Personalized monitoring and treatment in primary membranous nephropathy in the era of PLA2R antibodies

Jack F. Wetzels

Webinar 27 nov 2018

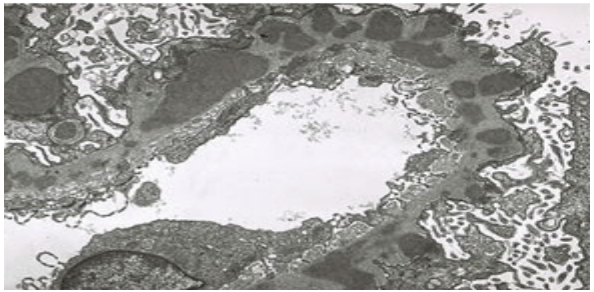
ERKNet

The European Rare Kidney Disease Reference Network

Membranous nephropathy:

most common cause of nephrotic syndrome

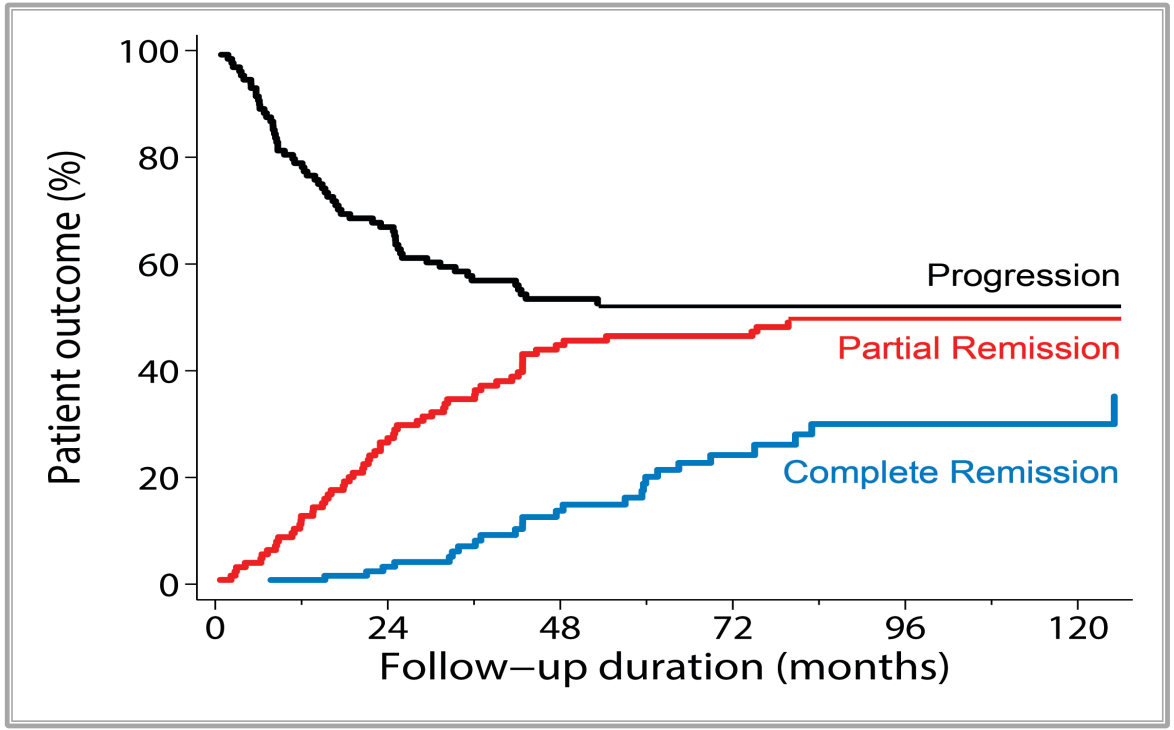
incidence 10/million/yr



primary MN: no underlying cause

secondary MN: cancer, systemic diseases, drugs

pMN: the natural history remains unchanged



Rule of thirds?

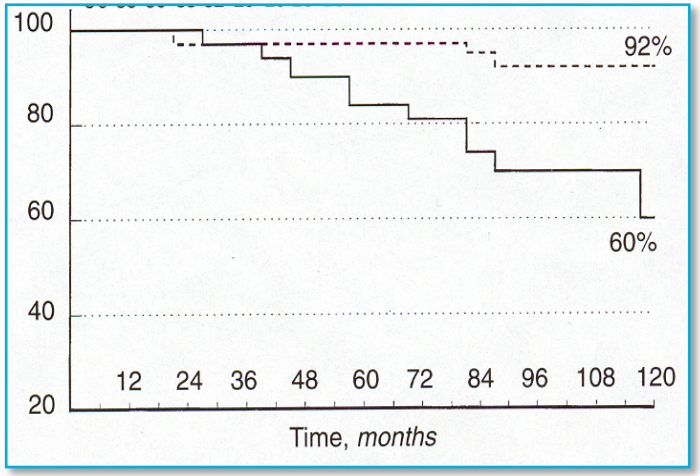
→ Rule of halves

~50% progression to ESRD

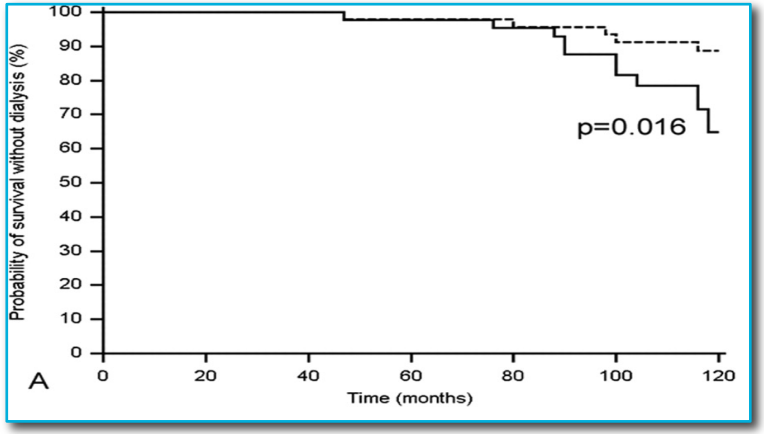
~40-50% spontaneous remission

vd Brand et al. CJASN 2012

Treatment of membranous Nephropathy (old)



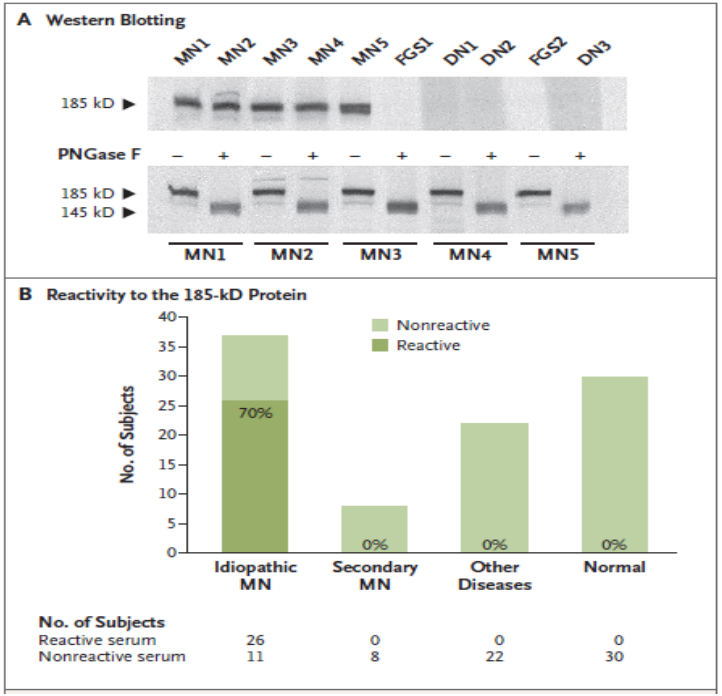
Ponticelli et al. Kidney Int 1995



Vivekanand Jha et al. JASN 2007;18:1899-1904

Alkylating agents: the only drugs proven effective in RCT's to prevent ESRD

2009: discovery of PLA_2R-antibodies



Beck et al. NEJM 2009

- 80% of patients with MN have PLA2R related disease

(PLA2R = phospholipase A2 receptor)

The Standard of Care (KDIGO)

Nephrotic syndrome

Diagnosis:
kidney biopsy

High risk definition
Proteinuria > 4 g/day ,
after 6 months

Treatment:
Alkylating agents/CNI

Outcome

Individualized patient care

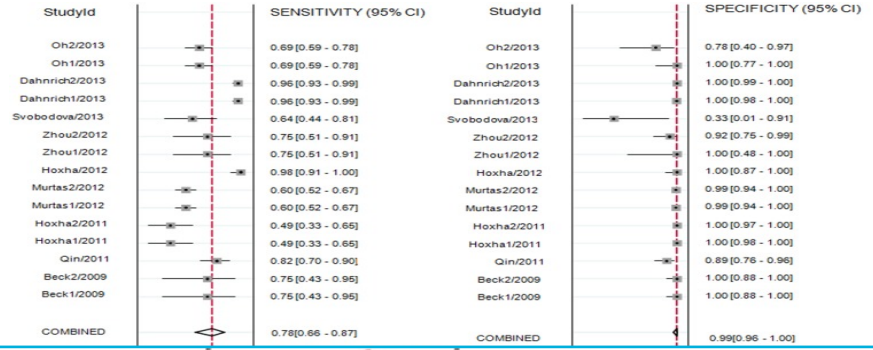
Diagnosis: the cause of MN is known (in > 80%)
Do we need a kidney biopsy?

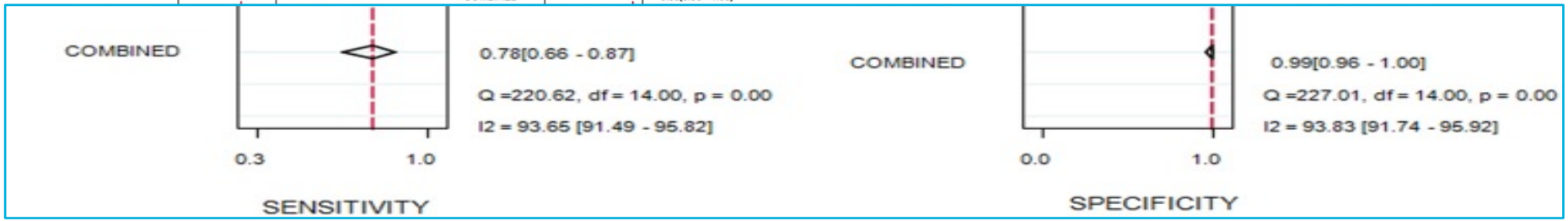
Prognosis: the KDIGO criteria are insufficient
Are there better predictors of progression?

Outcome: also thrombosis:
Who needs anticoagulant therapy? What therapy?

Treatment:
Guidance for personalized therapy? Rituximab?

Diagnosis: Do we need a kidney biopsy?

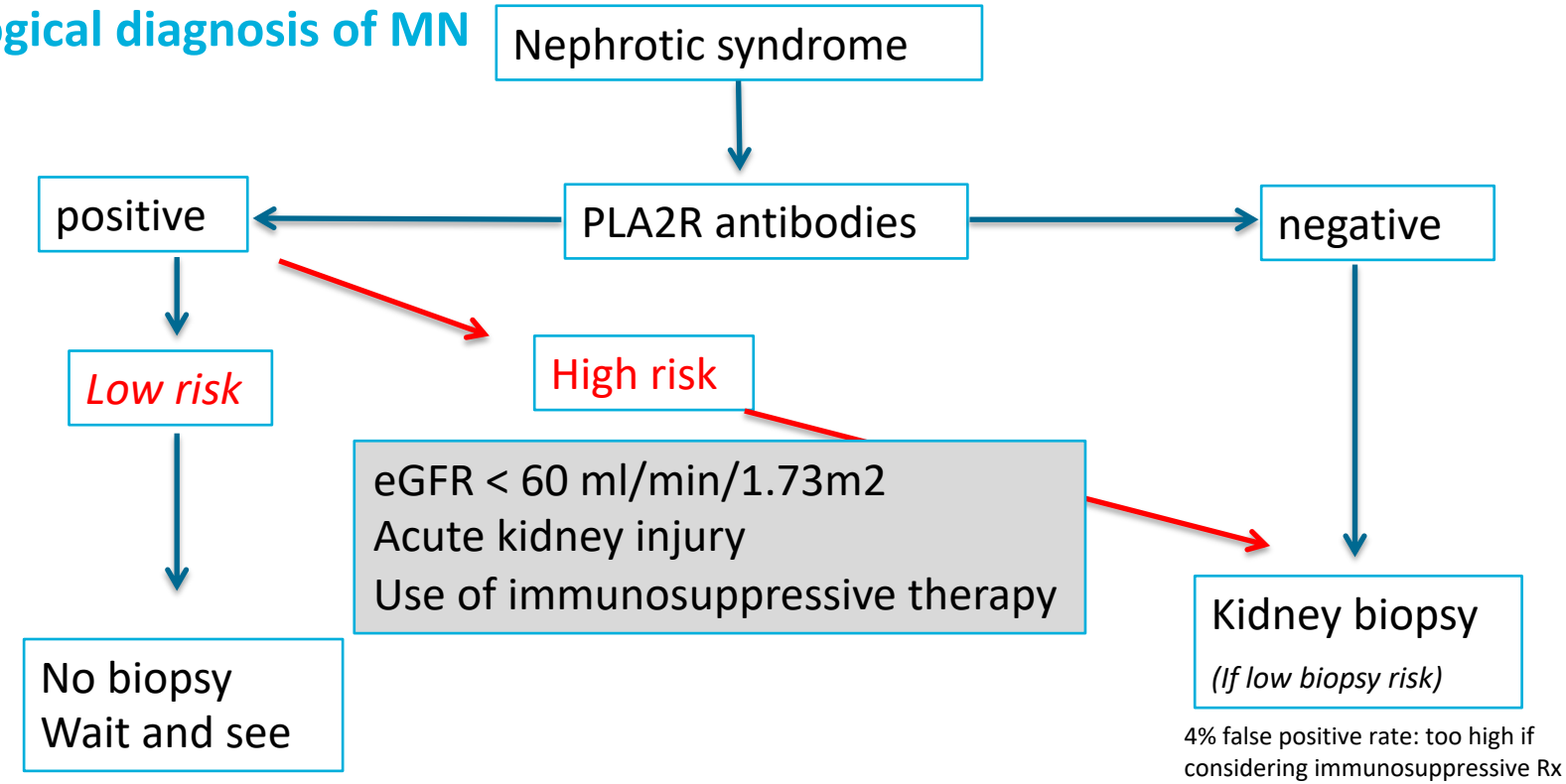




PLA2R antibody assay is accurate for diagnosing MN

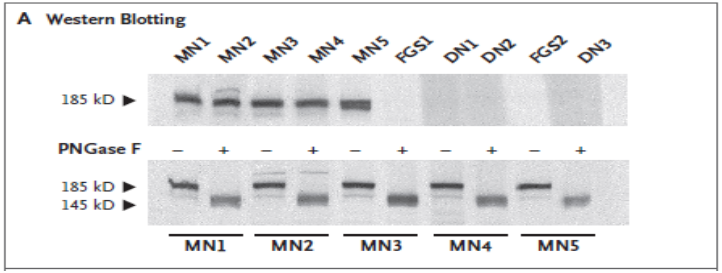
Du et al PlosOne 2014 Sensitivity 0.78 Specificity 0.99 (at least 0.96)

Serological diagnosis of MN



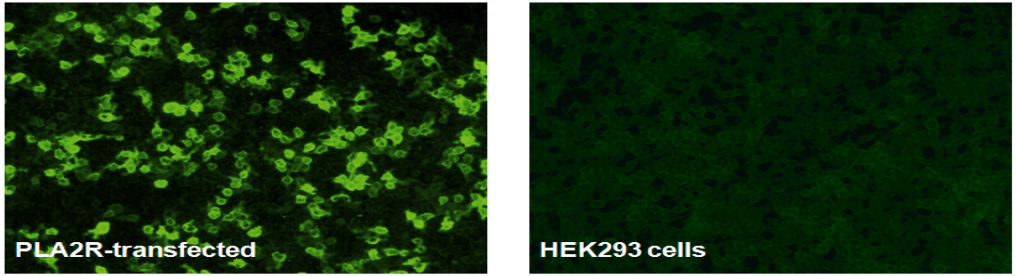
Take care: differences between PLA2Rab assays

Western Blot



Beck et al. NEJM 2009

Immunofluorescence (IIFT)



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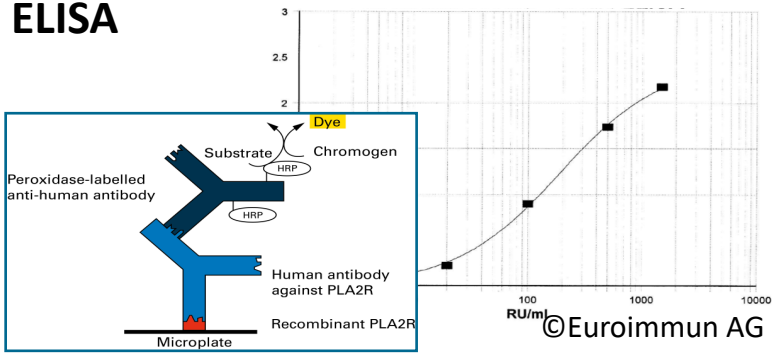
ELISA



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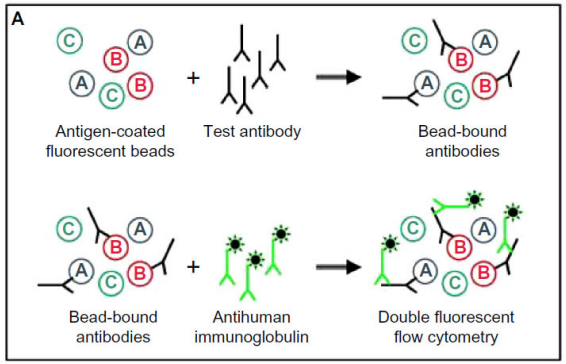
ALBIA



Behnert et al 2014

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ELISA: least sensitive!

	IFT +	IFT -
ELISA +	82	2
ELISA -	5	28
Agreement 94%		

Hofstra et al 2012

	IFT +	IFT -
ELISA +	250	0
ELISA -	9	86
Agreement 97%		

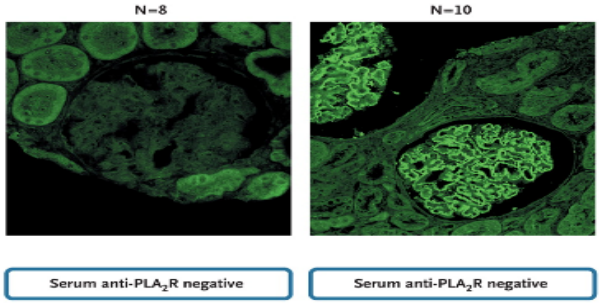
Hoxha et al 2016

	WB+	WB -
IFT+	133	
IFT-	20	Estimated n =50
Agreement 90%?		

Hoxha et al 2016

Use of ELISA → less likely to diagnose PLA2R associated MN!

Serum antibodies may be initially absent



	PLA-R Bx +	Bx-
Serum +	21	3
Serum -	10	8

Debiec et al. NEJM 2011

Case-description:

- A 47-year-old patient diagnosed with iMN in 2005. PLA2R staining in the initial biopsy appeared positive. Treatment (CP)resulted in a complete remission (2006). In June 2013 he developed a relapse.

Date	IIFT	Cr (mg/dl)	Albumin (g/dl)	PCR (g/g)
28-12-2004	ND	0.90	2.2	25.3
07-02-2005	ND	1.05	1.8	14.7
04-05-2005	ND	1.10	2.4	3.80
05-10-2005	ND	1.00	3.7	0.44
14-02-2006	ND	0.81	3.9	0
05-06-2013	inconclusive	0.92	2.4	2.40
25-09-2013	negative	0.96	2.4	5.82
09-10-2013	inconclusive	0.90	2.3	4.41
20-11-2013	positive 1+	1.00	2.1	4.84
19-02-2014	positive 2+	0.95	1.8	4.04
19-03-2014	positive 3+	0.94	2.2	7.28

vdLogt et al. kidney int 2015

Prognosis: are there better predictors of progression?

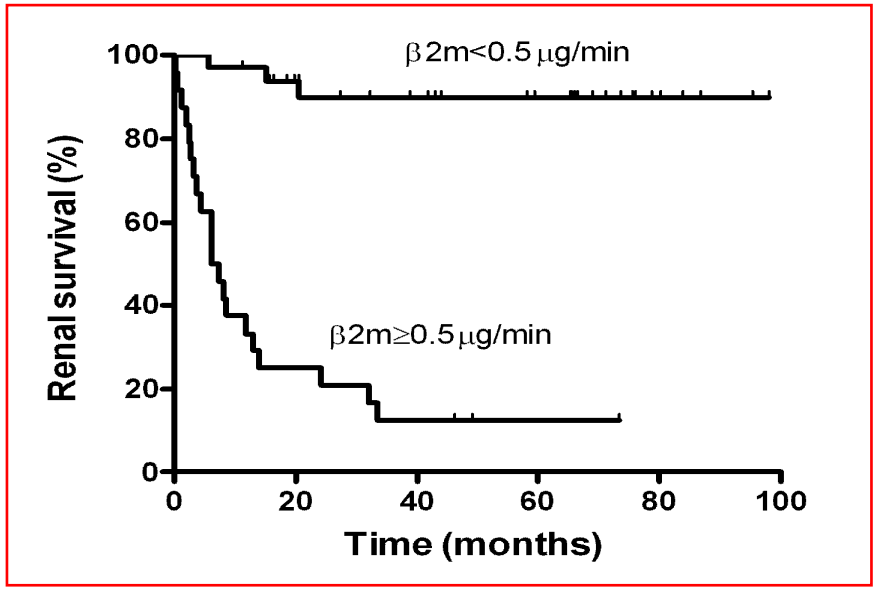
Remissions	6 months	17 months	23 months
placebo	21%	34%	45%

Accuracy of KDIGO recommendations: < 60%!

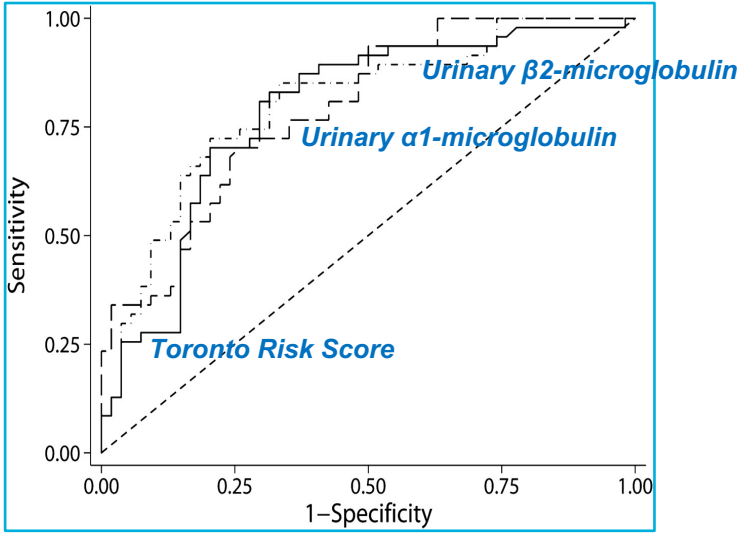
GEMRITUX RCT: Rituximab vs placebo

Dahan et al JASN 2017; Alexandra Rousseau (pc); Seitz-Polski 2017

Prognosis: risk prediction I



Branten et al 2005



van den Brand J A et al. CJASN
doi:10.2215/CJN.00670112

Accuracy of “old” predictors ~ 75%

Risk score: UPCR + Ccr + ΔCcr

Prognosis: risk prediction II

Measurement		Outcome	
Baseline	Repeated	Progression	No progression
uβ2m ≥ 1.0 µg/min	uβ2m ≥ 1.0 µg/min	11	0
uβ2m ≥ 1.0 µg/min	uβ2m < 1.0 µg/min	3	1
uβ2m < 1.0 µg/min	uβ2m ≥ 1.0 µg/min	10	2
uβ2m < 1.0 µg/min	uβ2m < 1.0 µg/min	0	17

Accuracy of “old” predictors with repeated measurement after 6-12 months ~ 90%

NEEDS VALIDATION!

van den Brand J A et al. CJASN
doi:10.2215/CJN.00670112

Prognosis: PLA2Rab in risk prediction

Outcome	low (n=26)	medium (n= 26)	high (n=27)	p-value
Part.remission	11	8	11	ns
Compl.remission	7	9	8	ns
Renal failure	1	3	5	ns
Spont. remission	10	8	1	<0.01

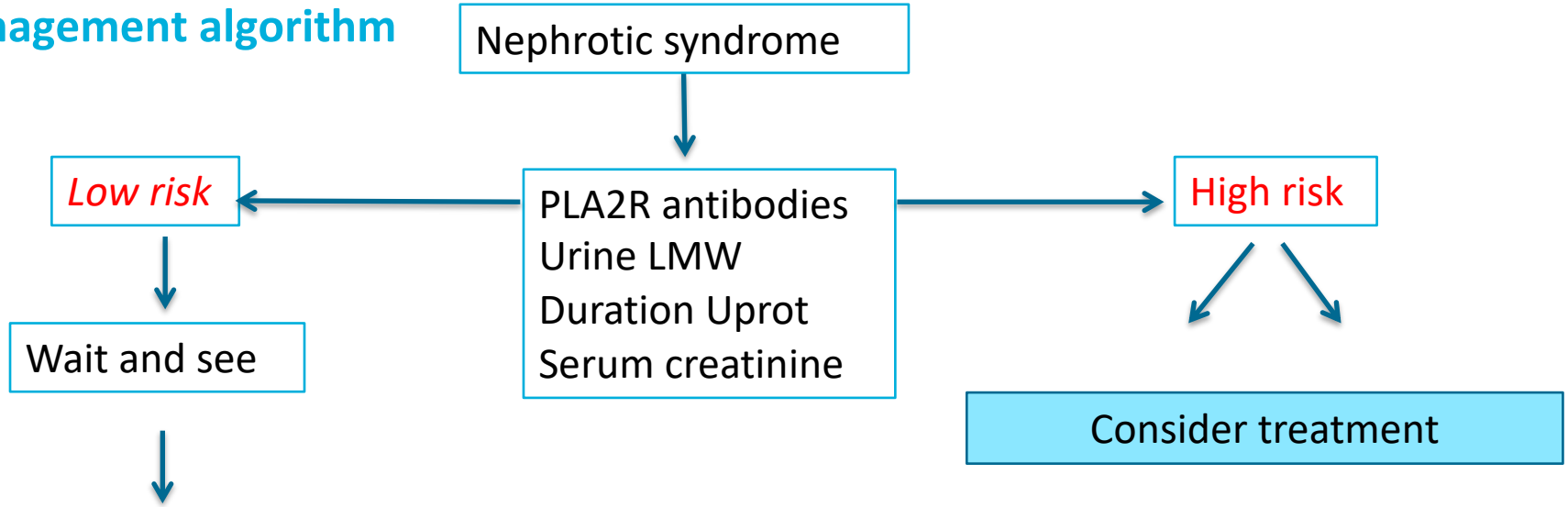
Hofstra, JASN 2012
" in house" ELISA- cut off for EUROIMMUN ELISA unknown

GEMRITUX data; EUROIMMUN Elisa
Alexandra Rousseau 2017

Specificity and sensitivity < 80%

Remissions	6 months	17 months
PLA2R < 275	30%	43%
PLA2R > 275	7%	20%

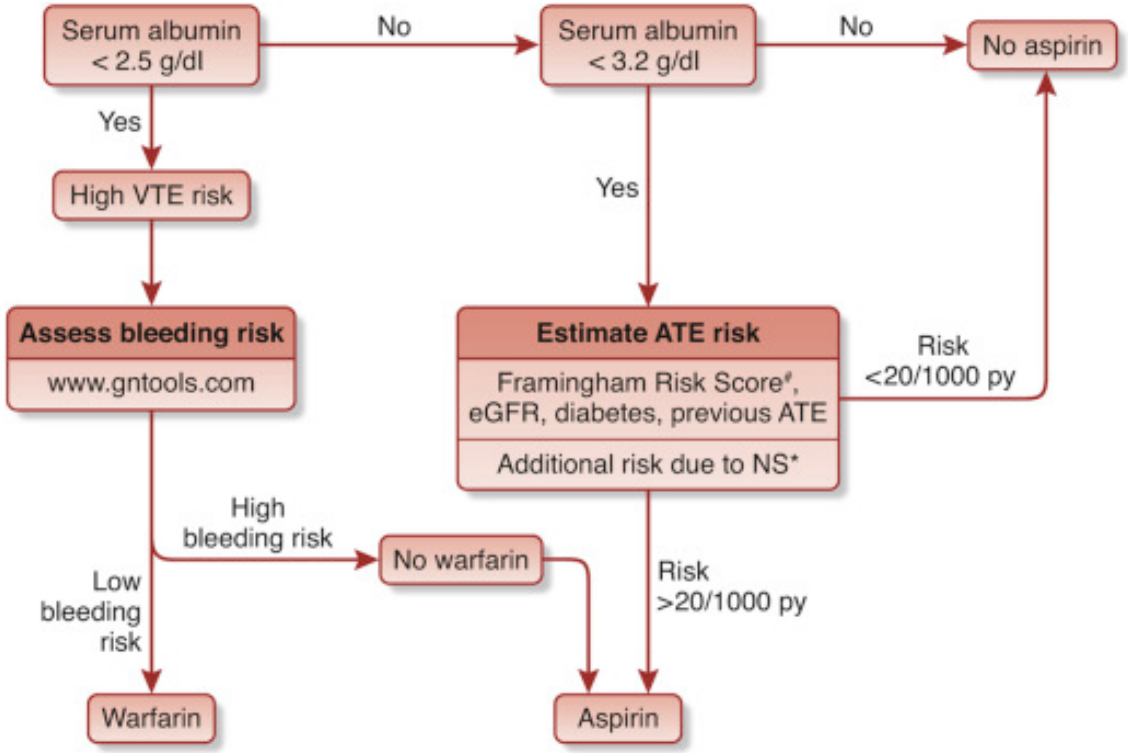
Management algorithm



Risk?

Arterial and venous trombo-embolic events!

Don't Forget: anticoagulant therapy



Rationale:

Patients with MN are at great risk of venous and arterial thrombosis

Risk: MN>FSGS>IgA

Risk: related to Serum albumin levels

Julia M. Hofstra, Jack F.M. Wetzels

Kidney International, Volume 89, Issue 5, 2016, 981–983

Anticoagulant therapy in pMN

- May consider LMW (prophylactic dose) + acetylsalicylic acid
- No evidence for efficacy of DOAC → do not use!
- Be aware of lack of standardisation of serum albumin assay
  - ❑ Immunonephelometric
  - ❑ Brome cresol purple(BCP)
  - ❑ Brome cresol green (BCG)

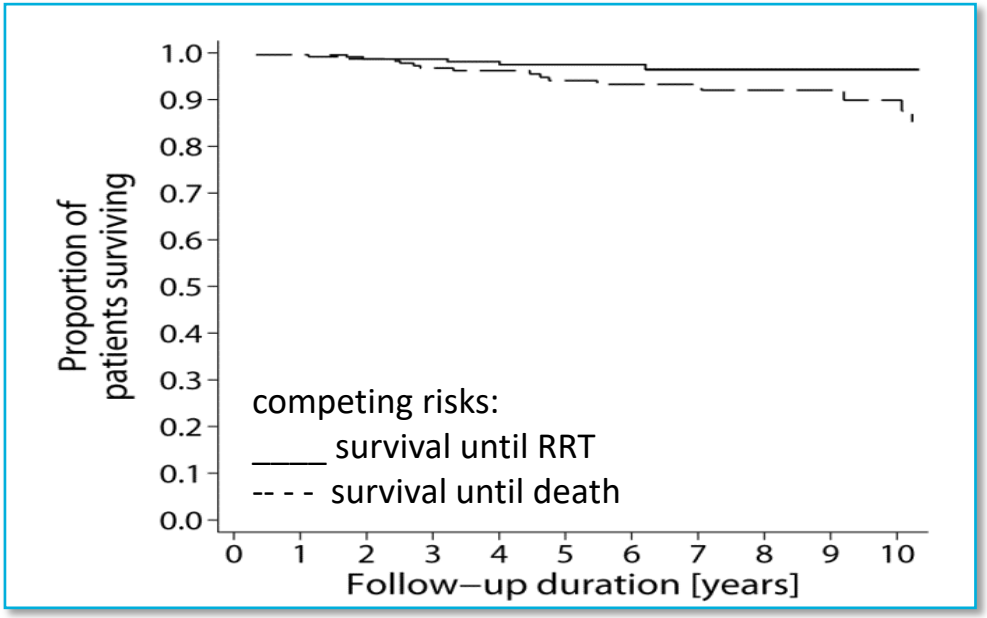
BCP = immunonephelometric albumin
BCG: overestimates by + 5g/L

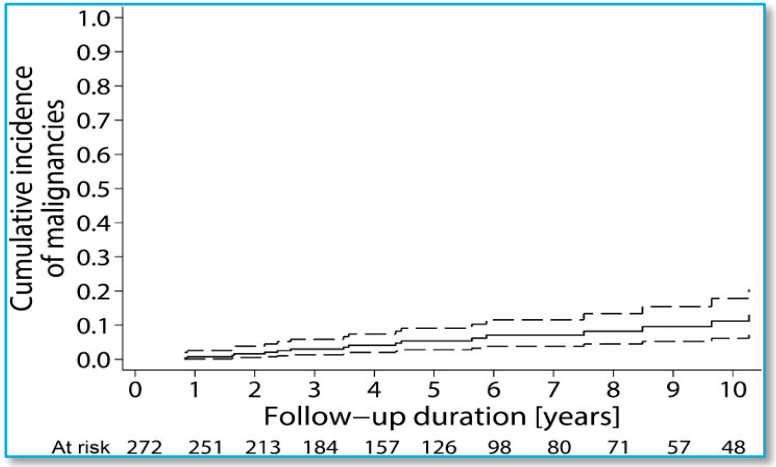
Cut-off: 20 g/L with BCP = 25 g/L with BCG

Treatment of patients with pMN

- Alkylating agents are effective, proven in RCT's and with renal end-points
- Side effects!
- Can we restrict treatment to high risk-patients?
- Can we use alternative agents?

Treatment can be restricted to high-risk patients





Van den Brand, JASN 2014; CJASN 2014

Cohort (n=254) : 49% immunosuppressive therapy, 51% supportive treatment
10-years dialysis free survival 86%; threefold higher risk of malignancies

Treatment of patients with pMN: alternative agents

- Calcineurin inhibitors: induce remission, high relapse rate! Relapses are associated with risk of ESRD. Need more data!

MENTOR study: comparison Rituximab vs CsA
STARMEN trial: comparison cyclophosphamide vs tacrolimus+Rituximab

- Rituximab? → cohort study showed high remission rate

Rituximab GEMRITUX: first RCT → more remissions!

	NIAT-RTX n=37	NIAT n=38	P value
Remission (6 mo)	13 (35 %)	8 (21 %)	0.21
Remission at end of follow-up (17 mo)	24 (65 %)	13 (34 %)	<0.01
Remission at end of follow-up (23 mo)*	19/29 (66%)	13/29 (45%)	

NIAT = non-immunosuppressive antiproteinuric therapy;
RTX = Rituximab 2 * 375mg/m^2
* PLA2R positive patients only

Dahan et al, JASN 2017; Seitz-Polski 2017

Membranous Nephropathy: lessons from RTX studies

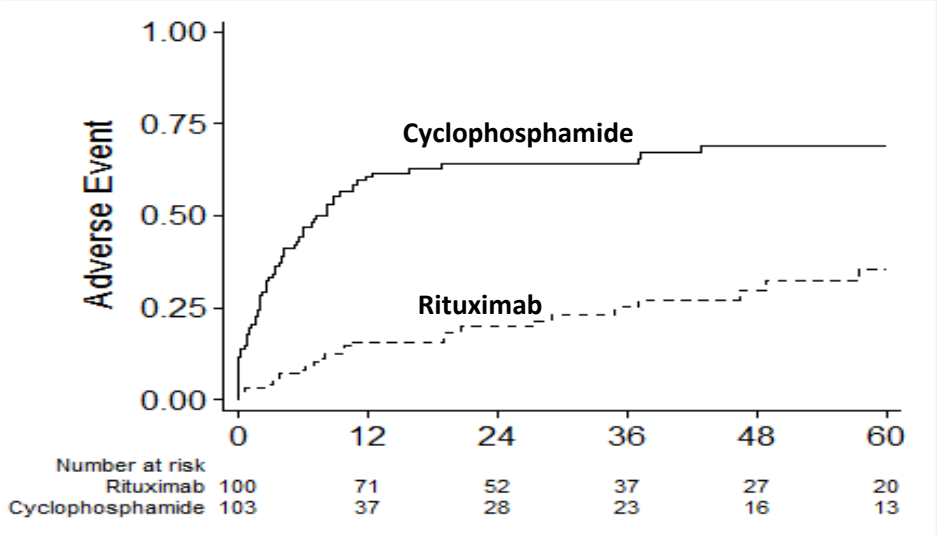
Rituximab: many non-responders (with current dose)

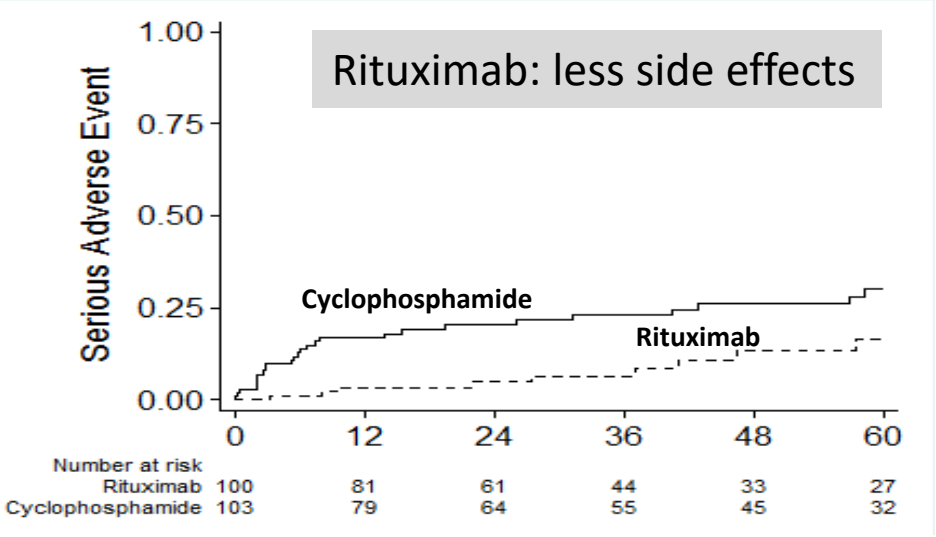
Bergamo cohort: n =100; **non - response 35%**

GEMRITUX cohort: n = 38; **non - response 34%**

MENTOR cohort: n = 64; **primary non-response 22% (no-remission 41%)**

Cyclophosphamide vs Rituximab: adverse events

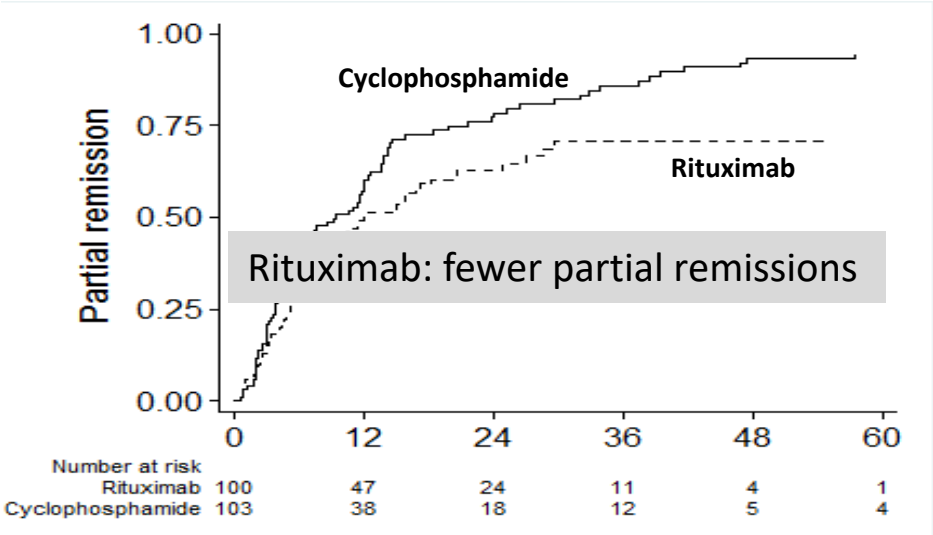


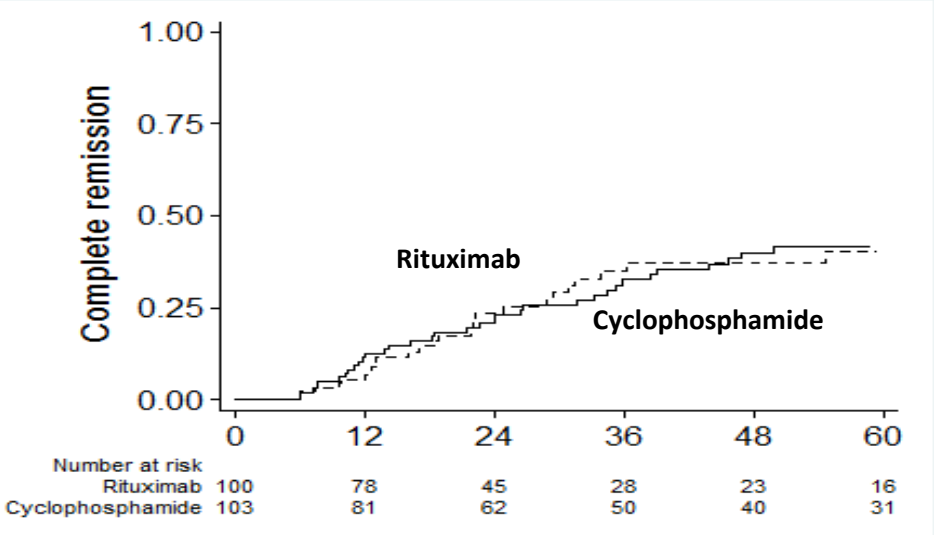


- HR_{adj} = 0.27 (0.16 – 0.44)
- HR_{adj} = 0.32 (0.15 – 0.68)

Van den Brand, JASN 2017

Cyclophosphamide vs Rituximab: difference in partial remission rate

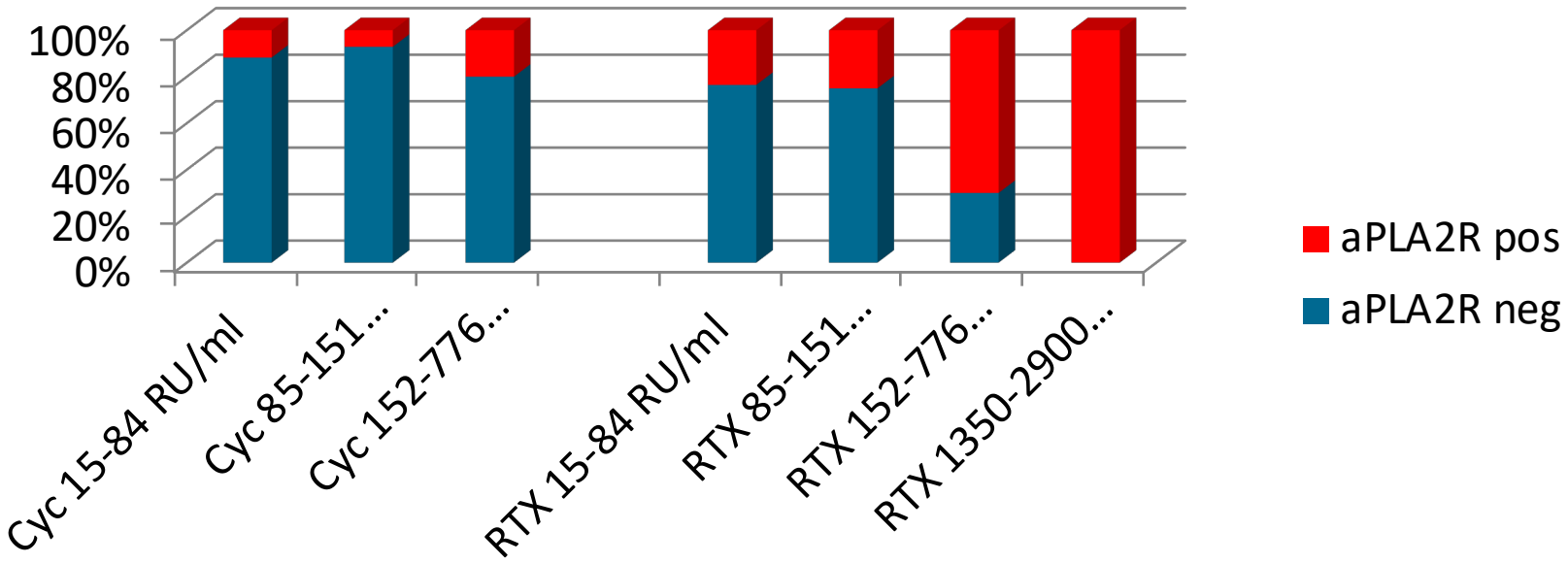




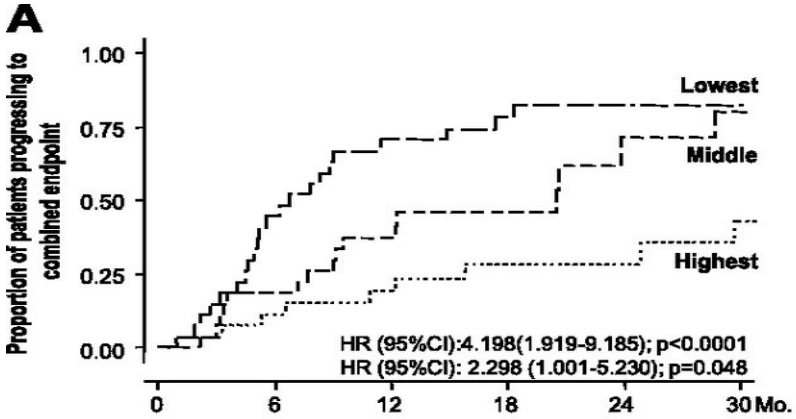
- HR_{adj} = 0.63 (0.45 – 0.89)
- HR_{adj} = 0.88 (0.50 – 1.54)

Van den Brand, JASN 2017

Results: disappearance of aPLA2R after 6 months

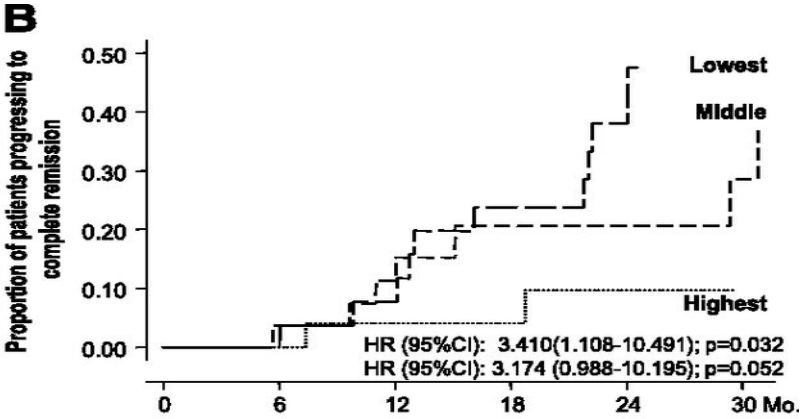


Rituximab is not effective in patients with high PLA2Rab titers



Patients at risk according to Tertile

Lowest	27	15	8	6	4	3
Middle	27	22	16	8	3	2
Highest	27	22	20	14	11	6



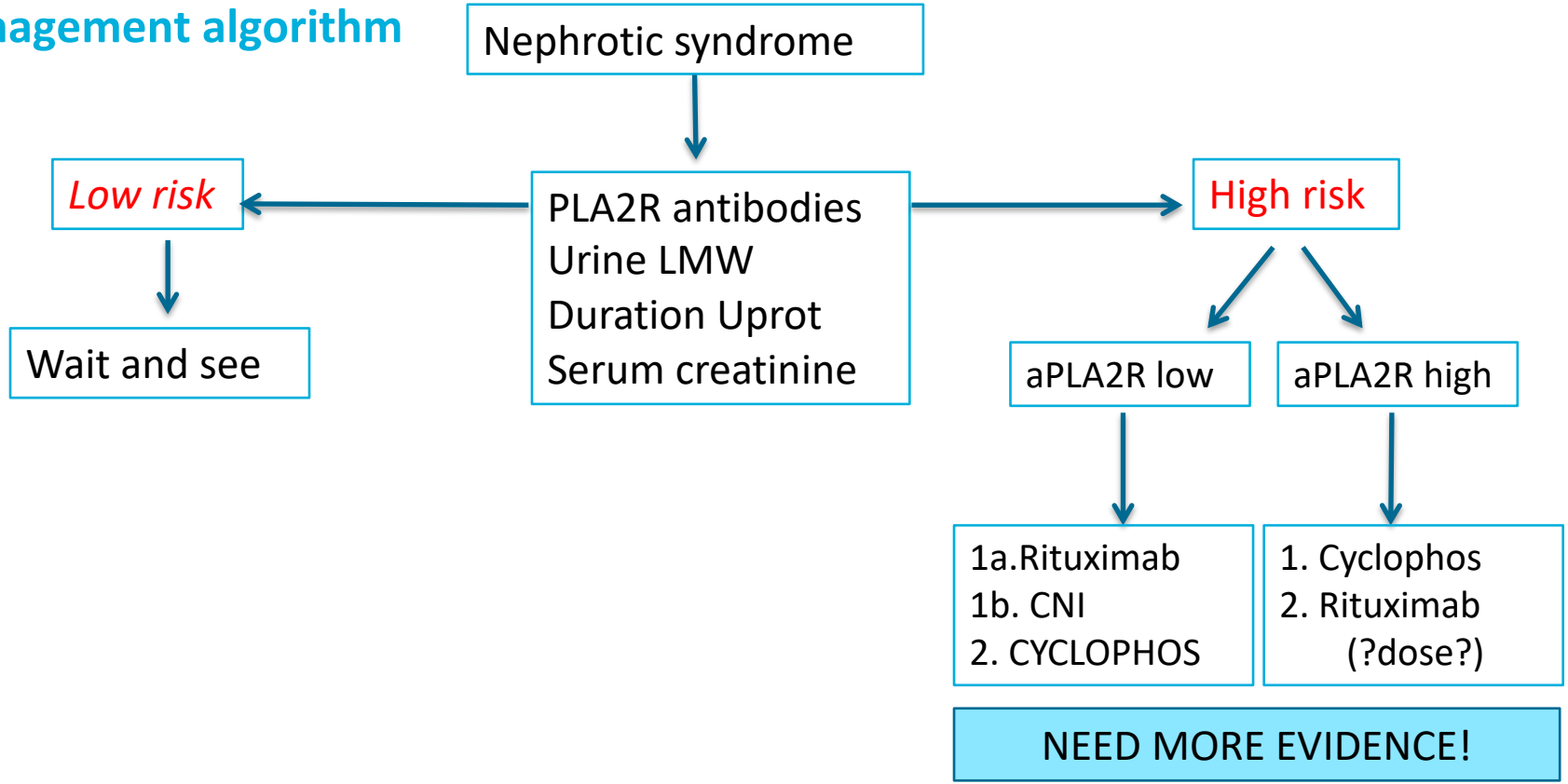
Patients at risk according to Tertile

Lowest	27	27	23	18	13	9
Middle	27	26	22	14	11	8
Highest	27	25	23	18	14	10

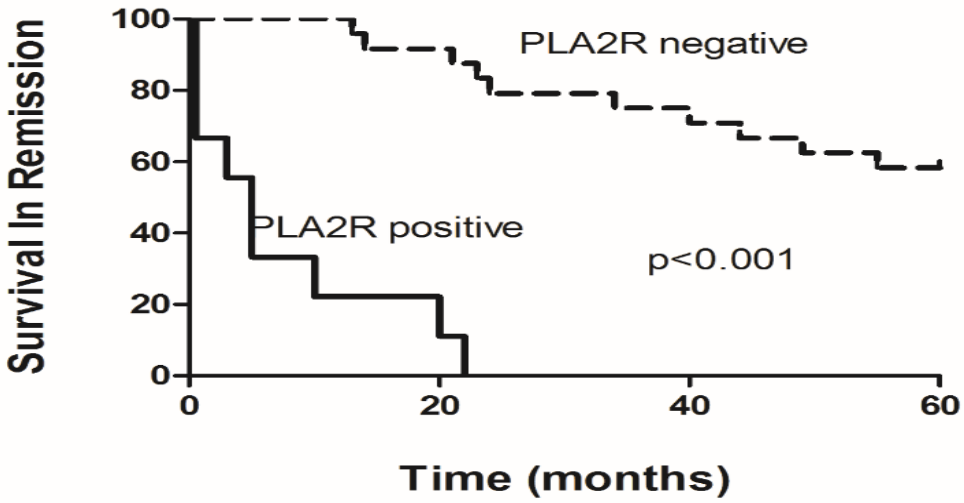
Piero Ruggenenti et al. JASN 2015;26:2545-2558

JASN

Management algorithm



Anti-PLA2R: guidance of treatment?



PLA2R positive	9	2	0	0
PLA2R negative	24	22	18	14

aPLA2R at end of CP therapy (12 months) predicts outcome

Bech et al, CJASN 2014

Conclusions: individualized treatment in MN is emerging

- Measurement of aPLA2Rab : reduced need for biopsy
- Be aware of differences between assays!
- Prediction of prognosis: urine LMW proteins, aPLA2Rab, serum creatinine, severity and duration of proteinuria
- Individualized thrombosis prophylaxis (www.gntools.com)
- Be aware of differences in serum albumin assays

Conclusions: individualized treatment in MN is emerging

- Cyclophosphamide should be restricted to high risk patients
- Rituximab and CNI induce remission
- Patients with high PLA2R antibody levels do not respond to rituximab at standard dose
- PLA2R antibody levels may guide therapy

Conclusions: individualized treatment in the future?

- PLA2R epitope spreading?
- Genetic information?
-

Questions?