THERAPY OF THE FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS (FSGS) LESION IN 2025

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Intensive Review of Nephrology

Brigham and Women's Hosptial

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BRIGHAM HEALTH
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SPEAKER
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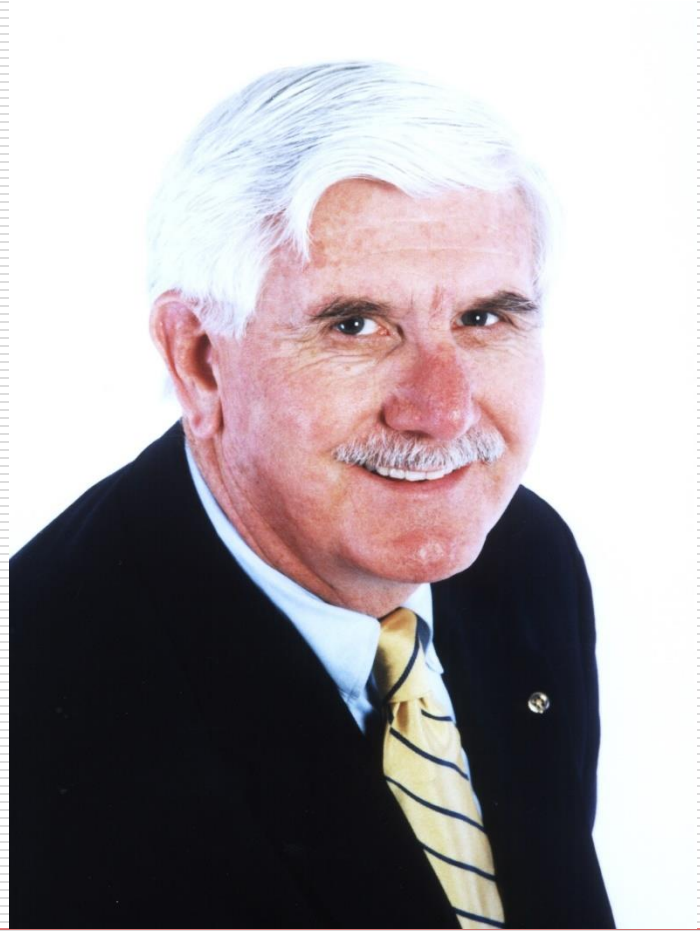

- Dr. Glassock is currently Professor Emeritus at the Geffen School of Medicine at UCLA. He has had a long standing interest in clinical nephrology (glomerular diseases) and hypertension and has published over 750 papers, books chapters and monographs. He is a former President of the ASN and NKF

DISCLOSURES

- ***I have provided and/or currently provide consultation services to the following commercial entities*:**
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  - **I receive Stipends from Wolters-Kluwer (UpToDate) for Editorial services**

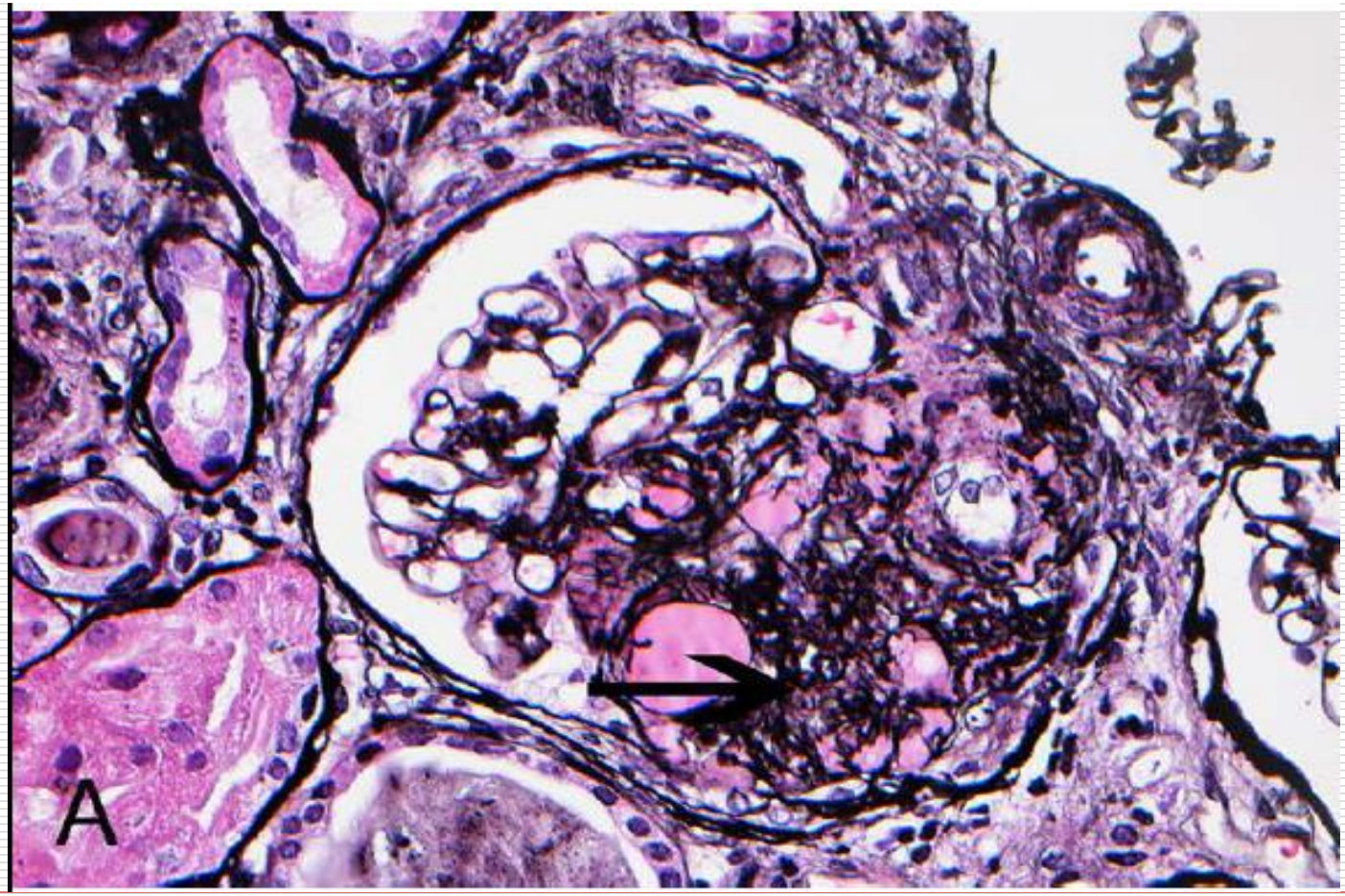
LEARNING OBJECTIVES- *OUTLINE*

- The *"lesion" of FSGS* and its categorization according to pathogenesis
- The *Prognosis* of "apparently" Primary FSGS
- *Therapy* of Primary FSGS- Evidence and Guidelines

THE LESION OF FSGS

THE LESION OF FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS

(PAS-Methenamine Silver [Jones] stain)



FOCAL and SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

AXIOMS TO REMEMBER

- **FSGS is a light microscopic *lesion* (a "pattern of injury"), *NOT A SPECIFIC DISEASE ENTITY*. It is one of the "patterns of injury" observed in the *diffuse podocytopathy* category of glomerular lesions.**

- **The extreme *heterogeneity* of pathogenesis underlying the *lesion* must be taken into account in evaluating prognosis and deciding on an appropriate therapy**

- **The treatment must be based on specific category (pathogenesis) and *highly individualized***

The LESION OF FOCAL and SEGMENTAL GLOMERULOSCLEROSIS:

A Modern Classification

(De Vriese, A, et al Nature Reviews Nephrology, 2021; KDIGO-GN-CPG, 2021)

- ***Primary*** **(permeability factor related)** ***FSGS*** **(pfFSGS)**
- ***Genetic FSGS*** **(gFSGS)**
- ***Secondary FSGS*** **(sFSGS)**
- ***Undetermined FSGS*** **(uFSGS)**

Primary (permeabilitity factor related) FSGS (pfFSGS):

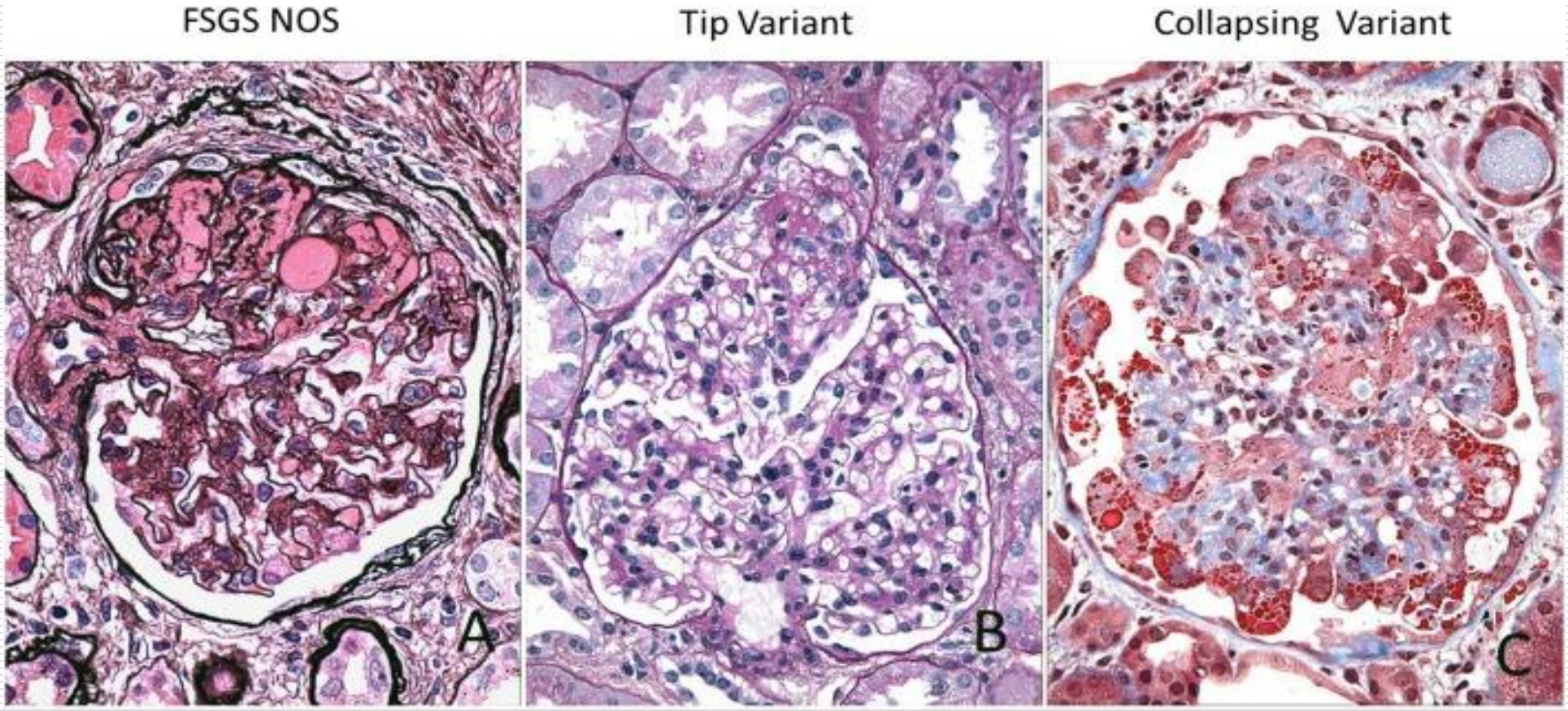
A clinico-pathologic diagnosis

- ***Diagnostic Criteria***
  - **Sudden onset of full- blown Nephrotic Syndrome (hypoalbuminemia- < 3.5gms/dL). Proteinuria commonly >8gms/d**
  - **Absence of family history of CKD, no defining syndromic features, no drugs or viruses known to provoke sFSGS**
  - **No proven genetic cause**
  - **A FSGS lesion, with any variant by LM**
  - **Diffuse (typically >80%) foot process (podocyte) effacement by EM (in an intact, non-globally sclerosed glomerulus), prior to any therapy**
- ***No proven serum/urine biomarker specific for this diagnosis (? Anti-nephrin antibodies may be an exception)***
- ***Very high risk (50-70%) for recurrence in Renal Allografts***

Common Histologic Variants of FSGS lesions by Light Microscopy

90% of all FSGS lesions

(from D'Agati V, et al CJASN 2013; 8:399-406)



The entity of "Biopsy–proven" Primary FSGS

does not exist!!

PRIMARY FSGS: *Pathogenesis*

- **Permeability Factors**
  - ***Anti- Nephrin Antibody*** **(30-70%? -Watts AJB, et al JASN, 2022; Hengel FE, et al NEJM, 2024)**
  - **Anti-Slit pore membrane antibodies (Raglianti V, et al Kidney Int, 2024)**
  - **Anti-synaptopodin or Anti-Annexin I (Chebotareva N, et al Front Nephro, 2024)**
  - **suPAR + anti- CD40**
  - **Cardiotropin-Like Factor (Savin-Sharma) Factor)**
  - **Il-13**
  - **Hemopexin**

Anti-Nephrin Antibody in Recurrent Primary FSGS in Kidney Allografts

(Hattori M, et al ERA Abstract #4635- Milan- June, 2023)

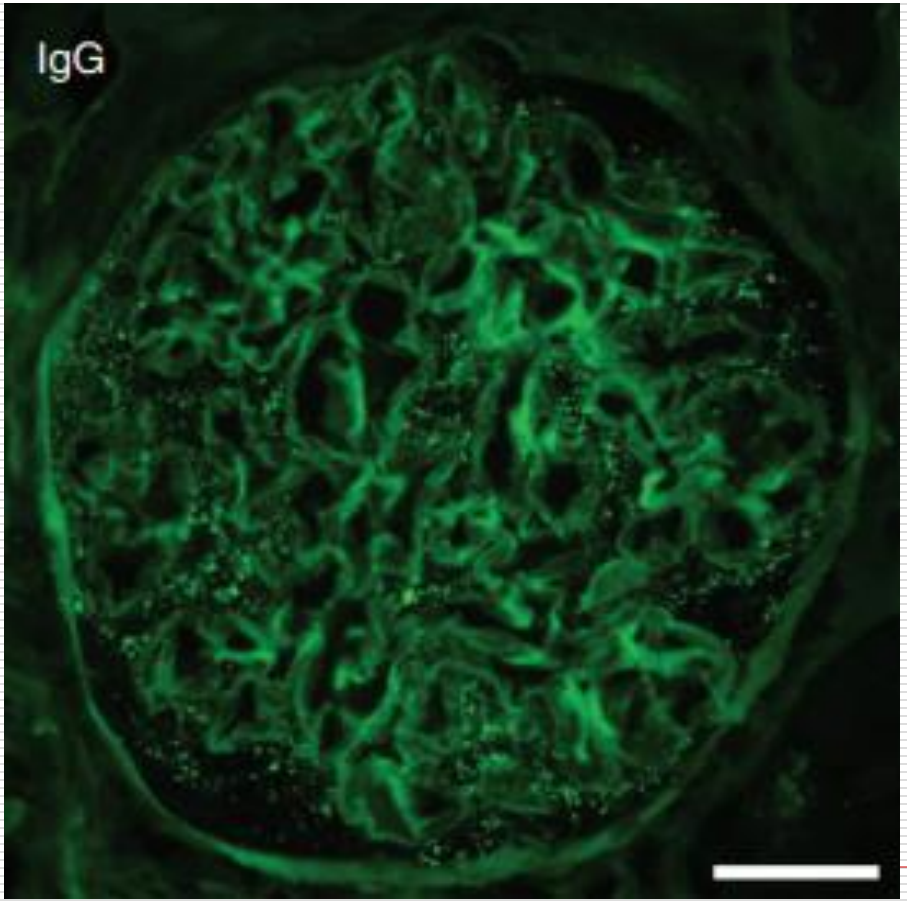
- **14 patients with Recurrent FSGS in Kidney Allografts studied for anti-nephrin auto-antibody (ELISA with huR-Nephrin extra-cellular domain; cutoff value= 172U/ml)**
  - **Recurrent Primary FSGS- *11/14* +**
  - **Genetic FSGS-0/9 +**
  - **MN- 0/13+**
  - **LN- 0/4 +**
  - **Healthy Controls- 0/13 +**

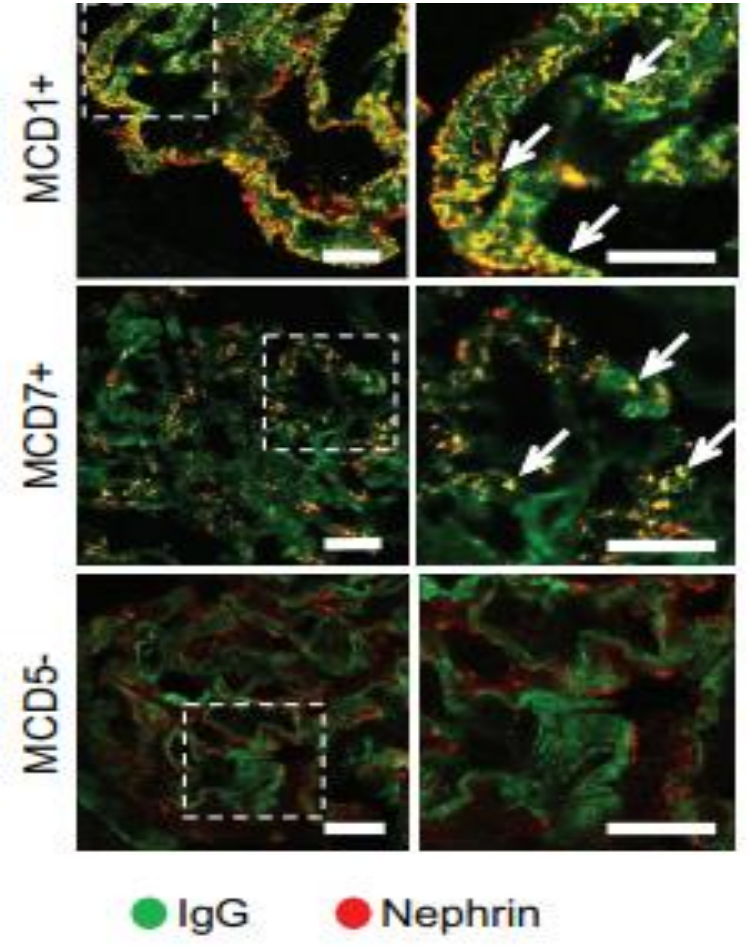
NO CURRENTLY AVAILABLE

FDA-APPROVED ASSAY FOR ANTI-NEPHRIN AUTO-ANTIBODIES

IgG and Nephrin in ANAb+ Primary MCL (MCD/FSGS)

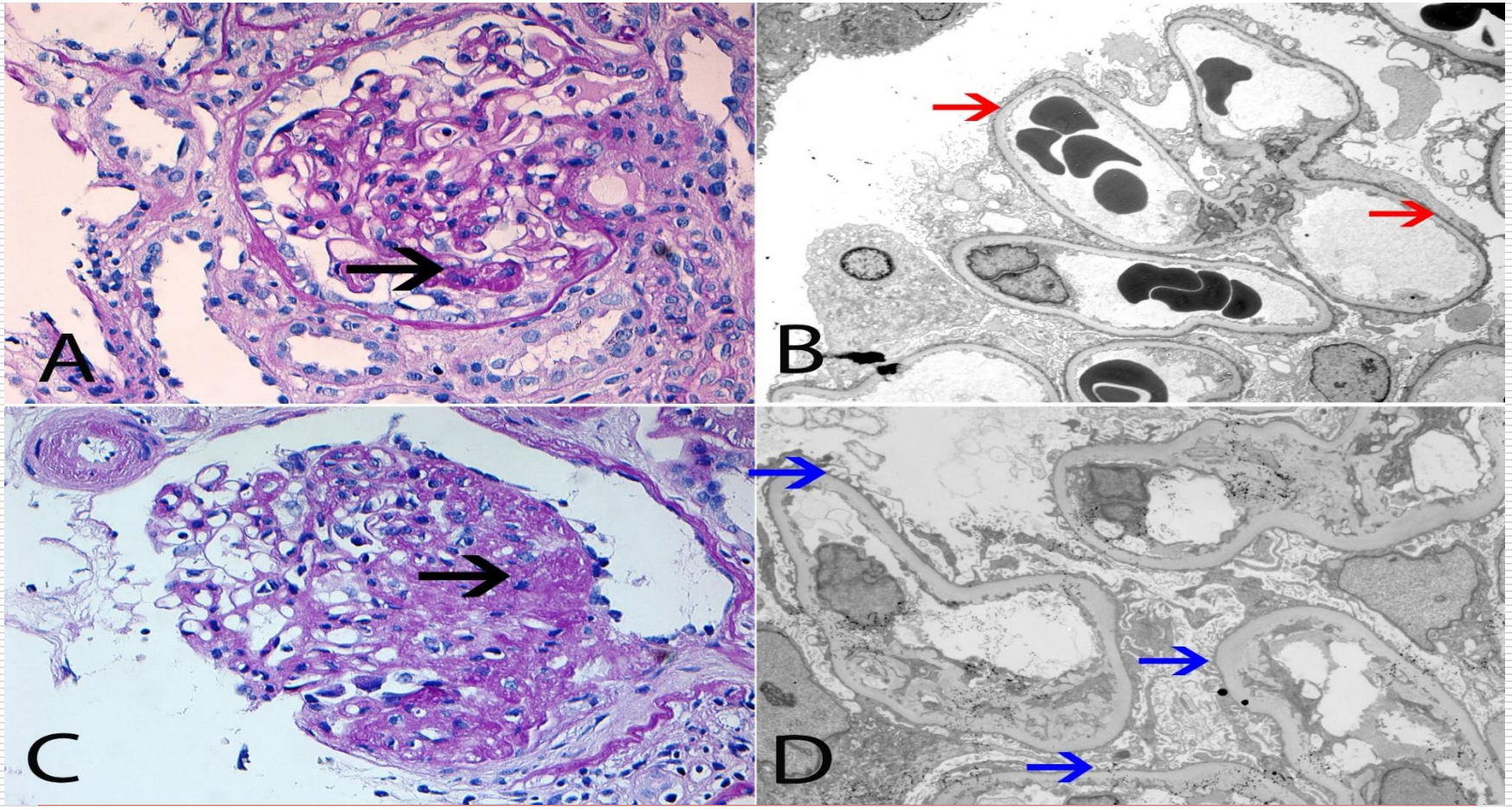
(Watts AJB, et al JASN 2022; 33:238-252)`





Electron Microscopy in FSGS

(Courtesy of Sethi S and Fervenza F, 2014)



Genetic Testing of patients with FSGS lesions is *very useful* as it may direct choices of therapy and lead to the avoidance of ineffective regimens

PROGNOSIS OF PRIMARY FSGS

The FSGS Lesion-

Outcomes related to remission

(Troyanov, et al 2005)

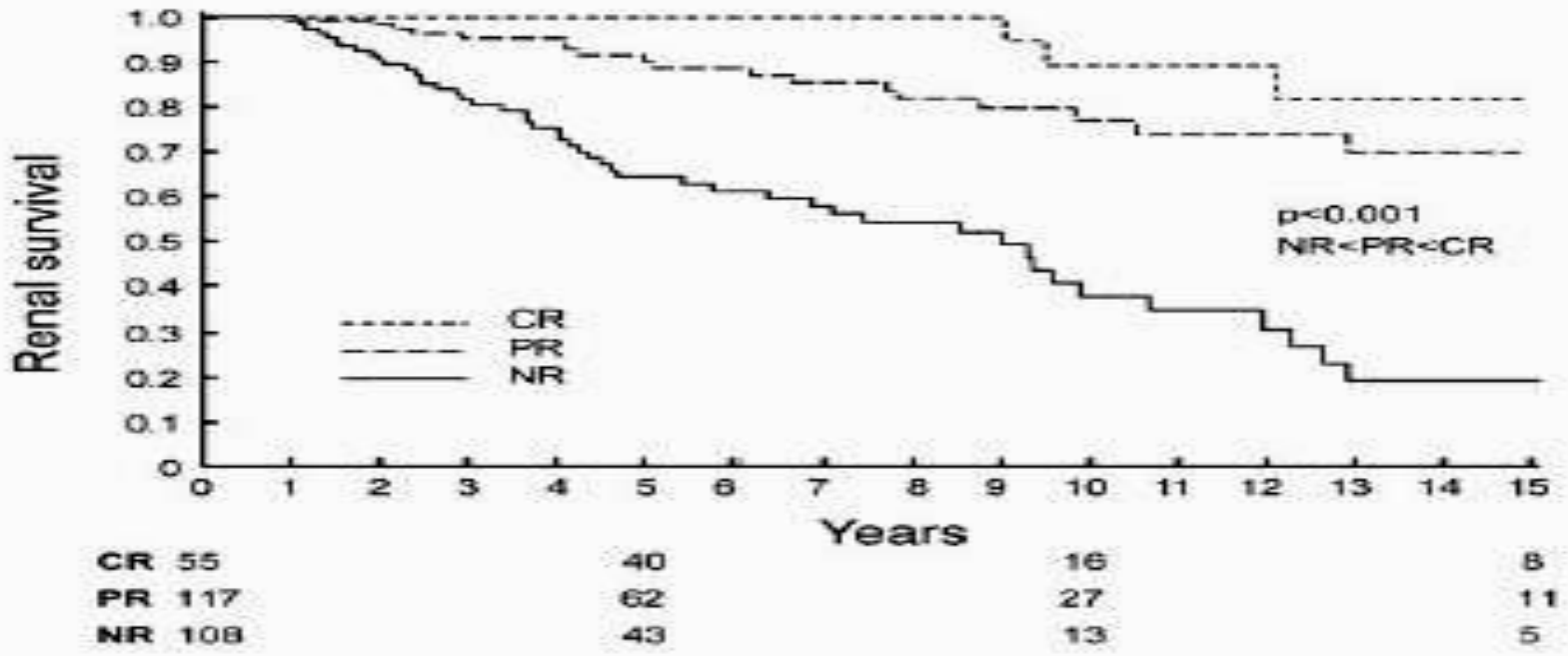
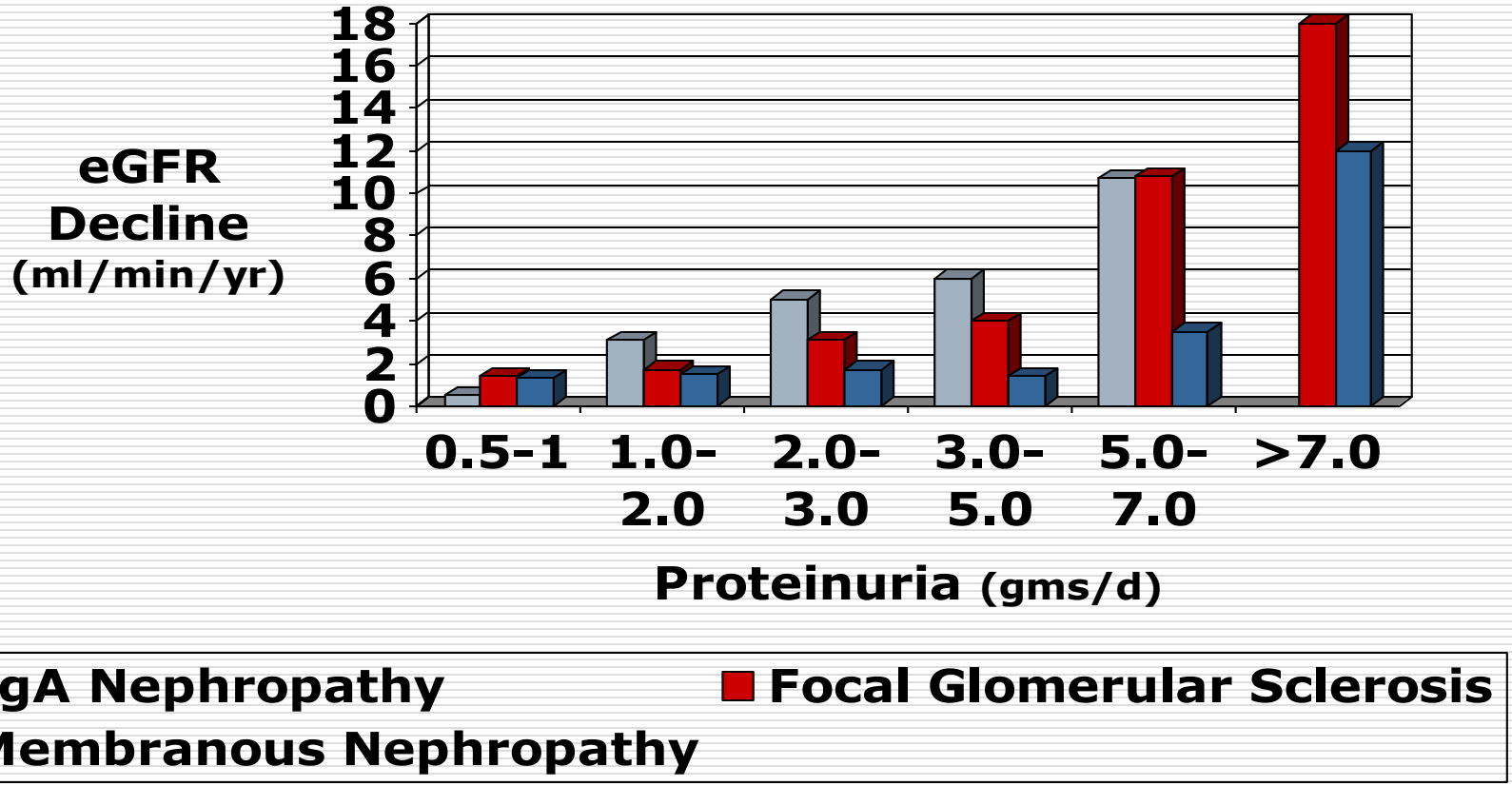


Figure 1. Survival from renal failure in patients with complete (CR), partial (PR), and no remission (NR). One patient in the NR group had a creatinine clearance <15 ml/min per 1.73 m^2 at presentation and was excluded from the survival analysis.

Time Averaged Proteinuria and Decline of eGFR (Males)

(Cattran D, et al NDT 23:2247-2253, 2008)



THERAPY OF PRIMARY FSGS

THERAPY of PRIMARY (permeability factor related) FSGS:

KDIGO-GN-CPG (Kidney Int- October, 2021)

- ***In Adults-*** **Treatment with IS agents (Steroids or CNI) can proceed without Genetic Testing (unless FH+ or syndromic presentation) irrespective of sub-variant of lesion (? Except Collapsing)**

- **Genetic testing (Whole Exome Sequencing Panels) should be *seriously considered* if Steroid and/or CNI resistant.**

- ***High-dose oral glucocorticoids*** **should be used as "first-line" treatment for presumed pfFSGS**

- ***CNI (Tacrolimus or CsA) monotherapy*** **can *also* be used for initial therapy in patients with relative or absolute contra-indications for high-dose glucocorticoids.**

pfFSGS:

Steroid or CNI regimens for initial therapy (From KDIGO- 2021

- ***Steroid****:
  - 1mg/kg/d (maximum 80mg/d) or 2 mg/kg/qod (maximum 120mg/qod. Single dose at 9-10AM
  - Continue high-dose for 4 weeks and complete remission achieved, or a of 16 weeks, whichever is earlier, Gradual reduction in dose can be employed if proteinuria diminishes during therapy.
  - Total duration of therapy- 6 months
- ***CNI*****
  - CsA- 3-5mg/kg/d in 2 divided doses; Tacrolimus- 0.05-0.1mg/kg/d in 2 divided doses
  - Trough levels monitored to avoid toxicity- CsA-= 100-175ng/ml; TAC- 5-10ng/ml
  - Treatment duration -12 months. If no response, 4-6 month maximum, Discontinue if eGFR declines to <30ml/min/1.73m2

(* based on observational studies, no RCT; ** based on RCT)

pfFSGS in nephrotic adults:

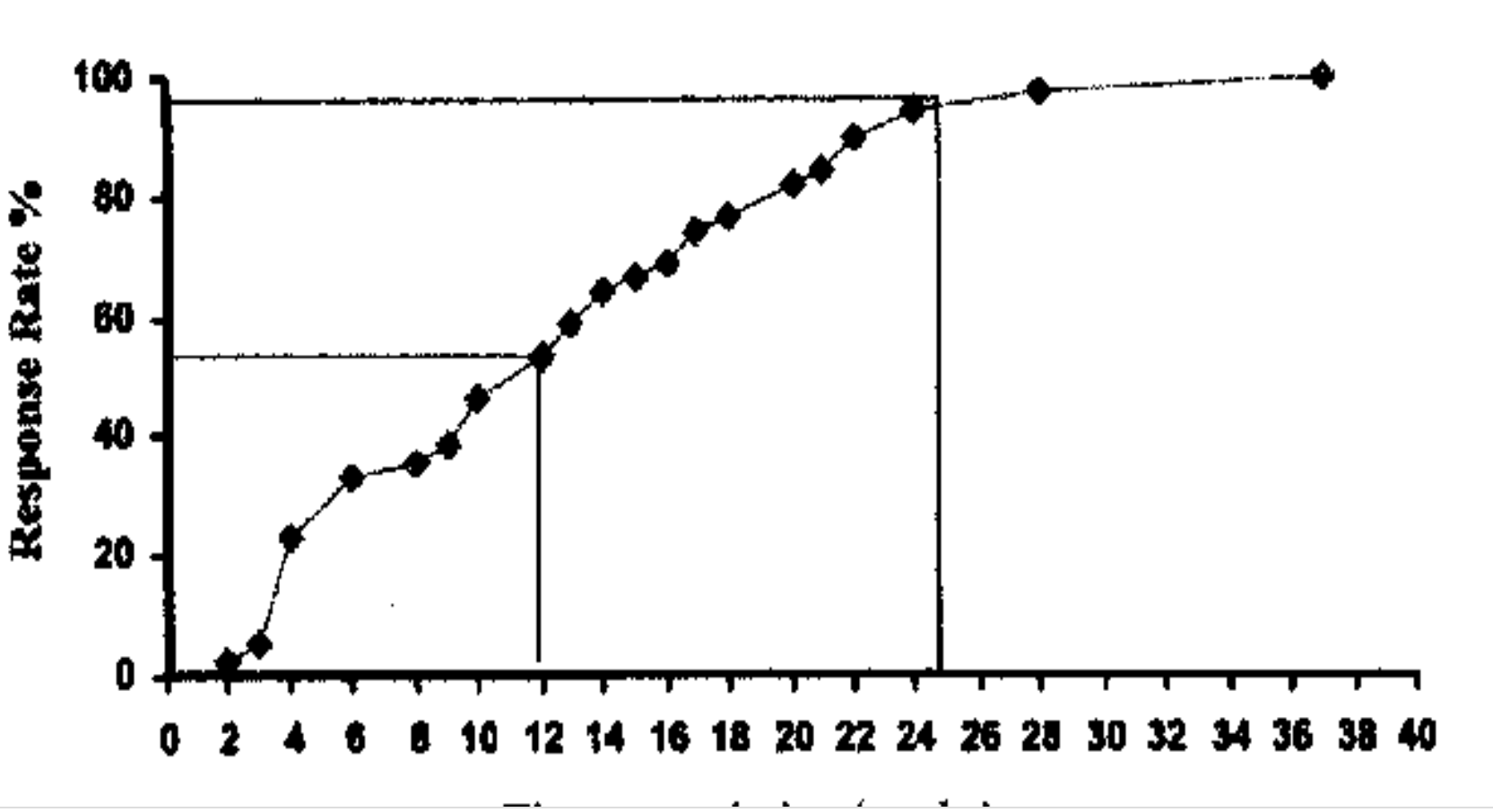
Response to Steroid Therapy

(Chun MJ et al JASN 2004;15:2169)

- **Out of *87* patients with presumed Primary FSGS, *63%* of treated patients responded with complete (33%) or partial (30%) remission**
- **10-year renal survival 92% for responders vs 33% for non-responders (P< 0.0001)**
- ***No difference* in response between patients with tip lesion, NOS, or Collapsing lesions**

Time to Remission (weeks) in Steroid-Treated Primary FSGS in Adults who developed a remission

(Jafry N, et al. NDT, 2012; 27:1101-1106)



Initial Response to Steroids may Predict Later Response to Alternative Therapy (especially CNI)

Rood IM et al 2022, KI Reports; 7: 87-98)

- **A decrease of *>20%* in proteinuria compared to baseline within the *first 8 weeks* was *strongly* associated with a subsequent response to continued steroids and/or addition of alternative IS therapy (e.g CNI)**

- **<20% decrease in proteinuria- *3/10 (30%)* responders**
- **>20% decrease in proteinuria- *23/24 (96%)* responders**

CsA in SRNS due to FSGS:

A RCT

(Cattran DC, et al KI. 1999;56:2220; (6 months at 4mg/kg; CsA/Untreated Control)

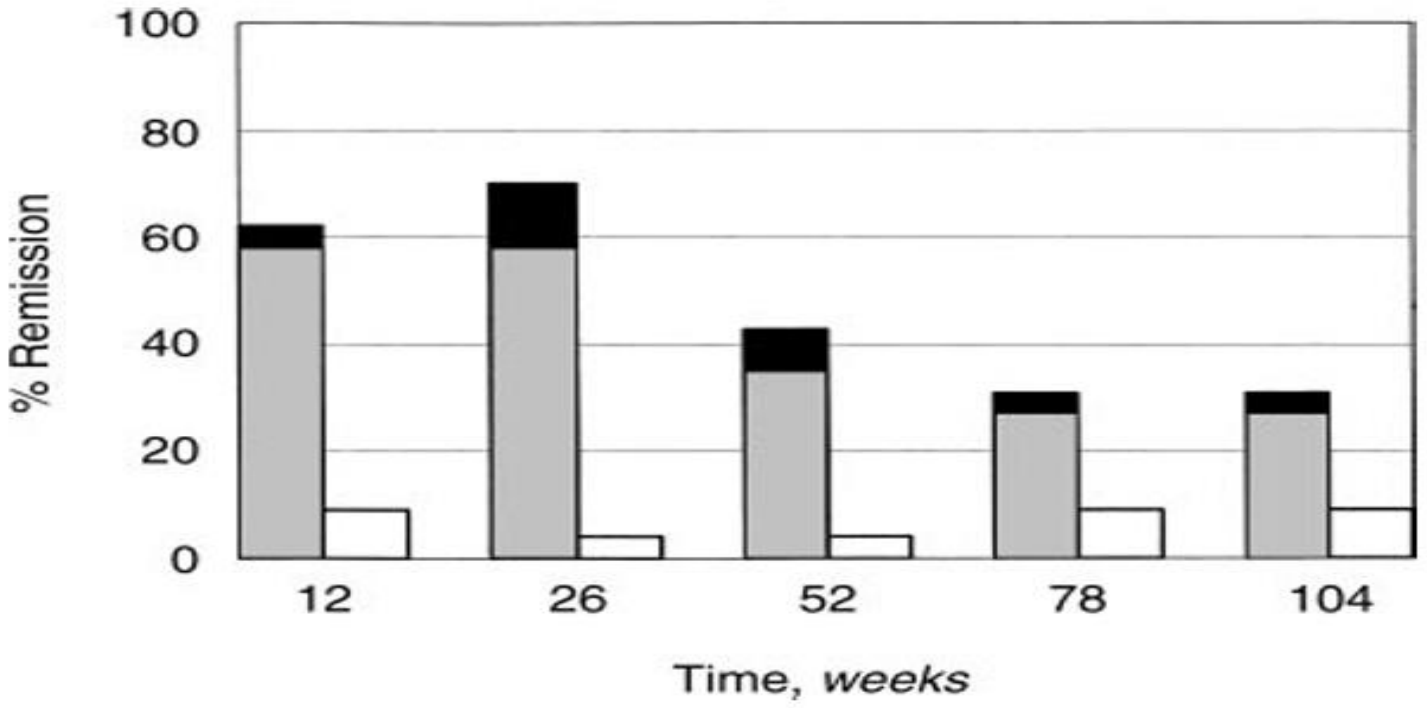
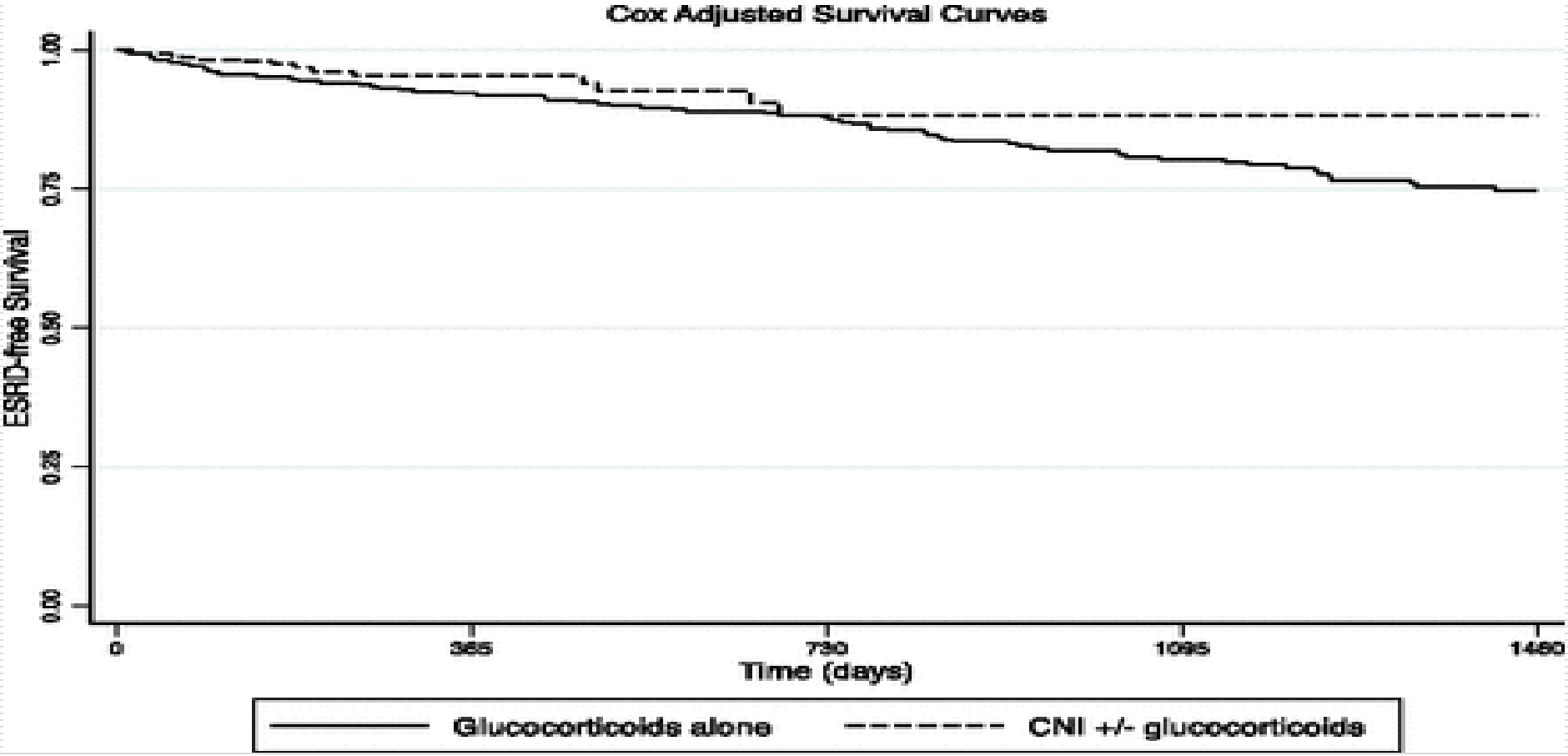


Fig. 1. Remission in proteinuria in the cyclosporine treated (▒, partial; ■, complete) compared with the placebo treated (□, partial) at different time points of the study. At week 26, $P < 0.001$, and at 104 weeks $P < 0.05$.

INITIAL TREATMENT OF PRIMARY FSGS WITH CNI OR STEROID MONOTHERAPY-

ESKD Outcomes at 3 years

(Laurin et al CJASN, 2016)



RITUXIMAB IN PRIMARY FSGS LESIONS

- **Repetitive doses (2-4 cycles) of RTX may be *effective* in sustaining CR or PR in *steroid-dependent, relapsing Primary FSGS* (Osterholt T, et al Sci Rep, 2023)**

- **Therapy of RTX is rather *ineffective* in *Steroid resistant Primary FSGS*, especially with elevated serum suPAR levels (Hladunewich M, et al KI Reports, 2022, Tedesco M, et al KI Reports, 2022)**

- **Will RTX be effective in steroid- resistant Primary FSGS with + anti-nephrin antibody? (*unknown*)**

RITUXIMAB in PRIMARY FSGS (Adults)

(Tedesco M, et al KI Reports. 2022; 7:1878-1886)

	Steroid-Resistant	Steroid Responsive/ Dependent
Responsive at 3 months	**0/9**	**8/13**
Responsive at 12 months	**1/9 (all partial)**	**8/14**

RITUXIMAB in CNI-RESISTANT FSGS

(>6 months of therapy with CNI)

(Chan EY, et al. Kidney Int 2024; 106: 1146-1157)

- Retrospective observational multi-institutional study of ***146*** children with CNI-treatment resistant NS and an FSGS (58%) , MCD (27%) or other lesion (12%) treated with RTX
- Complete Remission at 12 month- ***16%***
- Partial Remission at 12 months- ***19%***

Obinutuzumab for Immunosuppression Dependent/Resistant Primary FSGS

(Zand L, et Al ASN Renal Week, 2024)

MAYO CLINIC

A single center, phase 2 open-label trial evaluating the efficacy and safety of obinutuzumab in treatment of immunosuppression-dependent/ resistant primary FSGS, or contraindication to high-dose corticosteroids

Ladan Zand[1], Eddie L. Green[1], Wisit Cheungpasitporn[1], Maria J. Vargas[1], Mariam S.F.A. Machado[1], Sanjeev Sethi,[2] Pierre Ronco[3], Fernando C. Fervenza[1]

1. Division of Nephrology and Hypertension, Mayo Clinic, [illegible] 2. Division of Pathology and Laboratory Medicine, Mayo Clinic, [illegible] 3. [illegible], Paris, France

BACKGROUND

- High-dose corticosteroids are first line therapy for treatment of patients with primary FSGS
- Up to 60% if patients do not respond or relapse.
- Additional IS therapy with CNI or rituximab may be needed
- Many do not respond to additional IS and will have a progressive course.
- There is a need for alternate therapies in such patients

OBJECTIVES

To evaluate the safety and efficacy of obinutuzumab (a type II anti-CD20 drug) in patients with primary FSGS

METHODS

- An open label phase 2 clinical trial

Inclusion Criteria:

- Biopsy proven FSGS lesion on LM
- Presence of diffuse foot process effacement (>80%) on EM
- Clinically: >3.5 g/d of proteinuria and serum albumin < 3.5 g/dL
- eGFR > 20 ml/min/1.73m^2
- Resistant or dependent to IS therapy or patient unable or refused to take steroids

METHODS

Exclusion Criteria:

- Active infection (Hep B, Hep C, HIV)
- Hgb < 8.0 or platelet < 100'000
- Prednisone > 10 mg/day in the last 30 days
- If RTX previously, CD20 count of < 5 cells/microliter
- Cyclophosphamide use in the last 6 months
- Patient allowed to be on CNI but had to taper within 2 weeks after receiving obinutuzumab therapy
- Pregnant or breast-feeding

TREATMENT

Obinutuzumab IV 1 gram x 2 doses 2 weeks apart at months 0 and 6

Pre-treatment with acetaminophen, diphenhydramine and methylprednisolone

All patients received PCP prophylaxis

ENDPOINTS

Primary Endpoint:

- Change in proteinuria from baseline to 6 and 12 months post obinutuzumab treatment

Secondary Endpoints

- Rate of partial and complete remission (CR: proteinuria < 0.3g/d and no more than 20% decline in eGFR)

ENDPOINTS

- PR: 50% reduction in proteinuria and < 3.5 g/d and no more than 20% decline in eGFR
- Improvement in serum albumin at 6 and 12 months
- Stabilization of kidney function at 6 and 12 months
- Rate of serious adverse events
- Sustained effect on proteinuria up to 18 and 24 months
- Presenting 12-month data

RESULTS

- Twenty patients were enrolled
- Average age: 45.3 ± 17.5, 55% male, sBP: 132 ± 17.5 mmHg, dBP: 77.1 ± 9.5 mmHg
- On average patient had failed 2-3 prior therapies (steroids or CNI)
- At 12 months, 8/20 had entered CR/PR
- An additional 3 patients did not meet criteria for CR/PR but had at least 50% reduction in proteinuria

RESULTS

TABLE 1 patients laboratory and urine study data

	Baseline N=20	6 months N=20	12 months N=20	P-value*
Serum creatinine (mg/dL)	1.67 ± 0.83	1.65 ± 0.81	1.44 ± 0.67	0.15
eGFR (ml/min/1.73m^2)	48 (28 , 89)	48 (34 , 93)	62 (37 , 95)	**0.04**
Serum albumin (g/dL)	2.5 ± 0.6	3.1 ± 0.8	3.5 ± 0.8	**<0.001**
Total cholesterol (mg/dL)	285 ± 120	277 ± 132	213 ± 49	**0.002**
LDL cholesterol (mg/dL)	194 ± 122	175 ± 148	122 ± 40	**0.008**
Proteinuria (g/d)	10.7 (7.5 , 13.7)	7.3 (4.0 , 10.3)	3.8 (1.5 , 8.6)	**0.001**
B-cell counts (cells/µl)	160 (75 , 251)	0 (0, 1)	0 (0, 0)	**<0.001**

RESULTS

- 3 serious AE: 2 in one (suicidal ideation + pseudo-seizure) and 1 follicular lymphoma
- Most common AE: infusion-related reaction (7/20)
- There 7 infections but none required hospitalization
- Three of the 7 infections were COVID-19 pneumonia

CONCLUSIONS

Obinutuzumab significantly reduced proteinuria in patients with primary FSGS who had failed at least 2-3 prior therapies. Reduction in proteinuria was associated with an improvement in eGFR and serum albumin with an acceptable side effect profile and appropriate B-cell depletion

REFERENCES

1. [illegible]
2. [illegible]
3. [illegible] Zand L. [illegible] Am J Kidney Dis [illegible]

PLEX/Lipid Apheresis/Immunoadsorption in Treatment Resistant Primary FSGS:

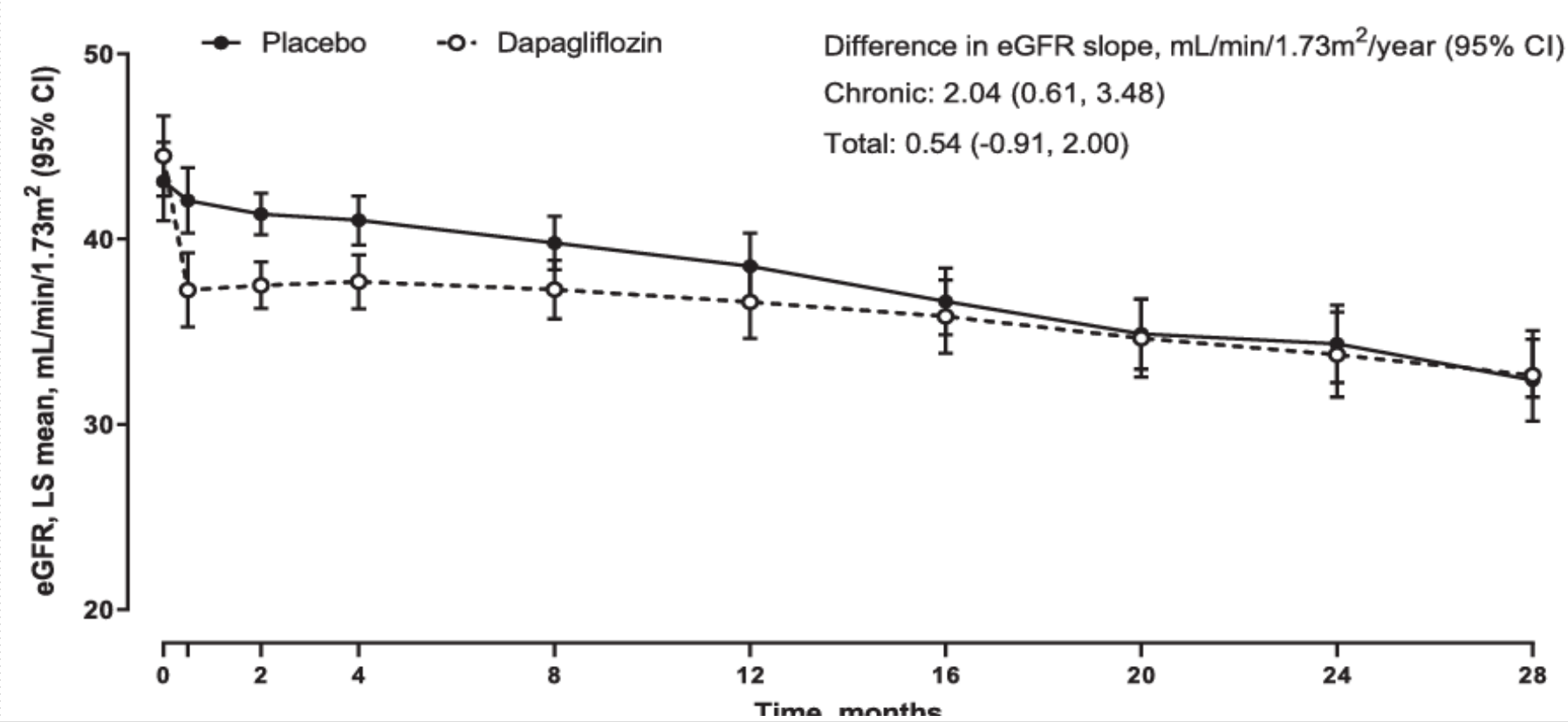
A Systematic Review

(Adapted from Miao J, et al Renal Failure 2023; 45: 2176694; non ESKD patients only)

	Complete Remission	Partial Remission	No Response
PLEX (n=30)	8/30	11/30	21/30
Lipid Apheresis (n=29)	12/29	1/29	17/29
Immunoadsorption (n=10)	0/10	4/10	6/10
TOTALS	*20/69* (29%)	*16/69* (23%)	*33/69* (48%)

SGLT2i in Steroid-resistant FSGS

(Wheeler DC, et al NDT 2022; 37:1647-1656)



Sparsentan in FSGS Lesion

The DUPLEX Trial

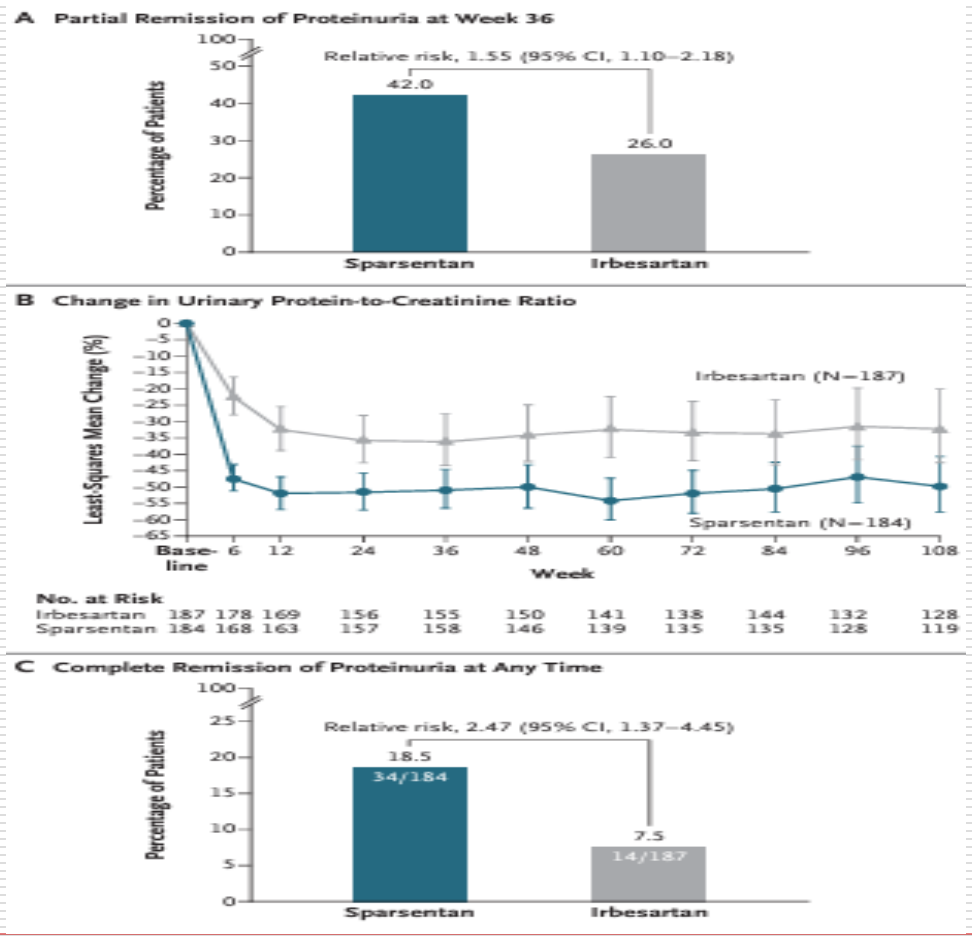
(Rheault MN, et al. NEJM 2023; 389:2436-2435)

- ***371*** **patients with FSGS lesions (either presumed Primary or Genetic) were randomized to Sparsentan (N=184) or Irbesartan for 108 weeks.**
- ***Surrogate*** **pre-specified EP at 36 weeks- UPCR <1.5gm/gm and and >40% reduction in UPCR from BL. *Primary* efficacy EP estimated Total eGFR slope (BL to 108 weeks). *Secondary* Efficacy EP Chronic eGFR slopoe (from 4week to 112 week- 4 weeks after end of treatment)**
- ***BL values*** **-UPCR (median)=3.1gm/gm (2.4-4.7 IQR); Salb= 3.5gms/dL; eGFR- 63.7ml/min/1.73m2. Genetic FSGS- (incuding APOLI High Risk alleles) 37/173 (21%) in Srasentan- 38/179 (21%) in Irbesartan**

Sparsentan in FSGS Lesions

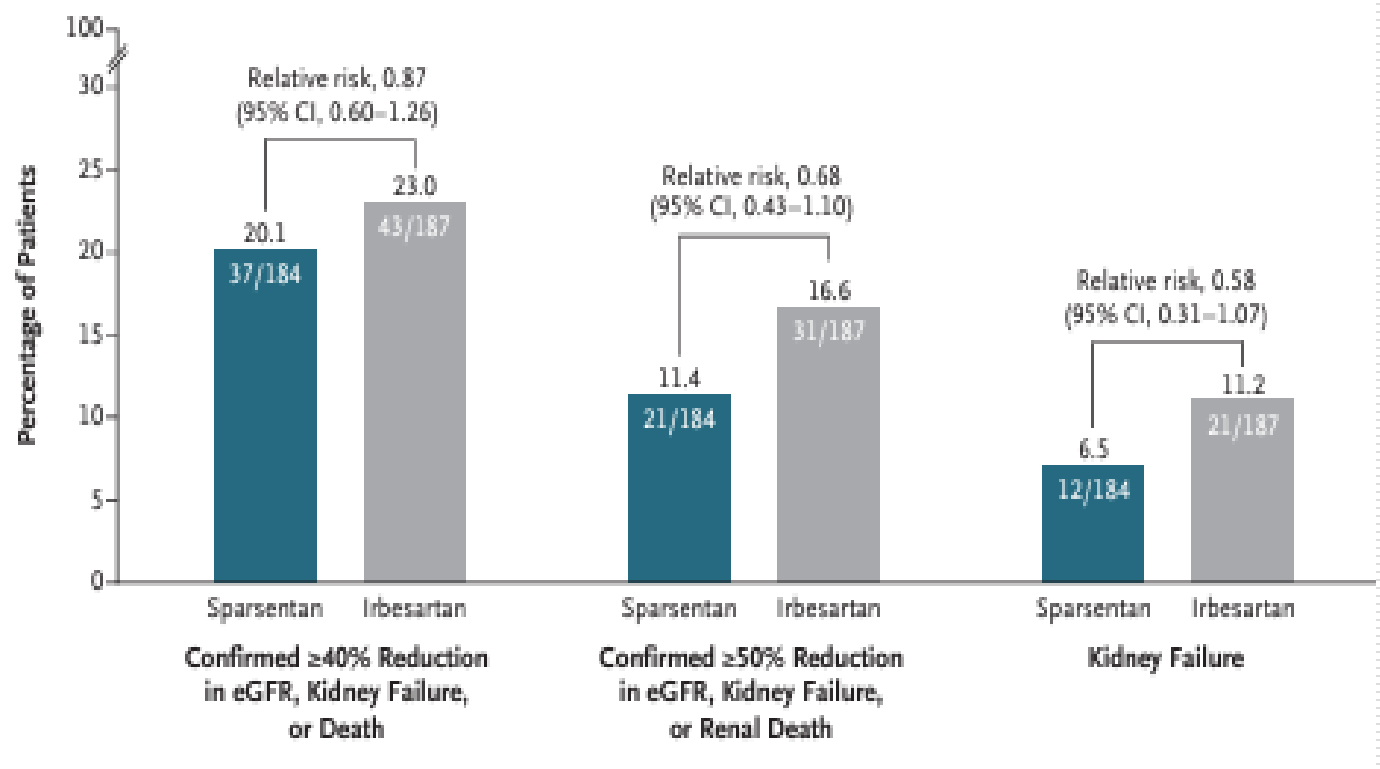
The DUPLEX Trial

(Rheault M, et al NEJM, 389:2436-2445)



DUPLEX Trial

Composite Kidney End-Points



Sparsentan in FSGS Lesions:

Long-Tem FU of the DUET Trial

(Campbell KN, et al, Kidney Med, 2024; 6:10833)

- **103 patients with either presumed Primary or genetic FSGS initially randomized to *Sparsentan* (n=68) or *Irbesartan* (n=35) for 8 weeks, were followed during an open-label extension period of 4.4 years (all patients received Sparsentan after the initial intervention double blind period)**

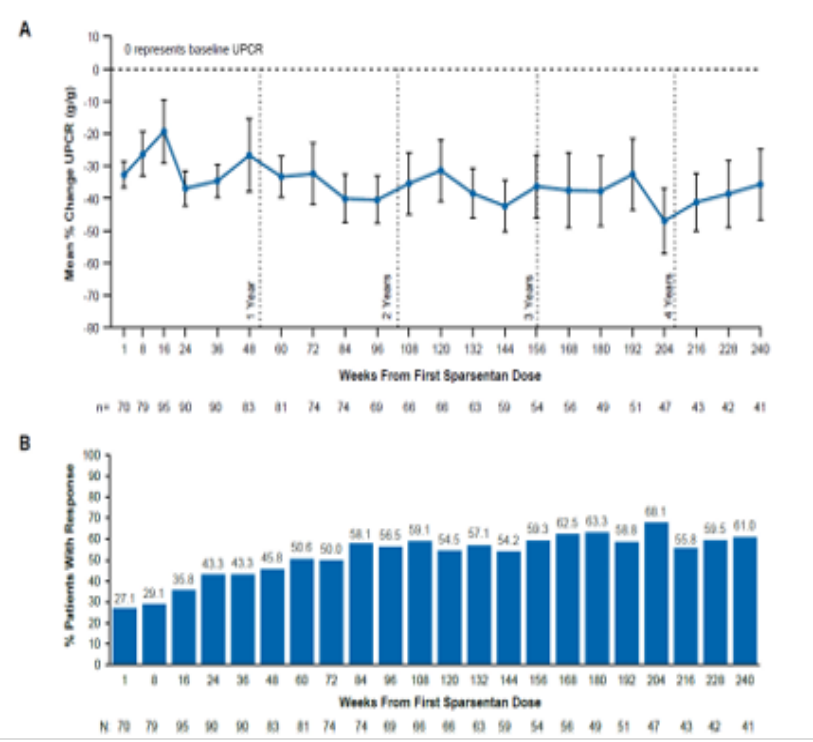
- **BL- UPCR >3.5gm/gm- 51%; eGFR= 75±39ml/min;1.73m2; Salb- unknown**

Sparsentan in FSGS Lesions

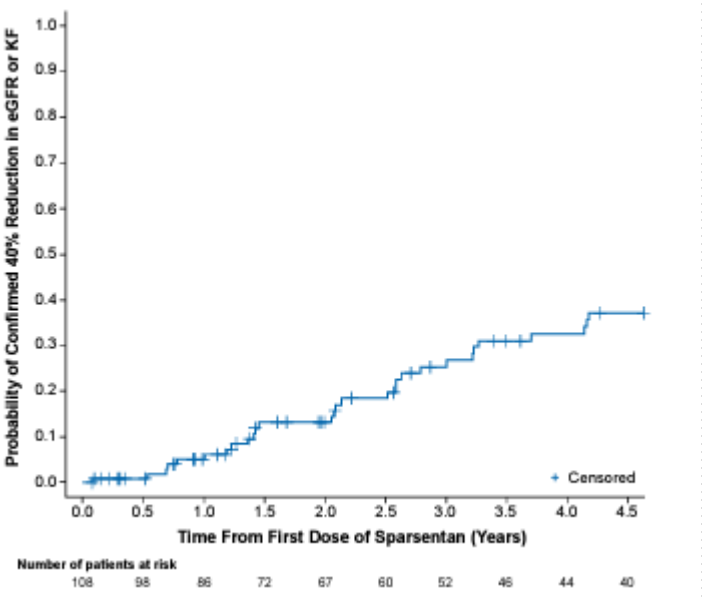
Long-Term FU of DUET Trial

(Campbell K, et al Kidney Med 2024; 6: 10833)

UPCR/Responses



Confirmed 40% or more Reduction in eGFR



FSGS
(not necessarily specific for pfFSGS)
The pipeline of investigative (novel) drugs

- **Atrasentan- an ET(A)inhibitor- not specific for pfFSGS- ALIGN**
- **CX-A-Nitro-FA (FIRSTx)**
- **FG-3019 (Fresolimumab)- anti-TGFBeta – (completed- ineffective)**
- **PF-06730512 (PODO)- SGLT2 inhibitor**
- **VX-147- (APOL1 high risk alleles only)**
- **Mesenchymal stem cell/ Autologous Stem cells**
- **Adalimumab (TNF receptor antagonist)**
- **Oral galactose- terminated- ineffective**
- **Bleselumab**
- **Losmapimod**
- **CCX-140B (completed- results not available)**
- **TRPC5 inhibitor (GFB-88)**
- **Bardoxolone (PHOENIX)- discontinued**
- **Dapagliflozin (TRANSLATE)**

KEY TAKE HOME MESSAGE- *I*

- **The *lesion* of FSGS by LM has a *very complex and highly varied* pathogenesis. The "pattern- of- injury" by LM is *insufficient* to guide treatment decisions. A FSGS lesion should *not* be regarded a disease diagnosis or a basis for deciding therapy**

- **A FSGS lesion can be *properly classified* by a clinico-pathologic approach involving history (family, drug, viral infections), serum albumin concentration, level of proteinuria, EM evaluation of the extent of FP effacement, and selective analysis of genetic mutations by whole exome sequencing. A new role for anti-nephrin serology is emerging**

- **Four categories: *pfFSGS, gFSGS, sFSGS, uFSGS***

KEY TAKE HOME MESSAGES- *II*

- **Underlying genetic mutations are *common in* adults (around 20-30%), especially in steroid- resistant disease and uFSGS with <8gms/d proteinuria.**

- ***Primary (permeability factor related) FSGS* is susceptible to treatment with immunosuppressive agents (Steroids/CNI) in about 50-60% of patients and perhaps in a few patients (<10%) with gFSGS. Supportive therapy (RASi) *only is* indicated in sFSGS, uFSGS**

KEY TAKE HOME MESSAGES- *III*

- **Treatment of *multi-drug resistant* forms of Primary (pf) FSGS is difficult, highly uncertain and evolving, but *PLEX/IA, RTX or Obinutuzumab* may be an effective approach in selected patients, especially Children. *Sparsentan* is currently being evaluated by the FDA for approval**

THANK YOU!!!

In Vitro Assays for Permeability Factor in Primary FSGS

- Albumin permeability in isolated glomeruli- (Savin-Sharma Factor)
- Anti-Nephrin Antibody antibody (Hengel-Huber Assay; Watts-Weins Assay)
- Cultured Podocyte/Endothelial Cell-lipid droplet/Perilipin-2 expression
- Kidney Organoids (Gupta- Gallon Assay)

Immunofluorescence in FSGS Lesions

- ***Punctate IgG deposits*** **associated with podocytes (co- deposition of nephrin and IgG with confocal IF microscopy) in a minority (=anti-nephrin Ab)**
- **IgM + C3 in 10-15% (?IgM Nephropathy)**
- **C1q and IgG deposits in <5%- (?C1q Nephropathy)**
- **IgG/IgA deposits in FSGS secondary to another glomerulopathy (MN, IgAN, LN)**