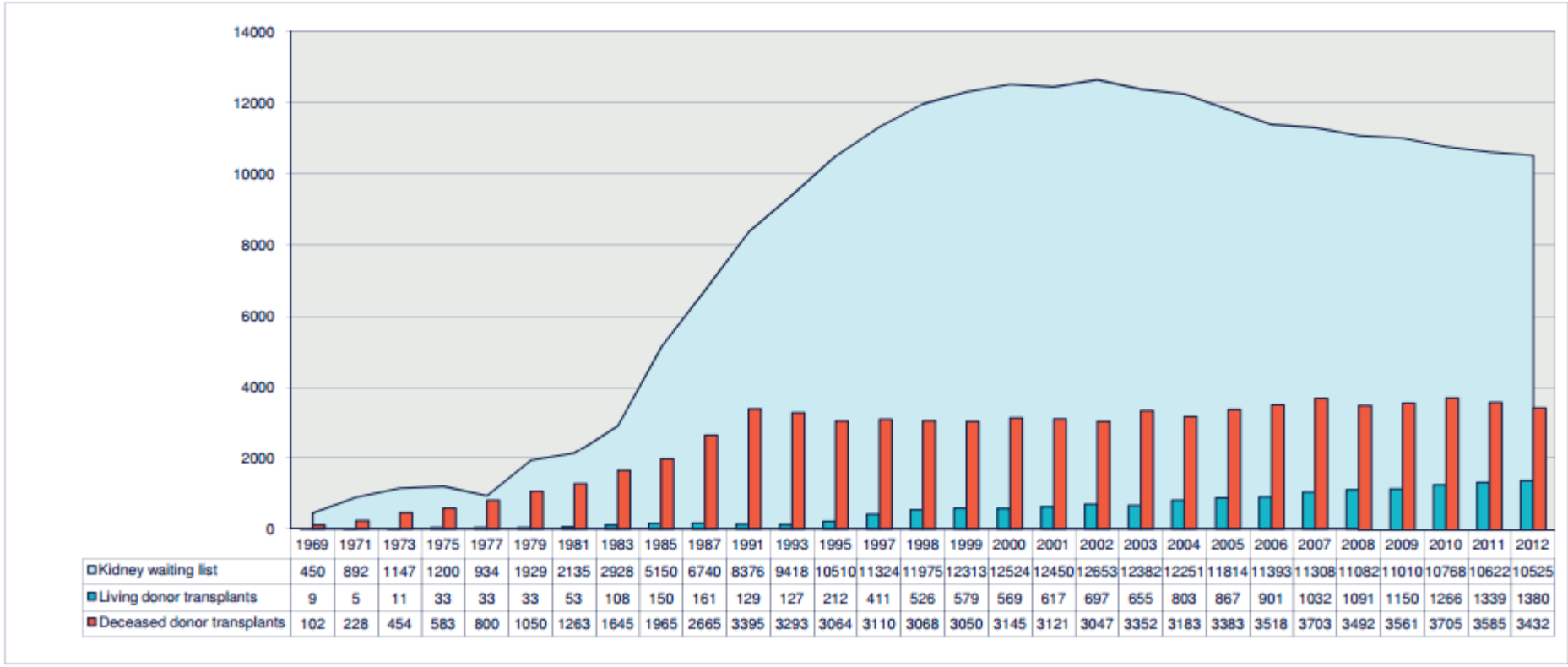
Donorpooluitbreidende maatregelen: levende donatie, cross-overs transplantatie, dual kidney transplantation, donation after cardiac death (DCD)

Prof. Dr. Karl Martin Wissing
Universitair Ziekenhuis Brussel
kwissing@uzbrussel.be

Universitair Ziekenhuis Brussel

Figure 5.5 Dynamics of the Eurotransplant kidney transplant waiting list and transplants between 1969 and 2012

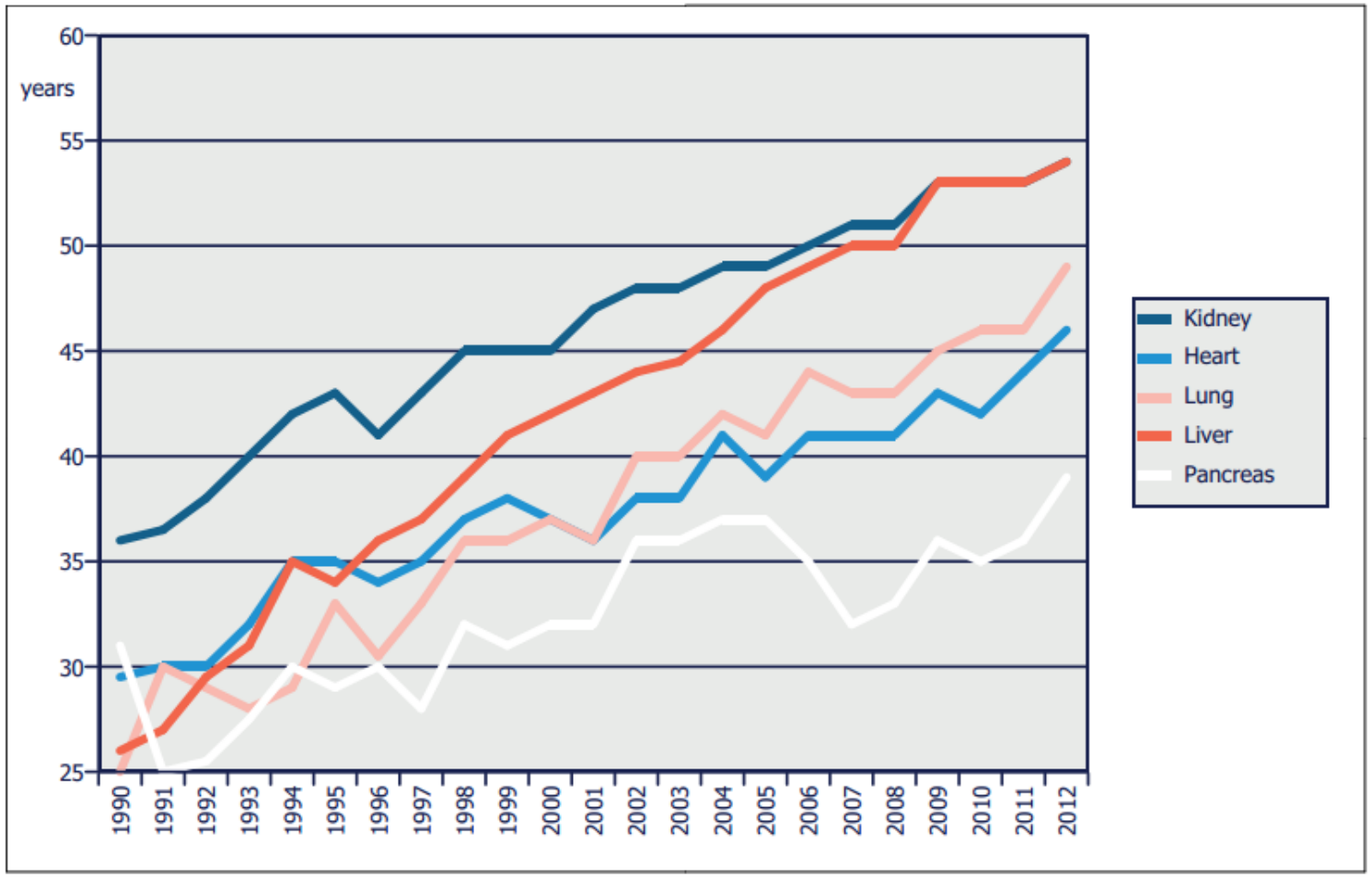


	1969	1971	1973	1975	1977	1979	1981	1983	1985	1987	1991	1993	1995	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Kidney waiting list	450	892	1147	1200	934	1929	2135	2928	5150	6740	8376	9418	10510	11324	11975	12313	12524	12450	12653	12382	12251	11814	11393	11308	11082	11010	10768	10622	10525
Living donor transplants	9	5	11	33	33	33	53	108	150	161	129	127	212	411	526	579	569	617	697	655	803	867	901	1032	1091	1150	1266	1339	1380
Deceased donor transplants	102	228	454	583	800	1050	1263	1645	1965	2665	3395	3293	3064	3110	3068	3050	3145	3121	3047	3352	3183	3383	3518	3703	3492	3561	3705	3585	3432

Eurotransplant Annual Report 2012

Evolution of the median age of organ donors in the Eurotransplant region

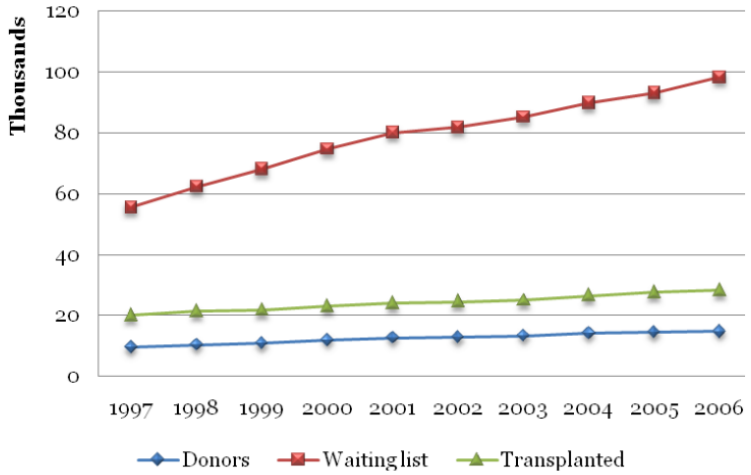
Figure 4.2 Median age of deceased donors in Eurotransplant, used for a transplant

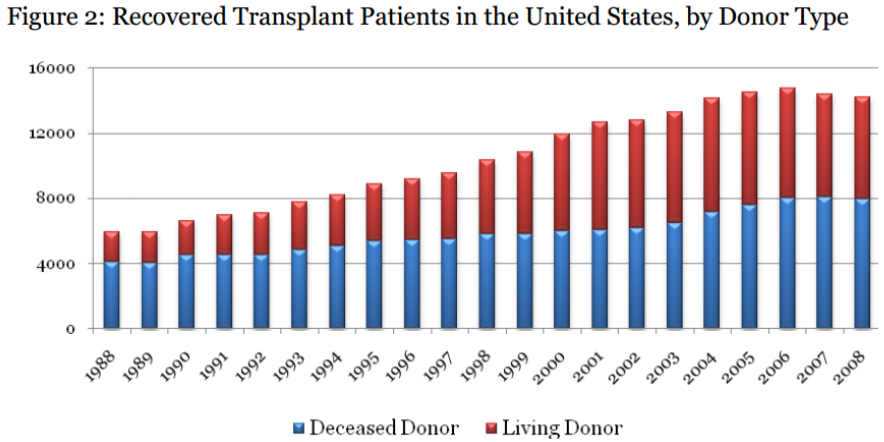


Eurotransplant Annual Report 2012

Universitair Ziekenhuis Brussel

Increase of patients on the waiting list results in increased used of living donor transplantation





USRDS database

Reasons to promote living donor transplantation

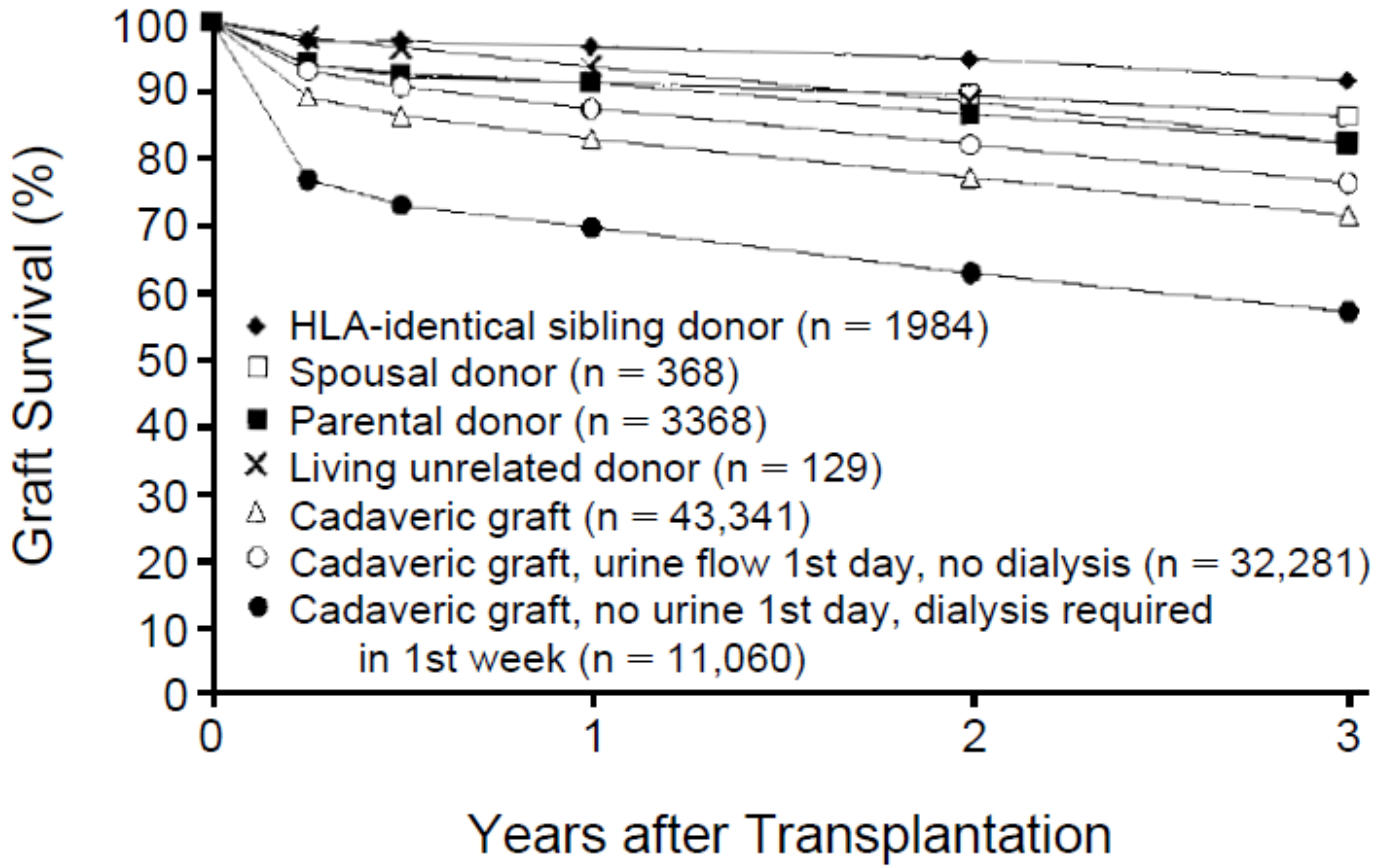
- Recipient:

1) Better patient survival than on dialysis or after transplantation with deceased donor kidney
2) High quality graft without injury due to brain death. Better graft function and graft survival.
3) Possibility of preemptive transplantation avoiding access creation and initiation of dialysis.
4) Little impact of HLA matching on outcomes after transplantation (Emotionally related but genetically unrelated donors)

- Collectivity:

1) Living donation leaves one kidney in the pool with reduced WT for the other patients.

HLA mismatches have only a limited impact on living donor kidney transplantation



Terasali NEJM 1995

Risk of donation to the donor

- Donor:
  → Donor needs complete medical and psycho-social workup to minimize the risk of a detrimental health effect through donation.

Risk of donation to the donor

- Early peri-operative complications:
  - → Atelectasis
  - → Pneumothorax
  - → Pneumonia
  - → Urinary tract infection
  - → Wound complication
  - → Deep vein thrombosis with or without pulmonary embolism
  - → **Death** (very rare ± 3/10000)
- Incidence of complications variable according to reports. Suggestion for systematic recording using standardized criteria (Tan et al Transplantation 2006; 81:1221)

Late complications of donation: Death and ESRD

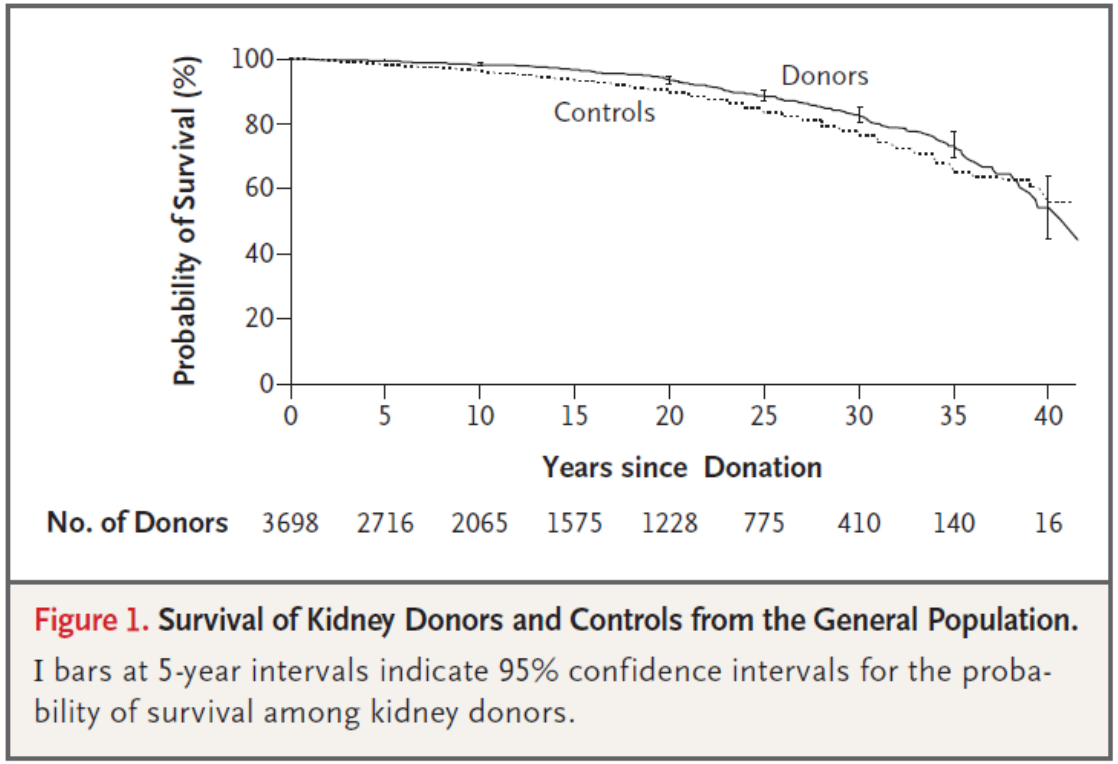


Figure 1. Survival of Kidney Donors and Controls from the General Population.
I bars at 5-year intervals indicate 95% confidence intervals for the probability of survival among kidney donors.

Ibrahim et al. NEJM 2009

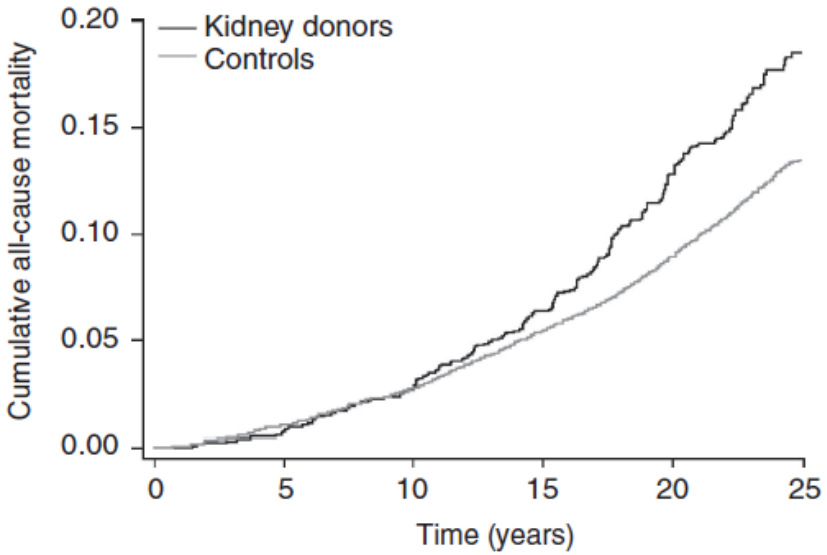


Figure 2 | Cumulative mortality risk in kidney donors and controls, adjusted for year of donation. Controls are matched to donors for age, sex, systolic blood pressure, body mass index, and smoking status.

Mjoen G et al. Kidney Int 2013

Hazards ratios of donors vs controls

- All cause mortality: 1.3 (1.11-1.52; P=0.001)
- CV death: 1.4 (1.03-1.91; P=0.03)
- ESRD: 11.4 (4.4-29.6; P<0.001)

Only 9/2269 donors in dialysis but incidence much higher than the expected

Relation between number of deceased donors and living donation

Table 4.5(ii) Living donor kidney transplants - kidney-only - 2009

Kidney-only	(A)	(B)	(HR)	(D)	(NL)	Total	%
Related	39	31	8	337	197	**612**	**53.3 %**
Non-related	30	18	5	263	220	**536**	**46.7 %**
Total	**69**	**49**	**13**	**600**	**417**	**1148**	**100.0 %**
Deceased donation rates (pmp)	**25.4**	**25.7**		**14.6**	**13.0**		

- Low donation rates of deceased donor kidneys increase living donation
- Inability to obtain a deceased donor kidney is also an incitement to buy a kidney and to obtain a transplantation in another country.
- Transplantation tourism is a problem in many countries
  - → "Industrial" transplantation in some developing countries
  - → Use of organs from executed prisoners (China)
  - → Influx of patients with ESRD into developed countries to obtain life-saving treatment with dialysis and transplantation

Organ traffic and transplant tourism is a crime !
Declaration of Istanbul on Organ Trafficking and Transplant Tourism 2008

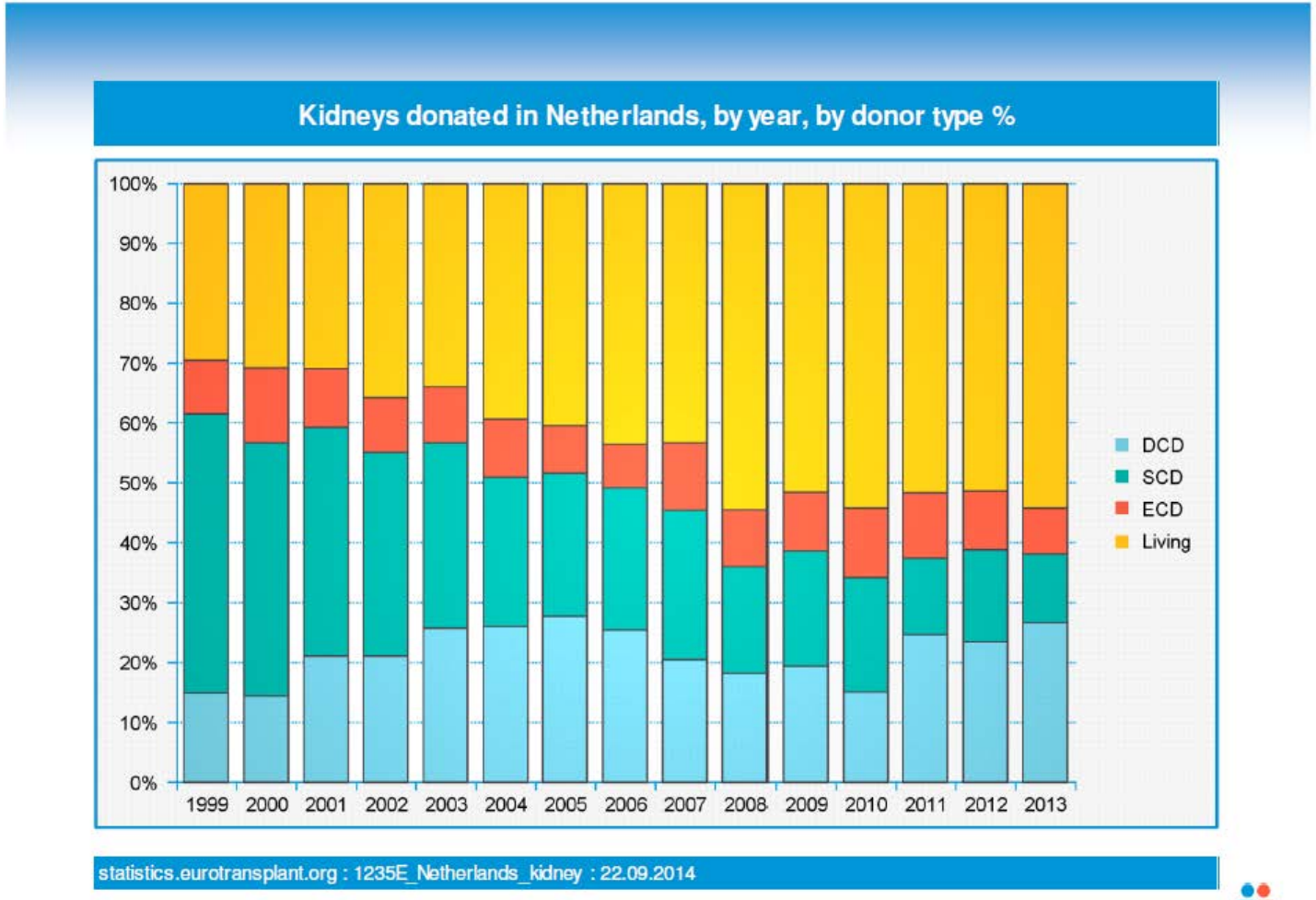
Philippines

Pakistan

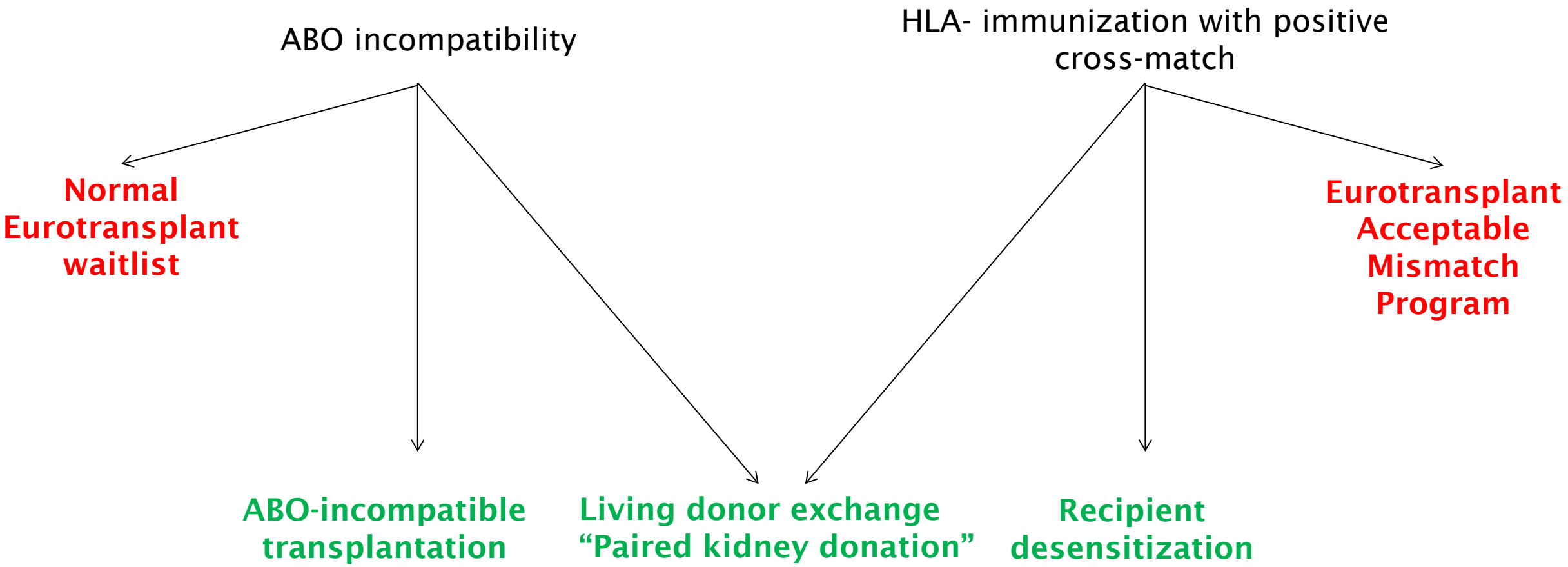
<u>Protection of donor rights and welfare</u>

- Autonomous decision by the donor
  Crucial importance of informed consent free of pressure
- Donation by adults (personal opinion)
- Review of the file by a patient advocate
- Indirect benefit to the donor

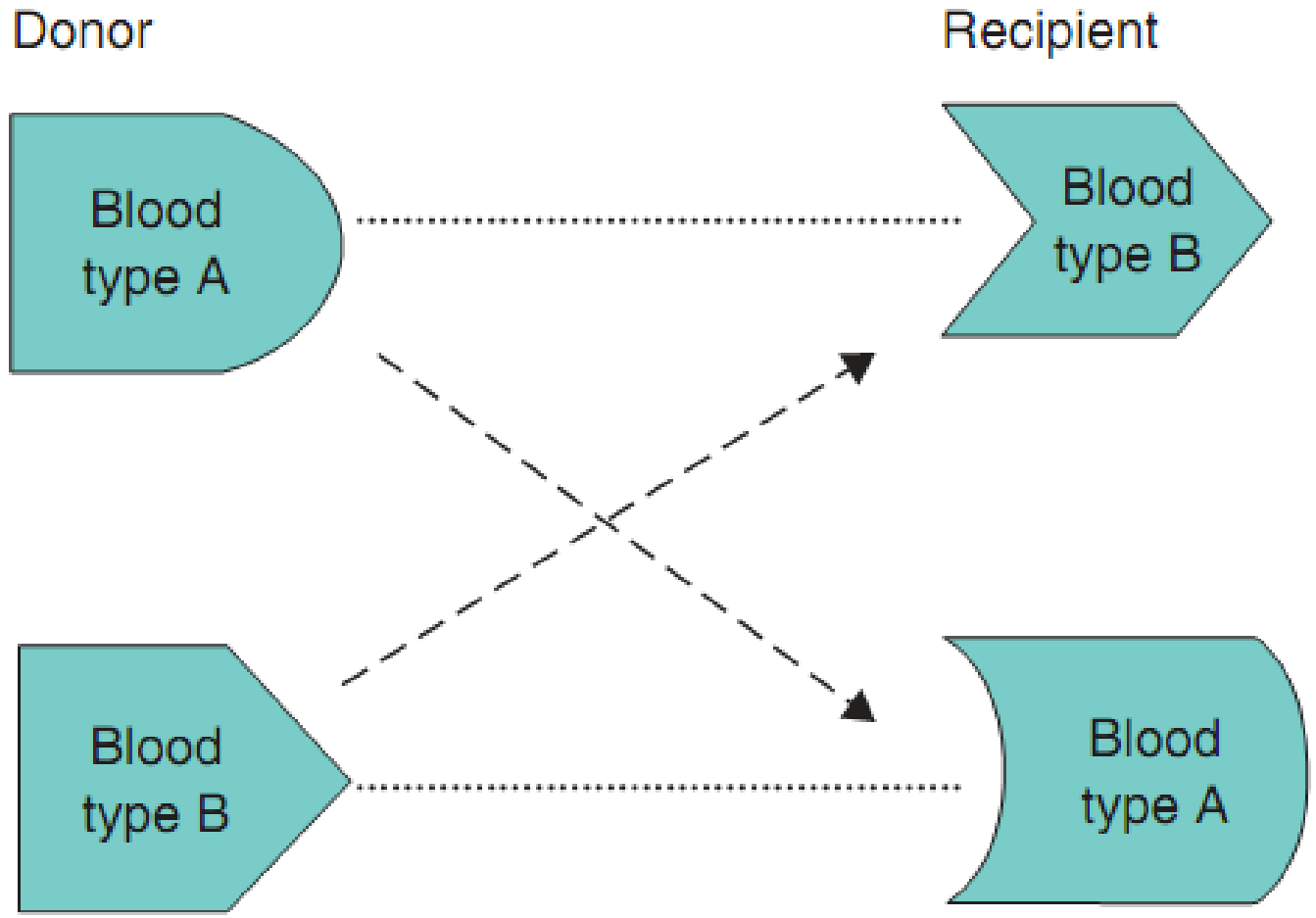
Increase in living donor transplantation does not necessarily increase the donor pool



Failure to find a matching living donor and potential solutions



Classical cross-over kidney transplantation – Paired kidney donation



a Conventional paired donation

(groupes A et B)

Problem of patients with O blood group accumulating in cross-over programs.

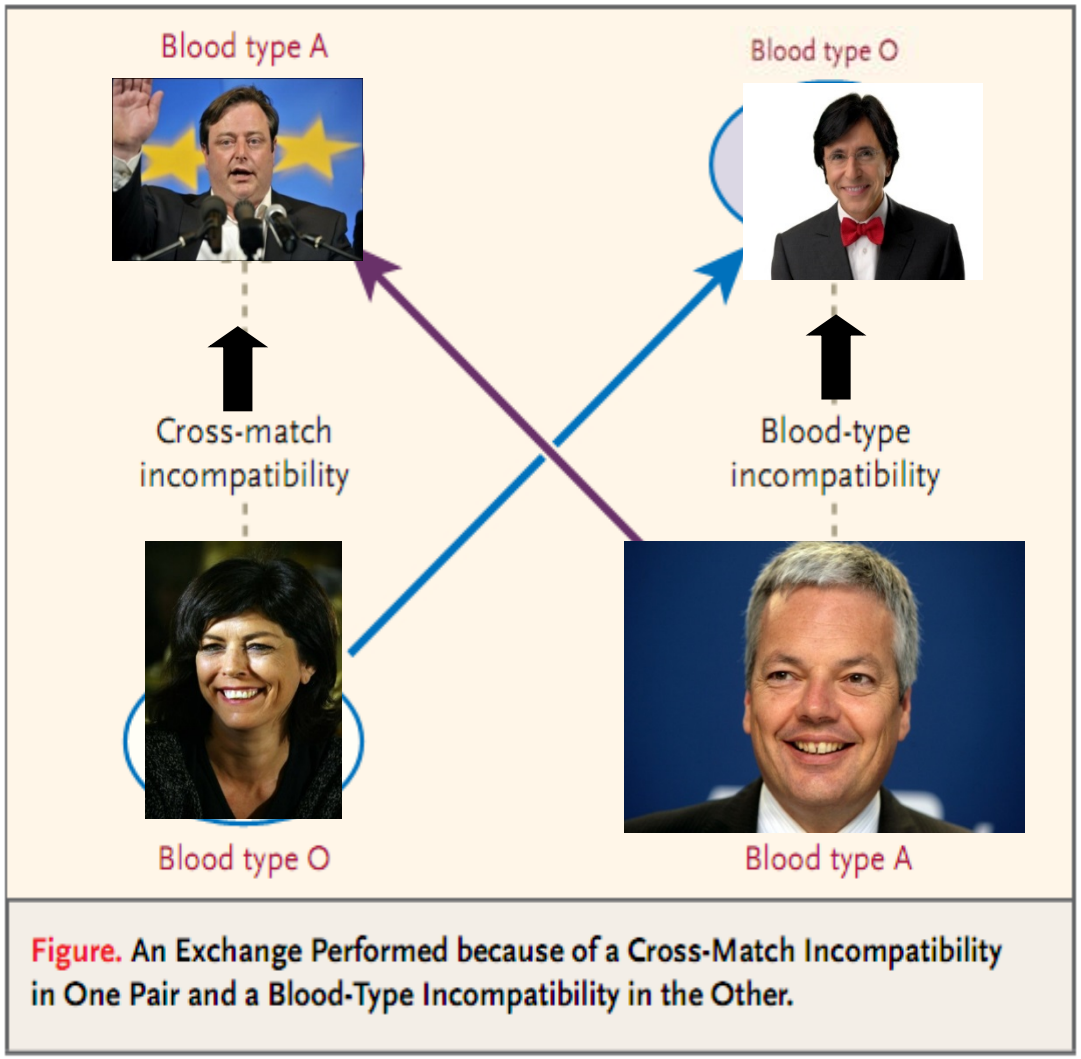


Figure. An Exchange Performed because of a Cross-Match Incompatibility in One Pair and a Blood-Type Incompatibility in the Other.

Delmonico et al NEJM 2004
Adapted by D. Abramowicz

Importance of large pools of pairs for optimal matching

Kidney Transplant Centers

THE LISTING OF TOP TRANSPLANT CENTERS IN THE UNITED STATES
This site is a service of the National Kidney Registry

Living Donor Transplants | Services & Capabilities | Deceased Donor Transplants | Patient Outcomes | Transplant Volumes | Good Samaritan Donors

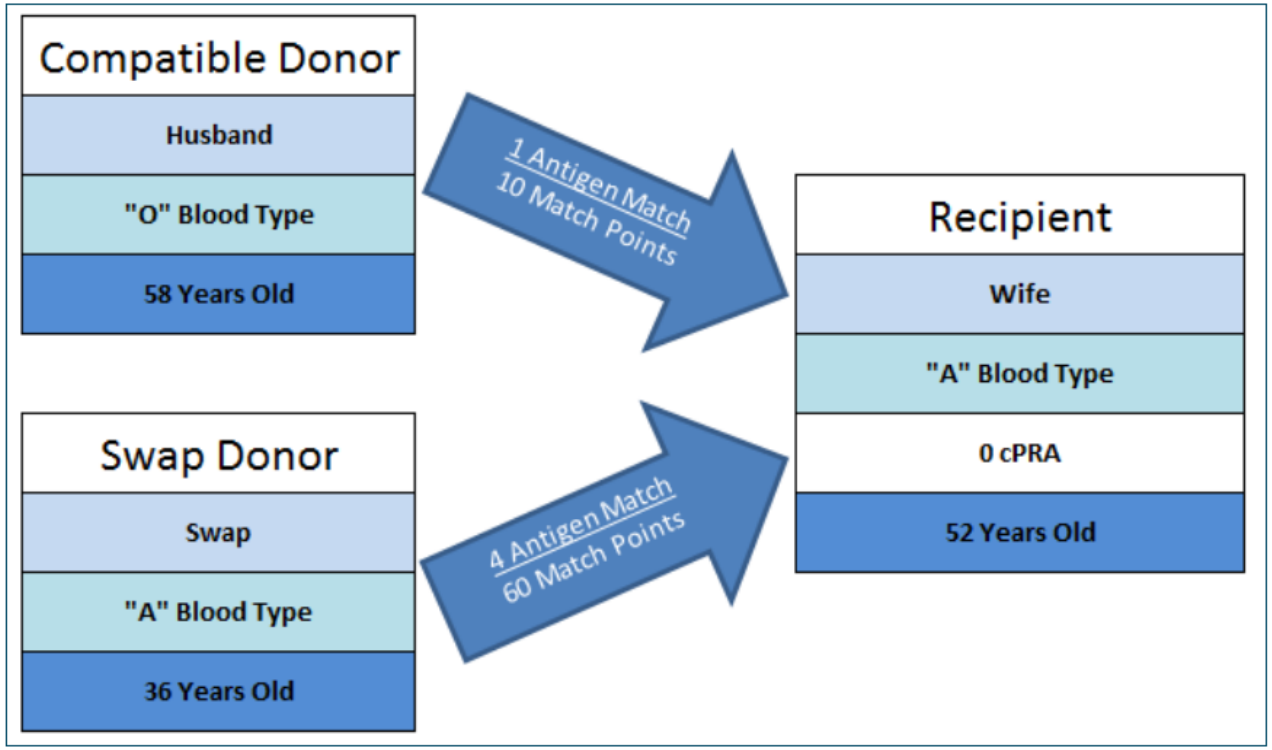
To have a transplant center contact you, please click on the center name below.

hover for explanation
NA data not available

Rank	Center Name	State	NKR Facilitated Transplants Last 12 Months	NKR Facilitated Transplants Since Joining	Median Wait Time NKR Facilitated Transplants	Unmatched Pairs Enrolled in NKR	Pairs Waiting More Than A Year	Match / Transplant Success Rate	Antibody Desensitization Transplant Capability	Blood Type Incompatible Transplant Capability	Center Provides Donor Insurance	Max Paired Donors that Center will Work Up
1	UCLA Medical Center	CA	25	125	3	25	8	94%	Yes	Yes	No	2
2	NewYork Presbyterian-WeillCornell Transplant	NY	20	118	2	9	3	97%	Yes	Yes	No	5+
3	UCSF Medical Center	CA	17	75	2	13	2	97%	Yes	Yes	No	5+
4	Saint Barnabas Medical Center	NJ	15	76	3	9	3	96%	Yes	Yes	No	3
5	University of Maryland Medical Center	MD	15	35	2	12	1	97%	Yes	No	No	5+
6	Emory Transplant Center	GA	13	30	2	12	3	90%	No	Yes	No	4
7	Froedtert	WI	13	20	2	3	1	95%	Yes	Yes	No	5+
8	University of Wisconsin, Madison	WI	12	63	5	19	9	86%	Yes	Yes	No	5+
9	Cleveland Clinic	OH	10	26	2	0	0	NA	No	No	No	2
10	Ohio State University Medical Center	OH	9	17	2	11	2	88%	No	No	No	2
11	California Pacific Medical Center	CA	8	39	3	10	3	92%	Yes	No	No	5+
12	Barnes-Jewish Hospital	MO	8	21	2	6	5	76%	No	No	No	4
13	U. Pittsburgh Thomas E. Starzl	PA	8	21	2	19	4	81%	Yes	No	No	5+
14	Loyola University Medical Center	IL	7	35	1	5	3	91%	Yes	No	No	2
15	Sharp Memorial Hospital	CA	7	32	3	8	3	91%	Yes	No	No	5+
16	Mount Sinai Medical Center	NY	7	27	3	5	1	96%	Yes	No	No	2
17	Johns Hopkins Hospital	MD	7	16	2	5	0	100%	Yes	Yes	No	4
18	Methodist University Transplant-TN	TN	7	11	2	3	2	82%	No	No	No	2
19	Hospital of the University of Pennsylvania	PA	6	21	2	8	5	76%	No	No	No	2
20	Centura Porter Adventist Hospital	CO	6	16	1	4	0	100%	No	No	No	2

http://www.kidneyregistry.org

How to motivate O group positive donor to provide kidneys to the living donor pool?



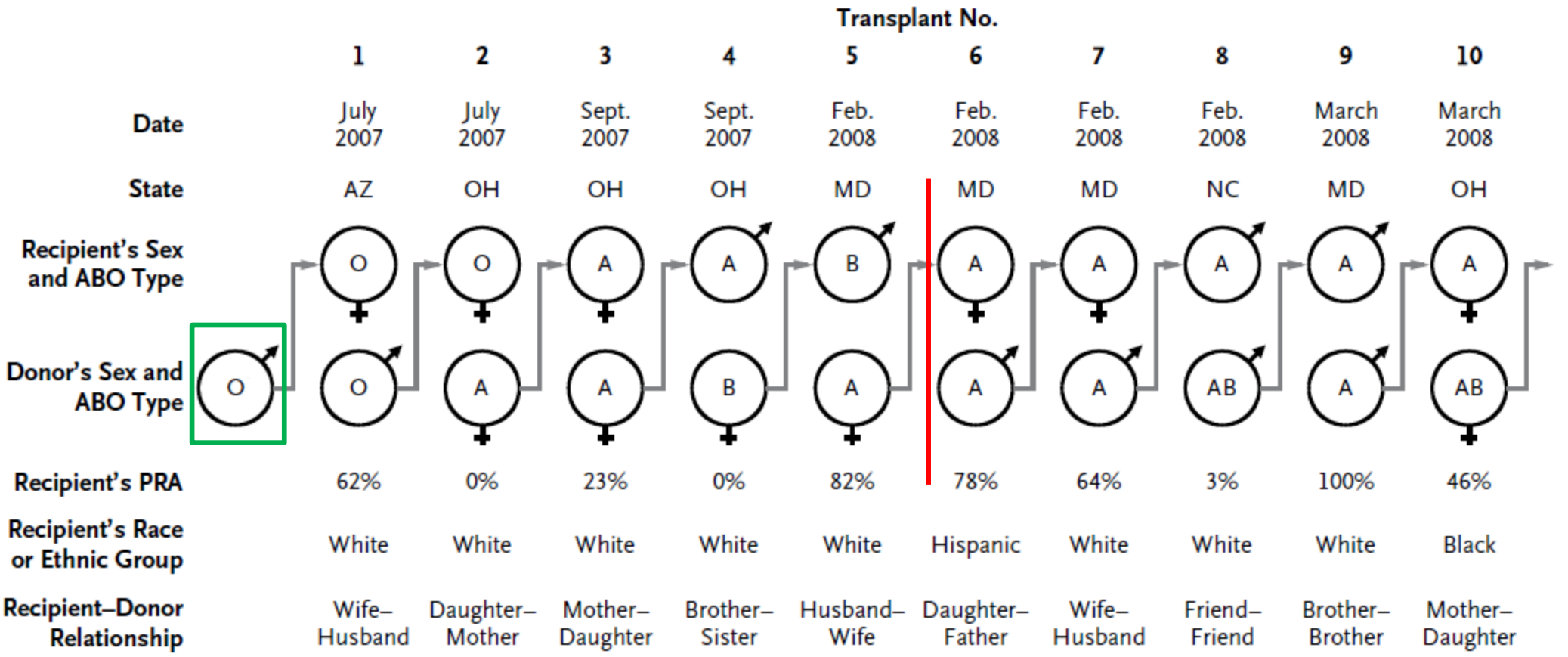
O donors with interest to swap:

- Parent-to-child (better age)
- Child-to-mother (avoid DSA)
- Unrelated living (better age and match)
- Viral mismatch (EBV or CMV+ donor for negative recipient)

In the example above, the swap donor is 22 years younger than the compatible donor and has 50 additional HLA match points compared to the compatible donor. This translates to an additional 26% mean kidney life years (50 HLA Match Points adds 11%, Donor Age < 55 adds 9%, Donor Age 22 Years Younger adds 6%). Matching variables and their impact on longevity of transplant are described in the next section.

http://www.kidneyregistry.org

Unspecified (non-directed) kidney donation triggering Nonsimultaneous, Extended, Altruistic-Donor Chains



Rees NEJM 2009

The Belgian LDEP: principles

- Initiated in 2009
- Participation of all the 7 Belgian transplant centers
- Pairs due to ABO or X-match incompatibility
- Recipients stay on the ET waiting list until living donor transplantation is completed
- No inclusion of undirected altruistic organ donations

The Belgian LDEP: principles

- Donor and recipient pairs receive information on the program in the local transplant centers and provide written informed consent.
- D+R evalutation are realized in local centers and clinical data are recorded in a common database hosted by ET
- The pairs remain anonymous
- Procurement of the pairs is realized at the same moment
- The original pairs remain hospitalized together as with a classical living donor transplantation. The procured kidneys are exchanged between centers.

The Belgian LDEP ranking procedure

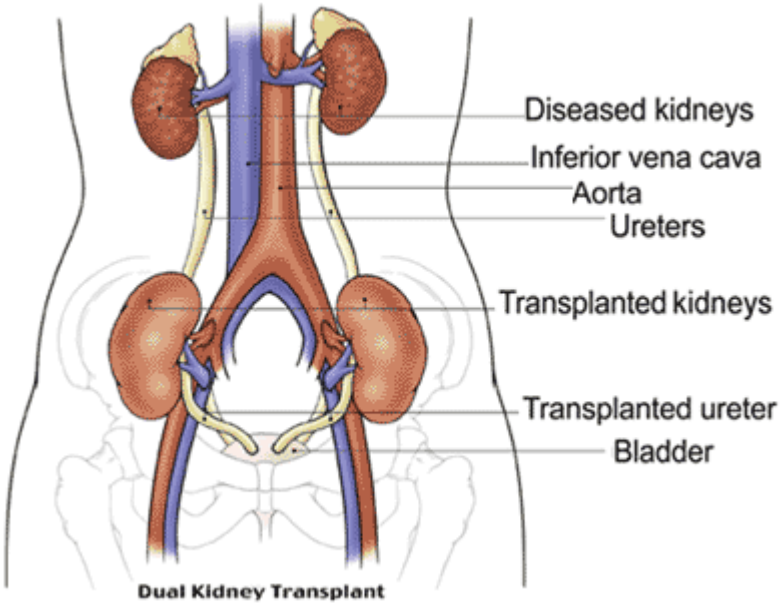
Ranking (every 3 months) of the LD-pairs will be based:

1. The highest possible number of matches.
2. Identical blood type has priority over compatible blood type (avoid accumulation of O recipients).
3. Matching probability (PRA, %ABO compatible, HLA forbidden Ags).
4. Dialysis time.
5. Age difference between donor and receptor of < or > 20 years.

→ Up to now one successful transplantation (ULB-UCL)

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
•Alternative: transplantation of two kidneys in one recipient

Which donors to select for dual transplantation

- Remuzzi model (NEJM 2006)
  - → Donors >60
  - → Core biopsy during procurement
  - → Histologic evaluation
    - 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

Score 5

Score 7

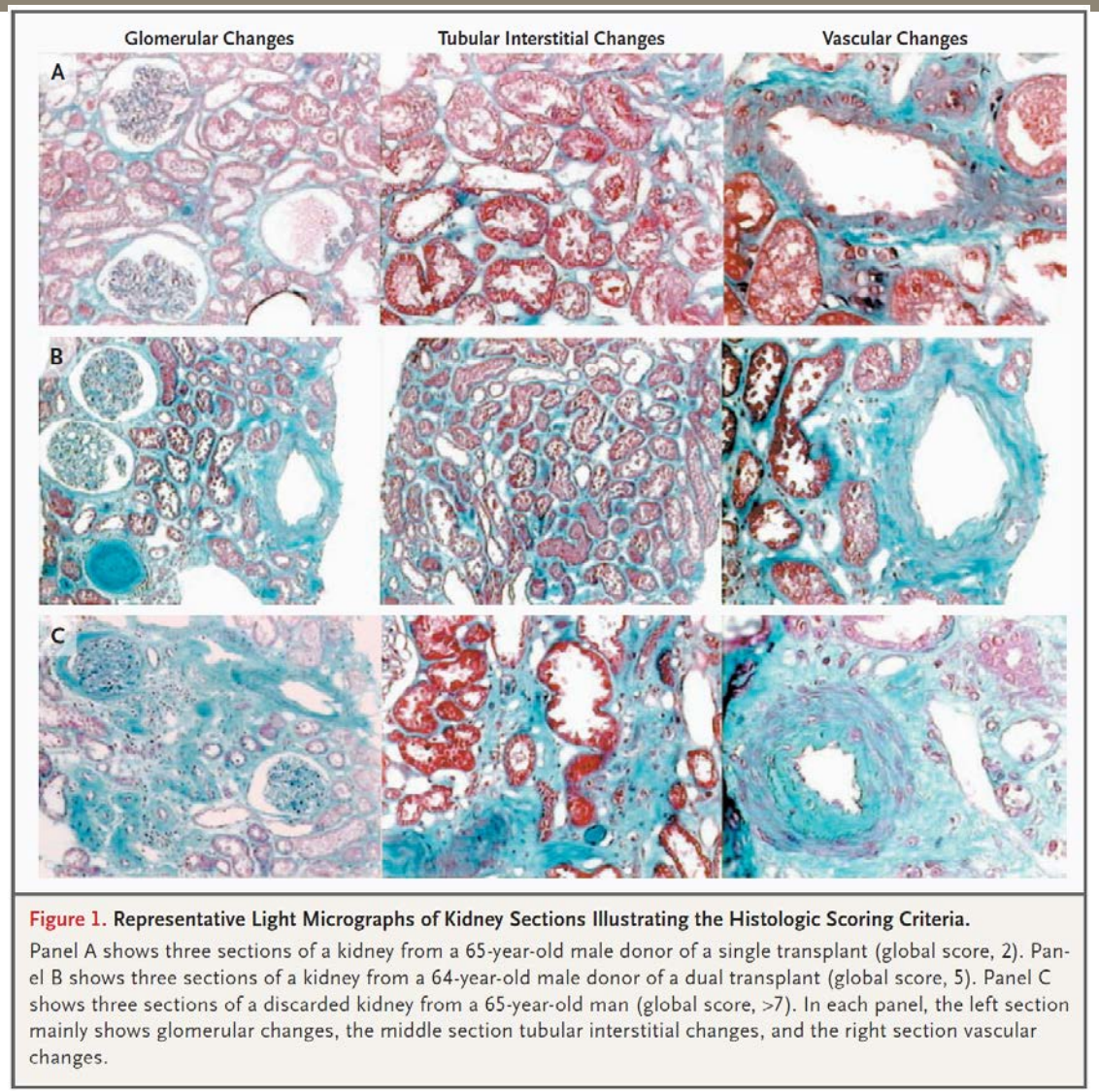


Figure 1. **Representative Light Micrographs of Kidney Sections Illustrating the Histologic Scoring Criteria.**
Panel A shows three sections of a kidney from a 65-year-old male donor of a single transplant (global score, 2). Panel B shows three sections of a kidney from a 64-year-old male donor of a 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.

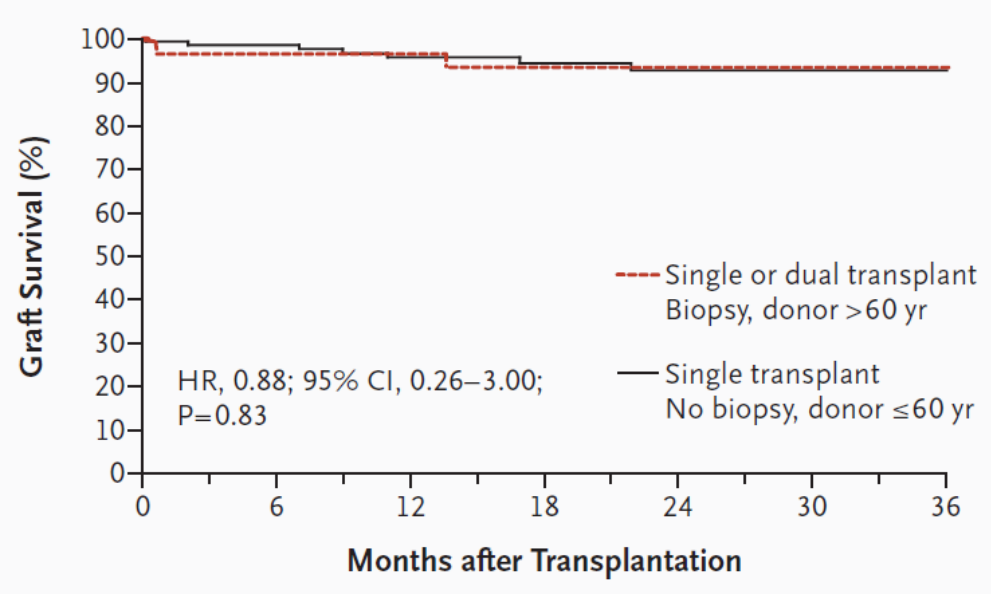
Single

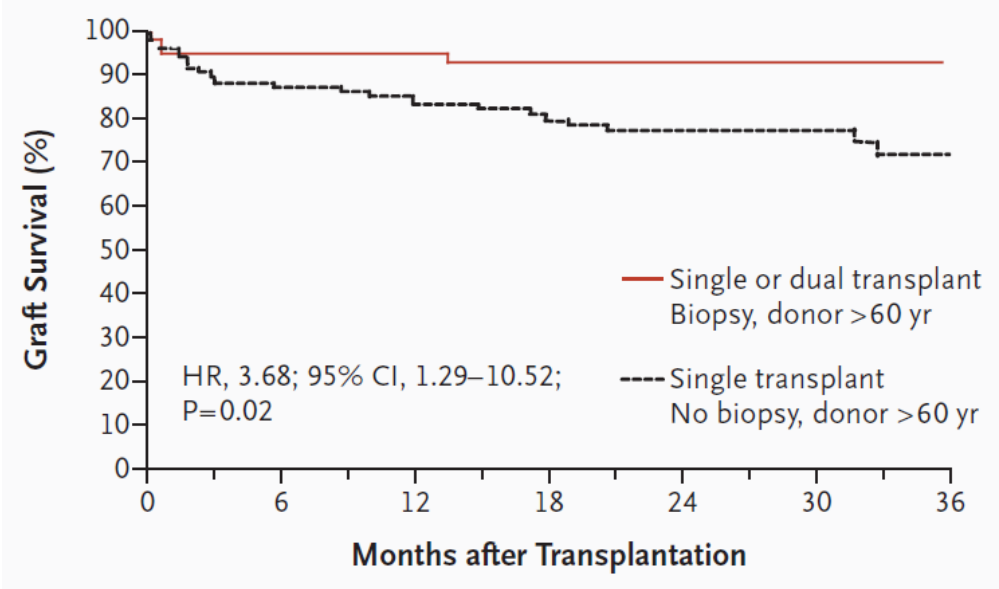
Dual

Discard

Universitair Ziekenhuis Brussel

Improved outcome of histologically evaluated older donor kidneys





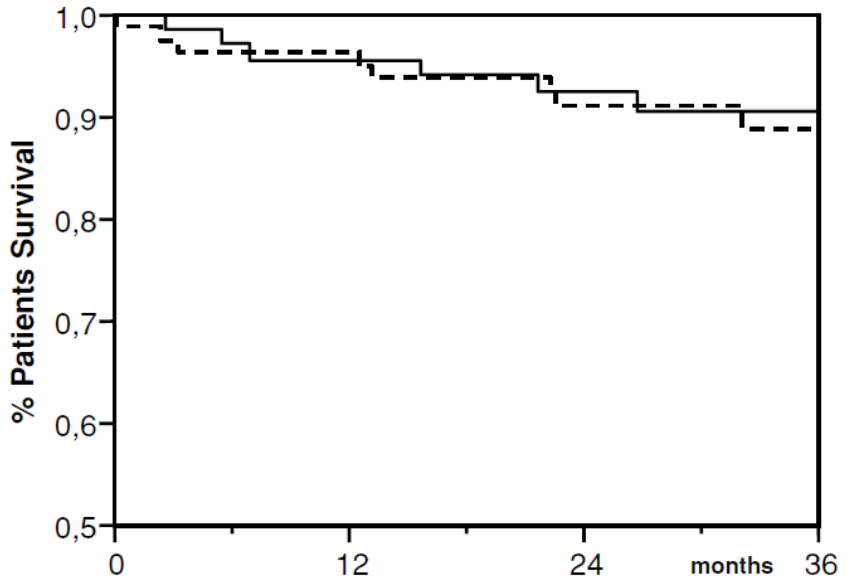
Remuzzi et al NEJM 2006

French model

- Reluctance of surgeons to do core biopsies
- Histological evaluation difficult on frozen samples. Insufficient time for paraffin fixing and processing
- Scoring system based on donor renal function (donors >65 years)
  → >60 ml/min : single kidney (N=70)
  → 30-60 ml/min: dual kidney (instead of discarding; N=81)
  → <30 ml/min discarding of kidney

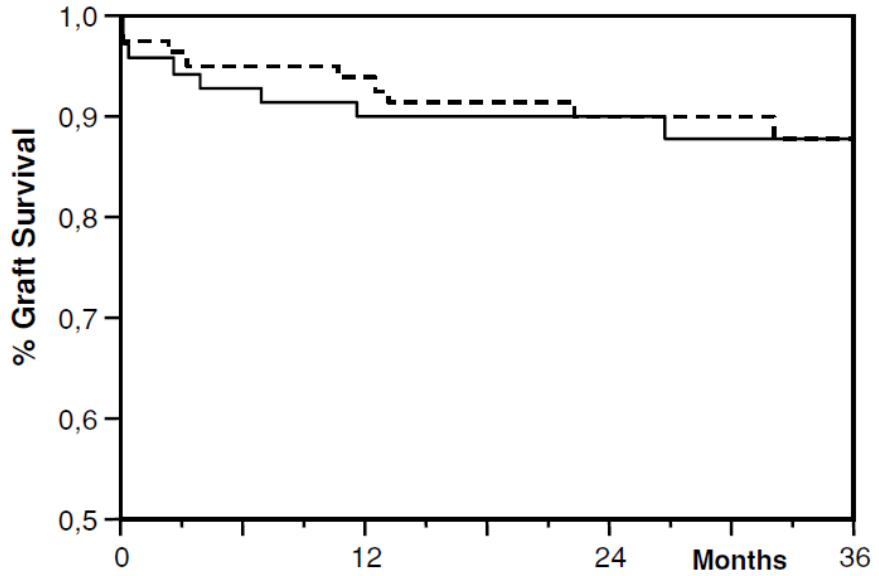
Snanoudj AJT 2009

Good patient and graft survival in case of dual kidney transplantation from marginal donors



Group		M12	M24	M36
Single	N	66	52	28
	%	95.7	92.6	90.6
Dual	N	78	63	37
	%	95.1	91.1	88.8

Figure 1: Kaplan–Meier estimates of patient survival.

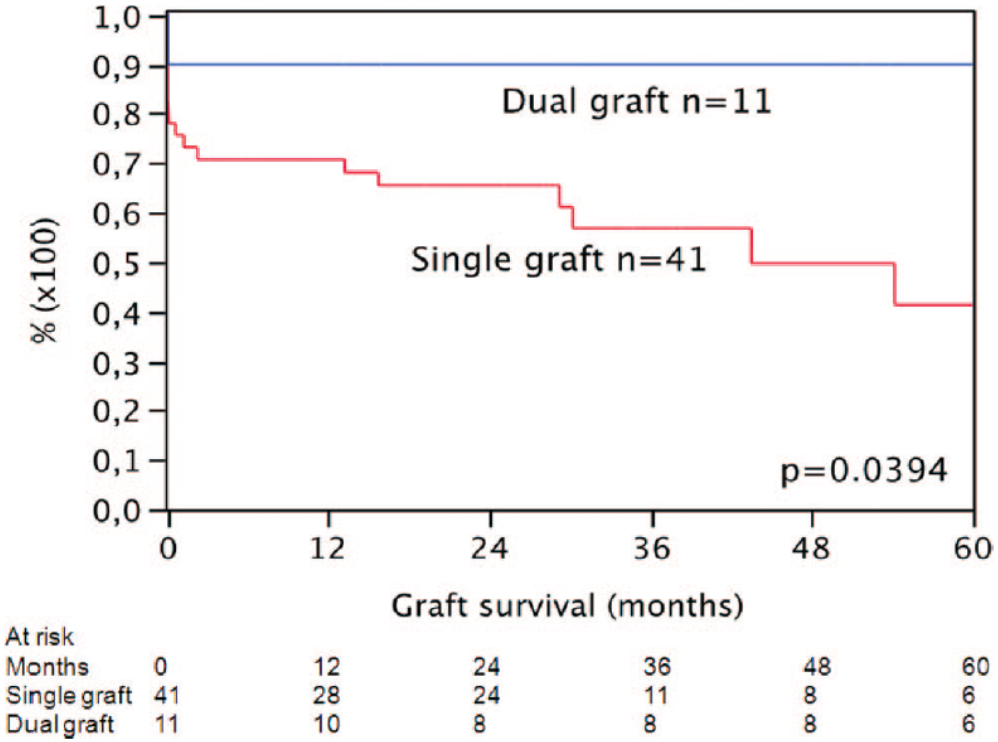


Group		M12	M24	M36
Single	N	63	49	26
	%	90.0	90.0	88.0
Dual	N	76	61	36
	%	92.6	90.0	87.7

Figure 2: Kaplan–Meier estimates of non-death-censored graft survival.

Snanoudj AJT 2009

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

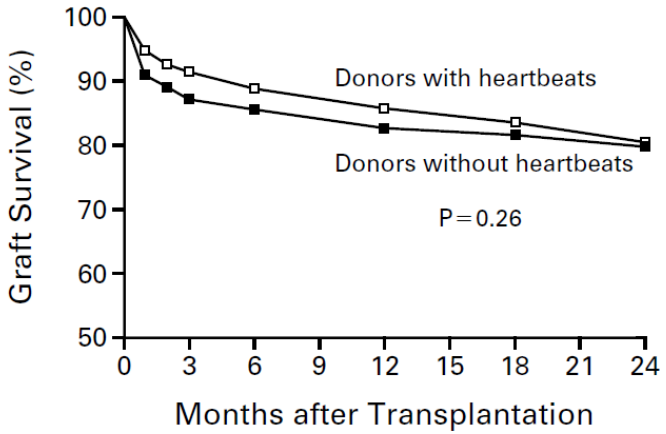
FIGURE 1. Kaplan-Meier survival analysis for dual graft and single graft kidney transplantation with donor grafts more than or equal to 75 years.

Gallinat et al. Transplantation 2011

First major report on donation after cardiac death in 1998

TABLE 2. EARLY FUNCTION OF KIDNEY GRAFTS FROM DONORS WITHOUT HEARTBEATS AND DONORS WITH HEARTBEATS.

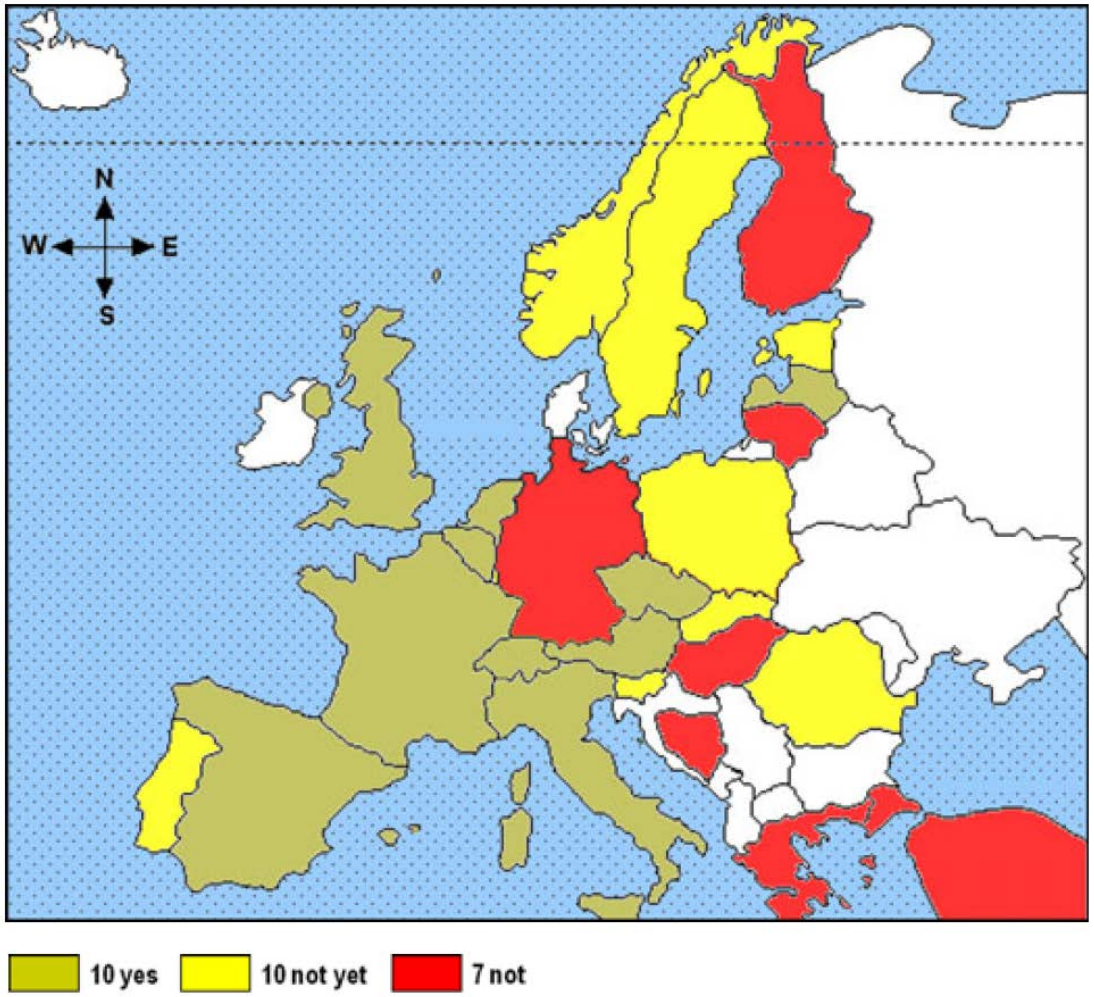
VARIABLE	DONORS WITHOUT HEARTBEATS (N=229)	DONORS WITH HEARTBEATS (N=8718)	P VALUE
	no. (%)		
No urinary output in first 24 hours	47 (21)	954 (11)	<0.001
Dialysis in the first week	109 (48)	1912 (22)	<0.001
Antirejection treatment	43 (19)	1209 (14)	0.04
Serum creatinine at discharge*			<0.001
<2.1 mg/dl	85 (38)	4703 (55)	
2.1–4.0 mg/dl	56 (25)	2301 (27)	
>4.0 mg/dl	84 (37)	1562 (18)	
Primary failure	9 (4)	99 (1)	<0.001



NO. OF GRAFTS						
Donors with heartbeats	8718	7136	6368	3983	2308	1169
Donors without heartbeats	229	178	153	97	61	40

Terazaki et al NEJM 1998

DCD in Europe



Dominguez et al Transplant Int 2011

Non heart beating donors (donation after cardiac death)

Classification for non-heart beating donors (Maastricht classification)

I	Brought in dead	uncontrolled
II	Unsuccessful resuscitation	
III	Awaiting cardiac arrest	controlled
IV	Cardiac arrest after brain death	uncontrolled
V	Cardiac arrest in a hospital inpatient	uncontrolled (added in 2000[2])

Table 4.4c(ii) Non-heart beating donors used for a transplant, in 2013

NHB Category	A	B	NL	Total	%
I - Dead on arrival	0	0	1	1	0.5 %
II - Unsuccessful resuscitation	1	0	0	1	0.5 %
III - Awaiting cardiac arrest	2	65	149	216	99.1 %
IV - Cardiac arrest in brain dead donor	0	0	0	0	0.0 %
Total	3	65	150	218	100.0 %

DCD procurement

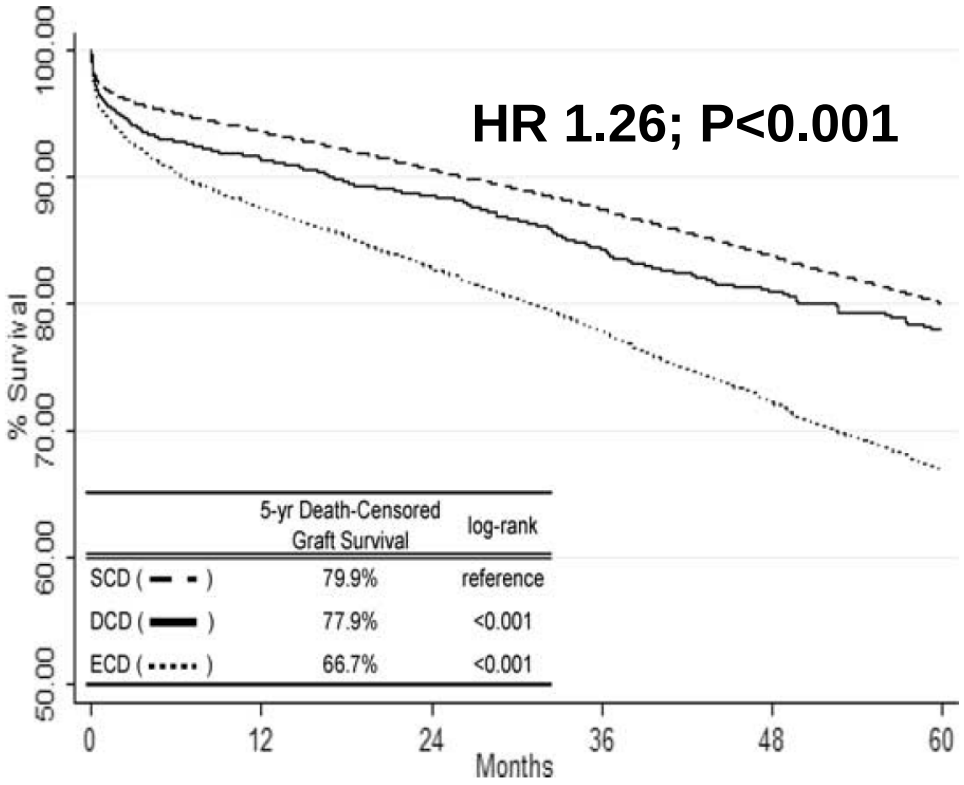
- Brain death criteria not met
- Catastrophic brain injury or other disease without meaningful prospect of survival.
- Decision to withdraw ventilatory support independent of the decision on organ donation.
- Withdrawal of ventilator and other organ-perfusion support in the operating room
- Morphine and analgesics might be provided to minimize discomfort (no influence of procurement team)
- Procurement team absent until declaration of death
- After cessation of cardio-respiratory activity 2 min non-touch period (no auto-resuscitation observed after 2 minutes)

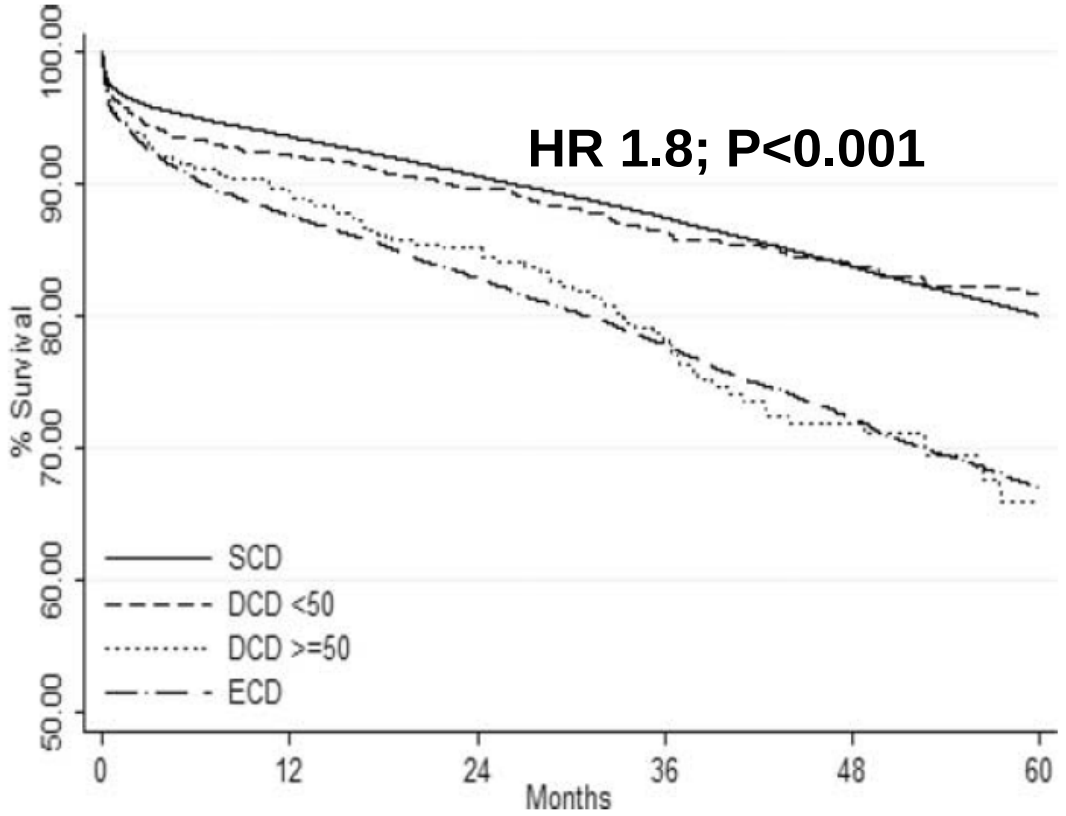
ASTS guidelines AJT 2009

Contentious issues

- Use of medication to shorten the “agony phase” between cessation of ventilation and cardiac arrest.
  - → Prolonged period often with severe hypotension
  - → Stressful for patient and medical team
- Length of “non-touch period” between heart arrest and declaration of death
  - → 2 min ASTS up to 20 minutes (Italy).
  - → Belgium 5 minutes
  - → Direct effect of warm ischemia time on the risk of DGF and primary non function
- Need for common protocol
  - → Ethical review
  - → Implication of non-medical representatives of society

Good outcome in young DCD donors with short cold ischemia times…..

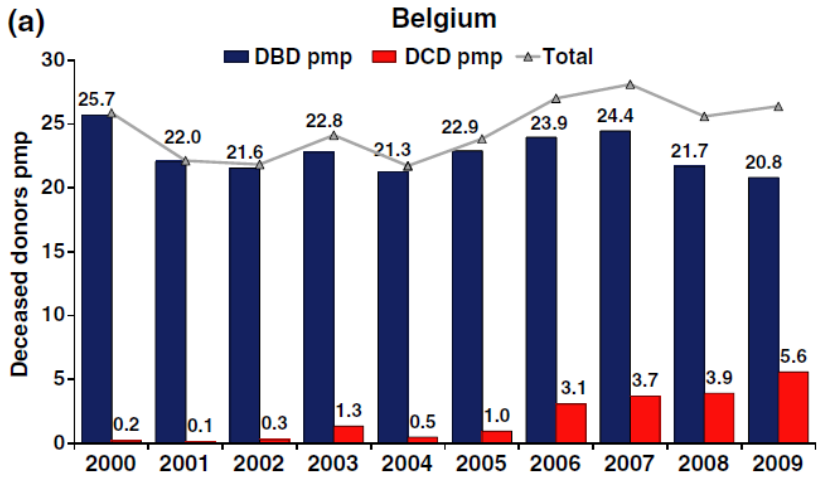


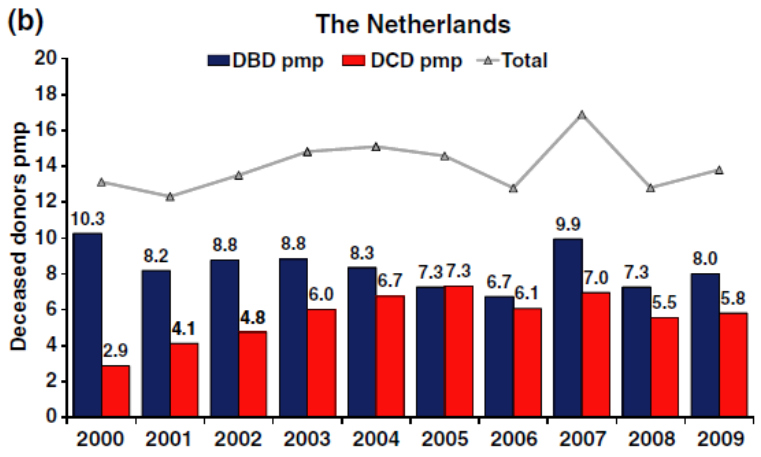


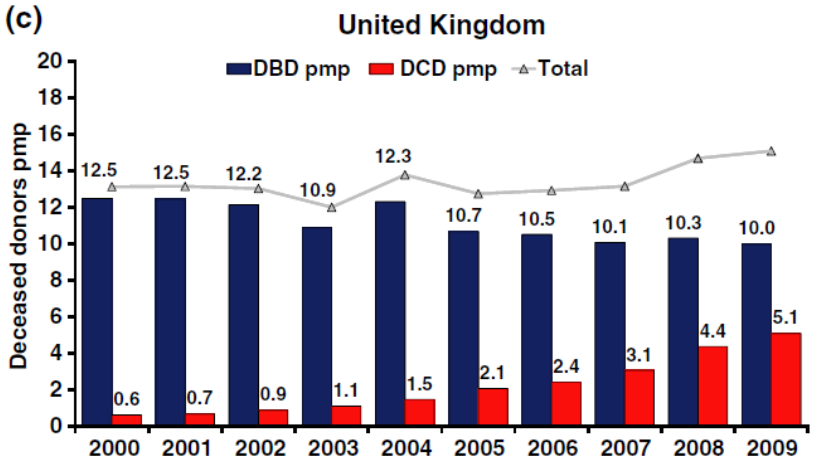
- But median donor age about 55 years old
- Most centers procure in the evening and transplant in the next morning with longer cold ischemia

Locke AJT 2007

Does DCD decrease DBD procurement







- Reasons for preferential use of DBD:
  - → Programmed activity (procurement in the evening and transplantation in the morning
  - → Less use of ICU resources for management of patients evolving towards brain death

Changing patterns of organ donation: Reading between the lines

Table 1: Comparing donors characteristics and their management in different eras

	Era 1 (1/98–12/01)	Era 2 (1/02–12/05)	Era 3 (1/06–11/08)	p-Value
No. potential donors	61	62	78	0.3
DBD	52 (85.2%)	32 (51.6%)	31 (39.7%)	0.003
DCD	8 (13.1%)	18 (29.1%)	28 (35.7%)	0.002
DCD-dnp	1 (1.7%)	12 (19.3%)	19 (24.3%)	0.001
Age	41.8 ± 20	39.3 ± 18	41.5 ± 17	0.76
Weight	159.1 ± 59	176.2 ± 47	175.7 ± 45	0.13
Cause of death				<0.001
Cardiovascular/CVA	57.1%	69.2%	74%	
Trauma	33.3%	28.8%	12%	
Aggressive neurological management	22 (34.4%)	37 (59.7%)	54 (69.2%)	<0.001
Aggressive neurosurgical management	1 (1.6%)	13 (20.9%)	21 (26.9%)	<0.001

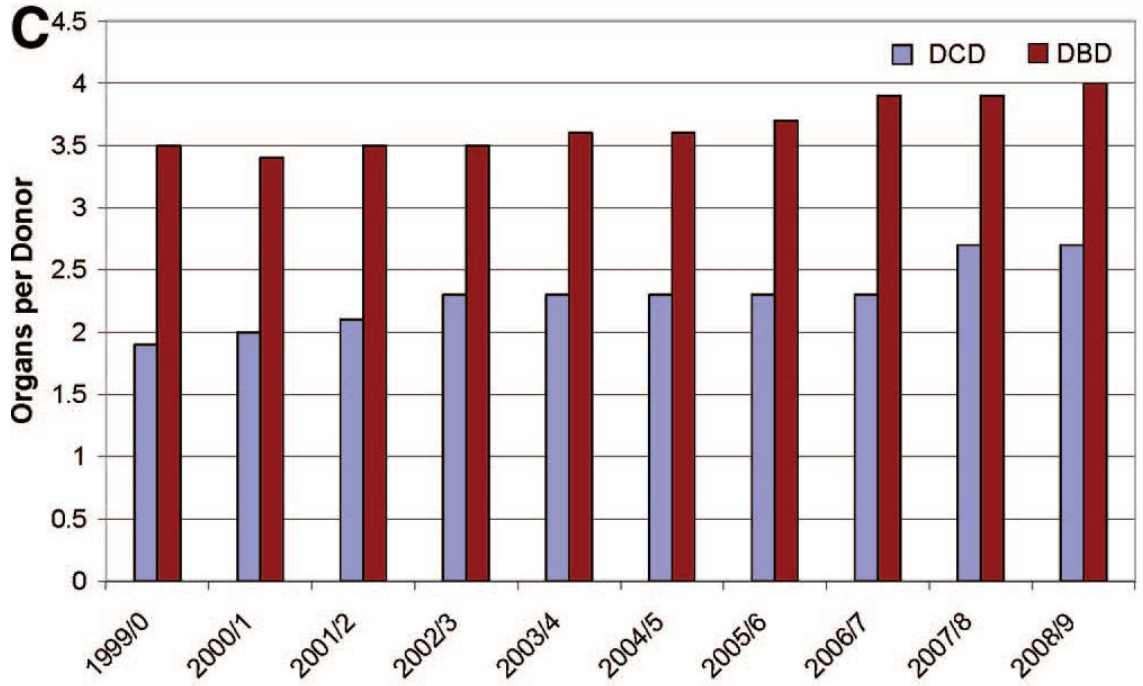
- Reasons for increased use of DCD donors ?
  - → More frequent aggressive neurosurgical management
  - → Lower incidence of trauma patients
  - → Pressure to free ICU ressources
  - → "Planned procurement activity"

Saidi et al. Am J Transplant 2010
Sharo et al Am J Transplant 2010 (editorial)

Universitair Ziekenhuis Brussel

Drawbacks of DBD

- Higher incidence of delayed graft function
  - → More frequent dialysis post-transplant
  - → Longer hospital stay and higher cost
  - → Worse outcome after kidney (?) and liver (!) transplantation
  - → Hardly any heart and lung procurement



Summers Transplantation 2010

Take home messages

- Living donor transplantation is the most efficient means to increase the donor pool.
  - → Superior outcomes
  - → Preemptive transplantation
  - → Beneficial for all patients by leaving more organs for waitlisted patients
- Paired kidney donation has the potential to increase the donor pool. Limited benefit for group O or hyperimmunized patients in case the number of participant pairs is small

Take home messages

- Dual kidney transplantation increases the donor pool with good outcomes. Drawback are increased workload and longer surgery
- Donation after cardiac death has the potential to increase the donor pool. If used indiscriminatly it reduces the procurement of non-renal organs and can have a detrimental effect on outcomes in case of older donors and long cold ischemia times.