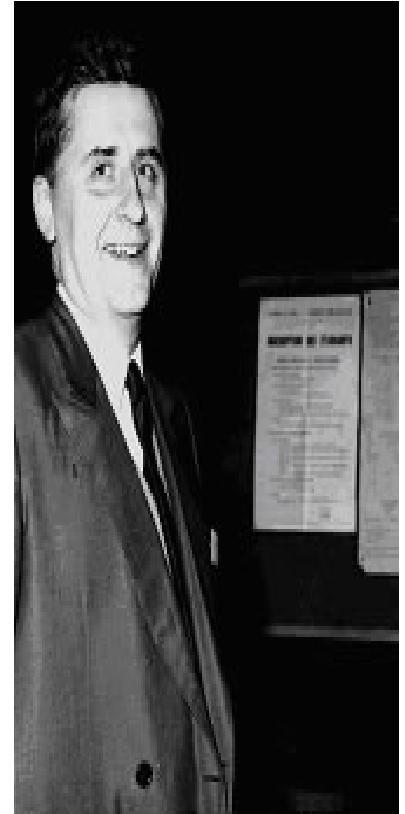


IGA NEPHROPATHY

Anjali Gupta, MD

Epidemiology

- Most common cause of primary glomerulonephritis
- Peak incidence in 2nd to 3rd decade of life
- 2:1 male to female ratio
- Most common in Caucasians and Asians
- Described in 1968 by Dr Berge



Clinical Presentations

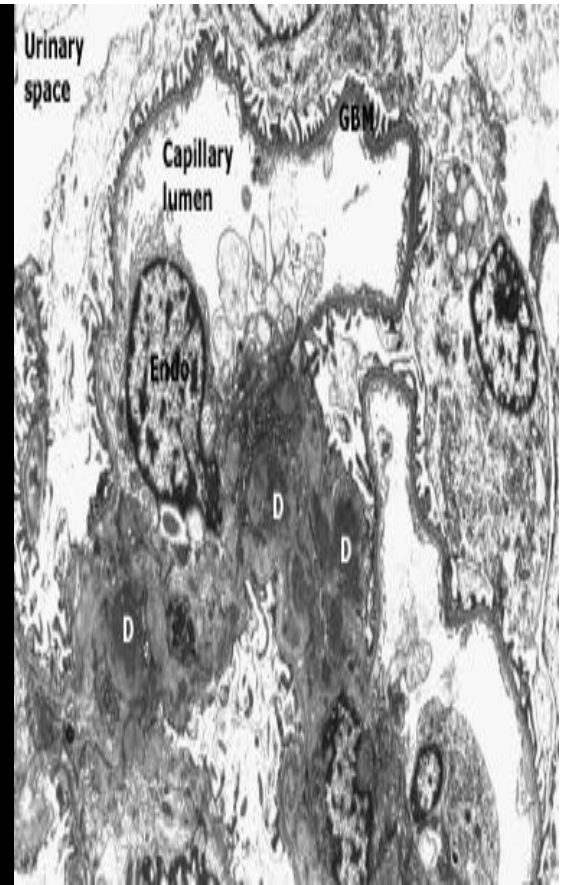
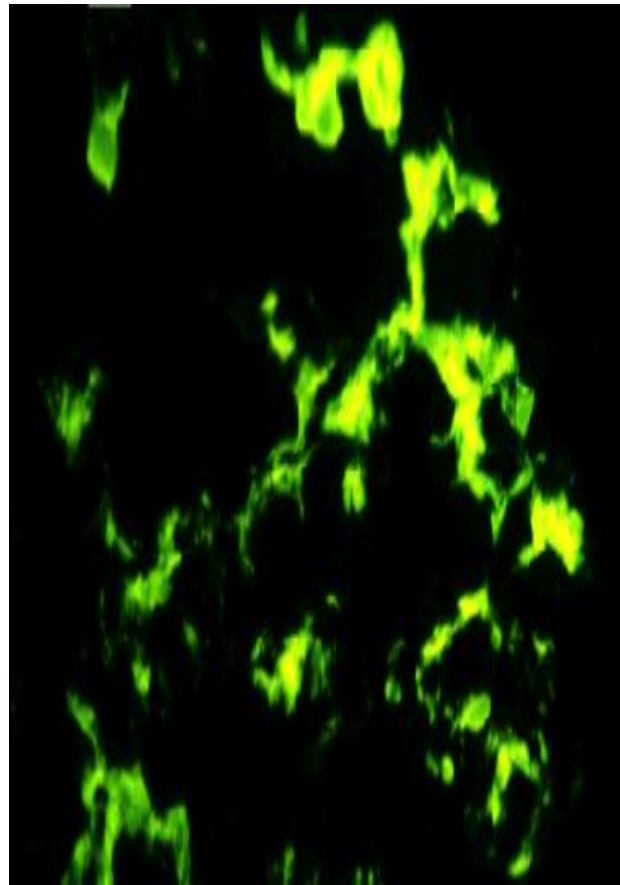
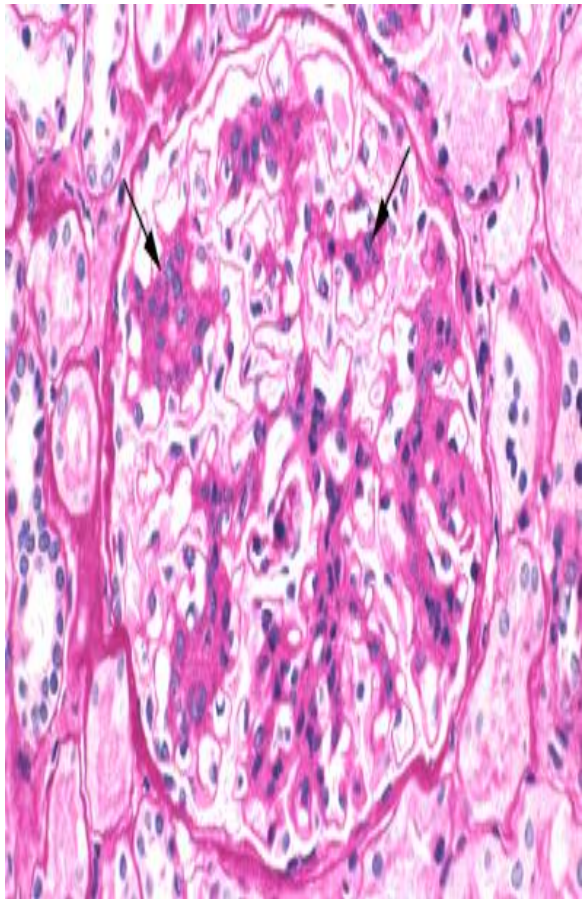
- 40-50% present with gross hematuria, usually following an upper respiratory infection- classic presentation
- 30-40% present with microscopic hematuria and non-nephrotic proteinuria
- <5% present with nephrotic syndrome
- <5% acute RPGN

Diagnosis



Renal Biopsy

Pathology—Light Microscopy

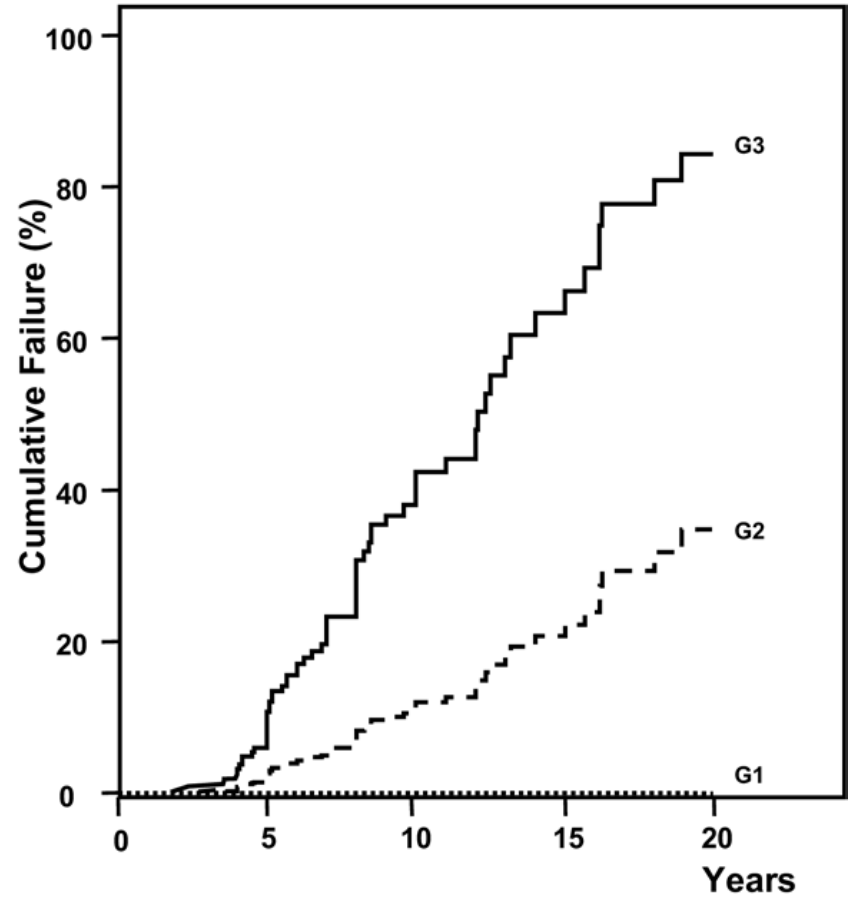
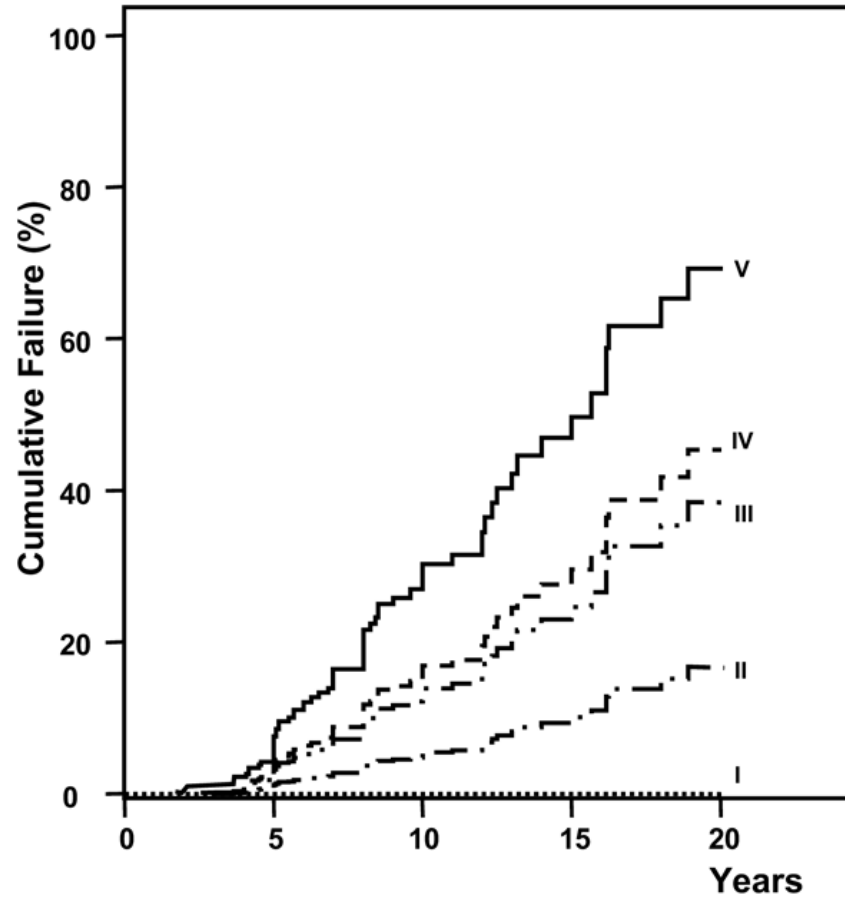


Pathological Classification

Table 1. Lee's Classification and the 3-Grade Classification

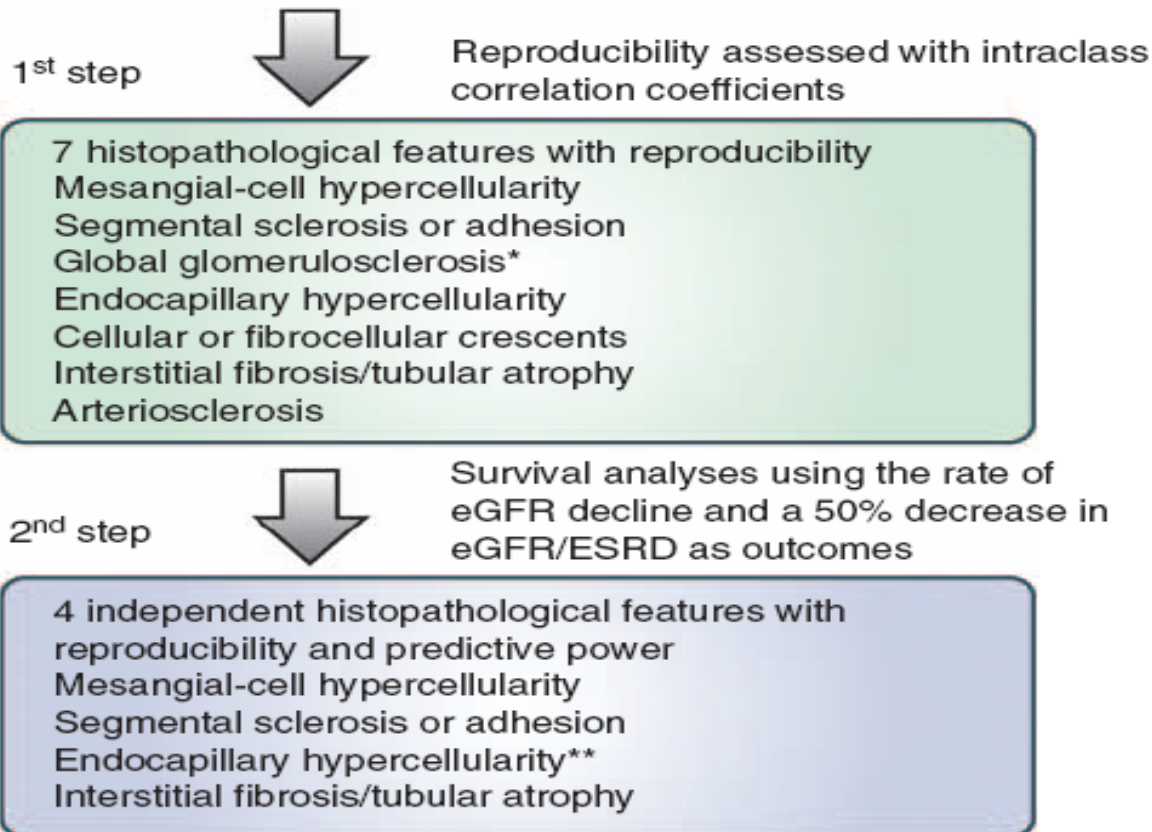
Grade	Glomerular Changes	Tubular and Interstitial Changes	Grade	Glomerular Changes	Tubular and Interstitial Change:
I	Mostly normal; occasional slight mesangial thickening (segmental) with or without hypercellularity	Absent	G1 (mild)	Normal glomeruli or slight increase in mesangial matrix and/or cellularity	None
II	Less than half the glomeruli show localized mesangial proliferation and sclerosis; rarely, small crescent	Absent			
III	Diffuse mesangial proliferation and thickening with focal and segmental variation; occasional small crescents and adhesions	Focal interstitial edema and infiltrate occasionally present; tubular atrophy rare	G2 (moderate)	Moderate focal or diffuse mesangial proliferation and/or focal segmental sclerosis and/or endocapillary proliferation and/or cellular crescents up to 50% of glomeruli	Tubular atrophy and interstitial fibrosis up to 1/3 of cortical area
IV	Marked diffuse mesangial proliferation and sclerosis; crescents present in up to 45% of glomeruli; partial or total glomerulosclerosis frequent	Tubular atrophy, interstitial inflammation, and occasional interstitial foam cells			
V	Similar to grade IV, but more severe; crescents present in > 45% of glomeruli	Similar to grade IV, but more severe	G3 (severe)	Cellular crescents in > 50% of glomeruli and/or global glomerulosclerosis or fibrous crescents involving > 1/3 of glomeruli and/or diffuse segmental sclerosis	Tubular atrophy and interstitial fibrosis involving > 1/3 of cortical area

Survival curves for ESRD

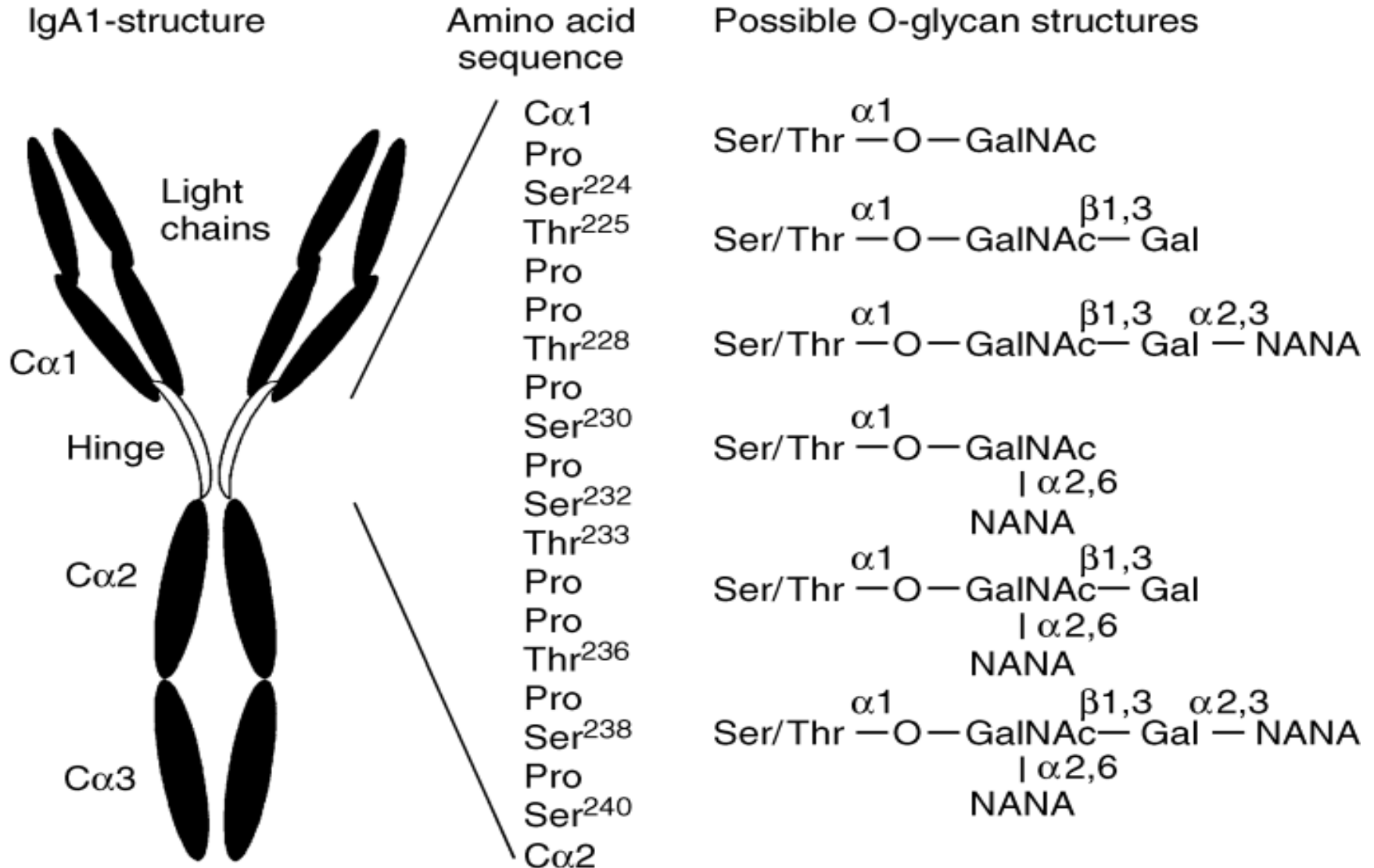


Oxford MEST score

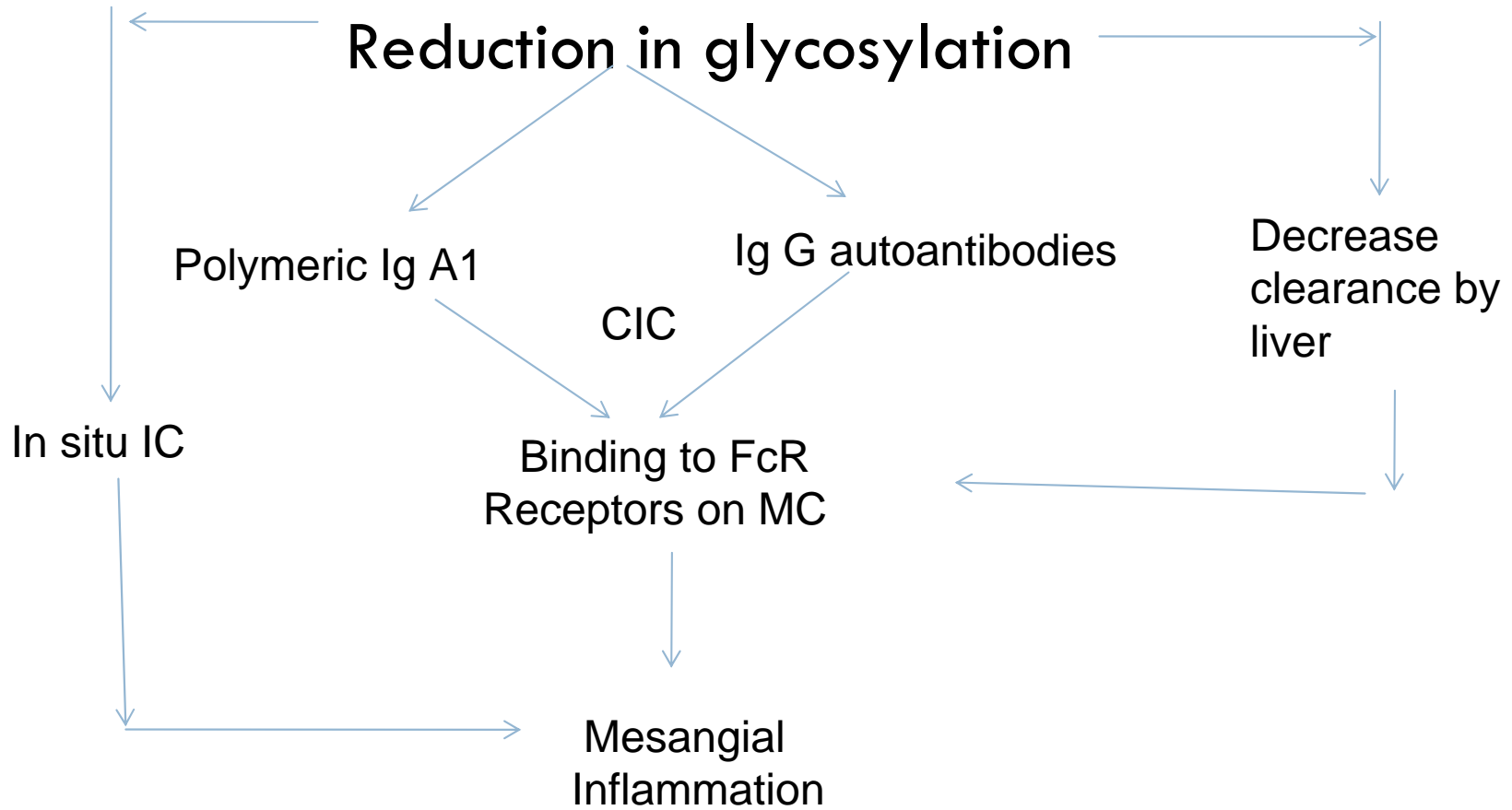
Pathological scoring of 265 renal biopsies of IgA nephropathy with proteinuria >0.5 g/d and eGFR ≥ 30 ml/min/1.73 m² followed for at least 1 year



Pathogenesis: Characteristics of IgA in IgAN



Pathogenesis



Clinical Prognostic Markers

Poor Prognosis:

- **Severity of proteinuria**
- **HTN**
- **Renal impairment**
- Increasing age
- Duration of preceding symptoms
- Increased BMI

Good Prognosis:

- Recurrent macroscopic hematuria

No Impact on Prognosis:

- Gender
- Ethnicity
- Serum IgA level

Prognosis

- 15% to 40% of adults and children will progress to ESRD
- 15 to 20% develop ESRD within 10 years of onset
- 30 to 35% develop ESRD within 20 years of onset

Treatment

- Conservative treatment
- ACE inhibitors
- Steroids
- Cytotoxic agent
- Combination therapies
- Others- Fish Oil

Conservative Treatment

- Normal renal function, normotension and only minor urinary abnormalities, such as isolated microscopic haematuria, and/or mild proteinuria
- Up to 23% of patients will have a spontaneous complete remission

Angiotensin II inhibition

ANGIOTENSIN INHIBITION

- Maschio et al randomized 44 patients to enalapril or other non-ACE/ARB antihypertensive
- Patients had $>0.5\text{g/day}$ proteinuria and $\text{Cr} < 1.6$
- At six years, renal survival more likely in ACE-I group (92%) than in control (55%)
- Other Trial- HKVIN and IgACE- underpowered Trials

ARB

Beneficial effects of high-dose losartan in IgA nephritis

Clin Nephrol. 2009 Jun;71(6):617-24.

- 6-year randomized trial, 207 patient ,high-dose ARB (losartan 200 mg/day) with normal dose ARB (losartan 100 mg/day), normal dose ACEI (20 mg/day) and low-dose ACEI (10 mg/day)
- High Dose ARB had significantly higher eGFR ($p < 0.0005$) and lower proteinuria ($p < 0.005$) at the end of the study
- Loss of eGFR was 0.7 ml/min/year for high-dose ARB compared to 3.2 - 3.5 ml/ min/year for the other 3 groups ($p = 0.0005$)

Angiotensin II inhibition

To Summarize.....

- Lowering blood pressure and decrease proteinuria, are modifiable risk factors for progressive disease
- Patient with persistent proteinuria (>500 or >1000 mg/day) should be started on a ACE/ARB

Fish Oil



A Controlled Trial of Fish Oil in IgA Nephropathy

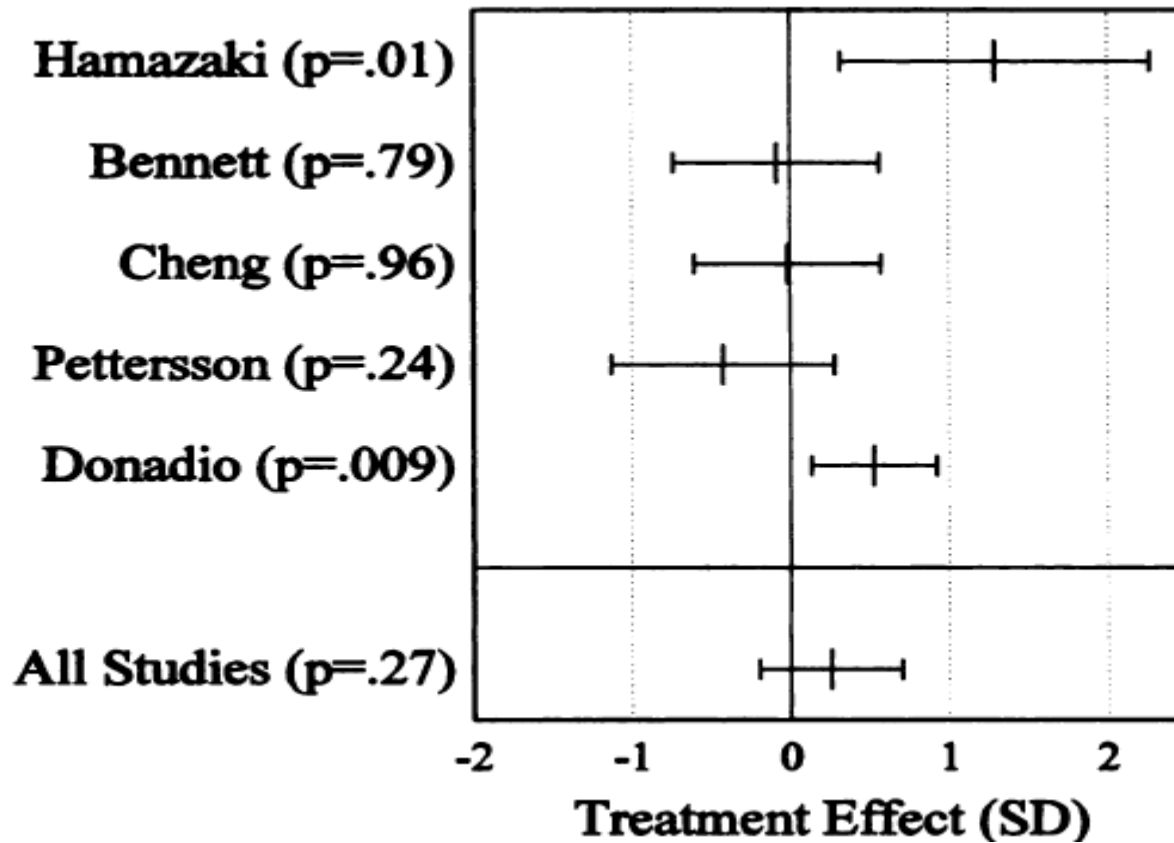
multicenter, placebo-controlled, randomized trial

James V. Donadio Jr., Erik J. Bergstralh, Kenneth P. Offord, Dorothy C. Spencer and
Keith E. Holley for the Mayo Nephrology Collaborative Group
N Engl J Med 1994

FISH OIL

- Denadio et al in 1994 published in NEJM a study that randomized 104 patients (Bl Cr 1.5 & proteinuria of 2.5-3gm) to fish oil 12g daily vs placebo with olive oil
- Primary end point: 50% increase in serum creatinine
- At four years of follow-up, fish oil group had lower incidence of primary end point (6% vs 33%) and lower incidence of death or ESRD (10% vs 40%)
- Benefits continued at six years of follow up

Forest plot- Fish Oil



Fish Oil

To summarize...

- Fish oil use shows a trend toward renal function preservation
- Patients who meet criteria for angiotensin inhibition
Should also receive fish oil

Immunosuppressive Therapy- Steroids

- Pozzi et al conducted a prospective trial of 86 patients with proteinuria and normal to mild renal function . Follow up 5 yrs
- Patients randomized to supportive therapy alone or 6 month of steroids
- Primary end point: doubling of serum Cr
- Those on steroids had lower incidence of primary end point at 5 years (2% vs 21%) and at 10 years (2% vs 30%)
- However, did not assess for effect of ACE-I

Efficacy and Safety of Glucocorticoids : Meta-Analysis

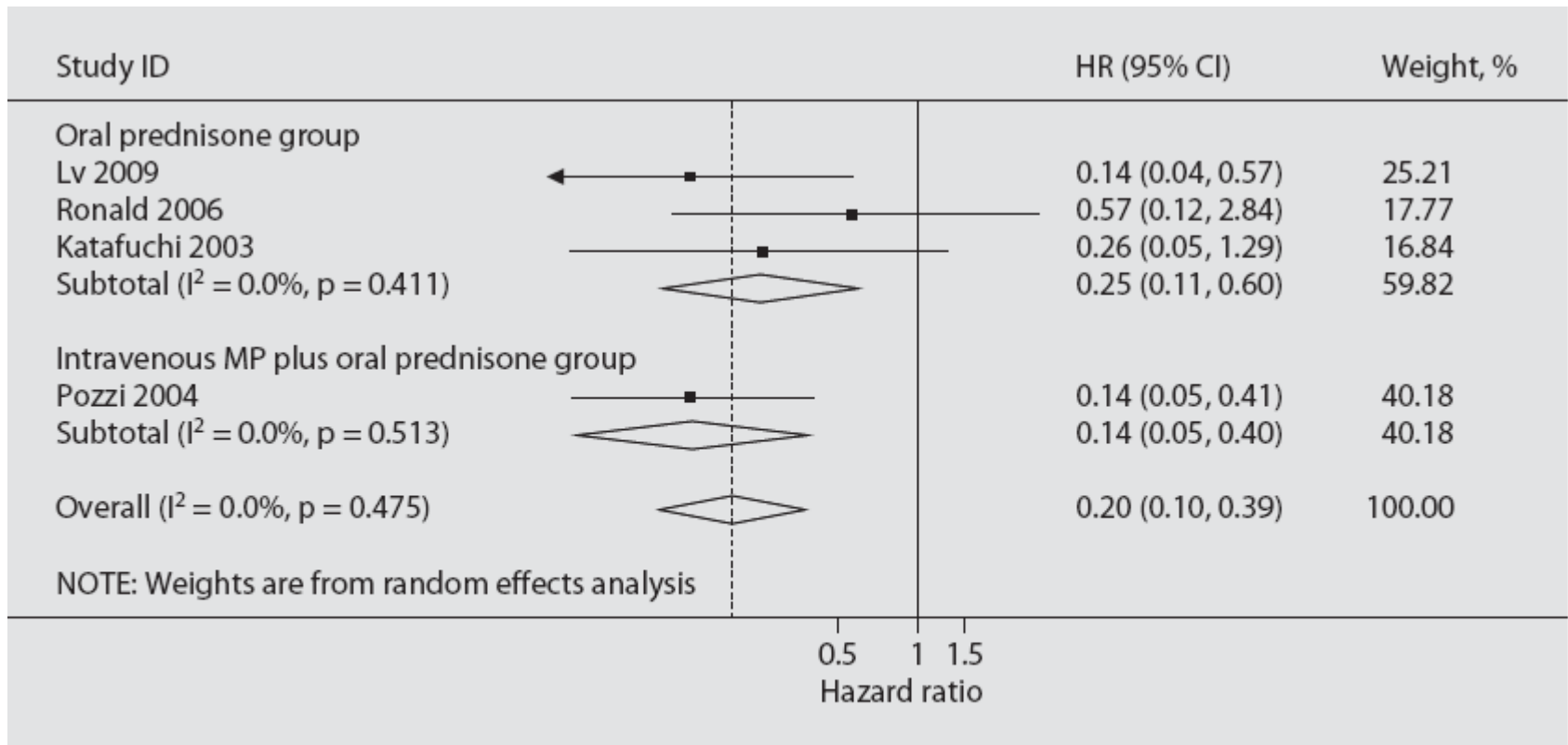


Fig. 2. Comparison of glucocorticoids versus controls on renal survival.

Efficacy and Safety of Glucocorticoids : Meta-Analysis

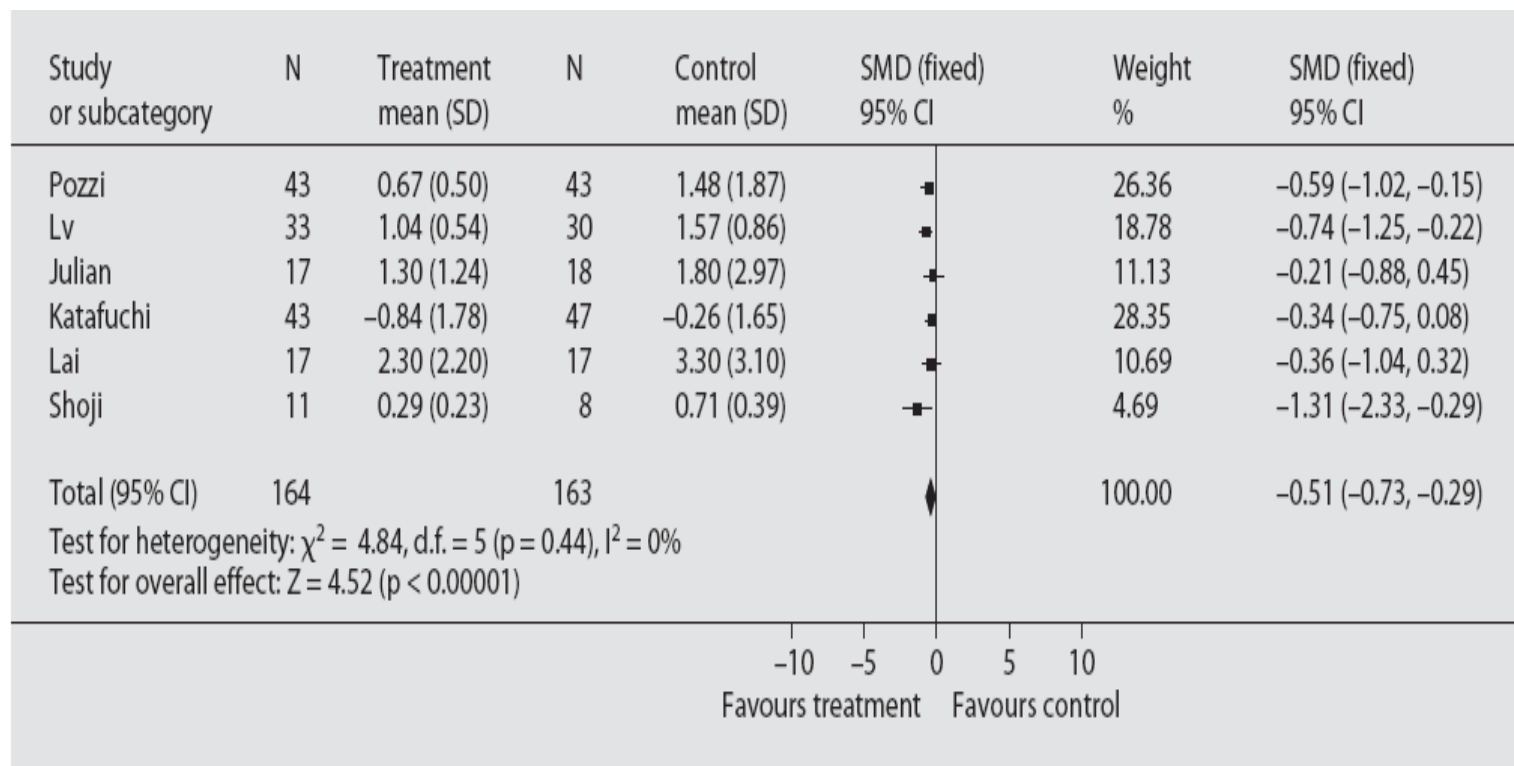


Fig. 3. Comparison of glucocorticoids versus controls on daily proteinuria.

Low gaded score studies, short follow up of 2-5 years, small limits
 Am J Nephrol 2009

ACE + STEROIDS

Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy

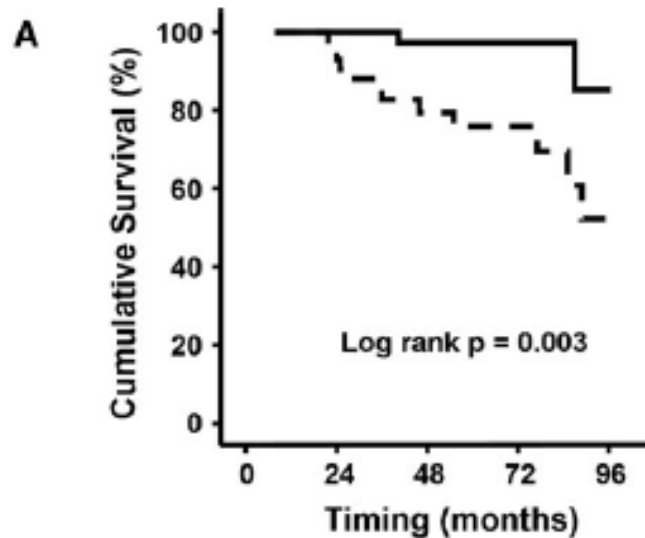
Carlo Manno, Diletta Domenica Torres, Michele Rossini, Francesco Pesce

Nephrol Dial Transplant (2009)

ACE + STEROIDS

- Prospective, open-label, multicentre, RCT
- Inclusion criteria: Moderate histologic lesions, 24-h proteinuria ≥ 1.0 g (< 3 gm) and (eGFR) ≥ 50 ml/min followed upto 96 months

ACE + STEROIDS

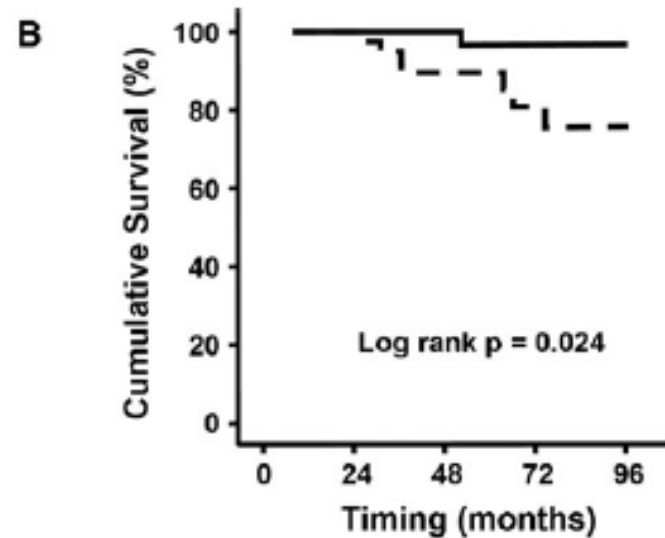


Patients at risk

Prednisone + Ramipril 48	37	32	19	4
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Ramipril	49	40	24	13	6
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Primary outcome



Patients at risk

Prednisone + Ramipril 48	29	29	19	4
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Ramipril	49	39	28	15	6
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ESRD

ACE + STEROIDS

- Primary end Point: 4.2% in combination group as c/w 26.5% in ACE alone $P=0.003$
- ESRD free survival 96.7% versus 75.5% $P = 0.024$
- Proteinuria no long term difference between the two groups
- Progression of renal disease HR 0.13 (0.03-0.61)

Steroids

- Patients with sustained proteinuria despite achieving BP of 125/75mm Hg with full RAS blockade
- Nephrotic range proteinuria

Immunosuppressive Therapy

Steroids + Cytotoxic agents

Controlled Prospective Trial of Prednisolone and Cytotoxics in Progressive IgA Nephropathy

Francis W. Ballardie* and Ian S. D. Roberts

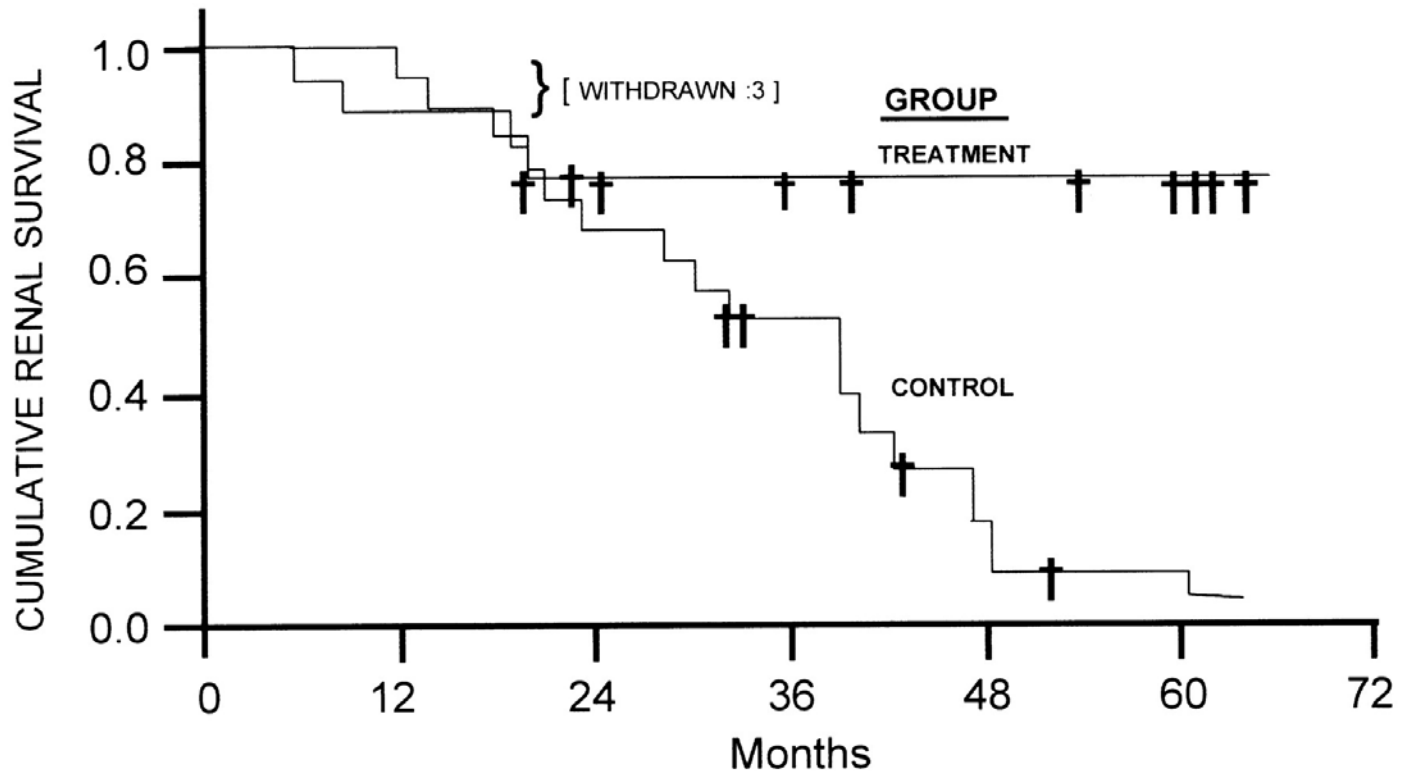
J Am Soc Nephrol 13:2002

Steroids + Cytotoxic agents

COMBINATION THERAPY

- single center study of 38 patients with IgAN with impaired renal function($Cr < 2.8$) and declining @15%/year
- Randomized to no therapy or prednisone, cyclophosphamide, and azathioprine
- Those with combination therapy had significant reduction in proteinuria during the first 6 months (1.8g/day vs 4.4g/day) and higher renal survival at 2 years (82% vs 68%) and at 5 years (72% vs 6%)

No Caption Found



No. at risk	38							
Treatment	19	18	14	9	7	5	1	
Control	19	19	19	15	9	6	2	

Ballardie, F. W. et al. J Am Soc Nephrol 2002;13:142-148

Steroids + Cytotoxic agents

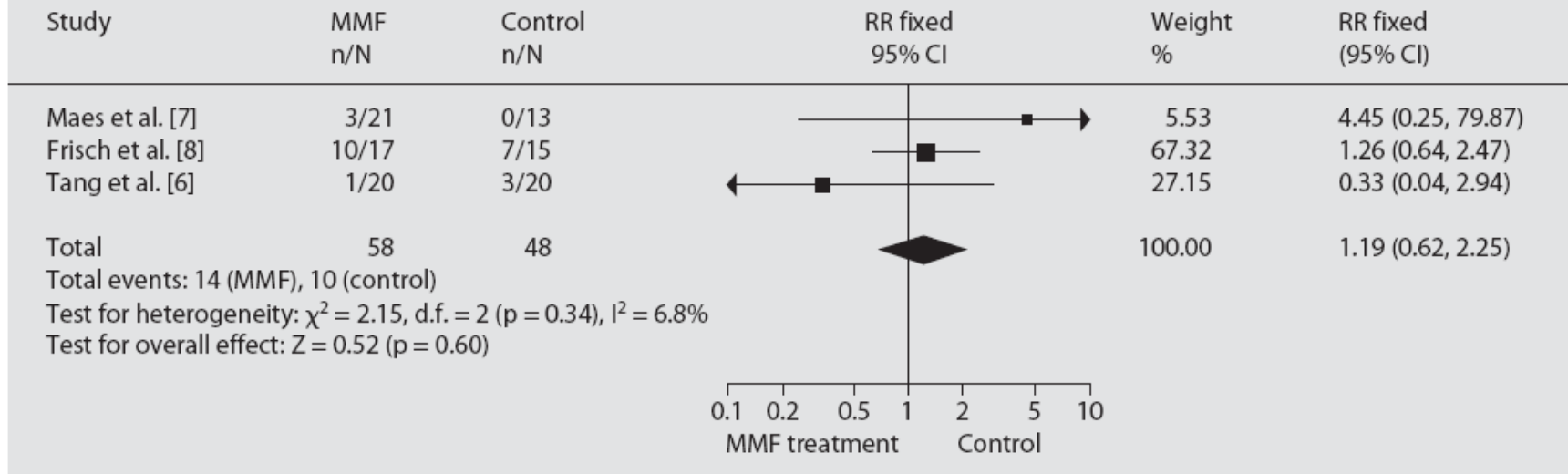


Insufficient evidence to support the use of cyclophosphamide in IgAN, except in crescentic IgAN with rapidly progressive renal failure

Immunosuppressive Therapy-Cellcept

Mycophenolate Mofetil Treatment for IgA Nephropathy: A Meta Analysis

Review: Meta-analysis of MMF treatment for IgAN (increase in SCr)
 Comparison: 03 MMF versus control
 Outcome: 03 Increase in SCr

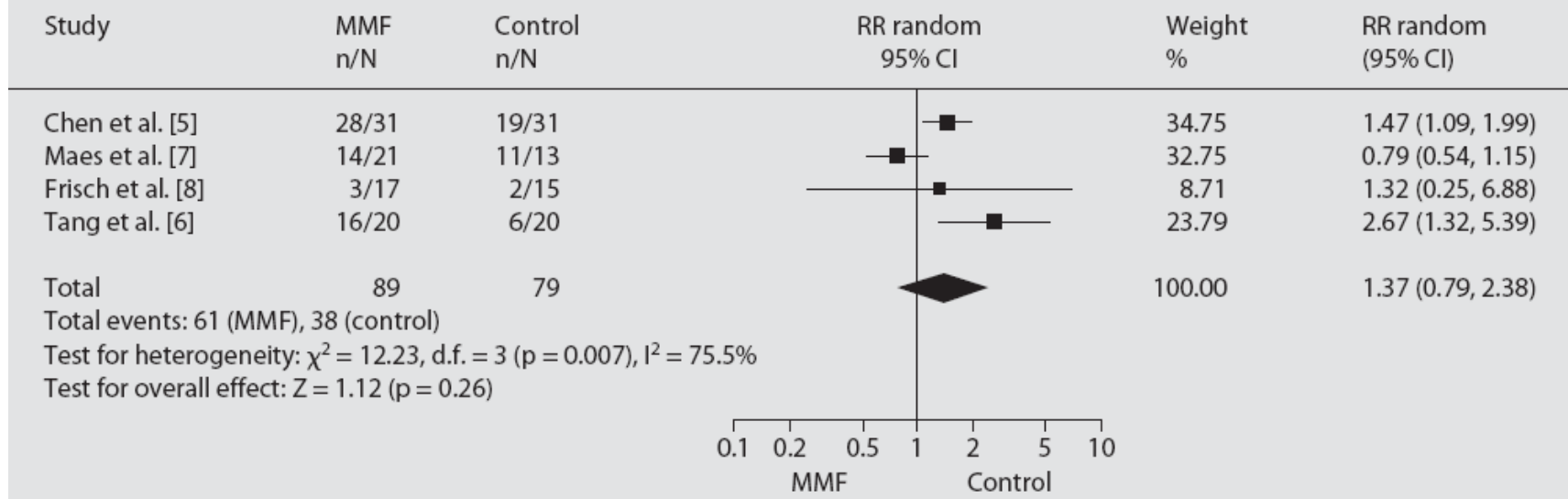


Am J Nephrol 2009;

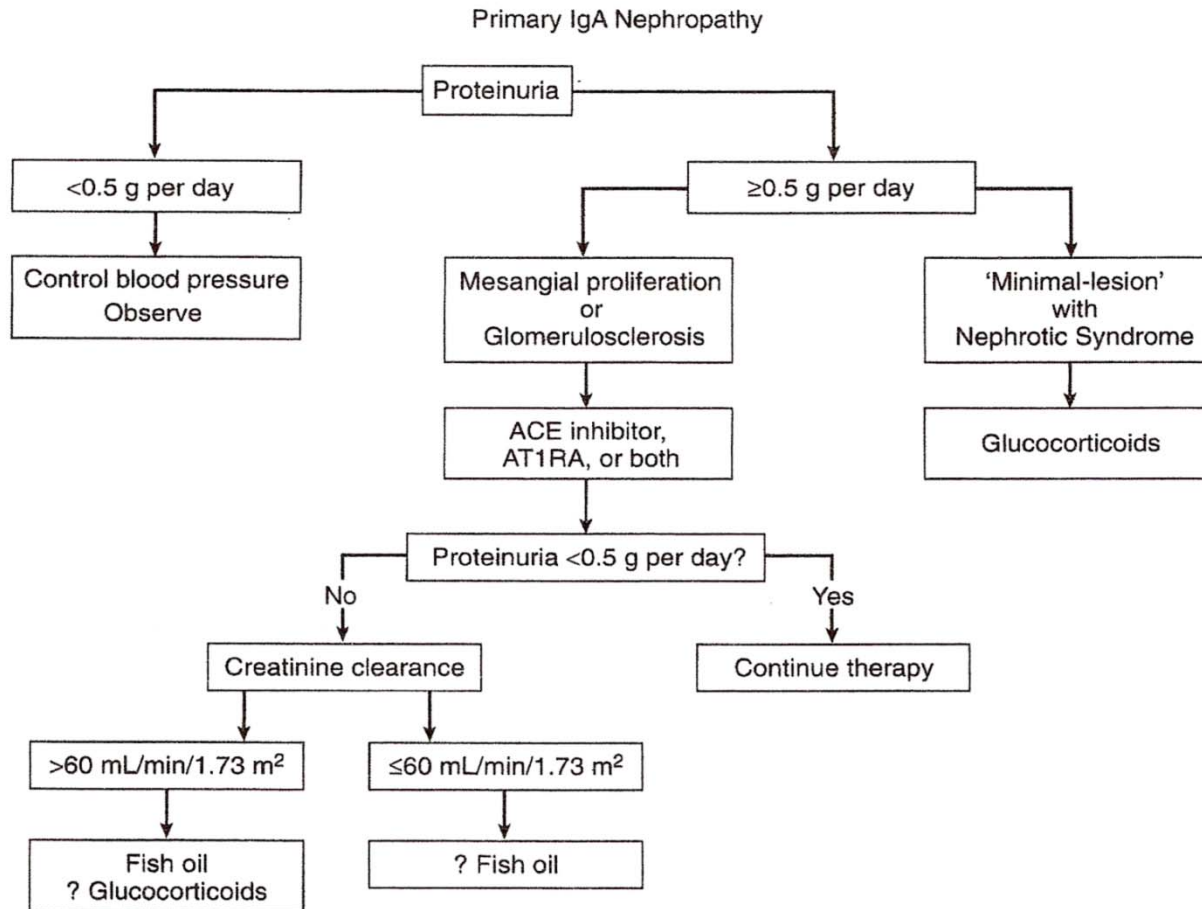
Immunosuppressive Therapy-Cellcept

Mycophenolate Mofetil Treatment for IgA Nephropathy: A Meta Analysis

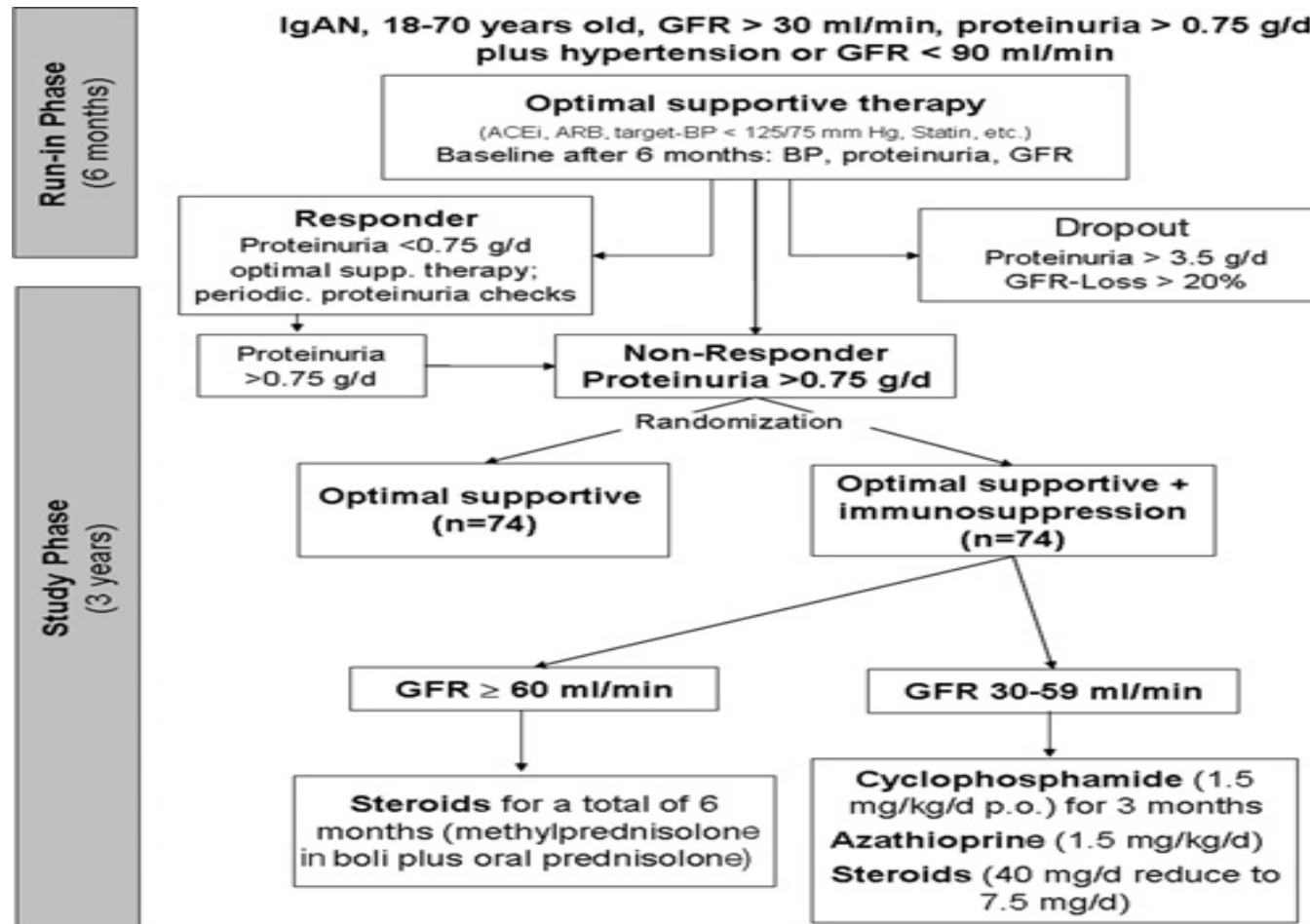
Review: Meta-analysis of MMF treatment for IgAN
 Comparison: 01 MMF versus control
 Outcome: 01 Decline in proteinuria



CONCLUSIONS



Ongoing Trials –STOP IGAN Trial





Thank
you