

# Update on Calcineurin Inhibitor Minimization After Kidney Transplantation

---

Donald E. Hricik MD

Case Western Reserve University

University Hospitals Cleveland Medical Center

Cleveland, Ohio USA

# CNI Inhibitors: Adverse Events

AE	Steroids	CsA	TAC	mTORi	MMF	AZA
New-onset diabetes mellitus	↑	↑	↑↑	↑		
Dyslipidemias	↑	↑		↑↑		
Hypertension	↑↑	↑↑	↑			
Osteopenia	↑↑	↑	(↑)			
Anemia and leukopenia				↑	↑	↑
Delayed wound healing				↑		
Diarrhea, nausea/vomiting			↑		↑↑	
Proteinuria				↑↑		
Decreased GFR		↑	↑			

↑ indicates a mild-moderate adverse effect on the complication.  
 ↑↑ indicates a moderate-severe adverse effect on the complication.  
 (↑) indicates a possible, but less certain adverse effect on the complication.

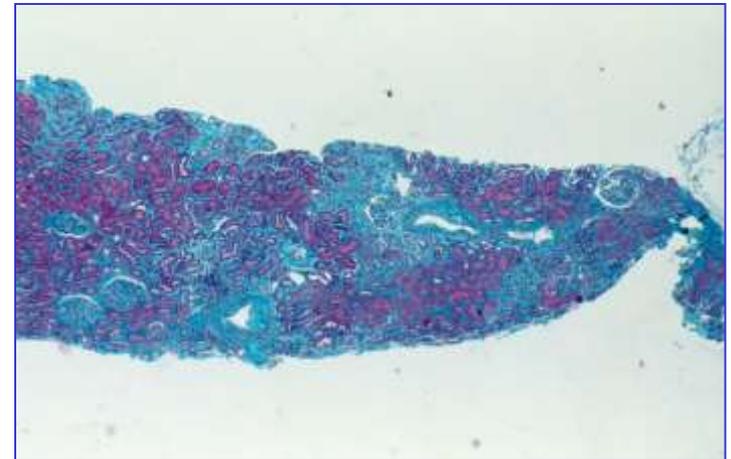
# Longitudinal assessment by protocol biopsy: CNI nephrotoxicity and subclinical rejection

## Timeline of biopsy protocol

0 3 12 mo. 2 3 4 5 6 7 8 9 10 years



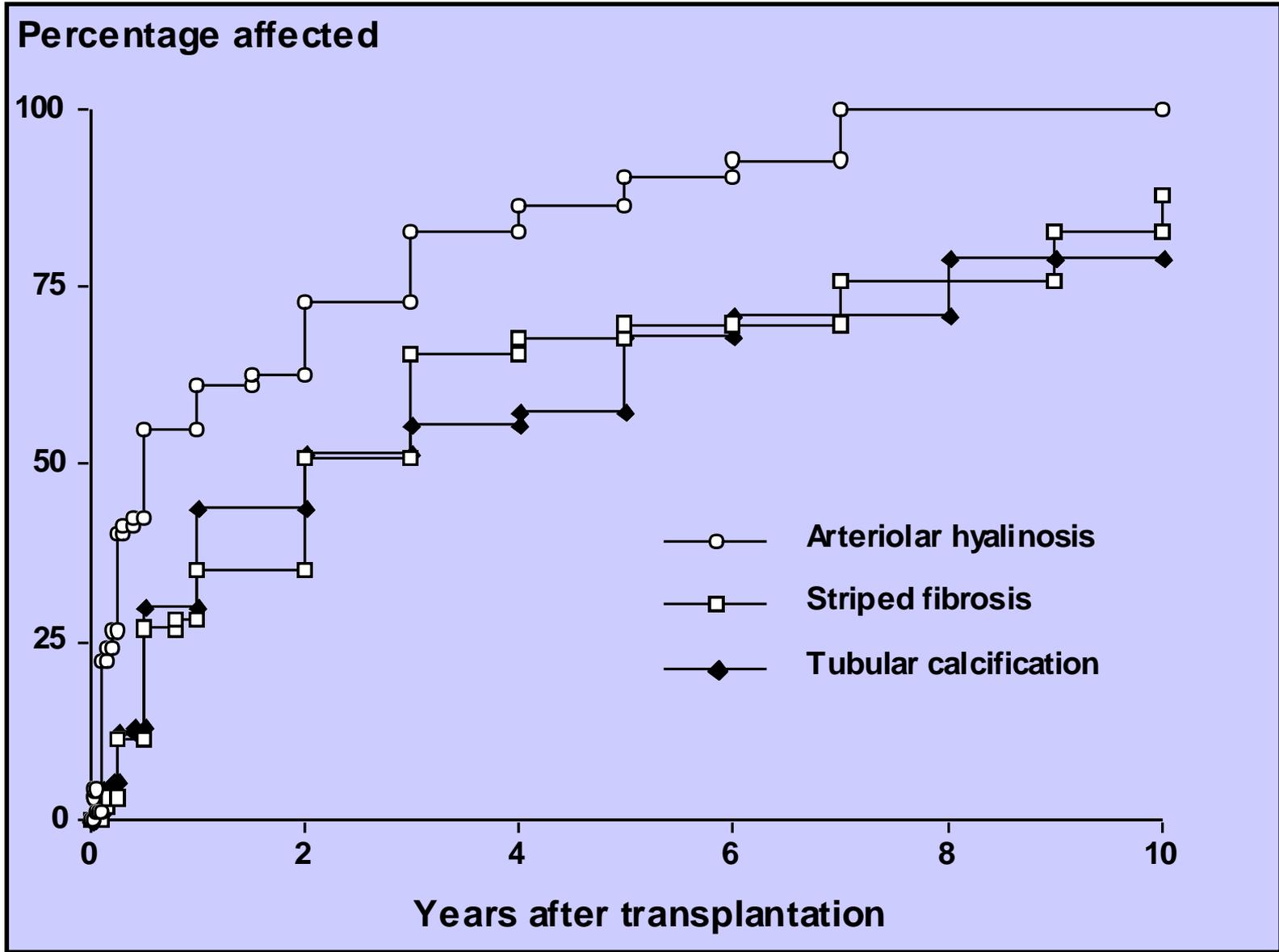
- 961 protocol kidney biopsies
- 120 kidney/pancreas recipients
- Young donors



Nankivell B, et al. NEJM 2003; 349: 2326-33



# Histological features of Cyclosporine Nephrotoxicity



# Objectives of CNI Minimization Protocols:

- Reduce CNI nephrotoxicity
- Reduce other side effects
- Maintain efficacy in preventing rejection

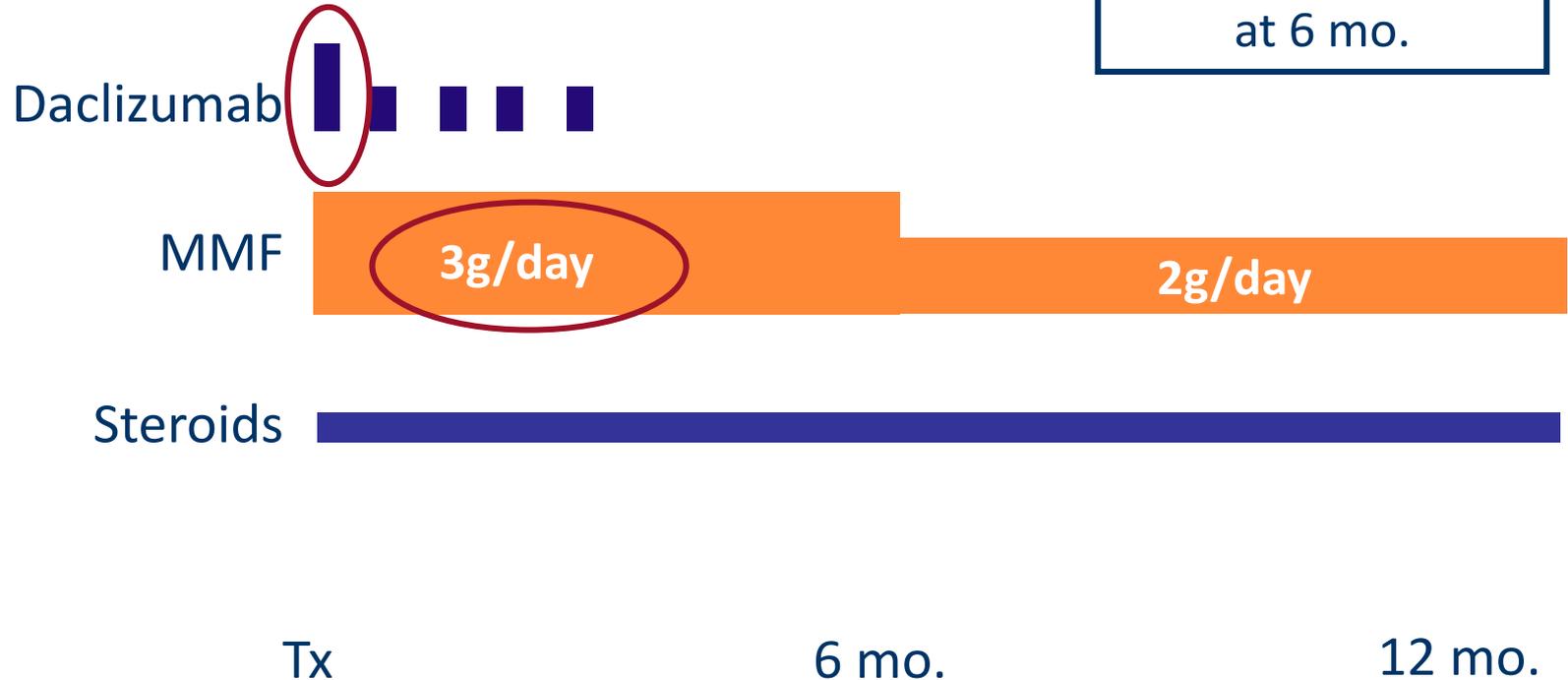
# Considerations in Reviewing CNI Minimization Studies

- Strategy
  - Avoidance
  - Withdrawal
  - Substitution or conversion to another class of drugs
  - Dose reduction
- Cyclosporine versus tacrolimus in the comparator arms
- Stable patients versus patients with renal dysfunction

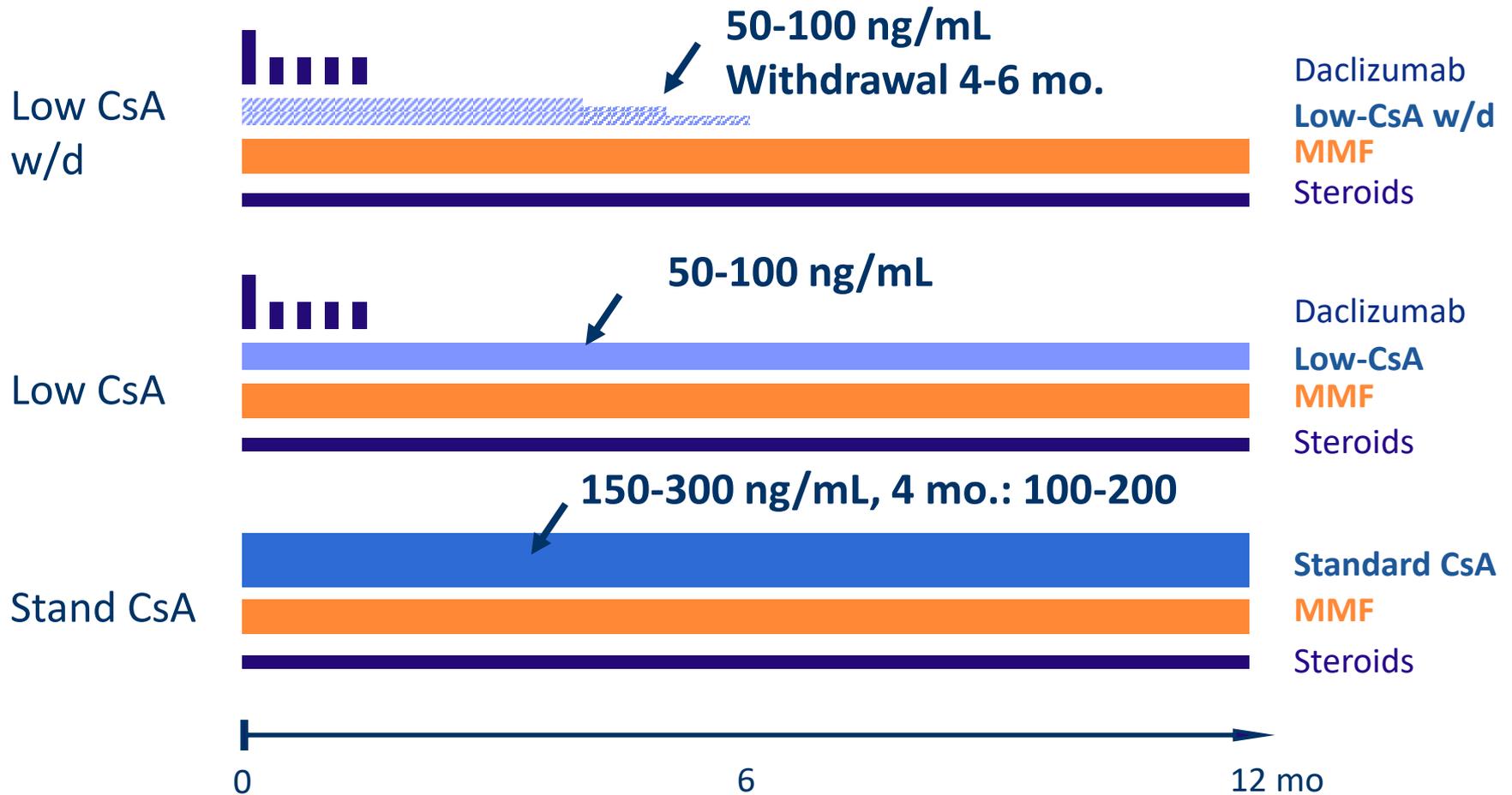
# CNI avoidance

## Daclizumab + MMF + CS

Multicenter, uncontrolled study of 98 “low risk” kidney transplant recipients

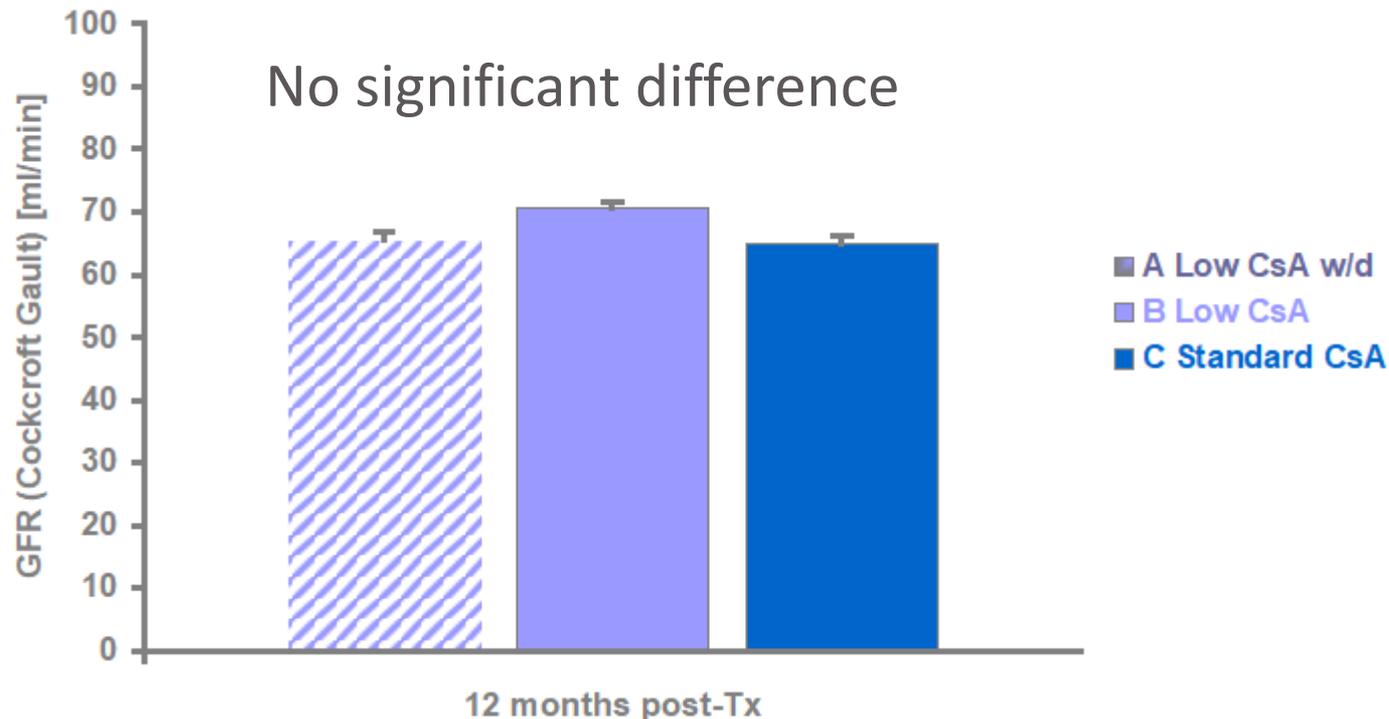


# CAESAR study design (n=536)



# CAESAR study

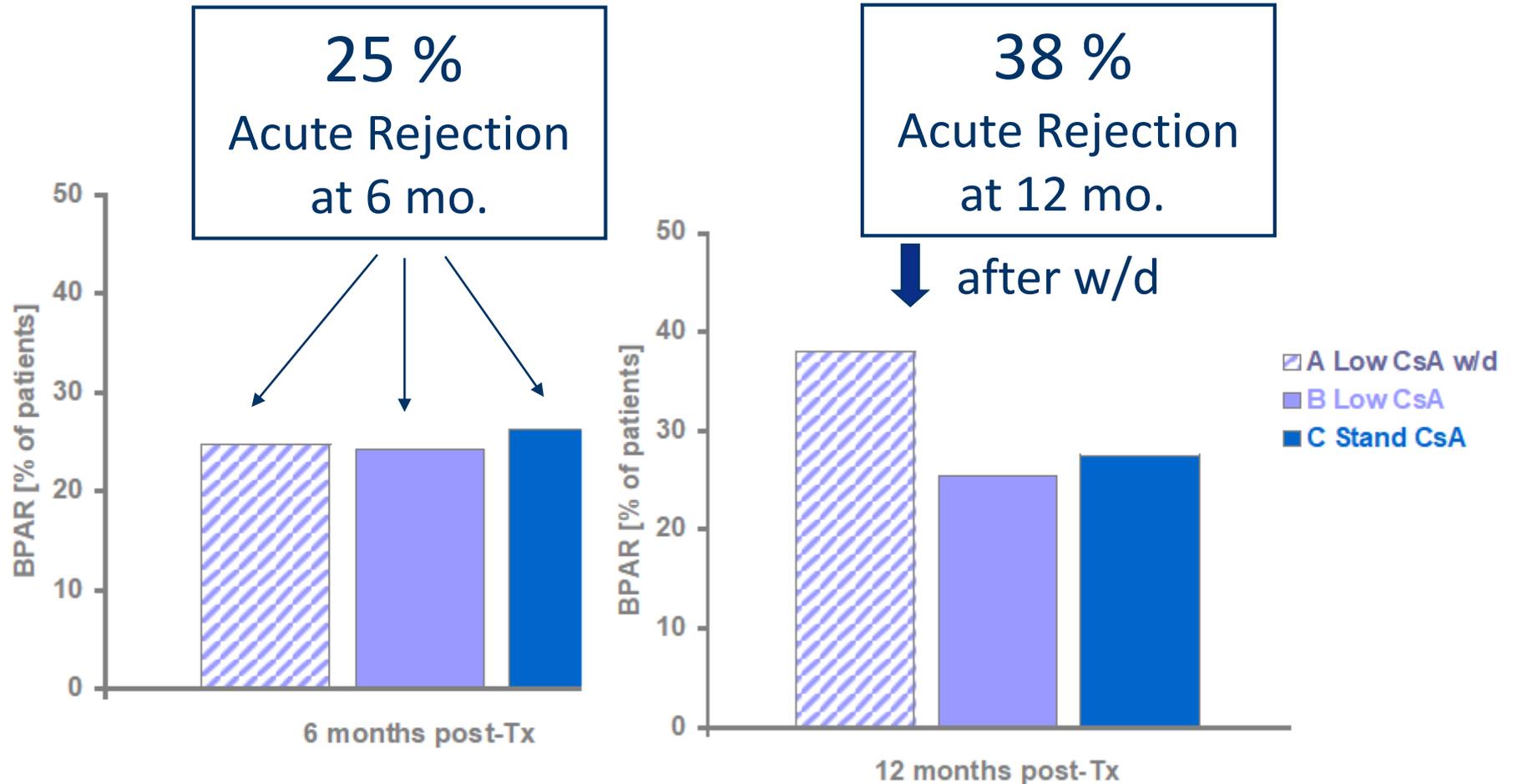
## GFR at 12 months (primary endpoint)



No improvement in GFR by dose-reduction or w/d of CsA

# CAESAR study

## BPAR at 6 and 12 months



# Use of mTOR Inhibitors to Facilitate CNI Miminization

---

## CNI AVOIDANCE

# Calcineurin Inhibitor Avoidance with Sirolimus and AZA/MMF (Pooled Data from Groth CG et al. *Transplantation*. 1999;67:1036-1042.

Kreis H et al. *Transplantation*. 2000;69:1252-126

### Efficacy outcomes at 2 years:

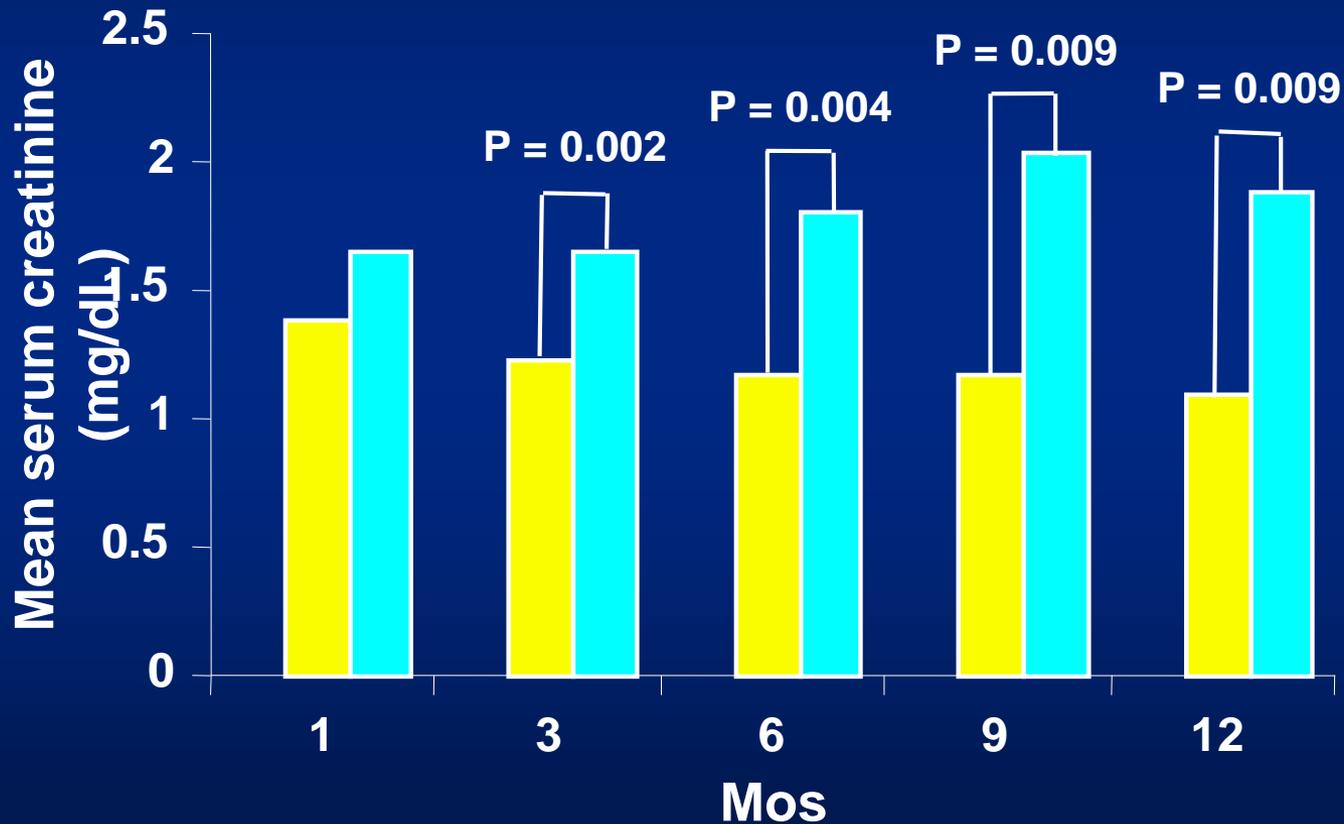
	<u>Sirolimus</u> (n=81)	<u>CsA</u> (n=80)	<u>p-value</u>
Biopsy proven rejection:	28( 34.6)	23(28.7)	NS
Graft survival:	73( 90.1)	71( 88.8)	NS
Patient survival:	76(93.8)	75(93.8)	NS
Calculated GFR (ml/min)	69.3	56.8	0.004

*Morales J. et al, Am. J. Transplant. 2002; 2: 436-442*

# Sirolimus vs Cyclosporine with Basiliximab Induction

(Flechner SM et al; Transplantation 2002; 74: 1070)

Mean serum creatinine (mg/dL)



■ Group I – sirolimus (N = 31) ■ Group II – CsA (N = 30)

# Sirolimus vs Tacrolimus (with rATG, MMF, steroids)

	Tacrolimus	Sirolimus	p
Acute Rejection in first 12 months	14%	19%	NS
eGFR at 12 months	55 ml/min	56 ml/min	NS

Larson T, et al. Am J Transplant 2006; 6: 514-522

# The ORION Study

- Tacrolimus elimination [13 wks]
- Tacrolimus avoidance
- Standard tacrolimus-MMF

RCT (n=443)

1. Tac→Srl: 66% withdrawn
2. Srl-MMF: 60% withdrawn (arm terminated)
3. Tac-MMF: 37% withdrawn

Primary endpoint: 1 year GFR: **no difference** between groups

Adverse events

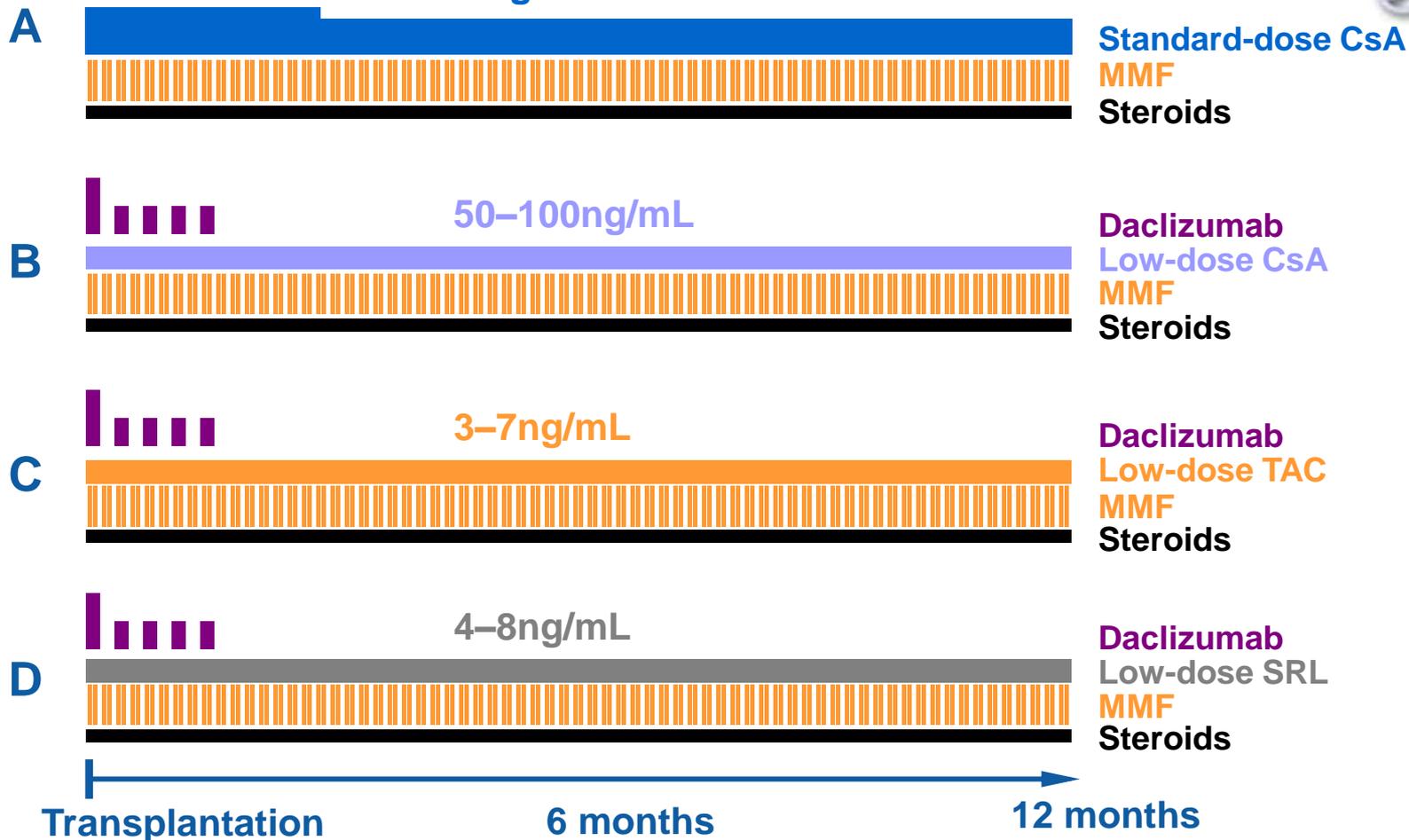
- SRL arms had higher rates of:
  - withdrawal from study
  - Acute rejection (15% vs 32% vs 8%)

# SYMPHONY Study Design

1645 patients at 83 sites in 15 countries

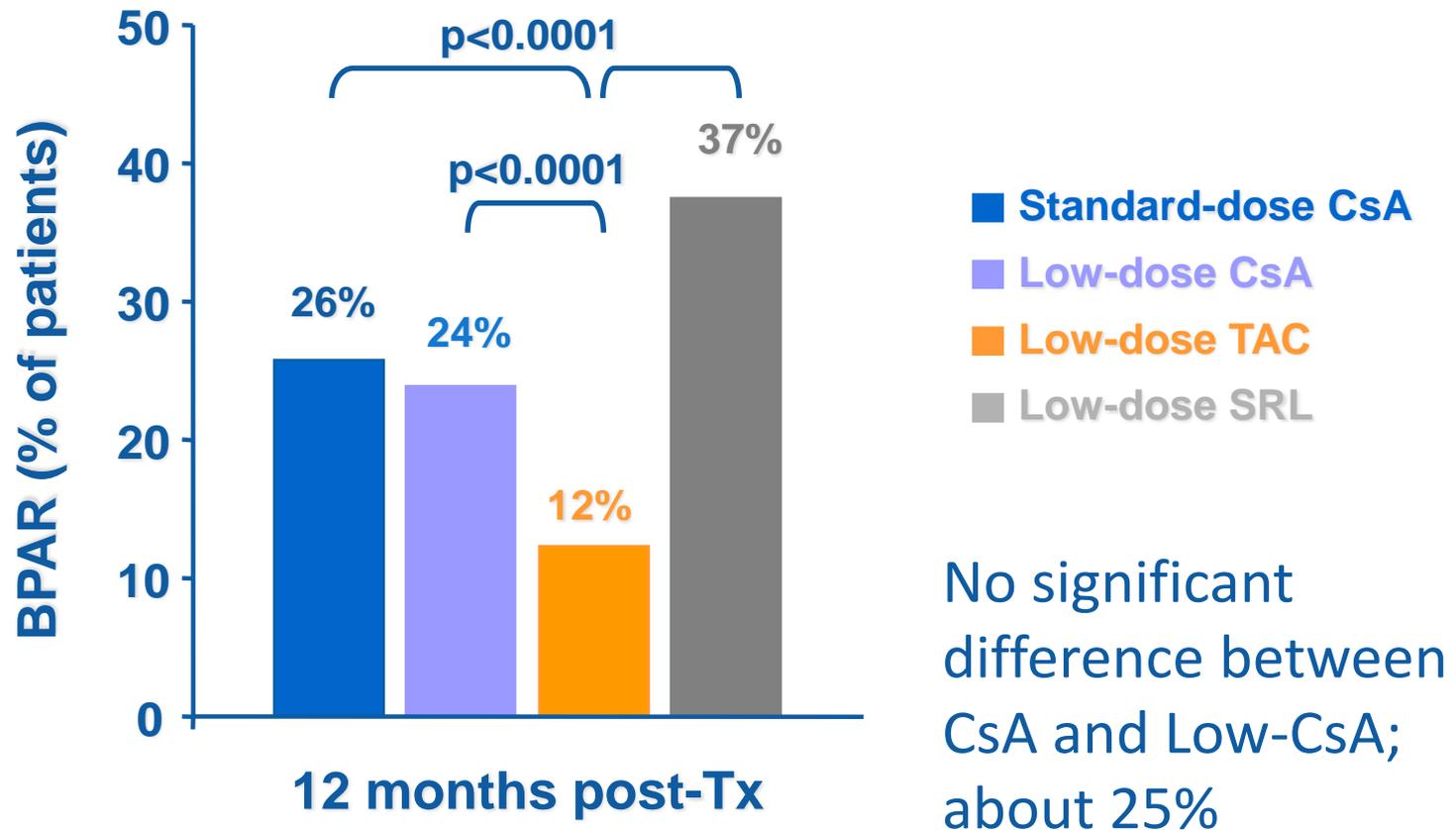


150–300ng/mL for 3 months  
100–200ng/mL thereafter



# Less Biopsy Proven Acute Rejection with Low-dose Tac

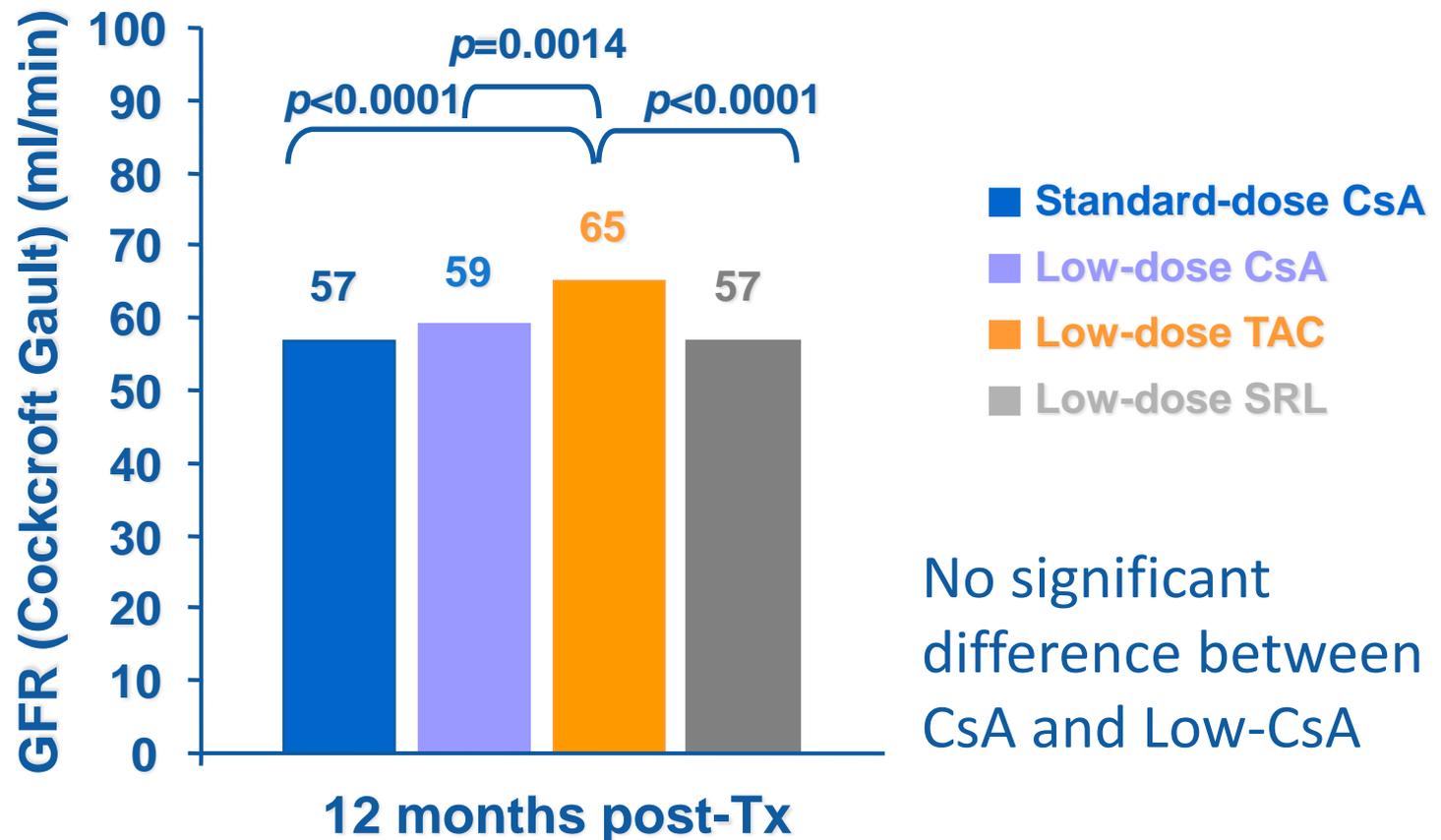
(ITT, Excluding Borderline)



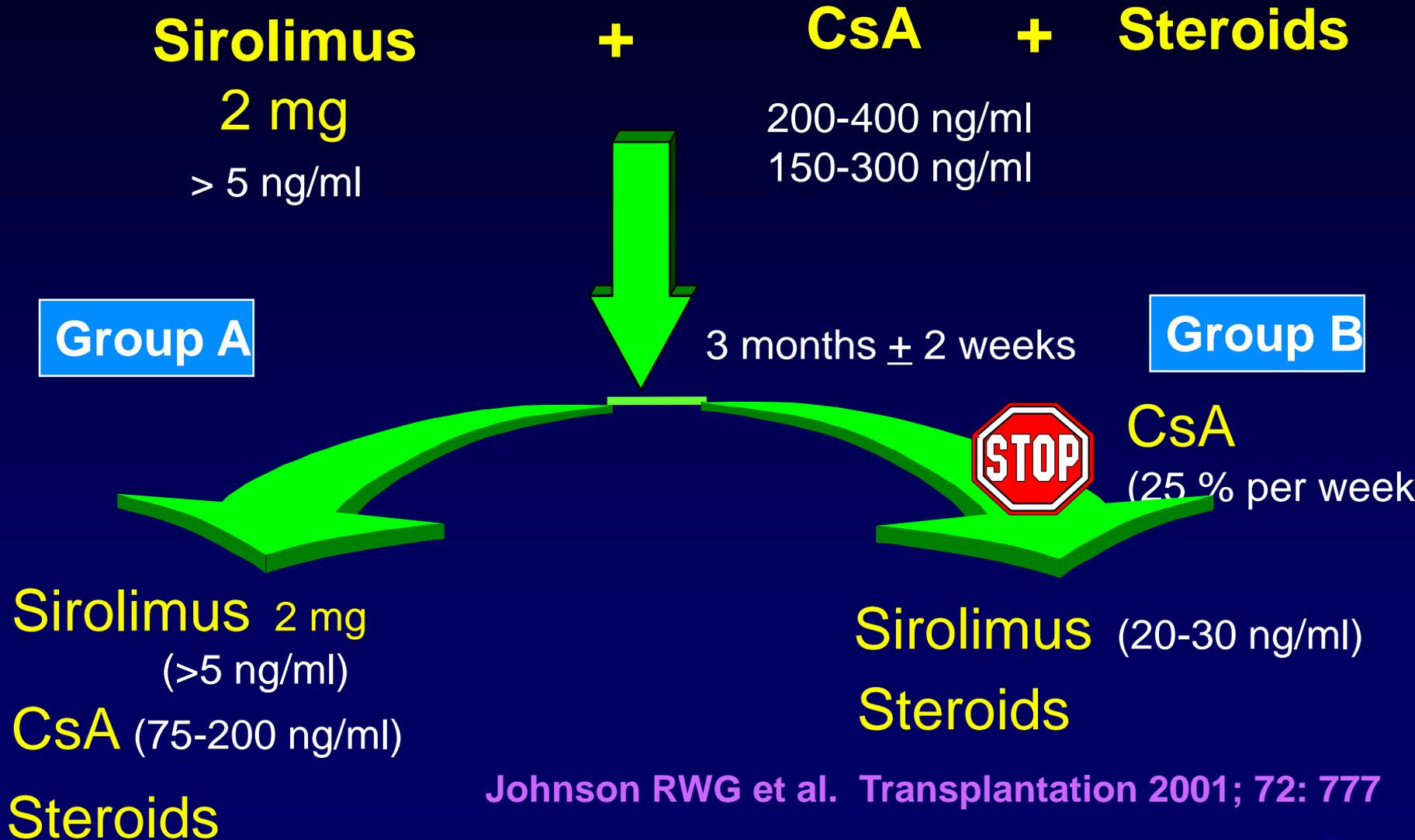
# Graft function was superior with Low-dose Tac



Calculated GFR Cockcroft-Gault (primary endpoint)

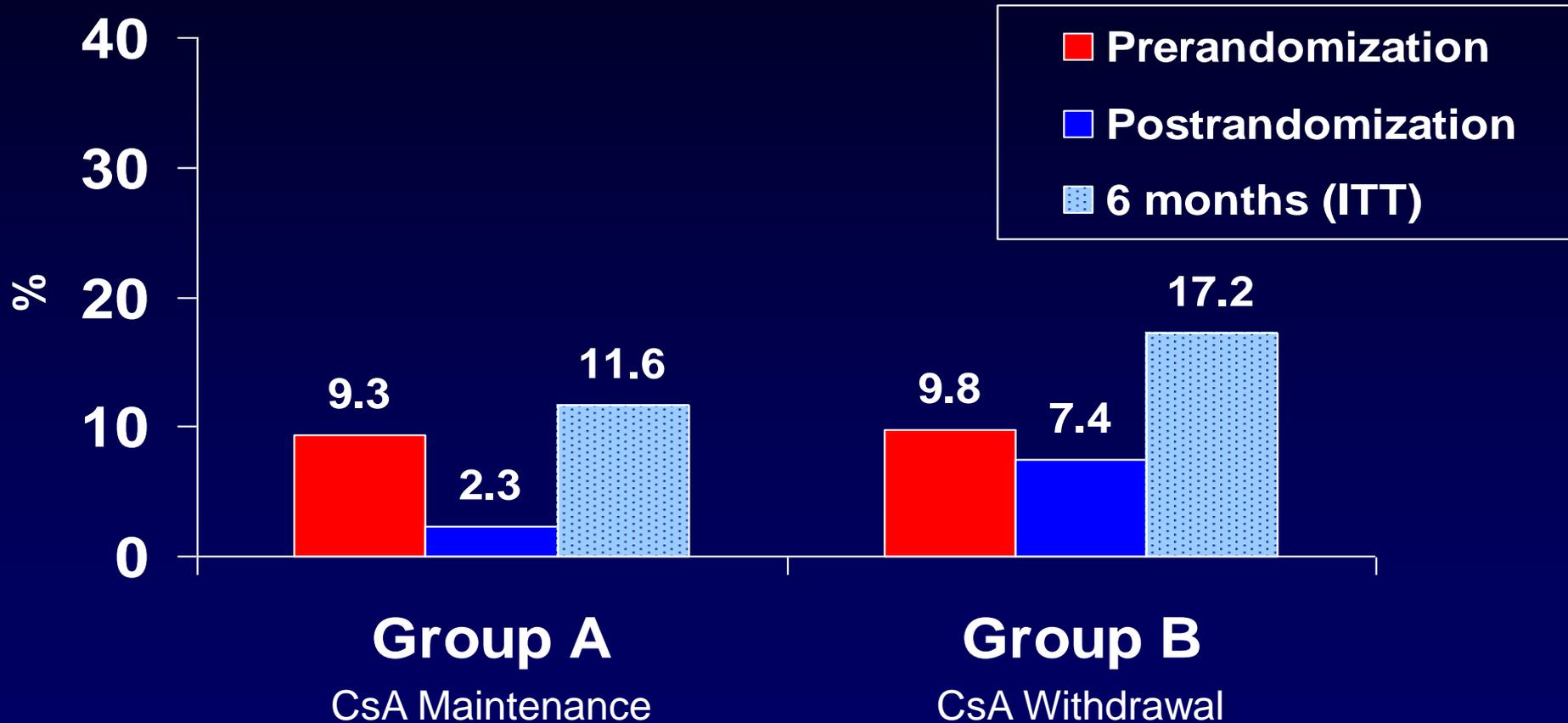


# Wyeth 310

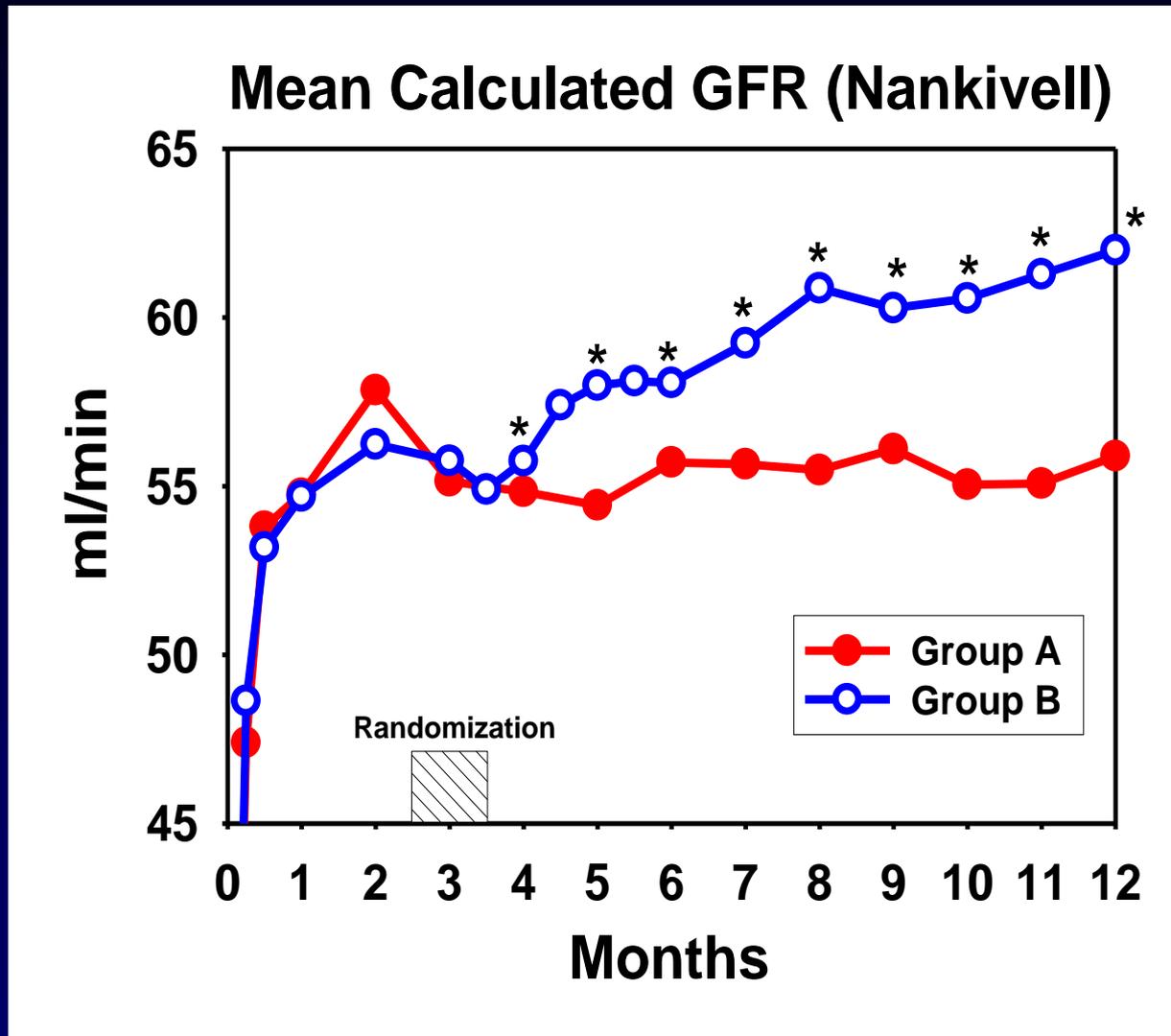


Johnson RWG et al. Transplantation 2001; 72: 777

# Incidence of Acute Rejection: 6 month data



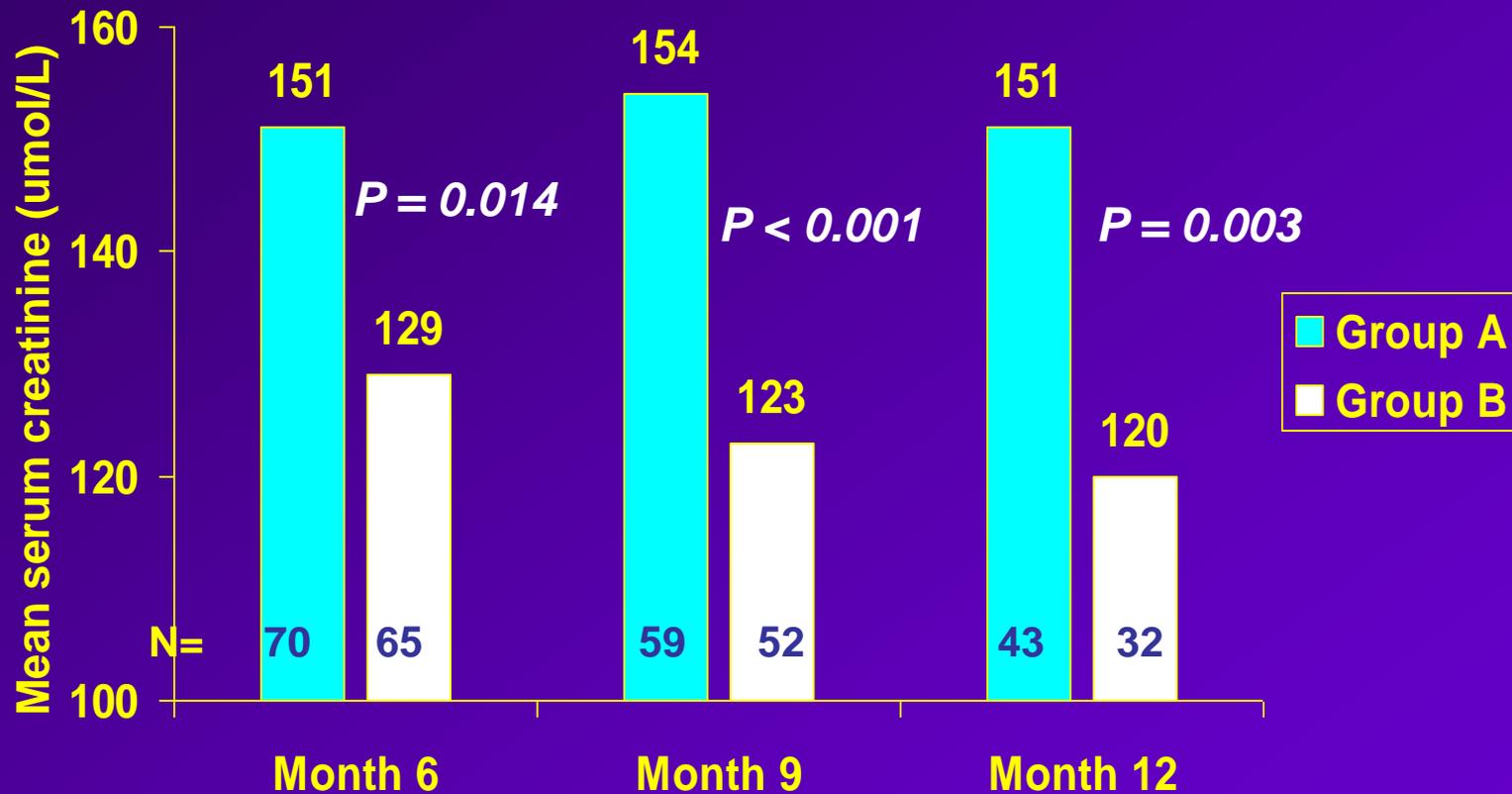
# Higher Calculated GFR Following CsA Elimination



\*p<0.001

## CNI LATE WITHDRAWAL

# Sirolimus and CsA Withdrawal at 3 months (Study 212) (multicenter, randomized)



\* Patients without acute rejection; Incidence of acute rejection not different between groups

# LATE CONVERSION IN STABLE PATIENTS

Study	Time to conversion (months)	Follow-up (months)	Baseline CNI	GFR, mL/min	Treatment Failure/ Graft Loss	BPARG
ZEUS (Evr) <sup>1</sup>	4.5	36	CyA	+7.8 <sup>a</sup>	↑	↑
ORION (Srl) <sup>2</sup>	3	12	Tac	-	↑	↑
SPARE THE NEPHRON (Srl) <sup>3</sup>	1-6	24	80% Tac	+3.6 <sup>b</sup>	- (but 27% back to CNI)	-

<sup>a</sup>  $P < 0.05$

<sup>b</sup>  $p = \text{NS}$

1. Budde K et al. *Lancet*. 2011;2:837-847.
2. Flechner SM et al. *Am J Transplant*. 2011;2:1633-1644.
3. Weir MR et al. *Kidney Int*. 2011;2:897-907.

## CONVERT TRIAL

Pre-Randomization: ----->

- Corticosteroids
- MMF or AZA
- CsA or Tacrolimus

Screening

2:1 Randomization

### SRL Conversion

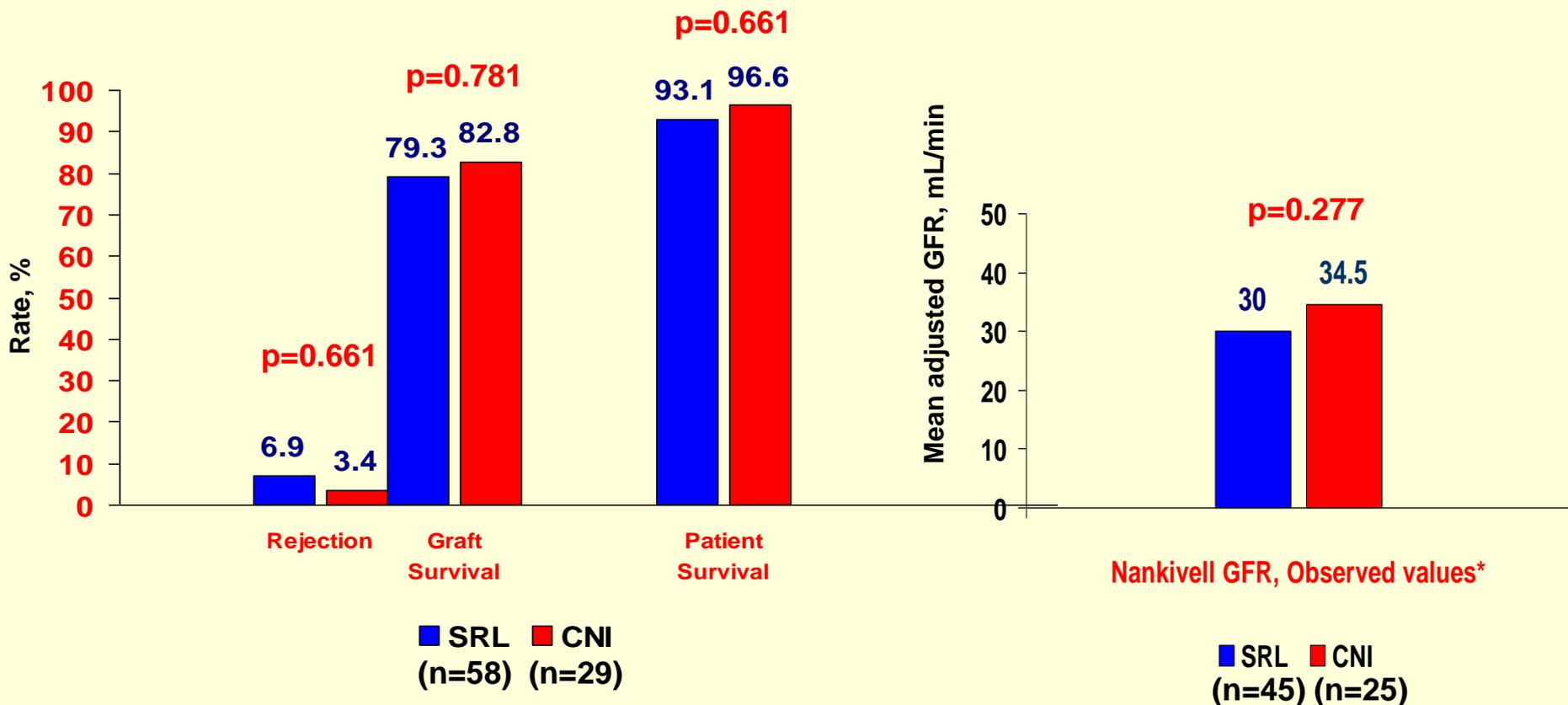
- Day 1: Stop CNI; SRL, 12-20 mg x1
- Day 2: SRL 4-8 mg/day
- Days 5-7: Adjust to 8-20 ng/mL
- MMF or AZA: Continue or stop
- Continue corticosteroids

### CNI Continuation

- Continue CsA or tacrolimus  
(*can switch CsA ↔ tacro*)
- MMF or AZA: Continue or stop
- Continue corticosteroids

Routine follow-up  
per protocol

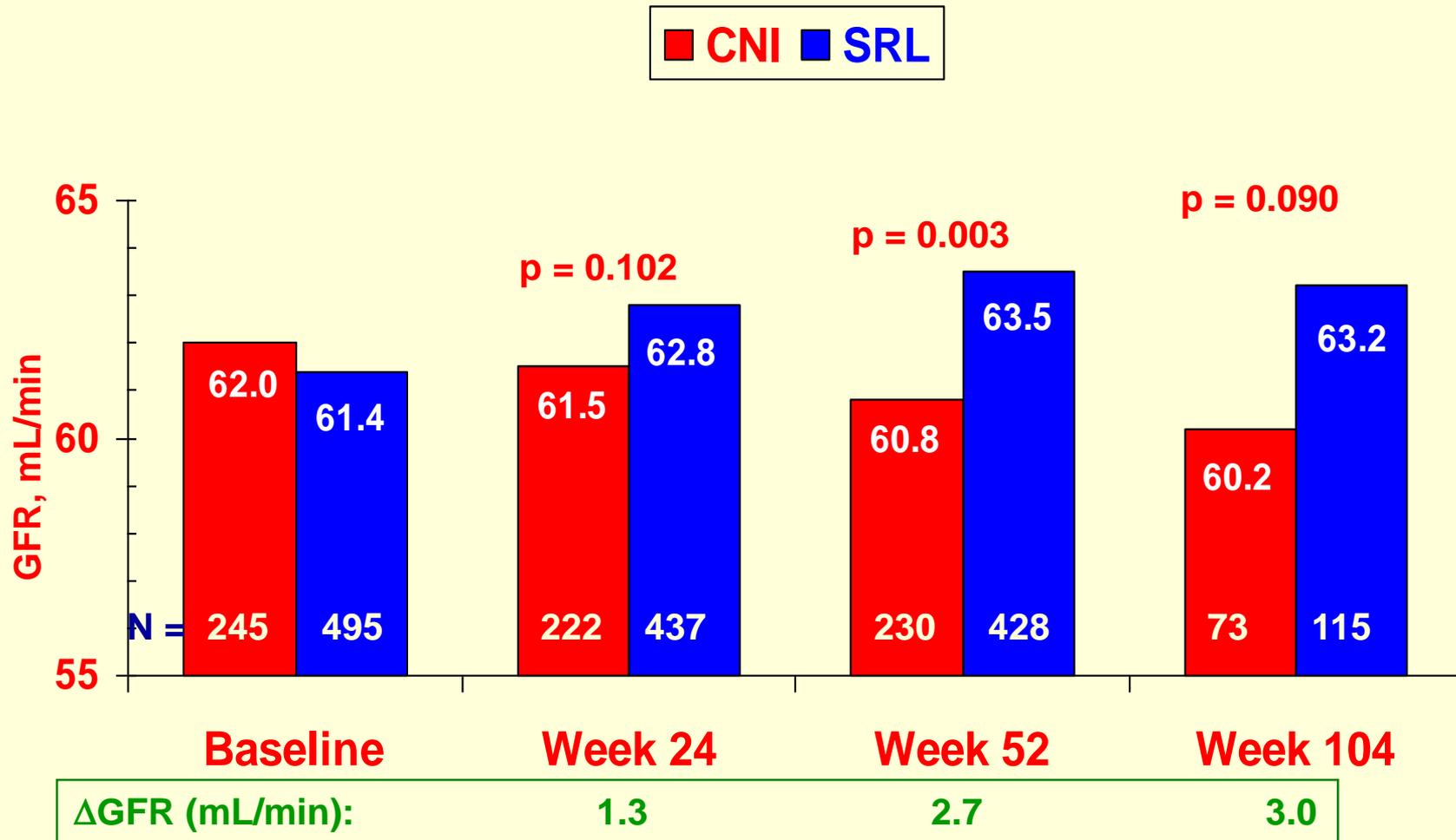
# Safety and Efficacy: Stratum With Baseline GFR = 20 to 40 mL/min



\*Includes all randomized patients

\*Includes all on-therapy and discontinued patients with graft function at week 52

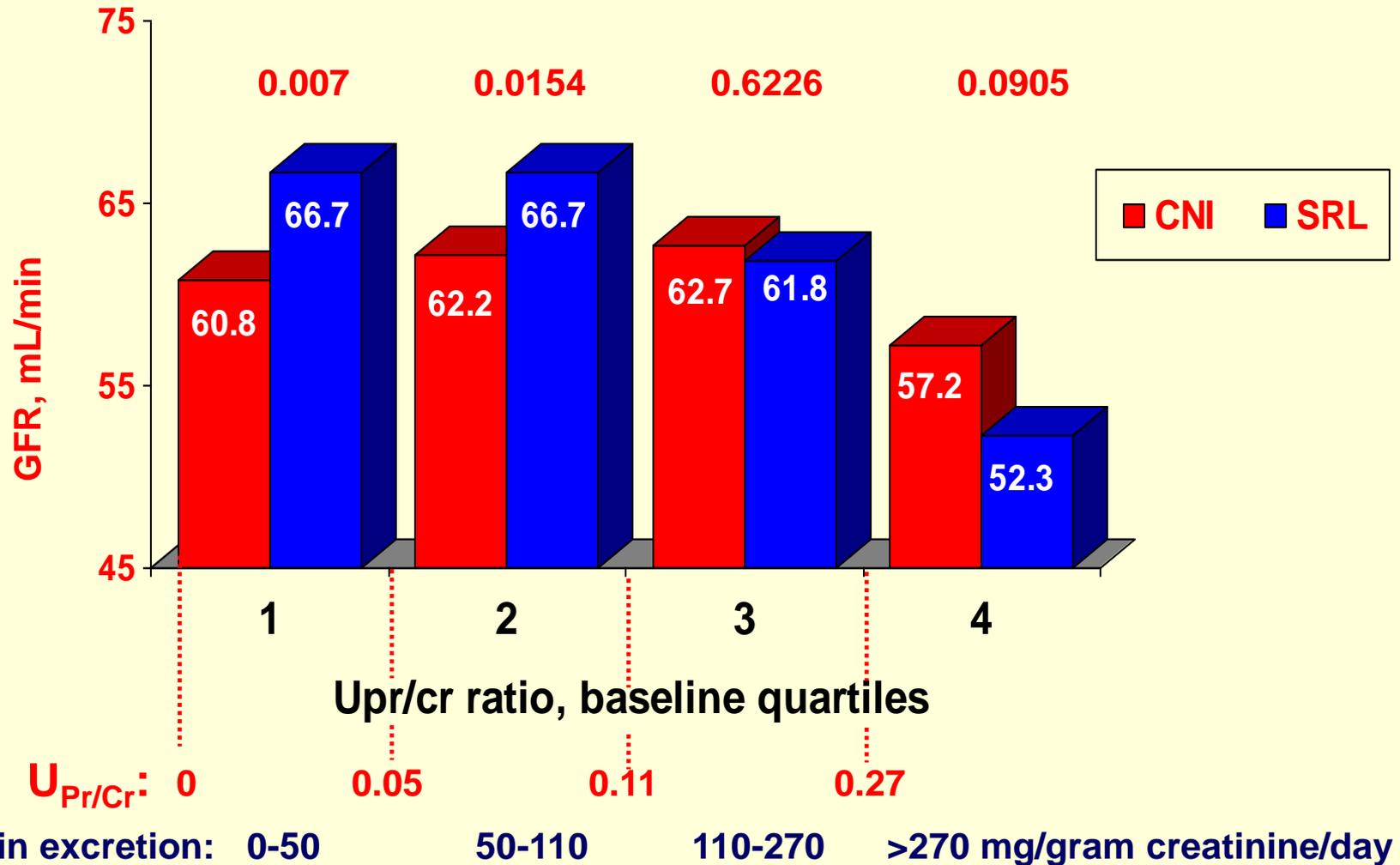
# Mean On-Therapy Nankivell GFR\*



\*Baseline GFR >40.0 mL/min; values adjusted for baseline and center

# Nankivell GFR at Week 52:

## Analysis by Baseline Quartiles of $U_{Pr/Cr}$ Ratio



# Use of mTORi to facilitate CNI dose reduction

## Atudy A2309

Efficacy Endpoint (ITT population)	12-Month Analysis <sup>1</sup> Primary Efficacy Endpoint: Composite Efficacy Failure <sup>a</sup>		24-Month Analysis <sup>2</sup> Secondary Efficacy Objective	
	EVR 1.5 mg/d (initial dose) + reduced-dose CsA (n = 277)	MPA 1.44 g/d + standard-dose CsA (n = 277)	EVR 1.5 mg/d (initial dose) + reduced-dose CsA (n = 277)	MPA 1.44 g/d + standard-dose CsA (n = 277)
<b>Composite endpoint</b>	<b>25.3%</b>	<b>24.2%</b>	<b>32.9%</b>	<b>27.4%</b>
Treated BPAR	16.2%	17.0%	19.9%	19.1%
Graft loss	4.3%	3.2%	5.8%	4.0%
Death	2.5%	2.2%	3.2%	2.9%
Loss to follow-up	4.3%	3.2%	7.6%	4.3%

<sup>a</sup> Defined as treated BPAR, graft loss, death, or loss to follow-up.

BPAR: biopsy-proven acute rejection; EVR: everolimus.

1. Silva HT et al. *Am J Transplant*. 2010;10:1401-1413. 2. Cibrik D et al. *Transplantation*. 2013;95:933-942.

# TRANSFORM TRIAL

---

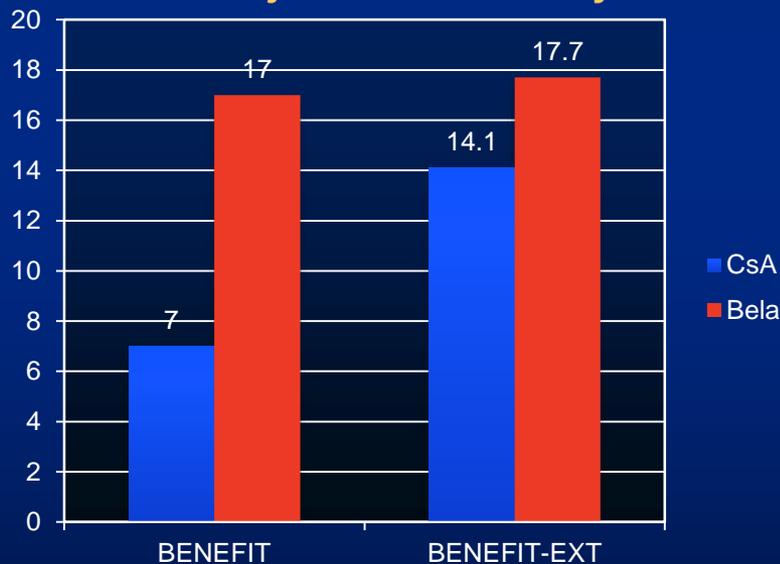
- 2-year, randomized, multicenter, open-label, two-arm study evaluating the graft function of everolimus and reduced CNI vs MPA and standard CNI in adult de novo KTRs
  - Recruiting more than 2,000 patients
  - Extended follow-up to 5 years
- Primary endpoint is a composite of tBPAR or eGFR  $<50$  mL/min/1.73 m<sup>2</sup> at 12 months post-transplant
  - Expected to be sensitive both to the effects of acute and chronic allograft rejection and nephrotoxic side effects of immunosuppressive therapies
  - Allows integration of a continuous outcome (graft function) with a logistic outcome (rejection)

# Belatacept and CNI-Avoidance

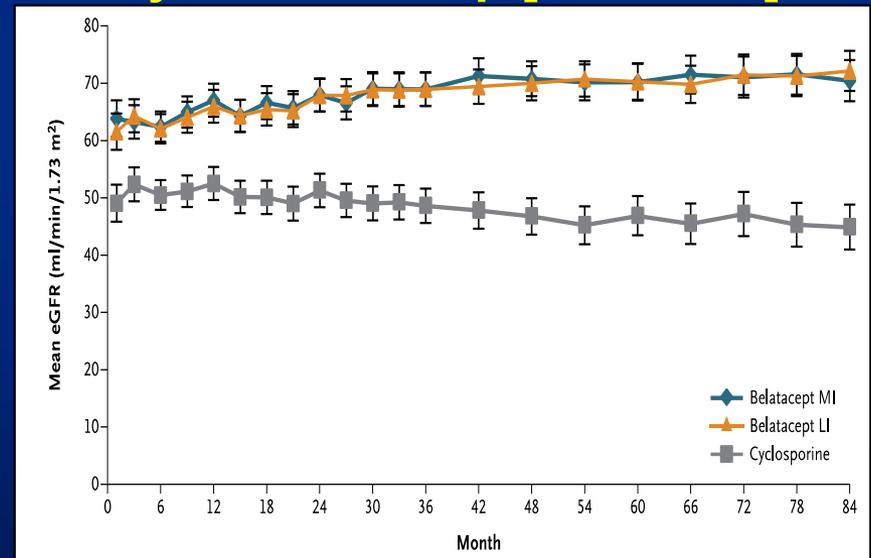
## BENEFIT and BENEFIT-EXT

- Simultaneous studies: Bela vs CyA
- EXT: ECD, DCD, and prolonged cold time

Acute rejection rates at 1 year



7-year follow-up [BENEFIT]



Vincenti F et al. *Am J Transplant.* 2010;10:535-546.

Durrbach A et al. *Am J Transplant.* 2010;10:547-557.

Vincenti F et al. *N Engl J Med.* 2016;374:333-343.

# What Are the Concerns about Belatacept?

- Higher rejection rates
- Histologically more severe rejection
- Post-transplant lymphoproliferative disorder risk (EBV negative recipients)
- IV administration and cost
- **No RCTs with tacrolimus as comparator agent**

Pestana JO et al. *Am J Transplant.* 2012;12:630-639.

Vincenti F et al. *Am J Transplant.* 2012;12:210-217.

Durrbach A et al. *Am J Transplant.* 2010;10:547-557.

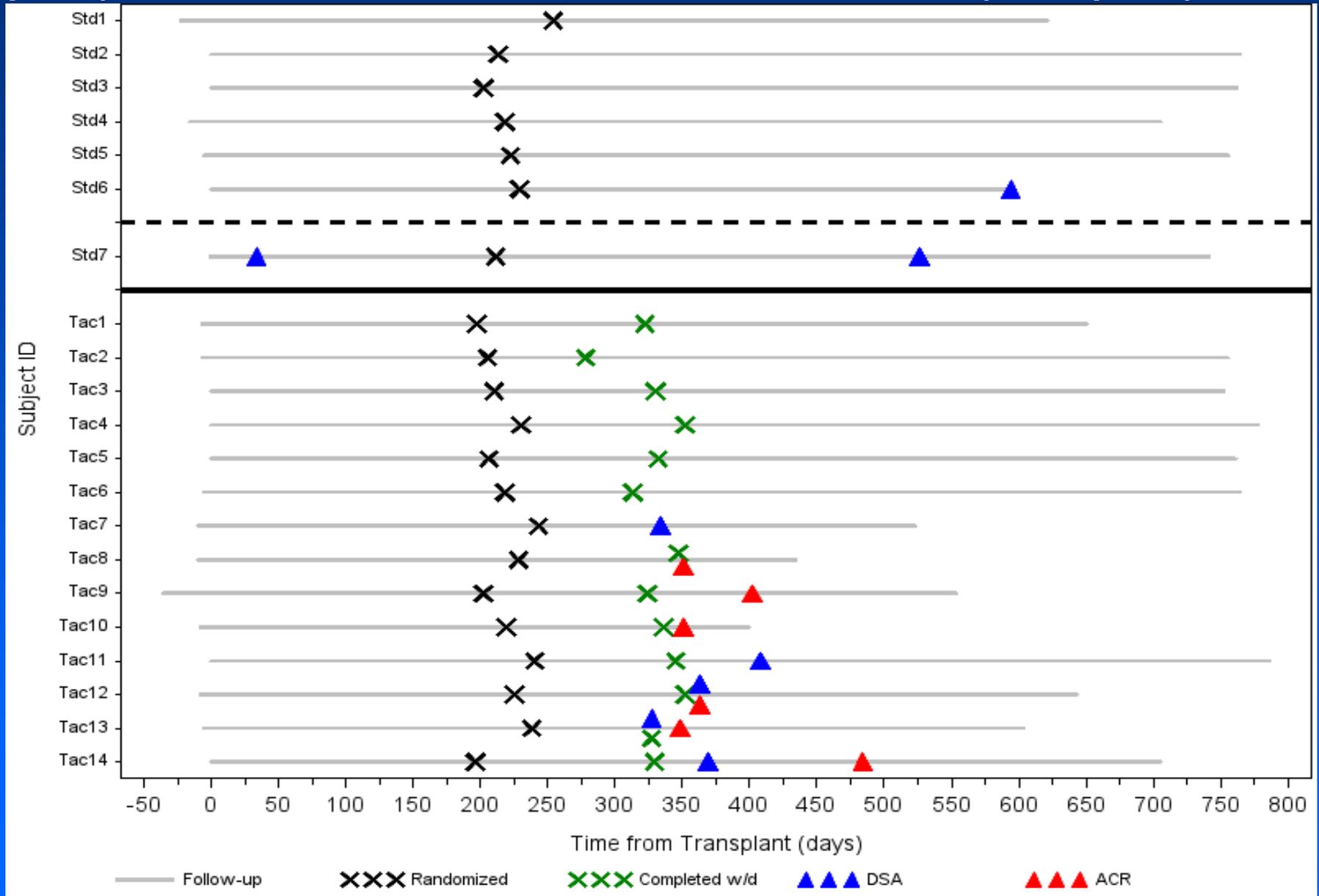
Vincenti F et al. *Am J Transplant.* 2010;10:535-546.

Heher et al. *N Engl J Med.* 2016;374:388-389.

# Is Immune Monitoring the Key to Safe CNI Minimization? CTOT-09

- Tacrolimus withdrawal in stable kidney transplant recipients
- Living donors, DSA negative, peak PRA < 20%
- Thymo, MMF, Tac, low dose prednisone for 6 mo
- Eligible for randomization (2:1 withdrawal) at 6 mo if
  - Absence of AR within first 6 mo
  - Absence of anti HLA antibody
  - 6 mo biopsy no rejection
- Withdraw tacrolimus over 3 months, serial urine for chemokines
- Biopsies driven by elevated urinary MIG (CXCL9) or IP10 (CXCL10) on 2 consecutive repeat studies

# Timing of Adverse Outcomes (DSA and/or ACR) in Control Patients (upper panel) vs Patients Randomized to Tacrolimus Withdrawal (lower panel)

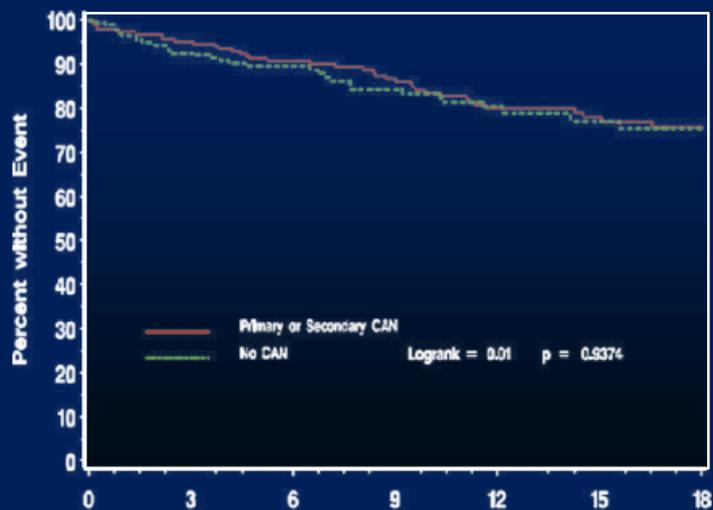


# Graft Survival in DeKAF

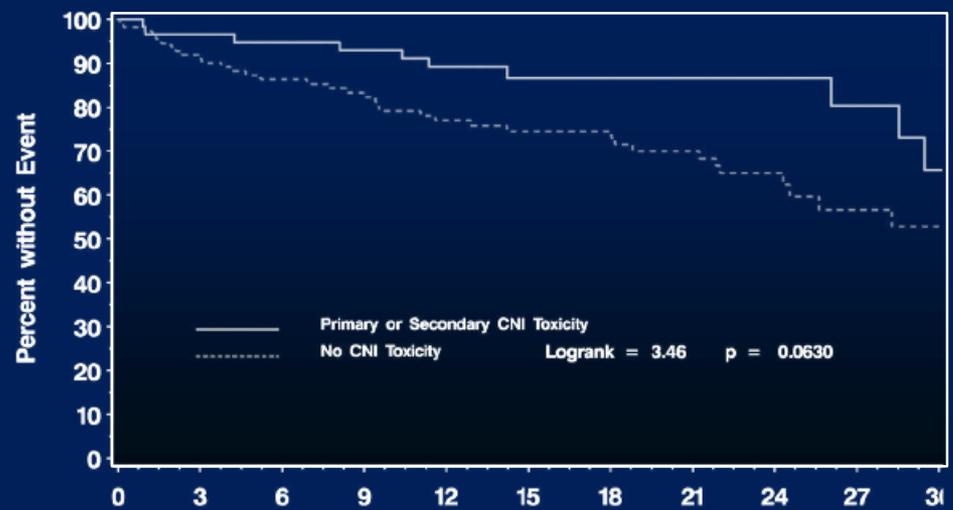
## Impact of Diagnosis of CAN or CNI Nephrotoxicity

### CAN Does not Predict Subsequent Graft Failure: DEKAF Study

- n=440 “troubled grafts”
- Baseline creatinine <2 mg/dL
- Creatinine increase >25%



CAN++:	204	173	148	130	111	75	51
CAN-:	215	159	126	91	76	45	35
	0	3	6	9	12	15	18



CNI++:	59	56	51	50	45	33	29	23	22	13	9
CNI-:	112	101	90	80	71	58	52	43	37	17	14
	0	3	6	9	12	15	18	21	24	27	31

Gaston RS et al. *Transplantation*. 2010;90:68-74.

Gourishankar S et al. *Am J Transplant*. 2010;10:324-330.

# Summary: CNI Minimization 2017

- Use of AZA/MMF and steroids alone generally not successful
- Use of mTOR inhibitors
  - In avoidance, withdrawal and conversion protocols, variable effects on preservation or improvement in renal function; higher rates of rejection in most
  - Benefits and risks of mTORi's to facilitate CNI dose reduction require further study
- Use of belatacept encouraging but risks of early rejection and costs remain concerning
- Immune monitoring not yet proven to enhance the safety of CNI minimization

# Summary: CNI Minimization 2017, continued

- Until better agents are available as substitutes, the CNIs remain the cornerstone of immunosuppression for kidney transplant recipients
- CNI minimization should be attempted with extreme caution