Pathology and Management of Chronic Allograft Dysfunction

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Mission Impossible?

PLAN

- To review the description of chronic allograft dysfunction (NOT “CAN” or “chronic rejection”)
- To review the “Banff 2007 Update”
- To review the causes of chronic allograft dysfunction
- To review the potential treatment modalities of chronic allograft dysfunction

Case Discussion

- 21 year old African American woman
- ESRD due to lupus nephritis (class V)
- Living donor transplant
- Microscopic hematuria, proteinuria (2.7 g/day) and elevated serum creatinine (2.5 mg/dl) six years after transplantation
- Kidney biopsy: Focal proliferative GN with crescents and immune complexes (WHO class III, consistent with SLE)

Case Discussion

- Steroid pulses (250 mg x 3), prednisone 60 mg/d for one month with taper over the next 3 months
- Severe herpes esophagitis and CMV infection
- ACE inhibitor, good blood pressure control, on 1000 mg twice a day of mycophenolate mofetil
- Returned to dialysis 8 years after transplantation-2 years after the biopsy

Kidney Transplantation

- The number of patients on the waiting list for a deceased donor (DD) kidney transplant: 73,555-competing for approximately 11,200 kidneys

USRDS 2009 Annual Data Report

- Shortage of kidneys suitable for transplantation
- Waiting times are quite long (4-7 years)
- **Need to maximize graft survival**

Chronic Allograft Dysfunction

- Progressive graft failure with slowly rising serum creatinine and decreasing GFR
- End-stage kidney disease from a variety of insults to the graft
- Independent of acute rejection
- Variable degrees of hypertension and proteinuria
- Features of chronic allograft nephropathy: vascular intimal hyperplasia, intersitial fibrosis and tubular atrophy

Causes of Allograft Injury

- Immunologic (Antigen-dependent)
  - Cellular immunity
    - Inadequate immunosuppression/noncompliance
  - Humoral immunity
  - Acute rejection
  - HLA-matching
  - **Donor-specific antibodies** (**DSA**)
- Infections
    - Cytomegalovirus (CMV)
    - **BK virus**

Causes of Allograft Injury

- Nonimmunologic (Antigen-independent)
  - Organ viability
    - Living vs deceased
    - Donor age
    - Brain death
    - **Prolonged cold ischemia time**
    - Ischemia-reperfusion injuries
    - **Delayed graft function**/acute tubular necrosis
  - Recipient-related factors
    - **Hypertension**
    - Hyperlipidemia
    - Compliance
    - Obstruction
    - **Recurrent disease**
  - Treatment-**nephrotoxicity due to CNIs**

Banff 2007 Update

- 1. Normal
- 2. Antibody-mediated changes
  - C4d deposition without morphologic evidence of active rejection
  - Acute antibody-mediated rejection
  - Chronic active antibody-mediated rejection
- 3. Borderline changes: “suspicious” for acute T-cell-mediated rejection
- 4. T-cell-mediated rejection
  - Acute T-cell-mediated rejection
  - Chronic active T-cell-mediated rejection
- 5. Interstitial fibrosis and tubular atrophy (IF/TA)
- 6. Other: Changes not considered to be due to rejection

Solez K, et al. AJT 2008

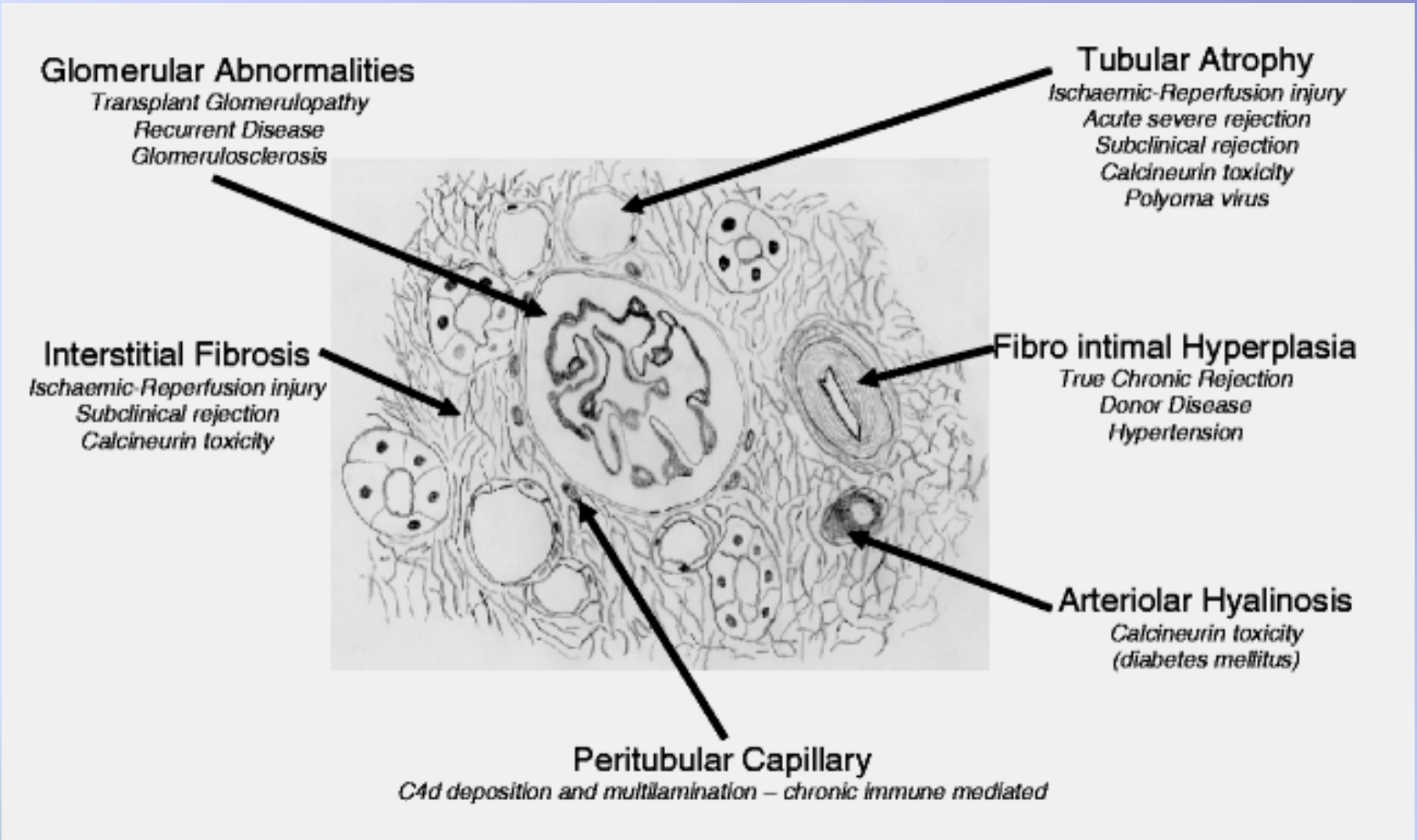
Mechanisms of Injury

- Acute cellular or acute humoral rejection: might leave residual injury predisposing to chronic injury
- Chronic humoral rejection with the presence of C4d as well as reduction in regulatory T-cell (Treg) numbers, and inhibition of their function

Table 1: Morphology of specific chronic diseases

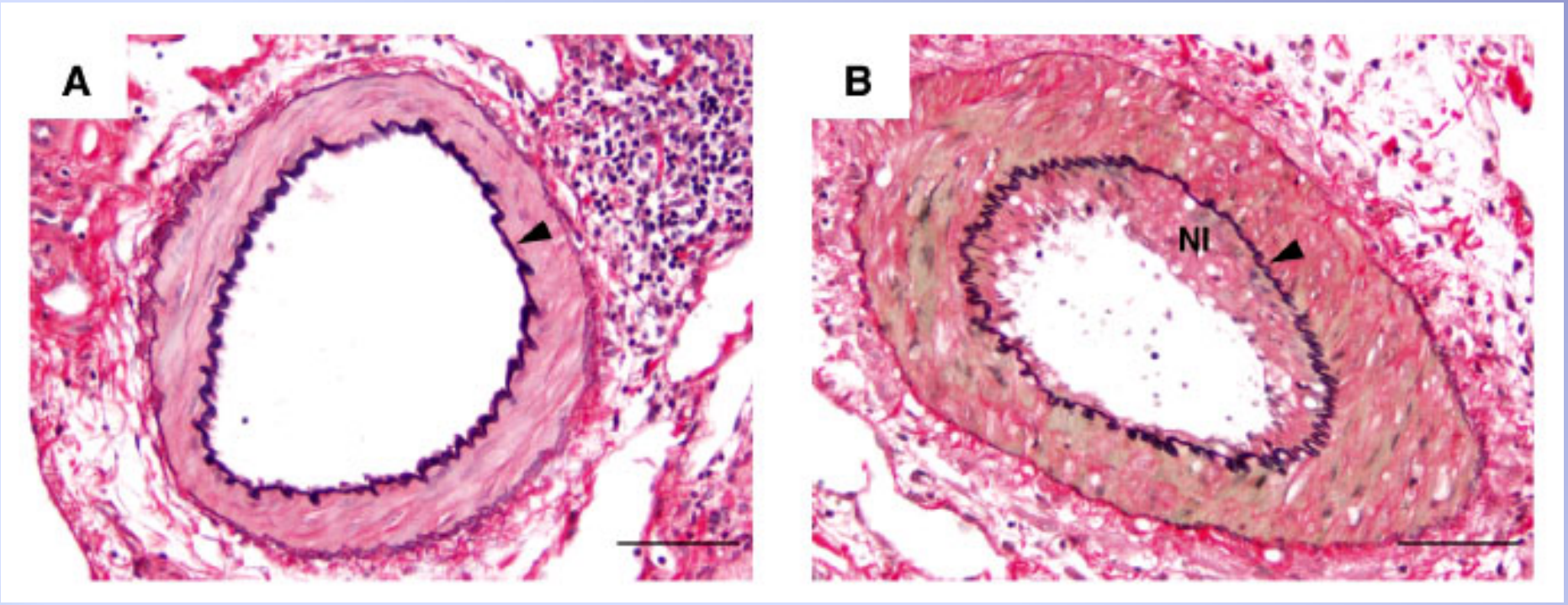
Causes of IF/TA (non-rejection)	
Etiology	Morphology
Chronic hypertension	Arterial/fibrointimal thickening with reduplication of elastica, usually with small artery and arteriolar hyaline changes.
CNI[1] toxicity	Arteriolar hyalinosis with peripheral hyaline nodules and/or progressive increase in the absence of hypertension or diabetes. Tubular cell injury with isometric vacuolization.
Chronic obstruction	Marked tubular dilation. Large Tamm–Horsfall protein casts with extravasation into interstitium, and/or lymphatics.
Bacterial pyelonephritis	Intratubular and peritubular neutrophils, lymphoid follicle formation.
Viral infection	Viral inclusions on histology and immunohistology and/or electron microscopy.

Solez K, et al. Am J Transplant 2007



Alexander SI, et al. Pediatric Nephrology 2007

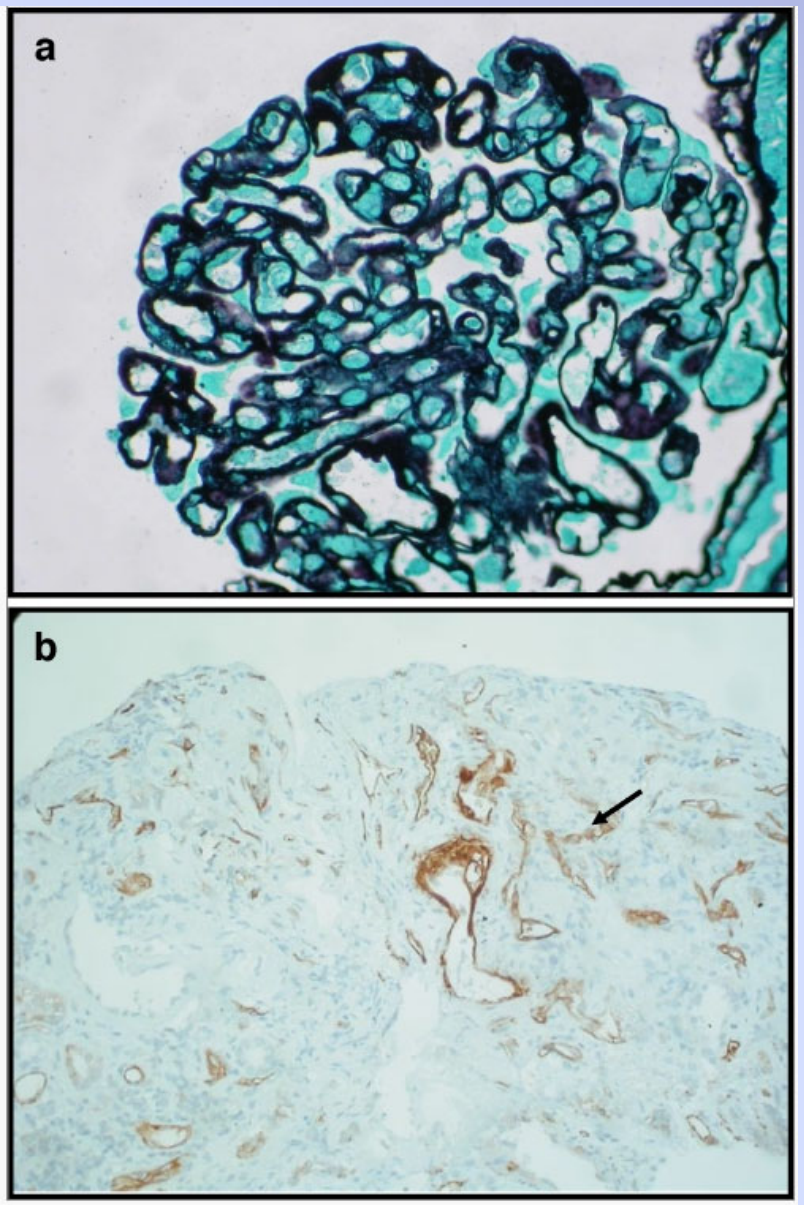
Transplant Vasculopathy (TV)



Artery from a vehicle-treated allograft

Artery with TV; NI: neointima; arrowhead: elastin

Waanders F, et al. Am J Physiol Renal Physiol 2009



•Renal allograft biopsy (***silver staining***)

•Evidence of “double contours” in capillary loops

•Mesangial proliferation and matrix expansion and basement membrane thickening

•Renal allograft biopsy with C4d deposition (***in brown***) in peritubular capillaries consistent with antibody-mediated rejection

Fletcher J, et al. Pediatr Nephrol 2009

The Natural History of Chronic Allograft Nephropathy

- A prospective study of 120 recipients with type 1 diabetes, all but 1 of whom had received kidney–pancreas transplants (1987-2000)
- 961 kidney-transplant–biopsy specimens taken regularly from the time of transplantation to 10 years thereafter

Nankivell BJ, et al. N Engl J Med 2003

Table 1. Characteristics of the Allograft at and after Transplantation.*

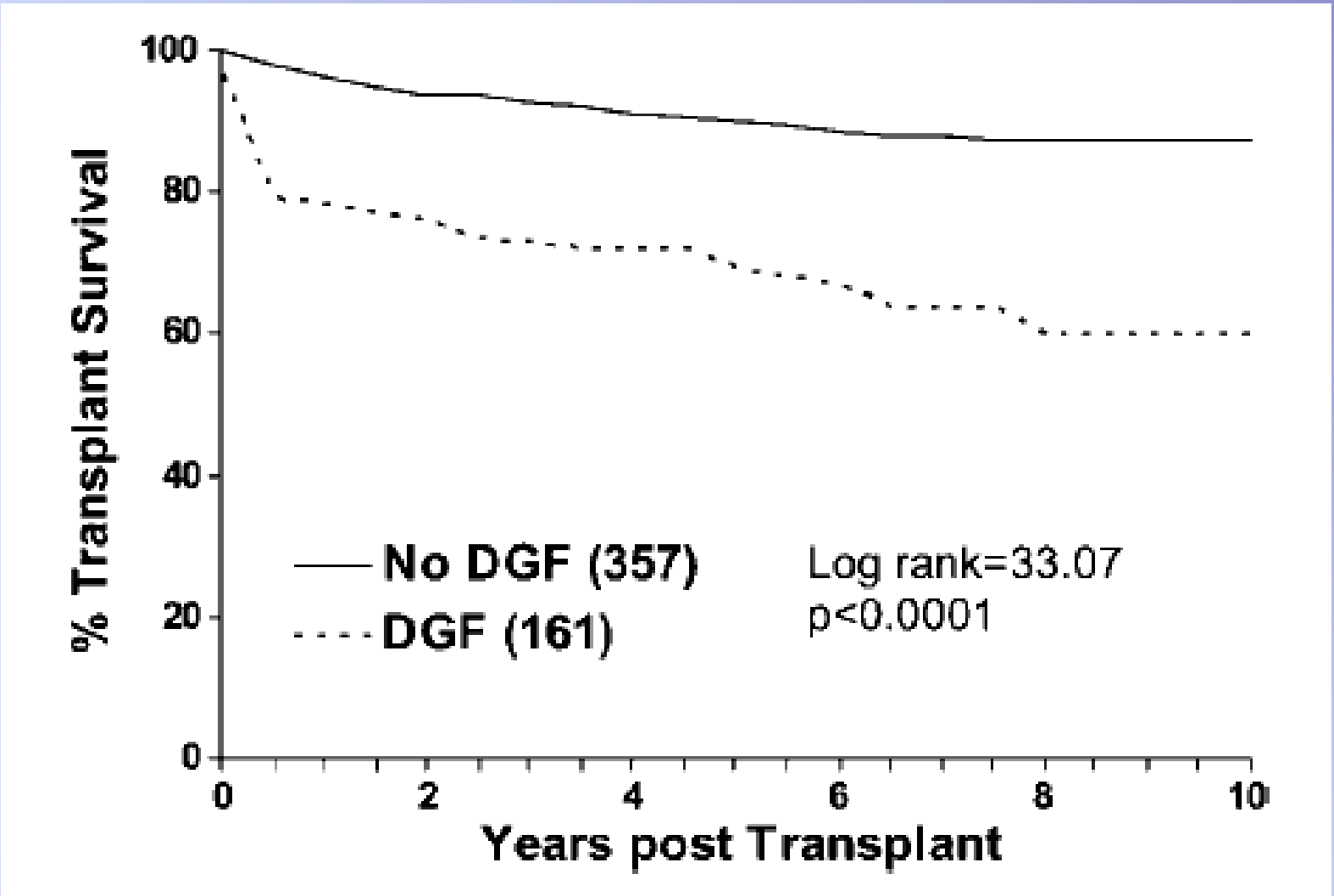
Characteristic	At Transplantation† (N=135)	3 Mo (N=138)	6–12 Mo (N=188)	2–5 Yr (N=223)	6–10 Yr (N=81)
Banff score‡					
Chronic interstitial fibrosis	0.09±0.24	0.70±0.53	1.07±0.56	1.34±0.67	1.64±0.74
Tubular atrophy	0.06±0.20	0.56±0.51	0.99±0.52	1.26±0.67	1.57±0.76
Fibrointimal thickening	0.03±0.16	0.11±0.30	0.17±0.38	0.31±0.51	0.33±0.51
Chronic glomerulopathy	0.0±0.04	0.08±0.10	0.08±0.26	0.12±0.30	0.24±0.48
Mesangial matrix (mm)	0.09±0.29	0.18±0.41	0.31±0.41	0.44±0.48	0.62±0.57
Arteriolar hyalinosis	0.16±0.35	0.29±0.48	0.39±0.54	0.72±0.71	1.22±0.83
Sclerosed glomeruli (%)	1.7±4.3	2.3±6.2	2.1±4.9	14.1±18.1	37.2±21.9
Subclinical rejection (%)	NA	41.8	36.8	19.5	12.3
Isotopic glomerular filtration rate (ml/min)	NA	59.3±16.8	60.7±17.0	54.7±19.8	50.2±27.2
Serum creatinine (mg/dl)	NA	1.48±0.61	1.45±0.33	1.56±0.55	1.62±0.48

* Plus–minus values are means ±SD. The numbers are the numbers of biopsy specimens. To convert values for serum creatinine to micromoles per liter, multiply by 88.4. NA denotes not applicable.
† Samples were obtained up to one week after transplantation.
‡ Banff scores range from 0 to 3, with higher scores indicating more severe abnormalities.

Nankivell BJ, et al. N Engl J Med 2003

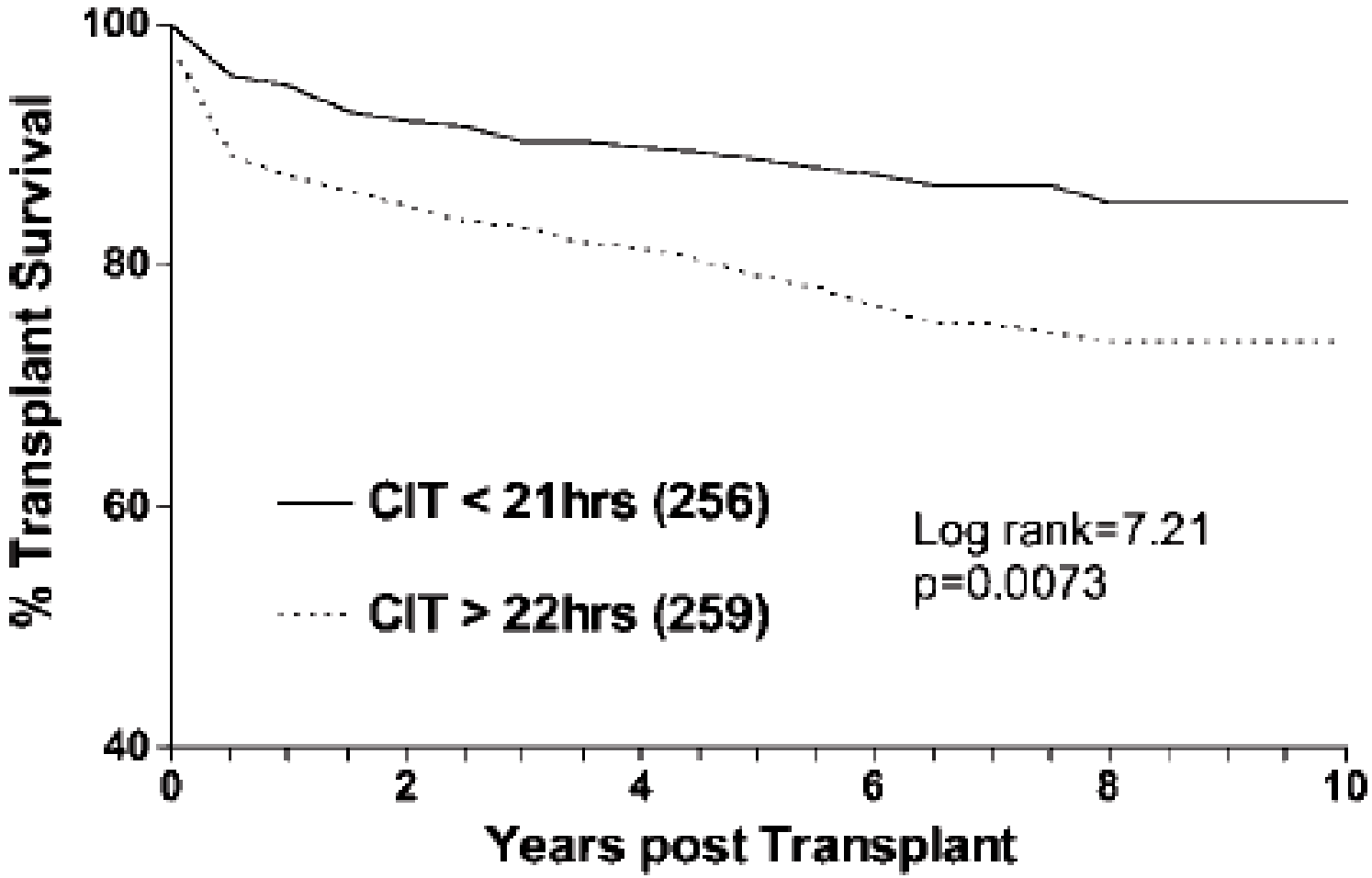
Relevant Donor Abnormalities

- Advanced donor age
- Pre-existing disease or injury to the donor: glomerulosclerosis (>20%), microvascular disease
- HLA-mismatch
- Prolonged cold ischemia time
- Living vs deceased donors: ischemia-reperfusion injury
- Using time-zero biopsies: might be very helpful to assess subsequent biopsies



*Delayed graft function (DGF): major predictor of graft failure overall with cold ischemia time (CIT) as an important independent factor

Quiroga I, et al. Nephrol Dial Transplant 2006



*Prolonged CIT, directly and independently of DGF and AR, compromises the long-term graft survival

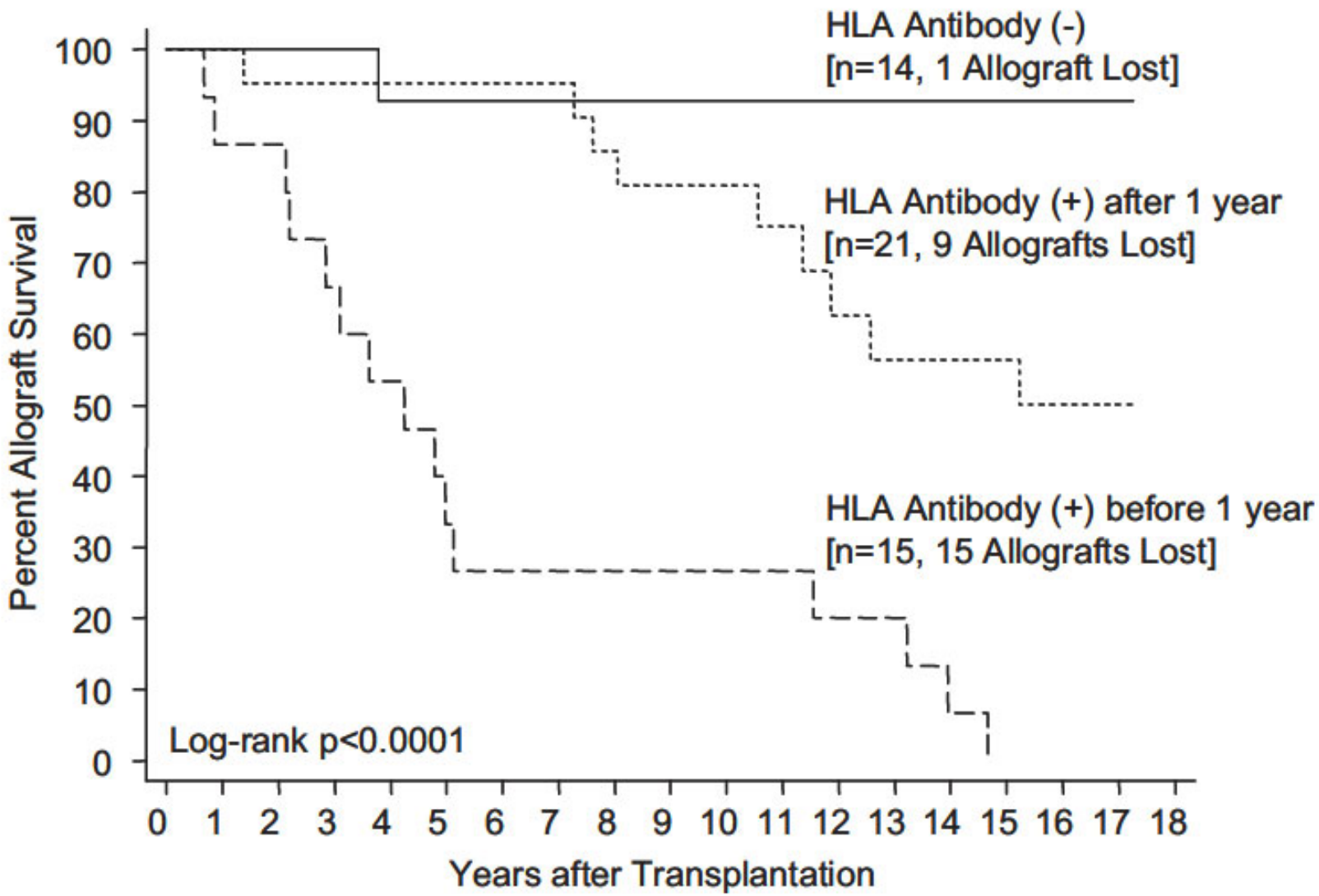
Quiroga I, et al. Nephrol Dial Transplant 2006

HLA-Specific Antibodies Developed in the First Year Posttransplant are Predictive of Chronic Rejection and Renal Graft Loss

Lee, Po-Chang; Zhu, Lan; Terasaki, Paul I.; Everly, Matthew J.

Transplantation 2009

- Retrospective case-controlled study from Taiwan
- 278 patients, transplanted between 1991-2004
- 25 patients with failed graft (230 serum samples) and 25 patients with a functioning graft (305 serum samples)



•HLA antibody development within 1-year posttransplant markedly lowers allograft survival

Lee PC, et al. Transplantation 2009

Hypertension after Kidney Transplantation

- Very common
- Not well controlled-despite multiple antihypertensive medications
- Independent risk factor for graft failure and mortality
- ACE inhibitor use (from 1993 to 2002): 25% of patients were treated in the first year after transplantation

Kasiske B, et al. Am J Kidney Diseases 2004

Opelz G, et al. Kidney International 1998

Improved Long-Term Outcomes with Blood Pressure Control

- 24,404 patients transplanted between 1987 and 2000-Collaborative Study Database
- Patients whose SBP was >140 mmHg at 1 year posttransplant but controlled to ≤140 mmHg by 3 years had significantly improved long-term graft outcome compared with patients with sustained high SBP to 3 years
- At 5 years : SBP lowering after year 3 was associated with improved 10-year graft survival

Opelz G, et al. Am J Transplant 2005

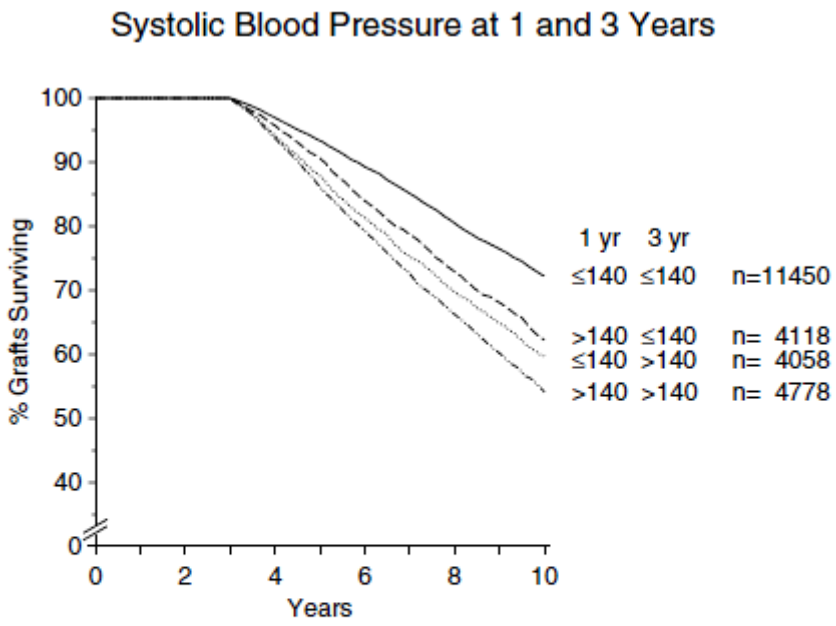


Figure 2: Long-term kidney graft survival calculated from 3 to 10 years in relation to systolic blood pressure of <140 or ≥140 mmHg at 1 and 3 years posttransplant. The respective 1- and 3-year pressures are indicated to the right of each curve, together with numbers of patients studied.

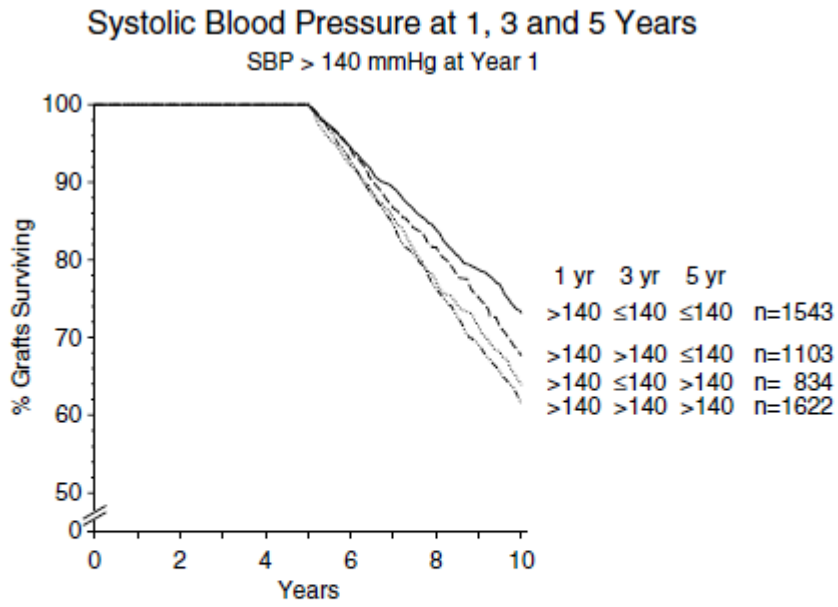


Figure 4: Relationship of blood pressure profiles examined over 5 years on kidney graft survival from 5–10 years. Systolic blood pressures >140 or ≤140 mmHg at 1, 3 and 5 years post-transplant are indicated for each patient group studied. All patients in this analysis had a SBP of >140 mmHg 1 year posttransplant.

Opelz G, et al. Am J Transplant 2005

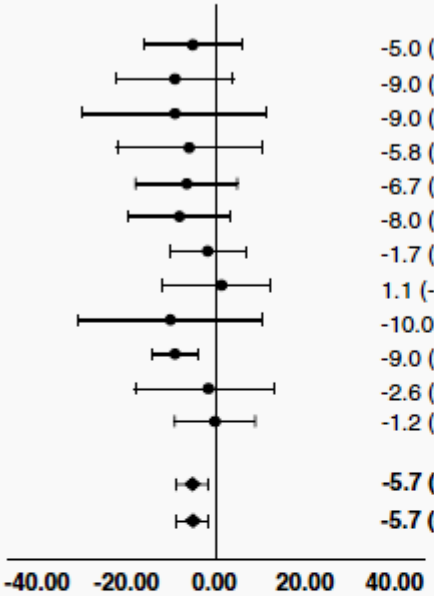
Antihypertensives for Kidney Transplant Recipients

- Meta-analysis of randomized controlled trials
- 60 trials, enrolling 3802 recipients
- Twenty-nine trials (2262 patients) compared calcium channel blockers (CCB) with placebo or no treatment
- 10 trials (445 patients) compared ACEi with placebo or no treatment
- 7 studies (405 patients) compared CCB with ACEi
- In direct comparison with CCB, ACEi decreased GFR, proteinuria, hemoglobin, and increased hyperkalemia
- Graft loss data were inconclusive

Cross AN, et al. Transplantation 2009

A

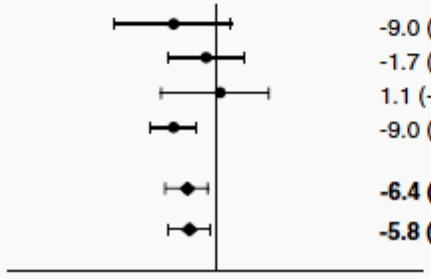
Study name	ACE/ARB N	ACE/ARB Mean	Control N	Control Mean	Mean Difference (95% CI)
Curtis	18	-8.0	18	-3.0	-5.0 (-16.0, 6.0)
Mourad	16	-3.0	15	6.0	-9.0 (-22.5, 4.5)
Hernandez E	10	-5.0	11	4.0	-9.0 (-30.1, 12.1)
Beckingham	15	-4.1	10	1.7	-5.8 (-23.0, 11.4)
Sennesael	10	-4.2	10	2.5	-6.7 (-18.9, 5.5)
Van der Schaff	20	-3.0	20	5.0	-8.0 (-19.6, 3.6)
Cieciura	43	-6.0	32	-4.3	-1.7 (-10.1, 6.7)
Suwelack	48	3.9	48	2.8	1.1 (-11.2, 13.4)
Inigo	17	-2.1	17	7.9	-10.0 (-30.4, 10.4)
Midtvedt	76	1.0	78	10.0	-9.0 (-14.0, -4.0)
Martinez-Castelao	42	-6.9	42	-4.3	-2.6 (-18.8, 13.7)
Tylicki	14	1.8	14	3.0	-1.2 (-9.5, 7.1)
Overall fixed	329		315		**-5.7 (-8.7, -2.8) P <0.001**
Overall random	329		315		**-5.7 (-8.7, -2.8) P <0.001**



ACE/ARB Worse ACE/ARB Better

B

Study name	ACE/ARB N	ACE/ARB Mean	Control N	Control Mean	Mean Difference (95% CI)
Mourad	16	-3.0	15	6.0	-9.0 (-22.5, 4.5)
Cieciura	43	-6.0	32	-4.3	-1.7 (-10.1, 6.7)
Suwelack	48	3.9	48	2.8	1.1 (-11.2, 13.4)
Midtvedt	76	1.0	78	10.0	-9.0 (-14.0, -4.0)
Overall fixed	183		173		**-6.4 (-10.3, -2.5) P = 0.001**
Overall random	183		173		**-5.8 (-10.6, -0.99)P = 0.02**



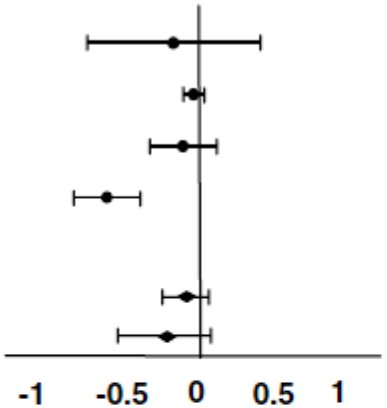
ACE/ARB Worse ACE/ARB Better

*Change in GFR

Hiremath S, et al. Am J Transplant 2007

A

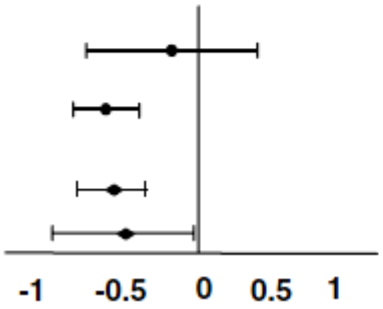
Study name	ACEI/ARB N	ACEI/ARB Mean	Control N	Control Mean	Mean Difference (95% CI)
Cieciura	43	-0.09	32	0.08	-0.17 (-0.73, 0.39)
Inigo	17	-0.02	17	0.02	-0.04 (-0.11, 0.02)
Martinez-Castelao	42	-0.24	42	-0.13	-0.11 (-0.32, 0.10)
El Agroudy	108	-0.4	54	0.2	-0.60 (-0.81, -0.39)
Overall fixed	210		145		**-0.09 (-0.15, -0.03) P = 0.002**
Overall random	210		145		**-0.23 (-0.52, 0.06) P = 0.12**



ACEI/ARB Better **ACEI/ARB Worse**

B

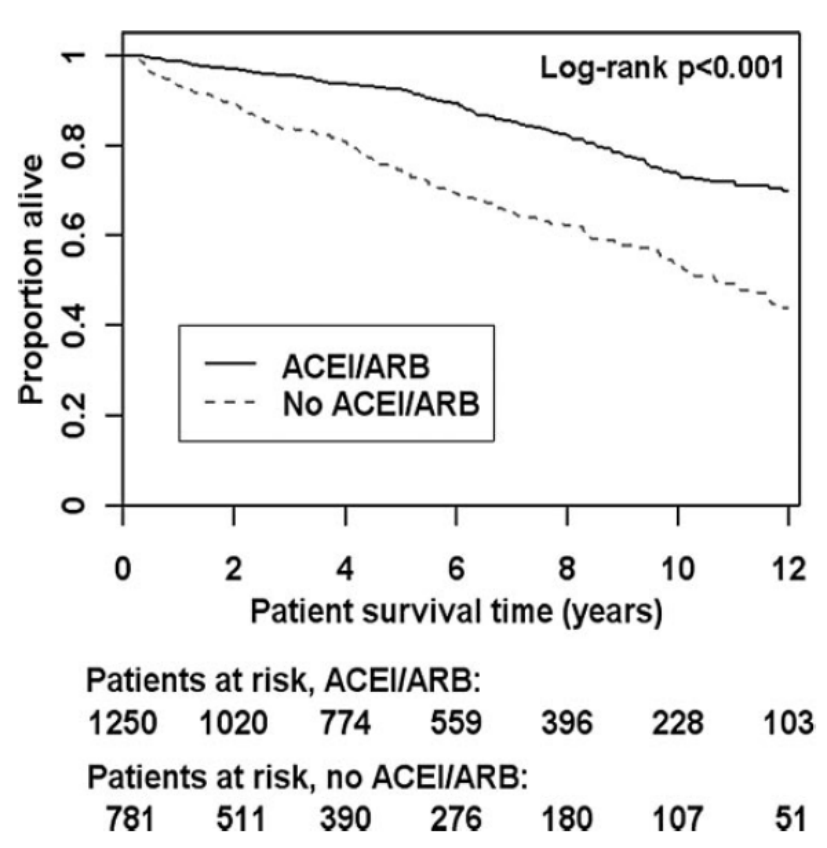
Study name	ACEI/ARB N	ACEI/ARB Mean	Control N	Control Mean	Mean Difference (95% CI)
Cieciura	43	-0.09	32	0.08	-0.17 (-0.73, 0.39)
El Agroudy	108	-0.4	54	0.2	-0.60 (-0.81, -0.39)
Overall fixed	151		86		**-0.55 (-0.74, -0.35) P = <0.001**
Overall random	151		86		**-0.47 (-0.86, -0.08) P = 0.02**

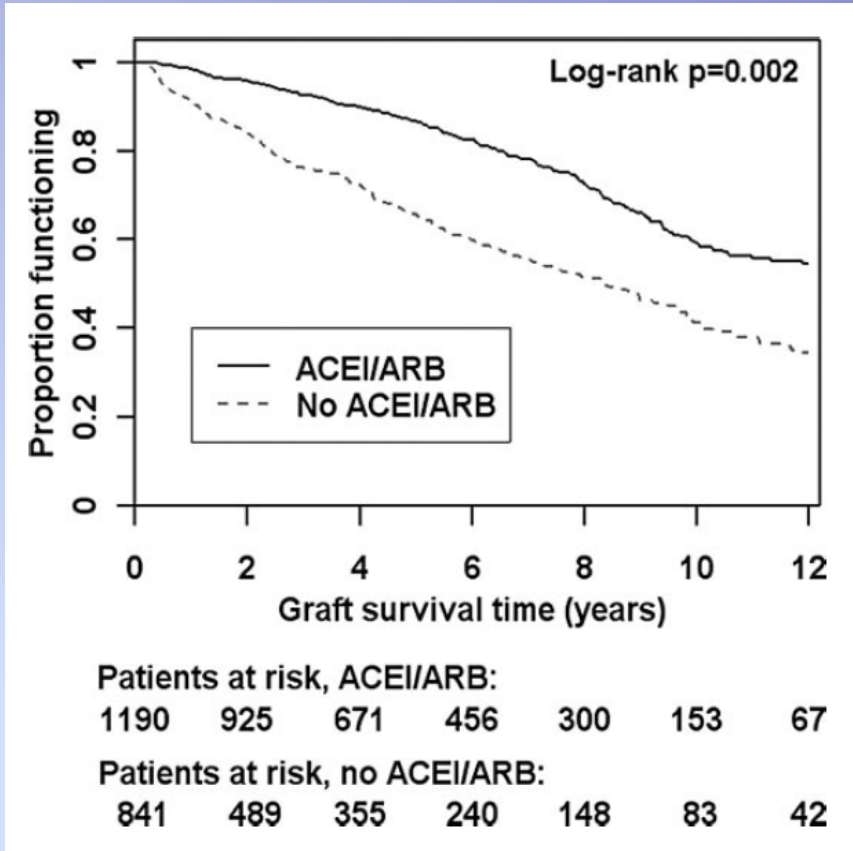


ACEI/ARB Better **ACEI/ARB Worse**

*Change in proteinuria

Hiremath S, et al. Am J Transplant 2007





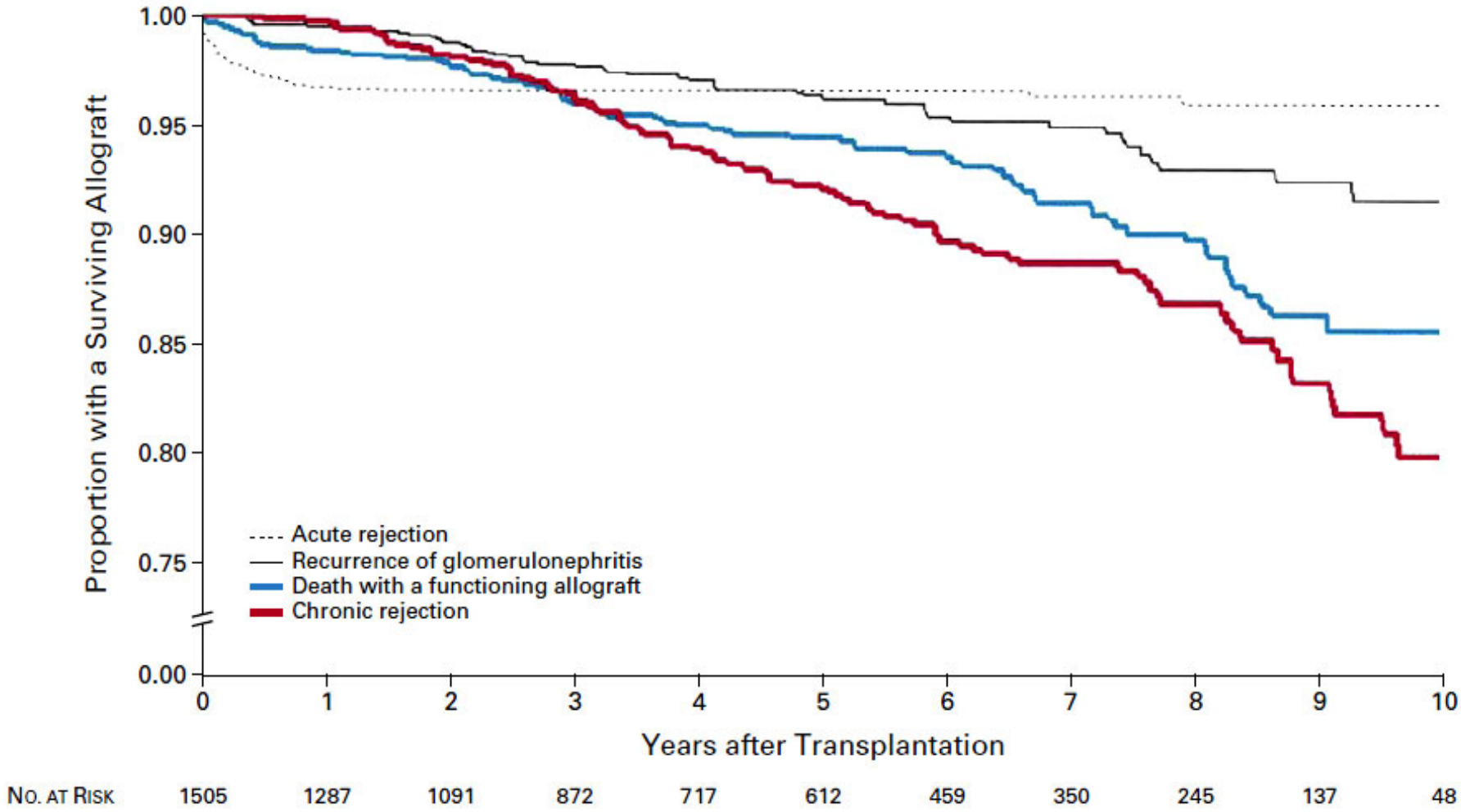
•The use of ACEI/ARB therapy was associated with longer patient and graft survival after renal transplantation (2,031 patients, transplanted 1990-2003)

Heinze G, et al. J Am Soc Nephrol 2006

Risk of Long-Term Graft Loss

- 1505 patients with biopsy-proven GN from Australia (1988-1997)
- Most frequent causes of allograft loss at 10 years: **1. Chronic rejection, 2. Death with a functioning graft, 3. Recurrence**
- The incidence of allograft loss due to recurrence at 10 years was 8.4% and increased overtime
- Recurrence is more frequent than acute rejection as a cause of allograft loss during first 10 years after transplant

Briganti EM, et al NEJM 2002



Briganti EM, et al NEJM 2002

Recurrent Disease (True Recurrence): Diagnosis

Biopsy proven disease on native kidney

↓↓

Posttransplant proteinuria or hematuria or elevated creatinine

↓↓

Same biopsy proven disease on kidney transplant

Recurrent Glomerular Diseases (GN)

- **Recurrence of primary GN**: FSGS, MPGN, IgA nephropathy
- **Recurrence of secondary GN**: SLE, Henoch-Schönlein, HUS/TTP, anti-GBM disease
- **Recurrence of metabolic or systemic disease**: diabetic nephropathy, amyloidosis, scleroderma, oxalosis, Fabry disease

Recurrent GN in the Transplant

- **The prevalence of GN as the cause of ESRD**: 10-25%, higher prevalence in children and white patients
- **The prevalence of recurrent GN**: 1.9%-31% in different series
- **True prevalence of recurrent GN**: patients who lost their grafts due to recurrence + patients who have recurrence with a functioning graft
- **Cause of graft loss:** 1-8.4% of all graft failures

Potential Problems for Identifying Recurrent GN in the Transplant

- Primary disease-native kidney disease-is unknown for many patients
- No unified approach for patients with urinary abnormalities and increased serum creatinine after transplantation (histological vs clinical diagnosis)
- Transplant biopsy is not routinely submitted for IF and EM examination

Potential Problems for Identifying Recurrent GN in the Transplant

- Interpretation of the biopsy: DIFFICULT, *de novo* vs recurrent-MPGN vs transplant glomerulopathy
- Most of the studies are small and retrospective with variable follow-up periods
- No randomized, prospective studies for different treatment regimens

Protocol Biopsies

- Processes that lead to late graft loss begin early and can be detected by protocol biopsies (1–3 months)
- Chronic tubulo-interstitial and vascular changes can be seen in one third of transplants after 1 year and at later times become nearly universal
- Detection of abnormalities in early protocol biopsies (**the presence of IF/TA**) is predictive of subsequent graft function and loss
- Biopsies at 3 months scored as Banff ci0 and cv0 have a significantly better graft survival at 5 years
- Early treatment may have a dramatic effect on the outcome of the graft-**No clear treatment options**

Treatment of Subclinical Rejection

- 72 patients: randomized to biopsies at 1, 2, 3, 6, and 12 mo (Biopsy group), or to 6- and 12-mo biopsies only (Control group)
- SCR: treated during the first 3 months with methylprednisolone boluses
- Treatment of SCR was associated with a reduced progression of IF/TA at 6 months and better graft function at 2 years
- The prevalence of SCR: 30%-patients were on cyclosporine, azathioprine, and steroids

Rush D, et al. J Am Soc Nephrol 1998

Protocol Biopsies

- Role is not clear on managing transplant patients
- Can we identify patients who are at risk of developing graft dysfunction?
- Benefit of this approach has yet to be evaluated in large, multicenter, and prospective trials (?efficacy variable in clinical trials)
- **Complications-**all within 4 hours: gross hematuria 3.5%, perirenal hematoma 2.5%, and A-V fistula with mostly spontaneous resolution 7.5%

Schwarz A, et al. Am J Transplant 2005

Minimizing the Impact of CNI-induced Nephrotoxicity

- CNI avoidance: not very successful in the past
- Conversion: CNI withdrawal at 3-mo or 6-mo; conversion to MMF or sirolimus
- Minimization of CNIs/additional agents: low dose CNI with MMF/MPA ± steroids or mTOR inhibitors

Minimizing the Impact of CNI-induced Nephrotoxicity

- CNI minimization:
  - The Symphony trial: 1 year follow-up
  - 4 arm study (1589 patients):
    - **Daclizumab induction, 2 g MMF, low-dose tacrolimus (target level 3-7) and steroids** resulted in better renal function and lower acute rejection and graft loss rates compared with three other regimens: two with **low-doses of cyclosporine or sirolimus** and one with **no induction and standard cyclosporine**
  - Similar results at additional 2-year follow-up (958 patients)

Ekberg H, et al. NEJM 2007

Ekberg H, et al. AJT 2009

End Point	Standard-Dose Cyclosporine (N=390)	Low-Dose Cyclosporine (N=399)	Low-Dose Tacrolimus (N=401)	Low-Dose Sirolimus (N=399)	P Value†
Primary end point					
Mean calculated GFR — ml/min‡	57.1±25.1	59.4±25.1	65.4±27.0	56.7±26.9	<0.001
P value for comparison with tacrolimus	<0.001	0.001	Reference	<0.001	
Secondary end points					
Mean measured GFR — ml/min§	63.5±25.4	65.3±26.6	69.6±27.9	64.4±28.5	0.04
P value for comparison with tacrolimus	0.01	0.10	Reference	0.02	
Mean calculated GFR — ml/min¶	46.2±23.1	50.2±23.1	54.3±23.9	47.5±26.1	<0.001
P value for comparison with tacrolimus	<0.001	0.007	Reference	<0.001	
Acute rejection‖					
At 6 mo					
Biopsy-proven (excluding borderline values) — %	24.0	21.9	11.3	35.3	<0.001
P value for comparison with tacrolimus	<0.001	<0.001	Reference	<0.001	
At 12 mo					
Suspected and treated — %	32.8	29.5	17.2	43.5	<0.001
P value for comparison with tacrolimus	<0.001	<0.001	Reference	<0.001	
Biopsy-proven (including borderline values) — %	30.1	27.2	15.4	40.2	<0.001
P value for comparison with tacrolimus	<0.001	<0.001	Reference	<0.001	

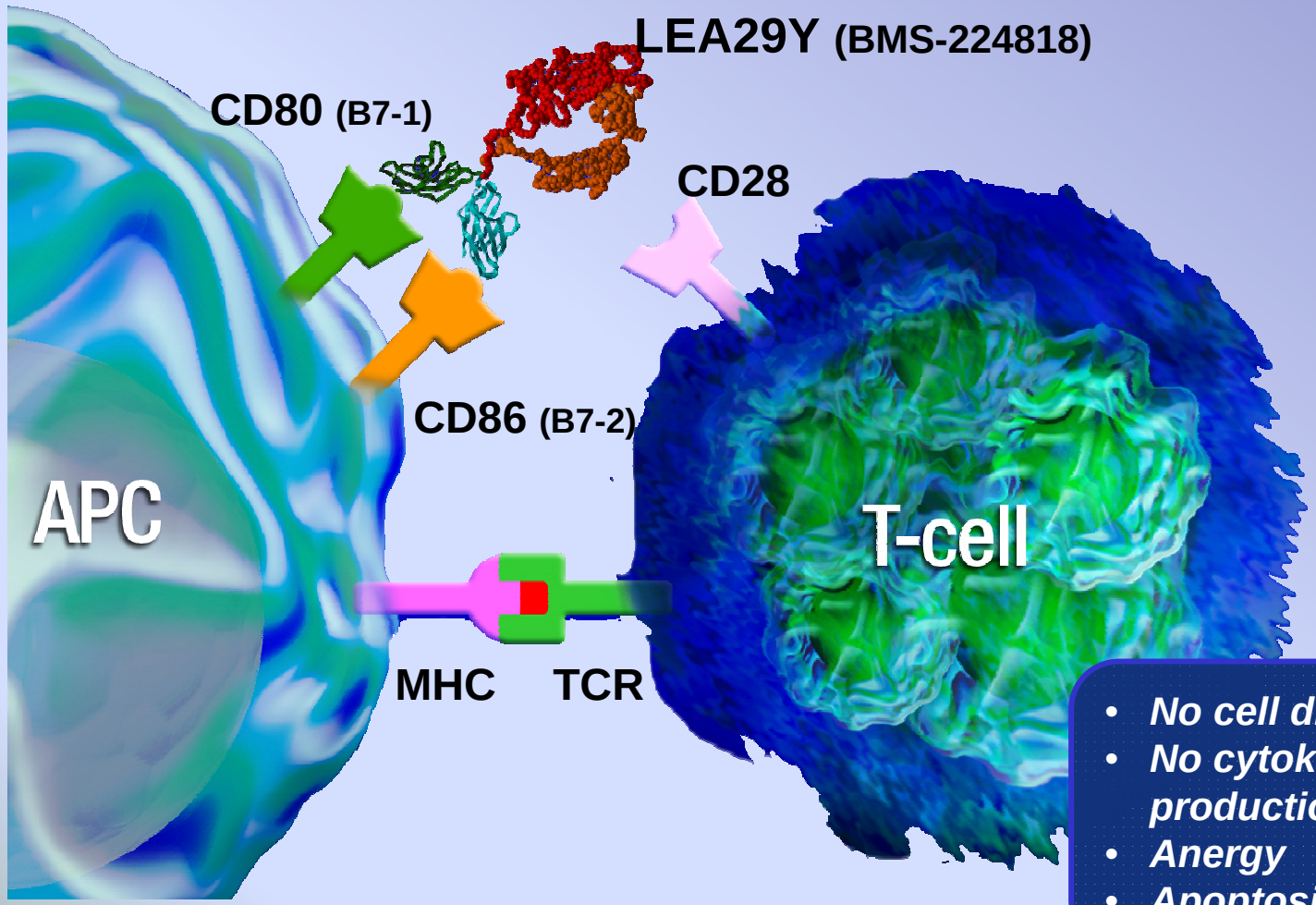
Ekberg H, et al. NEJM 2007

Minimizing the Impact of CNI-induced Nephrotoxicity

- New agents: biologics (belatacept, alefacept, efalizumab) and small molecules (Janus Kinase inhibitors)
  - 218 patients: randomized to intensive or a less intensive regimen of belatacept or cyclosporine
  - All patients received induction with basiliximab, MMF, and corticosteroids
  - At six months, the incidence of acute rejection was similar among the groups: 7 % for intensive belatacept, 6% for less-intensive belatacept, and 8% for cyclosporine
  - At 12 months, the GFR was significantly higher with belatacept and chronic allograft nephropathy was less common with belatacept than with cyclosporine

Vincenti F, et al. N Eng J Med 2005

Belatacept Potently and Selectively Blocks T-cell Activation



- *No cell division*
- *No cytokine production*
- *Anergy*
- *Apoptosis*

Belatacept Studies

- Less diabetes, better BP control, better lipids; very few patients with DSA
- More acute rejection (up tp 22%); but better GFR at 12 months
- PTLD: 8 in MI (6 CNS), 6 in LI (3 CNS), 2 in CsA arm; most of them EBV negative
- Despite a favorable vote from FDA Advisory Committee (3/2010), FDA did not approve the use of belatacept and requested longer-term clinical data for the product

Conversion Studies

- Conversion from cyclosporine to tacrolimus-5 year data (**CRAF** study): significant improvement in renal function but no impact on patient or graft survival

  Shihab F, et al. Transplantation 2008

- **Convert** trial: 830 patients, 6-120 mo posttx and receiving cyclosporine or tacrolimus, were randomly assigned to continue CNI (n=275) or convert to sirolimus (n=555)
- At 2 years, SRL conversion among patients with baseline GFR> 40 mL/min was associated with excellent patient and graft survival, no difference in BCAR, increased urinary protein excretion, and a lower incidence of malignancy compared with CNI continuation

  Schena FP, et al. Transplantation 2009

Mycophenolate Mofetil (MMF) versus Azathioprine (AZA)

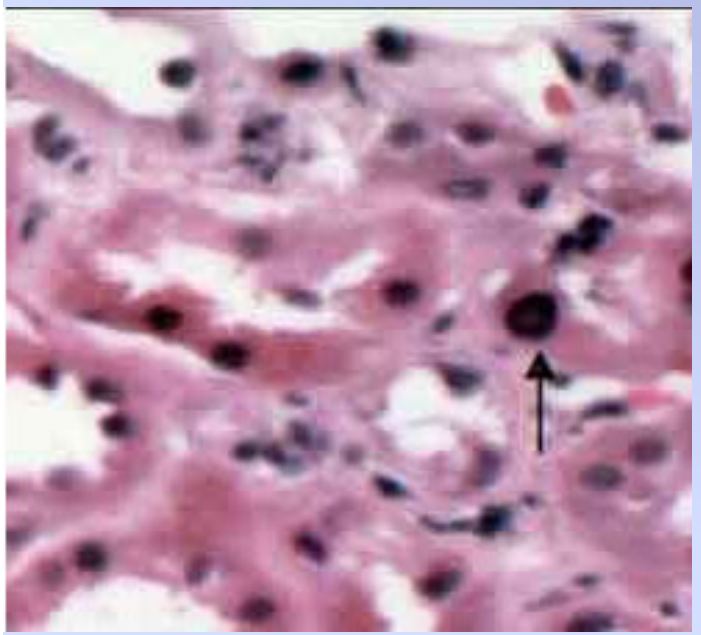
- Systematic review of the literature and meta-analysis (1985-2007)
- Randomized controlled studies
- Direct comparison of MMF vs AZA
- 27 publications from 19 trials included

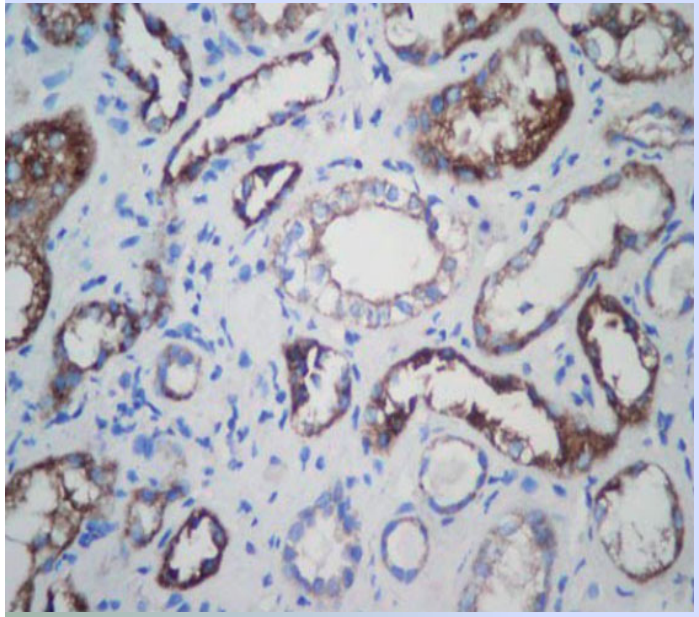
Knight SR, et al. Transplantation 2009

Mycophenolate Mofetil (MMF) versus Azathioprine (AZA)

- 3143 patients (1775 on MMF vs 1368 on AZA)
- The use of MMF significantly reduced the risk of acute rejection compared with AZA over all
- The hazard of graft loss was lower in the MMF group

Knight SR, et al. Transplantation 2009





BK Nephropathy

- Intranuclear inclusion bodies in epithelial cells and severe tubular injury
- Interstitial fibrosis
- Positive immunohistochemical staining
- Electron microscopy demonstrating viral particles

BK/JC Virus Infection

- 400 **healthy blood donors** aged 20-59 years were tested for BKV- and JCV-specific antibodies against virus-like particles
- **IgG seroprevalence was 82%** (328 of 400 donors) for BKV and 58% (231 of 400) for JCV
- Asymptomatic urinary shedding of BKV and JCV was observed in 28 (7%) and 75 (19%) of 400 subjects, respectively

Egli A, et al. J Infec Dis 2009

BK Nephropathy

- The prevalence rate varies from 1% to 10% due to different local immunosuppression protocols and diagnostic approaches
- Pathophysiology:
  - Replicates best in uroepithelial cells, but also found in lymphoid, other tissues
  - Asymptomatic viruria/viremia
  - Ureteral ulceration, stricture & stenosis, hemorrhagic cystitis
  - Progressive loss of renal allograft function
  - Urothelial malignancy & vasculopathy

Table 1. Diagnostic Testing for BK Virus Nephropathy

Test	Threshold Value	Correlation With PVAN on Biopsy
Decoy cells	>10 cells/cytospin	+
Urine BK virus DNA quantitative PCR	$>1 \times 10^7$ copies/mL	++
Blood/plasma BK virus DNA quantitative PCR	$>1 \times 10^4$ copies/mL	+++

Abbreviations: PCR, polymerase chain reaction; PVAN, polyomavirus-associated nephropathy.

	Sensitivity	**Specificity**	**PPV**
Decoy Cells (>10/cytospin)	25%	84%	5-20%
Viruria (>10^7 copies/ml)	100%	92%	31%
Viremia (>10^4 copies/ml)	100%	96%	50-60%

Wiseman AC. Am J Kid Dis 2009
Viscount HB, et al. Transplantation 2007

Treatment of BK Nephropathy

- No specific antiviral drug treatment
- Reduction/adjustment in immunosuppression remains the cornerstone
- Cidofovir, leflunomide, quinolones, and intravenous immunoglobulin: no randomized prospective clinical trial

Impact of Preemptive Reduction of Immunosuppression

- 200 adult renal transplant recipients: randomized to tacrolimus (n = 134) or cyclosporine (n = 66)
- Urine and blood were collected weekly for 16 weeks and at months 5, 6, 9 and 12 and analyzed for BK viral load
- By 1 year, 70 patients (35%) developed viruria and 23 (11.5%) viremia; neither were affected independently by immunos used
- Viruria was highest with TAC-MMF (46%) and lowest with CsA-MMF (13%), p = 0.005

Brennan DC, et al. Am J Transplant 2005

Impact of Preemptive Reduction of Immunosuppression

- Management of immunosuppression:
  - Identification of BK viremia triggered discontinuation of AZA or MMF
  - If viremia failed to clear within 4 weeks, the calcineurin inhibitor dose was tapered to trough CsA levels of 100–200 ng/mL or trough TAC levels of 3–5 ng/mL
- After reduction of immunosuppression, viremia resolved in 95%, without increased acute rejection, allograft dysfunction or graft loss
- No BK nephropathy was observed

Brennan DC, et al. Am J Transplant 2005

BK virus and Pre-Emptive Immunosuppression Reduction 5-Year Results

- A retrospective 5-year review
- 5 year follow up in 97% of patients
- Viremia resolved in 95% of patients with reduction of immunosuppression
- 5-year patient survival 91% and graft survival 84%
- Immunosuppression and viremia did not influence graft survival
- Acute rejection: 12% by 5-years after transplant
- No BK nephropathy-no protocol biopsies

Hardinger KL, et al. AJT 2010

Screening and Diagnostic Testing for BK

- Linear progression is an opportunity: from viruria (30-40%) to viremia (10-20%) to nephropathy (1-10%) and graft dysfunction/ loss
- Blood and/or urine samples every 3 months for first 2 years, then once a year and in the event of allograft dysfunction
- Careful reduction of immunosuppression and close follow-up for development of acute rejection

Evaluation of a Patient with Late Allograft Dysfunction

- Exclusion of obvious causes such as obstruction, dehydration, high CNI levels, uncontrolled hypertension, and UTI/urosepsis
- Urinalysis, spot urine protein/ creatinine ratio, and 24-h urine collection
- BK viral load (blood/urine)
- Kidney biopsy: consider early before significant graft dysfunction

Evaluation of a Patient with Late Allograft Dysfunction

- Adequate biopsy sample to make a correct diagnosis (**at least 10 glomeruli and two arteries; two cores of cortex preferably**); comparison with time-zero biopsies, if possible
- Light microscopy to assess fibrosis and tubular atrophy, as well as specific stains (PAS and silver stain)
- IF to assess recurrent or de novo GN or C4d deposition
- EM to detect early transplant glomerulopathy or immune deposits

New Diagnostic Methods

- Gene and protein expression profiles (peripheral blood, urine and graft)
- Predictors of interstitial fibrosis in biopsies
  - Early phenotypic changes indicative of epithelial-to-mesenchymal transition (*de novo* vimentin expression and translocation of β-catenin in to the cytoplasm of tubular cells)

Hertig A, et al. J Am Soc Nephrol 2008

- Validation of these tests in transplant patients-diagnosis of a certain disease and also specific treatment

Therapy for Chronic Allograft Dysfunction

- There is no single specific treatment; several therapies and approaches
- Early diagnosis/early intervention: IMPORTANT
- Changes in serum creatinine occur at a late stage
- Serum creatinine might underestimate deterioration in GFR

Therapy for Chronic Allograft Dysfunction

- Minimization of cold ischemia time
- Aggressive management of hypertension: BP goal <130/80 mmHg
- Management of diabetes/PTDM
- Treatment of hyperlipidemia-LDL target<100
- Reduction of proteinuria
- Treatment of infections-CMV/BK
- Treatment of recurrent diseases

Therapy for Chronic Allograft Dysfunction

- Manipulation of immunosuppression
  - **More potent immunosuppressive therapy early after transplantation followed by minimization of immunosuppression, especially CNIs, to avoid CNI toxicity and BK nephropathy**
  - Treatment of subclinical rejection
  - Monitoring and removal of HLA antibodies
  - Minimization or elimination of calcineurin inhibitors
  - Use of non-nephrotoxic immunosuppressive agents
  - Tolerance induction strategies

Mission Possible?

Recurrent FSGS

- Recurrence rate: 20-50% (difficult because of the focal nature of the distribution of lesions and possible sampling error)
  - Primary vs secondary vs *de novo*-rapamycin related?
  - Familial forms do not recur after transplantation (linked to genes encoding various podocyte-related proteins, such as podocin, alfa-actinin 4 and nephrin)
- In series with primary FSGS and including pediatric patients and young adults: the incidence of recurrence is as high as 50%

Treatment for Recurrent FSGS

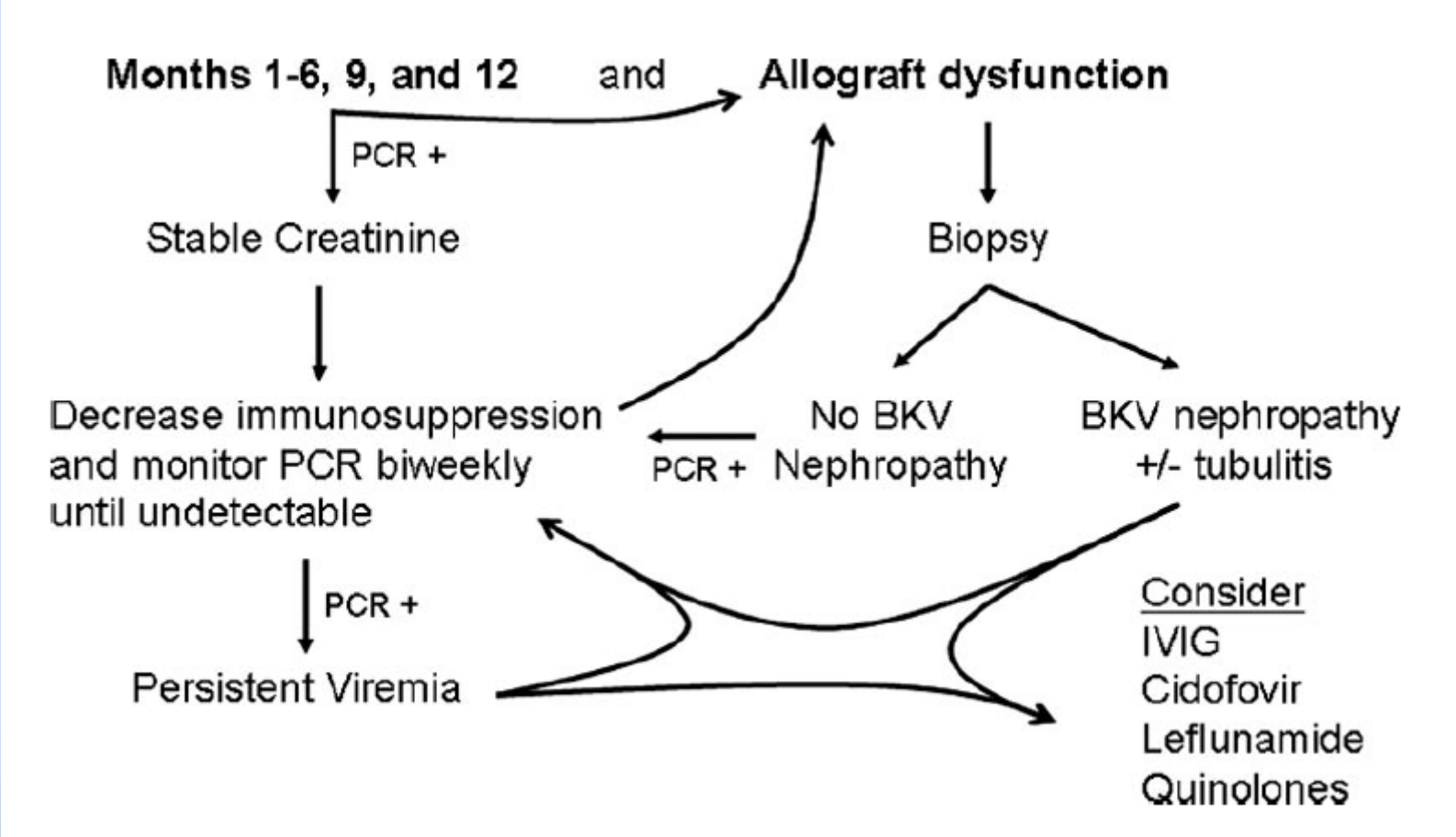
- No prospective randomized studies
- Plasmapheresis ± dipyridamole (pre-or post transplant), ~50% relapse after stopping plasmapheresis, less effective in adults
- Pre-transplant plasmapheresis in children
- Plasma protein adsorption
- High-dose cyclosporine, cyclophosphamide
- ACE inhibitors, NSAIDs, rapamycin use (controversial)

Treatment for Recurrent FSGS

- Combination of ACE-inhibitor, an AT 1 receptor blocker and the direct renin inhibitor aliskiren

  (Freiberger W, et al. Transpl Int 2009)
- Combination of plasmapheresis and rituximab
- Anti-TNF alpha treatment (infliximab then etanercept)
- Galactose (oral or IV): a sugar with high *in vitro* affinity for FSPF in chromatographic studies; a trace amount of galactose blocks or reverses the increase in P_{alb}
- High dose of oral steroids, IV cyclosporine followed by oral treatment, PE with 5% albumin replacement until month 9, and ramipril

Screening Protocol Based on BK Viral Load

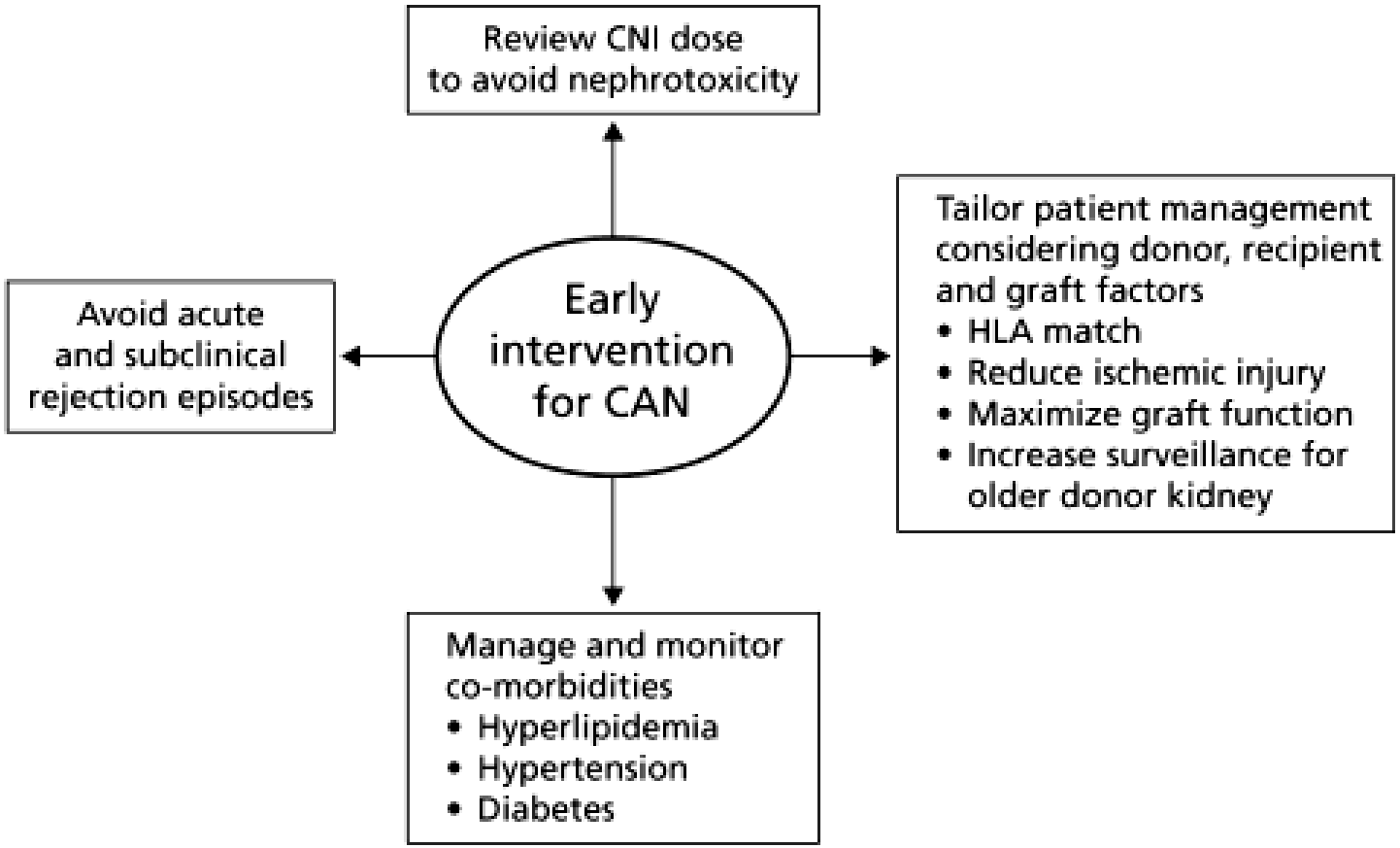


Brennan DC, et al. Am J Transplant 2005

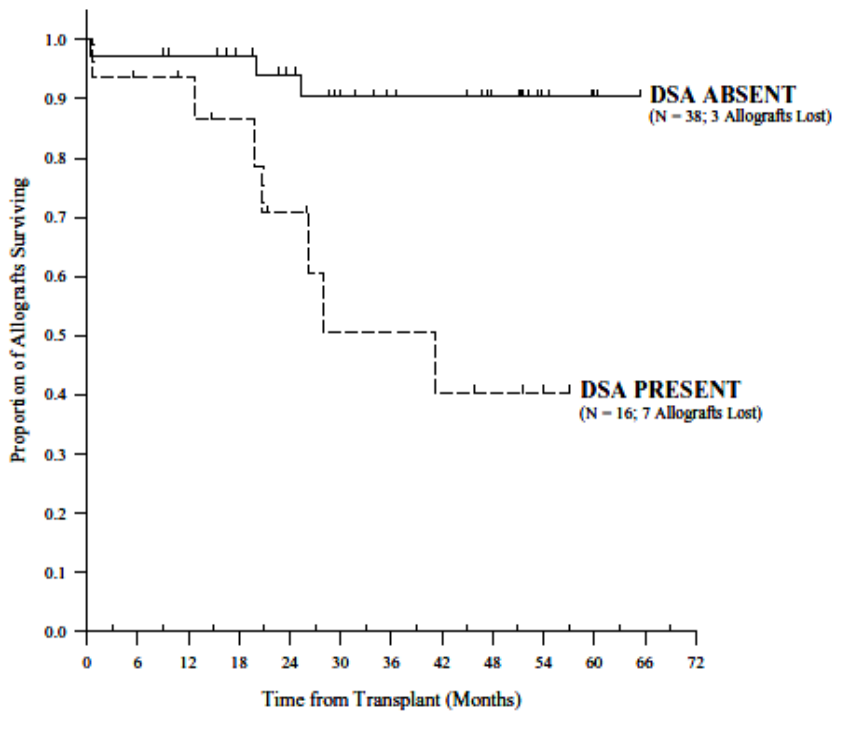
Treatment of BK Nephropathy

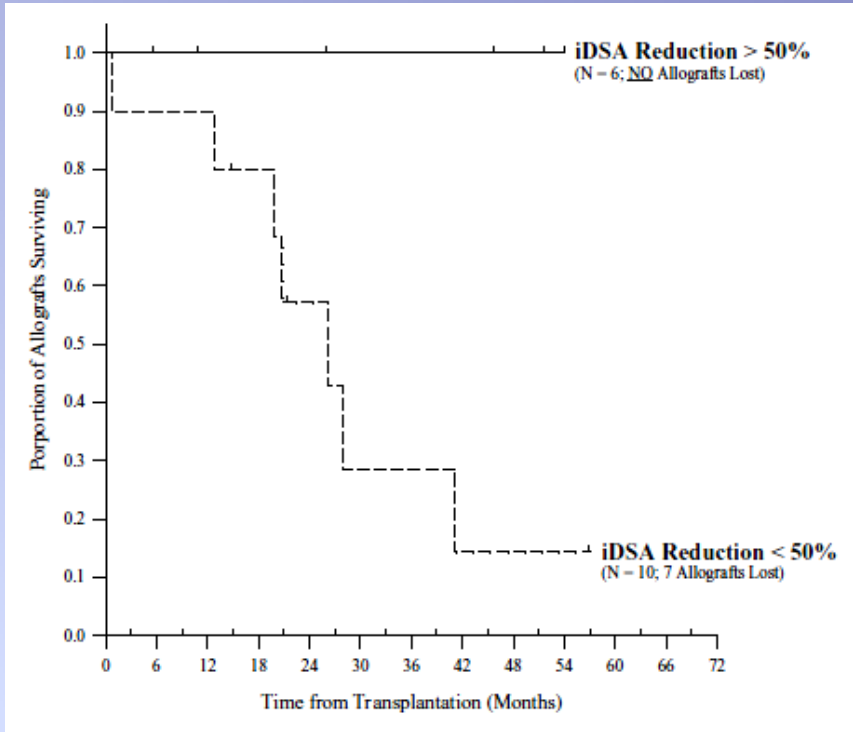
- Multicenter prospective studies are needed:
  - Stratifying histologic grading and renal function
  - Use of viral load for diagnosis
  - Evaluation of different treatment strategies: assessing the possibility of chronic allograft dysfunction due to systematic reduction of immunosuppression
  - Longer follow-up

Early detection and intervention before CAN occurs



Campistol JM, et al. Clin Transplant 2009





•Kaplan–Meier survival in patients with or without DSA at rejection diagnosis (p = 0.001; log-rank)

•Death-censored allograft survival stratified by % reduction in iDSA at 14 days postbiopsy (p = 0.021; log-rank)

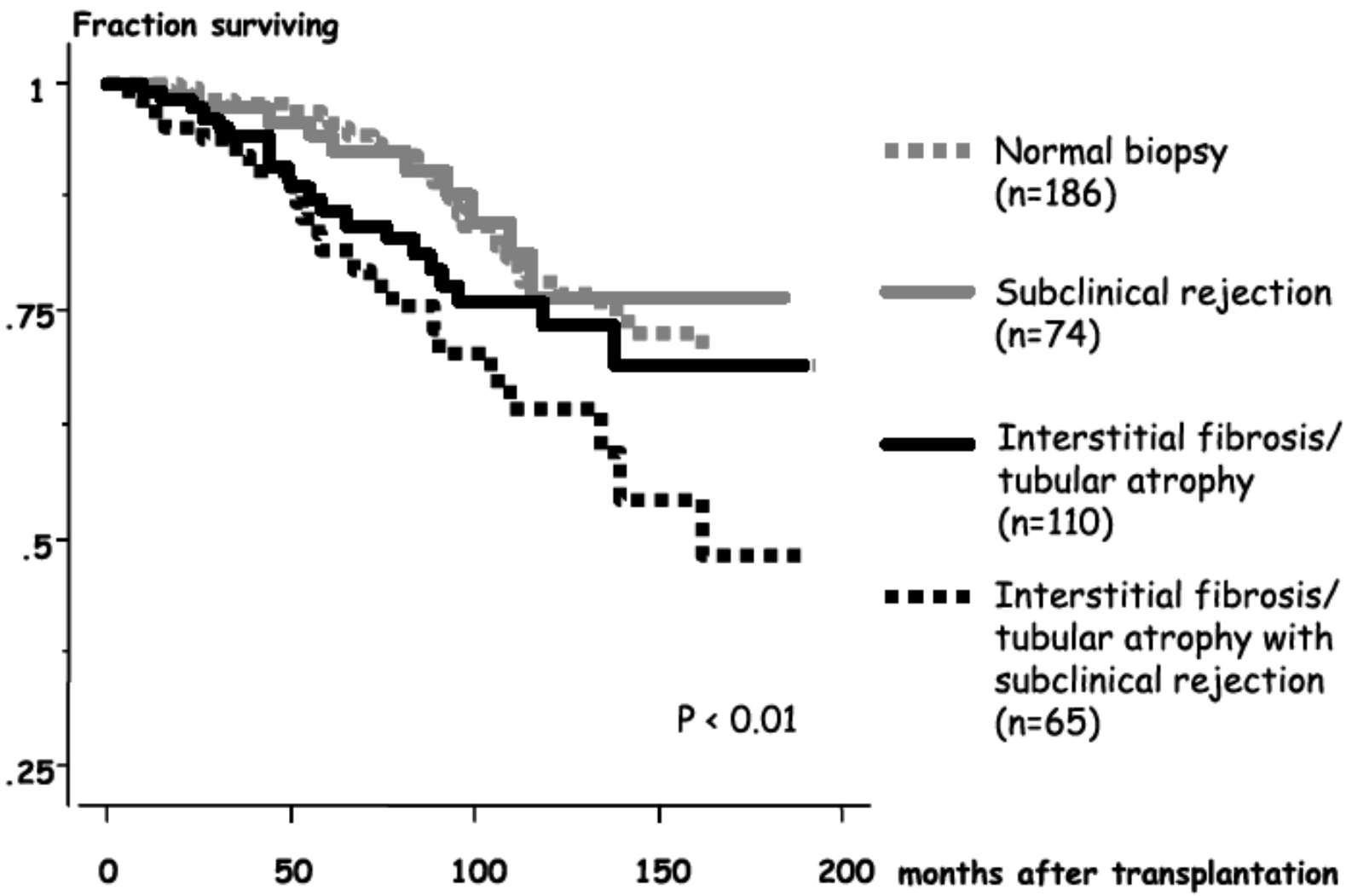
52 patients with acute rejection; 16 (31%) with *de novo* DSA; median follow-up 27.0±17.4 months post acute rejection; *de novo* DSA significant risk factor for allograft loss but prompt DSA reduction was associated with improved allograft survival

Everly MJ, et al. Am J Transplant 2009

Subclinical Rejection (SCR)

- Looking at the predictive value of SCR and/or CAN in protocol biopsies on death-censored graft survival
- Protocol biopsy was done during the first 6 months in stable grafts (n=435 transplants)
- Borderline changes and acute rejection: SCR
- Presence of interstitial fibrosis and tubular atrophy: CAN
- Mean follow-up was 91±46 months
- Biopsies were classified as normal (n=186), SCR (n=74), CAN (n=110) and SCR with CAN (n=65)

Moreso F, et al. Am J Transplant 2006



Cox regression analysis: SCR with CAN and hepatitis C virus were independent predictors of graft survival

Moreso F, et al. Am J Transplant 2006

Trial	Treatment Groups	GFR¶ (mL/min)	AR¶ (%)	Notes
Larson, *et al* [36]	Mod-High RAPA	63*	19*	*P=NS vs. standard TAC. Mostly living donors
	Standard TAC	61	14	
CAESAR [37]	CYA Withdrawal	51	38*	*P=0.04 vs. standard CYA;
	CYA Minimization	51	25	*P=0.03 vs. CYA minimization.
	Standard CYA	49	28	
SYMPHONY [19]	Low TAC	65*	12*	*P≤0.001 vs. others.
	Low CYA	59	24	"Low-medium risk" mostlydeceased donor transplants Serious adverse events highest in RAPA group.
	Low RAPA	57	37	
	Standard CYA	57	26	
Belatacept StudyGroup [18]	High Belatacept	66*	7	6-month results. *P=0.01;
	Low Belatacept	62§	6	§P=0.04 vs. standard CYA. Monthly IV infusions required for Belatacept.
	Standard CYA	54	8	
FREEDOM [22]	CS Avoidance	59	32*	*P=0.007 vs. standard CS.
	Early CS Withdrawal	59	26	Blacks underrepresented. CYA-based regimens.
	Standard CS	61	15	
Astellas Steroid Withdrawal Group [23]	Early CS Withdrawal	59	18*	5-year results. *P=0.04 vs. low
	Low CS	60	11	CS. More CAN (post hoc). TAC-based regimens
CONVERT [20]	CNI Conversion to RAPA	63*	16	2-year results. *P=0.009 vs.
	CNI Continuation	60	15	CNI Continuation. Adverse events higher but malignancy lower with RAPA.

Womer K and Kaplan B. Am J Transplant 2009

Why do Patients Reject on Belatacept?

- Low saturation of CD86/CD80
- Presence of memory cells
- T cell activation trough other costimulation pathways
- Blockade of negative signaling
- Inhibition of T regulatory cells

Belatacept

- BENEFIT study-phase III: 686 patients; 3-arm, basiliximab induction
  - At Month 12, both belatacept regimens had similar patient/graft survival versus cyclosporine (MI: 95%, LI: 97% and cyclosporine: 93%)
  - Belatacept patients experienced a higher incidence **(MI: 22%, LI: 17% and cyclosporine: 7%)** and grade of acute rejection episodes
  - **5 PTLD in the belatacept group vs 1 in CsA group**

Vincenti F, et al. AJT 2010

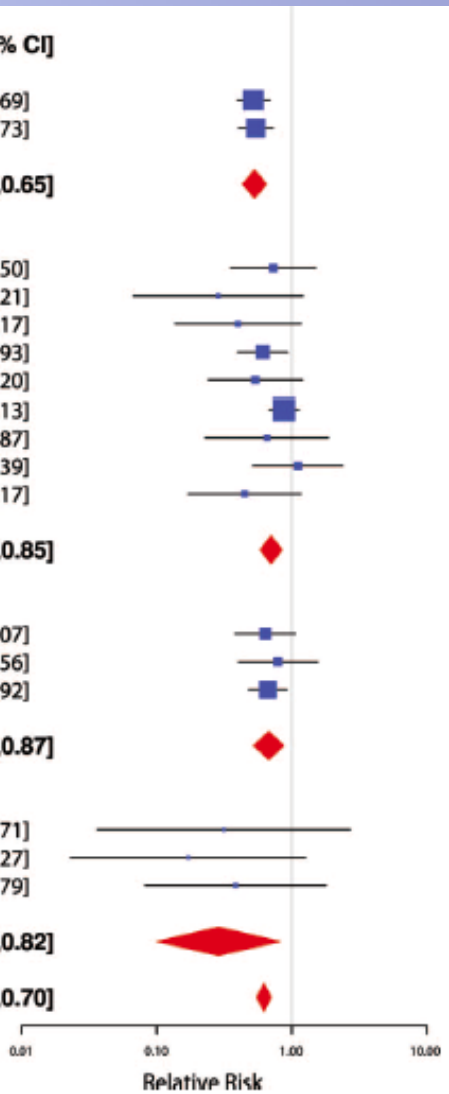
Belatacept

- BENEFIT-EXT study-phase III: 578 patients; 3-arm, basiliximab induction
  - Patient/graft survival with belatacept was similar to cyclosporine (86% MI, 89% LI, 85% cyclosporine) at 12 months
  - The incidence of acute rejection was similar across groups (18% MI; 18% LI; 14% cyclosporine)
  - One patient (0.5%) in the belatacept MI group and two patients (1%) in the LI group had PTLD during the 12-month period and one additional patient in each belatacept group developed PTLD after Month 12
  - **Four of the five cases involved the central nervous system**, and two of five (both of the post- Month 12 cases) had CMV disease
  - No patients on cyclosporine developed PTLD

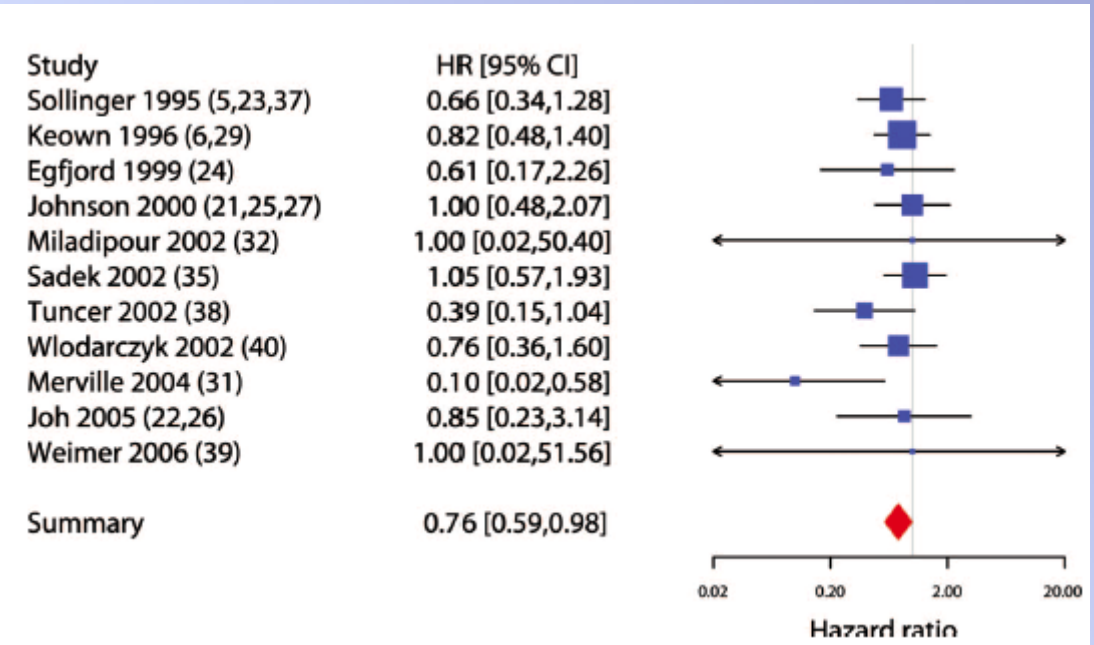
Durrbach A, et al. AJT 2010

Relative Risk of Acute Rejection

Study/subcategory	MMF (n/N)	AZA (n/N)	RR [95% CI]
1. CsA SIM			
Sollinger 1995	70/333	67/166	0.52 [0.39,0.69]
Keown 1996	66/337	60/166	0.54 [0.40,0.73]
Subgroup total	**670**	**332**	**0.53 [0.43,0.65]**
2. CsA ME			
Egfjord 1999	8/25	11/25	0.73 [0.35,1.50]
Suhail 2000	2/20	7/20	0.29 [0.07,1.21]
Miladipour 2002	4/40	10/40	0.40 [0.14,1.17]
Sadek 2002	27/162	43/157	0.61 [0.40,0.93]
Tuncer 2002	7/38	13/38	0.54 [0.24,1.20]
Remuzzi 2004	57/124	65/124	0.88 [0.68,1.13]
Merville 2004	5/37	7/34	0.66 [0.23,1.87]
Joh 2005	10/34	9/34	1.11 [0.52,2.39]
Weimer 2006	5/31	9/25	0.45 [0.17,1.17]
Subgroup total	**511**	**497**	**0.70 [0.58,0.85]**
3. Tacrolimus			
Mendez 1998	24/117	19/59	0.64 [0.38,1.07]
Johnson 2000	12/72	16/76	0.79 [0.40,1.56]
Wlodarczyk 2002	46/243	70/246	0.67 [0.48,0.92]
Subgroup total	**432**	**381**	**0.68 [0.52,0.87]**
4. CsA (unknown)			
Army Hospital Delhi 2002	1/17	3/16	0.31 [0.04,2.71]
Baltar 2002	1/14	5/12	0.17 [0.02,1.27]
Sun 2002	2/40	6/46	0.38 [0.08,1.79]
Subgroup total	**71**	**74**	**0.29 [0.10,0.82]**
Overall total	**1684**	**1284**	**0.62 [0.55,0.70]**

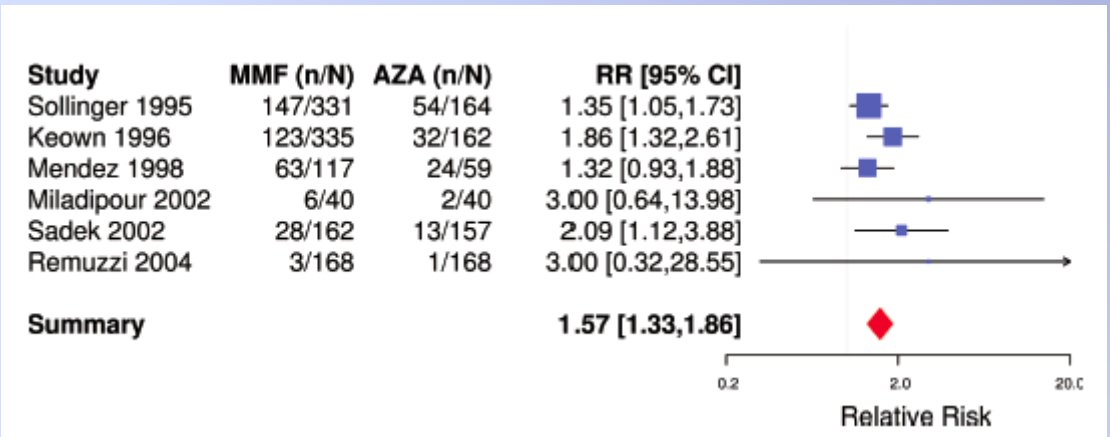


Knight SR, et al. Transplantation 2009



Hazard ratio for graft loss including death with a functioning graft

Relative risk of diarrhea



Knight SR, et al. Transplantation 2009