WELCOME TO 58TH ERA-EDTA VIRTUAL CONGRESS

- Khosravi Masoud, M.D.
- Nephrologist
- Guilan University of Medical Sciences
- 19 Nov 21
- 000828

58 ERA-EDTA CONGRESS FULLY VIRTUAL JUNE 5-8, 2021

Is immunosuppression needed in IgAN?

Jürgen Floege

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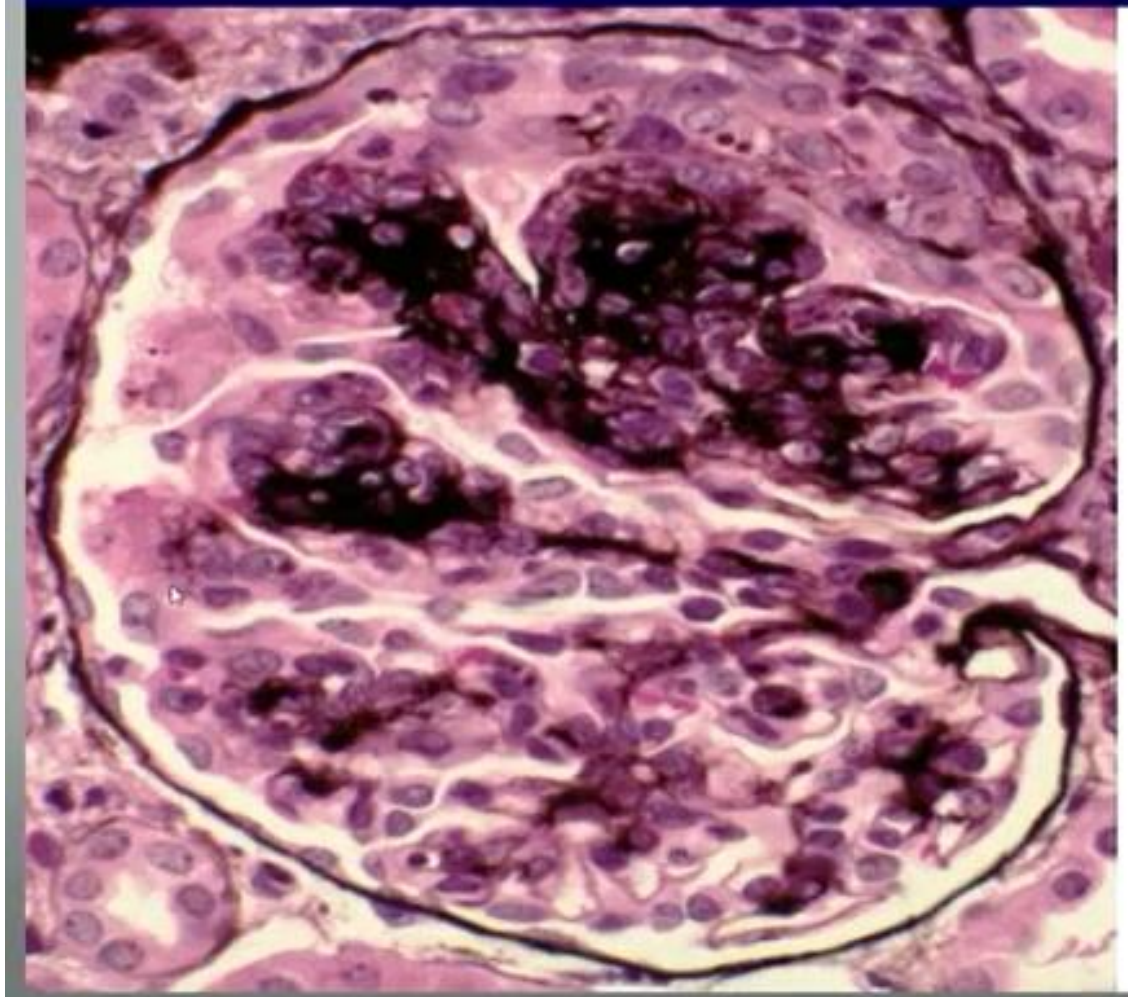
Jürgen Floege
IgA nephropathy: is immunosuppression needed?
Chairs : Rosanna Coppo, Alexander Rosenkranz

Disclosures

Employer	RWTH University of Aachen, Germany
Consultancy Agreements	Amgen, Bayer, Boehringer, Calliditas, Novo Nordisk, Morphosys, Omeros, Travere, Vifor
Honoraria	Amgen, Bayer, Calliditas, Novo Nordisk, Omeros, Travere, Vifor, Visterra
Scientific Advisor or Membership	Calliditas, Omeros, Vistera

Liu H et al, Am J Nephrol 2012;36:377–385

Cellular Crescents in IgAN Patients



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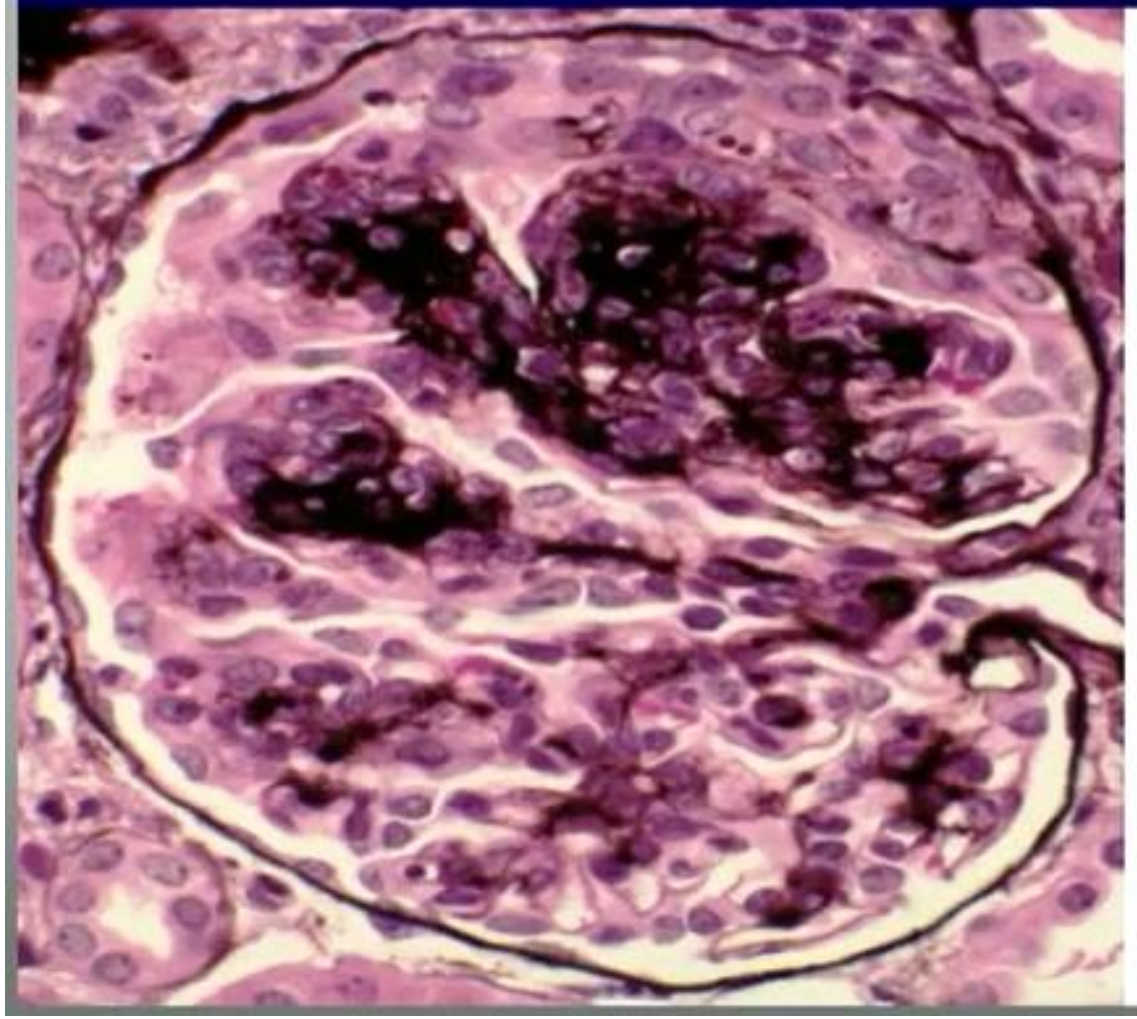
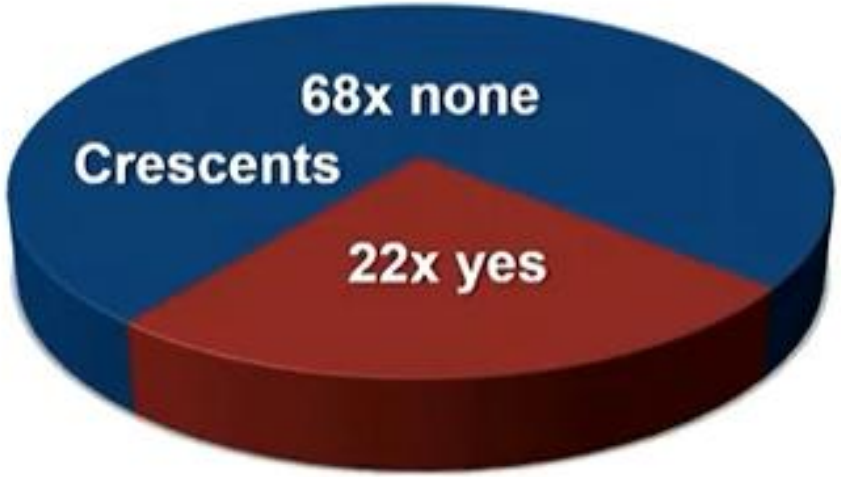
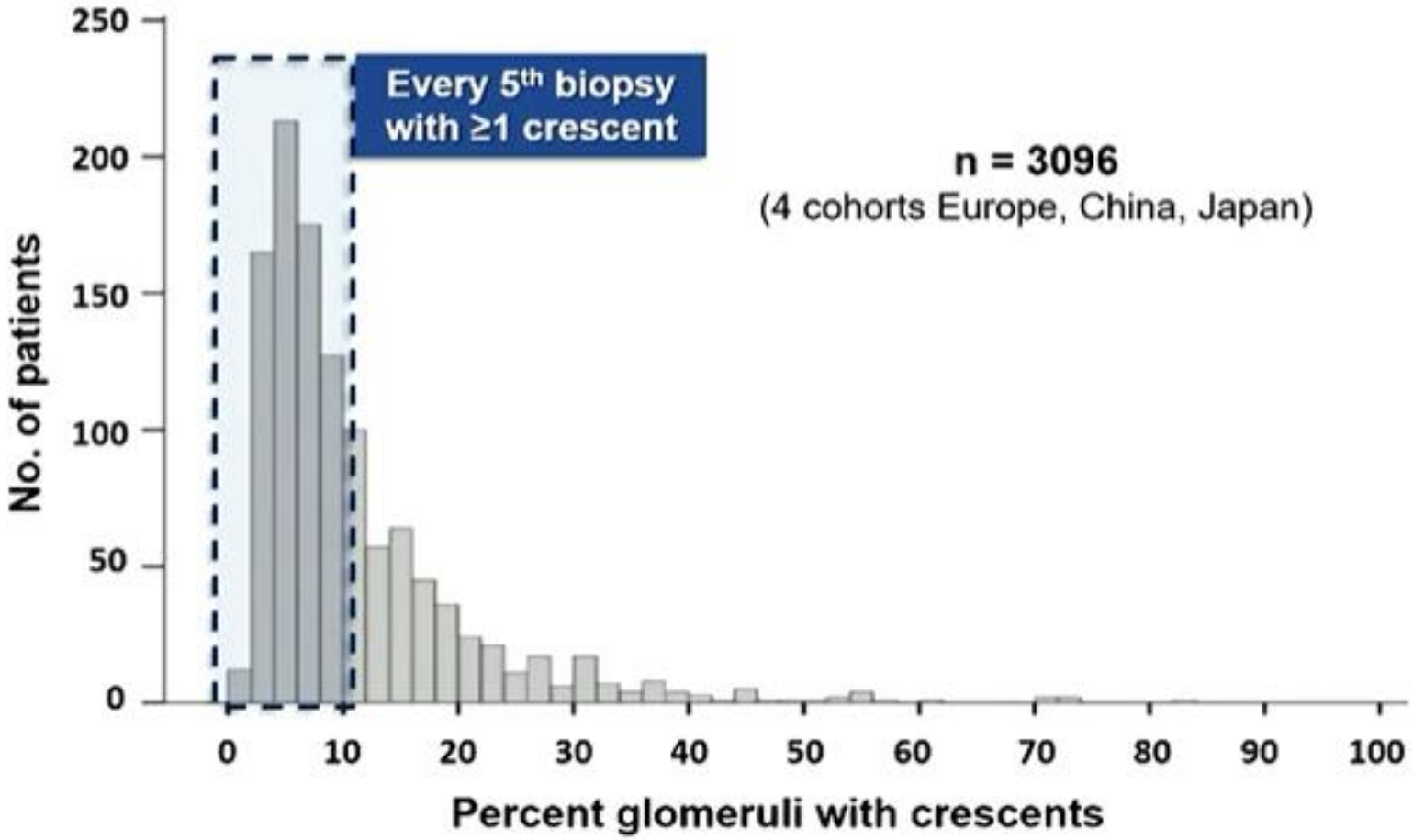


- 90 patients, biopsy-proven IgAN, 15-56 years old
- All with isolated microhematuria, proteinuria <0.5 g/d, eGFR normal



Haas M et al, J Am Soc Nephrol 28: 691–701, 2017

Glomerular Crescents in IgAN Patients



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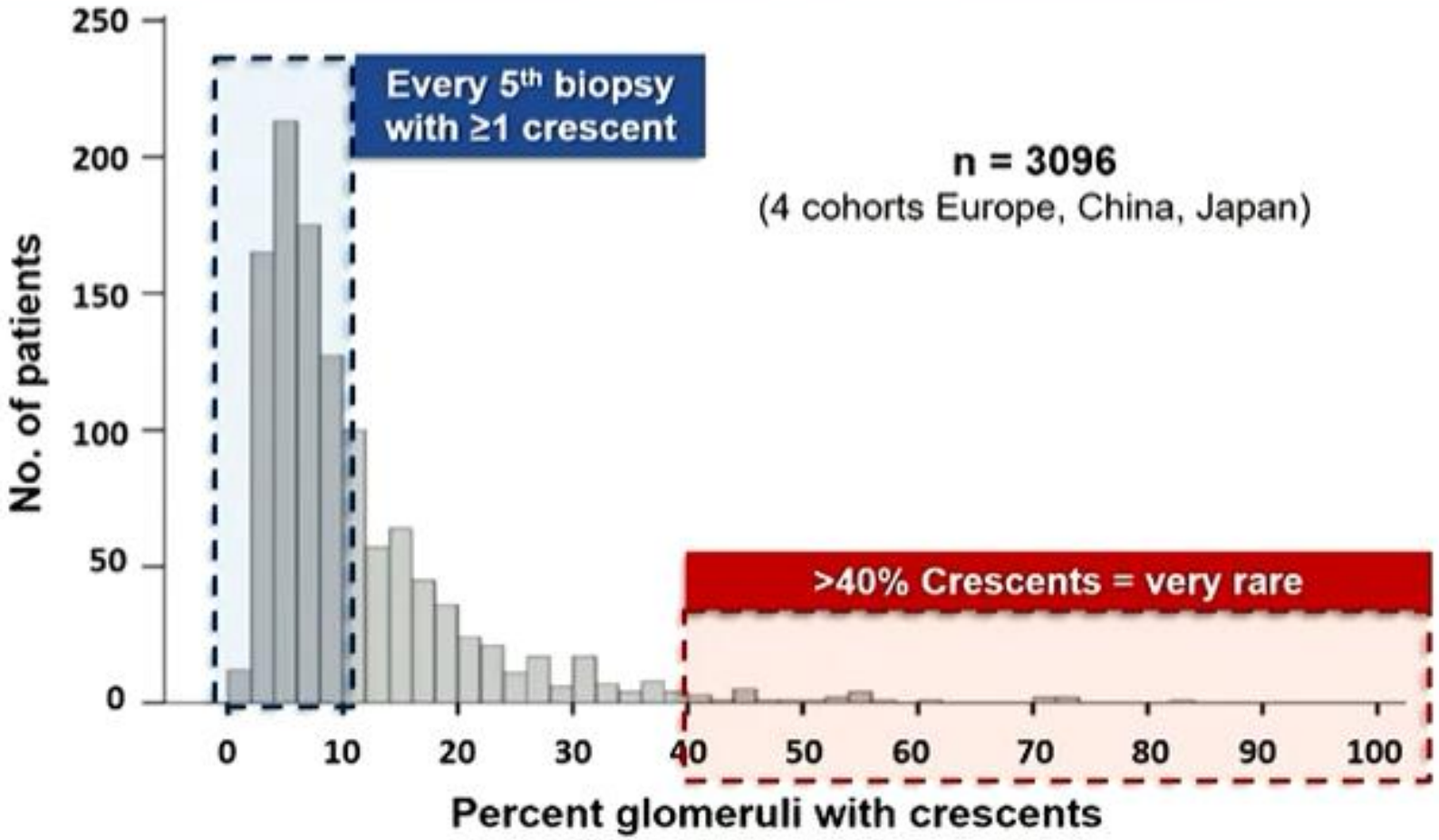

Lv J, et al, J Am Soc Nephrol 2013; 24: 2118-2125

Vasculitic IgAN (RPGN-variant)

>50% glomerular crescents and RPGN course

113 Chinese patients

At time of biopsy:

- 66±16% crescents
- Crea 4.3±3.4 mg/dl

Lv J, et al, J Am Soc Nephrol 2013; 24: 2118-2125

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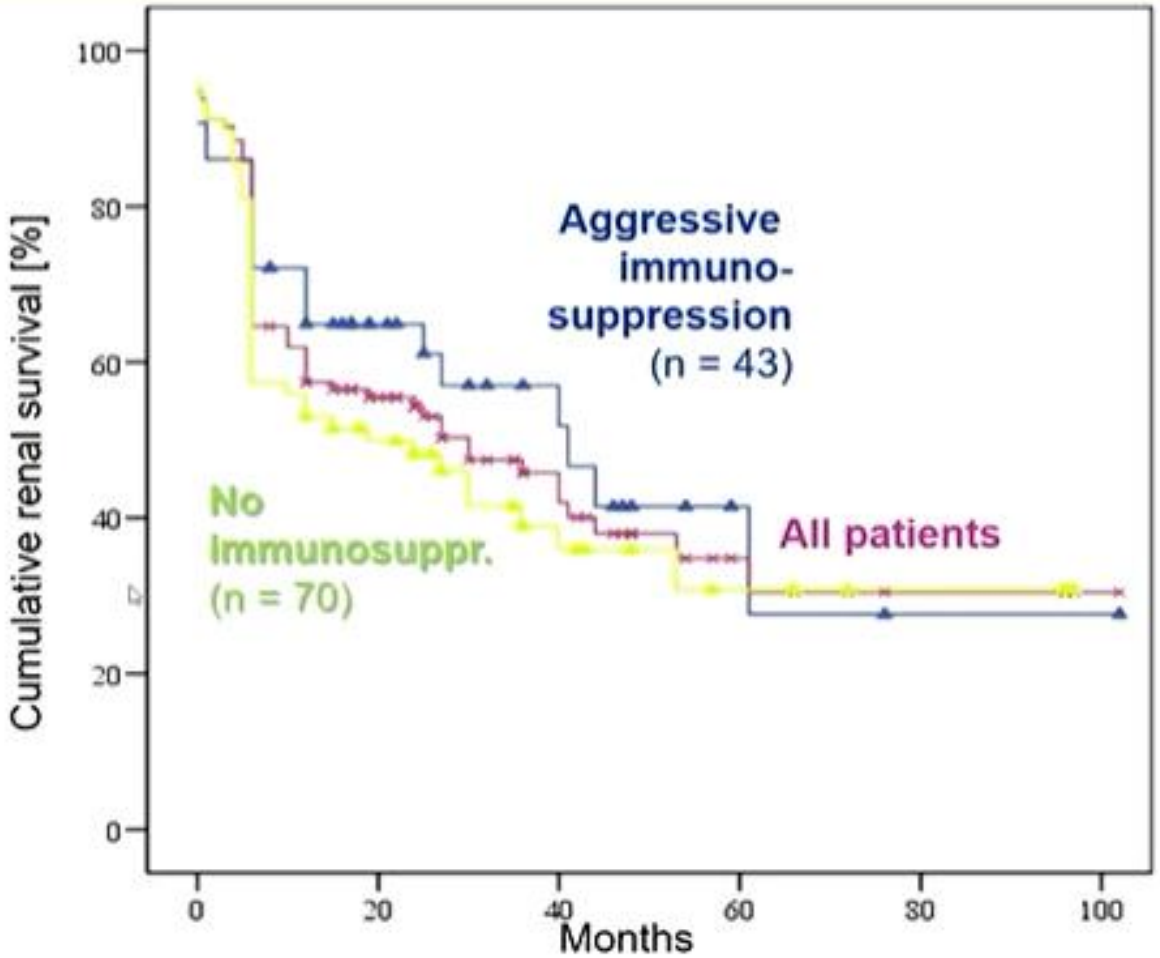

Floege & Feehally, Nat Rev Nephrol 2013

Floege & Eitner, J Am Soc Nephrol. 2011

If you were my IgAN patient in 2021…

„No Problem"

Minor urinay findings, GFR and BP normal

↓

(bi-)annual checks for at least 10 years

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„Attention!"

Acute or rapid loss of GFR

↓

Nephrotic syndrome or RPGN

↓

Supportive therapy

+ Immuno-suppression

AKI (Macro-hematuria or other etiology)

↓

Supportive therapy

Floege & Feehally, Nat Rev Nephrol 2013

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If you were my IgAN patient in 2021…

„No Problem"

Minor urinay findings, GFR and BP normal

↓

(bi-)annual checks for at least 10 years

„Stratify Risk"

Proteinuria >0.5-1 g/d ± GFR reduced ± hypertension

↓

Supportive therapy optimize for 3-6 months

„Attention!"

Acute or rapid loss of GFR

- **Nephrotic syndrome or RPGN** → **Supportive therapy** + **Immuno-suppression**
- **AKI** (Macro-hematuria or other etiology) → **Supportive therapy**

IgA nephropathy

Kidney Int Suppl. Oct 2021

Practice Point 2.3.1. Considerations for treatment of all patients with IgAN

- **The primary focus of management should be optimized supportive care.**
- **Assess cardiovascular risk and commence appropriate interventions as necessary.**
- **Give lifestyle advice including information on dietary sodium restriction, smoking cessation, weight control, and exercise as appropriate.**

Level 1 Recommendations

- Control blood pressure (sitting systol. BP in the 120s)
- ACEI or ARB therapy (uptitrate + maybe combine)
- Avoid dihydropyridine type calciumchannel-blockers
- Control protein intake

} ALL

Level 2 Recommendations

- Restrict NaCl- and fluid-intake, diuretics
- Non-dihydropyridine type calciumchannel-blockers
- Control all components of the metabolic syndrome
- Aldosterone antagonist, ß-blocker
- Stop smoking

} As many measures as possible

Floege & Eitner, JASN 2011

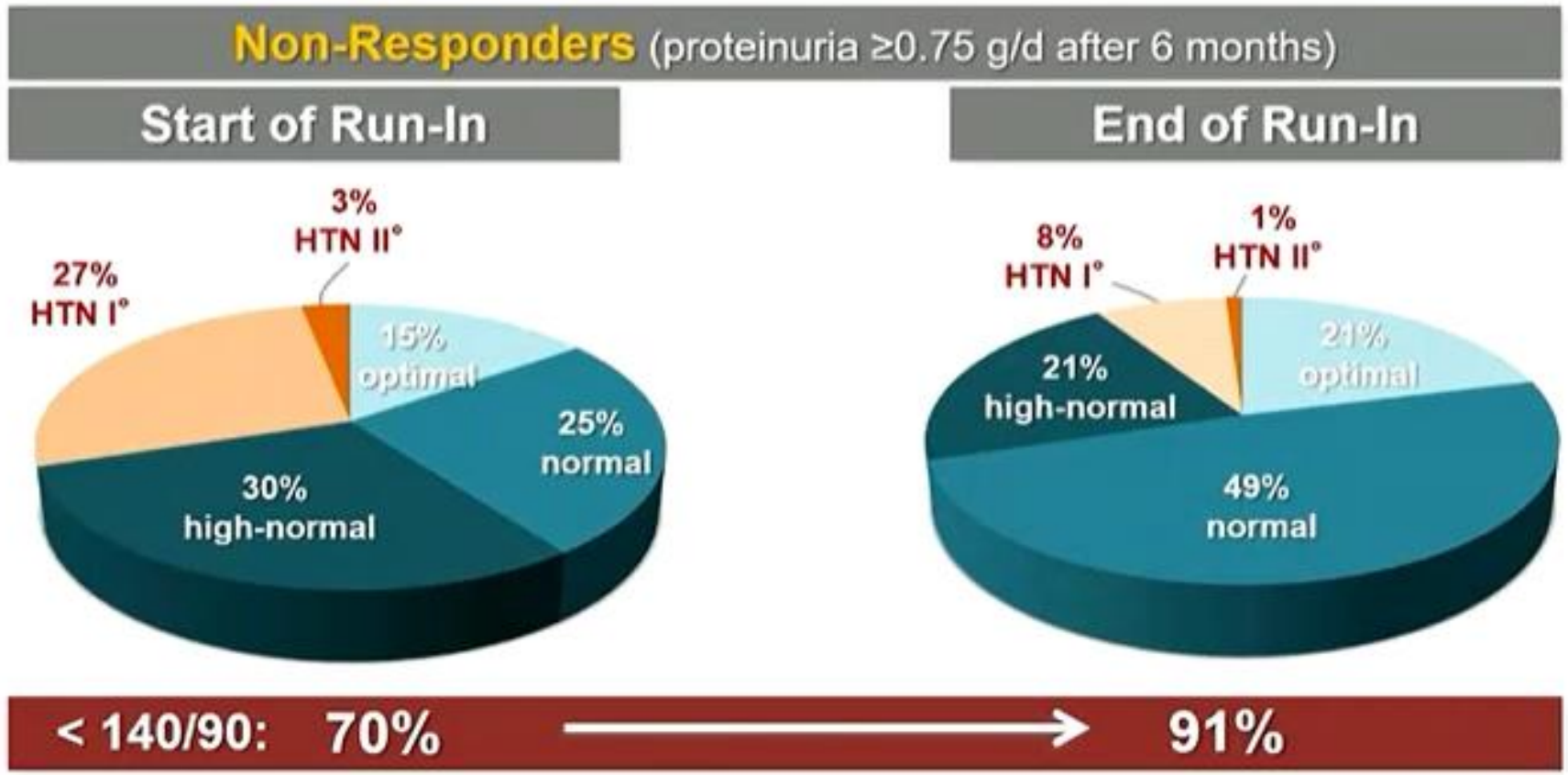
Floege & Feehally Nat Rev Nephrol 2013


IgAN
IgAN

Run-in Phase: Blood pressure

Rauen T et al,
N Engl J Med.
2015;373:2225-36

Non-Responders (proteinuria ≥0.75 g/d after 6 months)

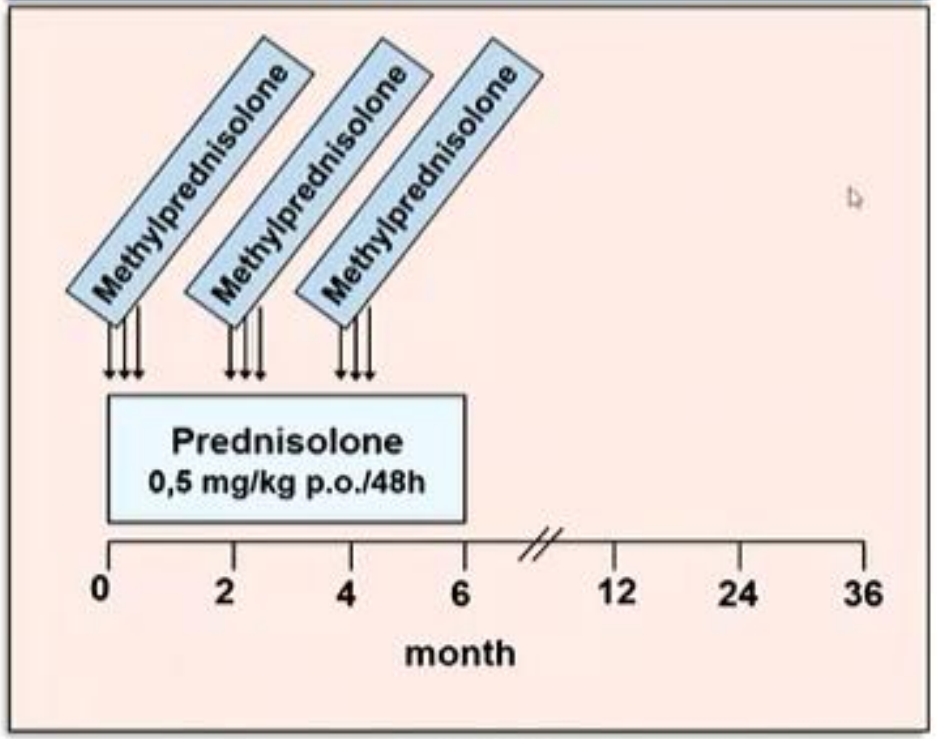


< 140/90: 70% → 91%

Immunosuppression

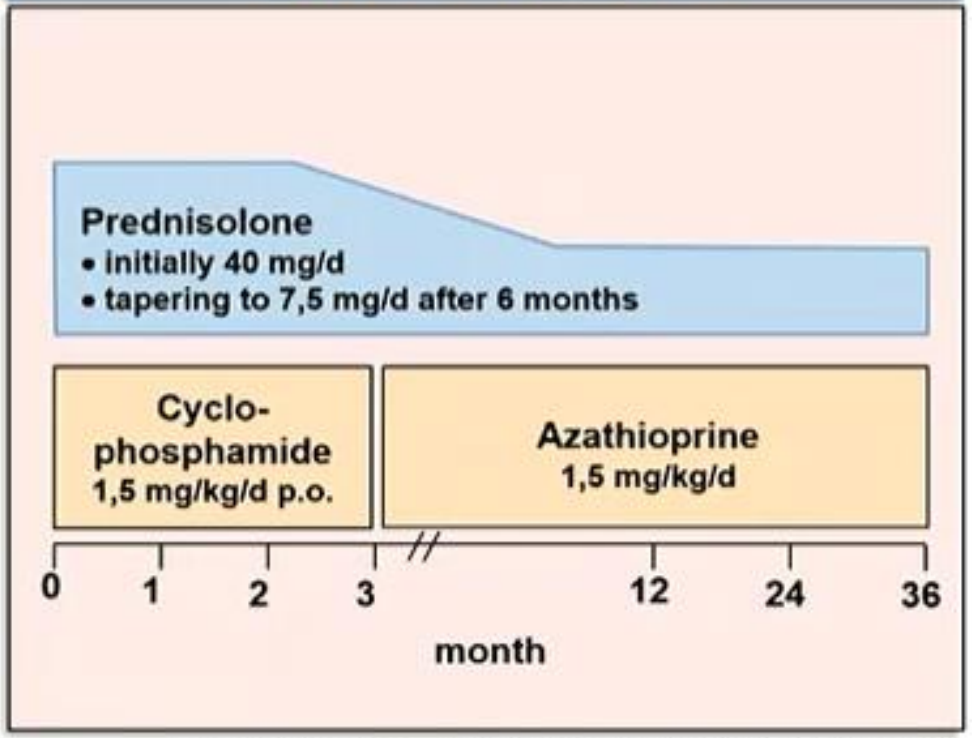
Rauen T et al,
N Engl J Med.
2015;373:2225-36

GFR ≥ 60 ml/min



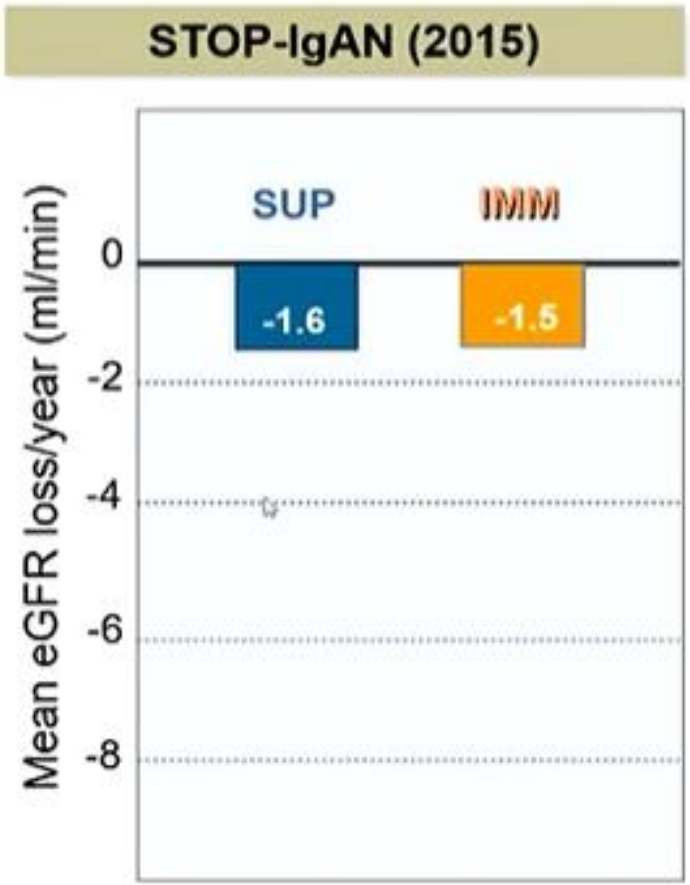
Pozzi et al. Lancet 1999; 353: 883

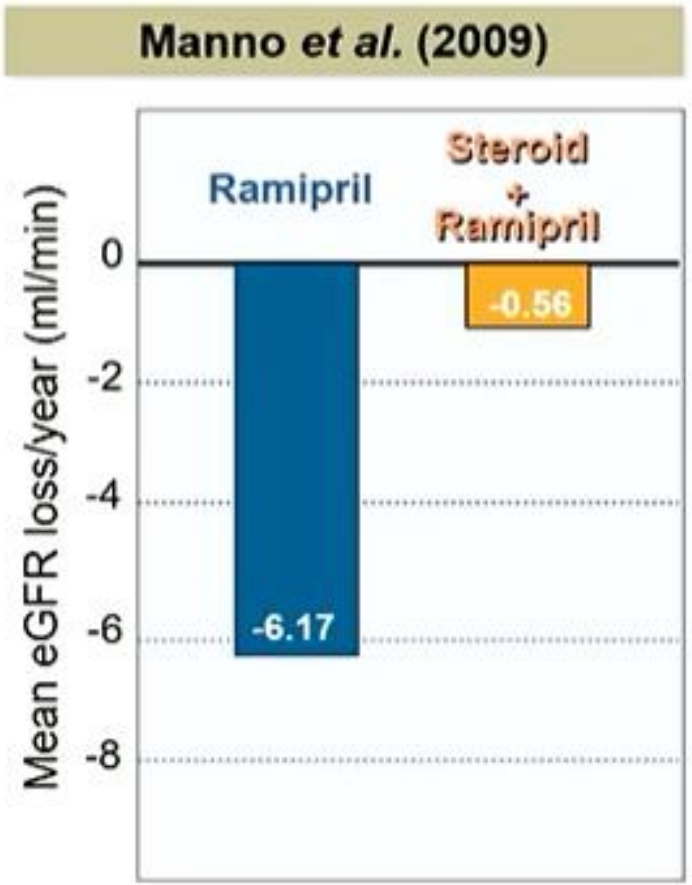
GFR 30-59 ml/min



Ballardie et al., J Am Soc Nephrol 2002; 13:142

3-Year Trial Phase: Annual GFR Loss





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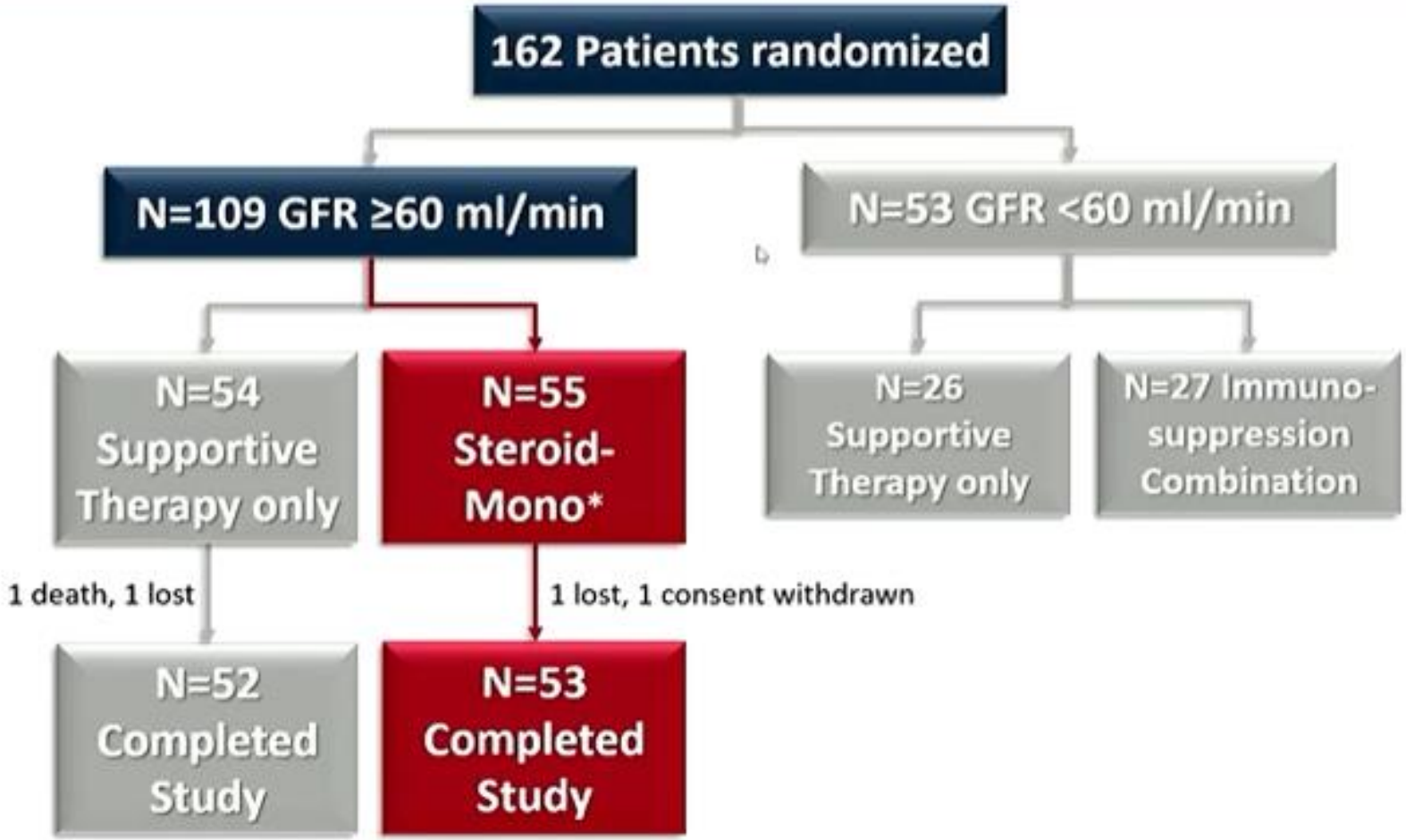


Rauen T et al, N Engl J Med 2015; 373: 2225

Rauen T et al, J Am Soc Nephrol 2018; 29: 317

The STOP-IgAN trial

Adverse Event	Supportive only (N=54)	Steroid Mono-therapy (N=55)
Total no. SAEs	19	14
Total no. Infections	69	115
Total no. infectious SAEs	2	4
Death	1 (car accident)	0
Malignancy	0	0
Glucose intolerance / diabetes	1	9
GI bleeding	0	0
Fracture	0	1
Osteonecrosis	0	0
Weight gain >5 kg first year	3	9

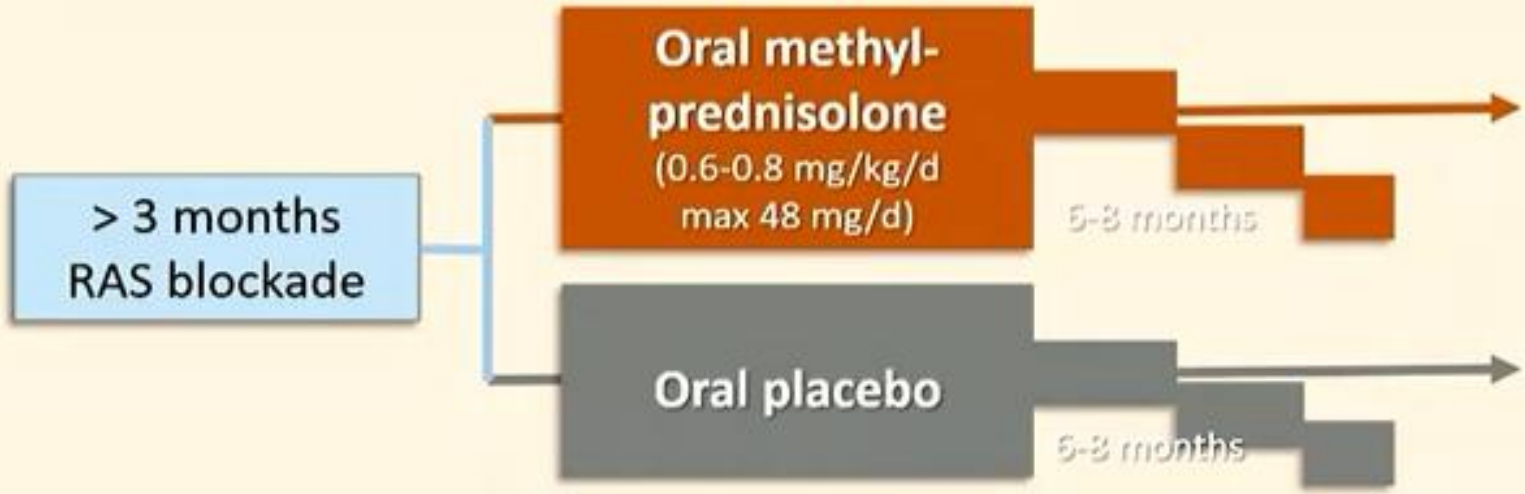
Research

JAMA. 2017;318(5):432-442

JAMA | Original Investigation

Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy
The TESTING Randomized Clinical Trial

Jicheng Lv, MD; Hong Zhang, PhD; Muh GeotWong, PhD; Meg J. Jardine, PhD; Michelle Hladunewich, MD; Vivek Jha, MD; Helen Monaghan, PhD; Minghui Zhao, MD; Sean Barbour, MD; Heather Reich, MD; Daniel Cattran, MD; Richard Glassock, MD; Adeera Levin, FRCPC; David Wheeler, FRCP; MarkWoodward, PhD; Laurent Billot, MSc; Tak Mao Chan, MD; Zhi-Hong Liu, MD; DavidW. Johnson, MD; Alan Cass, FRACP; John Feehally, MD; Jürgen Floege, MD; Giuseppe Remuzzi, MD; YangfengWu, MD; Rajiv Agarwal, MD; Hai-YanWang, MD; Vlado Perkovic, PhD; for the TESTING Study Group



Lv J et al, JAMA. 2017;318:432-442

The TESTING trial

Adverse Event	Placebo (N=126)	Steroid (N=136)
Total no. SAEs	4	**28**
Total no. Infections	n/a	n/a
Total no. infectious SAEs	0	**13**
Death	1 (stroke)	**2 (infection)**
Malignancy	n/a	n/a
~~Glucose intolerance /~~ diabetes	3	2
GI bleeding	0	**2**
Fracture	0	**1**
Osteonecrosis	0	**2**
Weight gain >5 kg first year	n/a	n/a

Lv J et al, JAMA. 2017;318:432-442

The TESTING trial: early termination

Adverse Event	Placebo (N=126)	Steroid (N=136)
Total no. SAEs	4	28
To		
To		
De		
M		
GI		
GI		
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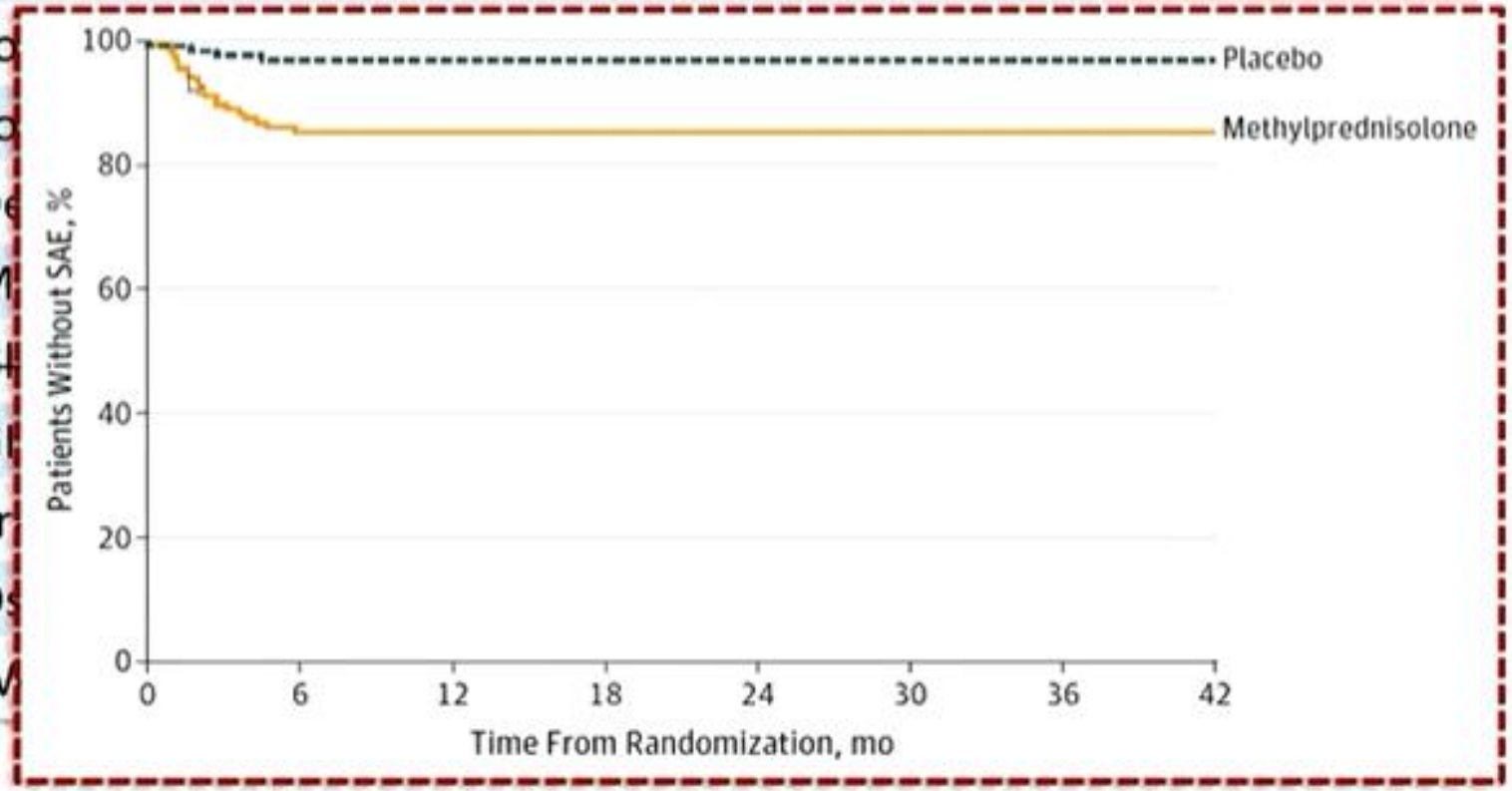


Floege & Eitner, Sem Nephrol 2008; 28: 38-47

Major adverse effects of immunosuppression

- Controlled trials in IgAN patients -

Corticosteroid monotherapy	
Pozzi et al. 1999	1 new type 2 diabetes mellitus
Shoji et al. 2000	none
Katafuchi et al., 2003	none
Hogg et al., 2007	none
Horita et al., 2007	n/a
Mycophenolate mofetil	
Maes et al., 2004	1 re-activation of pulmonary tuberculosis, 2 GI complaints.
Tang et al., 2005	3 transient anemia, 1 diarrhea, 2 UTIs, 1 cerv.lymphadenitis
Frisch et al., 2005	None
Immunosuppressive combination therapy	
Yoshikawa et al. 1999	1 each glaucoma, cataract, depression, peptic ulcer, alopecia and anemia. Sign. growth retardation + weight gain.
Yoshikawa et al. 2006	2 aseptic necrosis of femoral head, 4 with glaucoma, 4 with leukopenia. Significant increase in BMI
Ballardie et al. 2002	1 bone marrow suppression, 1 with new diabetes mellitus, 1 activation of pulmonary tuberculosis

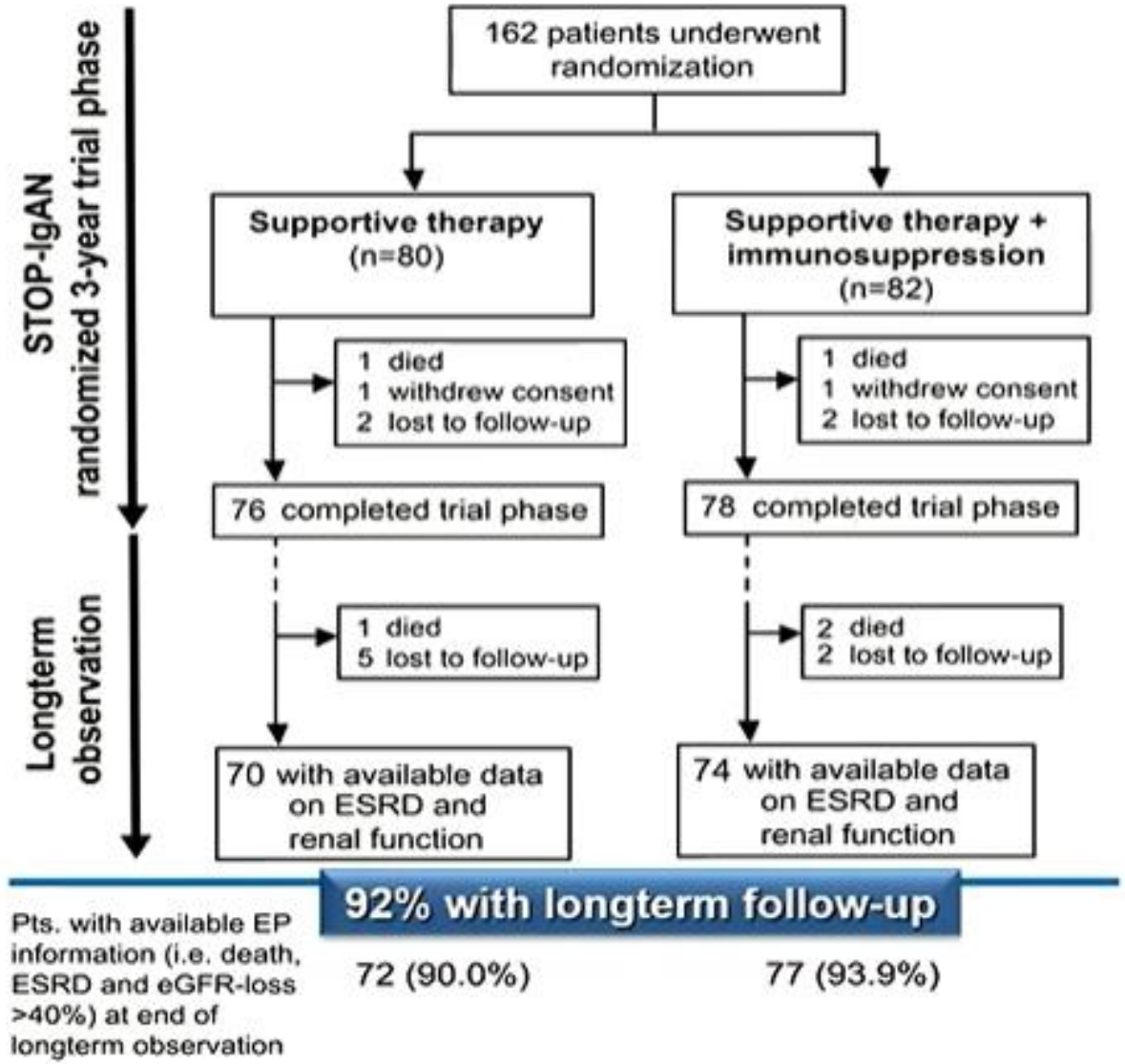
n/a – information not available

Rauen T et al,
Kidney Int. 2020 May 22
S0085-2538(20)30549-4.
doi: 10.1016/j.kint.2020.04.046

STOP-IgAN trial: Long-term Renal Outcomes

STOP IgAN

Long-term



Rauen T et al,
N Engl J Med.
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STOP-IgAN trial: Endpoints

Rauen T et al,
Kidney Int.
2020 May 22

Long-term

Primary endpoints (independent, hierachically ordered)

- Number of **patients in full clinical remission**, defined as: proteinuria < 0.2 g/g PLUS eGFR loss < 5 ml/min from baseline
- **eGFR loss ≥ 15 ml/min** from baseline to the end of the **3-year trial phase**

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STOP-IgAN trial: Endpoints

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2020 May 22

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Primary endpoint

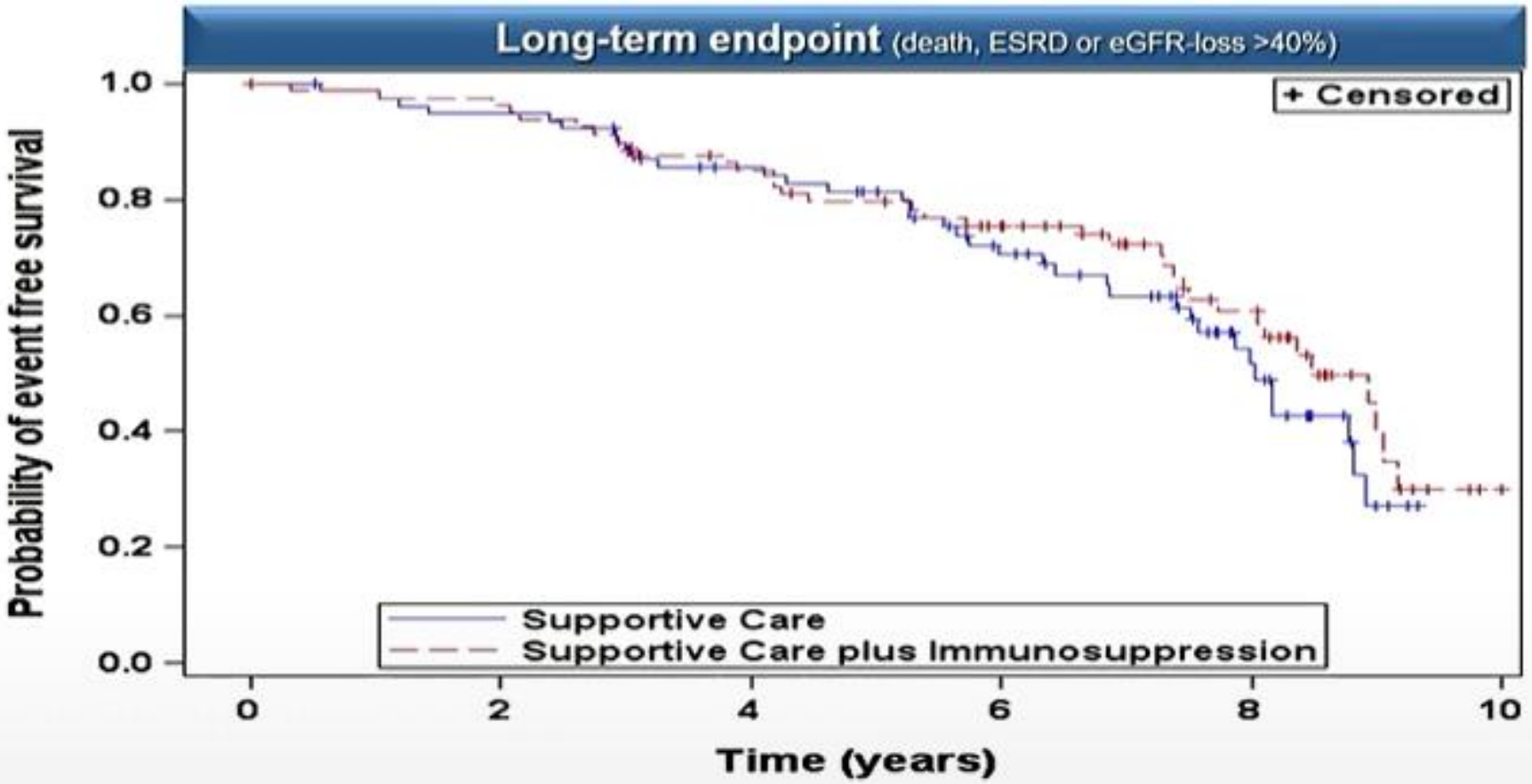
- Time to first occurrence of the **composite of**
  - **all-cause death**
  - **ESRD**
  - **eGFR loss exceeding 40%**

Rauen T et al,
N Engl J Med.
2015;373:2225-36

STOP-IgAN longterm: Primary endpoint

Rauen T et al,
Kidney Int.
2020 May 22

Long-term



IgA nephropathy

Recommendation 2.3.2.
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We suggest that patients who remain at high risk of progressive CKD despite maximal supportive care are considered for a six-month course of corticosteroid therapy.
The important risk of treatment-emergent toxicity must be discussed with patients, particularly those who have an eGFR below 50 ml/min/1.73 m2 (2B).

IgA nephropathy

Kidney Int Suppl. Oct 2021

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Use extreme caution or avoided entirely if:
eGFR < 30 mL/min/1.73 m^2 *
Diabetes
Obesity (BMI > 30 kg/m^2) **
Latent infections (e.g. hepatitis, TB)
Secondary disease (e.g. cirrhosis)
Active peptic ulceration
Uncontrolled psychiatric illness

IgA Nephropathy

other pharmacological approaches

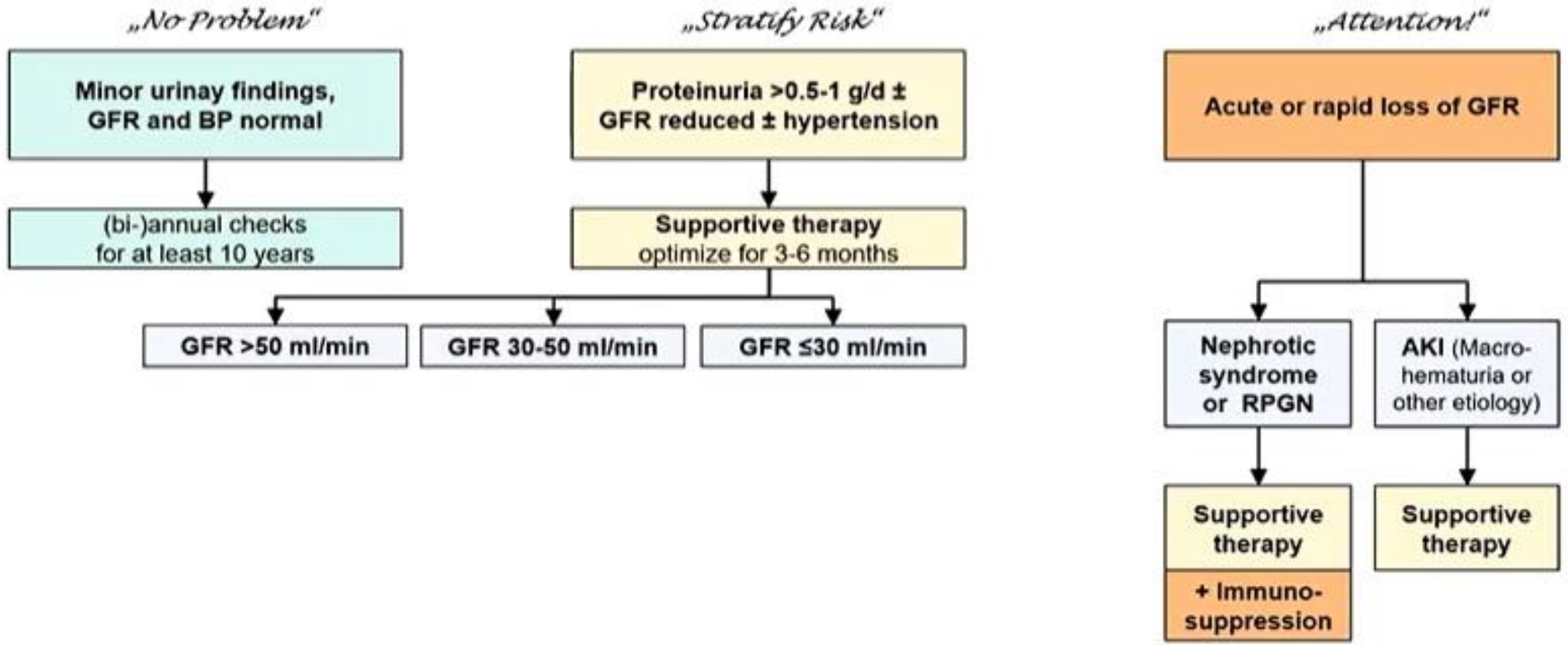
Agent	Suggested usage	Remarks
Antiplatelet agents	Not recommended	No documented evidence of efficacy
Anticoagulants	Not recommended	No documented evidence of efficacy
Azathioprine	Not recommended	No evidence for efficacy as monotherapy or when combined with glucocorticoids
Cyclophosphamide	Not recommended	Unless in the setting of rapidly progressive IgAN
Calcineurin inhibitors	Not recommended	No documented evidence of efficacy
Rituximab	Not recommended	No documented evidence of efficacy
Fish oil	Not recommended	Patients who wish to take fish oil should be advised of the dose and formulation used in the published clinical trials that reported efficacy
Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom glucocorticoids are being considered MMF may be used as a glucocorticoid-sparing agent	In a single RCT conducted in China, MMF with low dose glucocorticoids was non-inferior to standard dose glucocorticoids for the treatment of incident IgAN presenting with proliferative histologic lesions (E or C lesions with or without necrosis) on kidney biopsy and proteinuria >1.0 g/d. There were significantly fewer glucocorticoid related side effects in the combination therapy arm.[1,5]
	Non-Chinese patients There is insufficient evidence to support the use of mycophenolate mofetil	In the RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy.[2,3,4,5]

Kidney Int Suppl. Oct 2021

Floege & Feehally, Nat Rev Nephrol 2013

Floege & Eitner, J Am Soc Nephrol. 2011

If you were my IgAN patient in 2021…



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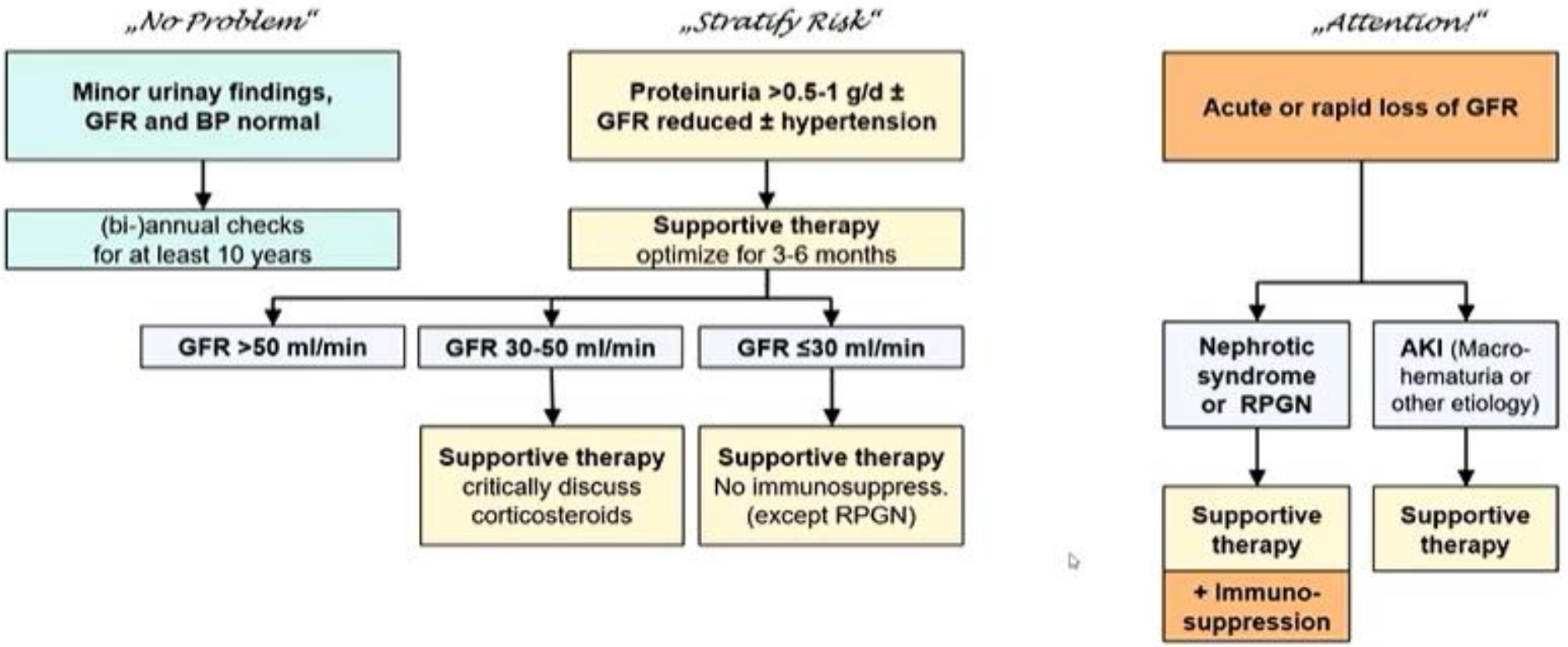

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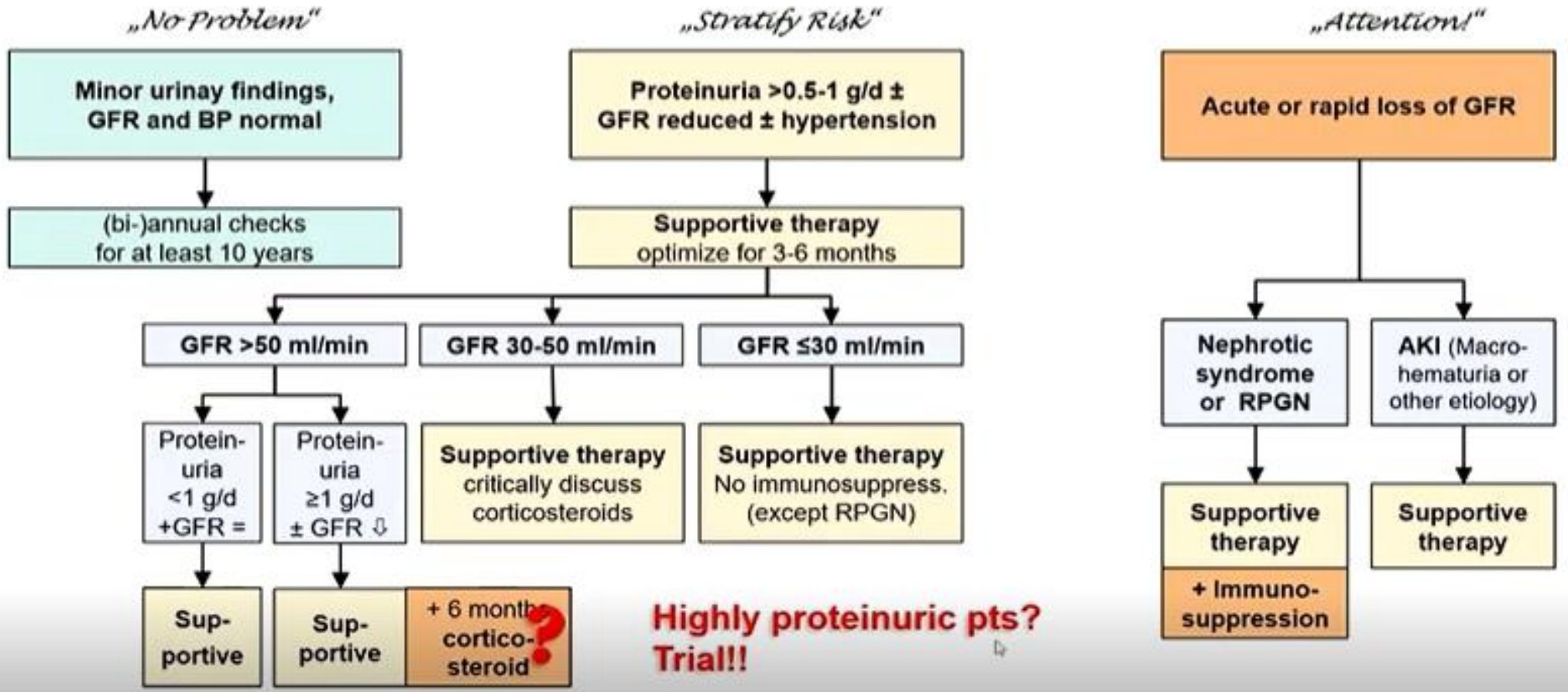
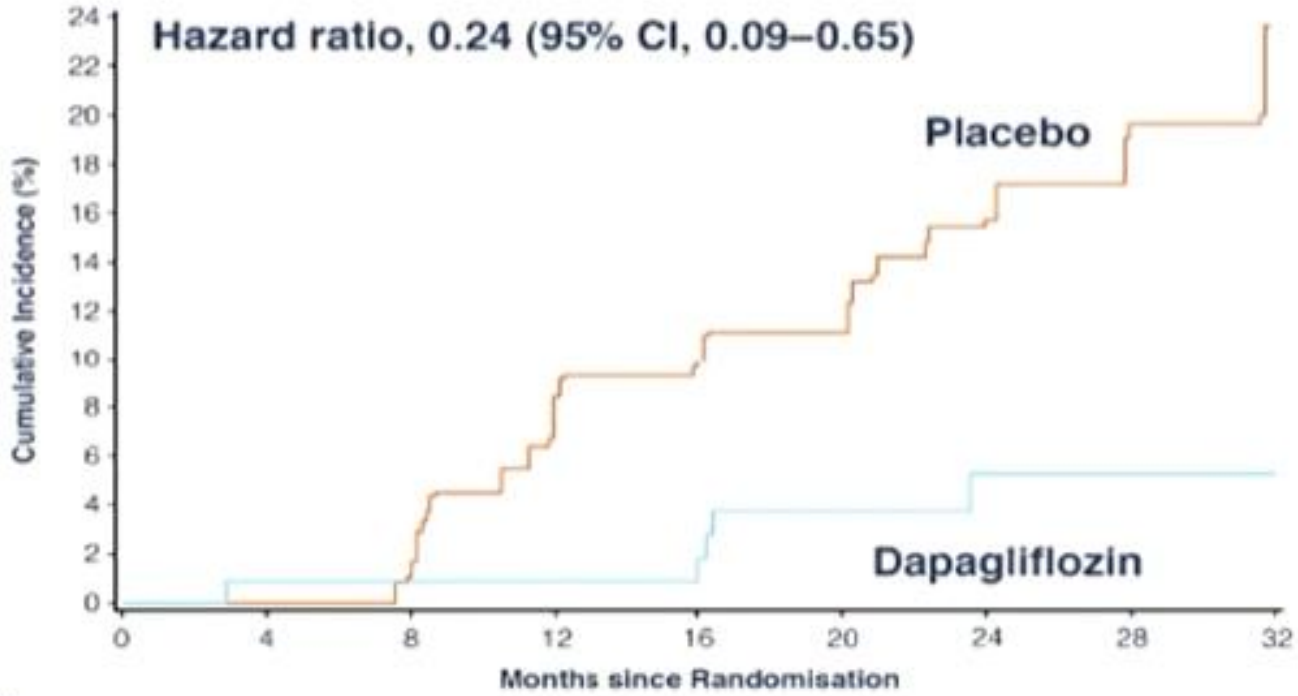


Wheeler DC et al, Kidney Int April 17, 2021

Dapaglifozin in patients with IgA nephropathy

- A subanalysis of the DAPA-CKD trial -

Renal endpoint (Death, dialysis, 50% eGFR loss)



No. at Risk									
Dapagliflozin	137	107	106	105	104	98	61	43	17
Placebo	133	113	108	101	96	92	51	32	19

Wheeler DC et al, Kidney Int April 17, 2021

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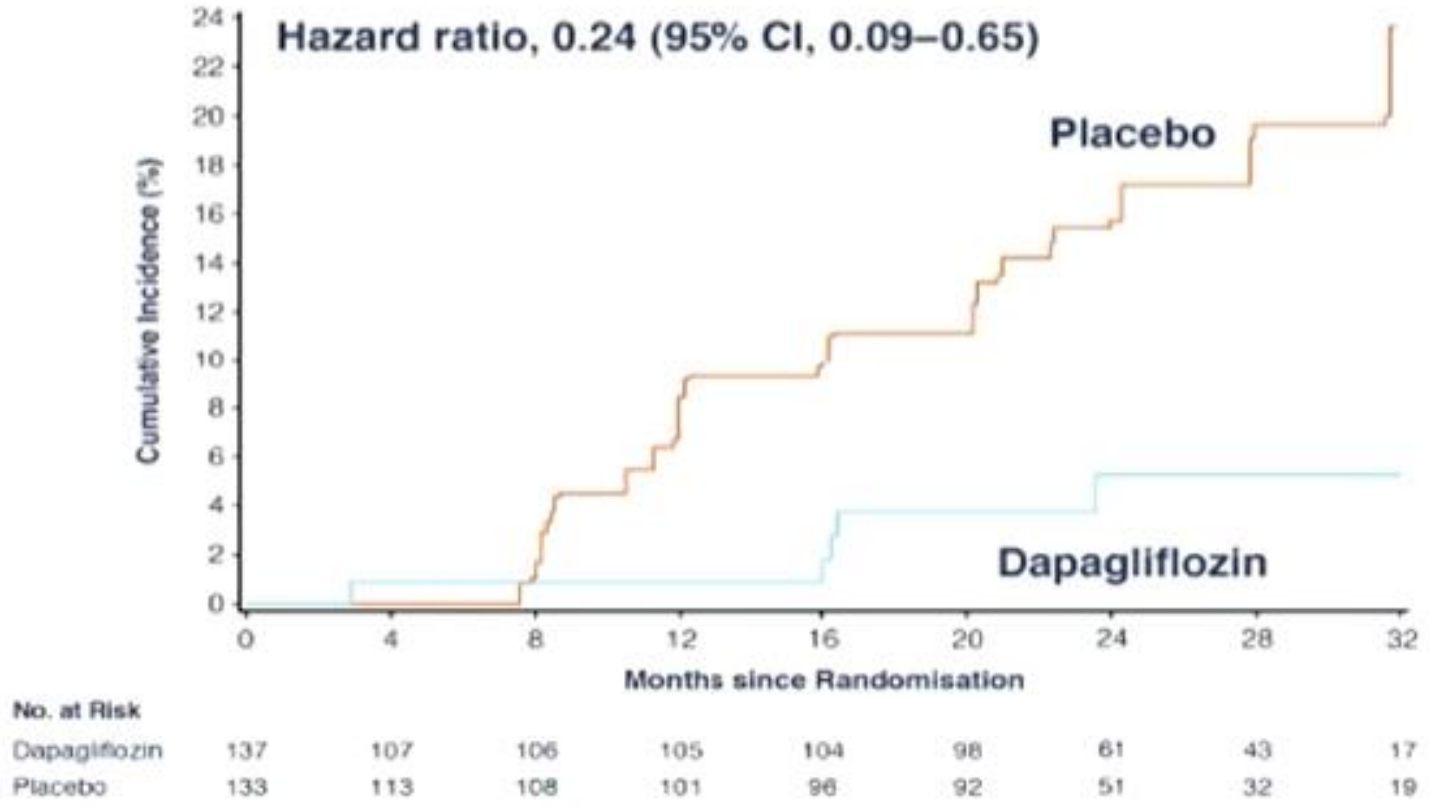

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Placebo	133	113	108	101	96	92	51	32	19

Comments:

- **38/270 patients diabetic**
- **16/270 patients without kidney biopsy**
- **Blood pressure lower in Dapa group**
- **Very bad prognosis of placebo group**
- **Selection of very advanced IgAN** (median eGFR 42 ml/min)

ISN

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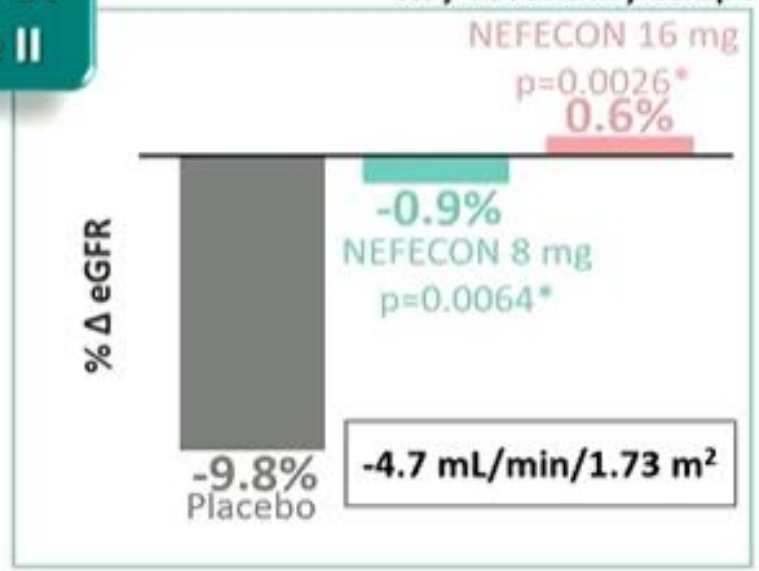
ENTERIC COATED BUDESONIDE (NEFECON) IN IGAN
eGFR AT 9 MONTHS

NEFIGAN Phase II

Key secondary endpoint: Reduction in eGFR



Fellström B et al, Lancet 2017

Calliditas Therapeutics. Press release. 2020. https://www.calliditas.se/en/calliditas-therapeutics-to-host-conference-call-on-positive-topline-results-from-pivotal-phase-3-nefigard-trial-3312/ (accessed Jan 2021). Calliditas Therapeutics. Data on File. 2021

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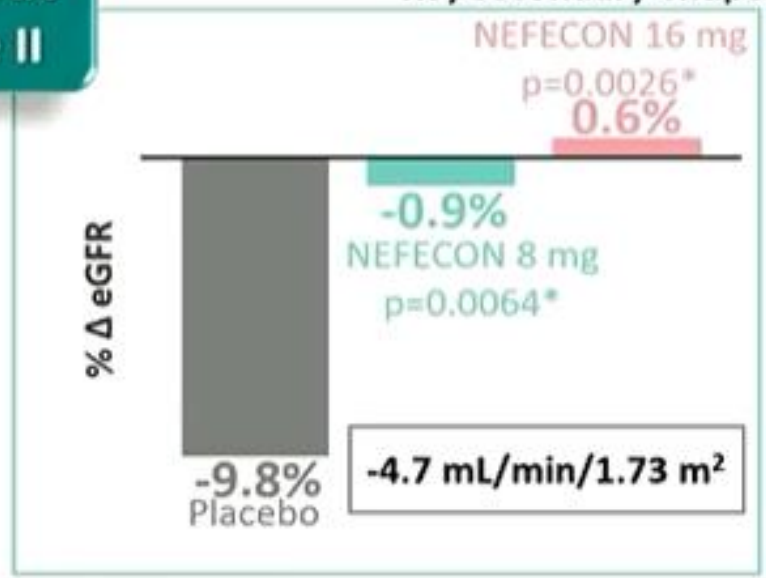
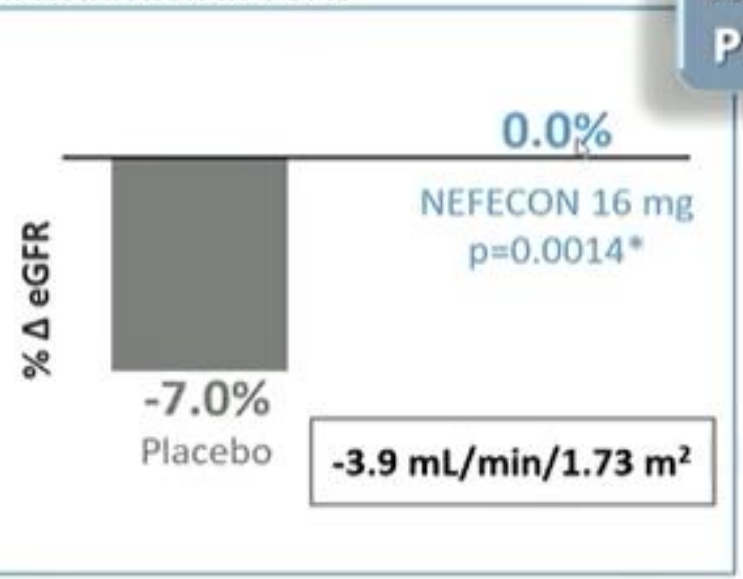


Fellström B et al, Lancet 2017

NefIgArd Phase III



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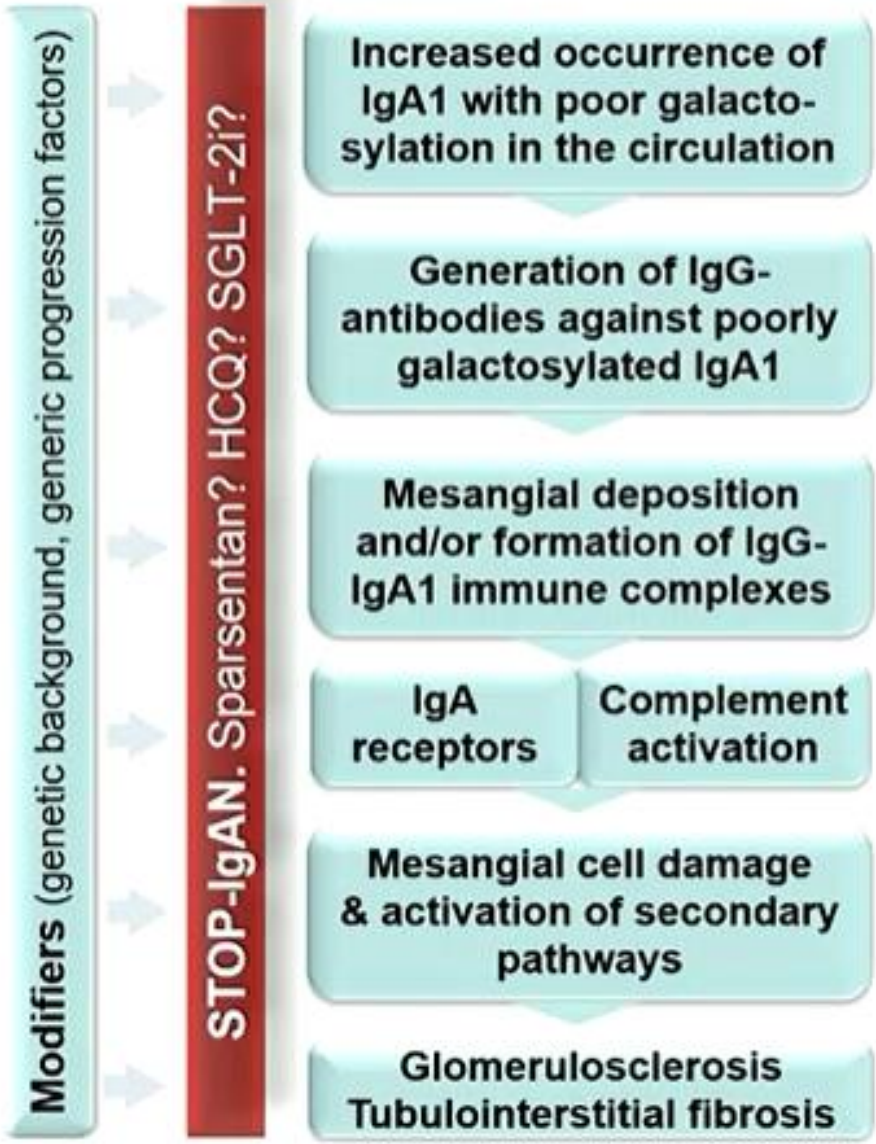
Am J Kidney Dis 2011

Central patho-genetic steps in progressive IgAN



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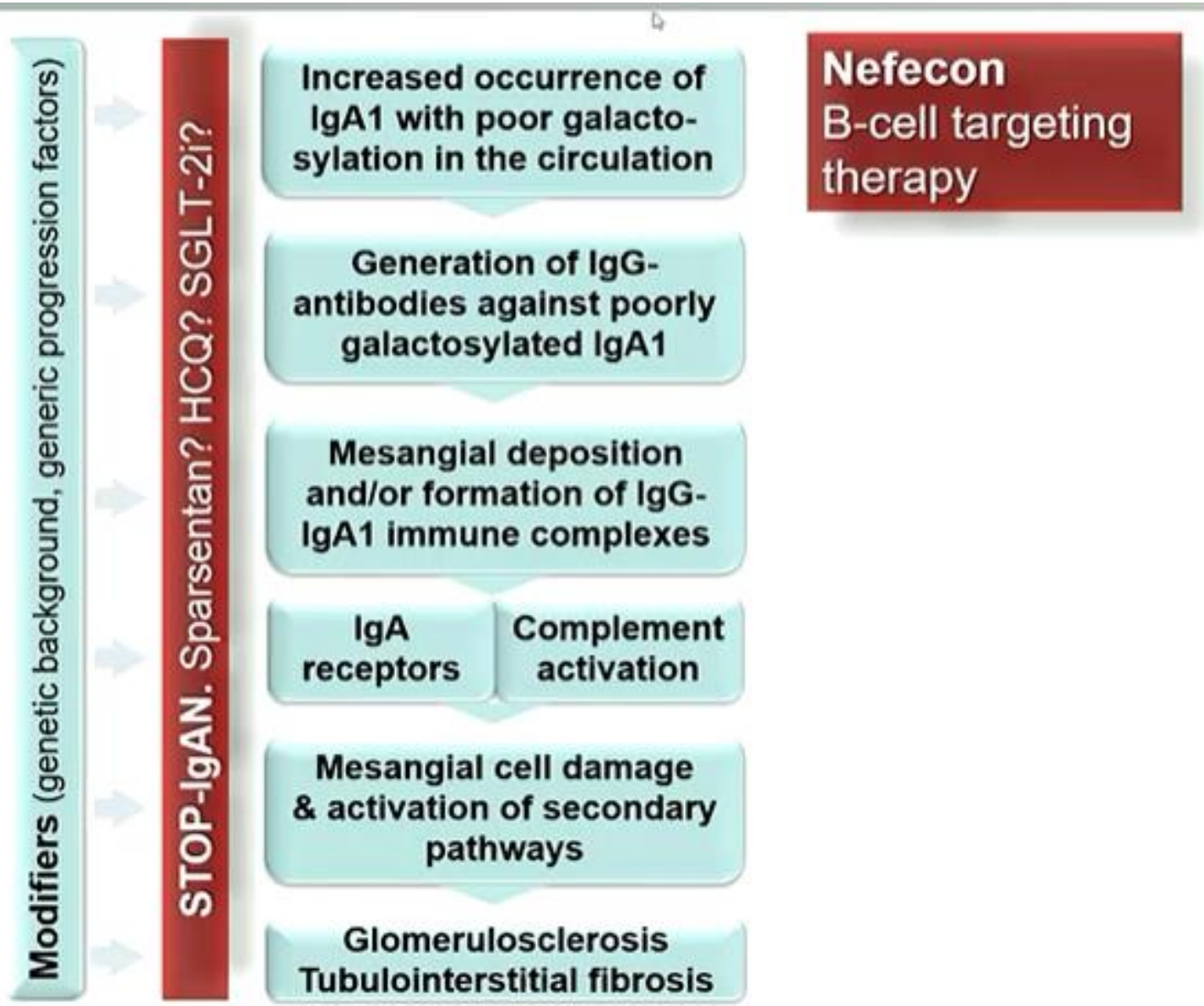

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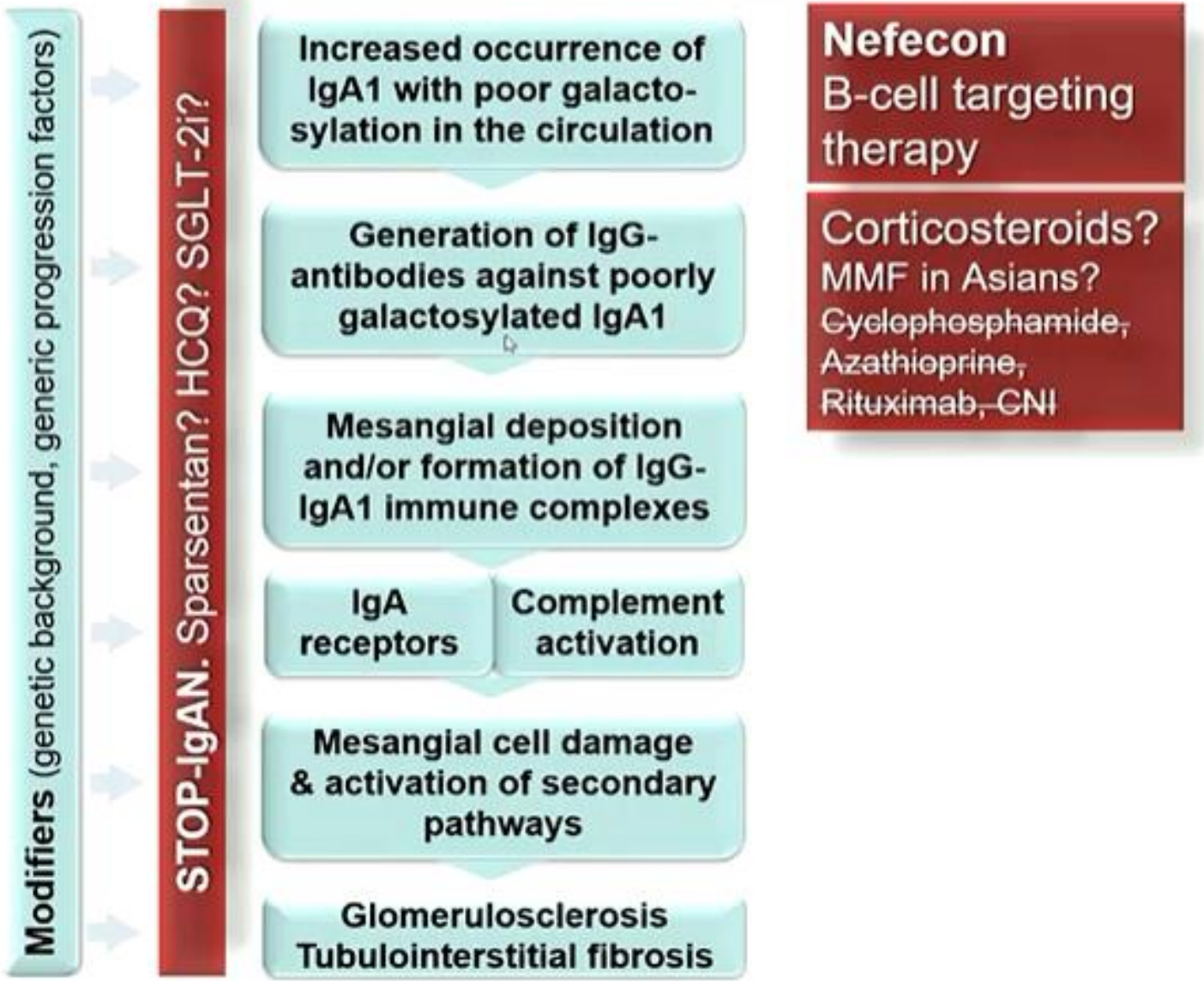

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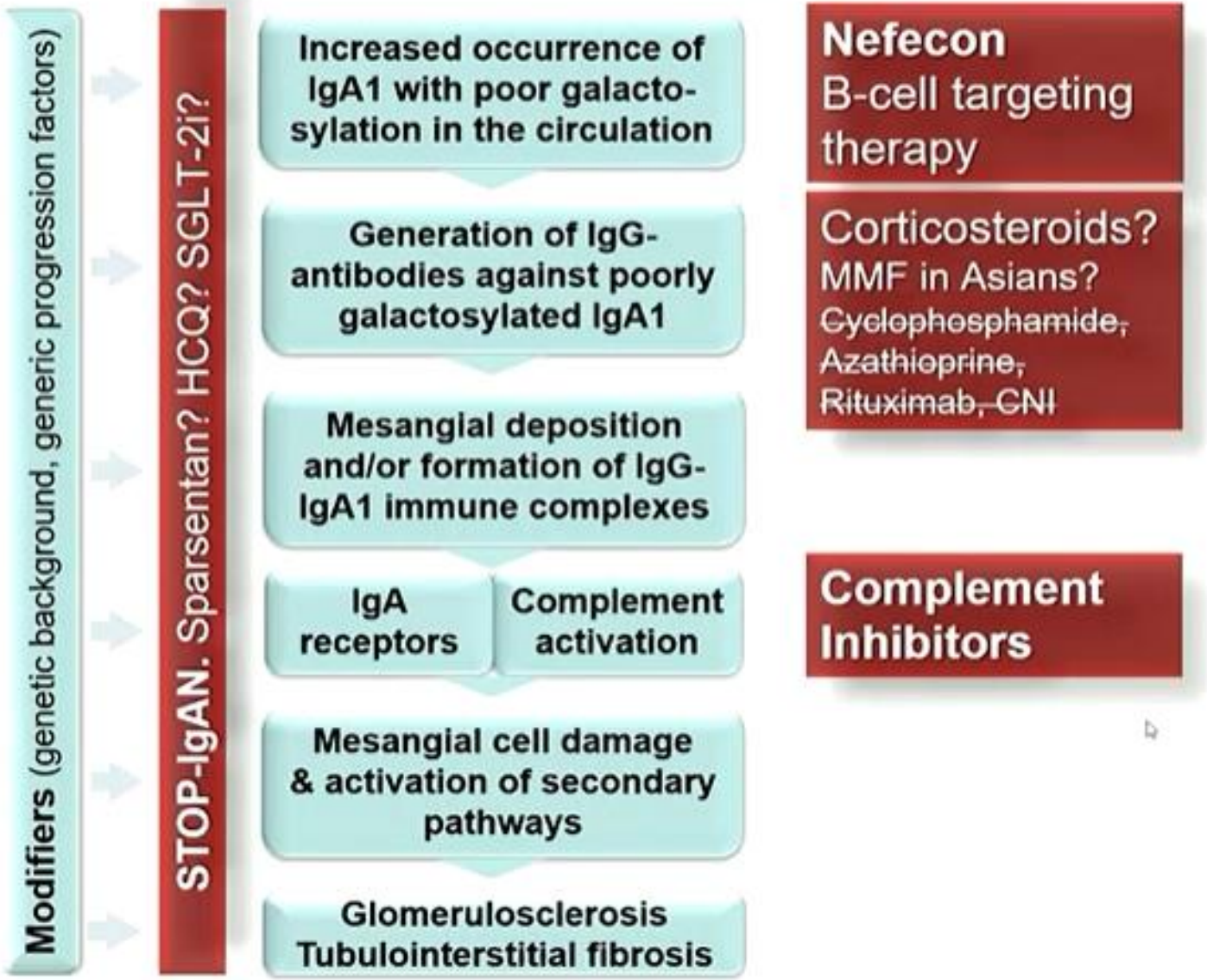
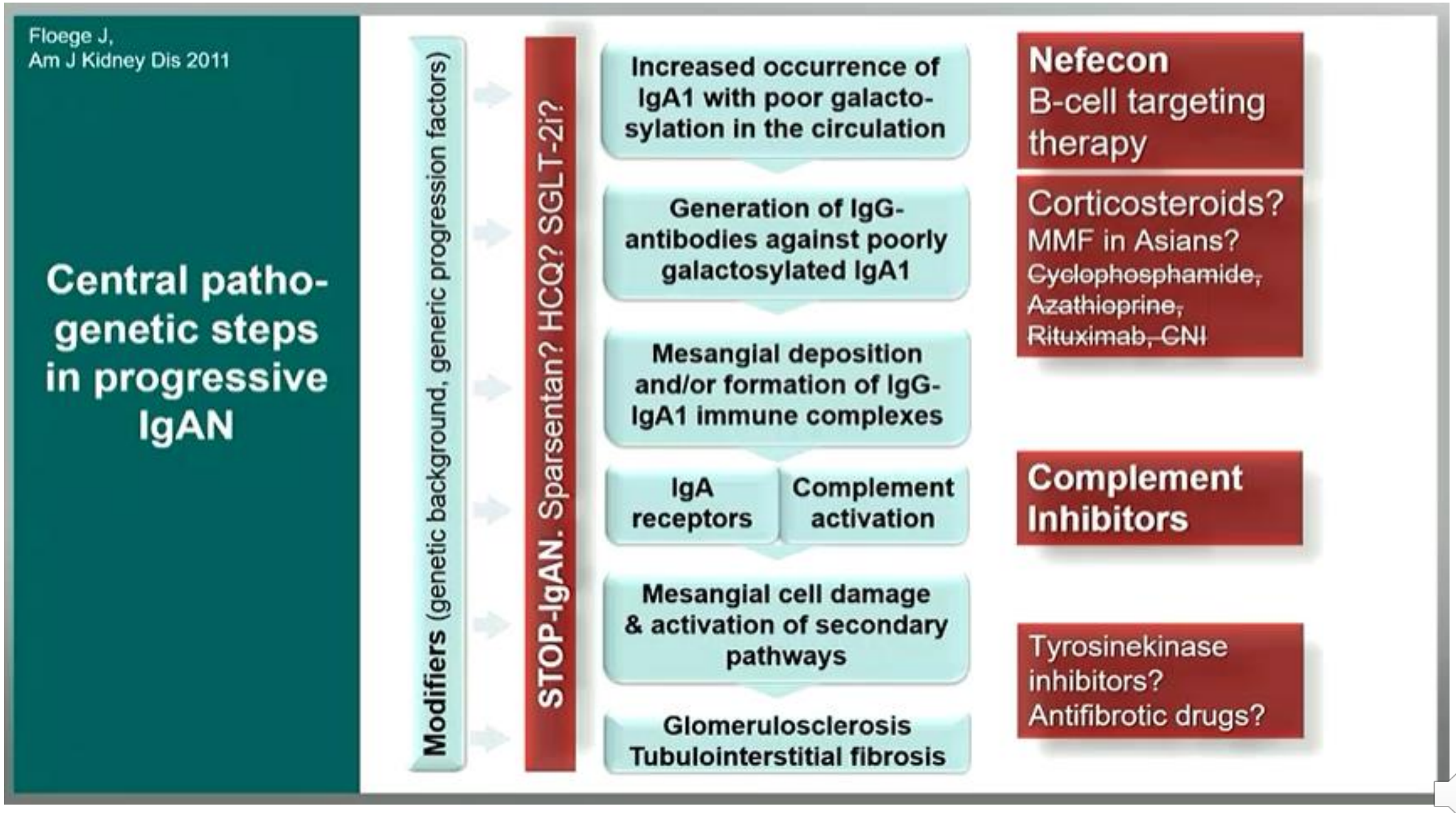
Central patho-genetic steps in progressive IgAN




Floege J,
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Central patho-genetic steps in progressive IgAN
Modifiers (genetic background, generic progression factors)
STOP-IgAN. Sparsentan? HCQ? SGLT-2i?
Increased occurrence of IgA1 with poor galacto-sylation in the circulation
Generation of IgG-antibodies against poorly galactosylated IgA1
Mesangial deposition and/or formation of IgG-IgA1 immune complexes
IgA receptors
Complement activation
Mesangial cell damage & activation of secondary pathways
Glomerulosclerosis Tubulointerstitial fibrosis
Nefecon B-cell targeting therapy
Corticosteroids? MMF in Asians? ~~Cyclophosphamide, Azathioprine, Rituximab, CNI~~
Complement Inhibitors
Tyrosinekinase inhibitors? Antifibrotic drugs?