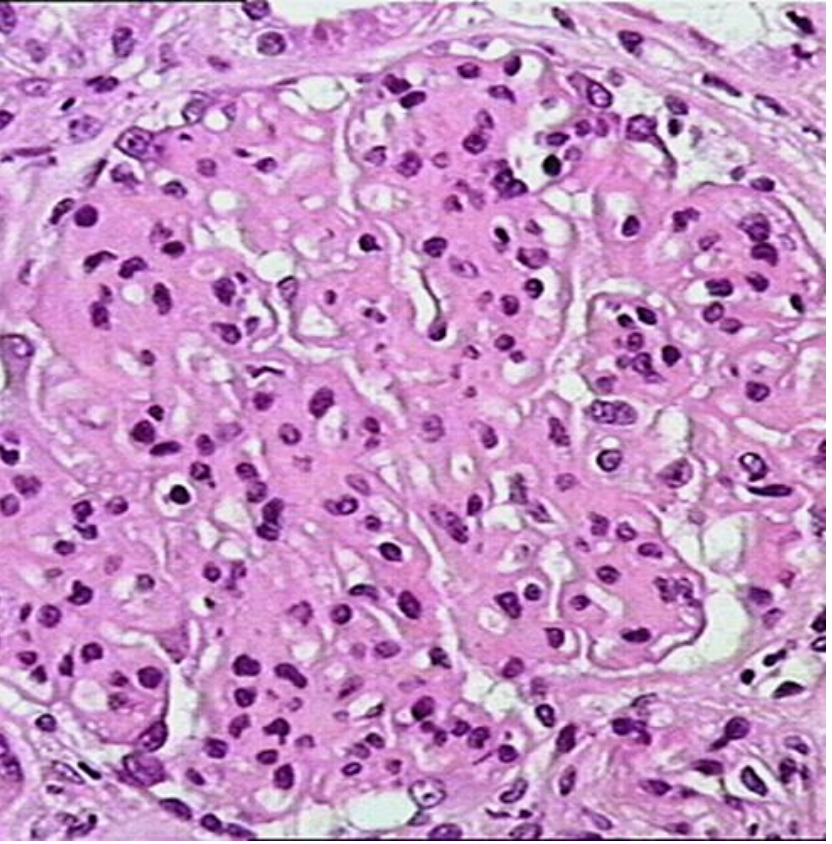
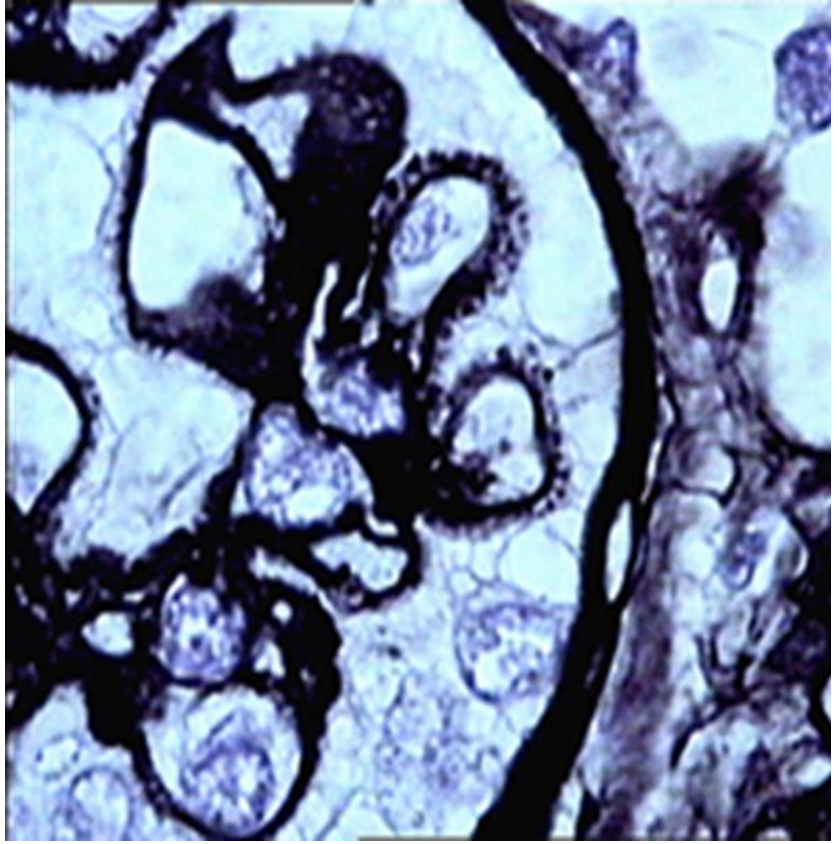
Rituximab is preferable than Cyclophosphamide in MN.

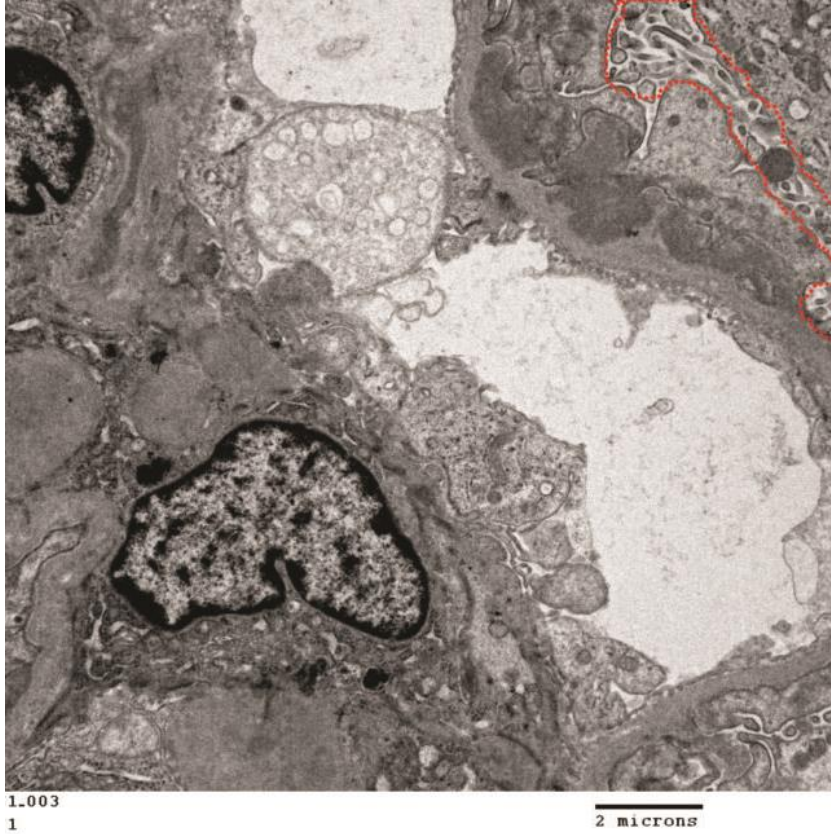
Prof: Iman Sarhan

Prof of nephrology ASU

Head of Department of Nephrology AFCM



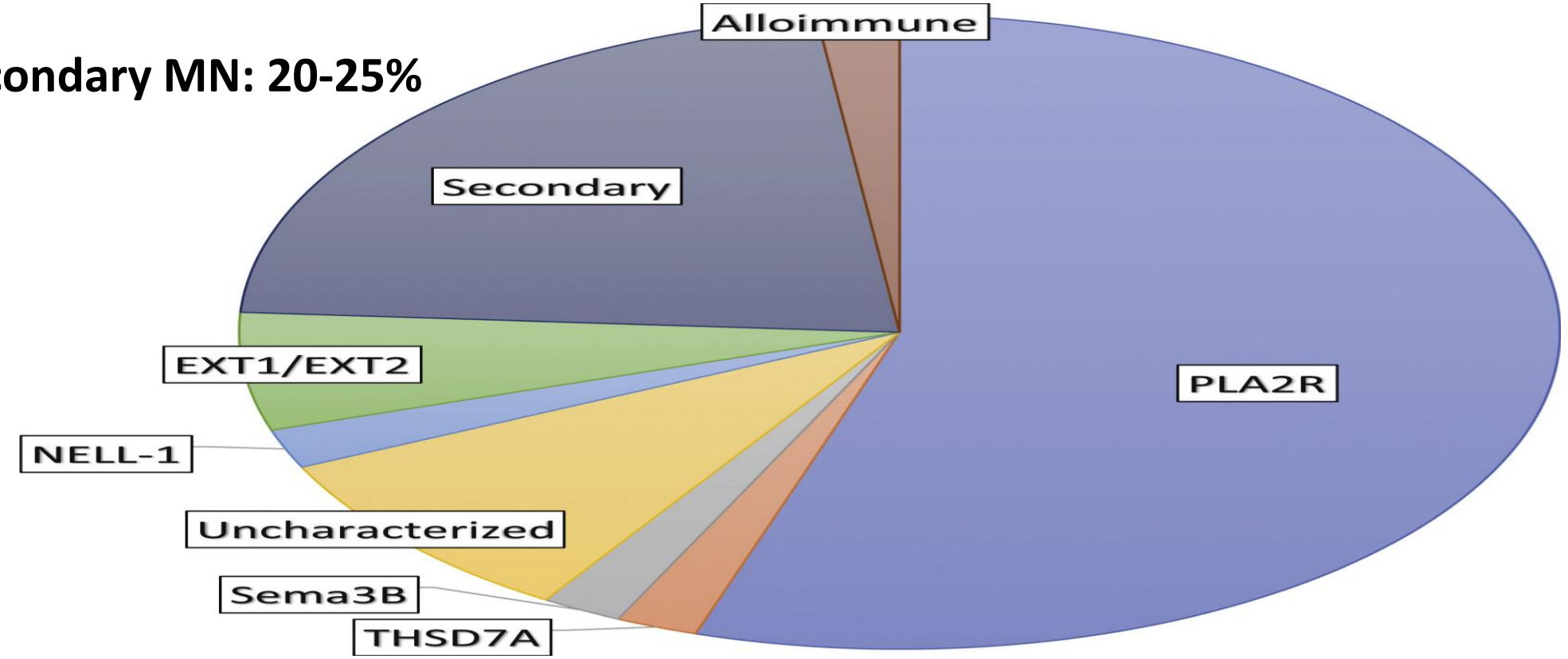




Membranous nephropathy (MN)

- The most common cause of nephrotic syndrome in adult (approximately 20 to 30%)

Secondary MN: 20-25%



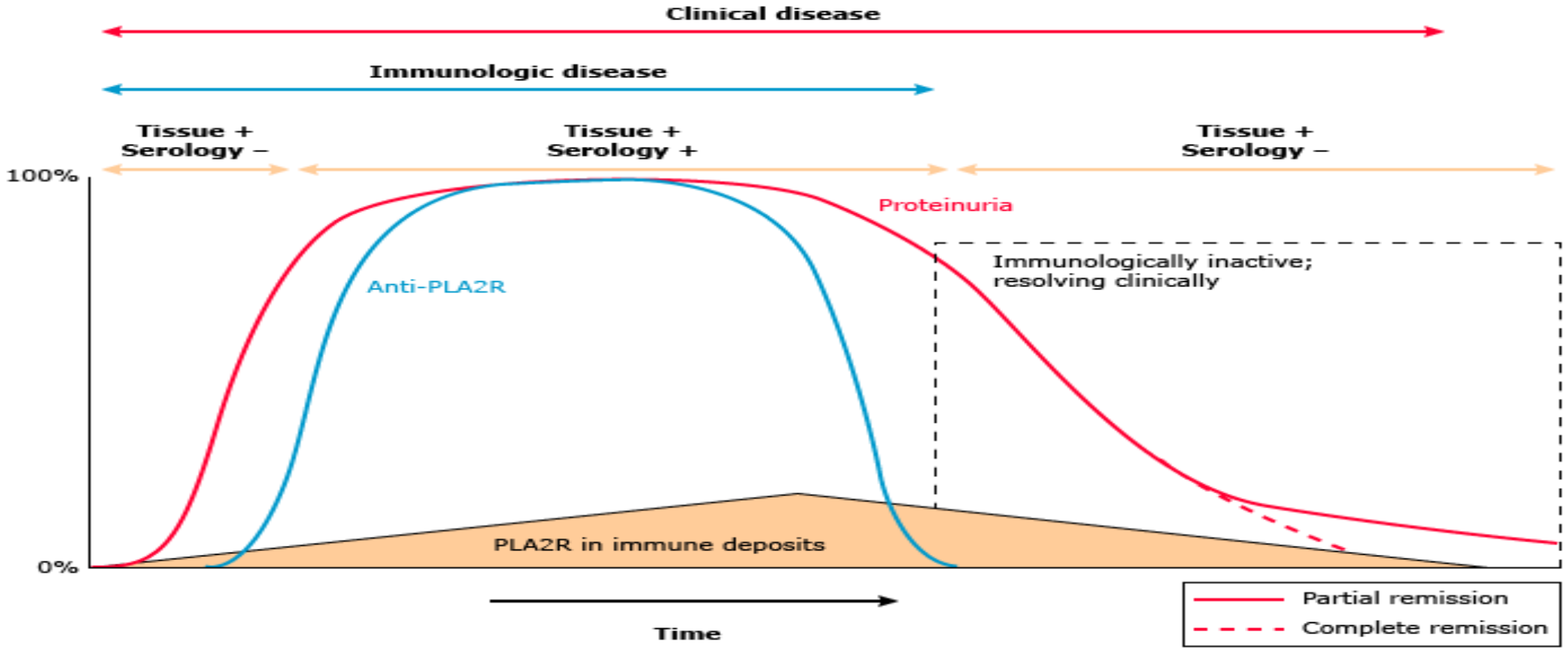
Non-PLA2R-associated MN

PLA2R-associated MN 70-80%

Primary membranous nephropathy 75 to 80 %

Loulwa Alsharhan, Laurence H. Beck . Membranous Nephropathy: Core Curriculum 2021 *American Journal of Kidney Diseases* **Volume 77 Issue 3 Pages 440-453 (March 2021)**

PLA2R staining versus anti-PLA2R versus proteinuria schematic



¶ In most patients who achieve an **immunologic remission**, a remission in proteinuria usually follows within 12 to 24 months.

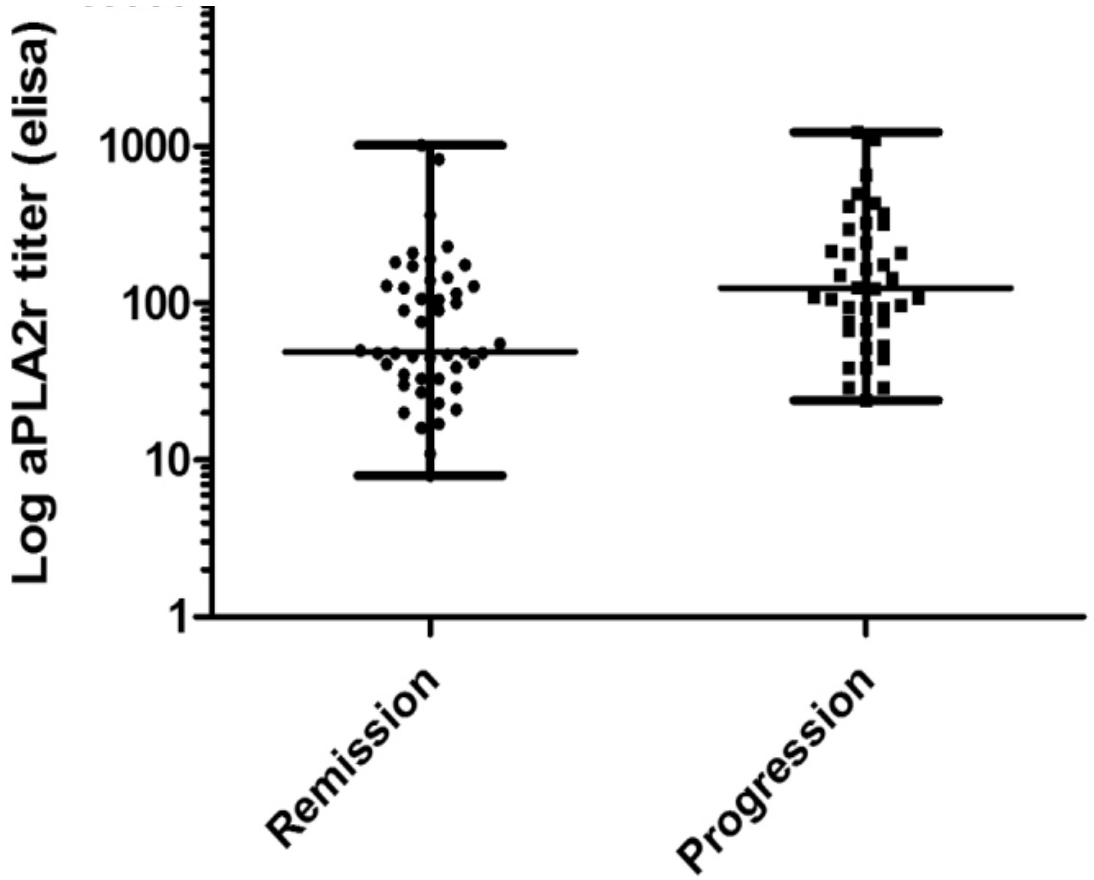
PLA2R: phospholipase A2 receptor.

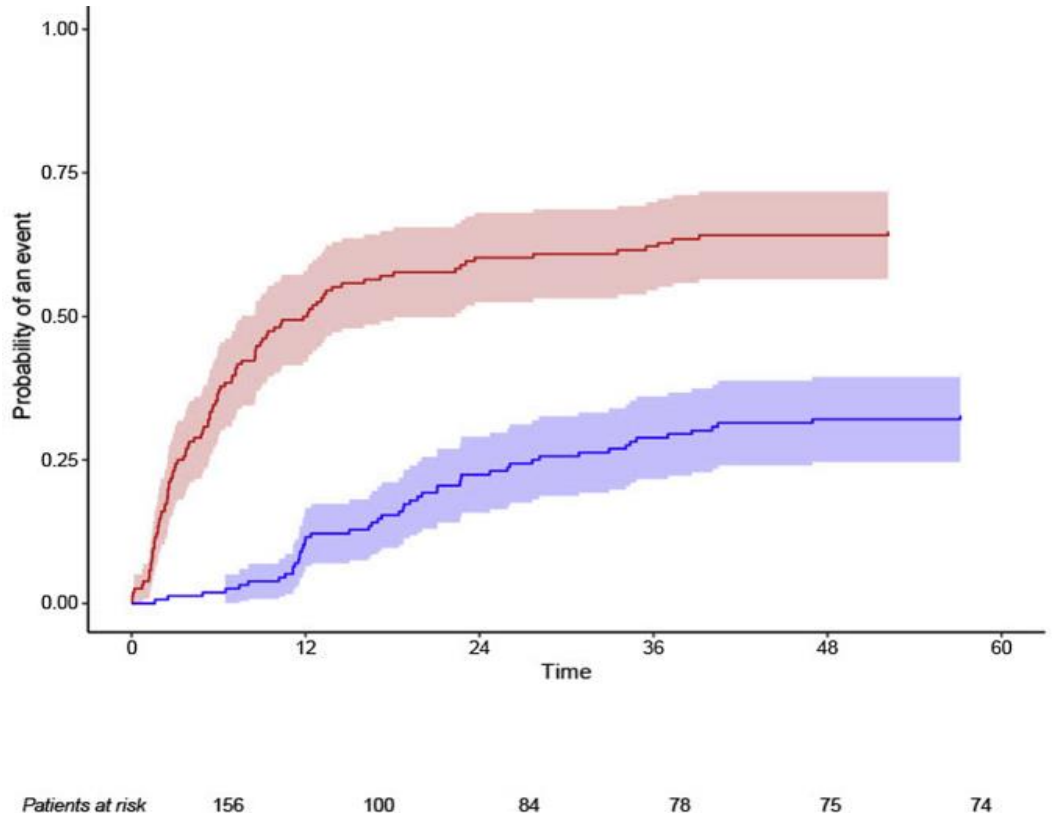
Reproduced from: Francis JM, Beck LH Jr, Salant DJ. Membranous nephropathy: A journey from bench to bedside. Am J Kidney Dis 2016; 68:138. Illustration used with the permission of Elsevier Inc. All rights reserved.

> Kidney Int Rep. 2021 Apr 22;6(6):1677-1686. doi: 10.1016/j.ekir.2021.04.002. eCollection 2021 Jun.

Anti–PLA2R1 Antibodies as Prognostic Biomarker in Membranous Nephropathy

Anne-Els van de Logt [1], Joana Justino [2], Coralien H Vink [1], Jan van den Brand [1], Hanna Debiec [3], Gérard Lambeau [2], Jack F Wetzels [1]

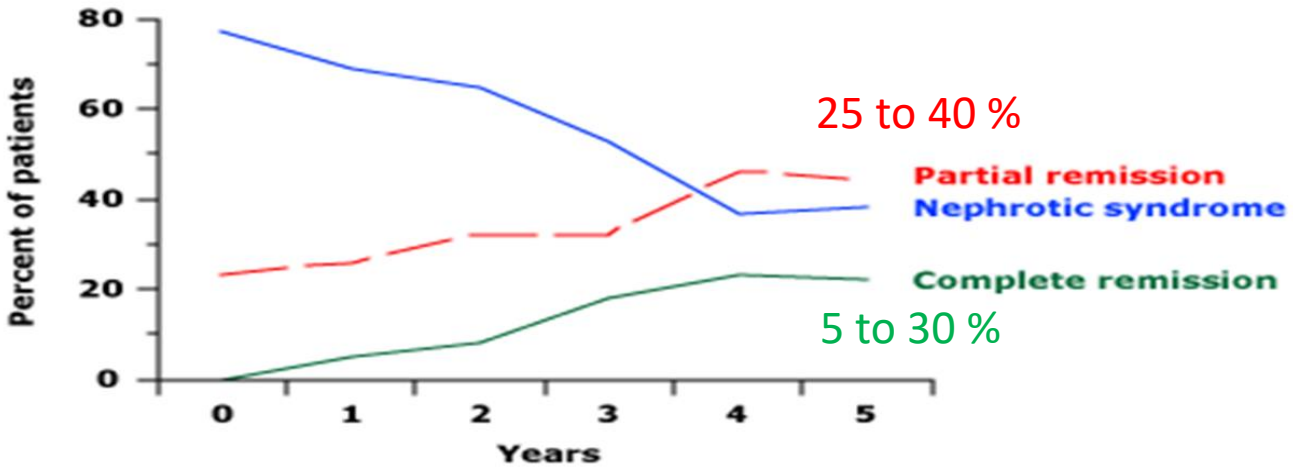




aPLA2R1ab levels at baseline of patients with normal serum creatinine with progression (*n* = 39) and or spontaneous remission (*n* = 46).

Natural history of MN (Likelihood of spontaneous remission)

High incidence of remission in untreated membranous nephropathy



Course of 100 consecutive untreated patients with idiopathic membranous nephropathy. Over a five-year period, there was a progressive increase in the incidence of partial or complete remission, while the incidence of the nephrotic syndrome fell.

Data from: Schieppati A, Mosconi L, Perna A, et al. Prognosis of untreated patients with idiopathic membranous nephropathy. N Engl J Med 1993; 329:85.

30-70 %

ESKD in untreated patients with nephrotic syndrome is 14 % at 5 years, 35% in 10 years, 41% in 15years.

- the rate of ESKD in untreated patients who remain non-nephrotic as low as 2 % at 10 years .

UpToDate®

Risk stratification of patients with primary membranous nephropathy*

	Risk of progression			
	Low	**Moderate**	**High**	**Very high**
	Over an observation period of 3 to 6 months¶, at least 2 of 3 criteria must be present:			2 or more of the following **at the time of diagnosis**:
Kidney function	▪ Normal or stable (<25% decrease) eGFR over the observation period	▪ Normal or stable (<25% decrease) eGFR over the observation period	▪ Decrease in eGFR ≥25%, not explained by other causes, **at any time** during the observation period	▪ Serum creatinine ≥1.5 mg/dL (≥133 micromol/L), considered due to active MN ▪ Decrease in eGFR ≥25% from baseline over the prior 2 years, considered due to active MN ▪ Severe, disabling, or life-threatening nephrotic syndrome◇
Proteinuria	▪ <4 g/day at the end of the observation period	▪ Between 4 and 8 g/day at the end of the observation period	▪ >8 g/day at the end of the observation period **or** Persistent nephrotic syndrome△	
Serum anti-PLA2R antibody levels (only in patients with anti-PLA2R antibody-positive MN)	▪ Serial titers are persistently low (arbitrarily defined as <50 RU/mL by ELISA) or are decreasing ≥25% by over the observation period	▪ Serial titers are <150 RU/mL and stable or increasing by <25%	▪ Serial titers are high (arbitrarily defined as ≥150 RU/mL by ELISA) and not declining **or** are increasing to ≥150 RU/mL	

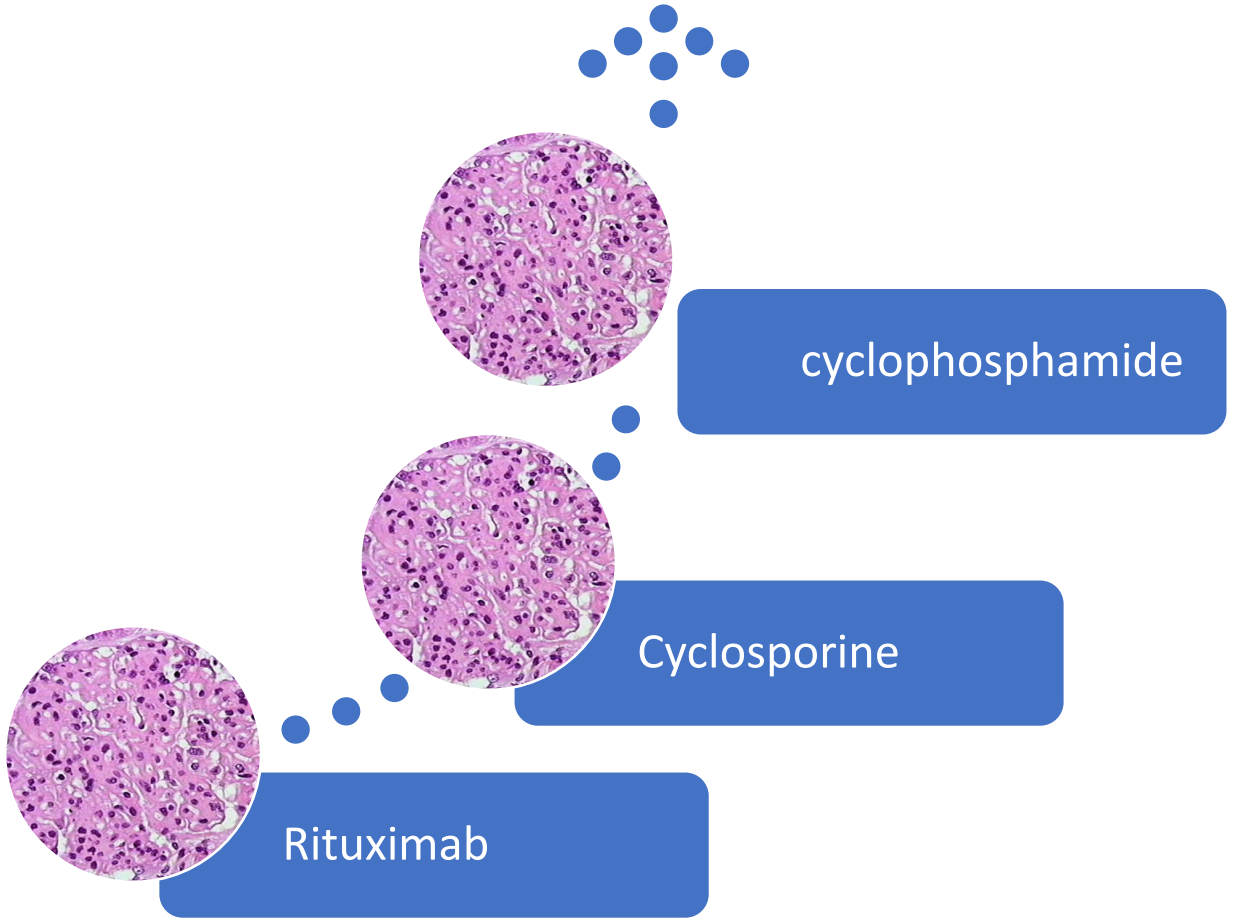
Target is induction of remission complete or partial.

Translated in improved kidney survival with long follow-up (**).

*van de Logt et al., 2016. Expert Rev Clin Pharmacol 9: 1463–1478 .
**Ponticelli et al., Kidney Int 48: 1600–1604, 1995

Remission in MN

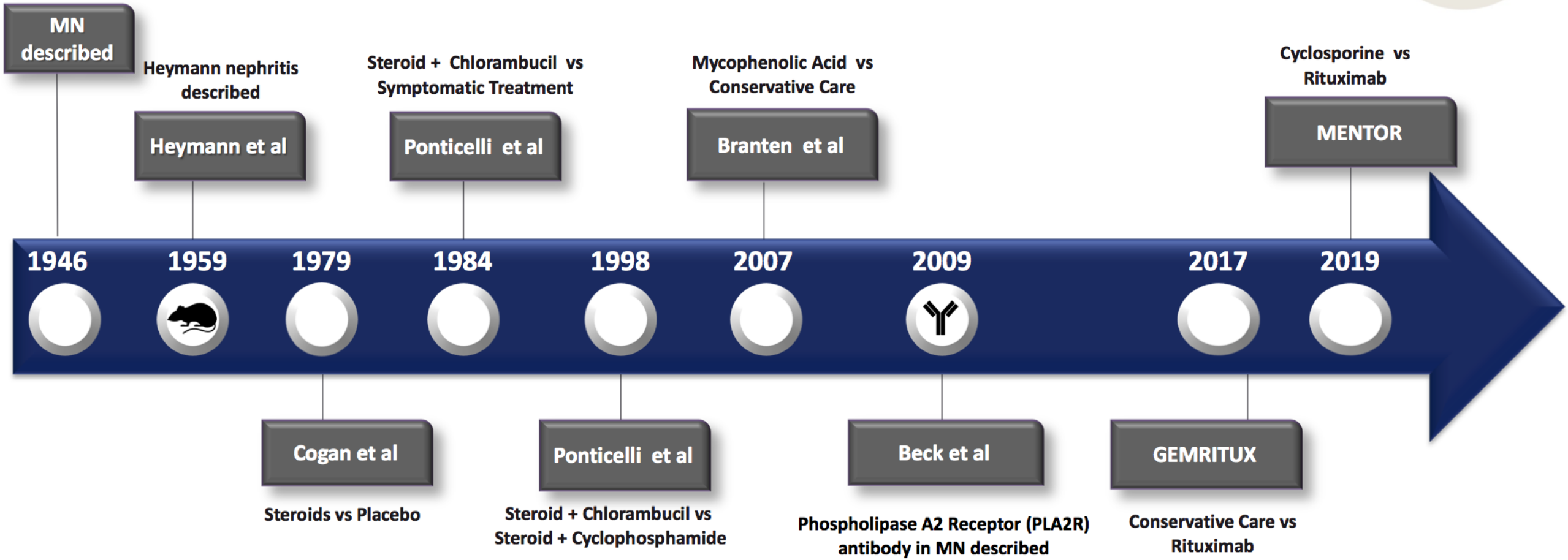
Conservative treatment
Low salt, diuretics.
Adjust protein intake
Treat HTN
ACEI, ARBs
Lipid lowering agent
Anticoagulant



+ Corticosteroids

Landmark Trials
Primary Membranous Nephropathy (MN)

Landmark Nephrology



@priti899 @hetpatel2006 @Landmark_Neph

Review

Pharmacological treatment of primary membranous nephropathy in 2016

Anne-Els van de Logt, Julia M. Hofstra & Jack F. Wetzels

Pages 1463-1478 | Received 29 May 2016, Accepted 15 Aug 2016, Accepted author version posted online: 18 Aug 2016, Published online: 16 Sep 2016

Table 1. Treatment schedules for primary membranous nephropathy.

Treatment	Agents	Dosage of therapy	Treatment period
Chlorambucil cyclical therapy [29]	Chlorambucil	0.2 mg/kg/day	Months 2,4,6
	Prednisolone	0.5 mg/kg/day	Months 1,3,5
'Classical Ponticelli schema'	Methylprednisolone	1 g i.v.	3 consecutive days, at start of months 1,3,5
Cyclophosphamide cyclical therapy [28]	Cyclophosphamide	2.5 mg/kg/day[a]	Months 2,4,6
	Prednisolone	0.5 mg/kg/day	Months 1,3,5
'Modified Ponticelli schema'	Methylprednisolone	1 g i.v.	3 consecutive days, at start of months 1,3,5
Cyclophosphamide daily therapy [30][b]	Cyclophosphamide	1.5 mg/kg/day	Months 1–6
	Prednisolone	0.5 mg/kg/qod	Months 1–5, then taper
	Methylprednisolone	1 g i.v.	3 consecutive days, at start of months 1,3,5
Cyclosporine [31][c]	Cyclosporine	Start with 3.5 mg/kg/day, achieve level 125–225 µg	Months 1–6, then taper by 25% per month; continue treatment at 50% of dose until 12 months, then taper to lowest possible maintenance dose[c]
	Prednisolone	0.15 mg/kg/day, max. 15 mg	Months 1–6, then taper
Tacrolimus [32,33][d]	Tacrolimus	Initial dose 0.5 mg/kg per day, achieve trough level 3–5 ng/L; if remission is not achieved after 2 months, increase to 5–8 ng/L	Months 1–12, then taper to lowest possible maintenance dose[c]
	Prednisolone	0.15 mg/kg/day	Months 1–6, then taper
Rituximab [34–36]	Rituximab	1000 mg i.v. 375 mg/m^2 i.v.	Days 1 and 15 1–4 weekly doses
Synthetic ACTH (Synacthen depot®) 1 mg/ml [37,38]	Synthetic ACTH	Start with 1 mg once a week i.m., in 8 weeks time increase to 1 mg 2 times a week	From week 8 on 18 weeks 1 mg 2 times a week; built down in 13 weeks time (9 months treatment duration in total)
HP Acthar gel® [39]	Acthar gel	Start with 40–80 units s.c. every other week, increase to 2 times a week	12 weeks of full dosage of 2 times a week; if no signs of improvement occur after 3 months with 40 units, increase to 80 units twice a week for a full dosage of 12 weeks

[a]KDIGO guidelines advice 2.0 mg/kg/day.
[b]Original study used cyclophosphamide for 12 months. Meanwhile, treatment period has been reduced to 6 months.
[c]It is not known if prednisolone coadministration is needed. Most studies with cyclosporine have used prednisolone.
[d]High relapse rate, treatment must be continued in the majority of patients.

Cyclophosphamide +steroids Vs conservative treatment

		Follow-up	Remission rate[a]	Relapse rate[b]	
	Treatment	(months)	(%)	(%)	Renal function end point
Ponticelli [40]	Treatment	120	83	26	Dialysis-free 10 yr-survival: 92%
	Control	120	38	NA	Dialysis-free 10 yr-survival: 60%
Jha [41]	Treatment	132 (126–144)	72	24	Dialysis-free 10 yr-survival: 89%
	Control	132 (126–144)	35	25	Dialysis-free 10 yr-survival: 65%
Howman [42]	Control	36	NA	NA	20% decline in eGFR[c] in 58% and ESRD in 3% of patients
	Treatment	36	NA	NA	20% decline in eGFR[c] in 84% and ESRD in 11% of patients
Torres [43]	Treatment	52 ± 37	42	25	Dialysis-free 7 yr-survival: 90%
	Control	47 ± 38	0	-	Dialysis-free 7 yr-survival: 20%
Du Buf [30]	Treatment	51 (5–132)	86	20	Dialysis-free 5 yr-survival: 86%
	Control	48 (12–65)	20	50	Dialysis-free 5 yr-survival: 32%

Remission rate is 83% in cyclophosphamide vs 38 % on conservative treatment

Renal 10 years survival was 92% cyclophosphamide vs 60% conservative treatment .

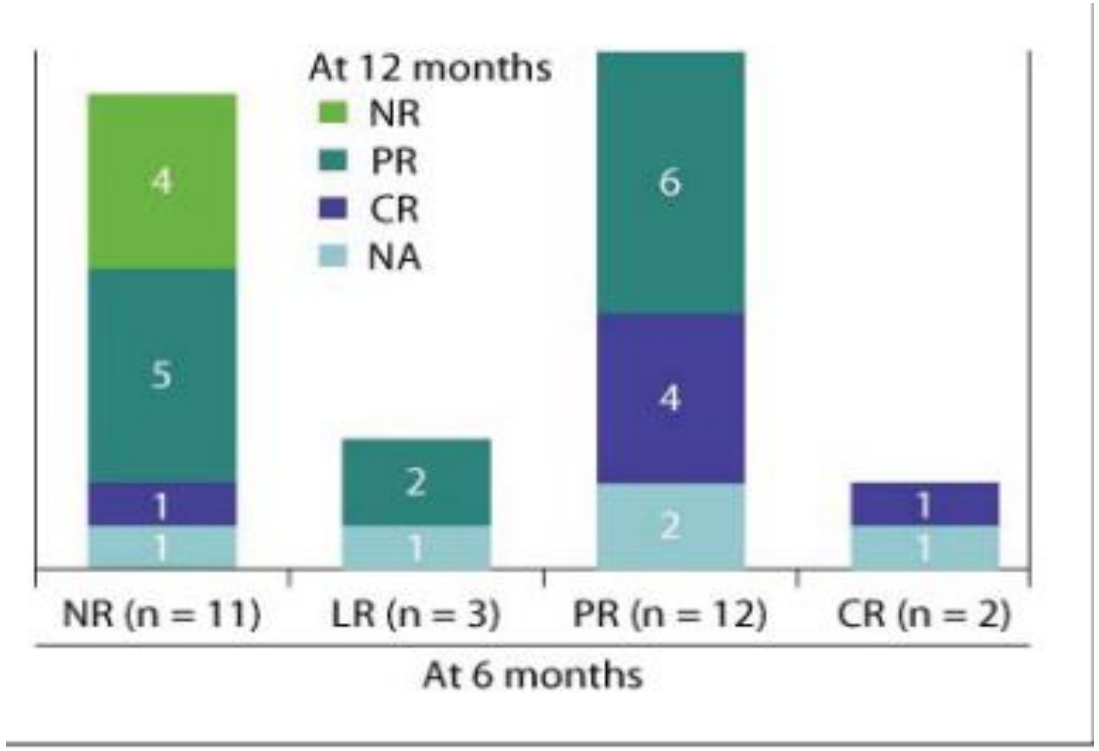
Ponticelli et al., Kidney Int 48: 1600–1604, 1995

EXTRA nephron Journals

Nephron Extra 2011;1:251–261
DOI: 10.1159/000333068
Published online: December 24, 2011

Original Paper

Rituximab Treatment for Membranous Nephropathy: A French Clinical and Serological Retrospective Study of 28 Patients



50% PR and CR at 6 months
reach to 60% at 12 months

Response 12 months after rituximab treatment in the 11 patients with no response (NR), 2 with LR, 12 with PR and 2 patients with CR at 6 months. NA = Not available.

Michel et al.: Rituximab in Membranous Nephropathy. Nephron Extra 2011;1:251–261

Rituximab induced remission in 64% of patient
However, the number of non-responders 36% and relapses 30%.

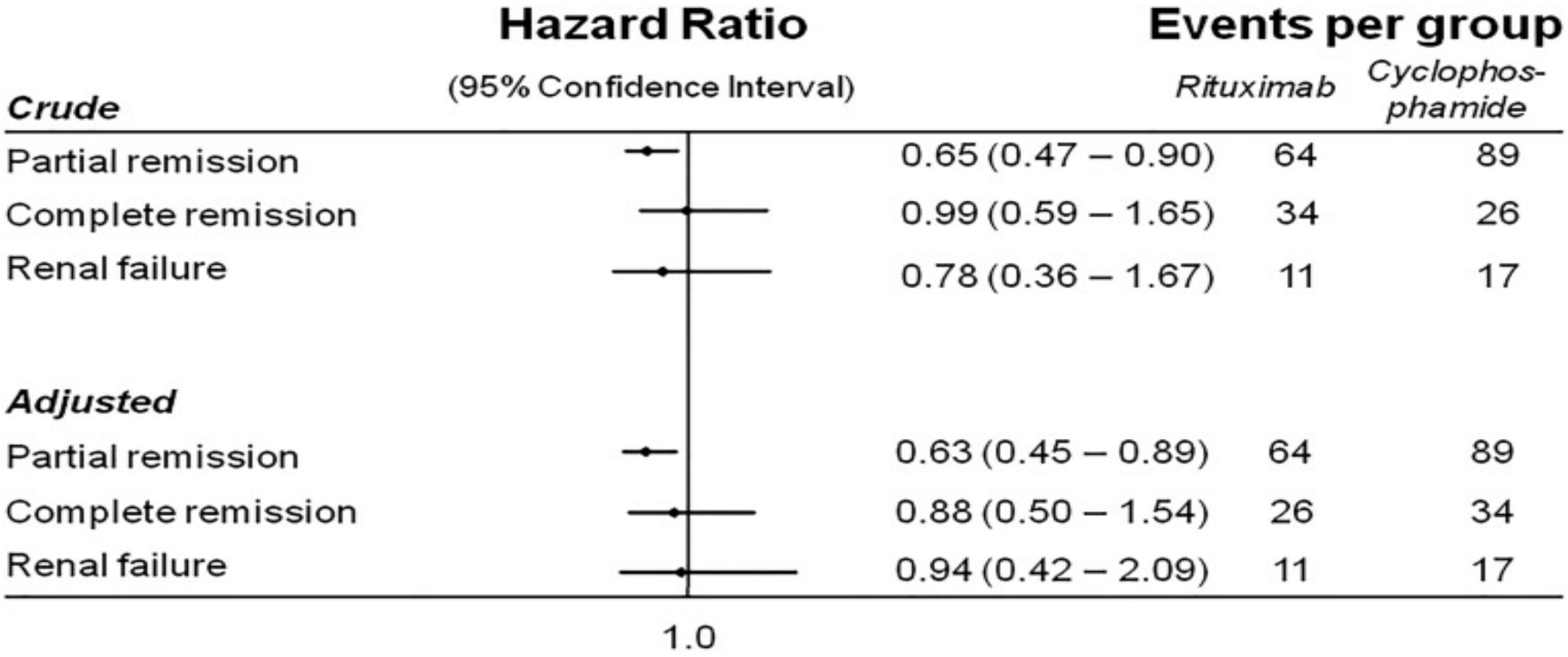
	Treatment	Type of study	Patients (*n*)	Sex (m/f)	Duration MN (months)	sCreat (umol/l)	Proteinuria (g/day)
Cravedi [67]	RTX 1 × 375 mg/m²	Cohort	12	8/4	NA	124 ± 44	10.3 ± 8.9

	Treatment	Follow-up (months)	Remission rate[a] (%)	Relapse rate[b] (%)	Renal function end point
Cravedi [67]	RTX 1 × 375 mg/m²(B-cell driven)	12	67	NA	NA
Cravedi [67]	RTX 4 × 375 mg/m²	12	67	NA	NA
Fervenza [34]	RTX 2 × 1 g	12	53	NA	ESRD 13%
Ruggenenti [68]	RTX 4 × 375 mg/m²	3	0	NA	NA
Ruggenenti [68]	RTX 4 × 375 mg/m²	12	75	NA	NA
Ruggenenti [68]	RTX 4 × 375 mg/m²	12	67	NA	NA
Fervenza [36]	RTX 4 × 375 mg/m², repeated after 6 mo.	24[c]	94	6	NA
Segarra [65]	RTX 4 × 375 mg/m²	30	100	23	NA
Ruggenenti [35]	RTX 4 × 375 mg/m² or B-cell driven	29	65	28	ESRD 4%
Busch [69]	RTX 4 × 375 mg	36 (12–72)	71[d]	7[d]	NA
Ruggenenti [70]	RTX 4 × 375 mg/m² or B-cell driven	31	64	30	NA
Dahan [71]	RTX 2 × 375 mg/m²	17 (13–24)	65	NA	NA
	Supportive	17 (13–23)	34	NA	NA

ESRD: end-stage renal disease.
[a]Definitions of remission as used by the authors.
[b]Relapse rate: percentage of relapses in patients with previous remission after withdrawal of medication.
[c]*n* = 18 in final analysis.
[d]12 months after the last infusion of rituximab.

Ruggenenti P, Cravedi P, Chianca A, et al. Rituximab in idiopathic membranous nephropathy. J Am Soc Nephrol. 2012;23(8):1416–1425.

Rituximab is inferior to cyclophosphamide.
The partial remission rate was lower in the rituximab-treated cohort



They compared two European cohorts that were treated with either rituximab or cyclophosphamide and steroids.

van den Brand et al., . J Am Soc Nephrol 28: 2729–2737, 2017

Immunological remission in PLA2R-antibody–associated membranous nephropathy: cyclophosphamide versus rituximab

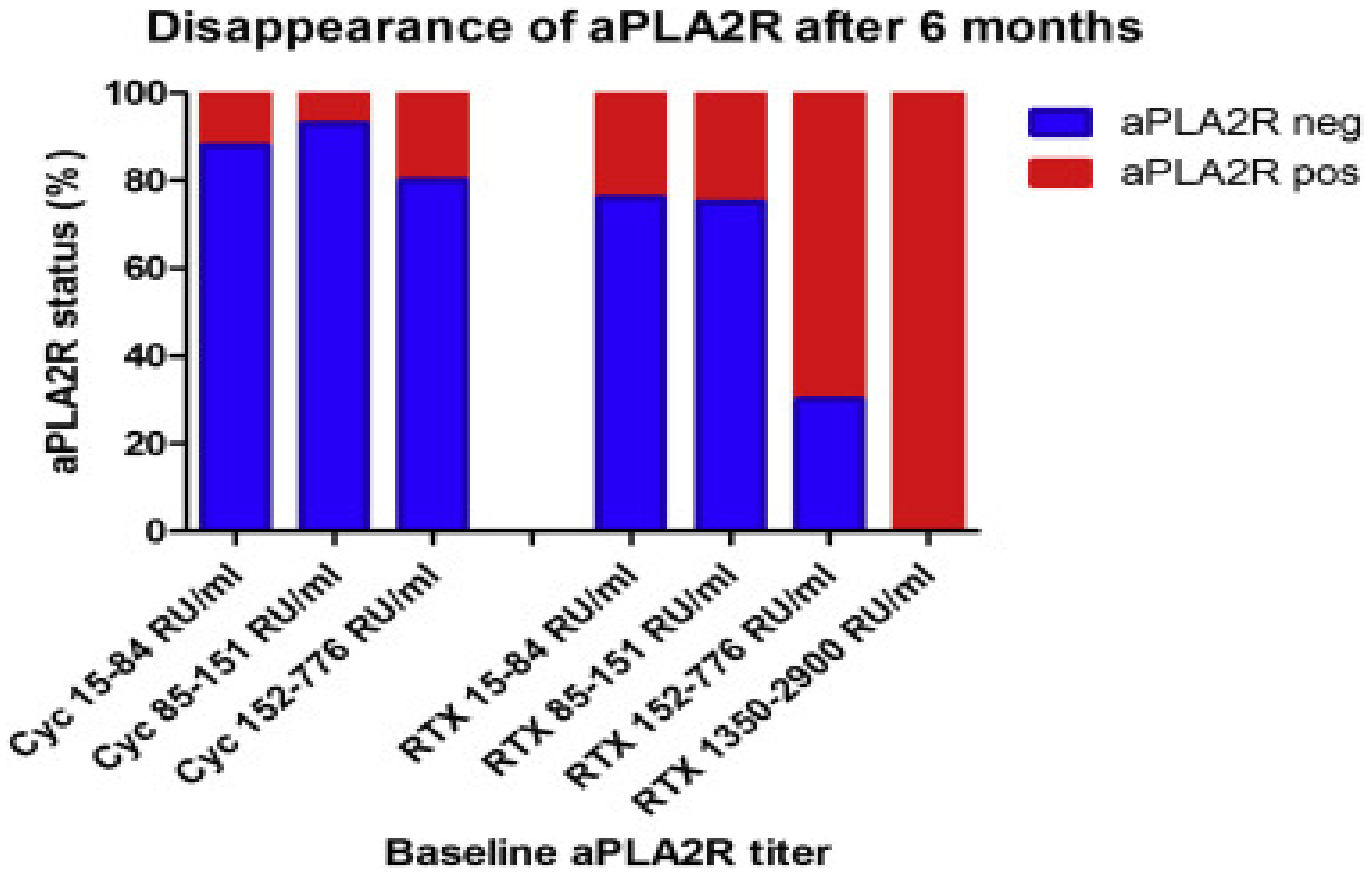
Anne-Els van de Logt • Karine Dahan • Alexandra Rousseau • ... Hanna Debiec • Pierre Ronco • Jack Wetzels • Show all authors

kidney INTERNATIONAL

Van de Logt et al., Kidney International 2018 93(4):1016-1017

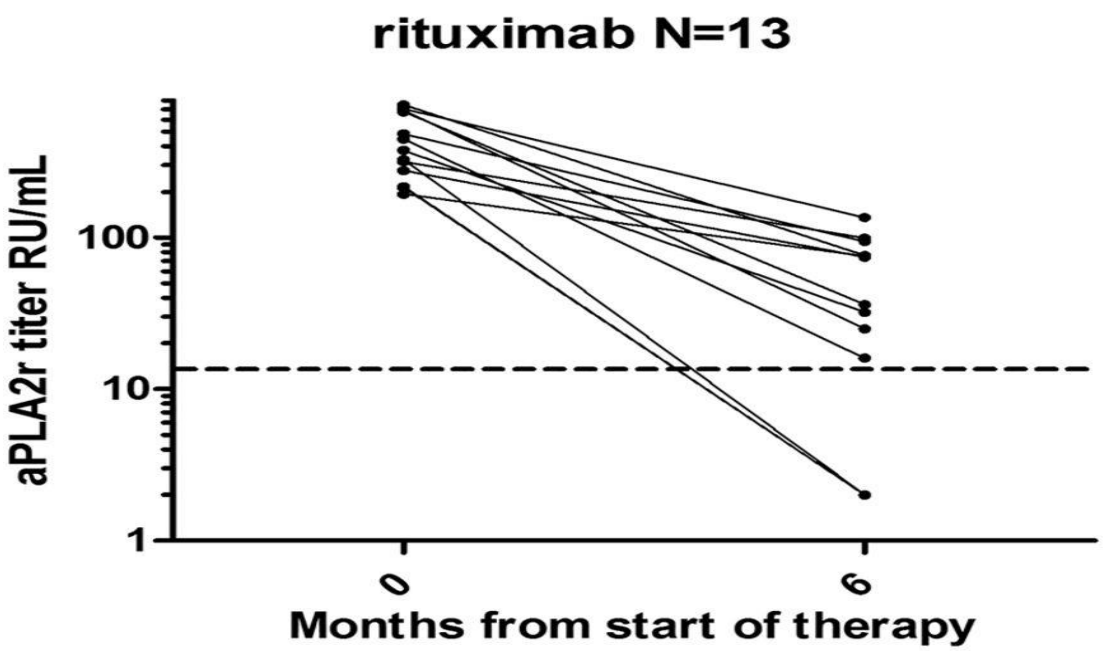
Evaluation of patients treated with cyclophosphamide (1.5 mg/kg/d, duration 8–24 weeks; Nijmegen cohort) or rituximab (cumulative dose 1.5–2.0 g; French cohort).

- Patients treated with cyclophosphamide, antibodies disappeared in almost all patients, independent of baseline level.
- In contrast, patients treated with rituximab disappearance of aPLA2R was less likely in with an aPLA2R titer higher than 152 relative units/ml.

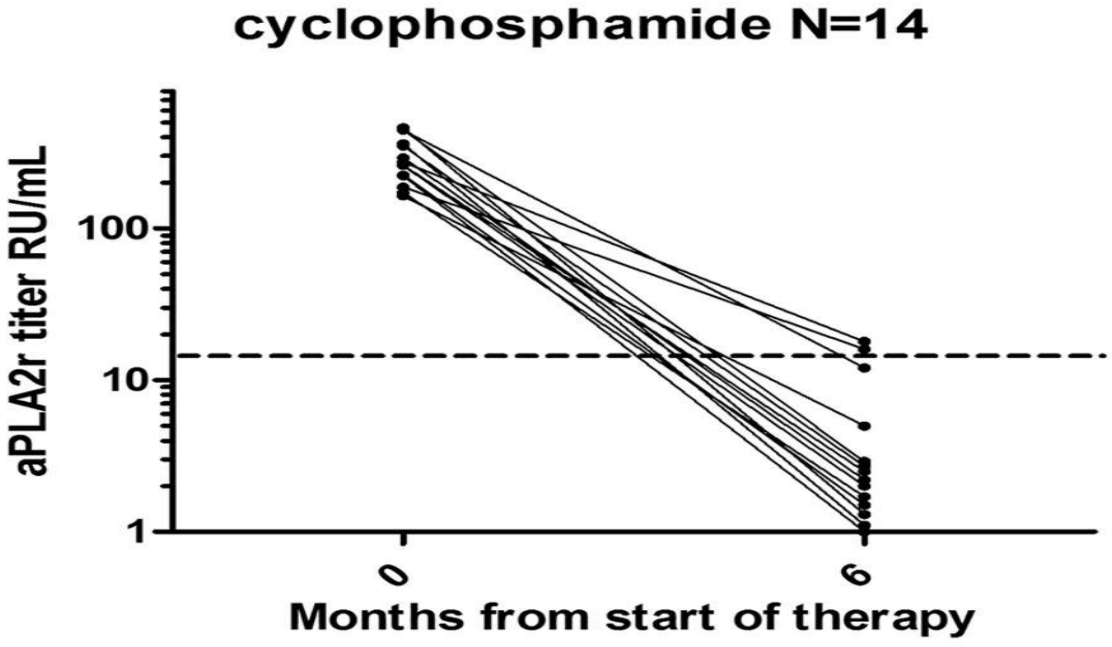


In Very high risk patient
Immunological remission (decrease aPLAR 1ab) is high with cyclophosphamide

23% (three of 13) decrease aPLAR 1ab



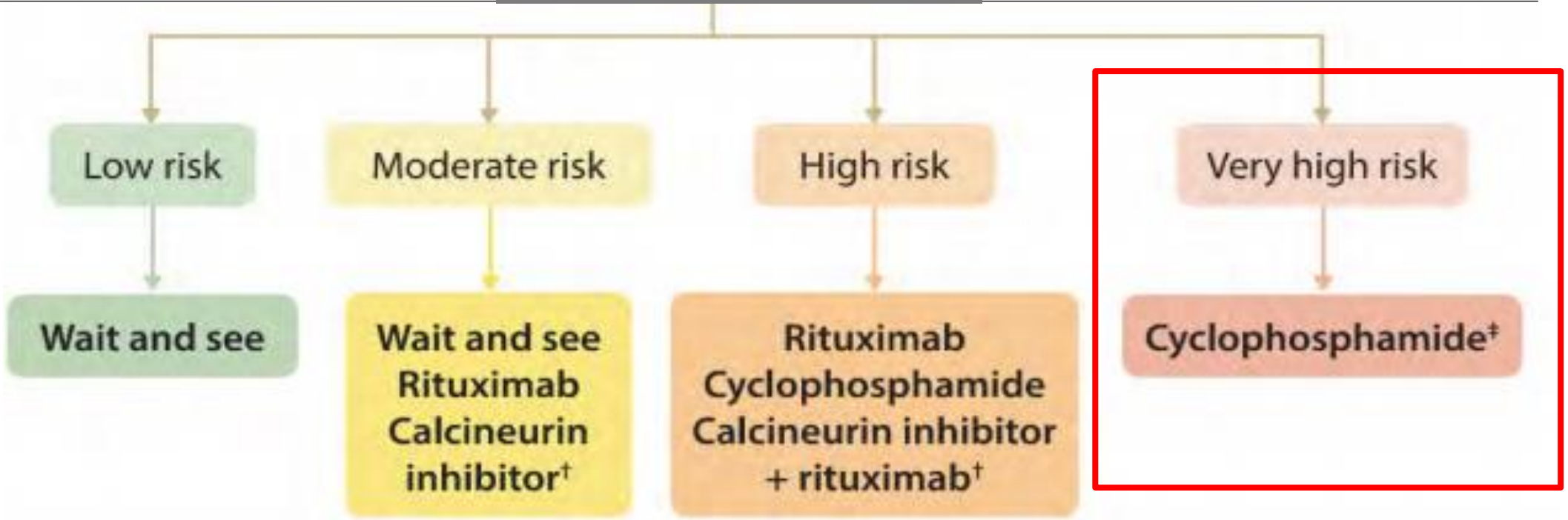
86% (12 of 14) decrease aPLAR 1ab



Anne-Els van de Logt, and Jack F. Wetzels Kidney360 2021;2:1699-1701

Membranous Nephropathy

Risk evaluation



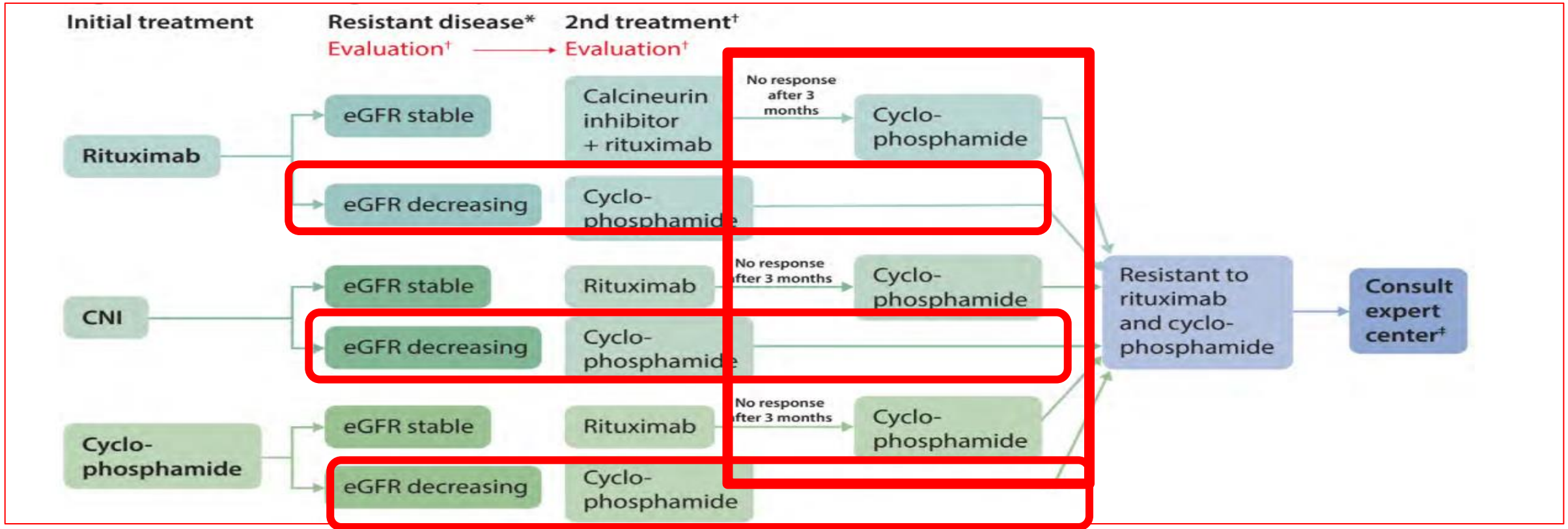
*See Practice Point 3.2.1 and Table MN1 for a detailed description of risk evaluation.

†Calcineurin inhibitor (CNI) monotherapy is considered less efficient. Treatment with CNI for 6-12 months with rapid withdrawal is associated with a high relapse rate. Still, its use may be considered in patients with normal estimated glomerular filtration rate (eGFR) and moderate risk of progression, since many of these patients will develop a spontaneous remission. The use of CNI will shorten the period of proteinuria. In patients with high risk of progression, addition of rituximab after six months of treatment with CNI is advised, with the possible exception of patients with documented disappearance of PLA2Rab after CNI treatment.

‡There is insufficient evidence that rituximab used in standard doses prevents development of kidney failure. In patients who do not tolerate or can no longer use cyclophosphamide, consultation with an expert center is advised.

Algorithm for management of patients with treatment-resistant membranous nephropathy

Second treatment is dependent on the severity of deterioration of eGFR as indicated

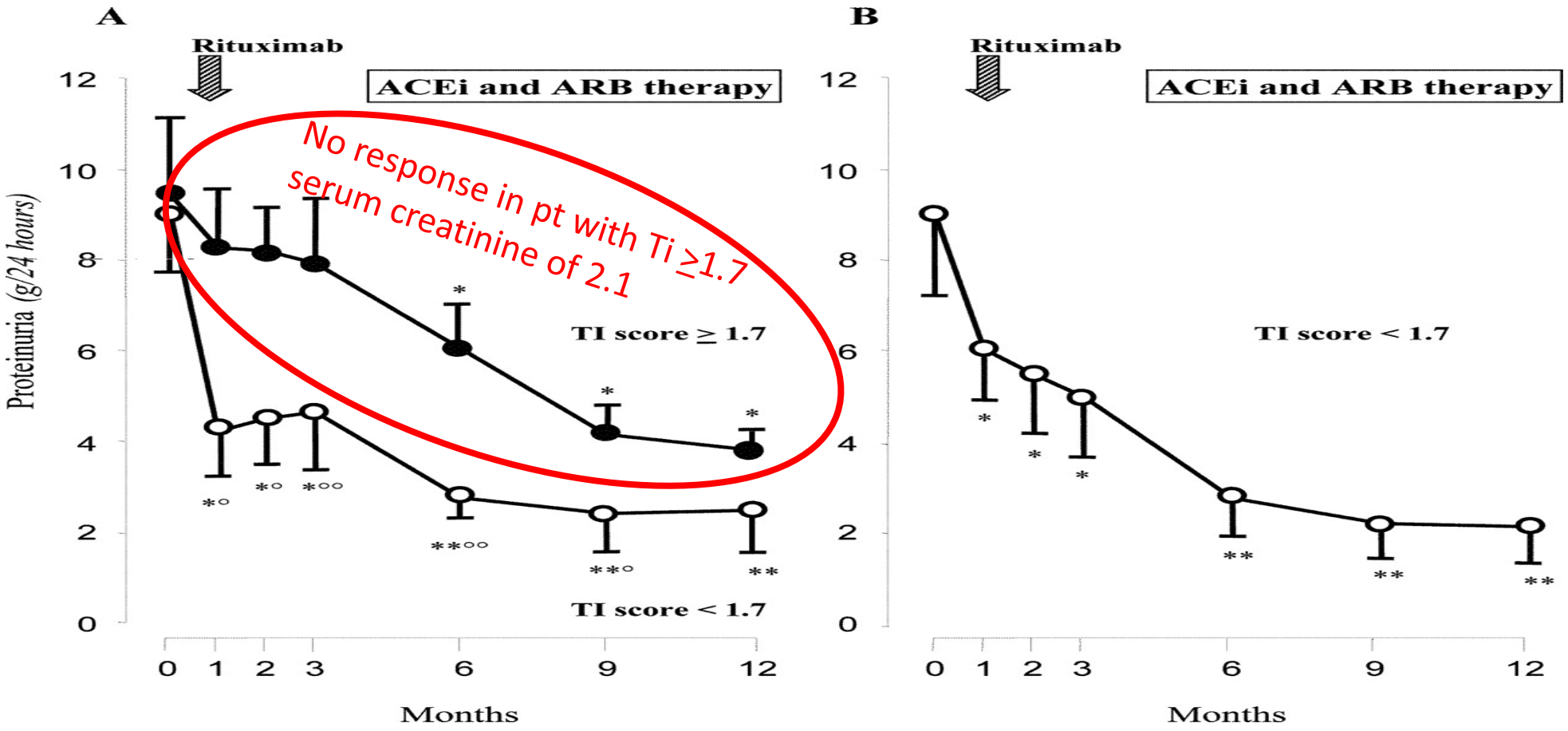


The efficacy of rituximab in patients with kidney insufficiency is unproven. Thus, there are no data to support its use in patients with reduced eGFR

***Evaluation: In patients with resistant disease, compliance should be checked and efficacy monitored (e.g., B cell response, anti-rituximab antibodies, IgG levels, leukocytopenia during cyclophosphamide, CNI levels).**

Rituximab in MN. Who can benefit?

Rituximab is of limited benefit in patients with severe kidney dysfunction

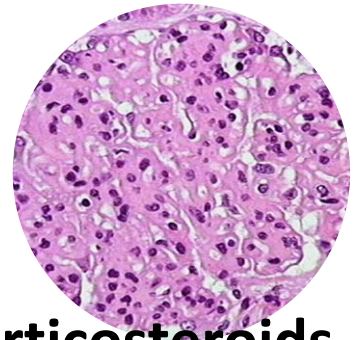


Twenty-four-hour proteinuria from baseline (month 0) to 12 mo after rituximab administration in two cohorts of patients with idiopathic membranous nephropathy (IMN) and a baseline tubulointerstitial (TI) score of <1.7 (responders) or ≥1.7 (nonresponders) wh...

CJASN
Clinical Journal of the American Society of Nephrology

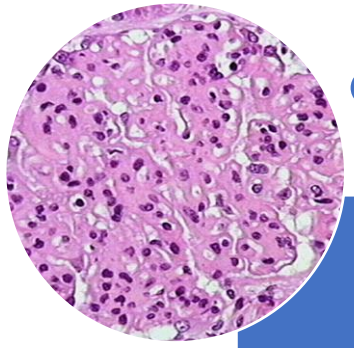
Piero Ruggenenti et al. CJASN 2006;1:738-748

Remission in MN



cyclophosphamide

+ Corticosteroids

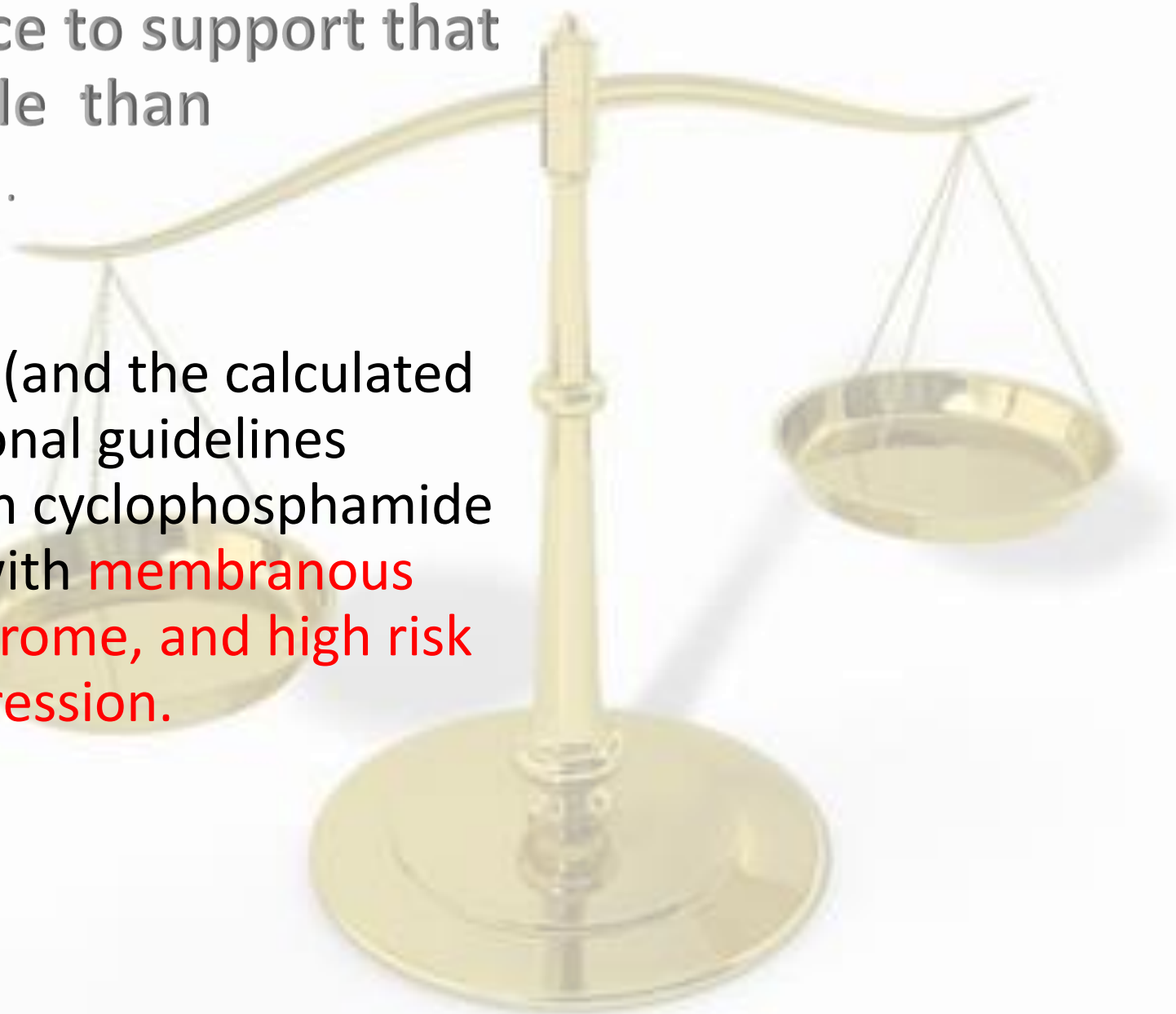


Rituximab

Higher renal survival 92%.
Higher rate of immunological remission 86 Vs 23%.
Recommended by guidelines for very high-risk patient, resistance , patient with low eGFR.
cost effectiveness.

Lower rate of immunological (23%) and clinical remission (86%).
Can not be use in very risk patient, limited effect on patient with low eGFR.
Expensive.

There is sufficient evidence to support that Rituximab is not preferable than Cyclophosphamide in MN.



On the basis of the evidence (and the calculated cost efficacy), international guidelines recommended treatment with cyclophosphamide and steroids for patients with membranous nephropathy, nephrotic syndrome, and high risk for disease progression.


Thank You