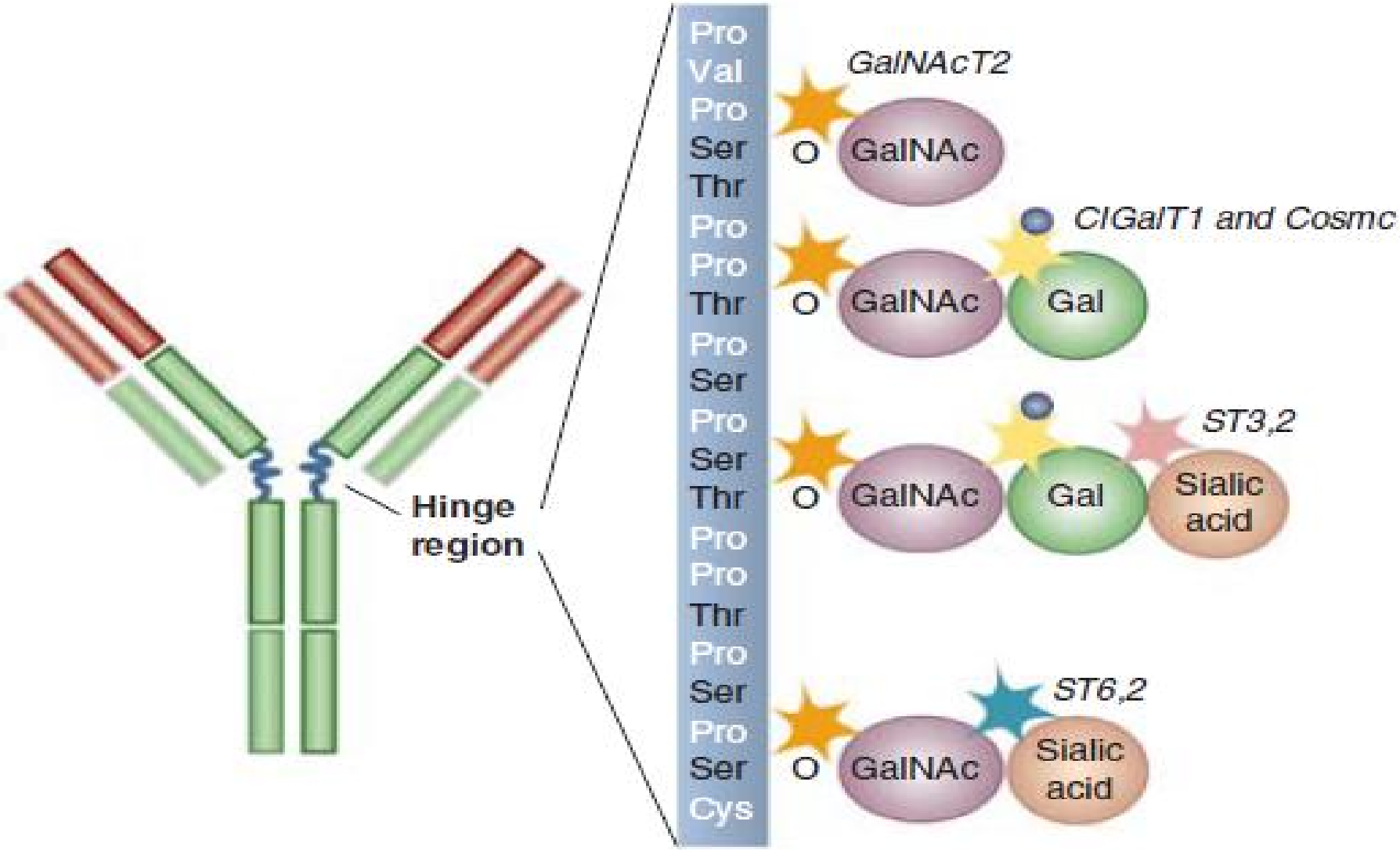
IgA Nephropathy Prognosis and Treatment

Shokoufeh –Savaj MD
Associate Professor of Medicine
Firoozgar hospital- IUMS

History

Immunoglobin A nephropathy was first described by Berger and Hinglais in 1968 in Paris


Hinge region
Pro
Val
Pro
Ser
Thr
Pro
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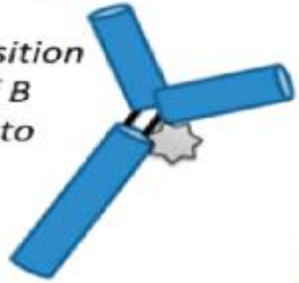
Pro
Pro
Thr
Pro
Ser
Pro
Ser
Cys
GalNAcT2
O
GalNAc
ClGalT1 and Cosmc
Gal
ST3,2
Sialic acid
ST6,2
Sialic acid

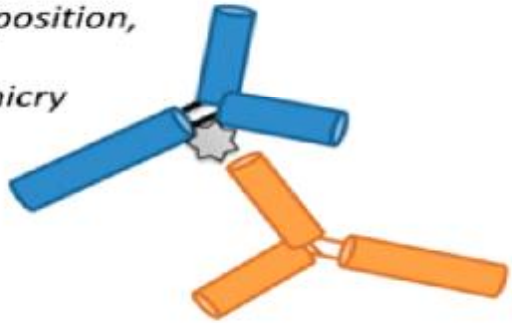
1. Increased circulating levels of Gd-IgA1

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



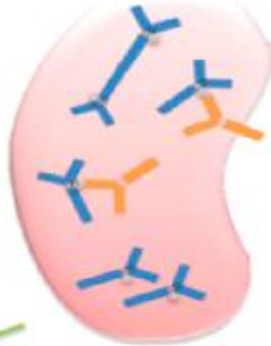
2. Production of Anti-IgA1 antibodies (IgA or IgG)

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



3a. Immune complexes form in the circulation

3b. Immune complexes form *in situ*



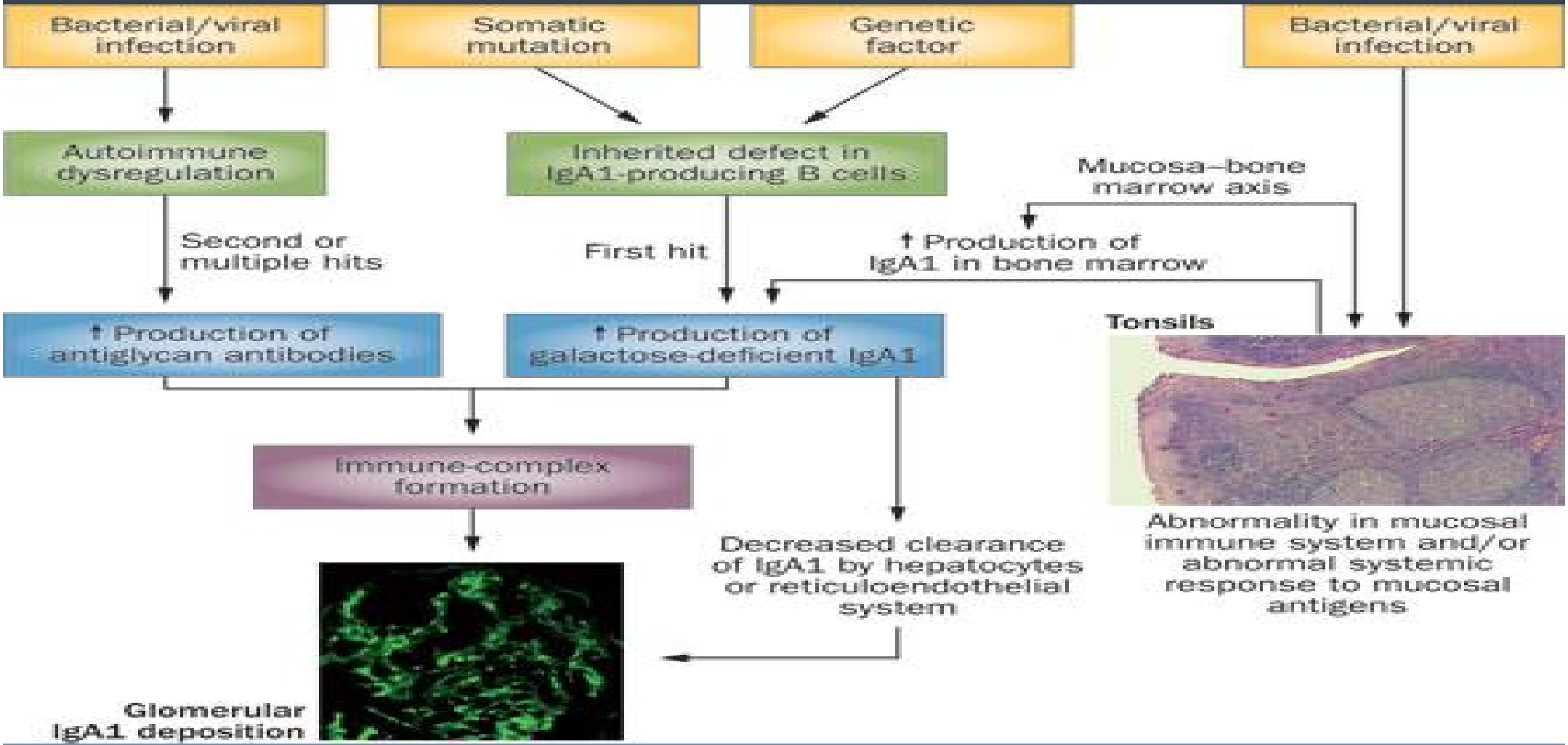
4. Immune complexes in the mesangium cause local immune activation & injury

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

Incidence

- Incidence rate : 2.5 % in 100,000 population
- Higher incidence in Eastern Asian population (40 % renal biopsy in primary GN in china)
- Lower incidence in Black population
- 15- 20% progress to ESRD in 10 years and 20-40% in 20 years.

Proposed pathways involved in the mesangial deposition of IgA1 in IgA nephropathy—a multihit mechanism



Lai, K. N. (2012) Pathogenesis of IgA nephropathy *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2012.58

Risk Factors for Progression

- Clinical
- Serologic
- Pathological
- Genetic

Clinical Factors for Progression

- Elevated serum creatinine concentration
- Hypertension (>140/90 mmHg)
- Persistent (eg, for more than six months) protein excretion above 1000 mg/day

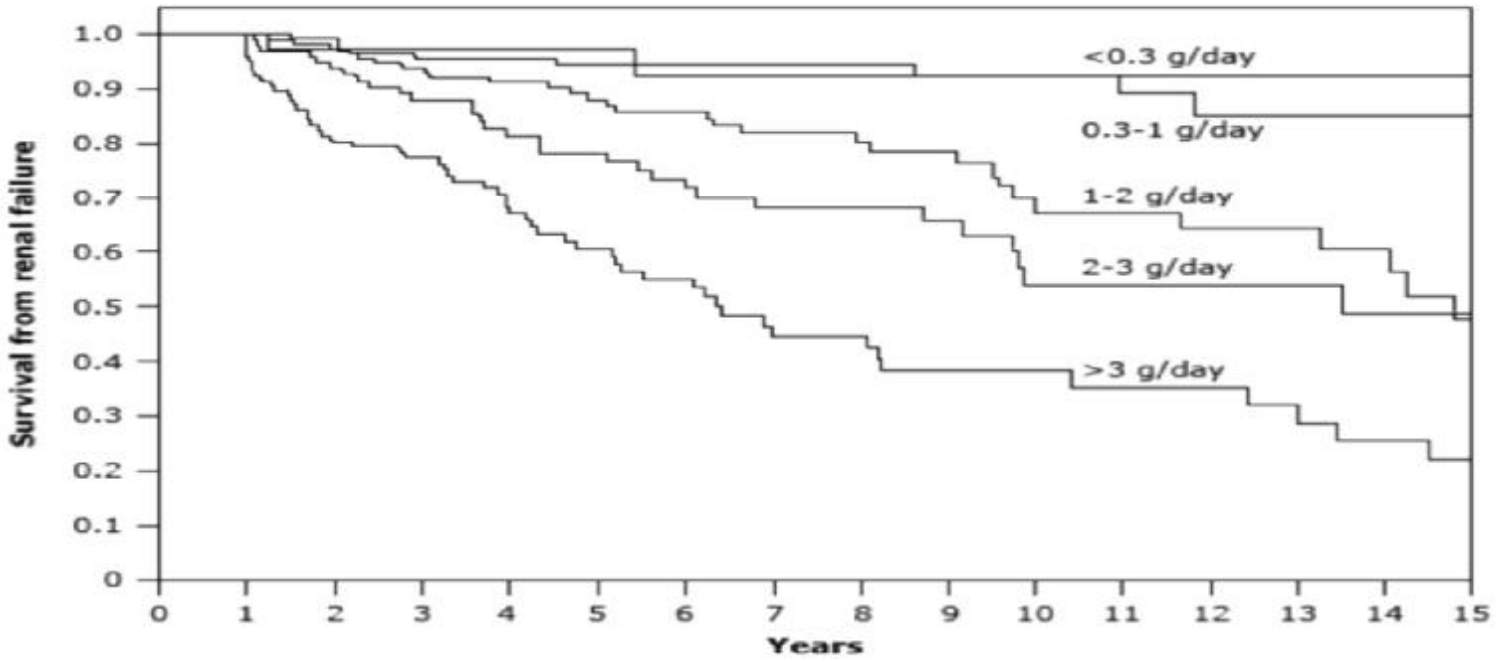
A scoring system to predict renal outcome in IgA nephropathy: from a nationwide prospective study

2269 patients ,follow up 7 years

- Serum Cr ≤1.25 mg/dL :% 2.5
- Serum Cr 1.26 - 1.67 mg/dL :% 26
- Serum Cr >1.68 mg/dL : %71

Nephrol Dial Transplant (2006) 21: 2800–2808

Effect of magnitude of proteinuria on renal survival in IgA nephropathy



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

Renal survival by category of TA-proteinuria. p<0.001.

J Am Soc Nephrol 2007; 18:3177

Table 7. Distribution of the ARR score at diagnosis and cumulative incidence rate of event at 10 and 20 years post-onset

Number of RF Present	ARR Score (Risk Level)	Number of Patients (%)	Number of D/D Events (%)	CKD-3 + Incidence		D/D Incidence	
				10 years	20 years	10 years	20 years
0	0 (very low)	151 (45.5)	4 (2.6)	8%	14%	2%	4%
1	1 (low)	69 (20.8)	3 (4.3)	15%	24%	2%	9%
2	2 (high)	65 (19.6)	10 (15.4)	37%	50%	7%	18%
3	3 (very high)	47 (14.1)	28 (59.6)	64%	74%	29%	64%

0 for none,
3 for their simultaneous presence
scores 1 and 2 for the presence of any one or two of these factors.

IgA Nephropathy Progression Calculator

Krzysztof Kiryluk, MD, MS and David A. Fasel

This risk score is based on the analysis of 619 biopsy-diagnosed Chinese patients with IgA nephropathy followed for an average of 41.3 months from the time of diagnosis. The calculator uses four baseline clinical variables assessed at the time of biopsy to predict the risk of progression to end stage kidney disease.

To calculate the risk of disease progression, enter the clinical values:

Glomerular Filtration Rate:	15 - 150	ml/min/1.73m^2
Hemoglobin:	5 - 18	g/dL
Serum Albumin:	0.0 - 6.0	g/dL
Systolic Blood Pressure:	80 - 250	mm Hg

Calculate Reset

IgA Nephropathy Progression Risk:

Enter values on the left to determine risk of progression to end stage kidney disease.

Risk Score Equation:

Risk Score = 6.932 - (0.039 × eGFR) - (0.230 × Hb) - (0.762 × Alb) + (0.016 × SBP)

eGFR = estimated Glomerular Filtration Rate [ml/min/1.73m]
Hb = Hemoglobin [g/dL]
Alb = Serum Albumin [g/dL]
SBP = Systolic Blood Pressure [mmHg]

(http://www.columbiamedicine.org/divisions/gharavi/calc_progression.php)

Oxford Classification

Mesangial Proliferation	M0 < 4 cells	M1 :4-5 cells	M2 : 6-7 cells	M3 >8 cells
Segmental Sclerosis	S0 : NO Sclerosis	S1 : Sclerosis		
Interstitial Fibrosis/ Tubular atrophy	T0 : 0-25% IF/TA	T1:26-50% IF/TA	T2> 50% IF/TA	
Endocapillary Hypercellularity	E0 :No Hypercellularity	E1: Hypercellularity		

KI ,2009,76 , 546 -556

Oxford classification and prognosis

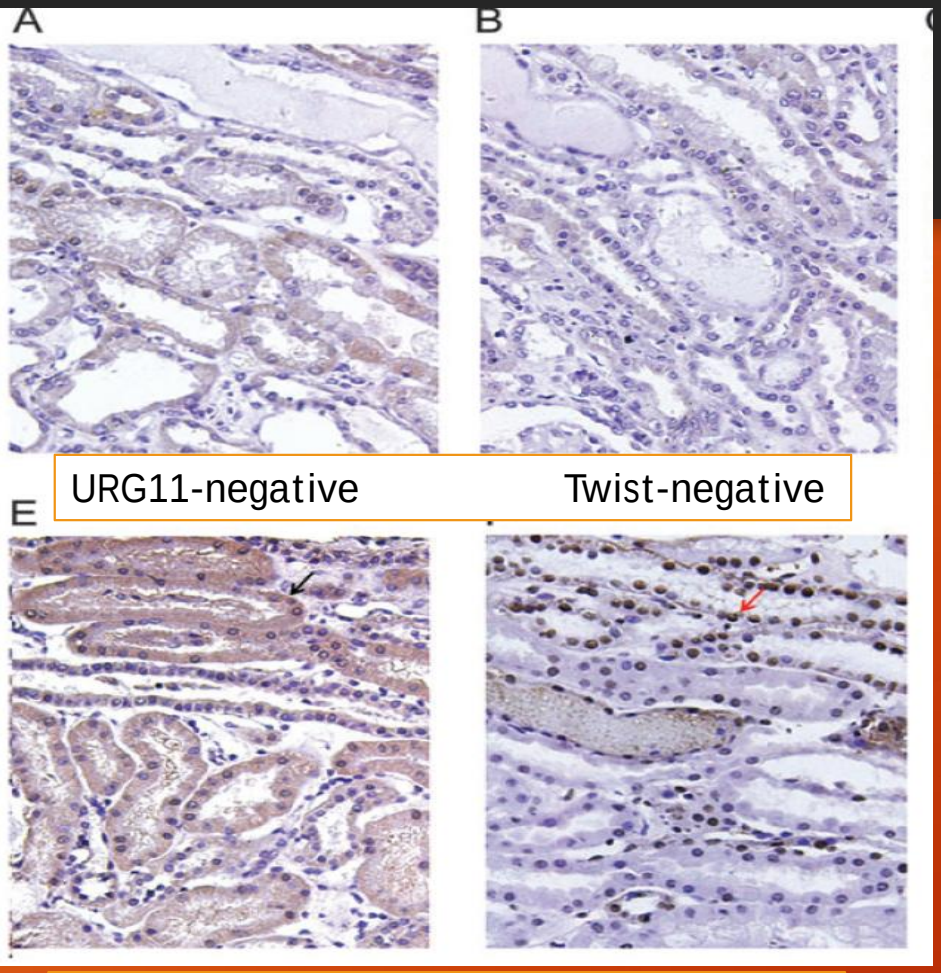
- 16 retrospective cohort with 3893 patients and 570 kidney failure
- M , S, and T lesions in oxford classification is associated independently with progression to kidney failure.
- Crescent lesions were associated with kidney failure.
- E lesions related to interaction to effect of immunosuppressive therapy.

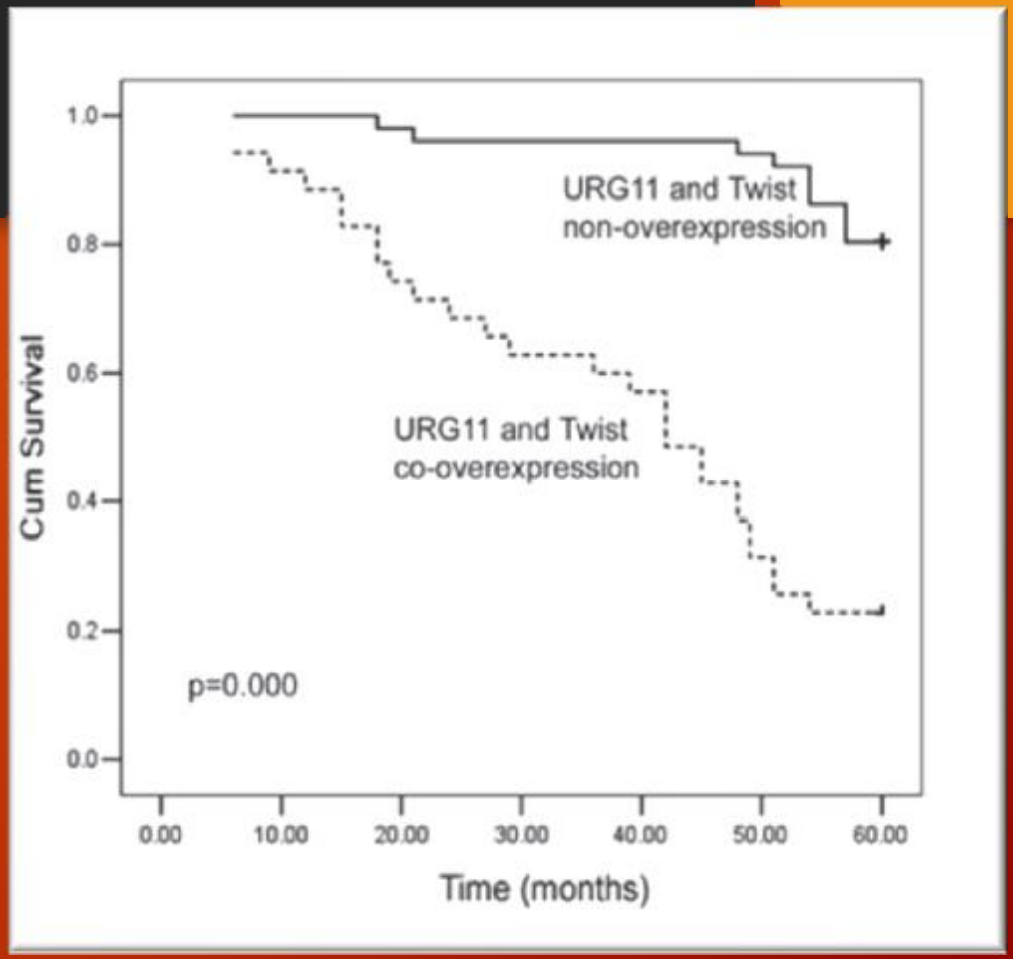
AJKD, 2013 ,65 :891-899

Association of URG11 and Twist with clinical pathological characteristics and prognosis in patients with IgA nephropathy

- URG11 and Twist has a critical functional role in tubular epithelial–mesenchymal transition (EMT) and kidney fibrosis.
- URG11 was predominantly located in the cytoplasm and Twist in nucleus of renal tubular epithelial cells from IgAN patients
- URG11 and Twist staining in renal biopsy specimens might be a novel histological marker for progression in IgAN patients.

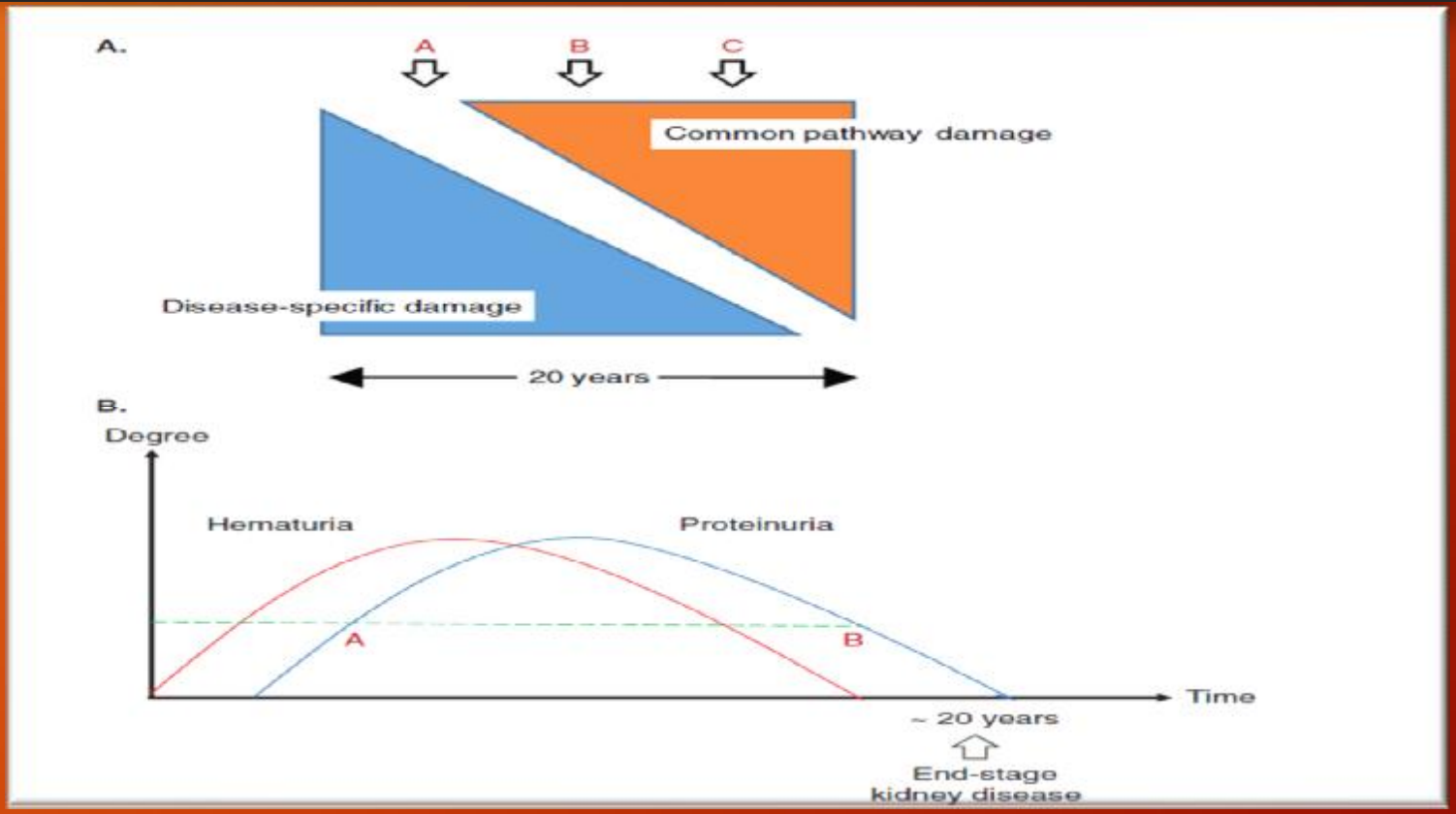
Nephrol Dial Transplant (2013) 28: 2268–2276





Nephrol Dial Transplant (2013) 28: 2268–2276

Clinical course of IgA nephropathy

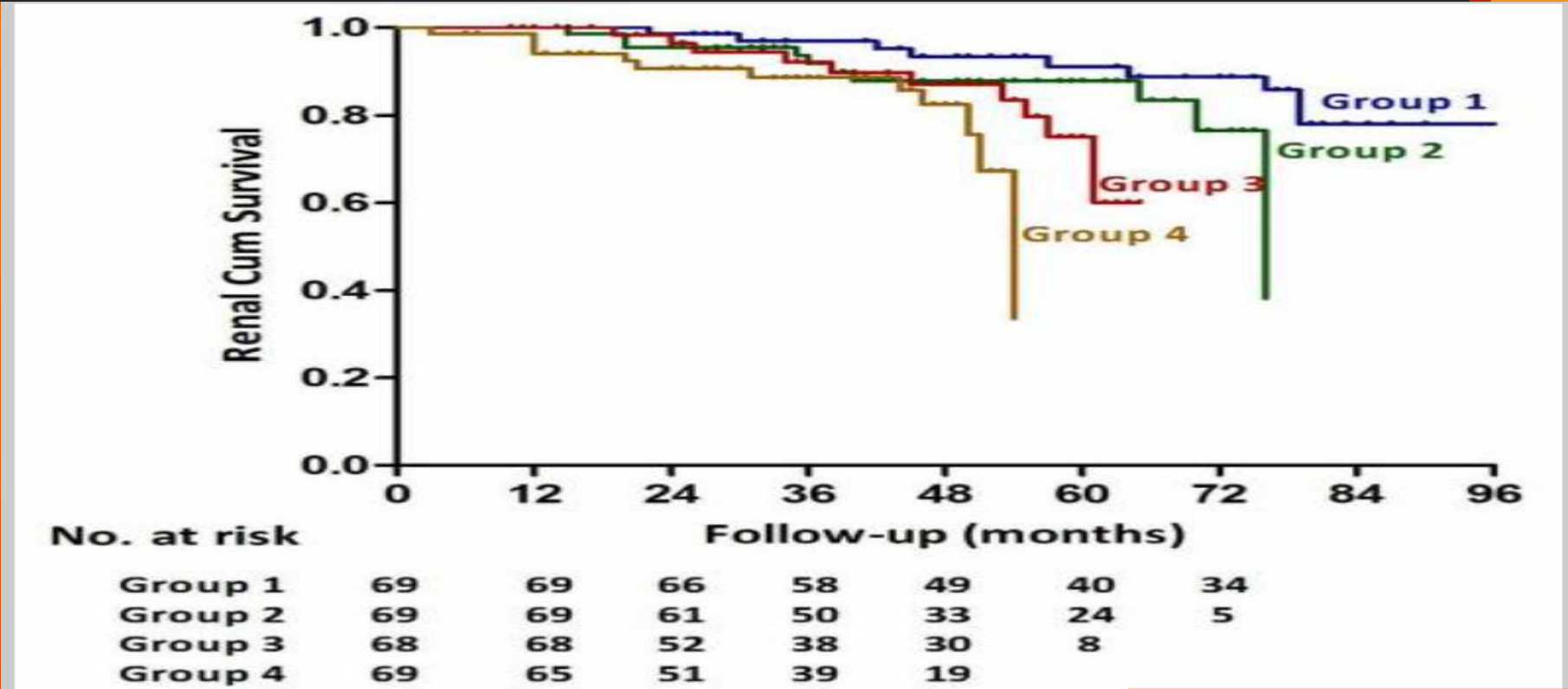


Clinical Course of IgA nephropathy

- Biopsy is not recommended in hematuria and mild proteinuria
- Snap Shot of disease status
- Early biopsy can not predict the outcome

Expert Opin. Biol.Suzuki et al ,2015

Renal survival in IgAN patients with four quartile Gd- IgA1 level



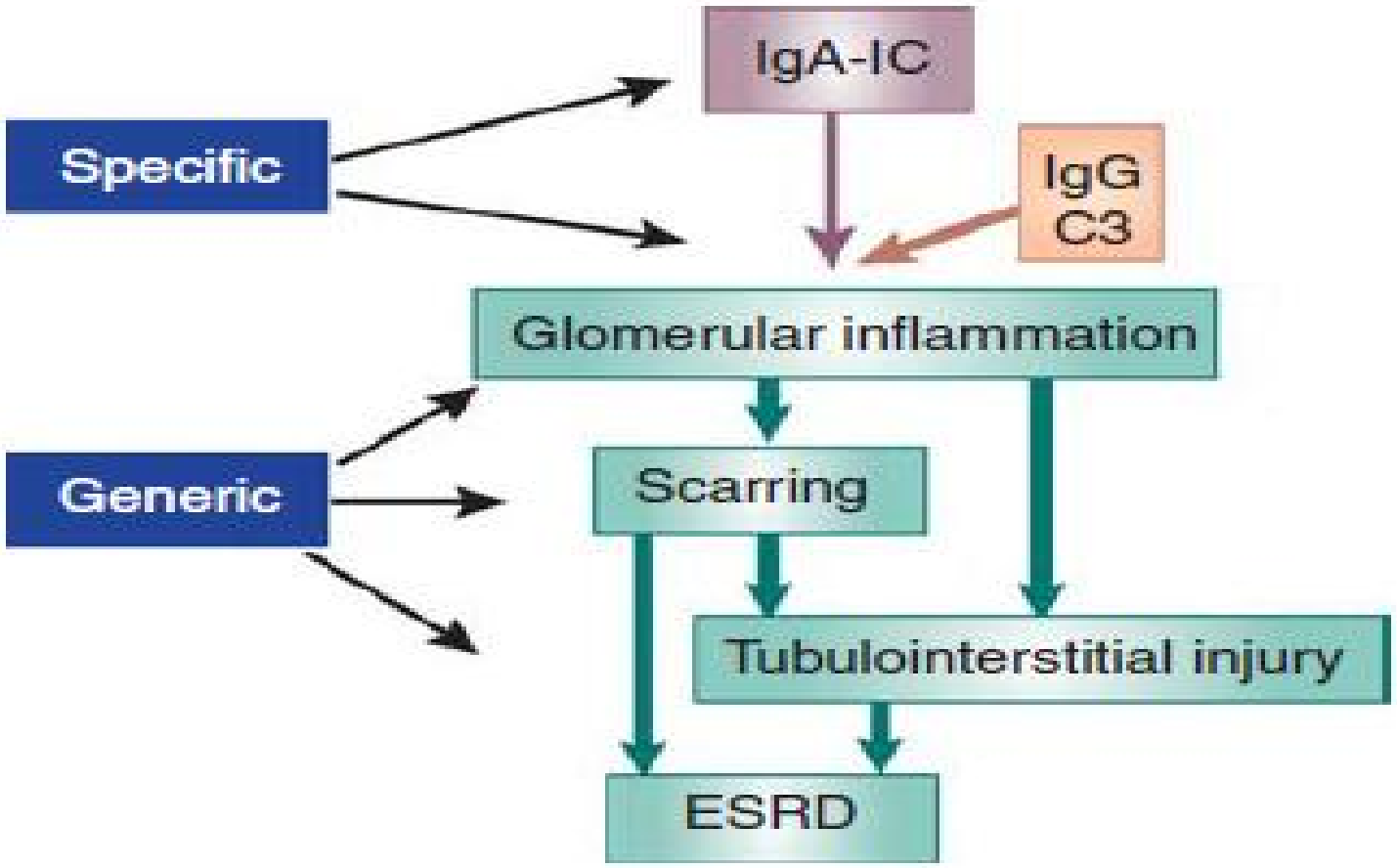
KI,Oct 2012,82(7):790-796

Autoantibodies targeting galactose-deficient IgA1 associate with progression of IgA nephropathy.

- In 97 patients ,prospective cohort ,follow up 13.8Yrs
- IgG autoantibody levels ≥1.33 predicted dialysis or death (both P≤0.01)
- Serum levels of IgG and IgA autoantibodies strongly associated with the progression of IgAN nephropathy.

Berthoux F.J Am Soc Nephrol. 2012;23(9):1579.

Approach to Treatment



Non immunosuppressive therapy in IgA nephropathy

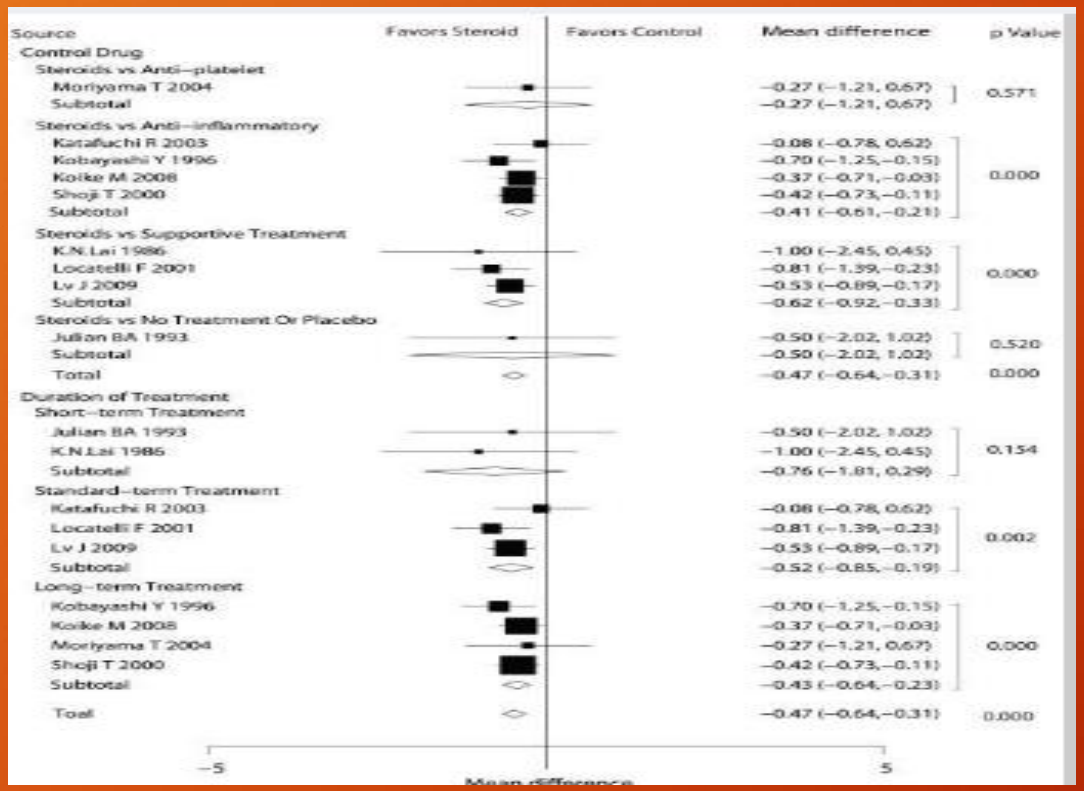
Fish Oil

- 56 RCT(2838 participants)
- Benefits of antihypertensive agents, particularly inhibitors of the renin angiotensin system, appear to potentially outweigh the harms in patients with IgAN. (decrease in proteinuria)
- No evidence for the other non- immunosuppressive therapies evaluated here.

Reid S.,Cochrane Database Syst Rev. 2011

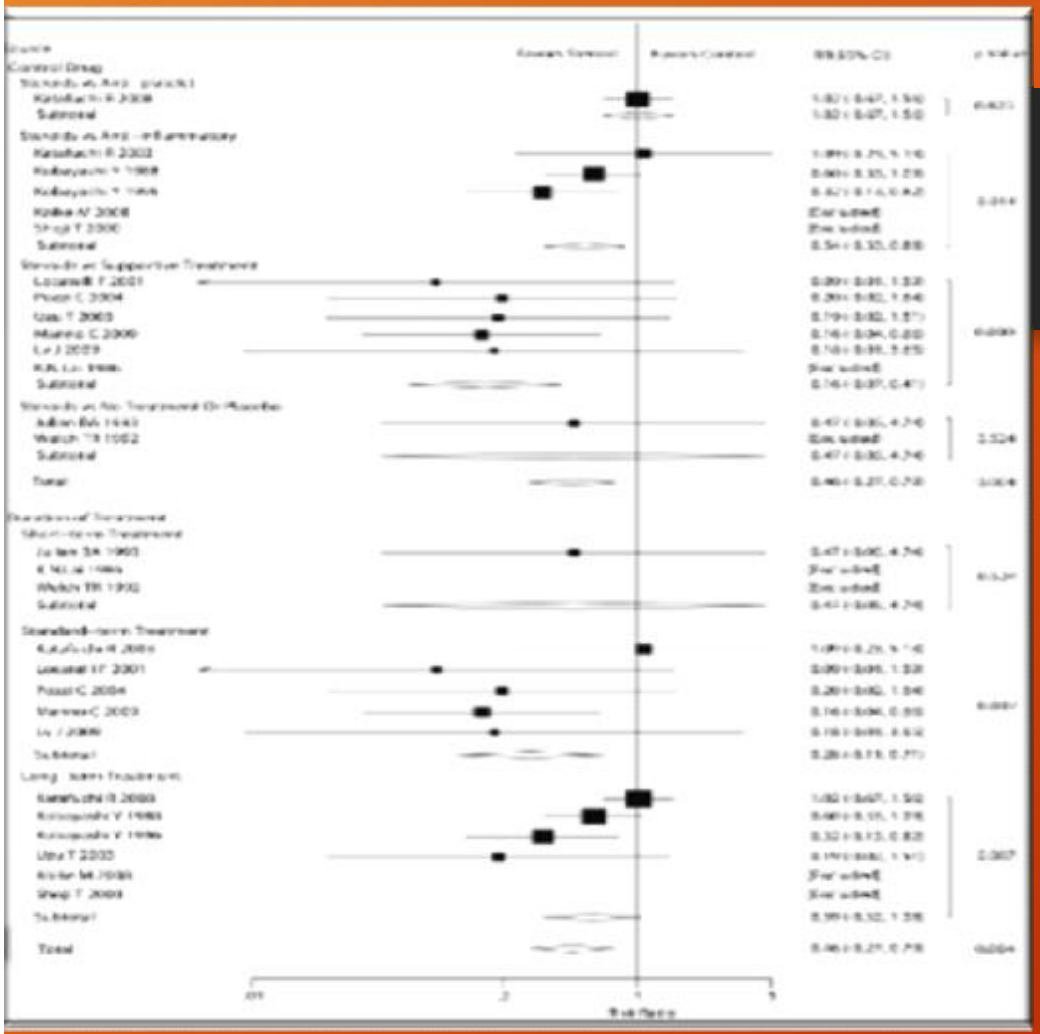
Steroids in the Treatment of IgA Nephropathy to the Improvement of Renal Survival: A Systematic Review and Meta-Analysis

Yu-Hao Zhou[1☯], Li-Gong Tang[5☯], Shi-Lei Guo[2], Zhi-Chao Jin[1], Mei-Jing Wu[1], Jia-Jie Zang[1], Jin-Fang Xu[1], Chun-Fang Wu[1], Ying-Yi Qin[1], Qing Cai[3], Qing-Bin Gao[1], Shan-Shan Zhang[6], Dand-Hui Yu[4], Jia He[1*]

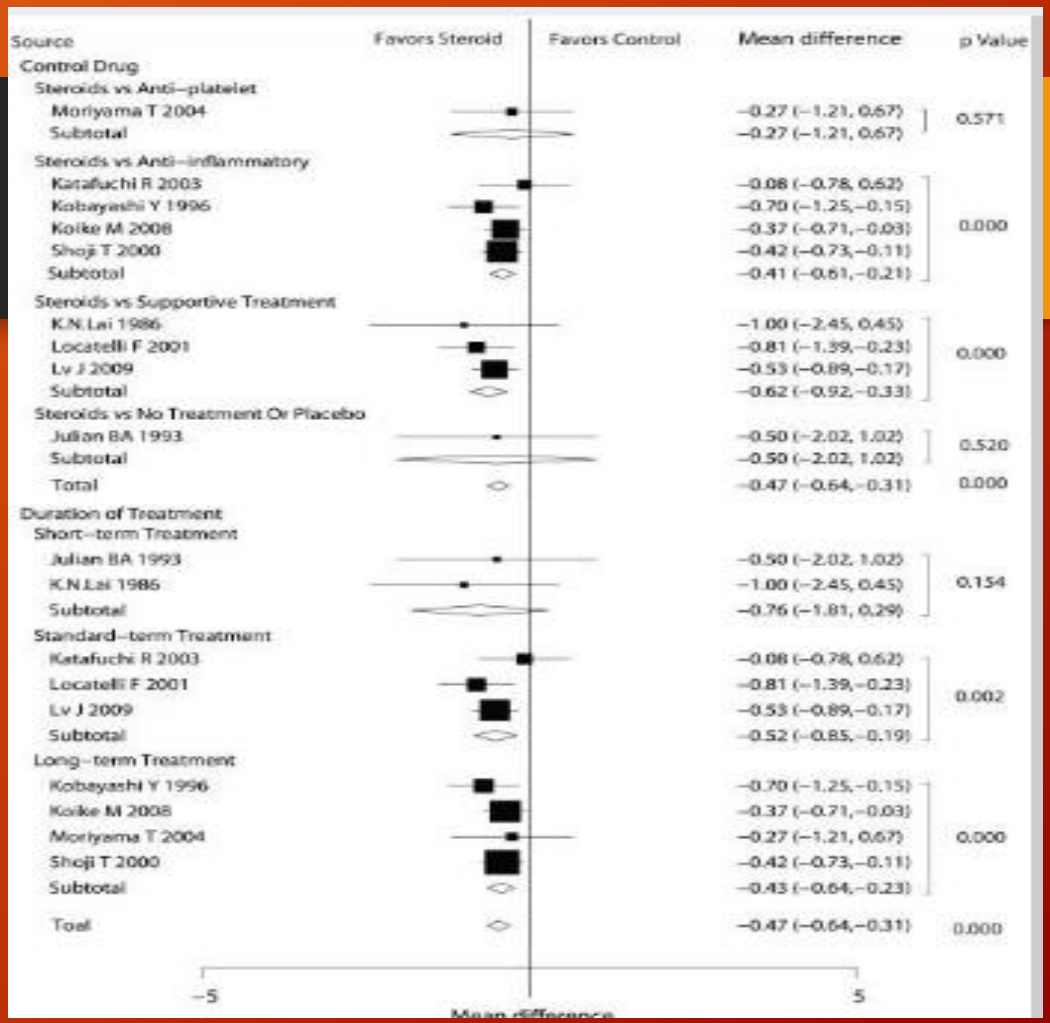


- 15 Articles (n= 1542) met the criteria
- Follow-up for patients ranged from 3 to 281 months.
- Reduced urinary protein excretion
- (MD=-0.47 g/day, 95%CI=-0.64 to -0.31).

Zhou YH et al .ploS One 2011



Steroid effect on ESRD occurrence
(RR: 0.46, 95% CI: 0.27 to 0.79),



Doubling of serum creatinine
(RR=0.34, 95%CI=0.15 to 0.77)

KDIGO practice guideline on glomerulonephritis

- We suggest that patients with persistent proteinuria >1 g/day, despite 3–6 months of optimized supportive care (including ACEi or ARBs and BP control), and GFR 45>ml/min per 1.73m2 receive a 6-month course of corticosteroid therapy .

Kidney International (2012) 82, 840–856

A meta-analysis of the clinical remission rate and long-term efficacy of tonsillectomy in patients with IgA nephropathy

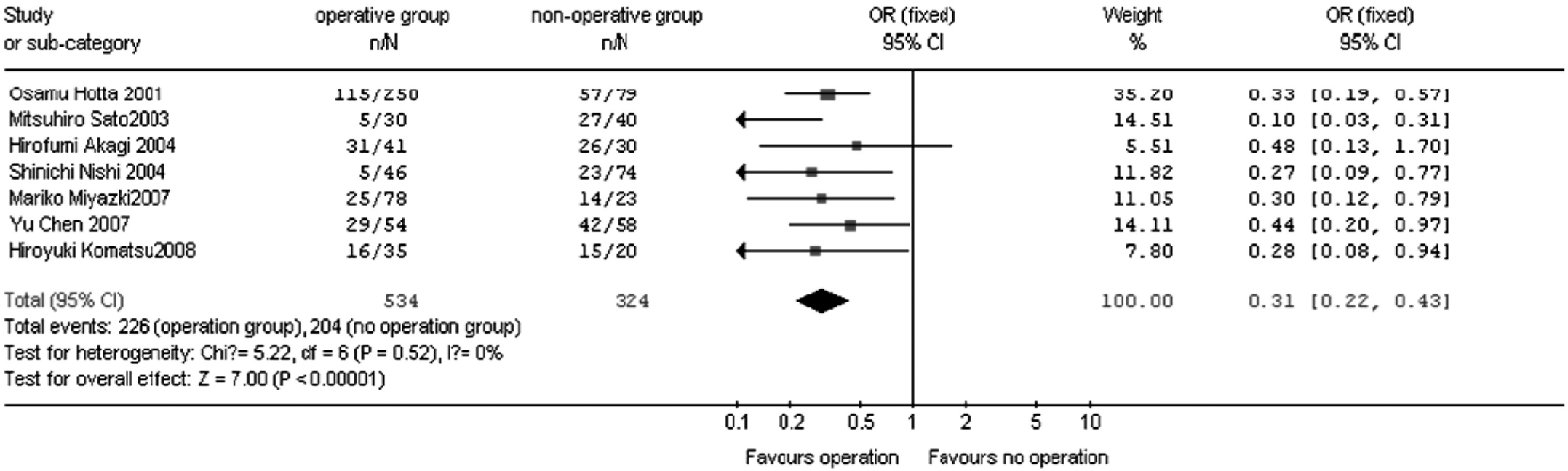
You Wang[1,2], Junying Chen[1], Yan'e Wang[1], Yan Chen[1], Le Wang[1] and Yongman Lv[1]

Study	F/U time (month)	Treatment		Randomized	Blind
		Operative group	Non-operative group		
Hotta *et al.* [1]	82.3	Tonsillectomy + steroid	Steroid	No	Yes
Sato *et al.* [2]	70.3	Tonsillectomy + steroid pulse	Normal-dose steroid or normal treatment	No	?
Akagi *et al.* [3]	>151	Tonsillectomy + normal-dose steroid	Normal-dose steroid	No	?
Shinichi Nishi *et al.* [4]	>191	Tonsillectomy	Without tonsillectomy	No	?
Yu Chen *et al.* [7]	130	Tonsillectomy + steroid	Steroid	No	?
Mariko Miyazki *et al.* [5]	60	Tonsillectomy + steroid pulse	Steroid pulse	No	?
Hiroyuki Komatsu *et al.* [6]	60	Tonsillectomy + steroid	Steroid	No	?

NDT , 2011, 26, 6

Total Clinical Remission

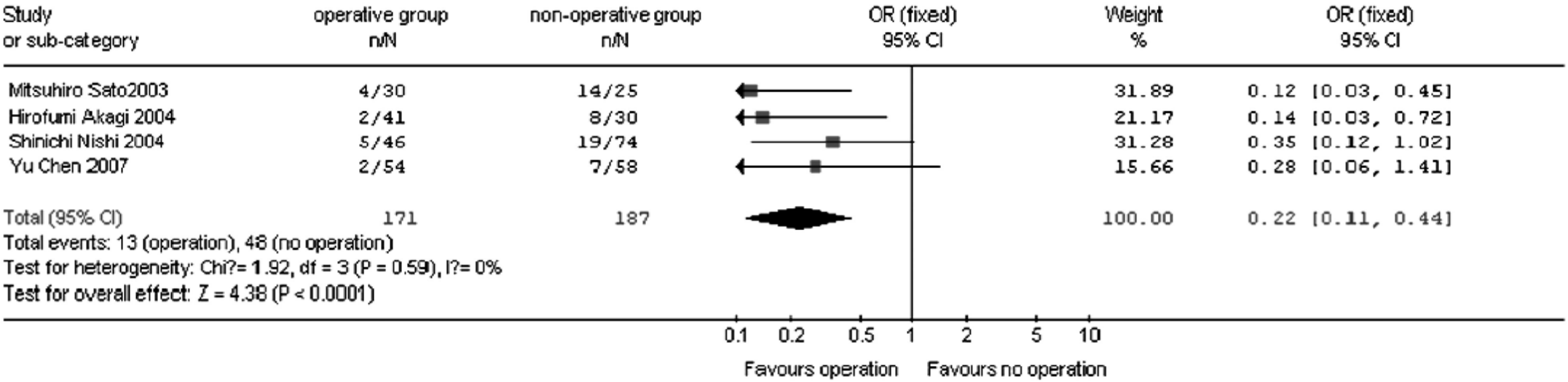
Review: meta-analysis of IgAN
Comparison: 01 operative group vs. non-operative group
Outcome: 01 total clinial remission at the final observation



Clinical remission: normal renal function with no frank haematuria, proteinuria between 0 and 1.5 g protein per 24 h, and a urinary erythrocyte count no more than 4 per high-power field.

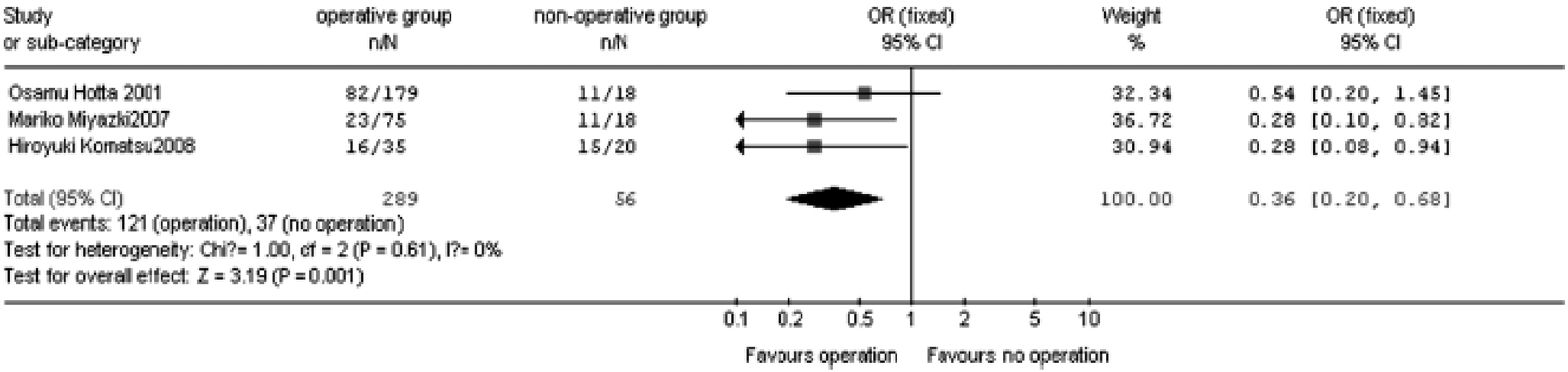
Effect of tonsillectomy on ESRD

Review: meta-analysis of IgAN
Comparison: 01 operative group vs. non-operative group
Outcome: 05 effect on EFSRF



Tonsillectomy Plus Steroid Compared with Steroid Pulse

Review: meta-analysis of IgAN
Comparison: 01 operative group vs. non-operative group
Outcome: 09 tonsillectomy plus steroid pulse compared with steroid pulse

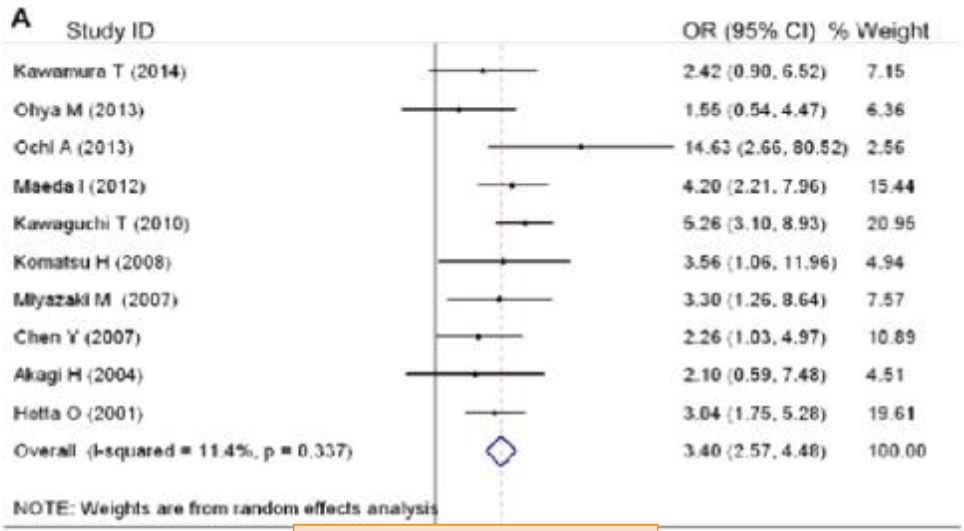


Tonsillectomy for IgA Nephropathy: A Meta-analysis

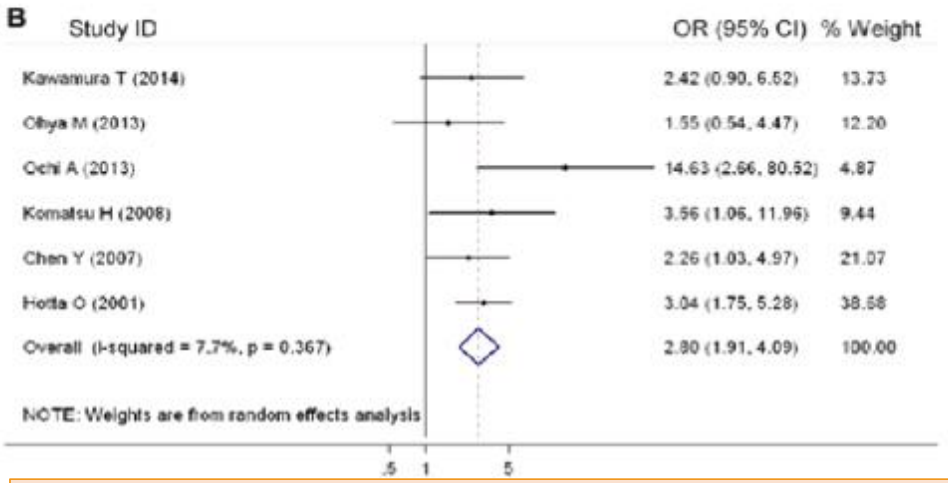
Lin-lin Liu, MD,[1] Li-ning Wang, MD,[1] Yi Jiang, MD,[2] Li Yao, MD,[1] Li-ping Dong, MLIS,[3] Zi-long Li, MD,[1] and Xiao-li Li, MD[1]

- 14 studies (1,794 patients)
- Greater odds of clinical remission with tonsillectomy (OR : 3.4)
- Tonsillectomy plus steroid pulse therapy was superior to steroid pulse therapy alone (OR: 3.15)
- Tonsillectomy plus conventional steroid therapy was superior to conventional steroid therapy alone (OR:4.13)
- Tonsillectomy was superior to general treatment (OR:2.21)

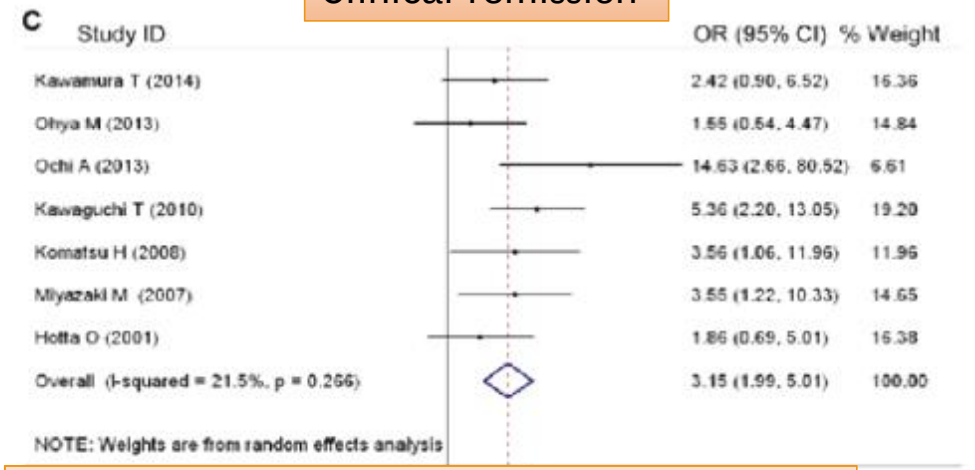
Am J Kidney Dis. 2015;65(1):80-87



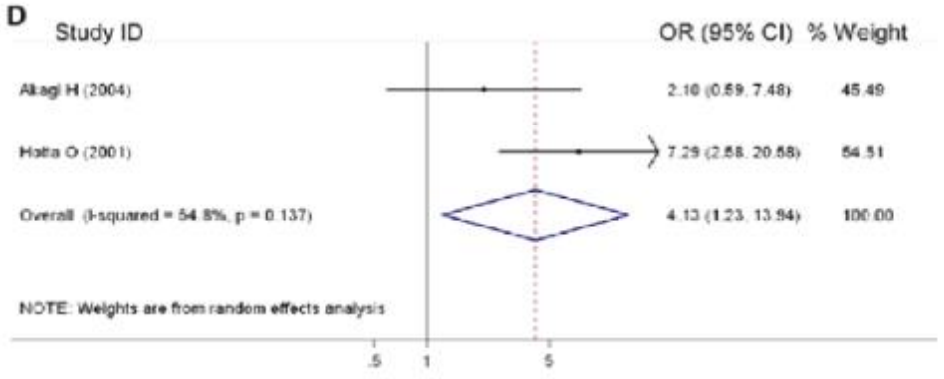
Clinical remission



Clinical remission after adjusting for ACE & ARB Use

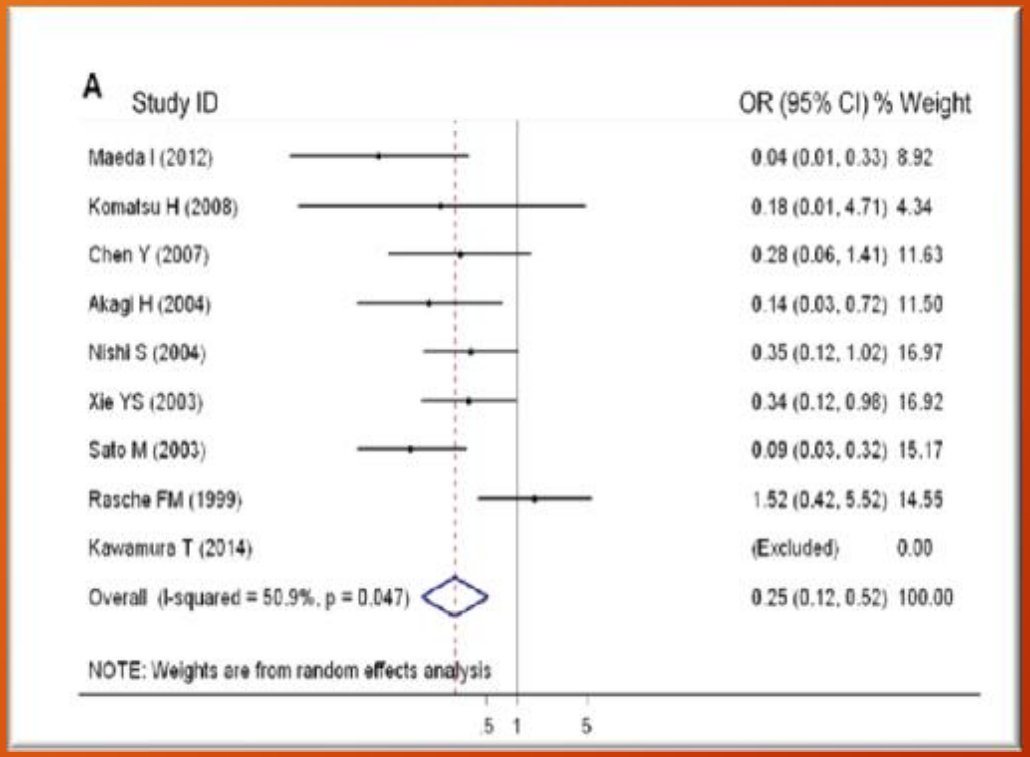


Steroid pulse with and without tonsillectomy



Conventional steroid with and without tonsillectomy

Tonsillectomy & ESRD



Tonsillectomy was associated with decreased odds of ESRD

9 studies, 873 patients; pooled OR,0.25; 95% CI, 0.12-0.52; P , 0.001

Mycophenolate Mofetil Treatment for IgA Nephropathy: A Meta-Analysis

Gaosi Xu[a, b] Weiping Tu[a] Dongfeng Jiang[b] Chengyun Xu[a]

Table 1. Characteristics of individual studies of MMF treatment for IgAN

Study	Year	MMF patients, n	Control patients, n	MMF dosage g/day	Period of treatment, months	Placebo or steroids	Jadad score
Chen et al. [5]	2002	31	31	1.0–1.5	18	steroids	3
Maes et al. [7]	2004	21	13	2.0	36	placebo	3
Frisch et al. [8]	2005	17	15	2.0	24	placebo	5
Tang et al. [6]	2005	20	20	1.5–2.0	18	placebo	3

American journal of nephrology , 2009

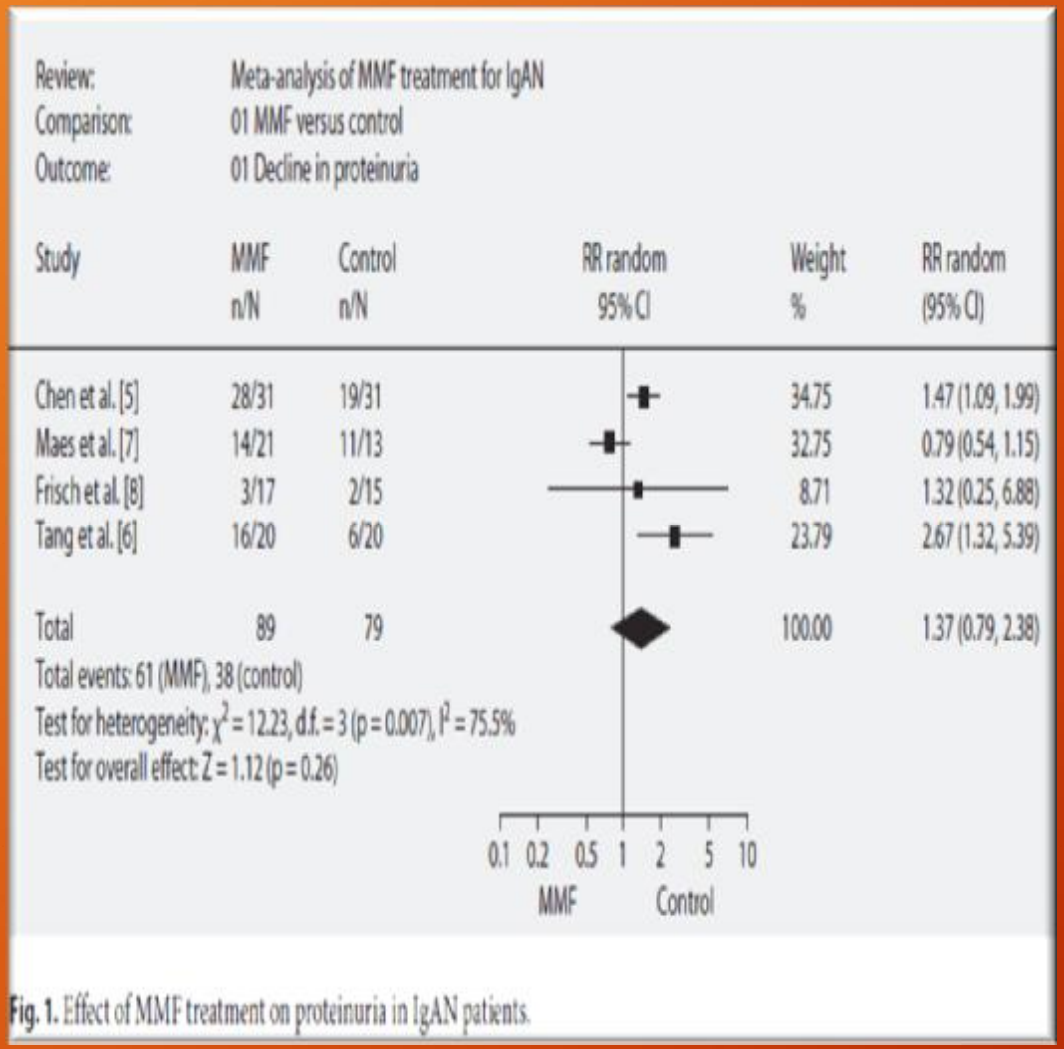


Fig. 1. Effect of MMF treatment on proteinuria in IgAN patients.

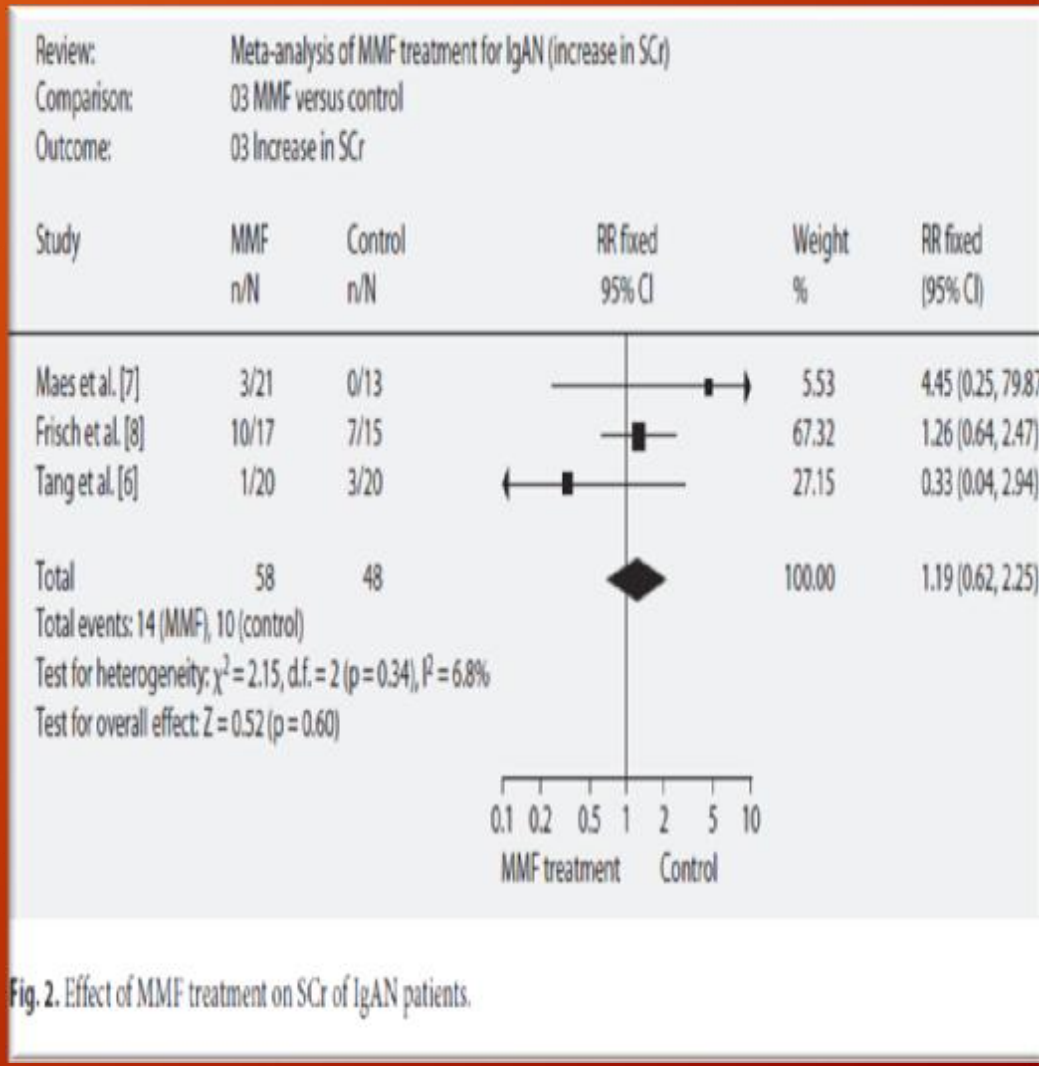
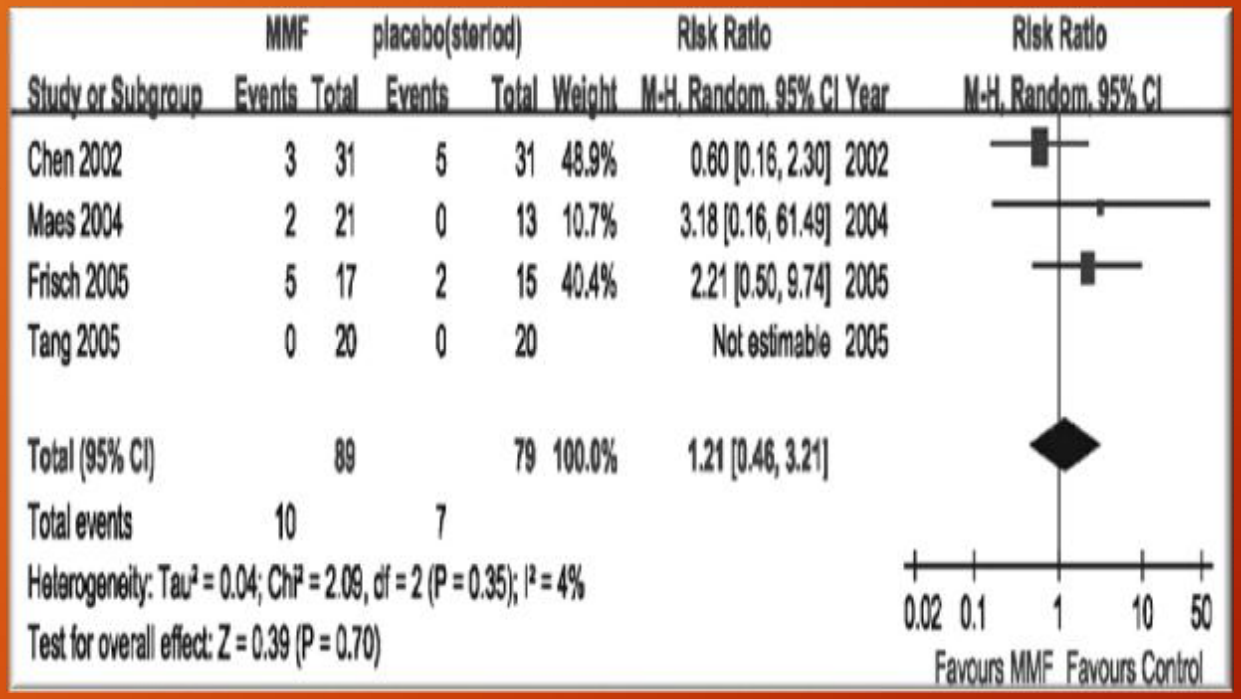


Fig. 2. Effect of MMF treatment on SCr of IgAN patients.

Efficacy and safety of mycophenolate mofetil treatment in IgA nephropathy: a systematic review

Youyuan Chen, YuMin Li, ShengLin Yang, Yan Li and Min Liang*



Comparing MMF treated group to control there was no difference in ESRD rate and rise (50%) in serum creatinine

Chen et al ,BMC,2014

Point of no return	Low GFR, typically ,30 ml/min per 1.73 m2 Biopsy with severe global glomerulosclerosis and tubular atrophy/interstitial fibrosis	No immunosuppression Prepare for transplant or renal replacement Therapy
Crescentic IgAN	Rapidly progressive GN 30%–50% cellular or fibrocellular crescents on biopsy	Pulse 1 high-dose oral glucocorticoids Consider cyclophosphamide
IgAN with minimal change disease	Sudden-onset nephrotic syndrome Mesangial IgA deposits on biopsy without sufficient sclerosis to explain proteinuria	Glucocorticoids, akin to treatment of minimal-change disease

Low-dose sirolimus combined with angiotensin-converting enzyme inhibitor and statin stabilizes renal function and reduces glomerular proliferation in poor prognosis IgA nephropathy

Josep M. Cruzado[1], Rafael Poveda[1], Meritxell Ibernón[2], Montserrat Díaz[3], Xavier Fulladosa[1], Marta Carrera[4], Joan Torras[1], Oriol Bestard[1], Itziar Navarro[1], José Ballarín[3], Ramón Romero[2] and Josep M. Grinyó[1]

- RCT, 2006- 2008,23 patients ,GFR ~ 30 -60cc/min and > 1 gr proteinuria
- Sirolimus 1mg/d with ACE and Atorvastatin
- At 1 year, SRL treatment was associated with significant reduction proteinuria, mesangial and endocapillary proliferation.
- Glomerular sclerosis, tubular atrophy and interstitial fibrosis were similar

Nephrol Dial Transplant (2011) 26: 3596–3602

Nephrol Dial Transplant (2011) 26: 3237–3242
doi: 10.1093/ndt/gfr052
Advance Access publication 4 March 2011

New treatment for IgA nephropathy: enteric budesonide targeted to the ileocecal region ameliorates proteinuria

Hilde Kloster Smerud[1], Peter Bárány[2], Karin Lindström[2], Anders Fernström[3], Anna Sandell[3], Peter Påhlsson[4] and Bengt Fellström[1]

- New enteric formulation of the locally acting glucocorticoid budesonide (Nefecon), designed to release the active compound in the ileocecal region.
- Budesonide 8 mg/day was given to 16 patients with IgAN for 6 months, followed by a 3-month follow-up period.

Future Drugs

1. Specific neutralization of Gd-IgA1 itself
2. Inhibition of abnormal enzymatic glycosylation of IgA1
3. Specific depletion of source cells that produce Gd-IgA1 or auto-antibody