

# **Calcineurin Inhibitor (CNI) and Corticosteroid Minimization/ Avoidance Protocols and HLA Antibodies**

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## **Calcineurin Inhibitor (CNI) and Corticosteroid minimization/ Avoidance Protocols and HLA Antibodies**

Changing endpoints for evaluation of minimization trials

DSA associated with increased rates of AbMR and graft loss

Pre single antigen bead testing for DSA

- acute rejection, graft loss

With single antigen bead testing

- dnDSA, acute rejection, graft loss

For prednisone minimization, there is long-term follow-up but  
no DSA data

# Goals of Prednisone Minimization Trials

- 1) Avoid prednisone side effects
- 2) No  $\uparrow$  in rate of acute rejection
- 3) No  $\uparrow$  in chronic graft loss or chronic graft dysfunction

# Late Prednisone Withdrawal Protocols

## CSA/P or CSA/AZA/P

Selected, clinically well, low risk, recipients:

30% rejection risk; Graft dysfunction, graft loss

Meta-analyses\*: ↑ acute rejection

↑ graft loss

(\*Hricik et al, J Am Soc Nephrol 1993; Kasiske et al, J Am Soc Nephrol, 2000)

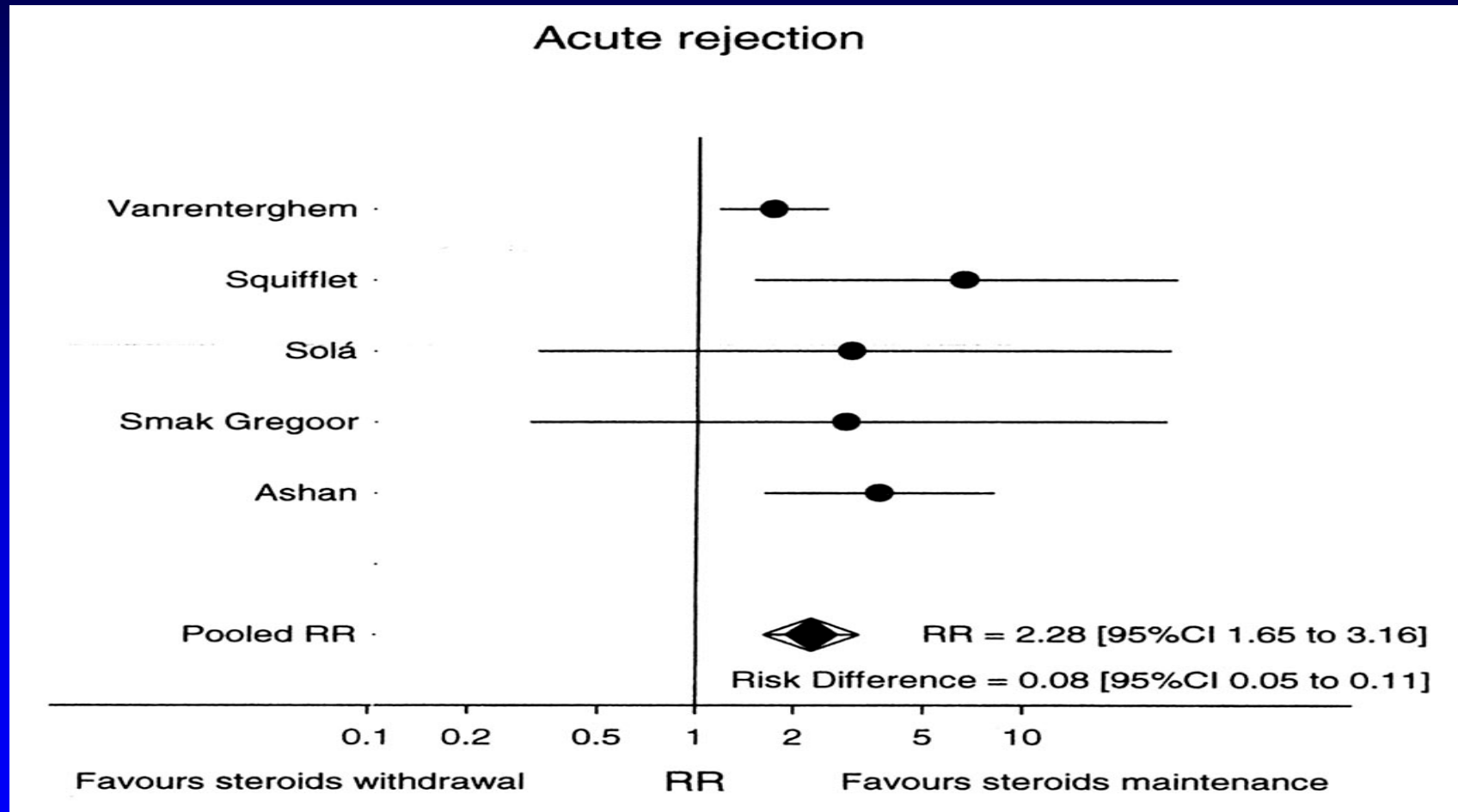
## CSA/MMF/P

2 large prospective, randomized, multicenter trials

- 1 in North America; 1 in Europe

Both showed ↑ incidence of acute rejection after steroid withdrawal

# Meta-analysis of CNI plus MMF trials: more AR with late withdrawal



No difference in graft survival – limited follow-up

Pascual et al, Transplantation, 2004

# Rapid Discontinuation of Prednisone (RDP) (ECSW)

(P stopped <2 weeks and usually <1 week posttx)

Numerous single center studies, randomized and nonrandomized trials, meta-analyses and registry reports of RDP have shown:

- 1) **Increase in AR rates** (vs long-term prednisone)
- 2) No increase in steroid-resistant AR
- 3) No impact on patient and graft survival rates
- 4) RDP is associated with significantly ↓ new onset diabetes, cardiovascular risk factors, avascular necrosis and fractures

Pascual J et al, Cochrane analysis,

2009 Knight and Morris, Transplantation, 2010

Luan et al, AJT 9:160-8, 2009

Luan et al, Transplantation 91: 334,

2011

# Pascual et al, Cochrane analysis, 2009

34 reports of 29 randomized trials; 5675 subjects

Major conclusions:

There is a **significant increase in AR** with rapid discontinuation of prednisone (RDP); **only seen when CSA was CNI** used for maintenance; not seen with TAC. NO difference in graft survival.

There is a significant **decrease in new onset diabetes** (NODAT) with RDP; this was **only seen when CSA** was used for maintenance

Limitation is that there are few studies of benefits of RDP

# Rapid discontinuation of prednisone

Woodle et al, Ann Surg, 2008, Prospective, randomized, double-blind placebo controlled study

Ab induction, TAC, MMF (n=386)

Prednisone for 7 days vs a *steroid taper to 5 mg/day by 6 mos*

## Major findings at 5 years:

↑ bx proven AR in RDP group (primarily steroid-sensitive Banff 1a (subanalysis; less AR with thymo vs IL-2R)

No difference in the primary endpoint: composite of death, graft loss or moderate/severe acute rejection

- no difference in Ab-treated rejection; renal function
- RDP group had improvements in cardiac risk factors



# Rapid discontinuation of prednisone

Cantarovich et al, AJT, 2014

ATG-Ab induction, CSA, MMF (n=197)

0 prednisone vs a *steroid taper for at least 6 months*

## Major findings at 5 years:

↑ bx proven AR in 0 pred group (earlier and milder with 0 pred)

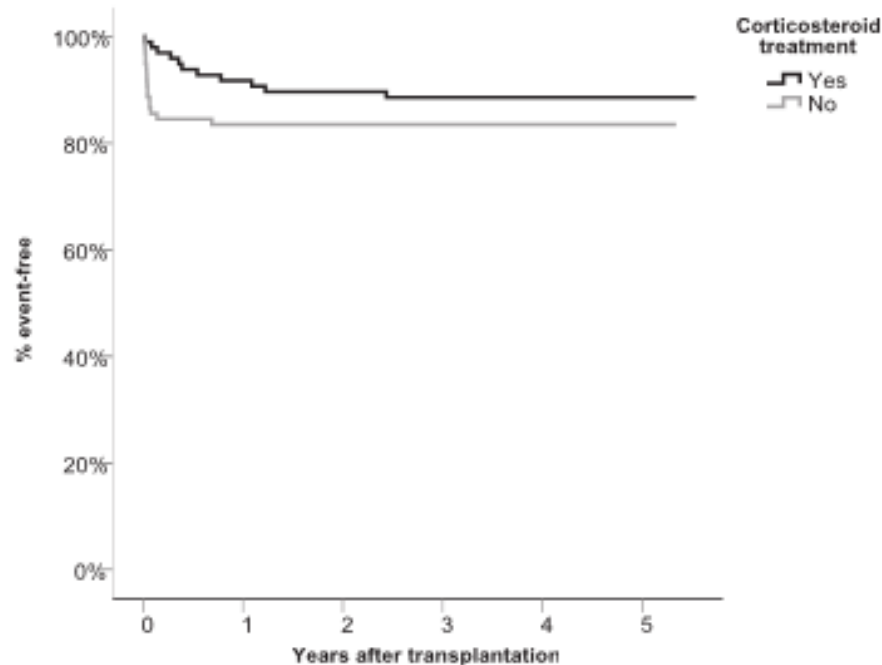
No signif diff in death, graft loss or renal function

**DSA not planned** but available in 151 (76 +CS; 75 –CS)

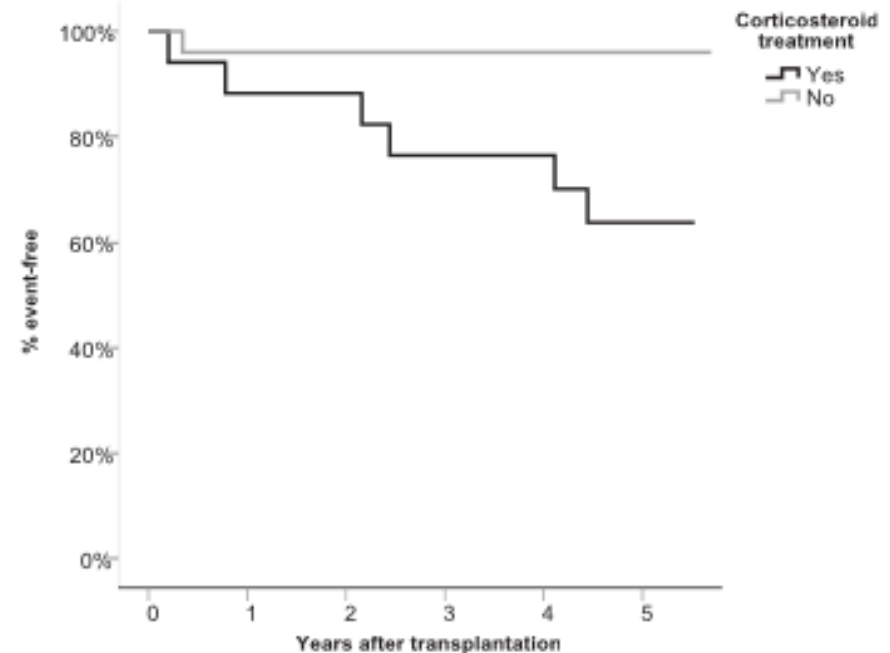
**11% developed DSA; no diff between groups**

More +CS patients developed diabetes, dyslipidemias and malignancies (skin and PTLN,  $p < 0.05$ )

# Rapid discontinuation of prednisone



**Figure 4: Time to first biopsy-proven acute rejection episode: 5 years, 88.9% versus 83.7% ( $p = 0.227$ ).**



**Figure 5: Graft survival censored for death in patients with history of acute rejection episode: time to graft loss: 5 years, 55.6% versus 92.0% ( $p = 0.005$ ).**

## Antibody formation after steroid withdrawal

Heart tx recipients, CNI, MMF, pred

- in select patients, pred withdrawal @ 6 mos

( pred < 5 mg for at least 1 mo; no AR on bx; normal LV ejection fraction fraction, no DSA); (characteristics diff at tx compared to those on P )

178 recips; attempted withdrawal in 127 (71%)

success in 103 (81%)

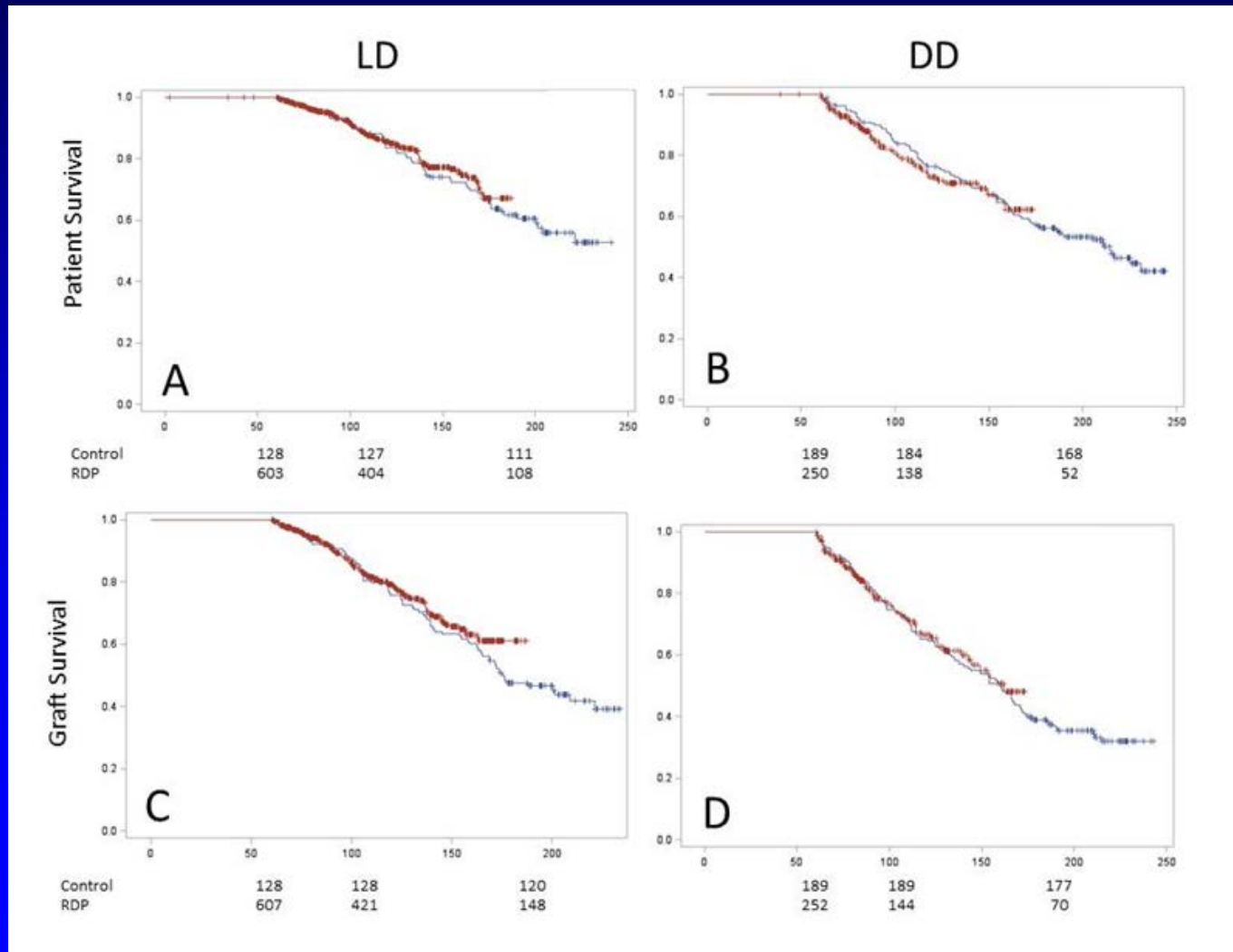
Of these, 68 had 0% PRA at tx; 7 (10%) developed antibodies;  
of these, only 2 were DSA

- high antibody rate in those on pred

Those successfully weaned had had less AR than those continuing pred or failing weaning

Elboudware O et al, Clinical Transplant 2017 (ePub)

# RDP vs controls with Graft function at 5 years (15 yr results) Transplantation, In Press



# **DSA in Trials of CNI Minimization**

## Ekberg et al, Caesar Study, AJT 2007

1<sup>st</sup> tx (n=536) randomized to:

dacluzimab, MMF, pred, low dose CSA; MMF, pred, and standard dose CSA; dacluzimab, MMF, pred, low dose CSA weaned by month 4 and withdrawn by month 6

signif increase AR in CSA withdrawal

## Abramowicz et al, JASN 2006

4 year follow-up of 2 trials in which there was CSA withdrawal from a MMF-based protocol

increased risk of AR and graft loss

## Smak Gregoor et al, JASN, 2002

prospective trial of withdrawal of CSA or prednisone in those on triple immunosuppression

BPAR in 22% after CSA withdrawal vs 4% of pred withdrawal (p=0.0001)

Asberg et al – Results of an aborted trial, Clin Tx, 2013

Prospective trial of withdrawal of CSA or MMF in those on triple immunosuppression

Eligible if tx >1 year before randomization; low immunologic risk

Aborted after enrolled 39 patients

AR in the MMF group = 30%

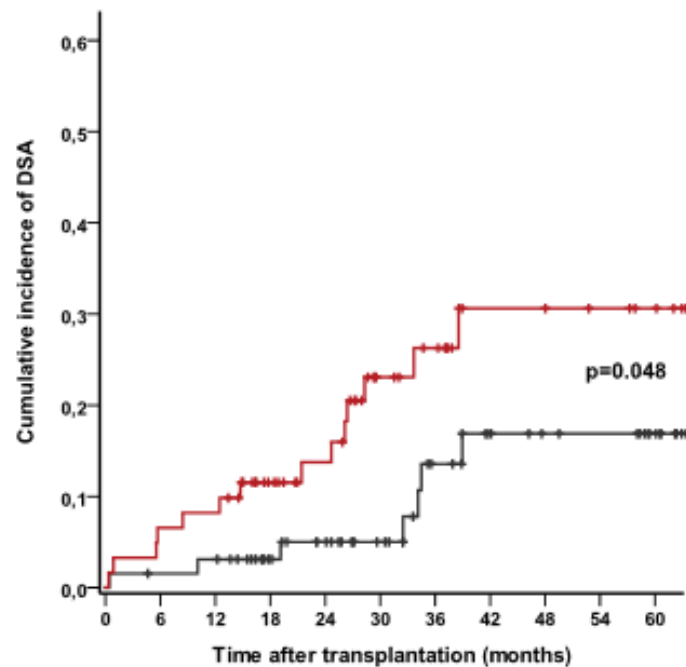
CSA group = 0

Liefeldt et al, Donor-specific HLA antibodies in a cohort comparing everolimus with cyclosporine after kidney transplantation, *AJT*, 2012

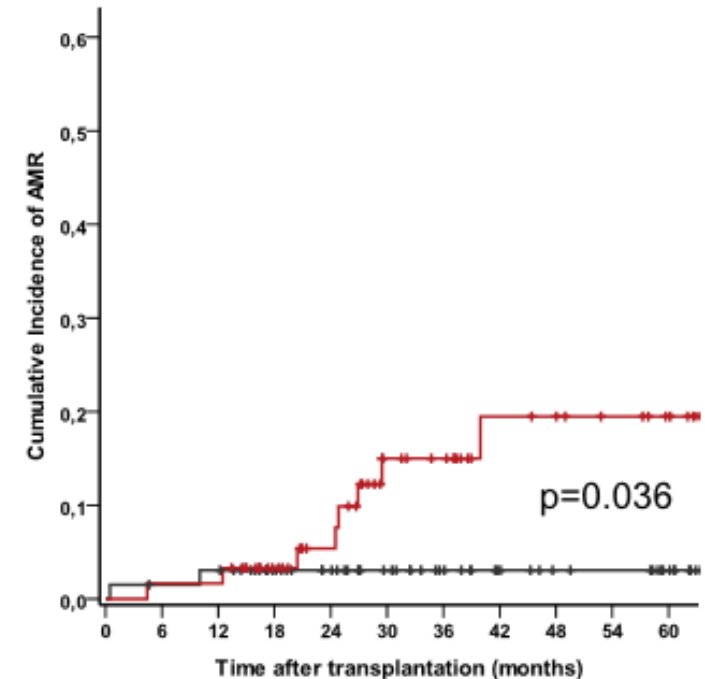
At 3-4.5 months posttransplant 127 patients were randomized to continue cyclosporine or converted to everolimus therapy

**Exclusions included:**, severe rejection ( $\geq$ Banff grade II), recurrent AR, steroid resistant AR, dialysis-dependent, proteinuria  $>1$  g/day, signif inf.

**DSA**



**AbMR**





# de Sandes-Freitas TV et al, Subclinical Lesions and DSA in Ktx Recipients Receiving Tac-Based Immunosuppressive Regimen Followed by Early Conversion to Sirolimus, Transplantation, 2015

169 patients

TAC, MMF, Pred for 3 months

**Randomized @ 3 months: continue TAC vs convert to SRL**

**Exclusion:** eGFR < 40 mL/min; urine protein/creatinine ratio of  $\geq 0.5$ ; previous AR Banff IIA or higher; AR within the last 4 weeks any wound healing event; patients with subclinical acute rejection, borderline infiltrates, BK virus nephropathy or glomerulopathies diagnosed at **protocol biopsy** at month 3

@ 24 mos: 48 on SRL group; 45 in TAC

<b>bx proven AR</b>	<b>SRL = 7.3%</b>	<b>TAC = 0</b>
<b>"I"&gt;0</b>	<b>= 14.6%</b>	<b>= 4.4%</b>
<b>DSA</b>	<b>= 17.8%</b>	<b>= 7.3%</b>

# Hricik et al, JASN, 2015, Adverse Outcomes of Tacrolimus Withdrawal in Immune-Quiescent Kidney Transplant Recipients

## Primary LD transplants

At tx: No DSA, PRA <30%, Thymo, Tac, MMF, prednisone

0-6 months: No rejection, no DSA

Protocol Bx at 6 months: normal histology

Goal – TAC withdrawal; Tacrolimus weaned over 3 months

21 randomized:

7 TAC, MMF, pred ----- no TCMR, 1 DSA

14 MMF, pred ----- 3 TCMR, 2 DSA, 3 both

Study stopped by the DSMB

## Gatault P et al, Reduction of Extended-Release Tacrolimus Dose in Low-Immunological-Risk Kidney Tx Recipients Increases Risk of Rejection and Appearance of Donor-Specific Antibodies: A Randomized Study. AJT ePub 2016

At tx - LD or DD; No DSA, No AR @ 3 mos

Assessed at 4 months; randomized at 4 months

**Exclusion** - biopsy-proven AR),  $\geq 30\%$  increase in serum Cr during the previous 30 days, protein:creatinine ratio  $> 1$  g/g, MMF daily dose  $< 1$ g ( $< 720$  mg/day for EC-MPS), BK viremia, and appearance of DSAs after transplantation (assessed at 3 mo after transplantation).

### Randomized

~50% reduction in the daily TAC dose: targeted trough level,  $> 3$  ug/L

or continuation:

targeted trough level, 7-12 ug/L

Gatault P et al, AJT ePub 2016

188 randomized: 87 patients, 50% reduction in TAC dose  
99 patients, stable TAC dose

	<u>50% reduction</u>	<u>Stable</u>	<u>p</u>
BPAR	11%	3%	0.016
DSA	6	0	0.008
Protocol BX @ 1 year			
i>0	21.4%	8.8%	0.047

**Conclude:** TAC level should be maintained during the 1<sup>st</sup> year

Dugast et al, Failure of Calcineurin Inhibitor (Tacrolimus)  
Weaning Randomized Trial in Long-Term Stable Kidney  
Transplant Recipients, AJT 2016 ePUB

prospective, randomized, multicenter, double-blind placebo-  
controlled clinical study of tacrolimus weaning on highly  
selected patients ( $\geq 4$  yrs posttx, normal histology, stable graft  
function, no anti-HLA immunization).

10 patients randomized

**TAC** – stable graft function and no immunologic events

**Placebo** – 3 AR; 2 anti-HLA antibodies (1 DSA; 1 not DSA)

all 5 restarted on TAC

**“Clearly, tacrolimus withdrawal must be avoided even in  
long-term highly selective stable kidney recipients”**

# Vincenti F et al , A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study), AJT, 2010

Prospective randomized; 100 centers (666 tx)

IL-2R induction, MMF, prednisone

more intensive belatacept vs less intensive vs CSA

At 1 year, no diff in patient or graft survival

AR: MI = 22%; LI = 17%; CSA = 7%

- more belatacept patients had Banff IIb rejection

Initial Ab treatment – MI, 13; LI,10; CSA, 2

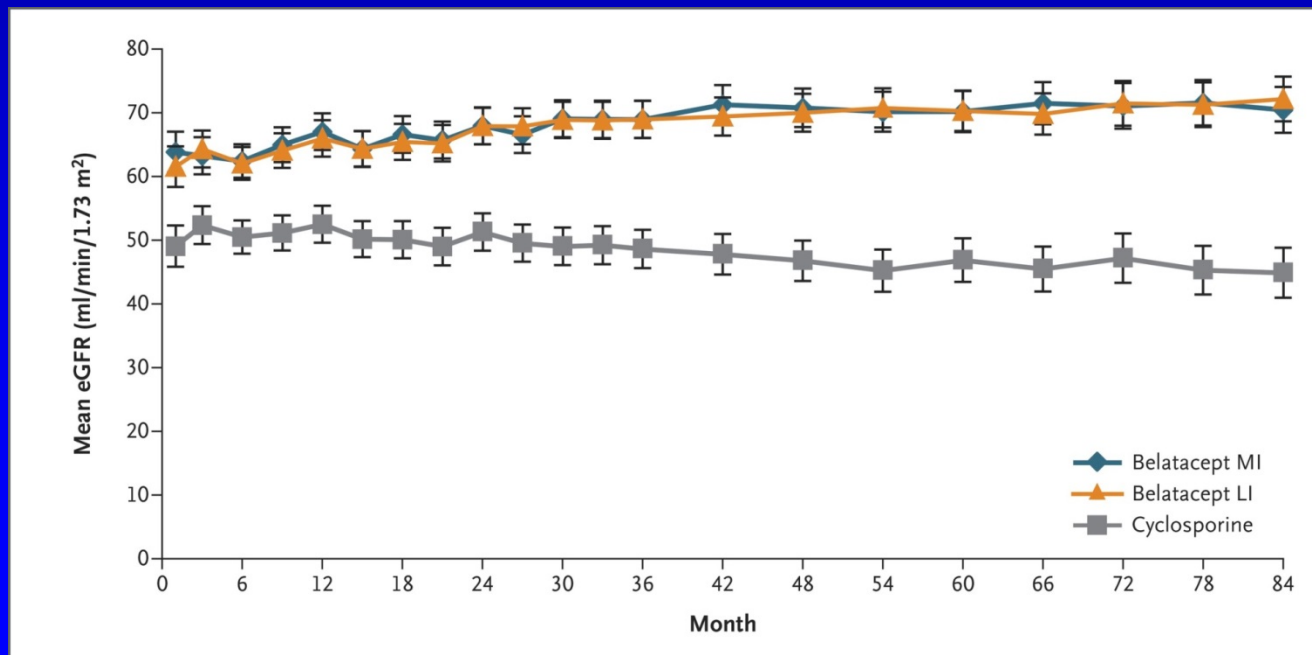
Steroid resistant - MI, 13; LI,10; CSA, 0

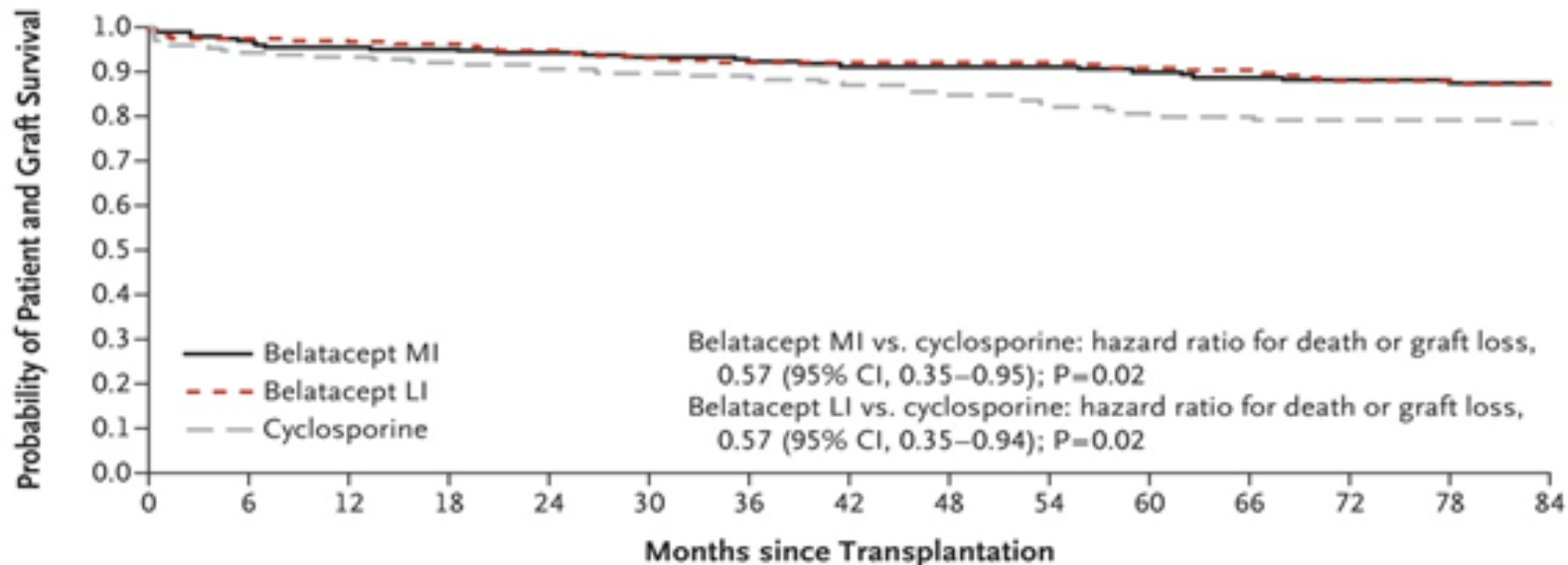
# Vincenti F et al , N Engl J Med 2016

<u>DSA</u>	<u>30 mos</u>	<u>60 mos</u>	<u>84 mos</u>
MI	1.2%	1.9%	1.9%
LI	3.4%	4.6%	4.6%
CSA	8.7%	16.2%	17.8%

Glomerular Filtration Rate  
Month 1 to Month 84

Vincenti F et al.





No. at Risk		0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Belatacept MI	219	212	208	206	204	202	199	153	151	149	146	142	135	131	128	
Belatacept LI	226	220	218	216	213	209	204	165	161	159	152	151	142	139	137	
Cyclosporine	221	208	206	202	199	197	186	137	123	117	112	107	102	100	92	

43% reduction in the risk of death or graft loss was observed for both the more-intensive and the less-intensive belatacept regimens as compared with the cyclosporine regimen

HR with the mi regimen, 0.57; 95% CI, 0.35 to 0.95; P = 0.02;

HR with the li regiment, 0.57; 95% CI, 0.35 to 0.94; P = 0.02,

equal contributions from the lower rates of death and graft loss.



# Summary

- 1) Steroid minimization trials were done b4 DSA testing
  - ↑ AR; no change in graft survival
  - mostly limited to low risk groups
- 2) CNI minimization (both cyclosporine and tacrolimus)
  - studies of minimization or conversion to SRL @ 3, 4, 6 mos or >4 yrs (in low risk or pristine patients)
  - ↑ AR, DSA, “i” on protocol bx, & graft loss 1 study
- 3) Belatacept vs CSA (Benefit study)
  - ↑ AR in belatacept group but less DSA



