

# Metabolic Syndrome After Kidney Transplantation: Risk Factor Management

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## NCEP ATP III\* Definition of Metabolic Syndrome Any 3 of the Following 5 Conditions:

Risk Factor	Defining Level
Abdominal Obesity Men Women	Waist Circumference > 40 inches > 35 inches
Triglycerides	> 150 mg/dl
HDL Cholesterol Men Women	< 40 mg/dl < 50 mg/dl
Blood Pressure	≥ 135/80 mm Hg
Fasting Glucose	> 110 mg/dl (recently lowered to > 100 mg/dl)

Grundy SM et al. *Circulation* 2004; 109: 433 \* Third Adult Treatment Panel

## IDF\* Definition of Metabolic Syndrome Central Obesity Plus Any 2 of the Following:

Risk Factor	Defining Level
Abdominal Obesity Men Women	Waist Circumference > 37 inches > 31.5 inches
Triglycerides	> 150 mg/dl
HDL Cholesterol Men Women	< 40 mg/dl <50 mg/dl
Blood Pressure	≥135/80 mm Hg
Fasting Glucose	> 100 mg/dl

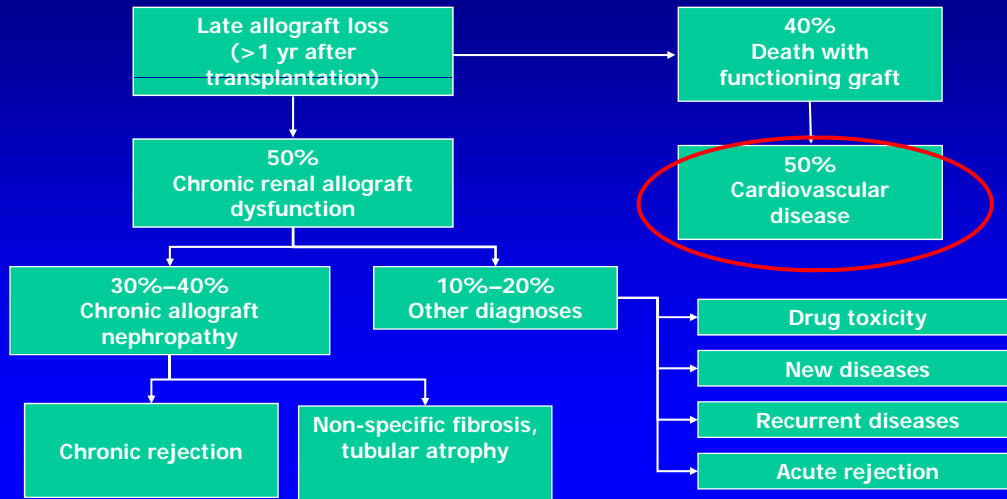
Alberti KG, et al. Diabet Med 2006; 23: 469 \* International Diabetes Federation

## Meta-analysis: Metabolic Syndrome and CVD in the General Population

Outcome	Studies (n)	RR	95% CI
CV Event	11	2.18	1.63-2.93
CHD Event	18	1.65	1.37-1.99
CV Death	10	1.91	1.47-2.49
CHD Death	7	1.60	1.28-2.01
Death	12	1.60	1.37-1.92

Gami AS, et al. J Am Coll Cardiol 2007; 49:403

## Causes of Late Kidney Allograft Loss



Pascual M et al. *N Engl J Med.* 2002;346:580-590.

## Prevalence of Metabolic Syndrome Among Kidney Transplant Recipients

Citation Patient Number (N)	Prevalence	Definition
de Vries APJ, et al <sup>1</sup> N=606	63% at 6 years (2.6-11.4 years)	NCEP ATP III
Porrini E, et al <sup>2</sup> N=230	22.6% at 1 year 37.7% at 18 months	<ul style="list-style-type: none"> <li>Modified NCEP ATP III</li> <li>BMI substituted for waist circumference</li> </ul>
Courivaud C, et al <sup>3</sup> N=337	32% at 1 year	<ul style="list-style-type: none"> <li>Modified NCEP ATP III</li> <li>BMI substituted for waist circumference</li> </ul>

BMI = body mass index; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

- de Vries APJ, et al. *Am J Transplant.* 2004;4(10):1675-1683.
- Porrini E, et al. *Am J Kidney Dis.* 2006;48(1):134-142.
- Courivaud C, et al. *Transplantation.* 2007;83(12):1577-1581.

## Metabolic Syndrome and CV Events in Transplant Recipients

Variable	Category	Hazard Ratio	95% CI	p
Cr Clearance (ml/min)	>50	1		
	<50	1.72	1.13-3.29	0.031
CRP (mg/dl)	<3	1		
	>3	2.07	1.12-4.59	0.041
Age (yrs)	<50	1		
	>50	2.11	1.01-4.43	0.048
PMH CV Disease	No	1		
	Yes	4.08	1.68-9.94	0.021
Metabolic Syndrome	No	1		
	Yes	3.40	1.58-7.32	0.002

Courivaud C, et al. Transplantation 2007; 83: 1577

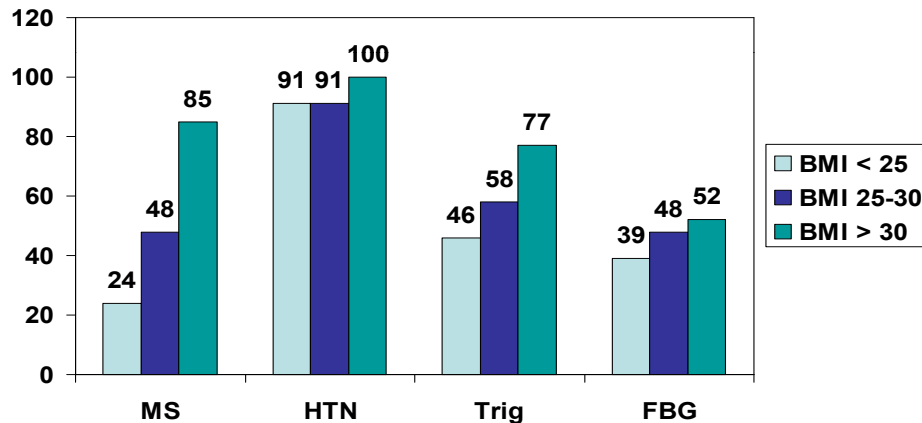
## Comparison of ATP III vs IDF Criteria Versus Putative Pathophysiological Components after Kidney Transplantation

ATP II Criteria

IDF Criteria

	ATP II Criteria			IDF Criteria		
	Yes	No	P	Yes	No	P
Insulin sensitivity ( $10^{-5}\text{min}^{-1}/$ mU/mL)	3.9±0.3	5.0±0.5	0.076	3.7+0.3	4.9+0.4	0.034
C-reactive Protein (mg/L)	6.2+1.2	3.7+0.7	0.062	7.2+1.3	2.9+0.3	0.004

## Metabolic Syndrome: Central Role of Obesity in Kidney Transplantation



Armstrong KA, et al. Am J Transplant 2005; 5: 2710

## Metabolic Syndrome and CV Events in Transplant Recipients

Courivaud C, et al. Transplantation 2007; 83: 1577

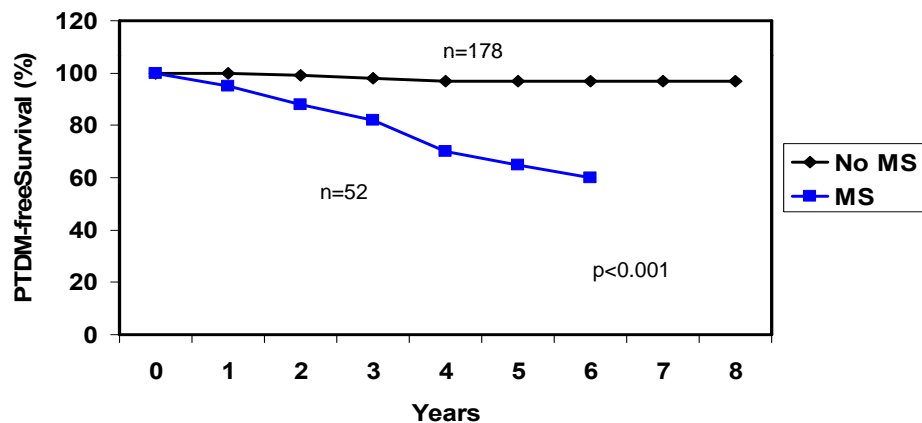
- 337 patients at 12 months
- 42 CV events > 12 months
- Csa/Tac, Aza/MMF, steroids
- MS in 108 patients; 32%

# Metabolic Syndrome and Risk of PTDM and Graft Failure

Porrini E, et al. Am J Kidney Dis 2006; 48: 134

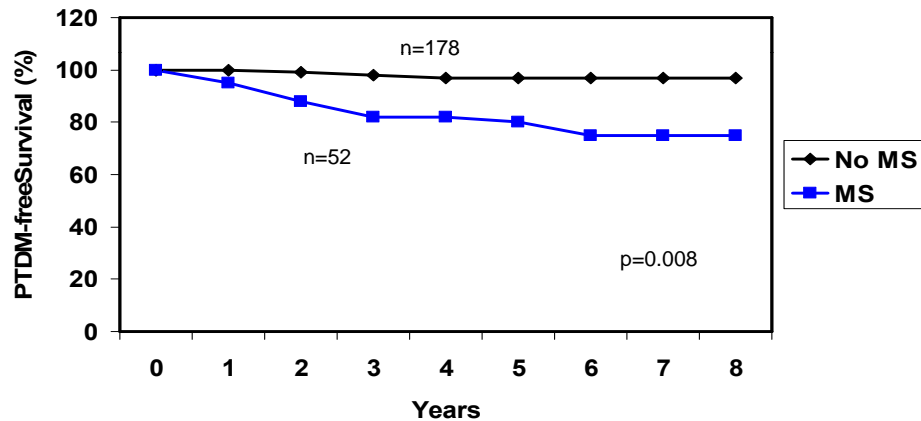
- 230 patients at 12 months
- Csa/Tac, Aza/MMF, steroids
- PTDM = FBG > 125 or use of medications
- MS any 3 of the following
  - BMI > 30
  - FBG > 100
  - BP > 130/85
  - Triglycerides > 150

## Metabolic Syndrome and Risk of PTDM



Porrini E, et al. Am J Kidney Dis 2006; 48: 134

## Metabolic Syndrome and Graft Survival



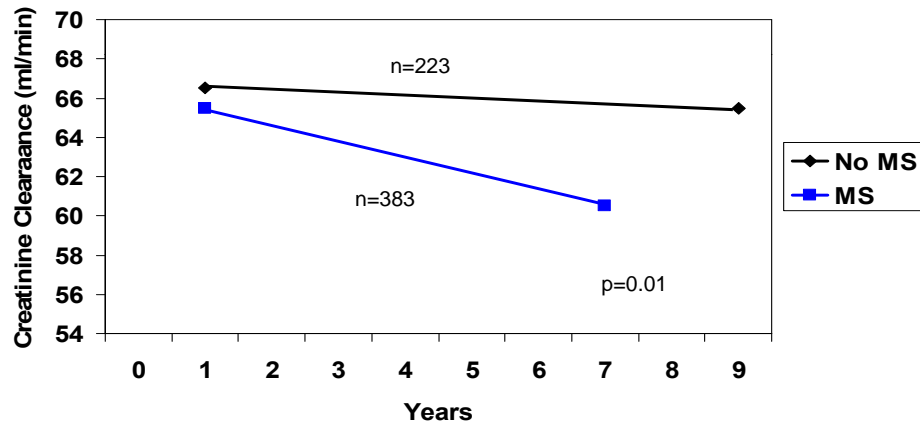
Porrini E, et al. Am J Kidney Dis 2006; 48: 134

## Metabolic Syndrome and Graft Function

deVries APJ et al. Am J Transplant 2004; 4: 1675

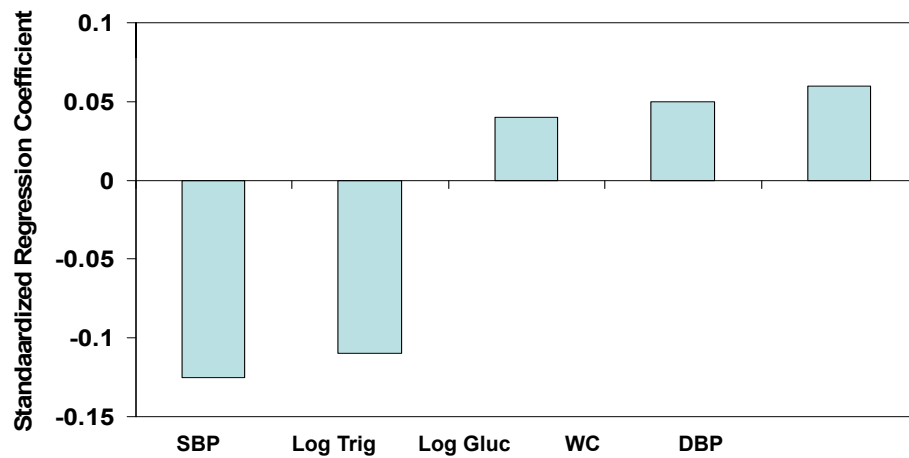
- 606 of 847 patients at 6 years
- 383 of 606 patients with metabolic syndrome (63%)
- CsA/Tac, Aza/MMF, steroids

## Metabolic Syndrome and Graft Function



Devries AP, et al. Am J Transplant 2004; 4: 1677

## Metabolic Syndrome Components and Graft Function



Devries AP, et al. Am J Transplant 2004; 4: 1677



## Effects of Immunosuppression on Traditional Cardiovascular Risk Factors

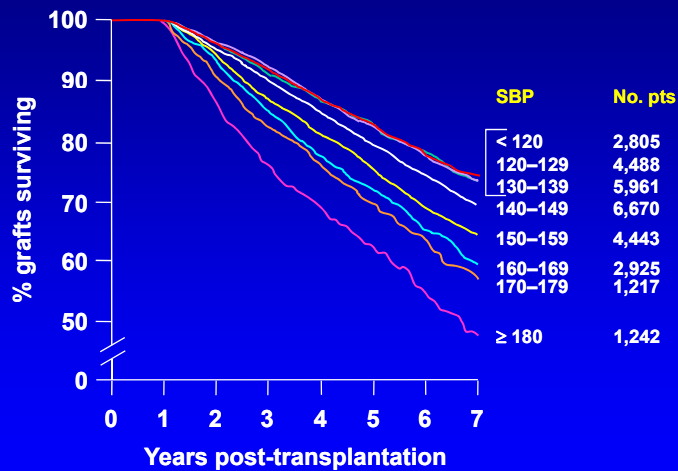
<ul style="list-style-type: none"> <li>• Weight gain</li> <li>• Hypertension</li> <li>• Enhanced atherogenic lipid profile</li> </ul>	<ul style="list-style-type: none"> <li>- CNI – CsA&gt;TAC</li> <li>- Corticosteroids</li> </ul>
<ul style="list-style-type: none"> <li>• New-onset diabetes after transplantation</li> </ul>	<ul style="list-style-type: none"> <li>- CNI – TAC&gt;CsA</li> <li>- mTOR inhibitor</li> </ul>
<ul style="list-style-type: none"> <li>• Posttransplant hyperlipidemia</li> </ul>	<ul style="list-style-type: none"> <li>- mTOR inhibitor</li> <li>- CNI – CsA&gt;TAC</li> </ul>

CsA = cyclosporine; TAC = tacrolimus.

Marcén R. *Drugs*. 2009;69(16):2227-2243.

Johnston O, et al. *J Am Soc Nephrol*. 2008;19(7):1411-1418.

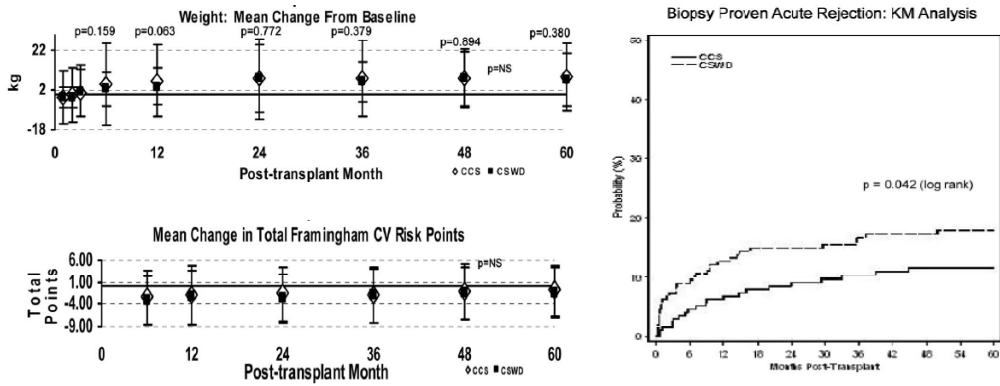
## Association of Hypertension at 1 Year With Decreased Graft Survival



SBP = systolic blood pressure

Opelz G et al. *Kidney Int*. 1998;53:217-222.

## Double-Blinded Randomized Trial of Early Steroid Withdrawal (Astellas Study)



Woodle et al, Annals Surg 2008

## Hypertension During 36 Months (Astellas Study)

	CCS N = 195	CSWD N = 191	p-value*
Experienced HTN	176 (90.3%)	176 (92.1%)	0.591
Severity of HTN			
Mild	129 (73.3%)	124 (70.5%)	
Moderate	37 (21.0%)	39 (22.2%)	
Severe	10 (5.7%)	13 (7.4%)	
Treatment for HTN	180 (92.3%)	172 (90.1%)	0.476
Mean # of Medications**	1.9	1.7	0.037

\*Based on Fisher's Exact test

\*\*Based on t-Test

## Treating HTN in kidney transplant recipients vs the general population

- **All BP meds work** but consider:
  - Interactions between immunosuppressive meds and BP meds.
  - “Nephrotoxicity” of BP meds
  - Side effects of BP meds
  - Cost and number of medications!
  - HTN is a side effect of IS medications

## Specific Issues with Anti-hypertensive Therapy in Transplant Recipients

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Non-dihydropyridine CCBs - CNI interaction

ACEI/ARBs

- Cardiac and renal benefit likely
- No good RCTs
- Retrospective studies
  - Selection bias
  - Conflicting outcomes
- Monitor kidney function, hemoglobin

## Pathogenesis of Hyperlipidemia in Renal Transplant Recipients (prevalence of 60-90% depending on immunosuppressive regimen\*)

- High prevalence of predisposing factors<sup>1</sup>
  - Age
  - Diabetes
  - Obesity
- Impaired renal function<sup>2</sup>
  - Renal insufficiency
  - Proteinuria
- Drugs<sup>3</sup>
  - Diuretics, beta-blockers
  - Immunosuppressive agents\*  
Steroids, CNIs, Sirolimus

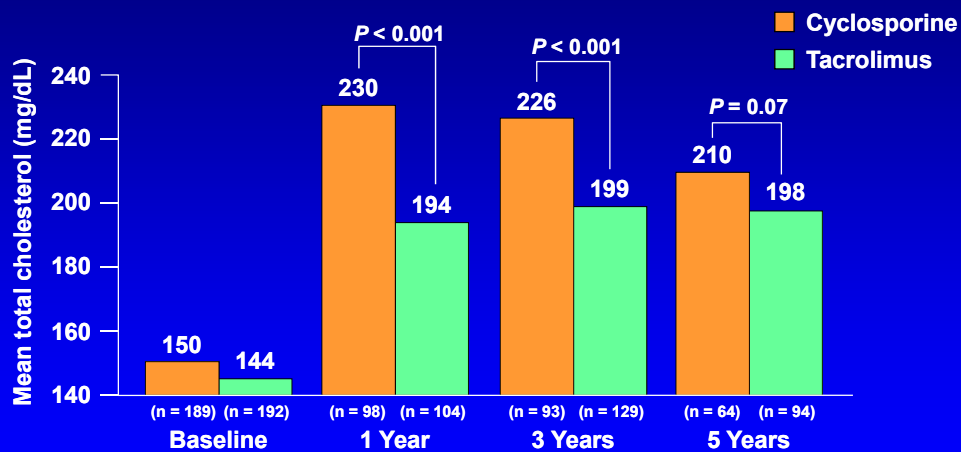
1. Keane WF. *Miner Electrolyte Metab.* 1997;23:166–169.

2. Kasiske BL. *Am J Kidney Dis.* 1998;32(suppl 3):S142–S156.

3. Aakhus S et al. *J Intern Med.* 1996;239:407–415.

## Cyclosporine vs Tacrolimus

### Mean Total Cholesterol Level Over Time



Randomized, multicenter trial with traditional formulation of cyclosporine  
Pirsch JD et al. Presented at Transplant 2000; Chicago, Illinois; May 13–17, 2000.

## Characterization of Hyperlipidemia Associated With Sirolimus

- ↑ Total-C and TG (increase LDL, VLDL, *and* HDL)
- Mechanism: ↓ catabolism of apoB-100–containing lipoproteins<sup>1</sup>
- Dose dependent
- Generally reversible upon cessation
- Responsive to lipid-reducing agents
  - No clinically significant interaction with atorvastatin<sup>2</sup>

1. Hoogeveen RC et al. *Transplantation*. 2001;72:1244–1250.

2. Zimmerman JJ et al. Presented at 10th Congress of European Society for Organ Transplantation; Lisbon, Portugal; October 6–10, 2001.

## Effect of Sirolimus on Aortic Atherosclerosis in ApoE-Deficient Mice



**Control**



**8 mg/kg/d x 2 d**

Adelman SJ et al. Presented at Transplant 2001; Chicago, Illinois: May 11–16, 2001.

## Hyperlipidemia at Month 36 (Astellas Study)

	CCS	CSWD	p-value*
Cholesterol (mg/dL)	175.6	168.0	0.123
HDL (mg/dL)	48.5	45.4	0.117
LDL (mg/dL)	92.2	88.9	0.441
Triglycerides (mg/dL)	192.1	174.8	0.372
Required Therapy (mg/dL)**	102 (65.4%)	86 (55.1%)	0.122

\*Based on t-Test

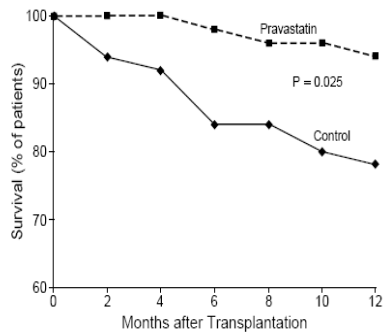
\*\*Based on Fisher's Exact test

## Beneficial Effects of Statins

- Lower lipid levels
- Reduce systemic inflammation
- Increase insulin sensitivity
- Attenuate kidney injury

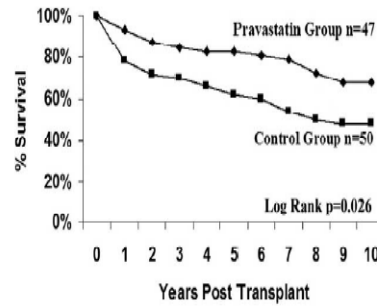
## Statins and Improved Survival - Heart

1-year



Kobashigawa et al. NEJM 1995

10 year



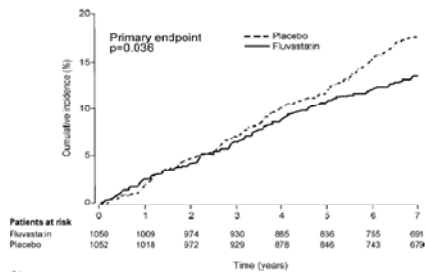
Kobashigawa et al. J. Heart Lung 2005

## Statins in Kidney Recipients (ALERT)

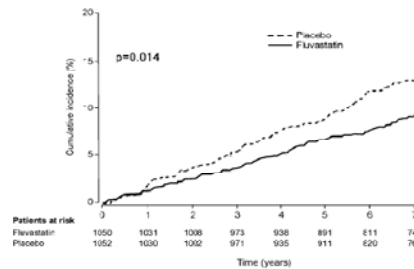
2102 patients, RCT  
fluvastatin vs placebo

74.2% fluvastatin pts had reduced LDL cholesterol

Major Adverse Cardiac Event



Cardiac Death or Non-fatal MI

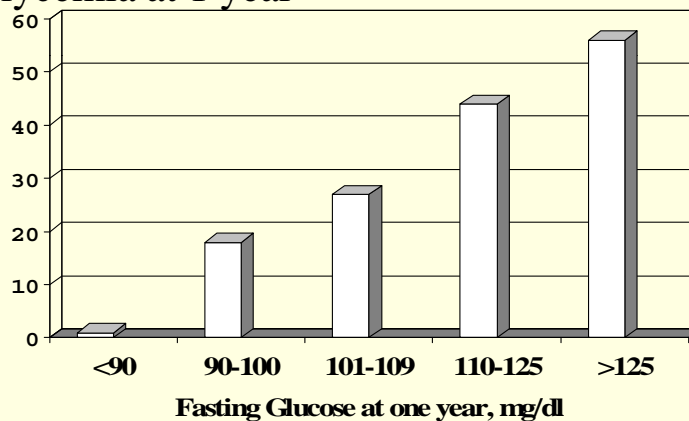


Holdaas H, et al. Am J. Trans. 2005

## Adjuncts to Statins in Txp Recipients

- Fibrates (e.g Fenofibrate, gemfibrozil)
  - Reduce creatinine clearance
  - Usually reversible
- Ezetimibe
  - Benefit unknown
  - Lowers LDL effectively
  - Appears to be safe in txp pts
  - Interactions with CNI unknown

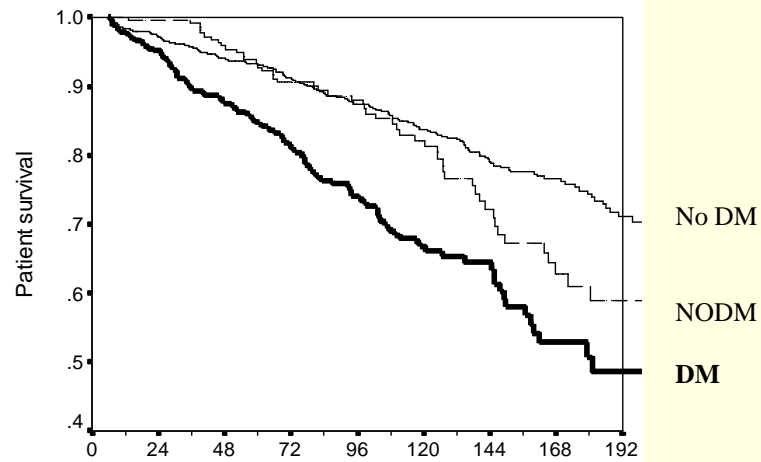
Cumulative incidence of cardiovascular events five years posttransplant in patients classified according to fasting glycemia at 1 year



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

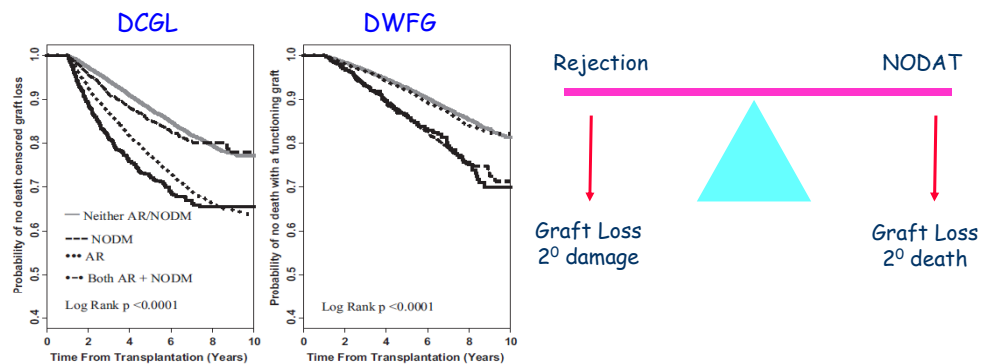


## Diabetes (pre or post-transplant) has a profound impact on recipient survival



Adapted from Cosio et al. K Int 2002;62:1440 Follow up months

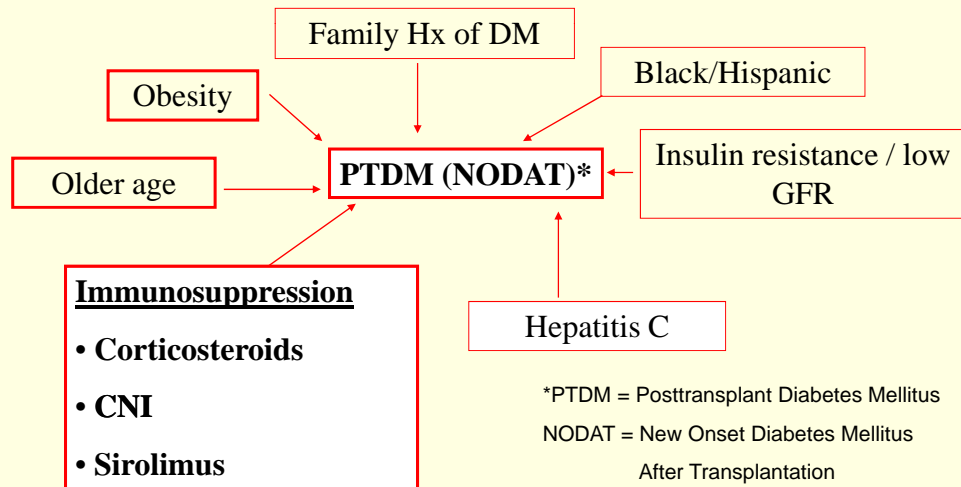
## Impact of NODAT and Acute Rejection on Patient Outcomes



USRDS data, n=27,707, txpd 1995-02

Cole et al. CJASN 2008

## Risk factors for the development of post-transplant hyperglycemia



## NODAT\* During 36 Months (Astellas Study)

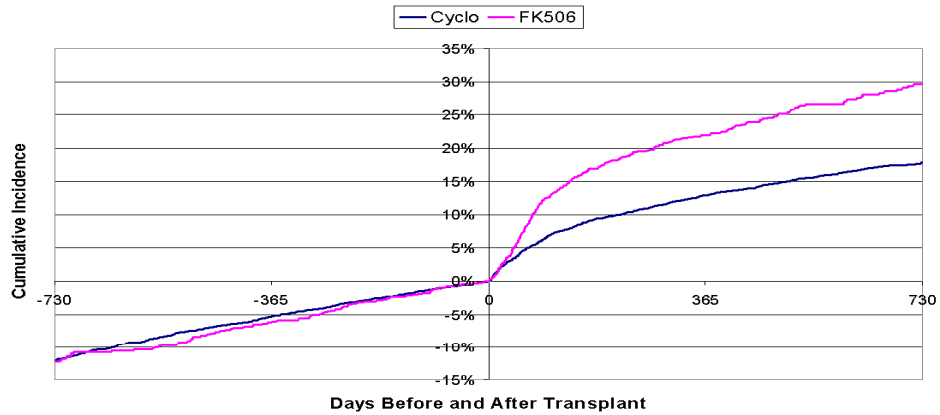
	CCS N=135	CSWD N=142	p-value**
One FBS $\geq$ 126 mg/dL ***	72 (53.3%)	74 (52.1%)	0.839
Two FBS $\geq$ 126 mg/dL ***	46 (34.1%)	44 (31.0%)	0.583

\*NODAT=new onset diabetes after transplant

\*\*Based on Chi-Square test

\*\*\*ADA criteria

### Incidence of Diabetes Before and After Transplant By Type of Calcineurin Inhibitor



**Note:**

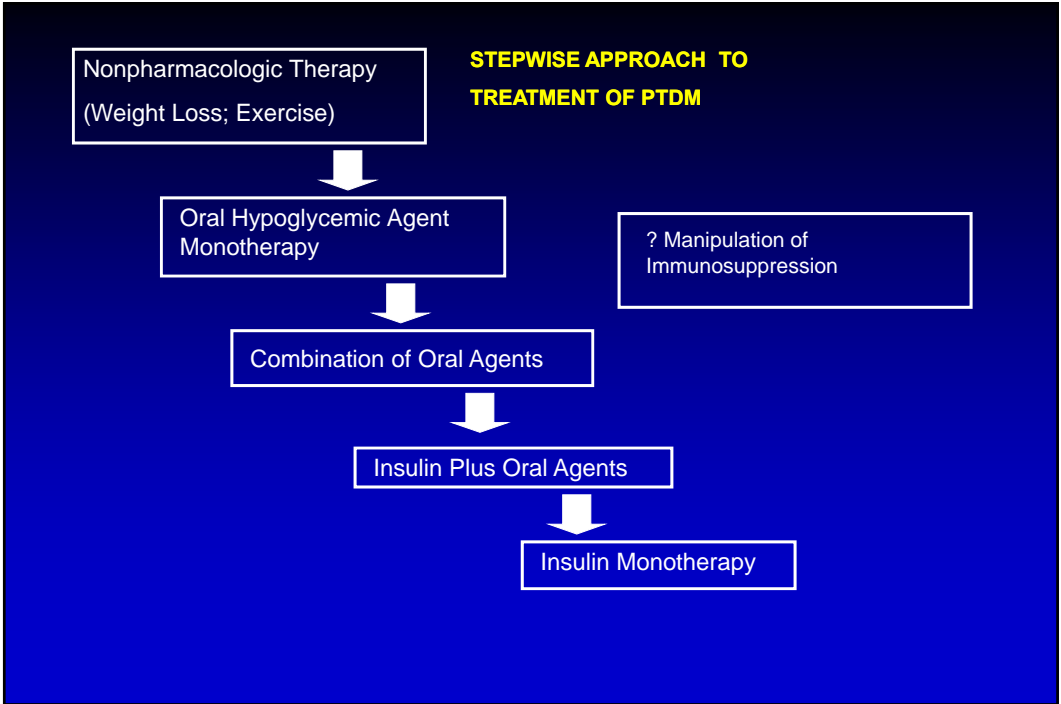
The incremental incidence of diabetes for cyclosporine was 9.4% at 1 year and 8.4% at 2 years.  
The incremental incidence of diabetes for tacrolimus was 15.4% at 1 year and 17.7% at 2 years.

Woodward et al, AJT. 2003;3 1-9.

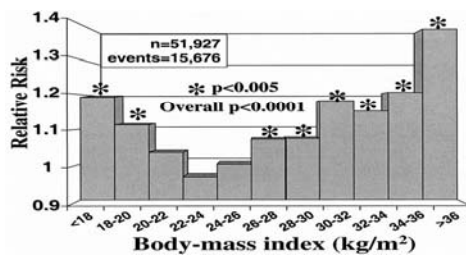
## Tailoring Immunosuppression to Limit the Risk of New Onset Diabetes

- **Individualize regimen**
  - Steroid minimization/avoidance
  - Steroid withdrawal
  - CNI minimization
  - Convert Tacro to CyA
  - Risk of NODAT vs rejection

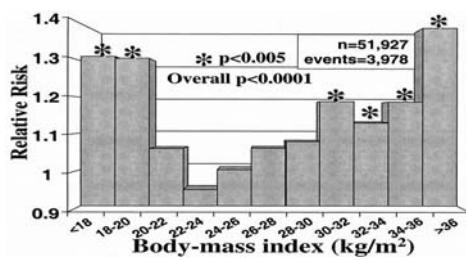
Davidson J., Transplantation, 2003



## Pre-Txp Obesity and Outcomes

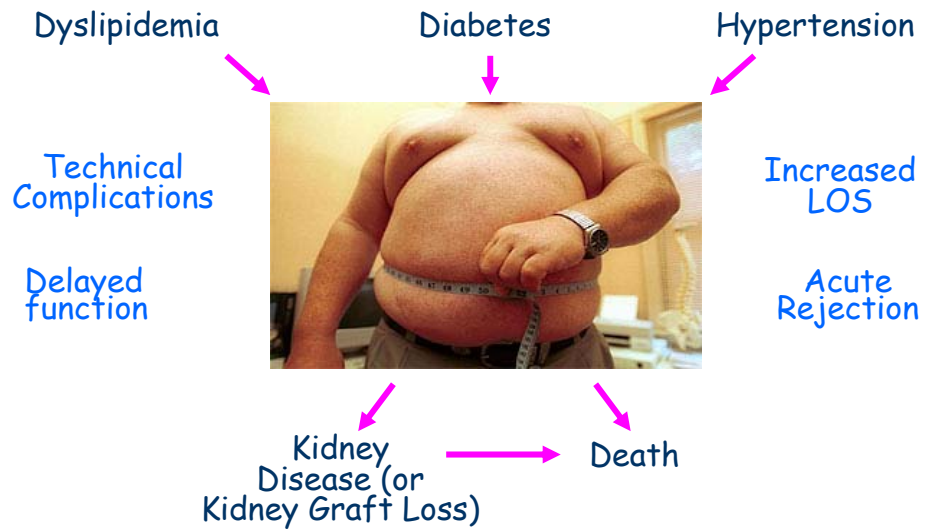


Graft loss

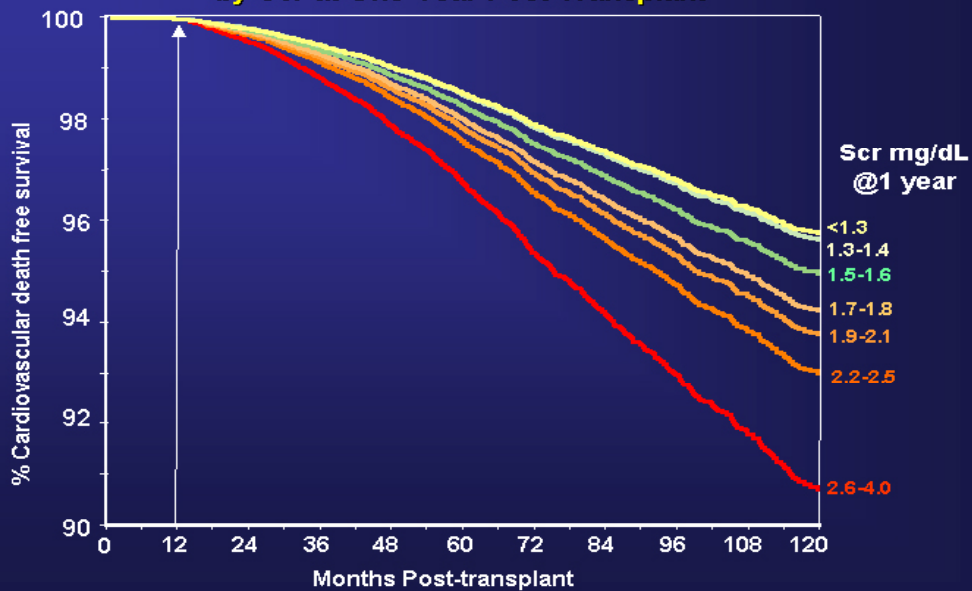


CV Death

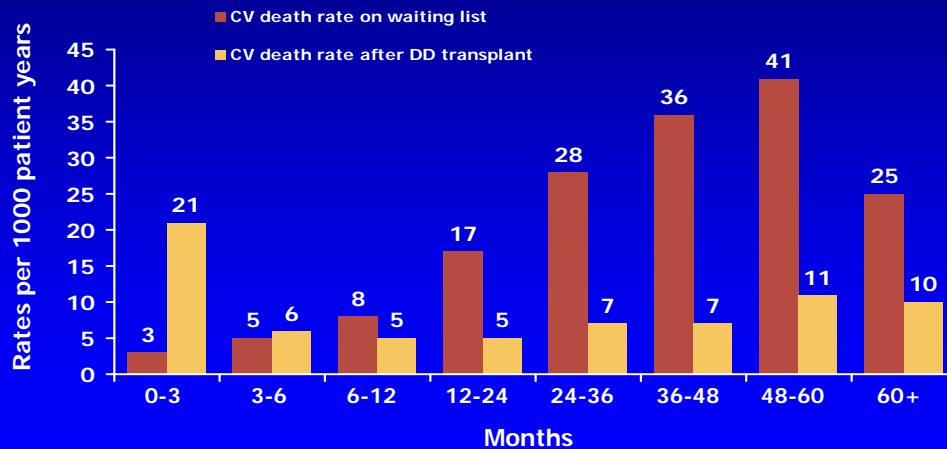
## Obesity Worsens Recipient Outcomes



## Cardiovascular Death by Scr at One-Year Post Transplant



## Kidney Transplantation Reduces CVD Risk in Patients With ESRD



Meier-Kriesche HU et al. *Am J Transplant.* 2004;4:1662-1668.

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## Summary

- Metabolic syndrome is common after kidney transplantation
- Prevalence increases in concert with weight gain
- MS is associated with CVD, deteriorating graft function, graft loss
- Not clear whether the entire syndrome is any more worthy of study than its individual components