

# **Immunosuppression in the Elderly: What are the Risks?**

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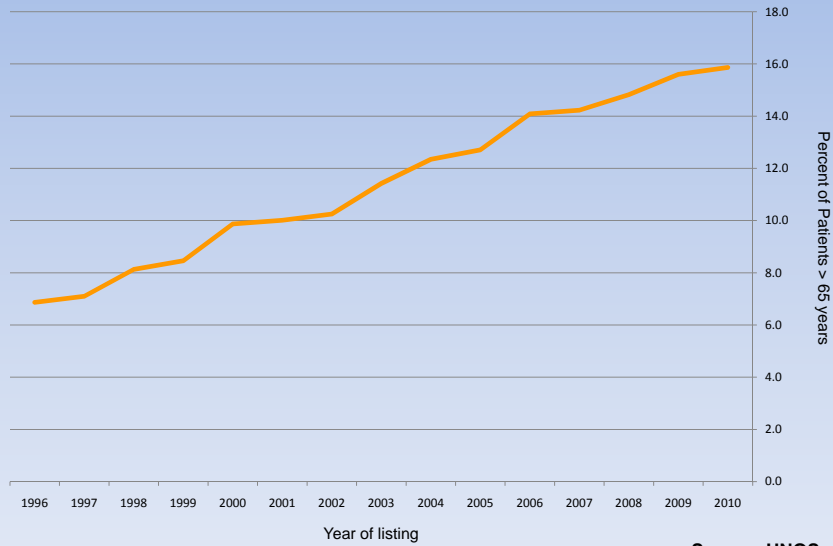
## **Disclosures**

## Objectives

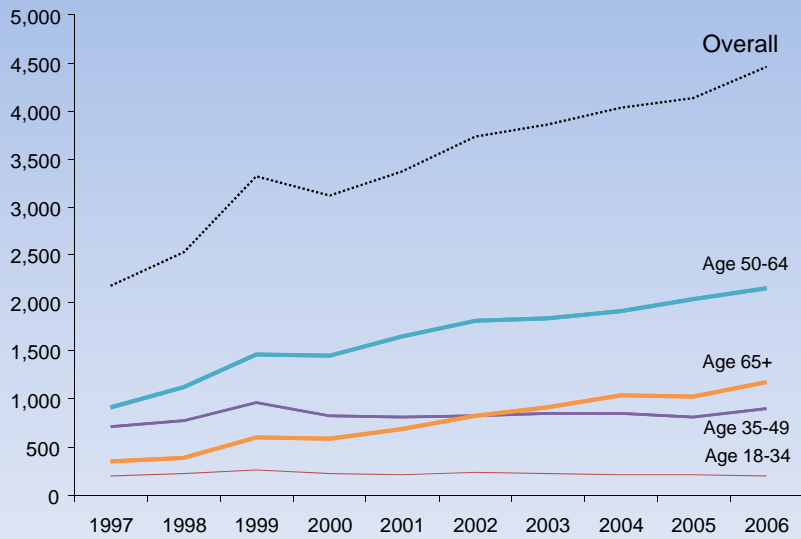
- Evaluate risks for elderly renal transplant patients
- Present current utilization patterns of immunosuppressive medications for elderly recipients
- Examine specific risks associated with elderly recipients associated with immunosuppression regimens

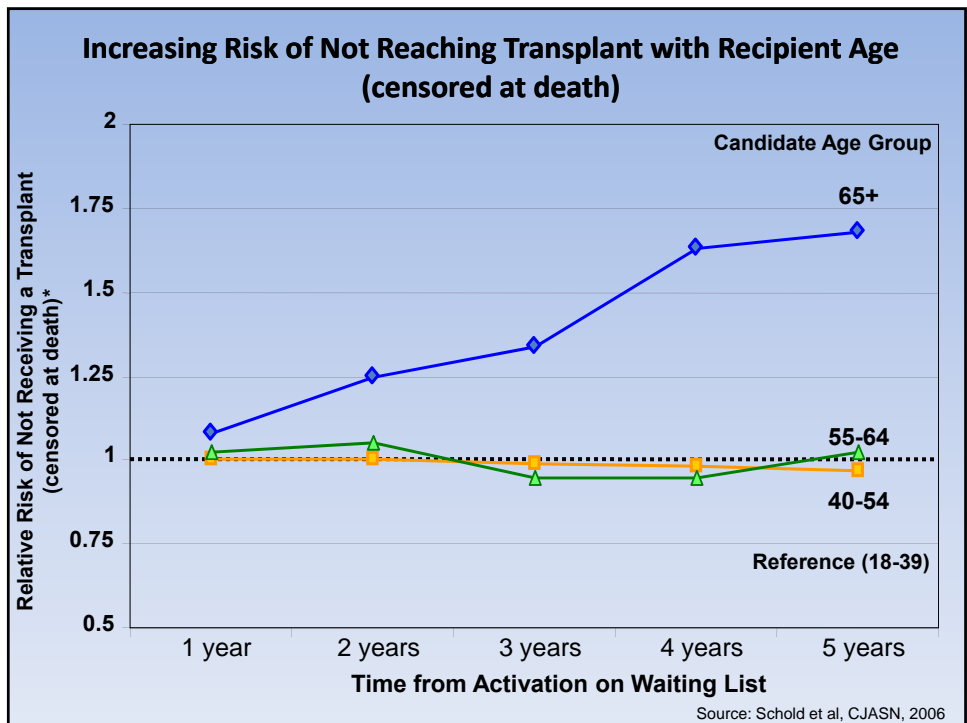
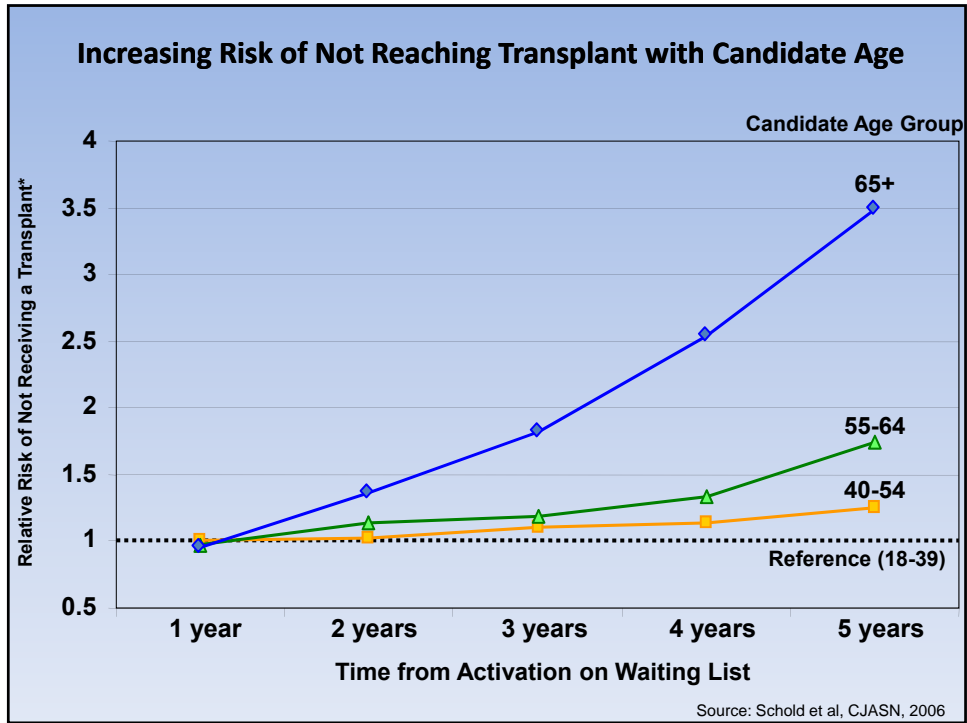
The Primary Risk for Elderly Renal  
Transplant Patients:  
Time Waiting for a Transplant

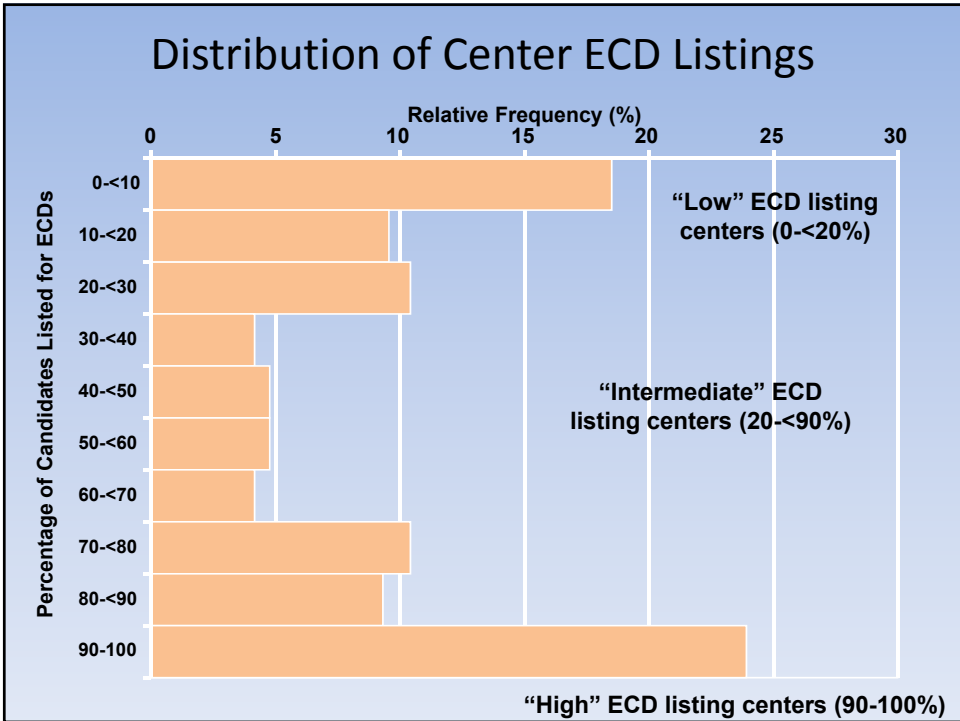
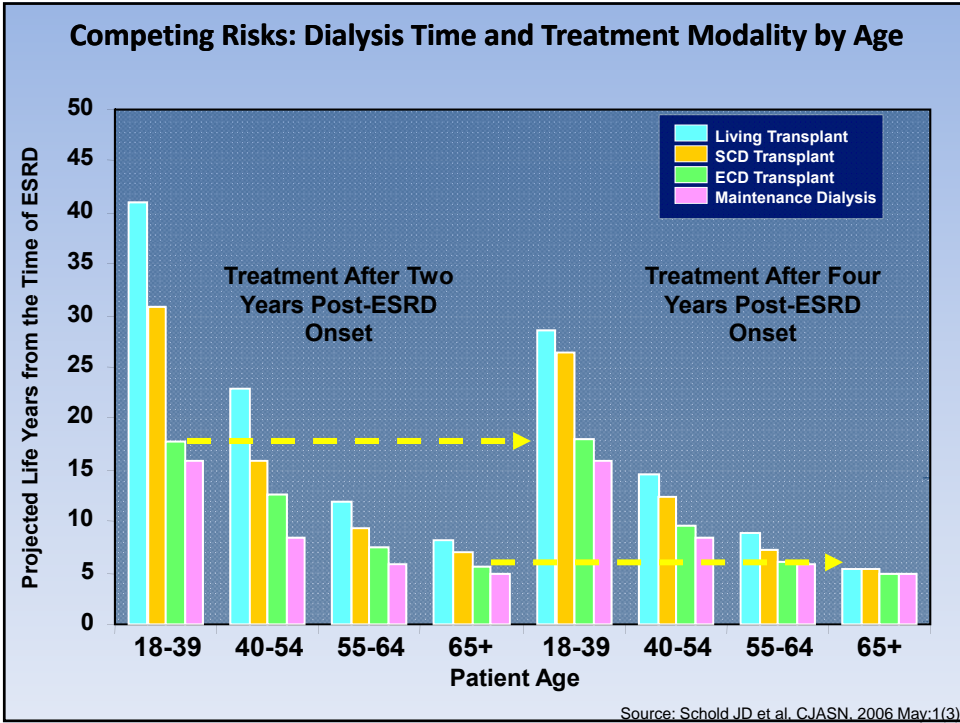
## Additions to the Transplant Waiting List - % of Patients > 65 years



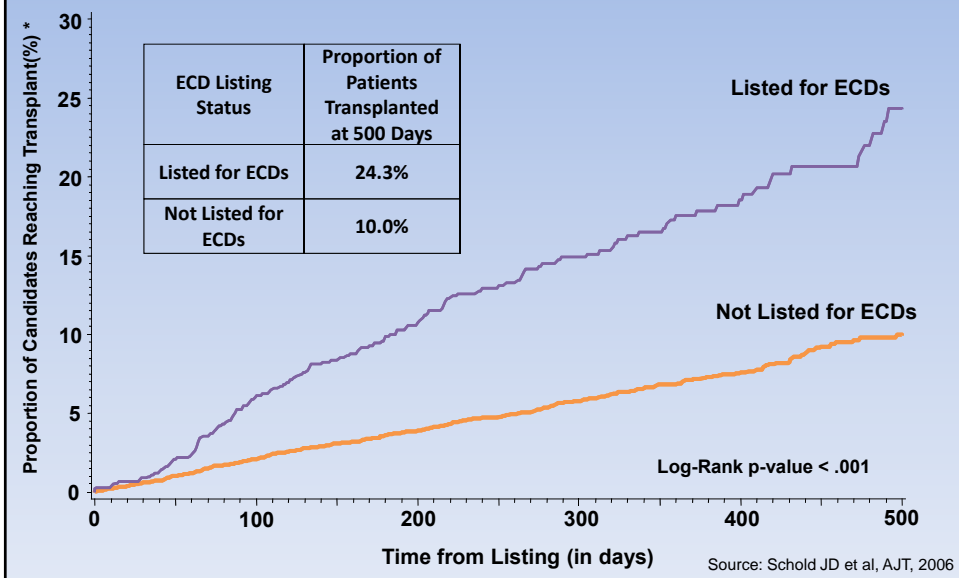
## Adult Candidate Mortality on the Kidney Transplant Waiting List



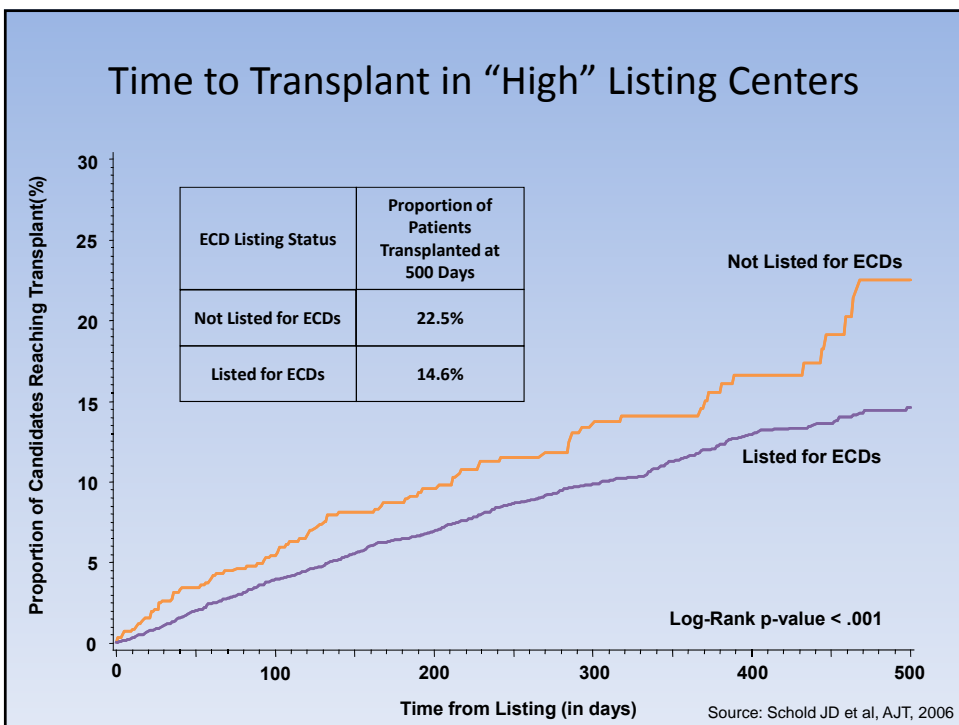




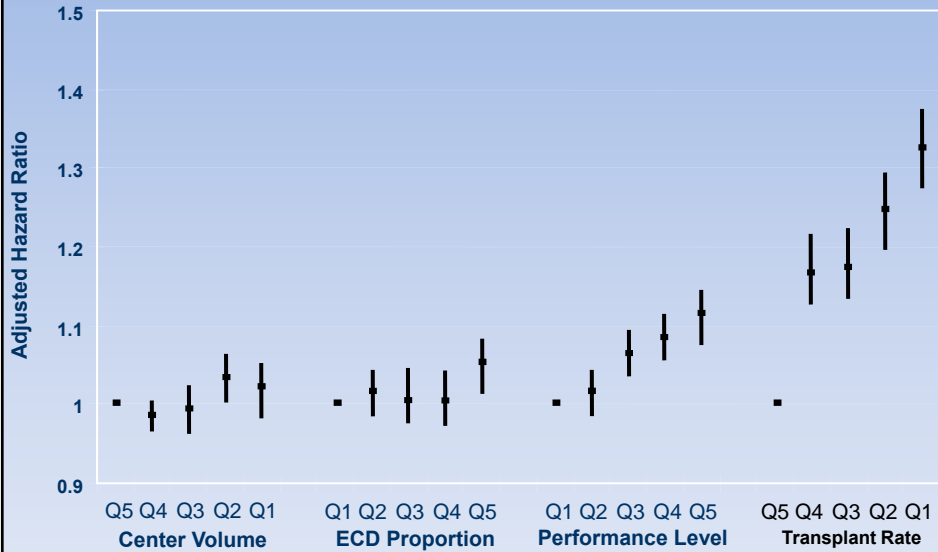
### Time to Transplant in “Low” Listing Centers



### Time to Transplant in “High” Listing Centers

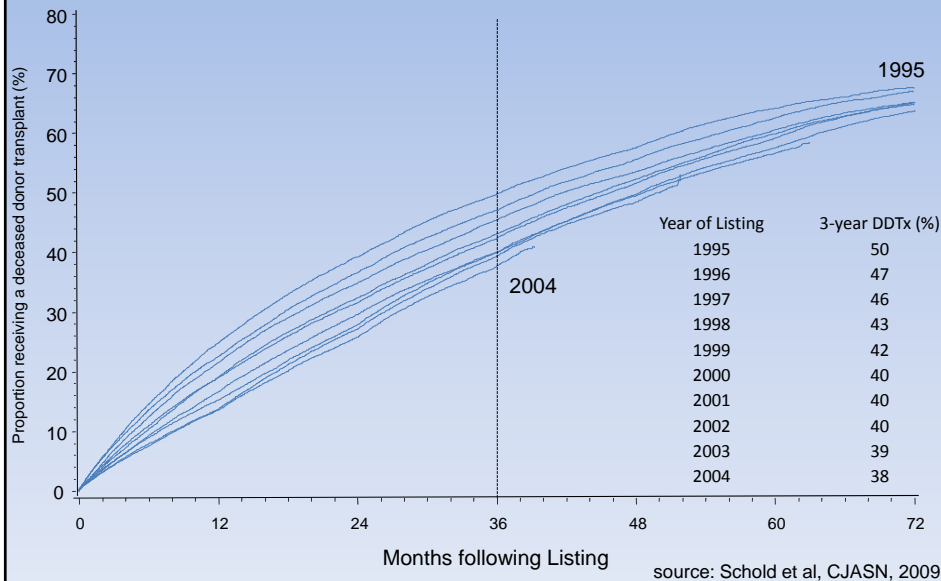


### Candidate Mortality after Listing by Center Characteristics

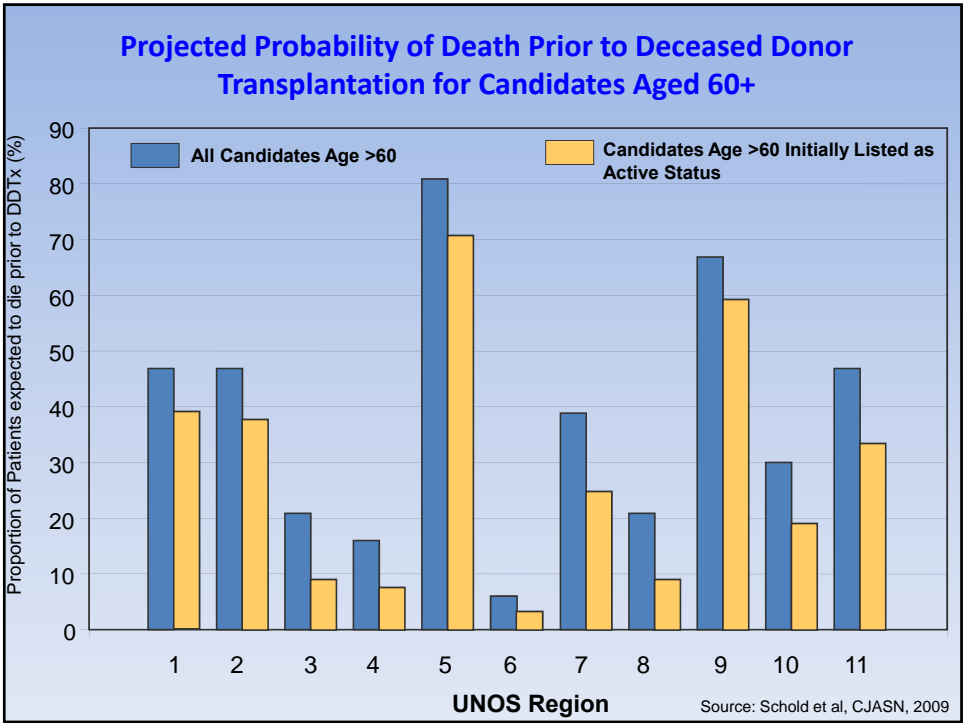
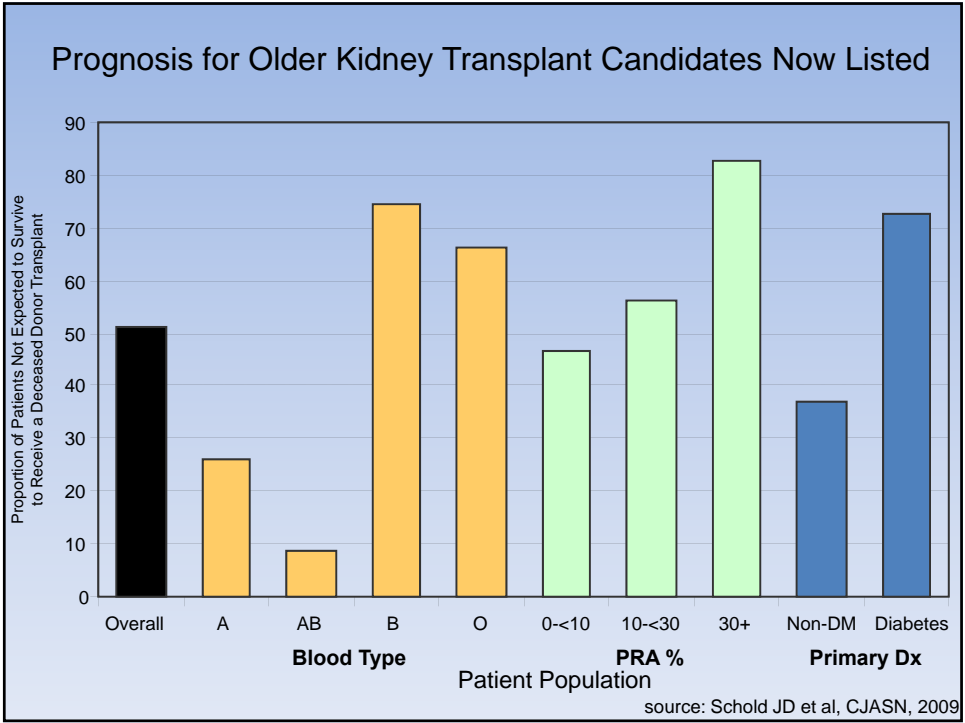


Source: Schold et al, Medical Care; 2009

### Time to Deceased Donor Transplantation by Year of Listing (1995-2004)

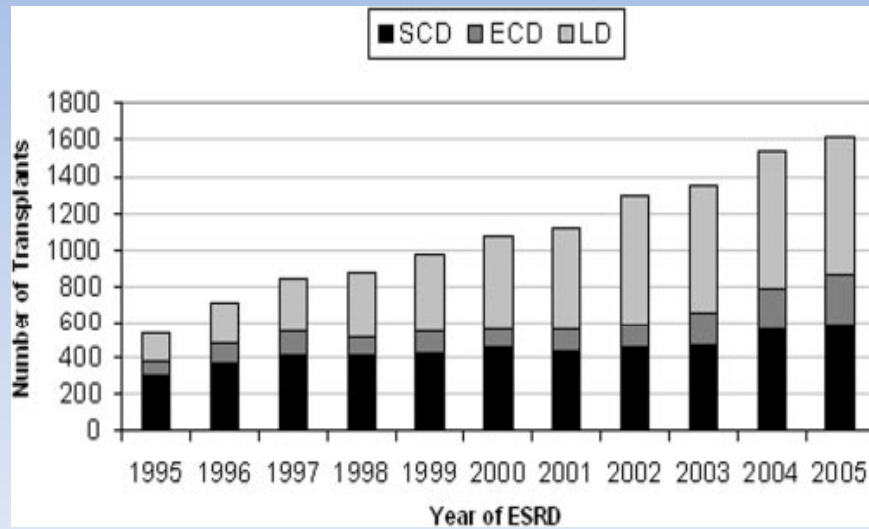


source: Schold et al, CJASN, 2009



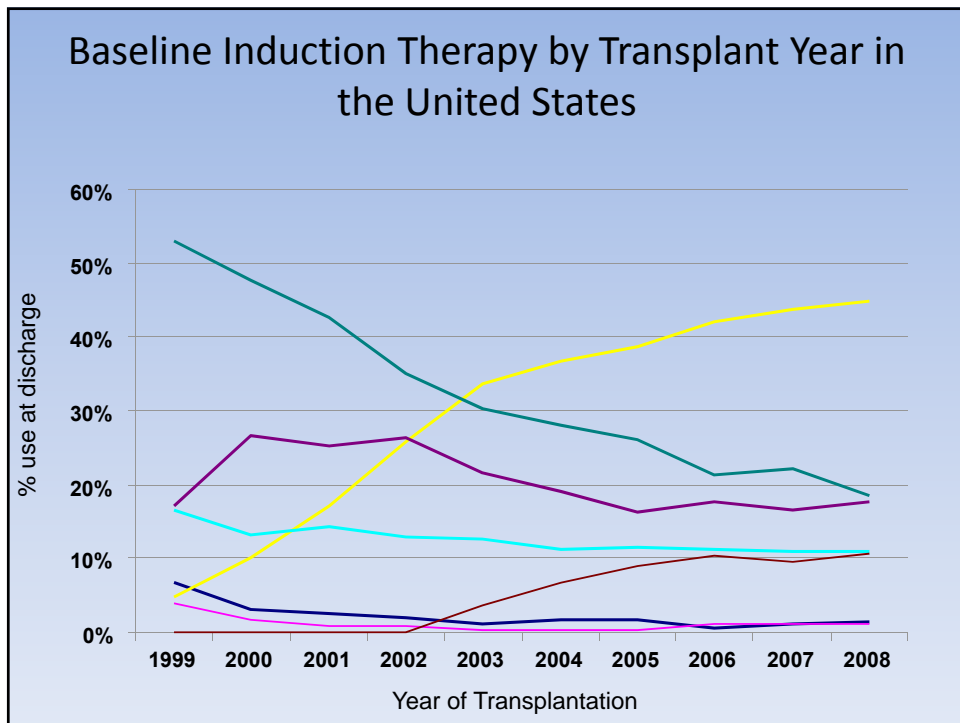
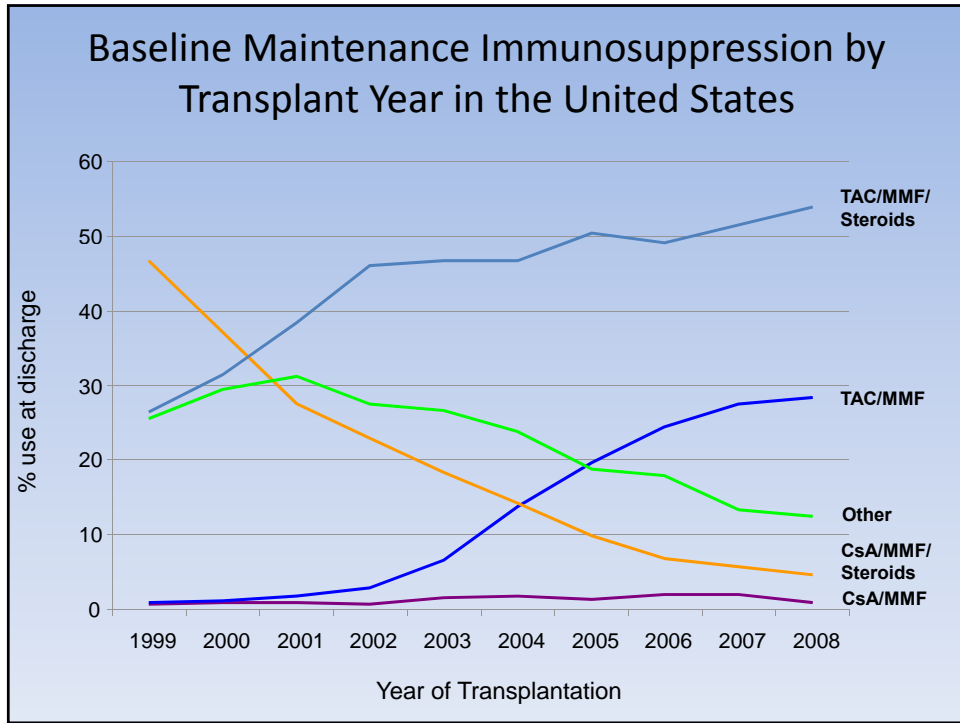


## Increasing Number of Elderly Recipients

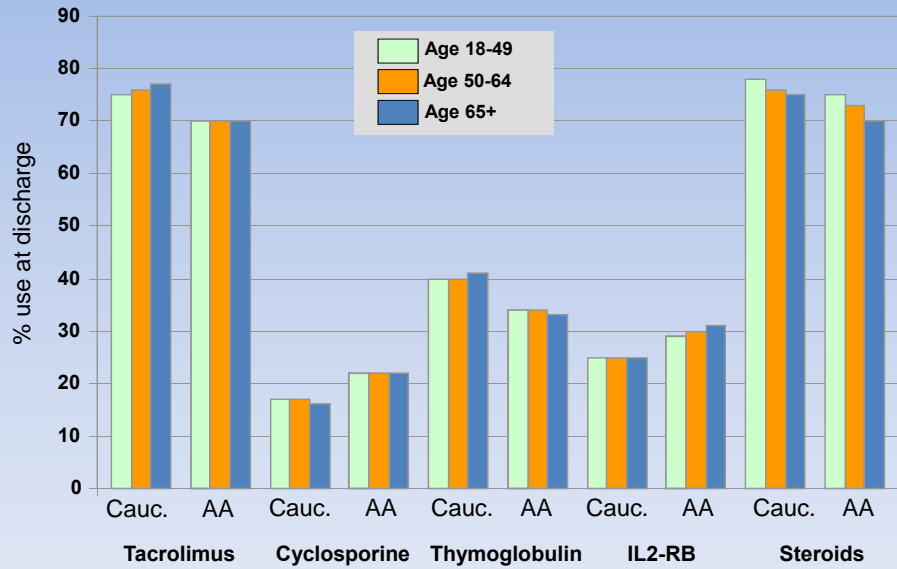


Schaeffner E et al, CJASN (in press)

## Utilization of Immunosuppression Medications in the United States Kidney Transplant Population



## Baseline Immunosuppression by Age and Race in the United States (2000-2009)

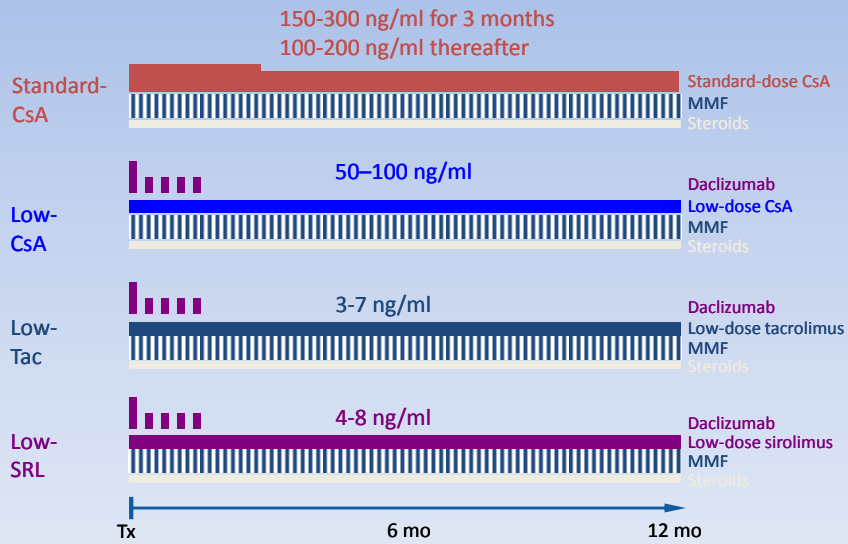


Source: Schold JD, Clin Transplant (in press)

Risk Profile for Elderly versus  
Younger Renal Transplant  
Recipients

# SYMPHONY study design

1645 patients, 15 countries



## Efficacy endpoints (month 12)

Age groups	20-40y	40-50y	50-60y	< 60y	≥ 60y
<i>n</i> (ITT)	523	364	367	1292	296
<b>Patient survival (%)<sup>‡</sup></b>	<b>98.6</b>	<b>98.6</b>	<b>96.3</b>	<b>98.0</b> *	<b>93.6</b>
<b>Graft survival (%)<sup>‡</sup></b>	<b>92.8</b>	<b>91.9</b>	<b>90.6</b>	<b>92.1</b> ns	<b>88.9</b>
<b>BPAR (%)<sup>‡</sup></b> (excluding borderline)	<b>26.1</b>	<b>24.9</b>	<b>25.2</b>	<b>25.3</b> ns	<b>22.3</b>
<b>GFR (Cockcroft-Gault)</b> (LOCF, imputation 10 ml/min)	<b>66.9</b>	<b>62.6</b>	<b>55.8</b>	<b>62.7</b> **	<b>46.1</b>
<b>DGF</b> (% of deceased donor patients)	<b>24.3</b>	<b>27.0</b>	<b>33.9</b>	<b>29.2</b> ns	<b>35.1</b>

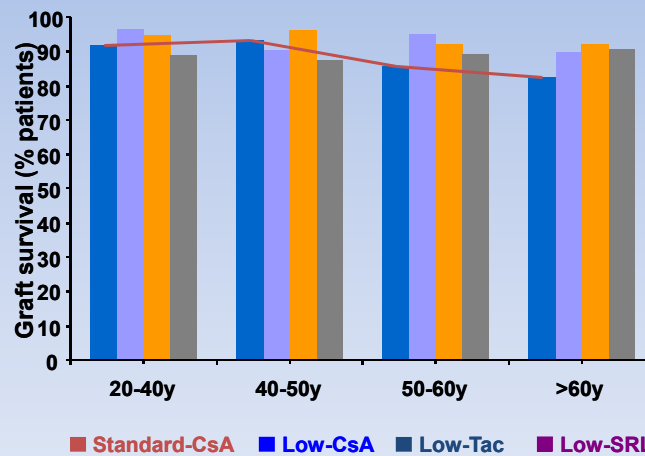
ITT population, <sup>‡</sup>Kaplan-Meier estimates, \*p < 0.05, \*\*p < 0.0001

## Symphony Study Safety endpoints (month 12)

Age groups	20-40y	40-50y	50-60y	< 60y	≥ 60y
<i>n</i> (Safety)	528	364	370	1301	300
Infections overall (%)	52.7	58.7	66.0	55.9 *	67.7
Pneumonia (%)	2.3	4.4	6.0	3.9 *	9.0
Sepsis (%)	4.0	3.3	6.0	4.2 **	10.3
UTI (%)	24.2	30.0	32.4	28.2 **	41.7
CMV (%)	8.3	8.0	15.1	10.2 ns	9.7
Diarrhoea (%) <sup>*</sup>	20.4	17.1	22.4	20.2 ns	23.1
Post-Tx diabetes (%) <sup>*</sup>	2.8	5.5	9.9	5.5 **	16.2
Lymphoceles (%) <sup>*</sup>	6.6	7.5	9.4	7.5 *	10.5
Wound not healed (at week 2)	8.1	11.0	13.8	10.5 **	17.7

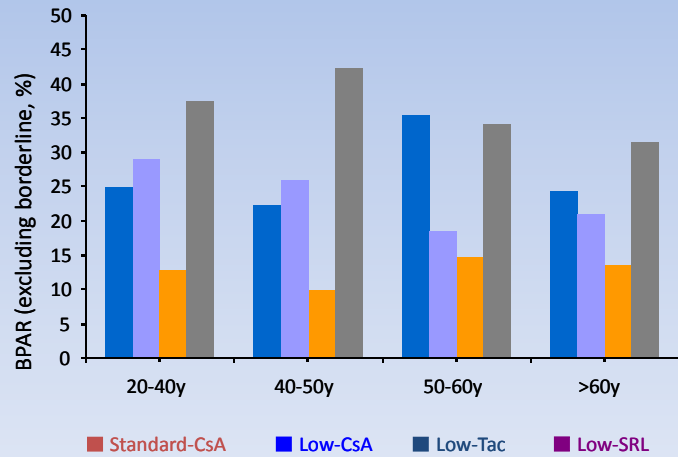
Safety population, <sup>\*</sup>Kaplan-Meier estimates, \*p <0.05, \*\*p <0.0001

## Graft survival by age group



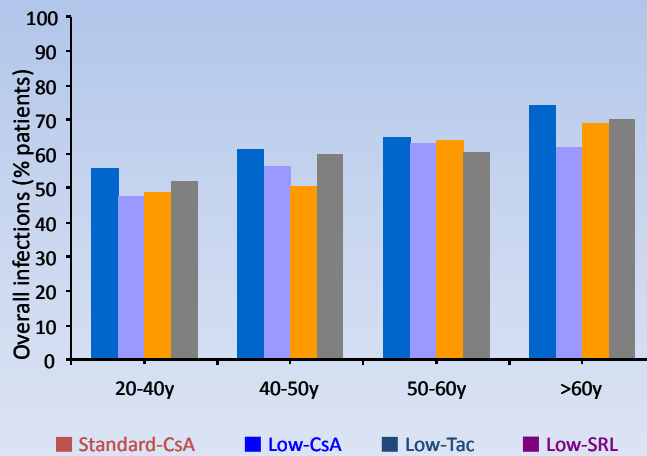
ITT population

## BPAR by age group (Excluding borderline)



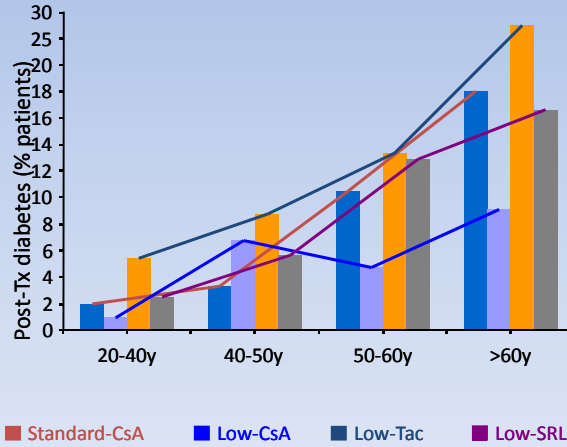
ITT population

## Overall infections by age group



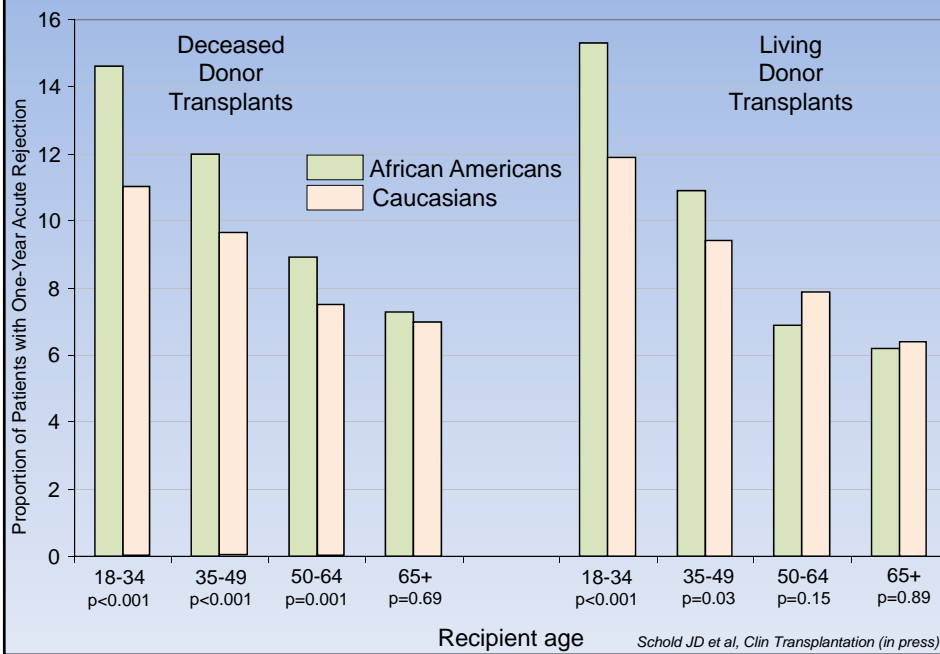
Safety population

## New onset diabetes by age group

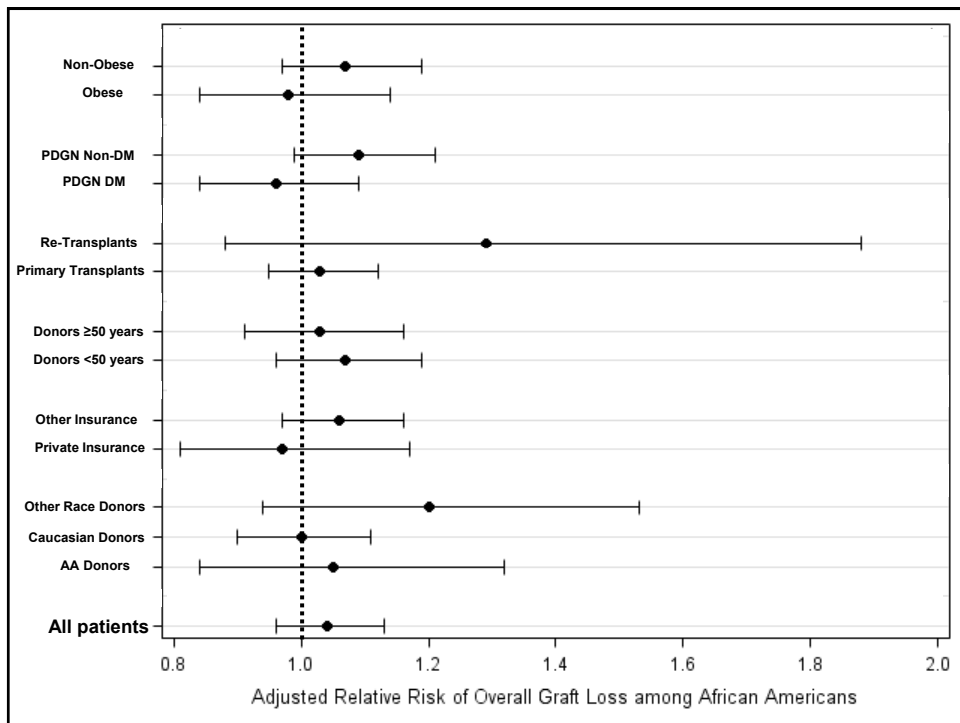
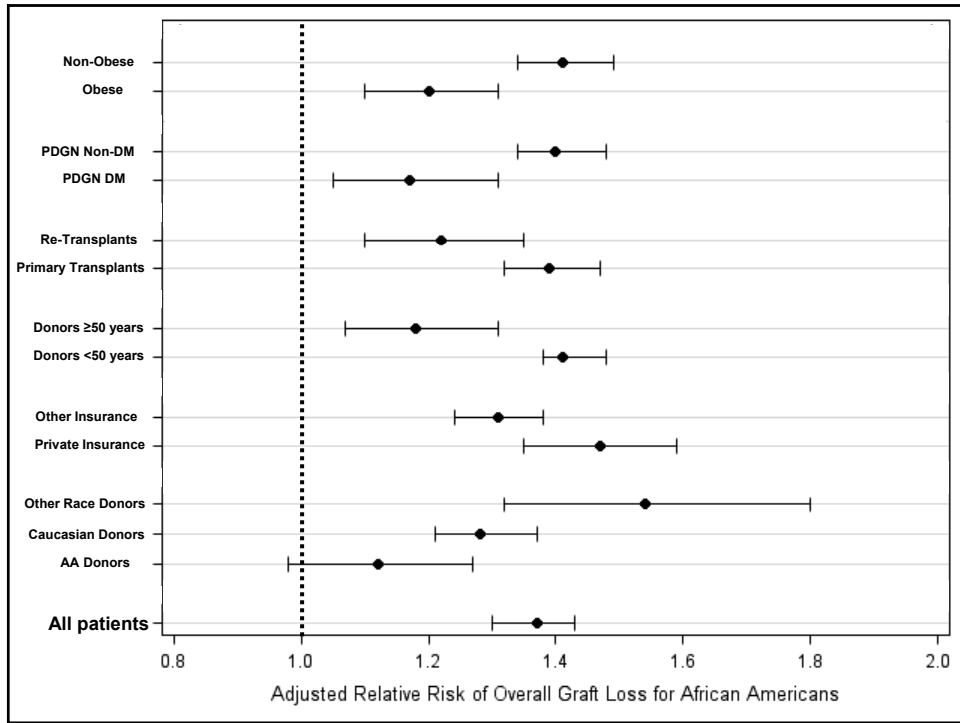


Safety population, Kaplan-Meier estimates

## Treatment for Acute Rejection by Race and Age



Schold JD et al, Clin Transplantation (in press)





## Switching immunosuppression after renal transplantation

- **Risk Factors**

- HLA mismatches(0): 1.04(1.00, 1.09)
- African Americans (Caucasians): 1.04(1.01, 1.08)
- Female recipient (males): 1.03(1.00, 1.06)
- Recipient age (per 10 years): 0.97(0.96, 0.98)

Meier-Kriesche et al., Nephrol. Dial. Transplant. (August 2006) 21 (8): 2256-2262

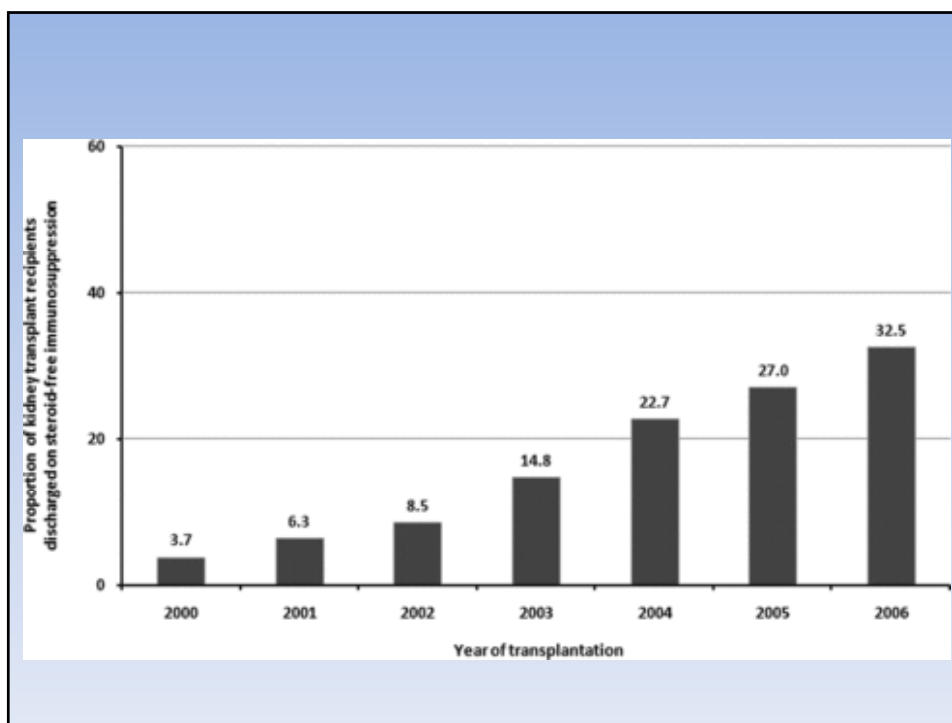
## Relative Risk of Discontinuation of Steroid-Avoidance Regimens

- **Deceased Donor Transplants**

- Recipient age (reference: 18–34 years)
  - 0–11 0.96 0.66, 1.41
  - 12–17 0.69 0.51, 0.93
  - 35–54 1.02 0.88, 1.17
  - 55–64 0.93 0.79, 1.08
  - **65+ 0.74 0.62, 0.89**

- **Living Donor Transplants**

- Recipient age (reference: 18–34 years)
  - 0–11 0.72 0.52, 1.01
  - 12–17 0.97 0.73, 1.31
  - 35–54 1.06 0.93, 1.21
  - 55–64 0.92 0.78, 1.07
  - **65+ 0.79 0.65, 0.97**



## Polyomavirus-associated nephropathy risk

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Recipient age <sup>a</sup>	1.3 (1.2–1.4)	0.004	1.3 (1.2–1.4)	0.001
Donor female gender	1.8 (1.1–2.9)	0.01	1.8 (1.1–2.8)	0.02
Acute rejection episode <sup>b</sup>	0.9 (0.4–1.6)	NS	1.02 (0.54–1.9)	NS
Induction therapy <sup>c</sup>	1.0 (0.65–1.5)	NS	1.47 (0.9–2.42)	NS
Maintenance immunosuppression <sup>d</sup>	0.7 (0.38–1.15)	NS	0.64 (0.37–1.1)	NS

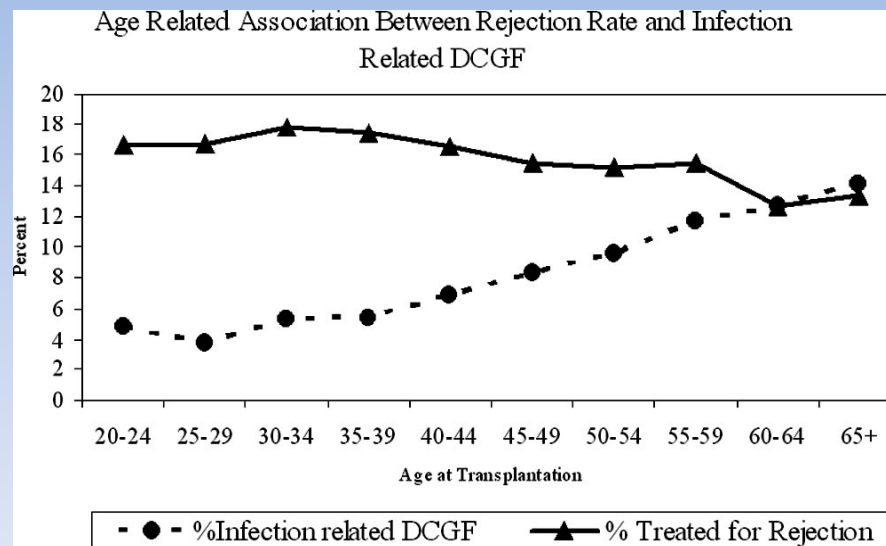
Khamash et al, Kid Int., 2007

## Adjusted Relative Risk for Treatment for BK Virus

- Baseline induction (reference = IL-2 RB)
  - None 0.91 0.75–1.09
  - Thymoglobulin 1.23 1.03–1.45
- Baseline immunosuppression (cyclosporine)
  - Sirolimus 0.70 0.47–1.03
  - Tacrolimus 1.35 1.04–1.74
- Baseline antiproliferative medication (MMF)
  - None 0.82 0.66–1.02
  - AZA 0.95 0.50–1.81

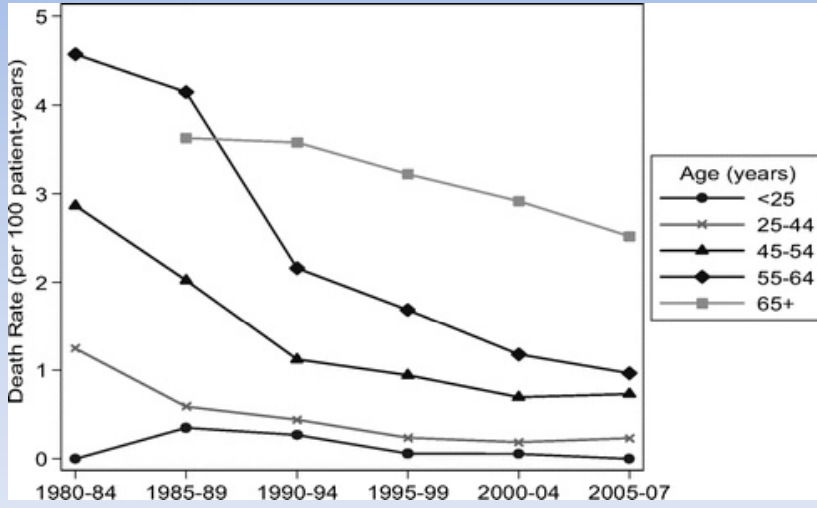
Schold JD et al, *Trans Int*: 22(6), 2009

## Variable Risk for Infectious Graft Failure and Acute Rejection by Age



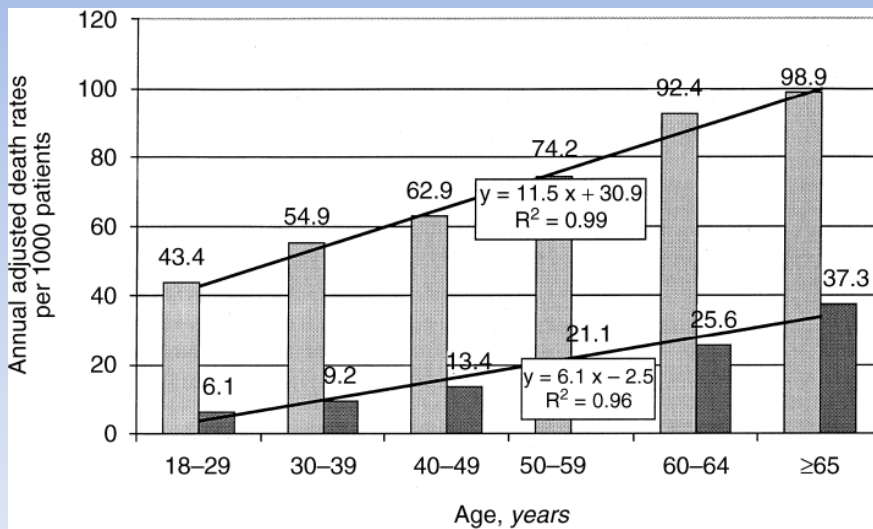
Parasuraman R, *Transplantation* (in press)

## Reduction in Cardiovascular Death after Kidney Transplantation



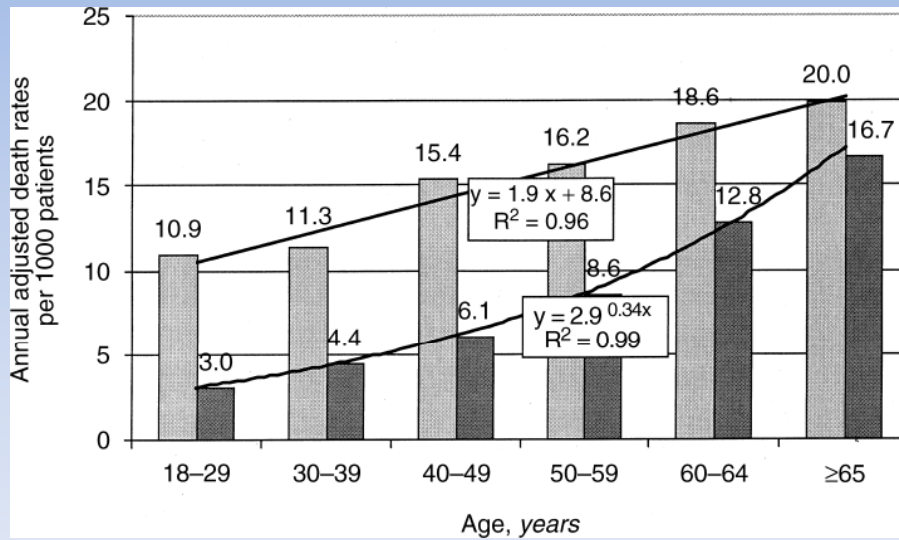
Pilmore H, Transplantation 89(7): p.851-57

## Mortality secondary to CV disease



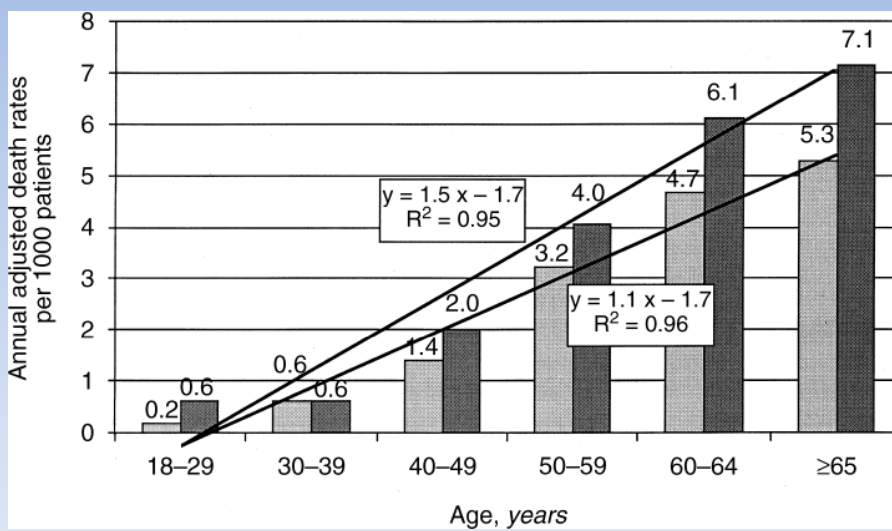
Source: Meier-Kriesche et al, Kidney Int. 2001 Apr;59(4):1539-43

## Infectious Death



Source: Meier-Kriesche et al, *Kidney Int.* 2001 Apr;59(4):1539-43

## Malignant Death



Source: Meier-Kriesche et al, *Kidney Int.* 2001 Apr;59(4):1539-43

## Summary

- Renal transplantation is an accepted and successful treatment modality in elderly patients with end-stage renal disease
- Age of the recipient is strongly associated with allograft loss independent of other known factors.
- Acute rejections are less frequent in older individuals;
- However the consequence of a rejection if it occurs is negative for long-term graft survival. On the other hand,
- Death by infection is vastly increased in older versus younger renal transplant recipients.
- In general, the pharmacokinetics of the immunosuppressive agents are little affected by age, but the tolerance to these agents seems to decrease with increasing age.
- Elderly renal transplant recipients present a very difficult clinical challenge.
- As the elderly become an ever-increasing segment of the renal transplant population, new and innovative immunosuppressive strategies will have to be considered and applied.

- Drugs Aging. 2001;18(10):751-9

## Conclusions

- There is substantial evidence that risks for elderly renal transplant patients differ compared to their younger counterparts
- These differential risks are salient from the time of ESRD and extend to therapeutic interventions following transplantation
- Tailored treatment protocols and decision-making may be critical to maximizing outcomes in this population