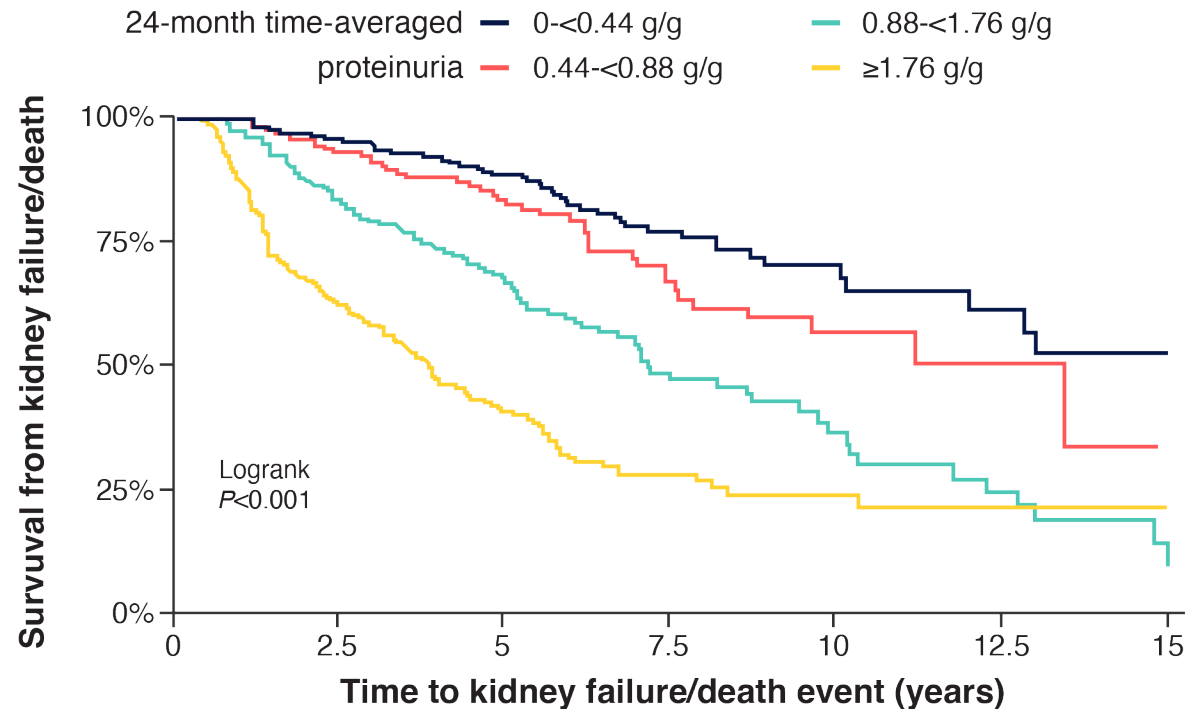


Proteinuria Level in IgAN

- Single strongest modifiable prognostic factor in IgAN



0-0.44 g/g	247	208	145	69	28	14	6
0.44-0.88 g/g	168	140	89	40	17	5	0
0.88-1.76 g/g	230	174	97	37	17	9	2
≥1.76 g/g	242	138	63	26	10	5	2

Kidney failure/death by category of time-averaged proteinuria

KDIGO 2021 Guidelines

Management of Patients with IgAN

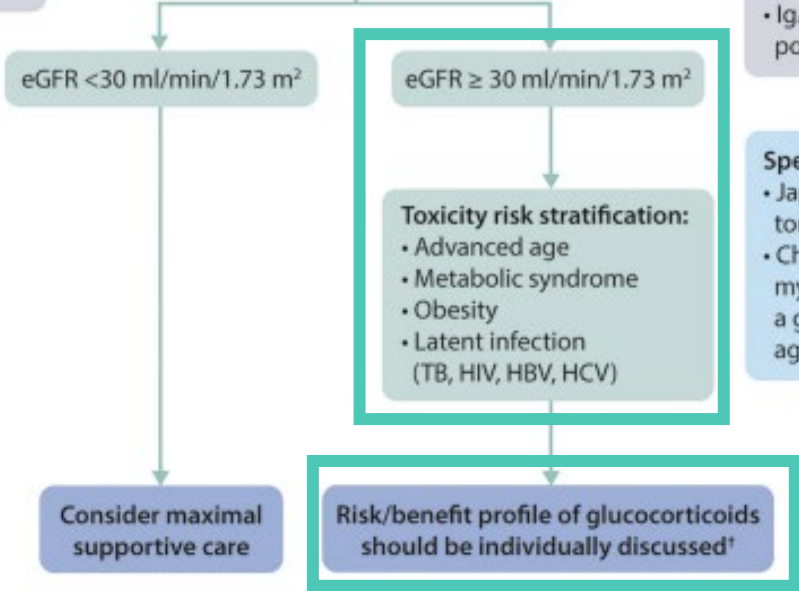
Glucocorticoids

- Benefit not well established
- Side effects including:
 - Latent infections
 - Osteoporosis
 - Obesity
 - Metabolic syndrome

Not applicable to variant forms of IgA:
• IgA deposition with minimal change disease
• IgAN with acute kidney injury
• IgAN with a rapidly progressive glomerulonephritis*

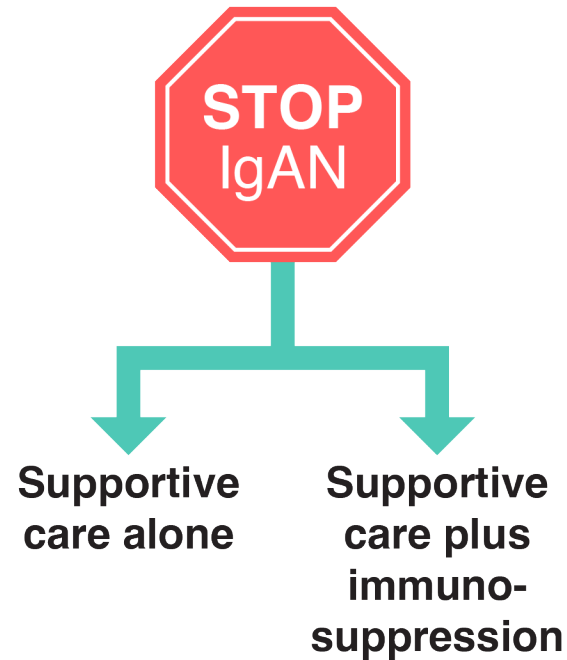
Proteinuria >1 g/d despite at least 3 months of optimized supportive care:
• BP management
• Maximally tolerated dose of ACEi/ARB
• Lifestyle modification
• Address cardiovascular risk

Not applicable to:
• IgA vasculitis
• IgA nephropathy secondary to:
- Viral (HIV, hepatitis)
- Inflammatory bowel disease
- Autoimmune disease
- Cirrhosis
• IgA-dominant postinfectious GN



Specific populations:
• Japanese – consider tonsillectomy
• Chinese – consider mycophenolate mofetil as a glucocorticoid-sparing agent



STOP IgAN Trial



Over a follow-up period of up to 10 years, patients with IgAN did NOT benefit from additional immunosuppression on top of supportive care measures



International IgAN Prediction Tool at Biopsy: Adults

  **International IgAN Prediction Tool at biopsy - Adults**

Determine prognosis in adults with IgA nephropathy

Questions

1. **Estimated GFR at biopsy**
2. Systolic blood pressure at biopsy
3. Diastolic blood pressure at biopsy
4. **Proteinuria at biopsy**
5. **Age at biopsy**
6. Race
7. Use of ACE inhibitor or ARB at the time of biopsy
8. MEST M-score
9. MEST E-score
10. MEST S-score
11. MEST T-score
12. Immunosuppression use at or prior to biopsy
13. At how many months after renal biopsy was...



Oxford Classification: MEST-C Score

Mesangial proliferation	M
Endocapillary hypercellularity	E
Segmental glomerulosclerosis	S
Tubular interstitial inflammation and fibrosis	T
Presence of crescents	C



Endothelin-1 (ET-1) & Angiotensin II (Ang II)

Key Players in Driving Kidney Injury, Proteinuria, and Disease Progression in IgAN

- Proteinuria has a central role in disease pathophysiology

The pathophysiologic effects of both ET-1 and Ang II on glomeruli, tubulointerstitial areas, and vasculature drive progression of kidney failure



↑ Proteinuria



PROTECT Trial

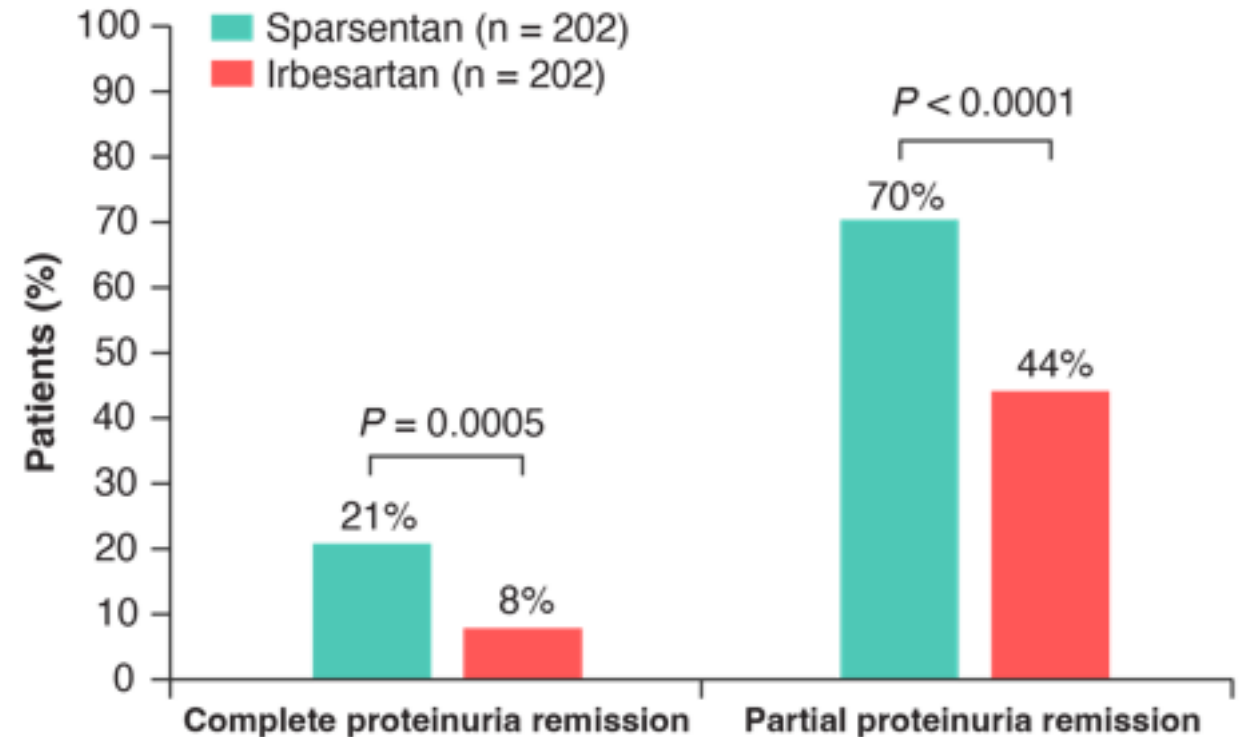
- International, randomized, double-blind, active-controlled phase 3 study
- Investigated sparsentan vs irbesartan in adults with IgAN and proteinuria of ≥ 1 g/day despite **maximized renin-angiotensin system inhibitor**

Sparsentan: novel non-immunosuppressive dual endothelin & angiotensin receptor antagonist



PROTECT Trial: Interim Analysis

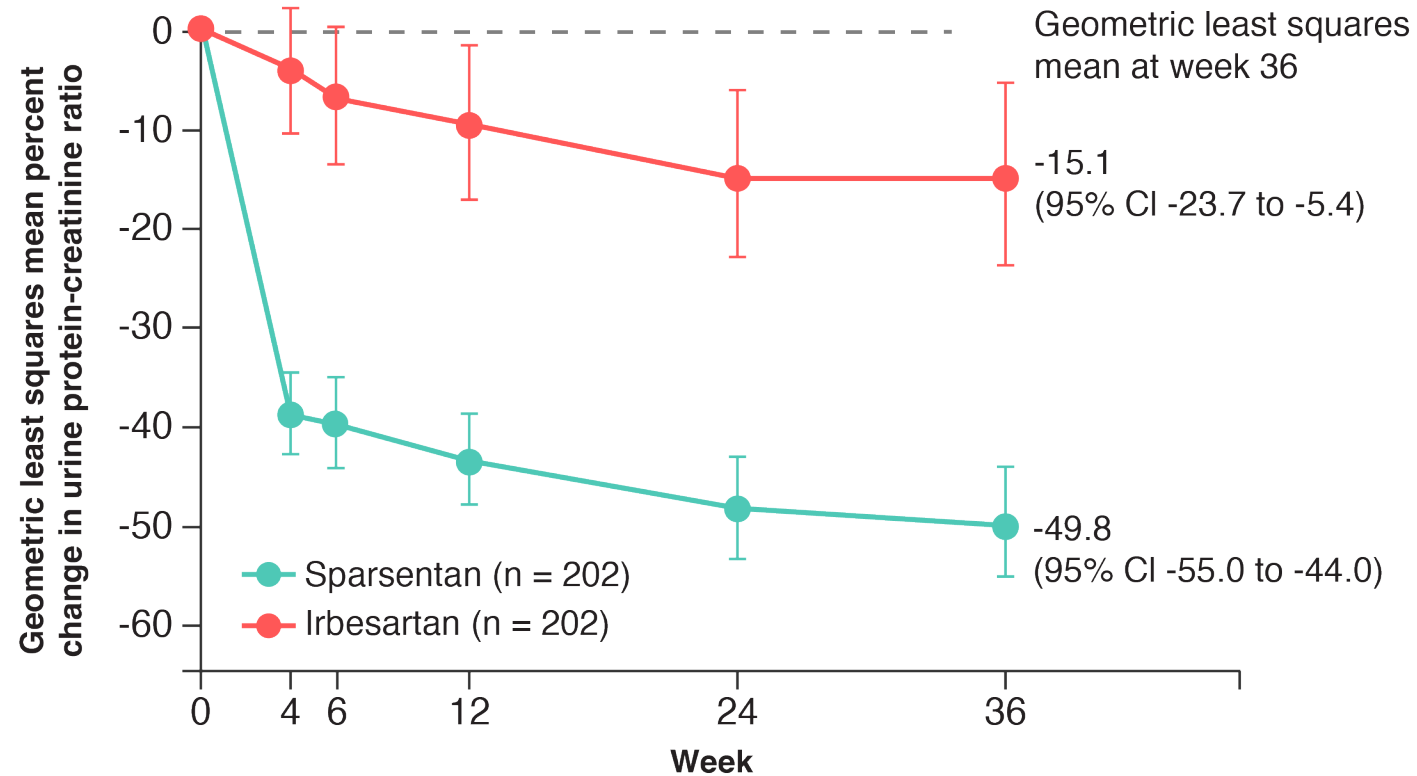
- Recruited patients at high risk of progression despite optimized standard of care for at least 3 months
- Compared sparsentan, a dual endothelin angiotensin receptor antagonist (DEARA), with the active control irbesartan
 - **Sparsentan** → **significant proteinuria reduction**



Percentage of patients with complete and partial remission of proteinuria at any time during treatment in the double-blind period



PROTECT Trial: Interim Analysis



Percentage change from baseline in urine protein-creatinine ratio in the sparsentan vs irbesartan group at week 36 (primary efficacy endpoint)

