Update on Calcineurin Inhibitor Minimization After Kidney Transplantation

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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		↑	↑			

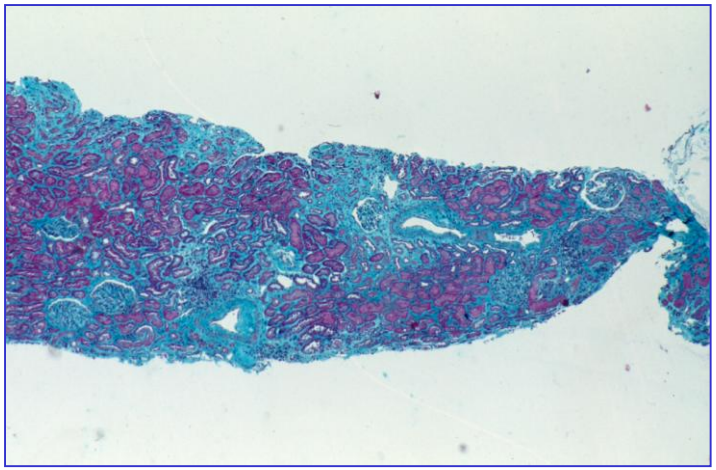
↑ indicates a mild-moderate adverse effect on the complication.
↑↑ indicates a moderate-severe adverse effect on the complication.
(↑) indicates a possible, but less certain adverse effect on the complication.

Longitudinal assessment by protocol biopsy: CNI nephrotoxicity and subclinical rejection

Timeline of biopsy protocol

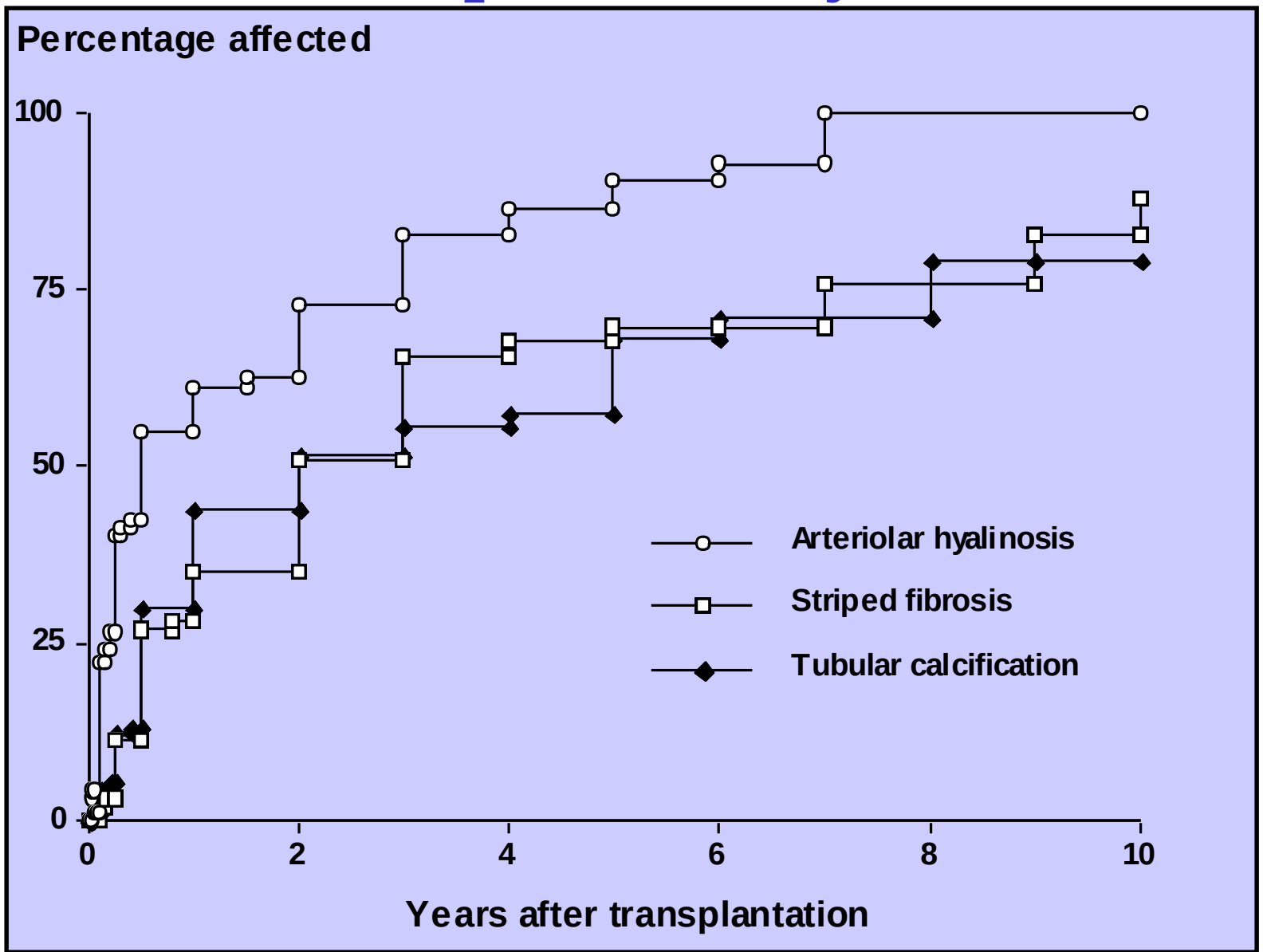
0 3 12 mo. 2 3 4 5 6 7 8 9 10 years

- 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

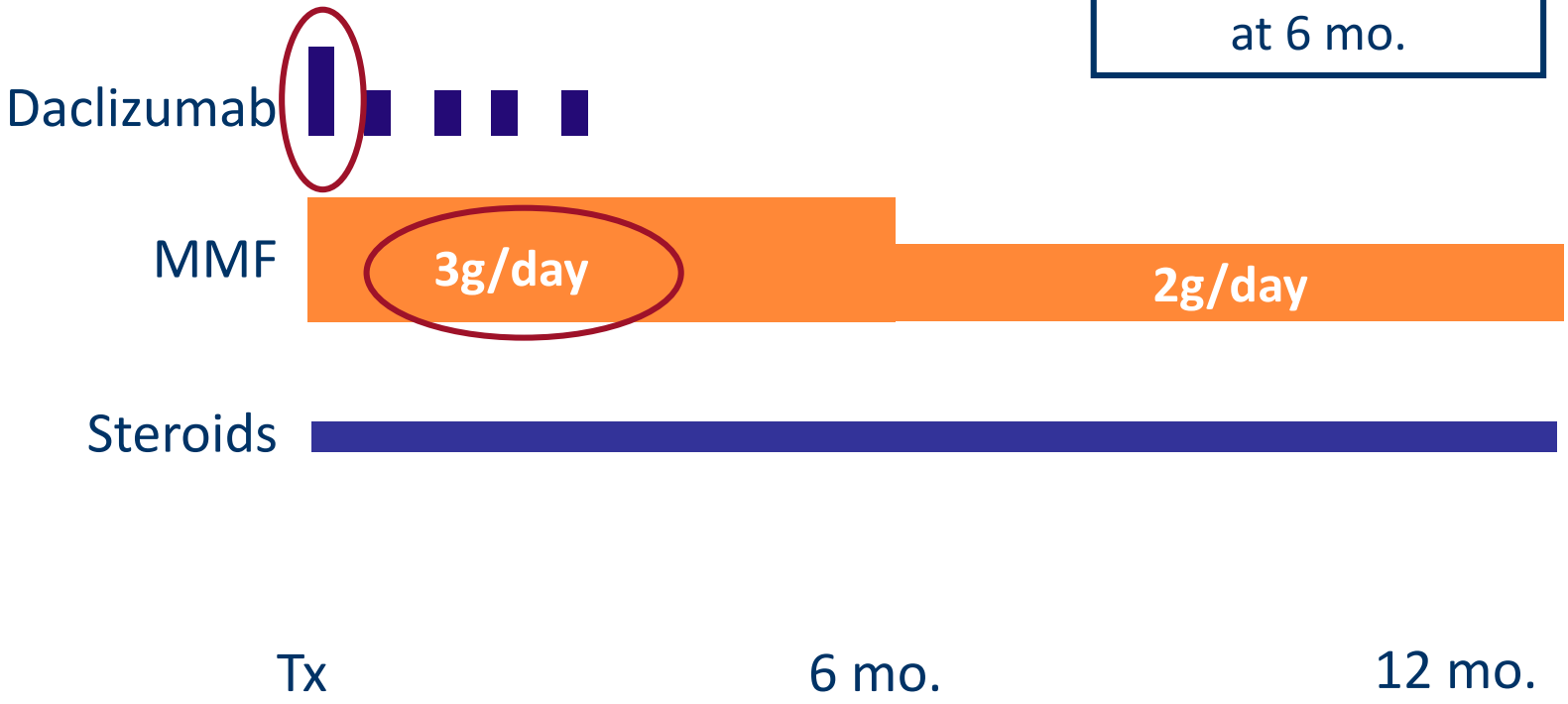
Considerations in Reviewing CNI Minimization Studies

- 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

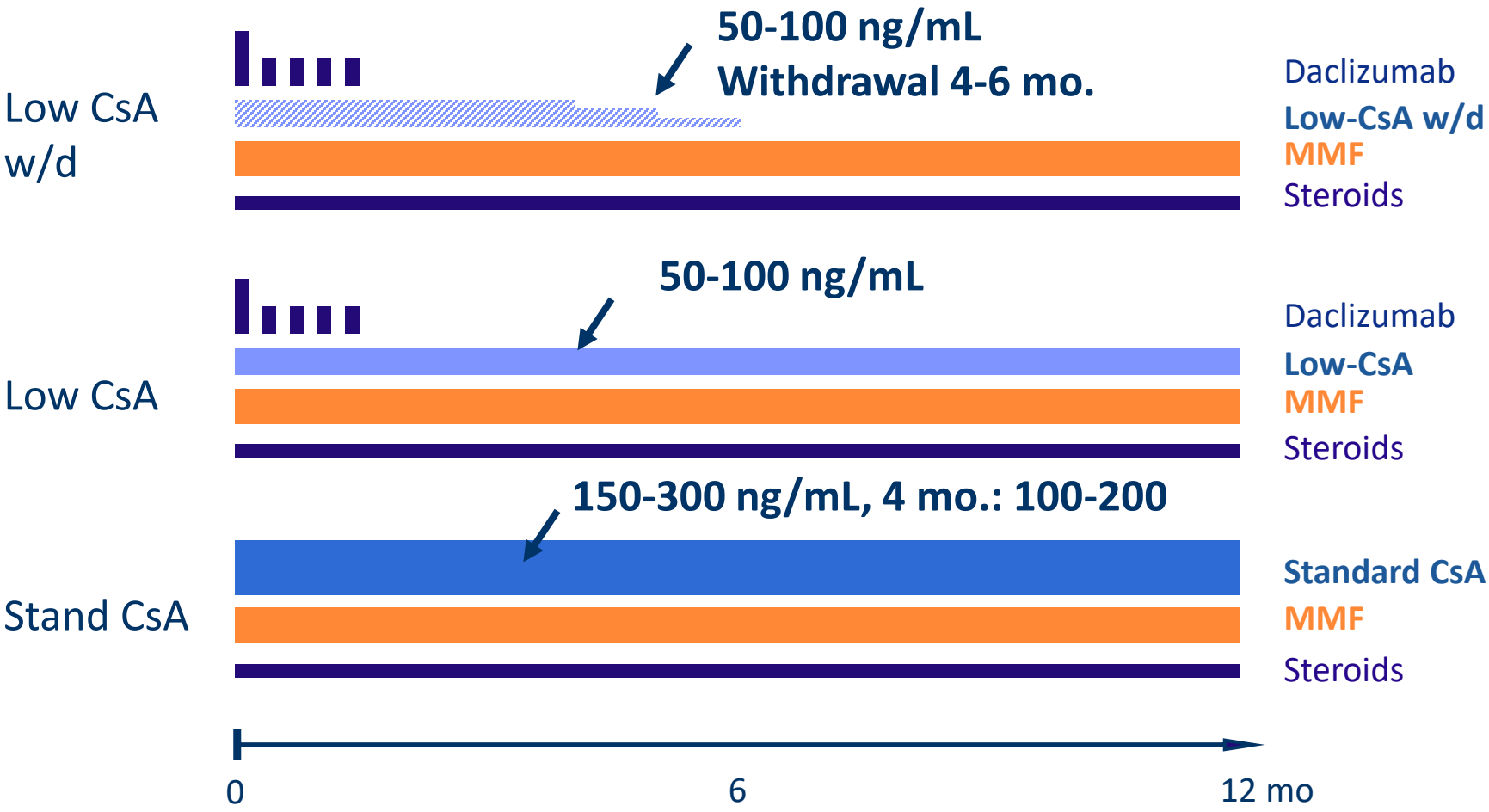
Multicenter, uncontrolled study of 98 “low risk” kidney transplant recipeints

48% incidence of acute rejection at 6 mo.



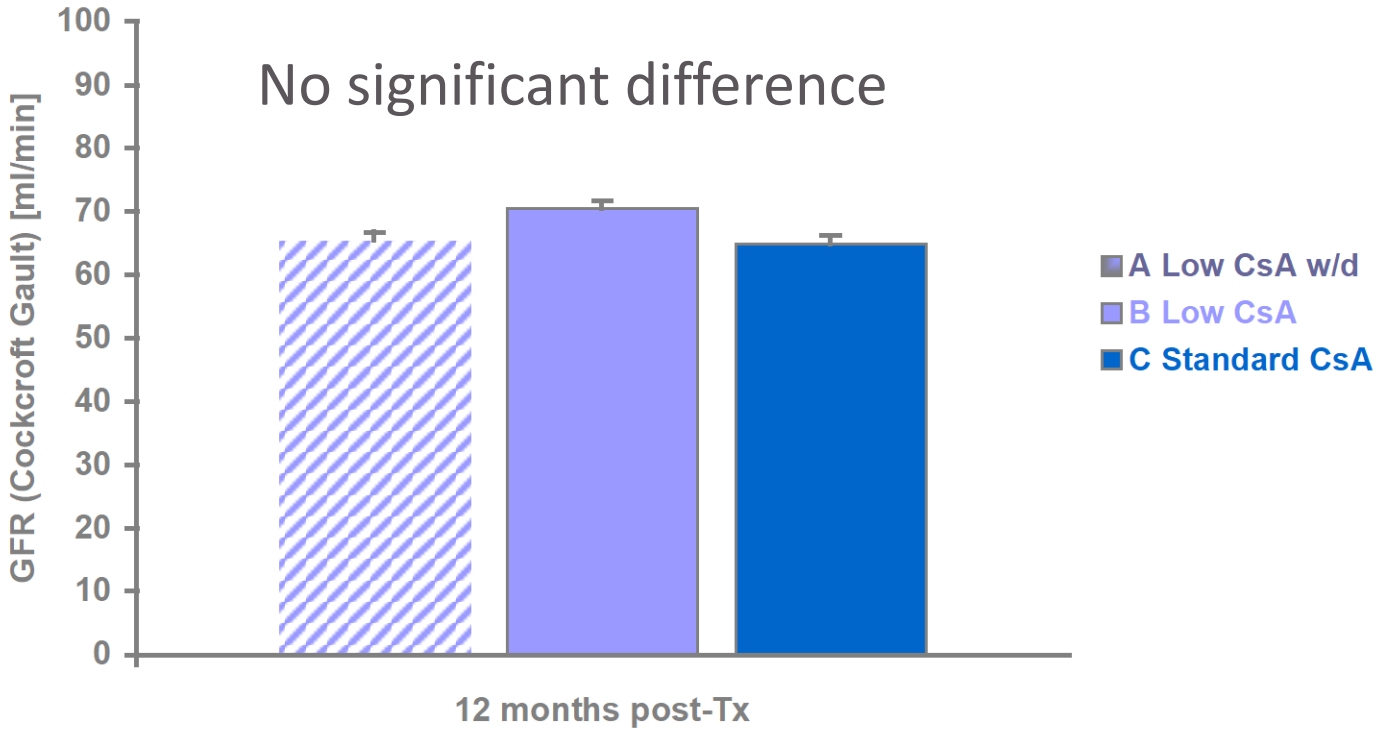
Vincenti F et al. *Transplantation* 2001; 71:1282–7.

CAESAR study design (n=536)



Ekberg H et al. *Am J Transplant* 2007; 7 (3): 560.

CAESAR study
GFR at 12 months (primary endpoint)



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

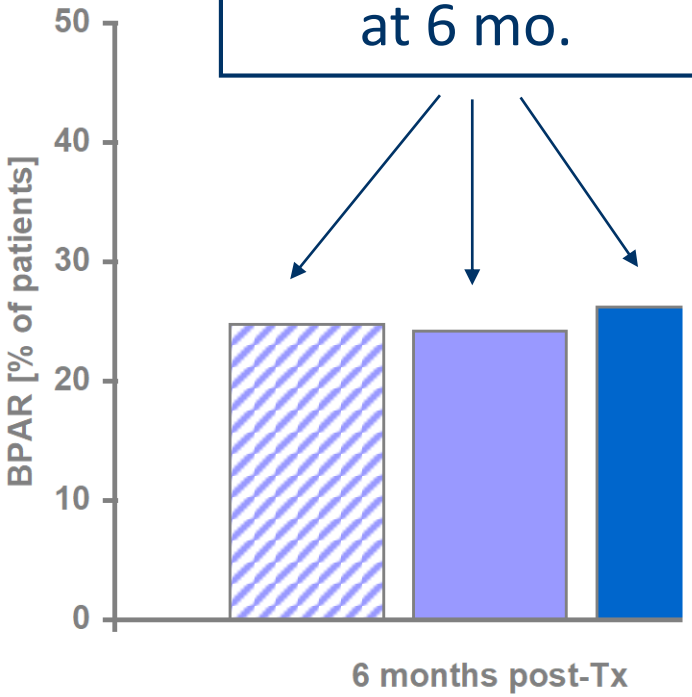
Ekberg H et al. *Am J Transplant* 2007; 7 (3): 560.

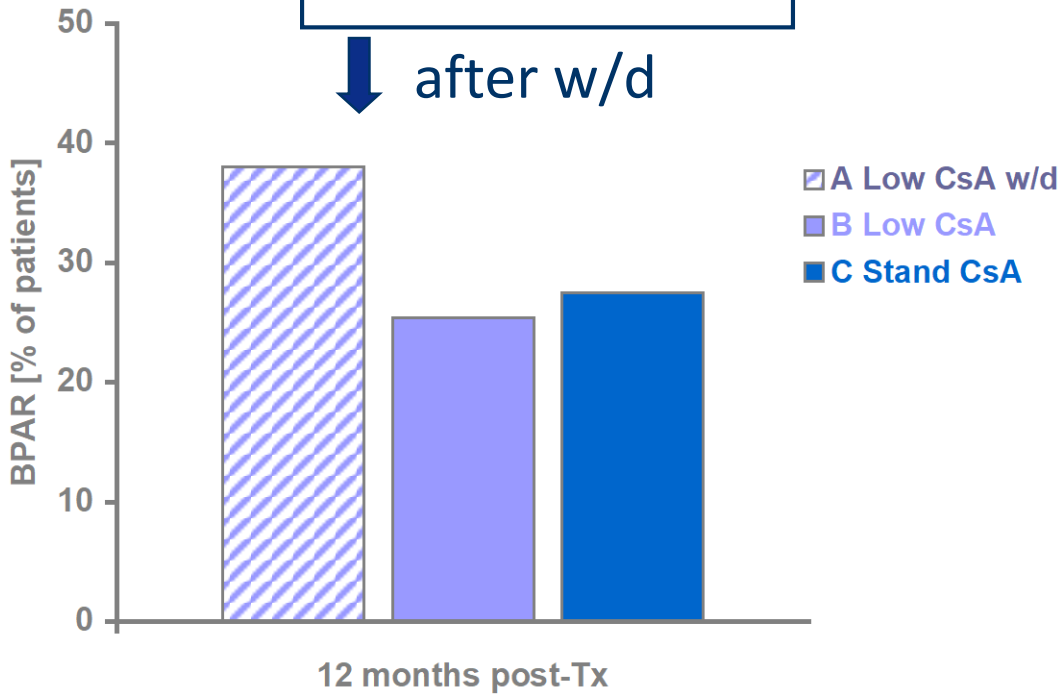
CAESAR study
BPAR at 6 and 12 months

25 %
Acute Rejection
at 6 mo.

38 %
Acute Rejection
at 12 mo.

after w/d





Ekberg H et al. *Am J Transplant* 2007, 7 (3): 560.

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:

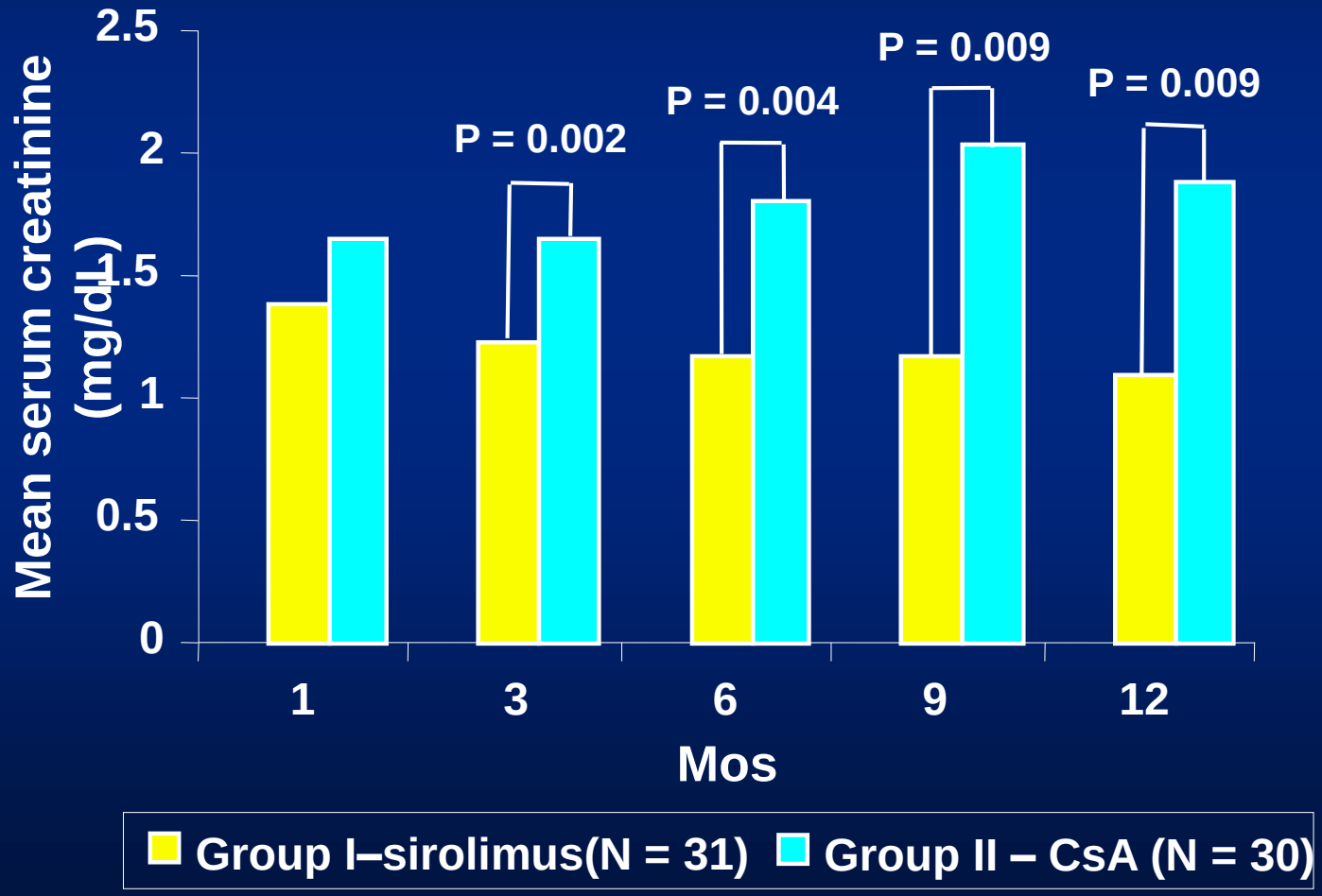
	Sirolimus (n=81)	CsA (n=80)	p-value
Biopsy proven rejection:	28(34.6)	23(28.7)	NS
Graft survival:	73(90.1)	71(88.8)	NS
Patient survival:	76(93.8)	75(93.8)	NS
Calculated GFR (ml/min)	69.3	56.8	0.004

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)



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

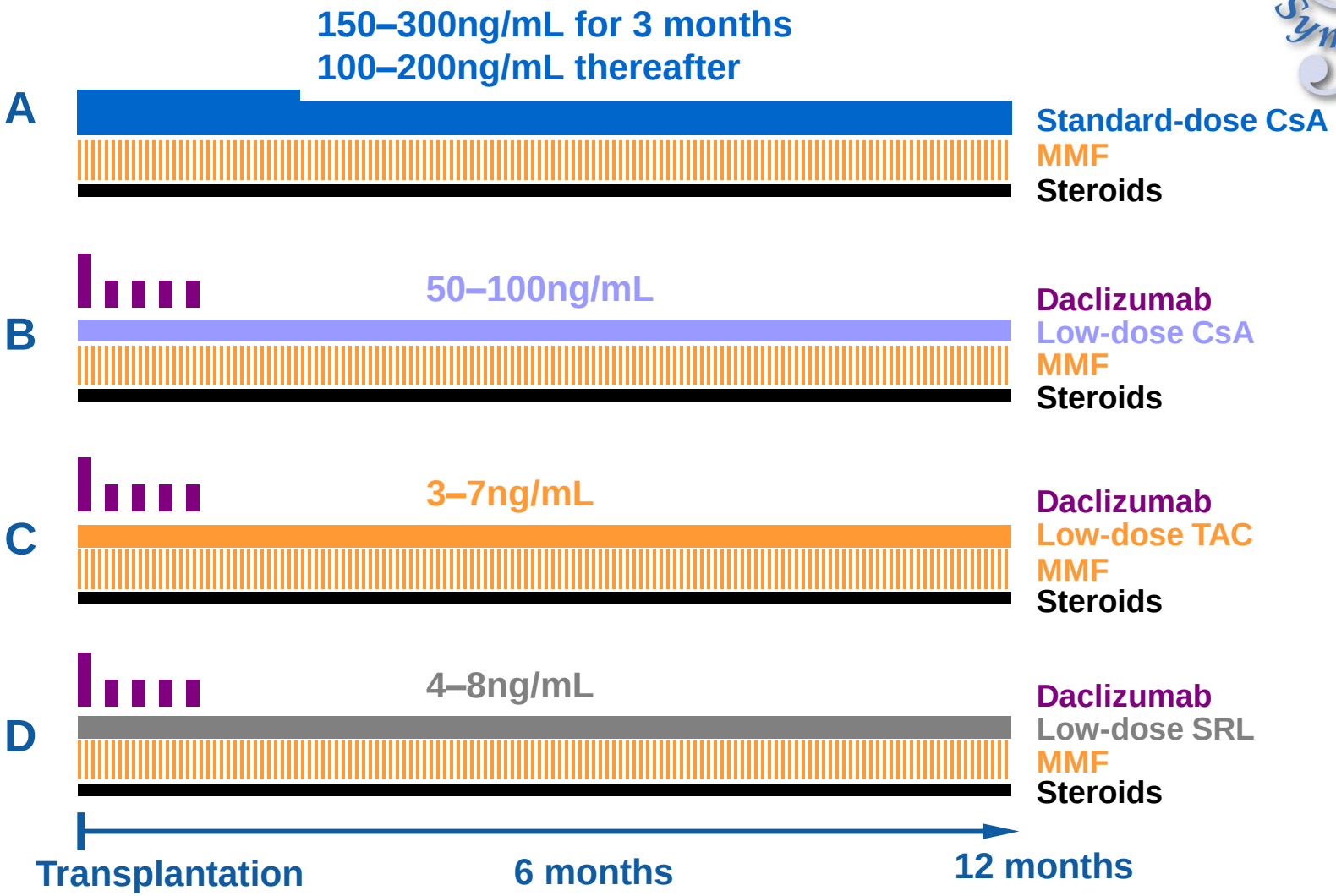
Adverse events

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

Flechner SM et al. *Am J Transplant.* 2011;11:1633-1644.

SYMPHONY Study Design

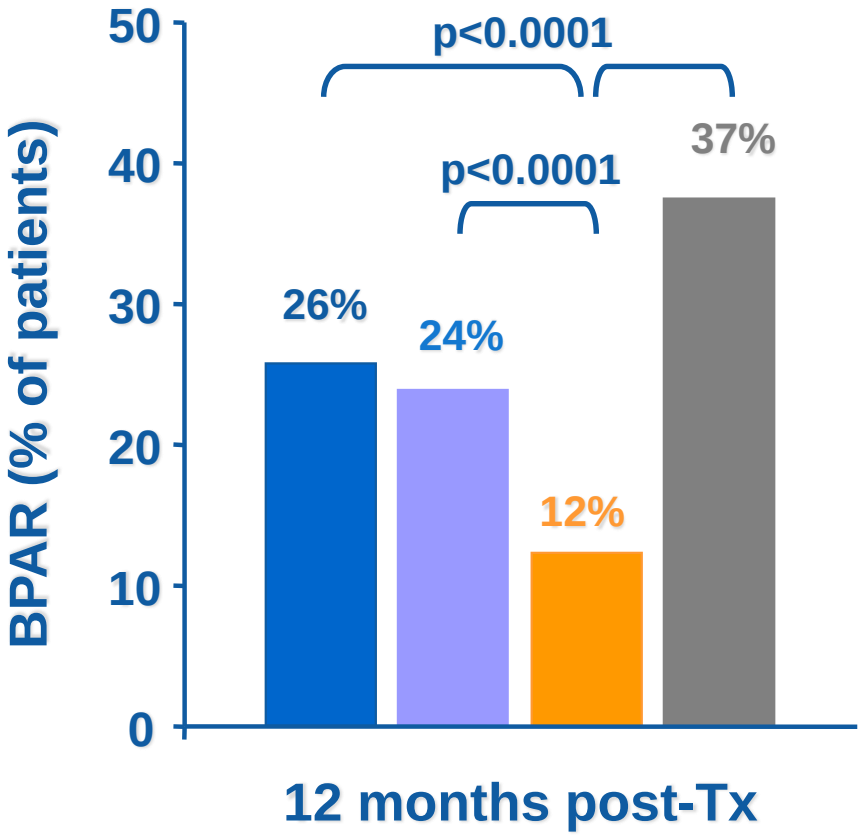
1645 patients at 83 sites in 15 countries



Ekberg H, et al. NEJM 2007;357:2562–75

Less Biopsy Proven Acute Rejection with Low-dose Tac

(ITT, Excluding Borderline)

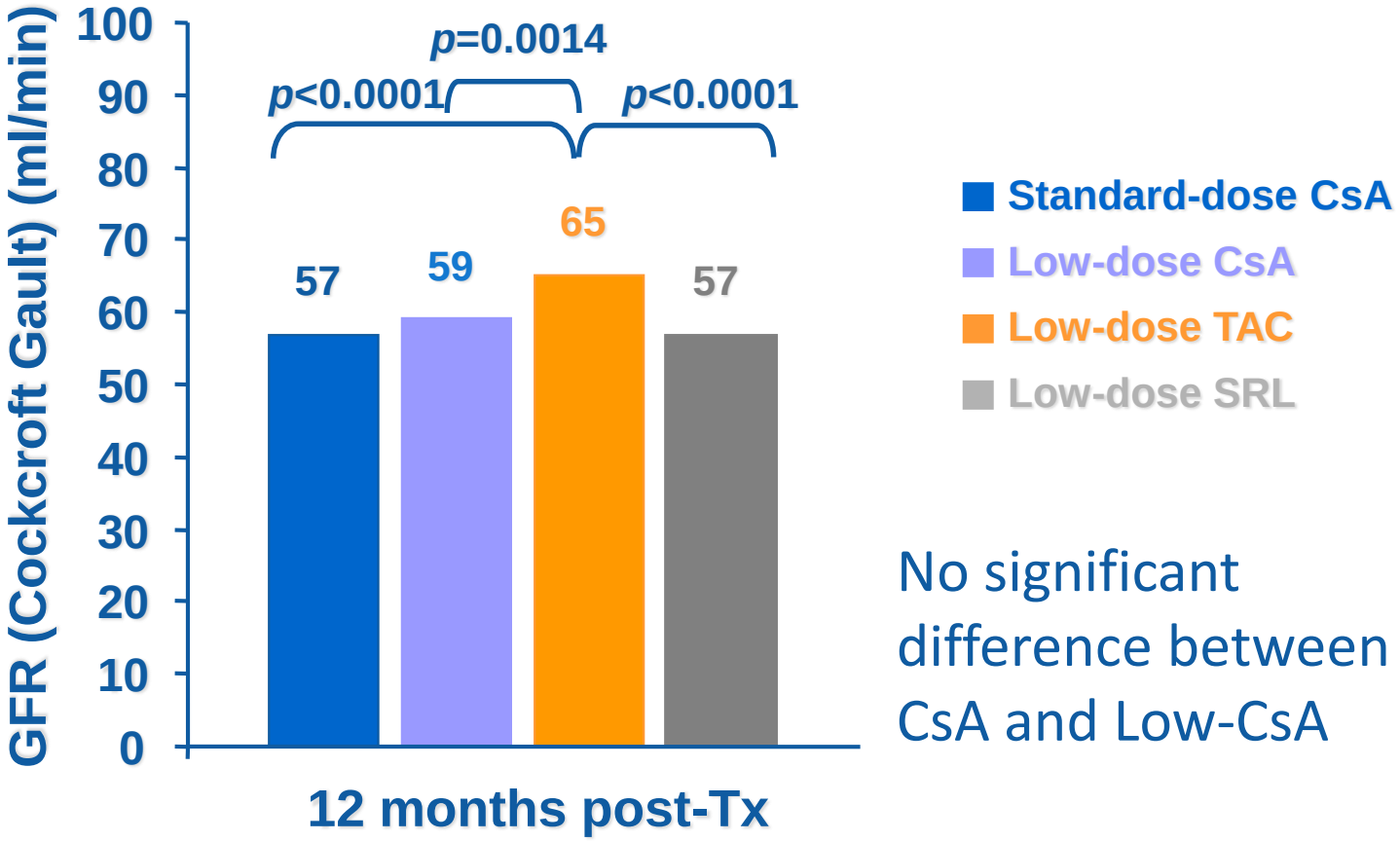


No significant difference between CsA and Low-CsA; about 25%

Ekberg H et al *NEJM 2007; 357: 2562*.

Graft function was superior with Low-dose Tac

Calculated GFR Cockcroft-Gault (primary endpoint)



No significant difference between CsA and Low-CsA

Ekberg H et al *NEJM* 2007; 357: 2562.

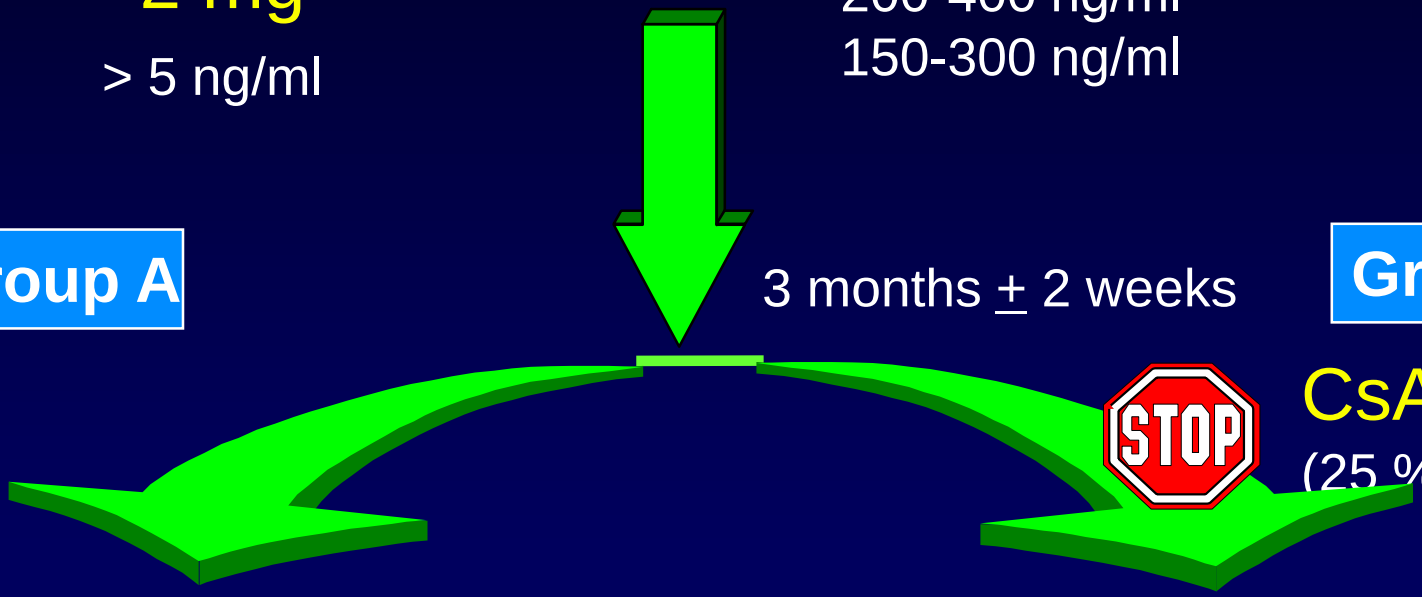
Wyeth 310

Sirolimus + **CsA** + **Steroids**

2 mg

> 5 ng/ml

200-400 ng/ml
150-300 ng/ml



Group A

Sirolimus 2 mg
(>5 ng/ml)

CsA (75-200 ng/ml)

Steroids

Group B

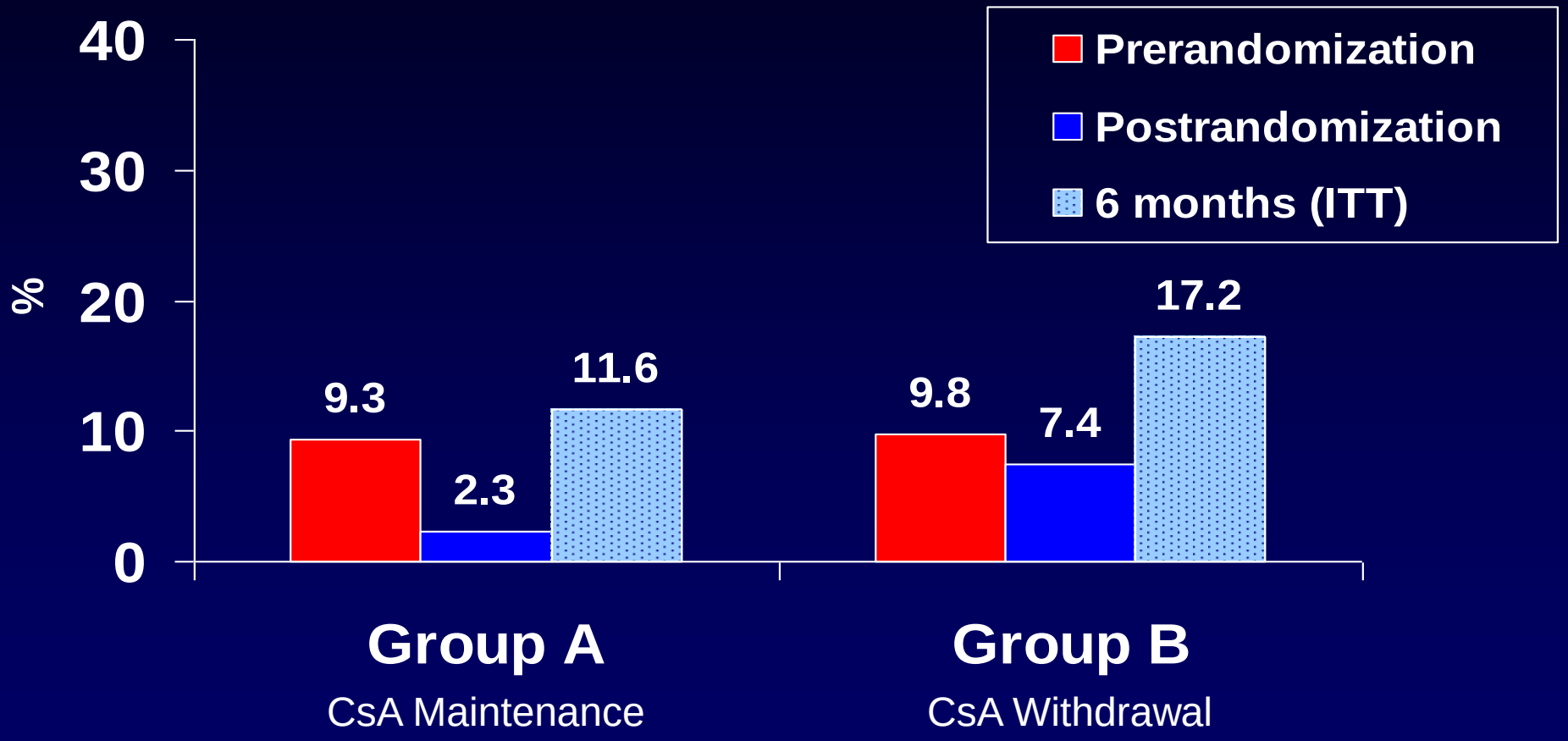
CsA
(25 % per week

Sirolimus (20-30 ng/ml)

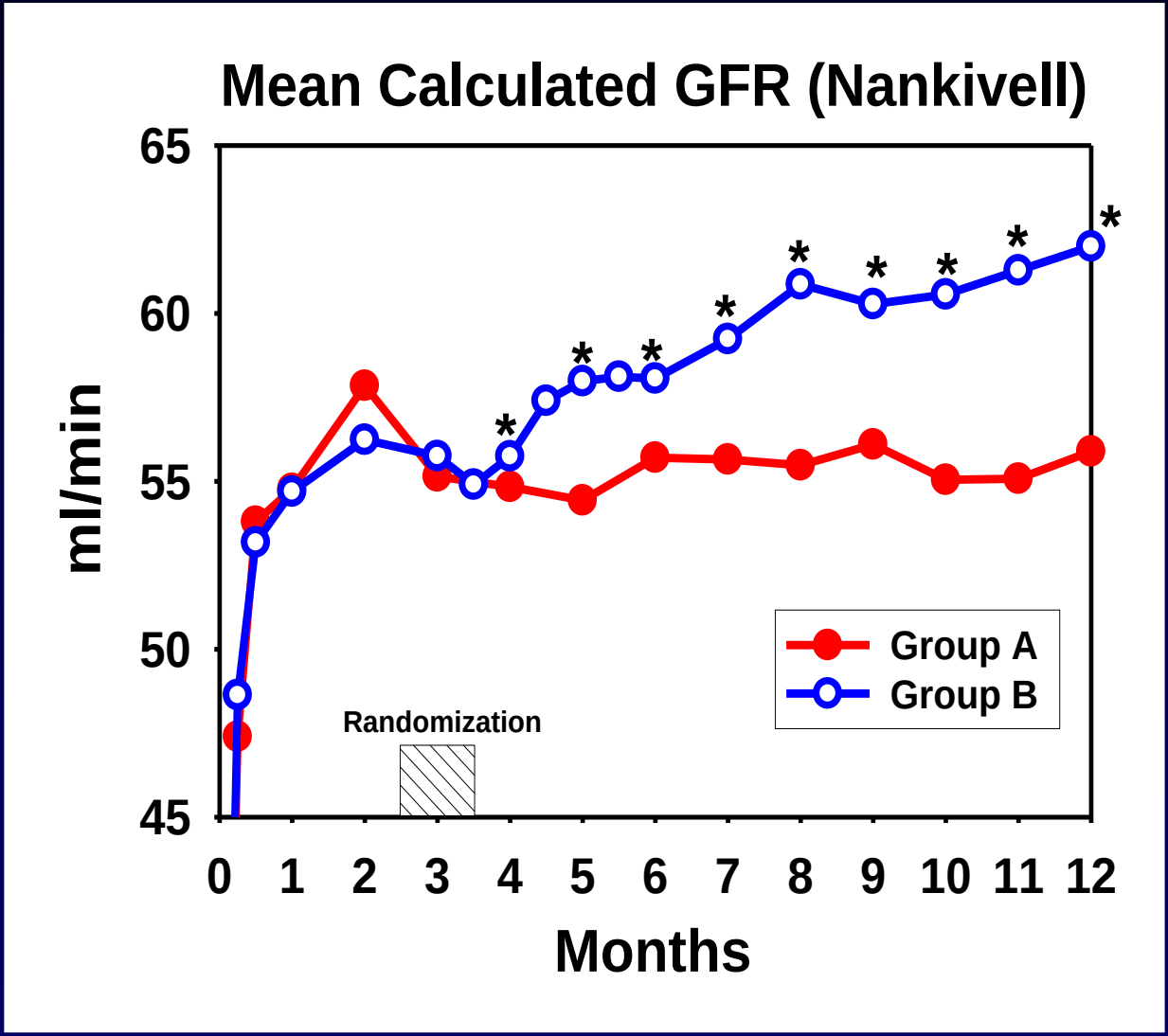
Steroids

Johnson RWG et al. Transplantation 2001; 72: 777

Incidence of Acute Rejection: 6 month data

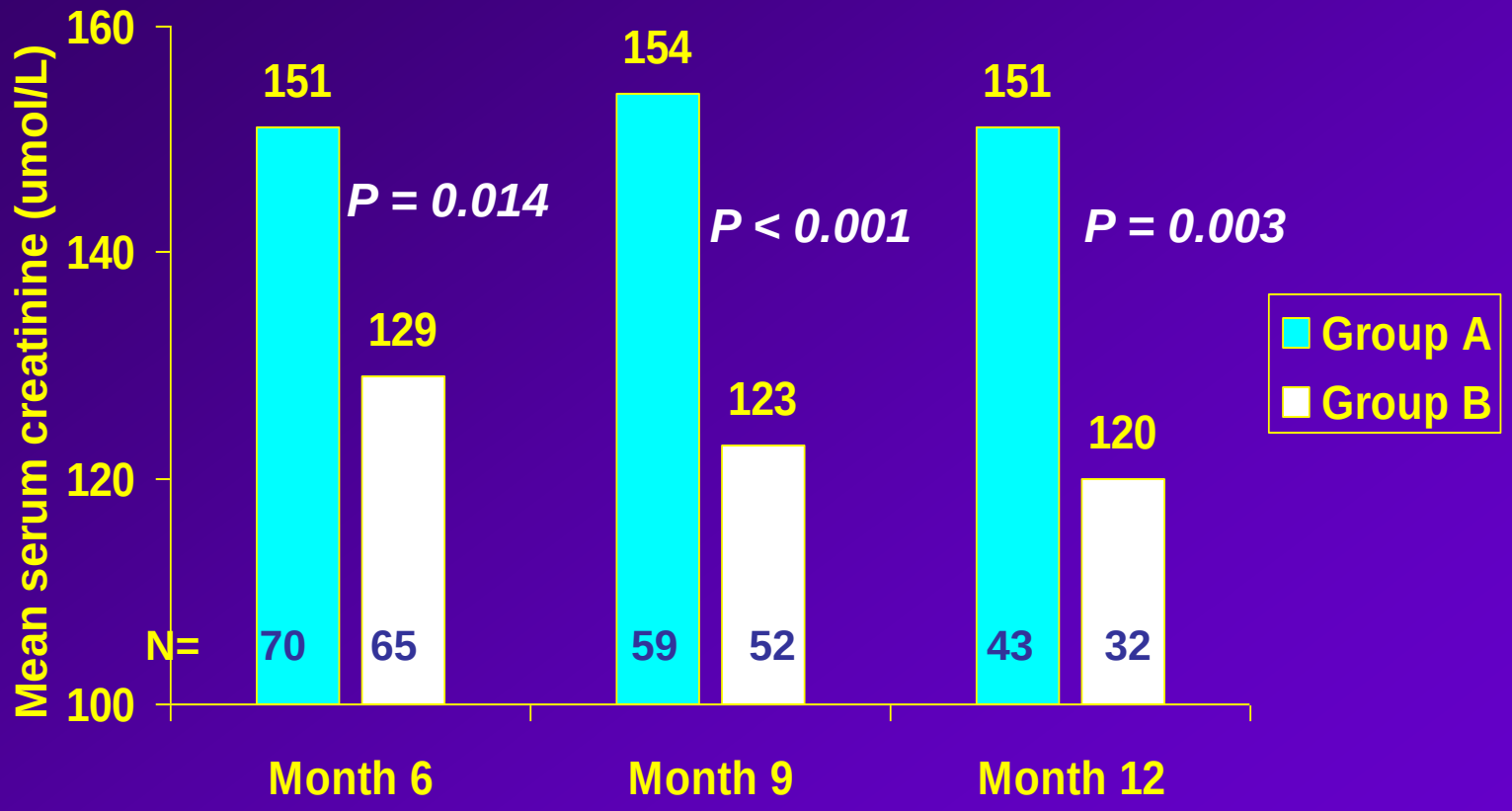


Higher Calculated GFR Following CsA Elimination



*p<0.001

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



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

Gonwa TA et al. Transplantation 2002; 74: 1560

LATE CONVERSION IN STABLE PATIENTS

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

[a] ***P*<0.05**

[b] **p=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.

LATE CONVERSION IN PATIENTS WITH RENAL DYSFUNCTION

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

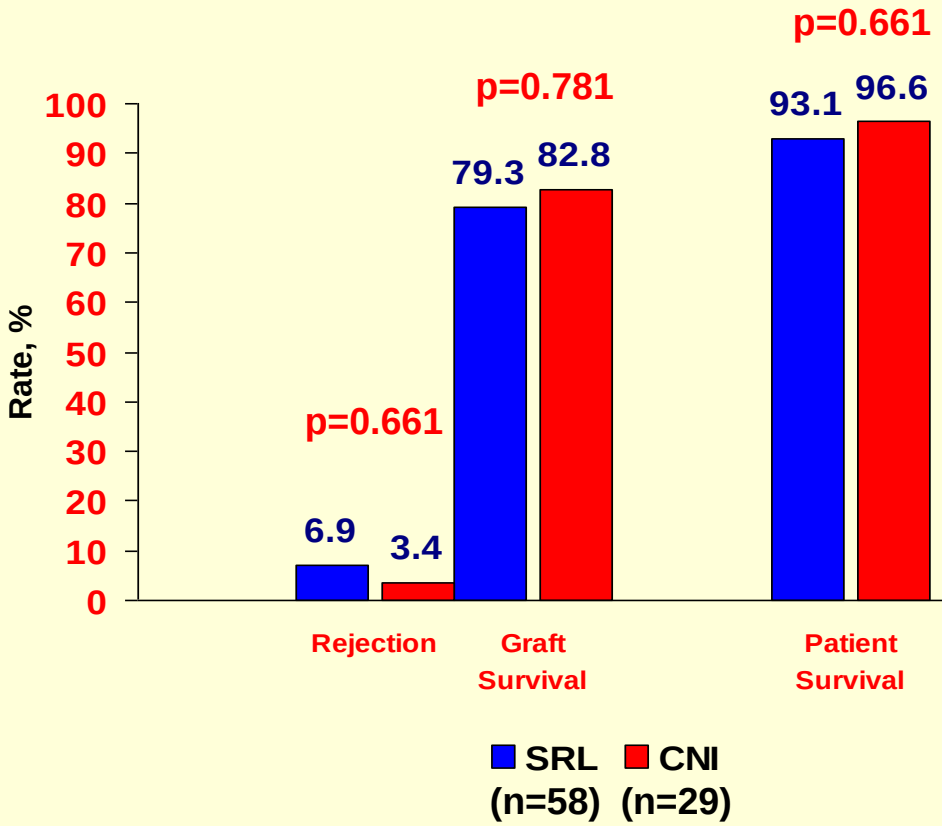
CNI Continuation

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

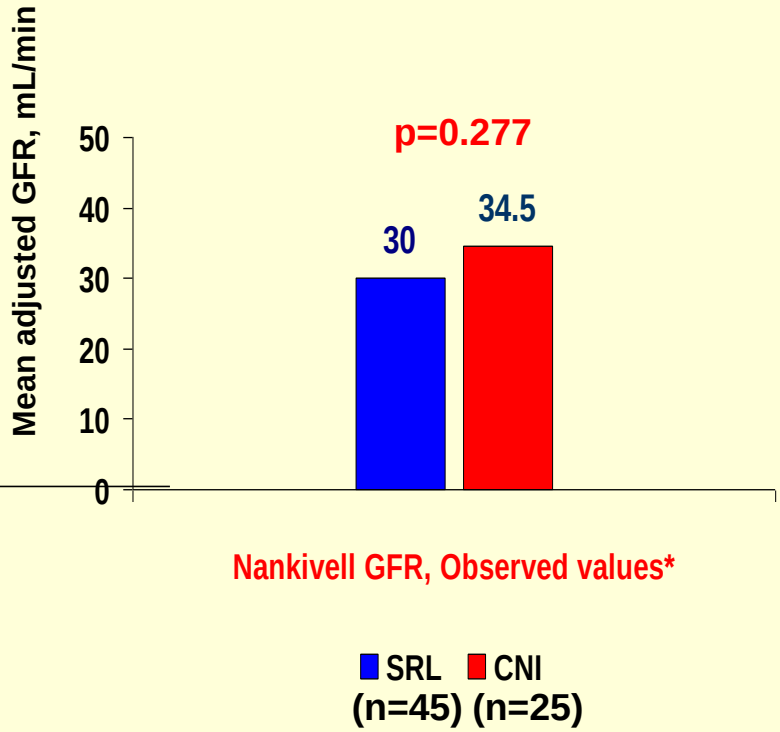
Routine follow-up per protocol

Schena FP, et al. Transplantation 2009; 87:233

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



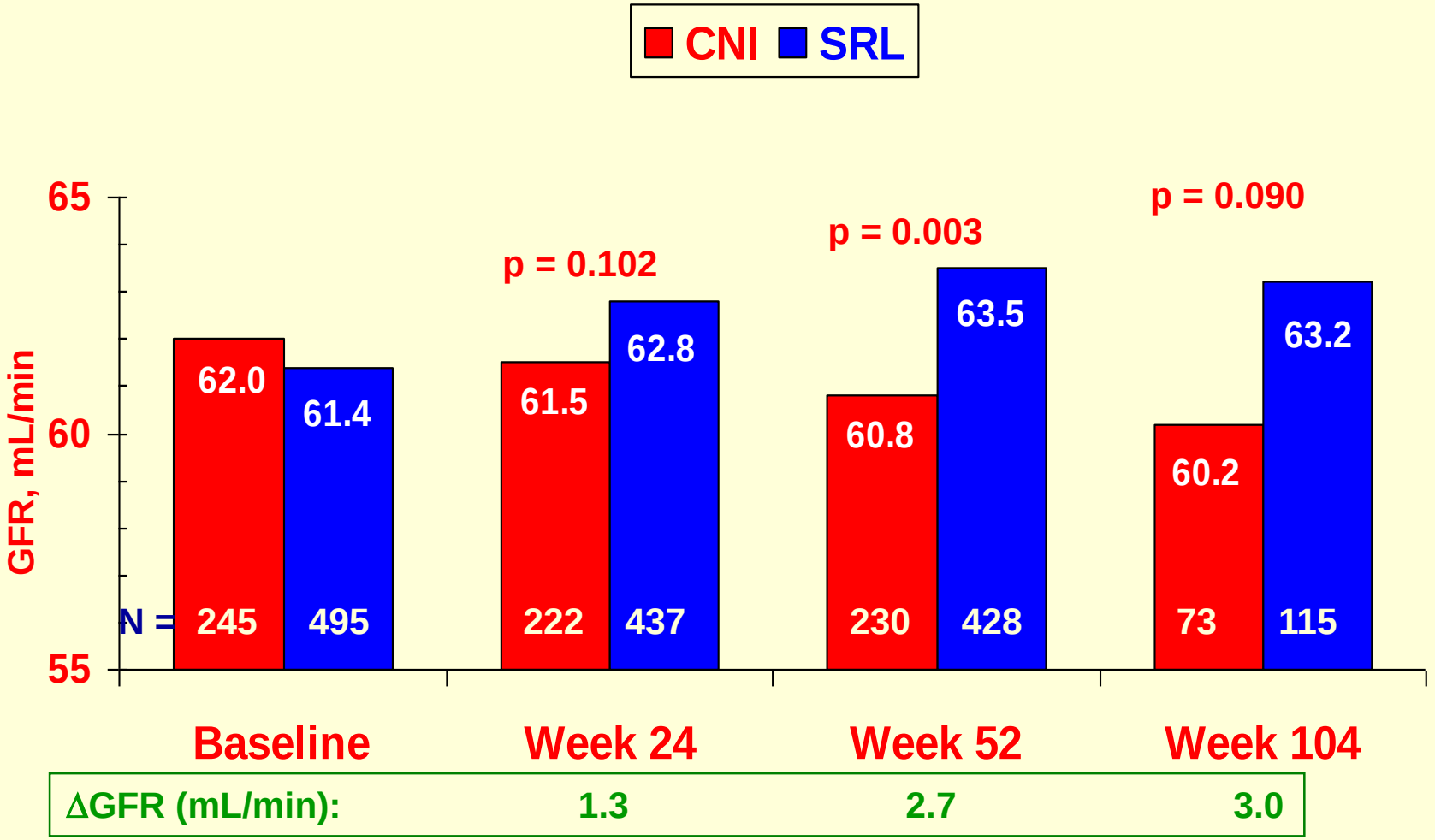
*Includes all randomized patients



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

Schena FP, et al. Transplantation 2009; 87:233

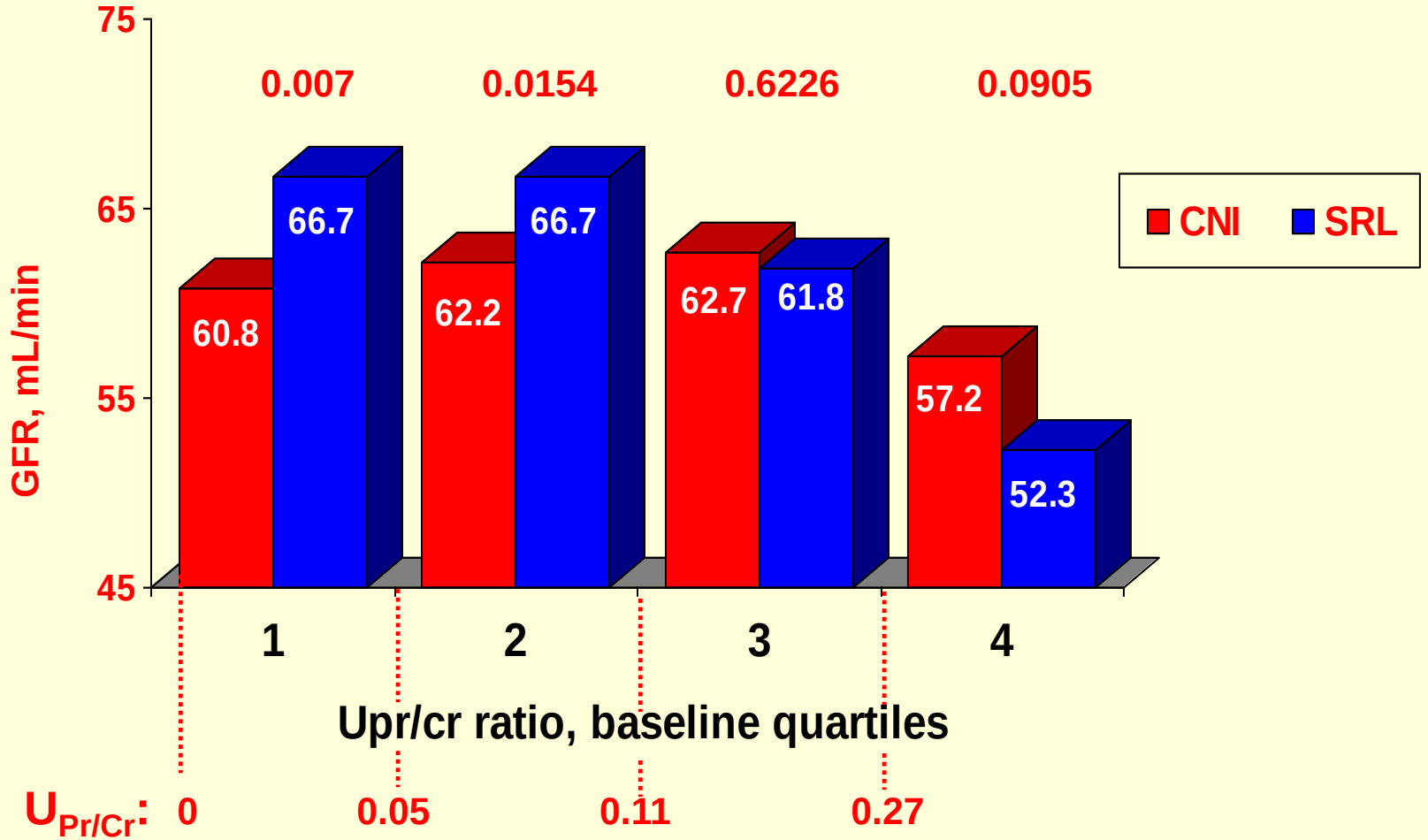
Mean On-Therapy Nankivell GFR*



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

Schena FP, et al. Transplantation 2009; 87:233

Nankivell GFR at Week 52:
Analysis by Baseline Quartiles of $U_{Pr/Cr}$ Ratio



Schena FP, et al. Transplantation 2009; 87:233

Use of mTORi to facilitate CNI dose reduction

Atudy A2309

Efficacy Endpoint (ITT population)	12-Month Analysis[1] Primary Efficacy Endpoint: Composite Efficacy Failure[a]		24-Month Analysis[2] 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)
Composite endpoint	**25.3%**	**24.2%**	**32.9%**	**27.4%**
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%

[a] 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

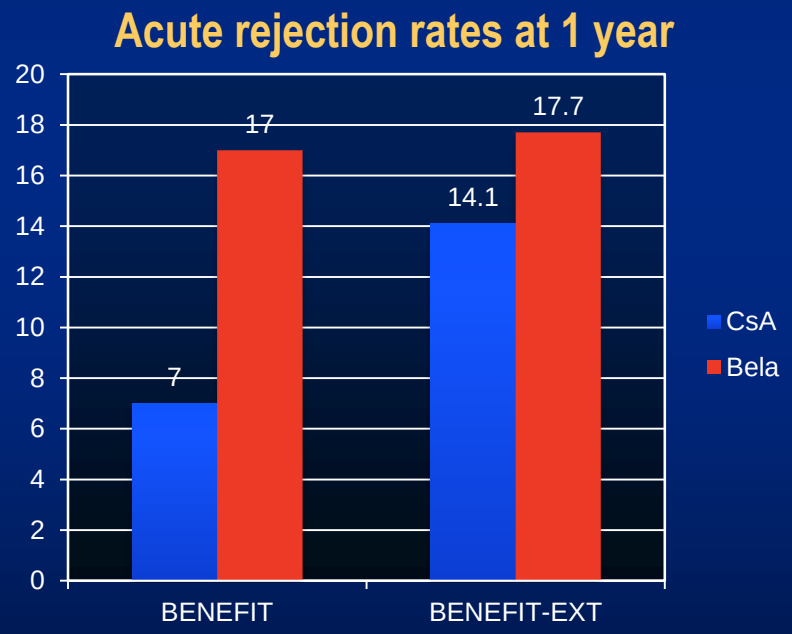
- 2-year, randomized, multicenter, open-label, two-arm study evaluating the graft function of everolimus and reduced CNI vs MPA and standard CNI in adult de novo KTRs
  - Recruiting more than 2,000 patients
  - Extended follow-up to 5 years

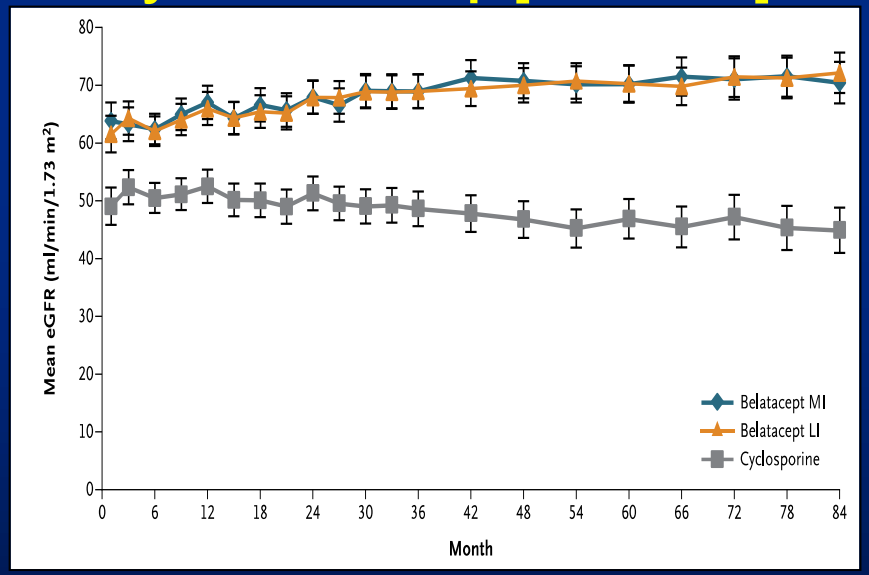
- Primary endpoint is a composite of tBPAR or eGFR <50 mL/min/1.73 m^2 at 12 months post-transplant
  - Expected to be sensitive both to the effects of acute and chronic allograft rejection and nephrotoxic side effects of immunosuppressive therapies
  - Allows integration of a continuous outcome (graft 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





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.

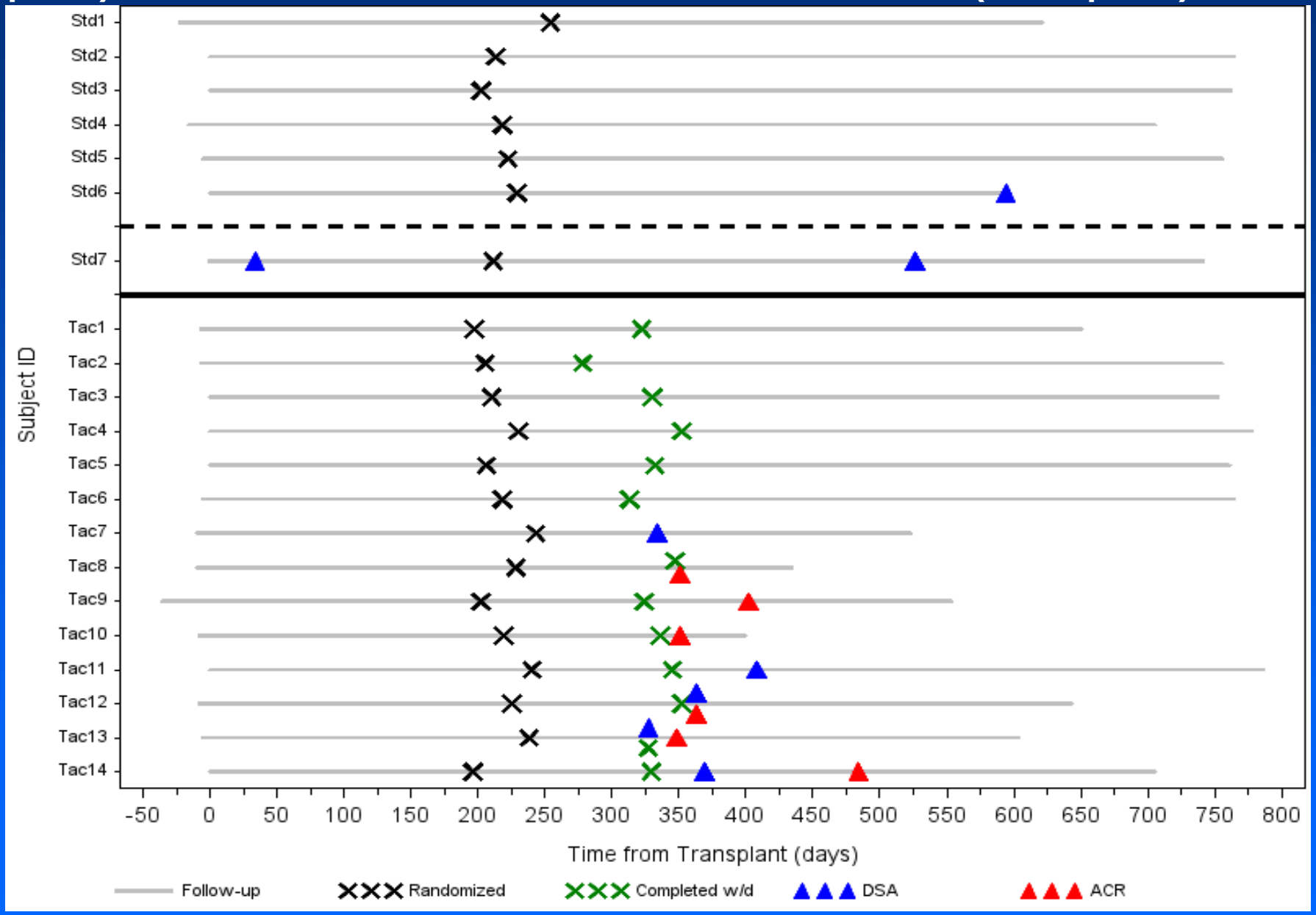
Heher et al. *N Engl J Med.* 2016;374:388-389.

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

Hricik DE et al. *J Am Soc Nephrol.* 2015;26:3114-3122.

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

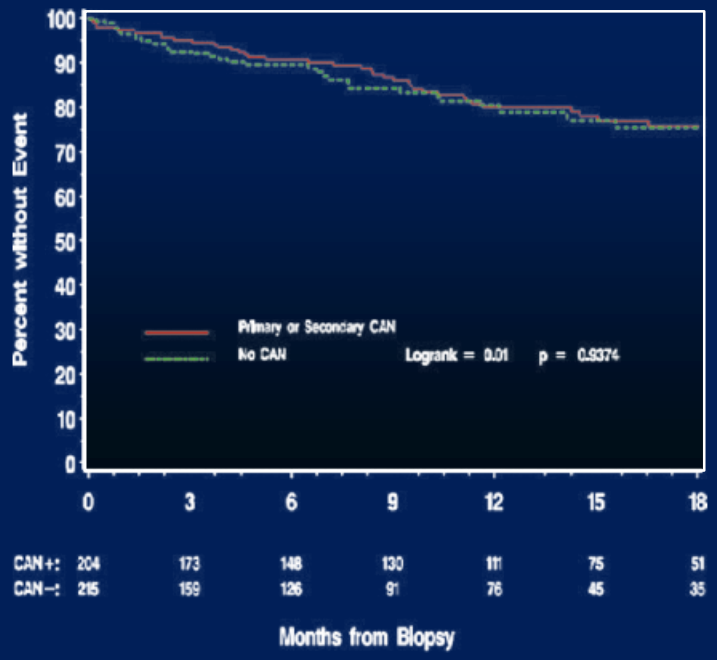


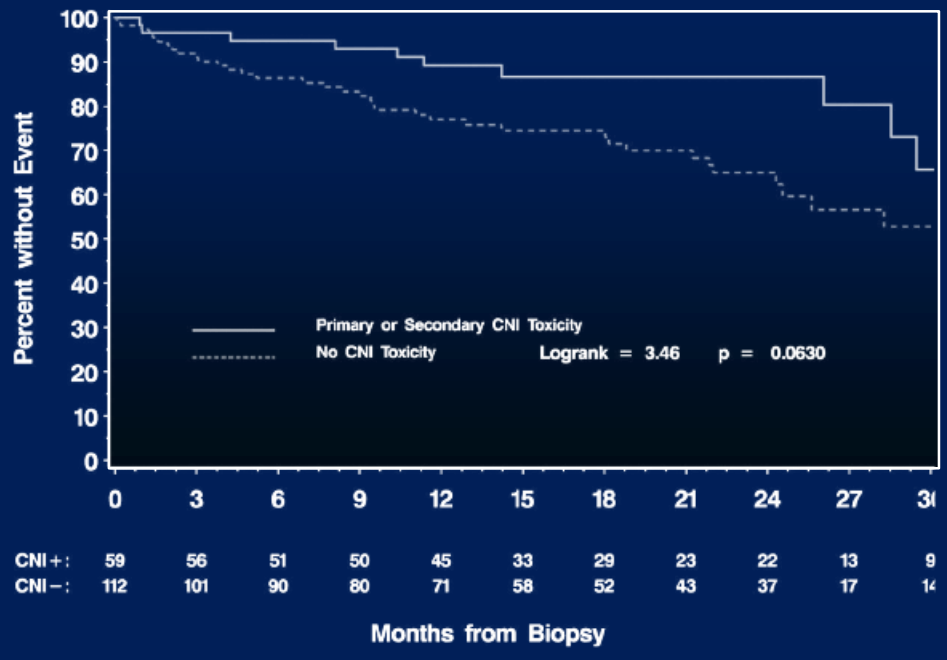
Graft Survival in DeKAF

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%





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