Optimal Utilization of Kidneys from Extended Criteria Donors

Optimal = Best use

If u or a family member had ESRD and and decided on a transplant,

Would your *first* recommendation be:

a) Living donor transplant

b) Standard criteria deceased donor transplant

c) Expanded criteria deceased donor transplant

If you or a family member had ESRD, and there were no living donors

What would you recommend:

a) SCD

b) ECD

If that is your choice for a family member, it should be your choice for your patients

To me, the optimal use of ECD kidneys is to NOT use them

We should be doing everything possible to increase donation (both SCD and Living), so that we will never have to use suboptimal kidneys

Today's reality – An organ shortage

What is our Goal?

a) To maximize the # of people transplanted (and improve survival vs dialysis)?

- use of ECD kidneys increases the number of people transplanted, improves average patient survival and shortens waiting time

Historically ECDs were not used

In 1980, average wait time for a DD transplant was about 1 year; currently it is about 5 years in many areas and approaching 10 years in some.

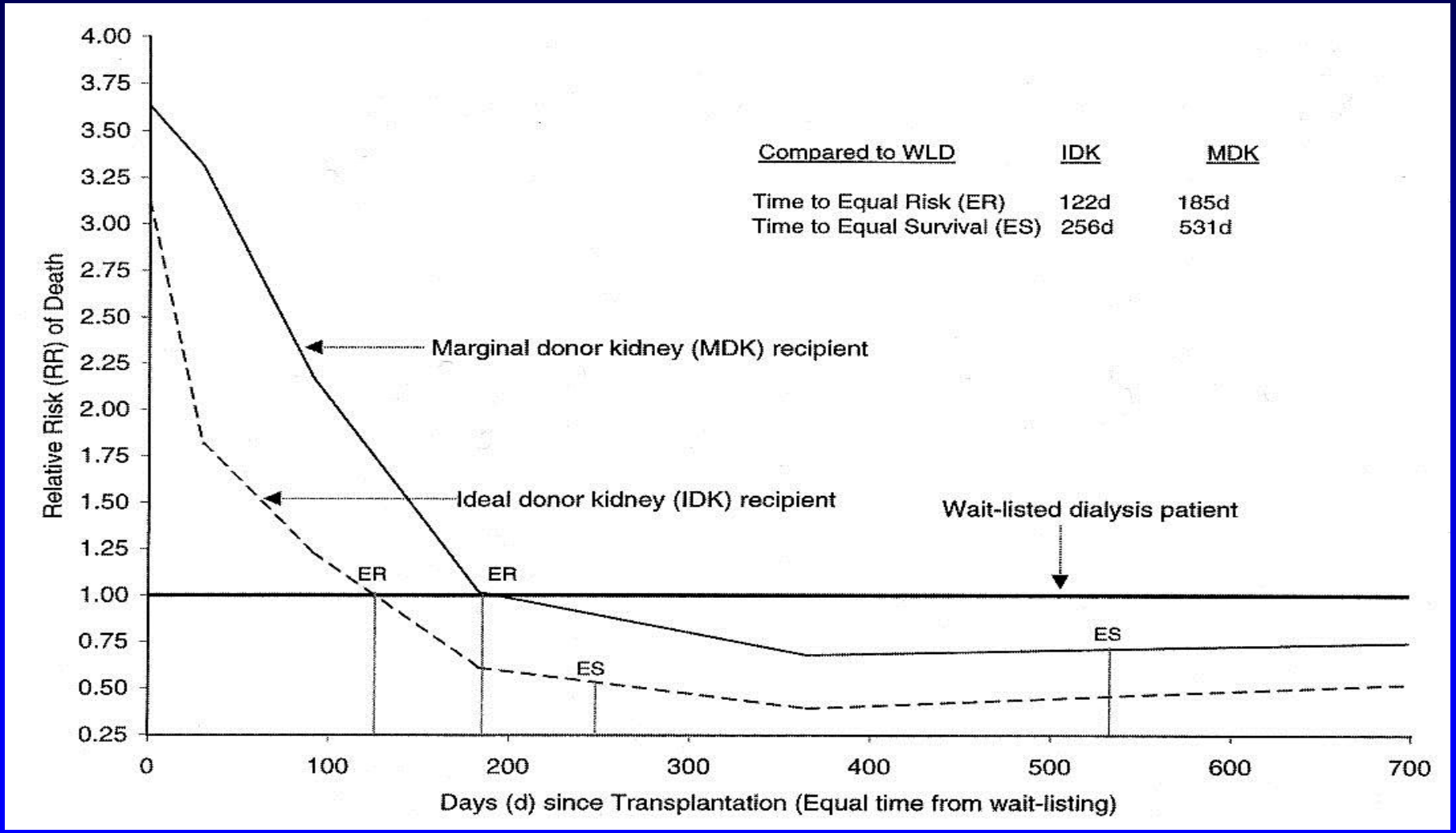
Many candidates – older or those with diabetes - will not survive 5-10 years on dialysis.

Schold J et al, Half of kidney transplant candidates who are older than 60 years now placed on the waiting list will die before receiving a deceased-donor transplant,

Clin J Am Soc Nephrol. 4: 1239-45, 2009.

- Using ECDs shortens waiting time and allows some of these candidates to be transplanted.

Patient survival (vs waitlist) (R.R. death)



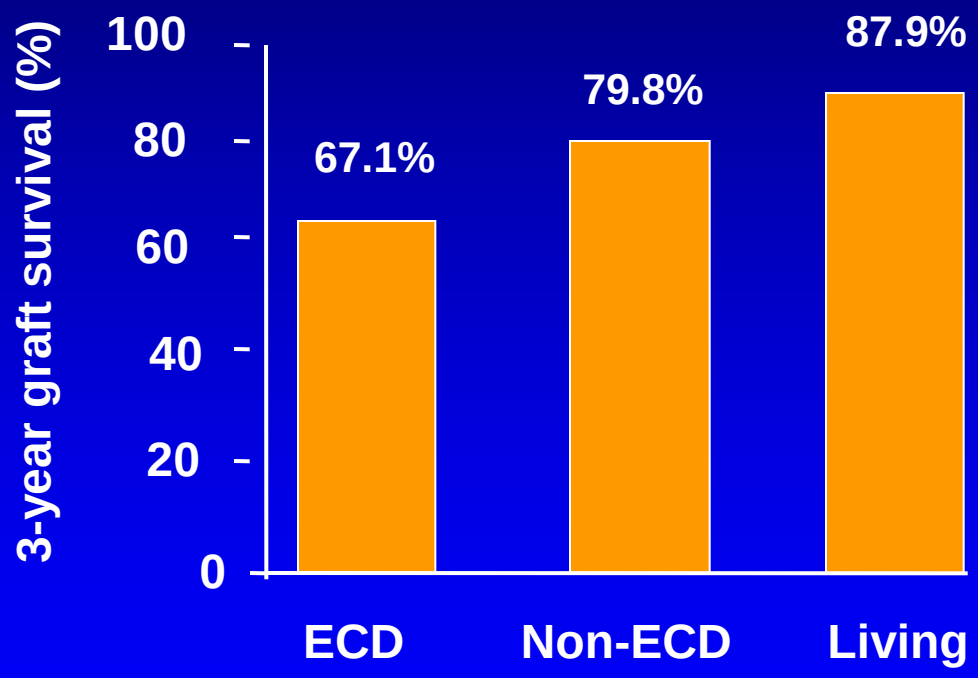
Ojo et al, JASN, 2001

What is our Goal?

OR, b) To optimize outcome for every patient?

- for any 1 patient, it is better to get a LD transplant or an SCD kidney than an ECD kidney

3-year Graft Survival by Donor Type



ECD indicates expanded criteria donor

OPTN/SRTR 2005 Annual Report. Available at: www.ustransplant.org.

Complicated by the fact that graft failure is a bad thing the recipient

The argument in favor of use of ECDs is that they prolong survival vs dialysis

However, for some:

1) The kidney will fail first;

2) For those patients it is not as if a graft survives 3 years doing well and then stops working

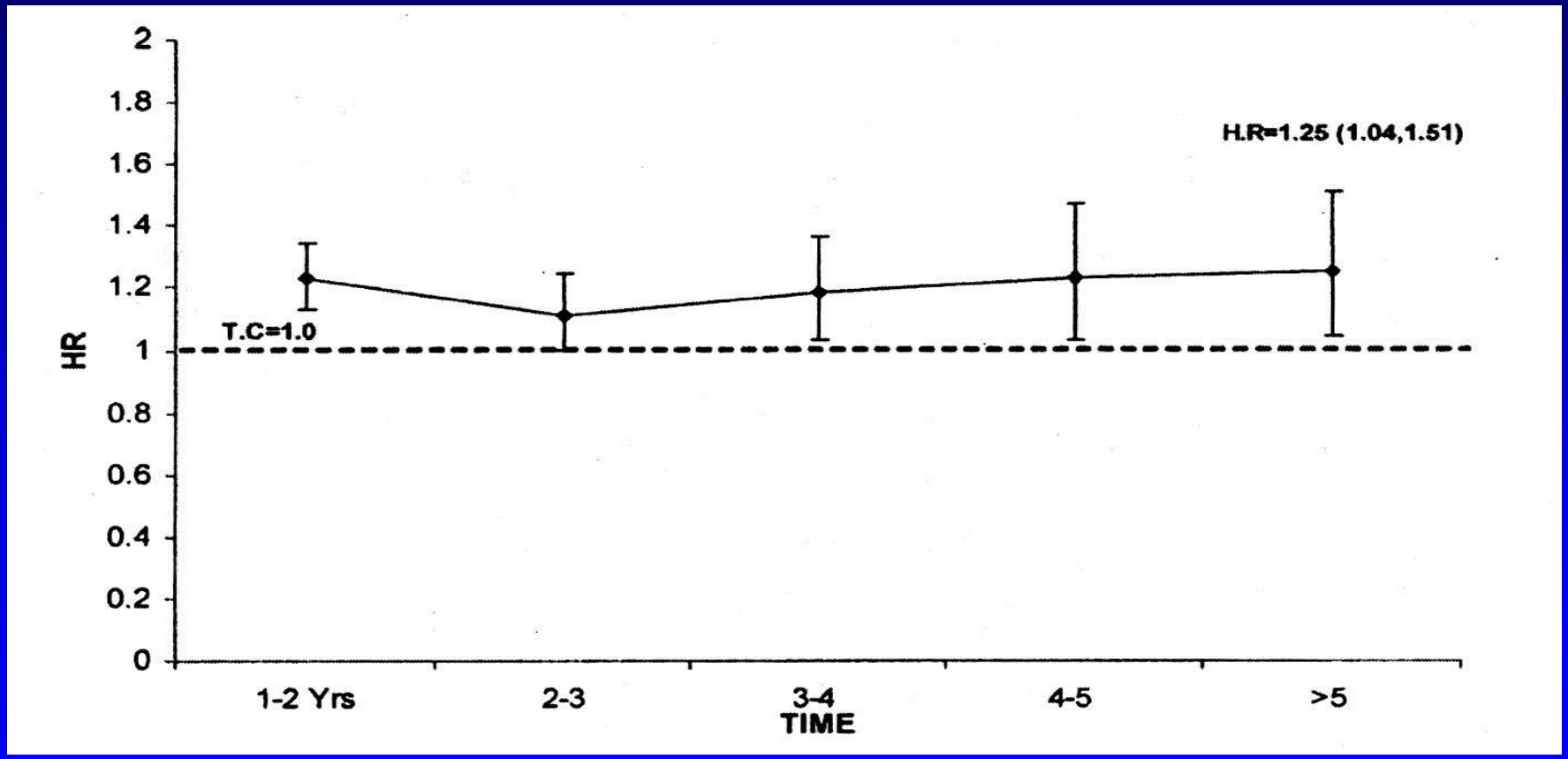
Importantly, annual adjusted death rates are 3x higher for those with graft loss vs those with a functioning kidney

Kaplan et al, AJT, 2002

Single center analysis; Risk factors for graft failure and death in elderly patients: for patients >50, graft failure was a risk factor. Faravardeh et al, Transplantation, 2013

Rao et al – Survival on dialysis after graft failure

Risk of death (after failure) vs. wait-listed for 1st tx



AJKD 49: 294, 2007

What is an Expanded Criteria Donor – ECD?

UNOS definition - relative risk of graft failure (vs SCD) >1.7

Deceased donors:

> 60 and

> 50 with at least ***two*** other criteria:

a) a terminal creatinine (most recent creatinine at time of placement) >1.5mg/dl,

b) cerebrovascular accident as a cause of death, or

c) a history of hypertension.

SRTR AGE (Years)	Relative Risk				
	Normal Creatinine			High Creatinine	
	No HTN	HTN		No HTN	HTN
	Cause of death was not cerebrovascular accident				
0-9	1.40**	1.59**		1.52**	-
10-39	1.00	1.14**		1.09*	1.24**
40-49	1.17**	1.33**		1.28**	1.45**
50-59	1.41**	1.60**		1.53**	1.74**
60+	1.90**	2.16**		2.07**	2.36**
	Cause of death was cerebrovascular accident				
0-9	1.60**	1.82**		1.74**	1.98**
10-39	1.14**	1.30**		1.24**	1.41**
40-49	1.34**	1.52**		1.46**	1.66**
50-59	1.61**	1.83**		1.75**	1.99**
60+	2.17**	2.47**		2.37**	2.69**

Graft Survival (%) by ECD Status*
(RR cut point of 1.7)

Status		Graft Survival (%)		
	N (%)	3 months	1 year	3 years
Non-Expanded	24,756 (85.2)	94.6	90.6	79.4
Expanded	4,312 (14.8)	92.3	84.5	68.0

*Adjusted for donor race and sex, recipient: age, race, ethnicity, sex, BMI, primary cause ESRD, time on dialysis, cold ischemia time, pre-transplant transfusion status, PRA, HLA mismatch

SRTR

Graft Survival (%) by Relative Risk Categories*

Status	Graft Survival (%)			
	N (%)	3 months	1 year	3 years
RR < 1.7	24,756 (85.2)	94.6	90.6	79.4
RR: 1.7-2.0	2,215 (7.3)	93.6	86.5	71.7
RR 2.0-2.5	2,054 (7.0)	91.2	82.8	65.6
RR > 2.5	133 (0.5)	86.7	78.7	49.4

*Adjusted for donor race and sex, recipient: age, race, ethnicity, sex, BMI, primary cause ESRD, time on dialysis, cold ischemia time, pre-transplant transfusion status, PRA, HLA mismatch

Problem with ECD definition - dichotomy

UNOS definition

Standard criteria vs expanded criteria donor

Yes – No

Reality

Continuum

Ideal donor ***Multiple Medical Issues***

Rao et al, A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index, Transplantation 2009

14 donor and transplant factors, each found to be independently associated with graft failure or death:

donor age	race
history of hypertension	history of diabetes
cerebrovascular cause of death	serum creatinine
Height	weight
donation after cardiac death	hepatitis C virus status
human leukocyte antigen-B and DR mismatch	
cold ischemia time	double or en bloc transplant.

The KDRI reflects the rate of graft failure relative to that of a healthy 40-year-old donor.

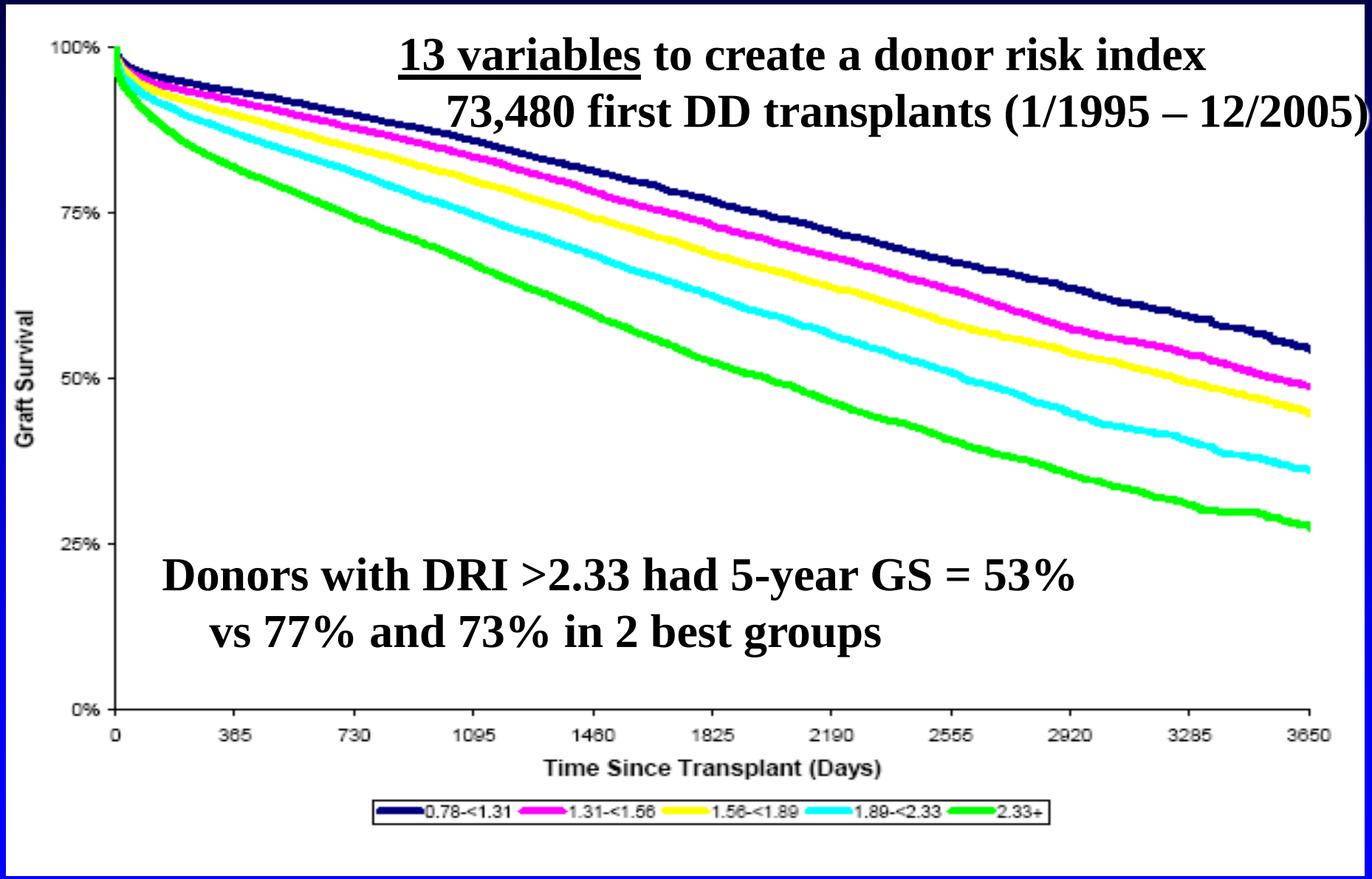
The reference donor (KDRI=1.00) had the following characteristics:

40-year-old, non-African American race, serum creatinine 1.0 mg/dL, nonhypertensive, nondiabetic, cause of death other than cerebrovascular accident, height 170 cm, weight more than or equal to 80 kg, brain dead donor (not donation after cardiac death), and HCV negative.

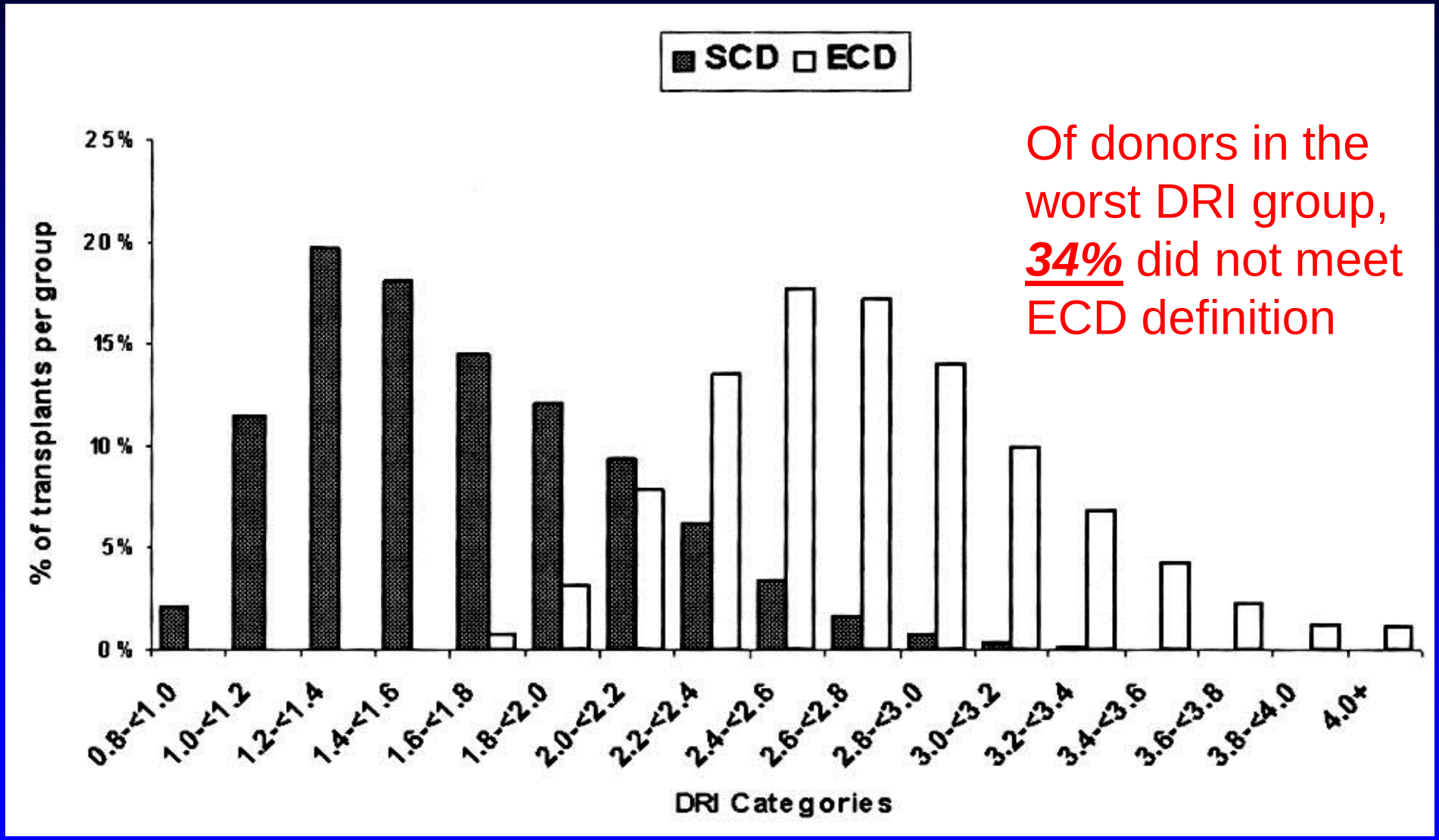
The reference transplant was characterized by two mismatches at the HLA-B locus and one mismatch at the HLA-DR locus and occurred after 20 hr of cold ischemia time

Rao et al, Transplantation, 2009

Rao et al, Abst 612, ATC, 2007



Overlap of SCD and ECD



Of donors in the worst DRI group, ***34%*** did not meet ECD definition

Rao et al, Abst 612, ATC, 2007

UNOS – Kidney Donor Risk Index (KDRI)

UNOS web site --- www.unos.org

Information For Professionals

KDRI

KDRI is ***relative risk*** of posttransplant graft failure for this donor compared to a reference donor (age = 40 yr old; non-Afr American; serum creatinine =1.0 mg/dl; nonhypertensive; nondiabetic; cause of death other than CVA; height = 170 cm; weight ≥ 80kg; brain dead (not DCD), and HCV negative)

UNOS – Kidney Donor Risk Index (KDRI)

10 factors available at the time of an organ offer

- Each independently associated with graft survival

Age (in years)
Weight (KG)
Hx hypertension
Cause of death
HCV status
Height (cm)
Ethnicity
Hx diabetes
Serum Creatinine
DCD status

This reference donor is not "ideal" or "average" but somewhere in between

However, for DonorNet, there is an additional calculation. The KDRI is "scaled" so that a value of 1 corresponds to the "median" donor of the previous year. In 2010, the median value was 1.24

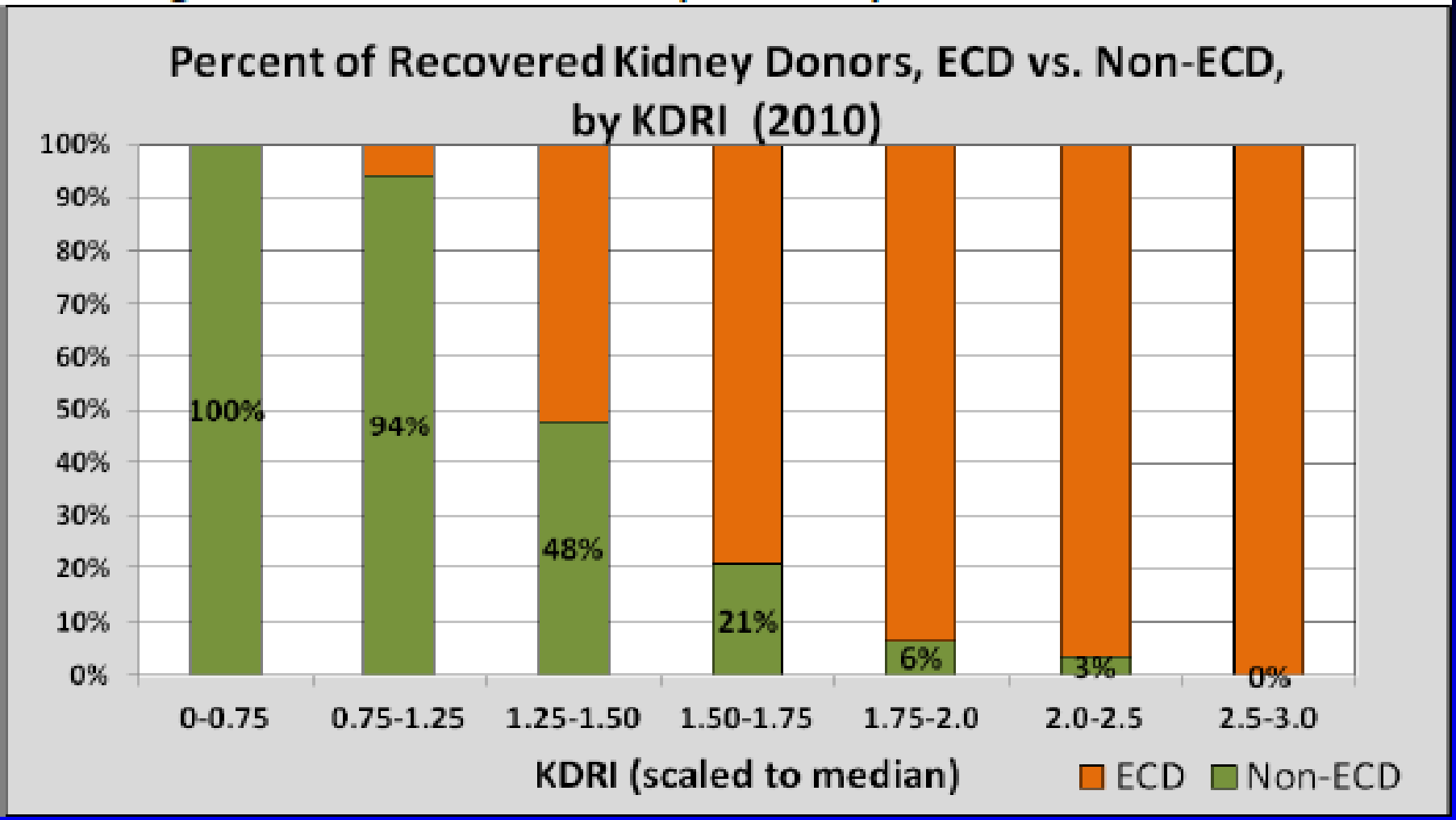
A donor with a KDPI >90% has higher KDPI than 90% of donors (from the previous year)

KDRI ranges from 0.5 to 3.5; higher numbers are associated with worse outcome

UNOS website – for professionals

KDPI	3 year GS	5 Year GS
20%	84%	75%
40%	81%	70%
60%	77%	65%
80%	72%	58%
90%	69%	53%
95%	65%	49%

Figure 1: Distribution of Kidney Donors by ECD/non-ECD and KDRI

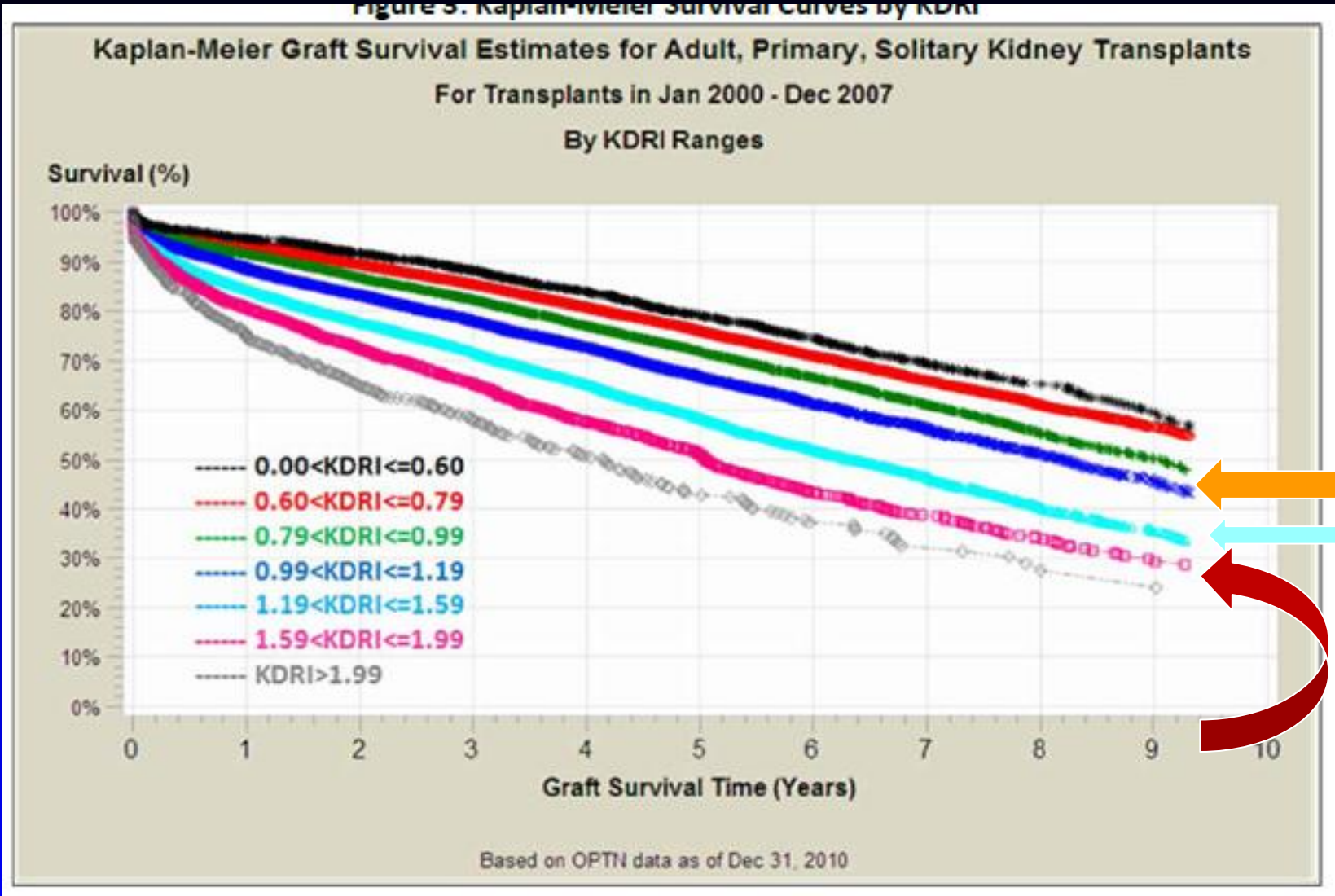


www.unos.org

2010: kidneys removed: mean = 1.02; median = 1.00

lower quartile = 0.77 upper quartile = 1.31

95th percentile = 1.87 max = 3.0



mean

Lower quartile

95th percentile

2010: kidneys removed: mean = 1.02; median = 1.00

lower quartile = 0.77 upper quartile = 1.31

95th percentile = 1.87 max = 3.0

Limitations of the KDPI

1) Outcome is related to *recipient characteristics* also; KDRI only provides info based on donor characteristics;

2) Power is limited and does not differentiate between kidneys with slight differences in KDPI;

3) Does not include all donor factors such as likelihood of disease or malignancy transmission;

4) Was calculated based on outcomes of adult transplants; pediatric recips were not included in the modeling process

Important

UNOS KDPI is scaled to the median of KDRI of donors' from the previous year

If the donor pool gets worse; the average kidney gets worse but the KDPI does not change

Optimal Utilization of Kidneys from Extended Criteria Donors

In 2009 in the U.S., 2762 (19%) of recovered kidneys were discarded.

	SCD	ECD	DCD
# recovered but not tx	987	1373	403
% discarded	10%	44%	23%

Shapiro et al, AJT, 2010

In Europe, a much lower % of ECD kidneys are discarded and outcomes are good

Possible differences:

a) donors are different in U.S. (more disease)

b) selection criteria in U.S. are too stringent

Difficult to sort this out

a) Reasons for organ refusal at UNOS are vague

b) Diff centers may turn down an organ for diff reasons

Remember – a kidney is not discarded because only 1 center turns it down

We ***need*** more detailed data!!!!!!!!!!!

Potential conclusions from this information:

a) we are not using some acceptable kidneys

b) we are making wise choices

There are many good reasons to discard a kidney that may not show up on a quick analysis of UNOS data (identification of donor disease (malignancy, infection), kidney lesions, trauma to the kidney, significant renovascular disease).

Data shows that selective use of ECD kidneys provides better survival than dialysis for a subset of patients; *but that does not mean that a less selective approach will have the same results.*

Why is this controversial: a) poor data

b) current discard criteria

Your 60 year old father with PKD, eGFR = 18, not on dialysis, 0% PRA

Is offered a kidney

- 60 year old donor; hx htn; death from CVA
- KDPI = 80 (upper quartile)
- you are in an OPO *with a short waiting time for a SCD kidney*

a) Accept the kidney
b) Continue waiting

Your 60 year old father with PKD, on dialysis, 0% PRA

Is offered a kidney

- 60 year old donor; hx htn; death from CVA
- KDPI = 80
- you are in an OPO *with a short waiting time for a SCD kidney*

a) Accept the kidney
b) Continue waiting

Your 60 year old father with PKD, on dialysis, 0% PRA, running out of vascular access

Is offered a kidney

- 60 year old donor; hx htn; death from CVA
- KDPI = 80
- you are in an OPO *with a short waiting time for a SCD kidney*

a) Accept the kidney
b) Continue waiting

Your 60 year old father with T2 DM, on dialysis, 0% PRA

Is offered a kidney

- 60 year old donor; hx htn; death from CVA
- KDPI = 80
- you are in *an OPO with a short waiting time for a SCD kidney*

a) Accept the kidney
b) Continue waiting

Your 60 year old father with PKD, on dialysis, 0% PRA

Is offered a kidney

- 60 year old donor; hx htn; death from CVA
- KDPI = 80
- you are in an OPO *with a long waiting time for a SCD kidney*

a) Accept the kidney
b) Continue waiting

Your 60 year old father with PKD, on dialysis, 0% PRA

Is offered a kidney

- 60 year old donor; hx htn; death from CVA
- KDPI = 80
- you are in an OPO *with a long waiting time for a SCD kidney*

a) Accept the kidney
b) Continue waiting

Your 60 year old father with T2 DM, on dialysis, 0% PRA

Is offered a kidney

- 60 year old donor; hx htn; death from CVA
- KDPI = 80
- you are in an OPO *with a long waiting time for a SCD kidney*

a) Accept the kidney
b) Continue waiting

Who Should Receive a ECD kidney?

ECD kidneys should be directed towards:

Any candidate over 60 years of age,

Any diabetic candidate over 40 years of age,

Any candidate with failing vascular access,

or, any candidate whose expected waiting time exceeds their life expectancy.

Gaston et al, (Management wait list), AJT, 2003

Older and frailer patients benefit form receiving an ECD kidney shortly after ESRD, whereas younger and healthier patients benefit from waiting

Schold and Meier-Kreische, cJASN, 2006

Merion et al, JAMA, 2005

Compared mortality after ECD vs. dialysis OR subsequent SCD transplant

ECD kidneys should be offered primarily to:

a) In OPOs with long waiting times (>1350 days [3.7 yrs]), candidates ≥ 40 yrs old;

b) In OPOs with short waiting times, ECD kidneys should be only offered to diabetics

Should Biopsy Results influence acceptance/turn-down

Controversial

Controversial – Role of biopsy

In Europe – much less emphasis

In U.S. – major reason for kidney discard

Literature supports both sides

 # factors biopsy; age; creatinine clearance

- papers arguing that *if CrCl is good*, biopsy does not matter;
  papers arguing that *even if* CrCl is good, bx is important

Sung et al, AJT 2008, SRTR

Performance of a biopsy (OR=1.2) and degree of glomerulosclerosis on biopsy were significantly associated with increased odds of discard

Degree of glomerulosclerosis was not consistently associated with DGF or graft failure; However, GFR @ 1 year was lower in recips of kidneys with >20% GS

Among pumped kidneys, those with resistance >0.26 were more likely to be discarded;

Reasons for discard	Percent	N
Biopsy findings	37.34	966
Other, specify	17.51	453
No recipient located – list exhausted	16.62	430
Poor organ function	9.24	239
Anatomical abnormalities	7.07	183
Diseased organ	3.48	90
Vascular damage	1.70	44
Organ trauma	1.24	32
Positive hepatitis	1.16	30
Too old on ice	1.08	28
Warm ischemic time too long	0.85	22
Too old on pump	0.70	18
Donor medical history	0.66	17
Recipient determined to be unsuitable	0.43	11
Organ not as described	0.27	7
Donor social history	0.23	6
Infection	0.19	5
Ureteral damage	0.15	4
Positive HIV	0.08	2

KI 2.6 **Reasons for kidney discards among kidneys removed for transplant but not transplanted, 2011**

Controversial - Biopsy

Gabor, Transplantation, 60:334; 1995

donor glomerulosclerosis >20% → signif ↑ DGF and graft loss;

measurement of serum Cr did not differentiate different degrees of GS found on bx (8 kidneys had >20%)

Escofet et, Transplantation, 75:344, 2003

Conclude – Bx at procurement provides important info; donor age alone was not a sufficient identifier

Controversial - Biopsy

Lu et al, Am J Surg, 180:470, 2001

Kidneys from donors with >20% GS had similar outcome to those with <20%

Edwards et al, UNOS, Transplantation, 77:1411, 2004

if CrCl >80 ml/min, no impact of >20% GS

Pokorna et al, Transplantation, 69:36,2000

GS correlated with age;

Considering donors >50, >20% vs <20% GS had similar outcome;

Conclude- bx provides only limited info (67 kidneys with >20% GS)

Problems with Reports on Importance (or not) of Biopsy

1) Different selection and allocation criteria
   -making interpretation of outcome data difficult

2) Some studies consider severity of glomerulosclerosis; others found degree of vasc pathology to be the better predictor

3) Some find pathology predicted outcome regardless of donor kidney function

4) Biopsy technique varied
   - wedge biopsies over represent the superficial cortex (which may overestimate severity as in older people glomerular and tubulo-interstitial scarring are worse in the superficial cortex

Europe

Biopsy-guided allocation

Remuzzi et al, JASN 1999

- “marginal kidneys” from donors ≥ 60 undergo biopsy
- biopsy findings determine single, dual, or no transplant

Remuzzi et al, JASN, 1999

Only biopsies with ≥25 glomeruli scored

Glomerular Global Sclerosis: 0 = none globally sclerosed
1 = <20% global glomerulosclerosis: 2 = 20-50%: 3 = >50%

Tubular atrophy: 0 = absent; 1 = <20%; 2 = 20-50%; 3 = >50%

Interstitial fibrosis: 0 = absent; 1 = <20%; 2 = 20-50%; 3 = >50%

Arterial and arteriolar narrowing: 0 = absent
1 = increased wall thickness but < diameter of lumen
2 = equal to or > diameter lumen; 3 = extreme luminal narrowing

Global score – 0-3, single tx; 4-6 dual; >6 discard

Comparative analyses

1) Kidneys from donors >60, allocated by this system, had better graft survival than ECDs transplanted without biopsy-related allocation

2) Kidneys from donors >60, allocated by this system had equivalent 3 year graft survival to kidneys from donors <60

3) Biopsy-related allocation increased the # kidney used

   15% discard rate (Fernandez-Lorente, AJT 2012)

4) Dual kidney tx associated (in some series) with more technical complications

1) What should be the “cut-off” score for single kidney

Remuzzi: 0-3

Fernandez-Lorente: score of “4” performed as well as 0-3 as a single tx

- for dual tx, 4-6 were equivalent

2) Is biopsy even necesaary?

Snanoudj et al, AJT, 2009

Allocation as single kidney tx if eGFR >60

Allocation as a dual tx of eGFR between 30-60 results equivalent to bx allocation

3) Leuven, Belgium

Optimal Use of ECD Kidneys

1) Don’t use them
2) In today’s reality – use for patients who will not survive on dialysis to get a SCD kidney

The only way to not use ECDs is to increase other types of donation:

- DCDs
- non-directed donors (and chains)
- paired exchange (and chains)

After 50 years of "new initiatives" to increase donation rates, # transplants (in the U.S.) has not significantly increased in the last few years:

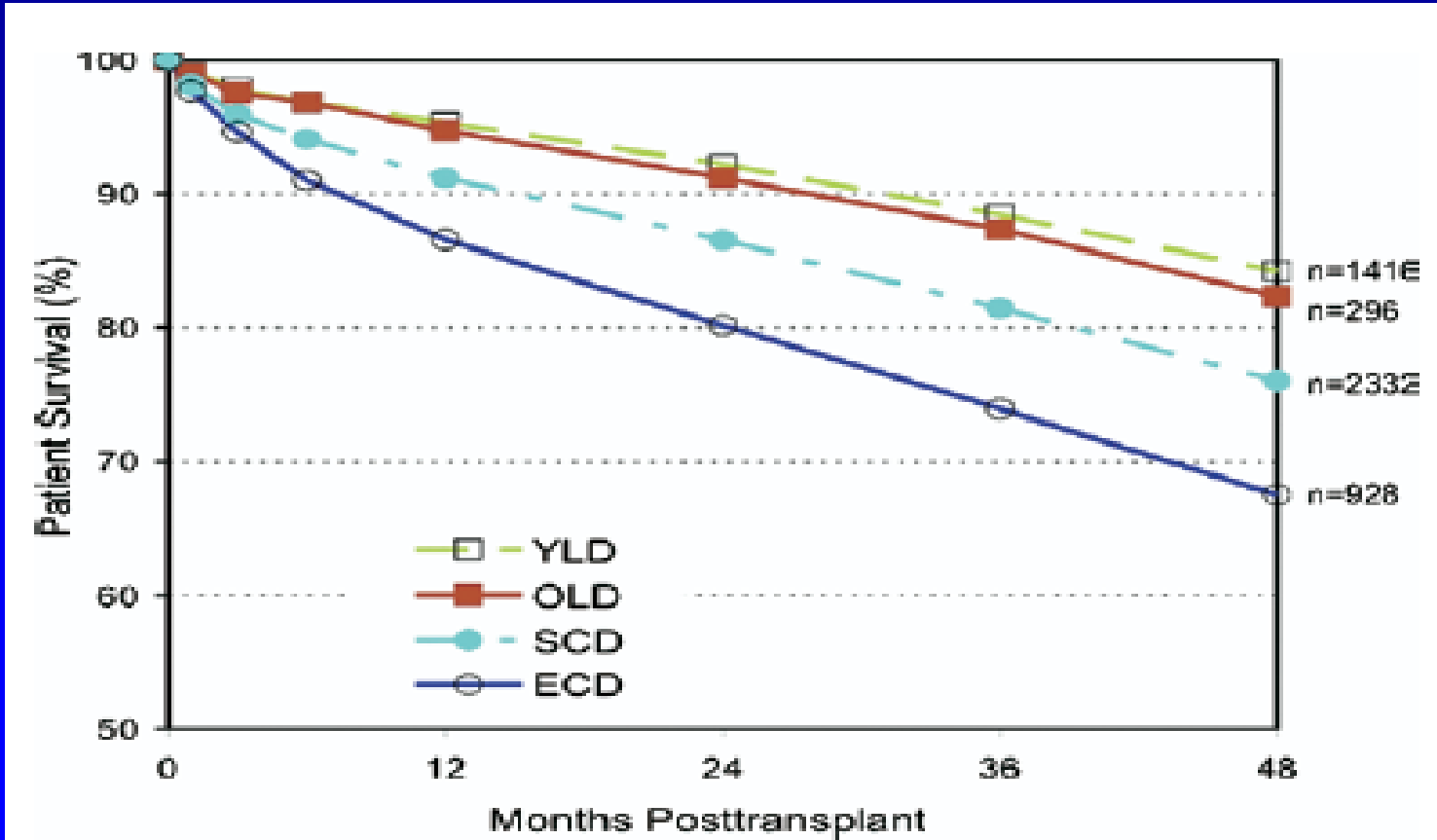
2011	2010	2009	2008	2007	2006	2005	2004	2003	2002	2001
13,202	13,518	13,635	13,156	13,283	13,614	13,273	12,972	12,226	11,879	11,575
7,433	7,241	7,248	7,188	7,240	7,178	6,700	6,325	5,753	5,638	5,528
5,769	6,277	6,387	5,968	6,043	6,436	6,573	6,647	6,473	6,241	6,047

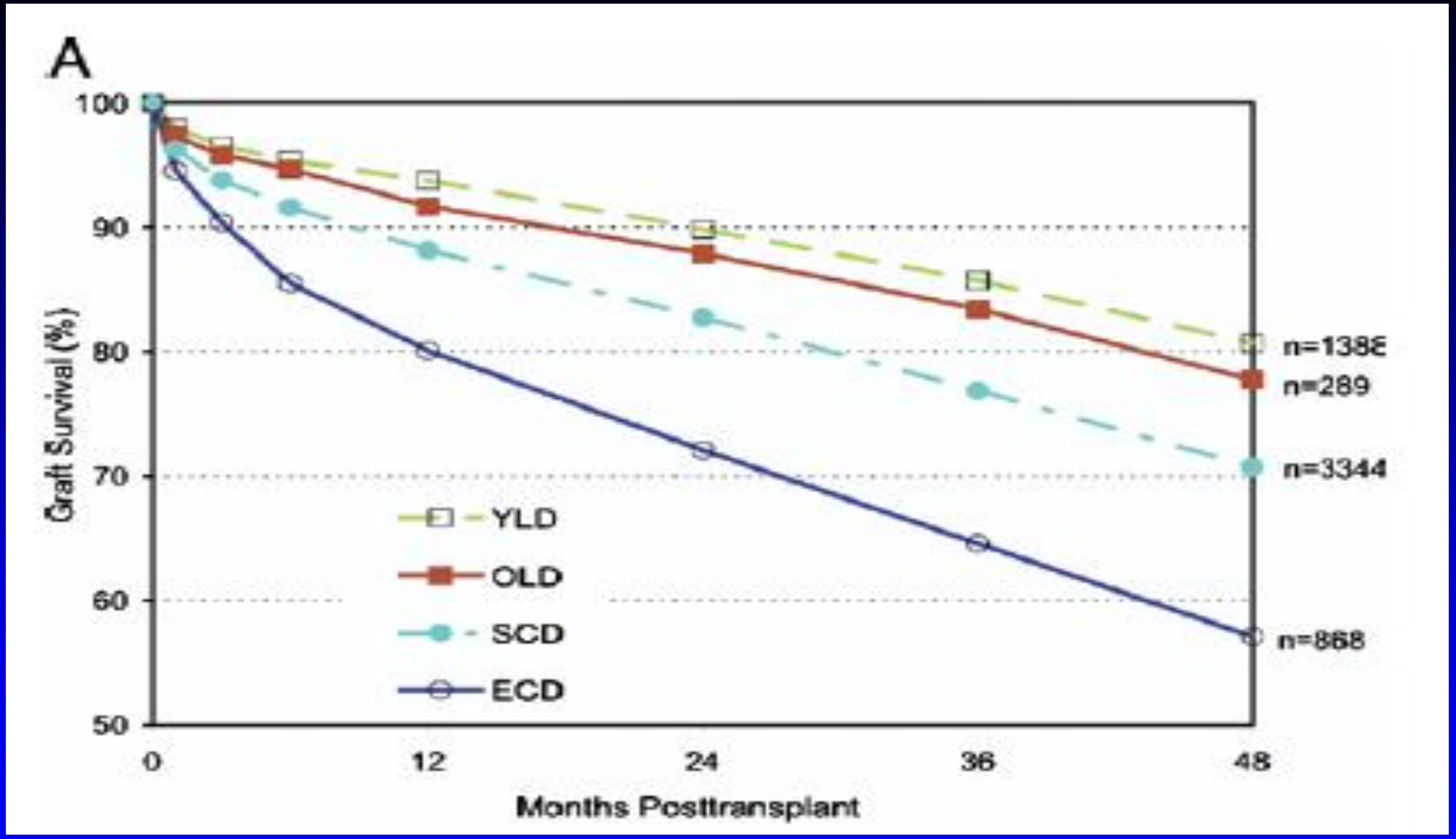
www.optn.transplant.gov

Outcomes of transplants from Older Donors to Older Recipients, Gill et al, AJKD, 2008

1996-2005, 23, 754 transplants to recipients ≥ 60

7,006 LDs; 12,197 SCDs; 4,551 ECDs





Gill J et al, AJKD, 2008

My Opinion

Every effort should be made to increase our conventional living and deceased donation.

- for DD, why are there discards and could some be successfully transplanted?

However, in reality in the U.S, organ donation rated have been unchanged for a decade.

I strongly believe that the only way that there will be a significant increase in donation is to provide incentives for donation (esp for LDs). Increasing LDs will shorten waiting time, provide the best outcomes fro our patients, and perhaps allow us to stop using these suboptimal organs.

A Regulated System of Incentives

Must: provide protection for donor and recipient
have regulation, oversight, and transparency

Consider: a) govt regulated system
b) evaluation by a neutral body (OPO)
c) kidney allocated to #1 person on list (same as DD)
d) incentive provided by the govt (NOT rich buying from the poor)

If evaluation, surgery, and follow-up is identical to today's donors, results (risks should be the same)

Why not?

Conclusions

1) Every effort should be made to expand the donor pool;

2) ECD kidneys have decreased long-term GS, and should be used for those with limited lifespan on dialysis;

3) Additional studies are necessary to:
   a) determine best use of ECD kidneys
   b) define the role of biopsy in discard
   c) understand discard rates in the U.S.

4) We need to recognize that ECDs are not going to solve the severe organ shortage and do not provide ideal outcome for our patients. We should be making every effort to expand the use of SCDs and living donation.

Machine Perfusion - Advantages

1) ↓ DGF vs cold storage

Moers et al, NEJM, 2009; randomized trial;

SCD and ECD donors

mean preservation time 15 hours

- 1 year GS (94% vs 90%)

3) For ECD donors

Gallinat et al, Nephrol Dial Tx (2012); randomized trial

- mean preservation time 11 hours
- no diff in DGF or in GS
- for those who developed GDF, GS was better in MP

4) Assess the transplant

Machine Perfusion - Disadvantages

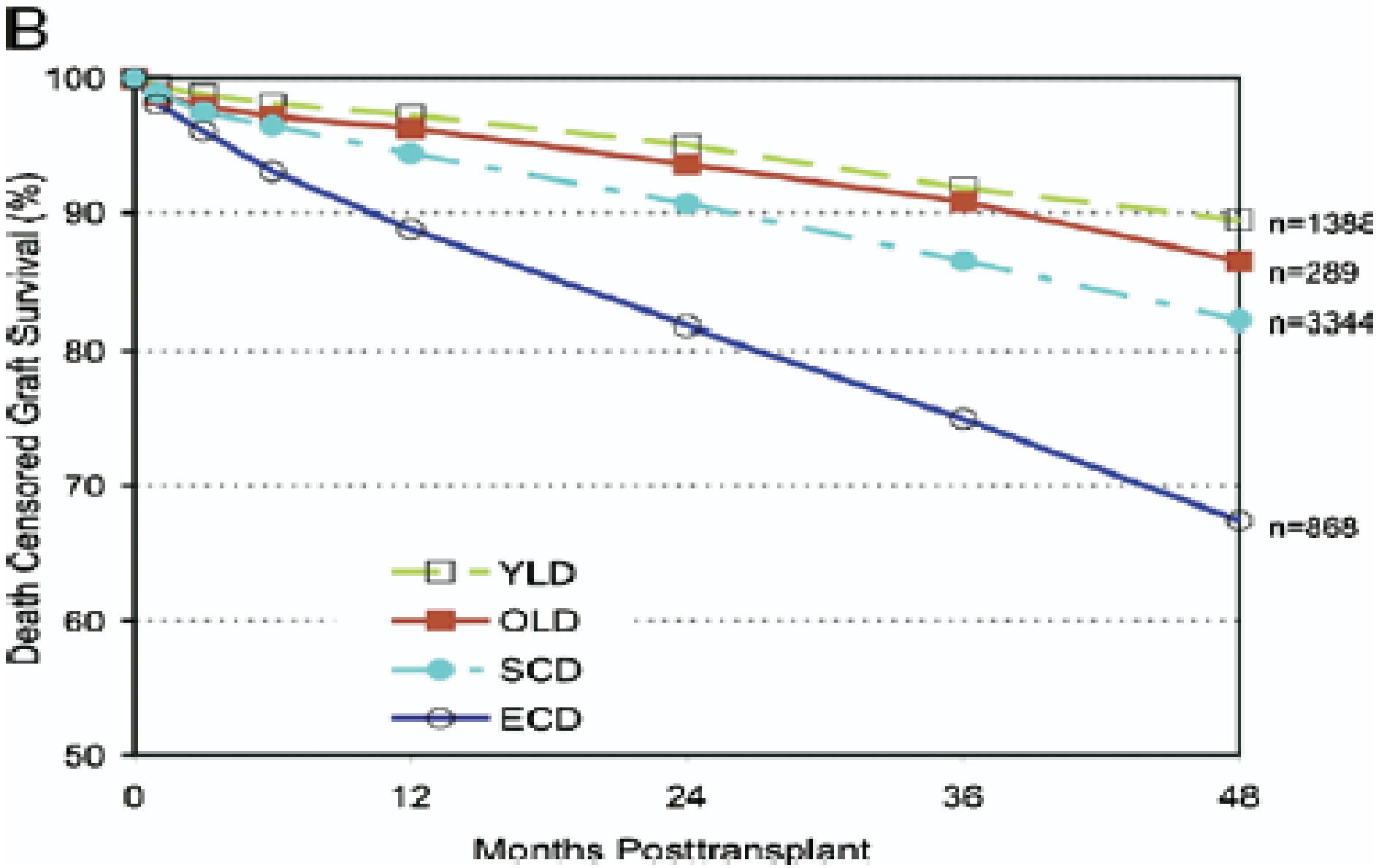
Labor intensive

Costly

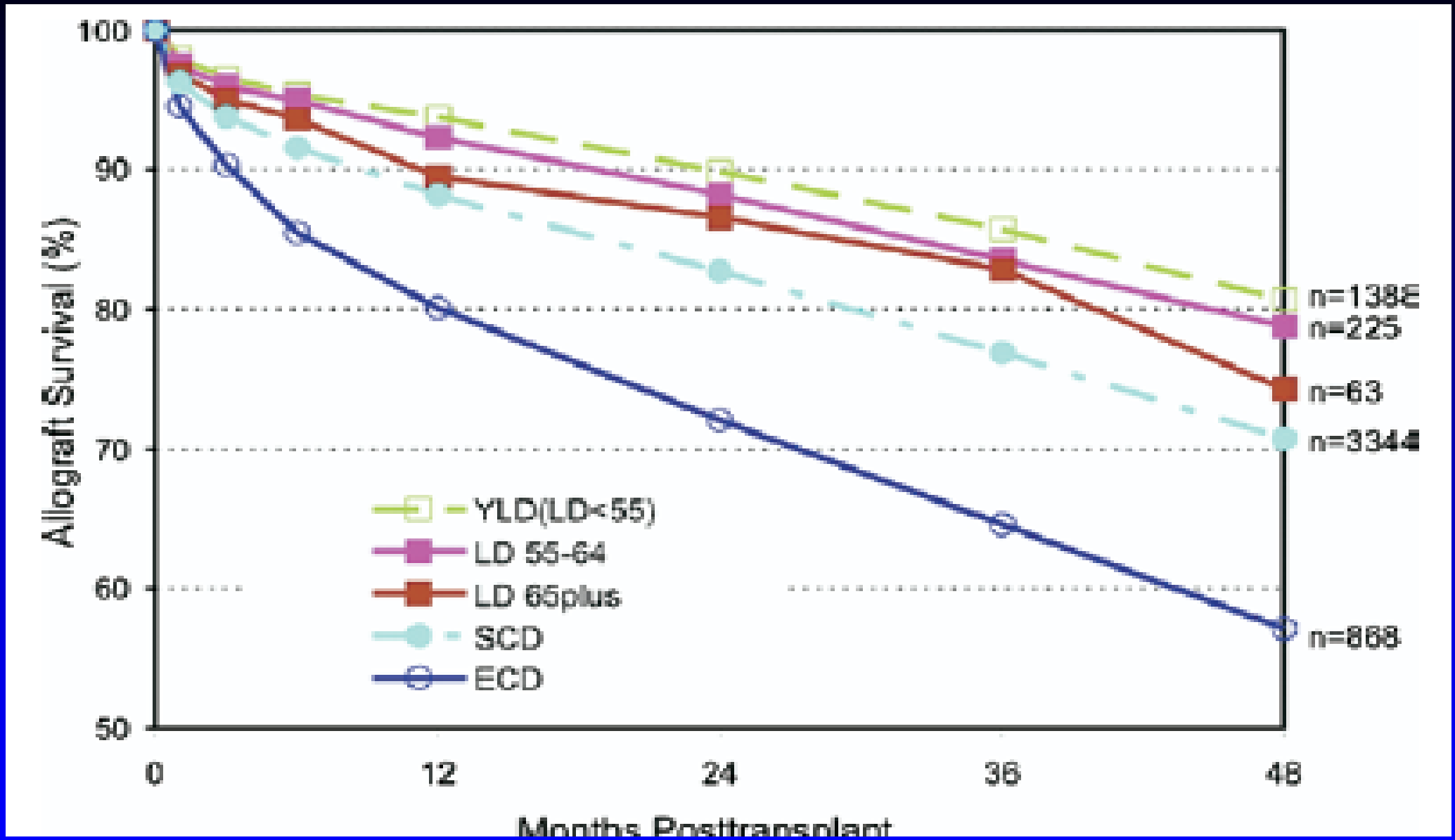
Mozes et al., Use of Perfusion Parameters in Predicting Outcomes of Machine-Preserved Kidneys

Trans Proc 2005

Sonnenday et al, the Hazards of Basing Acceptance of Cadaveric Renal Allografts on Pulsatile Perfusion Parameters Alone, Transplantation 2003



Gill J et al, AJKD, 2008


100
90
80
70
60
50
Allograft Survival (%)
0
12
24
36
48
Months Posttransplant
YLD(LD<55)
LD 55-64
LD 65plus
SCD
ECD
n=1385
n=225
n=63
n=3344
n=868