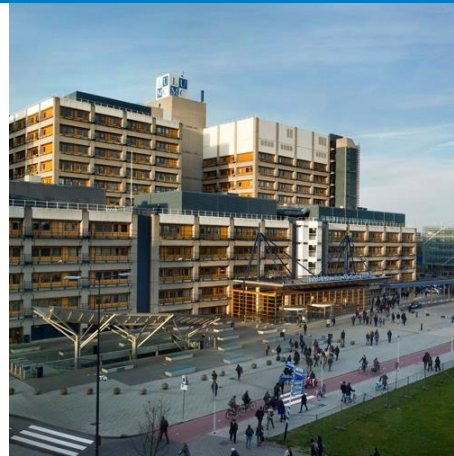


The Eurotransplant Acceptable Mismatch Program

Sebastiaan Heidt

Eurotransplant Reference Laboratory

17TH CONGRESS OF THE CATALAN TRANSPLANTATION
SOCIETY



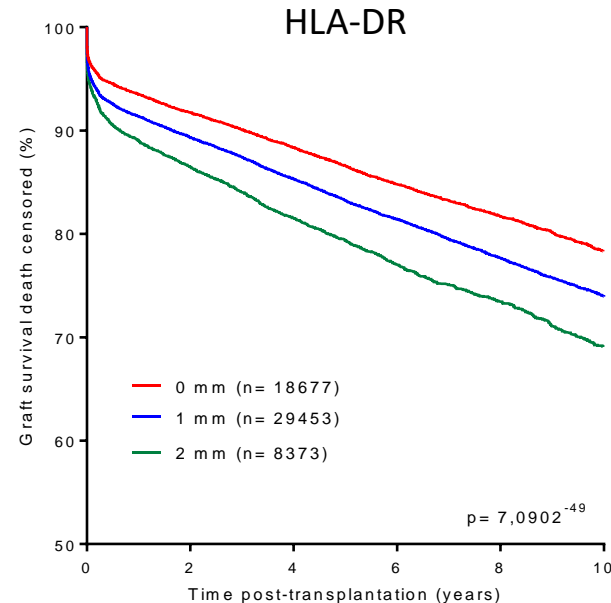
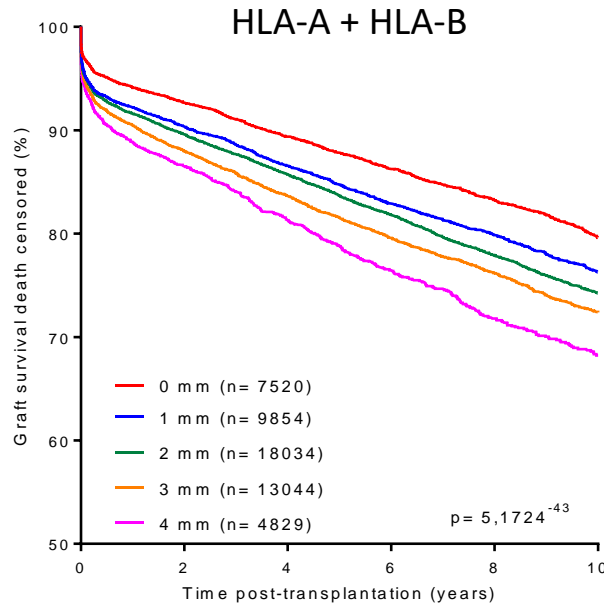
- Founded in 1967 by Prof. Jon J. van Rood



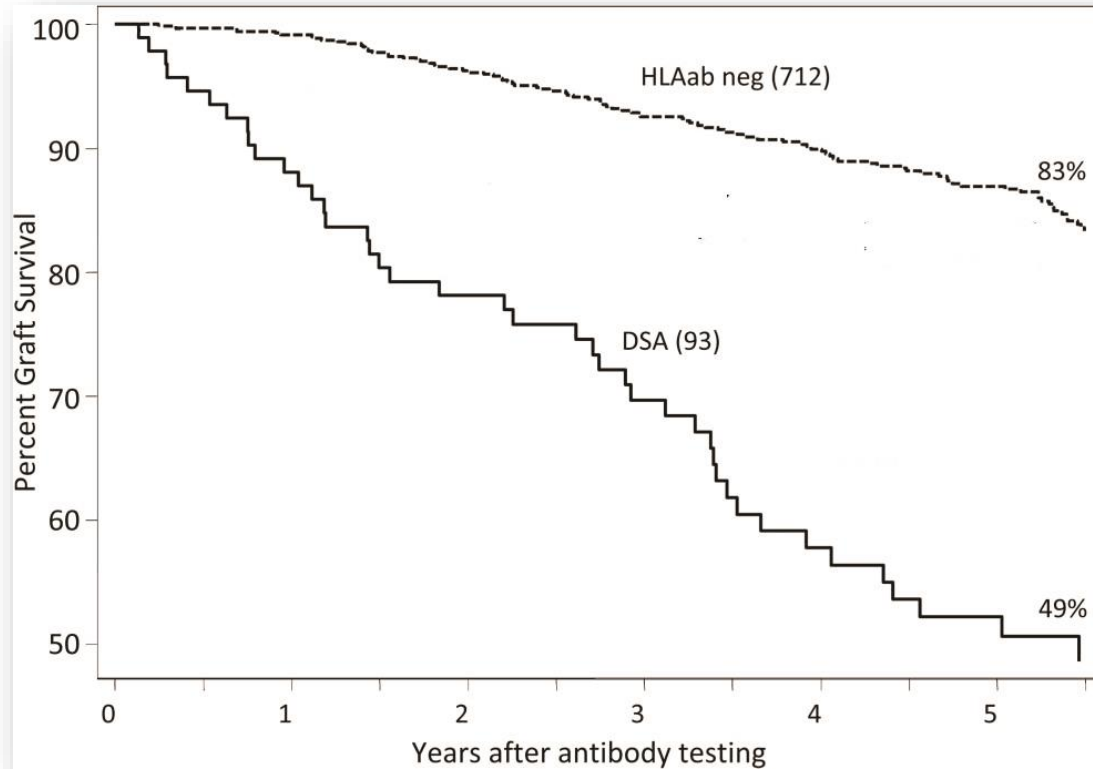
- 1960's: HLA type of donor and recipients influenced the results of transplantation
- The chances of finding a donor with matching HLA type were slight
- Rationale founding Eurotransplant: increase the donor pool, and therefore the chance to receive a well-matched transplant

HLA matching in kidney transplantation

- HLA matching improves graft survival rate
- Many transplants are performed with some degree of HLA mismatch



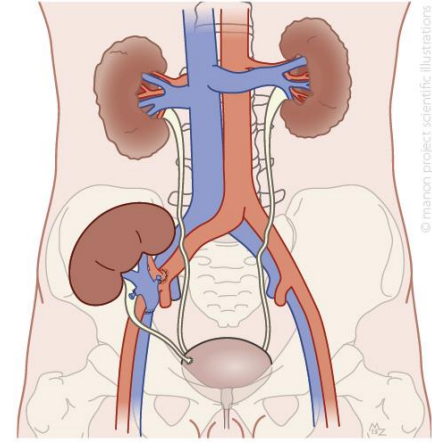
Epecially, production of de novo donor specific HLA antibodies (DSA) is associated with poor graft survival



Sensitization against HLA



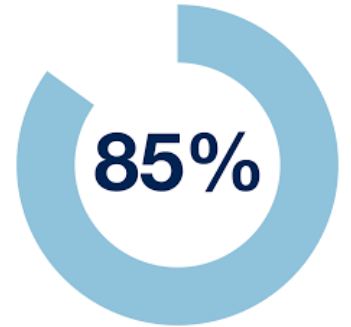
- Blood transfusion
- Pregnancies
- Prior organ transplants



Highly sensitized patients



- Highly sensitized patients awaiting a renal transplant are accumulating on the waiting list (many unacceptable antigens)
- Definition highly sensitized:
 - At least 85% PRA in two different sera excluding irrelevant antibodies
 - Virtual PRA of at least 85% (specificities of the HLA antibodies in context of the frequencies of the HLA antigens in the donor population)



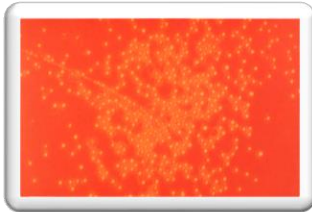
Options for highly sensitized patients



- Transplant with HLA identical or compatible donor (taking into account unacceptable antigens)

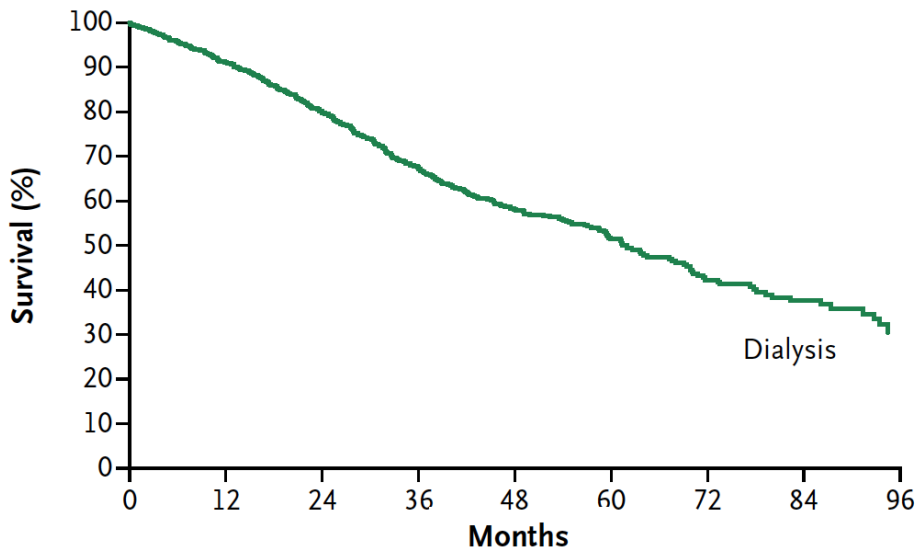
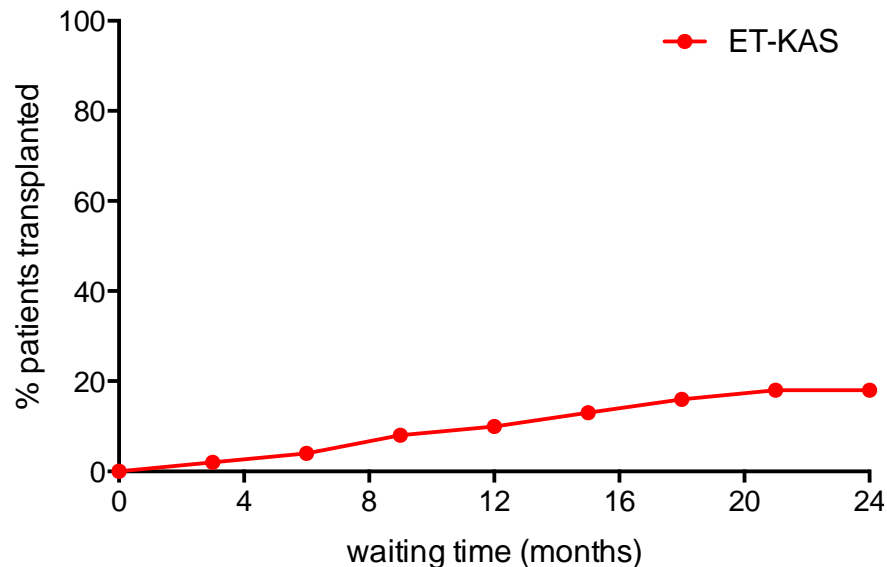


- Do not accept that the patient is sensitized and try to remove antibodies



- Accept that the patient is sensitized and try to stimulate the allocation of crossmatch negative donor kidneys to these patients

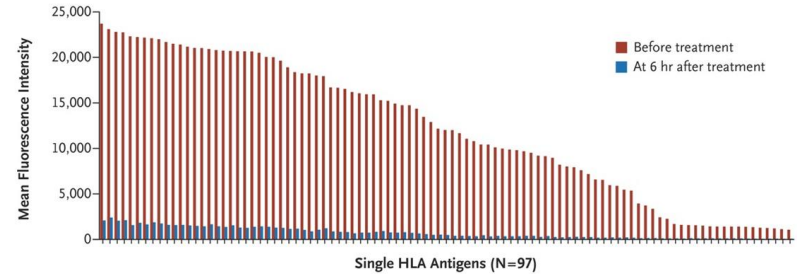
Low chance for highly sensitized patients to be transplanted through regular allocation



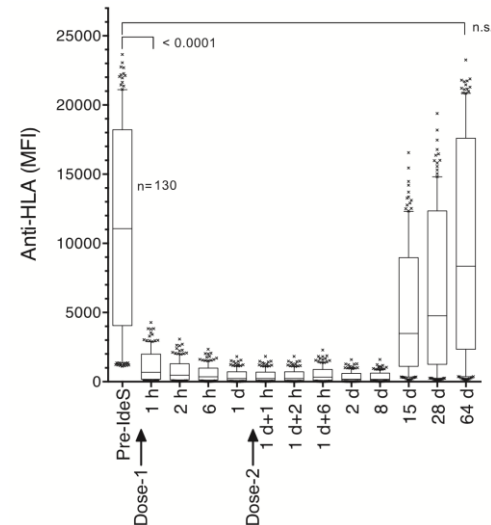
Adapted from Montgomery et al., N Engl J Med 2011

Desensitization: possible role for Imlifidase

- Imlifidase cleaves circulating IgG and allows for a window of opportunity to transplant with a negative crossmatch
- Rebound of HLA antibodies to approximately 80% of pre-treatment levels
- Up to 40% antibody mediated rejection



Jordan et al., NEJM 2017



Lorant et al., AJT 2017

The ET acceptable mismatch (AM) program



- **Basis:** definition of those HLA antigens toward which the patient never formed antibodies and use this knowledge for donor selection
- These antigens are called acceptable antigens and help to predict a negative crossmatch
- Acceptable antigens are added to the HLA phenotype of the patient to increase chance of an organ offer
- Mandatory shipment of compatible organ to AM patient



- Inclusion criteria evaluated for each patient:
 - Minimum of 2 years on ETKAS waiting list (defined by date of first dialysis)
 - At least 85% PRA tested by CDC in two different sera excluding irrelevant antibodies
 - Virtual PRA (vPRA) of at least 85% (antibodies detectable only by solid phase assays are only considered if explainable by immunizing event)
 - vPRA based on 11 loci on allelic, split, and/or broad level





How acceptable antigens are defined



- Original method:
 - Consider the HLA type of negative panel donors in screening
 - Extensive antibody screening against a patient specific panel (donors with a single HLA-A or -B mismatch), from a pool of 20,000 HLA typed blood donors
- Testing serum of patients against cells expressing only one HLA type (SAL)
- Use of solid phase assays
- Use of computer algorithms for determining acceptable antigens (HLAMatchmaker / HLA-EMMA)

Selection of acceptable antigens by CDC




Patient	HLA type	Crossmatch
	A24 A29; B8 B62; DR1 DR10	
Panel donor 1 	<u>A1</u> A24; B8 B62; DR1	Negative
Panel donor 2 	A24 <u>A32</u> ; B8 B62; DR1	Positive
Panel donor 3 	A1 <u>A2</u> ; B8 B62; DR10	Positive


A1 is an acceptable antigen
A32 and A2 are unacceptable antigens

Combination of patient HLA and AM: negative crossmatch

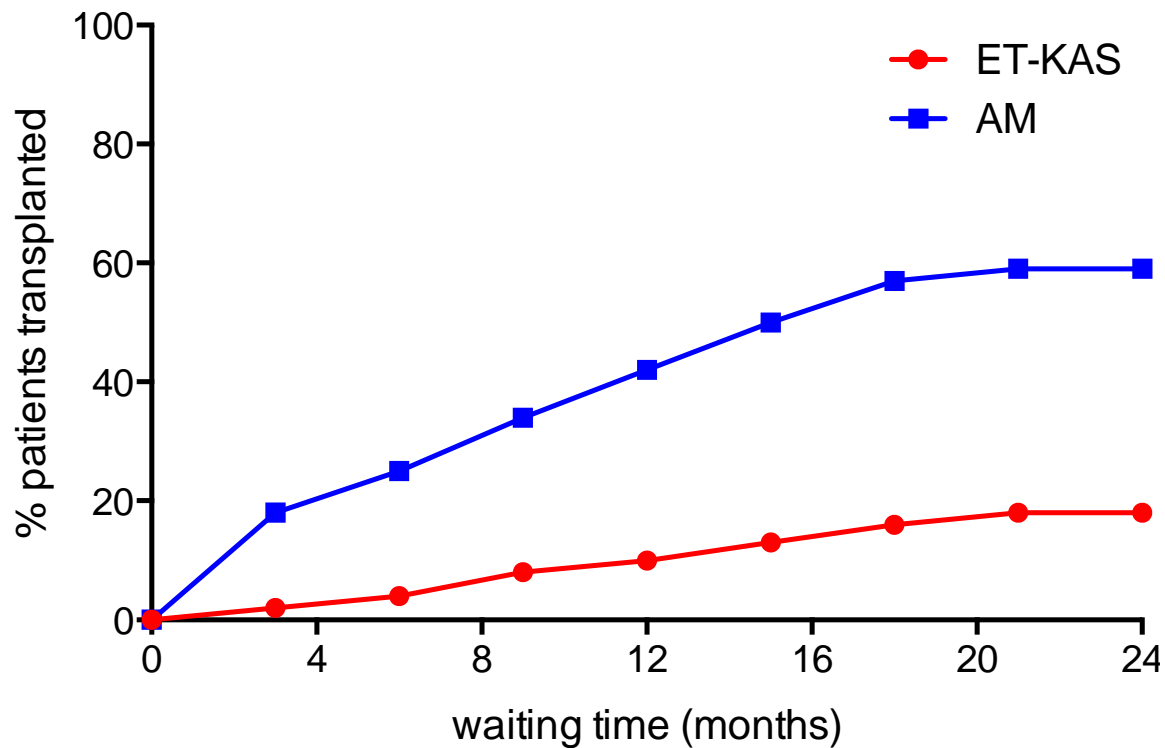


 Patient HLA: A24 A31; B27 B51; DR4

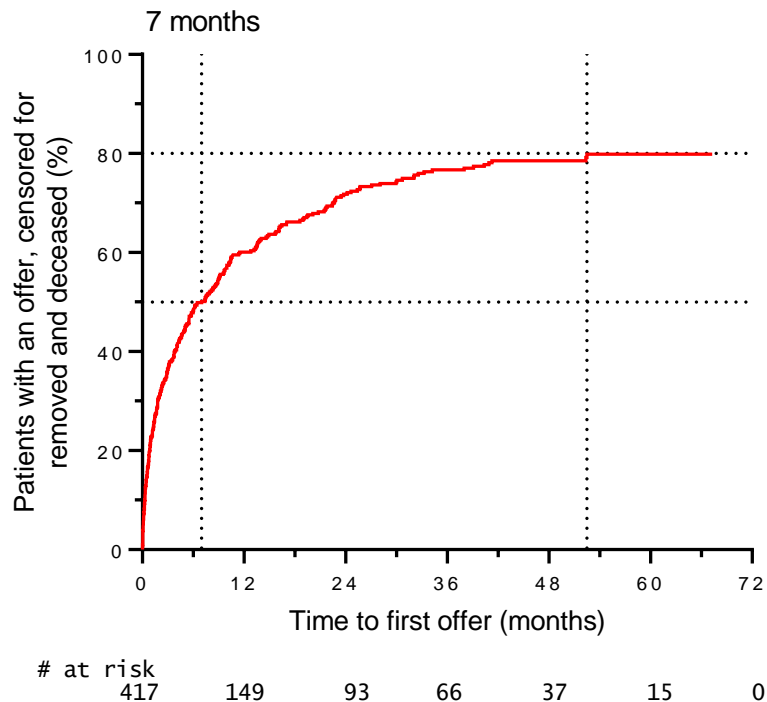
Suitable kidney donors:

A24, A31; B27, B51; DR4 

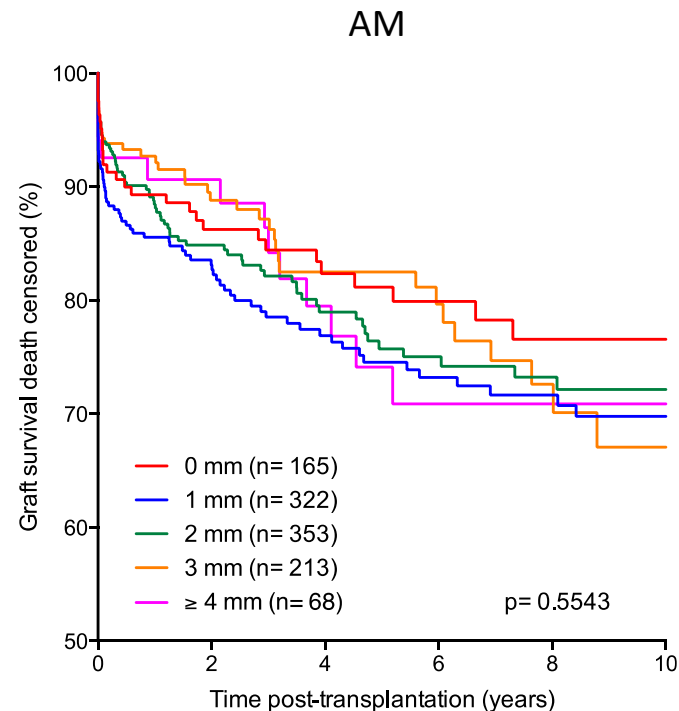
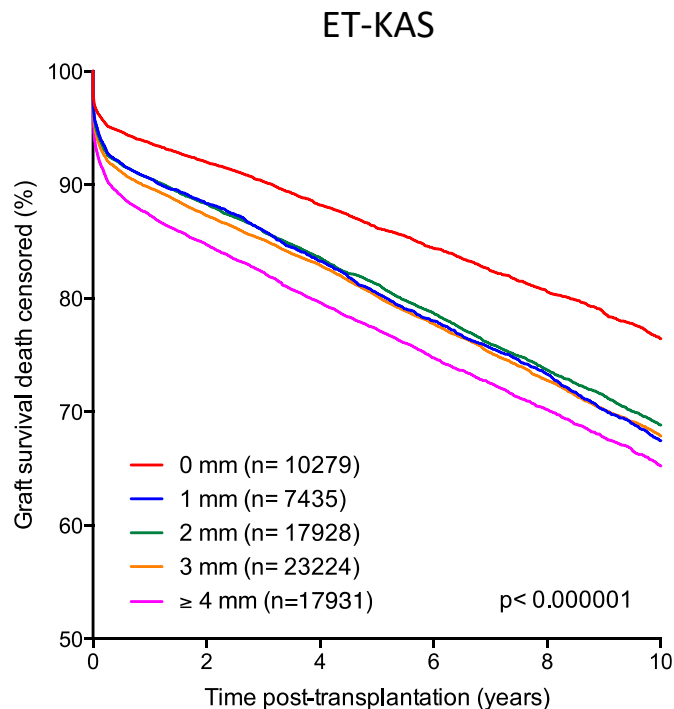
Increased chance to be transplanted



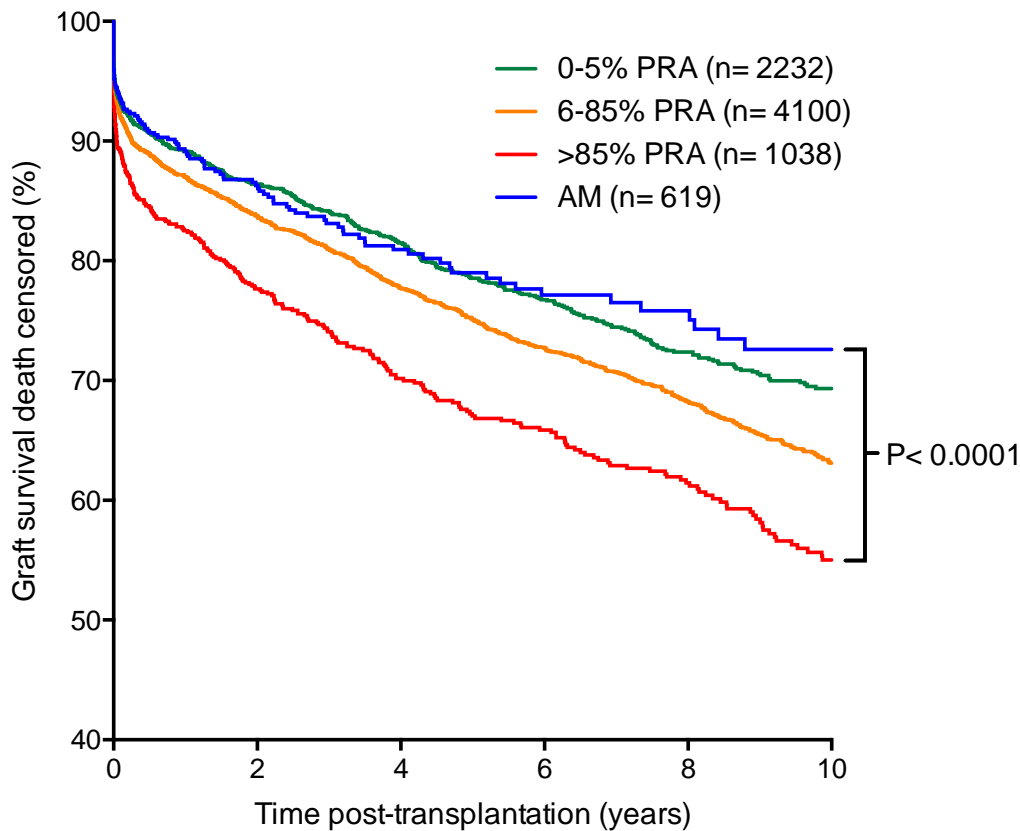
AM offers and transplant rate



Are acceptable mismatches truly acceptable?



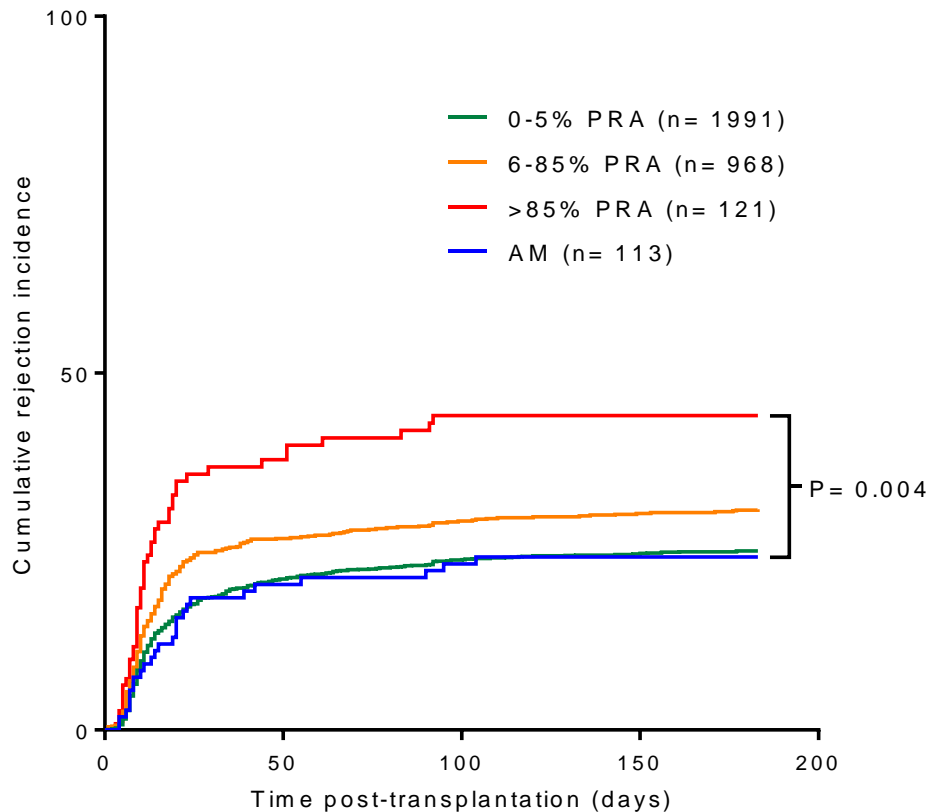
10-year graft survival re-transplant recipients



Selection:

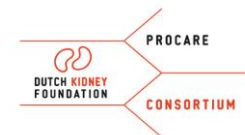
- ≥ 1996
- Renal only
- Deceased donor
- ≥ 1 HLA antigen mm
- Repeat transplant

Rejection incidence in AM patients comparable to non-immunized patients: all transplants



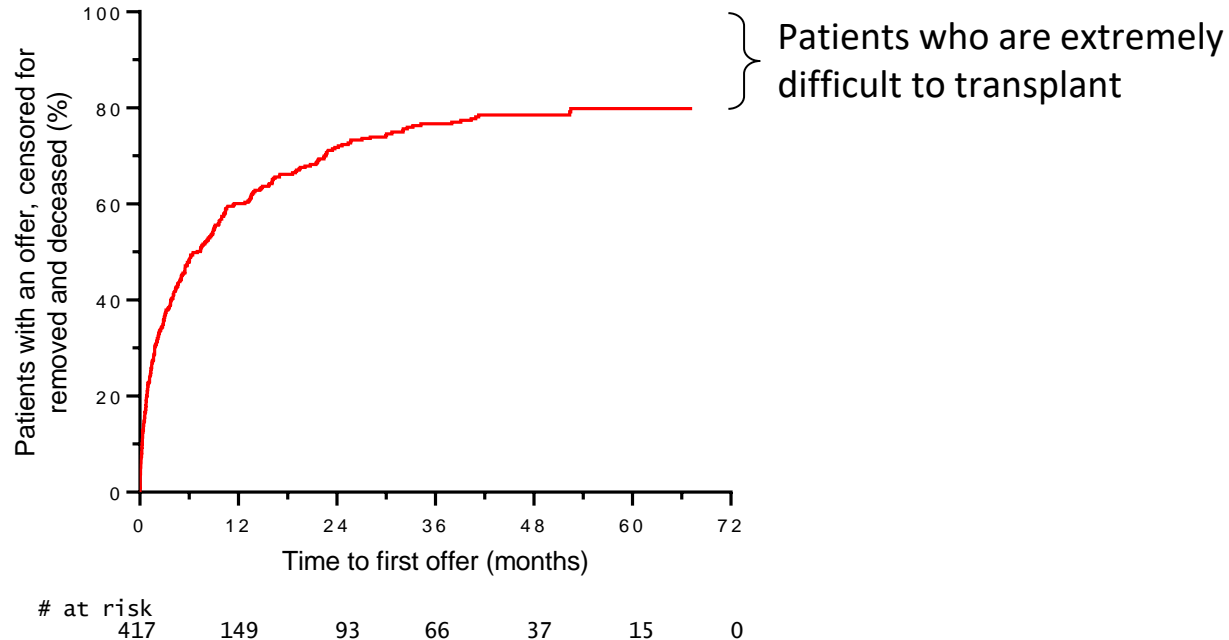
Selection:

- ≥ 1996
- Renal only
- Deceased donor
- ≥ 1 HLA antigen mm



However, not all AM patients can be transplanted

- Still some AM patients with ‘exotic’ HLA types within the ET donor population remain on the waiting list



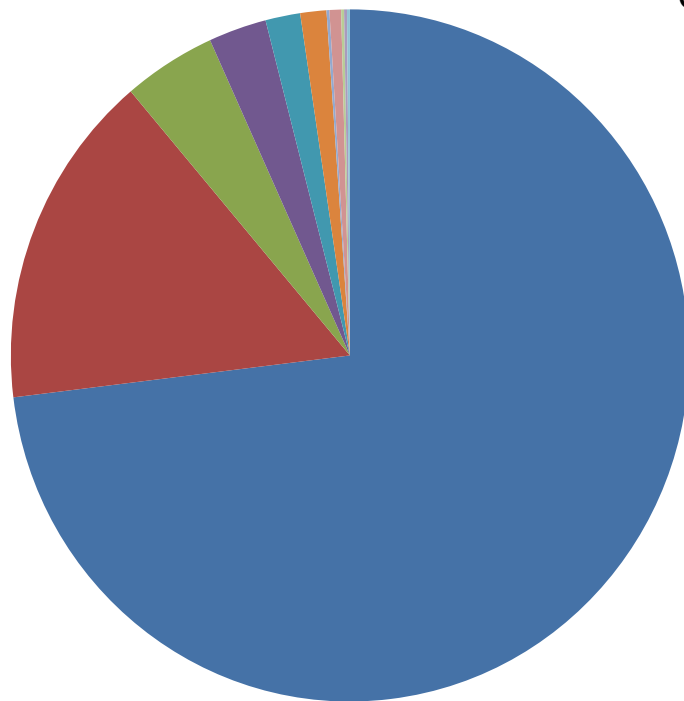
EUROSTAM project: a Europe-wide AM program



- Solution: look into donor populations where the 'exotic' phenotype is more common
- Exchange between allocation programs
- The EUROSTAM project (FP7):
 - Simulation studies on basis of the HLA phenotypes in different European populations
 - Feasibility study which lead to an advice to the European Union on how to achieve exchange between allocation organizations
 - Eurotransplant, UK transplant, Greece, Czech Republic, Barcelona



Simulation: >25% of patients with increased chance to find a suitable donor in another population



Change in access to transplant

- No better
- 1% (n=114)
- 2% (n=32)
- 3% (n=20)
- 4% (n=12)
- 5% (n=9)
- 7% (n=1)
- 9% (n=4)
- 10% (n=1)
- 23% (n=1)





- The AM program increased the chance for a highly sensitized patient to be transplanted
- The AM program has been highly successful, with over 1800 highly sensitized patients transplanted
- Acceptable mismatches are truly acceptable: no match-effect
- Excellent ten-year graft survival of AM patients
- HLA compatible transplants remain the preferred way to transplant highly sensitized patients
- Second option for those that still do not receive an organ: allocation outside geographical area (EUROSTAM)
- Last option for highly sensitized patients: desensitization (AM Imlifidase Program)

The Eurotransplant Acceptable Mismatch Program

The ETRL team:

Marissa van Oevelen
Geert Haasnoot
Yvonne Zoet
Cynthia Kramer

Thanks to:

- Screening and tissue typing laboratory Leiden
- ETRL immunologists
- Eurostam consortium
- Procure consortium
- ET transplant centers and TT laboratories