Understanding Glomerular Disease: IgA Nephropathy

Laura Maursetter, DO, FASN

Assistant Professor (CHS)

University of Wisconsin

School of Medicine and Public Health

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Disclosure

- Honorarium: American Society of Nephrology: Board Review Course Director
- Honorarium: Vizient: served on Mock P&T committee

- *Nothing related to this talk*

Learning Objectives

- Discuss glomerular disease diagnosis and the importance of recognition
- Use IgA Nephropathy as an example of glomerular disease
  - Epidemiology
  - Prognosis
  - Pathogenesis
  - Discuss the treatment strategies given evolving research

Case Example

20-year-old man

- Episode of 2 days of gross hematuria.
- Once prior at 10 yrs old but no work up
- Not sexually active, no trauma reported, no dysuria or history of kidney stones.
- BP 115/70 and creatinine was 1.0.

- What would be the next step in work up for this patient?
  - CT urography
  - Urinalysis
  - Kidney ultrasound
  - Serum immunoglobulin test
  - Kidney biopsy
  - No other testing needed

Epidemiology of chronic kidney disease: an update 2022

kidney INTERNATIONAL supplements

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Extremely common

843,6 Million in 2017

Approximately 1 in 10

More prevalent in

- Individuals with diabetes mellitus
- Racial minorities
- Women
- Elderly
- Individuals with hypertension

Increasing death rate

+41.5% 1990 to 2017

Rank in cause of death

Large burden in low- and middle-income countries

Among the **top 10 causes** of death in Singapore, Greece, and Israel

Kovesdy, 2022

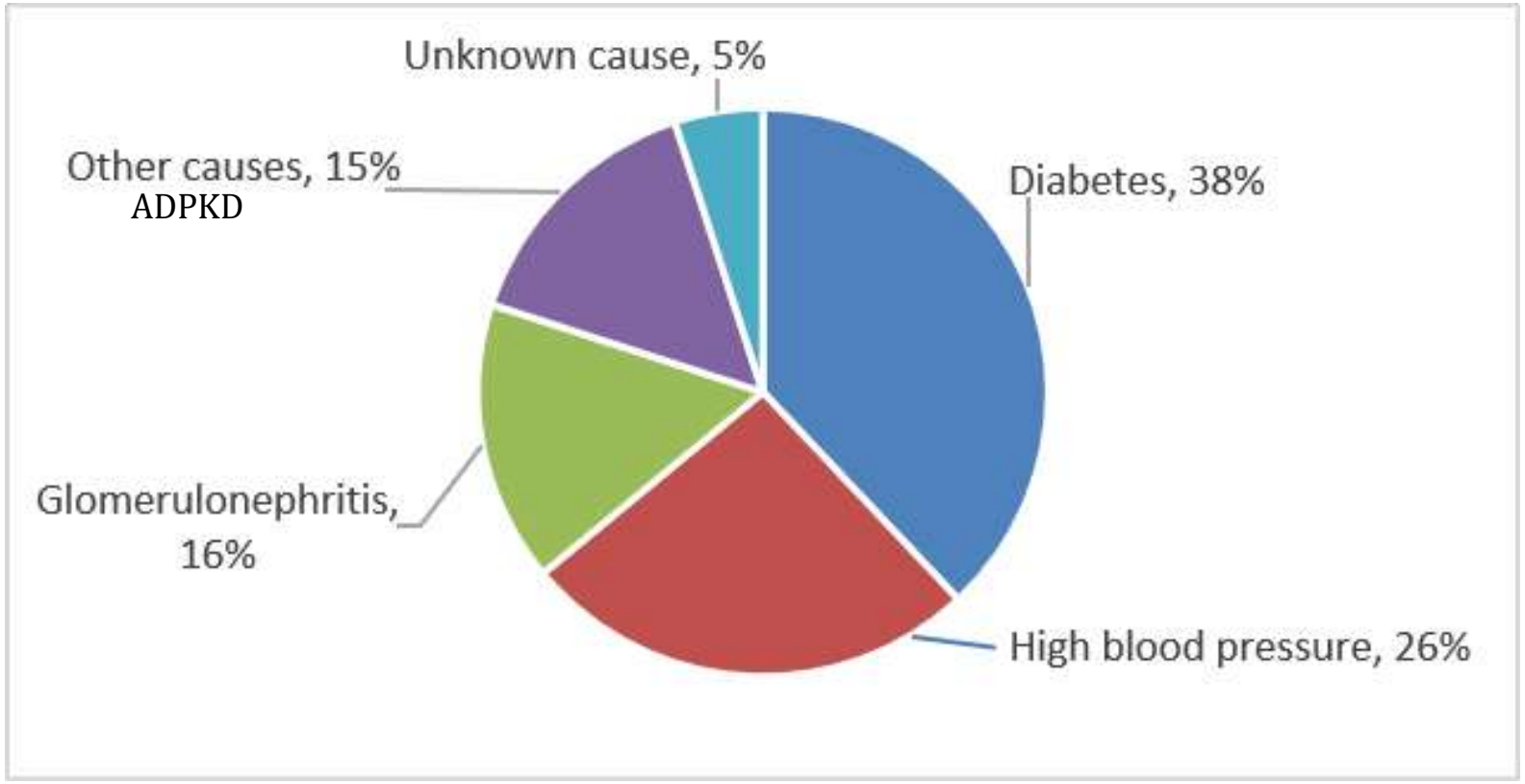
CONCLUSION

Chronic kidney disease (CKD) occurs frequently and has devastating consequences. This should prompt major efforts to develop preventative and therapeutic measures that are effective. The aim of these measures should be lowering the incidence of CKD and slowing its progression.

Identification of Kidney Disease

- Multiple Competing Factors
- Tricky to recognize
  - eGFR change
  - Imaging
  - Proteinuria
  - Hematuria
- When stray from natural progression of common causes

Data from USRDS for ESRD Patients: 2019



NIDDK Sept 2023

Natural History: Diabetes 10-20 yrs

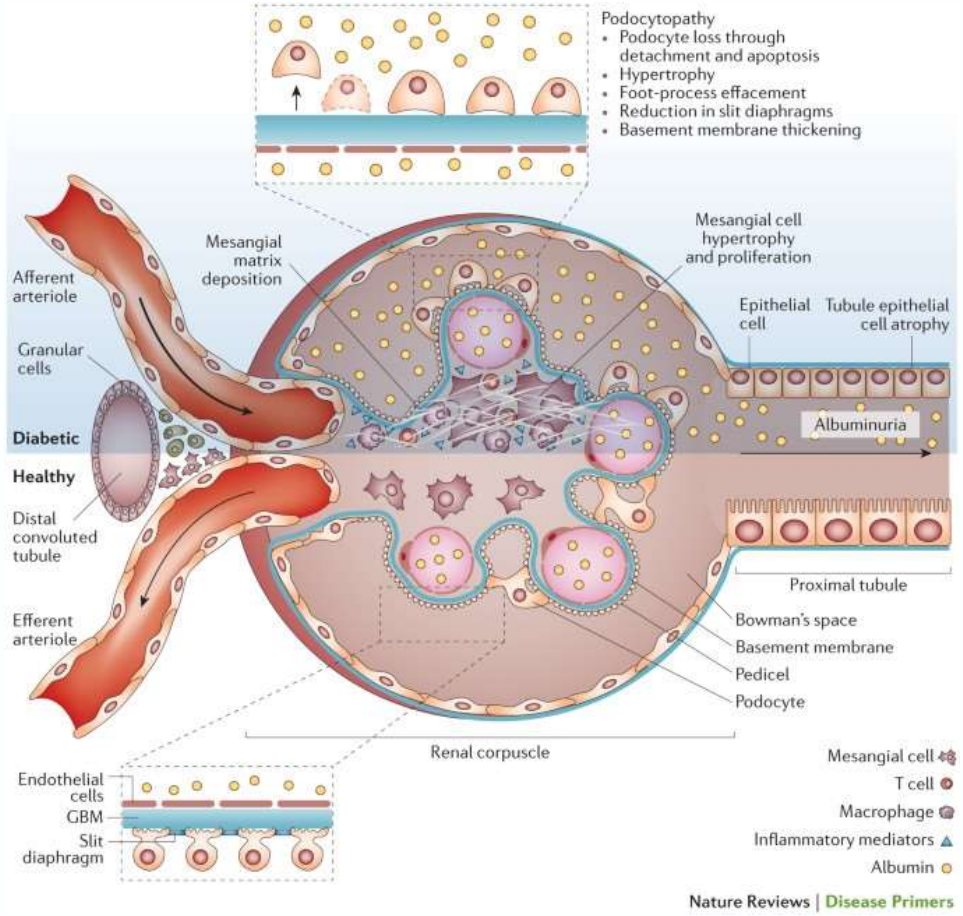
Pre
- Increased GFR with hyperfiltation and increased glomerular pressure leading to RAS acitvation
- Renal and glomerular hypertrophy

Incipient
- Microalbuminuria and hypertension
- Mesangial expansion, thickened basement membrane and arteriolar hyalinosis

Overt
- Proteinuria which may be within the nephrotic range and reduced GFR
- Kimmelstiel-Wilson lesions, tubulointerstitial fibrosis, loss of podocyte number

ESRD
- GFR < 15 ml/min/1.73 m^2
- Diffuse and progressive glomerulosclerosis

Wylie. Clin Med October 2012



Defronzo. Nature Review. 2015

Diabetes or something else?

- 42-year-old man with history of DM for 12 years.
  - A1C has fluctuated 8-12%.
  - Creatinine is 1.3
  - Microalbumin from 500mg 5 years ago to 1g 3 years ago to 2.5g now

- 42-year-old man with history of DM for 12 years.
  - A1C has been about 8%.
  - Creatinine is 1.3
  - Microalbumin negative 1 year ago and now is 4g

Case Example

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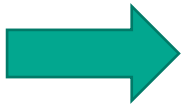
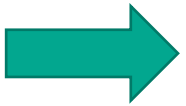
Urinalysis

- Is there protein?
  - How much?
- Is there blood?
  - How much?
  - Risk factors
- Is there a change in renal function?
- Nephrotic syndrome findings?

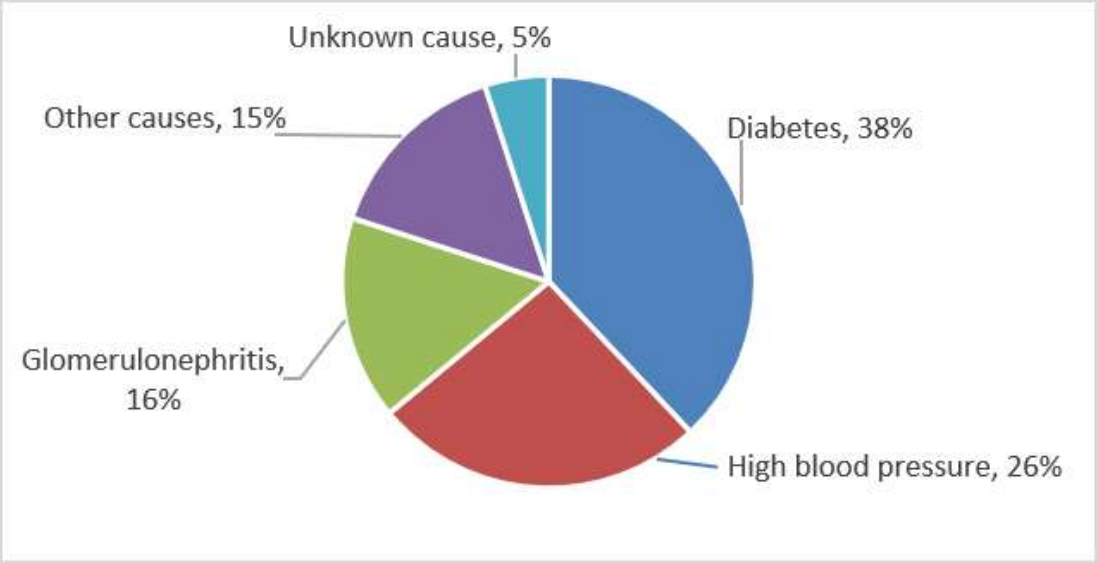




Chemical	Normal/range
pH	4.5-8.5
Specific Gravity	1.001-1.065
Glucose	Negative
Ketone	Negative
Bilirubin	Negative
Protein	Negative
Urobilinogen	Negative
Hemoglobin	Negative
Microscopic	
RBC	0-5
WBC	0-5
Casts	
Epithelial cells	
Bacteria	
Crystals	

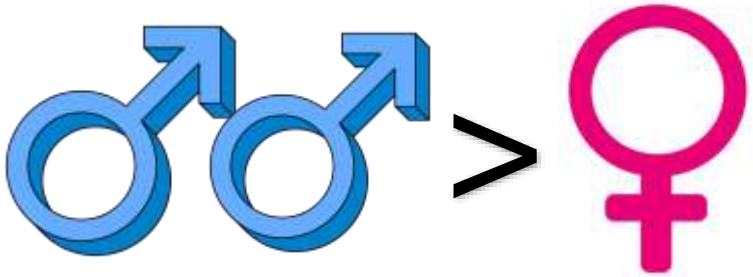
IgA Nephropathy

Example of glomerular disease



Epidemiology IgA Nephropathy

1968 Dr. Jean Berger first described



20-40% develop kidney failure in 10-20 years

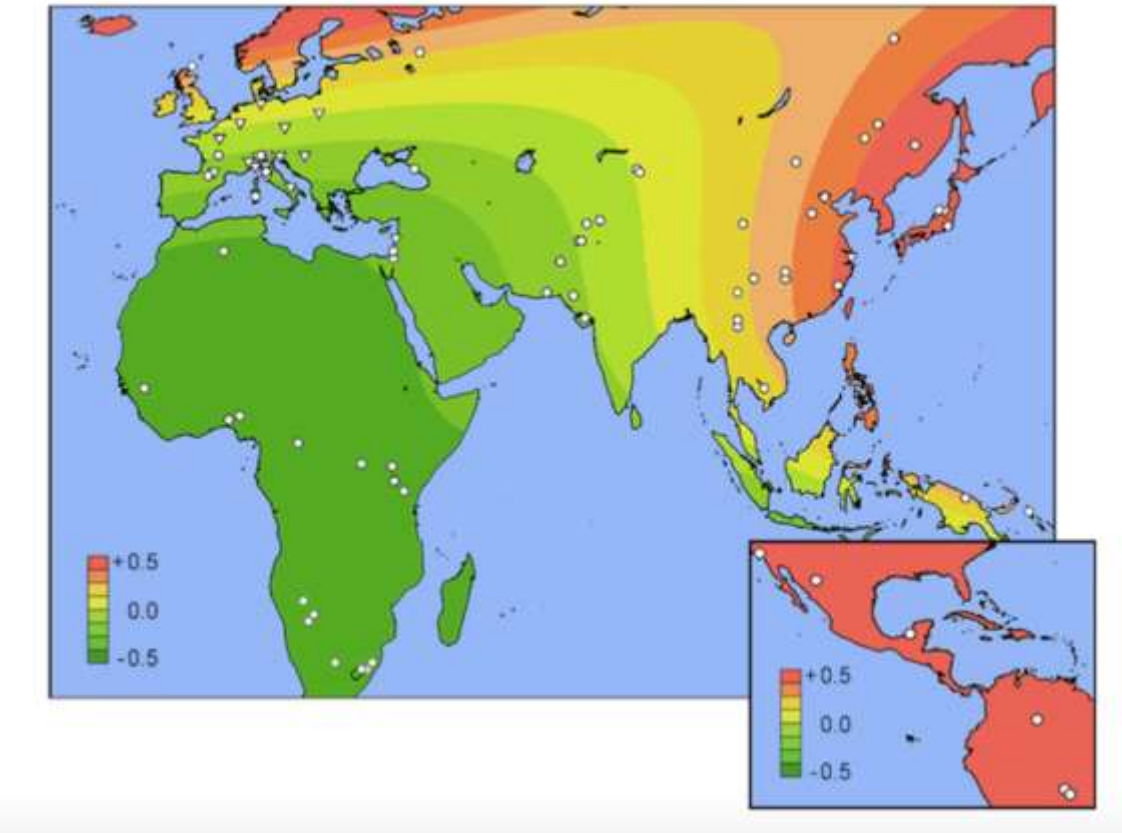
Common but how common?

2.5:100,000 Worldwide
1:600 Western World

Janzi. Clin Immunol. 2009
Pattrapornpisut. AJKD Sept 2021
Rodrigues. *CJASN* 2017

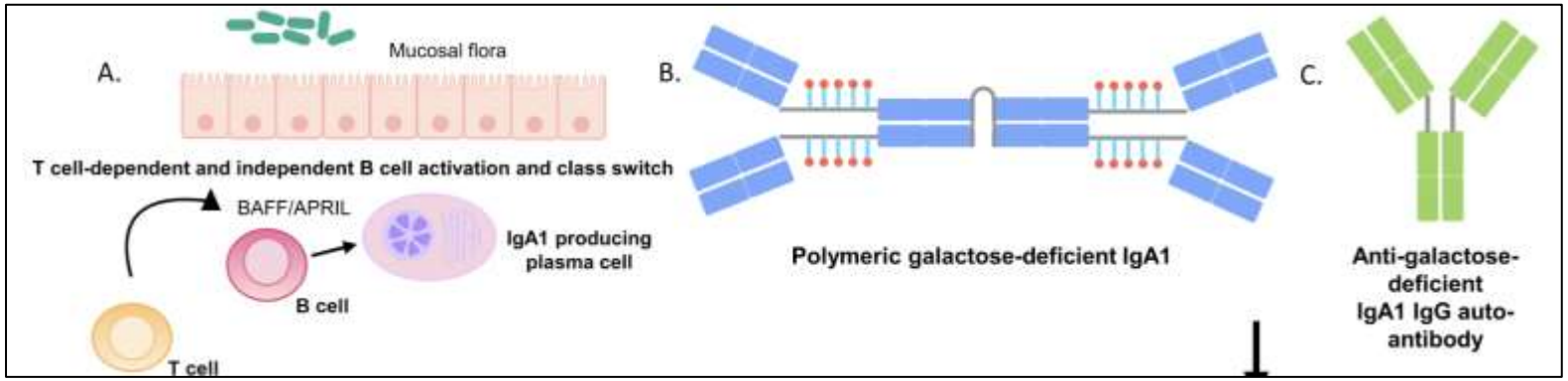
Genetic Variations

- Prevalence changes worldwide
- Location changes disease frequency
  - Asian ancestry living in Asia 40%
  - Asian ancestry living in North America 27%

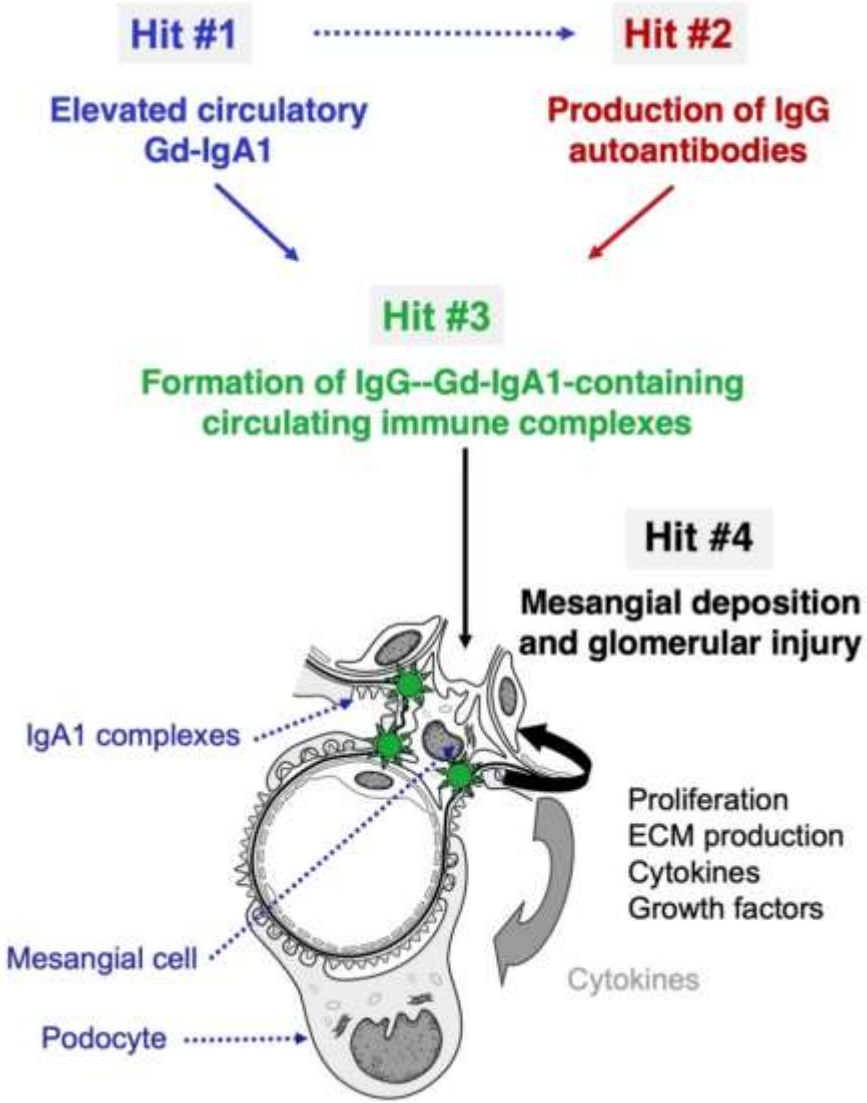


O'Shaughnessy. *Nephrology Dialysis Transplantation*, April 2018.

IgA Nephropathy Pathogenesis



Suzuki. JASN 2011



Knoppova.. *J. Clin. Med.* **2021**.

Changes in IgA

Deposition of Immune Complexes

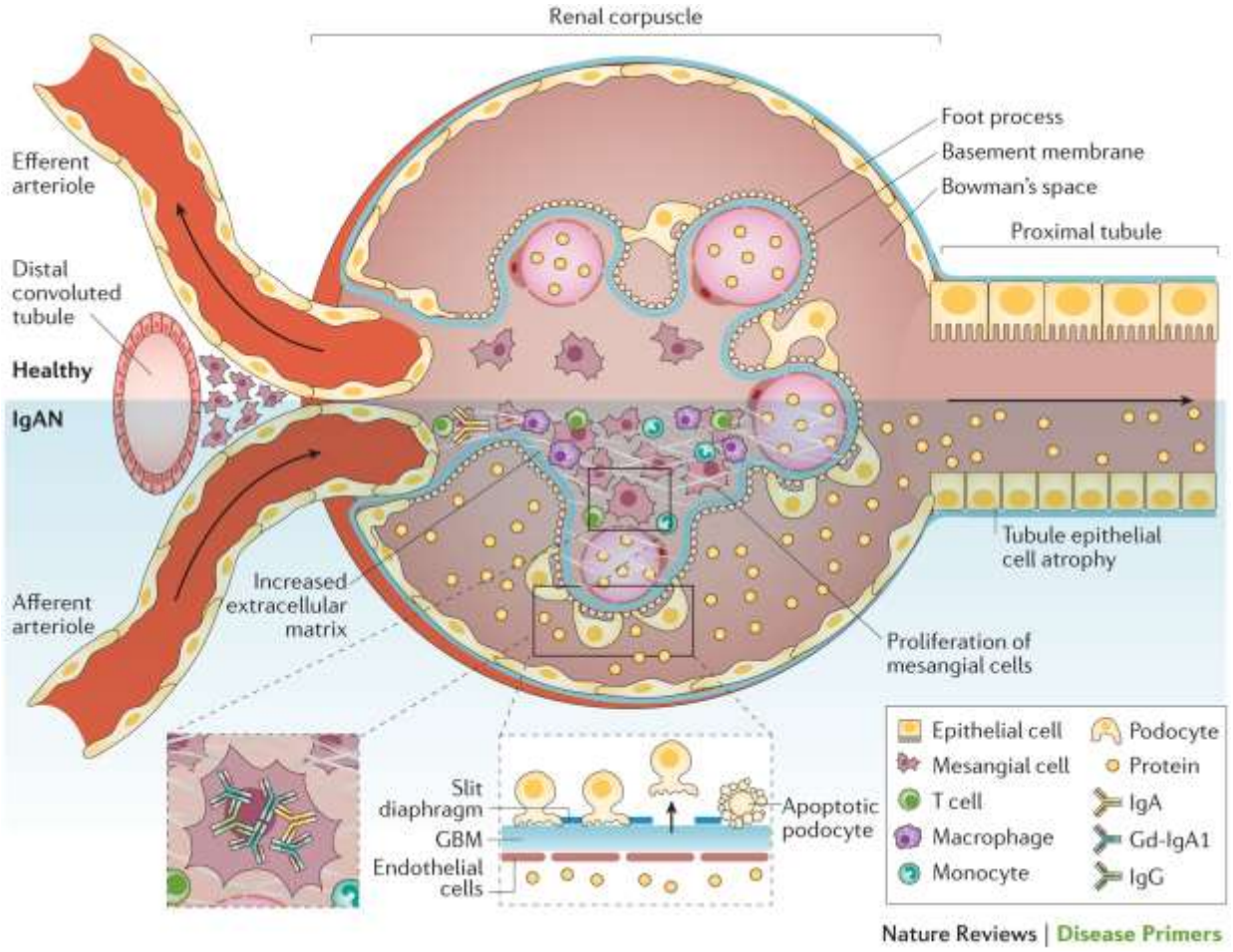
Mesangial Proliferation

Infiltration of inflammatory processes

Endocapillary proliferation

Podocyte injury

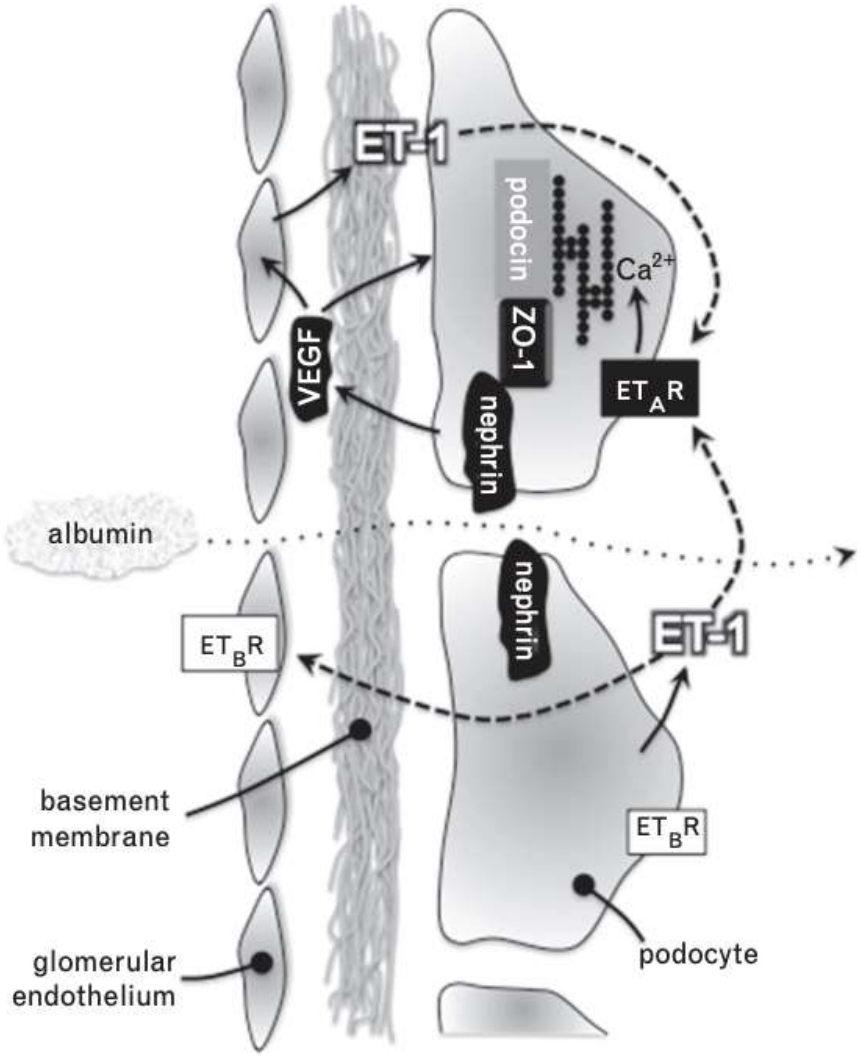
Tubulointerstitial injury



Lai et al 2016

Progression

- Endothelian 1 produced by all kidney cells
- Most potent vasoconstrictor in the body
- Overproduction leads to imbalance in Endothelian A/B receptor



Association with other diseases

Group	Disease
Gastrointestinal and liver diseases	Inflammatory bowel disease [a] (Crohn disease, ulcerative colitis), celiac disease, [a] cirrhosis [a]
Infection	HBV, [a] HCV, [a] HIV, [a] tuberculosis, leprosy
Autoimmune diseases	Ankylosing spondylitis, rheumatoid arthritis, Sjögren syndrome
Malignancy	Lung cancer, renal cell carcinoma, non-Hodgkin and Hodgkin lymphoma, IgA myeloma
Respiratory tract	Sarcoidosis, bronchiolitis obliterans, pulmonary hemosiderosis, cystic fibrosis, pulmonary fibrosis
Skin	Dermatitis herpetiformis, psoriasis

Pattrapornpisut. AJKD Sept 2021

How to Slow or Stop IgA?

Biopsy Informs Diagnosis and Prognosis: MEST-C

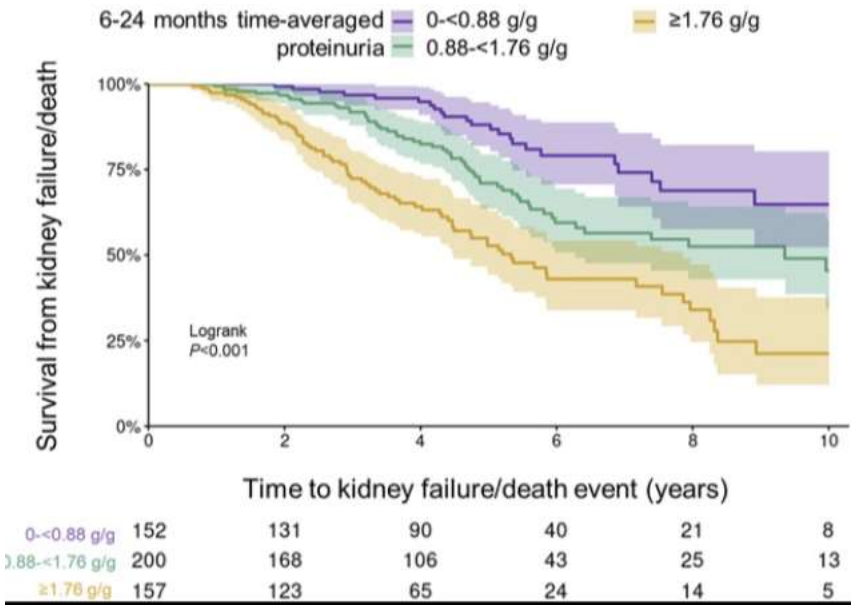
- Prognosis not a treatment tool
- C did not add further prognostic information
  - Can help avoid treatkent
    - <25% crescents = treat
    - >25% no treat as no change in outcomes

- M: mesangial hypercellularity
- E: endocapillary hypercellularity
- S: segmental glomerulosclerosis
- T: tubular atrophy/interstitial
- C: crescents

Barbour. KI. Jan 2016

Outcomes of IgA Nephropathy: Proteinuria

- Biopsy Proven IgA with >0.5g/g proteinuria 2299 adults and 140 kids



- Adult median kidney survival 10.9 years
- Increased risk
  - Proteinuria >0.44g/g
  - Asian ethnicity

Pitcher, et al. CJASN June 2023

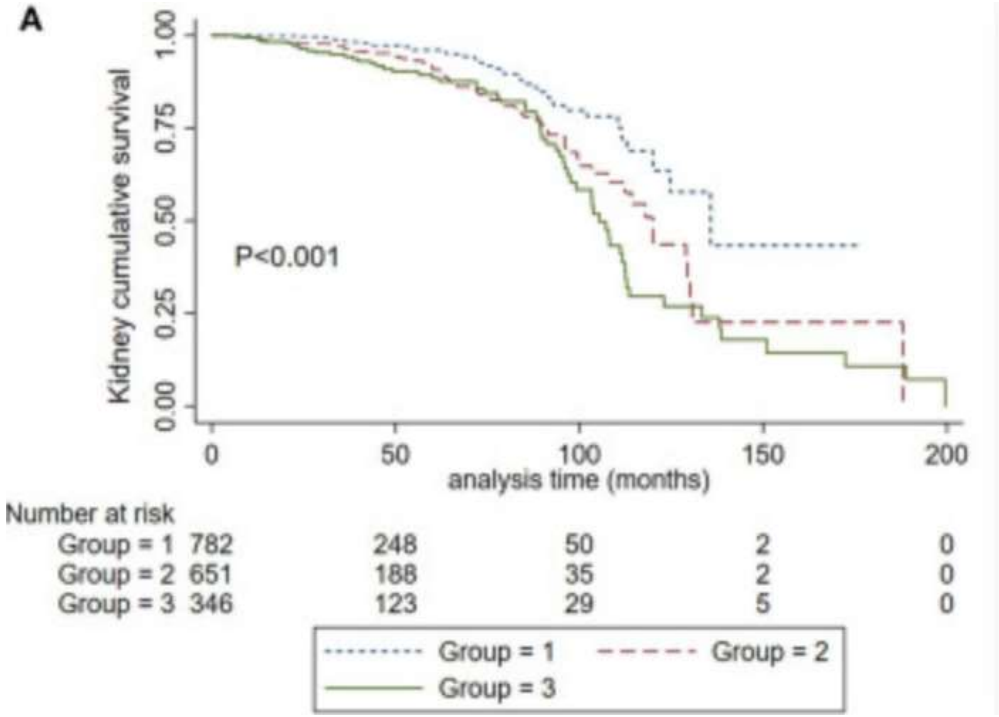
Impact outcome: Blood pressure control

IgA Nephropathy 2240 (China)

>1g proteinuria

BP goal of <120 vs <140

Primary outcome of 50% decline in renal function or ESKD



- Significant renal protection in those with CKD 1-3a, >1g proteinuria and age <50
- No difference in those with more advanced kidney disease or lower proteinuria

Yu. Front Med (Lausanne). Feb 2022

Prognostic Tool: IgA

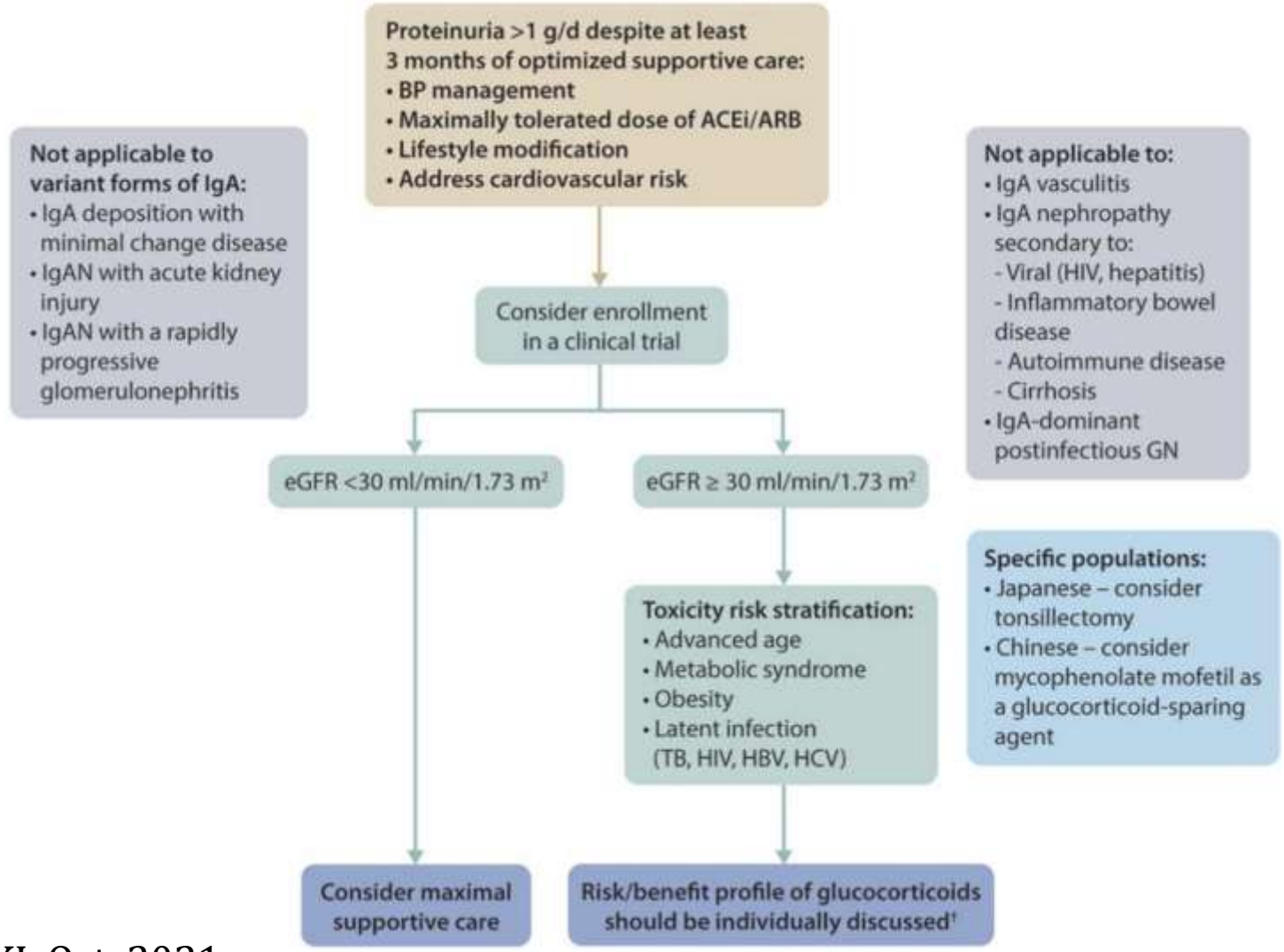
- eGFR
- Blood pressure
- Proteinuria
- Age
- Race
- Ace/ARB use at biopsy
- MEST score
- Immunosuppression use

- At designated # months
  - Risk of 50% decline in eGFR or progression to ESKD at 5 yrs is X%

Barbour. JAMA Internal Medicine July 2019.

Treatment

Smoking cessation, Diet – low sodium, BP control, healthy weight



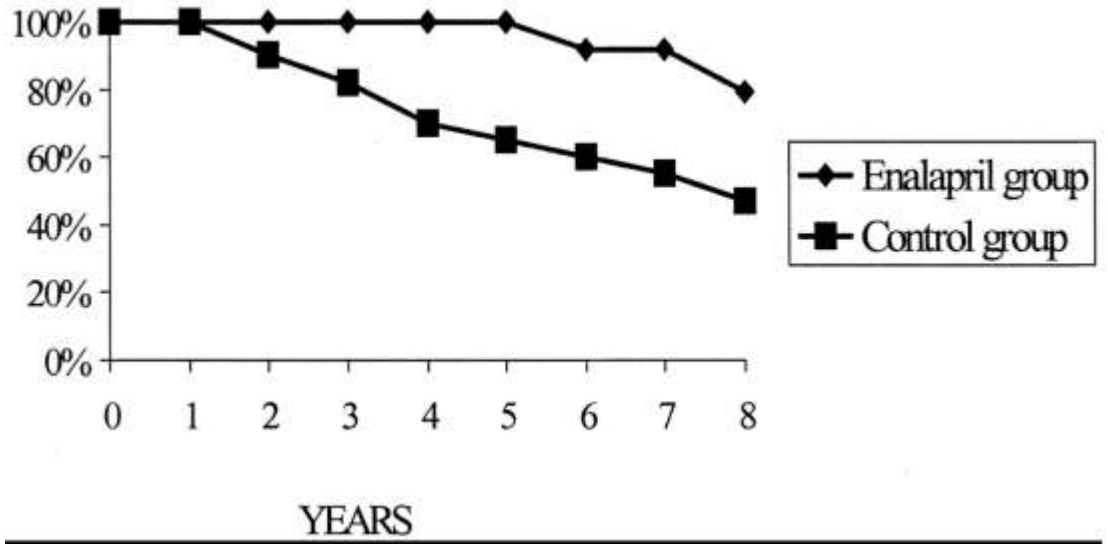
KDIGO Guidelines. KI. Oct. 2021

Impact outcome: RAAS Inhibitors

- Biopsy IgA (N=44)
- Proteinuria >0.5g/g
- Creatinine <1.5
- 7 years follow up

- RCT
  - Enalapril
  - Control

Praga JASN 2003



- Most predictive
  - Not BP, age or gender
  - Use of enalapril and reduction in proteinuria

Impact outcome: SGLT2

- Cohort of DAPA-CKD trial
- 270 IgA (94% bx proven)
- eGFR 43 and proteinuria 900mg/g
- Ace/ARB use then randomized
  - Dapagliflozin vs placebo
- 2.1 year follow up
- eGFR decrease -3.5 vs 4.7
- Proteinuria reduced 35%
- BP reduction

Vasquez-Rios. Kidney News. Feb 1, 2022

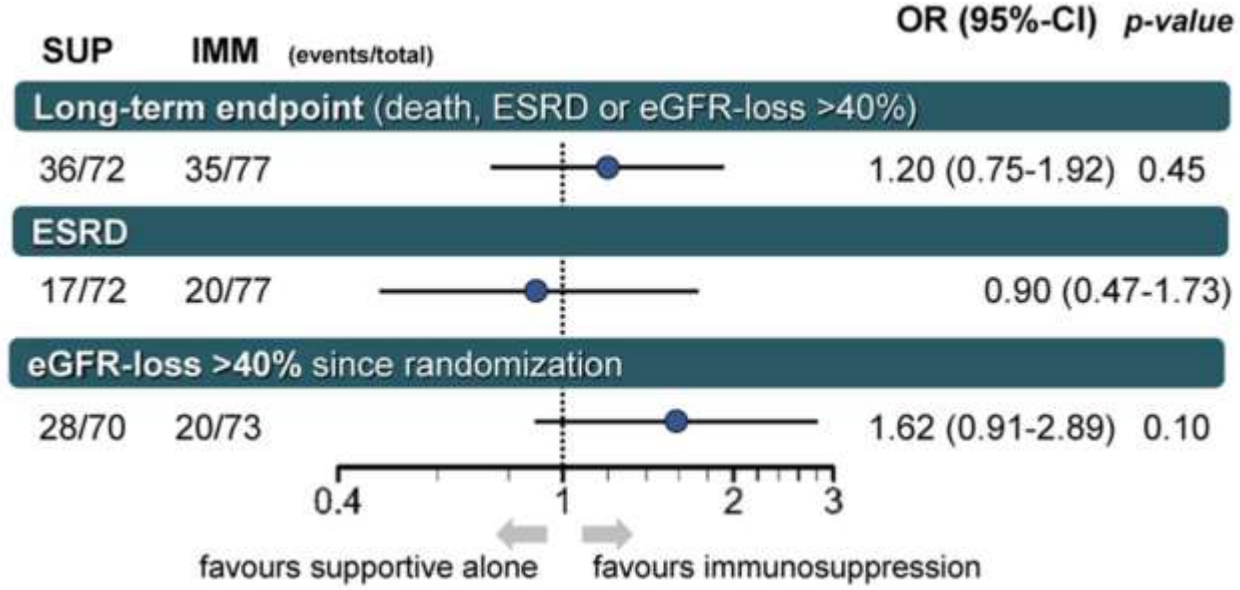
Impact outcome: Glucocorticoids STOP IgA Trial

- 162 patients (Germany)
- 0.75-3.5g/g proteinuria despite Ace/ARB 3-6 months
- RCT: Glucocorticoid therapy or not
  - 80 standard of care (BP, Lipids)
  - 82 with IS therapy
    - If eGFR >60= methylpred (n=55)
    - If eGFR <60 cyclophos +steroids then Azathioprine (n=27)
- 3 year follow up
- IS group showed more remission of proteinuria
- No difference in eGFR decline

Rauen. NEJM Dec 2015

STOP IgA Follow up

- Same IgA group
- Death, ESKD, 40% decline in eGFR
- 149 pts (92%)
- 7.4 years
- No difference in the end points



Rauen Kidney Int. Oct 2020

Impact outcome: Immunosuppression TESTING 1.0 and 2.0

- 503 patients (China, Australia)
- >1g proteinuria despite Ace/ARB 4-12 weeks
- IS therapy or not (6-9 mon)
  - Methylpred 0.6-0.8mg/kg/d then 0.4mg/kg/d (50/50)
  - Placebo
- 6.1 yr full dose follow up vs 2.5 year reduced dose follow up
- IS group showed improved composite outcome
  - 40% change eGFR, ESKD, Death
- Significantly more adverse events than placebo
  - Better with reduced steroid dose

Lv. JAMA May 2022

Novel Therapy

What does our future in IgA Nephropathy Hold?

Impact outcome: Budesonide (NEFIGAN)

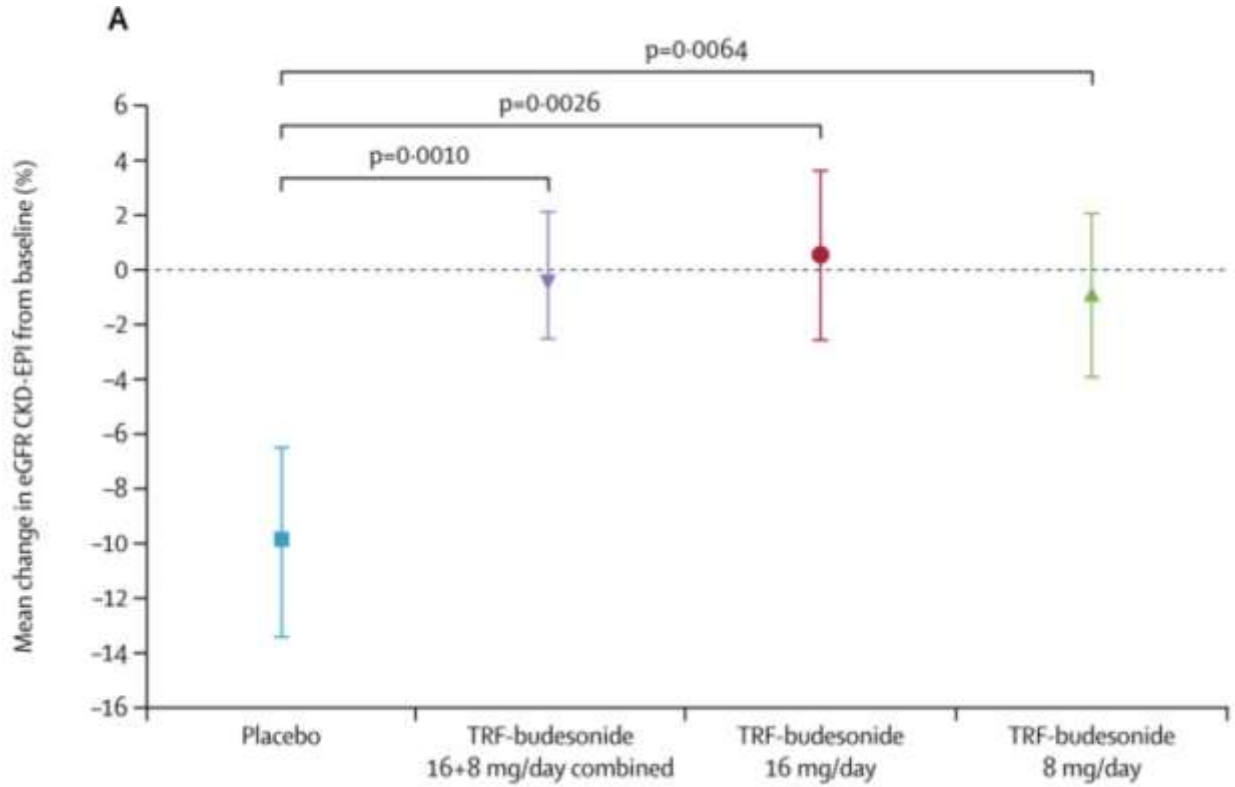
- Targeted release Budesonide
- Deliver drug to distal ileum
- 150 with IgA nephropathy
  - Europe, 97% Caucasian
  - eGFR 78, 1g proteinuria
- Optimized RAAS
- 16mg/d vs 8mg/d vs placebo
  - 9 month treatment

Fellstrom. Lancet. 2017

Impact outcome: Budesonide (NEFIGAN)

Results:

- Proteinuria
  - Decrease 27.3% in 16mg/d
  - Decrease 21.5% in 8mg/d
  - Increase by 2% in placebo



Fellstrom. Lancet. 2017

Impact outcome: Sparsentan = PROTECT Trial

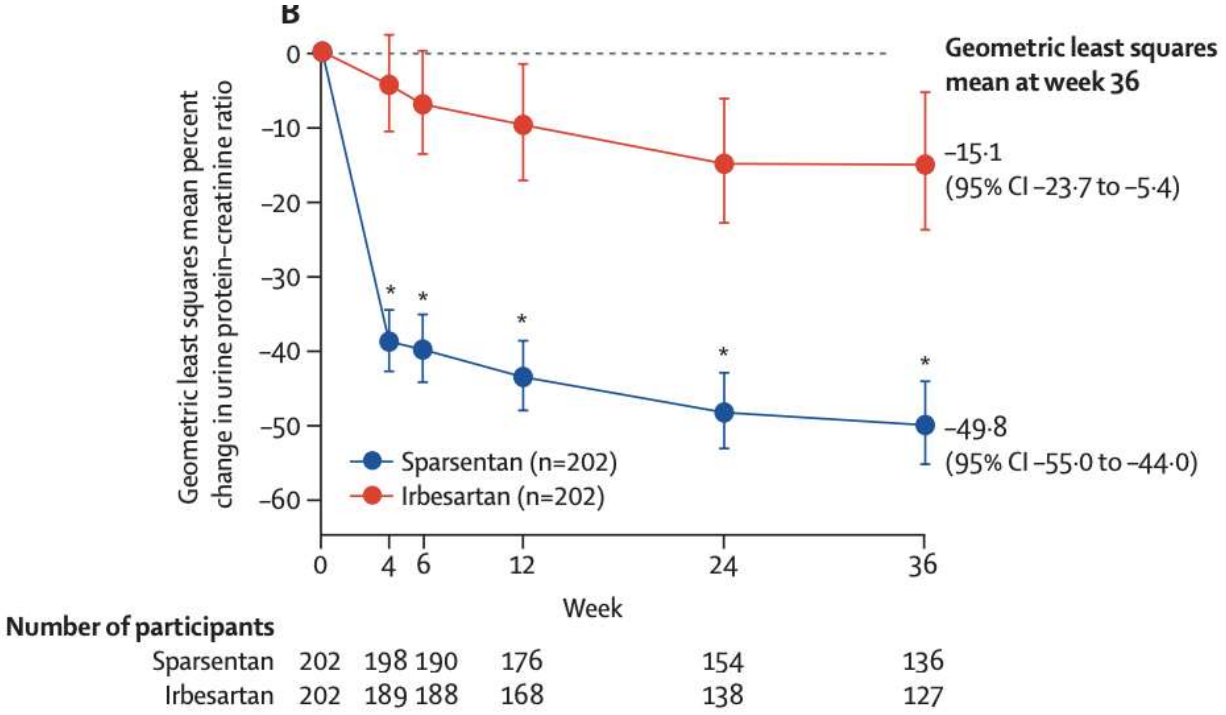
- Endothelin-1 and angiotensin2 receptor antagonist with hemodynamic and anti-inflammatory properties
- Comparing Sparsentan to irbesartan
- At least 12 weeks

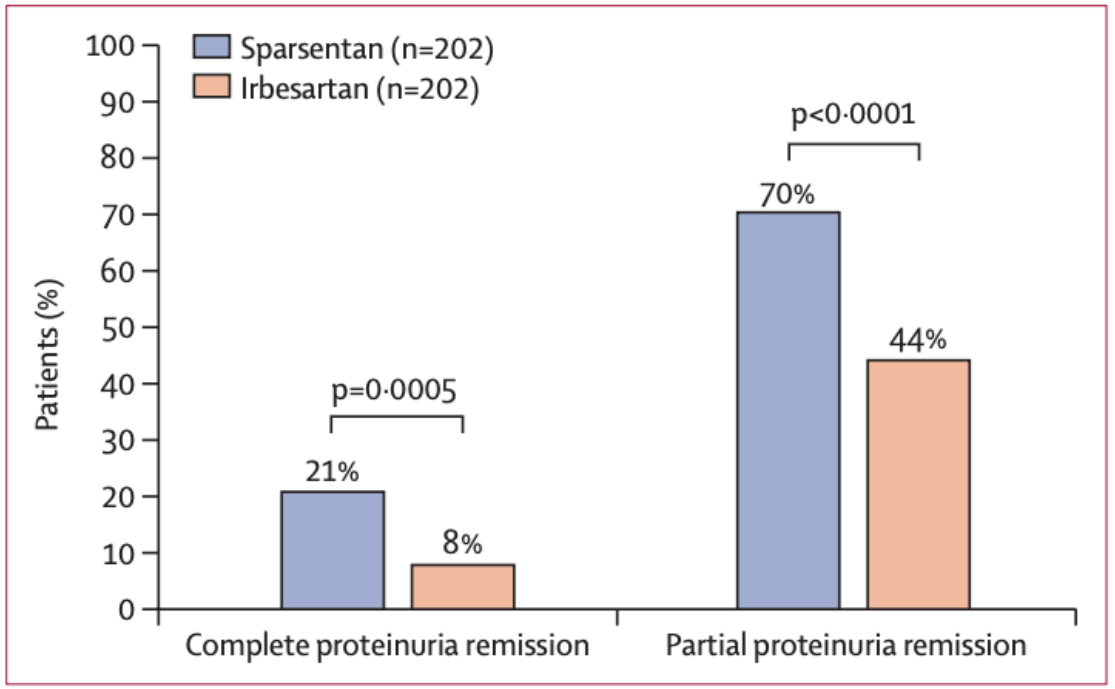
- 404 patients
  - Europe, North America, Asia
- 1.8g/g proteinuria
- Broad eGFR with 35% in CKD 3b

- Accelerated approval FDA

Heerspink. Lancet. April 2023

PROTECT Trial: Proteinuria





Heerspink. Lancet. April 2023

Summary

- CKD is prevalent and glomerular disease is important to recognize as it accounts for >16% of ESRD
- IgA nephropathy is common with a high risk of progression
  - Genetic and environmental influences
- Treatment strategies are important with novel medications on the horizon
  - Glucorcoticoids
  - Specific Targets

Thank you

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