Russian Dialysis Society
Peterhof, Russia
June 8, 2016

Update on the pathogenesis and treatment of IgA Nephropathy:

One disease or many?

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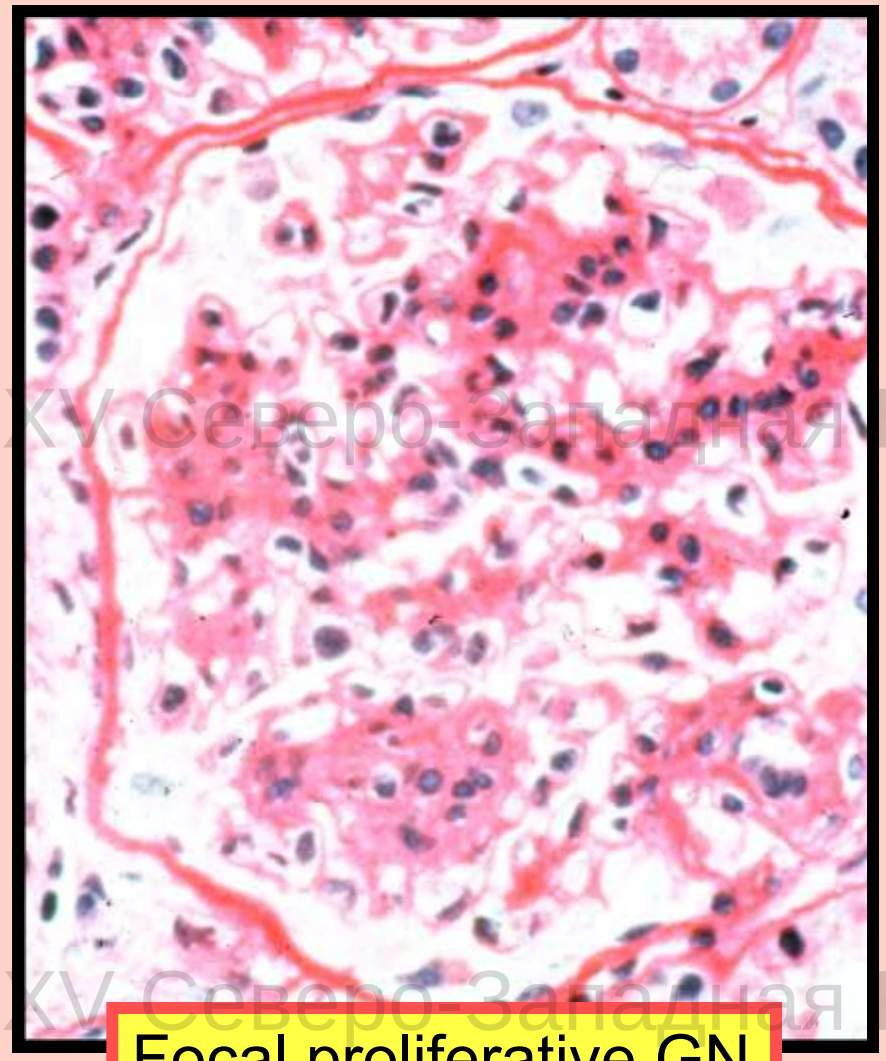
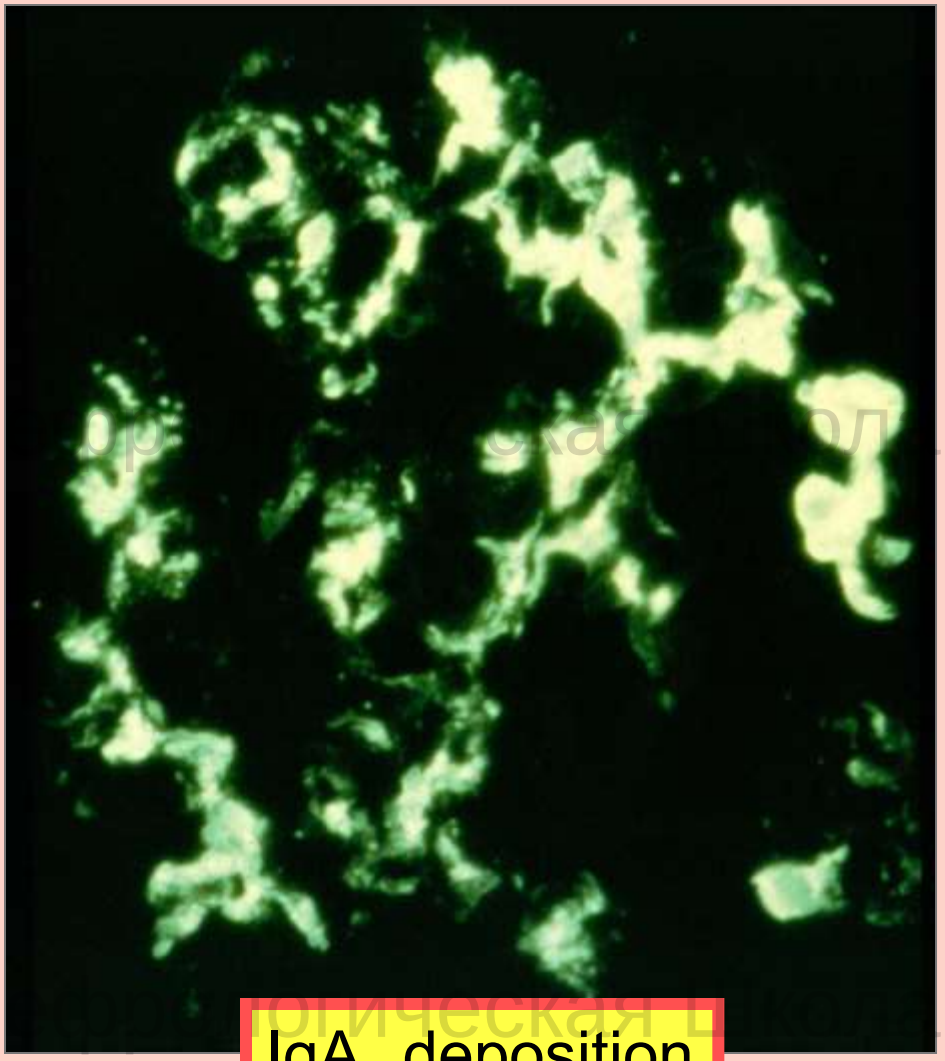
IgA Nephropathy



Focal proliferative GN



IgA_1 deposition

Pathogenesis of GN - IgAN

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Genetic Risk Factors → HLA, autoimmunity
Complement (CFH
Mucosal barrier function
GI Inflammation
IgA_1 glycosylation

↓

Environmental exposures → Viral URIs,
Bowel inflammation

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↓

Innate Immune response
(Toll like receptors, complement) → TLR4, MBL, C

↓

Adaptive Immune response
(Antibodies/complement, T cells) → IgG anti-glycan ab
IgA anti-glycan ab
C, C3, C5b-9

↓

Tissue injury → Focal prolif GN,
(MEST score)
Proteinuria

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Hit #1 - Genetics of IgAN

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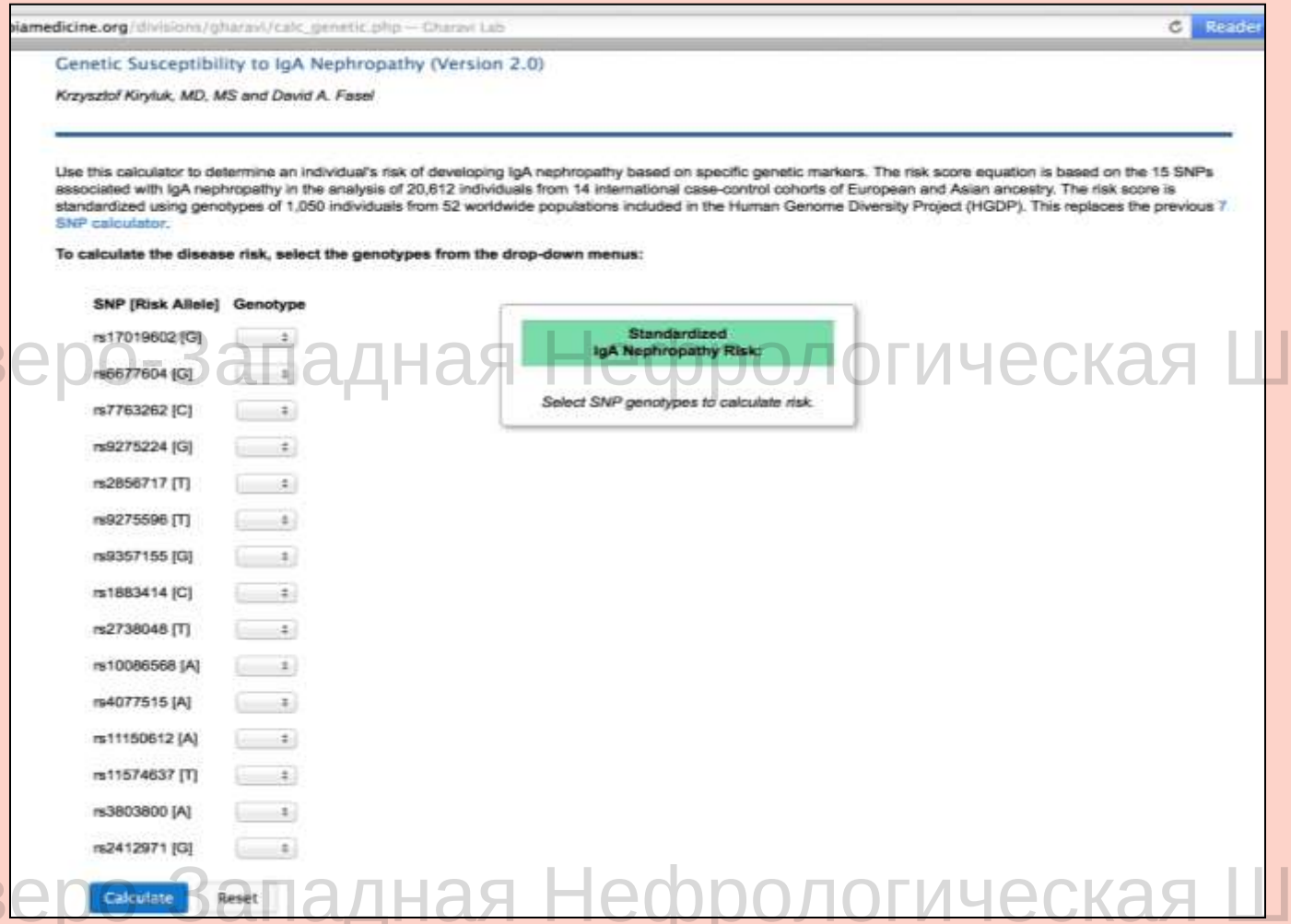
Kirlykuk et al. Nature Genetics 46:1187 (Nov) 2014; Zhu et al. JASN (Epub 5-15-15)

The IgA nephropathy genetic risk calculator

(Based on 15 SNPs)

www.columbiamedicine.org/divisions/gharavi/calc_genetic.php



Kirlykuk et al. Nature Genetics 46:1187, 2014

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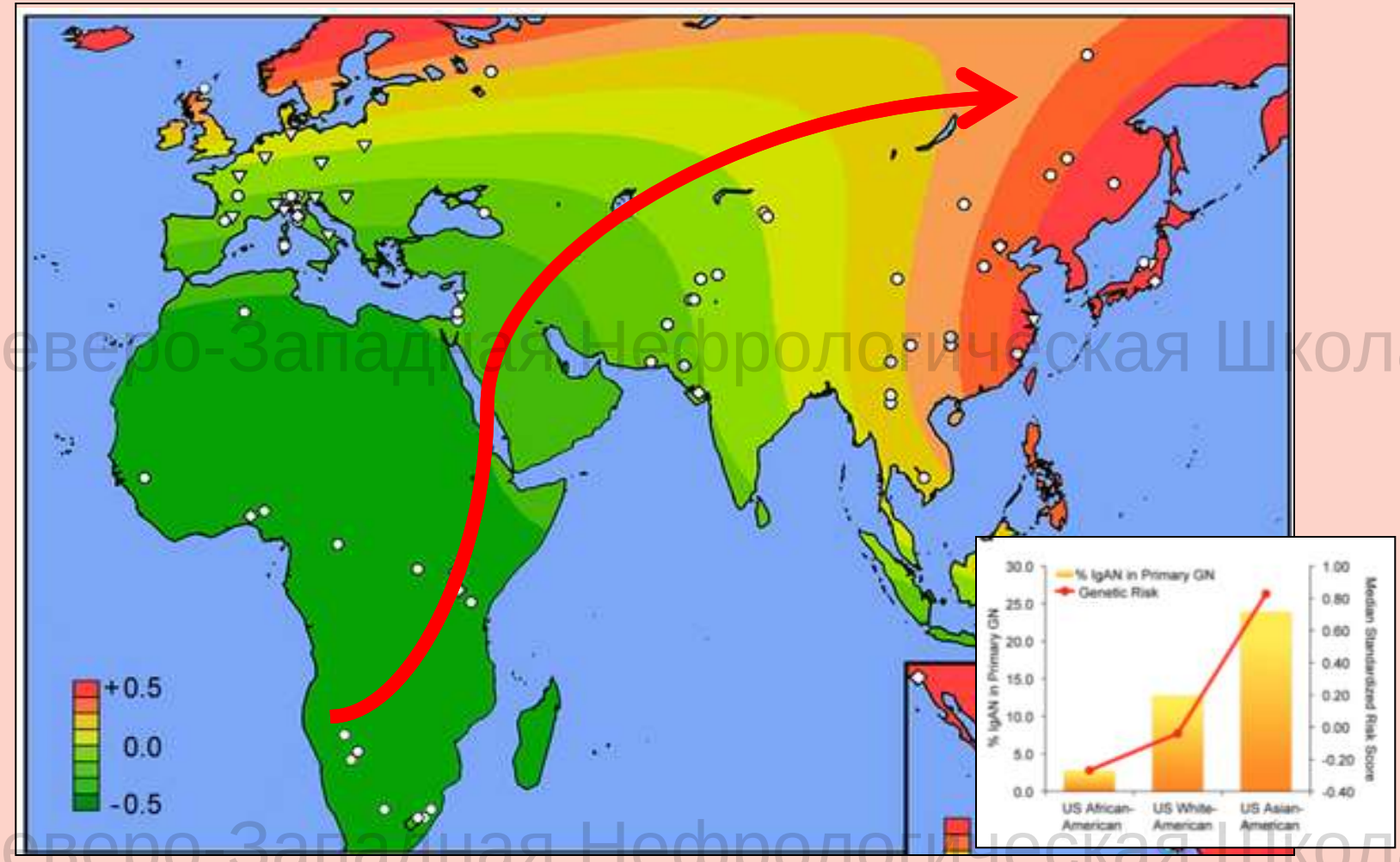
Geographic and racial prevalence of genetic risk scores determines the prevalence of IgAN



Modified from Kuryluk et al. Ann Rev Med 64:339, 2013

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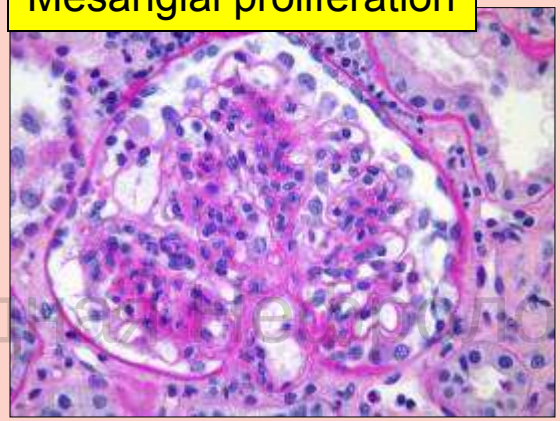
IgA Nephropathy is Morphologically Heterogeneous

Normal (MCD)

Mesangial proliferation

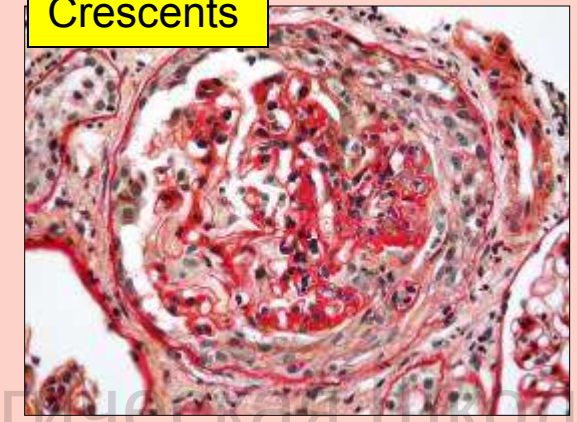


Diffuse proliferation

Focal sclerosis

Mesangial expansion

Crescents



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Roberts ISD et al. Kidney Int 76:546-56, 2009; Roberts ISD. Nat Rev Nephrol 10:445, 2014

The Oxford Classification of IgA nephropathy
(265 patients, Light Microscopy only)

- Other studies have suggested that the Oxford classification does not add predictive value more than serum creatinine at diagnosis. **(Alamartine et al, CJASN 6:2384, 2011)**
- Re IF, C3, IgG and C4d correlate with Scr and outcomes **(Nasri et al. J Nephropath 2:190, 2013; Wada et al: Clin Exp Nephrol 17:73, 2013**

E Endocapillary proliferation: Present (110/) or

Podocyte injury and podocytopenia in the form of FGS occurs in 80% of patients with IgAN and the presence of FGS on biopsy correlates with poor outcome.
Karoui et al Kidney Int 79:643, 2011

T Tubular atrophy/interstitial fibrosis (<25%, 25-50%, >50%) (21%)

Roberts et al, Kidney Int 78, 540, 2009; Cattran et al. Kidney Int 76:534, 2009

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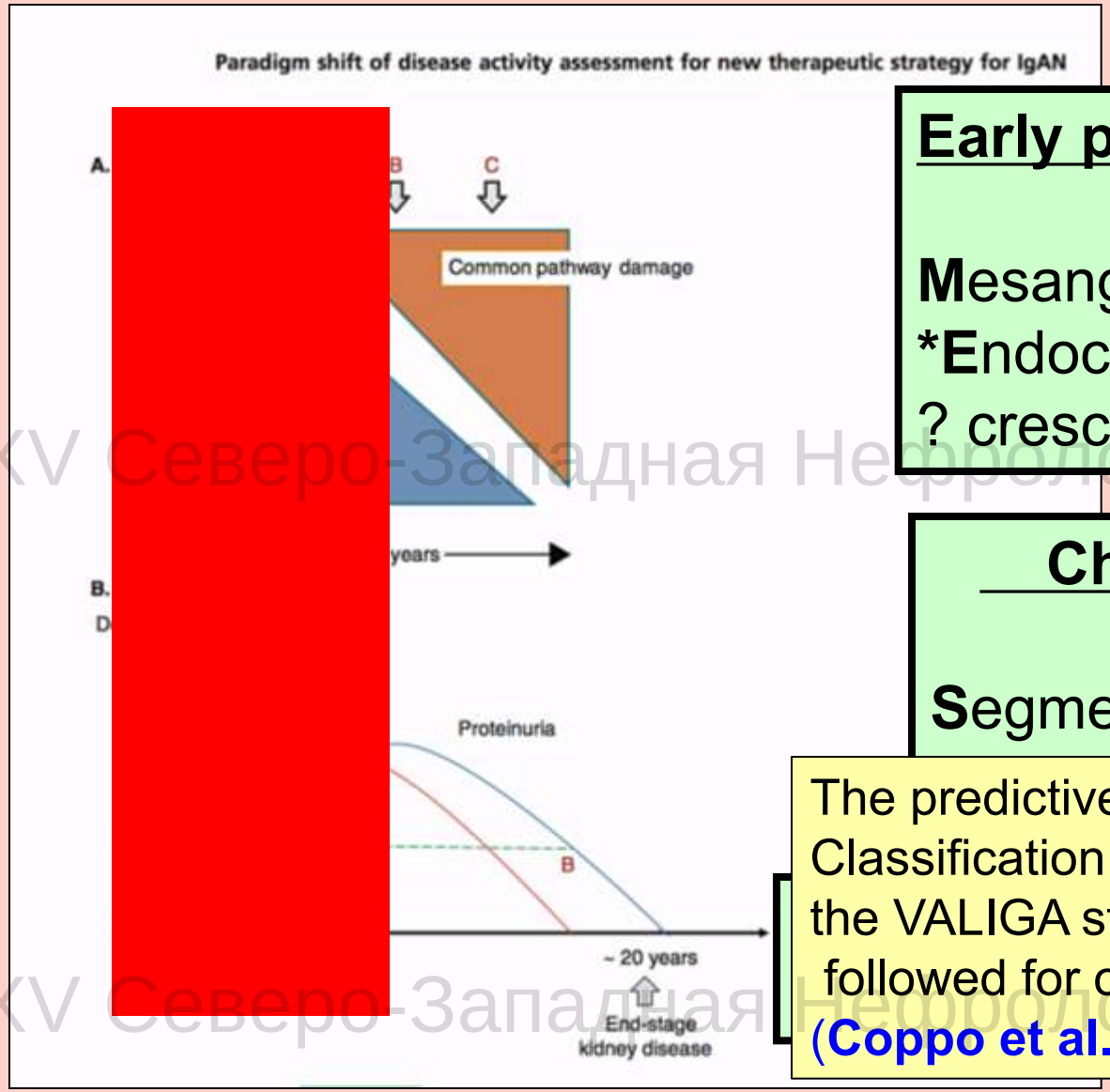
Evolution of IgA nephropathy and the MEST criteria



Early phase

Mesangial hypercellularity
***E**ndocapillary proliferation
? crescents

Chronic phase

Segmental sclerosis

The predictive value of the Oxford Classification has been validated in the VALIGA study of 1147 patients followed for over 4 years.
(Coppo et al. Kidney Int 86:828, 2014)

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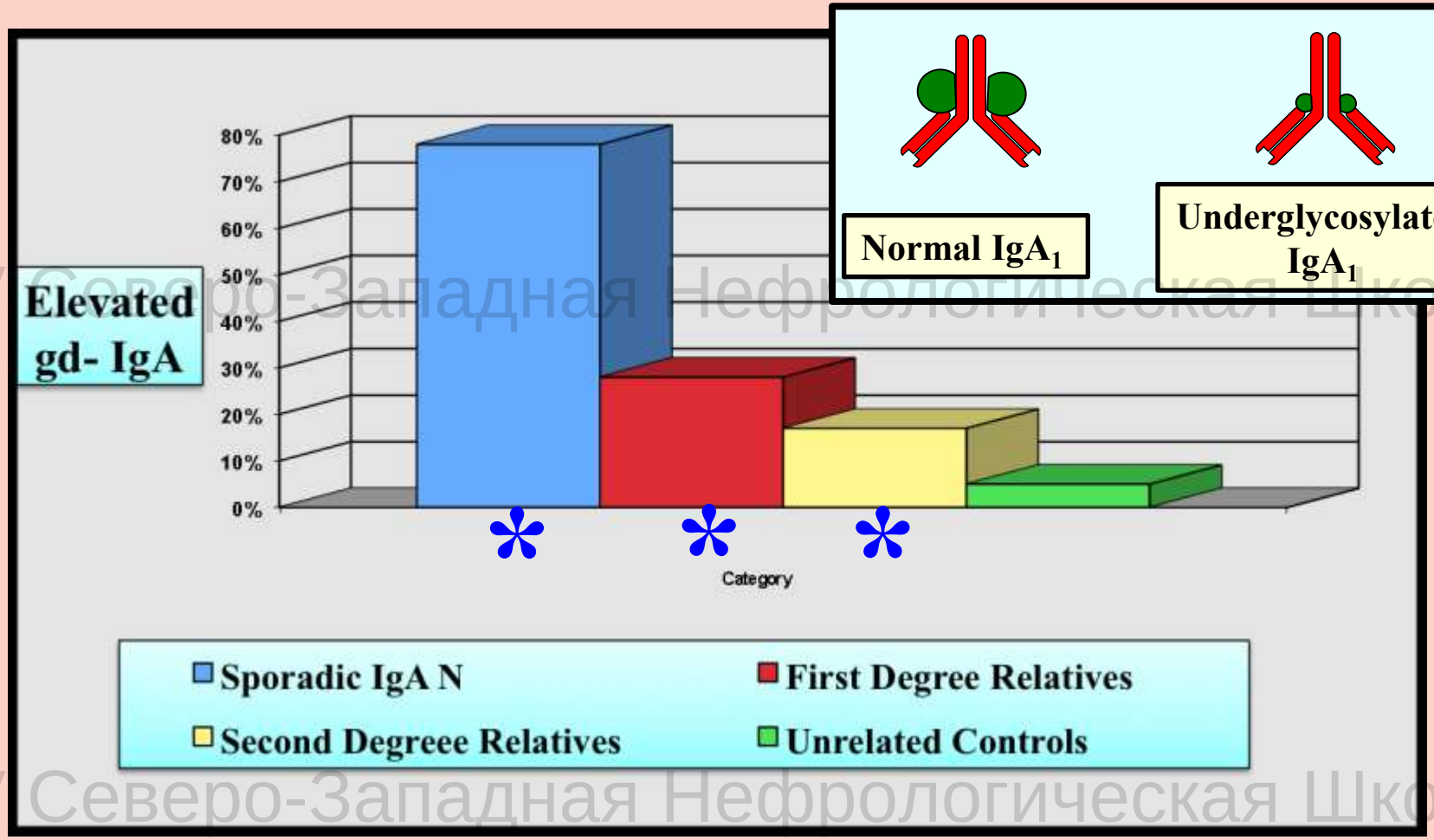
A major genetically determined risk factor is the levels of serum galactose-deficient IgA_1 (The first hit)



Gharavi, et al JASN 19:1008. 2008; Moldoveanu et al KI 71:1148, 2007

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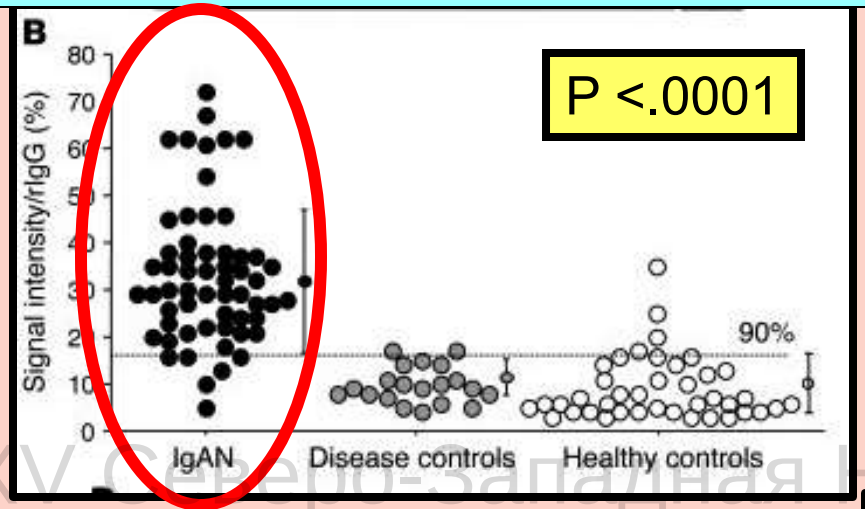
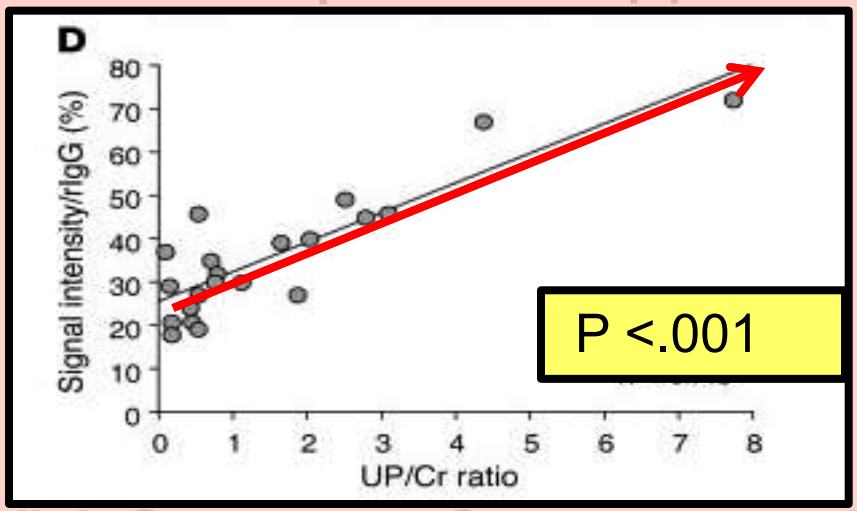
IgG antibodies to gal-deficient IgA_1 are specific for IgA nephropathy and correlate with clinical disease. (The second hit)



IgG anti-glycan antibodies are 88% specific and 95% sensitive for IgA nephropathy compared to healthy and GN controls.



IgG (and IgA) anti-glycan antibodies correlate with U Pr/Cr and predict outcomes

Note: Gal-NAC residues on Gd-IgA1, which anti-glycan antibodies bind to, are also present on several bacterial species (Tn antigens)

From Suzuki et al, J Clin Invest 119:1668, 2009

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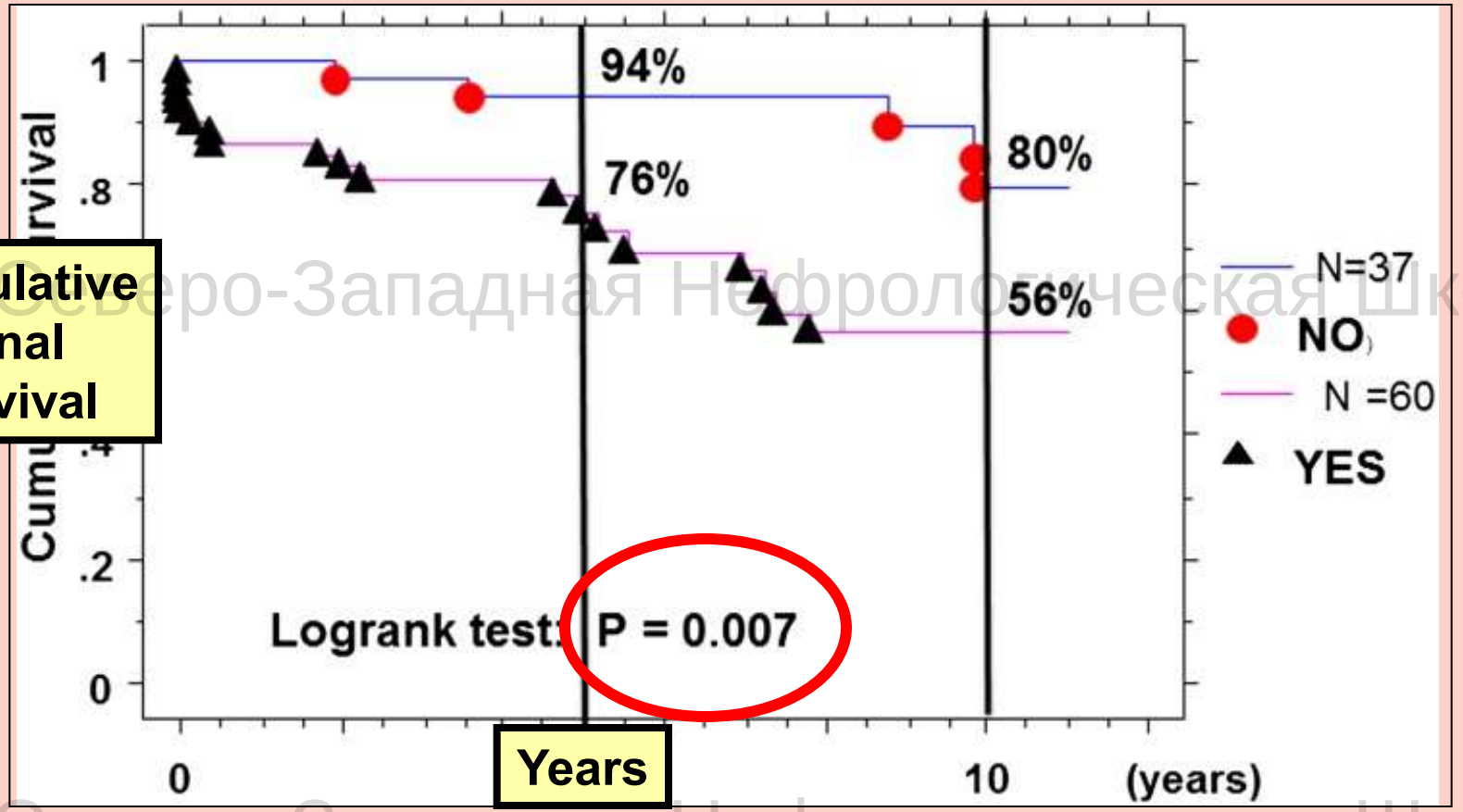
IgG anti-glycan antibodies at diagnosis predict outcomes at 10 years

(Also IgA anti-glycan antibody and total serum levels of gd-IgA1)



Berthoux et al. JASN 23:1579, 2012

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PATHOGENESIS OF IgA NEPHROPATHY
The mesangial response to injury

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Circulation

Under-galactosylated IgA_1 molecules are poorly cleared, self-aggregate, bind to IgG, FN and MBL and activate

C5b-9
(? MBL or AP)

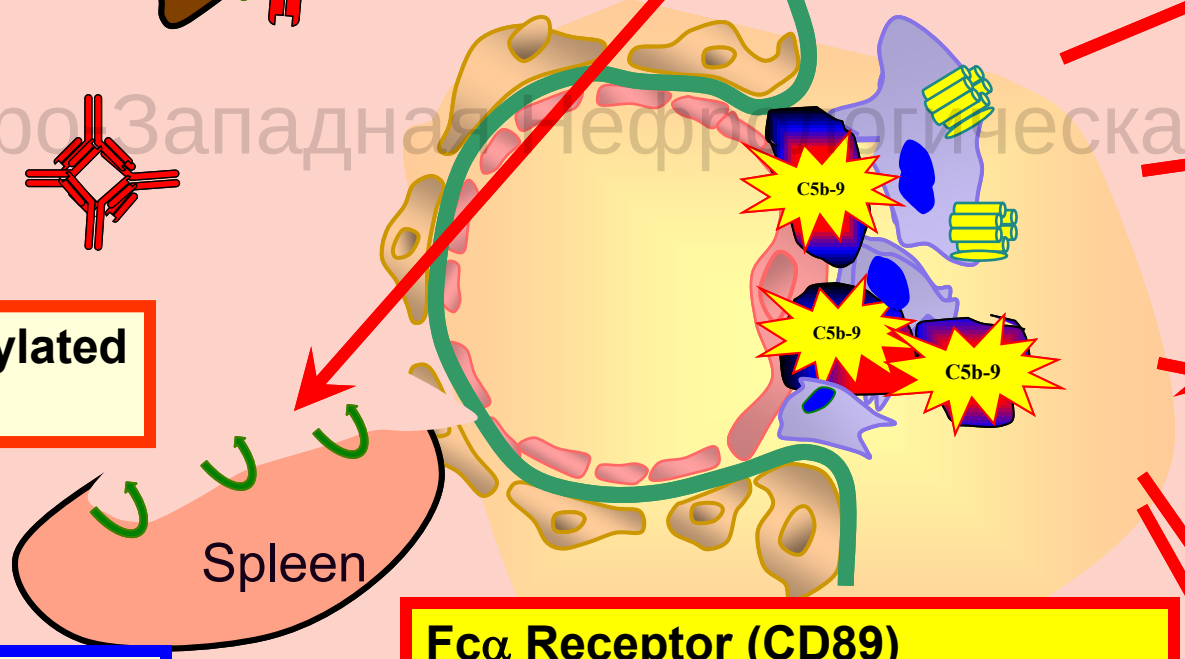
Inflammatory Mediators

- Cytokines (TGFβ, IL1, IL6)
- Growth factors (PDGF)
- Oxidants
- C3
- Proteases
- Matrix

Normal IgA_1

Undergalactosylated IgA_1

IgG or IgA anti-glycan (Anti-Tn antigen) antibodies



Fcα Receptor (CD89)
Transferrin (TF) receptor (CD71)
Toll-like receptors (TLRs)

Cumulative renal survival rate from renal biopsy until ESRD in 1,012 Japanese patients with IgAN.

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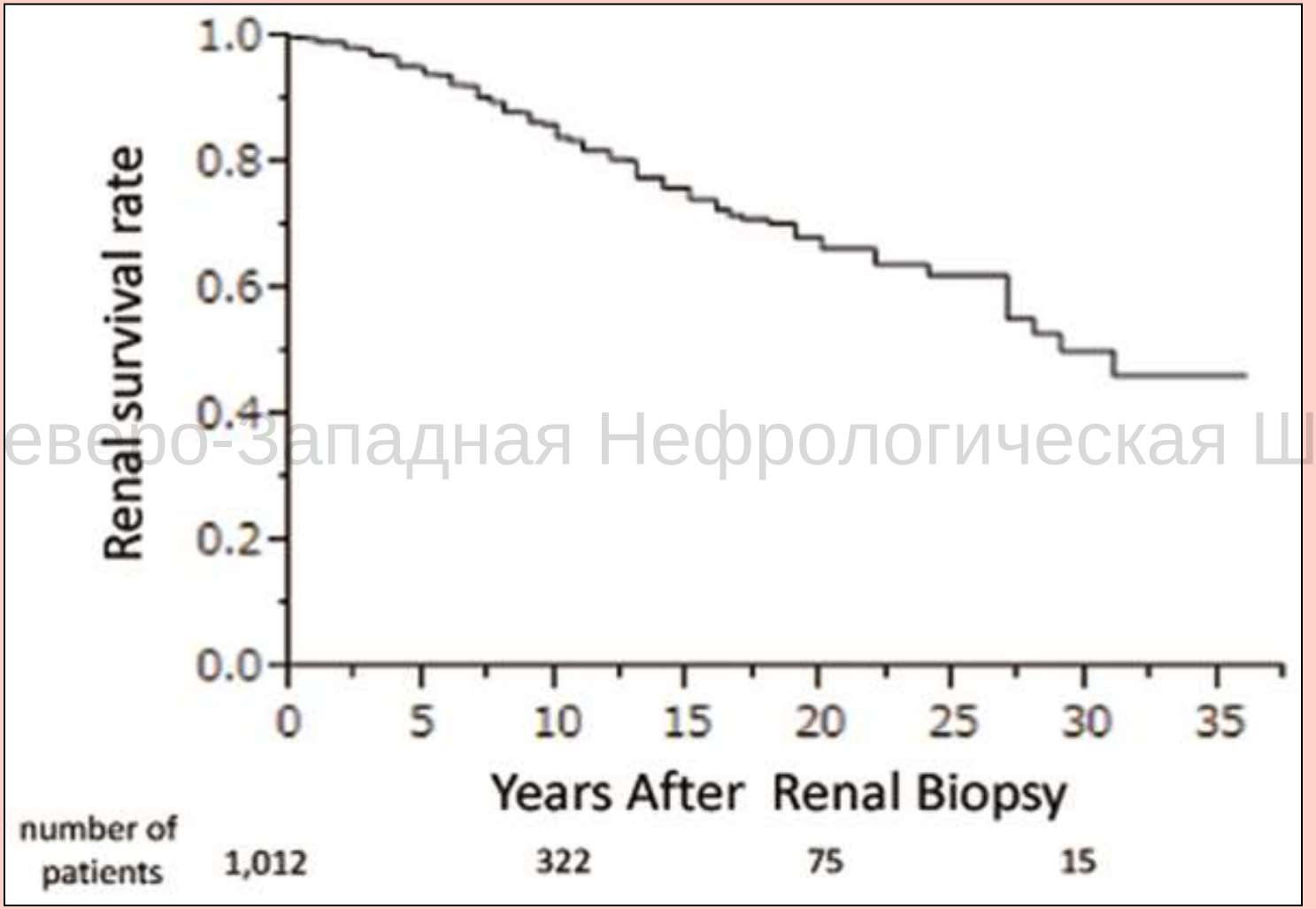

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Moriyama T, Tanaka K, Iwasaki C, Oshima Y, et al. (2014) Prognosis in IgA Nephropathy: 30-Year Analysis of 1,012 Patients at a Single Center in Japan. PLoS ONE 9(3): e91756.

IgA nephropathy: One disease or many?

Recognized atypical clinical variants

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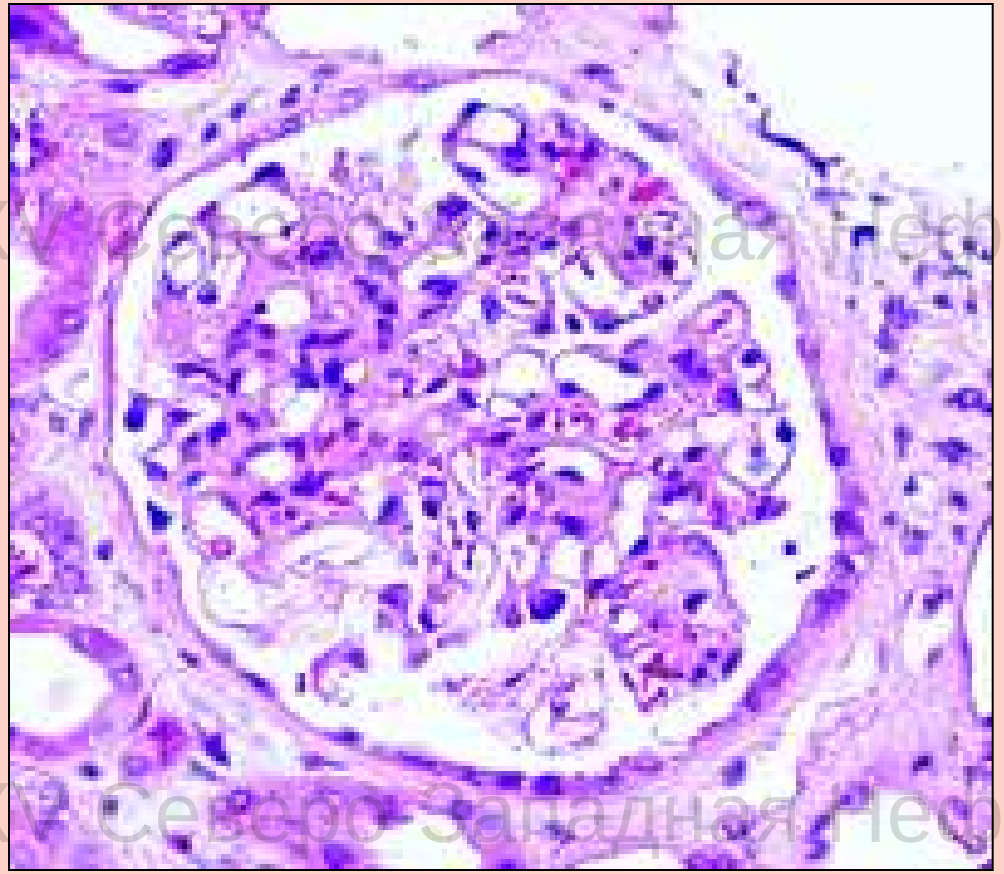
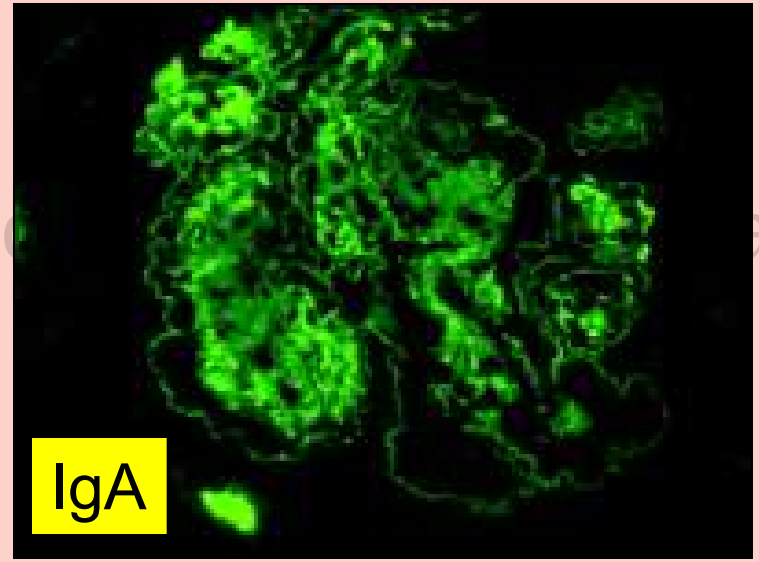
IgA-dominant post-infectious GN

Male, MRSA, diabetic, AKI, low C3





From Haas et al, Human Path 39, 1309, 2008

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IgA- dominant post-infectious GN

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Haas et al, Human Path 39, 1309, 2008;Satoskar et al, CJASN 1:1179, 2006

Outcome predictors in typical IgAN

From Lai KN et al. IgA Nephropathy. Nat Rev. Dis. Primers 2:1-19, 2016

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IgA nephropathy - Treatment

- "Intense supportive care"
- ACE inhibitors/ ARBs
- Fish oil
- Steroids (pulse, oral, local)
- Immunosuppression (CTX, AZA, MMF, CSA, Rituximab)
- Other
  - Low antigen diet
  - IV Ig
  - Rituximab
  - Eculizumab
  - Tonsillectomy

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“Intensive supportive care” in IgAN

- ACEI/ARB titrated to lowest achievable level of protein excretion (all patients).

Note: Use of combination therapy with ACEI followed by ARBs (if goals are not met) is controversial. It is probably better to add sodium restriction, a diuretic, diltiazem or verapamil and/or an aldo blocker before adding an ARB to ACEI therapy because of risks of hyperkalemia, increased Scr or hypotension.

- Fish oil for patients who choose it, but not in place of other therapy

Rauen et al (STOP study) NEJM 373, 23, 2015

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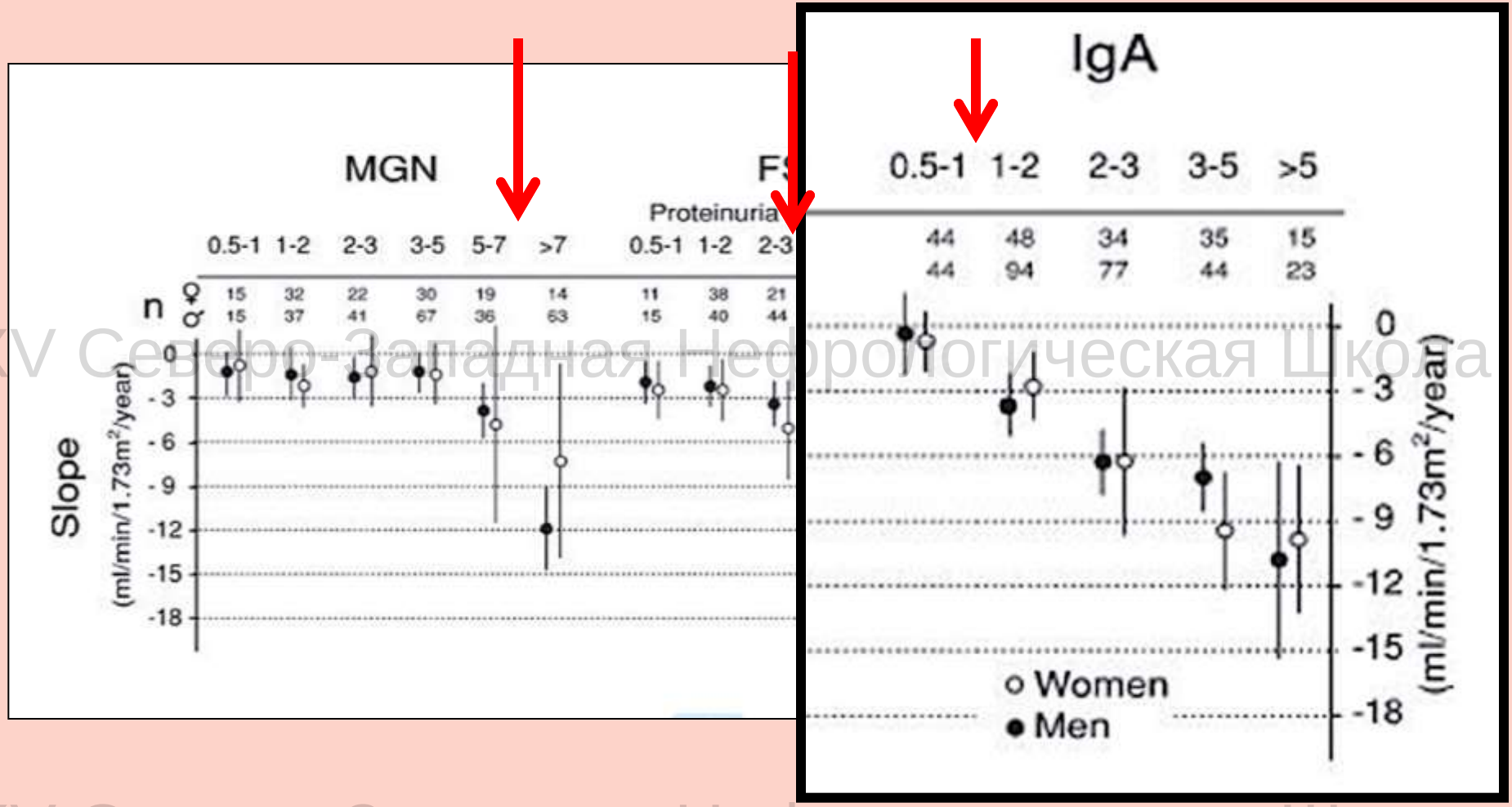
Proteinuria and progression in MN, FGS and IgAN



Modified from Thompson et al. JASN 26:2930, 2015

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ACEI reduce proteinuria and slow progression in IgA

BOTTOM LINE:
ANYONE WITH IgA NEPHROPATHY AND RISK FACTORS FOR PROGRESSION SHOULD BE RECEIVING ACE/ARBs.

U prot	[illegible]	[illegible]	[illegible]
Stable remission in Uprot	**57%**	**9%**	**<.05**
Ccr	**124 ml/min**	**109 ml/min**	**<.05**

Coppo, et al JASN 18: 1880, 2007

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IgA nephropathy - Treatment

Note: In the recent "STOP IgA" study, 70% of patients became ineligible for randomization during 6 mos of supportive care because proteinuria decreased to < 750 mg/day

- Steroids (pulse, oral, local)
- Immunosuppression (CTX, AZA, MMF, CSA, Rituximab)
- Other
  - Low antigen diet
  - IV Ig
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Corticosteroids improve outcomes in IgAN with proteinuria >1 gm/day

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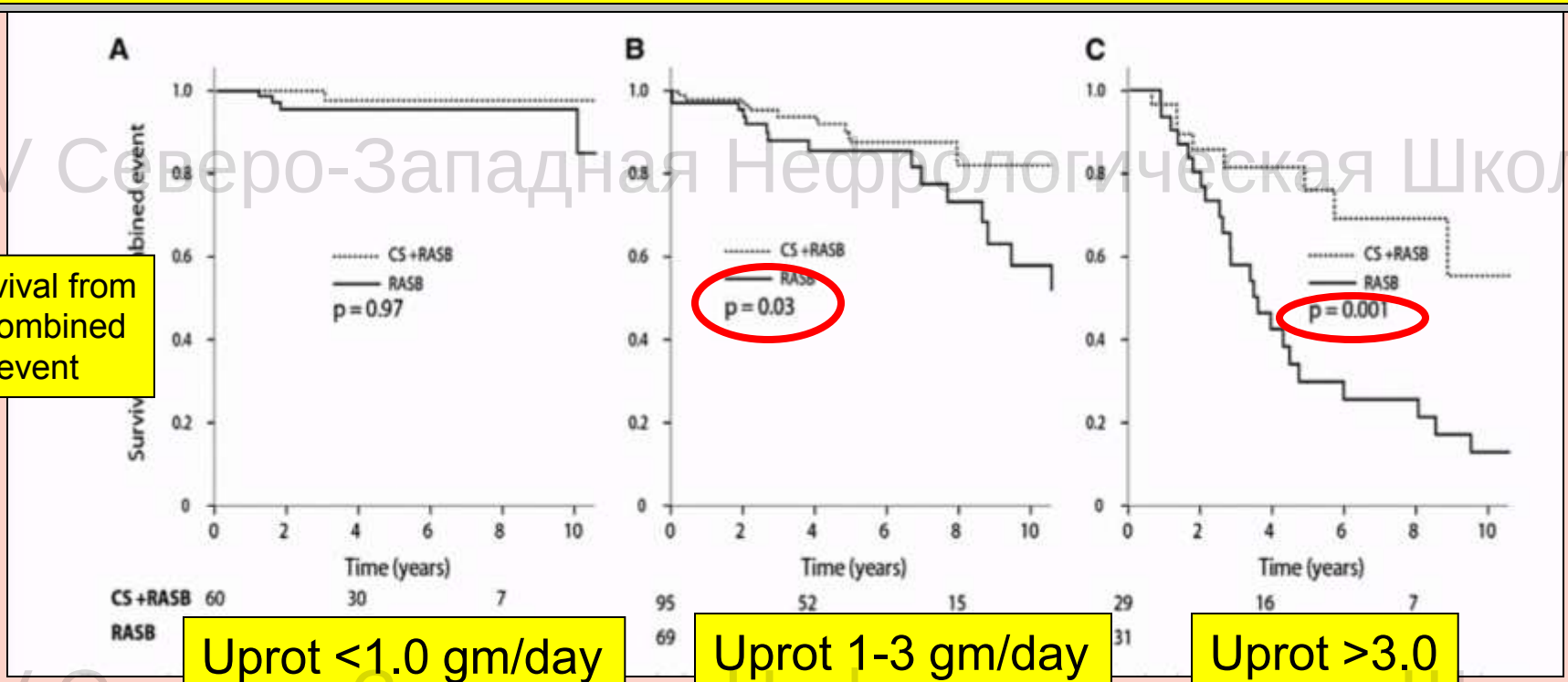
Many previous studies, including the several “Pozzi studies”, failed to include only patients who had failed supportive care and ACEI/ARB therapy first.



Survival from A combined event

Uprot <1.0 gm/day

Uprot 1-3 gm/day

Uprot >3.0

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Tesar et al. JASN 26:2248, 2015

Corticosteroids improve outcomes in IgAN with GFR <50 ml/min

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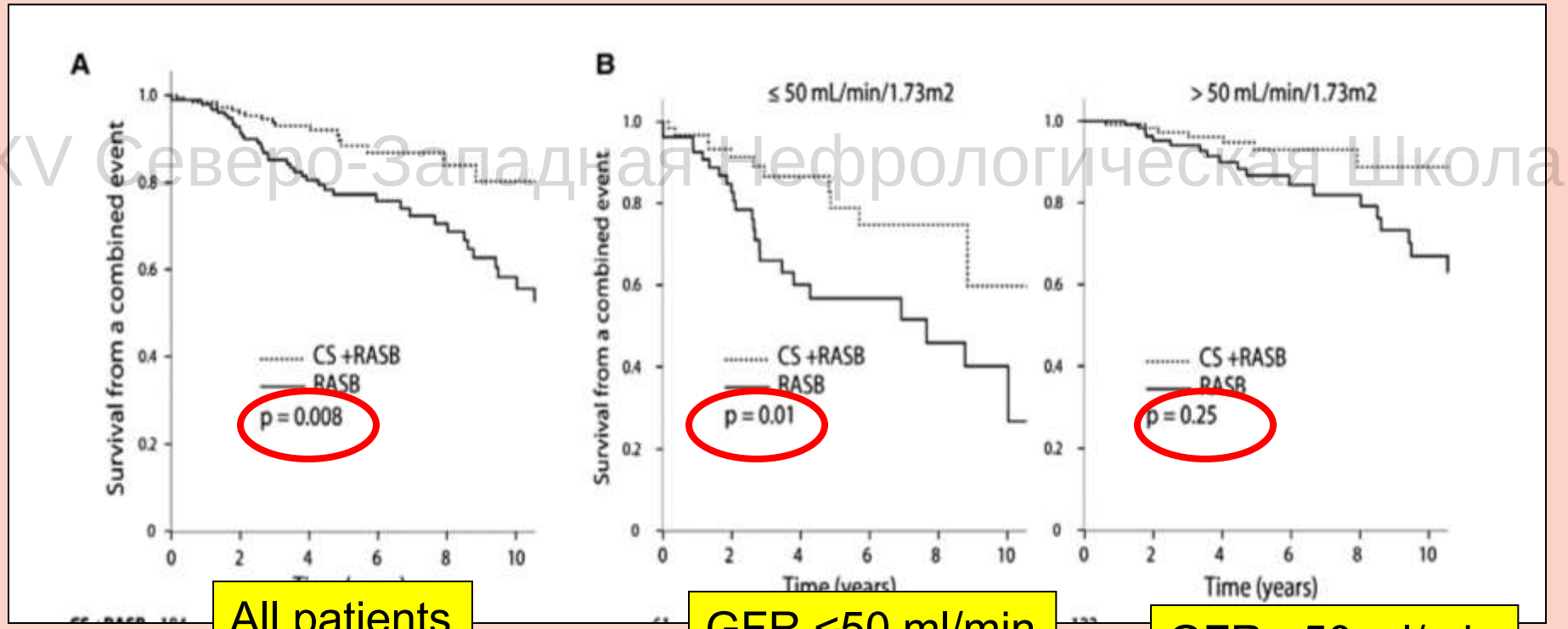
Retrospective analysis of the VALIGA study (1147 pts) comparing 184 patients who received RASB alone vs 184 matched patients who received RASB plus steroids. Mean follow up 4.7 yrs (2.4-7.9)



All patients

GFR <50 ml/min

GFR >50 ml/min

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Tesar et al. JASN 26: 2248, 2015

TREATMENT OF IgA NEPHROPATHY
Literature review: Steroids in IgA, 2004-16

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Bottom line on steroids:

There is reasonable data as of June 2016 to support using steroid therapy for 6 mos in IgA if there is continued proteinuria > 1 gm and/or loss of GFR despite maximal use of ACEI/ARB therapy for 6 mos and achievement of a BP goal of 125/75 mmhg.

Also steroids have been shown not to benefit patients with a GFR <45 (point of no return in IgA)

Canetta et al, CJASN 9:617, 2014

Relatively few patients will meet these criteria.

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Pred/ CTX (3 mos), then Immuran vs placebo
38 patients, Scr 1.5-2.8 mg/dl, ↑15%/ yr, 2 yr F/U

This study, the only RCT of cytotoxic drugs in IgA, looked only at very high risk patients losing 15% or more of GFR/yr, was underpowered and did not use ACEI/ARBS or achieve current BP goals. Smaller studies in milder disease have not shown a benefit of cytoxan in IgA.

5	**72**	**6**	**.05**

Ballardie et al, *JASN* 13:142, 2002

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Supportive care vs immunosuppressive therapy for progressive IgAN: The STOP IgAN study)

(3 year follow up)

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Although using two different immunosuppressive protocols (steroids alone and steroids plus cytotoxic drugs) is confusing, subsequent analysis showed no differences in outcomes between these two groups. (Floege et al. ASN abstract, November 2015)

immunosuppression, there was no effect on renal function (at 3 years), the adverse event rate was high, and the study is interpreted as showing no role for immunosuppression in typical progressive IgAN.

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Rauen et al. NEJM 373: 2225-2236, 2015

Summary: Current indications for steroid therapy in IgAN (June 2016)

Usual steroid regimen for IgAN:

1. **Oral prednisone 0.8-1.0 mg/kg/day for 2 mos, taper by 0.2 mg/kg/month, stop at 6 mos.**

Or

2. **Pulse methylprednisone, 750-1.0 gm iv daily X3 at the beginning of months 1,3 and 5 with 0.5 mg/kg po daily for 6 months (Ponticelli or Pozzi regimen)**

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There are case reports of responses to each of these, but insufficient data to recommend any of them.

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Treatment of IgA nephropathy

KDIGO CPG for GN (Kidney Int Suppl 2: June 2012)
(revised 5-23-14)

Tesar et al. VALIGA study suggests steroids are also beneficial in patients with GFRs of 30-50

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Trials and emerging therapies in IgAN
June 2016

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- China (TESTING)(Oral steroids vs placebo (13,000 pts!)
- China (MMF vs steroids)
- China (Pred/cytoxan vs pred alone)
- Asia (Blisibmod – BAFF antagonist)
- US. Rituximab in IgAN
- NEFIGAN study (Budesonide (non-absorbed GI steroid) vs placebo
- Fostamatinib (siRNA blocks serine tyrosine kinase pathway in B cell receptor)
- Bortezomib (Proteosome inhibitor)
- Atacicept (April/BAFF inhibitor) vs placebo
- ACTH trial

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Yeo et al. Nephrology 20:767, 2015, Lai, Nat. Rev. Dis. Primers 2:1, 2016

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Thank you!

спасибо

spasibo

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