Long-term outcome and unmet needs after kidney transplantation

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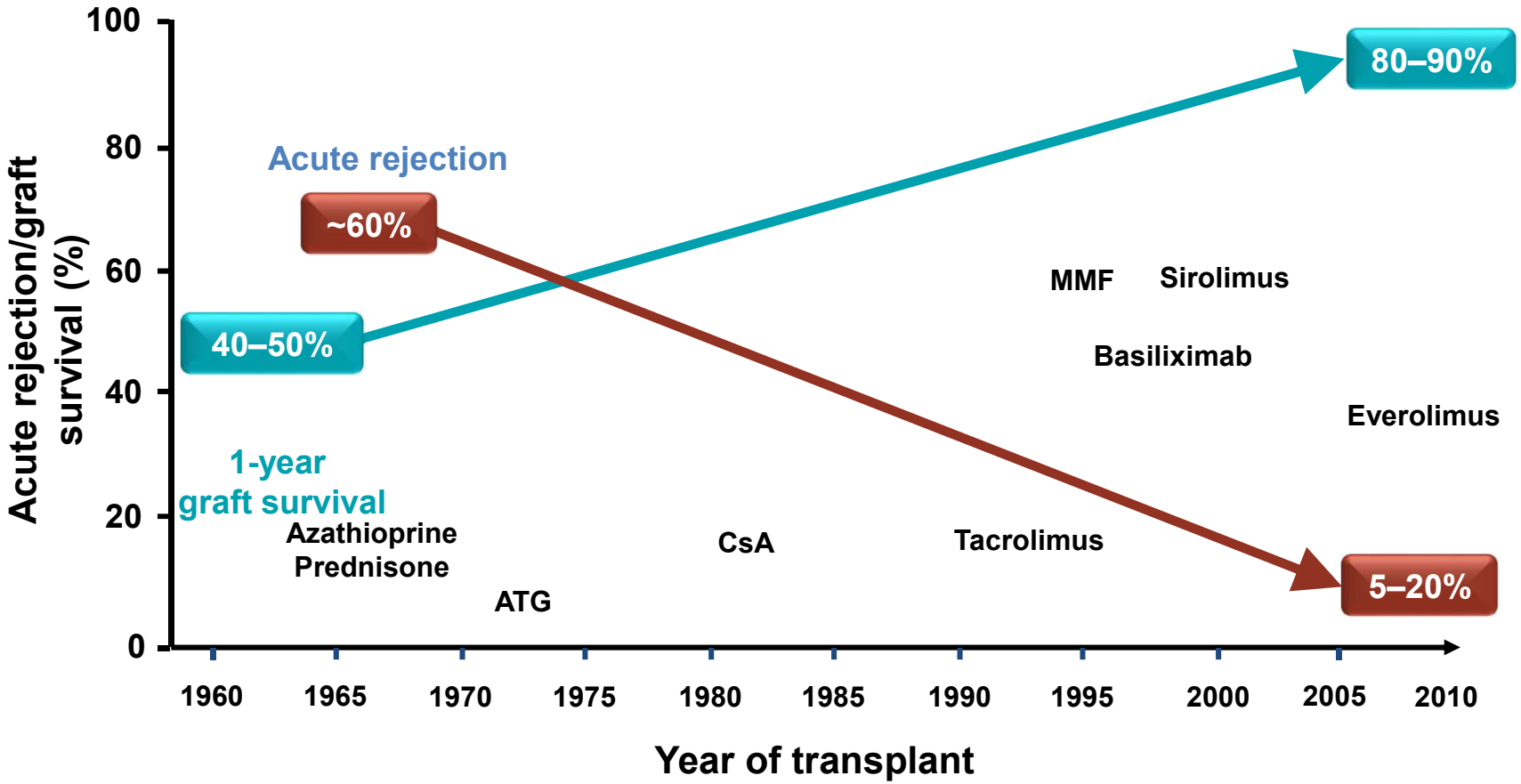
What are our challenges?

- Achieving good long-term allograft survival
  - Avoid/minimize calcineurin inhibitor-related nephrotoxicity
  - Prevent donor-specific alloantibody (DSA) formation
- Avoid virological infections, such as CMV, BKV
- Improve cardiovascular outcomes
  - Decrease the risk of *de novo* diabetes
  - Decrease left venticular mass index
- Prevent *de novo* posttransplant cancers

Considerable improvements have been made in acute rejection and short-term graft survival but…

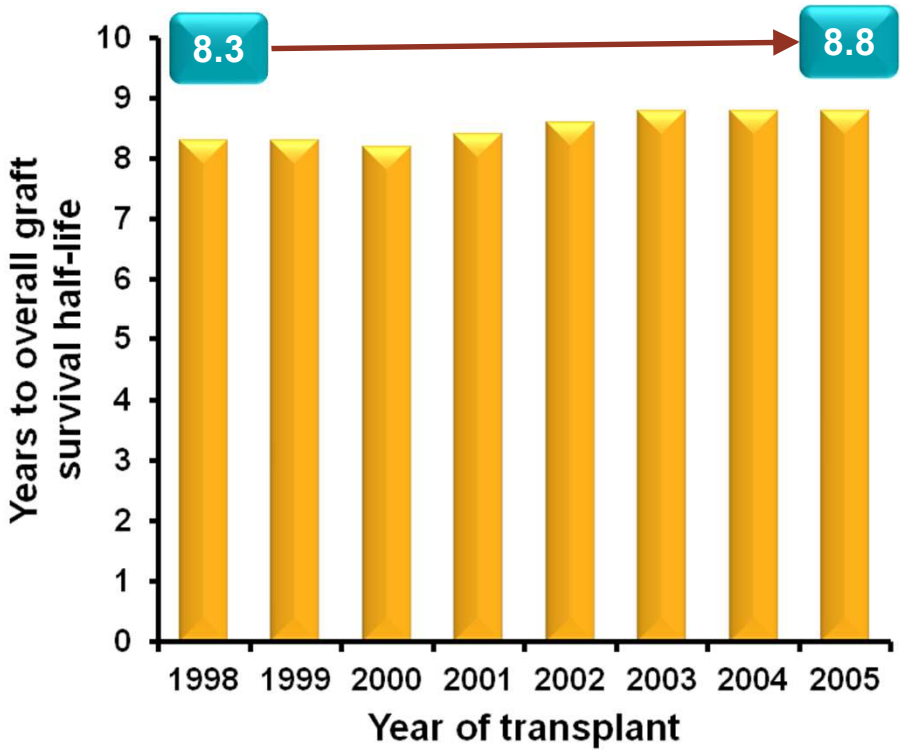


CsA, cyclosporine; ATG, anti-thymocyte globulin; MMF, mycophenolate mofetil.

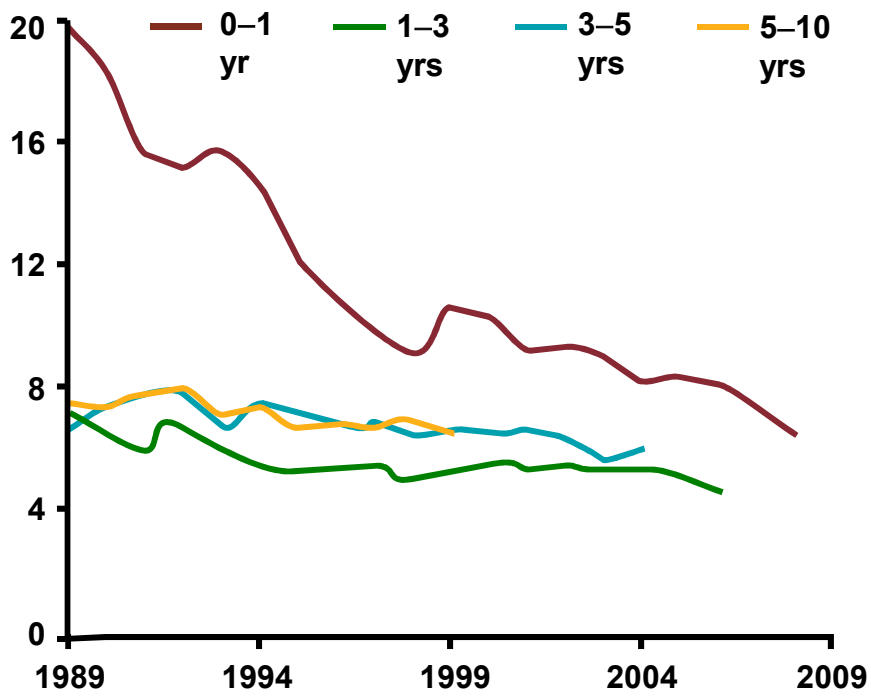
1. Morris PJ. *N Engl J Med.* 2004;351:2678–80;
2. Sayegh MH, *et al. N Engl J Med.* 2004;351:2761–6;
3. Khurana A, Brennan D. Current concepts of immunosuppression and side effects in *Pathology of Solid Organ Transplantation,* 2011

... long-term renal allograft survival has not improved…

Cumulative graft t½ by transplant year (forecasted Kaplan-Meier estimates)



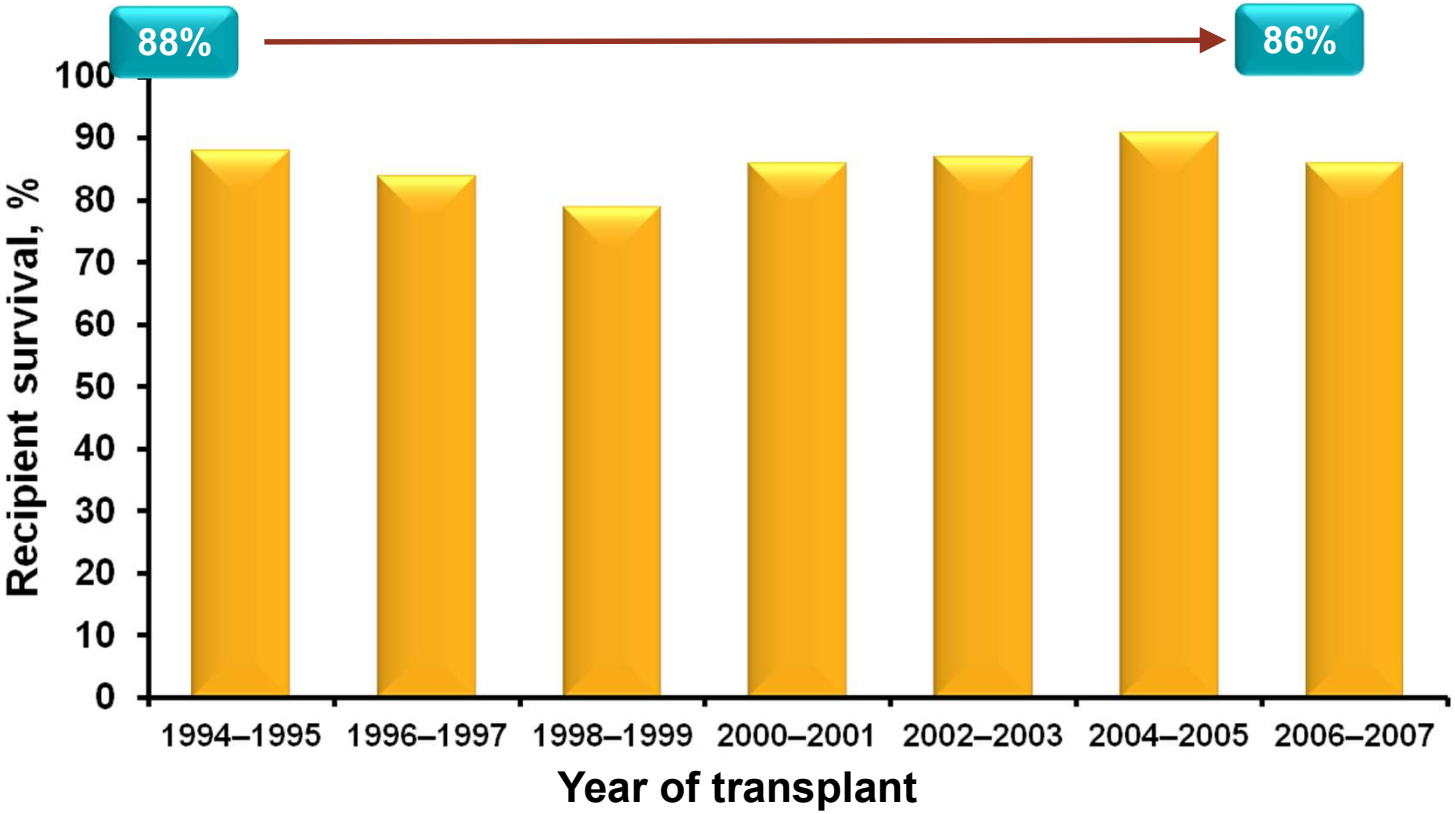
Deceased donor kidney transplant attrition rates in the USA (n=164,480)



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

... neither has long-term patient survival

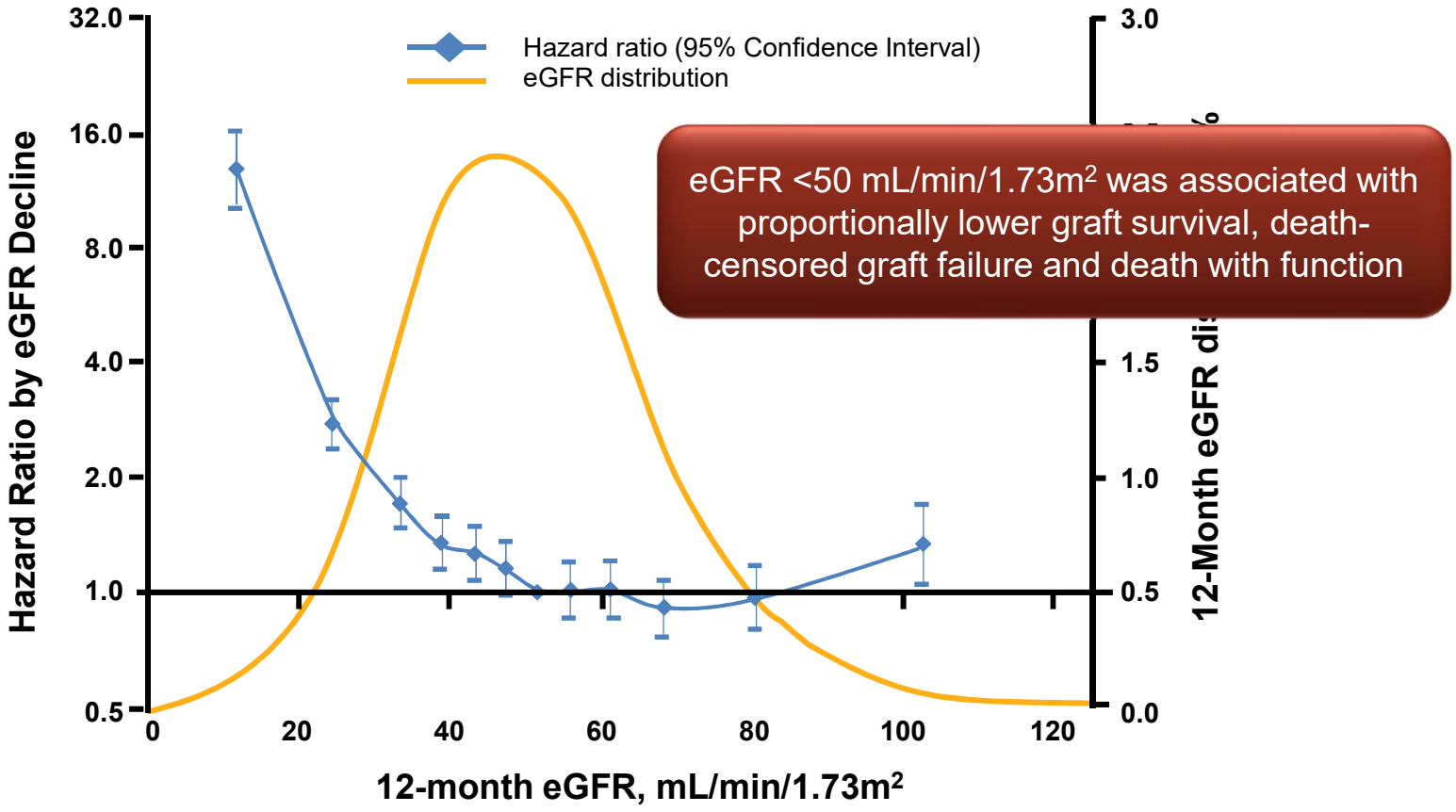
Patient 5-year survival 1994–2007
Recipients of a first deceased-donor kidney



ANZDATA registry 2012 report.
Available at: http://www.anzdata.org.au/anzdata/AnzdataReport/35thReport/2012c08_transplants_v1.pdf. Accessed 17 June 2013.

Kidney function at Month 12 is associated independently with graft failure

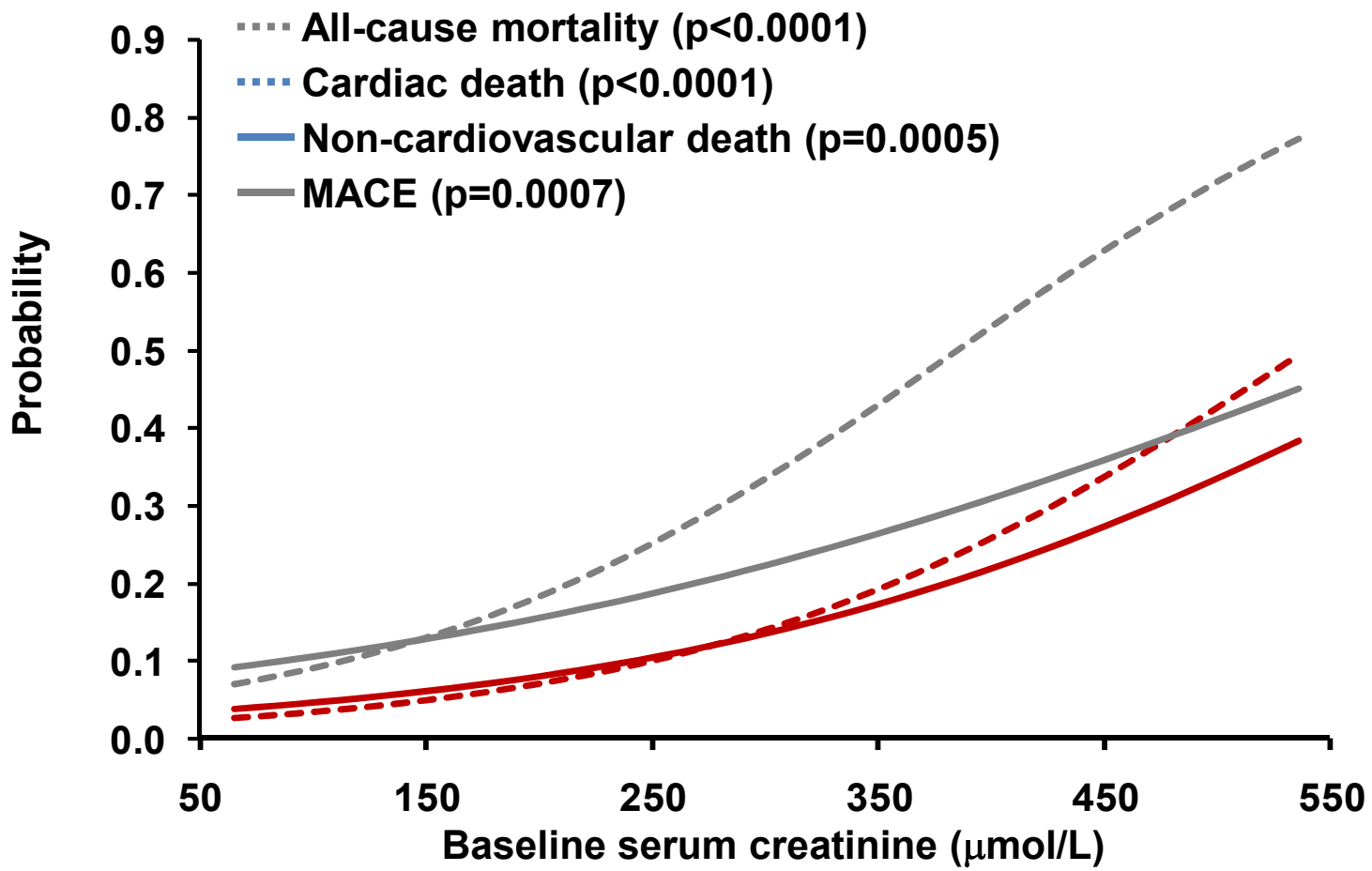
Relationship between eGFR and graft failure over 10-years of follow-up (Cox proportional hazard adjusted for multiple covariates)



eGFR, estimated glomerular filtration rate.

Kasiske B, et al. Am J Kidney Dis. 2011;57:466–75

Patients with good renal function have lower risk of CVD death (ALERT trial; placebo arm)

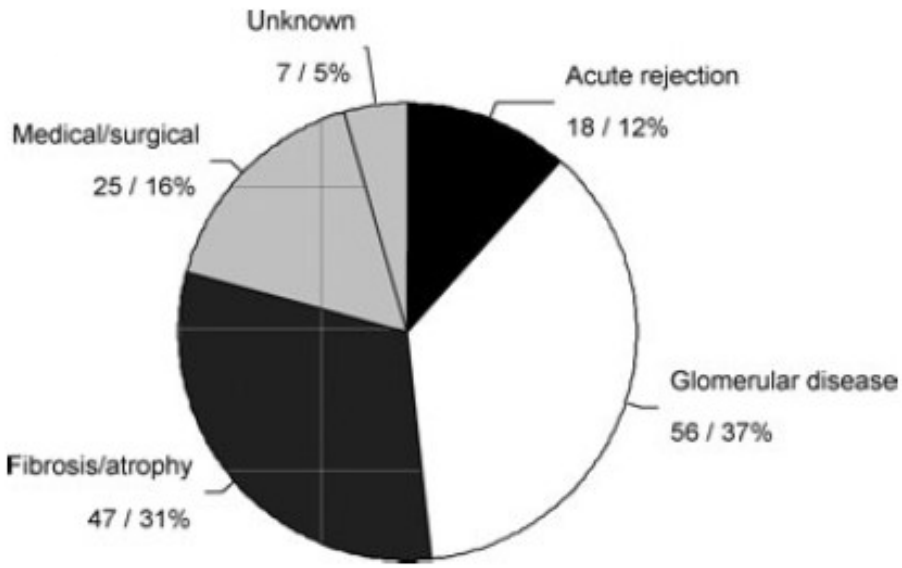


CVD, cardiovascular disease; MACE, major adverse cardiac event.

Fellström B et al. Am J Transplant 2005;5:1986–91.

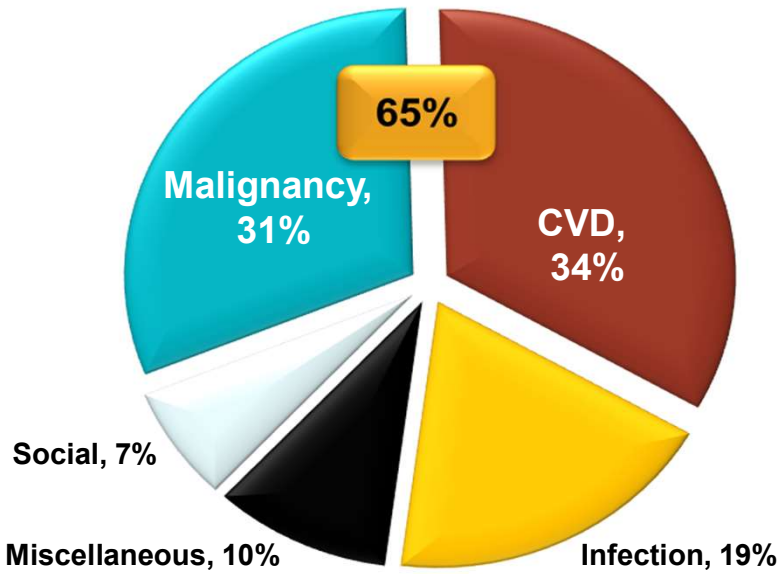
Causes of graft failure and death with a functioning graft

Causes of kidney graft failure



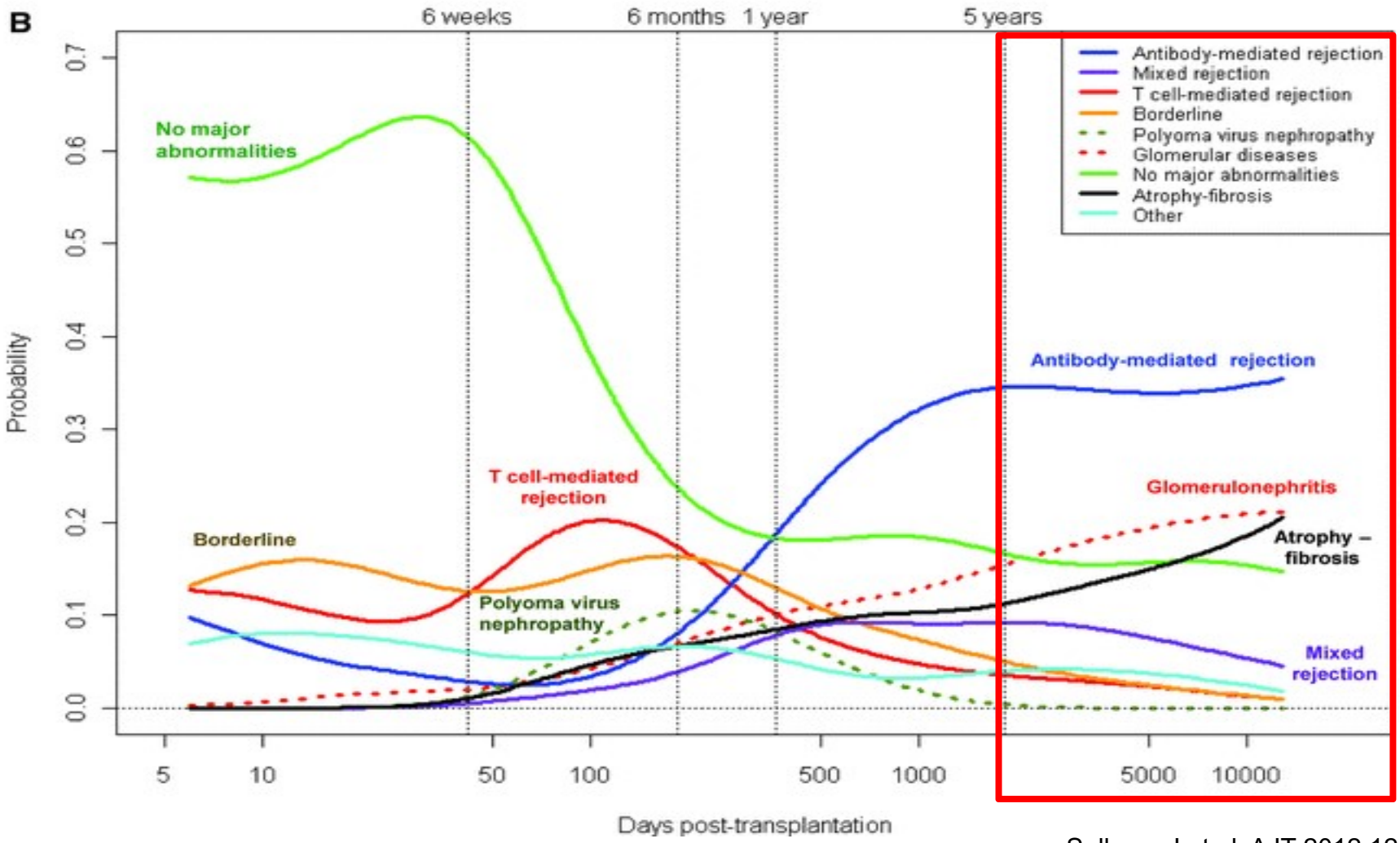
El-Zoghby ZM et al. Am J Transplant 2009; 9: 527-35

Causes of death with functioning graft



ANZDATA registry data 2007–2011

Understanding the causes of kidney transplant failure : the dominant role of antibody-mediated rejection and nonadherence



Sellares J et al. AJT 2012;12:388-399

CVD in kidney transplantation is a significant unmet need

CVD events continue to be a major cause of death with a functioning graft1

CVD events are a significant contributor to posttransplant graft loss[2]

Diabetes is a common PRETRANSPLANT finding and an increasing indication for kidney transplantation, but is a key risk factor for subsequent cardiovascular events[3]

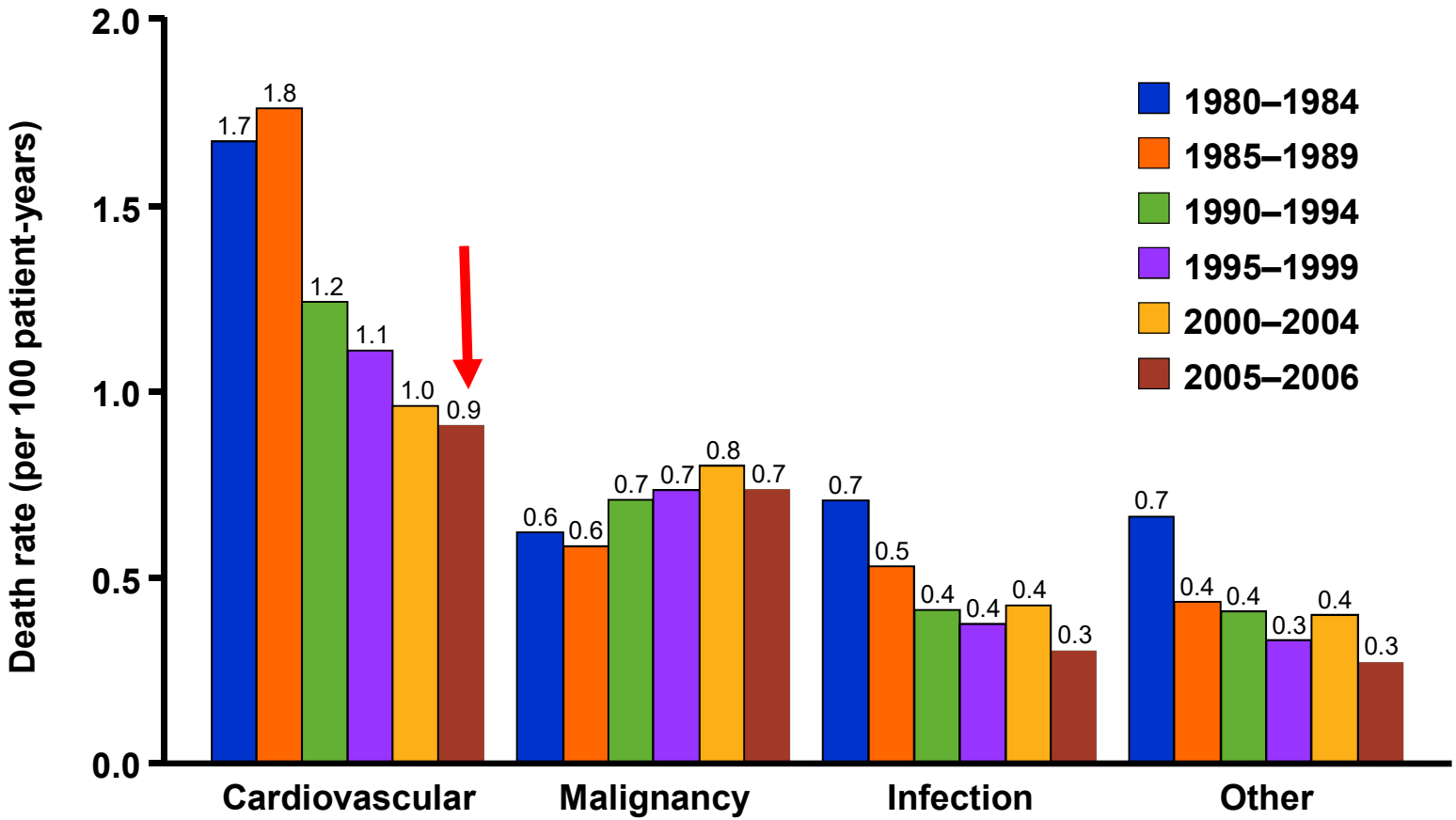
Post-transplant diabetes is frequent, and is also a key risk factor for subsequent cardiovascular events

Immunosuppressive medication can be modified to reduce the risk of CVC

1. Pilmore H *et al. Transplantation* 2010;89:851–7.
2. Fellström B *et al. Am J Transplant* 2005;5:1986–91.
3. Hjelmesaeth J *et al. Kidney Int* 2006;69:588–95.
4. Holdaas H. *Am J Cardiovasc Drugs* 2005;5:255–69.

CVD, cardiovascular disease.

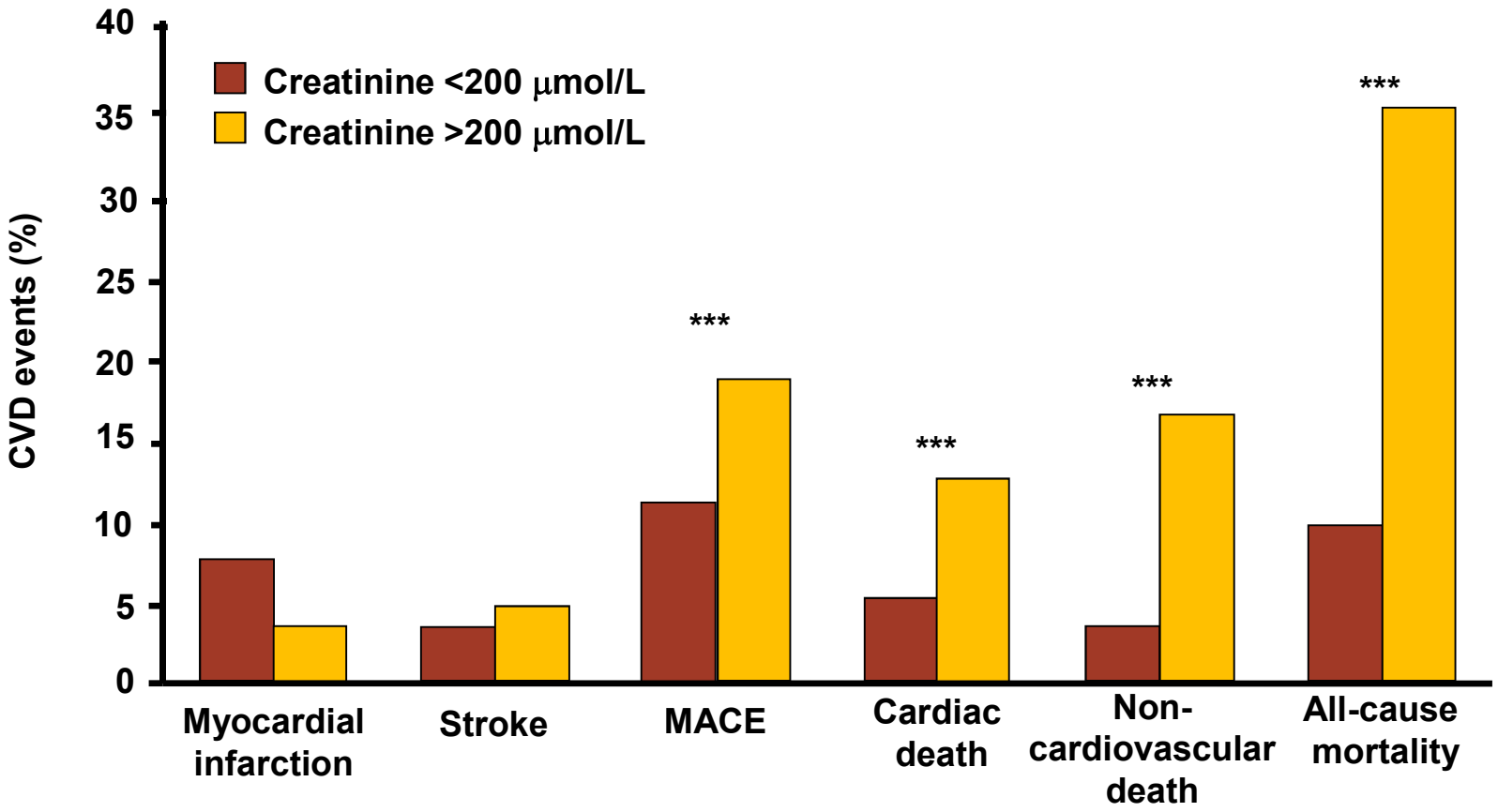
CVD continues to be a major cause of death with a functioning graft



CVD, cardiovascular disease.

Data from the Australia and New Zealand Dialysis and Transplant registry; Pilmore H et al. Transplantation 2010;89:851–7.

Renal allograft impairment increases the risk of some CVD events (ALERT trial; placebo arm)

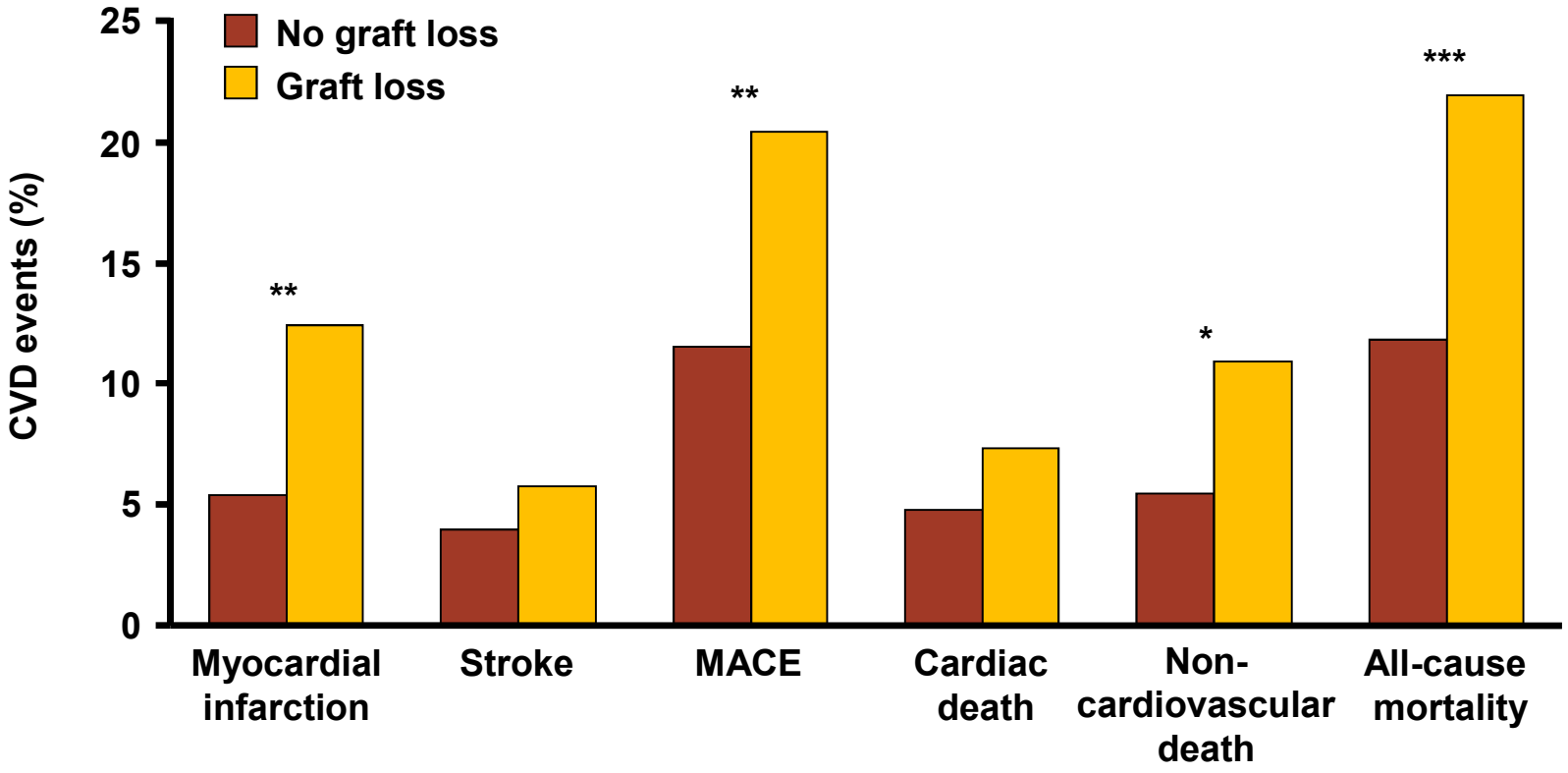


ALERT trial : 2102 adult KTR; > 6 months posttransplantation; CsA-based immunosuppresion; increased serum total cholesterol; 1st patient 1996; randomized to either placebo or fluvastatin therapy 40mg/d 2y then 80mg/d; follow-up > 5y.

***p<0.001.
CVD, cardiovascular disease;
MACE, major adverse cardiac event.

Fellström B et al. Am J Transplant 2005;5:1986–91.

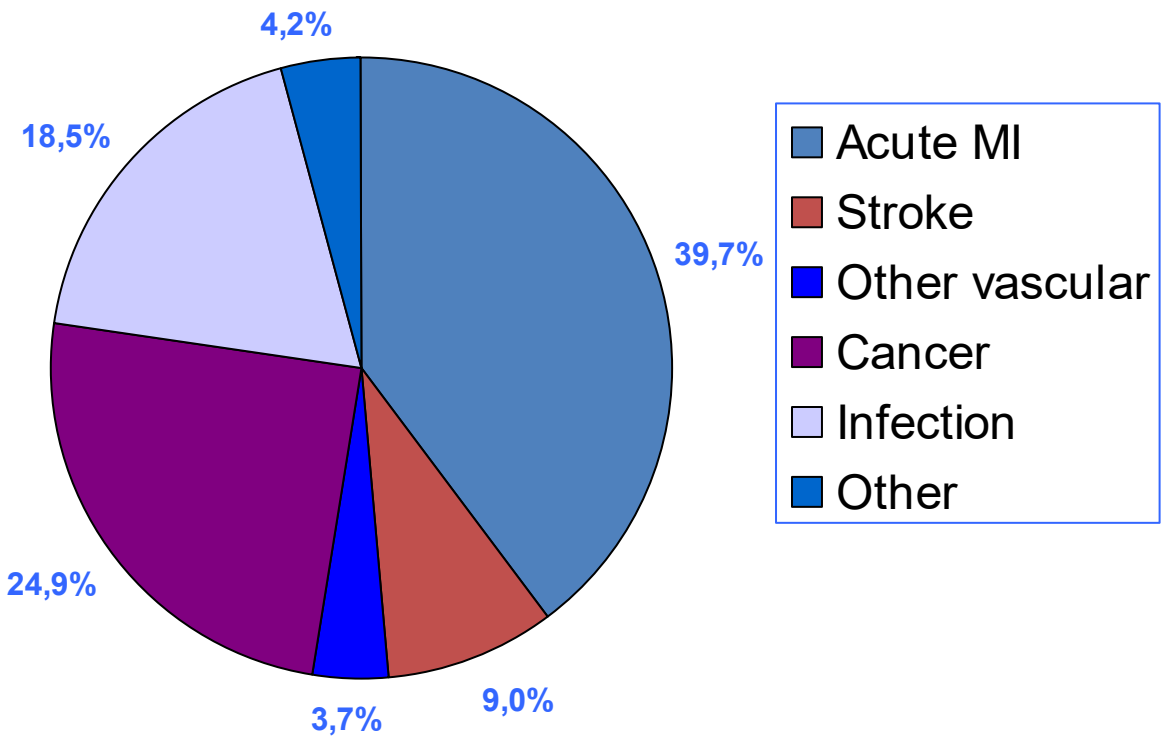
Graft loss increases the risk of some CVD events (ALERT trial; placebo arm)



*p<0.02; **p<0.005; ***p<0.001.
CVD, cardiovascular disease; MACE, major adverse cardiac event.

Fellström B et al. Am J Transplant 2005;5:1986–91.

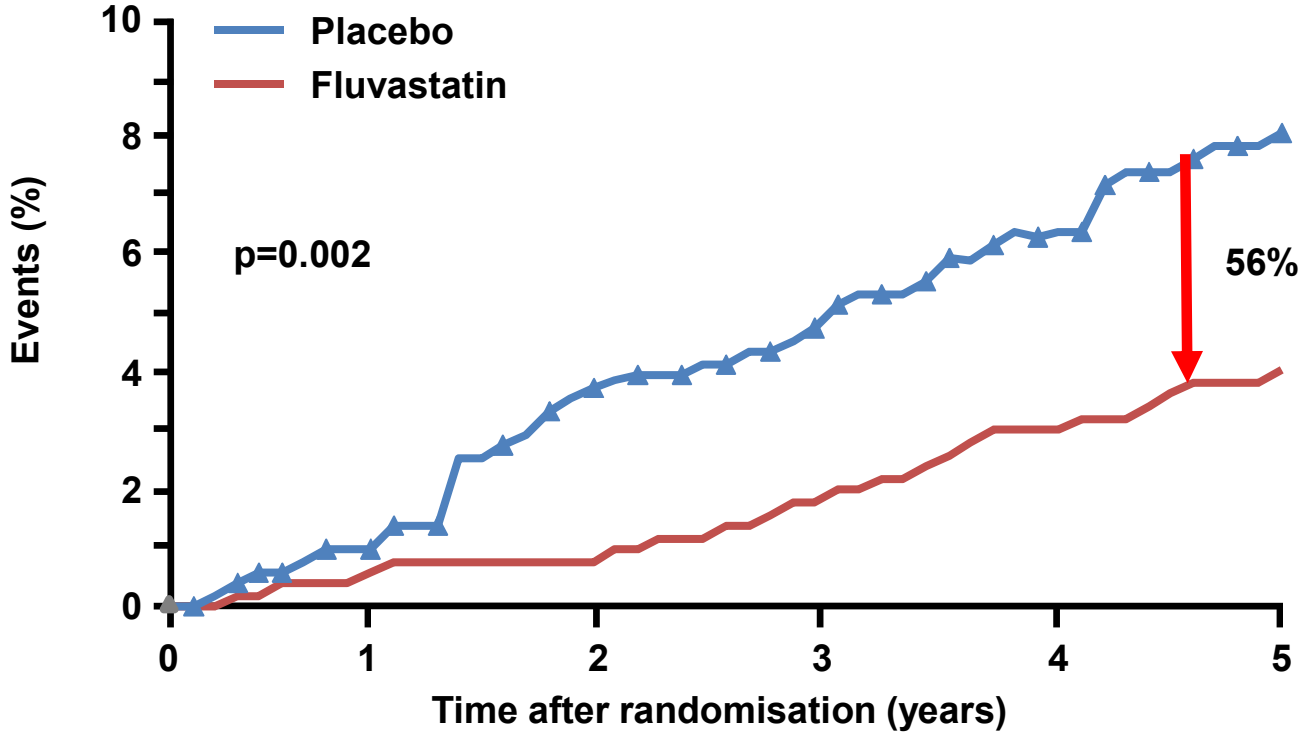
Causes of death in kidney transplant recipients in ALERT trial (placebo arm)



189 deaths in 1052 patients in the placebo arm.
MI, myocardial infarction.

Adapted from Holdaas H *et al*. *Am J Transplant* 2005;5:2929–36.

Impact of statin use: cardiac death and non-fatal AMI to 5 yrs (ALERT trial in those starting fluvastatin less than 4.5y posttransplantation)

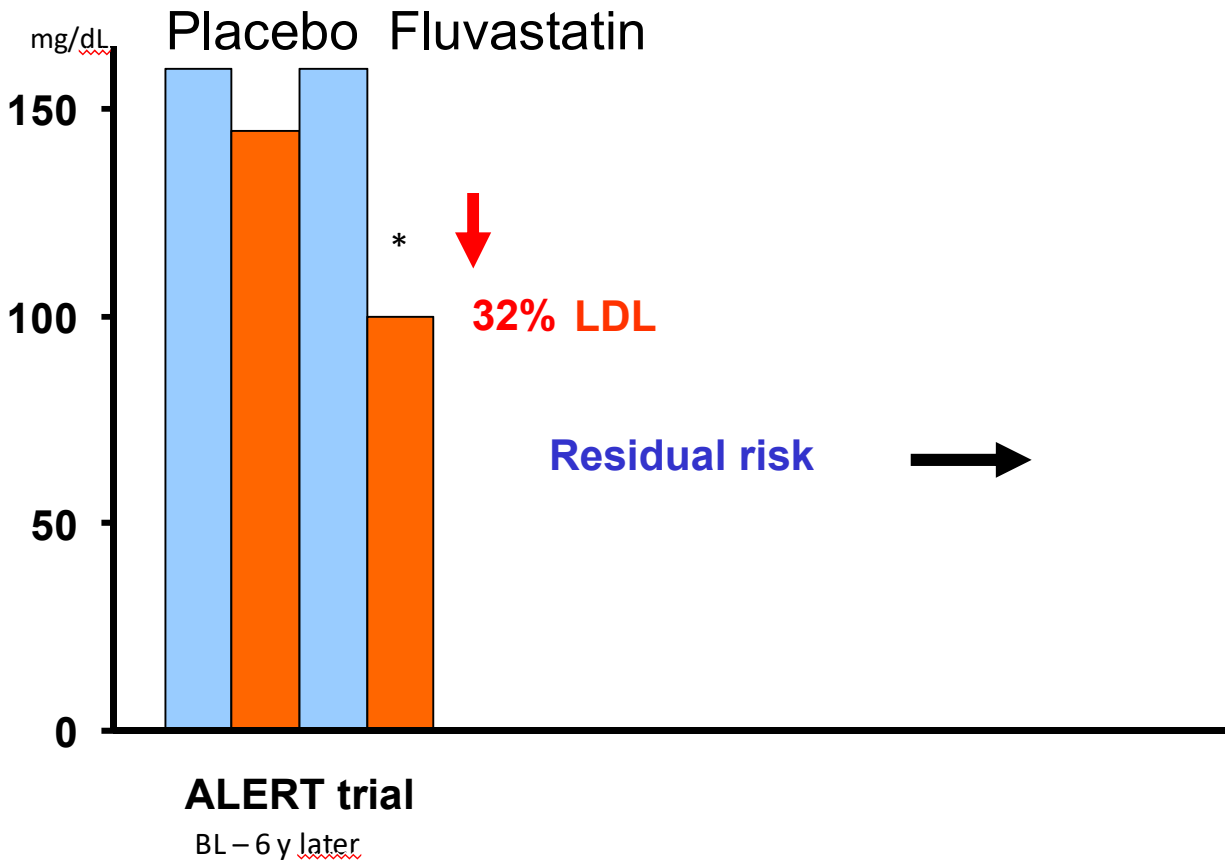


No. of patients at risk						
Fluvastatin	522	512	502	487	468	417
Placebo	521	503	483	466	449	417

AMI, acute myocardial infarction.

Holdaas H et al. Nephrol Dial Transplant 2005;20:974–80.

Management of cardiovascular disease after transplantation



Parathyroid hormone, phosphate

C-reactive protein, interleukin-6

Serum creatinine

Diabetes mellitus, metabolic syndrome

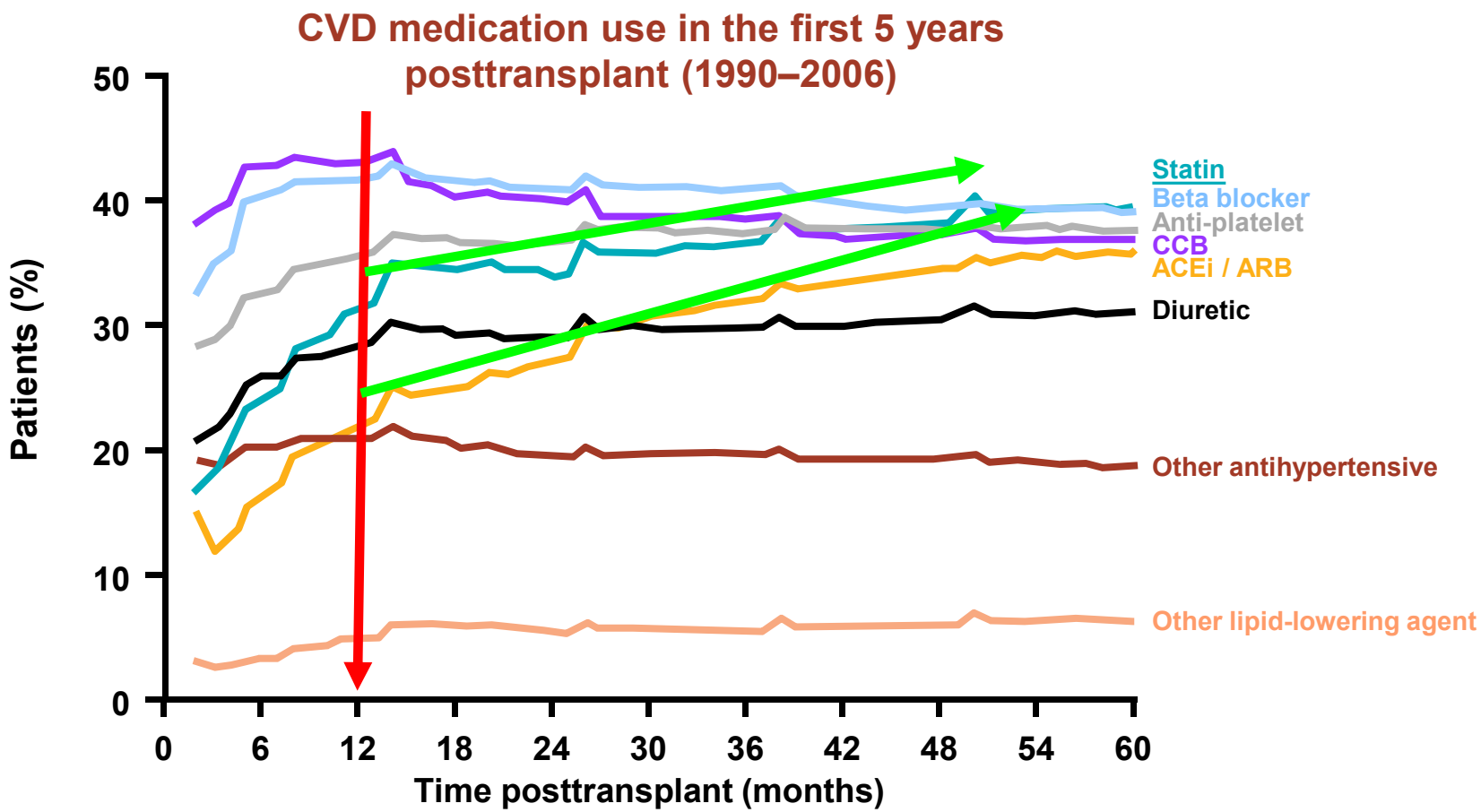
Obesity/increase in BMI

Hypertension

Vasculopathy (CNI)

BL, baseline; LDL, low-density lipoprotein; CNI, calcineurin inhibitor.

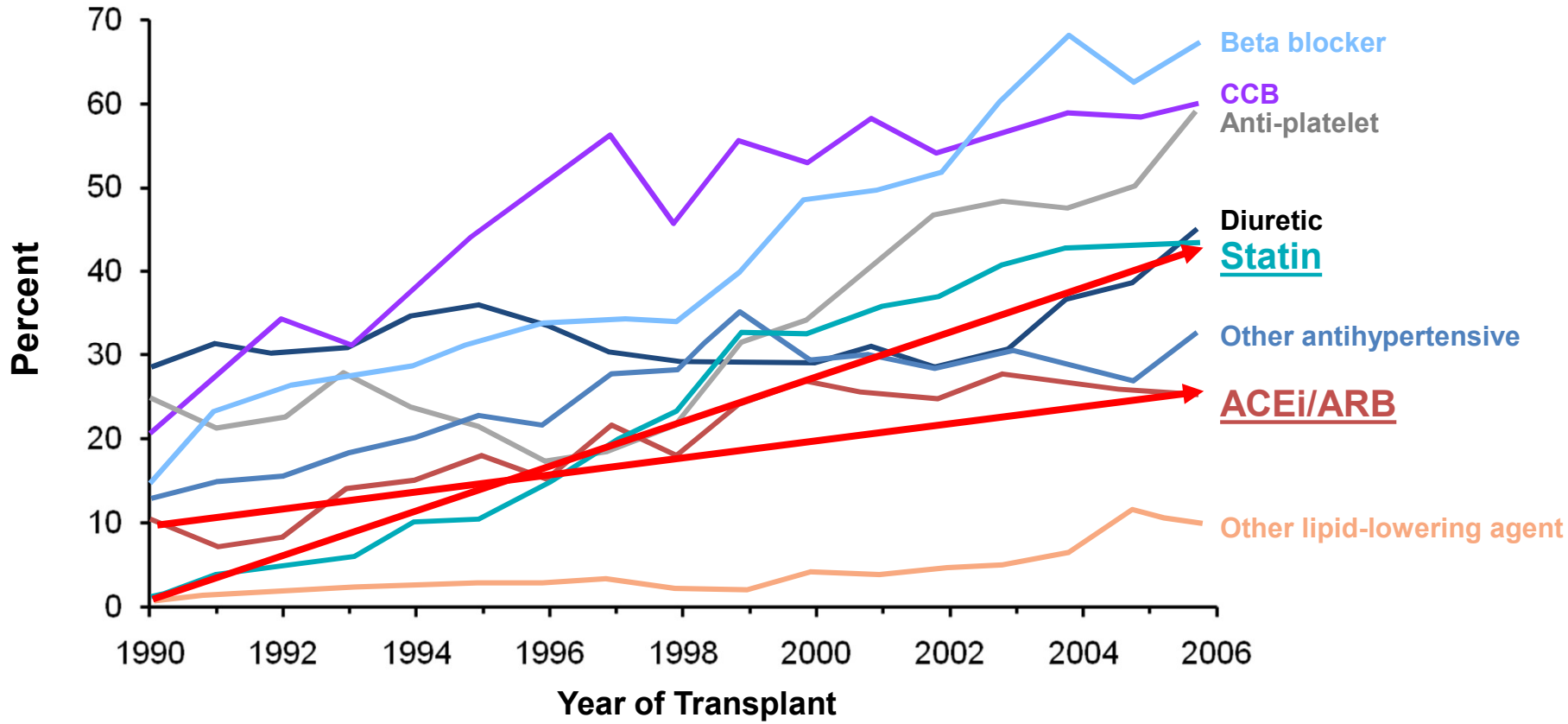
Use of CVD medications posttransplant may be suboptimal given the high CVD risk



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CVD, cardiovascular disease; CCB, calcium channel blocker.

Pilmore HL et al. Transplantation 2011;91:542-51.

Use of CVD medications increased significantly in more recent years



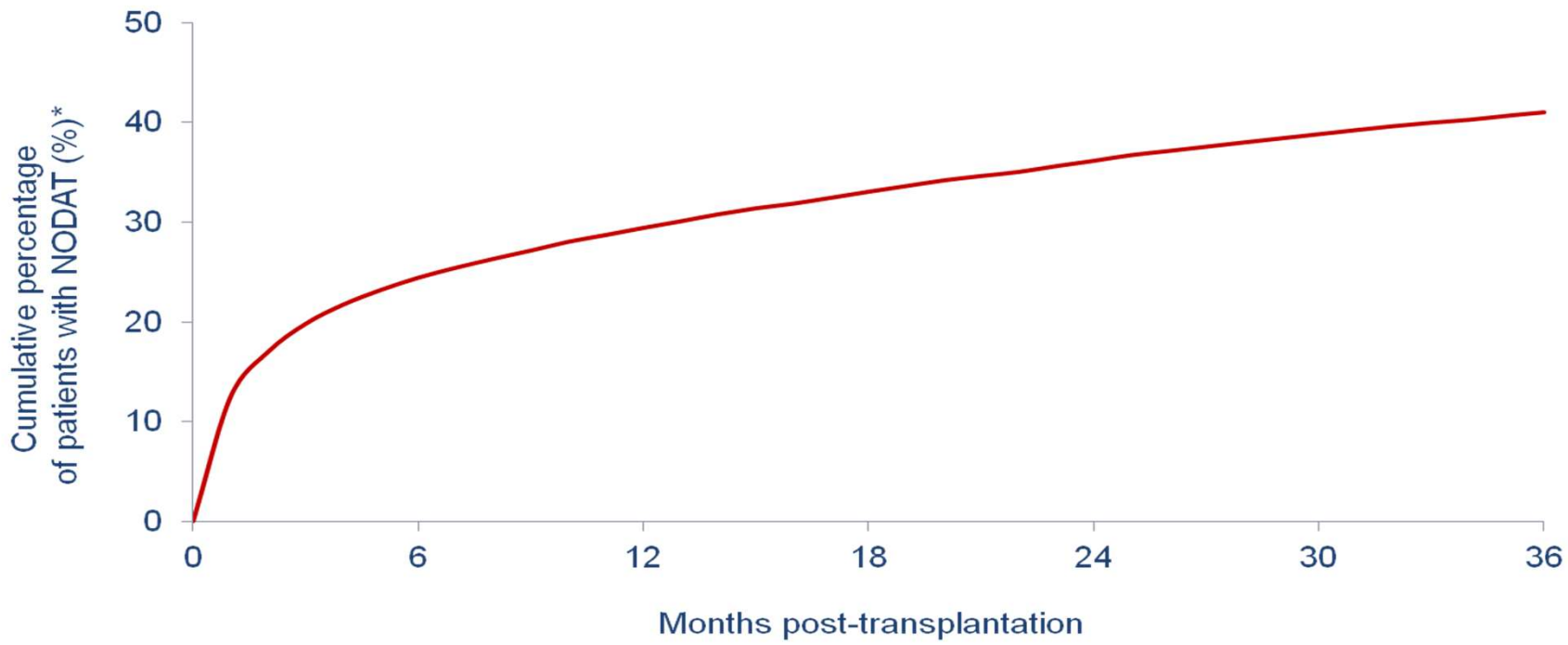
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CVD, cardiovascular disease; CCB, calcium channel blocker.

Pilmore HL et al. Transplantation 2011;91:542-51.

Post-transplant diabetes mellitus (PTDM)

The incidence of post-transplant diabetes mellitus (PTDM) increases with time after kidney transplantation

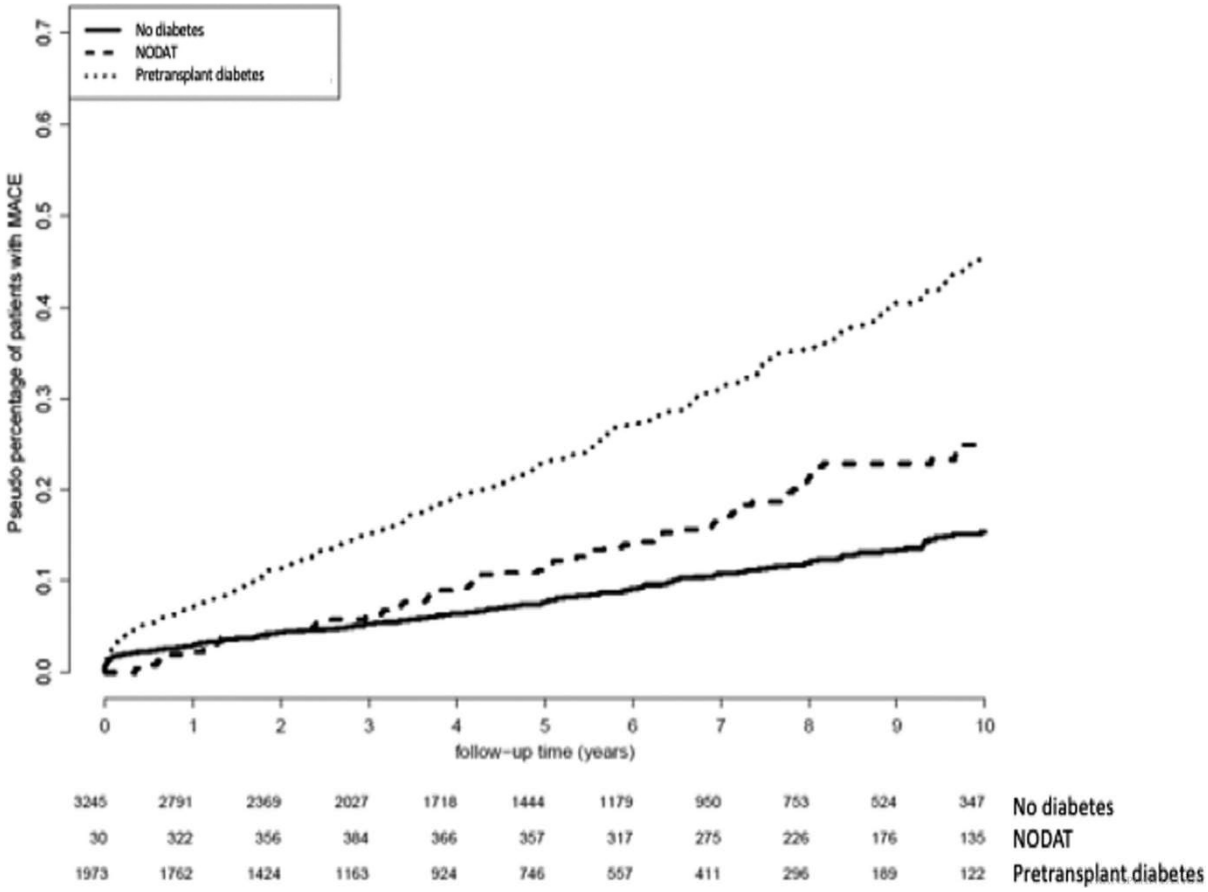
- In an analysis of the USRDS database, NODAT was present in 41% of kidney transplant recipients at 3 years



Graph shows the cumulative incidence of NODAT among recipients receiving a first-time, kidney-only transplant between 2000 and 2006 in the USA. NODAT=new-onset diabetes after transplantation; USRDS=United States Renal Data System (USRDS). United States Renal Data System. Chapter 7: Transplantation. In: Atlas ESRD (Volume 2). Available online at: http://www.usrds.org/atlas.aspx (accessed July 2012).

Impact of Pretransplant and PTDM on the risk of Major Adverse Cardiovascular Events (MACE) in kidney Transplant Recipients: A Population-based Cohort Study (Ontario, Canada)

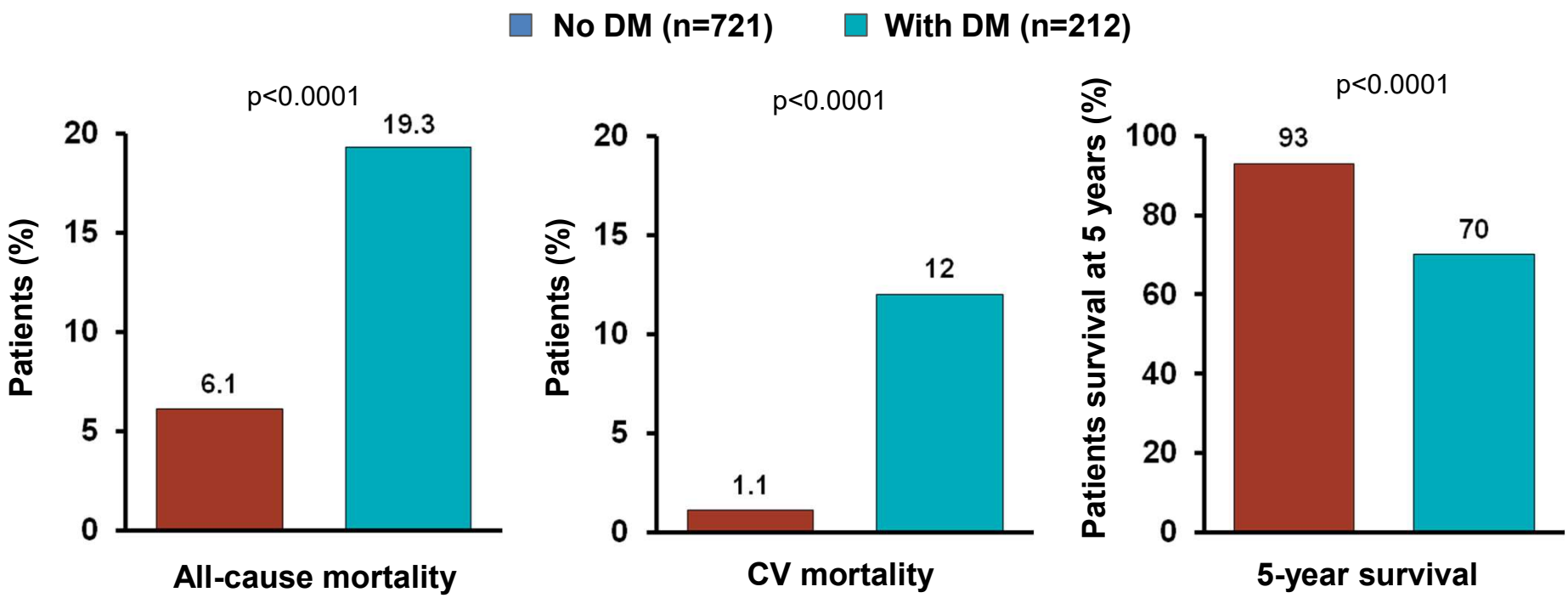
Extended Kaplan-Meier rates for MACE, stratified by the time-dependent indicator of the changing diabetes status posttransplantation. The "y-axis" represents the "pseudo-percent" of kidney transplant recipients with MACE as recipients can contribute to different curves at different times during the follow-up period (ie, recipients in the no diabetes group may switch into the PTDM group). MACE, major adverse cardiovascular event; NODAT, new-onset diabetes after transplantation.
5248 recipients



WH Lim, et al. Transplantation 2021;105(11):2470-2481

Survival in patients with diabetes mellitus after kidney transplantation

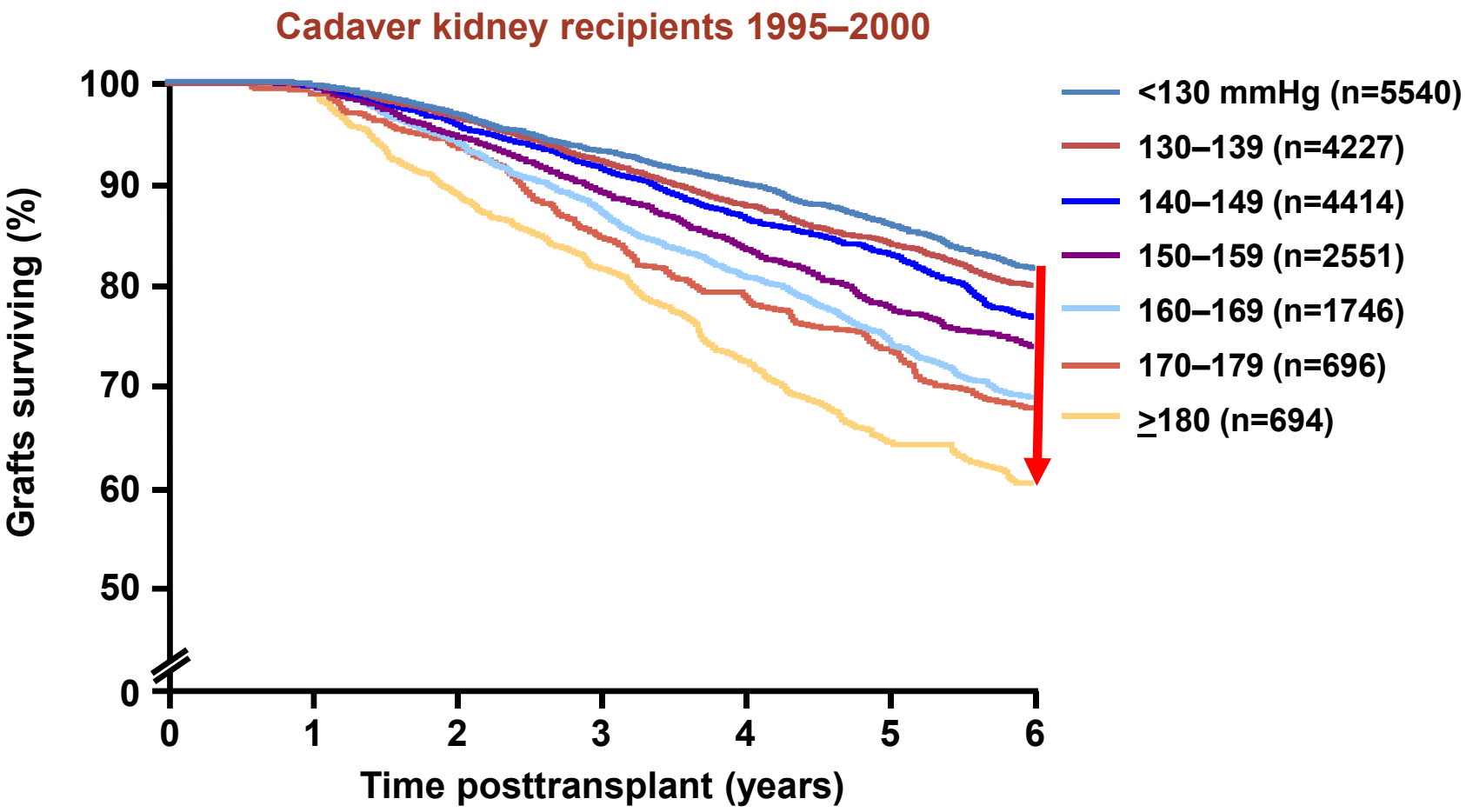
- 933 recipients of 1st transplant, 212 with diabetes mellitus[1]
- Patients followed for 47.3 ± 28.1 months (no DM), and 40.4 ± 25.3 months (with DM); p=0.001



CV, cardiovascular; DM, diabetes mellitus.

1. Cosio FG et al. Am J Transplant; 2008;8:593–9.

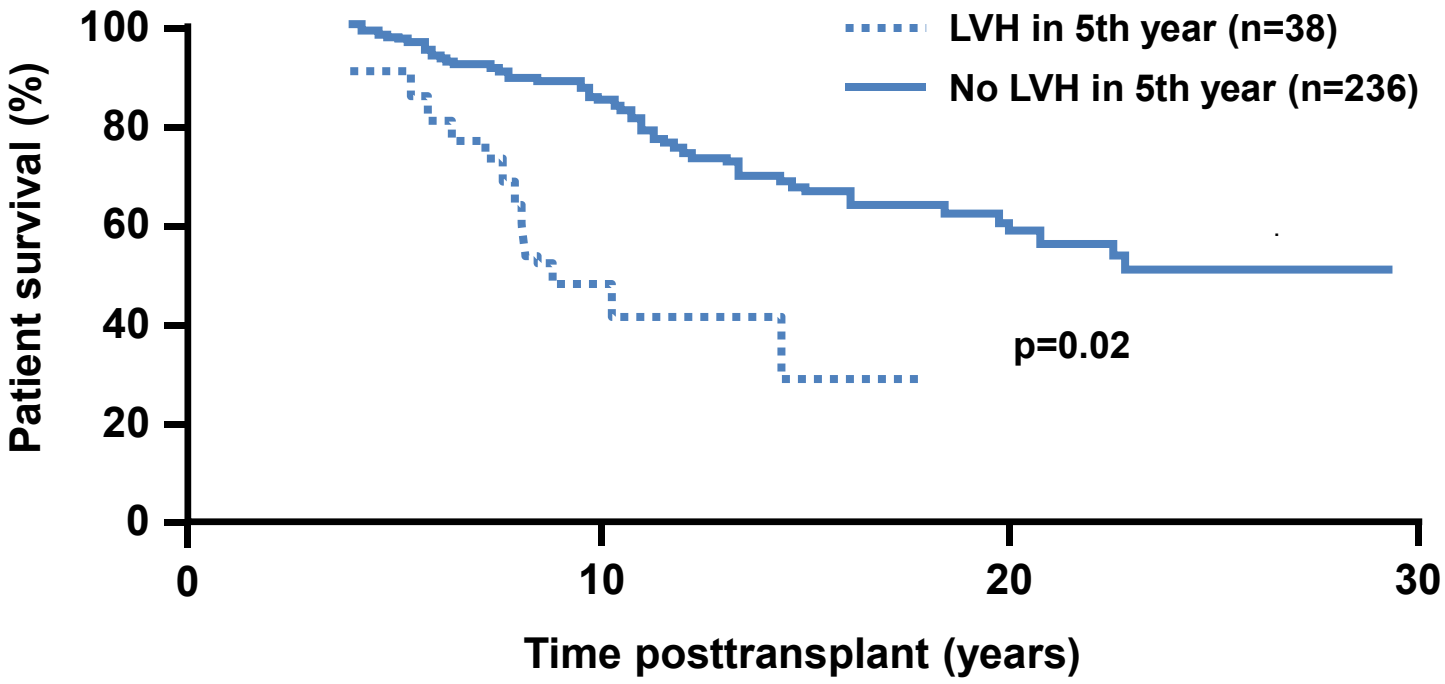
Graft survival is related to 1-year systolic blood pressure



Opelz G et al. Kidney Int 1998;53:217–22.

Presence of LVH is a strong determinant of risk of CVD

- LVH is detected in 74% of patients at start of dialysis[1]
- LVH in the 5th year after transplant predicted death (RR 2.15)[2]



CVD, cardiovascular disease; LVH, left ventricular hypertrophy; RR, relative risk.

1. Foley RN *et al. Kidney Int* 1995;47:186–92.
2. Rigatto C *et al. J Am Soc Nephrol* 2003;14:462–8.

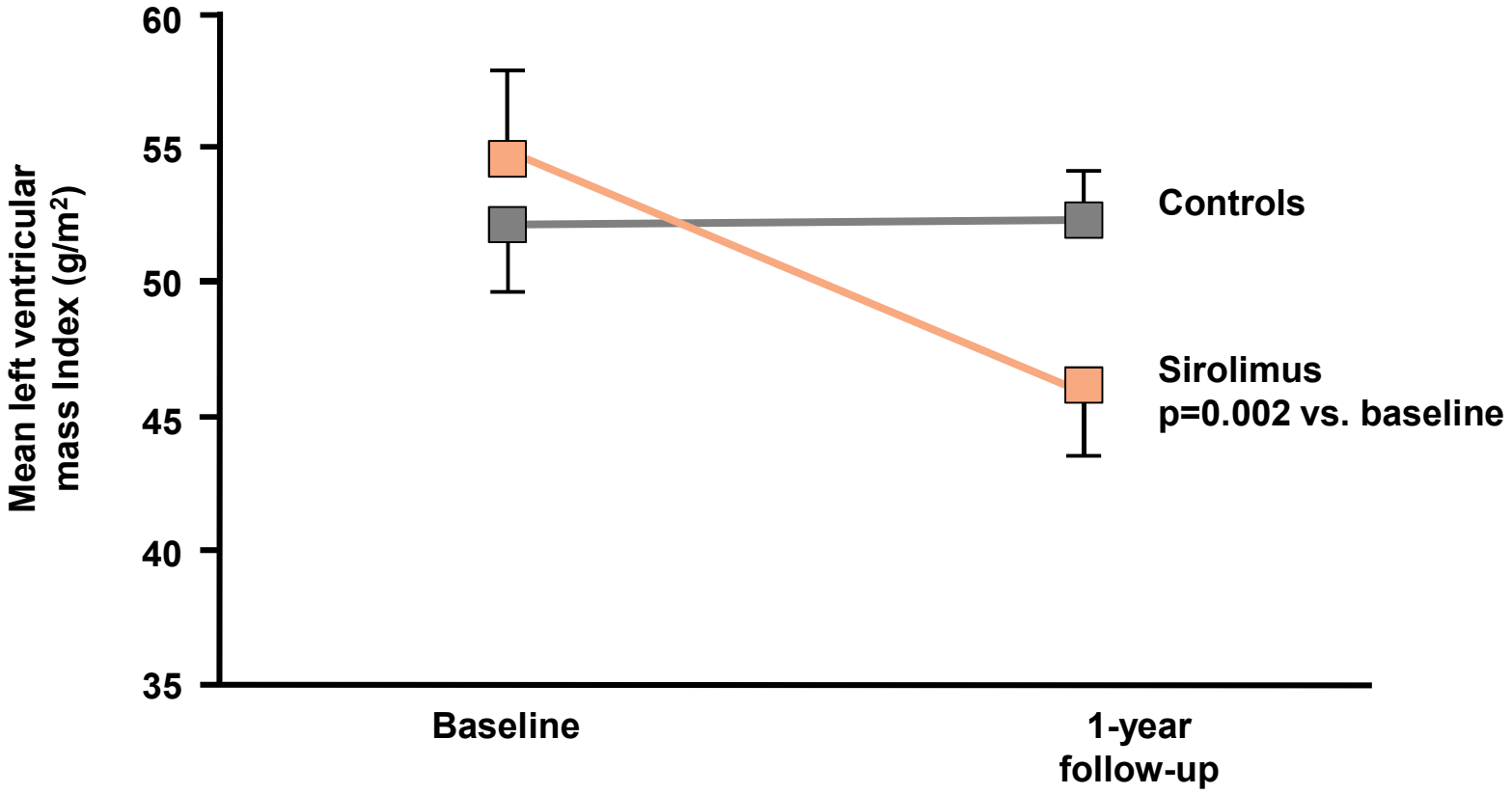
Can mTOR inhibitors reduce cardiovascular risk?

- mTOR inhibitors, particularly everolimus might be used at the place of mycophenolate mofetil with reduced doses of CNIs
- By sparing CNI doses the use of mTOR inhibitors can reduce CNI-related complications
  - May improve renal function[1,2]
  - Hypertension less frequent with mTORi therapy vs. CNI[3,4]
  - Dyslipidaemia more frequent with mTORi therapy[1,5–7] but is dose dependent[7] and can be well managed with statins

1. Tedesco Silva H Jr et al. Am J Transplant 2010;10:1401–13.
2. Budde K et al. Lancet 2011;377:837-47.
3. Morales JM et al. Transplant Proc 2005;37:693–6.
4. Zeier M, van der Giet M. Transpl Int 2011;24:30–42.
5. Webster AC et al. Transplantation 2006;81:1234–48.
6. Kasiske BL et al. Am J Transplant 2008;8:1384–92.
7. Walker R et al. Presented at: American Transplant Congress; Apr 30–May 4, 2011; Philadelphia, PA; Abstract 1295.

Conversion from CNI to mTORi may improve LVH

Non-randomised, single-centre trial in 13 kidney transplant patients and 26 matched controls



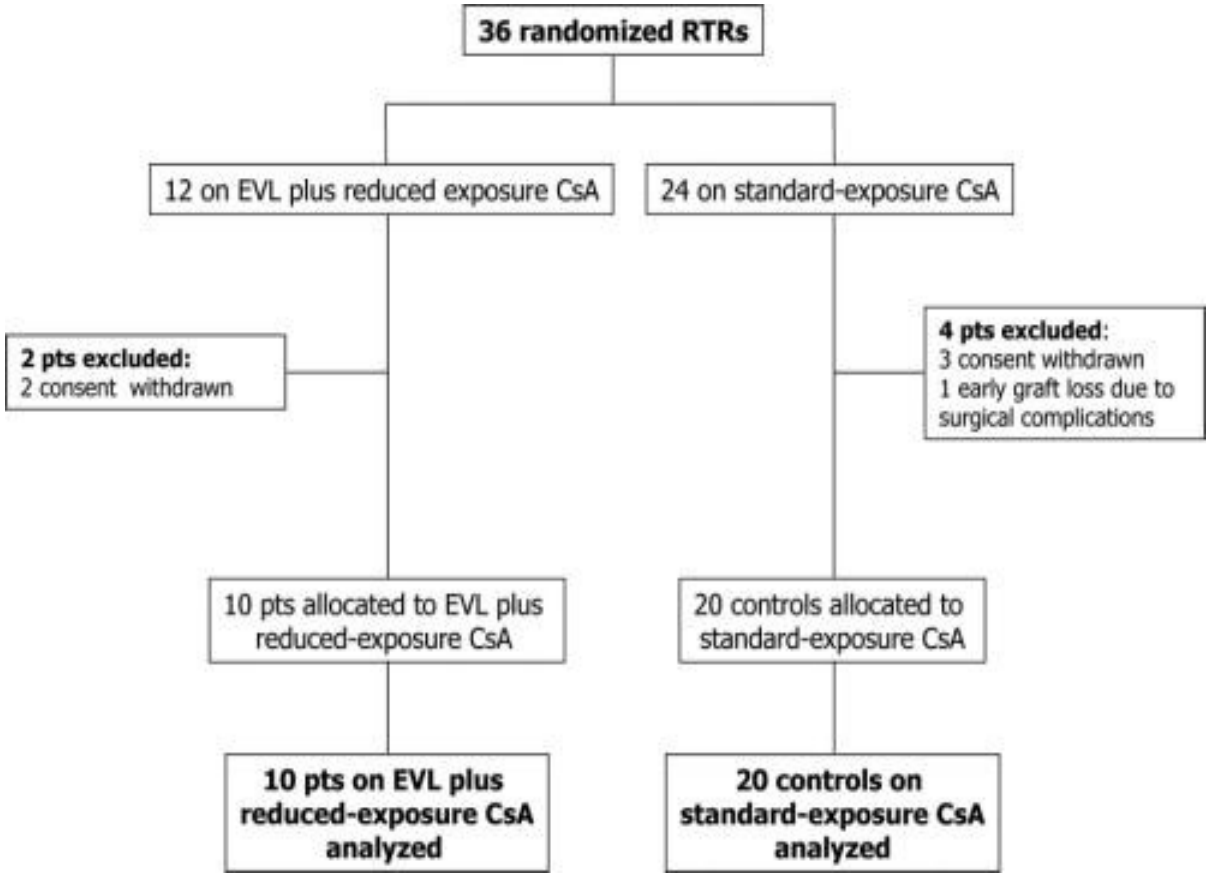
CNI, calcineurin inhibitor; mTORi, mammalian target of rapamycin inhibitor; LVH, left ventricular hypertrophy.

Paoletti E et al. Am J Kidney Dis 2008;52:324–30.

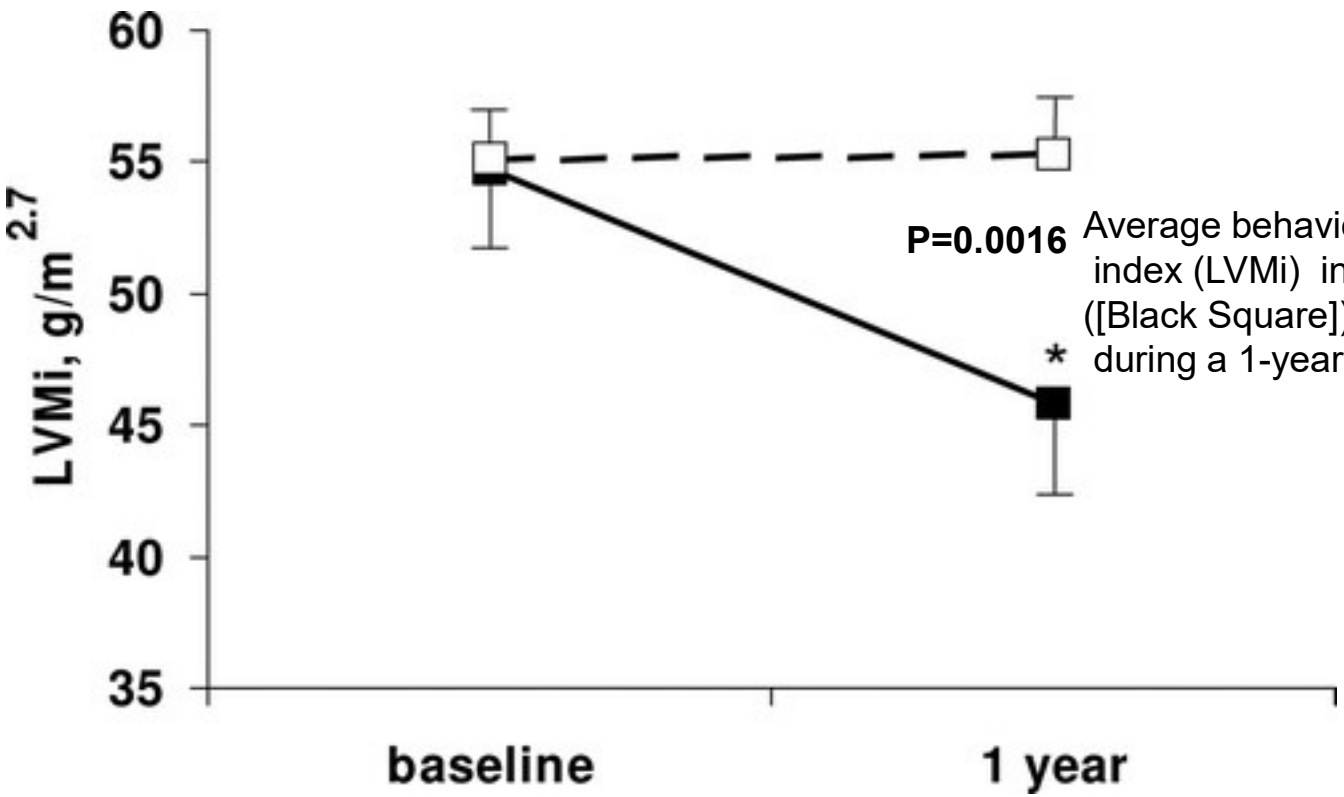
Everolimus for regression of left ventricular hypertrophy (1)

- 30 non diabetic *de novo* KT patients:

21 men, age 28-65 years) were randomized 1:2 ratio to EVR plus reduced exposure to CsA *vs.* standard exposure to CsA + MMF (steroids for all)



Paoletti E et al. Transplantation 2012:93:503.



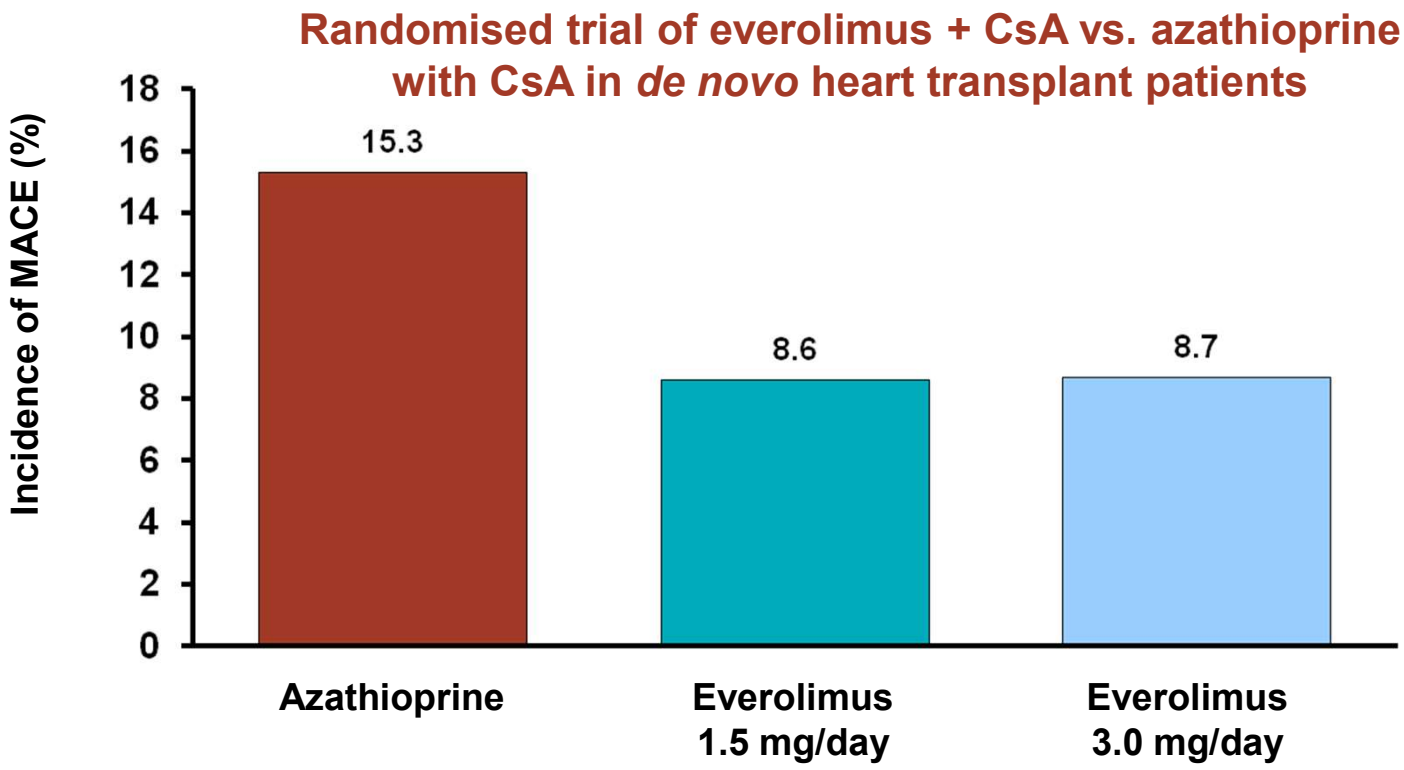
Average behavior of left ventricular mass index (LVMi) in KTRs receiving everolimus (EVL) ([Black Square]) and KTR controls ([white square]) during a 1-year observation period.

Variable	Beta coefficient	*P*
EVL therapy	7.825	0.0075
Baseline LVMi (g/m²)	-0.339	0.0024

Predictors of 1 yr changes in LVMi for 10 RTRs administered EVL and for 20 controls, by multivariate analysis

Paoletti E, et al. Transplantation 2012;93:503-508

…and heart transplant data show no increase in MACE with mTORi-based regimens

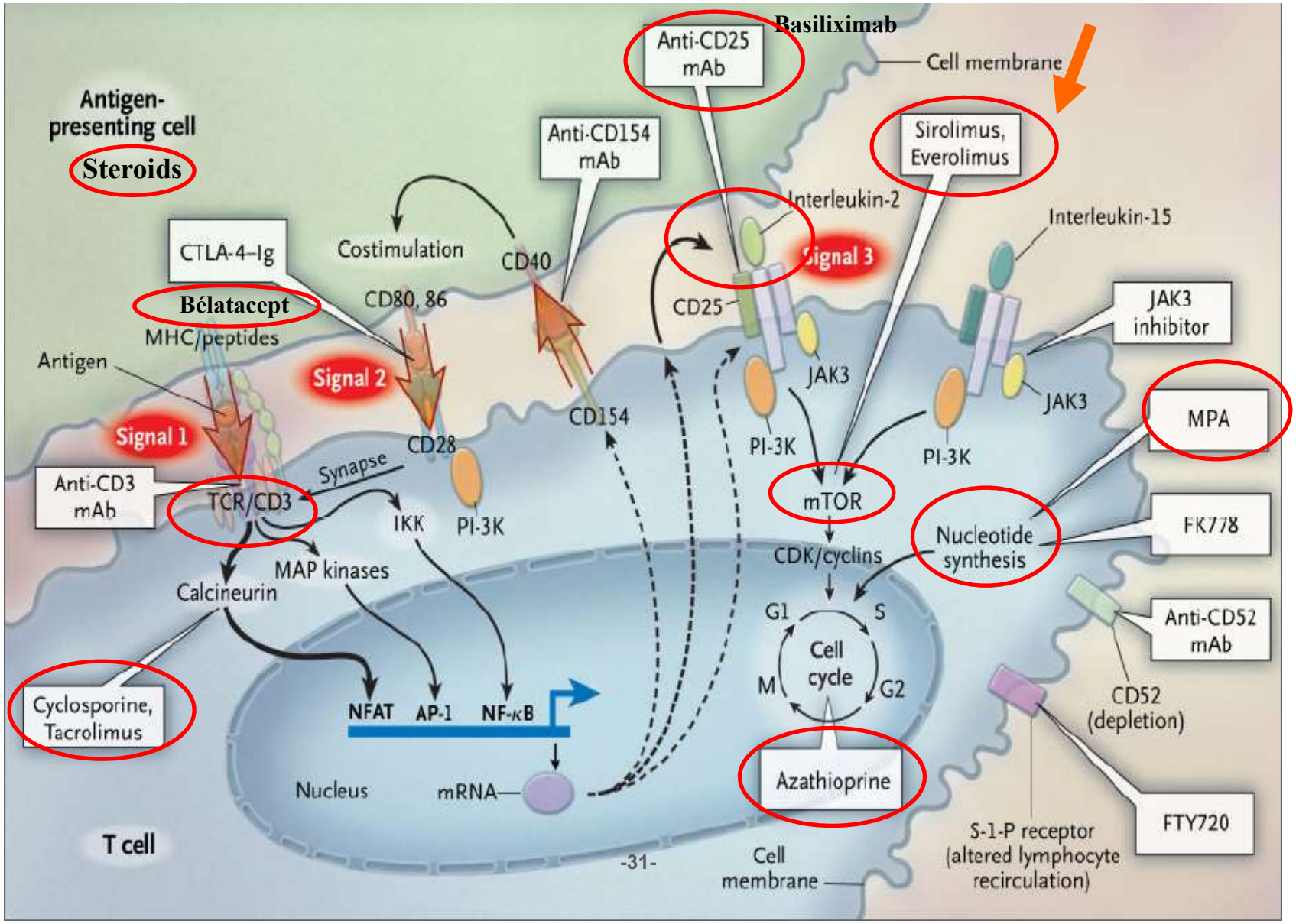


MACE, major adverse cardiac event (acute myocardial infarction, congestive heart failure, percutaneous cardiac intervention, coronary artery bypass grafting, implantable cardiac defibrillator, cerebrovascular accident ,or peripheral vascular disease);
mTORi, mammalian target of rapamycin inhibitor; CsA, cyclosporin.

Eisen H. Nephrol Dial Transplant 2006;21(suppl 3):iii9–13.

Immunosuppression and long-term outcomes

Mechanisms of action of immunosuppressants



Induction therapy

Induction immunosuppression improves long-term graft and patient outcome in organ transplantation : an analysis of united network for organ sharing (UNOS) registry data

Induction therapy and graft and patient survival (2003–2009)

Variables	Organs				
	Kidney	Pancreas	Liver	Heart	Lung
No. Cases	112,902	3,380	43,407	14,728	9,485
Induction recipient (%)	84	77	61	72	67
Graft survival (%) (induction vs. Non induction)					
3 mo	97-91	89-84	92-89	93-92	93-90
1 yr	93-87	79-73	85-81	88-86	83-80
5 yr	74-69	52-51	68-64	72-72	49-47
P	0.0000	0.0798	0.0000	0.1877	0.0020
Patient survival (%) (induction vs. Non induction)					
3 mo	99-95	98-97	95-92	94-92	93-91
1 yr	97-93	94-91	89-86	89-87	84-81
5 yr	86-83	80-79	73-70	74-73	52-51
P	0.0000	0.1023	0.0000	0.1665	0.0041

Cai J, Terasaki PI. Transplantation 2010;90:1511-1515

Induction therapy for living kidney transplantation

- Multivariate analysis of antibody induction therapy and their associated outcomes in living KT
  - Retrospective study (1998-2002 : n= 21919, and 2003-2008 : n=26830; OPTN/UNOS data
  - Primary adult living donor kidney recipients **with or without** induction therapy
    - ✓ Significantly less AR at 6 months with induction therapy in the 1st era but not in the 2nd era
    - ✓ No difference in graft survival at 5 years posttransplantation
    - ✓ Mutivariate analysis: no association between induction therapy and graft loss, or death-censored graft loss.

Emami S et al. Clin Transplant. 2012;26:351-8.

Basiliximab or Antithymocyte globulin for induction therapy in kidney transplantation : a meta-anlaysis (1)

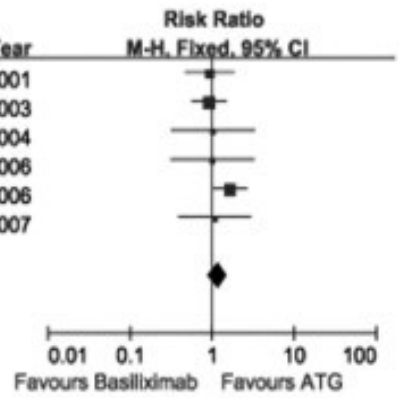
Primary outcome for basiliximab compared to antithymocyte globulin (ATG). (1)

Risk of Biopsy Proven Acute Rejection

Study or Subgroup	Basiliximab Events	Basiliximab Total	ATG Events	ATG Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Sollinger H(2001)	13	70	13	65	18.4%	0.93 [0.47, 1.85]	2001
Tullius SG(2003)	20	62	22	62	30.0%	0.91 [0.56, 1.49]	2003
Mourad G(2004)	5	52	5	53	6.7%	1.02 [0.31, 3.31]	2004
Lebranchu Y 2006	5	50	5	50	6.8%	1.00 [0.31, 3.24]	2006
Brennan DC(2006)	35	137	22	141	29.5%	1.64 [1.01, 2.64]	2006
Kyllönen LE(2007)	7	58	6	53	8.5%	1.07 [0.38, 2.97]	2007
Total (95% CI)		429		424	100.0%	1.15 [0.88, 1.52]	
Total events	85		73				

Heterogeneity: $Chi^2 = 3.46$, df = 5 (P = 0.63); $I^2 = 0\%$

Test for overall effect: Z = 1.02 (P = 0.31)

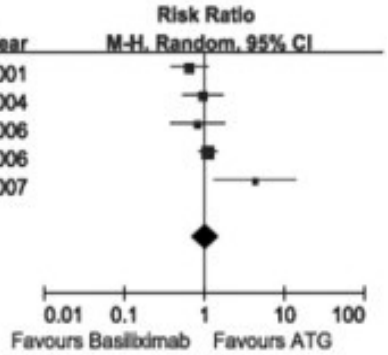


Risk of Delayed Graft Function

Study or Subgroup	Basiliximab Events	Basiliximab Total	ATG Events	ATG Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Sollinger H(2001)	16	70	23	65	22.5%	0.65 [0.38, 1.11]	2001
Mourad G(2004)	15	52	16	53	20.8%	0.96 [0.53, 1.73]	2004
Lebranchu Y 2006	9	50	11	50	15.2%	0.82 [0.37, 1.80]	2006
Brennan DC(2006)	61	137	57	141	33.0%	1.10 [0.84, 1.45]	2006
Kyllönen LE(2007)	14	58	3	53	8.5%	4.26 [1.30, 14.02]	2007
Total (95% CI)		367		362	100.0%	1.02 [0.69, 1.51]	
Total events	115		110				

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 8.99$, df = 4 (P = 0.06); $I^2 = 56\%$

Test for overall effect: Z = 0.09 (P = 0.93)



Liu Y et al. Transplant Proc. 2010;42;1667-1670

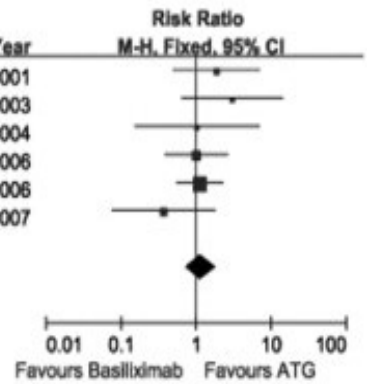
Basiliximab or Antithymocyte globulin for induction therapy in kidney transplantation : a meta-anlaysis (2)

Primary outcome for basiliximab compared to antithymocyte globulin (ATG). (2)

Risk of Graft Loss

Study or Subgroup	Basiliximab Events	Basiliximab Total	ATG Events	ATG Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Sollinger H(2001)	6	70	3	65	9.7%	1.86 [0.48, 7.12]	2001
Tullius SG(2003)	6	62	2	62	6.2%	3.00 [0.63, 14.29]	2003
Mourad G(2004)	2	52	2	53	6.2%	1.02 [0.15, 6.97]	2004
Lebranchu Y 2006	7	50	7	50	21.8%	1.00 [0.38, 2.64]	2006
Brennan DC(2006)	14	137	13	141	39.9%	1.11 [0.54, 2.27]	2006
Kyllönen LE(2007)	2	58	5	53	16.3%	0.37 [0.07, 1.80]	2007
Total (95% CI)		429		424	100.0%	1.15 [0.73, 1.80]	
Total events	37		32				

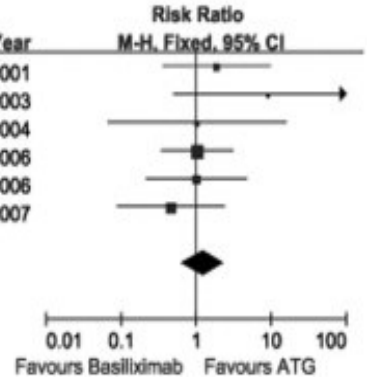
Heterogeneity: $Chi^2 = 4.02$, df = 5 (P = 0.55); $I^2 = 0\%$
Test for overall effect: Z = 0.60 (P = 0.55)



Risk of Patient Death

Study or Subgroup	Basiliximab Events	Basiliximab Total	ATG Events	ATG Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Sollinger H(2001)	4	70	2	65	12.5%	1.86 [0.35, 9.80]	2001
Tullius SG(2003)	4	62	0	62	3.0%	9.00 [0.49, 163.70]	2003
Mourad G(2004)	1	52	1	53	5.9%	1.02 [0.07, 15.87]	2004
Brennan DC(2006)	6	137	6	141	35.5%	1.03 [0.34, 3.11]	2006
Lebranchu Y 2006	3	50	3	50	18.0%	1.00 [0.21, 4.72]	2006
Kyllönen LE(2007)	2	58	4	53	25.1%	0.46 [0.09, 2.39]	2007
Total (95% CI)		429		424	100.0%	1.22 [0.65, 2.30]	
Total events	20		16				

Heterogeneity: $Chi^2 = 3.59$, df = 5 (P = 0.61); $I^2 = 0\%$
Test for overall effect: Z = 0.62 (P = 0.54)



Liu Y et al. Transplant Proc. 2010;42;1667-1670

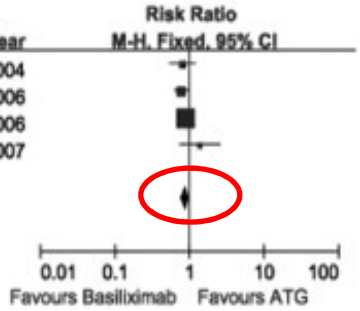
Basiliximab or Antithymocyte globulin for induction therapy in kidney transplantation : a meta-anlaysis (3)

Secondary outcome for basiliximab compared to antithymocyte globulin (ATG).

Risk of Infection

Study or Subgroup	Basiliximab Events	Basiliximab Total	ATG Events	ATG Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Mourad G(2004)	22	52	28	53	13.7%	0.80 [0.53, 1.20]	2004
Lebranchu Y 2006	33	50	43	50	21.2%	0.77 [0.61, 0.96]	2006
Brennan DC(2006)	103	137	121	141	58.9%	0.88 [0.78, 0.99]	2006
Kyllönen LE(2007)	18	58	12	53	6.2%	1.37 [0.73, 2.57]	2007
Total (95% CI)		297		297	100.0%	0.87 [0.78, 0.97]	
Total events	176		204				

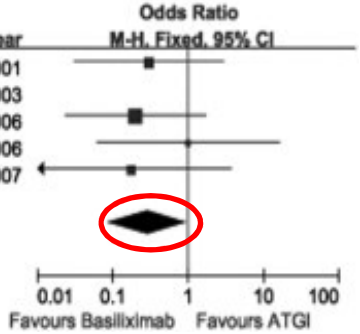
Heterogeneity: Chi² = 3.39, df = 3 (P = 0.34); I² = 11%
Test for overall effect: Z = 2.42 (P = 0.02)



Risk of Neoplasms

Study or Subgroup	Basiliximab Events	Basiliximab Total	ATG Events	ATG Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Sollinger H(2001)	1	70	3	65	26.6%	0.30 [0.03, 2.95]	2001
Tullius SG(2003)	0	62	0	62		Not estimable	2003
Brennan DC(2006)	1	137	5	141	42.4%	0.20 [0.02, 1.73]	2006
Lebranchu Y 2006	1	50	1	50	8.5%	1.00 [0.06, 16.44]	2006
Kyllönen LE(2007)	0	58	2	53	22.5%	0.18 [0.01, 3.75]	2007
Total (95% CI)		377		371	100.0%	0.29 [0.09, 0.97]	
Total events	3		11				

Heterogeneity: Chi² = 0.97, df = 3 (P = 0.81); I² = 0%
Test for overall effect: Z = 2.08 (P = 0.04)

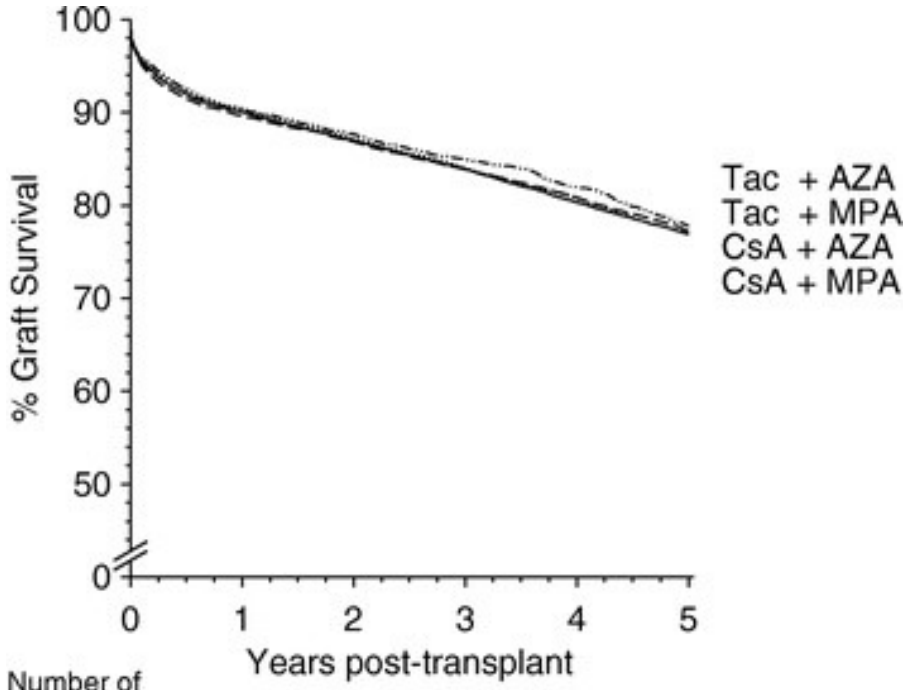


Liu Y et al. Transplant Proc. 2010;42;1667-1670

Calcineurin inhibitors

Influence of immunosuppressive regimens on graft survival and secondary outcomes after kidney transplantation (1)

Kaplan-Meier estimates of graft survival to year 5 after kidney transplantation according to type of immunosuppression (intention-to-treat basis). All differences were statistically nonsignificant.

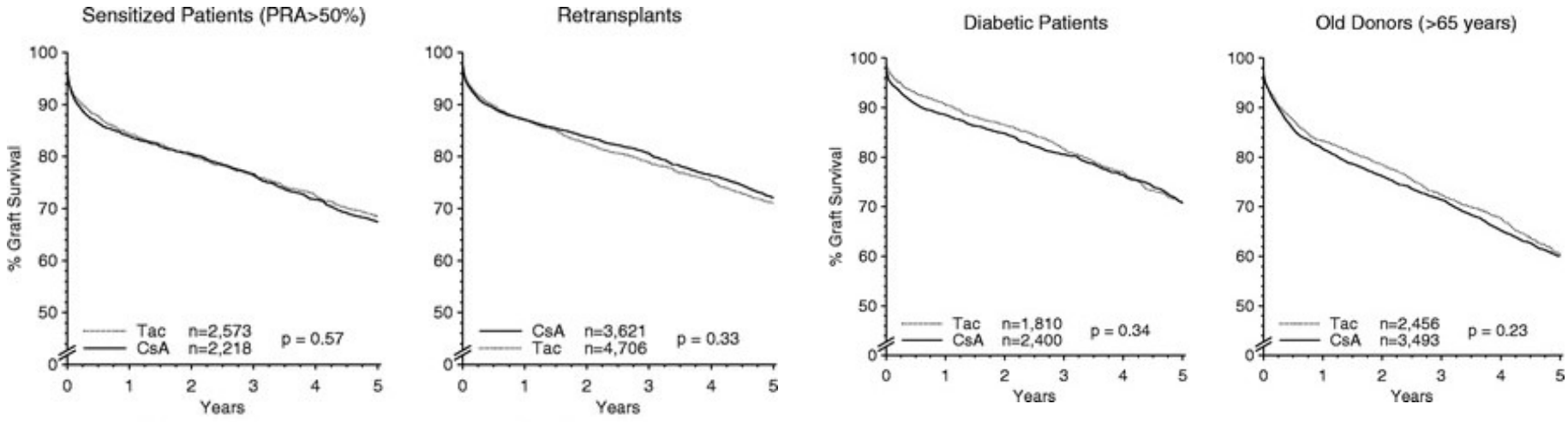


Number of transplants						
Tac + AZA	1,811	1,574	1,395	1,221	1,070	890
Tac + MPA	17,854	14,167	11,036	8,148	5,935	3,846
CsA + AZA	7,166	6,220	5,747	5,261	4,699	4,094
CsA + MPA	22,968	19,079	16,184	13,147	10,197	7,553

Opelz G et al. Transplantation 2009;87:795-802

Influence of immunosuppressive regimens on graft survival and secondary outcomes after kidney transplantation (2)

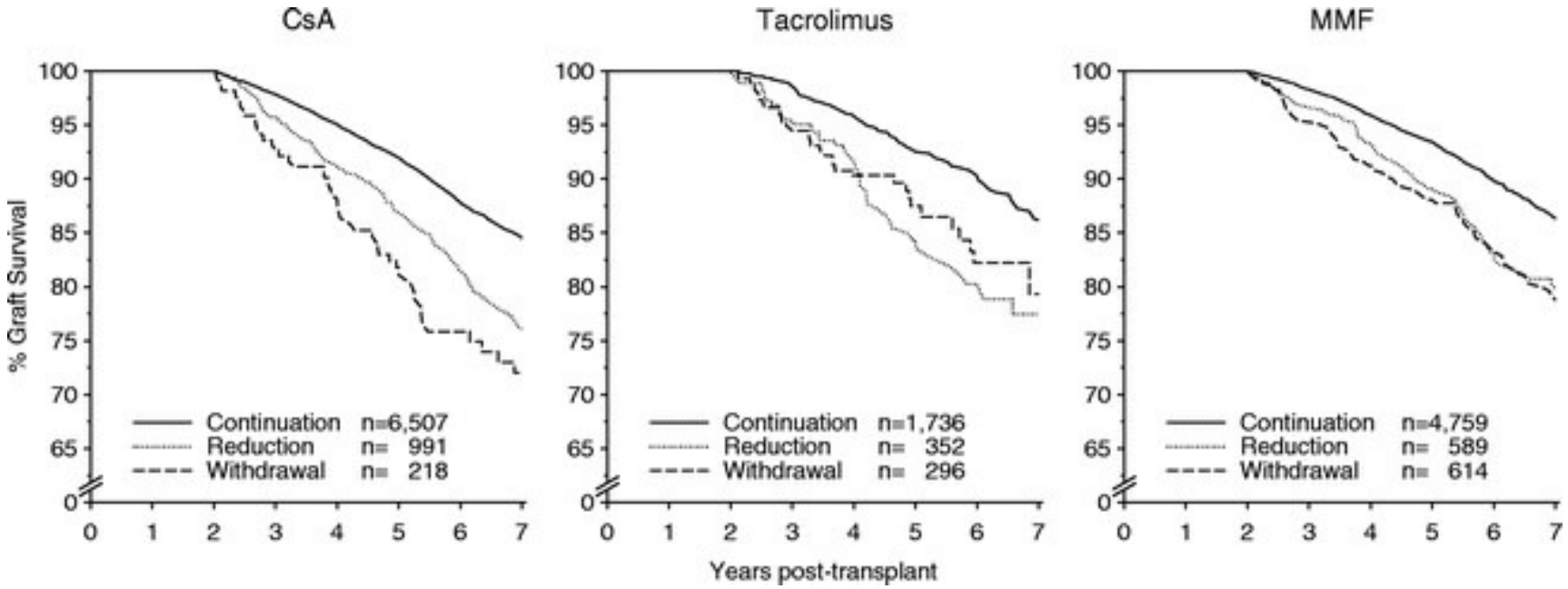
Graft survival in four subgroups of high-risk patients treated with cyclosporine A or tacrolimus (intention to treat). Numbers of patients studied and P values (log-rank) are indicated. All differences were statistically nonsignificant.



Opelz G et al. Transplantation 2009;87:795-802

Effect on kidney graft survival of reducing or discontinuing maintenance immunosuppression after the first year posttransplant (1)

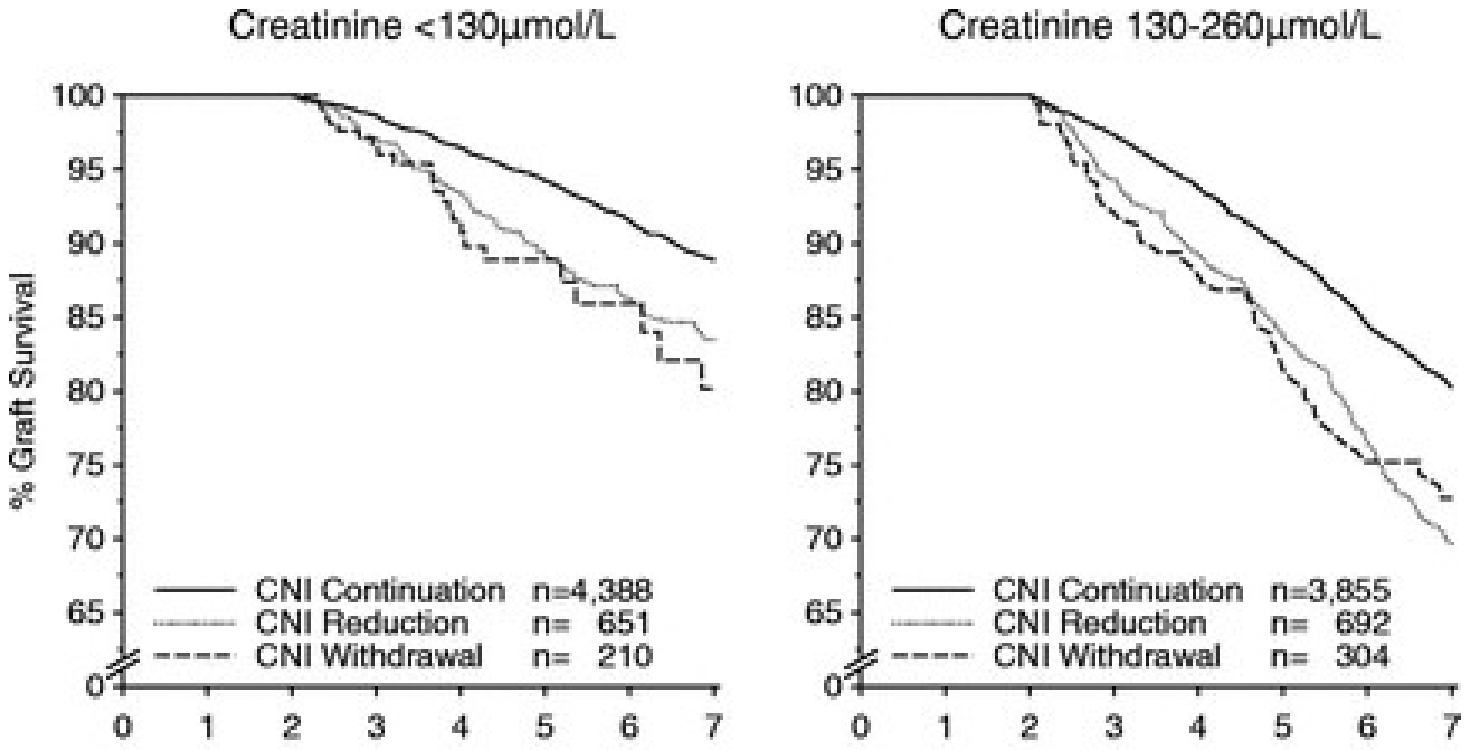
Graft survival during years 3 to 7 posttransplant according to dose reductions or withdrawal of CsA, tacrolimus, and MMF during the second posttransplant year, compared with patients continuing to receive an unchanged dose. All P values less than 0.001 for reduction or withdrawal vs. continuation (log rank).



Opelz G et al. Transplantation 2008;86:371-376

Effect on kidney graft survival of reducing or discontinuing maintenance immunosuppression after the first year posttransplant (2)

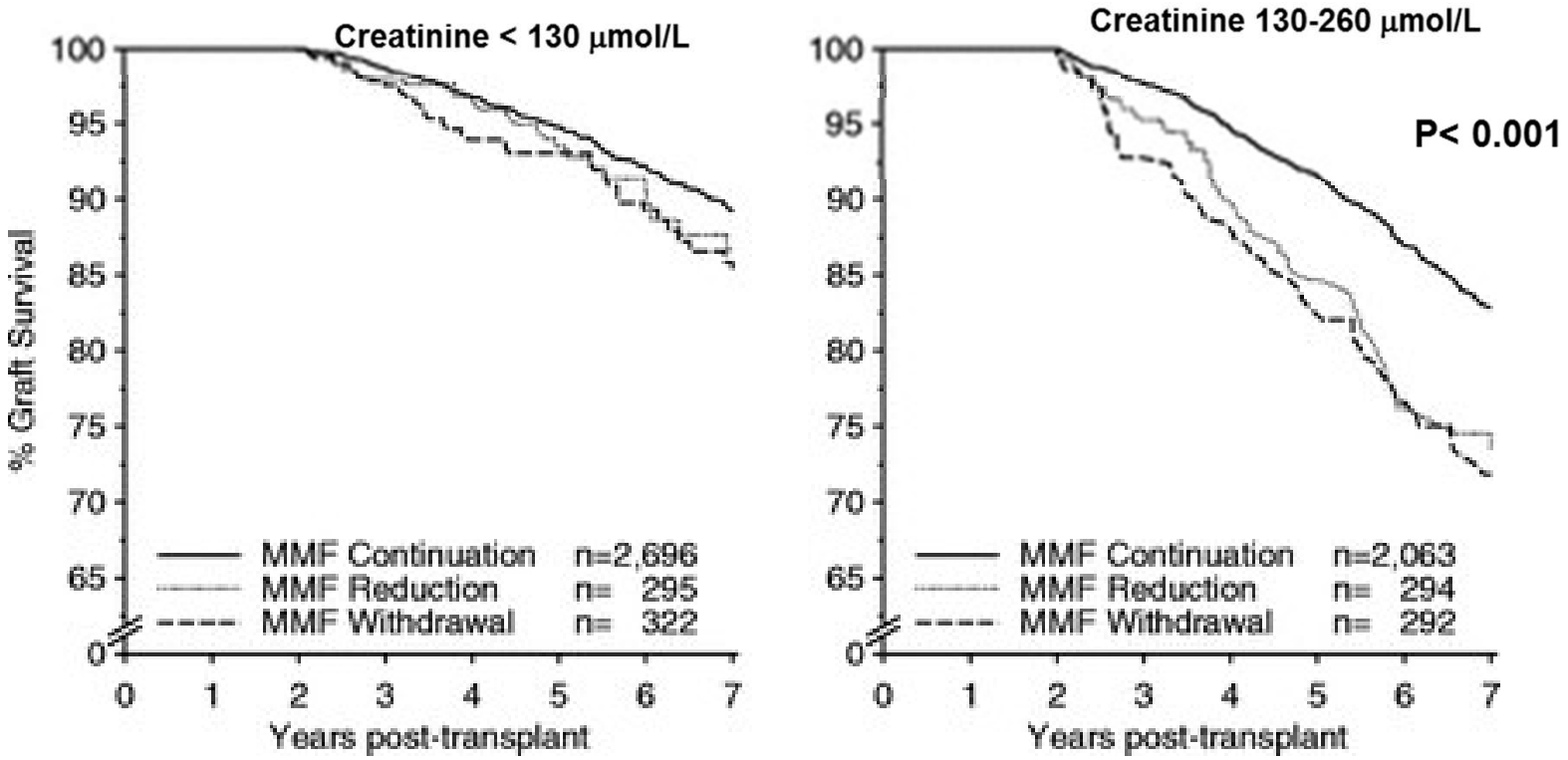
Graft survival during years 3 to 7 posttransplant in patients with a 1-year serum creatinine of less than 130 µmol/L (left) or 130 to 260 µmol/L (right) and in whom CNI or MMF were reduced below threshold or completely withdrawn. CNI (upper half of figure): All comparisons of continuation vs. reduction or withdrawal P<0.001 (log rank). MMF (lower half): Creatinine less than 130 µmol/L: MMF dose reduction, P=0.31; MMF withdrawal, P=0.047. Creatinine 130 to 260 µmol/L: MMF dose reduction or withdrawal, P<0.001. All P values vs. drug continuation.



Opelz G et al. Transplantation 2008;86:371-376

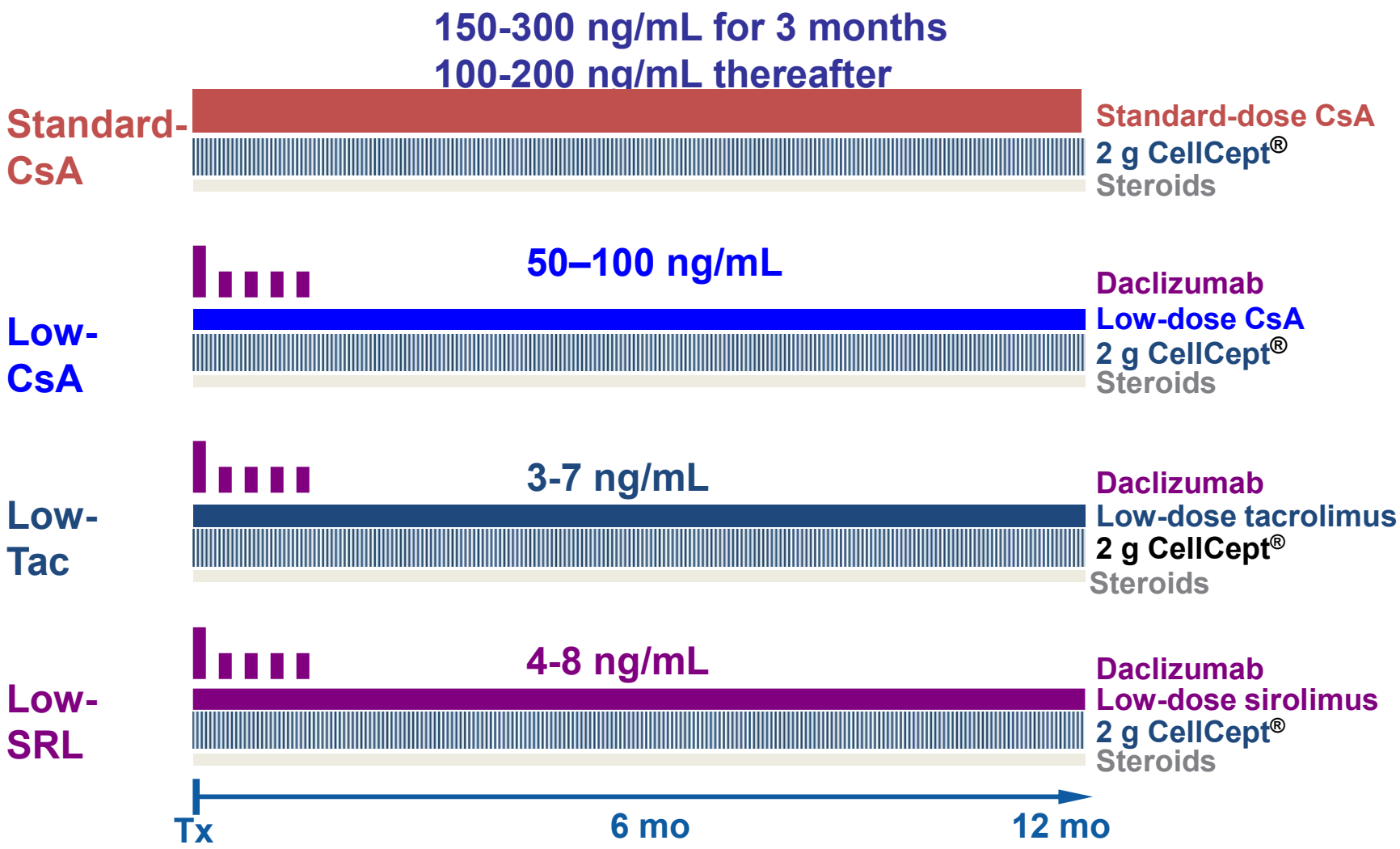
Effect on kidney graft survival of reducing or discontinuing maintenance immunosuppression after the first year posttransplant (3)

Graft survival during years 3 to 7 posttransplant in patients with a 1-year serum creatinine of less than 130 µmol/L (left) or 130 to 260 µmol/L (right) and in whom CNI or MMF were reduced below threshold or completely withdrawn. CNI (upper half of figure): All comparisons of continuation vs. reduction or withdrawal P<0.001 (log rank). MMF (lower half): Creatinine less than 130 µmol/L: MMF dose reduction, P=0.31; MMF withdrawal, P=0.047. Creatinine 130 to 260 µmol/L: MMF dose reduction or withdrawal, P<0.001.



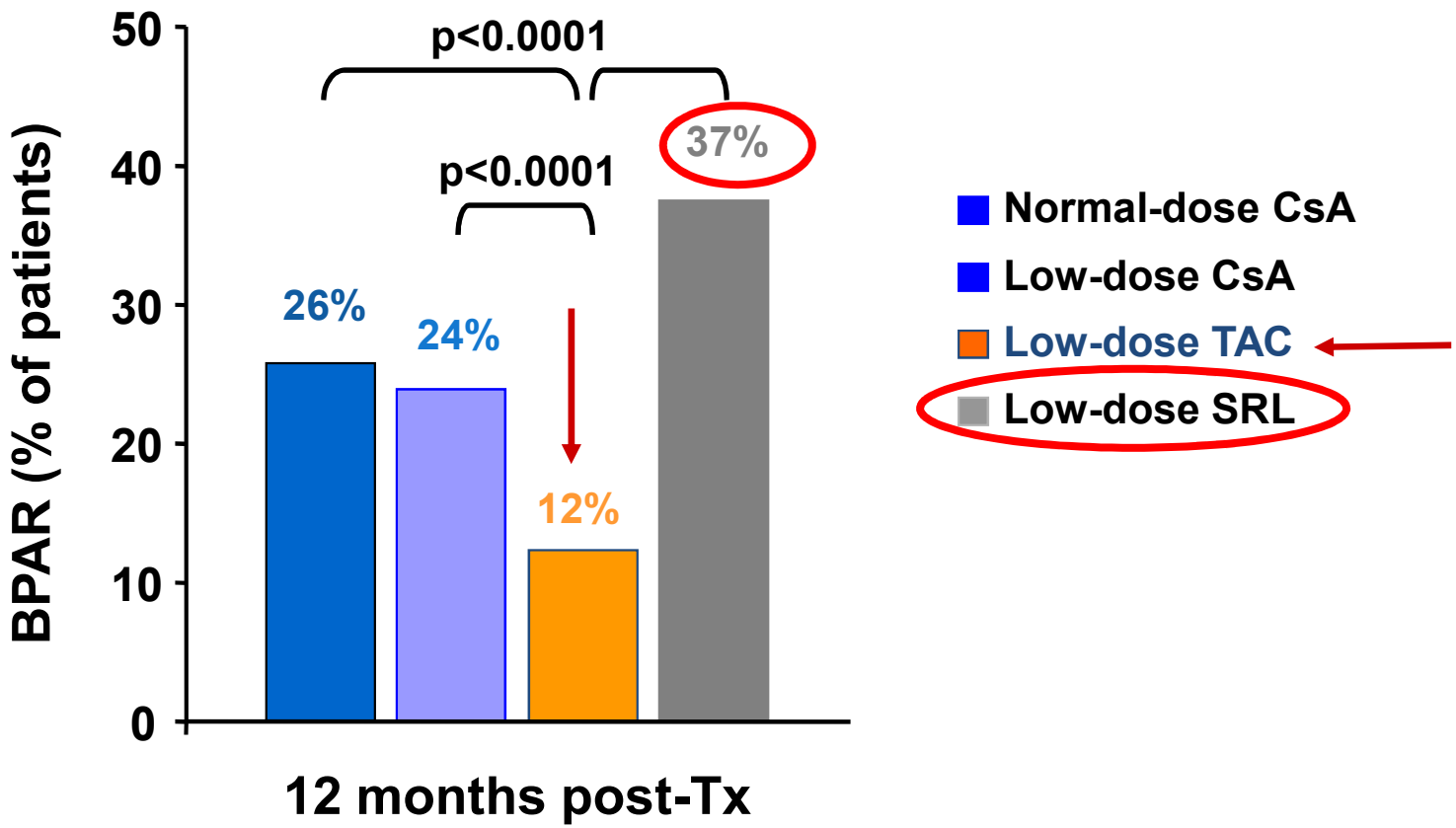
Opelz G et al. Transplantation 2008;86:371-376

SYMPHONY study: 1,645 patients



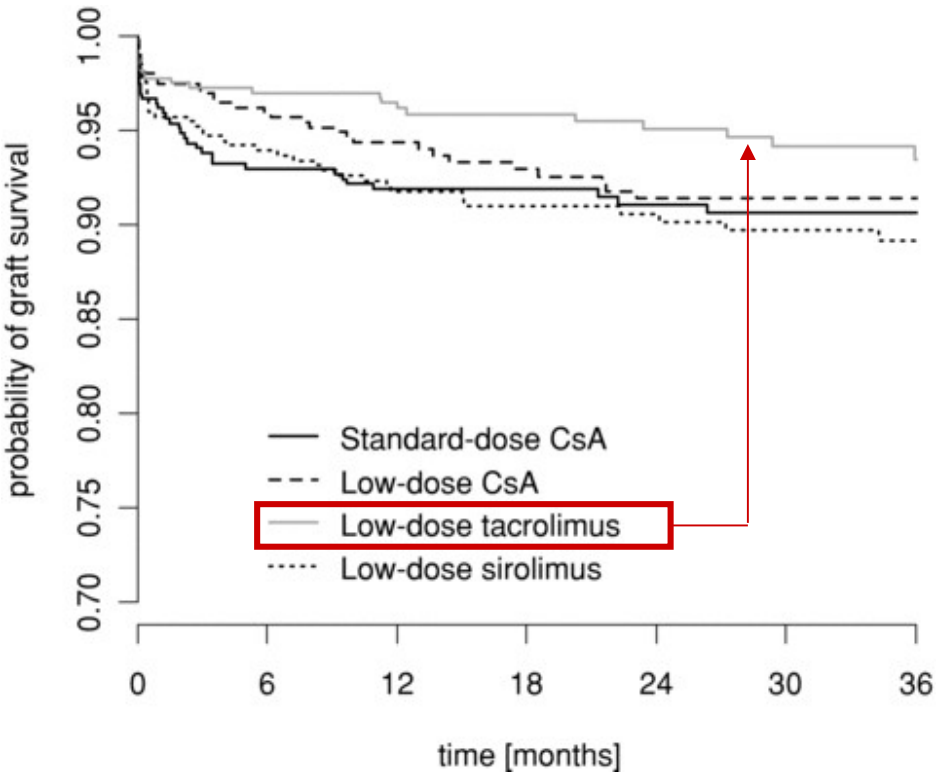
Ekberg *et al.*, NEJM 2007

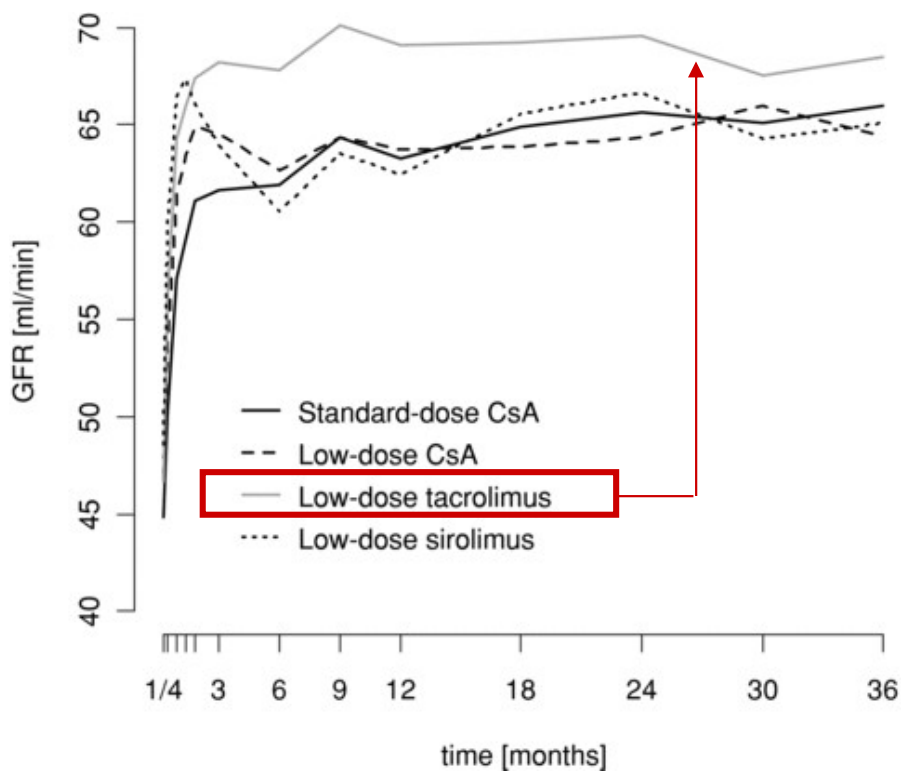
Biopsy Proven Acute Rejection at 1 year
(ITT, Excluding Borderline)



Ekberg *et al.*, NEJM 2007

SYMPHONY study: 3-year results





Graft survival censored for patient death with a functioning graft in the four treatment groups. The analysis is based on the entire ITT population of the core study and patients not participating in the follow-up from 1 year onward are censored at their last visit.

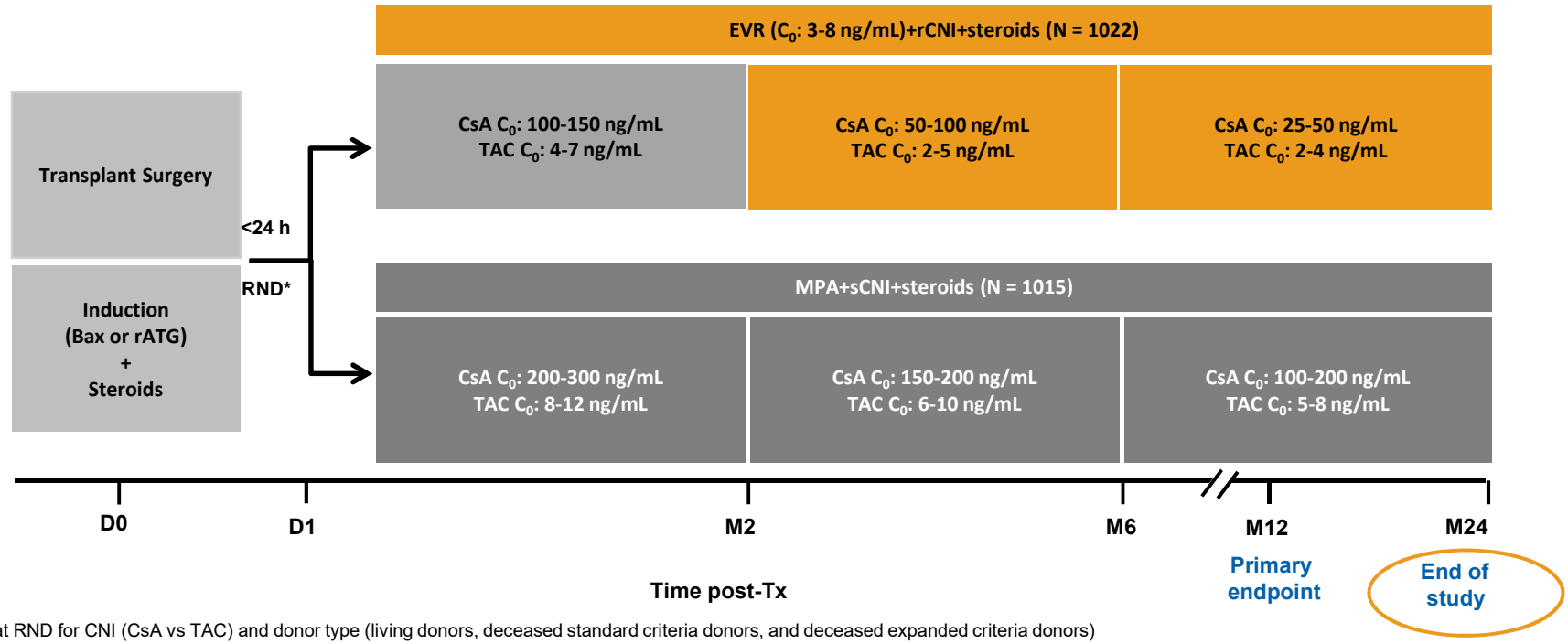
Renal function over time (week 1–month 36, mean Cockcroft–Gault estimated GFR, without imputation and without carrying forward of serum creatinine values). The analysis is based on the entire ITT population of the core study, i.e. the first year also includes patients who did not participate in the follow-up.

Ekberg H *et al*. AJT 2009;9:1876-1885

Can we achieve better results than those from SYMPHONY trial?

TRANSFORM study

A 24-month, randomized, multicenter, open-label, parallel group study in KTxRs

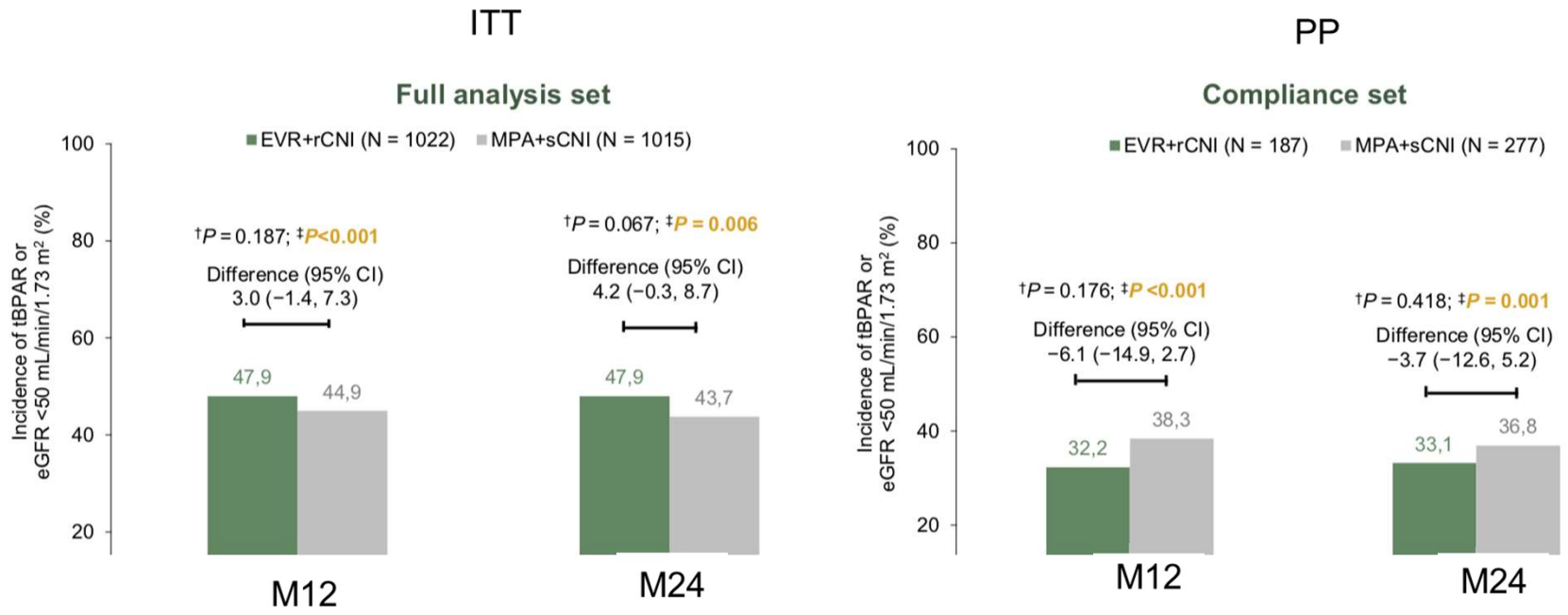


Stratified at RND for CNI (CsA vs TAC) and donor type (living donors, deceased standard criteria donors, and deceased expanded criteria donors)
Bax, basiliximab; C_0, trough level; CNI, calcineurin inhibitor; CsA, cyclosporine A; D, day; EVR, everolimus; KTxRs, kidney transplant recipients; M, month; MPA, mycophenolic acid; rATG, rabbit antithymocyte globulin; rCNI, reduced-exposure CNI; RND, randomization; sCNI, standard-exposure CNI; TAC, tacrolimus; Tx, transplantation

Pascual J, et al. J Am Soc Nephrol. 2018

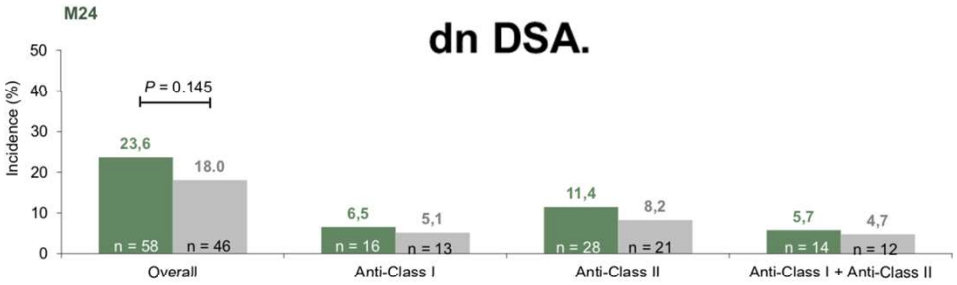
Incidence of primary efficacy endpoint : *EVR+rCNI was non-inferior to MPA+sCNI at M12 and M24*

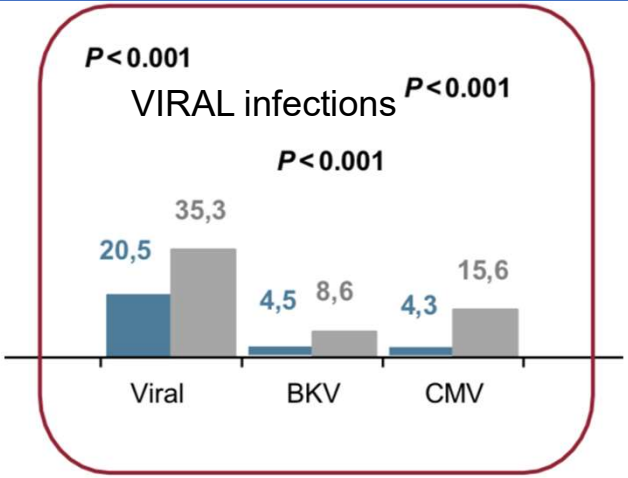
Composite of **tBAR** or **eGRF <50mL**/min/1.73 m²

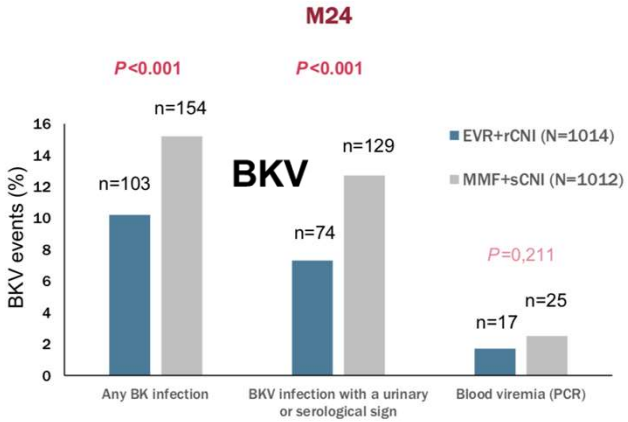


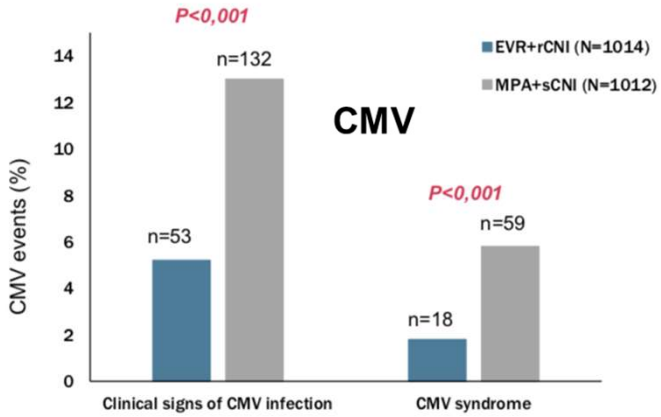
Berger SP et al. Am J Transplant. 2019 Jun 1.

Incidence of *de novo* DSA and viral infection (CMV, BKV) *at M12 and M24*









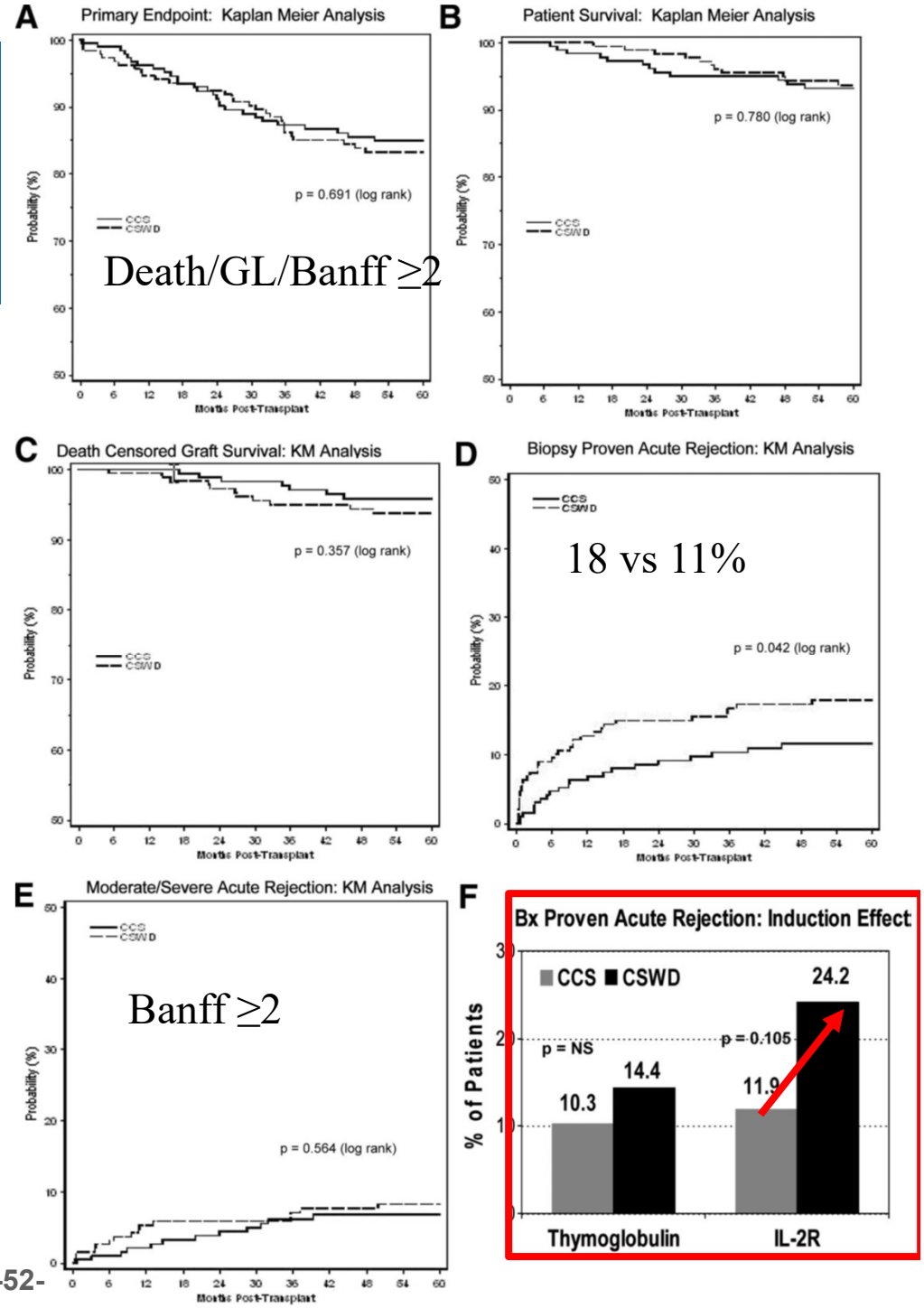
Berger SP et al. Am J Transplant. 2019 Jun 1.

Steroid avoidance

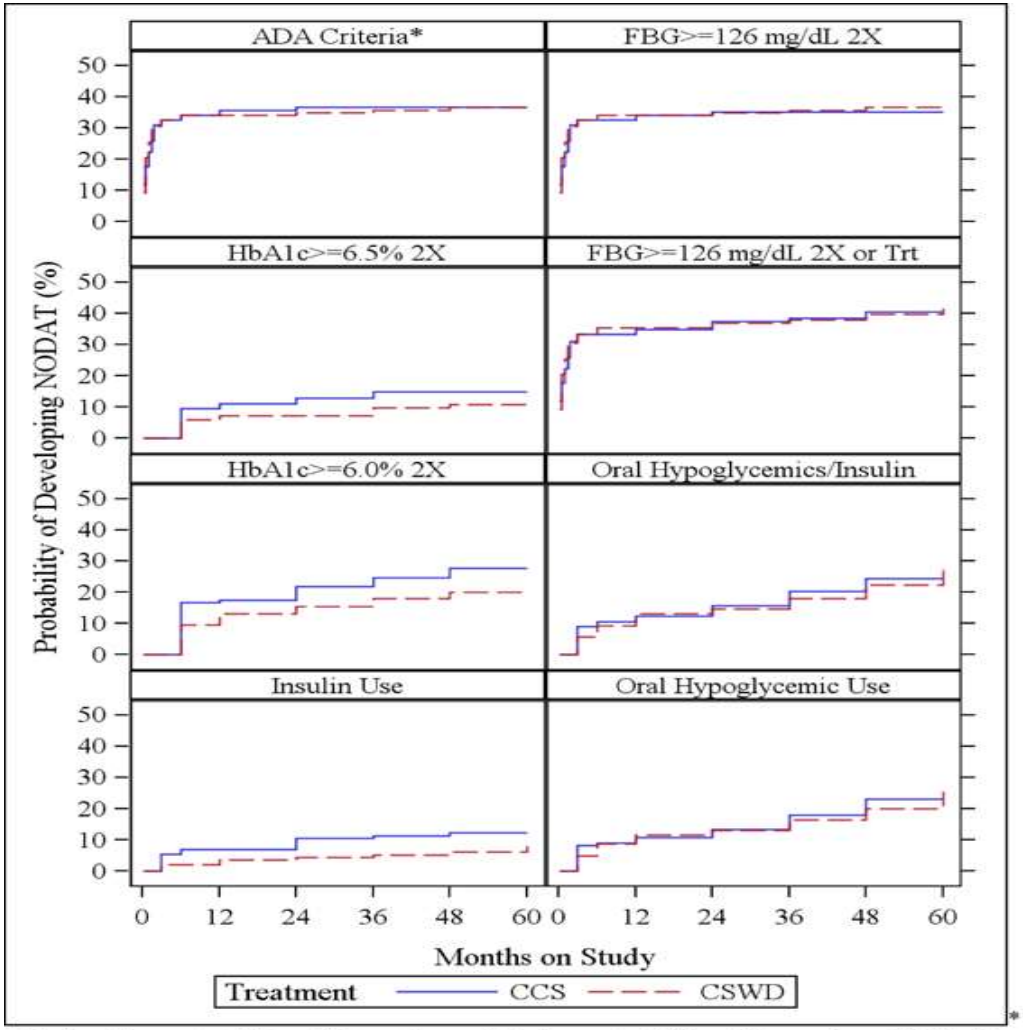
Does induction help use low-dose/avoid Steroids ?

- Early steroid discontinuation (7d) vs. maintenance, Thymo or anti-IL2 mAb; Tac and MMF (FU:5y) (Woodle, Ann Surg, 2008)
- Steroid withdrawal (CSWD) n=191; steroid continuation (CCS), n=195
- At 5y: mean creatinine 1.5 mg both groups

→More « benign » rejection on CSWD but excellent long-term outcomes



New-Onset diabetes after transplantation: results from a double-blind early corticosteroid withdrawal trial



* ADA Criteria: Glucose >=126 mg/dL two times; OR glucose >= 200 mg/dL one time; OR HbA1c >=6.5% two times; OR [glucose >=126 mg/dL AND HbA1c >=6.5% simultaneously one time]

- Early steroid discontinuation (7d) vs. maintenance, Thymo or anti-IL2 mAb; Tac and MMF (FU:5y) (Woodle, Ann Surg, 2008)
- Subanalysis of those who were NON diabetic pretransplant
- Steroid withdrawal (CSWD) n=142; steroid continuation (CCS), n=135

This RCT demonstrates that CSWD has a limited impact in reducing NODAT when compared to low-dose prednisone (5 mg/day from month 6 to 5 years)

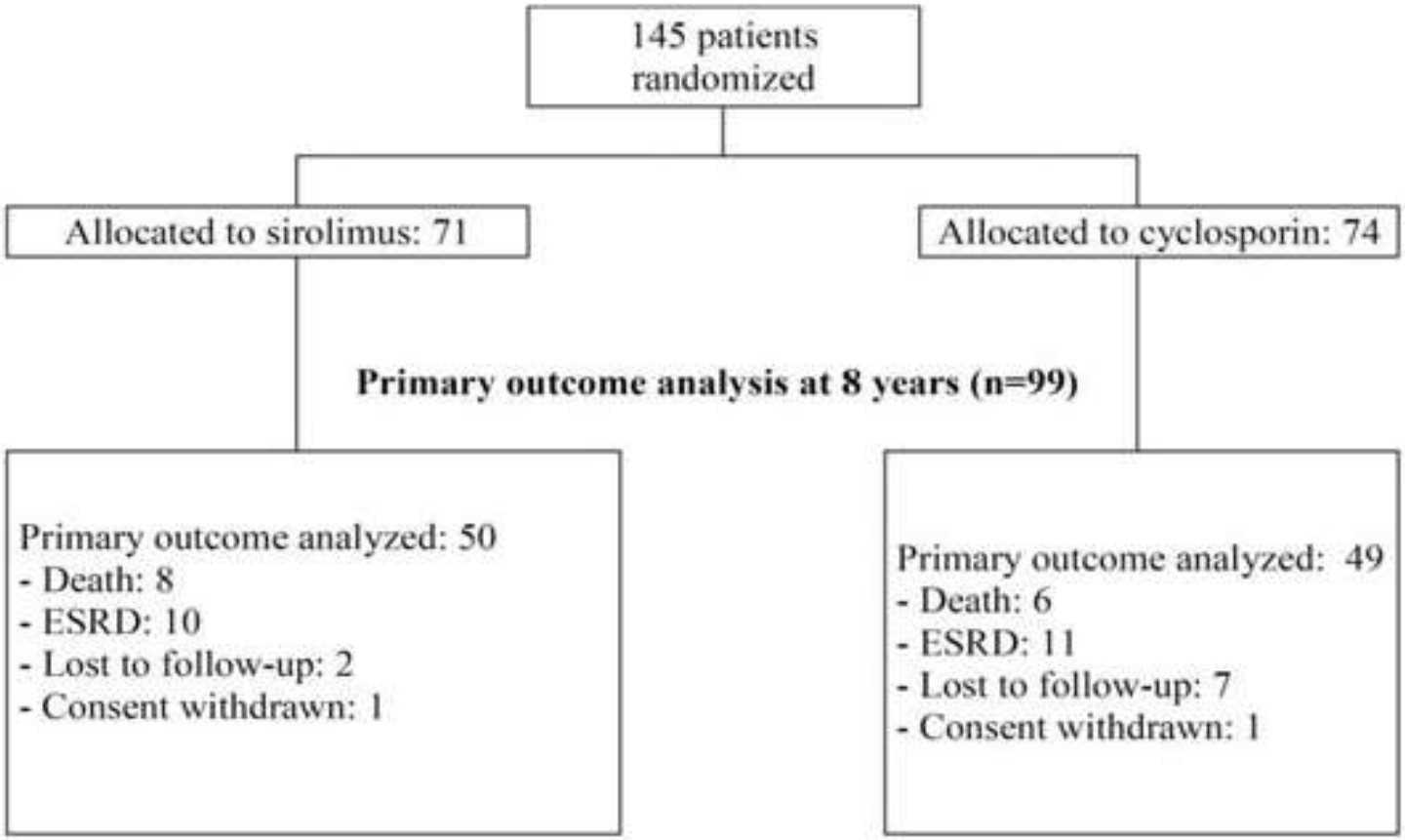
Life table probability of developing NODAT during follow-up by definition and treatment group. ADA, American Diabetes Association; CCS, chronic corticosteroids; CSWD, corticosteroid withdrawal; FBG, fasting blood glucose; NODAT, new-onset diabetes after transplantation.

Pirsch JD et al. AJT 2015;15:1982-1990

mTOR-inhibitors

- *Sirolimus*
- *Everolimus*

CONCEPT Study : Eight-year results (1)

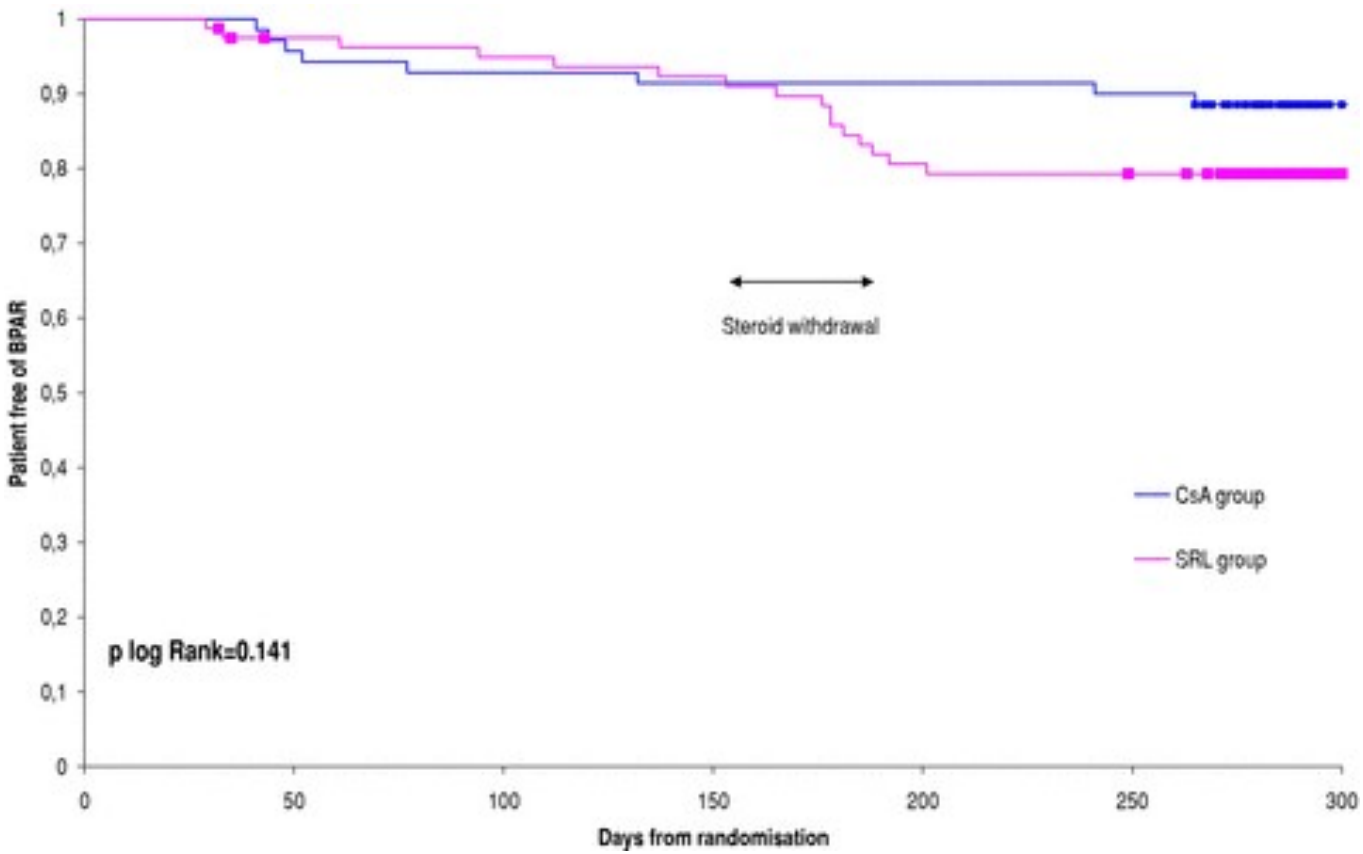


ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate

Gatault P et al. Transplant Int, 2015. Aug 18

Efficacy on renal function of early conversion from cyclosporine to sirolimus 3 months after renal transplantation : Concept Study

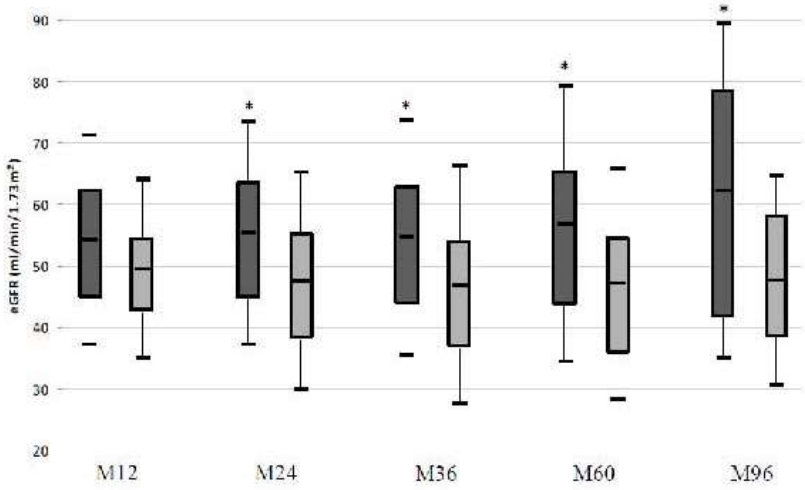
Kaplan–Meier analysis of biopsy-proven acute rejection-free after randomization (ITT population).



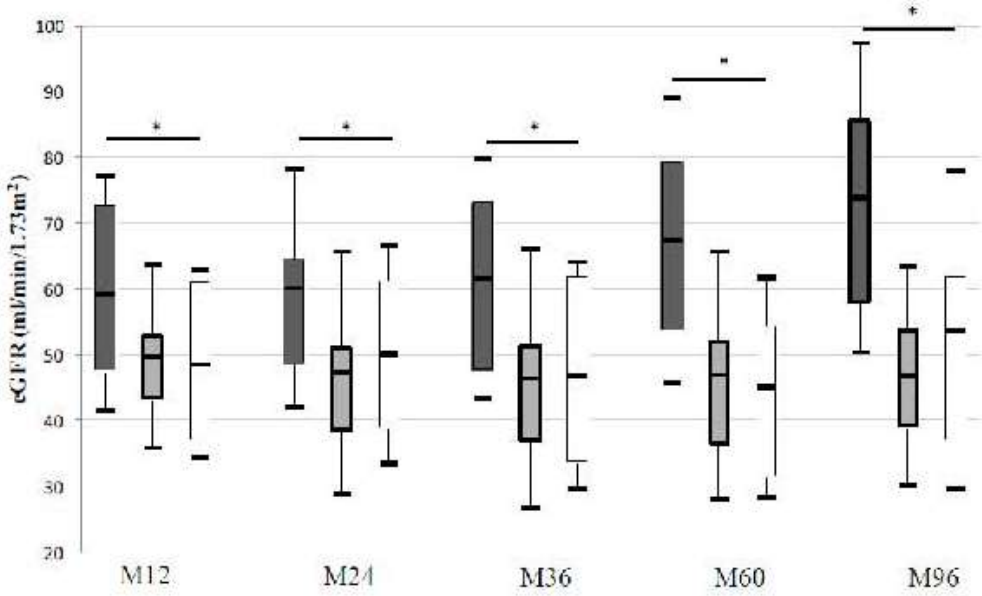
Lebranchu Y et al. AJT 2009;9:1115-1123

CONCEPT Study : Eight-year results (2)

ITT POPULATION



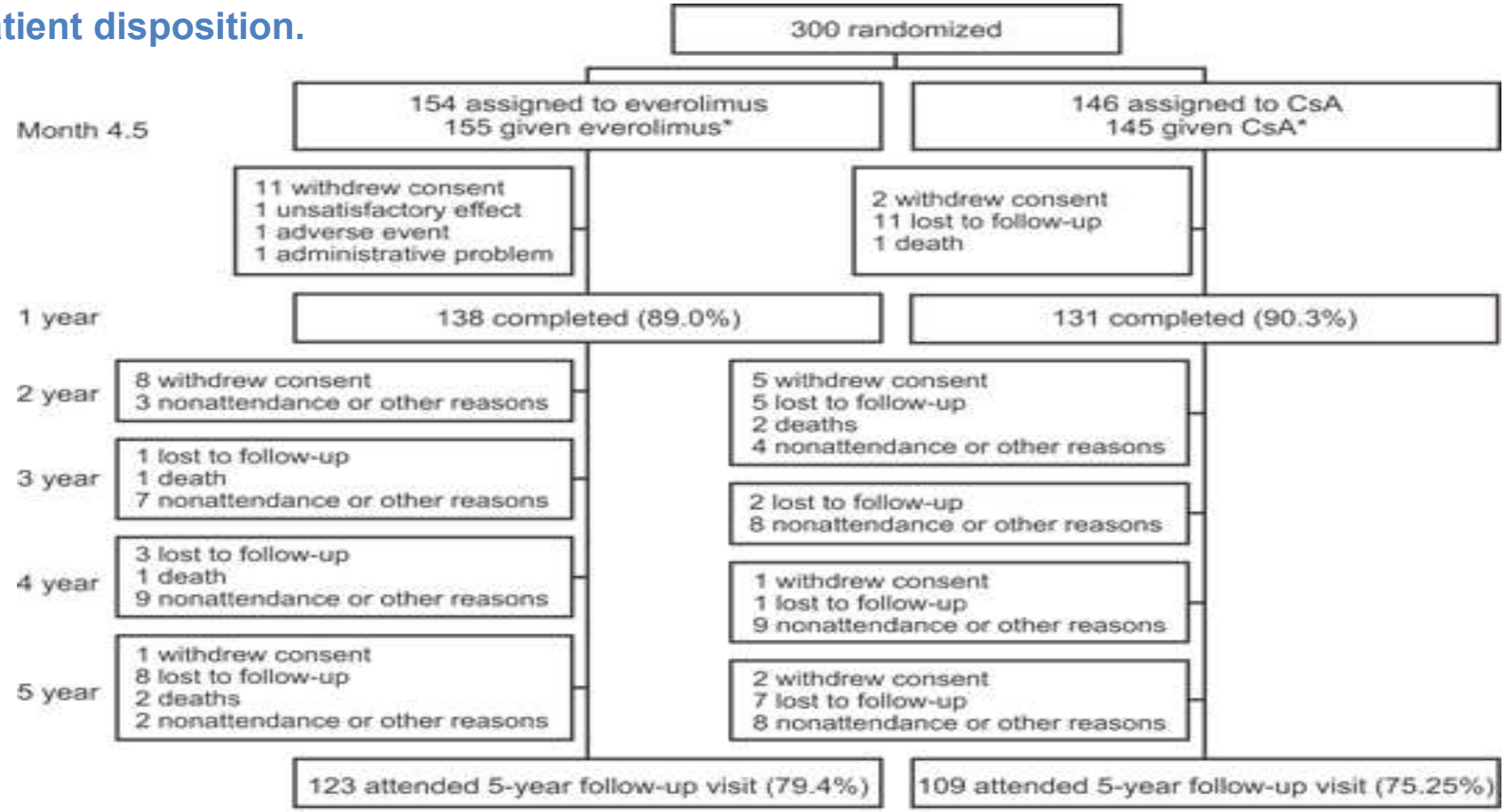
On treatment



Gatault P et al. Transplant Int, 2015. Aug 18

Five-year outcomes in kidney transplant patients converted from cyclosporine to everolimus : the randomized ZEUS study(1)

Patient disposition.



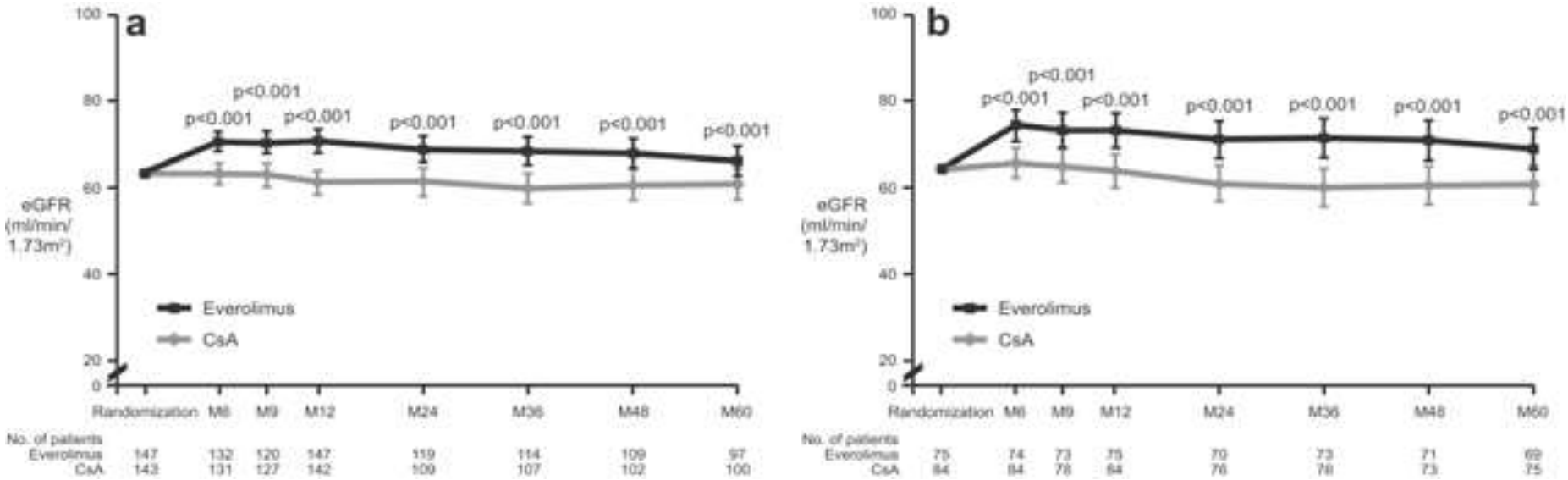
* 1 patient assigned to CsA was given everolimus in error

CsA, cyclosporine

Budde K et al. AJT 2015;15:119-128

Five-year outcomes in kidney transplant patients converted from cyclosporine to everolimus : the randomized ZEUS study(2)

Estimated GFR (Nankivell formula) from time of randomization (month 4.5) to 5 years posttransplant for (a) ITT population and (b) on-therapy population (defined as patients who remained on their randomized treatment).



Values shown are adjusted (least square) means from ANCOVA model (LOCF). Vertical bars indicate 95% confidence intervals. Values below graphs indicate the number of patients providing data at each time point, although the LOCF method was applied. CsA, cyclosporine; eGFR, estimated GFR; ITT, intent-to-treat; LOCF, last observation carried forward.

Budde K et al. AJT 2015;15:119-128

Five-year outcomes in kidney transplant patients converted from cyclosporine to everolimus : the randomized ZEUS study(3)

Efficacy events between randomization (month 4.5) and 5 years posttransplant (ITT population), n (%)

	Everolimus (n = 155)1	CsA (n = 145)1	p-Value2
Treatment failure3			
Months 4.5–12	29 (18.8)	23 (15.8)	0.543
Months 4.5–60	48 (31.2)	35 (24.0)	0.197
BPAR4			
Months 4.5–12	15 (9.7)	5 (3.4)	0.036
Months 4.5–60	21 (13.6)	11 (7.5)	0.095
Banff I	16 (11.0)	7 (4.8)	–
Banff II	4 (2.6)	2 (1.4)	–
Banff III	1 (0.6)	2 (1.4)	–
Acute rejection5			
Months 4.5–12	18 (11.7)	6 (4.1)	0.019
Months 4.5–60	24 (15.6)	11 (7.5)	0.032
Graft loss			
Months 4.5–12	0 (0.0)	0 (0.0)	–
Months 4.5–60	4 (2.6)	3 (2.1)	1.00
Death			
Months 4.5–12	0 (0.0)	1 (0.7)	–
Months 4.5–60	4 (2.6)	3 (2.1)	1.00

•BPAR, biopsy-proven acute rejection; CsA, cyclosporine.
•1One patient randomized to CsA was given everolimus due to a randomization error.
•2Fisher's exact test.
•3A composite end point of BPAR, graft loss, death, lost to follow-up, discontinuation due to lack of efficacy or toxicity, or conversion to another regimen.
•4On clinically indicated biopsies.
•5Clinically suspected acute rejection with or without biopsy confirmation.

Budde K et al. AJT 2015;15:119-128

Sirolimus and secondary skin cancer prevention in KT patients

- Multicenter, prospective controlled study in 120 maintenance KT patient on CNI-based immunosuppression having ≥ 1 cutaneous squamous cell carcinoma.
  - Randimization to
    - remain on CNI (n=56)
    - be converted to sirolimus (n=64)
  - Primary end-point : squamous cell carcinoma-survival free over 2 years.
- *Results at 2y:*
  - Recurrent SCC : 22% on SRL vs. 39% on CNI (median time to recurrence: 15 vs. 7 months); p=0.02. RR = 0.56 (0.32 – 0.98)
  - All *de novo* skin cancers : SRL : 47.6% vs. 70.5% (CNI); p=0.048
  - Graft function remained stable in both groups
  - **2y-results were maintained at 5y**

Euvrard S et al., NEJM 2012; 367:329-39
Dantal J et al. J Clin Oncol 2018; 36:2612-20

BELATACEPT

What is Belatacept ?

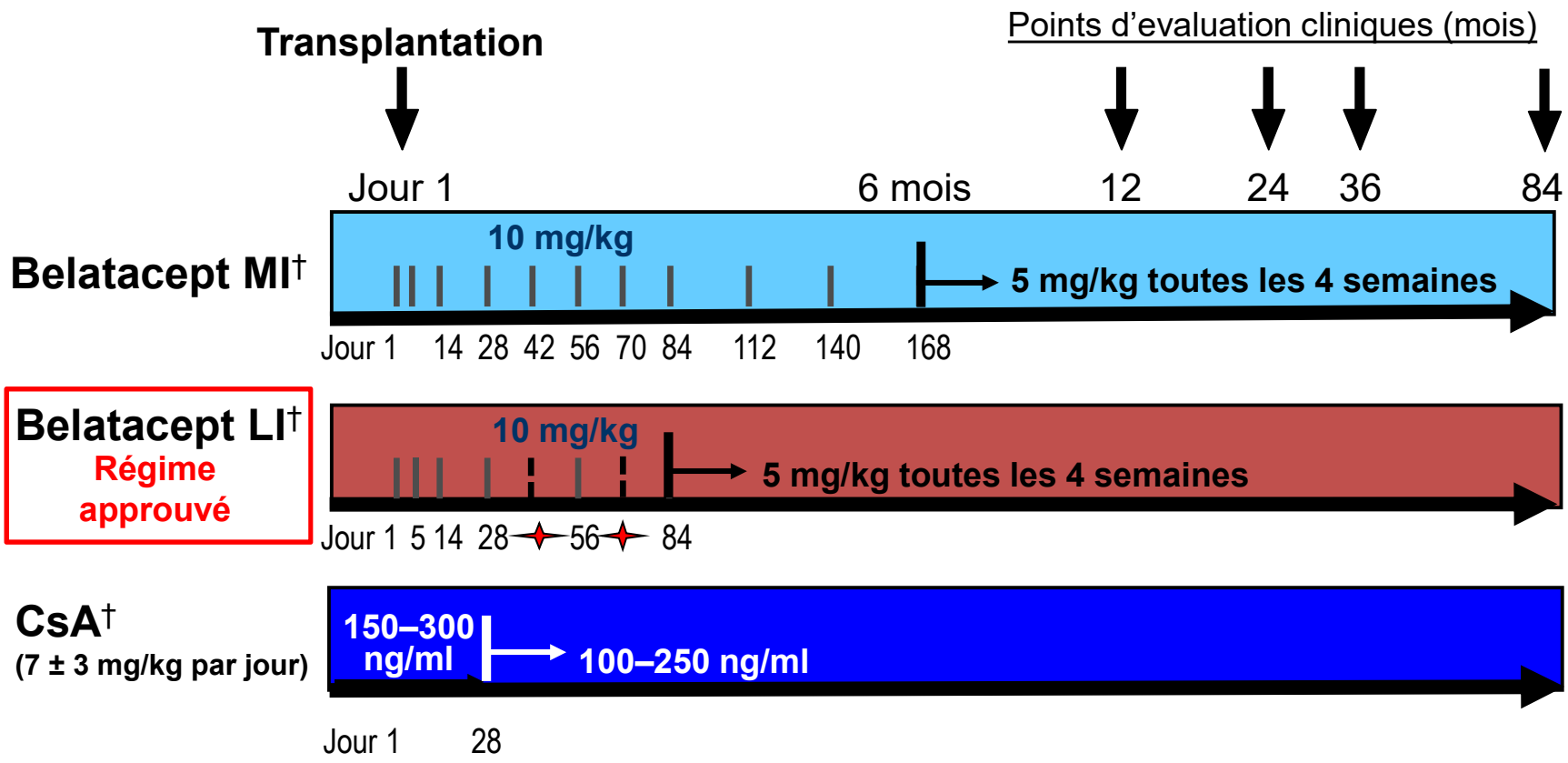
- Belatacept is a fusion protein that interferes T-cell activation
  - Due to its half life it is administered IV every month
- Belatacept is given at the PLACE of tacrolimus or ciclosporine, in addition to mycophenolic acid
  - It is a non nephrotoxic drug
  - It has neutral effet with regards to lipids and glycemia

Indications of Belatacept (conversion setting) :

CNI nephrotoxicity (biopsy-proven); metabolic syndrome

Conception des études BENEFITet posologie

Population étudie: patients ayant reçu un greffon rénal issu de donneur vivant ou décédé à critères standards (SCD: BENEFIT) ou à critères élargis (BENEFIT-EXT)



Perfusions de placebo

* belatacept en aveugle jusqu'à 12 mois.

†Tous les patients ont reçu basiliximab en induction, mycophénolate mofétil et des corticoides.

CsA = cyclosporine A ; LI = moins intensif ; MI = plus intensif ; SCD = donneur à critères standard.

BENEFIT Standard

Patients disposal

Median follow-up for each treatment was 84months

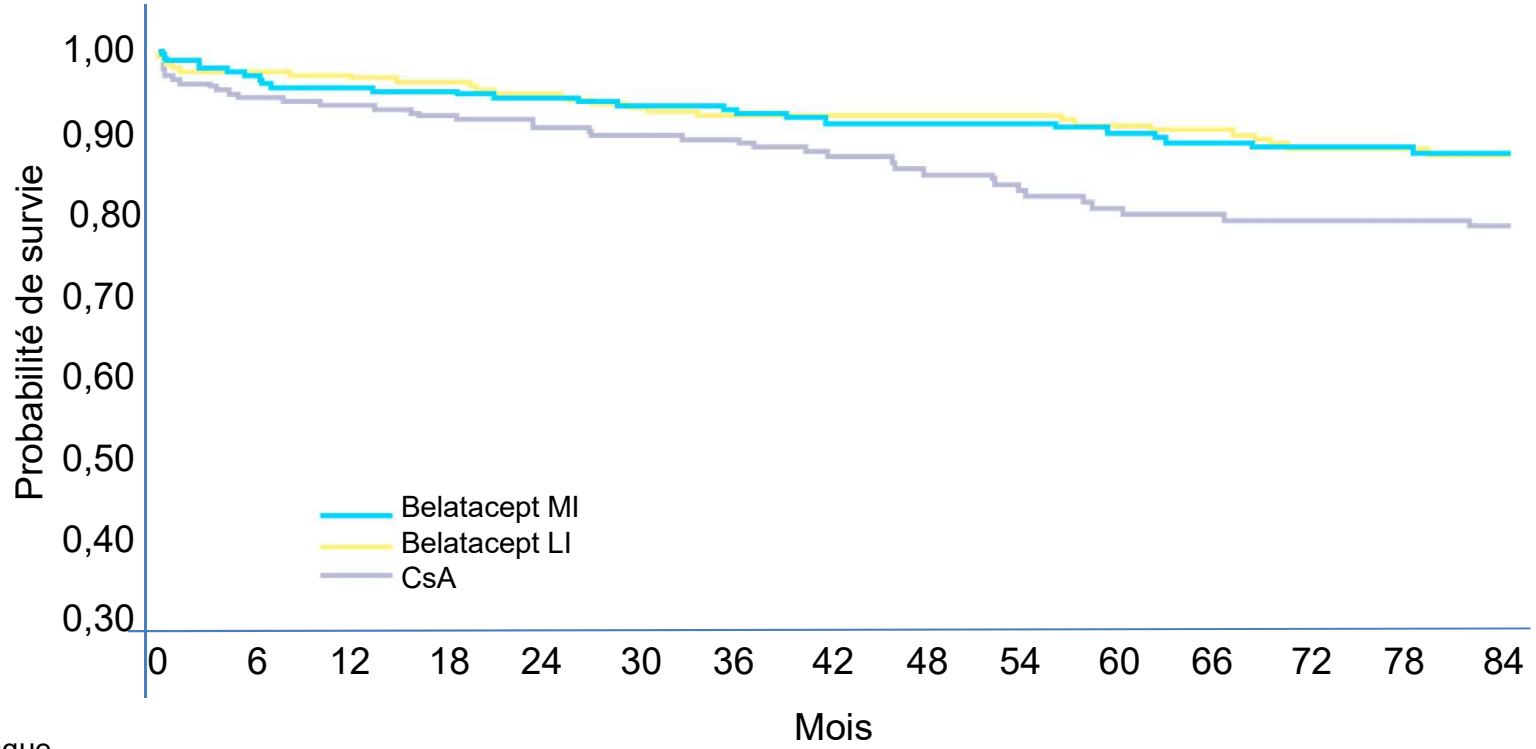
Screened, n = 738

Randomized, n = 666

Belatacept MI	Belatacept MI	CsA
Randomisés et transplantés, n = 219	Randomisés et transplantés, n = 226	Randomisés et transplantés, n = 221
Randomisés, transplantés et traités, n = 219	Randomisés, transplantés et traités, n = 226	Randomisés, transplantés et traités, n = 215
Interrompu, n = 91 Inadmissible pour entrée/refusé à LTE, n = 39 Retrait de consentement n = 14 Événement indésirable, n = 13 Décès, n = 13 Autre, n = 5 Perdus de vue n = 4 Grossesse, n = 2 Peu ou pas de conformité, n = 1 Manque d'efficacité n = 0 Raison administrative, n = 0	**Interrompu, n = 90** Inadmissible pour entrée/refusée à LTE, n = 34 Retrait de consentement n = 20 Événement indésirable, n = 11 Décès, n = 11 Perdus de vue n = 4 Autre, n = 4 Manque d'efficacité n = 3 Peu ou pas de conformité, n = 1 Grossesse, n = 1 Raison administrative, n = 1	**Interrompu, n = 123** Inadmissible pour entrée/refusé à LTE, n = 41 Décès, n = 23 Retrait de consentement n = 22 Événement indésirable, n = 12 Perdus de vue n = 8 Manque d'efficacité n = 6 Autre, n = 6 Peu ou pas de conformité, n = 4 Raison administrative, n = 1
84 mois accomplis, n = 128	**84 mois accomplis, n = 136**	**84 mois accomplis, n = 92**
Évaluable à 84 mois, n = 153	**Évaluable à 84 mois, n = 163**	**Évaluable à 84 mois, n = 131**

Les patients évaluables ont été suivis pendant plus de 84 mois ou ont décédé, ou ont perdu le greffon avant le 84e mois.

Patient and allograft survival from randomizationto 84th month

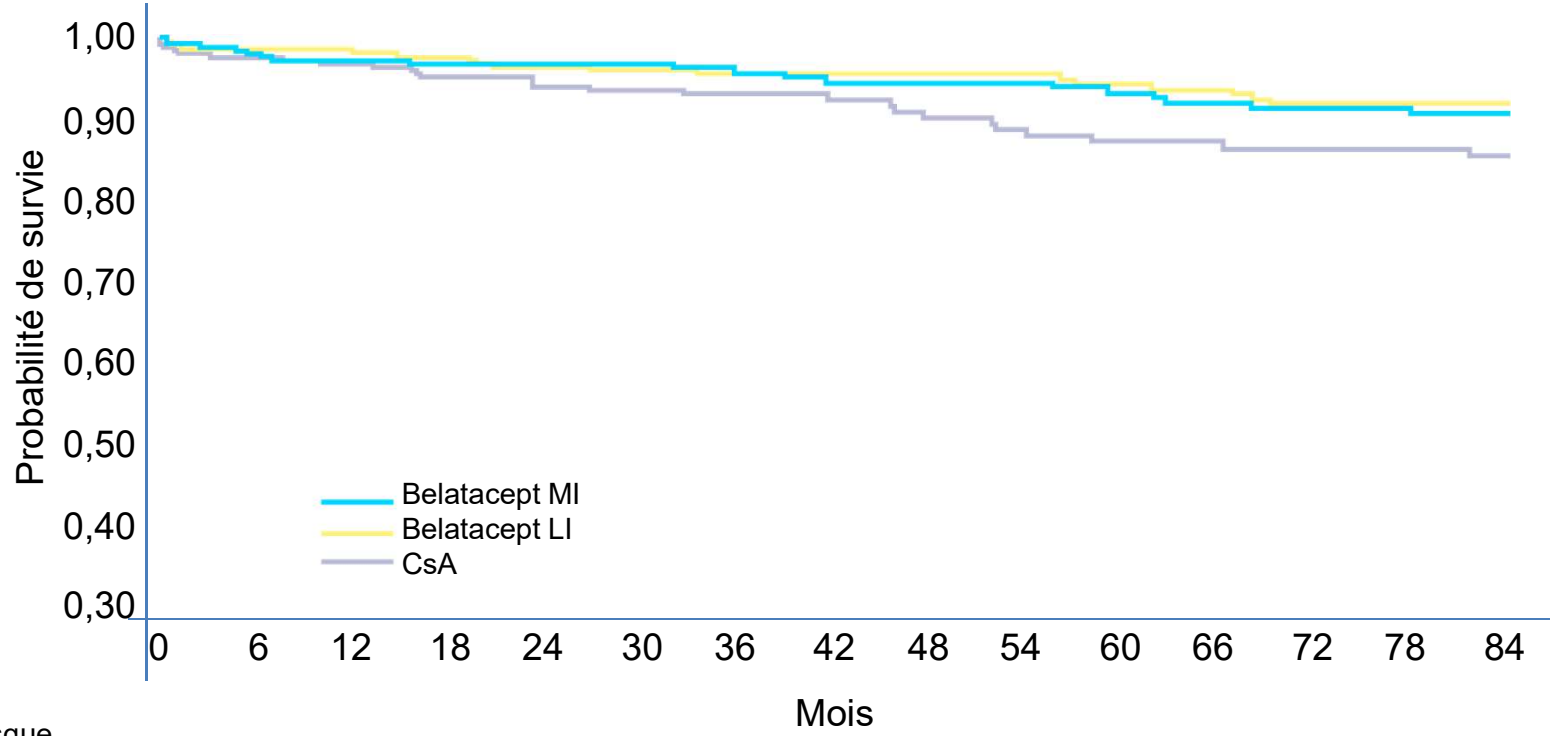


N à risque															
Belatacept MI	219	212	208	206	204	202	199	153	151	149	146	142	135	131	128
Belatacept LI	226	220	218	216	213	209	204	165	161	159	152	151	142	139	137
CsA	221	208	206	202	199	197	186	137	123	117	112	107	102	100	92

	Mois 60			Mois 84	
	Valeur P	HR (95 % IC)		Valeur P	HR (95 % IC)
Bela MI par rapport à CsA	0,0100	0,521 (0,306, 0,889)	Bela MI par rapport à CsA	0,0225	0,573 (0,348, 0,946)
Bela LI par rapport à CsA	0,0045	0,477 (0,277, 0,819)	Bela LI par rapport à CsA	0,0210	0,570 (0,348, 0,935)

Bela = belatacept ; IC = intervalle de confiance ; CsA =ciclosporine A ; HR = rapport de risque ; LI = moins intensif ; MI = plus intensif.

Patient survival from randomization to 84th month



N à risque

Belatacept MI	219	215	212	210	210	210	206	154	152	149	146	142	135	131	128
Belatacept LI	226	223	221	219	216	215	211	166	161	159	152	151	143	139	137
CsA	221	214	212	208	205	204	194	138	123	117	112	107	102	100	92

Mois 60

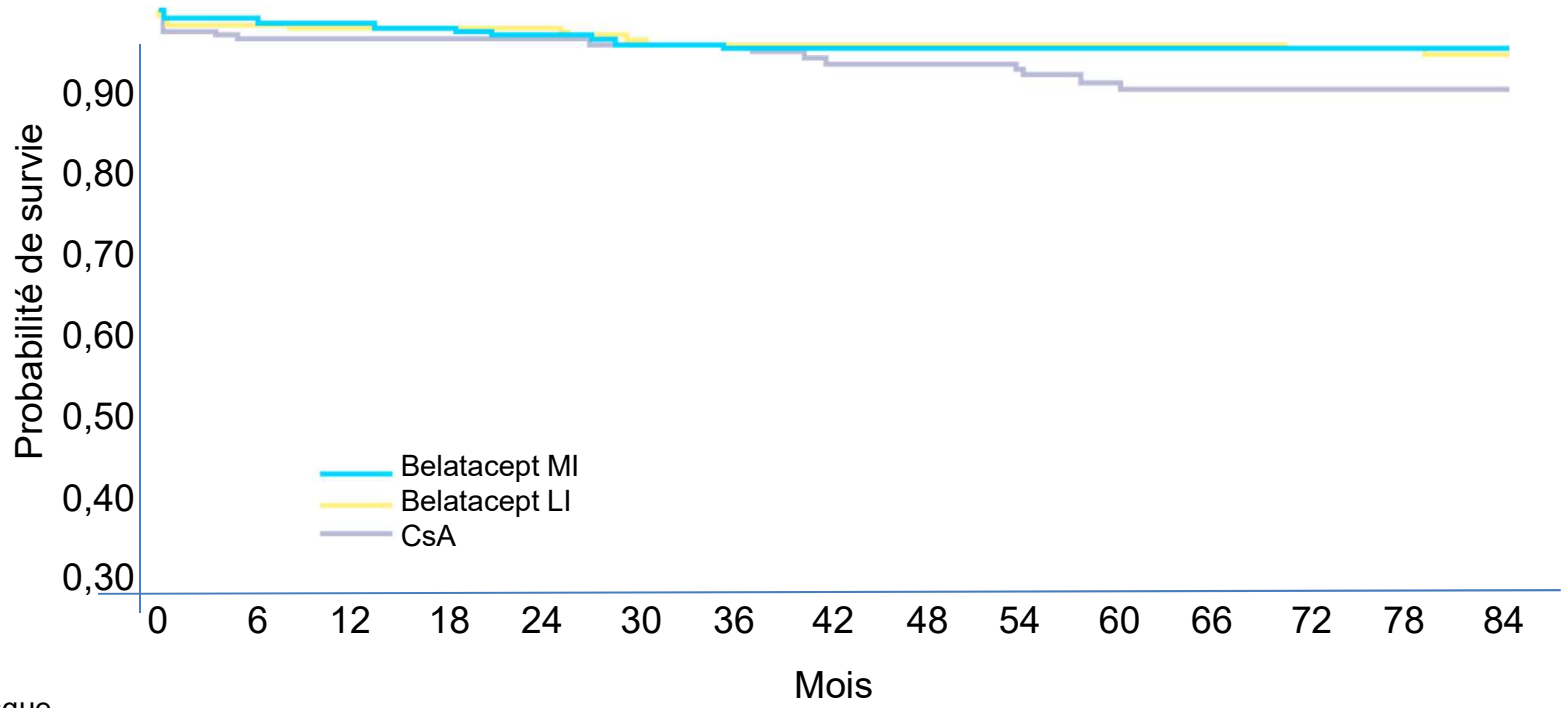
	Valeur P	HR (95 % IC)
Bela MI par rapport à CsA	0,0491	0,530 (0,268, 1,047)
Bela LI par rapport à CsA	0,0248	0,470 (0,234, 0,944)

Mois 84

	Valeur P	HR (95 % IC)
Bela MI par rapport à CsA	0,1076	0,616 (0,332, 1,141)
Bela LI par rapport à CsA	0,0574	0,554 (0,295, 1,038)

Bela = belatacept ; IC = intervalle de confiance ; CsA =ciclosporine A ; HR = rapport de risque ; LI = moins intensif ; MI = plus intensif.

Allograft survival from randomization to 84th month



N à risque

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
CsA	221	208	206	202	199	197	186	137	123	117	112	107	102	100	92

Mois 60

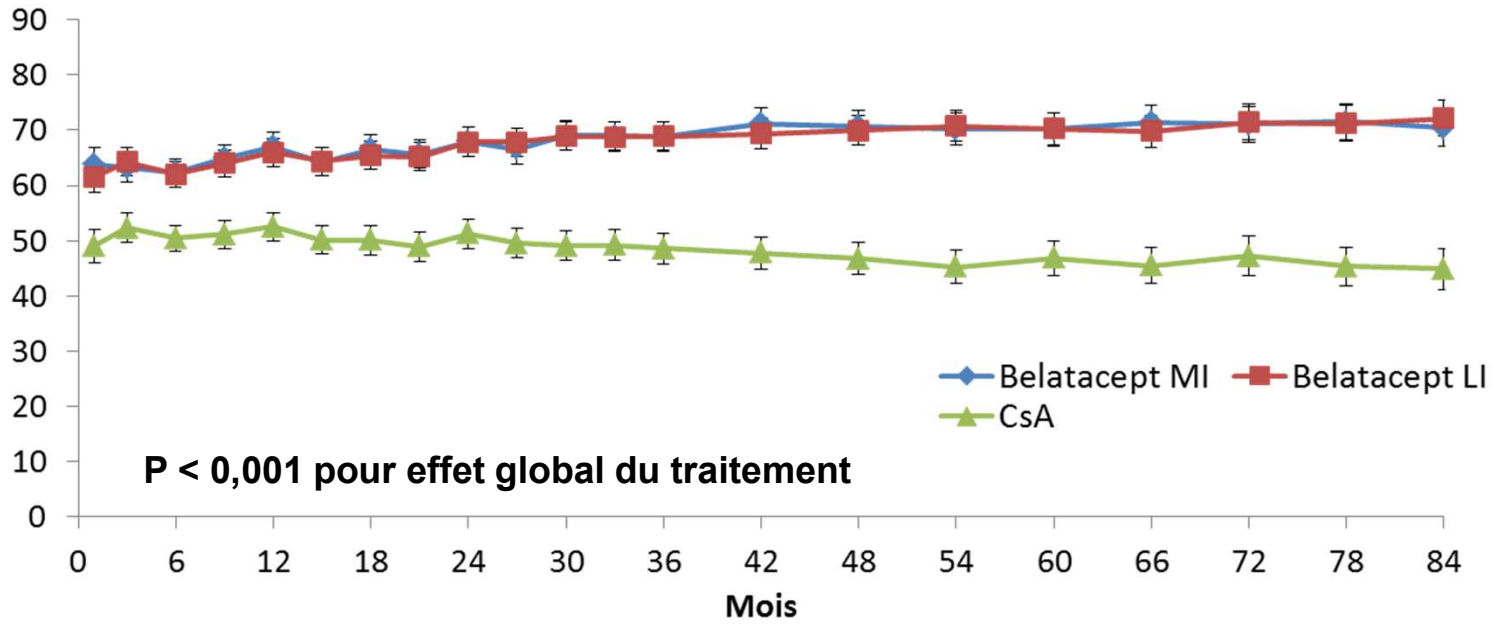
	Valeur P	HR (95 % IC)
Bela MI par rapport à CsA	0,1204	0,562 (0,257, 1,228)
Bela LI par rapport à CsA	0,0659	0,487 (0,217, 1,093)

Mois 84

	Valeur P	HR (95 % IC)
Bela MI par rapport à CsA	0,1215	0,555 (0,254, 1,213)
Bela LI par rapport à CsA	0,1505	0,587 (0,275, 1,254)

Bela = belatacept ; IC = intervalle de confiance ; CsA =cyclosporine A ; HR = rapport de risque ; LI = moins intensif ; MI = plus intensif.

eDFG over 84 months : Mixed model effect with imputation

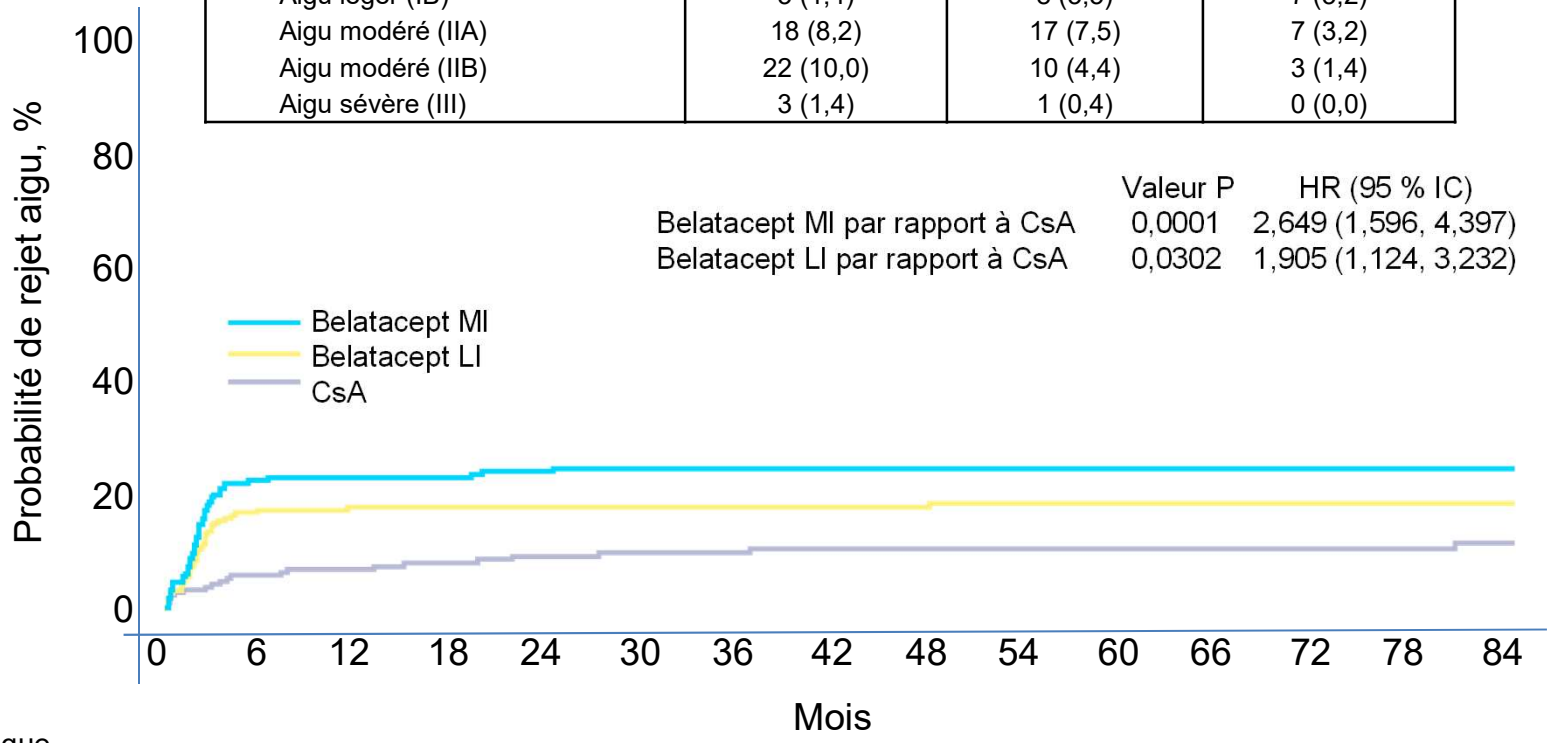


	Belatacept MI		Belatacept LI		CsA
	DFG	Différence par rapport à CsA	DFG	Différence par rapport à CsA	DFG
Mois 12	67,0	14,5	66,0	13,5	52,5
Mois 36	68,9	20,3	68,9	20,4	48,6
Mois 60	70,2	23,3	70,3	23,4	46,8
Mois 84	70,4	25,6	72,1	27,3	44,9

CsA = cyclosporine A ; DFG = débit de filtration glomérulaire ; LI = moins intensif ; MI = plus intensif. * valeurs moyennes

Acute rejection rate

	Belatacept MI (N = 219)	Belatacept LI (N = 226)	CsA (N = 221)
Degré Banff de rejet aigu*, n			
Aigu léger (IA)	7 (3,2)	4 (1,8)	6 (2,7)
Aigu léger (IB)	3 (1,4)	8 (3,5)	7 (3,2)
Aigu modéré (IIA)	18 (8,2)	17 (7,5)	7 (3,2)
Aigu modéré (IIB)	22 (10,0)	10 (4,4)	3 (1,4)
Aigu sévère (III)	3 (1,4)	1 (0,4)	0 (0,0)



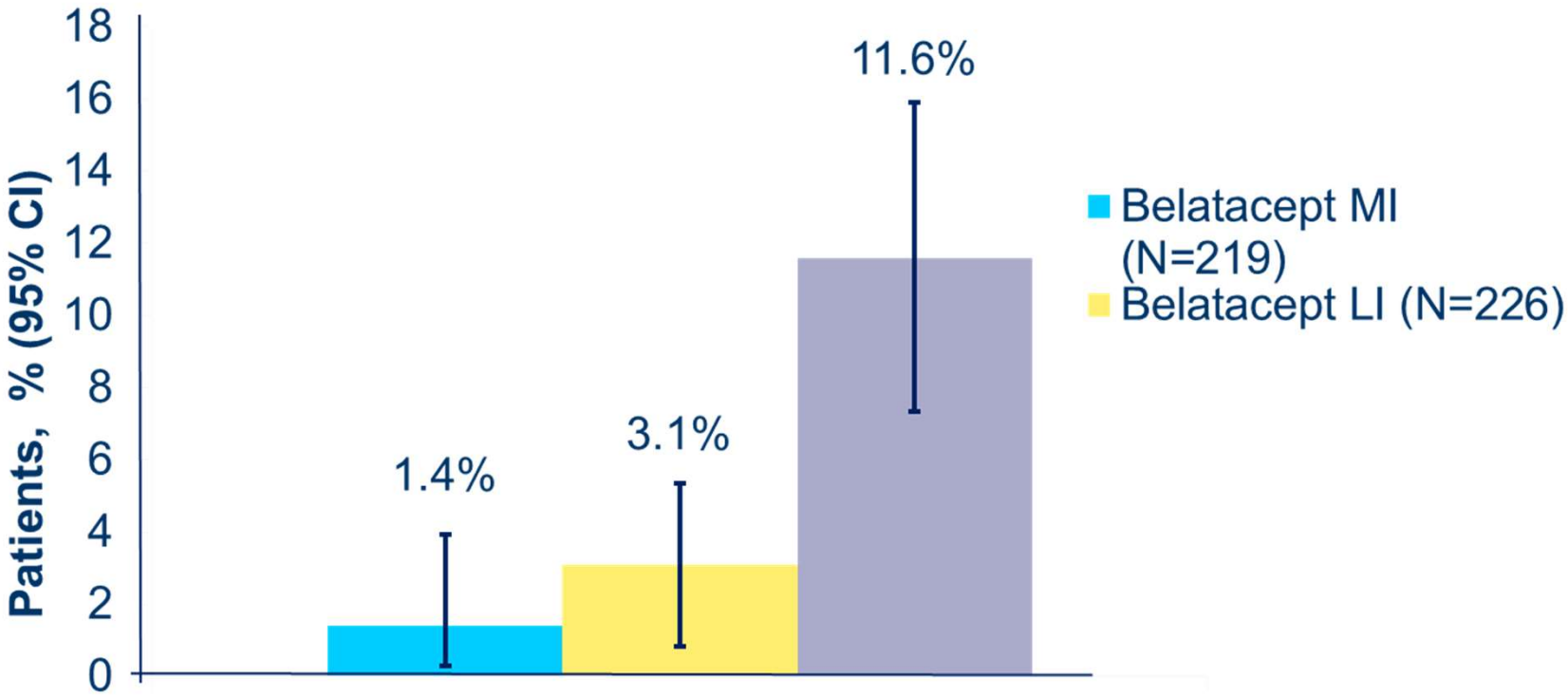
	Valeur P	HR (95 % IC)
Belatacept MI par rapport à CsA	0,0001	2,649 (1,596, 4,397)
Belatacept LI par rapport à CsA	0,0302	1,905 (1,124, 3,232)

N à risque

Belatacept MI	219	154	147	144	140	137	136	128	127	125	122	117	111	108	105
Belatacept LI	226	168	164	162	160	157	155	149	144	142	137	135	130	125	122
CsA	221	180	167	156	147	141	135	123	115	110	106	101	96	94	89

IC = Intervalle de confiance ; CsA = ciclosporine A ; HR = rapport de risque ; LI = moins intensif ; MI = plus intensif.

Incidence of *de novo* DSAs



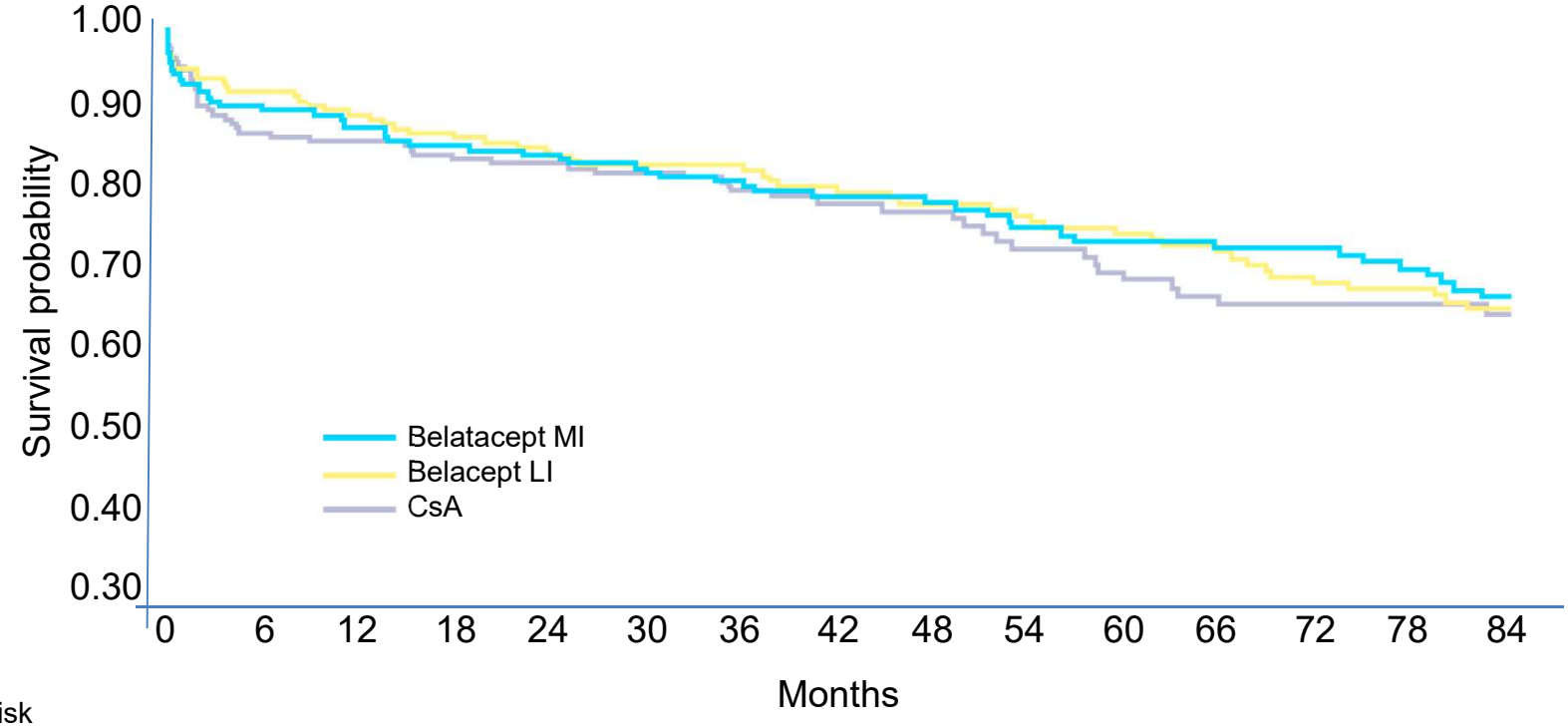
DSA Specificity	Bela MI	Bela LI	CsA
Total, n	3	7	25
Class I, n	1	3	7
Class II, n	2	4	14
Class I and II, n	0	0	4

95% CI
Belatacept MI: 0.28–3.95
Belatacept LI: 0.84–5.36
CsA: 7.34–15.91

CI=confidence interval; CsA=cyclosporine A; DSA=donor-specific antibody; LI=less intensive; MI=more intensive.

BENEFIT-EXT

Time to Death or Graft Loss From Randomization to Month 84



N at risk

Belatacept MI	184	166	161	157	154	151	146	107	100	95	91	89	85	81	75
Belatacept LI	175	161	156	152	147	144	143	113	108	105	100	95	89	88	84
CsA	184	160	158	152	150	148	140	90	84	77	72	62	60	60	56

Month 60

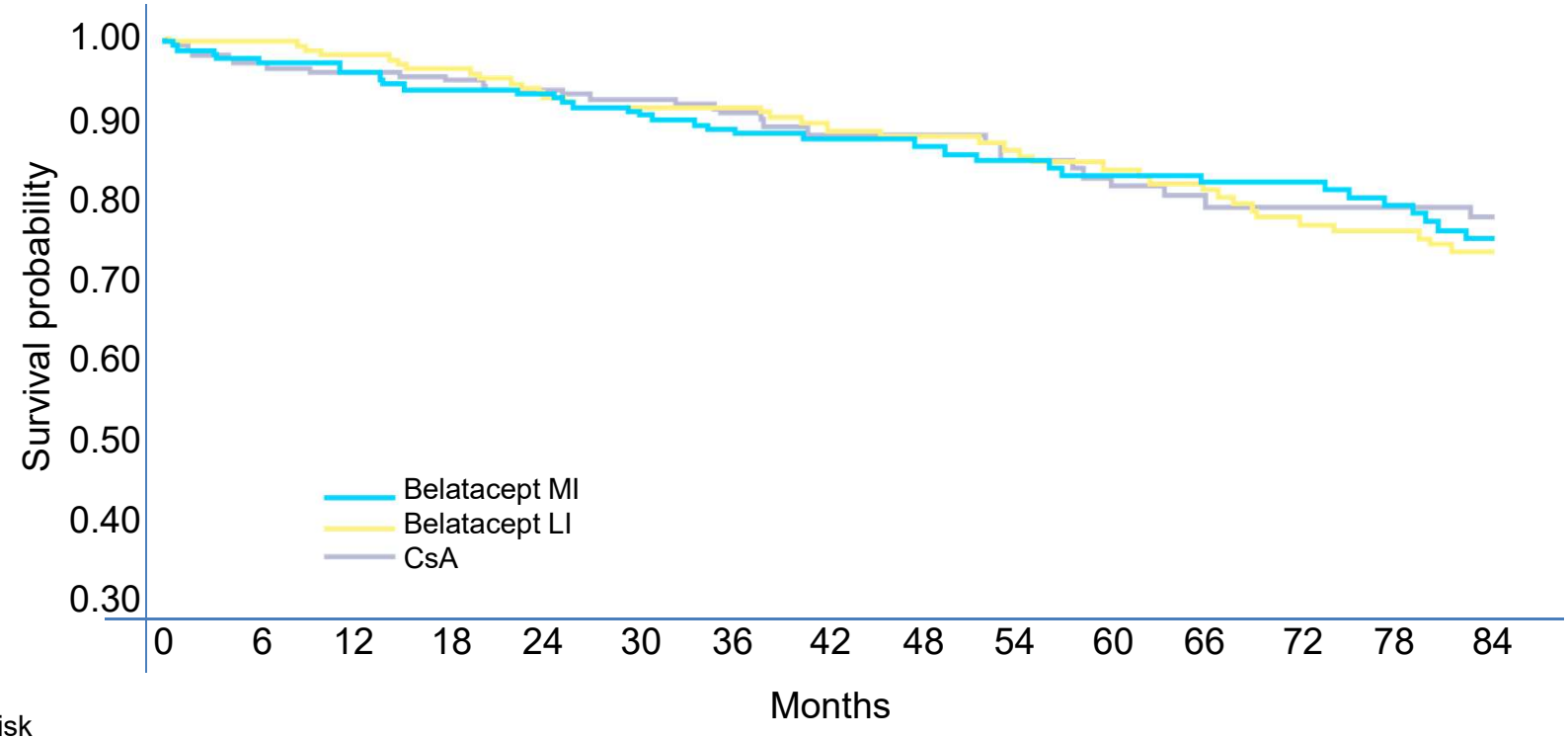
	P-value	HR (95% CI)
Bela MI vs. CsA	0.5107	0.874 (0.583, 1.310)
Bela LI vs. CsA	0.3500	0.822 (0.544, 1.242)

Month 84

	P-value	HR (95% CI)
Bela MI vs. CsA	0.6495	0.915 (0.625, 1.339)
Bela LI vs. CsA	0.6997	0.927 (0.634, 1.356)

Bela=belatacept; CI=confidence interval; CsA=cyclosporine A; HR=hazard ratio; LI=less intensive; MI=more intensive.

Time to Death From Randomization to Month 84



N at risk

Belatacept MI	184	179	176	172	170	166	160	108	101	95	91	89	85	81	75
Belatacept LI	175	172	169	166	160	157	155	115	108	105	100	95	89	88	84
CsA	184	176	174	169	166	162	155	93	87	79	73	63	61	61	57

Month 60

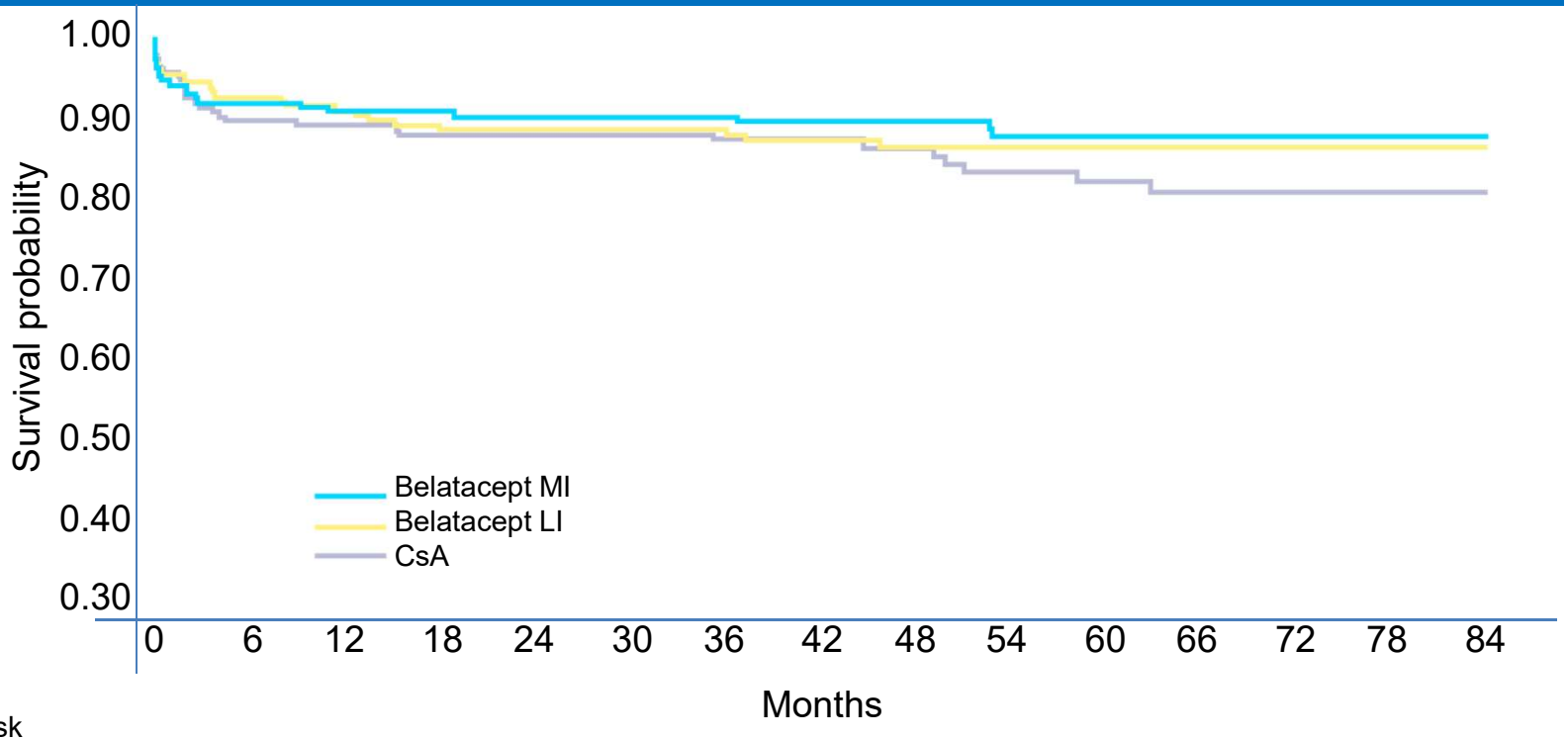
	P-value	HR (95% CI)
Bela MI vs. CsA	0.9532	1.014 (0.594, 1.729)
Bela LI vs. CsA	0.7263	0.907 (0.523, 1.571)

Month 84

	P-value	HR (95% CI)
Bela MI vs. CsA	0.6917	1.108 (0.679, 1.808)
Bela LI vs. CsA	0.6580	1.119 (0.688, 1.822)

Bela=belatacept; CI=confidence interval; CsA=cyclosporine A; HR=hazard ratio; LI=less intensive; MI=more intensive.

Time to Death-Censored Graft Loss From Randomization to Month 84



N at risk

	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Belatacept MI	184	166	161	157	154	151	146	107	100	95	91	89	85	81	75
Belatacept LI	175	161	156	152	147	144	143	113	108	105	100	95	89	88	84
CsA	184	160	158	152	150	148	140	90	84	77	72	62	60	60	56

Month 60

	P-value	HR (95% CI)
Bela MI vs. CsA	0.2650	0.728 (0.413, 1.282)
Bela LI vs. CsA	0.4515	0.815 (0.469, 1.415)

Month 84

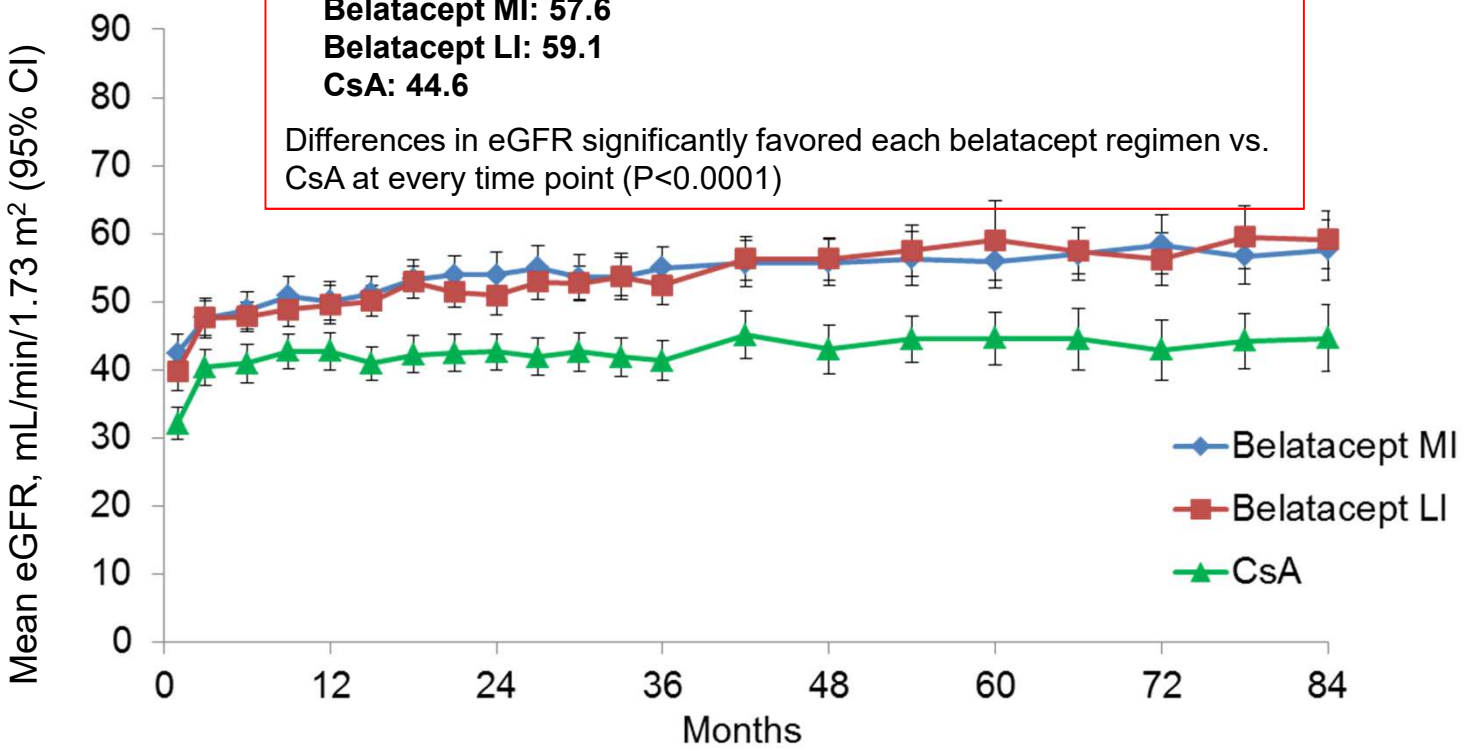
	P-value	HR (95% CI)
Bela MI vs. CsA	0.2058	0.700 (0.399, 1.228)
Bela LI vs. CsA	0.3626	0.783 (0.452, 1.353)

Bela=belatacept; CI=confidence interval; CsA=cyclosporine A; HR=hazard ratio; LI=less intensive; MI=more intensive.

eGFR Over 84 Months*: Without Imputation (ANOVA)

Mean eGFR (mL/min/1.73 m²) at month 84:
Belatacept MI: 57.6
Belatacept LI: 59.1
CsA: 44.6

Differences in eGFR significantly favored each belatacept regimen vs. CsA at every time point (P<0.0001)

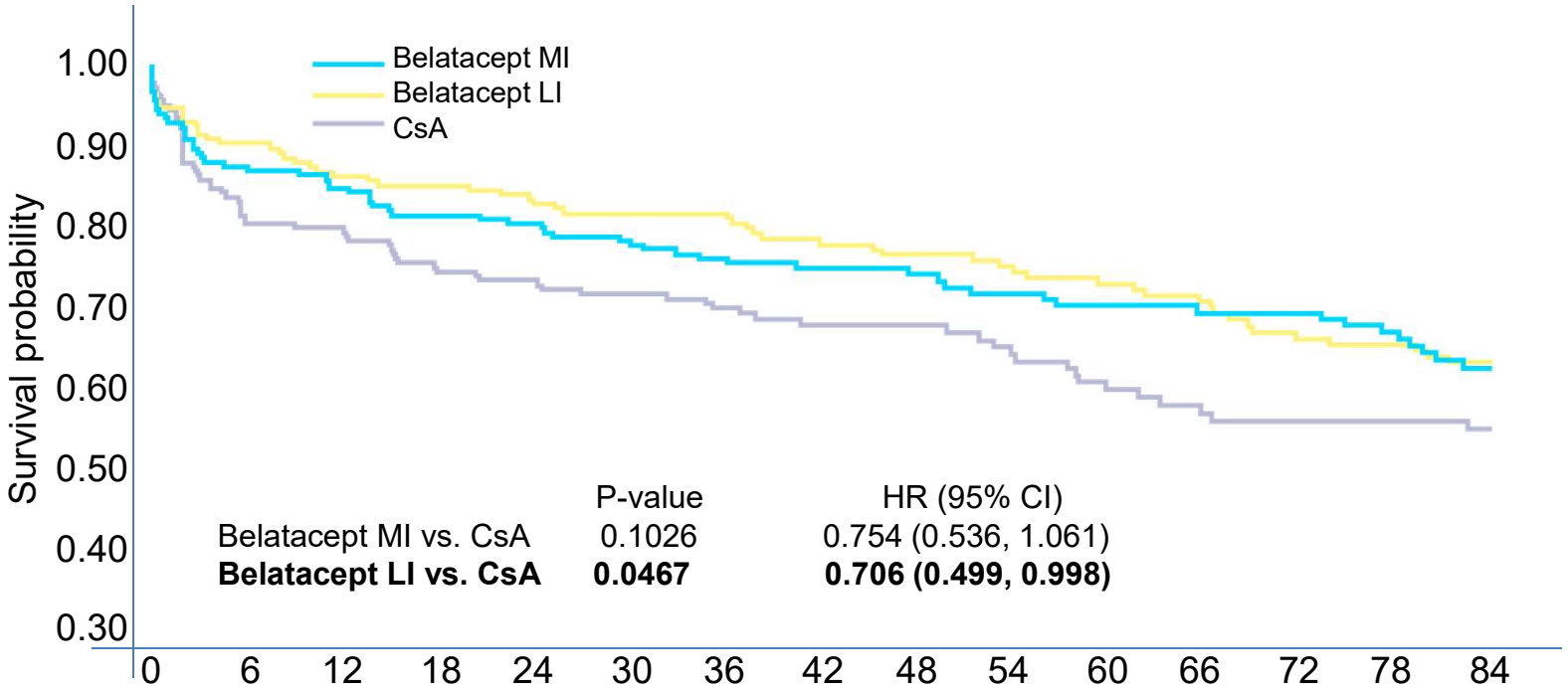


Belatacept MI	**176**	**146**	**125**	**118**	**91**	**84**	**76**	**69**
Belatacept LI	**172**	**142**	**133**	**124**	**97**	**96**	**81**	**79**
CsA	**182**	**136**	**126**	**109**	**76**	**70**	**54**	**51**

*eGFR values were as observed.

ANOVA=analysis of variance; CI=confidence interval; CsA=cyclosporine A; eGFR=estimated glomerular filtration rate; LI=less intensive; MI=more intensive.

First Occurrence of Death, Graft Loss, or eGFR <20 mL/min/1.73 m²



N at risk

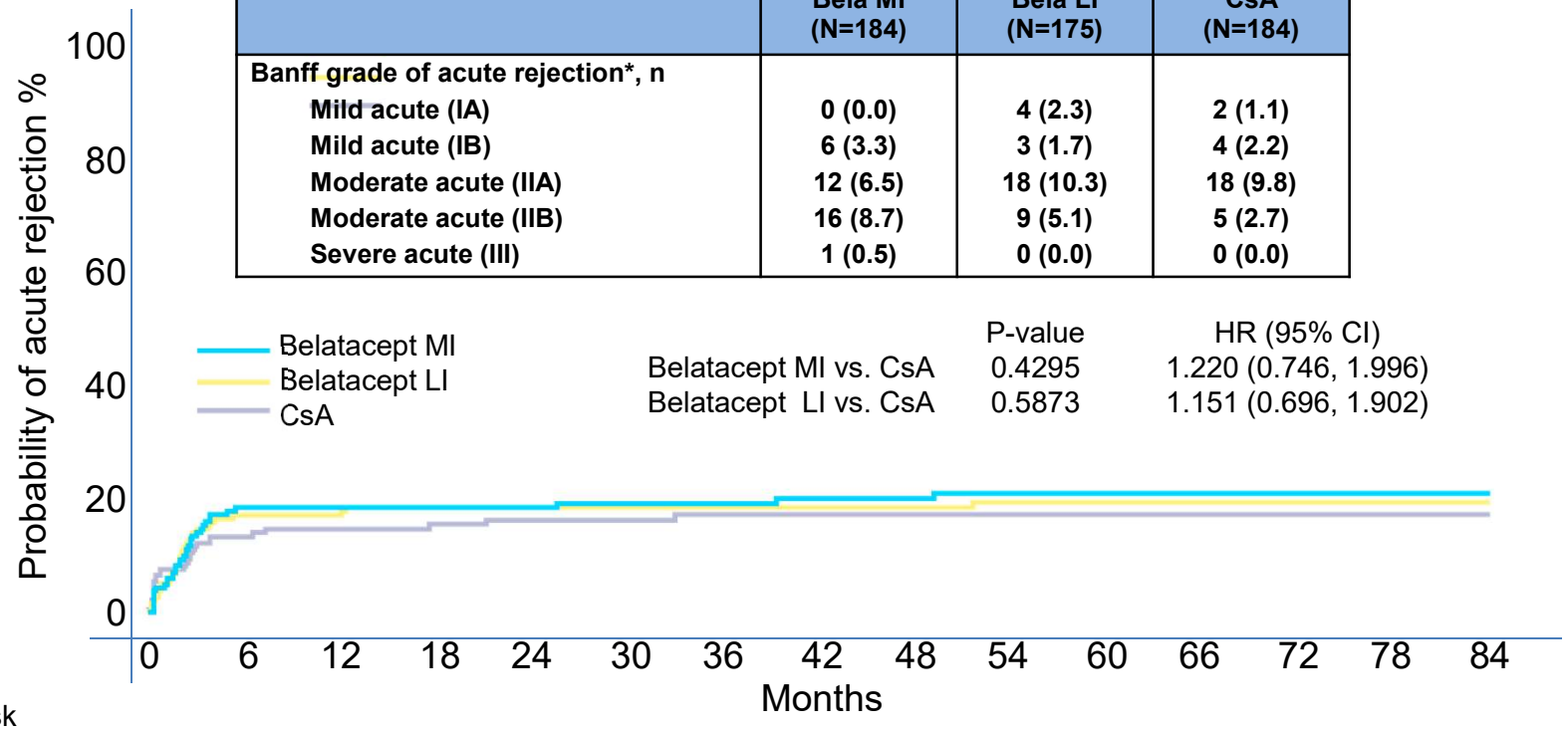
	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Belatacept MI	184	161	156	150	148	144	138	102	97	93	89	87	83	79	72
Belatacept LI	175	158	151	149	145	142	141	113	108	105	100	95	88	87	83
CsA	184	148	147	135	132	129	123	82	78	73	68	58	56	56	52

eGFR measurements on or after day 57 were included in the analysis.
If a subject had at least two eGFR measurements <20 mL/min/1.73 m² and these were at least 30 days apart, then the first event was counted; otherwise, if the last measurement before database lock was <20 mL/min/1.73 m², then this value was counted.

Bela=belatacept; CI=confidence interval; CsA=cyclosporine A; eGFR=estimated glomerular filtration rate; HR=hazard ratio; LI=less intensive; MI=more intensive.

Acute Rejection Up to Month 84

	Bela MI (N=184)	Bela LI (N=175)	CsA (N=184)
Banff grade of acute rejection*, n			
Mild acute (IA)	**0 (0.0)**	**4 (2.3)**	**2 (1.1)**
Mild acute (IB)	**6 (3.3)**	**3 (1.7)**	**4 (2.2)**
Moderate acute (IIA)	**12 (6.5)**	**18 (10.3)**	**18 (9.8)**
Moderate acute (IIB)	**16 (8.7)**	**9 (5.1)**	**5 (2.7)**
Severe acute (III)	**1 (0.5)**	**0 (0.0)**	**0 (0.0)**



	P-value	HR (95% CI)
Belatacept MI vs. CsA	0.4295	1.220 (0.746, 1.996)
Belatacept LI vs. CsA	0.5873	1.151 (0.696, 1.902)

N at risk

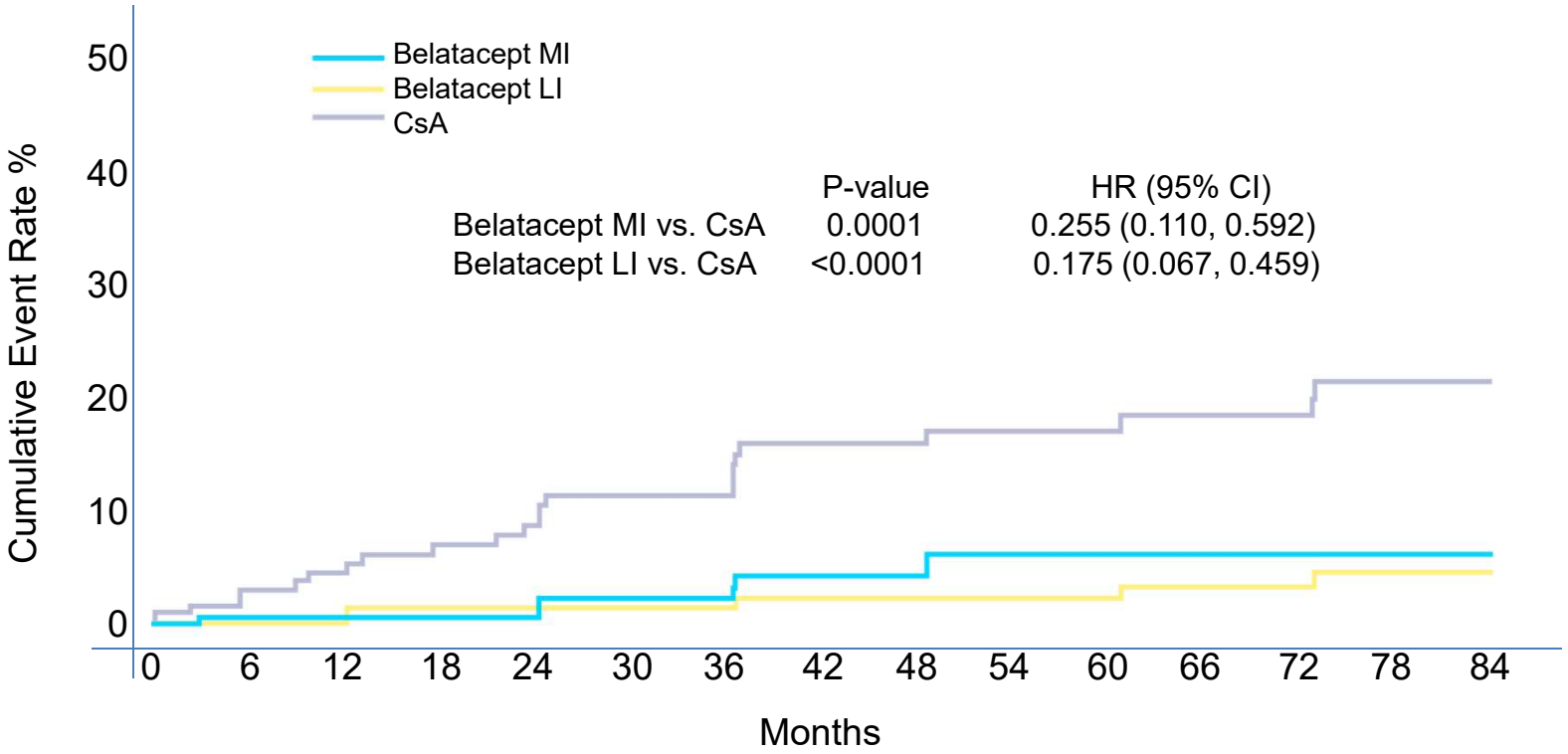
Belatacept MI	184	128	121	109	107	102	99	90	88	85	83	80	76	71	67
Belatacept LI	175	126	115	109	105	103	101	97	95	90	86	84	77	76	75
CsA	184	136	116	107	101	97	88	73	72	69	61	55	55	54	50

For patients with an event, the time to event was defined as minimum of event date and date of last dose (transplant date for non-treated patients) plus 56 days. For patients without an event, the time to event was defined as last follow-up date for on-treatment patients, date of last dose plus 56 days for off-treatment patients, and transplant date plus 56 days for non-treated patients. Between month 36 and month 84, 2 (grade IIA) belatacept MI-treated, 1 (grade IB) belatacept LI-treated, and 0 CsA-treated patients experienced acute rejection.

*Two patients (n=2 [grade IIA], belatacept LI) experienced acute rejection more than 56 days after treatment discontinuation.

Bela=belatacept; CI= confidence interval; CsA=cyclosporine A; HR=hazard ratio; LI=less intensive; MI=more intensive.

Kaplan-Meier Analysis of Cumulative De Novo DSA Over Time



	P-value	HR (95% CI)
Belatacept MI vs. CsA	0.0001	0.255 (0.110, 0.592)
Belatacept LI vs. CsA	<0.0001	0.175 (0.067, 0.459)

N at risk

Belatacept MI	183	147	135	119	116	110	107	95	93	88	86	83	80	75	71
Belatacept LI	174	144	132	123	118	116	113	107	105	101	98	94	88	86	82
CsA	179	144	122	112	106	100	95	77	75	70	63	56	56	54	50

CI=confidence interval; CsA=cyclosporine A; DSA=donor-specific antibody; HR=hazard ratio; LI=less intensive; MI=more intensive.

CONCLUSION

- To preserve long-term renal function
- To minimize cardiovascular risk
- To decrease the risk of *de novo* cancers
- m-TOR inhibitors are valuable specially when associated with low CNI doses
- Finally belatacept-based immunosuppression is associated with a very low rate of *de novo* DSA.

Thank you for your attention