Renal Transplant Immunosuppression

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Helderman's Laws of Immunosuppression

Law Number One:

The longer it stays in, the longer it stays in!

Law Number Two:

Enough early, Less late

Law Number Three:

A Kidney Transplant is a Kidney

Law Number Four:

A person with a Kidney Transplant is a person

Vanderbilt's Results

<u>From Unos Annual Report (2001-2004)</u>

Graft Survival 96.5% (1 year)

Patient Survival 98.5% (1 year)

Acute Rejection Rate 7.5% (1 year)

Standard Regimen of Immunosuppression for Renal Transplantation

It doesn't exist!

Three Time Periods

- Induction – Peri Operative Algorithm
- Early Maintenance – Weeks to Months
- Chronic Maintenance

Induction

- Antibody Induction
- Calcineurin Inhibitor Induction
- Sirolimus Induction

Vanderbilt's Induction Strategy

Low Immunologic Risk:

Anti CD 24 antibody induction, early Calcineurin I introduction

High Immunologic Risk-Redos, High PRA, AA

Polyclonal Anti T-Cell AB, CI use when Creat 3.0 or less.

Minimum of 5 days of AB

Obtain therapeutic CI level before stopping AB

Delayed Graft Survival – High Expectations or Presence

Start with or switch to Polyclonal or

Induce with Sirolimus/MMF and avoid AB and CI

Early Maintenance Depends on Induction and Assessed Immunologic Risk of the Recipient

Choosing an Immunosuppressive Regimen: Efficacy

Results at One Year

Regimen	Acute Rejection (%)	Graft Survival (%)
CsA/steroids (AZA)	40-50	85-90
CsA/MMF/steroids	15-20	90-95
Tacrolimus/MMF/steroids	10-15	90-95
CsA/sirolimus/steroids	10-20	90-95
Add antibody	Fewer (?)	Same

Maintenance Immunosuppression

- **“Classical immunosuppression”**
- **Calcineurin inhibitor based immunosuppression**
- **Sirolimus based immunosuppression**

Maintenance Immunosuppression

"Classical Immunosuppression"

- **Prednisone and Azathioprine**
- **Virtually no "starts" in USA on this regimen**
- **Many patients engrafted before 1984 with functioning transplants with still be on this regimen**
- **In the absence of graft difficulty, it is reasonable not to change away from the classical approach**

Maintenance Immunosuppression

Calcineurin inhibitor based immunosuppression

- CSA based regimens
- TAC based regimens

Maintenance Immunosuppression

Calcineurin inhibitor based immunosuppression

CSA based regimens

- **Two drugs versus three drugs – the original story**
- **CSA PRED AZA**
- **CSA PRED MMF**

MMF vs AZA in Renal Transplantation: Three-Year Tricontinental Results

Mathew TH et al. *Transplantation.* 1998:65:1450-1454.

Maintenance Immunosuppression

Calcineurin inhibitor based immunosuppression

TAC based immunosuppression

- **Two drugs versus three:**

  TAC/PRED vs TAC/PRED/AZA

- **TAC/PRED/MMF**

- **TAC/MMF with rapid PRED taper (one week)**

Potential Strategies to Address Newer Goals

Sparing Regimens

- Targeted dose reduction or drug elimination
  - Low-responder patients (defined clinically and immunologically)
  - Initiated after risk of rejection has receded
- Avoidance of drug-specific side effects
- Less risk immunologically

Maintenance Immunosuppression

Sirolimus based immunosuppression

- The marginal donor
- Delayed graft function
- Malignancy

Maintenance Immunosuppression

The Marginal Donor

Donor age >55 yr

Hx of Diabetes

Hx of high blood pressure on Rx

DGF 1) inc s creat of 0.5 in 12 hr

2) <50 cc/hr urine in first day

Shaffer et al 2002

Maintenance Immunosuppression

The Marginal Donor

Induction Thymoglobulin (12)

Basiliximab (7)

MMF 1 gm BID

Sirolimus 10 mg x 3, then 5 mg adjusting to 10-20 ng/ml

Prednisone – Solumedrol 500mg IV then 30 mg of pred tapered to 10 mg

Maintenance Immunosuppression

The Marginal Donor

- n = 19
- n = 11 DGF
  - 6 donor age and/or comorbid disease
  - 2 both
- 16 CKT
- 3 LD

Shaffer et al 2002

Maintenance Immunosuppression

The Marginal Donor

- **Mean S creat 1.7**
- **AR 3/19 (16%) day 4, 9, 45**
- **No AR thymo induction**
- **1 Lymphocele**
- **2 Superficial wound infection**
- **4 TAC conversions (3 AR, 1 wound)**
- **15 RAP for chronic maintenance**

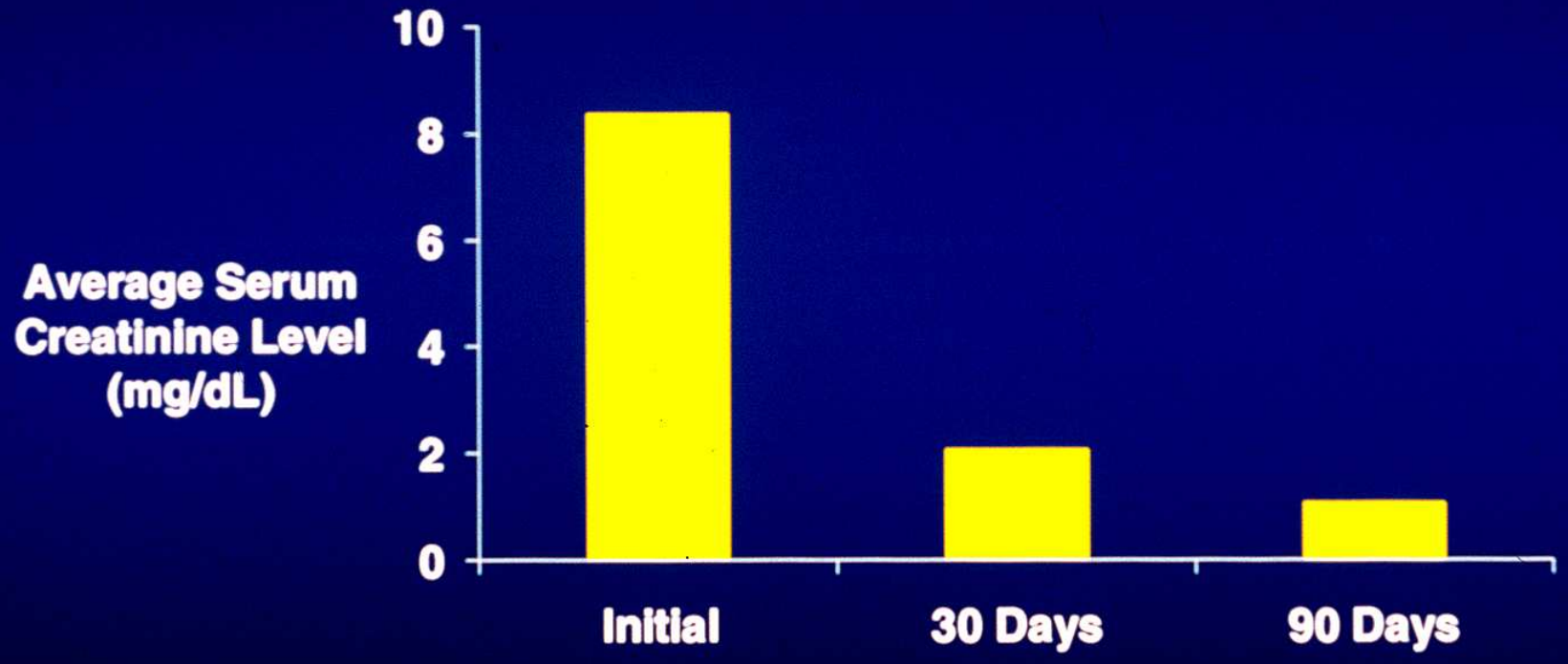
Maintenance Immunosuppression

The Marginal Donor

- **F/U 294 d (159-666)**
- **Pt Survival – 1 yr 100% (Actuarial)**
- **Graft Survival – 1 yr 93% (1 primary nonfunction 4 to rejection)**

Shaffer et al 2002

Delayed Graft Function: Sirolimus-Based Regimen



Chang GJ et al. *Clin Transplant.* 2000;14:550-554.

Calcineurin Inhibitor Minimization Regimens

- **Benefits**
  - **Improved renal function**
  - **Reduction in other calcineurin inhibitor–associated effects (hypertension, hyperlipidemia, glucose intolerance)**
- **Risks**
  - **Acute Rejection; ? Chronic allograft dysfunction**

Minimization of Calcineurin Inhibitors

- **Facilitated by availability of non-nephrotoxic immunosuppressants**
  - **Mycophenolate mofetil**
  - **mTOR inhibitors (sirolimus, everolimus)**
- **Protocols**
  - **Dose reduction**
  - **Withdrawal**
  - **Avoidance**

Calcineurin Inhibitor Avoidance

Argument For:

- Doses effective at reducing acute rejection rates to single digits too toxic.
- Activate profibrotic growth factor genes (e.g, TGFβ).
- Mechanism confined to inhibition of T cell activation.
- May delimit long term graft survival.

Calcineurin Inhibitor Avoidance

Argument For:

- "T ½ of grafts unchanged in CI era" is the mantra
- Important side effects may be avoided
  - nephrotoxicity
  - cosmetic
  - diabetogenesis
  - hyperlipidemia
  - hyperkalemia
  - hyperuricemia
  - neuro toxicity

CSA Reduction in Chronic Nephropathy

Weir and colleagues withdrew CsA and added MMF in 25 pts with bx proven CAN

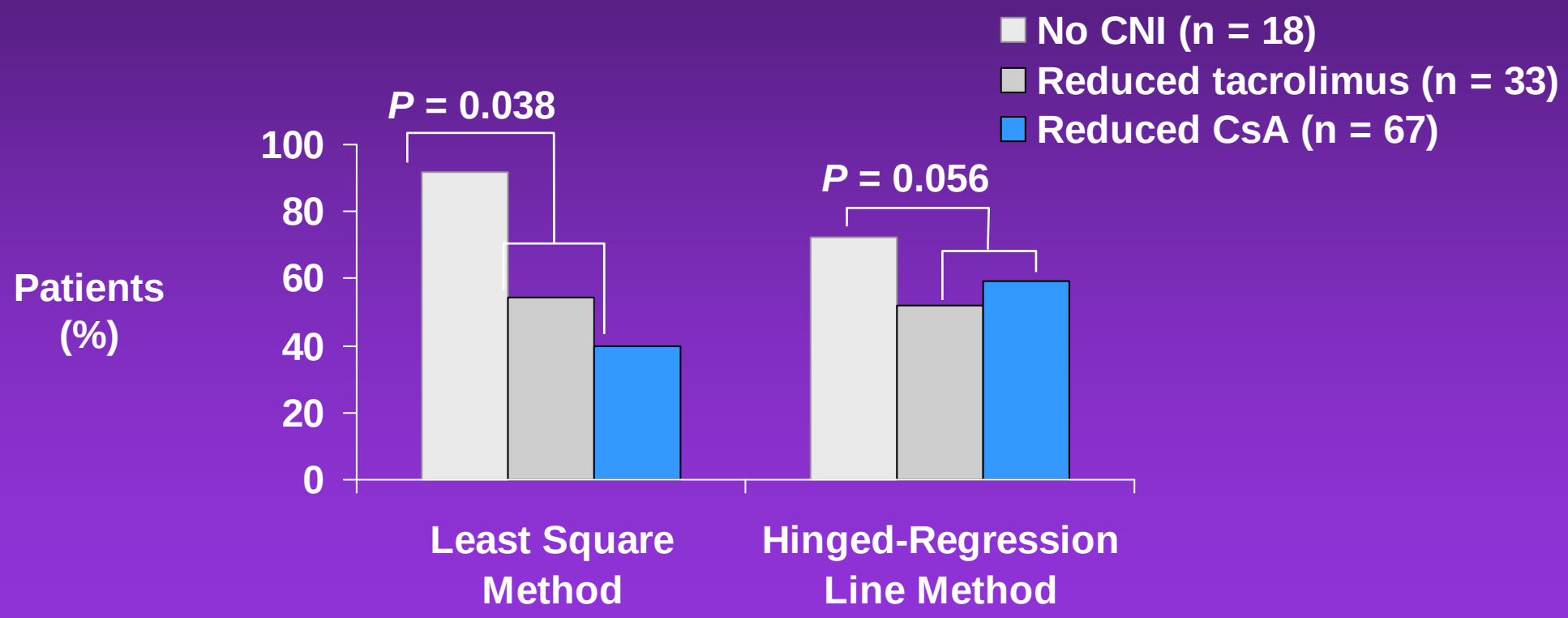
1. Creatinine fell significantly
2. Cholesterol fell
3. No acute rejections were encountered

Weir et al Transplantation 64:1706, 1997

Cyclosporine Sparing Regimens

- CsA withdrawal with or without AZA substitution
- Low dose CsA in triple therapy regiments containing MMF
- Introducing new immunosuppressive drugs and reducing CsA dose
- Avoiding CNI and substituting sirolimus

Calcineurin Inhibitor Dose Reduction and/or Withdrawal With MMF (single center, CsA or FK506 withdrawn (n=18) or reduced by 50% (n=100), 1.8 years follow-up)



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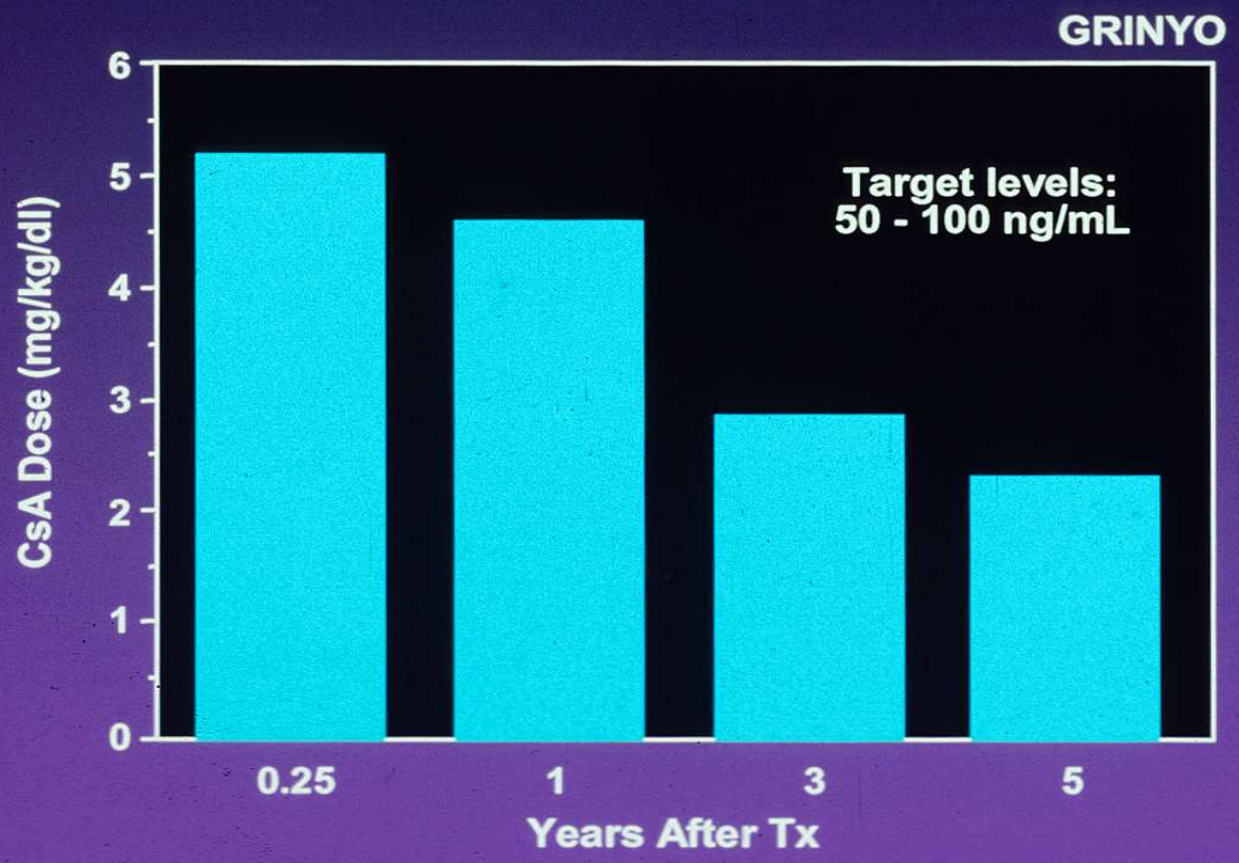
CNI = calcineurin inhibitor.

Weir MR et al. *Kidney Int.* 2001;59:1567-1573.

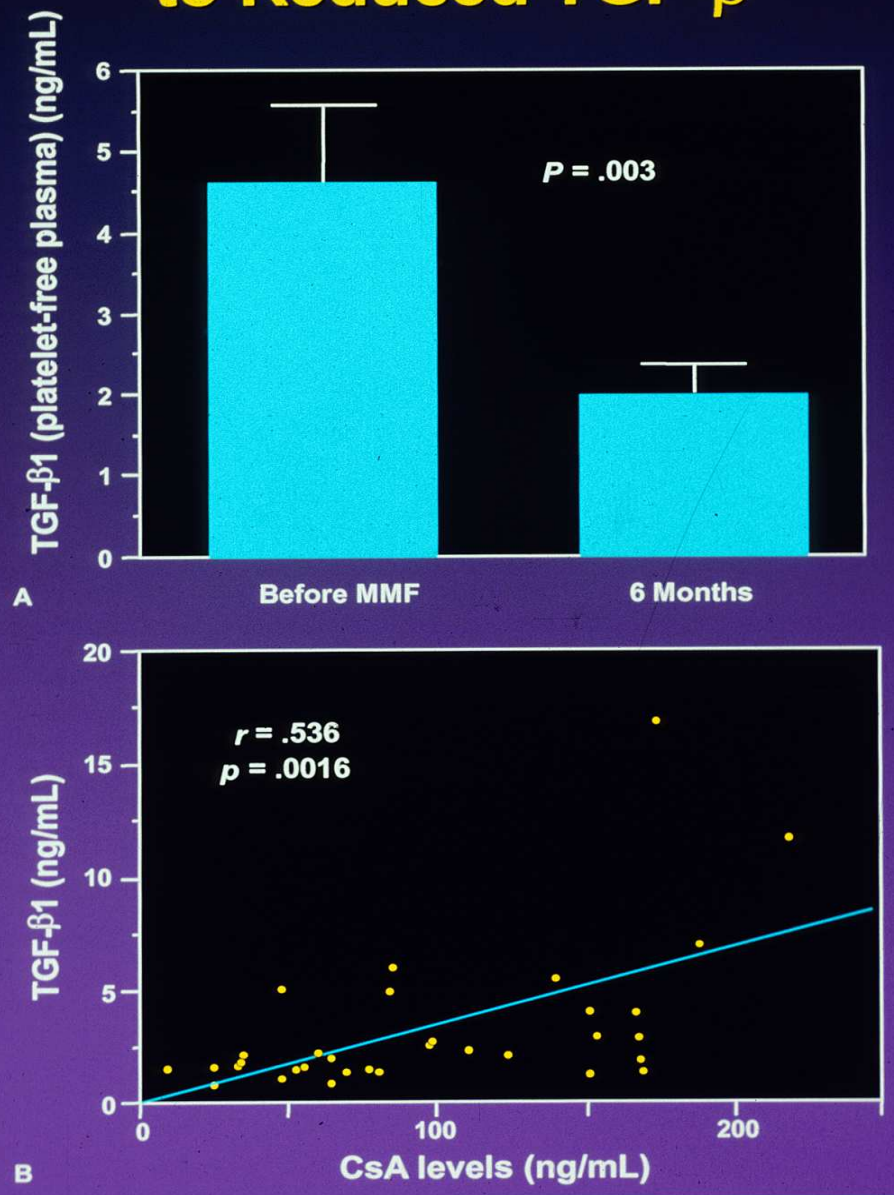
Grinyo CsA Sparing / MMF Trial

1. Under MMF umbrella, CsA dose gradually reduced
2. No acute rejections in 16 pts
3. Significant improvements in diastolic BP
4. Decreased creatinine, increased GFR
5. Reduced blood levels of TGF-β

Targeted CsA Dose Reductions when MMF Employed



Safe CsA Reduction Leads to Reduced TGF-β

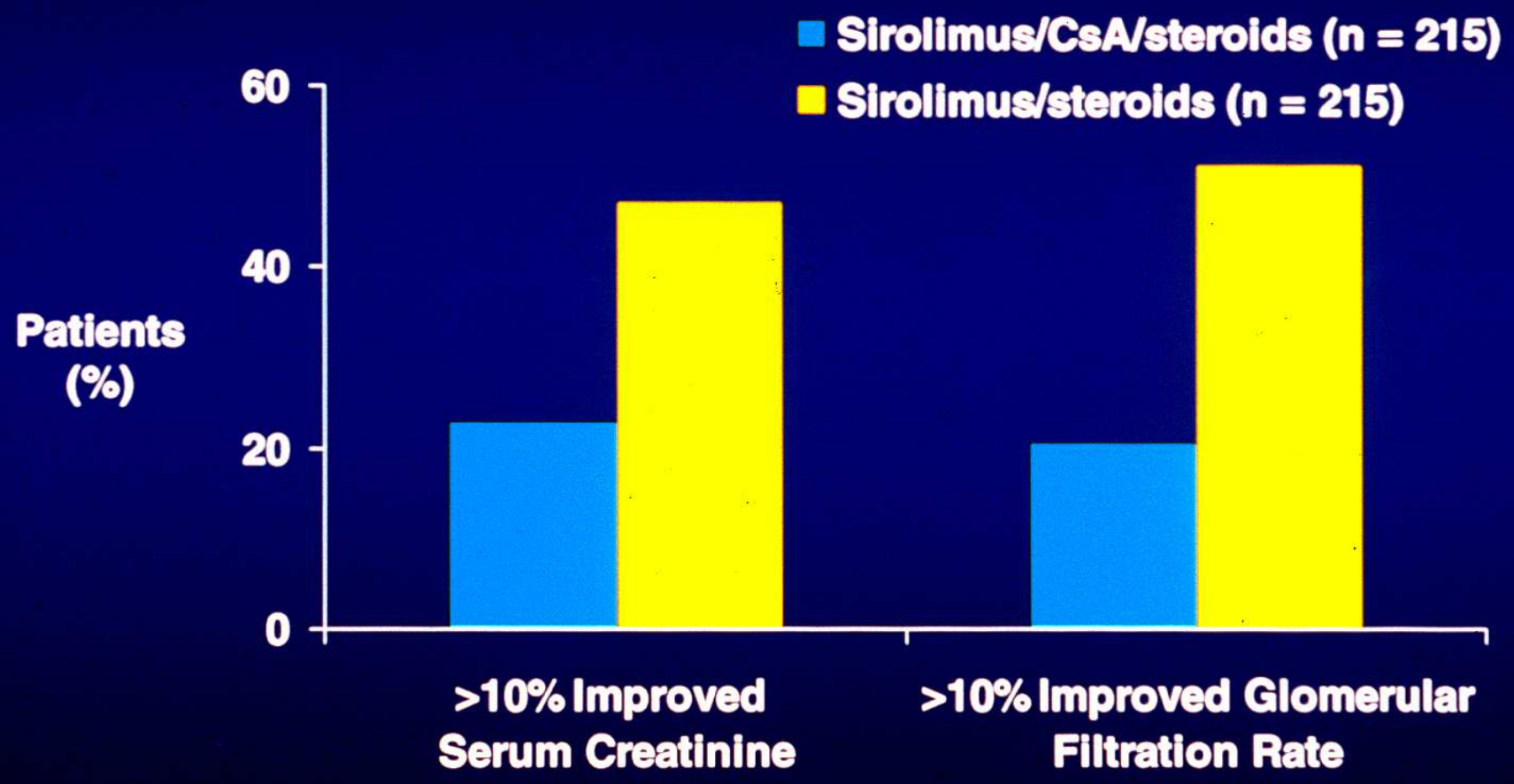


Calcineurin Sparing

Prograf Sparing

- Trials of MacDonald, Dalhousie Univ.
- Low dose Prograf + Sirolimus
- Results
  - single digit acute rejection rates
  - higher GFR, lower creatinines
  - excellent graft & pt survival
  - short follow times

Calcineurin Inhibitor Dose Reduction and/or Withdrawal Regimens With Sirolimus



Kreis H et al. *Am J Transplantation.* 2001;1(suppl 1):194. Abstract 234.

Use of Sirolimus to Facilitate Cyclosporine Withdrawal: Study 310

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

2 mg

> 5 ng/ml

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

3 months ± 2 weeks

Group A

Sirolimus 2 mg
(>5 ng/ml)

CsA (75-200 ng/ml)

Steroids

Group B

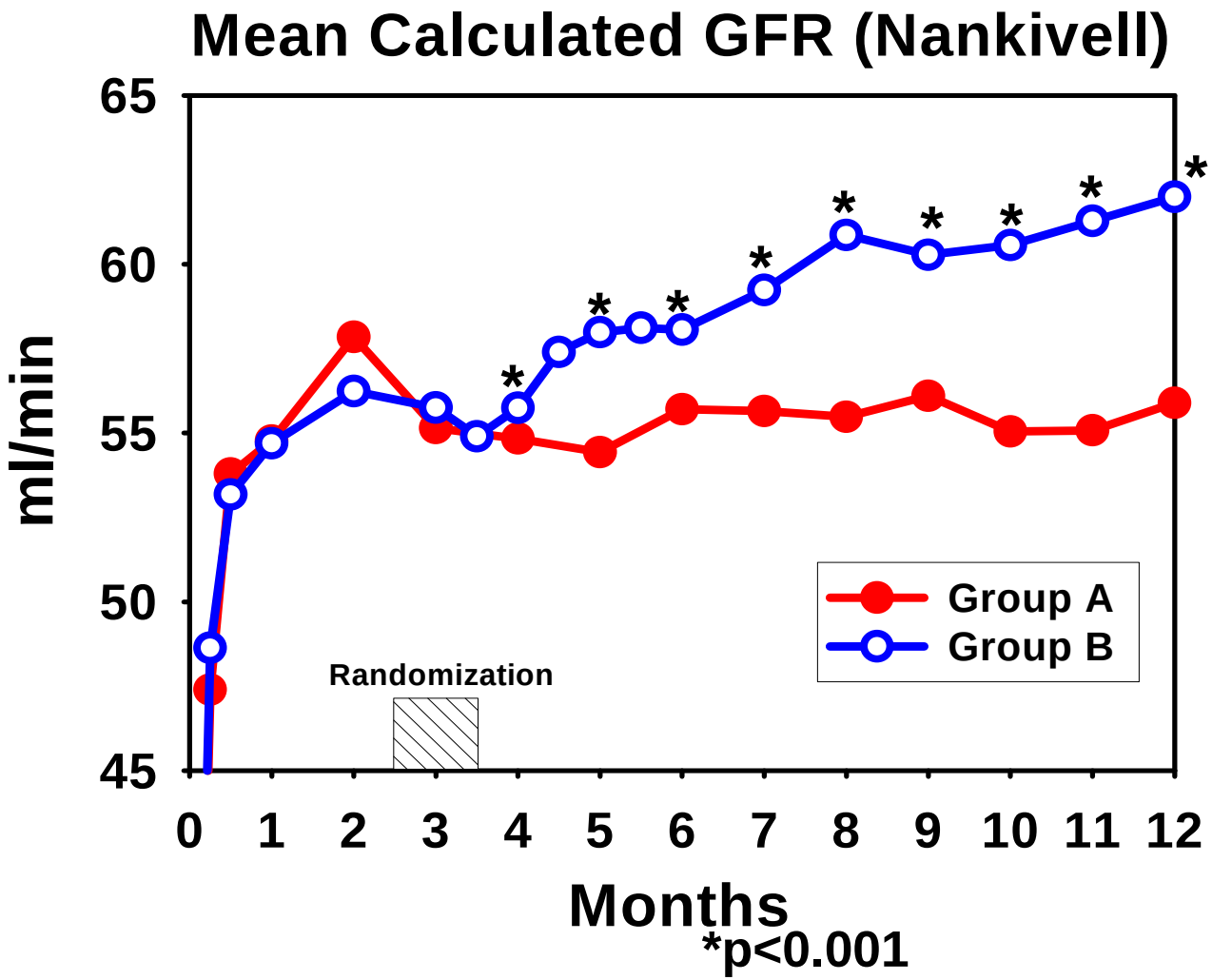
CsA
(25 % per week)

Sirolimus (20-30 ng/ml)

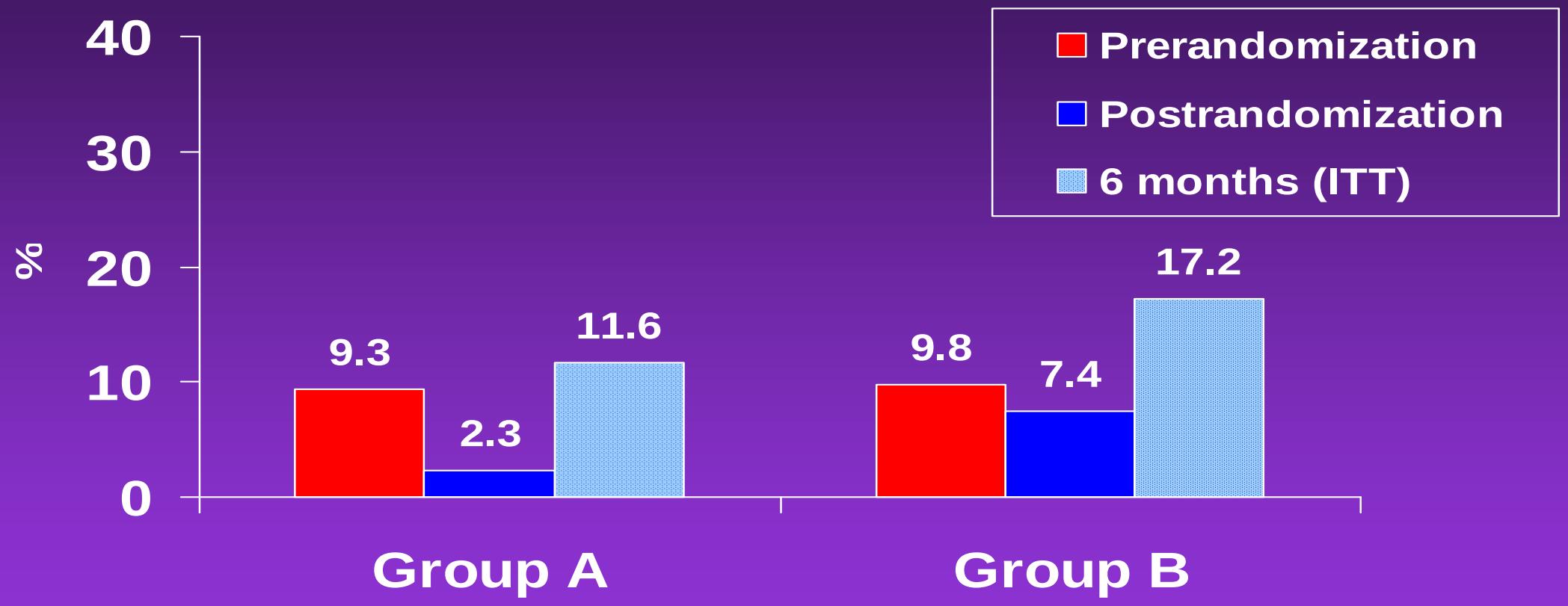
Steroids

Johnson RWG et al. Transplantation 2001; 72: 777

Higher Calculated GFR Following CsA Elimination



Incidence of Acute Rejection: 6 month data



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Vanderbilt Strategy of Early Maintenance

- **Low Risk** - CSA based triple therapy with MMF
- **Special Risk** - TAC based triple therapy with MMF
- **Under Study** - CI avoidance with RAP for high risk donors and when vasoconstriction should be avoided

Late Maintenance

General Rule – Taper Most of the elements of Early Maintenance

- Target blood levels for CI drugs change
- Reduce steroids to 0.1 mg/kg or less

Unique Issues of Late Maintenance

- Prednisone withdrawal
- CSA withdrawal
- Long term use of MMF

Vanderbilt Strategy of Chronic Maintenance

- Maintain CSA or TAC-No Withdrawal
- Maintain Low Dose Pred. 5 - 7.5mg
- Maintain Long Term MMF Use