Diabetes and Transplantation
New Onset Diabetes After Transplantation (NODAT)

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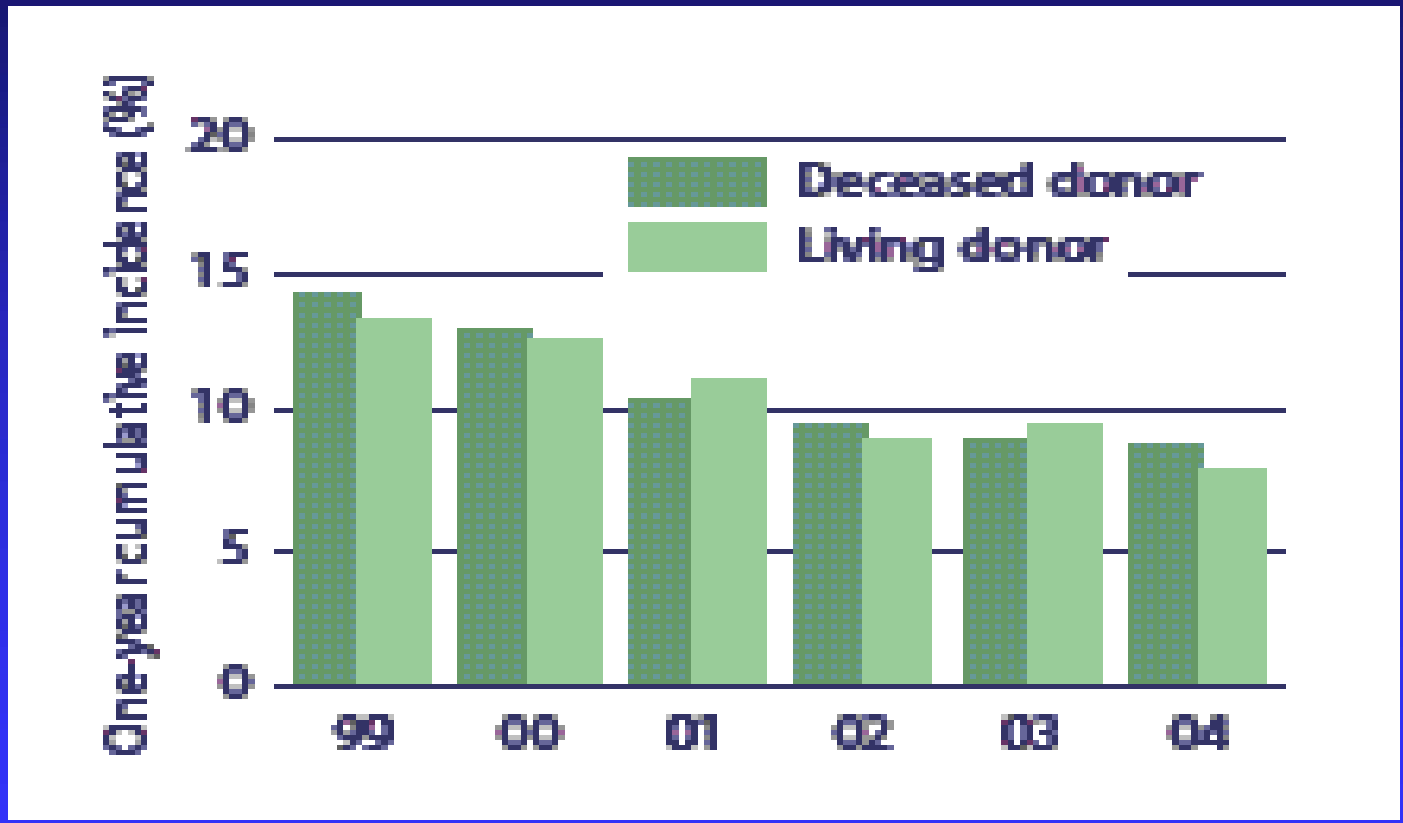
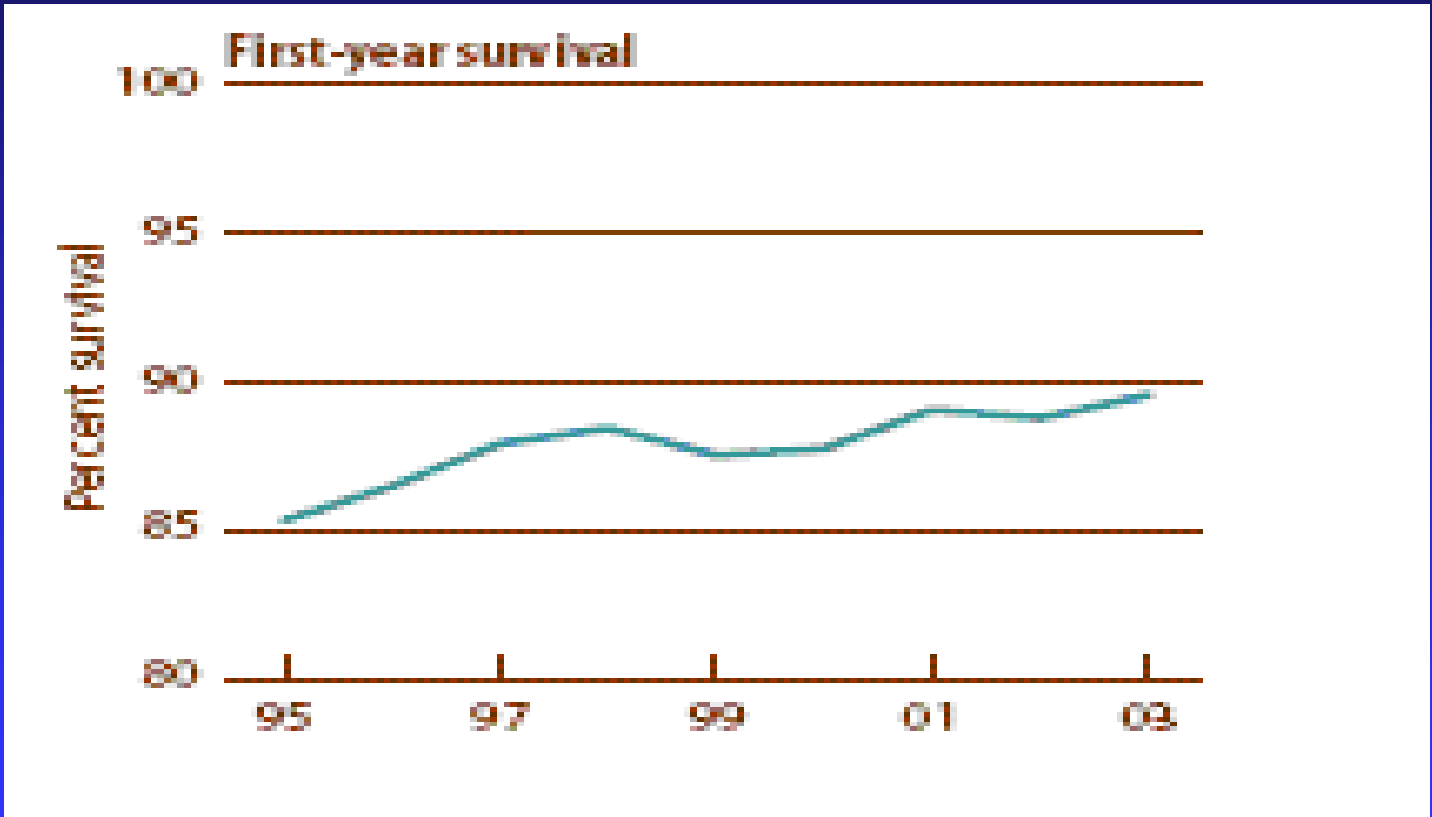
Kidney Transplantation
“Stuck in a Rut”

Acute Rejection Rate is Decreasing with Time



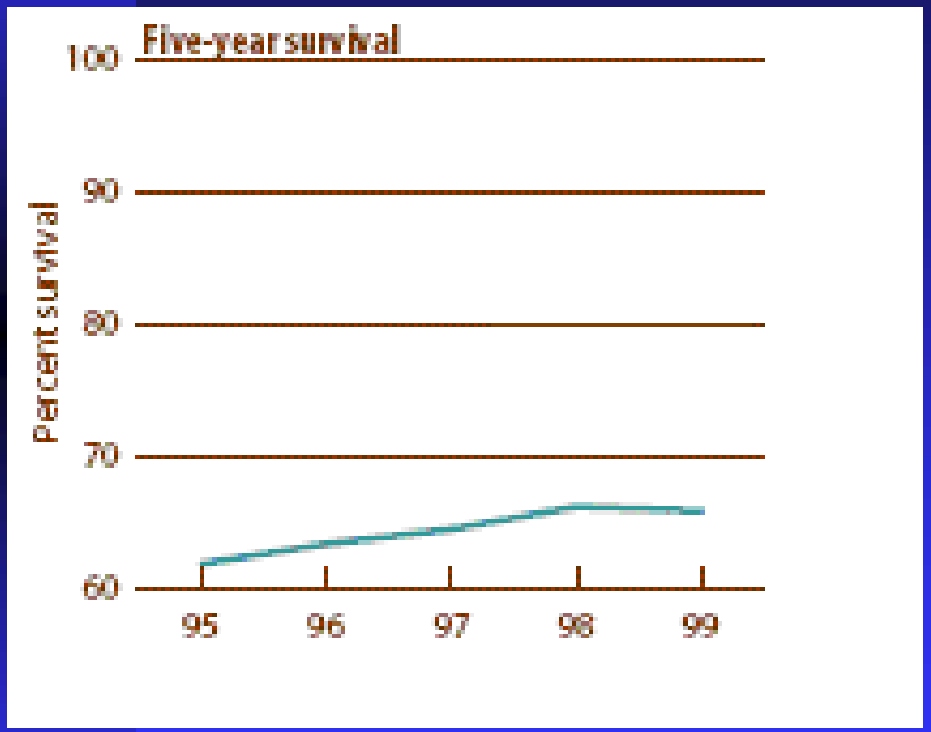
Short-Term Graft Survival is Improving

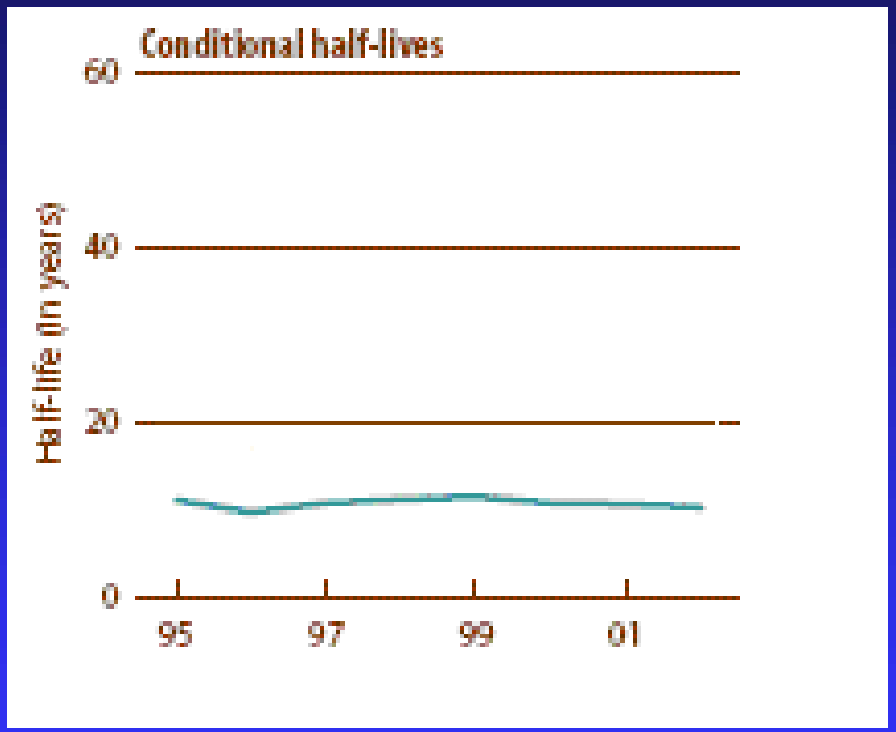


Based on deceased donor transplants

USRDS Annual Data Report 2006

BUT Little Change in Overall Long-Term Graft Survival





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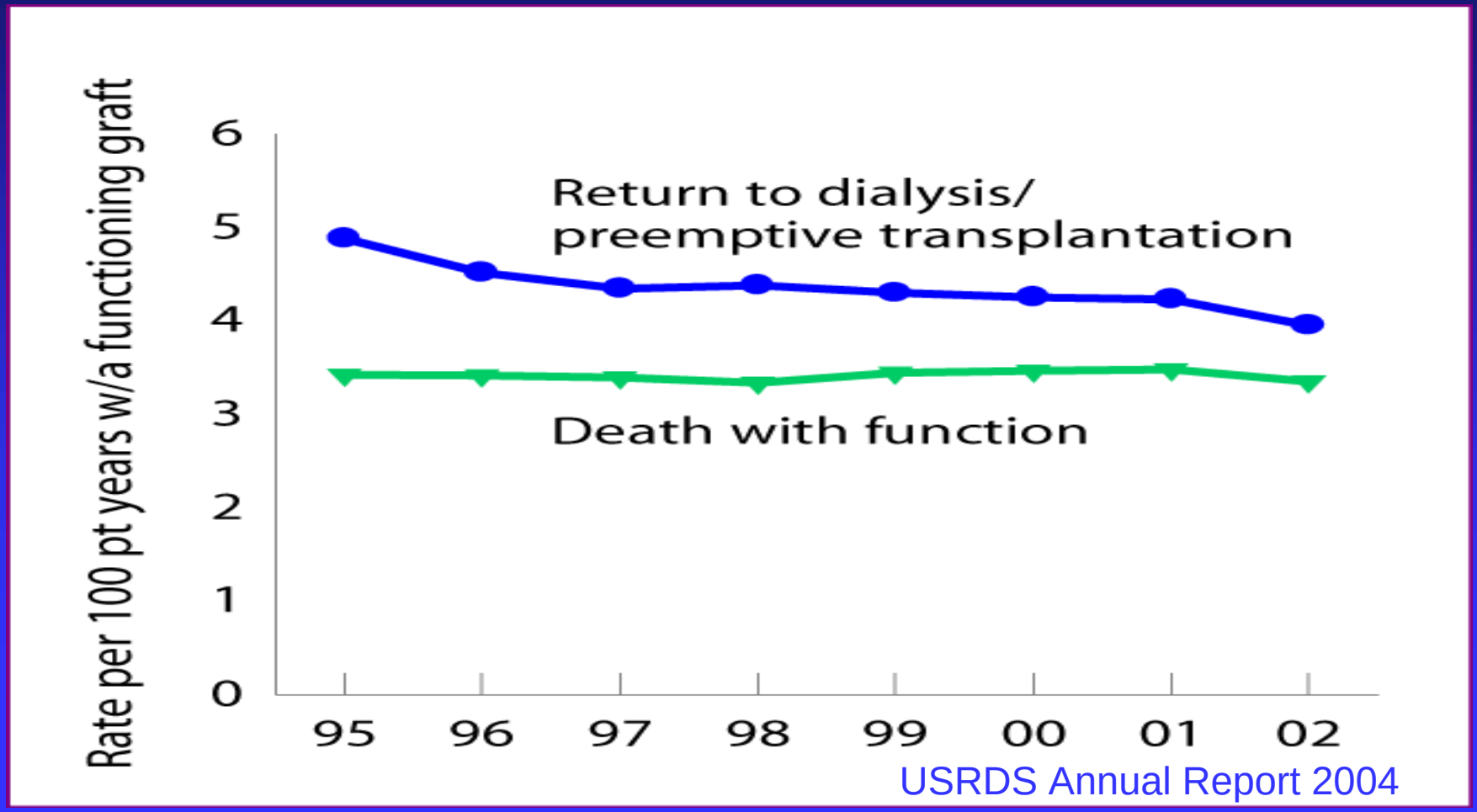
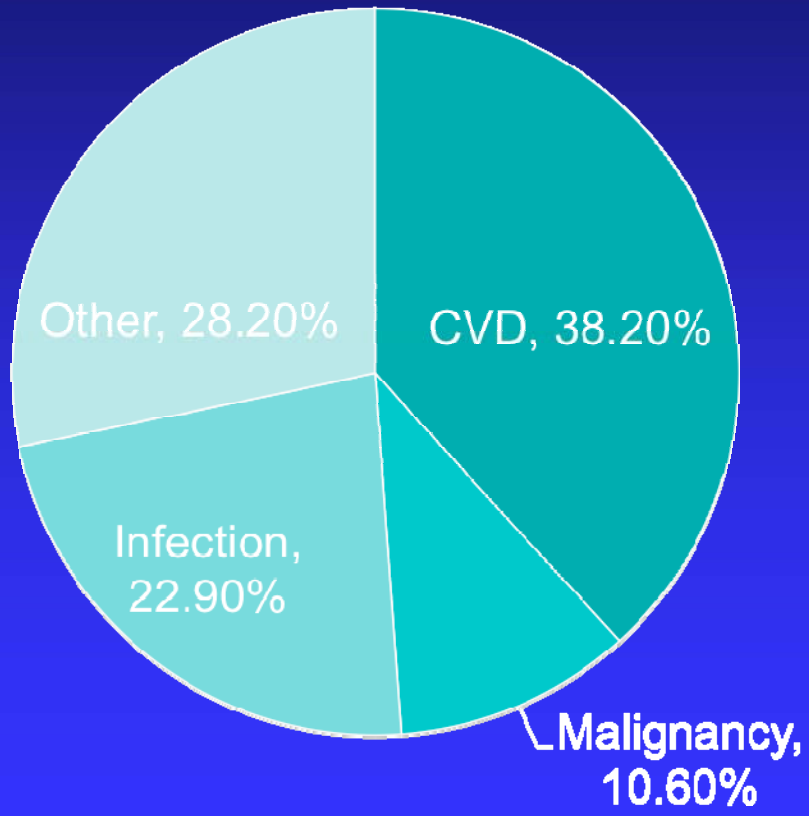
USRDS Annual Data Report 2006

Death censored graft loss vs. Death with a functioning graft



USRDS Annual Report 2004

Causes of Death with a functioning graft



USRDS ADR 2008 ADR

first-time, kidney-only transplant recipients, age 18 & older & transplanted 1997–2006, who died with a functioning graft (N=14,169). Cause of death obtained from OPTN when available, otherwise taken from ESRD Death Notification form. Excludes unknown.

Major risk factors for CV death

- Diabetes Mellitus
- Hypertension
- Obesity
- Dyslipidemia

Outline

- What is New Onset Diabetes After Transplantation?
- How common is it?
- What are the outcomes from NODAT?
- Who is at risk for NODAT?
- How do we prevent NODAT?
- How do we treat NODAT?

“What’s in a name?”

- Post transplant Diabetes Mellitus (PTDM)
- New Onset Diabetes Mellitus (NODM)
- New Onset Diabetes After Transplantation (NODAT)
- Transplant Associated Hyperglycemia (TAH)

Definition of DM - CDA

- FPG ≥7.0 mmol/L
- Casual PG ≥11.1 mmol/L + symptoms of diabetes
- 2hPG in a 75-g OGTT ≥11.1 mmol/L

*Fasting = no caloric intake for at least 8 hours

*Casual = any time of the day, without regard to the interval since the last meal Classic

*Symptoms of diabetes = polyuria, polydipsia and unexplained weight loss or

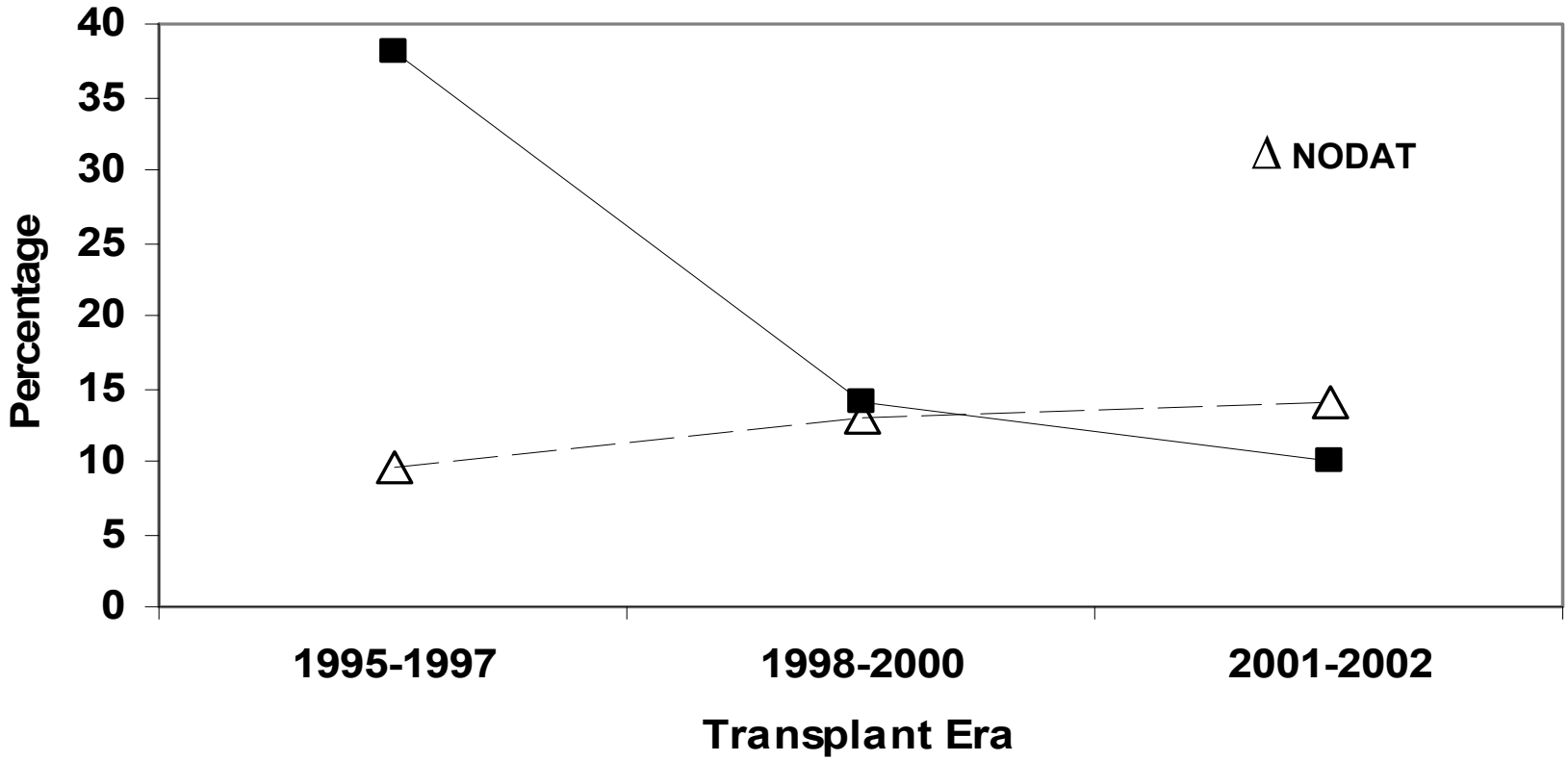
Spectrum of disease

	FPG	2 HR GLUC TOLERANCE (75G)
Impaired Fasting Glucose (IFG)	6.1-6.9	NA
Impaired Glucose Tolerance (IGT)	<6.1	7.8-11.0
IFG and IGT	6.1-6.9	7.8-11.0
Diabetes	≥ 7.0	≥11.1

Incidence of NODAT

- Variably reported incidence (2-40%) based on definitions and ability to exclude pre-existing diabetes prior to transplantation
- Cummulative incidence of NODAT reported at 9%, 16%, and 24% at 3, 12, and 36 months, respectively
- Incidence of NODAT attributable to factors related to transplantation per se is the incremental difference between the baseline rate among wait-listed patients and the observed rate after transplantation
- Woodward, et al. estimated the true incremental incidence of NODAT to be 8–10% during the first post-transplant year

NODAT now more common than AR



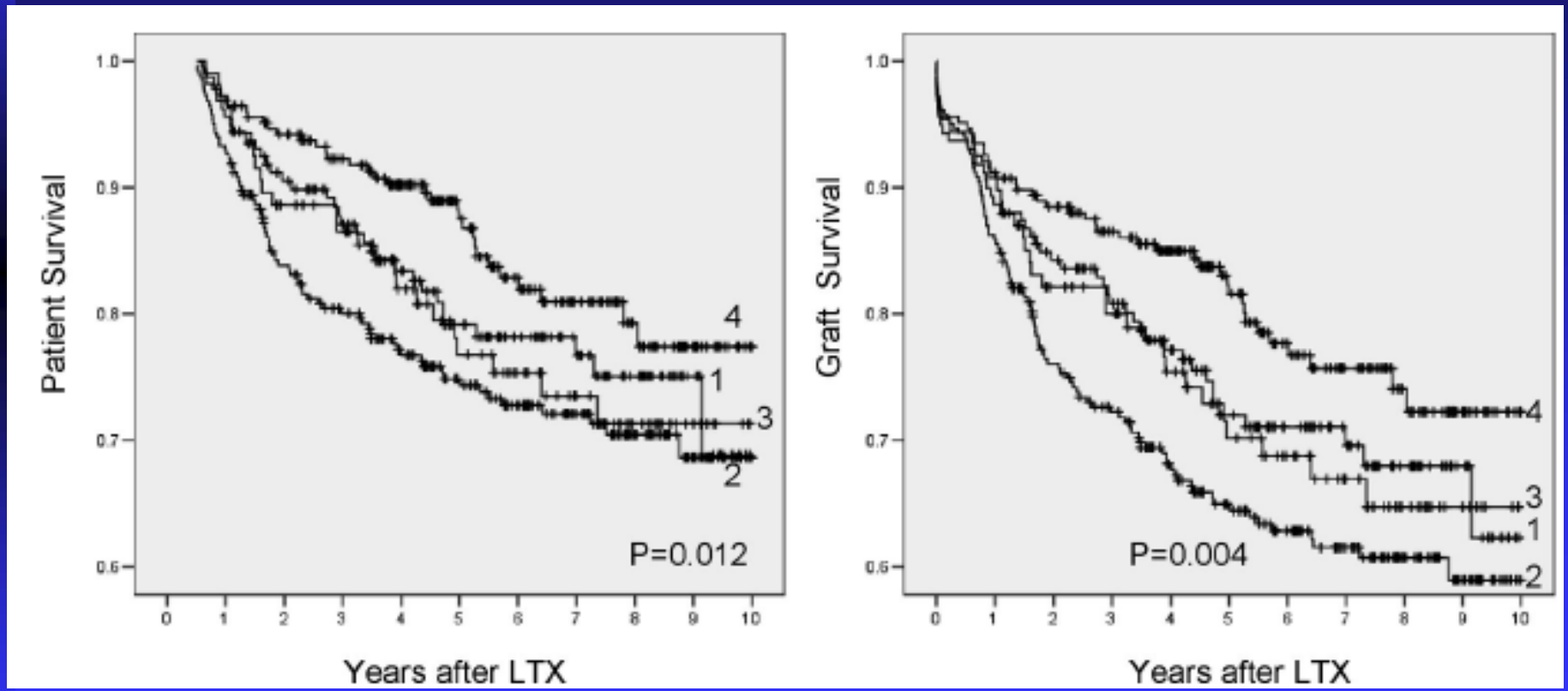
E. Cole, CJASN 2008

NODAT
Associated Outcomes
Kidney transplant recipients 1996-2000

- Graft failure: HR = 1.63, 95% CI (1.46-1.84)
- Death censored graft loss: 1.46, 95% CI (1.25-1.70)
- Mortality: HR = 1.87, 95% CI (1.60-2.18)

Kasiske et al. AJT 2003 3: 178

NODAT associated with patient death and allograft failure in liver transplant recipients



1 = preLTX DM, 2 = sustained NODM, 3 transient NODM, 4 normal

Moon J et al. Transplantation 2006: 82; 1625-28

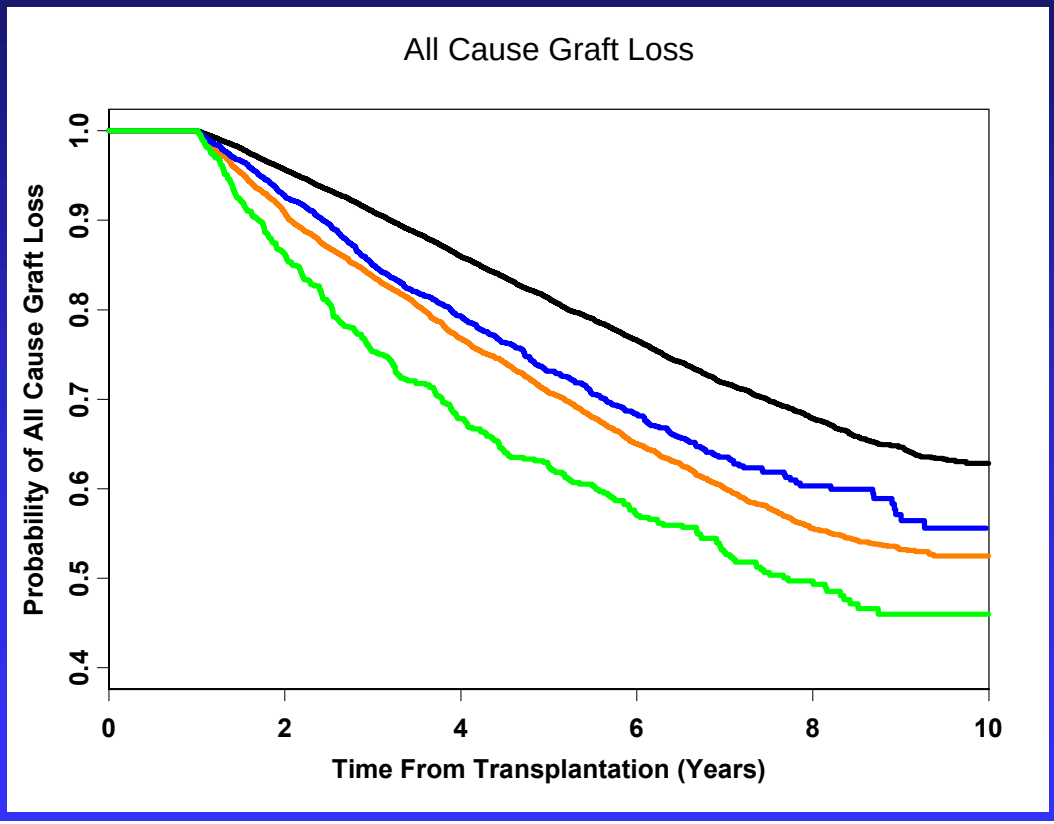
What's worse NODAT or AR ?

- USRDS data
- First kidney only transplant recipients, 1995-2002, n = 28,053
- Excludes patients with known pre transplant diabetes
- Graft survival of at least 12 m
- NODAT identified in first 12 m using Medicare claims (like Kasiske)
- AR identified in first 12 m

E Cole et al, CJASN, 2008

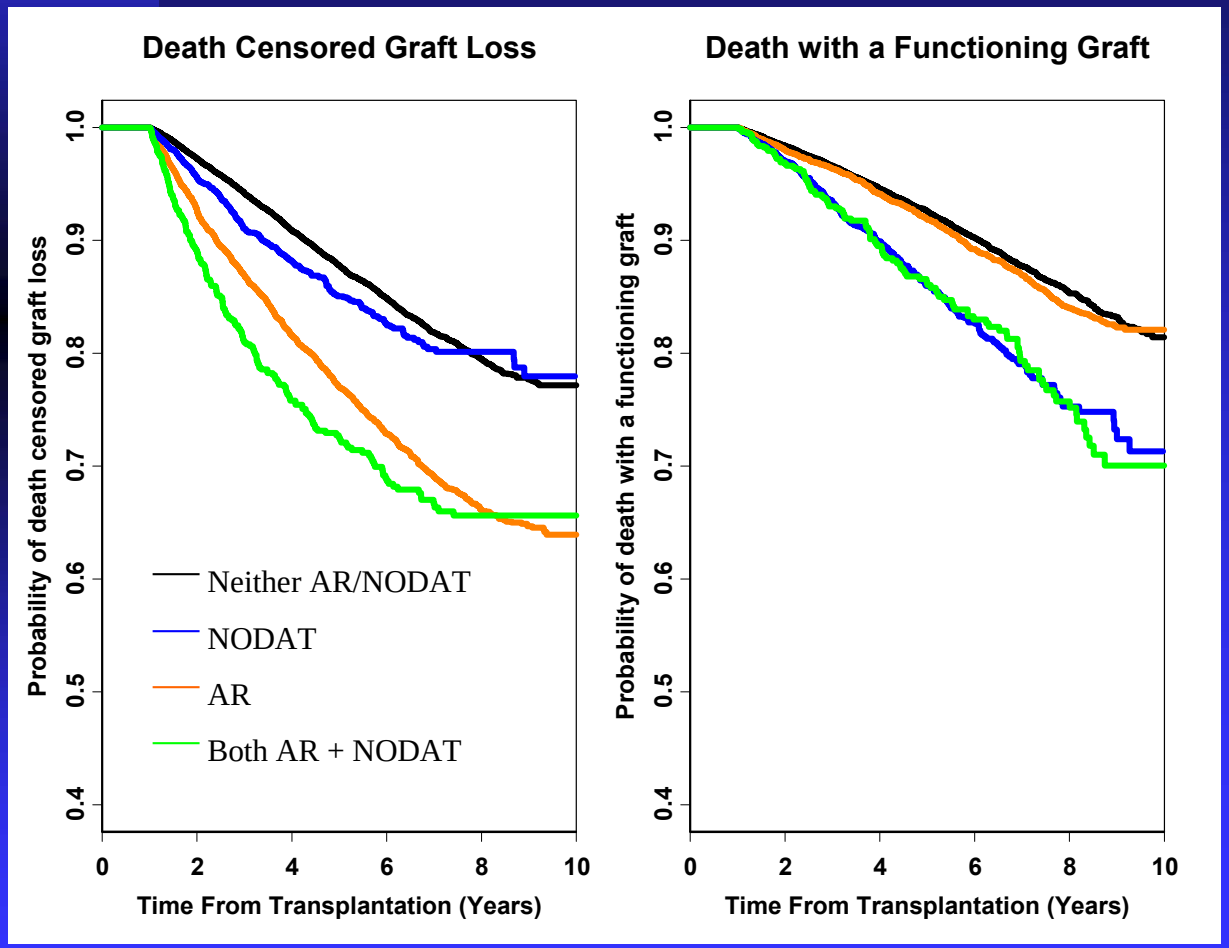
AR and NODAT had similar impact on graft survival

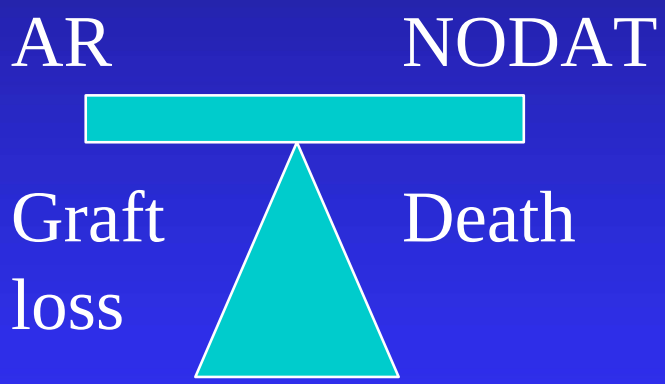
CJASN 2008



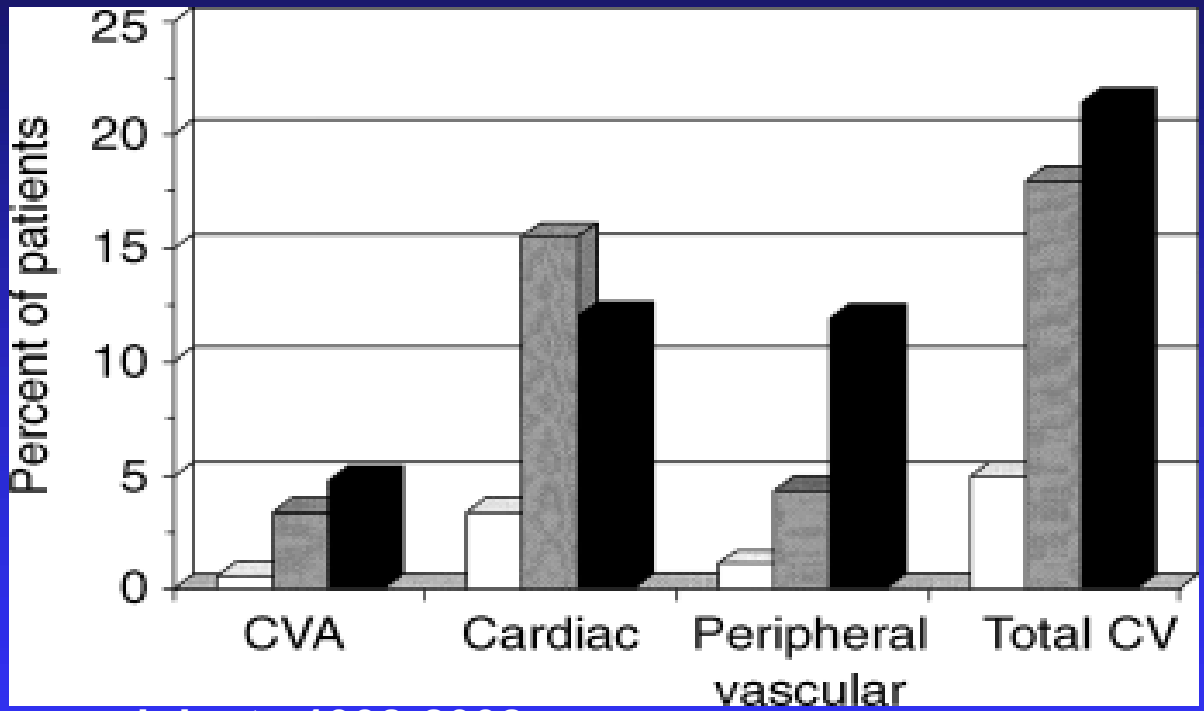
— Neither AR/NODAT — NODAT — AR — Both AR + NODAT

AR – mostly impacts graft
NODAT – mostly impacts patient





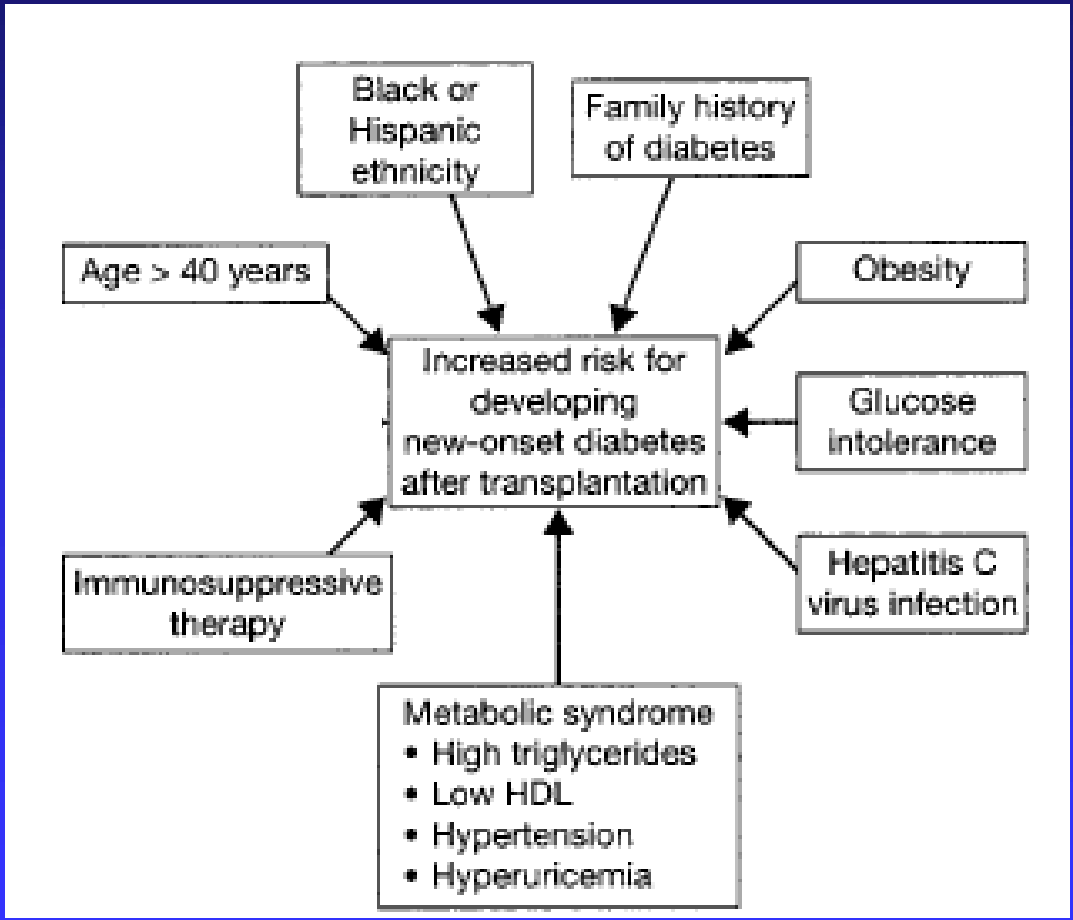
IFG and NODAT associated with increased CVD



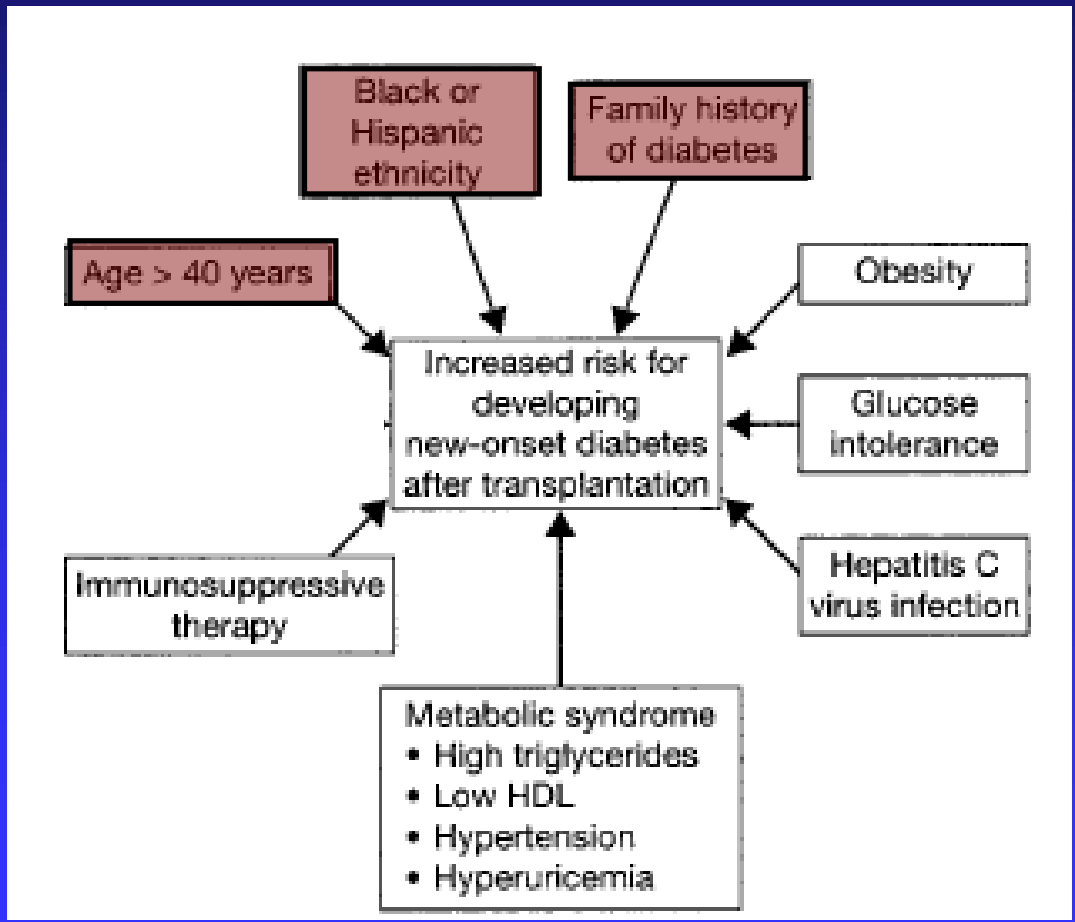
490 Kidney recipients 1998-2002
Immunosuppression: Thymoglobulin induction, maintenance steroids, CNI or sirolimus, and MMF.

Cosio FG et al. Kidney Int. 2005: 67; 2415-2421.

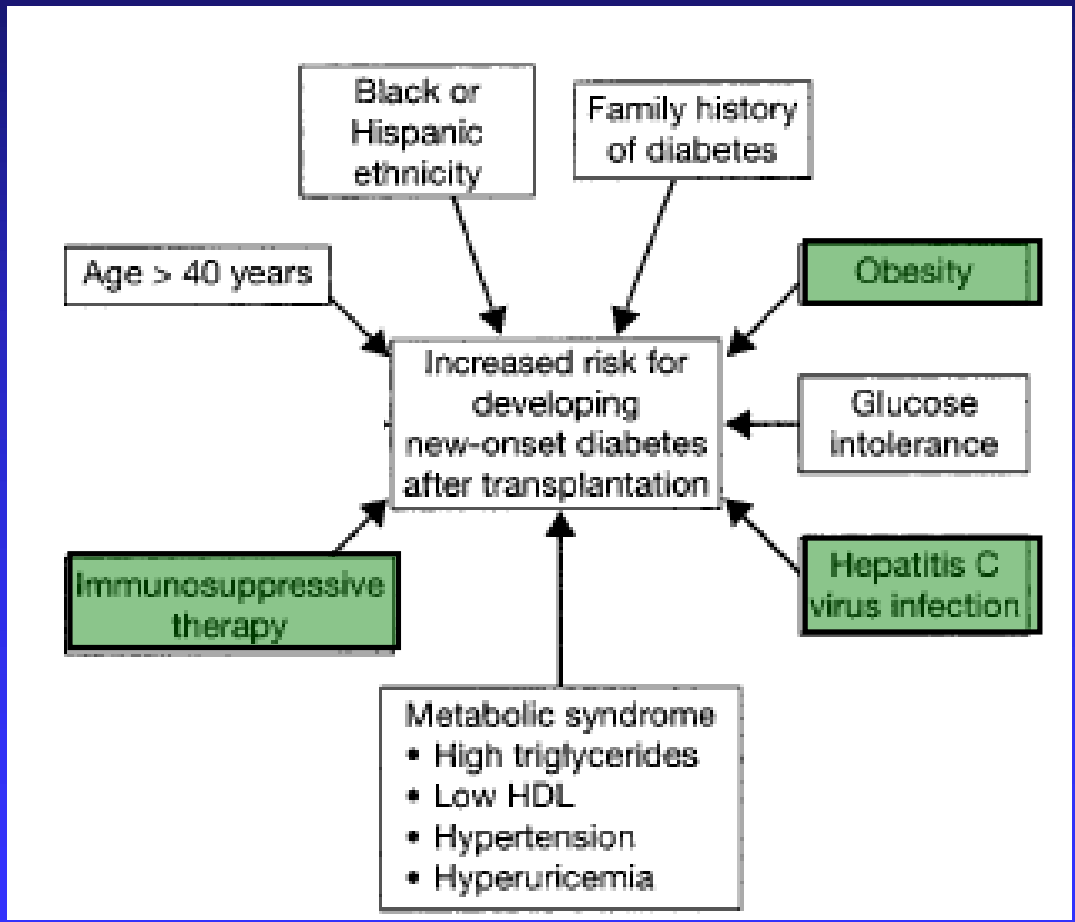
Risk Factors for NODAT



Non-modifiable risk Factors for NODAT



Potentially modifiable risk Factors for NODAT



Immunosuppression

- Calcineurin inhibitors (Tacrolimus, Cyclosporine)
- Antimetabolites (Mycophenolate Mofetil, Azathioprine)
- Corticosteroids
- mTOR (Sirolimus)

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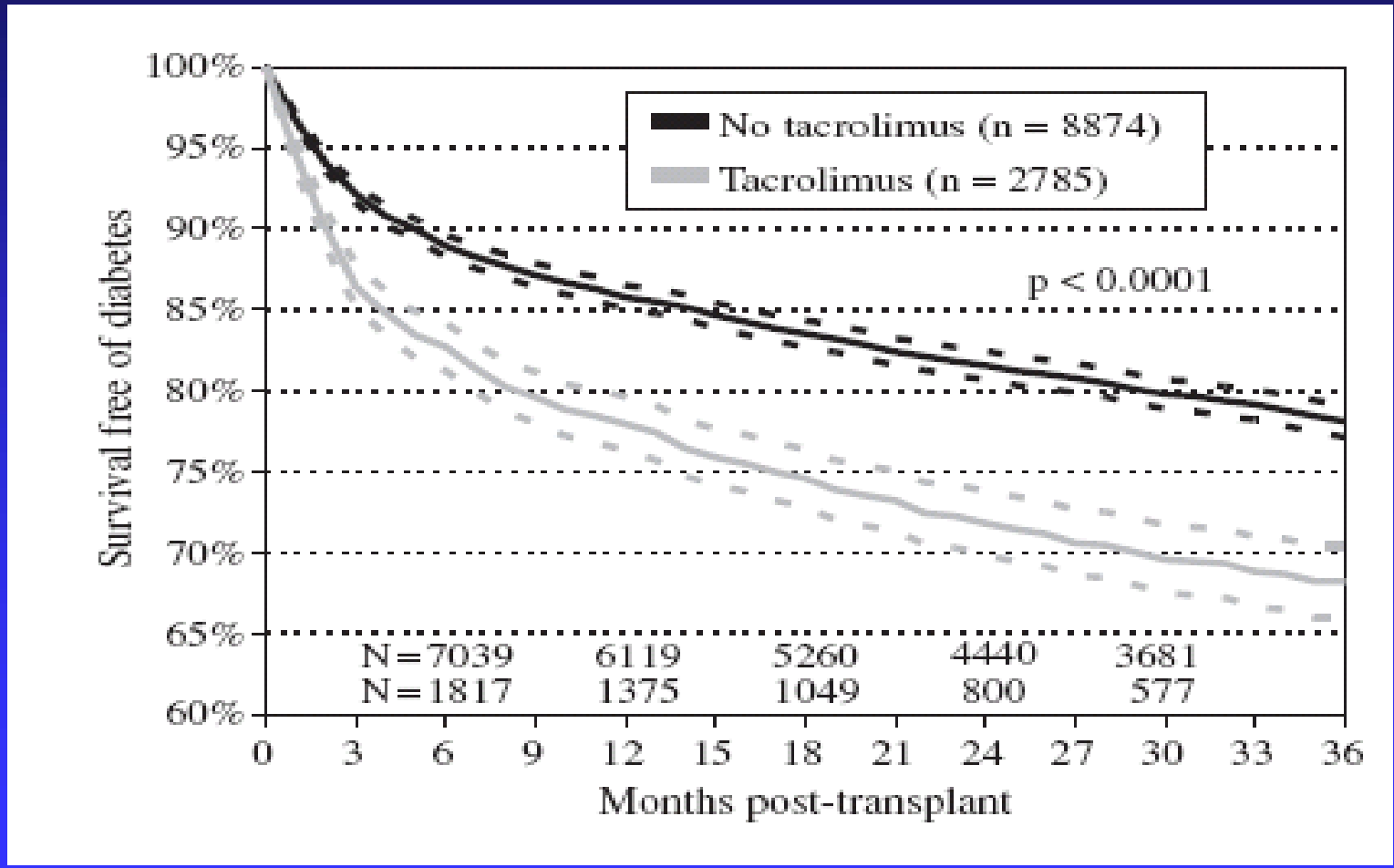
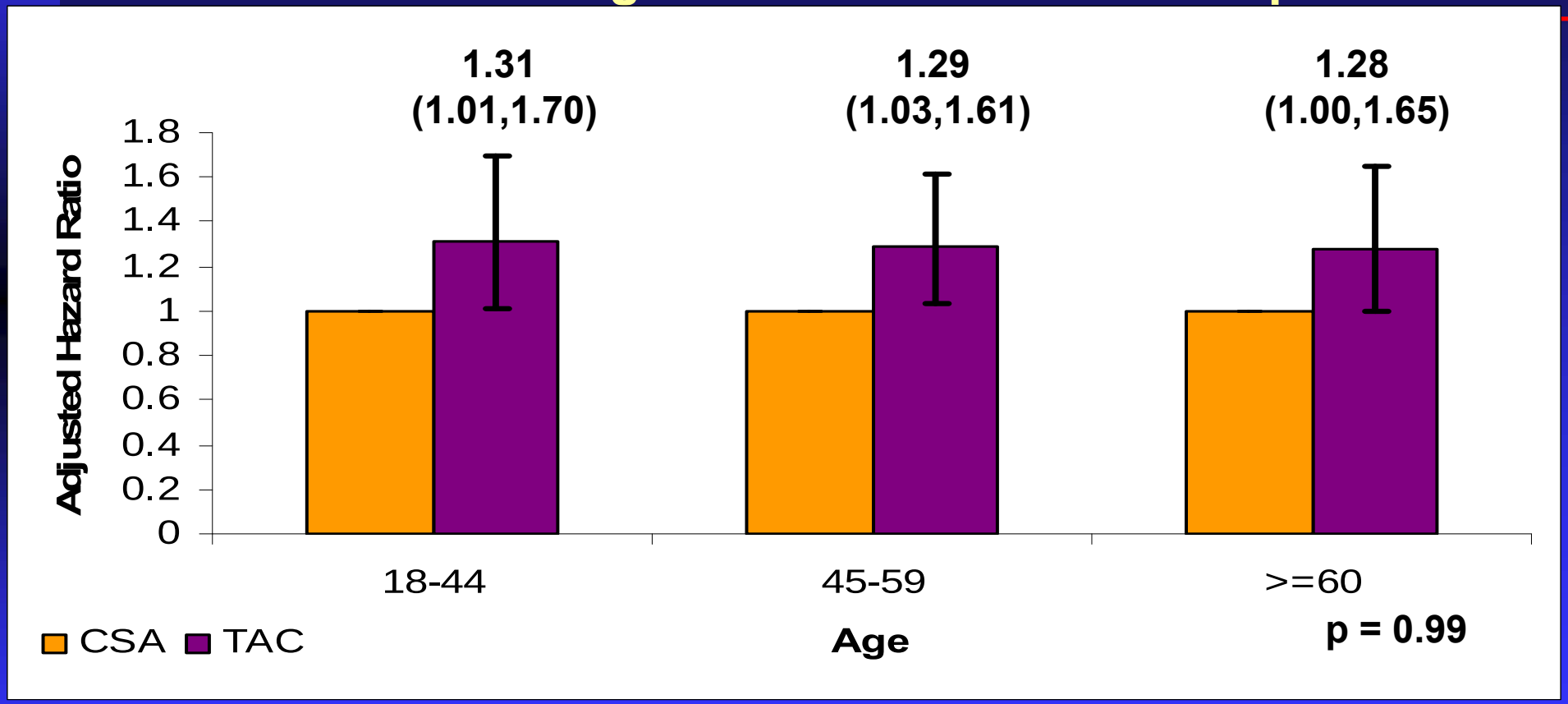
Tacrolimus is Associated with NODAT



Kasiske et al AJT 2003; 3: 178-85

Tacrolimus associated risk of NODAT did not vary by Age

Cox multivariate regression in steroid treated patients

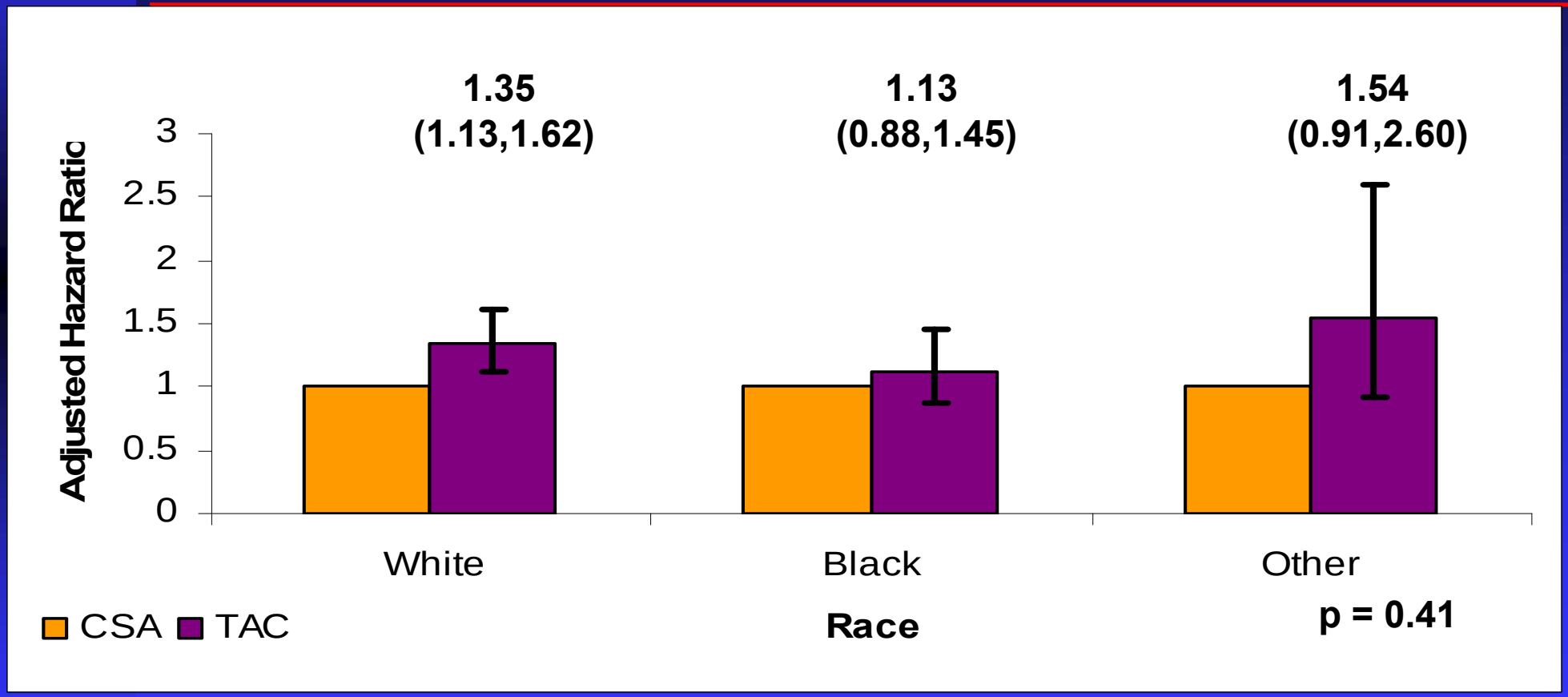


Adjusted for: Sex, Race, Hispanic Ethnicity, BMI, donor type, cause of disease, comorbidities, time on dialysis, HLA mismatch

O Johnston et al. Am J Transplant 2007; 7(s2):186

Tacrolimus associated risk of NODAT did not vary by Race

Cox multivariate regression in steroid treated patients



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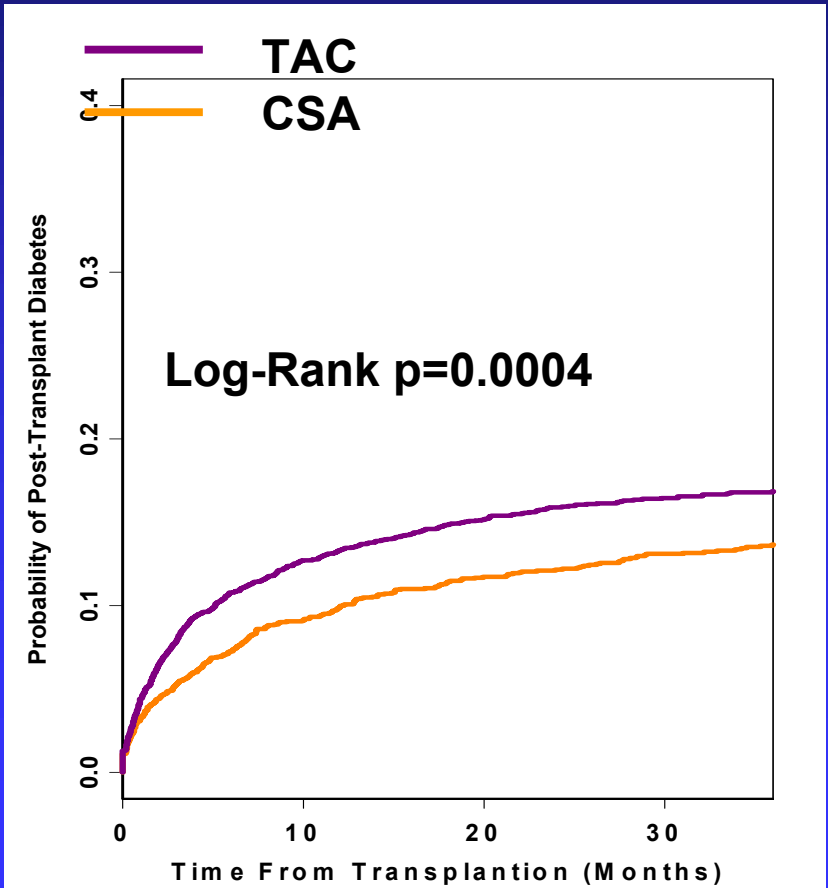
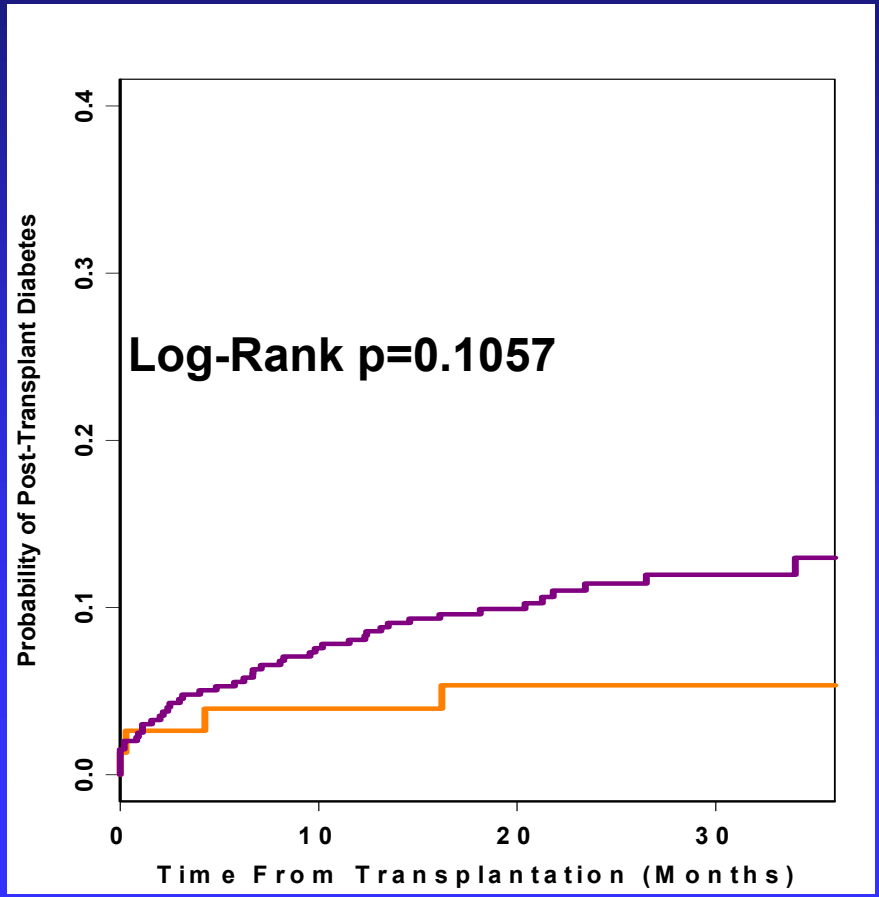
O Johnston et al. Am J Transplant 2007

Cumulative Probability of NODAT by CNI

Steroids



No Steroids



O Johnston et al. Am J Transplant 2007; 7(s2):186

Who should we not give tacrolimus to?

Who should we not give tacrolimus to?

Nobody…

…if we ONLY care about NODAT

…and DON’T care about rejection

Does the tacrolimus level matter?

Tacrolimus effect is dose dependent

Trough level	10-25 ng/ml	8-16 ng/ml	8-12 ng/ml
NODAT	19%	6.5%	5.7%
Year	1997	2000	2002
Reference	Pirsch JD et al Transplantation: 1997:63;977-83	Johnson C et al Transplantation 2000:69; 834	First MR et al Transplantation 2002: 73; 379-86

Reducing CNI levels may reduce risk of NODAT

	NODAT (%)
Standard dose cyclosporine (trough level of >200ng/ml in 1st year)	6.4%
Low dose cyclosporine (trough level of ~ 100ng/ml in 1st year)	4.7%

ELITE-SYMPHONY TRIAL

Corticosteroids

- Increased insulin resistance[1]
  - Decreased binding of insulin to insulin receptors
  - Increased hepatic gluconeogenesis
- Risk is dose related
  - 0.01 mg/kg/d increment in prednisolone 4% increase in glucose intolerance[2]
  - Lower rates with low steroid maintenance doses[1]
  - Effects of steroid withdrawal uncertain[3,4]

1 Weir et al, AJKD 1999;34:1
2 Hjelmesaeth J et al. Transplantation 1997; 64:979
3 Hricik D et al. Transplantation 1991; 53:374
4 Fabrega AJ et al. Transplantation 1995; 60: 1612.

Reduced CV risk with Early CS withdrawal vs chronic CS

- **Meta-analysis of 34 studies including 5,637 patients receiving steroid withdrawal or avoidance regimens vs maintenance steroids**

- **CV outcomes:**

	Studies reporting outcome		Meta-analysis			
Outcome	Studies	Patients	Type	RR (95% CI)	P	
HTN	15	2,833	Fixed	0.90 (0.85-0.94)	<0.0001	
Dyslipidemia	13	2,283	Random	0.76 (0.67-0.87)	<0.0001	
NODAT	16	2,849	Fixed	0.64 (0.50-0.83)	0.0006	

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Relative risks of new-onset diabetes all significantly reduced

Steroid withdrawal – Astellas double blind trial

- 386 patients randomized post transplant day 3-7
- SCr <=30%
- No HD

- Steroid maintenance (CCS) n = 195

- Steroid withdrawal (CSWD) by day 7 n = 191

- Study was stratified Living vs Deceased and AA vs non-AA

Astellas trial 24 months

No difference between steroid w/d group and controls tapered to 5 mg of prednisone at 1 month

	CCS	CSWD	P value
One FBS >= 126 mg/dl	72 (53.3%)	72 (50.7%)	0.66
Two FBS >=126 Mg/dl	43 (31.9%)	40 (28.2%)	0.50

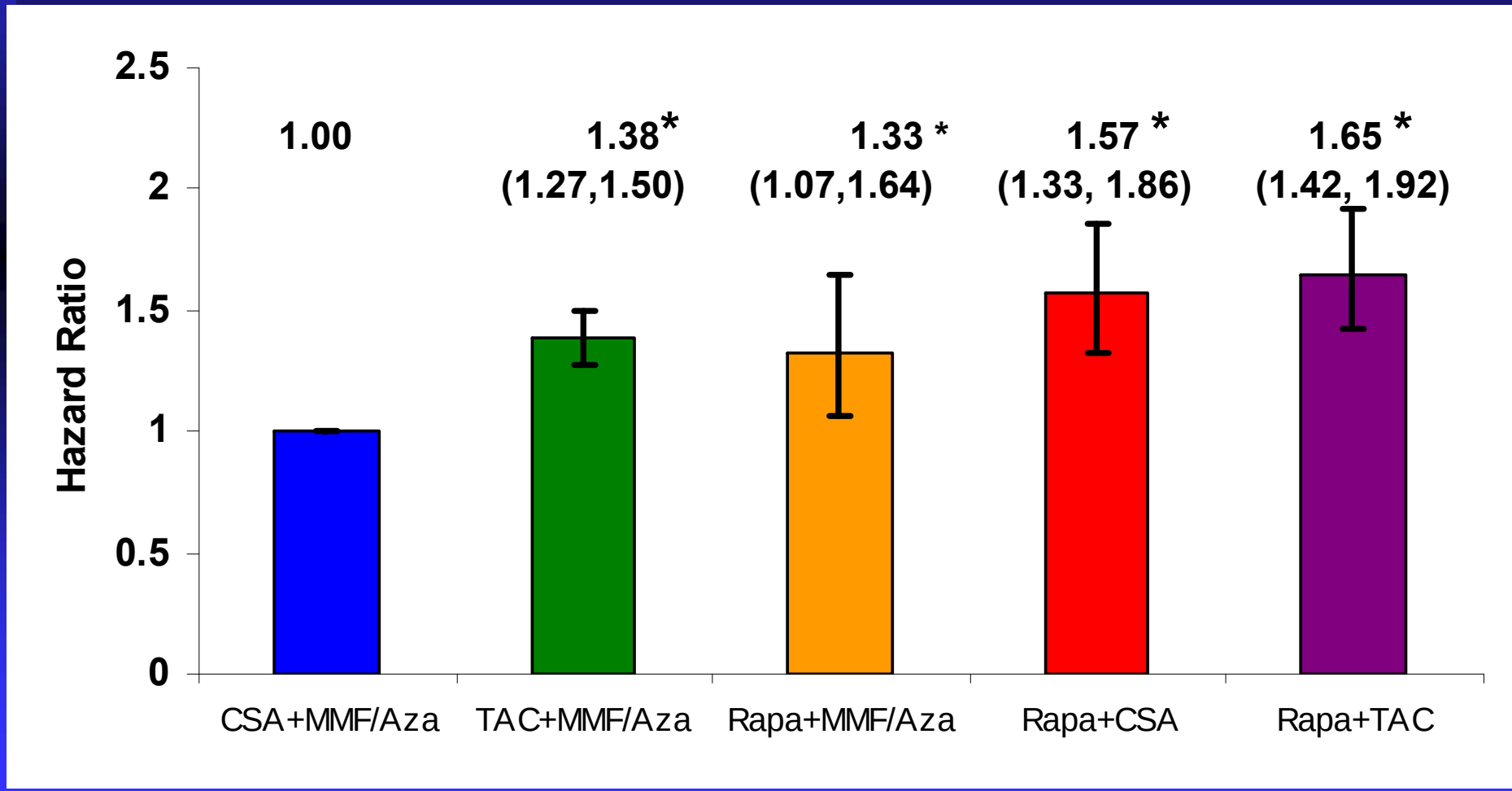
3 yr data – insulin usage is slightly higher in CCS group

Which drug regimen is associated with the lowest risk of NODAT?

Multivariate Analysis – drugs at hospital discharge

Adjusted for: steroid use, age, race, ethnicity, gender, ESRD etiology, BMI, donor type, comorbidities, Hep C, era, duration of dialysis

JASN 2008



Cyclosporine vs Tacrolimus

- Tacrolimus demonstrated superior efficacy in terms of acute rejection compared to cyclosporine
- DIRECT trial – compared cyclosporine and tacrolimus with MMF, steroids, basiliximab induction – with primary outcome of NODAT/IFG
  - Lower incidence of NODAT with cyclosporine
  - No significant difference in acute rejection rates at 6 months
  - Limited by open-label design and non-standardized steroid doses

Thymoglobulin induction, reduced Cyclosporine exposure and early Corticosteroid reduction to reduce New-onset Diabetes and Acute rejection in Kidney Transplant Recipients

- **Open-label, single arm, pilot**
- **N=49 recipients with PRA<20, first transplant, no overt DM (based on OGTT)**
- **Thymoglobulin induction induction**
- **Cyclosoporine, MMF, low dose prednisone**

6 MONTHS

- There was 1 death; no graft losses
- Two patients (4%) developed NODAT
- Four patients (8%) had impaired oral glucose tolerance testing at 6 months.
- One patient (2%) developed AR

LTA Study – Low Target Advagraf in A Steroid Free regimen to prevent NODAT

- Prospective, open label, randomized pilot study to examine the safety and efficacy of steroid withdrawal and low target tacrolimus
- TX ARM
  - Thymoglobulin induction/low target tacrolimus/MMF
  - Basiliximab induction/standard target tacrolimus/MMF
- 6 MONTH Outcomes
  - AR, NODAT

Obesity

- Weight gain is common following kidney transplantation
- Post-transplant obesity has been linked independently to reduced graft and patient survival
- Cosio et al. documented that the risk for developing NODAT increased by a factor of 1.4 for every 10 kg increase in body weight over 60 kg
- Multidisciplinary approach to weight management post-transplantation

HCV

- DM has been reported to be more common in patients with hepatitis C than in other types of liver disease
- Several recent studies also suggest a strong association between hepatitis C infection and the development of diabetes mellitus after either kidney or liver transplantation
- Postulated mechanisms include a direct cytopathic effect of the virus on beta cells, insulin resistance mediated by a postreceptor signaling defect, and decreased hepatic glycogenesis

- Treatment of hepatitis C with interferon-alpha results in improved glycemic control
- Interferon-alpha increases the risk of rejection

Prevention of NODAT

- Identify at risk population
- Tailor immunosuppressive therapies to minimize risk of NODAT
  - Steroid avoidance
  - Choice of CNI
- Mitigate additional risk factors
  - Obesity, dyslipidemia, hypertension
- Monitor for NODAT frequently post transplant
- Multidisciplinary approach

Management

	MOA	PROS	CONS
Biguanides (Metformin)	inhibit hepatic glucose production and increases peripheral glucose uptake	Low risk of hypoglycemia May help with weight loss	Lactic Acidosis
Sulfonylurias (glyburide)	Increase insulin excretion	Effective as primary agent	Hypoglycemia
Meglitinides (Repaglanide)	Augments food-stimulated insulin secretion	Very short acting	P450 3A4 metabolized
Alpha-glycosidase inhibitors (Acarbose)	Block carbohydrate digestion and decrease post prandial hyperglycemia	Effective as adjunctive agent	Malabsorption GI SE

Management

Thiazolidineidiones (rosiglitazone,pioglitazone)	Increase sensitivity to insulin	Effective in NODAT	metabolized by cp450 associated with fluid retention, weight gain Associated with CV disease
Incretins	Glucogon-like peptide agonists -targets post-prandial hyperglycemia	Effective Can help with weight loss	dose-adjust for renal function
Insulin		Effective	Labour intensive Risk of hypoglycemia

Summary

- NODAT is now more common than acute rejection
- It is associated with increased risk of death
- Screening and identification of at risk population is important
- Risk factor modification (obesity, metabolic syndrome, ?HCV)
- Immunosuppressive adjustment considered on a case-by-case basis
- Routine monitoring, consideration of pros/cons of individual therapies, and consultation with endocrinology to optimize glycemic control post-transplant is key to minimize implication of NODAT