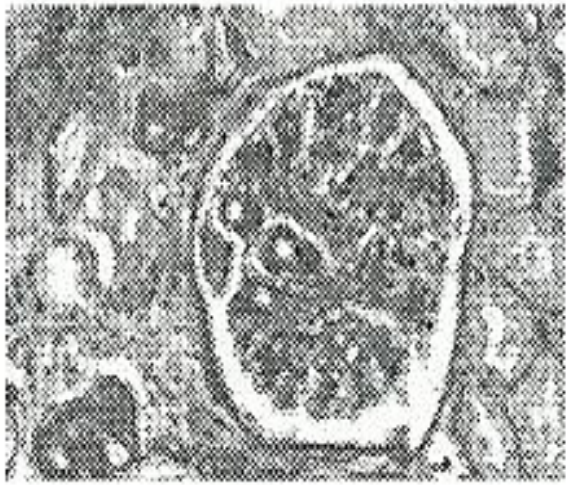
IgA nephropathy

Ιωάννης Γ. Γριβέας, MD, PhD

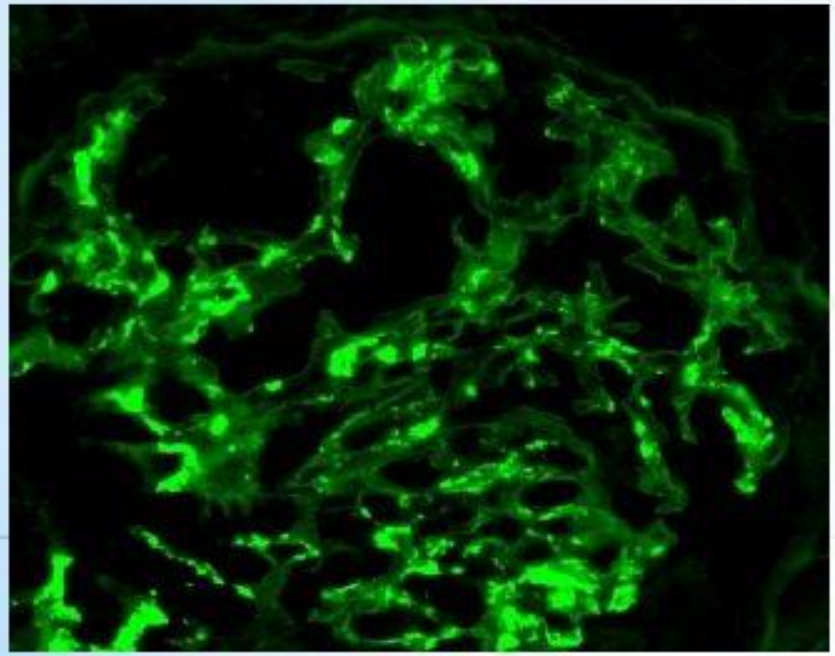
athens-NEPHROLOGY

Definition



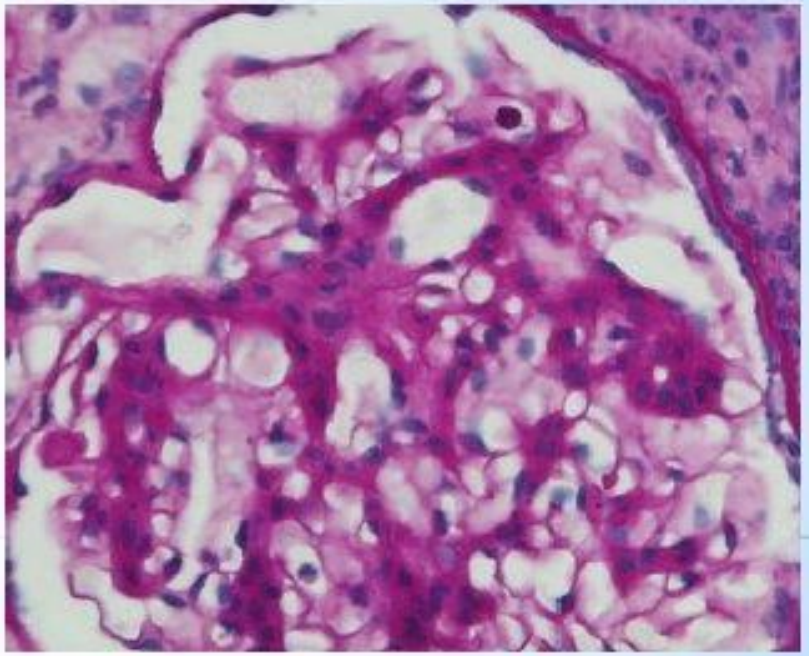
- Dominant or Co-dominant IgA deposition in glomeruli

IgA1 (with C3, IgG, or IgM)
Mesangial Immunodeposits



Immunofluorescence

Expansion of Extracellular Matrix
Proliferation of Mesangial Cells



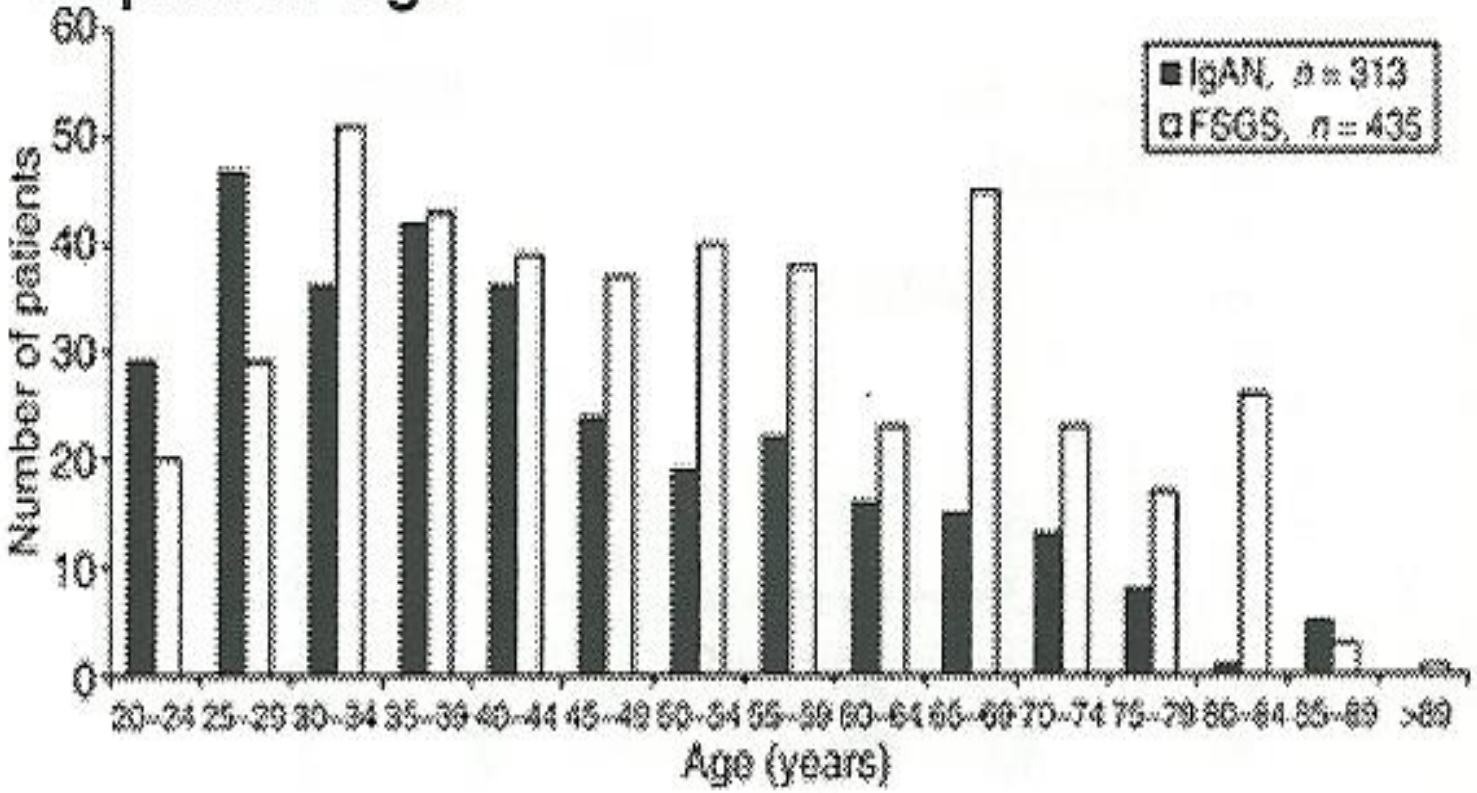
Periodic acid-Schiff stain

Epidemiology

- "Most common idiopathic GN in the world"

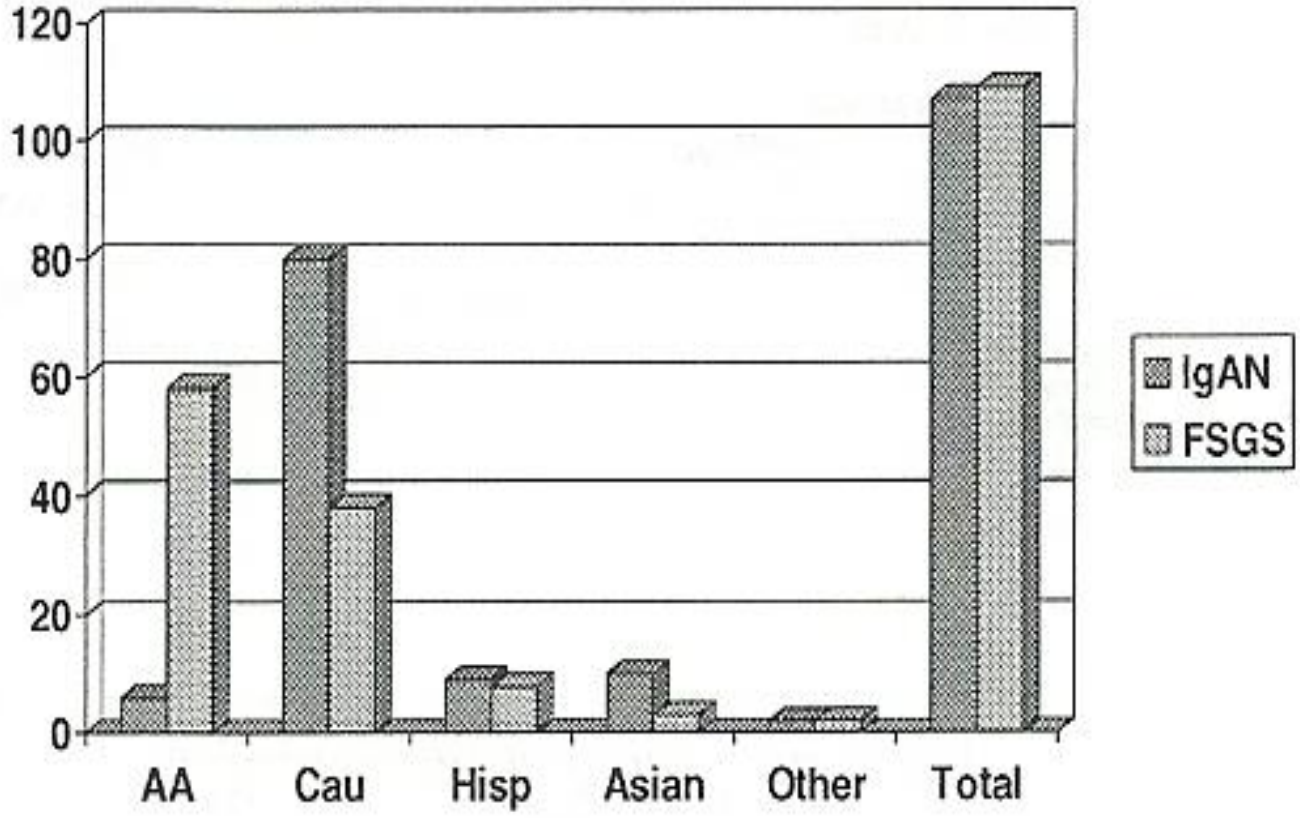
Prevalence of IgAN

Impact of Age



Nair R.. Kidney International (2006) **69**, 1455–1458

Prevalence of IgaN
Impact of Race



Nair R.. Kidney International (2006) **69**, 1455–1458

IgA Nephropathy

- Most commonly presents with bloody urine that occurs **ONE** to **THREE DAYS** after the onset of an upper respiratory infection.
- Urinalysis usually shows erythrocytes and mild proteinuria.
- Only **BIOPSY** can confirm the diagnosis; immunofluorescence or immunoperoxidase studies detect mesangial IgA deposits.
  - Biopsy is often unnecessary; isolated microscopic hematuria is **NOT** an indication for biopsy.
- Reassess at 6-12 month intervals if the patient is normotensive, has minimal proteinuria, and normal glomerular filtration rate.
- ACEi/ARBs indicated when the patient develops hypertension and/or proteinuria (>0.5 g/day).

Pathogenesis

Definition

Immunoglobulin A nephropathy is defined by the presence of IgA-dominant or co-dominant mesangial immunoglobulin deposits. Lupus glomerulonephritis, which may have IgA dominant or co-dominant deposits, is excluded from this diagnostic category.

Immunoglobulin A nephropathy occurs as :

1- **primary (idiopathic)** disease, as a component of Henoch- Schnlein purpura small-vessel vasculitis,

2- **secondary** to liver disease (especially alcoholic cirrhosis), and associated with a variety of inflammatory diseases including ankylosing spondylitis, psoriasis, Reiter's disease, uveitis, enteritis (e.g., Yersinia enterocolitica infection), inflammatory bowel disease, celiac disease, dermatitis herpetiformis, and HIV infection

Etiology/Pathogenesis

Immunoglobulin A nephropathy probably can result from multiple different etiologies and pathogenic processes, such as :

(1) Abnormal structure and function of IgA molecules.

(2) Reduced clearance of circulating IgA complexes.

(3) Increased affinity for or reduced clearance of IgA deposits from the glomerular mesangium.

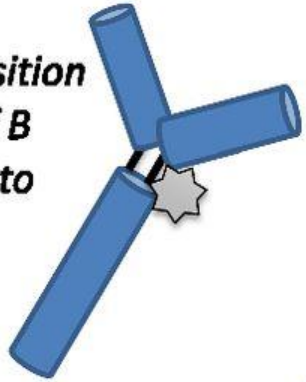
(4) Excessive IgA antibody production in response to mucosal antigen exposure.

(5) Increased permeability of mucosa to antigen.

(6) Combinations of these factors.

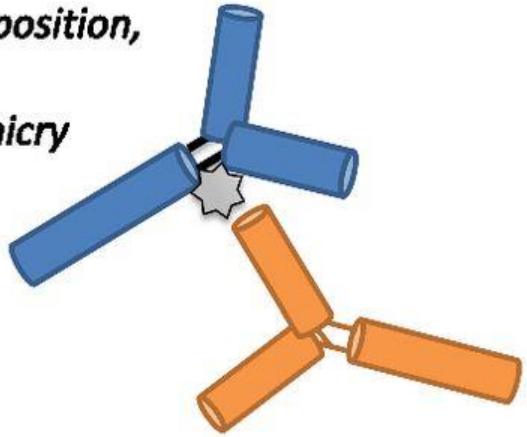
1. Increased circulating levels of Gd-IgA1

- *Genetic predisposition*
- *Mis-trafficking of B cells from mucosal to systemic sites*

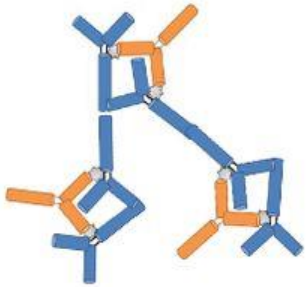


2. Production of Anti-IgA1 antibodies (IgA or IgG)

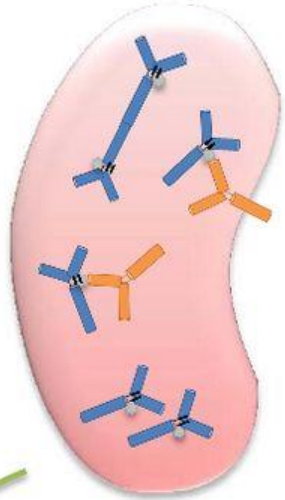
- *Genetic predisposition, HLA haplotype*
- *Molecular mimicry*
- *Viral infection*
- *Food antigens*



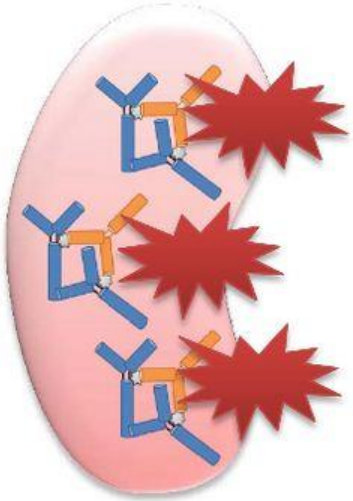
3a. Immune complexes form in the circulation



3b. Immune complexes form *in situ*



4. Immune complexes in the mesangium cause local immune activation & injury



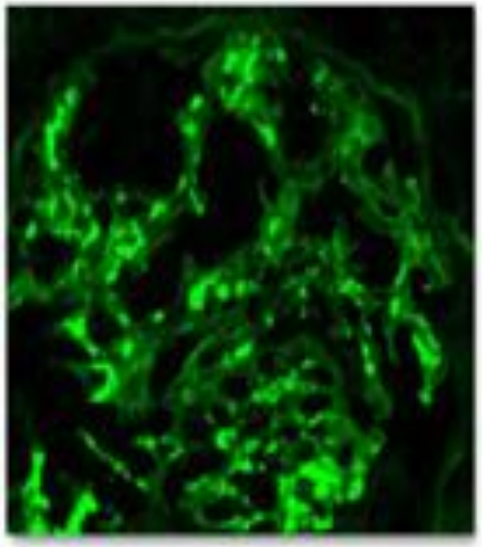
- *Complement activation*
- *Cytokine/chemokine release*
- *Matrix production*
- *Mesangial proliferation*
- *Glomerular sclerosis*
- *Interstitial fibrosis*

Inherited Defect in
B Cells Producing IgA1

"Second Hit"
Viral Infection? Genetic Factor? Somatic Mutation?

Increased Production of Gal-deficient IgA1

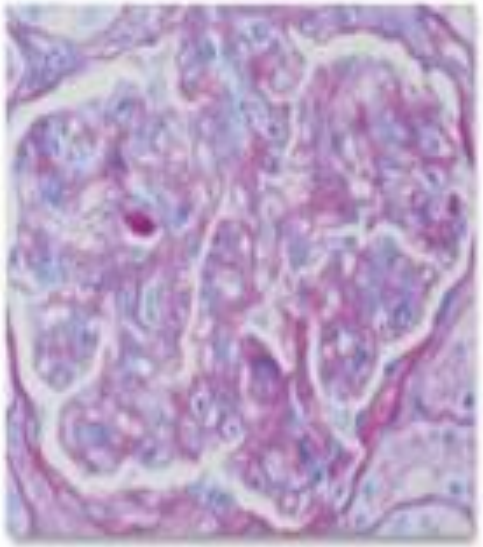
Production of Anti-Glycan Antibodies



Immune complex formation

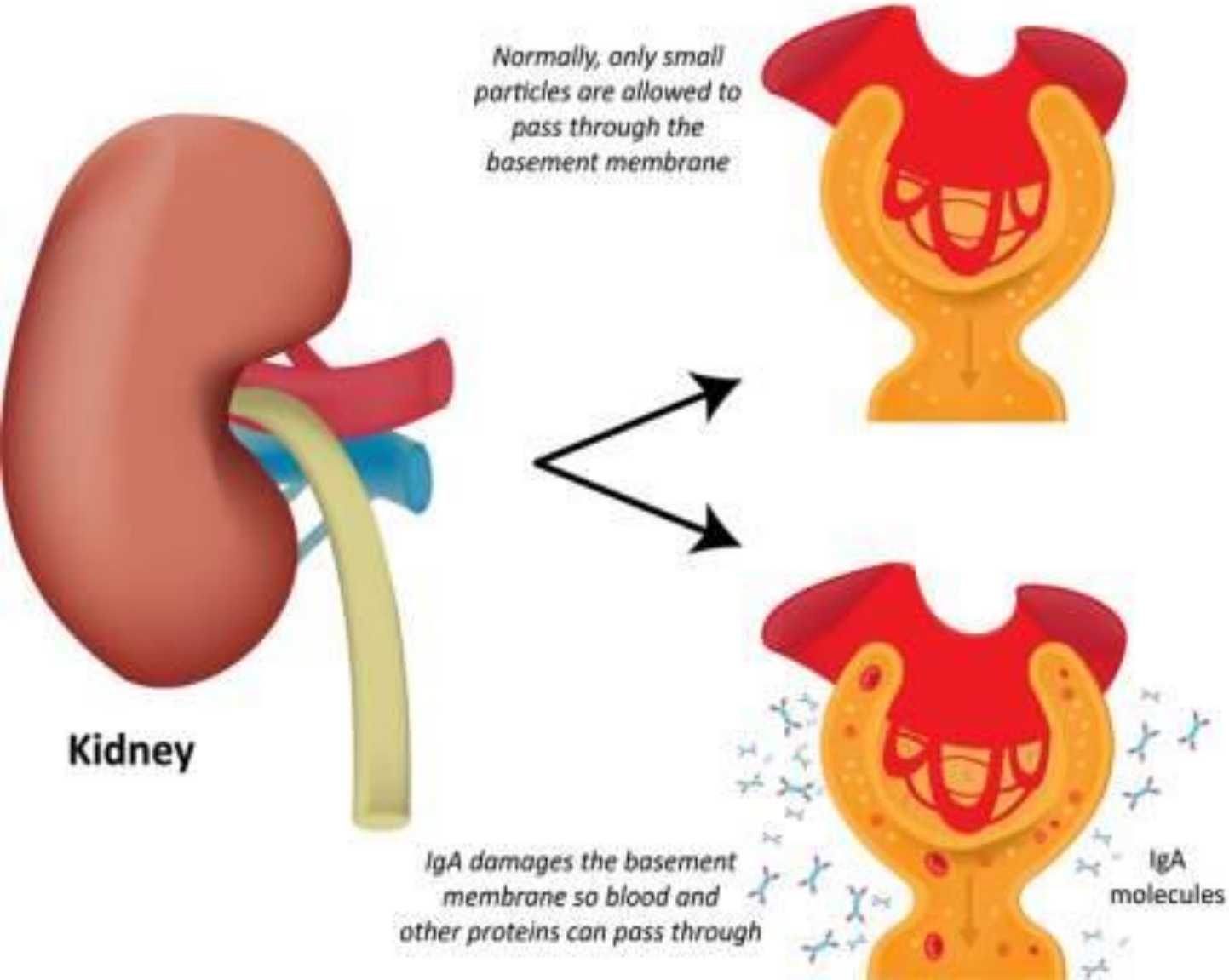
Glomerular deposition

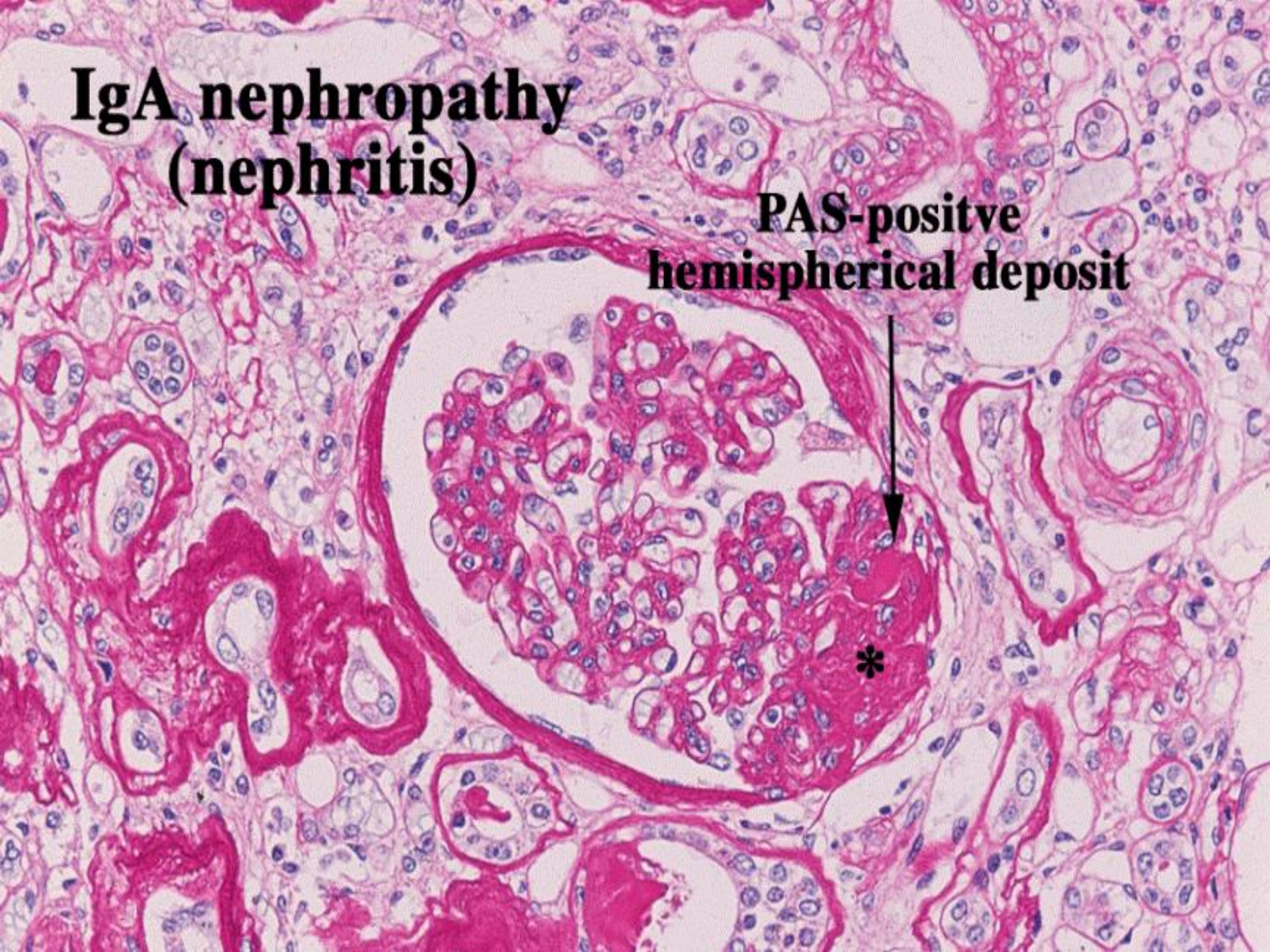
Inflammation, sclerosis

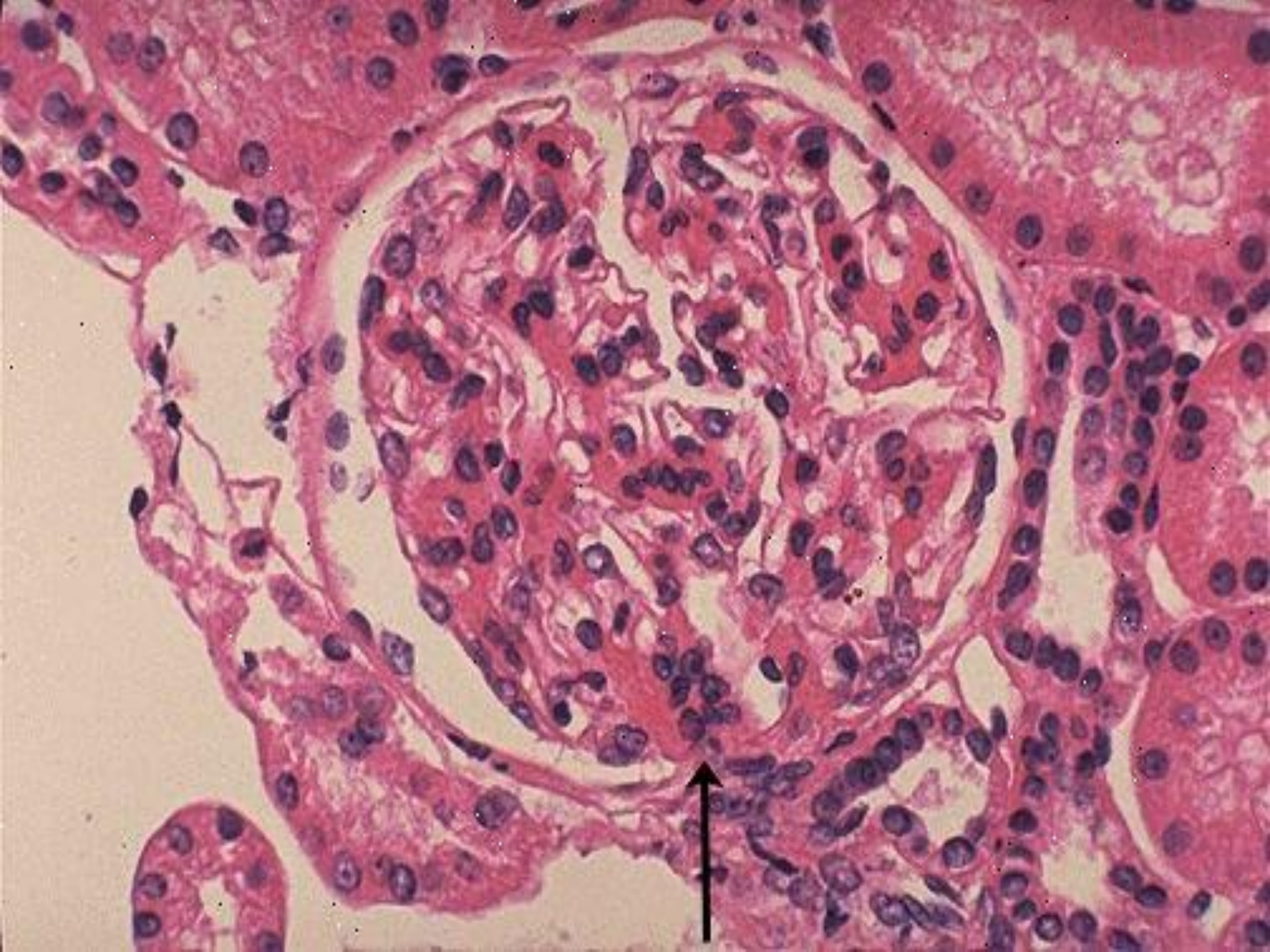


Hematuria, Proteinuria, Renal Failure

IgA Glomerulonephritis

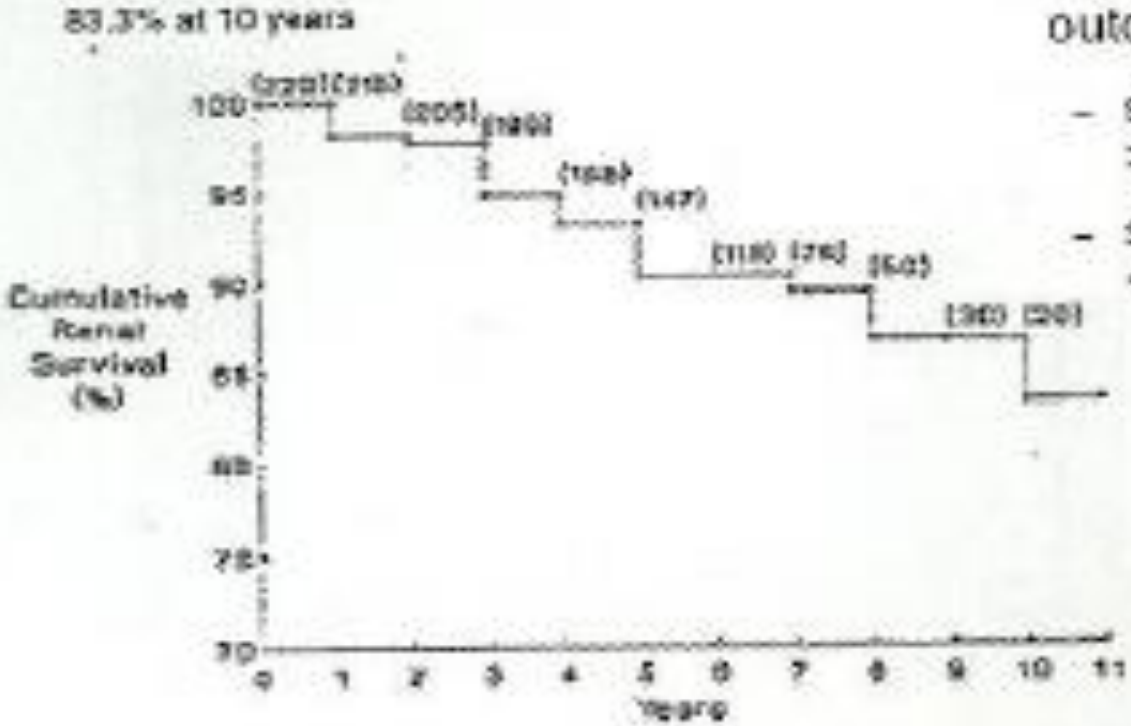



IgA nephropathy
(nephritis)
PAS-positve
hemispherical deposit
*



Renal Survival

MRC Glomerulonephritis Registry



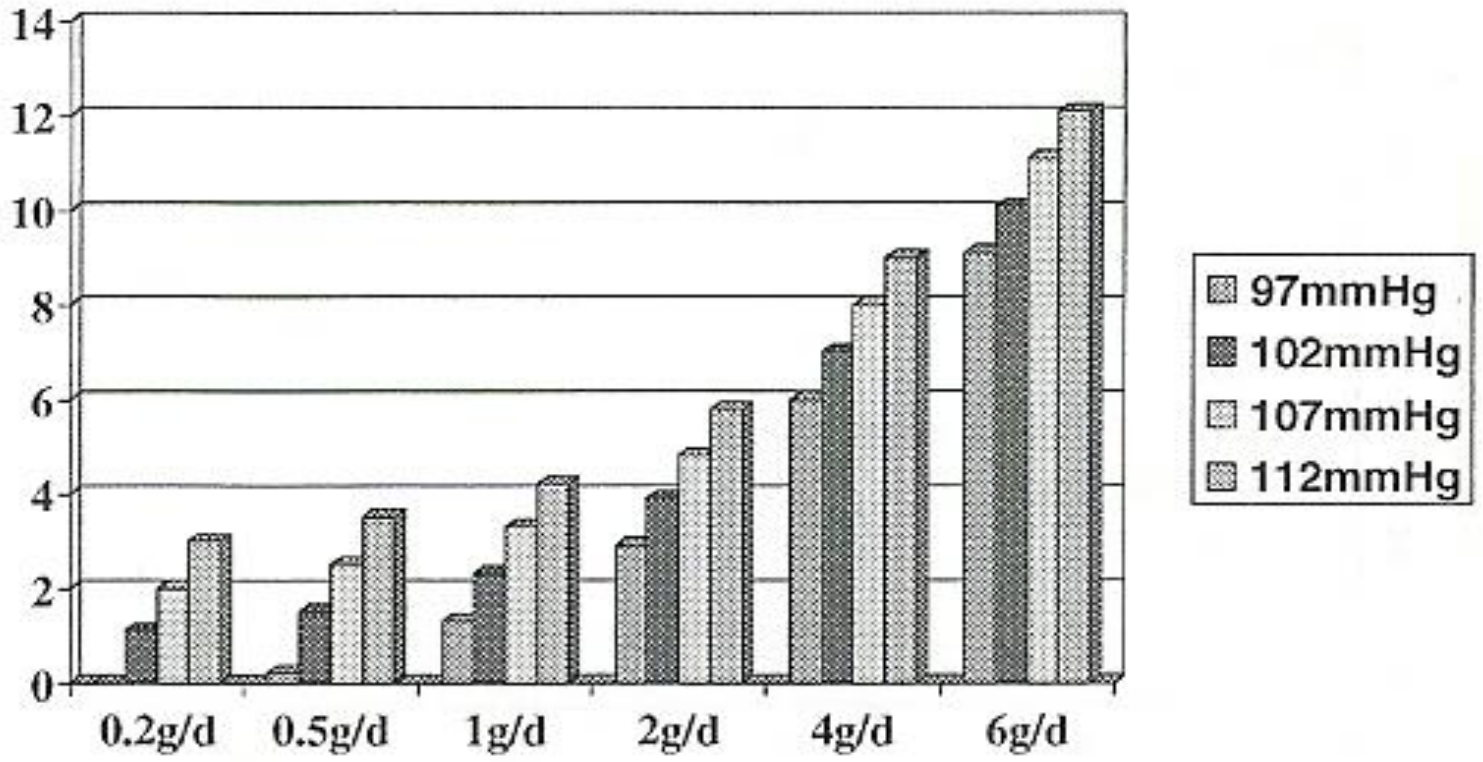
- Predictors of outcome
  - serum creatinine > 120 µmol/l
  - serum albumin <40 g/l

Q J Med 1992; 84: 619-627

Prediction of Progression in IgAN in 298 Pts

Toronto Glomerulonephritis Registry

Δ GFR Prediction



Bartosik, et al AJKD 38:728-735, 2001

Parameter	Regression Coefficient	Standardized β Coefficient
Intercept	1.57	
Urinary protein excretion at follow-up (g/d)	−0.133	−0.445
MAP at follow-up (mm Hg)	−0.0163	−0.277

Patient B over 2 years of observation has an MAP of 107 mm Hg (blood pressure, 140/90 mm Hg) and a urine protein excretion of 4 g/d. His rate of progression (slope) would be calculated as:

$$\text{Slope} = mx + nz + b$$

$$= [-0.13 \times 4] + [-0.016 \times 107] + 1.57$$

$$= -0.66 \text{ mL/min/mon}$$

$$= -7.9 \text{ mL/min annually}$$

Point of No Return ?

- "Point of no Return" is the level of renal function where no form of specific treatment will improve renal function or forestall eventual progression to ESRD
- Values vary between a Scr of 2.0 to 3.0mg/dL (eGFR=30-35ml/min-Stage 4 CKD)

Scholl U. Clin Nephrol. 1999 Nov;52(5):285-92
Komatsu et al J Nephrol. 2005 Nov-Dec;18(6):690-5

Definition of IgA Phenotypes for Treatment Purposes

- Asymptomatic hematuria
- Recurrent gross hematuria
- Significant Proteinuria (“>1g”) and/or renal insufficiency
- Rapidly progressive glomerulonephritis
- Nephrotic syndrome with minimal lesions
- Acute Renal Failure
- Henoch Schonlein Purpura

Acute Renal Failure in IgAN

- 3% of 865 IgAN patients
- Associated with macroscopic hematuria and red blood cells in tubules
- 4% patient developing chronic renal failure after a mean follow-up of 65 months.

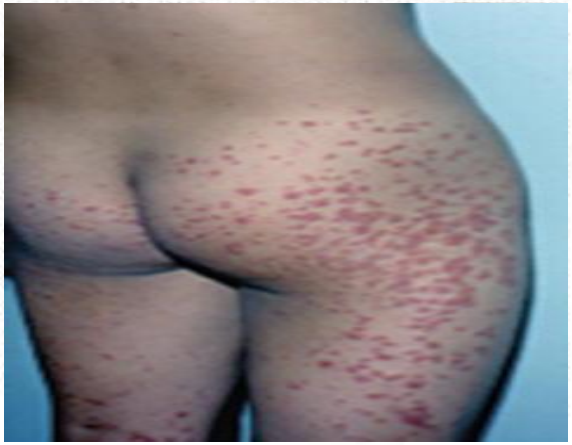
- 25% of 32 pts had SCr >25% of baseline
- Duration of Macroscopic Hematuria > 15 d
  [OR 12.3; 1.06 to 143.5; $P = 0.04$]

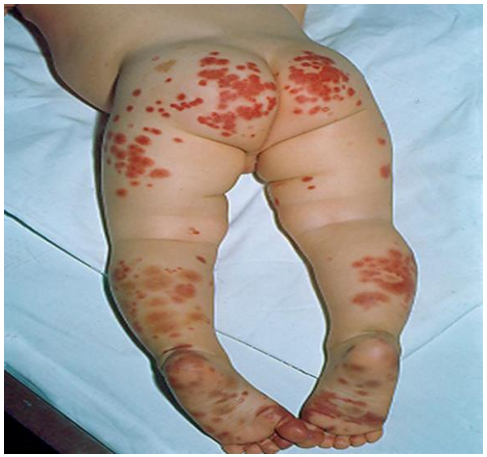
Packham D...Clin Nephrol. 1994 Dec;42(6):349-53

Gutierrez E. Clin J Am Soc Nephrol. 2007 Jan;2(1):51-

Henoch Schonlein Purpura

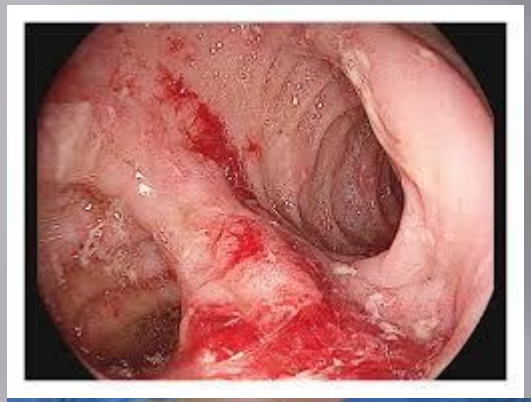
Retrospective analysis of 250 adults

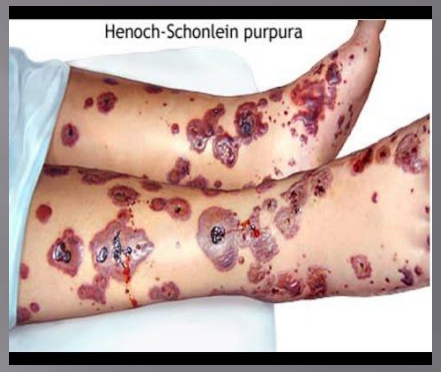


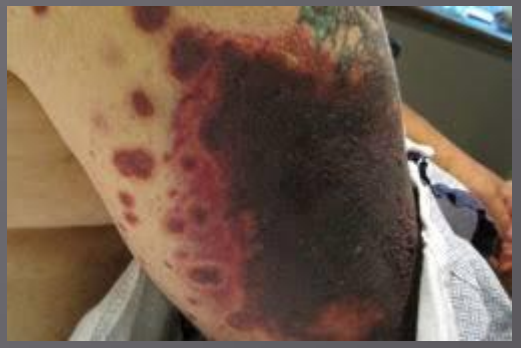


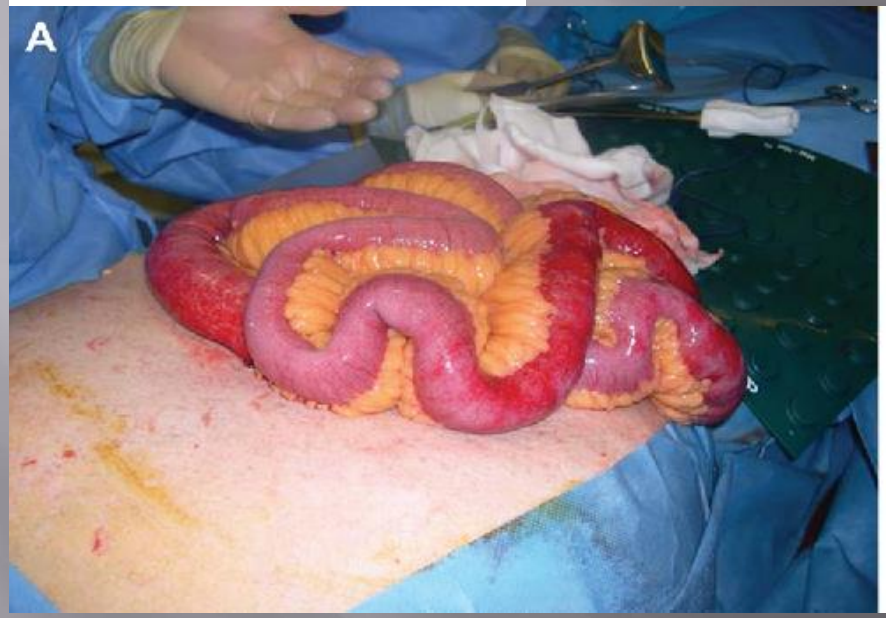
Parameter	Age <30 yr (n = 54)	Age 30 to 60 yr (n = 111)	Age >60 yr (n = 85)	P
Recent history of infection, n = 80	54.7%	28.4%	23.5%	0.0004
Presence of arthritis, n = 153	71.7%	67.9%	48.2%	0.005
Necrotic purpura, n = 87	16.7%	36.8%	44.7%	<0.0001
Serum IgA level (g/L)	3 ± 0.2	4 ± 0.2	5 ± 0.3	<0.0001
CrCl (ml/min)	99 ± 5	93 ± 3	46 ± 3	<0.0001

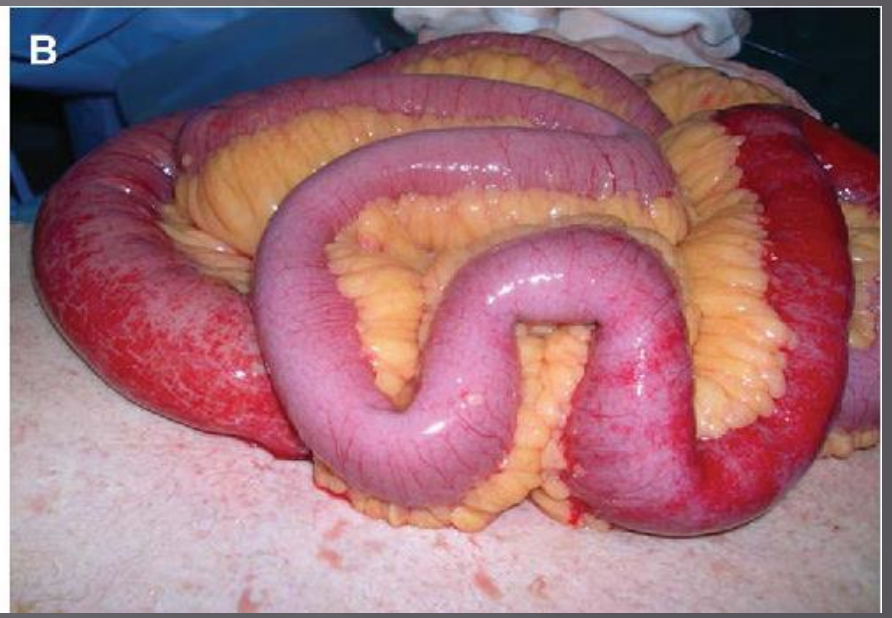
Pillebout …J Am Soc Nephrol 13:1271-1278, 2002

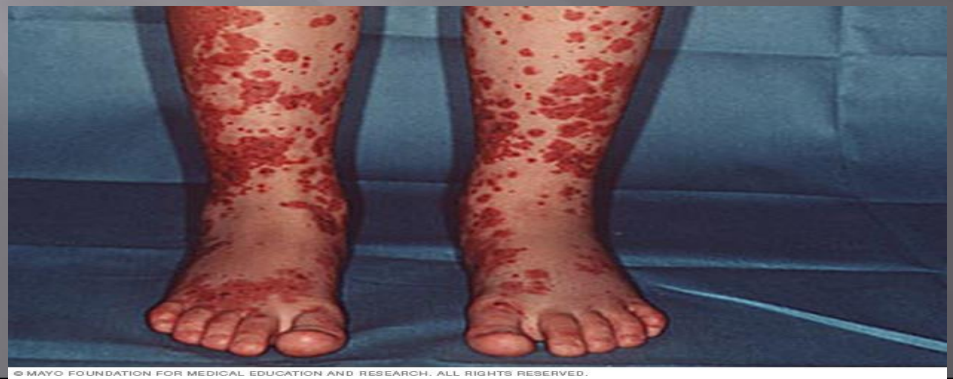


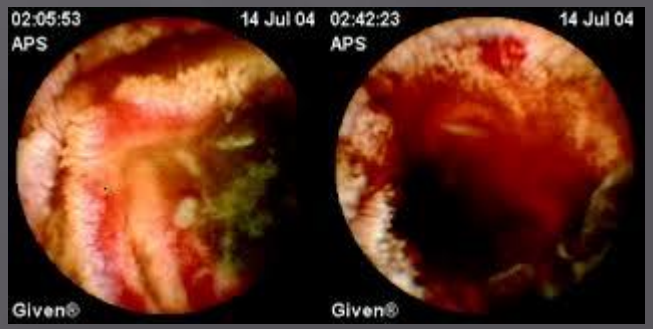






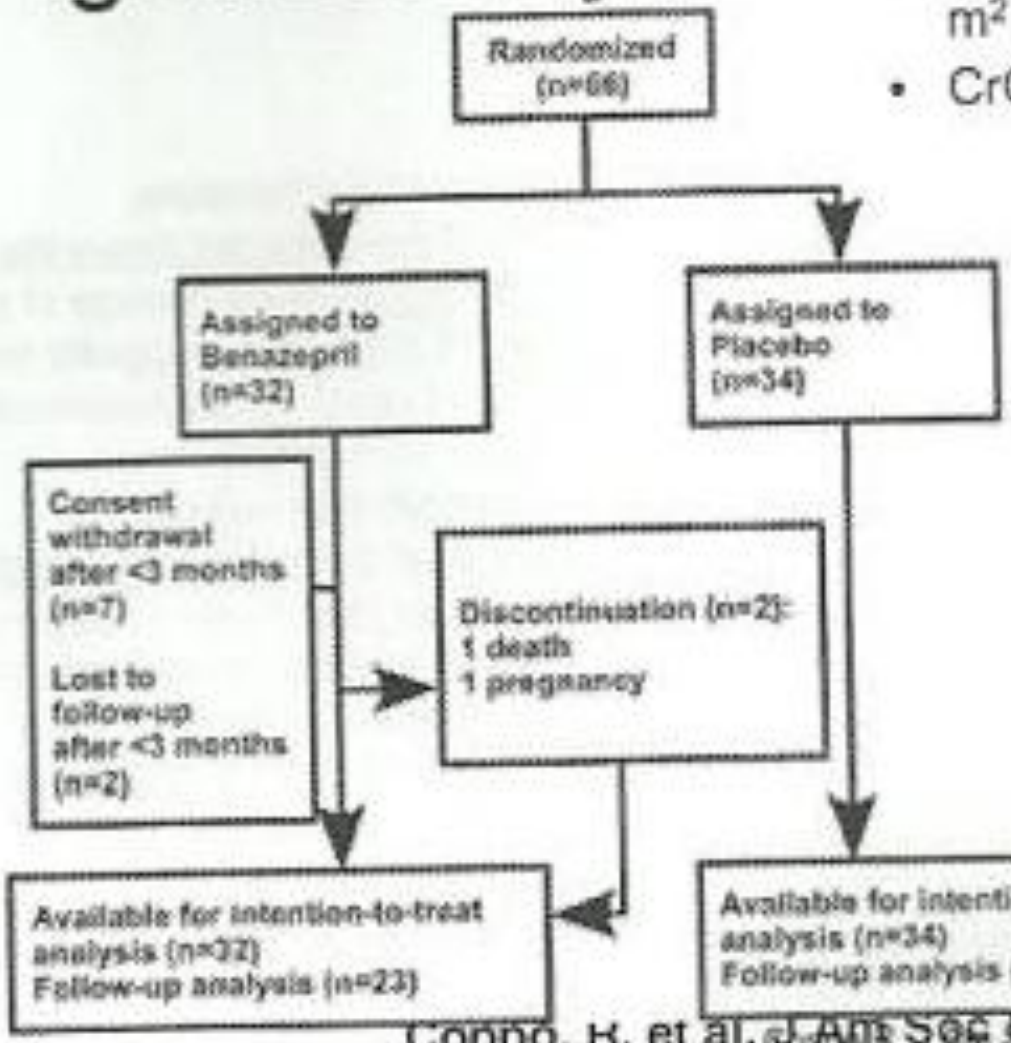






IgACE Study

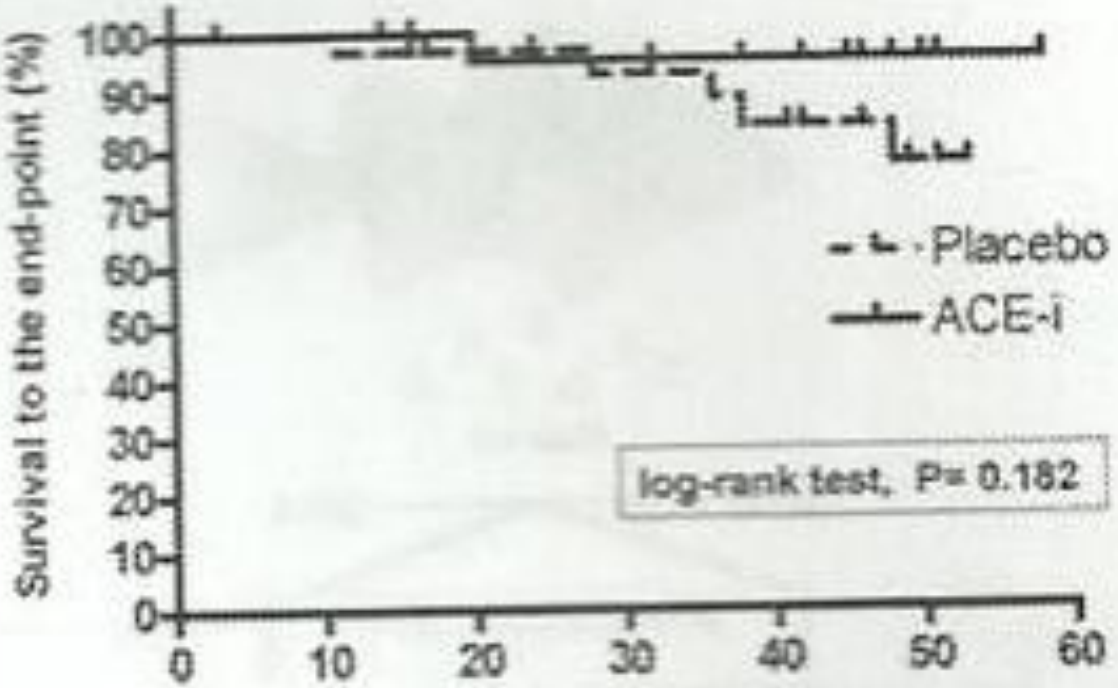
- Age 3 to 35 yrs
- Proteinuria 1 to 3.4 g/d/1.73 m^2
- CrCl >50 ml/min/1.73 m^2



Coppo, R. et al. J Am Soc Nephrol 2007;18:1880-1888

IgACE Study

Survival without end point of 30% reduction of baseline CrCl



Subjects at risk

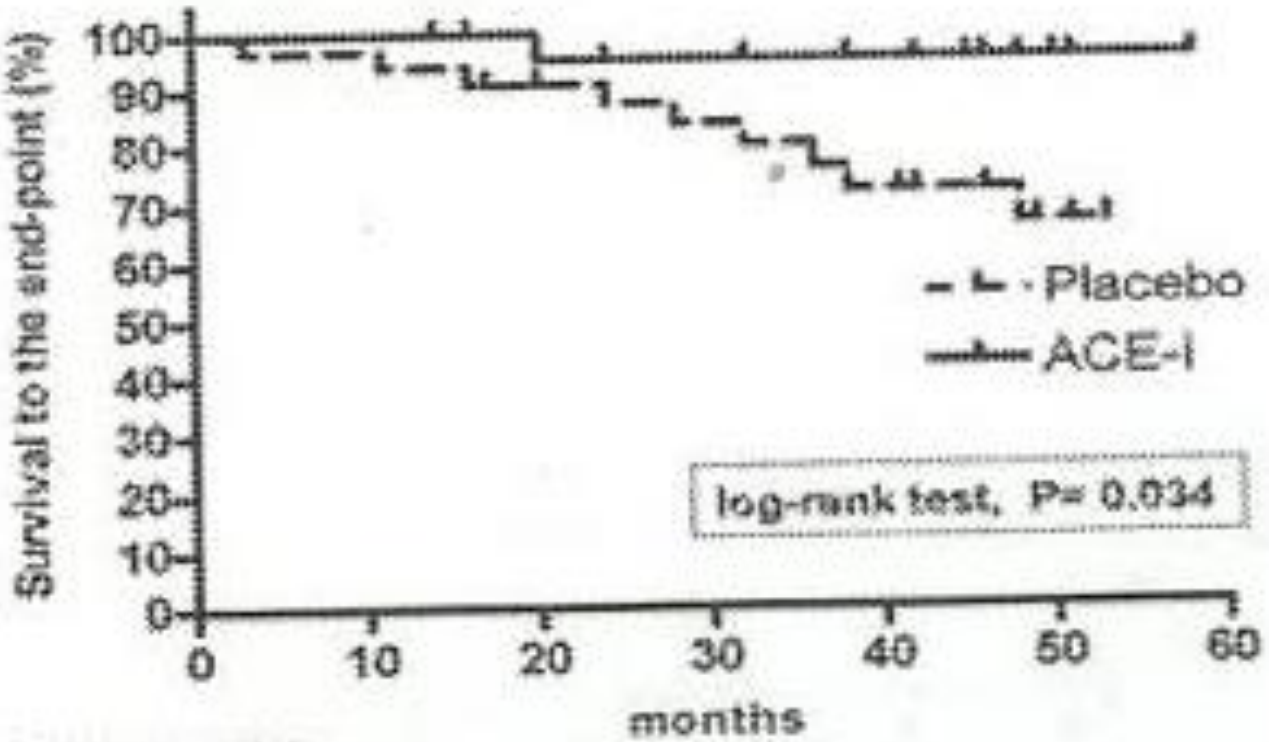
ACEI	32	23	20	17	15	8
PLACEBO	34	32	26	23	16	6

Coppo, R. et al. J Am Soc Nephrol 2007;18:1880-1888

Coppo R. J Am Soc Nephrol 18: 1880-1888, 2007

IgACE Study

Combined end point: 30% reduction CrCl +/- proteinuria >3.5 g



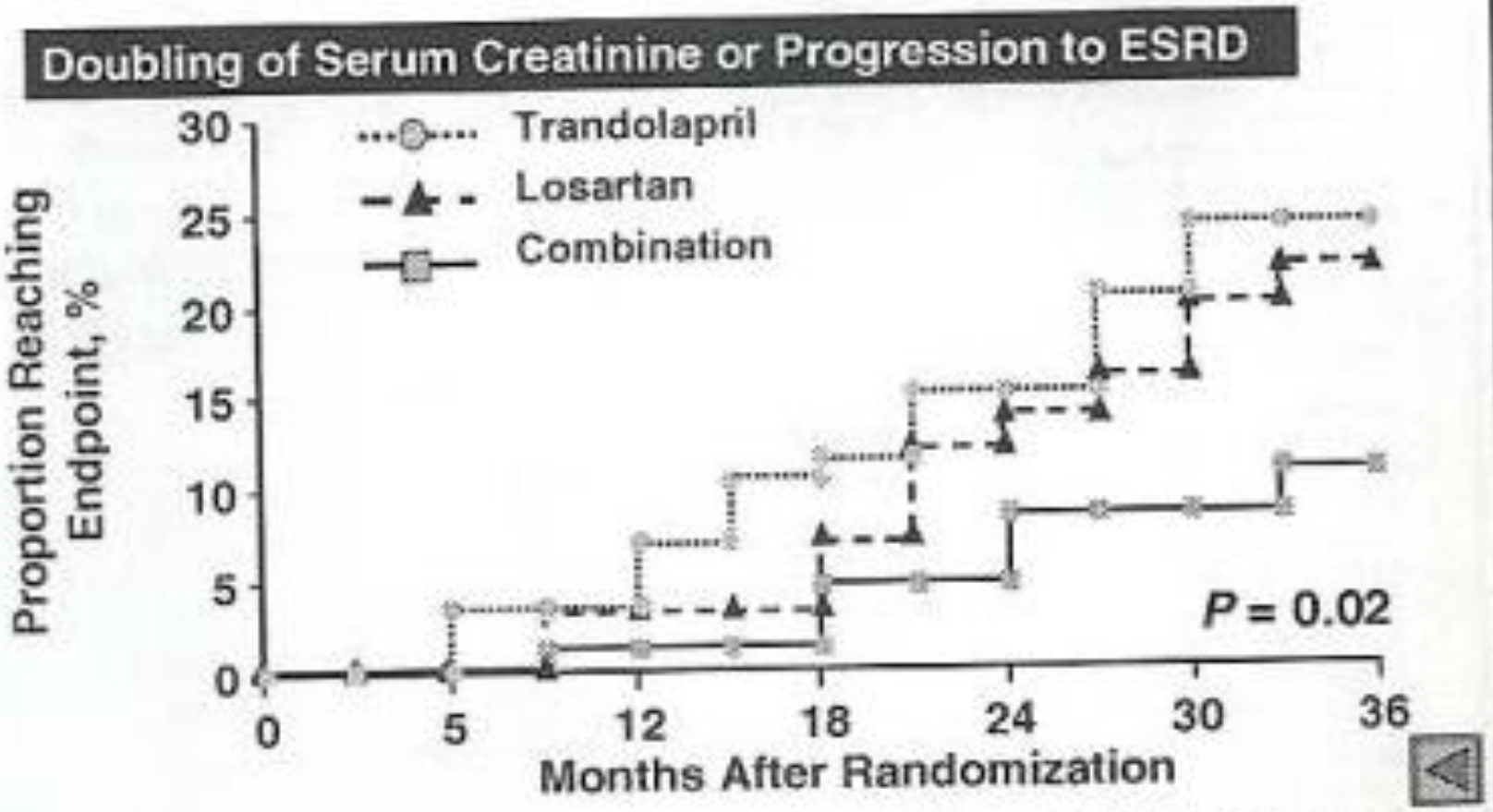
Subjects at risk

ACEI	32	23	21	17	15	8
PLACEBO	34	32	27	24	17	5

Coppo, R. et al. J Am Soc Nephrol 2007;18:1880-1888. 2007

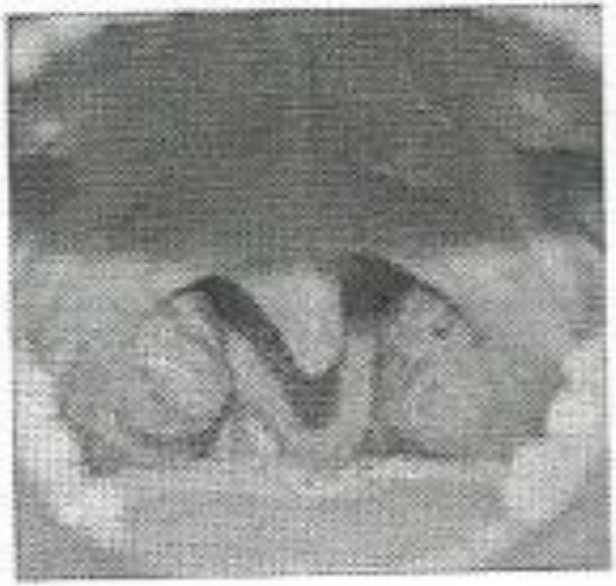
Combination ACE-i/ARB

COOPERATE (Non diabetic glomerular disease- 50% of 263 pts had IgAN)



Nakao N et al. *Lancet.* 2003;361:117–124.

Tonsillectomy



Characteristic of tonsils	IgAN(+)	IgAN(−)
T cell area (T nodules)	Expanded	Not expanded
Reticularization of crypt epithelium	Reduced	Not reduced
IgA cells:IgG cells	>1	<1
Polymeric IgA cells	Increased	Not changed
Polymeric IgA:IgA	Increased	Not changed
Follicular dendritic cells	IgA1+	IgA1−
J chain mRAN-positive cells	Increased	Not changed
Adhesion molecules CD31, CD54	Increased	Not changed
CD5+ B cells	Increased	Not changed

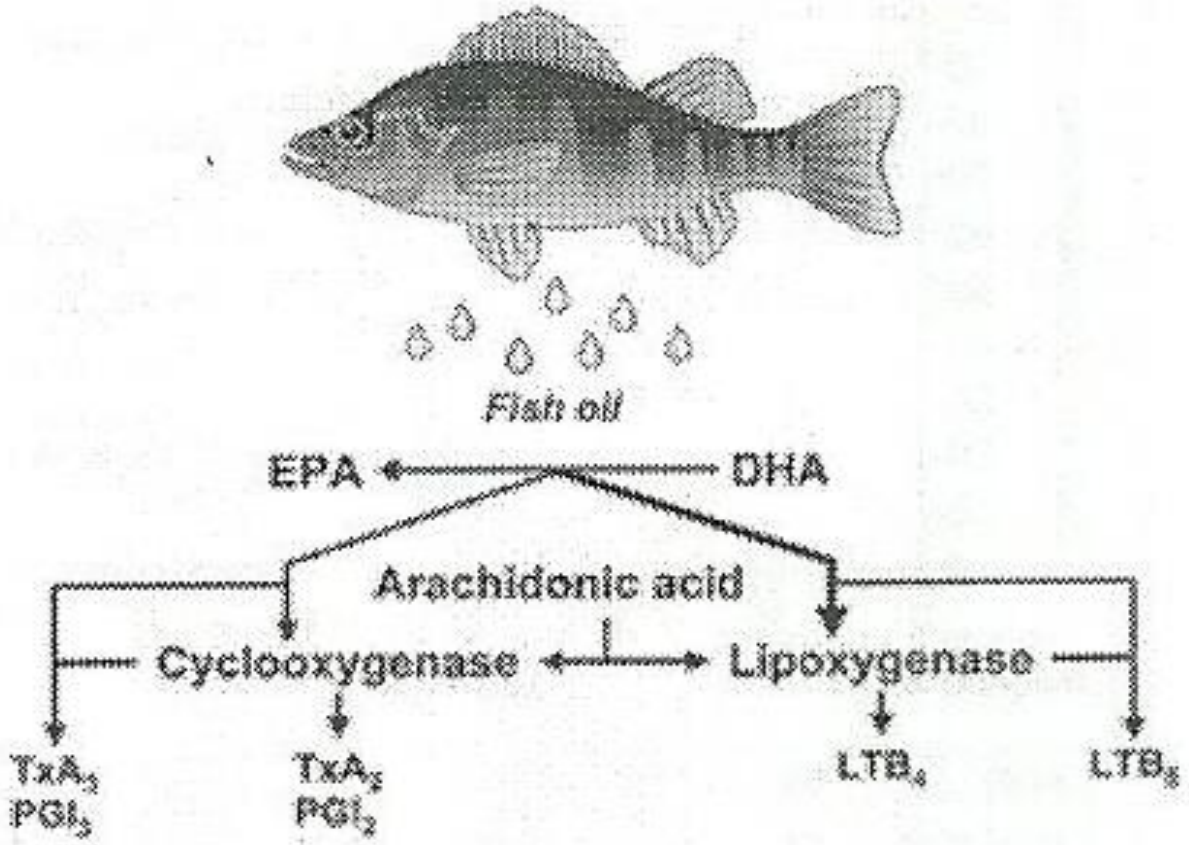
Xie Y...Kidney Int. 2004 Apr;65(4):1135-44.

Pulse Steroids ±Tonsillectomy

Parameter	24 Mo after Biopsy		
	Group C (*n* = 34)	Group M (*n* = 17)	*p**
Observation period (mo; mean ± SD)			
SBP (mmHg; mean ± SD)	117.5 ± 12.8	120.9 ± 10.0	0.364
DiBP (mmHg; mean ± SD)	73.0 ± 9.1	75.2 ± 8.3	0.438
Patients with BP >140/90 mmHg (*n* [%])	2 (5.9)	0 (0.0)	0.477
Serum creatinine (mg/dl; mean ± SD)	0.86 ± 0.22	1.01 ± 0.91	0.517
Patients with 100% increased sCr (*n* [%])	0 (0.0)	1 (6.7)	0.306
Disappearance of UP (*n* [%])	26 (76.5)	7 (41.2)	0.013†
Disappearance of UOB (*n* [%])	27 (79.4)	3 (17.6)	<0.001†
Remission of urinary abnormalities (*n* [%])	21 (61.8)	3 (17.6)	<0.001†

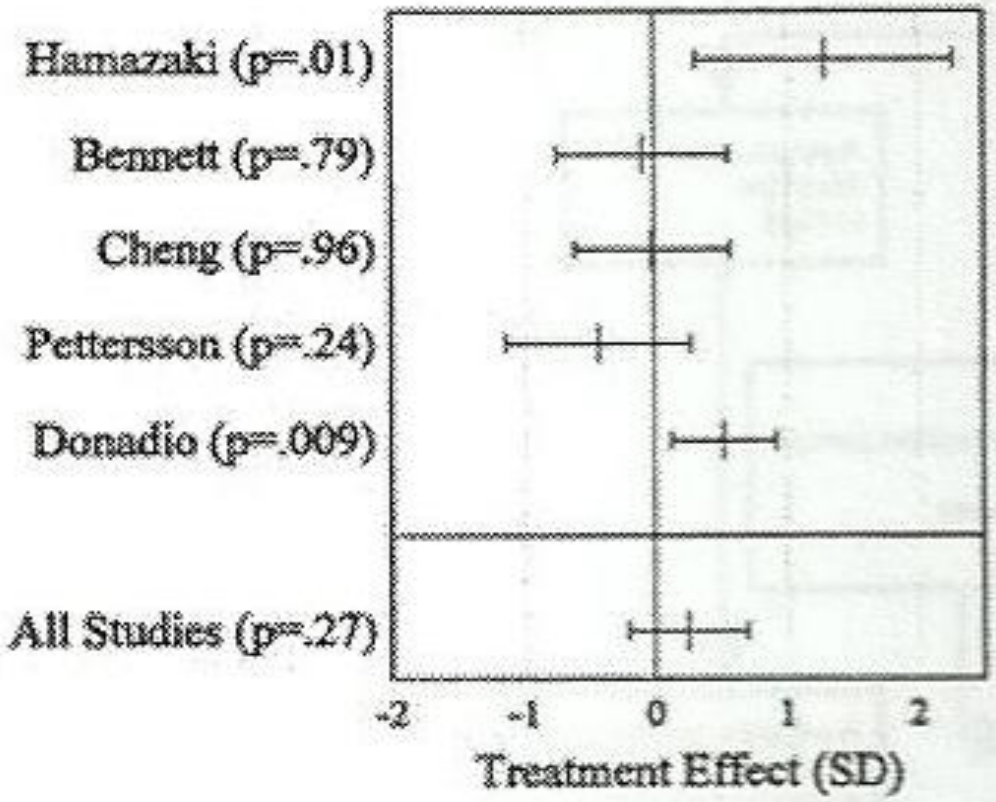
Komatsu H., Clin J Am Soc Nephrol. 2008 May 28.

Omega-3 Polyunsaturated Fatty Acids



J Ren Nutr. 2001 Jul;11(3):122-8

Fish Oil Therapy



The medical literature, therefore, does not prove the efficacy of fish oil therapy in IgA nephropathy, but suggests that an additional placebo-controlled trial is warranted.

A sample-size calculation indicated that such a trial should be larger than those to date or should attempt to increase the treatment effect, perhaps by treating for more than 2 yr or enrolling more severely proteinuric individuals

Dillon JJ. J Am Soc Nephrol. 1997 Nov;8(11):1739-44.

Corticosteroids

Characteristic	Control group (n=43)	Steroid group (n=43)
Clinical		
Duration of IgA nephropathy (months)	24 (4–48)	24 (6–52)
Age (years)	40 (28–51)	38 (26–45)
Urine protein excretion (g/day)	1·9 (1·4–2·4)	2·0 (1·6–2·4)
Plasma creatinine (µmol/L)	88·4 (79·6–114·9)	97·2 (79·6–114·9)
Creatinine clearance (mL/min)*	87 (72–112)	90 (70–111)
Male/female	31/12	31/12
Hypertension	15	14
Treatment with ACE inhibitors	8	6
Macrohaematuria	17	9
Histological		
Global glomerular sclerosis (%)	14 (5–23)	13 (0–25)
Crescents (%)	6 (0–19)	9 (0–19)
Focal glomerular sclerosis (%)	0 (0–6)	0 (0–7)
Tubular atrophy†	1 (1–2)	1 (1–2)
Interstitial fibrosis†	1 (1–2)	1 (1–2)
Interstitial infiltrate†	1 (0–1)	1 (0–1)
Vascular sclerosis†	1 (0–1)	1 (0–2)
Glomerular score (maximum 3)	2 (1–3)	2 (1–3)
Total score (maximum 21)	7 (4–9)	8 (4–10)

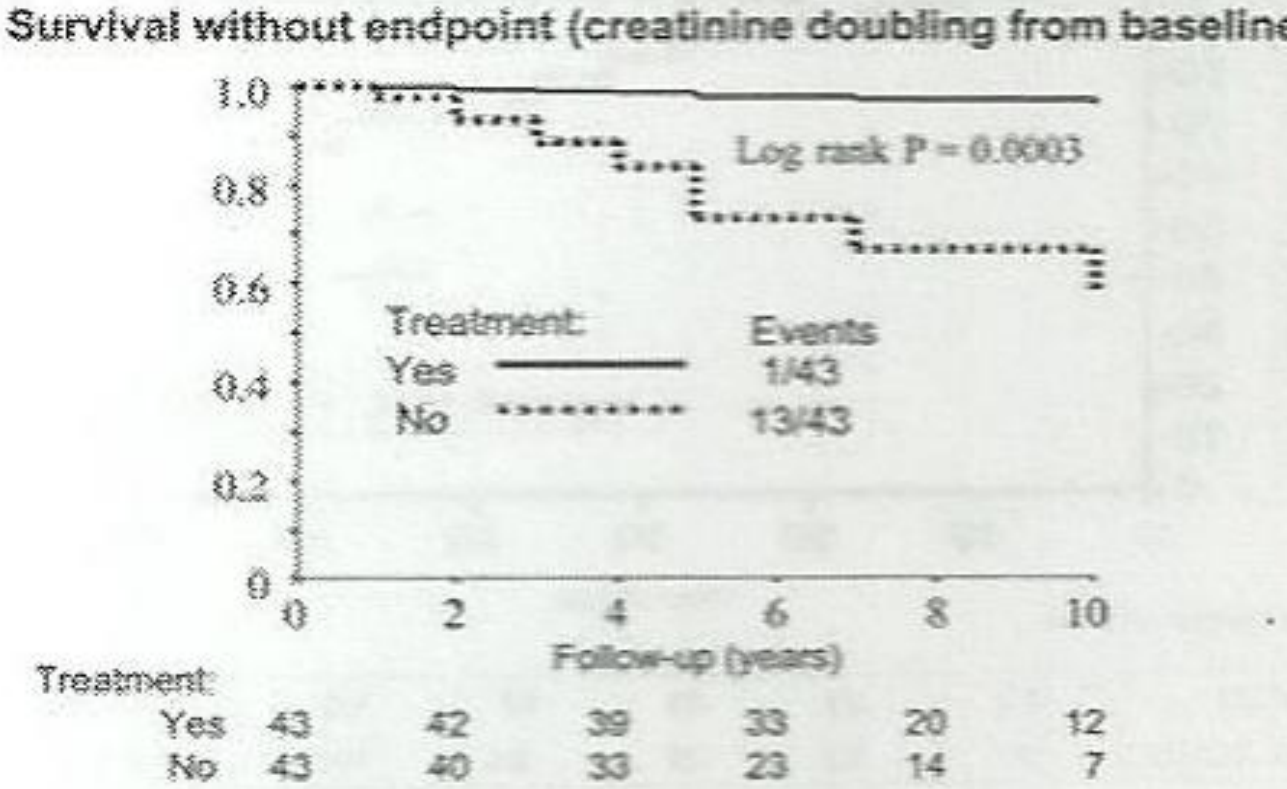
Data are median (IQR) or number of patients.
*Calculated from the Cockcroft formula.[20]
†Lesions scored as 0=absent, 1=focal, 2=multifocal, or 3=diffuse.

- Pulse MP 1g qd x 3
  - 0, 2, 4 months
- Prednisone 0.5mg qod x 6 months
- ACE-I for HTN

Lancet. 1999 Mar 13;353(9156):883-7

Corticosteroids

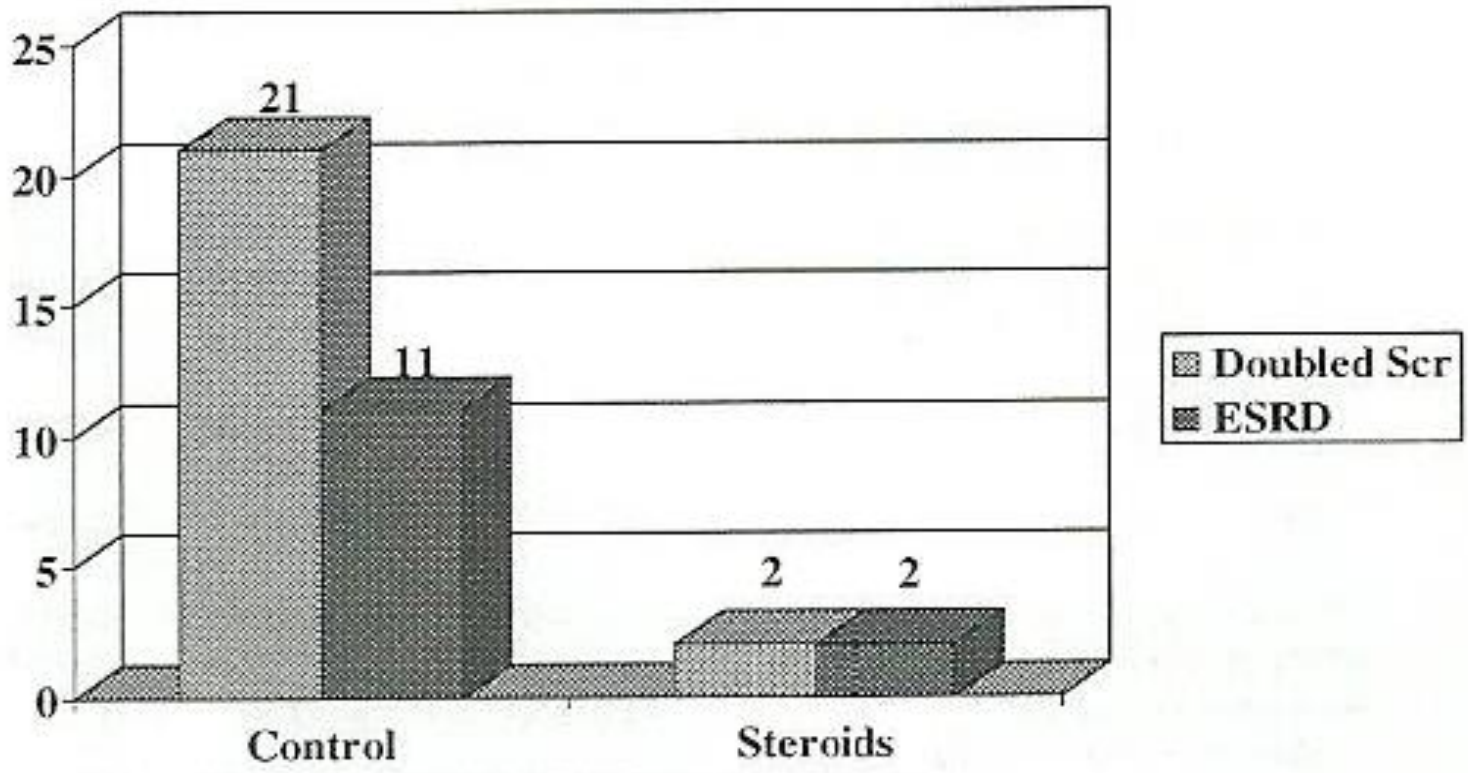
Long term results: Doubling of S Cr



Pozzi C... J Am Soc Nephrol. 2004 Jan;15(1):157-63

Corticosteroids

Long term results



Pozzi et al. JASN 15:157-163, 2004

Table 1 Results of trials of corticosteroids for IgA nephropathy

Table 1 Results of trials of corticosteroids for IgA nephropathy.

Study (year)	Trial design	Route of administration	Duration of treatment/ follow-up (months)	Number of patients	Baseline proteinuria	Change in proteinuria	Renal survival
Lai *et al.* (1986)[45]	Randomized, prospective	Oral	4/36	34	5.07 ± 5.30[a]	Decreased	No change
Kobayashi *et al.* (1989)[37]	Retrospective	Oral	12–36/>36	29	3.03 ± 0.79[a]	Decreased	Improved
Welch *et al.* (1992)[41]	Randomized, crossover	Oral	3/3	33	NR	No change	NR
Waldo *et al.* (1993)[38]	Retrospective	Oral	24–48/48–120	13	NR	Decreased	Improved
Julian *et al.* (1993)[42]	Randomized, prospective	Oral	24/12	35	3.35 ± 0.6[a]	No change	No change
Nicholls *et al.* (1994)[43]	Randomized, prospective	Oral	6/15	33	NR	No change	No change
Kobayashi *et al.* (1996)[39]	Nonrandomized	Oral	18/120	46	1.35 ± 0.3[a]	Decreased	Improved
Shoji *et al.* (2000)[44]	Randomized, prospective	Oral	12/12	19	0.754 ± 0.2[a]	Decreased	No change
Katafuchi *et al.* (2003)[46]	Randomized, prospective	Oral	24/55	90	2.2 ± 2.0[b]	Decreased	No change
Pozzi *et al.* (1999/2004)[46,47]	Randomized, prospective	Intravenous and oral	6/84	86	1.95[b]	Decreased	Improved

[a]Mean ± SD (g/24 h). [b]Urinary protein to urinary creatinine ratio. Yes/no, NR, not reported.

Locatelli F *et al.* (2006) IgA glomerulonephritis: beyond angiotensin-converting enzyme inhibitors
Nat Clin Pract Neprol 2: 24–31 doi:10.1038/ncpneph0055

Prednisone vs Omega-3 FA vs Placebo

Age<40yrs, GFR > 50ml/min, Up/Ucr >0.5

ACE-I for hypertension

33 : Pred 60mg/m2 QOD x3m with taper x 2yr

32 :OM-3 FA 4g/d (1.88g EPA, 1.48 g DHA) x 2 yrs

31 : Placebo x 2 yrs

Primary end-point GFR < 60% baseline

(Despite randomization OM3FA had higher> UVprotein)

Neither Rx group showed a benefit over PBO

Major factor associated w RF was higher baseline Up/Ucr

Hogg RJ, LeeJ, Nardelli NA, et al. Clin JASN 2006

Combination Therapy

Steroids plus ACEi versus ACEi alone

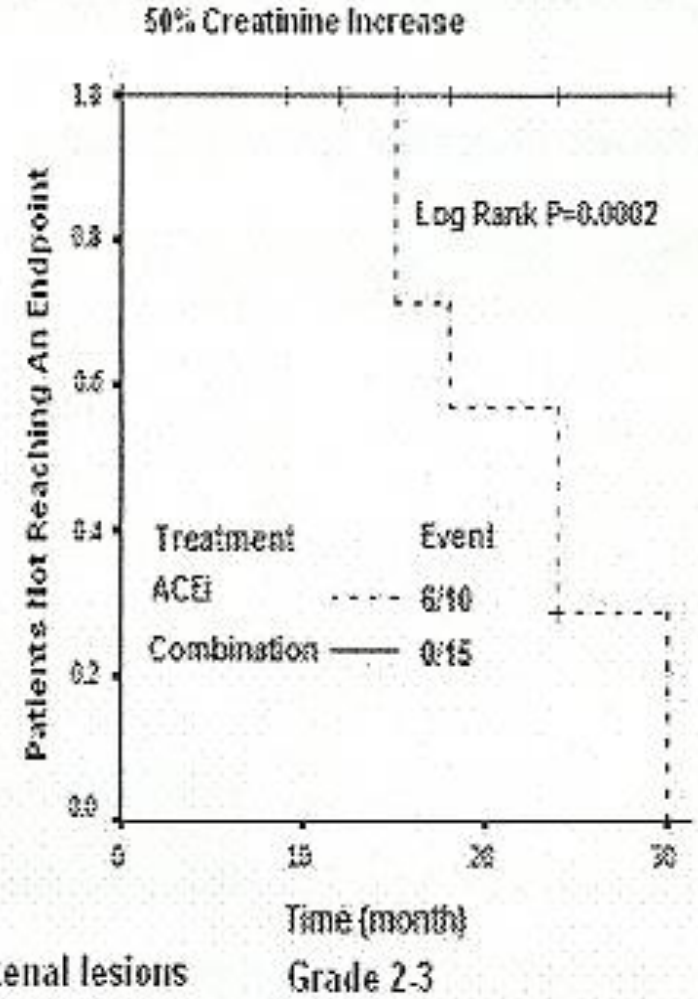
N = 63

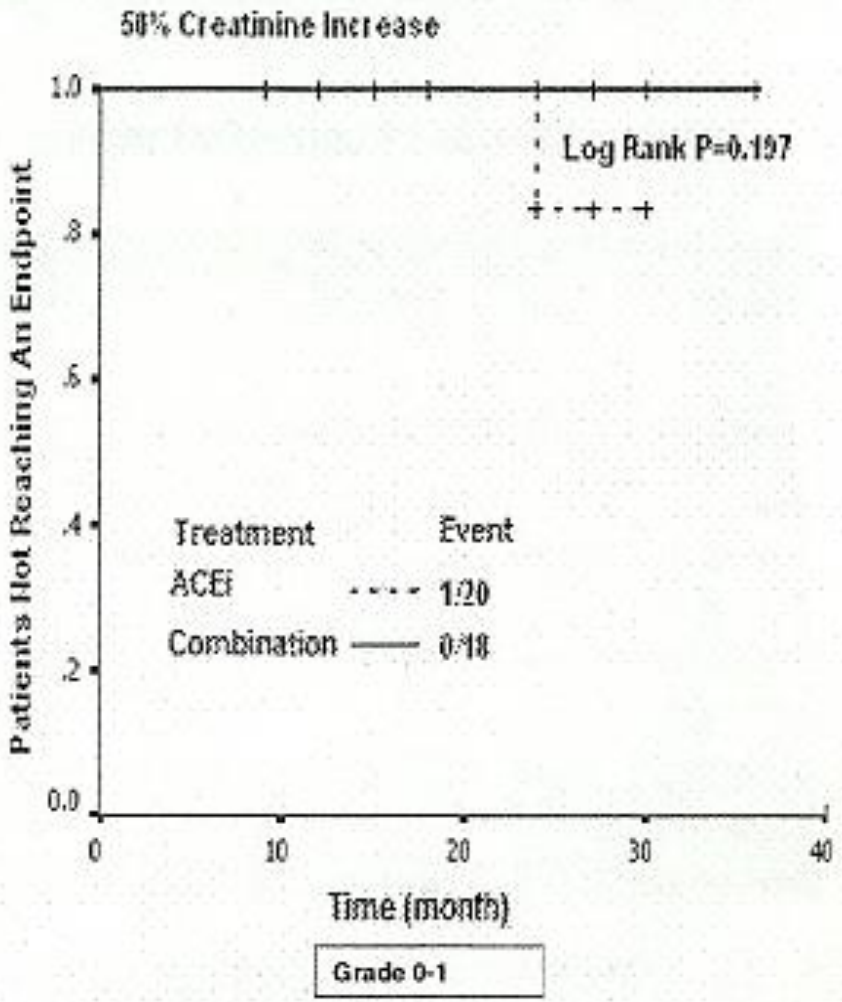
18 to 65 years old

Estimated (eGFR) >30ml/min/1.73m² according to a Modified MDRD equation for a Chinese population.

Treated with Cilazapril or Combination of cilazapril + prednisone: 0.8-1.0 mg/Kg/day X 8 weeks tapered by 5-10mg every two weeks

Jicheng L, ... Haiyan Wang. ASN2007



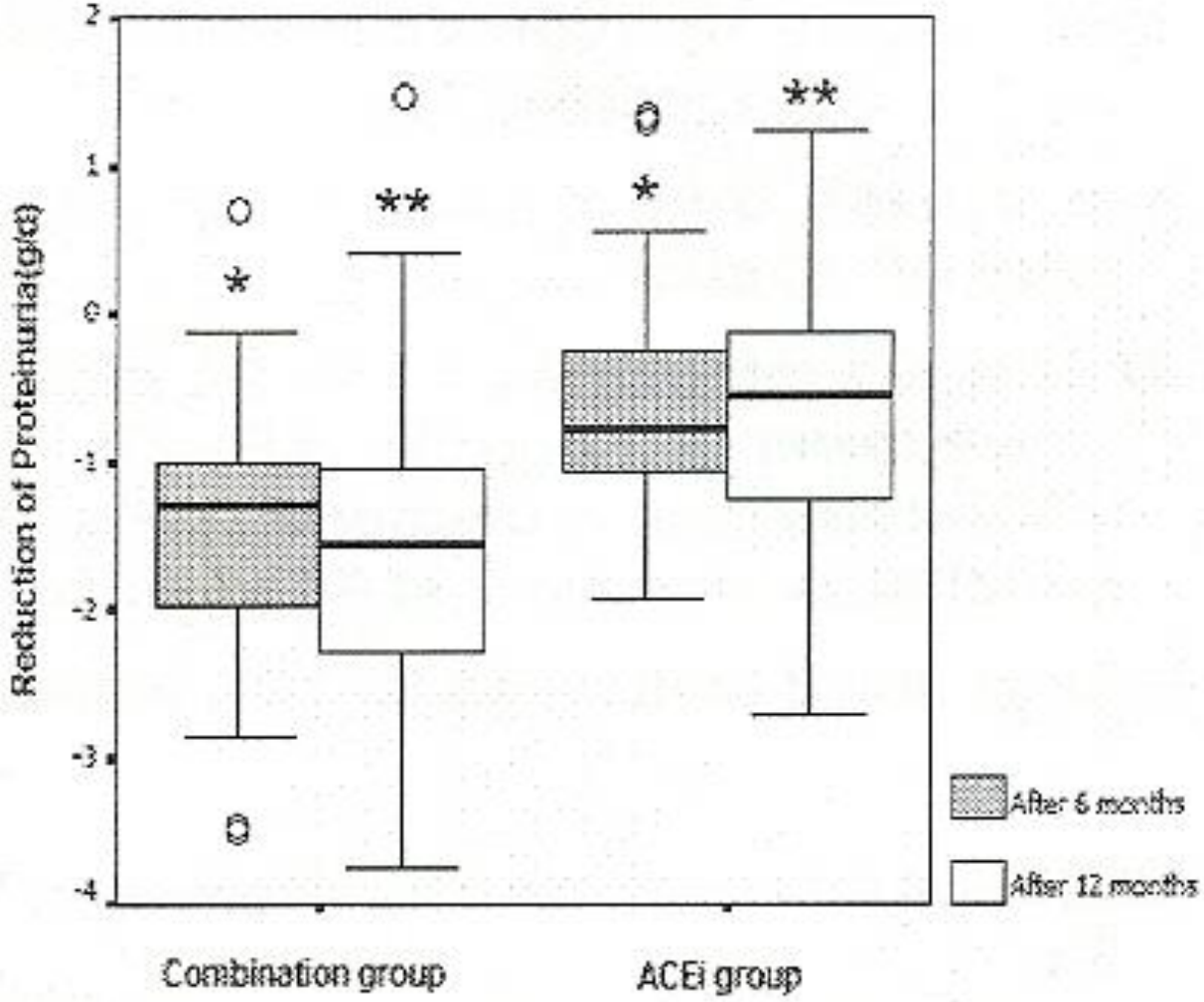


Patients with advanced renal pathologic lesions get more beneficial effect of preserved renal function with combination therapy

Jicheng L, ... Haiyan Wang. ASN2007

Reduction of urine protein excretion during follow-up

Patients in the combination group had a more rapid and stable reduction of urine protein excretion



Steroids + Cytotoxics

Progressive IgAN

Prednisolone 40 mg/d (reduced to 10 mg/d by 2 yr)

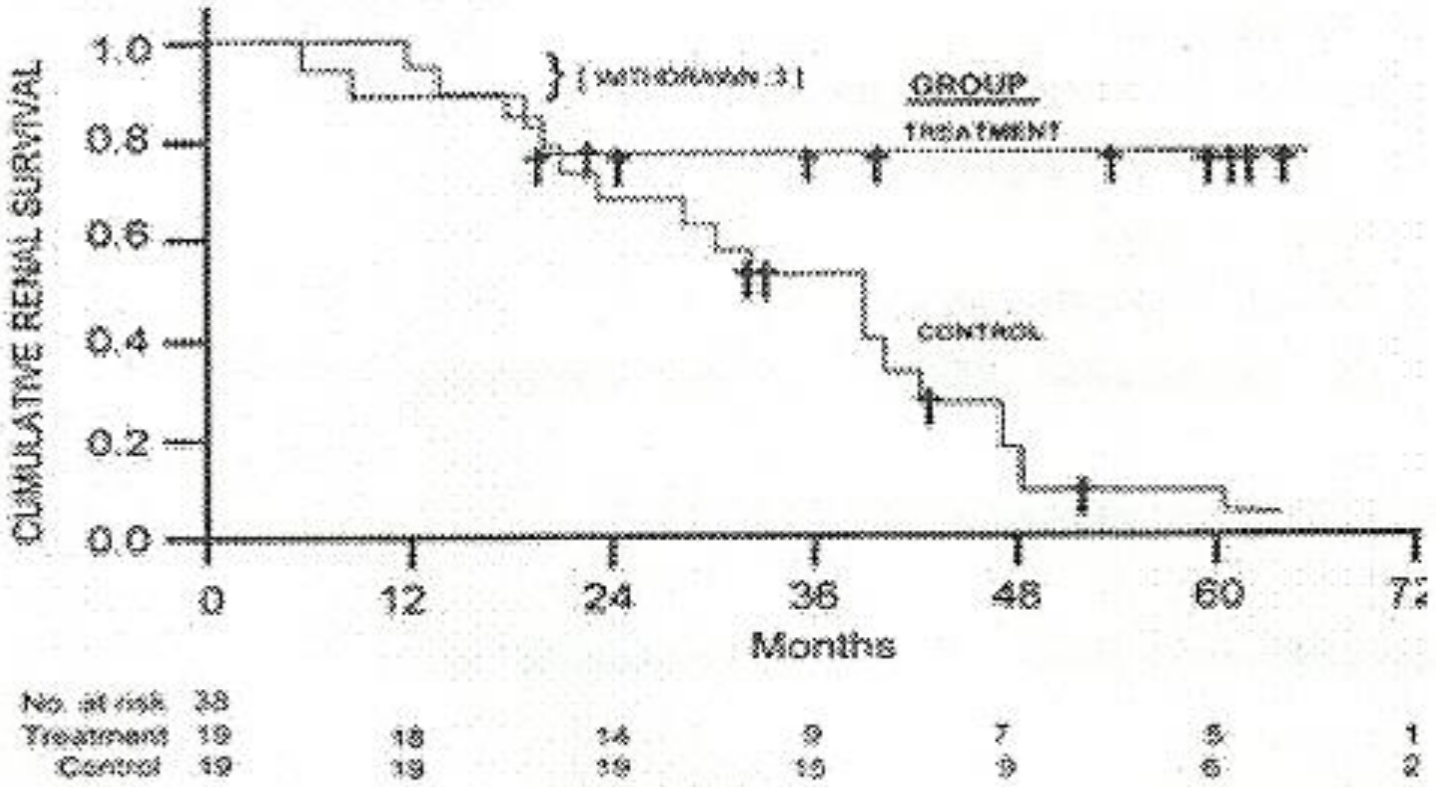
Oral Cyclophosphamide (1.5mg/kg/d) for 3 mo then 2 years or more of AZA(1.5mg/kg/d) Treated = 72% 5 year renal survival

Untreated =5% 5 year renal survival

Ballardie FW… J Am Soc Nephrol. 2002 Jan;13(1):142-8

Steroids + Cytotoxics

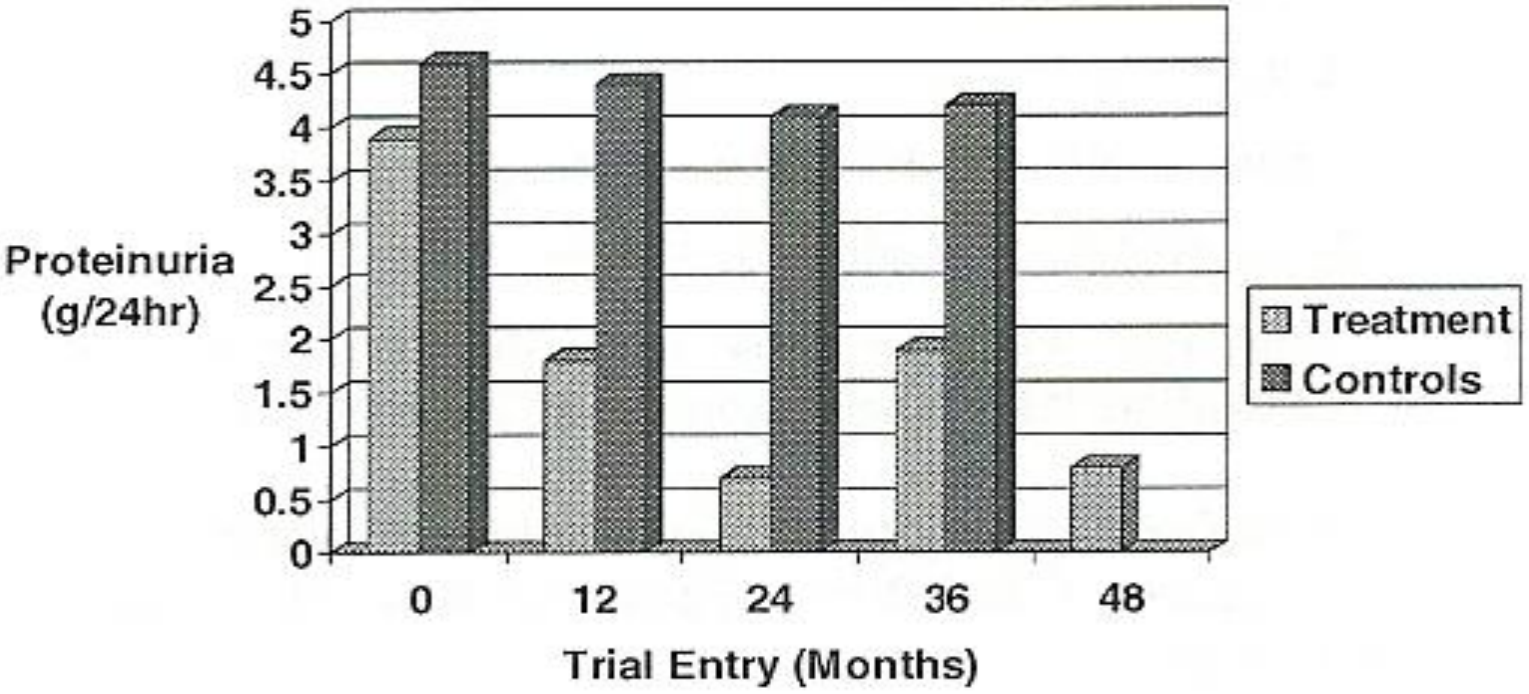
Renal Survival



Ballardie FW... J Am Soc Nephrol. 2002 Jan;13(1):142-8

Steroids + Cytotoxics

Change in proteinuria



Ballardie FW... J Am Soc Nephrol. 2002 Jan;13(1):142-8

Table 2 Results of controlled trials of cytotoxic drugs for IgA nephropathy

Study (year)	Trial design	Drugs	Duration of treatment/ follow-up (months)	Number of patients	Renal survival
Pozzi *et al.* (1999)[33]	Randomized, prospective	Cyclophosphamide	6/36	73	No change/ improved
Walker *et al.* (1986)[34]	Randomized, prospective	Cyclophosphamide	6/3	58	No change
Kobayashi *et al.* (1999)[35]	Randomized, prospective	Azathioprine	24/24	28	No change
Rocatello *et al.* (2003)[36]	Non-randomized	Cyclophosphamide	3/60	90	Improved
Ibernon *et al.* (2006)[37]	Retrospective	Cyclosporine/steroids	6/45	45	Improved
Balestrieri *et al.* (2006)[38]	Randomized, prospective	Cyclophosphamide and azathioprine	24/63	38	Improved
Soumelinos *et al.* (2003)[39]	Retrospective	Azathioprine	18/55	154	Improved
Yamin *et al.* (2000)[40]	Non-randomized, prospective	Cyclophosphamide	6/36	24	Improved
Maes *et al.* (2004)[41]	Randomized, prospective	Mycophenolate mofetil	36/36	34	No change

Locatelli F *et al.* (2006) IgA glomerulonephritis: beyond angiotensin-converting enzyme inhibitors
Nat Clin Pract Neprol 2: 24–31 doi:10.1038/ncpneph0055

Mycophenolate Mofetil

Belgium

- 33 pts - Pcreat 1.4 mg/dl UV prot 1.6 g/d
- Low Na+, ACEi
- MMF 2g/d vs. placebo x 2 yrs

	MMF	Placebo
Pcreat	1.48 - 1.71	1.40 – 1.53
UVprot	1.79 – 1.80	1.30 – 0.75

In IgA Nephrop. At mod risk no advantage to MMF

Maes BD et al. KI 65:1842-1849, 2004

Mycophenolate Mofetil

24 pts IgAN > 1g UVprot/d randomized to MMF 1.5-2g/d or Conventional RX

Age 43vs47, UVprot 2.0 vs 2.1 g/d, Scr 127 vs 186 uMol BP all similar

At 24 wks proteinuria (1.0 vs 2.4 g/d) Scr (128 vs 205) were lower in Rx group. 8 Rx pts and 2 control had > 40% reduction proteinuria . After D/C MMF proteinuria increased at 48 wks (1.5 v 2.2 NS).

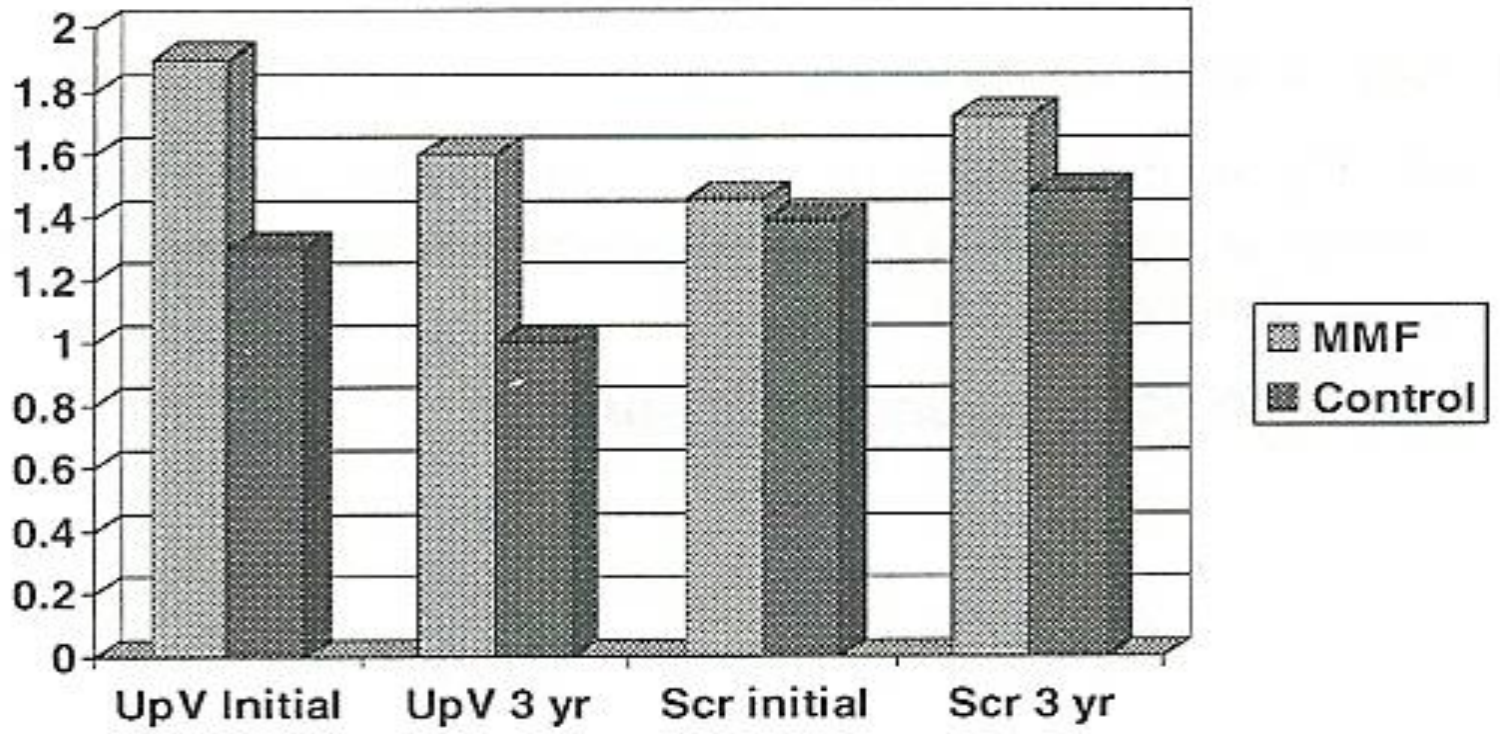
1 Rx pt and 3 control had > 30% increase in Scr.

MMF well tolerated causes decreased UV prot during Rx.

Tang et al, KI 68:802, 2005

Mycophenolate Mofetil

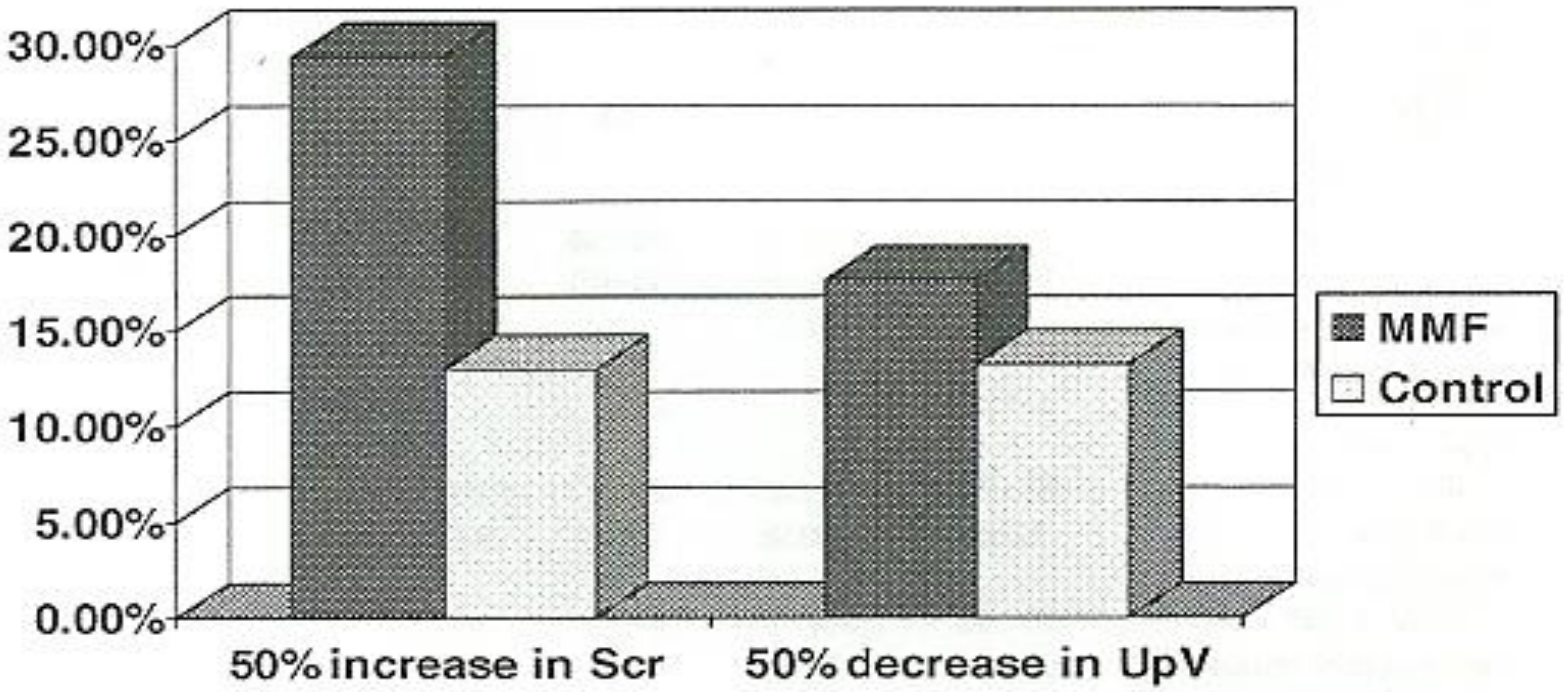
Belgium



Maes BD et al. KI 65:1842-1849, 2004

Mycophenolate Mofetil

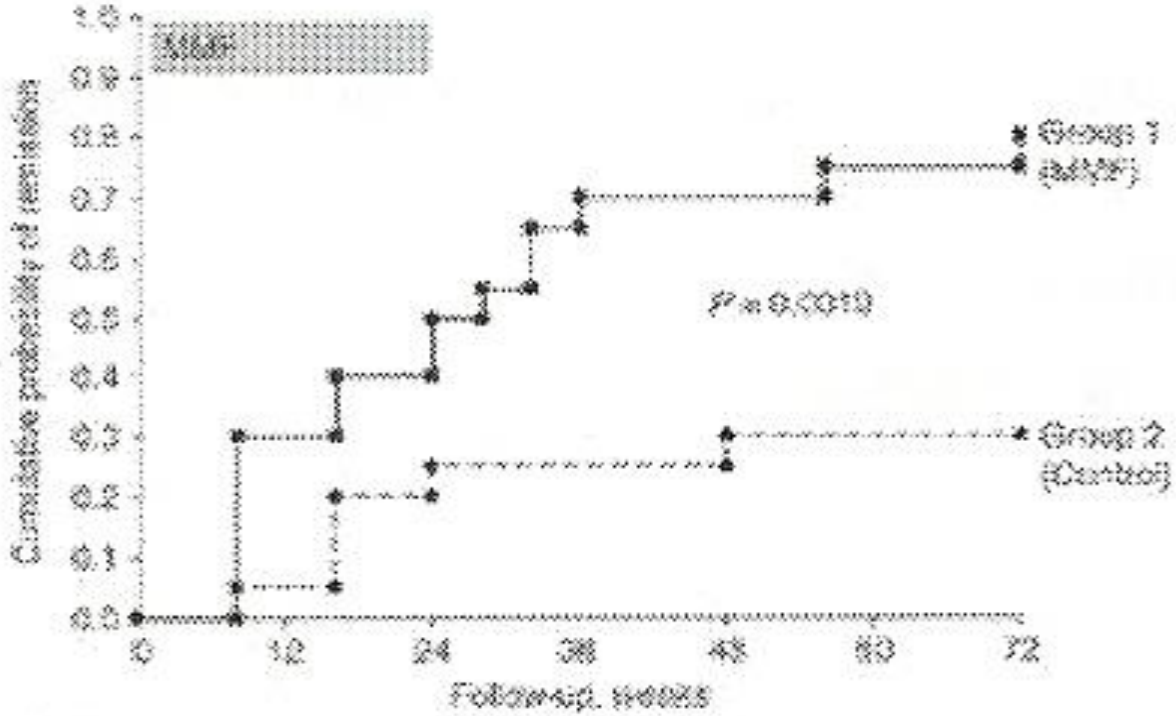
Columbia n=32



Frisch G.. Nephrol Dial Transplant. 2005 Oct;20(10):2139-45.

Mycophenolate Mofetil

Hong Kong



Cumulative no. of subjects in remission							
Group 1	0	6	10	14	14	15	16
Group 2	0	1	5	5	6	6	6

Tang et al, KI 68:802, 2005

General Recommendations

- Statins to keep LDL<100 (?<70)
- Consider low protein diet.
- BP <130/80.

- Tonsillectomy for pts with frequent bad URI and tonsillitis.

Mycophenolate Mofetil in IgA

	Maes (n=34)	*Tang (n=40)*	*Frisch (n=32)*
MMF-	2.0g/d x 3yr	1.5-2.0g/d x 6mo	2g/day x 1 year
eGFR-	71ml/min (Cin)	72ml/min (Ccr)	39ml/min (MDRD)
UpV-	1.6g/d	1.8gm/d	2.7g/d
SBP-	128mmHg	121mmHg	133
ACEi/ARB-	All	All	All
Histology-	II-III (Churg/Sobin)	3.0 (Haas)	4.6 (Haas)
Ethnicity-	N. European	Asian	Caucasian 70%

Specific Recommendations

Based on Phenotype

- Rapidly progressive glomerulonephritis
  - Cytotoxic + Steroids
- Nephrotic syndrome with minimal lesions
  - Steroids
- Acute Renal Failure
  - Steroids if persistent gross hematuria
- Henoch Schonlein Purpura
  - Steroids +/- cytotoxics in “high risk”

Specific Recommendations

Based on Phenotype

- Asymptomatic microhematuria
  - Close monitoring
- Recurrent gross hematuria
  - Tonsillectomy if documented tonsillitis
- Significant Proteinuria (“>1g”) and/or renal insufficiency
  - ACEi (+ ARB if tolerated)
  - Consider
    - Steroids alone
    - Cytotoxic + steroids
    - Mycophenolate + Steroids

Ongoing Trials

- MMF vs. IV cyclophosphamide in crescentic IgAN
- Sirolimus
- MMF vs. Placebo

Recurrence in Renal Transplants

Ohio State University

	Recurrence	No recurrence	Total	P
No. of patients	15	39	54	
No. of allografts	18	43	61	
Donor				NS
LRD	6	12	18	
CAD	12	31	43	
Age at transplantation (yr)				
Mean ± SD	27 ± 8	31 ± 10	30 ± 10	NS
Range	11–39	12–56	11–56	
Months to recurrence		N/A		
Mean ± SD	31 ± 28			
Range	1–121			
Follow-up (mo)				
Mean ± SD	75 ± 36	48 ± 29	61 ± 37	0.003
Graft loss	7/18	11/43	18/61	NS
Months to graft loss				
Mean ± SD	61 ± 38	20 ± 18	35 ± 33	0.005
Mean serum creatinine (mg/dl) of functioning grafts ± SD	2.9 ± 1.5 (n = 11)	1.7 ± 0.7 (n = 32)	2.0 ± 1.1 (n = 43)	0.001

Bumgardner GL.. Transplantation. 1998 Apr 27;65(8):1053-60

IGAN - KDIGO

- Αποκλεισμός δευτεροπαθούς IgAN
- Παρακολούθηση επιβαρυντικών παραγόντων για την πορεία της IgAN, όπως λευκωματουρία, υπέρταση, μείωση του GFR
- Συνεκτίμηση παθολογοανατομικών ευρημάτων που επηρεάζουν την πρόγνωση
- Σε ΟΝΑ μετά από επεισόδιο μακροσκοπικής αιματουρίας συνιστούμε βιοψία νεφρού αν δεν υπάρχει βελτίωση της νεφρικής λειτουργίας σε 5 μέρες μετά την έναρξη της αιματουρίας. Προτείνουμε συντηρητική αντιμετώπιση αν υπάρχουν αλλοιώσεις μόνο οξείας σωληναριακής νέκρωσης ή ενδοσωληναριακοί ερυθροκυτταρικοί κύλινδροι

IGAN - KDIGO

·**Συνιστούμε** μακροχρόνια χορήγηση ACE-I ή ARB σε λευκωματουρία >1g/d με αύξηση της δόσης στα μέγιστα ανεκτά από την ΑΠ επίπεδα με στόχο μείωση της λευκωματουρίας <1g/d

·**Προτείνουμε** την χορήγηση ACE-I ή ARB σε λευκωματουρία 0,5-1g/d

·**Συνιστούμε** η ΑΠ να είναι <130/80 mmHg όταν η λευκωματουρία είναι <1g/d και <125/75mmHg σε λευκωματουρία >1g/d

·**Προτείνουμε** την χορήγηση Omega-3 FA επί παραμονής της λευκωματουρίας >1g/d παρά τη θεραπεία με ACE-I ή ARB για 3-6 μήνες και τη ρύθμιση της ΑΠ

IGAN - KDIGO

- **Προτείνουμε** σε λευκωματουρία >1g/d παρά τη μέγιστη θεραπεία με ACE-I ή ARB για περισσότερο από3-6 μήνες και με **GFR>50mL/1΄** να λαμβάνουν κορτικοειδή επί 6μηνον, είτε με IV ώσεις (Pozzi) είτε per os (Manno)

- **Προτείνουμε** να μη χορηγείται συνδυασμός κορτικοειδών με κυκλοφωσφαμίδη ή αζαθειοπρίνη , εκτός από ΤΕΣΝ

- **Προτείνουμε** να μην χορηγείται ανοσοκαταστολή σε ασθενείς με GFR<30ml/1΄ εκτός από ΤΕΣΝ

- **Προτείνουμε** να μη χορηγείται MMF

MMF

IGAN - KDIGO

- **Προτείνουμε** να μην χορηγούνται αντιαιμοπεταλιακά και να μη γίνεται αμυγδαλεκτομή, εκτός αν υπάρχουν οι ενδείξεις που ισχύουν στο γενικό πληθυσμό

- **Προτείνουμε** σε νεφρωσικό σύνδρομο με χαρακτηριστικά ΝΕΑ να χορηγείται αγωγή ίδια με ΝΕΑ

- **Προτείνουμε** σε εξωτριχοειδική IgAN με μηνοειδείς σχηματισμούς >50% των σπειραμάτων και ταχεία εξέλιξη της νεφρικής ανεπάρκειας να χορηγούνται κορτικοειδή και κυκλοφωσφαμίδη όπως στις ANCA+ αγγειίτιδες