
Gastrointestinal bleeding	0	0	Not determined
Fracture	0	1	1.00
Osteonecrosis — no. of patients	0	0	Not determined
Weight gain (≥5 kg within the first year)	5	14	0.049

CONCLUSIONS

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

Rauen T, et al. NEJM 2015

Limitations

- Open label
- Short duration of FU (3y)
- Weaknesses in treatment design:
  - Steroid for patients with eGFR > 60 ml/min of questionable value
  - Steroid + CTX for patients with eGFR down to 30 ml/min also of questionable value
  - Lack of individualization based on histology
- Disregarded the potential legacy effect (observed in VALIGA, MMF study, REIN and RENAAL) of proteinuria reduction at 12m, albeit transient

TESTING

Therapeutic Evaluation of STeroids in IgA Nephropathy Global Study

Inclusion:

Proteinuria > 1 g/day & eGFR 20 – 120 ml/ml despite MTD RAS blockade

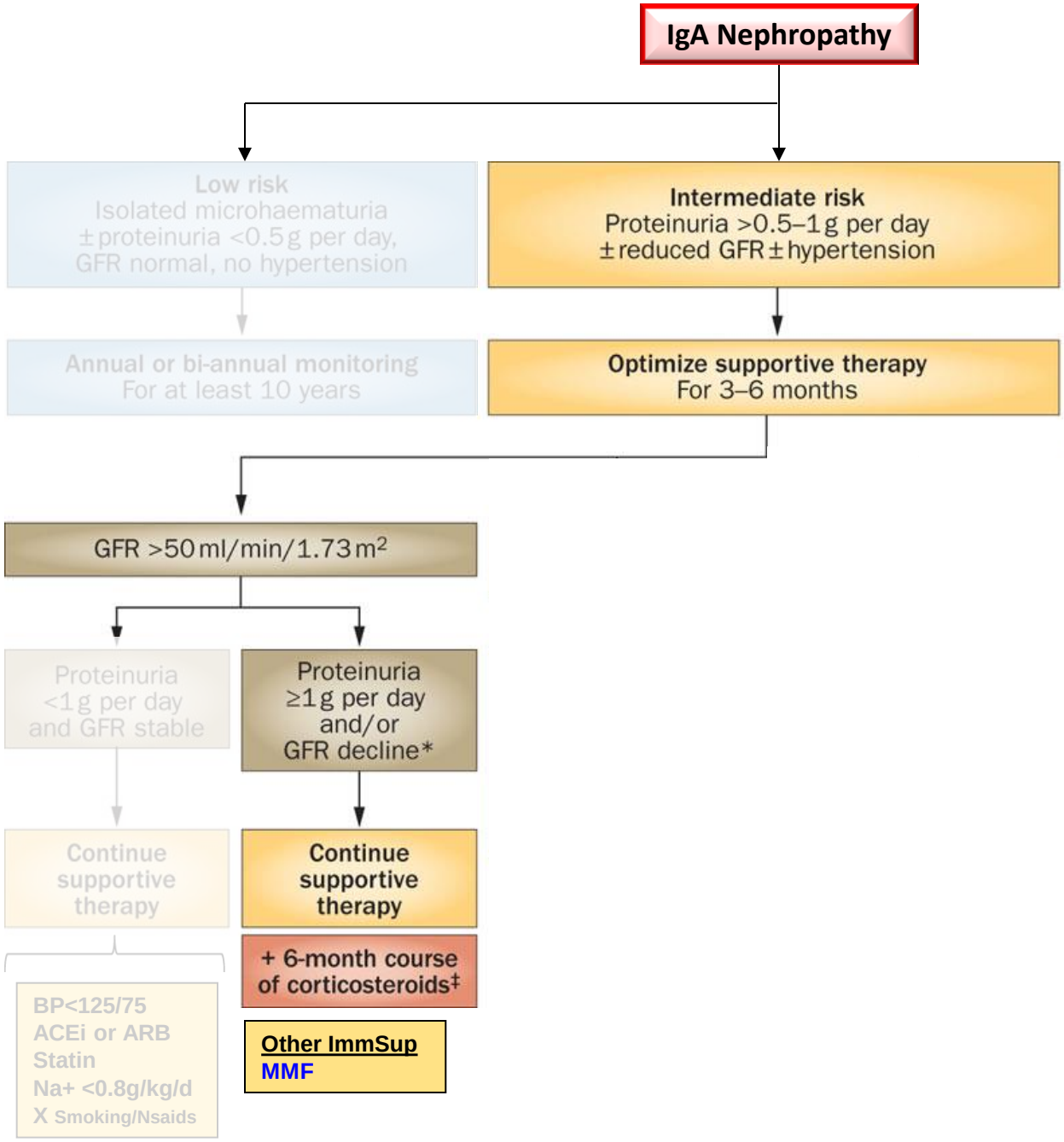
750 patients:

A: Support care

B: Support care + oral methylprednisolone or placebo 0.6-0.8mg/kg/day with a maximum 48mg/day x 2 months, tapered by 8mg/day every month to stop within 6-8 months

Primary outcome:

Progressive kidney failure, which is a composite of a 40 % decrease in eGFR, and ESRD (dialysis or kidney transplantation, and death due to kidney disease)



Floege & Feehally. Nat Rev Nephrol 2013

Mycophenolate mofetil: Chinese patients

N=62, UP > 2g/d

Beijing

MMF x 12 months: more effective than corticosteroid therapy in reducing proteinuria

FU: 18 m

Chen X et al. *Zhonghua Yi Xue Za Zhi* 2002

Xi'AN

N=84; UP > 2.5g/d;

Pred/MMF x 12 m: UP 2.83 → 0.6 g/d

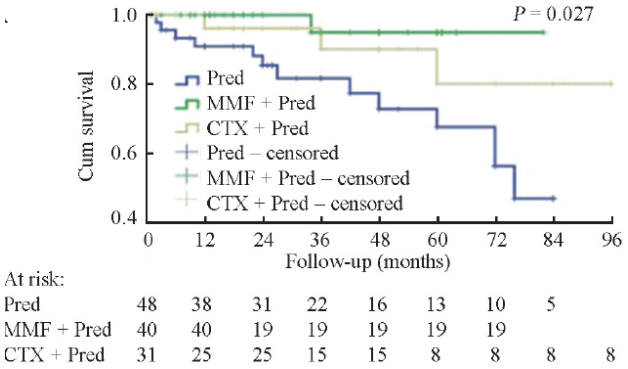
Pred/CTX x 12m: UP 2.77 → 1.4 g/d

FU: 18 m

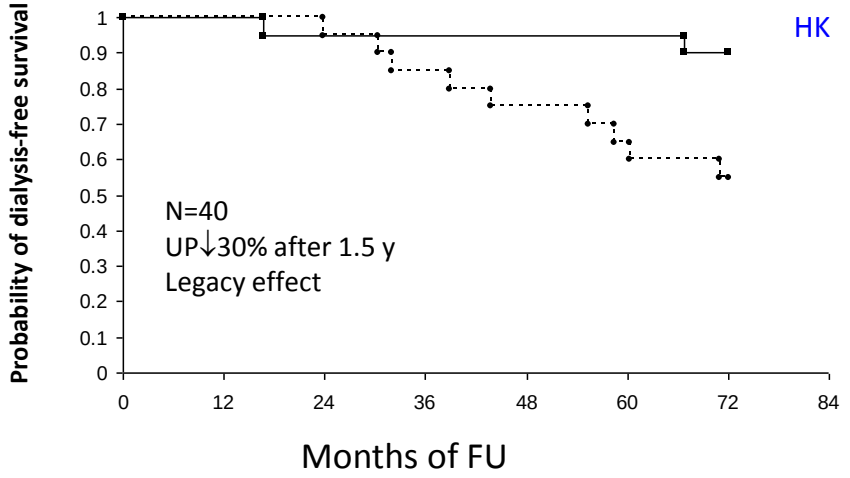
Liu X, et al. *Int J Clin Pharmacol Ther* 2014

N=119; UP ~ 3.5g/d

Zhengzhou



Yan L et al. *Chin Med J.* 2014



HK

N=40

UP↓30% after 1.5 y

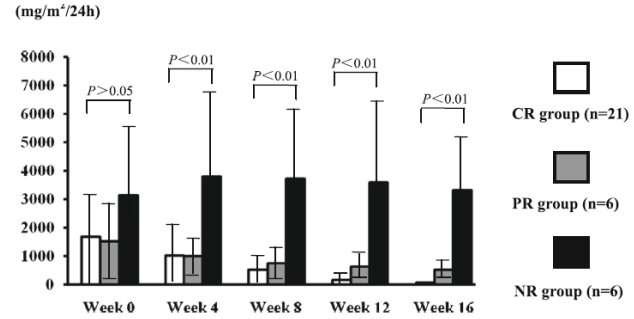
Legacy effect

Tang SC, et al. Kidney Int 2005 & 2010

Hunan

N=33 children with SRNS and IgAN

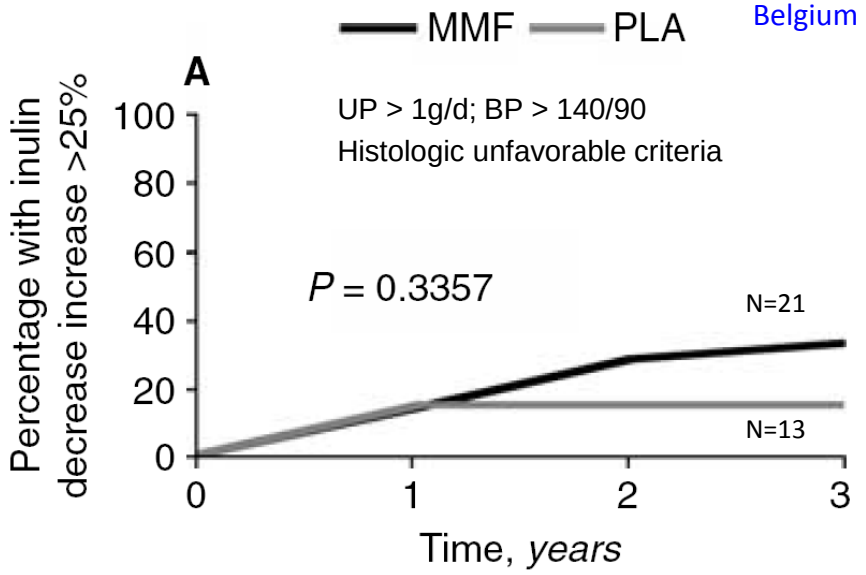
MMF → CR/PR in 27 (82%) at week 16



Kang Z, et al. *Pediatr Nephrol* 2015

Mycophenolate mofetil: Caucasian patients

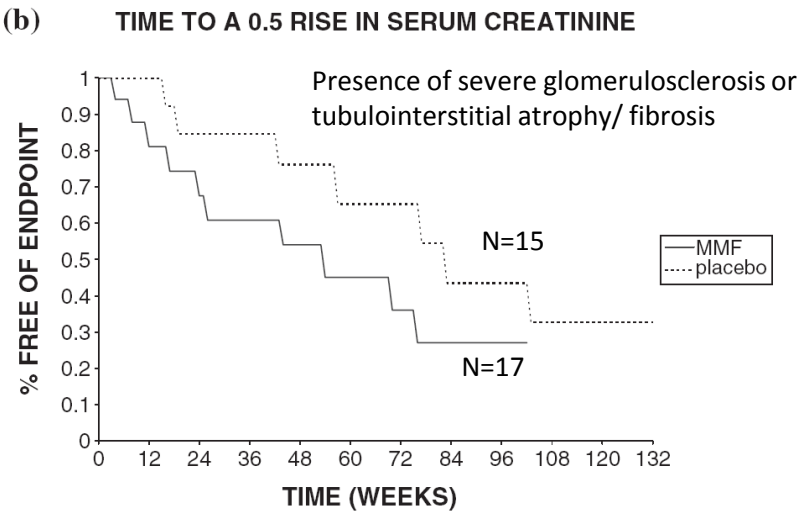
Belgium



UP > 1g/d; BP > 140/90
Histologic unfavorable criteria

Maes BD et al. Kidney Int 2004

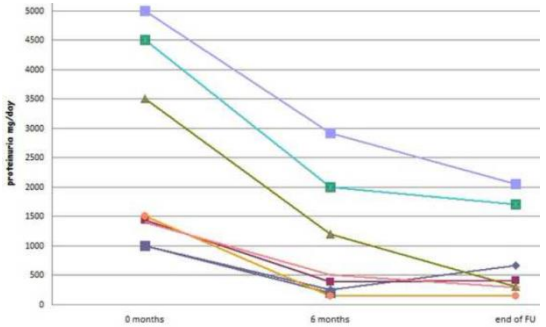
USA



Frisch G, et al. *Nephrol Dial Transplant* 2005

Italy

UP > 2.4g/d; RBC > 76/HPF
Bx: 10% florid crescents
MPx3/Pred + MMF x 6m



Roccatello D, et al. J Nephrol 2012

USA
Canada

N=52→44 (7-70y); RASB+FOx3m→MMF vs pla if UP >0.6 – 0.8 g/g

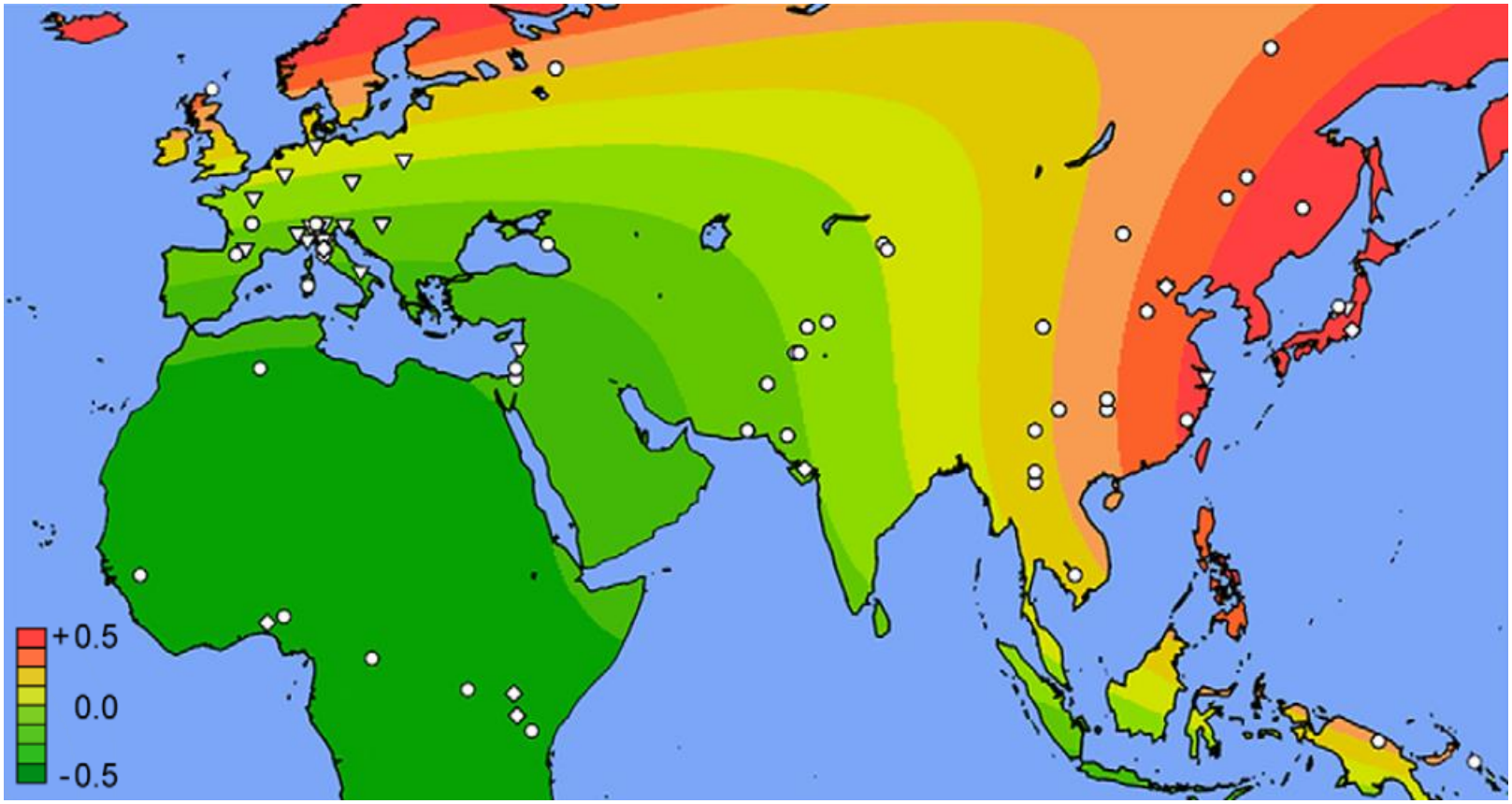
	MMF Group			Placebo Group		
	No.	Randomization Mean (95% CI)	Follow-up Mean (95% CI)	No.	Randomization Mean (95% CI)	Follow-up Mean (95% CI)
UPCR, in g/g						
Pts at randomization	25	1.59 (1.23 to 1.95)	—	27	1.40 (1.18 to 1.62)	—
Pts reaching 6 mo Rx	22	1.45 (1.16 to 1.75)	1.40 (1.09 to 1.70)	22	1.41 (1.17 to 1.65)	1.58 (1.13 to 2.04
Pts reaching 12 mo Rx	13	1.46 (1.00 to 1.92)	1.52 (0.94 to 2.11)	15	1.39 (1.09 to 1.70)	1.51 (0.79 to 2.22
Pts reaching 12 mo post-Rx	7	1.25 (0.94 to 1.55)	1.22 (0.70 to 1.74)	10	1.44 (1.00 to 1.88)	1.67 (0.53 to 2.82

Hogg R, et al. AJKD 2015

Is IgA nephropathy the same disease in all parts of the world?

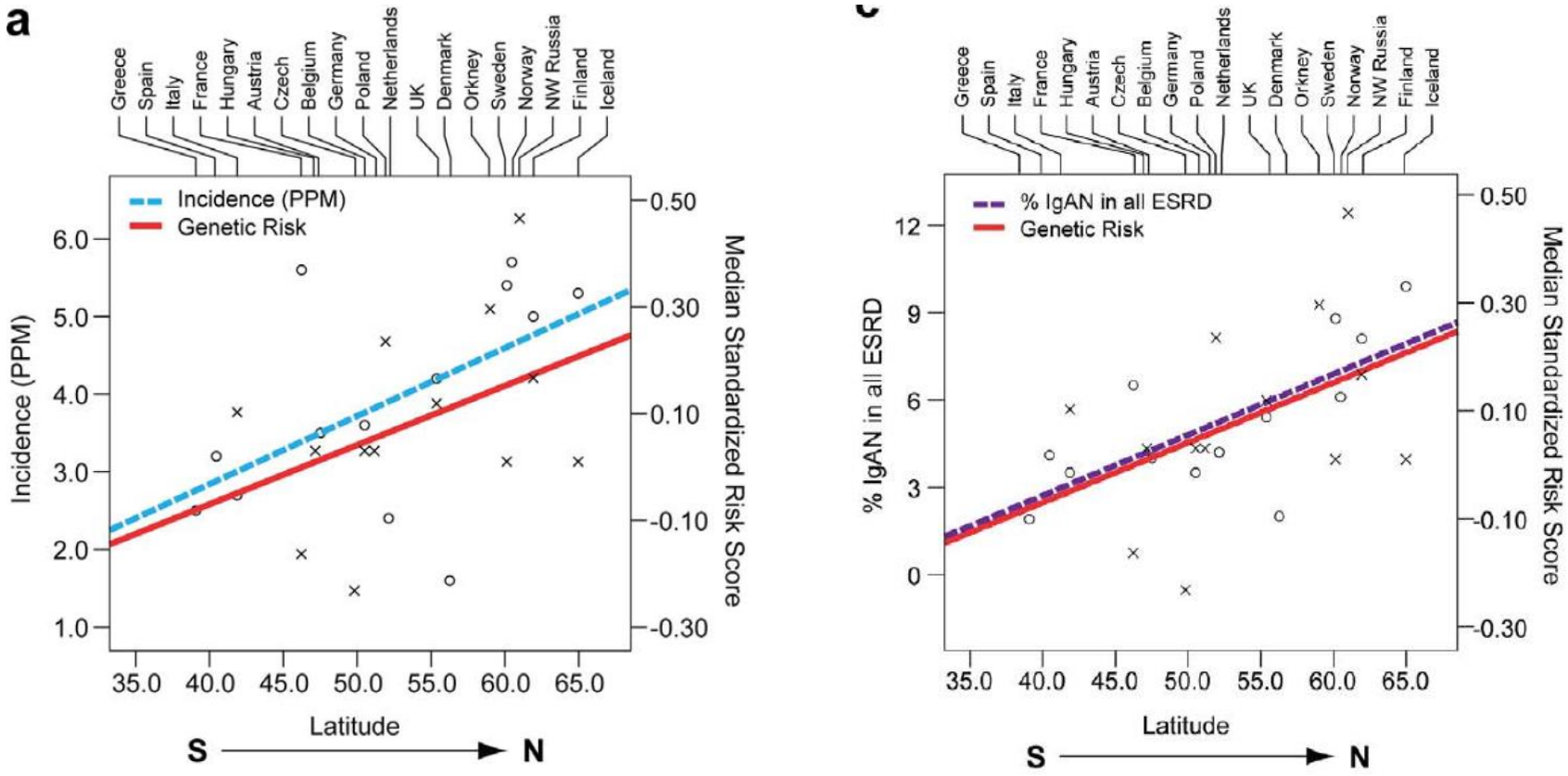
Probably not?

1. Worldwide geospatial risk differences



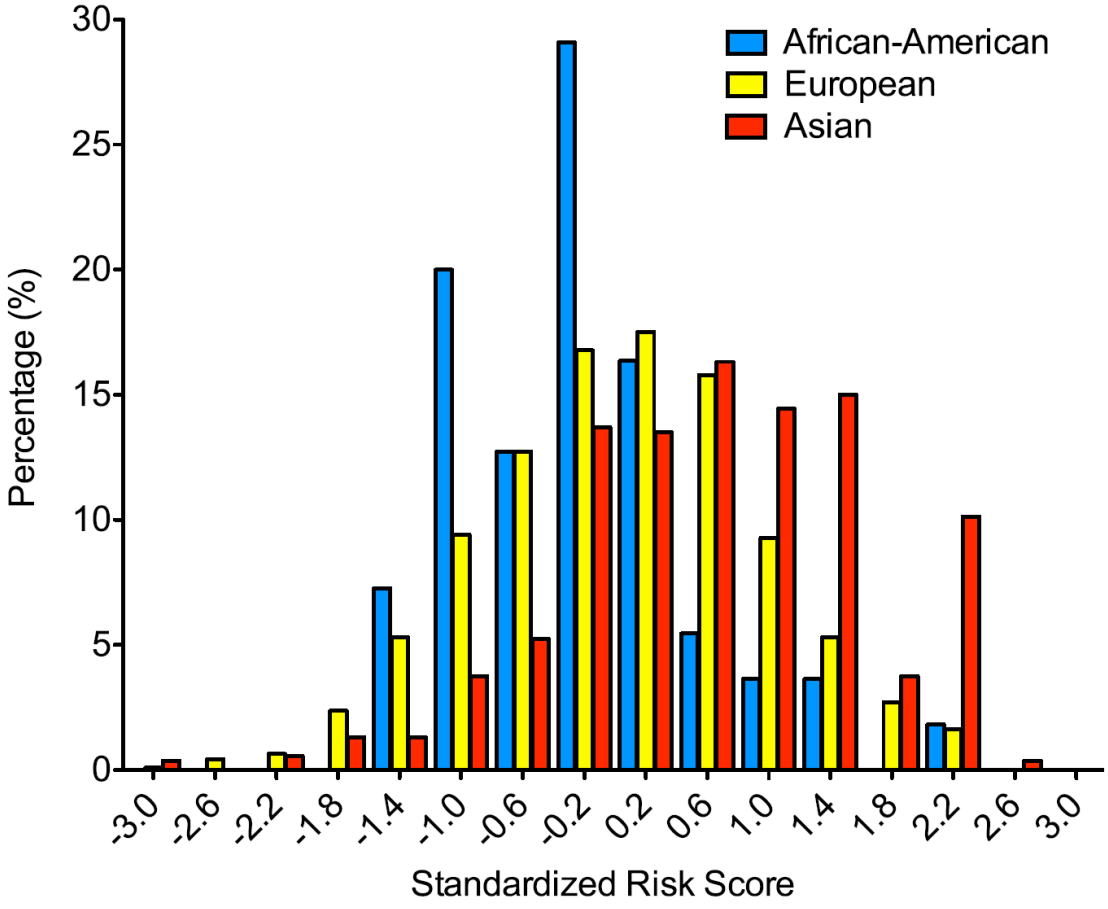
Kiryluk K, et al. PloS Gen 2012

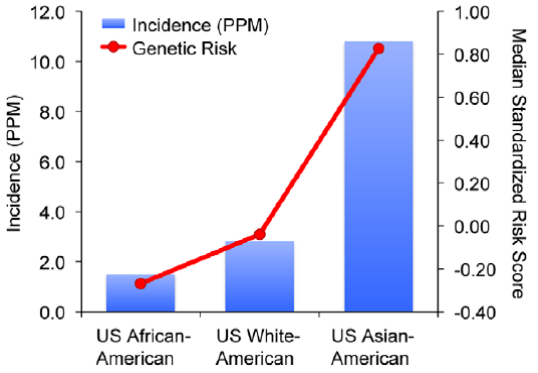
Correlation of average country latitude with country-specific genetic risk and IgAN–attributable ESRD across Europe

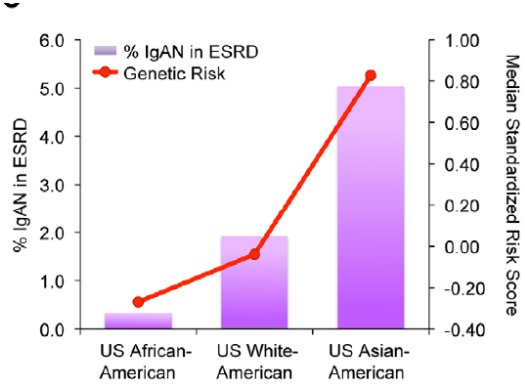


Kiryluk K, et al. PloS Gen 2012

2. Genetic risks from GWAS analysis by ethnicity



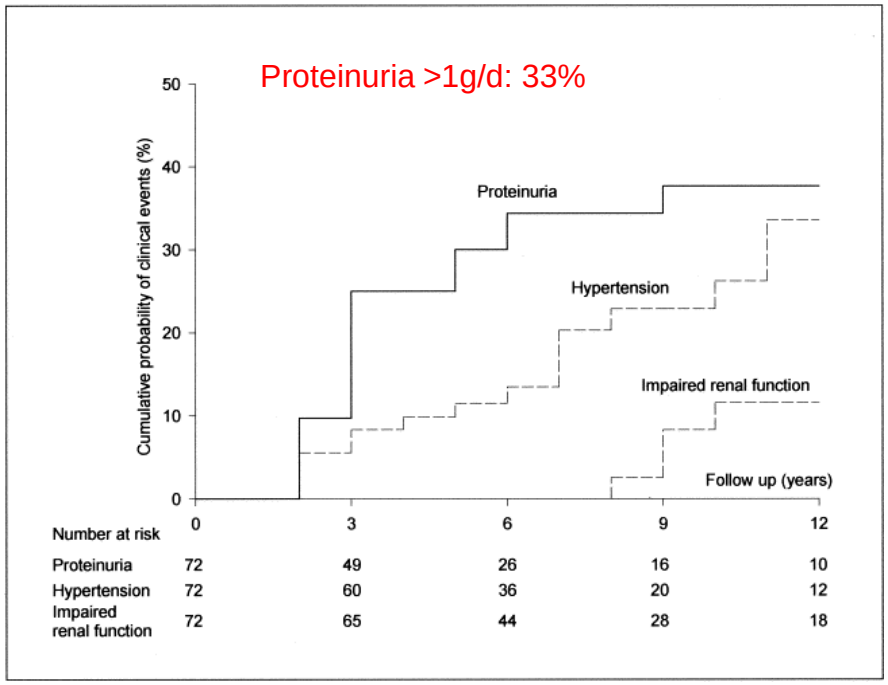




Kiryluk K, et al. PloS Gen 2012

3. Difference in Clinical Course between Chinese and Europeans

The Natural History of Immunoglobulin A Nephropathy among Patients with Hematuria and Minimal Proteinuria



Szeto CC, et al. Am J Med 2001

Long-Term Outcomes of IgA Nephropathy Presenting with Minimal or No Proteinuria

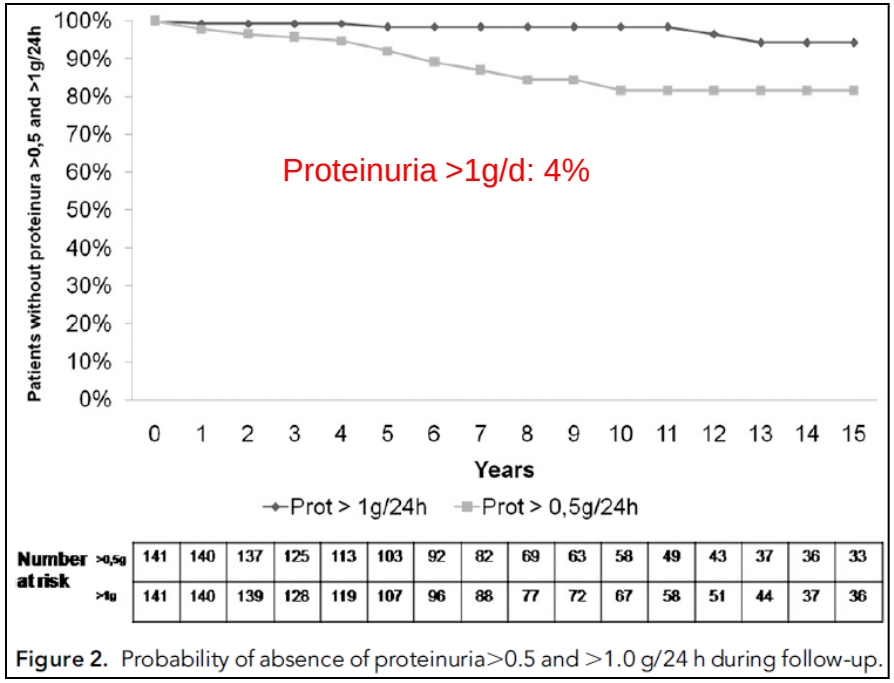
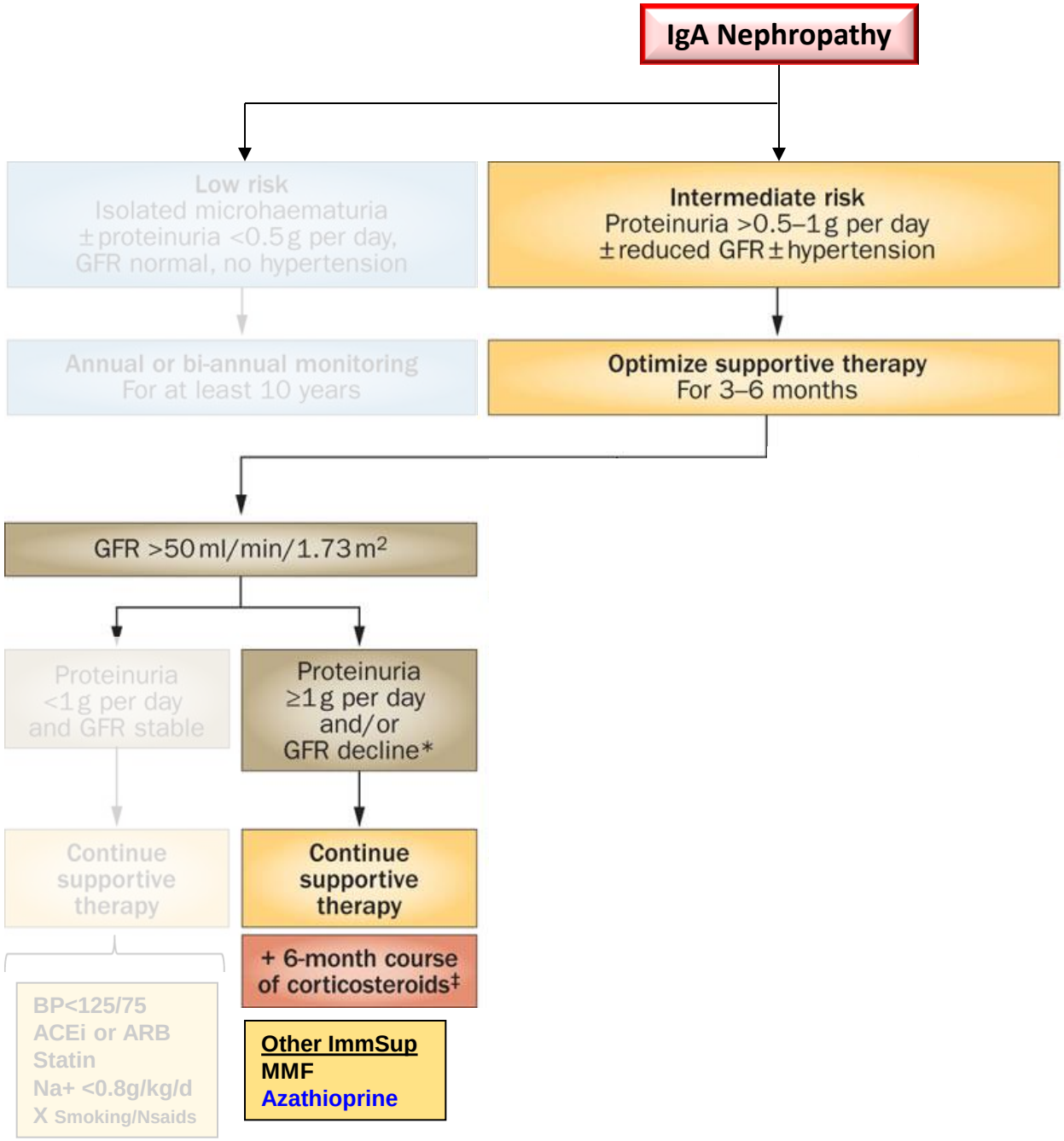


Figure 2. Probability of absence of proteinuria>0.5 and >1.0 g/24 h during follow-up.

Gutiérrez E, et al, JASN 2012

4. Difference in response to Therapy, e.g. MMF / CTX



Floege & Feehally. Nat Rev Nephrol 2013

Combination of Steroid + Azathioprine

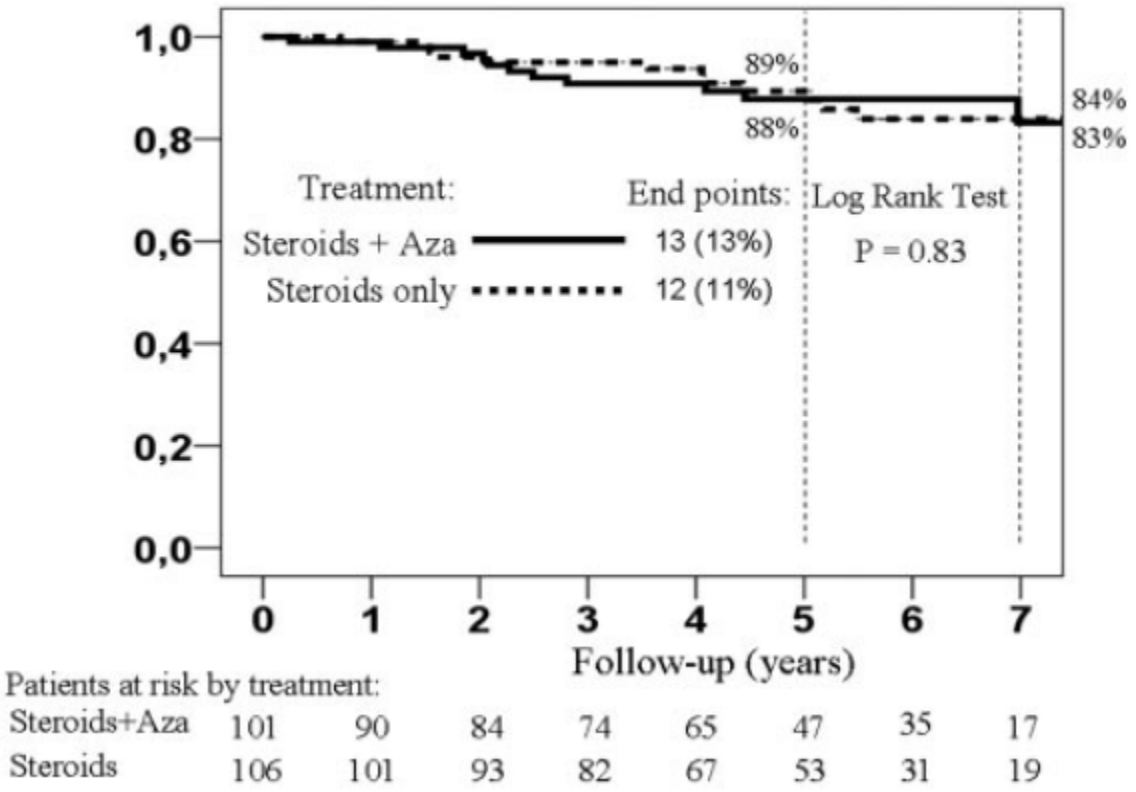
Patients with creatinine 2.0 mg/dl and proteinuria 1.0 g/d to either:

Steroid
N=106

3-day pulse of methylprednisolone in months 1, 3, and 5 in addition to both oral prednisone 0.5 mg/kg every other day

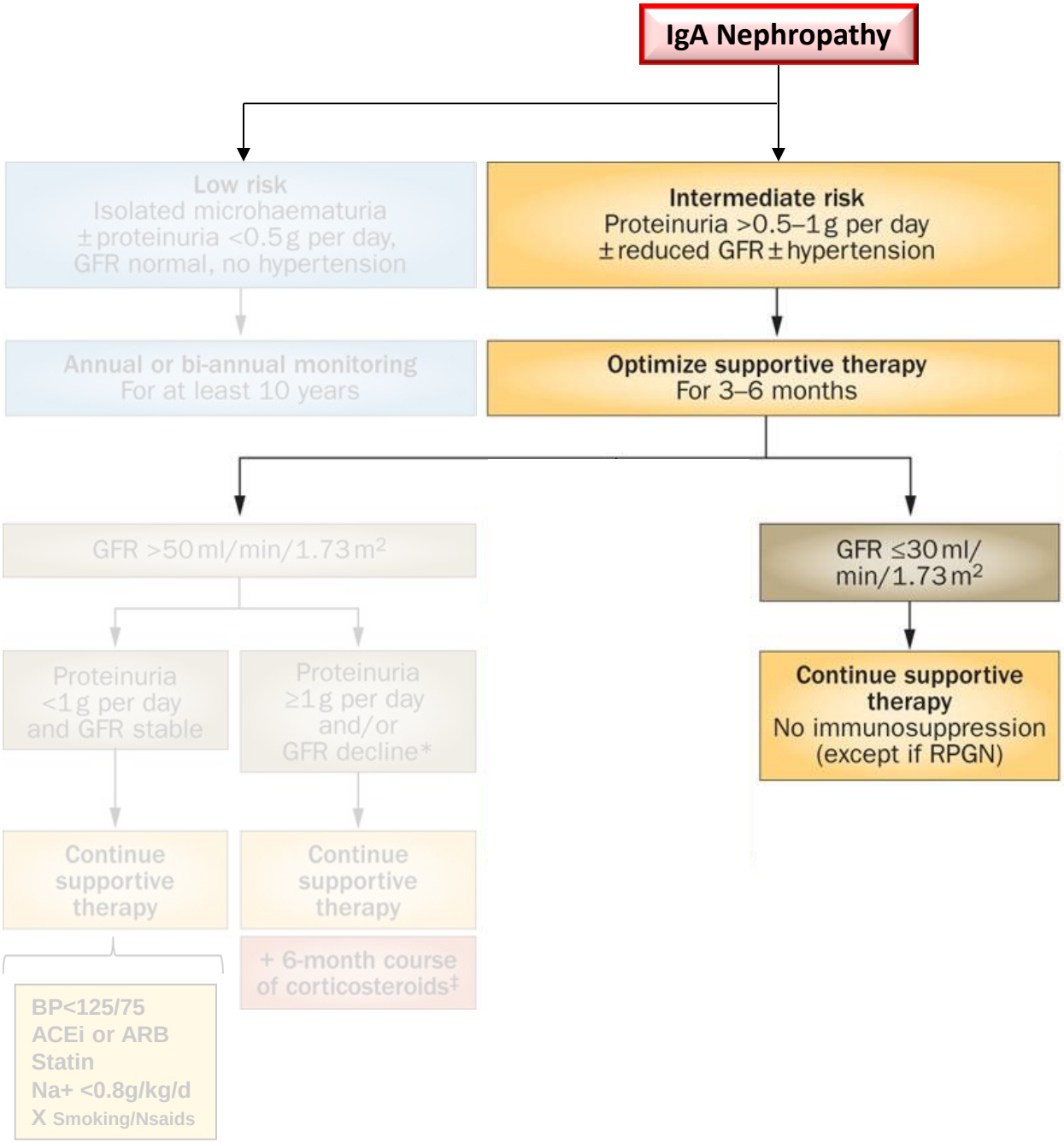
Steroid+Aza
N=106

Plus Aza 1.5 mg/d x 6/12

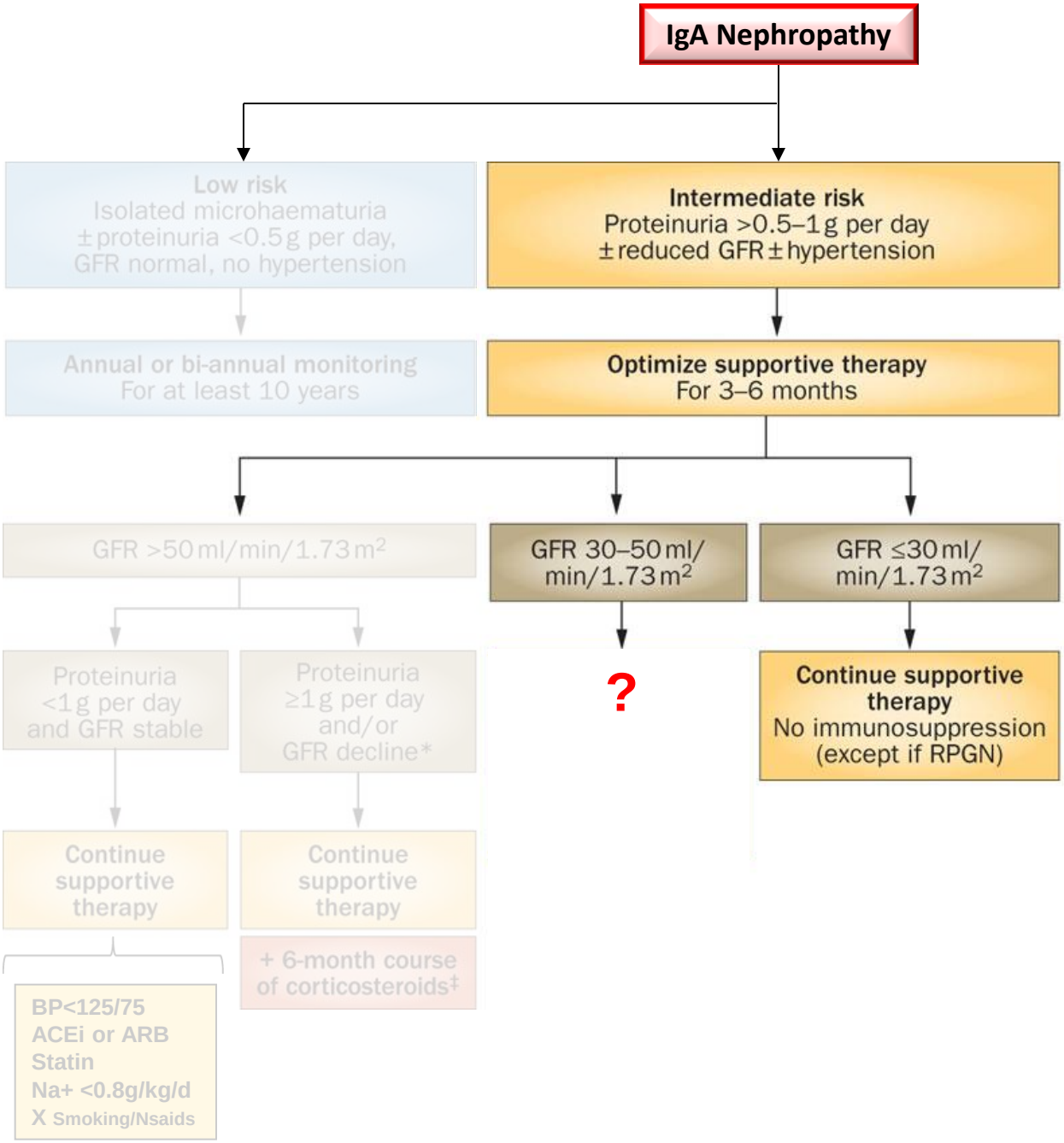


- No difference in proteinuria
- Increased treatment-related adverse effects

Pozzi C, et al. JASN 2010



Floege & Feehally. Nat Rev Nephrol 2013



Floege & Feehally. Nat Rev Nephrol 2013

IgA Nephropathy

Low risk
Isolated microhaematuria
±proteinuria <0.5 g per day,
GFR normal, no hypertension

Annual or bi-annual monitoring
For at least 10 years

Intermediate risk
Proteinuria >0.5–1 g per day
±reduced GFR±hypertension

Optimize supportive therapy
For 3–6 months

GFR >50 ml/min/1.73 m²

Proteinuria
<1 g per day
and GFR stable

Continue
supportive
therapy

BP<125/75
ACEi or ARB
Statin
Na+ <0.8g/kg/d
X Smoking/Nsaids

Proteinuria
≥1 g per day
and/or
GFR decline*

Continue
supportive
therapy

+ 6-month course
of corticosteroids‡

GFR 30–50 ml/
min/1.73 m²

Continue supportive therapy
Value of
immunosuppression
unknown
Critically weigh
pros and cons

GFR ≤30 ml/
min/1.73 m²

Continue supportive therapy
No immunosuppression
(except if RPGN)

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Corticosteroids in IgA Nephropathy: A Retrospective Analysis from the VALIGA Study

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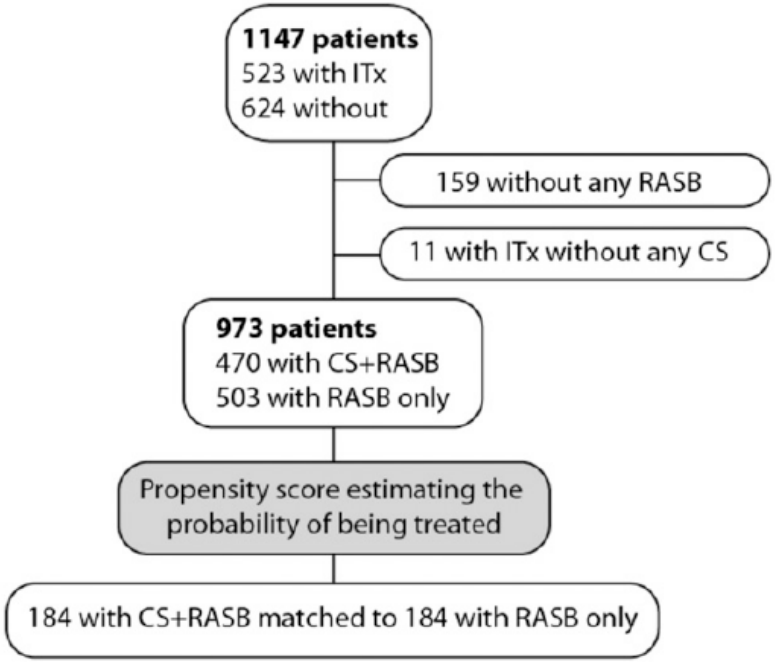
and on behalf of the VALIGA study of the ERA-EDTA Immunonephrology Working Group

Patient selection for the nested case control study on corticosteroids



Tesar V, et al. JASN 2015

Characteristics and outcome of propensity-matched individuals

Characteristic	RASB (*n*=184)	RASB+CS (*n*=184)	*P* Value
Clinical characteristics at biopsy			
Men	77	76	0.90
Caucasian	100	99	0.38
Age (y)	38±14	39±16	0.44
eGFR (ml/min per 1.73 m^2)	69±29	68±31	0.88
MAP (mmHg)	101±13	99±12	0.19
Prior RASB	53	46	0.15
Prior immunosuppression	1.1	1.1	1.00
Number of antihypertensive medication	1 (0 to 2)	1 (0 to 2)	0.67
Initial proteinuria (g/d)	1.1 (0.5 to 2.5)	1.3 (0.8 to 2.4)	0.12
Pathology findings			
M1	30	31	0.82
E1	9	12	0.73
S1	76	76	0.90
T1–2	27	28	0.73
Necrosis	7.1	9.2	0.45
Crescents	9.2	9.2	1.00
Follow-up (prior to immunosuppression in the treated group)			
MAP (mmHg)	99±9	99±11	0.89
Time-average proteinuria (g/d)	1.1 (0.5 to 2.3)	1.2 (0.8 to 2.3)	0.10
Treatments over entire follow-up			
Length of follow-up (y)	3.7 (1.9 to 6.7)	4.4 (2.3 to 6.5)	0.36
RASB	100	100	By design

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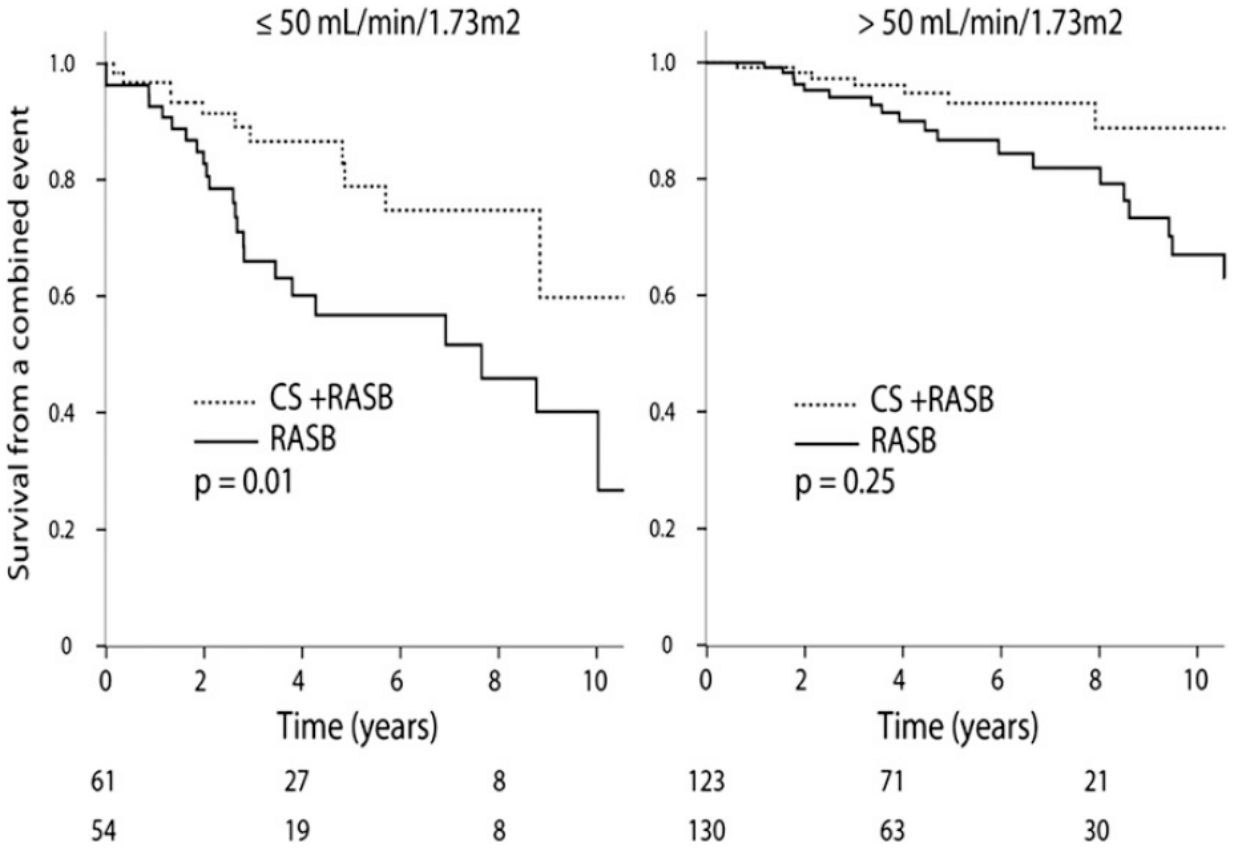
Renal survival by eGFR



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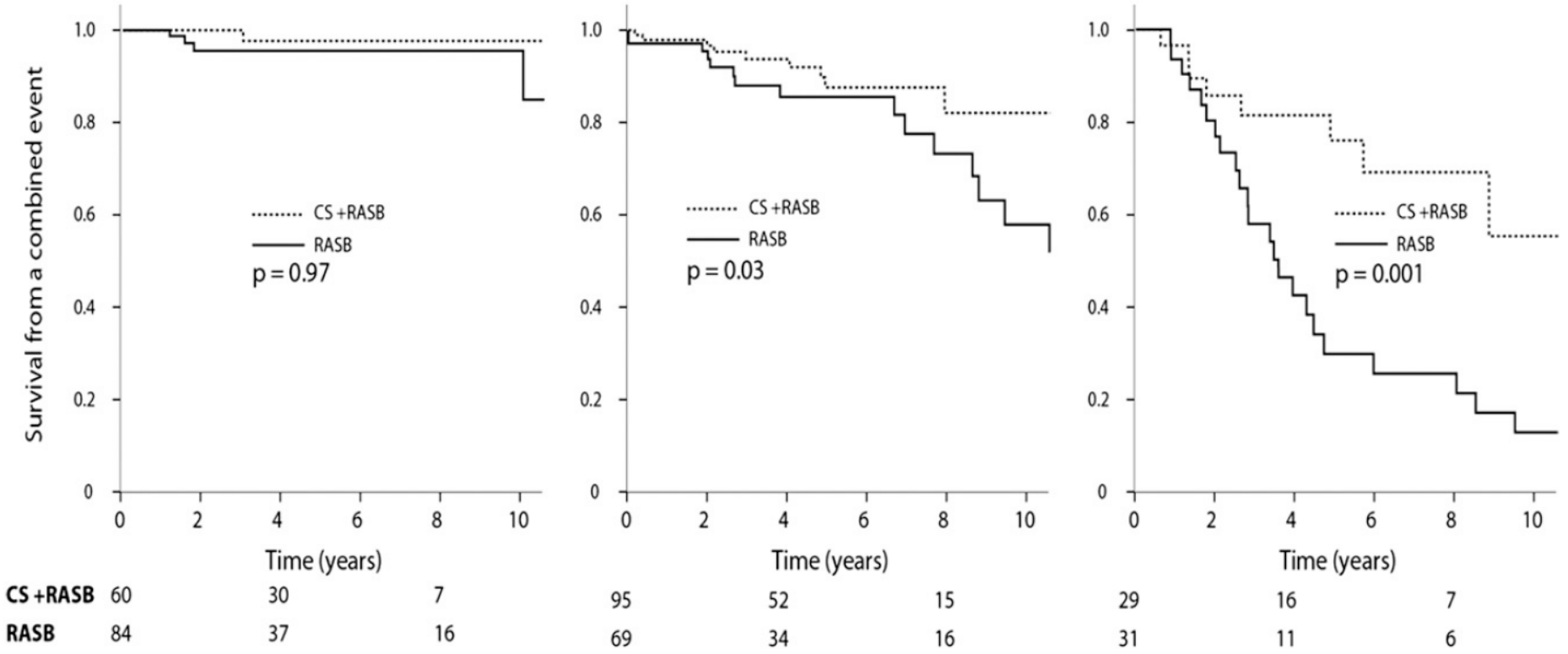
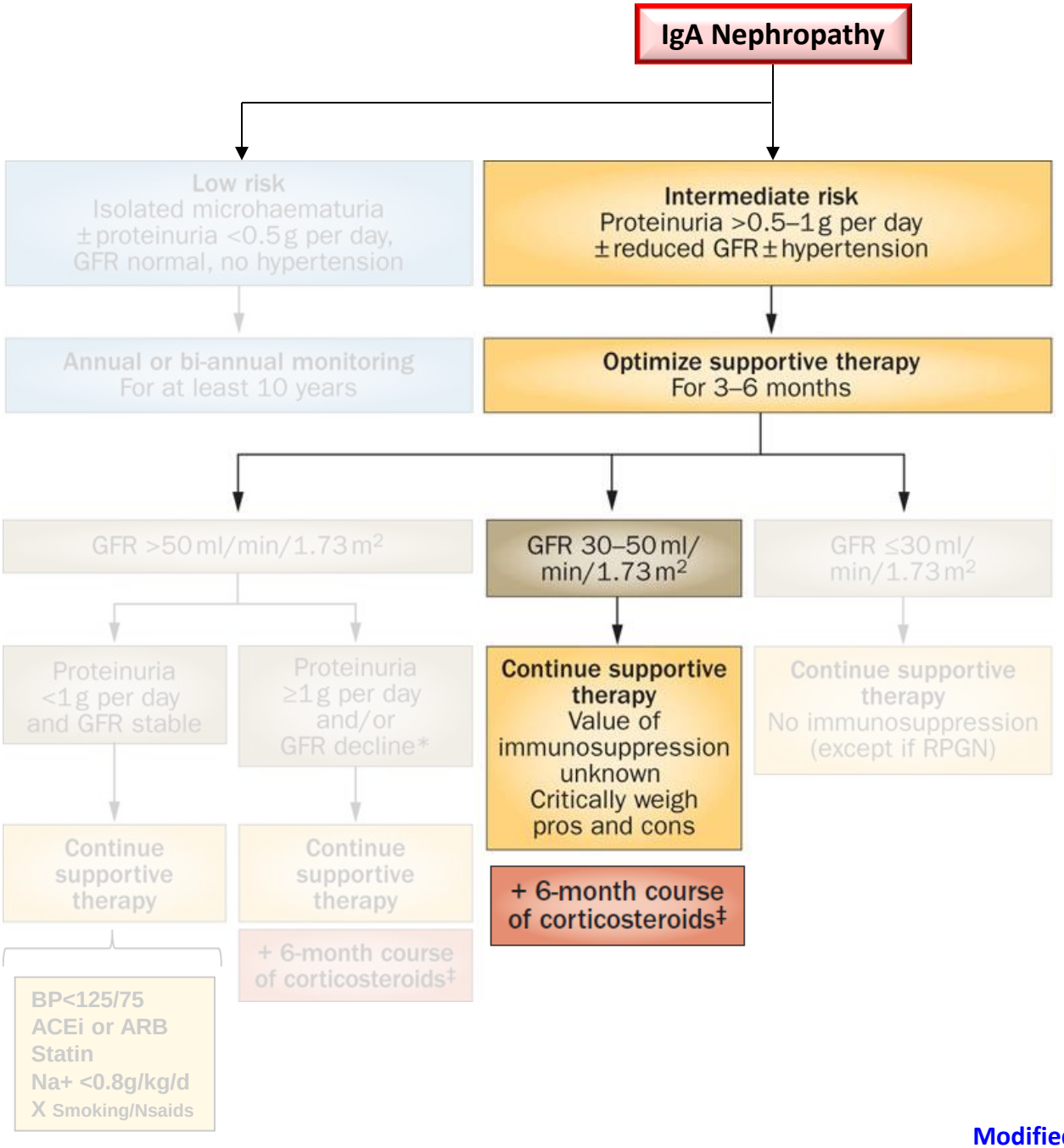
Renal survival by proteinuria during follow up



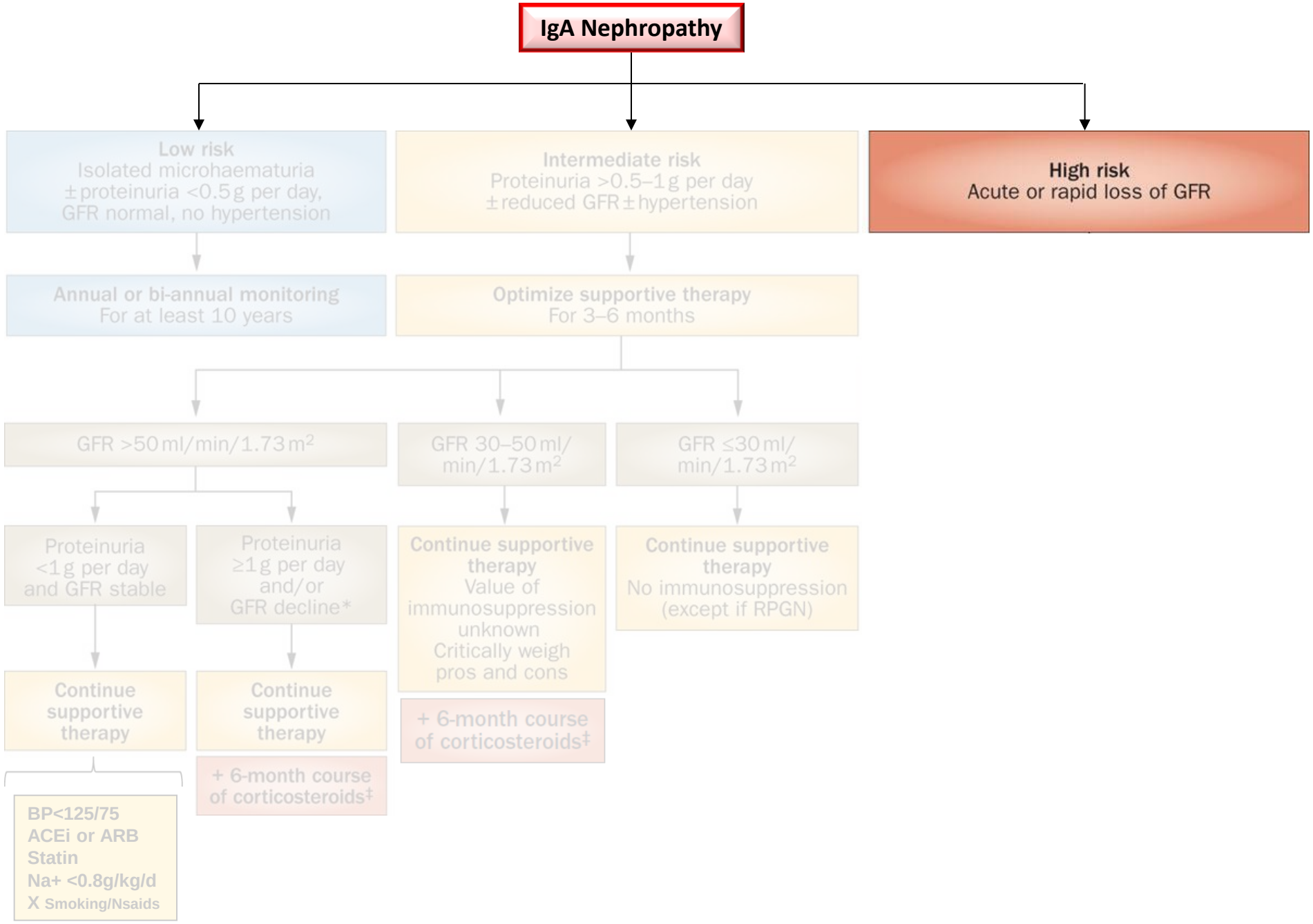
Tesar V, et al. JASN 2015

Points of note

- Retrospective nature
- Unknown corticosteroid dosing regimens, frequent combination of corticosteroids with other immunosuppressive therapies
- Potential for unmeasured and selection bias
- Legacy effect, whereby even a short course of corticosteroids (≤ six months) exerts long-term effects that extend well beyond the treatment duration



Modified from Floege & Feehally. Nat Rev Nephrol 2013



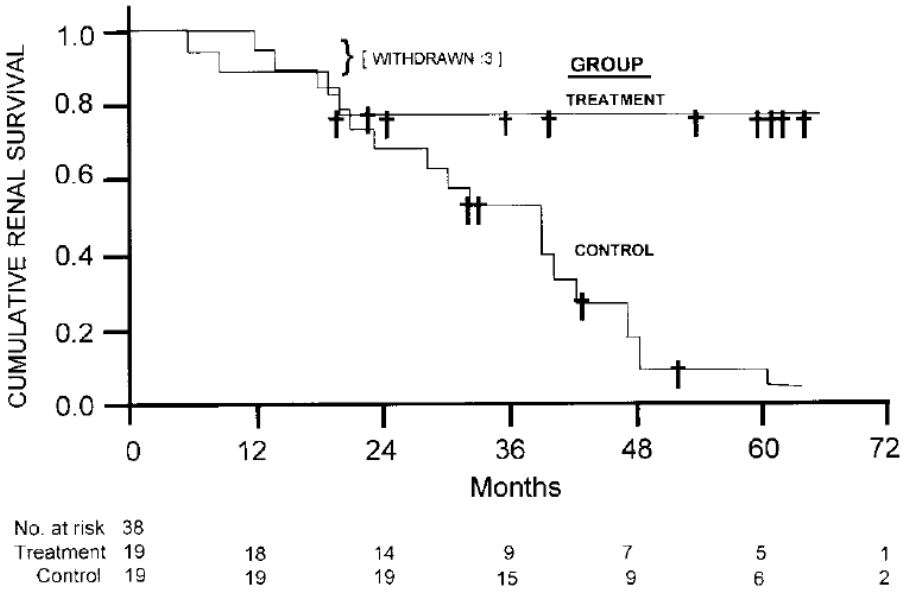
Modified from Floege & Feehally. Nat Rev Nephrol 2013

Crescentic IgAN

- Reserved for cases in which cellular crescents are present in at least 50% of glomeruli, in the context of rapidly deteriorating renal function.
- Response to immunosuppression / prognosis less favourable than in the crescentic nephritis seen in AAV
- No results from RCTs are available to guide the treatment of crescentic IgAN, although a number of observational studies support a role for immunosuppression
- An appropriate regimen is CTX and high-dose corticosteroids, followed by maintenance therapy with low-dose corticosteroids and azathioprine (KDIGO Guideline 2012; 2D Evidence)

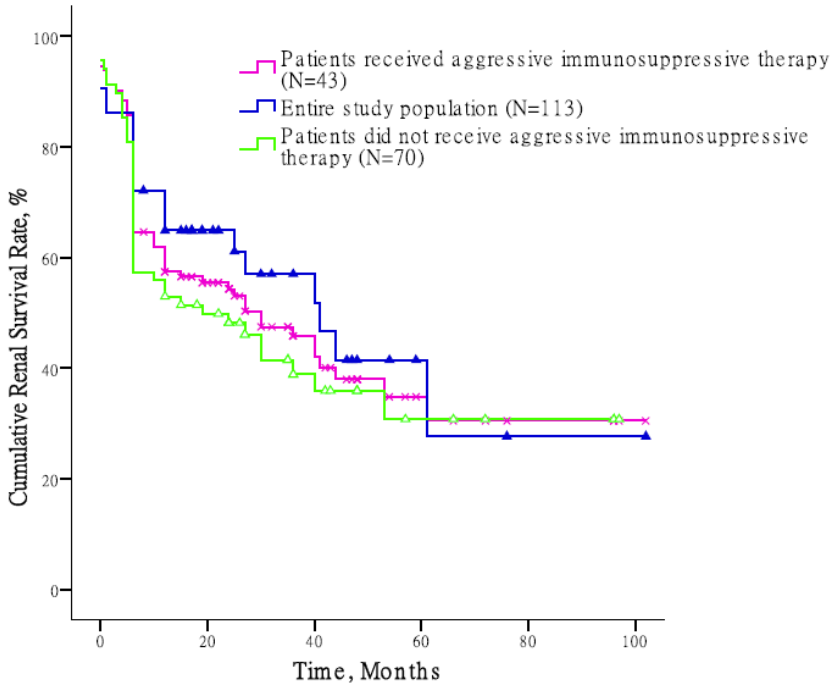
Renal survival of progressive / crescentic IgA nephropathy

European



Ballardie FW, et al. JASN 2002

Chinese

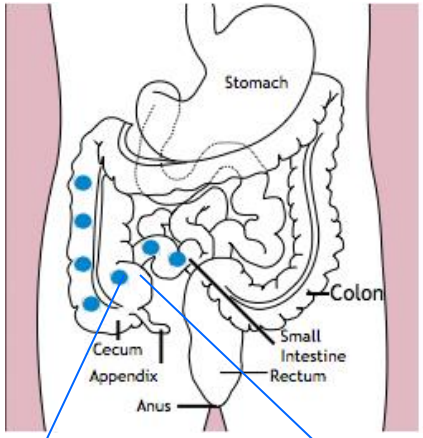


Lv J, et al. JASN 2013

Novel Therapies for the Future

Enteric Budesonide

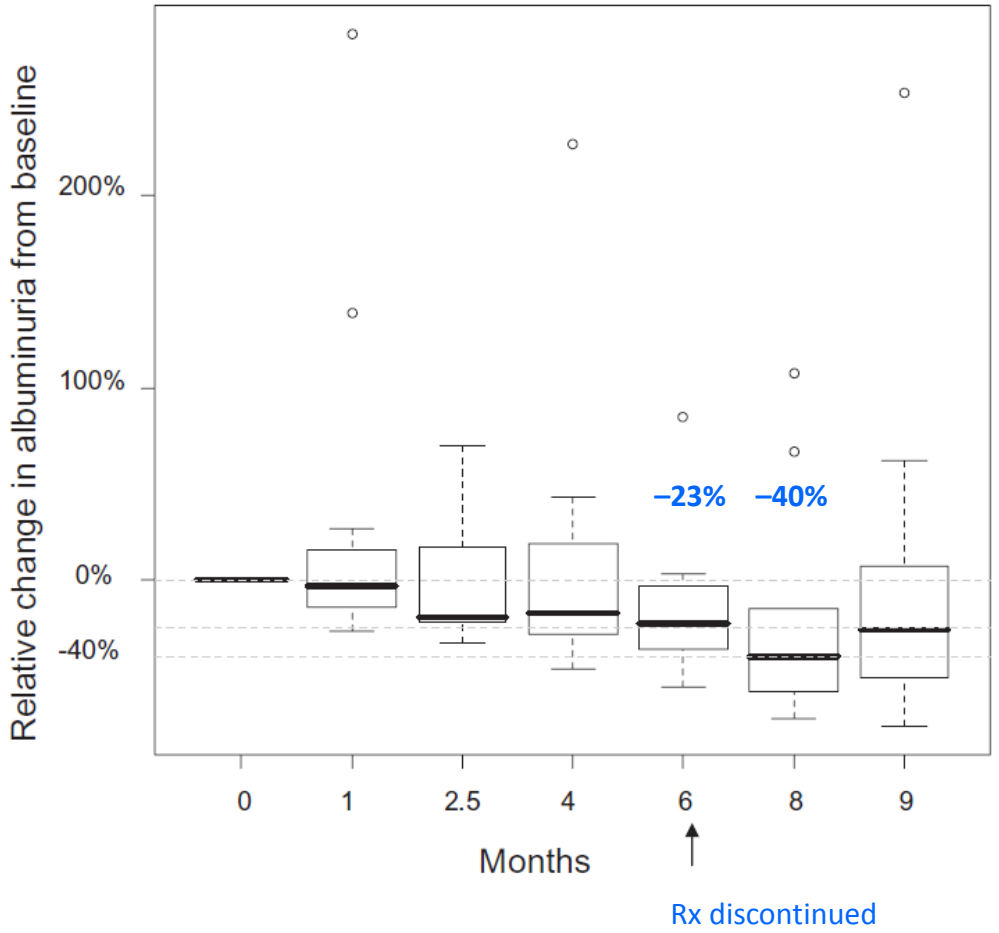
NEFECON, an oral formulation that releases budesonide in the lower ileum and ascending colon GI tract



topical budesonide treatment to the intestinal mucosa and in particular the highly immuno-active Peyer's patches

Eneteric Budesonide

Nefecon 8 mg/day was given to 16 patients with IgAN for 6 months, followed by a 3-month follow-up period.



Smerud HK, et al. NDT 2011

NEFIGAN

The Effect of NEFecon® in Patients With Primary IgA Nephropathy at Risk of Developing ESRD

Inclusion:

UPCR > 0.5g/g or Proteinuria > 0.75 g/day & eGFR > 50 ml/ml

750 patients:

A: Support care + placebo

B: Support care + Nefecon 8 mg/d

C: Support care + Nefecon 16 mg/d

Primary outcome:

Change from baseline in urine protein-creatinine ratio at 9 months

Study completed in Sept 2015

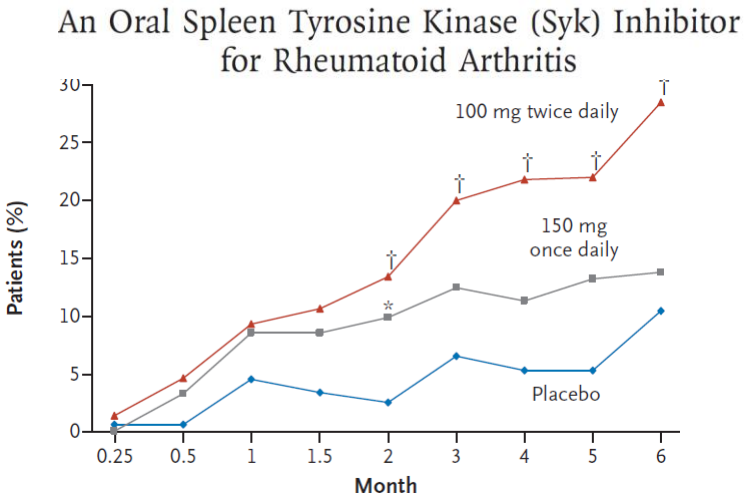
NEFIGAN – Major Results

- Reduced UPCR vs placebo at 9 months
  - Placebo: no change
  - Nefecon: – 25 to 30%
- Halted decline in eGFR vs placebo at 9 months
  - Placebo: – 10%
  - Nefecon: no change
- No difference in the efficacy between the 2 doses

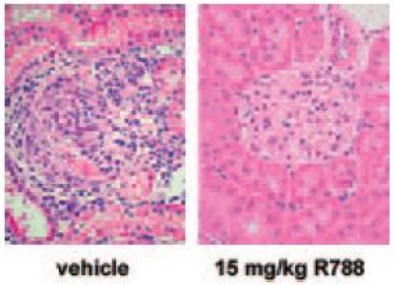
High-impact Clinical Trials Session,
Kidney Week, San Diego, 7 Nov 2015

Spleen Tyrosine Kinase Inhibition

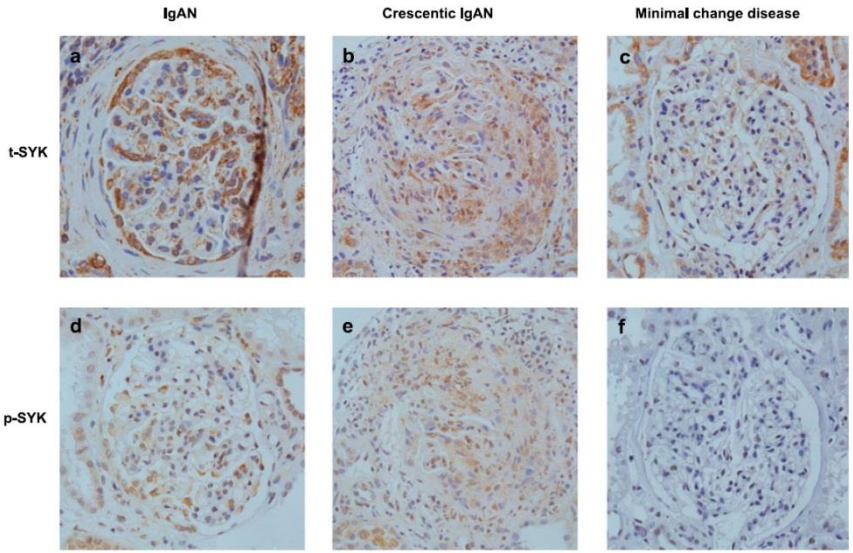
Syk signaling mediates maturation and survival of the B cell lineage

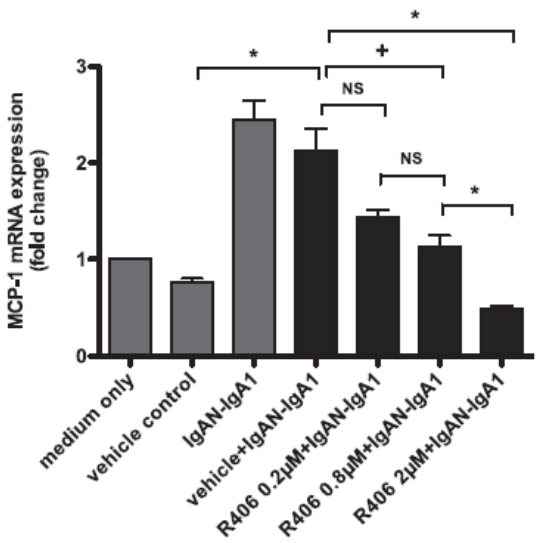


Weinblatt ME, et al. NEJM 2010



Amelioration of NTN in Wistar-Kyoto rats
Smith et al, JASN 2010





Kim MJ, et al. J Immunol 2012

SIGN

Syk Inhibition for GlomeruloNephritis

Safety and Efficacy Study of Fostamatinib to Treat Immunoglobin A (IgA) Nephropathy

Inclusion:

Proteinuria > 1 gm/day at diagnosis of IgA nephropathy and Proteinuria > 0.50 gm/day at the second Screening Visit

Central adjudication of recent kidney biopsy

75 patients:

A: Support care + placebo

B: Support care + **Fostamatinib** 100 mg/d

C: Support care + **Fostamatinib** 150 mg/d

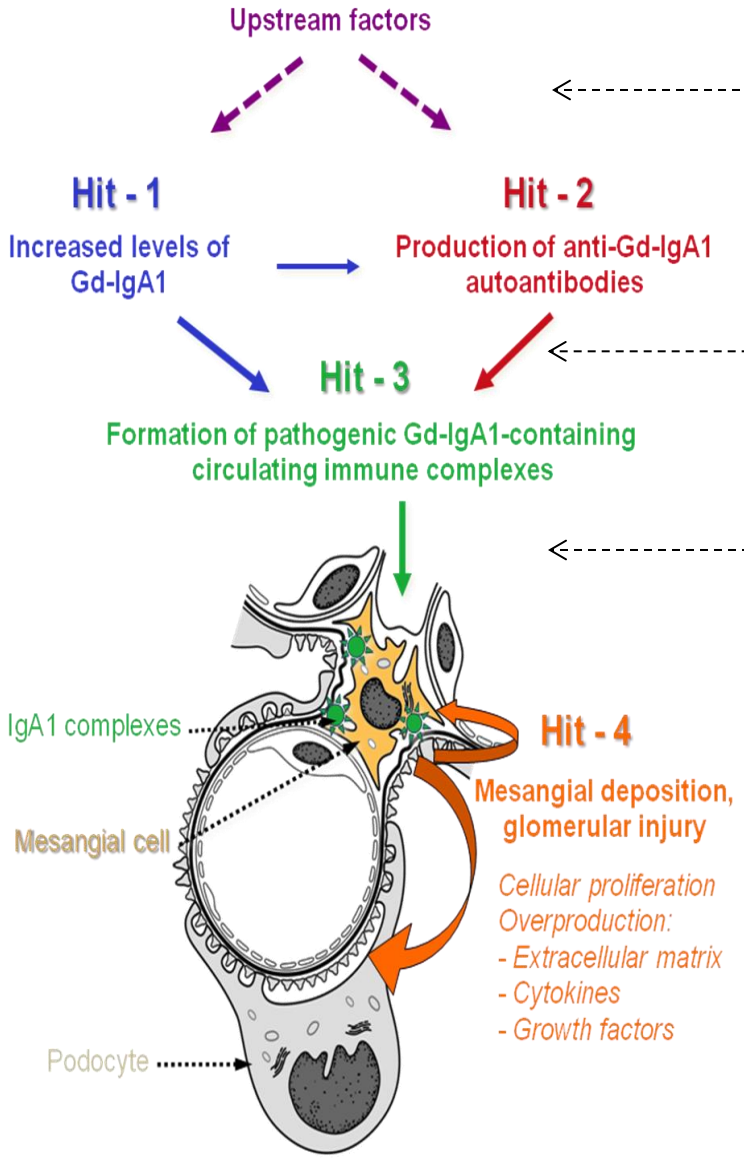
Primary outcome:

Change from baseline in urine protein-creatinine ratio at 24 weeks

Secondary outcome:

Change in histology

Future therapeutic options based on the understanding of disease pathogenesis

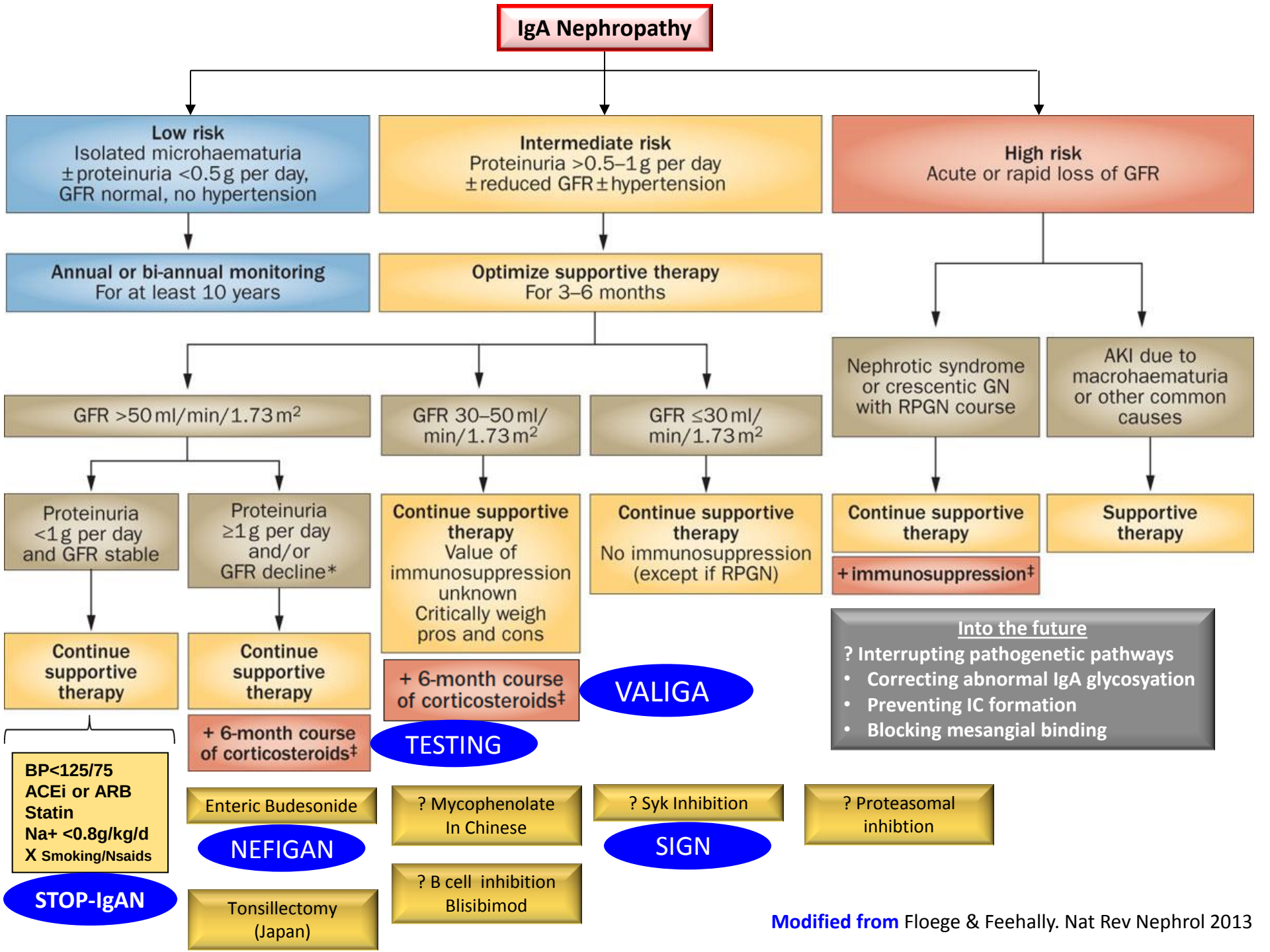


Correction of abnormal glycosylation and sialylation of Gd-IgA1 molecule

Targeting the activation of immune complex

Blockade of attachment of Gd-IgA1-containing complexes to mesangial cells

Lai KN, Tang SC, et al. Nat Rev Dis Primers (in press)



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