Long-term care of the renal transplant recipient

Kidney transplantation

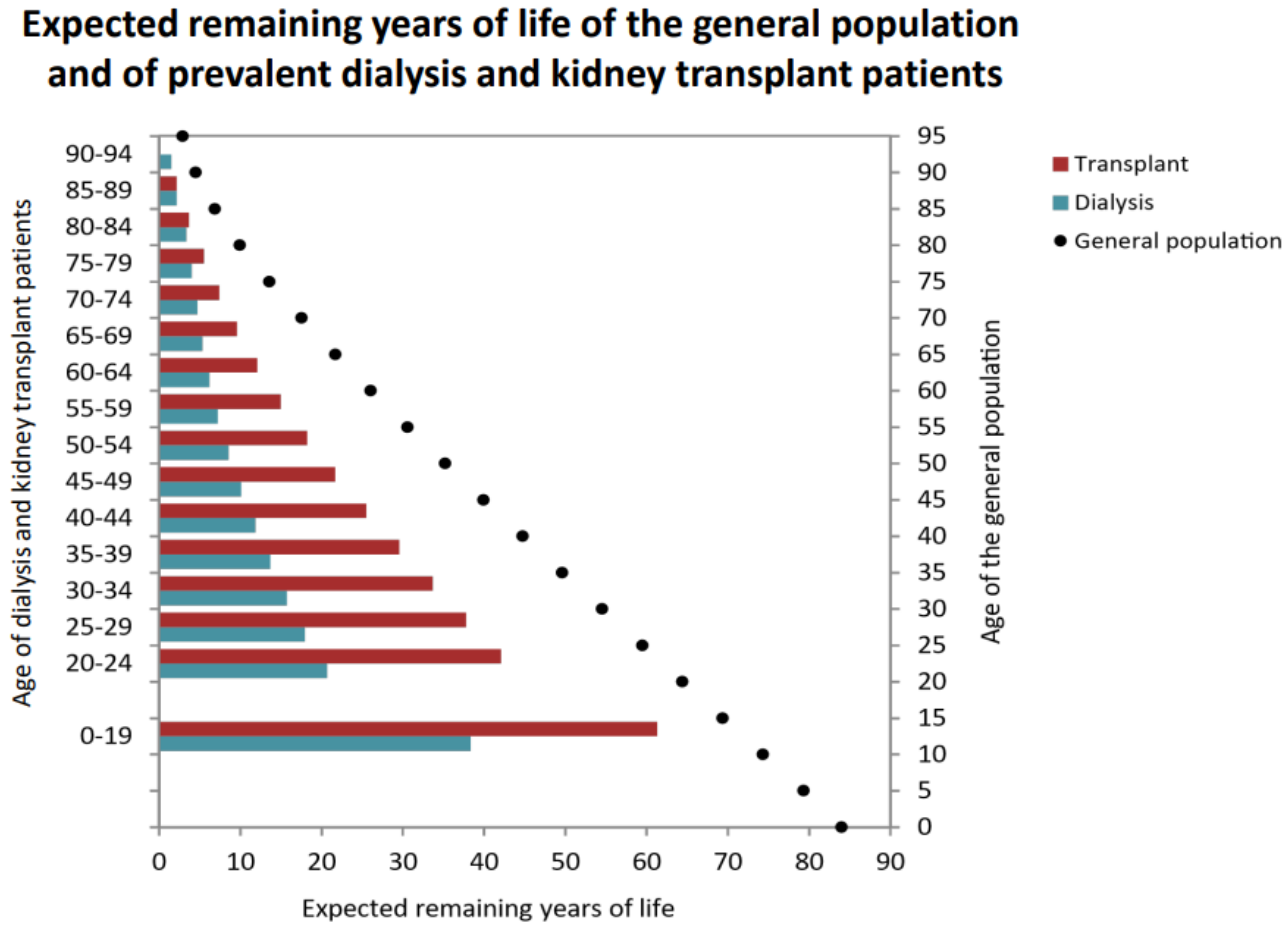
Renal transplantation is the treatment of choice for patients with ESRD

- it prolongs survival
- enhances life quality
- it is cheaper than dialyses

- further improvements may be achieved with living-donor transplantation
- better graft survivals may be obtained with pre-emptive transplantation
- all patients progressing to ESRD should be evaluated for transplantation

Expected remaining lifetime

prevalent patients (2017-2021)

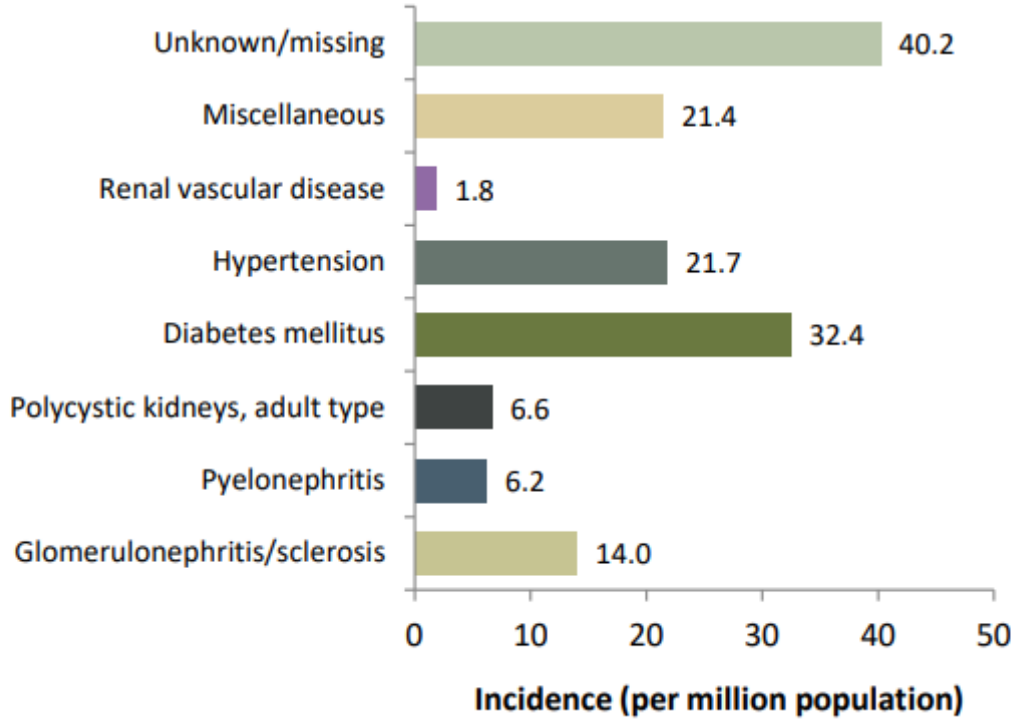


Incident patients accepted for KRT in 2021, at day 1

by primary renal disease

Incidence by primary renal disease

for all registries

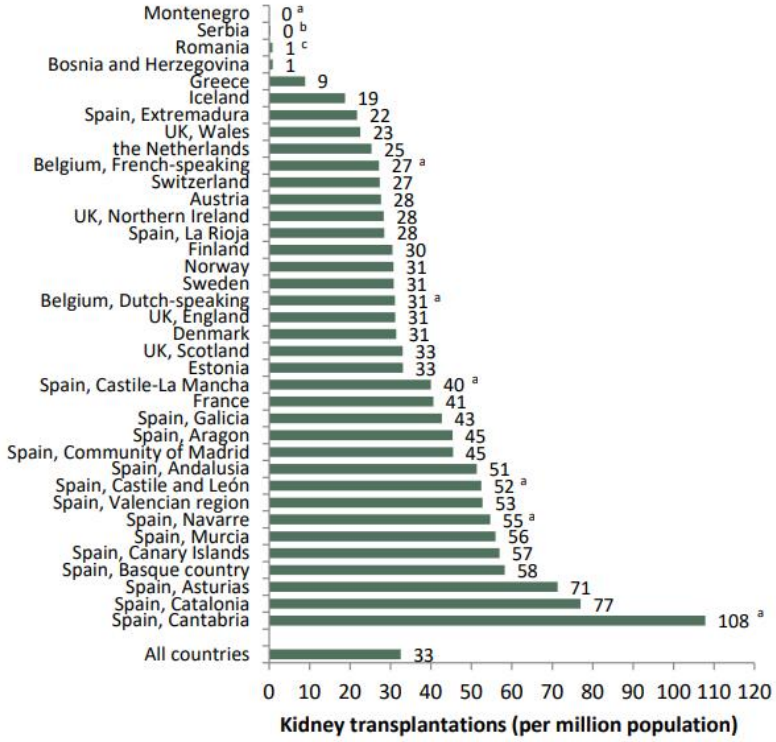


Kidney transplantations performed in 2021

transplants from deceased donors, by country

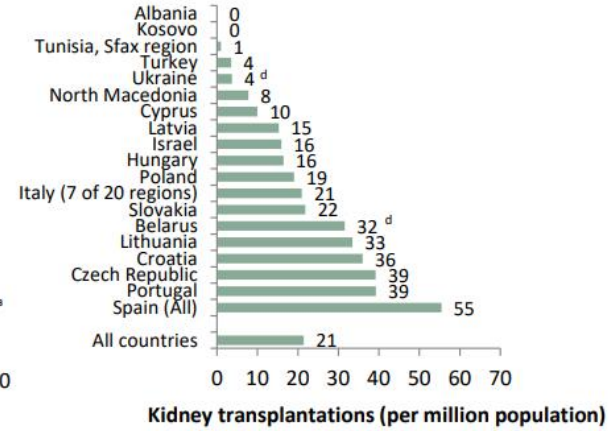
Deceased donor transplantation rate

renal registries providing individual patient data



Deceased donor transplantation rate

renal registries providing aggregated data

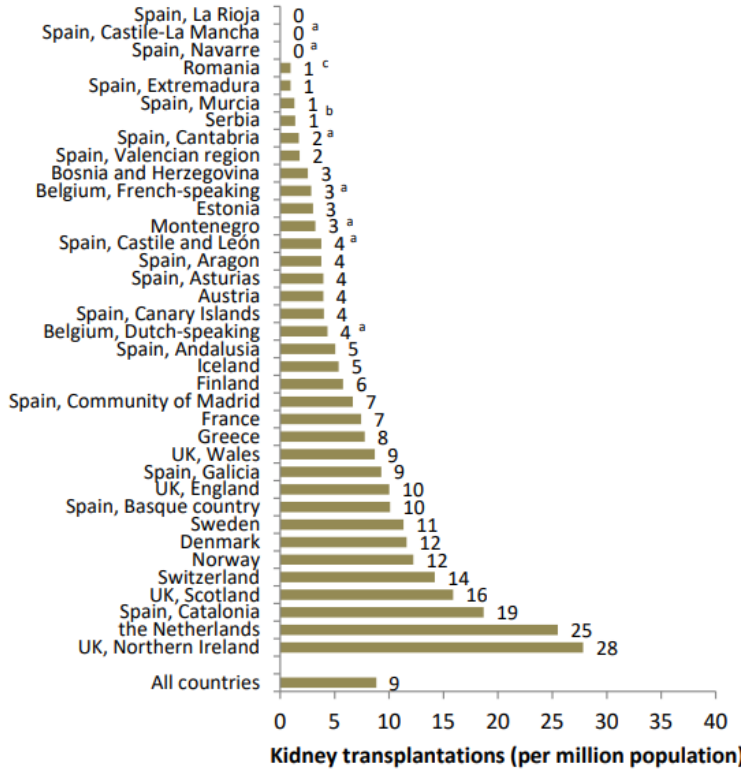


Kidney transplantations performed in 2021

transplants from living donors, by country

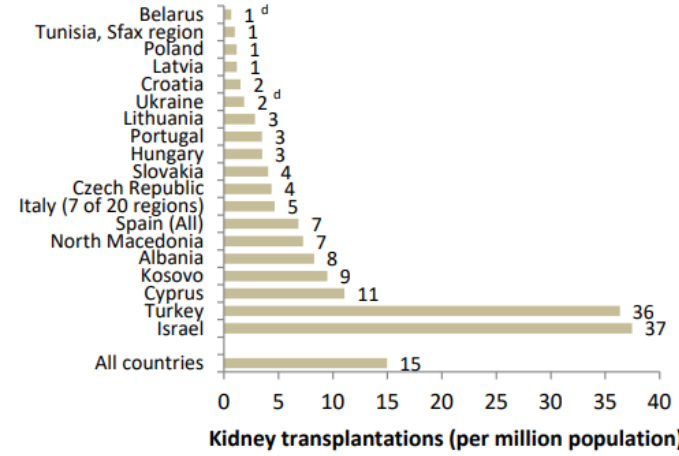
Living donor transplantation rate

renal registries providing individual patient data



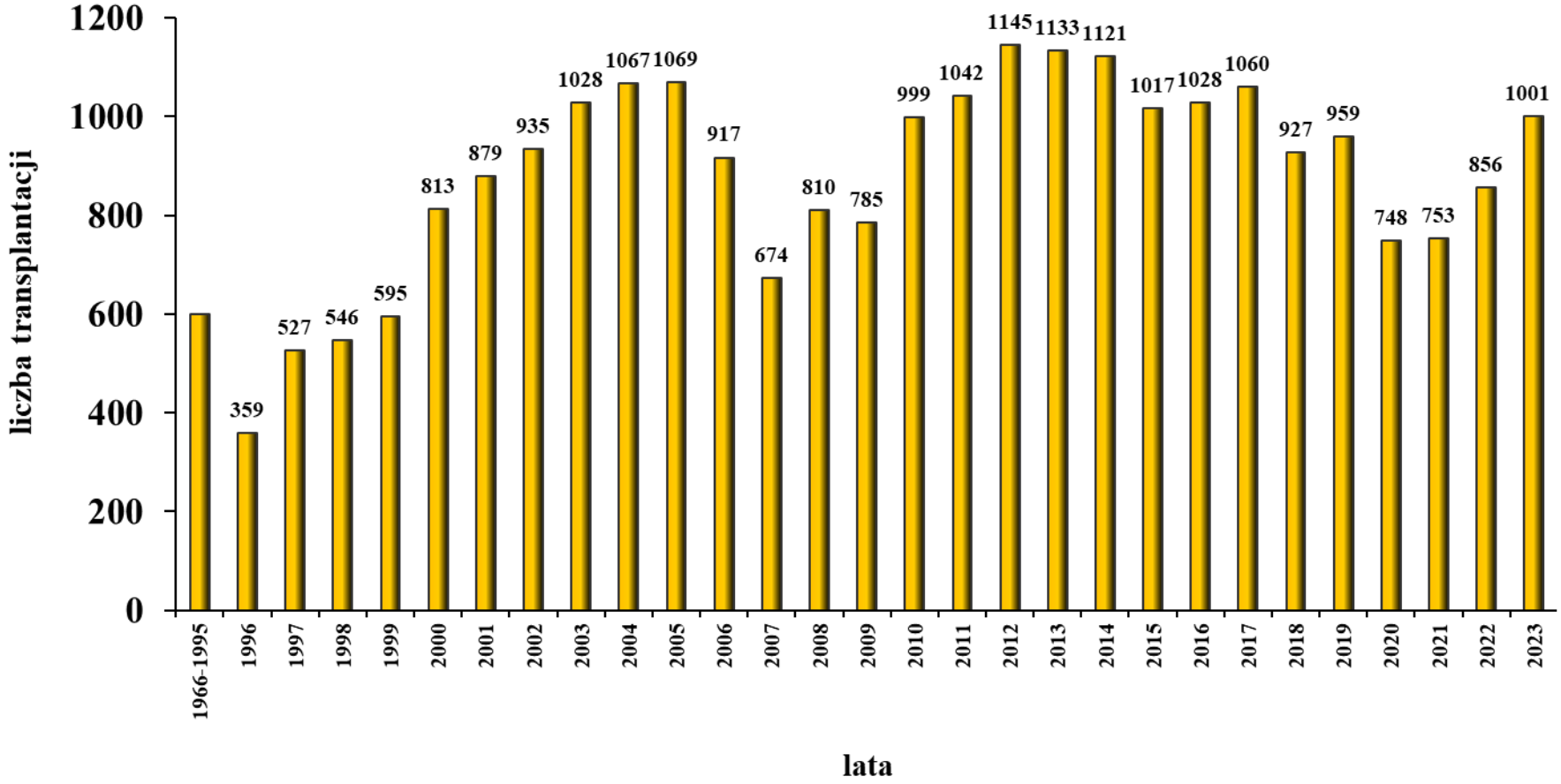
Living donor transplantation rate

renal registries providing aggregated data



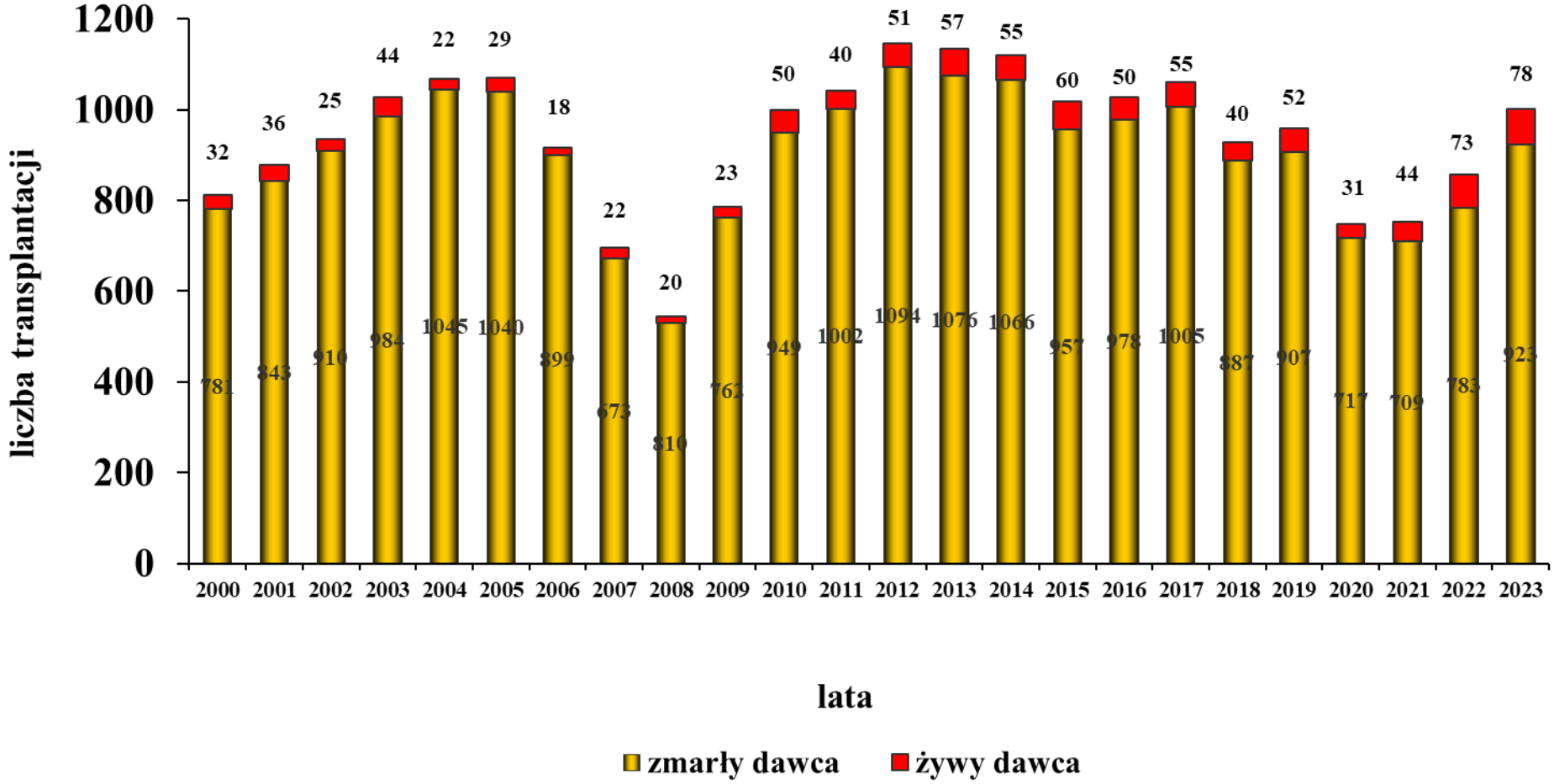
Kidney transplantations in Poland (1966–2023)

Patients on the Waiting List – 1193*



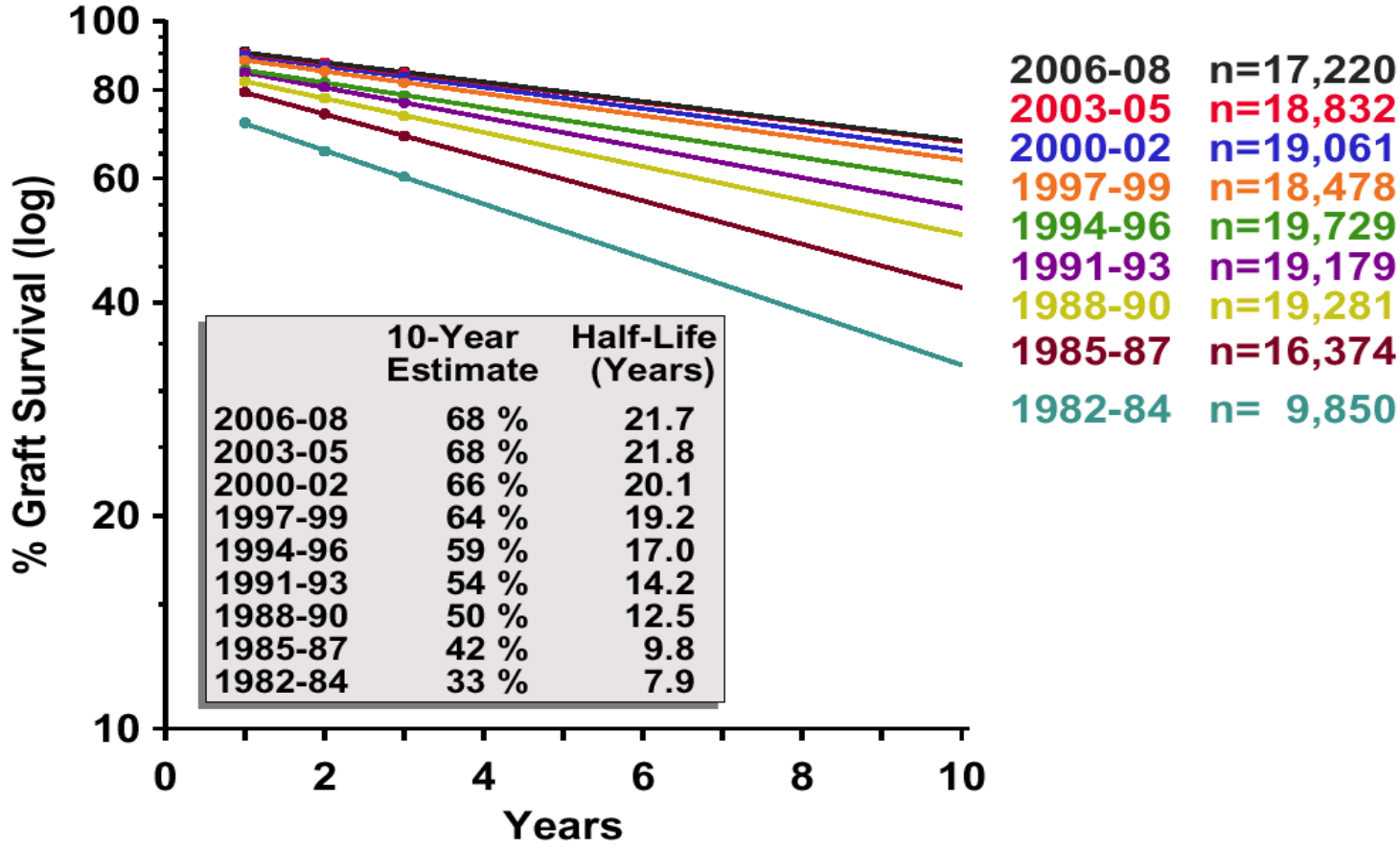
Poltransplant data 31.12.2023*

Kidney transplantations in Poland (2000–2023) deceased *vs* living donor



Transplant Year

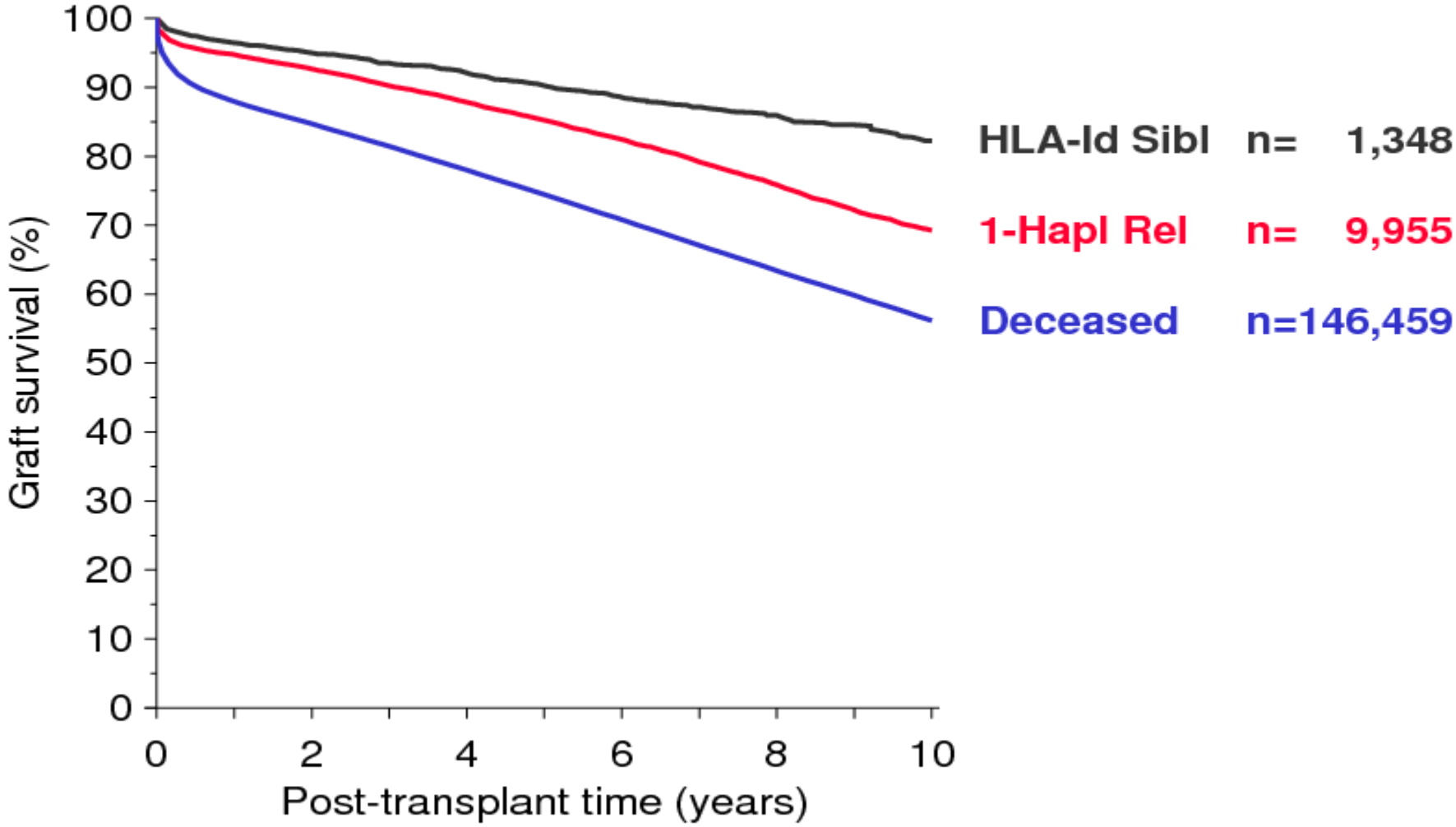
Deceased Donor, First Kidney Transplants
Europe



	10-Year Estimate	Half-Life (Years)
2006-08	68 %	21.7
2003-05	68 %	21.8
2000-02	66 %	20.1
1997-99	64 %	19.2
1994-96	59 %	17.0
1991-93	54 %	14.2
1988-90	50 %	12.5
1985-87	42 %	9.8
1982-84	33 %	7.9

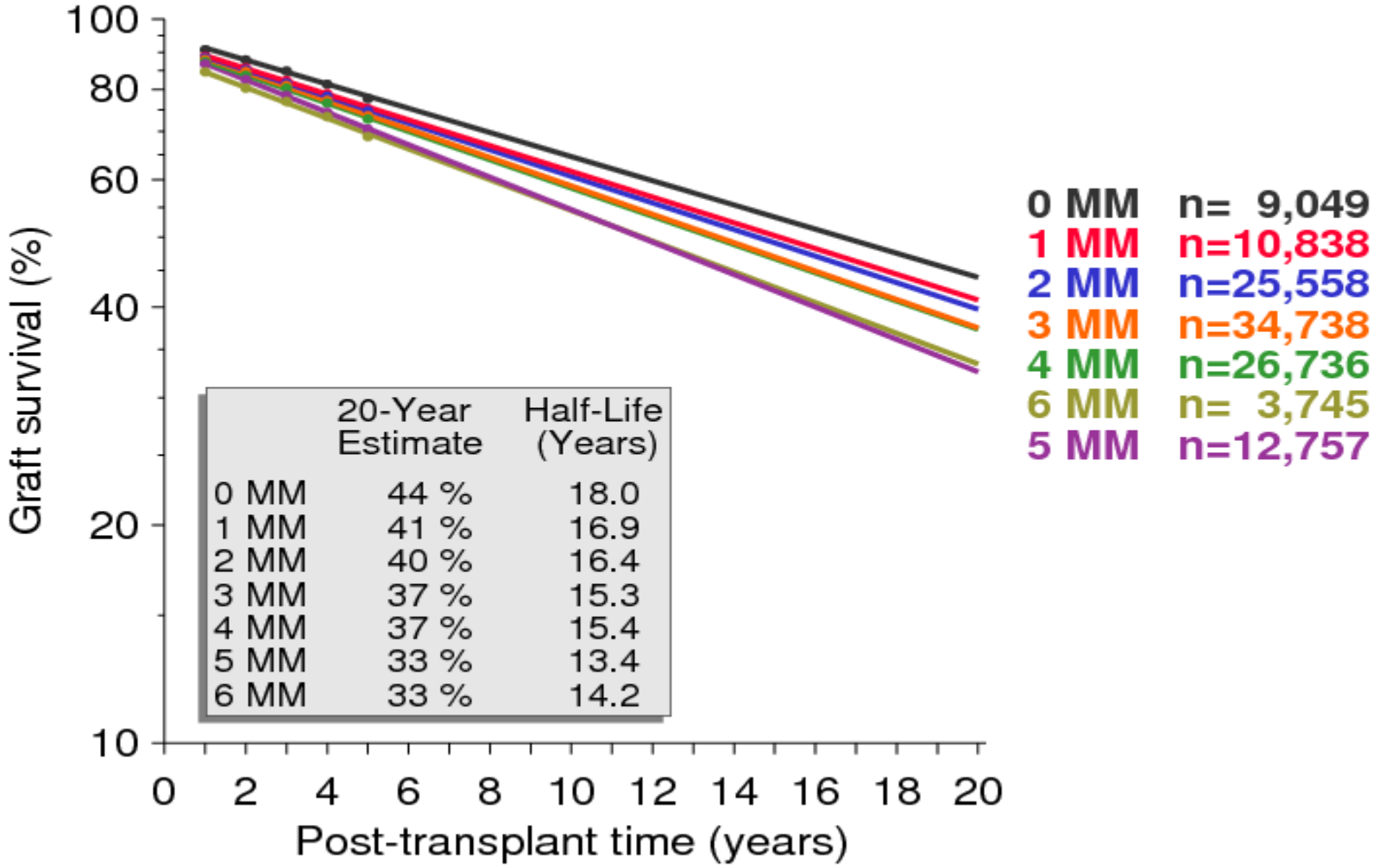
Donor Relationship

First Kidney Transplants 1990-2013
Europe



HLA-A+B+DR Mismatches

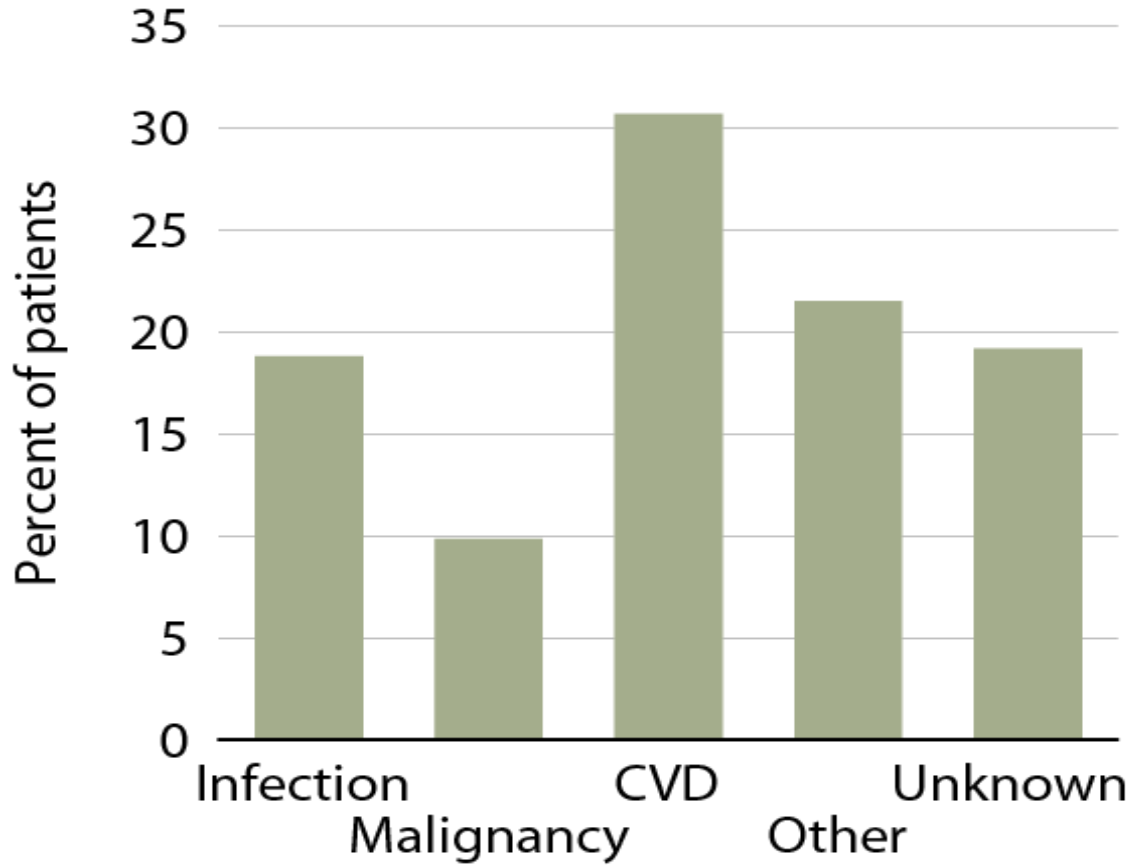
Deceased Donor, First Kidney Transplants 1990-2013



	20-Year Estimate	Half-Life (Years)
0 MM	44 %	18.0
1 MM	41 %	16.9
2 MM	40 %	16.4
3 MM	37 %	15.3
4 MM	37 %	15.4
5 MM	33 %	13.4
6 MM	33 %	14.2

Causes of death with function, 2007–2011

Figure 7.26 (Volume 2)



First-time, kidney-only transplant recipients, age 18 & older, 2007–2011, who died with functioning graft.

United States Renal Data System
2013 Annual Data Report

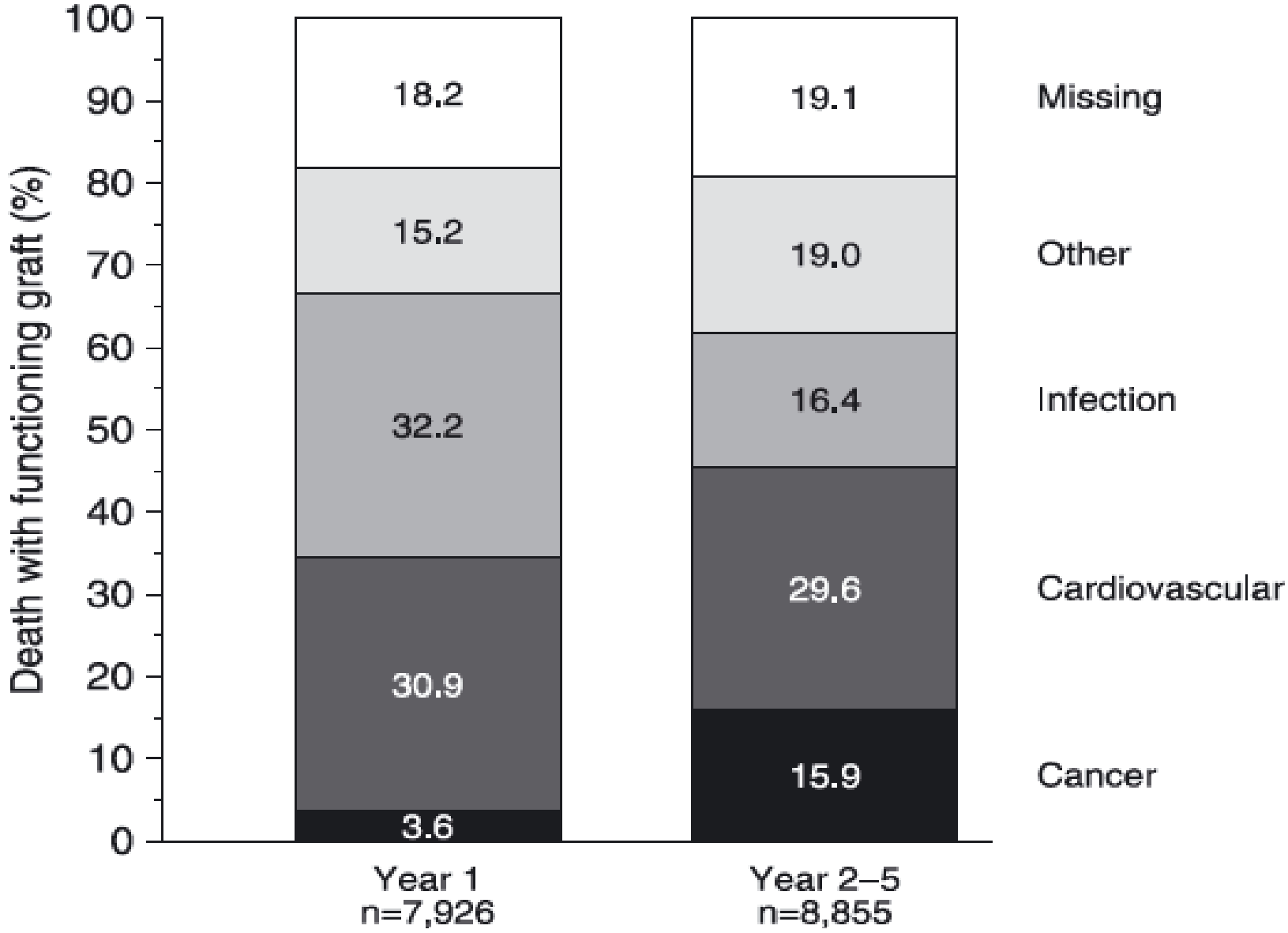


Figure 1: Cause of death with a functioning graft during year 1 and years 2–5 after kidney transplantation.

American Journal of Transplantation
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2012.04226.x

Association of HLA Mismatch With Death With a Functioning Graft After Kidney Transplantation: A Collaborative Transplant Study Report

G. Opelz* and B. Döhler

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University of Heidelberg, Heidelberg, Germany
*Corresponding author: Gerhard Opelz,
gerhard.opelz@med.uni-heidelberg.de*

N=177 584, 1990-2009

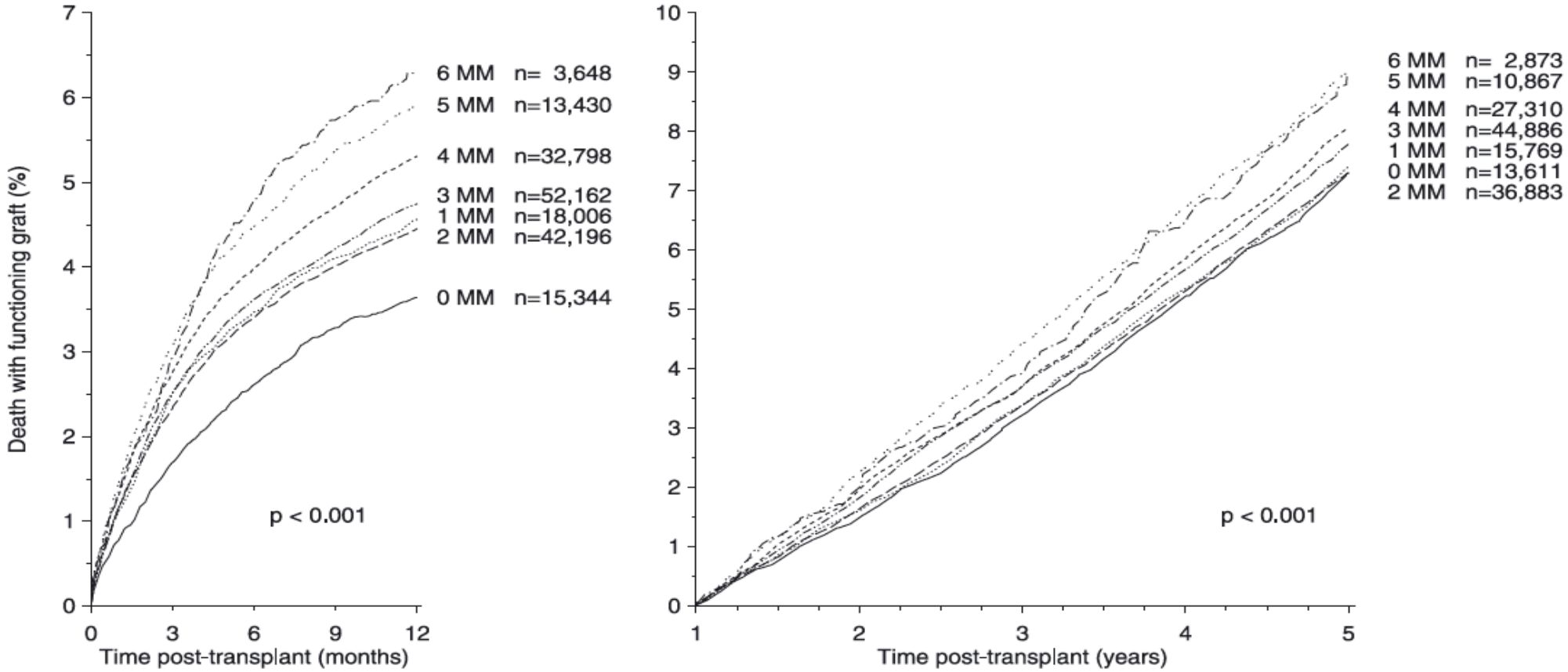
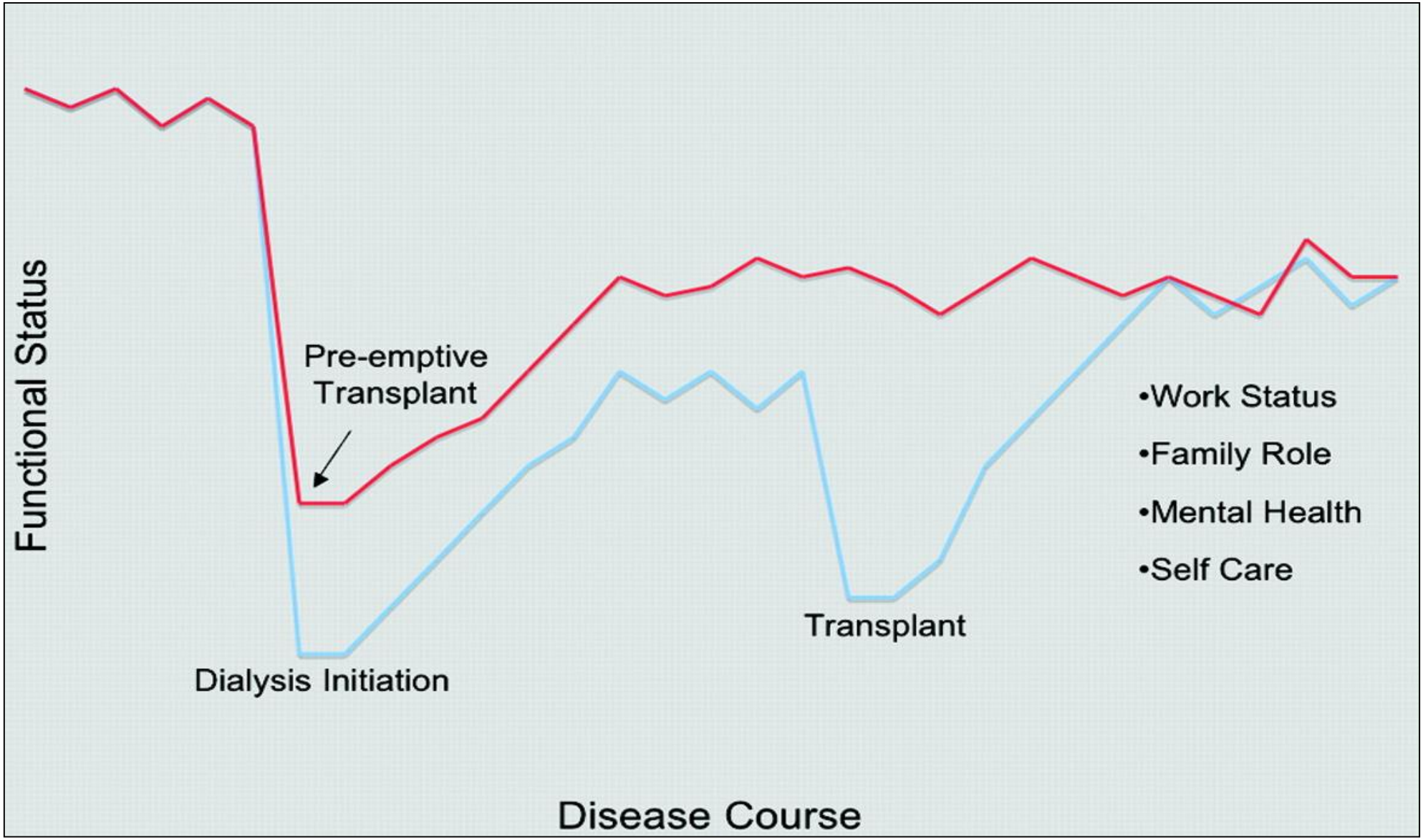


Figure 2: Cumulative rate of death with a functioning graft during year 1 and years 2–5 after kidney transplantation according to the number of HLA-A + B + DR mismatches.

Pre-emptive transplantation as a first-choice approach



NKF/KDOQI Abecassis, M. et al. Clin J Am Soc Nephrol 2008;3:471-480

Preemtive kidney transplantation

- Quality of life improvement
- Avoidance of dialysis-associated morbidities (CVD)
- Less DGF & rejection, better long-term patient and graft survival
- Less expensive than dialysis, dialysis avoidance reduces overall costs
- Allows an individual to further contribute to society in a healthier state

addressing the barriers to PRT

- Limited number of organs from deceased donors (increasing waiting time)
- Living donor programs increase number of organs available for Tx
- Education of patients and medical staff

When to transplant ?

- Lowest kidney function not associated with uremia symptoms
- Always individual decision depending of
  - eGFR decline (progression)
  - CKD symptoms and their severity
  - concomitant diseases severity
  - usually eGFR approx. 10 ml/min
- Preemtive KTx limited by:
  - Need for nephrectomy
  - Need for (coronary) angiography
  - Severe proteinuria /active primary disease

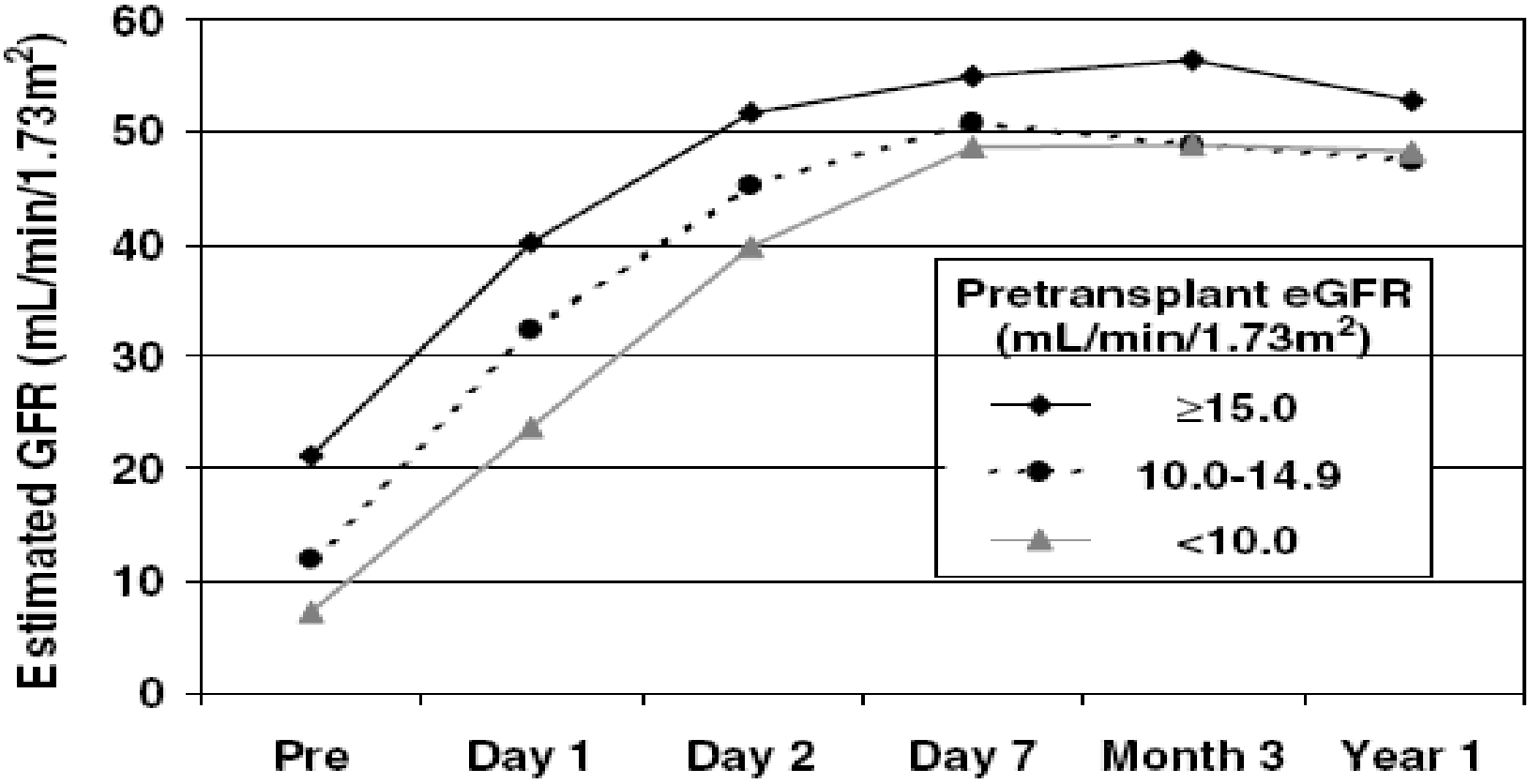


Figure 1: Relationship between pretransplant glomerular filtration rate (eGFR), estimated by the Modification of Diet in Renal Disease (MDRD) four-variable equation, and posttransplant eGFR.

Transplantation-associated aspects of CDK patient care

Preparation for kidney transplantation procedure

Being on the kidney transplant waiting list

Transplantation

Early complications:
surgical, immunological, infectious

Long-term complications of renal transplantation

Post Tx care includes

Stable graft function maintenance to prevent late loss

Enhancement of recipient survival and quality of life

- recipient qualification and enlisting
- organ handling
- immunosuppression optimization
  - monitoring of CNI and MPA concentrations
- kidney transplant monitoring
- early graft dysfunction diagnosis
- patient education

High immunological risk patients

- Leukocyte antigen (HLA) sensitized patients

  PRA (panel reactive antibodies test) under estimates number of patients with antiHLA antibodies, routine application of Luminex ? required
- Retransplants
- Two-organ transplantations: SPK , SLK, HTA
- ABO incompatible KT
- Recipients with historical positive cross-match

Desensitization protocols

- High-dose IVIG 1 to 2 g/kg bw prior to transplantation
- Plasmapheresis (PP) aimed at removing circulating DSA
- PP plus low-dose IVIG – 100 mg/kg cc
- Rituximab anti-CD20 monoclonal antibody aimed at B-cells
- Immunoadsorption
- rATG induction and maintenance immunosuppressive agents: Tac, MMF and steroid
- Imlifidase

Factors influencing kidney allograft function

- Early allograft function
  - delayed graft function (DGF)
  - anty-HLA antibodies prior to Tx
  - graft quality
  - center effect
- Late graft function
  - maintenance immunosupression
  - graft function at 1 year
  - acute rejection episodes
  - HLA mismatch
  - *de novo* anty-HLA Ab
  - cold ishemia time (CIT)
  - CMV infection
  - noncompliance
- Non-immunological factors
  - hypertension
  - hyperlipidemia
  - hyperfiltration
  - smoking
  - obesity
  - proteinuria

Risk factors of late kidney graft loss

Donor factors - the "quality" of the kidney

deceased, non-heart beating, age>60 yrs, female sex , CVD, prolonged CIT, DGF

Recipient factors

female sex, „small for size" organ, obesity, CVD, diabetes, proteinuria, smoking, non-adherence

Immunological factors

immunization prior to KTx, poor HLA matching, inadequate immunosuppression

First post-transplant month

Complications in the early post-operative phase

- delayed graft function (DGF)
- graft rejection
- primary graft non-function
- infections
- medications side effects

Surgical complications affecting kidney allograft

- Acute occlusion of transplant renal artery or vein
- Peritransplant haematoma
- Urinary leak
- Lymphocoele
- Obstructive uropathy
- Renal artery stenosis

Dialysis sessions prior to and after implantation

- With-in 24 hours before engraftment
- Avoid hypovolemia, 2-3 h, limited ultrafiltration
- After operation HD session 2-3 h, limited UF
- Peritoneal dialysis - increased risk of fluid leak, peritonitis. As an alternative - HD with temporal vascular catheter placement

New onset pain in transplanted kidney site

the most common causes of peritransplant pain

- **peritransplant haematoma**
- **urine leak**
- **lymphocele**
- **infection**
- **acute rejection**

Patients who undergo kidney transplant require intense pharmacotherapy

- Switch from iv to oral medications
- IS monitoring
- Other
  - antihypertensive drugs
  - analgesics
  - anti-infective prophylaxis
  - prevention of upper gastrointestinal haemorrhage
  - LMWH

Immunosuppressive medications side effects

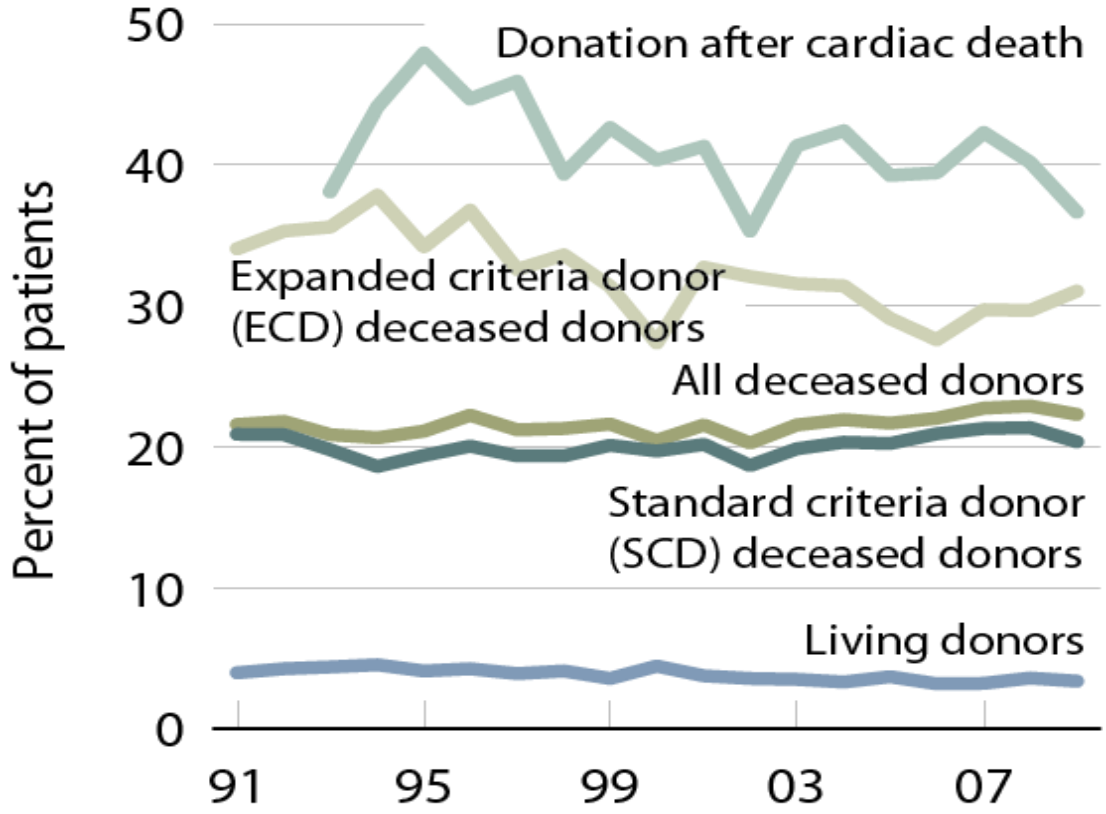
- Commonly seen in the early post-Tx transplant period when the doses and concentrations are highest
- In case of medication side effects the doses should be adjusted or switch to other medication should be considered
- Toxic effects of *CsA* or Tac may be associated with drug interaction with concomitant medications (e.g. metabolised by cytochrome P450 – clarithromycin, ketokonazole)

Use generic compounds only if certified by an independent regulatory agency to meet each of the following criteria

- contains the same active ingredient
- is identical in strength, form, route of administration;
- has the same use indications;
- was bioequivalent in appropriate bioavailability studies;
- meets the same batch requirements for identity, strength, purity, and quality;
- is manufactured under strict standards.

when compared to the reference compound

Transplants with delayed graft function (DGF), by donor type



and what may be hiding under DGF……

Expanded criteria donor (ECD)
25% of organs harvested in Poland

- Donor > 60 yrs

or

- Donor between 50 and 59 years and fulfilling two additional criteria:
  - known to have hypertension
  - with recent serum creatinine > 1.5 mg%
  - died due to cerebral stroke

  Mentioned criteria increase by 70% the risk for kidney allograft loss

Port FK., Transplantation 2002

Monitoring kidney allograft function

serum creatinine and eGFR

- creatinine usually reaches serum creatinine < 1.5 mg/dl
- the rise of 0.3 mg/dl or 25% from baseline value is regarded as significant and requires further evaluation

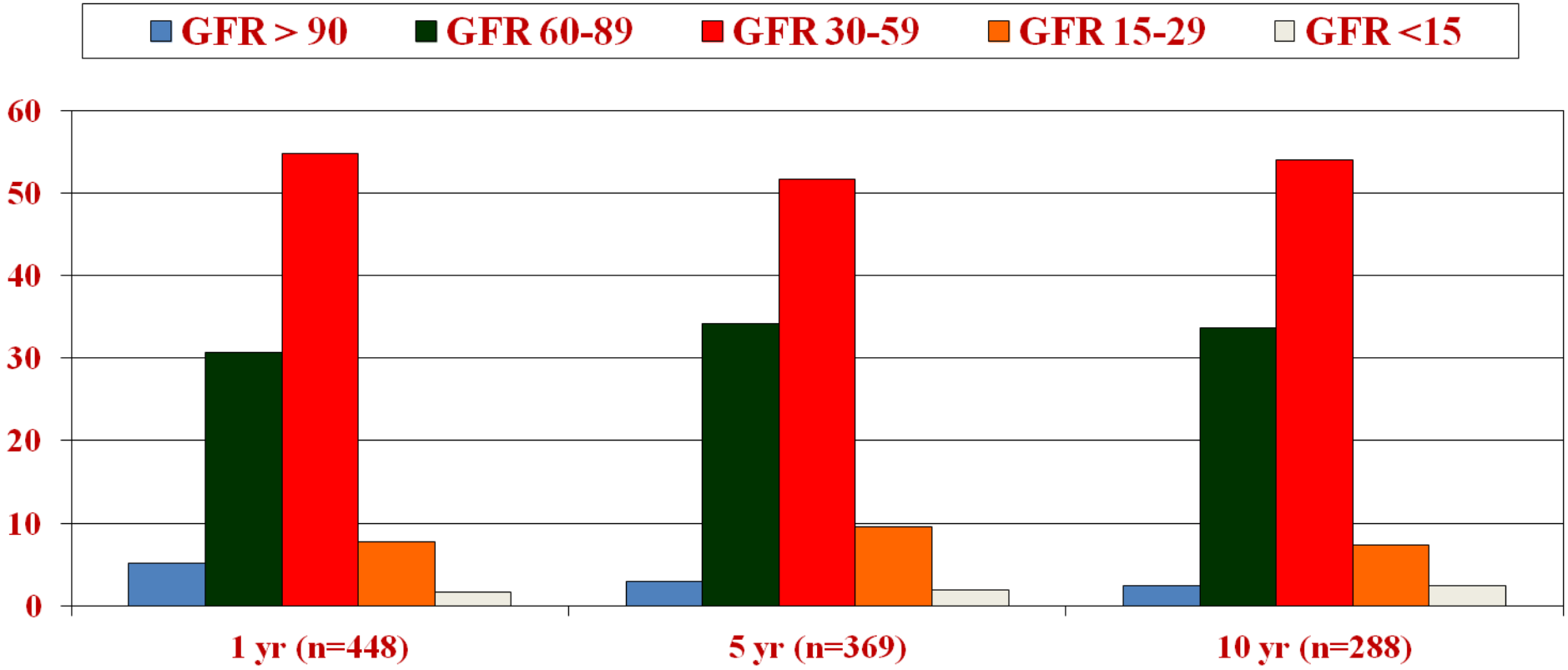
proteinuria

- new-onset P requires further evaluation

biopsy

- surveillance or on indication

Above 60% of kidney recipients experience graft function of eGFR below 60ml/min/1.73 m^2



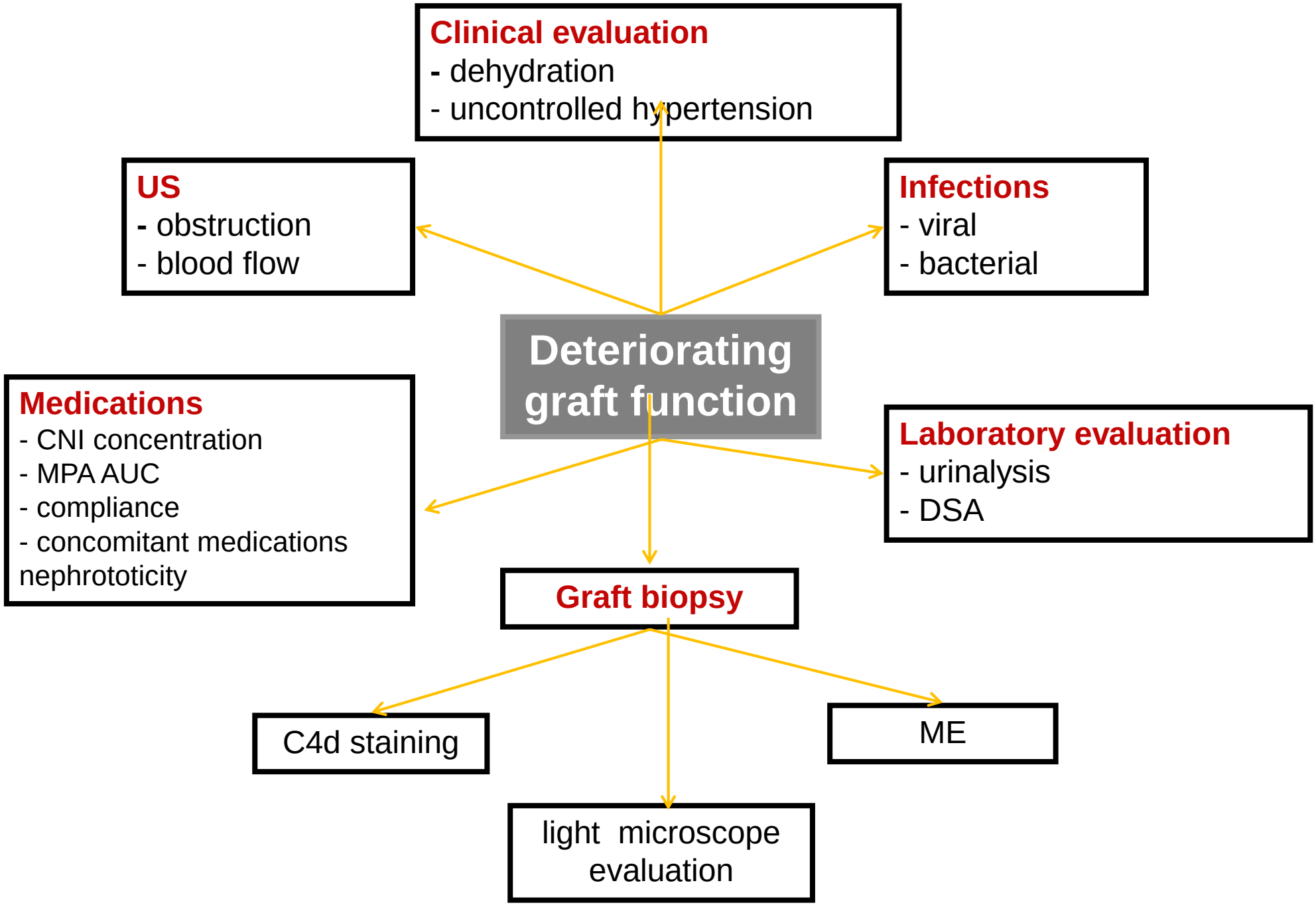
Marcén R et al. Transplant Proc 2005; 37:3718

Causes of graft function deterioration

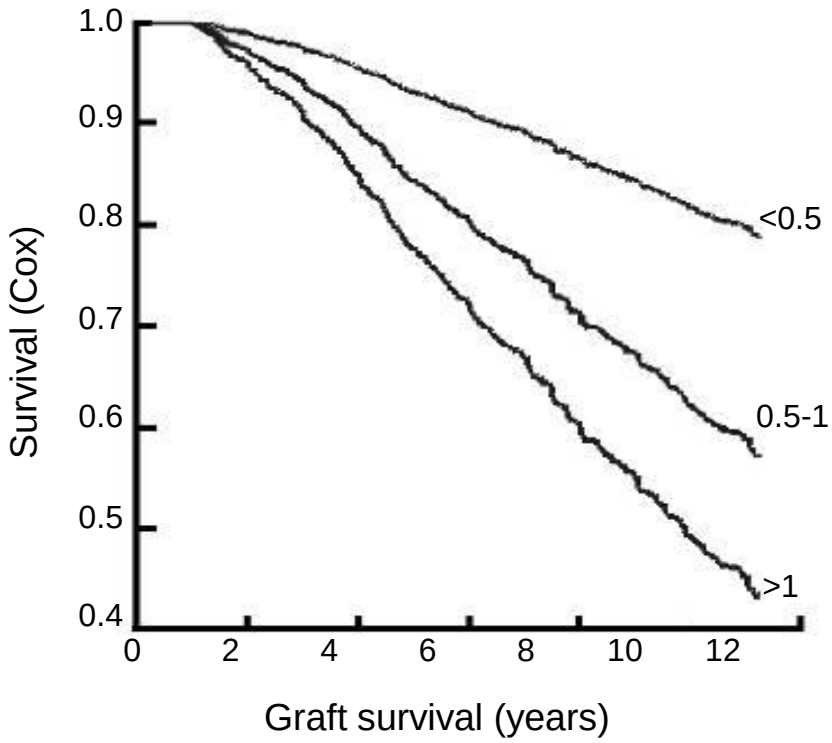
Prerenal
- hypovolemia, heart failure

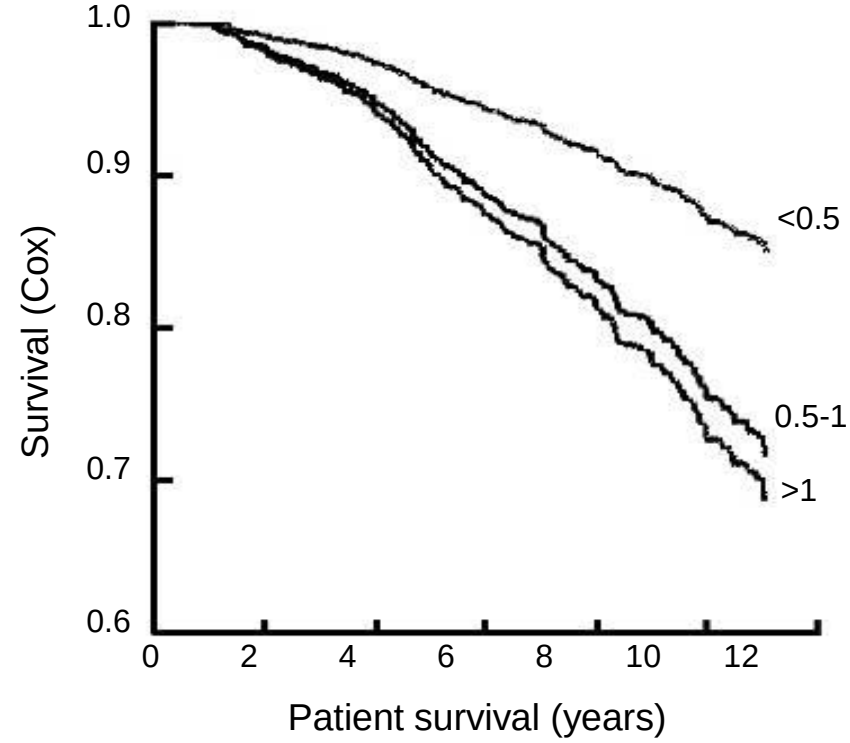
Renal
- acute rejection
- primary disease relapse
- chronic rejection
- BK nephropathy
- *de novo* glomerulonephritis
- urinary tract infection
- medications nephrotoxicity

Postrenal
- urinary tract obstruction below the kidney


Clinical evaluation
- dehydration
- uncontrolled hypertension
US
- obstruction
- blood flow
Infections
- viral
- bacterial
Deteriorating graft function
Medications
- CNI concentration
- MPA AUC
- compliance
- concomitant medications
nephrototicity
Laboratory evaluation
- urinalysis
- DSA
Graft biopsy
C4d staining
ME
light microscope evaluation

Proteinuria as predictor of graft and patient survival





Fernandez-Fresnedo G et al. Nephrol Dial Transplant 2004.

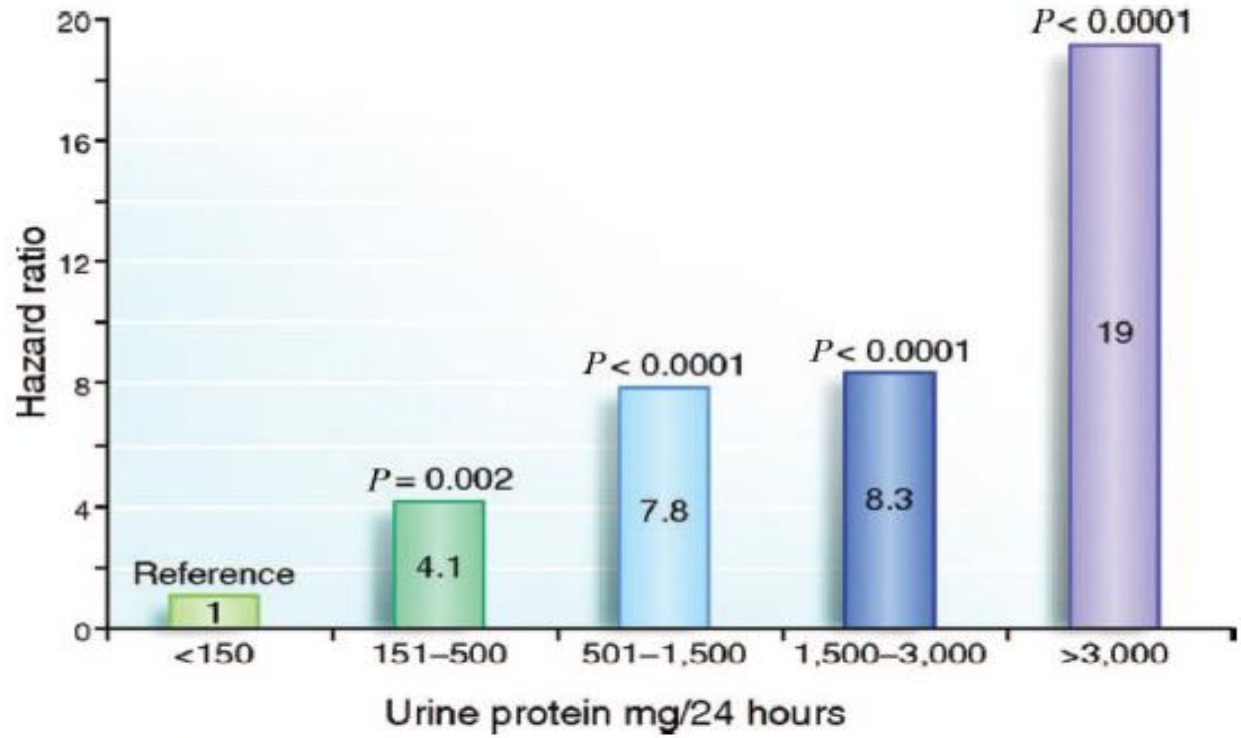


FIGURE 13. Relationship between increasing levels of proteinuria at 1 year posttransplant and subsequent graft survival. (Reproduced with permission from Amer H, Fidler ME, Myslak M, et al. Proteinuria after kidney transplantation, relationship to allograft histology and survival. *Am J Transplant* 2007; 7: 2748.)

Chronic Renal Allograft Damage: Existing Challenges

Manuel Arias,[1] Daniel Serón,[2] Francesc Moreso,[2] Oriol Bestard,[3] and Manuel Praga[4]

TABLE 8. Pharmacologic and nonpharmacologic antiproteinuric measures

Pharmacologic	Nonpharmacologic
Angiotensin-converting enzyme inhibitor	Blood pressure control <130/80 mm Hg
ARB	Reduced salt intake
	Reduced protein intake
Spironolactona-eplerenone	Weight loss
Thiazide diuretics	Cessation of smoking
Pentoxifylline	Exercise

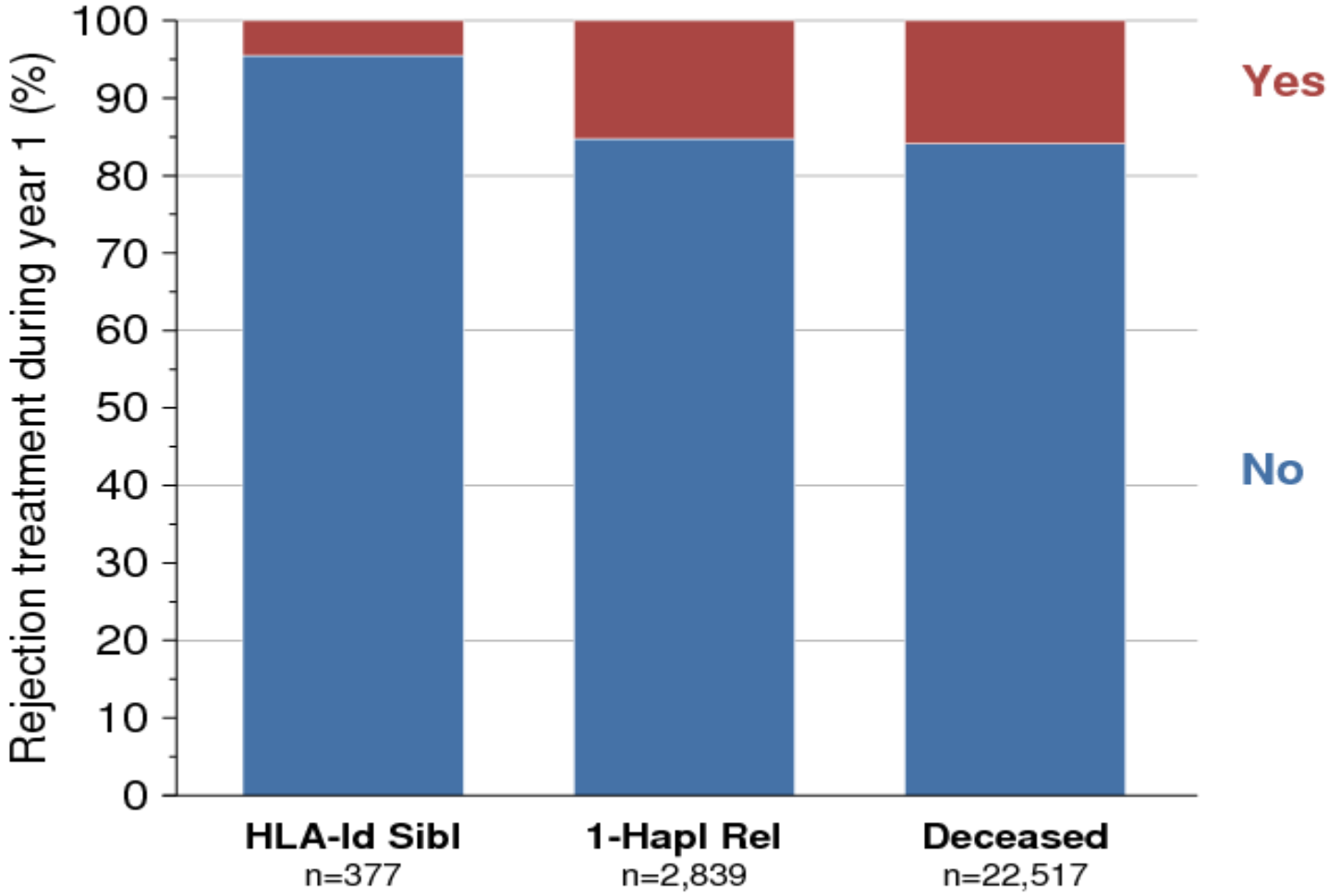
Transplantation. 91(9S):S4-S25, May 15, 2011

Acute rejection

- Alloantigen-driven inflammation of the graft
- Commonly occurs within first post-transplant three months
- Usually presents as at least 25% rise of serum creatinine, rarely accompanied by clinical symptoms: diminished urine output, graft tenderness and swelling, mild fever, hypertension
- The immune response to a transplanted organ consists of both cellular (lymphocyte mediated) and humoral (antibody mediated) mechanisms
- Diagnosis of rejection is based upon allograft biopsy
- 70% of cases acute cellular rejection
- AMR as component of acute cellular rejection - 25% of cases
- 5–7% of cases isolated antibody–mediated rejection (AMR)

1-Year Rejection Treatment

First Kidney Transplants 2000-2013
Europe, Functioning Graft at 1 Year



The Implications of Acute Rejection for Allograft Survival in Contemporary U.S. Kidney Transplantation

Krista L. Lentine,[1,5] Adrian Gheorghian,[1] David Axelrod,[2] Anu Kalsekar,[3] Gilbert L'italien,[3,4] and Mark A. Schnitzler[1]

Transplantation • Volume 94, Number 4, August 27, 2012

N=48 179, 2000-2007

Acute rejection associates with increased risk of allograft loss

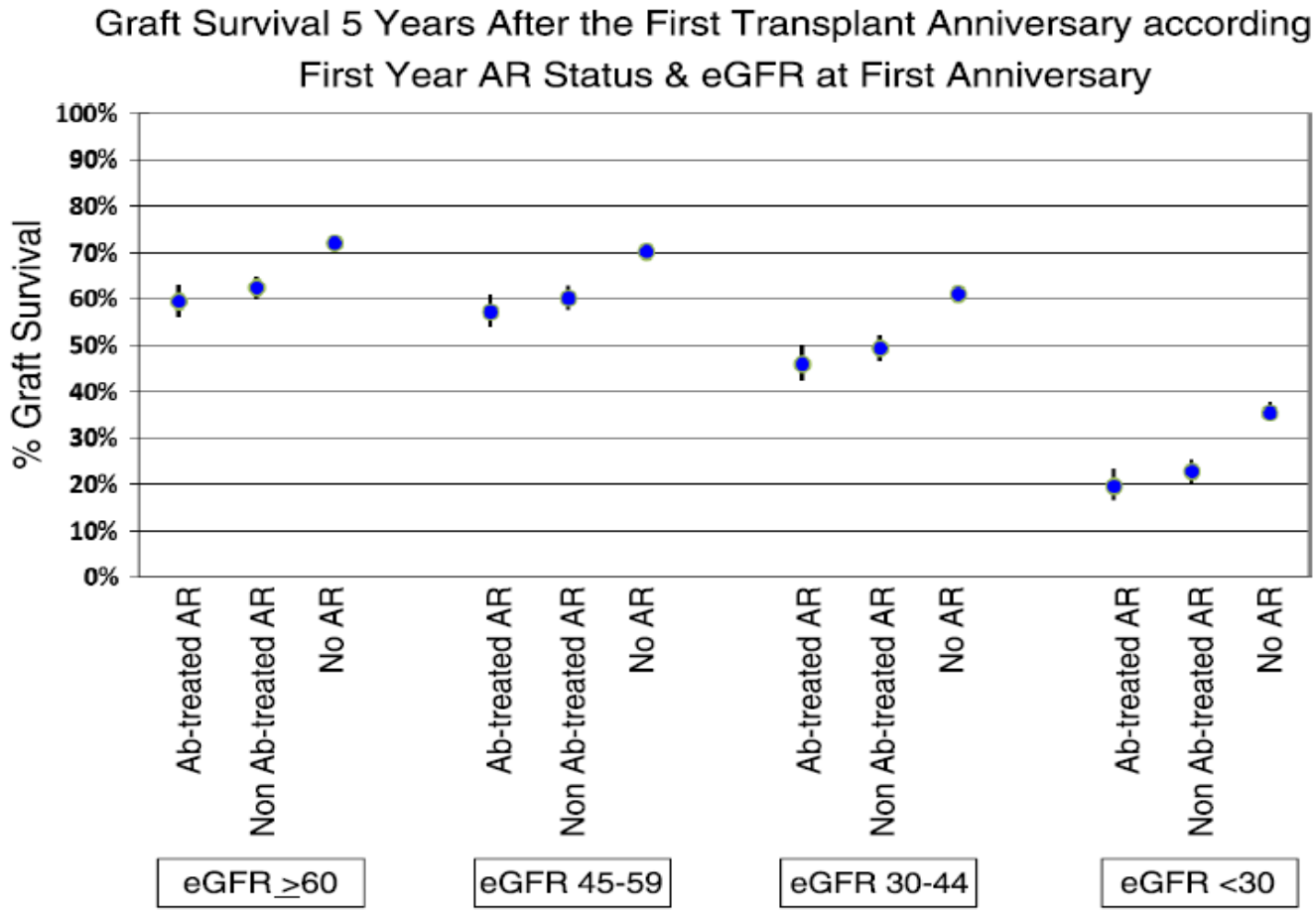


FIGURE 2. Predicted graft survival 5 years after the first transplant anniversary according to acute rejection (AR) status and estimated glomerular filtration rate (eGFR) at the first anniversary, among all transplant recipients who survived to 1 year after transplantation. Predicted from multivariate Cox regression models for all-cause graft survival after the first transplant anniversary, including adjustment for baseline recipient, donor, and transplant factors. Values of adjustment covariates were set to average sample values for prediction.

Late acute rejection

- Usually depends on suboptimal immunosuppression, commonly diagnosed between 1 and 2 post-transplant year, in noncompliant recipients taking medications irregularly
- Rarely diagnosed clinically – 1%
- In recipients with protocol biopsies performed, the incidence of subclinical late acute rejections reaches 12-28%
- late acute rejection poorly reacts to steroids treatment, increases risk of chronic AMR and graft loss

Thrombotic microangiopathy (TMA) after transplantation

- Presentation – days to year after engraftment (usually 3-6 months post Tx)
- Either clinically overt or presenting as HUS
- The incidence in transplanted kidney varies between 4 and 14%

TMA relapse

- recurrence according to genetic mutation of complement factors H/I/B, C3, MCP, THBD
- antibodies: anti-H, anti-ADAMTS13, lupus anticoagulant, scleroderma

De novo TMA in transplanted kidney

- calcineurin inhibitors
- mTOR inhibitors
- antibody mediated rejection (AMR)
- viral infections (CMV, HCV, parvovirus B19)
- pregnancy

atypical HUS (aHUS) relapse

- under-diagnosed as primary kidney disease
- usually relapses with-in first post-Tx months
- diagnosed upon kidney biopsy (TMA without laboratory signs of HUS)
- usually results in graft loss
- CNI-free immunosuppressive regimen does not preclude aHUS relapse

Kidney allograft loss

Early < 6 months

- technical/surgical complications
- severe acute rejection
- poor graft quality
- first-year graft survival exceeds 90%

Late graft loss 3%-5% per year

- death with the functioning graft
- chronic graft dysfunction
- relapse of primary disease

20%-40% of patients on the waiting list require retransplant

National Kidney Foundation

American Journal of Kidney Diseases

Volume 57, Issue 3, March 2011, Pages 466–475

Original Investigation

The Relationship Between Kidney Function and Long-term Graft Survival After Kidney Transplant

Bertram L. Kasiske, MD[1, 2], Ajay K. Israni, MD, MS[1, 2], Jon J. Snyder, PhD, MS[1], Melissa A. Skeans, MS[1], Patient Outcomes in Renal Transplantation (PORT) Investigators[□]

[1] Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, MN

[2] Department of Medicine, Hennepin County Medical Center, Minneapolis, MN

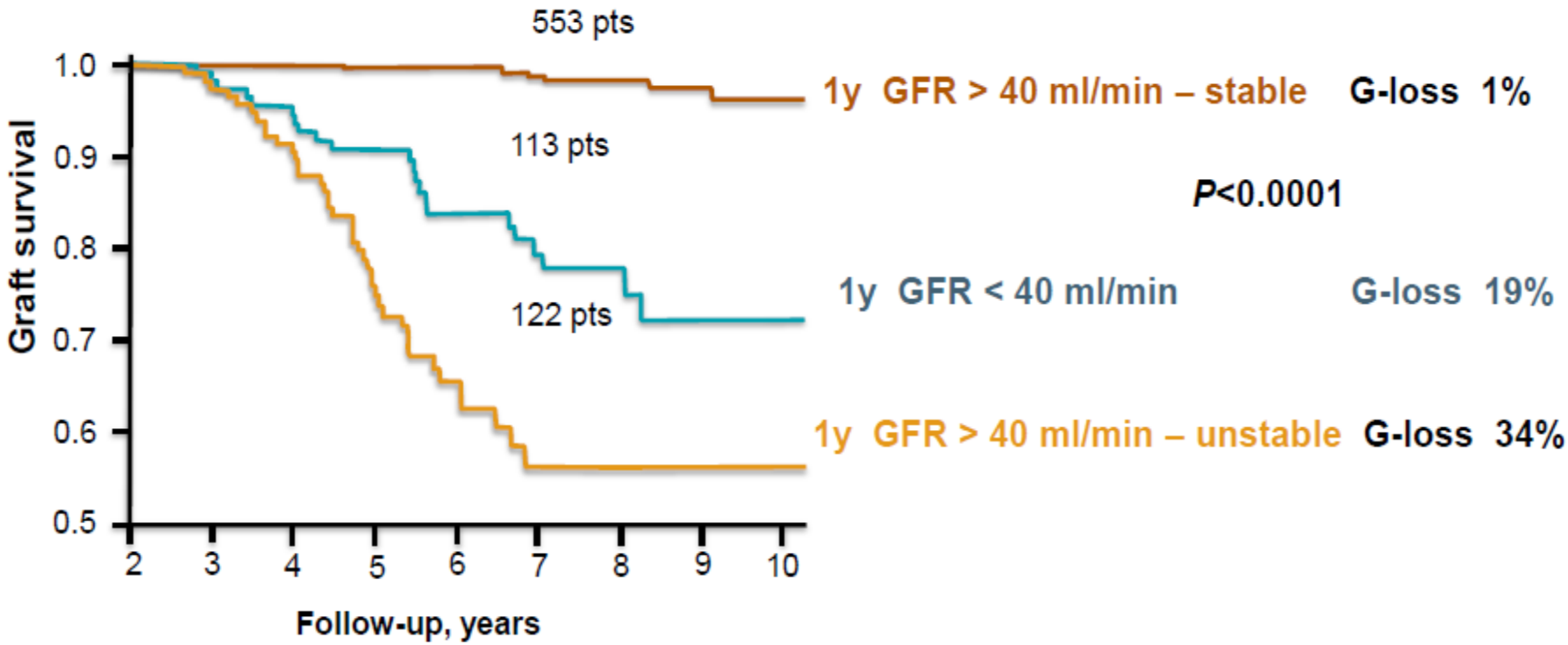
http://dx.doi.org/10.1053/j.ajkd.2010.10.054, How to Cite or Link Using DOI

Table 3. Relationship Between CKD Stage at 12 Months Posttransplant and Subsequent Graft and Patient Survival

CKD Stage (eGFR)	%[a]	HR (95% CI); *P*		
		Graft Failure	Death-Censored	Death With Function
1 (≥90 mL/min/1.73 m^2)	3	1.41 (1.13-1.75); 0.002	1.04 (0.73-1.48); 0.8	1.61 (1.22-2.14); <0.001
2 (60-89 mL/min/1.73 m^2)	24	1.00 (reference)	1.00 (reference)	1.00 (reference)
3a (45-59 mL/min/1.73 m^2)	34	1.13 (1.02-1.25); 0.03	1.25 (1.08-1.44); 0.003	0.98 (0.84-1.13); 0.8
3b (30-44 mL/min/1.73 m^2)	29	1.53 (1.38-1.69); <0.001	2.01 (1.75-2.32); <0.001	1.07 (0.92-1.25); 0.4
4 (15-29 mL/min/1.73 m^2)	9	2.97 (2.63-3.35); <0.001	4.63 (3.95-5.44); <0.001	1.58 (1.30-1.91); <0.001
5 (<15 mL/min/1.73 m^2)	1	14.11 (11.35-17.54); <0.001	26.69 (20.85-34.18); <0.001	2.80 (1.51-5.17); 0.001

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
[a]Percentage of the study population at each CKD stage.

Graft failure rate was higher among the high-eGFR progressors than the low eGFR group (34% vs 19%, *P*<0.0021)



Excluded allografts that failed before 2.5 years posttransplant

Czynniki ryzyka progresji po 1 roku: kolejny przeszczep, płeć żeńska, niestosowanie rATG, białkomocz

Chronic allograft dysfunction

- **Chronic AMR**
- Late acute rejection
- Acute interstitial nephritis of other causes (bacterial)
- Relapse or *de novo* glomerulonephritis
- BK nehropathy, other viral infections
- PTLD
- Medications nephrotoxicity

- Urological complications
- Vascular complications (RAS, TMA)

Differential of the key reason for allograft dysfunction allows therapeutic intervention and slowing the progression

Biopsy is the gold standard in the diagnosis of allografted kidney dysfunction

Natural course of antibody-mediated rejection

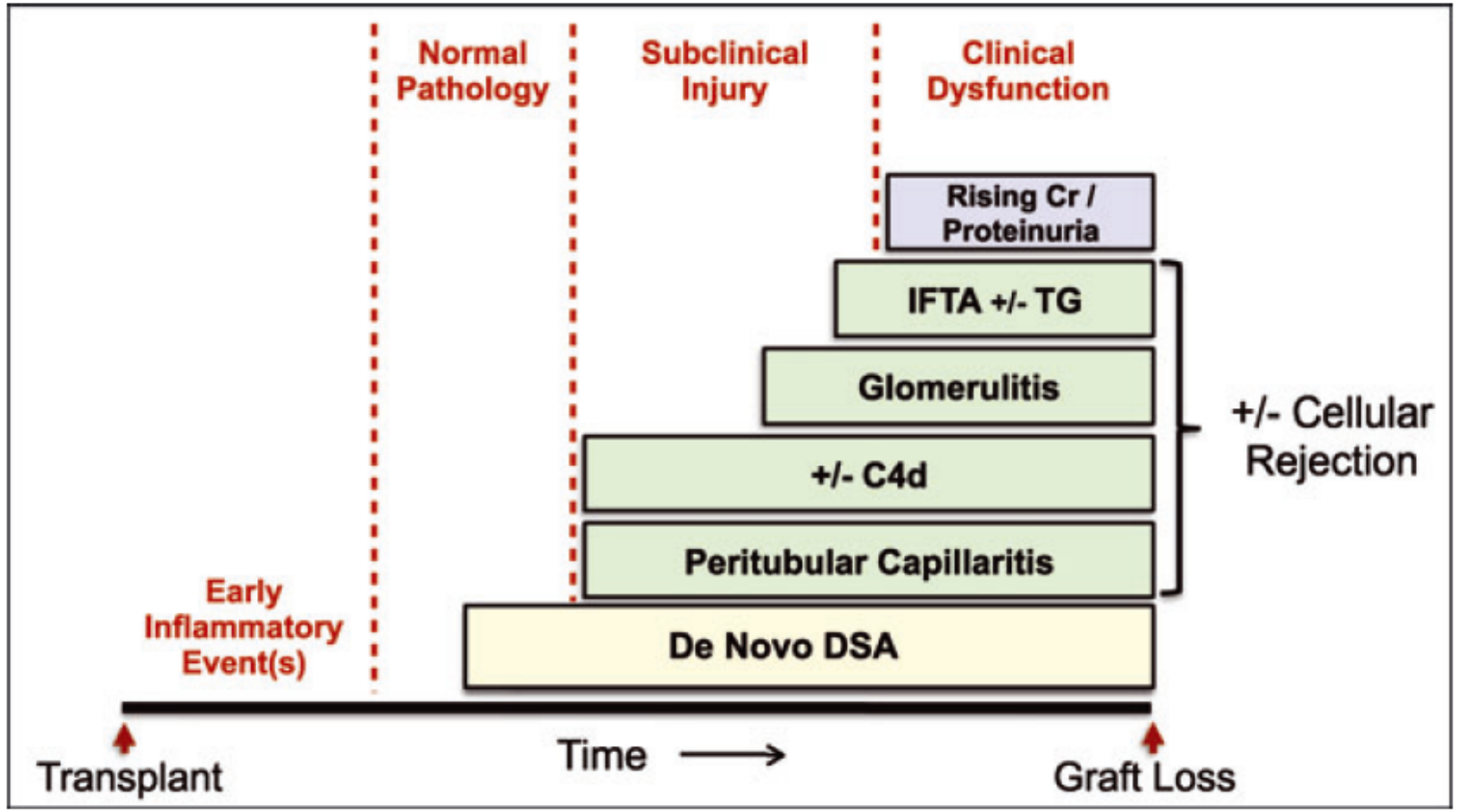


Figure 4: Proposed natural history of dnDSA. This figure shows a proposed model for patients developing *de novo* donor-specific antibodies as they evolve from transplantation to graft failure. IFTA, interstitial fibrosis and tubular atrophy; TG, transplant glomerulopathy. Adapted from Ref.

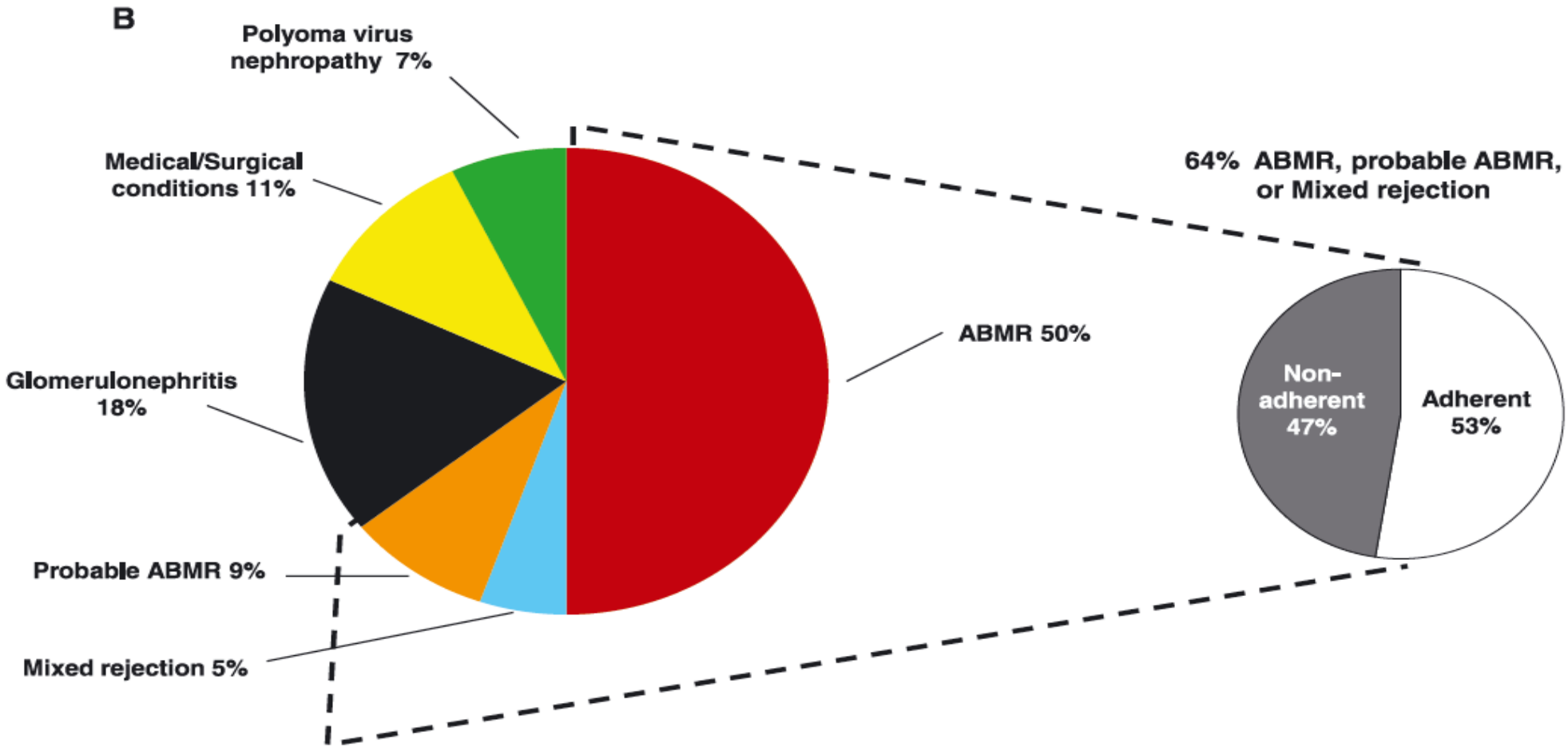


Figure 3: Attributed causes of graft failure in the biopsy-for-cause population. (A) Distribution of the attributed causes of failure (columns) according to the histological diagnosis in the last biopsy available per patient (rows). (B) Distribution of attributed causes of failure. Failures that could not be attributed due to missing clinical information are not represented (n = 4).

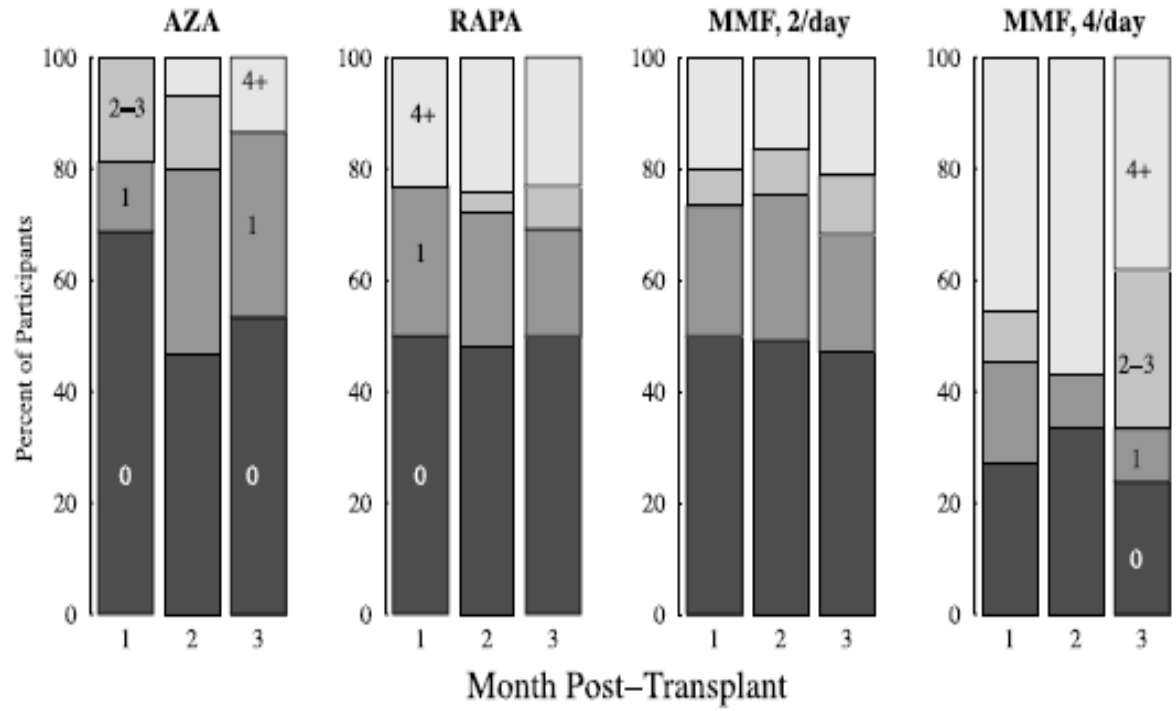


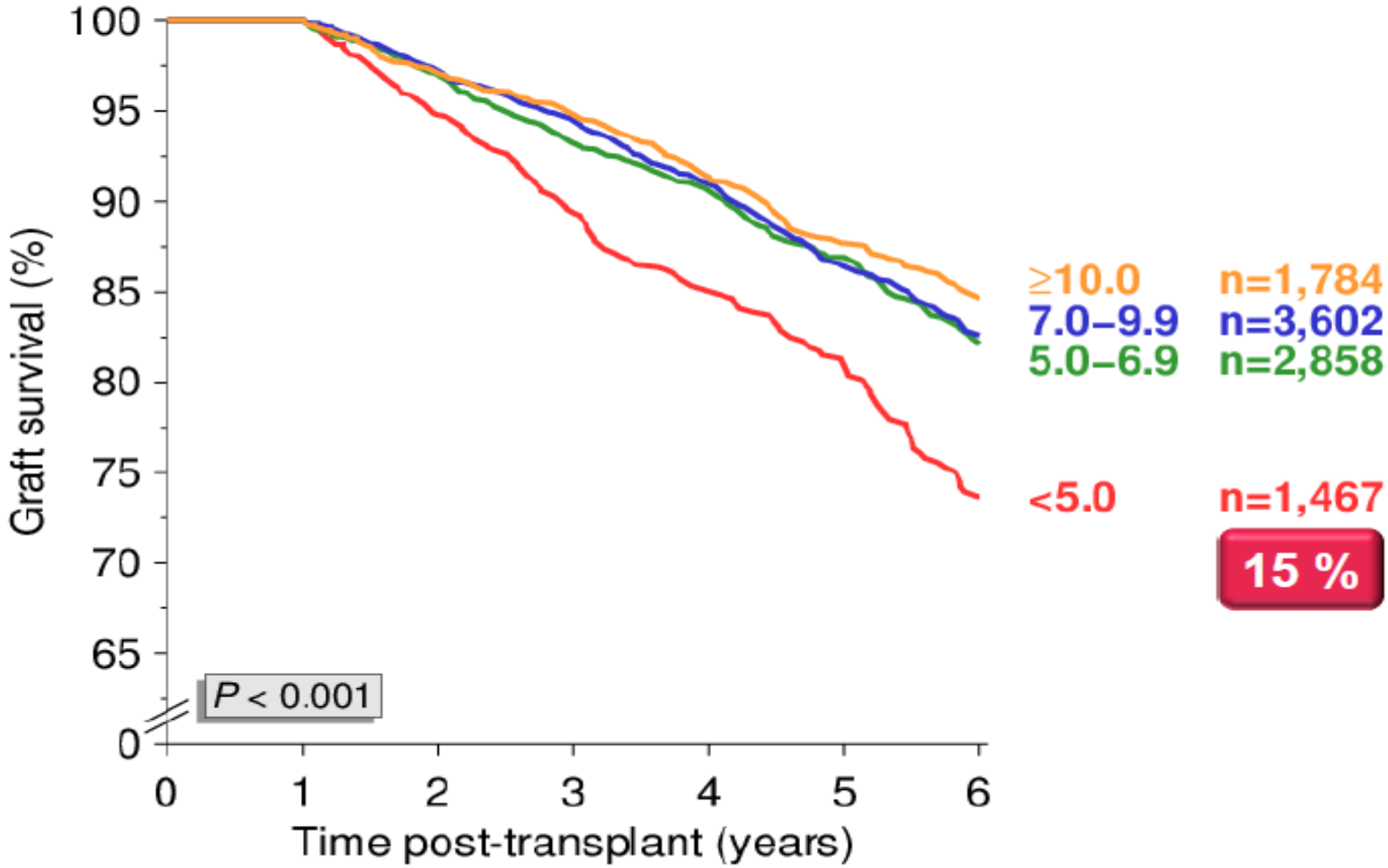
FIGURE 2. Sorted by drug and dose schedule, the *stacked bar graph* displays the percentage of patients missing no, one, two to three, and four or more doses per month during the first 3 months after transplant. There were 16 patients on once-daily azathioprine (Aza), 26 on once-daily sirolimus (Rapa), 124 on twice-daily mycophenolate mofetil (MMF), and 22 on four times-daily MMF. Seven patients were excluded because they either changed drug or dose schedule during the first month or had less than five evaluable days in any month.

Therapeutic drug monitoring

Clinical practice of measuring specific drugs at designated intervals to maintain a concentrations

- Methods
  - EMIT, FPIA, TDx
  - HPLC
  - LC/MC
  - monitoring drug effect (pharmacodynamics)
  - evaluating for pharmacogenetics

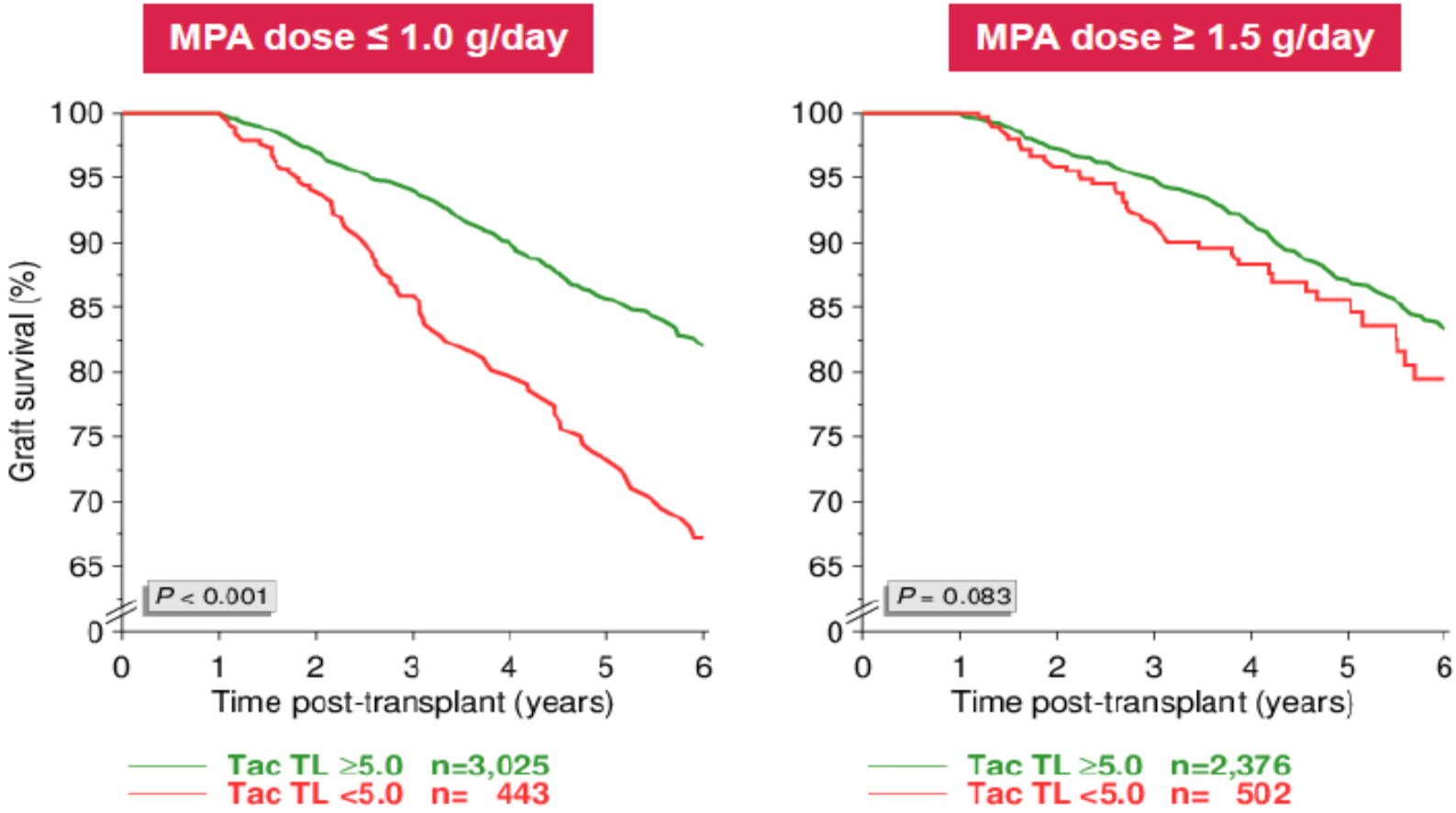
Trough level at year 1 (ng/ml)



CTS Collaborative Transplant Study

Personal communication, update to:
CTS Newsletter 1:2014

Trough level and MPA dose at year 1



CTS Collaborative Transplant Study

Personal communication, update to:
CTS Newsletter 1:2014

Glomerulonephritis of the transplant

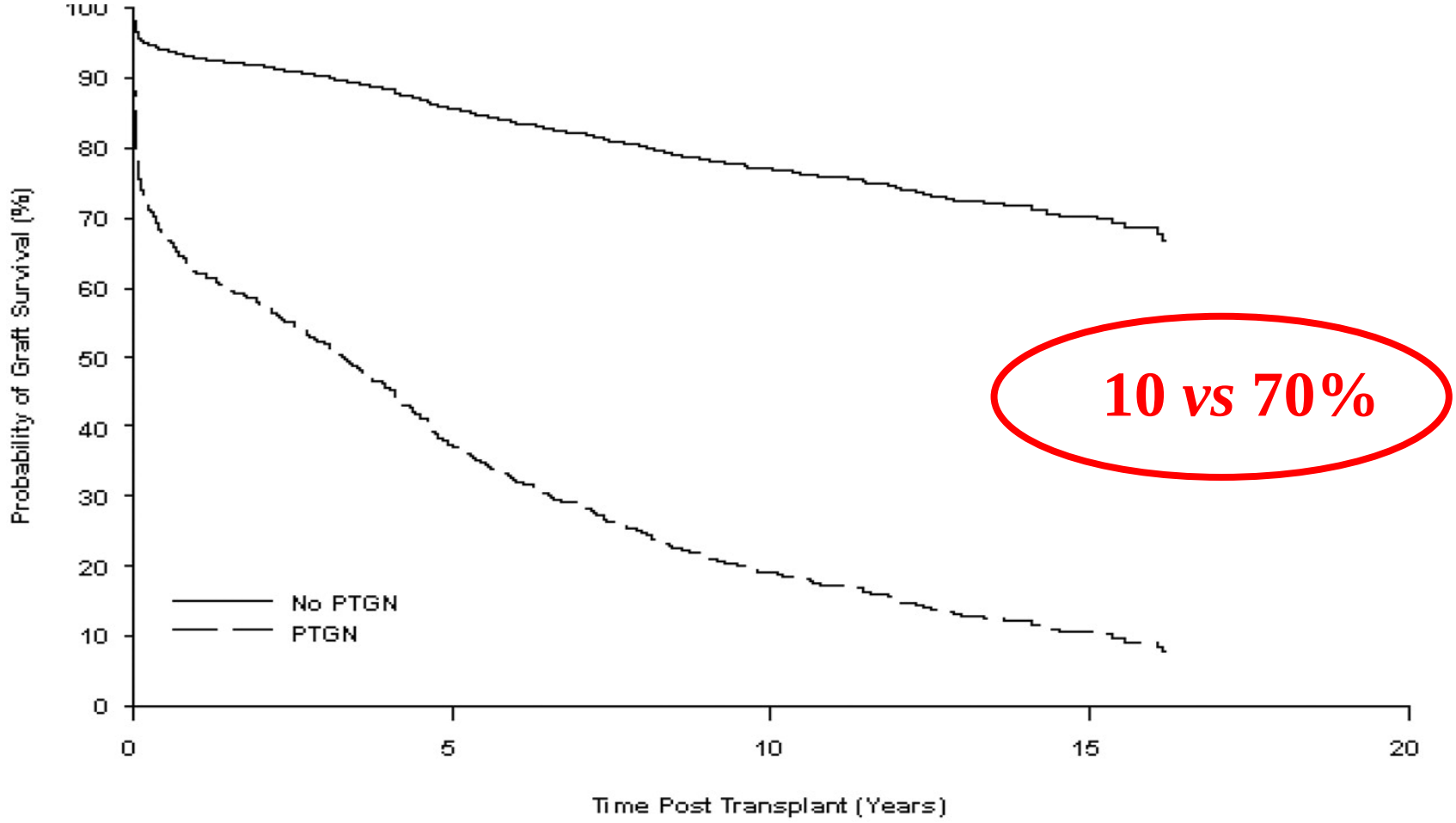
- relaps ? de novo? undefined ?
- Clinical presentation: proteinuria, erythrocyturia, hypertension, failing graft
- Differential of GN and chronic rejection
- Diagnosis based on biopsy with IFL, ME
- In protocol biopsies early relapse may be diagnosed before clinical presentation

IS regimen does not influence the risk of relapse and graft deterioration

FSGS		
IgAN	0 *vs* Aza *vs* MMF	ns
NM	0 *vs* CsA *vs* Tac	
MPGN	0 *vs* Sir	
LN	0 *vs* pred	
other GN		
undefined GN		

Mulay AV American Journal of Transplantation 2009;9:804-811

The impact of post-transplant glomerulopathy on the long-term graft survival



Chailimpamontree W. J Am Soc Nephrol. 2009

Clinical indications for graftectomy

- hematuria
- Proteinuria
- Graft swelling and tenderness
- Recurrent UTI
- Uncontrolled hypertansion
- Chronic inflamation
- Resistance to ESA reatment
- FUO

Standard evaluations in outpatient care for Ktx recispients

test	With-in first year	From second year
Serum creatine, eGFR	1-2 months	3 months
Urinalysis proteinuria	1-2 months	3 months
Whole blood count	1-2 months	3 months
Fasting glucose	1-2 months	3 months
Lipids	6 Months	6 months
BKV, EBV, CMV DNA	3 months	6 months
Calcium, phosphates	3 months	3 months
IS concentrations	1-2 months	3 months
DSA	3 months	12 months
Abdominal and gfaft US	When indicated	12 months
Chest X ray	Wlen indicated	12 months