Vergijzing van de dialysepopulatie: gevolgen voor de selectie van transplantkandidaten en de zorg na de transplantatie

Prof. Dr. K.M. Wissing
Nefrologie – UZ Brussel
kwissing@uzbrussel.be

6e Vlaamse Nefrologiedag
Essene, Belgium, March 2012

Universitair Ziekenhuis Brussel

Outline of the talk

- Age distribution of the dialysis population in Flanders
- Increasing number of older patients on the waiting list for kidney transplantation
- Obstacles to listing of older transplant recipients
- Optimal organ allocation for older transplant recipients
- Post- transplant care of the older transplant recipient

Increasing numbers of older patients on dialysis in Vlaanderen

Counts

	1995	2000	2005	2010
<25	23	33	24	38
25-44	217	247	261	288
45-64	716	820	897	988
65-74	846	988	988	1009
75-84	632	1065	1324	1586
85+	101	151	219	423
Total	2535	3304	3713	4332

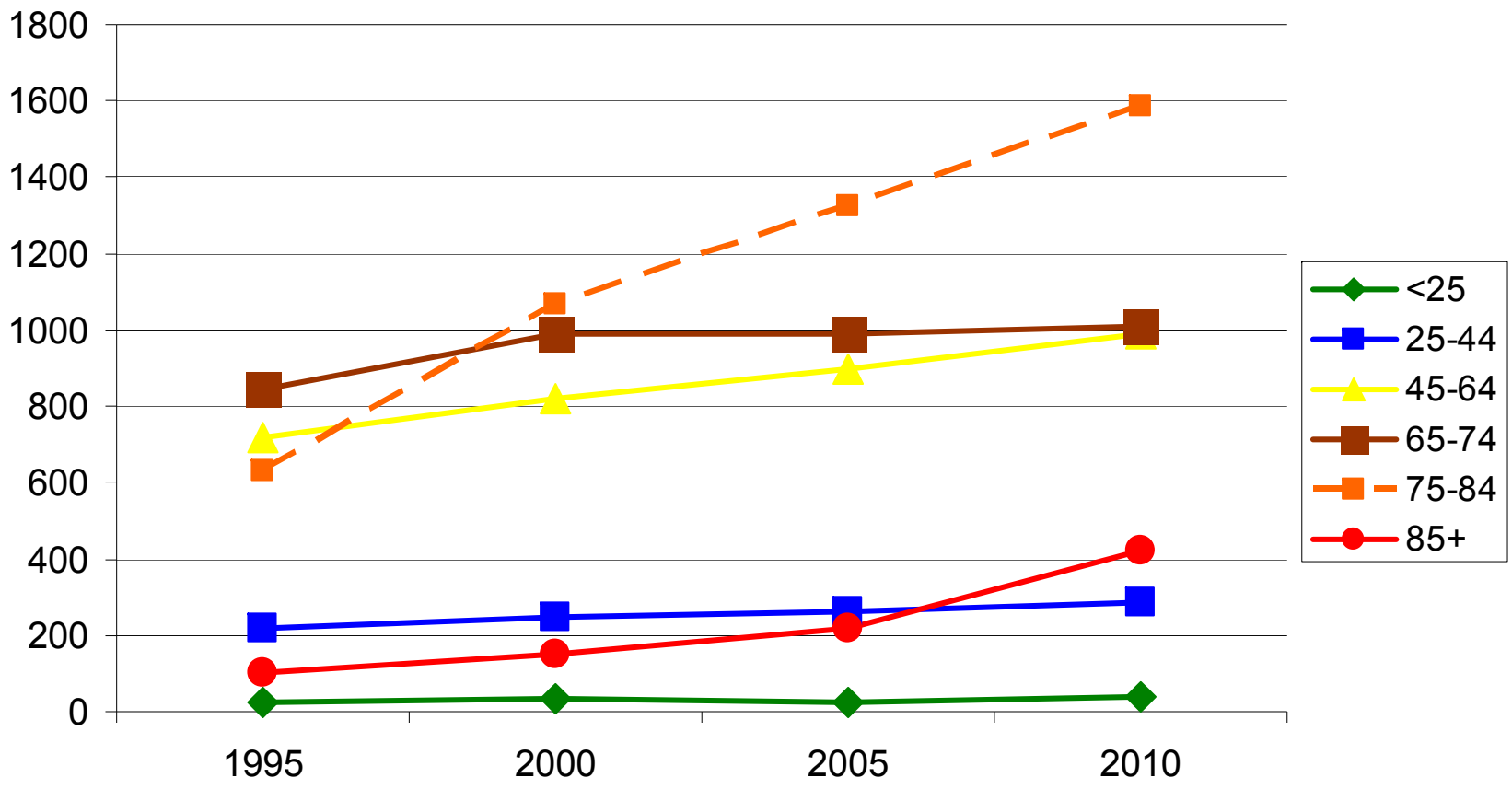
Percent

	1995	2000	2005	2010
<25	0.9	1	0.6	0.9
25-44	8.6	7.5	7	6.6
45-64	28.2	24.8	24.2	22.8
65-74	33.4	29.9	26.6	23.3
75-84	24.9	32.2	35.7	36.6
85+	4	4.6	5.9	9.8

NBVN jaarbilan 2010

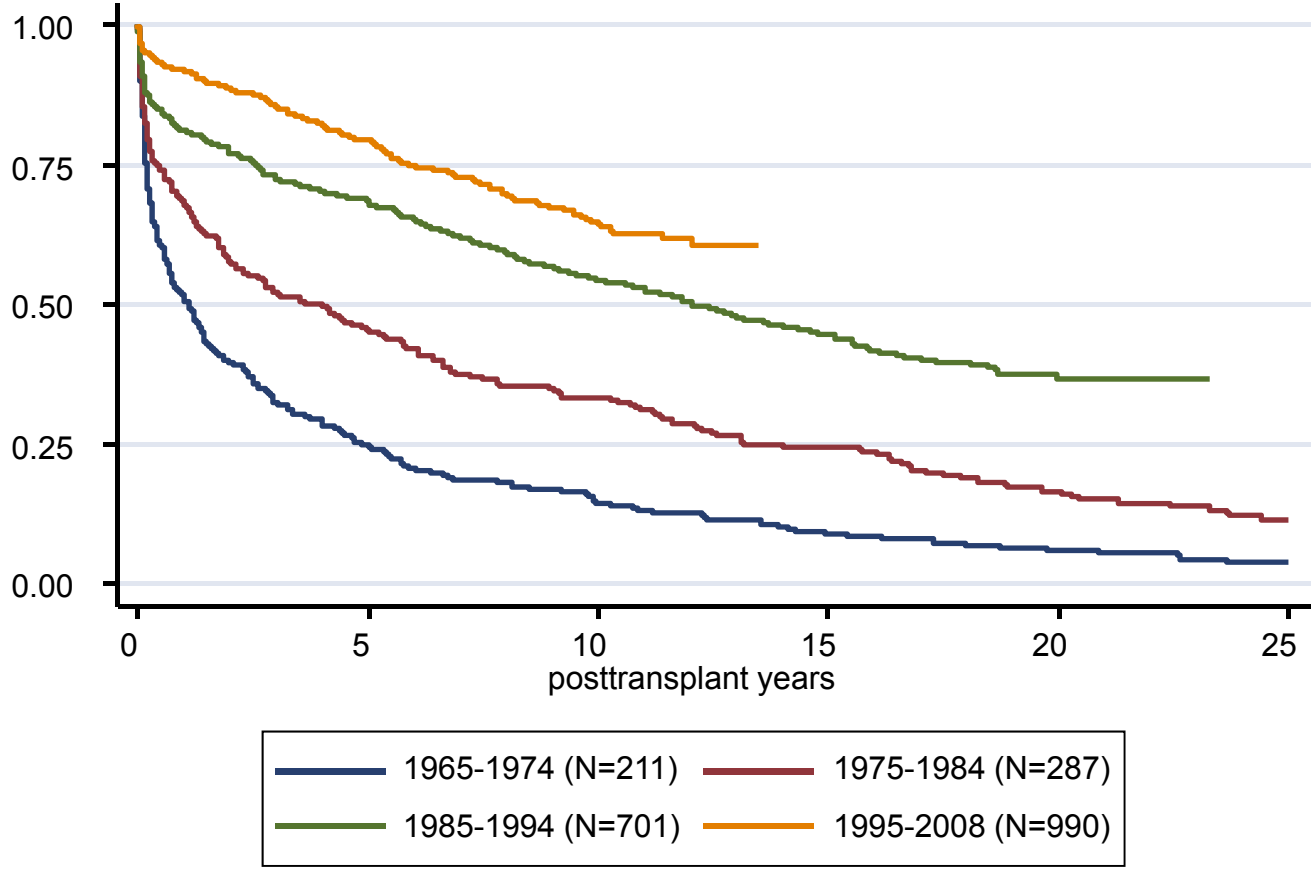
Universitair Ziekenhuis Brussel

Numbers of prevalent dialysis patients in Flanders according to age category



Universitair Ziekenhuis Brussel

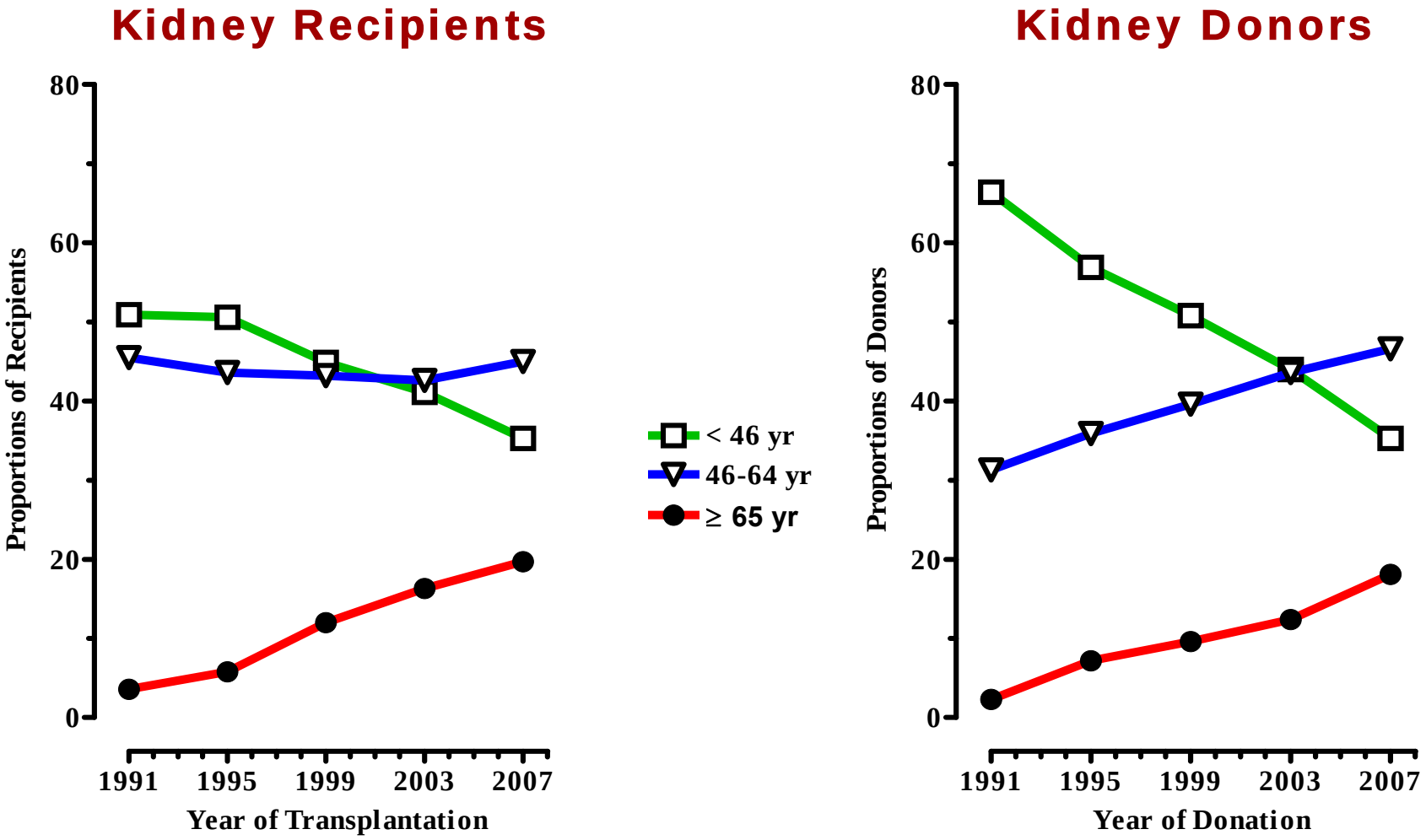
Overall graft survival of kidney transplant recipients at the University of Brussels (N=2189)



Universitair Ziekenhuis Brussel

First Kidney Transplants in Eurotransplant

Recipients and Donors according to Age



Universitair Ziekenhuis Brussel

Relative risk of death and projected years of life after renal transplantation as compared to patients on the waiting list

	RR 18 months after transplantation	Projected years of life without Txp (WL)	Projected years of life with transplantation
All	0,32	10	20
0-19	0,33	26	39
20-39	0,24	14	31
40-59	0,33	11	22
60-74	0,39	6	10

Wolfe et al. N Engl J Med 341:1725; 1999

Universitair Ziekenhuis Brussel

Does transplantation improve graft survival in older recipients?

TABLE 2. Unadjusted death rates and adjusted relative mortality risk for first deceased donor transplant recipients versus wait-listed dialysis patients older than 70 years of age, 1990–2005

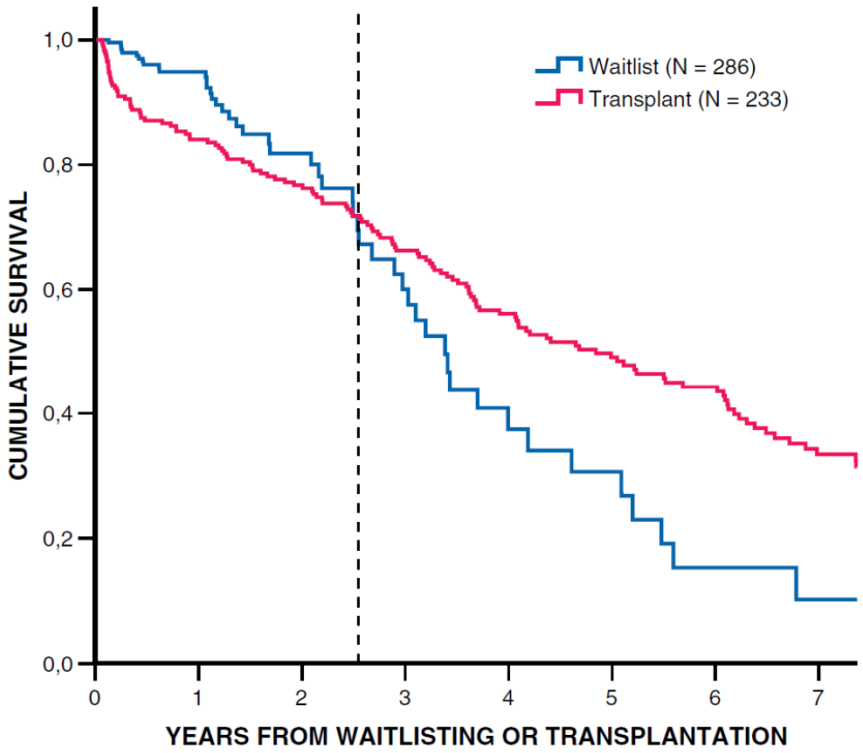
Group	Deaths per 100 patient years at risk (unadjusted)		Overall mortality RR compared with wait-listed patients	95% CI for RR
	Wait-listed patients	Deceased donor transplant		
All (age 70+ yr)	15.8	13.2	0.59[a]	(0.53–0.65)
Age 70–74 yr	15.3	12.9	0.58[a]	(0.52–0.65)
Age 75+ yr	17.8	15.0	0.67[b]	(0.53–0.86)
Glomerulonephritis	13.0	13.6	0.89 (ns)	(0.64–1.22)
Diabetes	18.5	14.5	0.53[a]	(0.41–0.68)
Hypertension	15.0	12.8	0.56[a]	(0.45–0.68)
Other ESRD cause	15.2	10.6	0.49[a]	(0.39–0.61)
Short wait OPO: <700 d	15.3	12.5	0.52[a]	(0.42–0.65)
Medium wait OPO: 700–1350 d	14.9	13.5	0.61[a]	(0.51–0.72)
Long wait OPO: >1350 d	16.4	13.6	0.58[a]	(0.50–0.68)

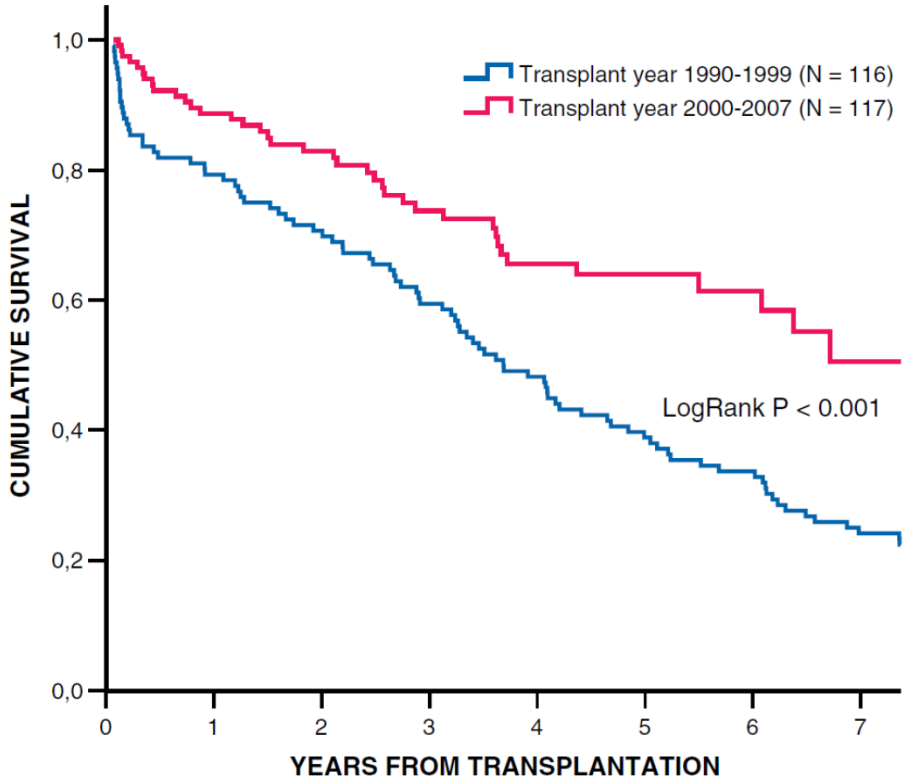
[a] $P<0.0001$.
[b] $P<0.05$.

Rao et al. Transplantation 2007; 83:1096

Universitair Ziekenhuis Brussel

Renal transplantation of elderly patients



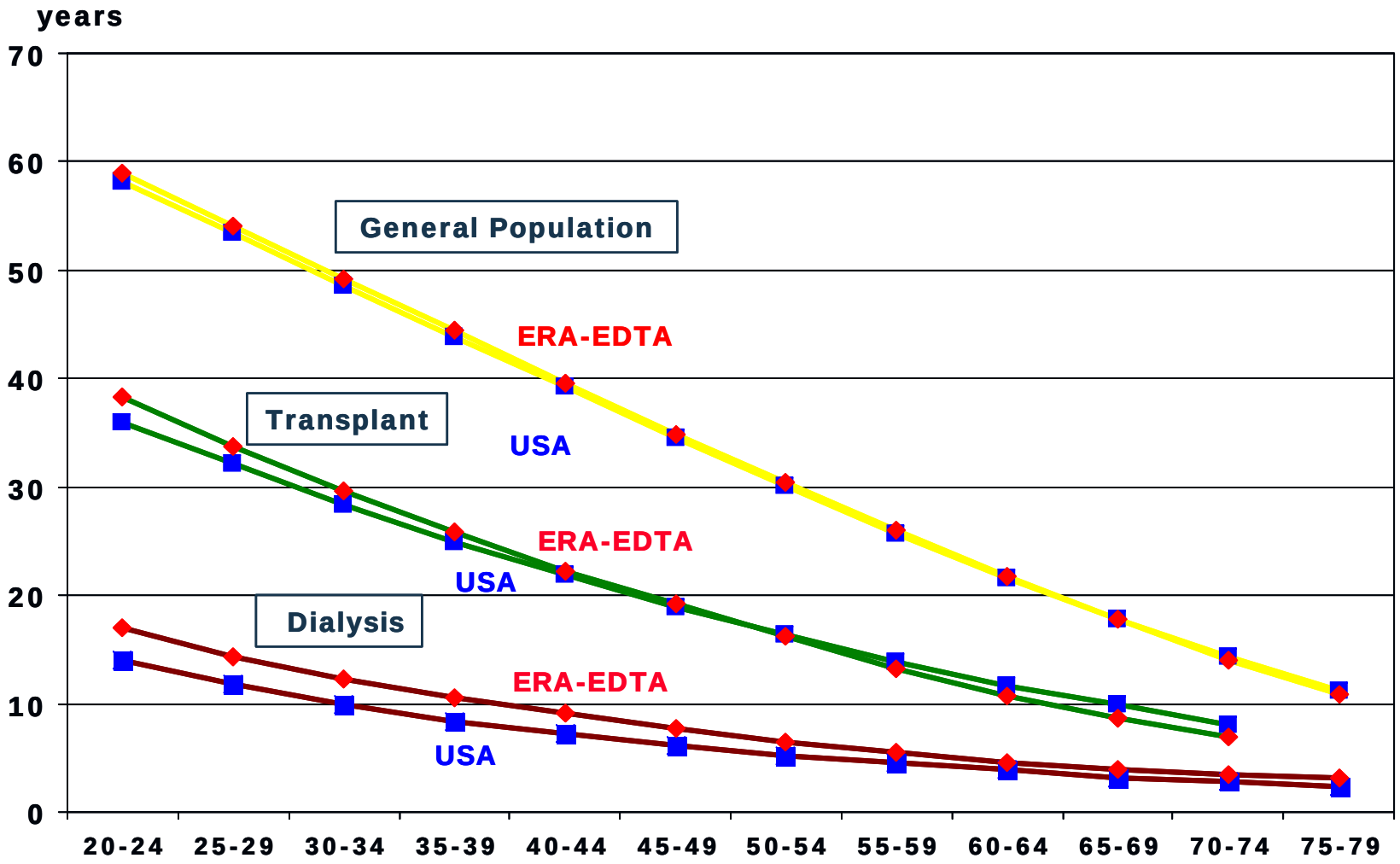


- Elderly patients (median age 74 years) can benefit from renal transplantation
- Patient survival after renal transplantation has improved in the recent period

Heldal K et al. NDT 2010

Universitair Ziekenhuis Brussel

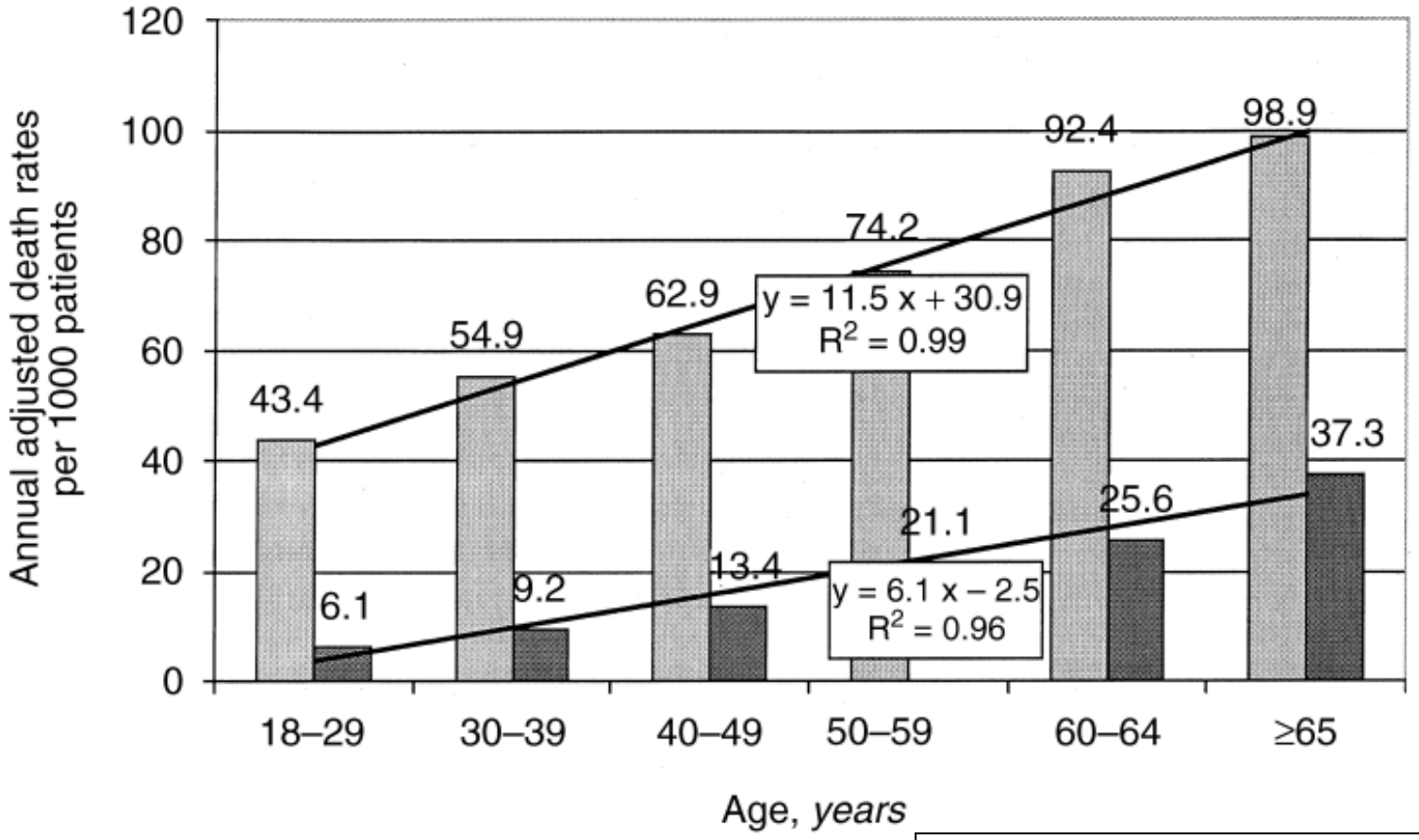
Expected remaining lifetimes
ERA-EDTA Registry vs USA whites



K. Jäger ERA-EDTA registry 2004

Universitair Ziekenhuis Brussel

Renal transplantation is reduces death from cardiovascular causes in all age categories



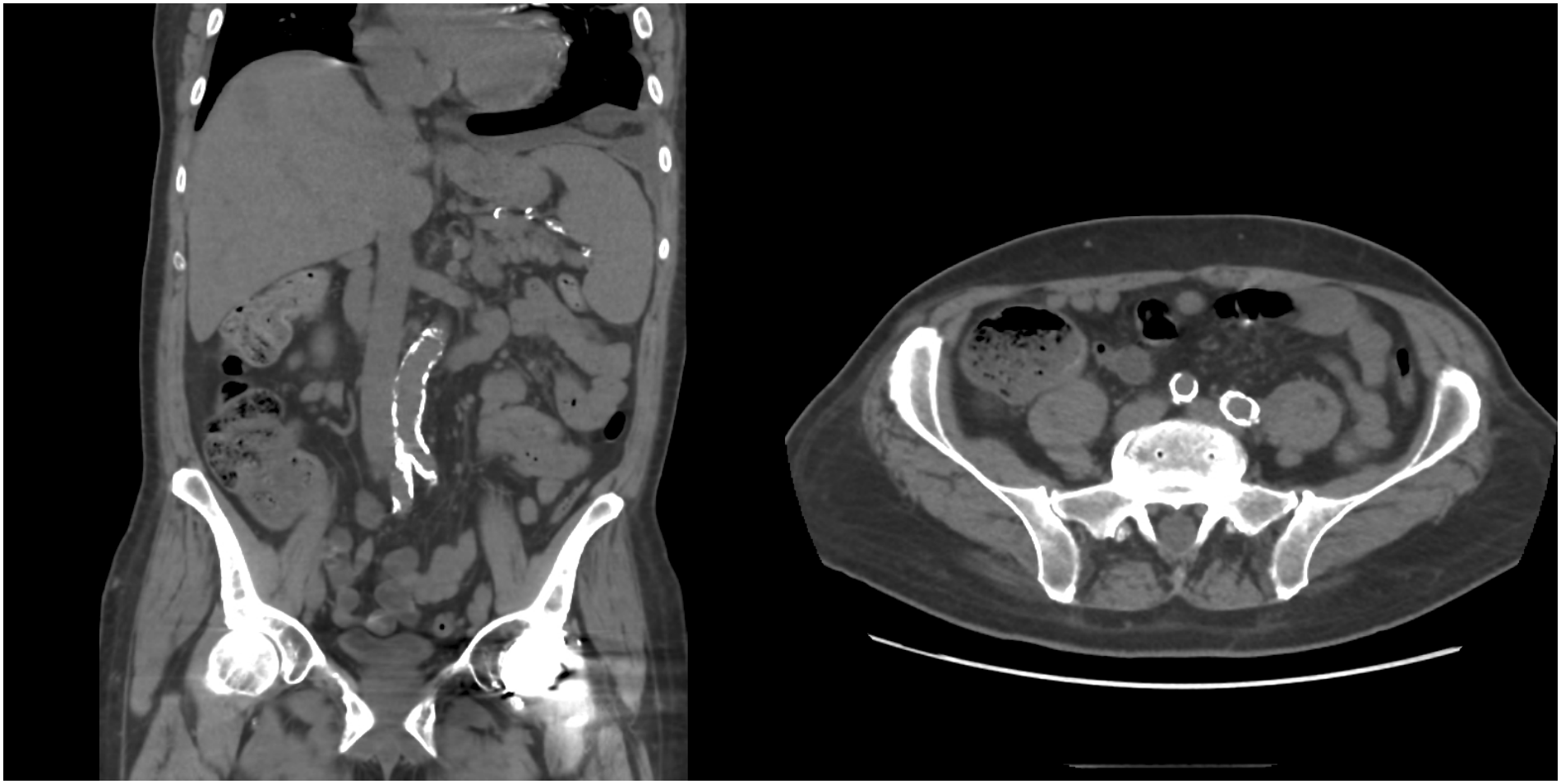
Meier-Kriesche H. Kidney Int. 2001; 59:1539

Universitair Ziekenhuis Brussel

Absolute contra- indications to renal transplantation

- Ongoing malignancy
- Recent myocardial infarction
- Severe atherosclerosis with extensive calcifications
- Active tuberculosis
- Active substance abuse
- Severe psychiatric disorder or cognitive disorder with problems of compliance
- Other end- stage organ disease (combined TXP)
- Systemic disease (oxalosis)
- Life expectancy of less than 3- 5 years

Aorto- iliac mediacalcinosis in a transplant candidate



Universitair Ziekenhuis Brussel

Eligibility of older candidates for transplantation

- Very few data
- Most decisions on ineligibility are taken at the referring dialysis centre
- Review of referred patients (Kianda Clin Transplant 2011)

  → N= 445 files with decision (2001- 2006)

  → 36 ineligible (8% (95% CI 5.5- 10.5%)

  → 339 transplanted

  → 70 still on WL (mostly NT)

Guidelines: Knoll CMAJ 2005; 173:S1; Kasiske BL AJT 2001;1:3

Universitair Ziekenhuis Brussel

Risk factors for ineligibility and outcome

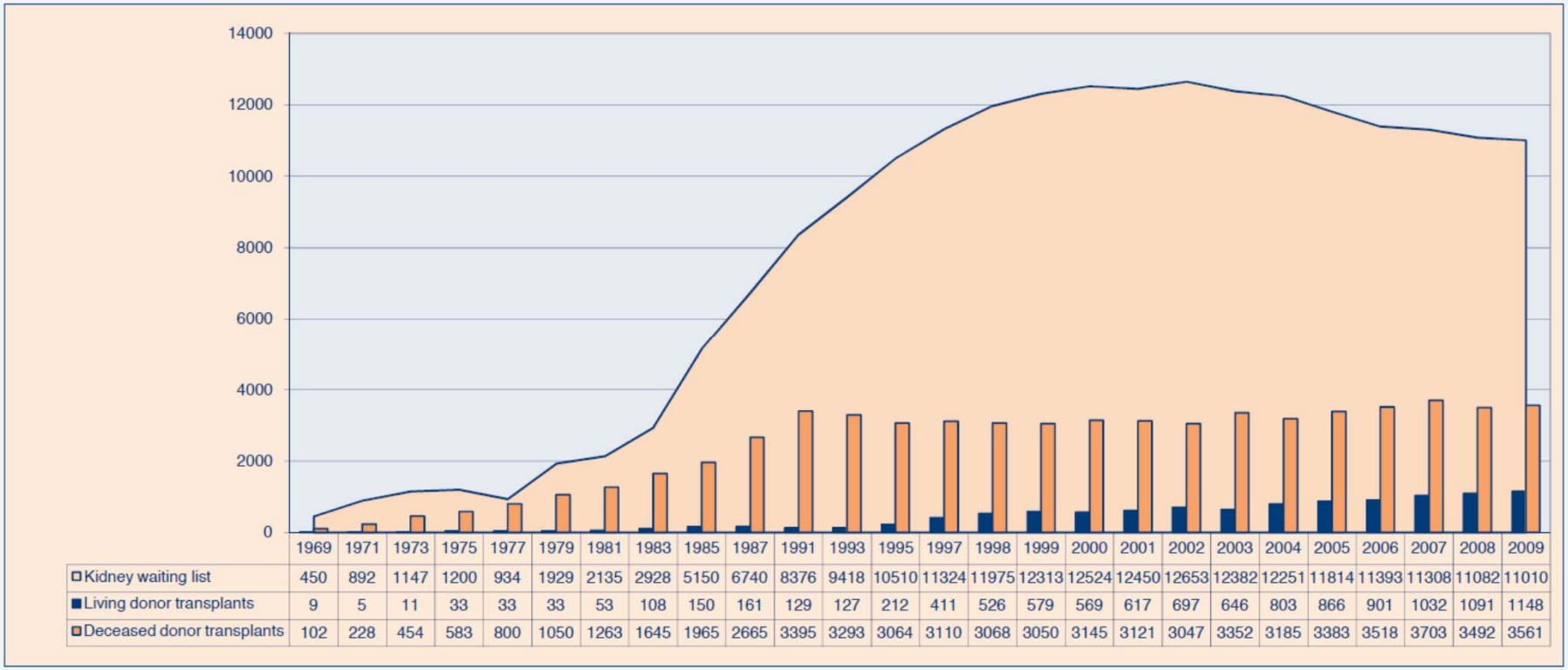
	Ineligible (N= 36)	Eligible (N= 409)	P
Age	60	41	< 0.001

	aRR	95% CI	*P*
0–49 years	1		
50–59 years	0.95	0.59–1.53	0.83
60–64 years	0.41	0.23–0.73	0.0022
65–69 years	0.07	0.03–0.20	< 0.0001

Villar E et al. NDT 2004

Kianda et al. Clin Transplant 2011

Evolution of the kidney transplant waiting list in the Eurotransplant region

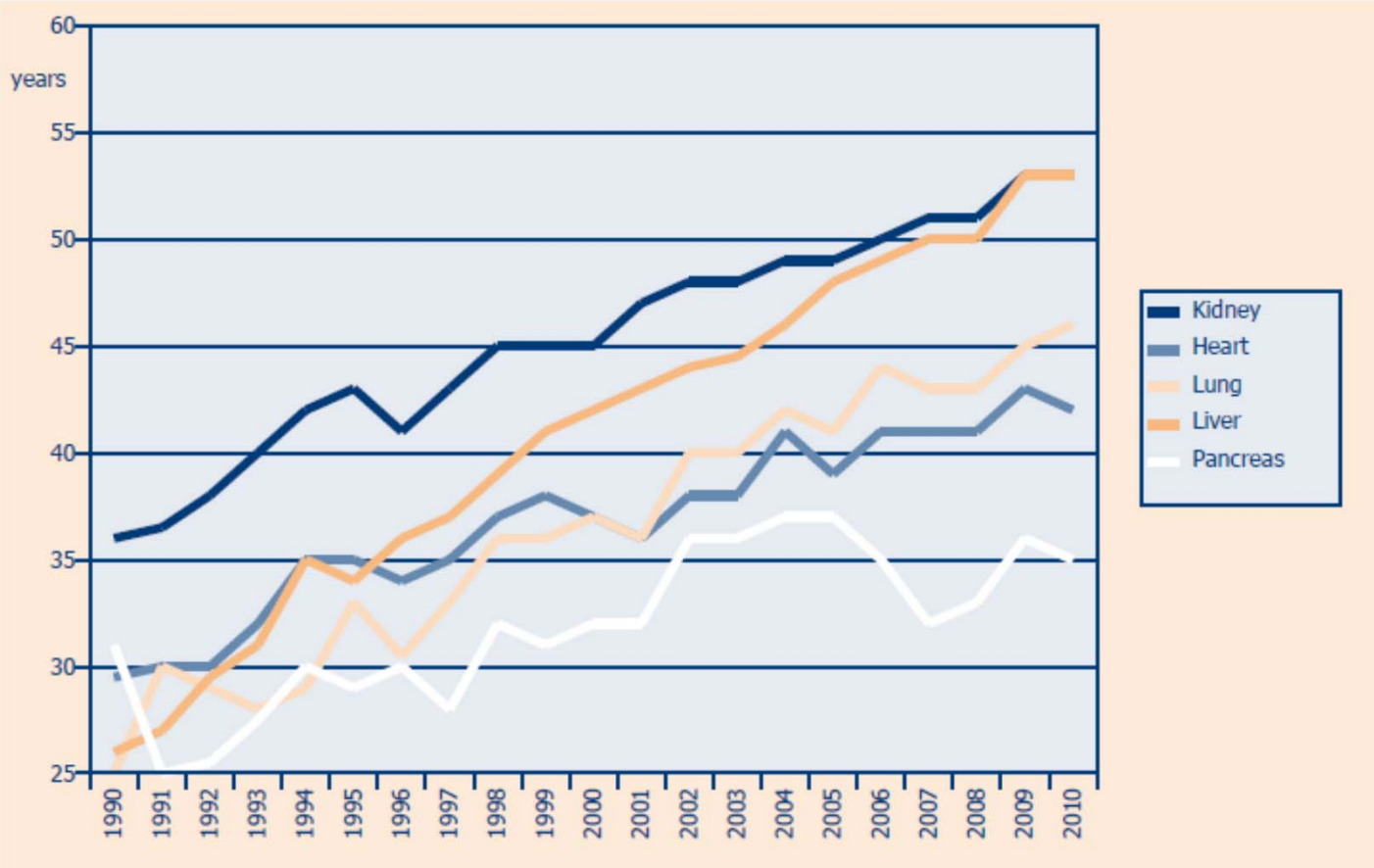


	1969	1971	1973	1975	1977	1979	1981	1983	1985	1987	1991	1993	1995	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Kidney waiting list	450	892	1147	1200	934	1929	2135	2928	5150	6740	8376	9418	10510	11324	11975	12313	12524	12450	12653	12382	12251	11814	11393	11308	11082	11010
Living donor transplants	9	5	11	33	33	33	53	108	150	161	129	127	212	411	526	579	569	617	697	646	803	866	901	1032	1091	1148
Deceased donor transplants	102	228	454	583	800	1050	1263	1645	1965	2665	3395	3293	3064	3110	3068	3050	3145	3121	3047	3352	3185	3383	3518	3703	3492	3561

Universitair Ziekenhuis Brussel

Eurotransplant annual report 2009

Median age of organ donors in the ET area



Eurotransplant Annual Report 2010

Universitair Ziekenhuis Brussel

Effect of donor age on graft function and survival

1-year serum creatinine

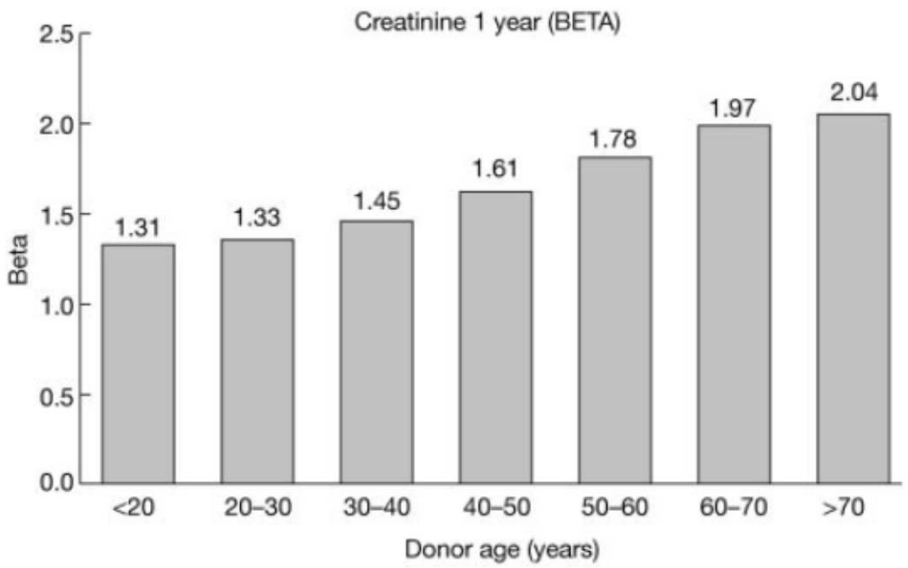


Fig. 1. Effect of donor age on serum creatinine.

Overall graft survival

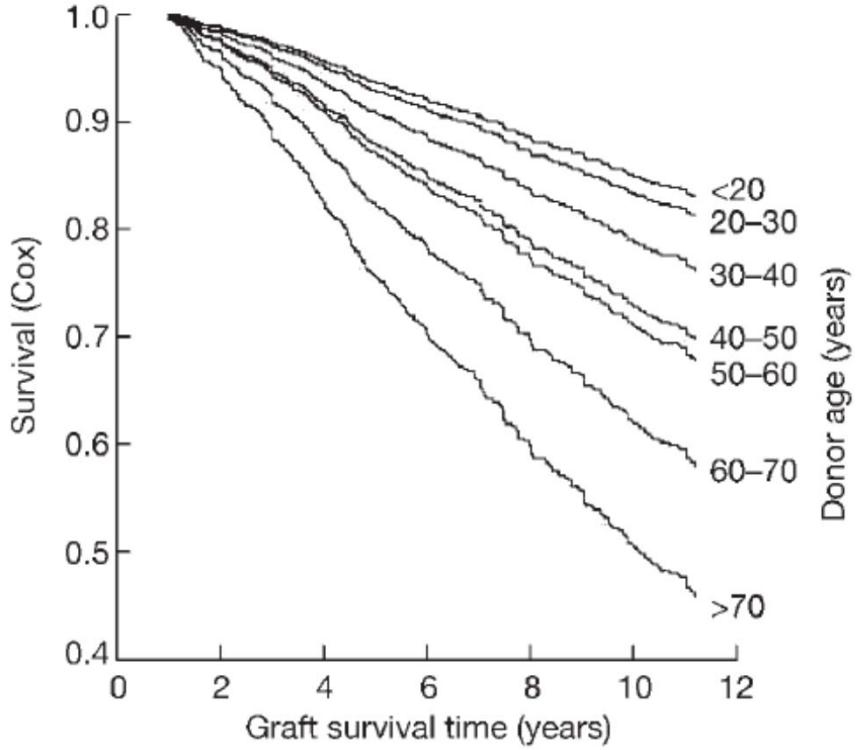
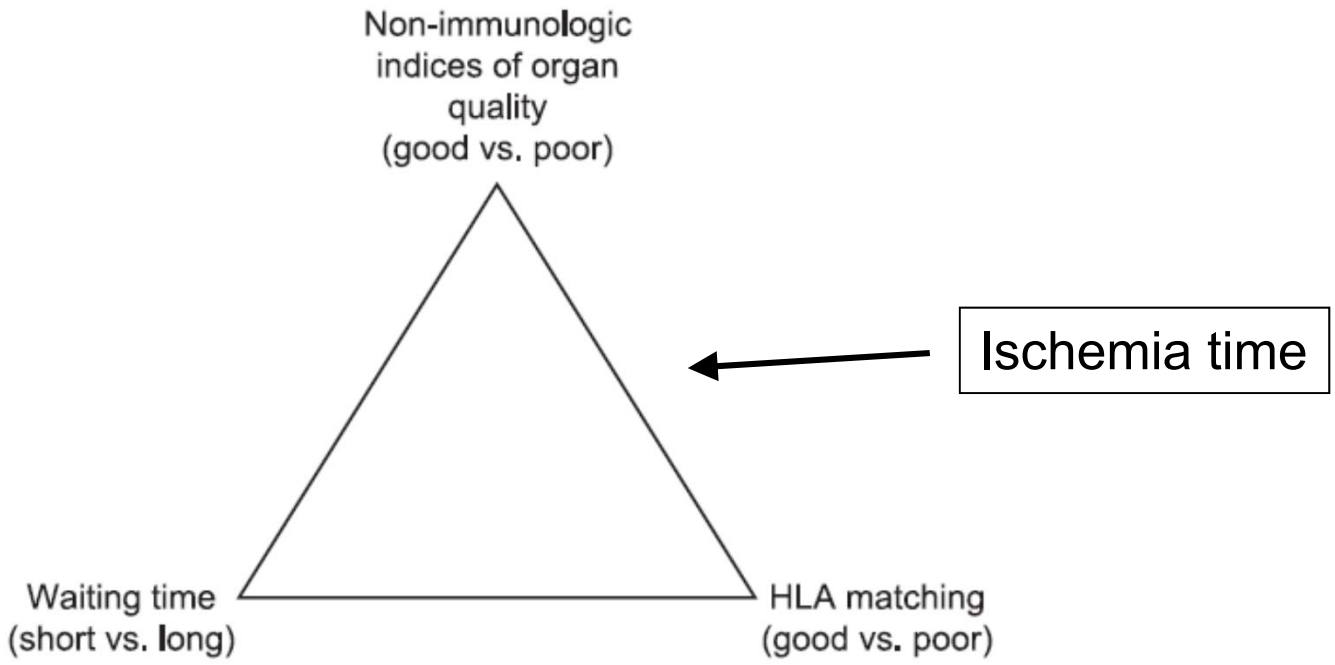


Fig. 2. Effect of donor age on long-term graft survival.

Oppenheimer F et al. NDT 2004
Idem: Moers et al. Transplantation 2009;88: 542–552

Universitair Ziekenhuis Brussel

Organ allocation is a question of trade- offs

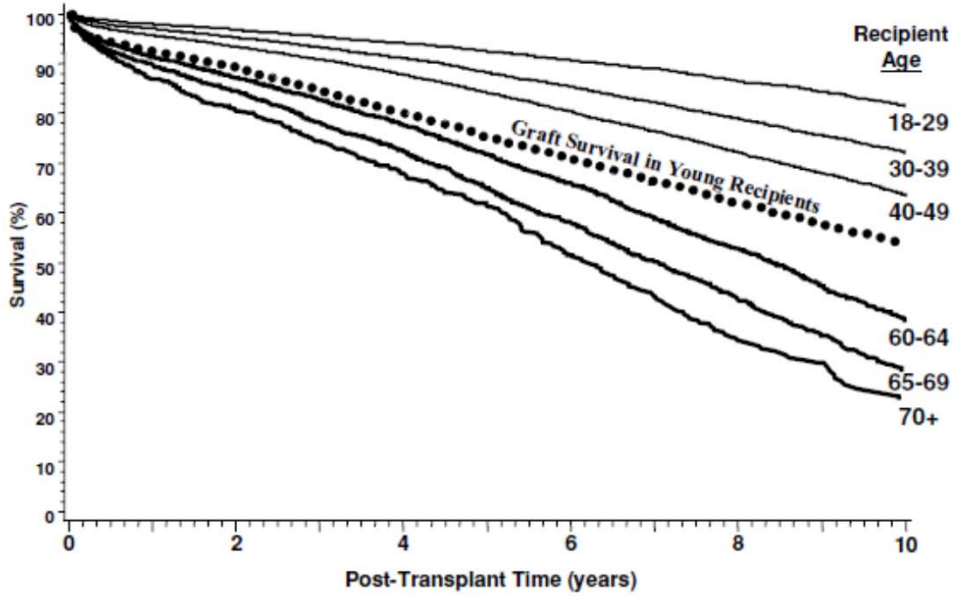


- Improving one parameter → less stringent on others
- Improvement of multiple parameters for predefined subpopulations of patients → violates equity principle

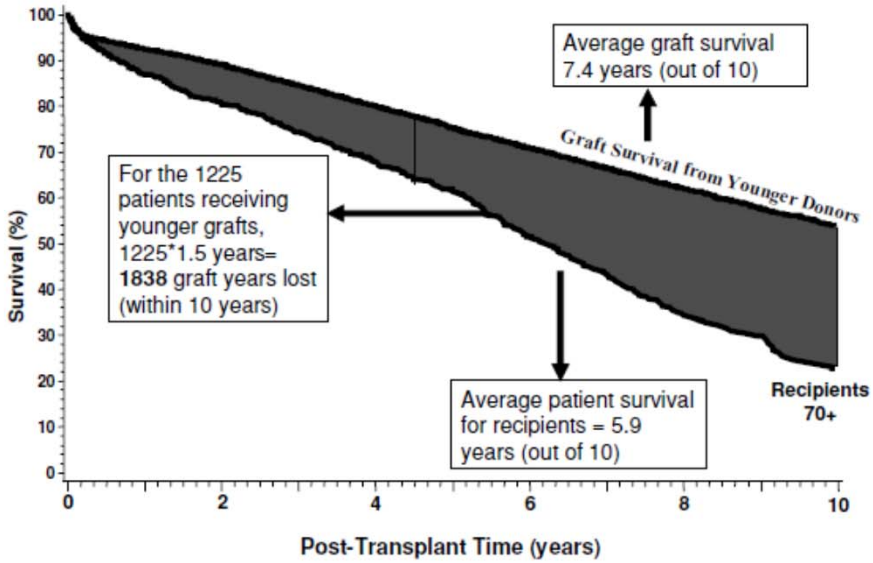
Crafter S et al. *Transplantation* 2007;83: 1411–1415

Young donor kidneys do not attain maximal potential survival in older recipients

Patient survival of 15-50 year-old donor kidneys



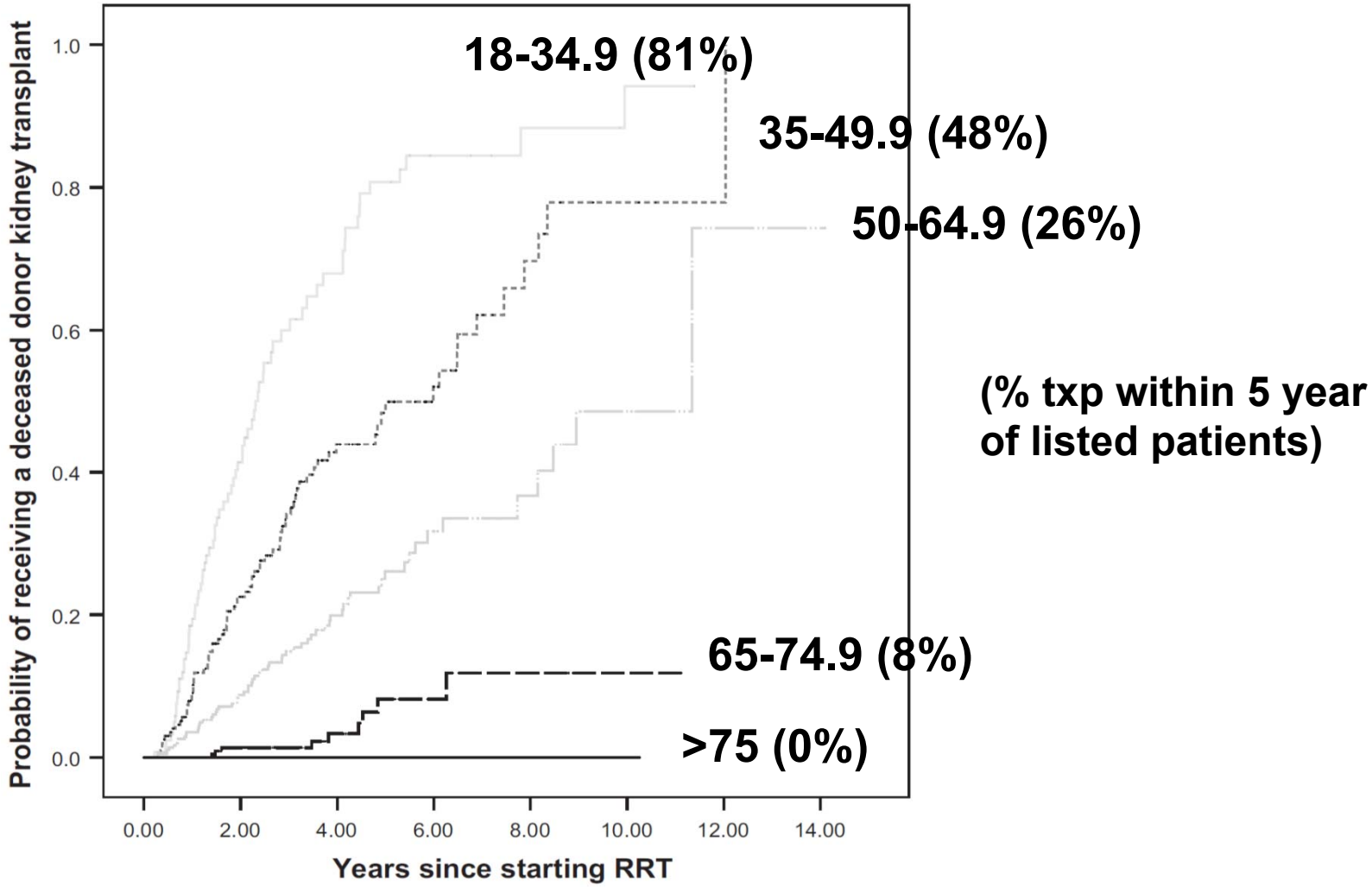
Functioning grafts loss to excess patient death in older recipients



- Age matching model:
  - → Increase of life expectancy by 27.1 months in younger recipients
  - → Reduction of life expectancy by 18.8 months in older recipients

Meier-Kriesche AJT 2005; 5:1725

Stevens K (NDT): Deceased donor transplantation in the elderly—are we creating false hope?

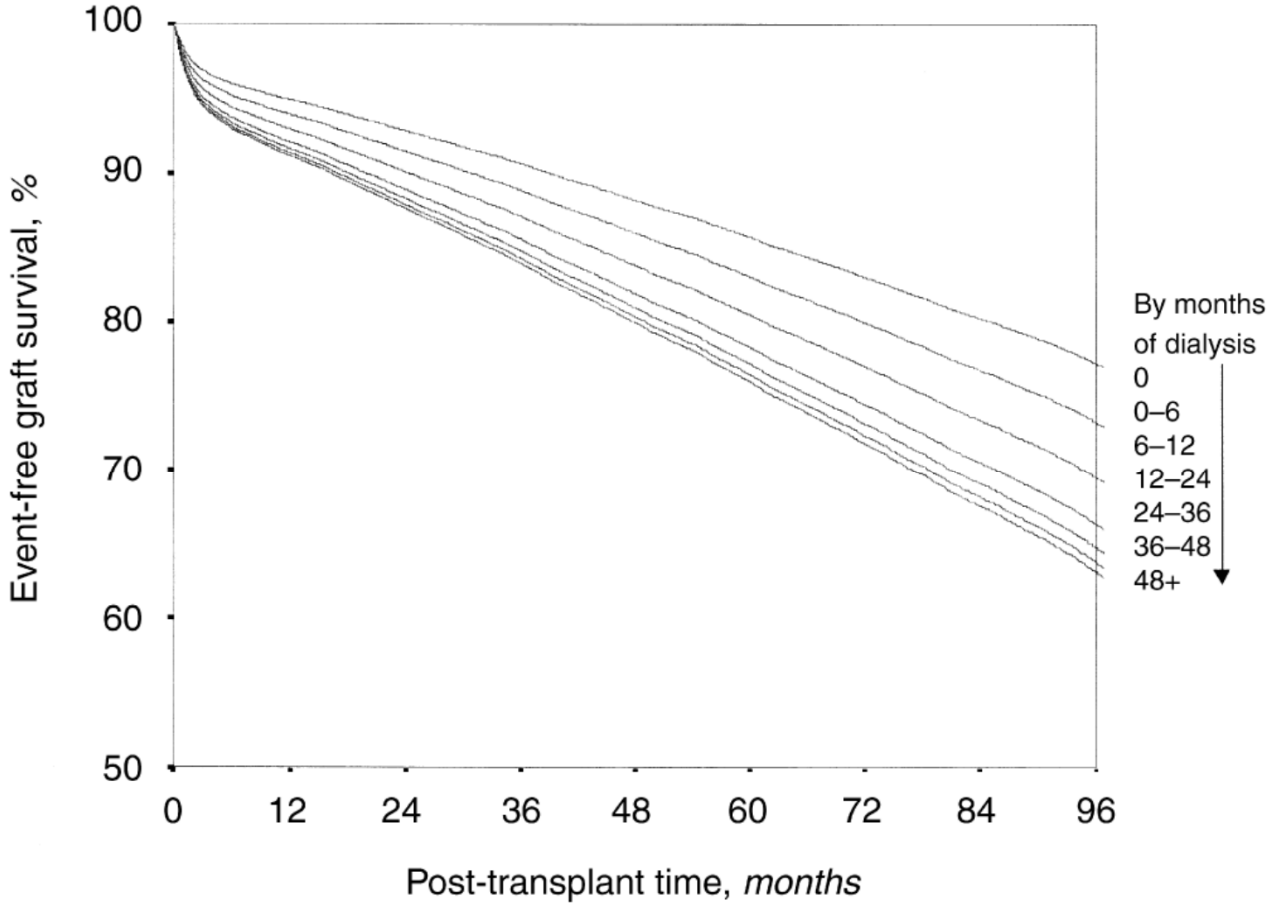


(% txp within 5 year of listed patients)

Stevens K NDT 2011(UNOS: Schold cJASN 2009, Schaeffner E cJASN 2010)

Universitair Ziekenhuis Brussel

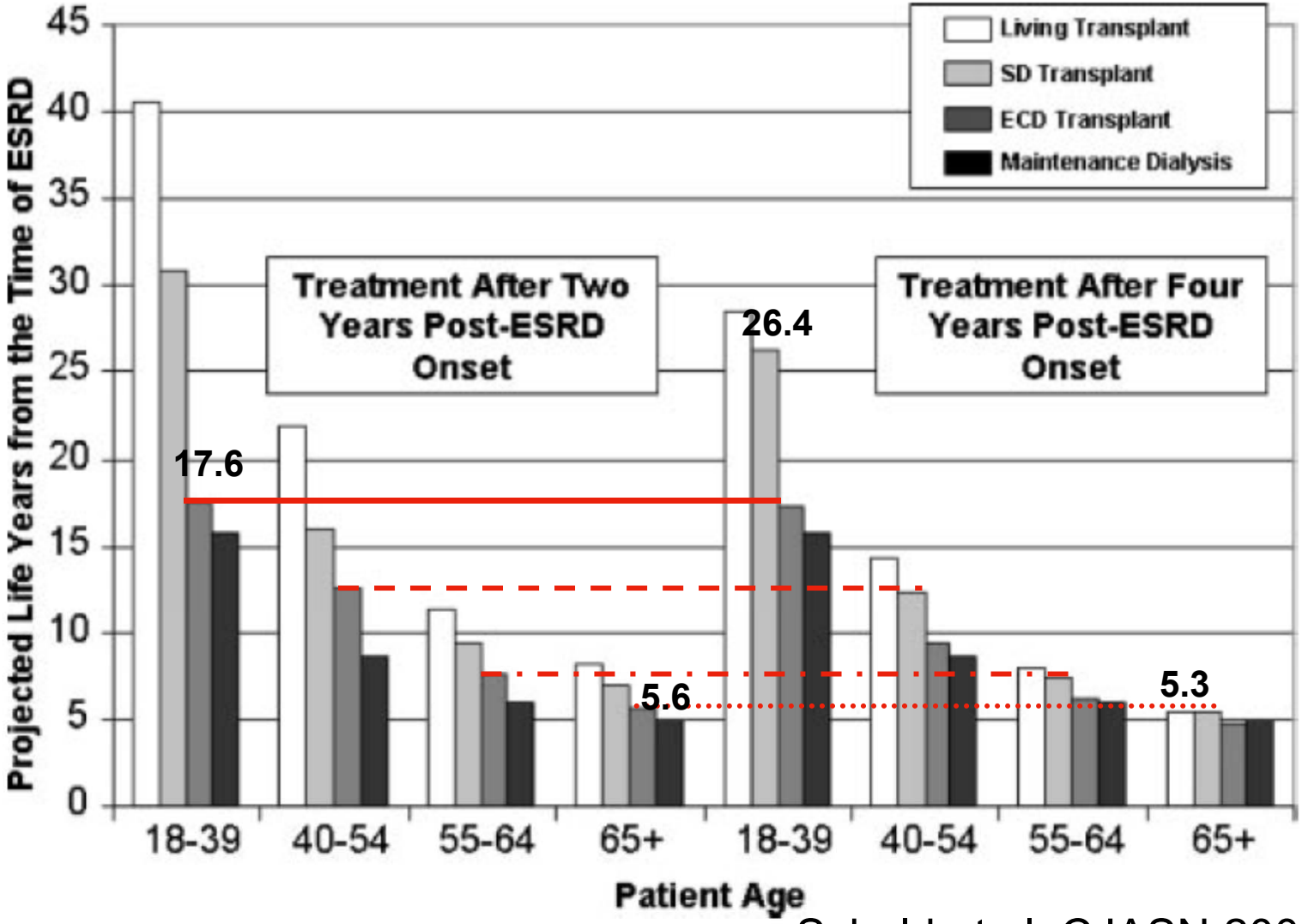
Duration of dialysis is a potent predictor for adverse outcomes after transplantation



Meier-Kriesche HU et al. KI 2000

Universitair Ziekenhuis Brussel

Older recipients might benefit from earlier transplantation with extended criteria kidneys



Schold et al. CJASN 2006;1:532

Universitair Ziekenhuis Brussel

Organ allocation in older recipients

- Need for speed
  - → Rapid evaluation (preemptive listing)
    - Avoid medical complications that preclude listing
  - → Rapid transplantation
    - Avoid death on the WL or becoming NT
- Need for a larger donor pool
  - → Increased use of older donors against shorter WT
  - → Improvement of outcomes with ECD kidneys
    - Machine perfusion
    - Dual kidney transplantation
    - Use of CNI- free immunosuppression (Belatacept)
  - → Living donor transplantation
    - Younger recipients (leaves deceased donor kidneys in the pool)
    - Older recipients with older LD kidneys

Older recipients experience less severe acute rejection episodes

Association of recipient age and the severity of first year acute rejection

Recipient age	First year acute rejection[1]				
	no AR	fully reversible AR	partially reversible AR	Irreversible AR	Total
>=55	173	13	8	0	194
	89.18%	6.70%	4.12%	0.00%	100%
<55	545	88	83	18	734
	74.25%	11.99%	11.31%	2.45%	100%
Total	718	101	91	18	928
	77.37%	10.88%	9.81%	1.94%	100%

chi^2 (3df) = 21.2; P<0.0001

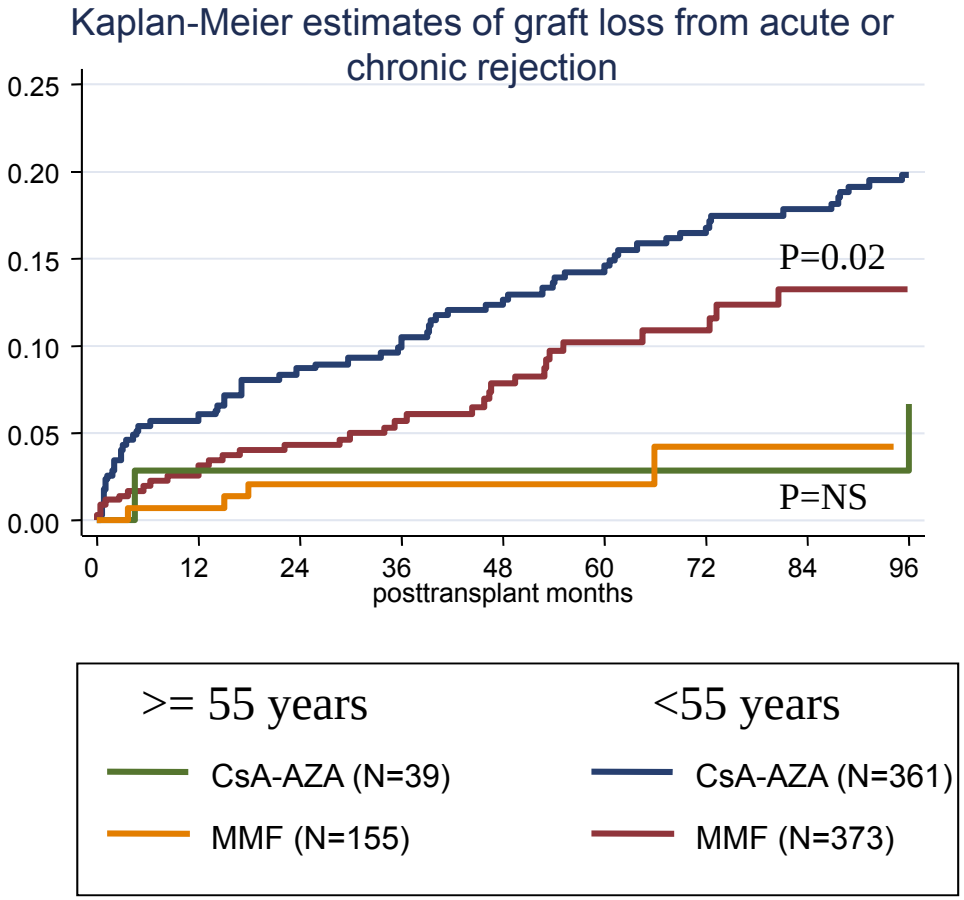
1. In case a patient experienced more than one episode of acute rejection during the first year the most severe grade is recorded.

Effect of older age on severe acute rejection
RR 0.3 (95%CI 0.15 to 0.6; P< 0.0001)

Wissing et al ATC 2009

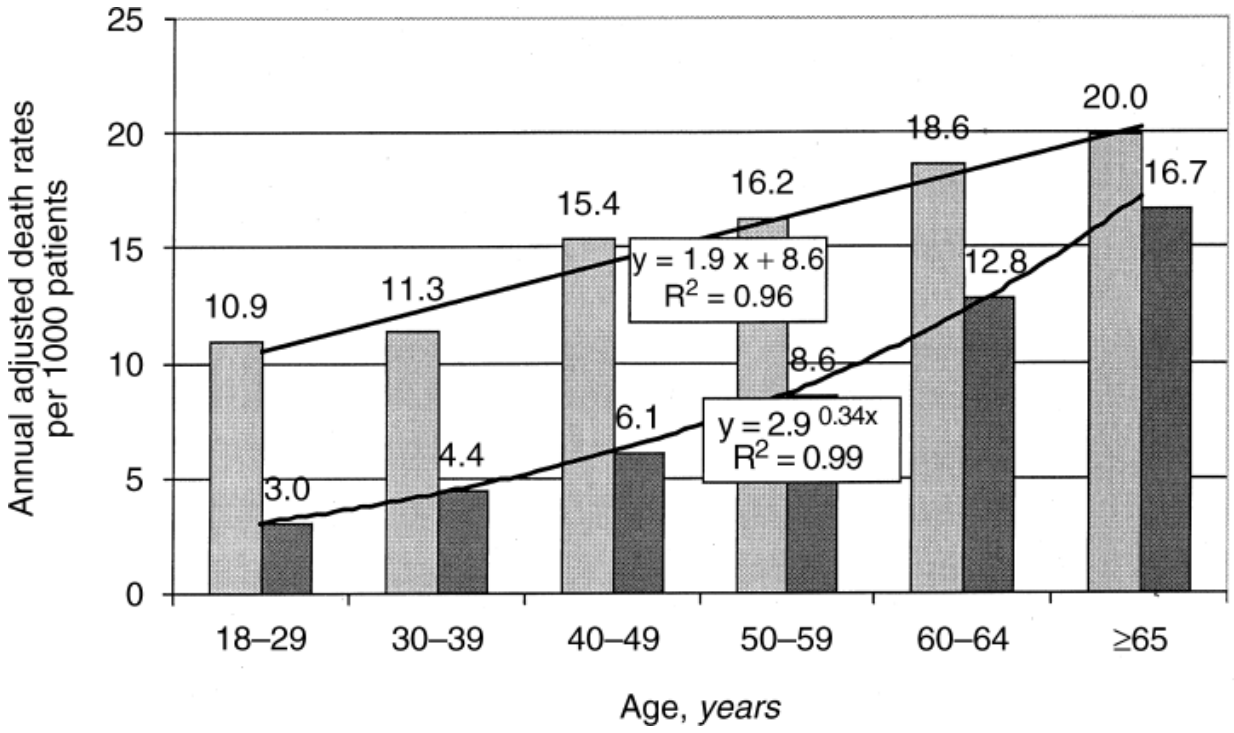
Universitair Ziekenhuis Brussel

Graft loss from acute or chronic rejection is rare in older transplant recipients



Wissing et al ATC 2009

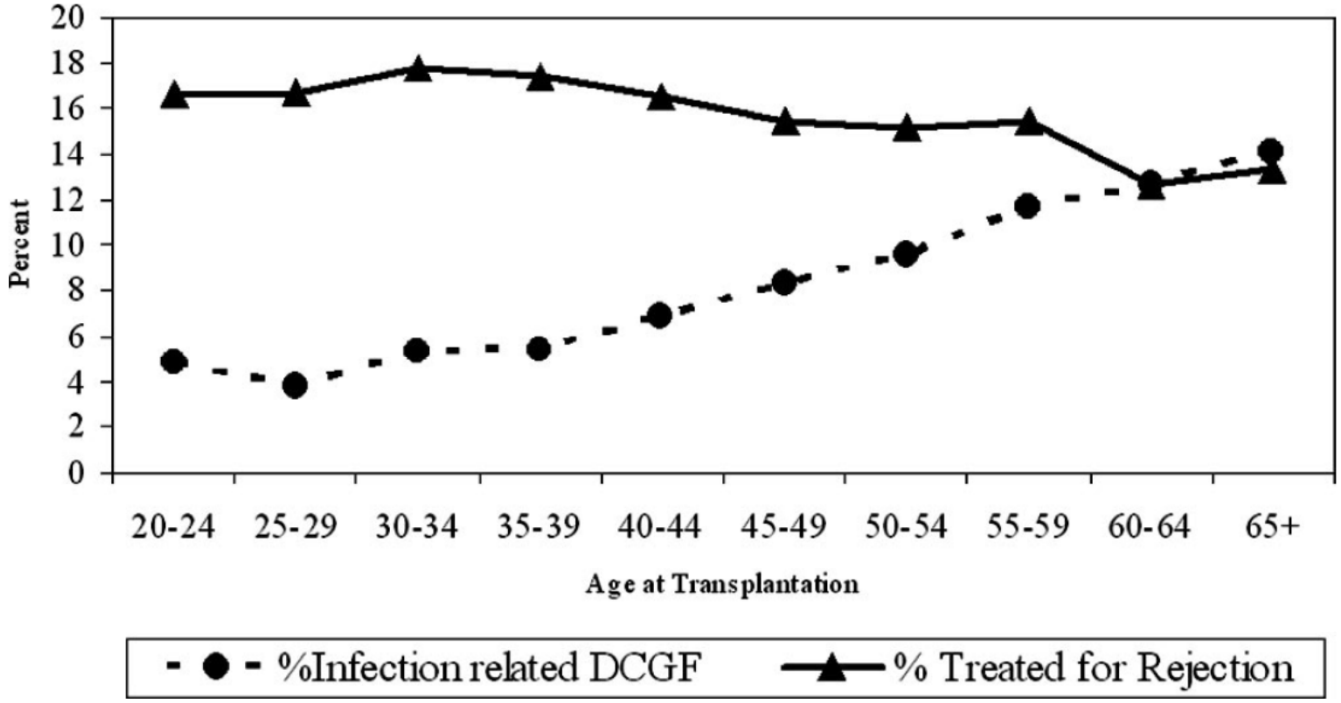
Death from infection increases exponentially with age after renal transplantation



Meier-Kriesche H. Kidney Int. 2001; 59:1539

Universitair Ziekenhuis Brussel

Increasing graft loss from infectious causes in older transplant recipients



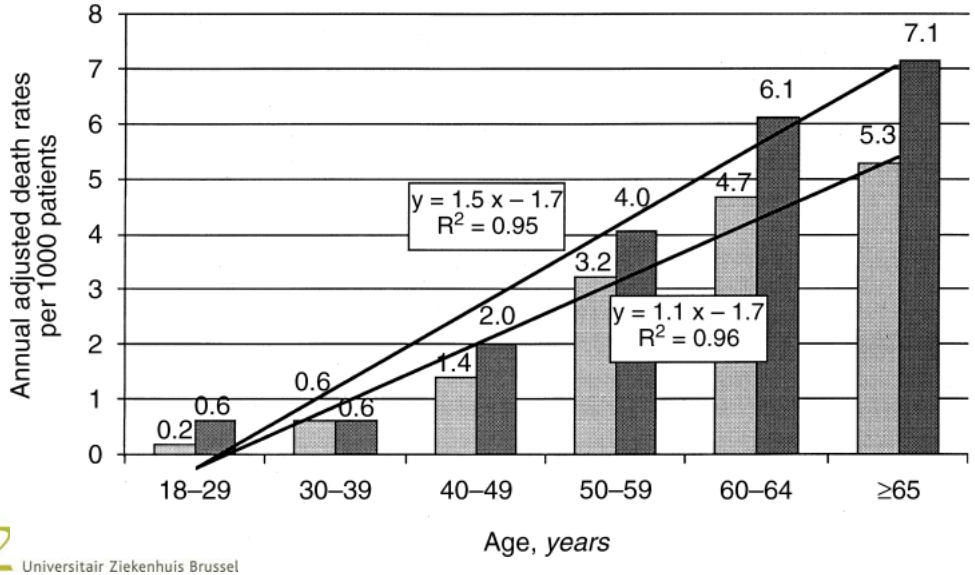
- **Age**, urological complications, induction therapy, BK polyomavirus infection and acute rejection are associated with infectious- related graft failure

Parasuraman et al Transplantation 2011;91:94

Universitair Ziekenhuis Brussel

Risk of cancer is increased in renal transplant recipients

Age	Any Non-Skin			Skin		
	Hazard	Lower	Upper	Hazard	Lower	Upper
0-17	1.217	0.981	1.511	0.084	0.012	0.6
18-34	1			1		
35-49	1.25	1.126	1.388	3.466	2.645	4.542
50-64	1.972	1.78	2.184	10.143	7.825	13.146
65+	2.972	2.644	3.341	19.032	14.604	24.803

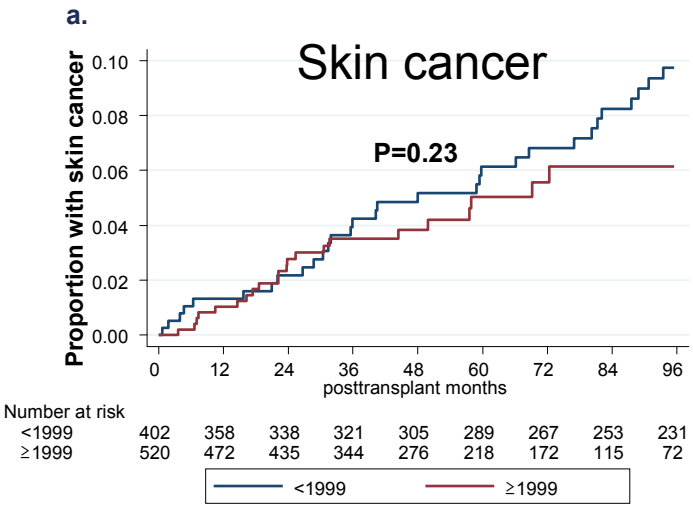


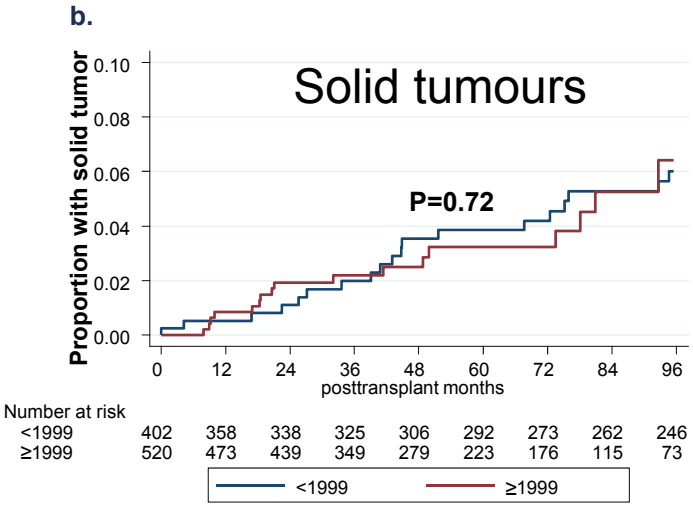
USRDS ADR 2002 www.usrds.org

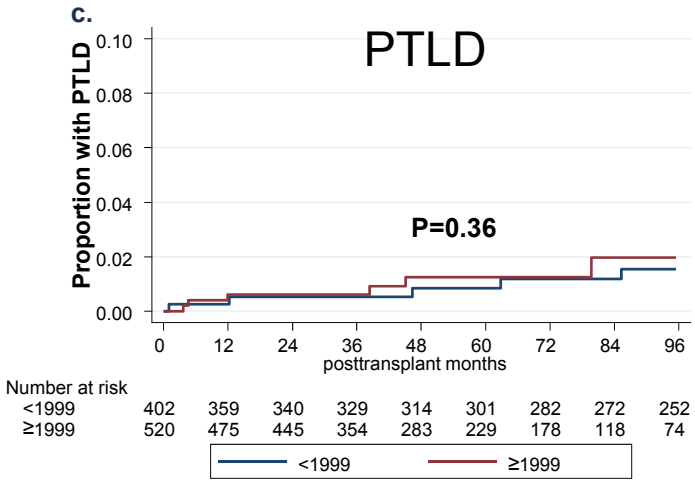
Meier-Kriesche H. Kidney Int. 2001; 59:1539

Universitair Ziekenhuis Brussel

Potent new immunosuppressive regimens to not increase the risk of post- transplant malignancy







<1999: CsA-AZA; N=402; mean age at transplantation 39.4 years
≥1999: CNI-MPA; N=520; mean age at transplantation 46.8 years

Braconnier P et al. NDT 2011

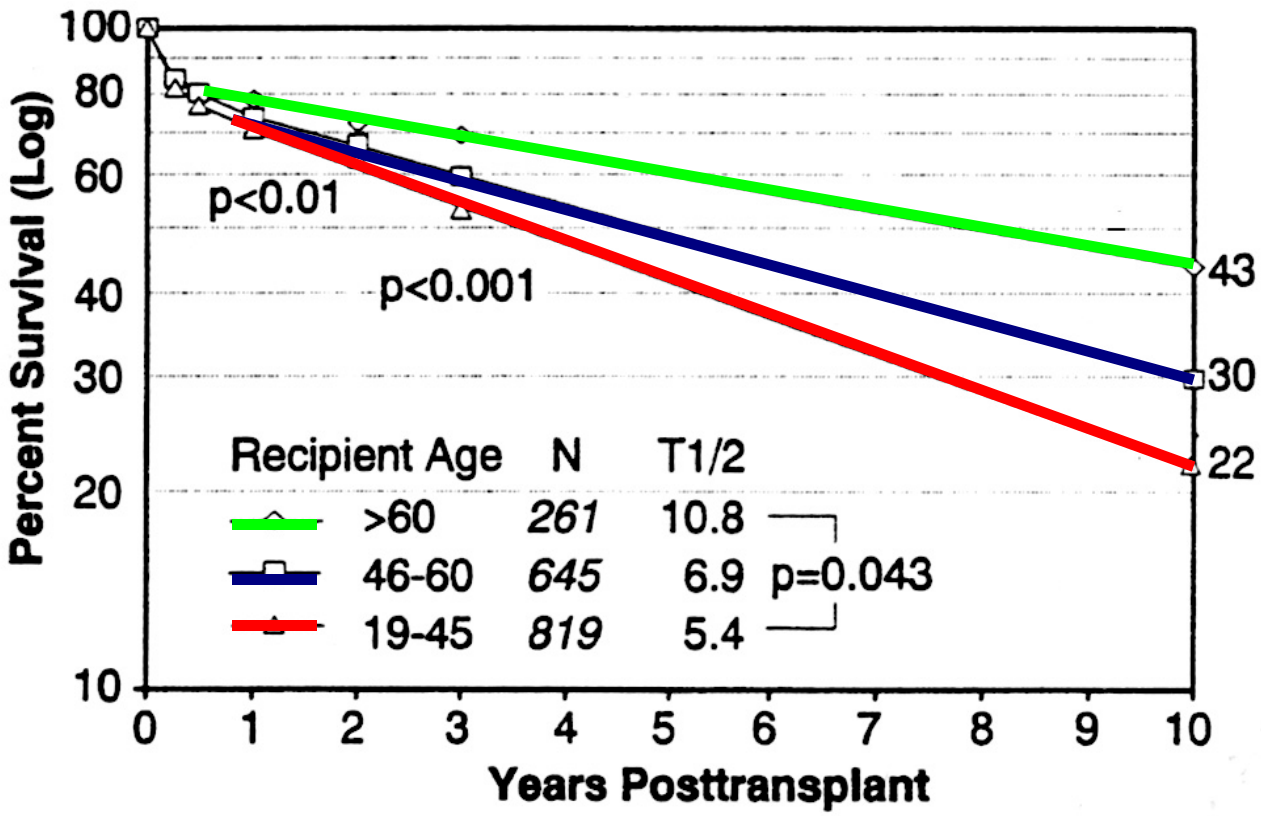
Universitair Ziekenhuis Brussel

Conclusions

- Renal transplantation improves survival and quality of life in older patients with end- stage renal disease.
- Transplantation of a significant proportion of the older dialysis population requires to increase the donor pool to avoid longer waiting times
- Older recipients require rapid evaluation and transplantation in order to avoid medical complications that preclude transplantation and death on the waiting list.
- Older patients have a high incidence of infections and cancer but rarely develop severe acute rejection and graft loss from rejection. Immunosuppression minimization studies targeting this population are urgently needed.

Kidneys from Deceased Donors >60 yrs

censored Graft Survival according to Recipient Age

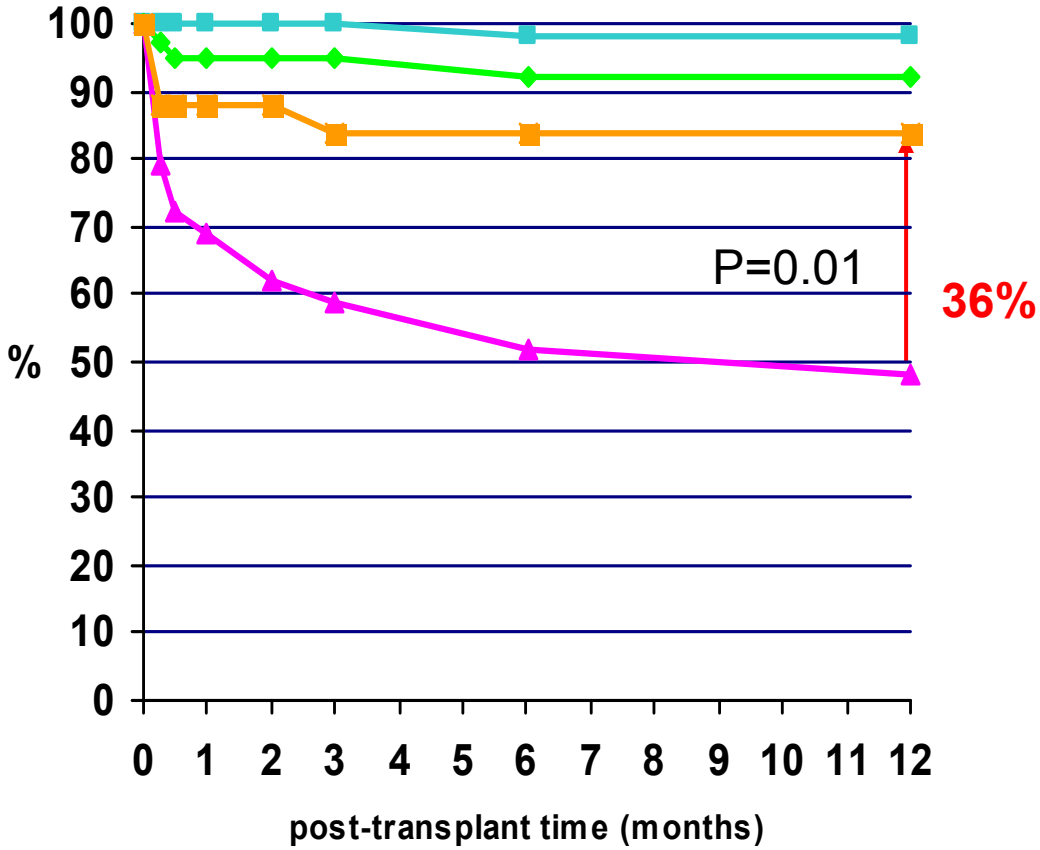


Cecka JM et. Transplant Proc 27:802,1995

Idem: Hariharan Transplantation 1997; Waiser NDT 2000, Moers Transplantation 2009

Universitair Ziekenhuis Brussel

ECD subanalysis: Death- censored graft Survival (1 year) according to DGF



CS and no DGF [n=56]

CS and DGF [n=29]

MP and no DGF [n=60]

MP and DGF [n=25]

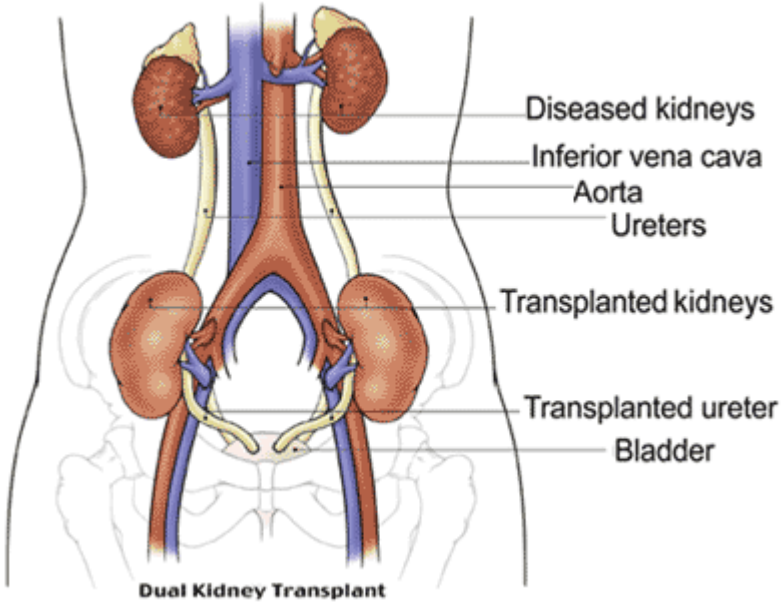
- Death-censored graft survival at 12 months
  - DGF: MP 85% vs CS 41% (P=0.01)
  - No DGF: MP 94% vs CS 97% (P=NS)
  - Overall: MP 92% vs CS 80% P=0.02)

Treckmann et al. submitted

Universitair Ziekenhuis Brussel

Dual kidney transplantation

- Transplantation of two kidneys from the donor in the same recipient.



Many kidneys become discarded
•>60-65 years
•GFR <70-60 ml /min
•Fear to transplant insufficient nephron mass
•Fear of underlying structural damage
•Donors rejection

Universitair Ziekenhuis Brussel

Which donors to select for dual transplantation

- Remuzzi model (NEJM 2006)
  - → Donors > 60
  - → Core biopsy during procurement
  - → Histologic evaluation (0- ')
    - Arteries
    - Glomeruli
    - Tubules
    - Interstitium
  - → Score 0- 3: Single kidney Transplant
  - → Score 4- 6: dual kidney transplant
  - → > 6 discarded

Histological scoring of the donor

Score 2 — **Single**

Score 5 — **Dual**

Score 7 — **Discard**

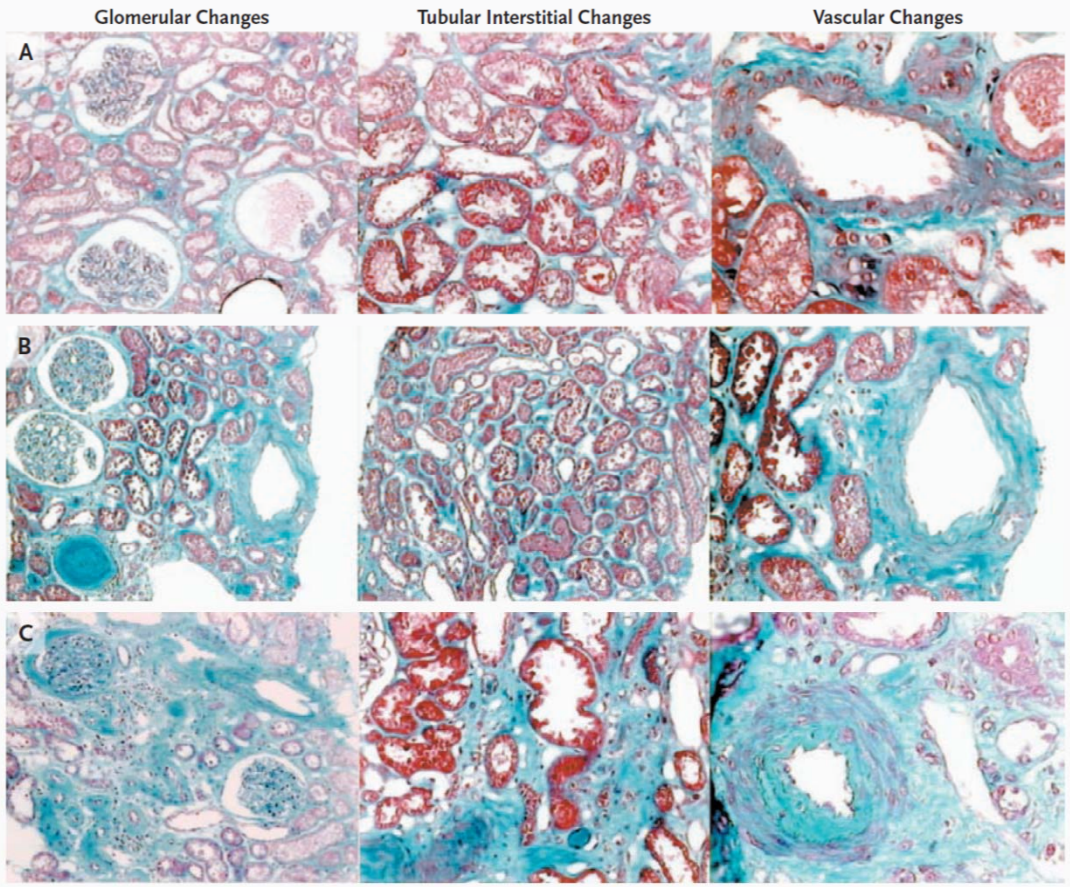
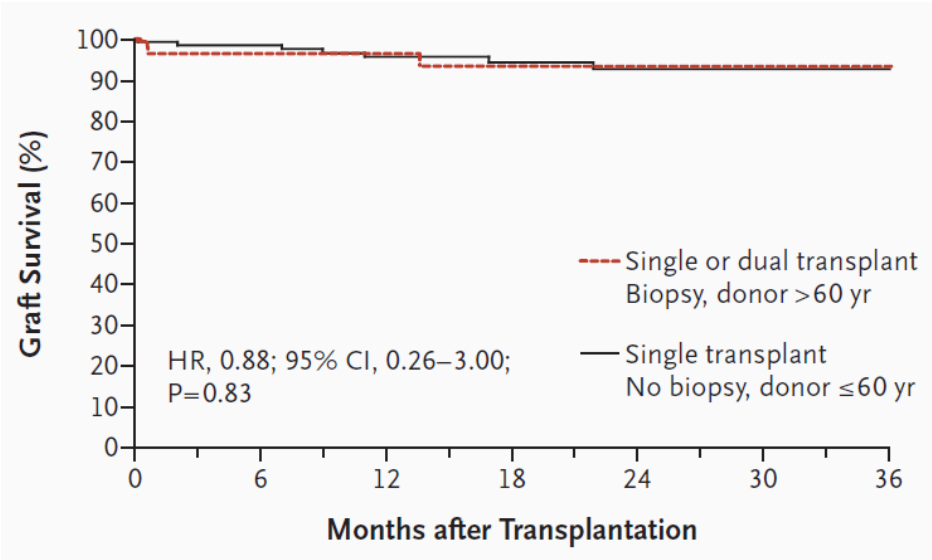
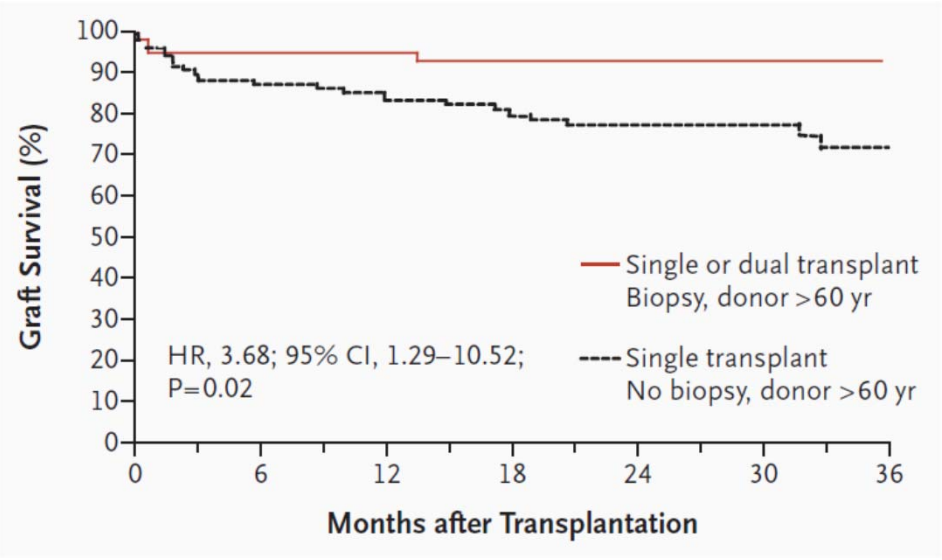


Figure 1. Representative Light Micrographs of Kidney Sections Illustrating the Histologic Scoring Criteria.
Panel A shows three sections of a kidney from a 65-year-old male donor of a single transplant (global score, 2). Panel B shows three sections of a kidney from a 64-year-old male donor of a dual transplant (global score, 5). Panel C shows three sections of a discarded kidney from a 65-year-old man (global score, >7). In each panel, the left section mainly shows glomerular changes, the middle section tubular interstitial changes, and the right section vascular changes.

Universitair Ziekenhuis Brussel

Improved outcome of histologically evaluated older donor kidneys

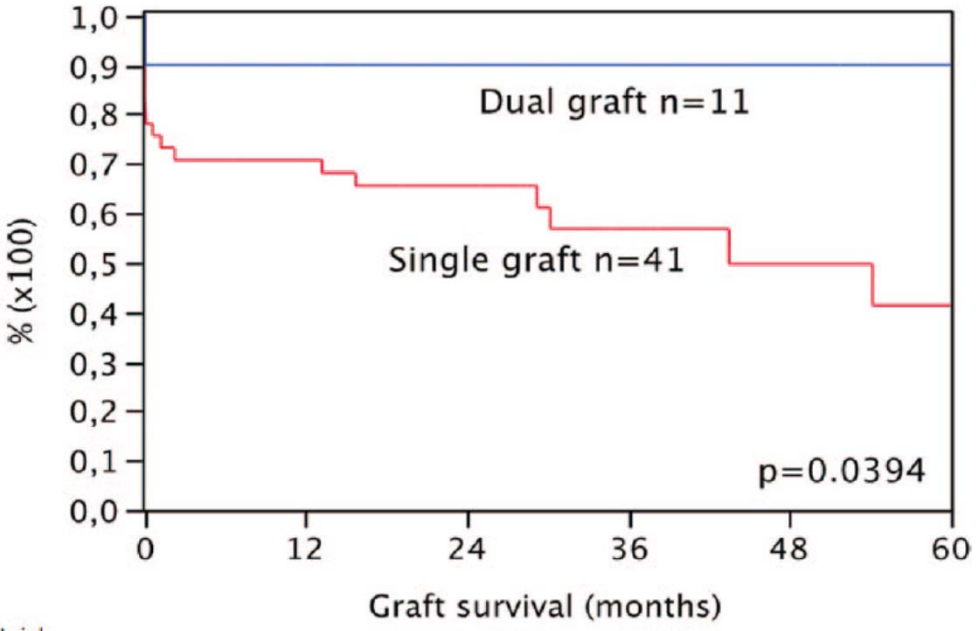




Remuzzi et al NEJM 2006

Universitair Ziekenhuis Brussel

Dual kidney transplantation is probably warranted systematically in very old donors (> 75 years)



At risk						
Months	0	12	24	36	48	60
Single graft	41	28	24	11	8	6
Dual graft	11	10	8	8	8	6

FIGURE 1. Kaplan-Meier survival analysis for dual graft and single graft kidney transplantation with donor grafts more than or equal to 75 years.

Gallinat et al. Transplantation 2011

Rationale of the ET Senior Program (ESP)

•Rapid transplantation of elderly patients given the high mortality on the waiting list.
•Efficient use of elderly kidneys → match life expectancy with expected graft survival.
•Match lower metabolic demand with lower excretory capacity.
•No shipping of organs. Short CIT to reduce risk of DGF and acute rejection.
•Local use in order to promote local procurement of donors over 65 years.
•No prospective HLA matching as patients are considered at low immunological risk.

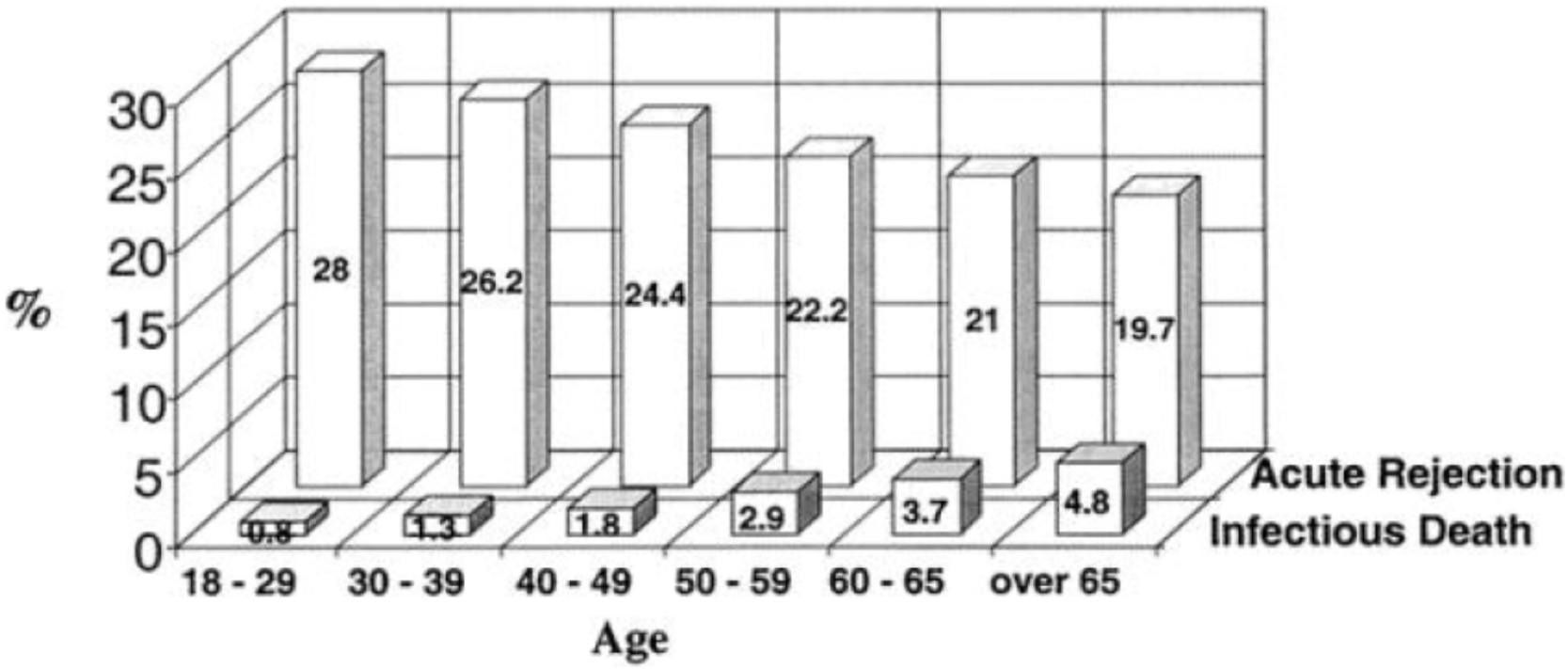
Eurotransplant: transplantation of ≥ 65 year old recipients between 01/2007 to 09/2010

	AT	B	CRO	D	NL	SL	**Total**
ESP	170	71	43	1850	191	2	**2327**
ETKAS	171	240	36	666	167	14	**1294**
Total	**341**	**311**	**79**	**2516**	**358**	**16**	**3621**
% ESP	**50**	**23**	**54**	**74**	**53**	**13**	**64**
ETKAS (donor age):							
0-64	90	194	4	239	137	14	**678**
65+	81	46	32	427	30		**616**
Total +65 donor	251	117	75	2277	221	2	**2943**
% +65 R & +65 D	**74**	**38**	**95**	**91**	**62**	**13**	**81**

Personal communication from Dr Jan de Boer Eurotransplant

Universitair Ziekenhuis Brussel

Lower incidence of acute rejection and higher incidence of death from infection in older transplant recipients during the first 6 months after transplantation



Meier-Kriesche Transplantation 2000; 69:885

Universitair Ziekenhuis Brussel