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# **Immunosuppressive Minimization Strategies Progress Report 2007**

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**Honoraria from: Novartis, Astellas, Roche, Wyeth, Genzyme**

**Some slides provided by Astellas, Novartis, Roche, Wyeth**

# Issues

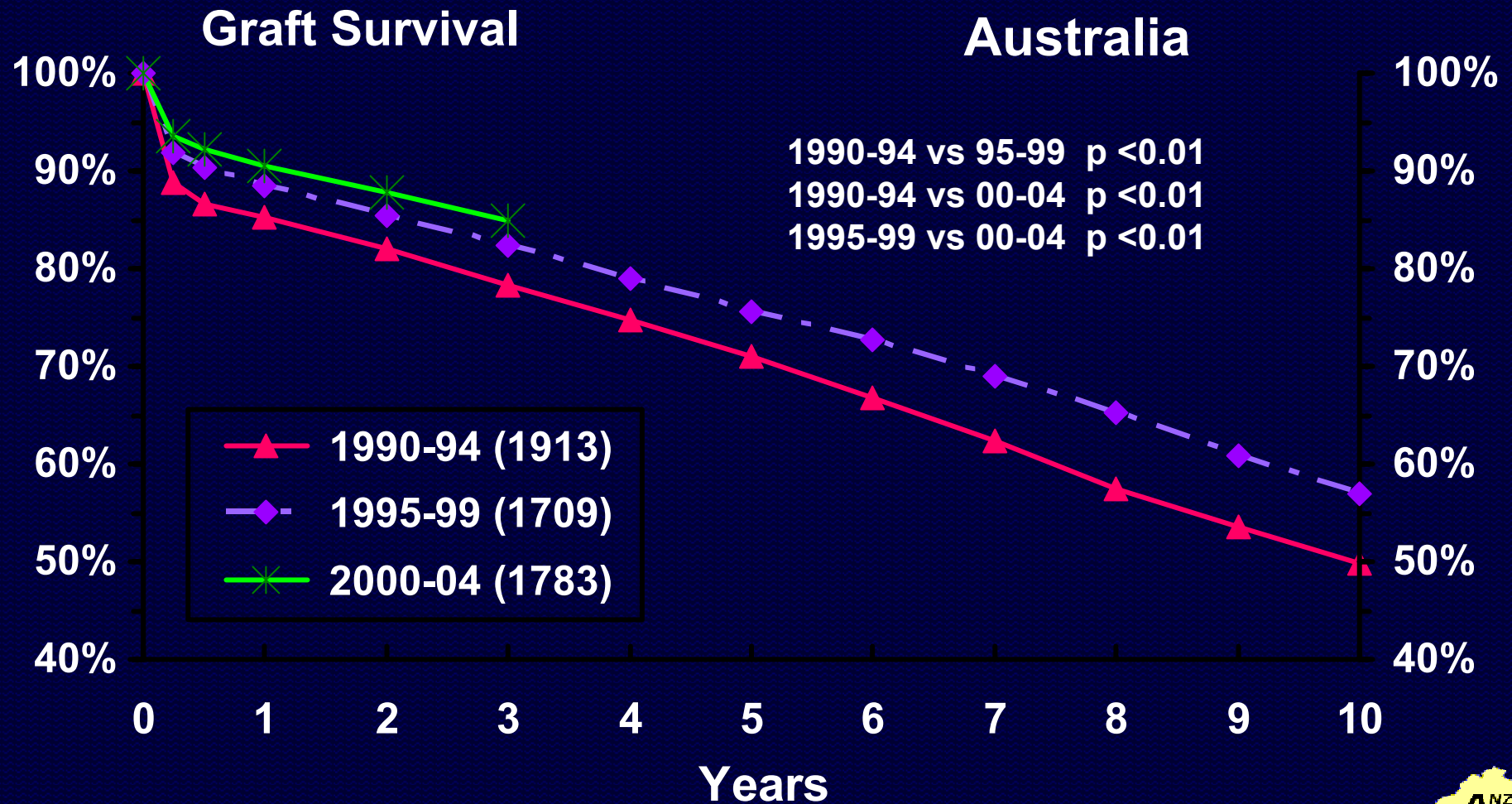
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- **Why Consider These Strategies?**
- **Results With:**
  - Steroid Minimization**
  - CNI Minimization**
- **Conclusions**

# Why Consider These Strategies?

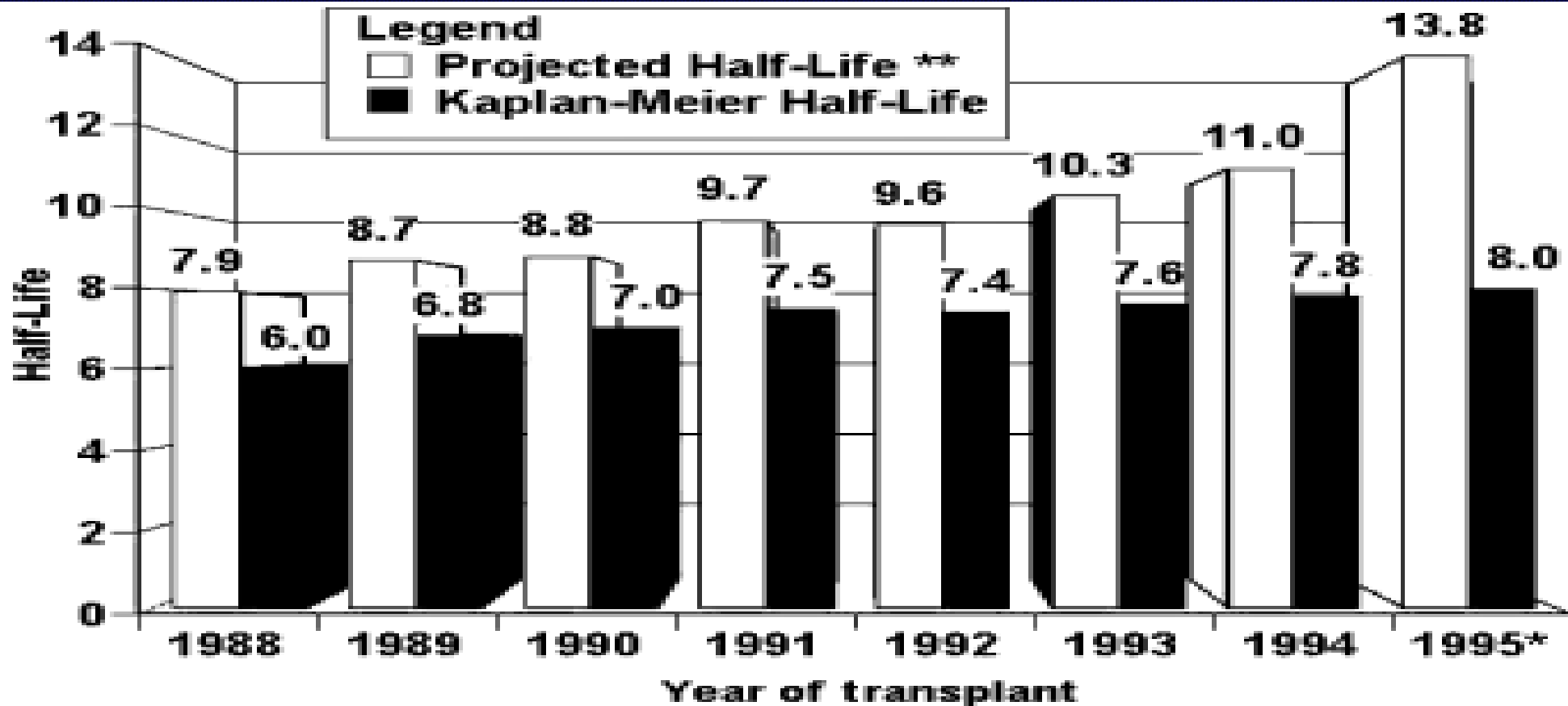
## Deceased Transplanted Graft Survival

### All Grafts 1990 - 2004



# Projected vs Actual Half Life

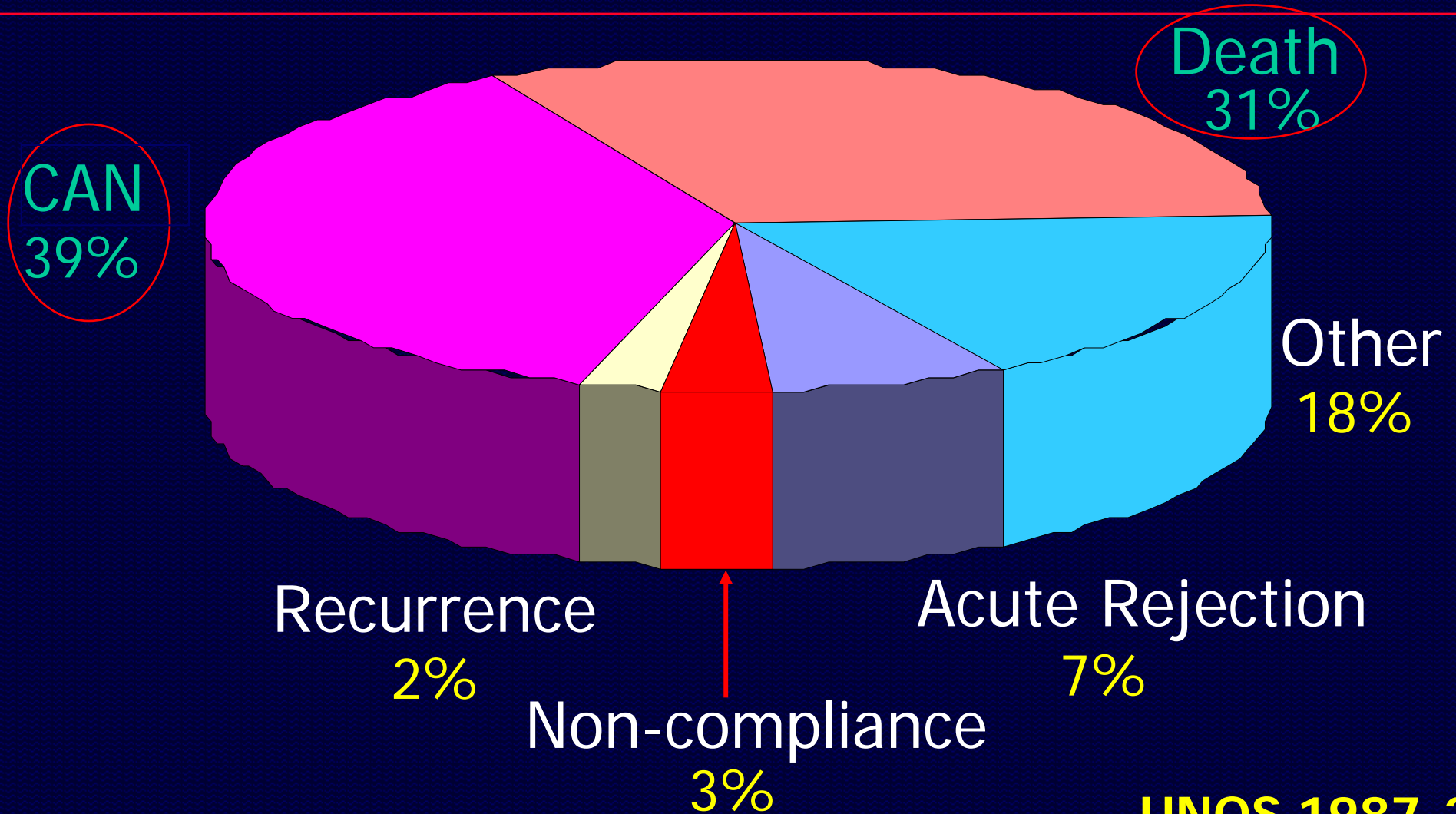
Meier-Kreische et al Am J Transpl 2004



\* Kaplan-Meier half-life based on time to 51.0% survival

\*\* as published in NEJM (March, 2000).

# Causes of Renal Graft Loss after First Year (120,000 transplants, 15,000 failures)



# Goals of Immunosuppression Perspective in 2007

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- **Early Era**
  - Goal was to reduce acute rejection and improve short term graft survival
- **Current Era**
  - Goal is to reduce toxicity to improve longterm survival:
    - reduce CV, infectious, malignant death
    - improve renal function
    - improve adherence
    - maintain low acute rejection rate
- **Have drug minimization regimens allowed us to achieve these goals?**

# **Drug Minimization Protocols Issues**

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- **Acute rejection**
- **Renal function**
- **Renal pathology**
- **Cardiovascular disease risk factors**
- **Malignancy**



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# STEROID MINIMIZATION

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# Goals of Steroid Minimization

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- **Maintain current acute rejection rate**
- **Improve adherence**
- **Reduce cardiovascular complications**
- **Improve graft and patient survival**

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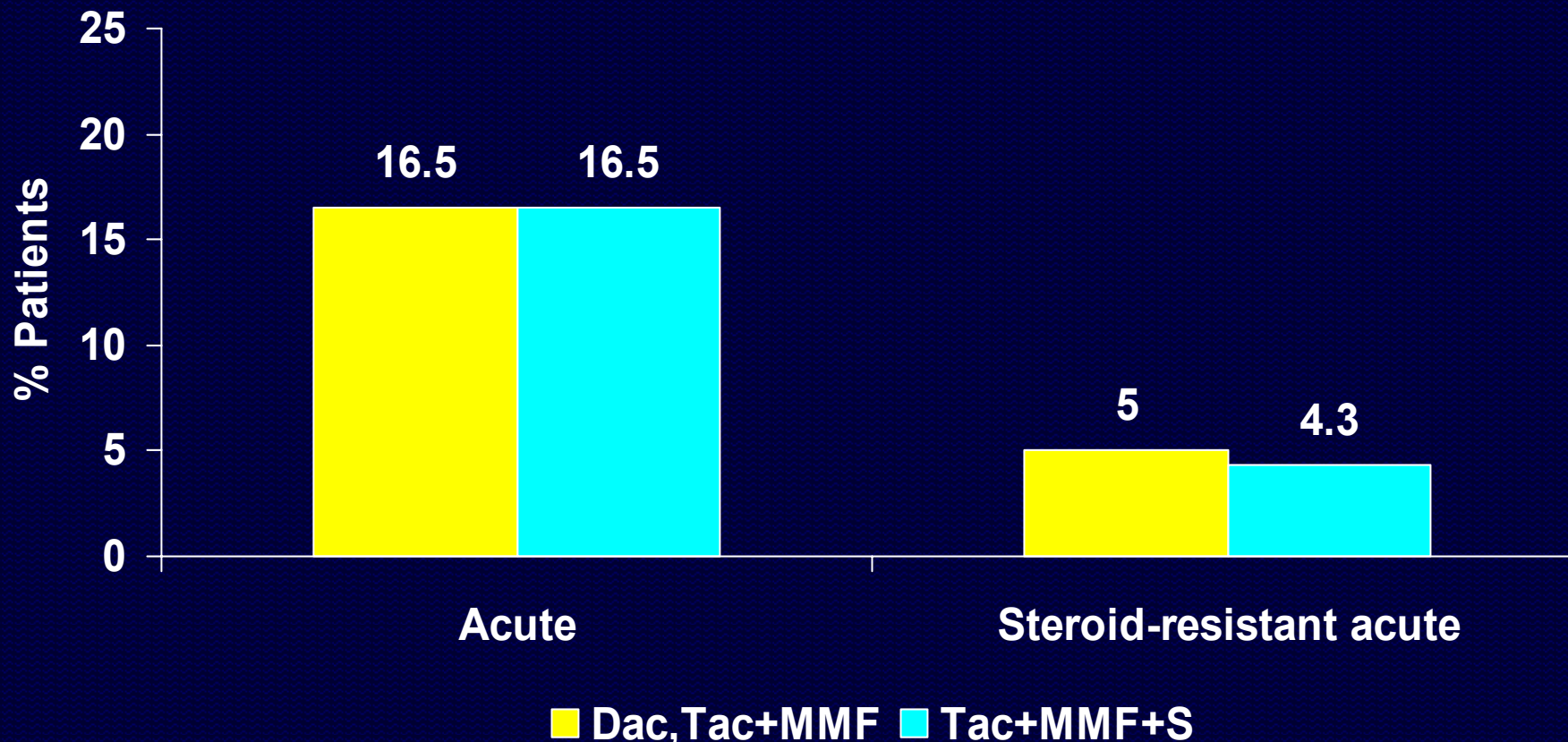
# Early Steroid Withdrawal

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# CARMEN Steroid Avoidance Study

## Biopsy proven acute rejection at 6 months

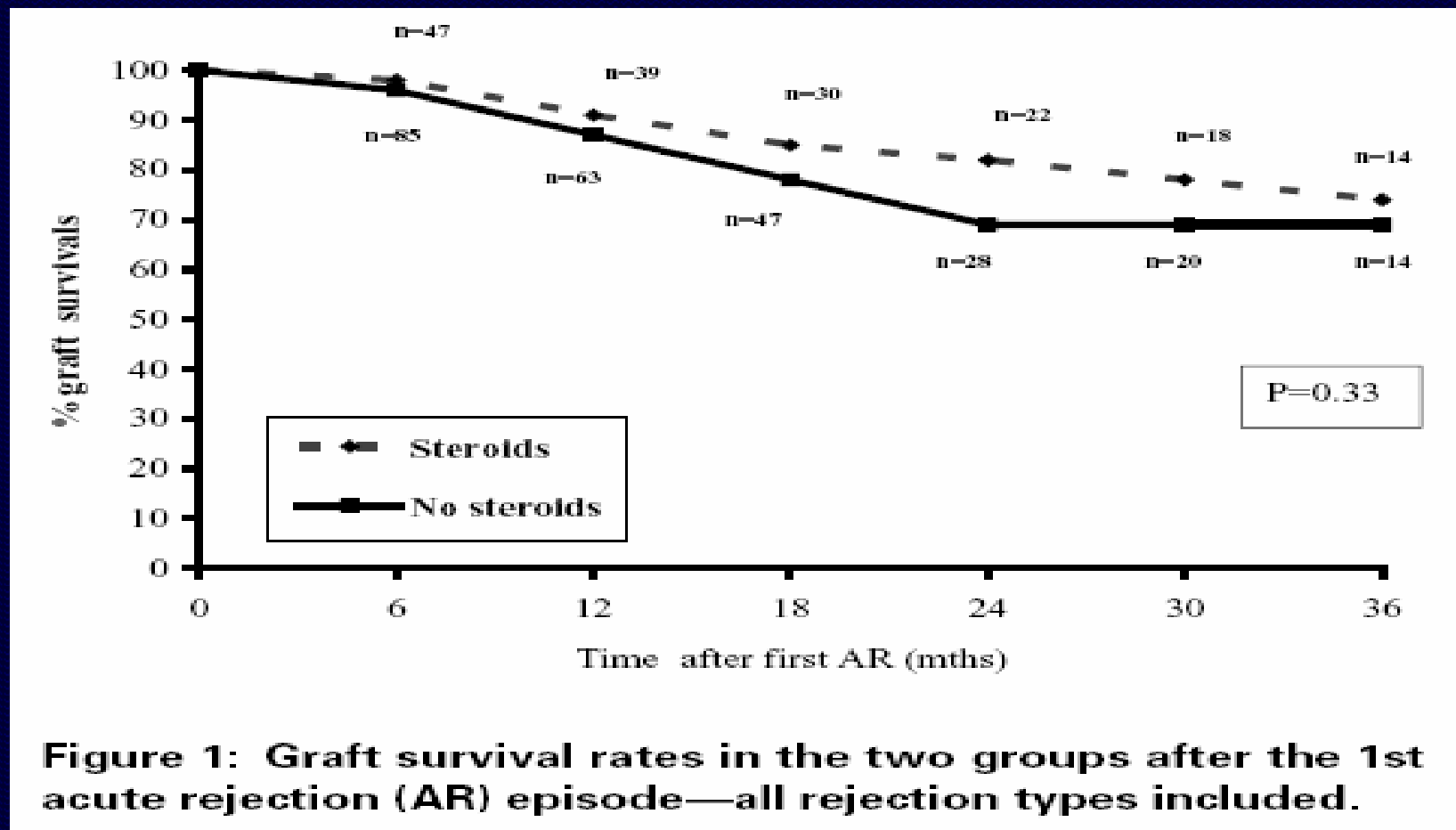
Rostaing et al Transplantation, 2005



**No difference in hyperglycemia or hypertension**

# Graft Survival After Acute Rejection in Steroid Withdrawal Patients

Humar et al AJT, 2007



# Effect of Steroid Withdrawal Below 5 mg/day on Glucose Disposal Rate and Insulin Sensitivity

Midtvedt et al JASN, 2004

Characteristic	Before SW		After SW		Mean Difference	95% CI	P Value
	Mean	SD	Mean	SD			
ISI ( $\mu\text{mol} \times \text{L} \times 10^{-2} / \text{kg} \times \text{min} \times \text{pmol}$ )	14.76	6.89	13.56	6.48	-1.20	-3.18 to 0.78	0.206
GDR ( $\mu\text{mol}/\text{kg} \times \text{min}$ )	66.3	24.5	67.6	24.4	1.2	-6.6 to 9.1	0.734
BMI ( $\text{kg}/\text{m}^2$ )	25.1	5.0	24.6	4.3	-0.5	-1.5 to 0.4	0.252
Weight (kg)	73.4	15.7	71.9	14.1	-1.5	-4.2 to 1.2	0.251
Lean body mass (kg)	50.7	6.4	50.3	6.1	-0.5	-1.3 to 0.4	0.250
Body fat mass percentage	32.5	8.7	31.9	7.9	-0.5	-1.7 to 0.6	0.312
Waist circumference (cm) ( $n = 8$ )	83.6	16.4	82.9	13.0	-0.8	-6.5 to 5.0	0.765
Triglyceride concentration (mmol/L) ( $n = 10$ )	1.0	0.3	1.1	0.4	0.0	-0.2 to 0.2	0.817
Fasting blood glucose (mmol/L)	4.2	0.6	4.8	0.6	0.6	0.0 to 1.2	0.036
Fasting insulin (pmol/L)	57	24	58	25	1	-12 to 13	0.901

<sup>a</sup> ISI, insulin sensitivity index; BMI, body mass index.

# Conclusions – Steroid Minimization

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- Large RCT using antilymphocyte products in both arms with both Tac and CSA in low immunologic risk patients suggest that steroid avoidance and early withdrawal are associated with a higher risk of acute rejection
- The impact of this on long term outcome is not yet clear
- The failure to find any significant reduction of total NODM is concerning
- It is unclear whether use of more potent antibodies or lower CNJ exposure would modify this result
- It might also be a consequence of persistent steroid use in a substantial percentage of patients in the withdrawal arms
- Nevertheless, at present, steroid withdrawal has not been demonstrated to offer an improvement in immunosuppressive risk:benefit and should NOT be considered standard therapy

# Goals of CNI Minimization

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- **Maintain current acute rejection rate**
- **Reduce nephrotoxicity to improve renal function**
- **Reduce cardiovascular risk factors**
- **Reduce malignancy**
- **Improve graft and patient survival**



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# **Approaches to CNI Toxicity**

**CNI Avoidance**

**CNI Withdrawal**

**CNI Dose Reduction**

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# CNI Avoidance

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# **CNI Avoidance Using CD25 Antibodies**

## **Wyeth Canada Release Aug 18, 2006**

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- **In a recent RCT comparing CSA, MMF, steroids with SRL, MMF, steroids (both arms receiving IL2RAb), biopsy confirmed AR was 2.5 vs 17.5% at 1 year (p=0.002)**
- **In another study, one arm with IL2RAb, SRL, MMF, steroids was terminated when 12 mo data showed an increase in AR and a numerically higher death rate**
- **“Based on information from recent clinical trials, the use of Rapamune, MMF, and corticosteroids, in combination with IL-2 receptor antibody induction, is not recommended in the de novo organ transplant setting”**

# MMF plus Tac or SRL Using Thymoglobulin

Larson et al AJT, 2006

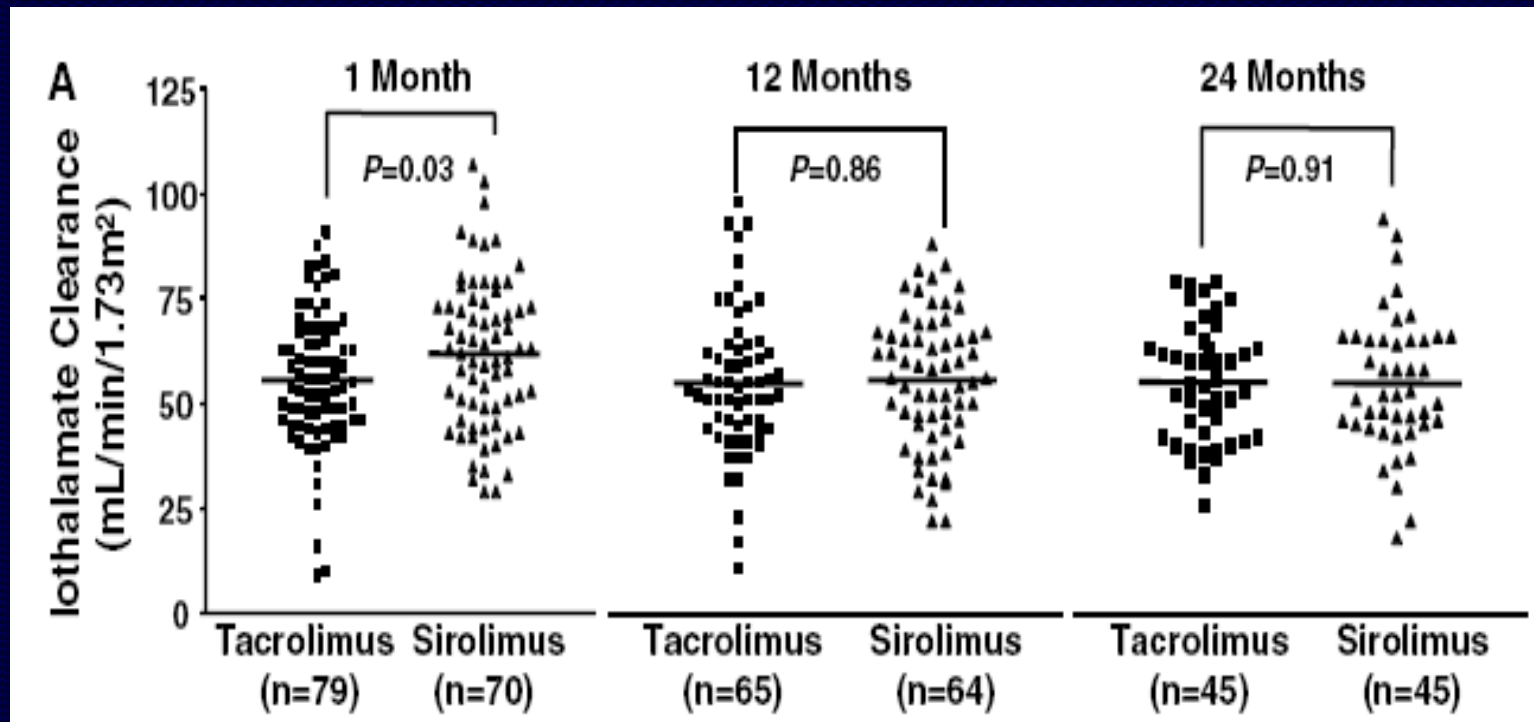
**Table 2:** Banff 97 classification of acute rejection episodes according to study group

	Tacrolimus group (N = 82)		Sirolimus group (N = 80)	
	N = 8		N = 10	
Clinical rejection	Borderline	1	Borderline	1
	Banff IA	3	Banff IA	1
	Banff IIA	2	Banff IB	3
	AHR	2	Banff IIA	3
			Banff IIA + AHR	1
		AHR	1	
	N = 6		N = 6	
Subclinical rejection	Borderline	4	Borderline	2
	Banff IB	2	Banff IA	2
			Banff IB	1
			AHR	1

AHR = acute humoral rejection.

# Iothalamate GFR in Tac vs SRL Treated Renal Transplant Recipients

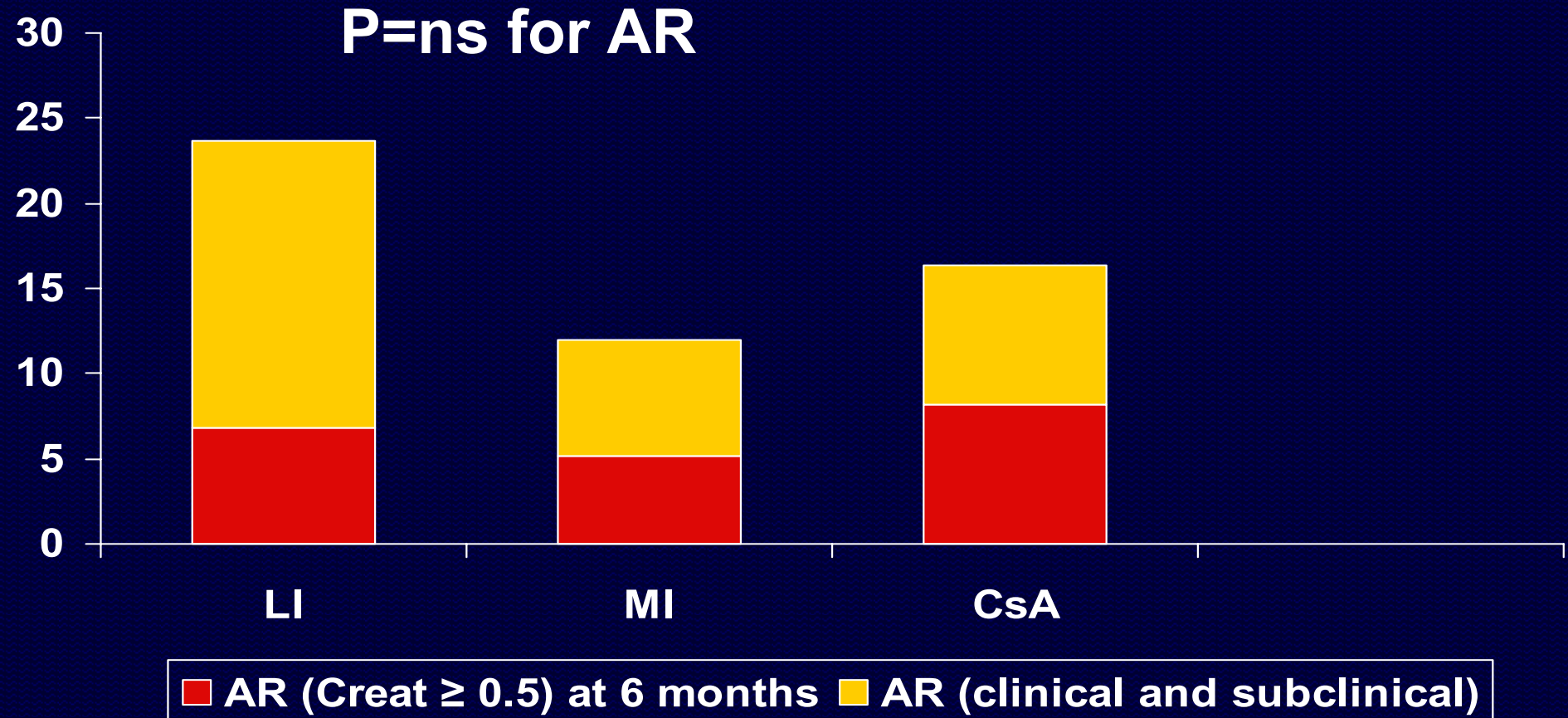
Larson et al AJT, 2006



# CTLA4Ig - Renal Transplant Trial

## Incidence of Acute Rejection at Six Months

Vincenti et al NEJM, 2005



**Table 3. Renal Function and Histologic Findings.\***

End Point	Intensive Belatacept	Less-Intensive Belatacept	Cyclosporine
<b>Measured GFR</b>			
No. of patients	32	37	27
Mean GFR — ml/min/1.73 m <sup>2</sup> †	66.3±20.7	62.1±15.9	53.5±16.4
Difference from cyclosporine group — ml/min/1.73 m <sup>2</sup> (95% CI)	12.8 (2.9 to 22.7)	8.6 (0.4 to 16.8)	—
<b>Chronic allograft nephropathy</b>			
No. of patients	52	54	45
CAN at 12 mo — no. (% [95% CI])‡	15 (29 [16.5 to 41.2])	11 (20 [9.6 to 31.1])	20 (44 [29.0 to 59.0])
Mild CAN (stage I) — no. (%)	11 (21)	6 (11)	16 (36)
Moderate CAN (stage II) — no. (%)	4 (8)	1 (2)	3 (7)
Severe CAN (stage III) — no. (%)	0	4 (7)	1 (2)
Absolute difference in rate from cyclosporine group — percentage points (asymptotic exact 95% CI)	-15.6 (-34.6 to 3.4)	-24.1 (-42.1 to 6.0)	—
<b>Calculated GFR</b>			
No. of patients	60	59	50
Mean GFR — ml/min/1.73 m <sup>2</sup>	72.4±22.5	73.2±22.5	68.0±28.1
Difference from cyclosporine group — ml/min/1.73 m <sup>2</sup> (95% CI)	4.4 (-5.2 to 14.0)	5.2 (-4.4 to 14.8)	—
No. of patients without CAN	49	50	37
Mean GFR — ml/min/1.73 m <sup>2</sup>	75.9±21.3	73.2±19.8	76.6±24.4
Difference from cyclosporine group — ml/min/1.73 m <sup>2</sup> (95% CI)	-0.7 (-10.5 to 9.1)	-3.4 (-12.8 to 6.0)	—
No. of patients with CAN	11	9	13
Mean GFR — ml/min/1.73 m <sup>2</sup>	56.9±22.2	73.1±35.9	43.6±23.5
Difference from cyclosporine group — ml/min/1.73 m <sup>2</sup> (95% CI)	13.3 (-6.2 to 32.8)	29.5 (3.2 to 55.8)	—

\* Plus-minus values are means ±SD. GFR denotes glomerular filtration rate, CI confidence interval, and CAN chronic allograft nephropathy.

† P<0.05 for the comparison of both belatacept regimens with cyclosporine.

‡ Patients in this group underwent at least one biopsy after baseline.

# CNI Avoidance – Conclusions

- CNI avoidance using MPA, TOR inhibitors and a CD25 Ab is associated with an unacceptably high rate of acute rejection
- The use of Thymoglobulin has reduced acute rejection to acceptable levels, but, so far, in one study, anticipated improvement in renal function has not been seen
- A phase 2 study using CTLA4 Ig has been associated with equivalent rejection rates and improved GFR but no significant difference in CAN
- The lesions in pt with CAN who have never been exposed to CNI could be immunologically mediated and reduce long term graft survival. Thus longer term data is needed
- Some cardiovascular risk factors have been reduced but no long term data is available to determine whether patient and graft survival have improved



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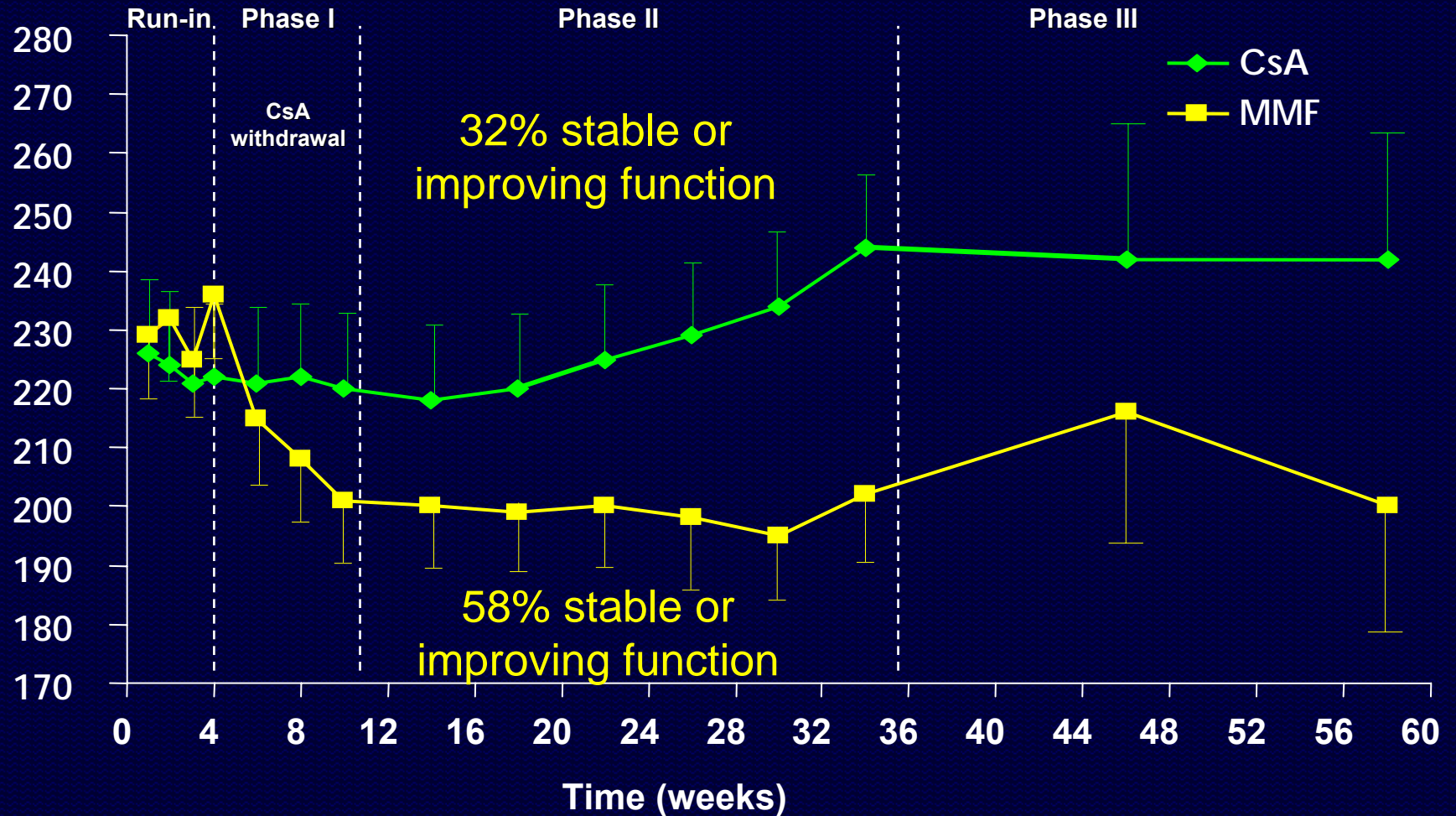
# CNI Withdrawal

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# The Creeping Creatinine Study

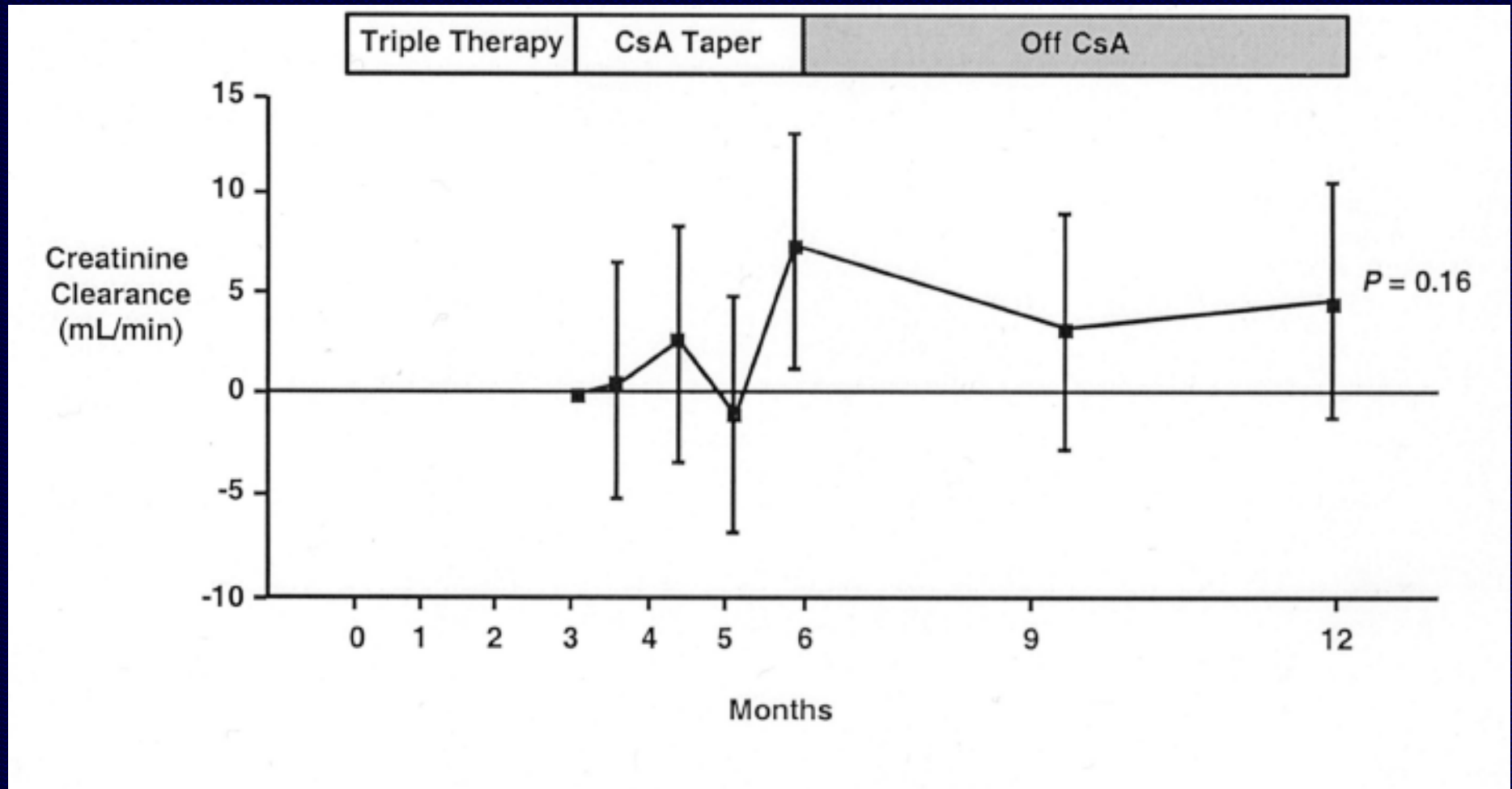
Dudley et al Transplantation, 2005

Creatinine ( $\mu\text{mol/L}$ )



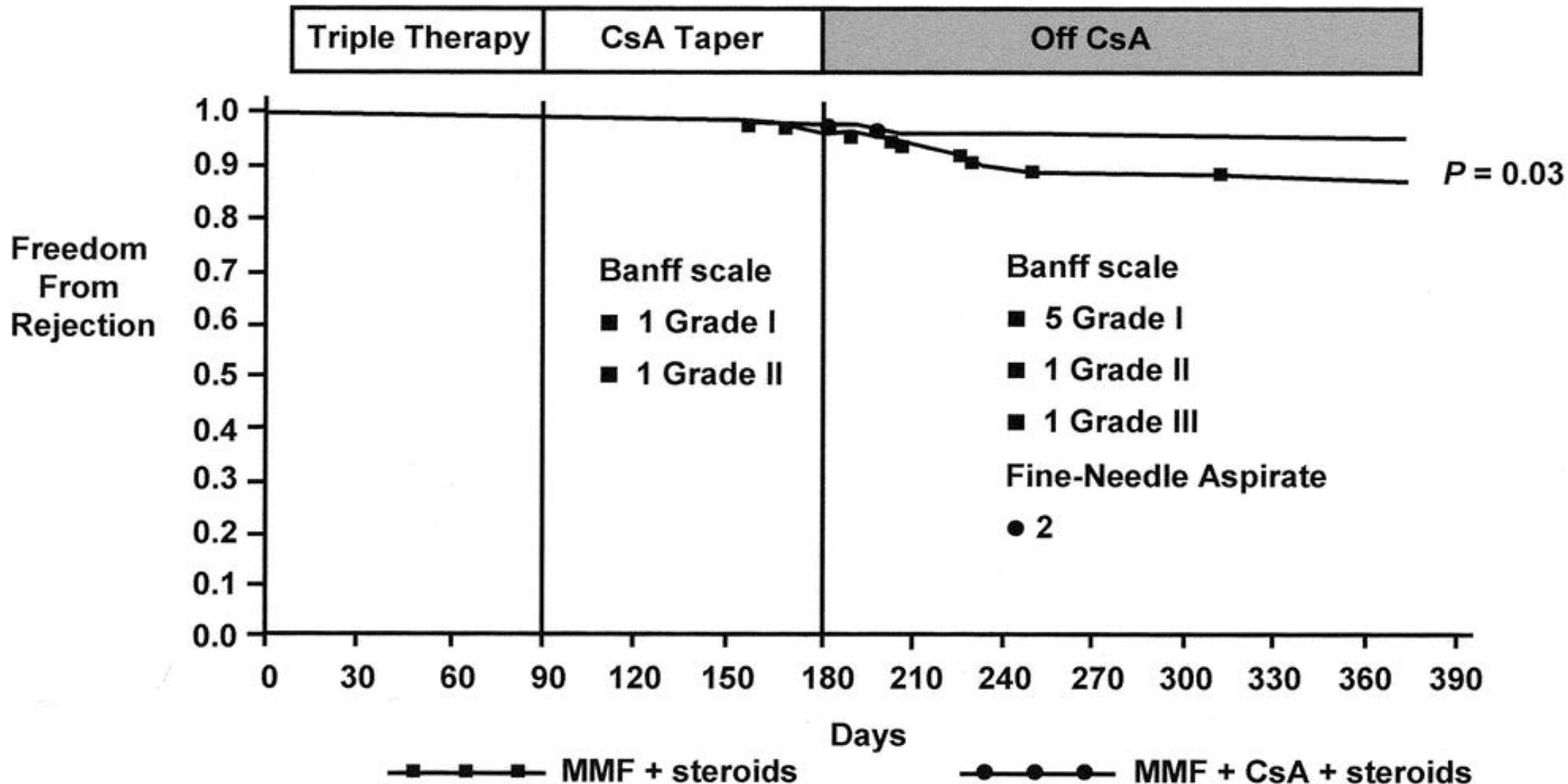
# RCT of CNI Withdrawal Using MMF

Abramowicz et al Transplantation, 2002



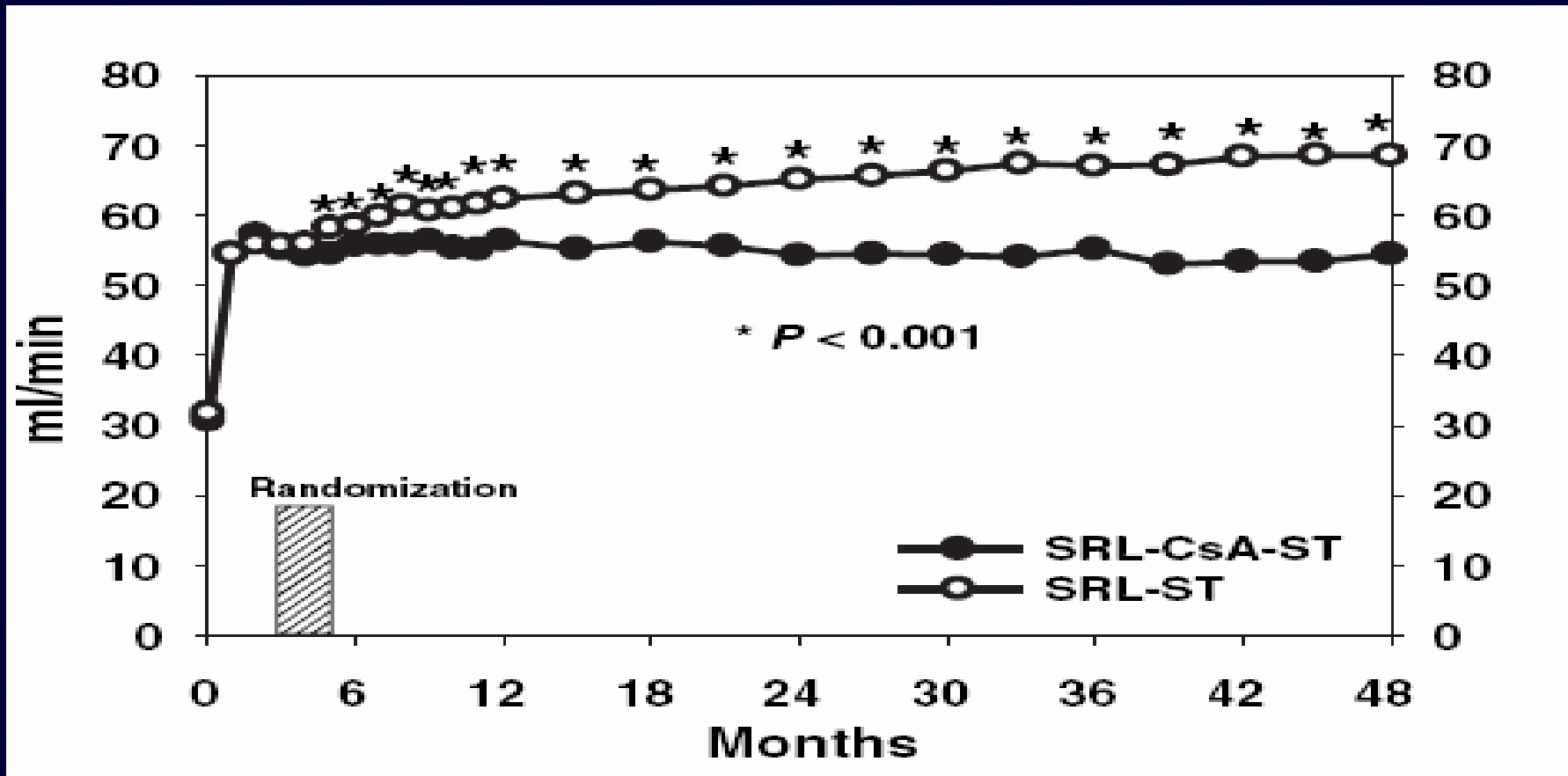
# CNI Withdrawal Using MMF

Abramowicz et al Transplantation, 2002



# Calculated GFR in CNI Withdrawal in SRL Study 310

Oberbauer et al Transplant Int, 2005



# **CNI Withdrawal Conclusions**

- **Results of studies of CNI withdrawal have varied. Best results are achieved when CNI are withdrawn before significant proteinuria or serious reduction in renal function occurs**
- **In the early post transplant period, it may be best to use both MPA and TOR inhibitor based therapies because of higher AR risk**
- **Whether withdrawal is the best strategy to optimize renal function has yet to be determined**
- **There are no good data regarding the impact of this strategy on NODM**

## Conclusions II

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- **As Nankivell et al have shown that reduction in GFR is a late consequence of fibrosis, perhaps protocol biopsies could be used to determine early onset of CNI toxicity and withdrawal introduced before GFR falls**
- **MPA monitoring might improve the results of CNI withdrawal but this remains speculative at present**
- **Initial data suggest that CNI withdrawal, especially using TOR inhibitors, might reduce malignancy. This needs to be confirmed in other longterm RCTs**

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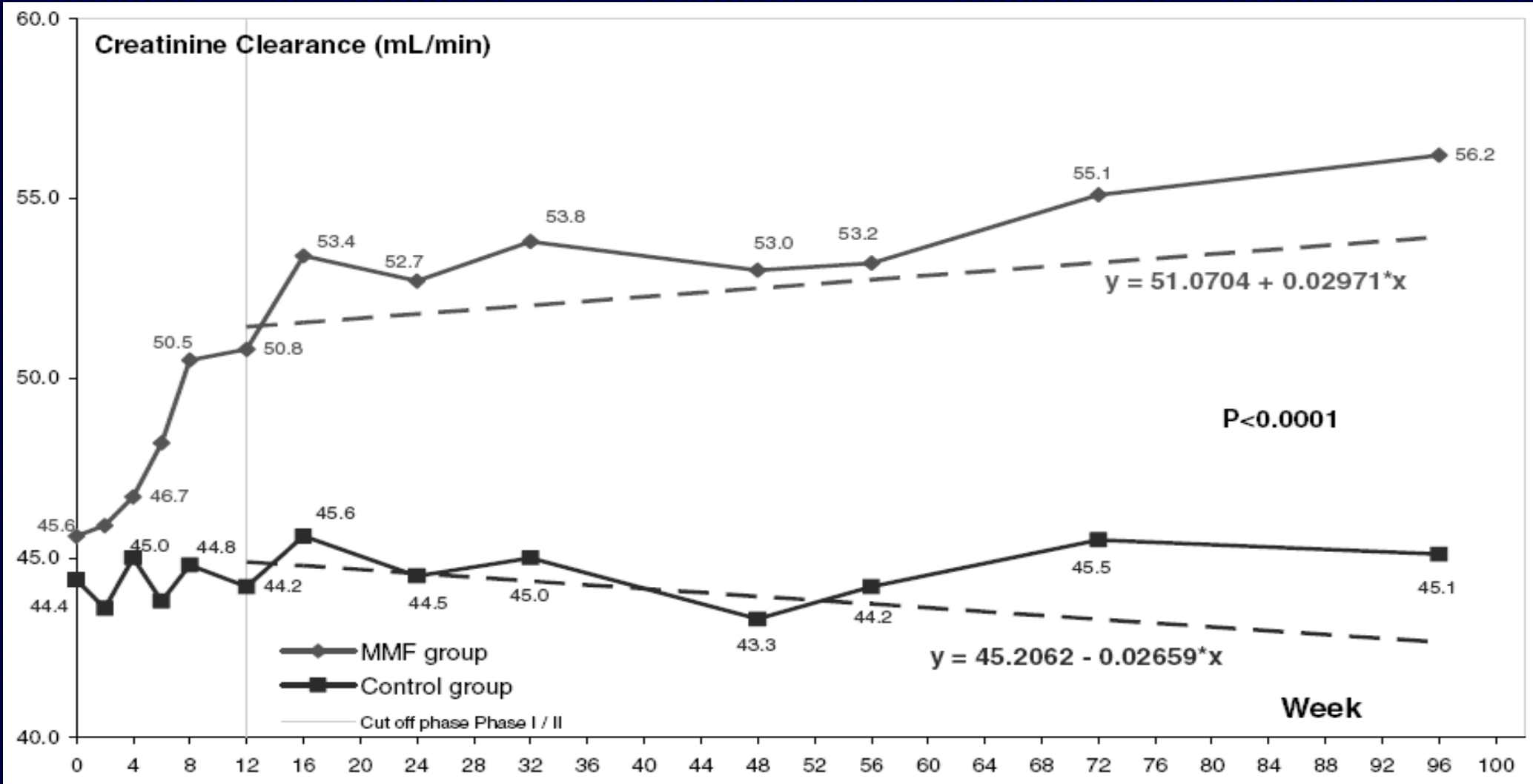
# CNI Reduction

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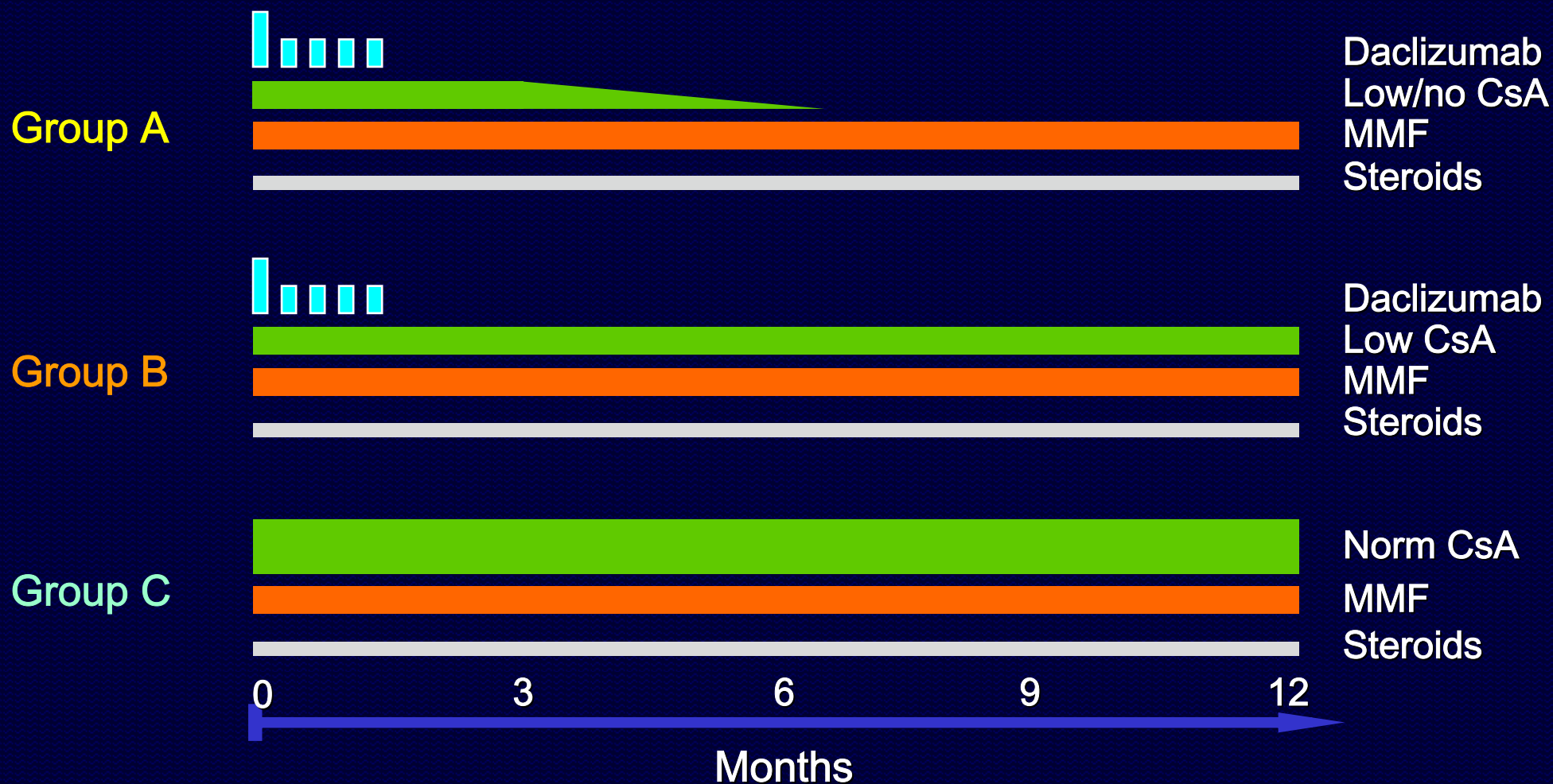
# RCT of MMF Plus Half Dose CSA and Renal Function: The Reference Study

Frimat et al AJT, 2006



# CAESAR - Study Design

Ekberg et al AJT, 2007



# CNI Dose Reduction

- **Studies of CNI reduction without withdrawal have achieved better preservation of renal function than avoidance and withdrawal protocols without an increase in acute rejection.**
- **The high incidence of NODM with low dose Tacrolimus in SYMPHONY is disappointing and suggests other strategies will be needed to reduce long term CV risk**
- **It will be interesting to see the long term benefit of Symphony strategy on malignancy**
- **However it is unlikely patients will remain on assigned therapy so useful long term results may not be forthcoming**

# Drug Minimization – Report Card 2007

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- Properly powered trials of steroid minimization have not demonstrated a clear improvement in risk:benefit over the short term
- CNI avoidance strategies have yielded variable results without optimal cardiovascular protection. Thus, they cannot be routinely recommended
- CNI withdrawal seems to improve or stabilize renal function in many patients if started early

## Conclusions II

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- **Low dose CNI from transplantation with CD25 Ab induction seems to provide improved renal function while avoiding incremental acute rejection**
- **However, the persistence of high NODM rates with Tacrolimus in Symphony is concerning and may prevent long term gains from being realized**
- **Thus the optimal drug minimization regimen has not yet been developed**