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CV risk and immunosuppressive therapy in Transplantation

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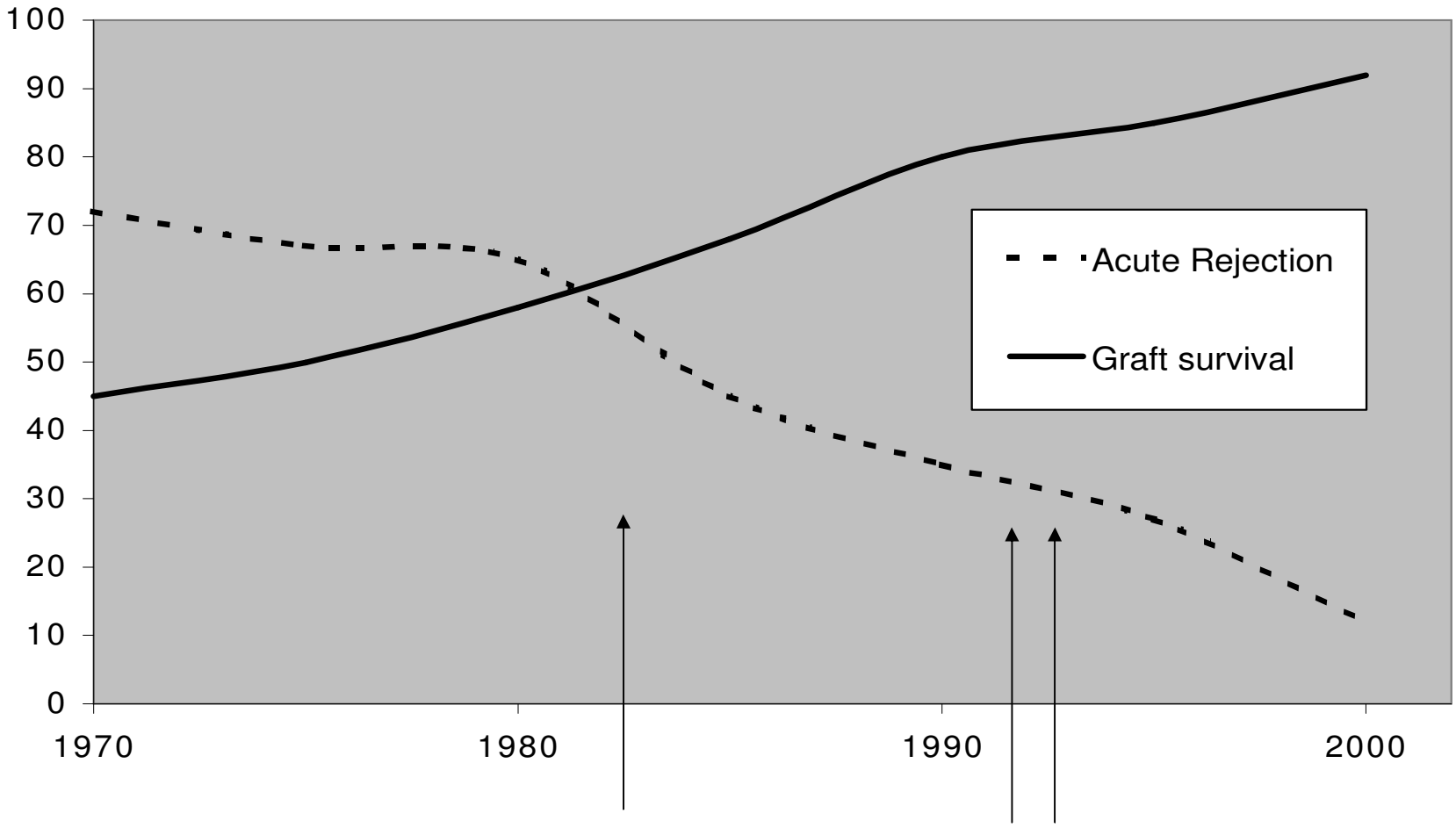
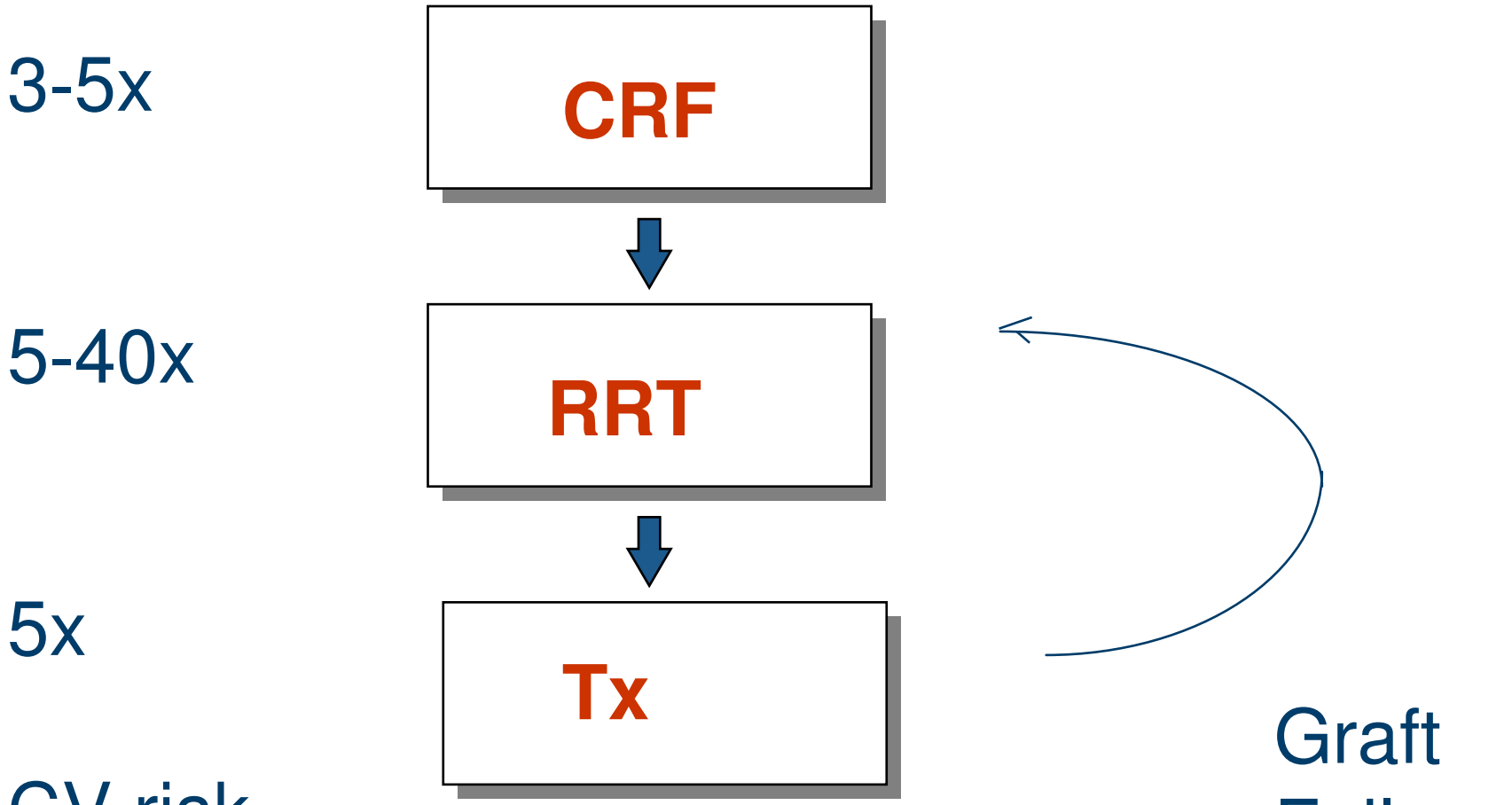
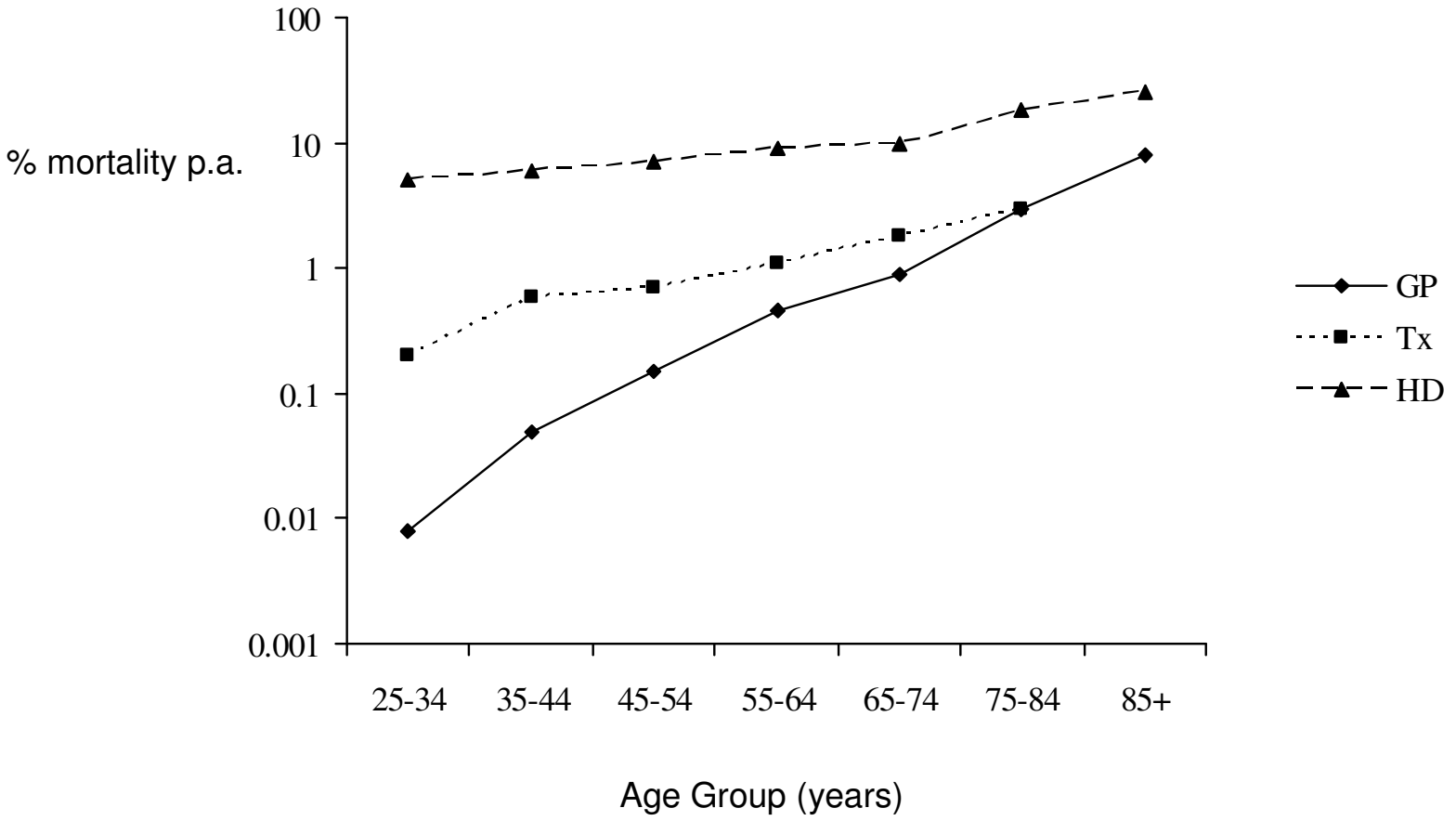
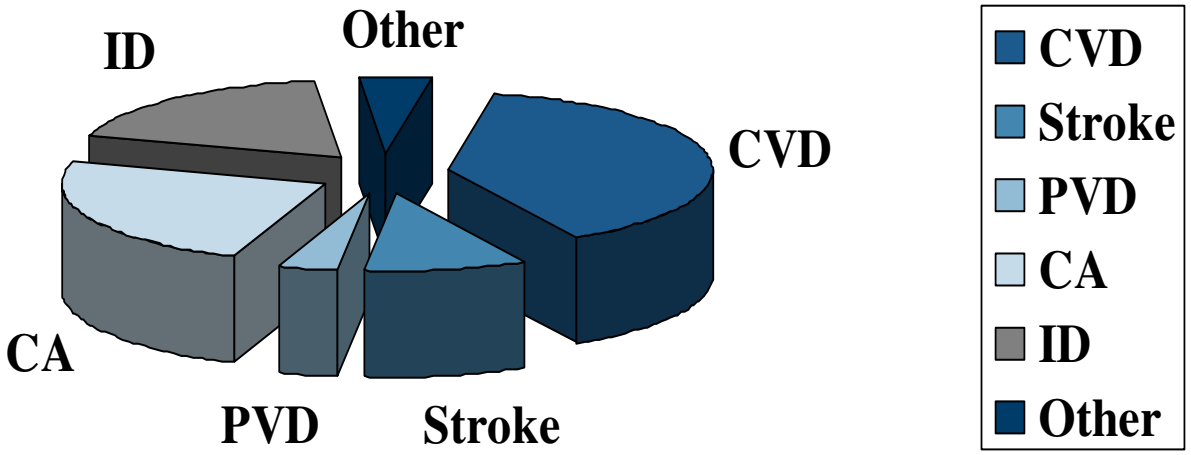


Renal Disease and CV risk (1)

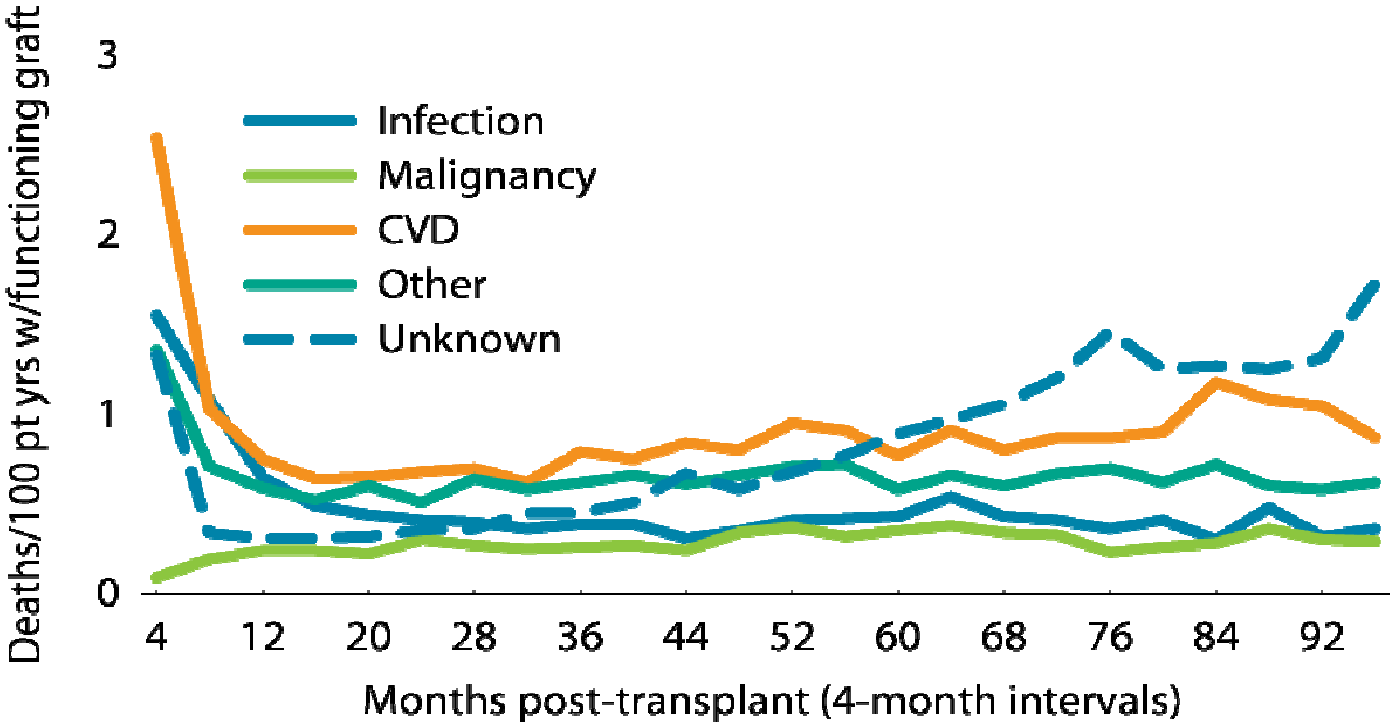


Renal Disease and CV risk (2)




ID
Other
CVD
CA
PVD
Stroke
CVD
Stroke
PVD
CA
ID
Other

Rates of death with function, by cause; adult transplant patients (USRDS)



first-time, kidney-only transplant recipients, age 18 & older & transplanted 1997–2006, who died with a functioning graft (N=14,169). Cause of death obtained from OPTN when available, otherwise taken from ESRD Death Notification form.

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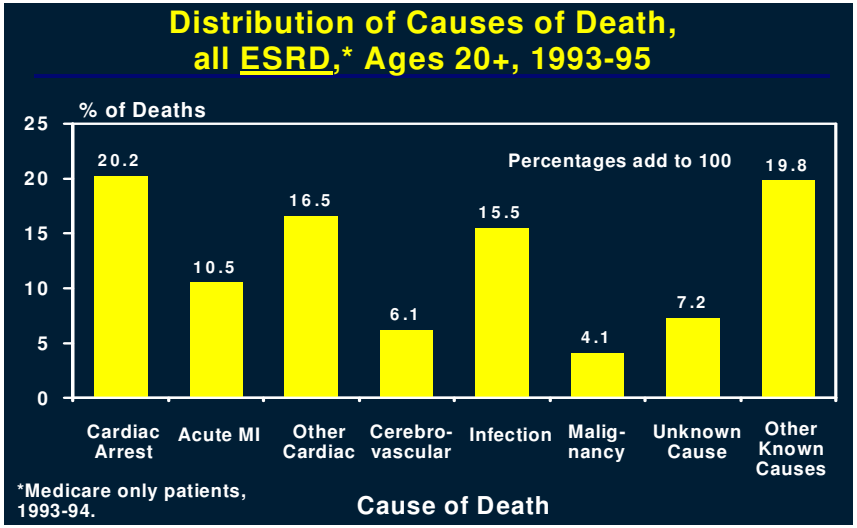
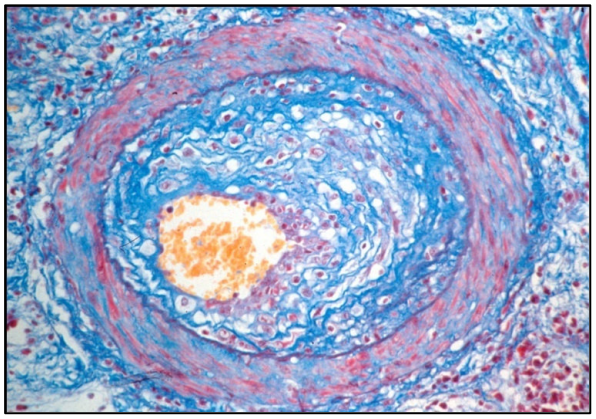
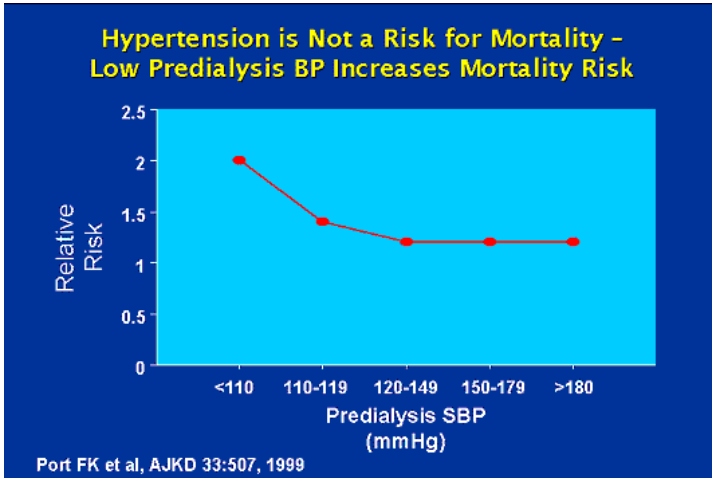
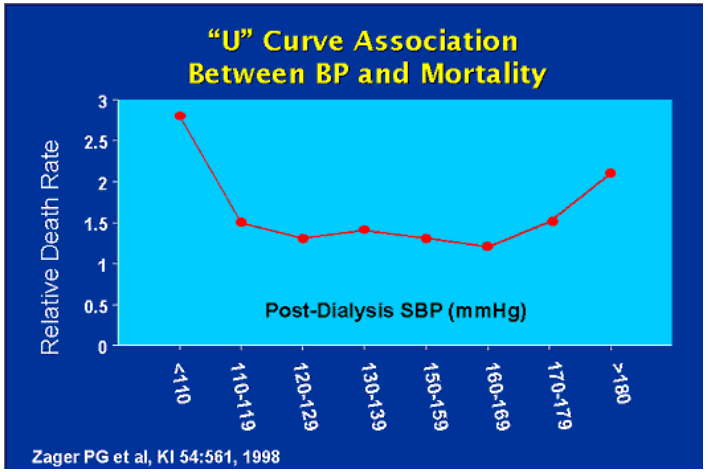
Cardiovascular Disease in Transplant Recipients

CVD in Transplant recipients (1)









Risk Factors for post-transplant CVD

Independent risk factor	Univariate	Multivariate
Age (decade)	1.49 (0.000)	1.71 (0.000)
Diabetes	2.09 (0.001)	1.67 (0.058)
Male	2.28 (0.001)	2.25 (0.000)
Splenectomy	1.65 (0.090)	1.98 (0.043)
Each acute rejection	1.26 (0.010)	1.31 (0.008)
HDL (each 10mg/dl)	0.80 (0.010)	0.80 (0.010)
Pre-transplant IHD	6.00 (0.000)	1.63 (0.091)
Post-transplant PVD	9.08 (0.000)	4.58 (0.000)
Post-transplant CVD	15.6 (0.000)	8.25 (0.000)

Modified from Kasiske et al., JASN 1996;7:158-165

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J Am Soc Nephrol 11: 1735–1743, 2000

Explained and Unexplained Ischemic Heart Disease Risk after Renal Transplantation

BERTRAM L. KASISKE, HARINI A. CHAKKERA, and JOSEPH ROEL
Department of Medicine, Hennepin County Medical Center, Minneapolis, Minnesota.

Kasiske et al., JASN 11;1735, 2000

123 events in 1124 RTR

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Risk Factors for Post Transplant CHD

Factor	OR	P value
Age (yr)	1.06	<0.0001
Diabetic NP	3.03	0.028
Smoking	1.85	<0.0001
2+ Rejections	1.62	0.034
TC > 280 mg/dL	2.18	0.048

Kasiske et al., JASN 11;1735-1743, 2000

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Risk Factors – MI

	RR	CI	P .
Age	1.03	(1.00,1.05)	0.0211
Diabetes	2.36	(1.42,3.04)	0.0010
Smoking	2.31	(1.78,5.63)	0.0017
CHD	3.17	(2.08,5.18)	0.0001
LDL	1.41	(1.12,1.77)	0.0038

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Risk Factors – Cardiac death

	RR	CI	P .
Age	1.05	(1.02,1.08)	0.0001
Diabetes	2.82	(1.62,4.91)	0.0002
Smoking	1.55	(0.86,2.80)	0.1490
CHD	3.60	(1.96,6.63)	<0.0001
LDL	1.28	(0.99, 1.65)	0.0607
SBP	1.01	(1.00,1.03)	0.0506
PP	1.01	(1.00,1.03)	0.0034
LVH	2.08	(1.11, 3.89)	<0.0001
ST-T	3.59	(2.07, 6.21)	<0.0001

Is CVD the same in Transplant recipients?

	4D	ALERT	4S	AURORA
EP	Placebo	Placebo	Placebo	Placebo
CD	23%	5.1%	8.5%	23.4%
AMI (NF)	12%	6.3%	22.6%	7.7%
Non-CVD	25%	6.2%	2.2%	19.4%

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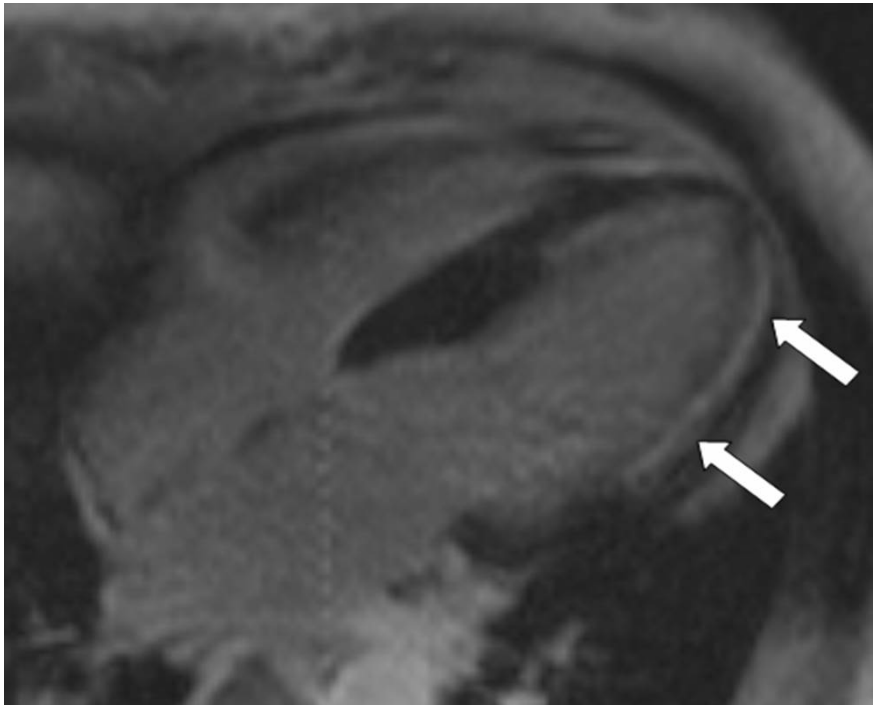

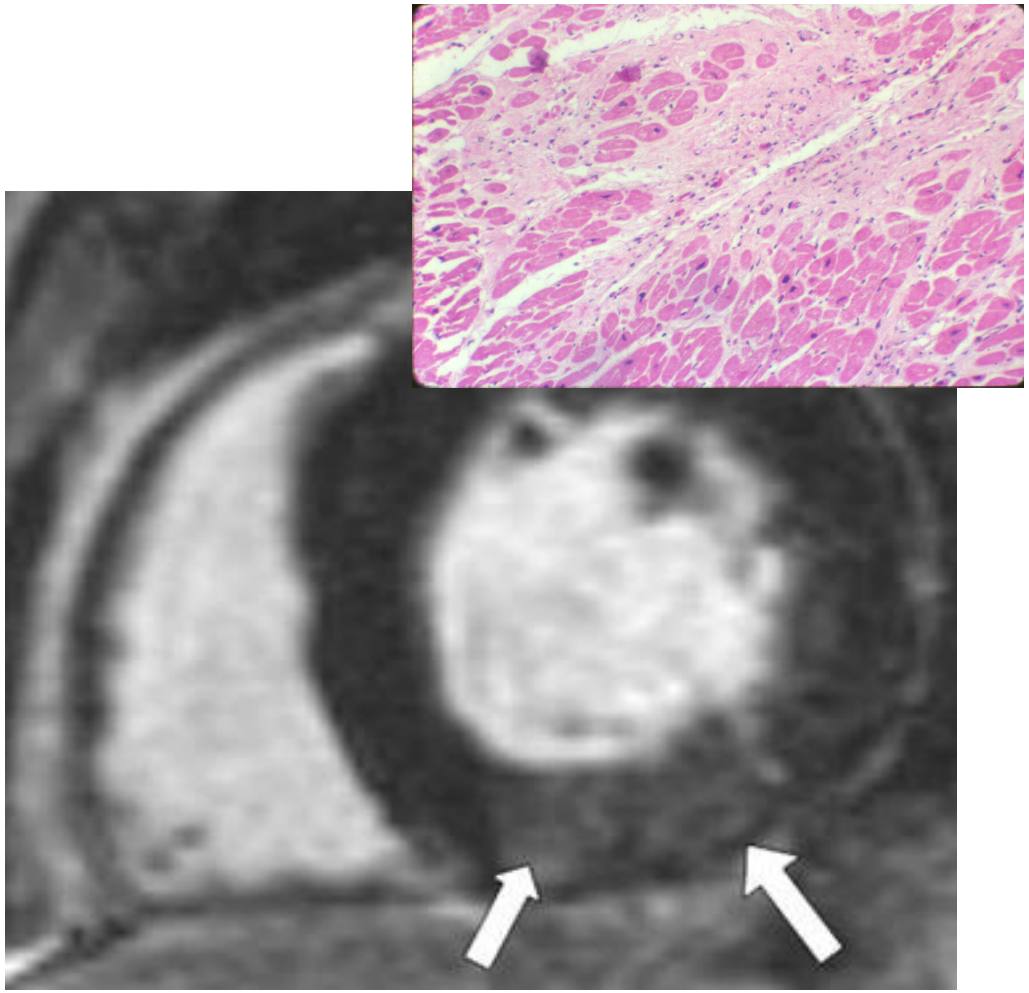

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CV risk in Renal Transplantation

Risk Factor	Modifiable?	Iatrogenic? (2º immunosuppression)
Age	No	No
Sex	No	No
Smoking	Yes	No
Diabetes	No	No
PTDM	Yes	Yes (+++)
Blood Pressure	Yes	Yes (++)
LVH	NK	Yes (BP)
Acute rejection	Yes	**Yes (++++)**
Graft function	Yes	**Yes (++/AR)**
Hyperlipidaemia	Yes	Yes (++)

Effect of immunosuppressive agents on CV risk factors

Cardiovascular risk factors	Steroids	Aza	MMF	CsA	Tac	TORi
Hypertension	↑	↔	↔	↑	↑	↔
LVH	↑	↔	↔	↑	↑	↑
Cholesterol	↑	↔	↔	↑	↑	↑
LDL	↑	↔	↔	↑	↑	↑
Triglycerides	↑	↔	↔	↑	↑	↑
Diabetes mellitus	↑	↔	↔	↑	↑	↑
Renal function	↔	↔	↔	↓	↓	↔

↑ Increase ↓ Decrease ↔ Neutral
LVH = left ventricular hypotrophy; LDL = low-density lipoprotein

What is the question?

Is it reasonable to reduce, stop or change immunsuppressive therapy to prevent the long-term consequences of transplantation (i.e Cancer, Diabetes, Infection and CVD)?

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What is the question?

Is it reasonable to reduce, stop or change immunsuppressive therapy to prevent the long-term consequences of transplantation (i.e Cancer, Diabetes, Infection and CVD)?

Do YOU reduce, stop or change immunosuppression to modify CV risk factors (Hypertension, Diabetes, Dyslipidaemia)?

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What is the question?

Is it reasonable to reduce, stop or change immunsuppressive therapy to prevent the long-term consequences of transplantation (i.e Cancer, Diabetes, Infection and CVD)?

Do YOU reduce, stop or change immunosuppression to modify CV risk factors (Hypertension, Diabetes, Dyslipidaemia)? WHY NOT?

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What is the question?

Is it reasonable to reduce, stop or change immunsuppressive therapy to prevent the long-term consequences of transplantation (i.e Cancer, Diabetes, Infection and CVD)?

Do YOU reduce, stop or change immunosuppression to modify CV risk factors (Hypertension, Diabetes, Dyslipidaemia)?

Or to improve renal function?

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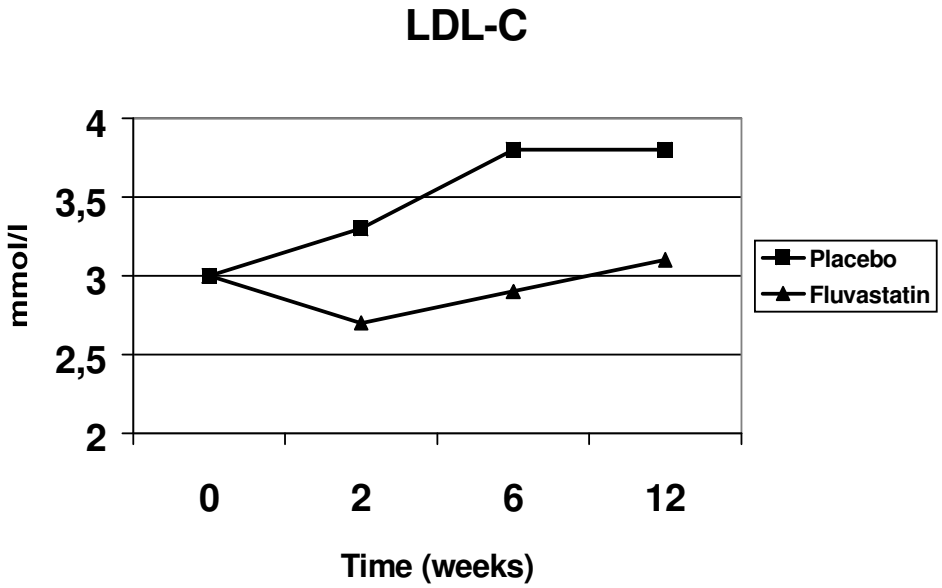
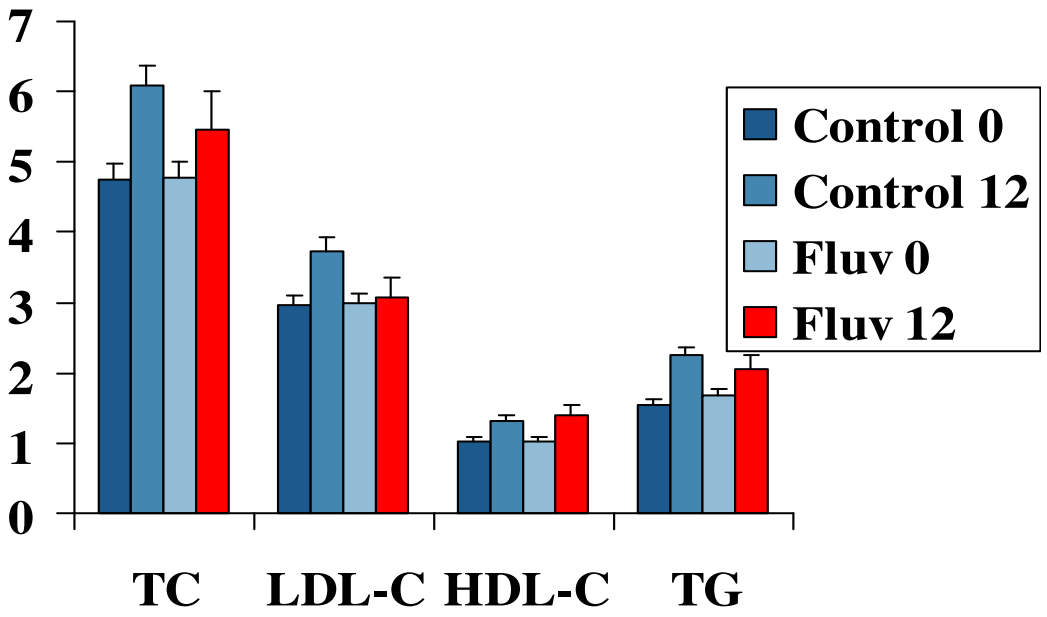
Lipids

Lipids in renal transplantation





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ALERT

Holdaas et al., Lancet 2003, NDT 2005

Jardine et al., Am. J. Transplant 2004

Fellstrom et al., Kidney Int. 2004, 2005

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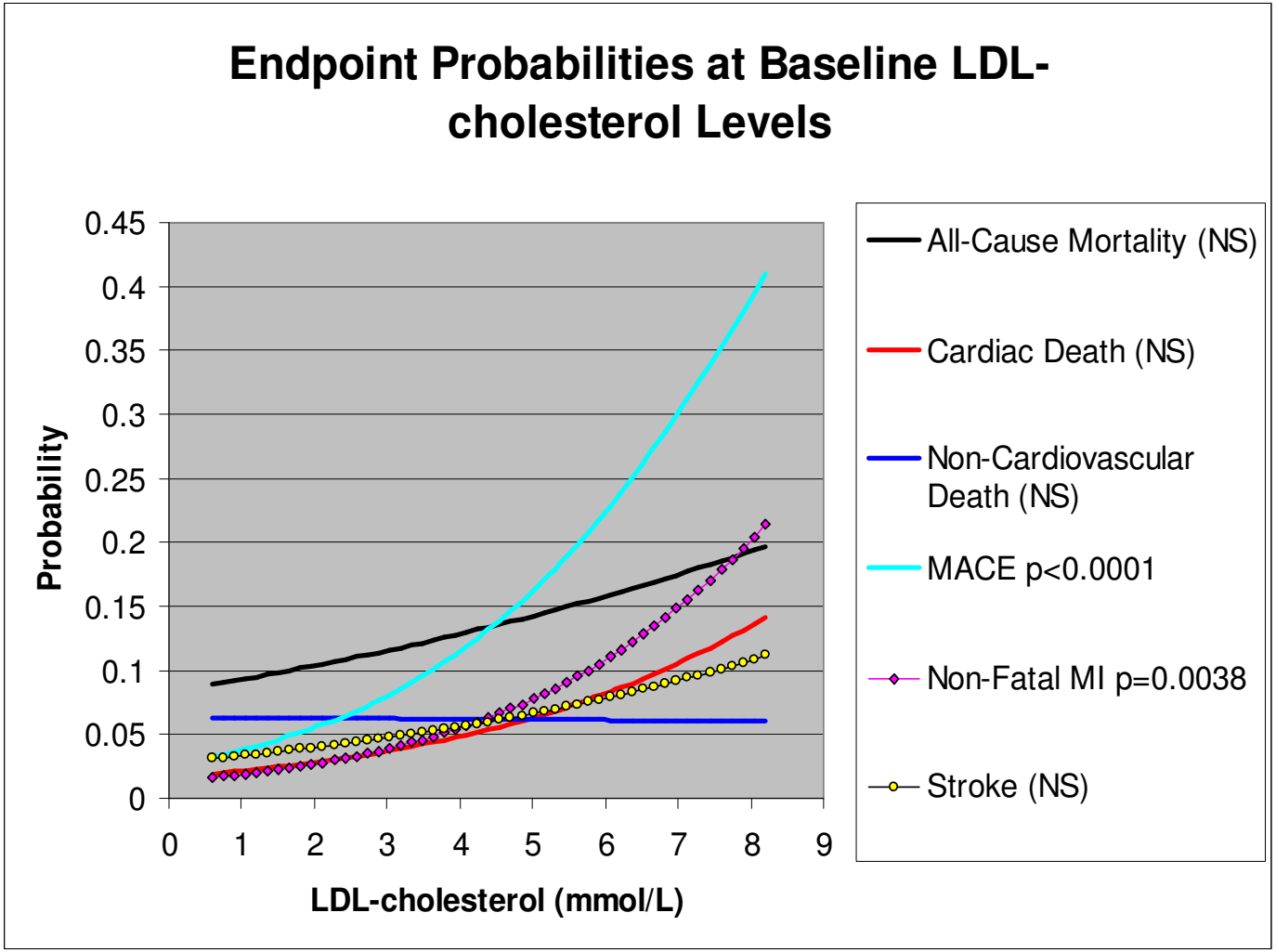
Soveri et al., NDT 2006;21:2282-6



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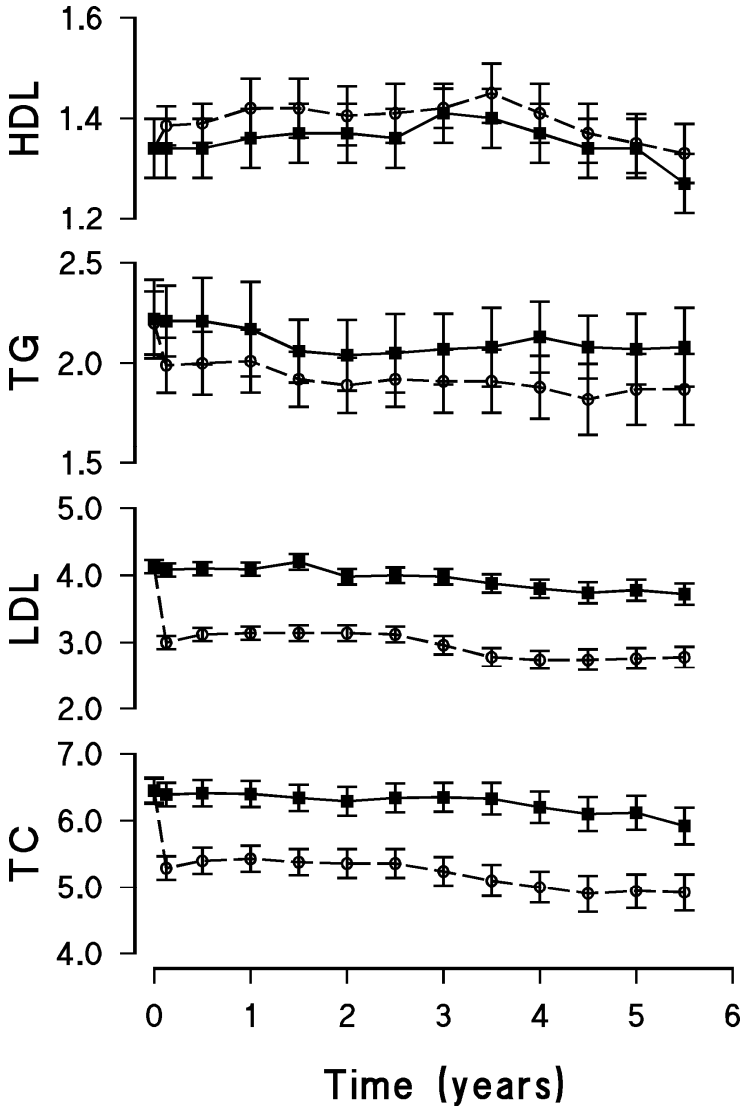
Lipid sub-fractions in ALERT.



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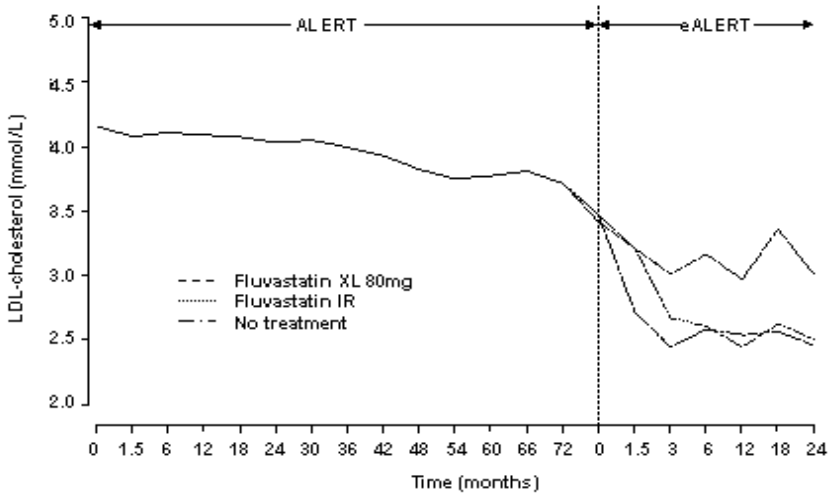
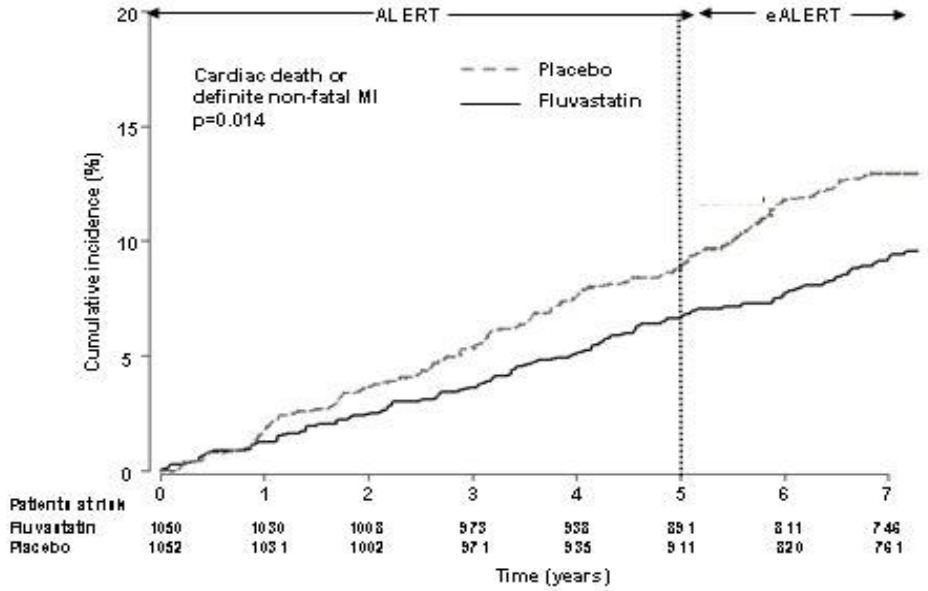
ALERT





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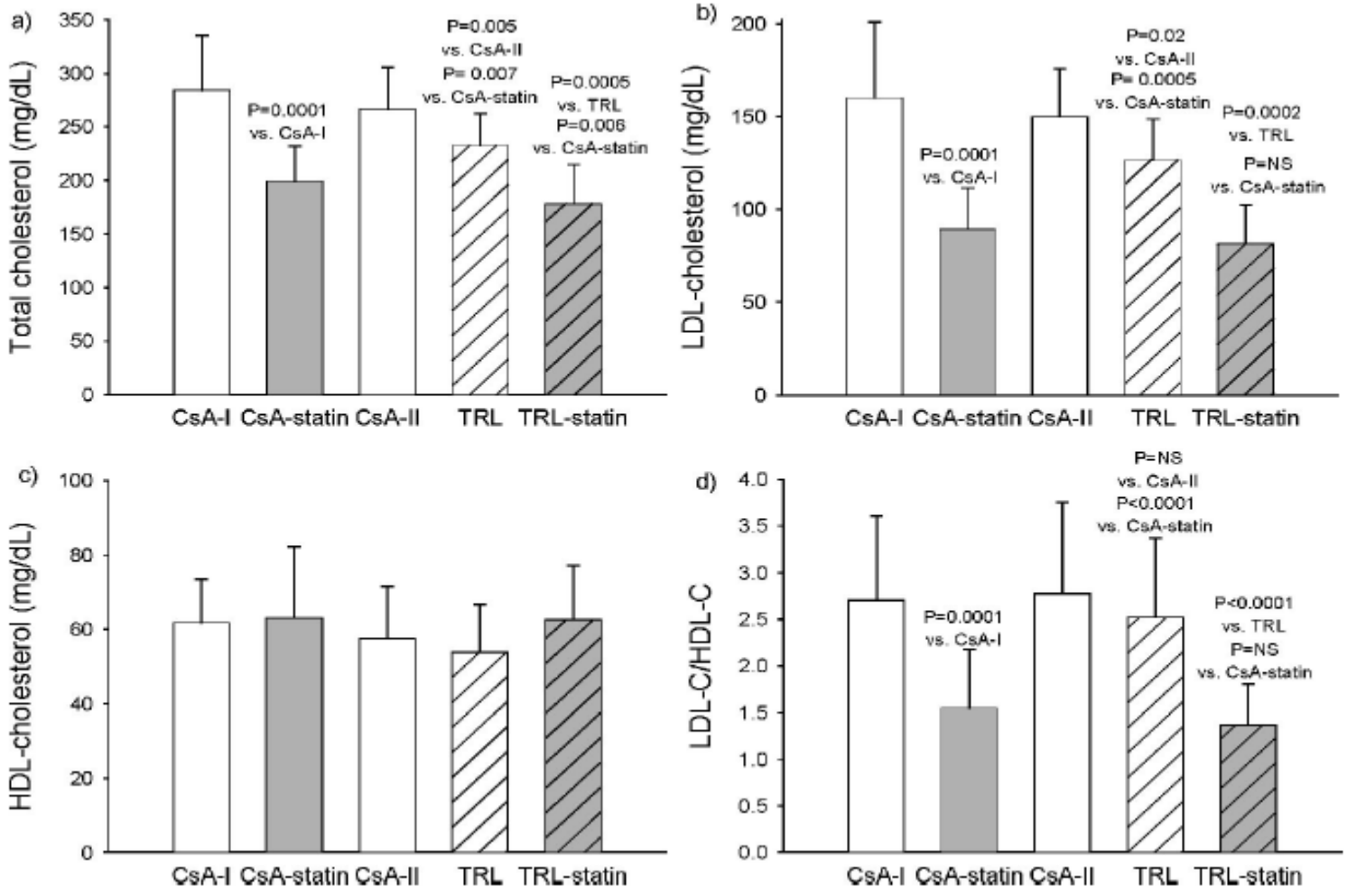
Wissing et al., Transplantation 2006; 82:771-778.



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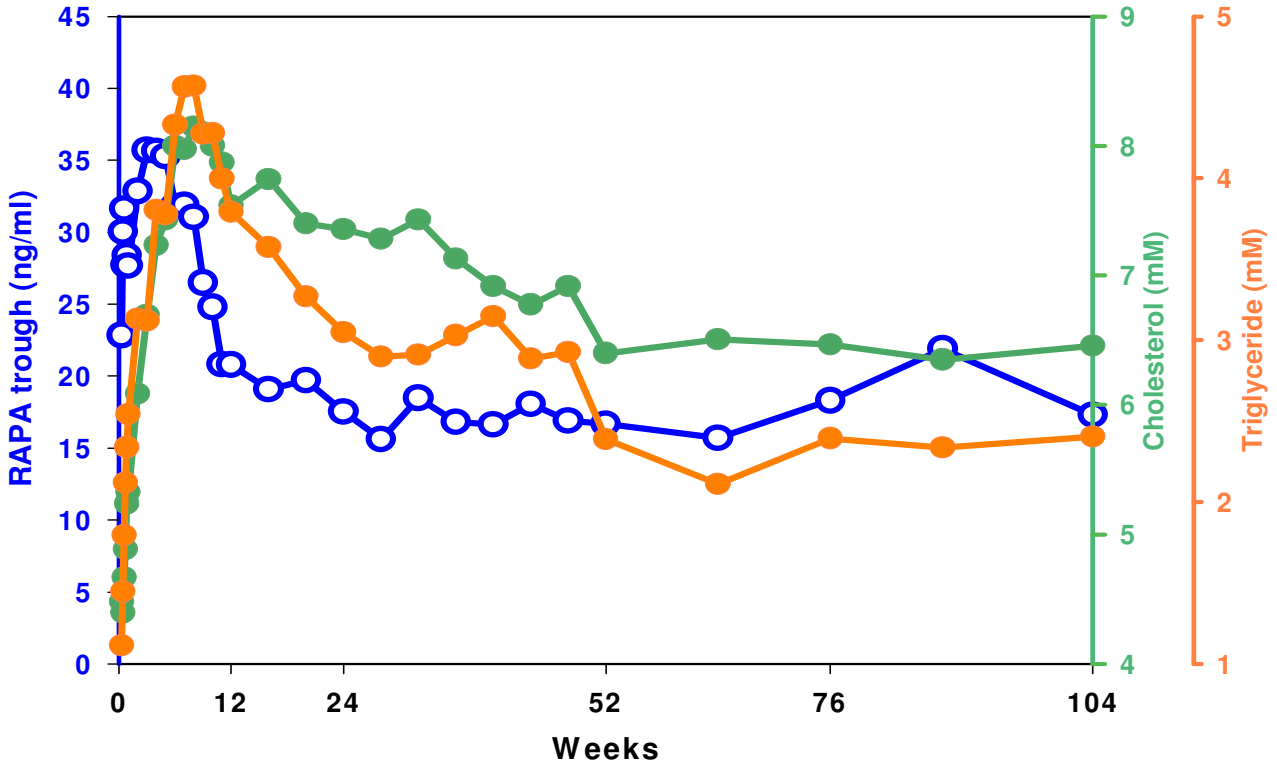
Lipid levels vs. Sirolimus level



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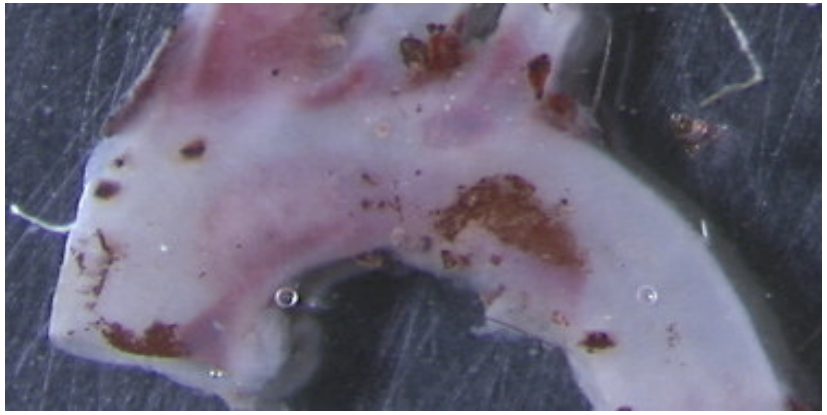
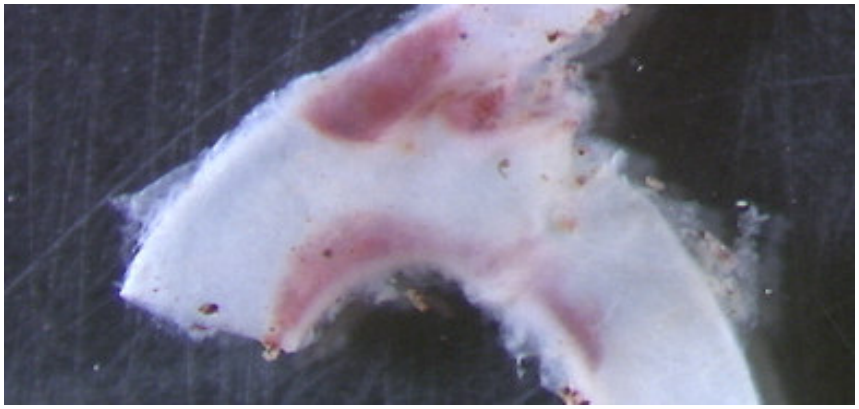
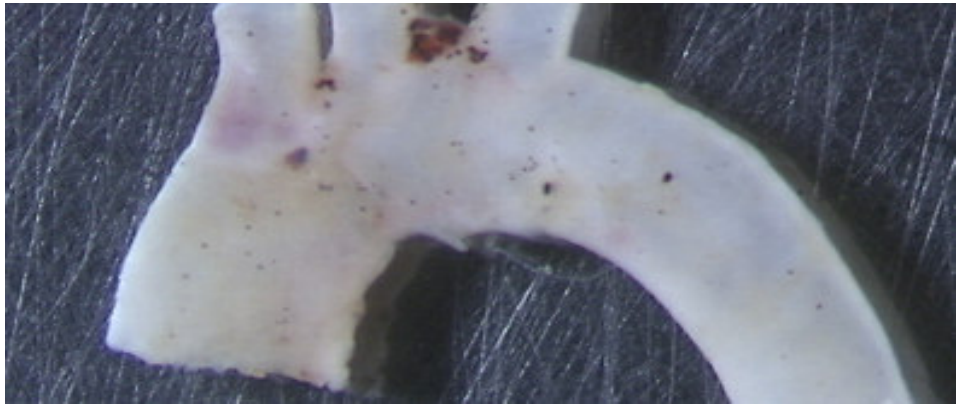
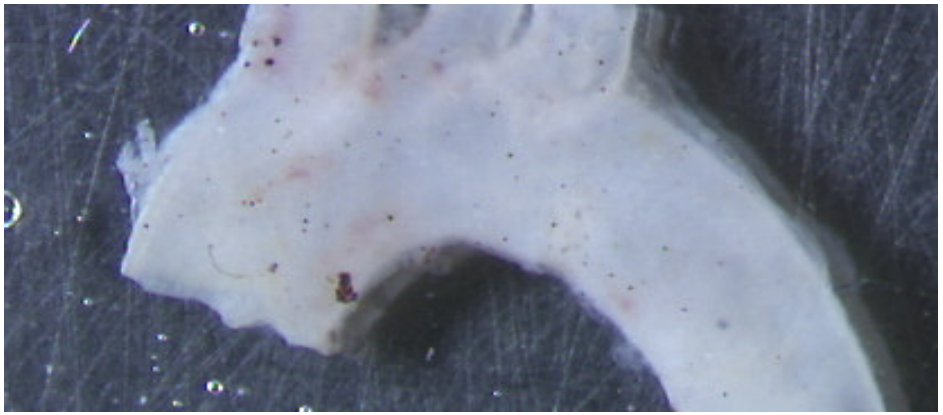
Control



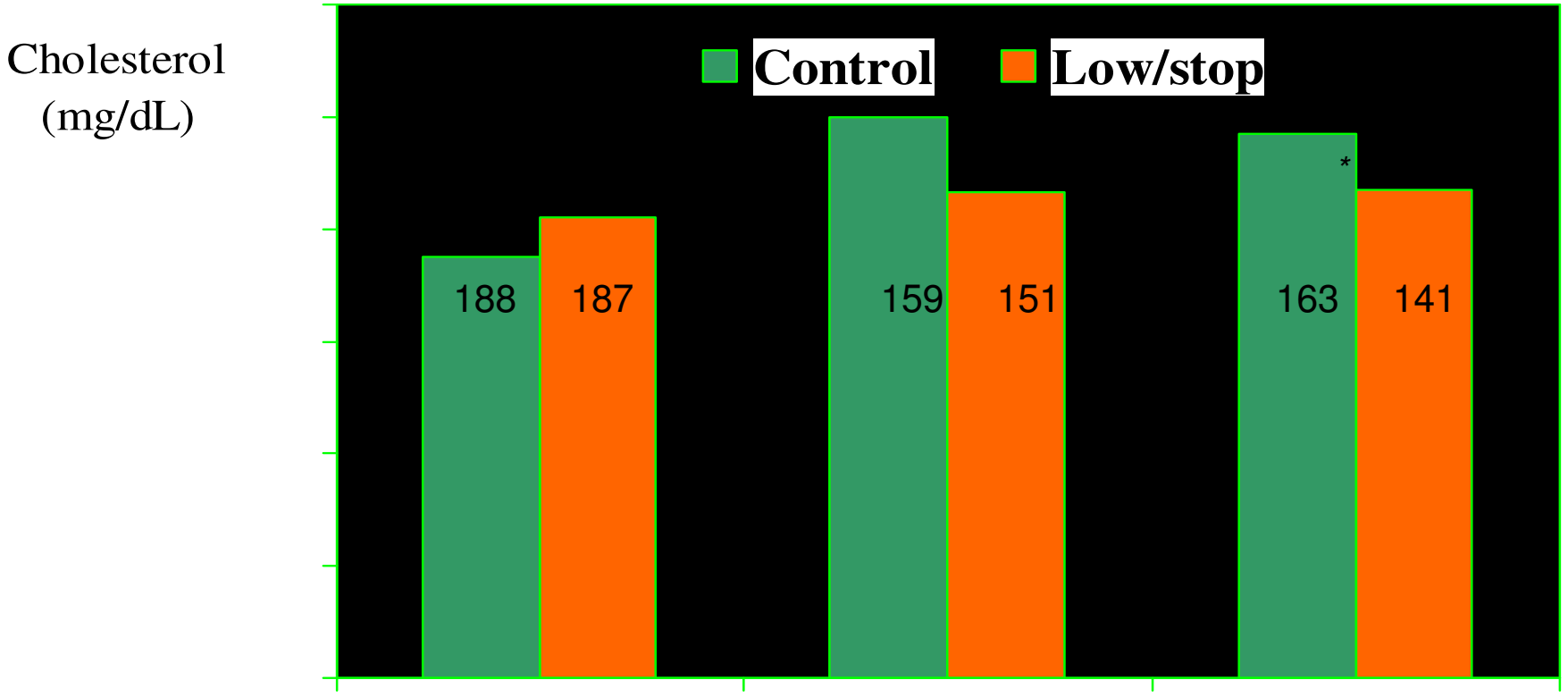


Sirolimus 2 mg/kg



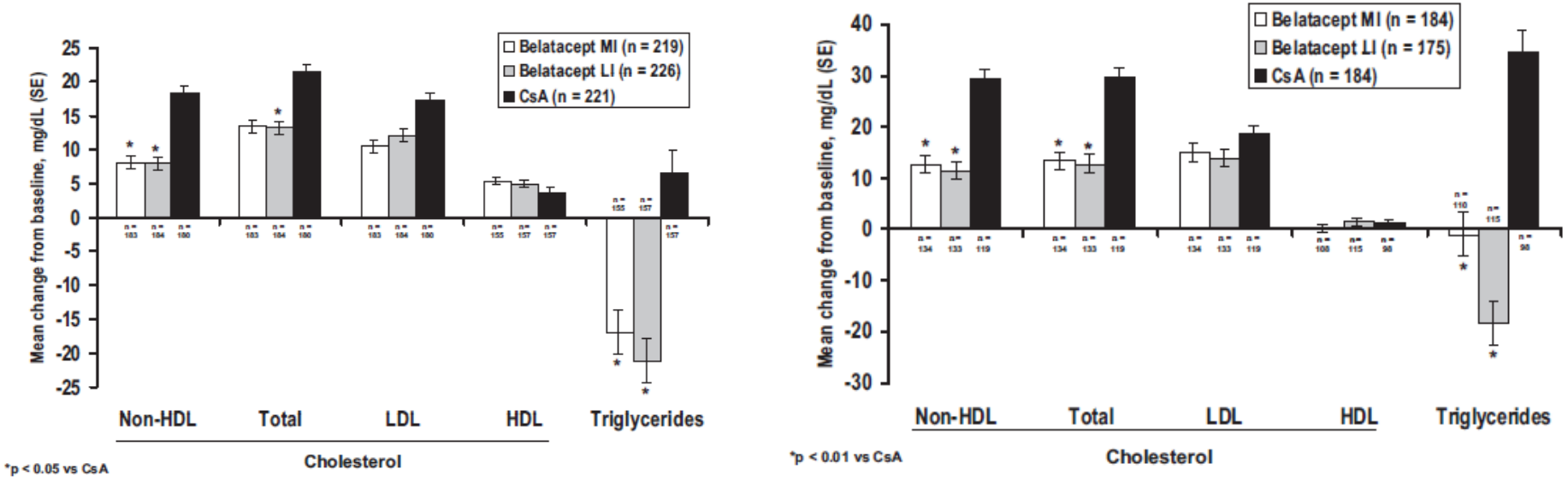


Corticosteroids and Dyslipidemia
Corticosteroid Withdrawal



Vanrenterghem, et al., *Transplantation* 2000; 70:1352

Belatacept



Vanrenterghem et al., Transplantation 2011 (ePub)

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Hypertension

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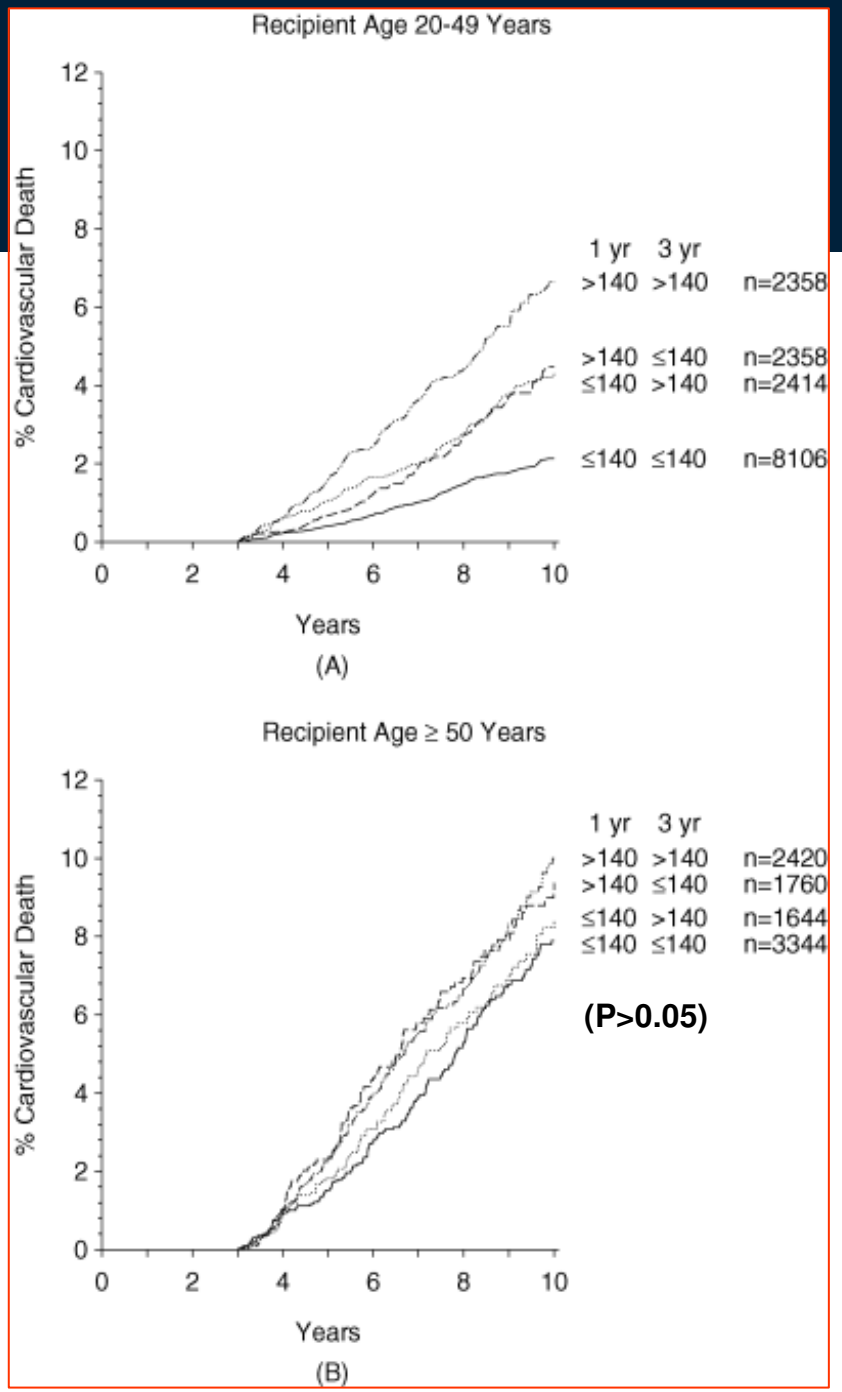
BP and Late CVD Mortality

Association between BP and CVD deaths in 1st deceased donor transplants performed in 1987-2000 (N=24,404).

G Opelz, et al., *Am J Transplant* 2005; 5:2725



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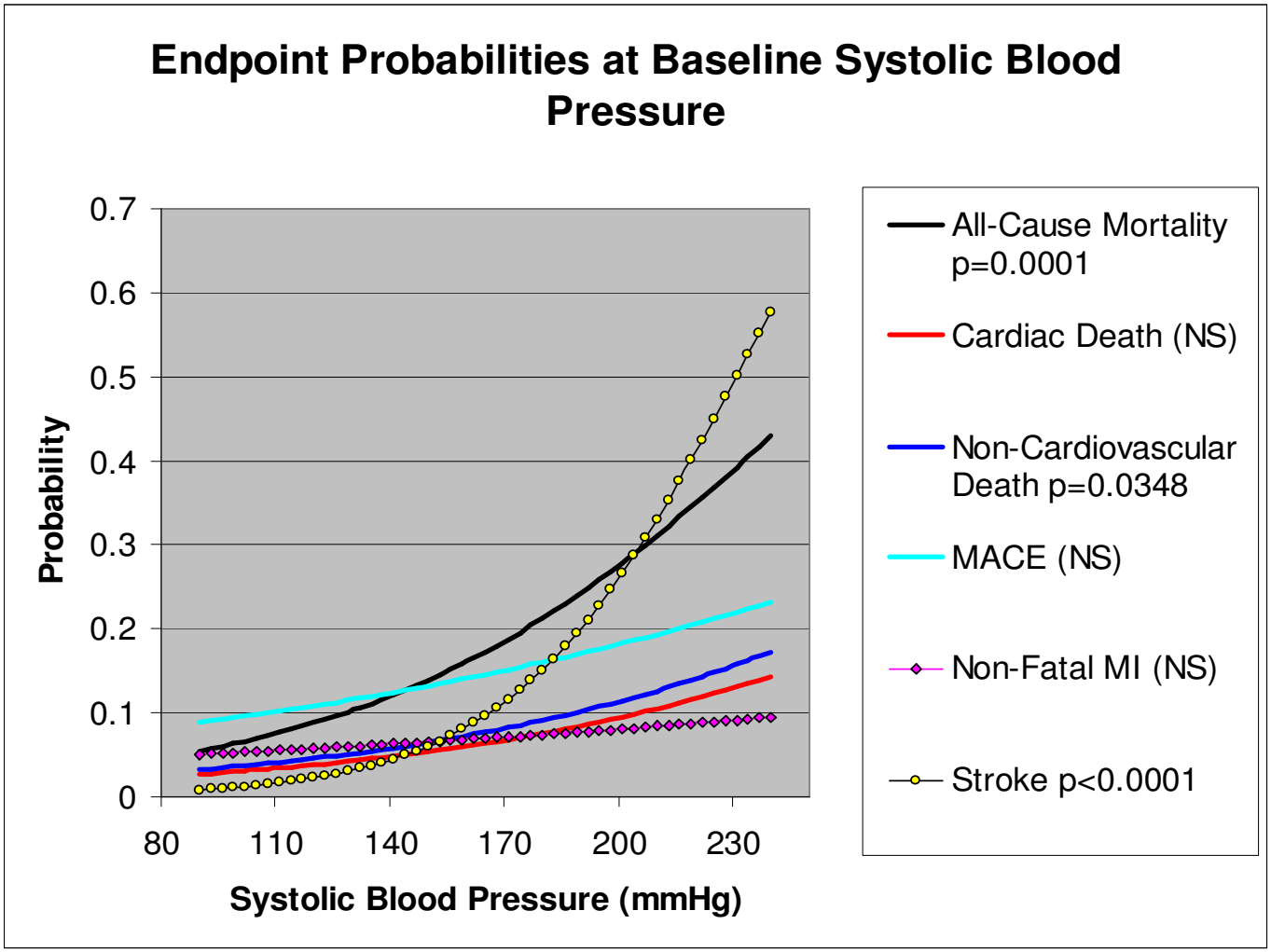
Soveri et al., NDT 2006;21:2282-6



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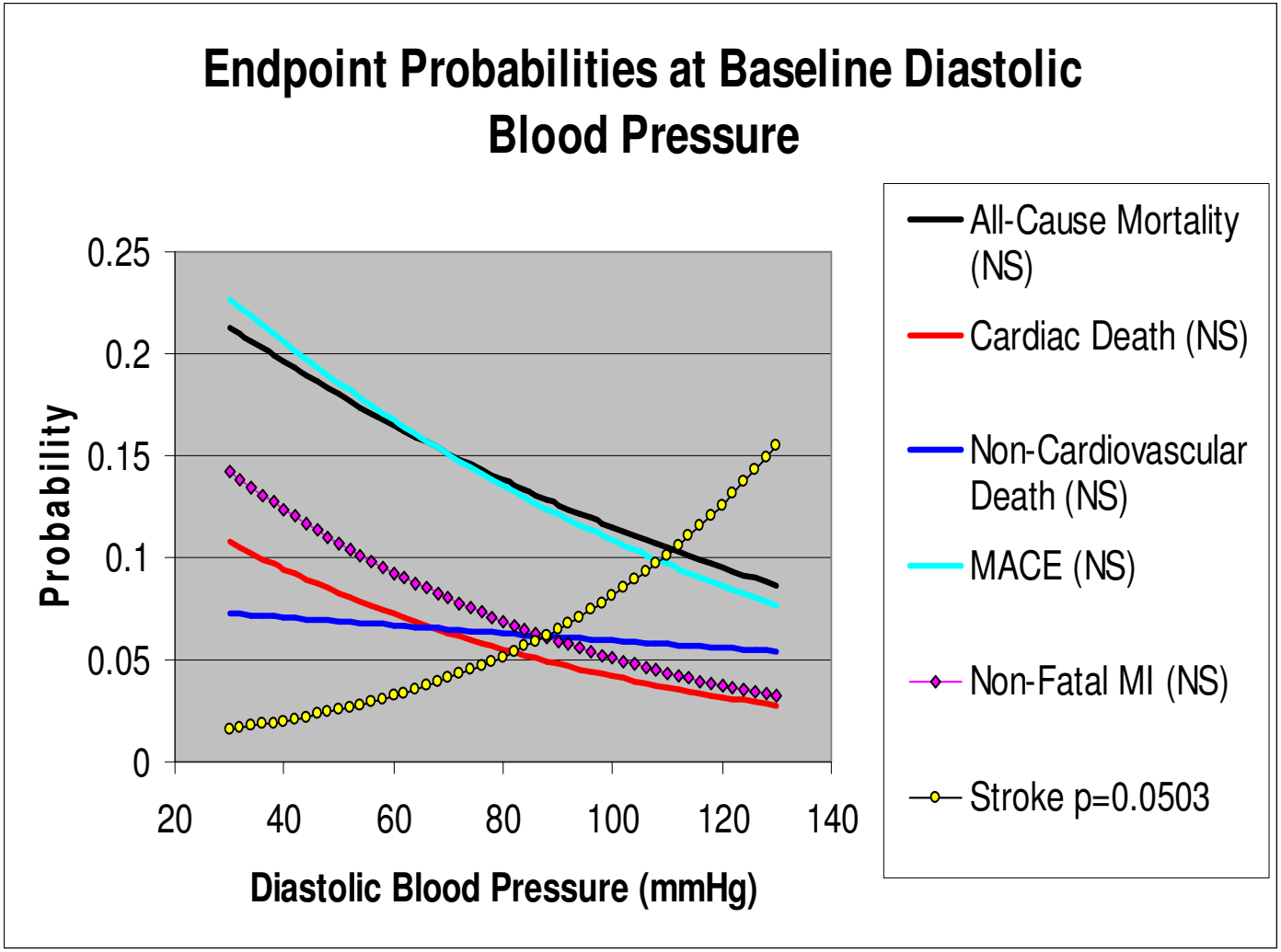
Soveri et al., NDT 2006;21:2282-6



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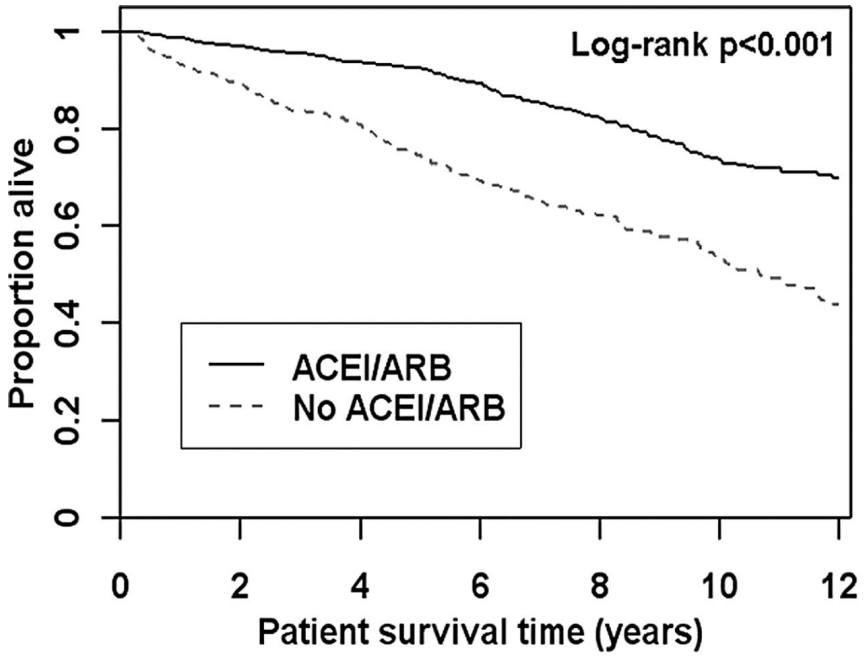
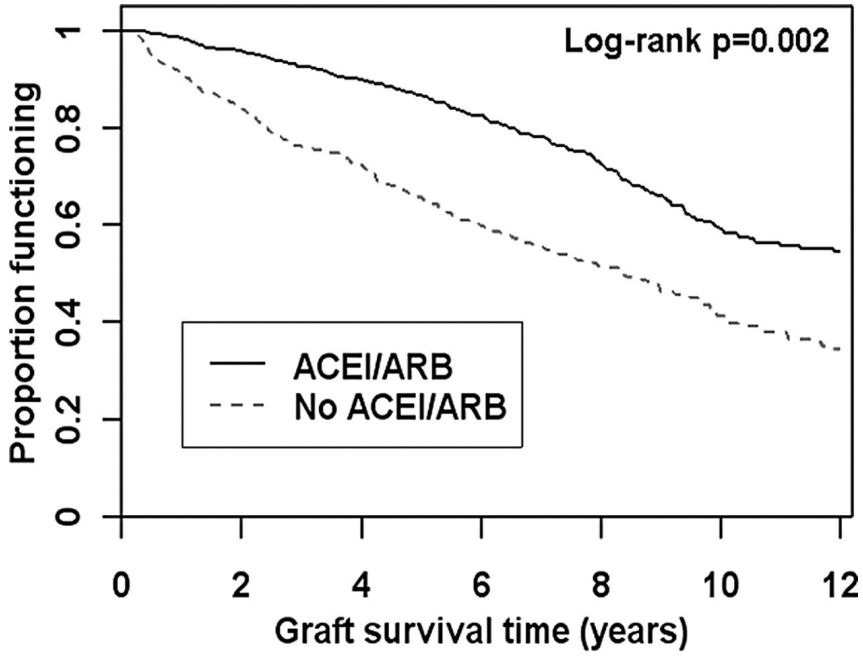


Patients at risk, ACEI/ARB:
1250 1020 774 559 396 228 103

Patients at risk, no ACEI/ARB:
781 511 390 276 180 107 51



Patients at risk, ACEI/ARB:
1190 925 671 456 300 153 67

Patients at risk, no ACEI/ARB:
841 489 355 240 148 83 42

Heinze et al., JASN 2006;17:889-899

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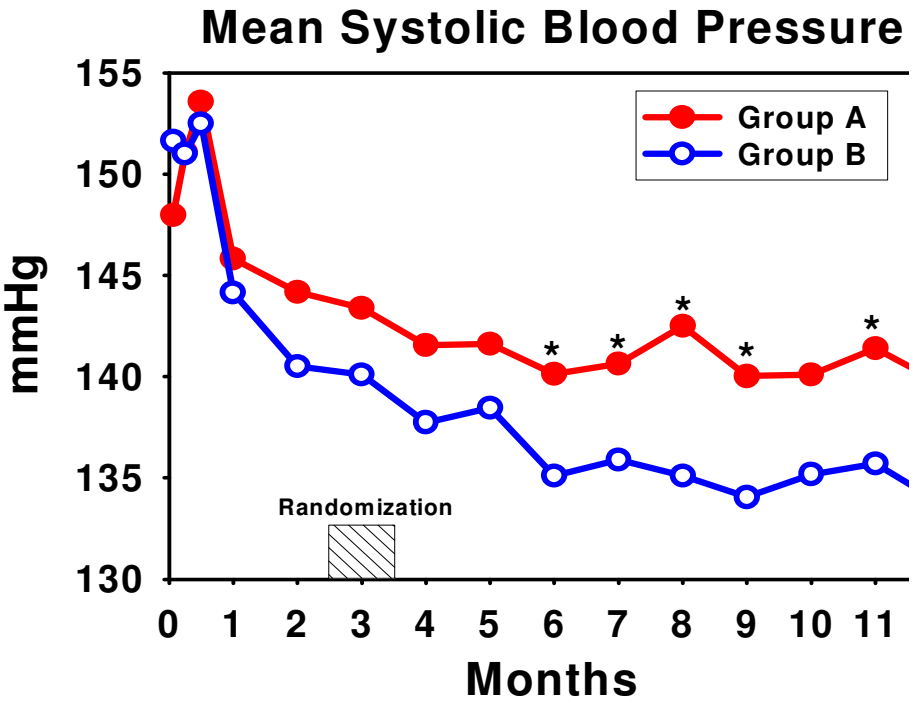
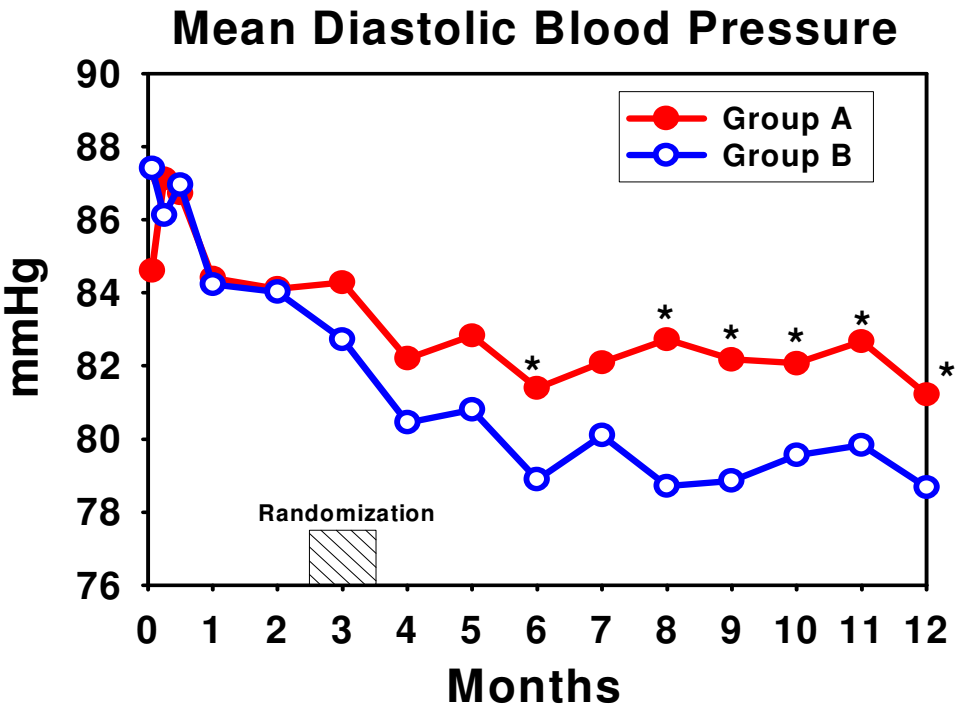
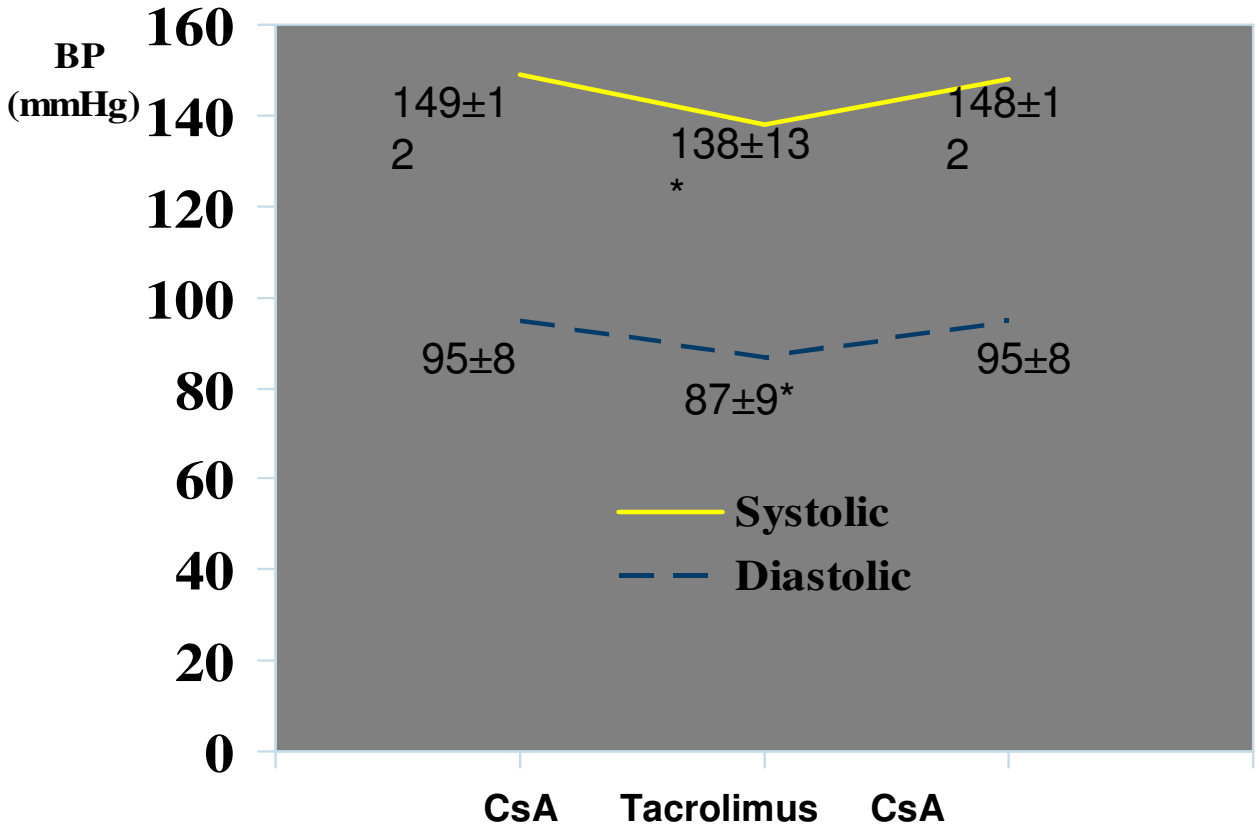
BP following CsA elimination





Legendre et al., Abstract 206, AST Chicago 2001

Effects of Calcineurin Inhibitors on Hypertension



*p<0.01 v. CsA (before and after); n=17 >1y post-transplant

Ligtenberg, et al., *J Am Soc Nephrol* 2001; 12:368

Improved CV risk profile after randomised conversion from CsA to Tac

Se Ct fell from 137 to 131 umol/L (P<0.01)

Mean BP fell from 104 to 99 mmHg (P<0.001)

LDL decreased from 3.48 to 3.11 mmol/L

TG reduced – 2.11 vs., 1.72 mmol/L (P<0.001)

Oxidation of LDL reduced

Transient rise in blood sugar

Artz et al.,J. Am. Soc. Nephrol. 14:1880-1888, 2003

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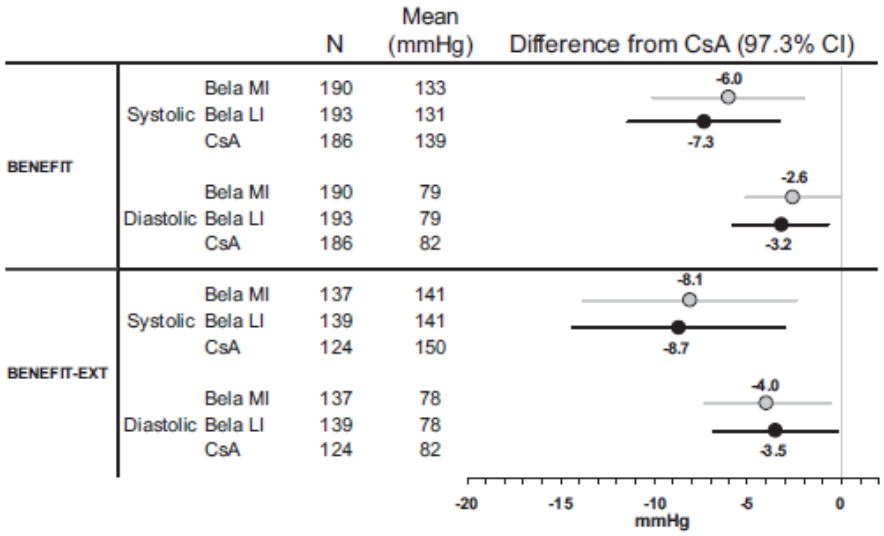
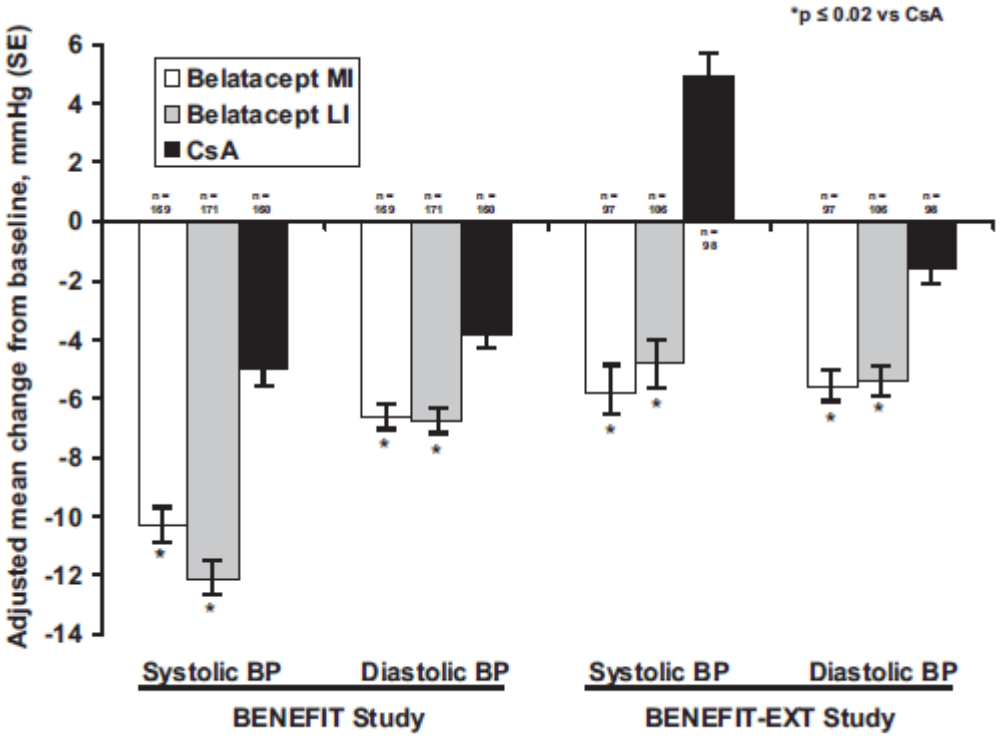
Belatacept-Based Regimens Are Associated With Improved Cardiovascular and Metabolic Risk Factors Compared With Cyclosporine in Kidney Transplant Recipients (BENEFIT and BENEFIT-EXT Studies)

Yves Vanrenterghem,[1,15] Barbara Bresnahan,[2] Josep Campistol,[3] Antoine Durrbach,[4] Josep Grinyó,[5] Hans-Hellmut Neumayer,[6] Philippe Lang,[7] Christian P. Larsen,[8] Eduardo Mancilla-Urrea,[9] José Medina Pestana,[10] Alan Block,[11] Tao Duan,[11] Alan Glicklich,[11] Sheila Gujrathi,[11] and Flavio Vincenti[12]





Vanrenterghem et al., Transplantation 2011 (ePub)

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The uraemic heart

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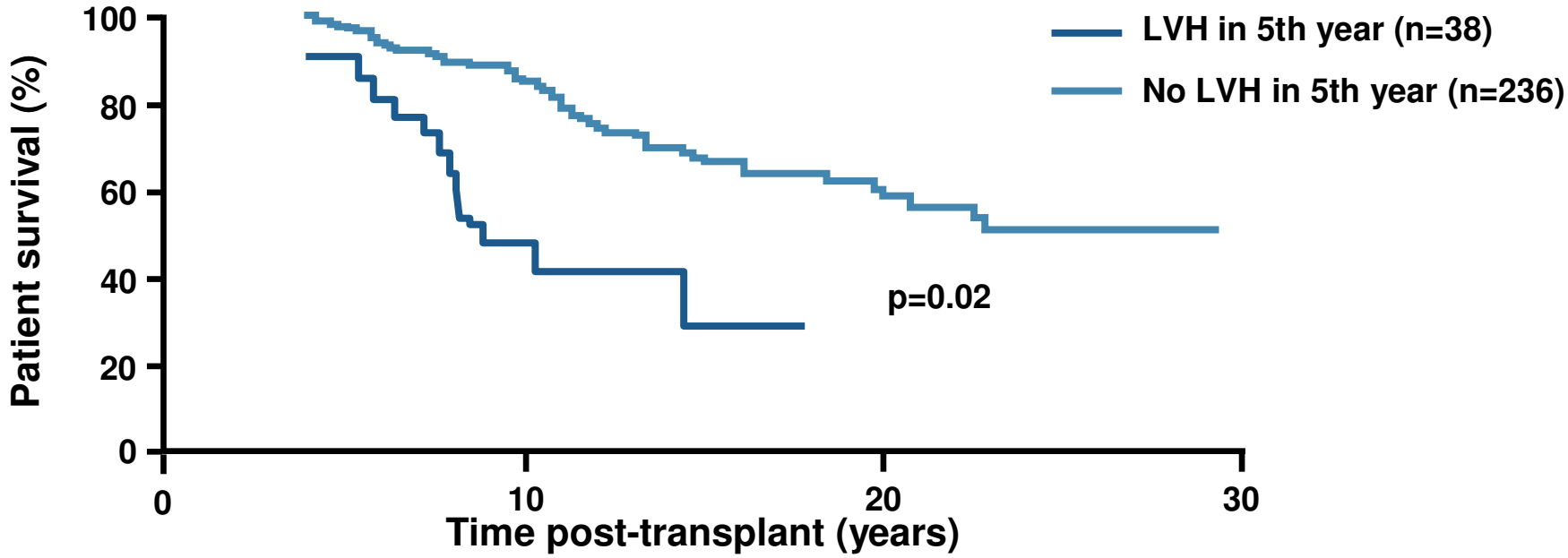
LVH is a determinant of risk of cardiovascular disease

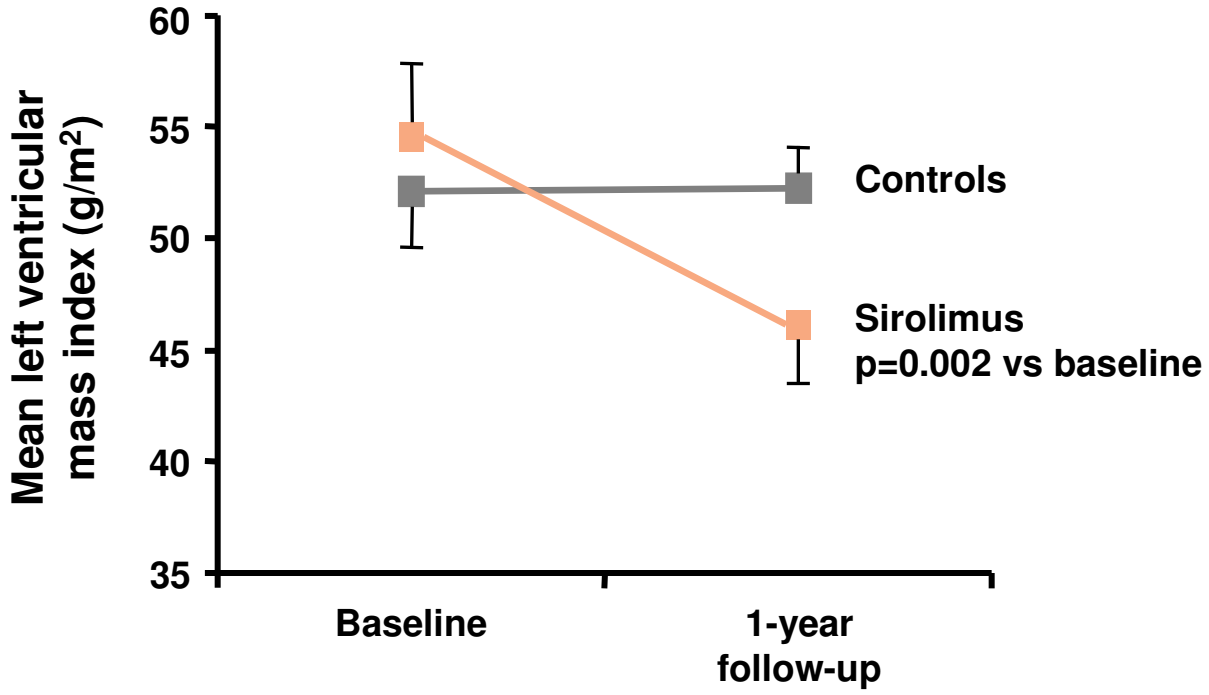
Retrospective cohort study of LVH in renal transplant recipients



Parfrey PS *et al. Nephrol Dial Transplant* 1996;11:1277–85;
Rigatto C *et al. J Am Soc Nephrol* 2003;14:462–8

Conversion from CNI to mTORi may improve LVH

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



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

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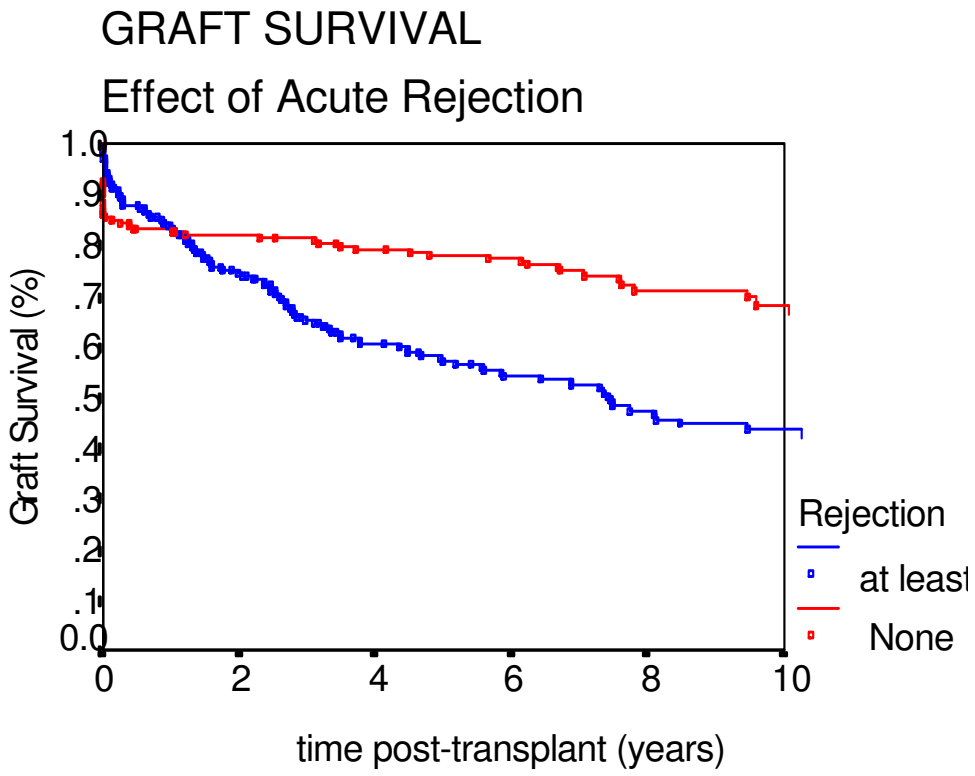
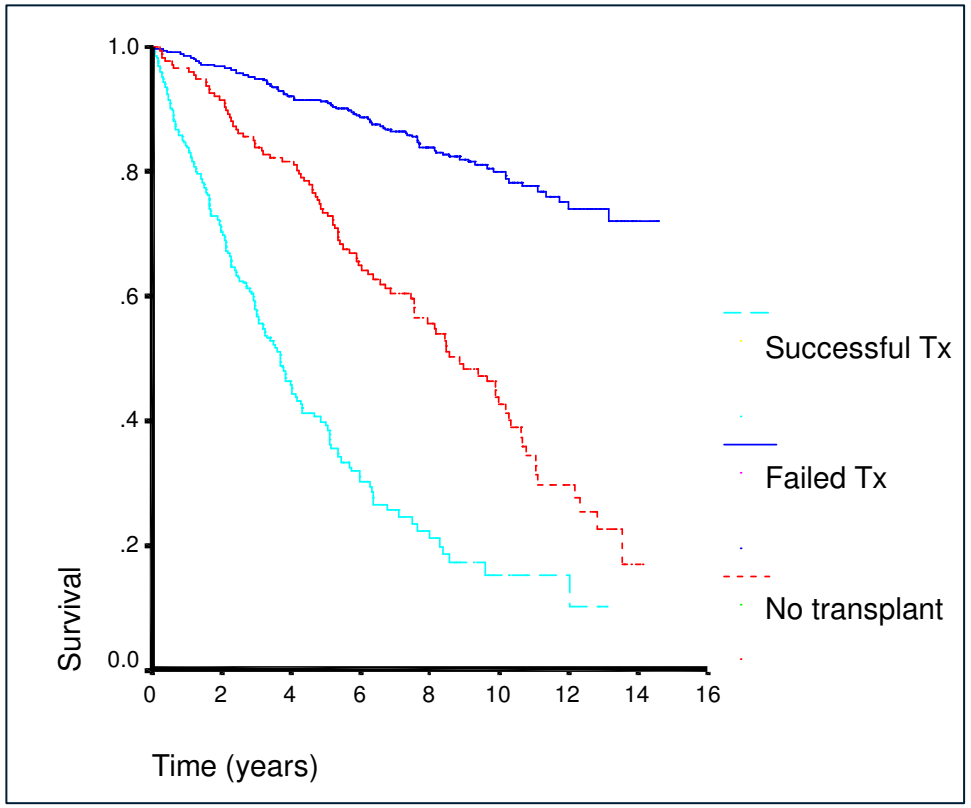
Rejection & Graft function

Rejection, graft failure and patient survival





Woo et al. Kidney International 1999;55:692-699

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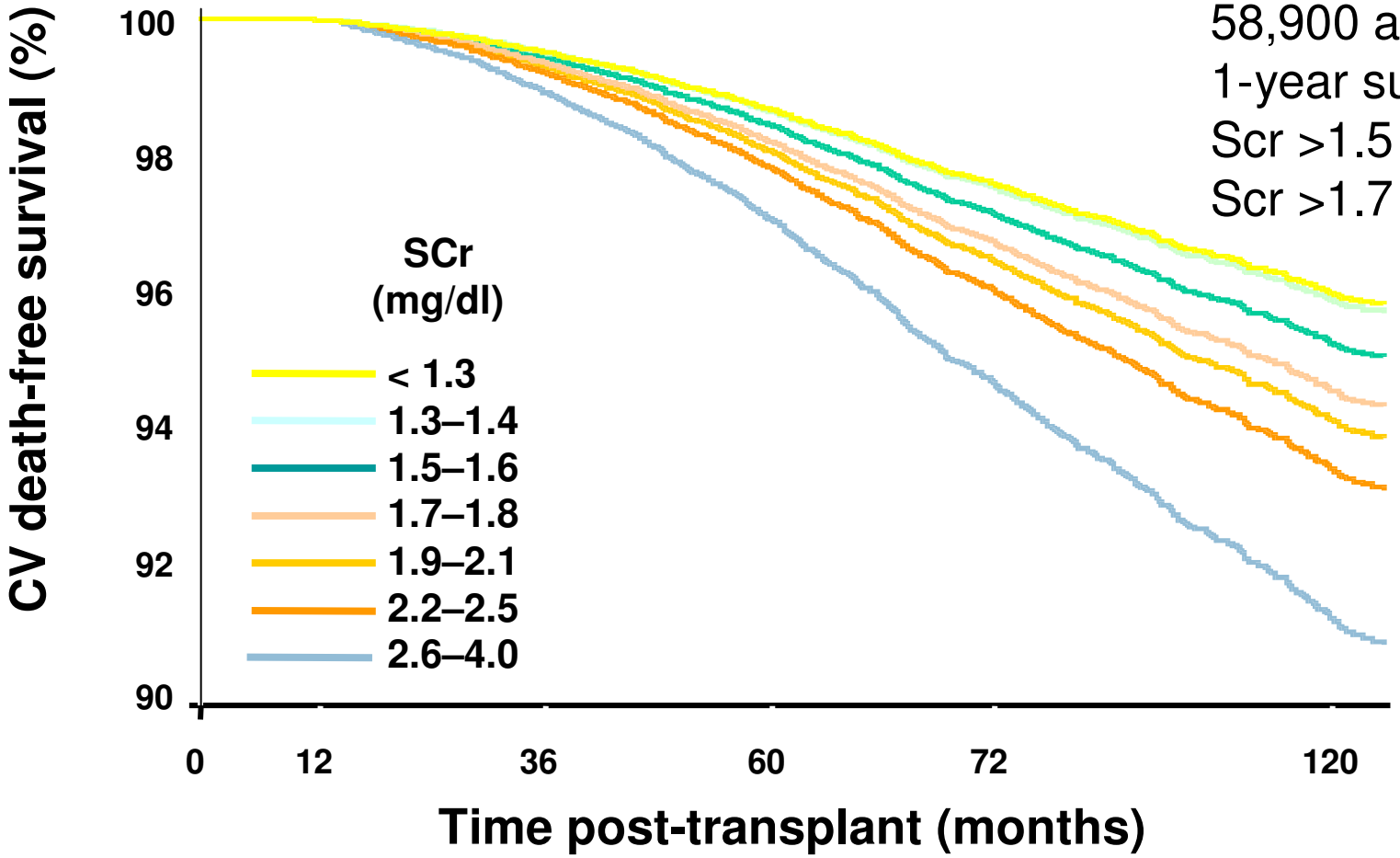
Graft Function Predicts Cardiac Mortality After First Year

USRDS, 1988-1998
58,900 adults
1-year survival
Scr >1.5 $p = 0.025$
Scr >1.7 $p < 0.001$



Meier-Kriesche H-U et al. *Transplantation* 2003; 75:1291–6.

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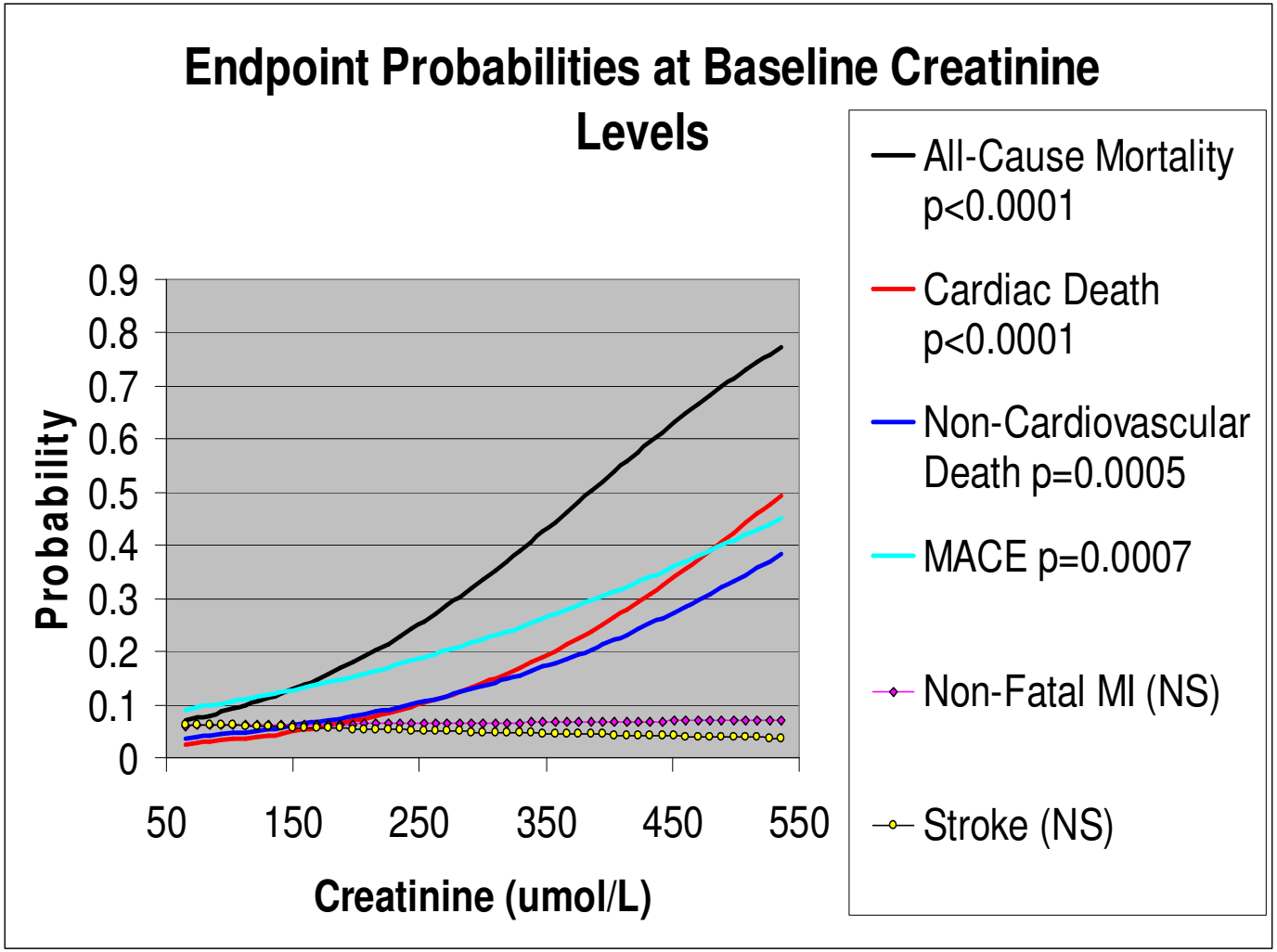
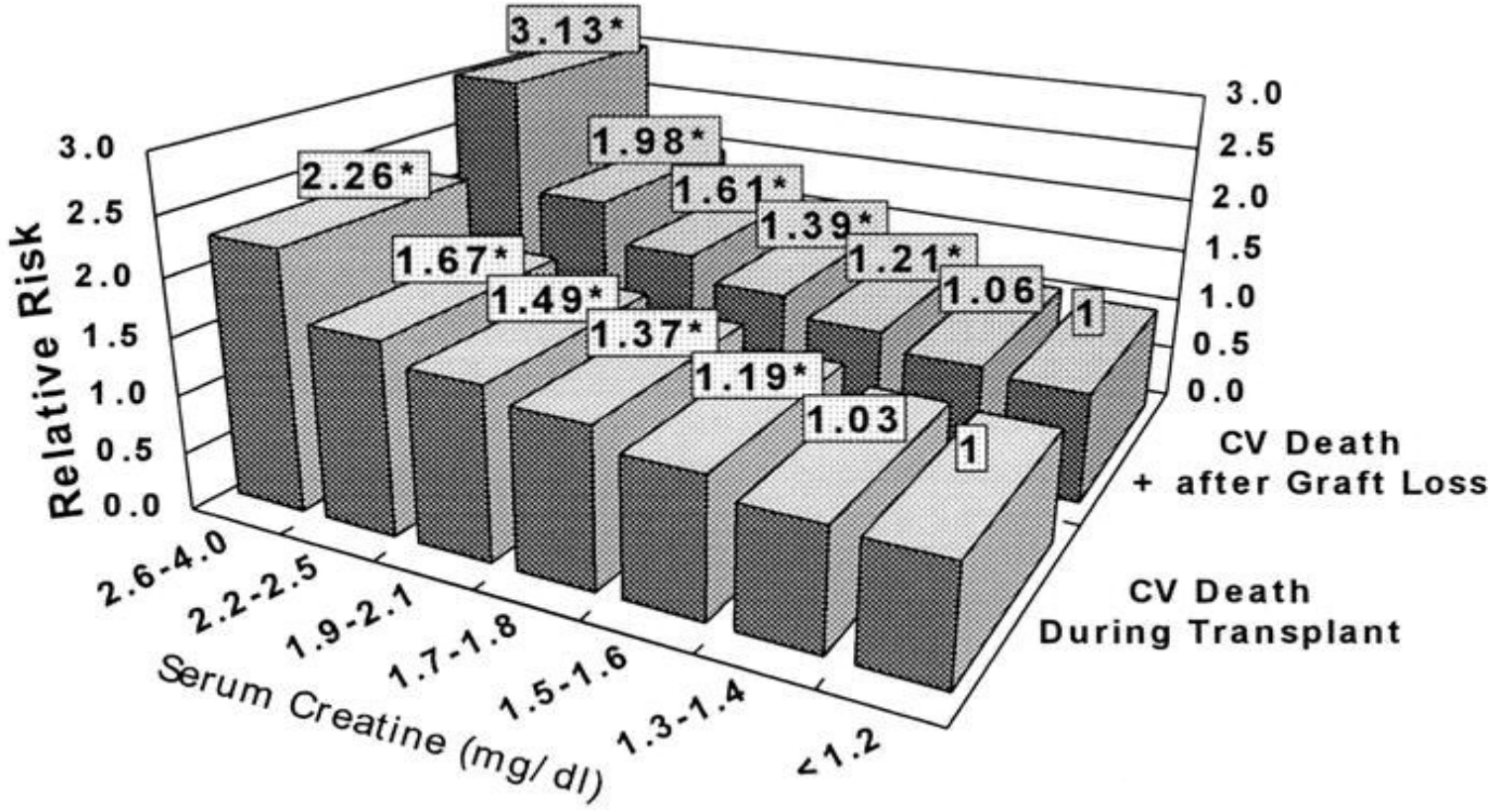
Soveri et al., NDT 2006;21:2282-6



One Year Ct Predicts CV Death



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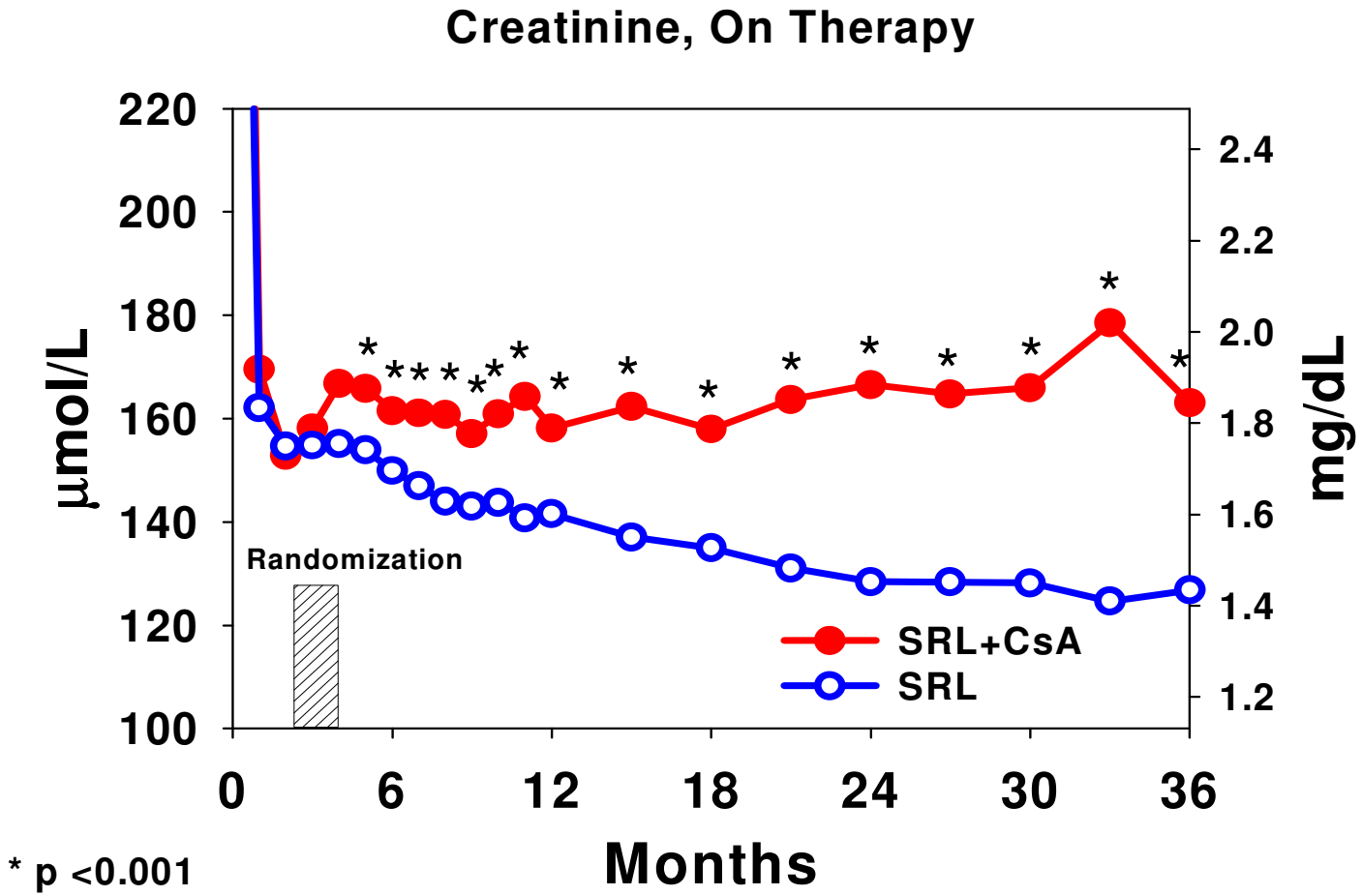
Renal Function RMR study



Improved CV risk profile after randomised conversion from CsA to Tac

Se Ct fell from 137 to 131 umol/L (P<0.01)

Mean BP fell from 104 to 99 mmHg (P<0.001)

LDL decreased from 3.48 to 3.11 mmol/L

TG reduced – 2.11 vs., 1.72 mmol/L (P<0.001)

Oxidation of LDL reduced

Transient rise in blood sugar

Artz et al.,J. Am. Soc. Nephrol. 14:1880-1888, 2003

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The SYMPHONY Study

	N	GFR (12 mo)	GFR (12 mo)	BPAR (6 / 12 mo)	Graft survival (12 mo)	Patient survival (12 mo)
	(ITT)	median [ml/min]	mean ± SD [ml/min]	[%]	[%]	[%]
Normal-dose CsA	385	56.8	56.2 ± 25.9	23.5 / 25.3	90.0	96.5
Low-dose CsA	399	60.9	58.9 ± 25.7	21.4 / 23.5	93.1	98.2
Low-dose TAC	402	65.4	64.5 ± 27.9	11.2 / 12.3	94.2	97.2
Low-dose SRL	399	57.3	55.9 ± 27.5	33.3 / 35.3	89.2	96.8

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American Journal of Transplantation 2011; 11: 66–76
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doi: 10.1111/j.1600-6143.2010.03338.x

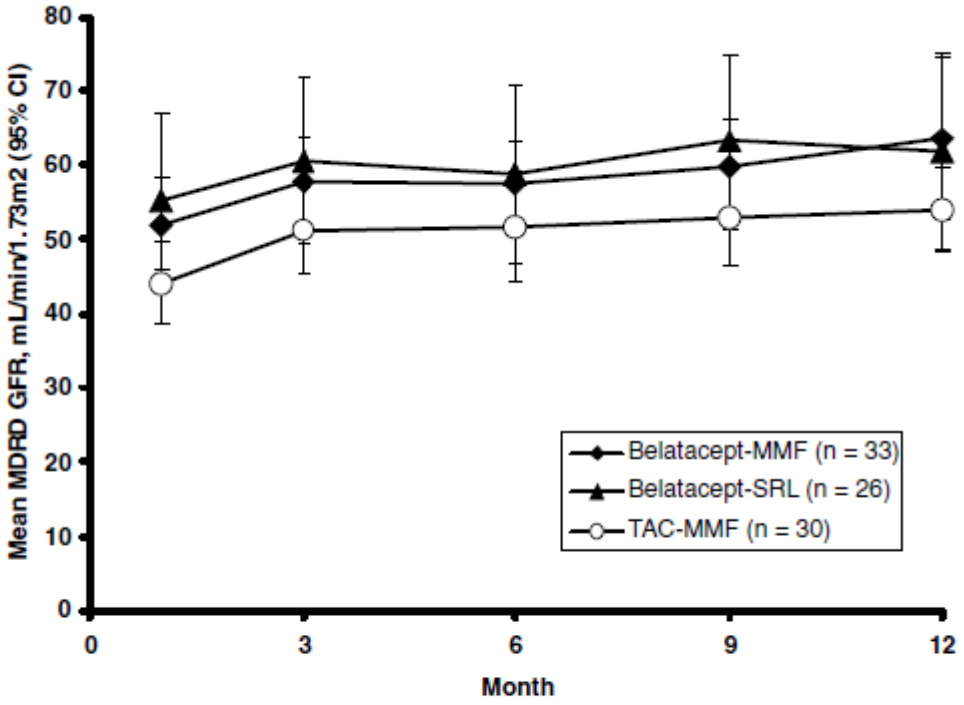
Immunosuppression with Belatacept-Based, Corticosteroid-Avoiding Regimens in *De Novo* Kidney Transplant Recipients

R. Ferguson[a,*,†], J. Grinyó[b,†], F. Vincenti[c], D. B. Kaufman[d], E. S. Woodle[e], B. A. Marder[f], F. Citterio[g], W. H. Marks[h], M. Agarwal[i], D. Wu[i], Y. Dong[i] and P. Garg[i]

ceptable rates of acute rejection and improved renal function relative to a TAC-based regimen.

Key words: Belatacept, calcineurin inhibitor, corticosteroid, immunosuppression, renal transplantation

Belatacept – Renal Function



Belatacept-MMF, n	33	29	29	26	27
Belatacept-SRL, n	26	24	24	21	23
TAC-MMF, n	29	27	25	24	29

Ferguson et al., Am J Transpl 2011;11:66-76

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NODAT

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Post-Transplant Diabetes Mellitus / PTDM

New Onset Diabetes After Tx/ NODAT

- Incidence
- Impact on patient outcomes
- Impact on graft outcomes

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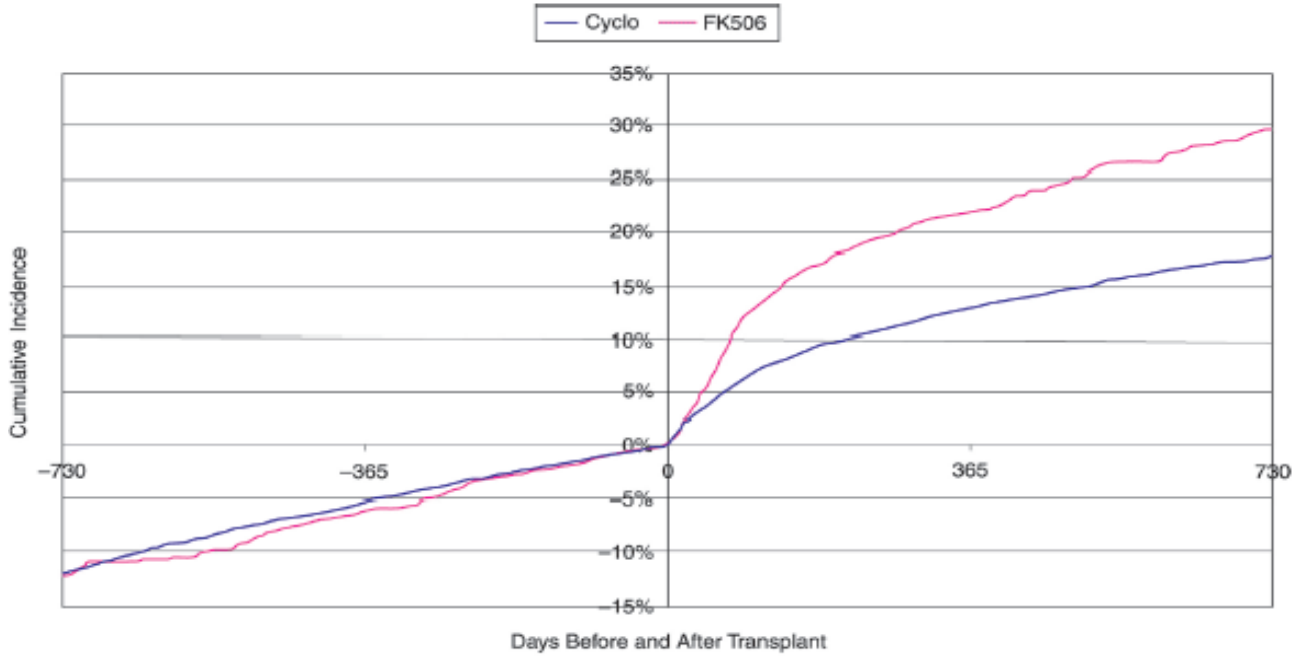
NODAT



Sample Size		Days Before Transplant			Days After Transplant		
		-730	-365	-1	1	365	730
Type of Calcineurin Inhibitor	Cyclosporine	1776	3954	5867	6014	5521	2551
	Tacrolimus	471	911	1260	929	835	302

Woodward et al., 2003 Am. J. Tx 2003;3:590-8

Incidence of NODAT

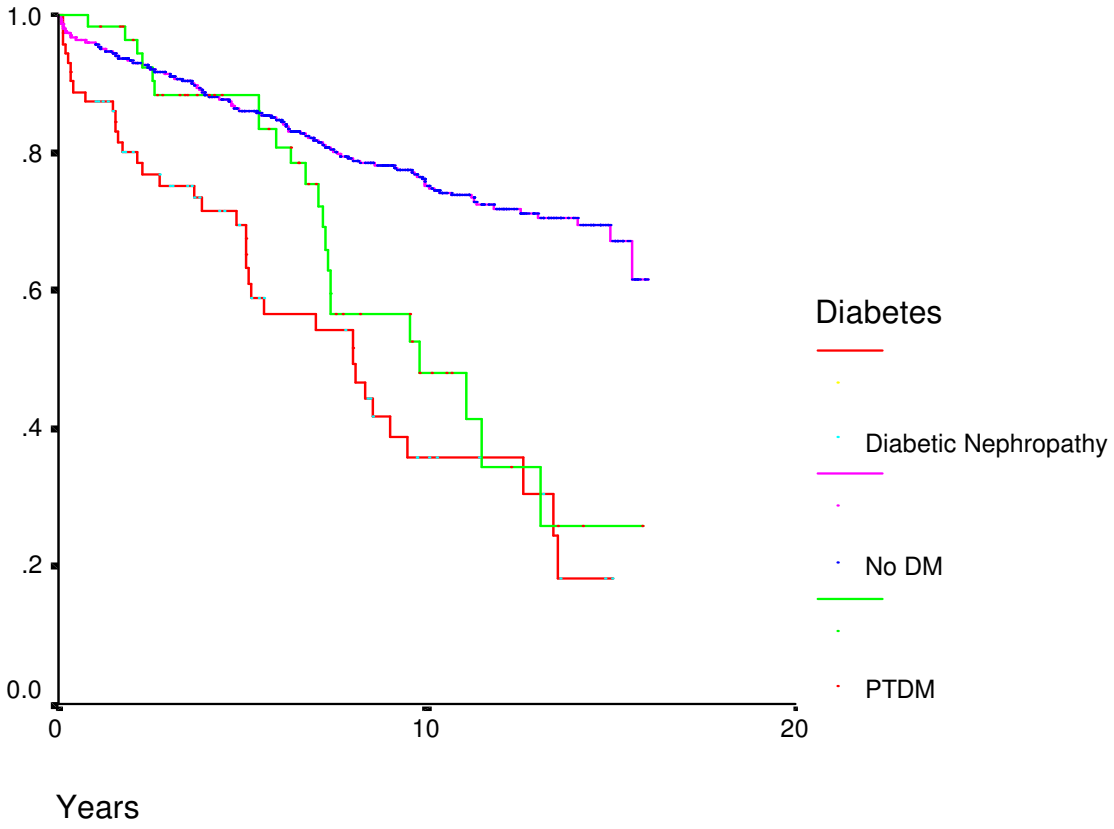
Montori et al., 2002
Systematic Review of 19 studies: 12 month cumulative incidence 1.8-21.7% of RTR

Woodward et al., 2003 Am. J Tx 3:590-598.
RTR - 13.2-14.9% at 1 year

Kasiske et al., 2003 Am J Tx 3:178-185.
11,659 RTR – 16%/6 months, 24%/3 years

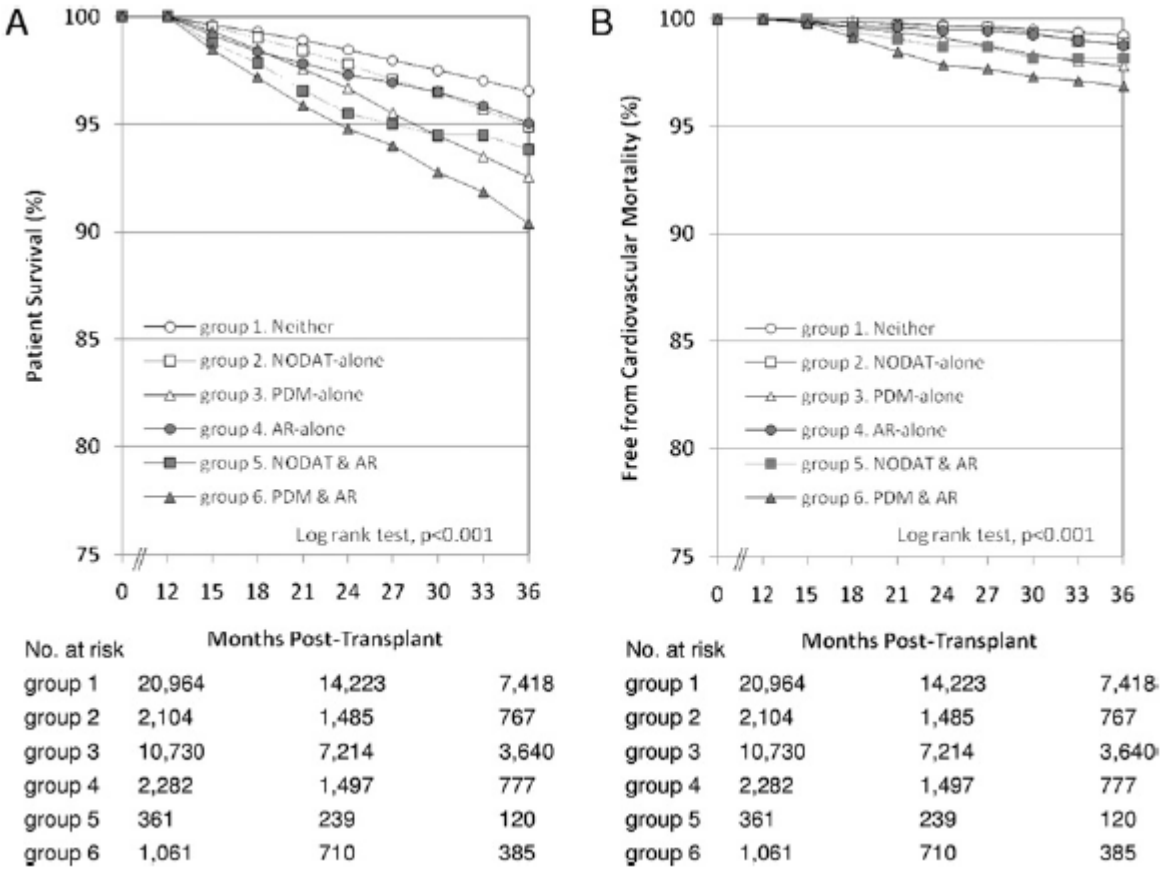
Heisel et al., 2004 Am. J. Tx 4:583-595.
Meta-analysis of 56 trials of CNI in ALL transplants
Overall 13.4%; 10.4% Tac vs., 4.5%.

NODAT and patient survival



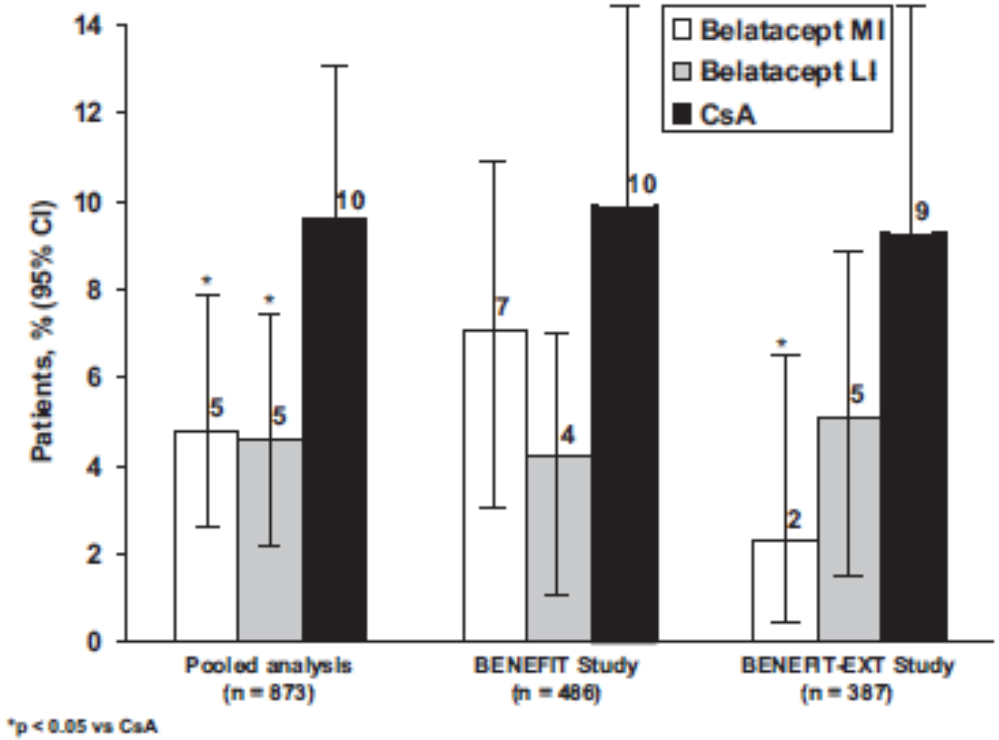
Revanur et al., Clin. Transplantation 2001; 15:89-94

UNOS NODAT survival



Kuo et al., AJKD 2010;56:1127-39

Belatacept - NODAT



Vanrenterghem et al., Transplantation 2011 (ePub)

NODAT and patient survival

Kasiske et al., 2003 Am J Tx 3:178-185.
11,659 RTR – HR for death 1.87

Gill et al., 2004 Am. J. Tx 4:583-595.
USRDS registry - RTR
All cause mortality increased; HR 1.76

Fernandez-Fresnedo et al.,2003.
10 year RTR survival reduced – 69% vs., 83%

Valantine et al., 2001
Heart Tx 8 year survival reduced – 63% vs., 95%

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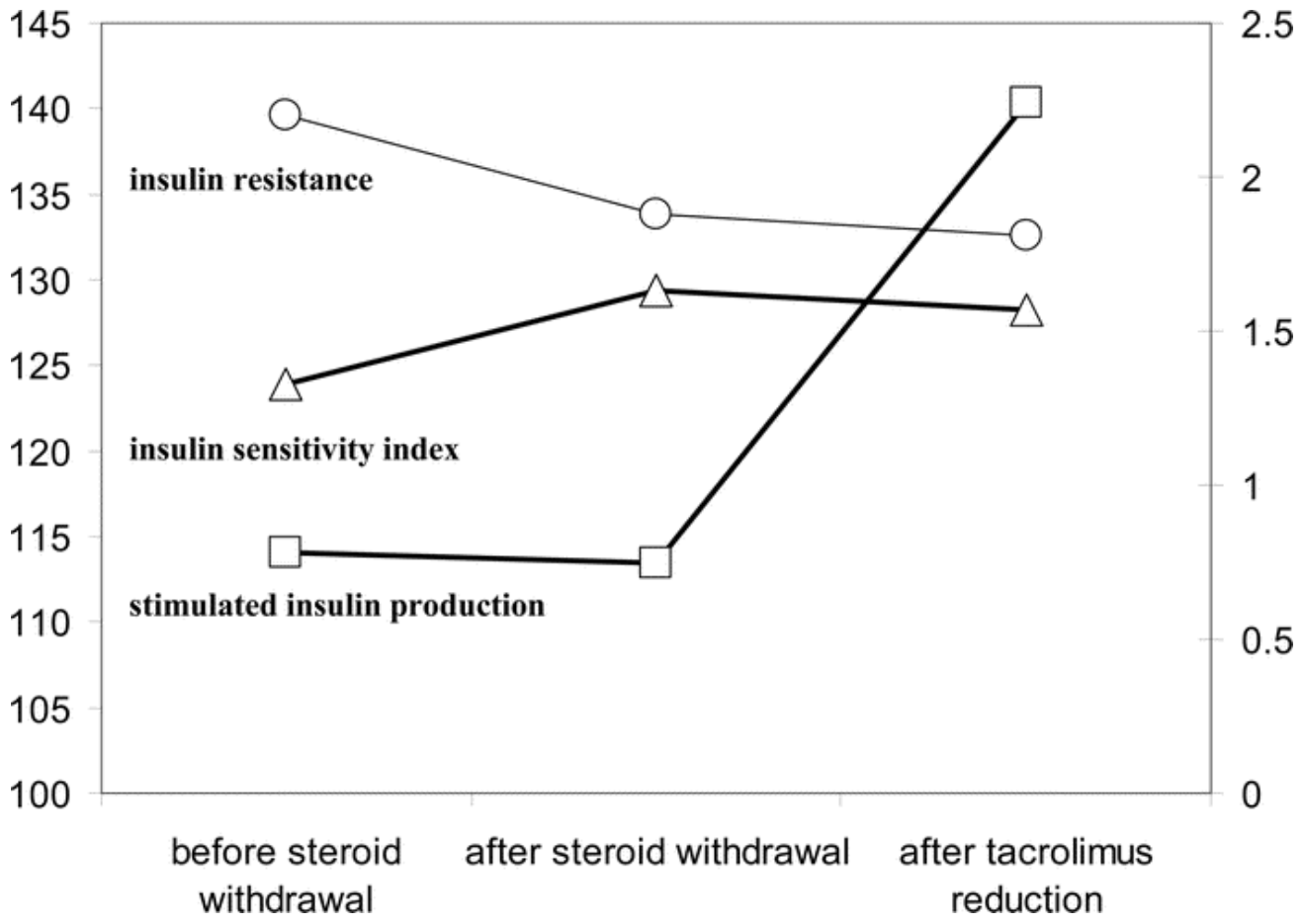
NODAT



Van Hooff et al.,Transplantation. 2005 (June)79:1465-69

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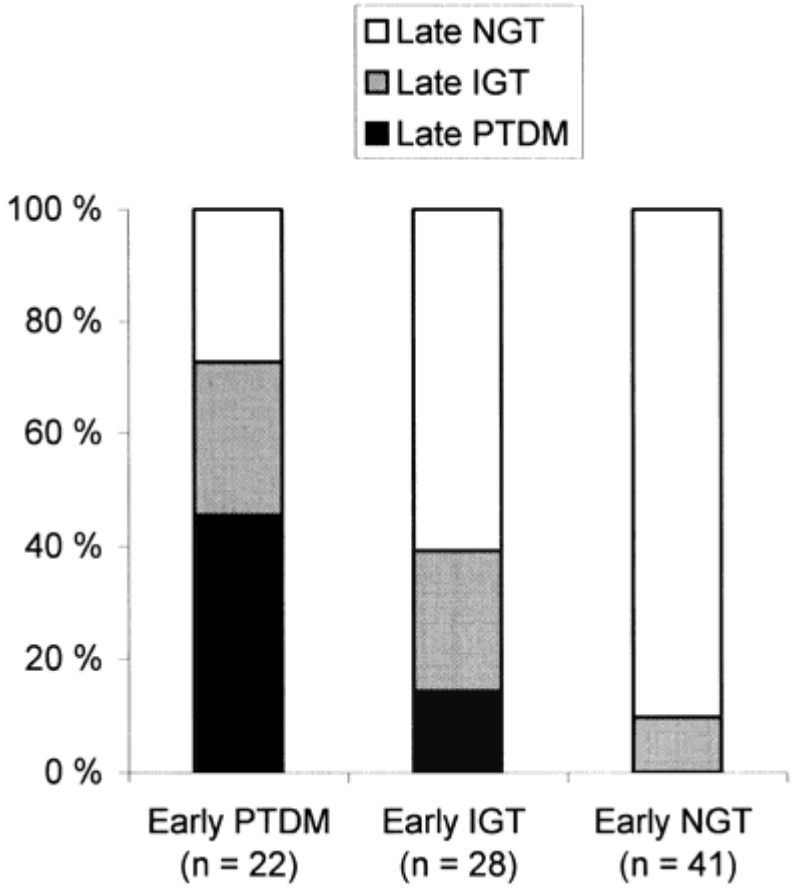
Hjelmesaeth et al., NDT 2001; 16:829-835



The CARMEN study – Steroid free

6 month trial; 538 patients randomised to:

Dac, Tac, MMF vs., Tac, MMF, Pred

AR 16.5% in both groups

Mean Ct. (125 vs., 131)

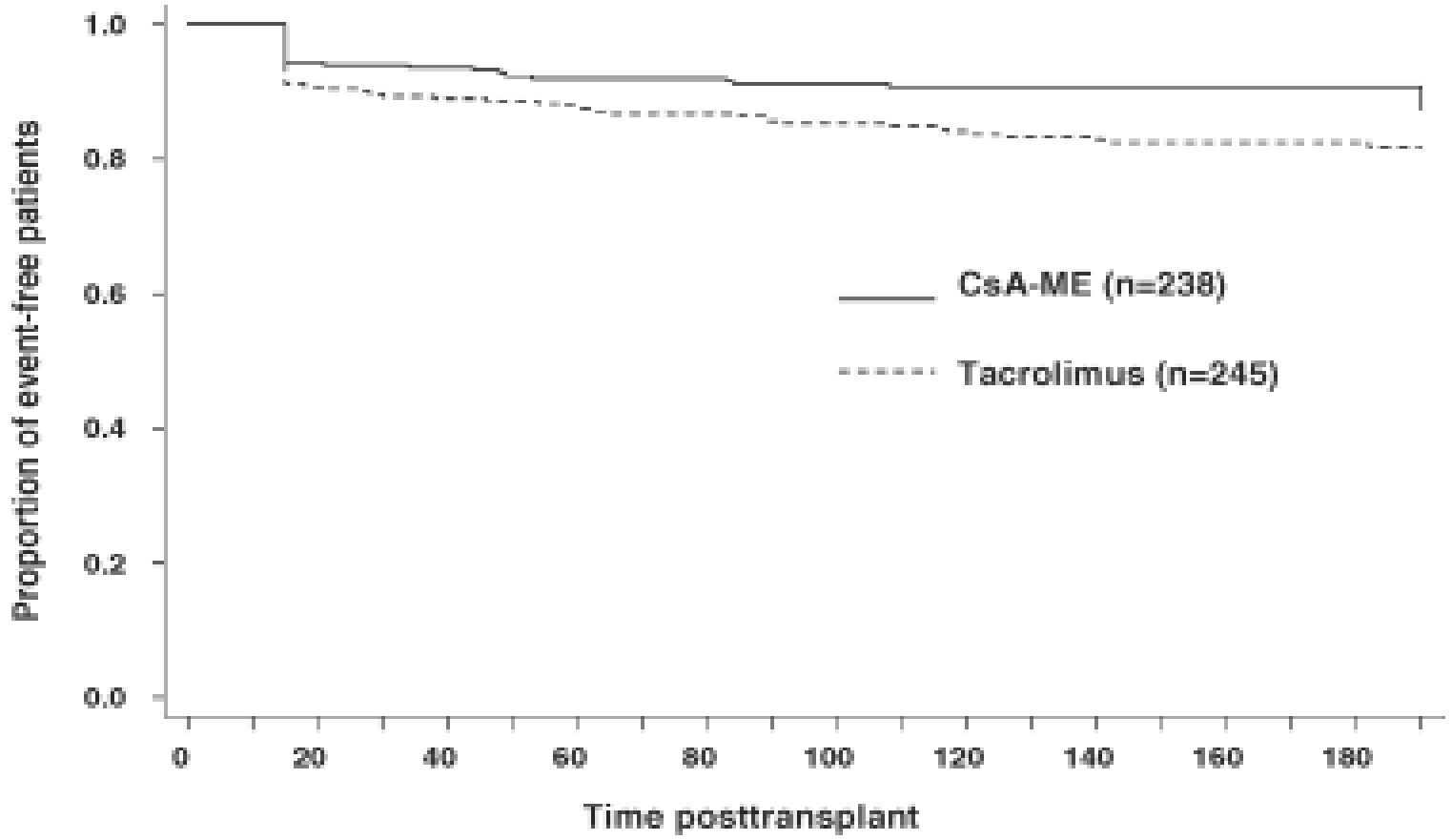
TC increased by 0.19 vs., decreased by 0.19 mmol/L

Reduced NODAT (5.4% vs., 0.4%)

Reduced hyperglycaemia (13.1 vs., 15.8%)

Rostaing et al., Transplantation 2005; 79:807-814.

The Direct Study



Vincenti et al., Am J Transplant 2007;7:1-9

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Steroid Withdrawal

No Steroid META-ANALYSIS

Steroid Avoidance or Withdrawal After Renal Transplantation Increases the Risk of Acute Rejection but Decreases Cardiovascular Risk. A Meta-Analysis

Simon R. Knight[1,2] *and Peter J. Morris*[1,3]

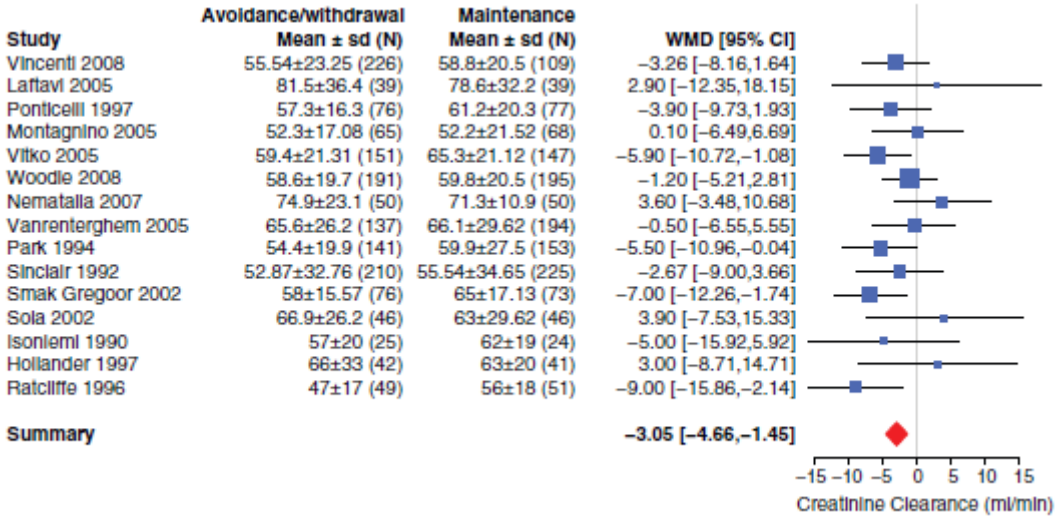
Rejection HR 1.56 (1.31-1.87) P<0.0001

Survival HR 0.82 (0.61-1.11) P=0.02

Knight and Morris Transplantation 2010;89:1-14

No Steroid META-ANALYSIS

Creatinine Clearance



Knight and Morris Transplantation 2010;89:1-14

No Steroid META-ANALYSIS

CV Risk Factors

Outcome	Studies reporting outcome		Meta-analysis				
	Studies	Patients	Type	Relative risk	95% CI	*P*	I^2 (%)
All studies							
Hypertension	15	2,833	Fixed	0.90	0.85–0.94	<0.0001	16.2
Hypercholesterolemia	13	2,283	Random	0.76	0.67–0.87	<0.0001	47.8
New-onset diabetes	16	2,849	Fixed	0.64	0.50–0.83	0.0006	22.3
Intention-to-treat analysis only							
Hypertension	9	2,173	Fixed	0.92	0.86–0.97	0.005	10.5
Hypercholesterolemia	9	2,055	Random	0.80	0.70–0.90	0.0005	48.9
New-onset diabetes	10	2,346	Fixed	0.74	0.56–0.96	0.02	11.0

CI, confidence interval; Random, random-effects analysis; Fixed, fixed-effects analysis; I^2, *I*-squared statistic (measure of heterogeneity, see text).

Knight and Morris Transplantation 2010;89:1-14

No Steroid META-ANALYSIS

Other Risk Factors

Outcome	Studies reporting outcome		Meta-analysis				
	Studies	Patients	Type	Relative risk	95% CI	*P*	I^2 (%)
Total infection	13	2,569	Random	0.90	0.79–1.03	0.13	39.1
CMV infection	11	3,109	Fixed	1.00	0.81–1.24	0.97	0
Malignancy	11	2,327	Fixed	0.93	0.64–1.34	0.69	0
Leucopenia	9	2,433	Fixed	1.66	1.42–1.93	<0.0001	0
Cataracts	6	936	Random	0.54	0.22–1.34	0.18	53.6

CI, confidence interval; Random, random-effects analysis; Fixed, fixed-effects analysis; I^2, *I*-squared statistic (measure of heterogeneity, see text).

Knight and Morris Transplantation 2010;89:1-14

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How are *we* doing?

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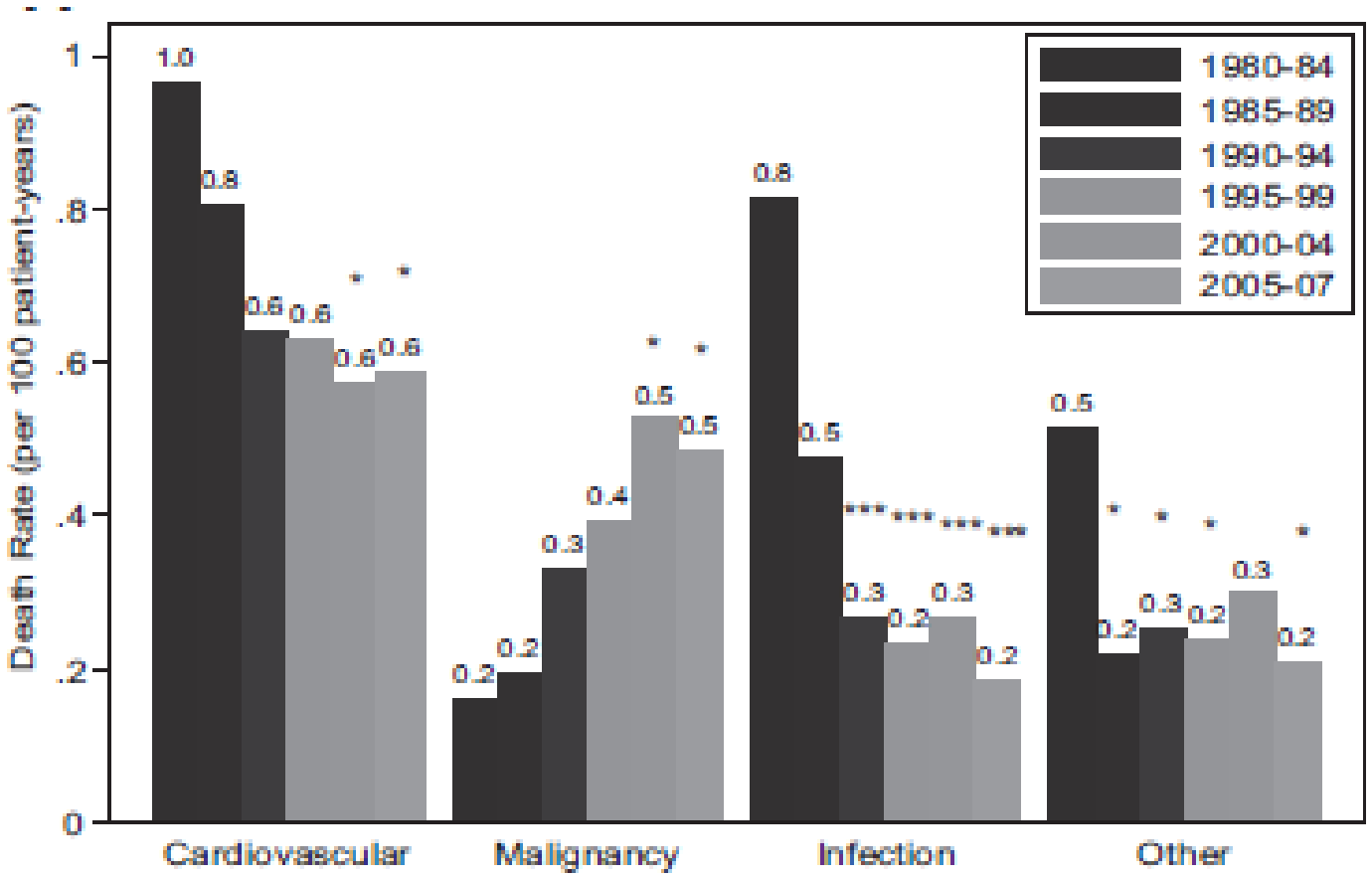
Reduction in Cardiovascular Death After Kidney Transplantation

Helen Pilmore,[1,4] Hannah Dent,[2] Sean Chang,[2] Stephen P. McDonald,[2] and Steven J. Chadban[2,3]



Pilmore et al., Transplantation 2010;89:851-857

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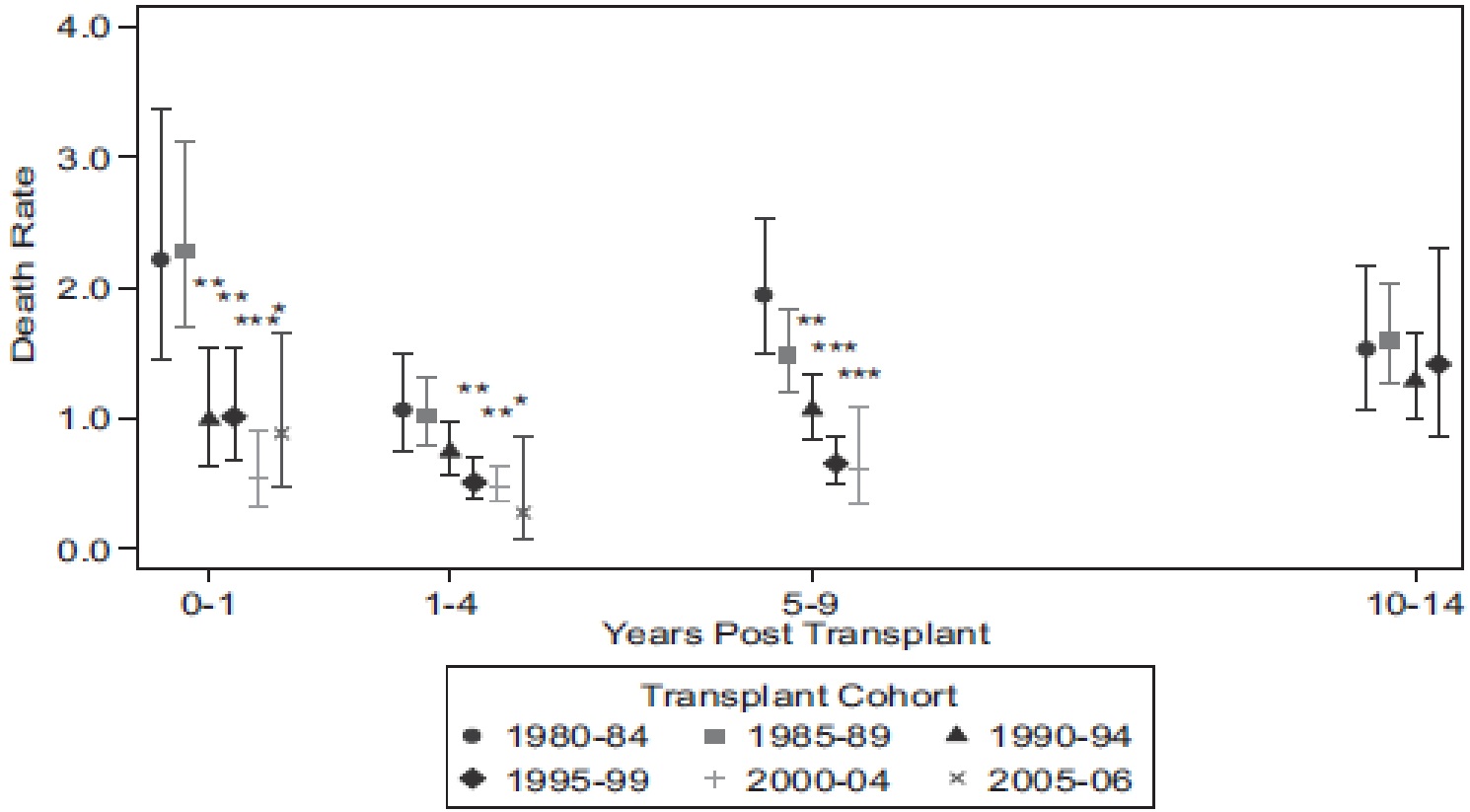

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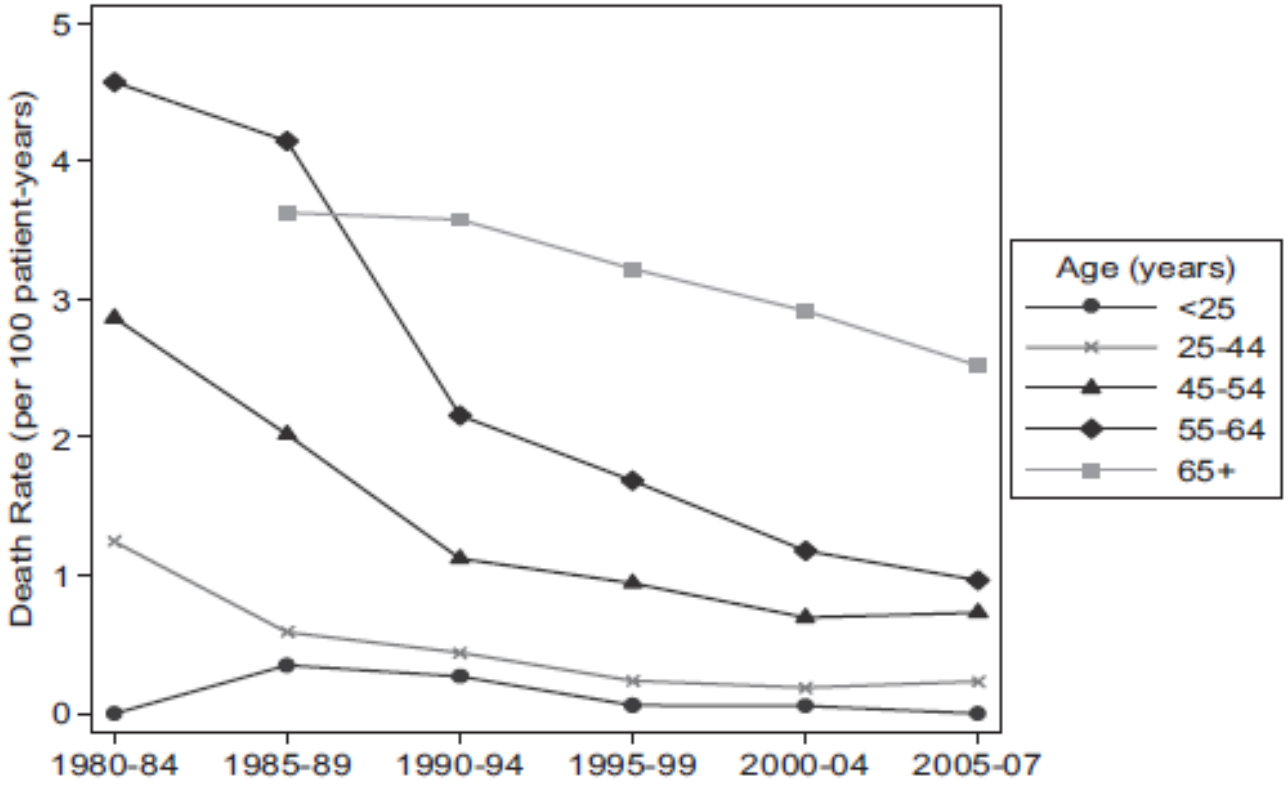

Pilmore et al., Transplantation 2010;89:851-857

Multivariate Analysis

Characteristic	Hazard ratio	95% CI	*P*
Age			
35–44	2.12	1.13–3.97	0.019
45–54	4.58	2.57–8.18	0.000
55–64	6.11	3.39–11.00	0.000
65+	8.76	4.39–17.47	0.000
Indigenous Australian	2.41	1.41–4.12	0.001
Primary kidney disease			
Vascular	1.94	1.16–3.26	0.012
DM	2.68	1.82–3.94	0.000
Previous CVS disease	2.09	1.55–2.82	0.000
Chronic lung disease	2.14	1.43–3.20	0.000
MDRD GFR, 48–<60 mL/min	0.66	0.45–0.95	0.024
Duration dialysis, >3 yr	1.54	1.03–2.30	0.035

DM, diabetes mellitus; CVS, cardiovascular; MDRD, Modification of Diet in Renal Disease; GFR, glomerular filtration rate.

Univariate Drugs

Tacrolimus	0.83	0.39–1.77	0.632
Cyclosporine	0.78	0.34–1.82	0.569
Mycophenolate	1.55	0.91–2.66	0.109
Azathioprine	1.62	0.94–2.79	0.079
Prednisolone	0.92	0.59–1.44	0.728

Pilmore et al., Transplantation 2010;89:851-857

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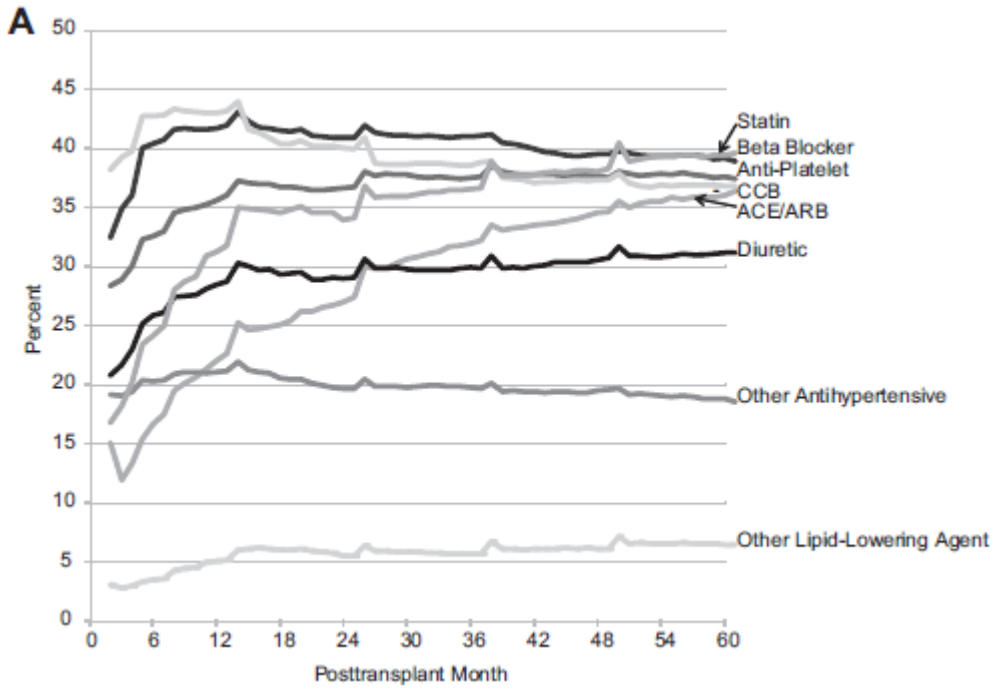
How are *we* doing?

How are we doing it?

The PORT study

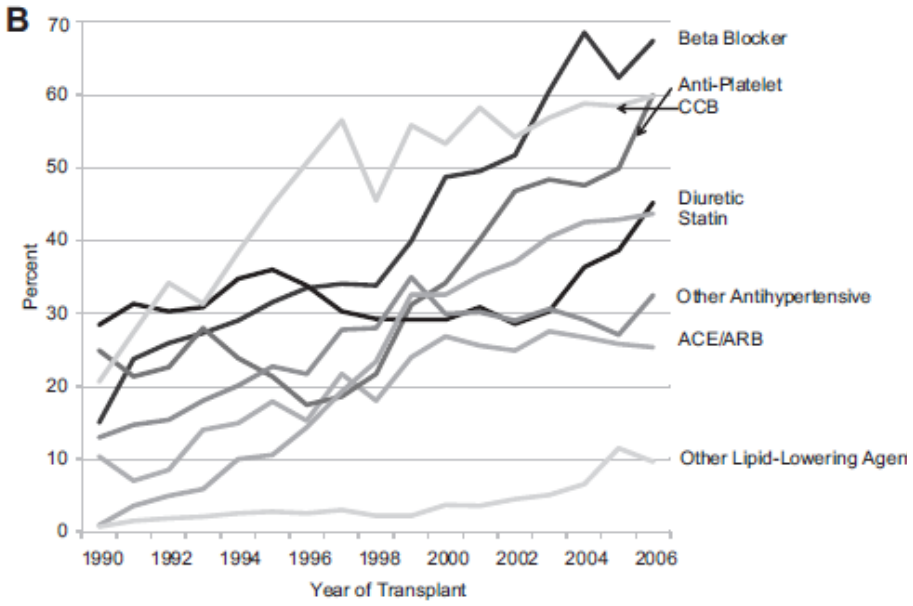
Cardiovascular Disease Medications After Renal Transplantation: Results From the Patient Outcomes in Renal Transplantation Study

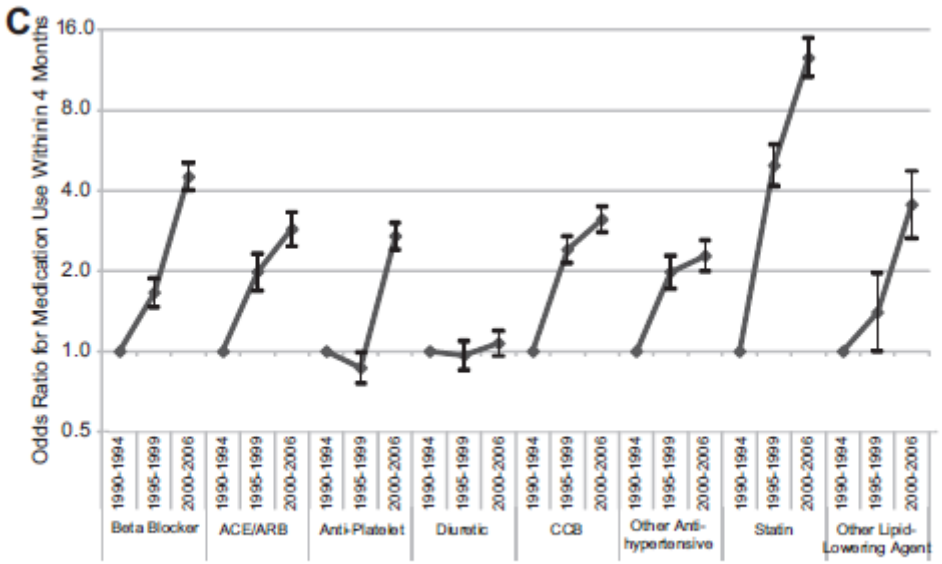
Helen L. Pilmore,[1,4] Melissa A. Skeans,[2] Jon J. Snyder,[2] Ajay K. Israni,[2,3] and Bertram L. Kasiske[2,3]



Pilmore et al., Transplantation 2011;91:542-551

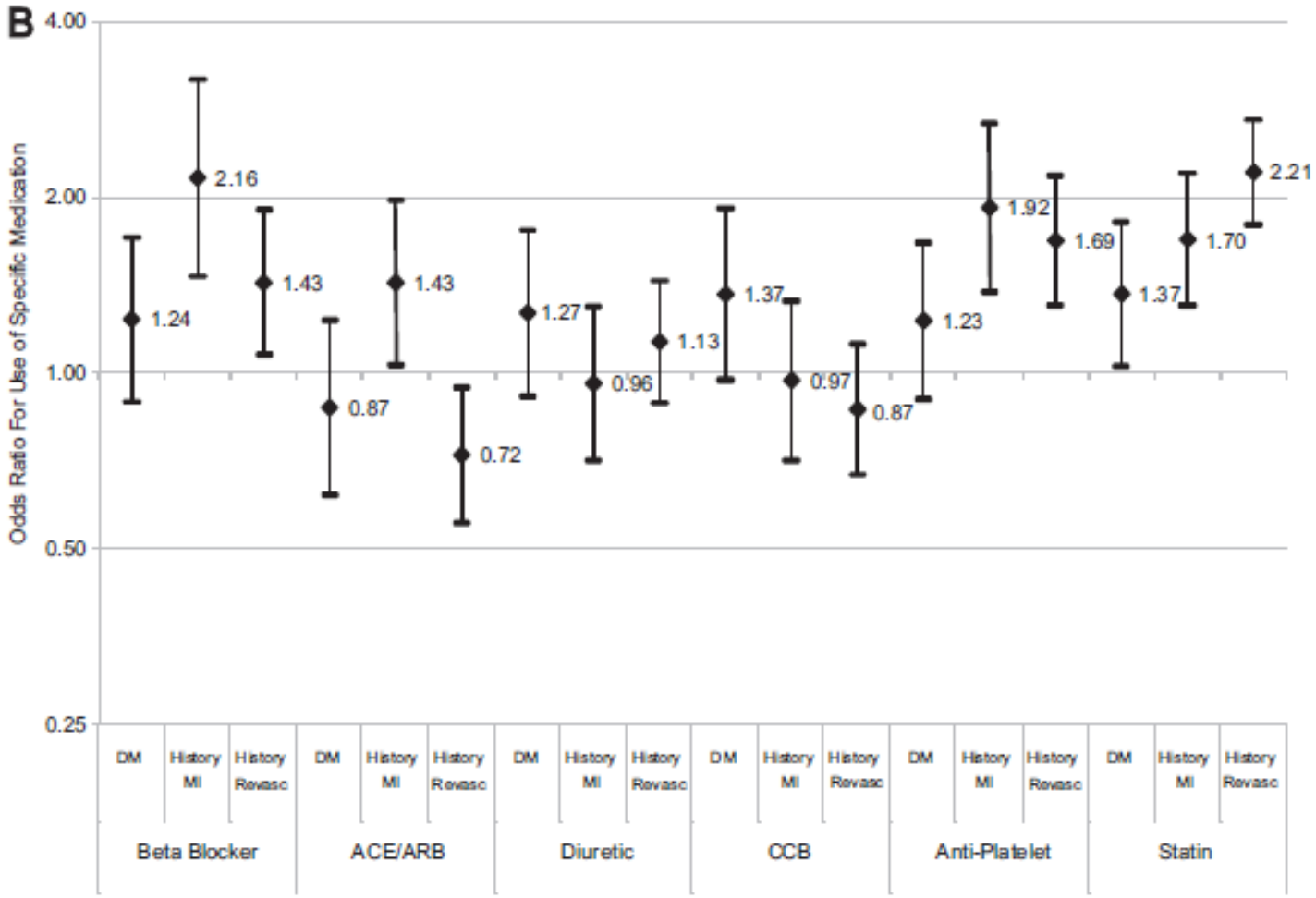
The PORT study





Pilmore et al., Transplantation 2011;91:542-551

The PORT study



Pilmore et al., Transplantation 2011;91:542-551

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What is the answer?

Do YOU reduce, stop or change immunosuppression to modify CV risk factors (Hypertension, Diabetes, Dyslipidaemia, Renal Dysfunction)?

NOT very often

Steroid withdrawal is the best studied approach

The most important CV risk factor is graft function

Better trials are needed

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Potential of emerging immunosuppressive strategies to improve the posttransplant cardiovascular risk profile

Arjang Djamali[1], Carolynn E. Pietrangeli[2], Robert D. Gordon[2] and Christophe Legendre[3]

[1]Department of Medicine, University of Wisconsin, Madison, Wisconsin, USA; [2]CTI Clinical Trial and Consulting Services, Cincinnati, Ohio, USA and [3]Hôpital Necker Paris, Paris, France

Djamali et al., Kidney Int 2010;78:S15-21