Extending Prednisolone Treatment Does Not Reduce Relapses in Childhood Nephrotic Syndrome (Journal Club)

Sara Al-Sharhan- PharmD candidate, KSU

10 Mar 2014

Background

- Nephrotic syndrome (NS) is the most common manifestation of glomerular disease in childhood.

- Corticosteroids induce remission of proteinuria in 90%–95% of patients. Despite this high initial response rate, relapses occur in 60%–90% of the initial responders.

- Recurrent or continuous corticosteroid therapy in these patients frequently results in corticosteroid toxicity.

Background

- Currently used prednisolone regimens vary in dose and duration.

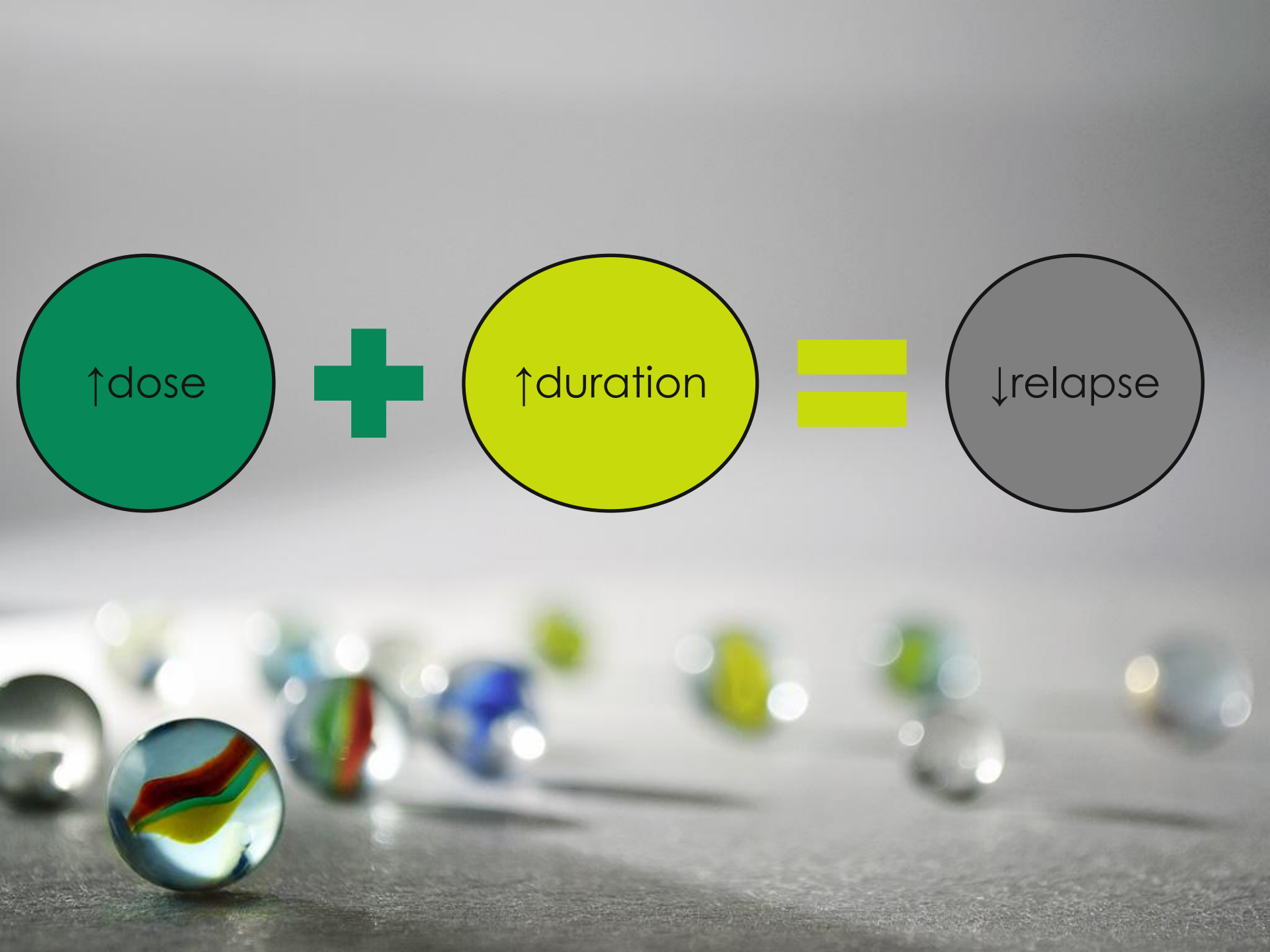
- The regimen prescribed in The Netherlands is made up of 60 mg/m2 prednisolone daily for 6 weeks followed by 40 mg/m2 prednisolone on alternate days for 6 weeks. The cumulative dose of this regimen is 3360 mg/m2.

Previous Studies

- In 2000, Hodson et al. performed a meta-analysis of corticosteroid therapy in childhood NS to evaluate the potential benefits of different corticosteroid regimens. It was concluded that the risk of relapse was significantly reduced by prednisolone regimens that were both longer and more intensive.

Previous Studies

- A subsequent study by Hiraokaetal. comparing 3 months of prednisolone treatment to 6 month of treatment was also inconclusive. In this study, prolonged treatment reduced the relapse rate in children ages under 4 years; however, this intervention also consisted of a higher cumulative dose.


↑dose
↑duration
↓relapse

CLINICAL RESEARCH www.jasn.org

Extending Prednisolone Treatment Does Not Reduce Relapses in Childhood Nephrotic Syndrome

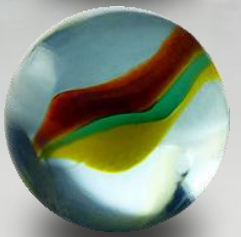
Nynke Teeninga,* Joana E. Kist-van Holthe,† Nienske van Rijswijk,* Nienke I. de Mos,‡ Wim C.J. Hop,§ Jack F.M. Wetzels,‖ Albert J. van der Heijden,* and Jeroen Nauta*

J Am Soc Nephrol 24: 149–159, 2013

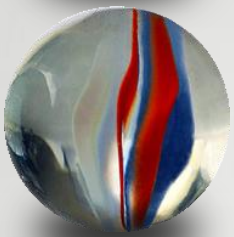
* This study was funded by Dutch Kidney Foundation Grant and the Vrienden van het Sophia Foundation.

PICO

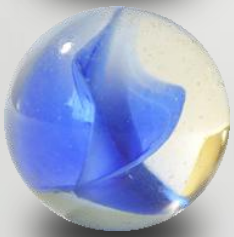
- Children with nephrotic syndrpme



- 6 months prednisolone



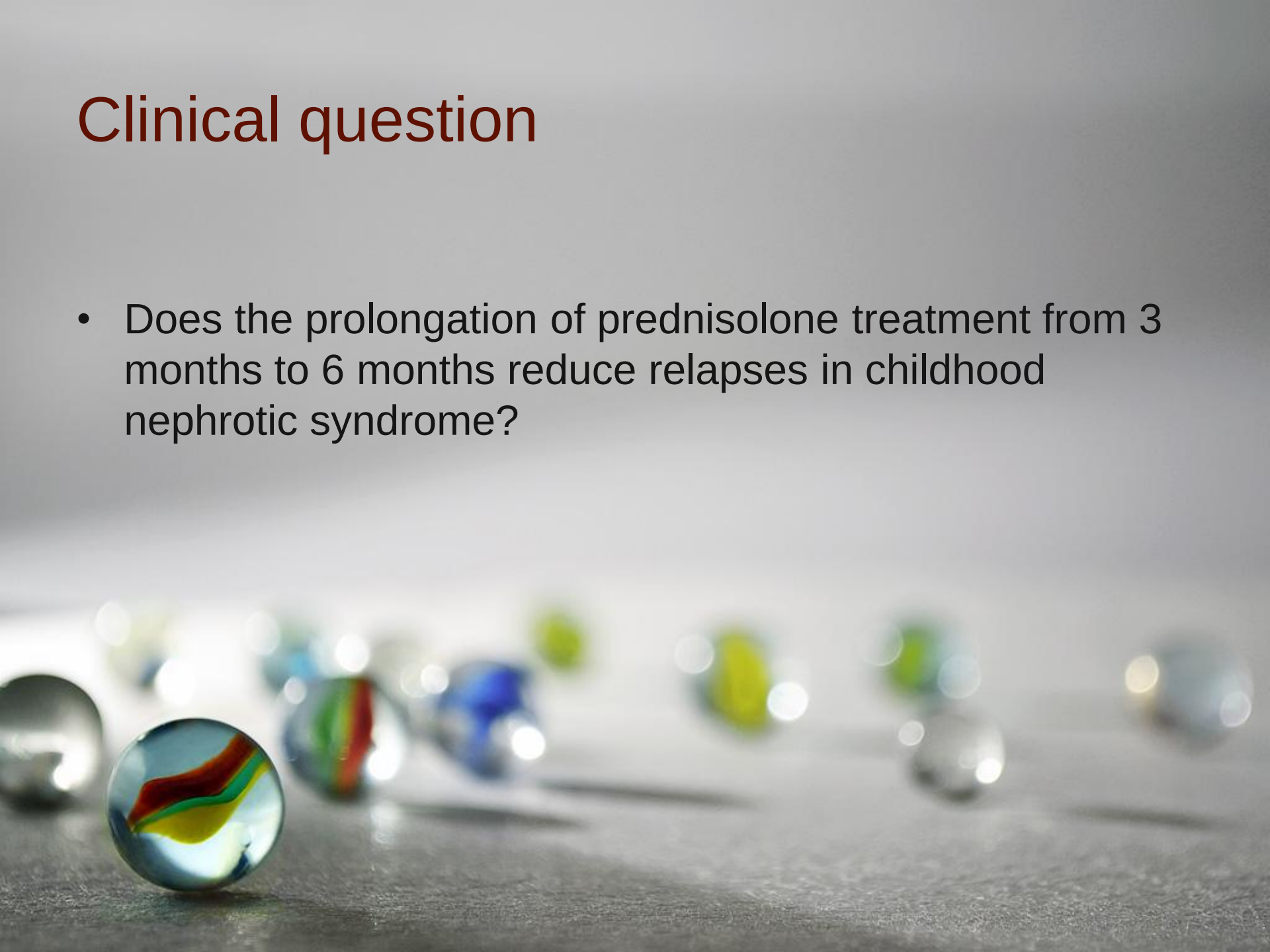
- 3 months prednisolone



- Relapses

Clinical question

- Does the prolongation of prednisolone treatment from 3 months to 6 months reduce relapses in childhood nephrotic syndrome?



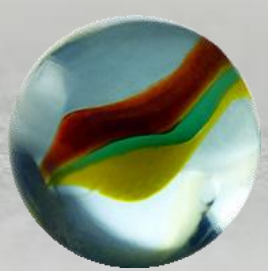
Objective

- To explore the independent effect of treatment duration using equal cumulative doses without increasing adverse events.

Method

Design

- Double-blind, randomized, placebo-controlled trial



Enrolment

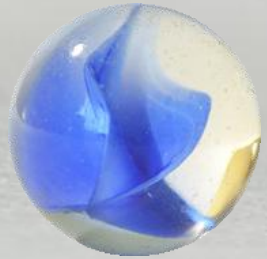
- Feb, 2005 – Dec, 2009

Setting

- 69 hospitals in Netherland

Analysis

- Intention to treat



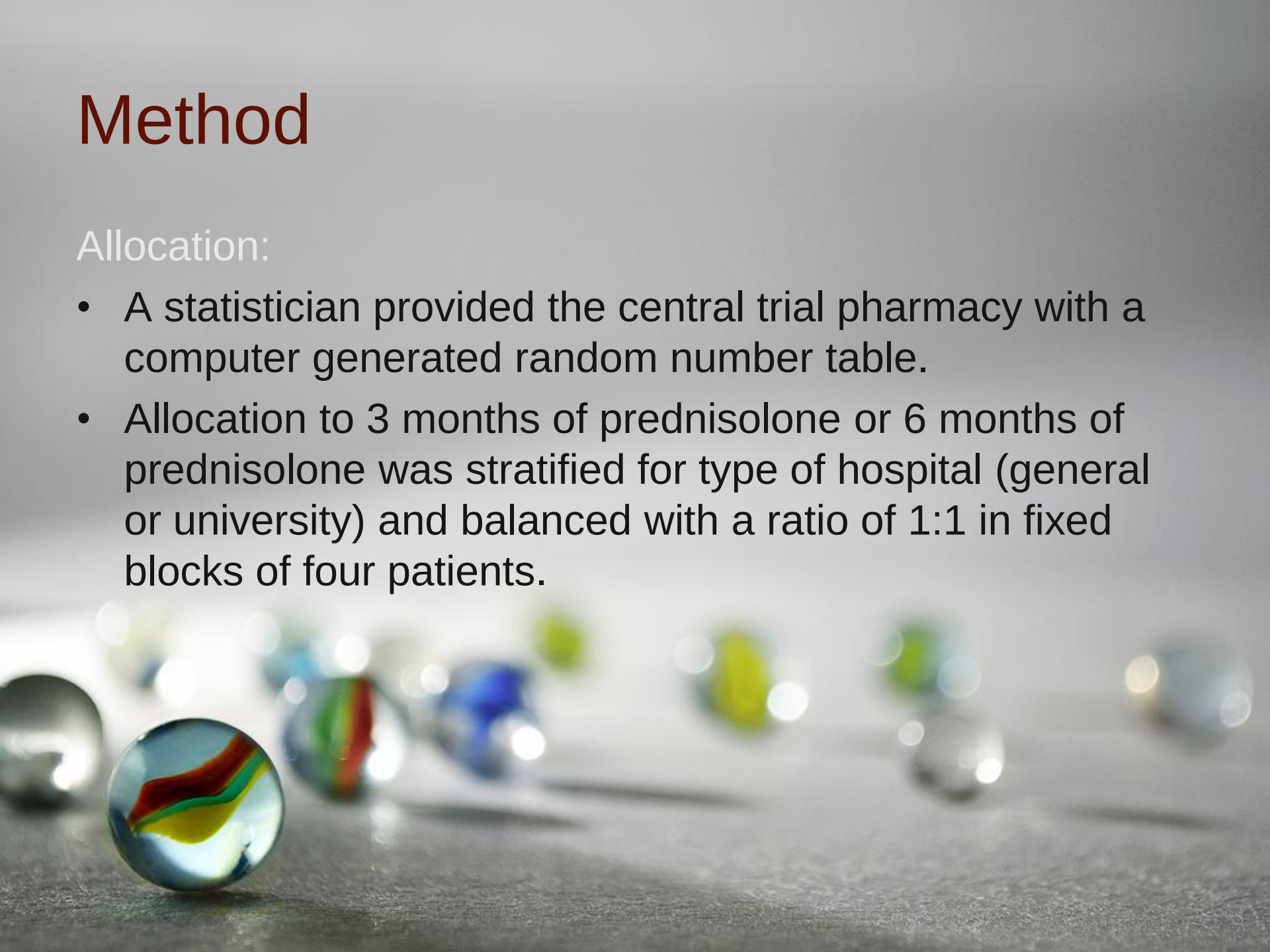
Follow up

- 47 months

Method

Allocation:

- A statistician provided the central trial pharmacy with a computer generated random number table.
- Allocation to 3 months of prednisolone or 6 months of prednisolone was stratified for type of hospital (general or university) and balanced with a ratio of 1:1 in fixed blocks of four patients.



Method

Blindness:

- Participants, health care providers, data collectors, and researchers were blinded to group allocation.

Method

Inclusion criteria:

- Children with a first episode of NS ages 9 months to 17 years
- >200 mg protein/mmol creatinine in urine
- Albumin <25 g/L in serum.

Exclusion criteria:

- Henoch–Schönlein purpura or postinfectious GN

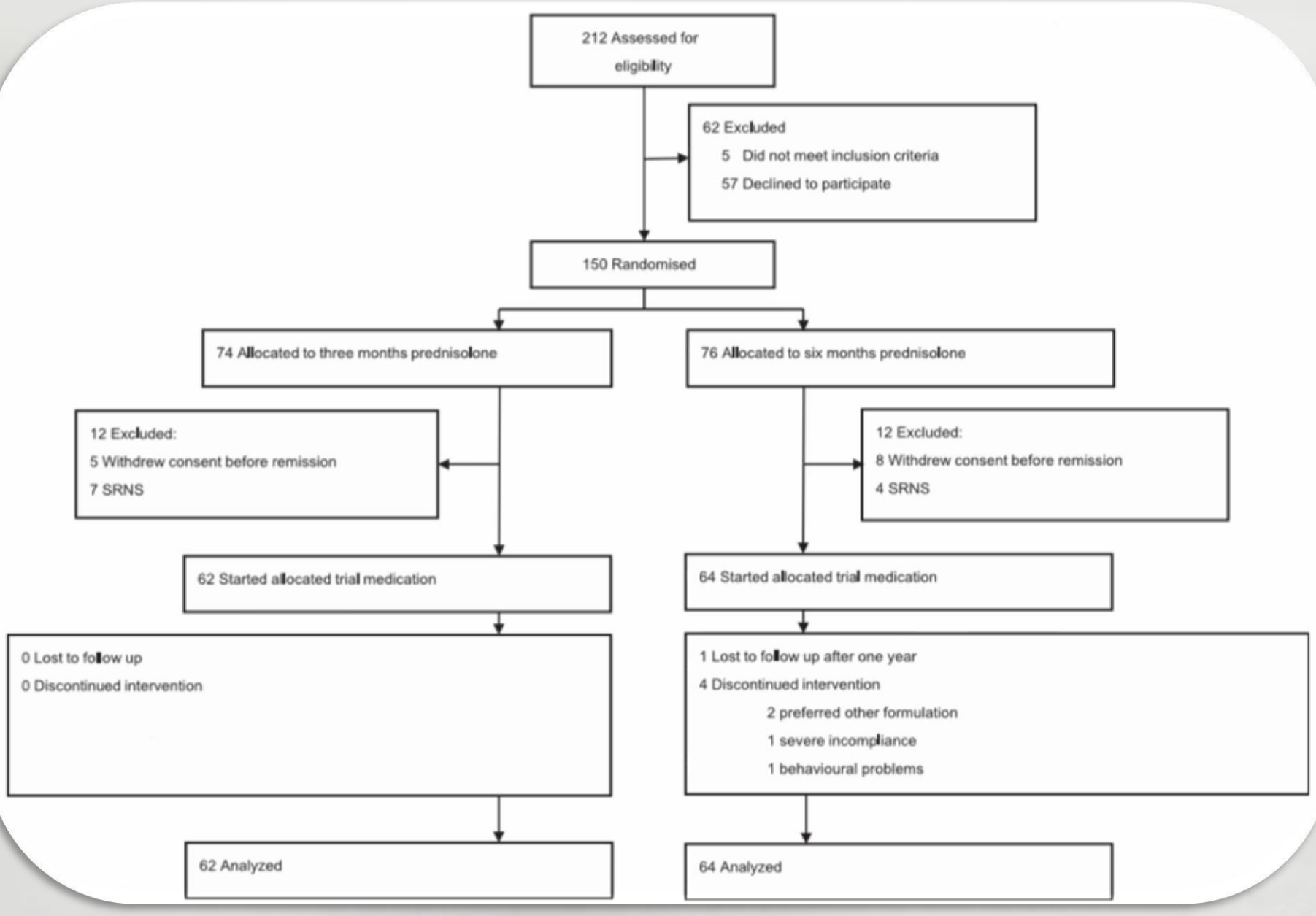

212 Assessed for eligibility
62 Excluded
5 Did not meet inclusion criteria
57 Declined to participate
150 Randomised
74 Allocated to three months prednisolone
76 Allocated to six months prednisolone
12 Excluded:
5 Withdrew consent before remission
7 SRNS
12 Excluded:
8 Withdrew consent before remission
4 SRNS
62 Started allocated trial medication
64 Started allocated trial medication
0 Lost to follow up
0 Discontinued intervention
1 Lost to follow up after one year
4 Discontinued intervention
2 preferred other formulation
1 severe incompliance
1 behavioural problems
62 Analyzed
64 Analyzed

Table 1. Baseline characteristics

	Overall (*n*=126)	3 Months Prednisolone (*n*=62)	6 Months Prednisolone (*n*=64)
Male, *n* (%)	86 (68)	39 (63)	47 (73)
Age (yr) median (IQR)	4.2 (3.2–6.2)	4.7 (3.2–5.8)	3.8 (3.2–6.4)
BP[a] (mean ± SD)			
Systolic, Z-value	1.7±1.3[b]	1.7±1.3[c]	1.6±1.3[d]
Diastolic, Z-value	1.6±1.1[b]	1.7±1.3[c]	1.6±1.0[d]
Serum albumin (g/L) median (IQR)	14.0 (10.0–16.2)	14.0 (10.0–17.0)	13.4 (10.0–16.0)
Microscopic hematuria[e], *n* (%)	40 (33)[f]	19 (32)[g]	21 (34)[h]
Hospital, *n* (%)			
University	14 (11.1)	5 (8.0)	9 (14.1)
General	112 (88.9)	57 (92.0)	55 (85.9)
Descent, *n* (%)			
Western European	83 (65.9)	46 (74.2)	37 (57.8)
Non-Western European	16 (12.7)	6 (9.7)	10 (15.6)
Mixed	13 (10.3)	3 (4.8)	10 (15.6)
Not reported	14 (11.1)	7 (11.3)	7 (10.9)
Quarterly distribution of disease onset, *n* (%)			
January to March	25 (19.8)	14 (22.6)	11 (17.2)
April to June	24 (19.0)	11 (17.7)	13 (20.3)
July to September	40 (31.7)	19 (30.6)	21 (32.8)
October to December	37 (29.4)	18 (29.0)	19 (29.7)

Similarity of the groups

- Induction therapy and trial medication were administered within a total of 24 weeks in both groups.

- Remission was defined as urinary protein excretion <20 mg/L or negative trace on dipstick analysis on 3 consecutive days.

Similarity of the groups

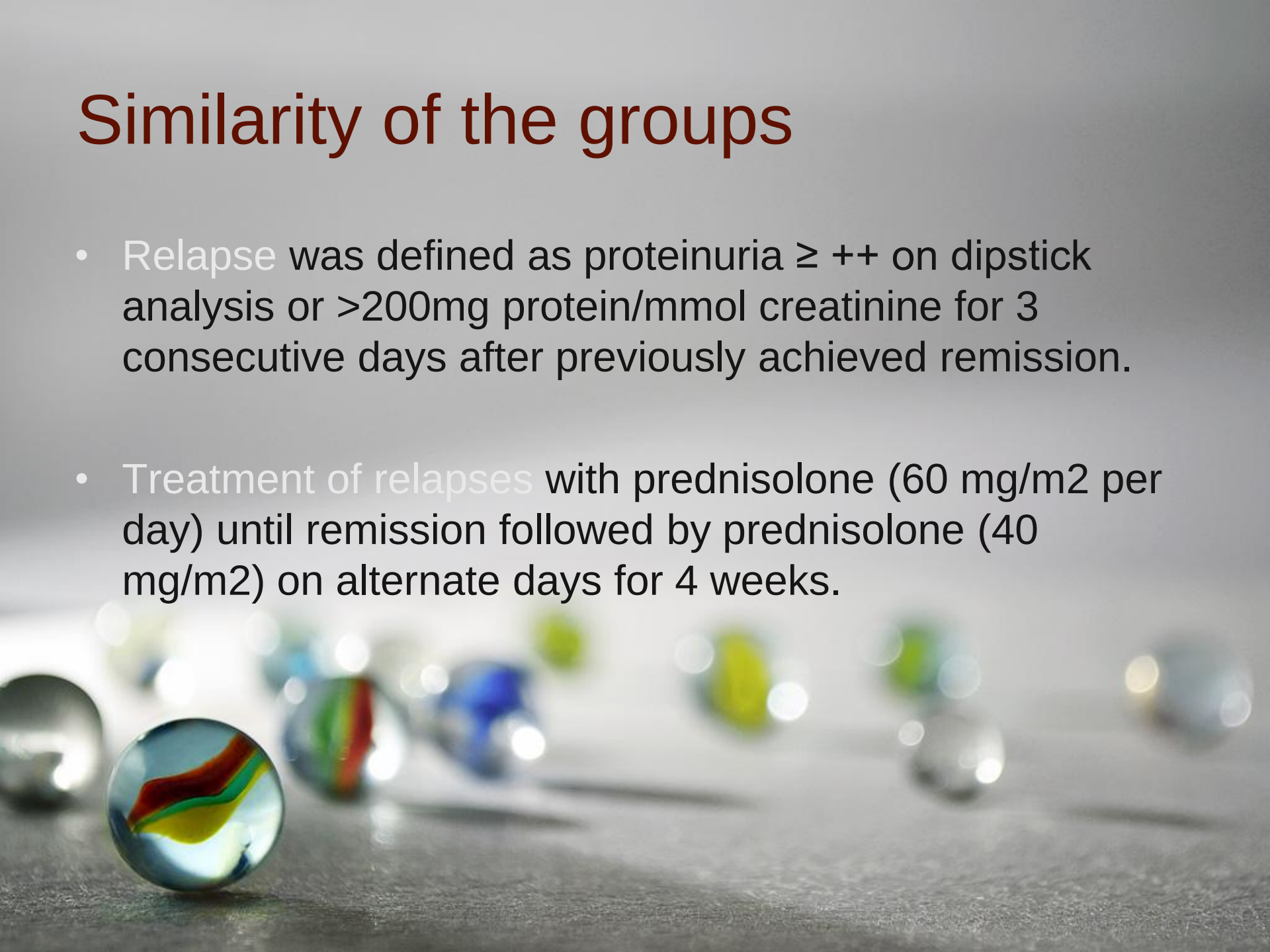
- Patients were characterized as steroid-resistant if they did not achieve remission within 6 weeks of 60 mg/m2 daily prednisolone.

- Steroid dependence was defined as two or more consecutive relapses either during or within 2 weeks after cessation of prednisolone.

Similarity of the groups

- Relapse was defined as proteinuria ≥ ++ on dipstick analysis or >200mg protein/mmol creatinine for 3 consecutive days after previously achieved remission.

- Treatment of relapses with prednisolone (60 mg/m2 per day) until remission followed by prednisolone (40 mg/m2) on alternate days for 4 weeks.



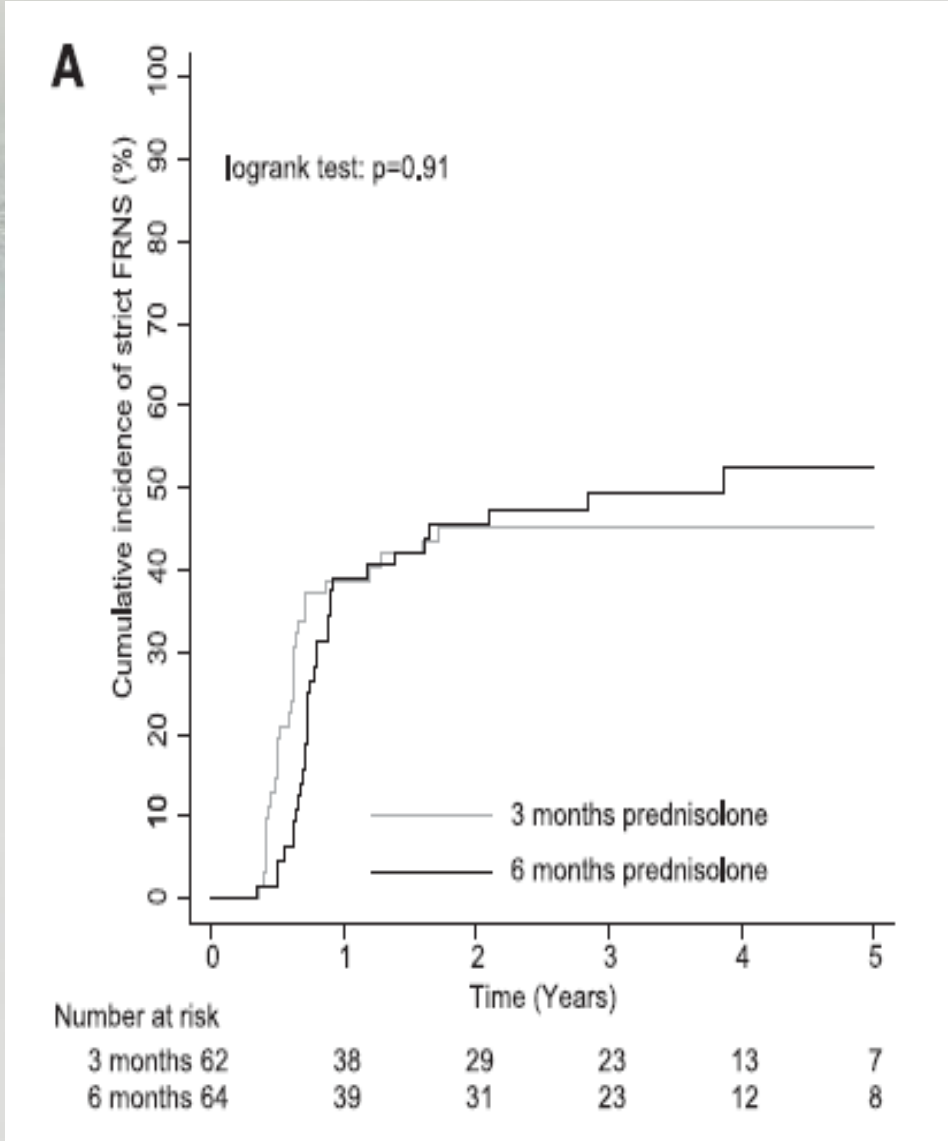
Relapses criteria

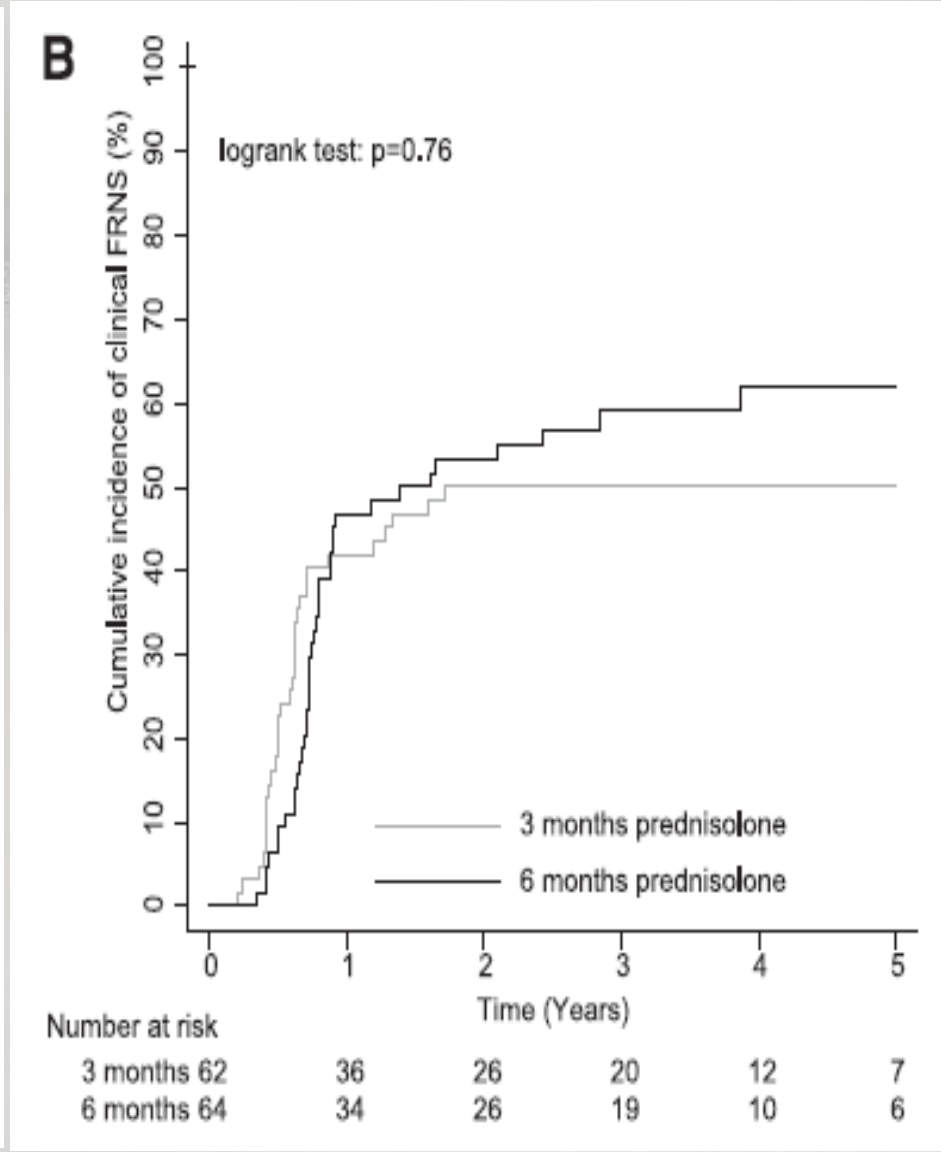
- A (two relapses within 6 months after ending first treatment)
- B (four relapses within any period of 12 months)
- C (need for additional treatment for other reasons than A or B)

Outcome

- Primary outcome: FRNS
- Secondary outcome: cumulative incidences of a first relapse, steroid dependence, number of relapses per patient per year, and adverse effects.

Results


A
logrank test: p=0.91
Cumulative incidence of strict FRNS (%)
0
10
20
30
40
50
60
70
80
90
100
0
1
2
3
4
5
Time (Years)
3 months prednisolone
6 months prednisolone
Number at risk
3 months 62 38 29 23 13 7
6 months 64 39 31 23 12 8


B
logrank test: p=0.76
Cumulative incidence of clinical FRNS (%)
0
10
20
30
40
50
60
70
80
90
100
0
1
2
3
4
5
Time (Years)
3 months prednisolone
6 months prednisolone
Number at risk
3 months 62 36 26 20 12 7
6 months 64 34 26 19 10 6

Result

	3-Month Group (*n*=62)	6-Month Group (*n*=64)	Difference (%; 95% CI)	Log Rank Test
Strict FRNS (%)				
6 months	14.5±4.5	3.1±2.2	−11.40 (−21.20, −1.60)	
1 year	38.7±6.2	39.1±6.1	0.40 (−16.60, 17.40)	
2 years	45.2±6.3	45.6±6.2	0.40 (−16.90, 17.70)	
3 years	45.2±6.3	49.3±6.4	4.10 (−13.50, 21.70)	
4 years	45.2±6.3	52.5±6.7	7.30 (−10.70, 25.30)	
5 years	45.2±6.3	52.5±6.7	7.30 (−10.70, 25.30)	*P*=0.91
Clinical FRNS (%)				
6 months	17.7±4.9	10.9±3.9	−6.80 (−19.10, 5.50)	
1 year	41.9±6.3	46.9±6.2	5.00 (−9.10, 19.10)	
2 years	50.1±6.4	53.3±6.3	3.20 (−14.40, 20.80)	
3 years	50.1±6.4	59.4±6.4	9.30 (−8.40, 27.00)	
4 years	50.1±6.4	59.4±6.4	12.20 (−5.70, 30.10)	
5 years	50.1±6.4	62.3±6.5	12.20 (−5.70, 30.10)	*P*=0.76

Results

Adverse effects

	3 Months Prednisolone	6 Months Prednisolone	*P* Value
BP≥P95			
At diagnosis	36/61 (59%)	28/62 (45%)	0.15
At 3 months FU	12/57 (21%)	7/60 (12%)	0.21
At 6 months FU	8/55 (14%)	10/52 (19%)	0.61
Cushingoid appearance at 6 months FU			
Cushing (moon face)	14/59 (23.7%)	21/58 (36.2%)	0.14
Striae	3/58 (5.2%)	4/60 (6.7%)	1.00
Ophtalmological abnormalities at 6 months FU			
Glaucoma	0/51 (0.0%)	0/45 (0.0%)	—
Cataract	1/53(1.9%)[a]	0/46 (0.0%)	1.00
Severe infections			
Pneumonia	1/62 (1.6%)	6/64 (9.4%)	0.16
Meningitis	0/62 (0.0%)	0/64 (0.0%)	—
Osteomyelitis	0/62 (0.0%)	0/64 (0.0%)	—
VZV reactivation	2/62 (3.2%)	1/64 (1.6%)	0.62
Whooping cough	0/62 (0.0%)	2/64 (3.1%)	0.50
Miscellaneous[b]	3/62 (4.8%)	1/64 (1.6%)	0.36
Overall	6/62 (9.7%)	10/64 (15.6%)	0.42
Dyspepsia	1/62 (1.6%)	2/64 (3.1%)	1.00
Thrombosis	0/62 (0.0%)	0/64 (0.0%)	—

Conclusion

- This study shows that prolongation of initial prednisolone treatment from 3 to 6 months, while maintaining an equal cumulative dose, does not reduce the risk of frequent relapses in childhood NS.

- This finding challenges the previous assumption that prolonged treatment duration improves clinical outcome.

Strength

- The study design.
- Nationwide setting $\longrightarrow$ avoid selection bias.
- Randomization and blindness.

Limitations

- Small sample size.
- Participants were observed and treated at their local hospital.

THANK YOU!