Association of Anti-PLA2R Antibodies with Outcomes after Immunosuppressive Therapy in Idiopathic Membranous Nephropathy

Anneke P. Bech, Julia M. Hofstra, Paul E. Brenchley and Jack F.M. Wetzels

Date

idiopathic membranous nephropathy

- some people just get better
- others don't and in those (and some of the former) it can cause major morbidity
  - ESRD
  - thromboembolic events

KDIGO Clinical Practice Guideline for Glomerulonephritis

VOLUME 2 | ISSUE 2 | JUNE 2012

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Chapter 7: Idiopathic membranous nephropathy

7.1: Evaluation of MN

7.1.1: Perform appropriate investigations to exclude secondary causes in all cases of biopsy-proven MN. (*Not Graded*)

7.2: Selection of adult patients with IMN to be considered for treatment with immunosuppressive agents (see 7.8 for recommendations for children with IMN).

7.2.1: We recommend that initial therapy be started only in patients with nephrotic syndrome *AND* when at least one of the following conditions is met:

- Urinary protein excretion persistently exceeds 4 g/d *AND* remains at over 50% of the baseline value, *AND* does not show progressive decline, during antihypertensive and antiproteinuric therapy (see Chapter 1) during an observation period of at least 6 months; (*1B*)
- the presence of severe, disabling, or life-threatening symptoms related to the nephrotic syndrome; (*1C*)
- SCr has risen by 30% or more within 6 to 12 months from the time of diagnosis but the eGFR is not less than 25–30 ml/min/1.73 m^2 *AND* this change is not explained by superimposed complications. (*2C*)

7.2.2: Do not use immunosuppressive therapy in patients with a SCr persistently >3.5 mg/dl (>309 µmol/l) (or an eGFR <30 ml/min per 1.73 m^2) *AND* reduction of kidney size on ultrasound (e.g., <8 cm in length) *OR* those with concomitant severe or potentially life-threatening infections. (*Not Graded*)

7.3: Initial therapy of IMN

7.3.1: We recommend that initial therapy consist of a 6-month course of alternating monthly cycles of oral and i.v. corticosteroids, and oral alkylating agents (see Table 15). (*1B*)

7.3.2: We suggest using cyclophosphamide rather than chlorambucil for initial therapy. (*2B*)

7.3.3: We recommend patients be managed conservatively for at least 6 months following the completion of this regimen before being considered a treatment failure if there is no remission, unless kidney function is deteriorating or severe, disabling, or potentially life-threatening symptoms related to the nephrotic syndrome are present (see also Recommendation 7.2.1). (*1C*)

7.3.4: Perform a repeat kidney biopsy only if the patient has rapidly deteriorating kidney function (doubling of SCr over 1–2 month of observation), in the absence of massive proteinuria (>15 g/d). (*Not Graded*)

7.3.5: Adjust the dose of cyclophosphamide or chlorambucil according to the age of the patient and eGFR. (*Not Graded*)

7.3.6: We suggest that continuous daily (noncyclical) use of oral alkylating agents may also be effective, but can be

7.4: Alternative regimens for the initial therapy of IMN: CNI therapy

7.4.1: We recommend that cyclosporine or tacrolimus be used for a period of at least 6 months in patients who meet the criteria for initial therapy (as described in Recommendation 7.2.1), but who choose not to receive the cyclical corticosteroid/alkylating-agent regimen or who have contraindications to this regimen. (See Table 18 for specific recommendations for dosage during therapy.) (*1C*)

7.4.2: We suggest that CNIs be discontinued in patients who do not achieve complete or partial remission after 6 months of treatment. (*2C*)

7.4.3: We suggest that the dosage of CNI be reduced at intervals of 4–8 weeks to a level of about 50% of the starting dosage, provided that remission is maintained and no treatment-limiting CNI-related nephrotoxicity occurs, and continued for at least 12 months. (*2C*)

7.4.4: We suggest that CNI blood levels be monitored regularly during the initial treatment period, and whenever there is an unexplained rise in SCr (>20%) during therapy. (*Not Graded*) (See Table 18 for specific CNI-based regimen dosage recommendations.)

7.5: Regimens not recommended or suggested for initial therapy of IMN

7.5.1: We recommend that corticosteroid monotherapy not be used for initial therapy of IMN. (*1B*)

7.5.2: We suggest that monotherapy with MMF not be used for initial therapy of IMN. (*2C*)

7.6: Treatment of IMN resistant to recommended initial therapy

7.6.1: We suggest that patients with IMN resistant to alkylating agent/steroid-based initial therapy be treated with a CNI. (*2C*)

7.6.2: We suggest that patients with IMN resistant to CNI-based initial therapy be treated with an alkylating agent/steroid-based therapy. (*2C*)

7.7: Treatment for relapses of nephrotic syndrome in adults with IMN

7.7.1: We suggest that relapses of nephrotic syndrome in IMN be treated by reinstitution of the same therapy that resulted in the initial remission. (*2D*)

7.7.2: We suggest that, if a 6-month cyclical corticosteroid/alkylating-agent regimen was used for initial therapy (see Recommendation 7.3.1), the regimen be repeated only once for treatment of a relapse. (*2B*)

7.8: Treatment of IMN in children

7.8.1: We suggest that treatment of IMN in children follows the recommendations for treatment of IMN in adults. (*2C*) (See Recommendations 7.2.1 and 7.3.1.)

7.8.2: We suggest that no more than one course of the cyclical corticosteroid/alkylating-agent regimen be given in children. (*2D*)

7.9: Prophylactic anticoagulants in IMN

7.9.1: We suggest that patients with IMN and nephrotic syndrome, with marked reduction in serum albumin (<2.5 g/dl [<25 g/l]) and additional risks for thrombosis, be considered for prophylactic anticoagulant therapy, using oral warfarin. (*2C*)

Real live nephrology clinical practice guidelines with a 1B recommendation and a smattering of 2B recs!

this is not your father's nephrology!

- the pain point in membranous nephropathy is that some patients have a really benign course and others a horrible one and we want to focus our treatment only on the later.

"Current therapy is not individualized according to disease severity or disease activity parameters during treatment. A complicating factor is the slow response; remissions can occur 12–18 months after completion of the treatment regimen"

–Anneke P. Bech, Julia M. Hofstra, Paul E. Brenchley, and Jack F.M. Wetzels

"PLA2R-abs are present in about 70% of patients with iMN"

"The aim of this study was to determine whether the measurement of PLA2R-ab at start and end of therapy is useful in predicting the outcome after immunosuppressive therapy."

–Anneke P. Bech, Julia M. Hofstra, Paul E. Brenchley, and Jack F.M. Wetzels

study population

- biopsy proved iMN
- 1997-2005
- Cr > 1.5 or severe nephrotic syndrome were treated at this center.
  - Oral steroids plus:
    - 1997-2002: oral cyclophosphamide for 12 months
    - 2002-2005 MMF 1000 bid for 12 months

- they had frozen serum samples and they thawed all they had and used an in-house ELISA assay for PLA_2R-ab

- Titers over 40 U/ml were considered positive

- Complete remission:
  - proteinuria < 0.2 g/d and
  - stable renal function
- Partial remission
  - proteinuria < 3.5 g/d and
  - More than a 50% reduction in proteinruia
  - stable renal function
- Achieving remission is by reaching complete of partial remission
- Relapse
  - proteinuria > 3.5 g/d and
  - More than a 50% increase in proteinruia from the lowest point reached in remission

48 patients

22 MMF

26 cyclophosphamide

34 anti-PLA_2R +

14 anti-PLA_2R –

39 were new diagnosis

9 were recurring from a previous remission

4 had previously been treated

34 anti-PLA_2R +

14 anti-PLA_2R –

baseline characteristics were indistinguishable

14 achieved persistent remission	7 achieved persistent remission

had the same response to treatment

Characteristic	PLA_2R Antibody Negative (n=14)	PLA_2R Antibody Positive (n=34)	P Value
Men (n)	11	26	0.88
Age (yr)	57 (38–75)	54 (34–74)	0.89
Serum creatinine (mg/dl)	1.72 (1.24–3.37)	1.54 (0.98–3.14)	0.19
Serum albumin (g/dl)	2.9 (1.5–3.9)	2.4 (1.8–3.5)	0.09
Protein/creatinine ratio (g/g)	7.9 (5.1–23.5)	10.5 (3.2–25.2)	0.10
SI	0.29 (0.12–0.51)	0.35 (0.18–0.53)	0.07
eGFR (ml/min per 1.73 m^2)[a]	41 (21–91)	48 (21–96)	0.50
PLA_2R antibody (U/ml)	9 (1–38)	428 (41–16,260)	<0.01
Severe nephrosis as reason for start treatment (n)	0	2	0.35
MMF (n)	7	15	0.71
Cyclophosphamide (n)	7	19	
Recurrent episode at presentation (n)	4	5	0.26
Previous immunosuppressive therapy (n)	2/4	2/5	0.33
Time from baseline to start treatment (mo)	4 (1–24)	7 (1–26)	0.40
Follow-up duration (mo)	60 (0–60)	47 (0–60)	0.65
Outcome			
Persistent remission	7	14	0.58
Relapse	5	12	0.98
Persistent proteinuria	1	1	0.51
Immunosuppressive therapy	0	3	0.25
Dead	1	4	0.63

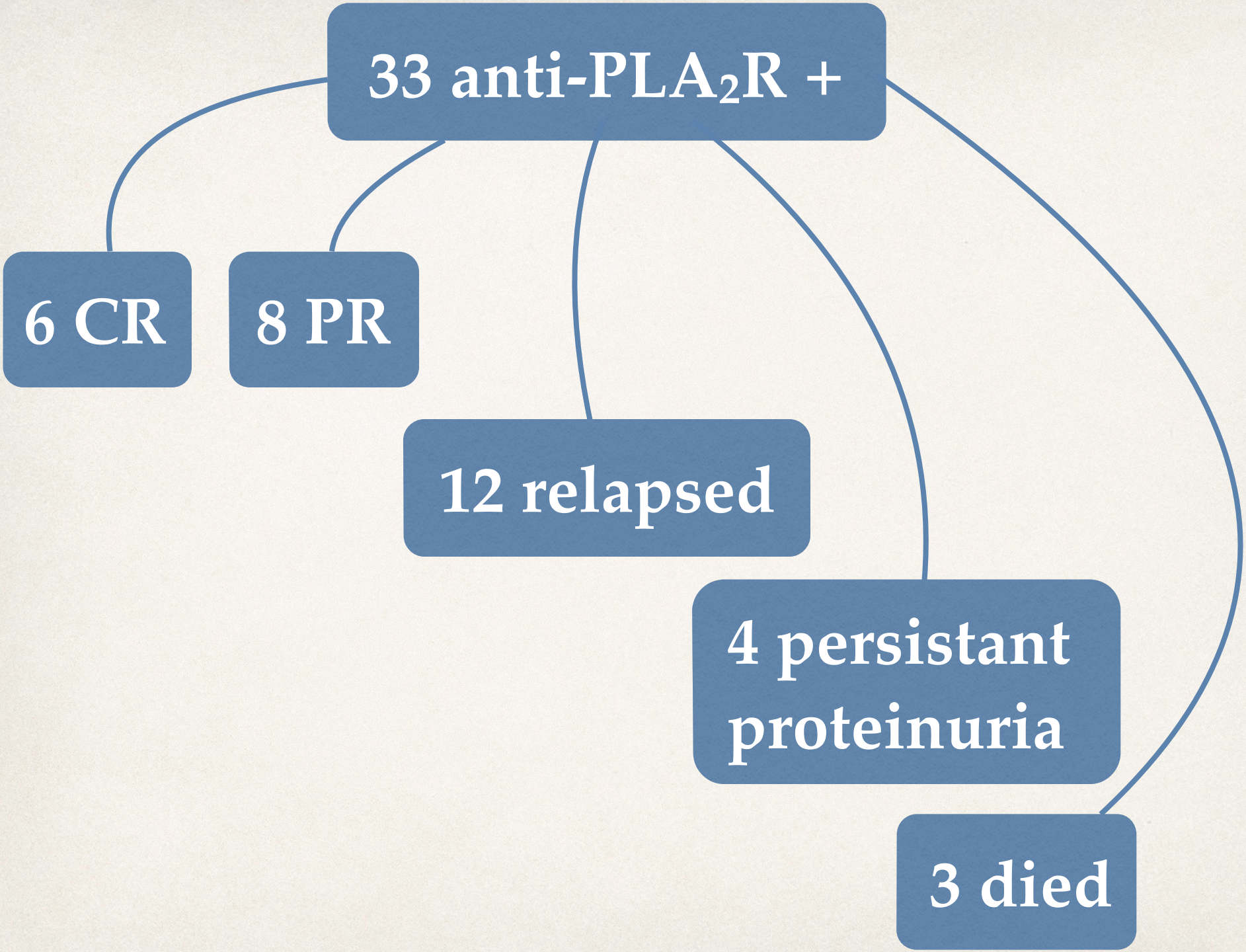
The PLA2R-ab levels at start of therapy did not predict the initial response or the final outcome

–Anneke P. Bech, Julia M. Hofstra, Paul E. Brenchley, and Jack F.M. Wetzels

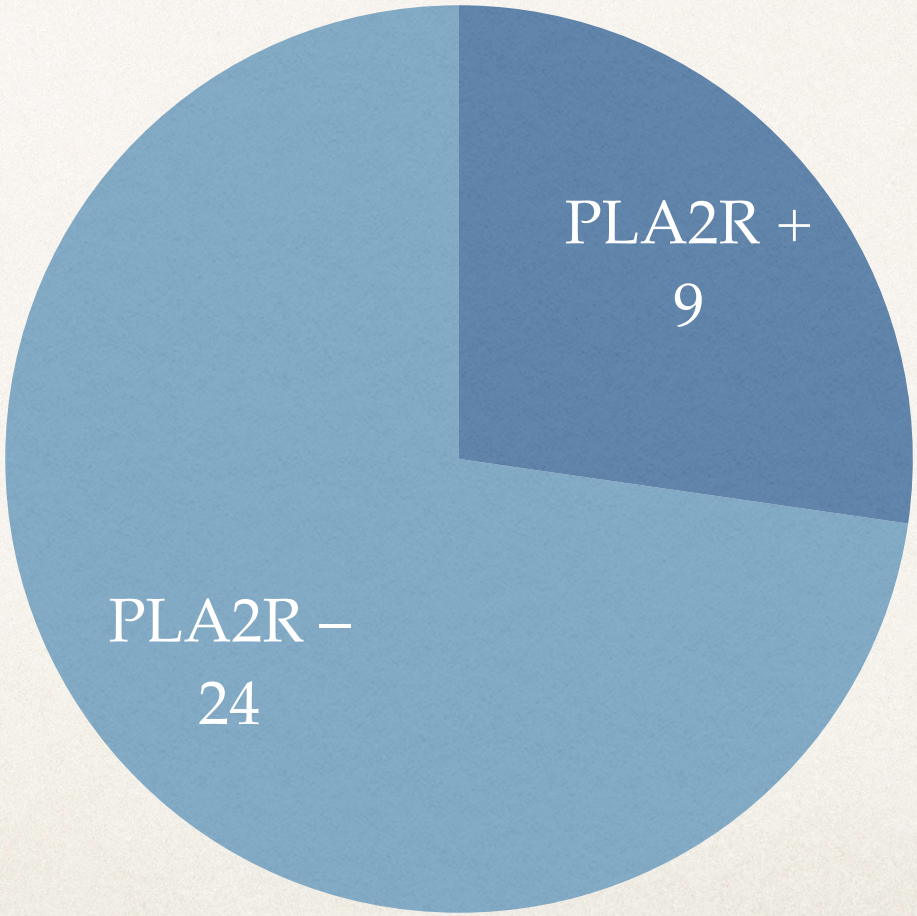
48 patients

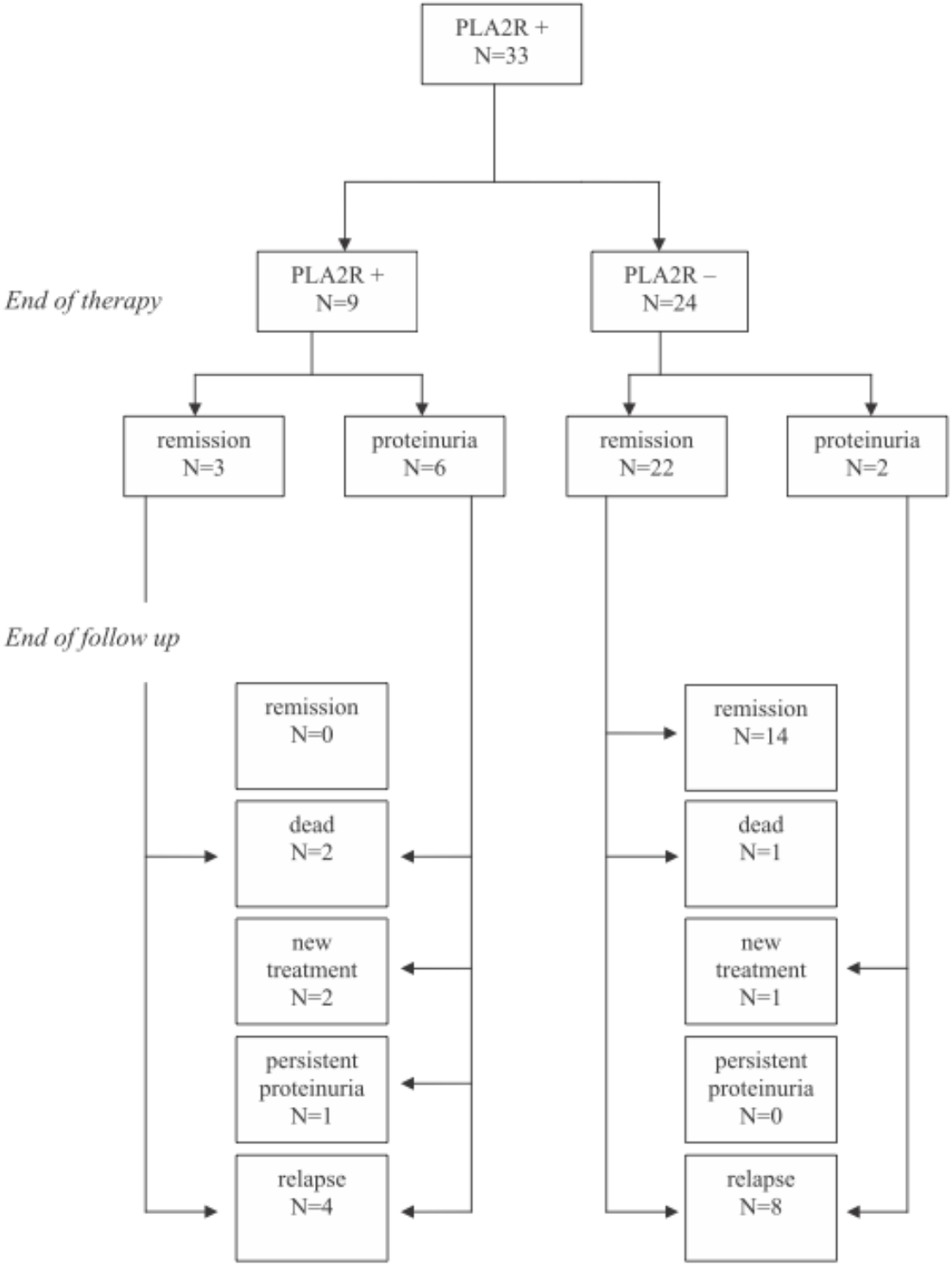
33 anti-PLA_2R +
(lost one due to lack of titers at the end of treatment)

25 developed a partial remission by the end of treatment at 12 months

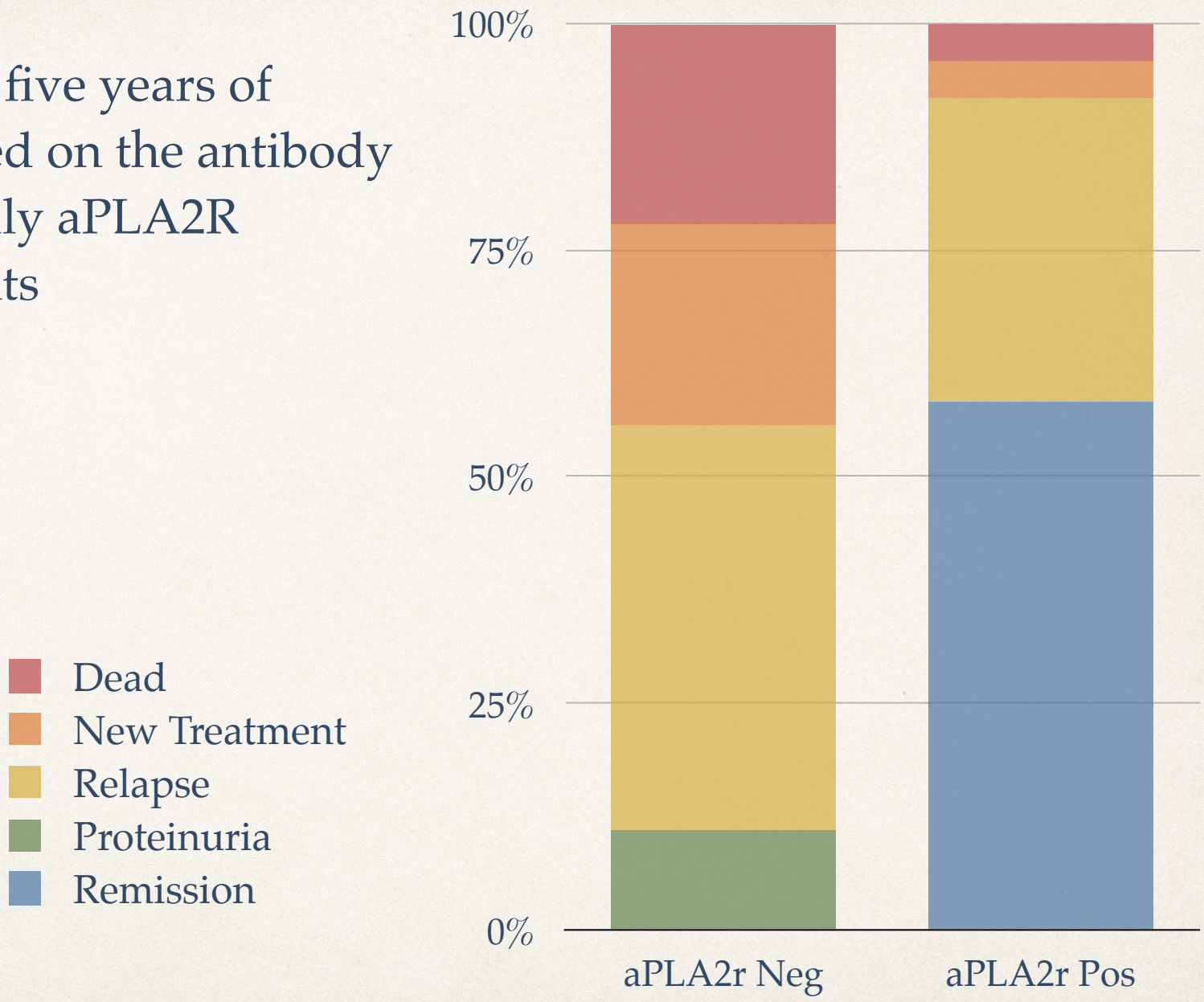

33 anti-PLA2R +
6 CR
8 PR
12 relapsed
4 persistant proteinuria
3 died

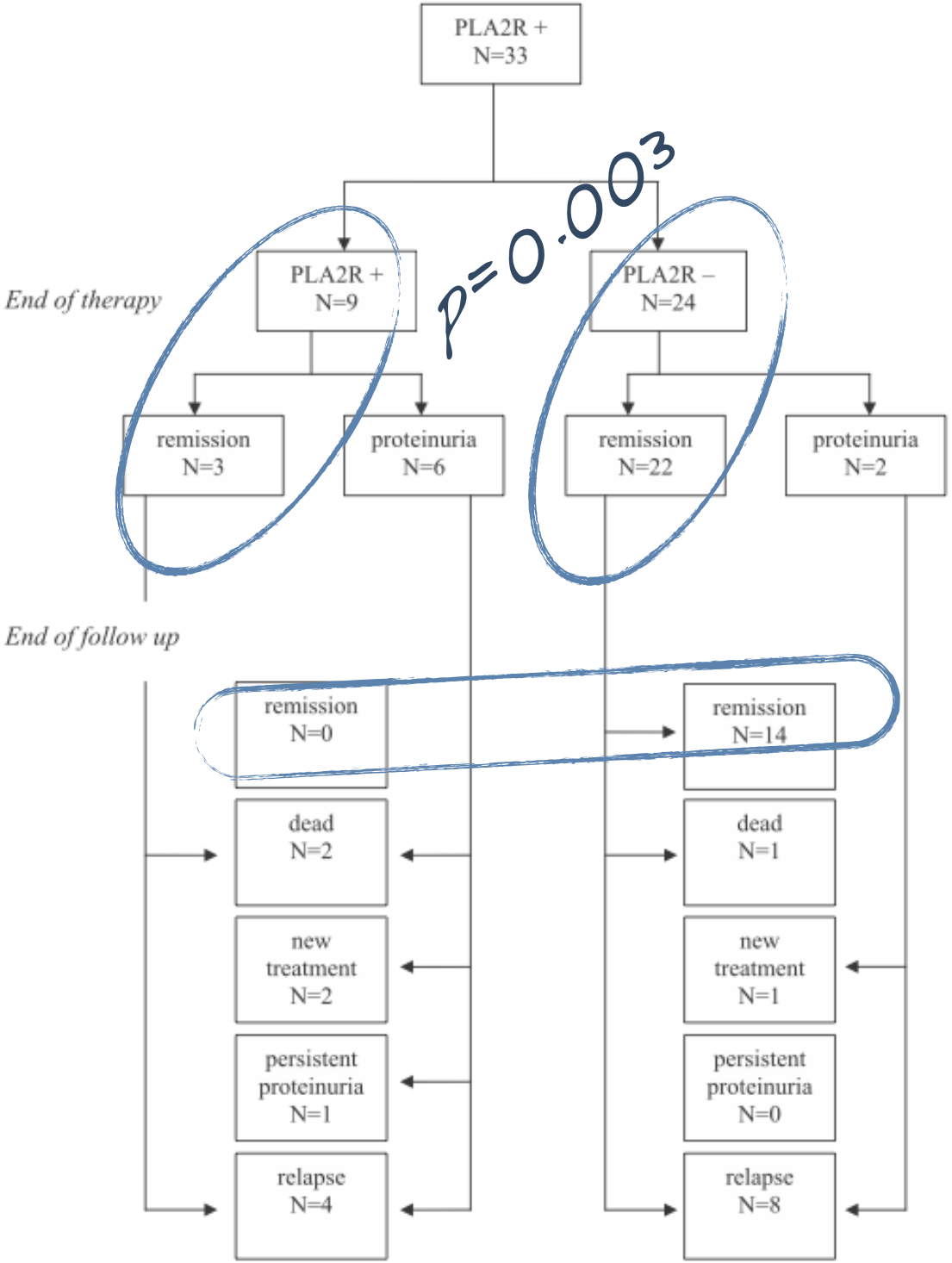
Among the patients that were PLA_2R-ab + at start of therapy the antibody status at the end of treatment did predict long term outcome.




PLA2R +
N=33
End of therapy
PLA2R +
N=9
PLA2R –
N=24
remission
N=3
proteinuria
N=6
remission
N=22
proteinuria
N=2
End of follow up
remission
N=0
dead
N=2
new
treatment
N=2
persistent
proteinuria
N=1
relapse
N=4
remission
N=14
dead
N=1
new
treatment
N=1
persistent
proteinuria
N=0
relapse
N=8

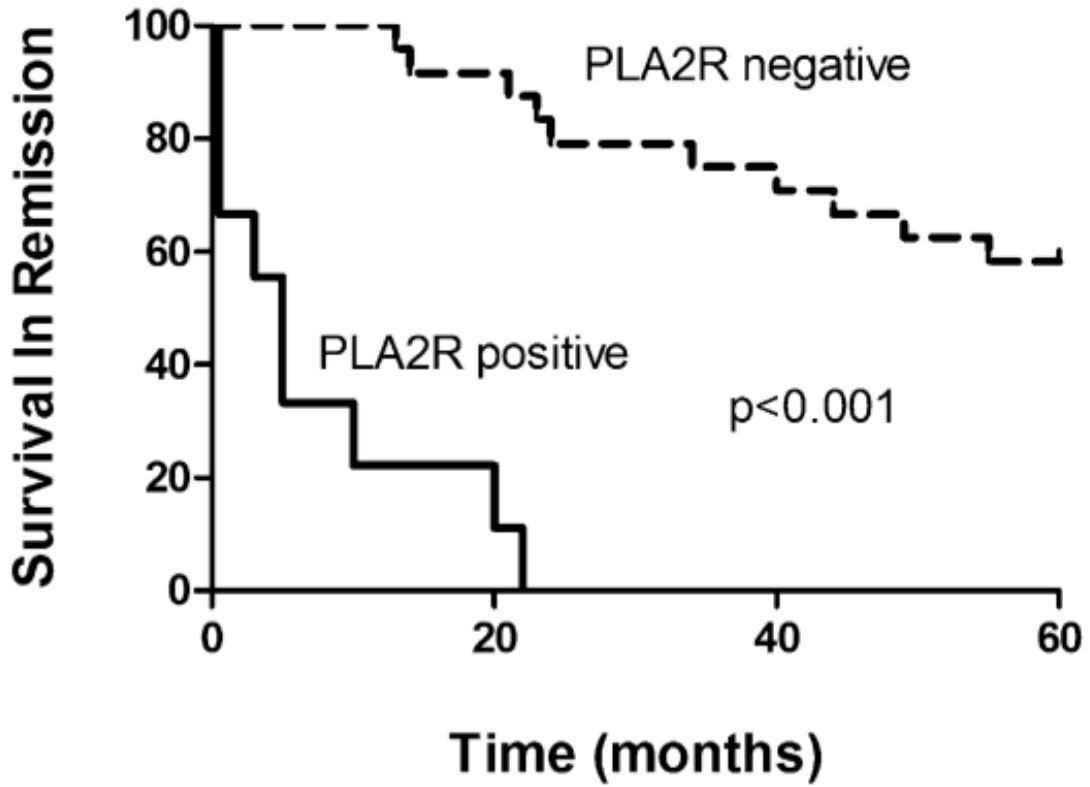
Outcome after five years of follow-up based on the antibody status of initially aPLA2R positive patients




PLA2R +
N=33
p=0.003
End of therapy
PLA2R +
N=9
PLA2R –
N=24
remission
N=3
proteinuria
N=6
remission
N=22
proteinuria
N=2
End of follow up
remission
N=0
remission
N=14
dead
N=2
dead
N=1
new
treatment
N=2
new
treatment
N=1
persistent
proteinuria
N=1
persistent
proteinuria
N=0
relapse
N=4
relapse
N=8

Long-term outcome in patients who became PLA2R-ab negative was independent of the type of immunosuppressive agent used.

–Anneke P. Bech, Julia M. Hofstra, Paul E. Brenchley, and Jack F.M. Wetzels



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

Our data suggest that measurement of PLA2R-abs at the end of immunosuppressive therapy in PLA2R-ab–positive patients predicts the subsequent course during prolonged follow-up.

–Anneke P. Bech, Julia M. Hofstra, Paul E. Brenchley, and Jack F.M. Wetzels

Cyclophosphamide versus MMF

Table 3. Course of PLA_2R antibody during therapy in PLA_2R-related disease

Variable	MMF (n=15)	CP (n=18)	P Value
Negative after 2 mo	4/9	11/13	0.05
Negative after 6 mo	6/8	13/13	0.06
Negative after 12 mo	8/15	16/18	0.02

Values are expressed as number of negative samples out of total available samples. MMF, mycophenolate mofetil; CP, cyclophosphamide.

*The denominators change because not everyone had serum for testing at 2 and 4 months.

This study also suggests that antibodies disappeared more often in patients treated with CP than in patients treated with MMF. These observations are compatible with previously reported study results: MMF induced clinical remission in iMN, but there were more patients with a primary nonresponse and more patients with a relapse soon after the end of therapy.

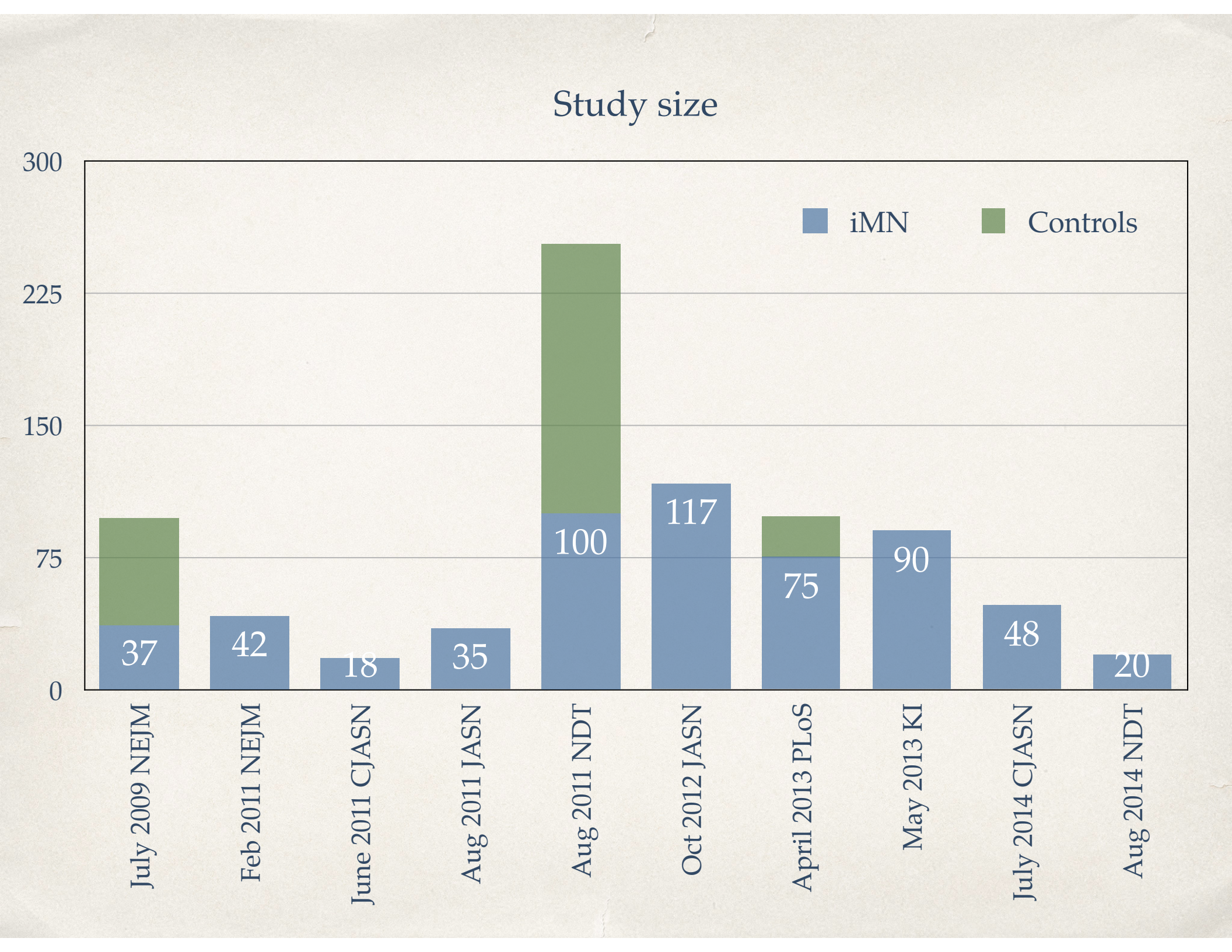
–Anneke P. Bech, Julia M. Hofstra, Paul E. Brenchley, and Jack F.M. Wetzels

antibody levels decreasing during therapy preceded the reduction of proteinuria, as was found in two earlier studies (16,17). Determination of antibodies during therapy could therefore be of additional value in predicting response to therapy at an earlier stage.

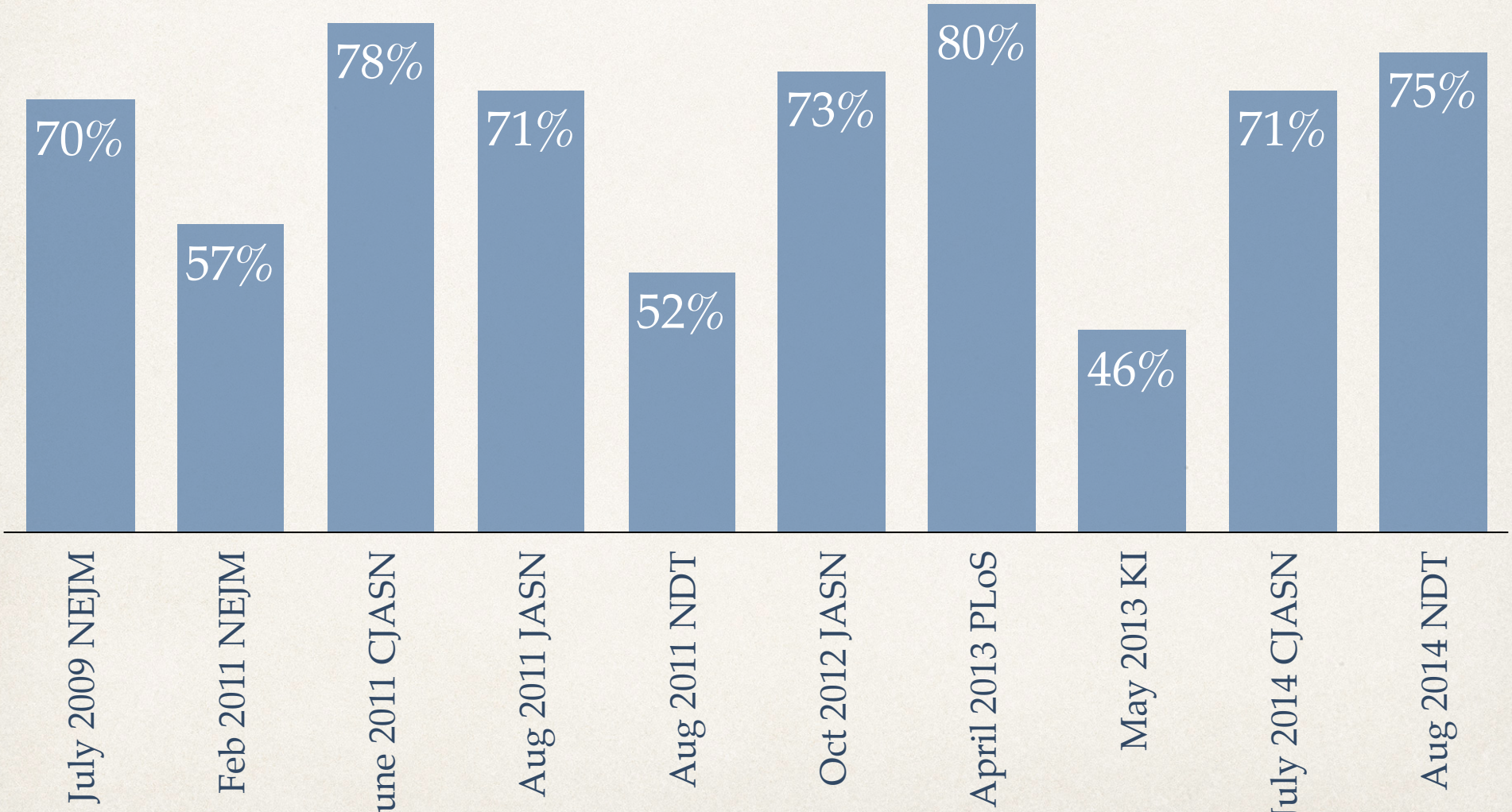
–Anneke P. Bech, Julia M. Hofstra, Paul E. Brenchley, and Jack F.M. Wetzels

The results should be confirmed in larger datasets and in different subsets of patients. If our findings are reproduced, then measurement of PLA2R-abs may allow individualized therapy, a strategy that is potentially safer and more cost-effective than current practice.

–Anneke P. Bech, Julia M. Hofstra, Paul E. Brenchley, and Jack F.M. Wetzels


Study size
300
225
150
75
0
iMN
Controls
37
42
18
35
100
117
75
90
48
20
July 2009 NEJM
Feb 2011 NEJM
June 2011 CJASN
Aug 2011 JASN
Aug 2011 NDT
Oct 2012 JASN
April 2013 PLoS
May 2013 KI
July 2014 CJASN
Aug 2014 NDT

Sensitivity



	July 2009 NEJM	Feb 2011 NEJM	June 2011 CJASN	Aug 2011 JASN	Aug 2011 NDT	Oct 2012 JASN	April 2013 PLoS	May 2013 KI	July 2014 CJASN	Aug 2014 NDT
PMID	19571279	21323563	21474589	21784898	21633097	22956816	23637987	23364522	25035272	24714414
N	37	42	18	35	100	117	75	90	48	20
therapeutic trial										
Specificity										
activity										
prognosis										
titers precede proteinuria										

Antiphospholipase A2 Receptor Autoantibody Guided Diagnosis and Treatment of Membranous Nephropathy: A New Personalized Medical Approach

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Clin J Am Soc Nephrol 9: ●●●–●●●, 2014. doi: 10.2215/CJN.05880614

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Medical care is entering into a new phase of "personalized" medical care in which diagnosis and management are tailored to the specific aspects of individual patients. This approach is often guided by the results of sophisticated biomarkers of disease, prognosis, or treatment responsiveness. In this issue of *CJASN*, Bech and coworkers from the Radboud University Medical Center (Nijmegen, The Netherlands) and Manchester Institute of Nephrology (Manchester, UK) describe their findings from an observational, prospective study of the clinical utility of measurement of antiphospholipase A2 receptor autoantibody (aPLA2R) in a cohort of patients with presumed primary (idiopathic) membranous nephropathy (iMN) and nephrotic syndrome (1). This study builds on the now well known and ground-breaking studies that defined a pathogenic role of such autoantibodies in iMN, described by Beck *et al.* in 2009 (2).

poorly understood issue that needs mention and much further study is the role of aPLA2R measurements in assessing the risk and the course of recurrence of iMN in renal allografts.

Bech and colleagues' study was sharply focused on the utility of pre- and post-treatment assays of aPLA2R on short- and long-term outcomes (mainly remissions and relapses of proteinuria during and after treatment with alkylating agents [cyclophosphamide], mycophenolate mofetil [MMF], or rituximab) in iMN. It is noteworthy that none of the patients included in this study received calcineurin inhibitors, at least initially, perhaps because of the potential for adverse events in patients with reduced renal function. The study size was relatively small (48 patients), and most of the study sample consisted of "high-risk" patients with impaired renal function and/or high-grade proteinuria and severe nephrotic syndrome. Whether the results apply equally