Management of Chronic Allograft Dysfunction

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Objectives

- Definition
- Importance
- Etiology
- Specific Strategies by Etiology
- Important Co-morbidities
- CKD Management
- The Failing Allograft

Definition

- GFR in most transplanted kidneys is well below normal

- A reduction in kidney function of more than 20%

OR

- Transplanted kidneys that have never worked well

Importance

- Patients with kidneys with chronic allograft dysfunction are at higher risk of graft loss and death
- Important morbidity and mortality associated with deteriorating renal function

- Important to prevent or delay deterioration of function

Diagnosis of Cause

- Search for reversible contributors

- History/Physical/Urinalysis
- Exclude obstruction with imaging
- DSA
- BK

Biopsy

- Biopsy if:

  -persistent serum creatinine rise of >/= 20% without other cause

  -24 hr urine protein of >/= 0.5-1 gm

  -new DSA positive especially if Class II

Causes of Allograft Dysfunction

- Donor derived
- Interstitial Fibrosis/Tubular Atrophy
- Acute and chronic rejection
  - -T cell
  - -Antibody mediated
- Recurrent or de novo glomerular disease
- BK Nephropathy
- CNI toxicity/Other drugs
- Vascular
- Urinary Tract Obstruction/infection

Monitoring

- Early detection is optimal

- Serum Creatinine - ?frequency
- Urinary Protein
- DSA
- BK

Immunologic

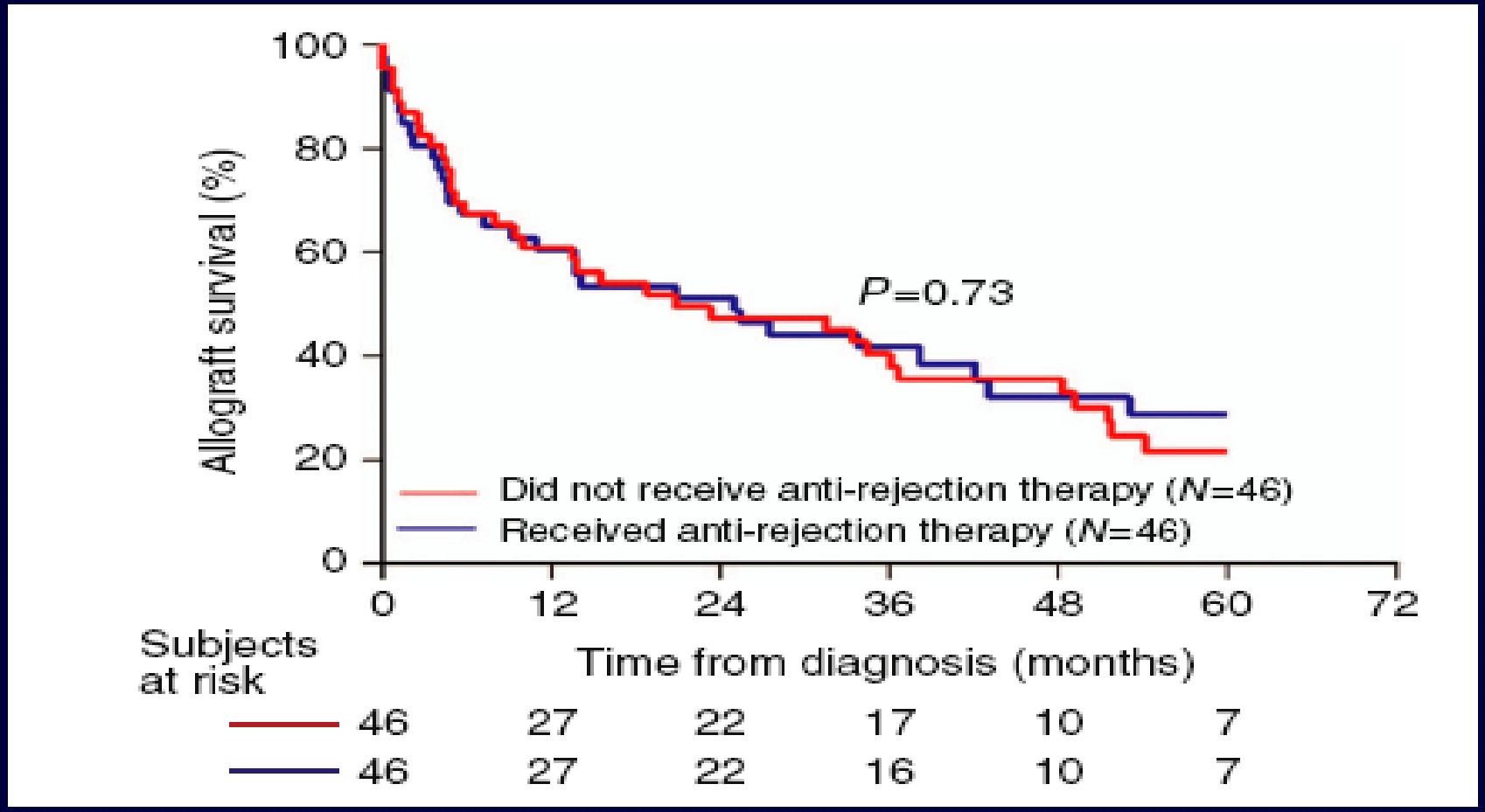
Late AMR – Hopkins Experience

Transplantation, 2014

- Reviewed 23 consecutive cases
- Preceded by reduction of immunosuppression in 20 cases
- 4 nonadeherence, MD reduction in 16
- Treated with IVIg, Rituximab, plasma exchange +/- bortezomib
- Following treatment 35% had improvement in function but no long term benefit in most
- 22% significant infection

Graft Survival in Patients Who Did vs Did Not Receive Therapy After Diagnosis of Transplant Glomerulopathy

Patri et al Kidney Int, 2016



Concerns About Immunosuppression Minimization

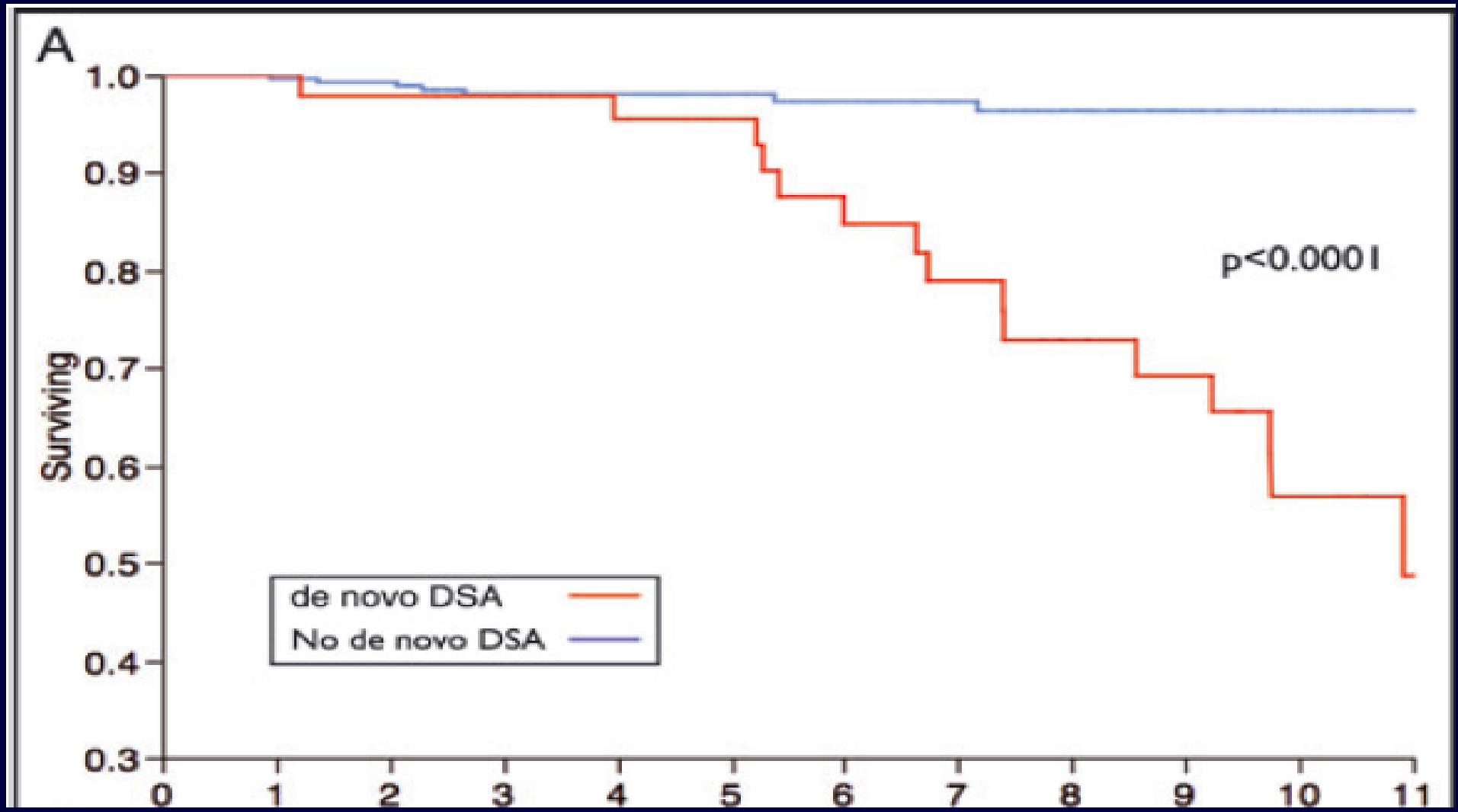
Rush and Gibson Current Opinion in Nephrology and Hypertension

KEY POINTS

- Rejection, often due to de-novo Class II donor-specific antibody (DSA), is the most common cause of renal transplant loss.
- Minimization of immunosuppression is often the cause of de-novo DSA development.
- Better HLA Class II matching and avoidance of excessive minimization of immunosuppression should lead to better graft outcomes.

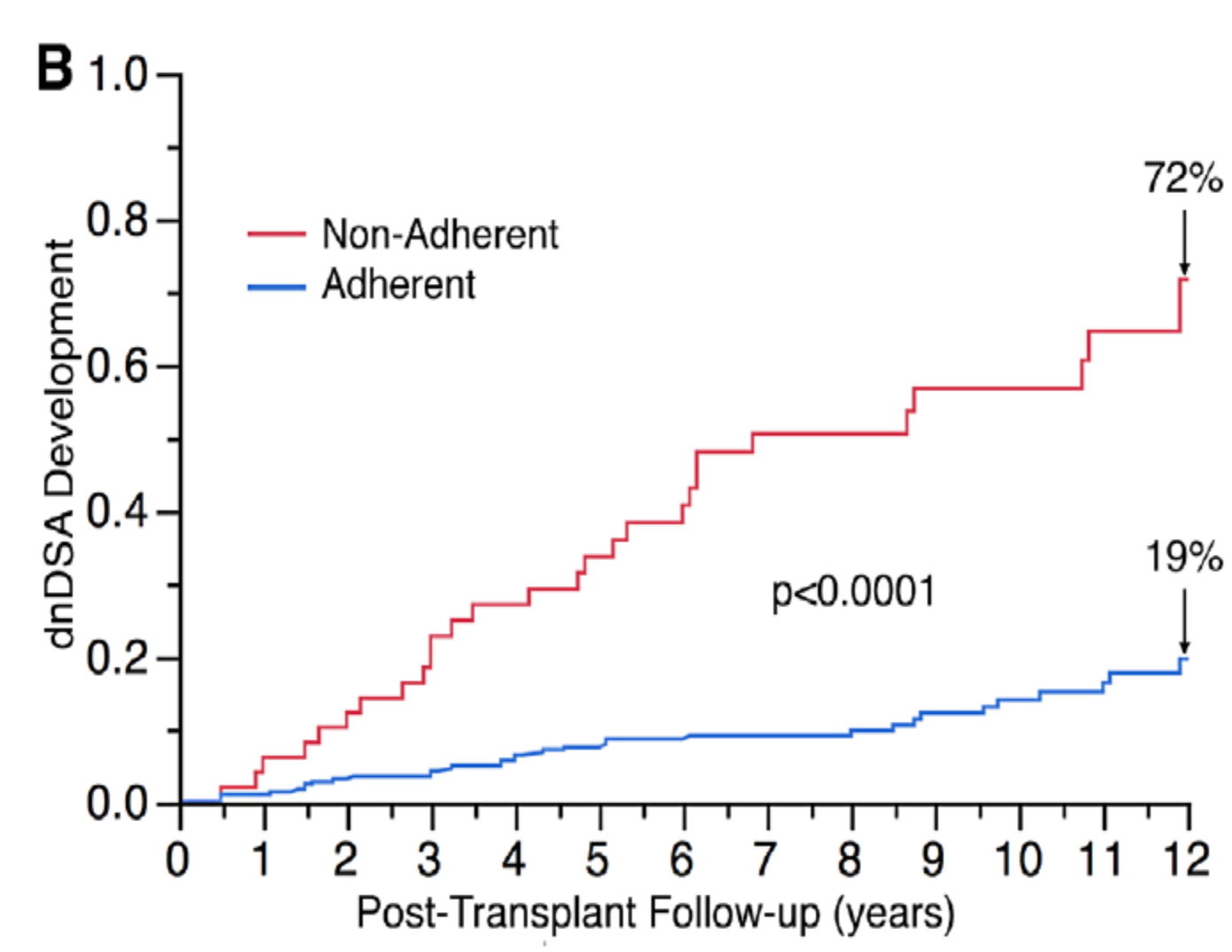
De Novo Post Transplant DSA and Graft Survival

Wiebe et al AJT, 2012



De Novo DSA vs Adherence

Wiebe et al AJT, 2015



Decision Analysis of DSA Screening After Year 1 Post Transplant

Kiberd et al AJT, 2016

Table 2: Base case analysis with variable treatment intervention efficacy (risk reduction in graft loss)

Baseline efficacy	Costs 2013 US $	QALYs years	Incremental costs $	Incremental QALYs	Cost effectiveness $Costs/QALY
0.65 risk reduction					
No Screen	439 486	12.281			
Screen	448 467	12.327	8981	0.0707	127 120
0.75 risk reduction					
No Screen	439 486	12.281			
Screen	449 048	13.351	9563	0.04618	207 066
0.85 risk reduction					
No Screen	439 486	12.281			
Screen	449 595	12.3037	10 109	0.0227	444 258

QALY, quality-adjusted life year.

DSA Monitoring-Caveats

Ma et al AJT, 2015

- Quality assurance in antibody testing is foundational
- Requires correlation with function and pathology
- Treating to elimination of DSA may not be feasible and risk of toxicity without consistent benefit
- Efficacy of treatment for late rejection unclear
- Further research required to assess benefits, harms and economic feasibility

Calcineurin Inhibitor Nephrotoxicity

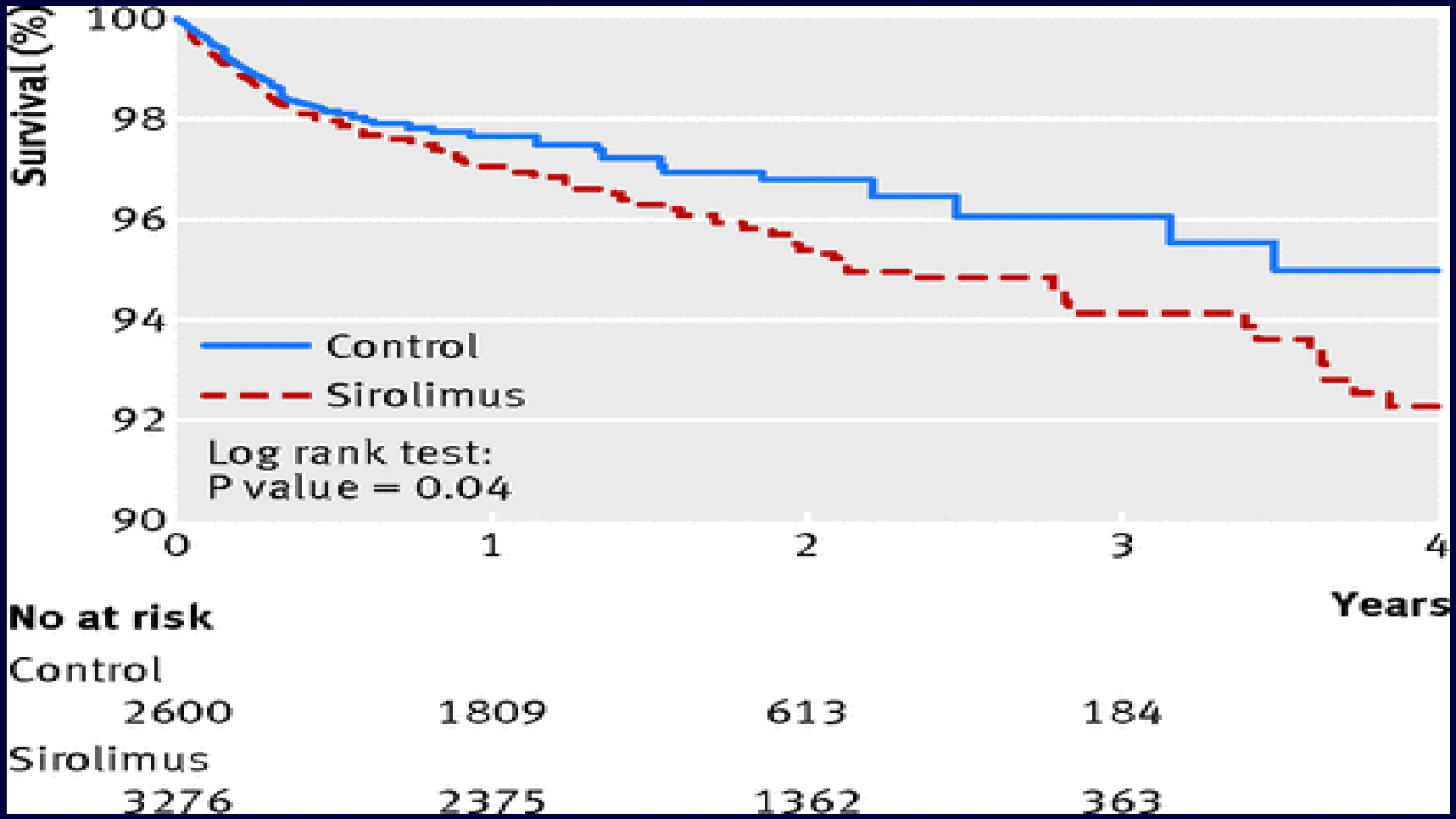
Issa et al Am J Nephrol, 2013

- It is clear that CNI are nephrotoxic
- However the role of chronic CNI nephrotoxicity in graft loss is controversial

- Specific pathologic lesion for CNI toxicity usually absent
- CNI levels have not correlated with IF/TA
- Carefully done protocol biopsy study from Mayo shows other causes of allograft failure in majority of cases
- Multiple studies show evidence of immune activation and/or antibody mediated injury in most cases of IF/TA

Survival Post Transplant SRL vs Other

Knoll et al, 2014



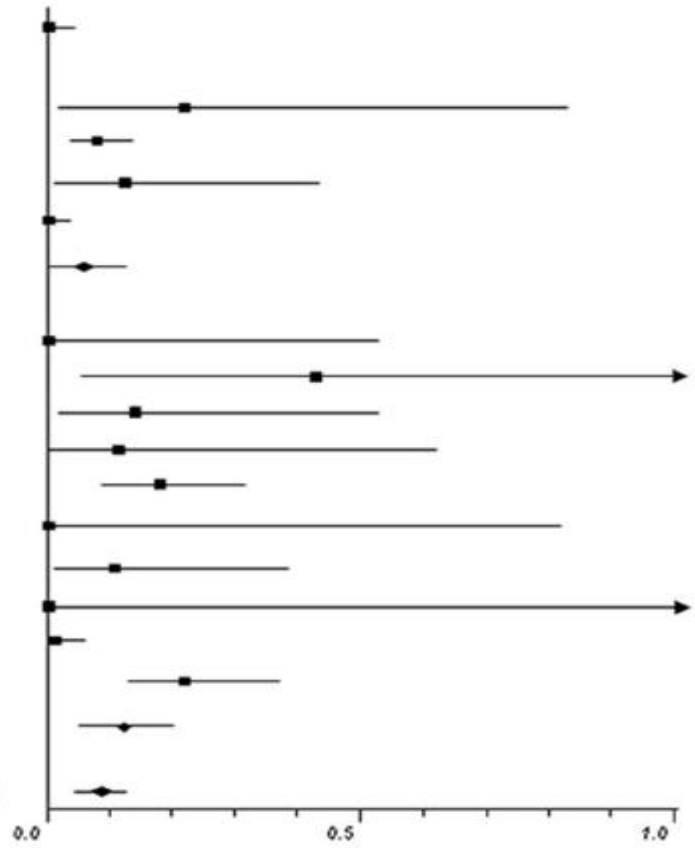
Approach to BK Virus

- Most successful strategies are those initiated early before nephropathy present
- Monitor regularly for first 2 years post transplant

Systematic Review of BK Virus Treatment By Reduction in Immunosuppression

Johnston et al Transplantation, 2010

	Study Name	Graft Fails	Person-years	Poisson Rate and 95% CI
Immunosuppression reduction alone				
RCT	Brennan, 2005	0	70	0.00 (0.00, 0.05)
Cohort	Limaye, 2001	2	8.7	0.23 (0.03, 0.83)
	Ramos, 2002	11	145.2	0.08 (0.04, 0.14)
	Nampory, 2005	2	16.7	0.12 (0.02, 0.43)
	Giraldi, 2007	0	90	0.00 (0.00, 0.04)
	Pooled Rate (Cohort)	15	260.6	0.06 (0.00, 0.12)
Case-Series	Mathur, 1997	0	7	0.00 (0.00, 0.53)
	Howell, 1999	2	4.6	0.44 (0.05, 1.57)
	Barri, 2001	2	13.7	0.15 (0.02, 0.53)
	Li, 2002	1	9	0.11 (0.003, 0.62)
	Celik, 2003	11	62	0.18 (0.09, 0.32)
	Wali, 2004	0	4.5	0.00 (0.00, 0.82)
	Kim, 2005	2	18.8	0.11 (0.01, 0.39)
	Funk, 2006	0	2.3	0.00 (0.00, 1.60)
	Saad, 2008	1	87	0.01 (0.00, 0.06)
	Weiss, 2008	16	70	0.23 (0.13, 0.37)
	Pooled Rate (Case Series)	35	278.9	0.12 (0.04, 0.21)
	Pooled Rate (Cohort / Case Series)	**50**	**539.5**	**0.08 (0.04, 0.12)**



Effect of Addition of Cidofovir or Leflunomide

Johnston et al Transplantation, 2010

Immunosuppression reduction plus Cidofovir

Cohort	Kuypers, 2005	0	16.5	0.00 (0.00, 0.22)
Case-Series	Scantlebury, 2002	4	20	0.2 (0.05, 0.51)
	Ramos, 2002	2	7	0.29 (0.04, 1.03)
	Lim, 2003	1	6.3	0.16 (0.004, 0.88)
	Kadampi, 2003	0	4.3	0.00 (0.00, 0.87)
	Tong, 2004	0	7.5	0.00 (0.00, 0.49)
	Araya, 2006	0	8	0.00 (0.00, 0.46)
	Josephson, 2006	2	3.5	0.57 (0.07, 2.06)
	Benavides, 2007	5	32.5	0.15 (0.05, 0.36)
	Pooled Rate (Case series)	14	89.1	0.12 (0.05, 0.18)
	Pooled Rate (Overall)	**14**	**105.6**	**0.08 (0.03, 0.13)**

Immunosuppression reduction plus Leflunomide

Case-Series	Josephson (Leflunomide), 2006	1	9.5	0.11 (0.003, 0.59)
	Josephson (Leflunomide&Cidofovir), 2006	2	3.5	0.57 (0.07, 2.06)
	Leca (Low-level Leflunomide), 2008	3	16	0.19 (0.04, 0.55)
	Leca (High-level leflunomide), 2008	1	12	0.08 (0.002, 0.46)
	Pooled Rate	**7**	**41**	**0.13 (0.02, 0.23)**

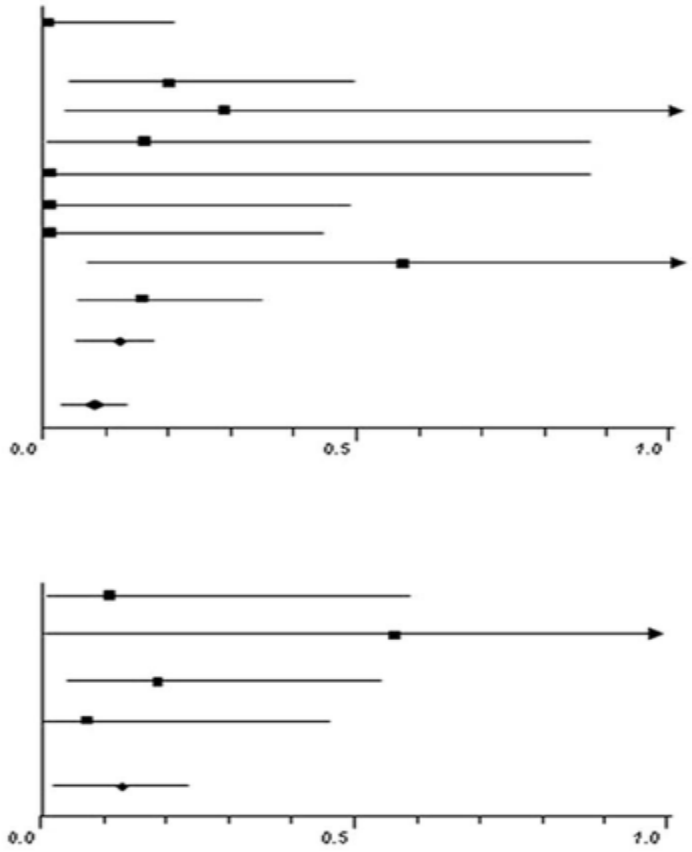


FIGURE 2. Rates of kidney transplant failure with specific therapies. RCT, randomized controlled trial.

Limitations

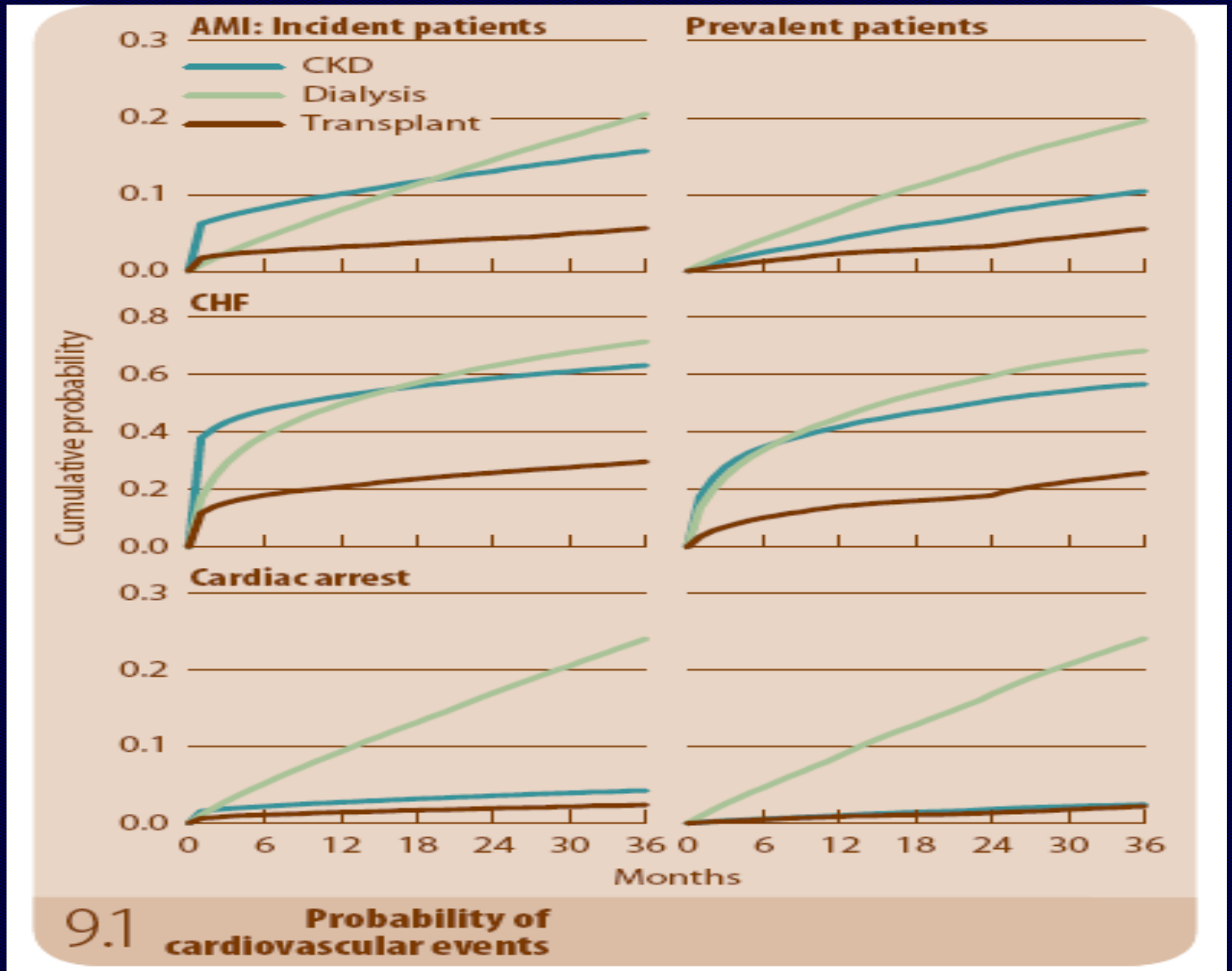
- Studies on patients with BK Nephropathy and not on those with positive PCR before nephropathy develops
- Little randomized controlled data
- Studies all small sample size
- While this study suggests limited benefit of drugs, it is not definitive
- IVIg also unproven and expensive

IMPORTANT CO-MORBIDITIES

Cardiovascular

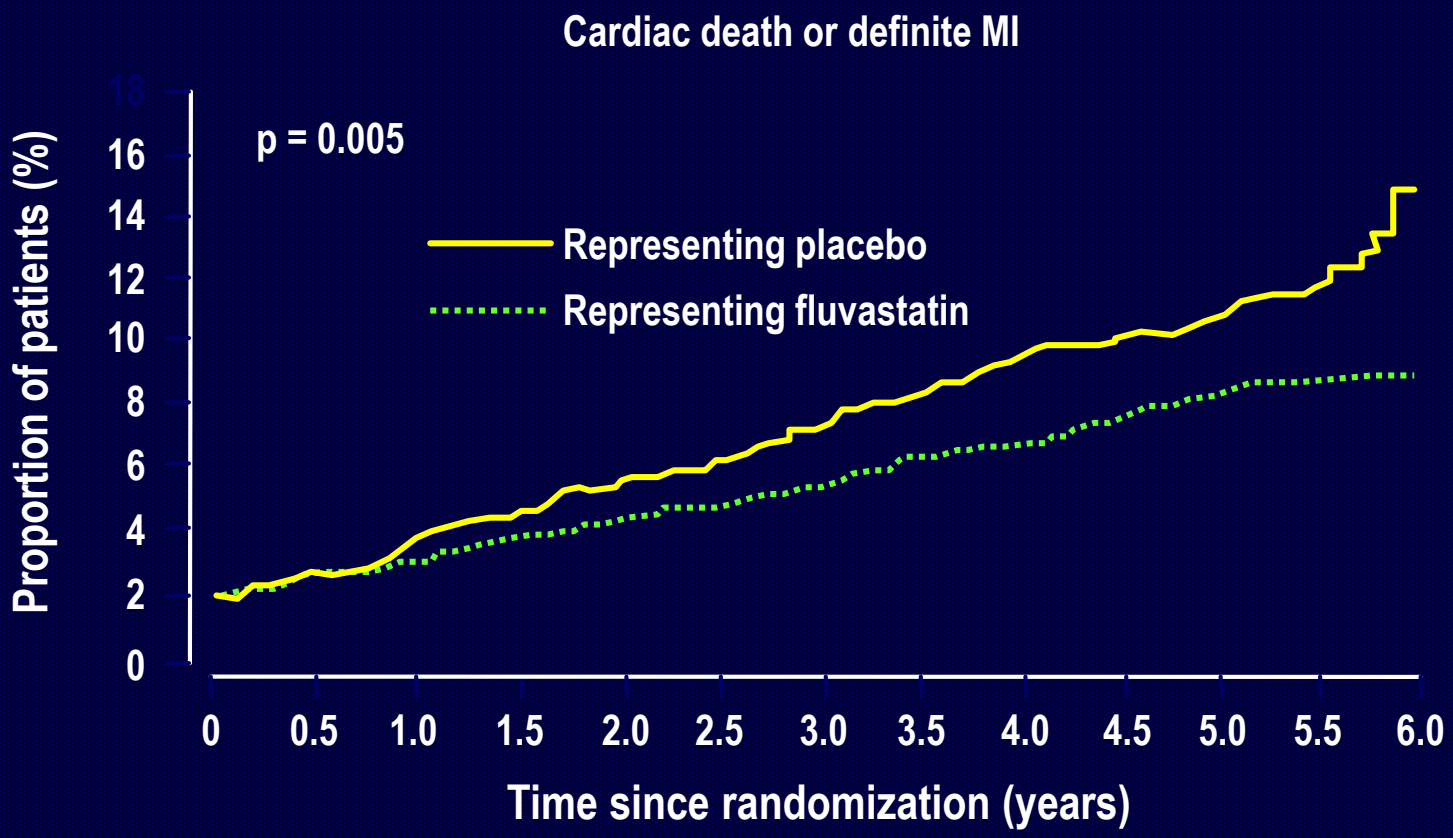
Rate of Cardiac Events in Incident and Prevalent ESRD Patients

USRDS Report AJKD, 2006



9.1 Probability of cardiovascular events

The ALERT trial: effect of fluvastatin on cardiac death or nonfatal MI



N = 2,102 RTRs receiving either fluvastatin or placebo; follow-up 5-6 years

Holdaas H. Lancet 2003;361:2024

Ca Channel Blockers and ACE inhibitors vs Placebo – Systematic Review and Meta Analysis

Cross et al Transplantation, 2009

TABLE 2. Summary of major outcomes across the 3 most commonly investigated comparisons

Outcome (dichotomous)	CCB vs. placebo/no treatment		CCB vs. ACEi		ACEi vs. placebo/no treatment	
	Trials (patients)	RR (95% CI)	Trials (patients)	RR (95% CI)	Trials (patients)	RR (95% CI)
Mortality	12 (804)	0.75 (0.35–1.62)	2 (221)	0.25 (0.03–2.22)	1 (30)	1.00 (0.07–14.6)
Graft loss	17 (1255)	0.75 (0.57–0.99)	1 (152)	0.14 (0.007–2.56)	2 (93)	Heterogeneous
Acute rejection[a]	10 (771)	1.02 (0.85–1.23)	2 (221)	Heterogeneous	1 (30)	0.9 (0.5–1.6)
Hyperkalemia			3 (211)	0.27 (0.13–0.53)		

Ramipril vs Placebo in Renal Transplant Recipients With Proteinuria

Knoll et al Lancet Diabetes Endocrinology, 2016

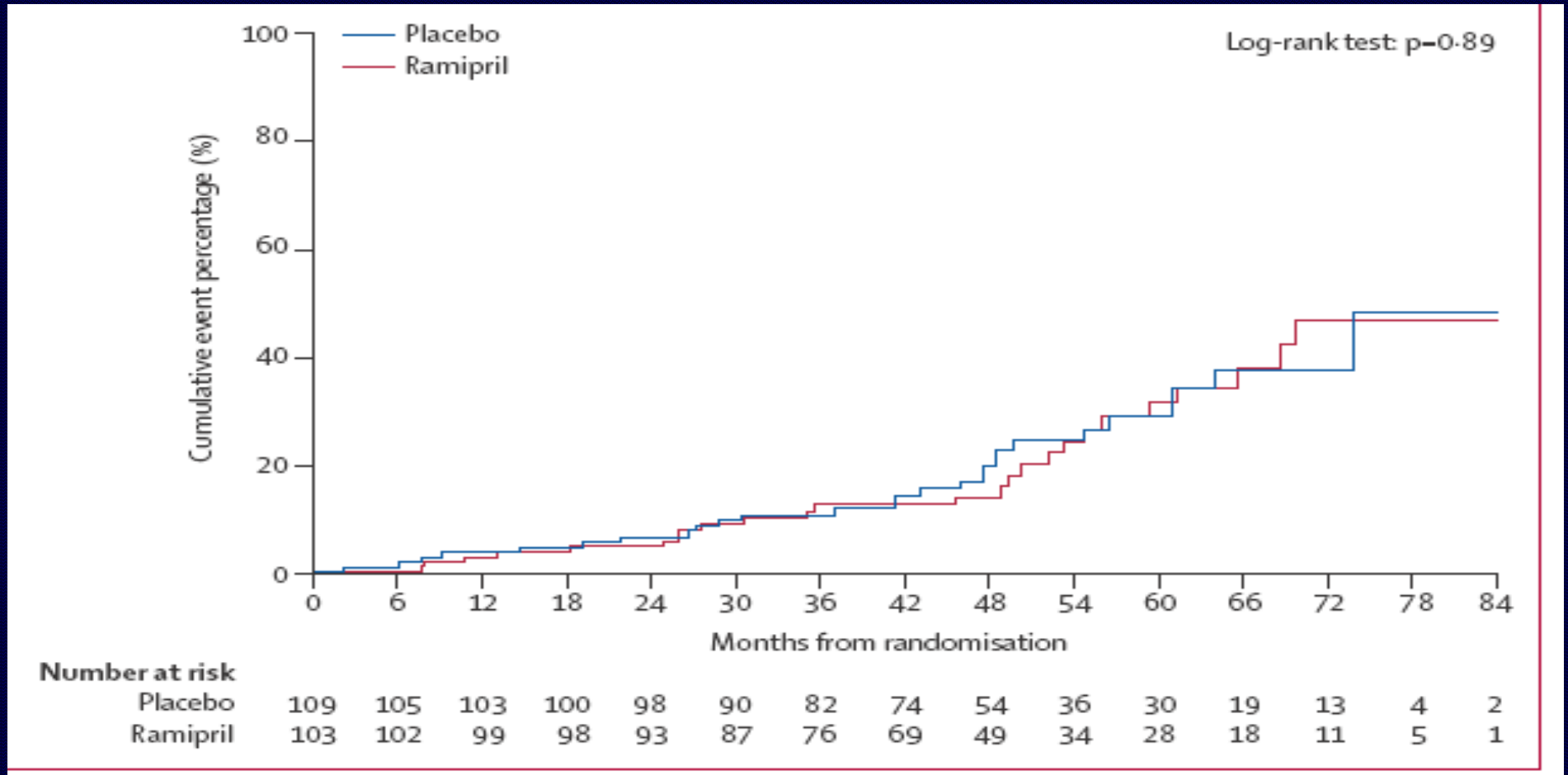
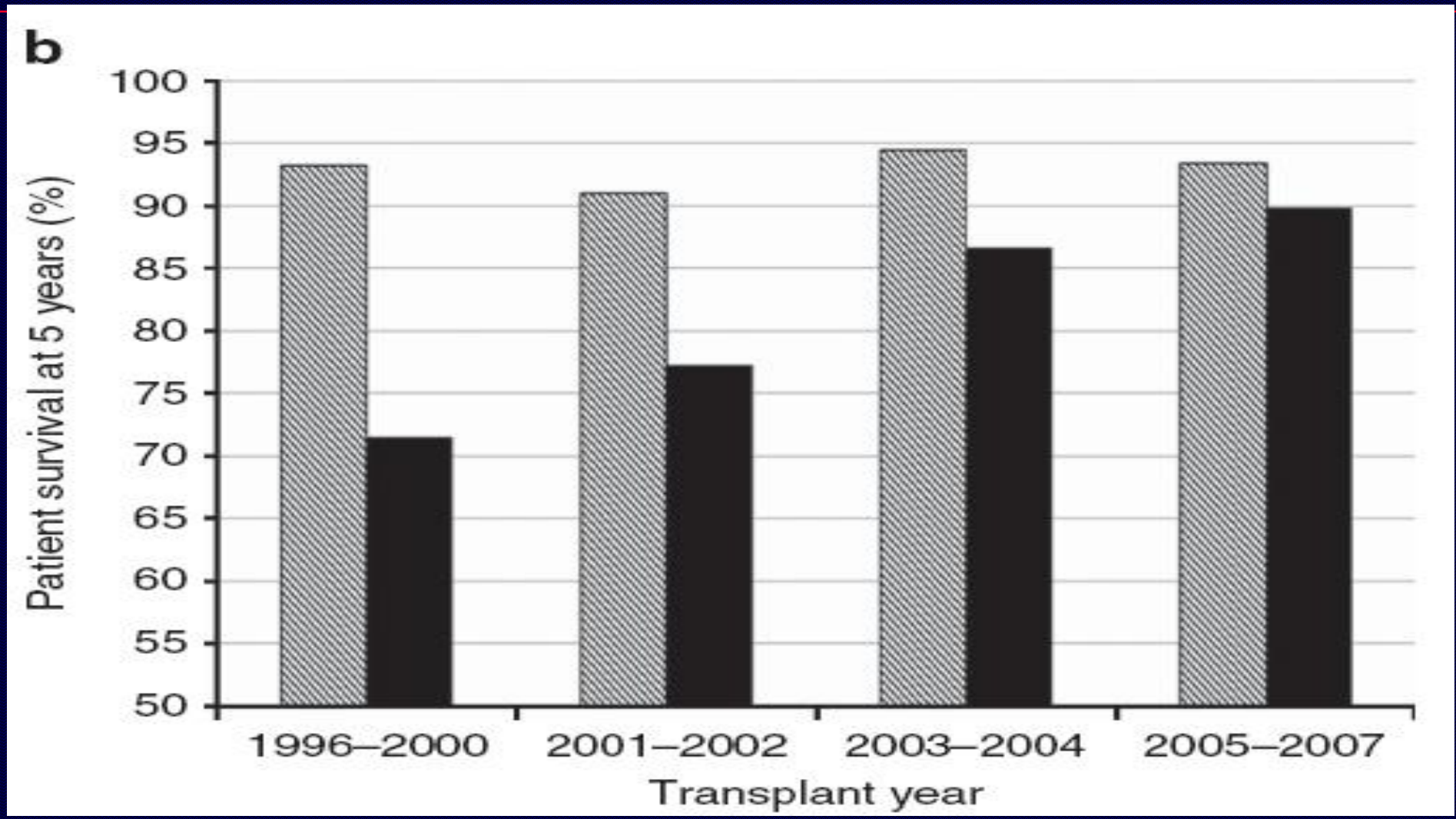


Figure 2: Time to the primary outcome of doubling serum creatinine, end-stage renal disease or death during the extension phase of the study

Improvement in Post Transplant Mortality in Diabetic Recipients

Keddis et al Kidney Int 2014



Diabetes

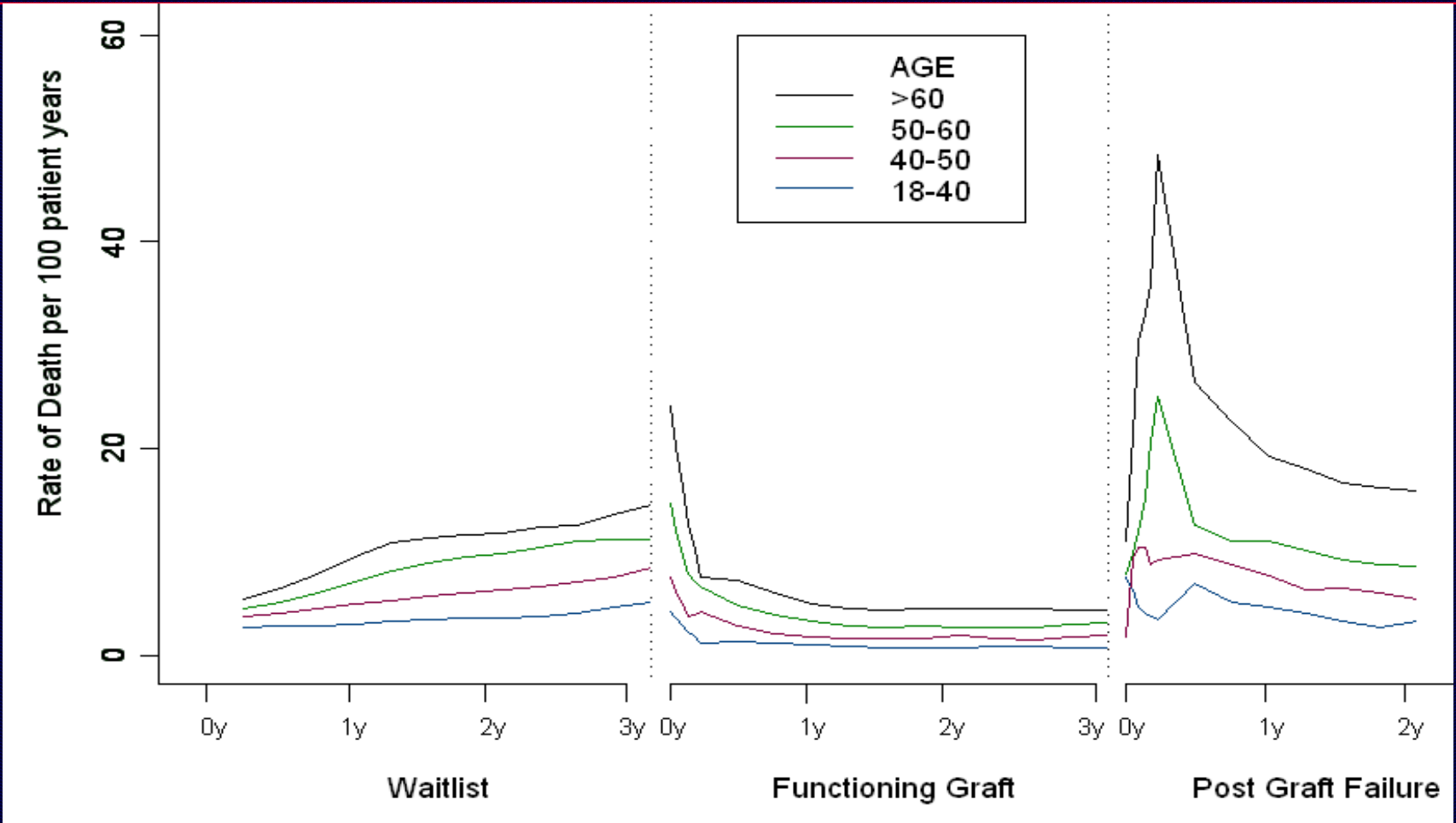
- Highest morbidity/mortality group
- Careful attention to new glucose intolerance
- Optimize glucose control
- Lower LDL targets (<2 mM)
- Lower threshold for cardiac testing

CKD Management

- These patients have significant chronic kidney disease
- Usual guidelines re:
  - -Anemia
  - -Calcium and Phosphate
  - -Bone Disease
  - -Acid/Base

The Failing Allograft

Mortality after allograft failure



Gill et al. KI 2007

Factors Associated With Death After Graft Failure

Johnston et al JASN, 2007

Table 3. Factors associated with death after transplant failure

Variable	HR	95% CI	*P*
Septicemia	2.93	2.64 to 3.24	<0.001
Multiple sepsis episodes (referent group one sepsis episode)	1.47	1.26 to 1.73	<0.001
Age at transplant failure ≥60	2.20	1.98 to 2.46	<0.001
BMI			
≥30	0.84	0.74 to 0.96	0.01
<20	1.01	0.86 to 1.18	0.93
Female	1.05	0.95 to 1.16	0.38
Race			
black	0.80	0.72 to 0.89	<0.001
other	0.53	0.40 to 0.71	<0.001
Diabetes	1.89	1.70 to 2.09	<0.001
Dialysis modality after transplant failure (hemodialysis)	0.97	0.81 to 1.17	0.75
Duration of allograft survival			
<1 yr	0.90	0.79 to 1.04	0.14
1 to 3 yr	1.09	0.96 to 1.24	0.17
Donor type cadaveric	1.23	1.10 to 1.39	<0.001
PVD	1.027	0.83 to 1.27	0.80
CHF	1.16	1.01 to 1.34	0.04
IHD	1.57	1.33 to 1.85	<0.001
CVA	0.97	0.73 to 1.30	0.86
Induction therapy			
depleting	0.90	0.81 to 1.01	0.07
nondepleting	0.84	0.73 to 0.96	0.01
neither	1.00		

Why Are Mortality and Septicemia Rates so High in Failed Allografts?

- Fragmentation of care
- Less than optimal CKD management by Transplant MD's/Late dialysis start
- Lack of optimal hemodialysis access
- Graft intolerance syndrome = chronic inflammatory state
- Over Immunosuppression

  -Immunosuppression

  -Added impact of uremia if late dialysis start

UK Guidelines For Failing Allograft,

Andrews Transplantation 2014

- We suggest that CNI targets be reduced when GFR below 20 ml/min (2C-low)
- We recommend considering the relative risk of benefits of tapering or withdrawal immunosuppression vs risk of sensitization and likelihood of future transplantation (1D-very low)
- If there is likelihood of retransplantation within 1 year we suggest immunosuppression be continued (2C-low)
- We suggest immunosuppression be withdrawn after graft failure if there have been severe complications, or delay in re transplantation (2C-low)

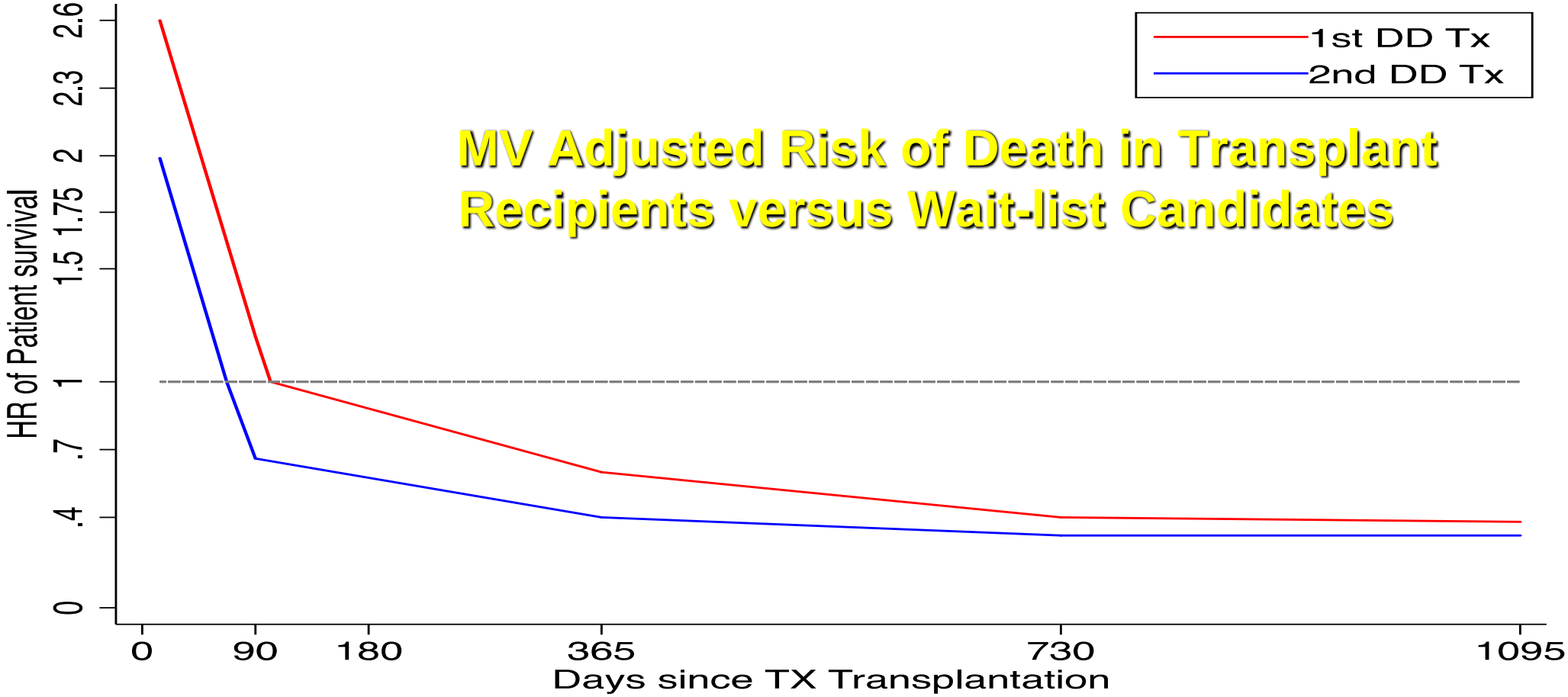
Conclusions

- Patients with chronic graft dysfunction at higher risk of graft failure and death
- Approach should seek to define contributing factors and treat if feasible
- Unless severe or recurrent infection or malignancy occur, immunosuppression should be continued at usual doses while acceptable function

- **CKD and cardiovascular management should be optimal**

- **Consideration of future transplantation, planning for dialysis and its optimal initiation are critical**

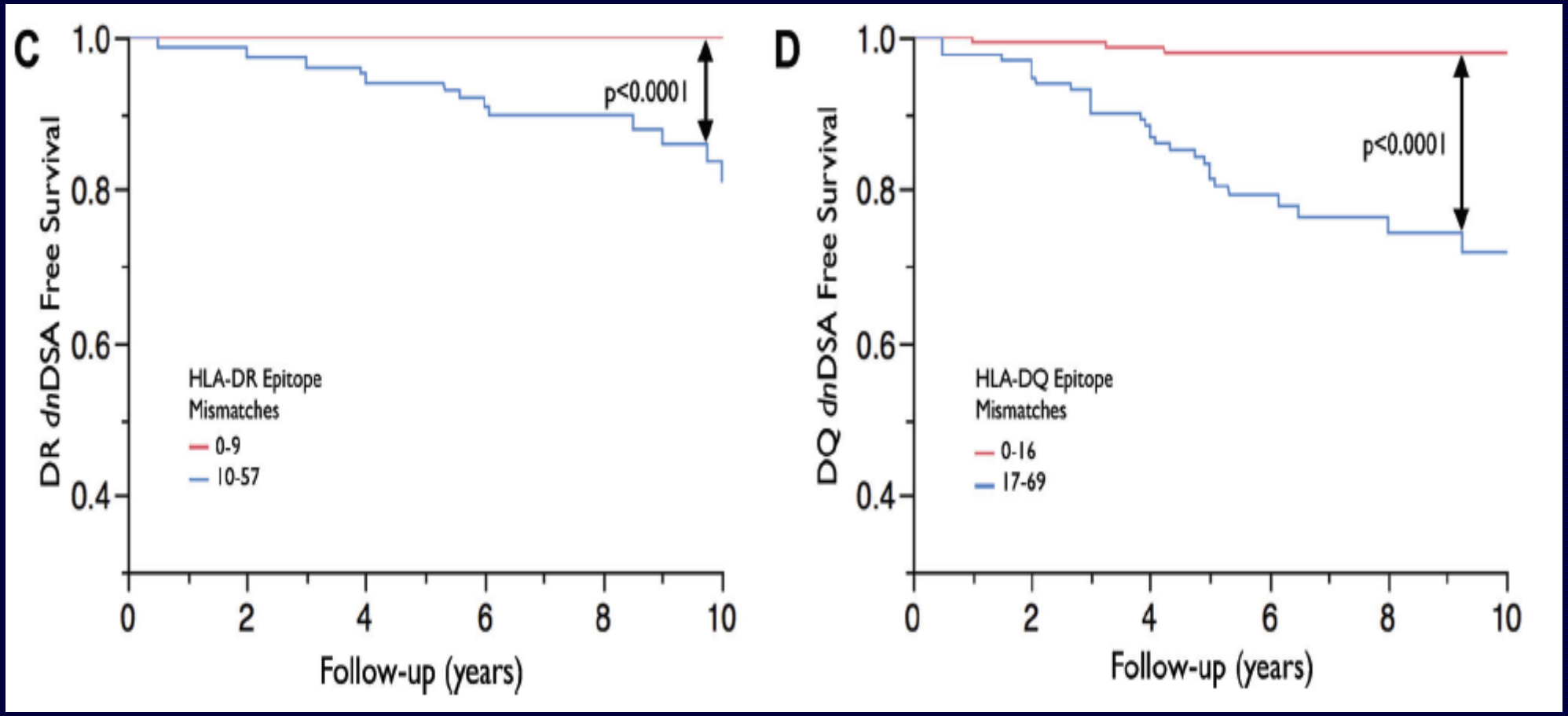
Re-transplantation provides a survival advantage



Gill et al. WTC 2014

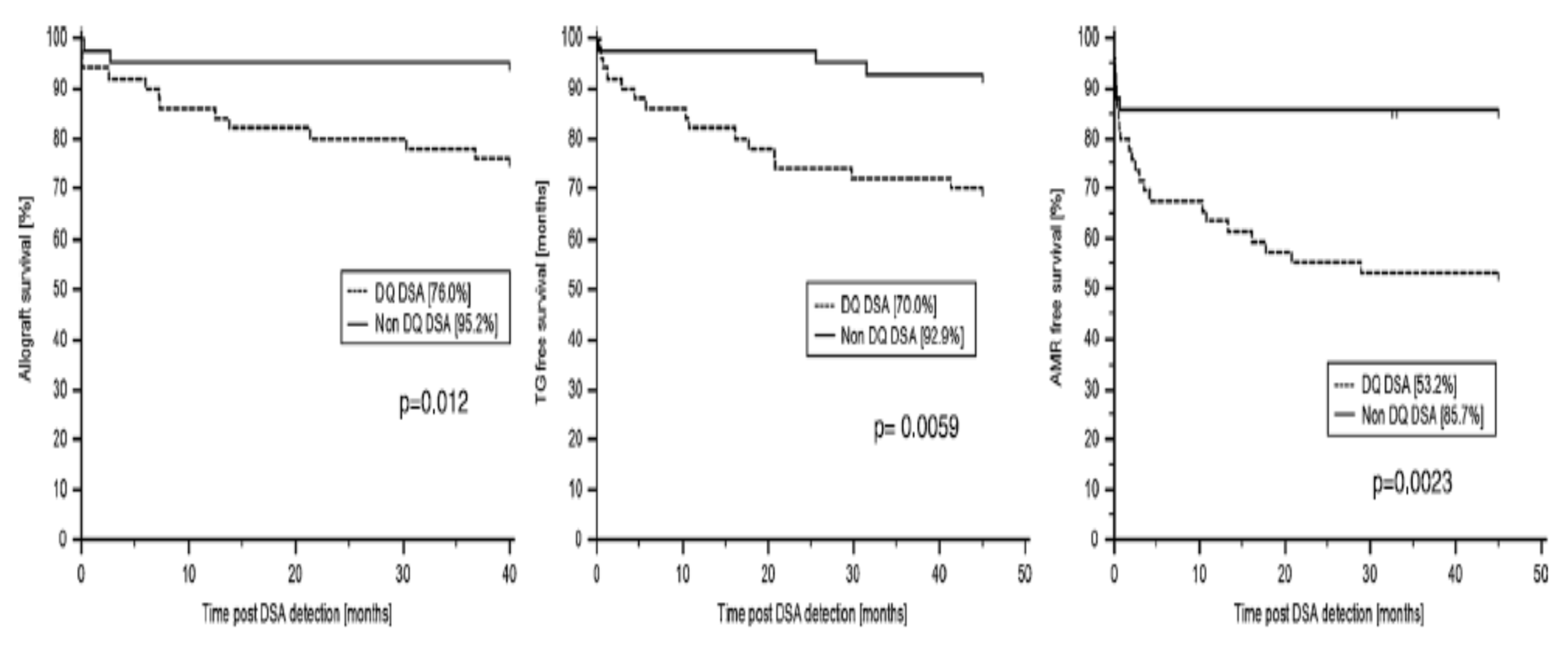
Importance of DQ Epitope Mismatches in de novo DSA

Wiebe et al AJT, 2013



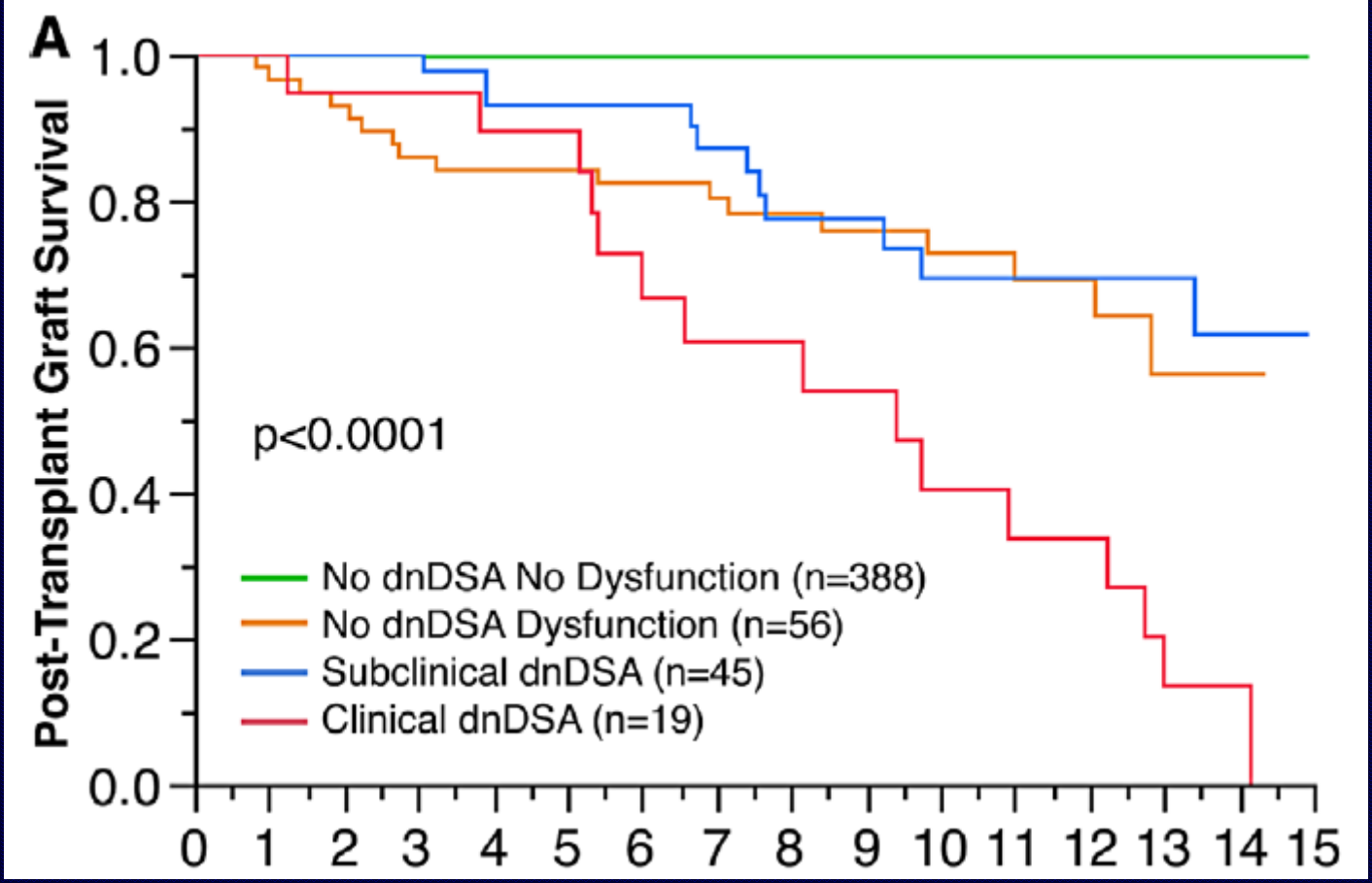
DQ DSA vs non DQ DSA and Outcome

Willicombe et al Transplantation, 2012



dnDSA and Death Censored Graft Survival

Wierbe et al, AJT, 2015



Biopsy Results in 173 Patients With Graft Dysfunction (DEKAF)

Gaston et al Transplantation, 2010

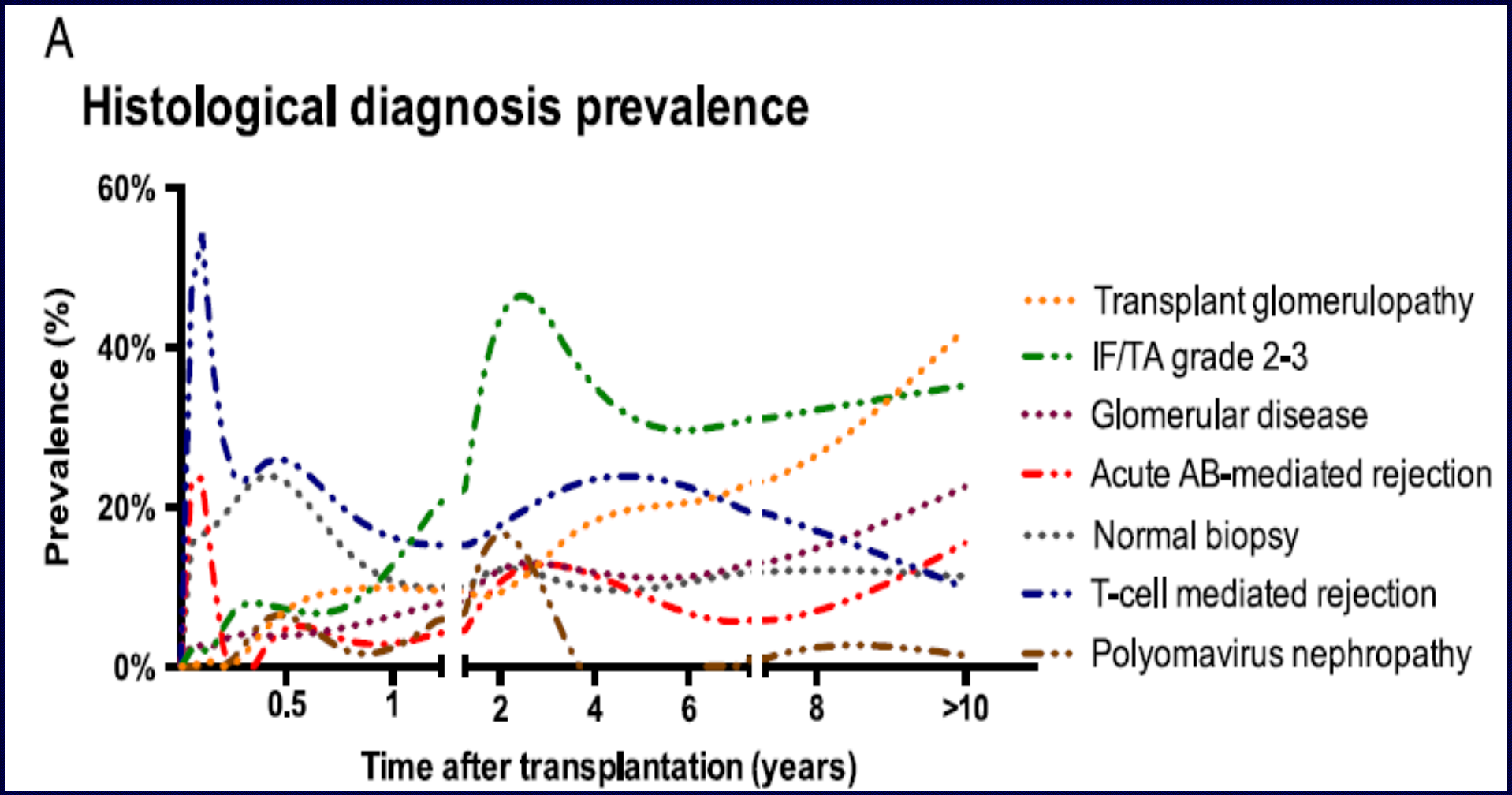
TABLE 2. Local primary and secondary diagnoses at entry biopsy, by % of patients with each diagnosis

Chronic allograft nephropathy	49%
Calcineurin inhibitor nephrotoxicity	35%
Acute rejection (CMR and AMR)	27%
Other (e.g., pyelonephritis)	23%
Transplant glomerulopathy	21%
Recurrent disease	9%

CMR, cell mediated rejection; AMR, antibody mediated rejection.

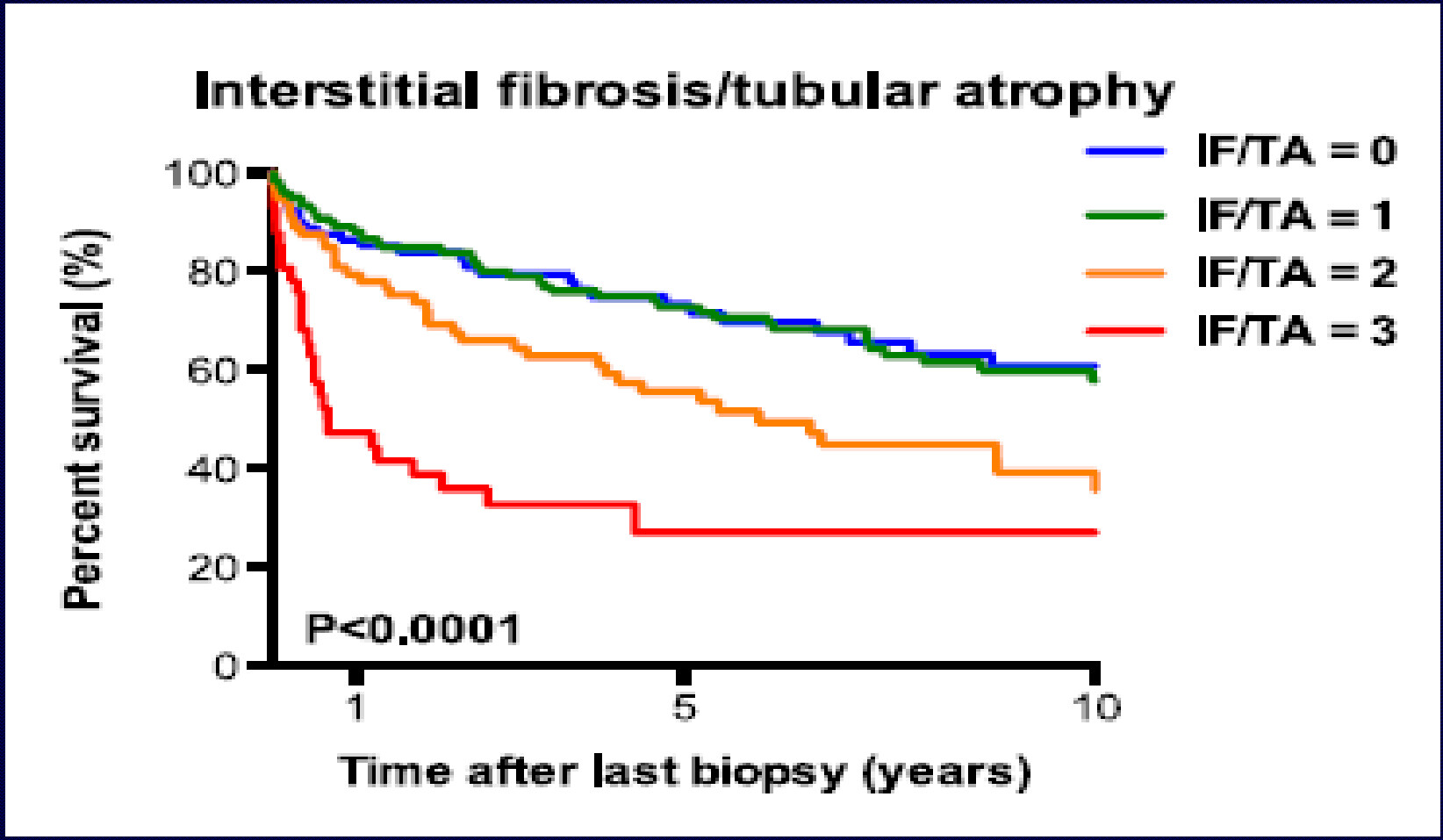
Renal Biopsy Findings

Naesens et al Transplantation, 2014



Pathology and Prognosis

Naesens et al Transplantation, 2014



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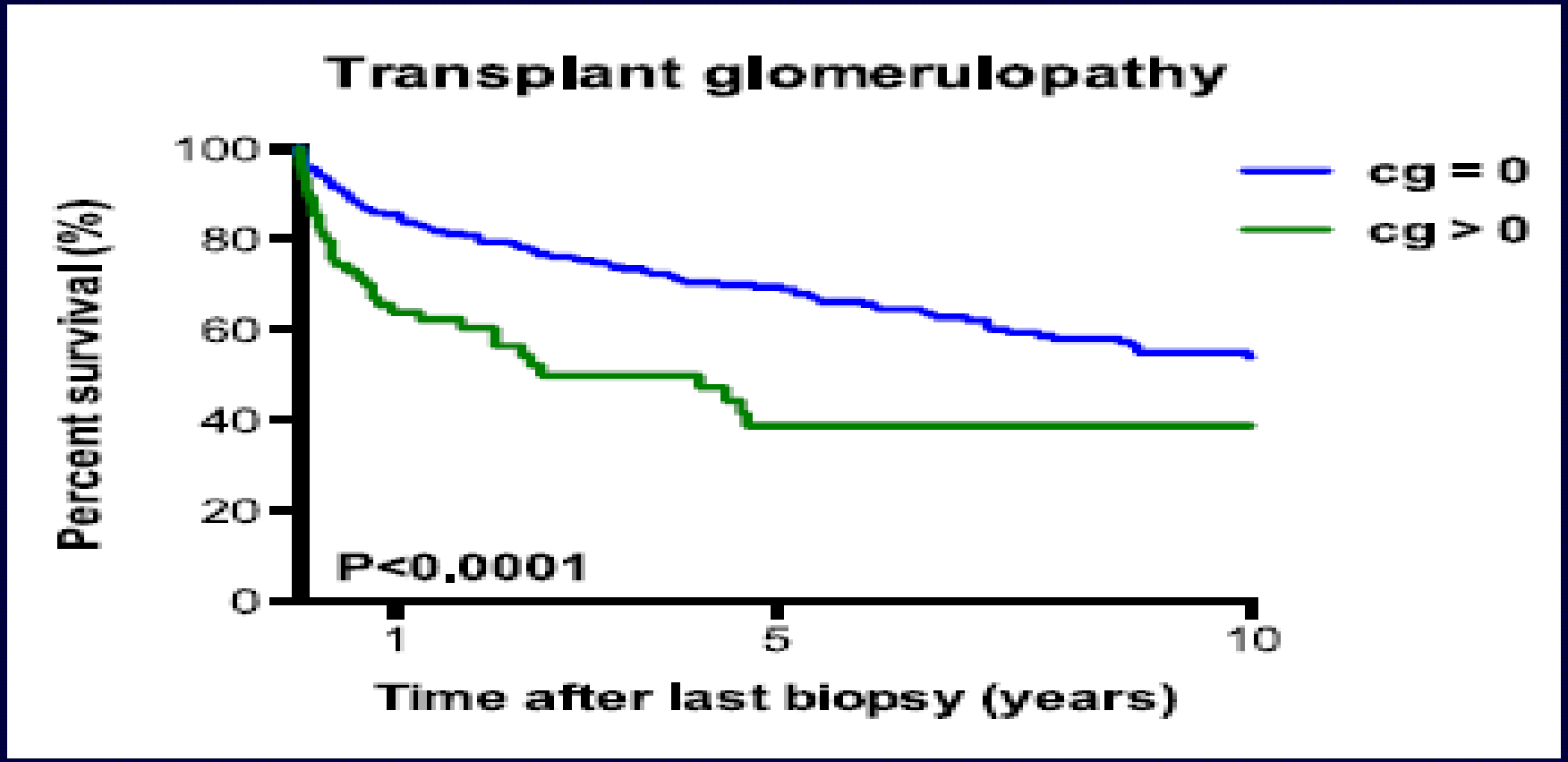
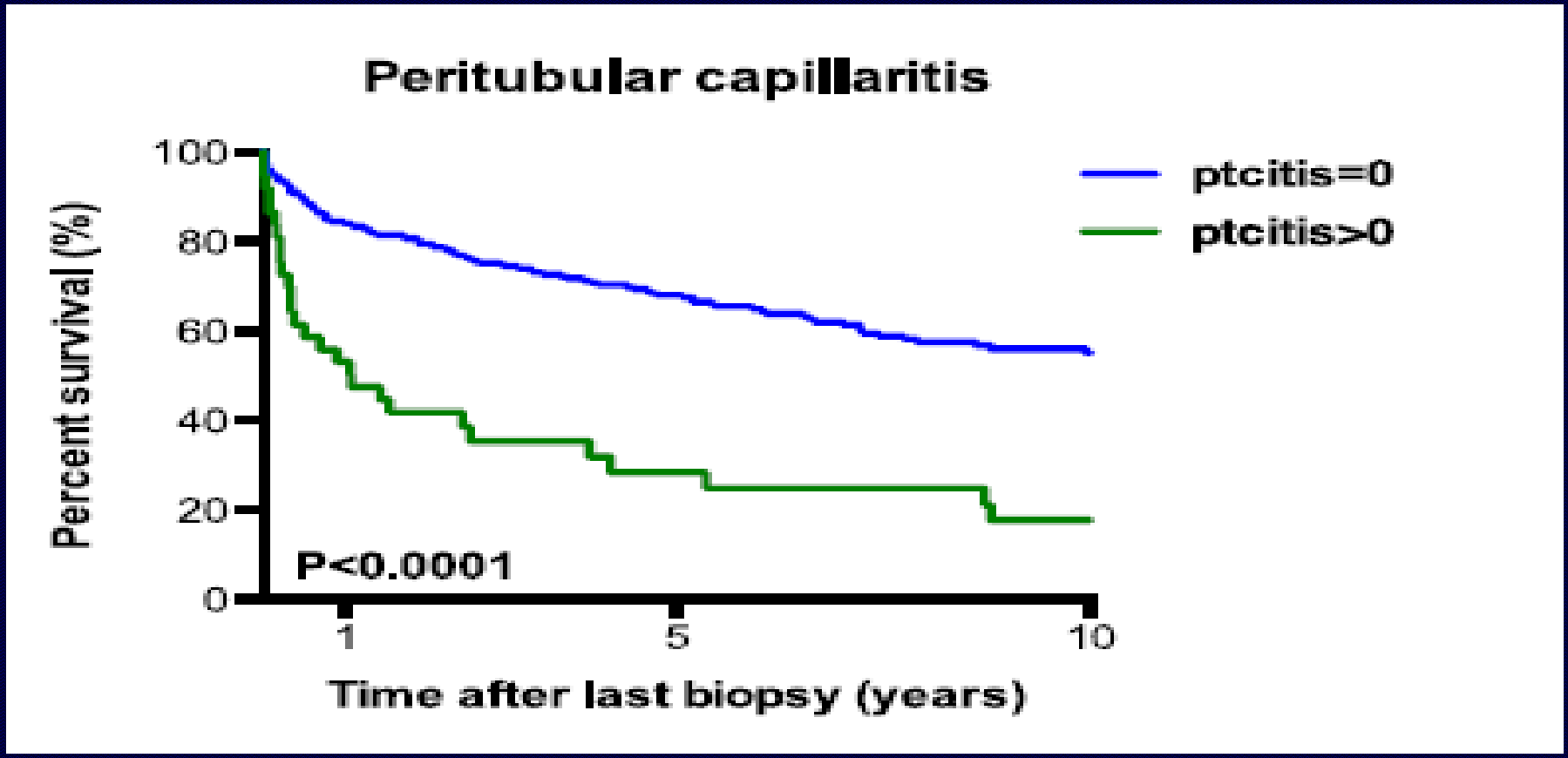
Naesens et al Transplantation, 2014



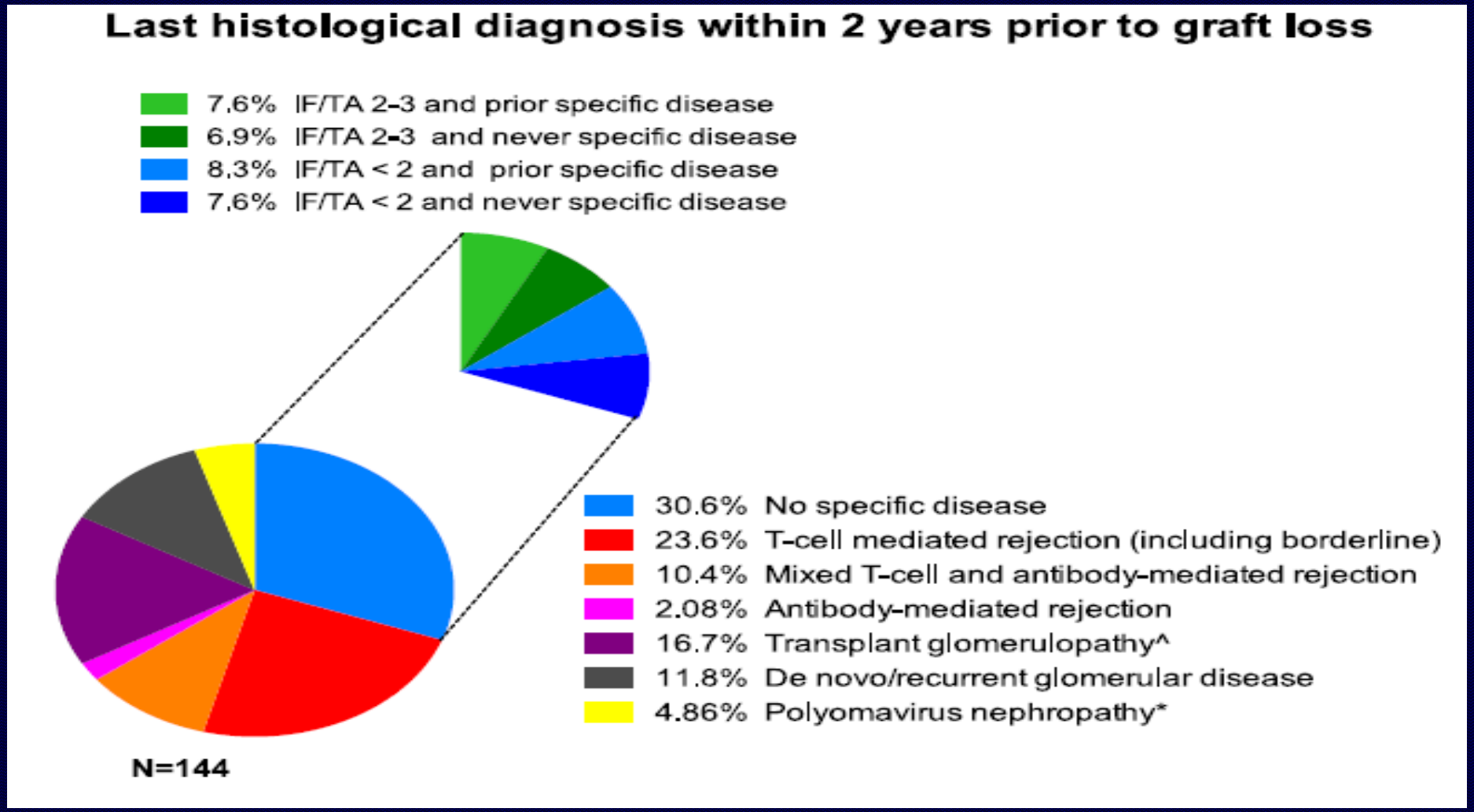
Pathology and Prognosis

Naesens et al Transplantation, 2014



Histology Prior To Graft Loss

Naesens et al Transplantation, 2014



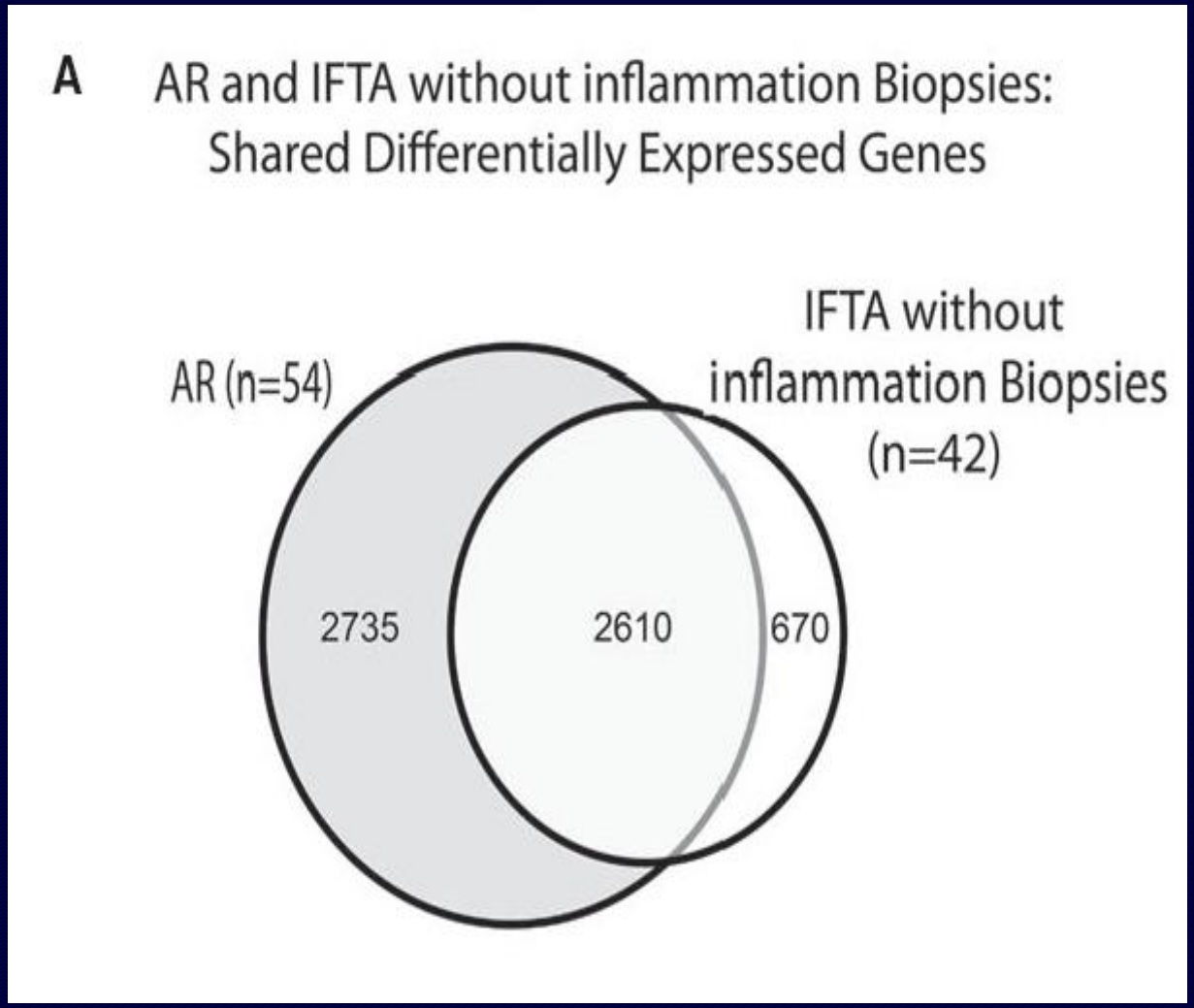
Characteristics Associated with Non Adherence

Prendergast and Gaston CJASN, 2011

Nonadherence
Younger patient (<25 yr); male gender; non-Caucasian; non-United States resident; poor social support
Poor illness insight; poorly perceived treatment benefits; lack of education about illness and treatment; presence of psychological or psychiatric illness
Poor provider-patient rapport; complex medical regimens; higher medication toxicity/side effects; high symptom distress
Lack of health care coverage; impediments to cost of medication, including unemployment/copayments; greater geographic distance to travel; poor transportation access
Patient without diabetes; increased period of time since transplantation

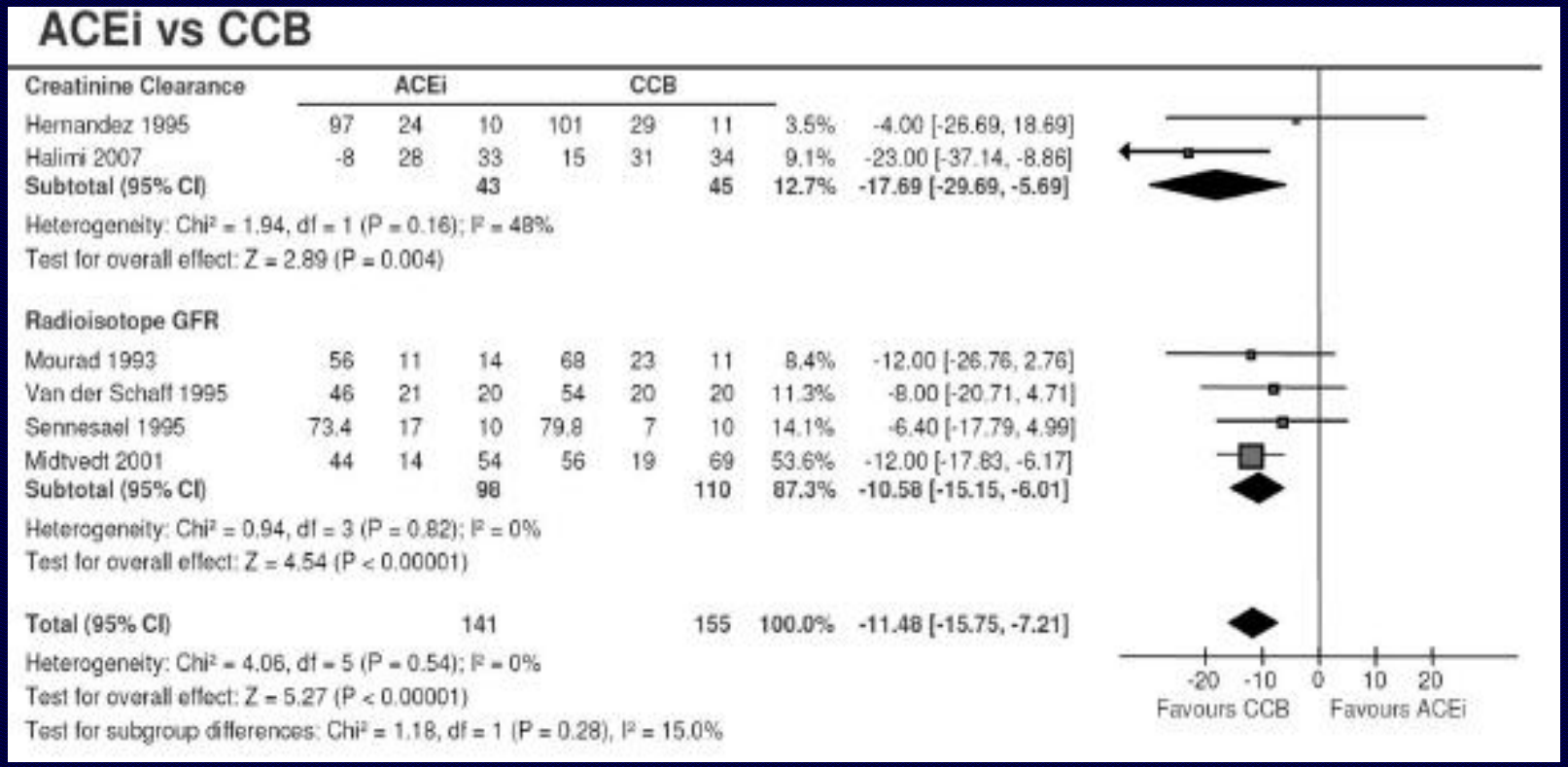
Biopsies with IFTA Without Inflammation and Those With Acute Rejection Share Differentially Expressed Genes

Modena et al AJT, 2016



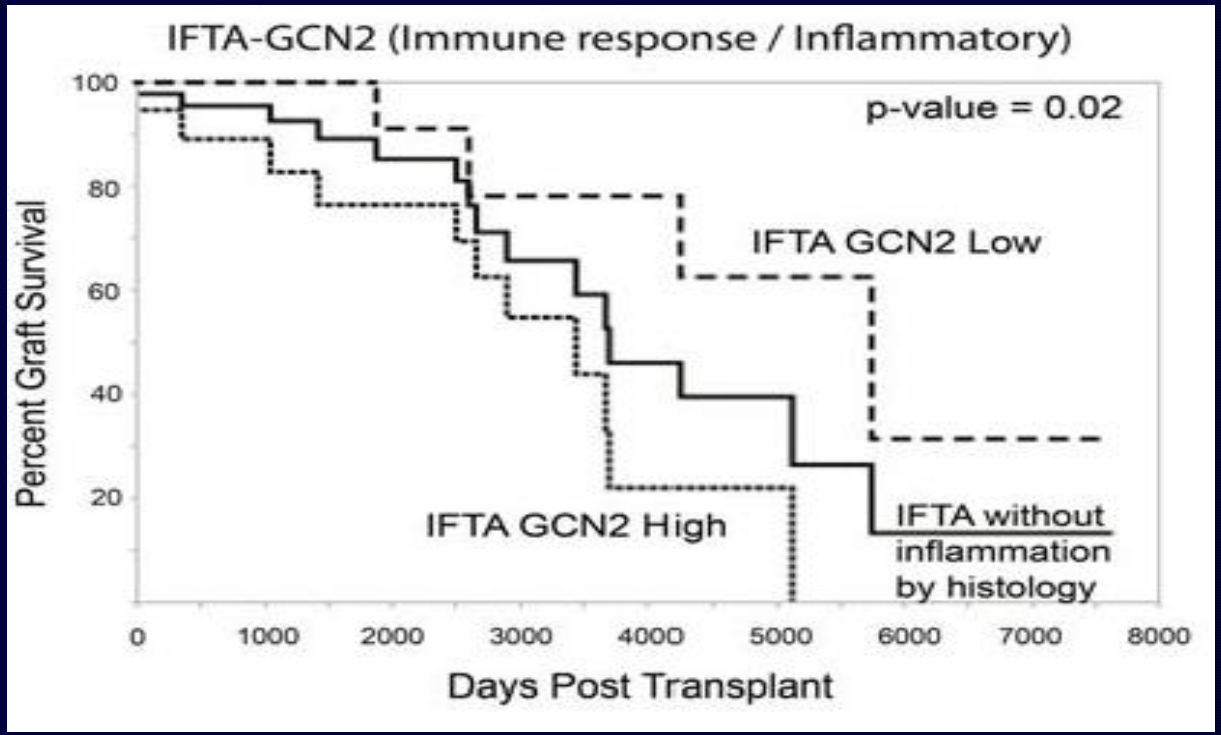
ACEi vs CCB in Transplant Recipients

Cross et al Transplantation, 2009



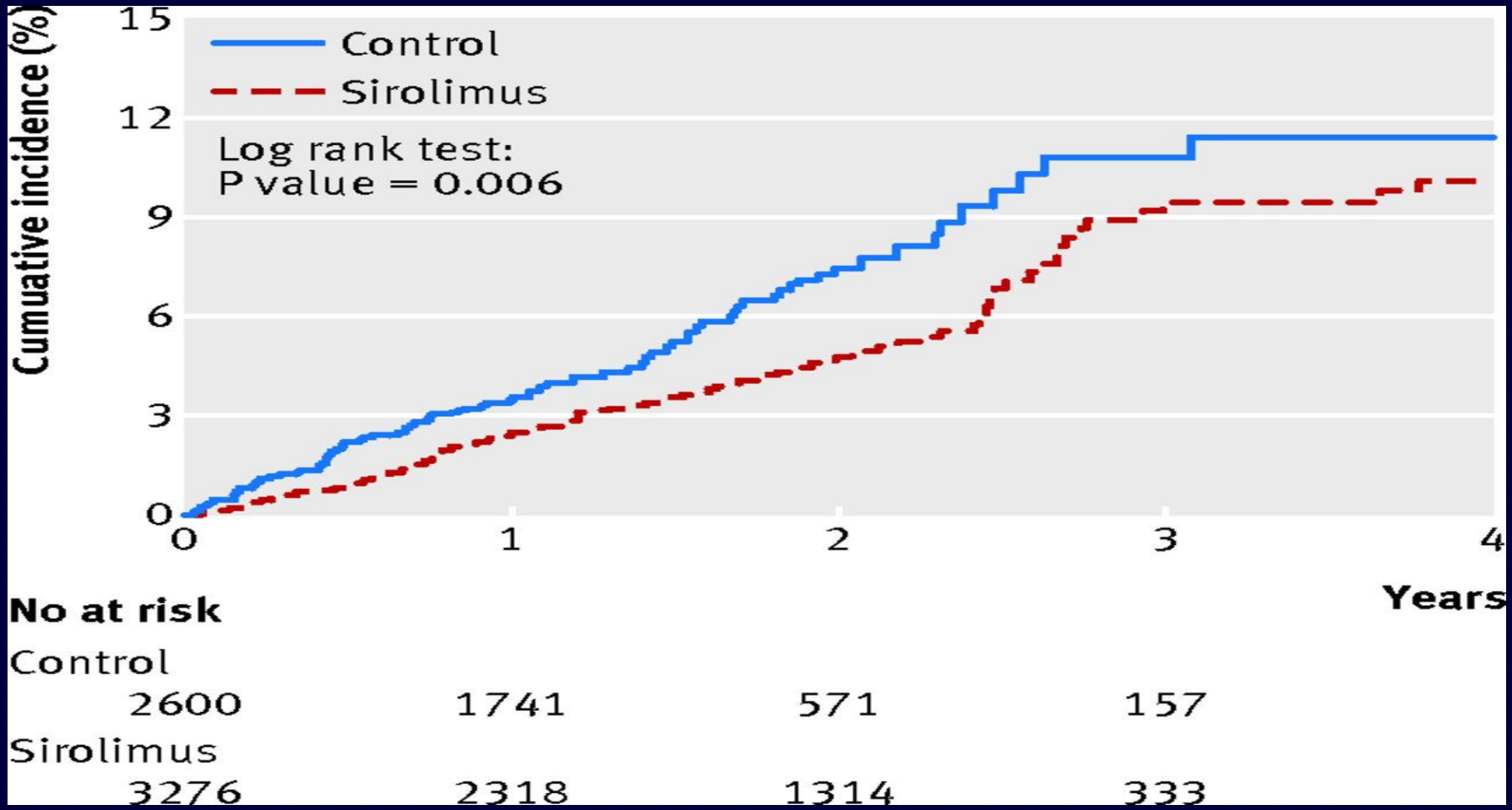
Graft Survival in IFTA without Inflammation Correlates With Gene Activation

Modena et al AJT, 2016



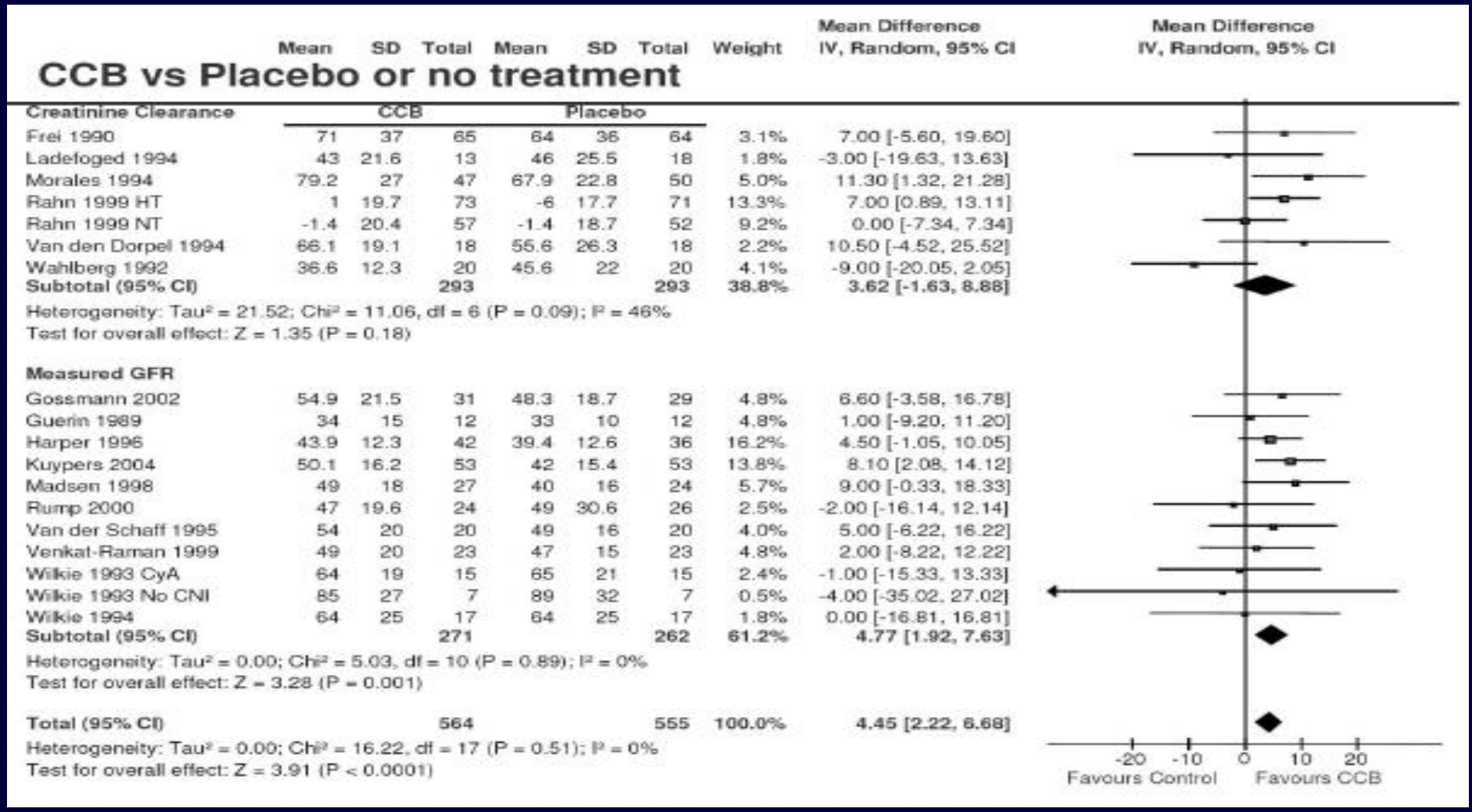
Time to First Malignancy Post Transplant

Knoll et al BMJ, 2014

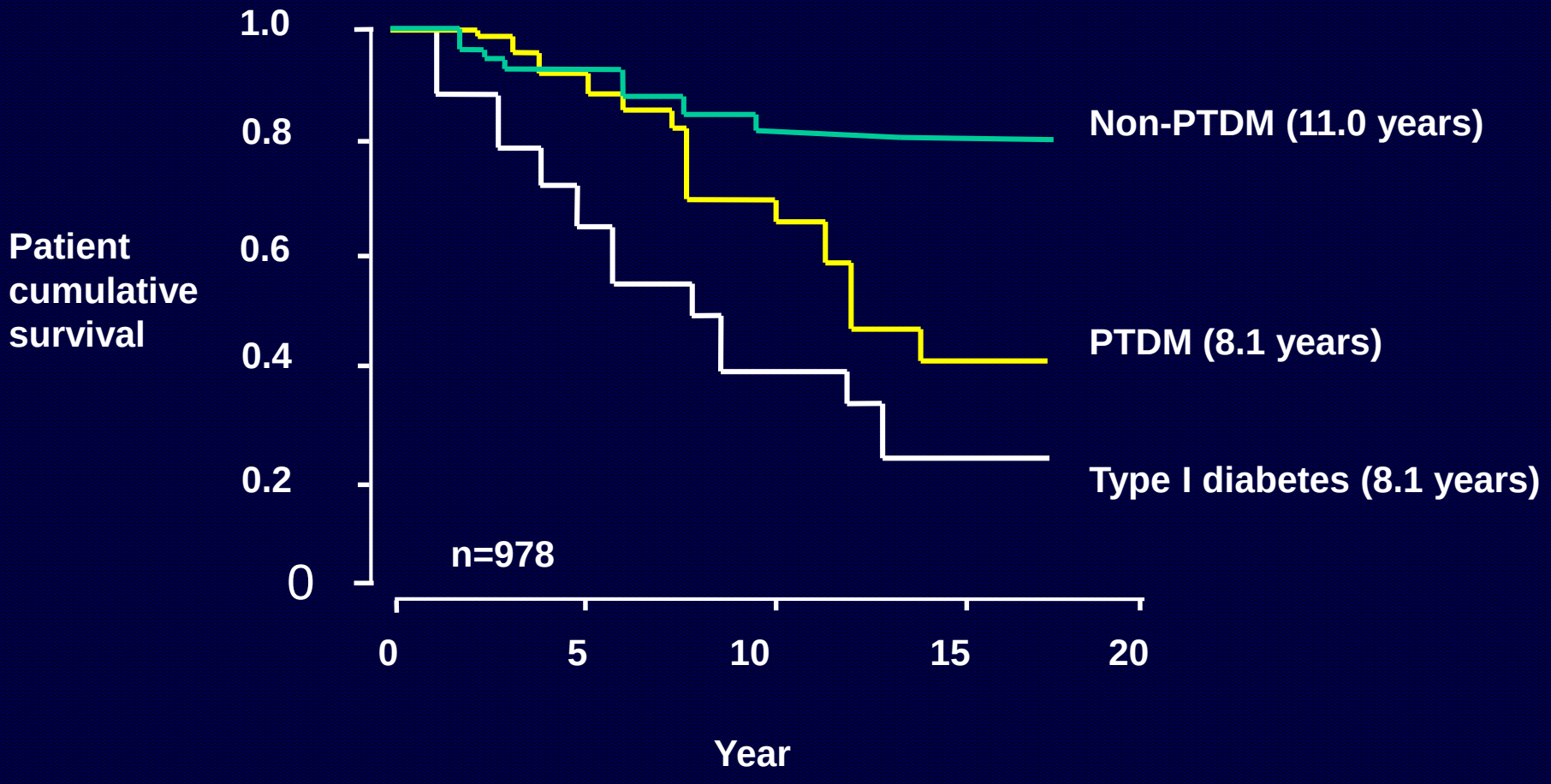


Systematic Review of Antihypertensive Treatment of Transplant Recipients

Cross et al Transplantation, 2009

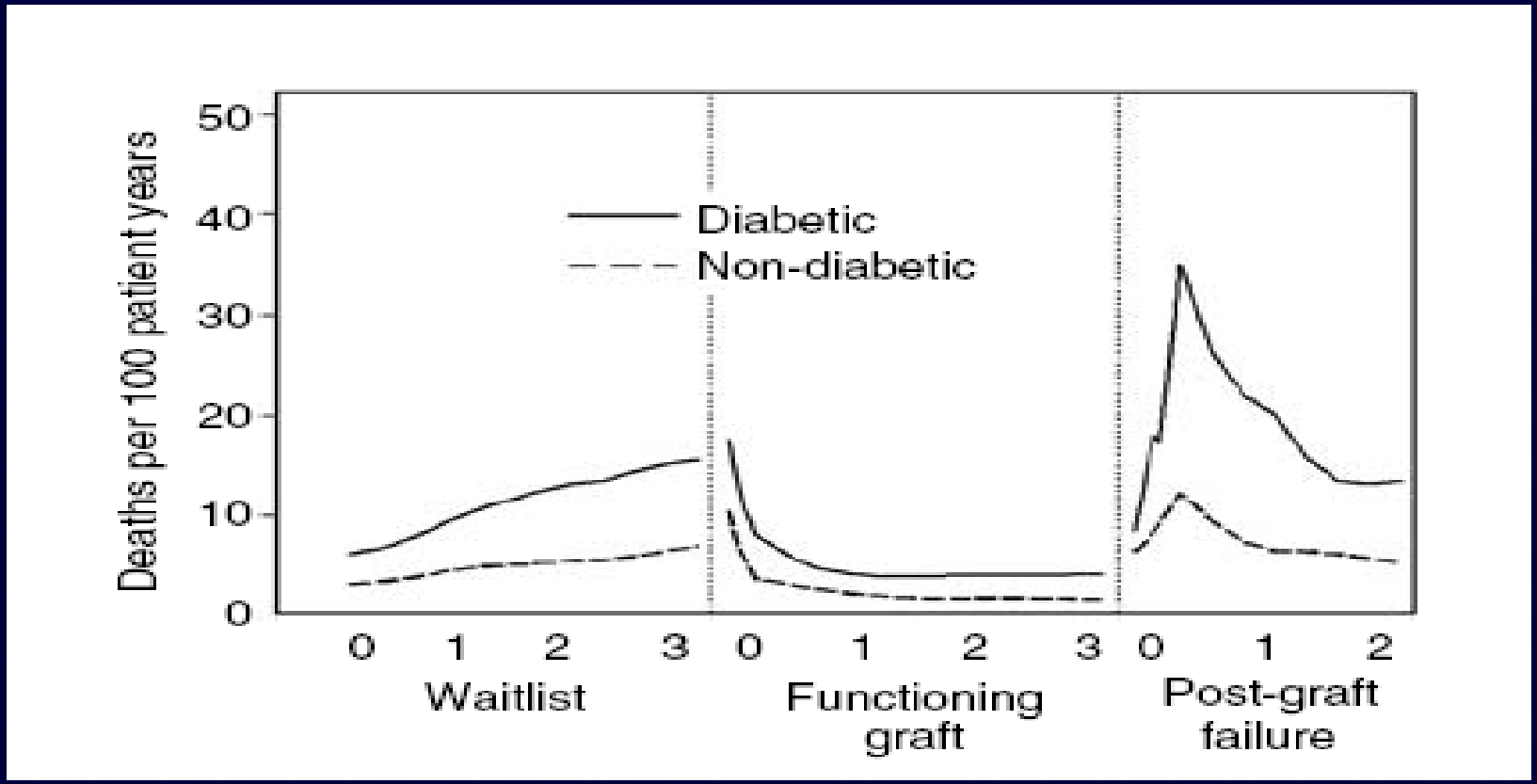


New-onset diabetes reduces patient survival



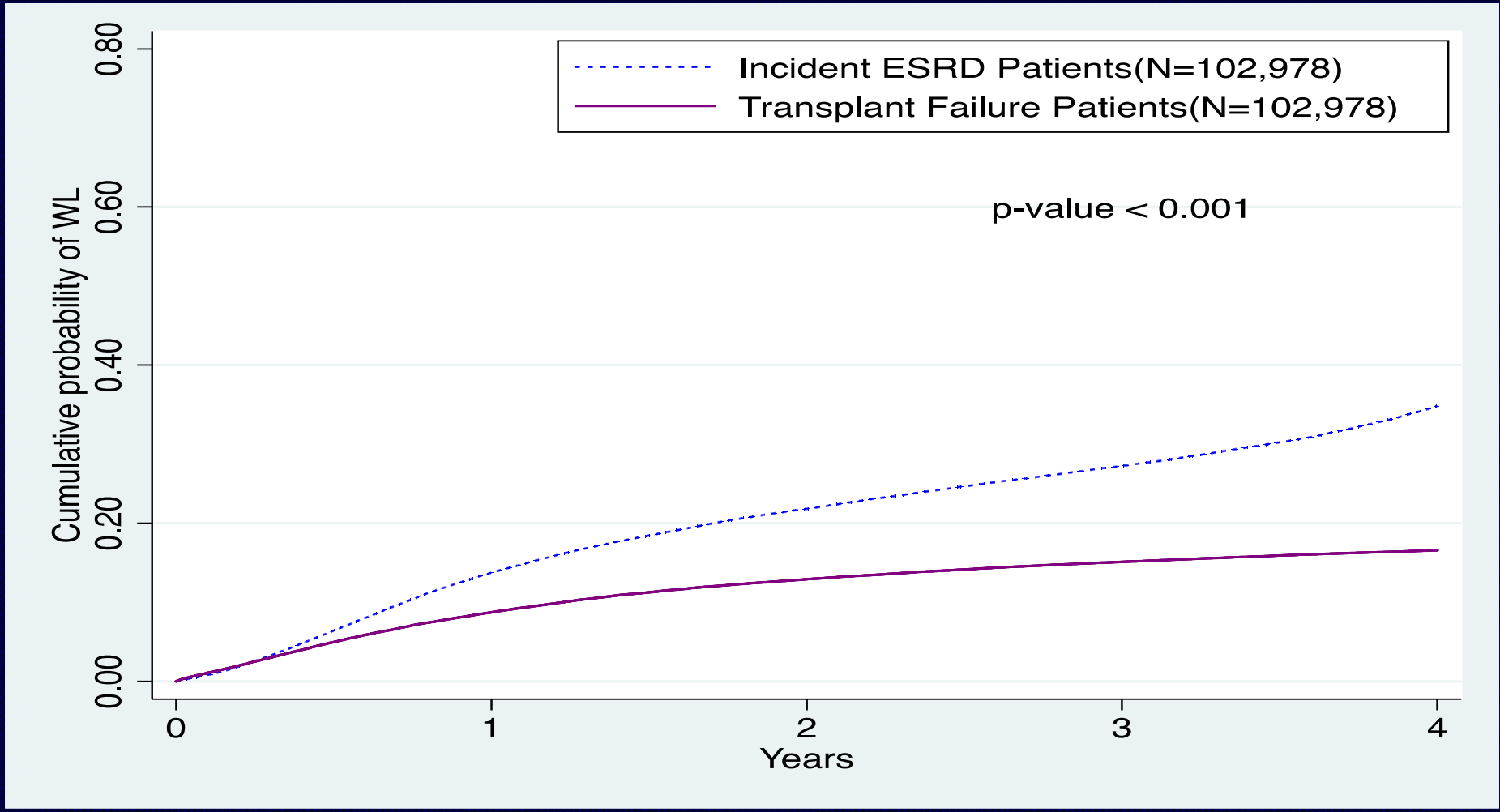
Jindal RM et al. Transplantation. 2000;70:SS58-63.

Why Is This Important?



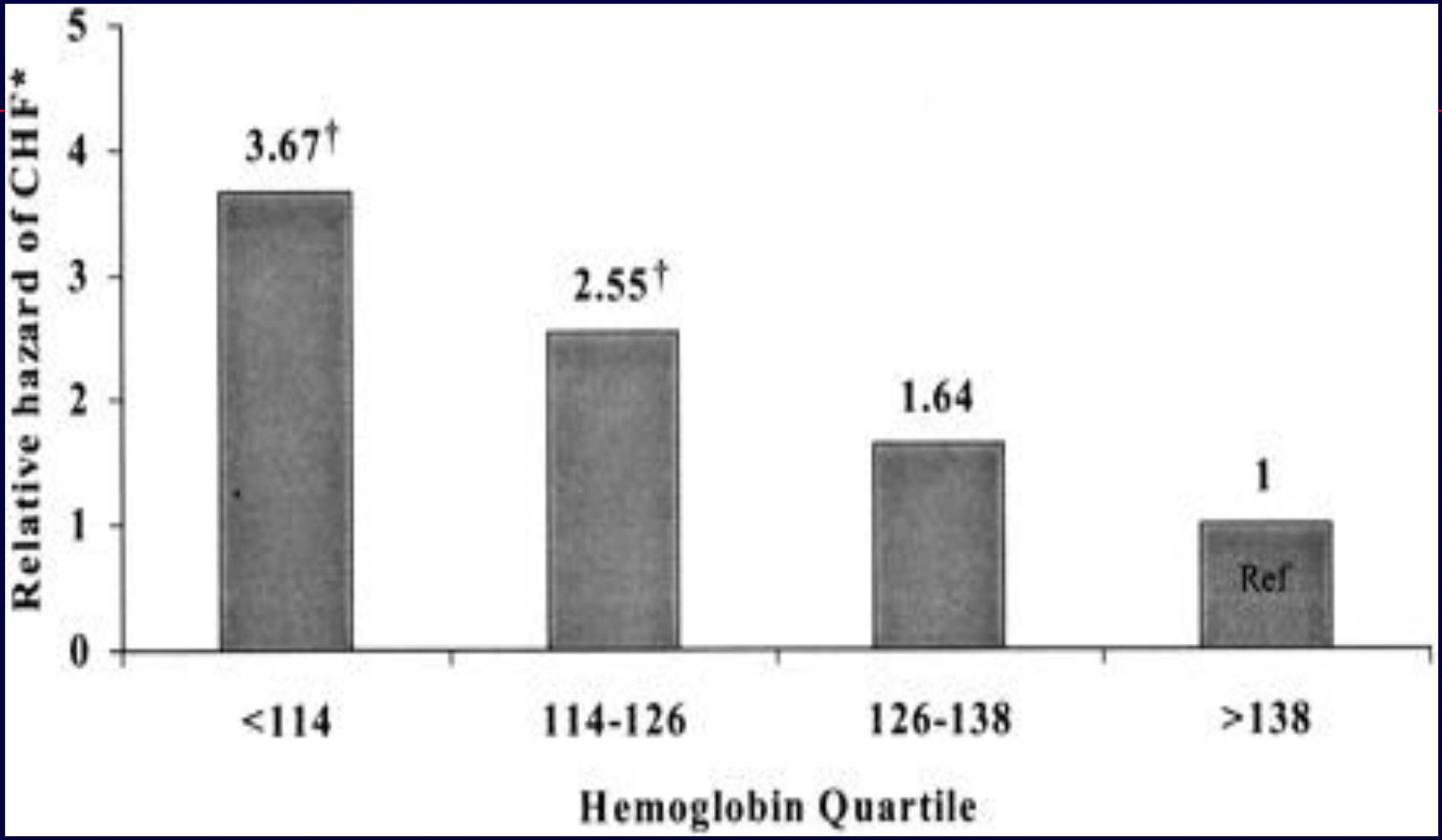
Unadjusted Death Rates per 100 pt years
Gill et al Kidney Int, 2007

Access to re-transplantation is poor



Gill et al. WTC 2014 USRDS cohort 2000-2012

Hemoglobin and CHF Risk

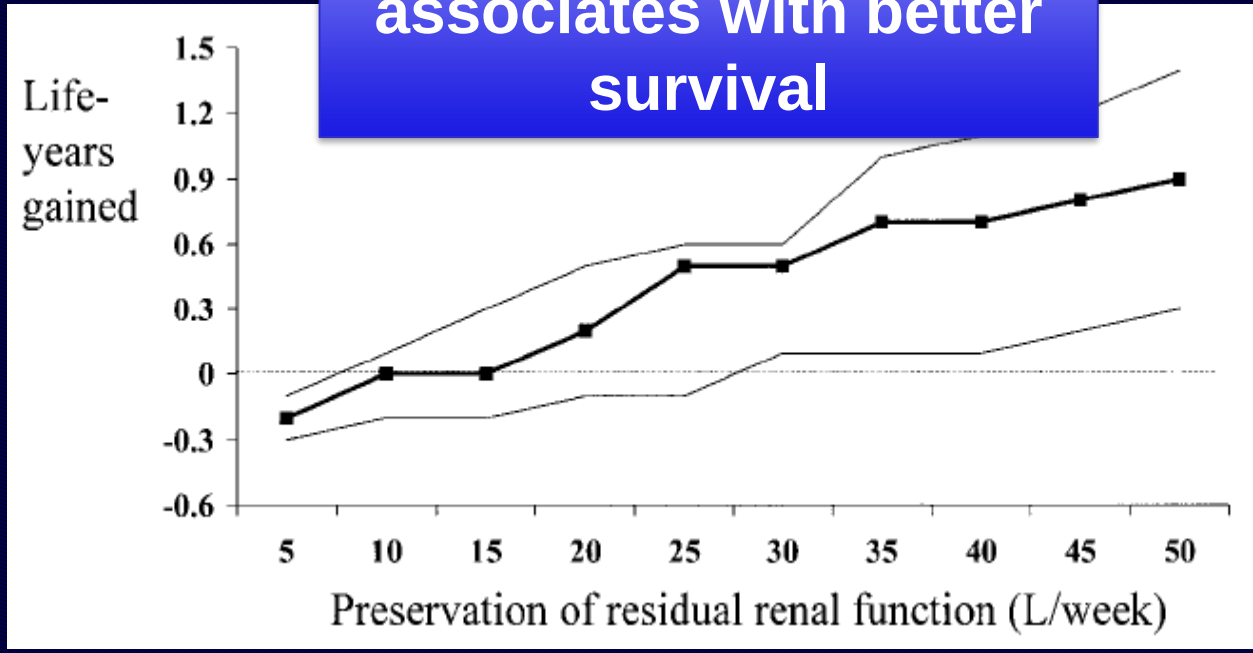


Rigatto et al JASN 2002

Maintaining renal function may improve survival on PD

- N= 42 patients started PD after allograft loss in TGH between 1989-1996
- N=41 had meds withdrawn
- 0.94/yr probability of losing residual renal function after graft loss

Increasing levels of GFR preservation associates with better survival



Jassal, et al. AJKD 2002

Incorporated probabilities for lymphoma, skin cancer, infection

Are The Assumptions Correct?

Jassal et al, 2002

- Uncertain whether immunosuppression will preserve residual function as it has already failed to preserve significant graft function
- Immunosuppression may have no effect on progressive scarring or antibody mediated change
- No proof that residual function preserves survival in this setting
- Gill et al Kidney Int, 2002, patients starting dialysis at higher GFR had higher death rate
- Davies PDI, 2001, 28 pt returning to PD from failed transplants had better survival than rest of PD starts in spite of more rapid function loss

Diagnosis

- **Bone Mineral Density**

  -compares density at spine and hip with young normals of same gender

  -T-score of –1.0 to -2.5 indicates osteopenia

  -T-score < -2.5 indicates osteoporosis

  -each SD reduction of lumbar spine below normal increases fracture risk by about 2 and indicates BMD loss of 10%
- **X-ray for fractures**

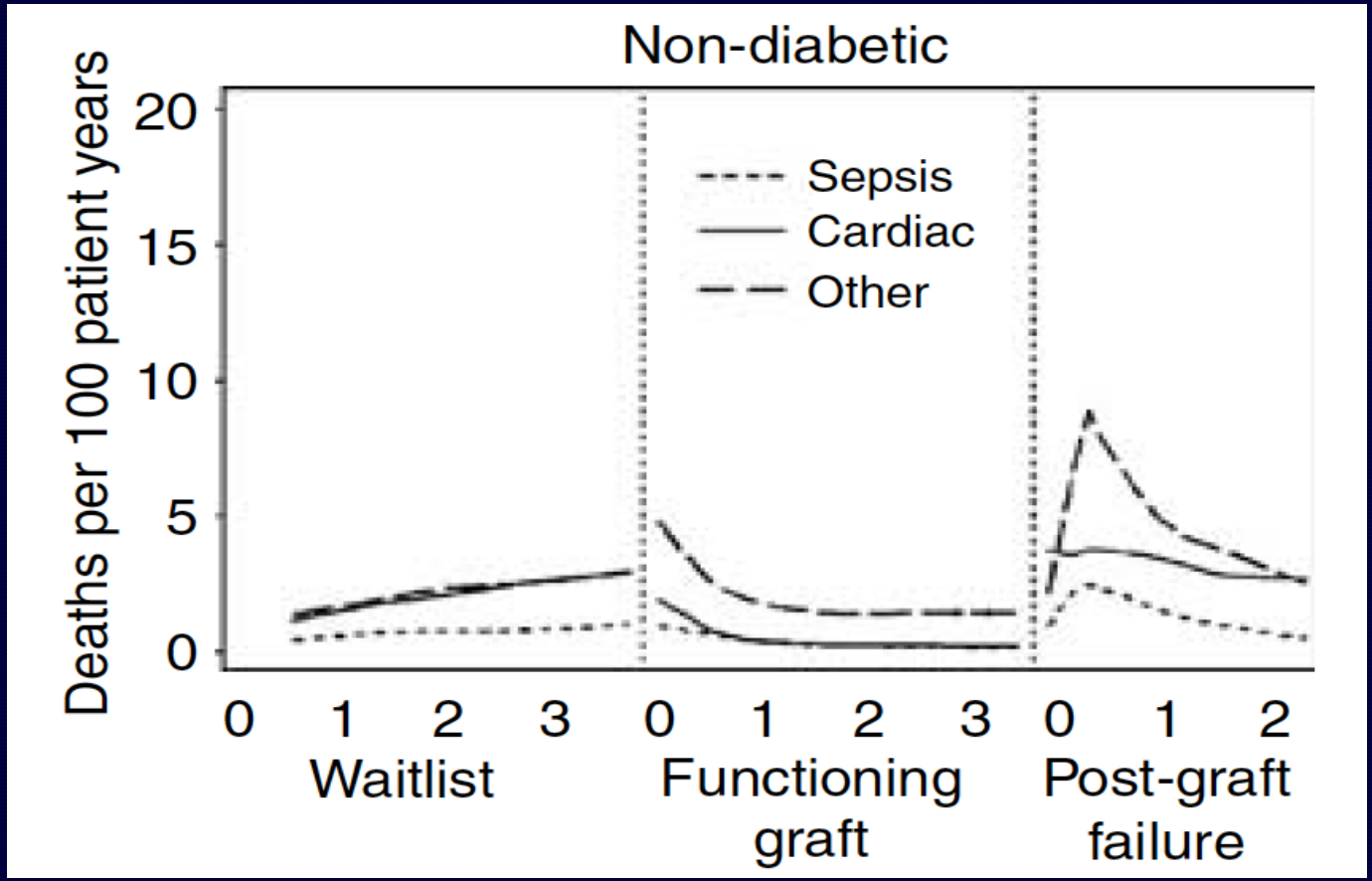
Management

- BMD at baseline and 6 months post transplant
- If abnormal consider therapy and repeat at 6 –12 months
- Treat reversible factors
- Use oral calcium and Vit D (calcitriol 0.5 ug OD) if normocalcemic
- Consider biphosphonates which inhibit osteoclast activity for osteoporosis or additional risks e.g. post menopausal females
- However, not recommended in mod to severe renal failure (CrCl < 35 ml/min)

Why Consider Separately?

- Focus on those kidneys at greater risk of deteriorating function and graft loss
- Strategies to improve function or prevent deterioration
- Associated with other complications that need to be managed

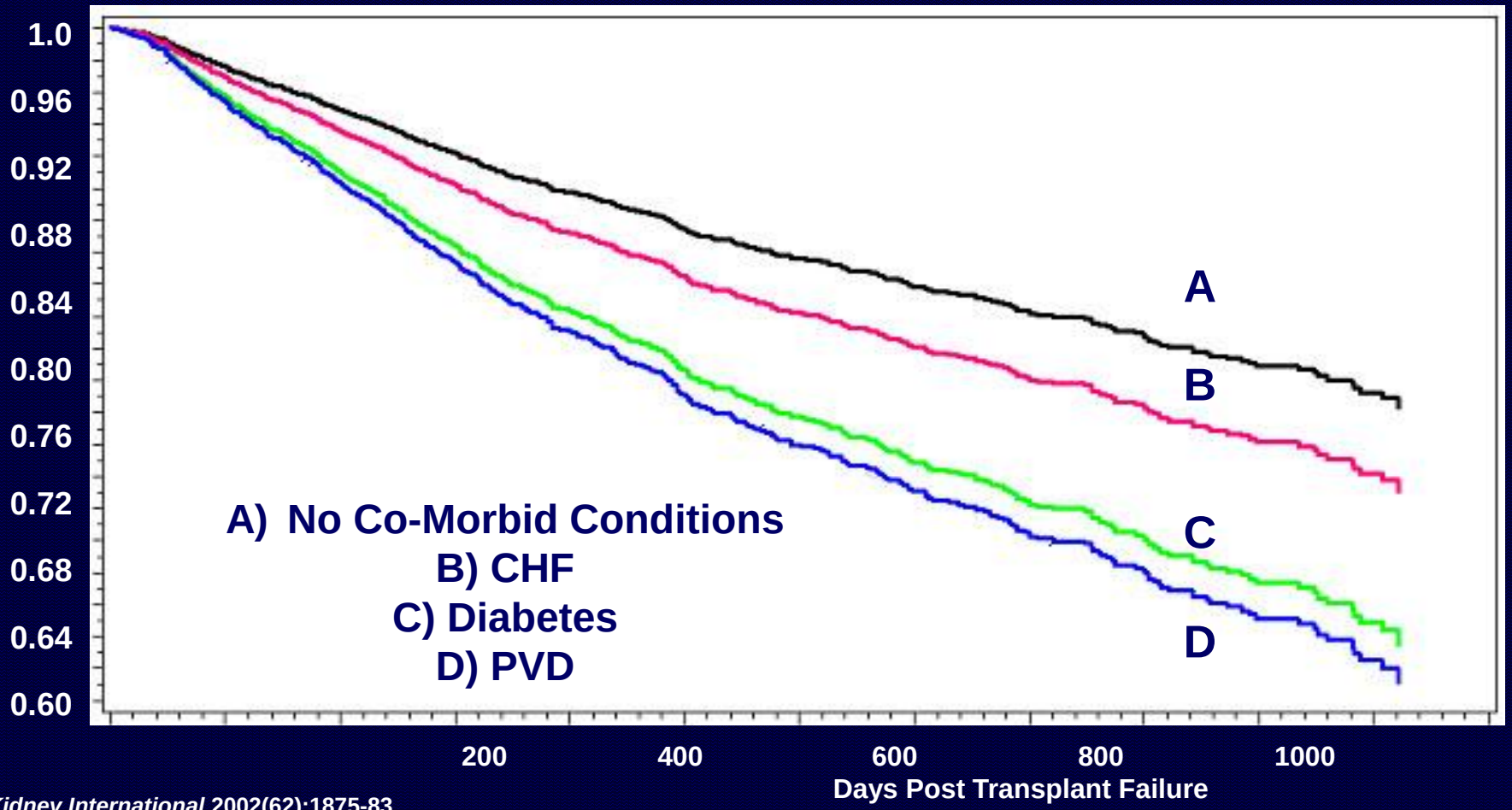
Infection is NOT the leading cause of death



Kidney International 2007 Mar;71(5):442-7

Especially in more complex patients

Adjusted Survival Curves



Gill et al., *Kidney International* 2002(62);1875-83

Detection of donor-specific HLA antibodies before and after removal of a rejected kidney transplant

Marilyn Marrari, Rene J. Duquesnoy *

Division of Transplant Pathology and Thomas E. Starzl Transplantation Institute, University of Pittsburgh Medical Center, Thomas E. Starzl Biomedical Science Tower, Room W1552, Pittsburgh, PA 15261, United States

Table 3
Frequencies of DSA reacting with individual class I antigens in pre-allonx and post-allonx sera.

Mismatched antigen	Nr of cases	Positive pre-allonx	Positive post-allonx
HLA-A1	12	58%	75%
HLA-A2	18	89%	89%
HLA-A3	8	38%	75%
HLA-A24	10	40%	70%
HLA-A26	7	71%	100%
HLA-A32	7	14%	43%
Other HLA-A antigens	19	53%	95%
All HLA-A antigens	**81**	**57%[a]**	**81%[a]**
HLA-B7	8	75%	88%
HLA-B8	9	56%	78%
HLA-B27	12	42%	75%
HLA-B35	9	44%	89%
HLA-B16 (B38 or B39)	7	0%	29%
HLA-B44	8	50%	100%
HLA-B5 (B51 or B52)	6	50%	67%
Other HLA-B antigens	27	30%	52%
All HLA-B antigens	**86**	**41%[b]**	**69%[b]**
HLA-Cw2	6	33%	33%
HLA-Cw3	7	43%	29%
HLA-Cw7	6	50%	50%
Other HLA-C antigens	14	14%	29%
All HLA-C antigens	**33**	**30%[c]**	**33%[c]**

[a] $p = 0.0007$.
[b] $p = 0.0002$.
[c] $p = 0.79$ (not significant).

Table 5
Frequencies of DSA reacting with individual class II antigens in pre-allonx and post-allonx sera.

Mismatched antigen	Nr of cases	Pre-allonx	Post-allonx
HLA-DR1	9	33%	67%
HLA-DR4	10	50%	90%
HLA-DR11	8	63%	75%
HLA-DR13	14	50%	64%
HLA-DR15	9	78%	89%
Other HLA-DR	23	31%	85%
All HLA-DRB1	**72**	**48%[a]**	**79%[a]**
HLA-DR51	11	73%	73%
HLA-DR52	19	53%	74%
HLA-DR53	10	80%	90%
All HLA-DRB3/4/5	**40**	**65%[b]**	**78%[b]**
HLA-DQ2	8	63%	88%
HLA-DQ5	10	40%	70%
HLA-DQ6	13	69%	85%
HLA-DQ7	17	94%	94%
Other HLA-DQ	9	78%	89%
All HLA-DQ	**57**	**72%[c]**	**86%[c]**

[a] $p = 0.0001$.
[b] $p = 0.22$ (NS).
[c] $p = 0.07$ (NS).

Independent of Nephrectomy, Weaning Immunosuppression Leads to Late Sensitization After Kidney Transplant Failure

Joshua J. Augustine,[1,3] Kenneth J. Woodside,[2] Aparna Padiyar,[1] Edmund Q. Sanchez,[2] Donald E. Hricik,[1] and James A. Schulak[2]

Transplantation • Volume 94, Number 7, October 15, 2012

TABLE 2. Univariate and multivariate logistic regression analyses for panel reactive antibody class I or II of 80% or more (highly sensitized) by late panel reactive antibody at 6 to 24 months after transplant failure

	Univariate Model			Multivariate Model[a]		
Variables	**Odds Ratio**	**95% CI**	***P***	**Odds Ratio**	**95% CI**	***P***
Age at failure (per year)	0.974	0.946–1.004	0.090	0.965	0.928–1.004	0.078
Female	0.979	0.470–2.039	NS			
African American	5.226	2.203–12.395	<0.001	3.110	1.011–9.567	0.048
HLA mismatch	1.390	1.093–1.768	0.007	1.803	1.257–2.587	0.001
Living donor	1.822	0.788–4.214	NS			
Allograft survival (per month)	0.993	0.987–0.999	0.030	1.000	0.992–1.008	NS
KP transplantation	0.120	0.038–0.383	<0.001	0.299	0.050–1.789	NS
Weaned immunosuppression	25.536	5.620–116.035	<0.001	14.342	2.334–88.144	0.004
Transplant nephrectomy	4.761	1.943–11.665	0.001	1.893	0.594–6.036	NS

[a] r^2=0.401.

CI, confidence interval; HLA, human leukocyte antigen; KP, kidney-pancreas; NS, not significant.

Prolonged Immunosuppression Preserves Nonsensitization Status After Kidney Transplant Failure

Michael J. Casey,[1,6] Xuerong Wen,[1] Liise K. Kayler,[2] Ravi Aiyer,[3] Juan C. Scornik,[4] and Herwig-Ulf Meier-Kriesche[5]

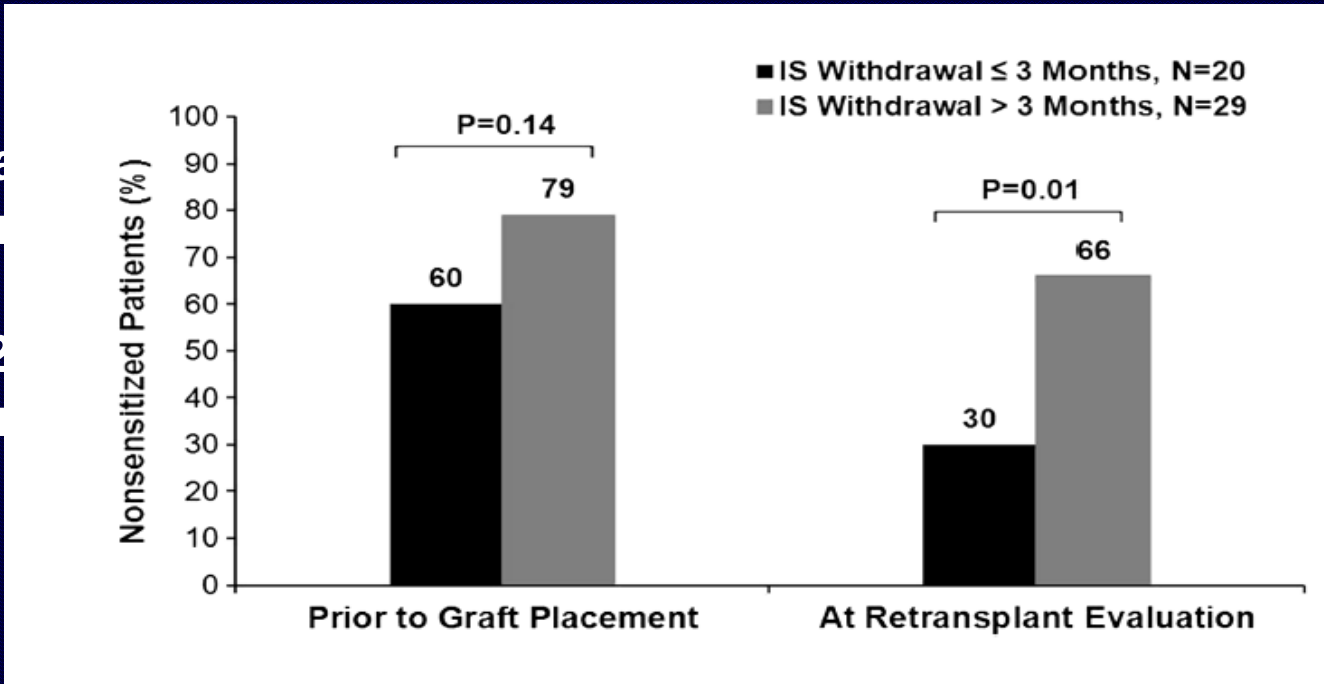
Transplantation • Volume 98, Number 3, August 15, 2014

N=49 patients with graft loss a
re-referred for TX evaluatio

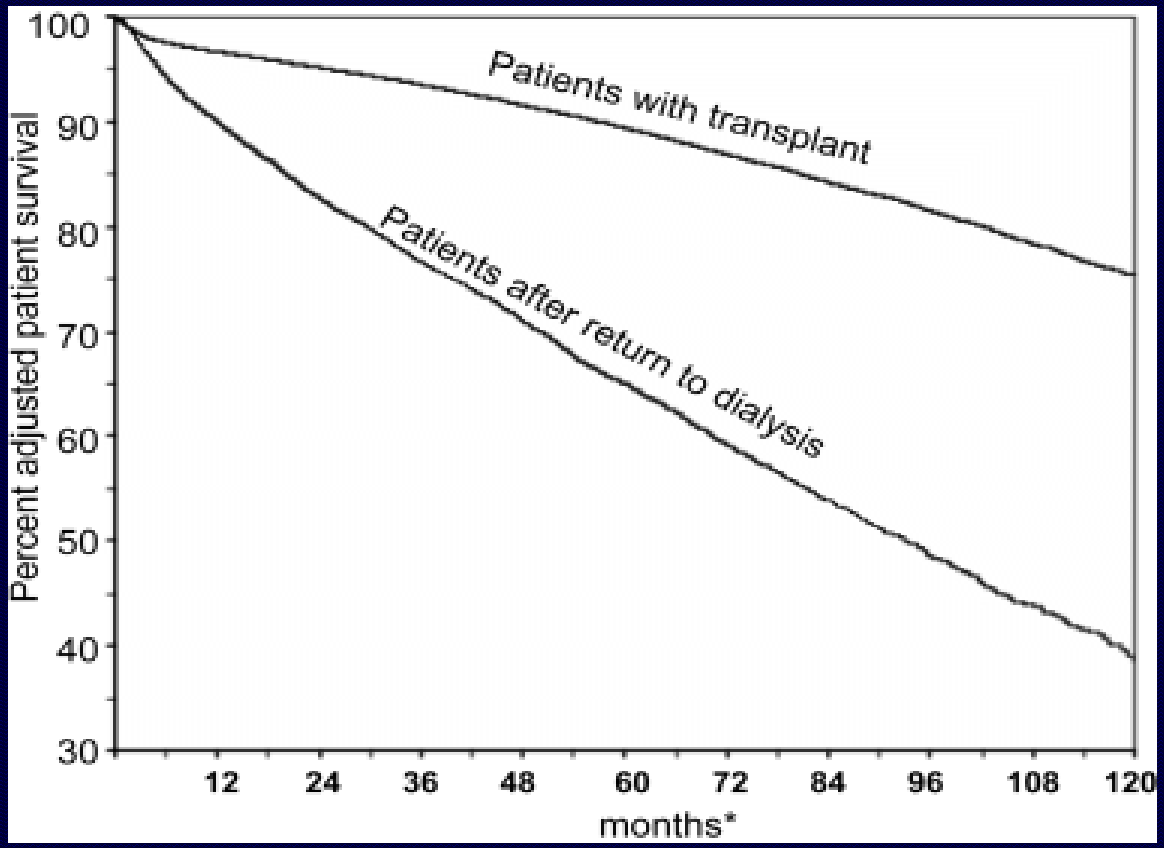
N=20 Early withdrawal: med 2
N=29 Late withdrawal (n=29): r
357 d

Non-sensitization = 0 PRA

Time to re-evaluation 147 vs 141 d



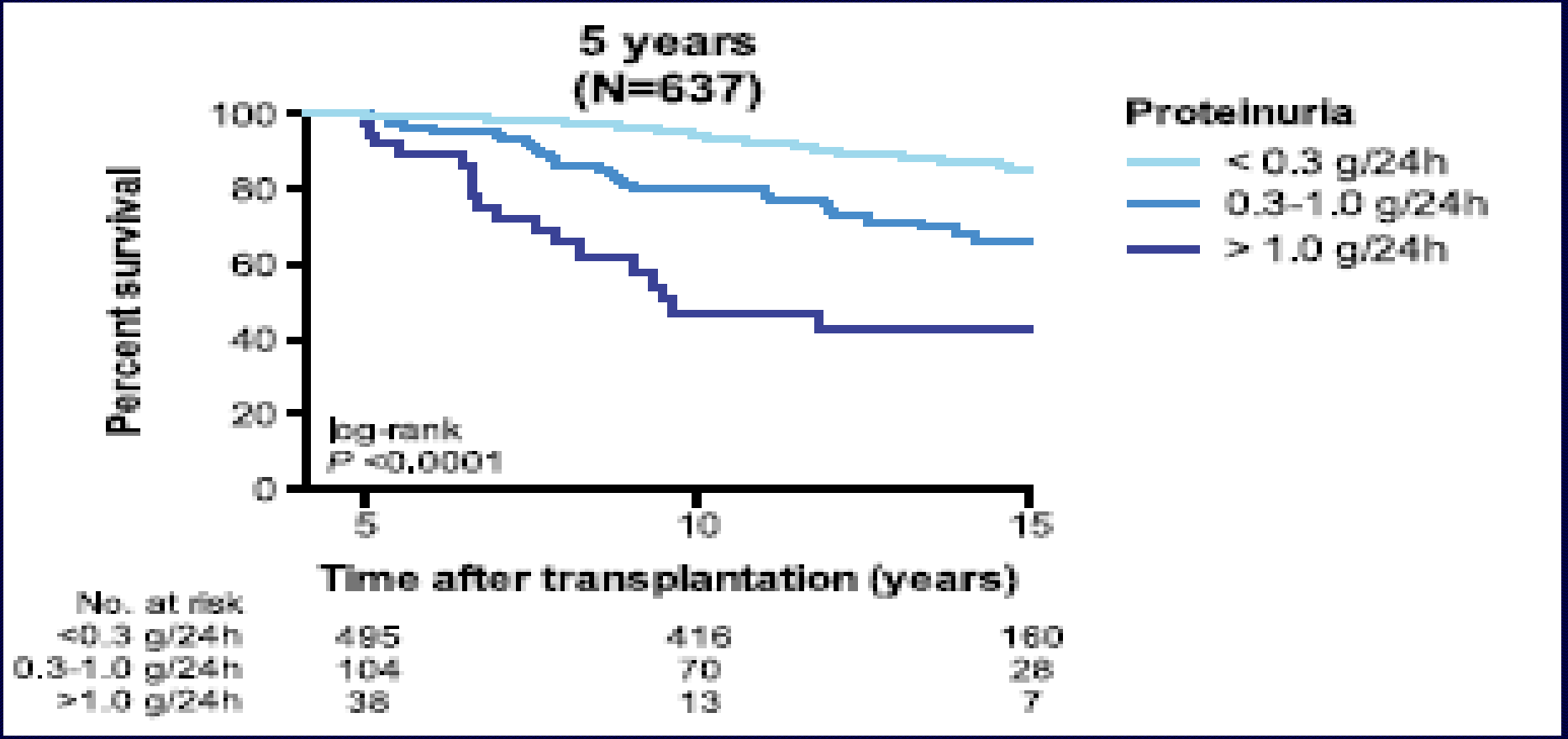
Outcomes are poor after allograft failure



Kaplan, B et al., *Am J Transplant* 2002;2:970-4

Proteinuria and Graft Survival

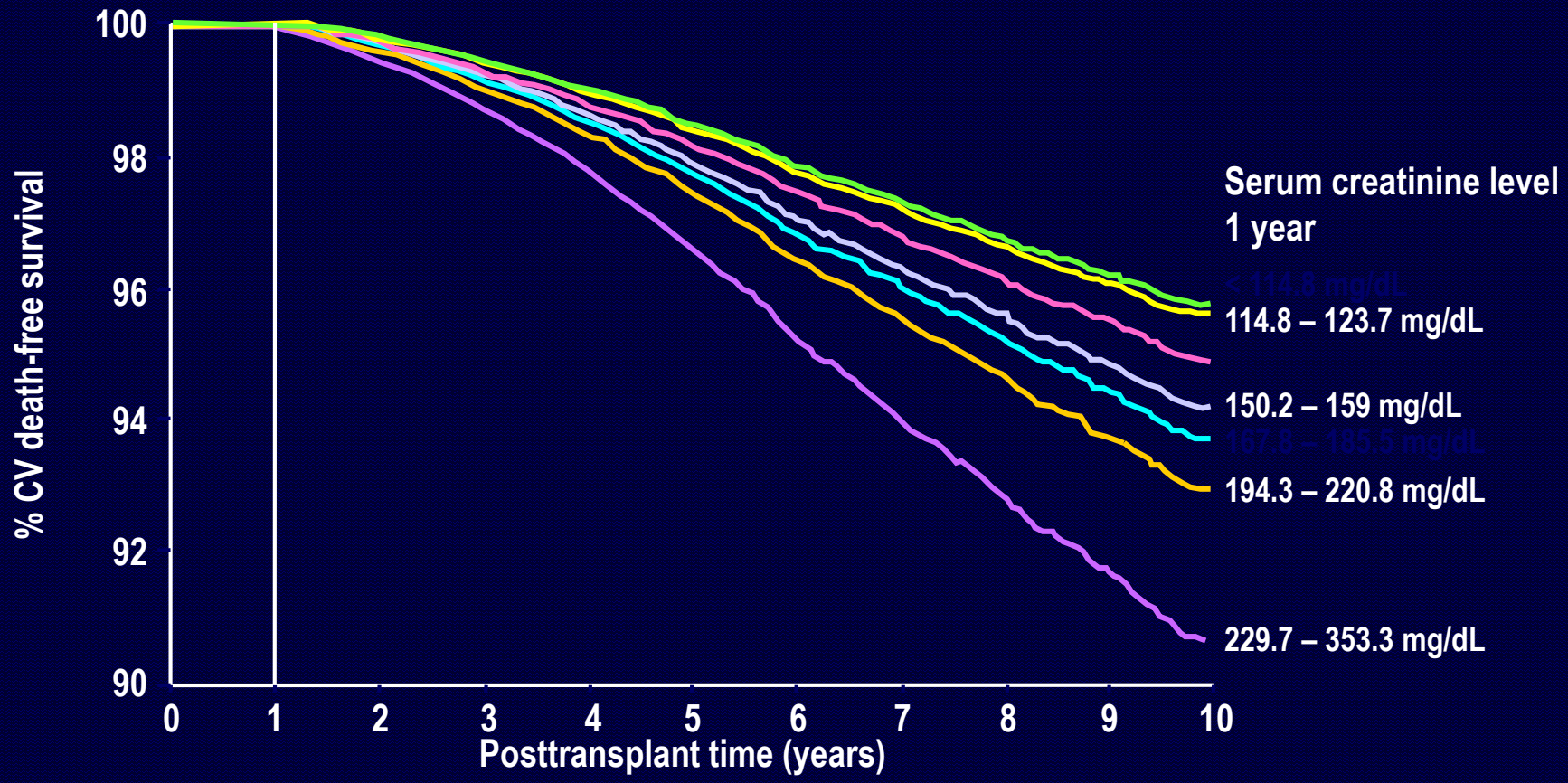
Naesens et al JASN, 2016



Main Causes of Graft Loss

- Acute and chronic rejection
- Interstitial Fibrosis/Tubular Atrophy
- Recurrent Glomerular Disease
- Polyomavirus 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

Changes in Causes of Mortality With Time in Diabetic Transplant Recipients

Keddis et al Kidney Int 2014

Table 2 | Five-year mortality and analyses of specific causes of death in kidney recipients with or without DM

Cause of death	No-DM		DM	
Transplant year	1996–2002	2003–2007	1996–2002	2003–2007
Number of patients	633	642	170	243
All causes	45 (7.1)	38 (5.9)	41 (24.1)[1]	29 (11.9)[b,1]
Cardiovascular	11 (1.8)[a]	12 (1.9)	16 (11.0)[1]	10 (4.5)[c,2]
Infection	3 (0.5)	5 (0.8)	5 (3.7)[3]	1 (0.5)[d]
Malignancy	6 (1.0)	4 (0.7)	5 (3.7)[4]	7 (3.2)[1]
Other	14 (2.3)	10 (0.7)	6 (4.4)	2 (0.9)[e,1]
Unknown	11 (1.8)	7 (1.1)	9 (6.5)[1]	9 (4.0)[1]

Transplant failure patients are 59% less likely to be wait-listed compared to a matched cohort of incident dialysis patients (N =102,978 in each group)

RR = 0.41 (95% CI 0.38 – 0.45)

Multivariate model adjusted for differences in age, comorbid conditions including IHD, CHF, PVD, CVA, cancer, clustered on state of residence

Gill et al. WTC 2014