MEDICAL UNIVERSITY VIENNA

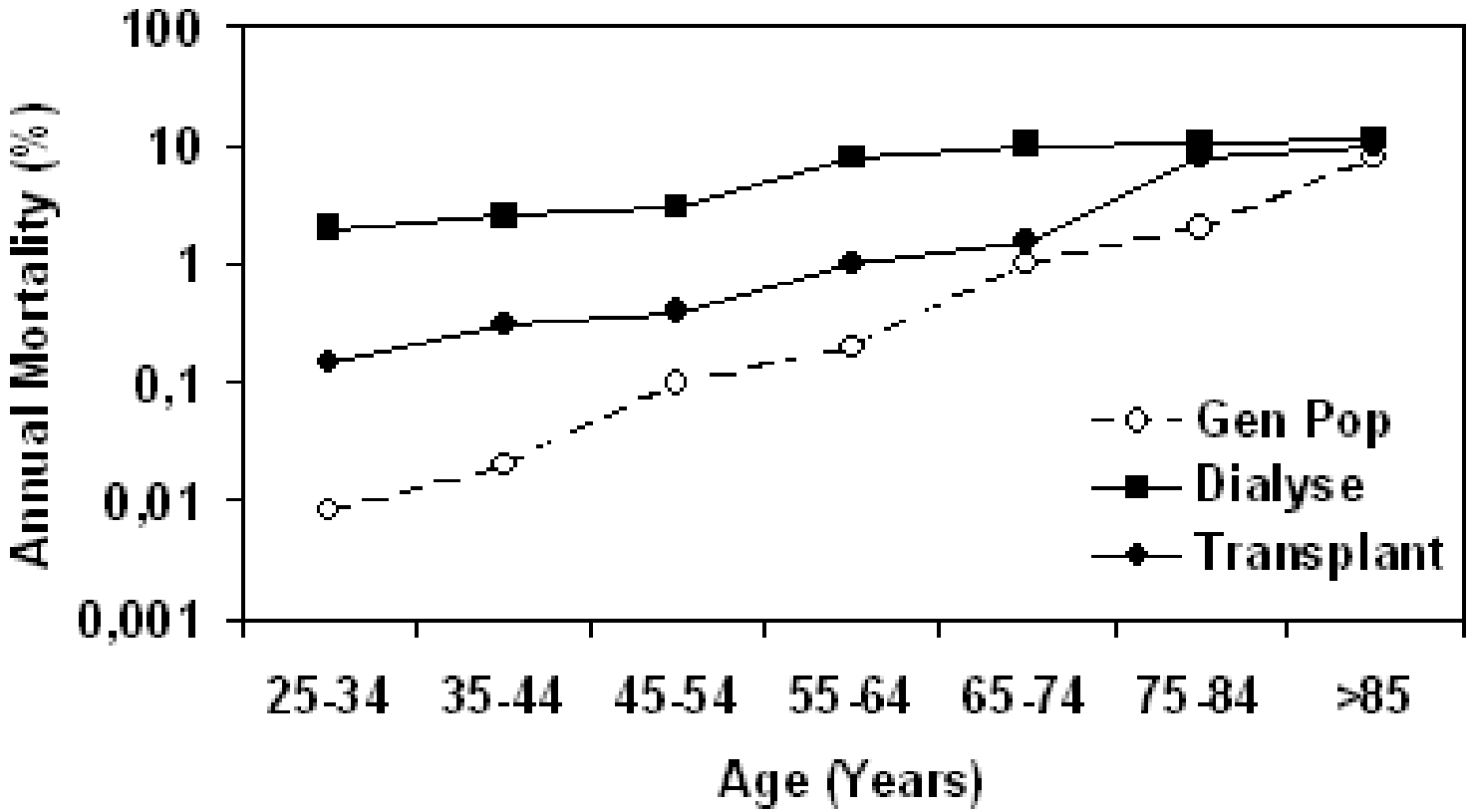
SysKid
Collaborative Project
Systems Biology towards Novel Chronic Kidney Disease Diagnosis and Treatment

Allgemein öffentliches Krankenhaus
Elisabethinen Linz

Cardiovascular Risk Reduction in Kidney Transplant Recipients

Rainer Oberbauer

CV Mortality in ESRD compared to the general population



Modified from Foley et al. AJKD 32 (suppl3):1998

Risk factors for the development of CVD after renal TX

Traditional Risk Factors	Transplant-Associated Risk Factors	Emerging Risk Factors
Modifiable/potentially modifiable		
obesity	Immunosuppression	Inflammation
diabetes	CKD[b]	homocysteine
hypertension	Proteinuria[b]	CRP
hyperlipidemia	Anemia[b]	AGE
smoking		
Nonmodifiable		
gender		
age		
family history		

[a]AGE, advanced glycation end products; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease.
[b]These risk factors are also relevant in the CKD population (9–11).

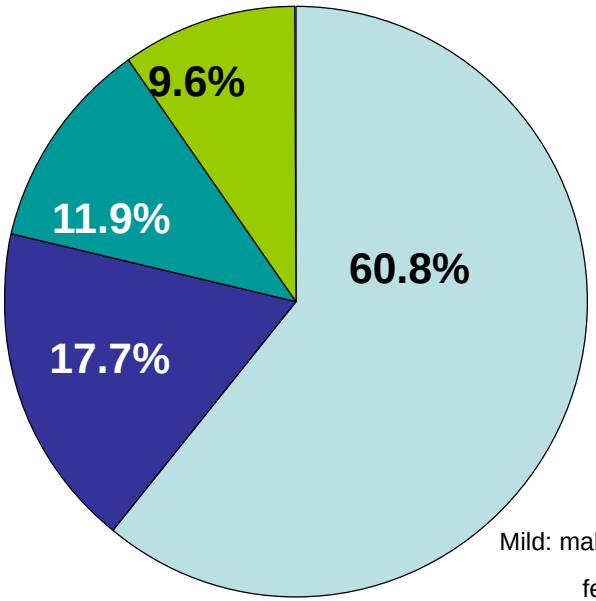
Shirali AC et Bia MJ. CJASN 2008 Mar;3(2):491-504

Agenda

Modifyable risk factors & CV outcomes

- Hemoglobin
- Lipids
- Glucose control
- Blood pressure
- BMI - Obesity

High prevalence of anemia after renal transplantation (TRESAM, n=4263)



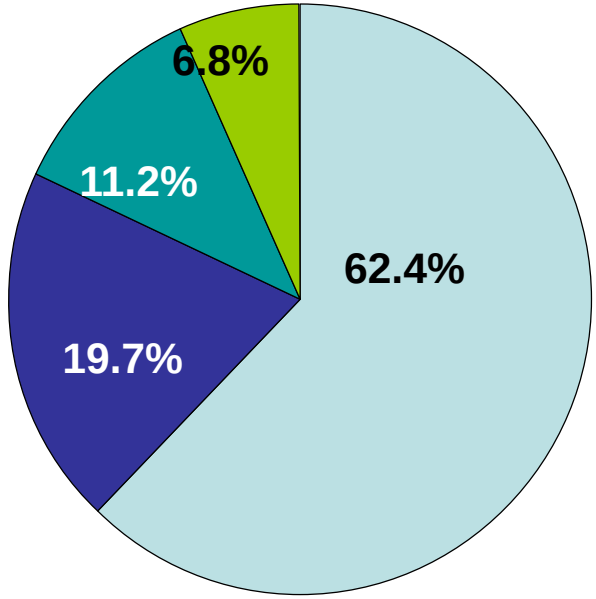
Male patients
n=2641

No anemia
Mild anemia
Moderate anemia
Severe anemia

Mild: males: Hb >12 g/dL and Hb ≤13 g/dL
females: Hb >11 g/dL and Hb ≤12 g/dL

Moderate: males: Hb >11 g/dL and Hb =12 g/dL
females: Hb >10 g/dL and Hb =11 g/dL

Severe: males: Hb ≤11 g/dL, females: Hb ≤10 g/dL



Female patients
n=1622

Vanrenterghem et al. Am J Transplant 2003;3:835

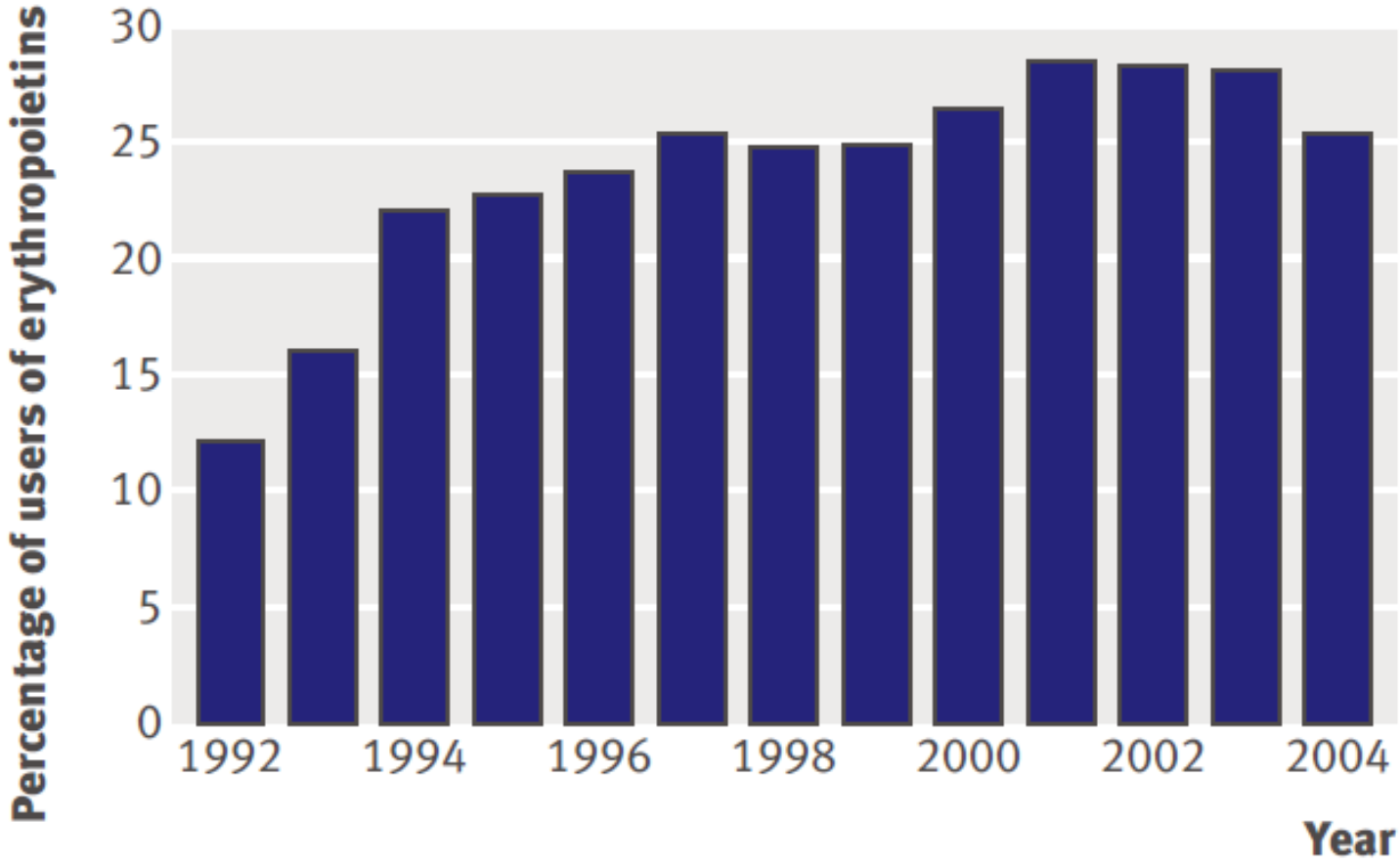
Anemia increase risk of mortality & graft loss (n=938, 118 events)

	Mortality			Return to dialysis		
	HR	95% CI	p value	HR	95% CI	p value
Hb (1 g/L decrease)	1.011	1.001–1.022	0.033	1.019	1.006–1.032	0.003
Presence of anemia	1.690	1.115–2.560	0.013	2.465	1.485–4.090	<0.001

Adjusted for age, gender, eGFR, serum albumin, serum CRP, transplantation "vintage", pretransplant time on dialysis, number of comorbid conditions, presence of hypertension.

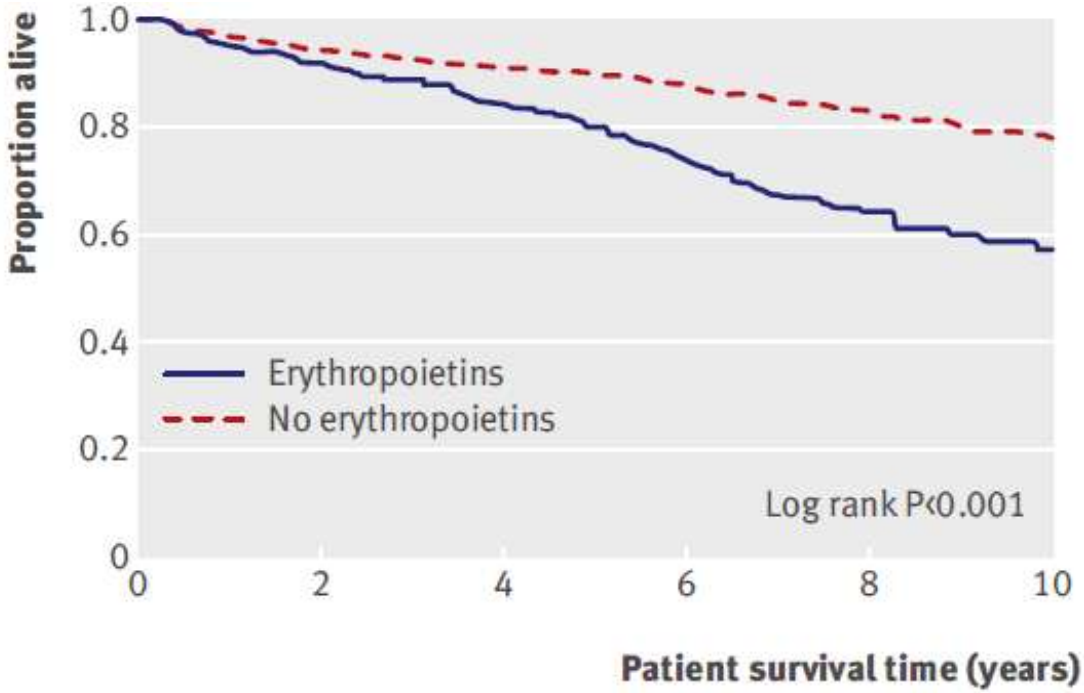
Molnar MZ et al. Am J Transplant. 2007 Apr;7(4):818-24

Rate of ESA users after KTX (OEDTR n=1794, 345 events, 1990-2005)



Heinze G et al. BMJ 2009;339:b4018

Extended KM plot OEDTR n=1794, 345 events, 1990-2005)

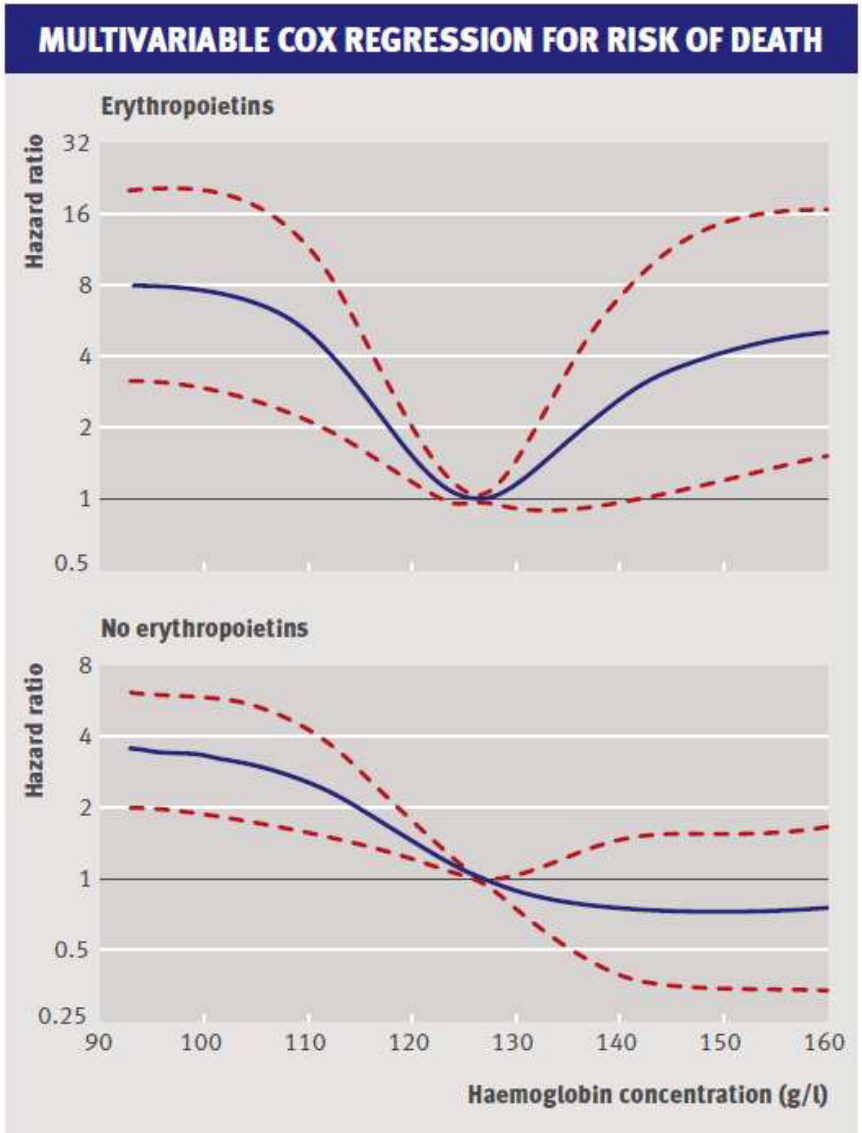


Patients at risk:

Erythropoietins	560	339	241	165	97	46
No erythropoietins	1234	1016	761	501	314	157

Heinze G et al. BMJ 2009;339:b4018

HR of death depending on Hb levels and ESA use (OEDTR n=1794, 345 events, 1990-2005)

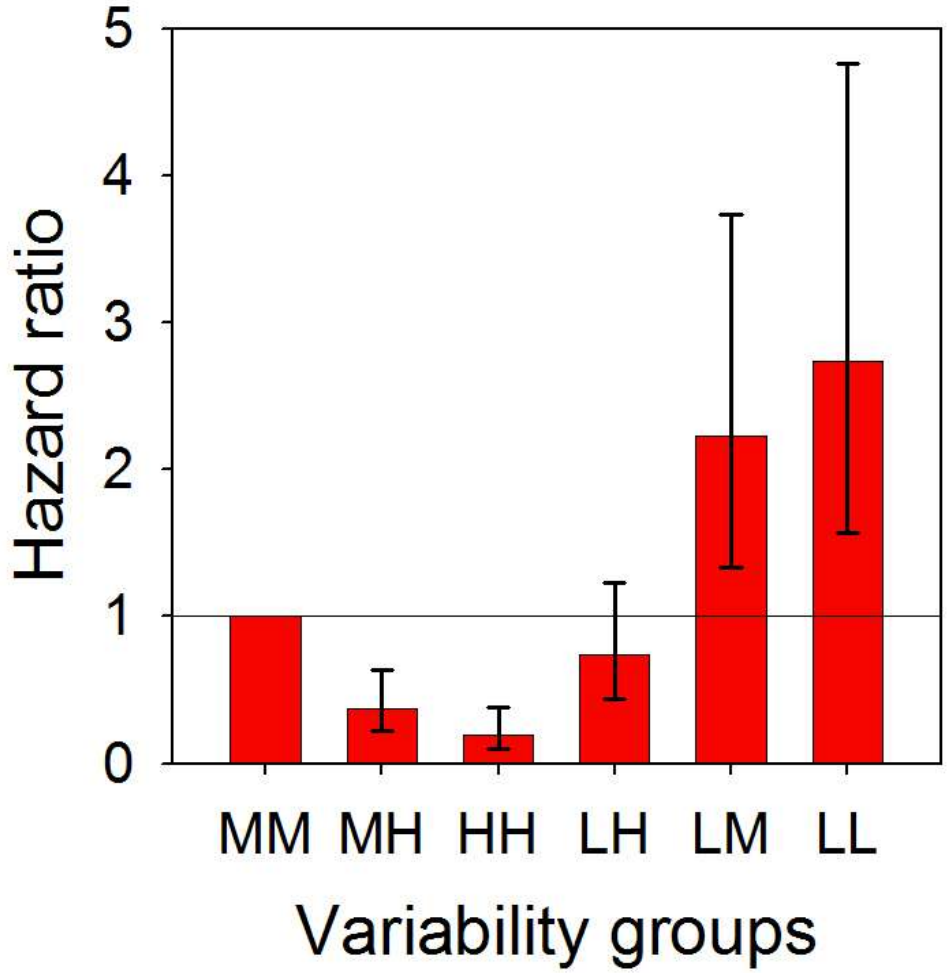


adjusted for:

dialysis status, cerebrovascular disease, peripheral vascular disease, coronary heart disease, heart failure, cholesterol level, immunosuppressive regimen, diabetes status, age at transplantation, cold ischemia time

Heinze G et al. BMJ 2009;339:b4018

Hb Variability and Mortality (OEDTR n=1794, 345 events, 1990-2005)



Hb Strata in g/dl:

L<10
10<**M**<12
12<**H**

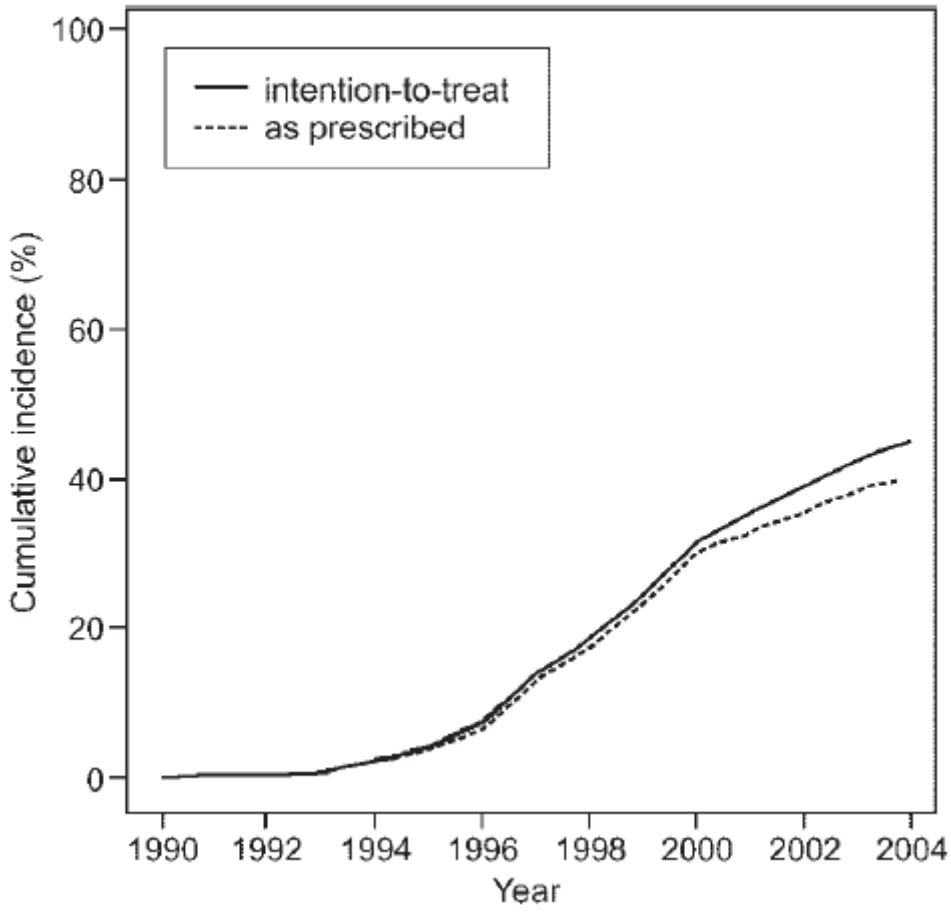
Kainz A J et al. 2010

Agenda

Modifyable risk factors & CV outcomes

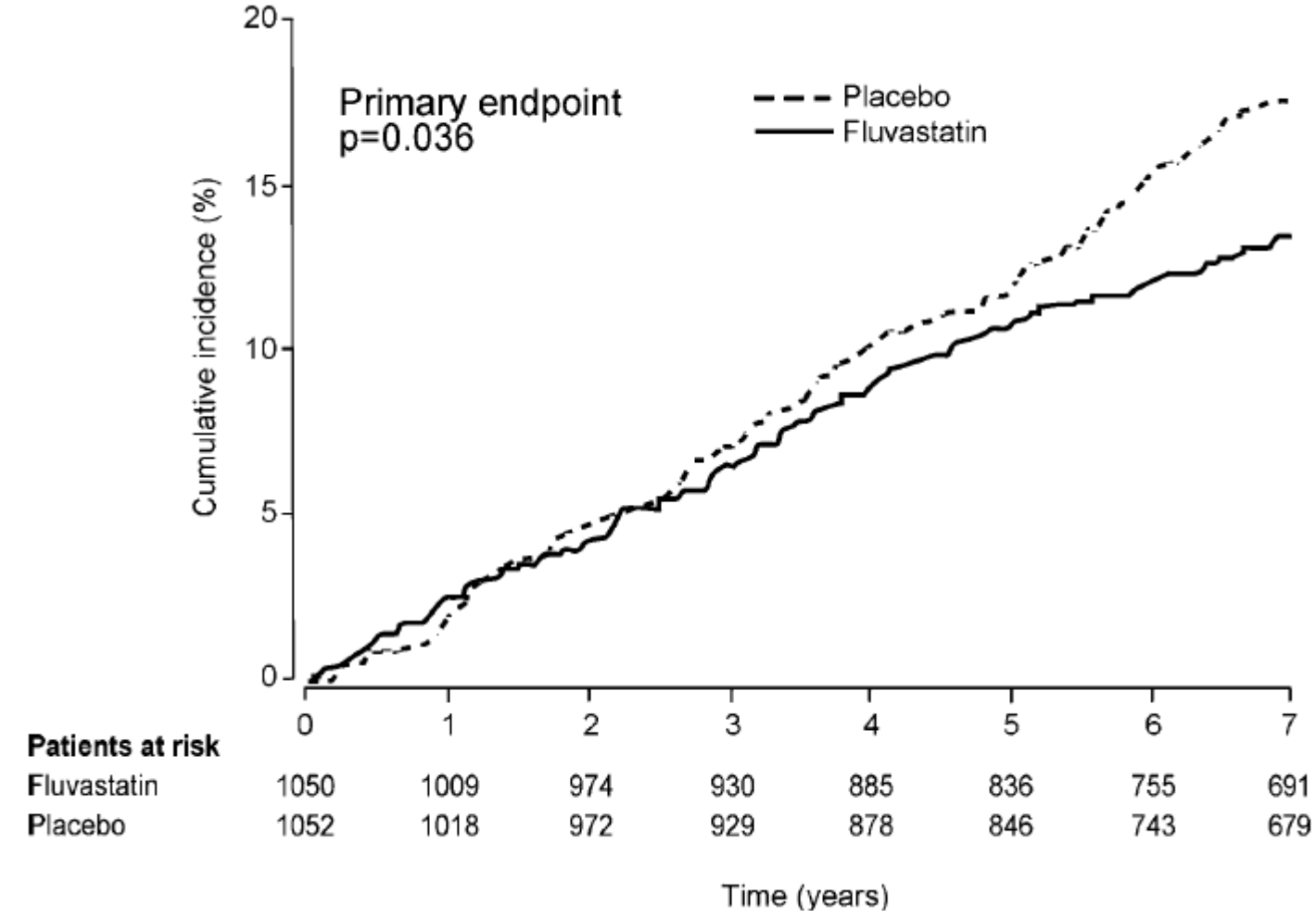
- Hemoglobin
- Lipids
- Glucose control
- Blood pressure
- BMI

Statin use and CV Mortality in RTX (OEDTR, N=2041, 223 CV deaths)



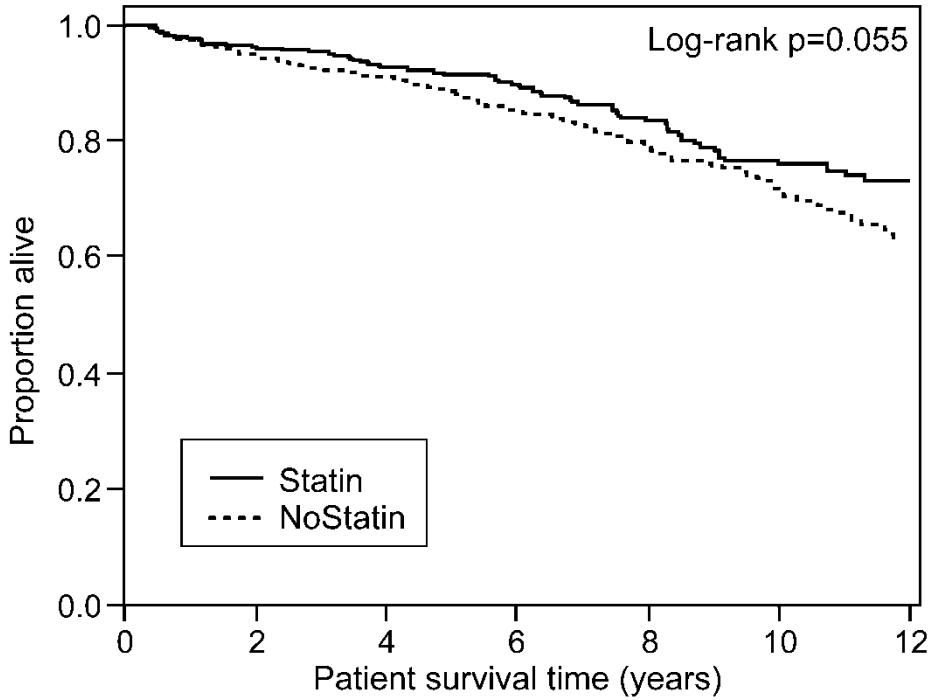
Wiesbauer F et al J Am Soc Nephrol. 2008 Nov;19(11):2211-8

ALERTex Study: Statin use and primary endpoint (MACE) in RTX (N=2102, 192 CV deaths)



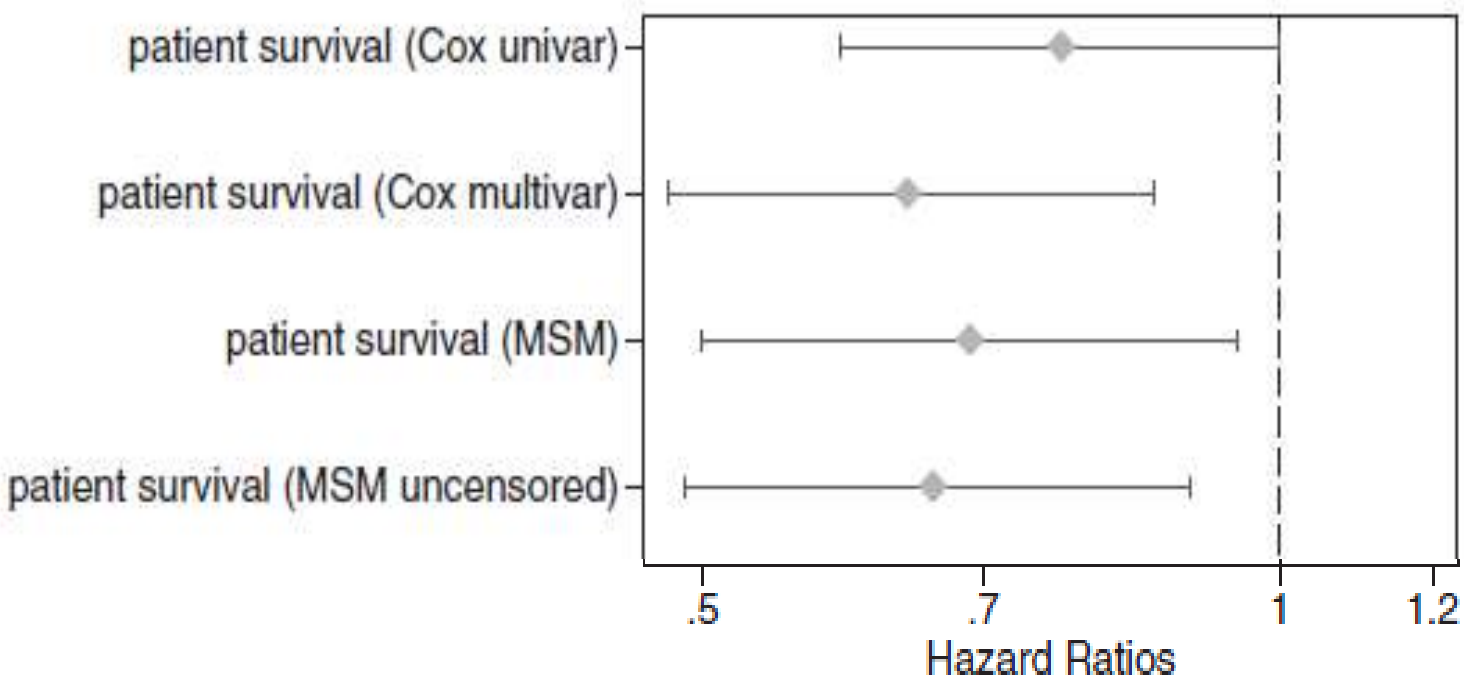
Holdaas H et al. Am J Transplant 2005; 5: 2929–2936

Statin use and CV Mortality in RTX (OEDTR, N=2041, 223 CV deaths)



Wiesbauer F et al J Am Soc Nephrol. 2008 Nov;19(11):2211-8

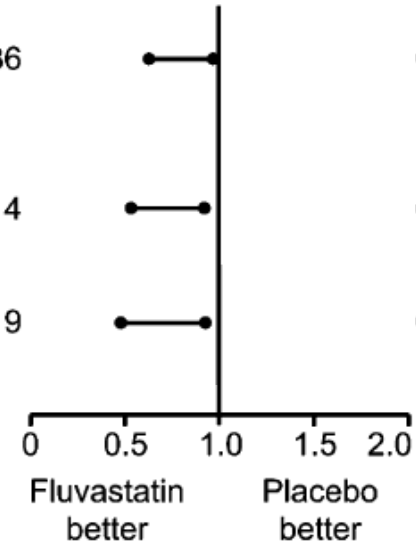
Crude and adjusted HR of events statin vs no-statin use (OEDTR, N=2041, 223 CV deaths)



Wiesbauer F et al J Am Soc Nephrol. 2008 Nov;19(11):2211-8

ALERTex Study

Endpoint	Proportion of patients				Incidence (number of events per 100 patient years)	
	Fluvastatin (n=1,050)	Placebo (n=1,052)	p*	Risk ratio (95% CI)	Fluvastatin (n=1,050)	Placebo (n=1,052)
Cardiac death, non-fatal MI, CABG, PCI	137 (13.0%)	174 (16.5%)	0.036	0.79 (0.63-0.99)	2.07	2.63
Cardiac death or non-fatal MI	95 (9.0%)	128 (12.2%)	0.014	0.71 (0.55-0.93)	1.39	1.89
CABG/PCI	59 (5.6%)	88 (8.4%)	0.019	0.67 (0.48-0.94)	0.88	1.31



Holdaas H et al. Am J Transplant 2005; 5: 2929–2936

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Modifyable risk factors & CV outcomes

- Hemoglobin
- Lipids
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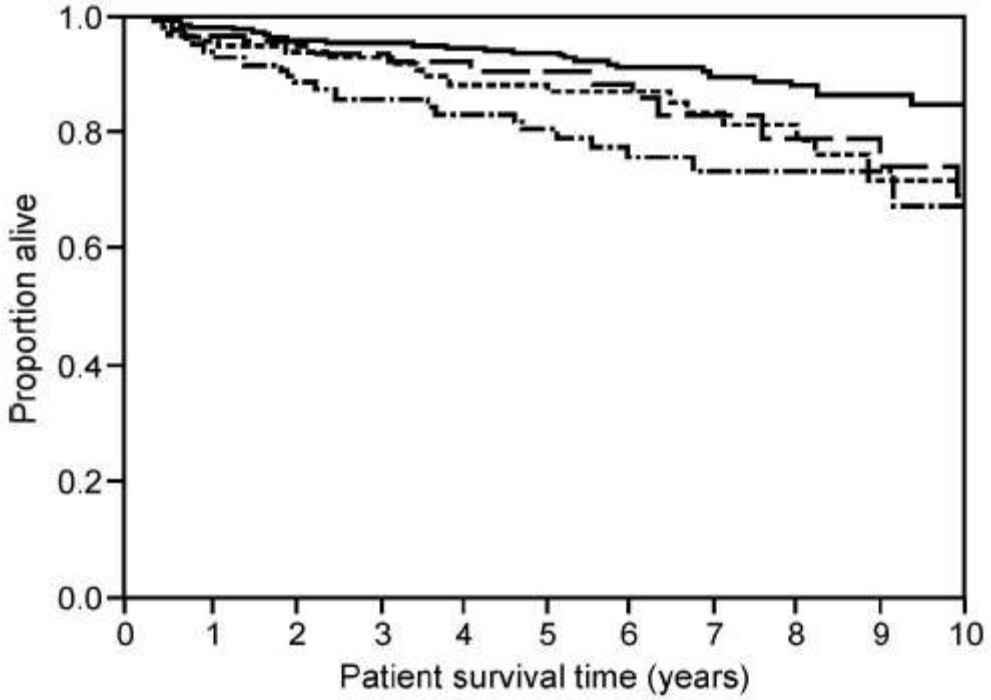
- Blood pressure
- BMI

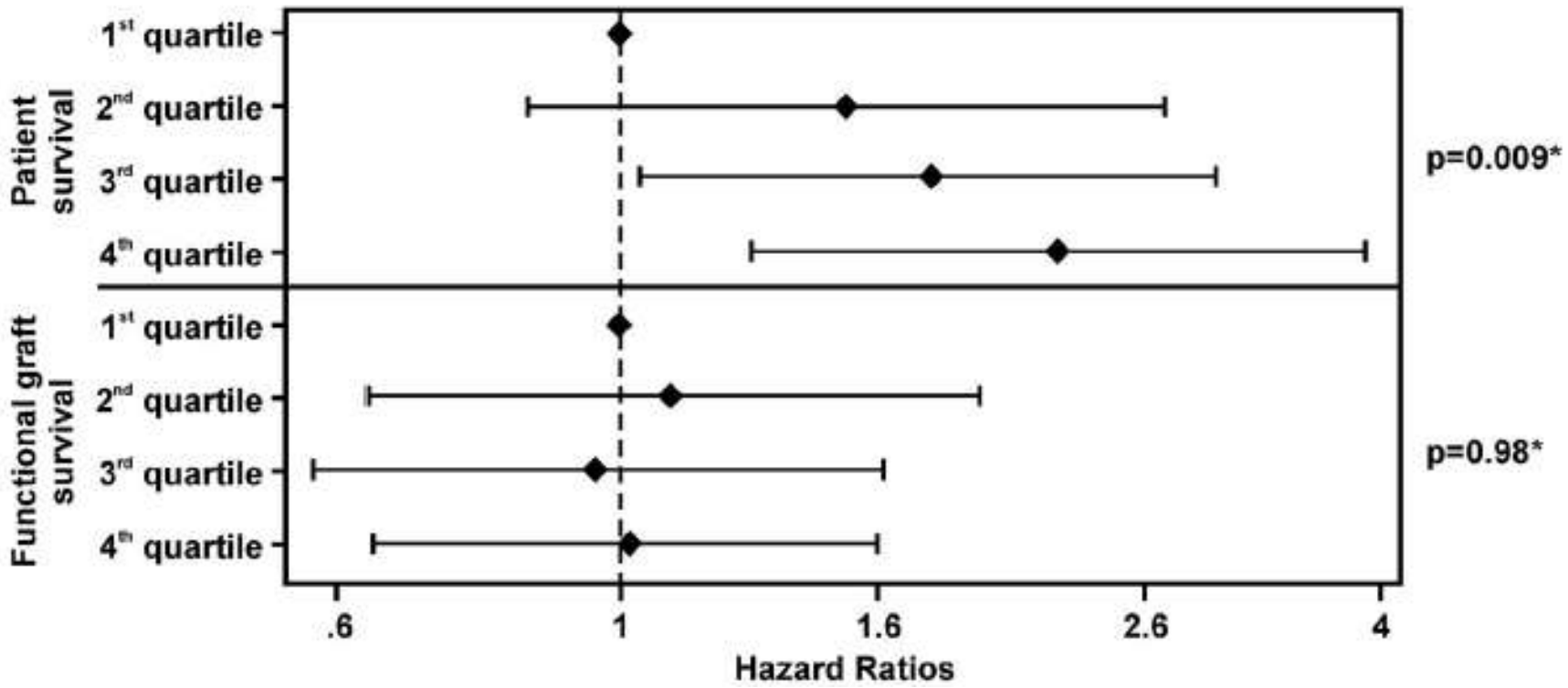
Kaplan-Meier estimates of survival according to quartiles of maximal nonfasting glucose level



1st	179	300	248	188	111	67
2nd	181	88	56	34	21	12
3rd	181	93	79	51	27	5
4th	174	88	65	40	11	5

Wiesbauer F et al Transplantation 2010; 89:612-619

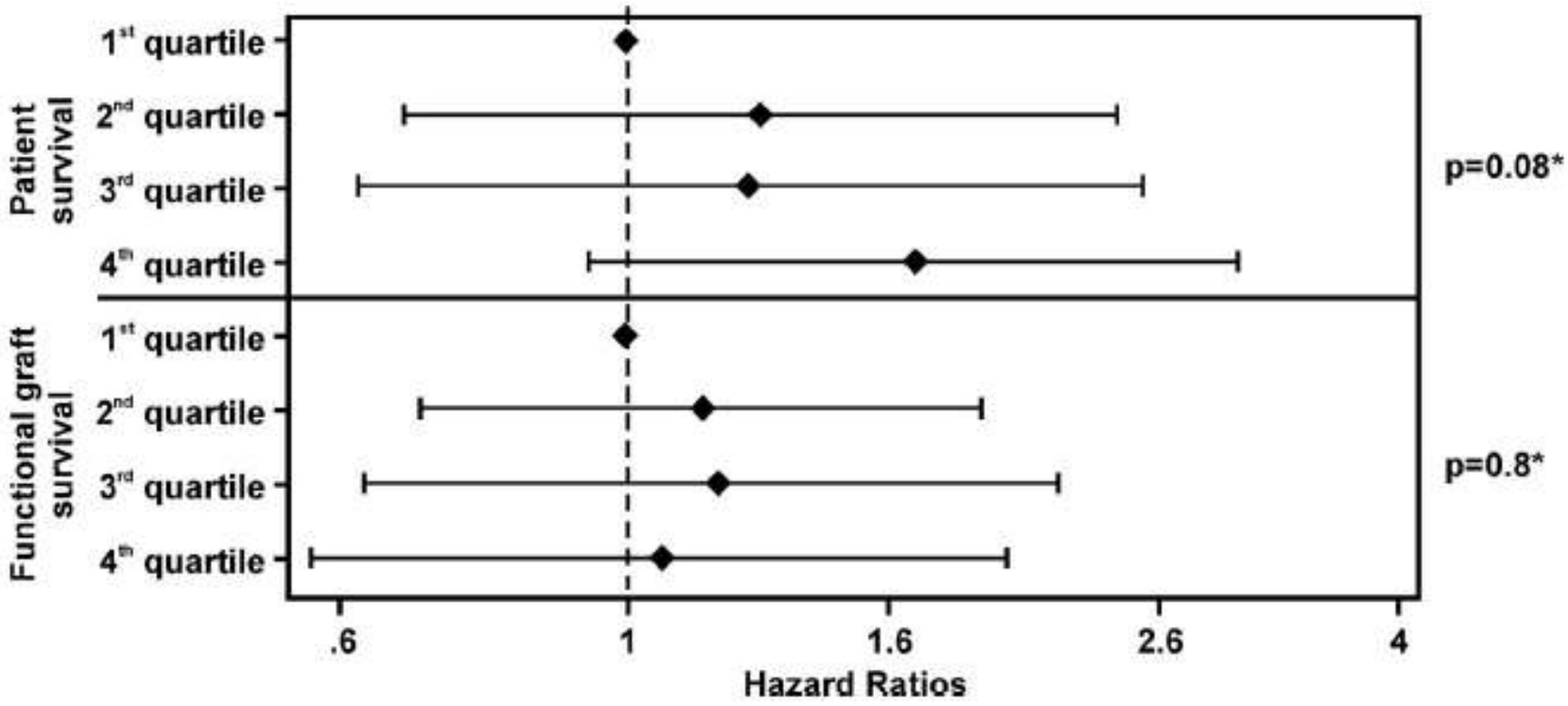
HR for quartiles of maximal nonfasting glucose levels



(adjusted for number of antihypertensive drugs, total cholesterol, type of immunosuppressive therapy, year of transplantation, MAP and donor age)

Wiesbauer F et al Transplantation 2010; 89:612-619

HR for quartiles of HbA1c



(adjusted for number of antihypertensive drugs, total cholesterol, type of immunosuppressive therapy, year of transplantation, MAP and donor age)

Wiesbauer F et al Transplantation 2010; 89:612-619

Agenda

Modifyable risk factors & CV outcomes

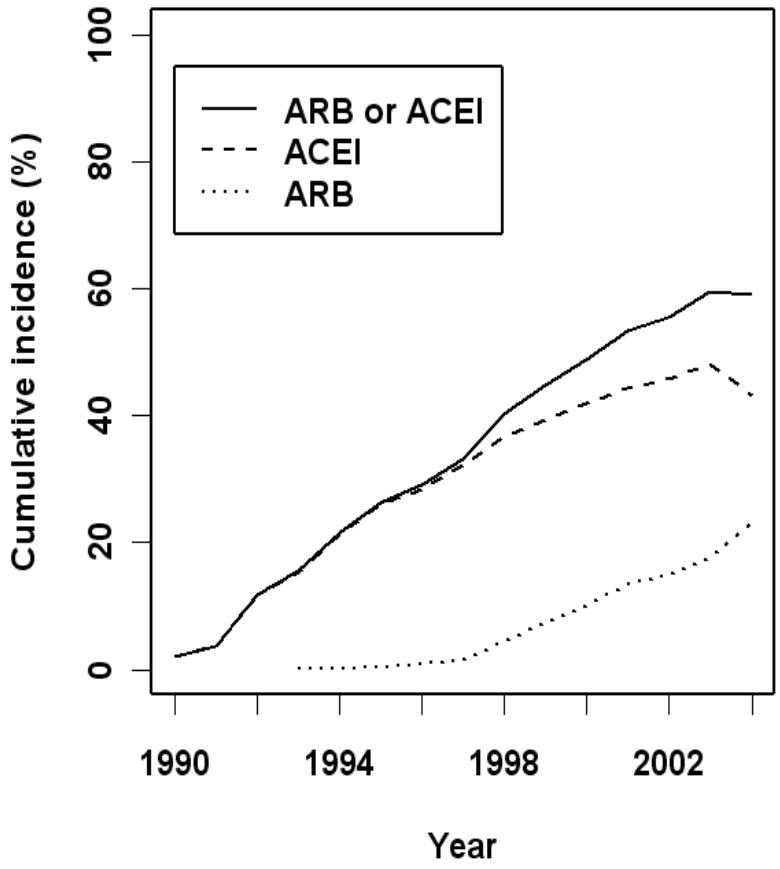
- Hemoglobin
- Lipids
- Glucose control
- Blood pressure
- BMI

Effect of ACEI/ARB & hypertension on CV death after RTX (n=2031, 157 CV deaths)

Variable	HR	95% CI	*P* Value
Multivariable model based on clinical expertise			
ACEI/ARB	0.57	0.40 to 0.81	0.002
no. of antihypertensive drugs	1.10	1.00 to 1.24	0.10
cumulative time on dialysis (per year)	1.13	1.04 to 1.24	0.006
recipient age at transplantation (per decade)	1.75	1.54 to 1.99	<0.001
year of first renal replacement therapy	1.05	1.00 to 1.11	0.075
transplant numbers	0.82	0.55 to 1.22	0.32
type 1 diabetes	1.46	0.36 to 5.97	0.61
type 2 diabetes	1.50	1.07 to 2.11	<0.018
$15 < GFR \leq 30$ *versus* $GFR > 30$ ml/min	2.92	2.08 to 4.10	<0.001
$GFR \leq 15$ *versus* $GFR > 30$ ml/min	6.00	4.15 to 8.68	<0.001

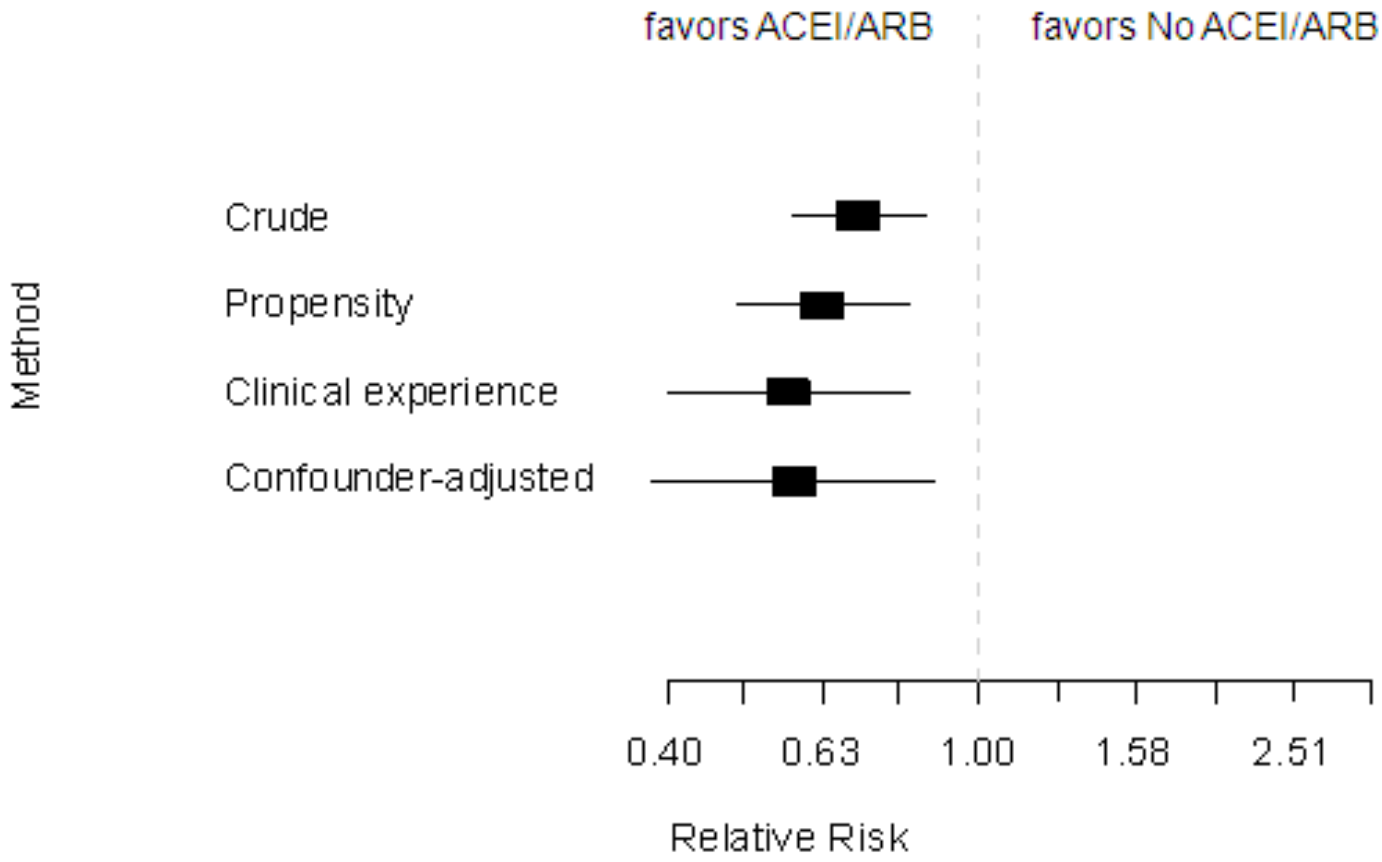
J Am Soc Nephrol. 2006 Mar;17(3):889-99

Cumulative incidence of patients that received ACEI or ARB during the lifetime of their transplant(s) (n=2246)



Heinze G et al. 2006J Am Soc Nephrol. 2006 Feb 15; [Epub ahead of print]

ACEI/ARB therapy after renal TX was associated with reduced risk of mortality



Heinze G et al. 2006J Am Soc Nephrol. 2006 Feb 15; [Epub ahead of print]

Agenda

Modifyable risk factors & CV outcomes

- Hemoglobin
- Lipids
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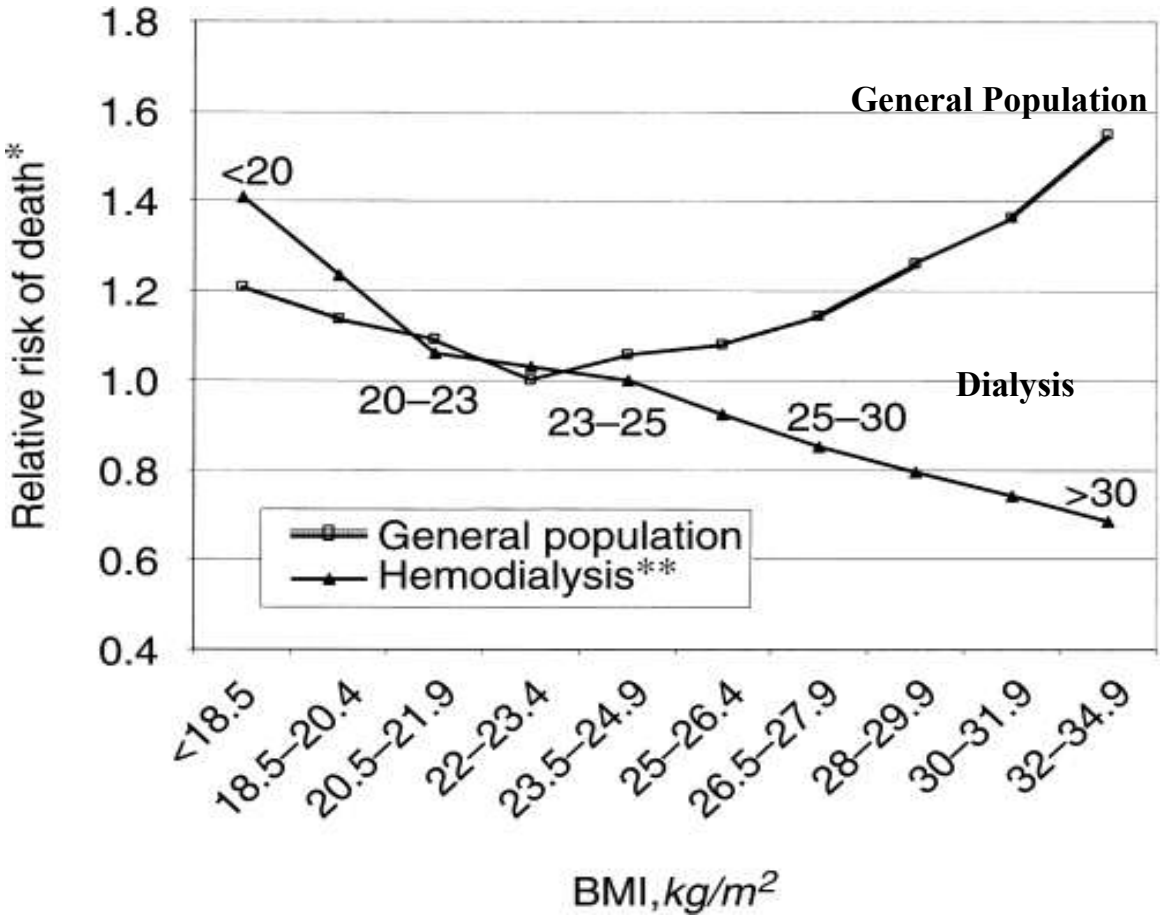
- BMI

The ‚risk factor' paradox



DOPPS 2004

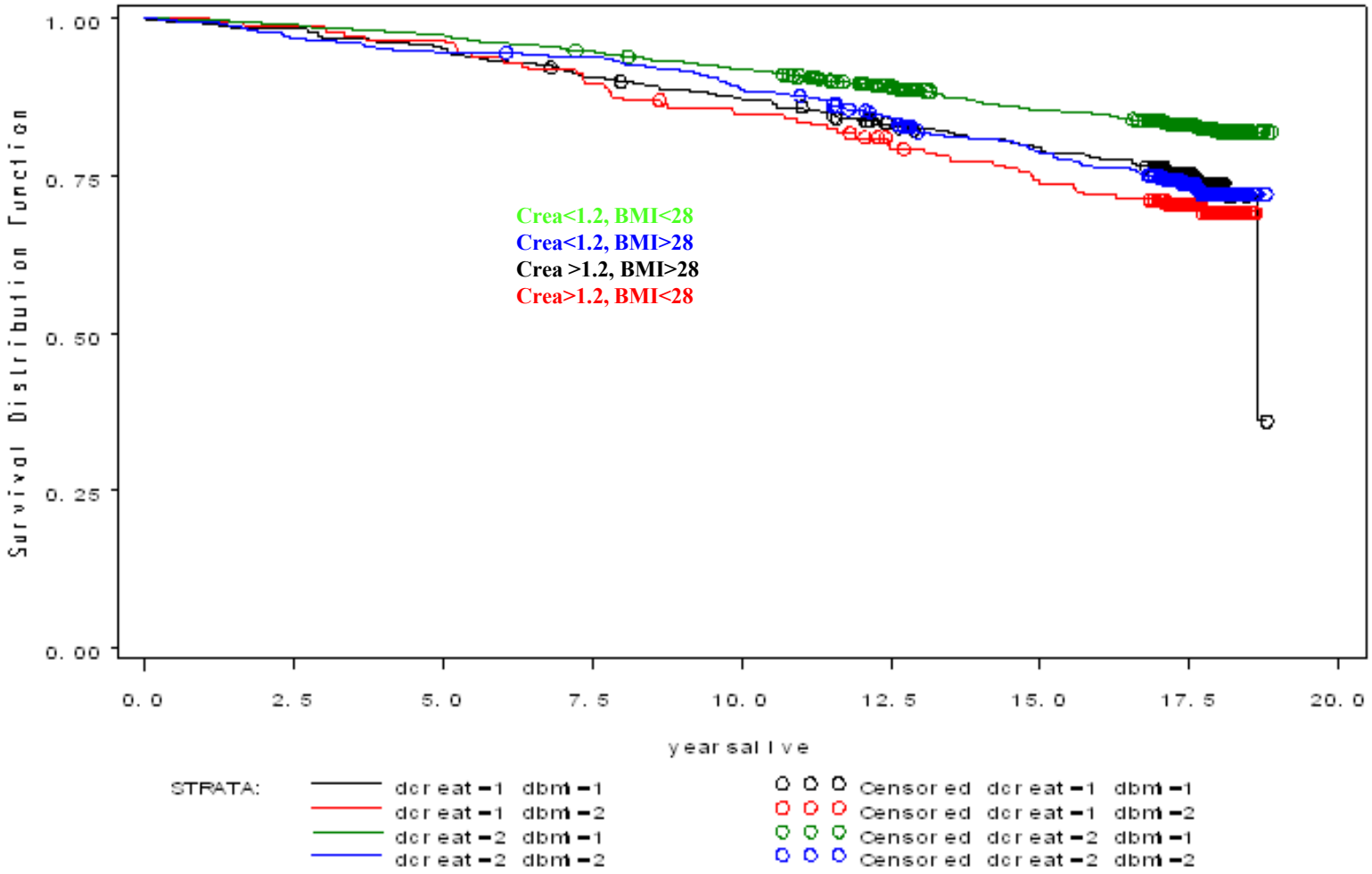
Research Design & Methods

- NHANES I - NHEF linked by SEQN
- subjects 25-74 years of age
- Median 17yr f/u
- weighted size of 29,807,750 subjects
- 19.6% high-normal to elevated creatinine

  (cut-off 1.2 mg/dl)

Results II

Elevated creatinine is associated with mortality, BMI modifies that risk



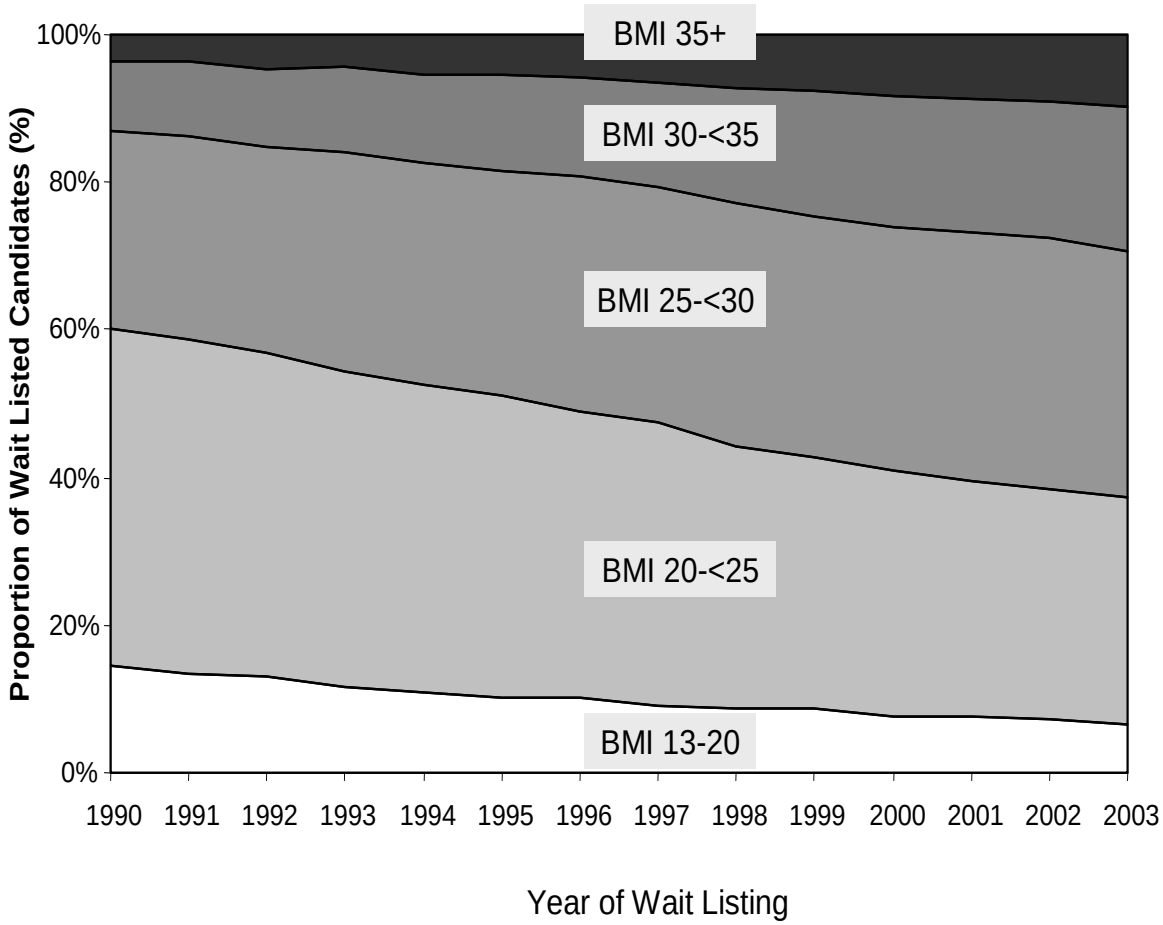
Oberbauer R & Ayanian J 2008

NHANES I and NHEF - Effect Modification

	RR	95%CI
SCr >1.2 x BMI (>28 vs <28)	0.72	0.49-1.07

Oberbauer R & Ayanian J 2008

Candidate BMI Levels by Year of Listing USRDS n=162,284



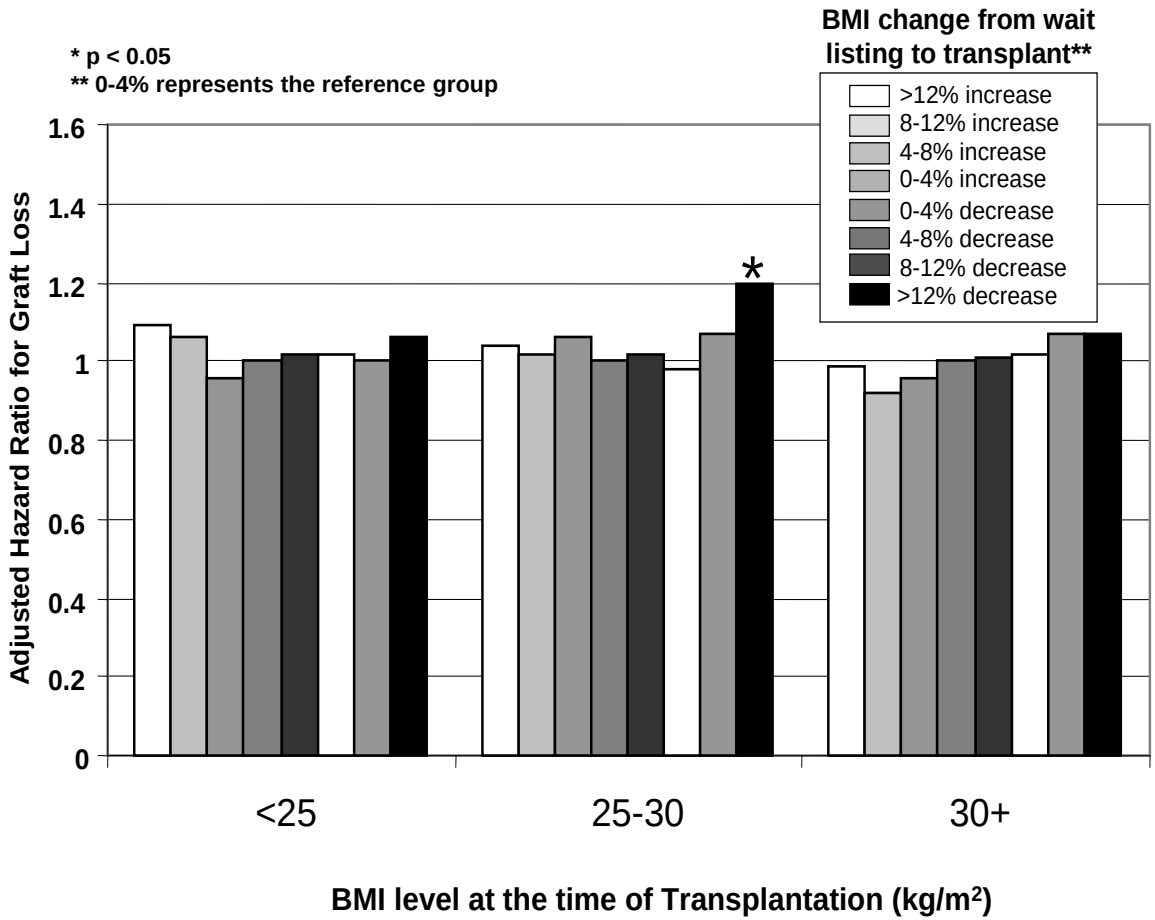
Schold, Oberbauer, Meier-Kriesche. Am J Transplant 2006, 6:1-10.

Table 4. Risk factors for patient weight increase to obese or morbidly obese levels from the time of candidate listing to transplantation (n=95,831*)

Variable (reference level)	Level	Odds Ratio	95% C.I.
Primary Cause of ESRD (GN)	Type-I Diabetes	1.02	0.93 – 1.13
	Type-II Diabetes	1.19	1.10 – 1.30
	Secondary GN/Vasculitis	0.85	0.73 – 0.98
	Interstitial Nephritis	1.02	0.89 – 1.16
	Hypertension	1.08	1.00 – 1.17
	Congenital Diseases	0.99	0.89 – 1.09
	Neoplasms/Tumors	0.76	0.55 – 1.06
Gender (Male)	Female	1.39	1.32 – 1.46
Age (50-<60)	18-<40	1.02	0.95 – 1.09
	40-<50	1.06	0.99 – 1.13
	60-<70	0.94	0.87 – 1.02

Schold, Oberbauer, Meier-Kriesche. Am J Transplant 2006, 6:1-10.

Adjusted HR for Overall Graft Loss by Change in BMI from Wait Listing to Transplant USRDS n=162,284



Schold, Oberbauer, Meier-Kriesche. Am J Transplant 2006, 6:1-10.

Conclusions

Modifyable risk factors & CV outcomes

- Hemoglobin
- Lipids
- Glucose control
- Blood pressure
- BMI

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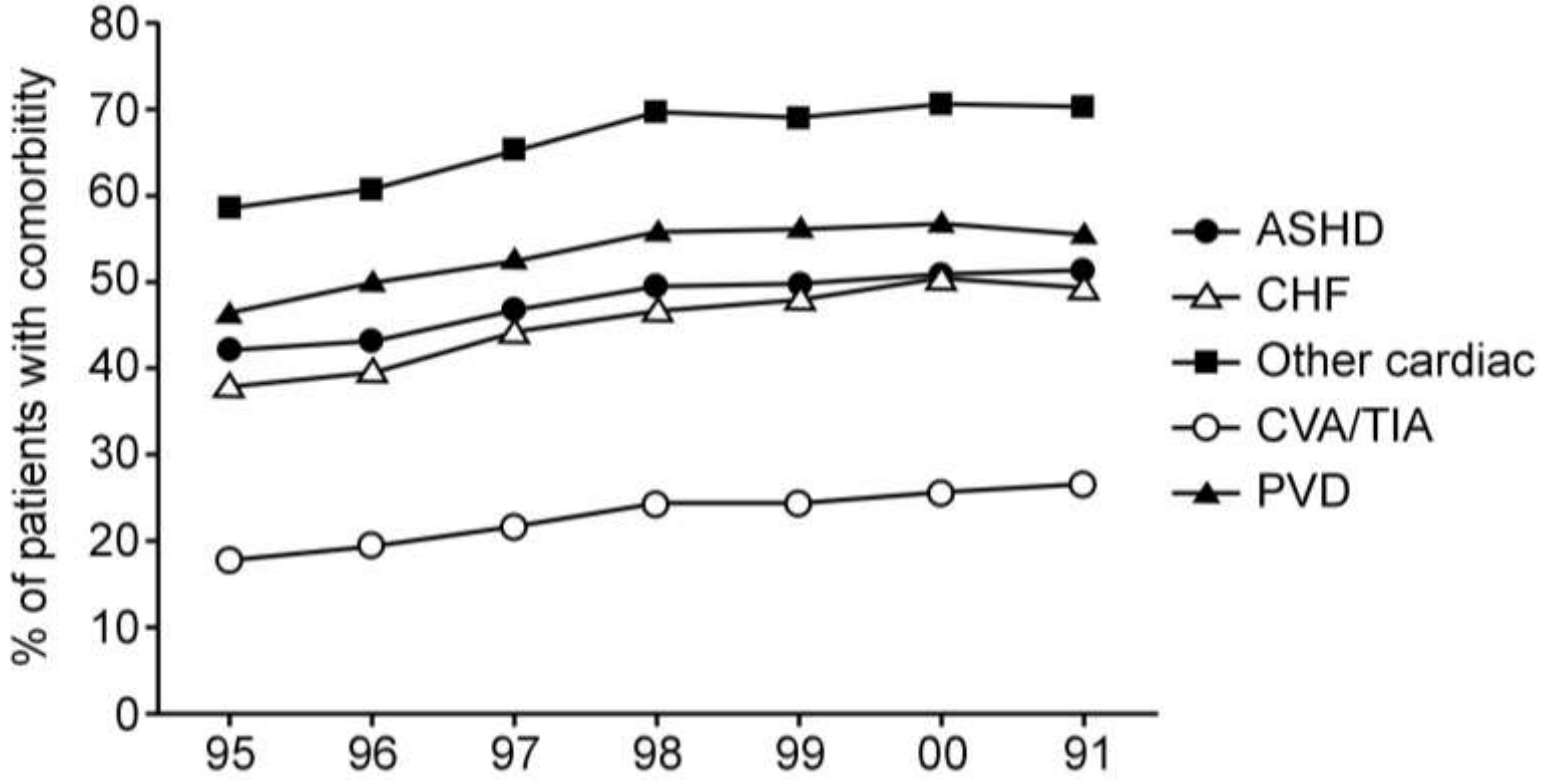
	Interstitial Nephritis	1.02	0.89 – 1.16
	Hypertension	1.08	1.00 – 1.17
	Congenital Diseases	0.99	0.89 – 1.09
	Neoplasms/Tumors	0.76	0.55 – 1.06
Gender (Male)	Female	1.39	1.32 – 1.46
Age (50-<60)	18-<40	1.02	0.95 – 1.09
	40-<50	1.06	0.99 – 1.13
	60-<70	0.94	0.87 – 1.02

Schold, Oberbauer, Meier-Kriesche. Am J Transplant 2006, 6:1-10.

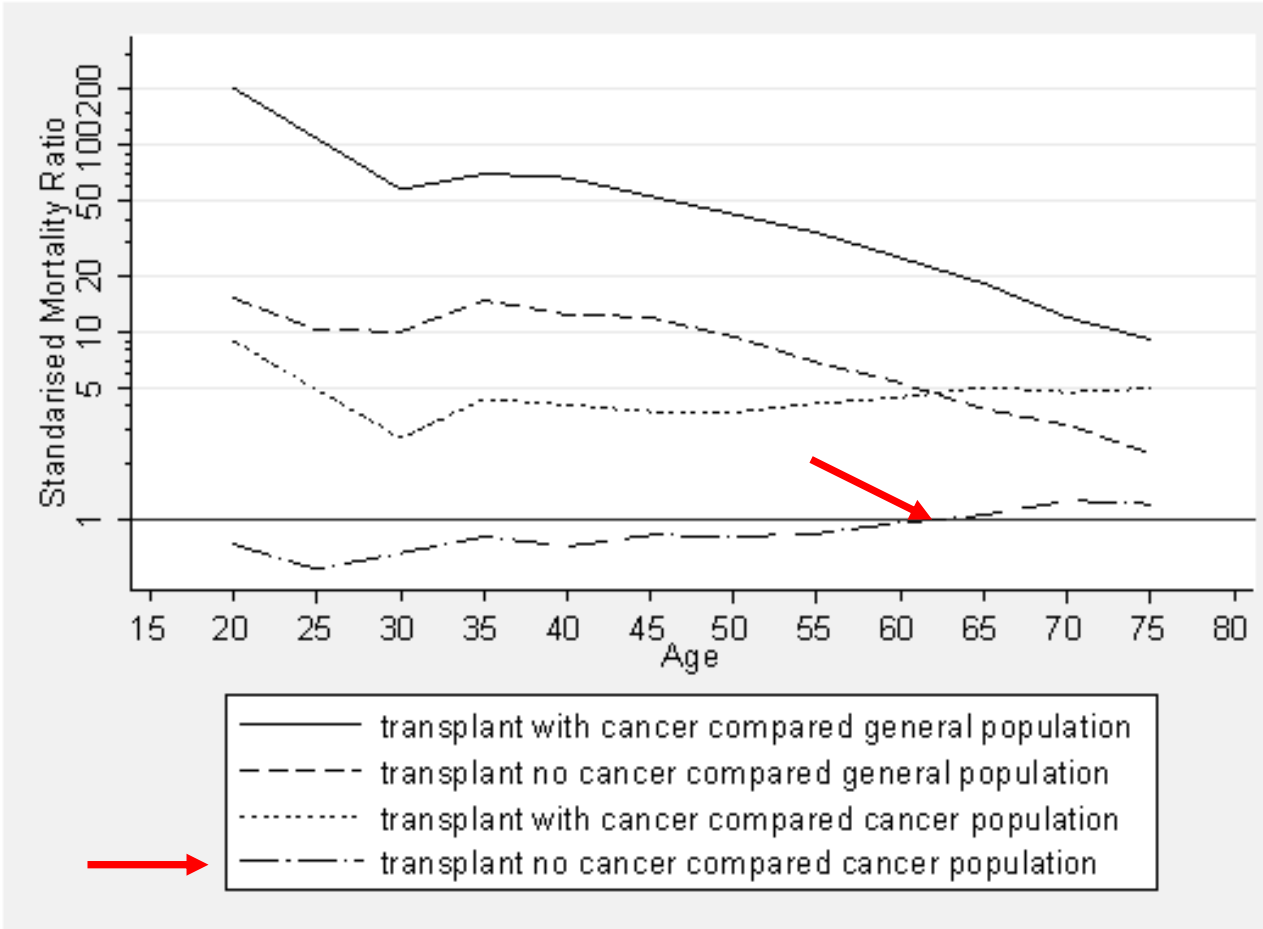
CV Morbidity in ESRD at time of transplantation



The probability of cardiac events averages 25 % in the first year after engraftment and 10 % thereafter, the annual probability of actual myocardial infarction is about 2 % (USRDS ADR 2005, Fig. 9.17 and 9.10).

 Modified from USRDS , ADR 2005, Fig 9.9

Survival following Diagnosis of Cancer (1980-2004)



Courtesy of Angela Webster, ANZ Data Registry 2007

DM2 after TX (OEDTR, n=779)

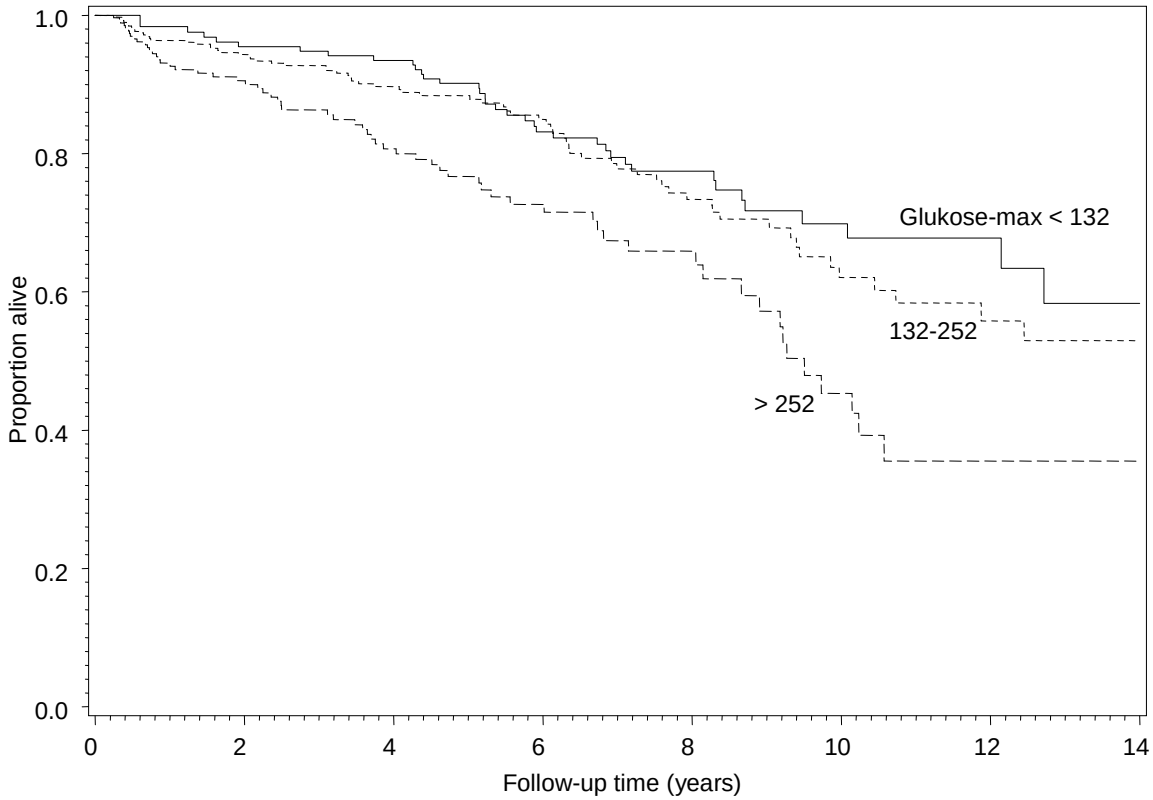
Patient survival (end point: dead)

ClinExp Model (ohne Glukose/hba1c) hat R-Squared 17.3%

Parameter	Marginal R-Squared (univariate)	Partial R-Squared ClinExp-Model
Glukose-median	0.41%	0.1%
Glukose-max	2.24%	0.9%
HBa1c	1.18%	0.1%

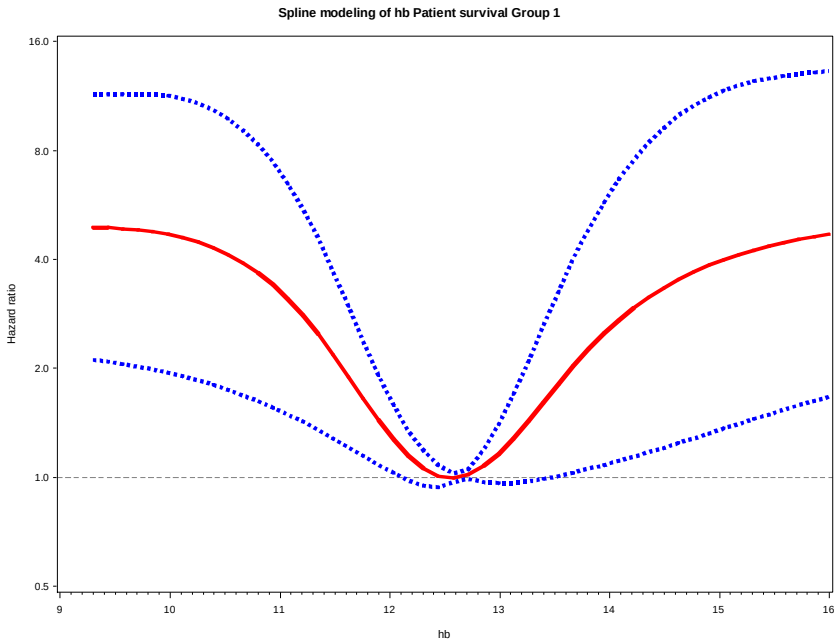
Wiesbauer F et al 2009

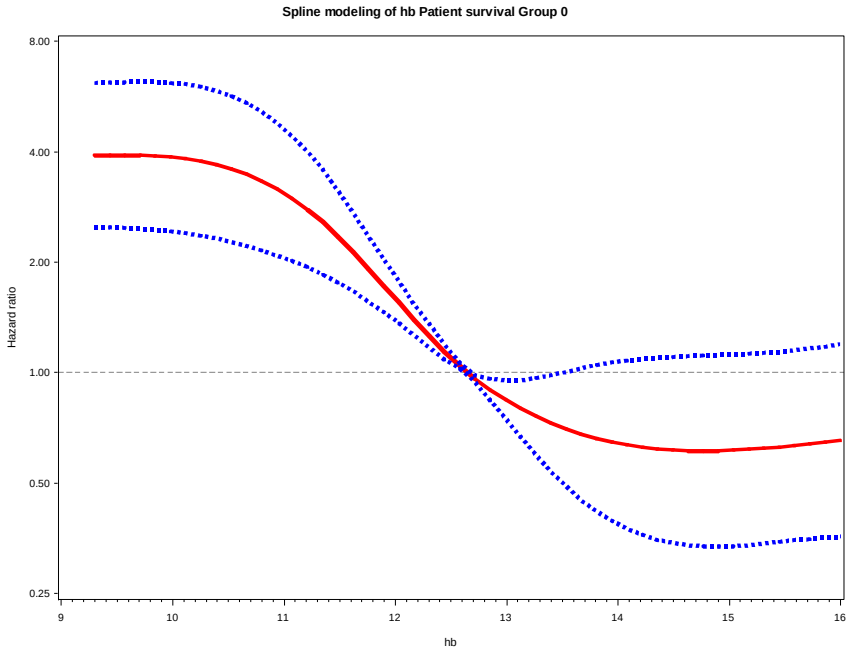
Association of glucose control and mortality in patients with DM2 (OEDTR, n=779)



Wiesbauer F et al 2009

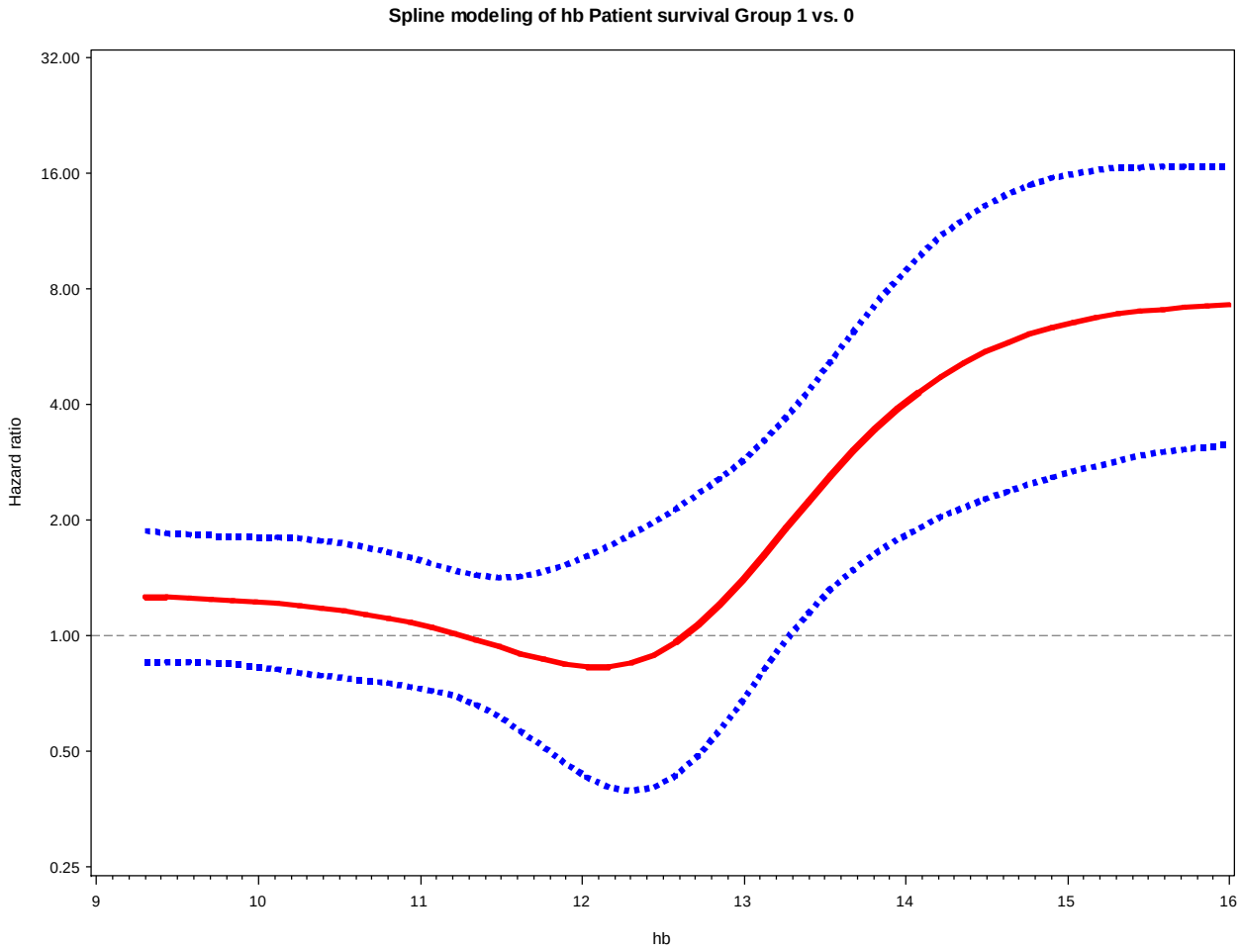
CV Mortality in RTX depending on hemoglobin levels and ESA treatment (OEDTR, N=1878, 242 events)





R.O.40/22 **Heinze G et al. 2009**

CV Mortality in RTX depending on hemoglobin levels and ESA treatment (OEDTR, N=1878, 242 events)



R.O.41/22 **Heinze G et al. 2009**

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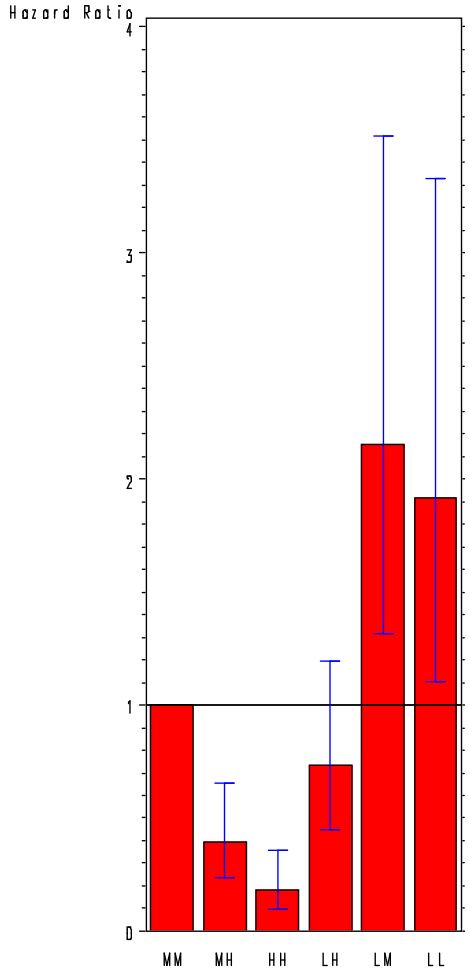
Elisabethinen Linz

Hb Variability and TX-graft loss (OEDTR n=2041, 360 events, 1990-2005)

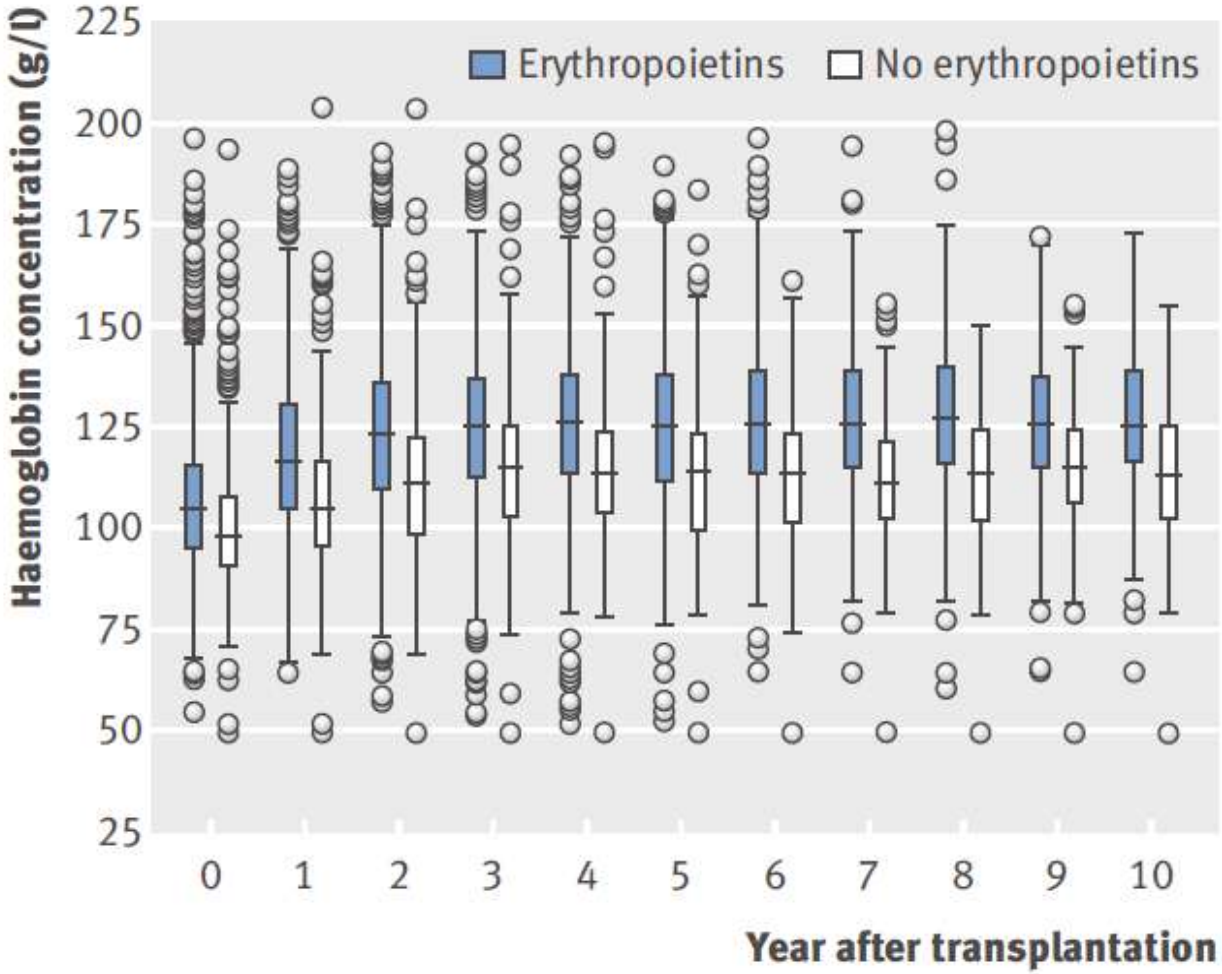


Covariables used in OEDTR n=1794, 345 events, 1990-2005

Variable	Erythropoietins	No erythropoietins	P value	No. of patients (erythropoietins /no erythropoietins)
Age at transplantation (years)	48.6 (15.0)	48.7 (16.4)	0.889	1794 (805/989)
Donor age (years)	47.1 (15.3)	42 (15.8)	<0.001	1597 (774/823)
Female donor	331 (42.5%)	347 (42%)	0.829	1606 (779/827)
Female recipient	350 (44.9%)	281 (34%)	<0.001	1606 (779/827)
Years on dialysis before transplantation	1.8 (0.9-3.1)	1.8 (0.9-3)	0.871	1794 (805/989)
Year of transplantation	1998 (1995-2001)	1999 (1995- 2002)	<0.001	1794 (805/989)
Body weight (kg)	71.3 (16)	71.5 (17.9)	0.837	1224 (575/649)
Haemoglobin concentration (g/l)	100 (91-110)	105 (96-116)	<0.001	1572 (752/820)
STRF	191 (156-227)	192.1 (160-232.8)	0.388	1073 (545/528)
TRFS	24.2 (16.4-32.8)	23.6 (16.1-32.4)	0.431	1056 (538/518)
Panel reactive antibodies	0 (0-4)	0 (0-4)	0.728	1596 (779/817)
Sum of HLA mismatches	2.5 (1.3)	2.4 (1.3)	0.239	1542 (756/786)
Cold ischemia time (days)	16.4 (8.4)	16.8 (8)	0.332	1408 (694/714)
Type of immunosuppression:				
S+MMF+CNI	180 (22.4)	188 (19)	<0.001	1794 (805/989)
S+AZA+CNI	153 (19)	125 (12.6)	<0.001	1794 (805/989)
S-free*	23 (2.9)	12 (1.2)	<0.001	1794 (805/989)
Other†	449 (55.8)	664 (67.1)	<0.001	1794 (805/989)
Induction therapy (ATG)	188 (23.4)	114 (11.5)	<0.001	1794 (805/989)
CNI based	415 (80.7)	478 (83.7)	0.200	1085 (514/571)
Hypertension	730 (90.7%)	709 (71.7%)	<0.001	1794 (805/989)
No of antihypertensive drugs prescribed	2 (1-4)	2 (0-3)	<0.001	1794 (805/989)
Systolic arterial pressure (mm Hg)	140.3 (51.1)	118 (52)	<0.001	1117 (513/604)
Diastolic arterial pressure (mm Hg)	82.2 (33.6)	70.2 (41.3)	<0.001	1118 (513/605)
Cholesterol concentration (mmol/l)	5.26 (1.64)	5.10 (1.46)	0.046	1523 (736/787)
Coronary heart disease	132 (27.3%)	186 (29.5%)	0.410	1114 (484/630)
Heart failure	90 (18.6%)	107 (17%)	0.485	1114 (484/630)
Any heart disease	214 (45.1%)	283 (46.9%)	0.560	1077 (474/603)
Cerebrovascular disease	74 (16.1%)	70 (12%)	0.058	1045 (461/584)
Peripheral vascular disease	110 (23.9%)	132 (22.6%)	0.632	1045 (461/584)
Any vascular disease	153 (34.2%)	164 (29.9%)	0.149	997 (448/549)
Biopsy confirmed acute rejection	366 (46%)	250 (29.5%)	<0.001	1642 (795/847)
Chronic allograft nephropathy	164 (20.4%)	75 (7.6%)	<0.001	1794 (805/989)
Cadaveric donor	736 (91.4%)	855 (86.5%)	0.001	1794 (805/989)
Diabetes	233 (28.9%)	299 (30.2%)	0.552	1794 (805/989)
Primary indication for transplantation:				
Diabetes	166 (20.6%)	249 (25.2%)	0.023	1794 (805/989)
Immune mediated	102 (12.7%)	121 (12.2%)	0.781	1794 (805/989)
PCKD	90 (11.2%)	124 (12.5%)	0.378	1794 (805/989)
Other or unknown	444 (55.2%)	485 (49.0%)	0.010	1794 (805/989)

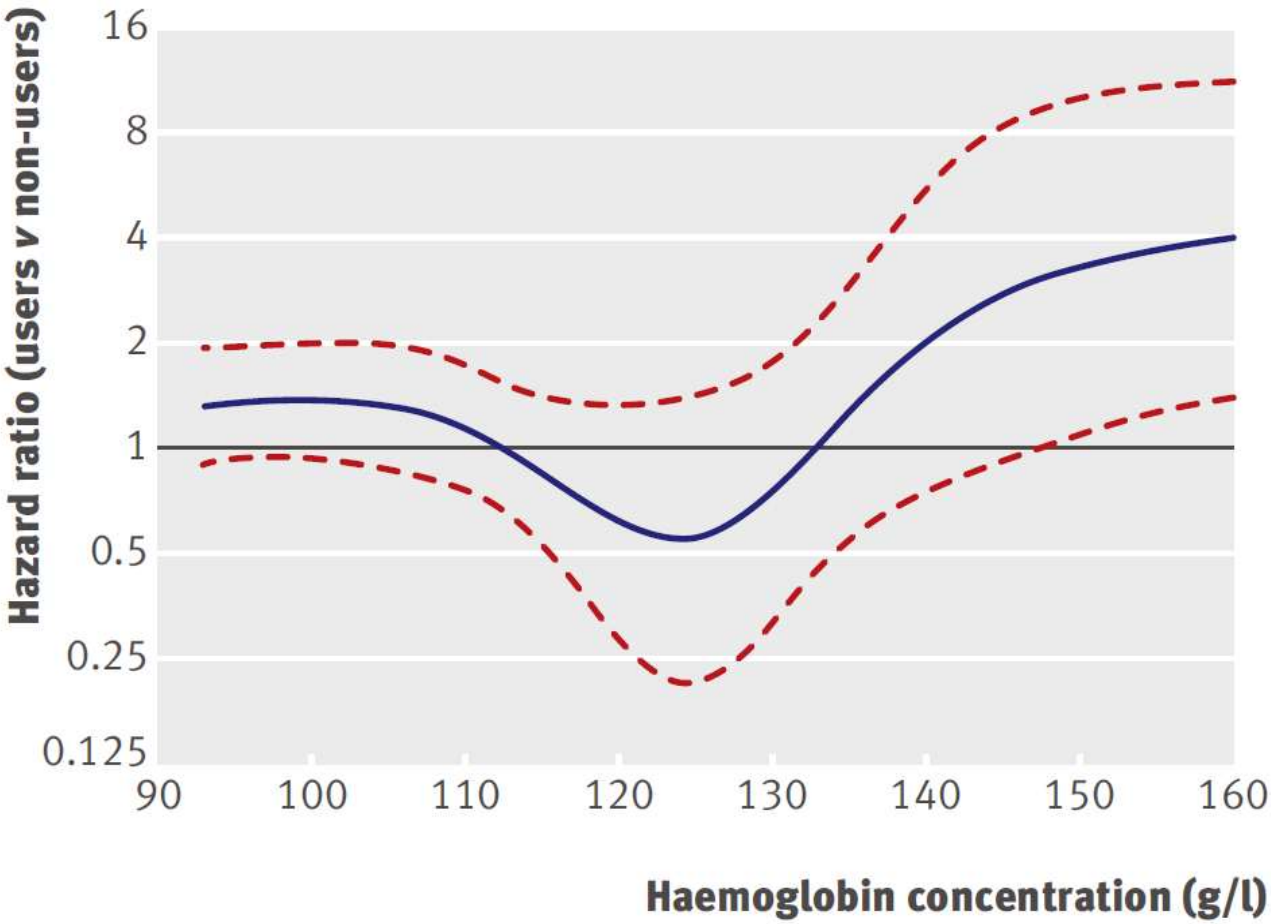
Heinze G et al. BMJ 2009 Oct (in press)

Distribution of Hb over time after TX (OEDTR n=1794, 345 events, 1990-2005)



Heinze G et al. BMJ 2009 Oct (in press)

HR of death depending on Hb levels and superimposed ESA use/nonuse



adjusted for:

dialysis status, cerebrovascular disease, peripheral vascular disease, coronary heart disease, heart failure, cholesterol level, immunosuppressive regimen, diabetes status, age at transplantation, cold ischemia time

Heinze G et al. BMJ 2009 Oct (in press)

Glucose control in RTR

Table 6. Classes of drugs used to treat diabetes in RTR (102)[a]

Class	Drug	Dosing Recommendations	Adverse Effects/Drug Interactions
Second-generation sulfonylureas	Glipizide	Preferred agent	Hypoglycemia
	Glyburide	Not recommended	
	Glimiperide	Begin with low dosage	
Thiazolidinediones	Pioglitazone Rosiglitazone	None	Volume retention/edema, CHF
Meglitinide	Repaglinide	Preferred agent	Levels may be increased with statin/fibrate use
	Nateglinide	Renally cleared; begin with low dosage	
Biguanides	Metformin	Not recommended, especially with reduced GFR	Lactic acidosis
α -Glucosidase inhibitors	Acarbose	Not recommended with creatinine $\geq$2.0 mg/dl	GI distress
GLP-1 (incretin mimetic)	Exenatide	None	No published data on interactions
DPP-IV inhibitor	Sitagliptin	Reduce dosage: 50% for GFR 30 to 50 75% for GFR <30	No published data on interactions
Insulin	Rapid acting: regular, lispro, aspart Intermediate acting: NPH Long acting: glargine	None	Hypoglycemia

[a]DPP-IV, dipeptidyl peptidase IV; GLP-1, glucagon-like peptide-1; NPH, neutral protamine Hagedorn.

Shirali AC et Bia MJ. CJASN 2008 Mar;3(2):491-504

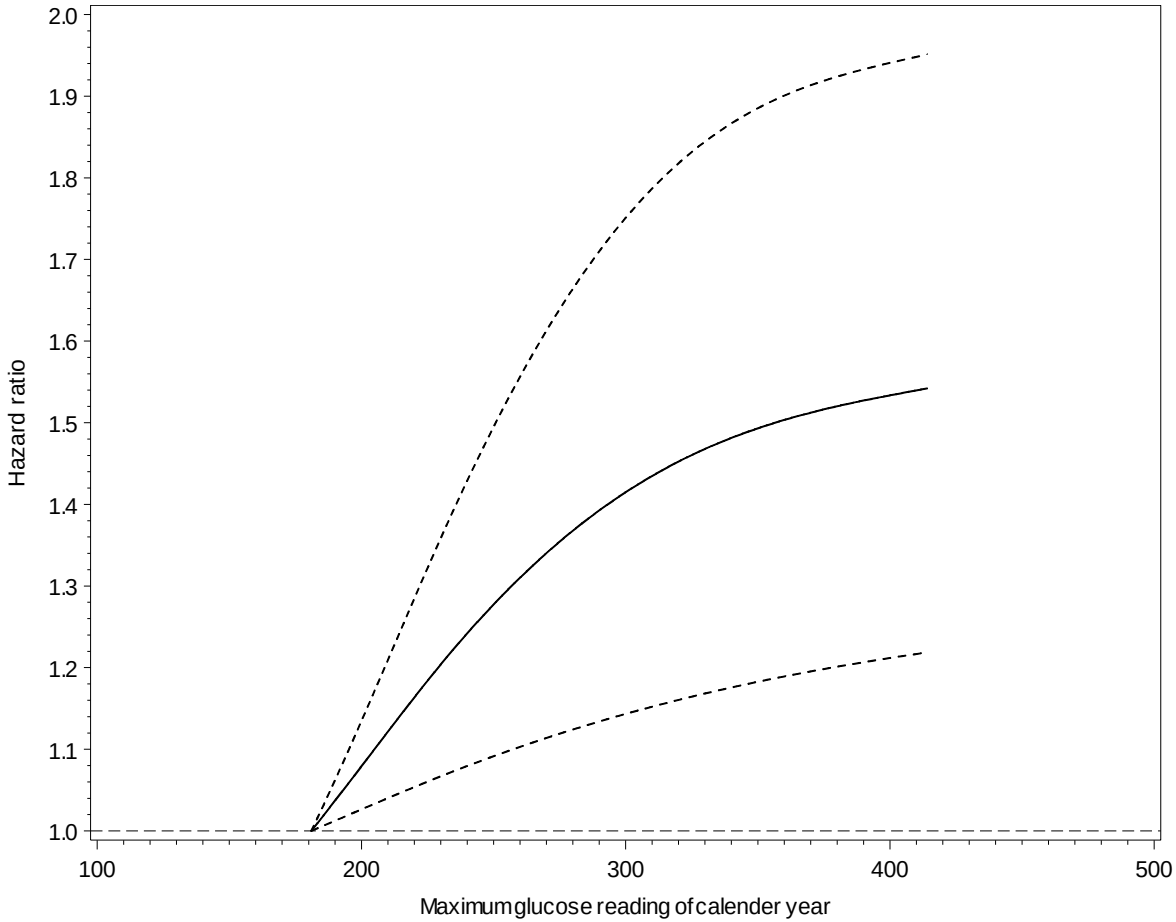
Statin use and CV Mortality in RTX (OEDTR, N=1878, 242 events)

Type of analysis	Hazard ratio	Lower 95% limit HR	Upper 95% limit HR	Pr > |t|
MSM analysis (adjusting for informative censoring due to death of other causes and graft loss)	0.591	0.344	1.014	0.067
Cox regression analysis (not adjusting for informative censoring)	0.802	0.565	1.139	0.217

The results from MSM analysis are very similar to those from all-cause mortality. Cox regression analysis, which does not account for informative censoring (death from other than cardiovascular causes) yields a higher hazard ratio.

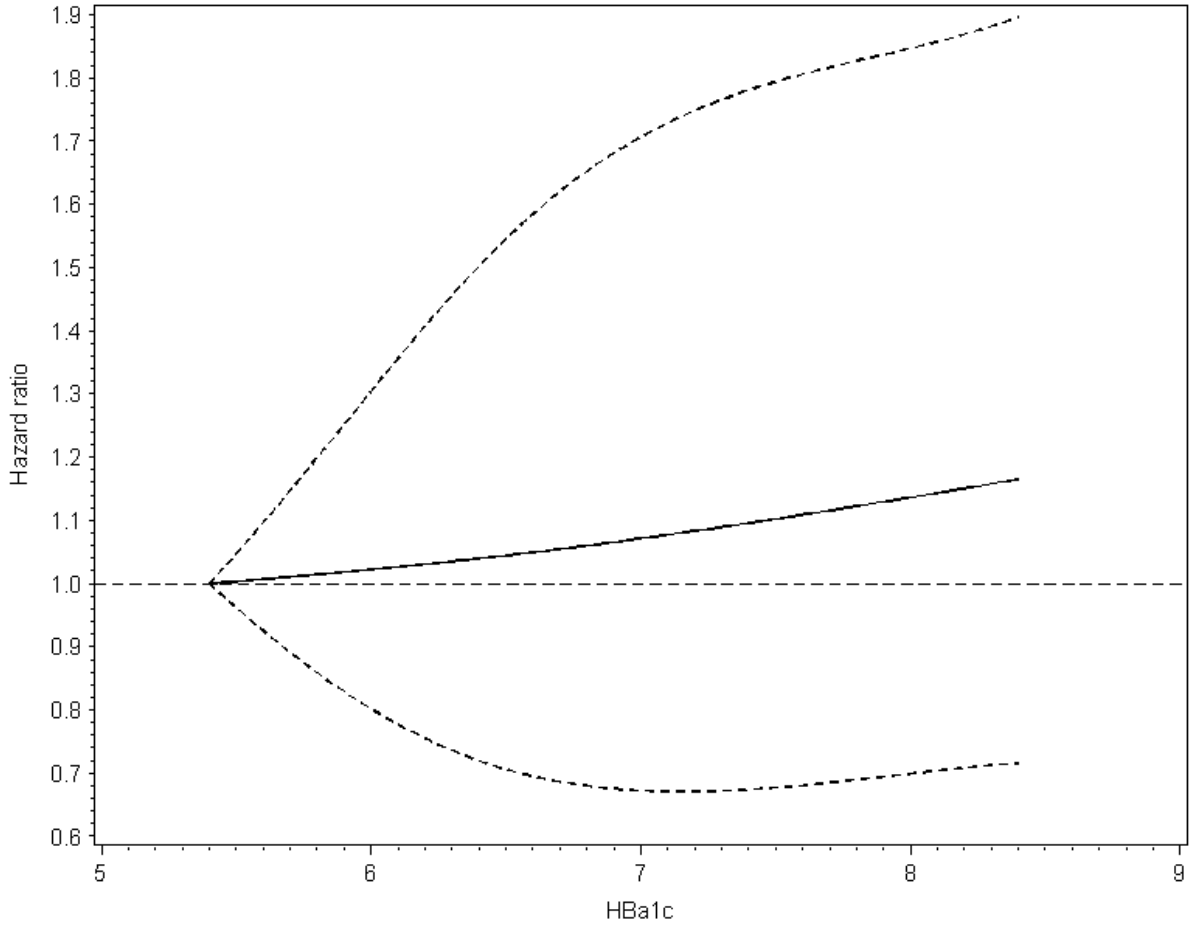
Wiesbauer F et al J Am Soc Nephrol. 2008 Nov;19(11):2211-8

Cox proportional hazard model for glucose control and mortality using cubic splines (OEDTR, n=779)



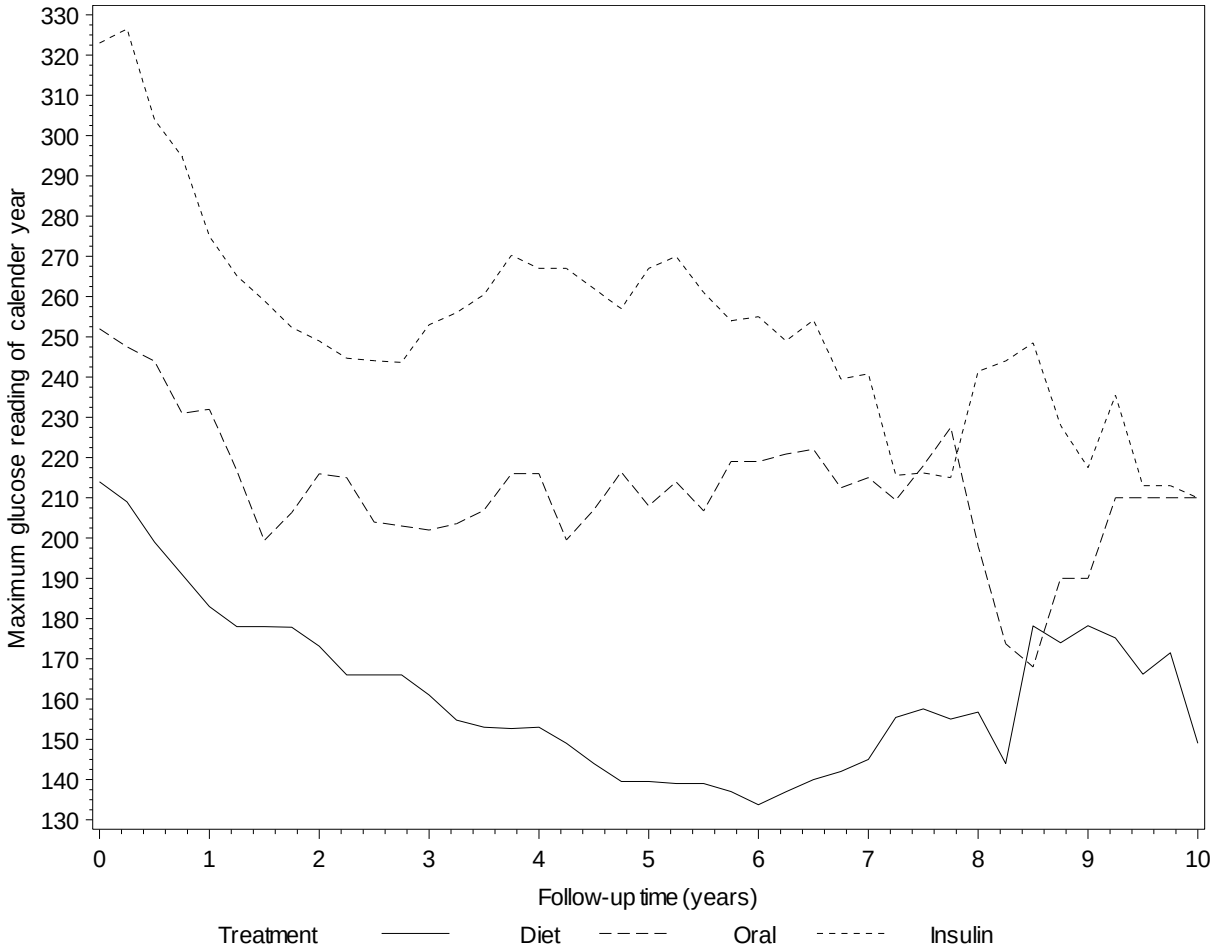
Wiesbauer F et al Transplantation 2010; 89:612-619

HR of death of DM2 after TX (OEDTR, n=779)



Wiesbauer F et al Transplantation 2010; 89:612-619

Maximum glucose levels per calendar year over the observation time of ten years.



Wiesbauer F et al Transplantation 2010; 89:612-619

HR of death of DM2 after TX treated with oral ADD vs insulin (OEDTR, n=779)

---------- Variable=TREAT2 (oral vs insulin) ----------
-

confounder	95% Lower Confidence Limit for Hazard Ratio	Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio	min 0.296 max 0.912
*** Marginal Structural Model ***	0.296	0.456	0.702	
Currently on dialysis	0.306	0.463	0.701	
Diabetes at 1st RRT	0.308	0.471	0.720	
Time on dialysis	0.313	0.474	0.718	
ImmId	0.317	0.481	0.729	
TX Number	0.321	0.486	0.735	
bcar	0.321	0.486	0.735	
*** Crude ***	0.321	0.486	0.735	
can	0.322	0.488	0.738	
KHK/CMP	0.324	0.490	0.742	
BP	0.328	0.496	0.751	
Glukose_max	0.328	0.497	0.755	
Year of 1st RRT	0.332	0.502	0.760	
HB	0.336	0.509	0.772	
Age	0.339	0.512	0.775	
Cholest	0.341	0.517	0.785	
HBa1c	0.346	0.525	0.796	
*** Glukose_max+HB+Age+CurrDial+Vasc ***	0.353	0.544	0.838	
Vasc	0.364	0.554	0.844	
*** Heart/VascDis+BP+TimeOnDialysis+Age+Year1RRT+Diab1RRT+ImmID ***	0.378	0.587	0.912	

Wiesbauer F et al 2009

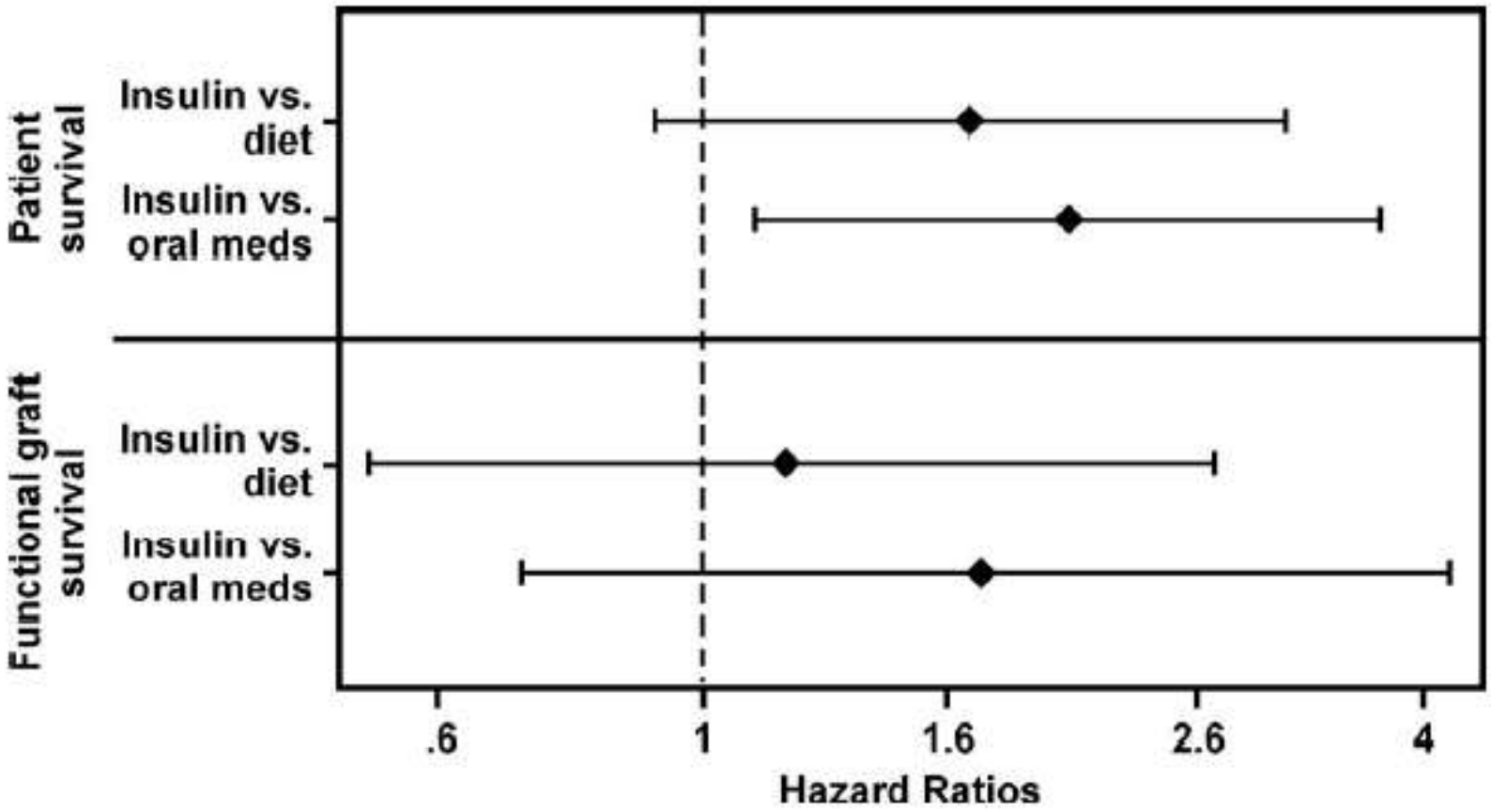
Higher risk of IV iron and ESA use of failed KTX (n=9922 vs HD n=210,635 USRDS)

	AOR (95% CI)			
	IV iron by month 6	p	Epoetin by month 6	p
Incident dialysis patients	Reference		Reference	
Failed transplant patients	1.47 (1.40, 1.55)	<0.0001	1.57 (1.48, 1.67)	<0.0001

Adjusted for incident dialysis or failed transplant, year of dialysis initiation, sex, race, and comorbid conditions.

Solid CA et al. Kidney Int 2007;71:425–430

HR derived from the analysis using MSM according to treatment group and outcome (OEDTR, n=779)



Wiesbauer F et al Transplantation 2010; 89:612-619