

# Protocolos de inmunosupresión de mantenimiento según grupos de riesgo

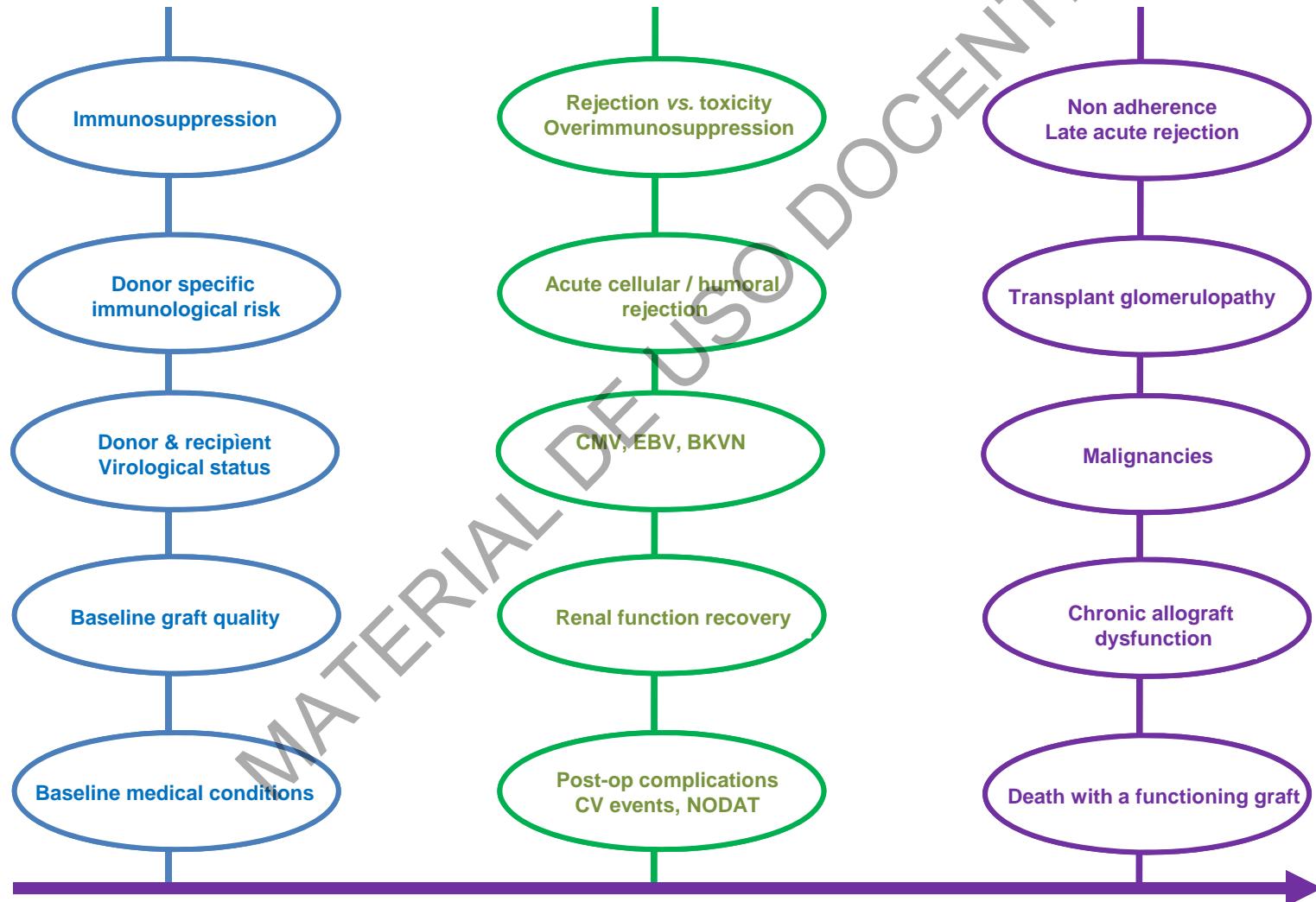
Federico Oppenheimer

Servicio de Nefrología y Trasplante Renal

Hospital Clínic de Barcelona

[oppen@clinic.ub.es](mailto:oppen@clinic.ub.es)

# How to improve long-term survival in kidney transplantation



# **Factores asociados al donante, al receptor y al trasplante (1)**

## ■ Tipo de donante

- Donante vivo
- Donante en muerte encefálica sin criterios expandidos
- Donante en muerte encefálica con criterios expandidos
- Donante en asistolia no controlada
- Donante en asistolia controlada

## ■ Factores de riesgo asociados al receptor

- Nefropatía de base y/o nefropatías asociadas a enfermedades sistémicas
- Riesgo inmunológico previo

## ■ Factores asociados al trasplante

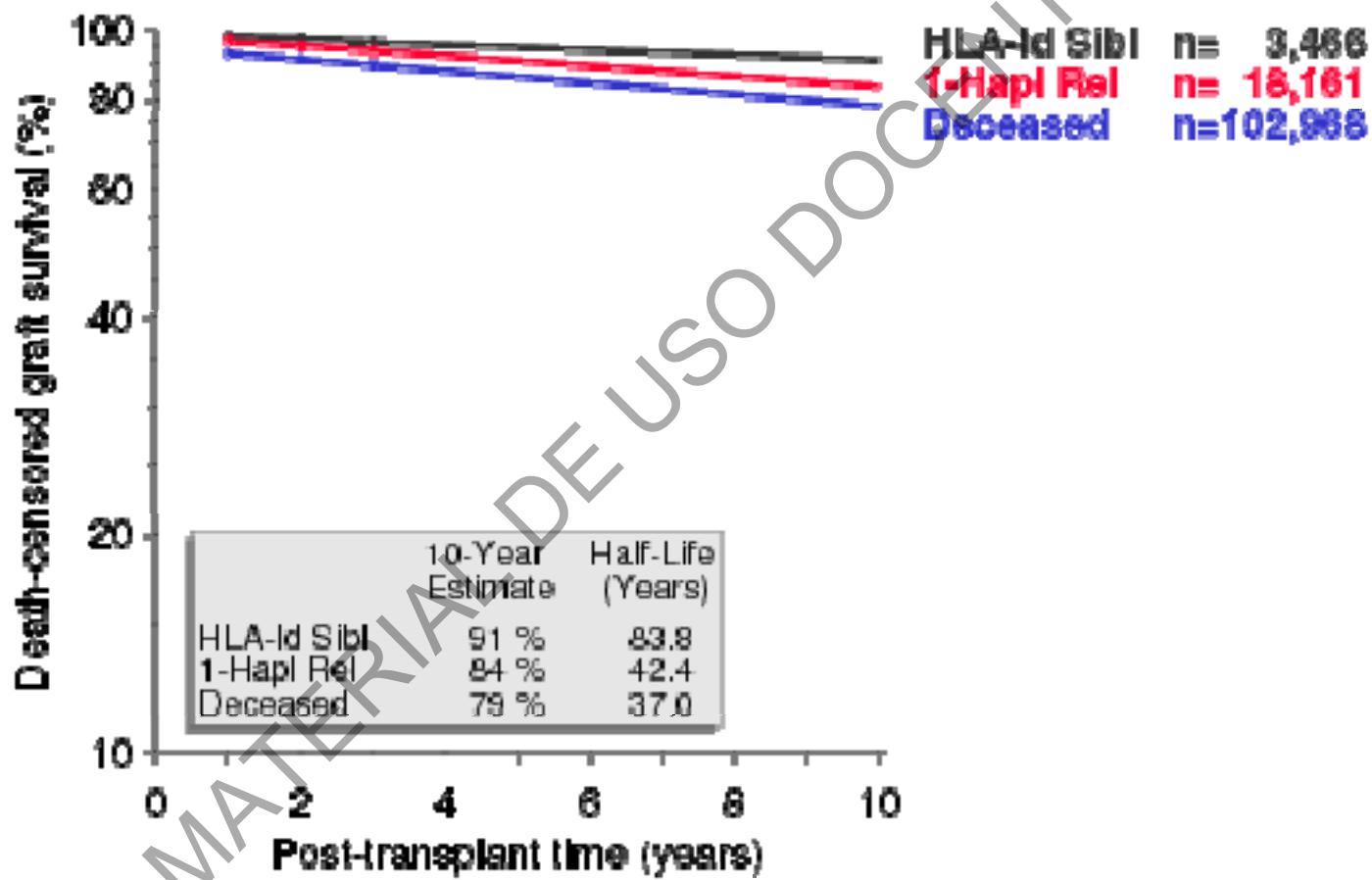
- Compatibilidad HLA
- Régimen inmunosupresor

# **Factores asociados al donante, al receptor y al trasplante (2)**

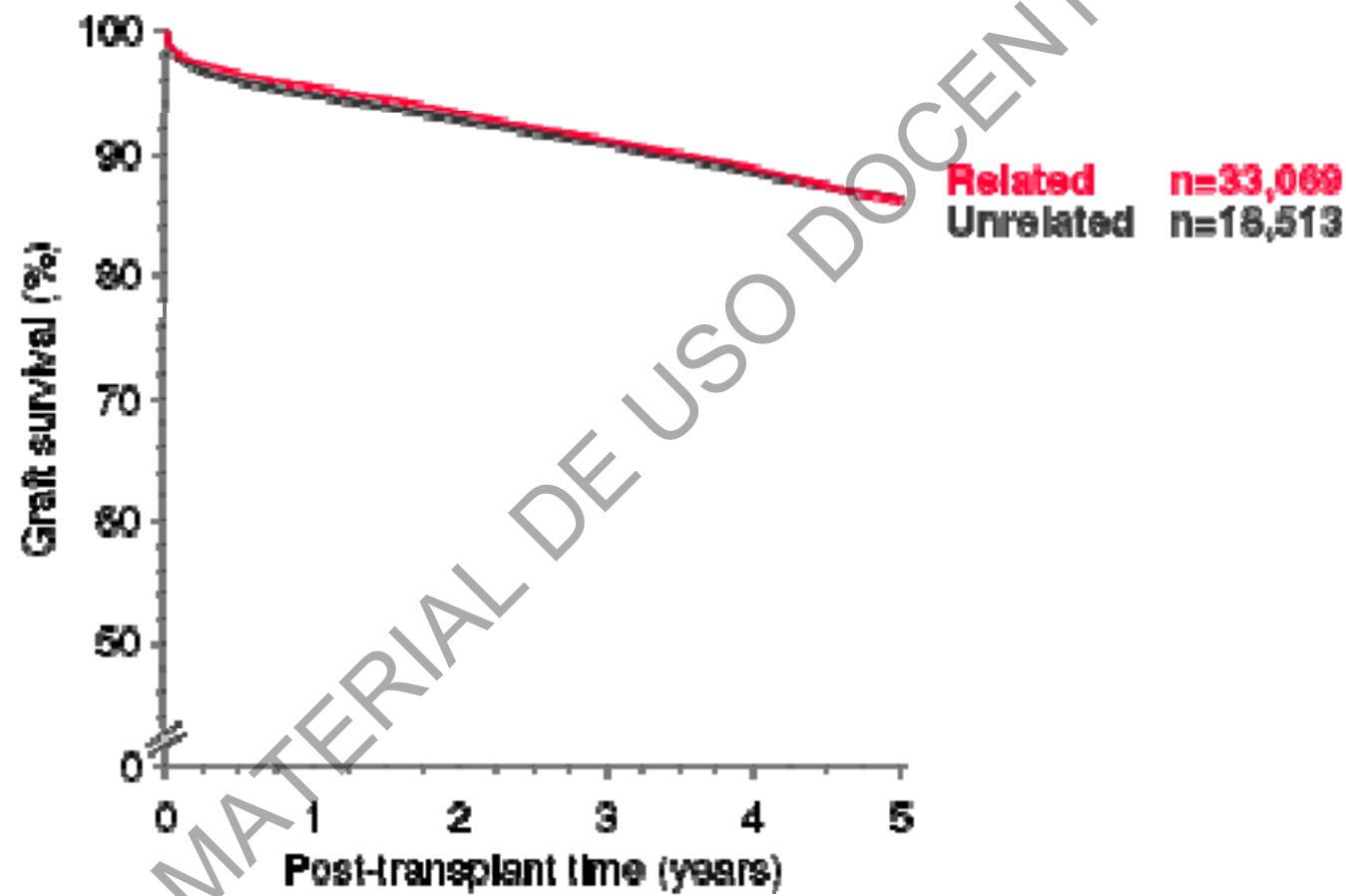
## ■ Variables evolutivas

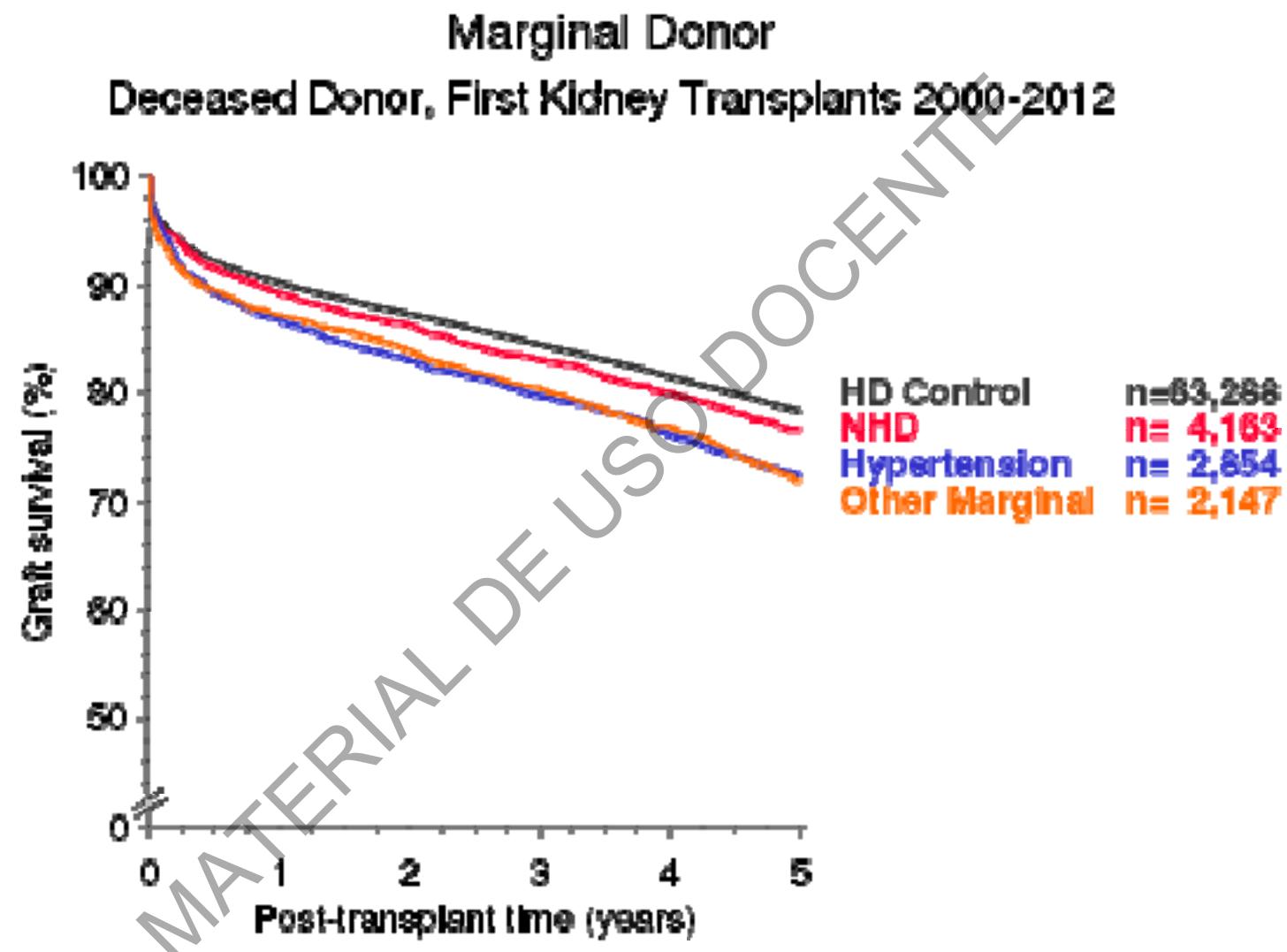
- Función retrasada del injerto
- Función renal en el primer año
- Proteinuria
- Rechazo agudo clínico y subclínico
- Anticuerpos donante-específicos
- Adherencia al tratamiento

## Donor Relationship First Kidney Transplants 2000-2012

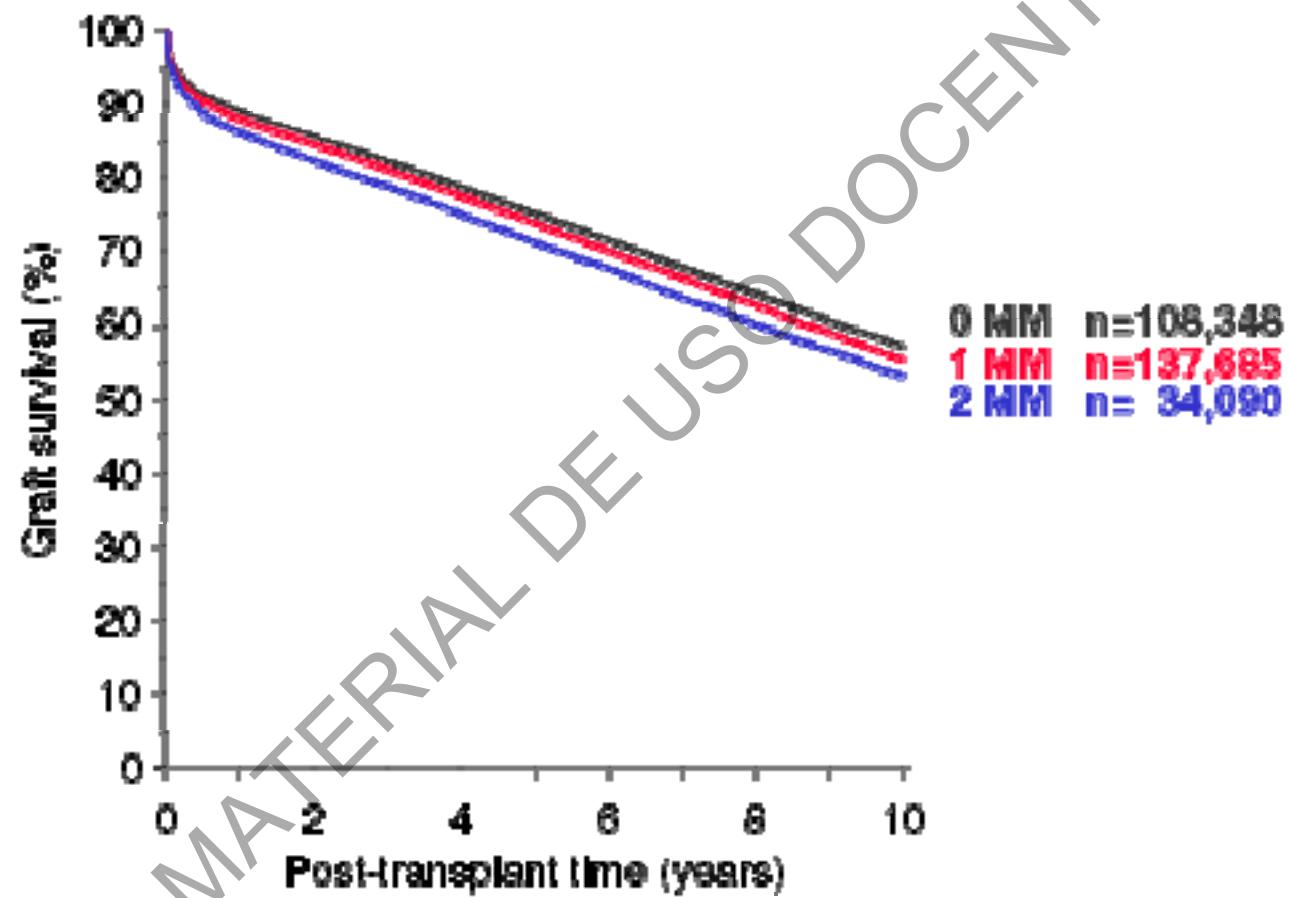


Living Donors  
First Kidney Transplants 2000-2012

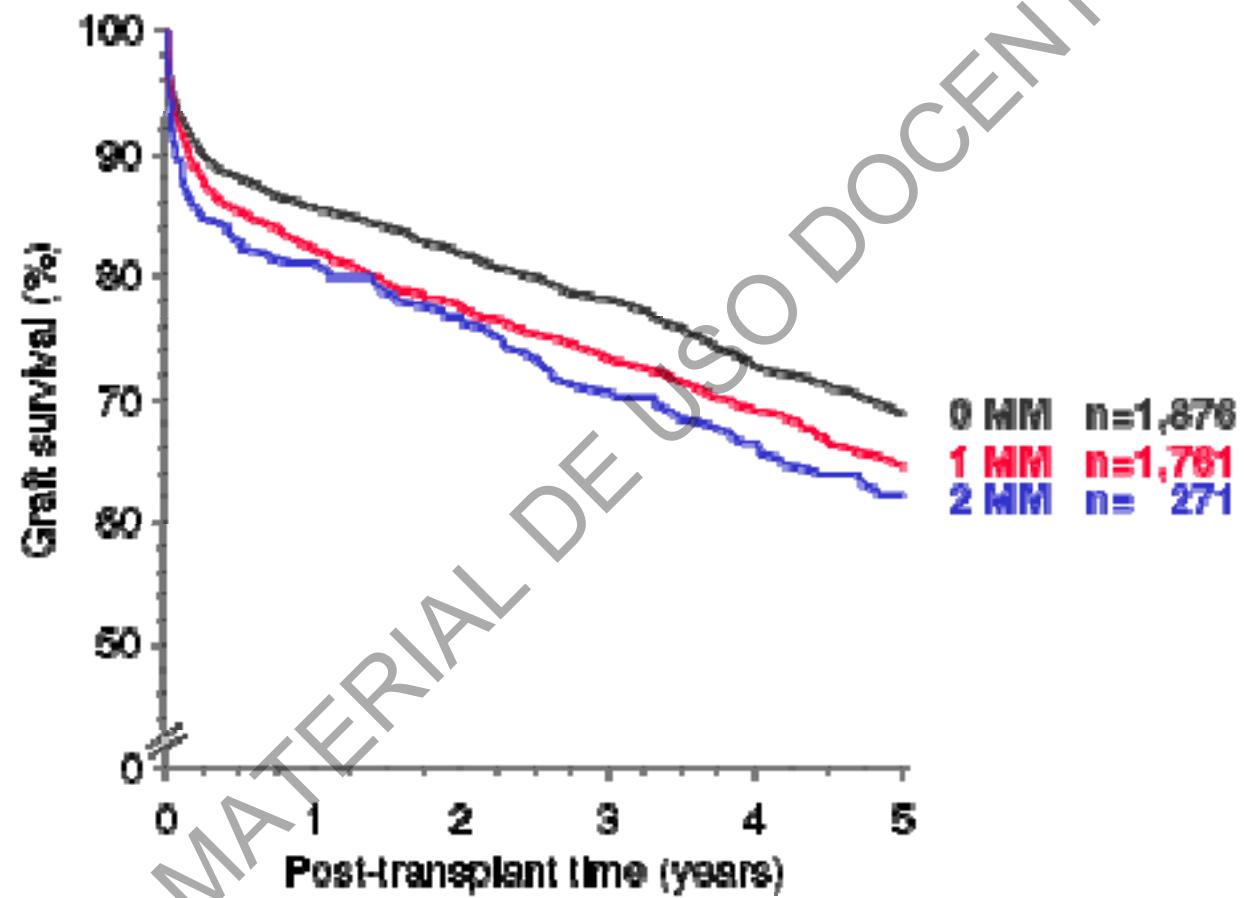


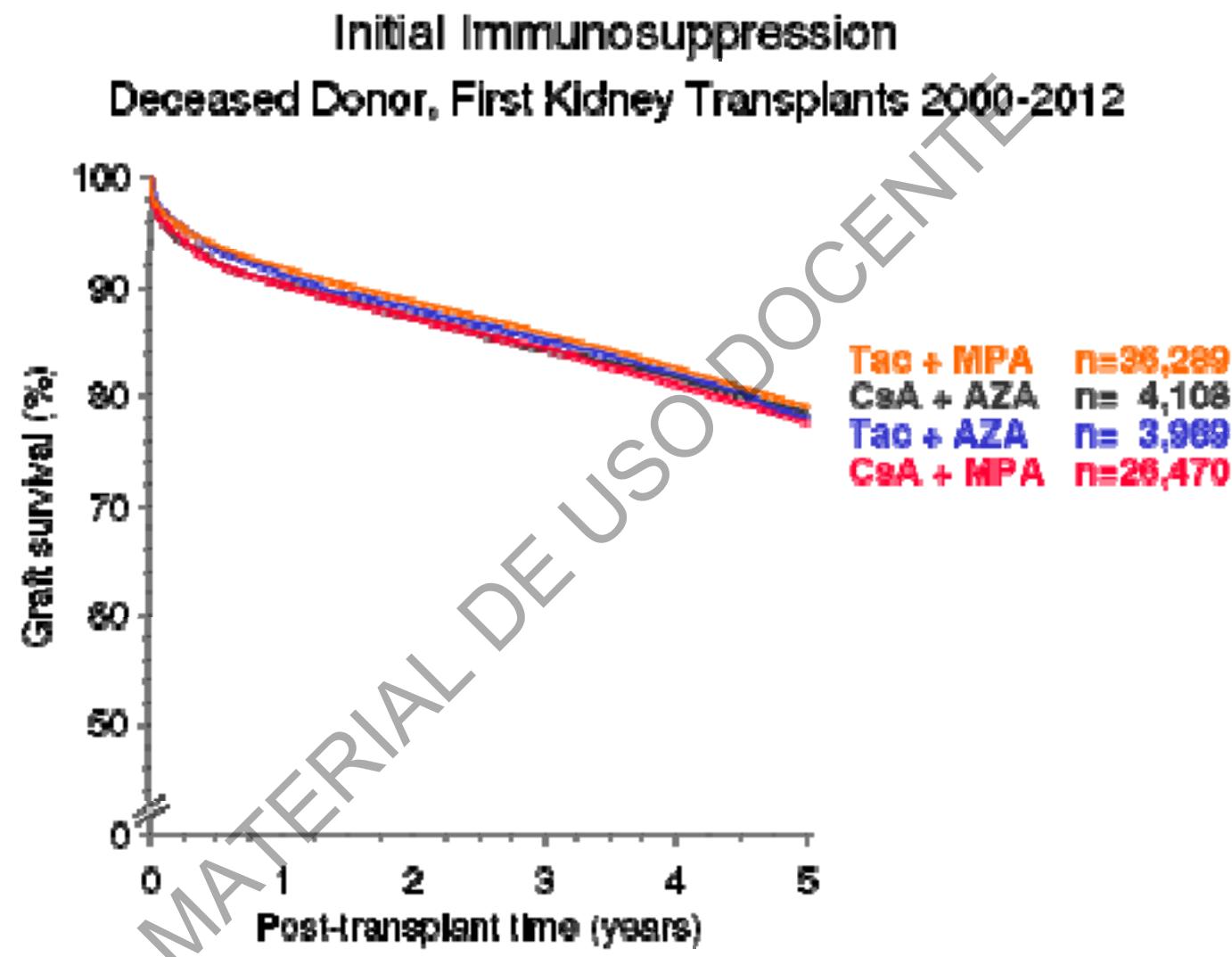


## HLA-DR Mismatches Kidney Transplants 1990-2012

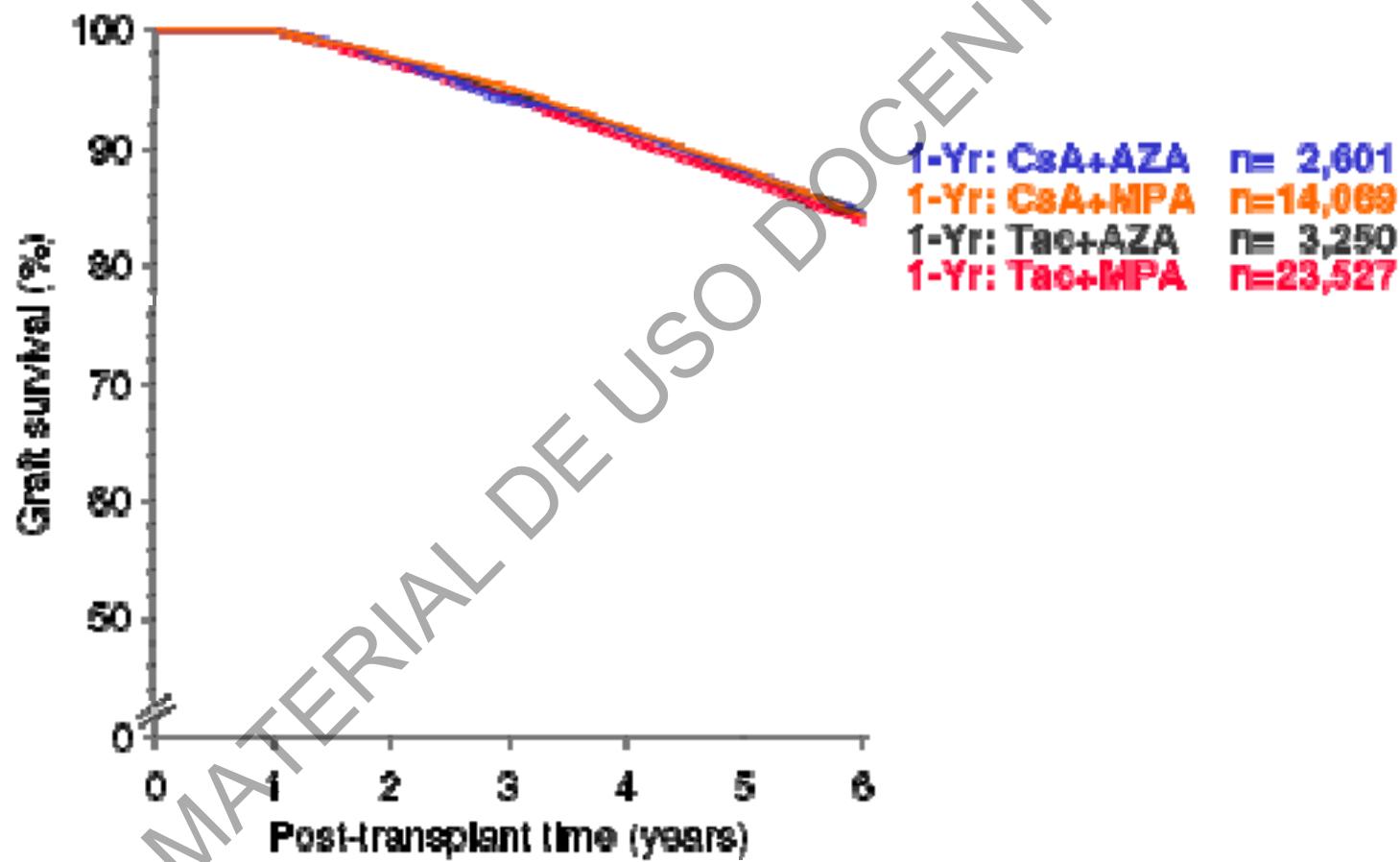


DNA Typing HLA-DQB Mismatches  
Deceased Donor Kidney Retransplants 1990-2012





## 1-Year Immunosuppressive Maintenance Treatment Deceased Donor, First Kidney Transplants 2000-2012



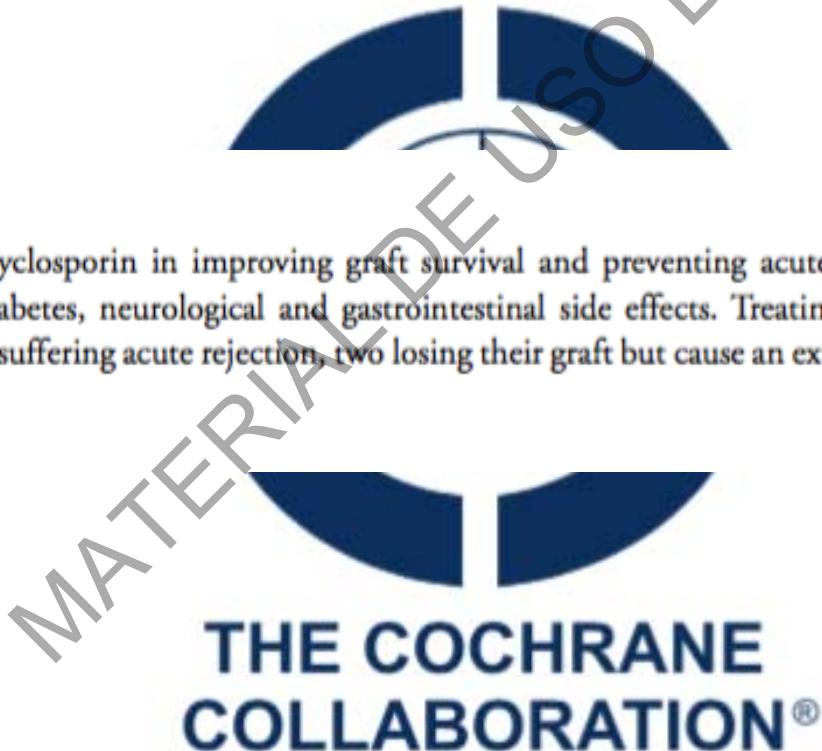
## **Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients (Review)**

**Webster AC, Taylor RRS, Chapman JR, Craig JC**



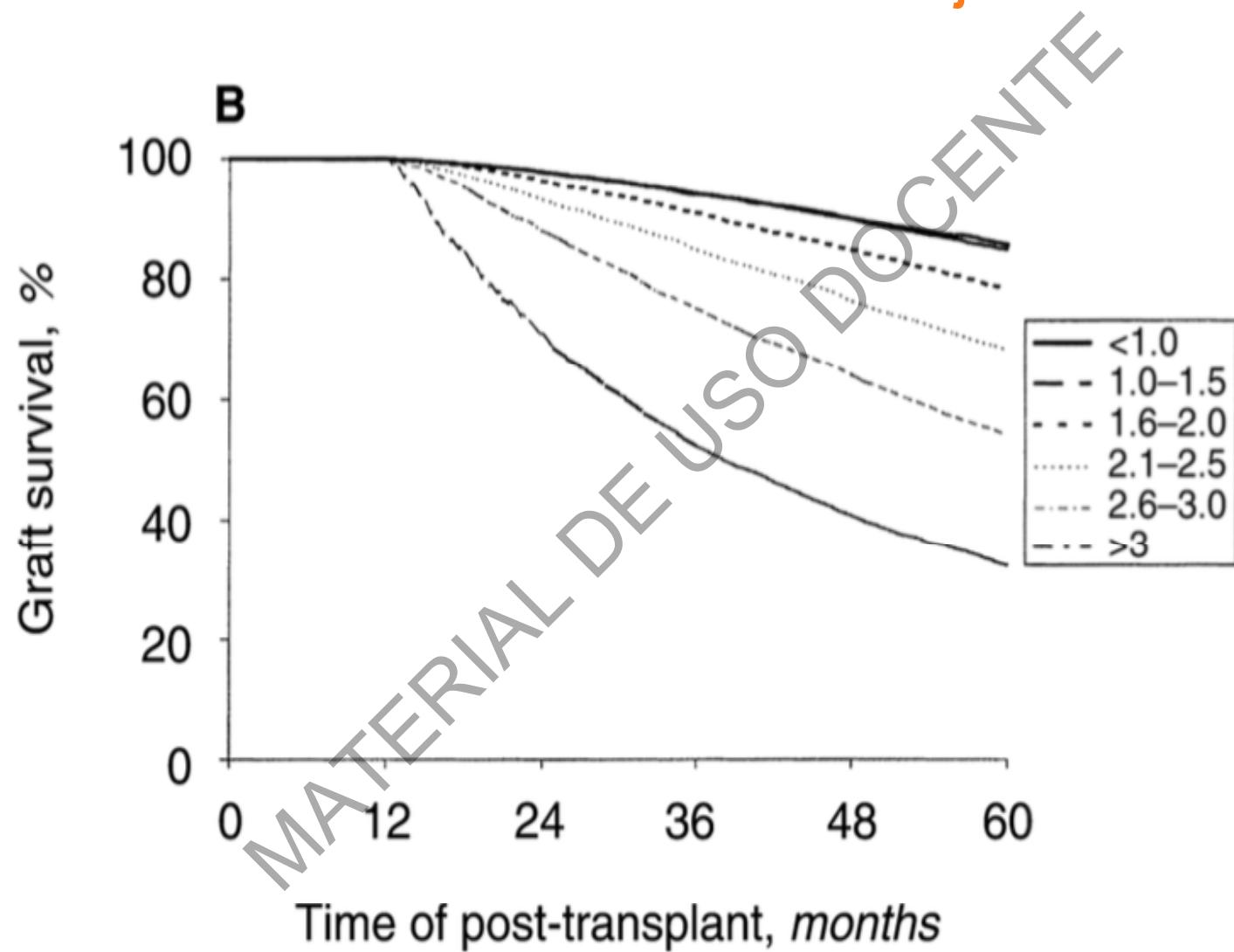
### **Authors' conclusions**

Tacrolimus is superior to cyclosporin in improving graft survival and preventing acute rejection after kidney transplantation, but increases post-transplant diabetes, neurological and gastrointestinal side effects. Treating 100 recipients with tacrolimus instead of cyclosporin would avoid 12 suffering acute rejection, two losing their graft but cause an extra five to become insulin-requiring diabetics.

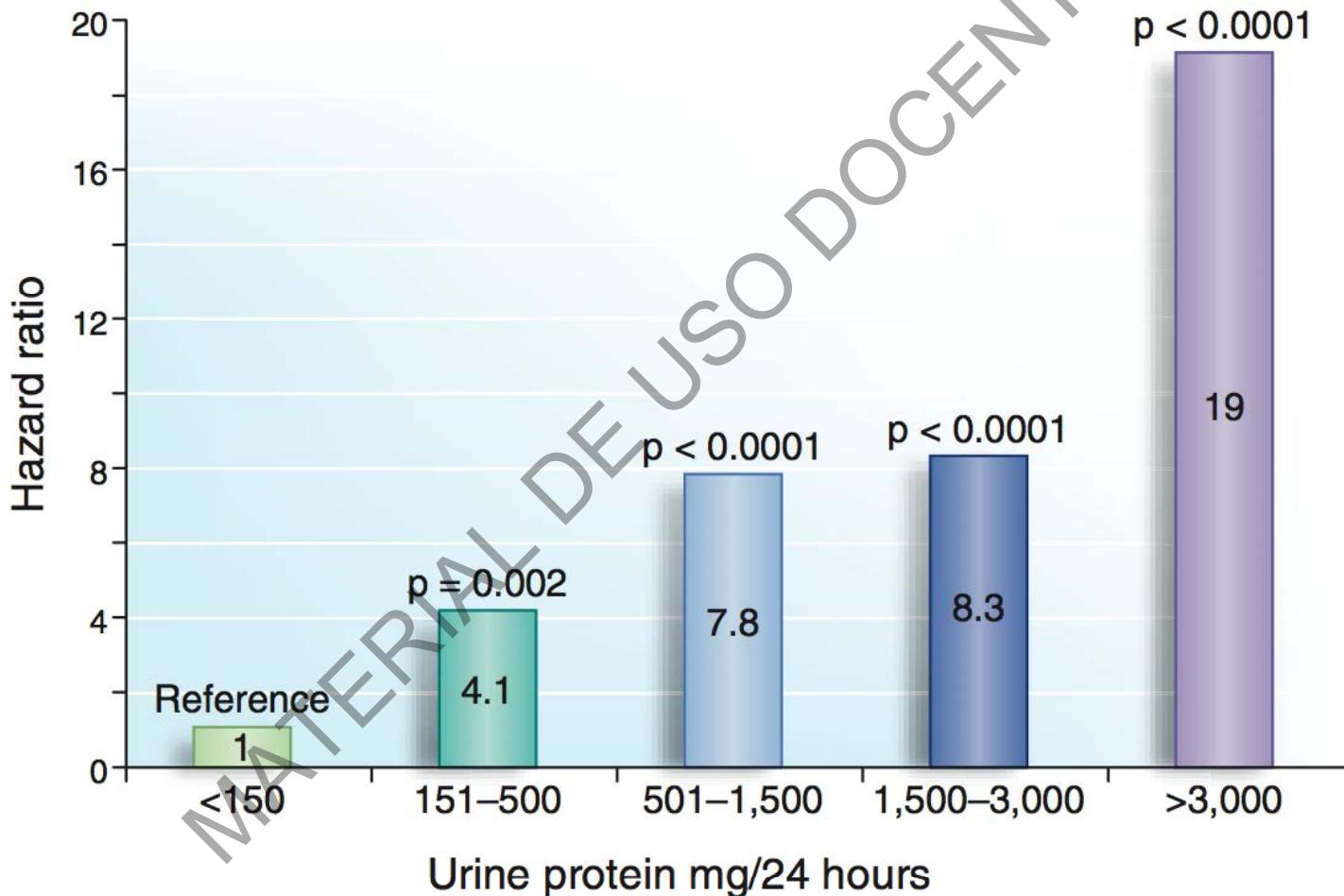


*The Cochrane Library 2005, Issue 4*

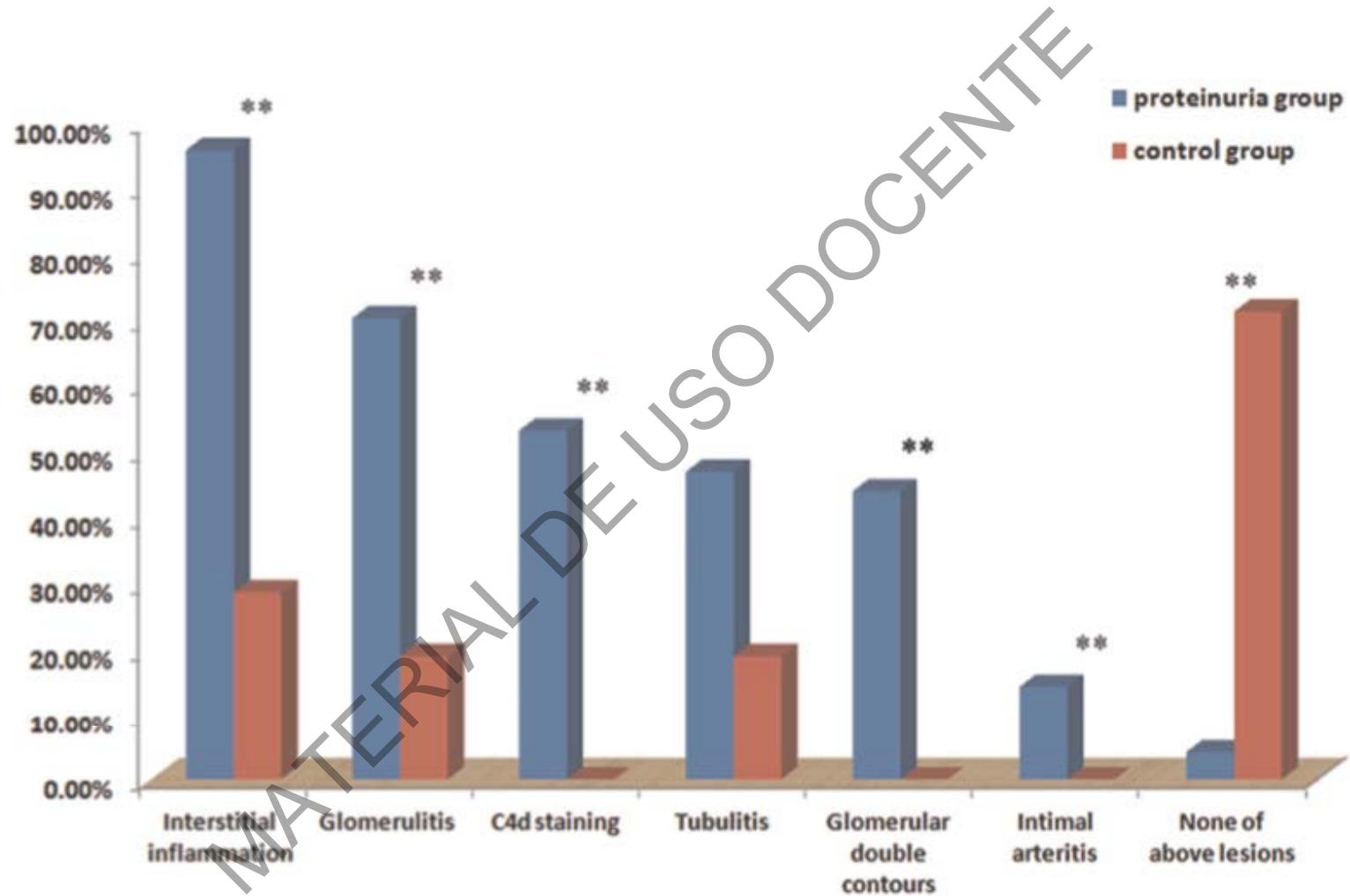
## Influencia de la función renal alcanzada en el primer año en la sobrevida del injerto



## Relación entre la proteinuria a 1 año de evolución y la sobrevida del injerto

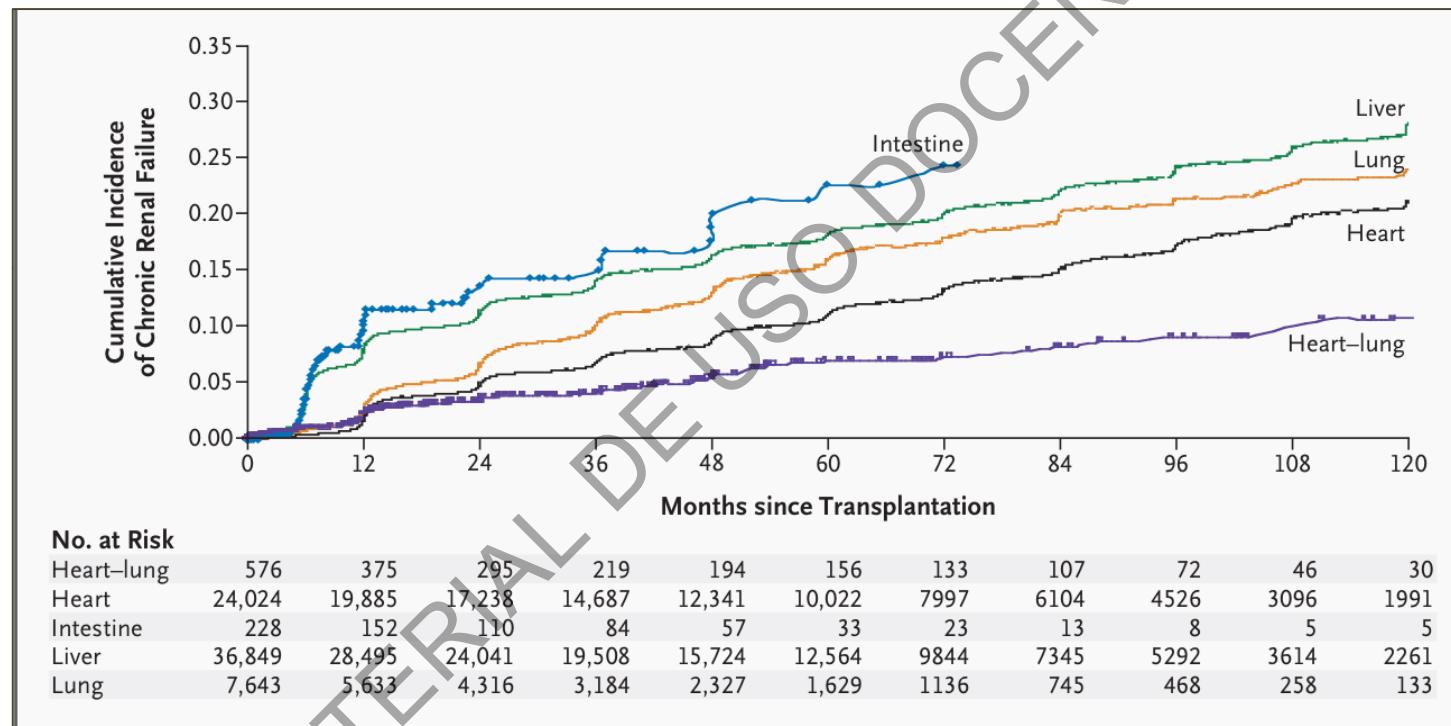


## Prevalencia de lesiones histológicas relacionadas con actividad inmunológica en pacientes con proteinuria > 400mg/d



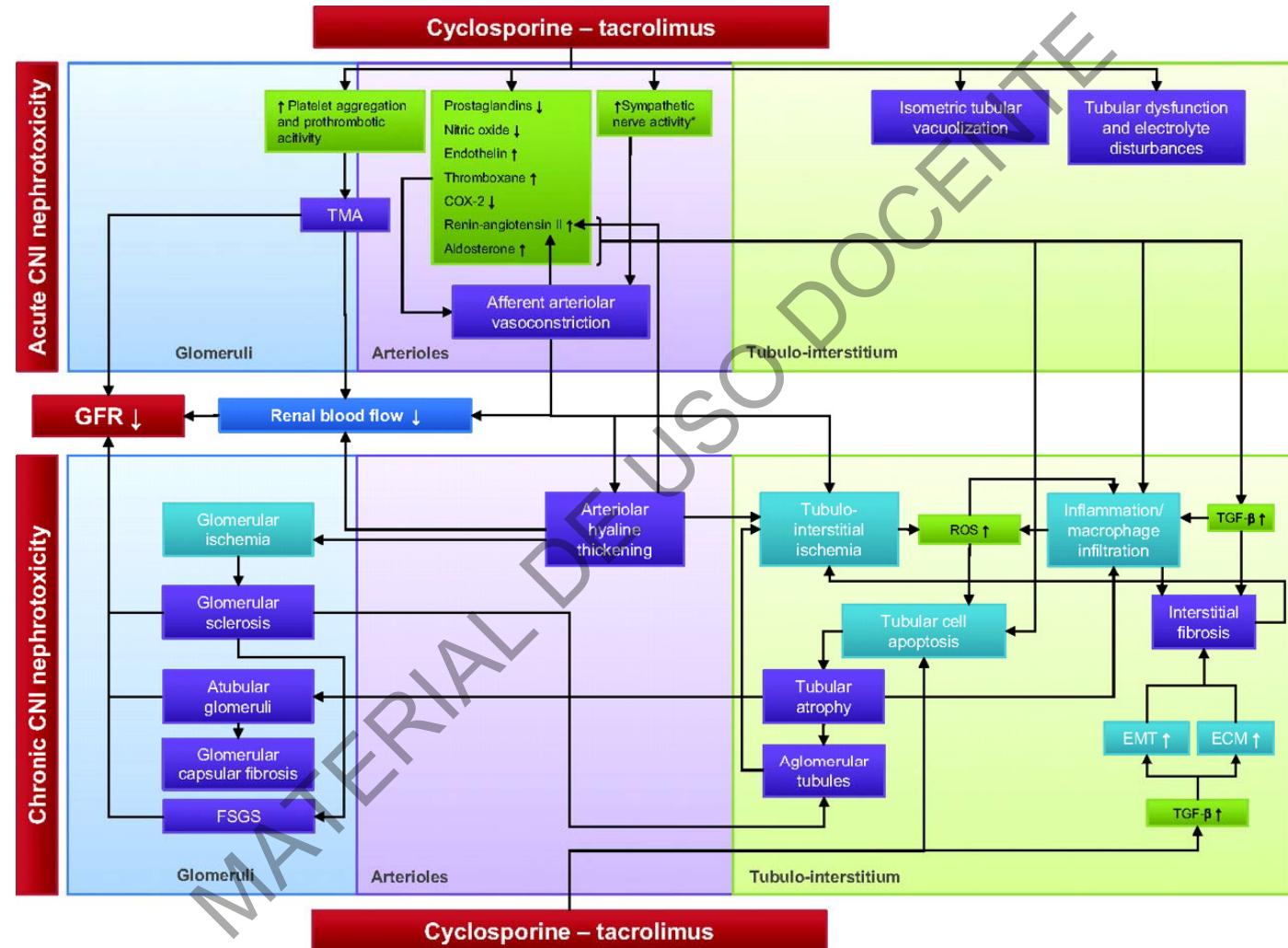
Sun O et al, PLoS ONE 2012, 7(5): e36654.

# Cumulative Incidence of Chronic Renal Failure among 69,321 Persons Who Received Nonrenal Organ Transplants in USA 1990-2000



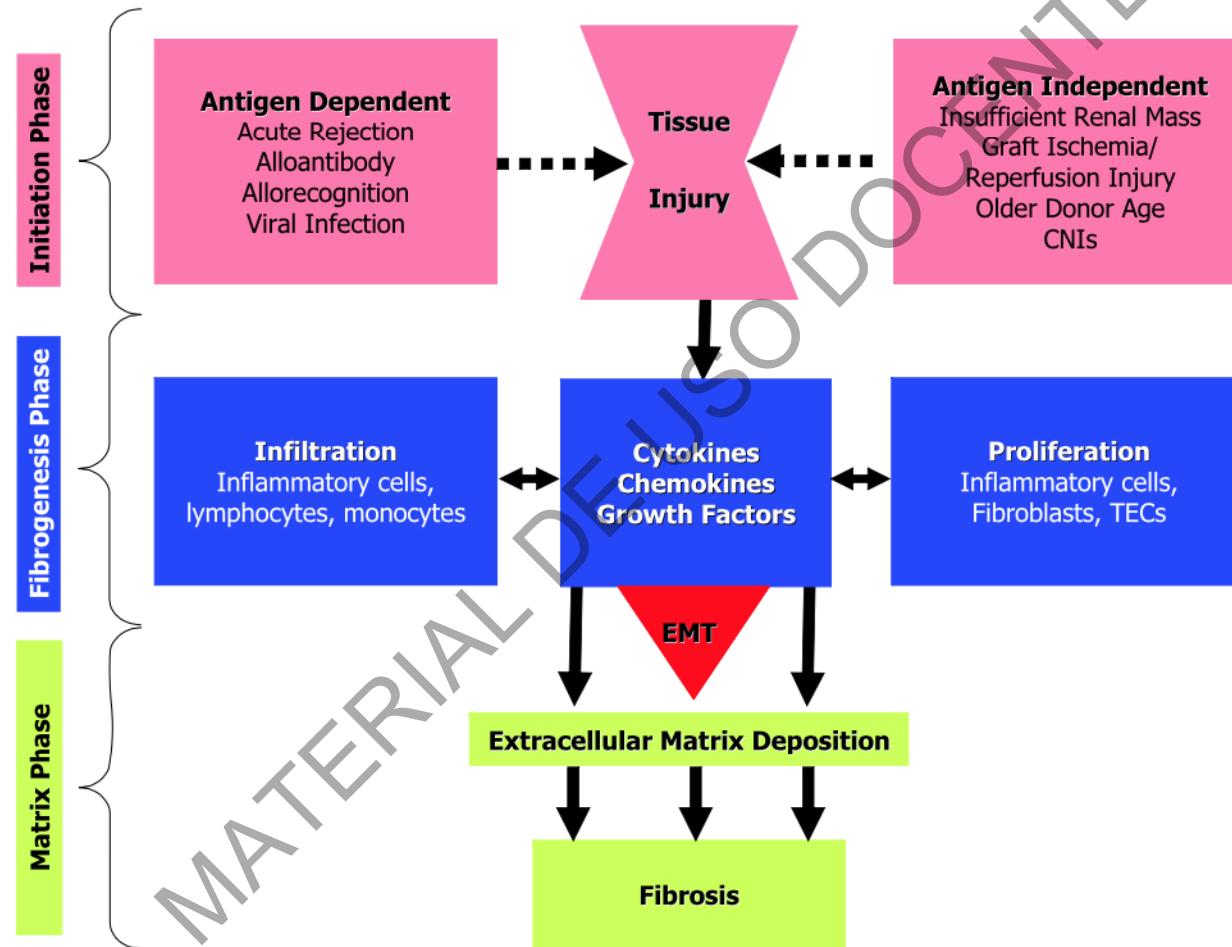
Ojo, AK. et. al. N Engl J Med 2003; 349;10: 931-40

# Schematic representation of the etiology of calcineurin inhibitor nephrotoxicity.

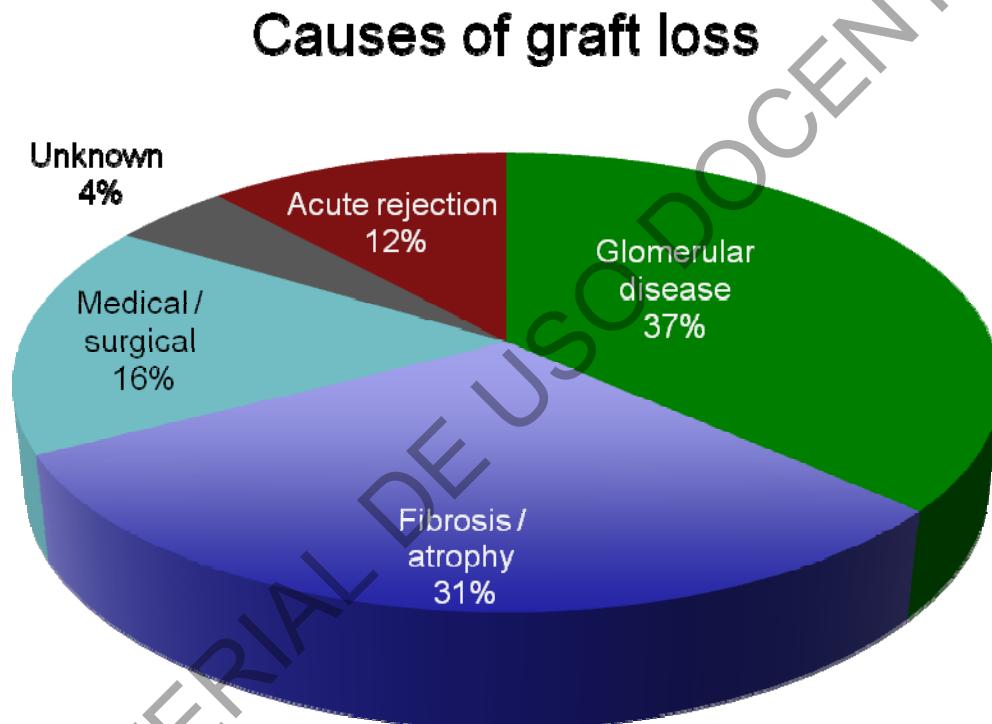


Naesens M et al. CJASN 2009;4:481-508

Tubulointerstitial fibrosis is considered the final common mechanism leading to end-stage renal disease regardless of the initiating insult



# Identifying Specific Causes of Kidney Allograft Loss



Most of the 153 cases of kidney graft loss were associated to an identifiable cause that was not idiopathic fibrosis/atrophy or CNI toxicity

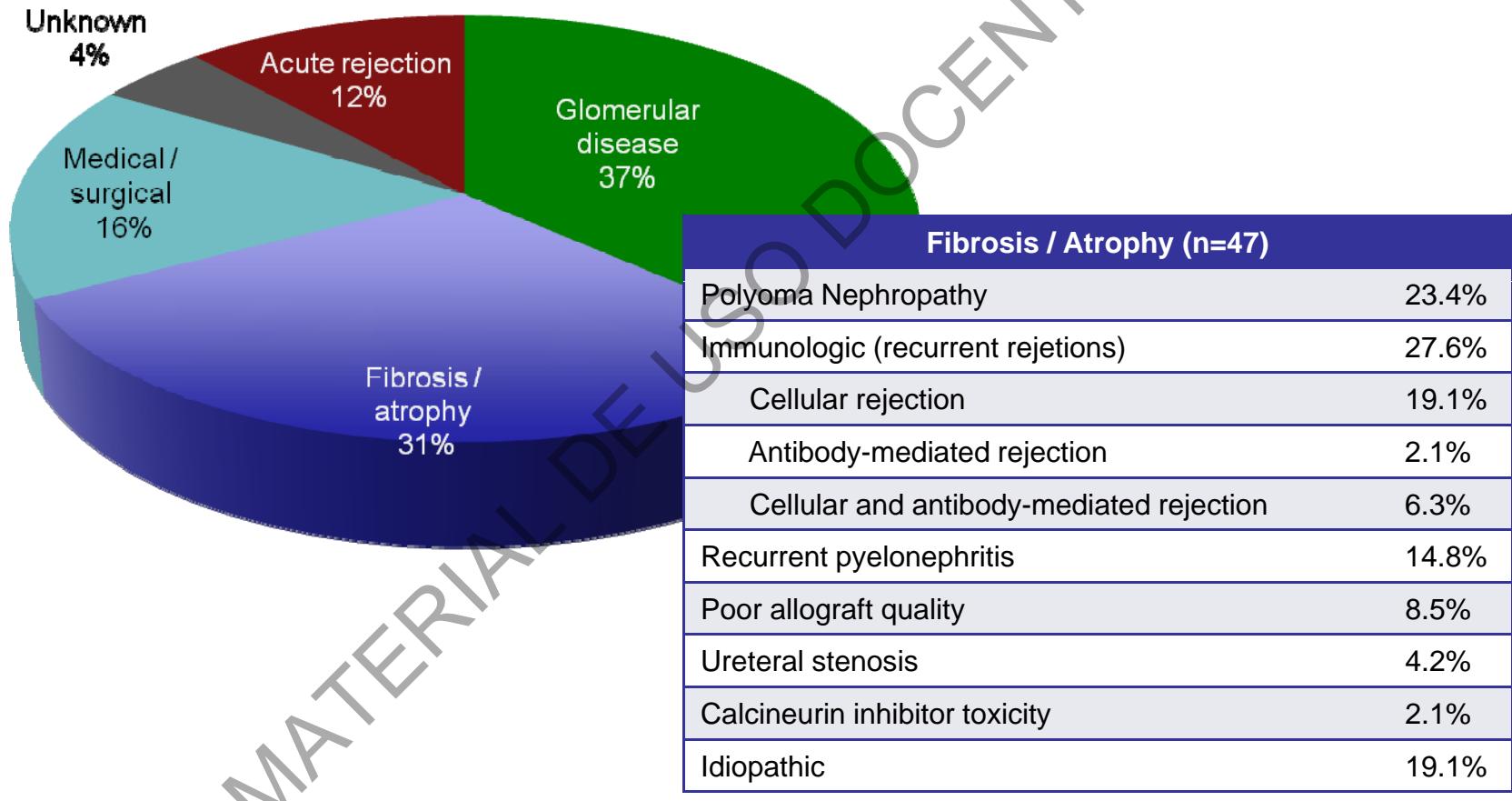
# Identifying specific causes of kidney allograft loss

**Table 4:** Causes of loss of functioning grafts at different periods of time posttransplant<sup>1</sup>

Cause of graft lost	All	Year 1	Years >1–5	Years >5
Patients at risk	1317	1317	1185	505
Grafts lost during the period	153	32	81	40
Acute rejection	18 (11.8%) <sup>1</sup>	6 (18.8%) <sup>1</sup>	10 (12.3%) <sup>1</sup>	2 (5%) <sup>1</sup>
Glomerular pathology	56 (36.6%)	9 (28.1%)	32 (39.5%)	15 (37.5%)
Recurrent disease	23 (15%)	8 (25%)	12 (14.8%)	3 (7.5%)
Transplant glomerulopathy	23 (15%)	1 (3.1%)	16 (19.8%)	6 (15%)
<i>De novo</i> disease	10 (6.6%)	0 (0%)	4 (4.9%)	6 (15%)
Fibrosis/atrophy (IF/TA)	47 (30.7%)	3 (9.4%)	26 (32.1%)	18 (45%)
Medical	25 (16.3%)	14 (43.8%)	10 (12.3%)	1 (2.5%)
Unknown	7 (4.6%)	0 (0%)	3 (3.7%)	4 (10%)

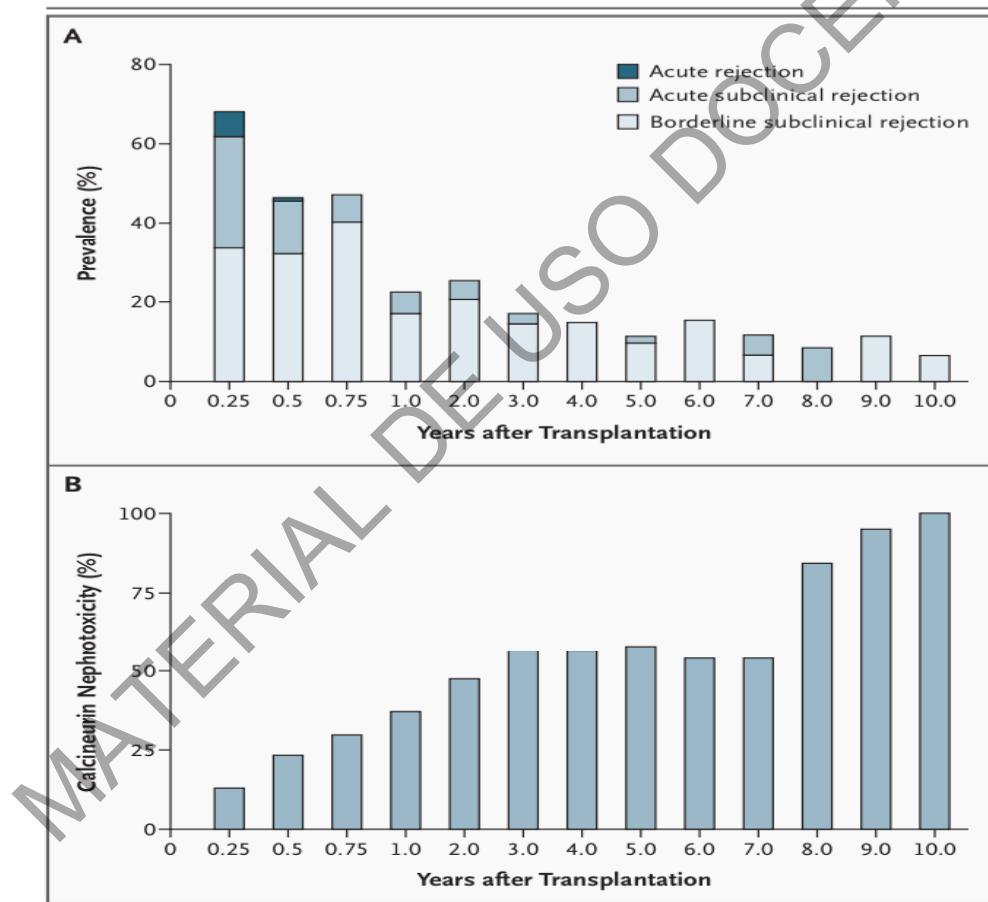
<sup>1</sup>Values represent number of graft losses and percent of the grafts lost during the period indicated in the column head.

# Etiologic classification of losses of functioning grafts

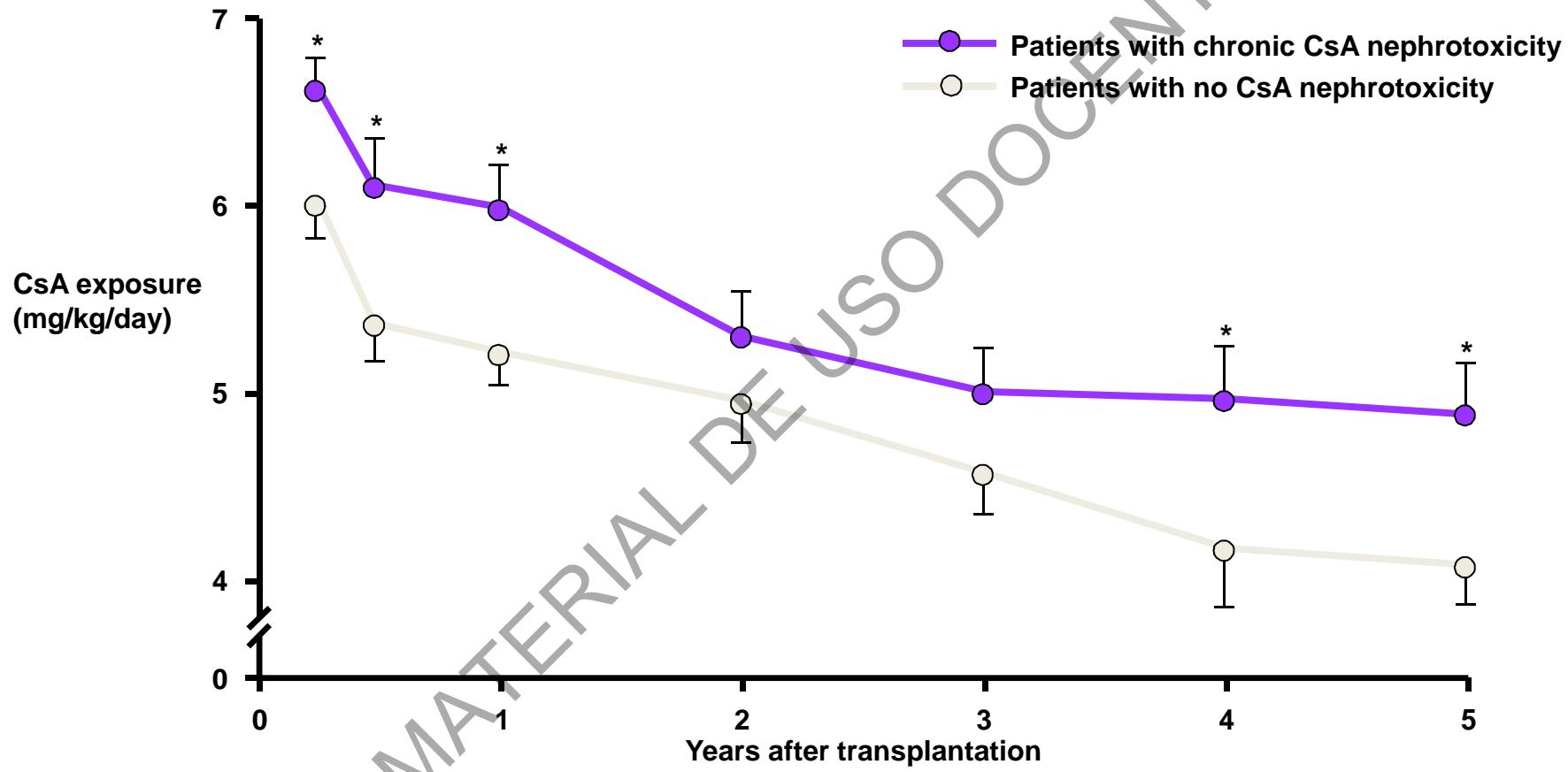


Most of the 153 cases of kidney graft loss were associated to an **identifiable cause** that was not idiopathic fibrosis/atrophy or CNI toxicity

The prevalence of CNI nephrotoxicity is substantially increased,  
in contrast with the reduction of subclinical rejection



Lower CNI exposure is associated with a reduction in  
CNI nephrotoxicity in renal biopsies

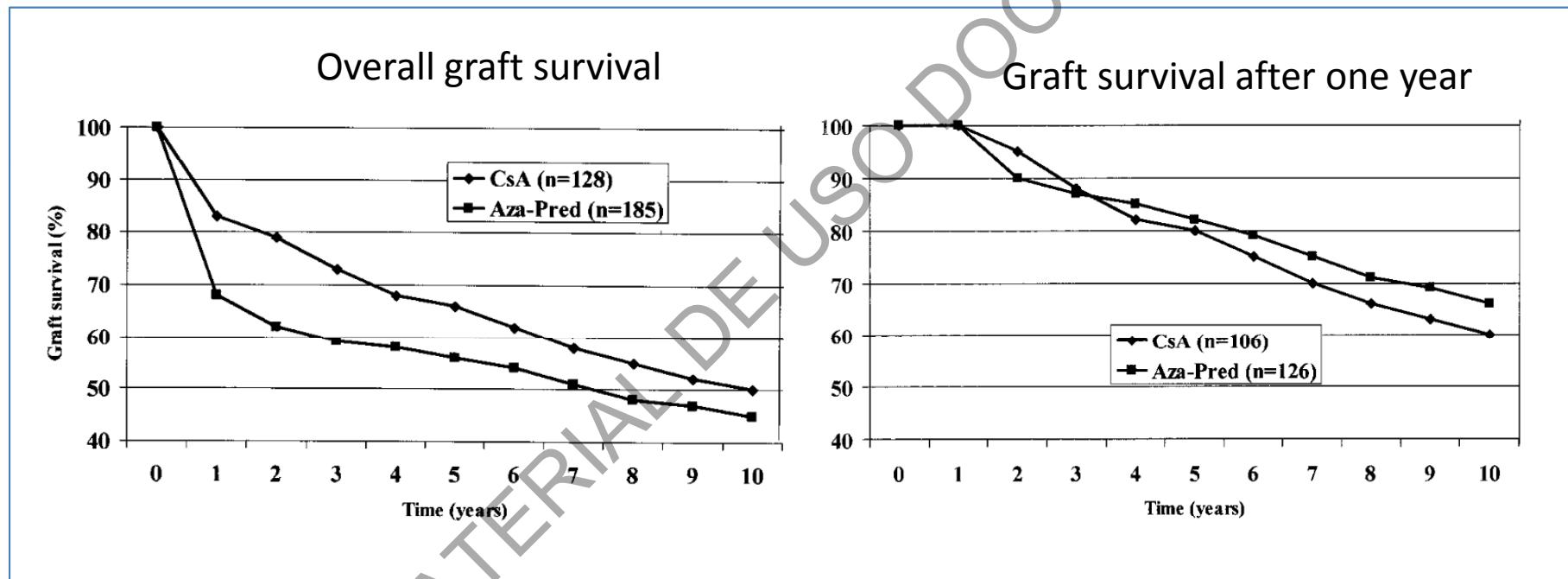


Data taken from 888 biopsies (99 patients)

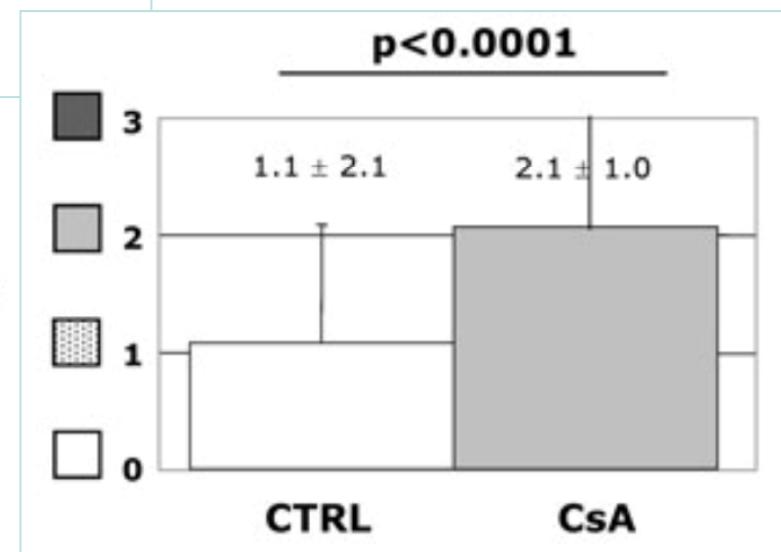
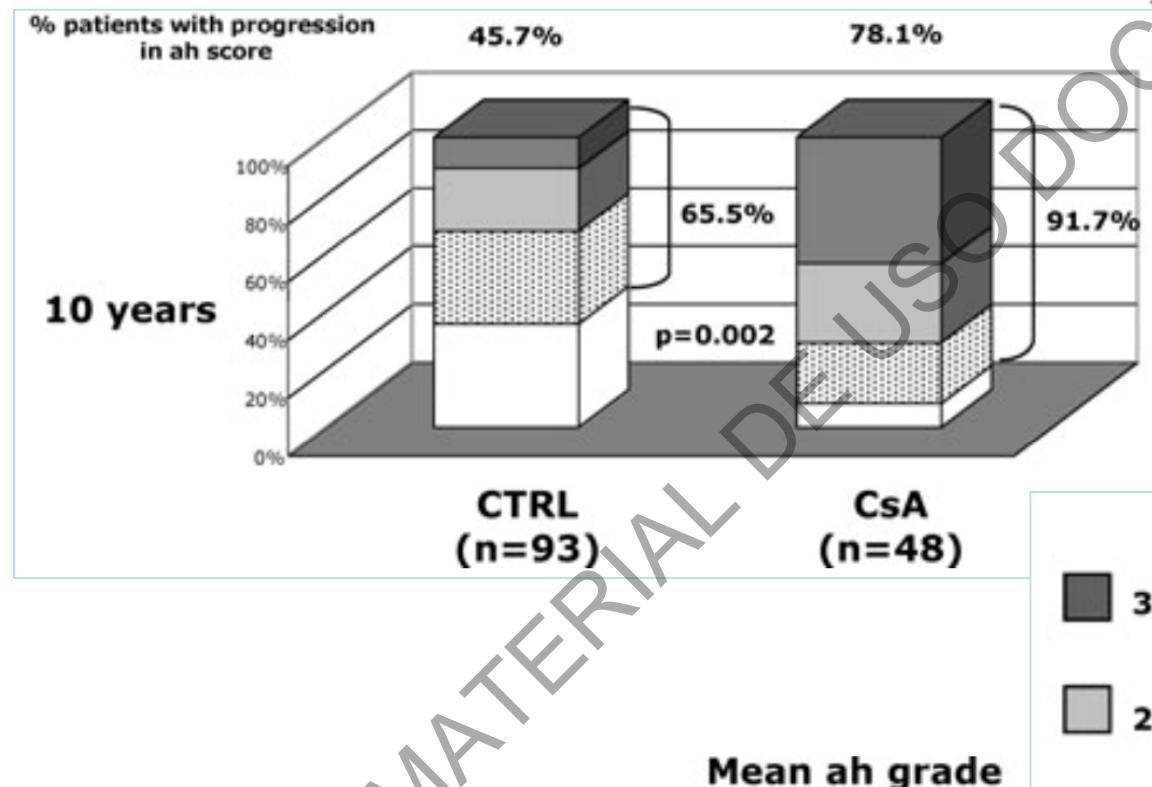
\* $p<0.05$ ; CNI, calcineurin inhibitor; CsA, cyclosporin

Nankivell BJ et al. *Transplantation* 2004;78:557–65

# CsA results in a better short-time graft survival that is not maintained in the long-term outcome

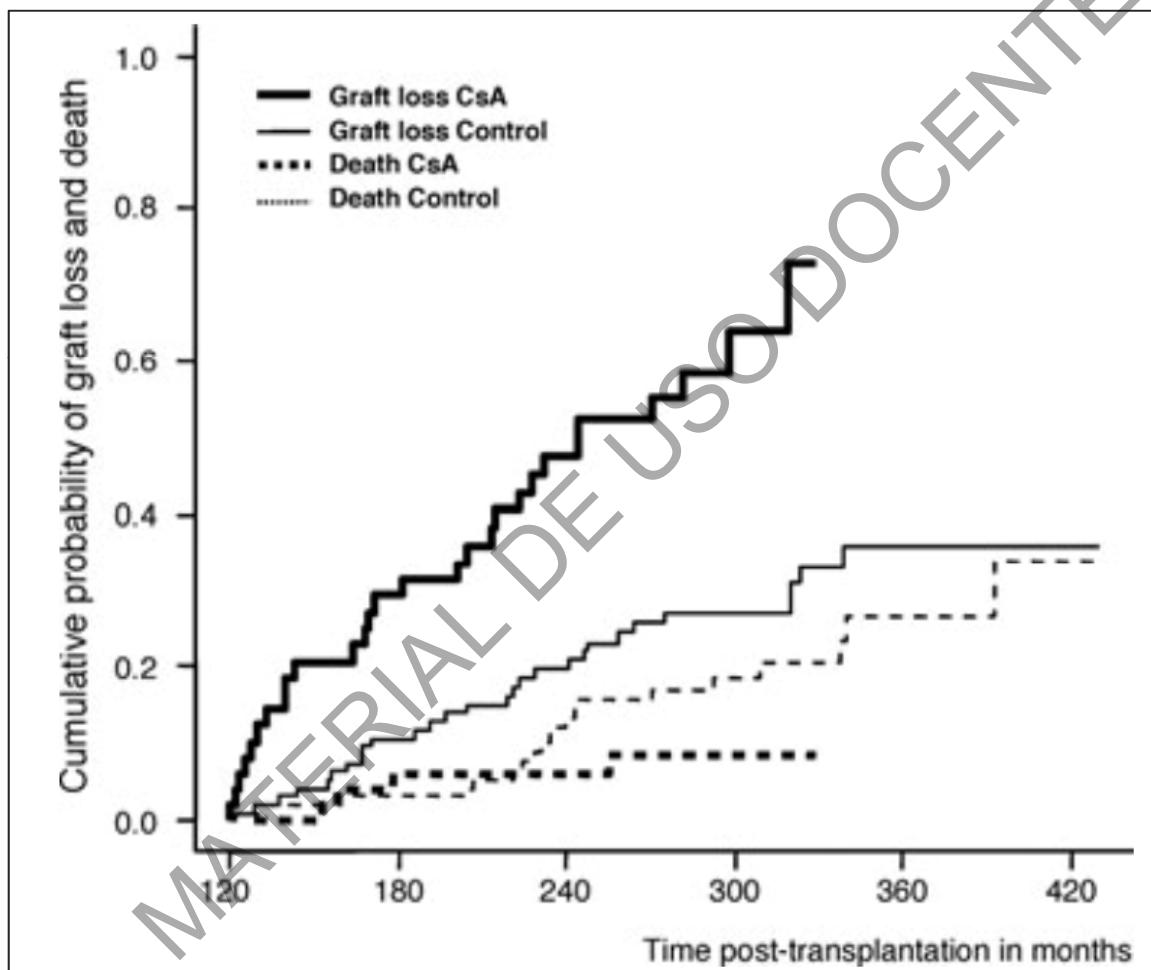


# Frequency and severity of arteriolar hyalinosis in transplant recipients imunosuppressed with or without CsA



Snanoud R et al, Am J Transplant 2011; 11: 2635–2646

## Cumulative probability of graft loss and death in patients treated with or without CsA

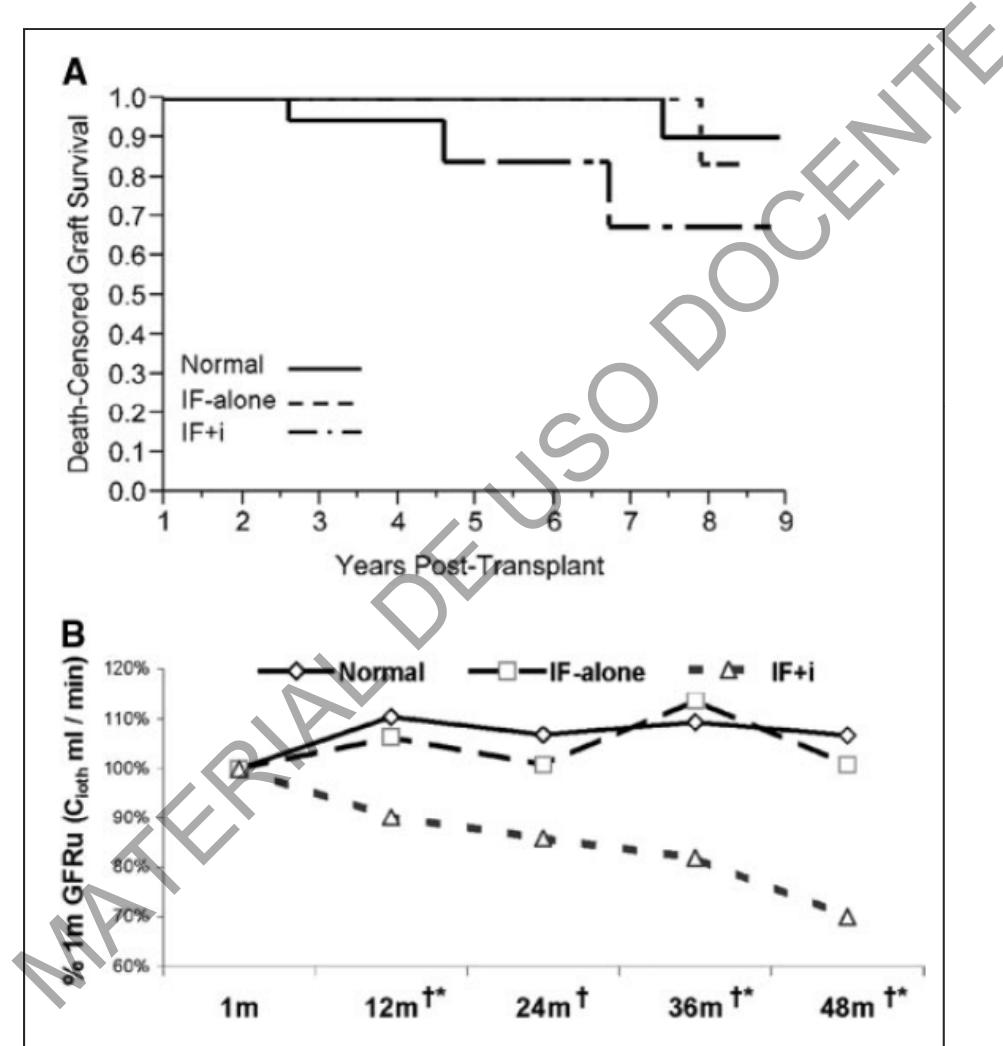


Renal allografts from the era of 1998–2004 demonstrate fewer, less severe and less progressive chronic histologic changes in the first 5 years after transplantation than reported in earlier eras (1987-2000)

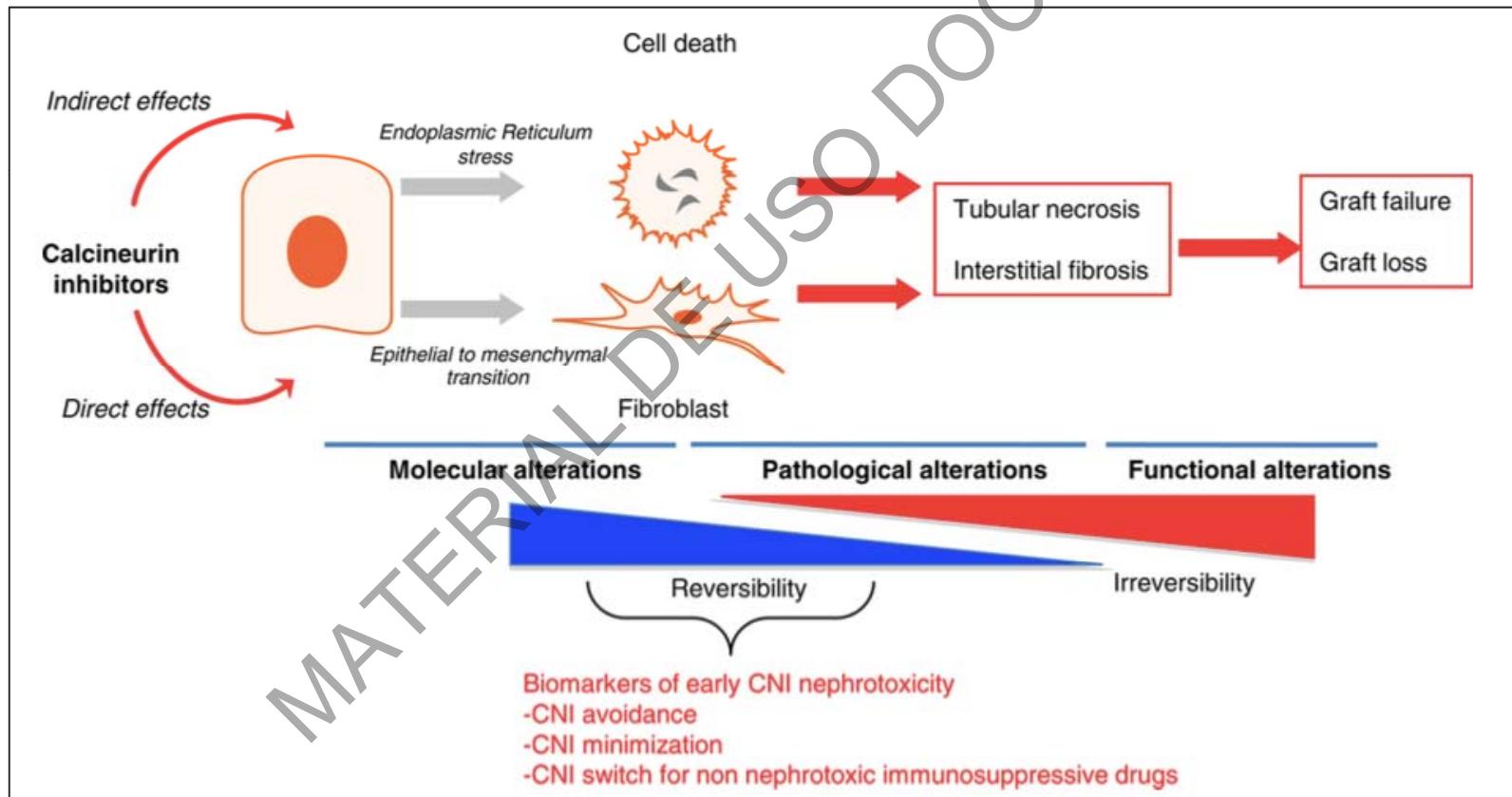
**Table 1:** Comparison of histologic changes on protocol biopsies at 5 years after kidney transplantation: Nankivell (Westmead) and Stegall (Mayo Clinic). Adapted from Refs. 6 and 7

Cohort	Era	Immuno-suppression	5-year biopsy results			
			ci0	ci1	ci2/3	ah2/3
Nankivell N = 70	1987–2000	Cyclosporine	0%	34%	66%	90%
Stegall N = 343	1998–2004	Tacrolimus	38%	45%	17%	19%

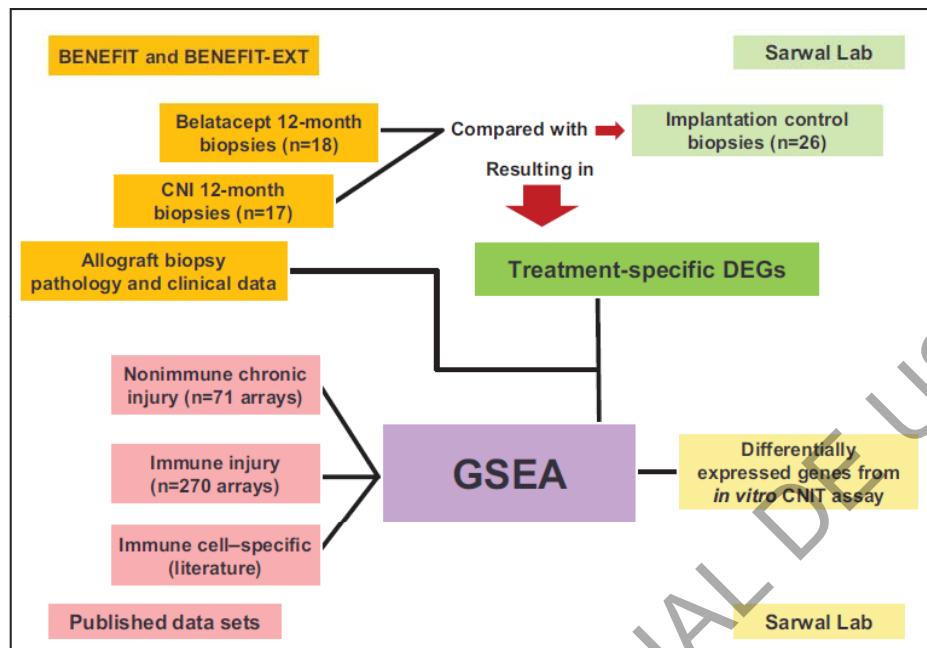
## Fibrosis with inflammation at one year predicts transplant functional decline



# Can we predict CNIs nephrotoxicity?

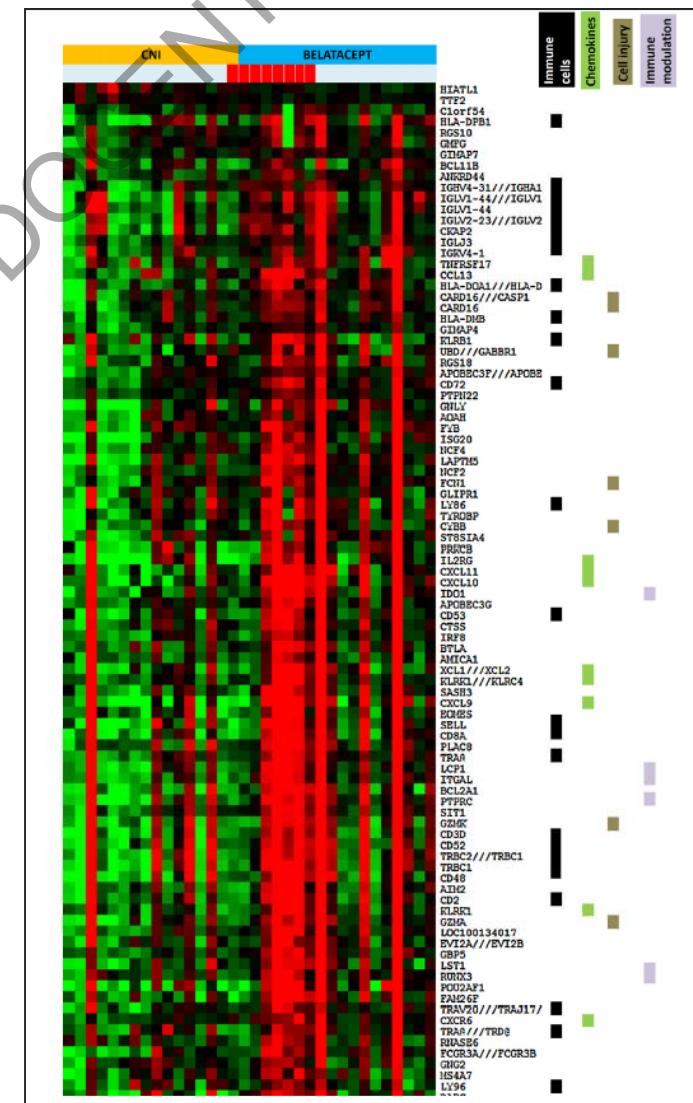


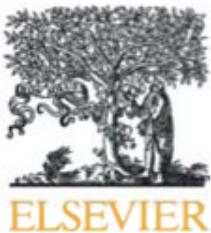
# Transcriptional Profiling of Belatacept and Calcineurin Inhibitor Therapy in Renal Allograft Recipients



CNI-treated patients exhibited signs of tubulointerstitial damage in both histopathologic and transcriptome analyses.

The accelerated pattern of cellular stress, tissue fibrosis and tissue injury seen in biopsies from CNI-treated patients was absent in biopsies from belatacept-treated patients



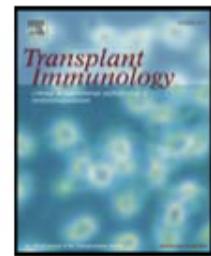


Transplant Immunology 20 (2008) 21–28

Contents lists available at ScienceDirect

## Transplant Immunology

journal homepage: [www.elsevier.com/locate/trim](http://www.elsevier.com/locate/trim)



Review

### Minimization of calcineurin inhibitors to improve long-term outcomes in kidney transplantation

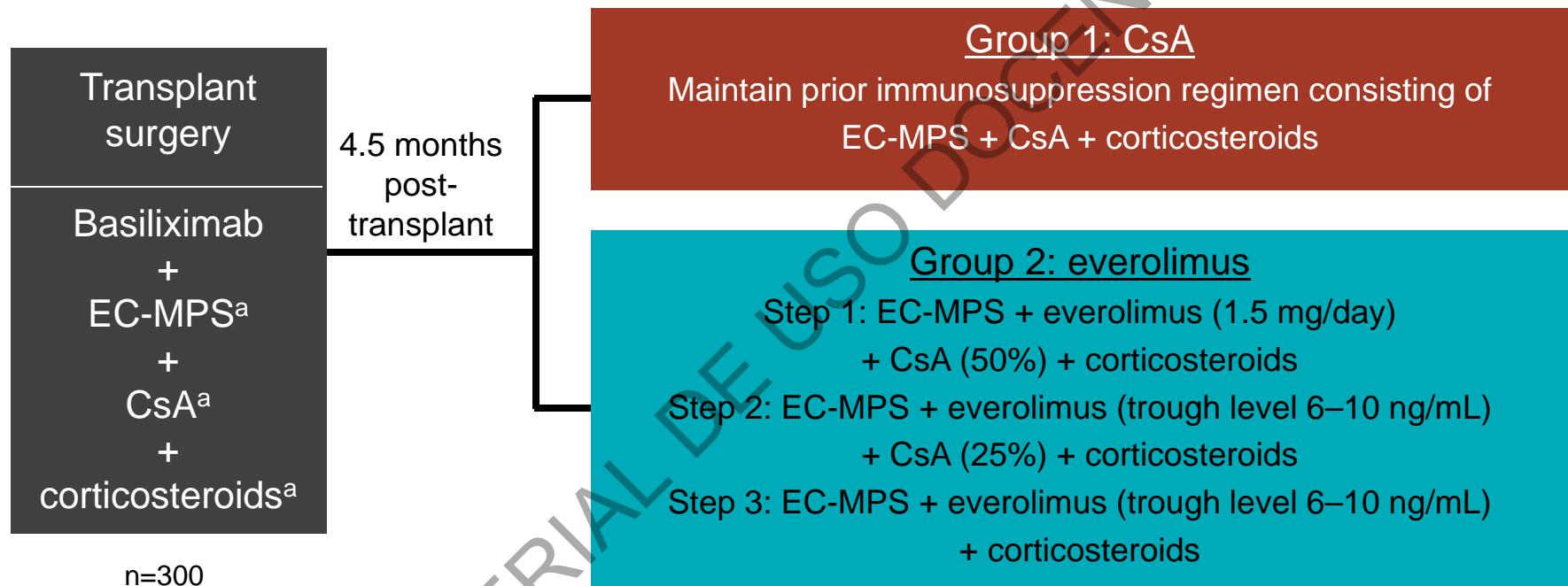
Dela Golshayan\*, Manuel Pascual

# Minimization of Cyclosporine A to improve long-term outcomes in kidney transplantation

**Table 1**  
CNI-minimization or withdrawal in recipients with stable renal function

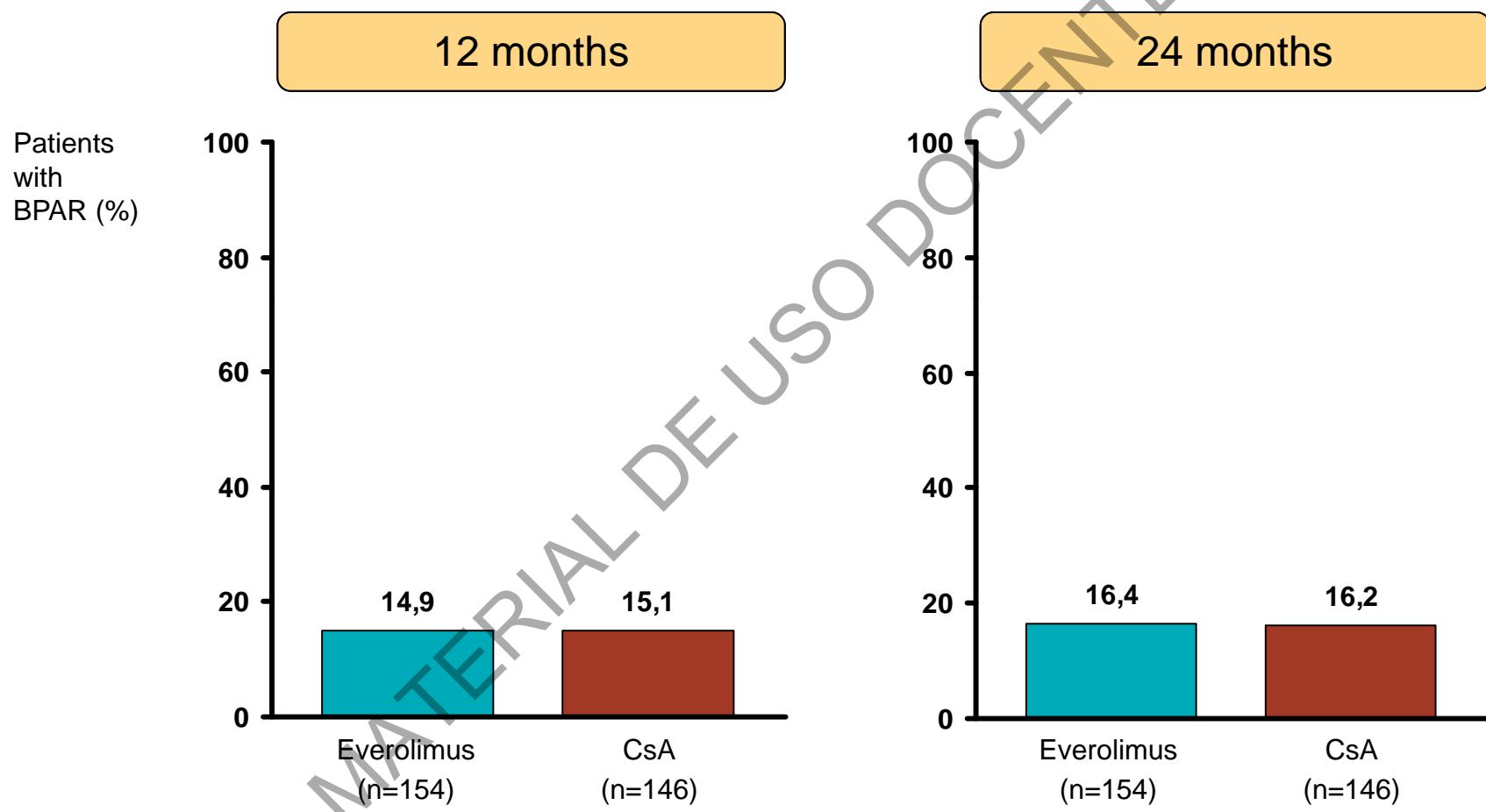
Reference	Patients number	Time of IS change (after Tx)	IS therapy (withdrawal vs. control)	AR rates	Renal function change vs. control	Follow-up
Smak Gregoor et al. [30]	34/30	12 mo	MMF-Pred vs. AZA-Pred	11.8% vs. 36.7% ( $P<0.05$ )	Improved from baseline in both arms	20 mo
Smak Gregoor et al. [31]	63/73	6 mo	MMF-Pred vs. CsA-MMF-Pred	22% vs. 1.4% ( $P<0.05$ )	Improved	24 mo
Abramowicz et al. [33]	74/77	12–30 mo	???	9.5% vs. 1.3% ( $P<0.05$ )	Improved	5 yr
Schnuelle et al. [34]	44/40	???	???	???	Improved	12 mo
Pascual et al. [35]	???	???	???	???	Improved	6 mo
Ekberg et al. [37] (CAESAR)	???	???	???	???	Improved	12 mo
Oberbauer et al. Pearson et al. (Sparc)	???	???	???	???	???	48 mo
<b>“ ..... accumulating data indicate that low-dose CNI-based regimens would provide an interesting balance between efficacy and toxicity”</b>						
Pascual et al. [38]	???	???	???	???	???	???
Afzali et al. [45]	???	???	???	???	???	???
Ducloux et al. [46]	???	???	???	???	???	???
Weir et al. [47]	???	???	???	???	???	???
Dudley et al. [48] (Creeping Creatinine study)	73/70	>6 mo	MMF-Pred vs. CsA-MMF-Pred	No rejection	Stabilized or improved	21 mo
Suwelack et al. [49]	18/20	>12 mo	MMF-Pred vs. CNI-Pred	No rejection	Improved	12 mo
Frimat et al. [50] (Reference Study)	70/33	>12 mo	50%CsA-MMF-(Pred) vs. CsA-based	No rejection	Improved	>14 wks
					Improved	24 mo

# ZEUS: evaluating everolimus with CNI elimination vs a standard CNI regimen



<sup>a</sup>For the 1st 4.5 months post-transplant, all patients treated with EC-MPS, CsA and corticosteroids. Corticosteroids administered throughout the study according to local practice at a minimum dose of 5 mg CNI, calcineurin inhibitor; EC-MPS, enteric-coated mycophenolate sodium; CsA, cyclosporin

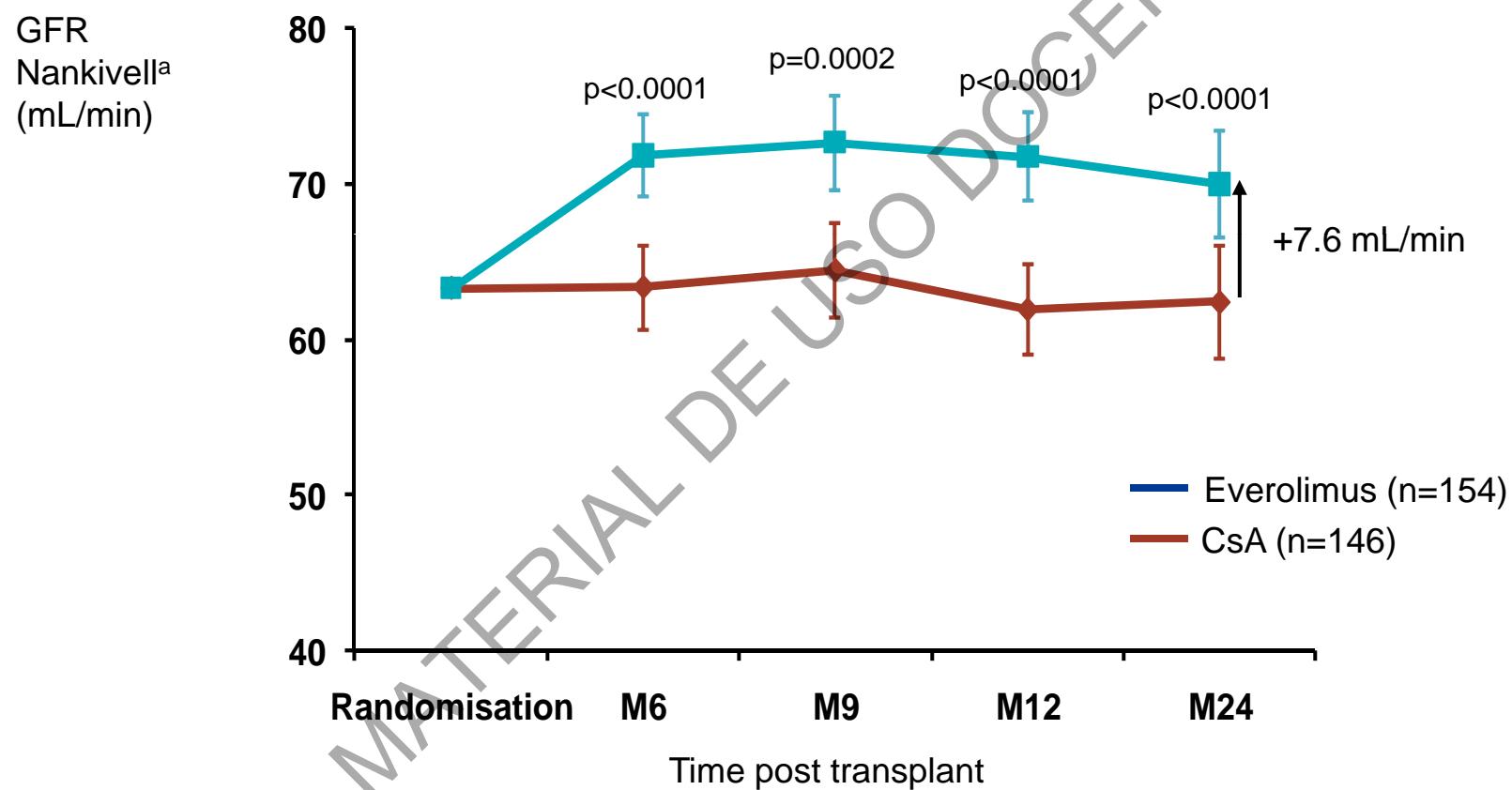
# ZEUS: incidence of BPAR is similar for everolimus and a standard CNI regimen



BPAR, biopsy-proven acute rejection;  
CNI, calcineurin inhibitor; CsA, cyclosporin

Budde K et al. Lancet 2011;377:837-47  
Arns W et al. Oral presentation at ASN 2010

# ZEUS: early improvement in renal function after early CNI elimination is maintained over 24 months



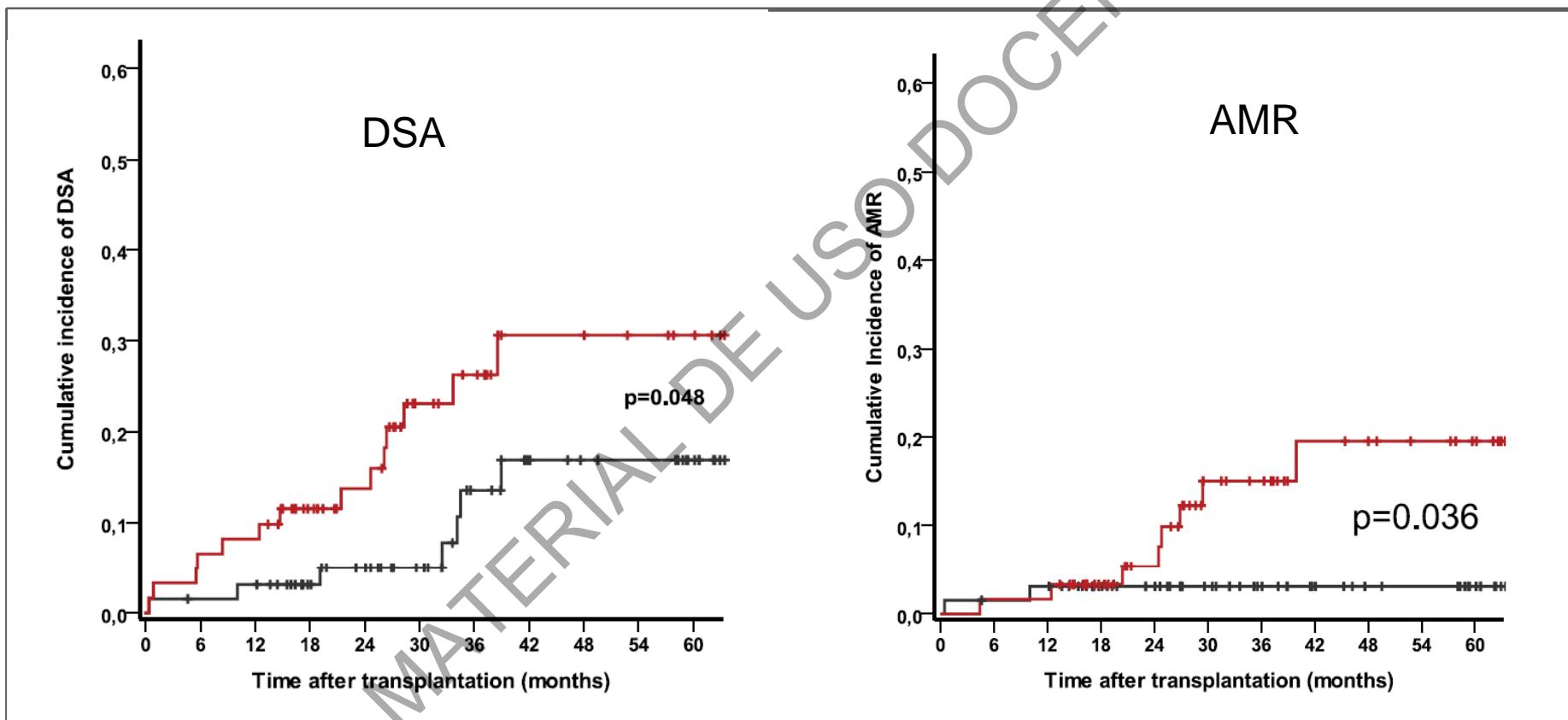
<sup>a</sup>Adjusted values (means from analysis of covariance model, 95% CI)

GFR, glomerular filtration rate; CsA, cyclosporin;

M, month; CI, confidence interval

Arns W et al.  
Oral presentation at ASN 2010

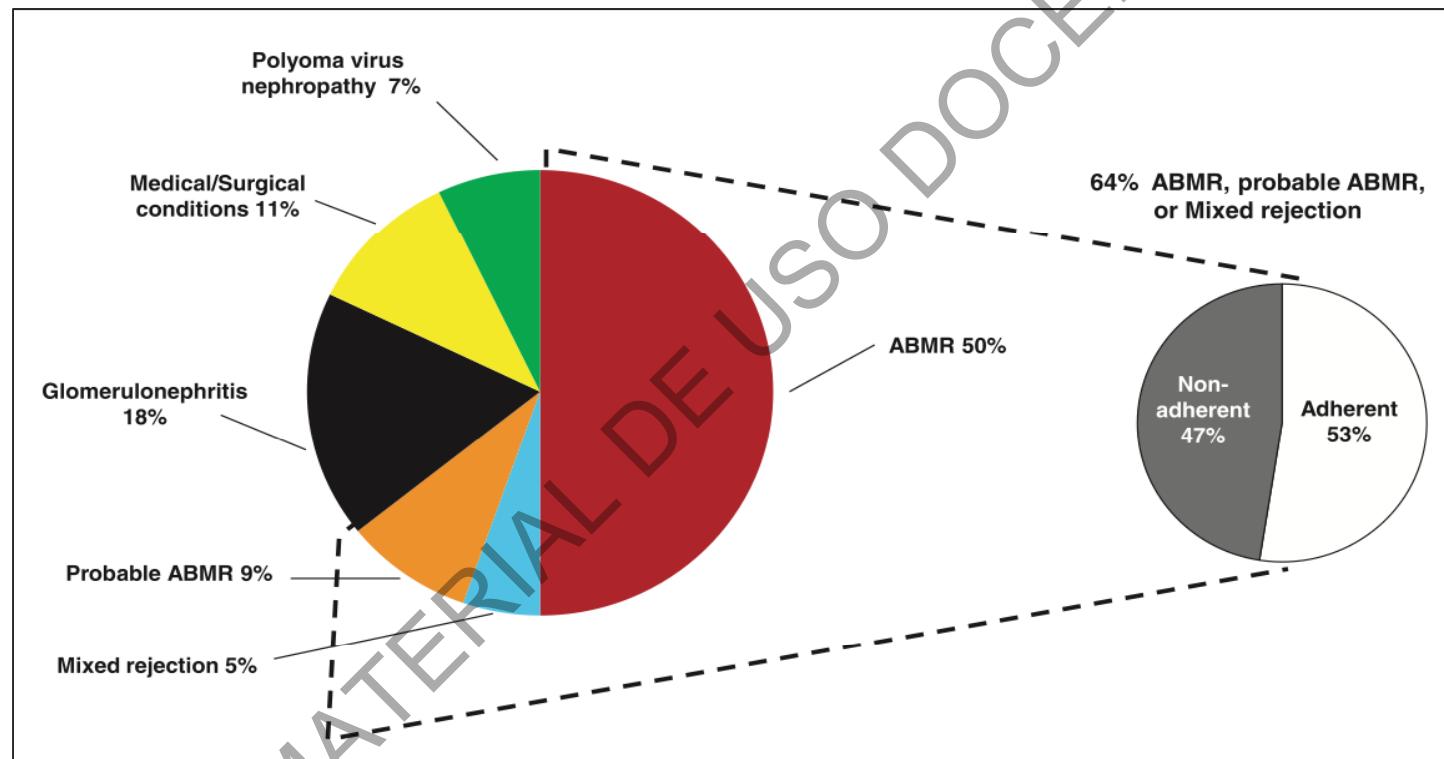
## ZEUS: Donor-specific HLA antibodies and AMR after conversion \*



\* Use of Everolimus in CNI free regimen is not approved by health authorities

Liefeldt et al. *Am J Transplant* 2012; 12: 1192–1198

# Understanding the Causes of Kidney Transplant Failure: The Dominant Role of Antibody-Mediated Rejection and Nonadherence



Sellarés J et al, Am J Transplant 2012, 12:388-399



## Review of combination therapy with mTOR inhibitors and tacrolimus minimization after transplantation

### Kidney transplantation:

9 prospective randomized studies (856 patients)

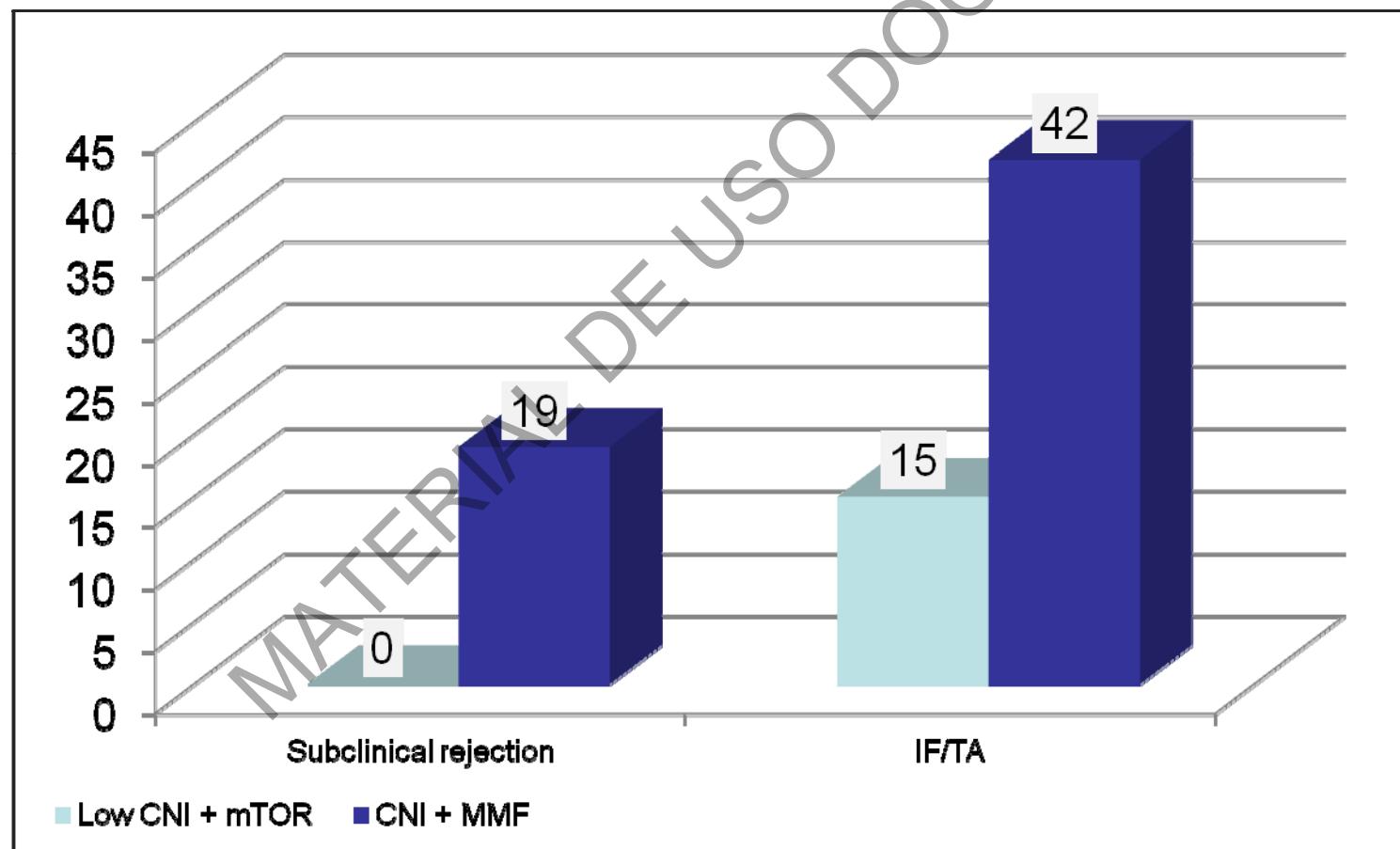
mTOR inhibitor + tacrolimus reduction

- Improvement of renal function
- Low rates of infection (BK, CMV, or EBV) and malignancy (0% to 7%)

Review of these studies suggests that immunosuppressive regimens including an mTOR inhibitor and TAC minimization therapy better preserve renal function versus standard-dose TAC, without significant changes in patient survival or graft rejection rates.

## Correlations with six-month protocol biopsy findings in pediatric transplant recipients on low- and regular-dose CNI regimens

79 pediatric recipients  
Protocol biopsy at 6months



# **Protocolos de inmunosupresión**

## **Hospital Clínic de Barcelona**

- A. Trasplante renal sin factores de riesgo inmunológicos o nefrológicos
  - Donante cadáver
  - Donante vivo
- B. Trasplante renal de alto riesgo inmunológico
- C. Trasplante renal con donante en asistolia
- D. Trasplante renal con donante con criterios expandidos o riesgo nefrológico

# Trasplante renal de cadáver sin factores de riesgo

Protocolo	Observaciones
<b>Metil-prednisolona</b> 500mg (D0), 125mg (D1), 0,5mg/kg/dia (D2) i reducción a 15mg/dia (M1), 10mg/dia (M2) i 5mg/dia (M3)	En pacientes con alergia a mTORi, obesos severos (IMC > 30), EPOC severos y pacientes con dislipemia severa pre- trasplante se utilizará MMF/MPS en vez de imTOR
<b>Prograf</b> 0.15mg/kg/dia 1ª dosis pre-Tx	Valorar la retirada progresiva de corticoides a medio plazo
<b>Certican</b> 1mg c/12hr Iniciar D0 o D1 niveles 3-5 ng/ml	

# Trasplante renal de vivo sin factores de riesgo

Protocolo	Observaciones
<b>Metil-prednisolona</b> 500mg (D0), 125mg (D1), 0,5mg/kg/dia (D2) i reducción a 15mg/dia (M1), 10mg/dia (M2) i 5mg/dia (M3)	En pacientes con alergia a mTORi, obesos severos (IMC > 30), EPOC severos y pacientes con dislipemia severa pre- trasplante se utilizará MMF/MPS en vez de imTOR
<b>Advagraf</b> 0.15mg/kg/dia 1ª dosis 3 días pre-Tx Niveles 6 – 9 ng/mL (1er mes)	Valorar la retirada progresiva de corticoides a medio plazo
<b>Certican</b> 1mg c/12hr Iniciar D0 o D1 niveles 3-5 ng/ml	

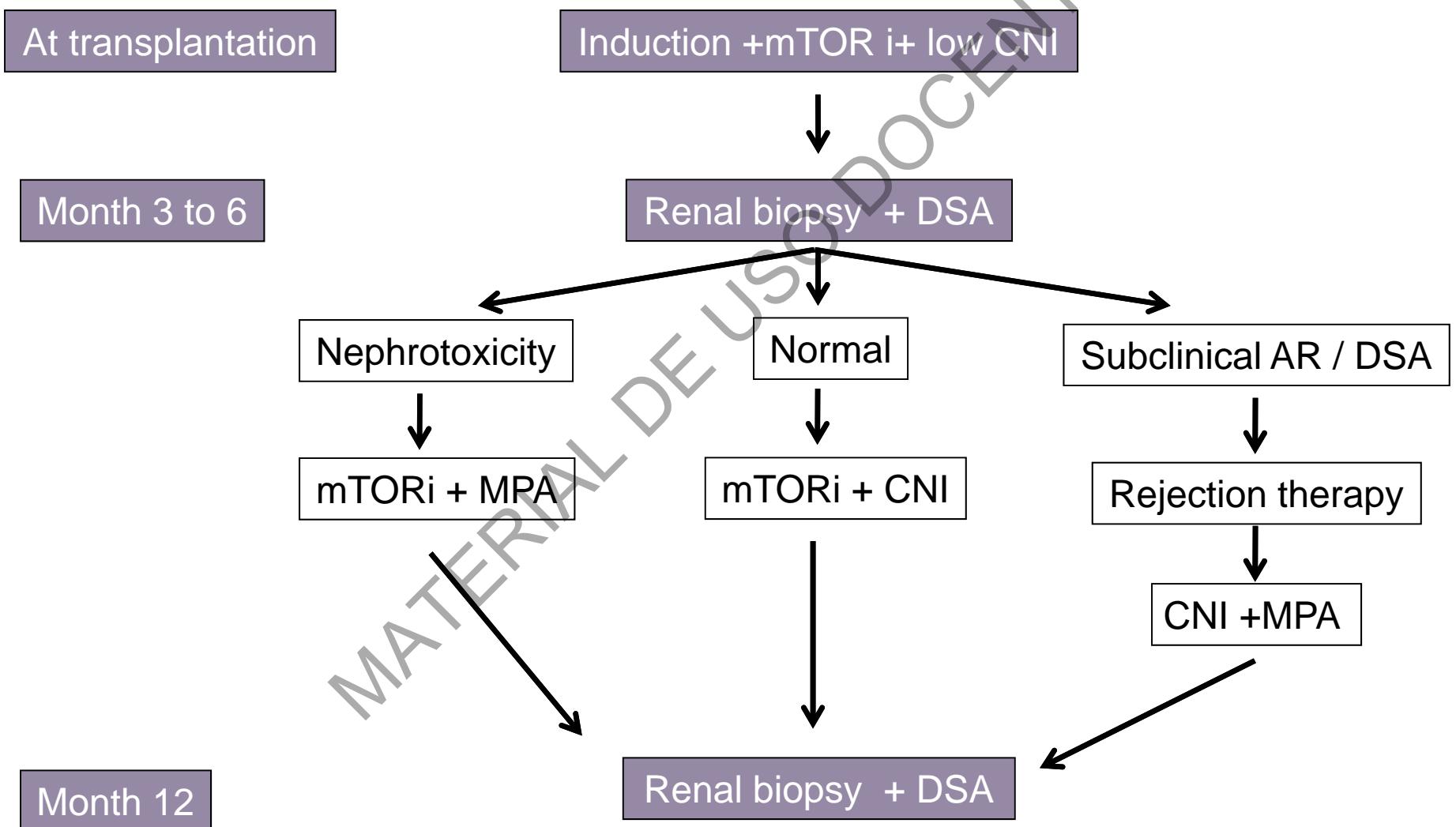
# Trasplante renal con donante ECD

Protocolo	Observaciones
<b>Simulect</b> 20mg D0 + 20mg D4	En pacientes con alergia a mTORi, obesos severos (IMC > 30), EPOC severos y pacientes con dislipemia severa pre-trasplante se utilizará MMF/MPS en vez de imTOR
<b>Metil-prednisolona</b> 500mg (D0), 125mg (D1), 0,5mg/kg/dia (D2) i reducción a 15mg/dia (M1), 10mg/dia (M2) i 5mg/dia (M3)	Valorar la retirada progresiva de corticoides a medio plazo
<b>Advagraf</b> 0.10 mg/kg/dia 1ª dosis pre-Tx Niveles 4 – 8 ng/ml (1er mes)	Después del primer año valorar la retirada progresiva de tacrolimus: <b>monoterapia con Certican</b> , con niveles entre 5-8 ng/ml
<b>Certican</b> 1mg c/12hr Iniciar D0 o D1 niveles 3-5 ng/ml	

# Trasplante renal con donante en asistolia

Protocolo	Observaciones
<b>ATG Fresenius</b> 2,5mg/ Kg/ dia (5dosis)	En pacientes con alergia a mTORi, obesos severos (IMC > 30), EPOC severos y pacientes con dislipemia severa pre-trasplante se utilizará MMF/MPS en vez de imTOR
<b>Metil-prednisolona</b> 500mg (D0), 125mg (D1), 0,5mg/kg/dia (D2) i reducción a 15mg/dia (M1), 10mg/dia (M2) i 5mg/dia (M3)	<b>Valorar la retirada progresiva de corticoides a medio plazo</b>
<b>Advagraf</b> 0.10 mg/kg/dia 1ª dosis pre-Tx Niveles 4 – 8 ng/ml (1er mes)	
<b>Rapamune</b> 2mg c/24hr Iniciar entre D3 y D5 niveles 3-5 ng/ml	

# Immunosuppression tailoring based on histological and immunological monitoring





Thank you very much