University of Glasgow

Cardiovascular Risk in Kidney Transplant Recipients

Alan Jardine

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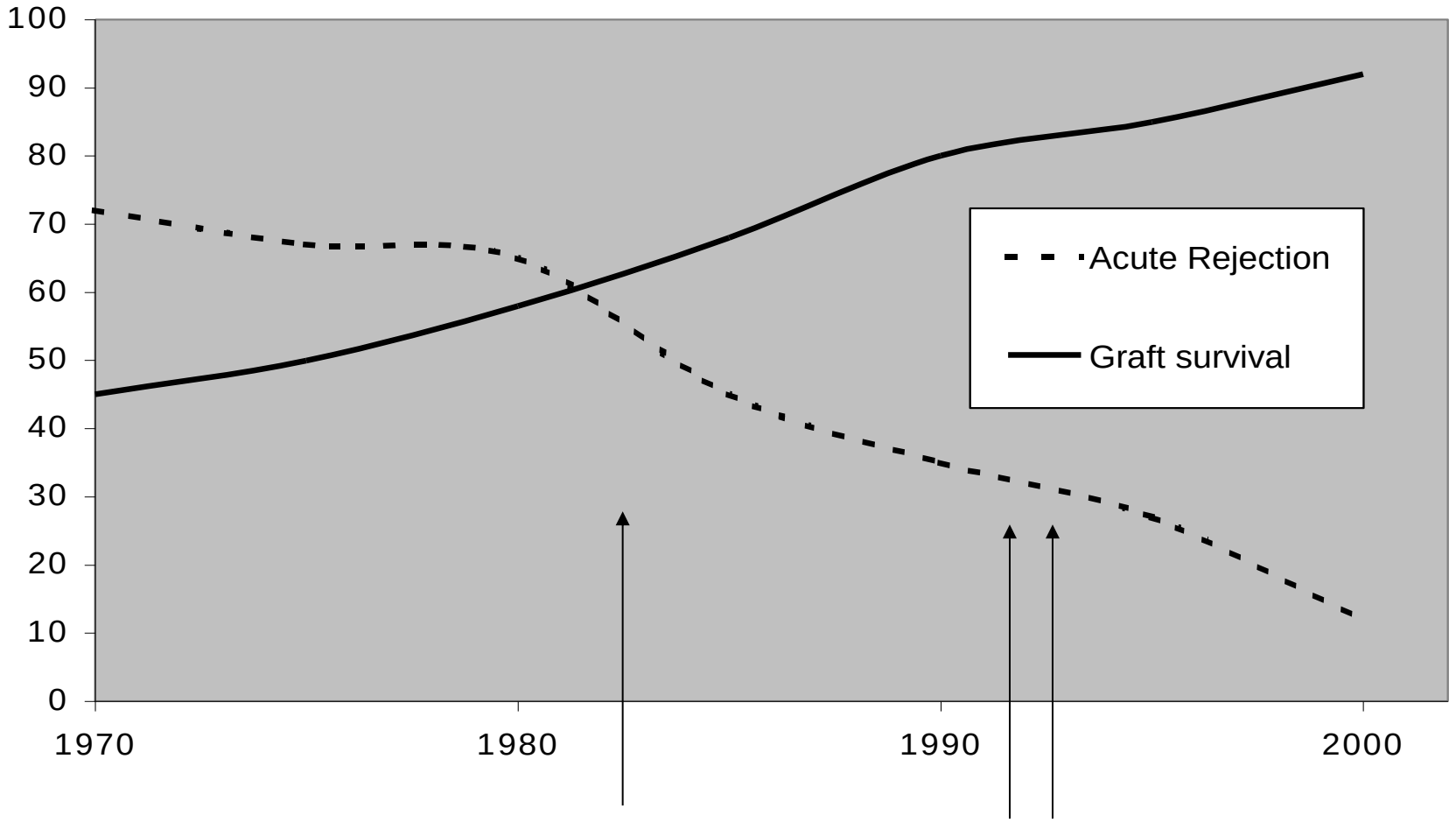
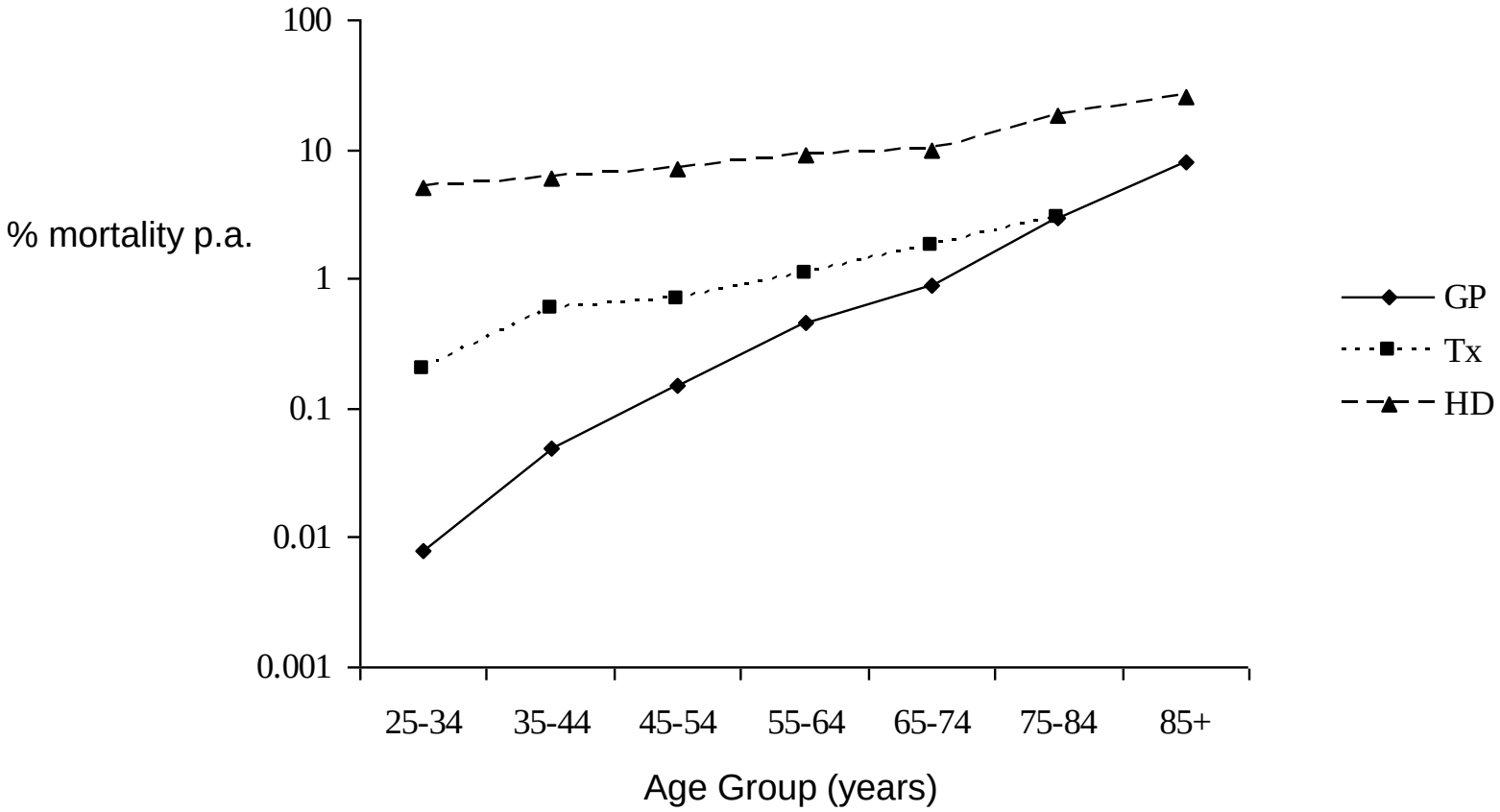


CsA Tac/MMF Srl Evl/Bela

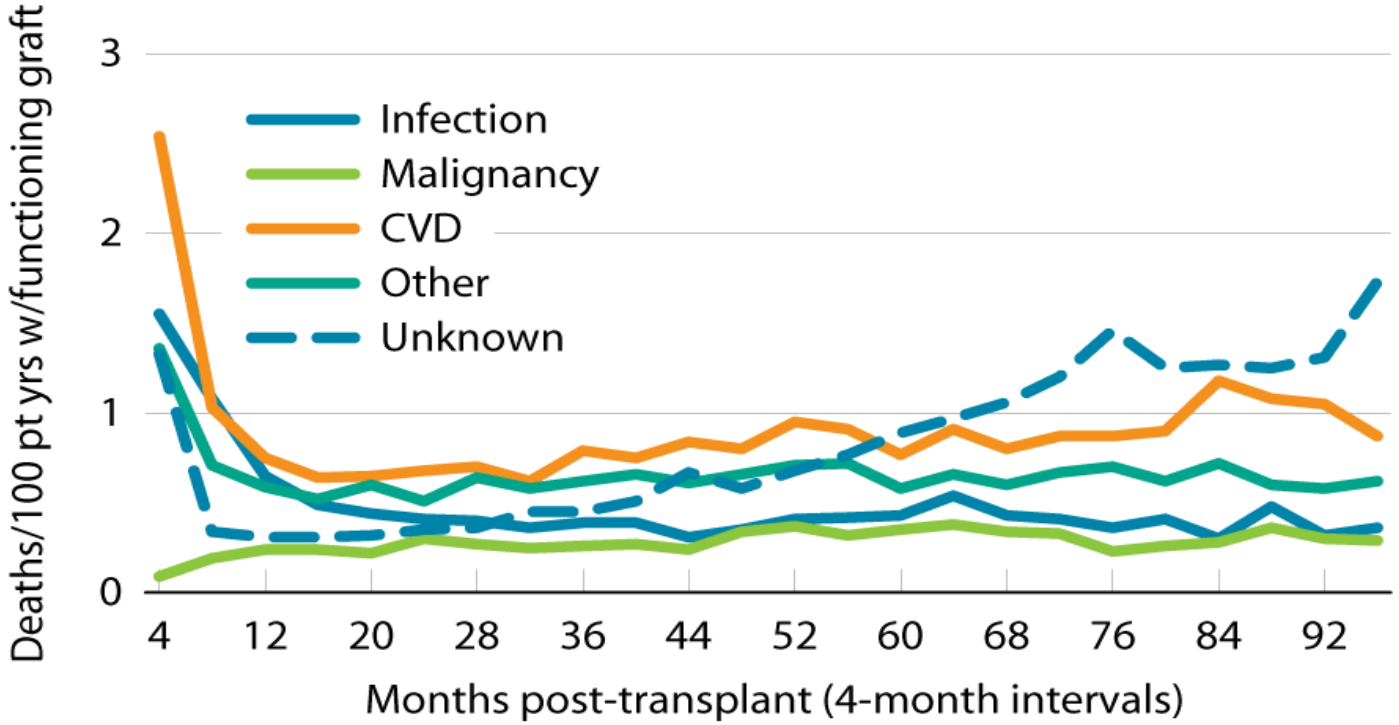
Renal Disease and CV risk



Modified from Foley et al.,

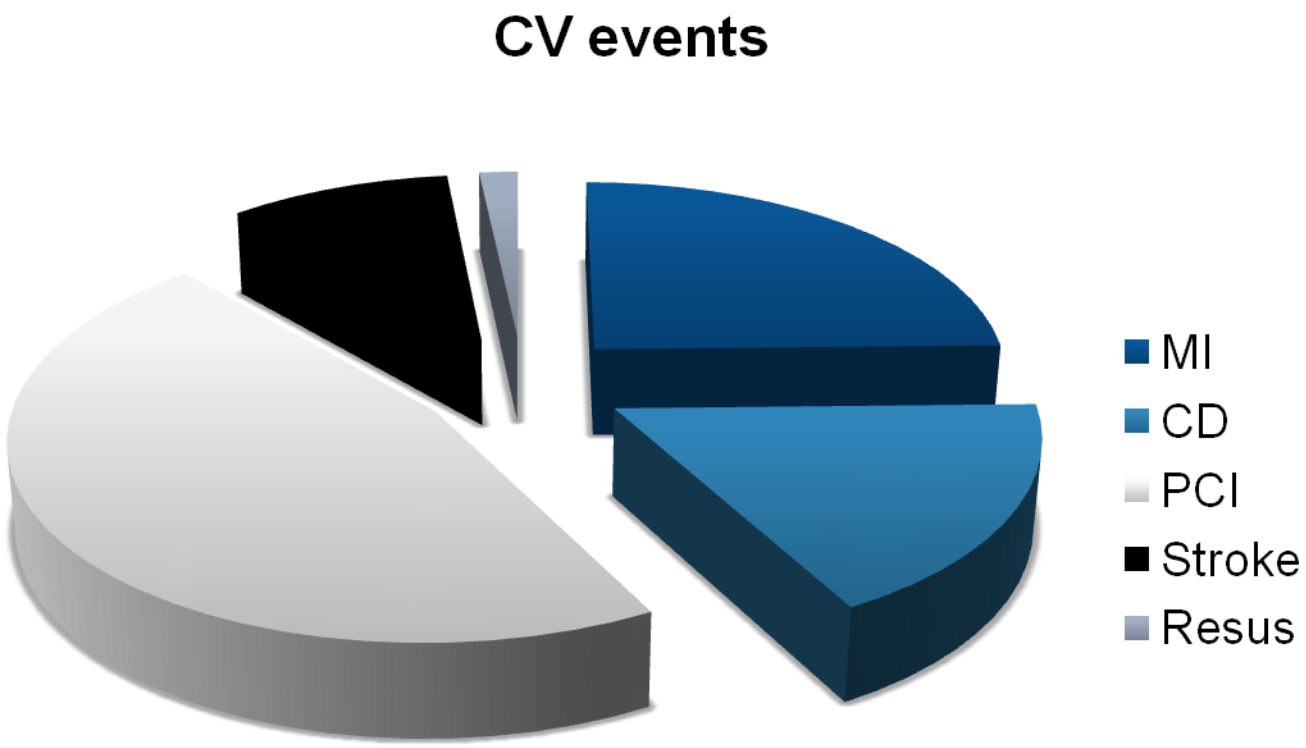
Cardiovascular Disease in Transplant Recipients

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.

The FAVORIT study



Weiner DE et al., Am J Transplant 2012;12:2437-45

Risk Factors for CVE

The FAVORIT study- CV risk

	RR	CI	P .
Age	1.13	(1.08,1.19)	<0.0001
Diabetes	2.30	(1.90,2.80)	<0.0001
Smoking (Current)	1.38	(1.05, 1.82)	0.07
CVD	2.06	(1.71,2.48)	<0.0001
LDL	1.01	(0.98,1.04)	0.41
SBP	1.17	(1.11,1.23)	<0.0001
DBP	0.89	(0.81,0.98)	0.02
BMI	0.91	(0.84, 0.98)	0.02
LD	0.84	(0.70, 1.01)	0.07

Weiner DE et al., Am J Transplant 2012;12:2437-45

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

Jardine AG et al., Am. J. Kid. Dis. 2005;46:529-536

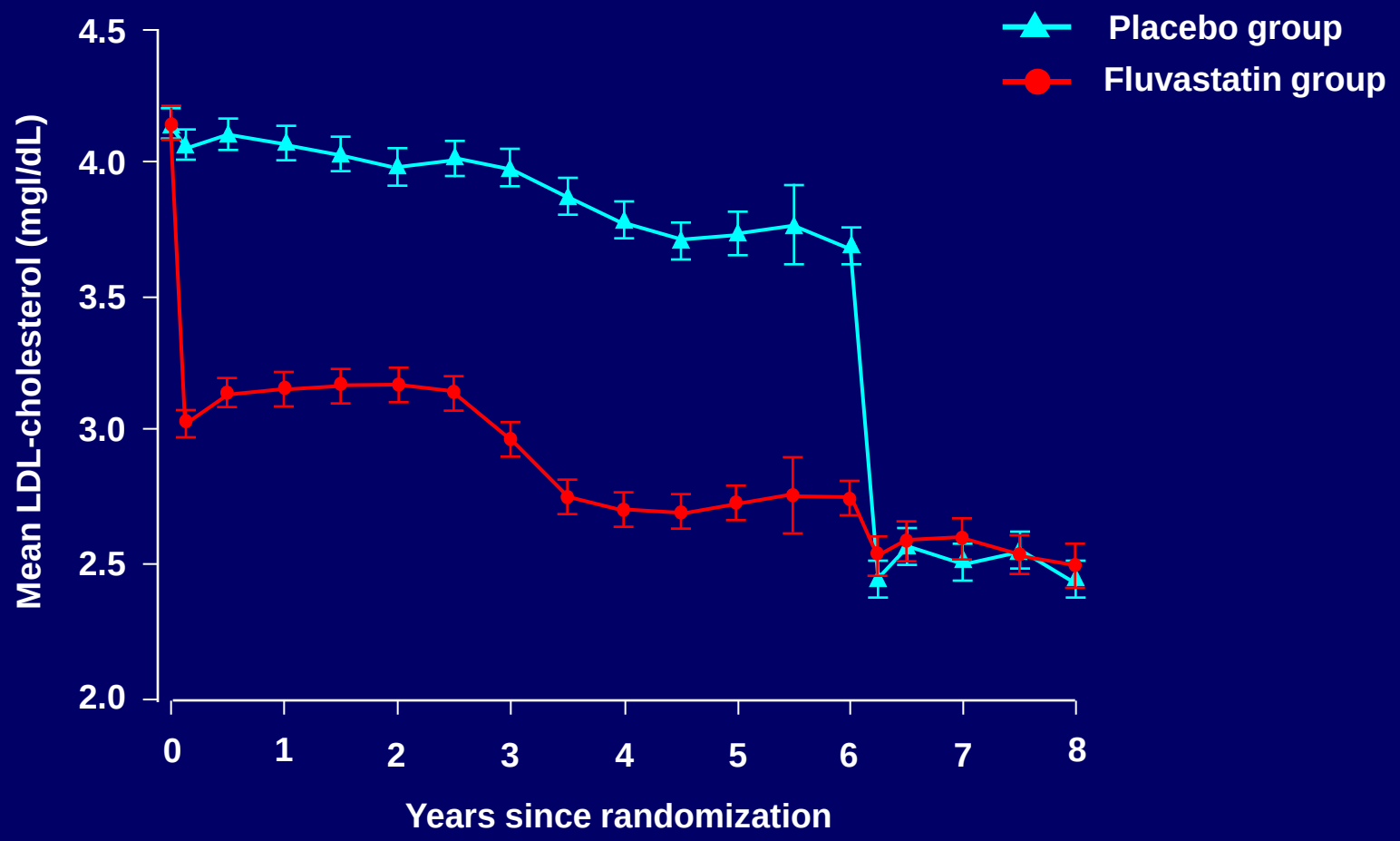
Effect of immunosuppressive agents on CV risk factors

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

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

Lipids

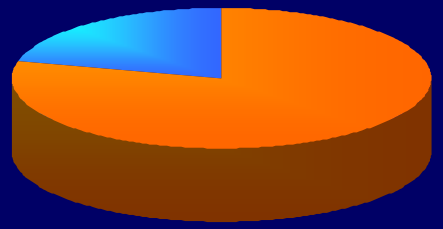
LDL-cholesterol



Attainment of cholesterol targets

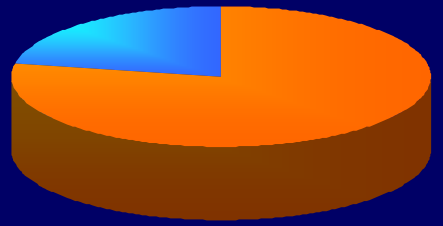
Attainment of targets at the end of the extension phase among patients receiving fluvastatin XL

Total cholesterol
Target <5.0mmol/L



79% below target*

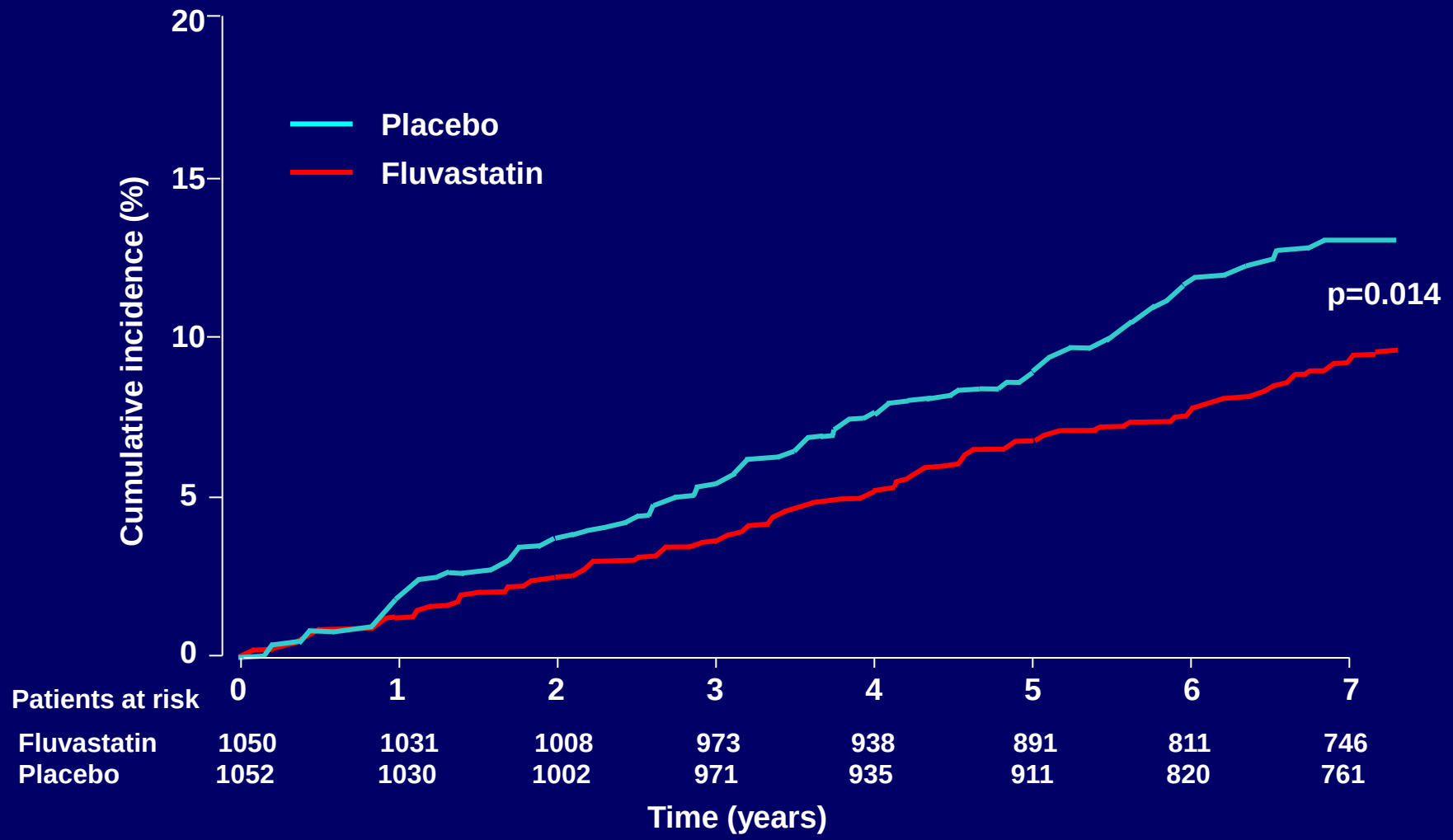
LDL-cholesterol
Target <2.6mmol/L



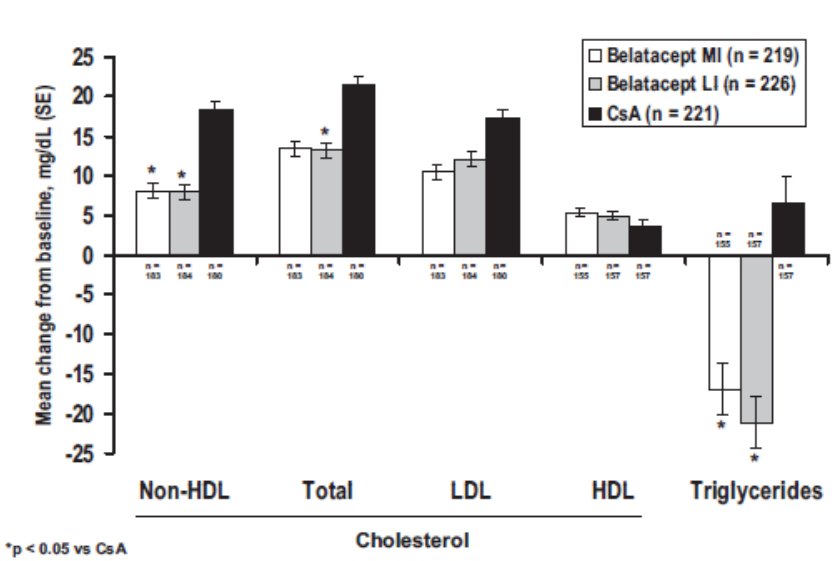
78% below target*

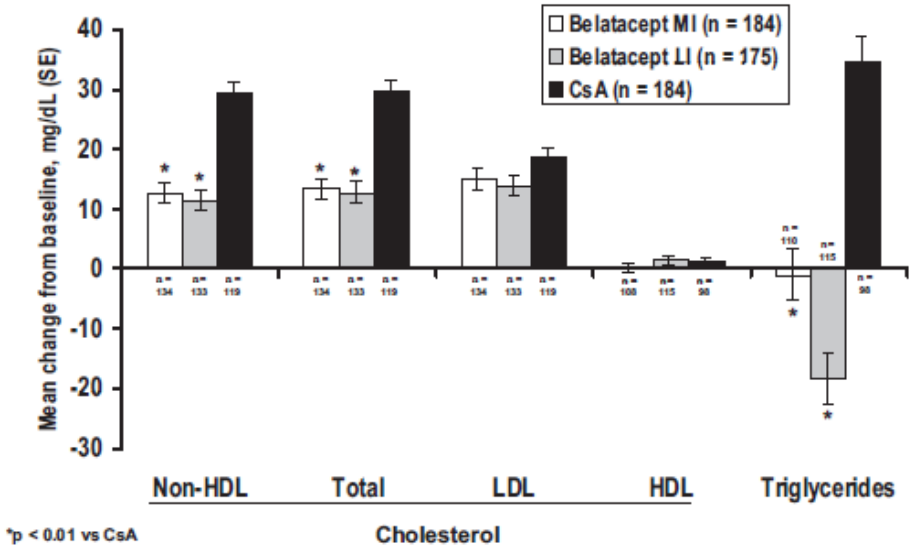
* On at least one occasion

Occurrence of cardiac death or definite non-fatal MI



Belatacept





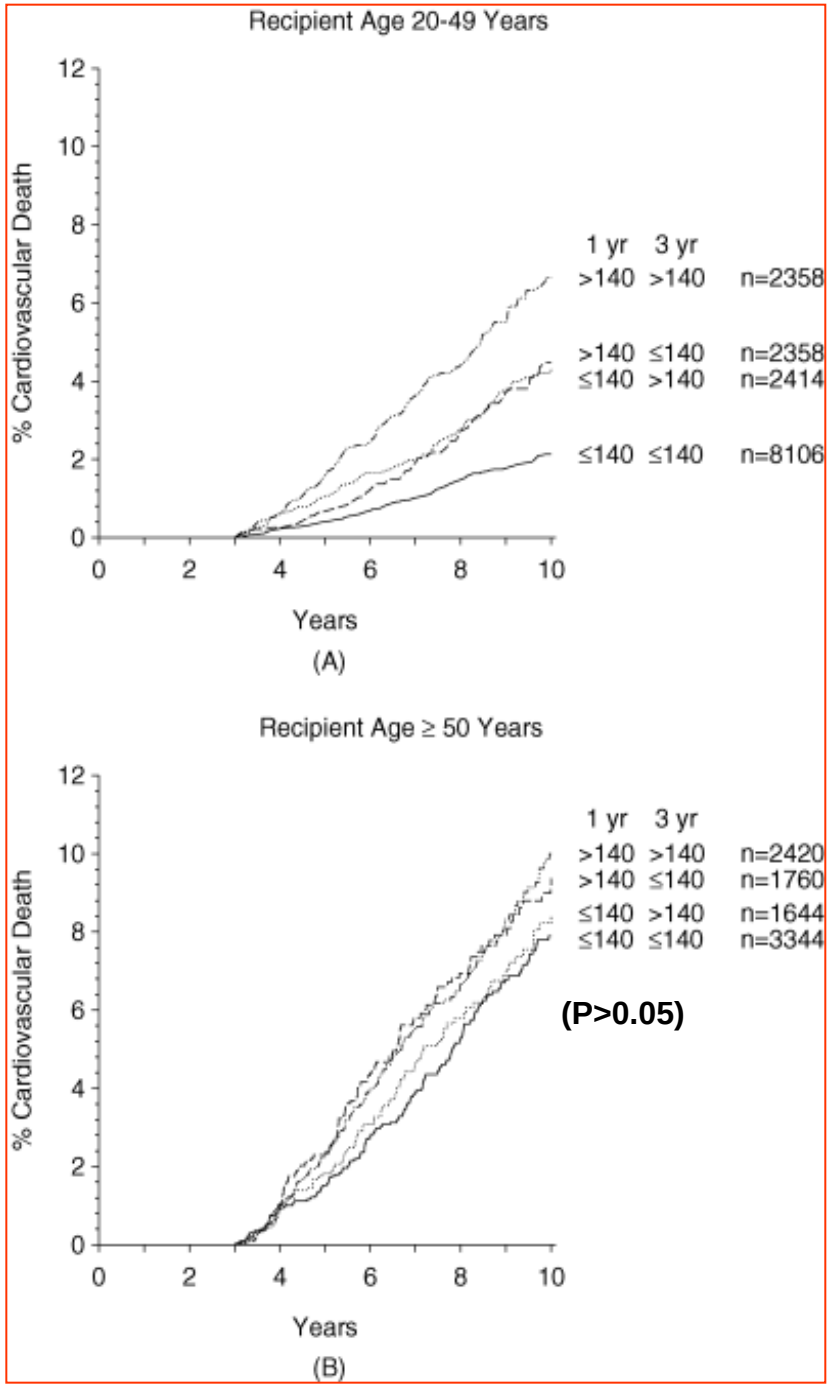
Vanrenterghem et al., Transplantation 2011 (ePub)

Hypertension

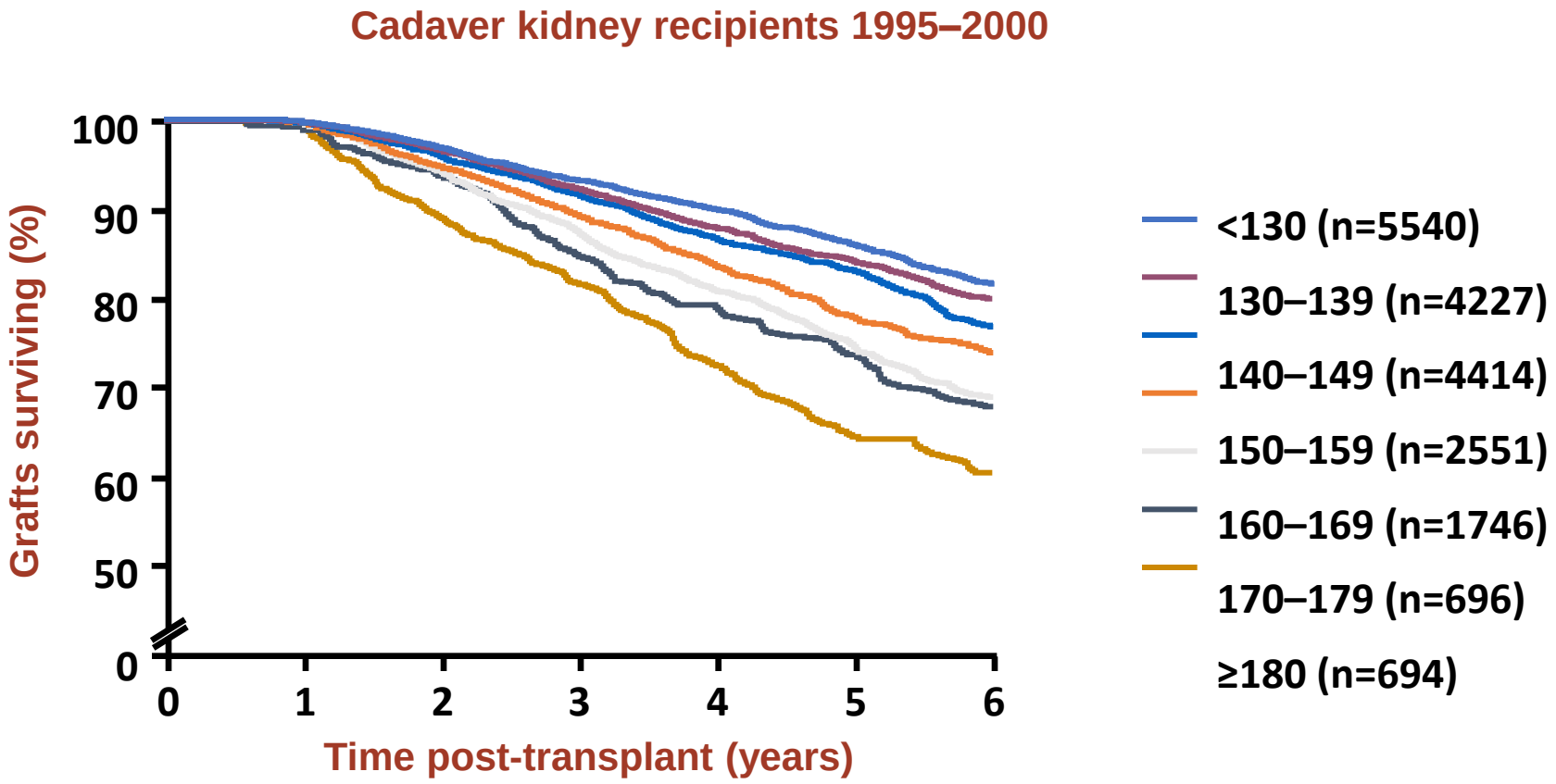
BP and Late CVD Mortality

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



Graft survival is related to 1-year systolic blood pressure



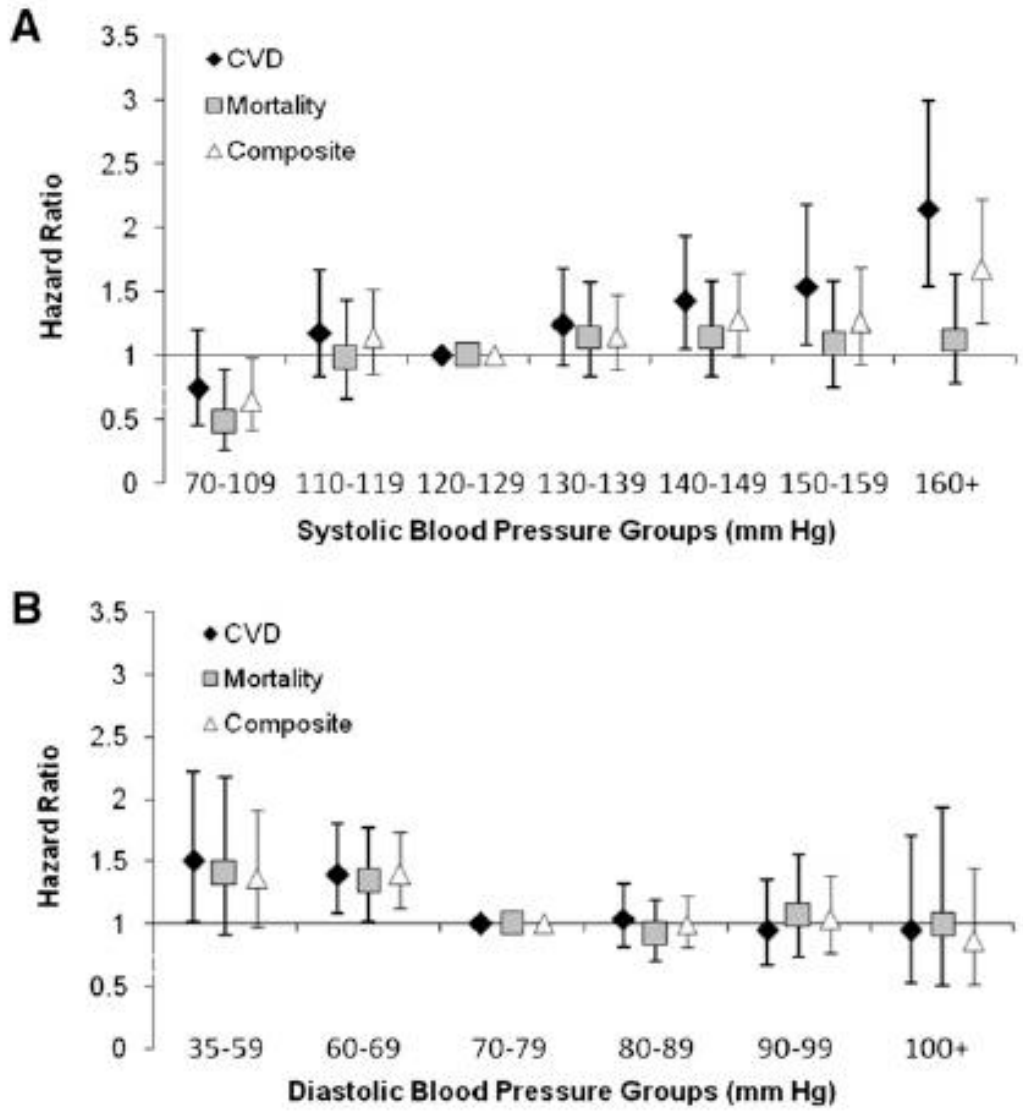
Opelz G *et al*. *Am J Transplant* 2005;5:2725–31

CLINICAL EPIDEMIOLOGY www.jasn.org

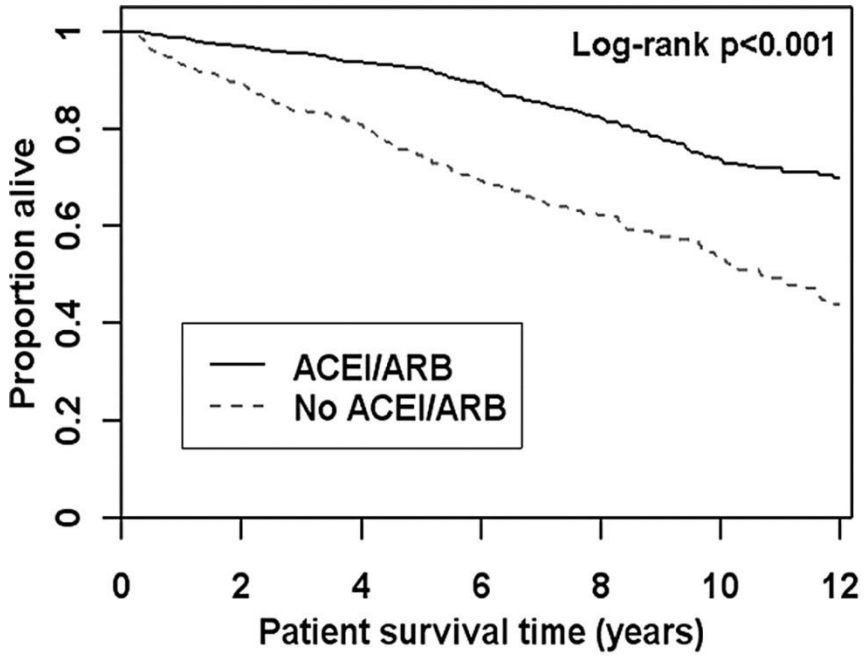
BP, Cardiovascular Disease, and Death in the Folic Acid for Vascular Outcome Reduction in Transplantation Trial

Myra A. Carpenter,* Alin John,† Matthew R. Weir,‡ Stephen R. Smith,§ Lawrence Hunsicker,‖ Bertram L. Kasiske,¶ John W. Kusek,** Andrew Bostom,†† Anastasia Ivanova,* Andrew S. Levey,† Scott Solomon,‡‡ Todd Pesavento,§§ and Daniel E. Weiner†

Carpenter et al., JASN 2014;12:2437-45

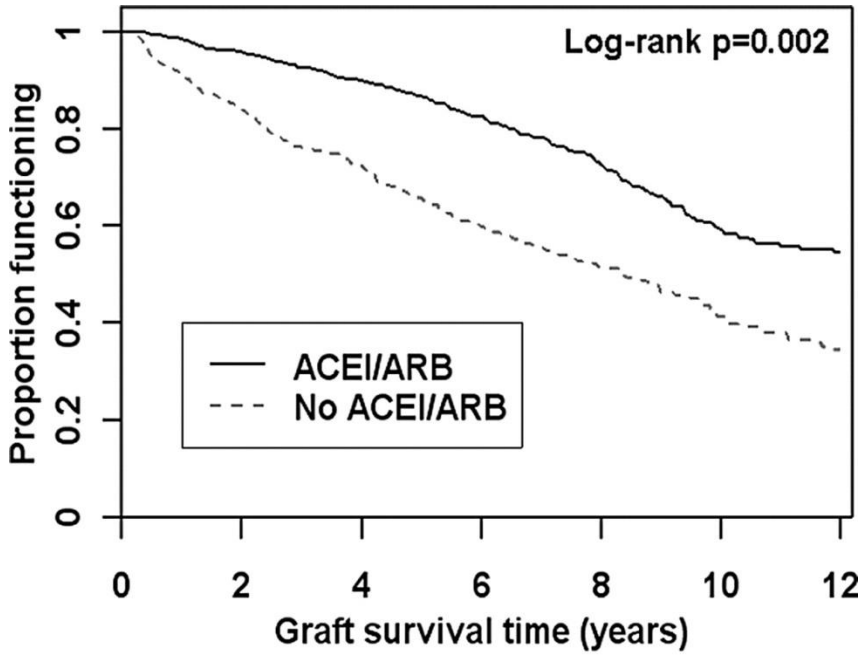


Carpenter et al., JASN 2014;12:2437-45



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



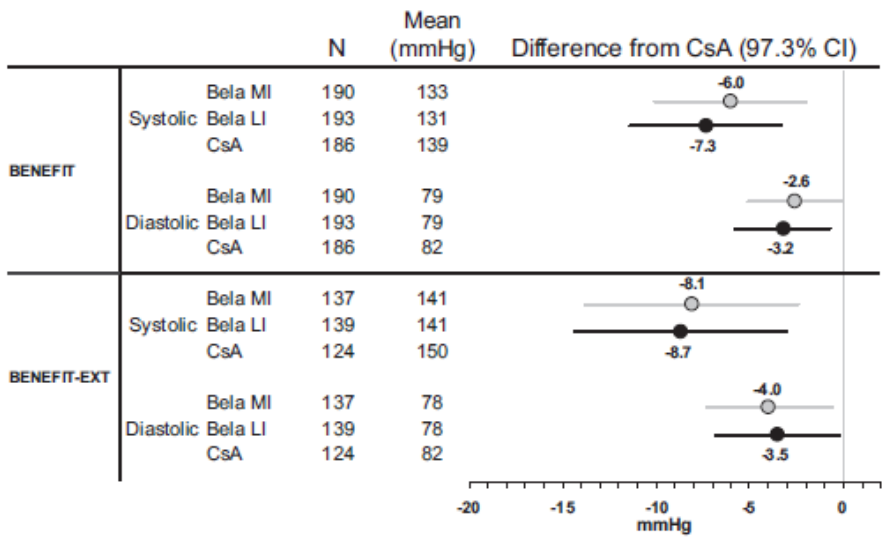
Patients at risk, ACEI/ARB:
1190 925 671 456 300 153 67

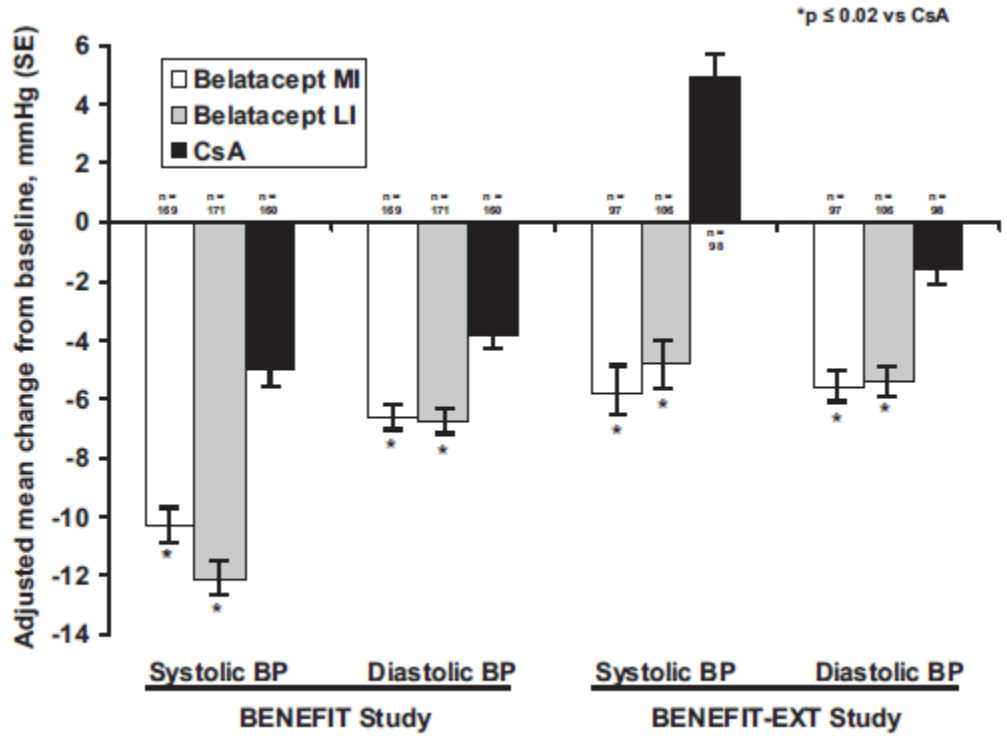
Patients at risk, no ACEI/ARB:
841 489 355 240 148 83 42

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

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]

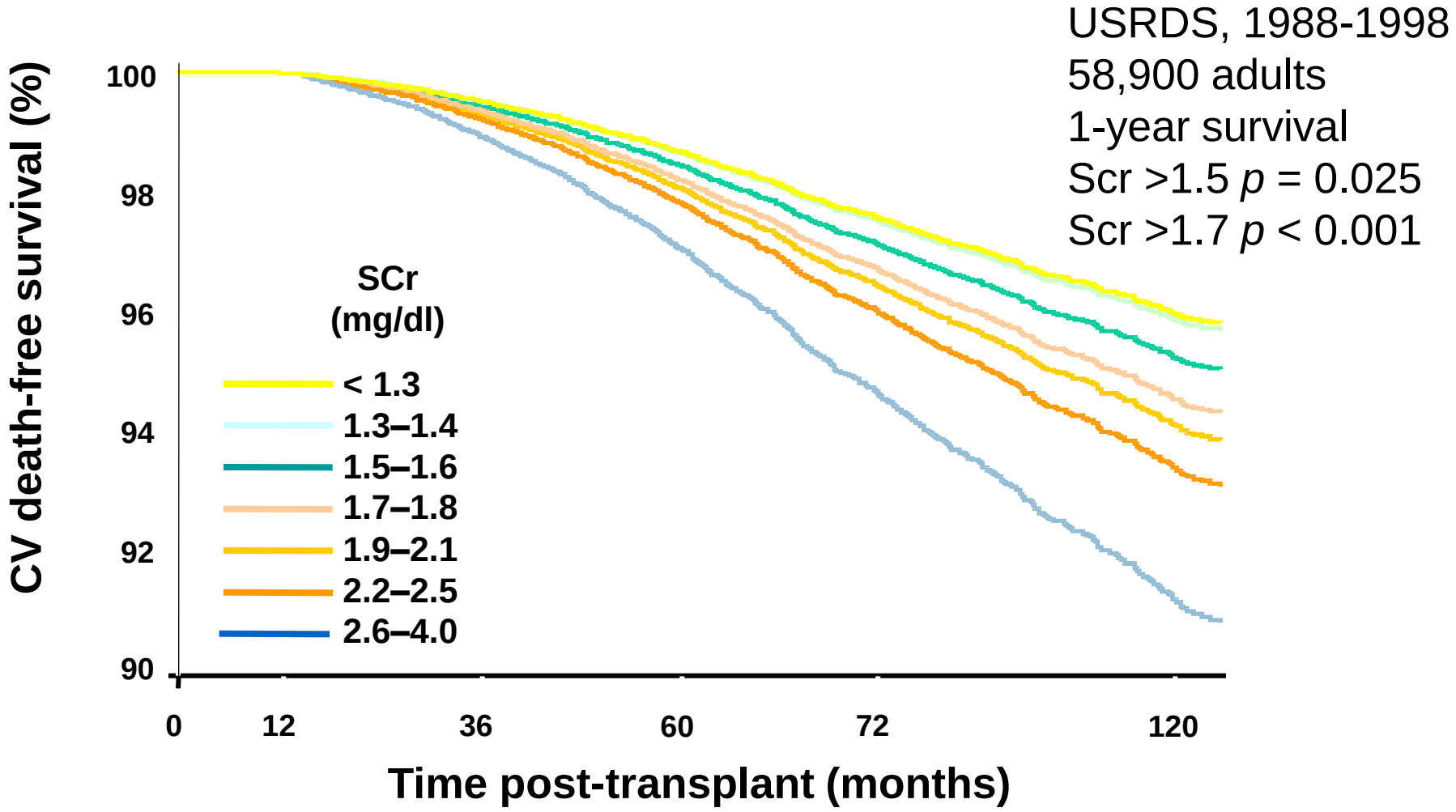




Vanrenterghem et al., Transplantation 2011 (ePub)

Rejection &
Graft function

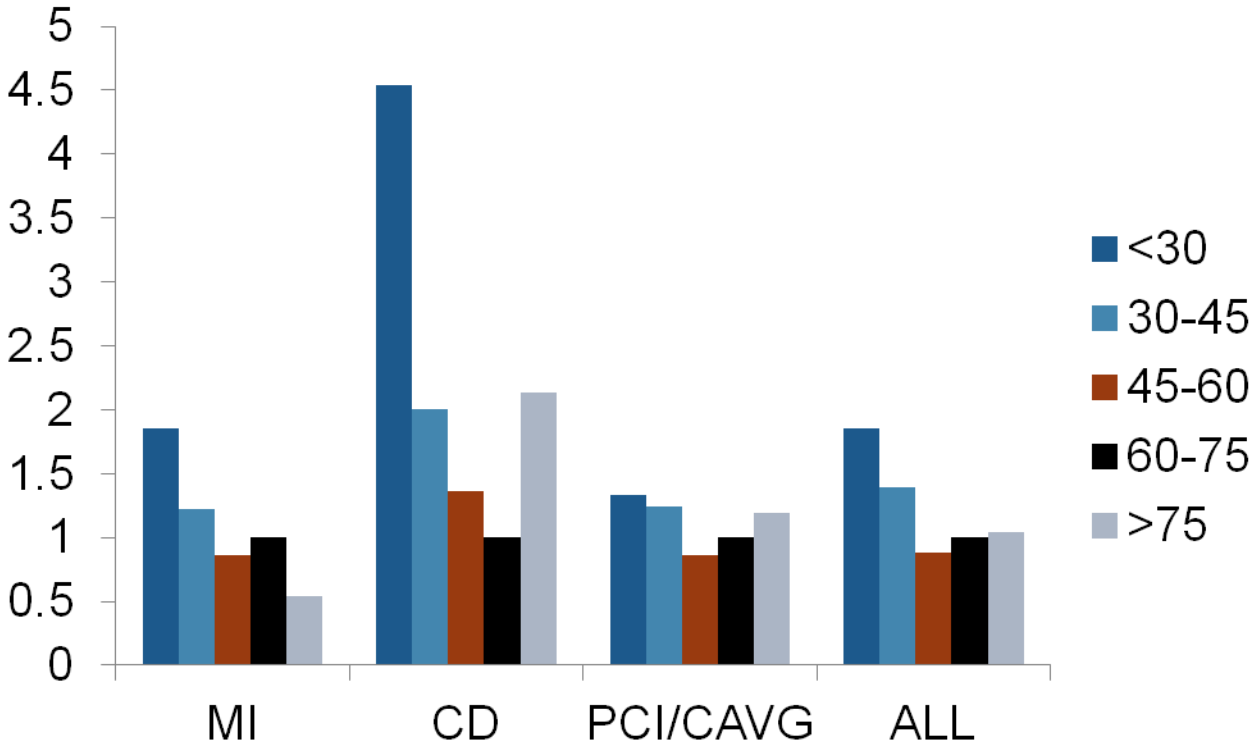
Graft Function Predicts Cardiac Mortality After First Year



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

The FAVORIT study

FAVORIT – Cardiovascular Risk (HR) by eGFR

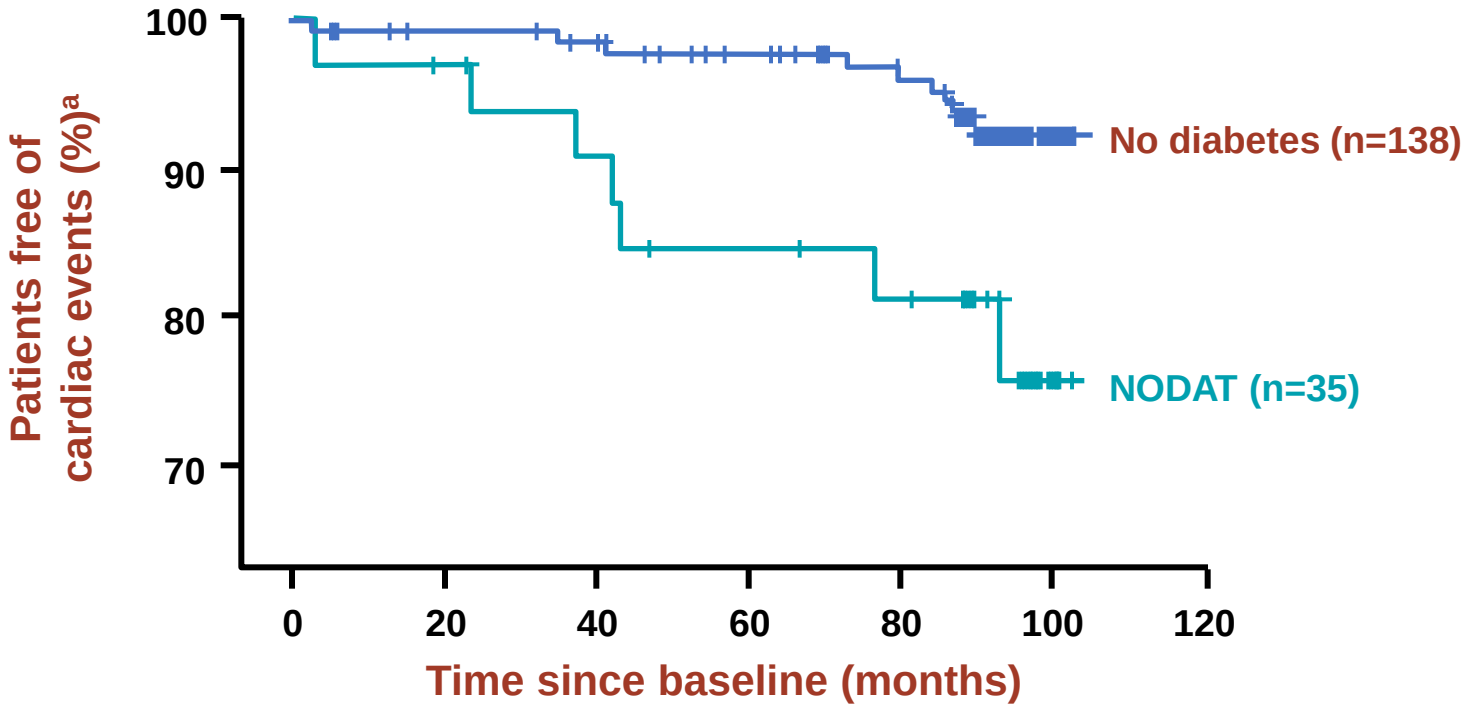


Weiner DE et al., Am J Transplant 2012;12:2437-45

NODAT

NODAT has a strong impact on long-term CV outcomes:
3-fold increase in major cardiac events after kidney transplant

Prospective 8-year analysis of 201 consecutive renal transplant (1995–1996) patients at a single centre



[a]Kaplan-Meier estimates
NODAT, new-onset diabetes after transplantation; CV, cardiovascular

Adapted from Hjelmesaeth J *et al. Kidney Int* 2006;69:588–95

Other risk factors

Original Investigation

Impact of Hyperuricemia on Long-term Outcomes of Kidney Transplantation: Analysis of the FAVORIT Study

Roberto S. Kalil, MD,[1] Myra A. Carpenter, PhD,[2] Anastasia Ivanova, PhD,[2] Lisa Gravens-Mueller, PhD,[2] Alin A. John, MD,[3] Matthew R. Weir, MD,[4] Todd Pesavento, MD,[5] Andrew G. Bostom, MD,[6] Marc A. Pfeffer, MD, PhD,[7] and Lawrence G. Hunsicker, MD[1]

Model	HR[a] (95% CI)	Coefficient *P*[b]
Uric acid alone		
CV events	1.06 (1.02-1.10)	0.007
All-cause mortality	1.09 (1.04-1.14)	<0.001
Kidney transplant failure	1.18 (1.12-1.24)	0.001
Uric acid and eGFR		
CV events	1.02 (0.97-1.06)	0.5
All-cause mortality	1.04 (0.99-1.08)	0.09
Kidney transplant failure	1.05 (0.99-1.11)	0.06
Intermediate model[c]		
CV events	1.02 (0.98-1.07)	0.3
All-cause mortality	1.05 (1.00-1.11)	0.04
Kidney transplant failure	1.04 (0.99-1.10)	0.2
Full model[c]		
CV events	1.02 (0.97-1.06)	0.5
All-cause mortality	1.04 (0.99-1.10)	0.09
Kidney transplant failure	1.04 (0.99-1.10)	0.1
Full model excluding BP variables		
CV events	1.02 (0.98-1.07)	0.4
All-cause mortality	1.05 (1.00-1.11)	0.06
Kidney transplant failure	1.05 (0.99-1.10)	0.1

Am J Kid Disease 2017;70:762-769

AJKD

Original Investigation

Serum Phosphorus and Risk of Cardiovascular Disease, All-Cause Mortality, or Graft Failure in Kidney Transplant Recipients: An Ancillary Study of the FAVORIT Trial Cohort

Basma Merhi, MD,[1] Theresa Shireman, PhD,[2] Myra A. Carpenter, PhD,[3] John W. Kusek, PhD,[4] Paul Jacques, ScD,[5] Marc Pfeffer, MD, PhD,[6] Madhumathi Rao, MD,[7] Meredith C. Foster, ScD, MPH,[7] S. Joseph Kim, MD, PhD,[8] Todd E. Pesavento, MD,[9] Stephen R. Smith, MD,[10] Clifton E. Kew, MD,[11] Andrew A. House, MD,[12] Reginald Gohh, MD,[1] Daniel E. Weiner, MD,[7] Andrew S. Levey, MD,[7] Joachim H. Ix, MD,[13] and Andrew Bostom, MD, MS[1]

Serum Phosphorus Concentration

	Outcome				
Cox Proportional Hazards Model	CVD (436 events)	Transplant Failure (238 events)	All-Cause Mortality (348 events)	CVD Mortality (135 events)	Transplant Failure or All-Cause Mortality (534 events)
Model 1[a]: unadjusted	1.25 (1.08-1.45)	1.73 (1.44-2.07)	1.43 (1.22-1.67)	1.39 (1.10-1.77)	1.54 (1.35-1.76)
Model 2[a]: multivariable adjusted, without kidney measures[b]	1.14 (1.00-1.31)	1.72 (1.46-2.01)	1.34 (1.16-1.55)	1.34 (1.05-1.71)	1.47 (1.31-1.64)
Model 3[a]: fully adjusted[c]	1.06 (0.92-1.22)	1.36 (1.15-1.62)	1.21 (1.04-1.40)	1.15 (0.89-1.48)	1.25 (1.11-1.41)

Am J Kid Disease 2017;70:377-385

Original Investigation

Aspirin Use and Incident Cardiovascular Disease, Kidney Failure, and Death in Stable Kidney Transplant Recipients: A Post Hoc Analysis of the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) Trial

Taimur Dad, MD,[1] Hocine Tighiouart, MS,[1,2,3] Alin Joseph, MD, MS,[1] Andrew Bostom, MD,[4] Myra Carpenter, PhD,[5] Lawrence Hunsicker, MD,[6] John W. Kusek, PhD,[7] Marc Pfeffer, MD, PhD,[8] Andrew S. Levey, MD,[1] and Daniel E. Weiner, MD, MS[1]

Dad T et al., Am J Kid Disease 2016;68:277-286

Outcome	Unadjusted		Parsimonious Adjusted Model		Extended Adjusted Model	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Primary CVD	1.16 (0.89-1.50)	0.3	1.20 (0.92-1.58)	0.2	1.20 (0.92-1.58)	0.2
All-cause mortality	0.87 (0.66-1.15)	0.3	0.92 (0.69-1.22)	0.6	0.92 (0.69-1.23)	0.6
Kidney failure	1.00 (0.71-1.42)	0.9	1.18 (0.81-1.72)	0.4	1.19 (0.81-1.74)	0.4
Kidney failure/all-cause mortality	0.94 (0.75-1.18)	0.6	1.03 (0.82-1.30)	0.8	1.03 (0.82-1.31)	0.8
Primary CVD/all-cause mortality	1.05 (0.84-1.31)	0.7	1.11 (0.88-1.38)	0.4	1.11 (0.88-1.38)	0.4

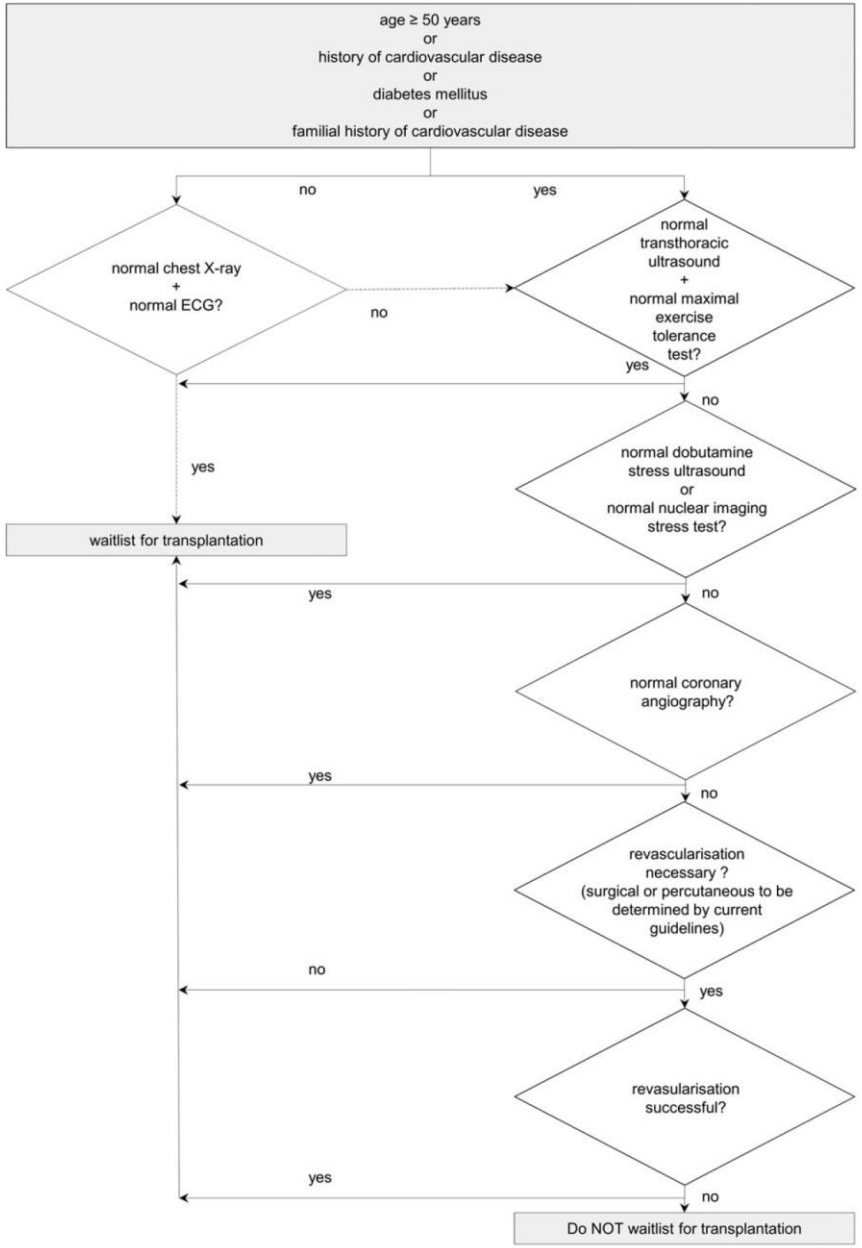
Dad T et al., Am J Kid Disease 2016;68:277-286

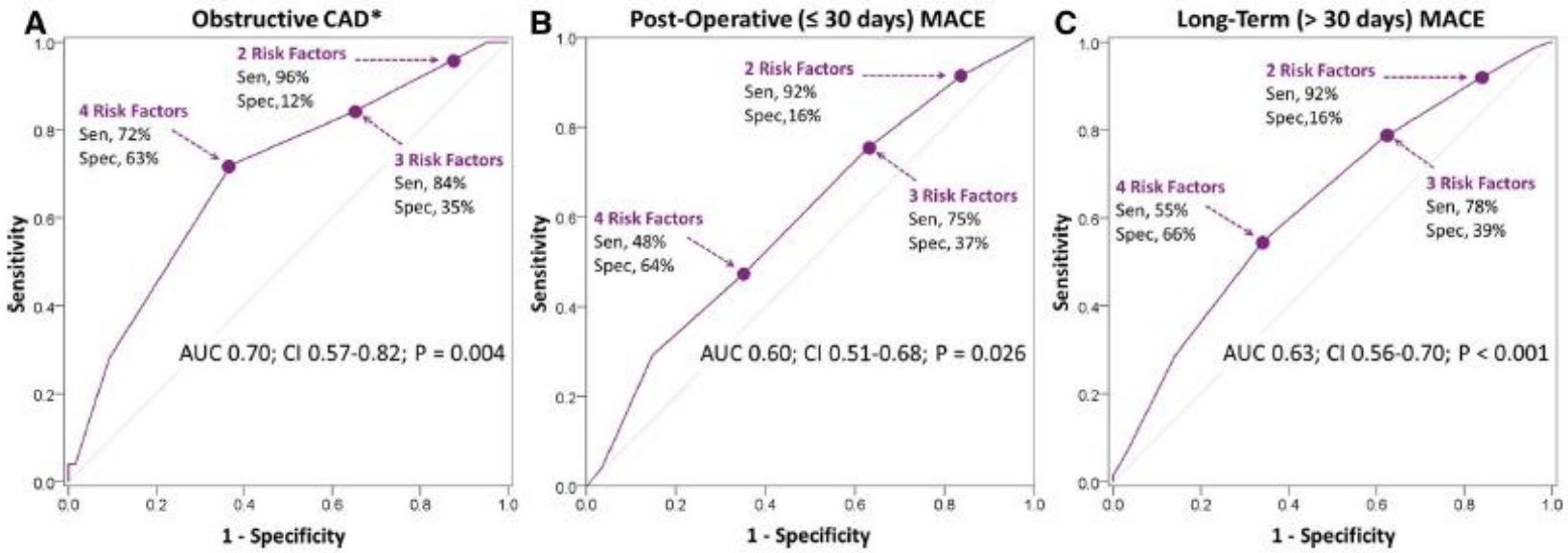
CV Screening

ndt
Nephrology Dialysis Transplantation

Nephrol Dial Transplant (2013) 28: ii1–ii71
doi: 10.1093/ndt/gft218

Guideline





	Obstructive CAD[a]			Post-operative MACE[a]			Long-term MACE[b]		
	OR	95% CI	*P* values	OR	95% CI	*P* values	HR	95% CI	*P* values
Tobacco use	5.79[c]	0.94-35.49	0.060	2.19[c]	0.88-4.65	0.096	2.46[c]	1.38-4.36	0.002
Age > 60 years	1.46	0.45-4.75	0.530	2.03[c]	1.17-4.11	0.014	2.09[c]	1.29-3.39	0.003
CVD	9.72[c]	2.42-39.02	0.001	1.36	0.72-2.57	0.338	1.71[c]	1.03-2.83	0.036
Dialysis > 1 y	0.59	0.11-3.28	0.547	1.23	0.50-3.03	0.655	1.20	0.61-2.36	0.601
Hypertension	0.20	0.01-4.82	0.321	0.72	0.23-2.23	0.568	1.07	0.38-2.98	0.901
Diabetes mellitus	2.73[c]	0.84-8.88	0.096	0.75	0.39-1.42	0.372	1.05	0.64-1.72	0.854
Dyslipidemia	1.32	0.41-4.25	0.646	1.58	0.80-3.11	0.189	0.97	0.58-1.62	0.901
LVH	0.40	0.11-1.45	0.162	1.02	0.54-1.95	0.942	0.92	0.56-1.50	0.726

Bourke JM et al., J Nucl Cardiol 2017:10.1007/s12350-017-0944-6
Doukky R et al., J Nucl Cardiol 2017;doi10.1007/s12350-017-0901-4

Guidelines

Guidelines

16.1.1: We recommend measuring blood pressure at each clinic visit. *(1C)*

16.1.2: We suggest maintaining blood pressure at <130 mm Hg systolic and <80 mm Hg diastolic if ≥18 years of age, and <90th percentile for sex, age, and height if [illegible] years old. *(2C)*

16.1.3: To treat hypertension *(Not Graded)*:

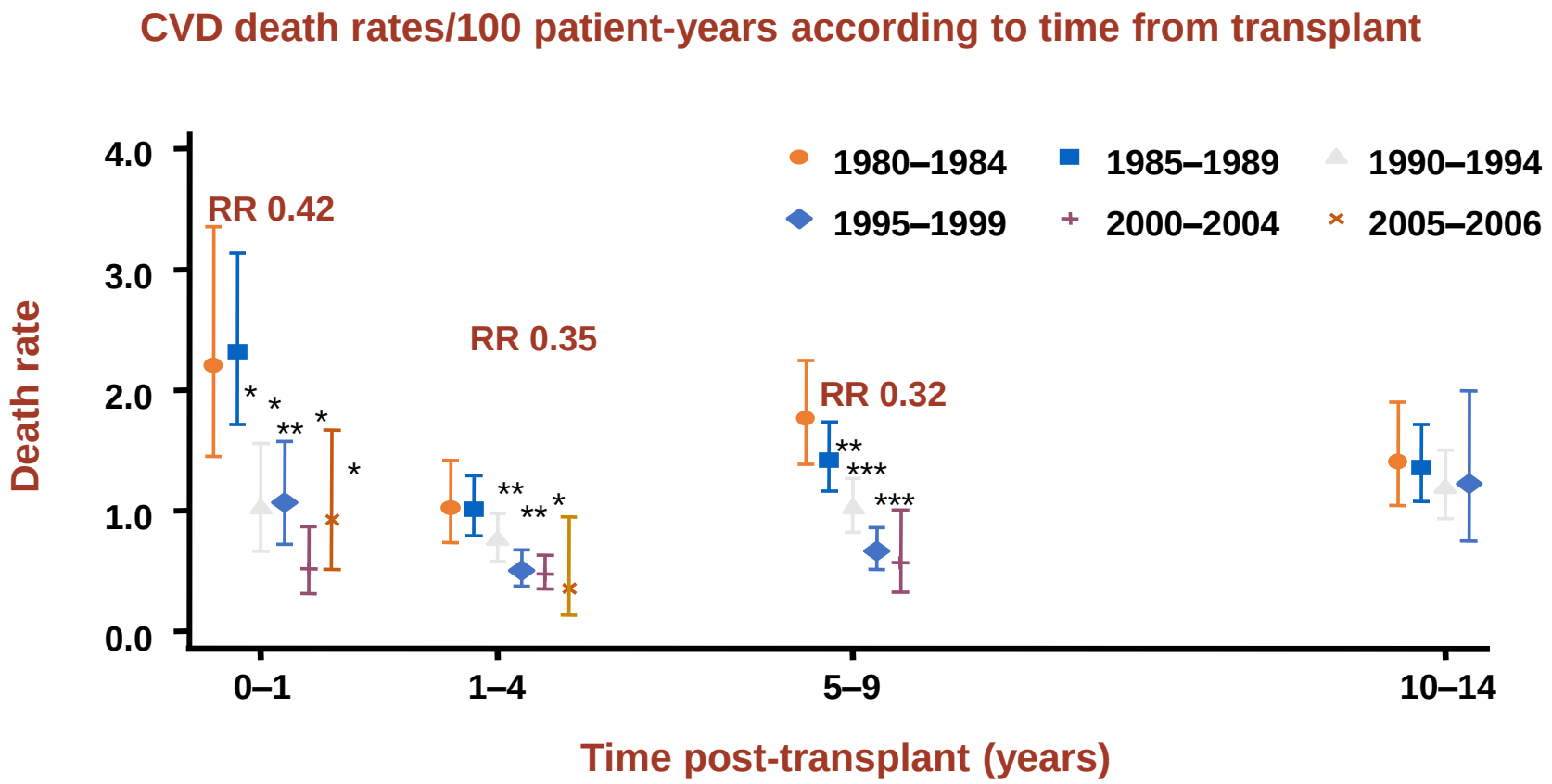
- use any class of antihypertensive agent;
- monitor closely for adverse effects and drug–drug interactions; and
- when urine protein excretion ≥1 g/day for ≥18 years old and ≥600 mg/m^2/24 h for <18 years old, consider an ACE-I or an ARB as first-line therapy.

2.4: In adult kidney transplant recipients, we suggest treatment with a statin. (*2B*)

KDIGO Am J Tx 2009;9: 571-9

How are *we* doing?

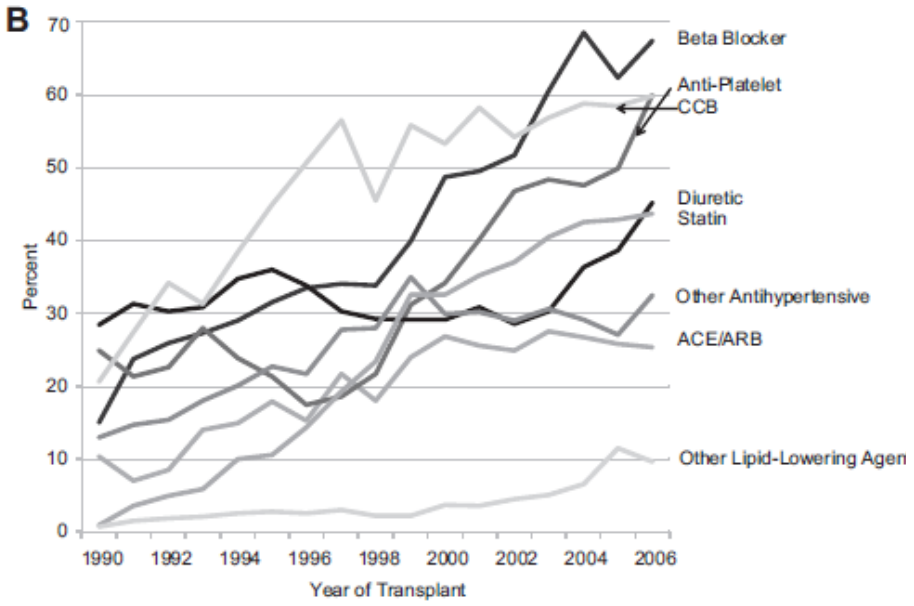
CVD death: time from transplant

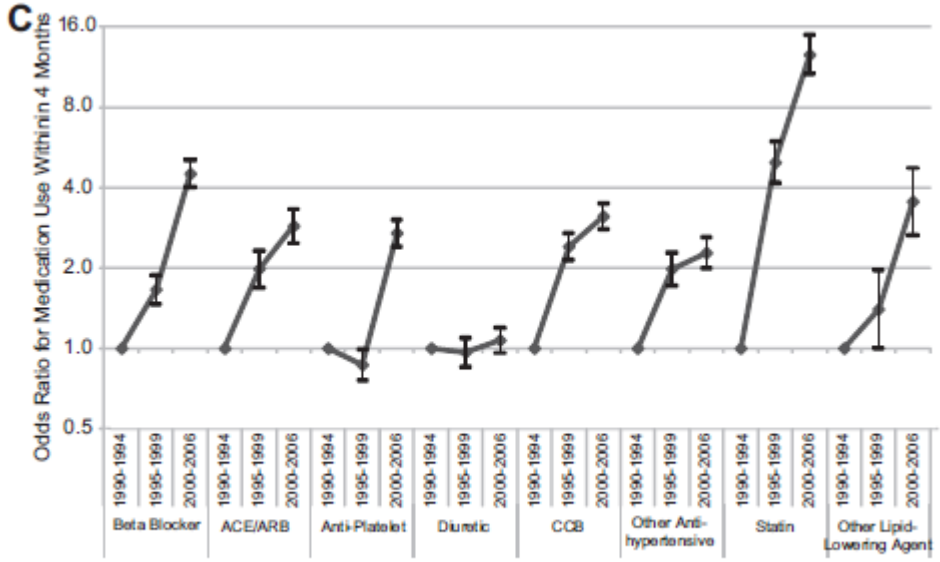


*p<0.05; **p<0.01; ***p<0.001
CVD, cardiovascular disease; RR, relative risk

Pilmore HL *et al. Transplantation* 2010;89:851–7

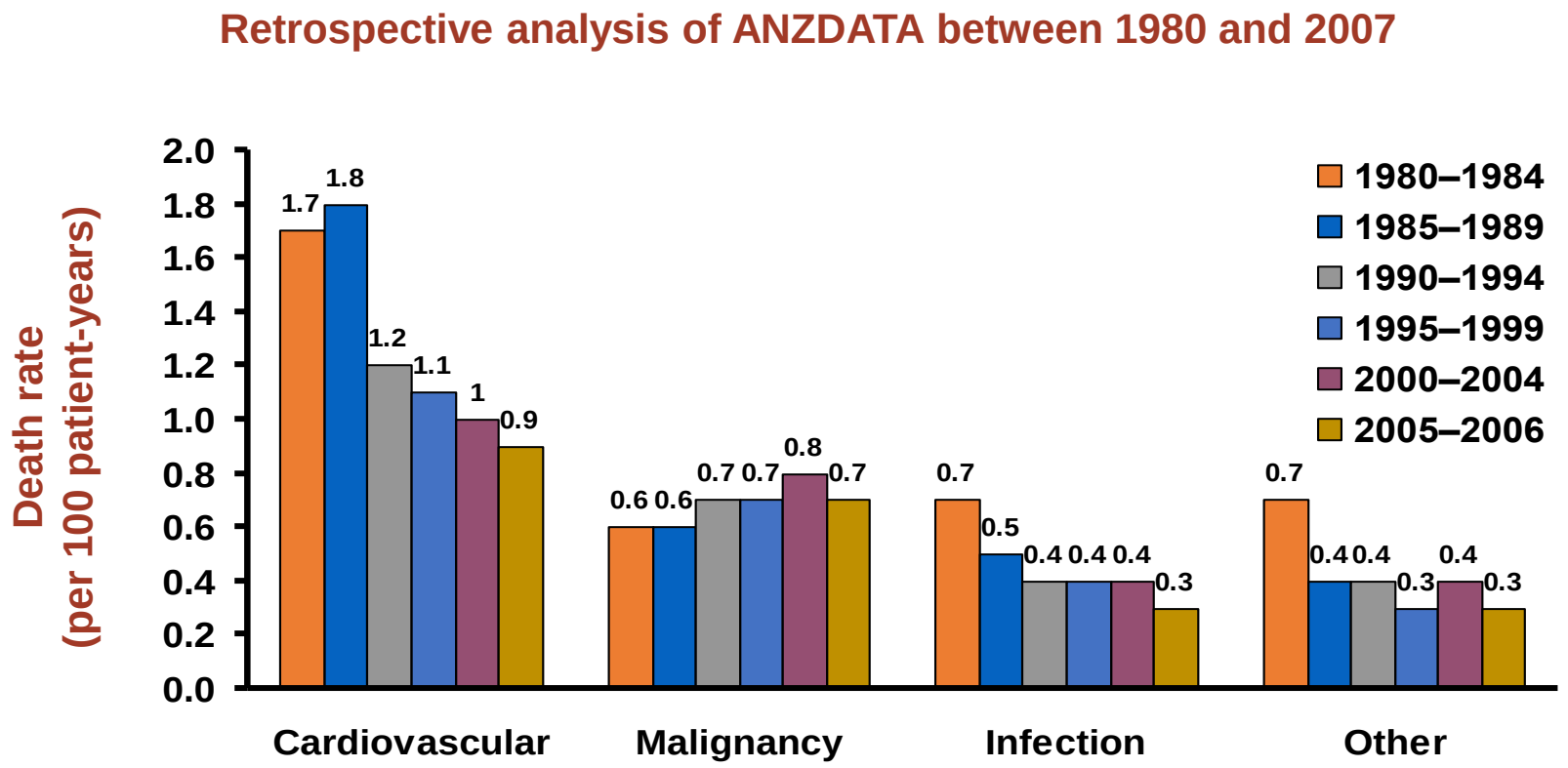
The PORT study





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

CVD is a leading cause of death with a functioning graft



CVD, cardiovascular disease

Pilmore HL *et al. Transplantation* 2010;89:851–7