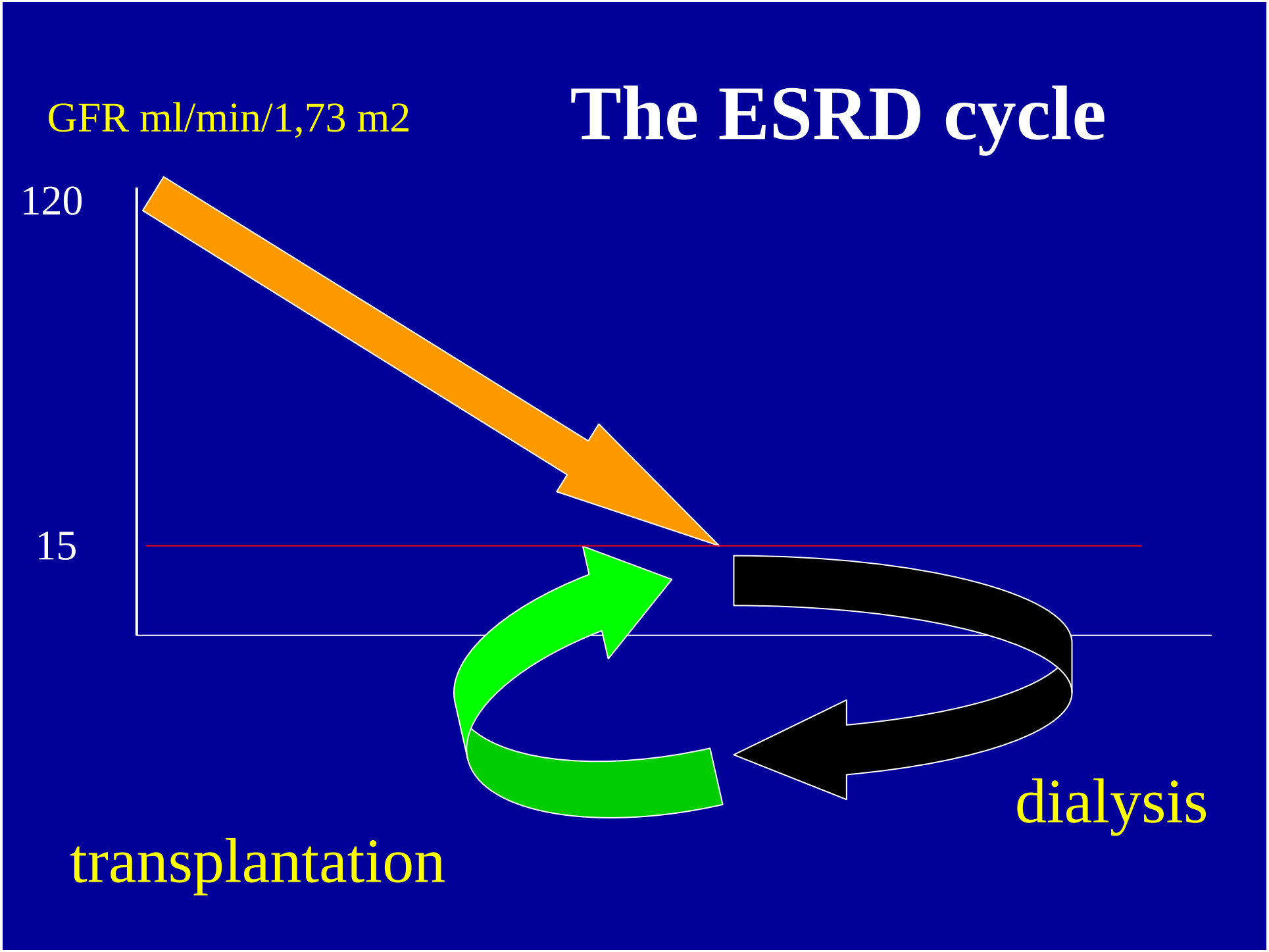
The complex management of kidney transplanted patients - beyond immunosuppression

Istvan Mucsi
Semmelweis University, Budapest, Hungary

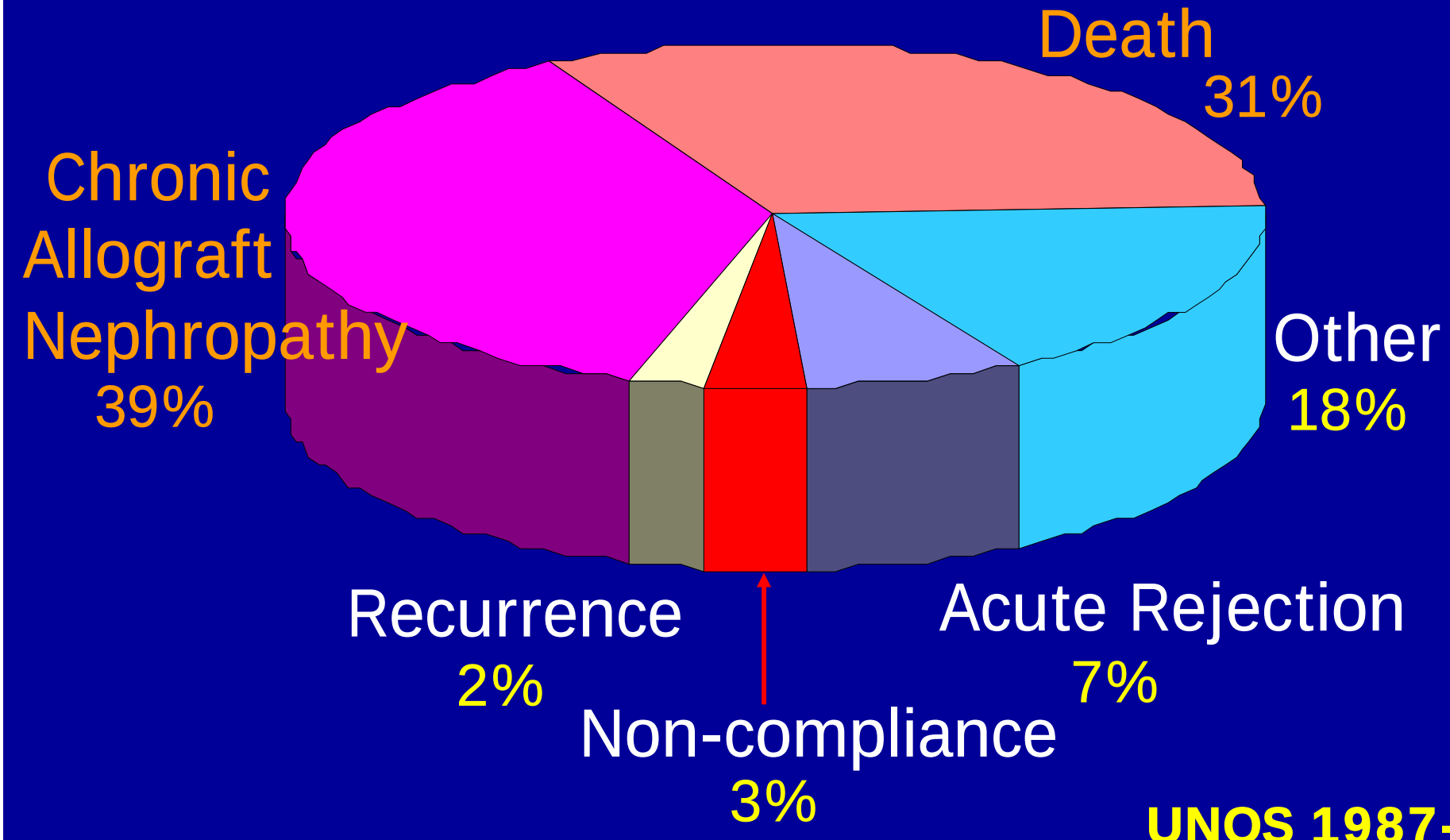
- The ESRD cycle
- CKD in the kidney transplant (Tx) population
- Cardiovascular disease in the Tx population
- Post-transplant anemia
- Post-transplant metabolic disorders (diabetes, lipids)
- The multidisciplinary model

The ESRD cycle



CARDIOVASCULAR DISEASE IN KIDNEY TRANSPLANTED PATIENTS

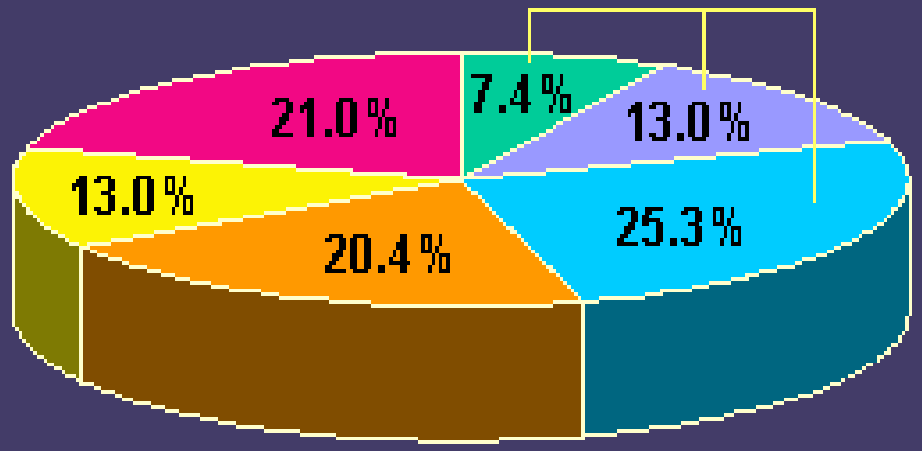
Causes of Renal Graft Loss after First Year
(120,000 transplants, 15,000 failures)



UNOS 1987-01

Cause of Death in Renal Transplant Recipients With Functioning Transplants

Total CVD: 45.7%

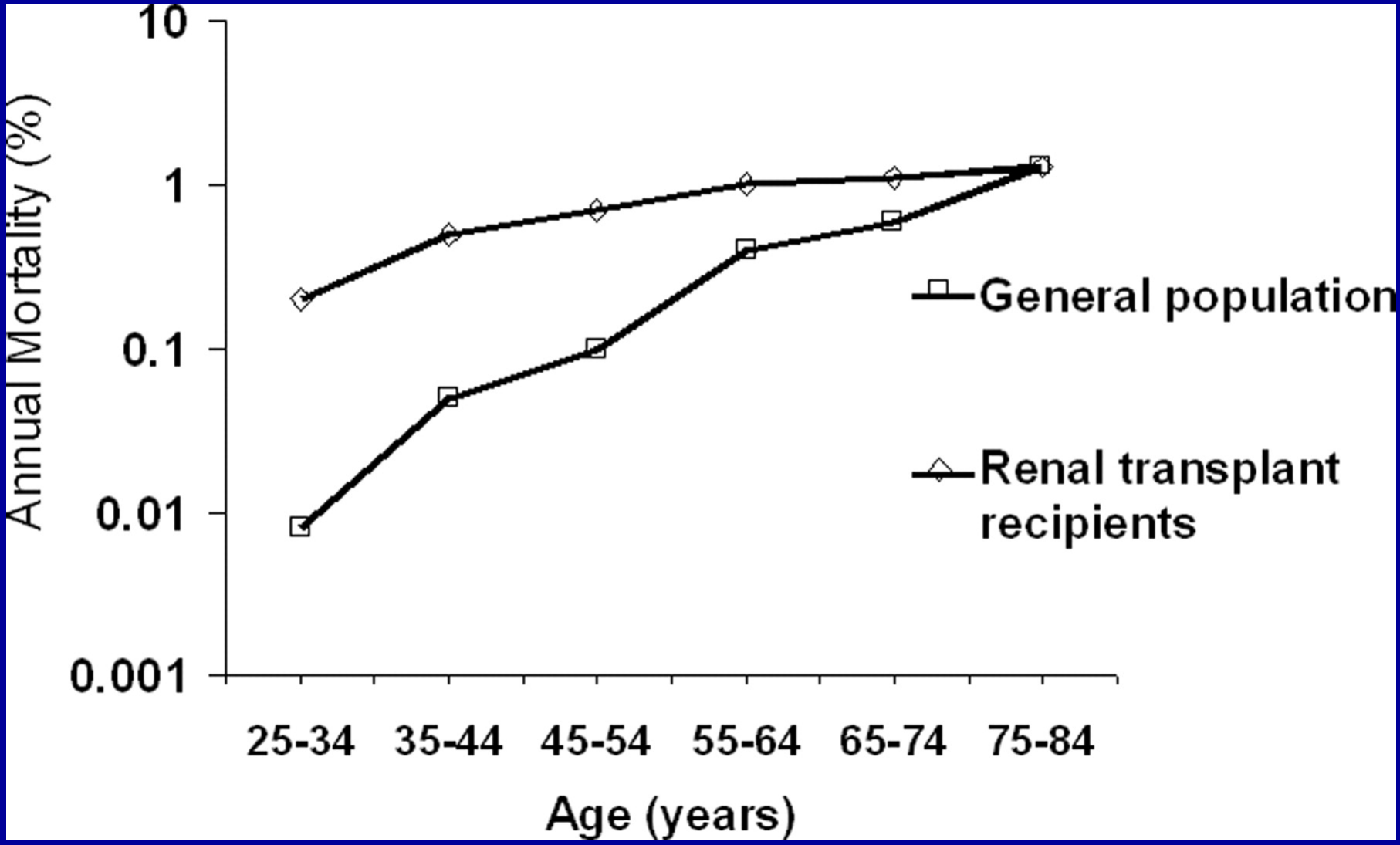


US Renal Data System: 2005 Annual Data Report.

Caveat :

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

Cardiovascular mortality in kidney transplant recipients



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

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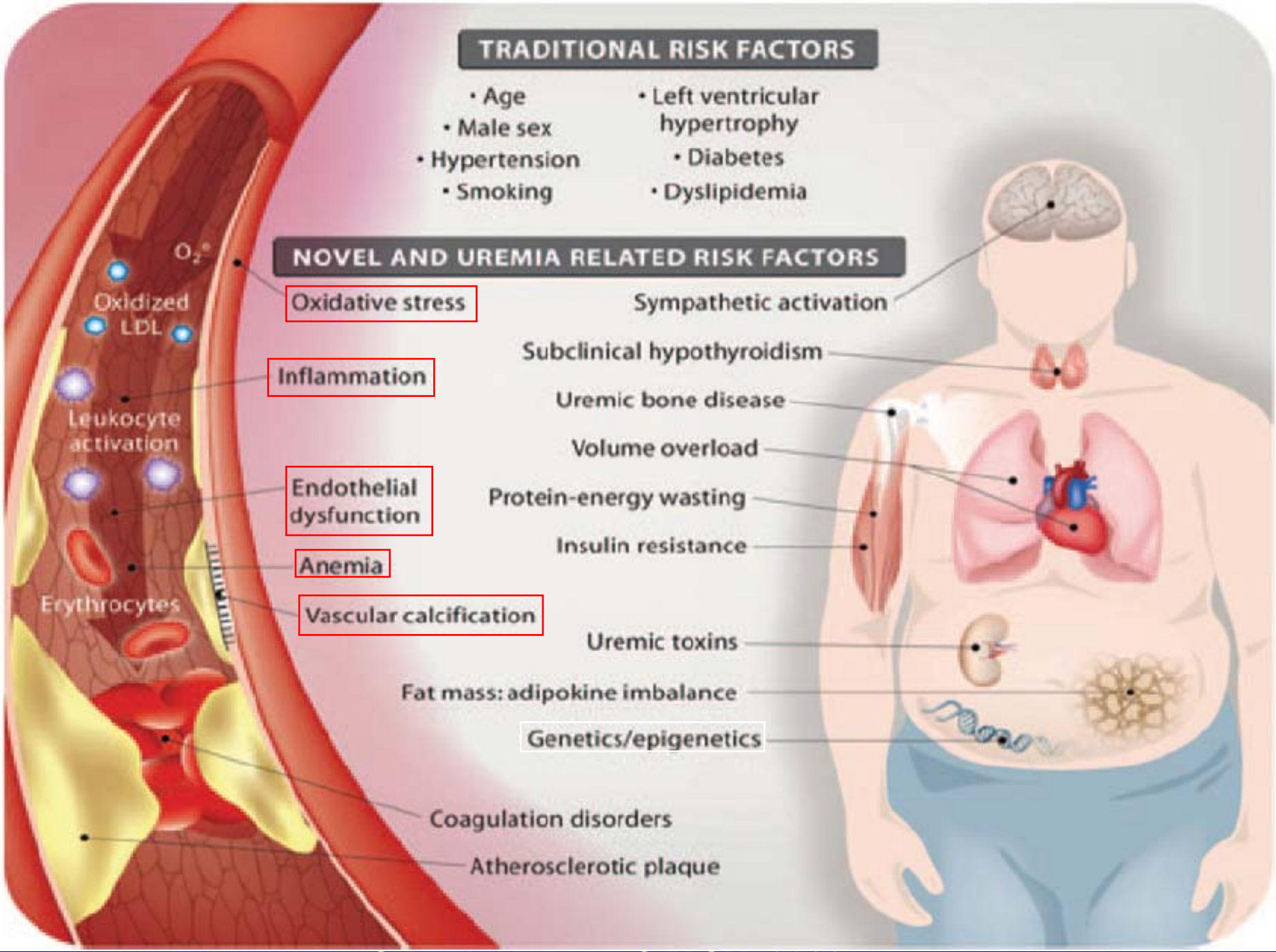
CJASN

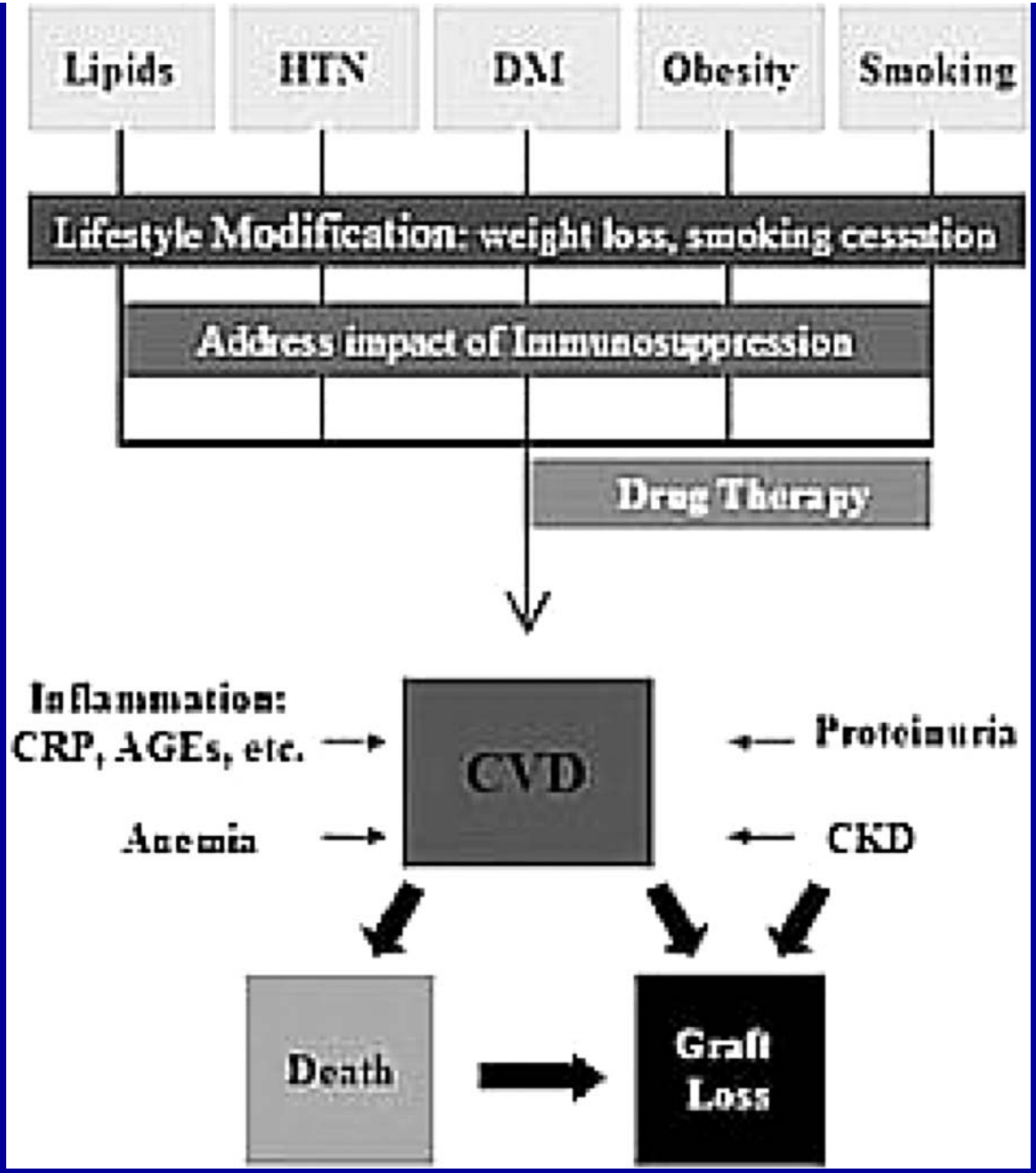


Stenvinkel et al CJASN, 2008

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/MICS



cardiovascular disease management after renal transplantation

Shirali, A. C. et al. Clin J Am Soc Nephrol 2008;3:491-504
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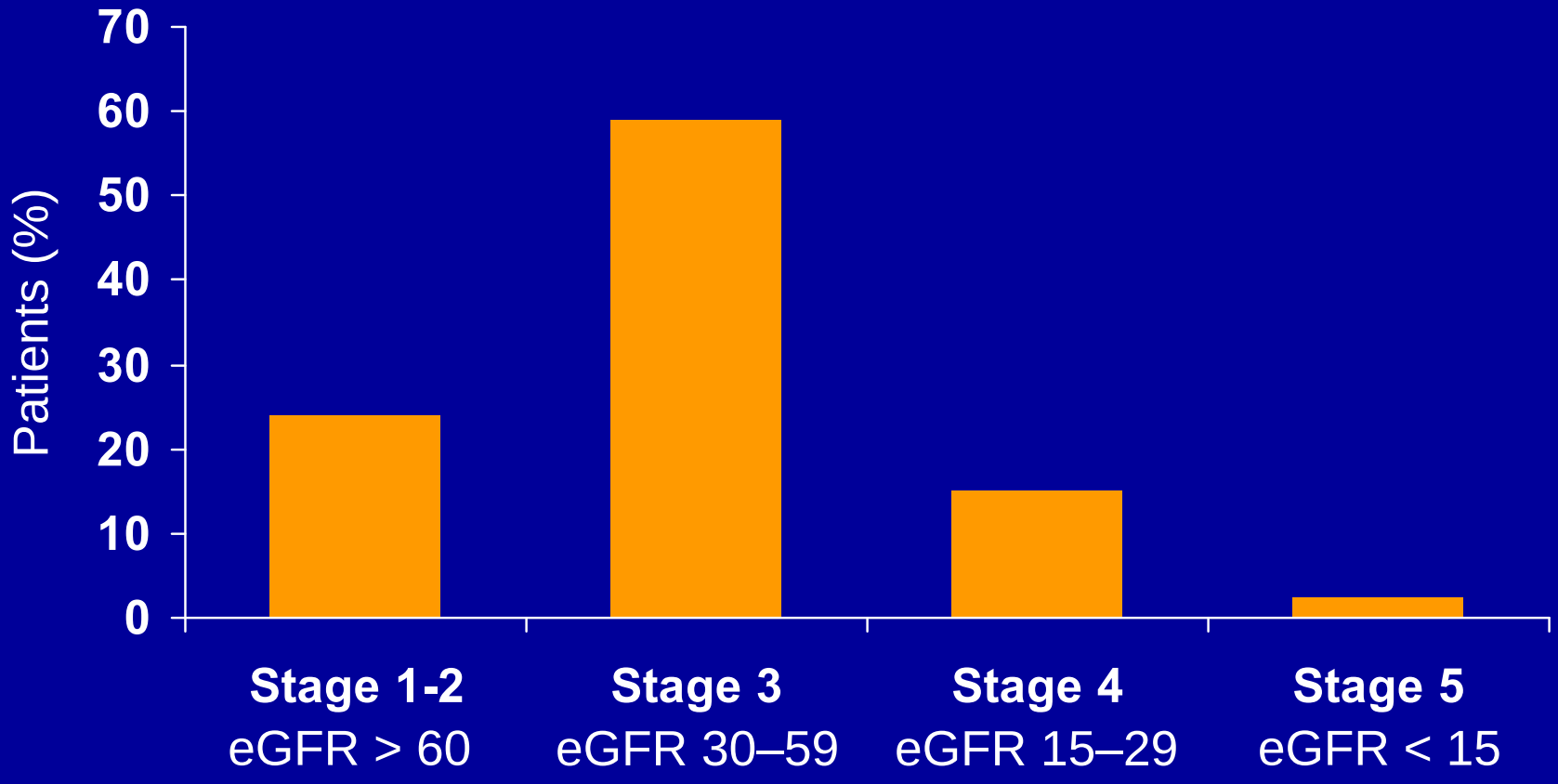
CKD IN KIDNEY TRANSPLANTED PATIENTS

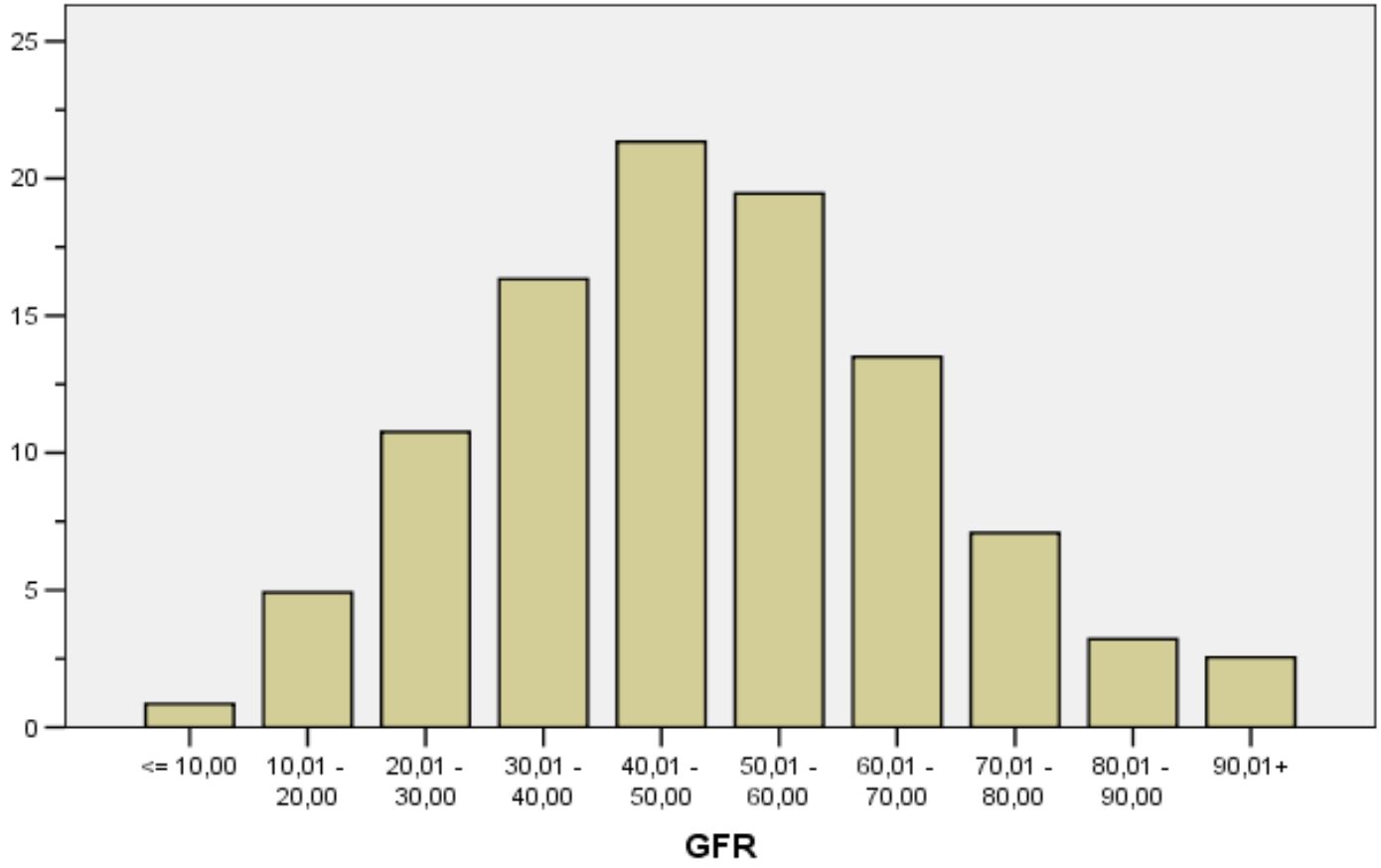
Majority of transplant recipients have kidney function equivalent to stage 3 CKD or worse (UK data)



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



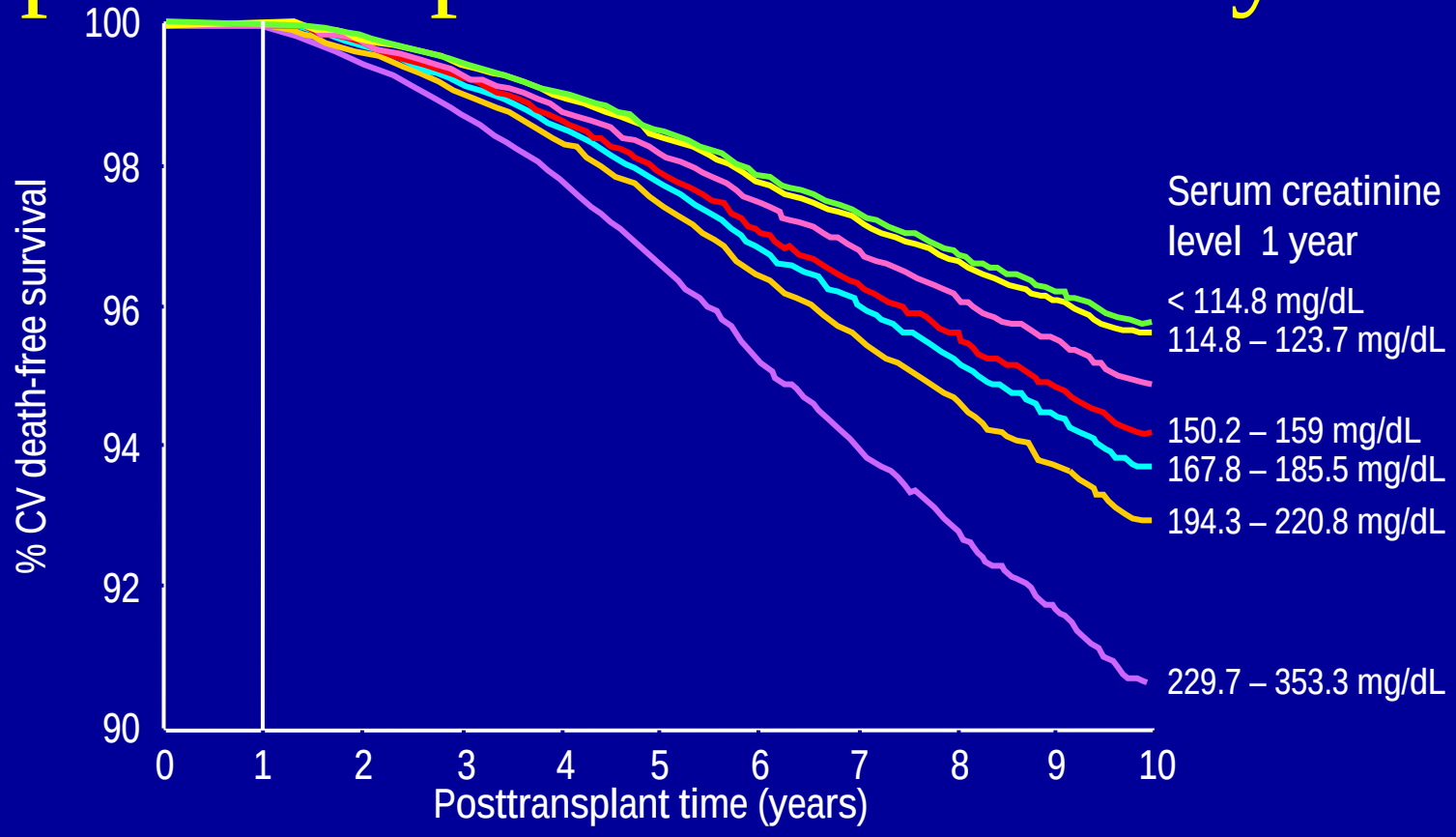
Std	V	IV	III	II	I
%	2	14	58	24	2
GFR	12.7 ±1.6	23.9 ±4.1	45.4 ±8.1	69.9 ±7.7	98.9 ±8.2

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

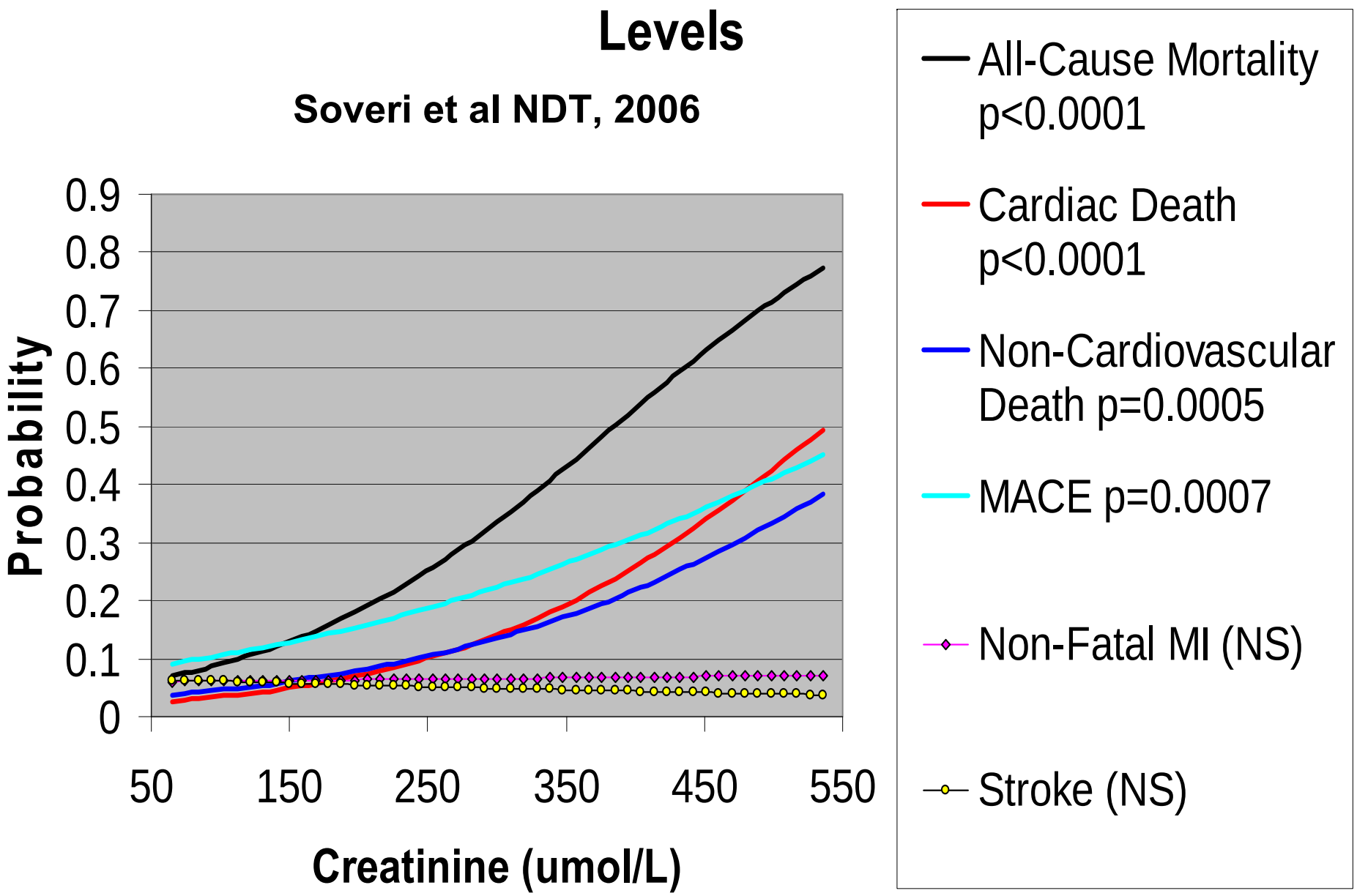
Effect of renal function on posttransplant CV mortality



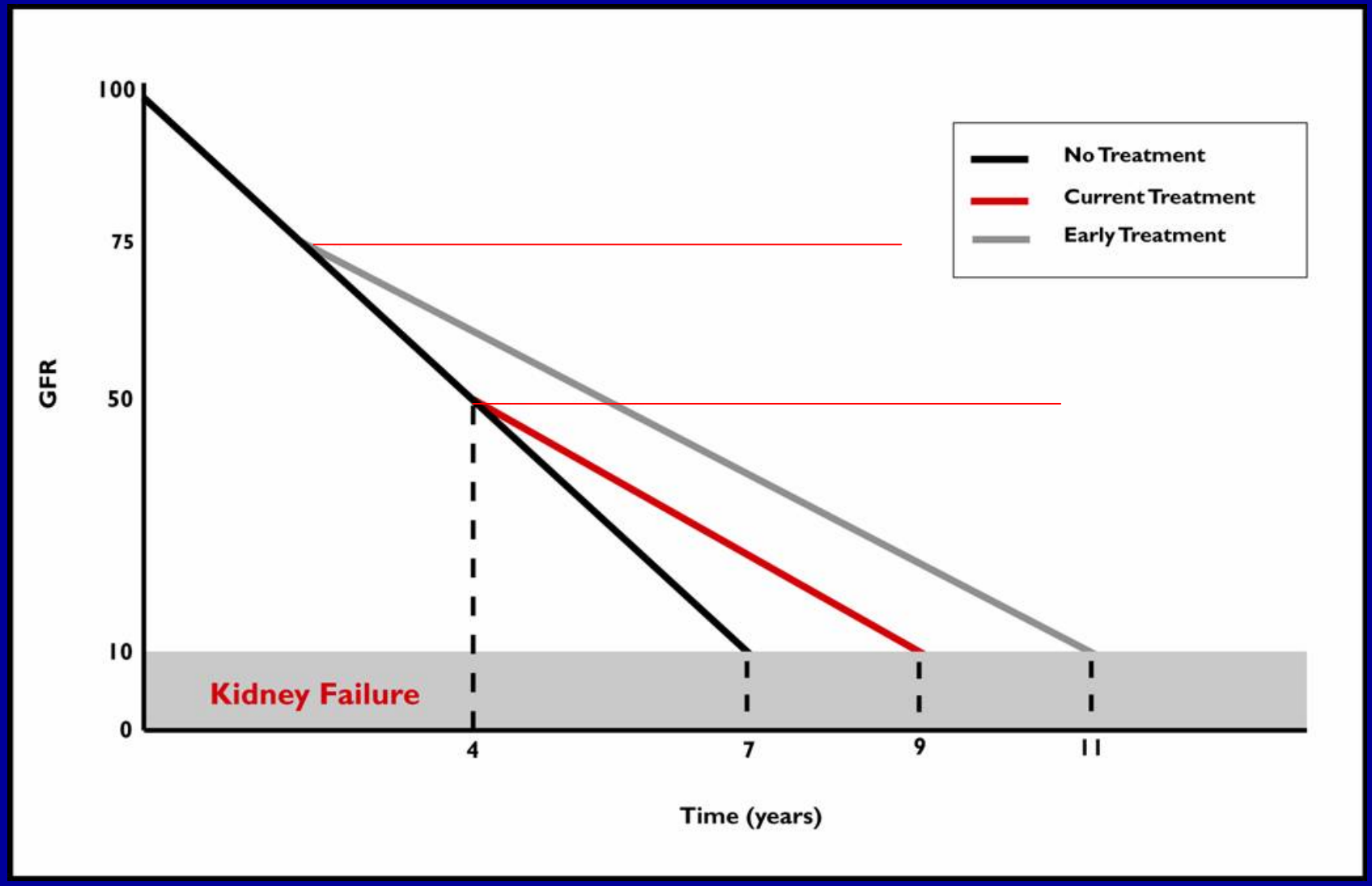
Retrospective study, n = 58 900 adult RTRs in USRDS registry, transplanted 06/88-06/98 with ≥ 1 year graft survival

Meier-Kriesche H. Transplantation 2003;75:1291

Endpoint Probabilities at Baseline Creatinine Levels

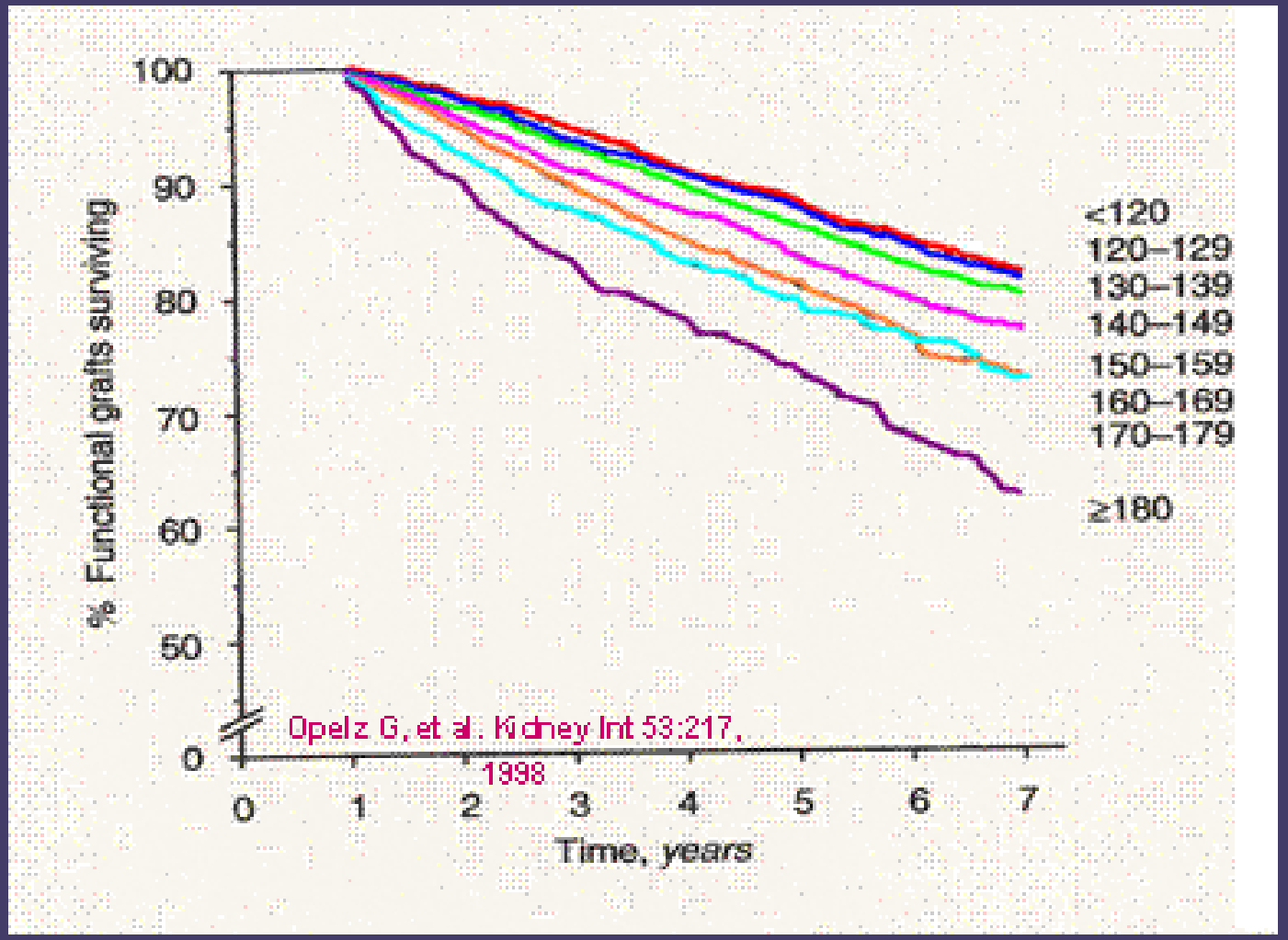


Progression of CKD



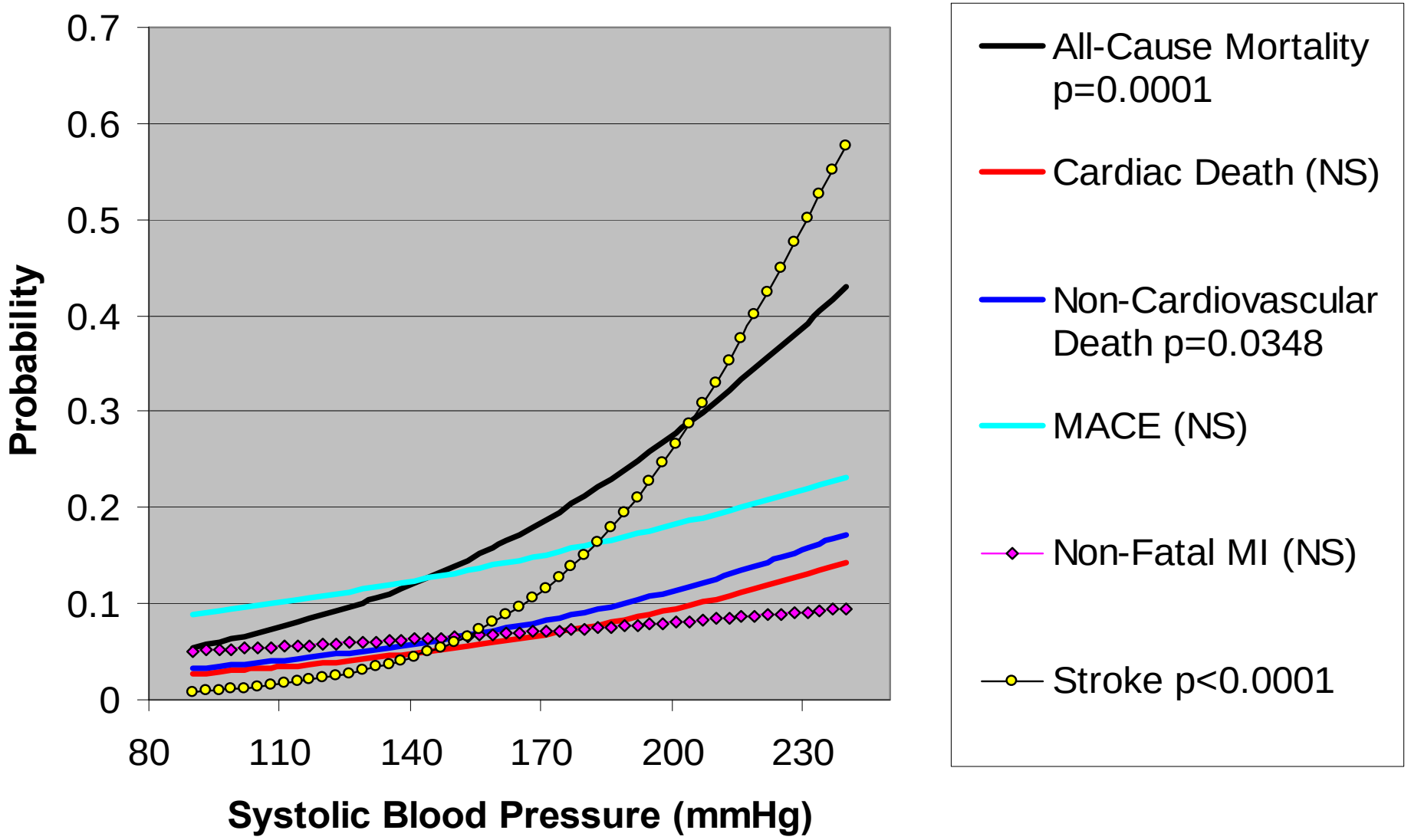
BLOOD PRESSURE

Blood Pressure One Year after Kidney Transplantation and Graft Outcome



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

Endpoint Probabilities at Baseline Systolic Blood Pressure



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

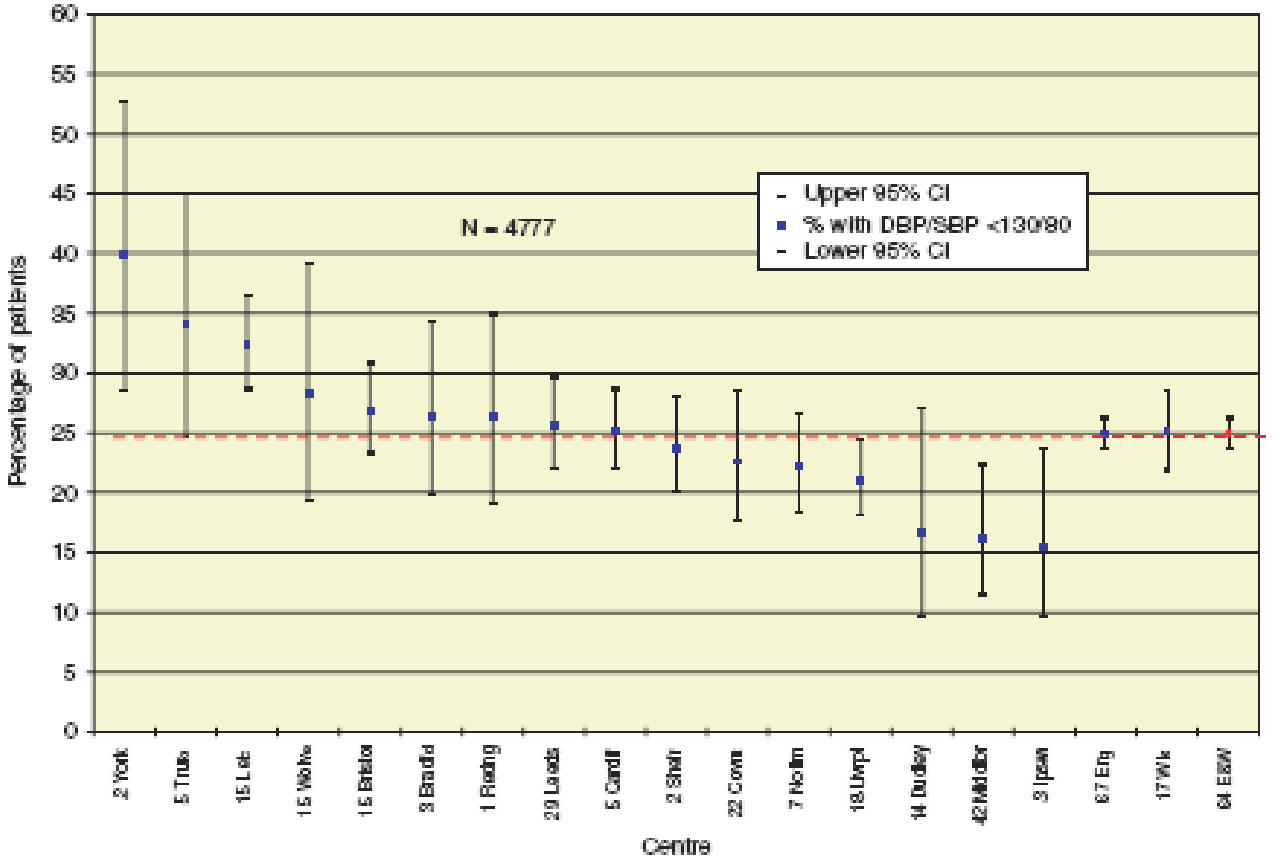
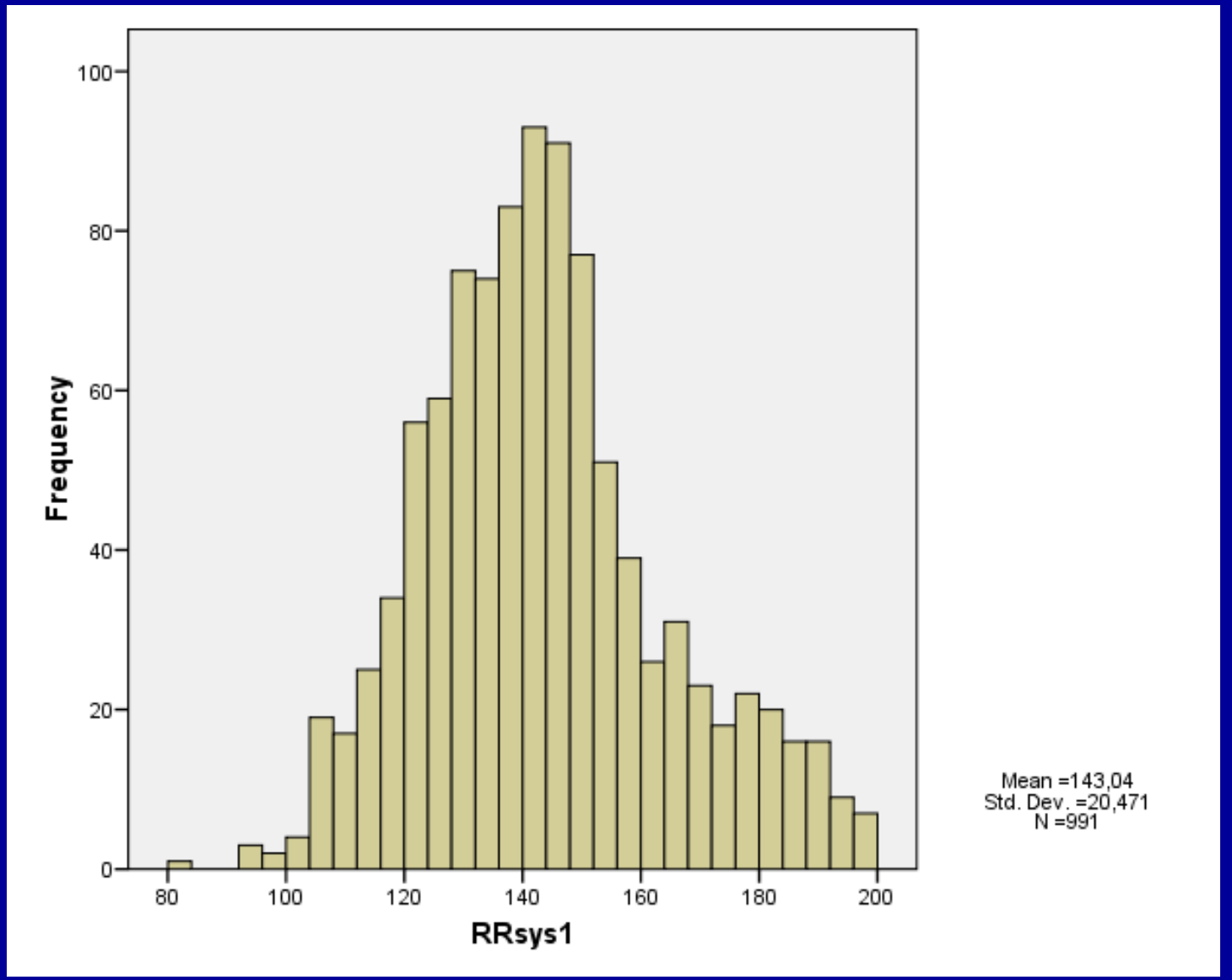
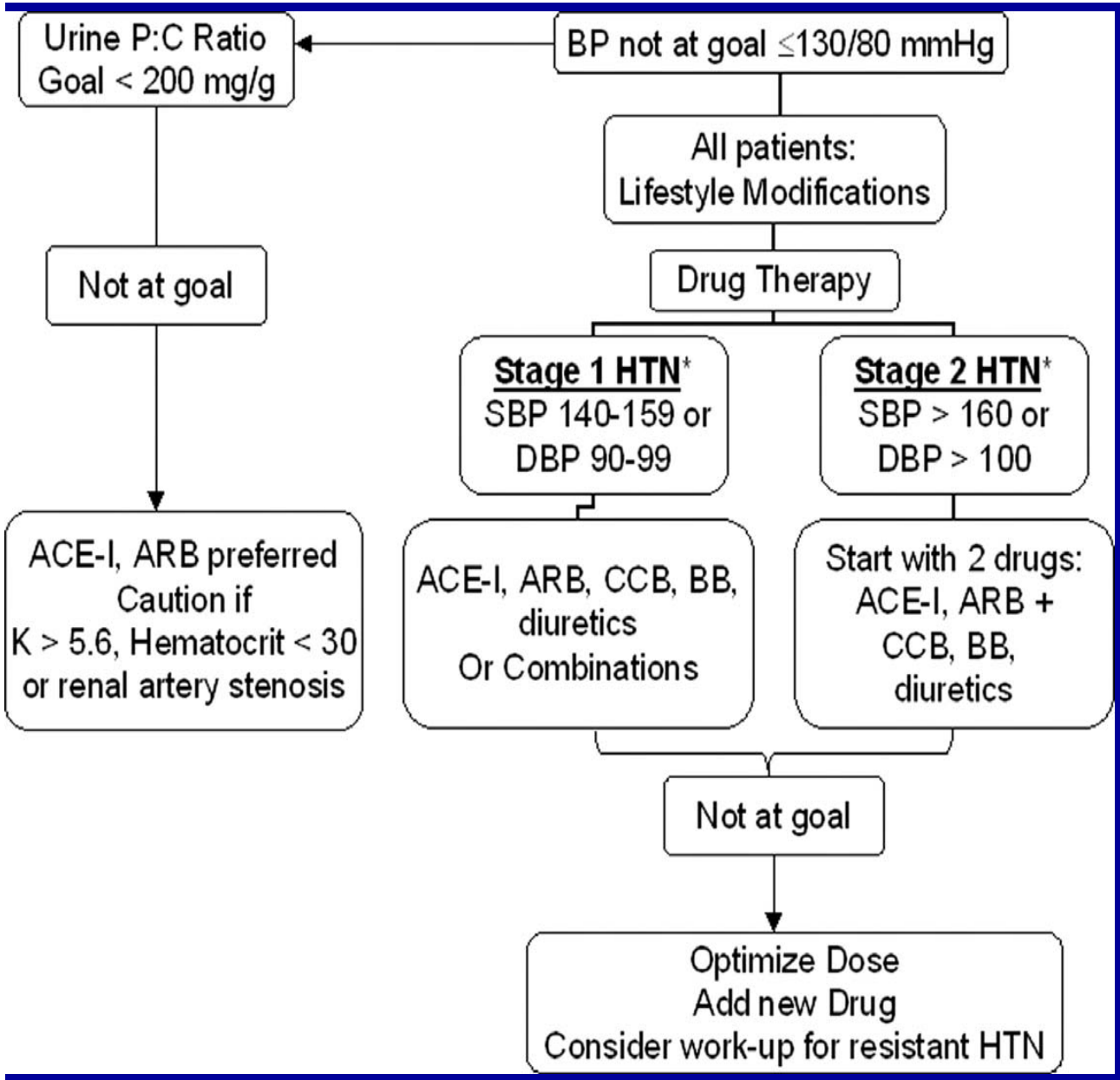


Fig. 11.11. Percentage of patients with renal transplants in different renal units who achieve the RA standards for BP.

Nephrol Dial Transplant (2007) 22 [Suppl 7]: vii138–vii154
doi:10.1093/ndt/gfm334

BP control in Budapest





BP management after the first posttransplant year

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

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DIABETES

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

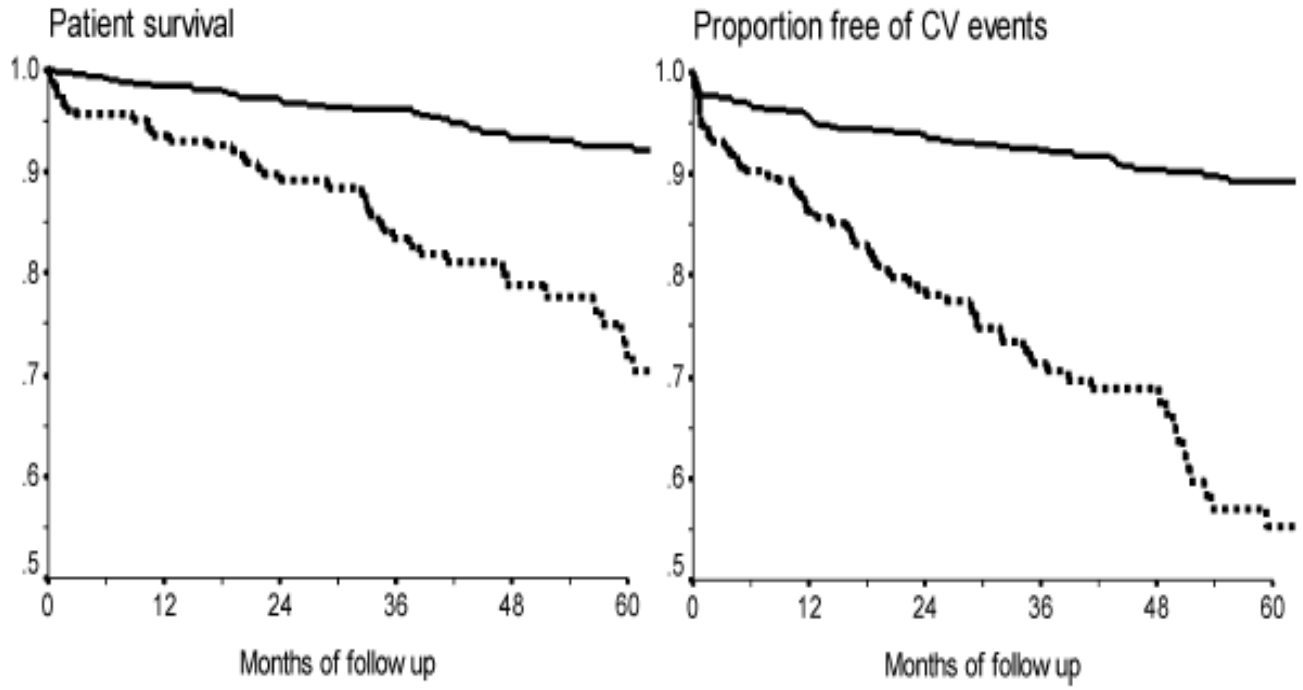
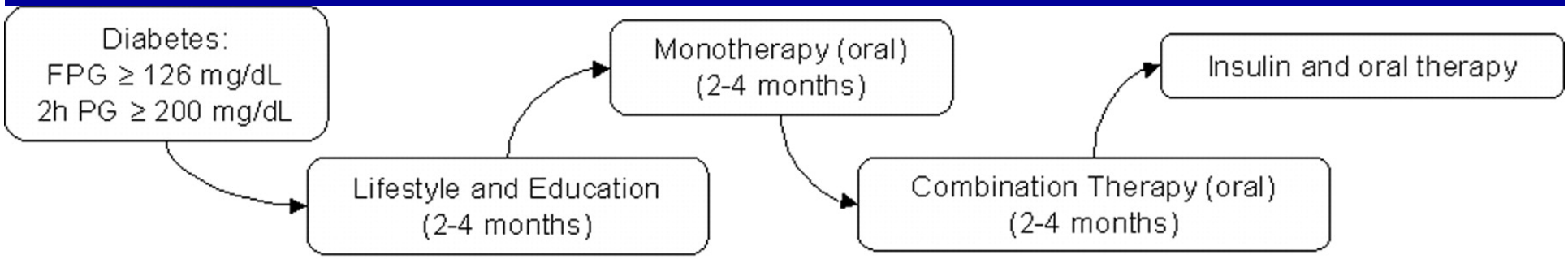


Figure 1: Left: Kaplan–Meier plots of patient survival after transplantation in recipients without DM (—) and those with DM (.....) (log-rank, $p < 0.0001$). Right: Kaplan–Meier plots of the incidence of fatal and nonfatal posttransplant CV events in recipients without DM (—) and those with DM (.....)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

American Journal of Transplantation 2008; 8: 593–599
Blackwell Munksgaard

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

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

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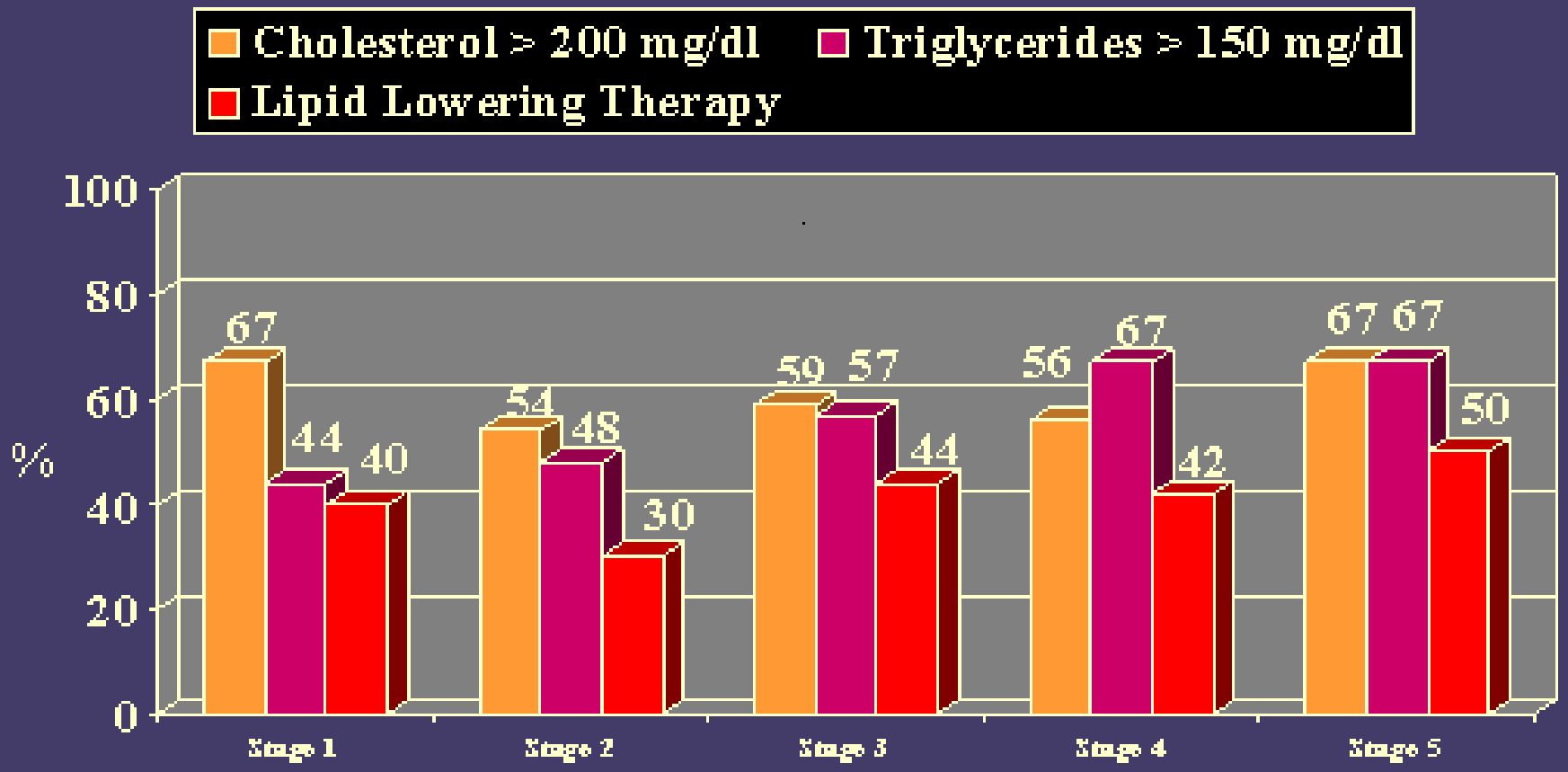
DYSLIPIDAEMIA

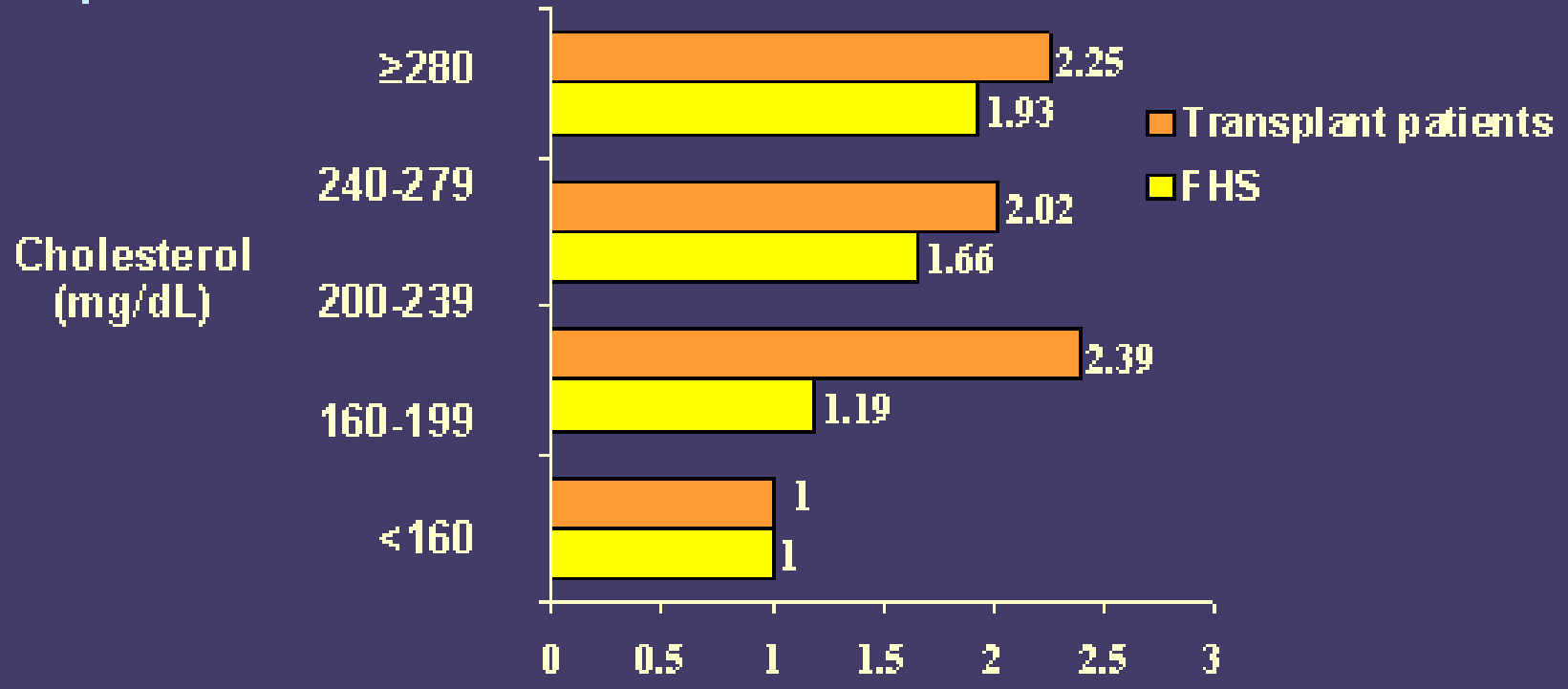
Prevalence of Hyperlipidemia in Renal Transplant Patients Based on CKD Stage

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



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

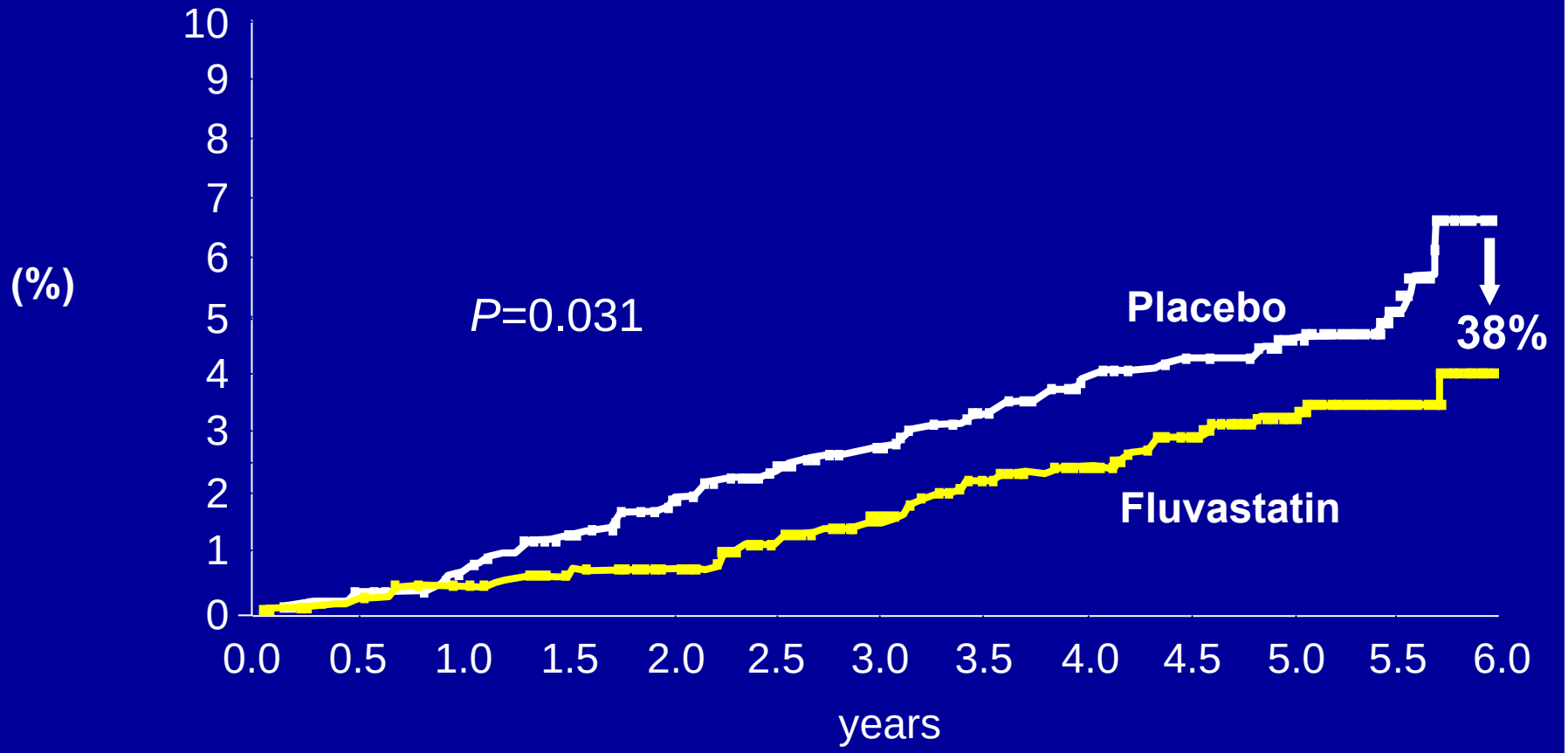


Kasiske BL et al. *J Am Soc Nephrol.* 2000;65:1735-1743.
Wilson PWF et al. *Circulation.* 1998;97:1837-1847.

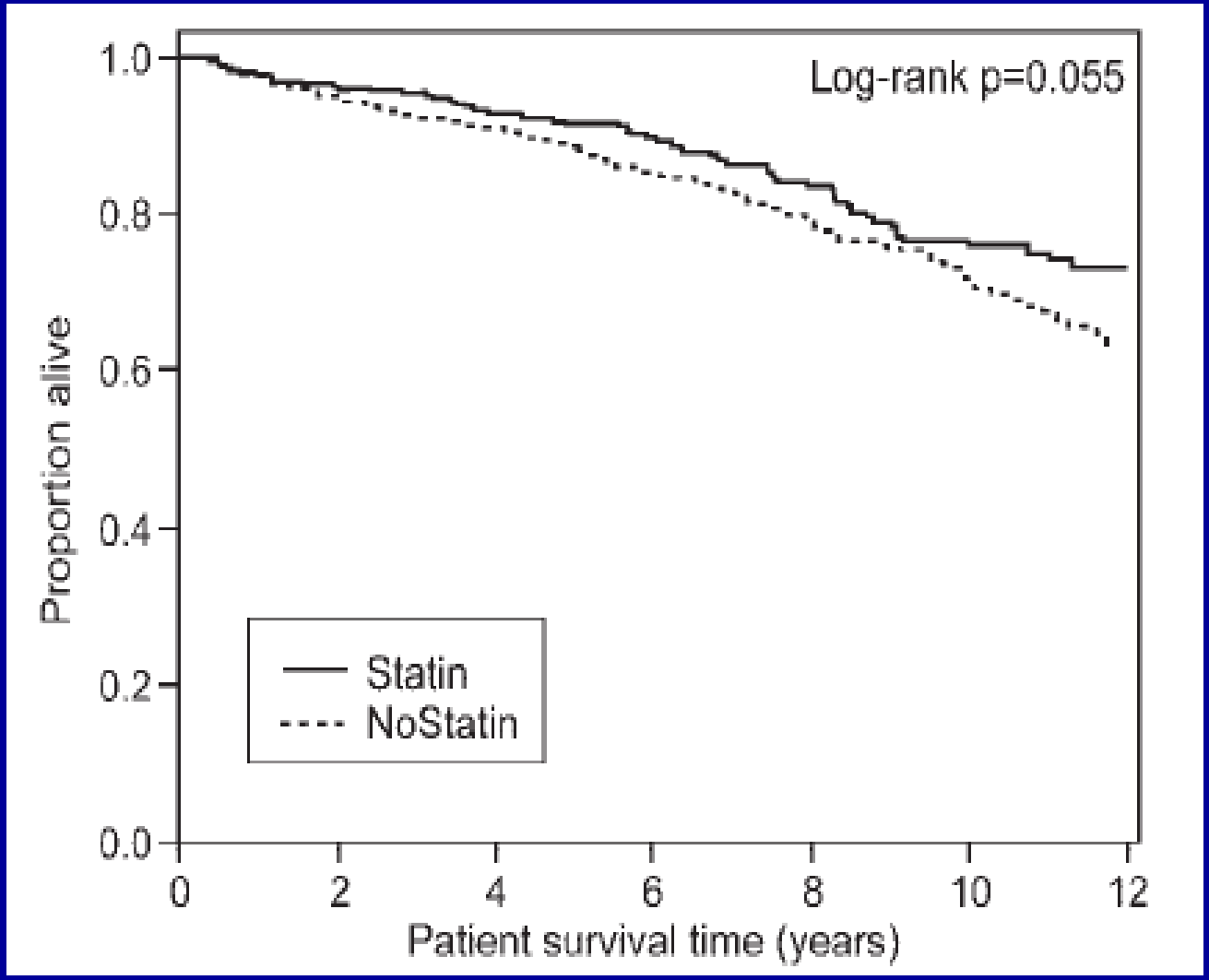
ALERT: Assessment of Lescol in Renal Transplantation

- 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

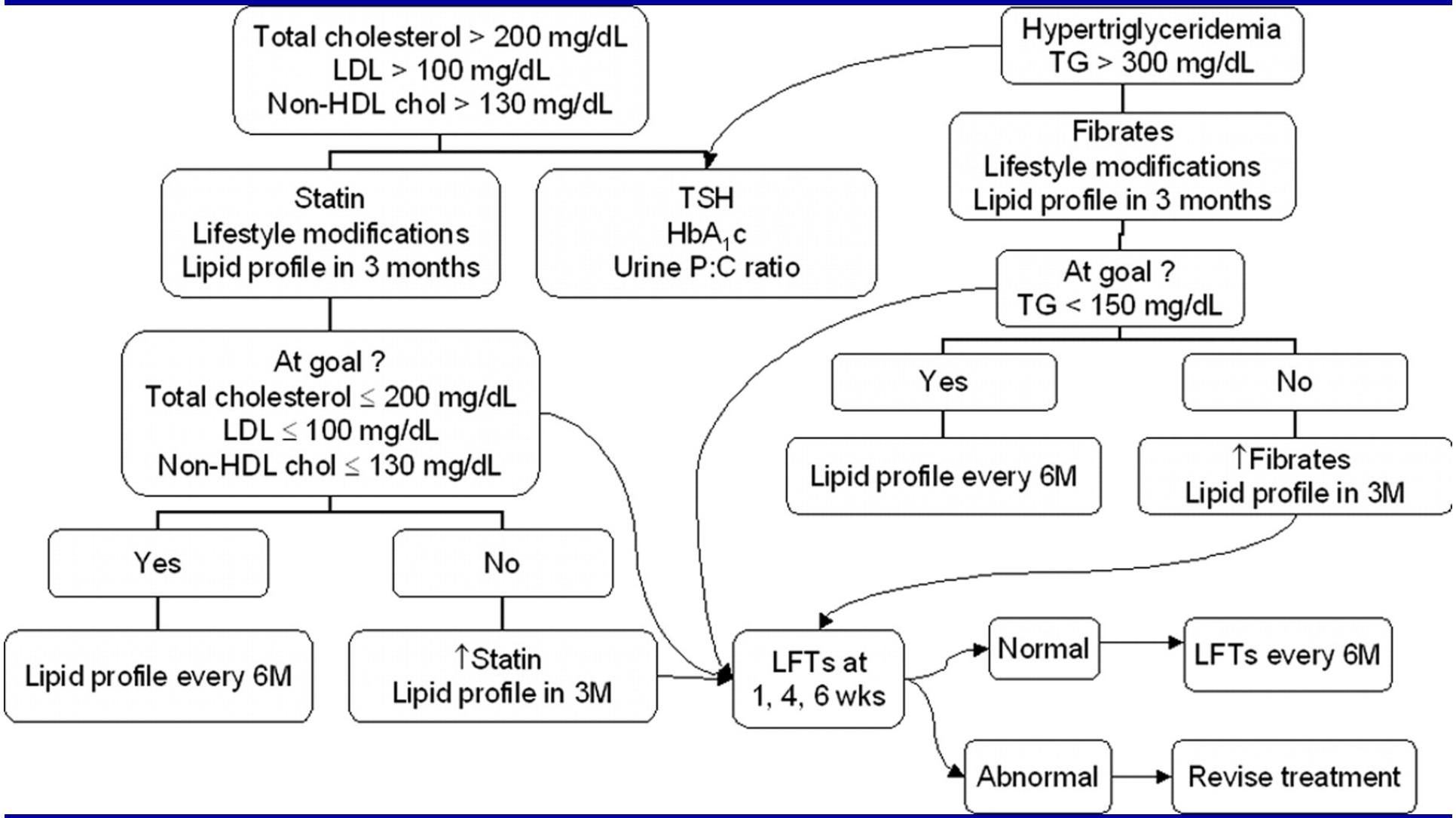
Cardiac mortality



Patient Survival Statin vs Non Statin Treated Wiesbauer et al JASN, 2008



Dyslipidemia management after the first posttransplant year



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

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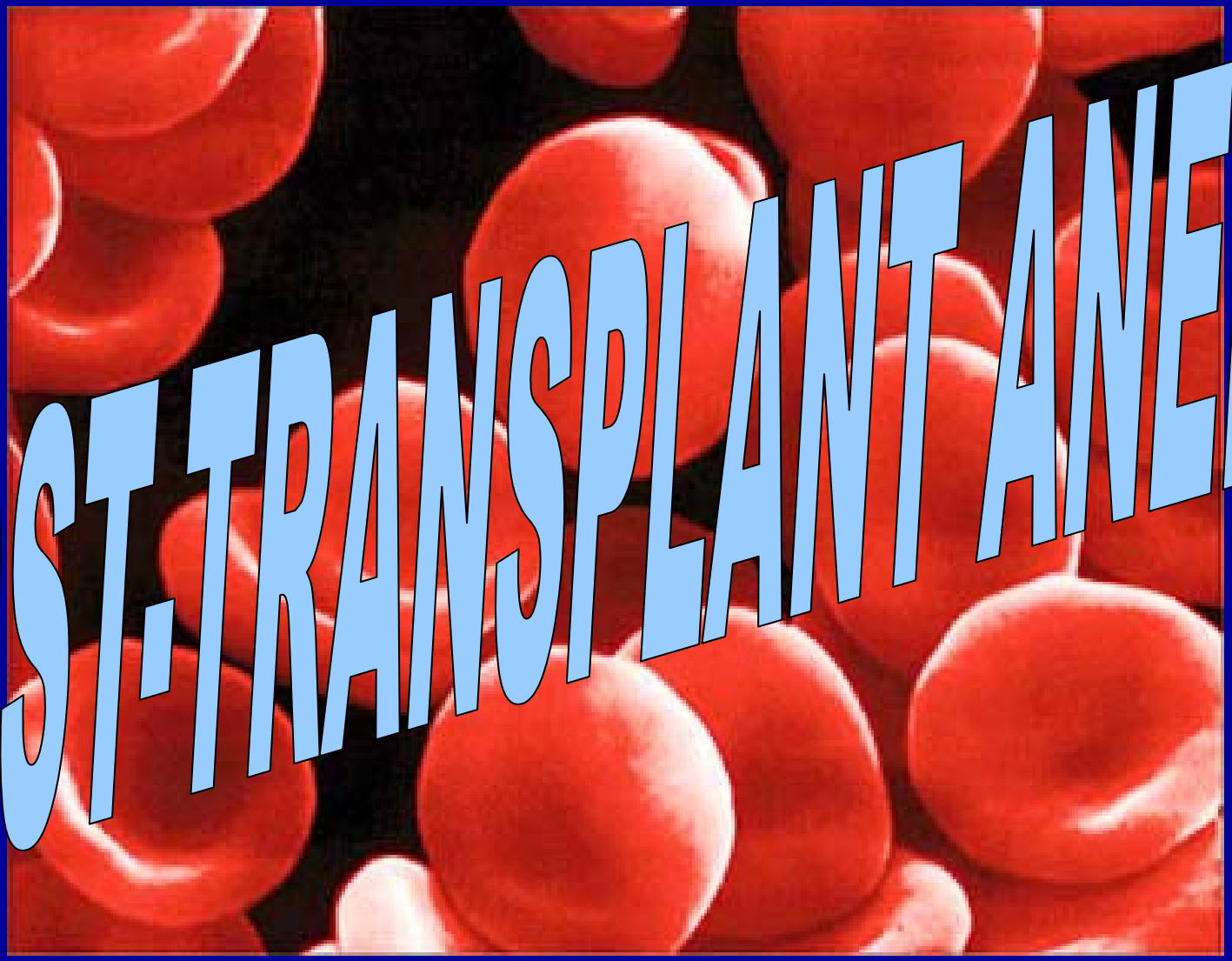
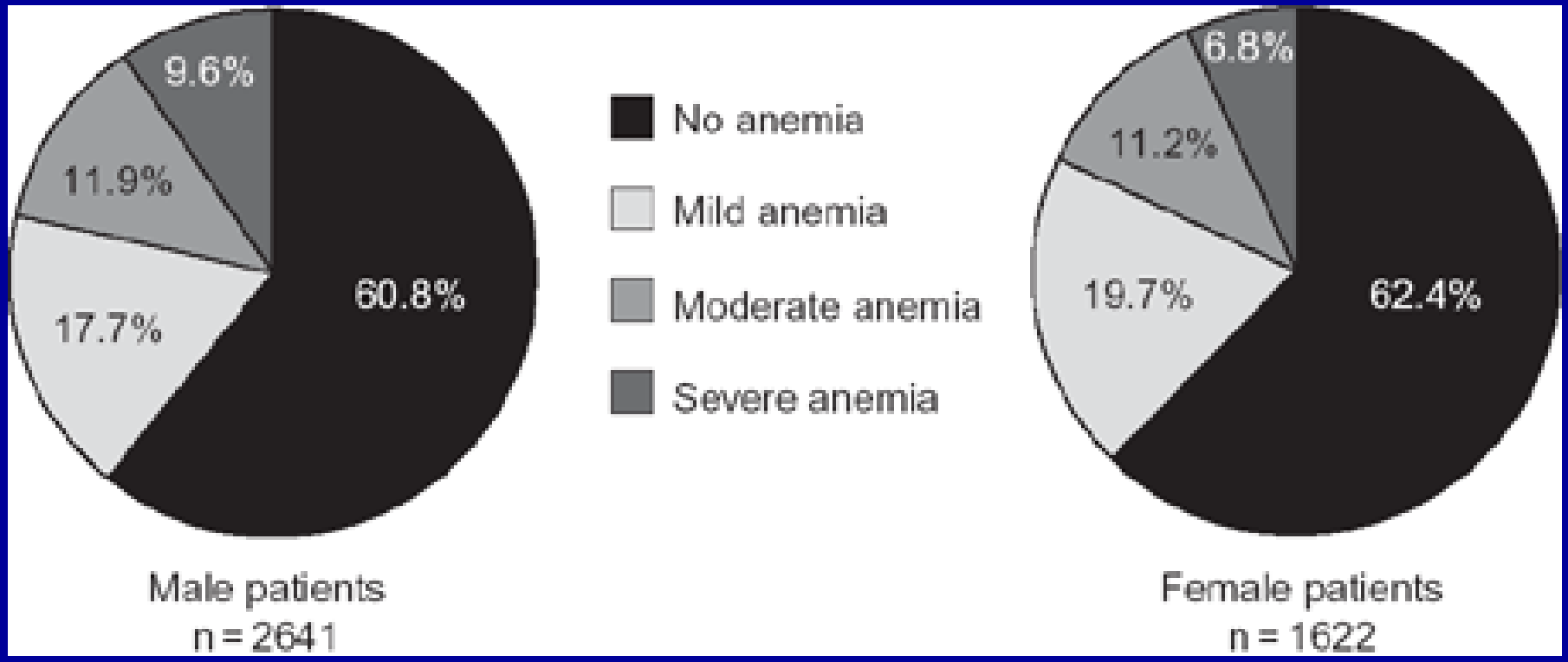
POST-TRANSPLANT ANEMIA



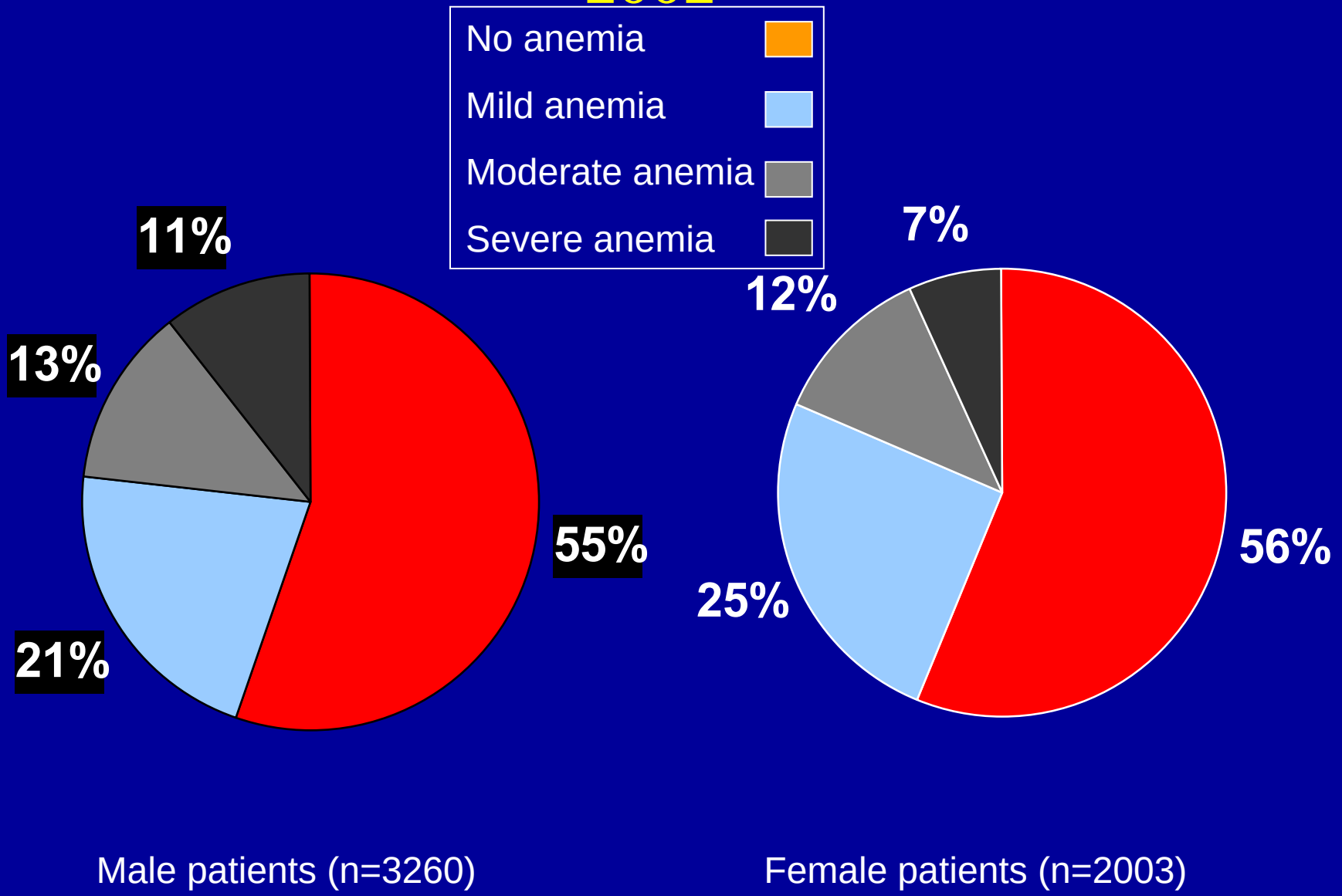
Prevalence and Management of Anemia in Renal Transplant Recipients: A European Survey

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 Sarmento[i] and Flavio Vincenti[j]

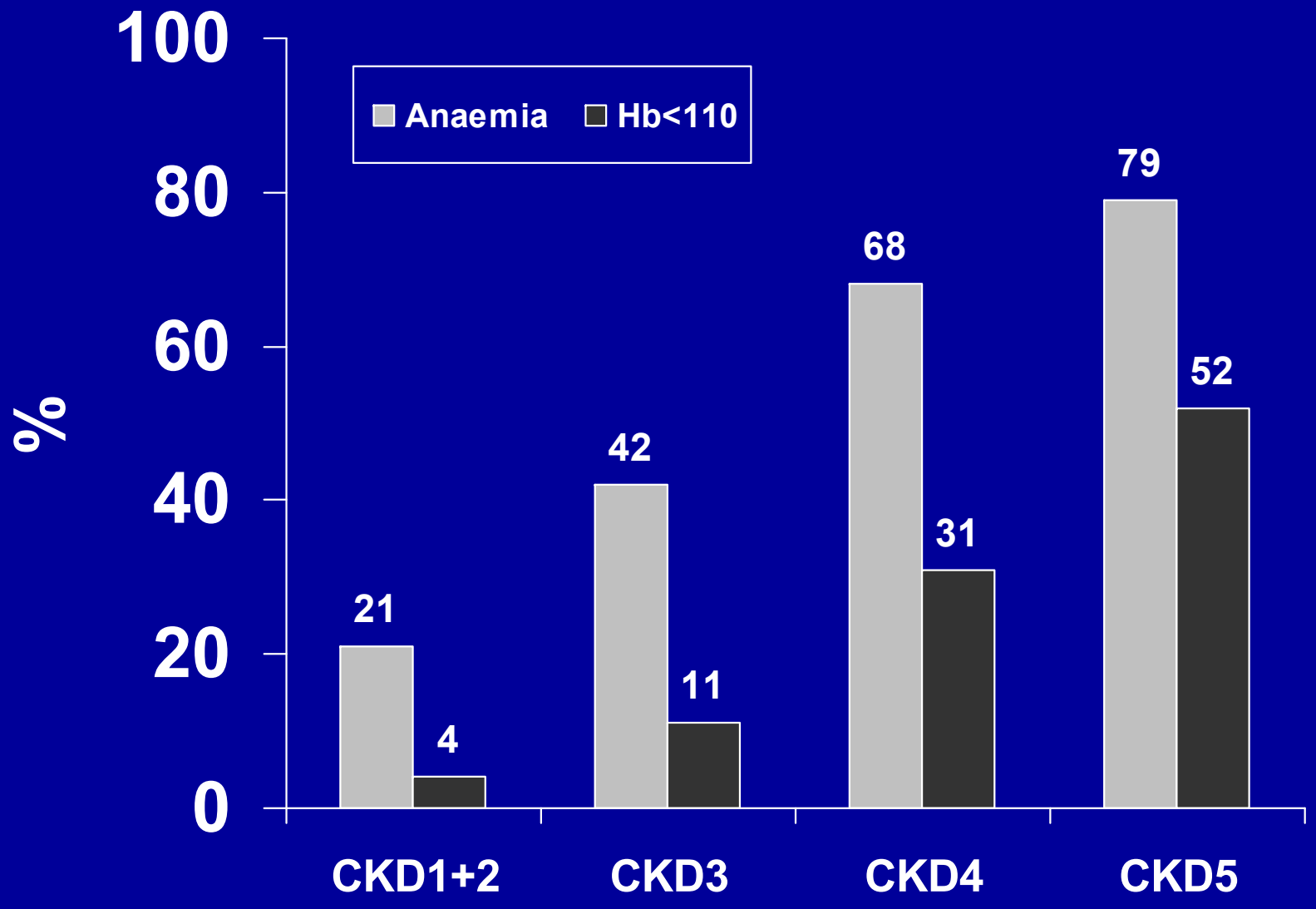


American Journal of Transplantation 2003; 3: 835–845
Blackwell Munksgaard

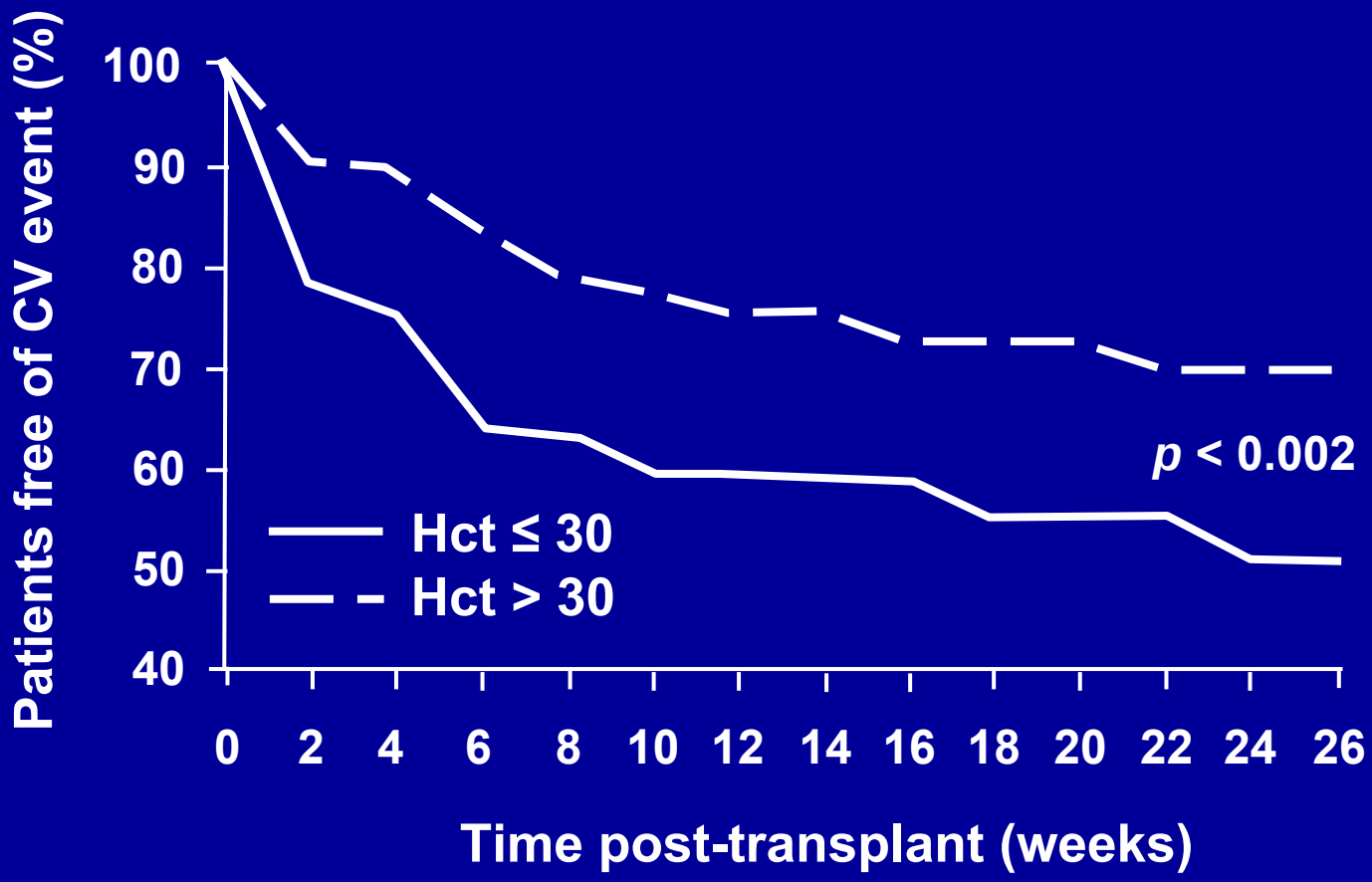
Prevalence of anemia by gender – Transqol-HU 2002



Anemia and CKD stages



Cardiovascular events are more common in anaemic patients

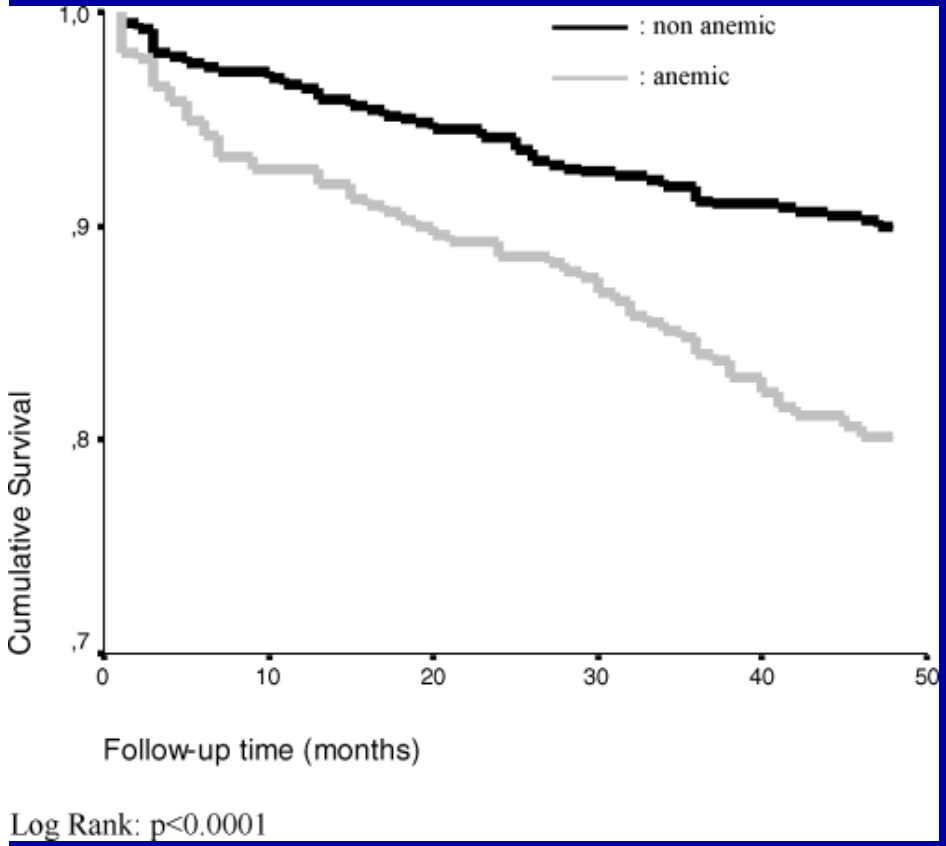


404 type 1 diabetic ESRD who underwent either cadaveric kidney transplantation alone or simultaneous pancreas-kidney transplantation

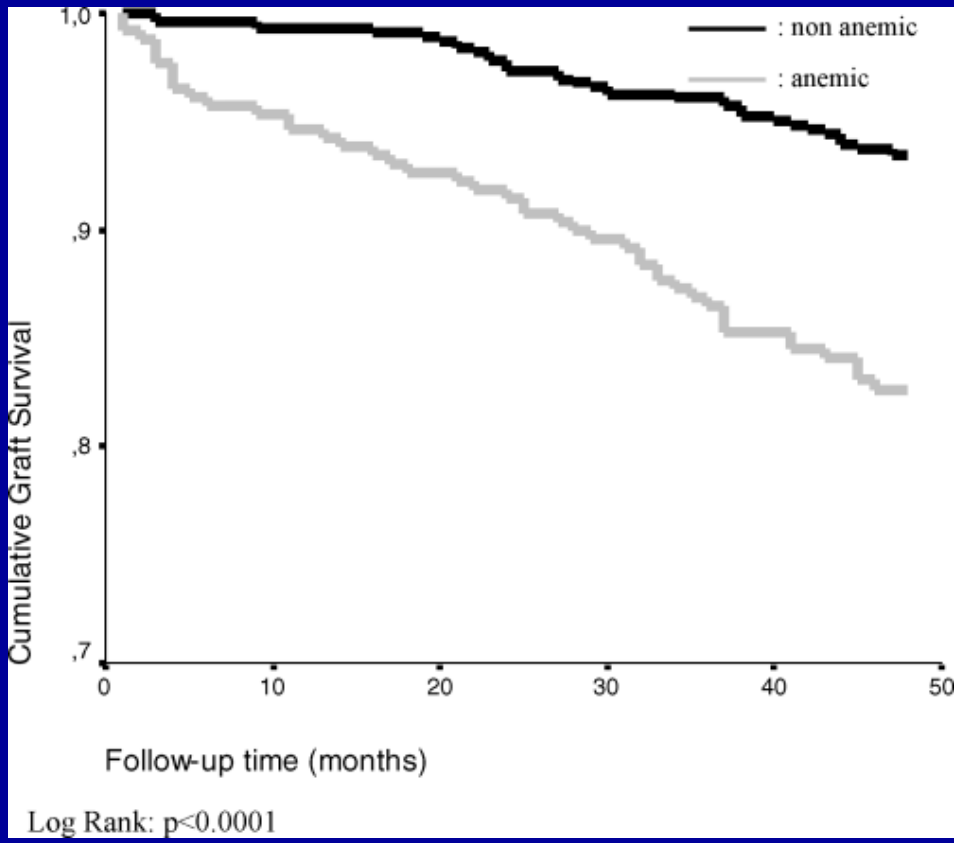
Djamali A et al. *Transplantation* 2003; 76:816-20.

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. Remport[f], M. Novak[a,g] and I. Mucsi[a,b,e,*]



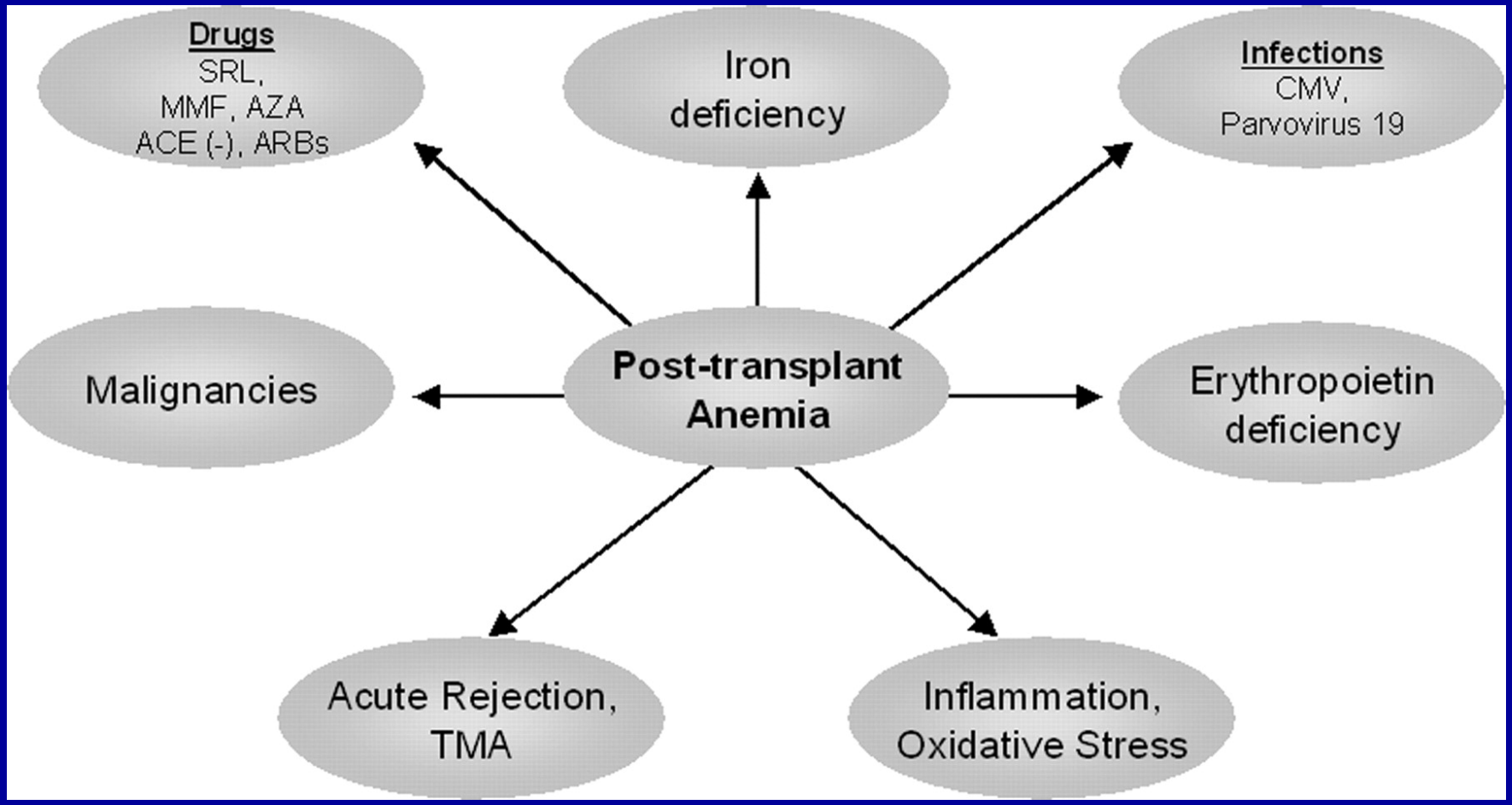
Log Rank: p<0.0001



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

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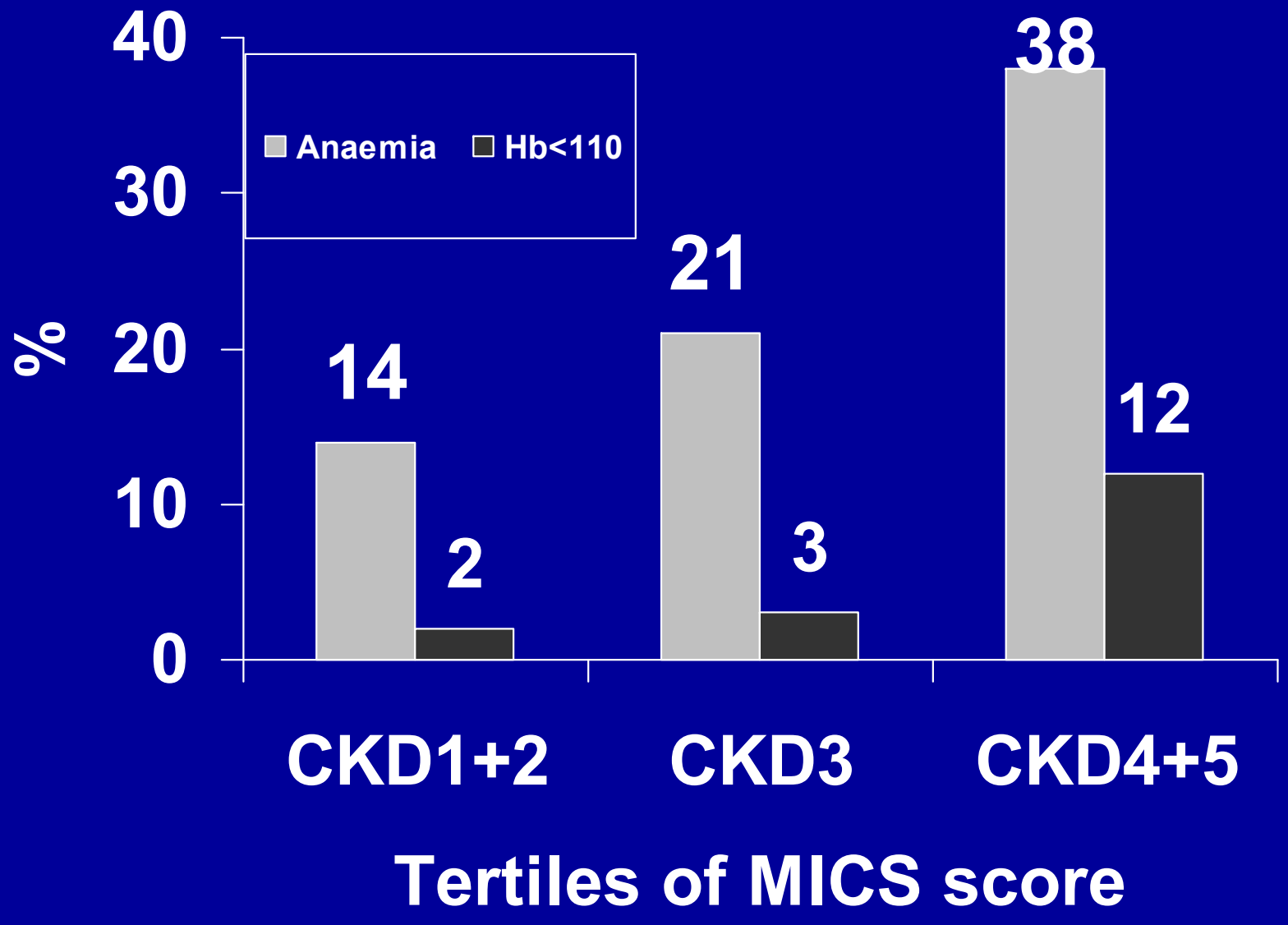
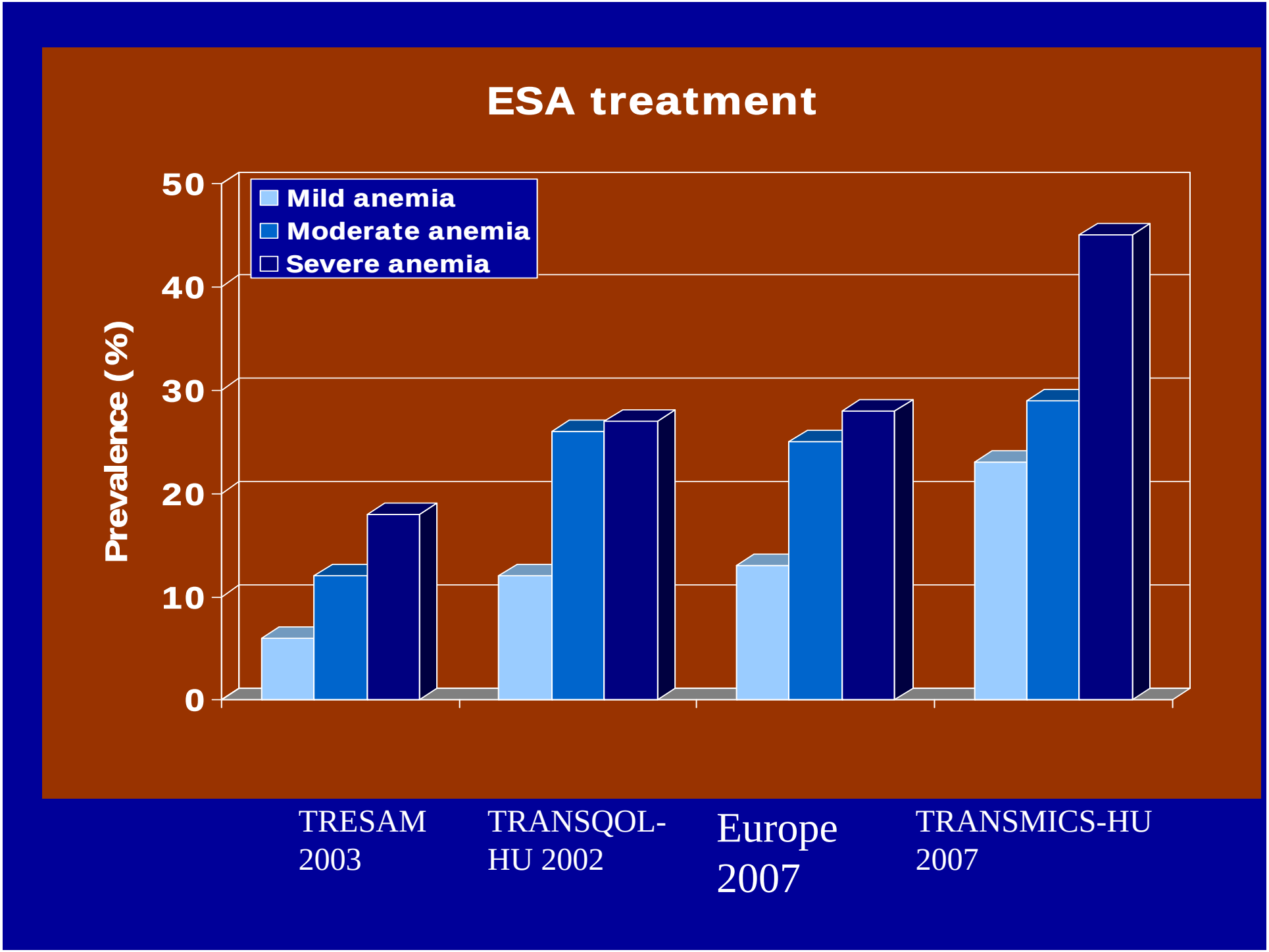
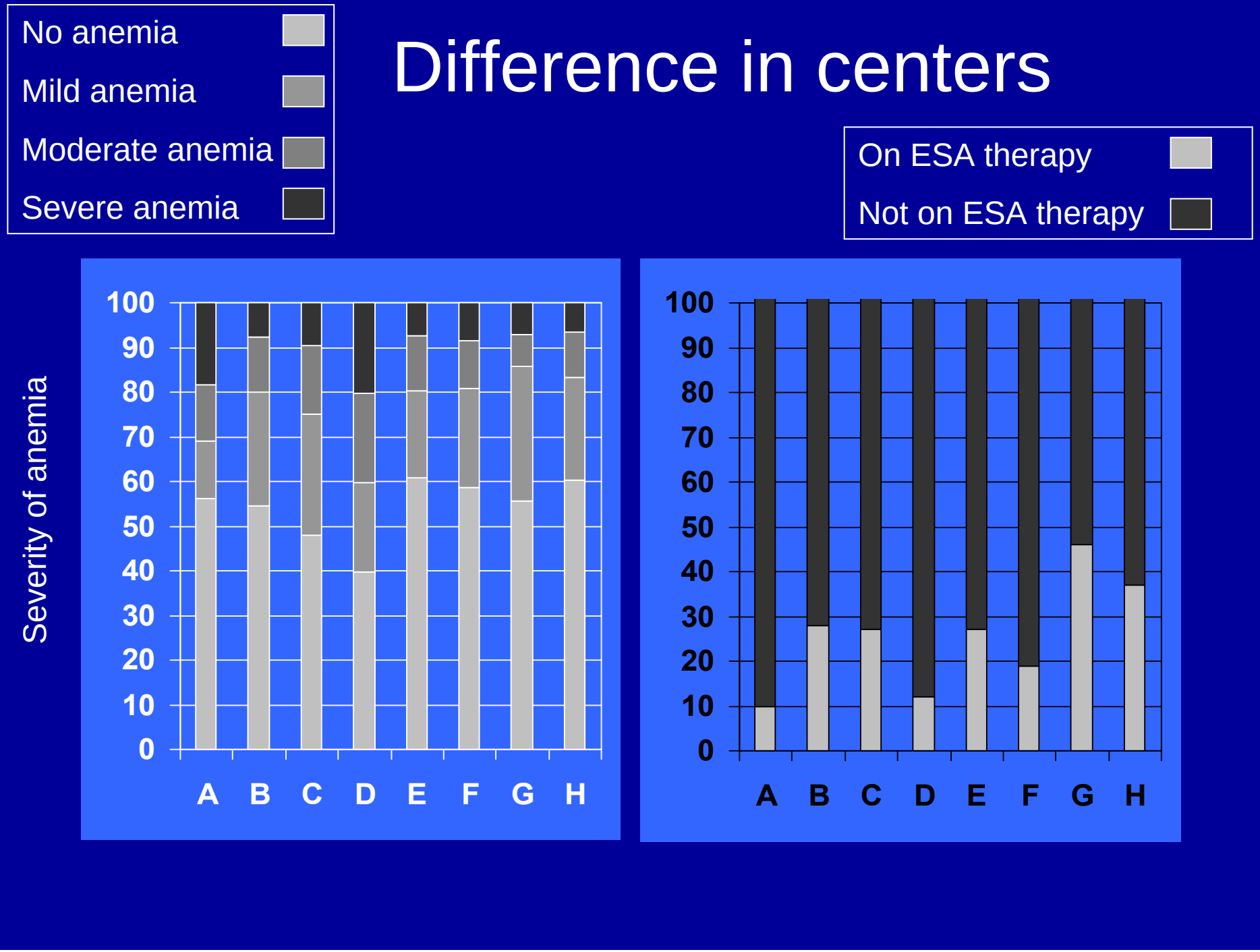
Anemia and MICS



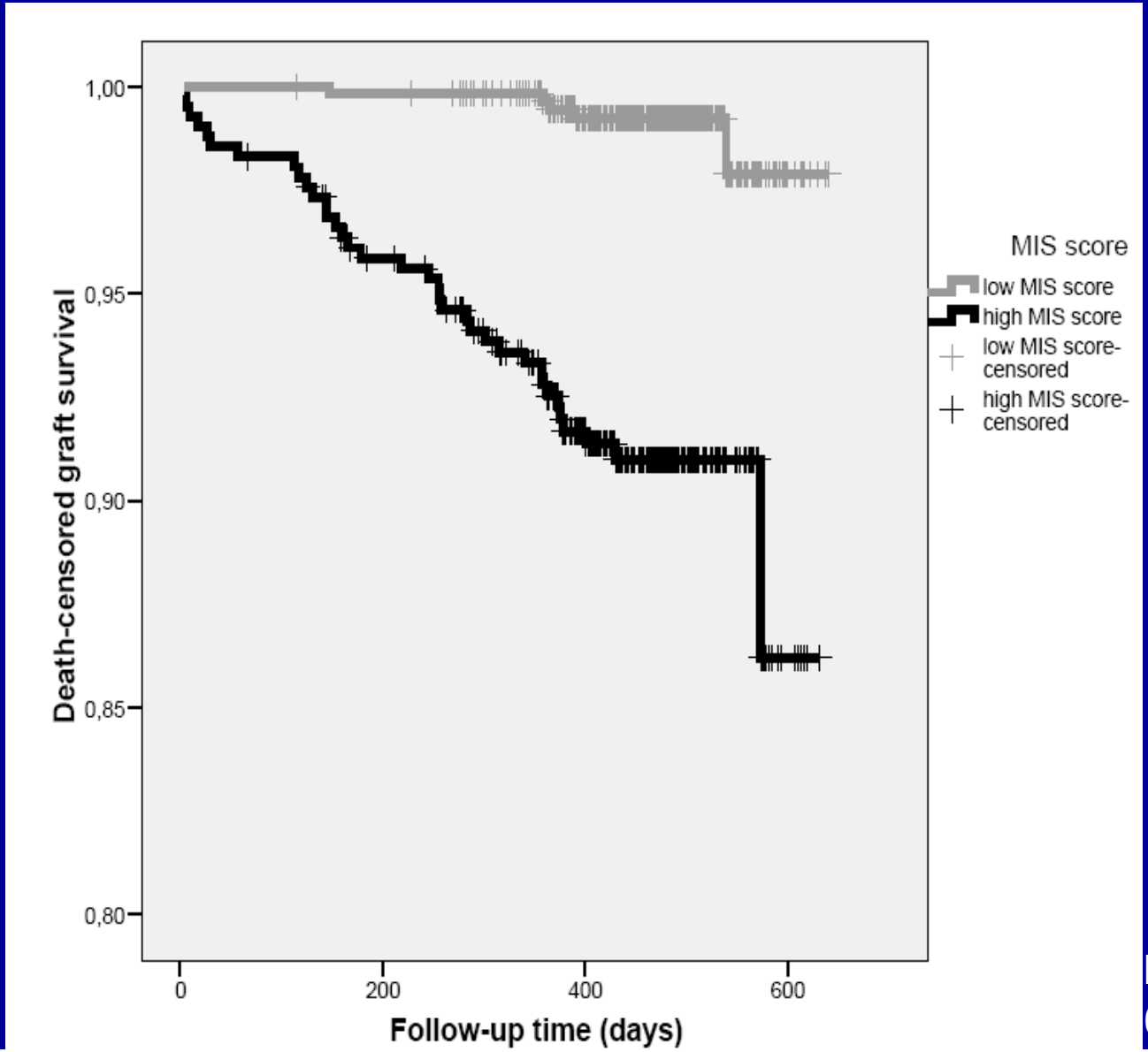

ESA treatment
Mild anemia
Moderate anemia
Severe anemia
Prevalence (%)
50
40
30
20
10
0
TRESAM 2003
TRANSQOL-HU 2002
Europe 2007
TRANSMICS-HU 2007

Difference in centers



MIS and return to dialysis

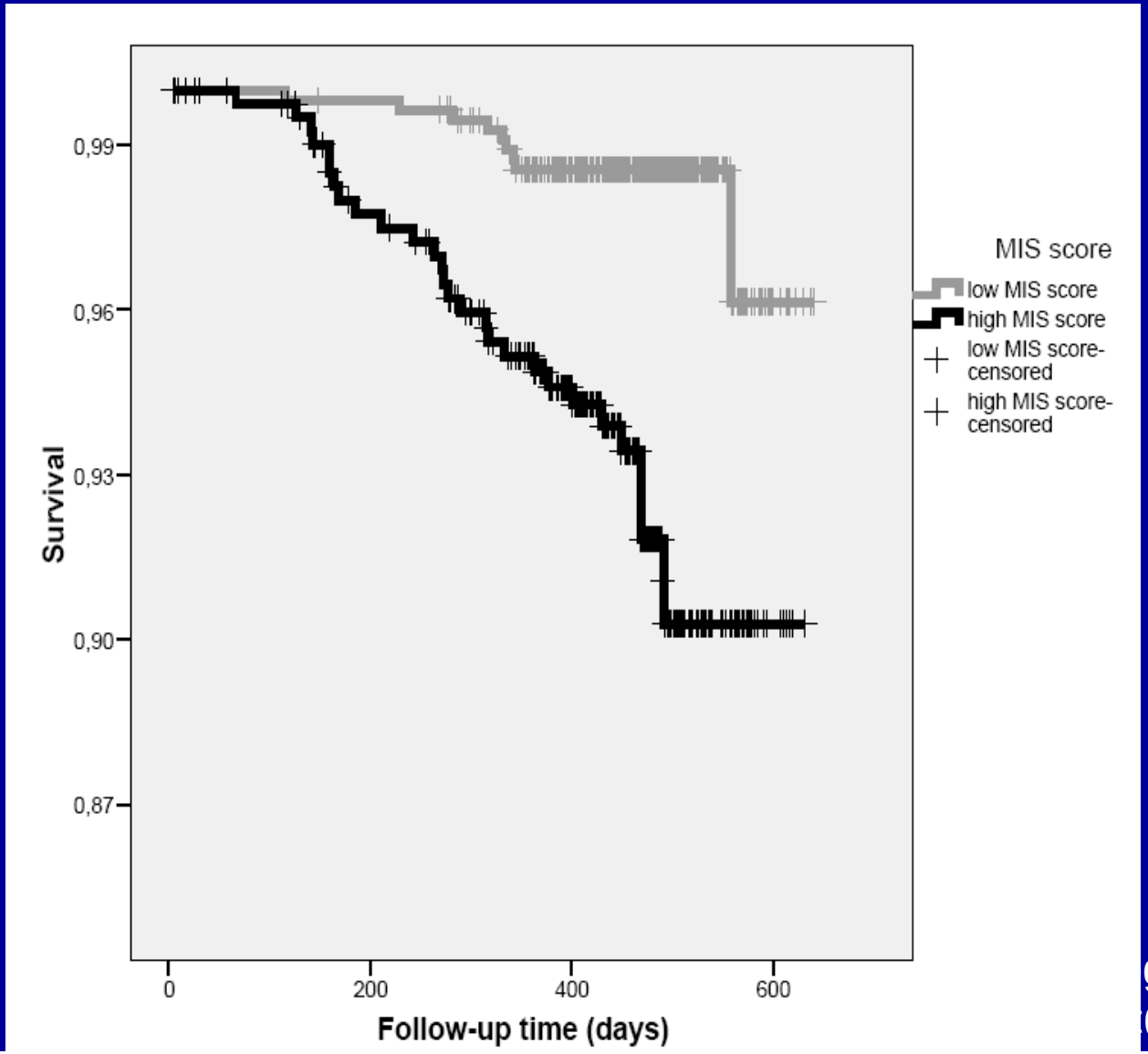
(Kaplan-Meier curve)



Rank: 001

MIS and survival

(Kaplan-Meier curve)



g Rank:
0.001

MULTIDISCIPLINARY CARE

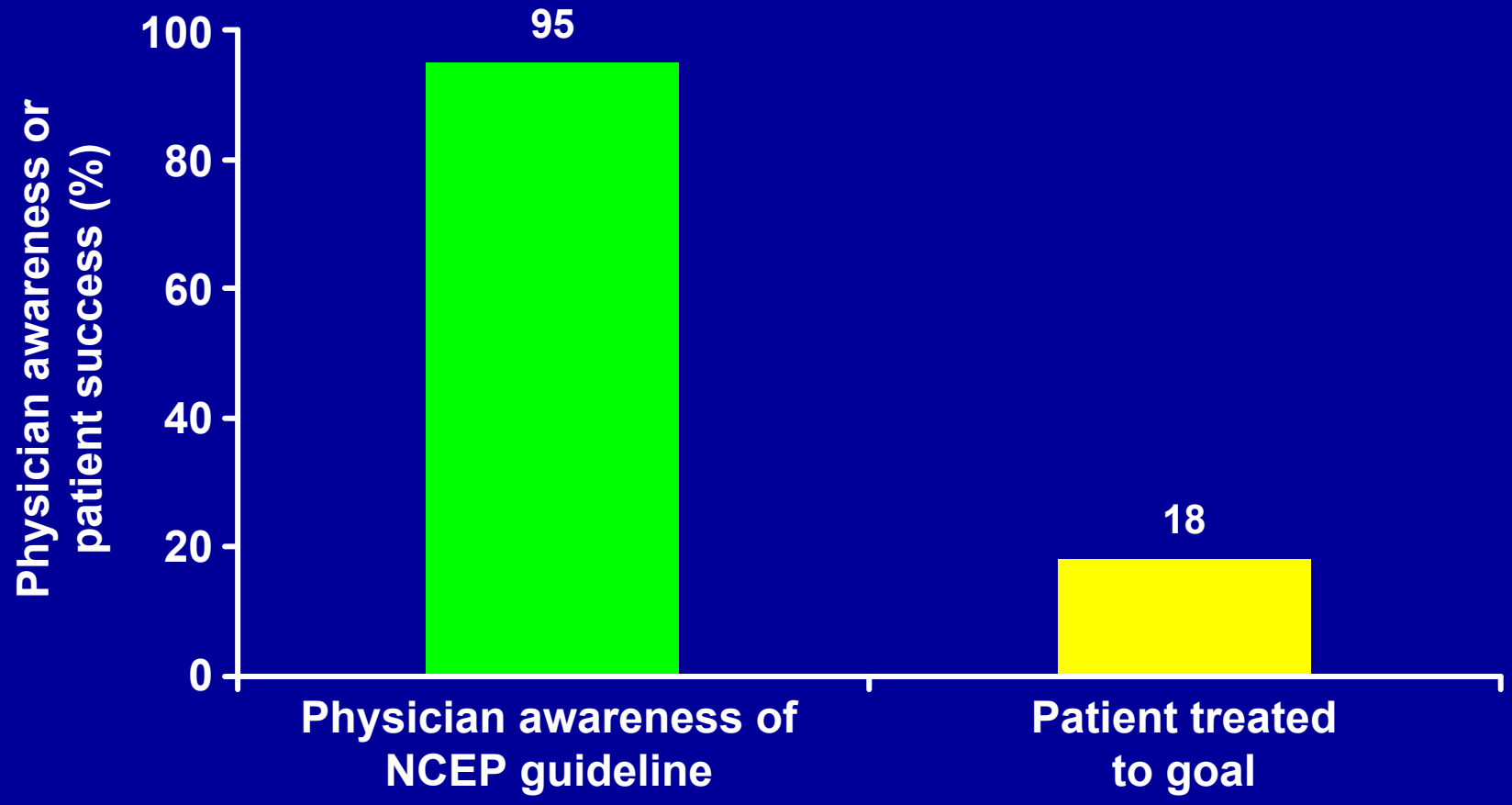
Multidisciplinary care

- 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

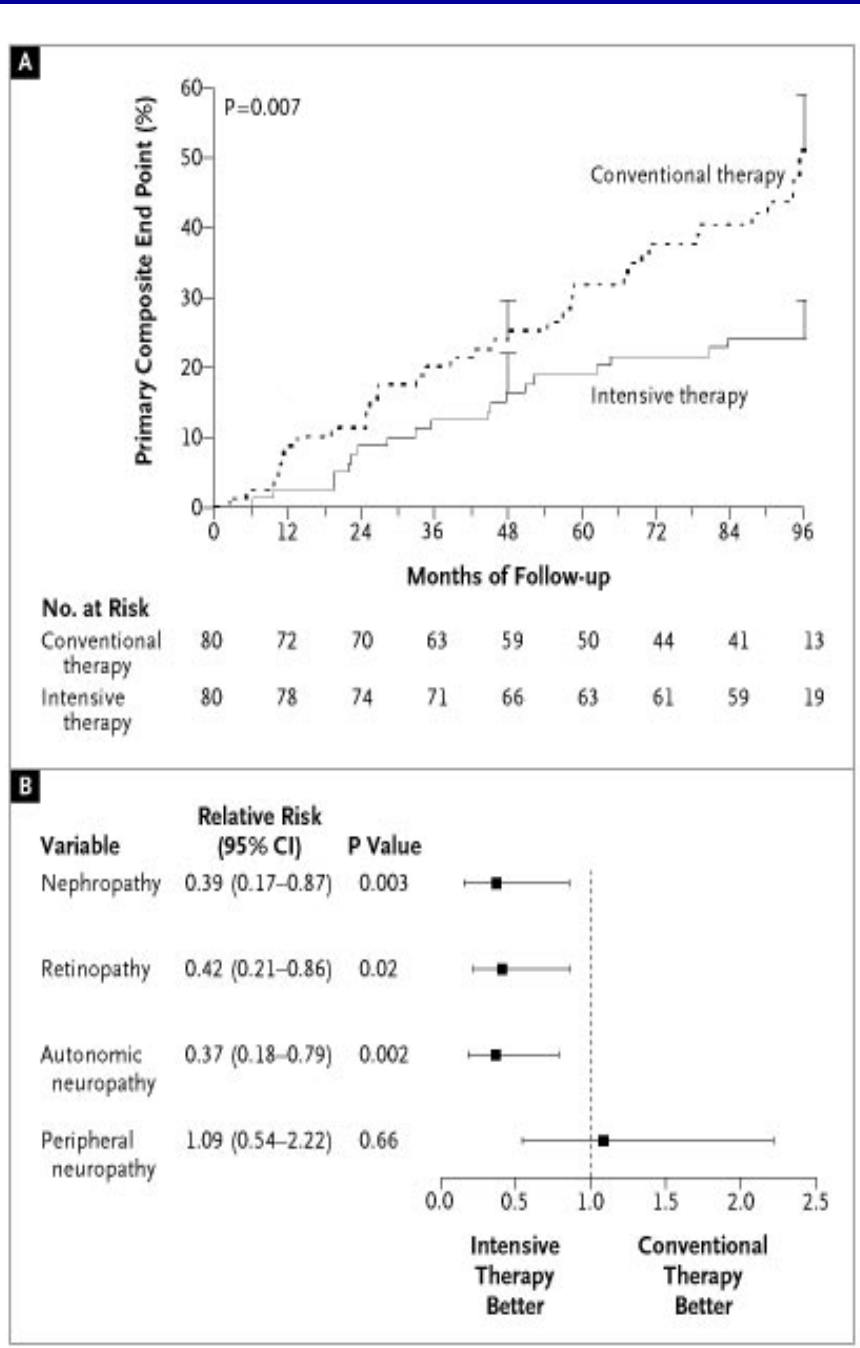
NB: combined cardio/renal protection

- 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

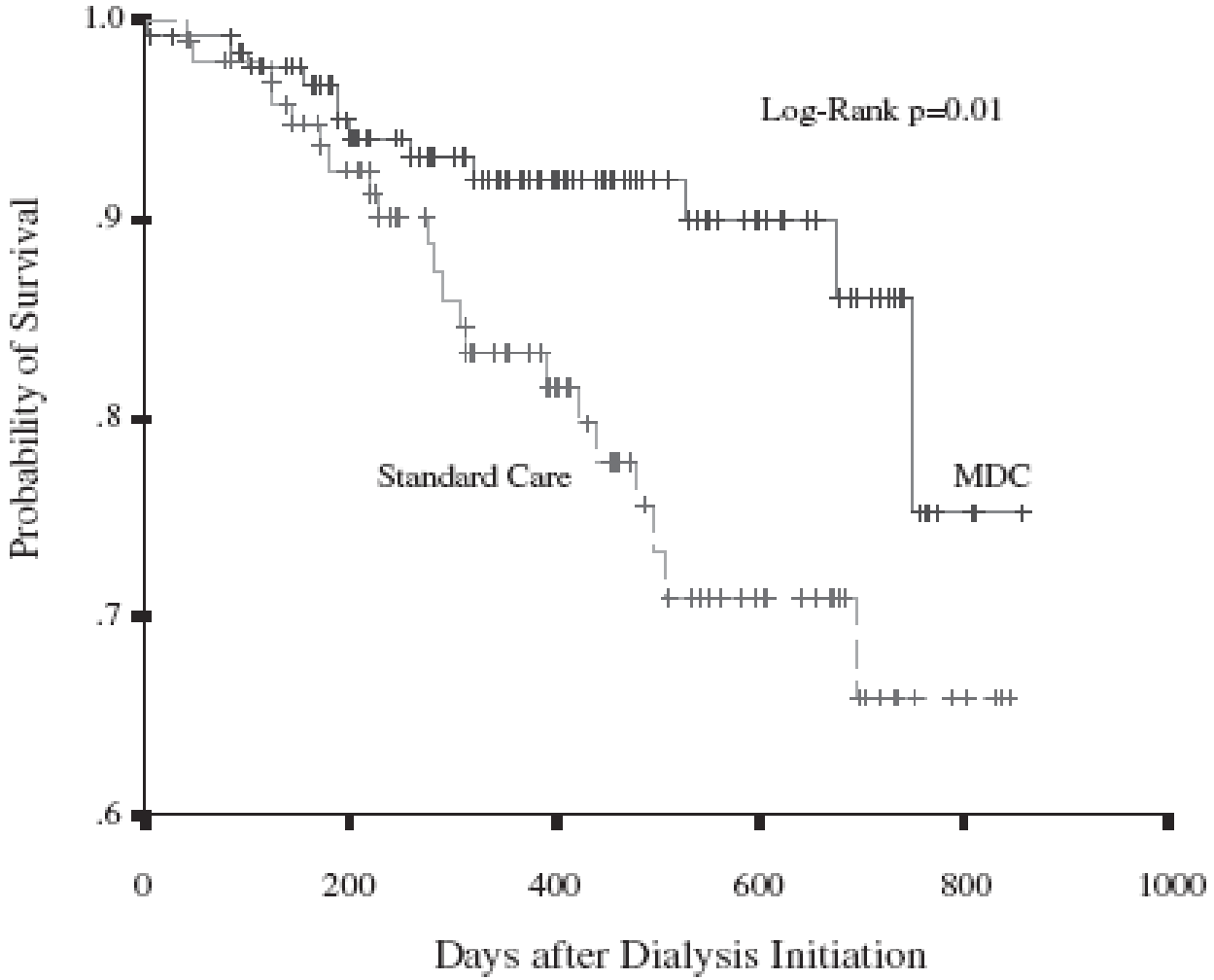
Steno 2: Outcomes

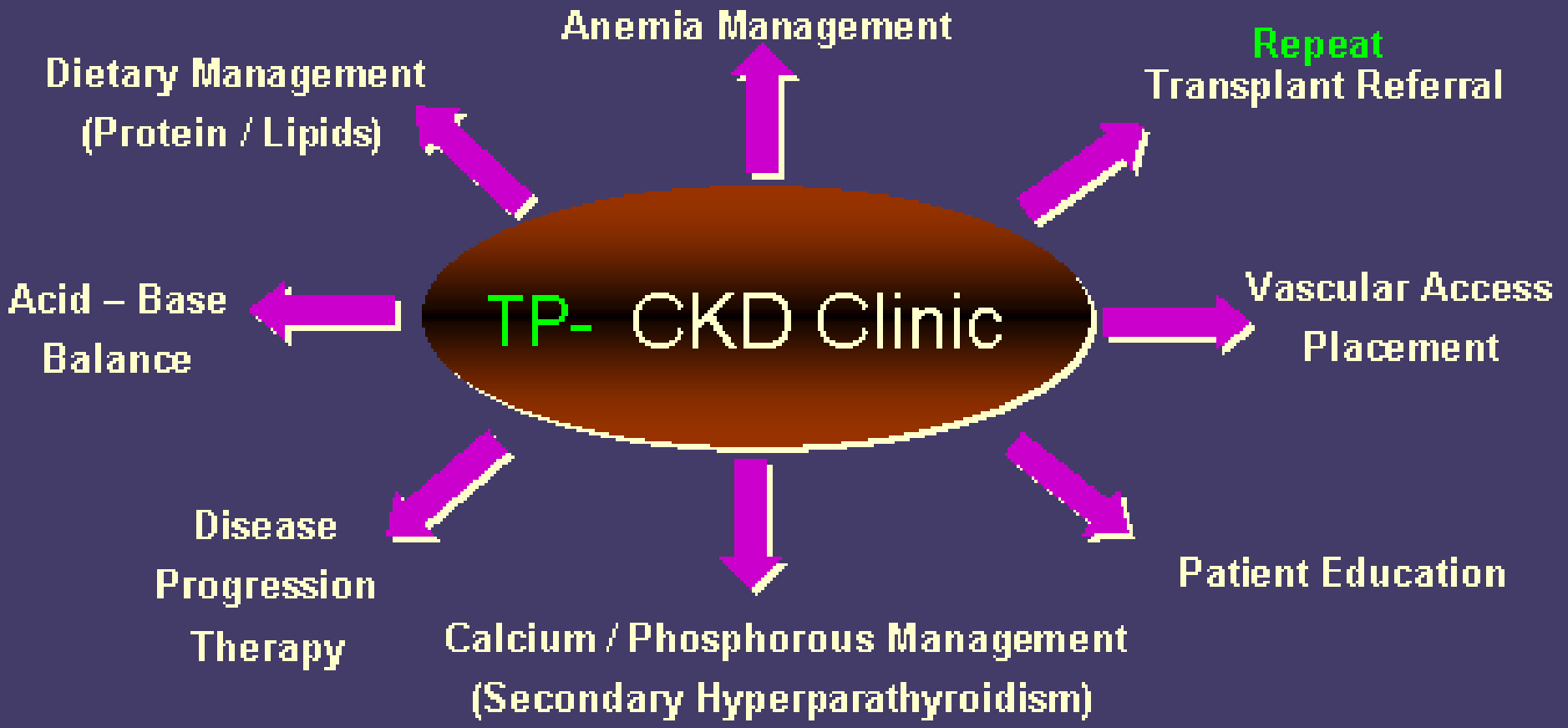
- Hazard ratio = 0.47 in favor of intensive group (.24 - .73, p=0.008)
- Absolute RR = 20%
- NNT 5 patients to prevent one CV event in 7.8 years



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



Nephrol Dial Transplant (2005) 20: 147–154

Chronic Kidney Disease (CKD)
After Organ Transplantation