Risk Stratification and the Choice of the Right Protocol in kidney transplantation

Mohamed Hany Hafez
Professor of nephrology-cairo University

WHY RISK ASSESSMENT?

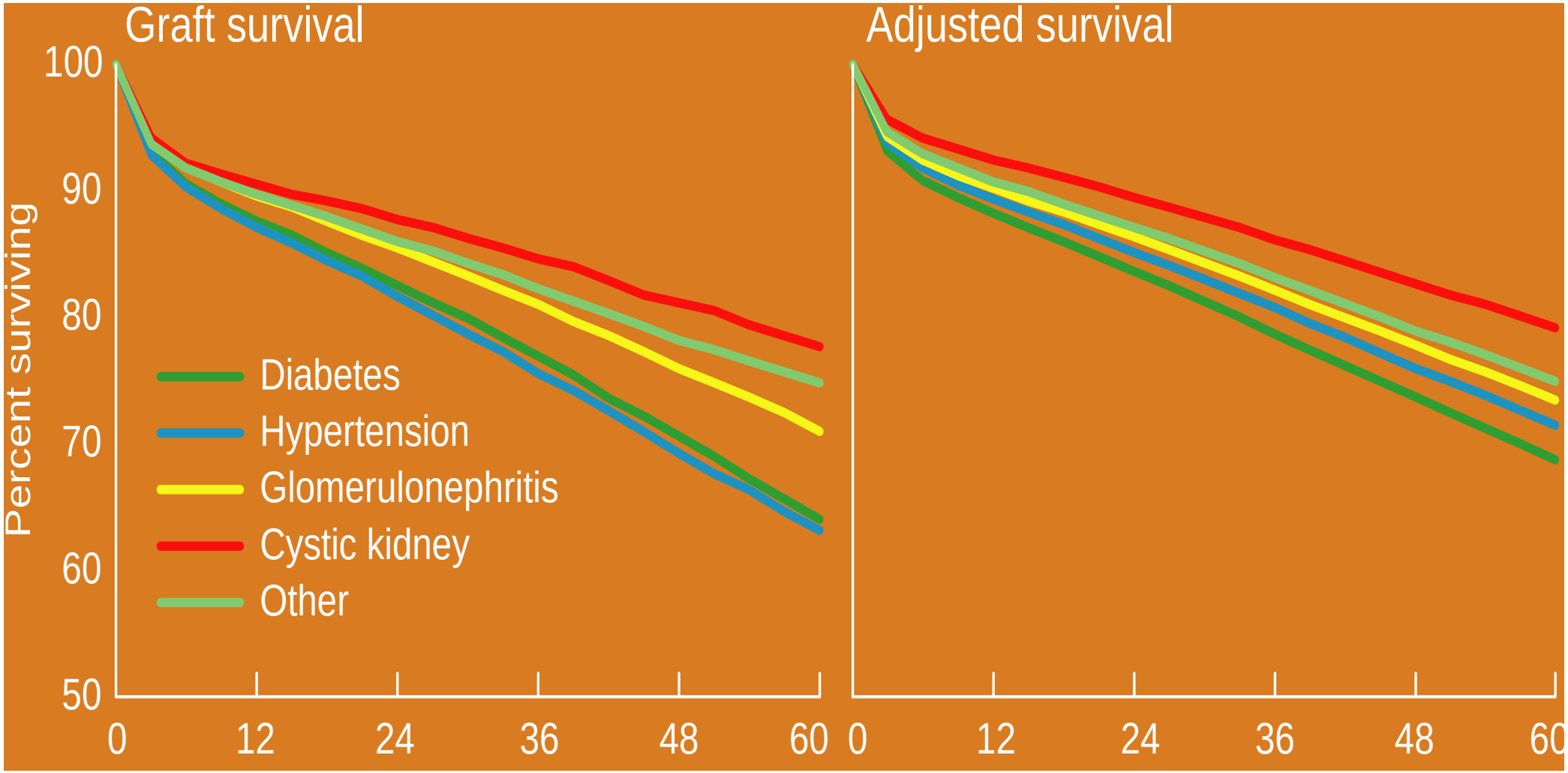
- to determine most appropriate donor/recipient pair and minimize the occurrence of rejection.
- To select appropriate immunosuppression methods Ensuring protection against rejection while minimizing drug toxicity, viral infections and malignancies.
- To determine frequency of post-transplant follow-up visits and potential immunosuppression tapering.

Some known risk factors

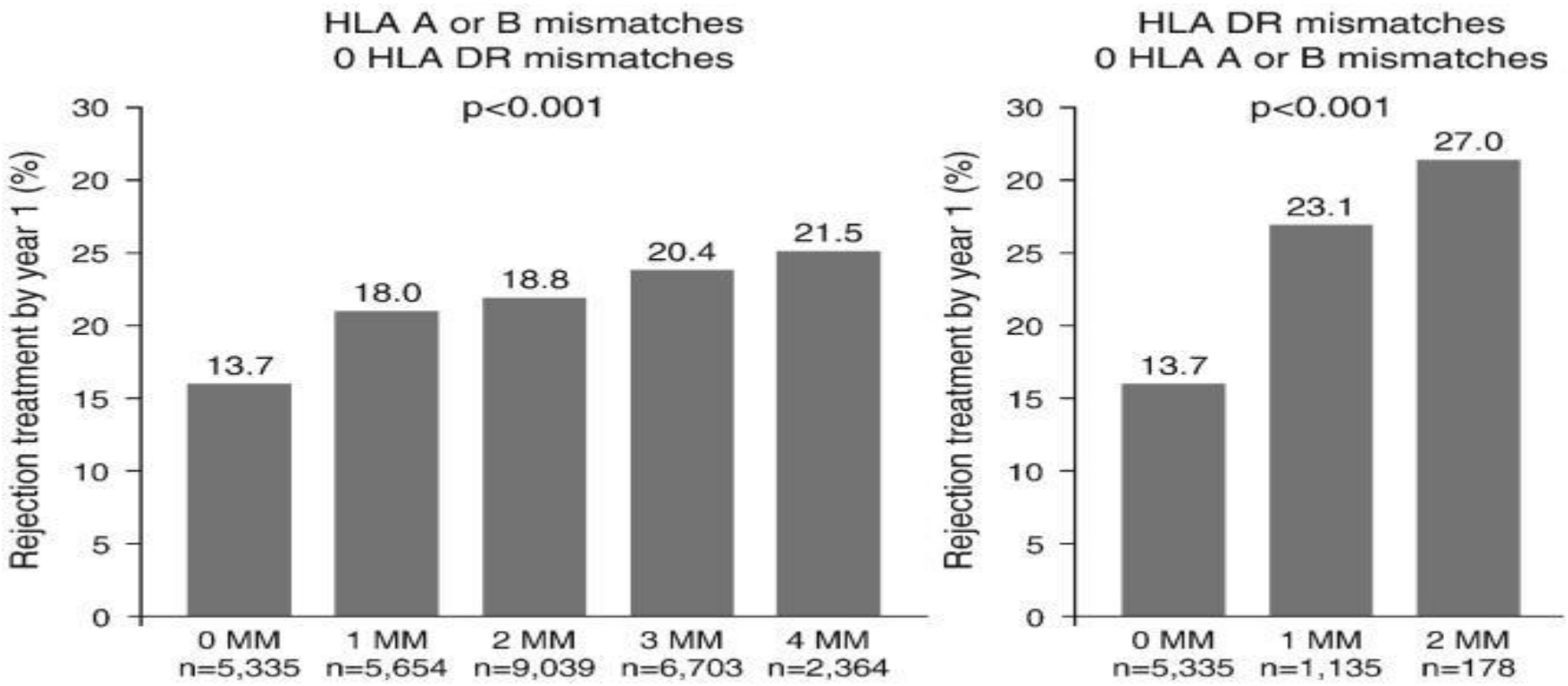
- Younger recipient age.
  - Younger recipients are at substantially higher risk than older recipients, although there is no clear age threshold for the risk of acute rejection.
  - compounded by higher rates of non-adherence in adolescents
- Older donor age
  - Kidneys from older donors may impart increased risk for acute rejection to the recipient, but a distinct age threshold has not been clearly defined.
- African-American ethnicity
- . Low Vitamin D Exposure Is Associated With Higher Risk of Infection in Renal Transplant Recipients
- Husband to Wife Renal Transplants Are Associated With a Higher Risk of Early Antibody Mediated

KDIGO Clinical Practice Guideline For The Care Of Kidney Transplant Recipients'. *American Journal of Transplantation* 9 (2009): S1-S155.

Kaplan-Meier graft survival: recipient primary cause of disease



HLA Mismatch : REJECTION TTT by YEAR 1



Transplantation Reviews 2016 30, 77-84DOI: (10.1016/j.trre.2016.02.002)

Qualitative assessment of Pre-transplant Risk factors for Acute rejection

	Quality of evidence	Impact
Recipient clinical characteristics		
Younger age	*Good*	*Strong**
Gender	Moderate	No
Black race	*Moderate*	*Strong*
High BMI	Weak	No
Retransplantation	Moderate	No
CMV infection	Weak	No
HIV infection	Weak	No
HCV infection	Weak	No
Recipient immunological characteristics		
HLA mismatch	*Good*	*Strong*
Presence of anti-HLA antibodies	*Good*	*Strong*
Presence of pretransplant DSA	*Good*	*Strong*
DSA titer	*Moderate*	*Strong*
Panel reactive antibodies	*Moderate*	*Moderate*
Donor clinical characteristics		
Deceased donor	*Moderate*	*No*
Older donor age	*Good*	*Moderate†*
Donor–recipient age matching	*Moderate*	*Strong‡*
Donor–recipient gender matching	Moderate	No
Extended criteria donor	Poor	No§
Cause of death	Poor	No
Nonheart-beating	Moderate	No
Transplant-related factors		
Cold ischemia time	Moderate	Weak¶
Delayed graft function	*Good*	*Strong*

Variables relevant for assessing immune risk are in italics

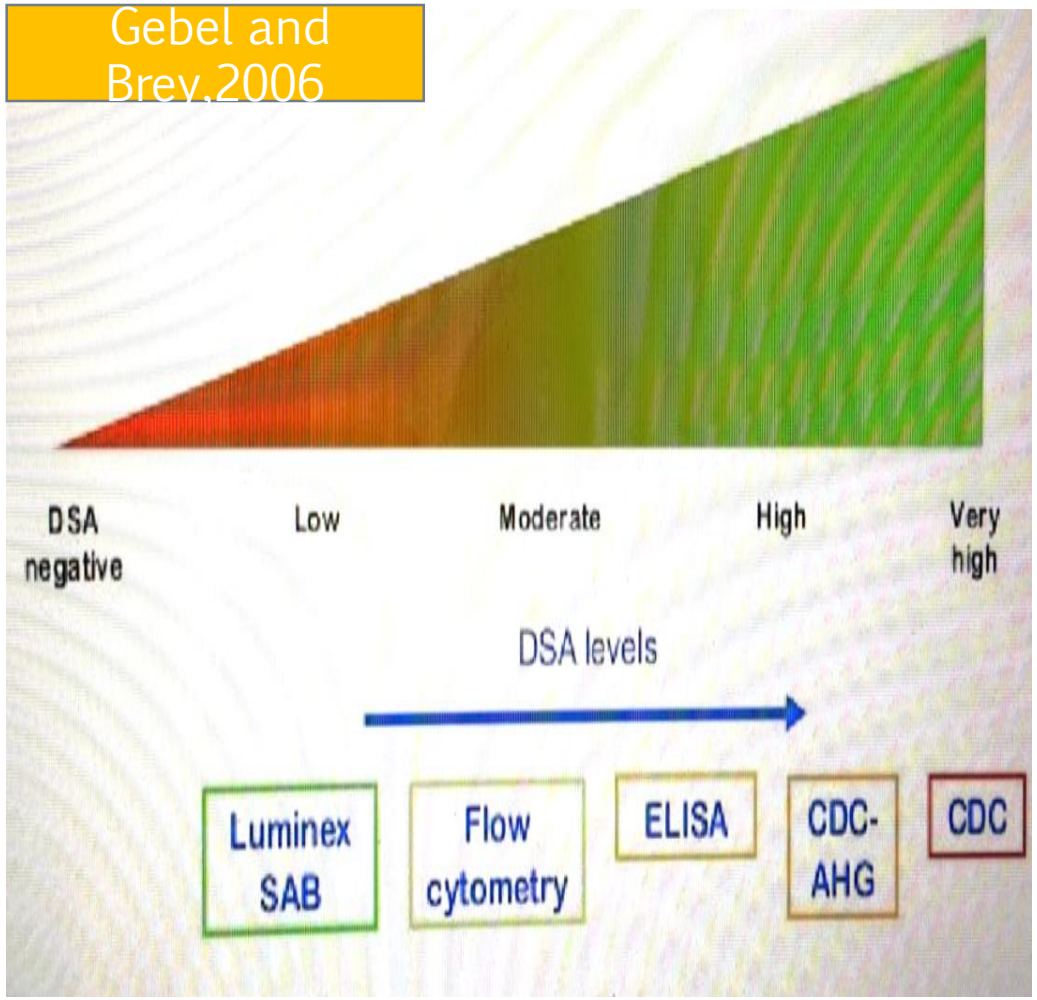
Transplant International ESOT 27 (2013) 129–138

Immunological risk assessment: The key to individualized immunosuppression after kidney transplantation

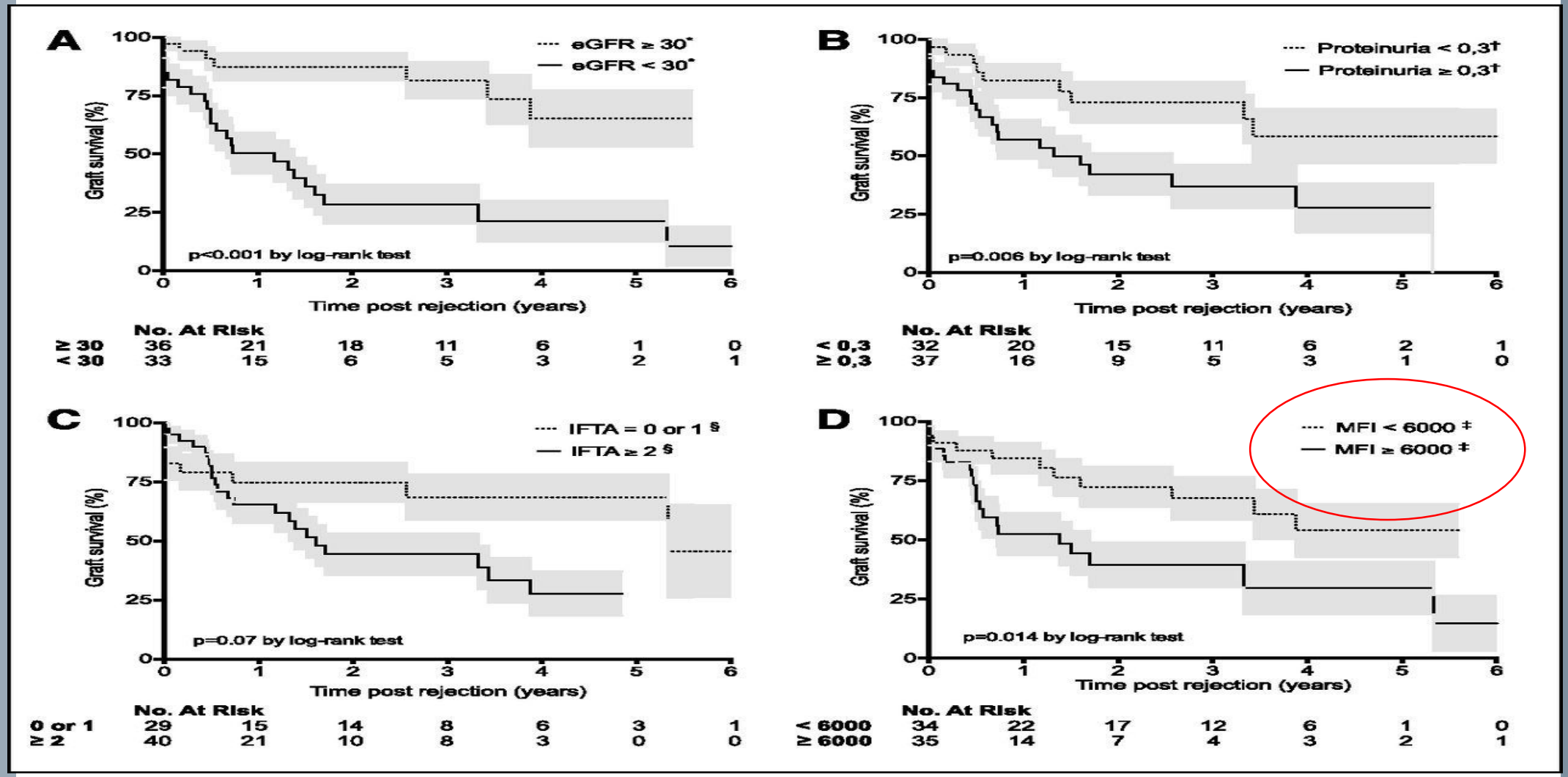
Johann Pratschke, Duska Dragun, Ingeborg A. Hauser, Sabine Horn, Thomas F. Mueller, Peter Schemmer, Friedrich Thaiss

› Cross-match testing with cytotoxic analysis has long been supplemented by flow cytometry, but development of solid-phase single-bead antigen testing of solubilized human leukocyte antigens (HLA) to detect donor-specific antibodies (DSA) permits a far more nuanced stratification of immunological risk status, including the different classes and intensities of HLA antibodies Class I and/or II, including HLA-DSA.

Transplantation Reviews
Volume 30, Issue 2, Pages 77-84 (April 2016)
DOI: 10.1016/j.trre.2016.02.002



Factors associated with worse kidney graft survival at diagnosis of AMR. Kaplan–Meier curves for kidney graft survival after AMR



eGFR by MDRD

Sicard A et al. JASN 2015;26:457-467

JASN

Risk and immune status assessment Tests

- panel reactive antibody (PRA) test
- stimulation-dependent adenosine triphosphate (ATP) release from CD4T+ cells (analyzed using the ImmuKnow assay (Cylex, Inc. Columbia, MD) have been examined as a marker of increased T cell immune activation.
- the presence of soluble CD30, a membrane-bound molecule proteolytically cleaved in activated T cells .
- Protocol biopsies
- mixed lymphocyte reactions (MLR orMLC)
- A more sensitive modification of MLR is the **ELISPOT assay**.

Poggio ED, Augustine JJ, Clemente M, Danzig JM, Volokh N, Zand MS, Hricik DE, Heeger PS Transplantation. 2007 Apr 15; 83(7):847-52).

Interpretation of Panel Reactive Antibody

PRA (% panel reactive)	Interpretation	Treatment indication
<20	Non- or low- sensitized	None
20-50	Moderately sensitized	Increased post-transplant monitoring. Possibly increased immunosuppression
>50	Highly sensitized	Increased immunosuppression. Consider pre- and post-transplantation apheresis

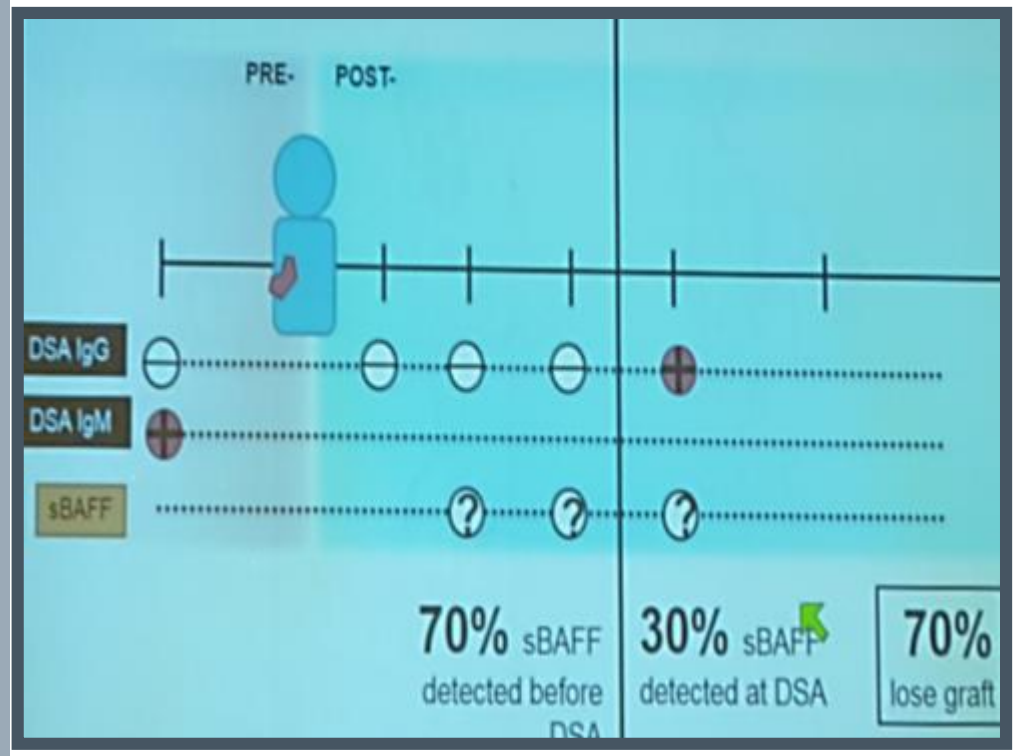
Liapis H, Wang H. Pathology of solid organ transplantation. Berlin: Springer; 2011.

Recent Risk and immune status assessment Tests

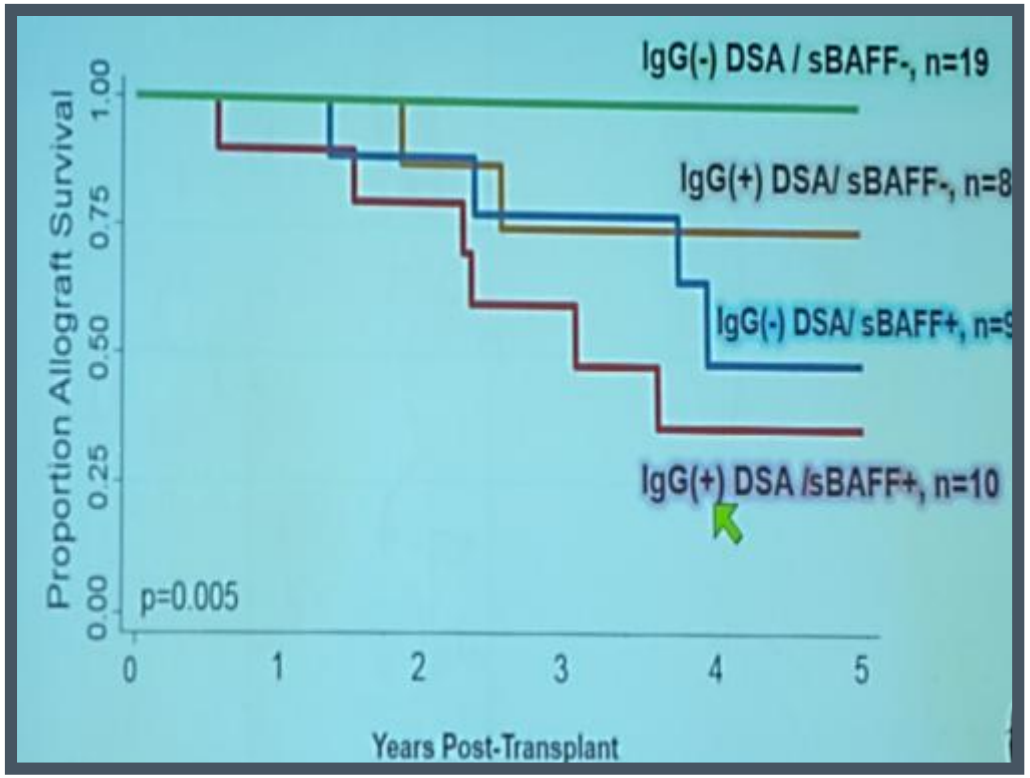
- Several groups have used microarrays to determine protein or microRNA “signatures” in blood and urine as a means to assess post-transplant risk of poor graft outcome
- Markers in the blood and urine such as B-cell activating factor (BAFF) ,The expression of B-cell activating factor belonging to tumor necrosis factor superfamily (BAFF) significantly correlated with C4D in kidney allograft rejection.
- Value of Subclasses of IgG & Complement
- Immunogenetics (K-sort Test)

Soluble B-cell activating factor (sBAFF) is Associated with increased Risk of Graft Loss

SBAFF WAS DETECTED PRIOR TO IGG DSA IN 70% OF PATIENTS WITH POST-TRANSPLANT IGG DSA



SBAFF MIGHT BE INDEPENDENT OF DSA IGG



(*Ann Niguyen etal* BOSTON ,2016,AST)

, terasaki foundation laboratoty, LA,California &East Carolina Univ

Evaluation of DSA class, MFI and complement binding Capacity

- N=125 failed grafts: 19 Median follow up :1year
- DSA Characteristics and kidney allograft loss
- IgG3 is a strong determinant of allograft loss
- DSA IgG subclasses segregate distinct allograft injury phenotypes:
  -IgG3 is associated with acute ABMR
  -IgG4 is associated with subclinical ABMR

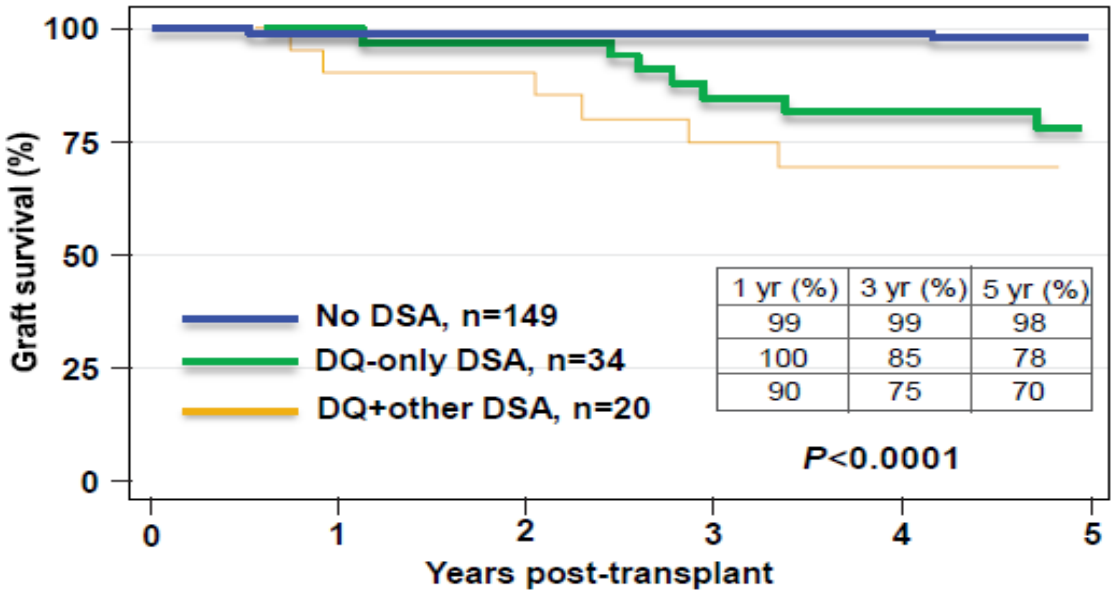
	HR	95%CI	p
MFI	1.0	1.0-1.0	NS
HLA class	1.7	0.6-4.7	NS
C1q-binding capacity	6.2	2.1-18.8	0.001
IgG1	1.8	0.5-6.2	NS
IgG2	0.9	0.4-2.3	NS
IgG3	7.4	2.8-19.6	<0.001
IgG4	0.3	0.07-1.4	NS

(French group.ESOT,brussels2015)

De novo persistent, complement-binding DQ DSAs negatively impact allograft outcomes

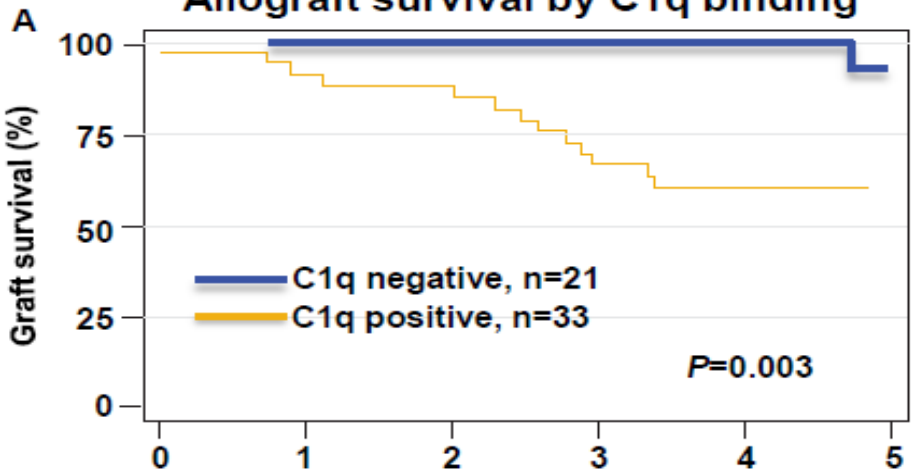
Graft survival among 284 first-time kidney transplant recipients retrospectively screened for the presence of posttransplantation DSA

De novo DQ DSA, death-censored: allograft survival

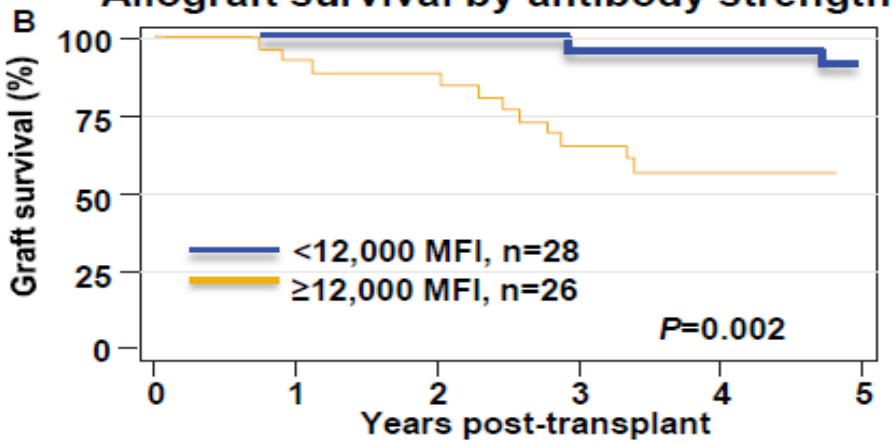


	1 yr (%)	3 yr (%)	5 yr (%)
No DSA, n=149	99	99	98
DQ-only DSA, n=34	100	85	78
DQ+other DSA, n=20	90	75	70

Allograft survival by C1q binding



Allograft survival by antibody strength



Correlation between Cell numbers and Graft survival

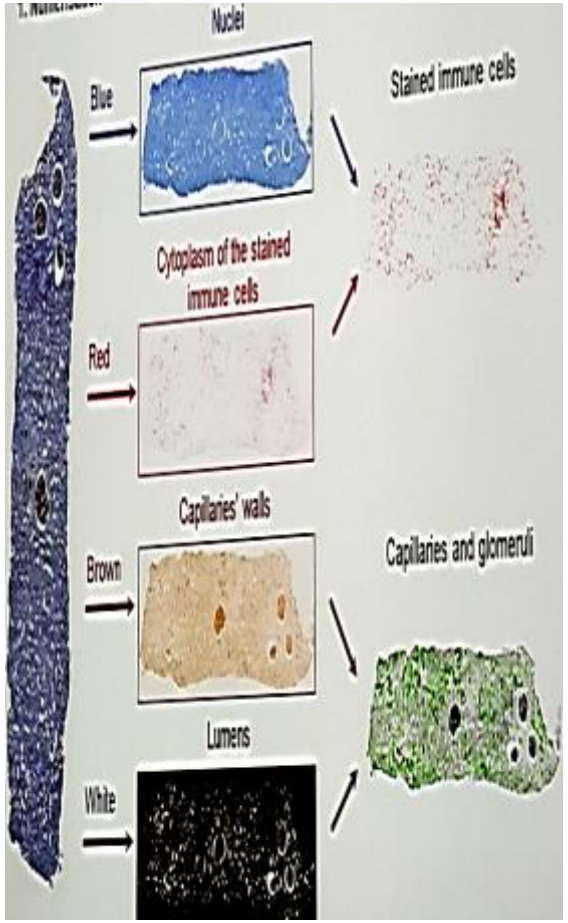
Computer Assisted inflammation Analysis (CIA) on Kidney graft biopsies of 52 patients with AMR between 2005-2012in Lyon

-Division of patients into 2 groups according to median number of cells

Table 1. Risk for allograft loss according to the type and number of immune cells in the different renal compartments

	Glomeruli			Capillaries			Interstitium		
	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value
T lymphocytes (CD3+)									
Lower quantile	1.00			1.00			1.00		
Higher quantile	1.31	(0.62-2.79)	0.48	1.18	(0.58-2.42)	0.65	1.50	(0.73-3.10)	0.27
B lymphocytes (CD20+)									
Lower quantile	1.00			1.00			1.00		
Higher quantile	2.38	(1.02-5.55)	**0.04**	1.51	(0.70-3.24)	0.28	1.56	(0.72-3.39)	0.26
Granulocytes (CD66b+)									
Lower quantile	1.00			1.00			1.00		
Higher quantile	1.04	(0.35-3.04)	0.94	1.19	(0.48-2.93)	0.71	1.19	(0.48-2.93)	0.71
Natural Killers (CD56+)									
Lower quantile	1.00			1.00			1.00		
Higher quantile	0.95	(0.29-3.12)	0.92	0.33	(0.10-1.04)	0.06	0.81	(0.28-2.3)	0.69
Monocytes-macrophages (CD68+)									
Lower quantile	1.00			1.00			1.00		
Higher quantile	1.02	(0.46-2.25)	0.96	3.18	(1.43-7.07)	**<0.01**	2.62	(1.20-5.72)	**0.01**

Abbreviations: HR: Hazard Ratio, CI: Confidence Interval

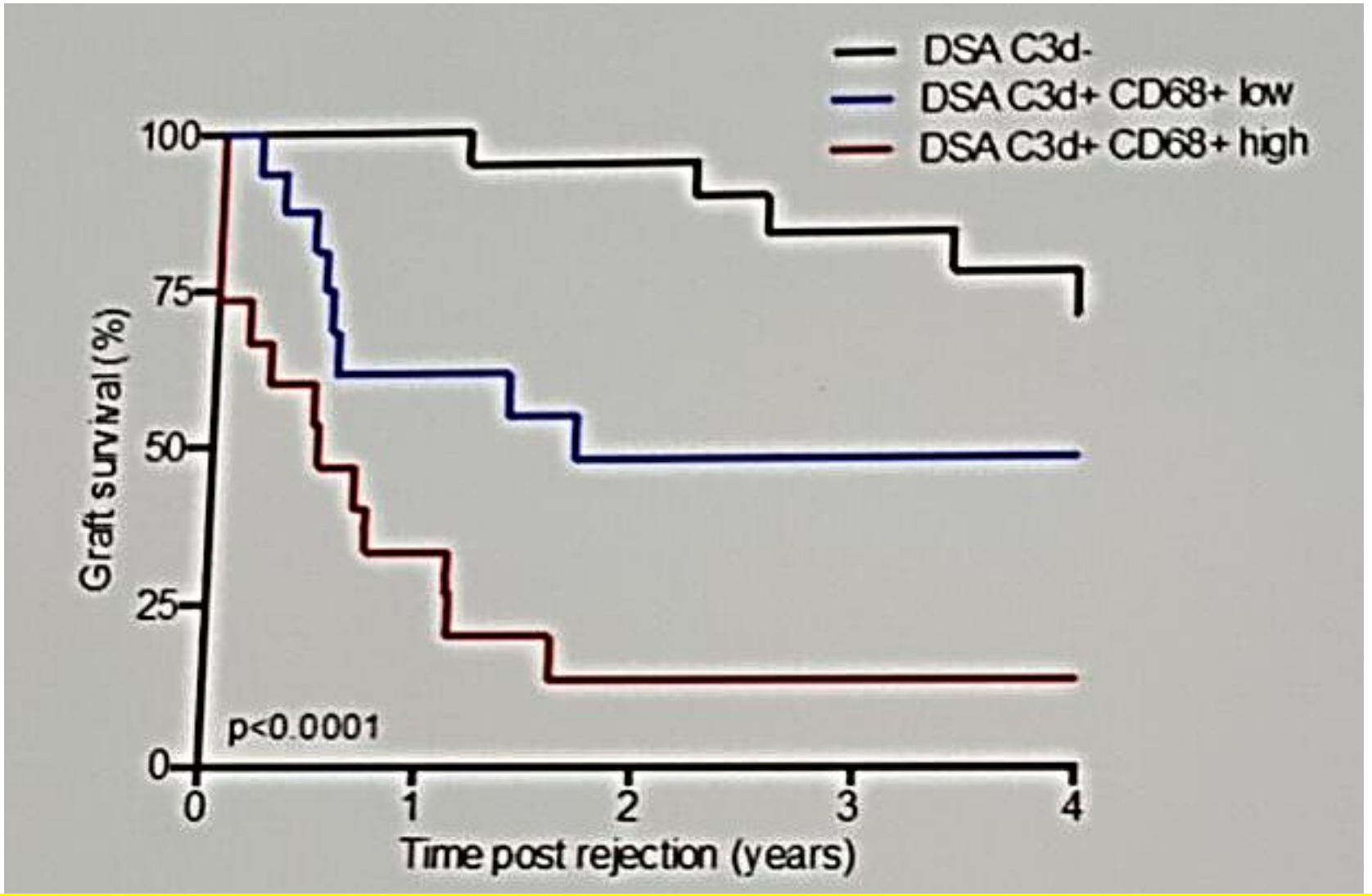


Antoine secard ,lyon ESOT 2015

Conclusion :CIA allowed to

-show a correlation between the capacity of DSA to bind Complement in vitro and monocyte infiltration

-Improve the prognosis evaluation of patients with C3D-Binding DSA



Integration of the C3D assay and CD68+cells quantification

The kSORT Assay to Detect Renal Transplant Patients at High Risk for Acute Rejection: Results of the Multicenter AART Study

Silke Roedder[1,9], Tara Sigdel[1,9], Nathan Salomonis[2,9], Sue Hsieh[1], Hong Dai[3,10a], Oriol Bestard[4], Diana Metes[5], Andrea Zeevi[5], Albin Gritsch[6], Jennifer Cheeseman[7], Camila Macedo[5], Ram Peddy[3], Mara Medeiros[8], Flavio Vincenti[1], Nancy Asher[1], Oscar Salvatierra[9], Ron Shapiro[5], Allan Kirk[7,10b], Elaine Reed[6], Minnie M. Sarwal[1,9]

1 Department of Surgery, University of California San Francisco, San Francisco, California, United States of America, 2 Biomedical Informatics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America, 3 California Pacific Medical Center, San Francisco, California, United States of America, 4 Renal Transplant Unit, Bellvitge University Hospital, Barcelona, Spain, 5 Thomas E. Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, 6 Immunogenetics Center, University of California Los Angeles, Los Angeles, California, United States of America, 7 Department of Surgery, Emory University, Atlanta, Georgia, United States of America, 8 Laboratorio de Investigacion en Nefrologia, Hospital Infantil de México Federico Gómez, Mexico City, Mexico, 9 Stanford University, Stanford, California, United States of America

Is a non Invasive genomic blood test (17 Genes) for monitoring renal Transplant Rejection BUT without discriminating betweenCell-mediated and antibody-mediated immune rejection

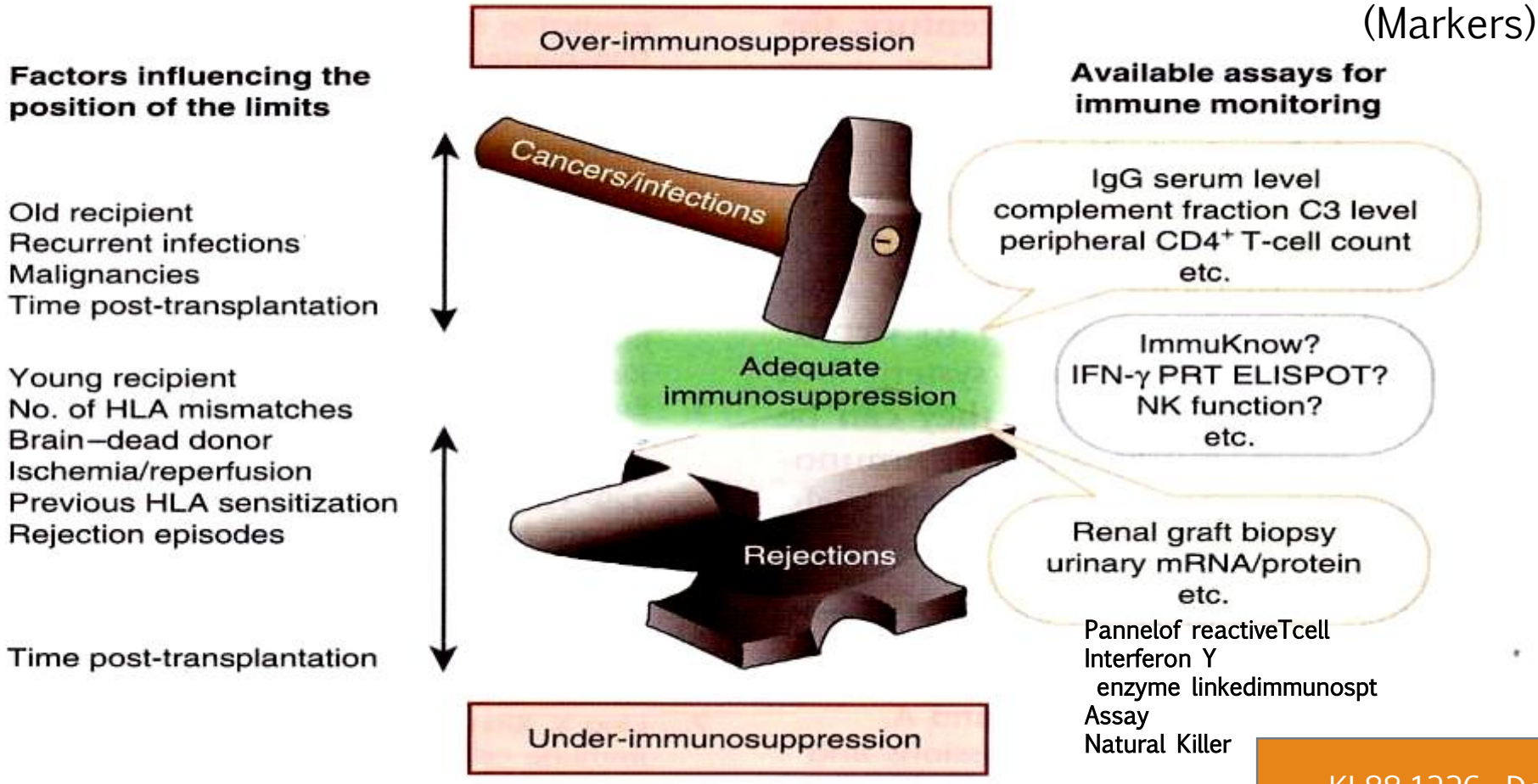
- kSORT is a surveillance and monitoring assay clinicians can utilize to measure alloimmune response over time.

KSORT(KidneySolid Organ Response Test)3-4 months before Current Diagnostic tools(Creatinine and Biopsy)

Silke et al,PLOS Medicine,11:1-15,Nov 2014

SO ADEQUATE IMMUNOSUPPRESSION? Is Finding safe place between hammer (of Over) and Anvil(of under)

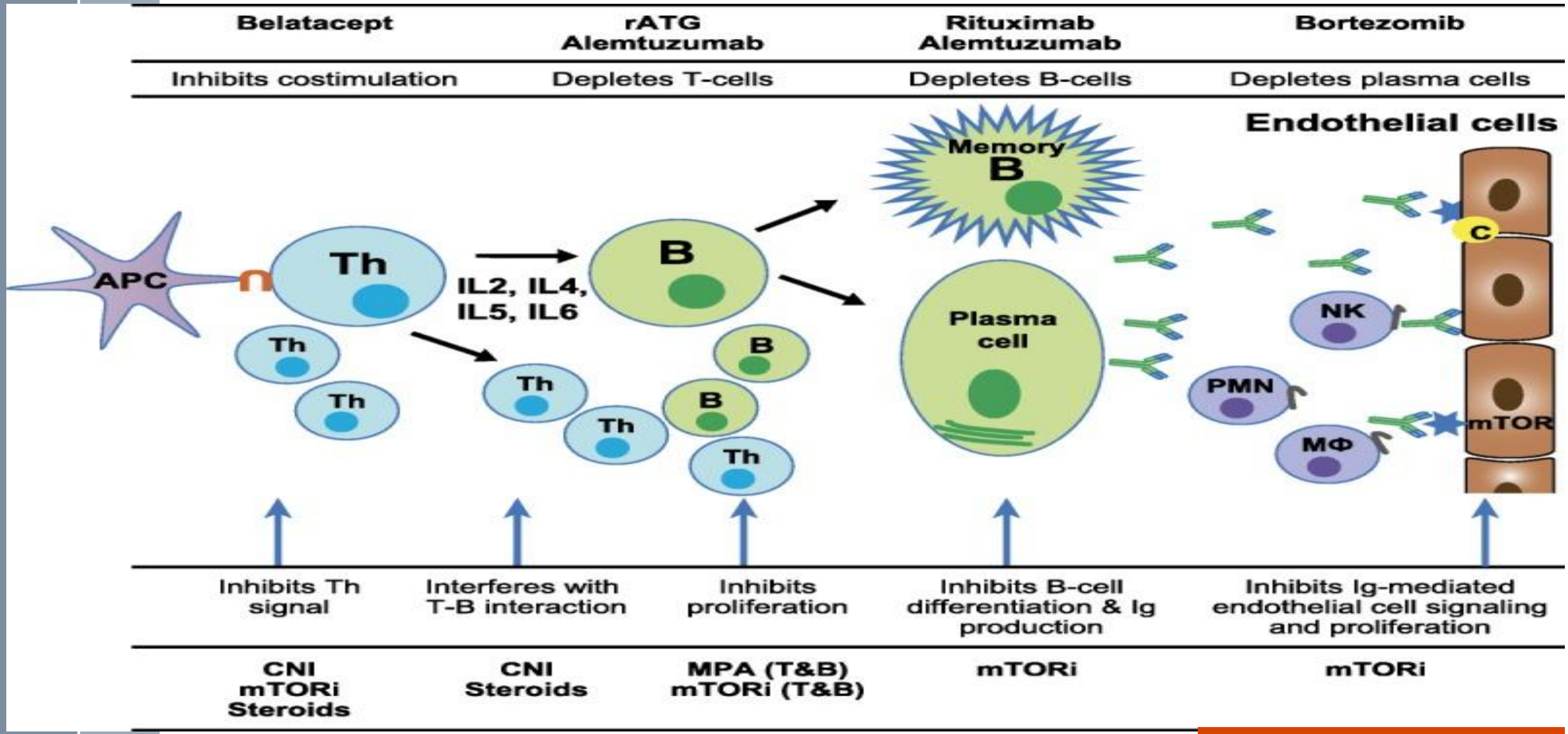
(Markers)



Pannelof reactiveTcell
Interferon Y
enzyme linkedimmunospt
Assay
Natural Killer

KI 88,1226 December 2015(Olivier Thaunat,Lyon

Which Protocol among armementum of immunosupressants ?



APC, antigen presenting cell; B, B-cell; C, complement; CNI, calcineurin inhibitor; Mϕ, macrophage; mTORi, mammalian target of rapamycin inhibitor; NK, natural killer; PMN,polymorphonuclear

Transplantation. 2016 Jan; 100(1): 39–53.

Many transplant centers, utilize a maintenance regimen consisting of triple immunosuppression therapy :

- A calcineurin inhibitor (Cyclosporin or Tacrolimus)
- An antimetabolite (AZA.MMF,Mycophenolate sodium)
- and Prednisone
- M-TORs(everolimus and Sirolimus) are also used by some transplant centers in triple-therapy regimens with the low-dose calcineurin inhibitor without an antimetabolite.
- Why?Numerous multicenter randomized controlled trials and meta-analyses, triple immunosuppressive regimens are generally associated with >90 percent allograft survival at one year in combination with acute rejection rates of <20 percent.

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Optimized MPA dose with EC-MPS drives efficacy

Myfortic vs. CellCept: A Large, Single-Center Comparison.
Hans Sollinger, Glen Leverson, Barbara Voss, John Pirsch. Dept of Surgery, Division of Transplantation, Univ of Wisconsin, Madison, WI.

Optimized MPA dose with EC-MPS drives efficacy

Material and Methods

- Retrospective of 2,216 patients from DD, LRD, LURD or SPK between 2000 and 2006.
- 1,709 transplants qualified for the study and were compared between a group receiving EC-MPS and a group receiving mycophenolate mofetil (MMF).
- Post-initiation of MPA therapy dose levels, post-transplant dose levels, and post-transplant e-GFR levels were compared between groups using a Wilcoxon rank-sums test.

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Objectives

- Time to first dose reduction
- Drug discontinuation
- Anti diarrheal use
- Infection
- Acute rejection
- Biopsy-proven acute rejection
- Graft loss

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Results

	CellCept	Myfortic	p-value
N	1,111	598	
Kidney graft survival	86.4%	84.4%	NS
Acute kidney rejection	31%	24.7%	0.0212
Biopsy-proven kidney rejection	30.2%	21.9%	0.0004
Dose reduction	74.4%	64%	0.0001
Drug discontinuation	33.3%	27.9%	0.0130
Post-tx anti-diarrheal use	6.5%	3.6%	0.0132
Infection	64.7%	59%	NS
Bacterial infection	36.4%	37.3%	NS
Viral infection	21.3%	19.5%	NS
Fungal infection	14.3%	9.4%	0.0091

Percentages listed are based on 2-yr Kaplan-Meier estimates. P-values are based on a log-rank test

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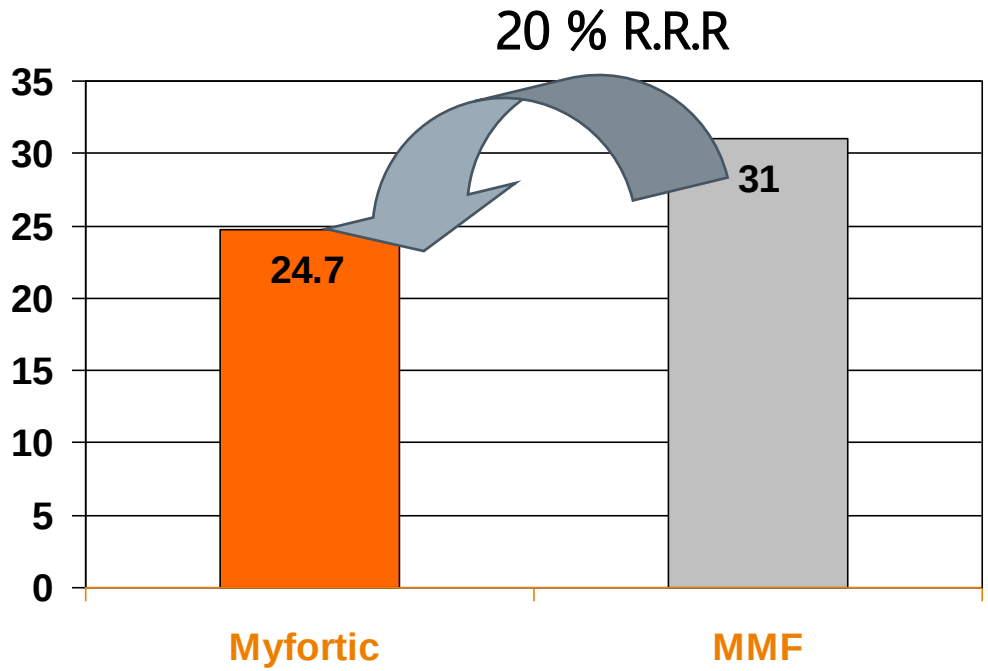
Acute Kidney rejection



P=0.0212

Incidence of Acute kidney rejection with EC-MPS was 20 % RRR (Relative Risk Reduction)lower than that with Cellcept

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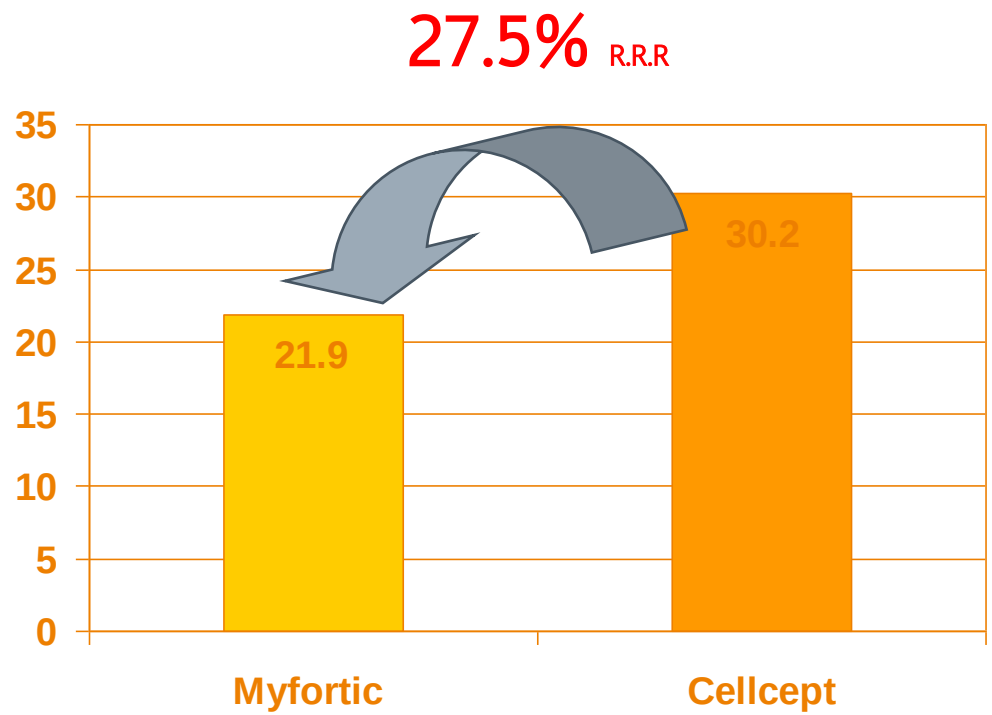
Biopsy proven kidney rejection



P=0.0004

Incidence of biopsy proven kidney rejection with EC-MPS was

27.5 % R.R.R. lower than that with Cellcept

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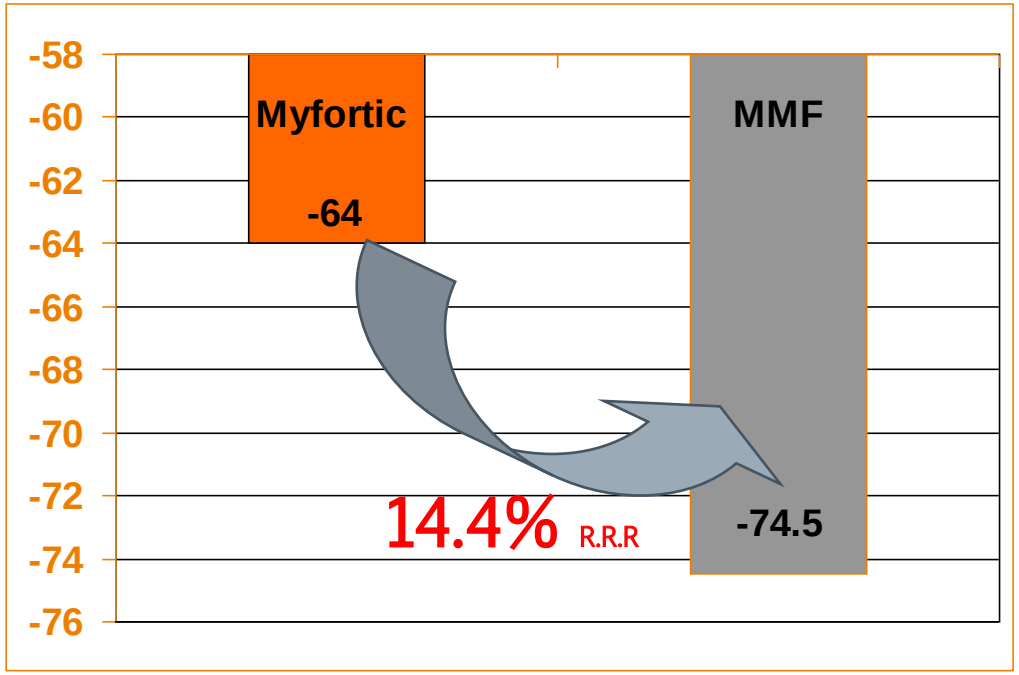
Dose reduction



P=0.0001

EC-MPS was associated with 14.4% R.R.Rlower incidence of dose reduction

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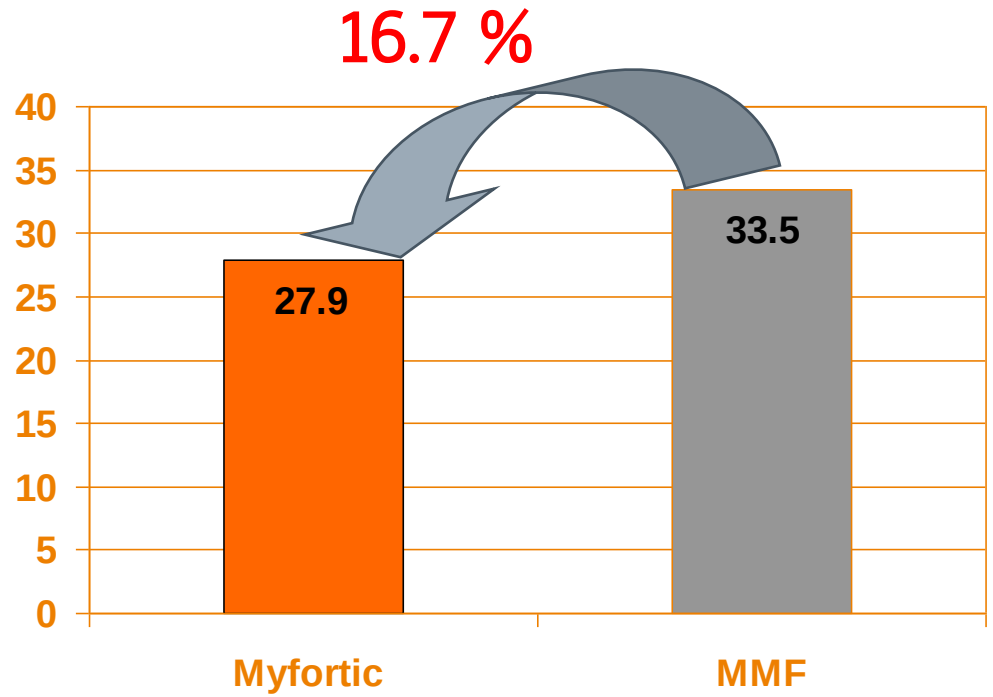
Drug discontinuation



P=0.0130

EC-MPS was associated with 16.7 % lower incidence of drug discontinuation

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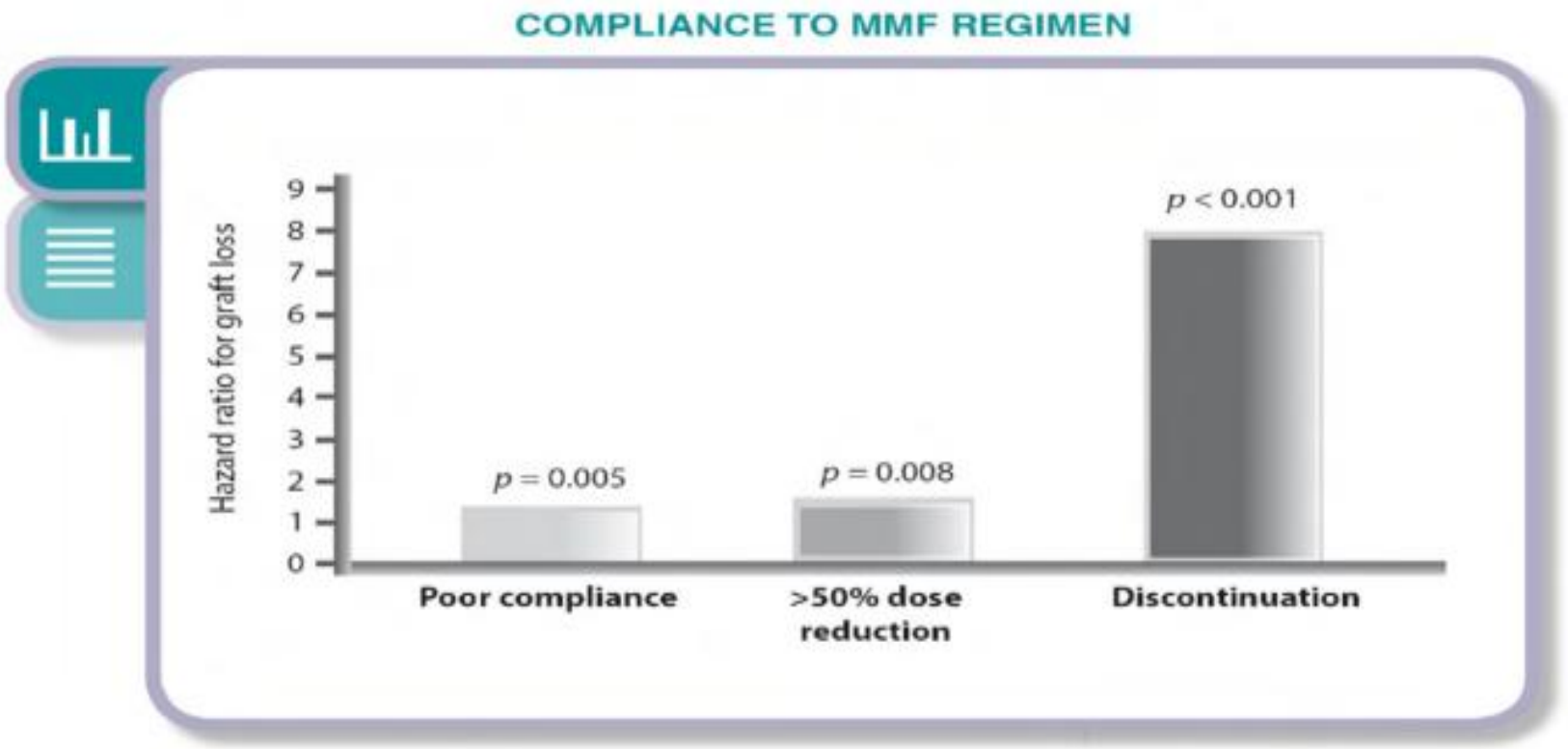
Poor adherence to the MMF regimen is associated with an increased risk of graft loss*

Poor compliance to the MMF regimen is associated with an increased risk of graft loss



Adapted from ref. 3

Takemoto SK et al.
Am J Transplant 2007;7:2704–11

Conclusions

- EC-MPS was found to be associated with fewer adverse GI side effects requiring dose reduction or discontinuation. (*Better tolerance ± adherence*)
- This may have translated into the observed significantly lower incidence of biopsy-proven rejection.
- EC-MPS patients also have a trend toward a lower incidence of infections and a significantly lower incidence of fungal infections.
- Based on these observations, EC-MPS has become the IMPDH (Inosin Monophospate Dehydrogenase enzyme inhibitor) of choice at this large center.

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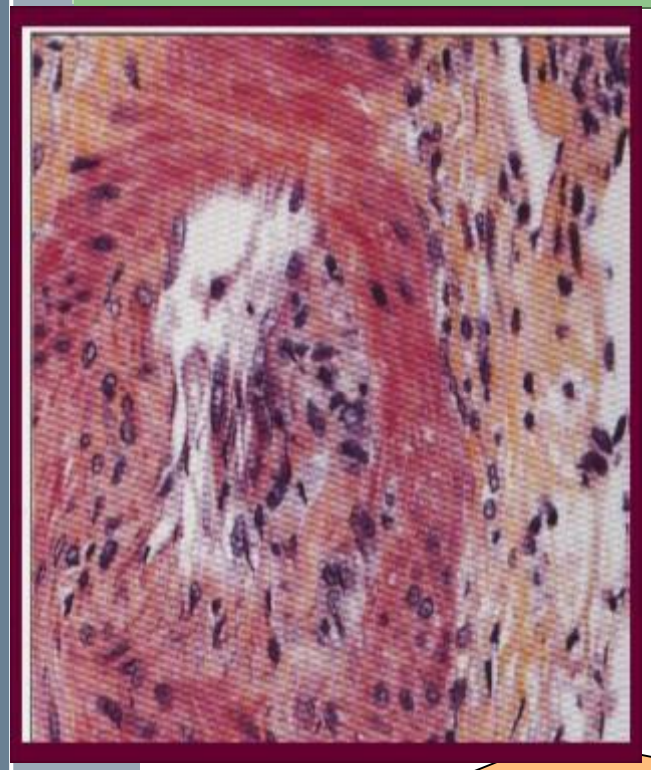
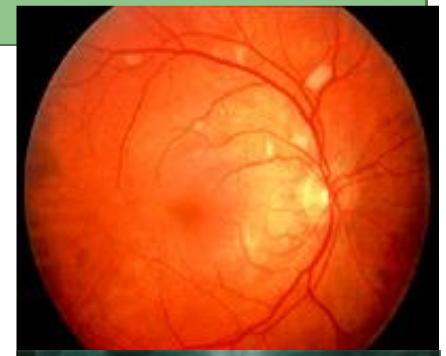
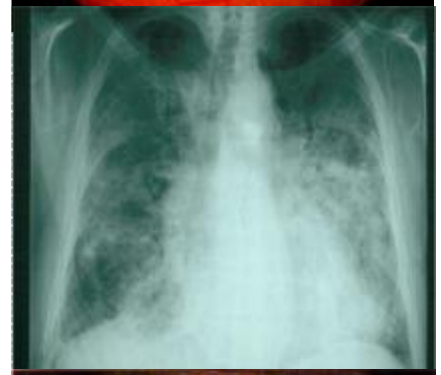
Still Optimising immunosuppression is the key to avoid death with functioning graft

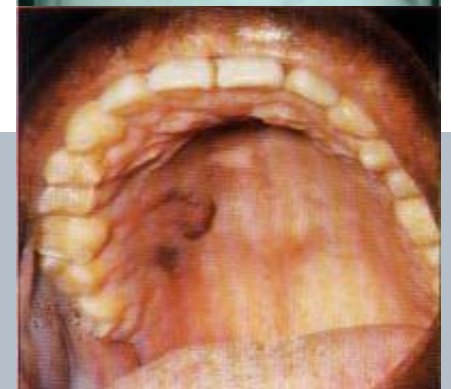


UNDER

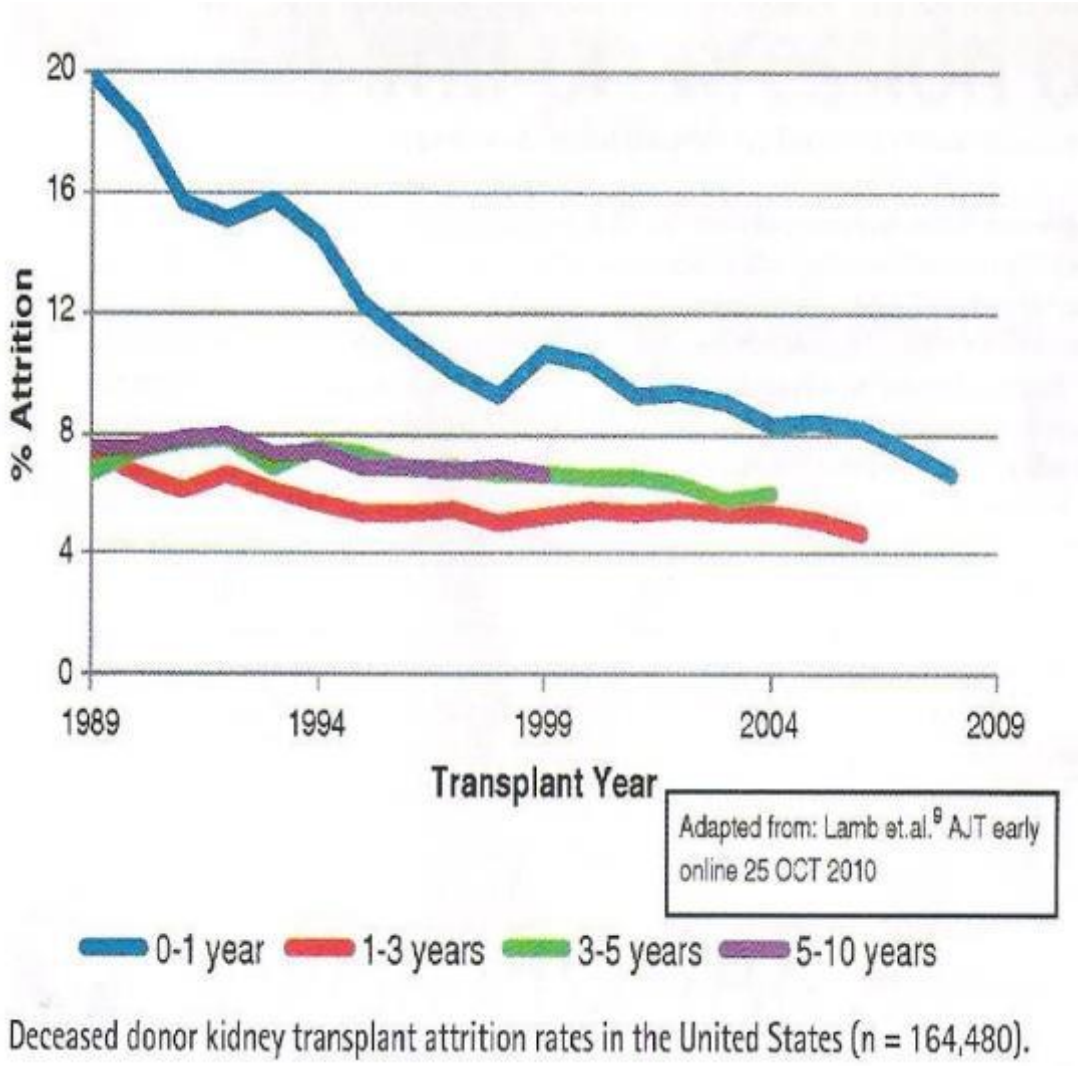
OVER







LONG TERM GRAFT ATTRITION
5-6% Annually



Deceased donor kidney transplant attrition rates in the United States (n = 164,480).

Table 1 | Five important reasons for the failure of CNI-based regimens to improve long-term outcome

1. Early cellular rejection, decreased by the CNIs, does not impact long-term graft survival
2. Immunosuppression with CNIs may be inadequate in controlling the emergence of DSA and chronic antibody-mediated rejection, a major cause of late graft failure either because of minimization regimens and/or non-adherence
3. Late graft failure may occur from mechanisms unrelated to alloimmune injury: nephrotoxicity, accelerated senescence, and glomerular disease
4. Graft loss from BK nephropathy
5. Persistence of graft loss from premature death from infections and cardiovascular disease

Abbreviation: BK, polyomavirus; CNIs, calcineurin inhibitors.

KI ,Nov 2012

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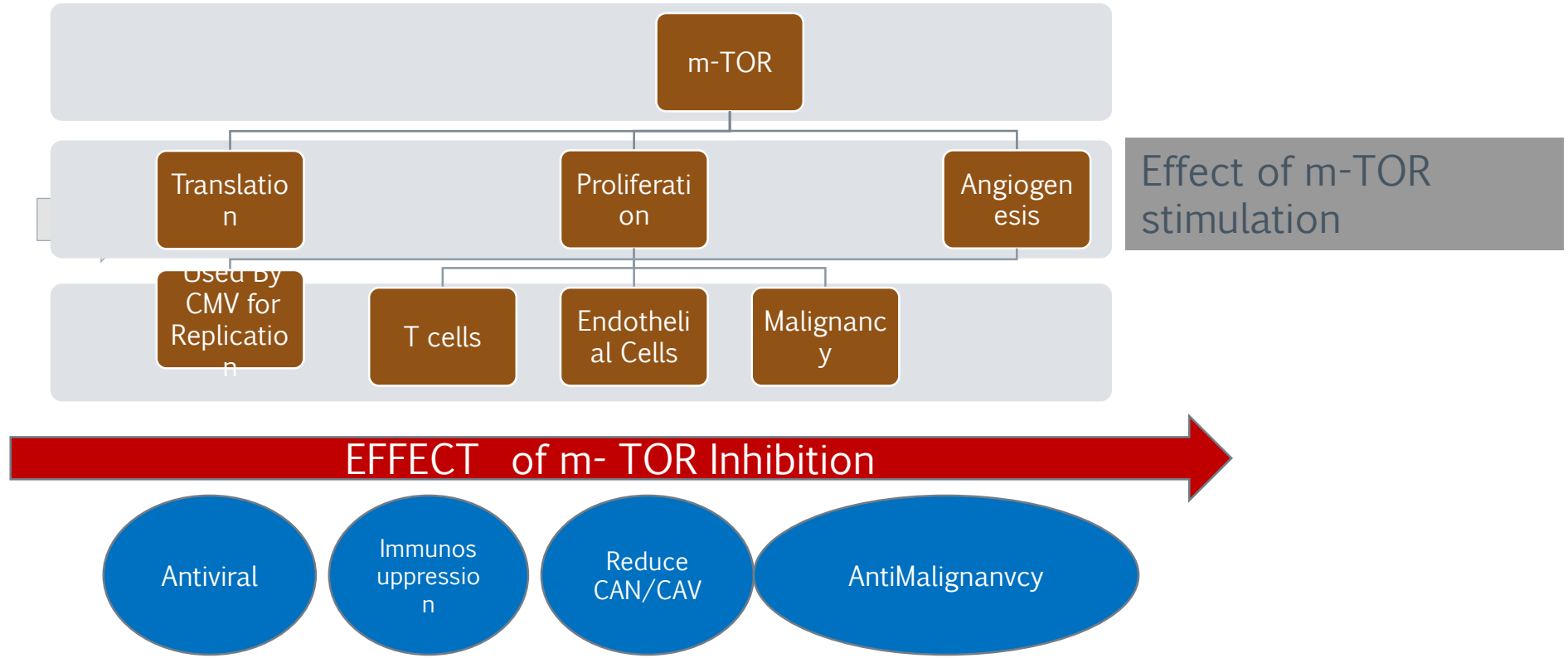
- M-TORs(everolimus) are also used by some transplant centers in triple-therapy regimens with the low-dose calcineurin inhibitor without an antimetabolite.

Many transplant centers, utilize a maintenance regimen consisting of triple immunosuppression therapy :

- A calcineurin inhibitor (Cyclosporin or Tacrolimus)
- An antimetabolite (AZA.MMF,Mycophenolate sodium)
- and Prednisone
- M-TORs(everolimus) are also used by some transplant centers in triple-therapy regimens with the low-dose calcineurin inhibitor without an antimetabolite.

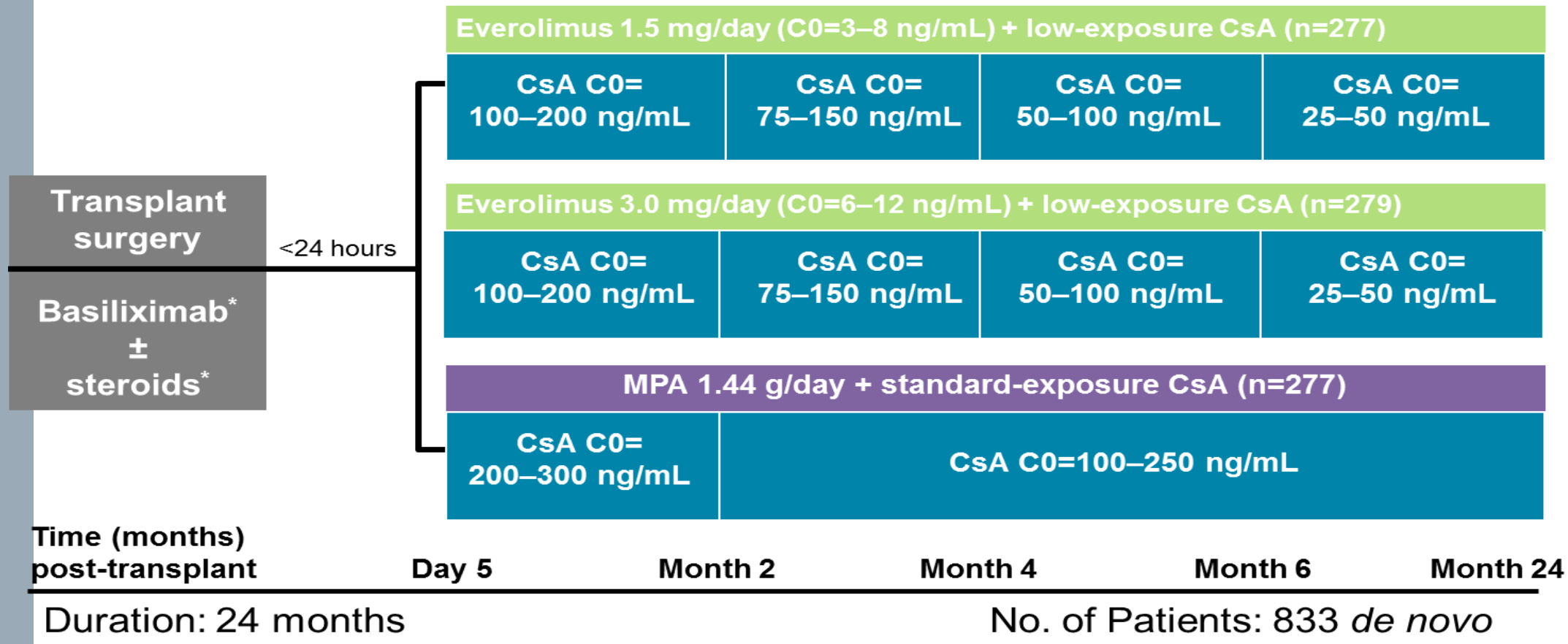
mTOR pathway:role in several physiological processes



Clinical benefits of EVR – Evidence from clinical trials

Efficacy

Study A2309: Study Design



*All patients were administered basiliximab within 2 hours pre-transplantation and 4 days thereafter. Oral steroids administered according to local practice throughout the trial
CsA, cyclosporine

Study A2309: Study Endpoints

- **Primary Endpoint: at 24 months**
  - Treated biopsy acute rejection, graft loss , loss to follow up and death within 12 months.

- **Secondary Endpoint: (All at 12 months)**
  - Graft loss
  - Death
  - Renal function

Comparable composite efficacy failure with EVR + low CsA vs MPA + standard CsA over 2 years

Incidence of primary efficacy composite endpoint (tBPAR, graft loss, death or loss to follow-up)

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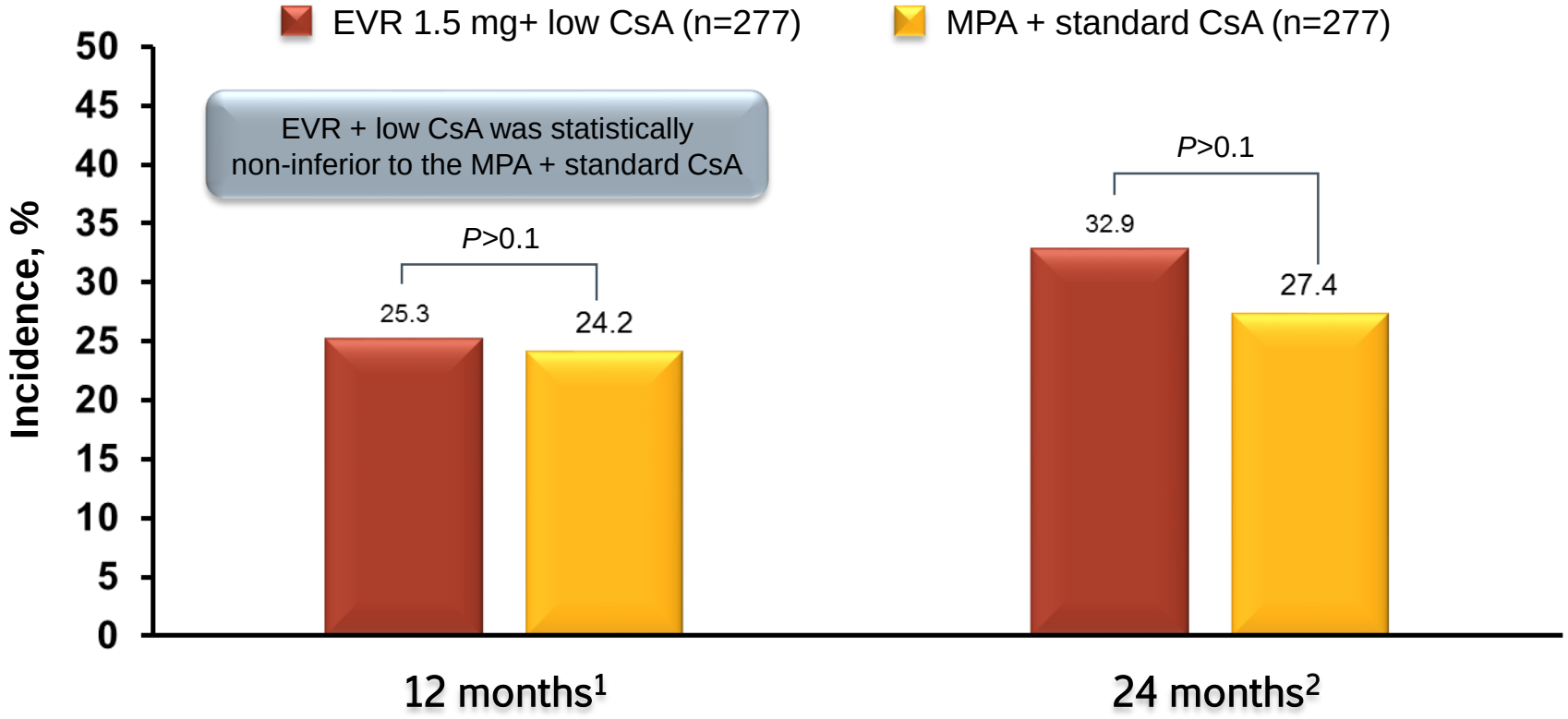

CsA, cyclosporine; EVR, everolimus; tBPAR, treated biopsy-proven acute rejection; MPA, mycophenolic acid.

1. Tedesco Silva H Jr, et al. *Am J Transplant.* 2010;10:1401–1413; 2. Cibrik D, et al. *Transplantation.* 2013;95:933–942.

Individual components of primary composite endpoint were **comparable** at Months 12 and 24

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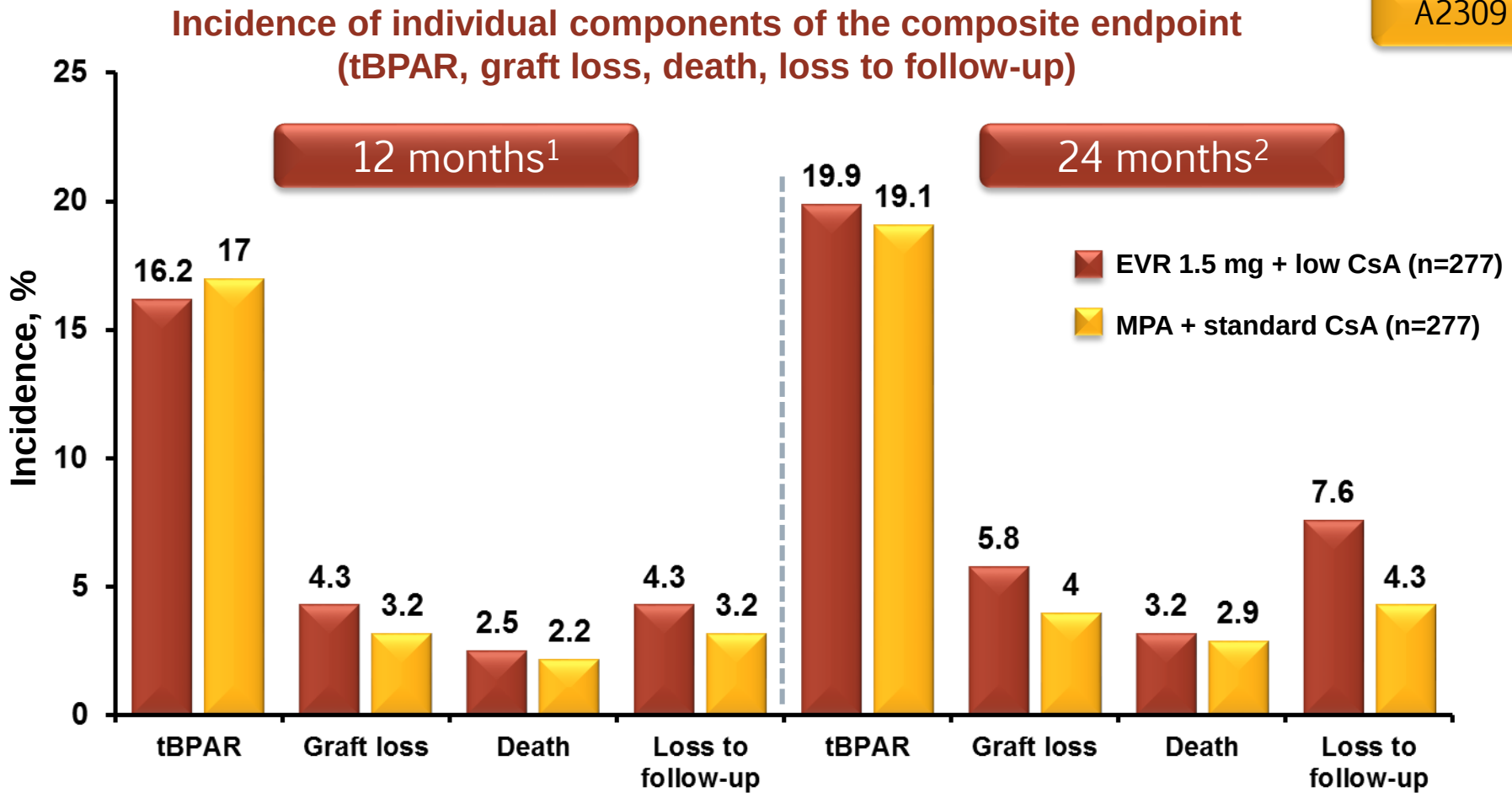


CsA, cyclosporine; EVR, everolimus; tBPAR, treated biopsy-proven acute rejection; MPA, mycophenolic acid.

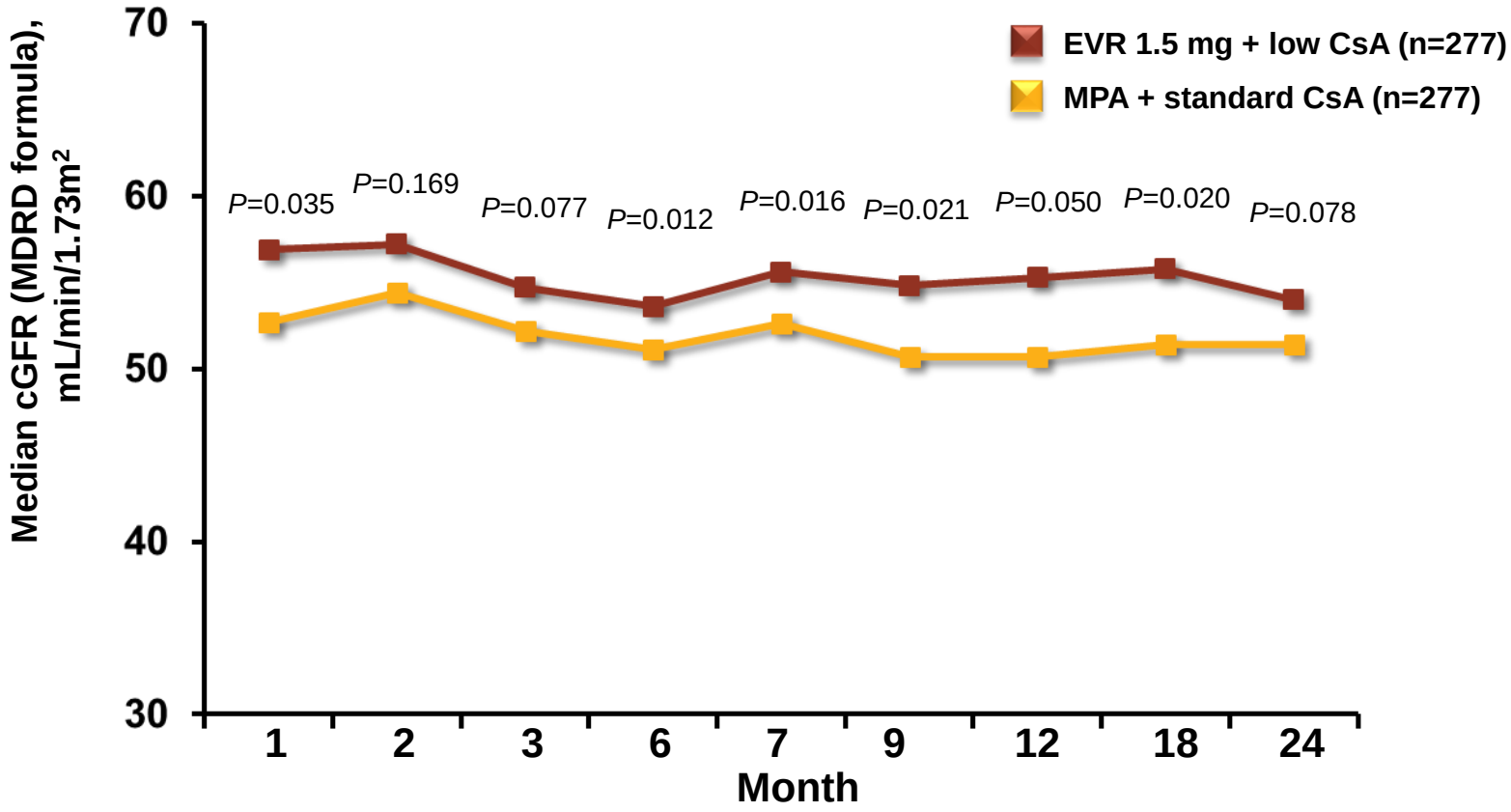
1. Tedesco Silva H Jr, et al. *Am J Transplant.* 2010;10:1401–1413; 2. Cibrik D, et al. *Transplantation.* 2013;95:933–942.

Renal function benefits -1

Early improvements in renal function with EVR plus low CsA were sustained at 24 months

Renal function by visit: Calculated GFR (MDRD)[1]

ITT population – 24 month analysis



cGFR, calculated glomerular filtration rate; EVR, everolimus; ITT, intention-to-treat; MDRD, Modification of Diet in Renal Disease; CsA, cyclosporine; MPA, mycophenolic acid.

1. Data on file. Basel, Switzerland: Novartis Pharma AG; 2013; 2. Cibrik D, et al. *Transplantation.* 2013;95:933–942.

Renal function benefits-2

Numerically more patients treated with *de novo* EVR had improvement in renal function vs MPA

Percentage of patients with mean eGFR <60mL/min/1.73m² at Month 1 who achieved eGFR ≥60 mL/min/1.73m² at Month 24

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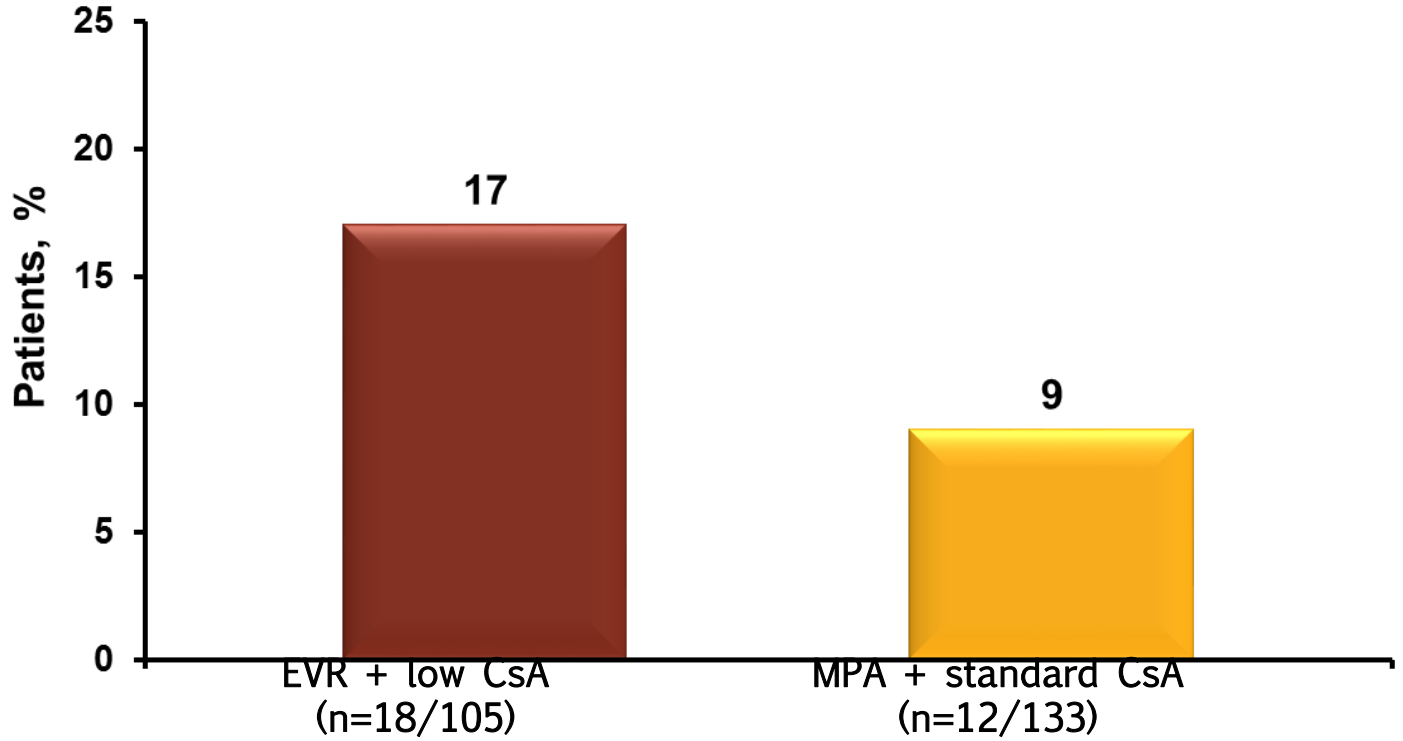

CSA, CYCLOSPORINE; EGFR, ESTIMATED GLOMERULAR FILTRATION RATE; EVR, EVEROLIMUS; MPA, MYCOPHENOLATE SODIUM.

DATA ON FILE. BASEL, SWITZERLAND: NOVARTIS PHARMA AG; 2013.

Renal function benefits-3

Numerically more patients in EVR group had good renal function at Month 24

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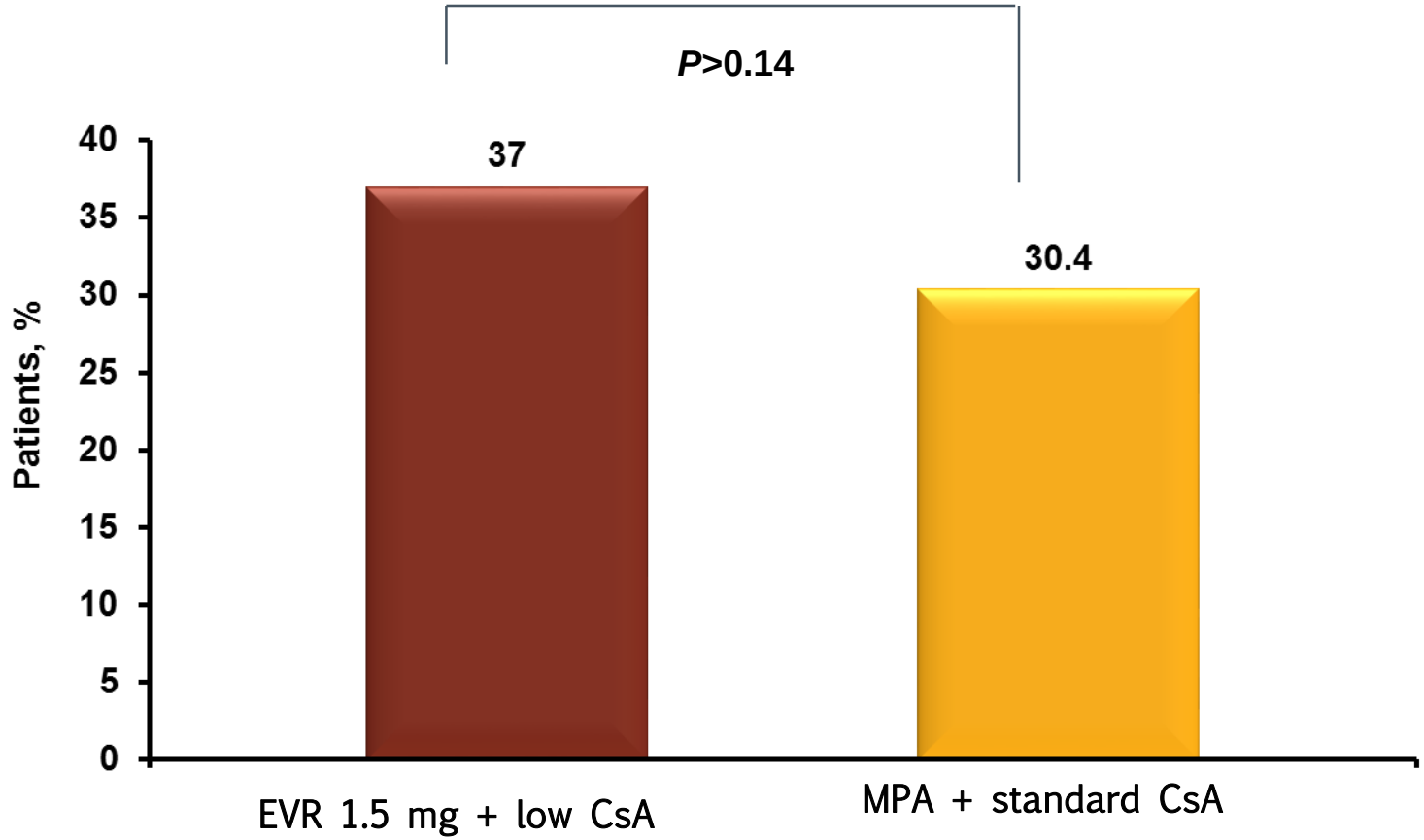
eGFR (MDRD) values ≥60 mL/min/1.73m^2 at Month 24 by NKF categories



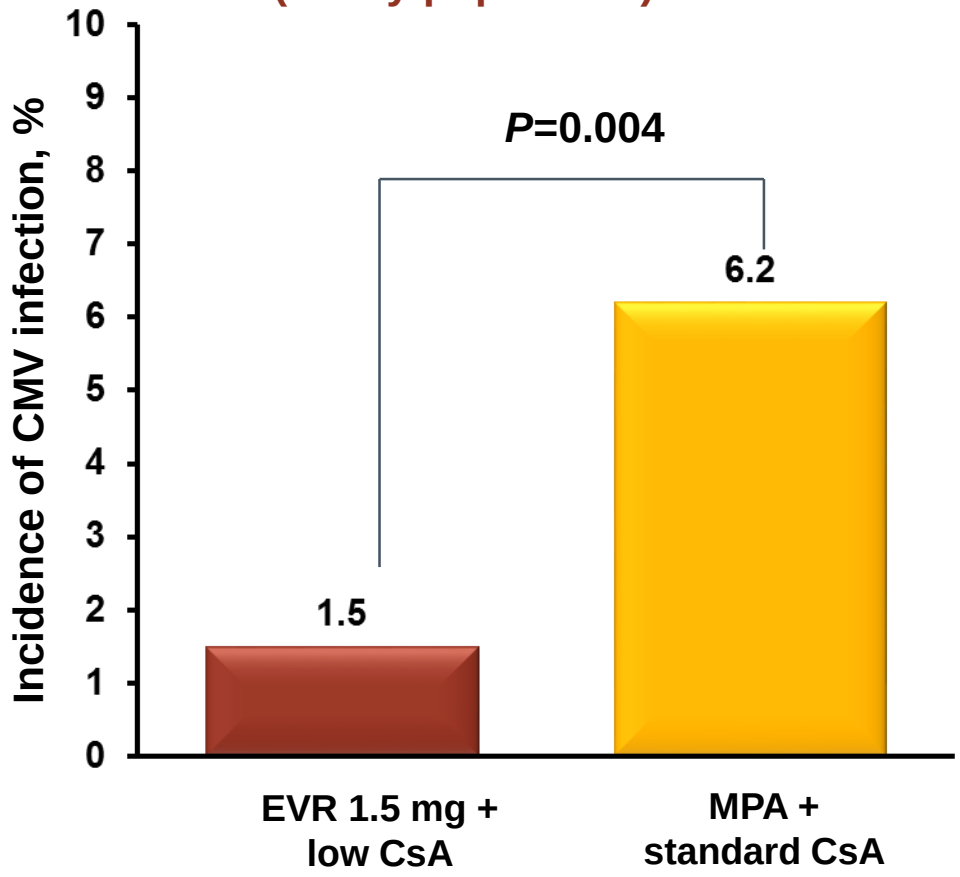
CSA, CYCLOSPORINE; EGFR, ESTIMATED GLOMERULAR FILTRATION RATE; EVR, EVEROLIMUS; MPA, MYCOPHENOLATE SODIUM; MDRD, MODIFICATION OF DIET IN RENAL DISEASE. NKF, NATIONAL KIDNEY FOUNDATION
CIBRIK D, ET AL. *TRANSPLANTATION.* 2013;95:933–942.

Anti-viral benefits

Significantly reduced incidence of CMV infection in patients treated *de novo with* EVR plus low CsA

Incidence of CMV infection reported as AE over 24 months of treatment (safety population)

A2309



AE, ADVERSE EVENT; CMV, CYTOMEGALOVIRUS; CSA, CYCLOSPORINE; EVR, EVEROLIMUS. MPA, MYCOPHENOLIC ACID

CIBRIK D, ET AL. *TRANSPLANTATION.* 2013;95:933–942.

Anti-viral benefits

Reduced incidence of CMV infection in all serology subgroups with EVR plus low CsA

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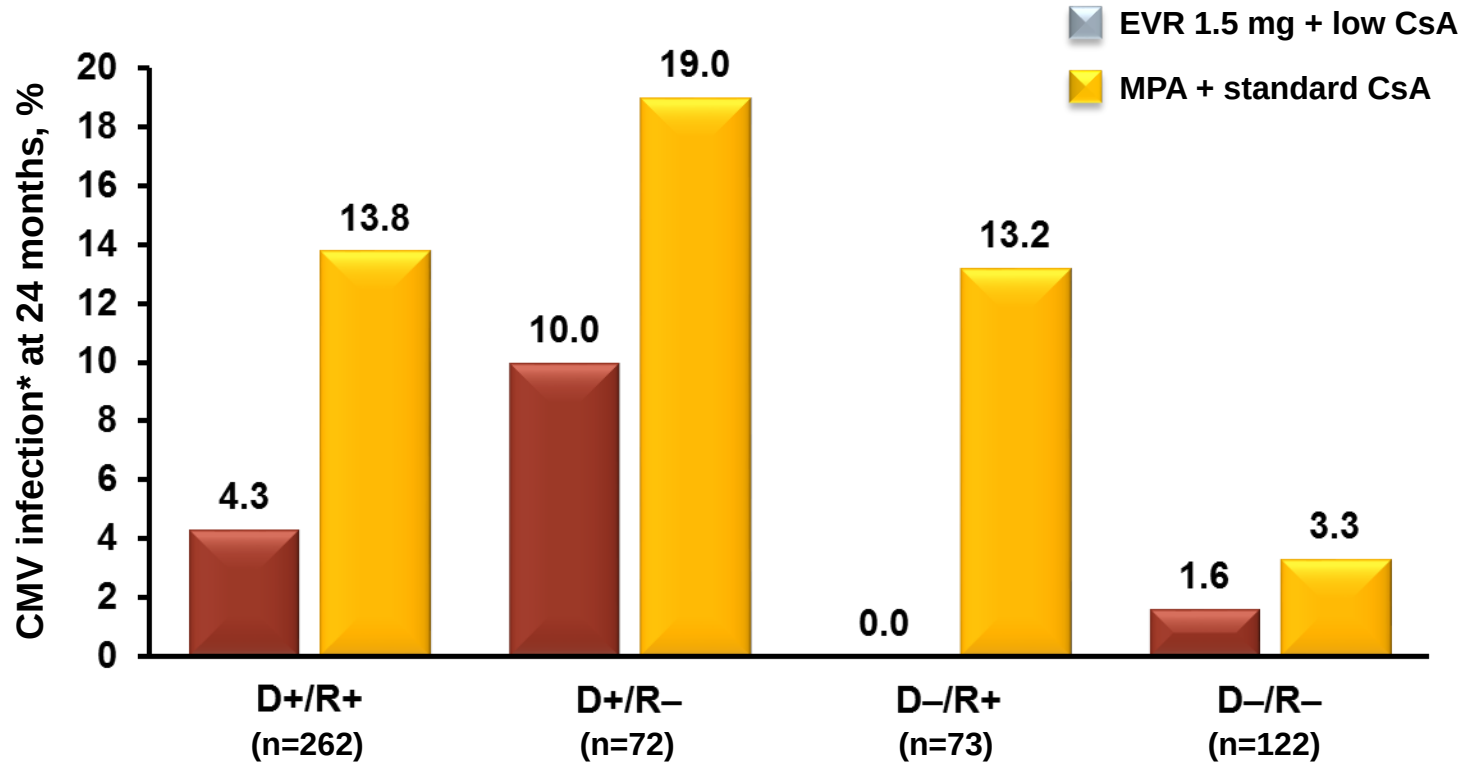
Safety Population – 24 Month Analysis



- Distribution of patients in the serology subgroups was similar in the two treatment groups
- 93% of high-risk patients (D+/R–) received CMV prophylaxis

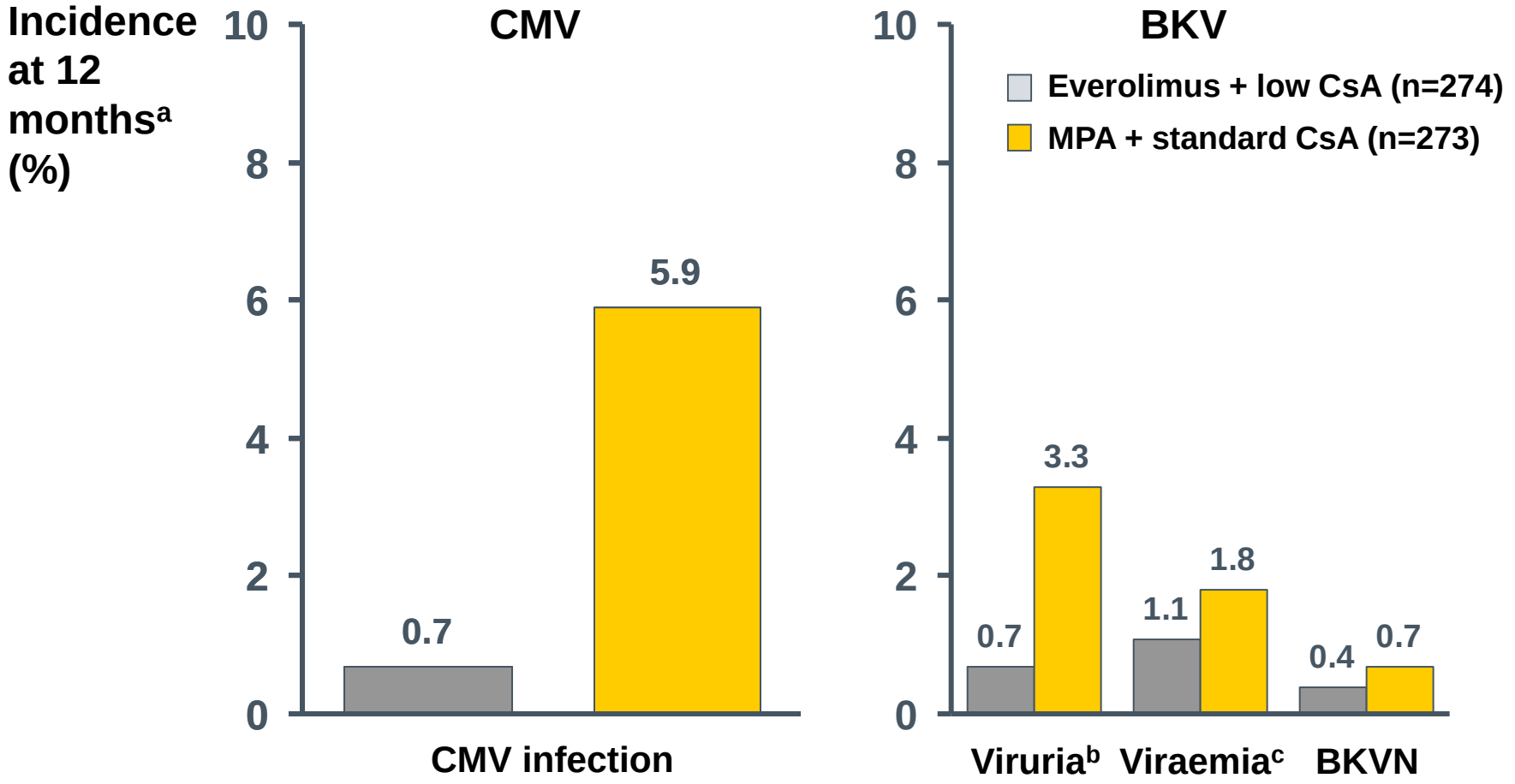
*INFECTION REPORTED AS ADVERSE EVENT USING THE SNOMED CT® CLASSIFICATION SYSTEM

CMV, CYTOMEGALOVIRUS; CSA, CYCLOSPORINE; D, DONOR; EVR, EVEROLIMUS; MPA, MYCOPHENOLIC ACID; R, RECIPIENT.

SHIHAB F, ET AL. AMERICAN TRANSPLANT CONGRESS (ATC) APRIL 30 - MAY 4, 2011, PHILADELPHIA, USA. LOWER INCIDENCE OF CYTOMEGALOVIRUS AND BK VIRUS ADVERSE EVENTS WITH EVEROLIMUS VERSUS MYCOPHENOLATE WAS MAINTAINED OVER 24 MONTHS IN DE NOVO RENAL TRANSPLANT RECIPIENTS.

Anti-viral benefits

Certican® with CNI minimisation: reduced incidence of CMV and BKV infection



A2309: 12-month analysis

[a]Infection reported as adverse event; [b,c]BKV virus detected in the [b]urine or [c]plasma:
CNI, calcineurin inhibitor; CMV, cytomegalovirus; BKV, BK virus; BKVN, BKV nepropathy ; CsA, cyclosporin; MPA, mycophenolic acid

Tedesco-Silva Jr H *et al*. *Am J Transplant* 2010;10:1401-1413

Anti-viral benefits

Reported incidence of BKV infection was lower with EVR plus low CNI at 24 months

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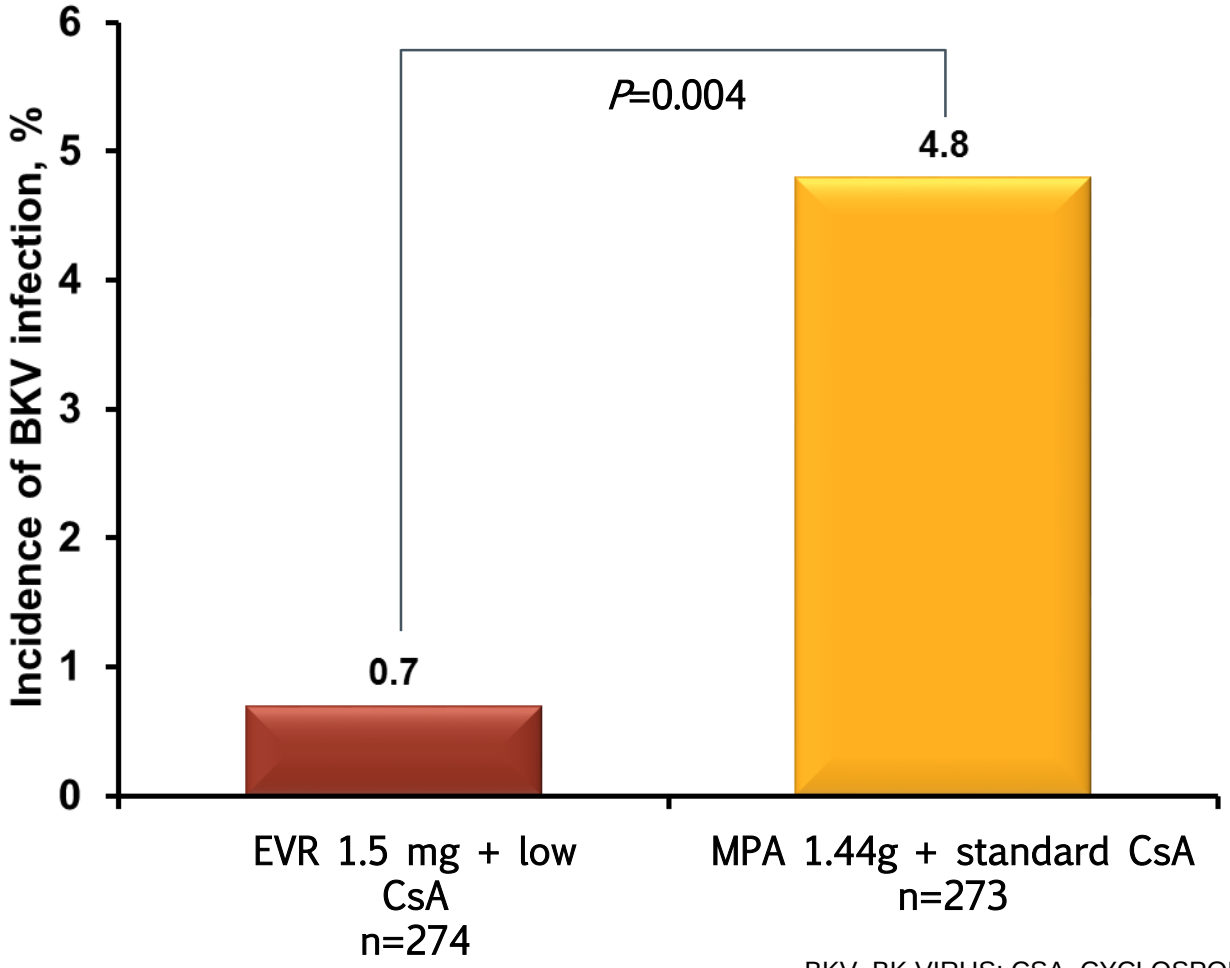
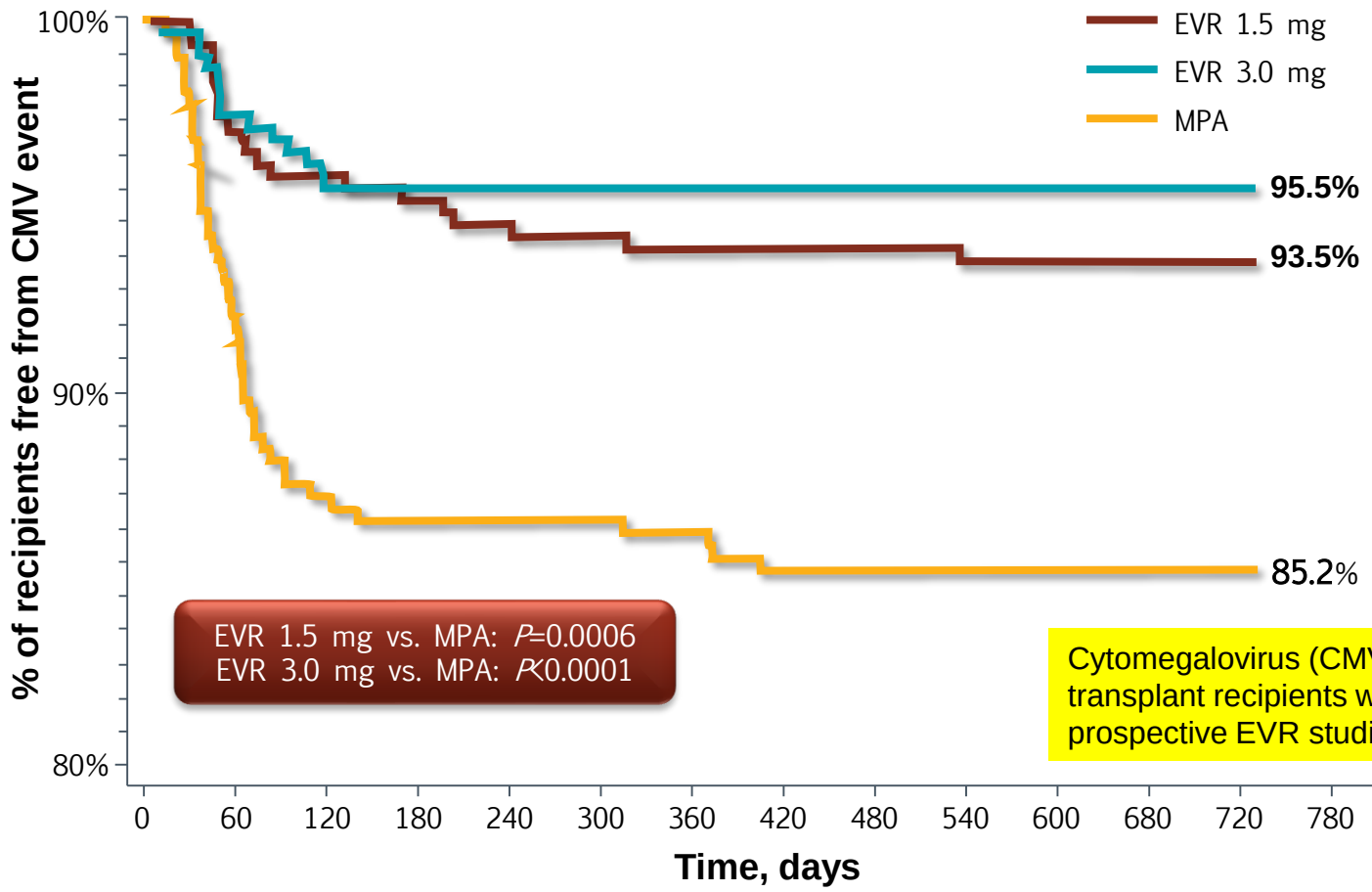


BKV, BK VIRUS; CSA, CYCLOSPORINE; EVR, EVEROLIMUS; MPA, MYCOPHENOLIC ACID.

CIBRIK D, ET AL. *TRANSPLANTATION*. 2013;95:933–942.

Fewer CMV infections with EVR than with MPA *Pooled analysis of 3 RCTs*

A2309 (N=833)
B201 (N=588)
B251 (N=583)



Cytomegalovirus (CMV) data from 2,004 *de novo* renal transplant recipients were pooled from three randomized, prospective EVR studies A2309, B201 and B251

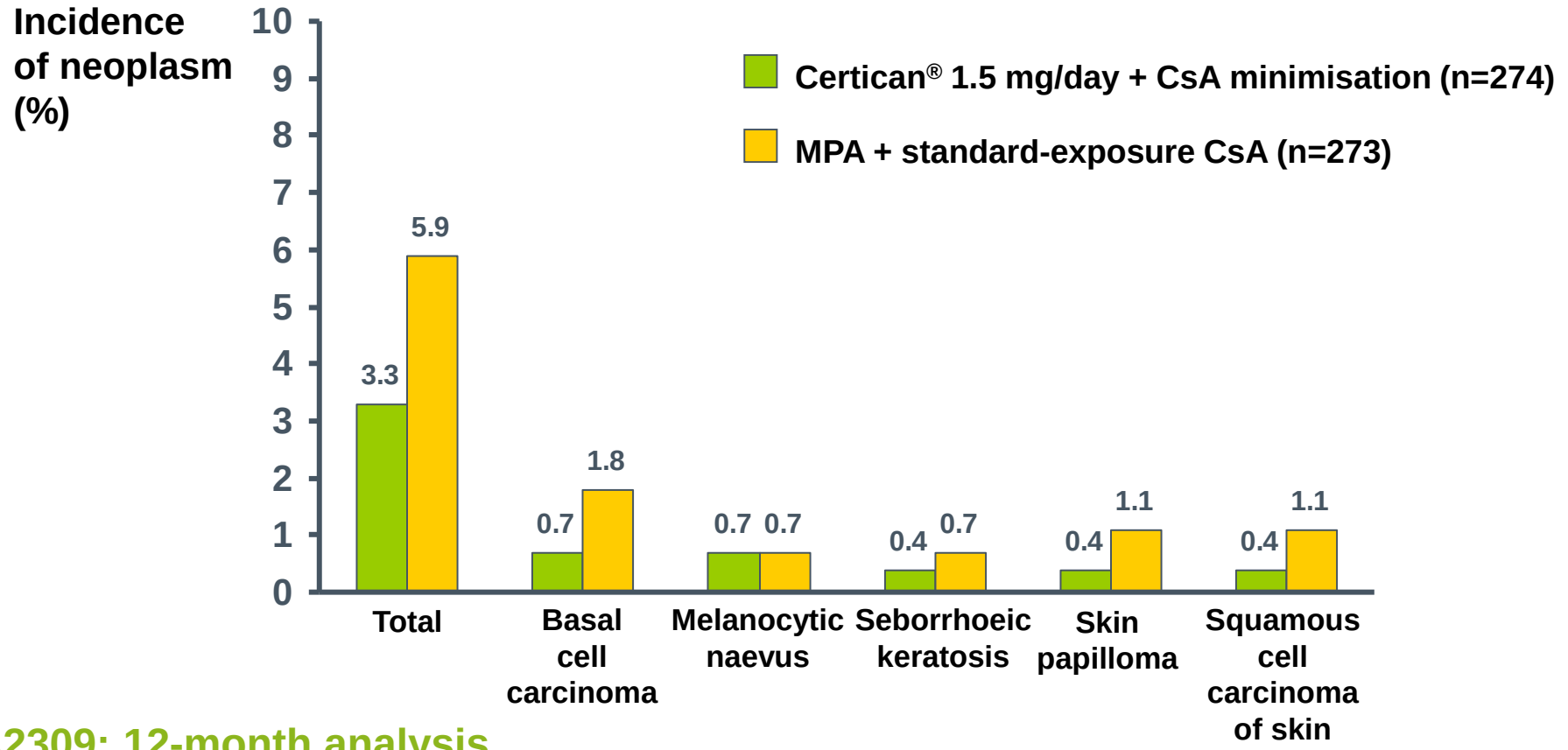
Figure reproduced with permission from John Wiley and Sons: Brennan DC, et al. *American Journal of Transplantation.* 2011;11;2453–62.

***An initial dose regimen of 0.75 mg twice daily, is recommended for the general kidney transplant population.**

CMV, cytomegalovirus; EVR, everolimus; MPA, mycophenolic acid; RCT, randomized controlled trial.
Brennan DC, et al. *Am J Transplant.* 2011;11;2453–62.

Fewer neoplasms

EVEROLIMUS® with CNI minimisation is associated with fewer neoplasms at Month 12 than MPA with standard-exposure CNI



A2309: 12-month analysis

CNI, calcineurin inhibitor; MPA, mycophenolic acid; CsA, cyclosporin

Tedesco H *et al*. Oral presentation at ASN Renal Week 2009

Fewer neoplasms

Incidence of malignancies was numerically lower in EVR plus low CsA arm at 24 months

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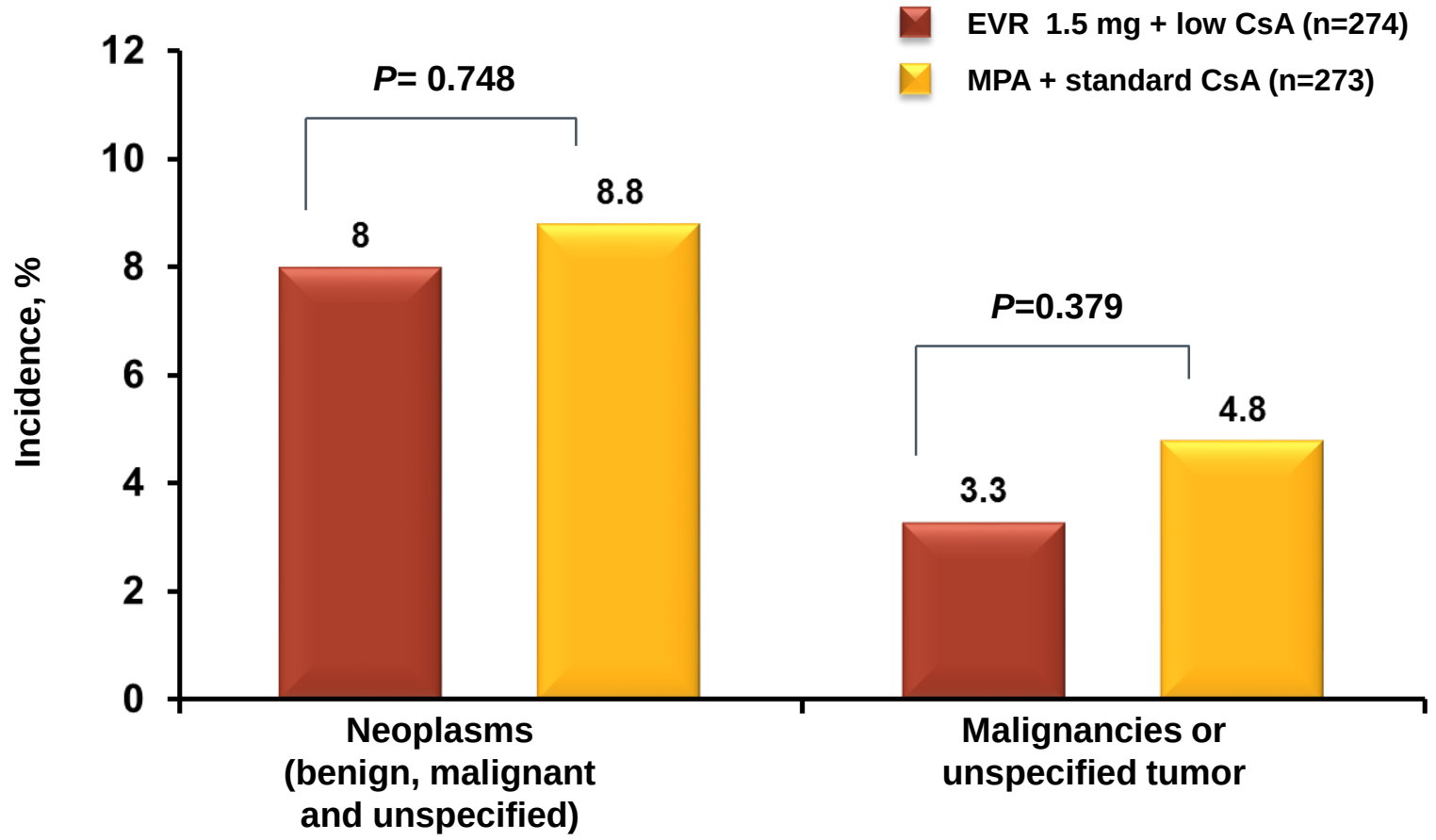
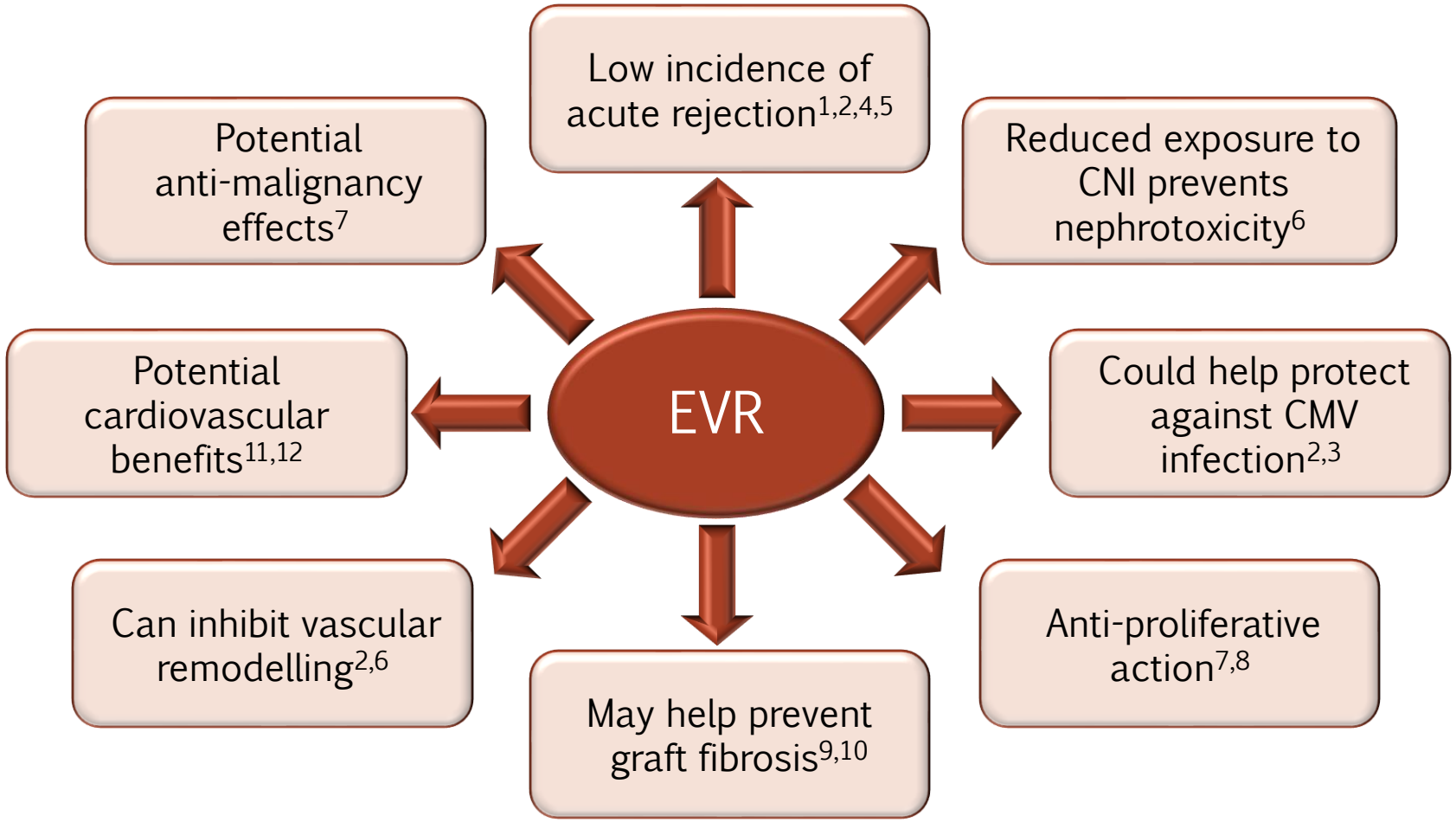


CSA, CYCLOSPORINE; EVR, EVEROLIMUS; MPA, MYCOPHENOLIC ACID

CIBRIK D, ET AL. *TRANSPLANTATION*. 2013;95:933–942.

EVR: a multifaceted drug with the potential to improve long-term outcomes



› CNI, calcineurin inhibitor; CMV, cytomegalovirus. EVR, everolimus.

1. Pascual J. *Transplantation.* 2005;79(Suppl 9):S76–S79; 2. Eisen H, et al. *N Engl J Med.* 2003;349:847–58; 3. Vitko S, et al. *Am J Transplant.* 2005;5:2521–30; 4. Tedesco-Silva H, et al. *Transpl Int.* 2007;20:27–36; 5. Nashan B, et al. *Transplantation.* 2004;78:1332–40;
6. Nashan B. *Transplant Proc.* 2001;33:3215–20; 7. Majewski M, et al. *Transplantation.* 2003;75:1710–7; 8. Schuler W, et al. *Transplantation.* 1997;64:36–42; 9. Viklicky O, et al. *Transplantation.* 2000;96:497–502; 10. Koch M, et al. *Transplantation.* 2007;83:498–505;
11. Andrés V, et al. *Nephrol Dial Transplant.* 2006;21(Suppl 3):iii14–7; 12. Pascual J, et al. *Nephrol Dial Transplant.* 2006;21(Suppl 3):iii38–41.

Non Significant Difference in the Incidence of Adverse Events between Everolimus and MPA

- **Incidence of proteinuria AEs at 24 months was 11.3%** in EVR 3–8ng/mL arm and 8.1% in MPA arm (P=0.198 vs. MPA)
- **Incidence of wound event AEs at 24 months was 0.4%** in EVR 3–8ng/mL arm and 0.4 % in MPA arm (P=1.00 vs. MPA)
- **Incidence of stomatitis and oral ulcers AEs at 24 months was 6.9 %** in EVR 3–8ng/mL arm and 3.3 % in MPA arm (P=0.05 vs. MPA)
- **Incidence of hyperlipidemia AEs at 24 months was 20.4 %** in EVR 3–8ng/mL arm and 16.1 % in MPA arm (P=0.19 vs. MPA)
- **Incidence of Peripheral edema 48.9%** in EVR 3–8ng/mL arm and 42.9% in MPA arm (P=0.16 vs. MPA)

Cibrik D et al. Transplantation. 2013;95:933-942

Management of AEs
Overview

Adverse event	Intervention
Hyperlipidemia	Statins
Proteinuria	ACEI/ARB
Mouth ulcers	Local corticosteroids
Acne	Local or systemic antibiotics and retinoids
Edema	Diuretics

ACEI, ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR; AE, ADVERSE EVENT; ARB, ANGIOTENSIN RECEPTOR BLOCKER.

PASCUAL J. *TRANSPLANT REV.* 2006;20:1–18.

Conclusion

- Risk Stratification for renal transplant patients is essential for the enhanced management of patient outcomes both short-term and long-term and serves for better patient and graft survival.
- Enteric coated MPA could offer optimal MPA exposure .
- Tailoring CNI minimization regimen with Everolimus could improve long term outcomes

The Most Wise person I met, was my tailor Who Insisted

To Take my Measurements every Time I visit Him...

J Bernard shaw

THANK YOU