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

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

Eurotransplant Annual Report 2012
Evolution of the median age of organ donors in the Eurotransplant region
Increase of patients on the waiting list results in increased use 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
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

Ibrahim et al. NEJM 2009

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

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.

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
Relation between number of deceased donors and living donation

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

Protection of donor rights and welfare
• 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

Philippines

Pakistan
Increase in living donor transplantation does not necessarily increase the donor pool.
Failure to find a matching living donor and potential solutions

- ABO incompatibility
  - Normal Eurotransplant waitlist
  - ABO-incompatible transplantation

- HLA-immunization with positive cross-match
  - Eurotransplant Acceptable Mismatch Program
  - Recipient desensitization
  - Living donor exchange “Paired kidney donation”
Classical cross-over kidney transplantation – Paired kidney donation

Donor

Blood type A

Recipient

Blood type B

Blood type B

Blood type A

(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.
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

<table>
<thead>
<tr>
<th>Rank</th>
<th>Center Name</th>
<th>State</th>
<th>Living Donor Transplants</th>
<th>Deceased Donor Transplants</th>
<th>Patient Outcomes</th>
<th>Transplant Volumes</th>
<th>Good Samaritan Donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>UCLA Medical Center</td>
<td>CA</td>
<td>25</td>
<td>12</td>
<td>8</td>
<td>94%</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>New York Presbyterian-Weill Cornell Transplant</td>
<td>NY</td>
<td>20</td>
<td>118</td>
<td>3</td>
<td>97%</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>UCSF Medical Center</td>
<td>CA</td>
<td>17</td>
<td>75</td>
<td>2</td>
<td>97%</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Saint Barnabas Medical Center</td>
<td>NJ</td>
<td>15</td>
<td>76</td>
<td>3</td>
<td>96%</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>University of Maryland Medical Center</td>
<td>MD</td>
<td>15</td>
<td>35</td>
<td>2</td>
<td>97%</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Emory Transplant Center</td>
<td>GA</td>
<td>13</td>
<td>30</td>
<td>2</td>
<td>90%</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Fredrick</td>
<td>WI</td>
<td>13</td>
<td>20</td>
<td>2</td>
<td>95%</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>University of Wisconsin, Madison</td>
<td>WI</td>
<td>12</td>
<td>63</td>
<td>5</td>
<td>86%</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Cleveland Clinic</td>
<td>OH</td>
<td>10</td>
<td>26</td>
<td>2</td>
<td>88%</td>
<td>No</td>
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<tr>
<td>10</td>
<td>Ohio State University Medical Center</td>
<td>OH</td>
<td>9</td>
<td>17</td>
<td>11</td>
<td>88%</td>
<td>No</td>
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<tr>
<td>11</td>
<td>California Pacific Medical Center</td>
<td>CA</td>
<td>8</td>
<td>39</td>
<td>3</td>
<td>92%</td>
<td>Yes</td>
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<tr>
<td>12</td>
<td>Barnes-Jewish Hospital</td>
<td>MO</td>
<td>8</td>
<td>21</td>
<td>2</td>
<td>76%</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>U. Pittsburgh Thomas E. Starzl</td>
<td>PA</td>
<td>8</td>
<td>21</td>
<td>2</td>
<td>81%</td>
<td>Yes</td>
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<tr>
<td>14</td>
<td>Loyola University Medical Center</td>
<td>IL</td>
<td>7</td>
<td>35</td>
<td>1</td>
<td>91%</td>
<td>Yes</td>
</tr>
<tr>
<td>15</td>
<td>Sharp Memorial Hospital</td>
<td>CA</td>
<td>7</td>
<td>32</td>
<td>3</td>
<td>91%</td>
<td>Yes</td>
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<tr>
<td>16</td>
<td>Mount Sinai Medical Center</td>
<td>NY</td>
<td>7</td>
<td>27</td>
<td>3</td>
<td>96%</td>
<td>Yes</td>
</tr>
<tr>
<td>17</td>
<td>Johns Hopkins Hospital</td>
<td>MD</td>
<td>7</td>
<td>16</td>
<td>2</td>
<td>100%</td>
<td>Yes</td>
</tr>
<tr>
<td>18</td>
<td>Methodist University Transplant-TN</td>
<td>TN</td>
<td>7</td>
<td>11</td>
<td>2</td>
<td>82%</td>
<td>No</td>
</tr>
<tr>
<td>19</td>
<td>Hospital of the University of Pennsylvania</td>
<td>PA</td>
<td>6</td>
<td>21</td>
<td>2</td>
<td>76%</td>
<td>No</td>
</tr>
<tr>
<td>20</td>
<td>Centura Porter Adventist Hospital</td>
<td>CO</td>
<td>6</td>
<td>16</td>
<td>1</td>
<td>100%</td>
<td>No</td>
</tr>
</tbody>
</table>

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 28% 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 evaluation 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.
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

Figure 1: Kaplan–Meier estimates of patient survival.

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)

**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.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Donors without Heartbeats (N=229)</th>
<th>Donors with Heartbeats (N=8718)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%)</td>
<td>no (%)</td>
<td></td>
</tr>
<tr>
<td>No urinary output in first 24 hours</td>
<td>47 (21)</td>
<td>954 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dialysis in the first week</td>
<td>109 (48)</td>
<td>1912 (22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antirejection treatment</td>
<td>43 (19)</td>
<td>1209 (14)</td>
<td>0.04</td>
</tr>
<tr>
<td>Serum creatinine at discharge*</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;2.1 mg/dl</td>
<td>85 (38)</td>
<td>4703 (55)</td>
<td></td>
</tr>
<tr>
<td>2.1–4.0 mg/dl</td>
<td>56 (25)</td>
<td>2301 (27)</td>
<td></td>
</tr>
<tr>
<td>&gt;4.0 mg/dl</td>
<td>84 (37)</td>
<td>1562 (18)</td>
<td></td>
</tr>
<tr>
<td>Primary failure</td>
<td>9 (4)</td>
<td>99 (1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Graft Survival (%)**

<table>
<thead>
<tr>
<th>Months after Transplantation</th>
<th>Donors with heartbeats</th>
<th>Donors without heartbeats</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>15</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>20</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>24</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

**P = 0.26**

**No. of Grafts**

<table>
<thead>
<tr>
<th>Donors with heartbeats</th>
<th>8718 7136 6368</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donors without heartbeats</td>
<td>229 178 153</td>
</tr>
</tbody>
</table>

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
II Unsuccessful resuscitation } uncontrolled
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

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

Reasons for increased use of DCD donors?

- More frequent aggressive neurosurgical management
- Lower incidence of trauma patients
- Pressure to free ICU resources
- “Planned procurement activity”

Saidi et al. Am J Transplant 2010
Sharo et al Am J Transplant 2010 (editorial)
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
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. Drawbacks are increased workload and longer surgery.
- Donation after cardiac death has the potential to increase the donor pool. If used indiscriminately 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.