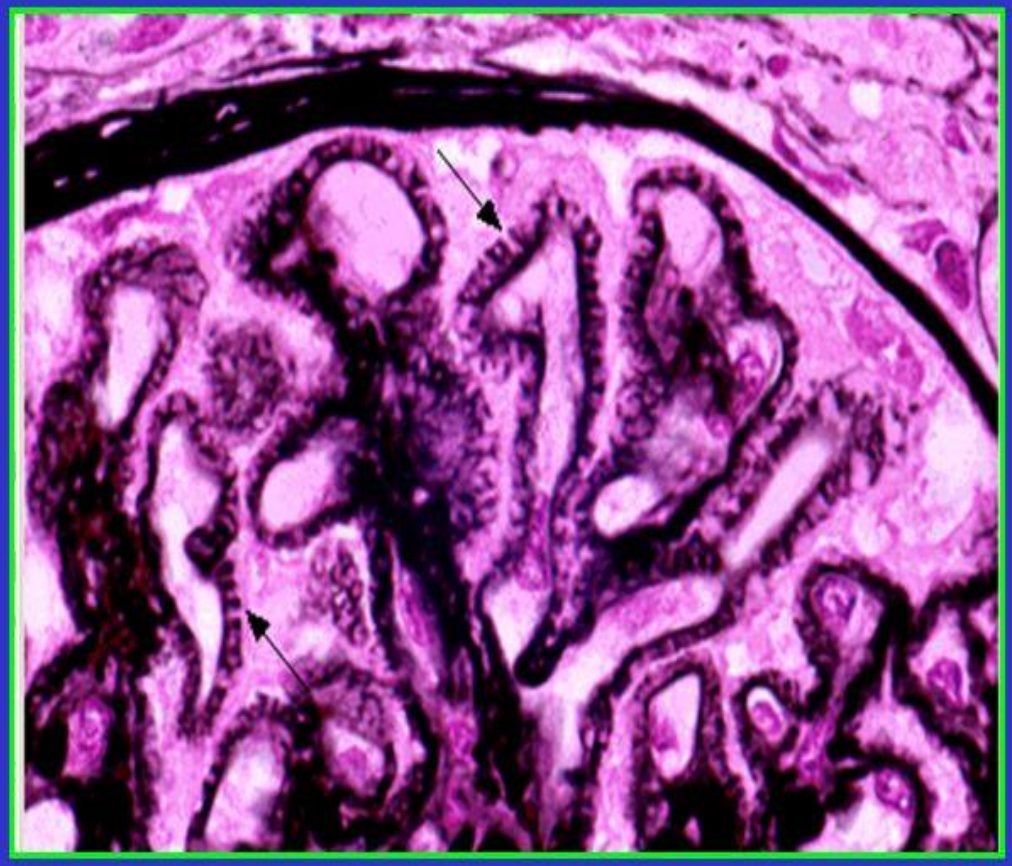
Membranous Nephropathy

Ιωάννης Γ. Γριβέας,MD,PhD

athens-NEPHROLOGY



Light micrograph silver stain of membranus nephropathy. Spike appearance (arrows). The spikes represent new basement membrane growing between the subepithelial immune deposits (visible on EM)

Epidemiology

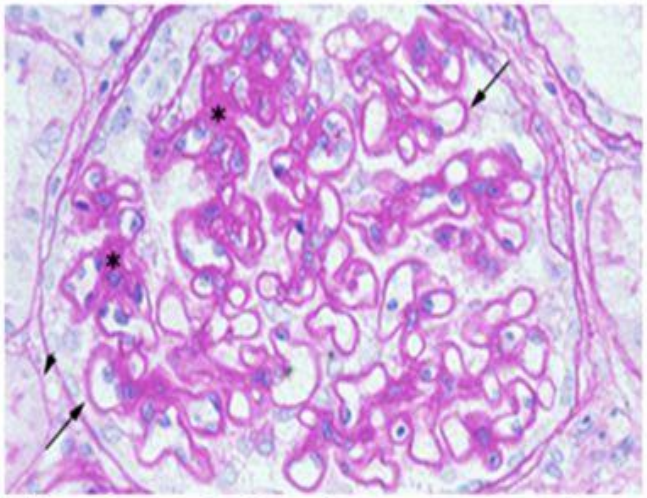
- 2nd /3rd common cause of ESRD within primary GN group
- USRDS 2002 - 2006:
  [0.4% ESRD was due to Idiopathic Membranous GN]
- Has been reported in < 1 year old and > 90 years old.
  but uncommon in < 30 years old.
- Peak age 30-40 and 40-50 years
- M:F- 2-3:1
- Caucasians > Asians > African-Americans > Hispanics

Membranous Nephropathy

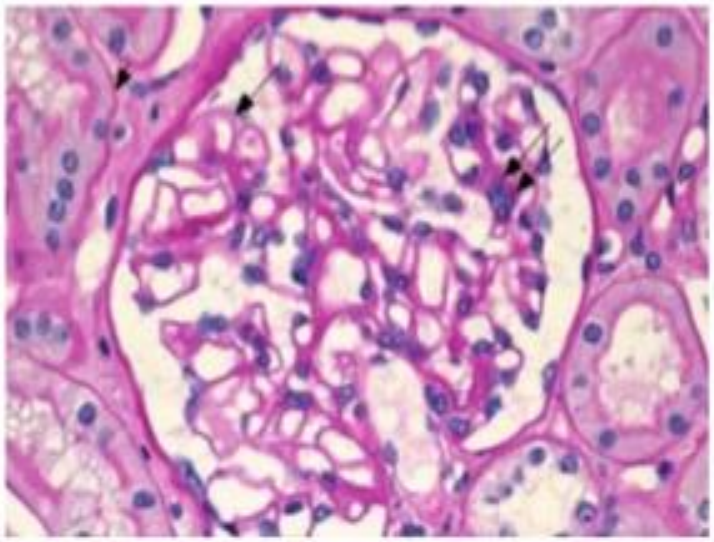
- Second most common cause of primary nephrotic syndrome in adults
- Associated with hepatitis B infection
- Autoimmune diseases, thyroid disease, use of certain drugs
- Underlying cancer – solid tumor

Source: http://dc146.4shared.com/doc/tLt3NKse/preview.html

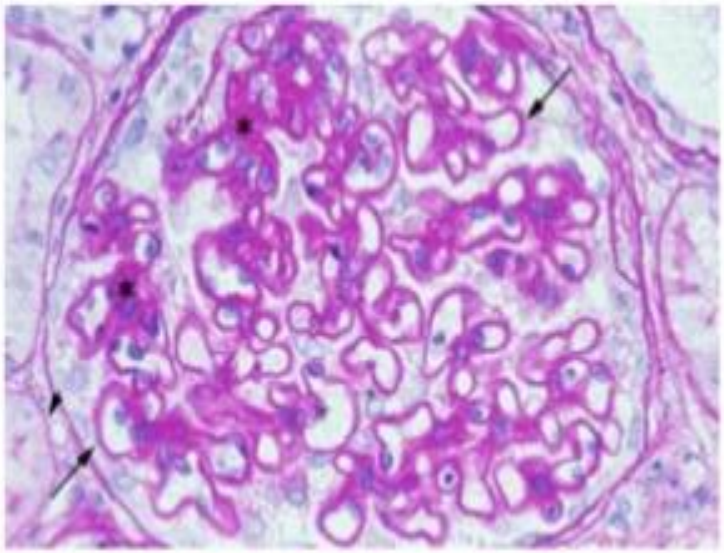
Membranous nephropathy



Light micrograph of membranous nephropathy, showing **diffuse thickening of the glomerular basement membrane** (long arrows) with essentially normal cellularity. Note how the thickness of the glomerular capillary walls is much greater than that of the adjacent tubular basement membranes (short arrow). There are also areas of **mesangial expansion** (asterisks). Immunofluorescence microscopy (showing **granular IgG deposition**) and electron microscopy (showing **subepithelial deposits**) are generally required to confirm the diagnosis. Courtesy of Helmut Rennke, MD.



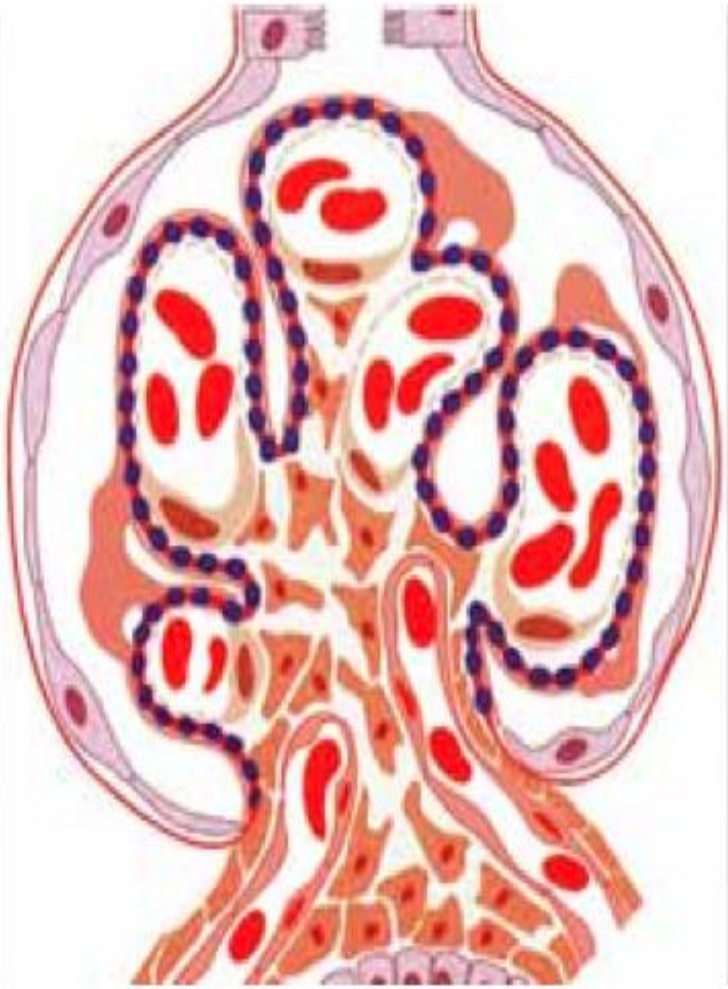
- **Normal Glomerulus**
  - thin GBM (equivalent to tubular basement membrane)
  - mesangium limited to stalk of capillary tuft (double arrows)



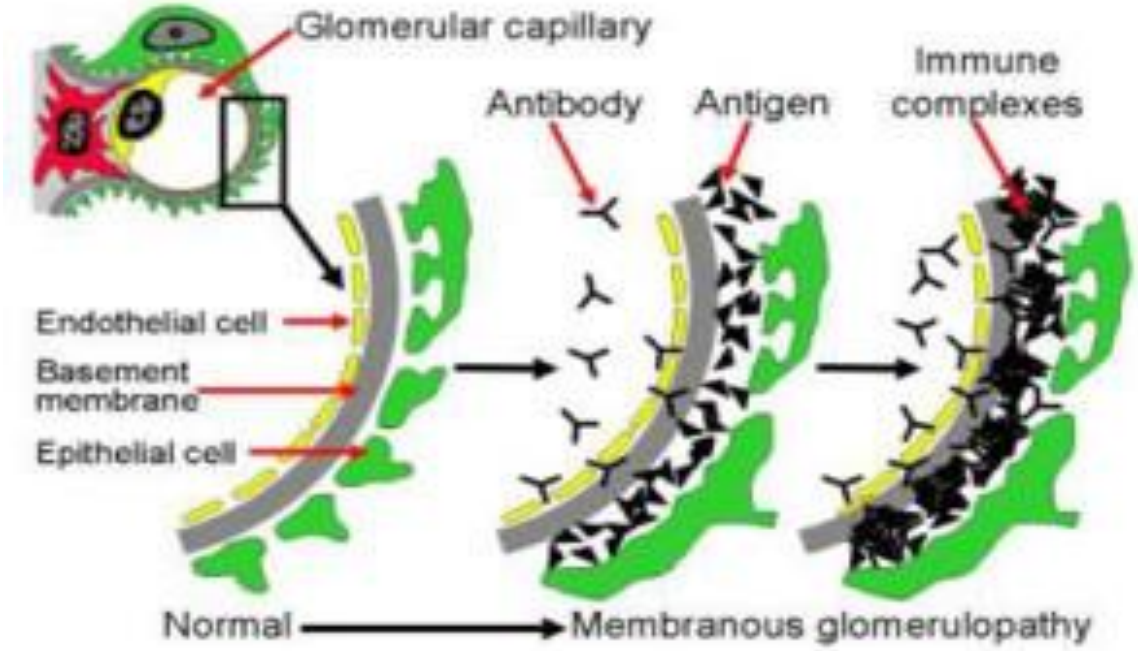
- **Membranous Nephropathy**
  - thick GBM (in relation to tubular basement membrane)
  - mesangial expansion (asterisks)

images from www.uptodate.com

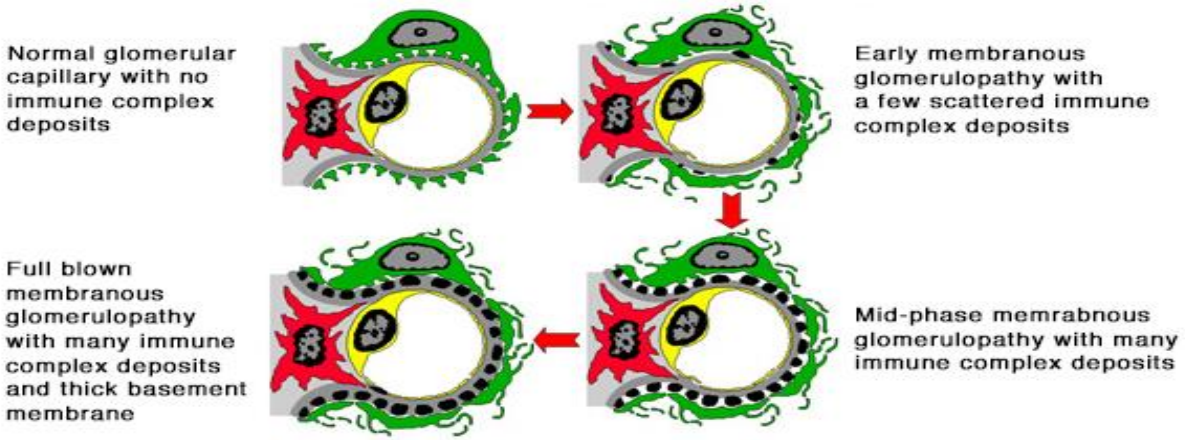
Membranous Nephropathy



- Capillary wall diffusely thickened
- Immune complexes
  - IgG, C3
  - Granular, subepithelial
  - 'Spikes' of basement membrane between deposits



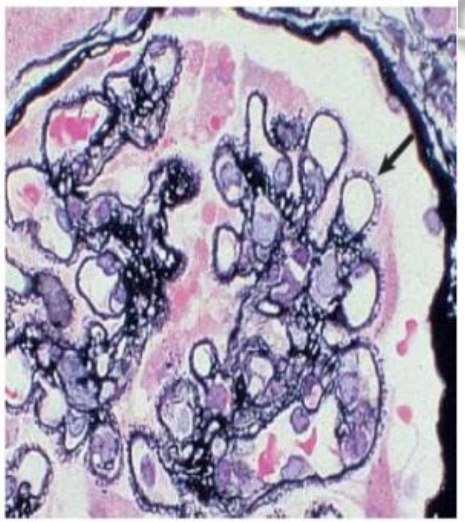
Progressive stages in the development of membranous glomerulopathy

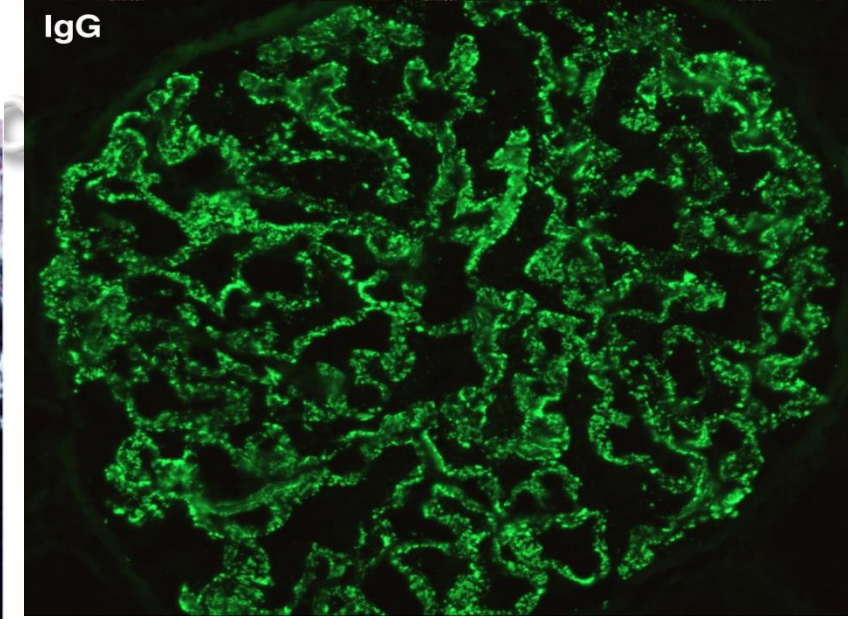


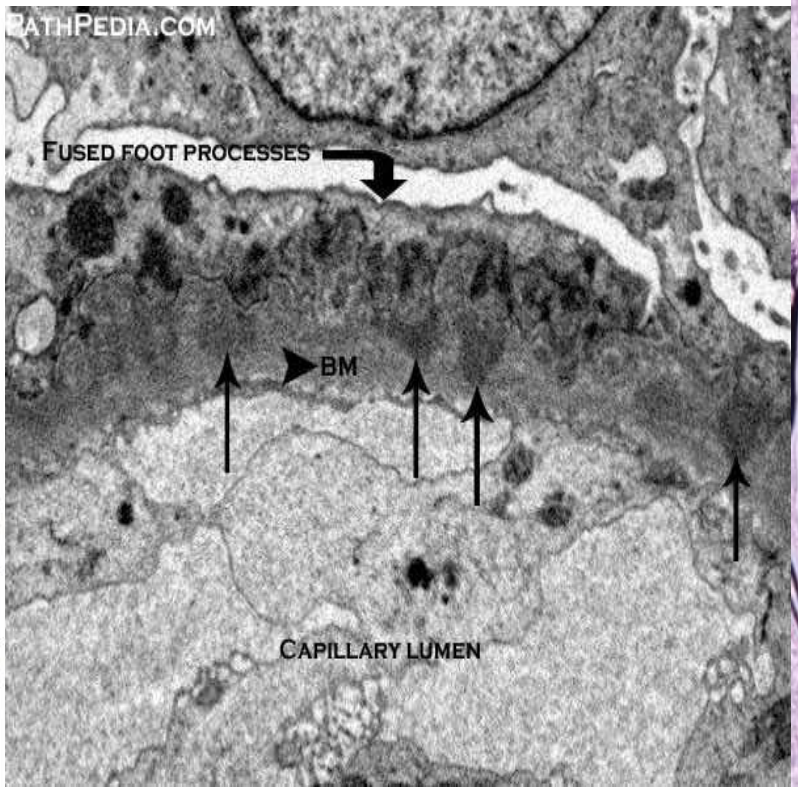
Light Microscopy

- **Morphologically more advanced MN –**

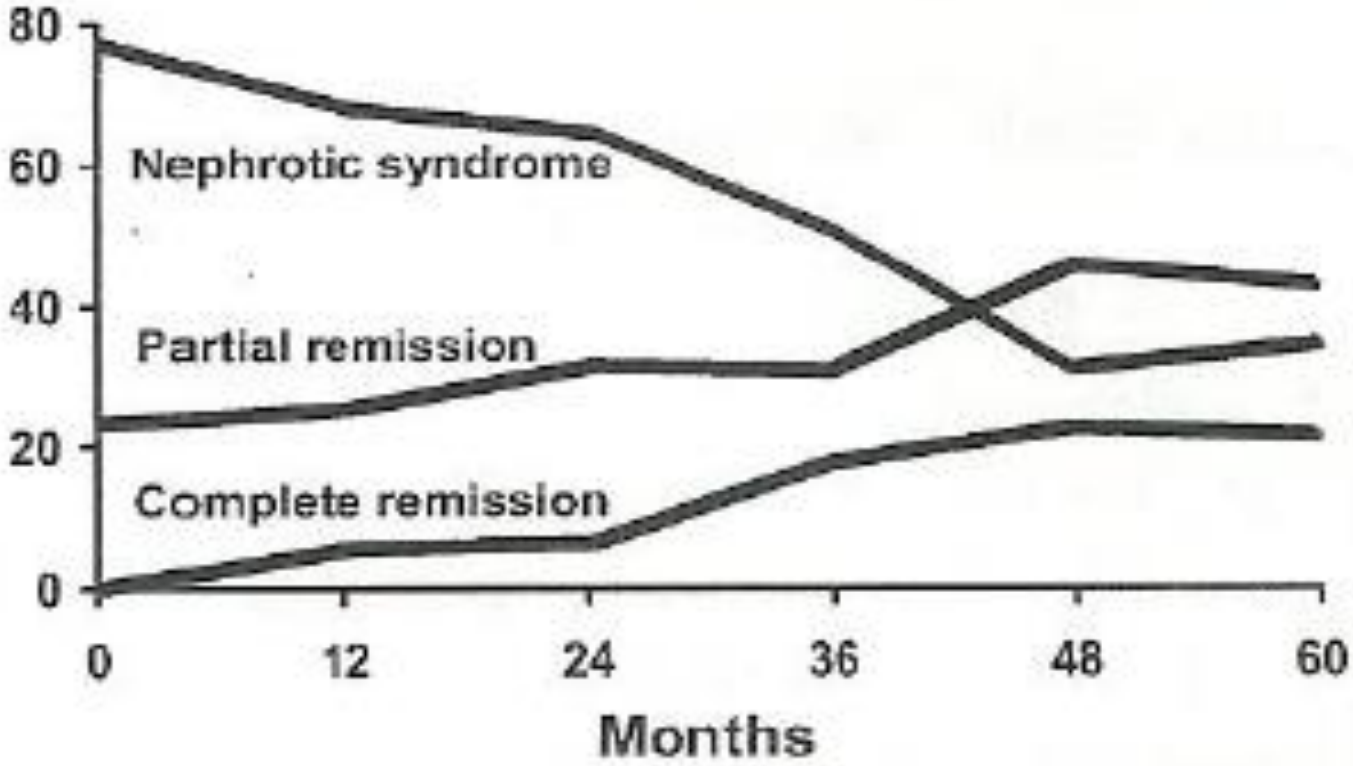
  discrete spikes of matrix emanating from the outer surface of the basement membrane *(arrow) indicative of advanced MN*







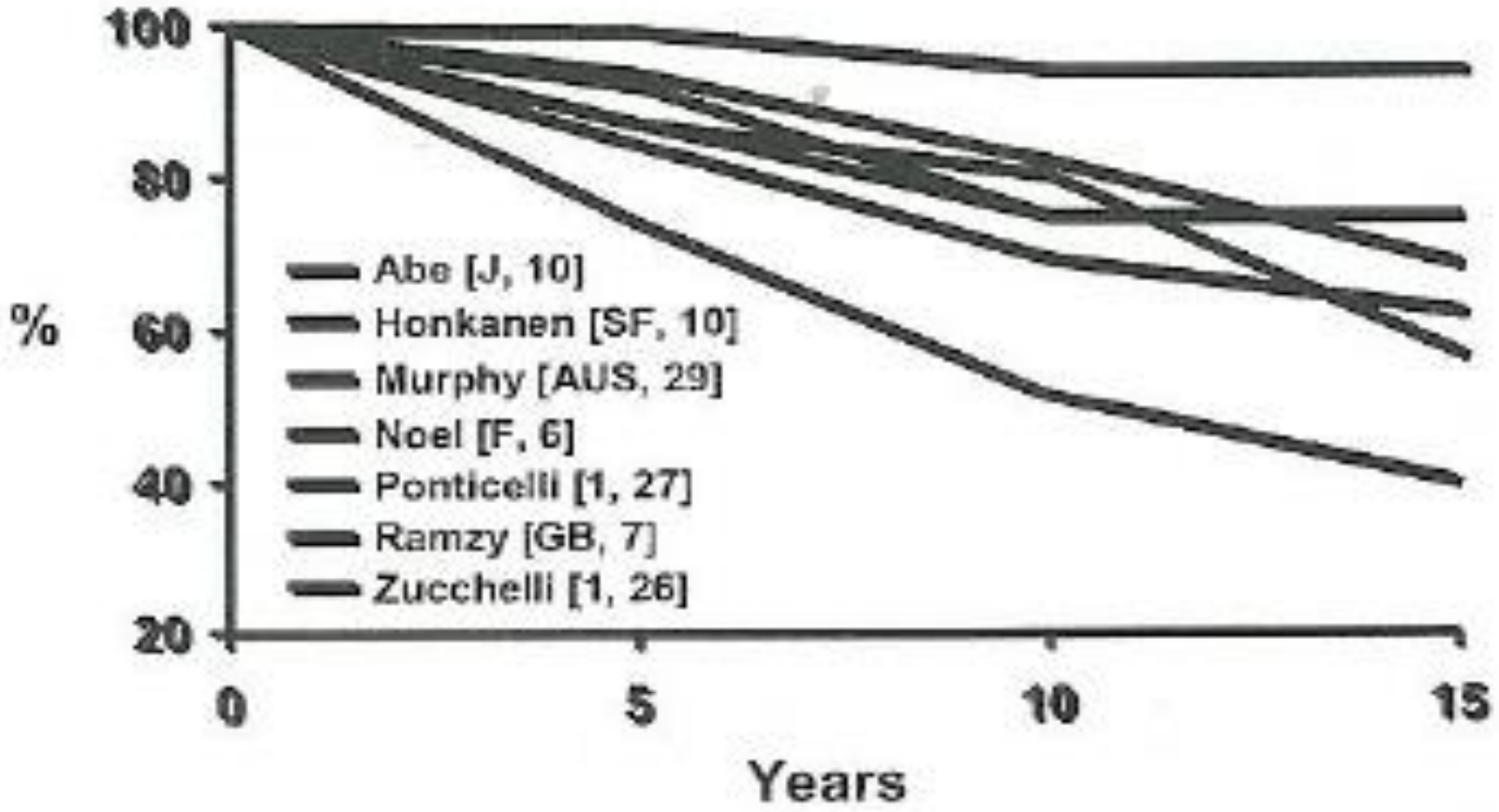
Changes in Clinical Status of Patients with Idiopathic Membranous Nephropathy



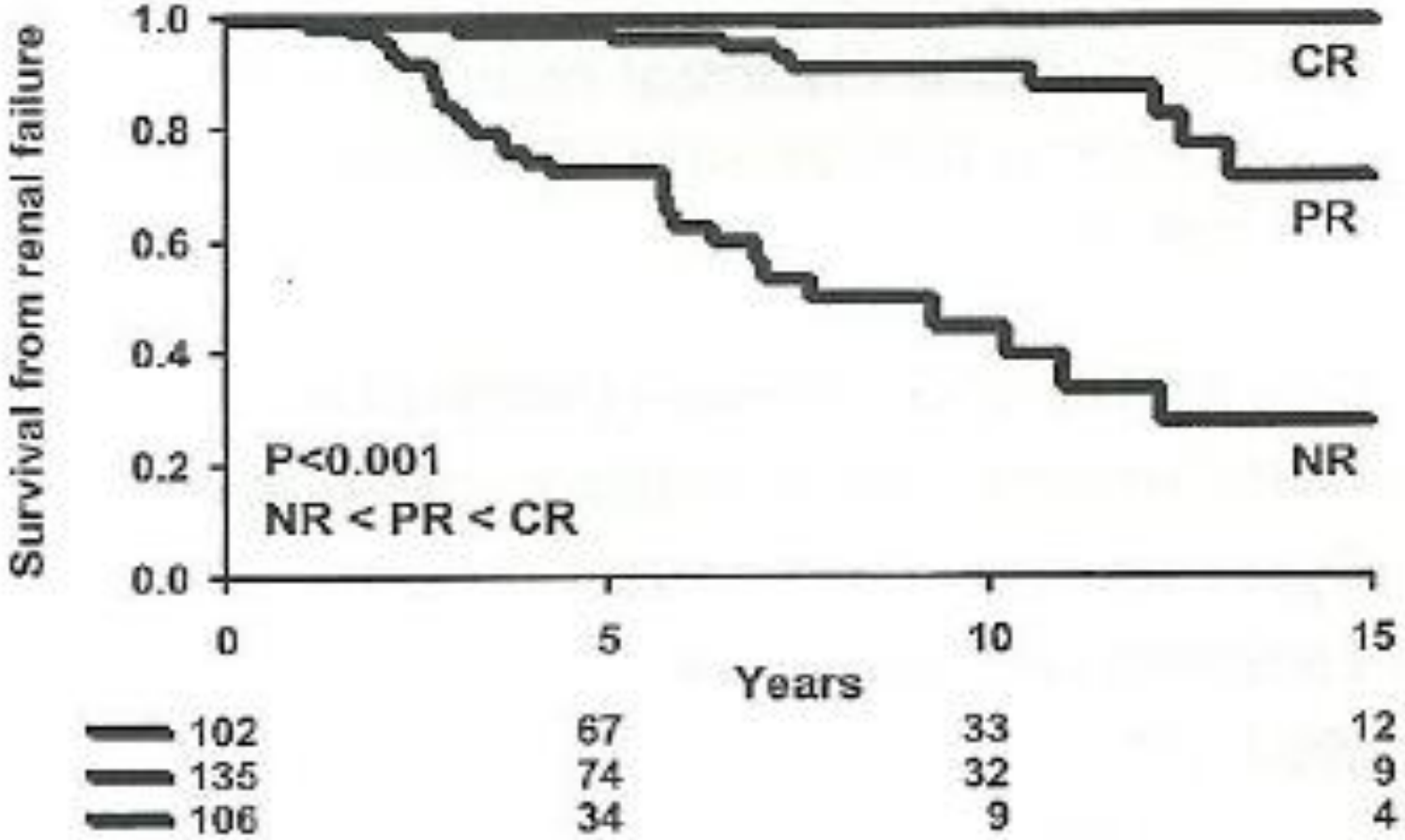
Patients (no.)	100	73	60	51	44	37

Schieppati et al, NEJM 329: 85, 1993

Actuarial Patient Survival Rates for Idiopathic Membranous Nephropathy in 7 Studies

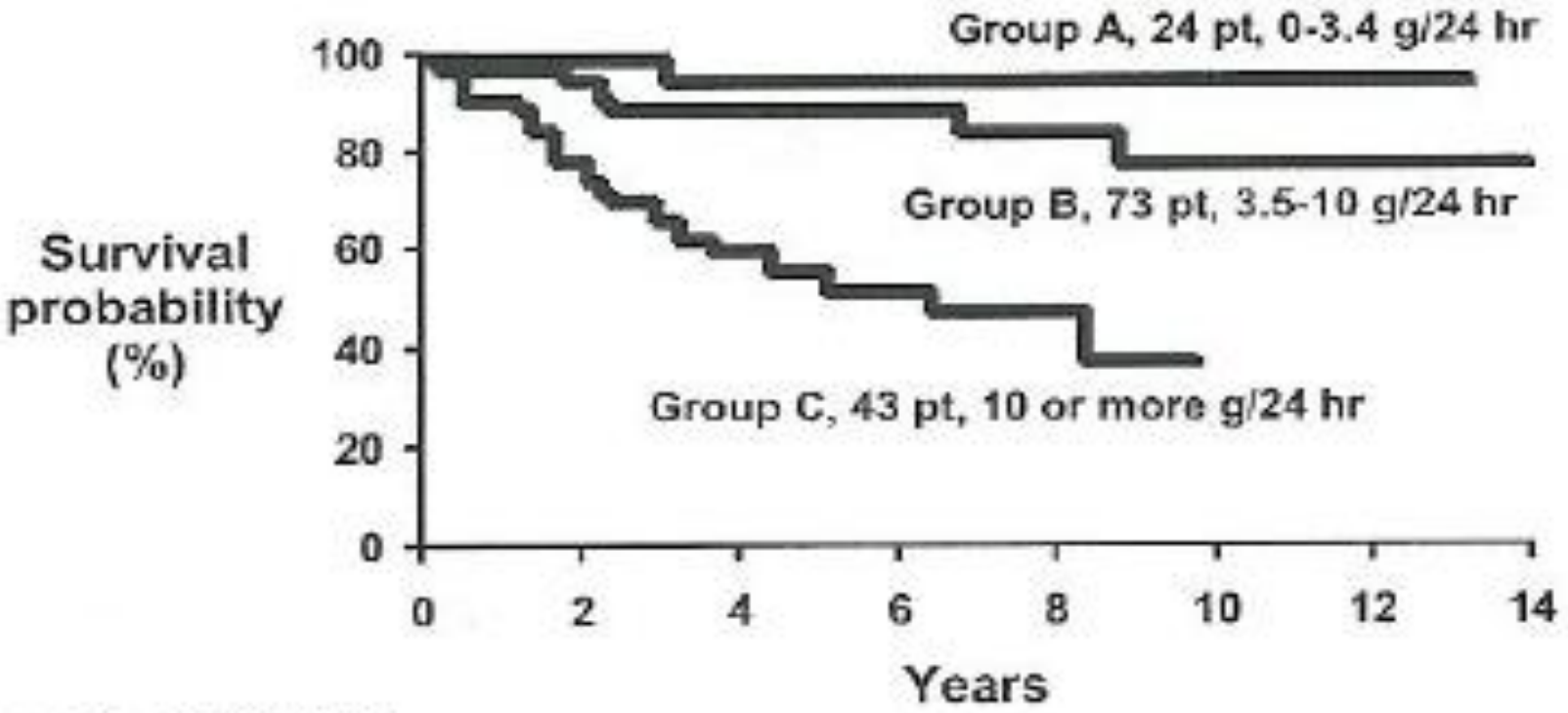


Survival from Renal Failure in Patients with Complete, Partial, and No Remission*



* 5 pt out of 348 had a creatinine clearance <15 mL/min at initial assessment and were excluded from this analysis

Idiopathic Membranous Nephropathy
The Natural History of Untreated Patients
Probability of Surviving Without Developing End-Stage Renal Disease According to Baseline Proteinuria



Donadio et al: KI, 1988

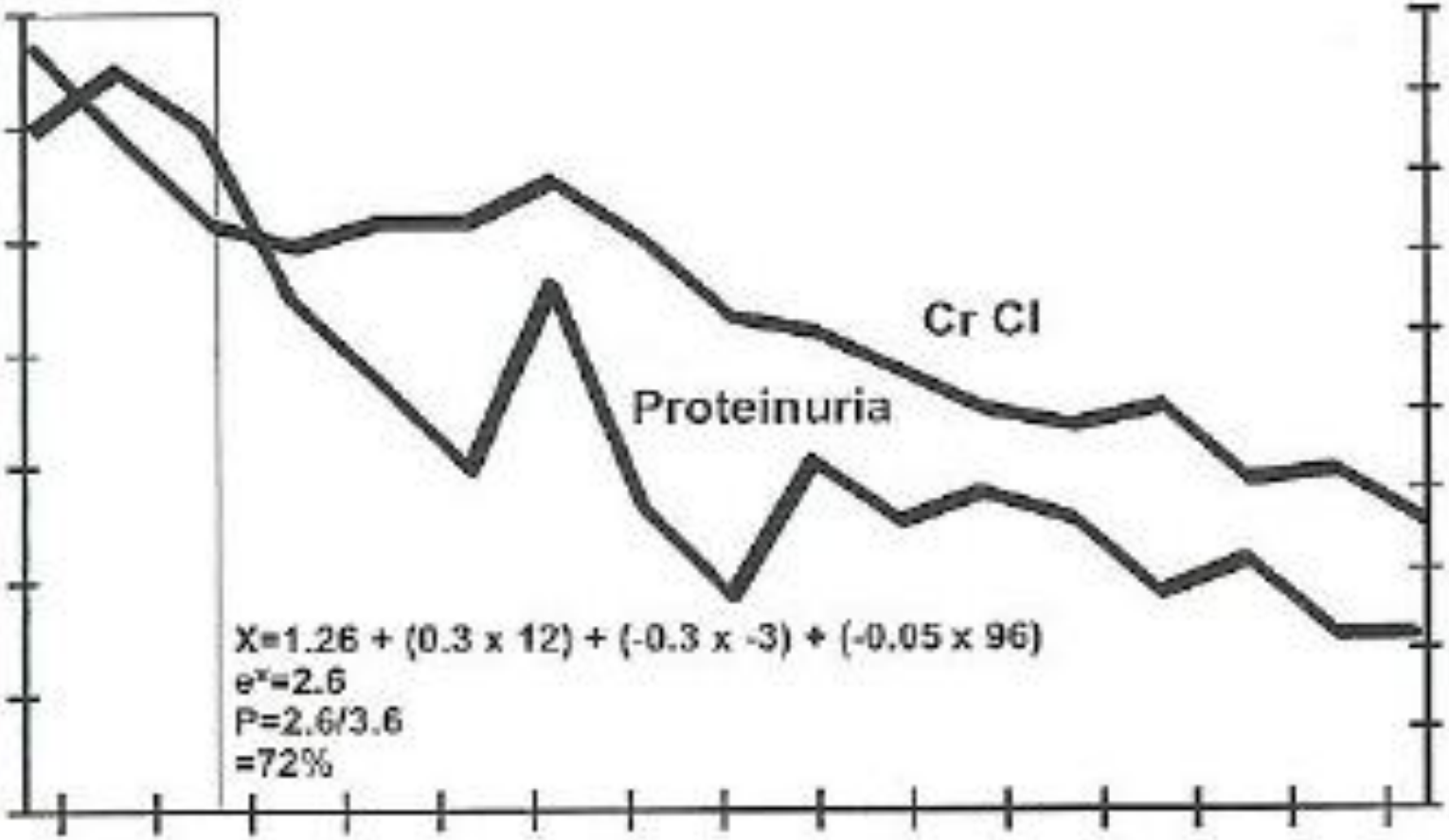
Risk of Progression Categories

Low risk
- Laboratory
- Normal Function
- Proteinuria < 4 g/d

Medium risk
- Normal function
- Persistent proteinuria
  - ≥ 4<8 g/d

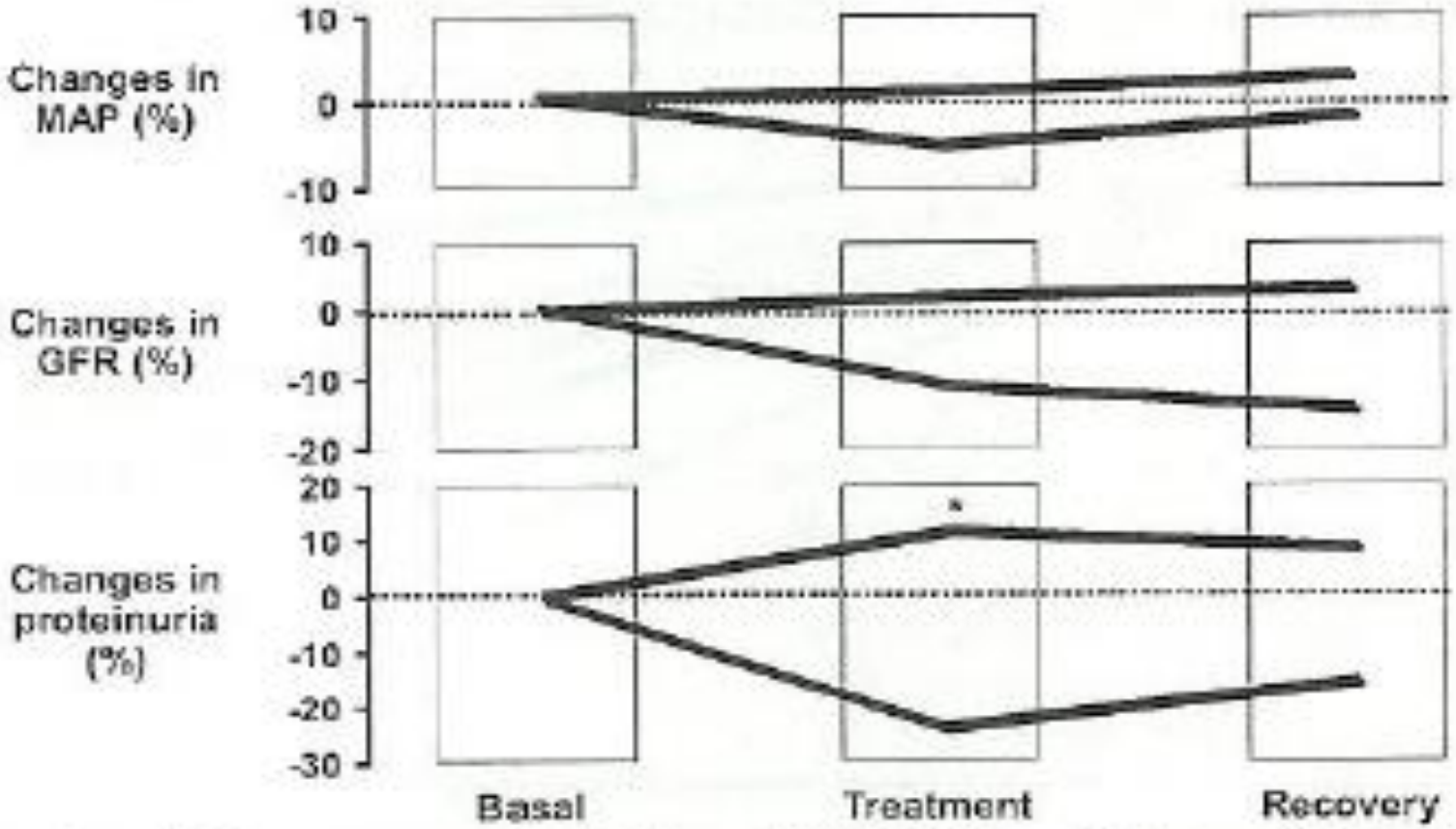
High risk
- Abnormal function and/or
- Persistent proteinuria
  - ≥ 8 g/d

Membranous Nephropathy



Cattran et al. Kidney Int 51: 901-907, 1997.

ACE Inhibition in Membranous Nephropathy



Percentage of changes versus basal values in MAP, GFR, and 24-hour urinary protein excretion rate measured in patients ( ) and controls ( ) at the end of the treatment and recovery periods

Ruggenenti et al: AJKD 35(3):381, 2000

Specific Treatment

Low Risk - Normal renal function and proteinuria < 4g/24h

~ 5% risk of progression

Treatment

i) reduce proteinuria

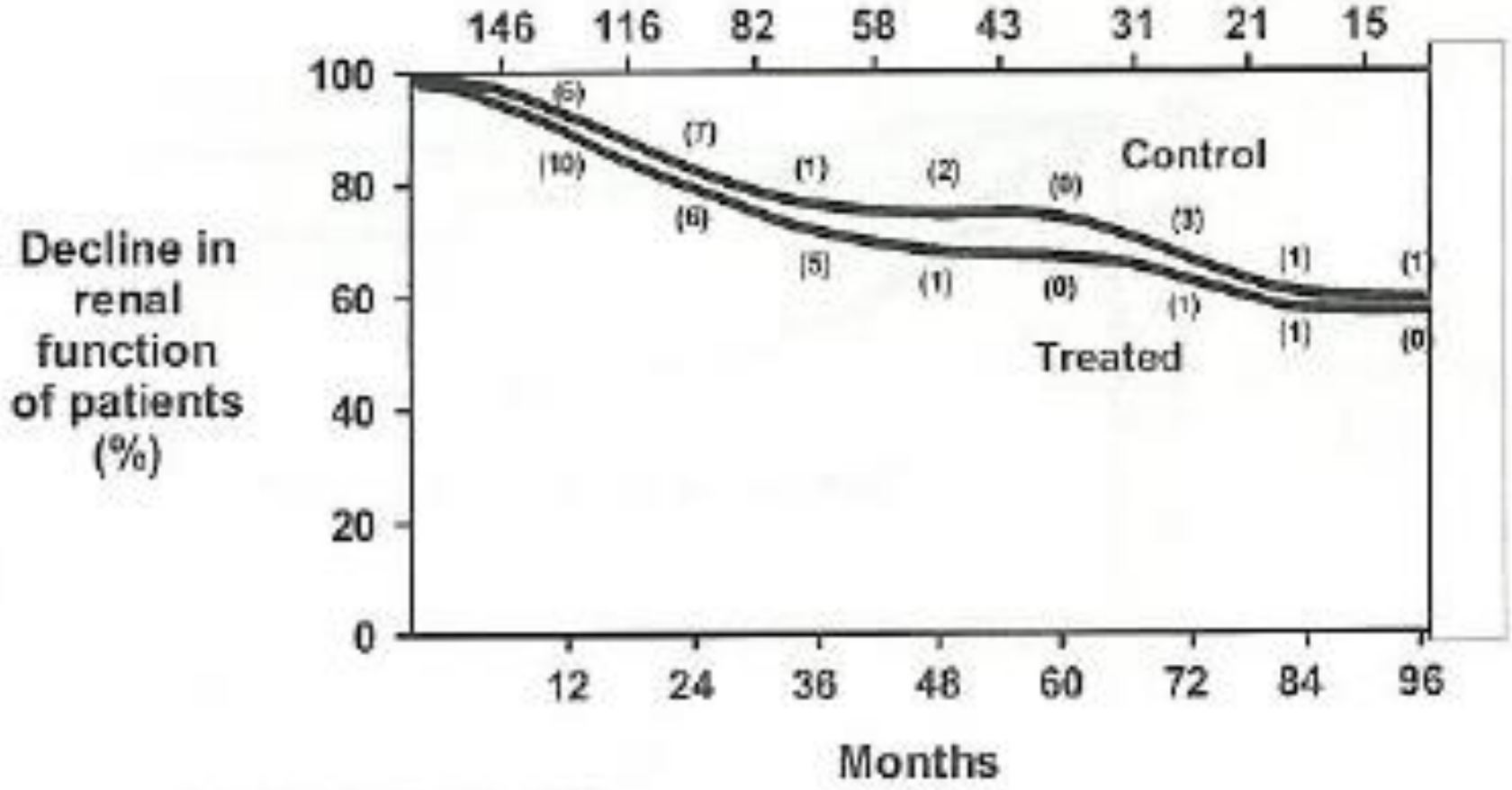
ii) idealize blood pressure

iii) use ACEi-ARB

Continue to monitor

Renal Function in MN Patients Treated with Prednisone vs Controls

Six-month alternate day prednisone 45mg/m2 vs no specific treatment



Cattran et al: NEJM, 320: 210, 1989

Specific Treatment

Medium Risk - Normal renal function and persistent proteinuria (4-8g/24h) over 6 months

Corticosteroids alone – ineffective

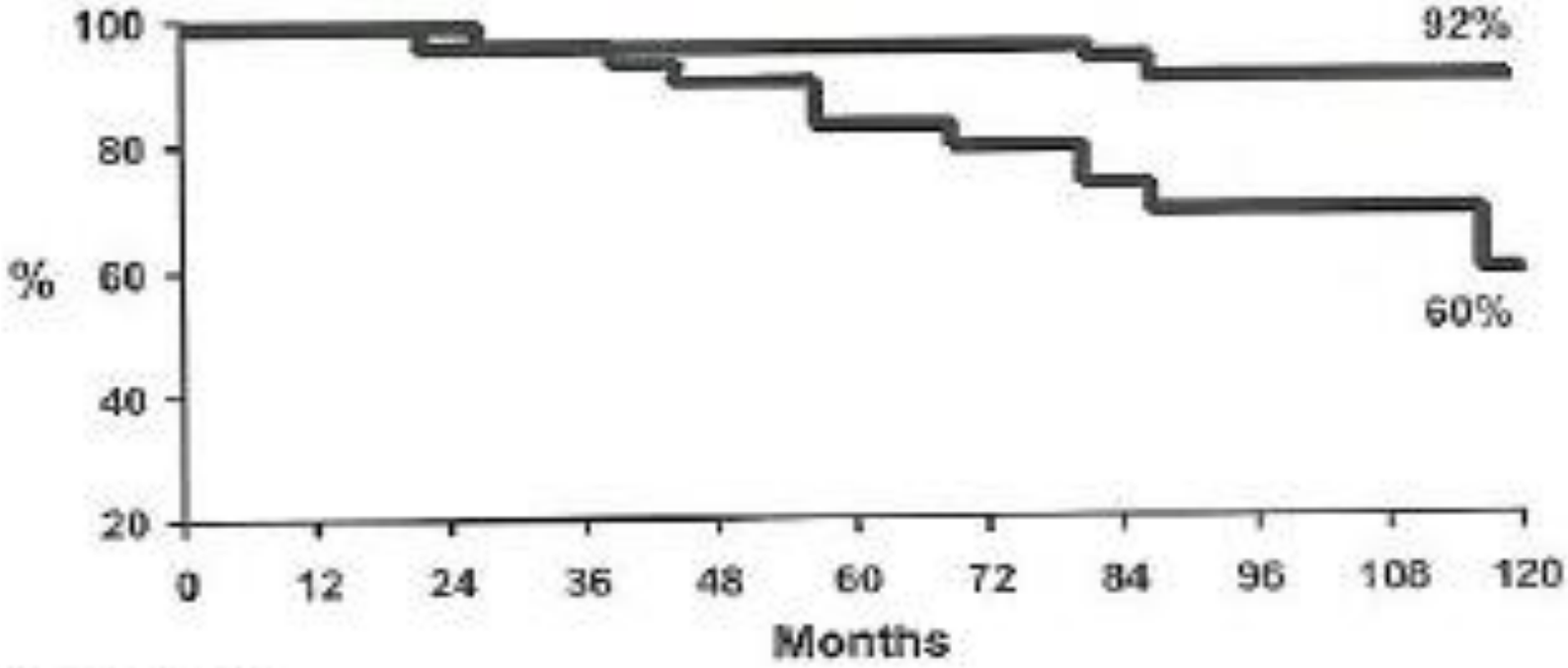
Corticosteroids + cytotoxic – effective

Cyclosporine – effective

Tacrolimus – effective

MMF - ?

A 10-year follow-up - Renal Survival



Treated patients

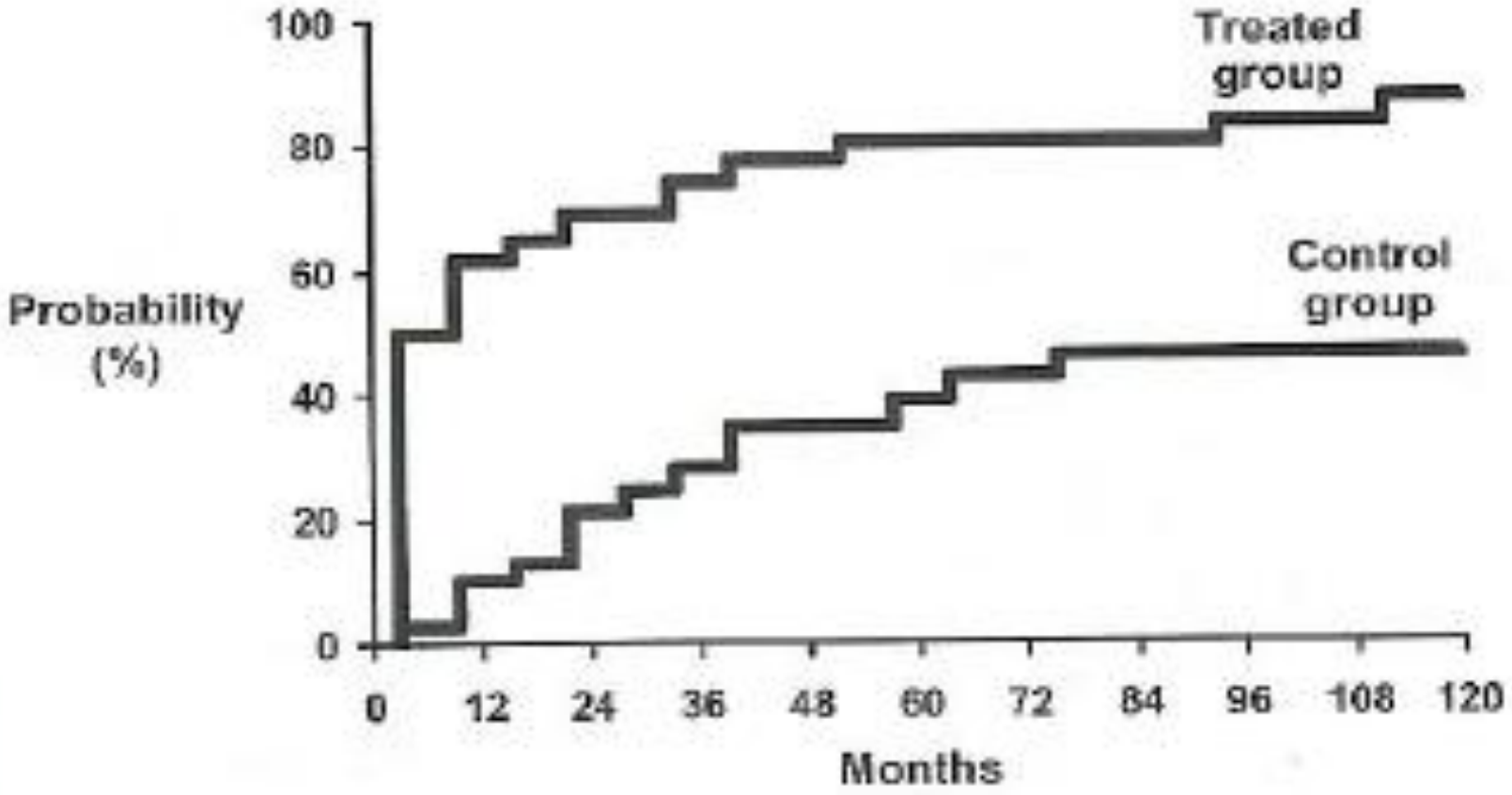
42 42 41 40 40 39 37 37 36 35 34 34 34 33 32 30 30 30 30 30 30

Untreated patients

39 38 36 35 32 29 29 28 28 27 26 25 23 22 20 20 20 20 20 20 17

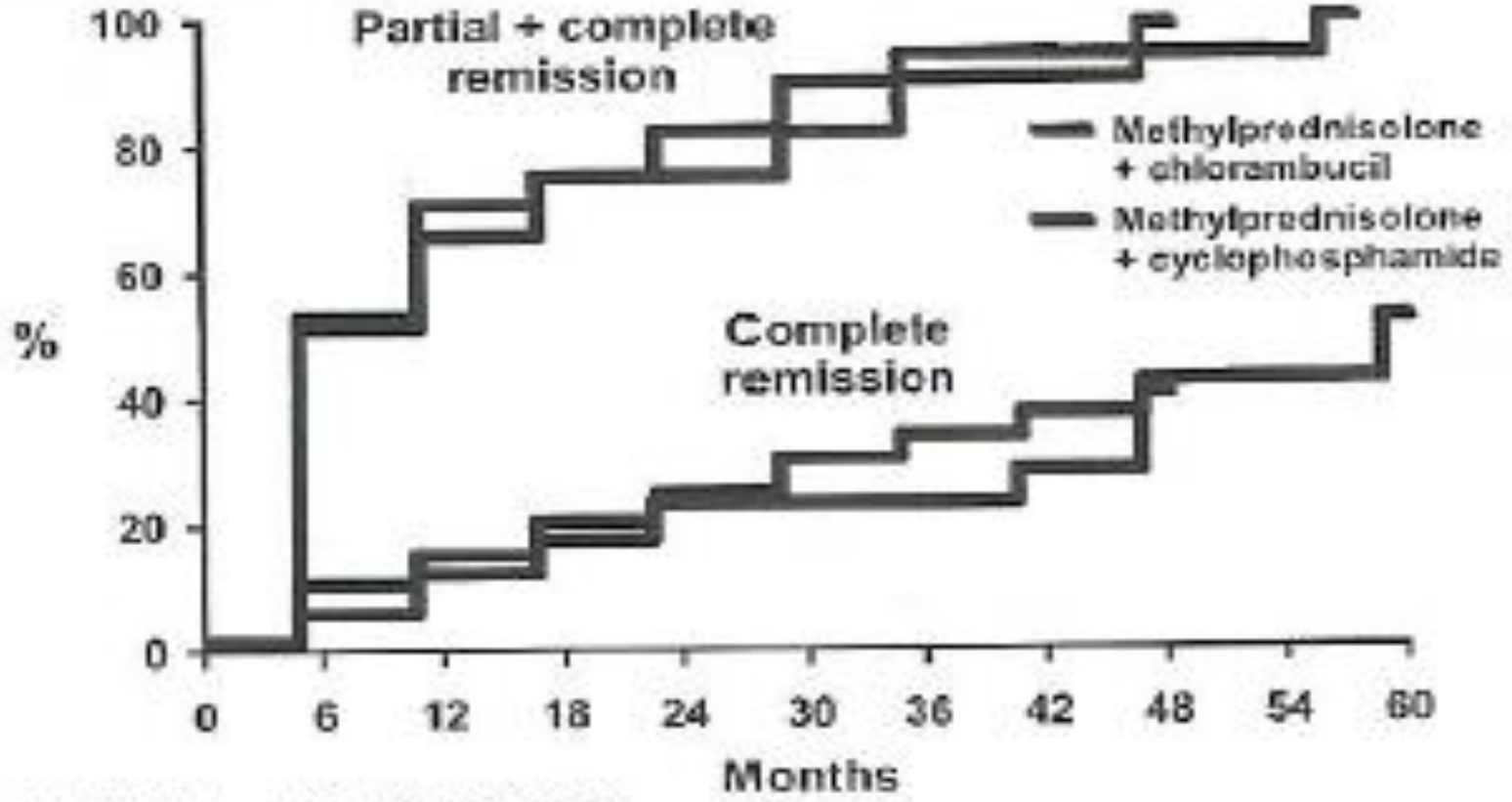
Ponticelli C et al: KI 48;1600, 1995

Probability of (C) or (PR)



Ponticelli et al: K Int 48:1600, 1995

Cumulative Probability of Obtaining (P) or (C) Remission



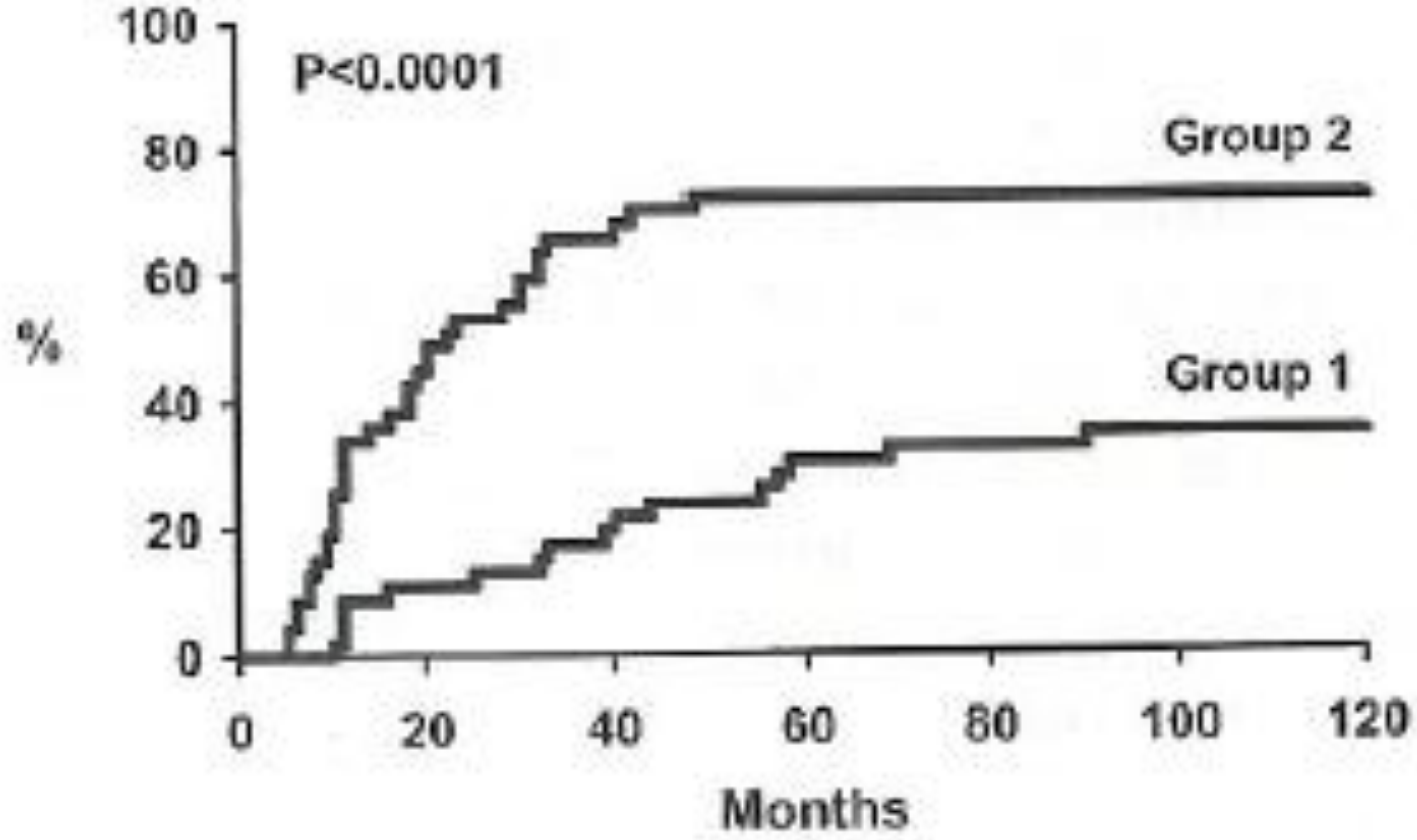
Ponticelli et al: JASN 9:444, 1998

Patient Characteristics in the 2 Groups at Baseline

Characteristic	Group 1	Group 2	P
Cases (no.)	46	47	
Age (yr)	37.2±12.4	38.0 ± 13.6	0.77
Range	16-66	18-64	
Gender ratio	27:19	30:17	0.67
Disease duration (mo)	11.7±6.2	10.8±7.9	0.48
Serum creatinine (mg/dL)	1.17±0.22	1.21±0.31	0.48
MDRD GFR (mL/min)	84±22	89±26	0.32
Serum albumin (g/dL)	2.42±0.81	2.34±0.58	0.58
Serum chol (mg/dL)	306.4±88.2	336.7±99.6	0.12
Proteinuria (g/d)	5.91±2.2	6.11±2.5	0.68

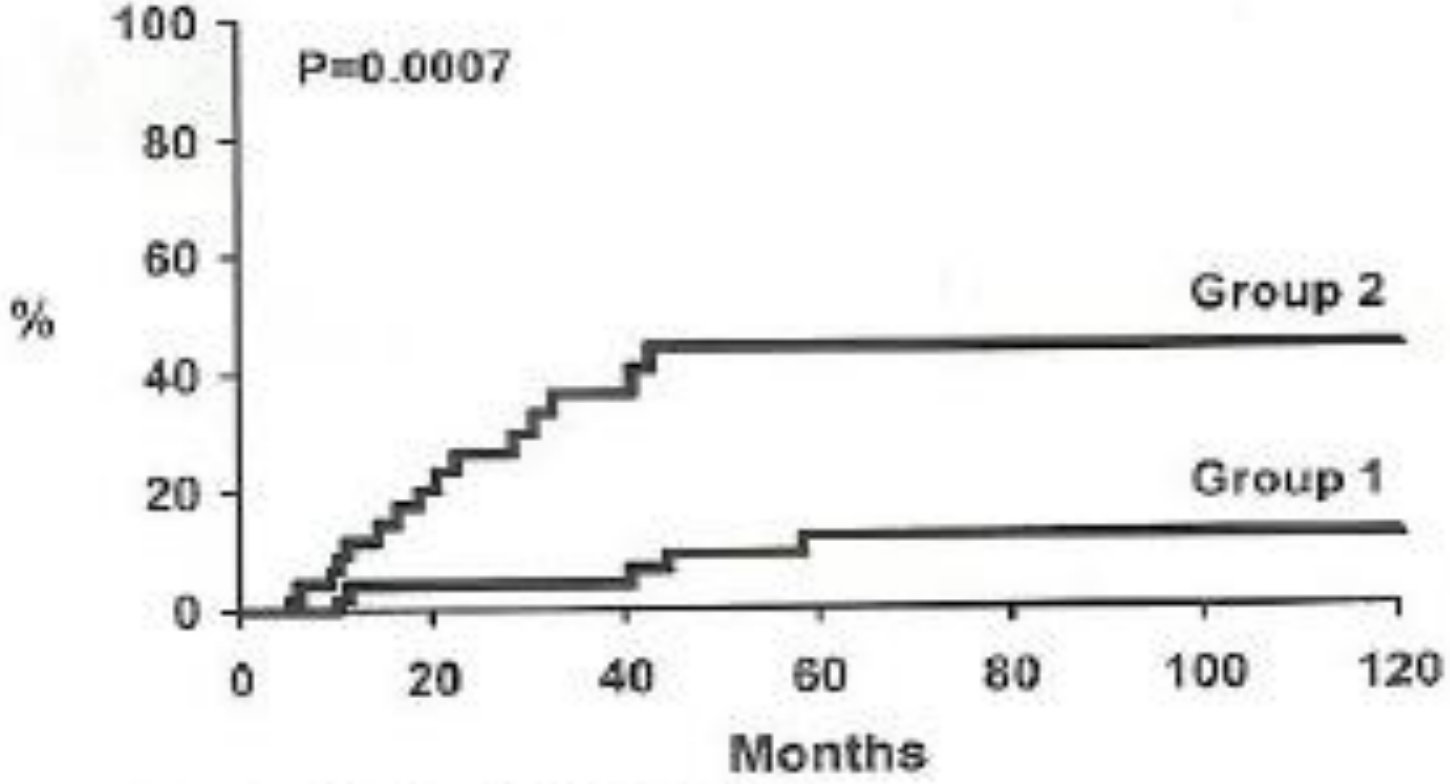
JHA et al: J Am Soc Nephrol 18:1899, 2007

Probability of Reaching a Remission



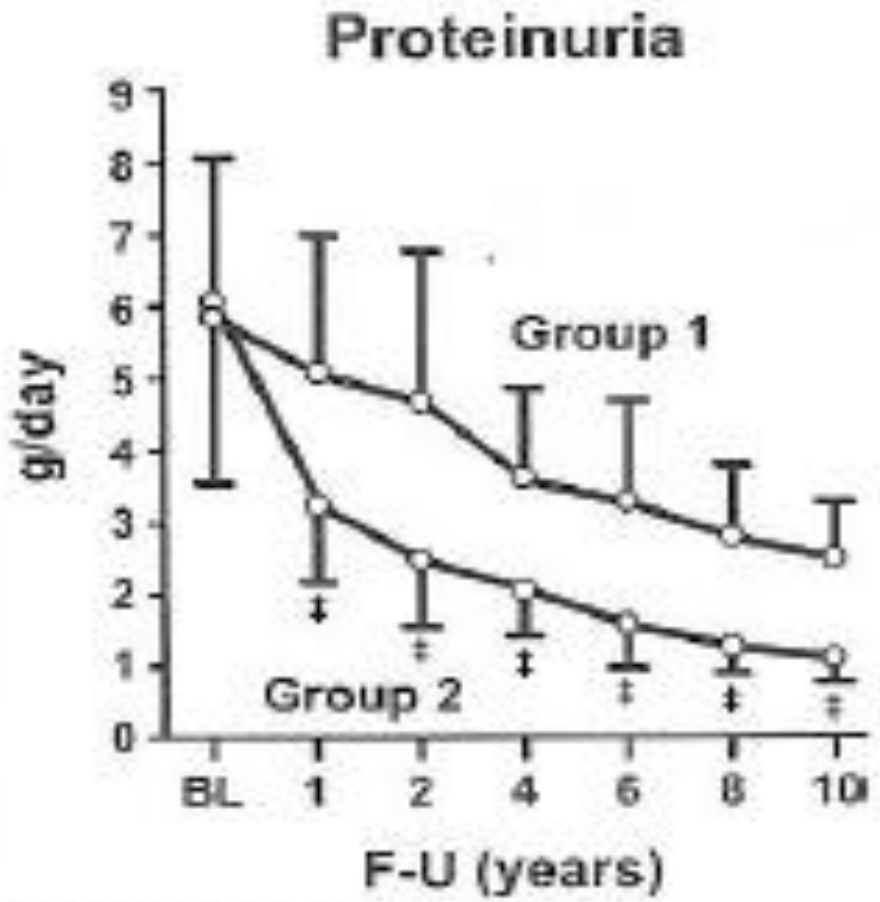
JHA et al: J Am Soc Nephrol 18:1899, 2007

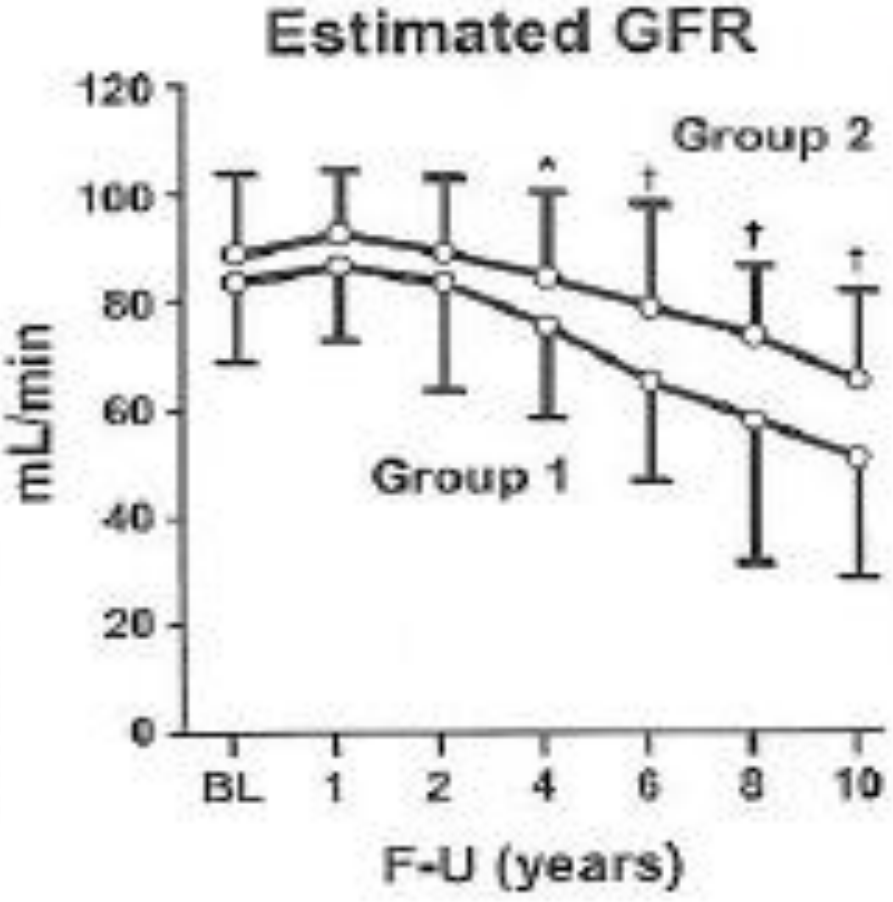
Probability of Reaching Complete Remission



JHA et al: J Am Soc Nephrol 18:1899, 2007

Follow-Up Period





*P<0.05; †P<0.01; ‡P<0.0001

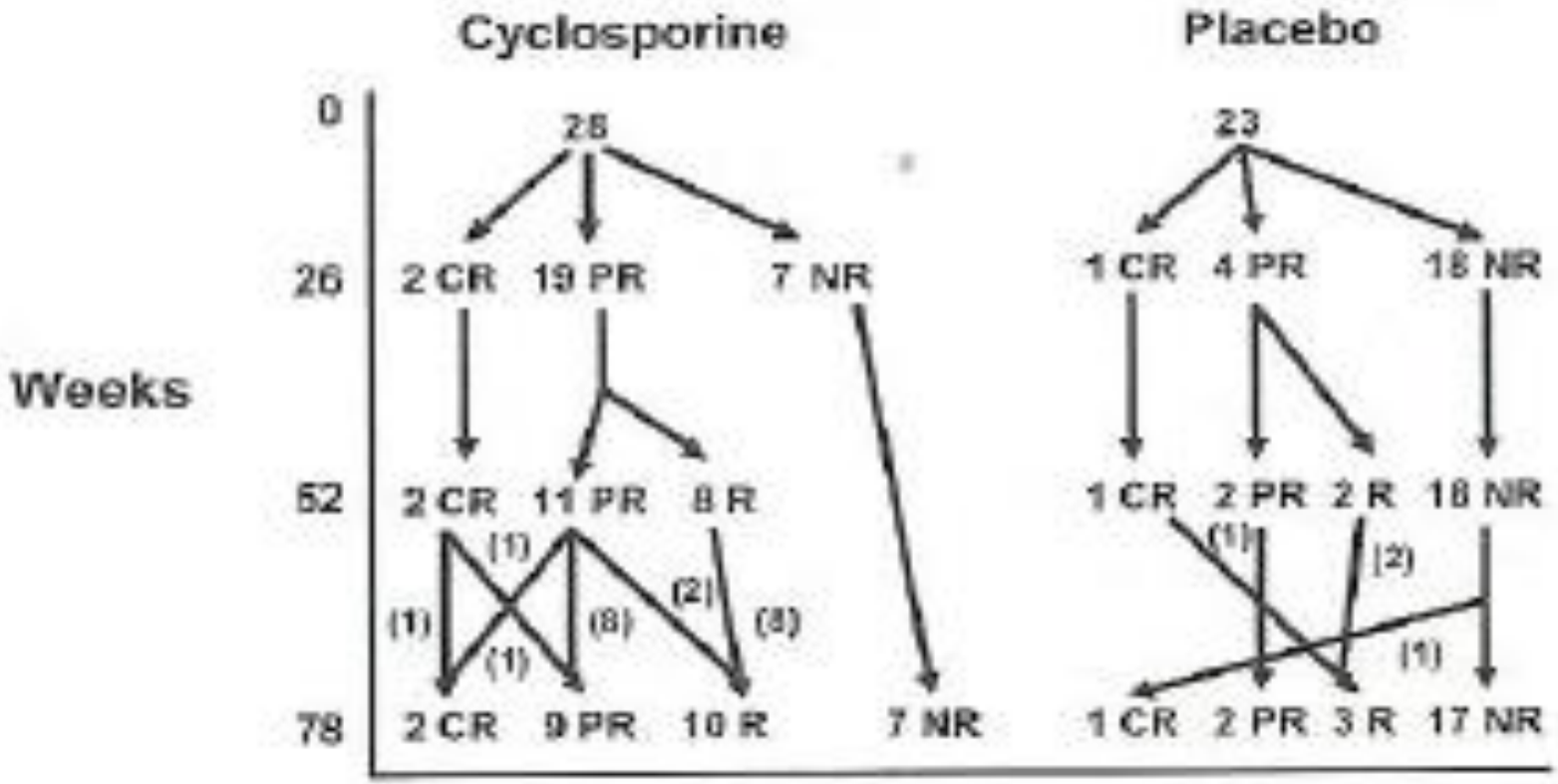
JHA et al: J Am Soc Nephrol 18:1899, 2007

Cyclosporine in Steroid-Resistant MN
Baseline Demographic and Laboratory Data of 51 Randomized Patients

Initial	Placebo n=23	Cyclosporine n=28
Age range	49±14	47±11
Gender (M:F)	16/7	26/2
Blood pressure (mm Hg)		
Systolic	138±16	137±18
Diastolic	84±9	84±7
Racial group, No. (%)		
Caucasians	20 (87)	24 (86)
African-American	0 (0)	1 (4)
Other/mixed	3 (13)	2 (10)
Serum albumin (g/dL)	2.7±0.6	2.8±0.6
Serum creatinine (mg/dL)	1.1±0.3	1.3±0.5
Creatinine clearance (mL/min/1.73 m^2)	95±37	90±27
Proteinuria (g/day)	8.8±4.7	9.7±5.3
Urine urea (g/day)	9.5±3.6	10.3±4.0

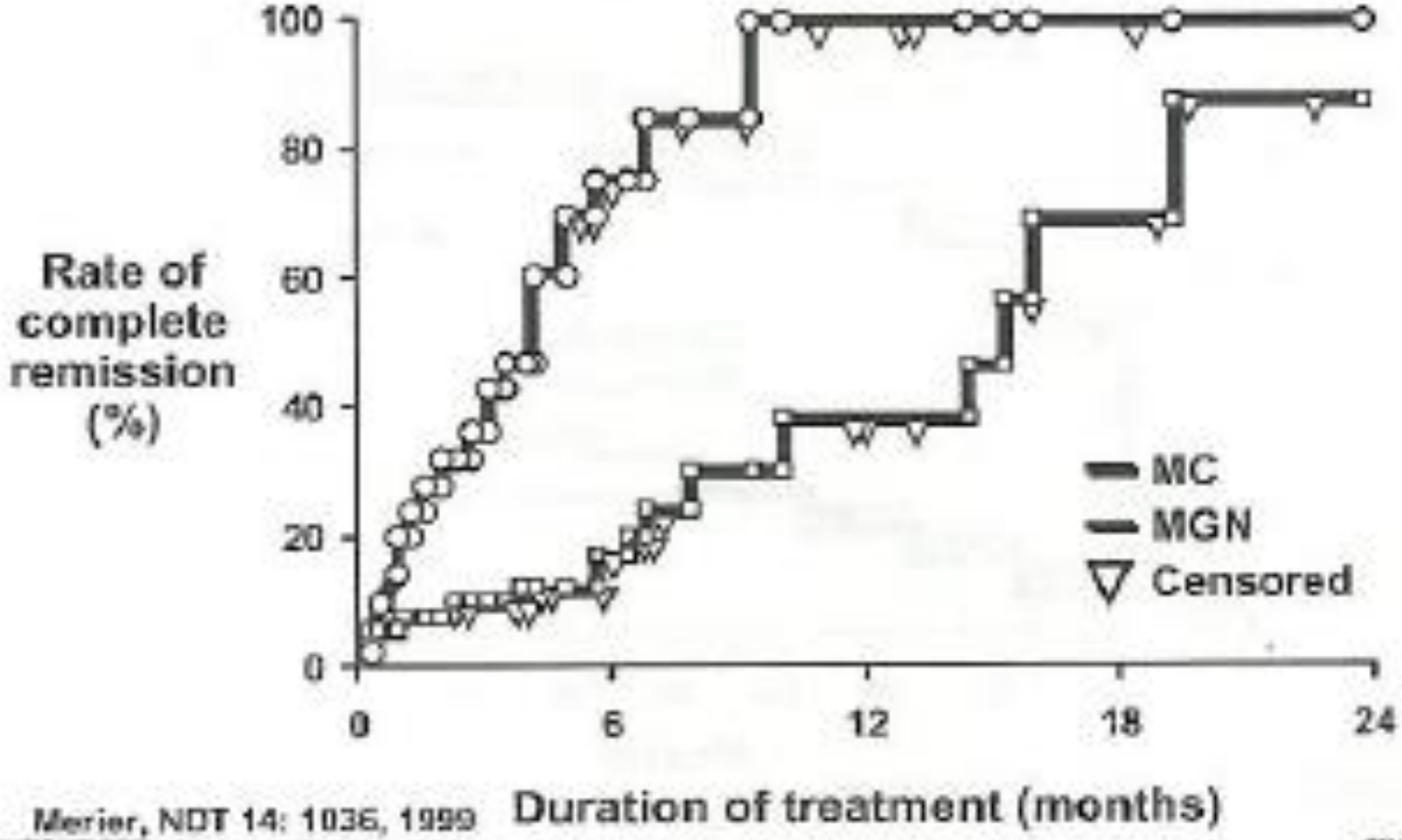
Data ± SD
Cattran et al: KI 59:1484, 2001

Cyclosporine in MGN



Cattran et al: Kidney Int 59:1484, 2001

CyA Treatment in Membranous Nephropathy



Merier, NDT 14: 1036, 1999

Nephrol Dial Transplant (2006) 21: 3127–3132
doi:10.1093/ndt/gfl380
Advance Access publication 13 September 2006

NDT
nephrology dialysis transplantation

Original Article

Induction and long-term treatment with cyclosporine in membranous nephropathy with the nephrotic syndrome

Efstathios Alexopoulos[1], Aikaterini Papagianni[1], Meir Tsouchnikwski[2], Mario Leotsinidis[2] and Dimitrios Memmos[1]

[1]Department of Nephrology and [2]Department of Pathology, Hippokration General Hospital, Thessaloniki, Greece

Initial Treatment

I) Treatment groups
- Pred + CyA 31 patients
- CyA alone 20 patients

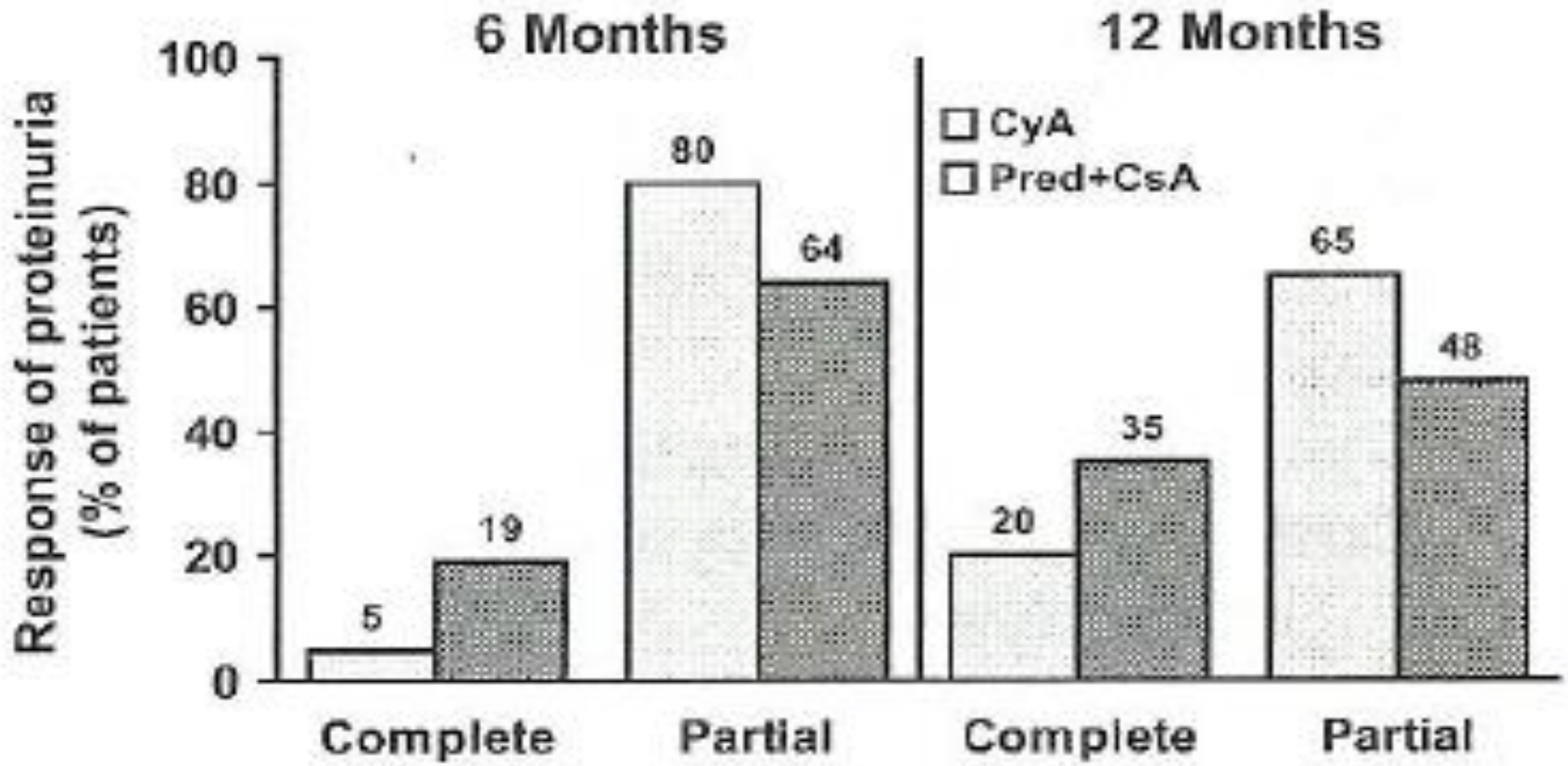
II) Treatment regimen
- Pred 0.6 mg/kg BW with tapering
- CsA 2-3 mg/kg BW

Target whole blood 12-hour trough levels
100-200 ng/mL

III) Duration of treatment
- 12 months

Alexopoulos et al. NDT 21: 3127-3132, 2006

Outcome



Alexopoulos et al. NDT 21: 3127-3132, 2006

Long Term Treatment of IMN

I) Treatment groups

- Pred + CyA 26 patients
- CsA alone 17 patients

II) Treatment regimen

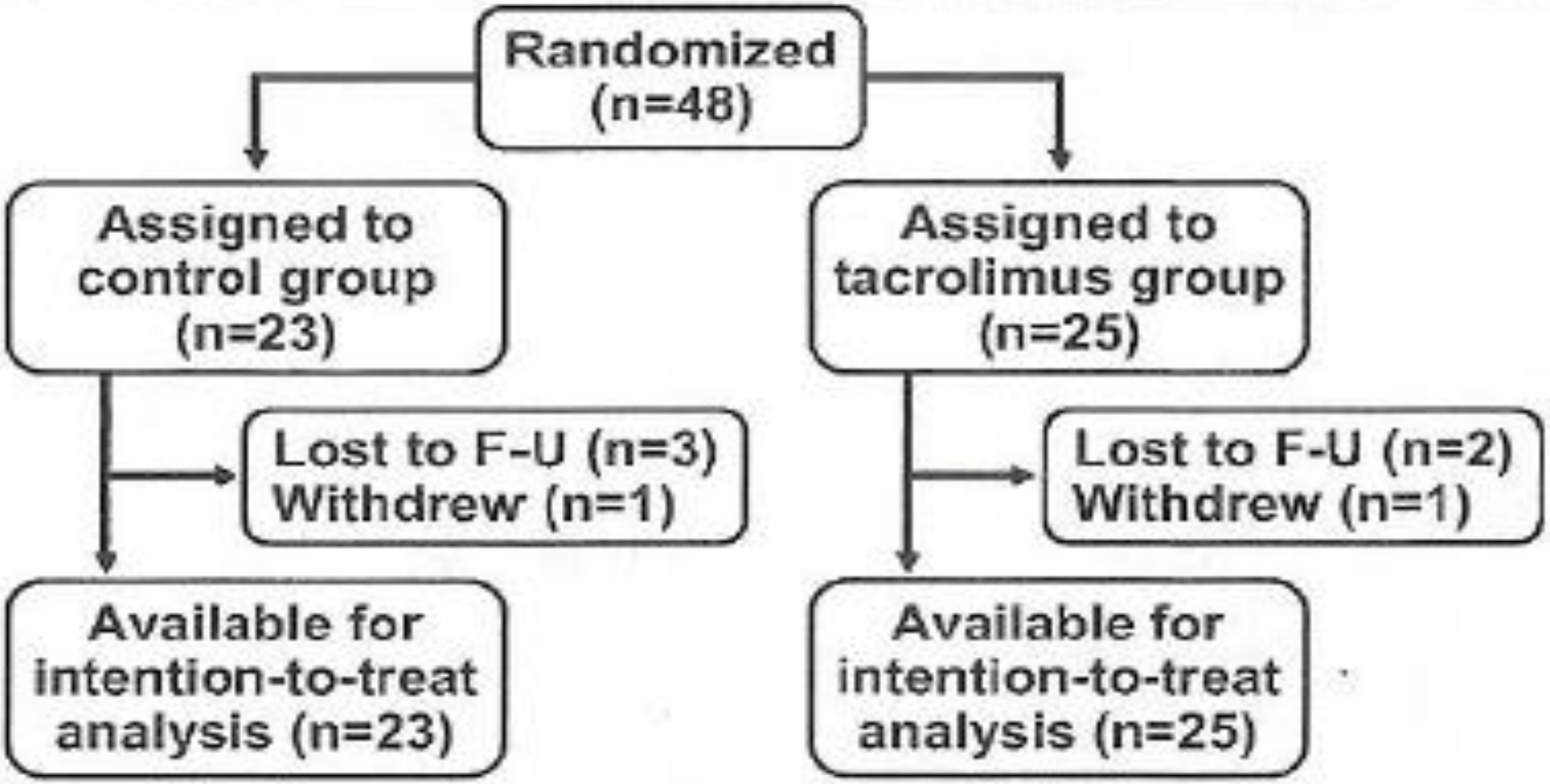
- Pred ~0.1 mg/kg BW
- CSA ~1.5/kg BW over 2 months

Alexopoulos et al. NDT 21: 3127-3132, 2006

Final Outcome

	Pred+CsA n=26		CsA N=17	
Remission	12 months	End of follow-up	12 months	End of follow-up
Complete	11	10	4	4
Partial	15	16	13	13
SCr (mg/dL)	1.3±0.6	1.3±0.4	1.1±0.3	1.1±0.2
Proteinuria (g/24 hr)	1.1±1.7	1.0±1.4	1.1±0.8	1.0±0.7

Tacrolimus Monotherapy Randomized Controlled Trial



Praga et al: Kidney Int, 2007

Tacrolimus Monotherapy
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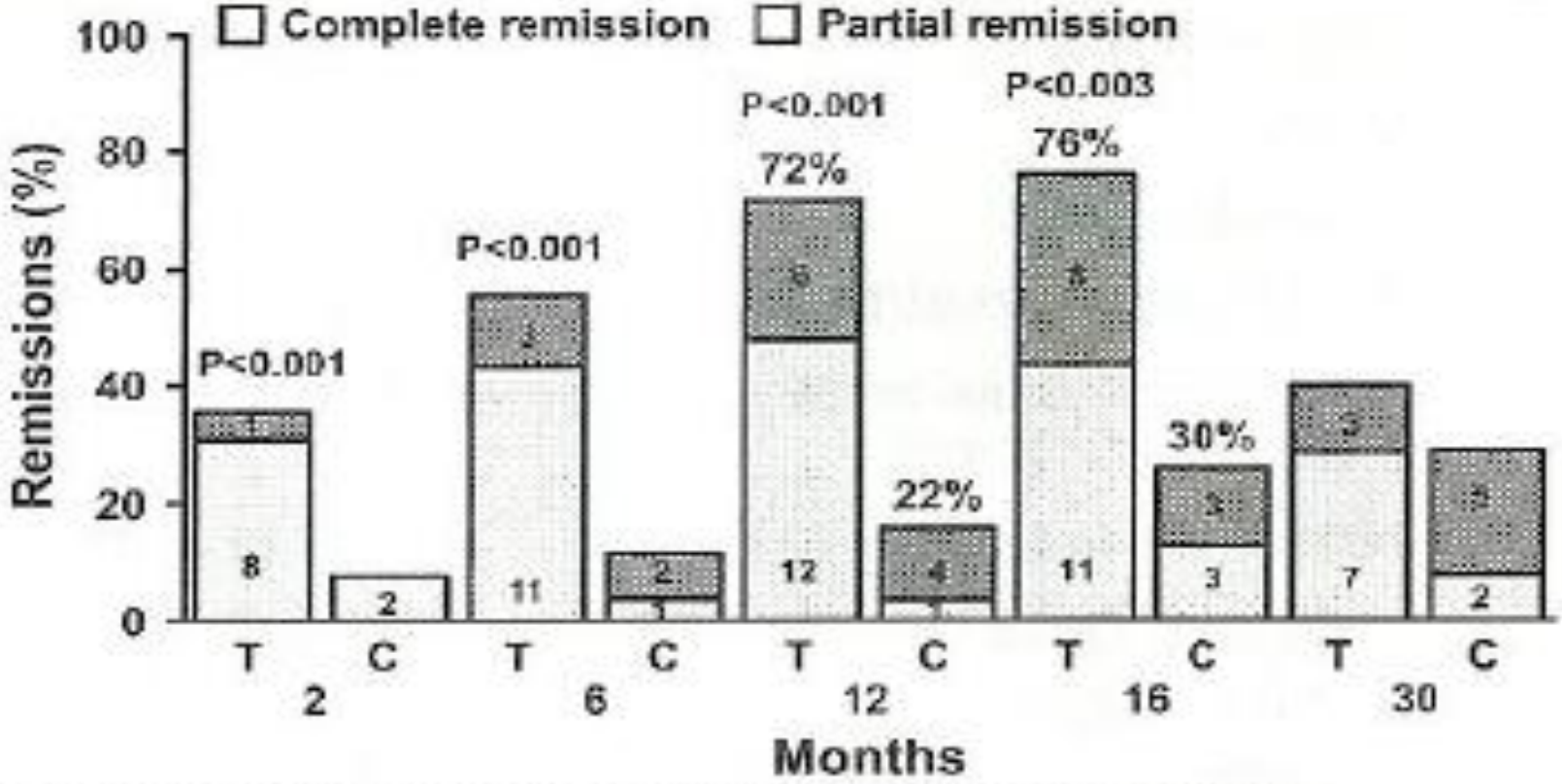


T = tacrolimus; C = control; numbers within columns indicate the total number of pt in CR or PR in both groups

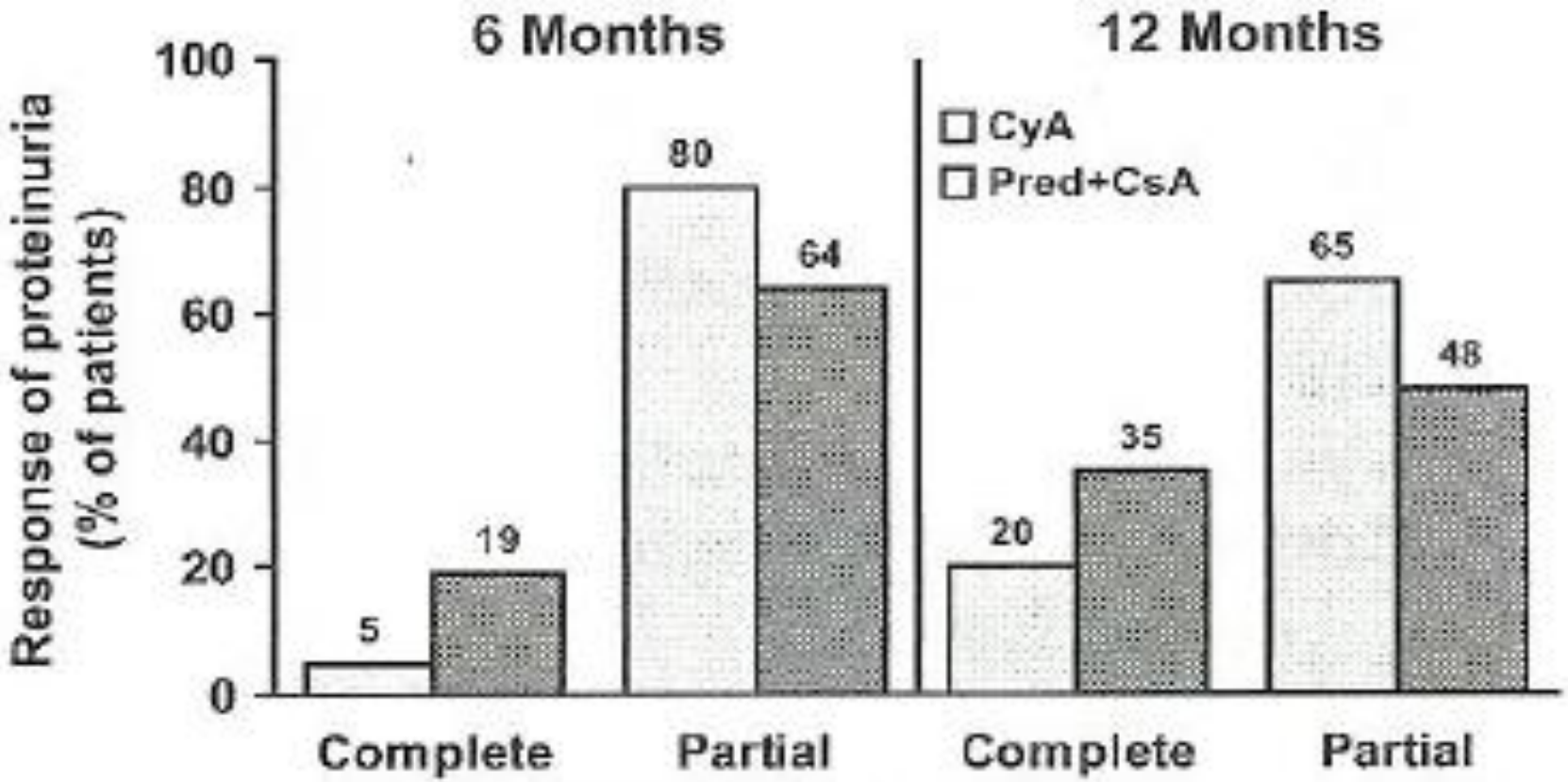
Praga et al: Kid Int, 2007 (in press)

Tacrolimus Monotherapy Randomized Controlled Trial (0.05 mg/kg/day for 12 months; 6 months taper)

	Control (n=23)	Tacrolimus (n=25)	P
Age	50.1±12.2	43.7±12.1	NS
Distribution of ages by tertiles (<40/40-50/>50 yr)	8/4/11	10/9/6	NS
M/F	20/3	20/5	NS
Time since Dx (renal Bx) (mo)	45±66	58±100	NS
Glomerular stage at renal Bx (I, II, III, & IV)	4/18/1/0	4/15/3/0	NS
Scr (mg/dL)	1.1±0.3	0.96±0.2	NS
eGFR (mL/min/1.73 m^2)	107±63	104±26	NS
Dist of eGRF (>90/60-89/ 50-59 mL/min/1.73m^2)	12/7/4	15/9/1	NS
Proteinuria (g/24 hr)	8.4±5.4	7.2±3.3	NS
Dist of proteinuria by tertiles (3.5-5/5-9/>9 g/24 hr)	8/5/10	6/11/8	NS
Serum albumin (g/dL)	2.9±0.8	2.7±0.8	NS
Systolic BP (mm Hg)	133.5±23.5	123.8±16.8	NS
Diastolic BP (mm Hg)	79.7±8.9	73.8±8.6	0.03
Prev Rx with steroids/steroids plus cytotoxics	5/4	6/4	NS

Praga et al: Kid Int, 2007 (in press)

Outcome



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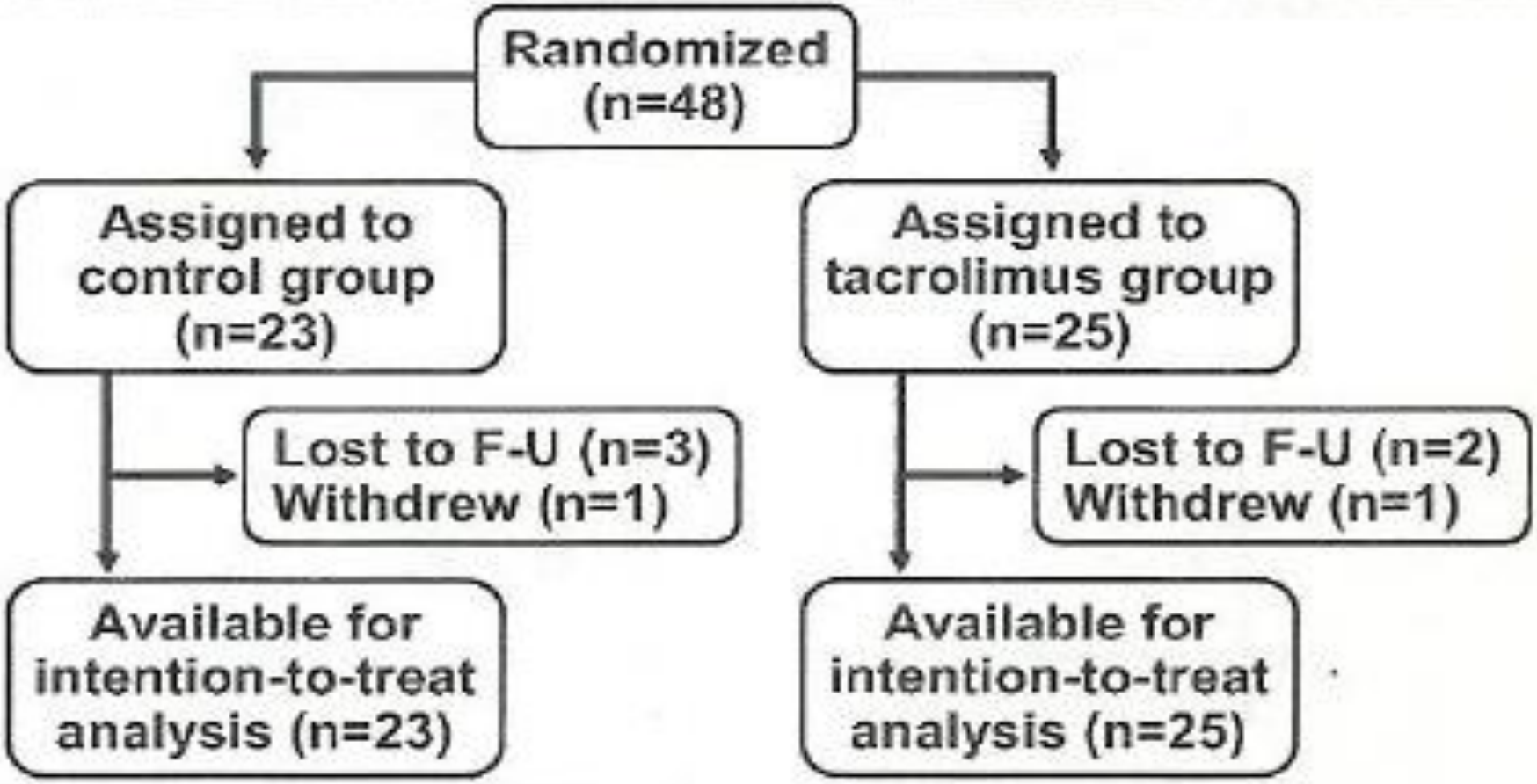
Tacrolimus Monotherapy Randomized Controlled Trial



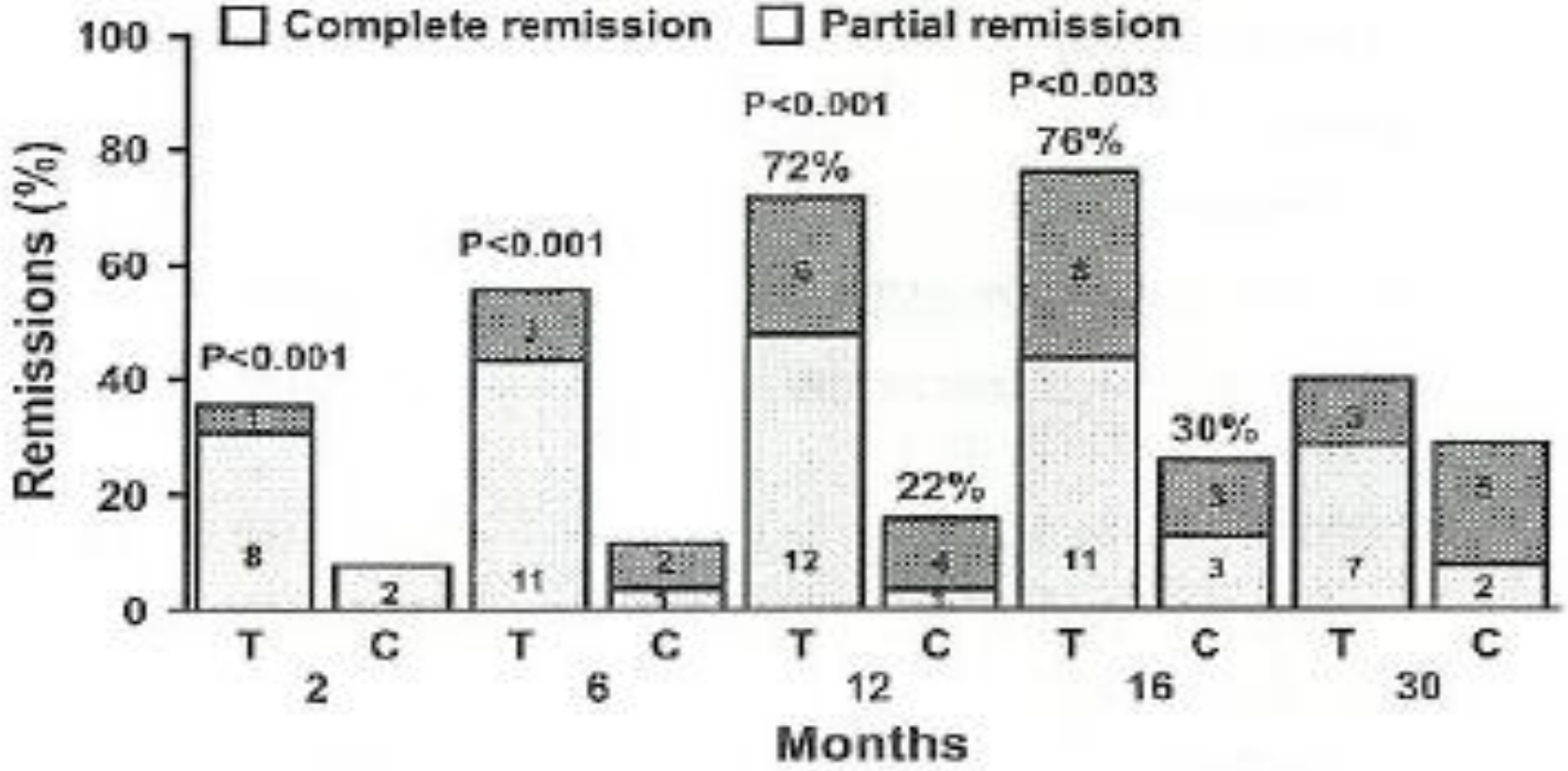
Praga et al: Kidney Int, 2007

Tacrolimus Monotherapy Randomized Controlled Trial (0.05 mg/kg/day for 12 months; 6 months taper)

	Control (n=23)	Tacrolimus (n=25)	P
Age	50.1±12.2	43.7±12.1	NS
Distribution of ages by tertiles (<40/40-50/>50 yr)	8/4/11	10/9/6	NS
M/F	20/3	20/5	NS
Time since Dx (renal Bx) (mo)	45±66	58±100	NS
Glomerular stage at renal Bx (I, II, III, & IV)	4/18/1/0	4/15/3/0	NS
Scr (mg/dL)	1.1±0.3	0.98±0.2	NS
eGFR (mL/min/1.73 m^2)	107±63	104±26	NS
Dist of eGRF (>90/60-89/ 50-59 mL/min/1.73m^2)	12/7/4	15/9/1	NS
Proteinuria (g/24 hr)	8.4±5.4	7.2±3.3	NS
Dist of proteinuria by tertiles (3.5-5/5-9/>9 g/24 hr)	8/5/10	6/11/8	NS
Serum albumin (g/dL)	2.9±0.8	2.7±0.8	NS
Systolic BP (mm Hg)	133.5±23.5	123.8±16.8	NS
Diastolic BP (mm Hg)	79.7±8.9	73.8±8.6	0.03
Prev Rx with steroids/steroids plus cytotoxics	5/4	6/4	NS

Praga et al: Kid Int, 2007 (in press)

Tacrolimus Monotherapy
Randomized Controlled Trial



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Praga et al: Kid Int, 2007 (in press)

Specific Treatment

High Risk (10-15%) - >8g/24h
Proteinuria
  Corticosteroids - ineffective
Progression
  Cyclosporine - effective
  Corticosteroids + cytotoxic
    - effective

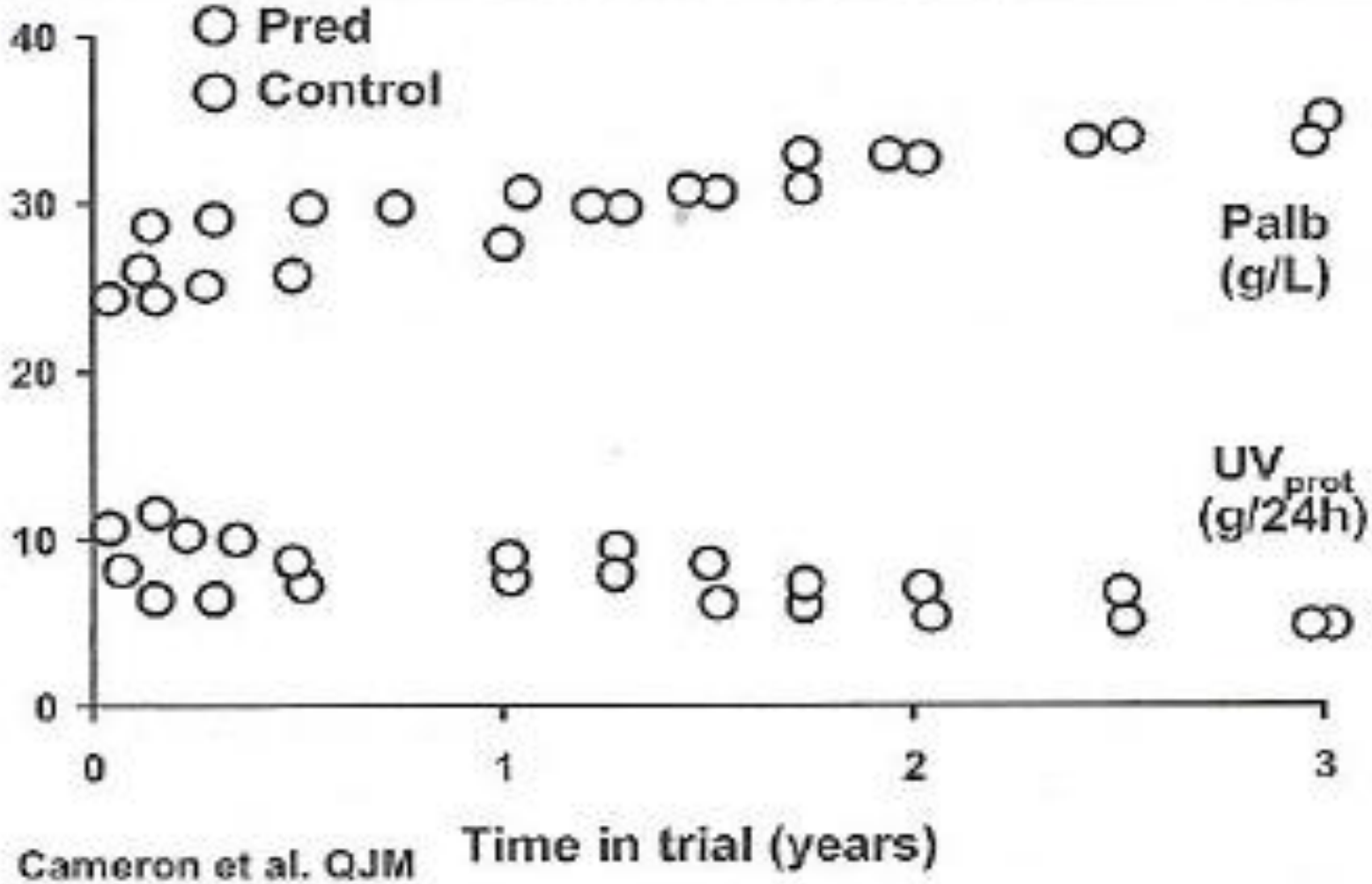
Conclusions

- Cyclosporine (± steroids) for 12 months is effective for inducing remission in most NS patients with IMN and normal or near normal renal function
- The combination increases the changes of CR
- Prolonged treatment with lower doses is a useful and safe way for maintenance of remission provided CsA dose 1.4-1.5 mg/kg/day
- Relapses are more frequent in the monotherapy group, when dose is lower (1.0-1.1 mg/kg) or when CsA levels are below 100 mg/mL

Alexopoulos et al. NDT 21: 3127-3132, 2006

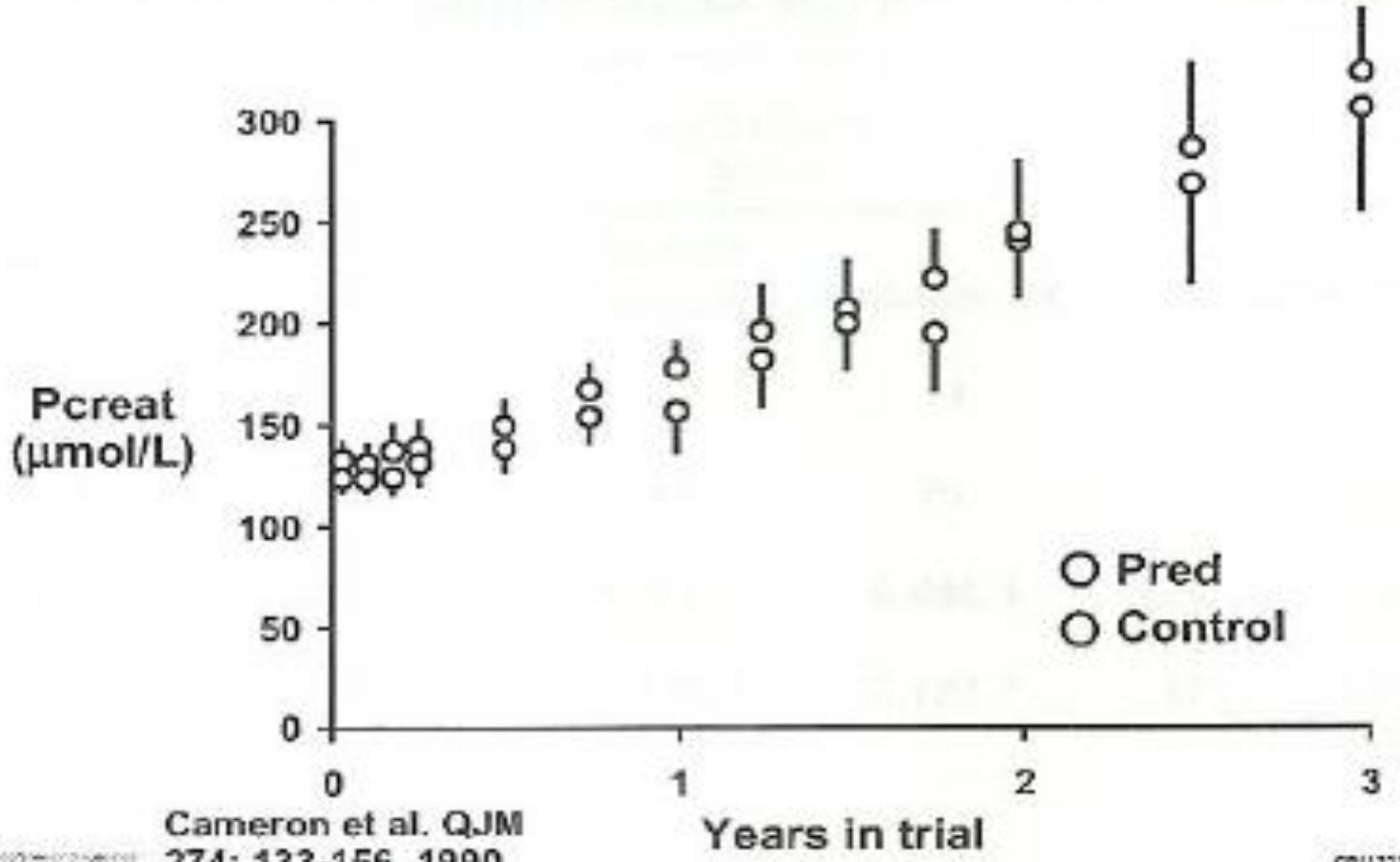
MRC- UK Trial

Alternate day prednisone (125-150 mg) on adults nephrotics for 8 weeks



Cameron et al. QJM
274: 133-156, 1990

MRC- UK Trial



Cameron et al. QJM
274: 133-156, 1990

Cyclosporine in Progressive MN
Patients Characteristics at Part II

	Cyclosporine n=9	Placebo n=8
Age (range)	44 (22-59)	40 (20-61)
Males (%)	8 (89)	6 (75)
Creatinine (µmol/L)	186±65	204±81
C_{cr} (mL/min/1.73 m^2)	51±20	46±16
Proteinuria (g/day)	11.5 (9-18)	12.8 (4-21)
Serum albumin (g/L)	29±6.6	30±9.2
Systolic BP/mm Hg	141±6	138±16
Diastolic BP (mm Hg)	82±12	83±7
Ultra structural stage	2.2 (1-4)	2.0 (1-4)
Interstitial fibrosis (0-4+)	0.9 (0-1)	0.4 (0-1)
Tubular atrophy (0-4+)	0.7 (0-2)	0.3 (0-2)
Observation period (mo)		
Part 1	9.3 (6-13)	9.7 (7-12)
Part 2	10.1 (4-13)	8.9 (4-13)
Post-med	20 (0-41)	22 (6-56)
Total	49 (17-75)	48 (25-88)

Cattran et al: KI 47:1130, 1995

CSA in Progressive MN

Patient Characteristics at Entry to Part I (n=64)

Age (range)	47 (19-65)
Male	47
Female	17
Creatinine (µmol/L)	127±49
Creatinine clearance (mL/min/1.73 m^2)	77±29
Proteinuria (g/d)	6.4 (1.1-23.9)
Albumin (g/L)	30.6±7.2
BP (mm Hg)	
Systolic	133±17
Diastolic	82±7

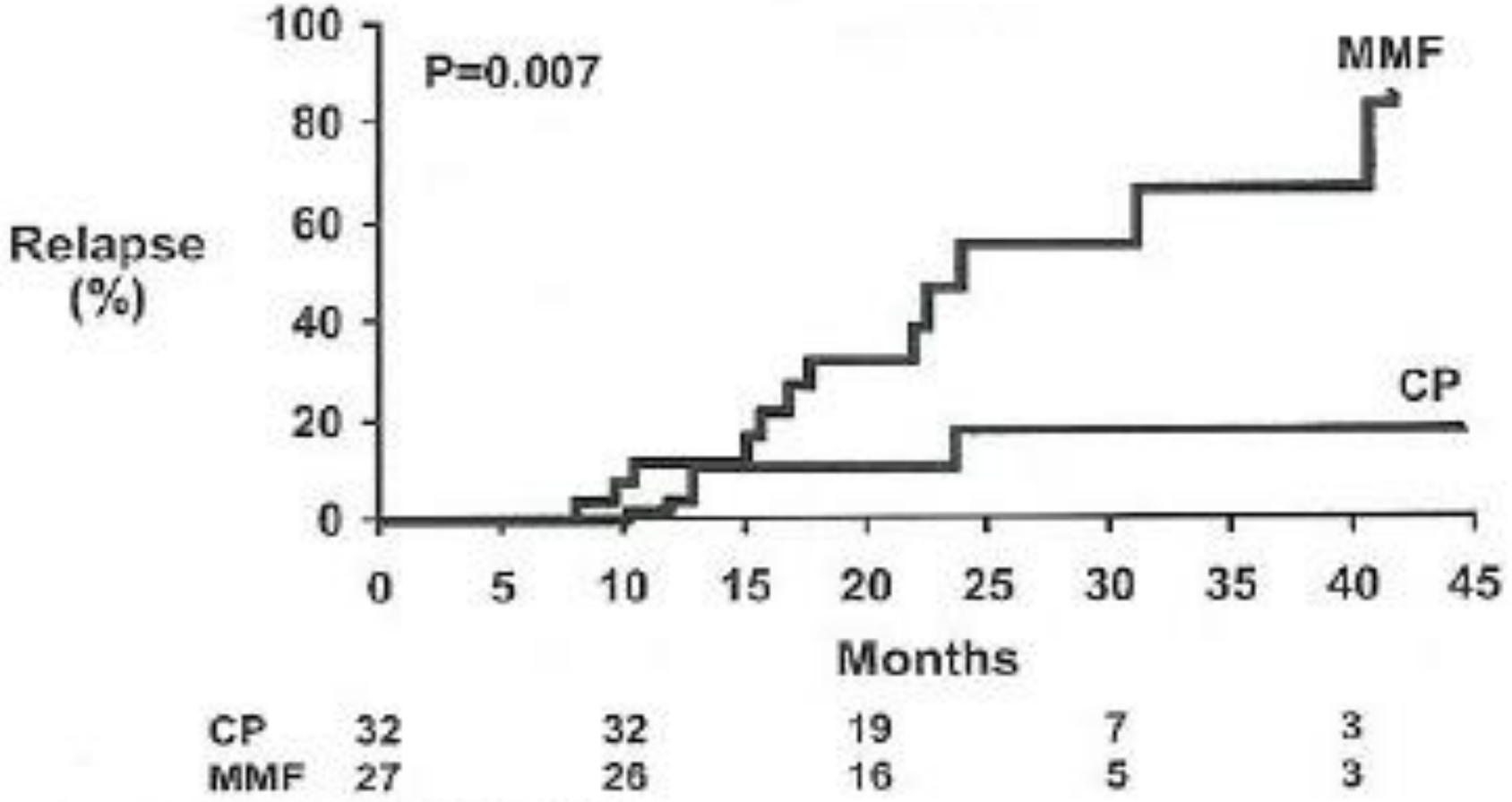
Cattran et al: KI 47:1130, 1995

Treatment-Related Complications

	MMF (n=32)			CP (n=32)		
	Patients			Patients		
Side effect	No.	%	Dose dec	No.	%	Dose dec
BM depression						
Leukocytopenia	0	0	–	9	28	6
Anemia	5	16	1	7	22	8
Infections						
All together	9	28	2	9	28	4
Respiratory	7	22		5	16	
Diarrhea	8	25	8	0	0	–
Malaise	5	16	3	3	9	3
Steroid-induced DM	5	16	–	2	6	–
Malignancy	2	6	–	0	0	–
Total no. of patients	24	75	14	22	69	16

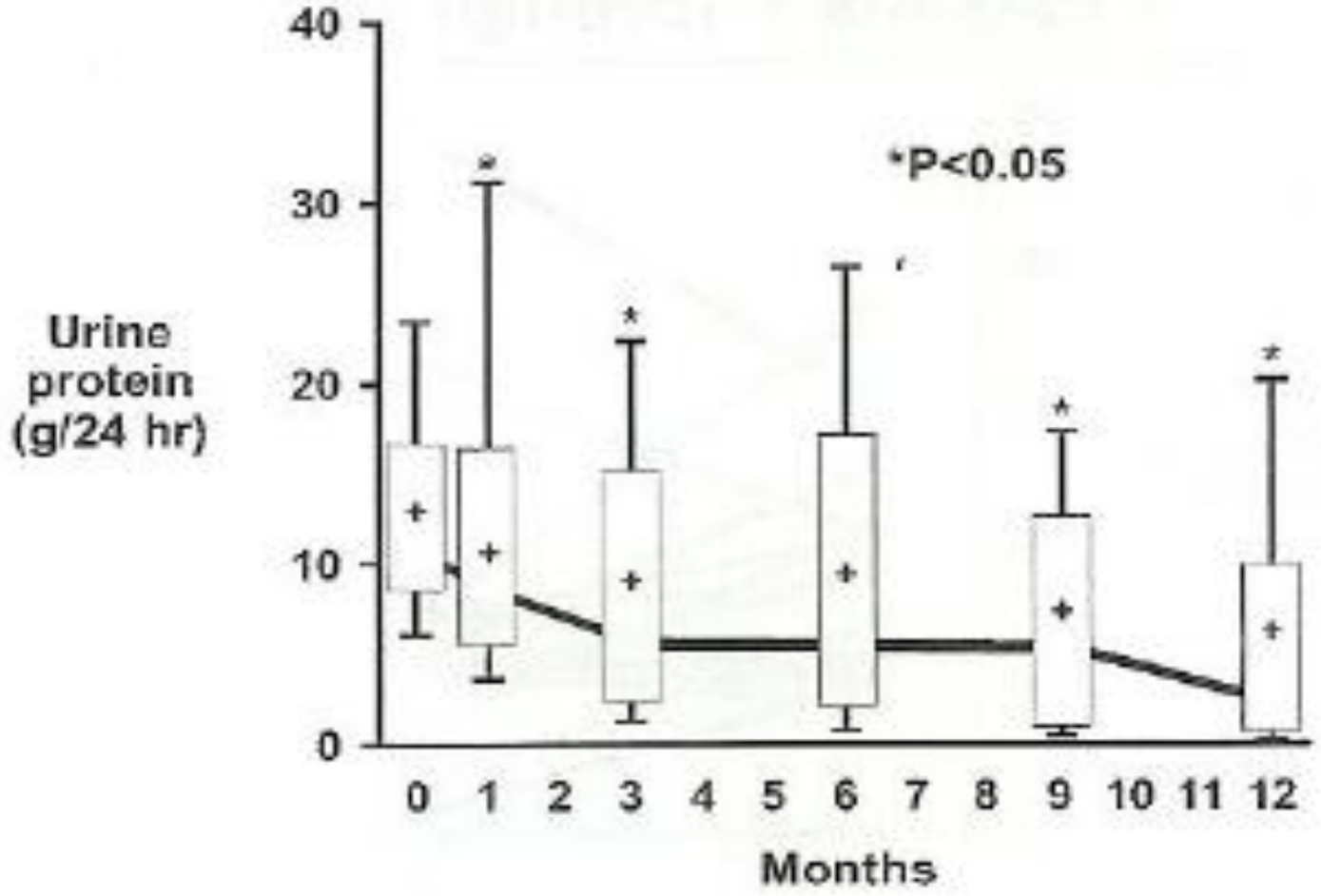
Branten et al: AJKD 50:248, 2007

Cumulative Incidence of Relapses in Patients Treated with MMF or CP



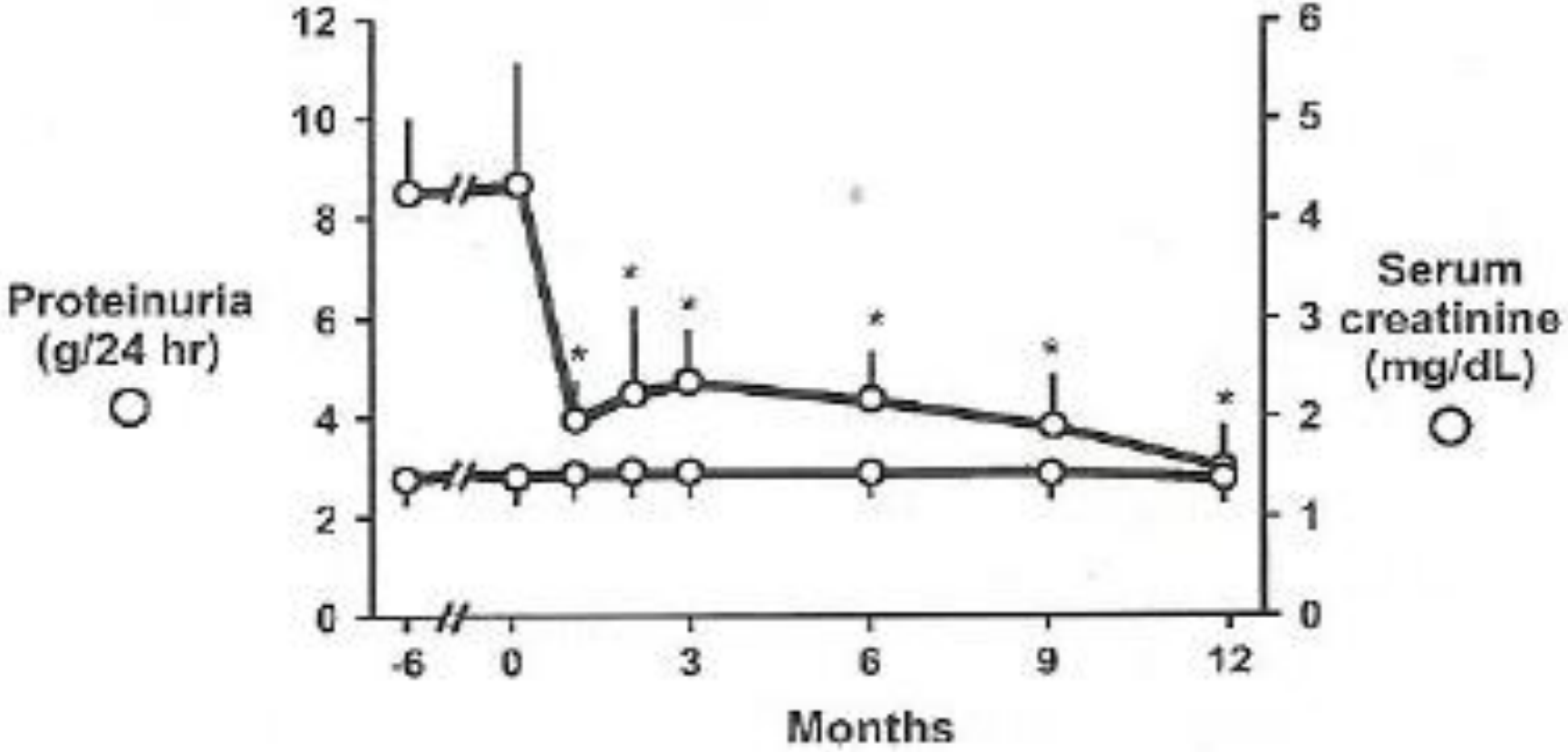
Branten et al: AJKD 50:248, 2007

Rituximab in MN – 1g D1 and D15



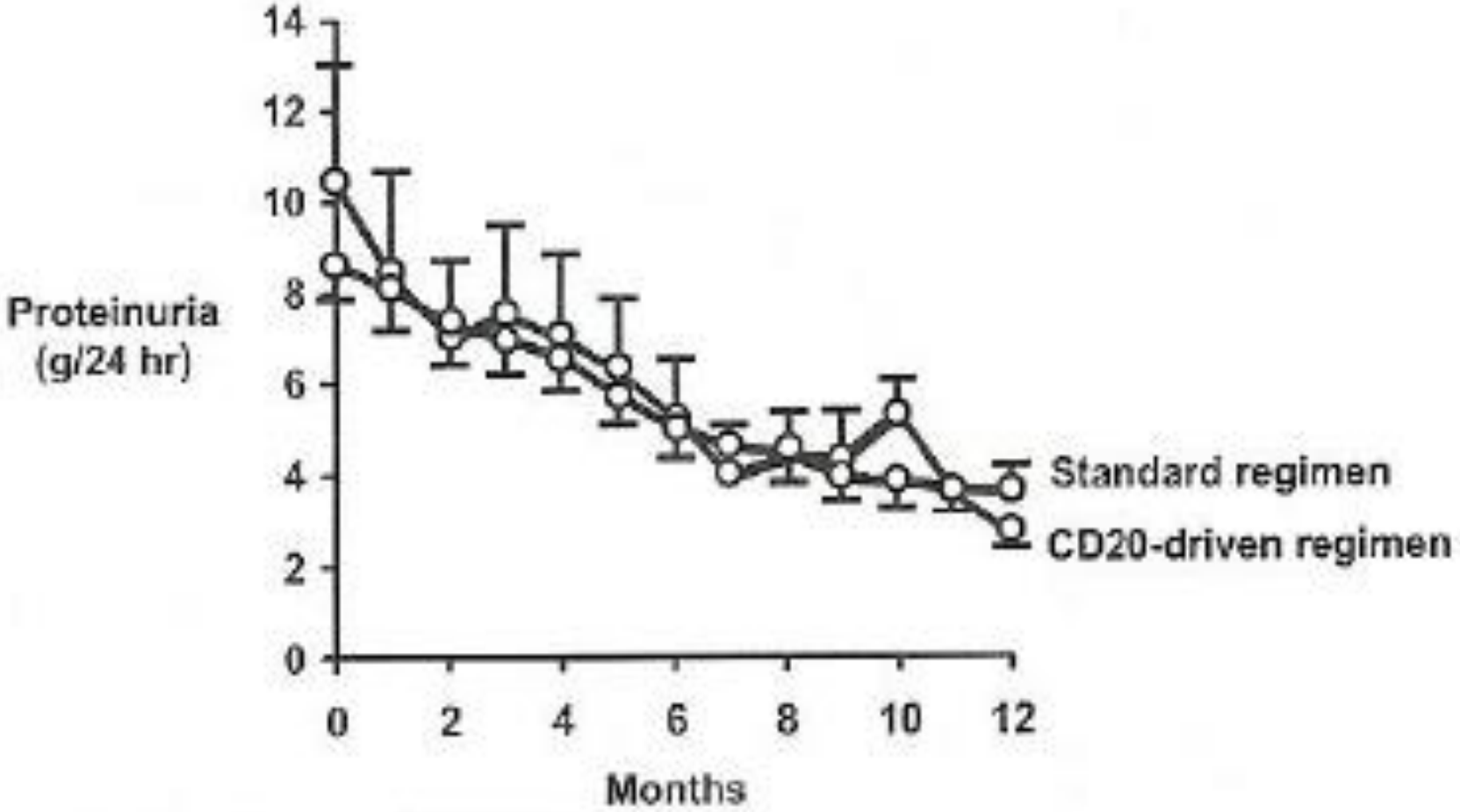
Fervenza et al. Kidney Int 73: 117-125, 2008

Rituximab in Membranous Nephropathy



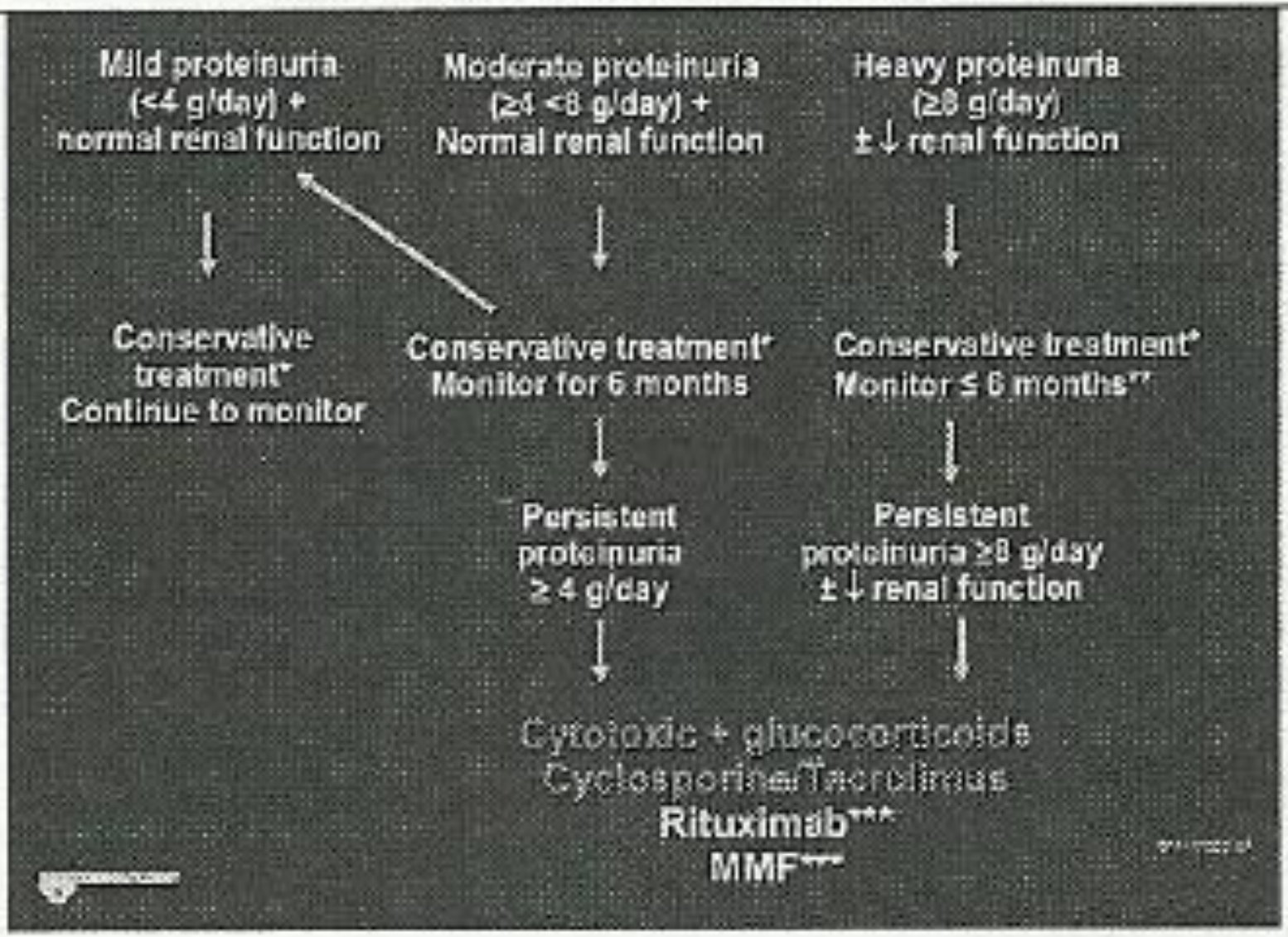
* P<0.01 vs months -6 and 0
Ruggenenti et al: JASN 14:851, 2003

B Cell-Titrated Rituximab Treatment vs Standard 4-Weekly Dose Protocol



Clin J Am Soc Nephrol 2:932, 2007

MN Treatment Algorithm



Artificial
Organs

Effect of Cyclosporine Therapy With Low Doses of Corticosteroids on Idiopathic Nephrotic Syndrome

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Artif Organs, Vol. 34, No. 3, 2010

TABLE 1. *Primary causes of nephrotic syndrome*

Membranous nephropathy	15
Minimal change disease	4
IgM nephropathy	1
IgA nephropathy	1
Mesangiocapillary glomerulonephritis	1

shown in Table 2. All of the patients received CyA (2–3 mg/kg) in combination with methylprednisolone (0.4 mg/kg body weight). Nineteen patients were on

The mean proteinuria of our patients before treatment was 11 972 ± 7953 mg/24 H (M ± SD) and the mean creatinine level (Cr) was 0.99 ± 0.37 mg/dL (M ± SD). The majority of our study population was

TABLE 3. *Proteinuria and cyclosporine levels during treatment*

	Proteinuria (mg/24 H)	C0 (ng/mL)	C2 (ng/mL)
1 month	3578 ± 2470	135 ± 107	725 ± 256
2 months	2653 ± 1431	167 ± 97	793 ± 218
3 months	1491 ± 1073	148 ± 65	669 ± 47
4 months	832 ± 1273	104 ± 61	448 ± 144
5 months	668 ± 76	74 ± 36	237 ± 14

A study by Alexopoulos et al. (10) has shown that prolonged treatment of patients with membranous nephropathy (12 months) with low-dose cyclosporine increased remission rates and that prolonged treatment with low-dose cyclosporine (1.4–1.5 mg/kg) is useful in maintaining remission. Relapse occurred more frequently when C0 CyA levels decreased below 100 ng/mL. Patients who relapsed had a mean C0 CyA level of 72 ± 48 ng/mL, compared to the mean level of nonrelapsers of 194 ± 80 ng/mL ($P <$

0.03). According to recent workshop recommendations on membranous nephropathy, treatment targets include complete or partial remission of proteinuria, maintenance of stable glomerular filtration rate (GFR) (±20% of pretreatment level), avoiding hypertension, and a cyclosporine level regarded as nontoxic (C0 = 125–175 ng/mL and C2 = 400–600 ng/

Cattran DC, Alexopoulos E, Heering P, et al. Cyclosporin in idiopathic glomerular disease associated with the nephrotic syndrome: workshop recommendations. *Kidney Int* 2007;72: 1429–47.

CONCLUSION

It seems that C2 levels, approximately between 650–750 ng/mL, are effective enough at the beginning of the therapy (2–3 months) and at lower levels (250–450 ng/mL) are tolerated and have potential in stable patients after 3 months of therapy. CyA therapy pro-

Renal Failure, 31:192–195, 2009

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CLINICAL STUDY

The Role of Pure Diffuse Mesangial Hypercellularity in Patients with Proteinuria

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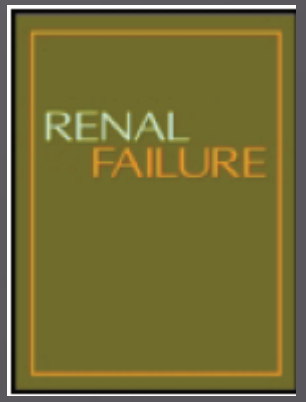

PATIENTS AND METHODS

From a study period of 36 months, clinical and histological data of adult patients with NS and renal biopsies showing DMH were reviewed. The diagnosis of DMH was based on the following criteria[10]:

- the presence of three or more cells per mesangial region in a thin, 2–3 μm section away from the vascular pole;
- a lesion involving >80% of the glomeruli in the specimen;
- the absence of double contours or spikes of the glomerular capillary walls visible by silver impregnation;
- the absence of dense deposits in the basement membranes visible with the trichrome stain; and
- no clinical or histological evidence of associated disease such as IgA nephropathy, lupus, vasculitis, HIV and hepatic disease.

Table 1
Clinical data of eight patients with DMH

Male/female	5/3
Age	55.5 ± 16.31
Plasma creatinine (mg/dl)	1.65 ± 1.01
Proteinuria	3.78 ± 2.94
Hematuria	5 (62.5%)

Table 2
Histological findings in eight patients with DMH

Mesangial hypercellularity	5 (62.5%)
Mesangial sclerosis	4 (50%)
Synechiae	3 (37.5%)
Tubular atrophy	3 (37.5%)
Interstitial fibrosis	4 (50%)
Arteriosclerosis	4 (50%)

At present, it seems that adult patients with DMH and proteinuria represent a heterogeneous group with different clinical courses despite similar morphological appearance in initial biopsies.[20] Many items concerning therapy and clinicopathological features remain controversial. The group of patients that respond to therapy with a combination of drugs have IgM deposition and appear to have mesangial hypercellularity. We conclude that serial biopsies taken at regular intervals coupled with a longer follow-up may provide answers concerning the real intentity of DMH.