Sociedad Peruana de Nefrologia

Everolimus con bajas dosis de ICN en pacientes de novo.

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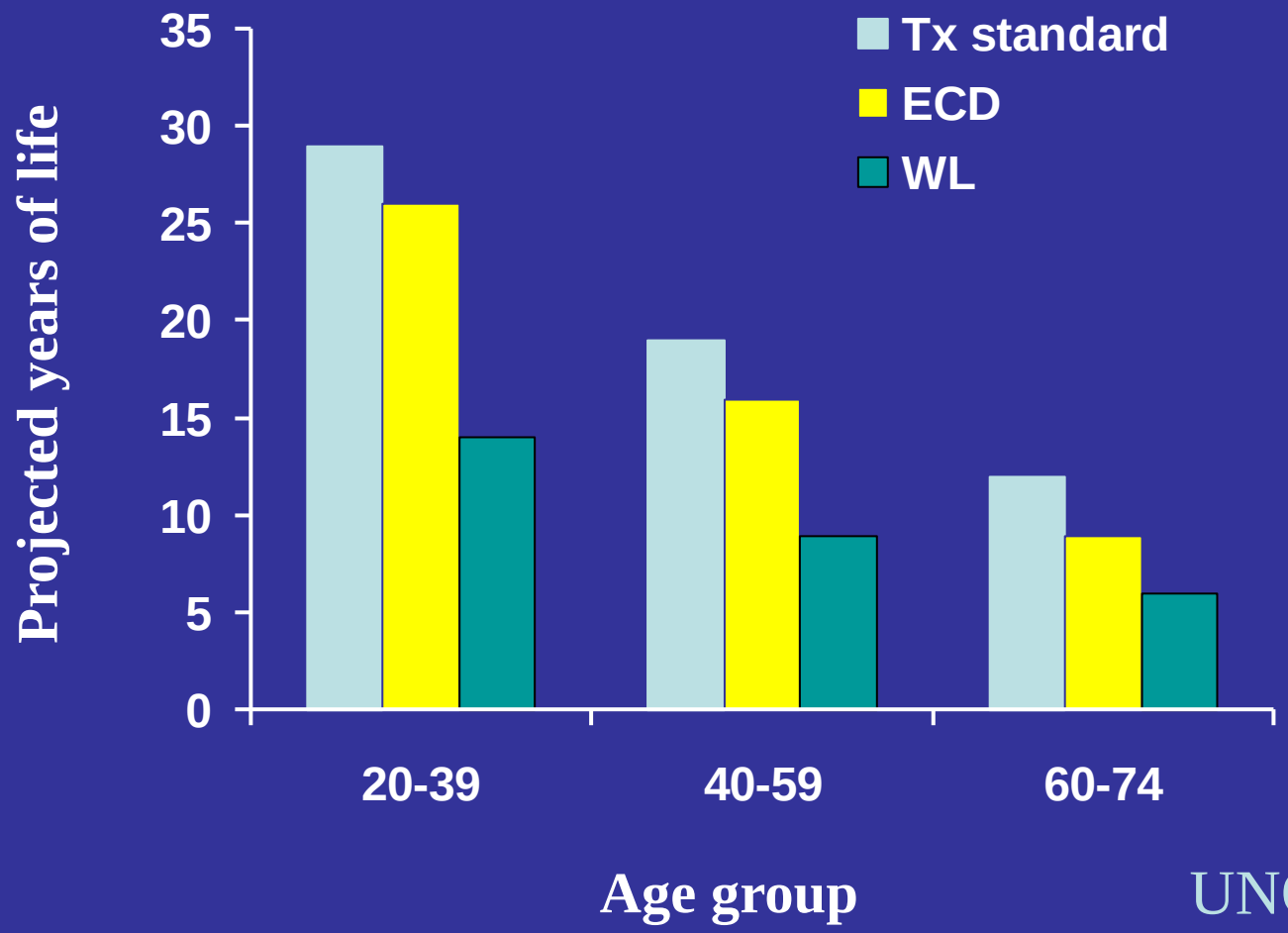
Lima 4 de Noveimbre de 2014

Vida media proyectada: Tx renal standard vs Tx con donantes “expandidos”vs lista de espera



UNOS 2002

1954

1959

1961 — Steroids

1963

1967 — Polyclonal lymphocyte-specific sera

Co-trimoxazole

1983 — Muromonab (CD3 specific)

1986

Ganciclovir

1993

1997 — Mycophenolate

Anti-fungals
Anti- malarials
Anti-mycobacterials
Anti-virals
Antibiotics

1998 — Basiliximab (CD25 specific)

1999 — Alemtuzumab (CD52 specific)

2001

Valganciclovir

2003

2007 — Eculizumab (C5 specific)

2011

Azathioprine

CDC Xm

HLA

Cyclosporine

Protocol Bx

Tacrolimus

Banff

Ritixumab (CD20 specific)

Daclizumab (IL-2-RA)

Sirolimus

Bortezomib (proteasome inh.)

Luminex

Belatacept

Mouse

Dog

Pig

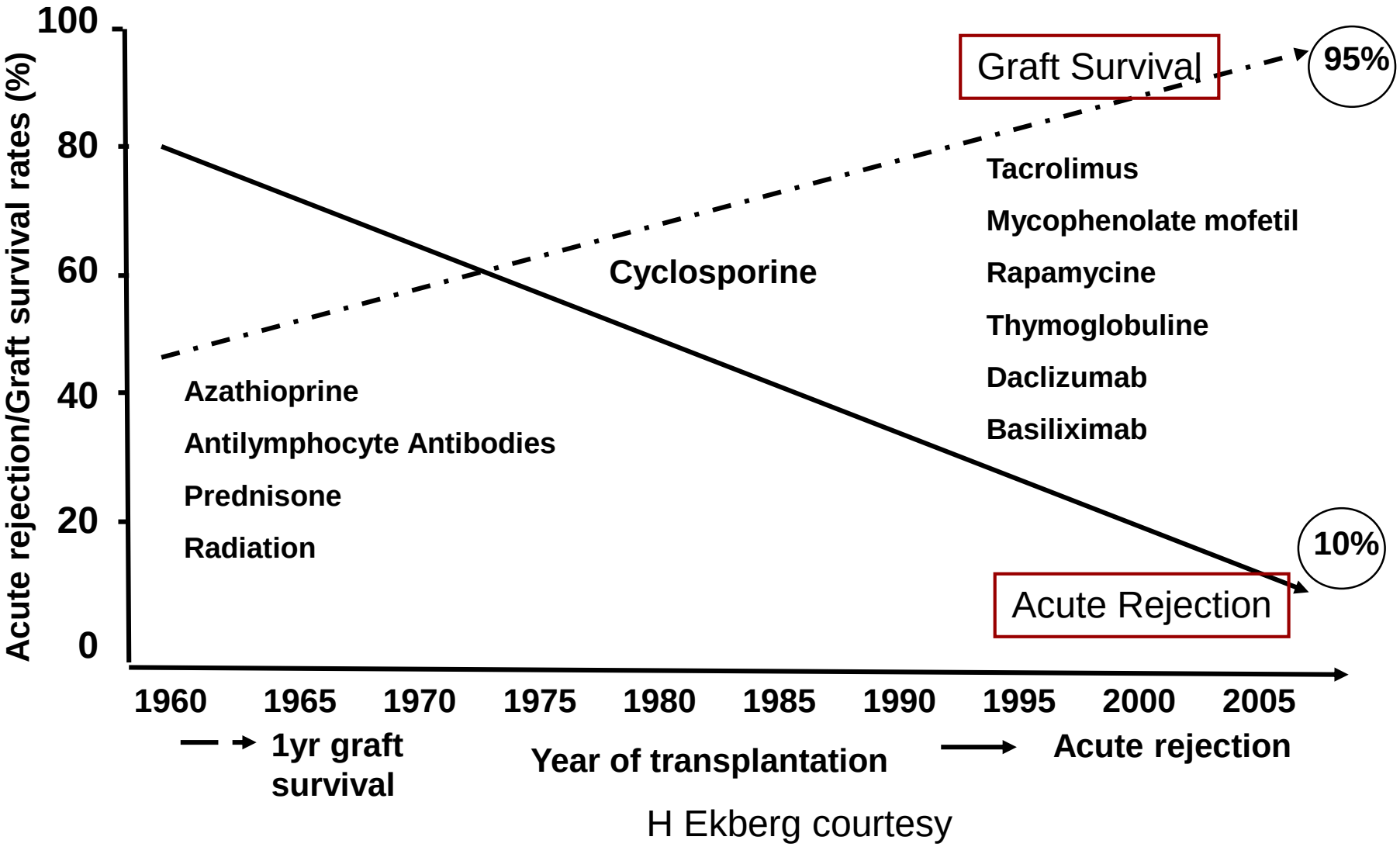
Monkey

Man

Individualised Therapy

Tolerance

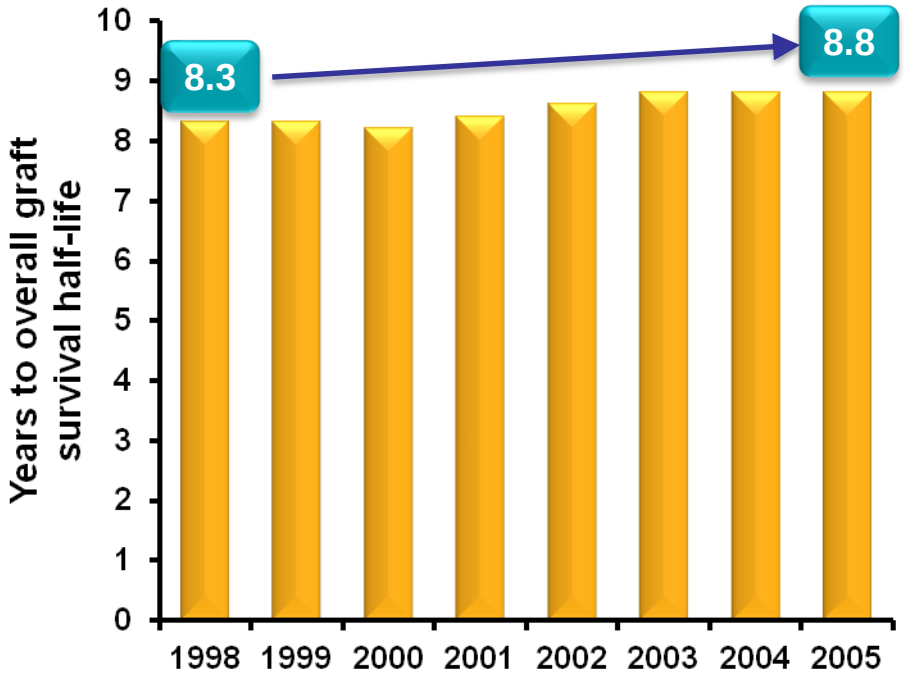
Improvements in acute rejection and graft survival are associated with more efficient immunosuppression



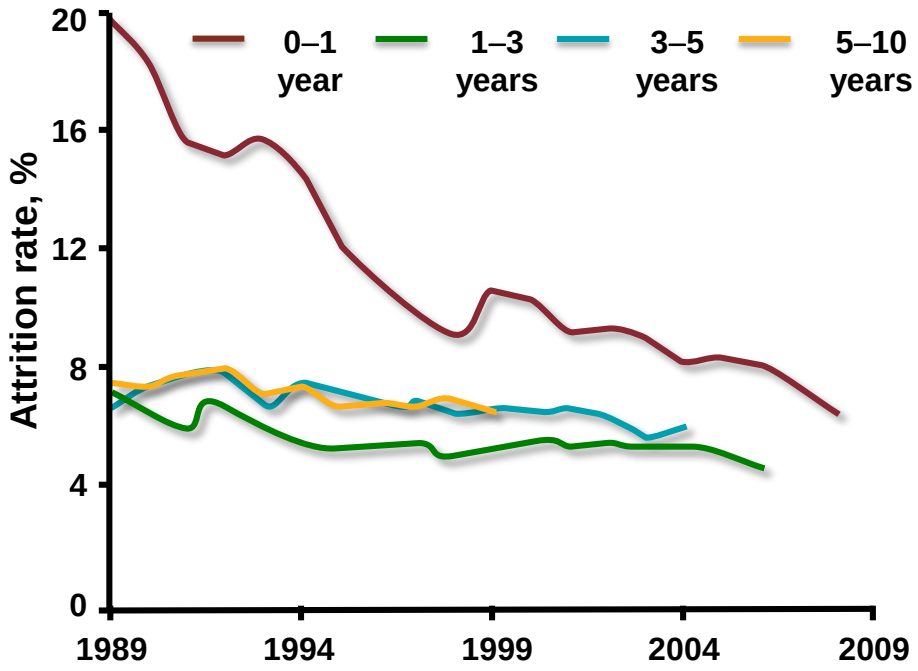
H Ekberg courtesy

… the improvement in long-term renal allograft survival was modest

Kaplan–Meier estimates of cumulative graft half-lives by transplant year (forecasted)



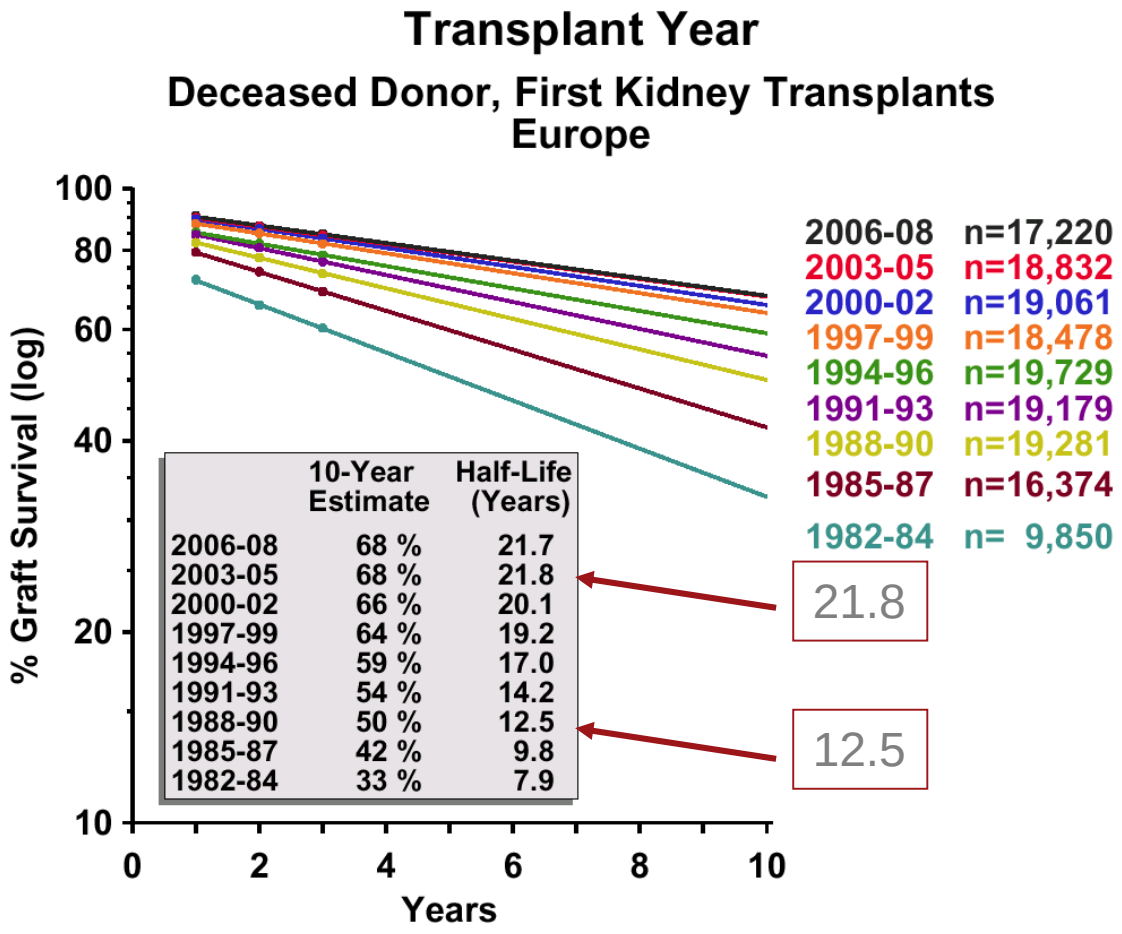
Cumulative graft failure yearly attrition rates of first kidney transplant from deceased SCD donor in USA (n=120,675)



SCD, standard criteria donor.

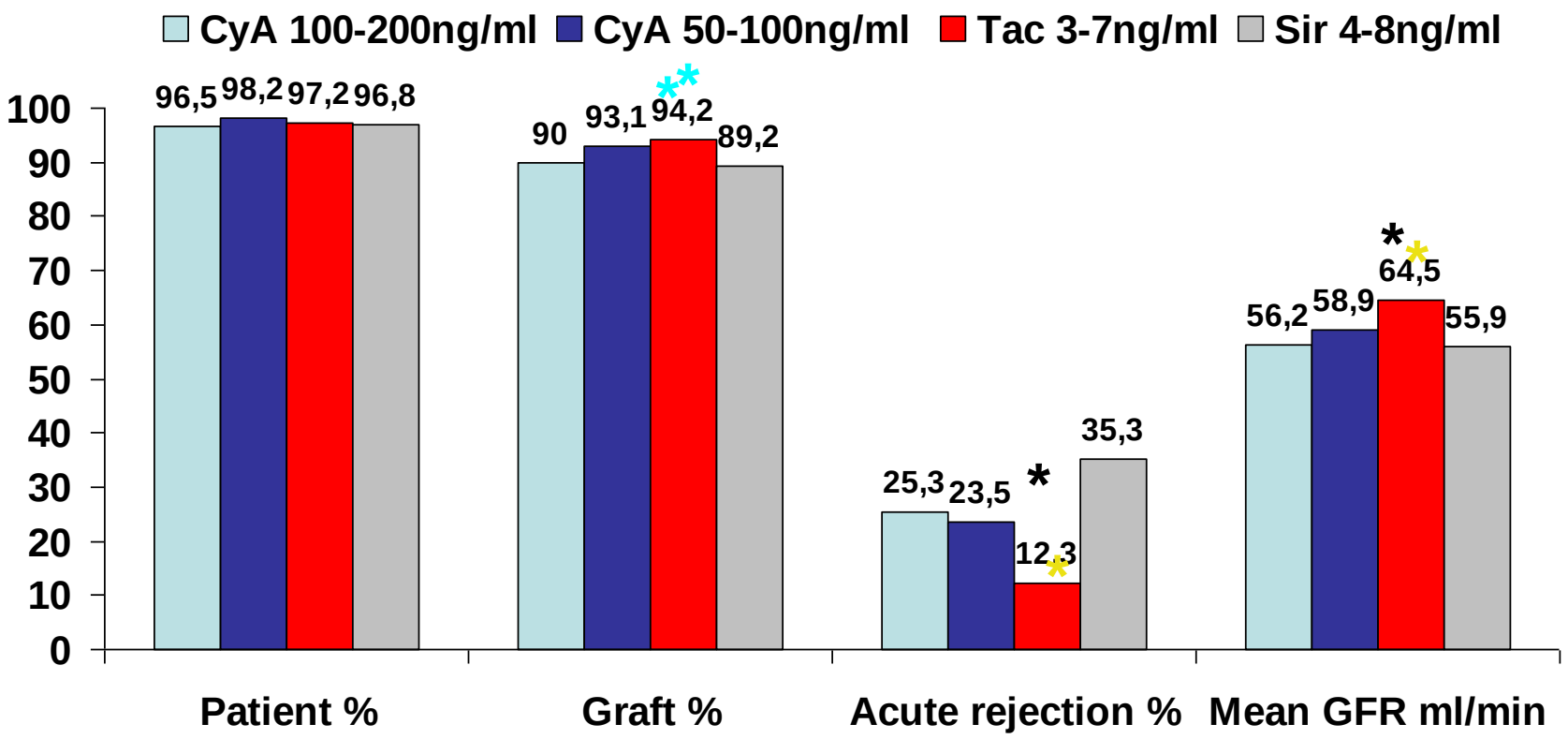
Lamb KE, et al. *Am J Transplant.* 2011;11:450–462.

Long-term Graft Survival Improvements Half-life (years): Europe



SYMPHONY global 4-arm study – 1 year

CyA (arm 1) versus daclizumab with CyA low-dose (2) or Tac low-dose (3) or Sir low-dose (4) with MMF and steroids N=1645

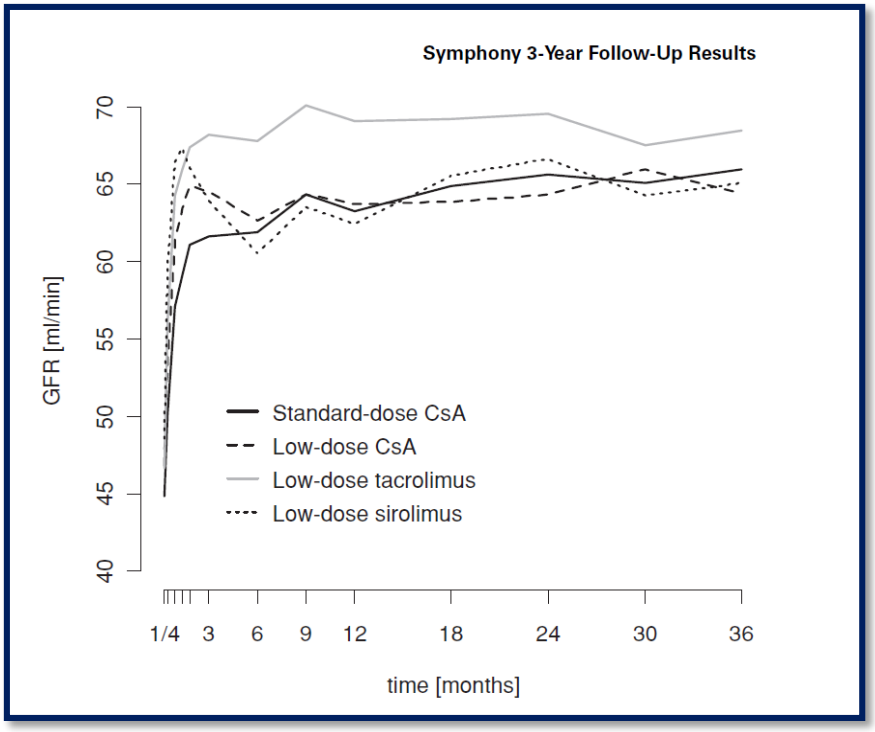


*p<0.05 vs. 1 & 4; *p<0.01 vs. 1, 3 & 4

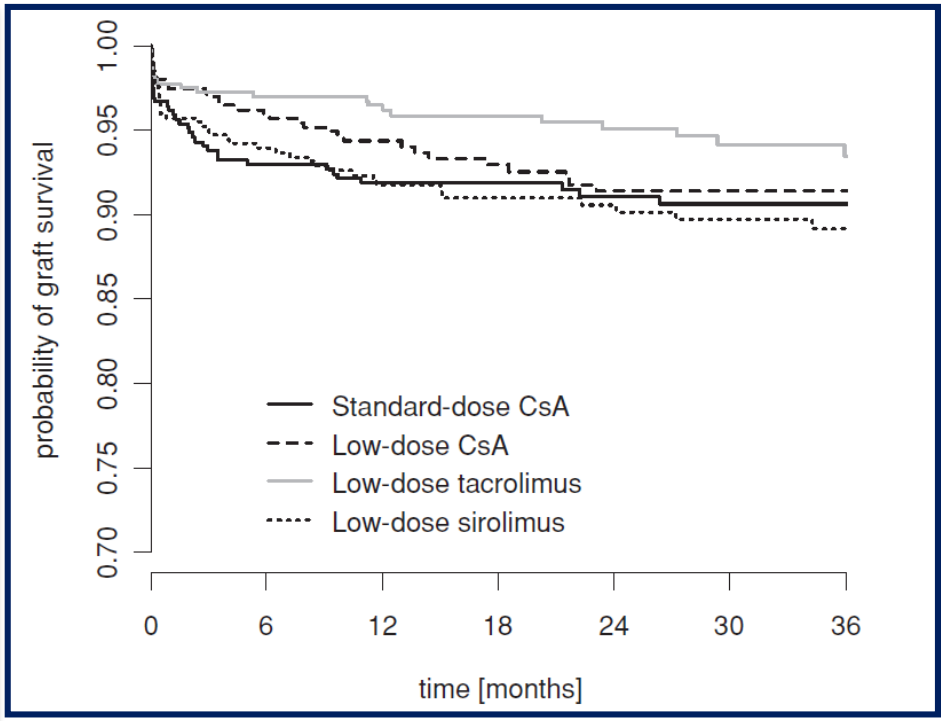
Ekberg NEJM 2007

Symphony: 3 años

GFR estimado C-G



Supervivencia injerto



AJT 2009; 9:1876

Adverse events at 12 months post-transplantation
Estudio Symphony

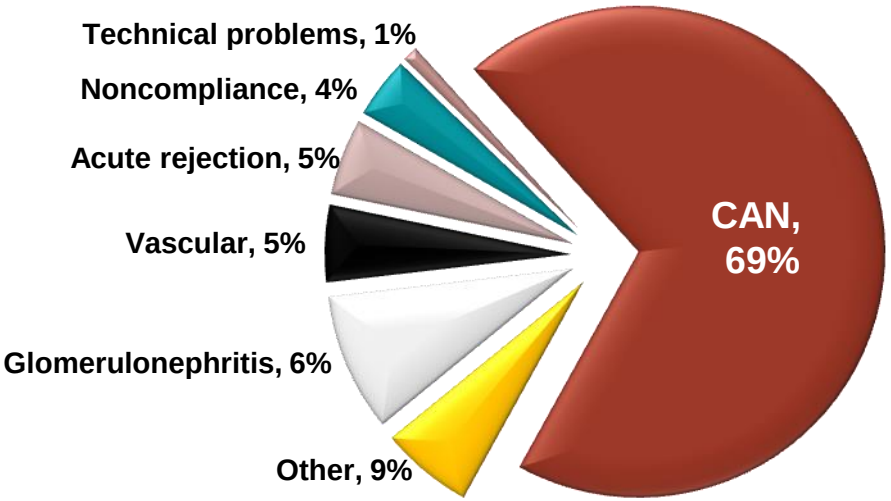
	CMV infections	Lympho-cele	Delayed wound healing	Diarrhoea	Diabetes mellitus	Malig-nancy
2 g CellCept + standard-dose CsA	14.3%	6.3%	10.8%	15.6%	6.0%	1.3%
2 g CellCept + low-dose CsA	11.0%	5.6%	11.0%	13.0%	4.2%	1.0%
2 g CellCept + low-dose Tac	9.7%	4.0%	9.4%	25.3%	8.4%	2.0%
2 g CellCept + low-dose Srl	6.1%	11.6%	16.6%	19.5%	6.6%	2.4%
p value between groups	0.003	< 0.001	0.006	< 0.001	0.02	n.a.

n.a. = not assessed

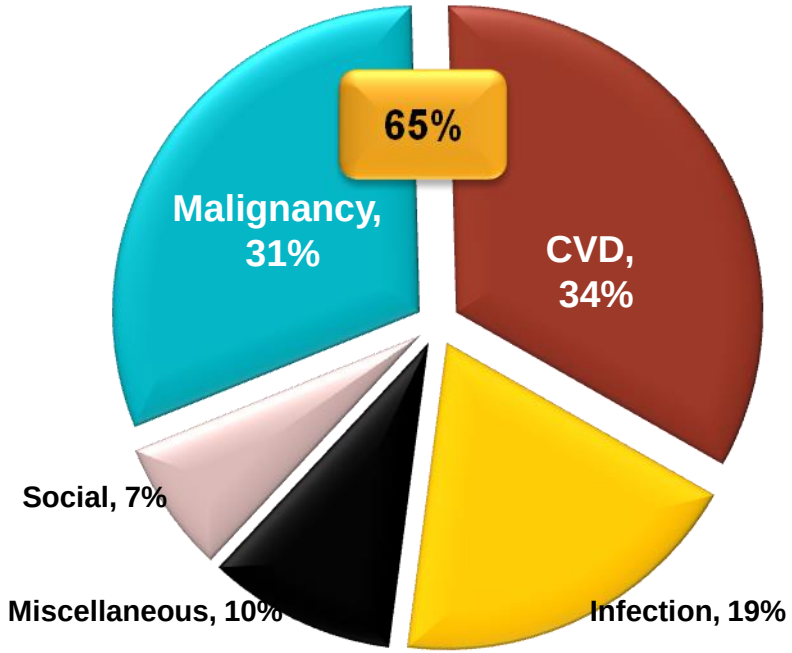
CAN, CVD and malignancy are the leading causes of graft failure and death with a functioning graft

ANZDATA registry data 2007–2011[1]

Causes of kidney graft failure[a]



Causes of death with functioning graft[b]



[a]Data from 2007–2011; n=1071 patients in Australia; [b]Data from 2007–2011; n=852 patients in Australia. CAN, chronic allograft nephropathy; CVD, cardiovascular disease; IFTA, interstitial fibrosis and tubular atrophy. ANZDATA registry 2012 report. Available at: http://www.anzdata.org.au/anzdata/AnzdataReport/35thReport/2012c08_transplants_v1.pdf.

Forum Renal: 2600 pacientes (2000-2002, España)
Graft loss during 60 months

	< 40	40 - 60	> 60	total	
Vascular/Thrombosis	22	33	18	**73**	
Exitus (graft function)	**9**	**73**	**75**	**157**	**30%**
Acute Rejection	20	32	19	**71**	
CAN	**38**	**48**	**42**	**128**	**23%**
Non primary fuction	2	10	12	**24**	
***de novo* GN**	2	0	1	**3**	
Recurrent GN	7	4	1	**12**	
Others*	24	39	32	**32**	
Total graft loss	**124**	**239**	**200**	**563**	

•*Included: surgical, infecction,*
• *lost follow-up*

Acute rejection 12 m (14.8%) Morales et al, NDT 2012

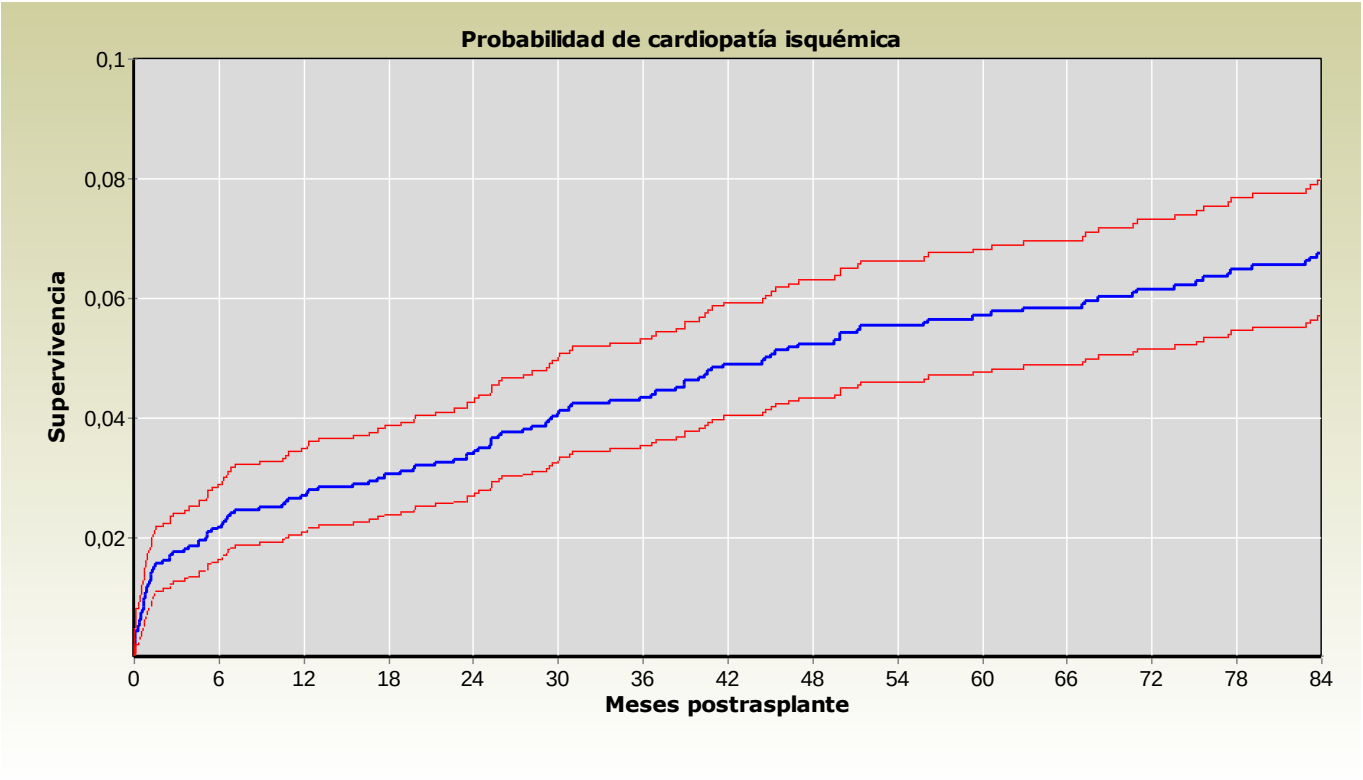
Forum Renal (2000-2002)
Causes of death during 5 years

	n=2592	1er year	2º year	3º year	4º year	5º year
CDV disease*		32 (36%)	11 (37%)	13 (39%)	7 (24%)	14 (31%)
Infection		30 (33.7%)	4 (13.3%)	2 (6,1%)	5 (16,6%)	11(24.4%)
Others		15 (16.9%)	3 (10%)	3 (9,1%)	8 (26.6,1%)	9(20%)
Neoplasias		5 (5.6%)	8 (26.7%)	7 (21.2%)	3 (10%)	6 (13.3%)
Unkwon		4 (4.4%)	4 (13.3%)	6 (18.2%)	6 (20%)	4(8.8%)
Liver Disease		2 (2.2%)	0	2 (6.1)	1 (3,3%)	1(2.2%)
Accidental		1 (1.1%)	0	0	0	0
Total	**227* (8.8%)**	**89**	**30**	**33**	**30**	**45**

Morales et al, NDT 2012

* *Included: isquemic cardiophaty, sudden death, other cardiac cause y CVAC*

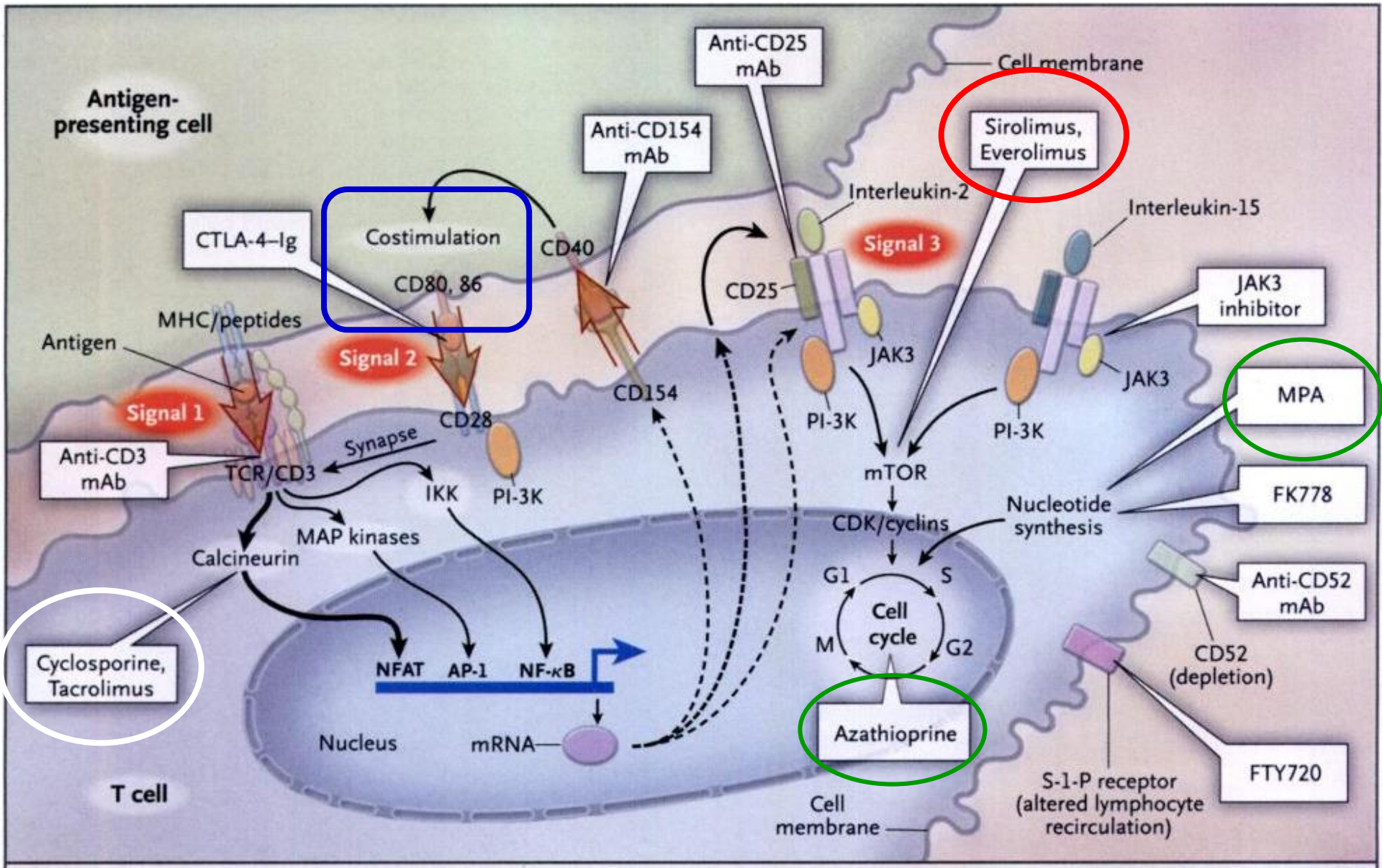
Probabilidad del primer episodio de enfermedad coronaria hasta los 7 años postrasplante = 6,8 %, IC del 95 % (5,7% al 8,0 %)



Enfermos con EC= 190
Enfermos con EC y datos basales = 130
Enfermos con EC a partir de 6 meses = 85

Marcen, ATC 2012
Forum Renal

Actuacion de los principales inmunosupresores en el modelo de las tres señales



Individual Immunosuppressive Drugs and Sites of Action in the Three-Signal Model.

Halloran.NEJM.2004

Classes of small molecule immunosuppressive drugs (ISDs)

- Immunophilin binding drugs
  - Cyclophilin binding
    - CNIs: cyclosporine; voclosporine (ISA247)
  - FKBP binding
    - CNI: tacrolimus
    - MToR inhibitors: sirolimus, everolimus
- Inhibitors of *de novo* purine or pyrimidine synthesis
  - IMPDH inhibitors: MMF, MPA
  - (DHODH inhibitors: leflunomide; brequinar)
- Antimetabolites
  - Azathioprine
- Sphingosine phosphate analogues
  - Fingolimod (FTY720)
- JAK3 inhibitors, eg CP690550
- PKC inhibitors, eg sotrastaurin (AEB071)

Adapted from P. F. Halloran.
Immunosuppressive drugs for kidney transplantation.
N.Engl.J.Med. 351 (26):2715-2729, 2004.

Examples of protein based ISDs in use or in development for transplantation

- Depleting
  - Polyclonal anti-thymocyte globulin
  - Anti CD52 (alemtuzumab, campath-1H)
    - Limited availability by Genzyme (Sanofi) for kidney transplantation
- Non depleting/partially depleting
  - Anti CD25 (IL-2Rα): daclizumab, basiliximab
  - CTLA4Ig (belatacept/LEA29Y) – **not going well commercially**
  - Anti CD2 (alefacept)
  - Anti LFA3 (efalizumab)
  - TCR101: anti-TCR murine monoclonal antibody IgM
  - Mukomonab-CD3
- Managing/preventing ABMR (see below)

Adapted from P. F. Halloran.Immunosuppressive drugs for kidney transplantation. *N.Engl.J.Med. 351 (26):2715-2729, 2004.*

Strategies to suppress anti-HLA or ABMR

- Conventional agents
- IVIG: low dose, high dose
- Plasmapheresis
- Immunoabsorption
- Rituximab
- Bortezomib
- Eculizumab
- Co-stimulation blockers
  - –?anti CD40, eg 4D11
  - –Belatacept

No sign of Phase 2–3 program in ABMR?

Slide provided by Dr Halloran

Inmunosupresion ideal en 2014

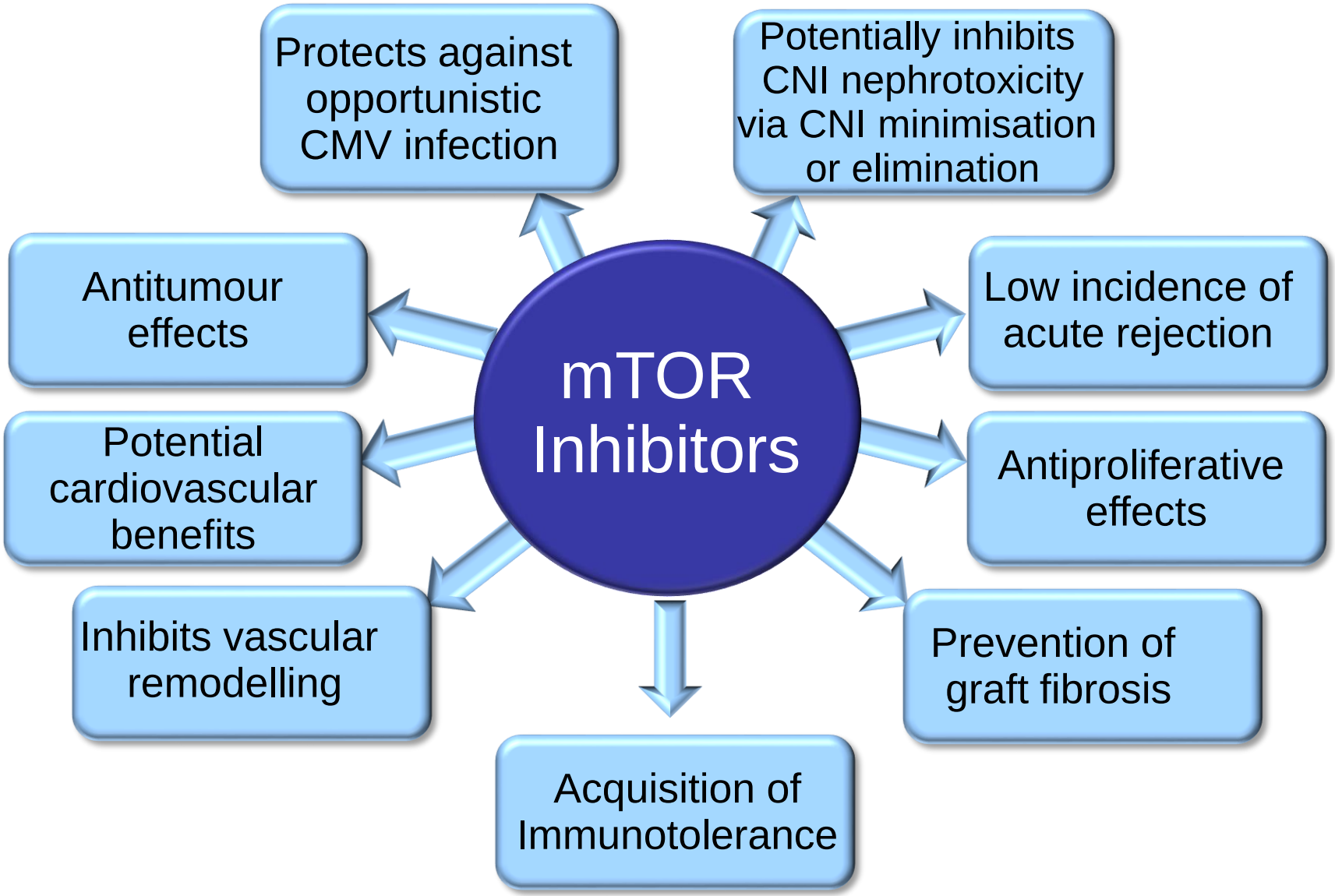
- Control del rechazo agudo y del RA Humoral
- Farmacos no nefrotoxicos
- Prevencion de la NCI/Rechazo cronico humoral
- Buen perfil cardiovascular
- Disminuir infecciones (CMV, BK…)
- Disminuir neoplasias

Need for new immunosuppressive strategies

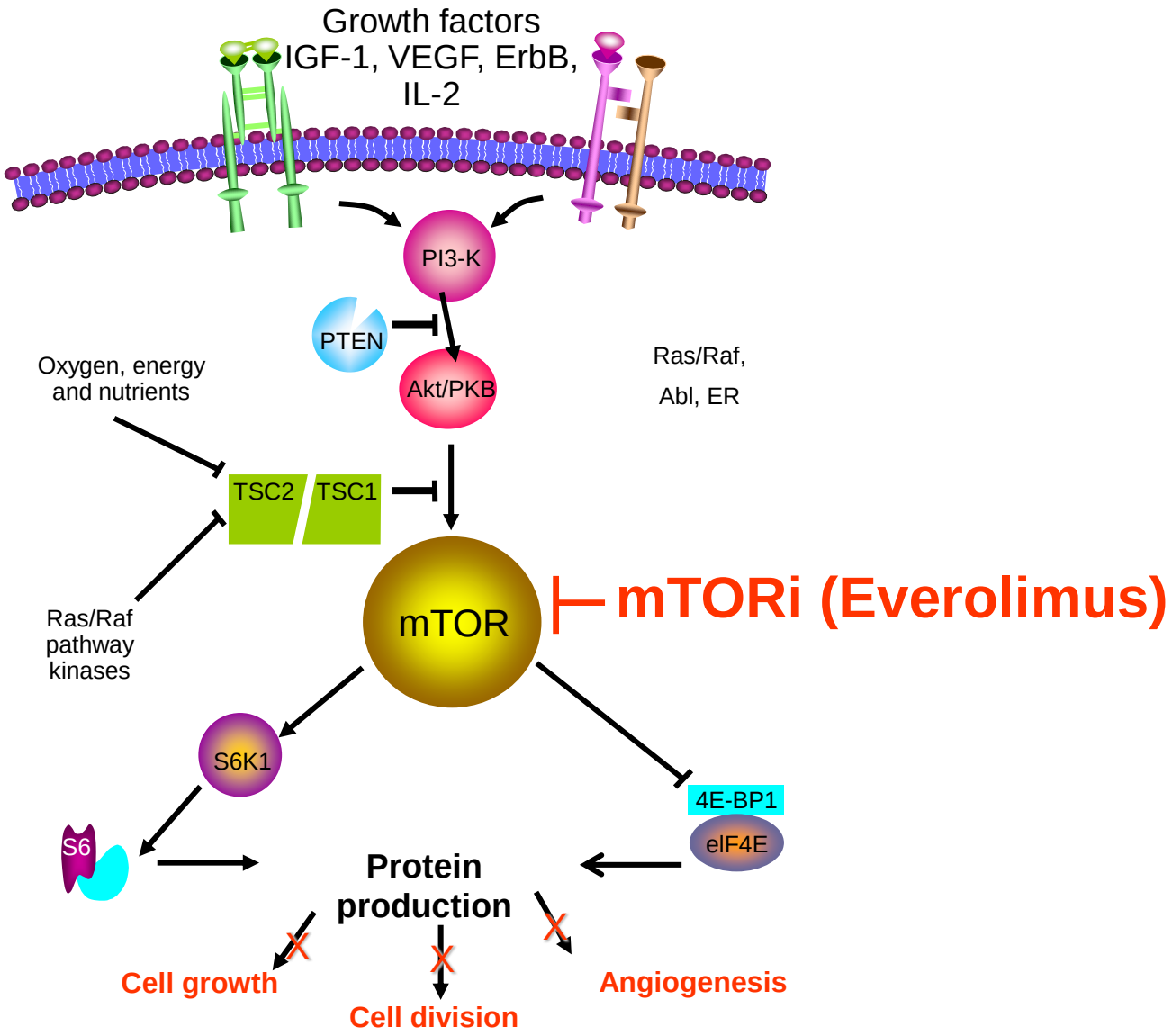
Improvement of immunosuppressive protocols with currently available drugs

- **new combinations**
- **time adapted protocols**
- **optimized MPA therapy**
- **CNI reduction/withdrawal**
- **safe steroid withdrawal**
- **new diagnostics**
- **individualization**
- **.....**

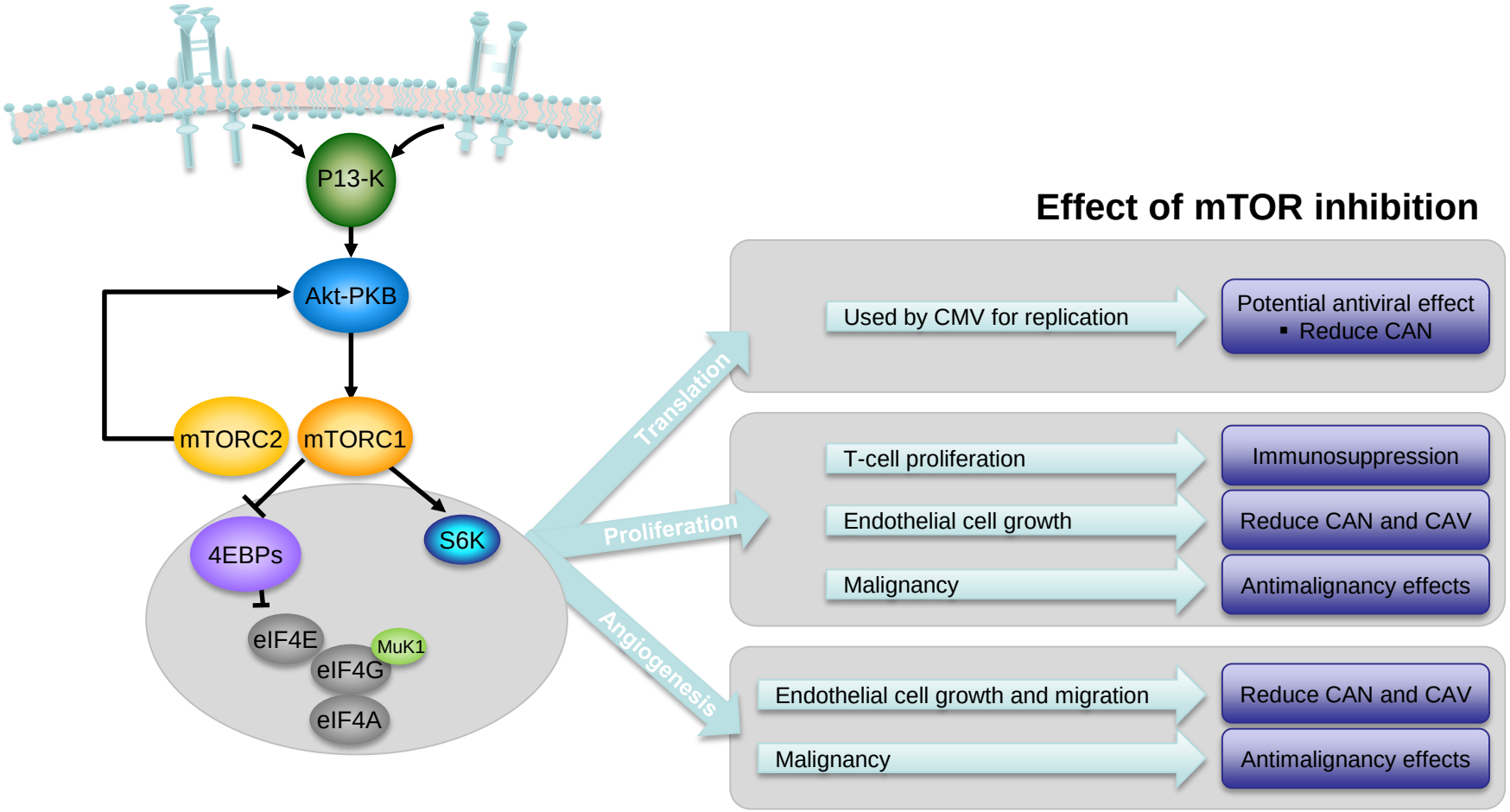
mTORi: a multifaceted approach to help improve long-term outcomes



Antiproliferative effects of mTORi: blocking the mTOR pathway

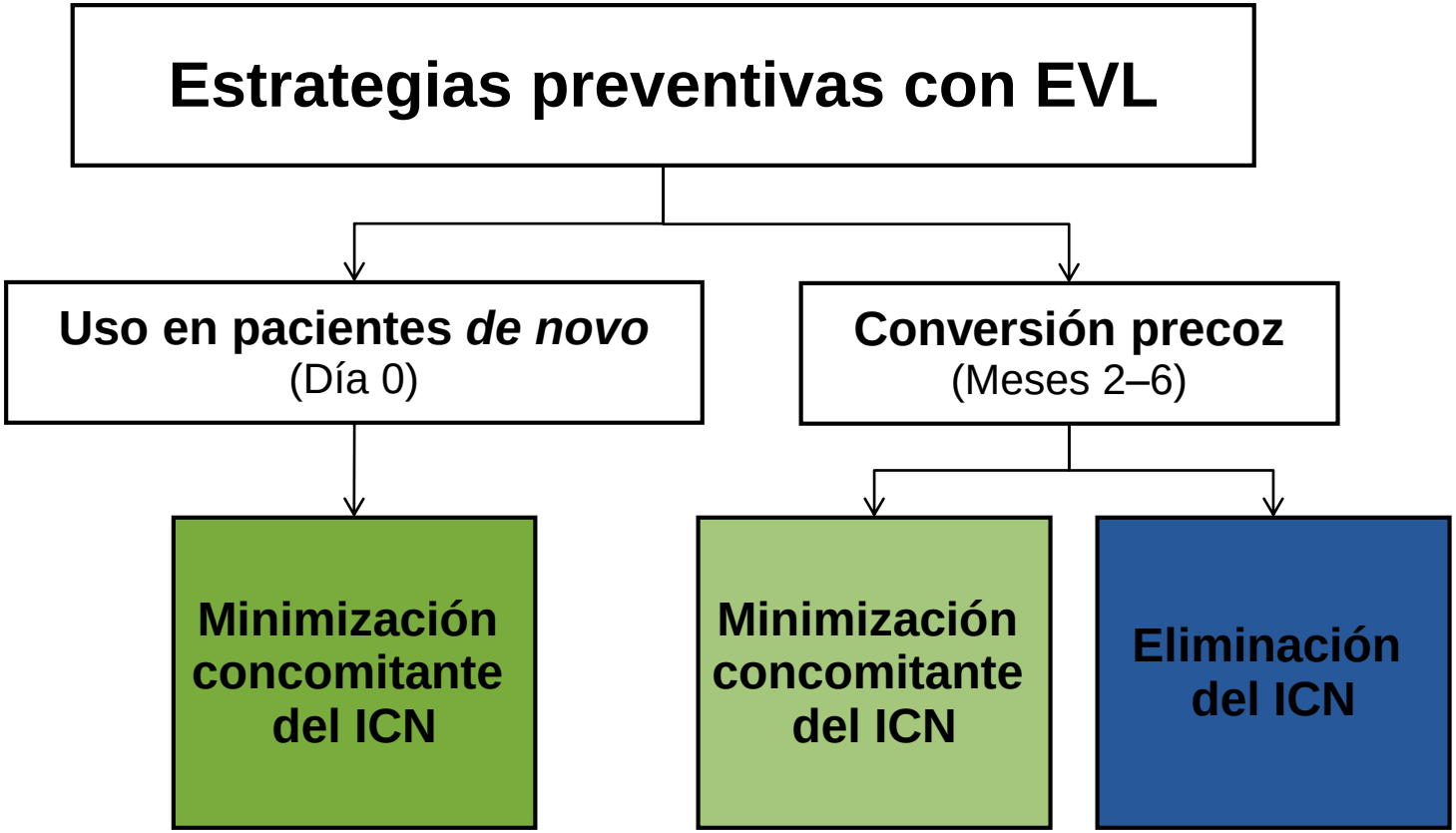


mTOR pathway and Inhibition: pleiotropic effects



CMV, cytomegalovirus; CAN, chronic allograft nephropathy; CAV, cardiac allograft vasculopathy.

CÓMO Y CUÁNDO PODEMOS EMPLEAR EVEROLIMUS?



ICN: Inhibidor de la calcineurina

The New England
Journal of Medicine

VOLUME 343 JULY 27, 2000 NUMBER 4

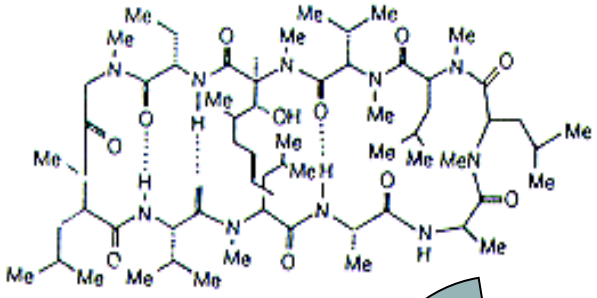
ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

A.M. JAMES SHAPIRO, M.B., B.S., JONATHAN R.T. LAKEY, PH.D., EDMOND A. RYAN, M.D., GREGORY S. KORBUTT, PH.D., ELLEN TOTH, M.D., GARTH L. WARNOCK, M.D., NORMAN M. KNETEMAN, M.D., AND RAY V. RAJOTTE, PH.D.

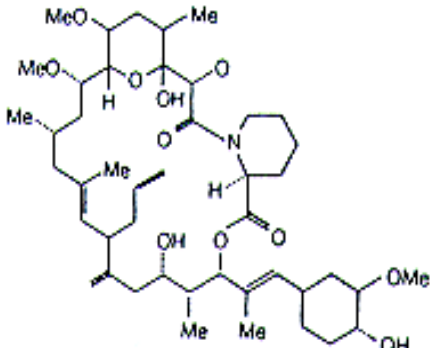
- N=7 patients with type 1 diabetes mellitus
- **Immunosuppressive protocol:**
  - Tac: 2 mg 3-6 ng/ml
  - SRL: 0.2 mg/Kg 0,1 mg/Kg/day 12-15 ng/ml (3 months) 7-10 ng/ml
  - Dac: 5 doses
  - No steroids
- **Islet infusion until insulin-independence**

12 months:
- No acute rejection
- Insuline-independence 100%
- Mouth ulcers
- No significant increase in lipids, creatinine

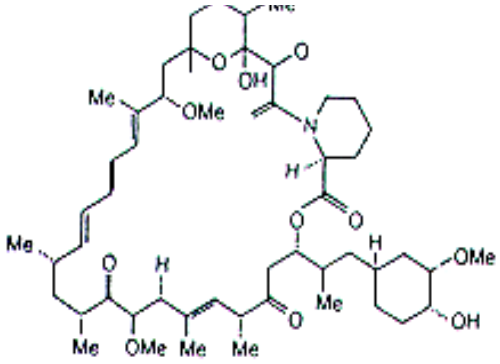
CsA



Tacrolimus



Sirolimus



CYCLOPHILIN

FKBP-12

CALCINEURIN INHIBITORS

mTOR INHIBITOR

Studies to support mTOR + CNI (CsA/FK)

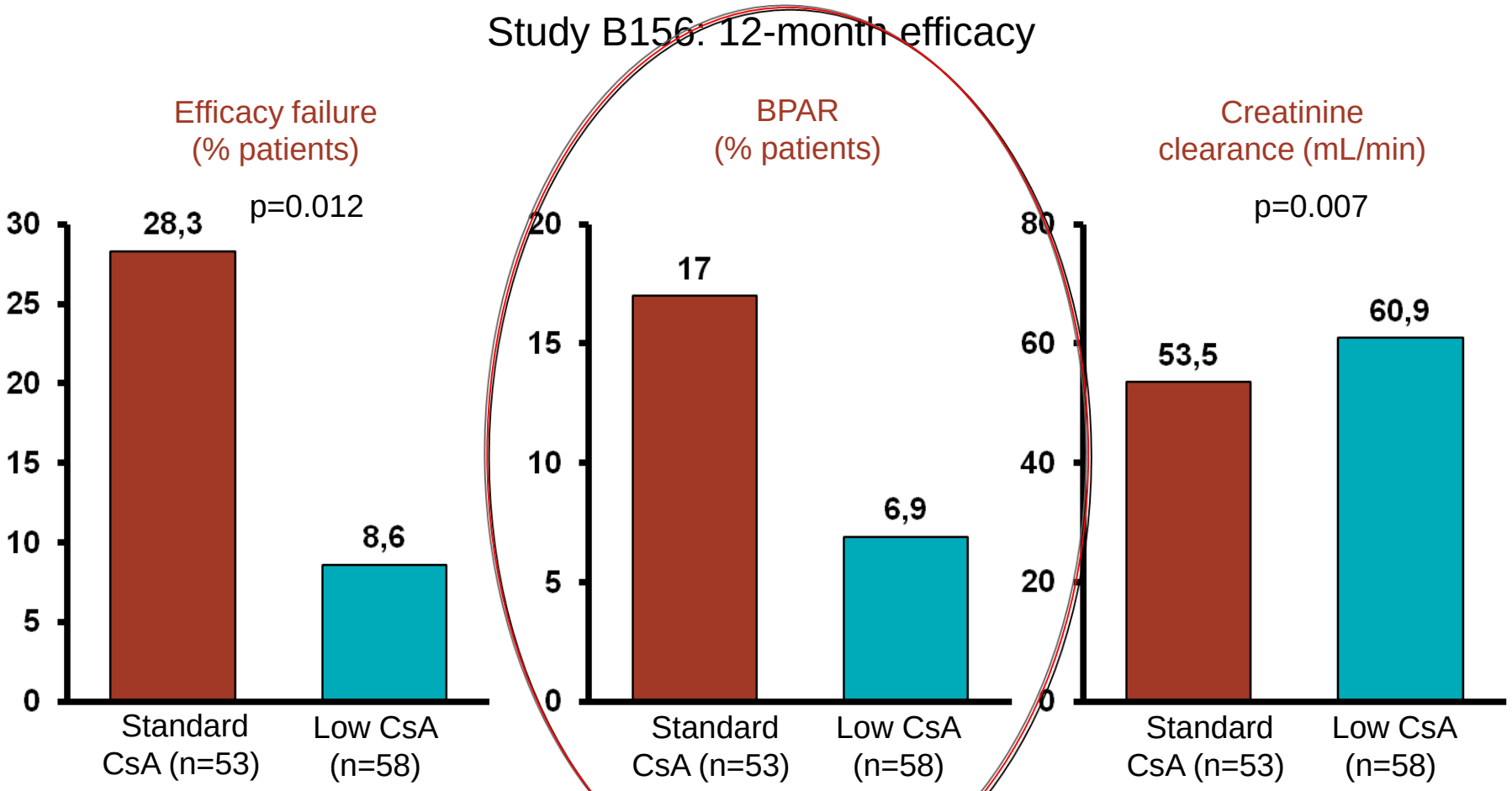
- Studies 301 – 302: SRL + CsA (FDA Approval)
- Study 310 (RMR) (EMEA Approval)
- Houston Experience (B.Kahan): SRL + Csa/FK
- Nebraska Experience (B.Stevens): SRL + CsA
- Mendez R – Prograf Study Group (Transplantation'05)
- TERRA Study (Astellas): SRL + FK (Vitko – Tx'06)
- Drexel University (Kumar et al. Transplant Immunology'08)
- OA.Gaber – Houston (Transplantation'10)
- Everolimus development: EVL + CsA

“Beneficios de los im-TORs en Trasplante Renal”

1. Prevención de la lesión inmunológica
2. Preservación de la función renal
3. Reducción en la incidencia de cáncer
4. Prevención de las infecciones víricas
5. Reducción riesgo cardio-vascular
6. Prolongación supervivencia injerto

Everolimus with CsA minimisation provides similar efficacy when compared with standard CsA

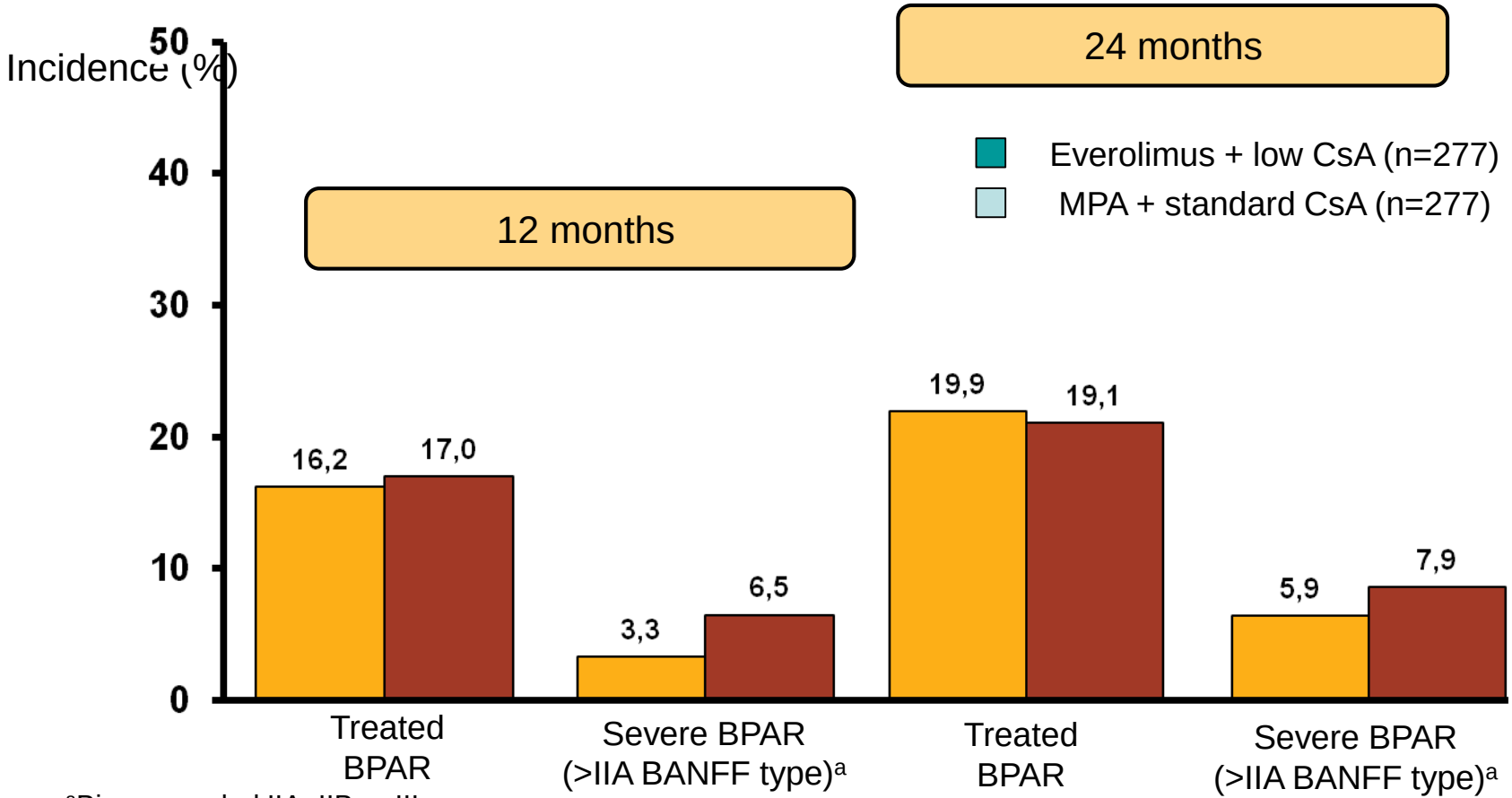
Study B156: 12-month efficacy



All patients received basiliximab, everolimus 3mg/day and steroids
Data from 1 year post-transplant
Efficacy failure = acute rejection, death, graft loss or loss to follow-up
CsA, cyclosporin; BPAR, biopsy-proven acute rejection

Nashan B *et al*. *Transplantation* 2004;78:1332–40

Low incidence of severe BPAR with everolimus + low CNI versus standard CNI

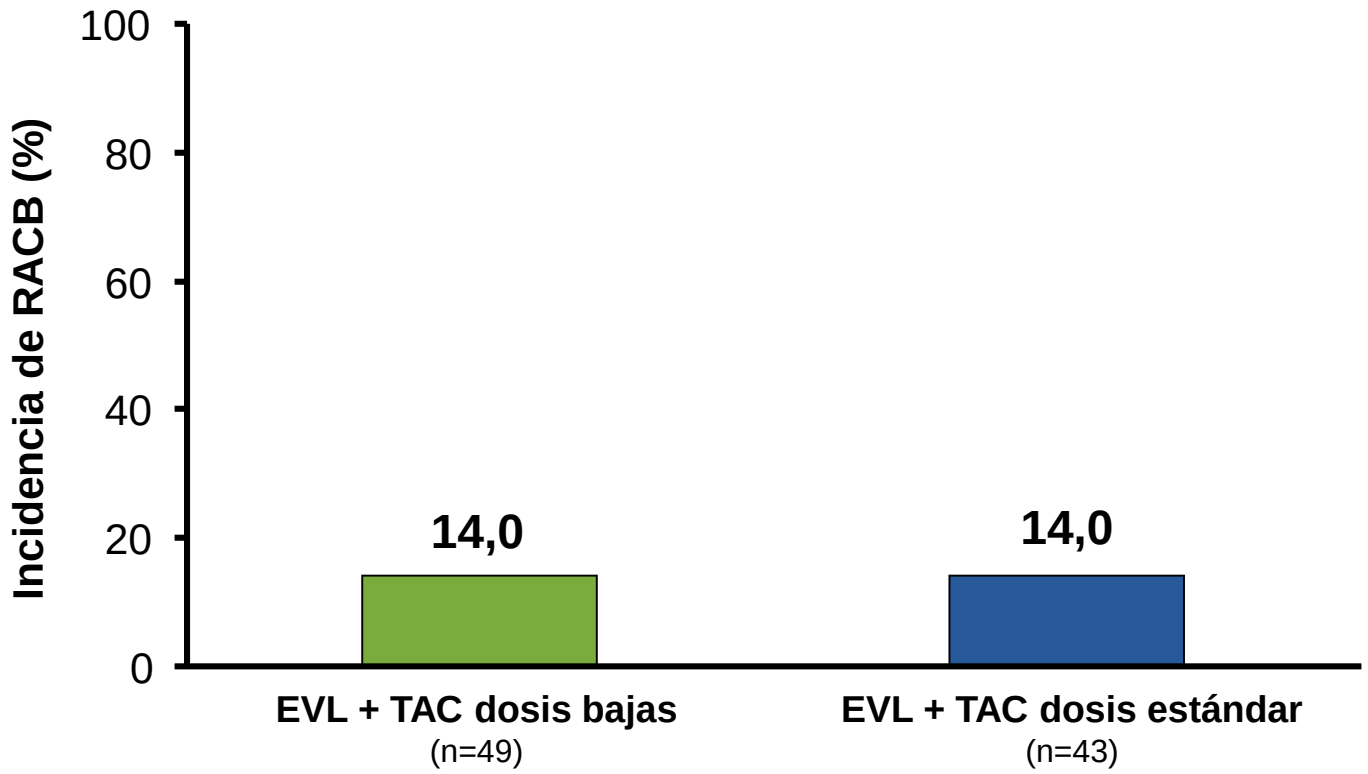


[a]Biopsy graded IIA, IIB or III
BPAR, biopsy-proven acute rejection;
CNI, calcineurin inhibitor;
CsA, cyclosporin;
MPA, mycophenolic acid

Tedesco Silva H Jr *et al*. *Am J Transplant* 2010;10:1401–13;
Tedesco-Silva H *et al*. ATC 2011 abstract 57

EVL PERMITE REDUCIR LAS DOSIS DE TACROLIMUS MANTENIENDO LA EFICACIA INMUNOSUPRESORA

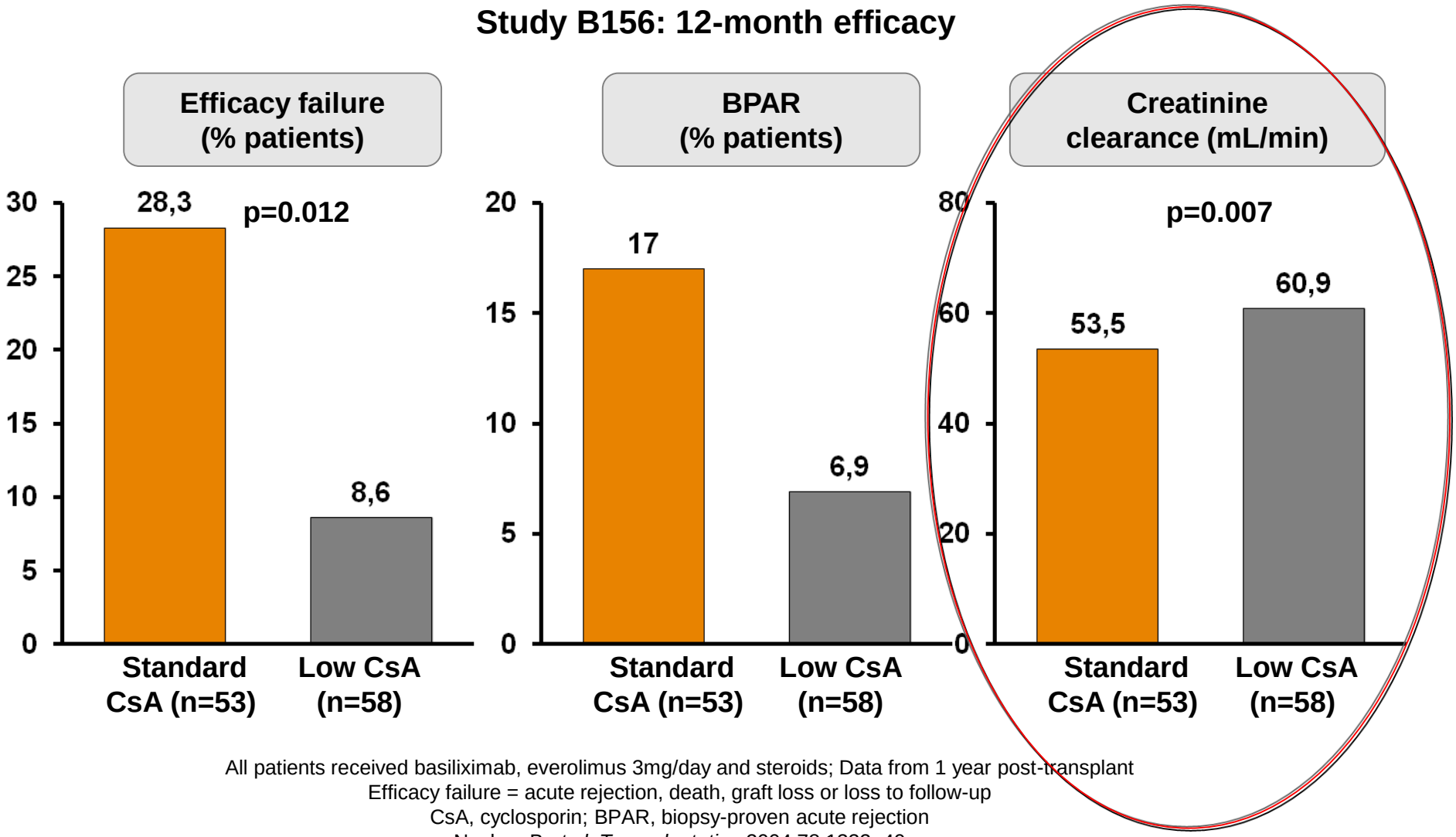
US09: Resultados a 6 meses



RACB: Rechazo agudo comprobado por biopsia

Chan L *et al*. *Transplantation* 2008;85:821–6

Everolimus with CsA minimisation provides similar efficacy when compared with standard CsA



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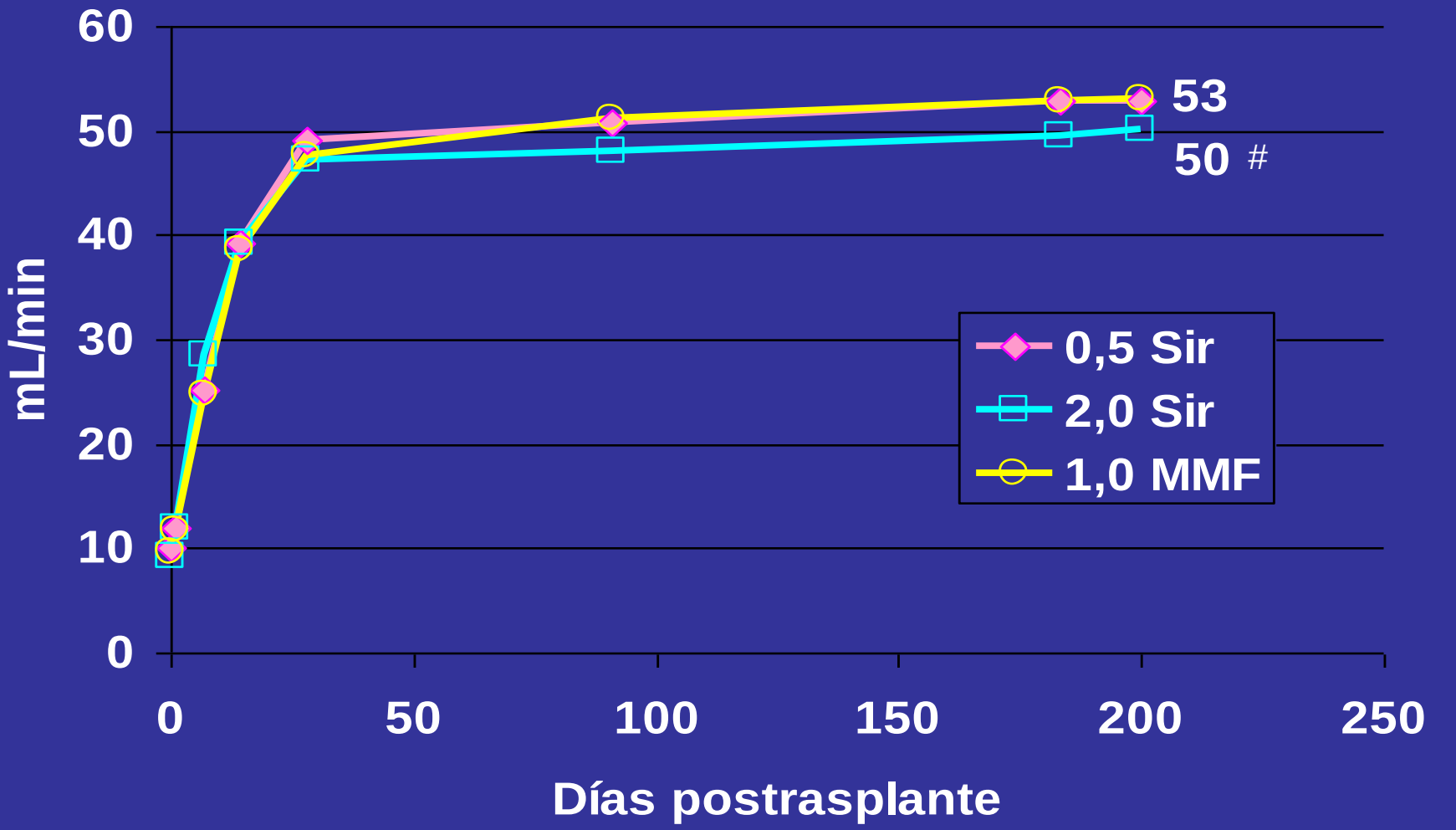
Efficacy failure = acute rejection, death, graft loss or loss to follow-up
CsA, cyclosporin; BPAR, biopsy-proven acute rejection
Nashan B *et al*. *Transplantation* 2004;78:1332–40

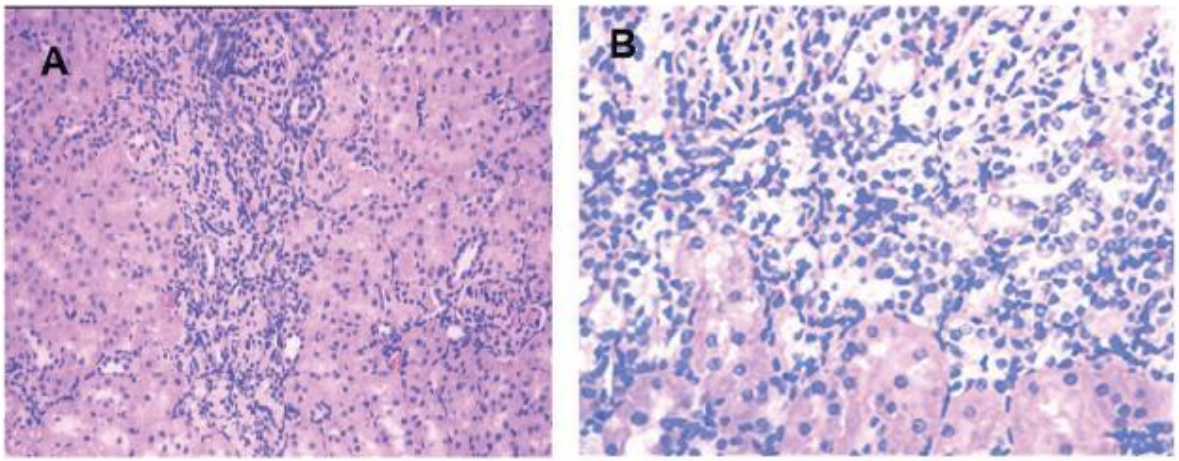
Aclaramiento de creatinina (Cockcroft-Gault)
Tacrolimus+MMF vs Tacrolimus +SRL



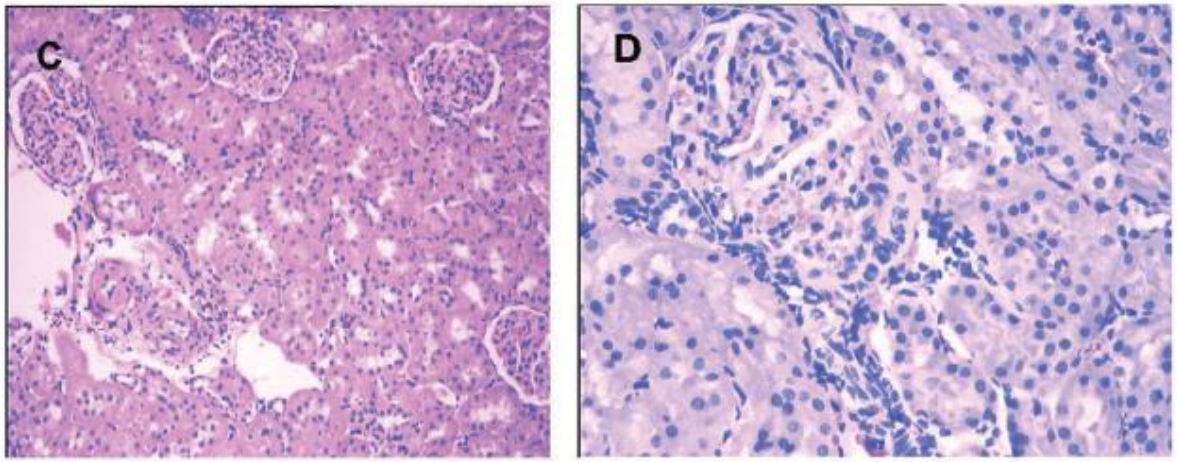
Vitko, Am J Transplant 2006

 # Kruskal Wallis test p=0.019

Different renal toxicity profiles in the association of CyA and Tacrolimus with Sirolimus in rats. Lloberas et al, NDT 2008



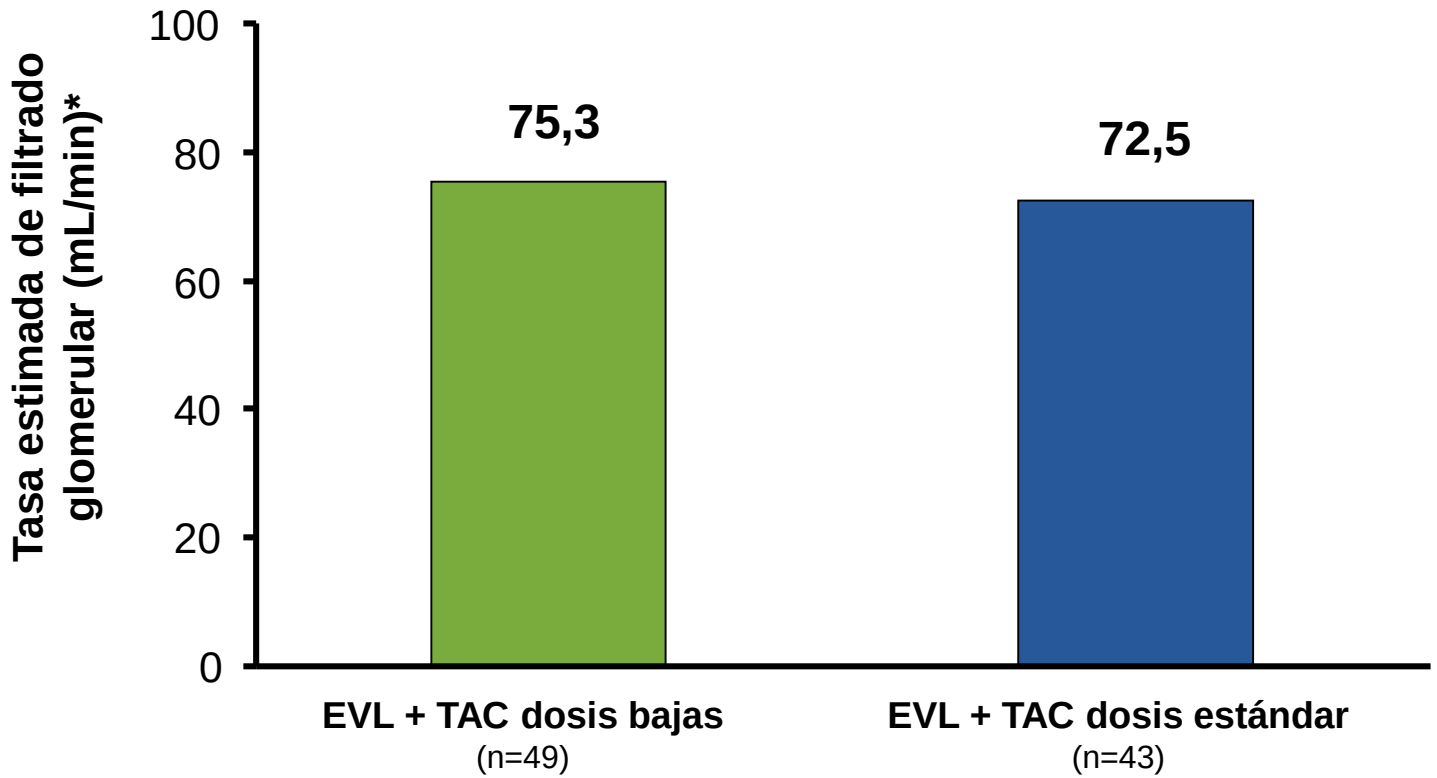
CsA+SRL



Tac+SRL

US09 MANTENIMIENTO DE LA FUNCIÓN RENAL

US09: Resultados a 6 meses

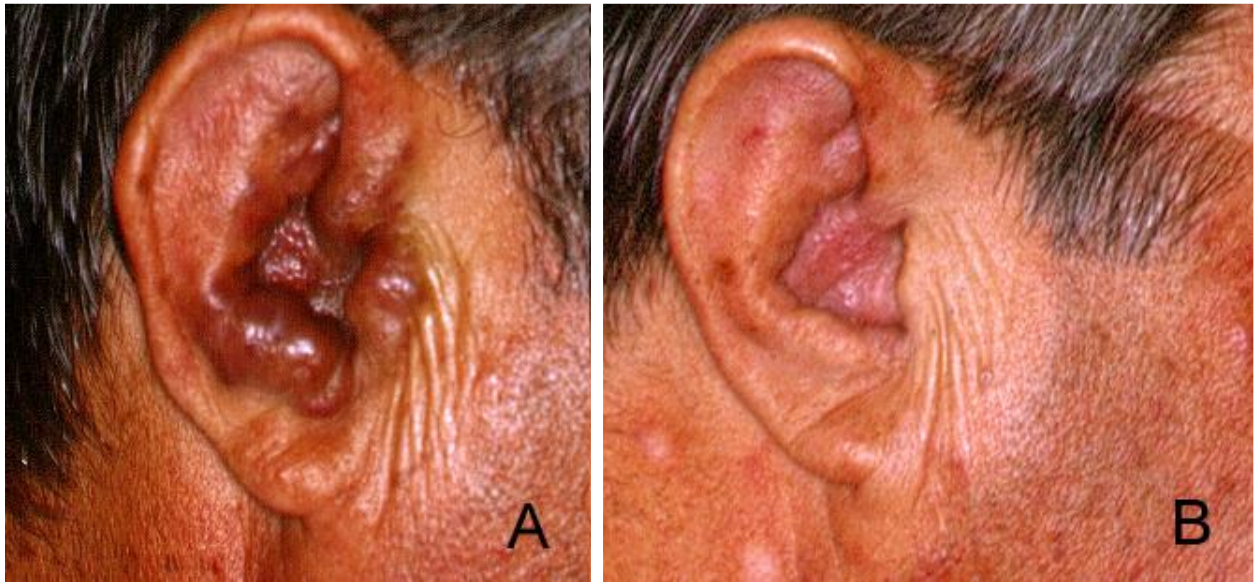


Everolimus con TAC a bajas dosis permite mantener la función renal con una excelente eficacia

*Según la formula de Nankivell

Chan L *et al*. *Transplantation* 2008;85:821–6

Actividad antitumoral de los inhibidores de mTOR

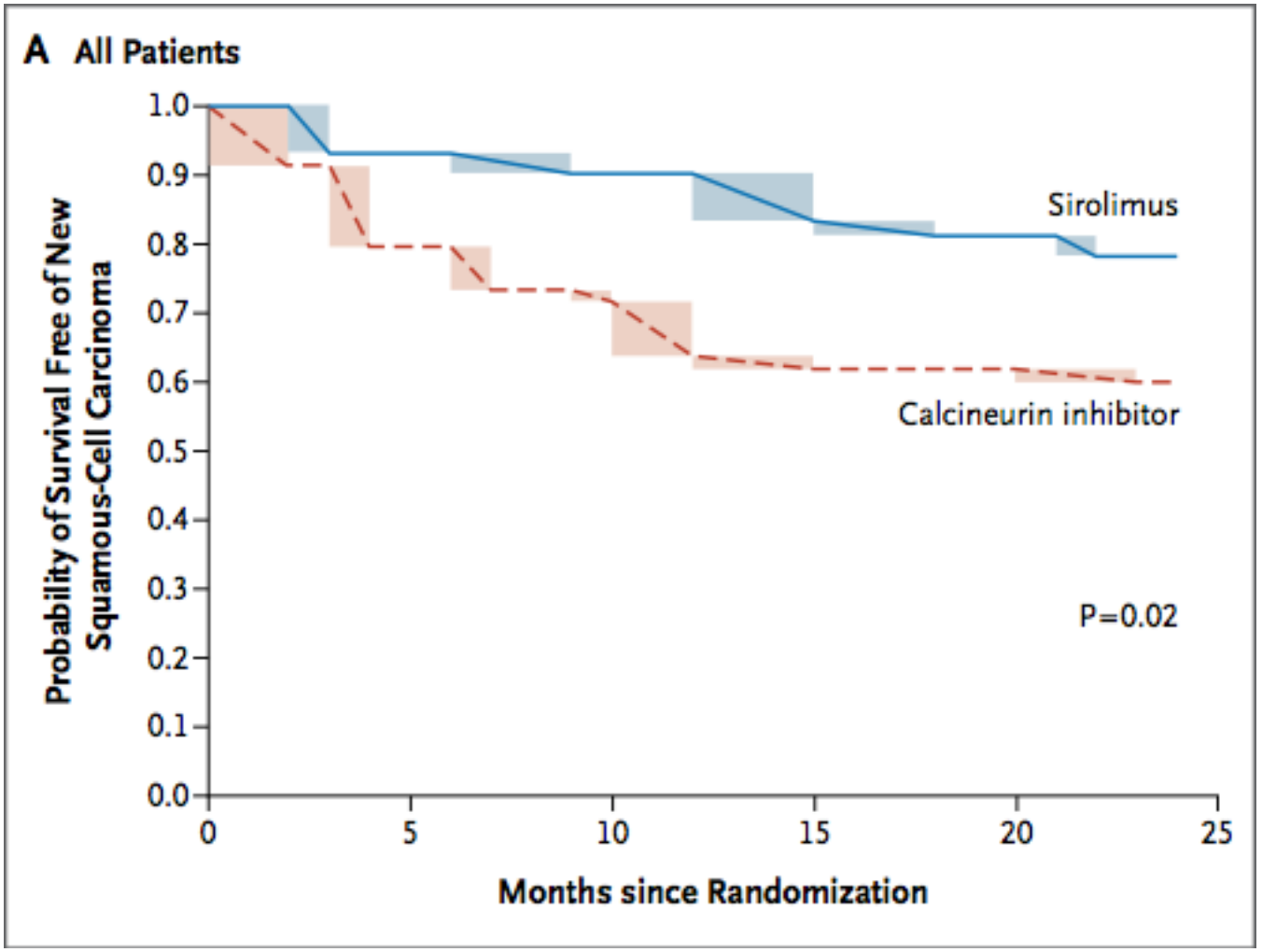


CONVERSION TO SIROLIMUS: A SUCCESSFUL TREATMEN[illegible] POSTTRANSPLANTATION KAPOSI'S SARCOMA[1,2]

JOSEP M. CAMPISTOL,[3,4] ALEX GUTIERREZ-DALMAU,[3] AND J. VICENTE TORREGROSA[3]

2004 March 15;77(5):760-2

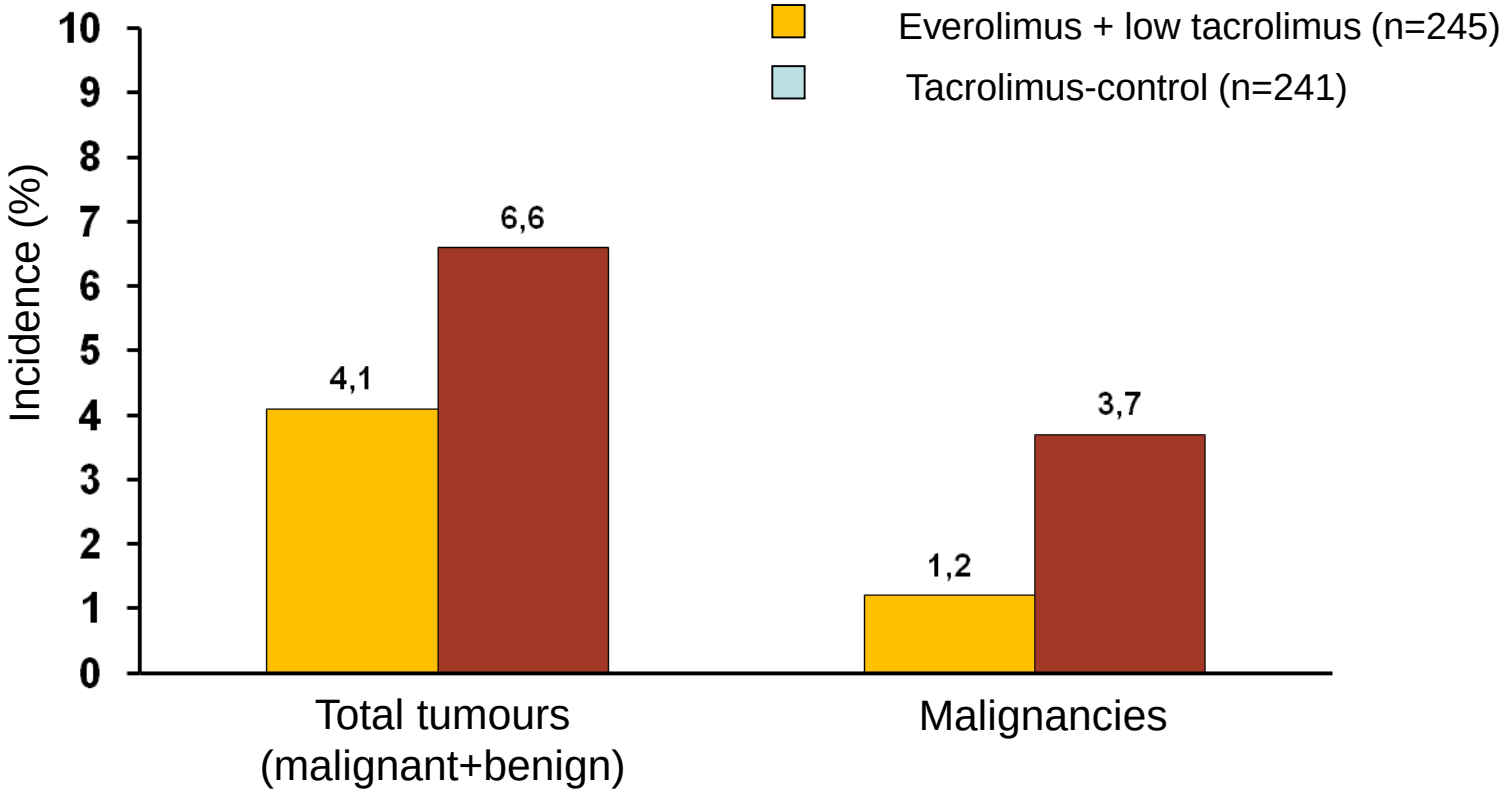
Prevention of secondary skin cancer with sirolimus: all patients



S Euvrard et al. *N Engl J Med* 2012; 367:329-39

Everolimus with early CNI minimization is associated with fewer malignancies than standard CNI

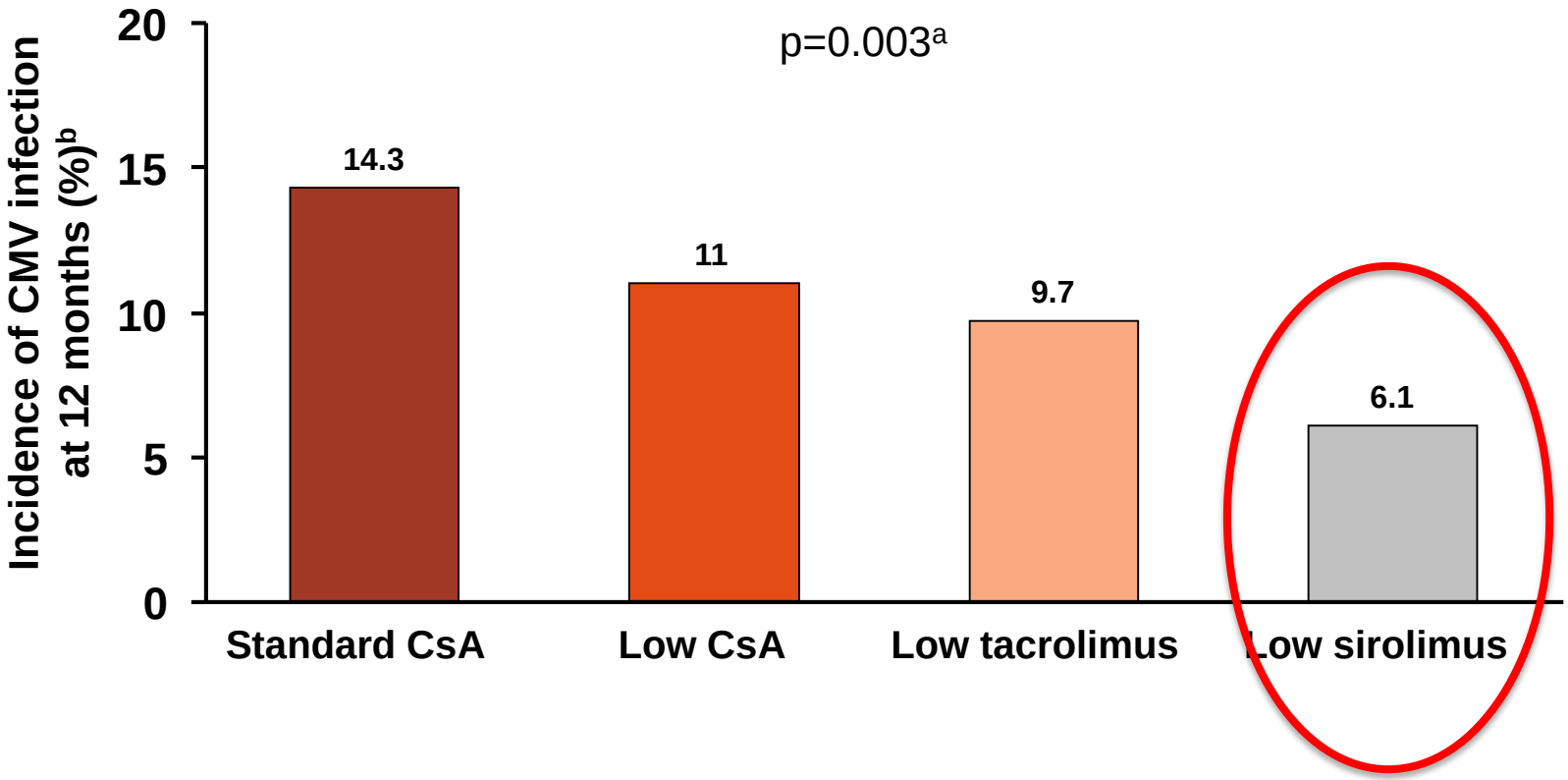
H2304: 12-month analysis



CNI, calcineurin inhibitor;
Novartis data on file, H2304

mTOR inhibitor are associated with a significantly lower incidence of CMV infection

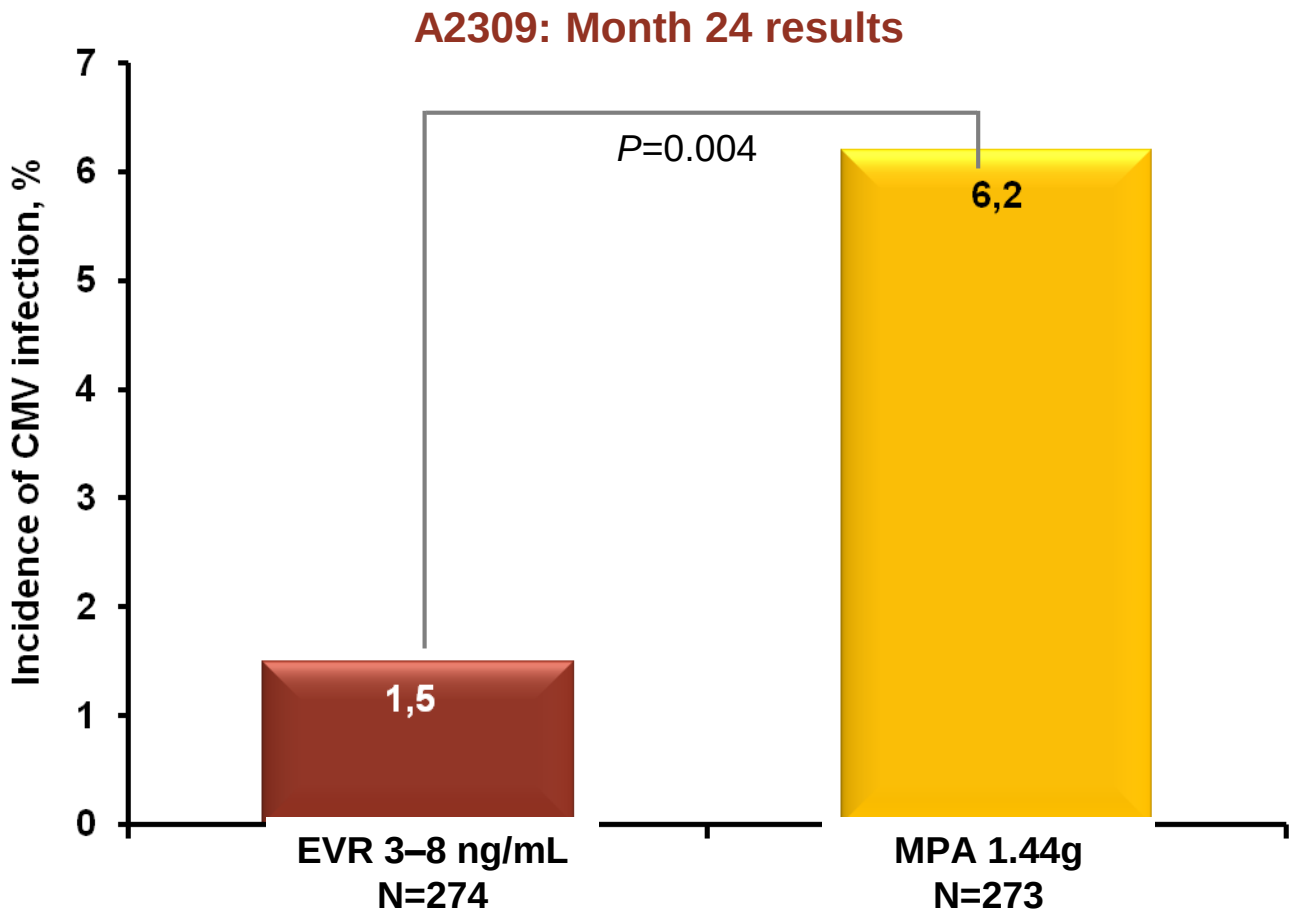
SYMPHONY: randomized, open-label, multicentre study investigating safety and efficacy of CNI-minimization or -elimination regimens in 1645 renal transplant recipients



[a]p value across all arms; significant between-group difference; [b]reported AEs
mTOR, mammalian target of rapamycin; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CsA, cyclosporine A

Ekberg H *et al. N Engl J Med* 2007;357:2562–75

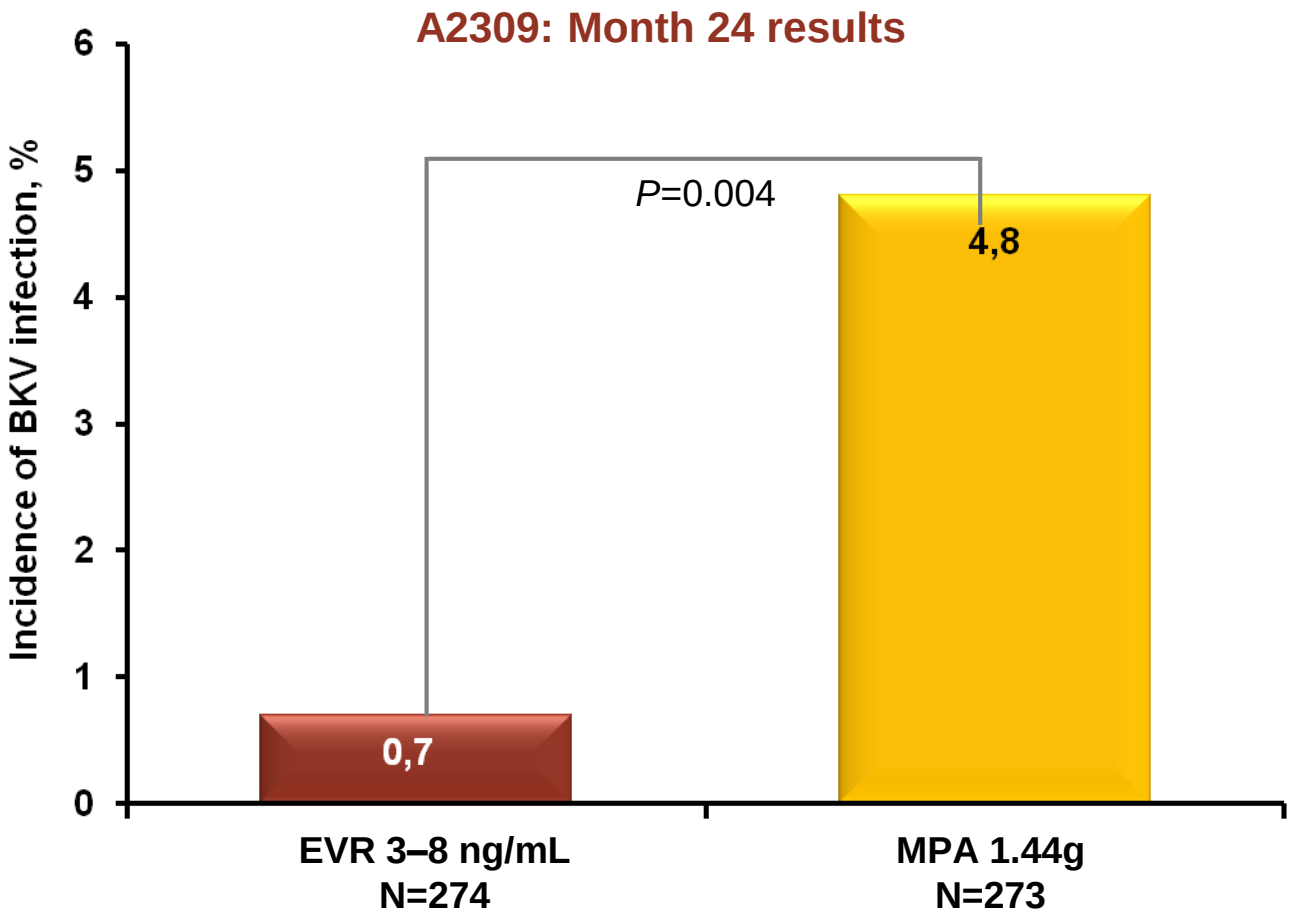
CMV infections were less frequent with *de novo* everolimus + low CNI at 24 months



CMV, cytomegalovirus; EVR, everolimus; MPA, mycophenolic acid.

Cibrik D, et al. *Transplantation.* 2013;95:933–942.

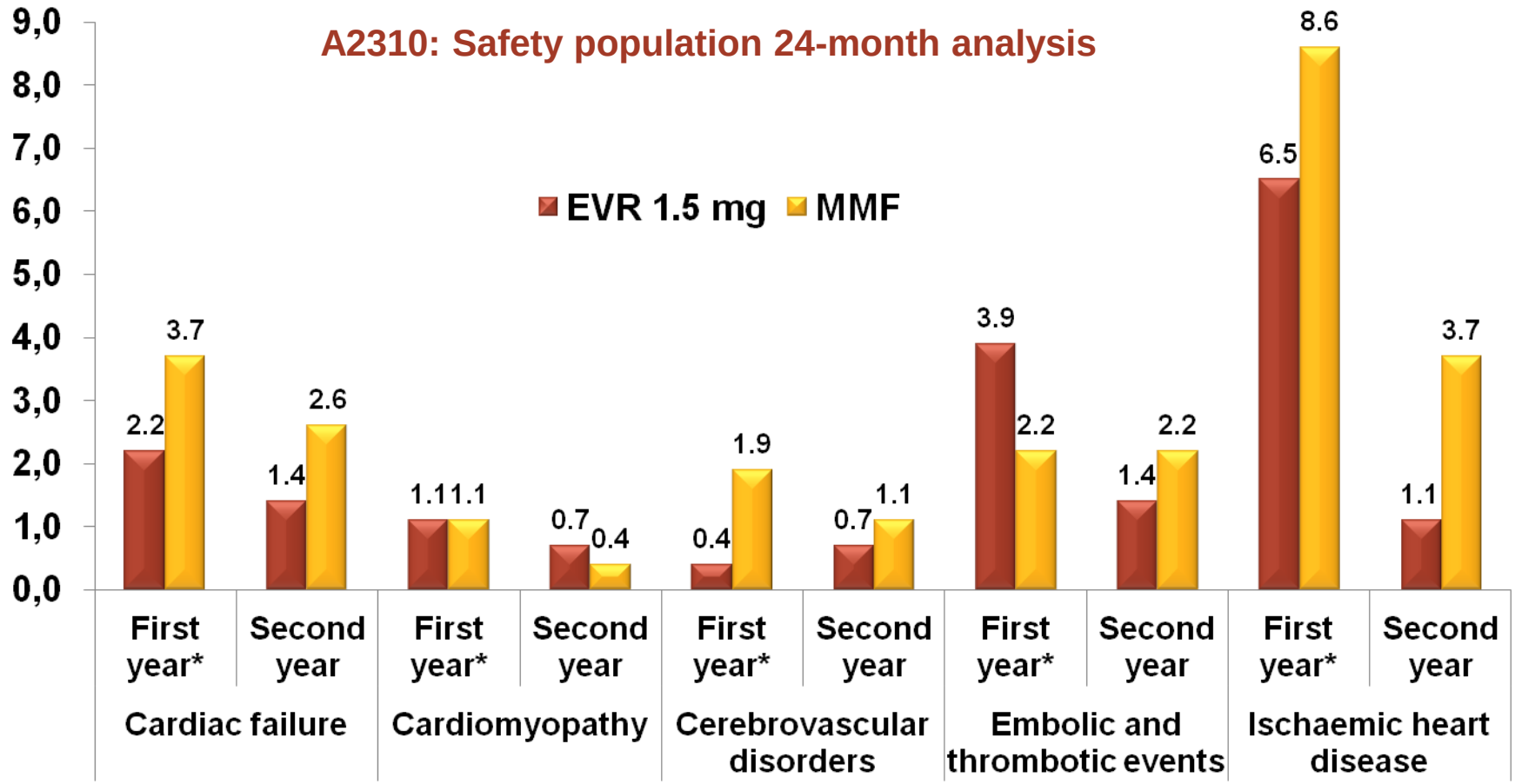
BKV infections were less frequent with *de novo* everolimus + low CNI at 24 months



BKV, BK virus; EVR, everolimus; MPA, mycophenolic acid

Cibrik D, et al. *Transplantation.* 2013;95:933–942.

Lower incidence of cardiac failure, cerebrovascular disorders and ischemic heart disease with EVR vs MPA

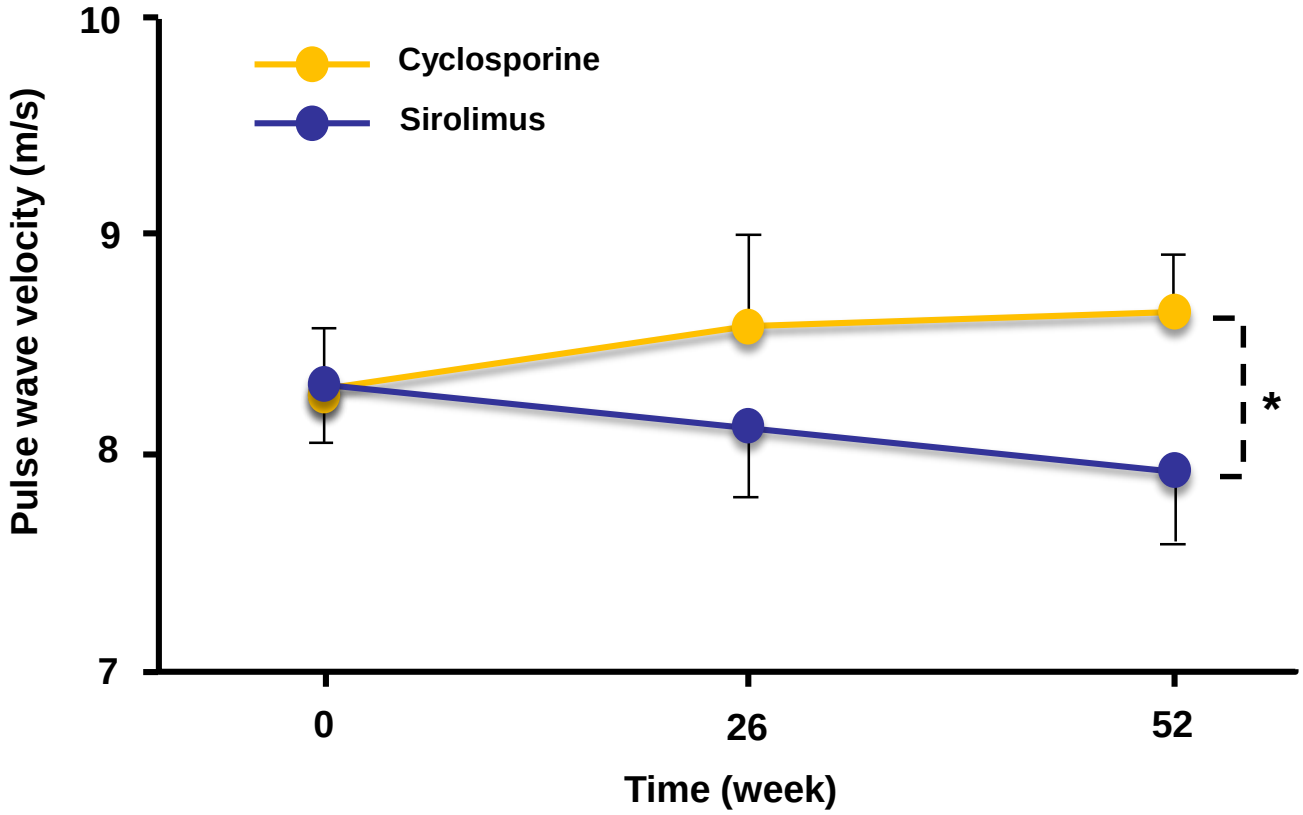


***Excluding adverse events during the first 30 days (period of highest graft instability)**

EVR, everolimus; MPA, mycophenolic acid

Potena L, et al. ISHLT 2013 Presentation. Cardiovascular Events with De Novo Use of Everolimus in Heart Transplant Recipients: 24-Month Analysis of the A2310 Study.

Sirolimus decreases aortic stiffness in renal transplant recipients vs. cyclosporine

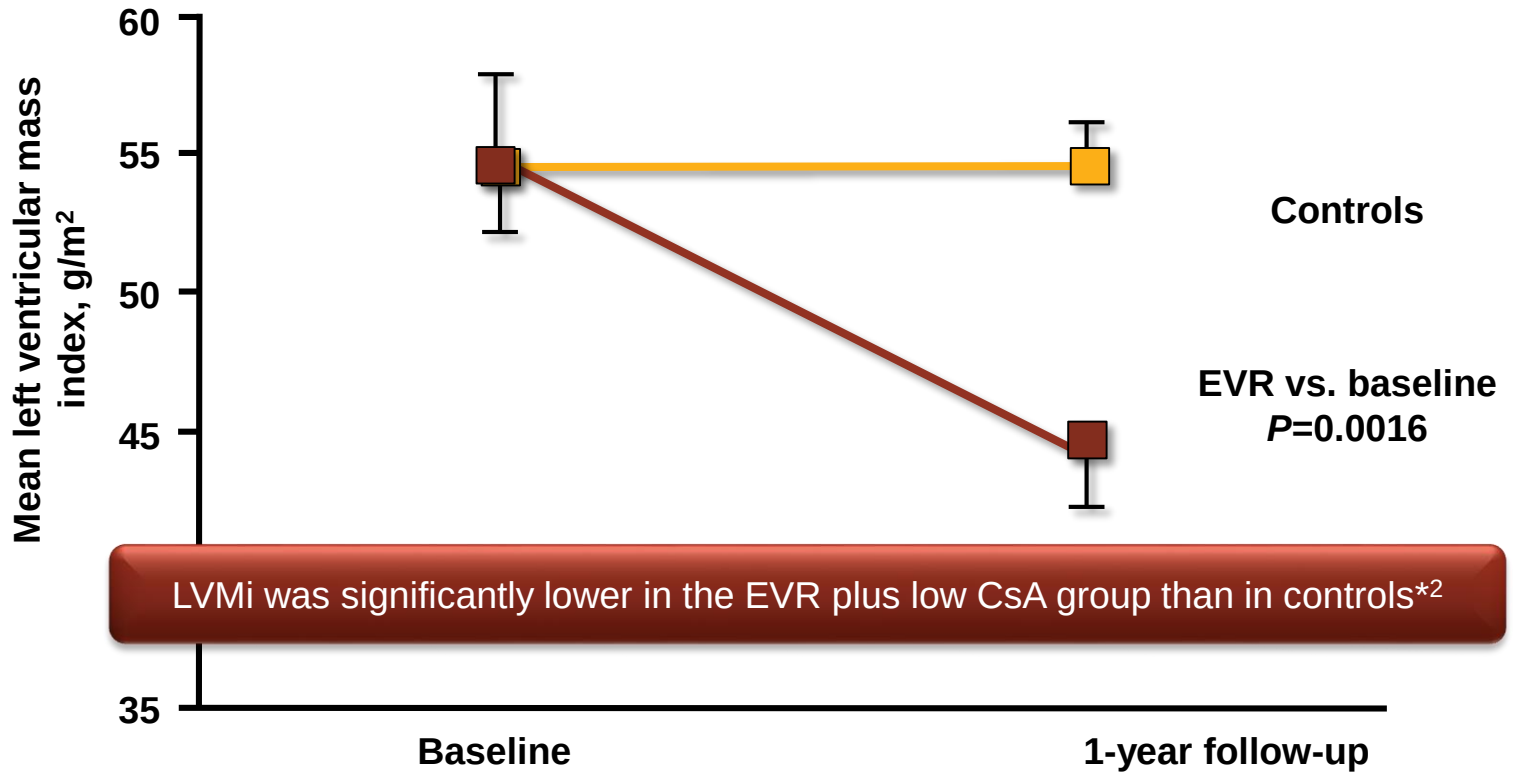


*p<0.05 versus cyclosporine

Joannides et al. Am J Transplant 2011;11:2414–22

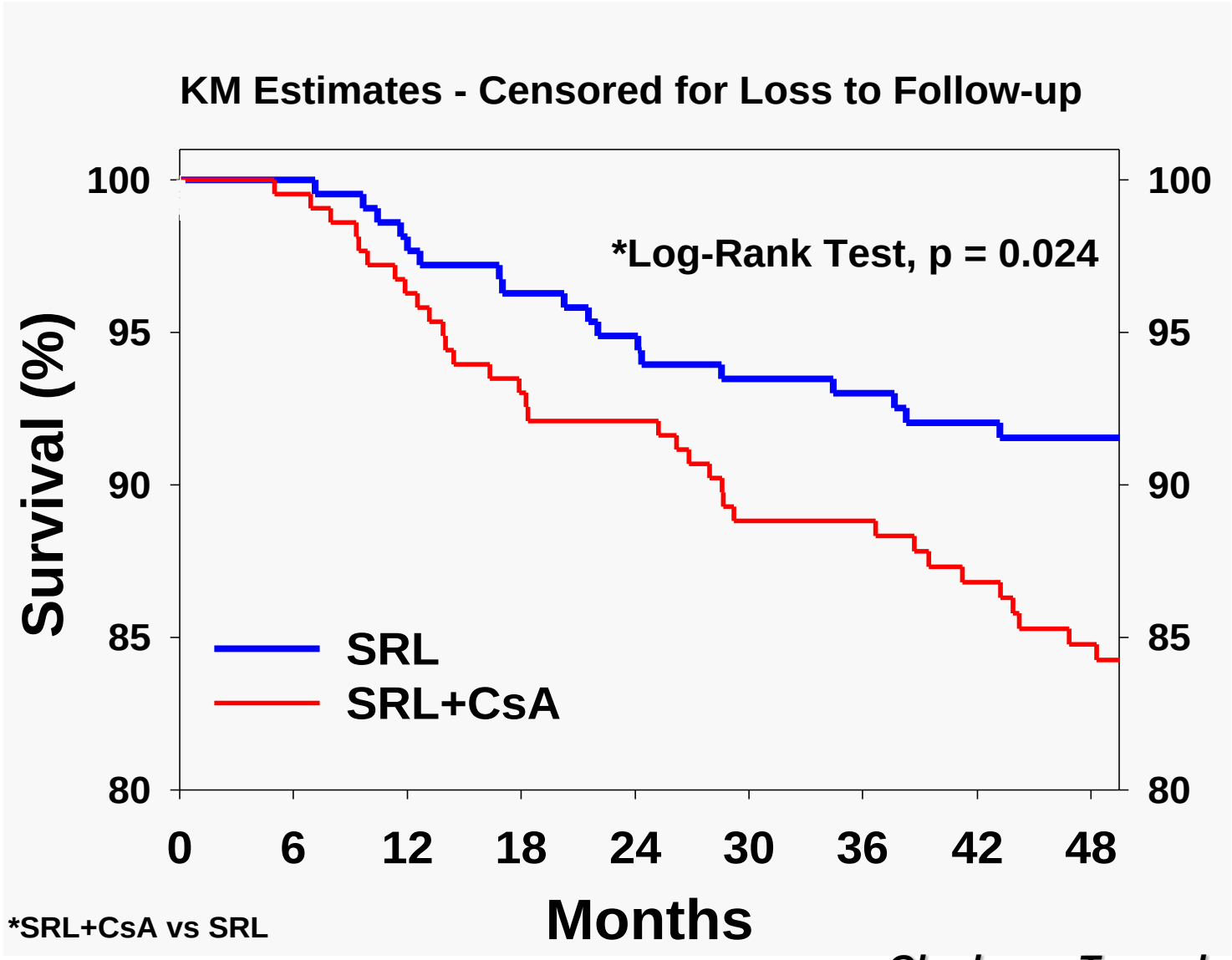
De novo EVR plus minimized CNI improves left ventricular hypertrophy

- **Left ventricular hypertrophy 1 year after kidney transplantation is associated with reduced long-term survival and increased risk of *de novo* heart failure[1]**



*Randomized controlled single-center trial in kidney transplant patients.
CsA, cyclosporine; EVR, everolimus; LVH, left ventricular hypertrophy.
1. Rigatto C, et al. *J Am Soc Nephrol* 2003; 14:462–8; 2. Paoletti E, et al. *Transplantation.* 2012;93:503–8.

Graft Survival at 48 Months



Oberbauer Transplant Int 2006

Inhibidores de imTOR en la individualización del tratamiento inmunosupresor *de novo*

A favor:

Inmunosupresión potente

No nefrotóxica (sin ICN o con minimización)

Reduce el riesgo de infecciones virales (CMV, BK)

Protección cardiovascular

Reduce el riesgo de cáncer

En contra:

Efectos adversos en general poco graves pero muy mal tolerados

Complicaciones post-quirúrgicas

Proteinuria

El potencial beneficio de su indicación en uso precoz requiere años para demostrar su eficacia

Los efectos secundarios de los im-TOR son dosis-dependiente

- Dehiscencia de la herida quirurgica
- Linfocele
- Retraso en al cicatrizacion de las heridas
- Leucopenia, trombopenia y anemia
- Hiperlipidemia
- Proteinuria
- Diabetes
- Hipopotasaemia
- Neumonitis

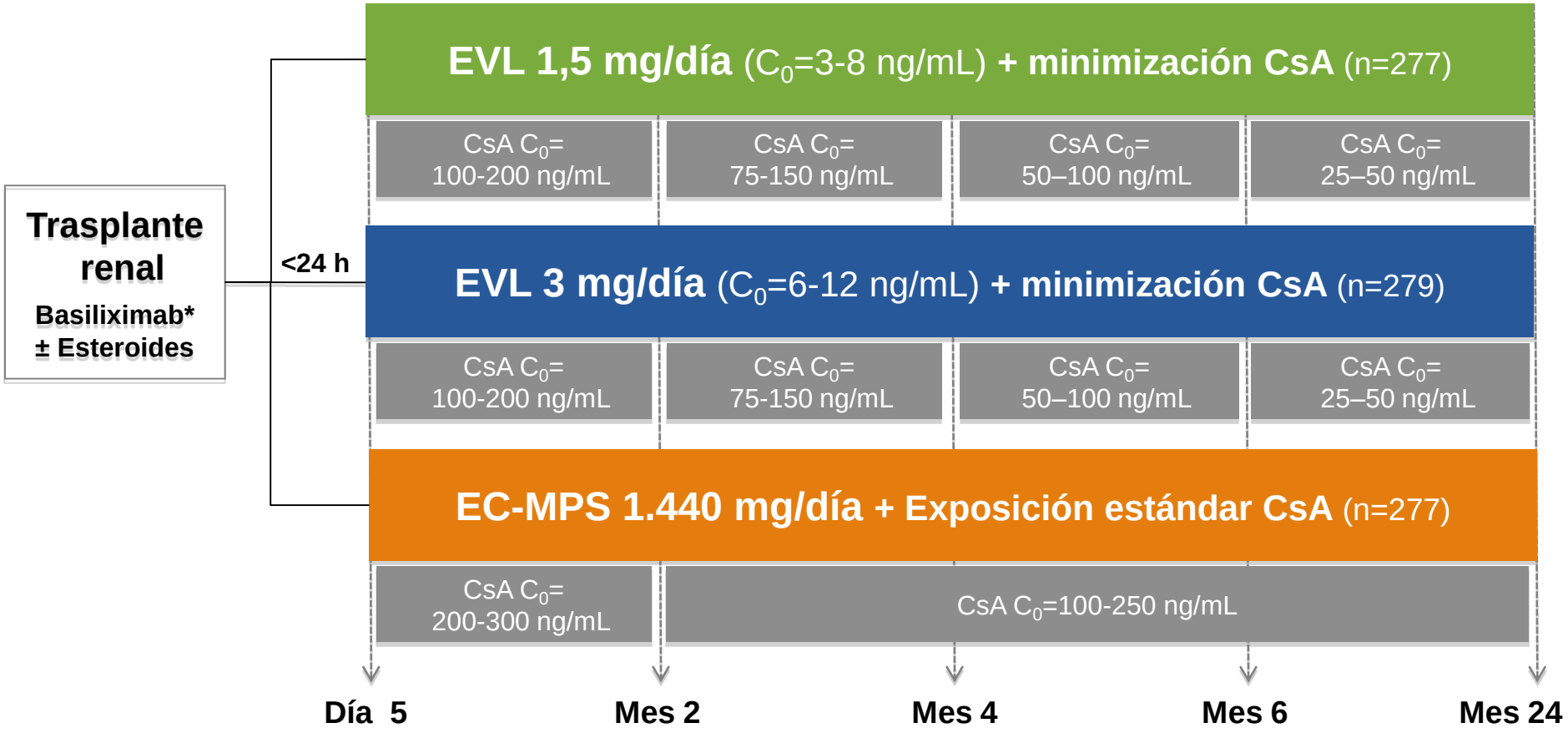
¿Qué pacientes no debería ser tratado de novo con un inhibidor de mTOR?

- Obesidad mórbida
- Dislipemia severa
- EPOC
- Insuficiencia venosa en EEII
- Malnutrición
- Cirugía compleja (injerto vascular simultáneo)
- Pacientes mayores de 65 años, diabeticos y obesos.

ESTUDIO A2309:

EVL con dosis reducidas de CsA como estrategia para la optimización de la función renal a largo plazo: Resultados de un estudio aleatorizado con 833 pacientes *de novo*

Diseño del estudio



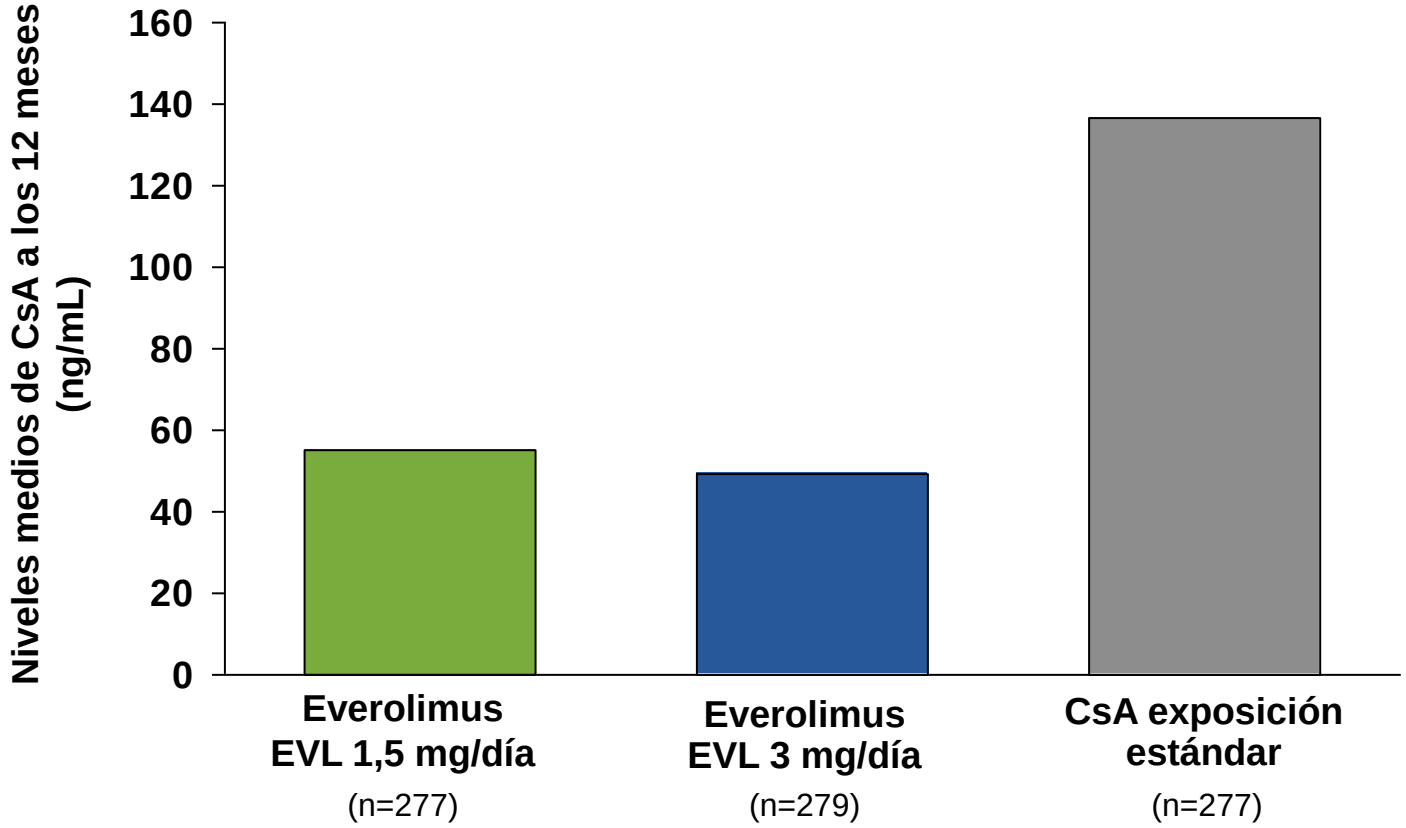
* Todos los pacientes recibieron basiliximab a las 2 h pre-trasplante y a los 4 días post-trasplante.
Los esteroides orales se administraron según la práctica de cada centro.
EC-MPS: Micofenolato sódico con recubrimiento entérico.

Tedesco-Silva H *et al*. Poster P-371, ESOT 2009

ESTUDIO A2309

EVL 1,5 MG/DÍA: ~60% DE REDUCCIÓN NIVELES MEDIOS DE CSA

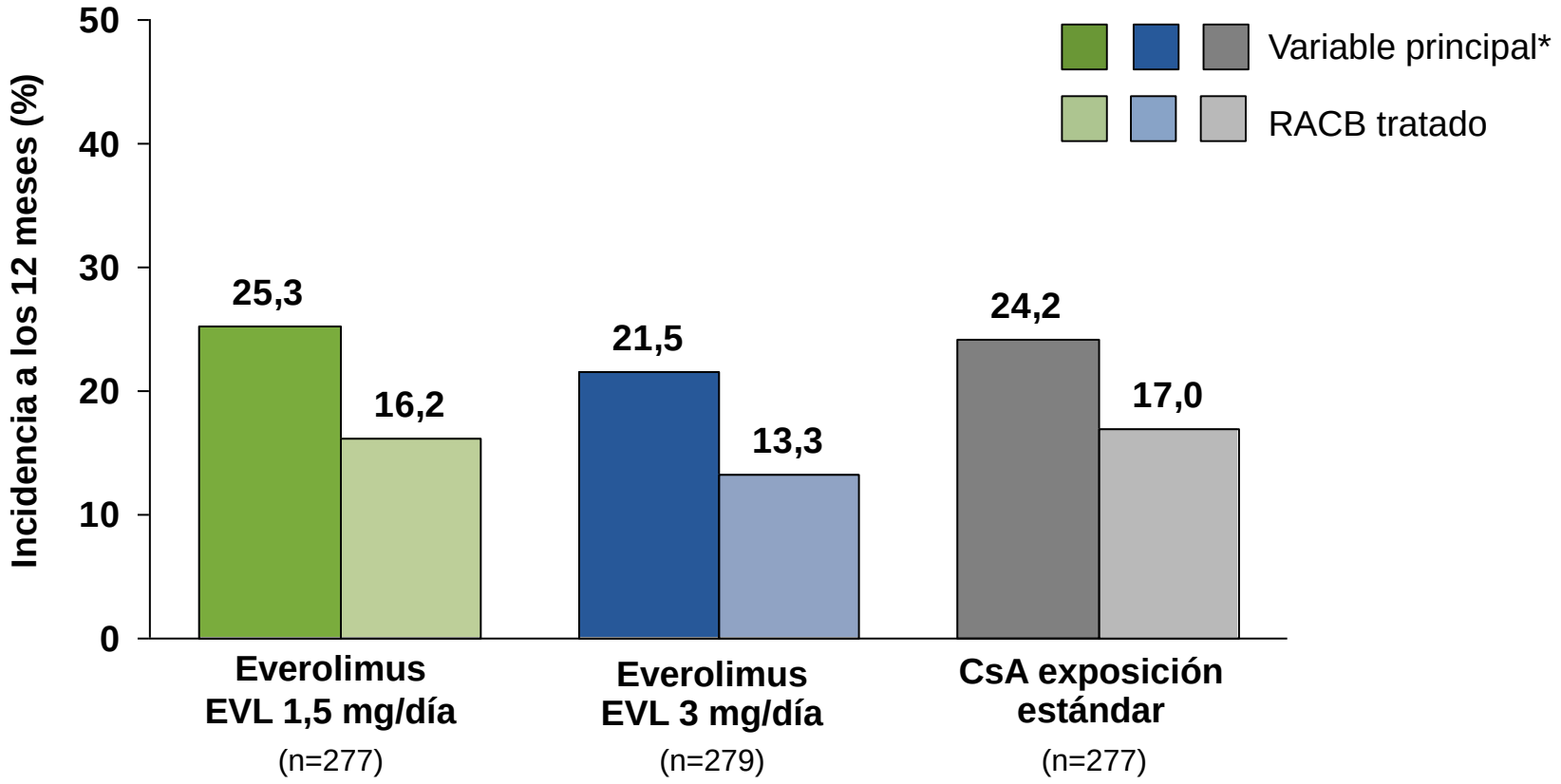
A2309: resultados a 12 meses



Tedesco-Silva H *et al*. Poster P-371, ESOT 2009

ESTUDIO A2309 El tratamiento con EVL + exposición reducida de CsA logra una eficacia similar al tratamiento con exposición estándar de CsA

A2309: resultados a 12 meses

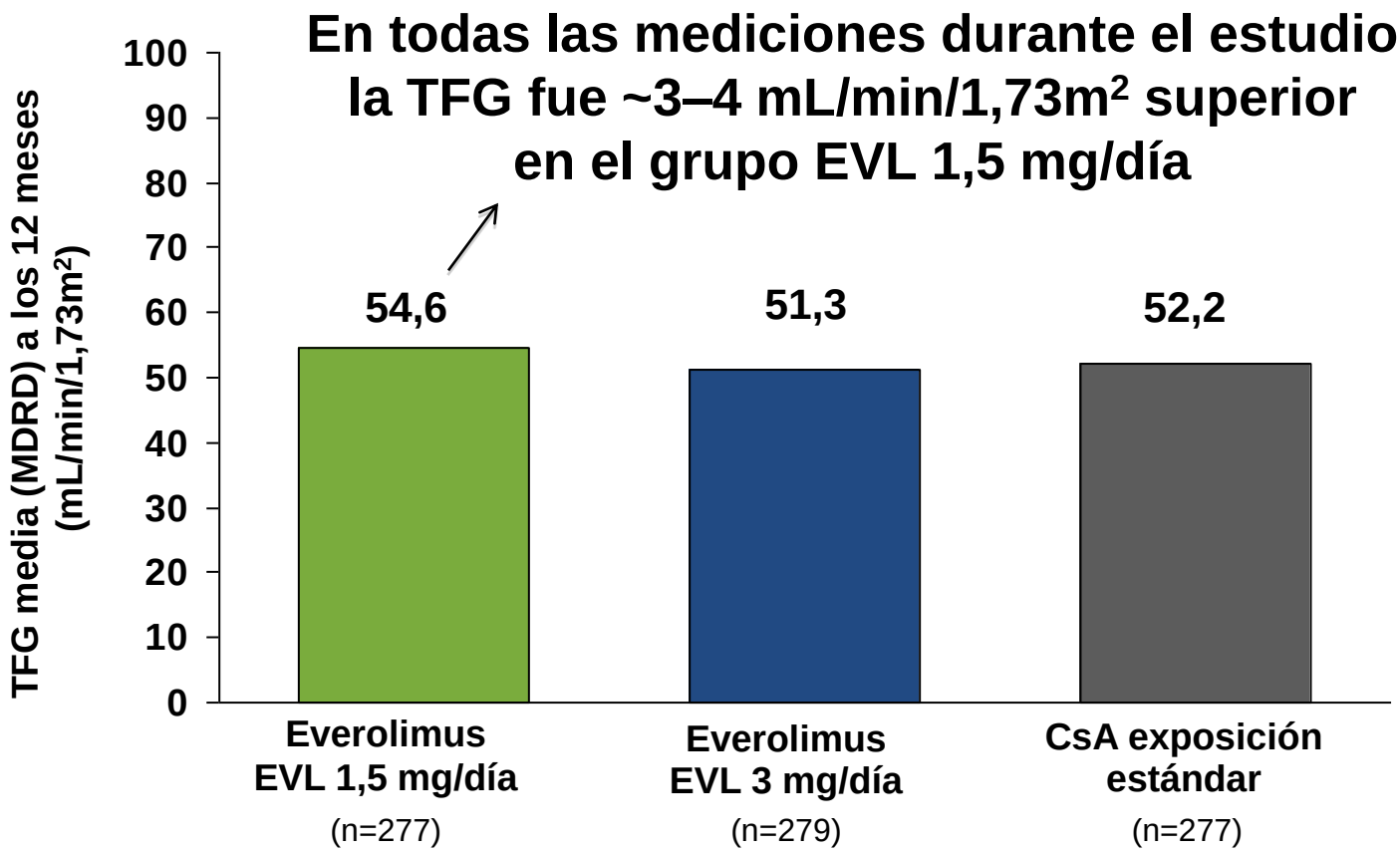


* RACB, pérdida del injerto, muerte o pérdida para el seguimiento

Tedesco-Silva H *et al*. Poster P-371, ESOT 2009

ESTUDIO A2309 FUNCIÓN RENAL MANTENIDA

A2309: resultados a 12 meses



TFG: tasa de filtrado glomerular

Tedesco-Silva H *et al*. Poster P-371, ESOT 2009

ESTUDIO A2309 SEGURIDAD

A2309: resultados a 12 meses

	EVL 1,5 mg/día (n=274)	EVL 3 mg/día (n=278)	CsA exposición estándar (n=273)
Cualquier efecto adverso	271 (98,9)	276 (99,3)	270 (98,9)
Virus BK	2 (0,7)	3 (1,1)	11 (4,0)
CMV	3 (1,1)	1 (0,4)	23 (8,4)
Edema periférico	123 (44,9)	120 (43,2)	108 (39,6)
Complicaciones de la herida quirúrgica	96 (35,0)	108 (38,8)	70 (25,6)
Hipercolesterolemia	47 (17,2)	50 (18,0)	34 (12,5)

Tedesco-Silva H *et al*. Poster P-371, ESOT 2009

Efficacy and safety of *de novo* or early everolimus with low cyclosporine in deceased-donor kidney transplant recipients at specified risk of delayed graft function: 12-month results of a randomized, multicenter trial

- Population at protocol-specified risk of DGF:

  Deceased-donor kidney Tx recipients (≥ 18 years old) with at least one of the following criteria :

  – Donor > 55 years old, and/or
  – CIT ≥ 24 hours and < 40 hours, and/or
  – Retransplantation

- "Primary failure endpoint", is a composite efficacy/safety endpoint of :

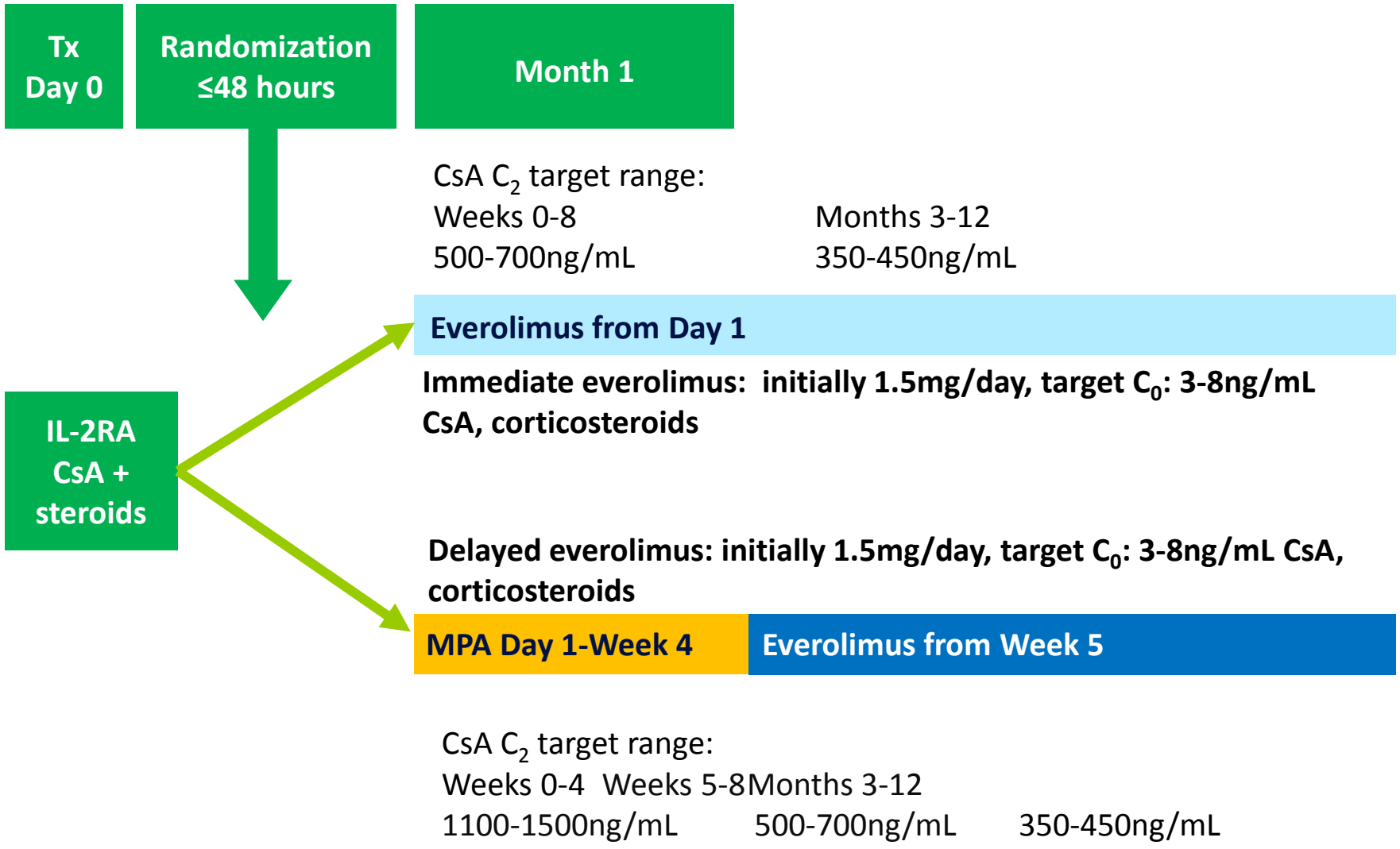
  – DGF, defined as ≥1 dialysis session within first week post-transplant (except on D1)
  – Composite efficacy endpoint, defined as BPAR, GFL, death or loss to follow-up
  – WH disorder related to initial transplant surgery

  Evaluated at 3 months

Dantal J *et al*. Transplant Int 2010

Study design

12-month, multicenter, open-label study



Primary and Efficacy endpoints to Month 3 and 12

	Month 3		Month 12		P value
	Immediate everolimus (n=65)	Delayed everolimus (n=74)	Immediate everolimus (n=65)	Delayed everolimus (n=74)	
Primary endpoint*	36 (55.4%)	47 (63.5%)	42 (64.6%)	49 (66.2%)	0.860
DGF	16 (24.6%)	18 (24.3%)	16 (24.6%)	18 (24.3%)	1.00
BPAR	7 (10.8%)	7 (9.5%)	13 (20.0%)	15 (20.3%)	1.00
Graft loss	5 (7.7%)	3 (4.1%)	6 (9.2%)	5 (6.8%)	0.75
Death	4 (6.2%)	2 (2.7%)	5 (7.7%)	2 (2.7%)	0.25
Wound healing complications	24 (36.9%)	28 (37.8%)	26 (40.0%)	28 (37.8%)	0.86
Loss to follow-up	0 (0.0%)	2 (2.7%)	0 (0.0%)	3 (4.1%)	0.24

* DGF (≥ 1 dialysis days 2-7), BPAR, graft loss, death, wound healing complication related to initial transplant surgery, loss to follow-up

CIRUGÍA DE TRASPLANTE RENAL

Día 0

EVL: INICIAR Y CONTINUAR INDEFINIDAMENTE

Día 1

- Administrar EVL 0,75 mg 2 veces/día por vía oral con CsA o tacrolimus.

Día 3-5

- Realizar monitorización terapéutica del fármaco para medir los niveles plasmáticos del EVL y mantenerlos entre 3 y 8 ng/mL.

Día 7

Niveles objetivo ICN (ng/mL)

	CsA	CsA + inducción	Tacrolimus
Día 7	C_2 1.100 – 1.300 C_0 200 – 300	C_2 600 – 800 C_0 100 – 200	7 – 9
Mes 1	C_2 900 – 1.200 C_0 200 – 300	C_2 500 – 700 C_0 100 – 150	5 – 8
Mes 3	C_2 500 – 700 C_0 100 – 150	C_2 400 – 600 C_0 75 – 100	4 – 7
Mes 6	C_2 400 – 600 C_0 50 - 100	C_2 300 – 500 C_0 50 – 75	4 – 7
Mes 12	C_2 300 – 500 C_0 25 – 75	C_2 300 – 500 C_0 25 – 75	–

Administrar esteroides según la práctica local de cada centro

im-TOR + ICN
Recomendaciones: Everolimus de novo y mantenimiento

- Asociar preferentemente con Tacro
- Evitar la dosis de carga de Certican
- Utiliar dosis bajas de ambos
- Evitar la nefrotoxicidad (bajas dosis de Tacro)
- Mantener niveles de 5 TAC-5 Certican
- Considerar eliminar Esteroides

Beneficio potencial im-TOR+CNI

- **Pacientes de alto riesgo inmunologico**
- **TX pancreas-riñón e islotes**
- **Nefropatia cronica del injerto (fases iniciales)**
- **Incidencia de CMV**
- **Incidence de virus BK**
- **Incidencia de neoplasia**
- **Potencial para eliminar esteroides**
- **Riesgo cardiovascular ?**

Necesaria mayor experiencia a largo plazo…Estudio Transform

De novo Sirolimus US High-Risk Study (BCAR @ 1yr)

Thymo induction in 88% of pts

	SRL+TAC (n=224)	SRL+CsA (n=224)
Grade of rejection,[c,d] n (%)		
None	193 (86.2)	185 (82.6)
Any	31 (13.8)	39 (17.4)
Mild	12 (38.7)[e]	31 (79.5)
Moderate	13 (41.9)	5 (12.8)
Severe	2 (6.5)	2 (5.1)
Unclassified	4 (12.9)	1 (2.6)

Gaber O et al. Transplantation 2008;86:1187–1195

TRANSFORM: a novel study design to evaluate the effect of everolimus on long-term outcomes after kidney transplantation

- **Everolimus with reduced-exposure calcineurin inhibitor (CNI) therapy is a strategy designed to reduce the risk of chronic nephrotoxicity and other dose-dependent complications associated with CNI therapy.**
- **Primary end-point: Renal function at one year + incidence of acute rejection**
- **Number of patients: 2000**
- **40 countries**
- **Follow-up: 2 and 5 yr**
- **Novartis sponsor**

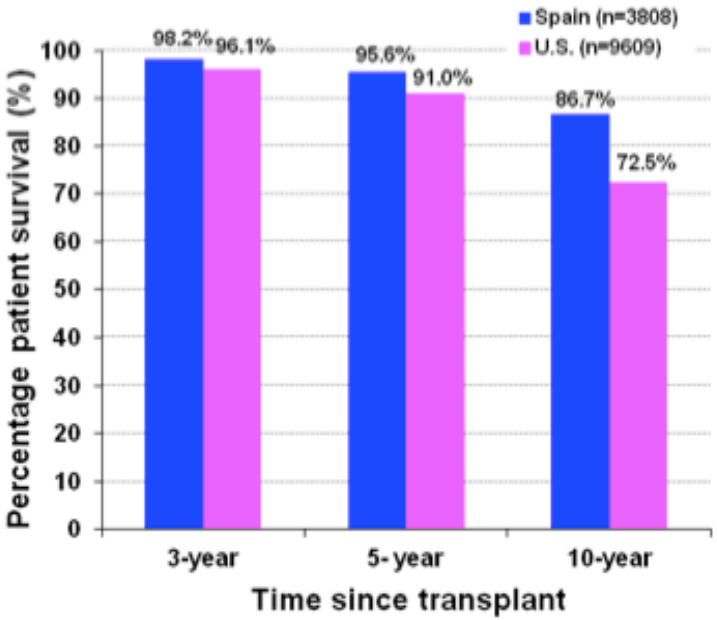
Nephrol Dial Transplant (2013) 28: 213–220
doi: 10.1093/ndt/gfs287
Advance Access publication 2 July 2012

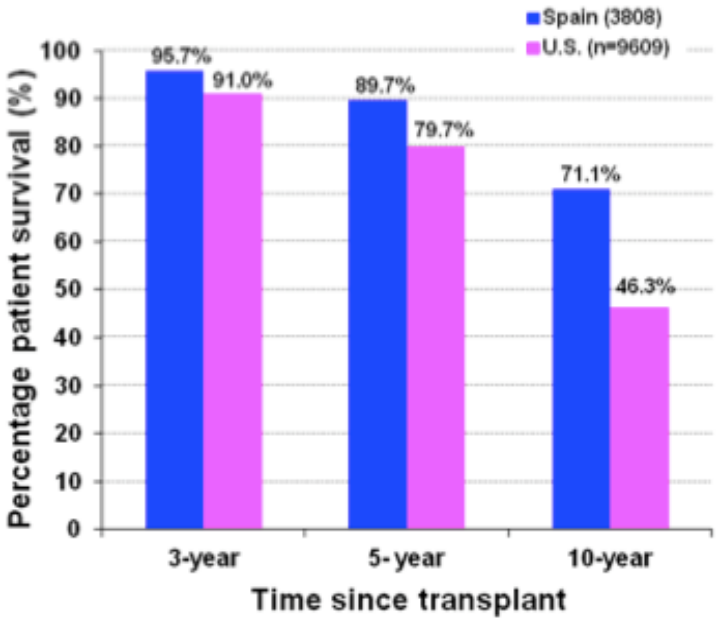
Original Articles

NDT
Nephrology Dialysis Transplantation

Comparison of the long-term outcomes of kidney transplantation: USA versus Spain

Akinlolu O. Ojo[1,2], José María Morales[3], Miguel González-Molina[4], Diane E. Steffick[2], Fu L. Luan[1], Robert M. Merion[2,5], Tammy Ojo[1], Francesc Moreso[6], Manuel Arias[7], Josep María Campistol[8], Domingo Hernandez[9], Daniel Serón[10] and for the Scientific Registry of Transplant Recipients and the Spanish Chronic Allograft Study Group



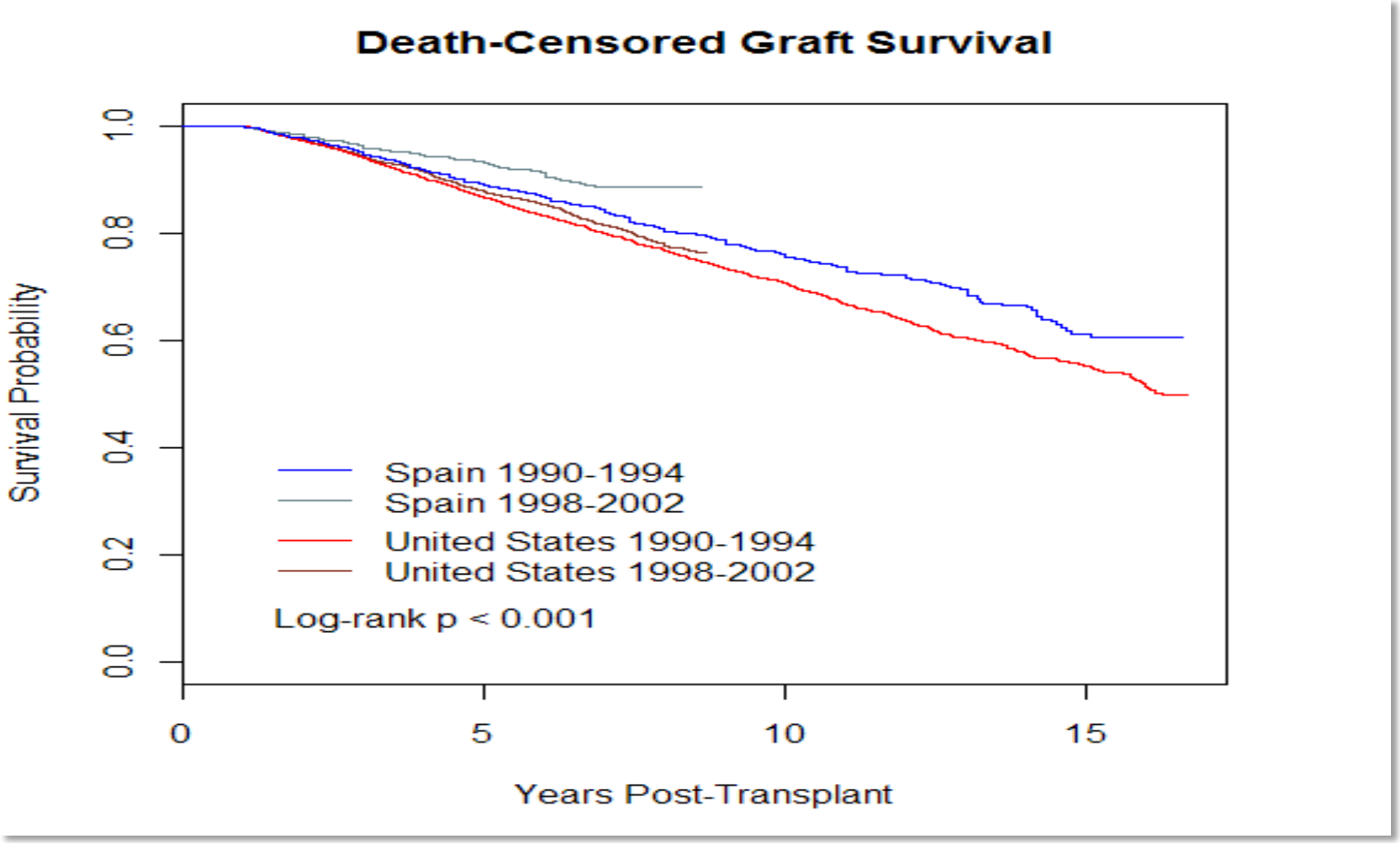


The 10-year recipient survival was 86.7% for Spanish and 76,5% for US recipients (P < 0.001).

In recipients with diabetes, the survival at 10 years were 71.1 and 46.3% (P < 0.001).

USA vs SPAIN

Death-censored Graft Survival: 1990-2002



Ojo, Morales, Glez Molina et al, 2011

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Conclusions. US kidney transplant recipients had more than twice the long-term hazard of DWGF compared with Spanish kidney transplant recipients and similar levels of death-censored graft function. Pre-transplant medical care, comorbidities, such as cardiovascular disease, and their management in each country's health system are possible explanations for the differences between the two countries.

Nephrol Dial Transplant (2013) 28: 9–11
doi: 10.1093/ndt/gfs374
Advance Access publication 17 September 2012

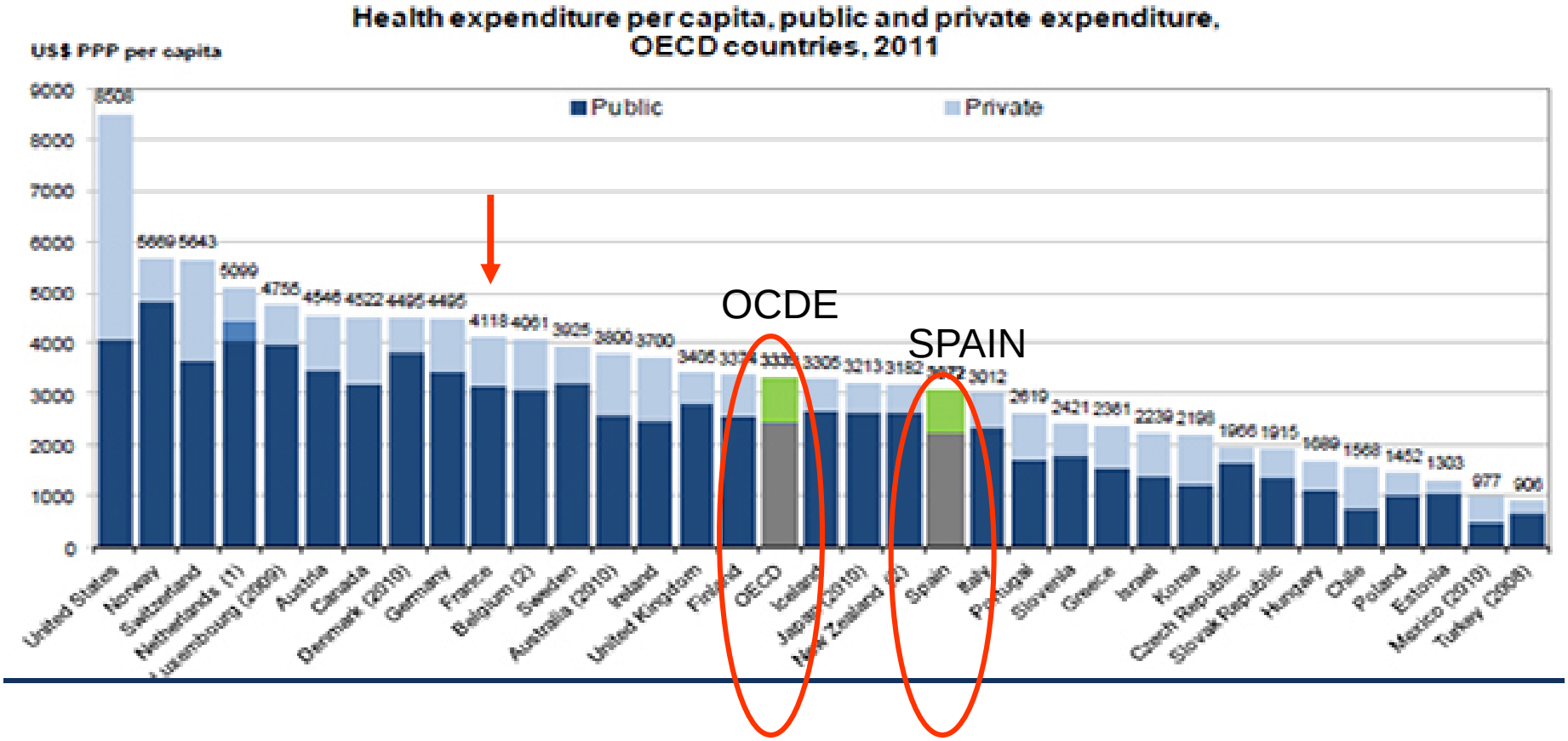
Editorial

Comparing kidney transplant outcomes; caveats and lessons

Sarah E. Yost[1] and Bruce Kaplan[2,3]

It is possible that the long-term outcomes of kidney transplant in the USA are hampered by **financial barriers leading to non-adherence and lack of access to specialists** in the field of transplant. These factors undoubtedly contribute far greater than in other countries **that have nationalized healthcare or provide medication coverage for all constituents including Spain** Kidney transplant recipients **from Spain receive their care from the same medical team from the onset of ESRD through the post-transplant period** which could contribute to longterm patient and allograft survival. **In Spain, patients have access to medications including immunosuppressio**n paid by a publicly funded National Health Service regardless of their ability to pay

However, the study by Ojo et al. also highlights that mortality in renal transplant recipients can be influenced by factors **not easily captured on databases** and challenges us to consider variables in national registries that are currently unavailable.



The percentage of the GDP, Gross Domestic Product, that Spain dedicates to healt
is fallen from 9.6 to 9.3 % in the last year (European most developped countries :

Spain invests in health 600 Euros less per inhabitant and year than the average of the Eurozone

Mensajes para llevar a casa
im-TOR + ICN
de novo

- Potente y especifica terapia inmunosupresora
- Alta eficacia: baja incidencia de rechazo
- Capacidad para individualizar el tratamiento inmunosupresor
  - Eliminar ICN
  - Eliminar Esteroides
- Baja incidencia de infecciones virales
- Baja incidencia de cancer

Muchas gracias por su atencion