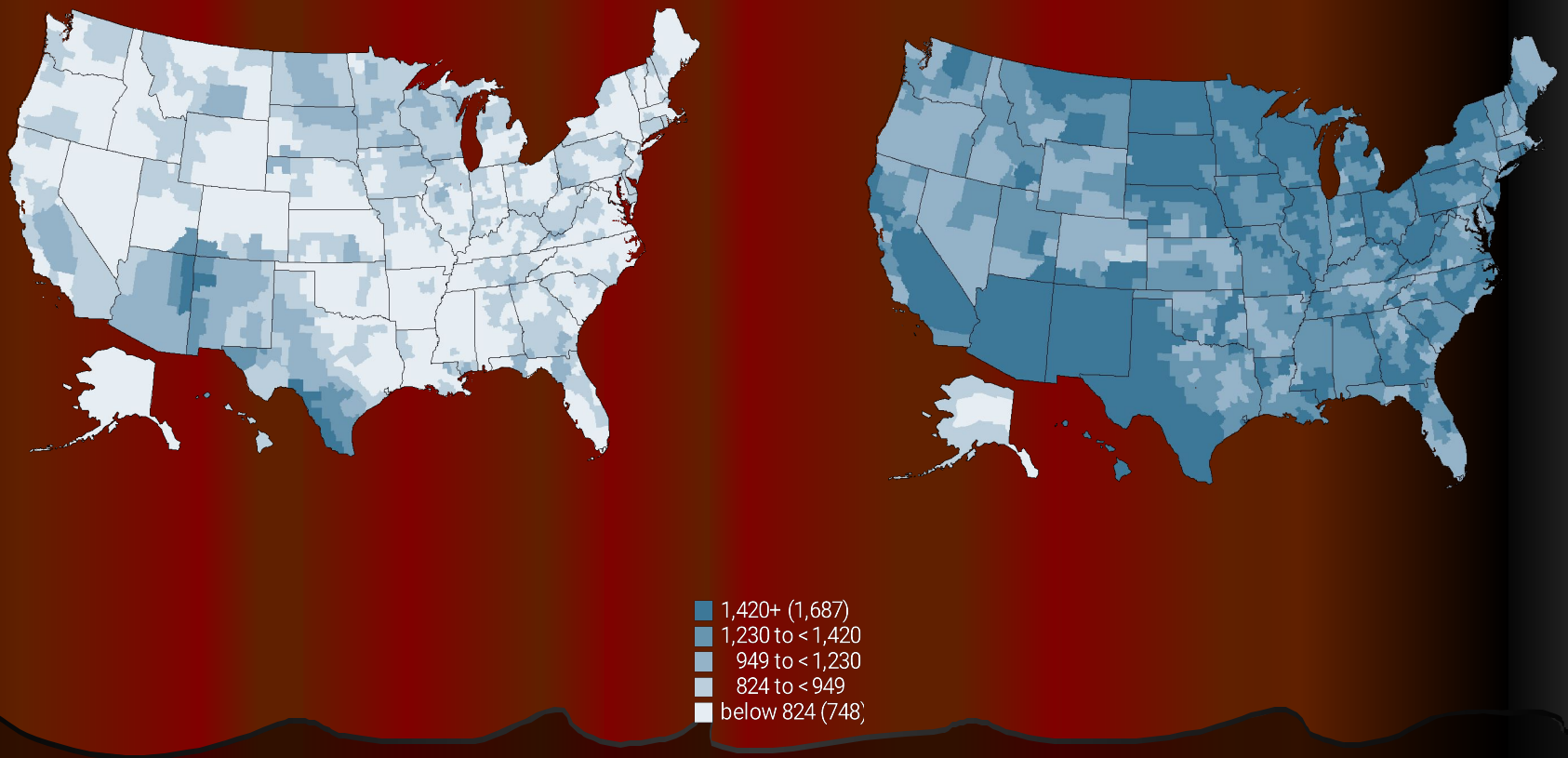
Marginal Donors 2004

Prevalence of ESRD: 1991 versus 2001

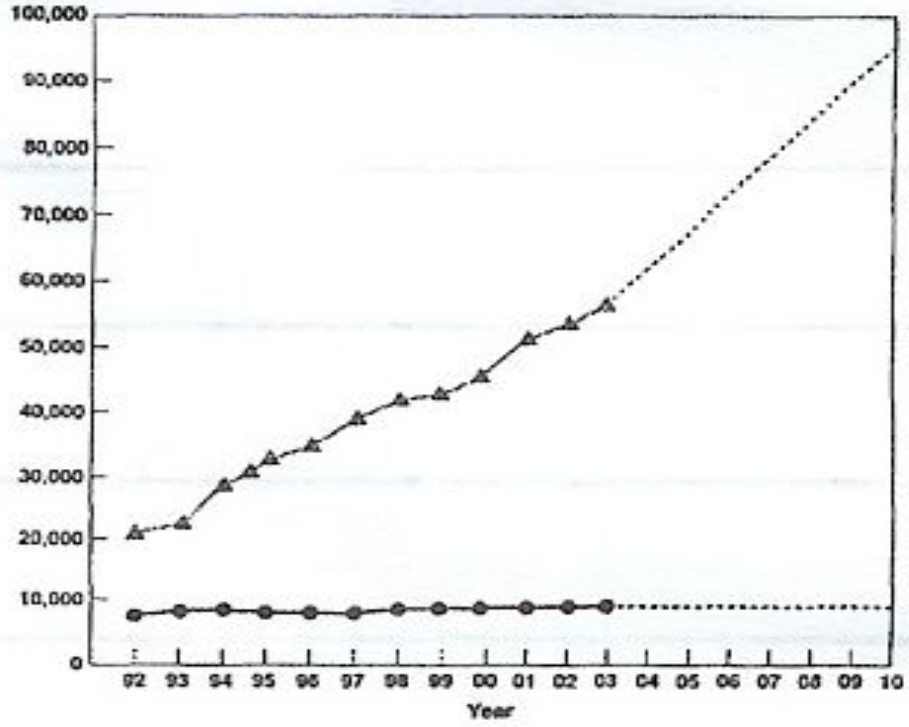
(per million population)



Organ Shortage: Incident & Transplant rates

Welcome to the Waiting List!

Current and projected waitlist for deceased donor kidneys

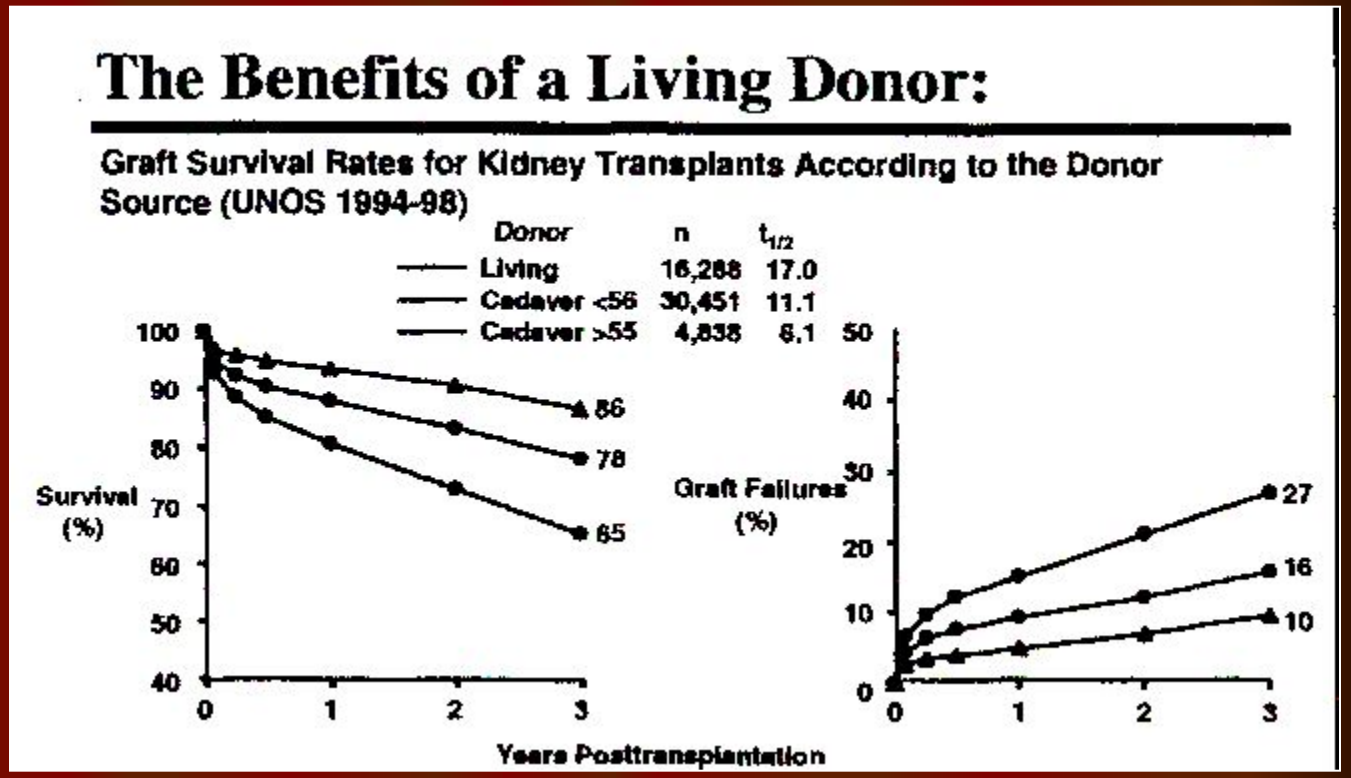


As of May 2003
54,000 awaiting CRT

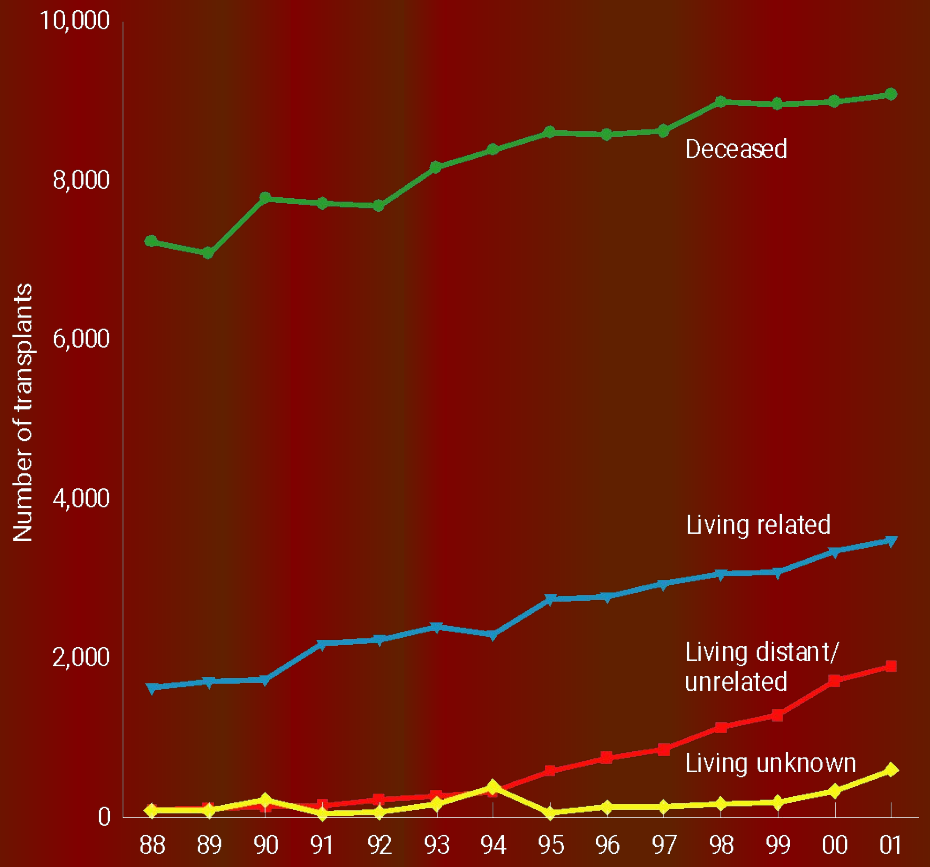
Projected waitlist
95,550 in 2010 (Xue et al. JASN12:2753,2001)

Approx 9,000 CRTs per annum

Expanding the Donor Pool: Optimal Solution



Number of Transplants, by Donor Type



Transplant counts as known to the USRDS (reconciled from various sources).

Expected Survival Times- General Population versus Dialysis

	All races			White			Black		
	All	M	F	All	M	F	All	M	F
0	76.7	73.9	79.4	77.3	74.6	79.9	71.4	67.8	74.7
1	76.3	73.5	78.9	76.8	74.1	79.3	71.5	67.9	74.7
5	72.4	69.6	75	72.9	70.2	75.4	67.6	64.1	70.9
10	67.4	64.7	70.1	67.9	65.3	70.5	62.7	59.2	66
15	62.5	59.8	65.1	63	60.3	65.5	57.8	54.3	61
20	57.7	55	60.2	58.2	55.6	60.7	53.1	49.6	56.2
25	53	50.4	55.4	53.4	50.9	55.8	48.5	45.2	51.4
30	48.2	45.7	50.5	48.6	46.2	50.9	43.9	40.7	46.6
35	43.5	41.1	45.7	43.9	41.5	46.1	39.3	36.3	41.9
40	38.8	36.5	41	39.2	36.9	41.3	34.8	31.9	37.4
45	34.3	32	36.3	34.6	32.4	36.6	30.6	27.8	33
50	29.8	27.7	31.7	30.1	28	32	26.6	24	28.7
55	25.5	23.5	27.3	25.7	23.8	27.5	22.8	20.4	24.7
60	21.5	19.6	23.1	21.6	19.8	23.2	19.3	17.2	20.9
65	17.7	16.1	19.1	17.8	16.1	19.2	16	14.3	17.3
70	14.3	12.8	15.4	14.4	12.9	15.5	13	11.6	14
75	11.2	10	12.1	11.2	10	12.1	10.4	9.2	11.1
80	8.5	7.5	9.1	8.5	7.5	9.1	8.2	7.3	8.6
85	6.3	5.5	6.6	6.2	5.5	6.6	6.2	5.6	6.5
90	4.6	4.1	4.8	4.5	4	4.7	4.8	4.4	4.8
95	3.4	3	3.5	3.2	2.9	3.3	3.6	3.5	3.6
100	2.6	2.4	2.7	2.3	2.2	2.4	2.8	2.8	2.7

Dialysis

	White		Black		N Am		Asian	
	Male	Female	Male	Female	Male	Female	Male	Female
0-14	19.8	18.5	20.1	18.1	22.5	23.0	30.6	29.5
15-19	17.0	15.8	18.4	16.5	18.9	18.7	24.5	24.0
20-24	14.5	13.5	16.2	14.3	15.9	16.0	21.5	21.1
25-29	12.3	11.3	14.2	12.6	13.7	13.6	18.6	18.5
30-34	10.1	9.6	12.3	11.0	11.7	11.7	15.7	15.9
35-39	8.6	8.2	10.7	9.7	9.8	10.0	13.1	13.5
40-44	7.4	7.2	9.3	8.4	8.3	8.6	11.0	11.5
45-49	6.3	6.0	7.7	7.3	7.0	7.3	9.0	9.5
50-54	5.3	5.1	6.7	6.3	6.0	6.5	7.6	8.0
55-59	4.6	4.5	5.6	5.5	5.3	5.4	6.4	6.7
60-64	3.9	3.8	4.7	4.8	4.4	4.7	5.3	5.7
65-69	3.2	3.2	4.0	4.0	3.7	4.0	4.5	4.9
70-74	2.8	2.8	3.4	3.3	3.2	3.4	3.7	4.1
75-79	2.4	2.4	2.8	2.8	2.5	2.8	3.1	3.3
80-84	2.0	2.0	2.3	2.3	2.1	2.3	2.6	2.8
85+	1.7	1.7	1.9	1.9	1.7	1.8	2.0	2.2

Expected Survival Times: Dialysis versus Transplantation

Dialysis

	White		Black		N Am		Asian	
	Male	Female	Male	Female	Male	Female	Male	Female
0-14	19.8	18.5	20.1	18.1	22.5	23.0	30.6	29.5
15-19	17.0	15.8	18.4	16.5	18.9	18.7	24.5	24.0
20-24	14.5	13.5	16.2	14.3	15.9	16.0	21.5	21.1
25-29	12.3	11.3	14.2	12.6	13.7	13.6	18.6	18.5
30-34	10.1	9.6	12.3	11.0	11.7	11.7	15.7	15.9
35-39	8.6	8.2	10.7	9.7	9.8	10.0	13.1	13.5
40-44	7.4	7.2	9.3	8.4	8.3	8.6	11.0	11.5
45-49	6.3	6.0	7.7	7.3	7.0	7.3	9.0	9.5
50-54	5.3	5.1	6.7	6.3	6.0	6.5	7.6	8.0
55-59	4.6	4.5	5.6	5.5	5.3	5.4	6.4	6.7
60-64	3.9	3.8	4.7	4.8	4.4	4.7	5.3	5.7
65-69	3.2	3.2	4.0	4.0	3.7	4.0	4.5	4.9
70-74	2.8	2.8	3.4	3.3	3.2	3.4	3.7	4.1
75-79	2.4	2.4	2.8	2.8	2.5	2.8	3.1	3.3
80-84	2.0	2.0	2.3	2.3	2.1	2.3	2.6	2.8
85+	1.7	1.7	1.9	1.9	1.7	1.8	2.0	2.2

Transplant

	White		Black		N Am		Asian	
	Male	Female	Male	Female	Male	Female	Male	Female
0-14	50.4	51.3	45.9	45.4	49.4	46.1	56.6	57.0
15-19	39.2	40.3	36.6	36.4	39.2	36.7	46.4	46.3
20-24	35.3	36.5	33.1	33.1	35.4	33.2	41.4	42.5
25-29	31.5	32.9	29.7	29.9	31.9	30.0	37.6	38.8
30-34	27.5	29.0	26.0	26.5	28.0	26.3	33.5	34.8
35-39	24.1	25.7	22.7	23.4	24.5	23.1	29.7	31.3
40-44	20.9	22.8	19.7	20.6	21.4	20.3	26.0	27.8
45-49	17.9	19.9	16.8	17.8	18.4	17.5	22.6	24.4
50-54	15.3	17.4	14.1	15.1	15.7	14.7	19.3	21.1
55-59	12.8	15.0	11.7	12.9	13.5	12.8	16.4	18.3
60-64	10.6	12.8	9.7	11.1	11.5	10.9	13.9	15.7
65-69	8.8	10.9	8.1	9.6	9.9	9.8	11.8	13.7
70-74	7.1	9.1	6.6	8.1	8.2	8.4	10.0	12.0
75-79	6.1	7.7	5.6	7.3	7.1	8.5	8.9	10.5

Organ Shortage: Why Bother?

- **Hemodialysis**:

-less clearance

-oscillating levels of toxins, potassium, water, osmoles

-frequent hemodynamic compromise-hypervolemia and delayed vascular refill

- **Transplantation:**

-clearances up to 60 ml/min

-continuous clearance

-frequent hypertension but less hemodynamic compromise

-lower cardiovascular risk even despite drug effects

Risk Factors for Transplant Graft Survival

Prior dialysis time (years)

- None (pre-emptive)

0.75 (0.70-0.81) <.0001 Graft Survival Risk
0.78 (0.72-0.85) <.0001 Death Censored
0.68 (0.61-0.76) <.0001 Death

- 1-<2

1.09 (1.04-1.14) 0.0002 Graft Survival
1.01 (0.96-1.07) Death Censored
0.66 1.22 (1.14-1.30) <.0001 Death

- 2-<3

1.11 (1.06-1.17) <.0001 Graft Survival
0.99 (0.93-1.06) Death Censored
0.88 1.32 (1.23-1.42) <.0001 Death

- 3+

1.16 (1.10-1.22) <.0001 Graft Survival
0.97 (0.92-1.04) 0.42 Death Censored
1.49 (1.39-1.59) <.0001 Death

USRDS Annual Report 2002

We Pride Ourselves on Service!

- Hemodialysis:

"It is so good patients limp away from it"
(Lu-ya Zhong, **Tang Dynasty** Chinese Scholar)

<u>Expected remaining lifetimes in a 60-64 year old man in years:</u>

Dialysis 3.8
Transplant 10.5
General population 21.6

USRDS 2002 Annual Report

Conclusion from the Introductory Slides

- Get people out of dialysis as soon as possible
- Transplant may not be ideal solution but it is way better than dialysis as it is currently done
- Expand the donor pool by any means that are safe and ethical
- If living donors are not available try to expand the cadaveric donor pool

Ways to Expand the Donor Pool

- Use of “Expanded criteria organs”
- Use of organs from non-heart beating donors
- Cold ischemia time>36h
- Use of organs across positive cross-match or incompatible blood type

“Expanded criteria donors”-an euphemism for marginal or suboptimal donors

Marginal Organs-Definition

1. **UNOS definition**:

   Using organs associated with a 70% additional risk for graft failure due to one of the following donor factors:

   -age>60

   -age 50-60 plus 2 of the following:

   -creatinine>1.5mg/dl; CVA as cause of death; history of hypertension

Marginal Organs: Definition 2

European Best Practice Guidelines:

Creatinine clearance of 50-60 ml/min/kidney or long-standing hypertension, diabetes or vascular disease, proteinuria or vascular changes or glomerular sclerosis (>15%) on donor biopsy

Two Bad Almost Equals One OK

- Combined creatinine clearance<100 ml/min and glomerular sclerosis>20% or advanced vascular changes in donors aged>60-consider dual kidney transplantation

Karpinski et al, Transplantation 1999;67: 1162-67

Fast Facts

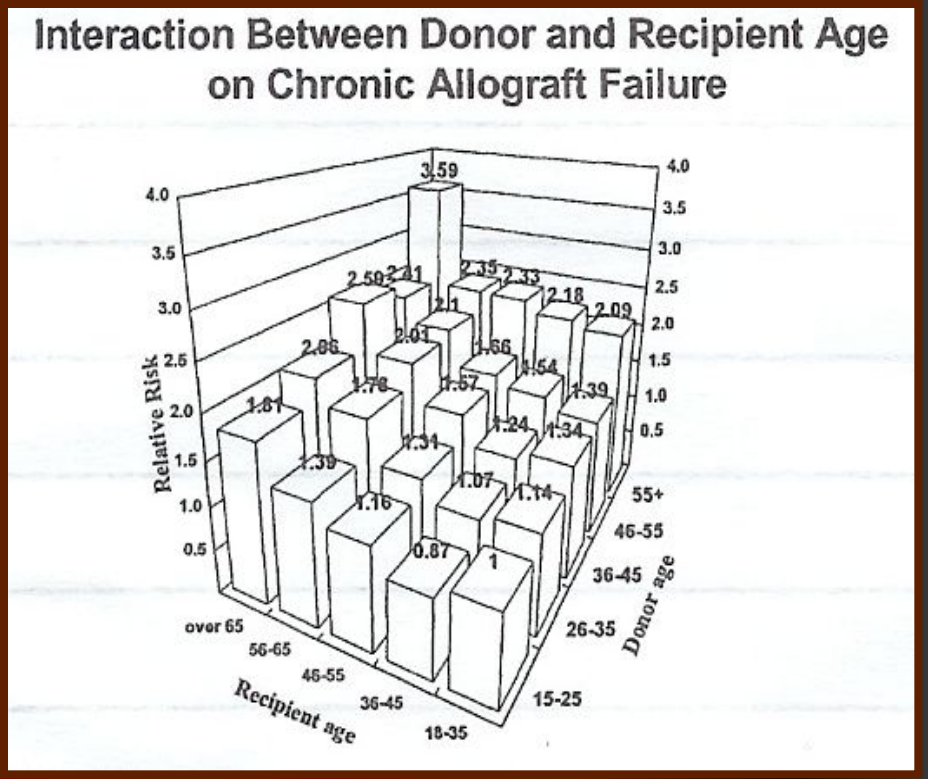
- About 50% of marginal grafts are *discarded*
- There is a remarkable variability among different transplant programs in the acceptance of marginal organs
- About 15-20% of all cadaveric organs donated in the last 10 years *are* marginal organs

Increasing Donor Age and its Price

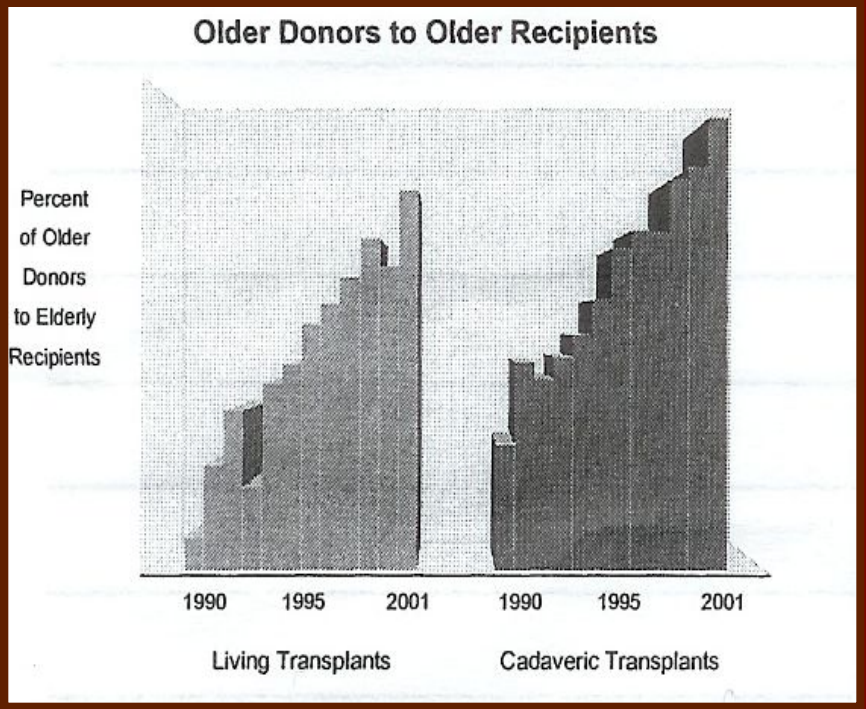
Cadaveric Donors – They're Getting Older

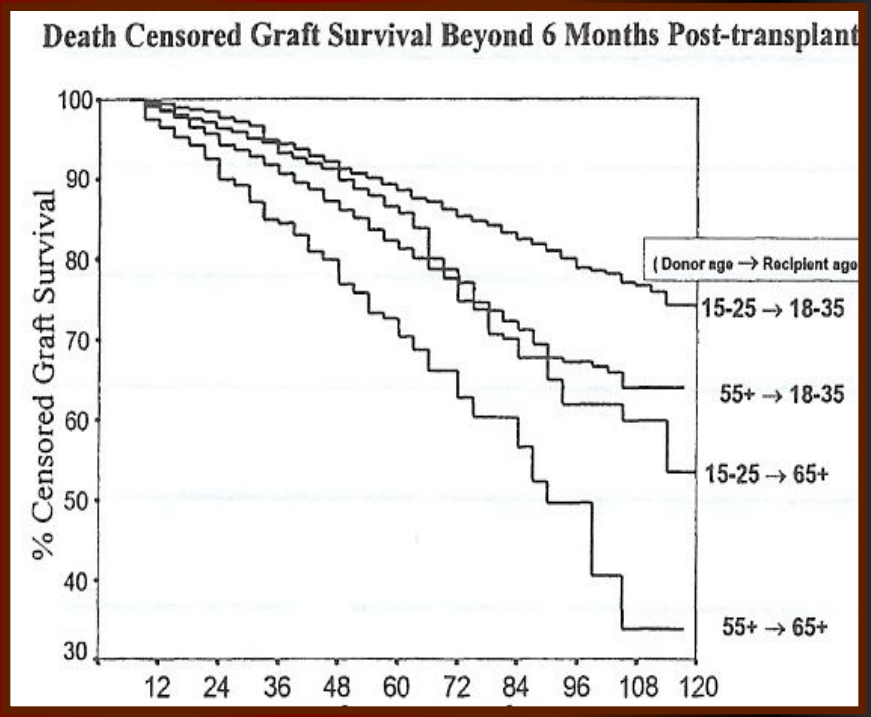
	<50	50-60	>60	Total
1991	80%	13%	7%	55
1992	87%	13%	0%	54
1993	73%	27%	0%	60
1994	83%	14%	3%	59
1995	68%	24%	8%	76
1996	65%	22%	13%	76
1997	69%	14%	17%	83
1998	68%	15%	17%	78
1999	62%	21%	17%	89
2000	63%	15%	22%	101
2001	70%	16%	14%	103
2002	62%	15%	23%	103

Interaction Between Donor and Recipient Age on Chronic Allograft Failure



Both Donors and Recipients are Getting Older





Marginal Donors-Outcome

- Concept: marginal donors may decrease overall waiting time
- Most patients waiting (>90%) are *on dialysis*
- Survival benefit from marginal donors is expected if they decrease waiting time
- Survival benefit is expected to be less than in case of ideal donors
- Marginal donor may be a bad idea if it is found that on average between refusal of marginal donor and acceptance of ideal donor time is short versus if survival advantage is very different

Survival Study

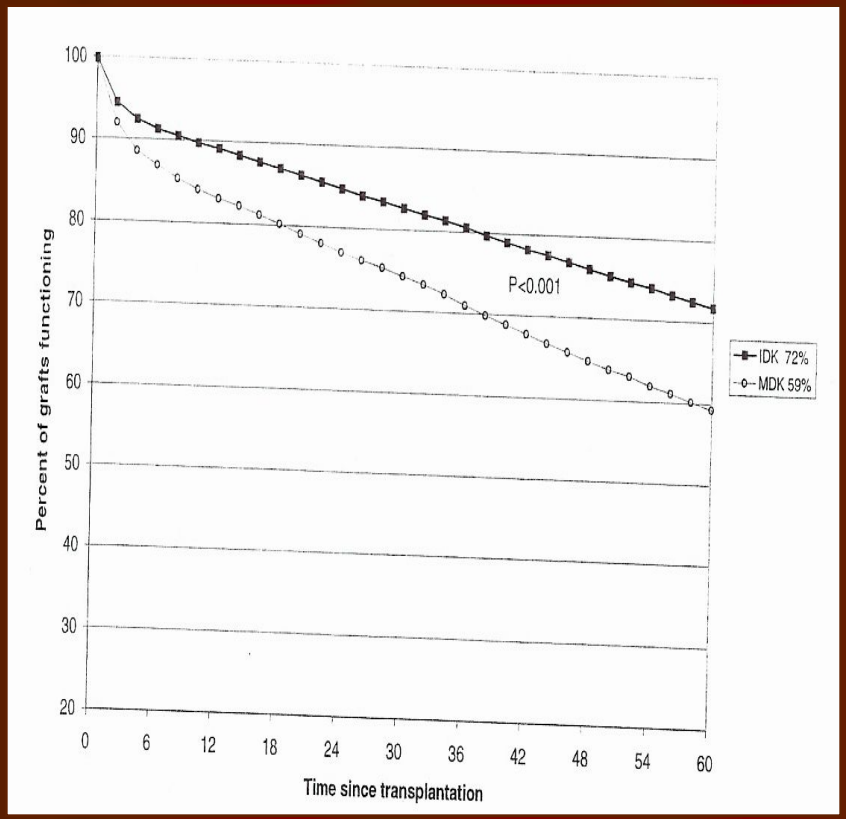
- Ojo et al JASN 2001- compare mortality risk of 3 cohorts: remaining on waiting list (WLD),

  receiving marginal kidney (MDK), receiving ideal kidney (IDK)
- All ESRD patient on UNOS waiting list between 1992-1997 considered
- Follow-up until 6/30/1998

Methods

- Survival analysis: intention-to-treat non-proportional Cox regression analysis
- Adjustment made for age, race, cause of ESRD and time on waiting list
- Marginal donors included non-heart beating donors and CIT>36h dual transplant not distinguished
- Only single organ (kidney) cadaveric transplants

The No-Surprise Slide



- MDK patients were on average older, more of them European origin, less diabetics
- Overall graft survival was shorter; other risk factors for graft failure: D/R race, age, cause of death/cause of ESRD, time on

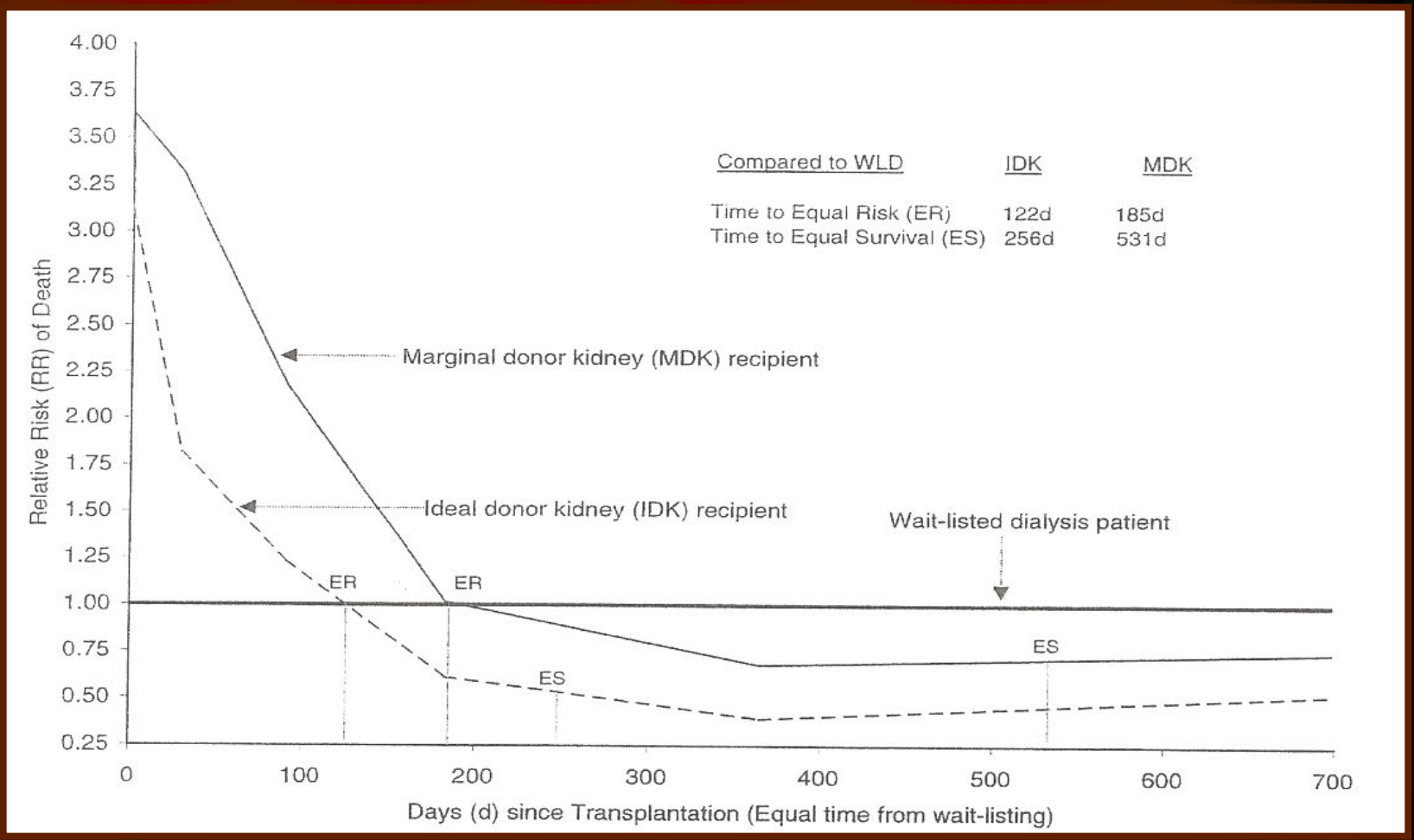
Death Rates

- WLD: 6.3% annual death rate (selected population!)
- MDK: 4.7% annual death rate ($p<0.001$)
- IDK 3.3% annual death rate ($p<0.001$)
- 5 year survival MDK versus IDK: 77% ;85%
- Survival advantage of IDK maintained at any time after transplantation

Another Concept: Time to Equal Survival

- Excess mortality immediately after transplantation is expected to dissipate
- Following this point transplant mortality risk is lower than on dialysis: this is strongly age dependent
- In this study: for MDK it was 185, 122 for IDK (all in days)

Time to Equal Mortality Risk



Life Expectancy

- WLD:MDK:IDK- 15.3: 20.4: 28.7 in years
- Young patients had longer survival benefits in years but equal proportional risk benefit
- Subgroup differences: diabetics and Europeans higher risk of death on dialysis
- Patients with lower mortality risk on dialysis benefited less from MKD

Who benefits most?

Patient Group	Annual Death Rate Among WLD (%)	Days to Equal Risk	Days to Equal Survival	RR[a] (*P* Value)	Projected Extra Lifetime (yr)
All	6.3	185	531	0.75	5.1
Age (yr)					
18–29	2.2	163	547	0.85	6.4
30–44	5.4	134	309	0.78	4.9
44–54	6.5	196	521	0.70	6.3
55–64	6.5	193	580	0.66	7.3
≥65	10.0	171	475	0.71	3.8
Race					
white	7.5	184	481	0.68	5.9
black	4.8	172	691	0.86	3.1
other	6.3	211	513	0.59	9.9
Gender					
male	6.3	185	526	0.74	5.1
female	6.3	184	528	0.73	5.4
Cause of ESRD					
glomerulonephritis	4.3	192	501	0.82	4.6
hypertension	4.3	169	>700	0.71	8.5
diabetes mellitus	10.8	164	352	0.62	5.6
other diagnoses	4.3	194	663	0.75	6.7

Conclusions so far…

- Marginal kidneys are on the rise-closing 20% now
- Marginal kidneys decrease death risk versus *dialysis*
- Survival benefit may be very different in different subgroups
- Marginal kidney- this is reality ant it is happening

Courage in Science-a Contradiction in Terms

- **Their question: If marginal kidney donation is a reality then who is the real beneficiary?**
- **My question: Are these authors still alive? (1984+20=2004)**

Another No-Surprise Slide

- “The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US Government”
- Study (Transplantation 2003 volume 75 pp 1940-45) from the *Washington University of Medicine, St Louis, Mo* and……*Semmelweiss University, Budapest, Hungary*

Methods and Concepts

- Patient data obtained from UNOS registry
- Comprehensive quality-adjusted life years model developed for individual patients who has been offered marginal donors while on waiting list
- Outcome of model to answer question: should the individual patient accept a marginal donor?

Results

- In this patient population patients receiving marginal kidneys had a longer waiting time than recipient of an ideal donor
- For equal outcome a waiting time duration difference of 3.2 years would have been necessary
- Older patients may only need a difference of 11 months
- In contrast, savings for Medicare was substantial with marginal donors irrespective of quality of life

Scientific Authors with Actual Insight?????????????

- “ …our analysis highlights the disquieting fact that what is best for the individual is not always best for society”
- Marginal donors may be more beneficial for elderly recipients with long expected waiting times other than due to high PRAs
- Small waiting list, individualized decisions, informed consent……

What about a Nice Diabetic Kidney?

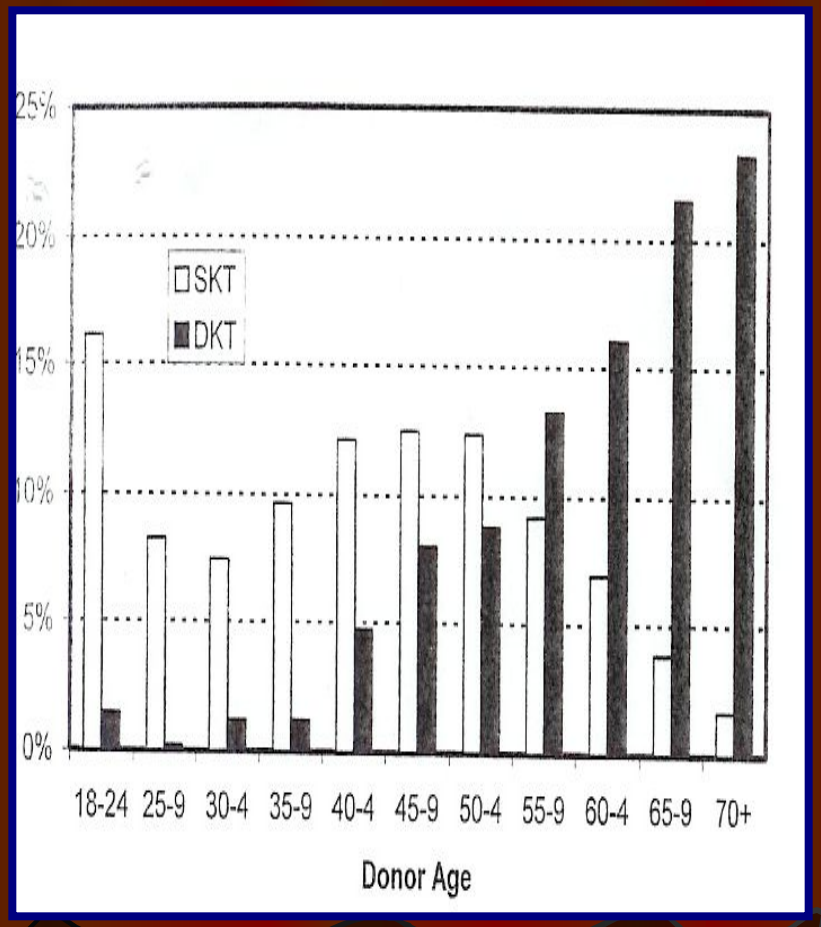
Category	Risk ratio (95% CI)	*P* value
D0/R1	1.44 (1.24, 1.67)	0.0001
D0/R2	1.67 (1.24, 2.24)	0.0007
D1/R0	1.58 (0.59, 4.22)	NS
D1/R1	0.7 (0.56, 1.53)	NS
D2/R0	0.29 (0.41, 2.06)	NS
D2/R1+R2*	0.8 (0.11, 5.70)	NS

- Study: diabetic recipient (both type I and II) status was a risk factor for graft failure, donor status was not
- Note: D1R1 or D2R1 +2 were very rare
- Long term patient and graft survival close to equivalent (donor DM versus no donor DM)

Back to Two Bad Equals One OK-or does it?

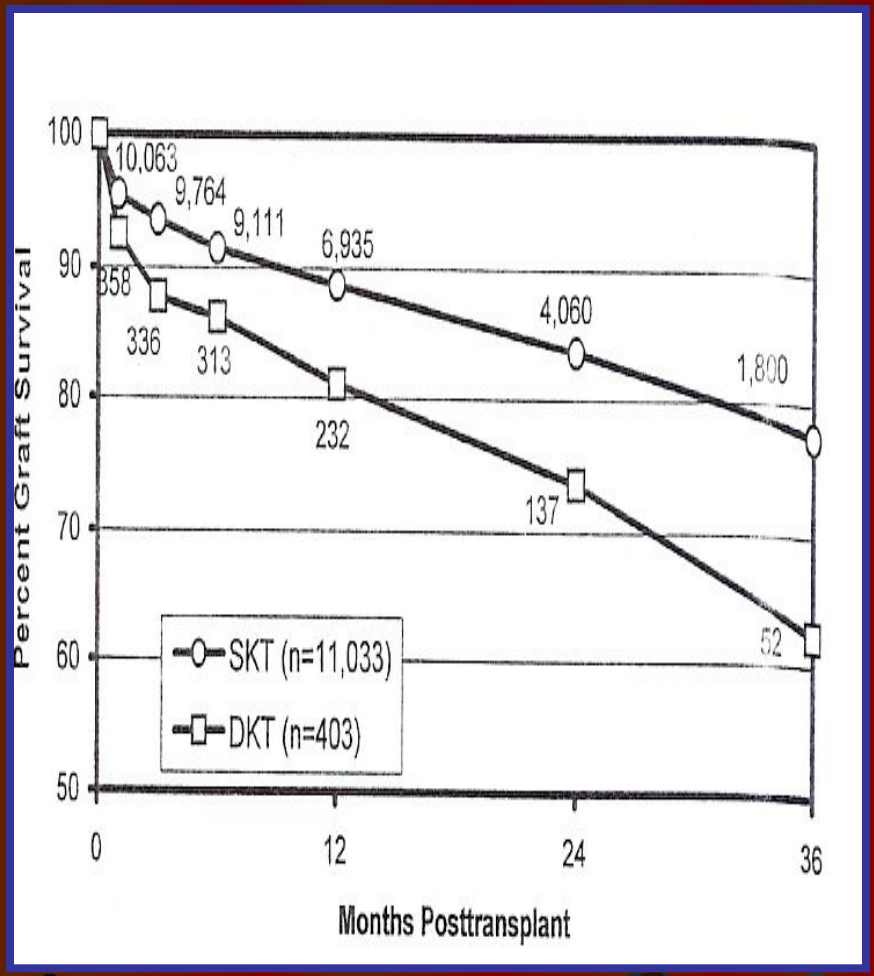
- UNOS database registry 1997-2000
- 11,033 single versus 403 dual kidney transplants
- 70 transplant centers with wide variablility of number of dual kidney transplants
- Graft and Kidney survival evaluated

Dual Kidney versus Single Kidney Donation



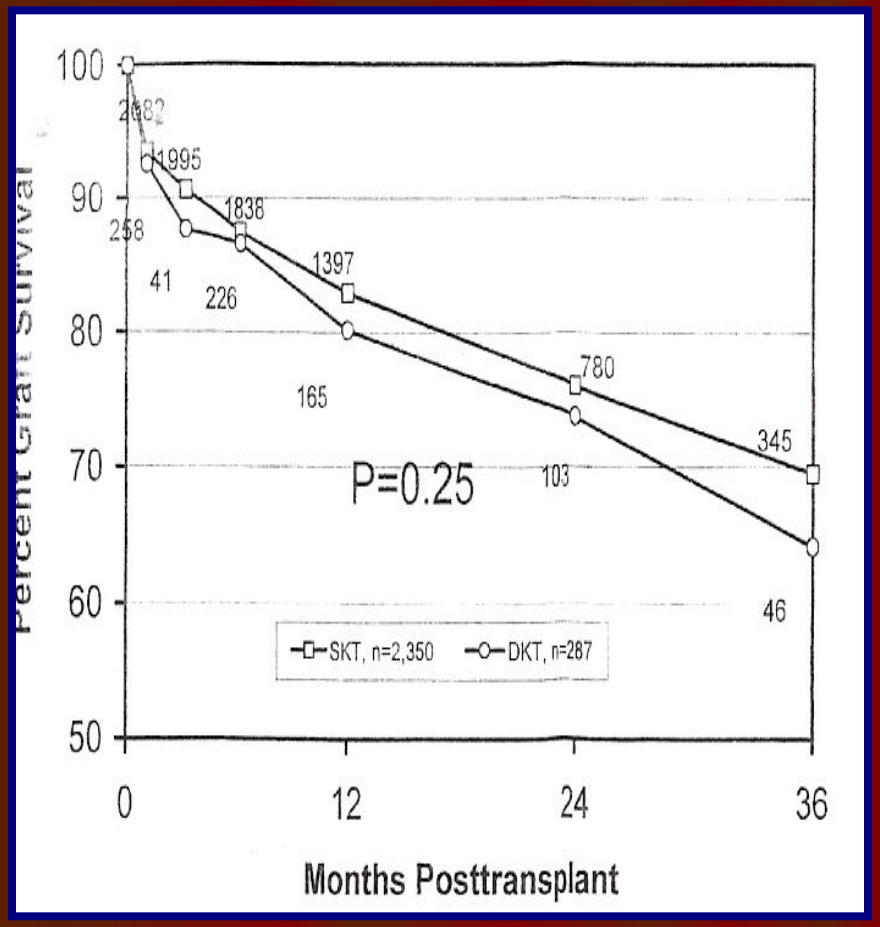
- DKT recipients were older, less sensitized, more African Americans
- DKT donors were older, more diabetes and hypertension, more African Americans,
- DKT more mismatch and longer cold ischemia times

Graft Survival



- DKT: poorer survival, more primary non-function
- No difference in delayed graft function, early rejections, graft thrombosis
- Main risk factors of graft loss: African American ethnicity, recipient age, diabetic donor and re-transplant

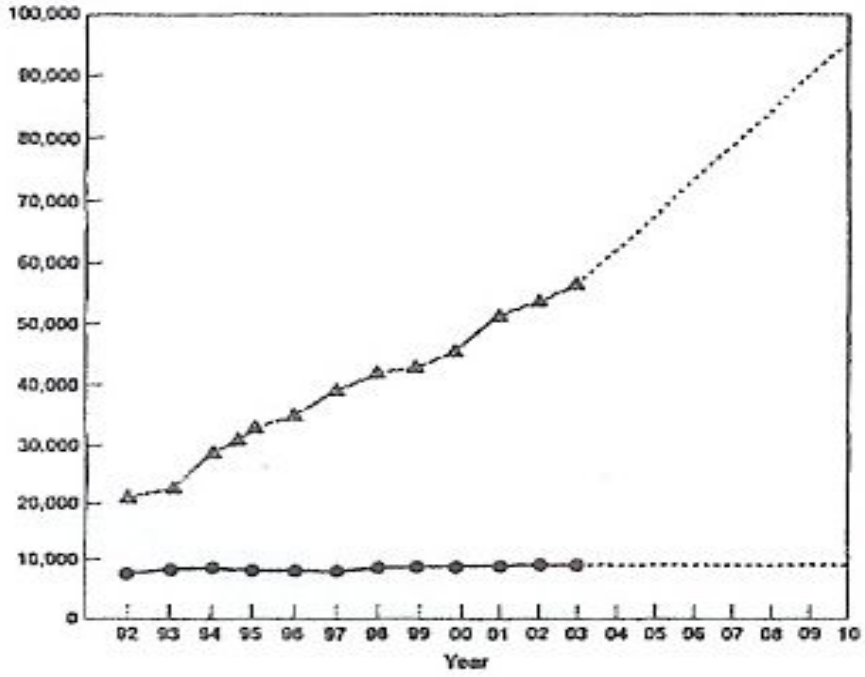
Donors over 55



- DKT versus SKT: when subgroup of donor age>55 considered the survival difference almost disappears (difference non-significant) despite overall poorer quality, match, cold ischemia time of

So now what….

Current and projected waitlist for deceased donor kidneys



As of May 2003
54,000 awaiting CRT

Projected waitlist
95,550 in 2010 (Xue et al. JASN12:2753,2001)

Approx 9,000 CRTs per annum

Change Allocation Guidelines

Additional waiting list for marginal kidneys for:

1. Those who consent
2. Those doing poor on dialysis
3. Those with poor life expectancy (life expectancy<waiting time) such as older, diabetic recipients, access failure etc

To Better Characterize and Quantitate Individual Risk Factors….

- Scoring system for marginal donors-measure importance of individual risk factors
- Characterize each donor with a score system based on presence of risk factors
- Use this in predicting outcome and donor allocation

Predicting Graft Function at 6 months

Donor variable	p-value by univariate analysis	p-value by multivariate analysis	Delta R^2 [1]
Age	<0.001	<0.001	0.0950
Creatinine clearance	<0.001	<0.001	0.0044
History of hypertension	<0.001	<0.001	0.0027
HLA mismatch	<0.001	<0.001	0.0019
Cause of death	<0.001	<0.001	0.0013
Duration of cold ischemia	<0.001	<0.001	0.0009
Ethnicity	<0.001	<0.001	0.0003
CMV antibody status	<0.001	0.019	0.0002
History of diabetes mellitus	<0.001	0.022	0.0001

CMV = cytomegalovirus.
[1]Improvement in R^2 by adding donor variable to linear regression model.

- Marginal kidney donor status as an almost continuous spectrum based on multiple risk factors for graft loss

Marginal Donors- the Scoring System

Variable	Score
Age, y	
< 30	0
30–39	5
40–49	10
50–59	15
60–69	20
≥ 70	25
History of hypertension	
None	0
Yes; duration unknown	2
≤ 5 y	2
6–10 y	3
> 10 y	4
Creatinine clearance, mL/min[1]	
≥ 100	0
75–99	2
50–74	3
< 50	4
HLA mismatch, no. of antigens	
0	0
1–2	1
3–4	2
5–6	3
Cause of death	
Non-CVA	0
CVA	3
Total points, range	0–39

CVA = cerebrovascular accident, including ischemic and hemorrhagic types.
[1]To convert values to mL/s, multiply by 0.01667.

- Scoring system applied to 34324 UNOS registry patients receiving cadaveric kidney between 1994 and 1999
- Below 20 points little survival difference-above 20 major survival difference for graft survival at 6 months

Conclusions

- This is a highly controversial and relatively little researched, yet very important area.
- Marginal kidney transplantation is reality. It is happening.
- Marginal kidney transplantation appears to improve survival with respect to dialysis but is inferior to ideal kidney transplantation.
- Patients with little life expectancy may benefit most, provided they are offered a marginal kidney as an additional option.

Conclusions 2

- At present, there is no universally accepted allocation policy among individual transplant centers.
- Any new allocation policy must take into account individual characteristics of the given patient at a given time.
- Alternative means of expanding the donor pool must be sought.