Ahorro de esteroides en el trasplante renal

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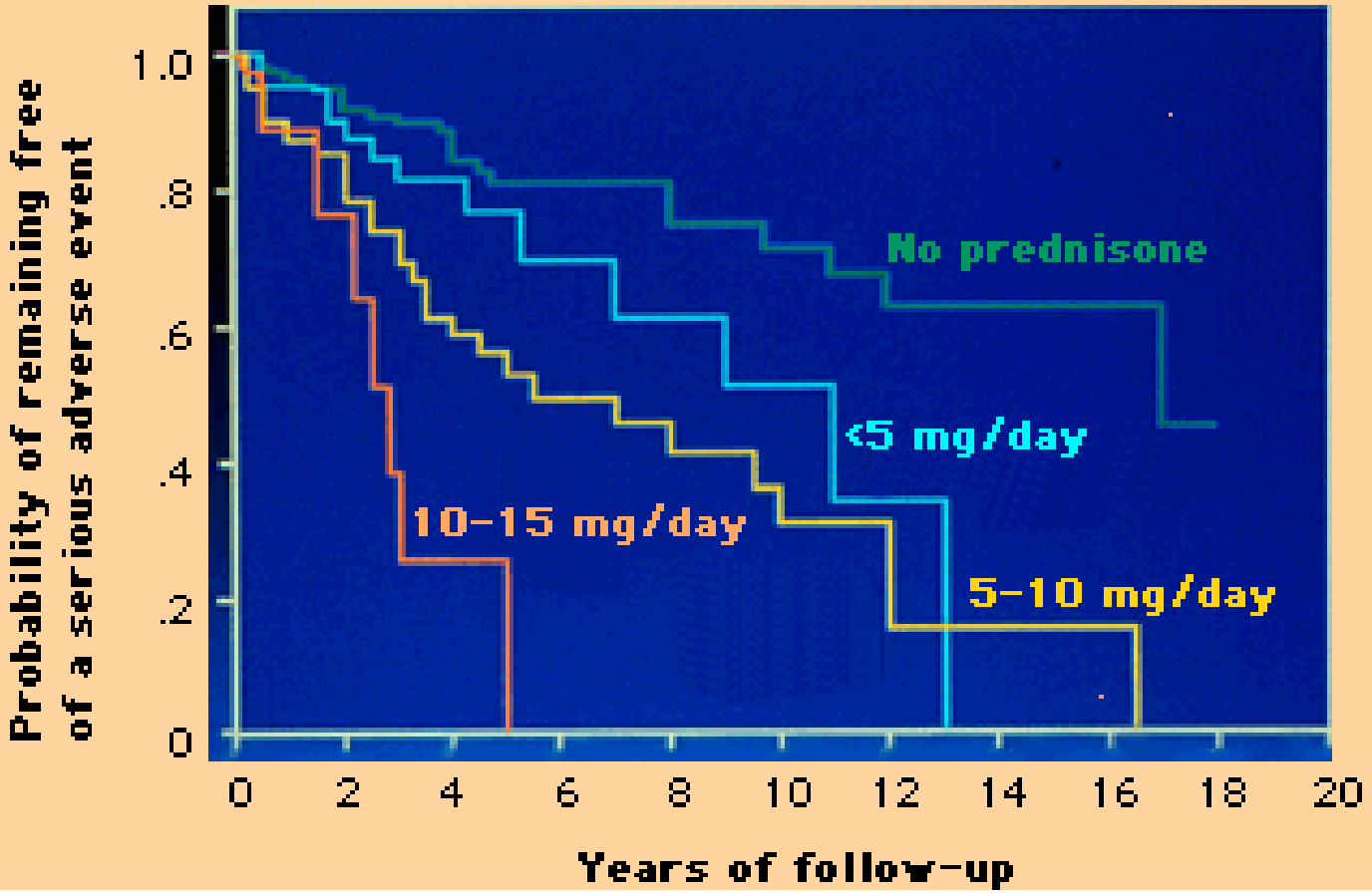
Serious adverse events in RA patients treated with steroids (Saag et al, 1994)



European best practice guidelines for renal transplantation

Late steroid or cyclosporine withdrawal.

GUIDELINES: A.

n order to reduce or avoid long-term serious adverse effects of corticosteroids,
such as bone fractures, diabetes mellitus,
arterial hypertension, osteoporosis and eye complications,
steroid withdrawal should be considered

EBPG Expert Group on Renal Transplantation.
Nephrol Dial Transplant. 2002;17 Suppl 4:19-20

Questions in steroid sparing/withdrawal

- Concomitant immunosuppression
- Patients' selection (age, race, previous AR..)
- Time after transplantation
- …..

Steroid-sparing strategies in the “CsA era”

Changes in renal function after steroid withdrawal in established patients (n=100; Time after Tx : 1- 6 y)

AZA + CSA

Ratcliffe PJ et al : Lancet 1996; 348:643

CsA MONOTHERAPY vs AZATHIOPRINE-PREDNISONE FROM THREE MONTHS AFTER KT (CsA+PDN)

	CsA monotherapy (n= 64)	AZA+ST (n=63)	p
AR (3 m)	30%	25%	ns
2-y sCr (µmol/l)	180±78	126±35	0.001
5-y GS	78%	87%	
Cost (DFL)	53±44	40.8±18	<0.005

HILBRANDS et al . Transplantation 1996;61:1105.

Late STW in CsA-treated KTx patients

	STW (n= 42)	ST main (n= 42)	Dif (95% CI)
↓ Renal F (%)	40	10	30 (14-48)
AR (%)	26	2	24 (10-38)
Cholest-low d	21%	56%	(-54 - -15)
Glyc Hb	5.8±0.7	6.2±0.9	0.4 (0.1-0.8)

Hollander et al. JASN 1997; 8: 294.

CsA MONOTHERAPY vs AZATHIOPRINE + CsA AT STEROID WITHDRAWAL (6 m after Tx; sCr < 2 mg/dl/))

	CsA monotherapy (n= 58)	CsA+AZA (n=58)	p
5-y Steroid resumption (AR)	57%	29%	<0.02
2-y sCr (mg/dl)	1.7	1.4	ns
5-y GS	90%	88%	ns

Sandrini et al. Transplantation 2000; 69: 1861.

A Meta-Analysis of steroid withdrawal trial

Acute rejection (9 studies, n=1461)

	Δ%	95% CI	p
AR after SRW	14	10-17	<0.001

Graft survival (9 studies, n=1899)

	RR	95%CI	
RR graft failure	1.38	1.08-1.67	<0.012

Kasiske et al, JASN 2000

European best practice guidelines for renal transplantation

Late steroid or cyclosporine withdrawal.

GUIDELINES:

B. Steroid withdrawal is safe only in a proportion of graft recipients and is recommended only in low-risk patients.

The efficacy of the remaining immunosuppression should be considered.

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Nephrol Dial Transplant. 2002;17 Suppl 4:19-20

European best practice guidelines for renal transplantation

Late steroid or cyclosporine withdrawal.

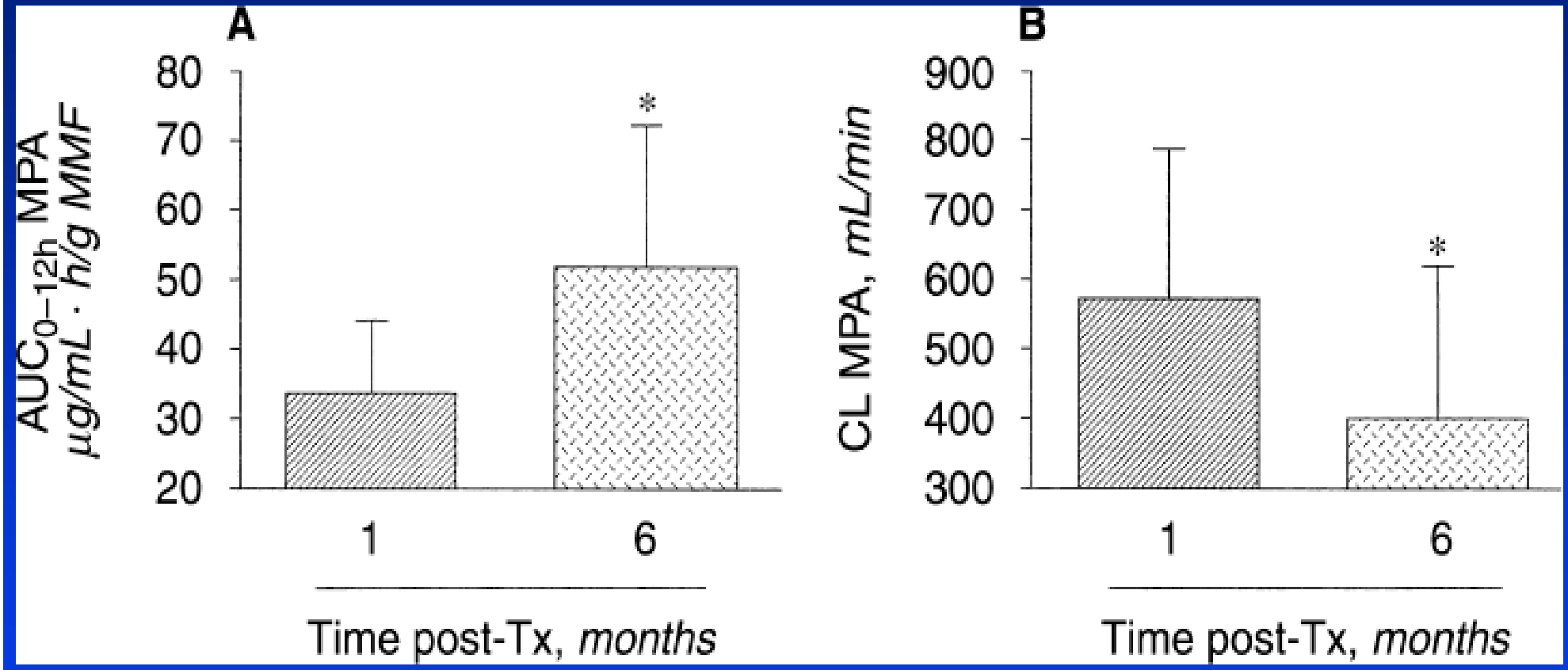
GUIDELINES:

C. After steroid withdrawal, graft function
has to be monitored very carefully
because of the risk of a delayed but continuous loss of function
due to chronic graft dysfunction.
In the case of functional deterioration or dysfunction,
steroids should be re-administered.

EBPG Expert Group on Renal Transplantation.
Nephrol Dial Transplant. 2002;17 Suppl 4:19-20

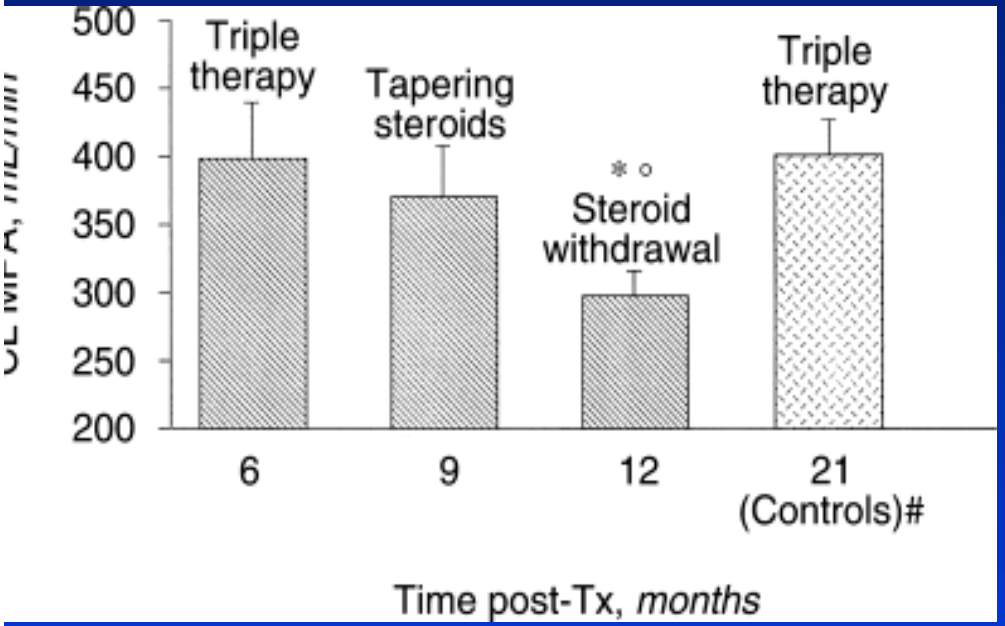
Steroid-sparing strategies with new immunosuppressants

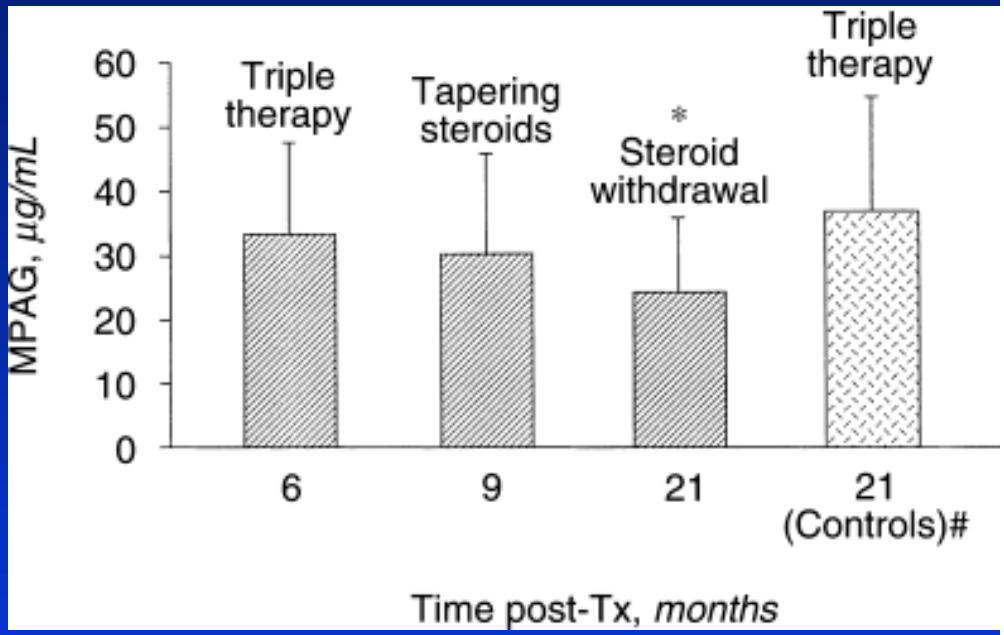
AUC and plasma clearance of MPA within the first month after Tx (high dose steroids) and at 6 months post-Tx (lower maintenance steroid regimen)



Cattaneo et al., *Kidney Int 2002;* 62: 1060.

Changes in in MPA clearance and MPAG levels





Reversion of the enhanced activity of uridine diphosphate-GT* induced by steroid ?
(*responsible for MPA metabolism)

Cattaneo et al., Kidney Int 2002; 62: 1060.

Steroid-free (day 0) immunosuppression after kidney transplantation

	MMF+ATG+CsA n = 68	ATG+CsA n = 190 (hist controls)	p
Acute rejection	**15%**	**37.4%**	**0.0006**
EBV i	**15%**	**46.8%**	**0.0005**

Similar CMVi
Similar renal function

Birkeland, 1998

Complete steroid avoidance immunosupression protocol in pediatric renal transplantation

Prevalence of Hypertension

Daclizumab + Tacrolimus + MMF

Months posttransplant	Steroid free	Steroid based	*p*
1	40% (4/10)	81.1% (30/37)	*0.024*
3	10% (1/10)	73.0% (27/37)	*0.0009*
6	0% (0/7)	70.2% (26/37)	*0.003*

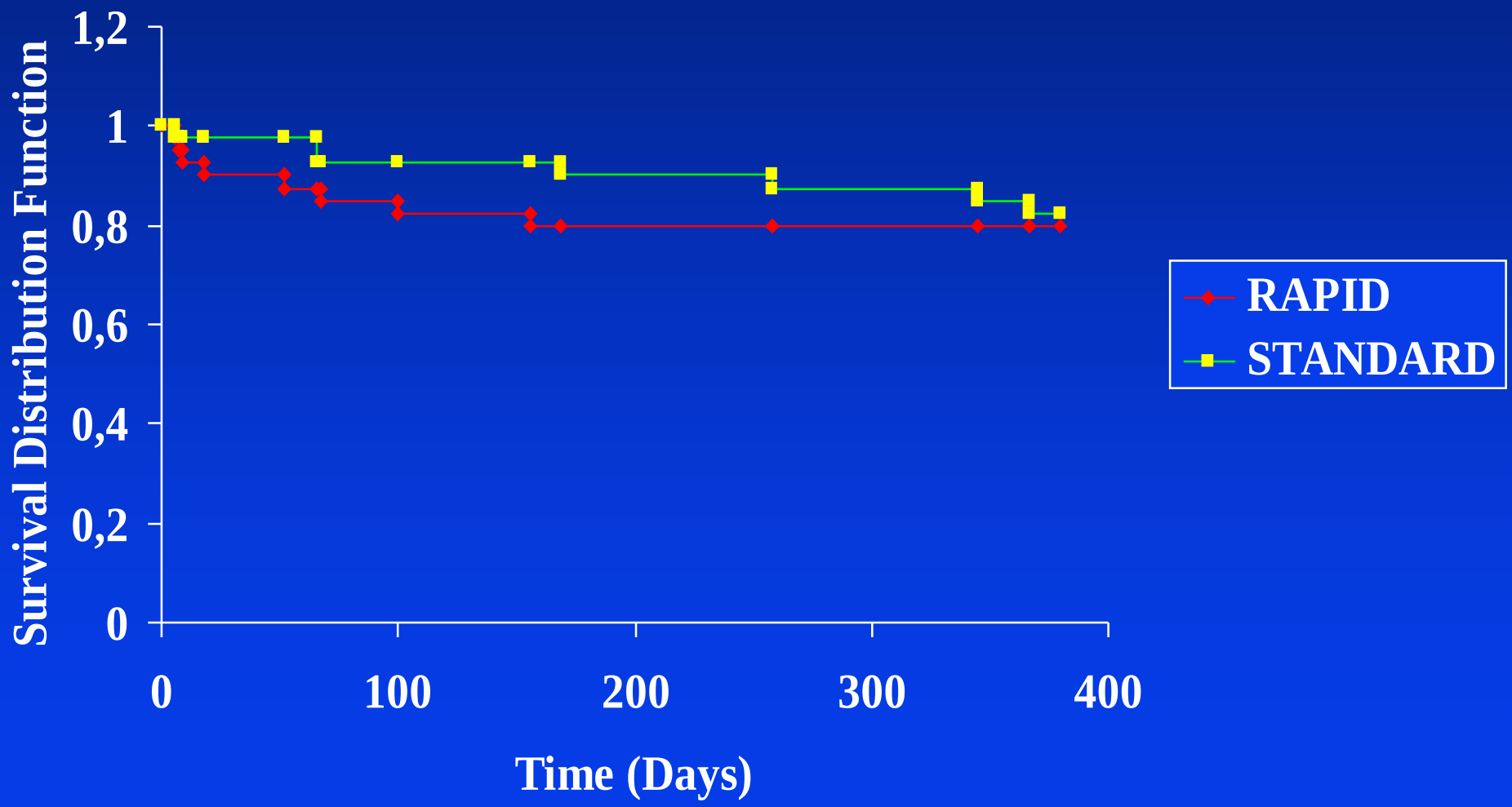
Sarwal et al, Transplantation, 72, No 1, 2001

Rapid steroid withdrawal (day 5) with Simulect, CsA and MMF

	Rapid	Standard
	N=40 (%)	N=43 (%)
Biopsy Proven Rejection		
at 6 months	8 (20.0)	4 (10.0)
at 12 months	8 (20.0)	7 (17.7)
Banff '97 Grade		
IA	6 (75.0)	4 (57.0)
IB	0 (0.0)	0 (0.0)
IIA	2 (25.0)	2 (29.0)
IIB	0 (0.0)	1 (14.0)
III	0 (0.0)	0 (0.0)

Vincenti et al. Am J Transplant. 2003;3:30

Kaplan-Meier Survival Function Estimates Biopsy Confirmed Rejections



Serum Creatinine (mg/dL)

		Rapid	Standard
Week 12	n	40	39
	mean (+/-SD)	1.39 +/-0.42	1.68 +/-1.10
	median	1.30	1.30
Week 24	n	40	38
	mean (+/-SD)	1.47 +/-0.54	1.61 +/-1.20
	median	1.60	1.37
Week 52	n	40	39
	mean (+/-SD)	1.46 +/- 0.55	1.48 +/- 0.41
	median	1.30	1.40

Rapid steroid discontinuation in LRD Kt (n= 51)

- Thymoglobulin (1.25 mg/kg intraop and qdx4);

- Methylprednisolone 500 mg intraop.,

-Prednisone 1 mg/kg 1 day, 0.5 mg/kg 2 days, 0.25 mg/kg 2 days, then d/c

-MMF, 1 g b.i.d

-CSA 4 mg/kg/d

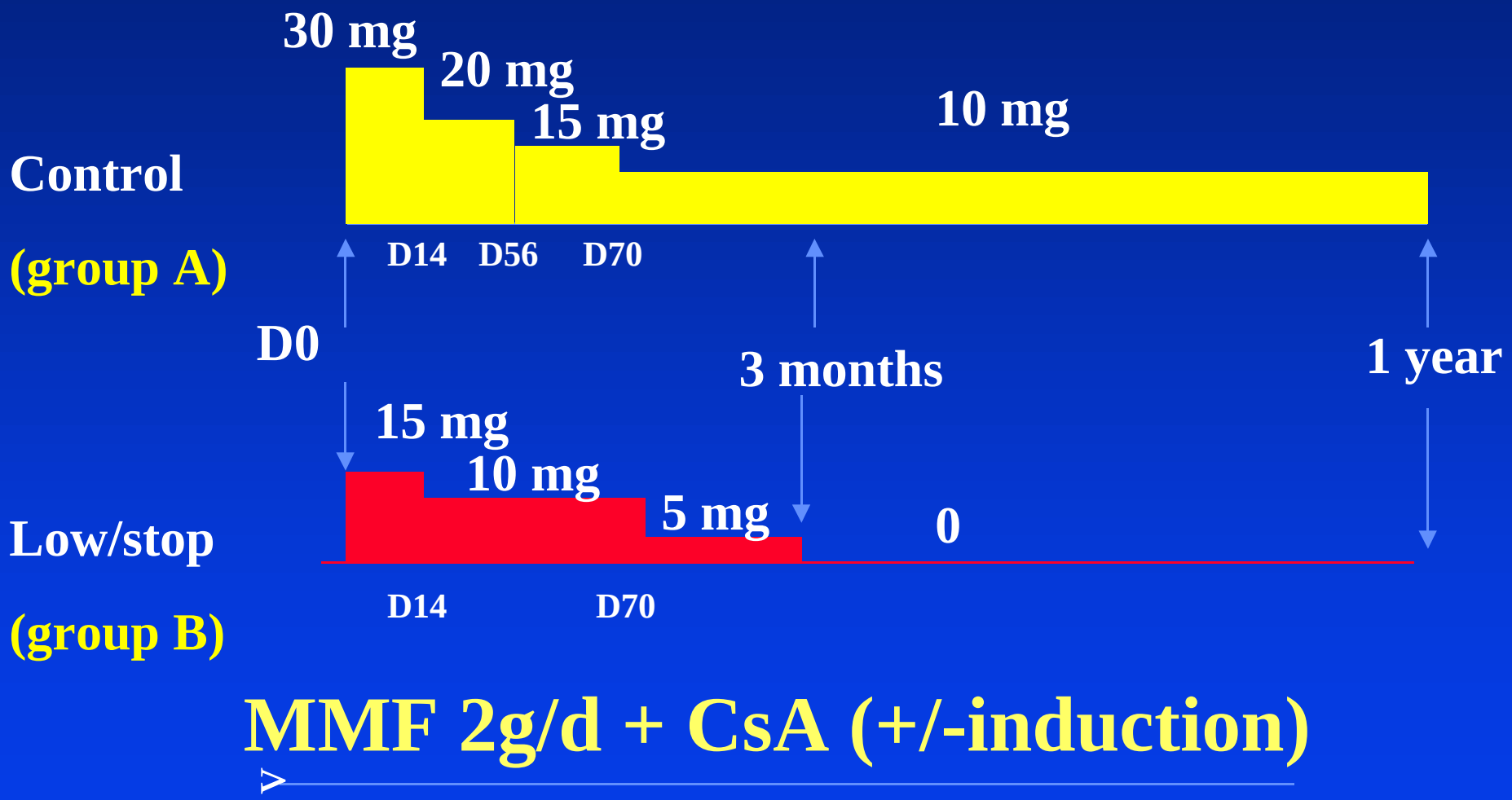
Matas et al, Am J Transplant. 2001 ;1:278.

Rapid steroid discontinuation in LRD Kt (n= 51)

- Acute rejection free (6 and 12 m): 87%
- sCr (3 and 6 m) : 1.7 +/- 0.5 mg/dl
- No differences with historical controls
  (triple therapies AZA/MMF without induction)

Matas et al, Am J Transplant. 2001 ;1:278.

Steroid dose reduction and withdrawal (3 m) in MMF-treated KTx patients (n= 500)



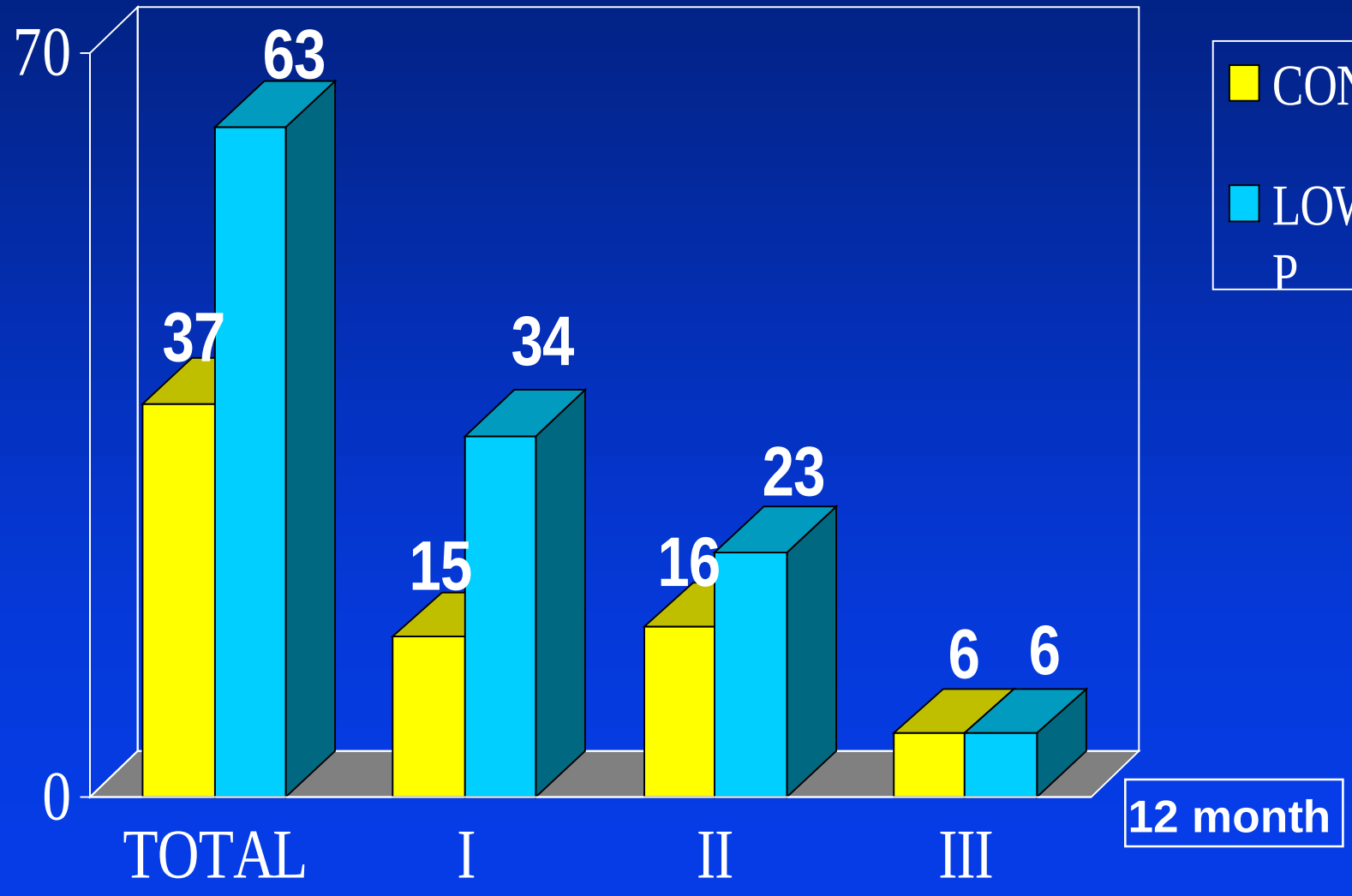
(double-blind, multicenter, randomised study)

Vanrenterghem et al. Transplantation. 2000; 70:1352.

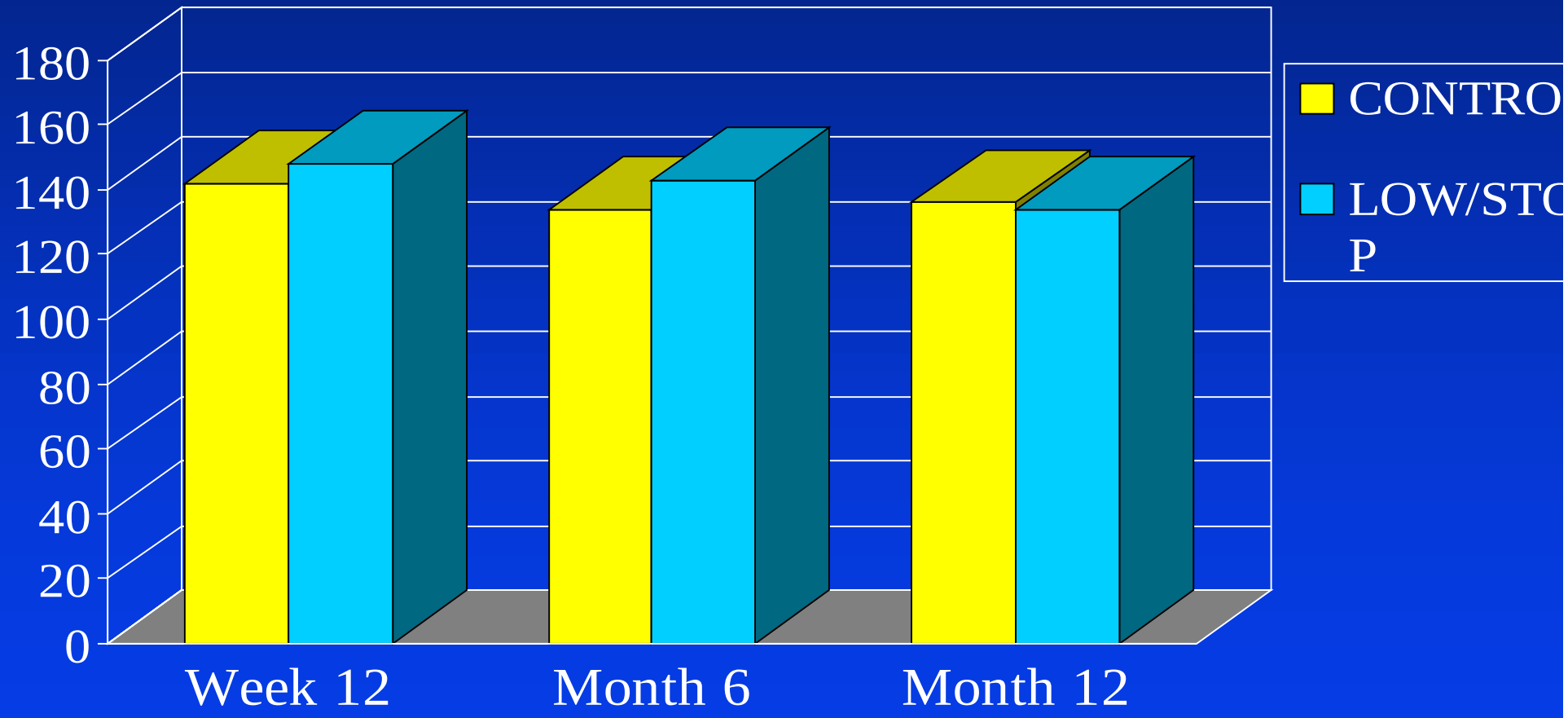
Biopsy-Proven Acute Rejection during 12 months (percentage of pts)

	CONTROL STEROIDS	LOW / STOP STEROIDS
DAY O TO D82	14%	23%
DAY O TO D365	15%	25%

Severity of Biopsy-Proven Acute Rejection Episodes (number of pts)



Changes in mean serum creatinine (µmol/L)



Long term cardio-vascular risk factors at 12 months

	CONTROL STEROIDS	LOW/STOP STEROIDS
Systolic B.P.	141	134**
Diastolic B.P.	83	79*
Cholesterol (mmol/L)	6.27	5.6*
Triglycerides (mmol/L)	2.16	1.88*

*** p < 0.01 ; ** p < 0.001**

Bone density at 12 months

	CONTROL STEROIDS	LOW/STOP STEROIDS
L2 (%)	94.3	100.3*
L3 (%)	93.4	99.5*
L4 (%)	91.2	94.1**

*** p < 0.01 ; ** p=0.09**

STW at 3 months in KTx recipients on CsA + MMF
(planned recruitment: n= 500)

Groups	maintenance (n = 134)	withdrawal (n=132)
1-y AR-TF	9.8%	30.8%
1-y BPAR	4.9%	22.4%

Enrollment stopped at 266 pts

STW Study Group. Transplantation 1999; 68: 1865.

STW at 3 months in KTx recipients on CsA + MMF (planned recruitment: n= 500)

Cumulative incidence of biopsy-proven acute rejection stratified by race and treatment (1-y)

STW/blacks	47%
STW/non-blacks	18%
STM/blacks	7%
STM/non-blacks	6%

n= 266

STW Study Group. Transplantation 1999; 68: 1865.

Tacrolimus-based immunosuppression and steroid withdrawal

Patients	Steroid withdrawal
Adults	69%
Pediatric	66%

Shapiro et al, 95, 99.

Sirolimus-based immunosuppression and steroid withdrawal

Study group	12 m		18 m	
	on treatment	STW	on treatment	STW
1 (n=20)	16	75%	14	100%
2 (n=20)	16	81%	15	87%
Total		78%		93%

(initial doses of SRL : 0.5 - 7 mg/m^2)

Kahan et al. 1998.

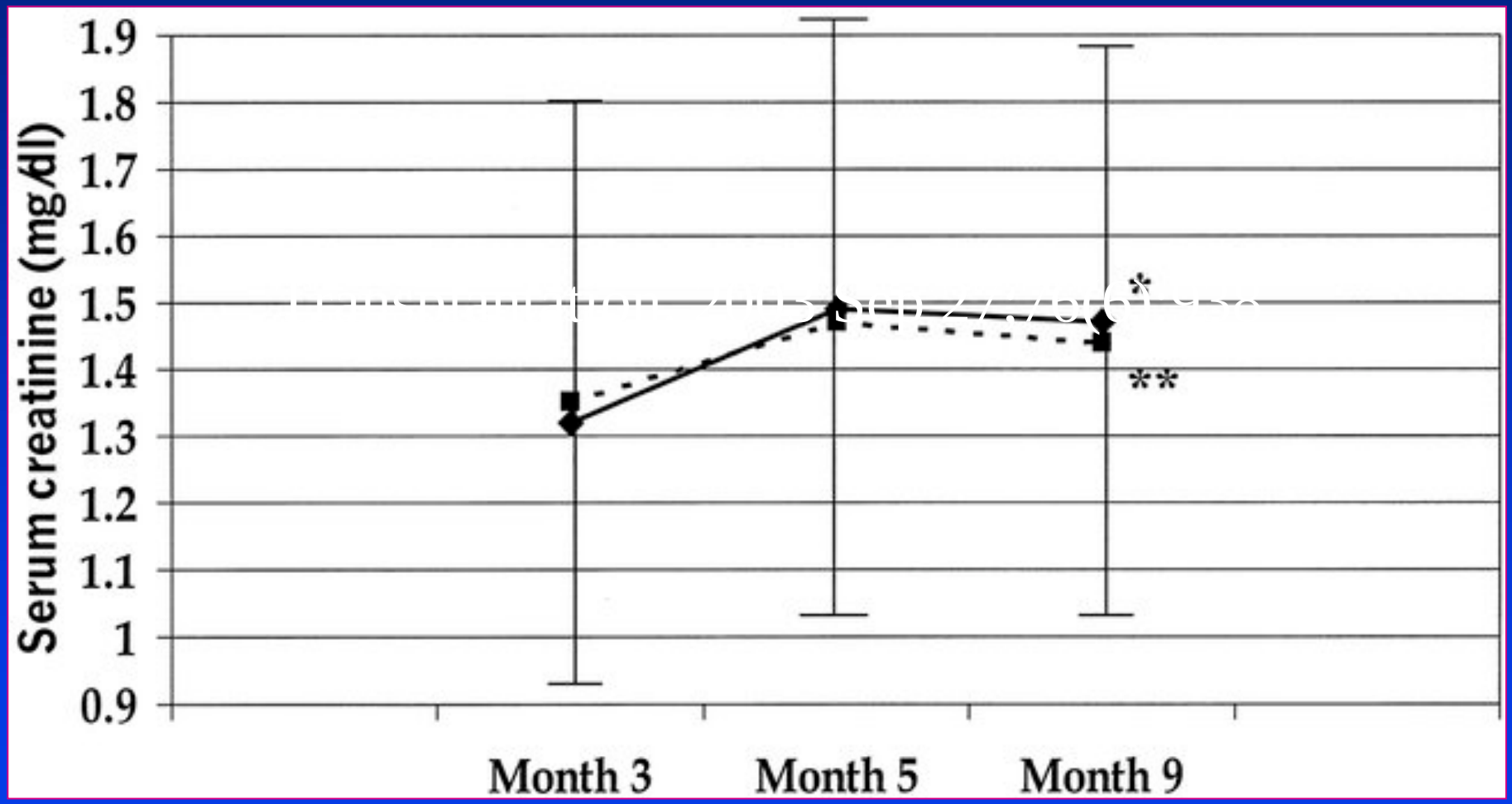
MMF(2 g/d), low-dose TAC, ZPX (5 doses) and steroid withdrawal at 150 d after Tx (n= 79, 12 m)

BPAR	11.4%
PS	98.7%
GS	97.5%
CrCl	54.5 ml/min

Improved lipidic profile

Kuypers et al., Clin Transplant. 2003 ;17:234.

Withdrawal of steroids in AA treated with SRL-TRL



Hricik et al, Transplantation. 2003, 27;76: 938.

STW vs CsAW in Renal Transplantation (6 m)

(Dutch Multicentre Study)

	MMF/PD	MMF/CsA	MMF/CsA/PD	p
Patients	63	76	73	
AR	14(22%)	3(4%)	1(1%)	0.0001
Banff I	5	2	1	
Banff 2≥	9	1	0	
Anti-rejection				
MPD	13	4	1	
Anti-T cell	6	2	0	
BPCR	9	4	1	

Smak Gregoor et al. JASN 2002 ;13:1365.

Steroid withdrawal in MMF-treated patients

Early : < 6 m post-Tx (n= 35)

Late : > 6 m post-Tx (n= 56)

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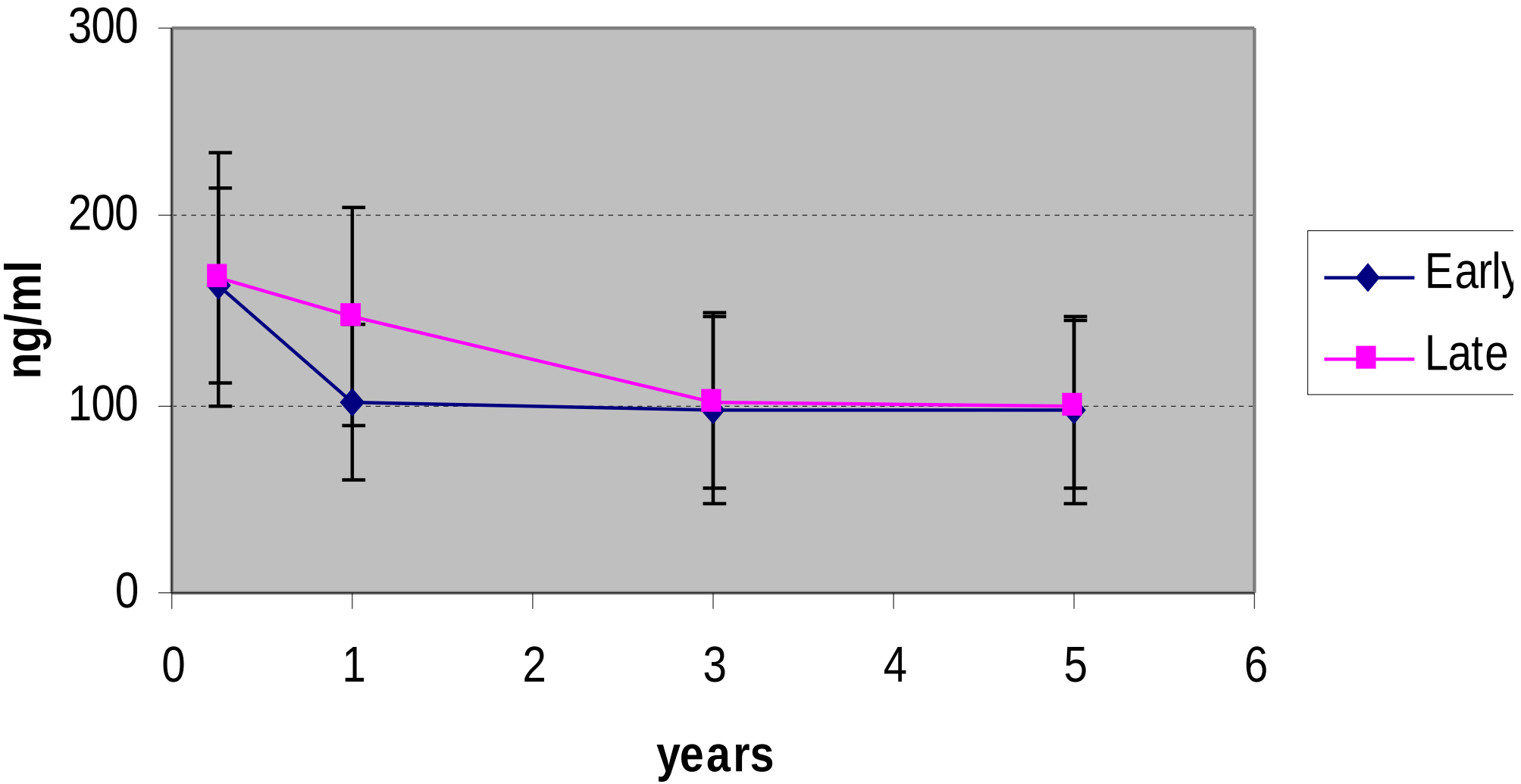
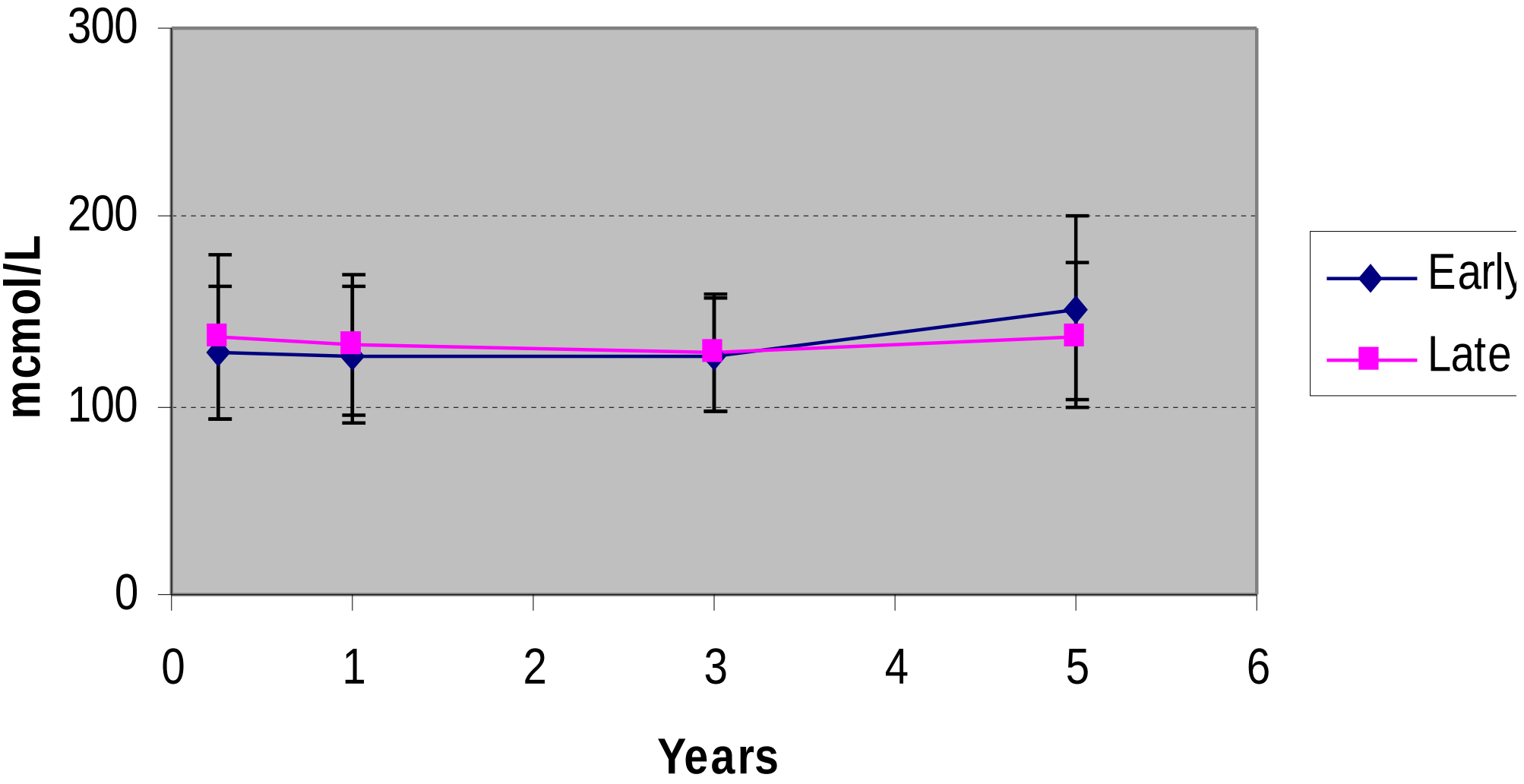
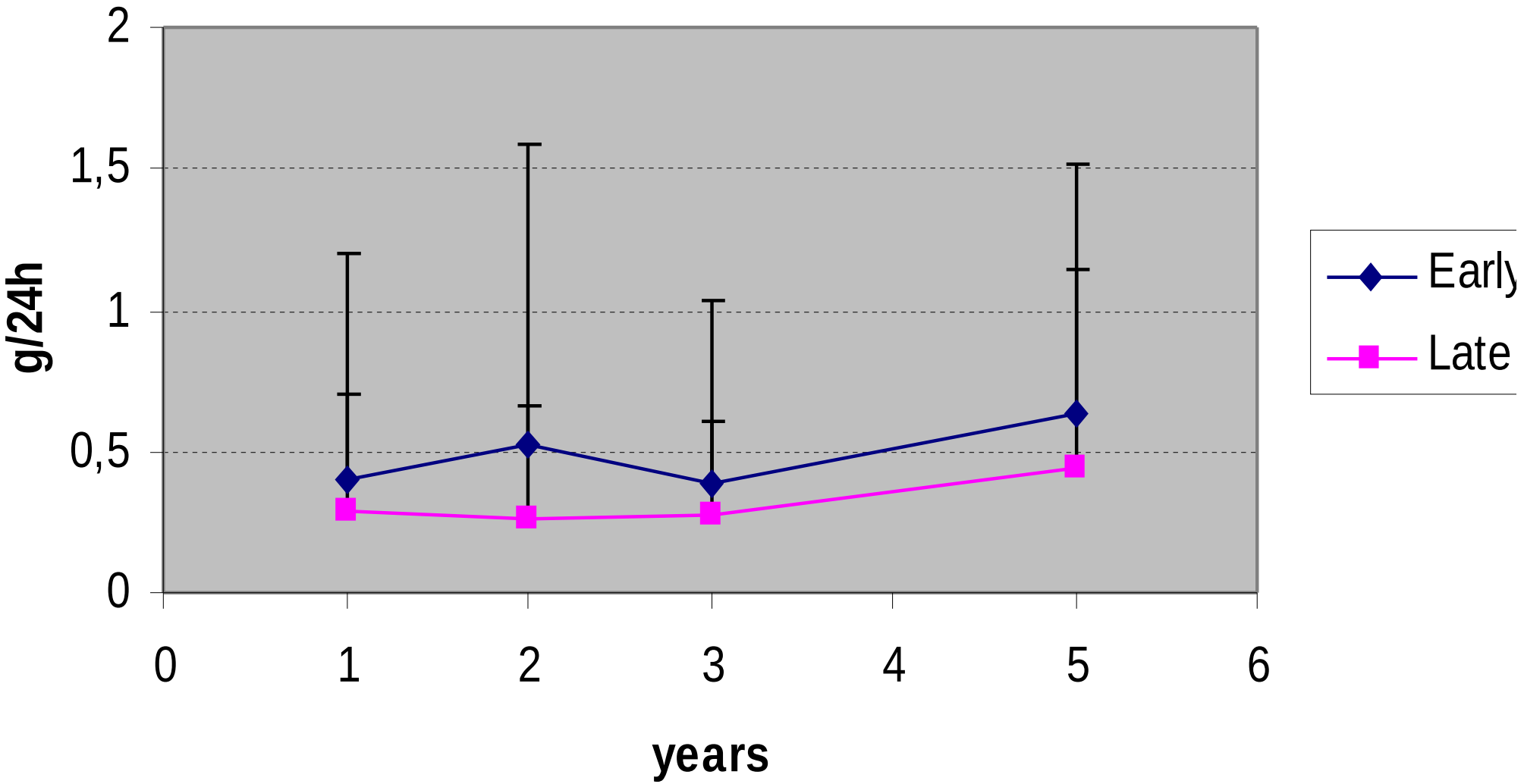
CsA levels



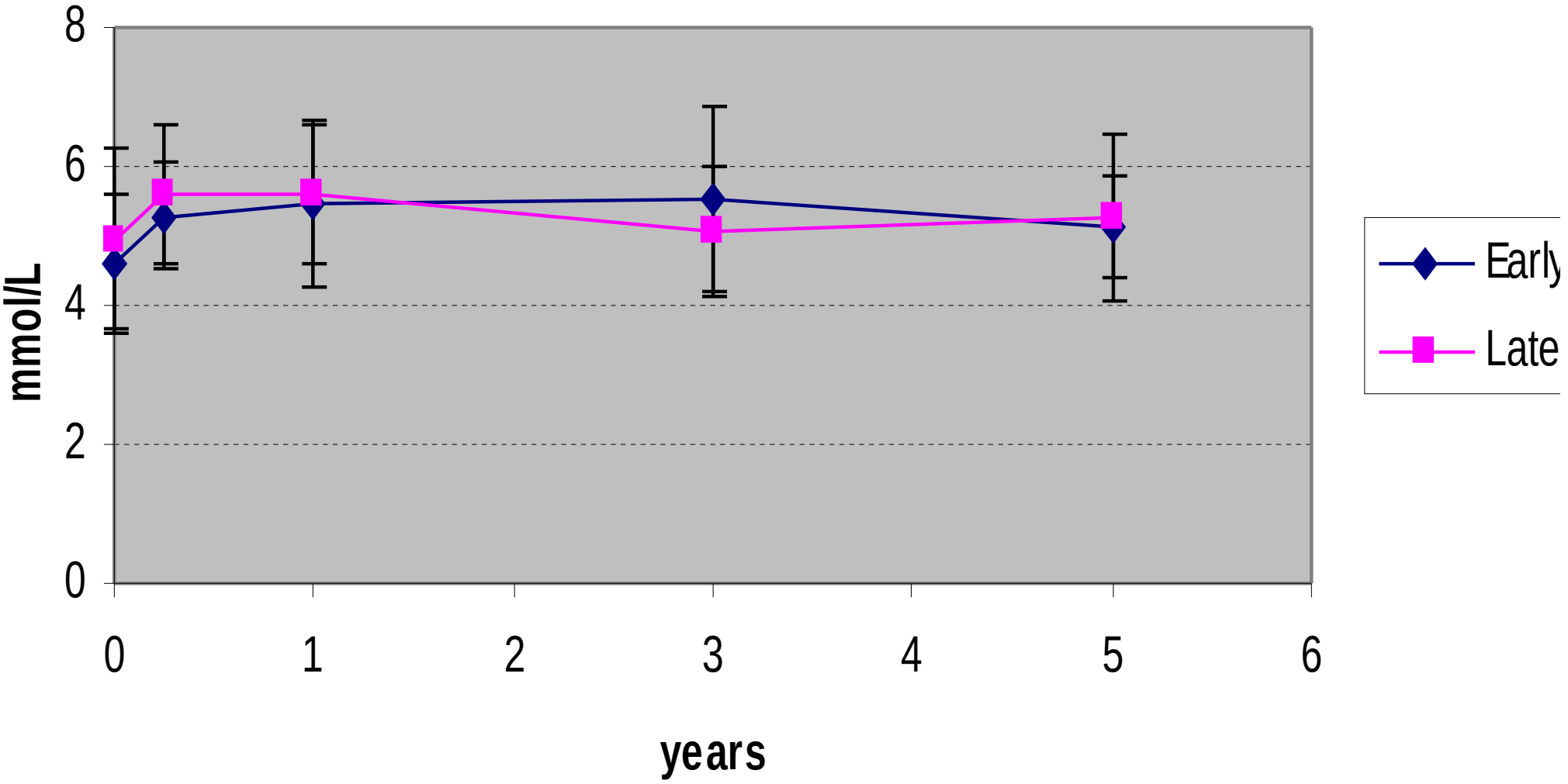
Serum creatinine



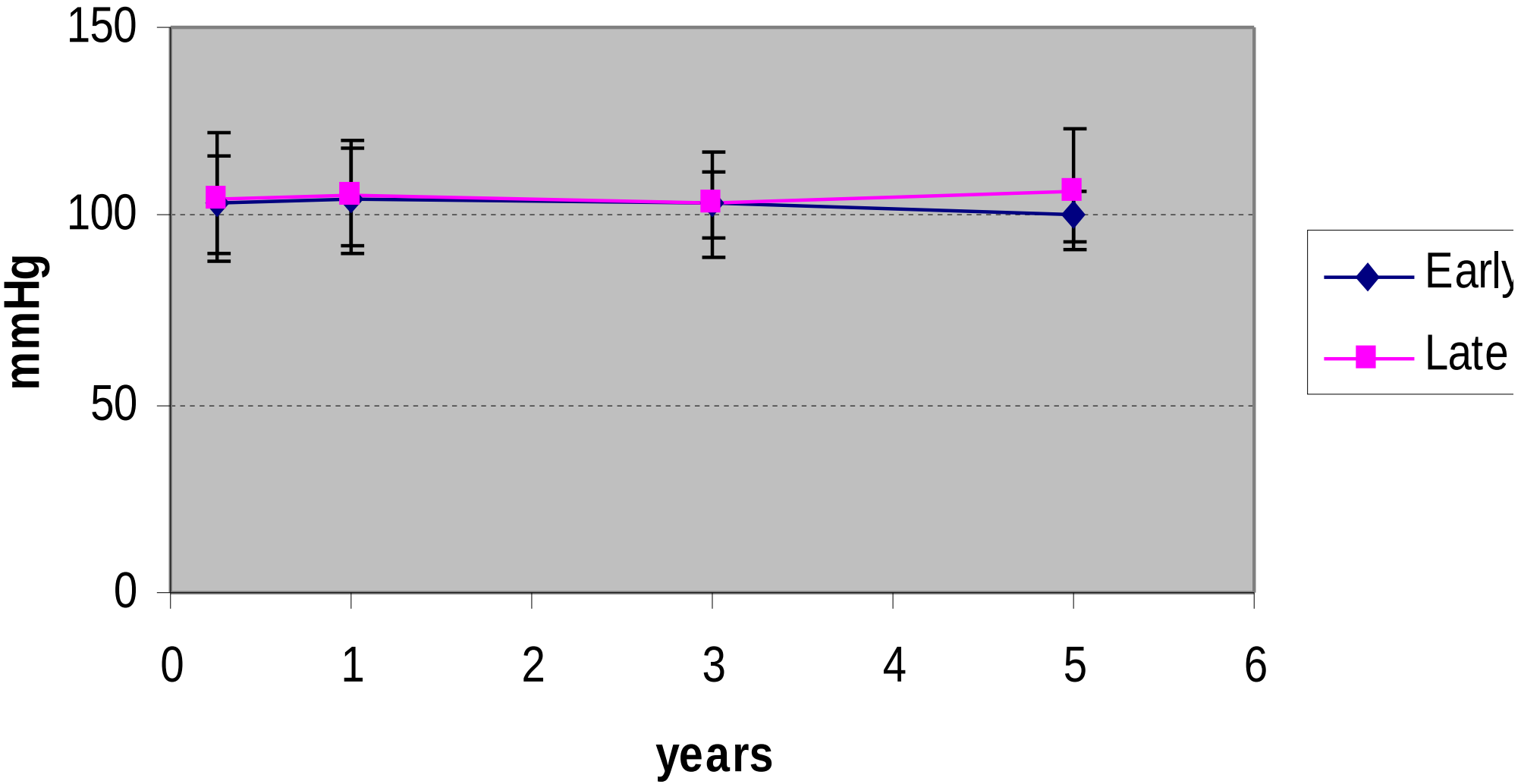
Proteinuria



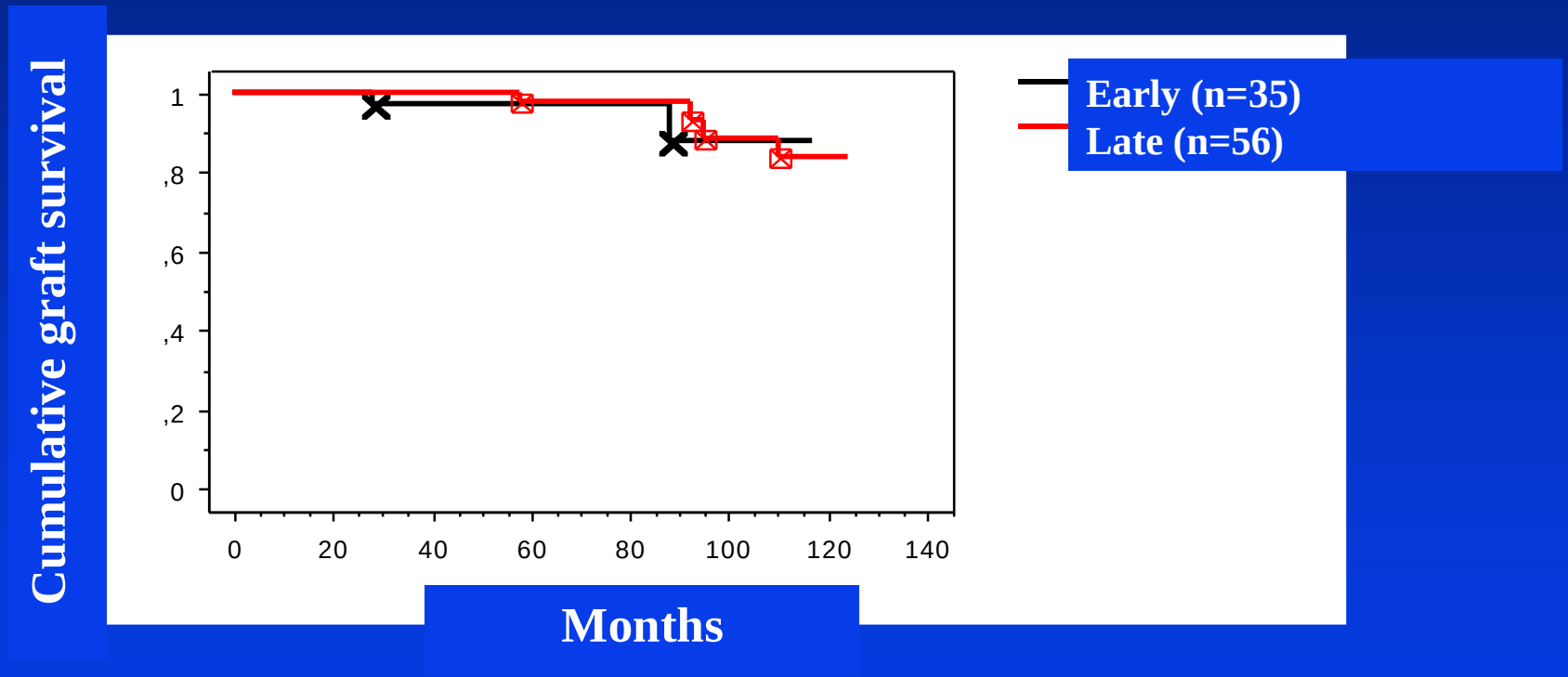
tCholesterol



MAP



Graft survival (censoring for DFG)



Early ; HCV-MPGN; CTN

Late. 4 CTN

Logrank test (Mantel-Cox) P = 0,8

Risk factors for graft failure

Multivariate analysis

Variable	RR	95% CI	P
Dialisis time	1.0	0.984-1.017	1
PRA (%)	1.074	1.017-1.134	0.01
AR (yes)	6.1	0.95-39.2	0.01

Conclusiones

- El ahorro de esteroides aparece factible con los nuevos inmunosupresores
- Los pacientes de alto riesgo deberian ser excluidos de estas esatrategias
- Control estricto a corto y largo plazo
- Evitar esteroides o retirarlos ?