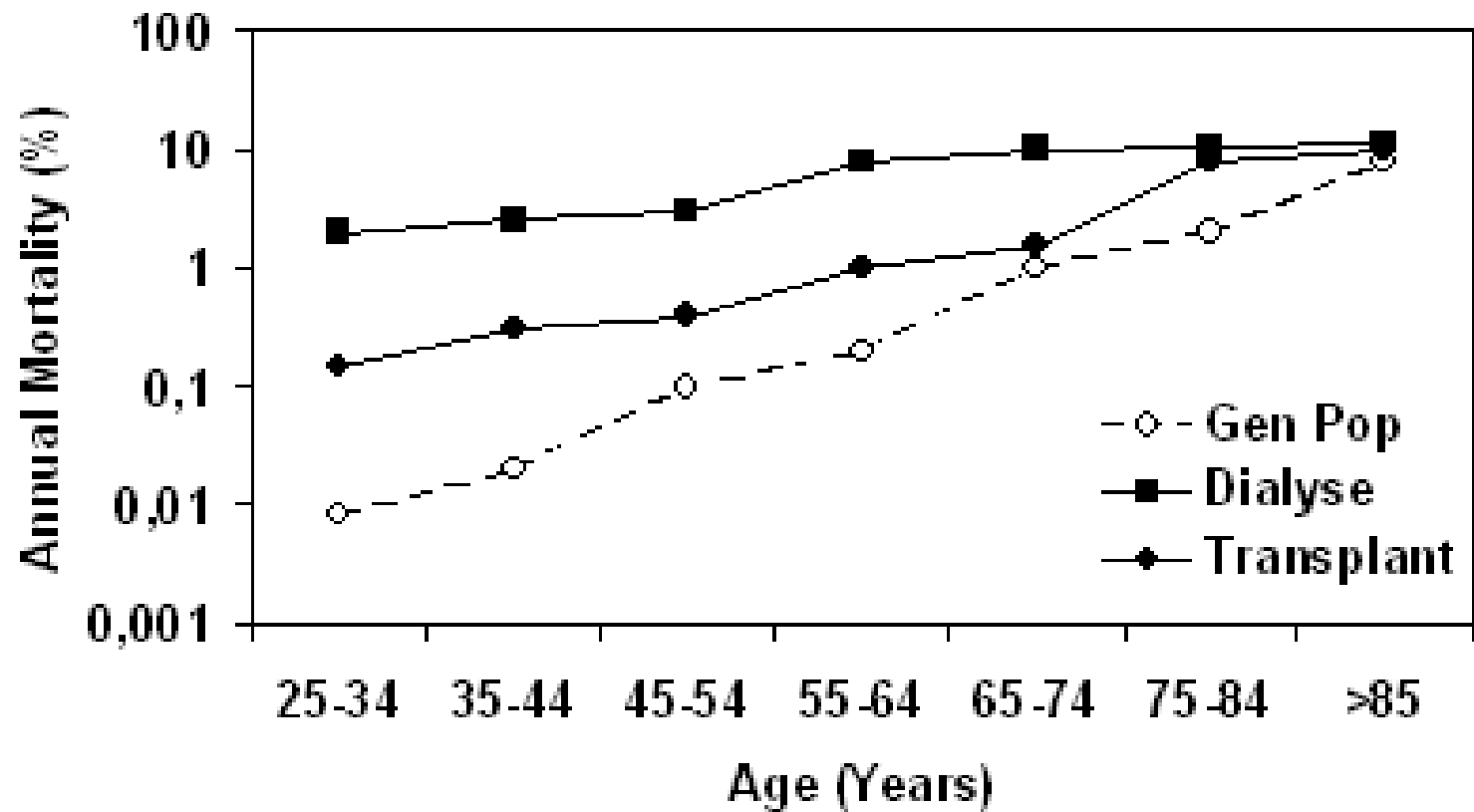


# Cardiovascular Risk Reduction in Kidney Transplant Recipients

Rainer Oberbauer

## CV Mortality in ESRD compared to the general population



# Risk factors for the development of CVD after renal TX

Traditional Risk Factors	Transplant-Associated Risk Factors	Emerging Risk Factors
<p>Modifiable/potentially modifiable</p> <ul style="list-style-type: none"> <li>obesity</li> <li>diabetes</li> <li>hypertension</li> <li>hyperlipidemia</li> <li>smoking</li> </ul> <p>Nonmodifiable</p> <ul style="list-style-type: none"> <li>gender</li> <li>age</li> <li>family history</li> </ul>	<ul style="list-style-type: none"> <li>Immunosuppression</li> <li>CKD<sup>b</sup></li> <li>Proteinuria<sup>b</sup></li> <li>Anemia<sup>b</sup></li> </ul>	<ul style="list-style-type: none"> <li>Inflammation</li> <li>homocysteine</li> <li>CRP</li> <li>AGE</li> </ul>

<sup>a</sup>AGE, advanced glycation end products; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease.

<sup>b</sup>These risk factors are also relevant in the CKD population (9–11).

# Agenda

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## Modifyable risk factors & CV outcomes

Hemoglobin

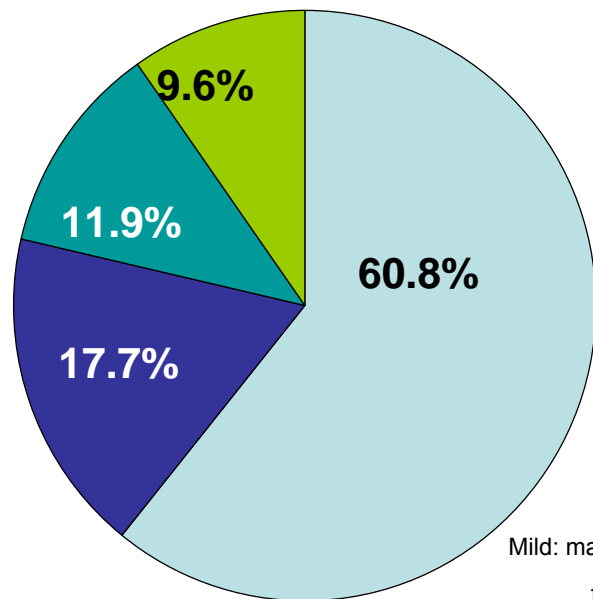
Lipids

Glucose control

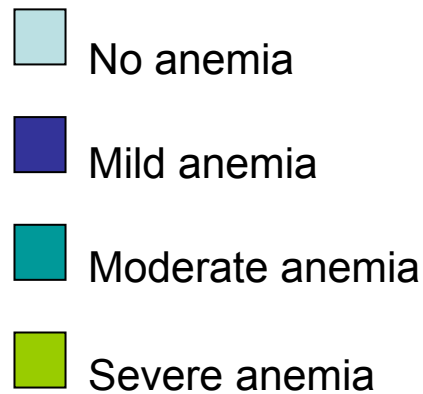
Blood pressure

BMI - Obesity

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



Male patients  
n=2641



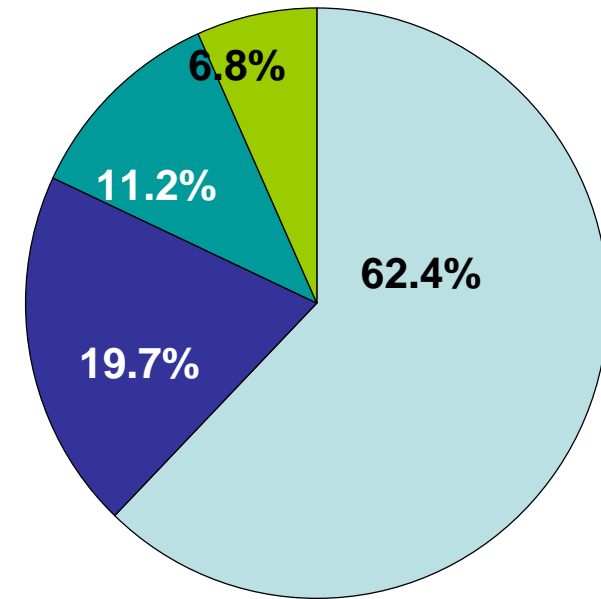
Mild: males: Hb >12 g/dL and Hb ≤13 g/dL

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



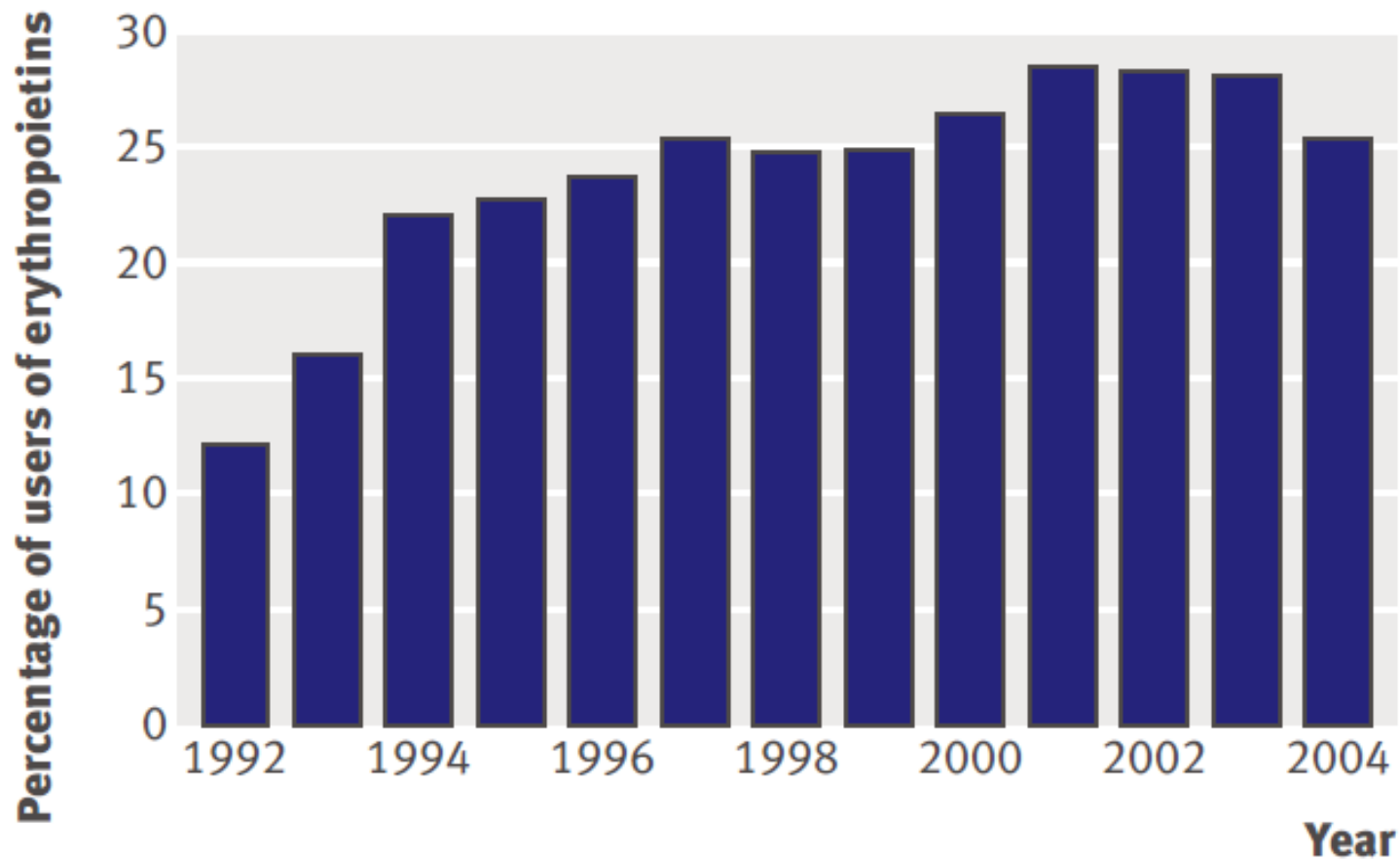
Female patients  
n=1622

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

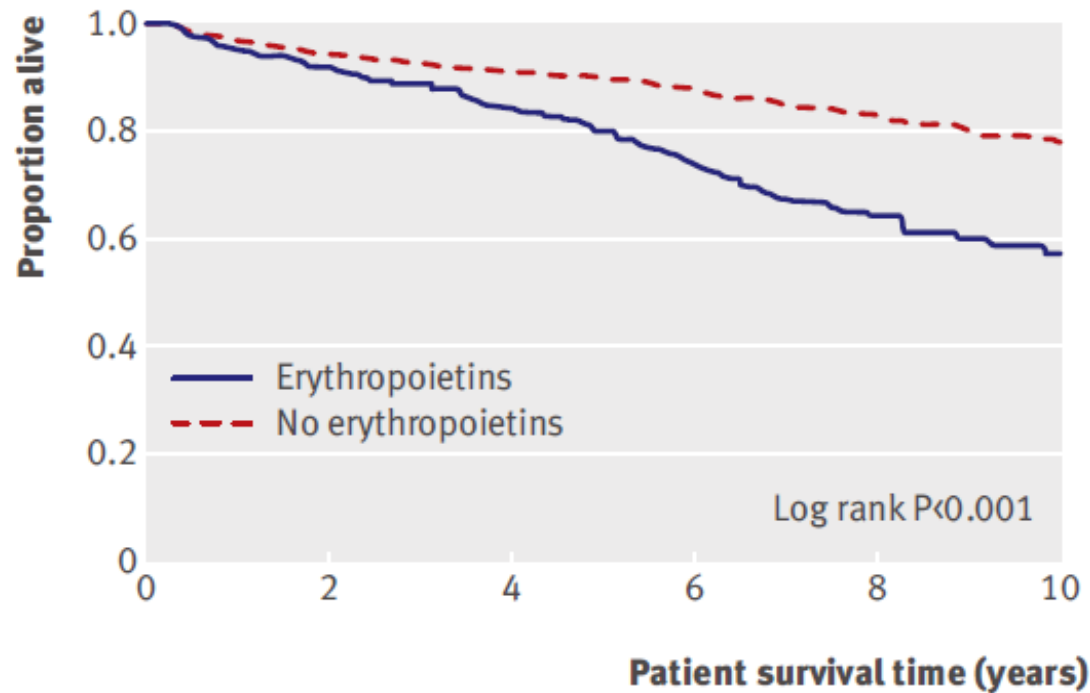
	Mortality			Return to dialysis		
	HR	95% CI	p value	HR	95% CI	p value
Hb (1 g/L decrease)	1.011	1.001–1.022	0.033	1.019	1.006–1.032	0.003
Presence of anemia	1.690	1.115–2.560	0.013	2.465	1.485–4.090	<0.001

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

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



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



### Patients at risk:

#### Erythropoietins

560    339    241    165    97    46

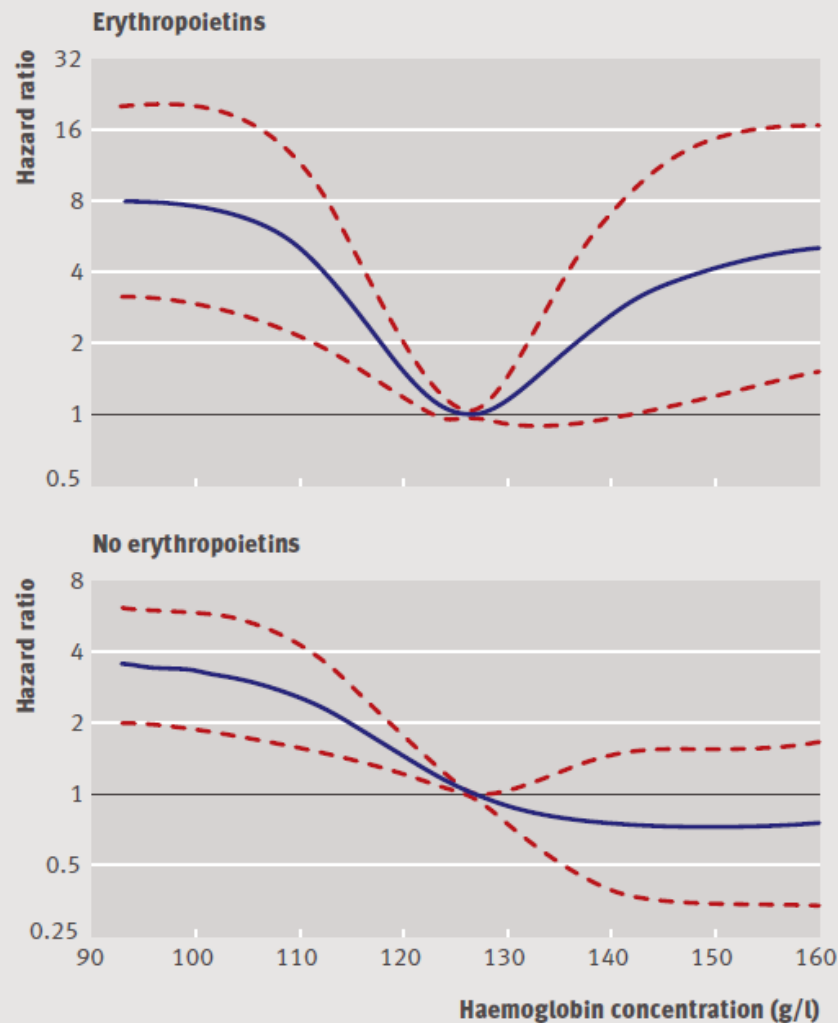
#### No erythropoietins

1234    1016    761    501    314    157



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

## MULTIVARIABLE COX REGRESSION FOR RISK OF DEATH

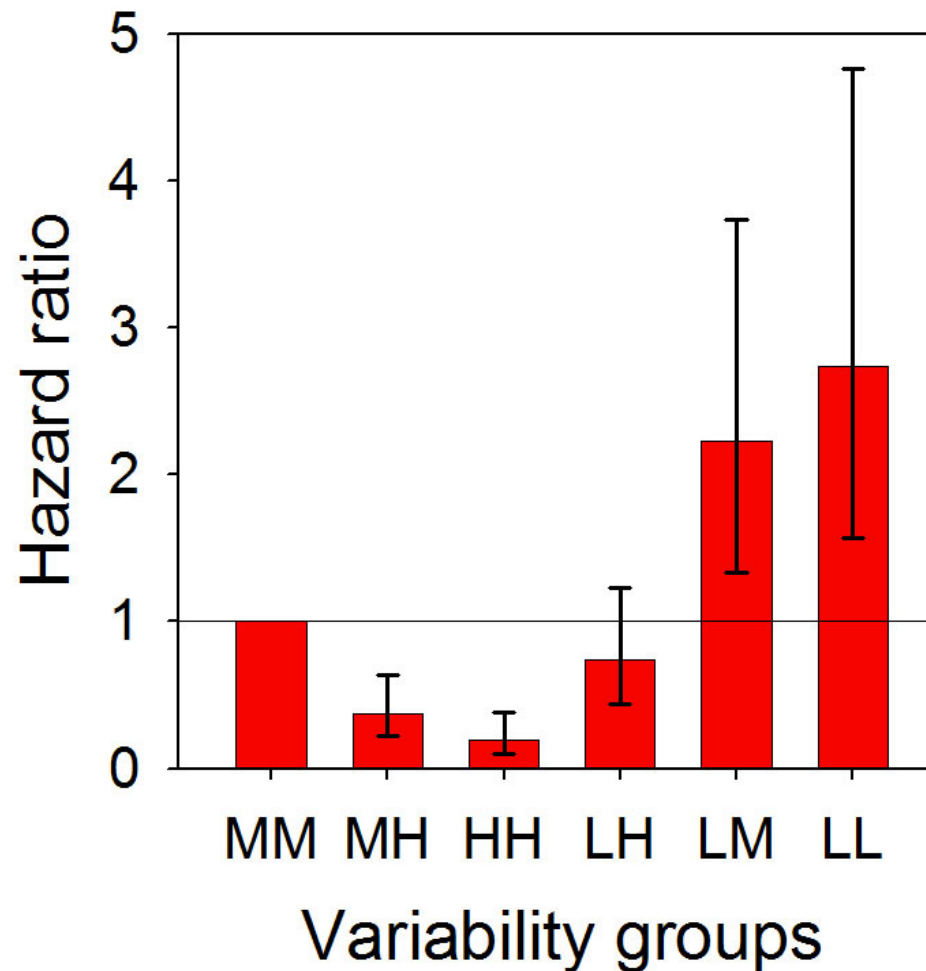


adjusted for:

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

# Agenda

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## Modifyable risk factors & CV outcomes

Hemoglobin

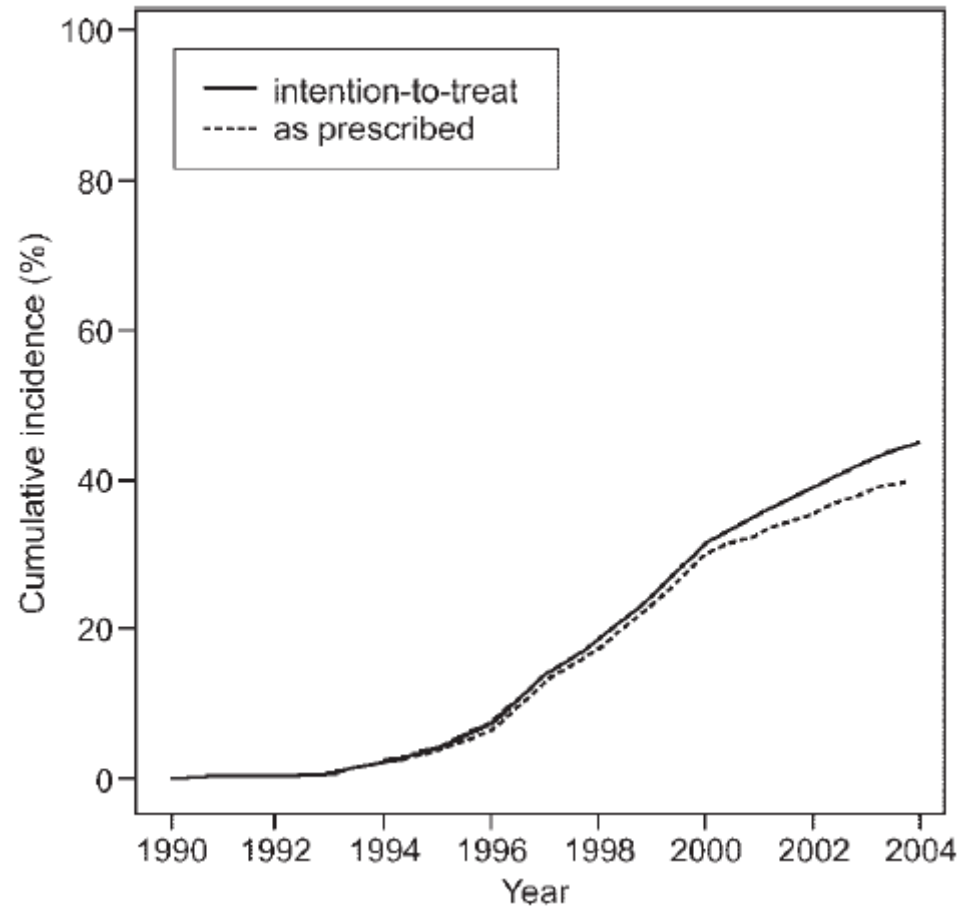
Lipids

Glucose control

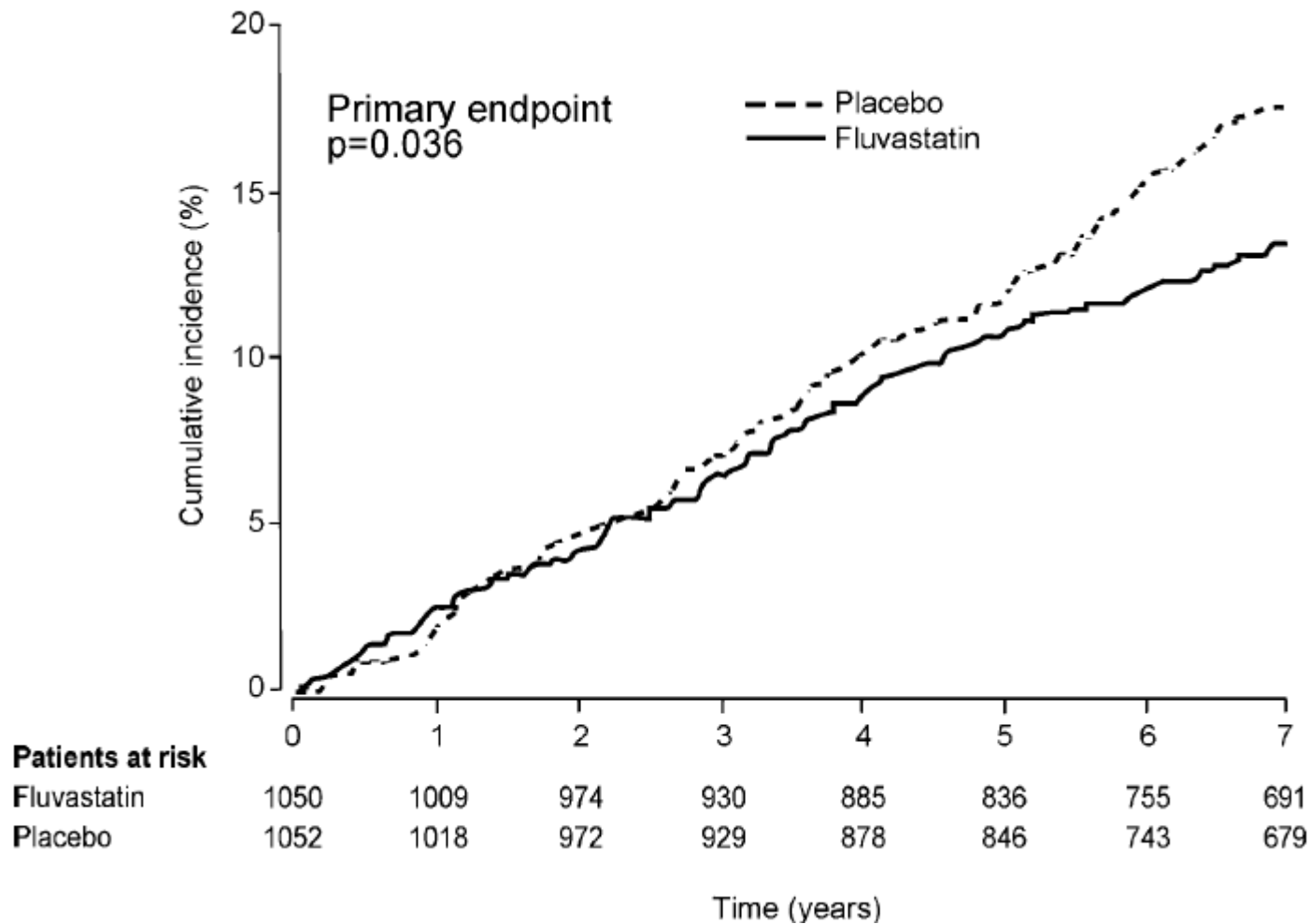
Blood pressure

BMI

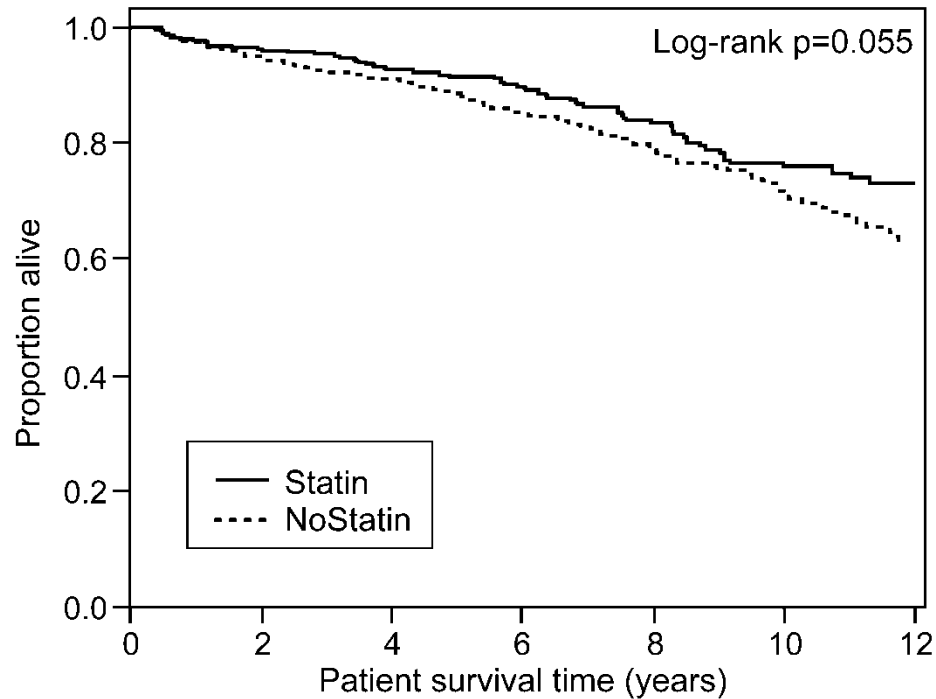
# Statin use and CV Mortality in RTX (OEDTR, N=2041, 223 CV deaths)



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



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



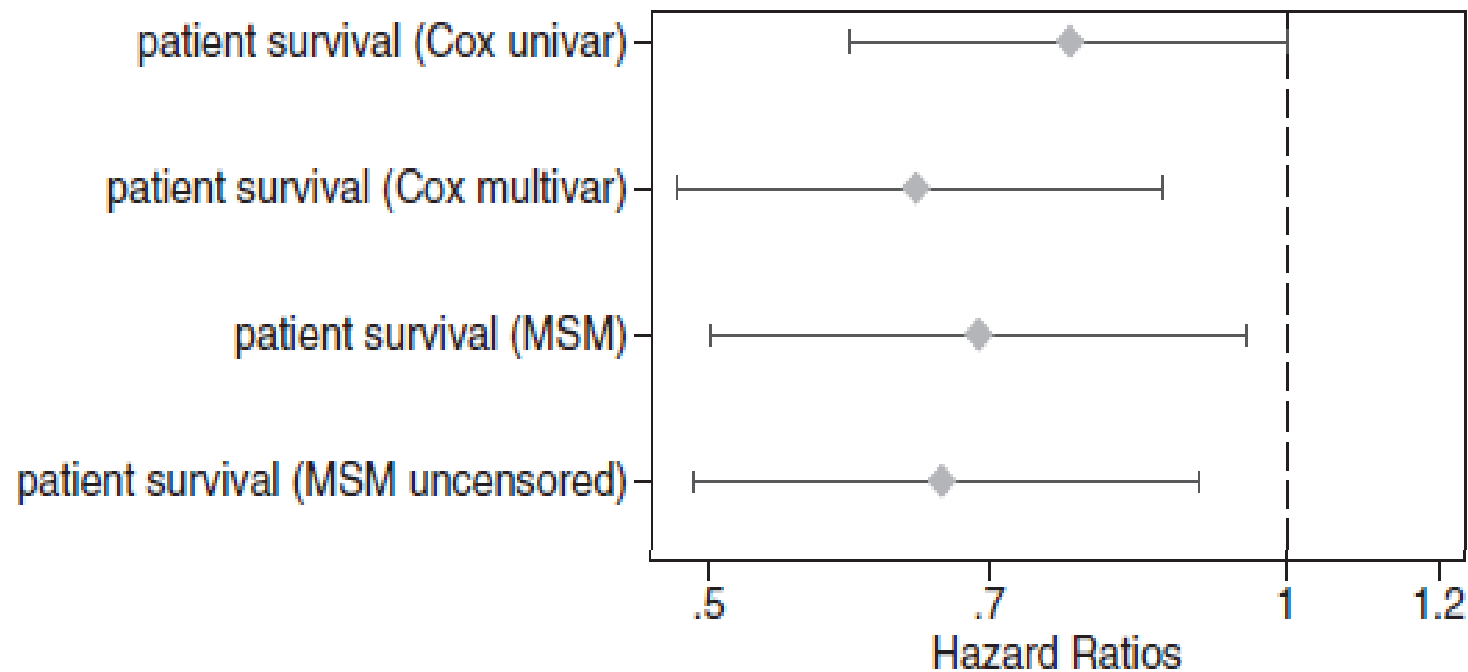
Patients at risk, Statin:

302	377	313	241	178	108	65
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Patients at risk, NoStatin:

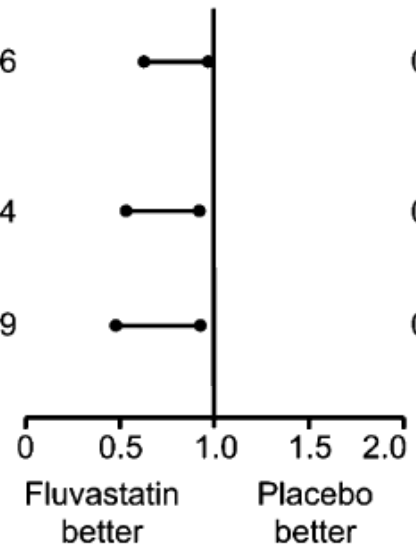
1739	1163	863	567	337	197	97
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## Crude and adjusted HR of events statin vs no-statin use (OEDTR, N=2041, 223 CV deaths)



# ALERTex Study

Endpoint	Proportion of patients			Risk ratio (95% CI)	Incidence (number of events per 100 patient years)	
	Fluvastatin (n=1,050)	Placebo (n=1,052)	p*		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





# Agenda

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## Modifyable risk factors & CV outcomes

Hemoglobin

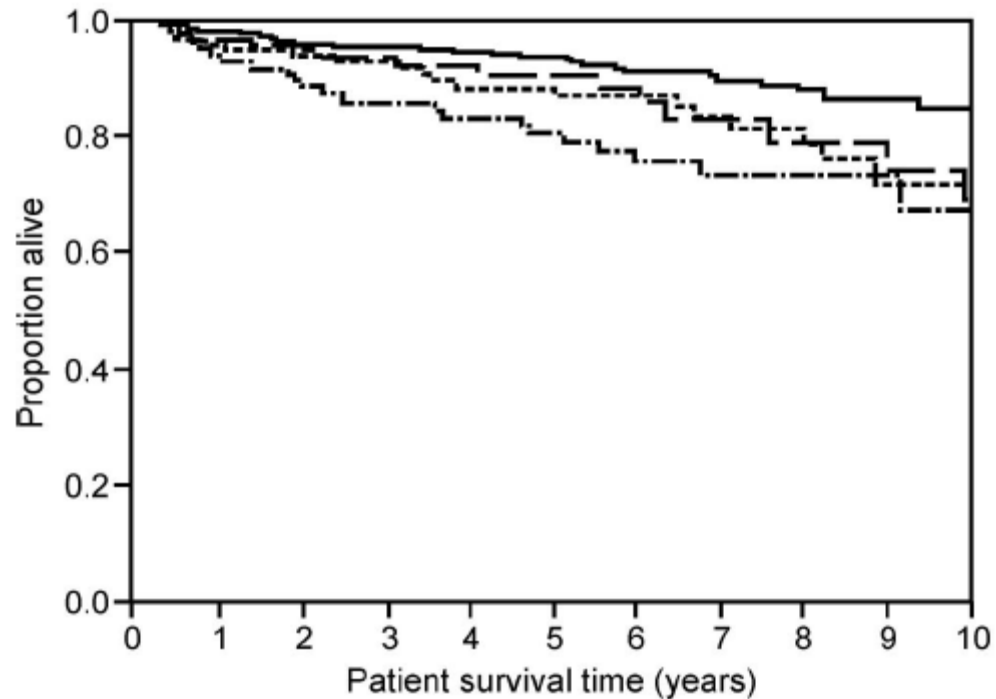
Lipids

Glucose control

Blood pressure

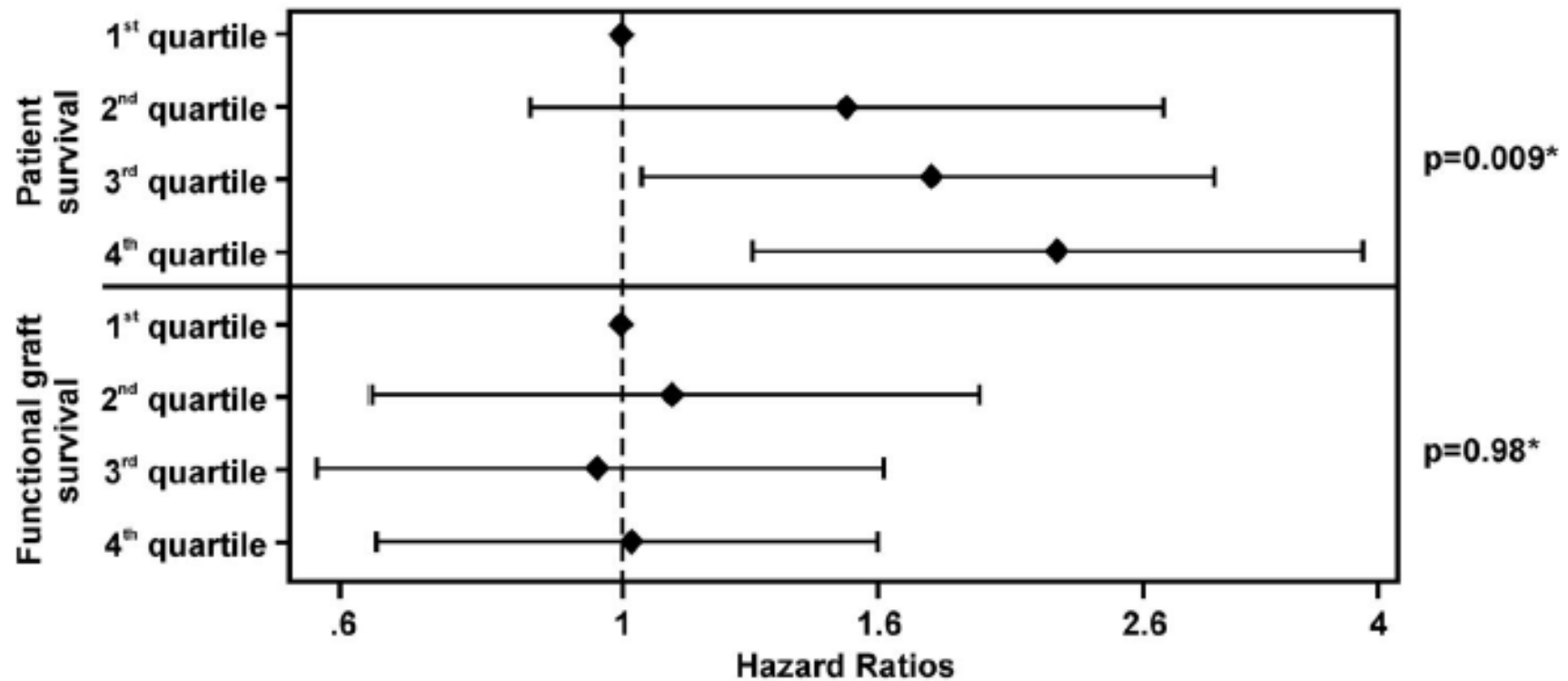
BMI

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



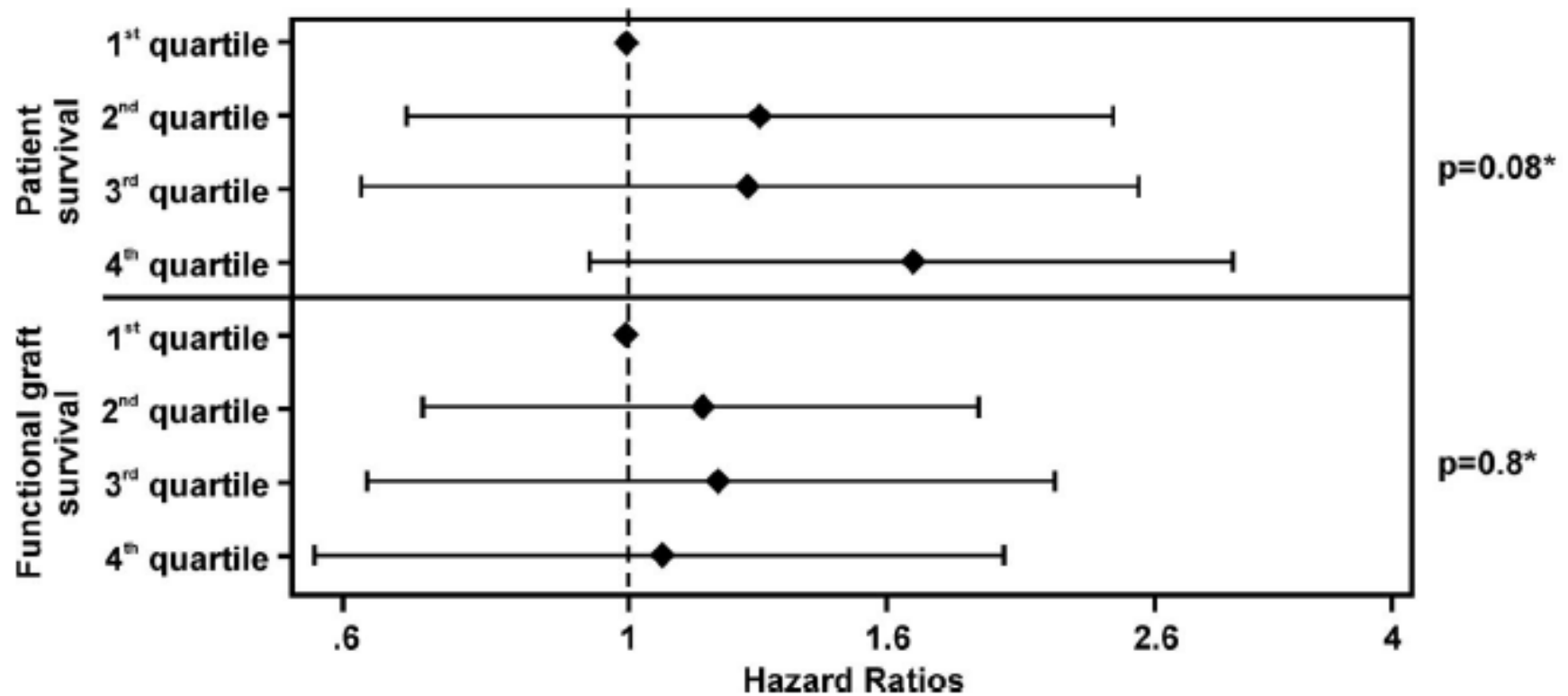
1 <sup>st</sup>	179	300	248	188	111	67
2 <sup>nd</sup>	181	88	56	34	21	12
3 <sup>rd</sup>	181	93	79	51	27	5
4 <sup>th</sup>	174	88	65	40	11	5

# 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)

# HR for quartiles of HbA1c



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

# Agenda

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## Modifyable risk factors & CV outcomes

Hemoglobin

Lipids

Glucose control

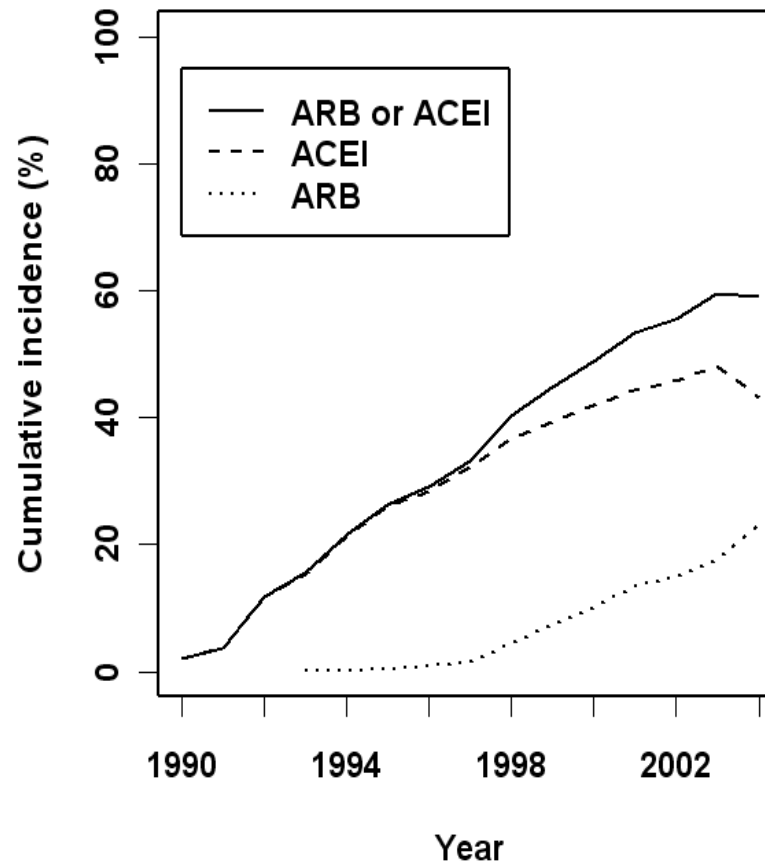
Blood pressure

BMI

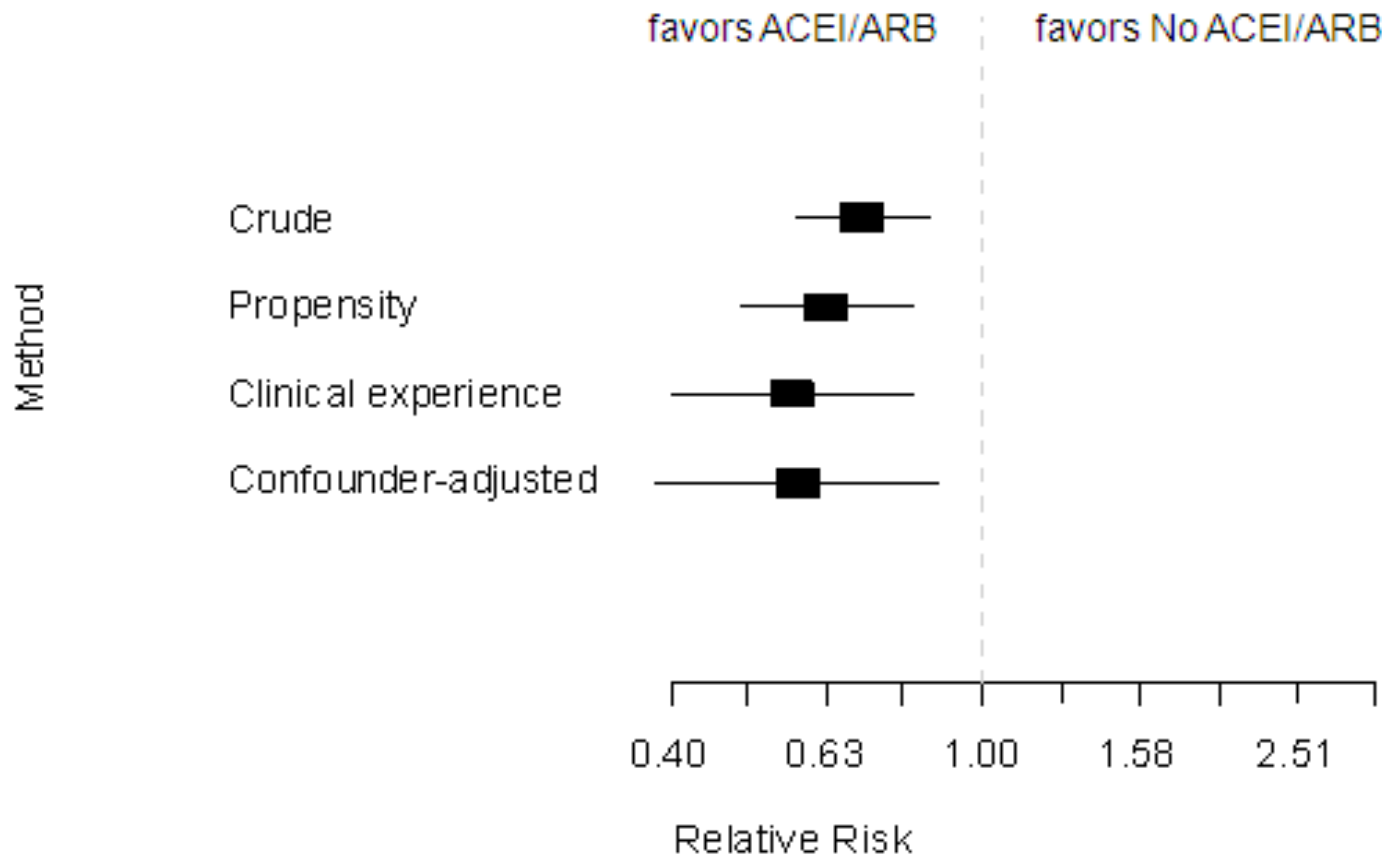
## Effect of ACEI/ARB & hypertension on CV death after RTX (n=2031, 157 CV deaths)

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 ≤ 30 <i>versus</i> GFR > 30 ml/min	2.92	2.08 to 4.10	<0.001
GFR ≤ 15 <i>versus</i> GFR > 30 ml/min	6.00	4.15 to 8.68	<0.001

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



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





# Agenda

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## Modifiable risk factors & CV outcomes

Hemoglobin

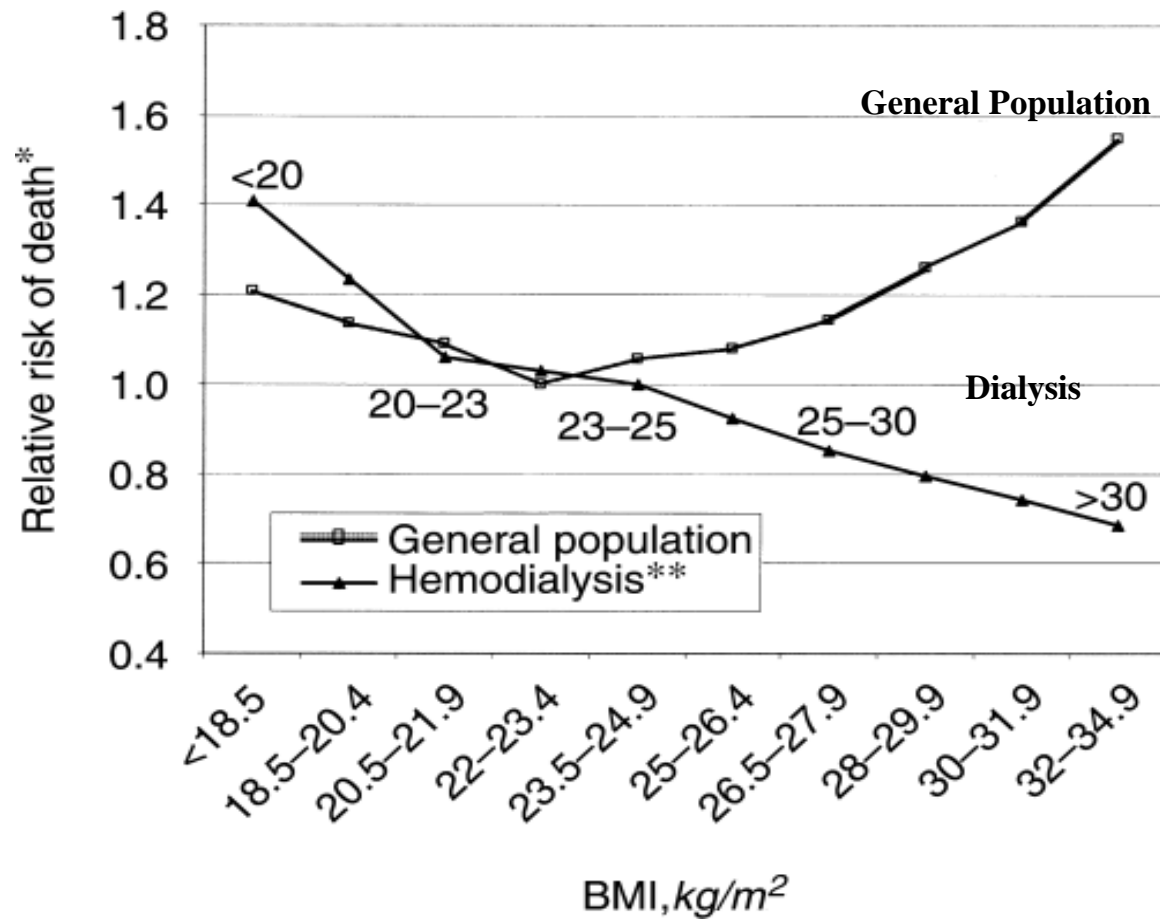
Lipids

Glucose control

Blood pressure

BMI

# The 'risk factor' paradox



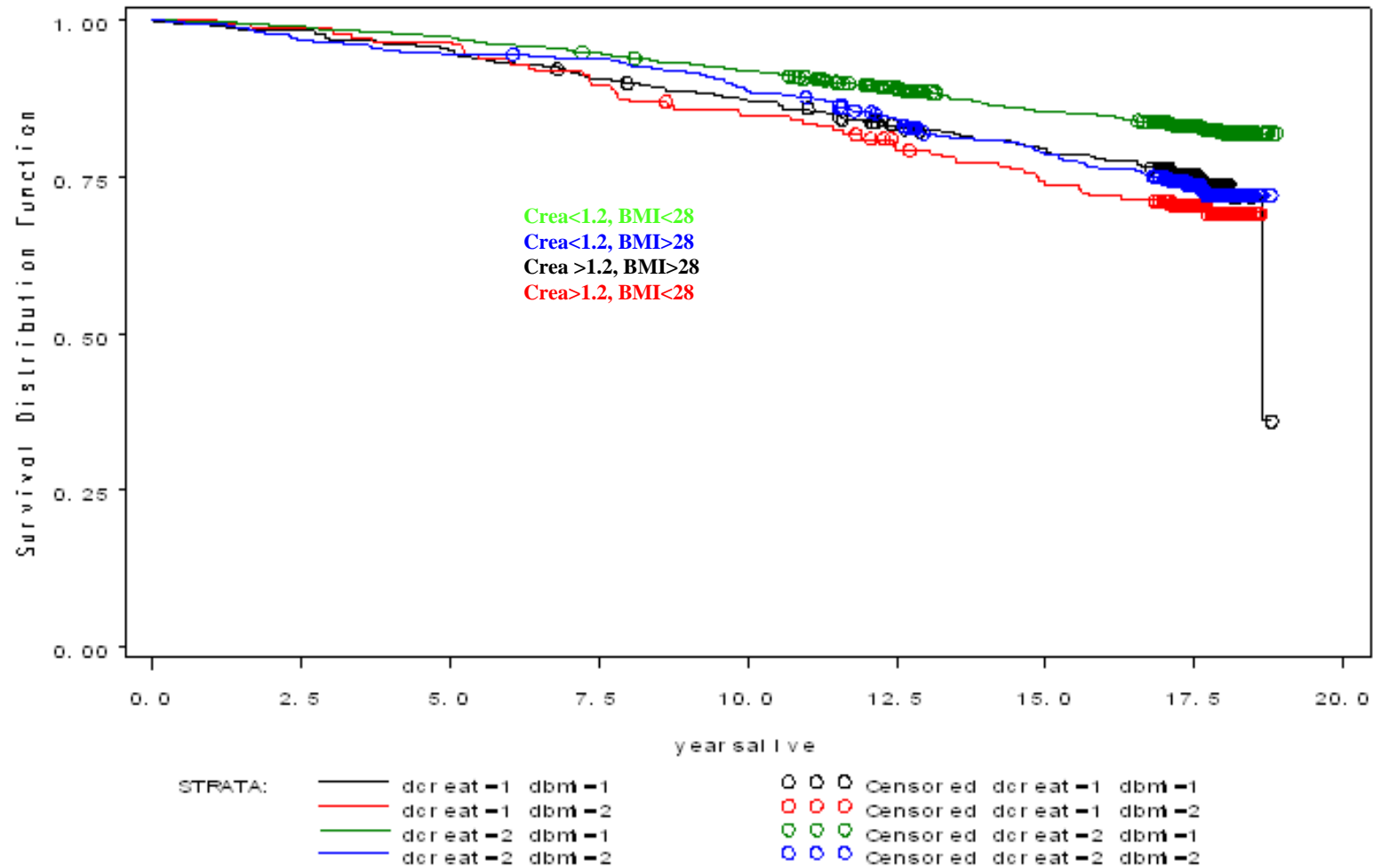
## Research Design & Methods

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- 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



# NHANES I and NHEF - Effect Modification

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

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

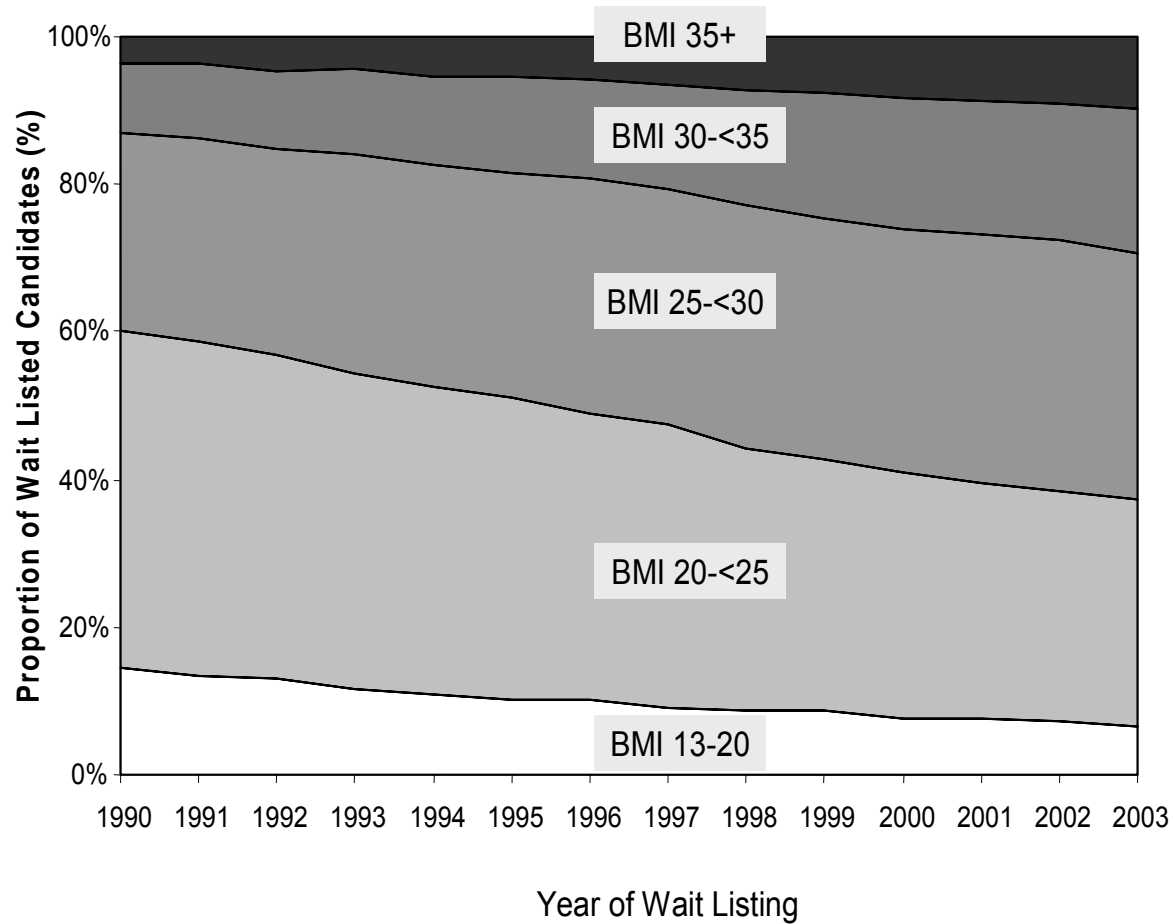
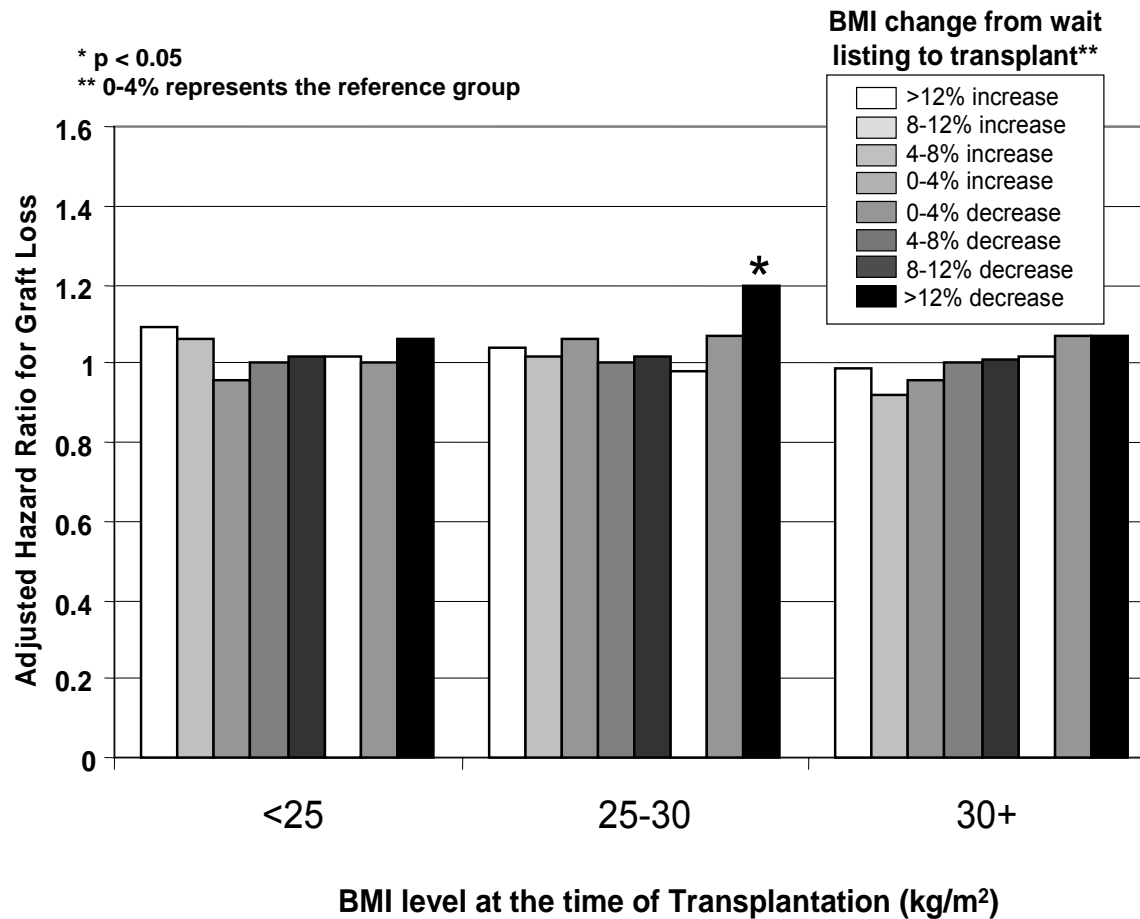


Table 4. Risk factors for patient weight increase to obese or morbidly obese levels from the time of candidate listing to transplantation (n=95,831\*)

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

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





# Conclusions

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## Modifyable risk factors & CV outcomes

Hemoglobin

Lipids

Glucose control

Blood pressure

BMI