

The complex management of kidney transplanted patients - beyond immunosuppression

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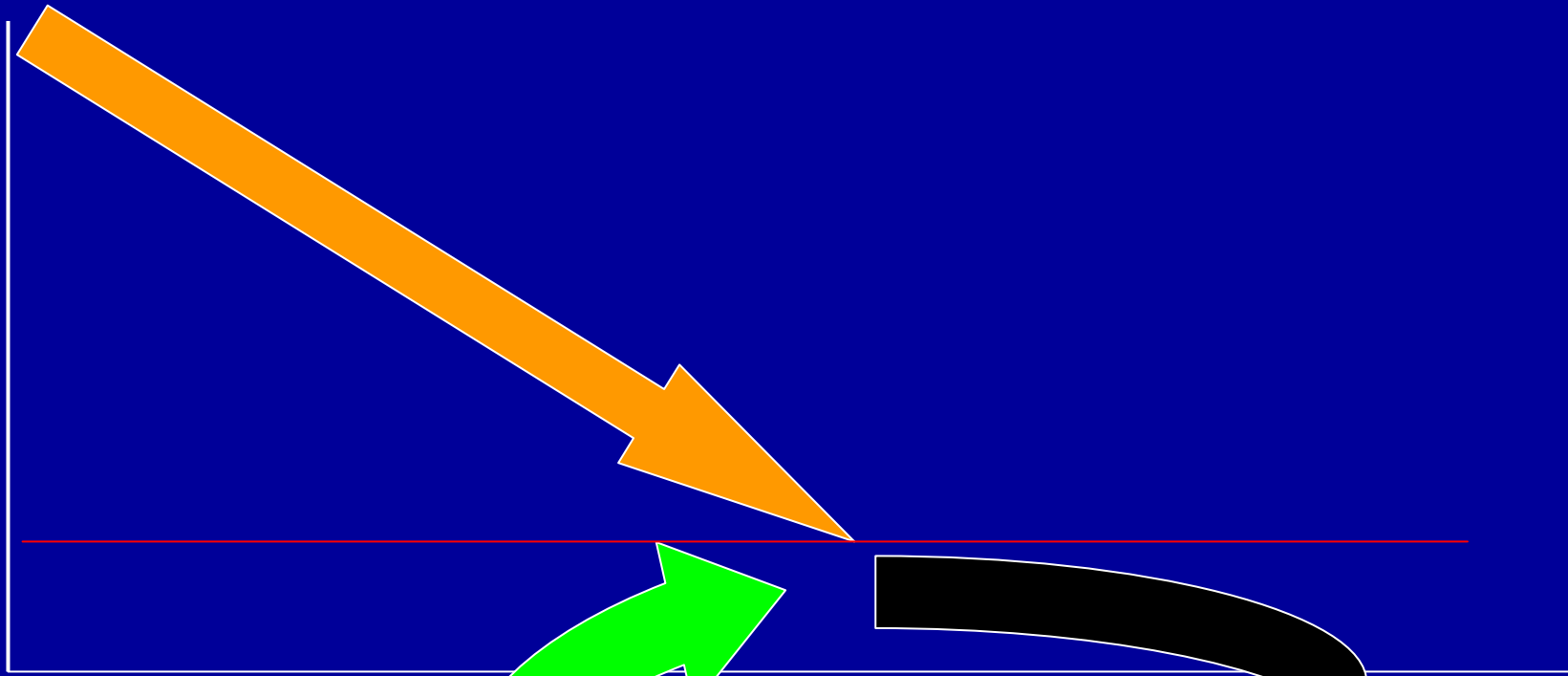
- The ESRD cycle
- CKD in the kidney transplant (Tx) population
- Cardiovascular disease in the Tx population
- Post-transplant anemia
- Post-transplant metabolic disorders (diabetes, lipids)
- Depression and quality of life in the Tx population
- The multidisciplinary model

The ESRD cycle

GFR ml/min/1,73 m²

120

15

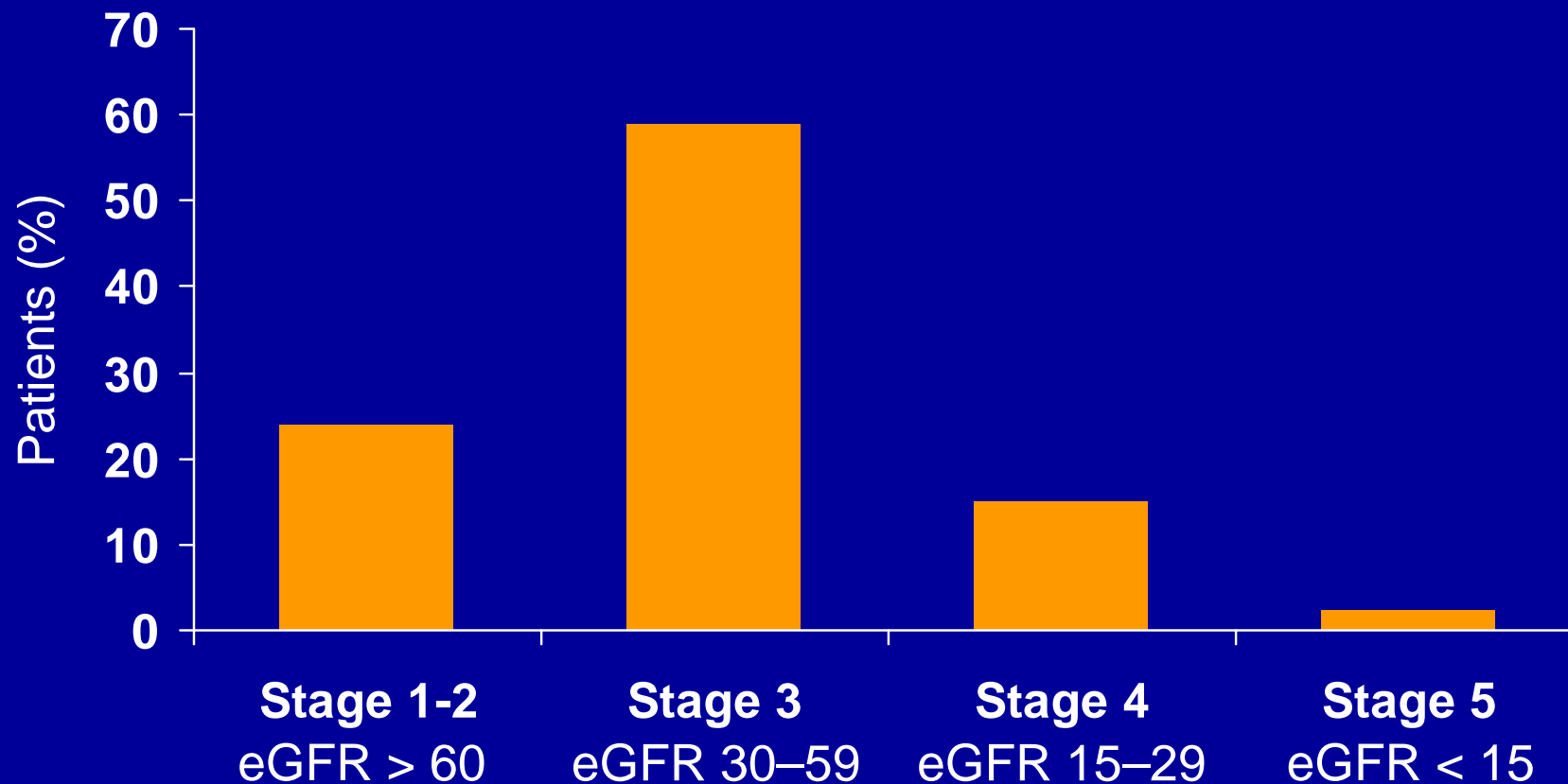


transplantation

dialysis

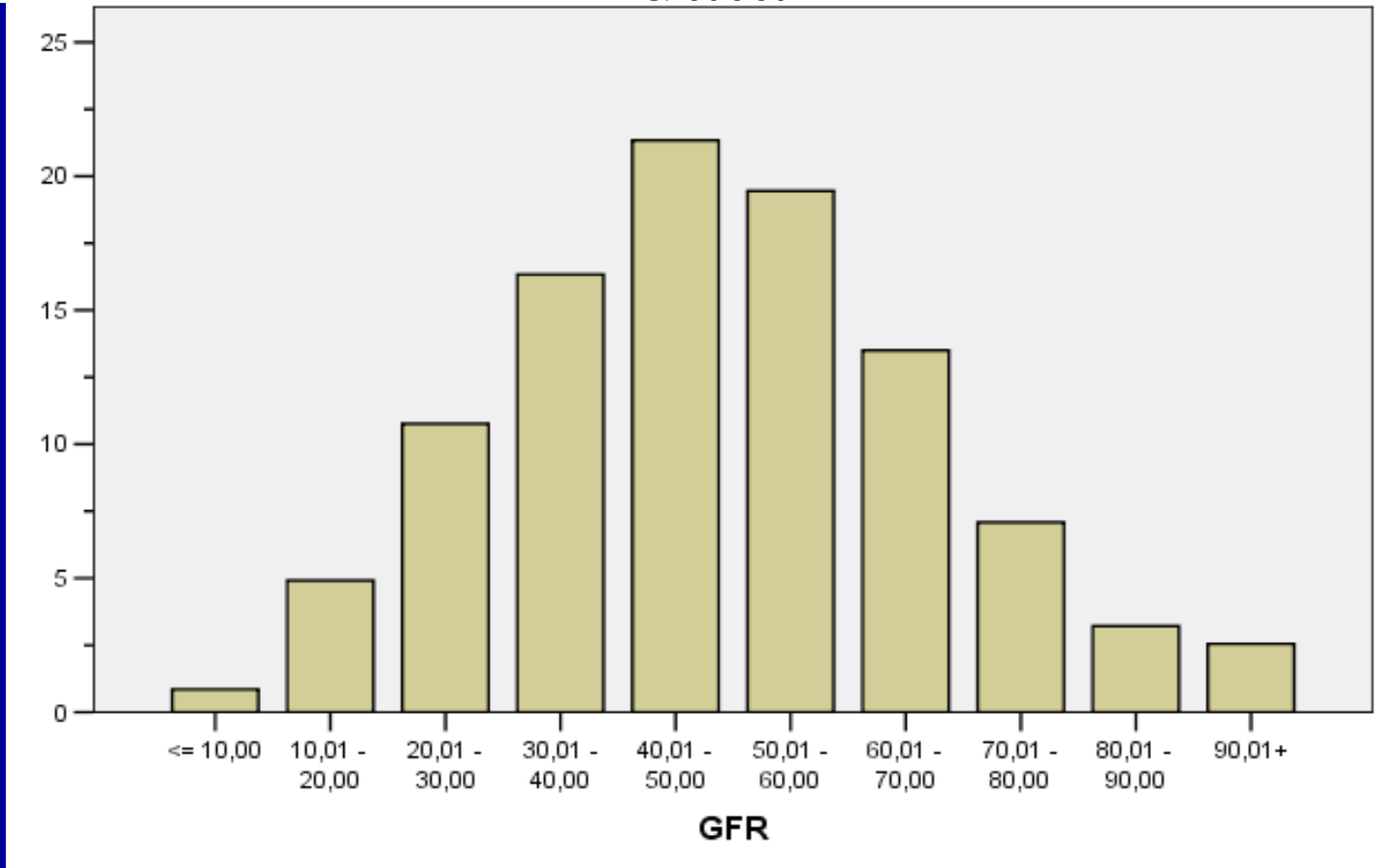
CKD STAGES IN KIDNEY TRANSPLANTED PATIENTS

Majority of transplant recipients have kidney function equivalent to stage 3 CKD or worse (UK data)



19,074 adult patients with a functioning kidney transplant at the end of 2005
UK Renal Registry Report 2006. Chapter 1.

Renal function in Tx patients – Hungarian data



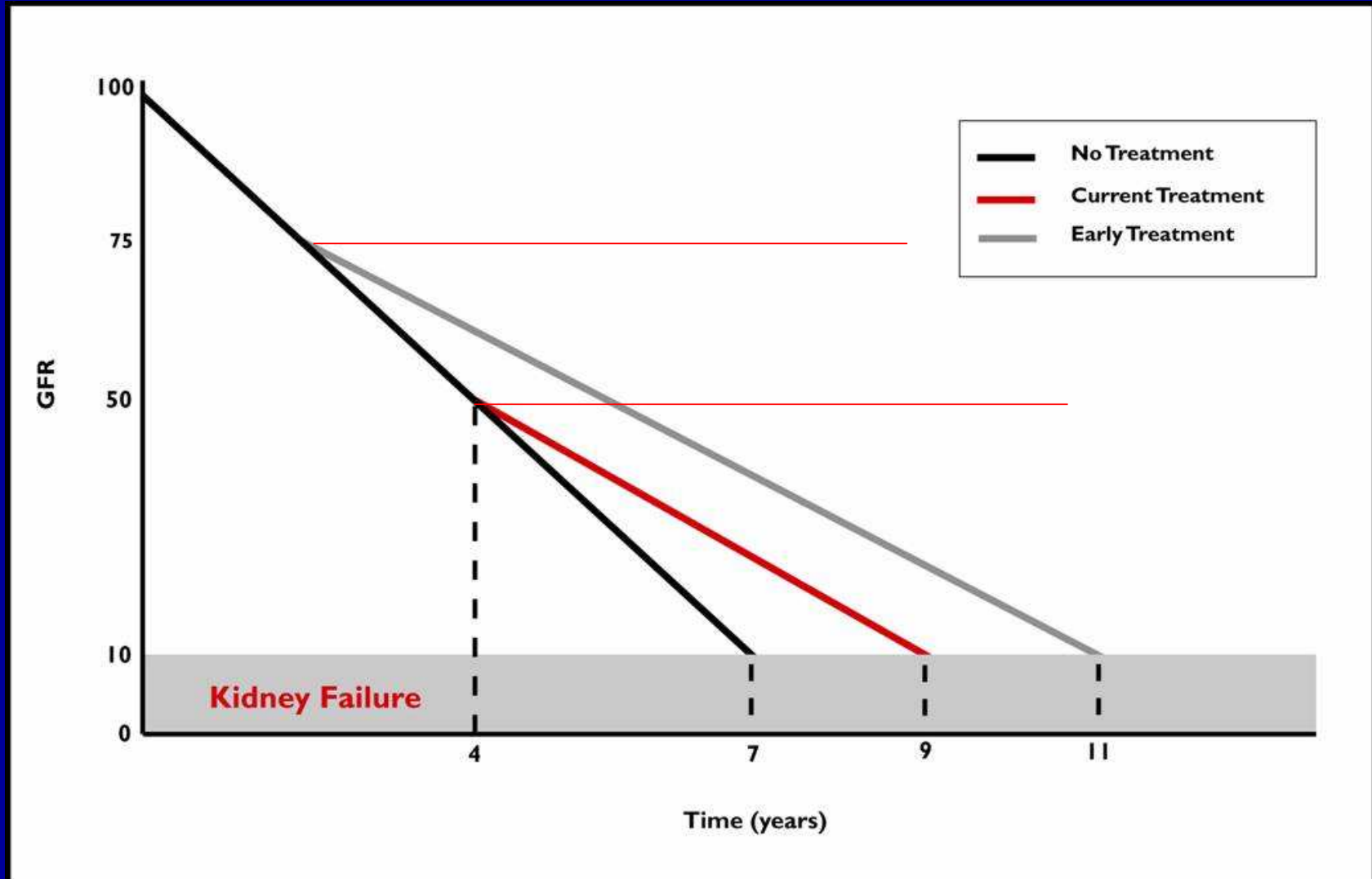
Std	V	IV	III	II	I
%	2	14	58	24	2
GF	12.7	23.9	45.4	69.9	98.9
R	±1.6	±4.1	±8.1	±7.7	±8.2

Kidney Disease : Improving Global Outcomes (KDIGO) Guidelines

Levey As, et al. *Kidney Int* 67:2089, 2005

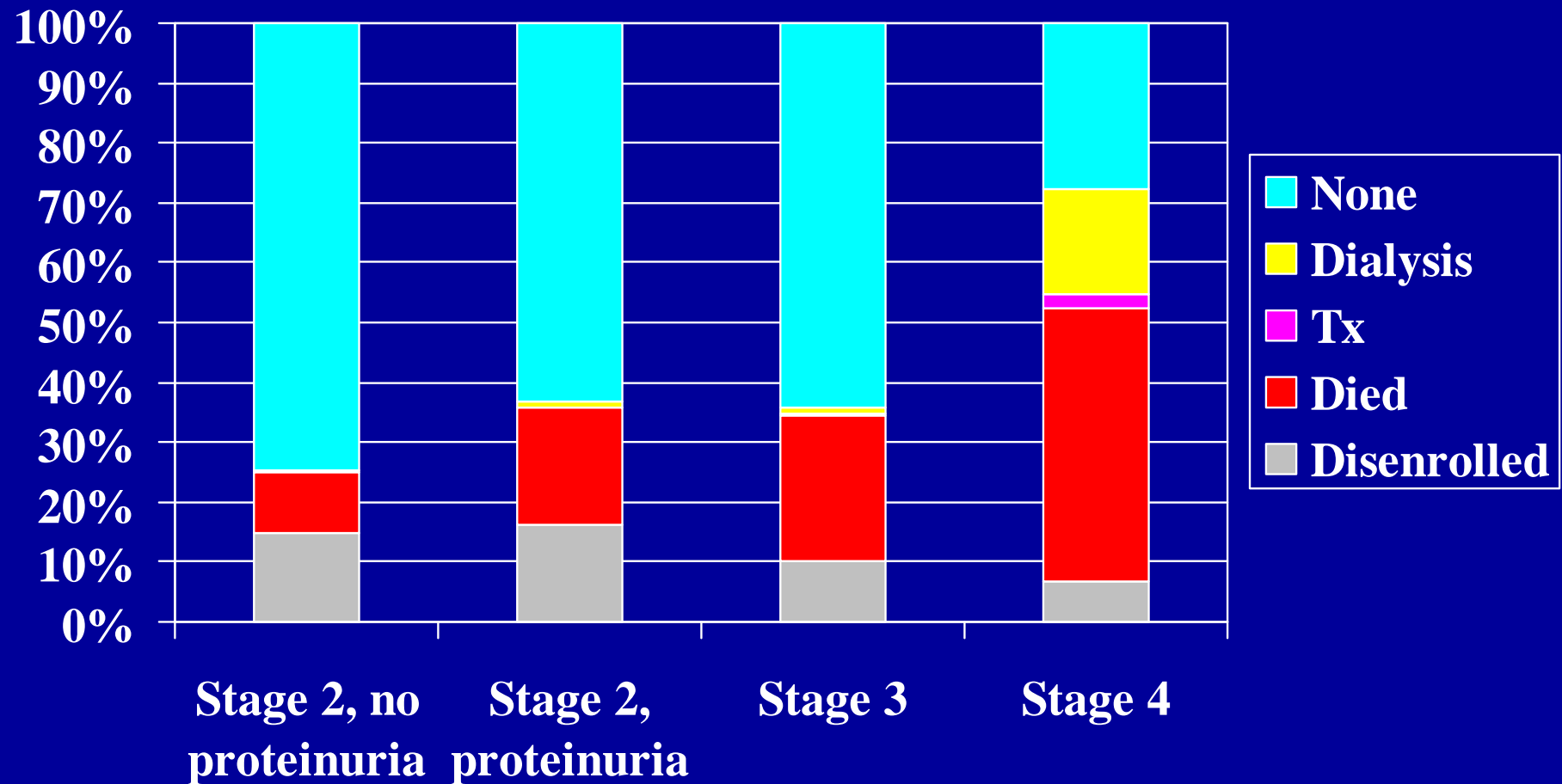
- Consider all kidney transplants recipients to have CKD, irrespective of GFR level or presence or absence of markers of kidney damage.
- The rationale for this is based on damage to native kidneys, presumed damage to the kidney transplant based on studies of "protocol biopsies," and need for life-long care caused by complications of prior CKD and chronic allograft nephropathy

Progression of CKD



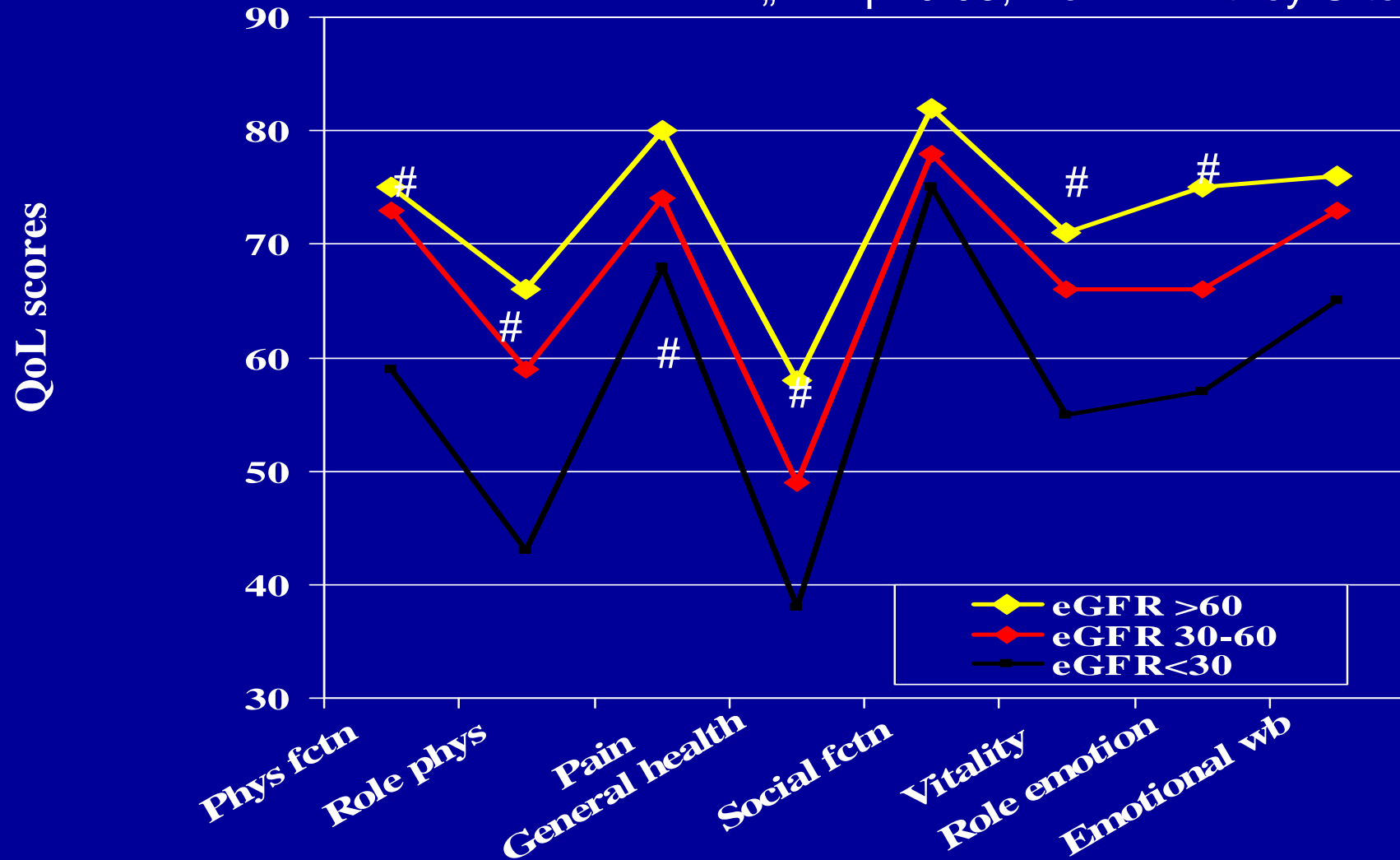
Outcomes with CKD in Managed Care

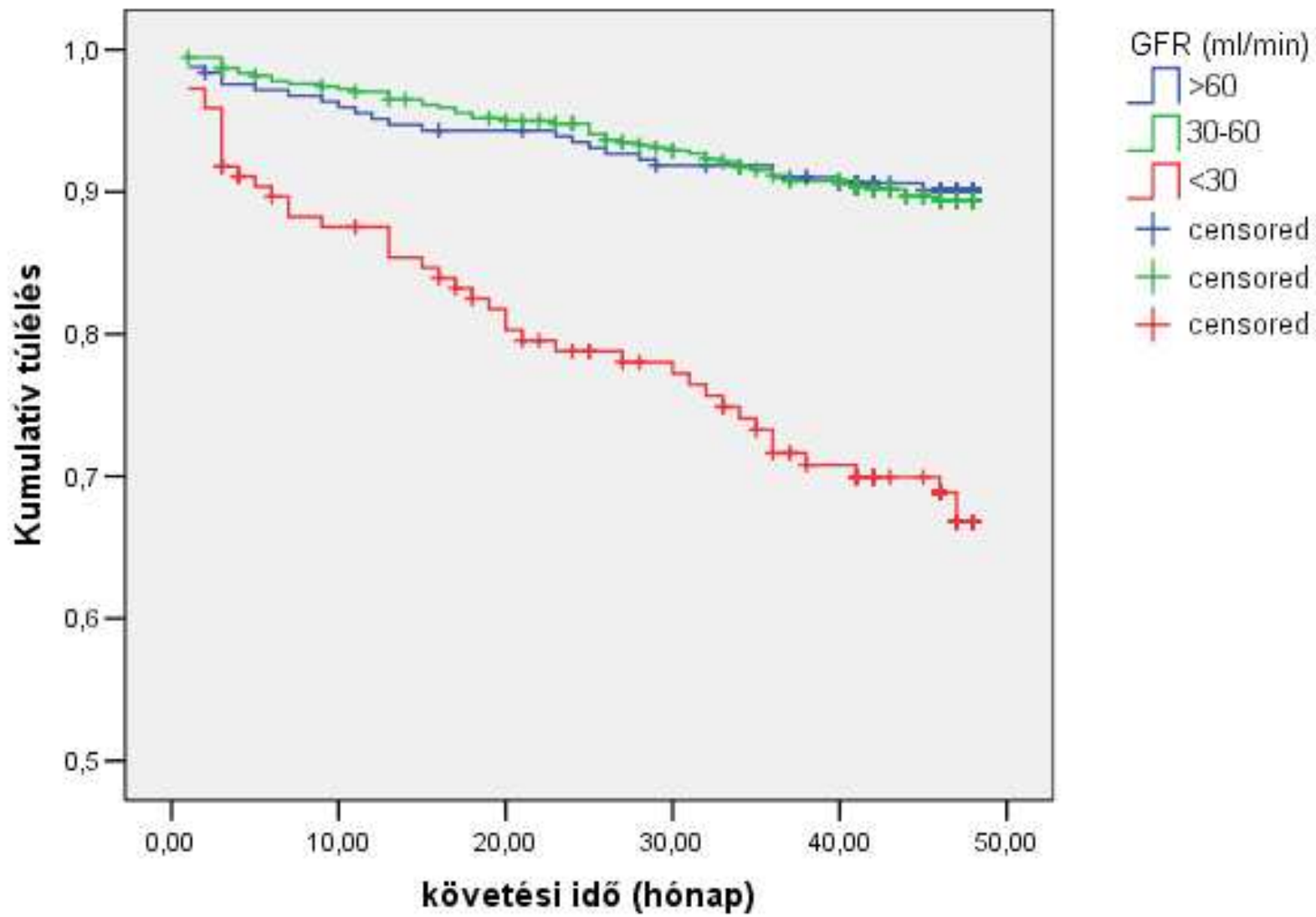
N = 27,998, 5 year F/U, mean age stage 2: 61, stage 3-4: 72



Renal function versus SF-36 scores

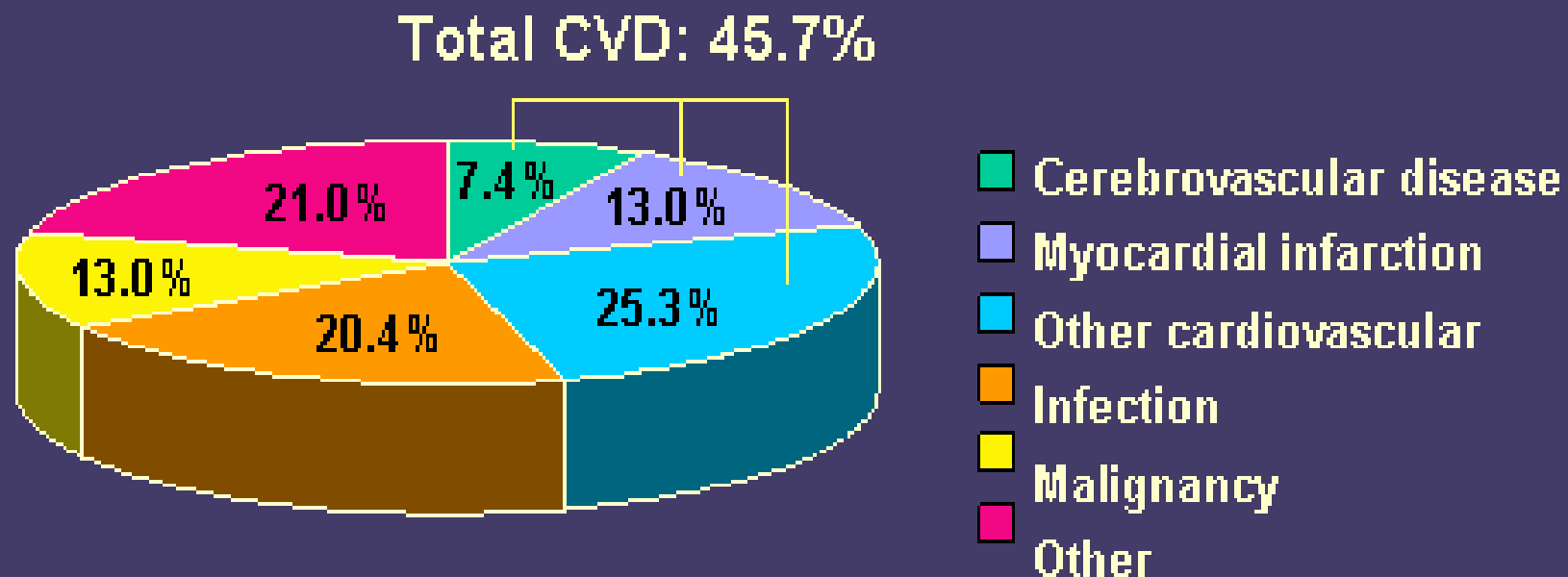
„#” = $p < 0.05$, Mann-Whitney U test





**CARDIOVASCULAR DISEASE
IN KIDNEY TRANSPLANTED
PATIENTS**

Cause of Death in Renal Transplant Recipients With Functioning Transplants

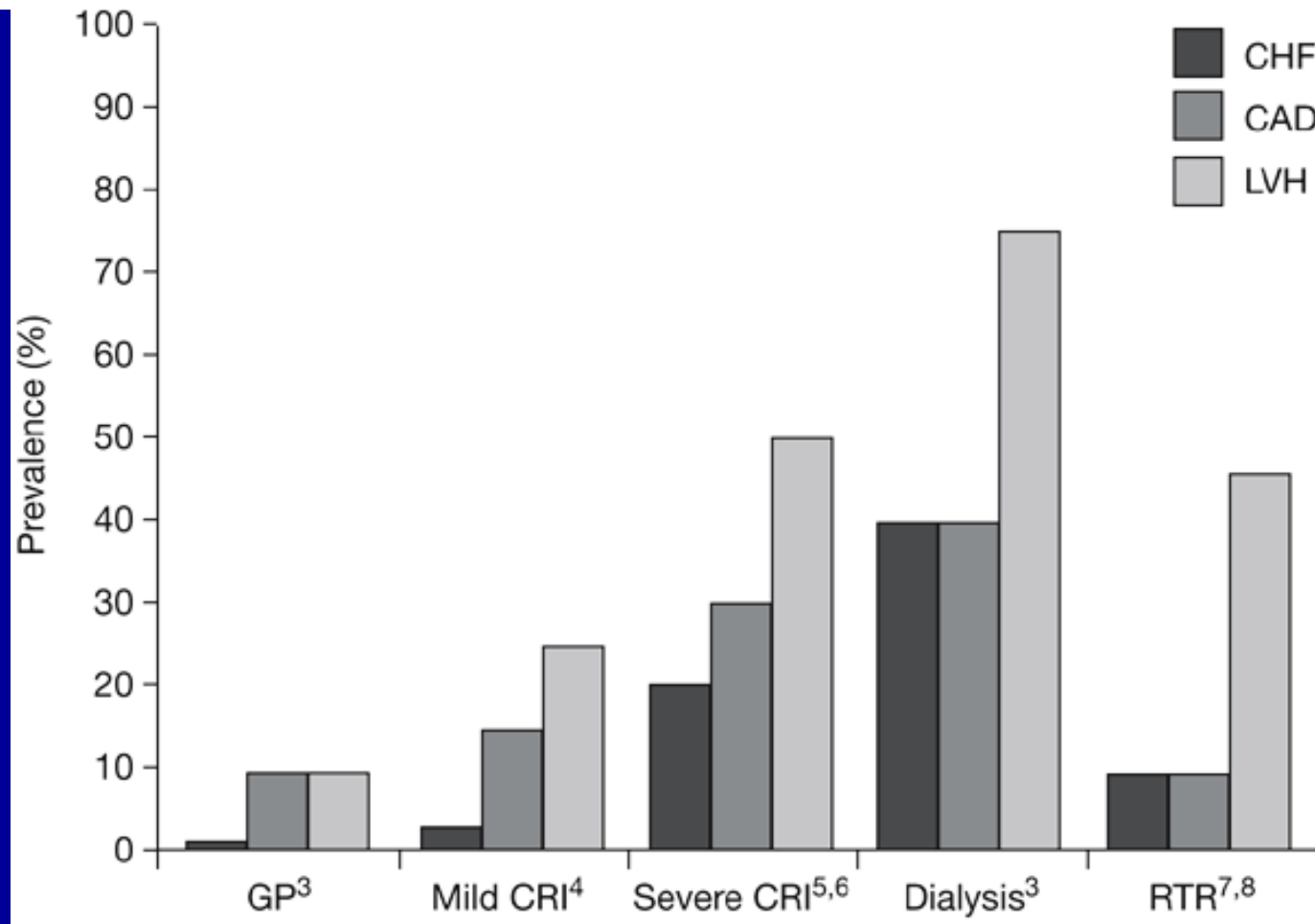


US Renal Data System: 2005 Annual Data Report.

Caveat :

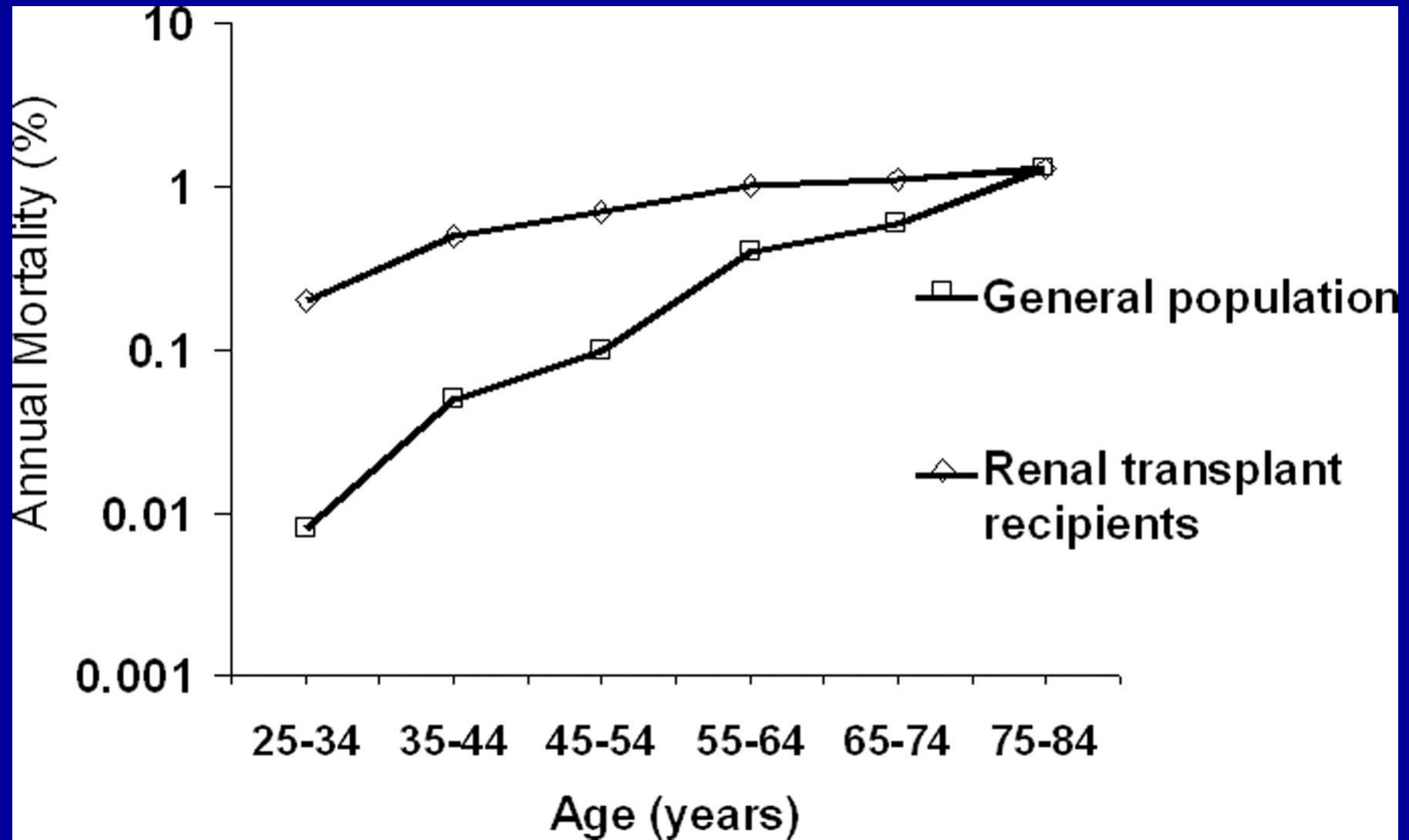
Cardiovascular Disease remains a significantly greater risk for renal transplant recipients compared to infection and malignancy

Figure 1 Prevalence of cardiovascular disease in patients with renal disease



Rigatto C and Parfrey P (2006) Therapy Insight: management of cardiovascular disease in the renal transplant recipient *Nat Clin Pract Nephrol* 2: 514–526 doi:10.1038/ncpneph0253

Cardiovascular mortality in kidney transplant recipients



Djamali, A. et al. Clin J Am Soc Nephrol 2006;1:623-640

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CJASN

Table 4. Traditional and nontraditional risk factors for CVD in renal transplant recipients

Traditional Risk Factors	Nontraditional Risk Factors
Older age	Decreased kidney function
Male gender	CNI
Family history of CVD	Proteinuria
Diabetes	Anemia
Hypertension	C-reactive protein
Dyslipidemia	Oxidative stress
low HDL	Advanced glycation end products
high LDL	Inflammation
Physical inactivity	Homocysteine
Left ventricular hypertrophy	Uric acid
Menopause	Hyperparathyroidism
Tobacco use	Obesity
	Thrombogenic factors

Djamali, A. et al. Clin J Am Soc Nephrol 2006;1:623-640

Table 1. Risk factors for the development of CVD after kidney transplantation^a

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		

Shirali, A. C. et al. Clin J Am Soc Nephrol 2008;3:491-504

Immuno-suppression and atherogenesis

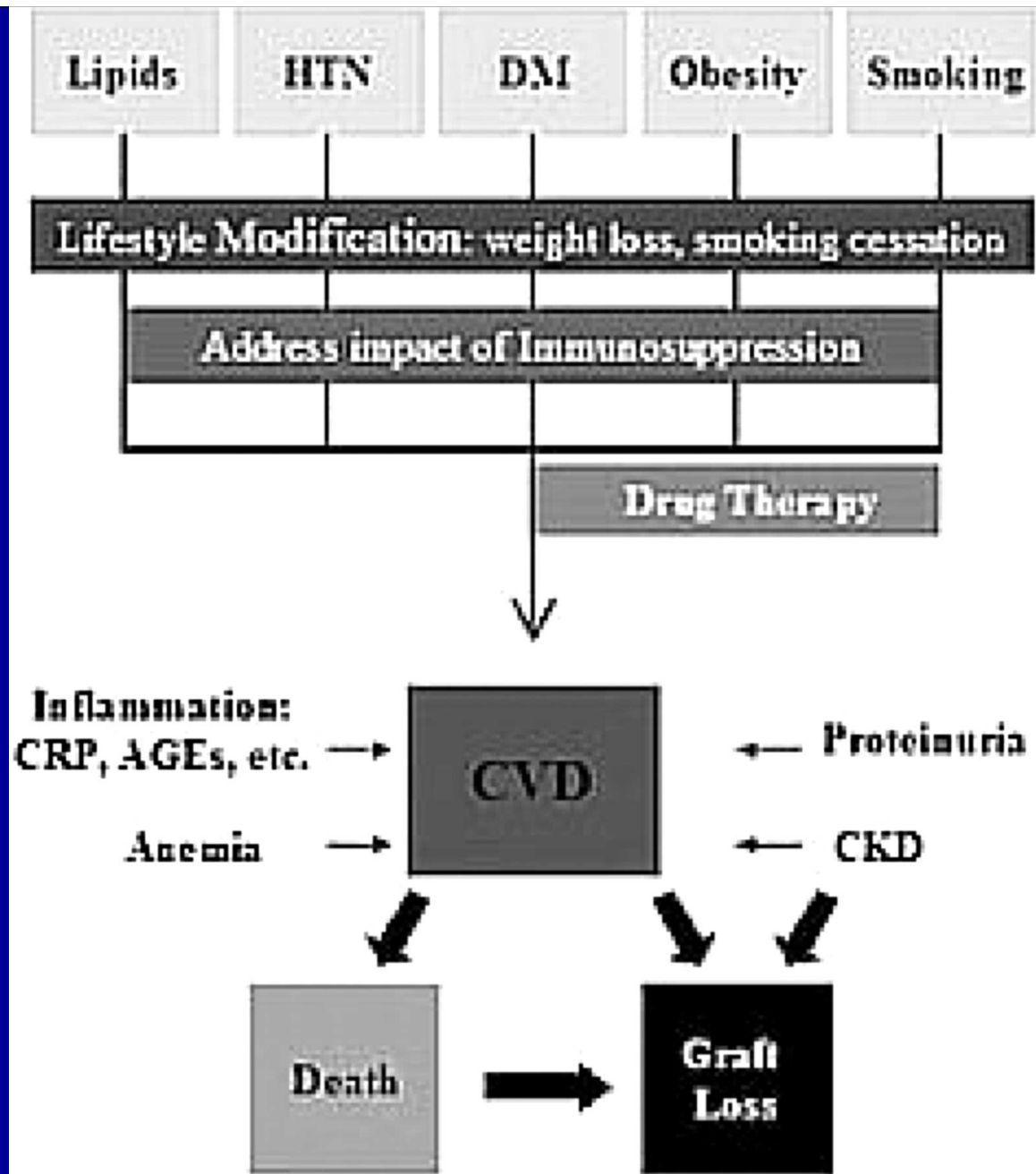
	CSA	TAC	SRL	MMF	AZA	Steroid
Dyslipidaemia	++	+	+++	-	-	++
Hypertension	++	+	-	-	-	++
NODAT	+	+(+)	-	-	-	+++

Shirali, A. C. et al. Clin J Am Soc Nephrol 2008;3:491-504

How to improve outcome in kidney transplanted patients?

The main issue for long term outcomes is to reduce ISU toxicity and to manage CV disease.

- Before Tx :
 - Dialysis vintage
 - CV management
 - CV interventions
- After Tx: medical management
 - Anemia
 - Dyslipidaemia
 - Hypertension
 - NODAT
 - Smoking
 - Obesity

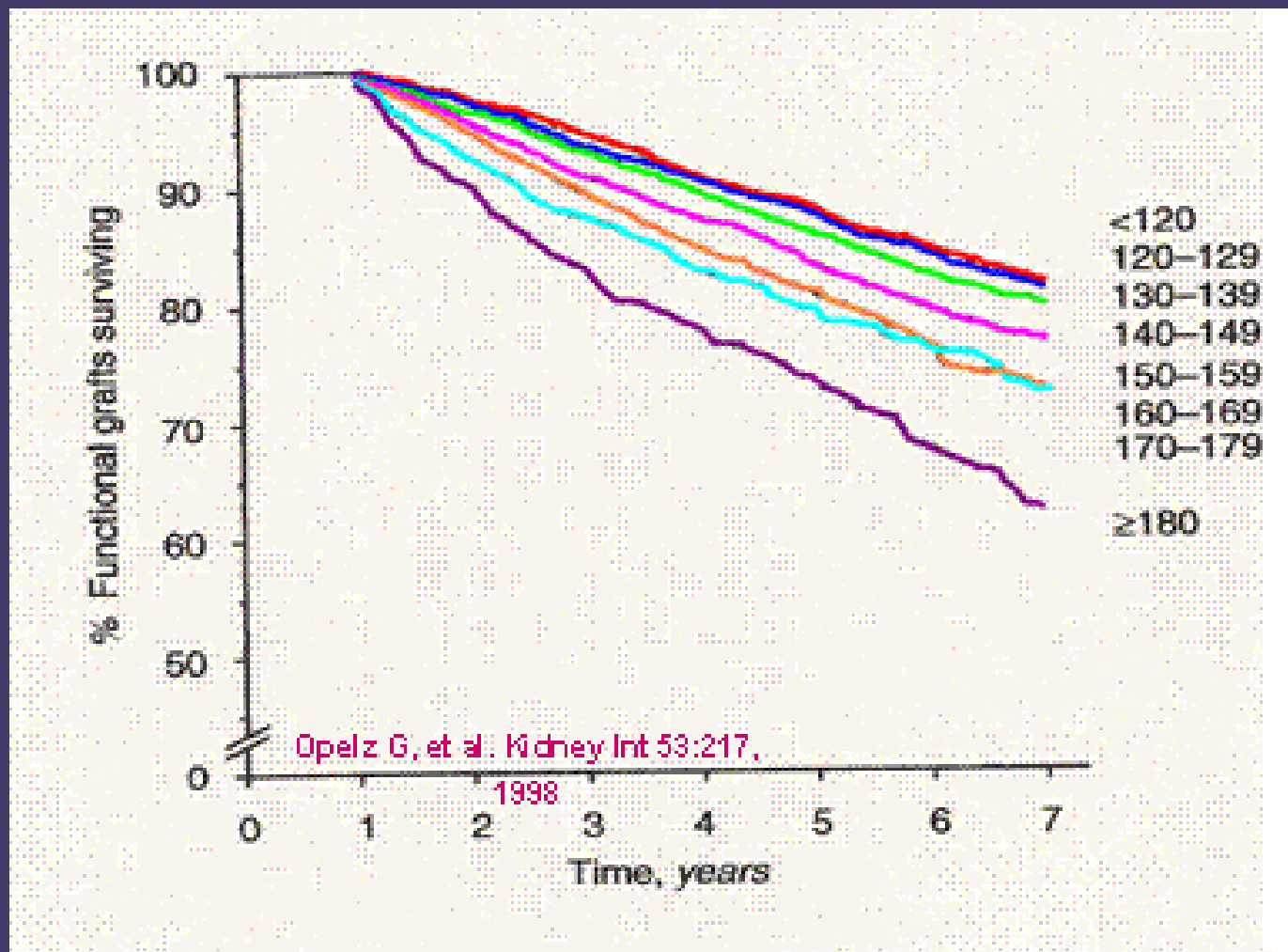


cardiovascular disease management after renal transplantation

Shirali, A. C. et al. Clin J Am Soc Nephrol 2008;3:491-504
 Copyright ©2008 American Society of Nephrology

BLOOD PRESSURE

Blood Pressure One Year after Kidney Transplantation and Graft Outcome



Opelz G et al. [*Kidney Int.* 1998 Jan;53\(1\):217-22.](#)

Measures of care in adult renal transplant recipients in the United Kingdom (Chapter 11)

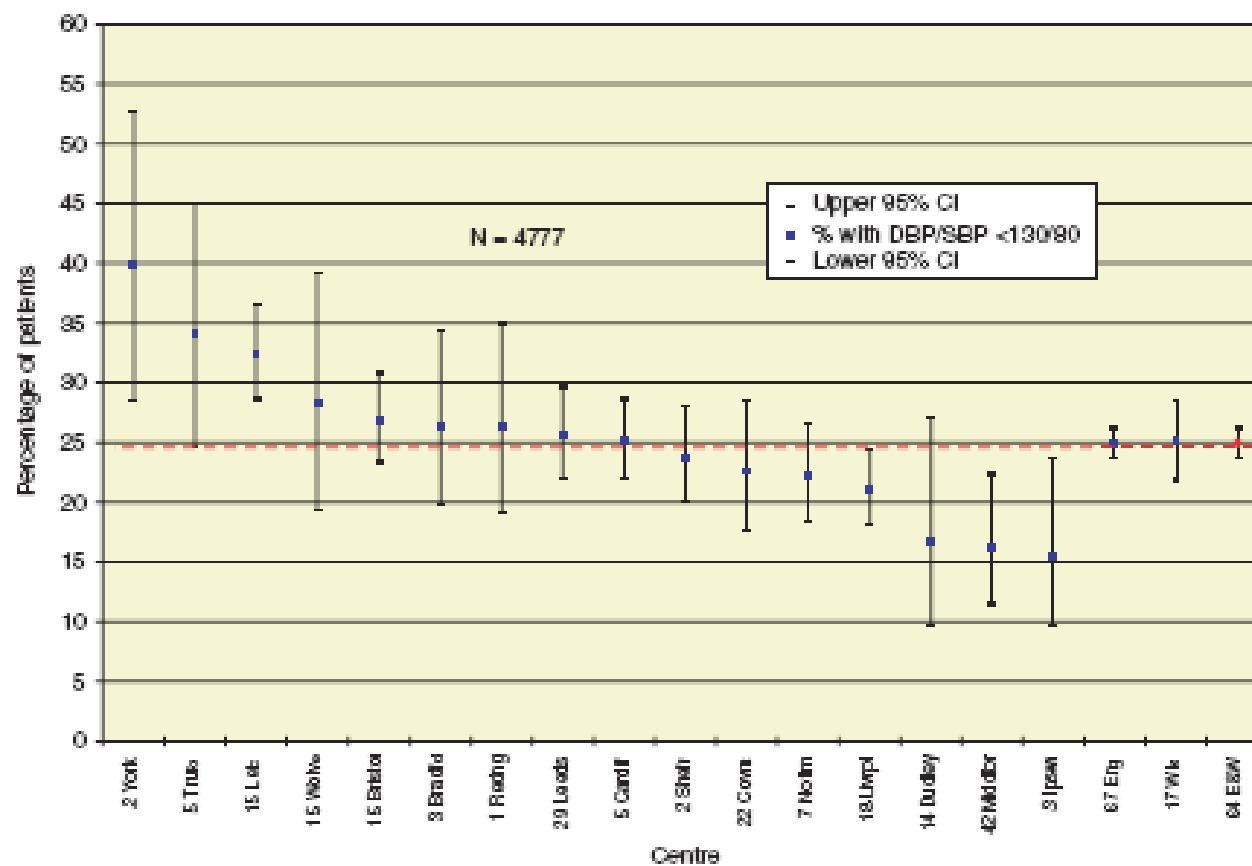
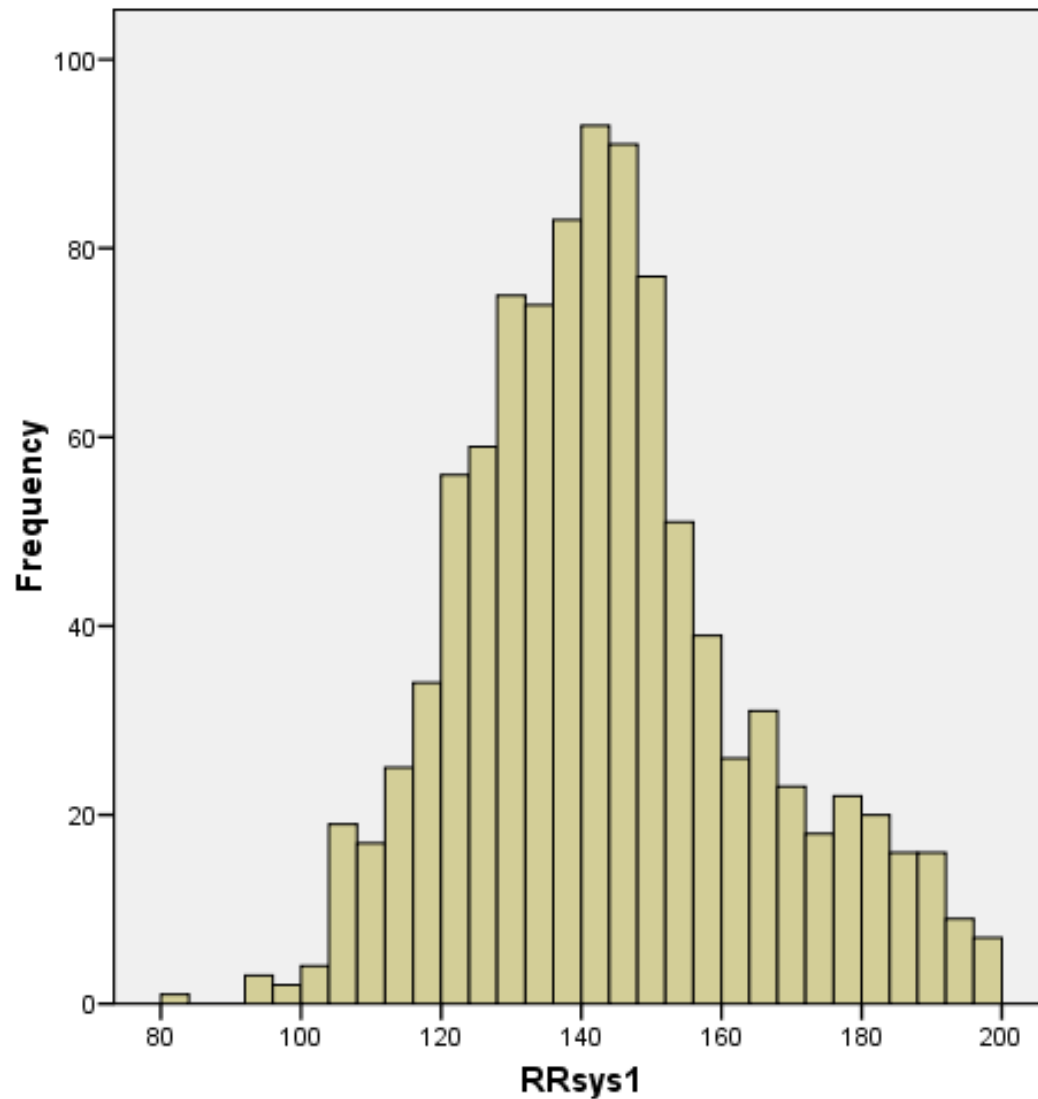
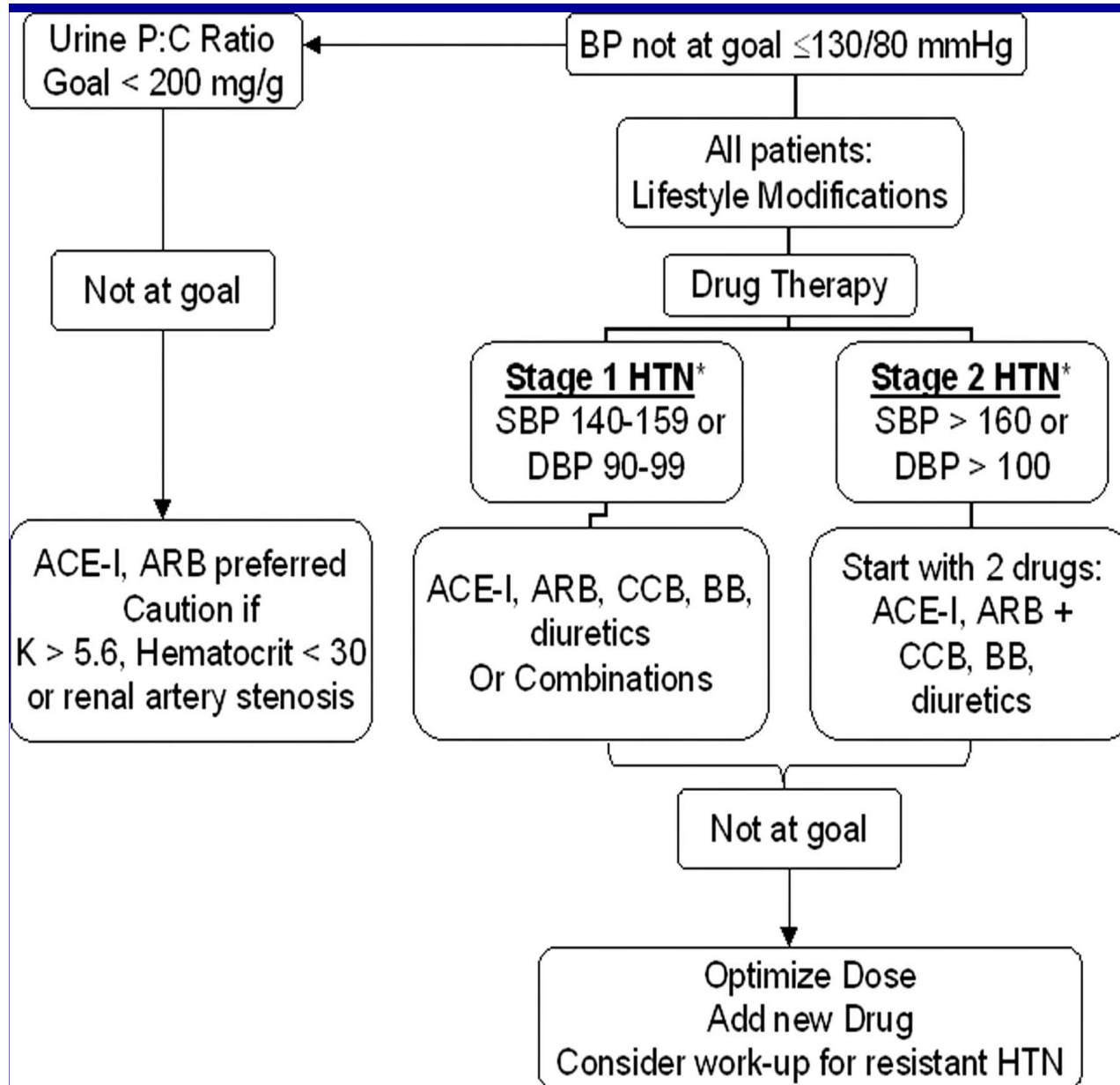


Fig. 11.11. Percentage of patients with renal transplants in different renal units who achieve the RA standards for BP.

BP control in Budapest



Mean =143,04
Std. Dev. =20,471
N =991



**BP management after
the first posttransplant
year**

DIABETES

Table 5. Risk factors for NODAT^a

Recipient characteristics
older age (>45 yr)
higher body mass index (≥ 30)
black race
family history of diabetes
Hispanic ethnicity
education (no college degree)
Donor
deceased donor
male gender
Transplant era (after 1995)
Tacrolimus use
HLA mismatch
Acute rejection
HCV infection

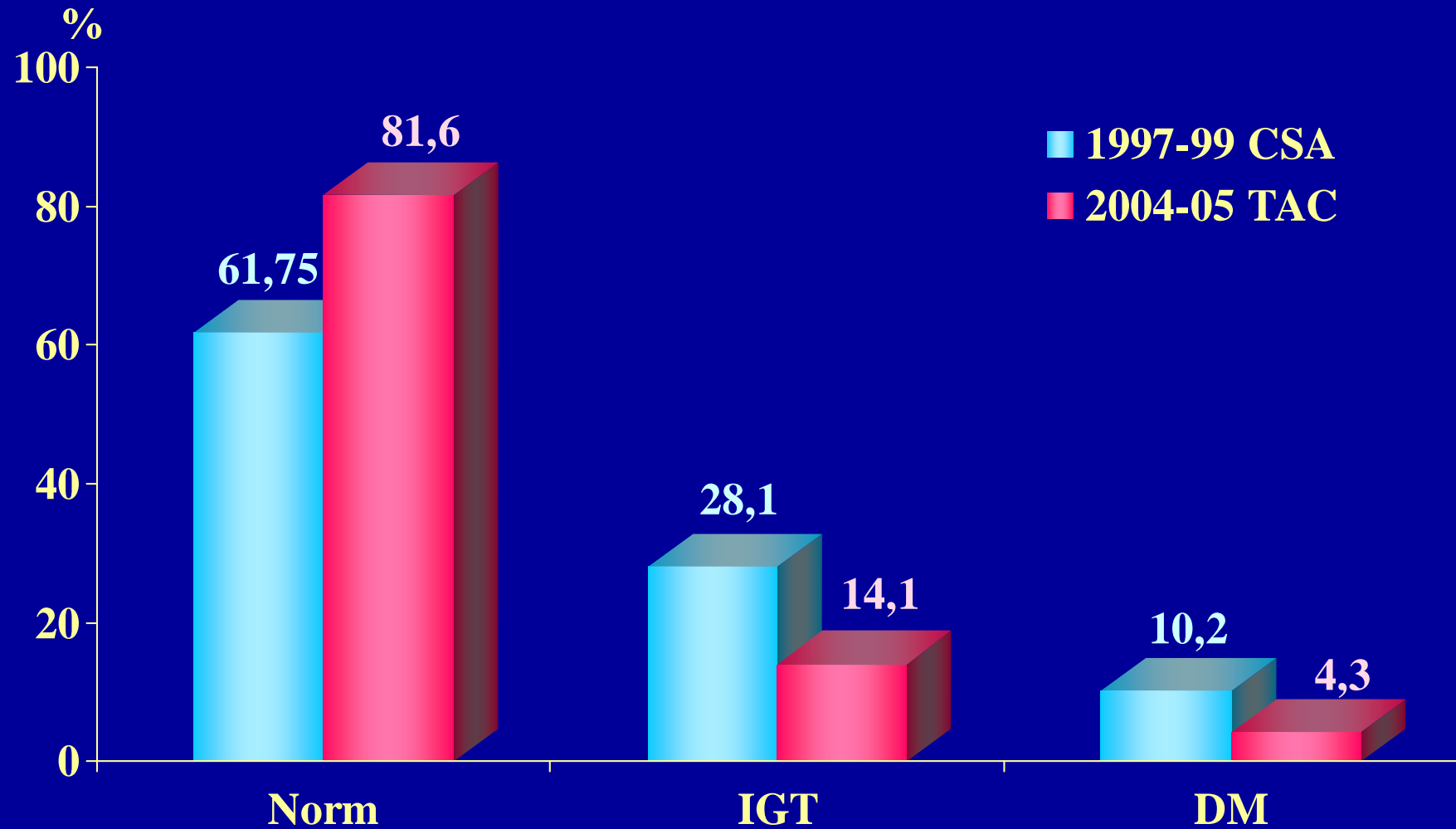
^aHCV, hepatitis C virus; NODAT, new-onset diabetes after transplantation.

NODAT risk factors

Djamali, A. et al. Clin J Am Soc Nephrol 2006;1:623-640

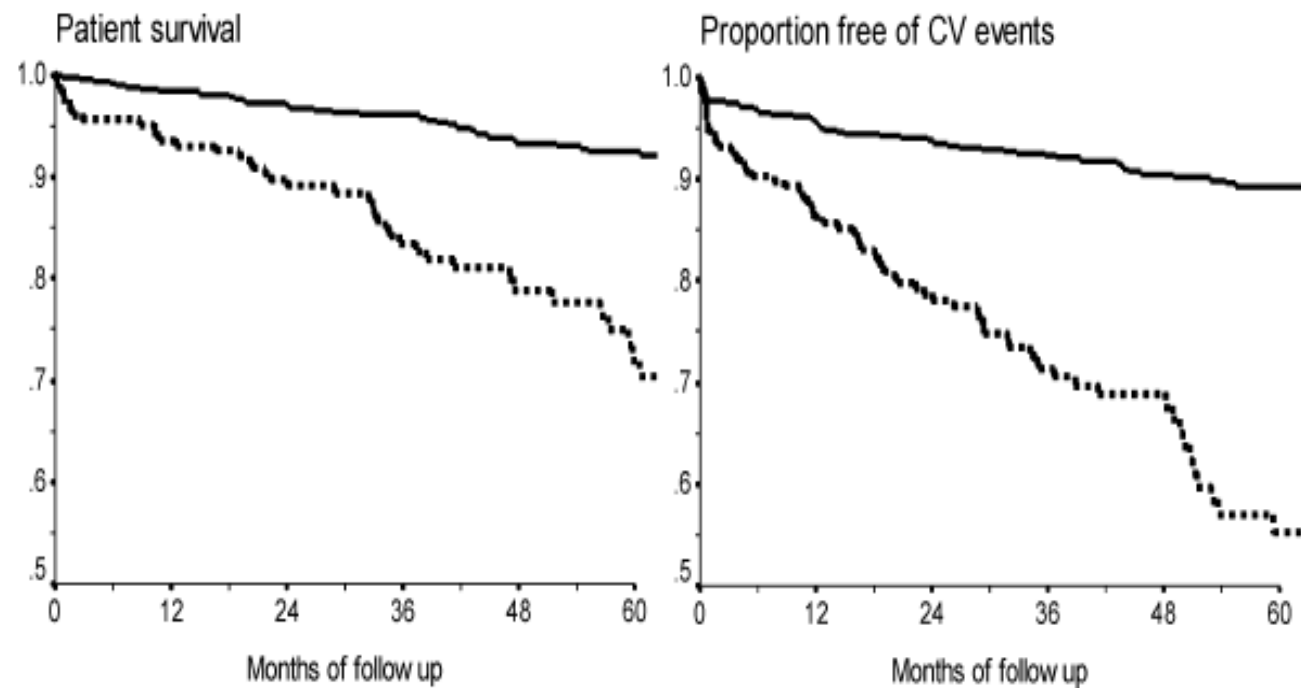
Disordered CH metabolism

OGTT 120' 1997-1999 / 2004-2005.

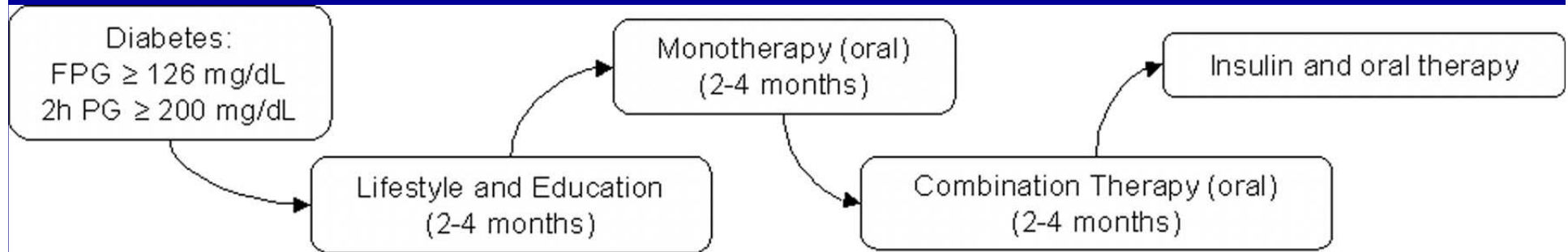


Patient Survival and Cardiovascular Risk After Kidney Transplantation: The Challenge of Diabetes

Figure 1: Left: Kaplan-Meier plots of patient survival after transplantation in recipients without DM (—) and those with DM (.....) (log-rank, $p < 0.0001$). Right: Kaplan-Meier plots of the incidence of fatal and nonfatal posttransplant CV events in recipients without DM (—) and those with DM (.....) (log-rank, $p < 0.0001$).



Diabetes management after the first posttransplant year



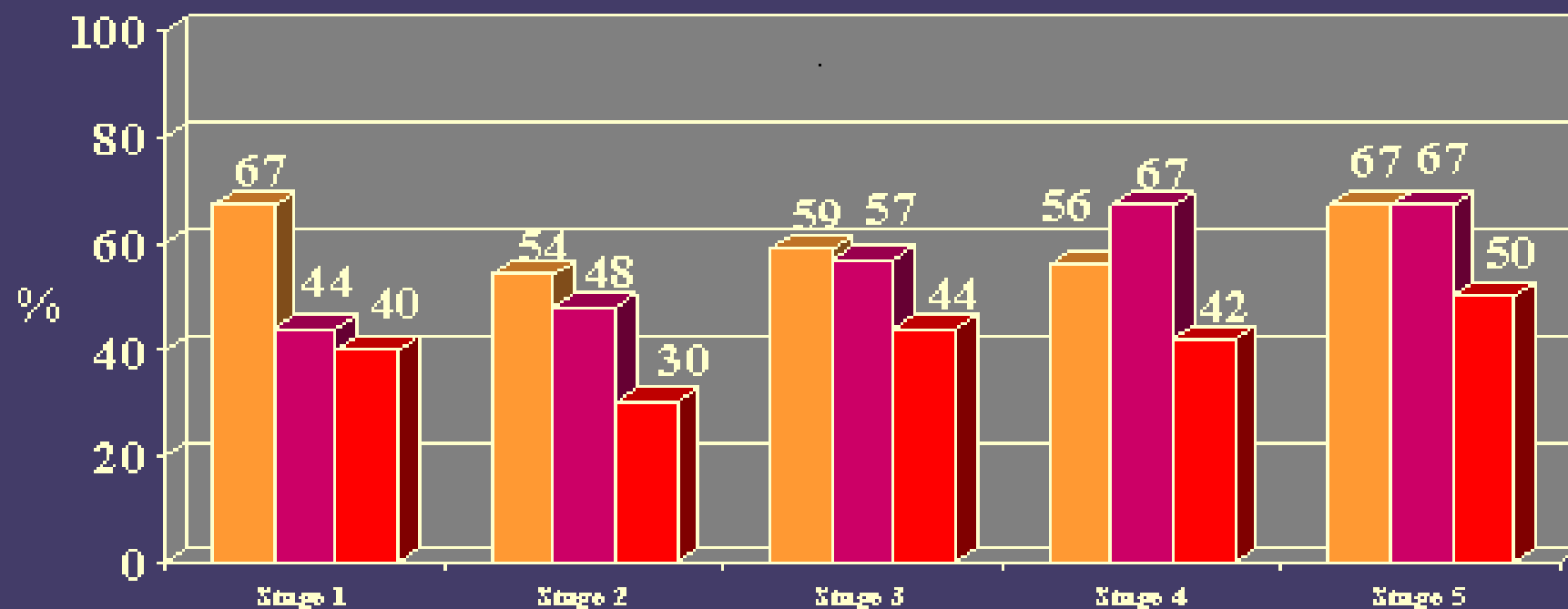
Oral Agent	Target Population	Advantage	Disadvantage
Sulfonylurea	DM2 < 5 year duration	↓ cost Rapid effect	↑ Weight ↑ hypoglycemia
Meglitinides	Recent DM2 ↑ PPG	↓ hypoglycemia short acting	↑ cost
Biguanides	Overweight/Obese Insulin resistance	No ↑ weight ↓ hypoglycemia	GI side-effects Lactic acidosis (rare)
Thiazolidinediones	Overweight/Obese Insulin resistance	↓ Insulin requirement ↓ hypoglycemia	↑ Cost, weight ↑ Liver toxicity Slow onset of action
α-glucosidase inhibitor	↑ PPG	↓ hypoglycemia	GI side-effects ↑ cost

DYSLIPIDAEMIA

Prevalence of Hyperlipidemia in Renal Transplant Patients Based on CKD Stage

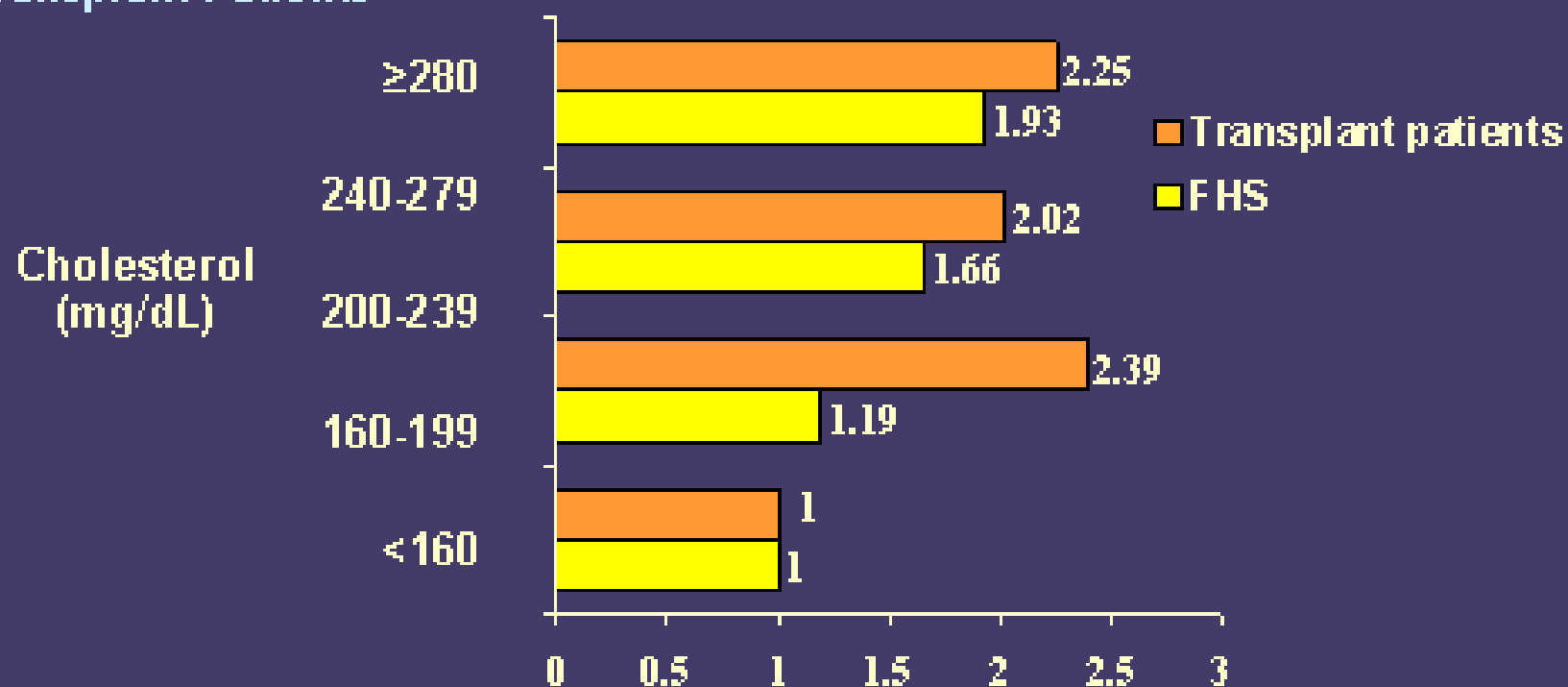
Karthikeyan V, Am J Transplant 4:262-269,2004

Cholesterol \geq 200 mg/dl Triglycerides \geq 150 mg/dl
Lipid Lowering Therapy



Hypercholesterolemia: Relative Risk for Ischemic Heart Disease in Patients More Than One Year After Renal Transplantation

Relative Risk of IHD in Males From the Framingham Heart Study (FHS) or Transplant Patients



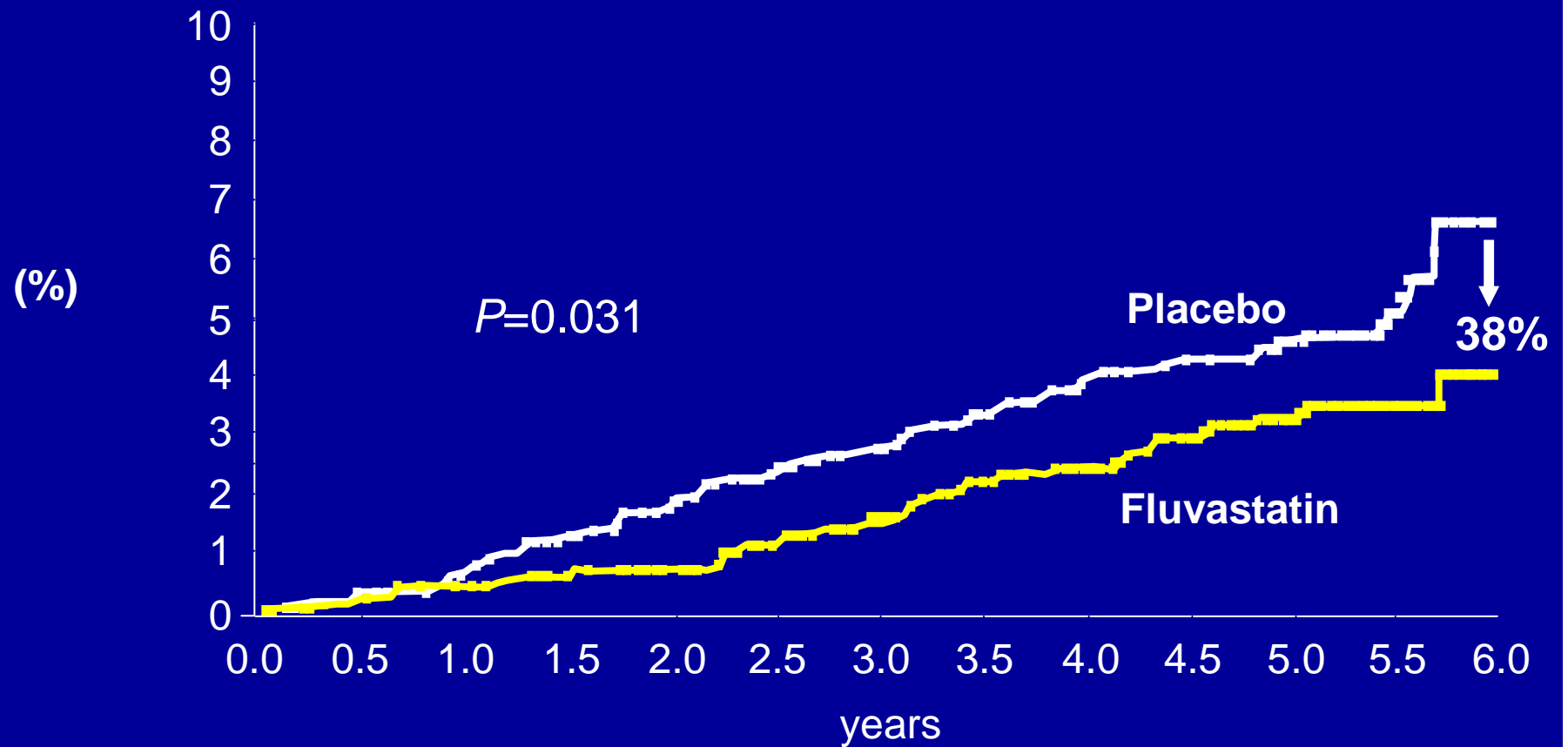
Kasiske BL et al. *J Am Soc Nephrol.* 2000;65:1735-1743.

Wilson PWF et al. *Circulation.* 1998;97:1837-1847.

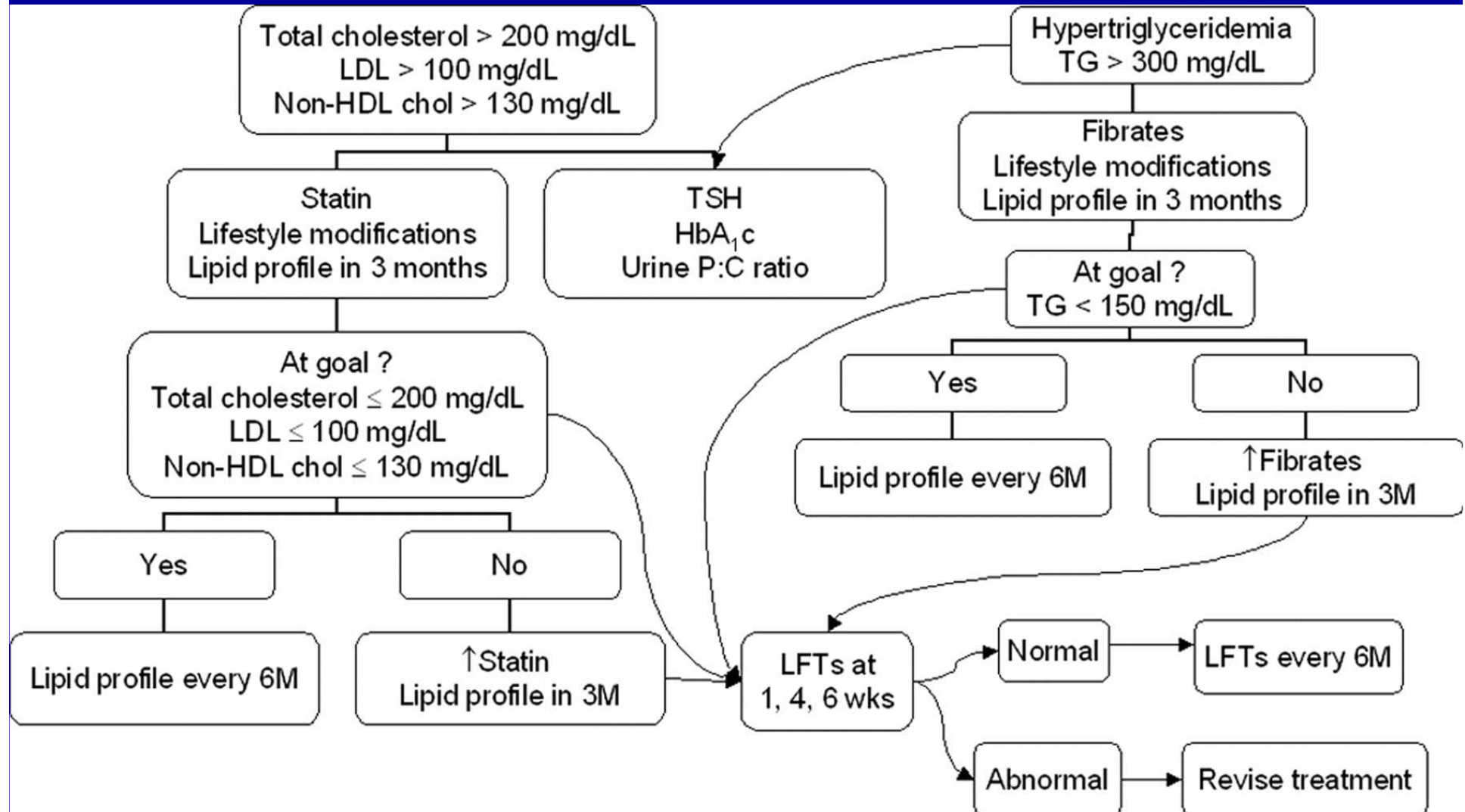
ALERT: Assessment of Lescol in Renal Transplantation

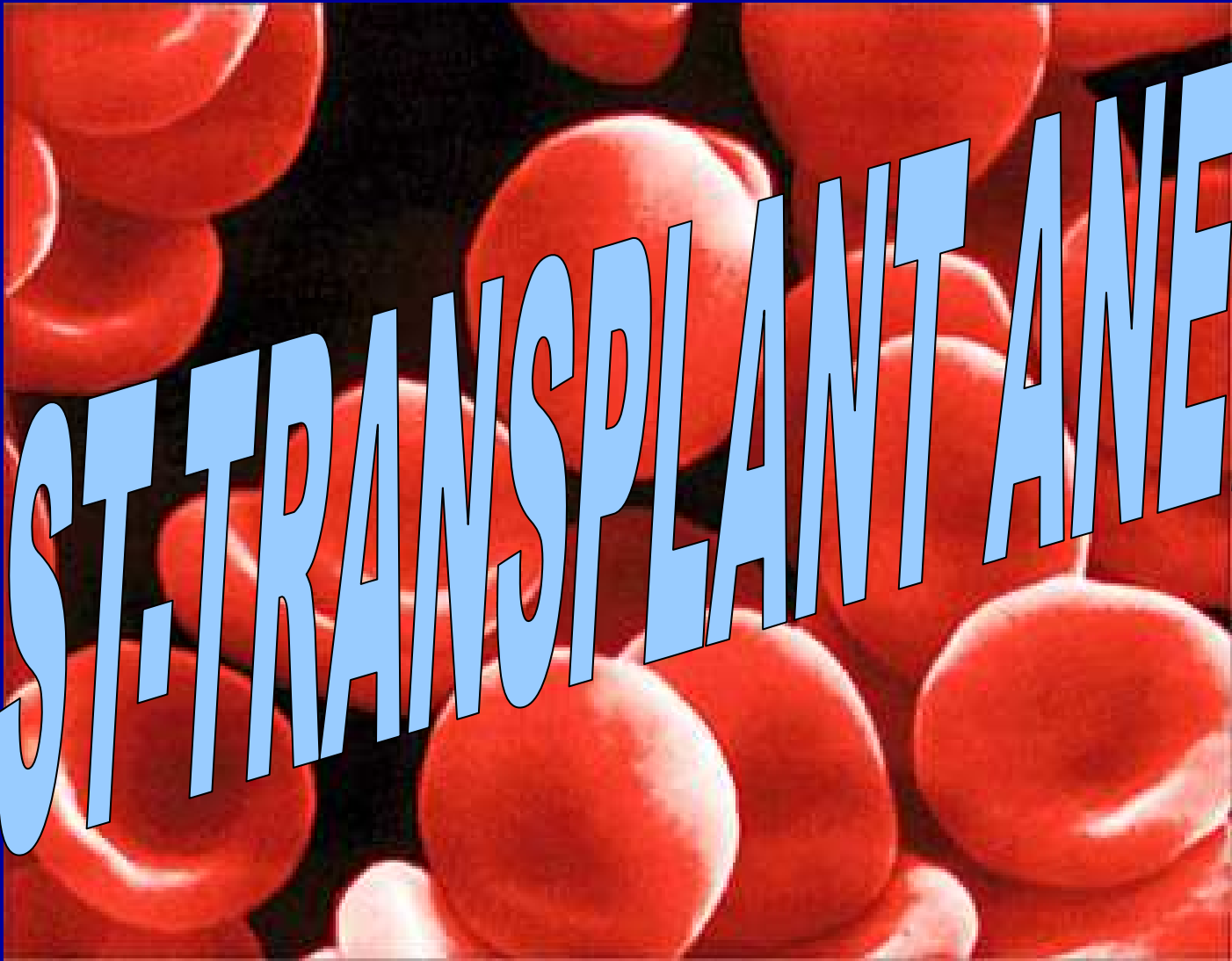
- Randomized, double blind, placebo controlled multicentric study, 2102 Tx patients
- Fluvastatin (40 mg/d - 80 mg/d) or placebo
- Outcome: cardiac mortality, AMI, coronary intervention

Cardiac mortality



Dyslipidemia management after the first posttransplant year

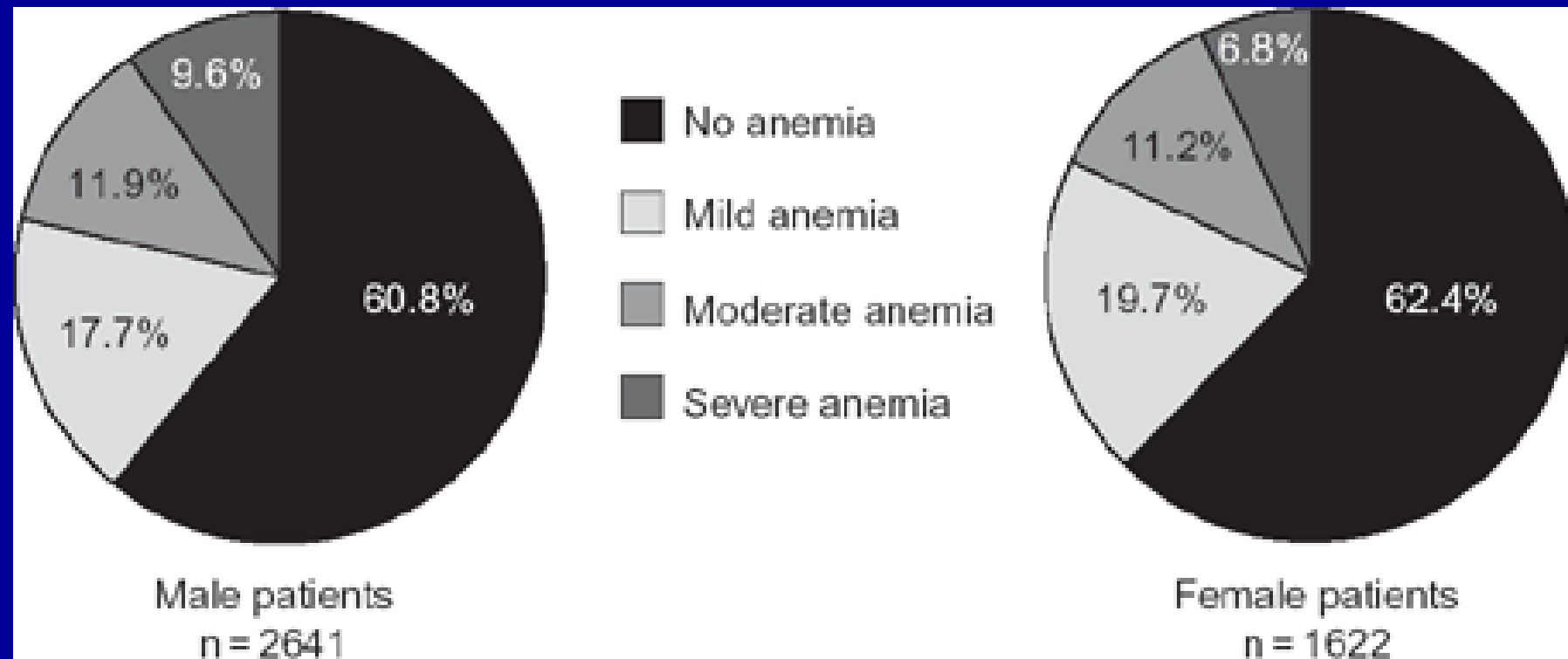


A microscopic view of numerous red blood cells, appearing as bright red, biconcave discs against a dark background. The cells are scattered across the frame, with some in sharp focus and others blurred in the background.

POST-TRANSPLANT ANEMIA

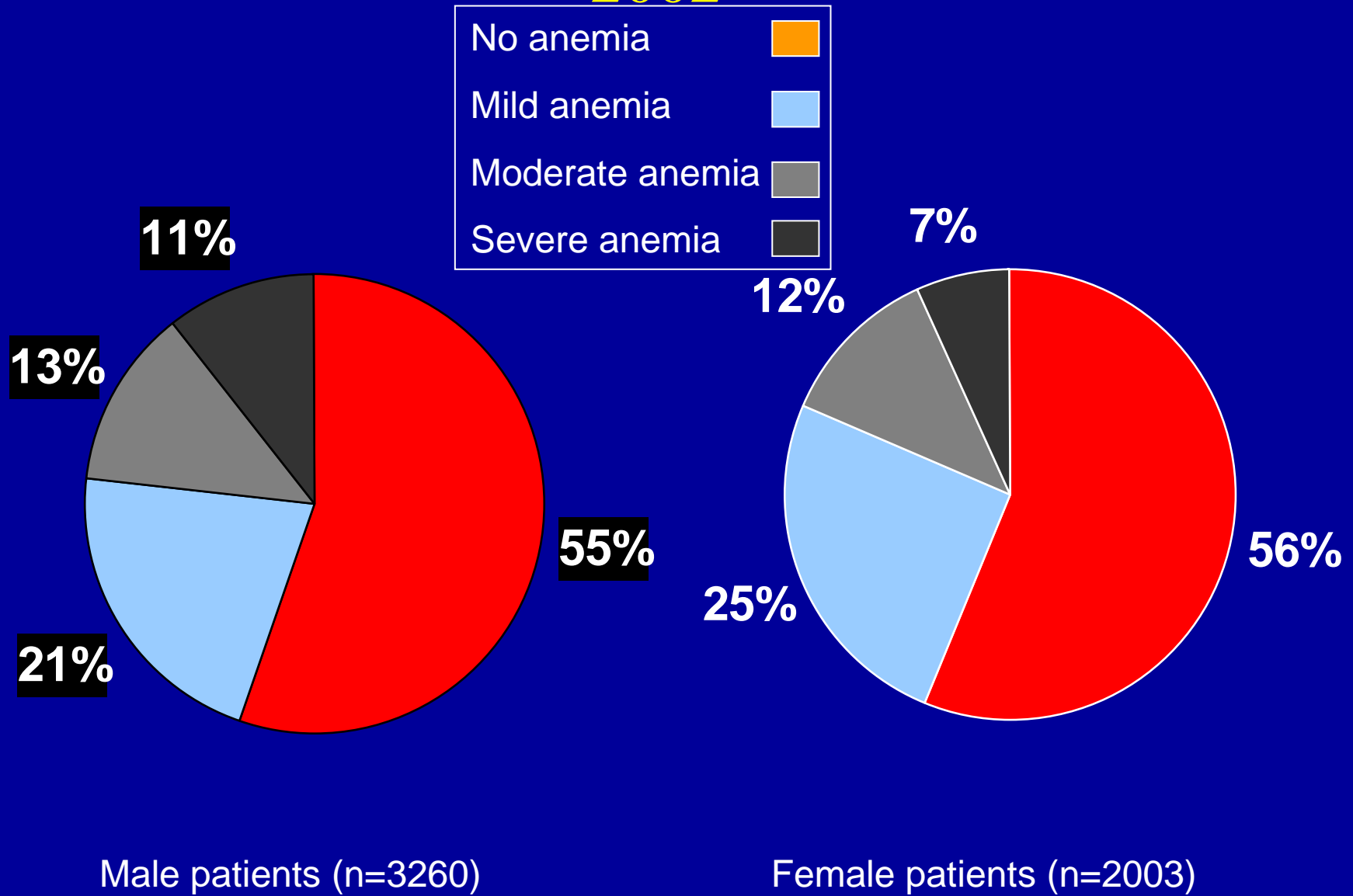
Prevalence and Management of Anemia in Renal Transplant Recipients: A European Survey

Yves Vanrenterghem^a, Claudio Ponticelli^b, José Maria Morales^c, Daniel Abramowicz^d, Keshwar Baboolal^e, Björn Eklund^f, Volker Kliem^g, Christophe Legendre^h, Antonio Luis Morais Sarmientoⁱ and Flavio Vincenti^j

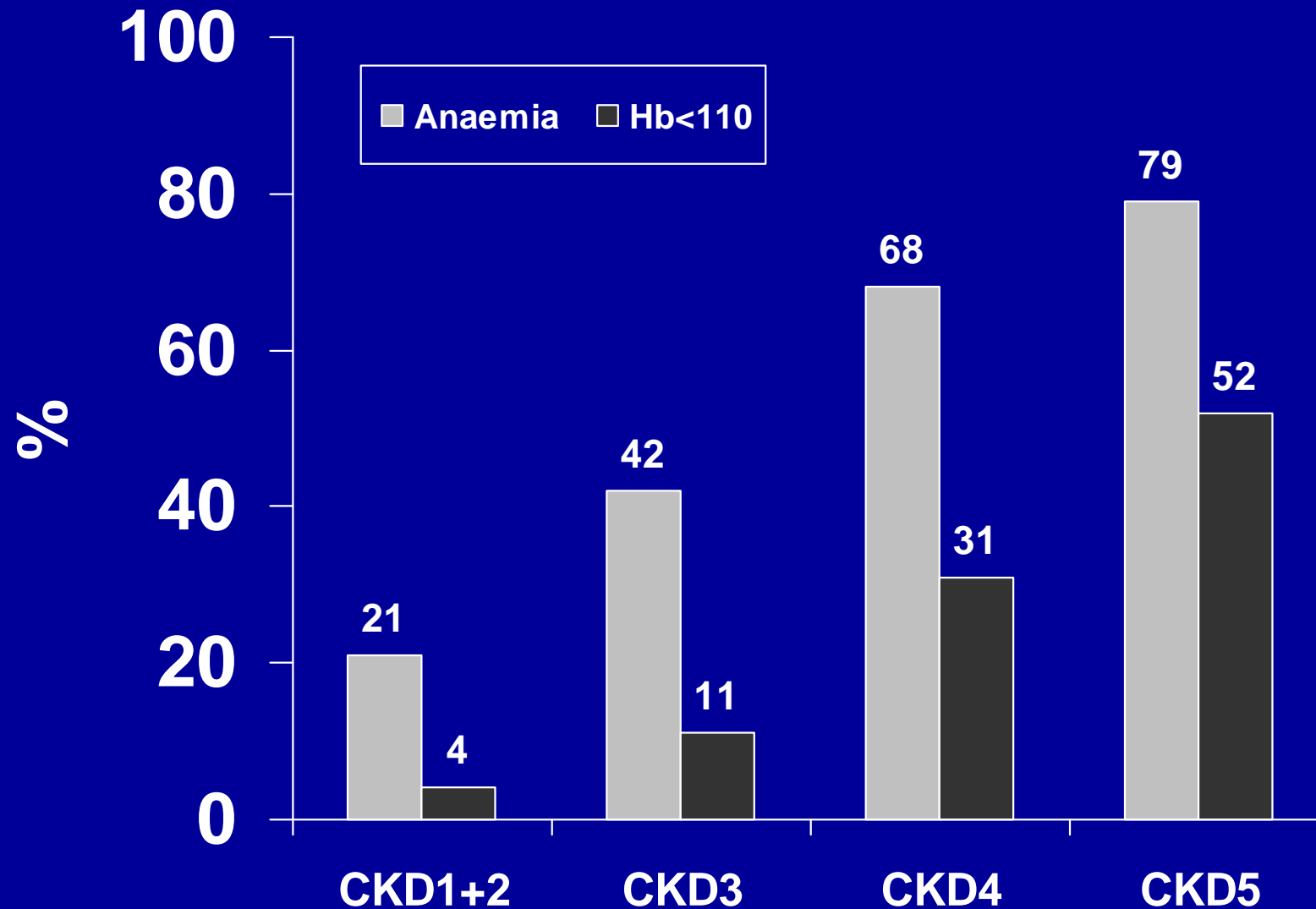


American Journal of Transplantation 2003; 3: 835–845
Blackwell Munksgaard

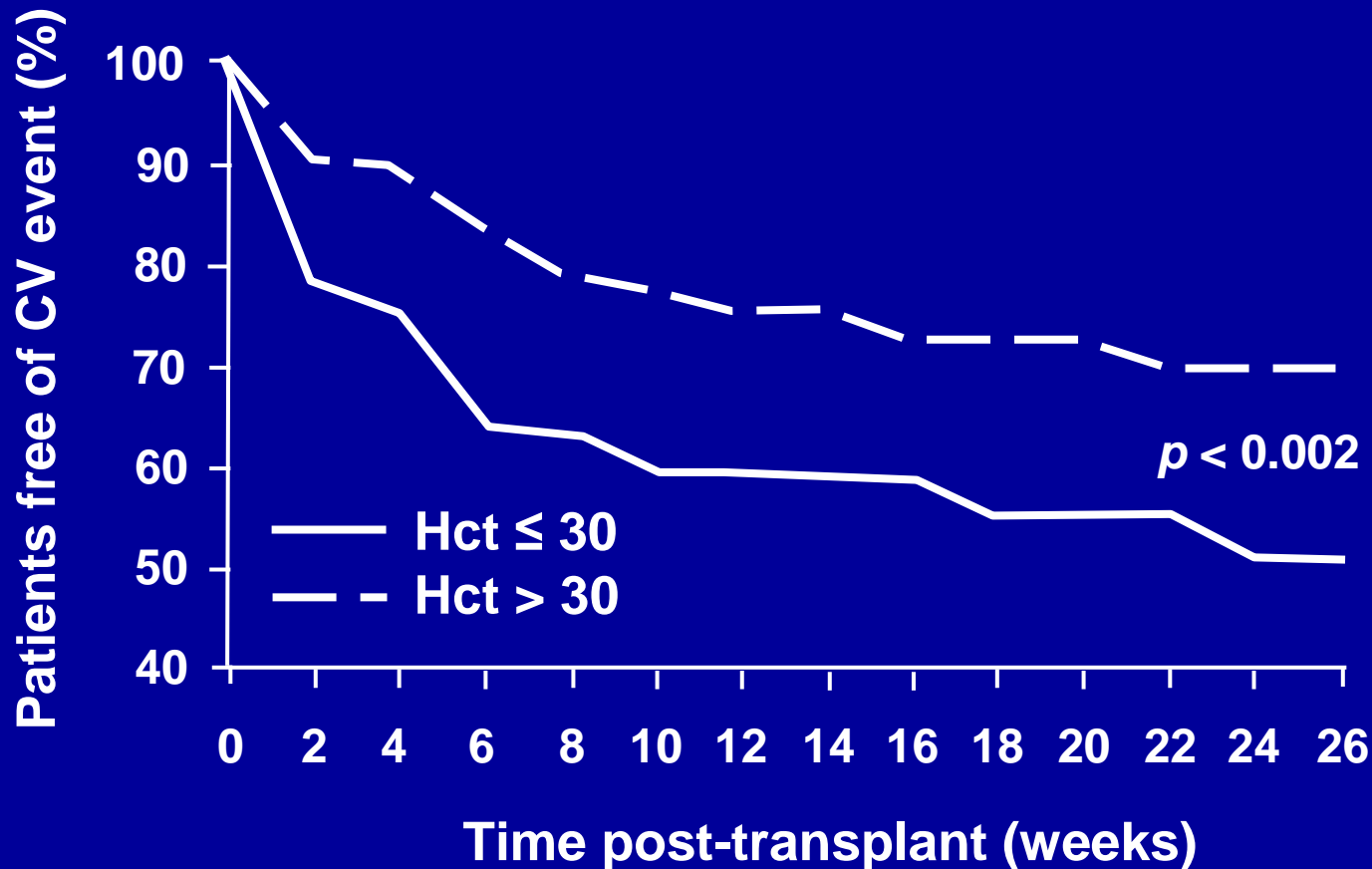
Prevalence of anemia by gender – Transqol-HU 2002



Anemia and CKD stages



Cardiovascular events are more common in anaemic patients

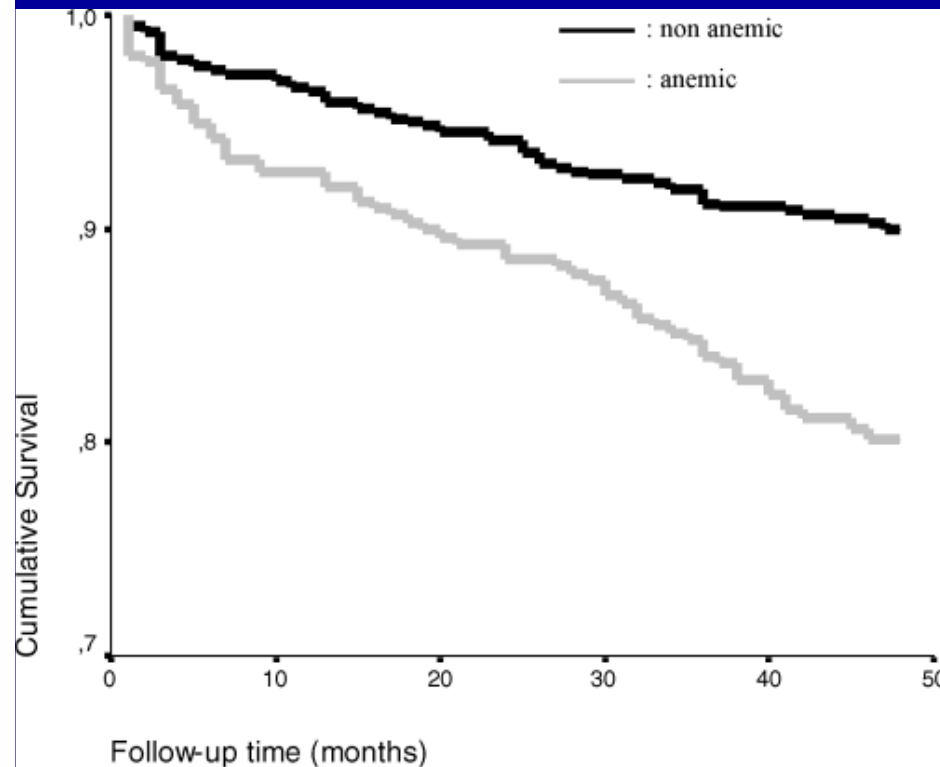


404 type 1 diabetic ESRD who underwent either cadaveric kidney transplantation alone or simultaneous pancreas-kidney transplantation

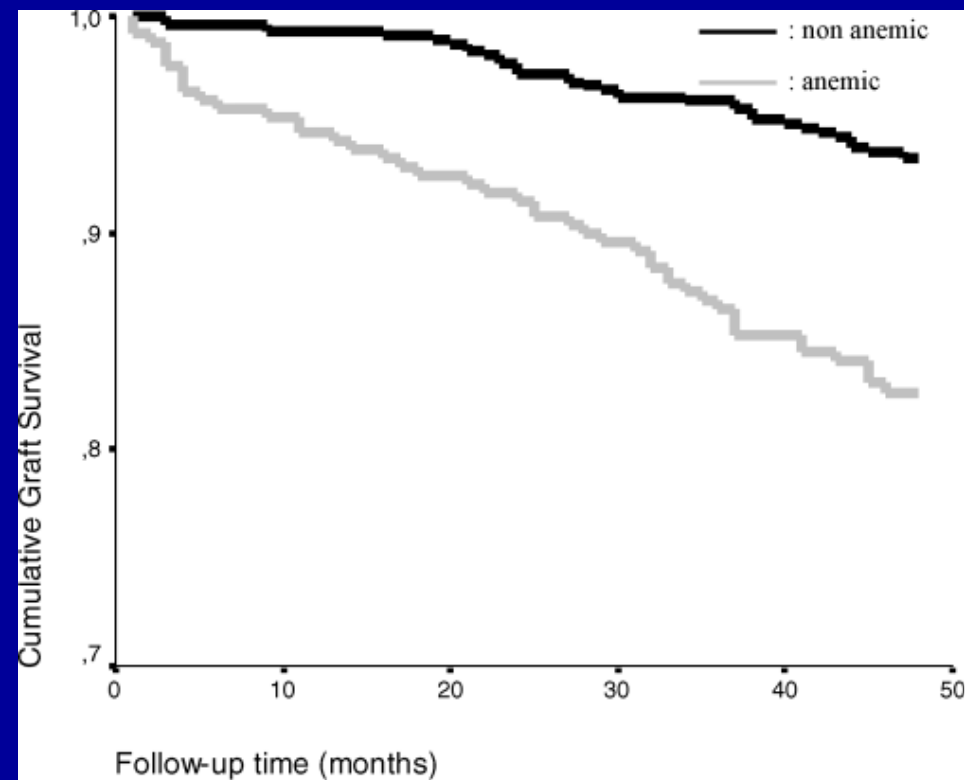
Djamali A et al. *Transplantation* 2003; 76:816-20.

Anemia Is Associated with Mortality in Kidney-Transplanted Patients—A Prospective Cohort Study

M. Z. Molnar^{a,b,c}, M. Czira^a, C. Ambrus^{b,c},
L. Szeifert^a, A. Szentkiralyi^a, G. Beko^d,
L. Rosivall^e, A. Rempert^f, M. Novak^{a,g}
and I. Mucsi^{a,b,e,*}



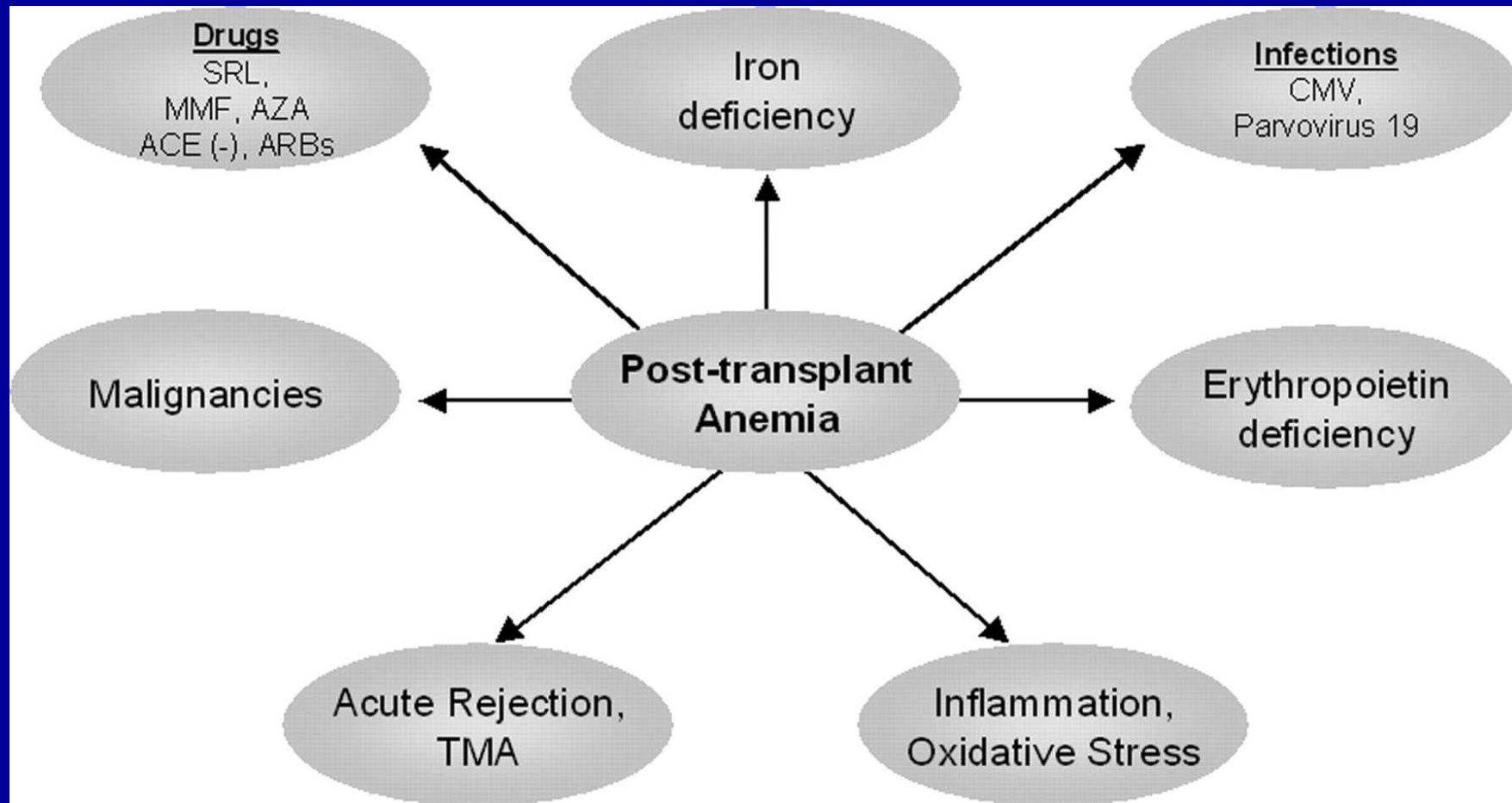
Log Rank: $p < 0.0001$



Log Rank: $p < 0.0001$

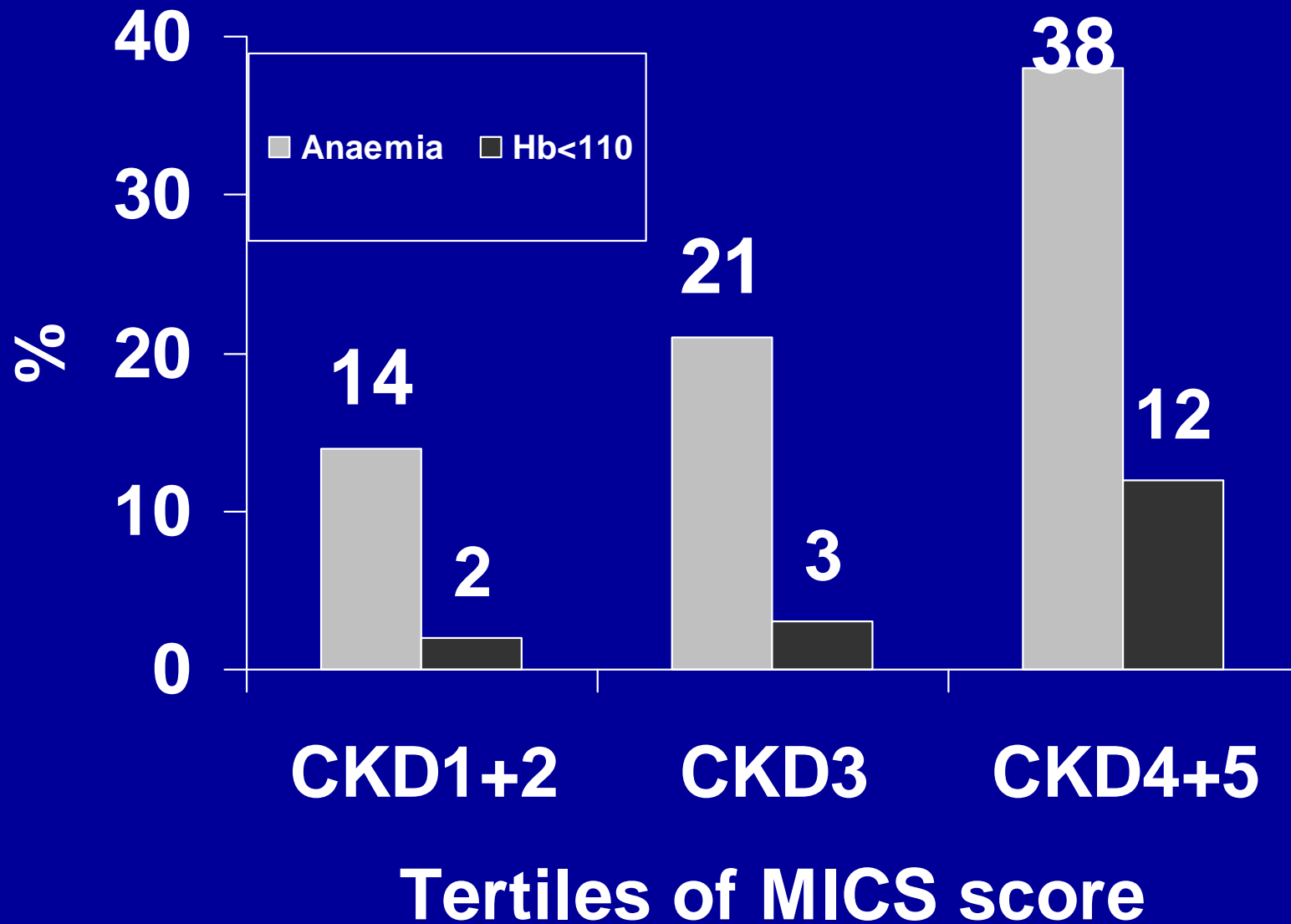
*American Journal of Transplantation 2007; 7: 818–824
Blackwell Munksgaard*

Common causes of posttransplantation anemia

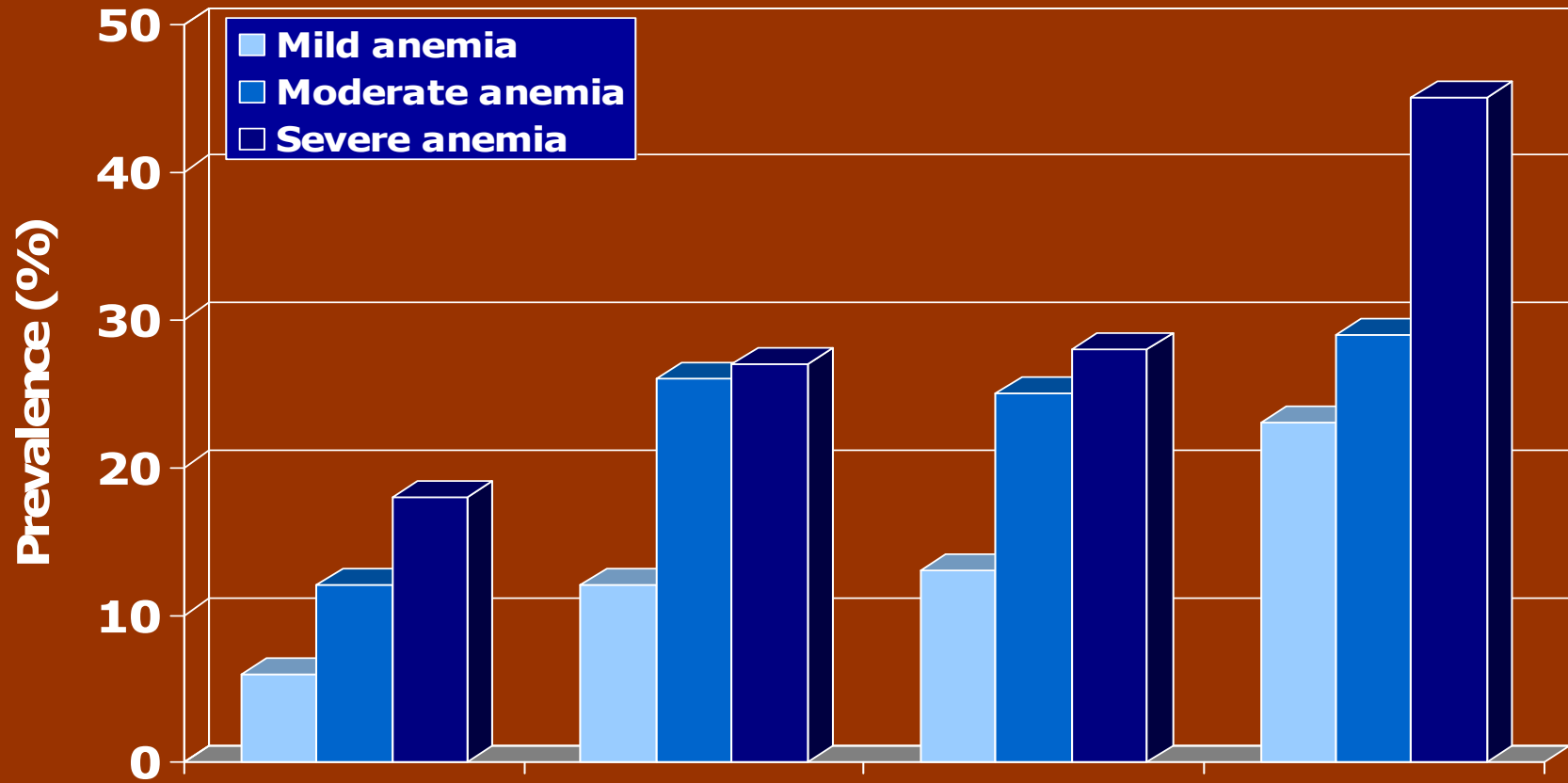


Djamali, A. et al. Clin J Am Soc Nephrol 2006;1:623-640

Anemia and MICS



ESA treatment



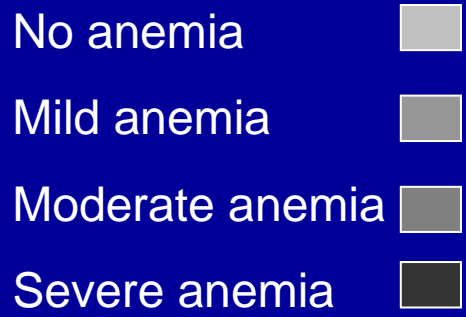
TRESAM
2003

TRANSQOL-
HU 2002

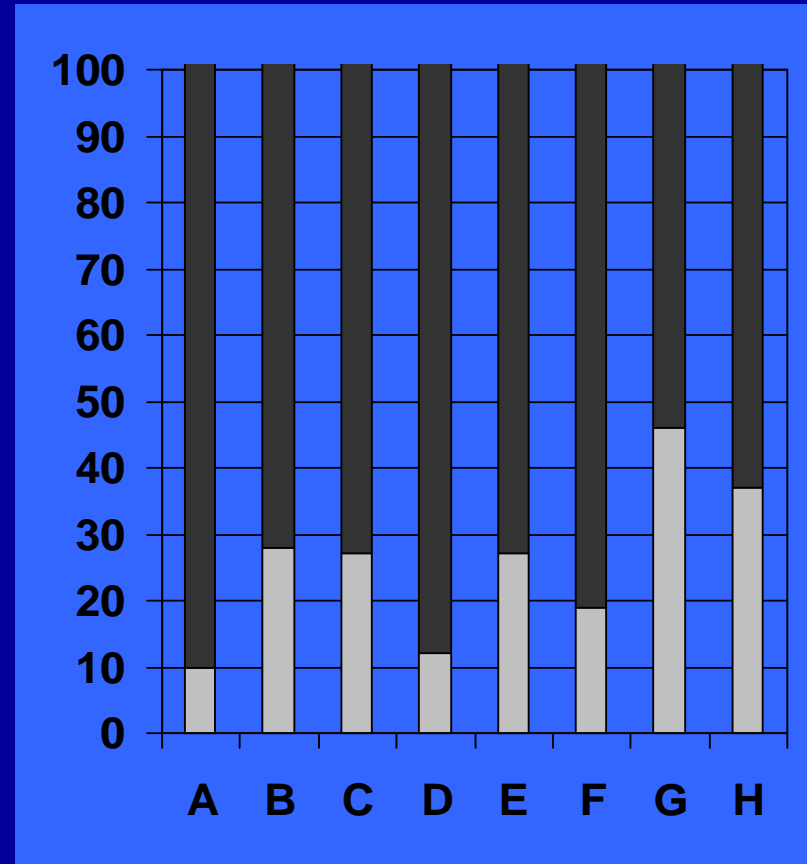
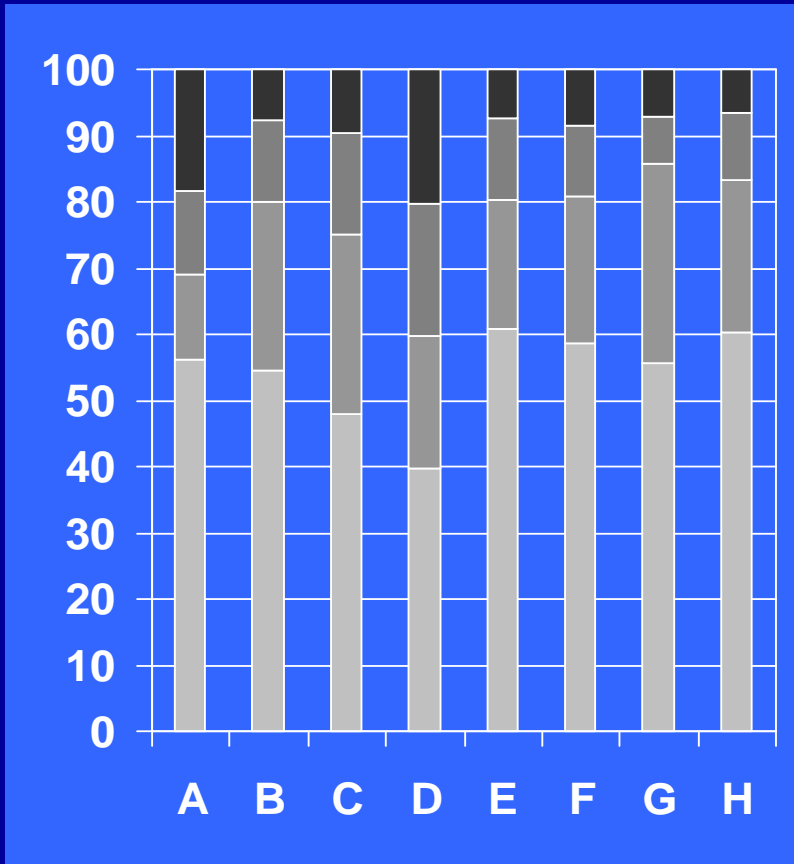
Europe
2007

TRANSMICS-HU
2007

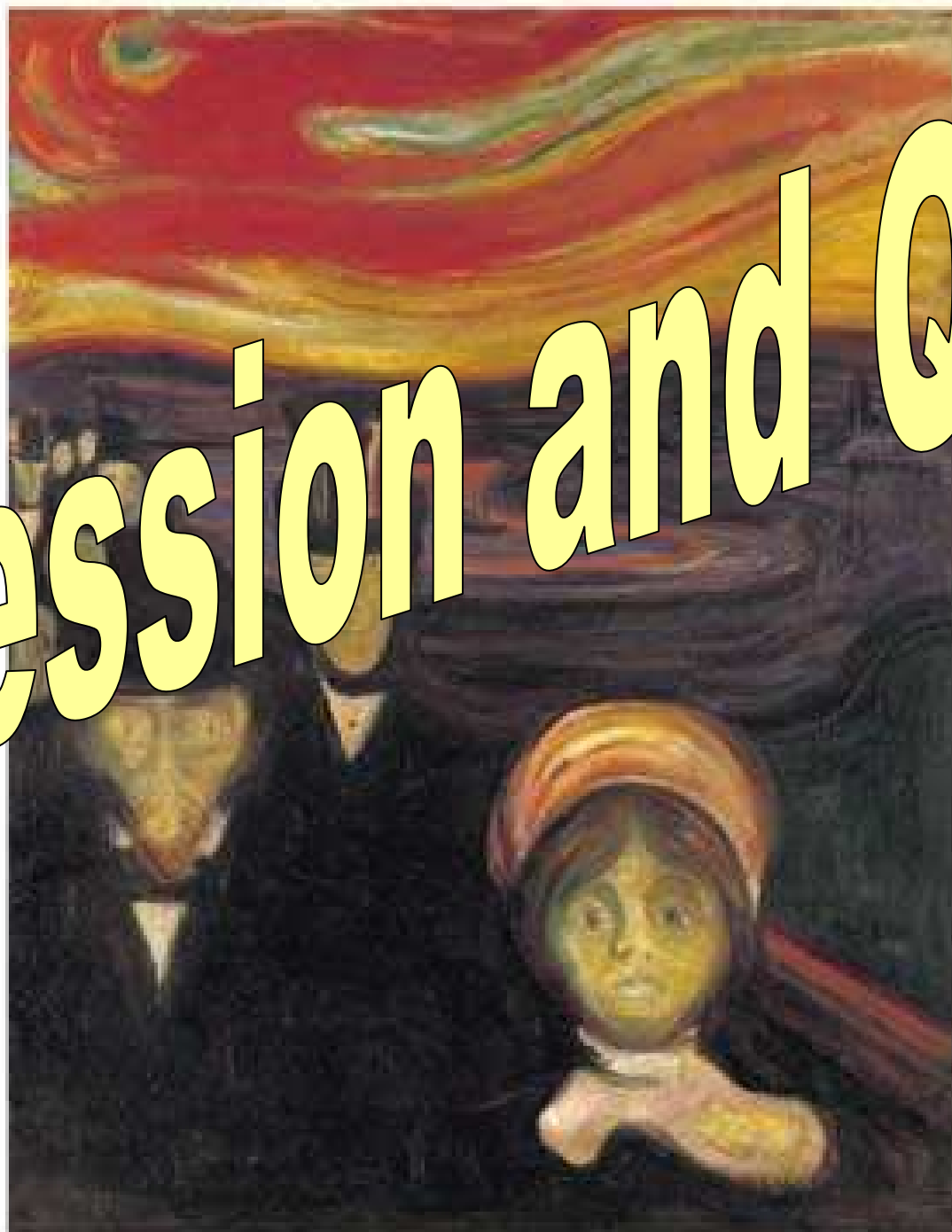
Difference in centers



Severity of anemia



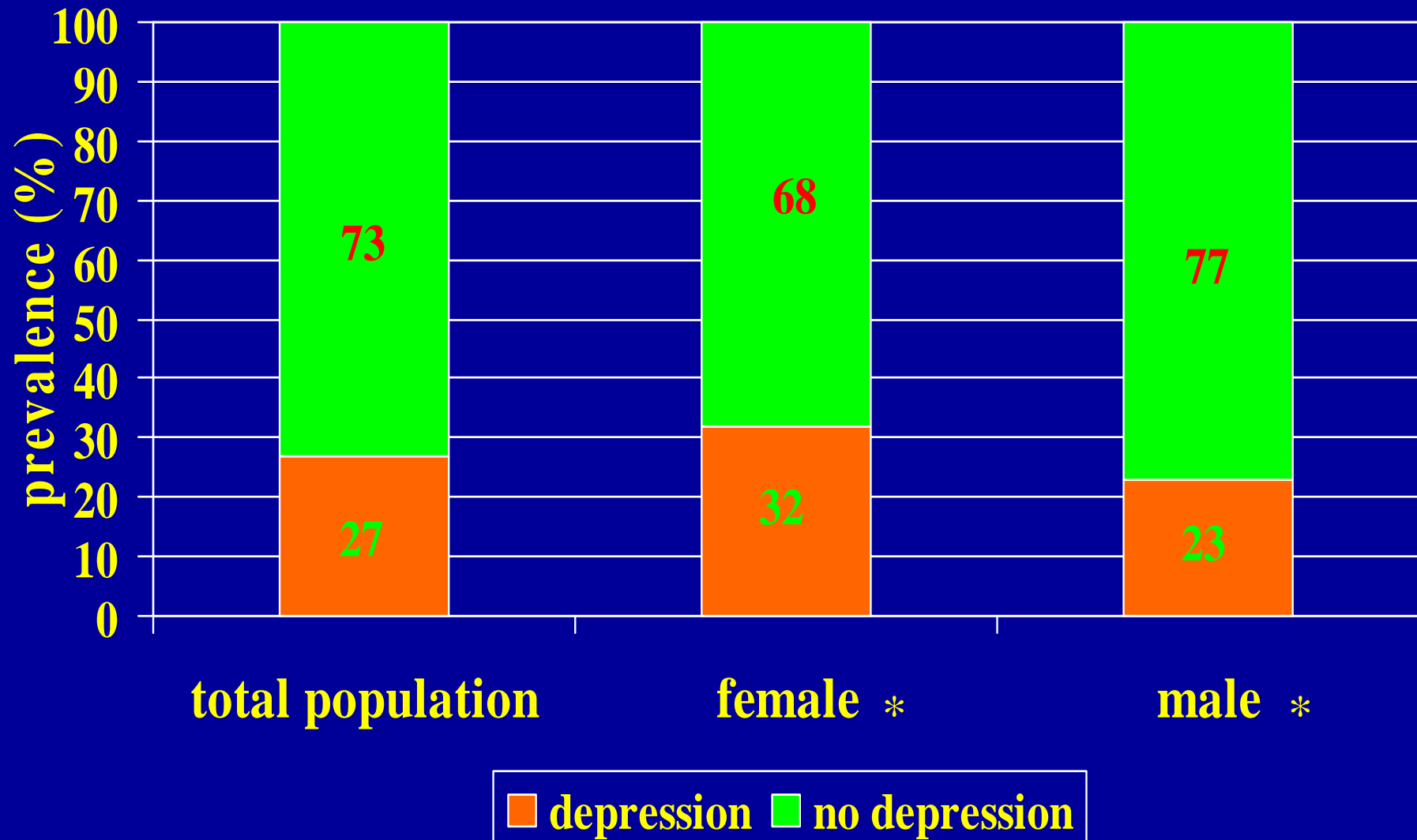
Depression and QoL



Significance of depression

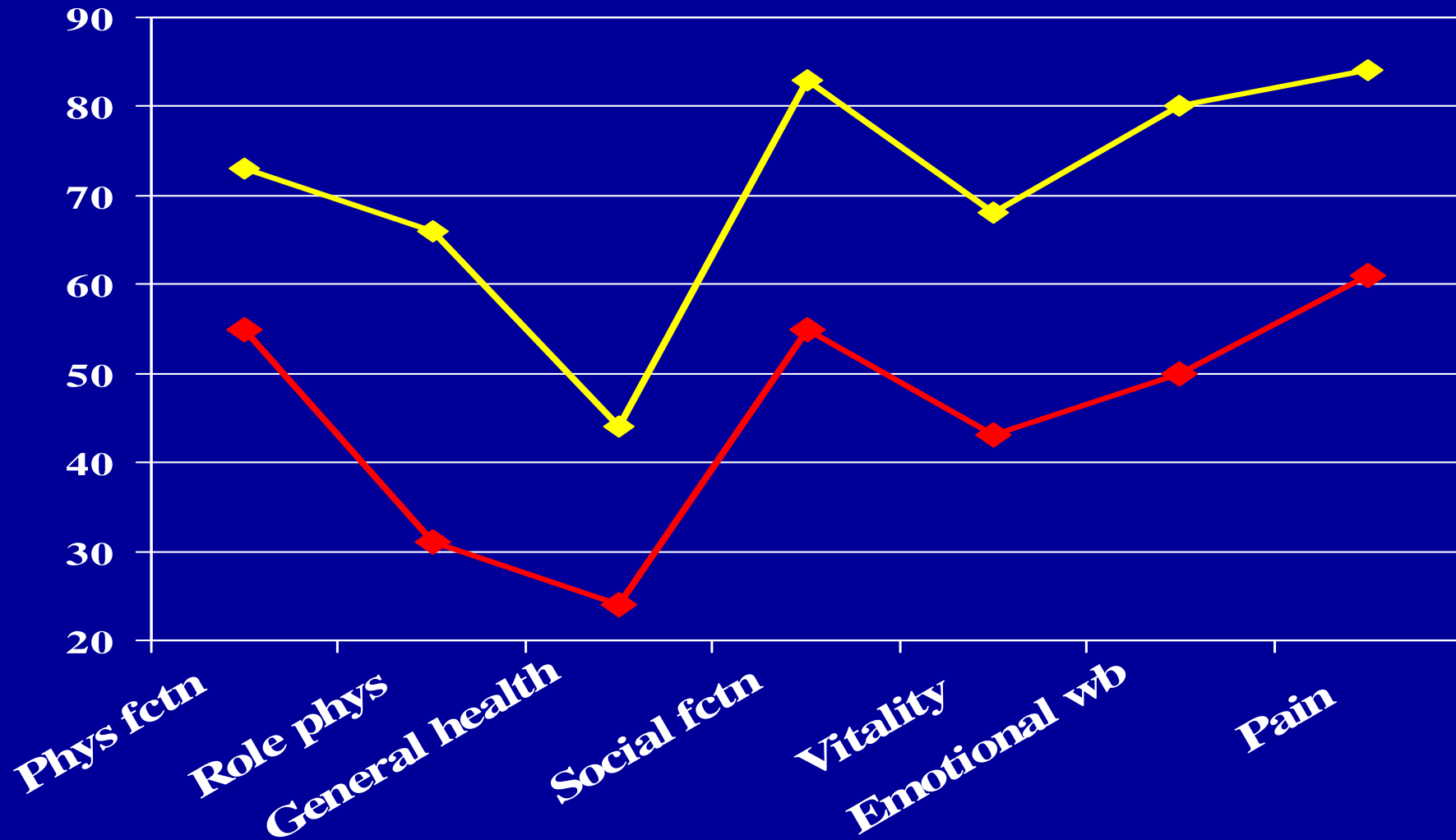
- A major predictor of QoL in different Pt groups
- High prevalence, large social and economic burden
- Treatment adherence
- Rehabilitation
- Association with CV diseases, diabetes, outcome

Prevalence of depression

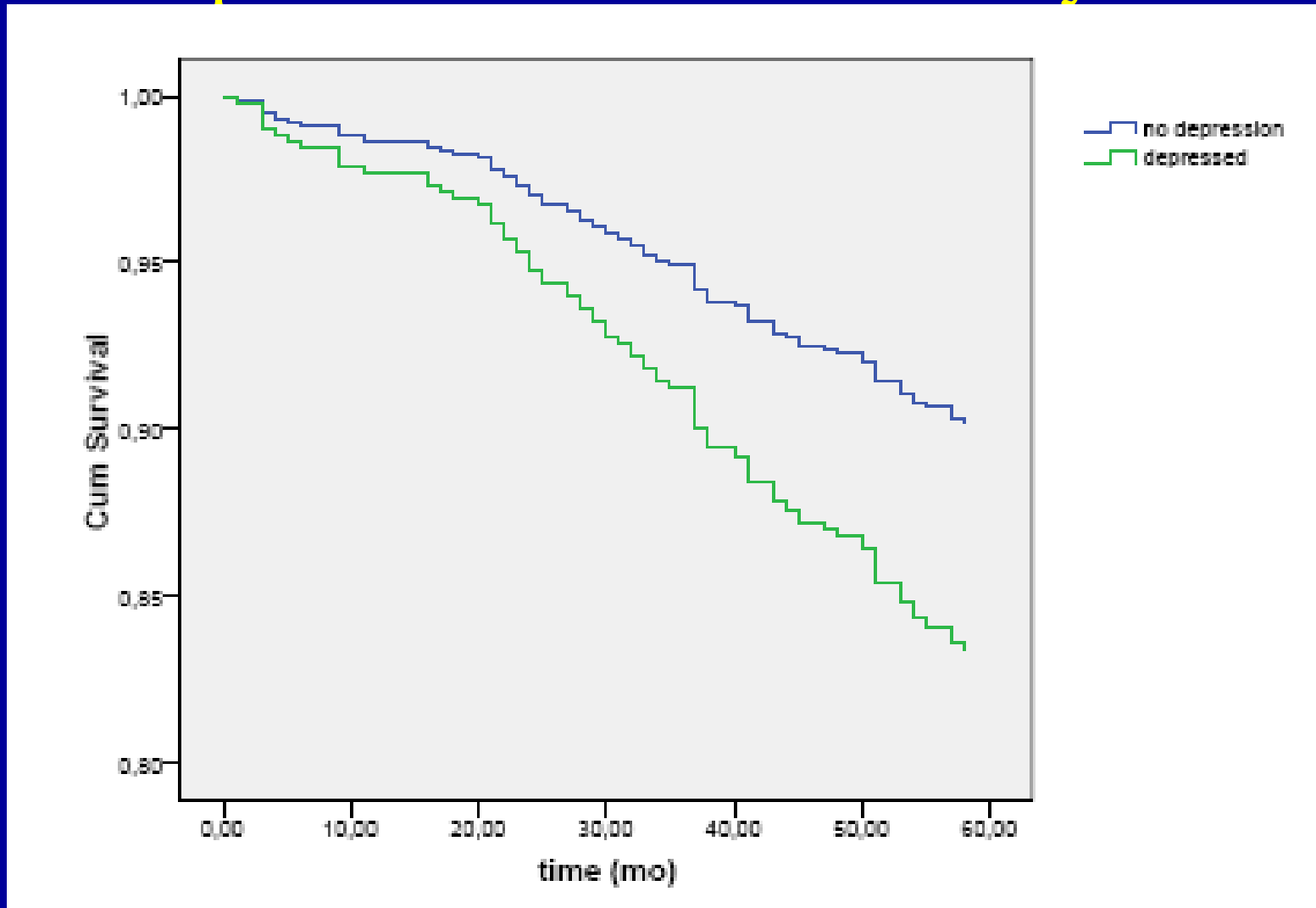


Depression (CESD) and QOL

◆ High risk for depression ◆ Low risk for depression

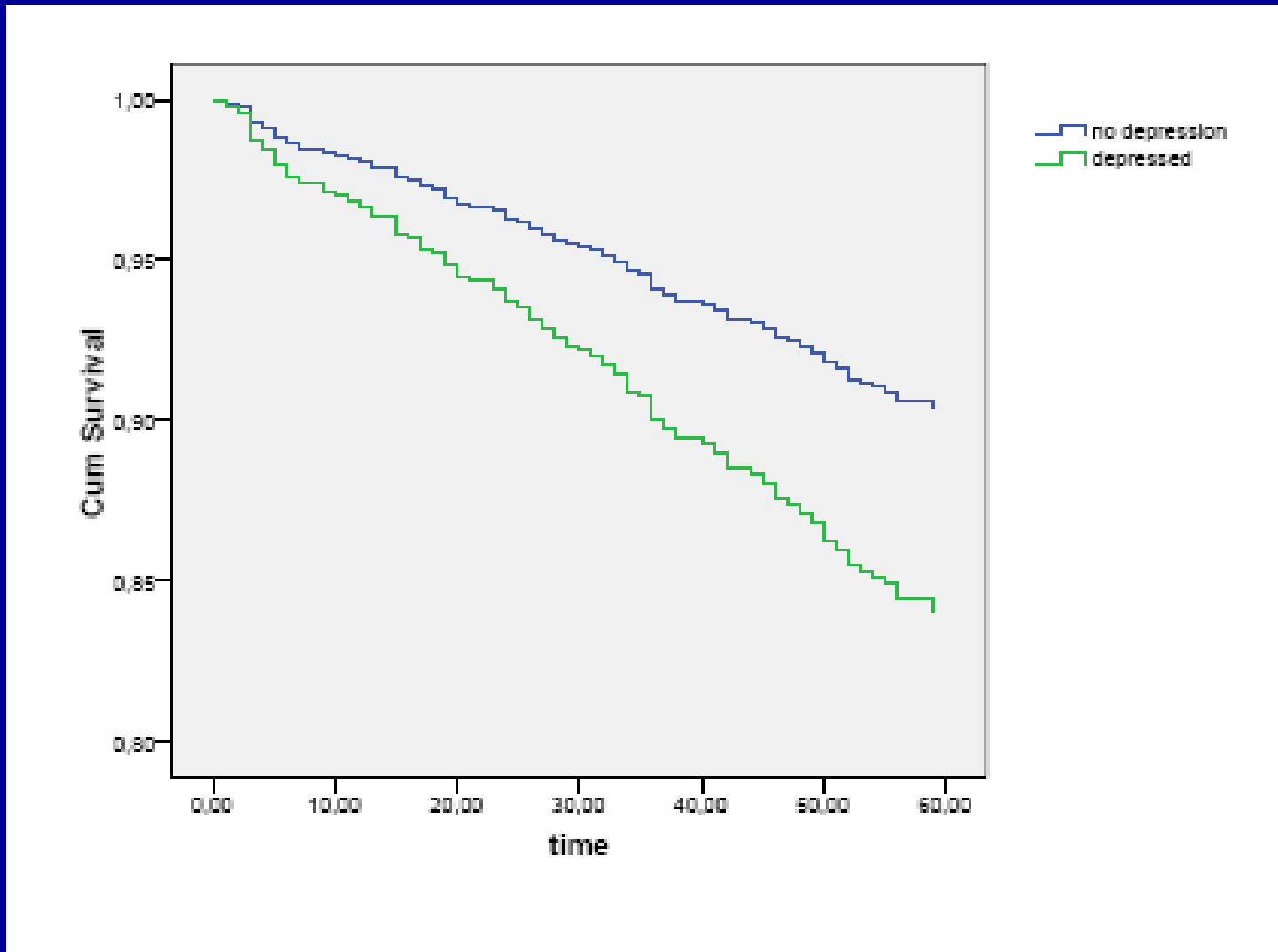


Depression and return to dialysis



Age, gender, education, eGFR, alb, Hb, diabetes, HTN, CRP,
tx vintage

Depression and mortality



Age, gender, education, eGFR, alb, Hb, diabetes, HTN, CRP,
tx vintage

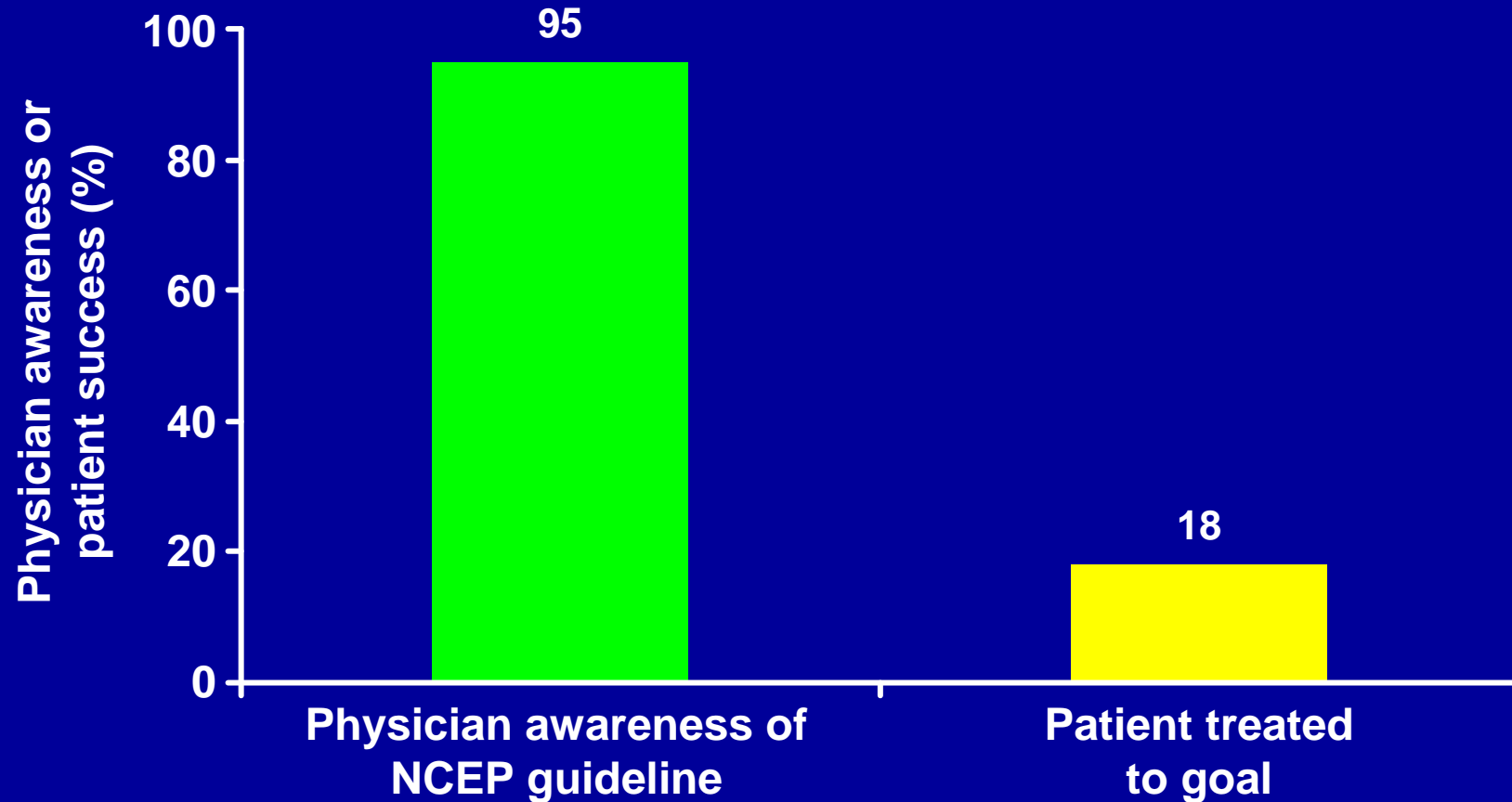
MULTIDISCIPLINARY CARE

Multidisciplinary care

- Education program
- Protocollized clinic f/u
- Protocollized lab
- Nephrologist
- Nurse practitioner
- Social worker
- Dietician
- Pharmacist
- Physiotherapist

CAD treatment gap in the community

Provider awareness does not equal successful implementation



NCEP = National Cholesterol Education Program

Pearson TA, et al. Arch Intern Med 2000;160:459-67

Drug utilization - Budapest

- Acei/ARB 29%
- Plt aggreg. Inhibitors 39%
- Statins 30%

Steno 2: Intensive Therapy

NB: combined cardio/renal protection

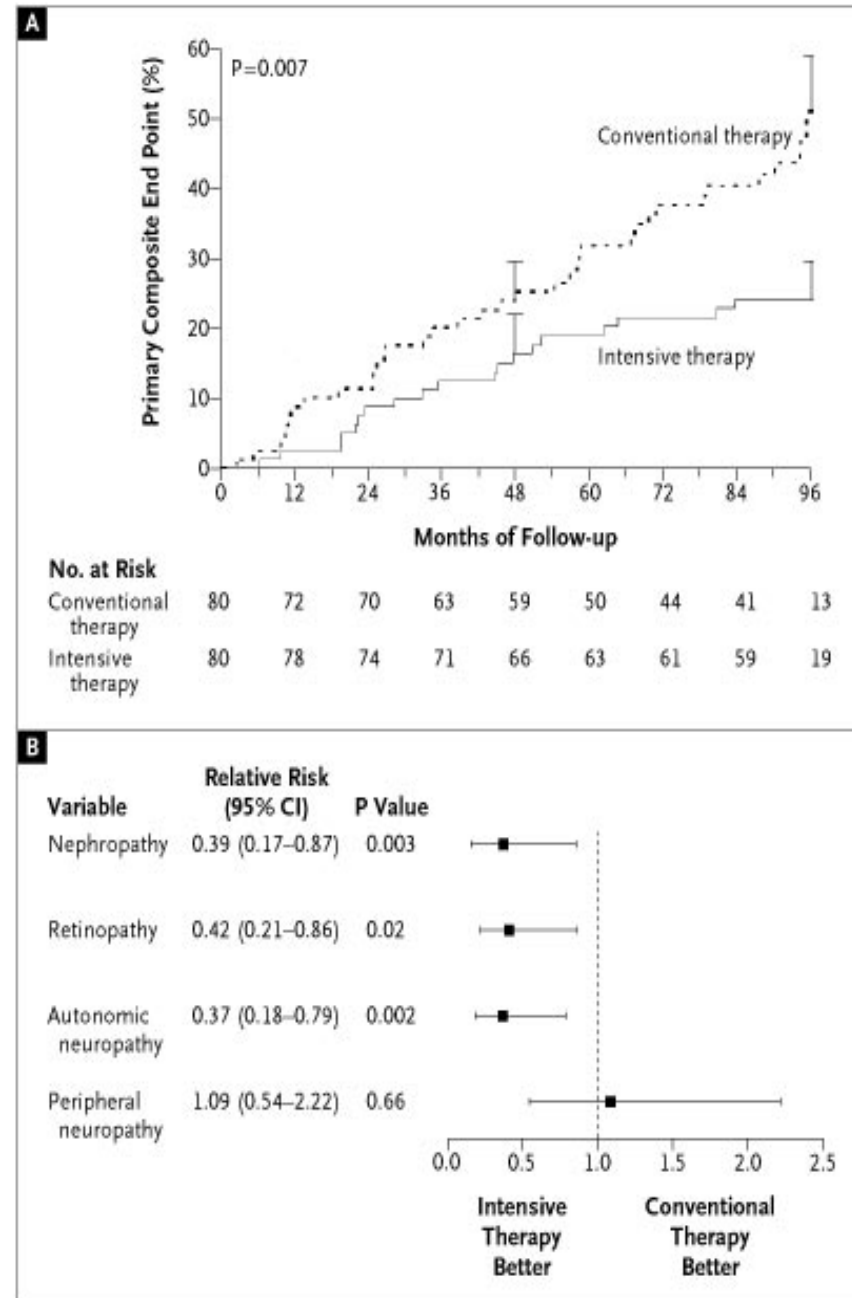
- Multidisciplinary team (MD, nurse, dietician)
- Diet
- Exercise 30 minutes 3 – 5x/wk
- Smoking cessation courses
- ACEI/ARB independent of BP
- Vitamin – mineral supplement
- ASA
- Glycemic control
- BP control
- Lipid control

Gaede P et al. NEJM 2003; 348: 383-393

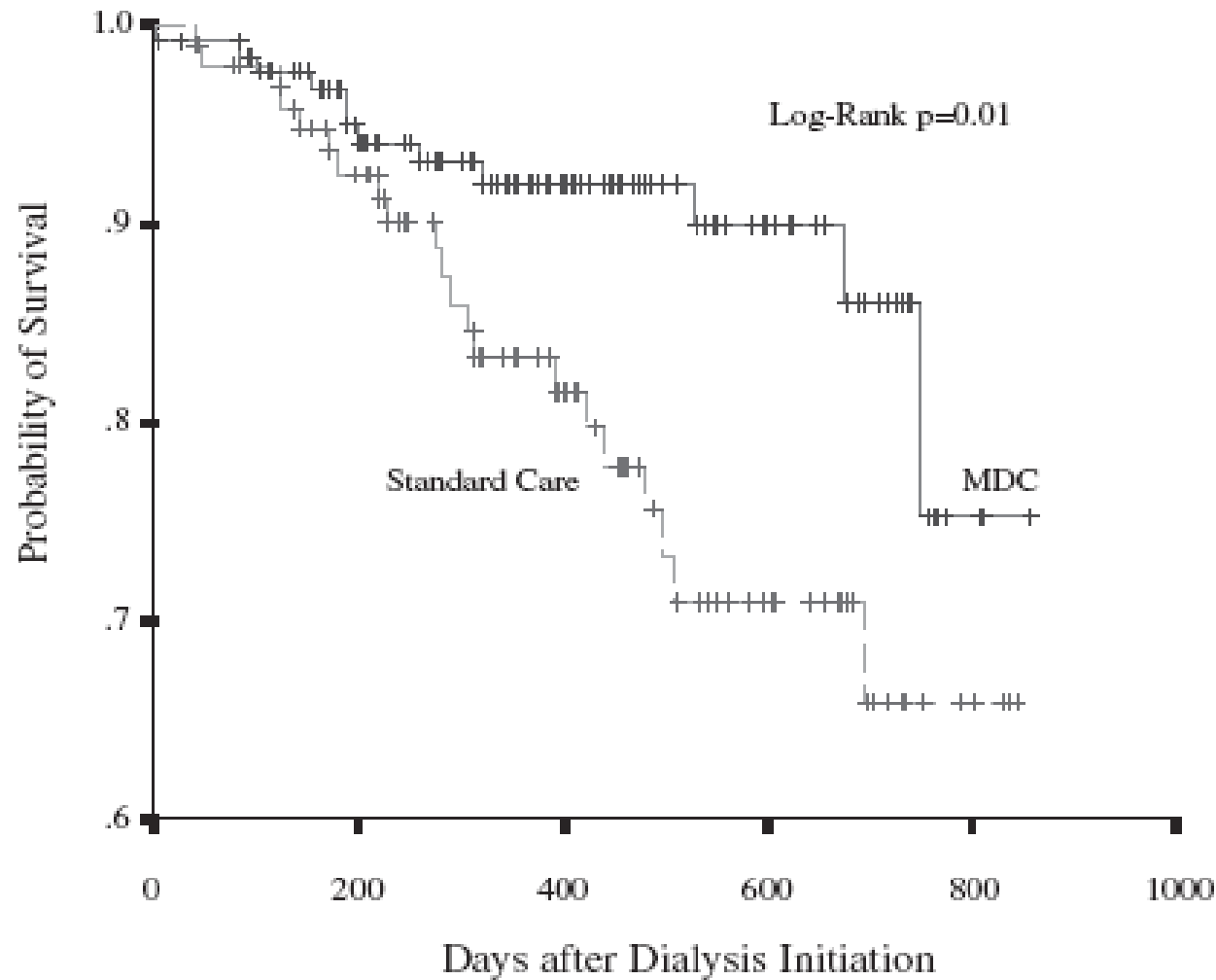
Steno 2: Outcomes

- Hazard ratio = 0.47 in favor of intensive group (.24 - .73, $p=0.008$)
- Absolute RR = 20%
- NNT 5 patients to prevent one CV event in 7.8 years

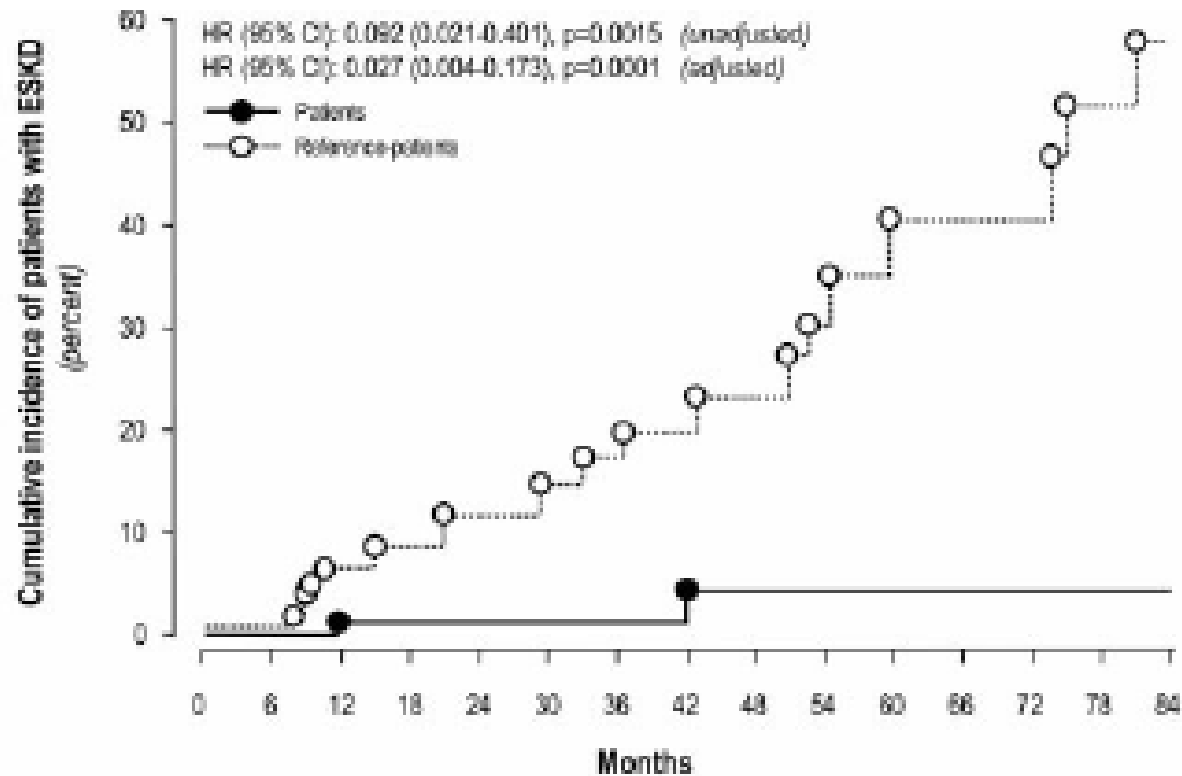
Gaede P et al. NEJM 2003; 348: 383-393



The short- and long-term impact of multi-disciplinary clinics in addition to standard nephrology care on patient outcomes



Role of Remission Clinics in the Longitudinal Treatment of CKD



Subjects at risk

Patients	54	56	55	55	53	51	48	37	36	32	30	22	18	7	6
Reference-patients	54	54	48	44	42	40	39	28	22	18	12	10	10	6	4

Chronic Kidney Disease (CKD) After Organ Transplantation

