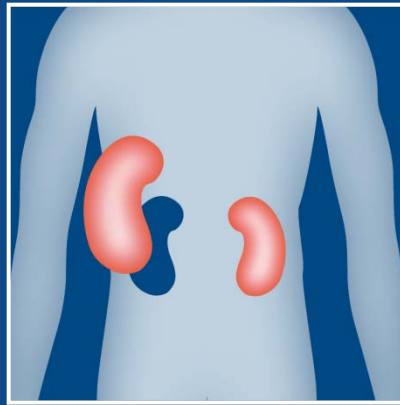


Nephro Update Europe 2017

6-7 October, Vienna

Transplantation



Rainer Oberbauer, Austria

Subtopics

- Epidemiology of kidney transplantation
- Donor selection
- Basics of Alloimmunity
- The sensitized patient
- Strategies to improve long term outcomes

Epidemiology of Kidney Transplantation

State of the Art - Epidemiology

- Kidney transplantation is the treatment of choice for ESRD
- In EU <10-50% of HD/PD are waitlisted
- Transplantation is cost effective (still true in 2017?)
 - Better QoL and cheaper

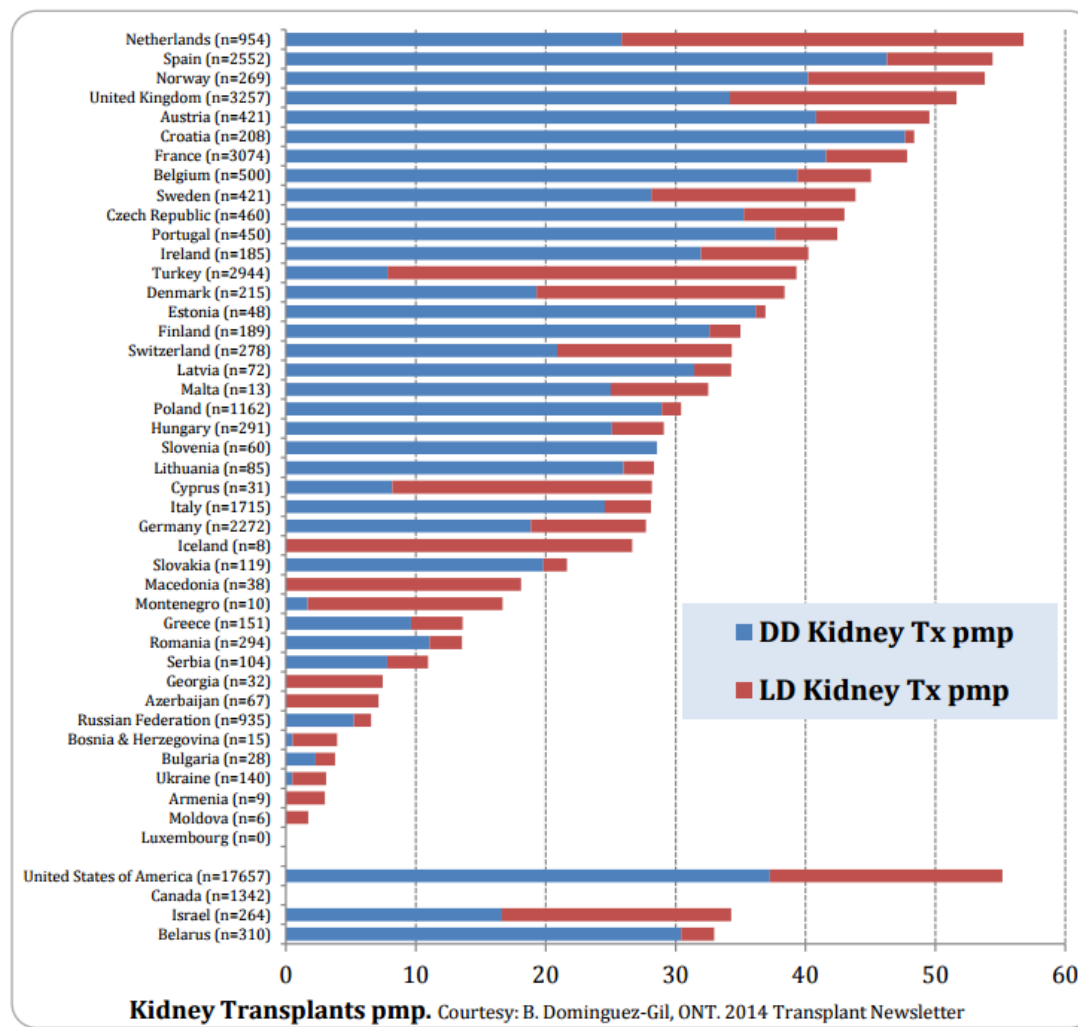
KDIGO Guidelines on waitlisting – 2017 (pending)

Haller M et al. Nephrol Dial Transplant. 2014 Nov;29(11):1994-7

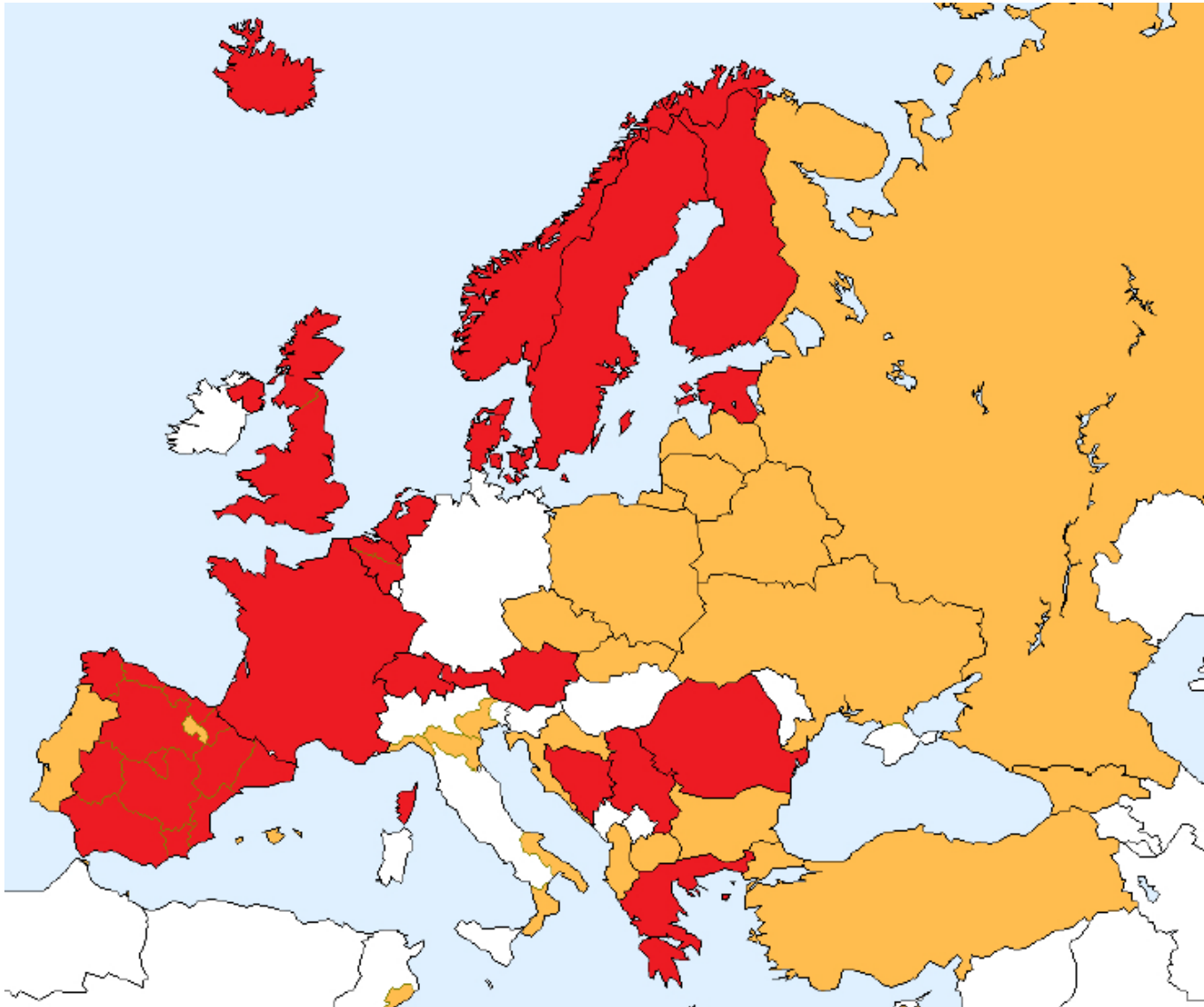
Haller M et al. Nephrol Dial Transplant. 2011 Sep;26(9):2988-95

Vanholder R et al. Nat Rev Nephrol. 2017 Jul;13(7):393-409

Kidney Transplant in the EU 28+



ERA-EDTA Annual Report 2015



www.era-edta-reg.org/files/annualreports/pdf/AnnRep2015.pdf

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Take-Home Message

- KDIGO-Waitlisting GL 2017

We recommend that all CKD G4-5 patients expected to reach ESRD, regardless of socioeconomic status, sex, or race/ethnicity, should be informed of, educated about, and screened for further transplant evaluation. (1D/Ungraded)

- KTX is likely cost effective (was in 2012)

- Epidemiology of KTX in EU 28+ varies considerably

List of References - Epidemiology

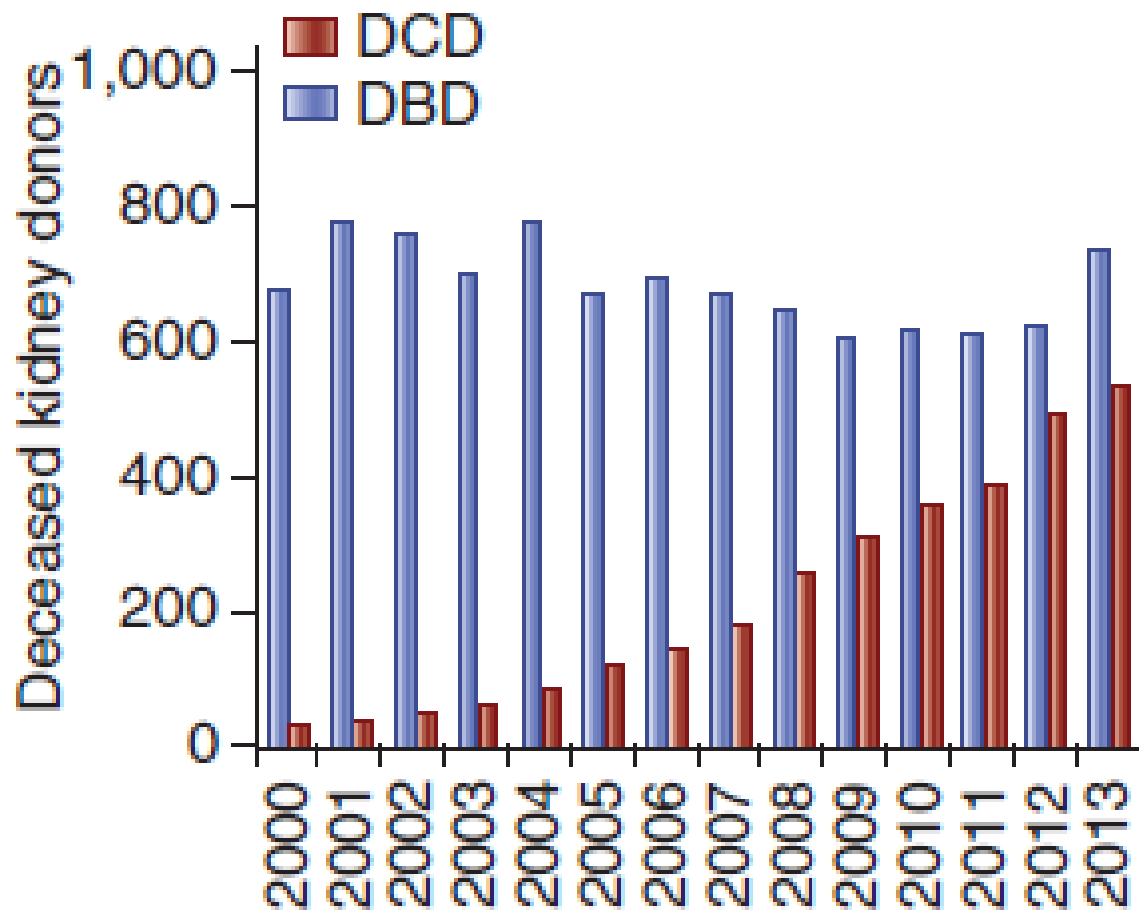
1. KDIGO Guidelines on waitlisting – 2017 (pending)
2. Haller MC, Vanholder R, Oberbauer R, et al. Health economics and European Renal Best Practice--is it time to bring health economics into evidence-based guideline production in Europe? *Nephrol Dial Transplant* 2014; 29: 1994-1997.
3. Haller M, Gutjahr G, Kramar R, et al. Cost-effectiveness analysis of renal replacement therapy in Austria. *Nephrol Dial Transplant* 2011; 26: 2988-2995.
4. Vanholder R, Annemans L, Brown E, et al. Reducing the costs of chronic kidney disease while delivering quality health care: a call to action. *Nat Rev Nephrol* 2017; 13: 393-409.
5. Gleiss A, Oberbauer R, Heinze G. An unjustified benefit: immortal time bias in the analysis of time-dependent events. *Transplant Int* 2017; (pending).
6. Haller M, Kammer M, Heinze G, et al. Survival Benefit of Kidney Transplantation compared to Maintenance Dialysis in Elderly End Stage Renal Disease Patients. (pending 2017).
7. European Directorate for the Quality of Medicines & HealthCare (EDQM) Volume 21: 2016
8. www.era-edta-reg.org/files/annualreports/pdf/AnnRep2015.pdf

Donor Selection

State of the Art – Donor Selection

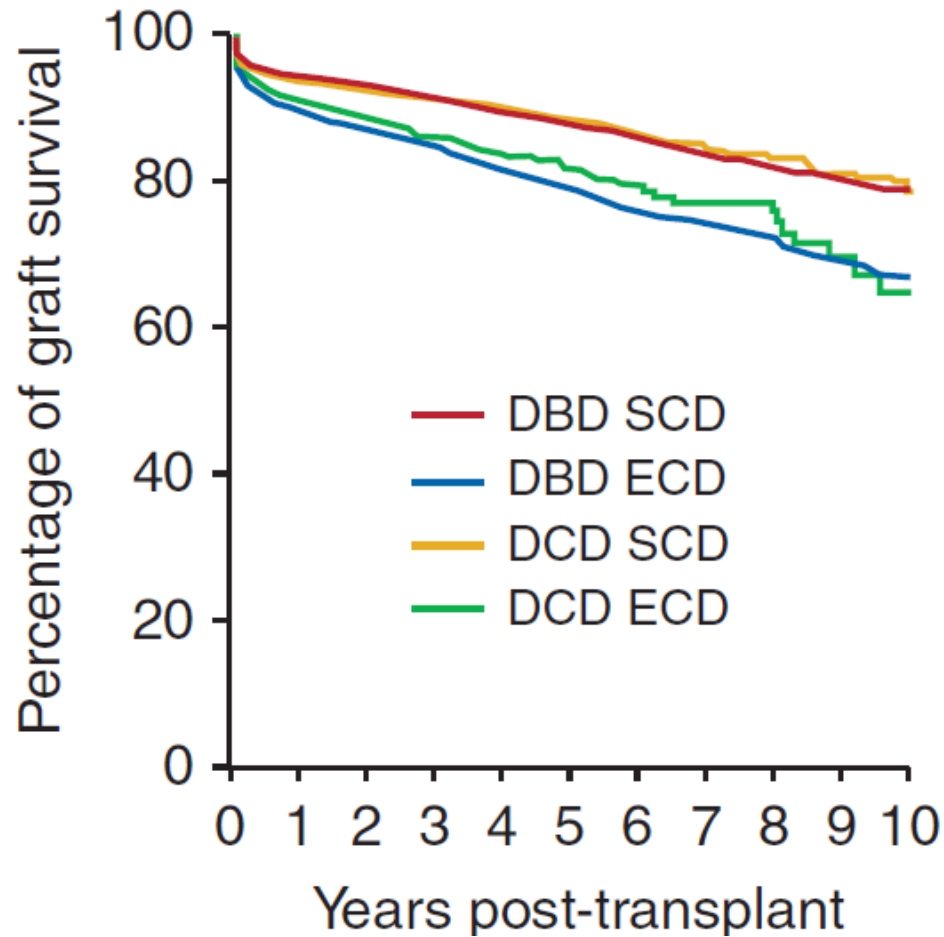
- Deceased donors (DBD, DCD)
- Living donors (KDP)
- Considerable differences between countries and even within countries

DCD & DBD in U.K.



Summers DM et al. *Kidney Int.* 2015 Aug;88(2):241-9.

DCD & DBD in U.K. & outcomes



Summers DM et al. *Kidney Int.* 2015 Aug;88(2):241-9.

State of the Art – Donor Selection

Selected Strategies	% of Recipients	Estimated (Qualitative) Effect Size	Likelihood of Realization in the next Decade
Utilitarian allocation of DD kidneys (KDPI & EPTS)	68 *	7% in average median life-years per TX	effective since December 2014 (in US)
Deceased donor hypothermia	68 *	OR of DGF 0.62; Impact on graft survival uncertain	potentially high
Donor kidney machine perfusion	Potentially all	aOR of DGF 0.57; Impact on graft survival uncertain	effective in some OPOs for some years
Increased live donations	>10%		country specific policy

Wekerle T et al. The Lancet 2017 May 27;389(10084):2152-2162

Take-Home Message

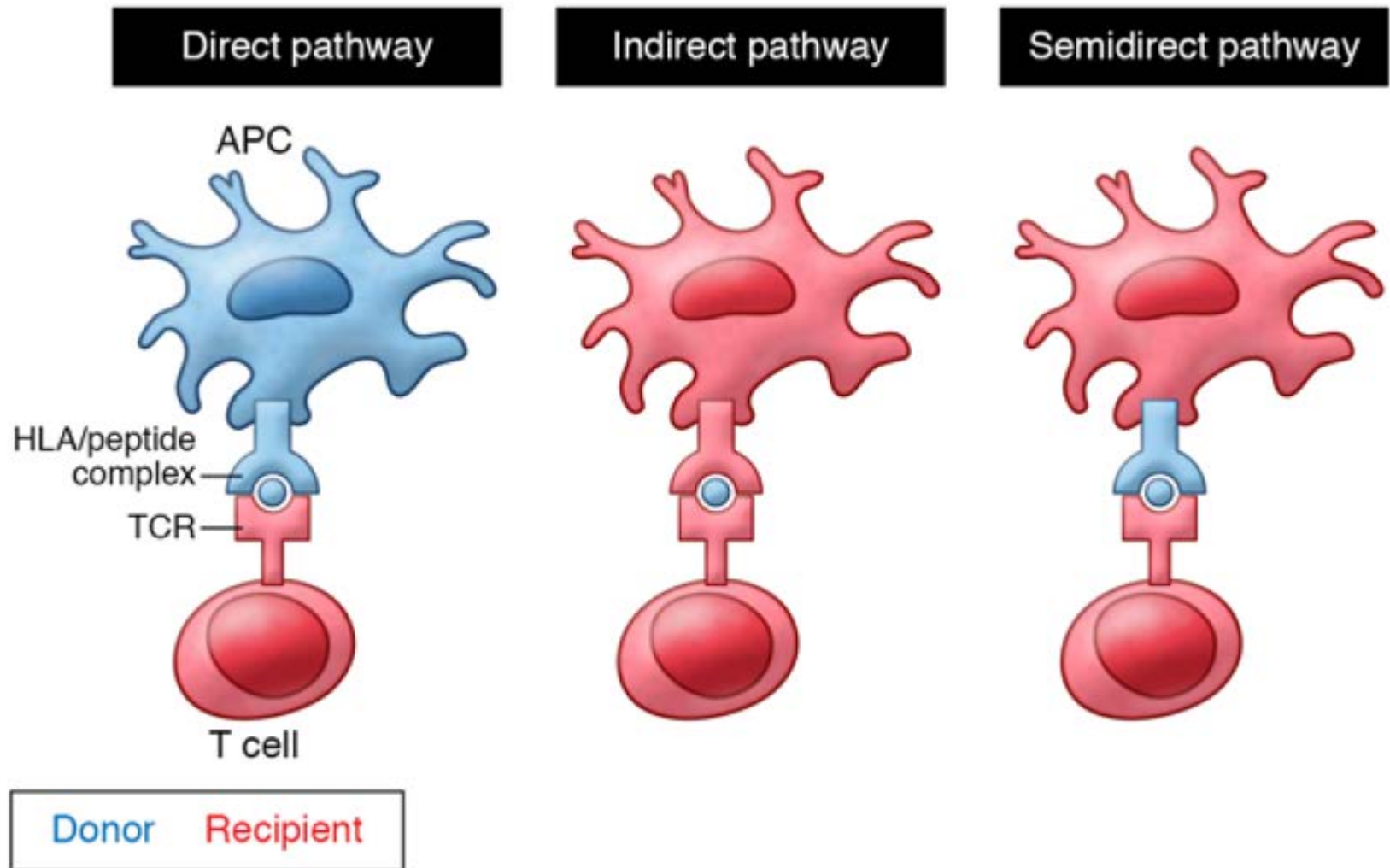
- Deceased donors (DBD, DCD) – Cold storage vs Machine perfusion vs Donor hypothermia?
- DD Acceptance: Expanding the limits
- Equity: Utilitarian vs Fairness?
- Living donors – Sensitive issue, allow for compatibility through KDP vs desensitization

List of References – Donor Selection

1. Summers DM, Watson CJ, Pettigrew GJ, et al. Kidney donation after circulatory death (DCD): state of the art. *Kidney Int* 2015; 88: 241-249.
2. Wekerle T, Segev D, Lechler R, et al. Strategies for long-term preservation of kidney graft function. *Lancet* 2017; 389: 2152-2162.

Basics of Alloimmunity

State of the Art – Indirect Allorecognition



DeWolf S & Sykes M. *JCI* 2017, 127:2473-81

State of the Art – Current Controversies

- Which subset of anti-donor HLA antibodies allows individual treatment decisions?
- What is the interrelationship of T-cell-mediated and B-cell-mediated immunity and their relative contribution to graft injury?

The Sensitized Patient


State of the Art – The sensitized patient

UNOS - AM Program

[Am J Transplant](#). 2017 Aug 8. doi: 10.1111/ajt.14457. [Epub ahead of print]

The Kidney Allocation System Claims Equity; It Is Time to Review Utility and Fairness.

[Klintmalm GB](#)¹, [Kaplan B](#)².





 **Author information**

Fairness: As many patients with a high calculated PRA are retransplants, the current system prioritizes a patient with a previous transplant to receive another kidney graft before a patient who has never been given this chance. Clearly, neither utility and equity nor fairness are realized under this quite frequent situation. The question must be raised: Should not recipients who never received a transplant have a higher priority than those looking for a second or third?

Klintmalm G & Kaplan B. AJT. 2017 Aug 8. doi: 10.1111/ajt.14457. [Epub ahead]


State of the Art – Sensitized Patient

ET-AM Program

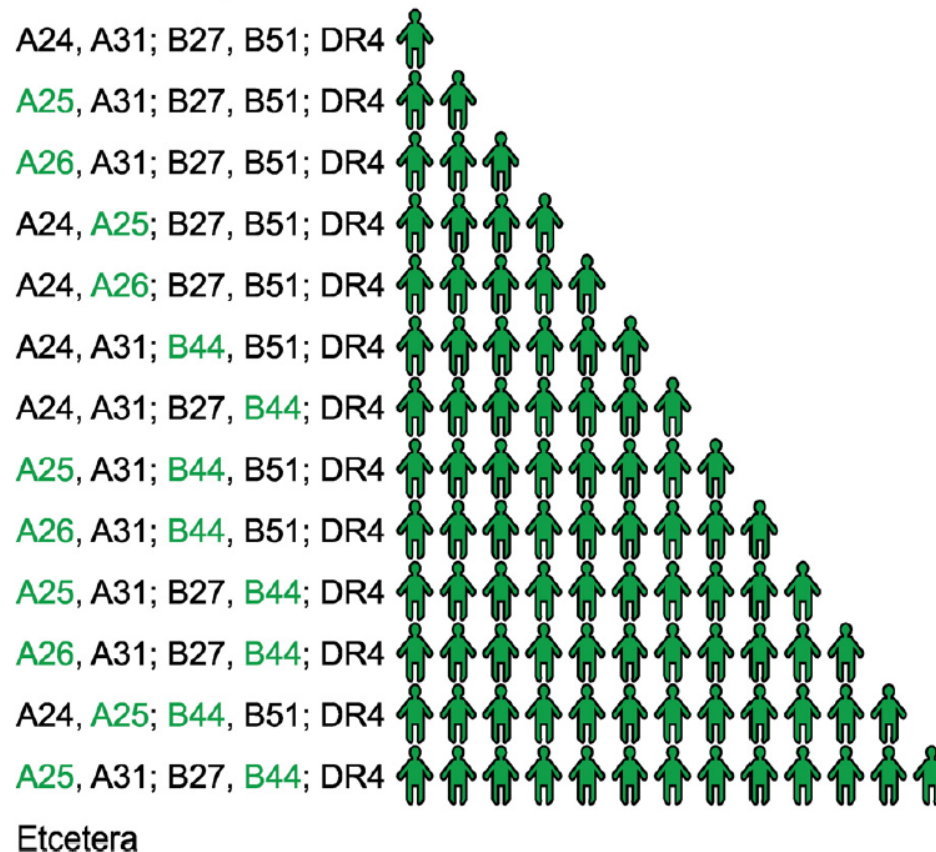
Patient	HLA type	Crossmatch
	A24 A29; B8 B62; DR1 DR10	
Panel donor 1		
	<u>A1</u> A24; B8 B62; DR1	Negative
Panel donor 2		
	A24 <u>A32</u> ; B8 B62; DR1	Positive
Panel donor 3		
	A1 <u>A2</u> ; B8 B62; DR10	Positive

Heidt S et al. *Transpl Immunol.* 2015 Oct;33(2):51-7

State of the Art – Sensitized Patient ET-AM Program

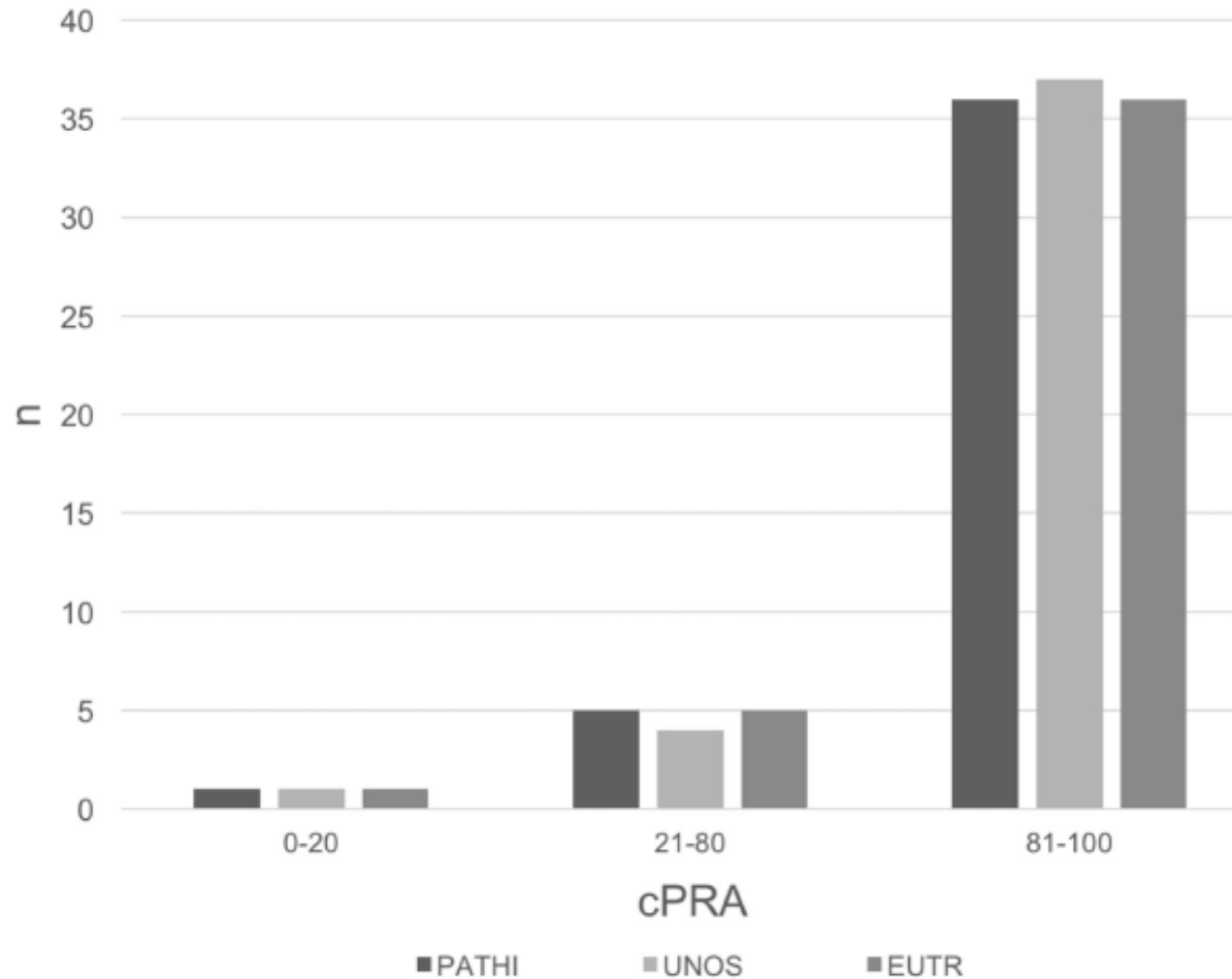
 Patient HLA: A24 A31; B27 B51; DR4
Acceptables: A25 A26; B44

Suitable kidney donors:



Heidt S et al. *Transpl Immunol.* 2015 Oct;33(2):51-7

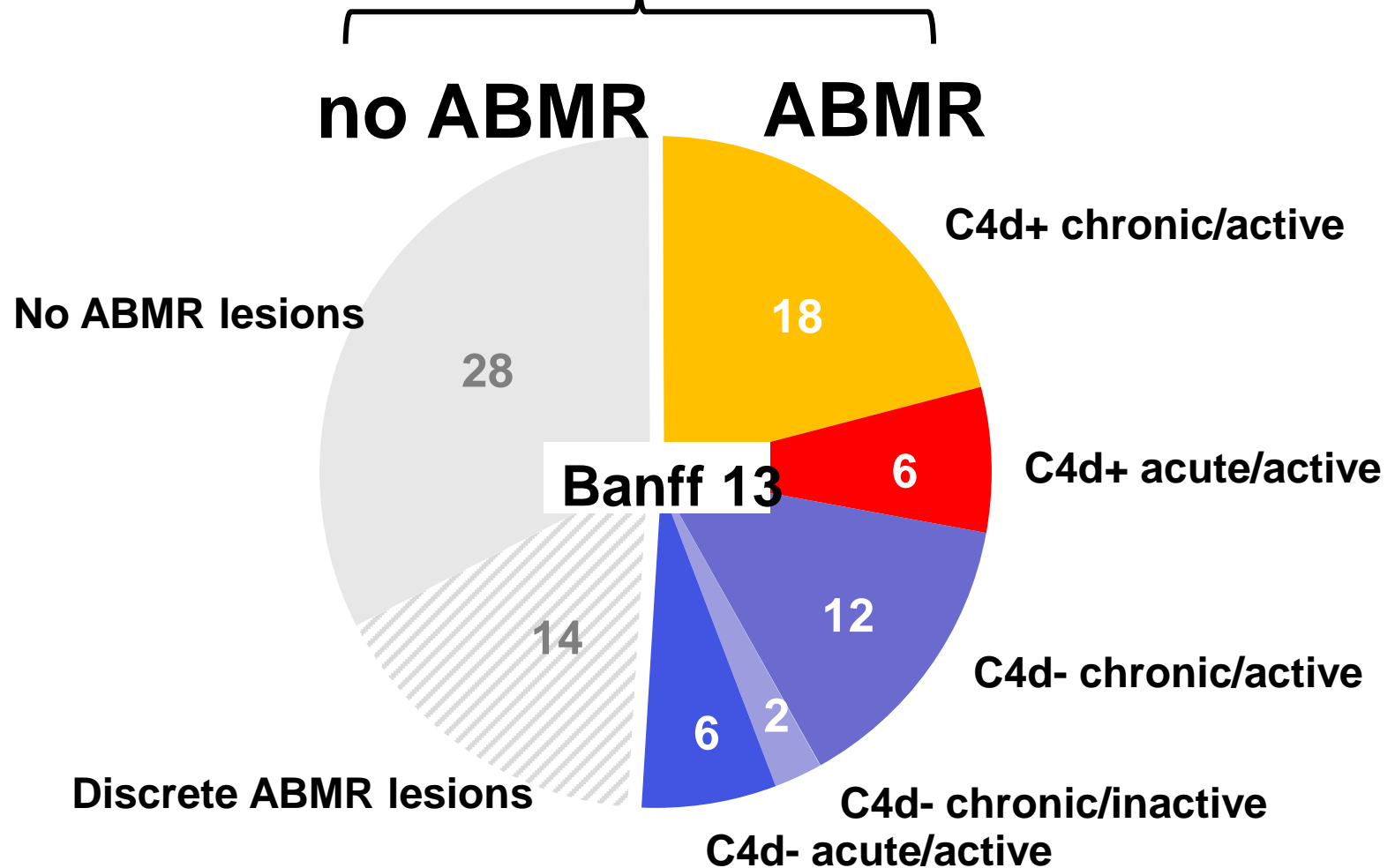
State of the Art – Sensitized Patient cPRAs



Asensio E et al. Front Immunol. 2017 May 11;8:54

Effects of anti HLA-DSAs

86 DSA+ patients



Eskandary F et al. JASN 2017 (pending)

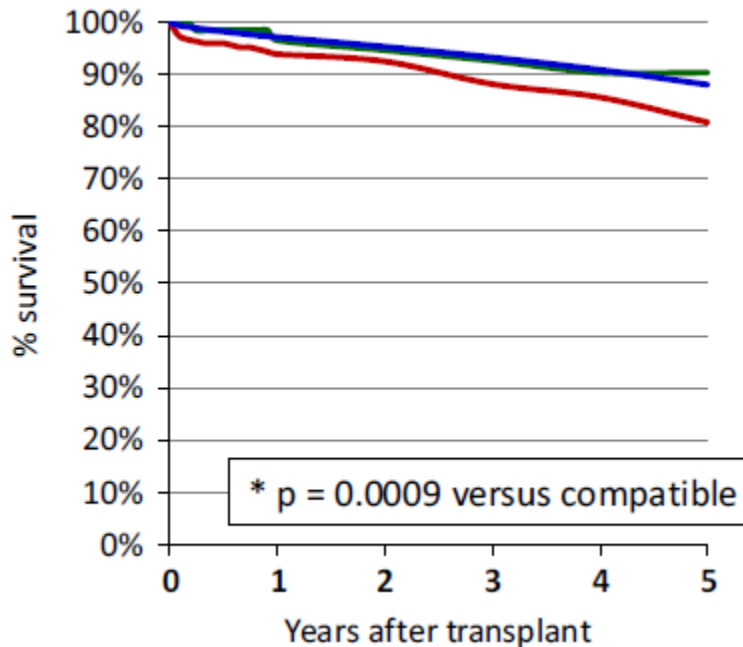
Screening for dnDSA?

Baseline efficacy	Costs 2013 US \$	Cost effectiveness \$Costs/QALY
<hr/>		
0.85 risk reduction		
No Screen	439 486	
Screen	449 595	444 258
<hr/>		

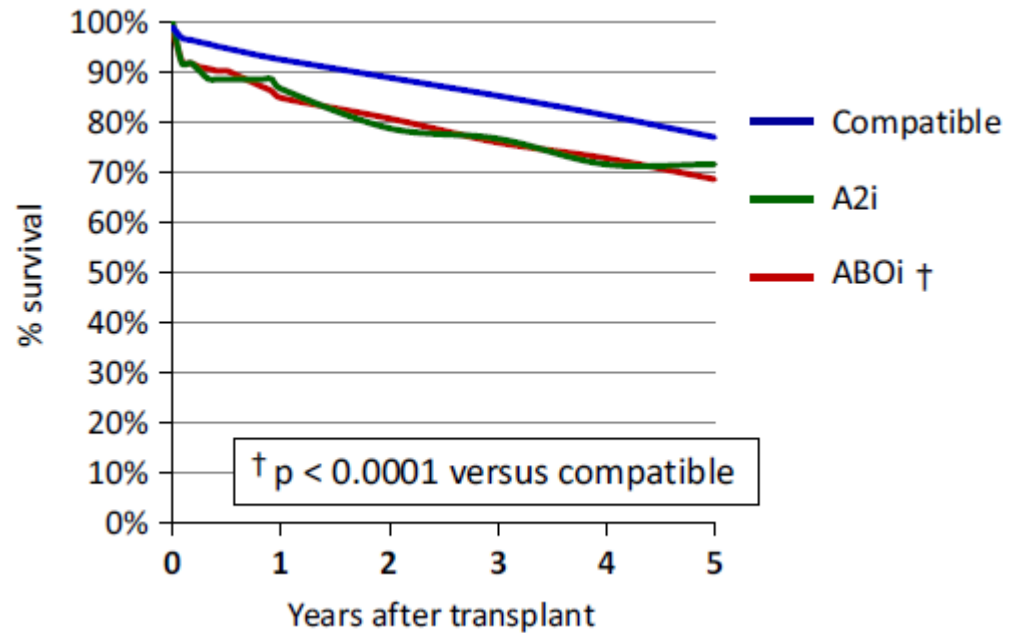
Kibert BA et al. Am J Transplant. 2016 Nov;16(11):3212-3219

ABO-i Transplantation

Patient survival

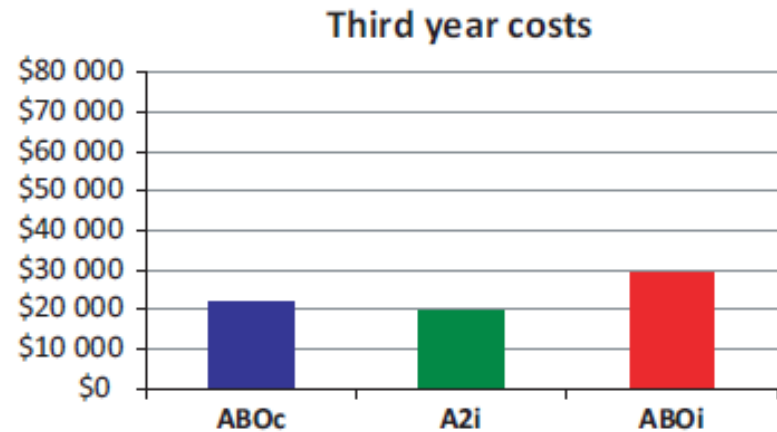
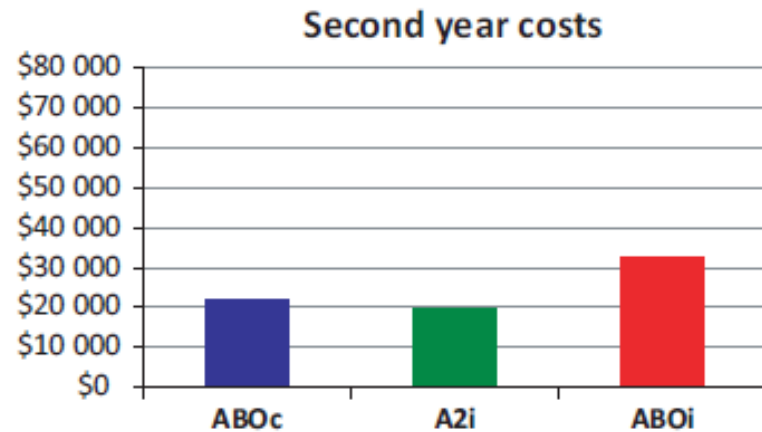
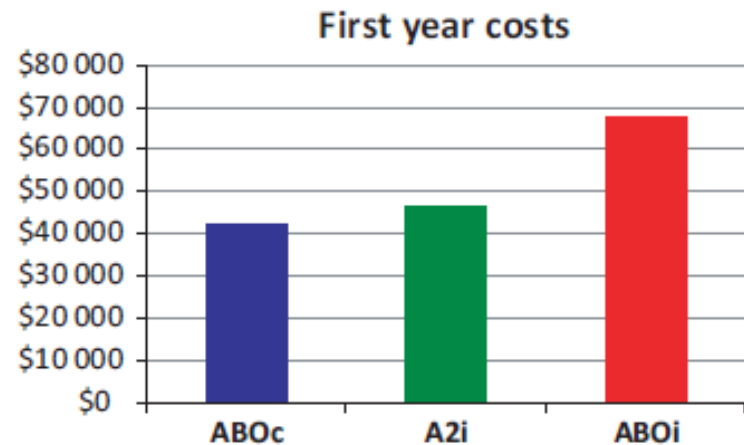
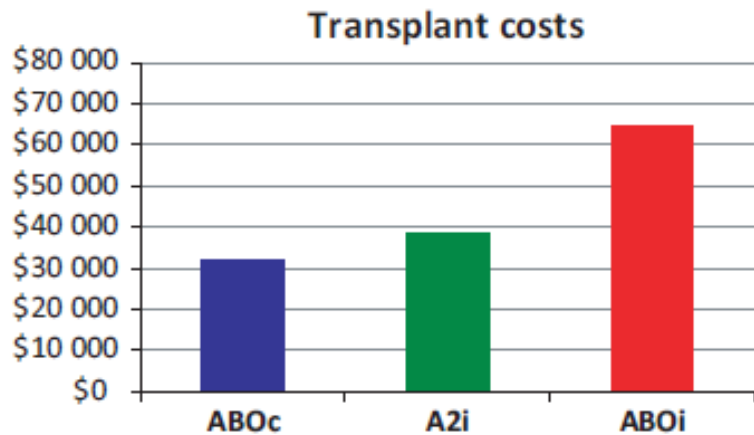


DC graft survival



Axelrod D et al. Am J Transplant. 2016 May;16(5):1465-73.

Costs of ABO-i Transplantation



Axelrod D et al. *Am J Transplant.* 2016 May;16(5):1465-73.

ABO-Incompatible Kidney Transplants: Twice as Expensive, Half as Good (Editorial)

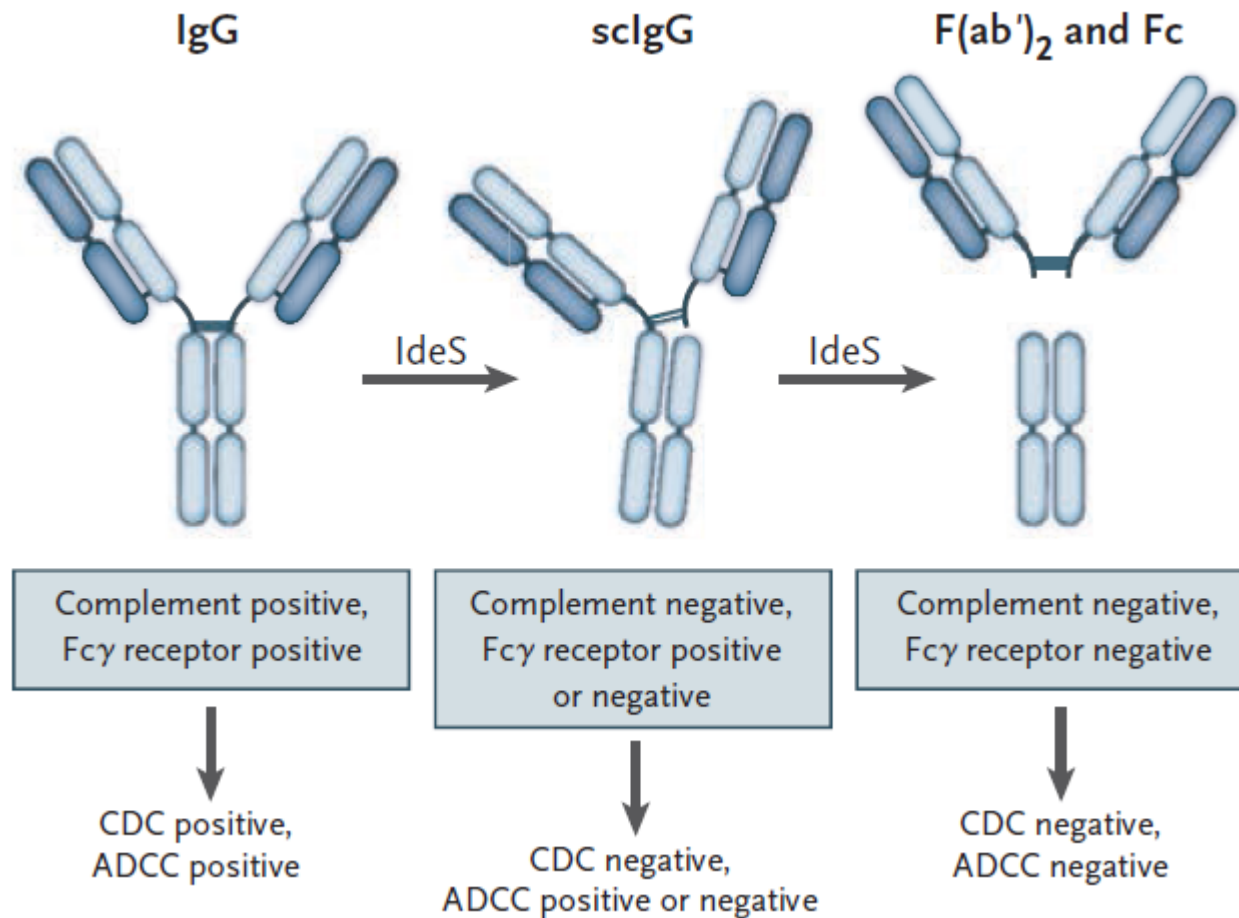
Held PJ et al. AJT 2016; 16: 1343-1344

Options of desensitization

- Plasmapheresis
- Immunoadsorption
- Cascade filtration
- Complement inhibition
- Proteasome inhibitor
- Lymphocyte depleting antibodies
- Anti T-cell therapy
- Anti B-cell therapy
- IVIG
- KPD program

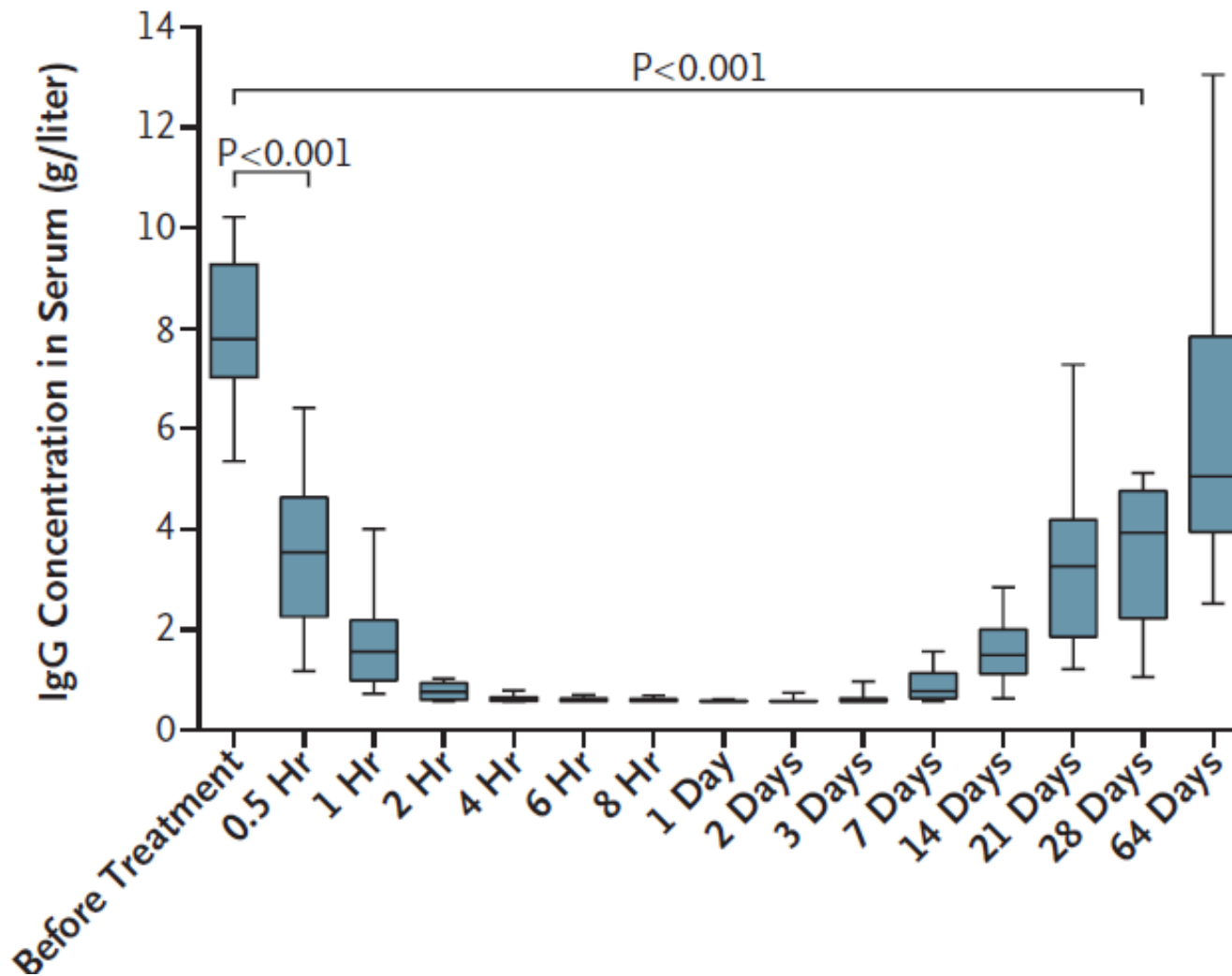
Clearing of intact IgG by **IdeS**

(Immunoglobulin G-degrading enzyme of **S**treptococcus pyogenes)



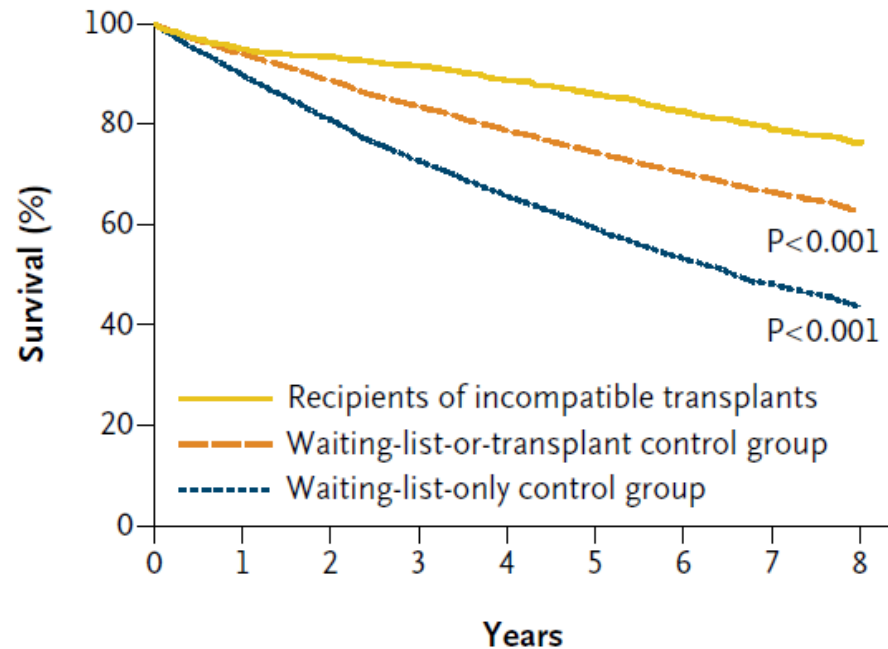
Jordan S et al. *N Engl J Med*. 2017 Aug 3;377(5):442-453

Effect of IdeS on IgG



Jordan S et al. *N Engl J Med*. 2017 Aug 3;377(5):442-453

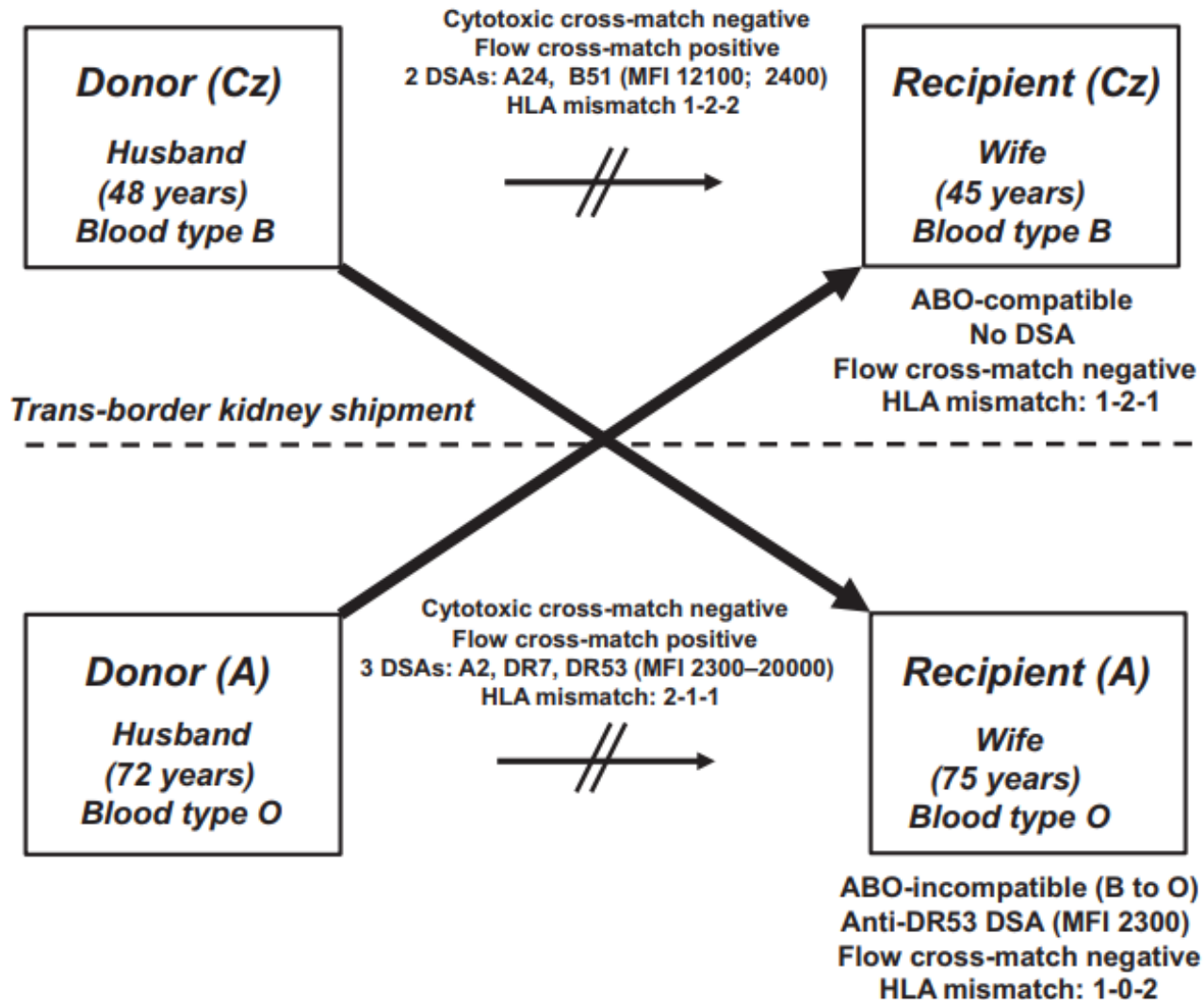
Survival Benefit of HLAi-TX



No. at Risk					
Recipients of incompatible transplants	1025	958	832	584	327
Waiting-list-or-transplant control group	5125	4546	3673	2493	1414
Waiting-list-only control group	5125	4141	3024	1810	916

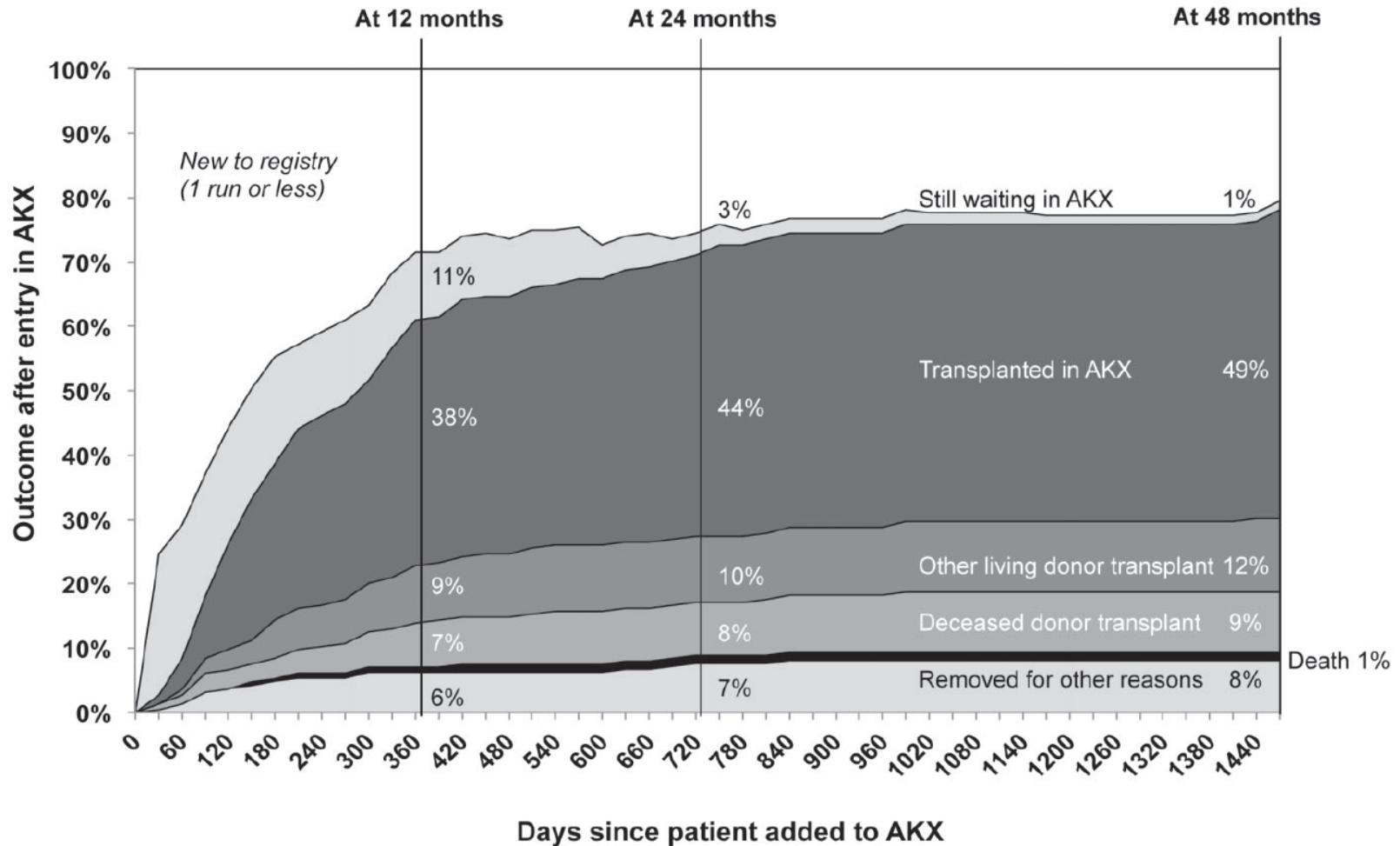
Orandi BJ, et al. *NEJM*. 2016; 374(10): 940-50.

Kidney Exchange Strategies



Böhmig GA et al. *Transpl Int.* 2017 Jun;30(6):638-639.

KPD waiting time



Cantwell L et al. Nephrology (Carlton). 2015 Mar;20(3):124-31

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Take-Home Message

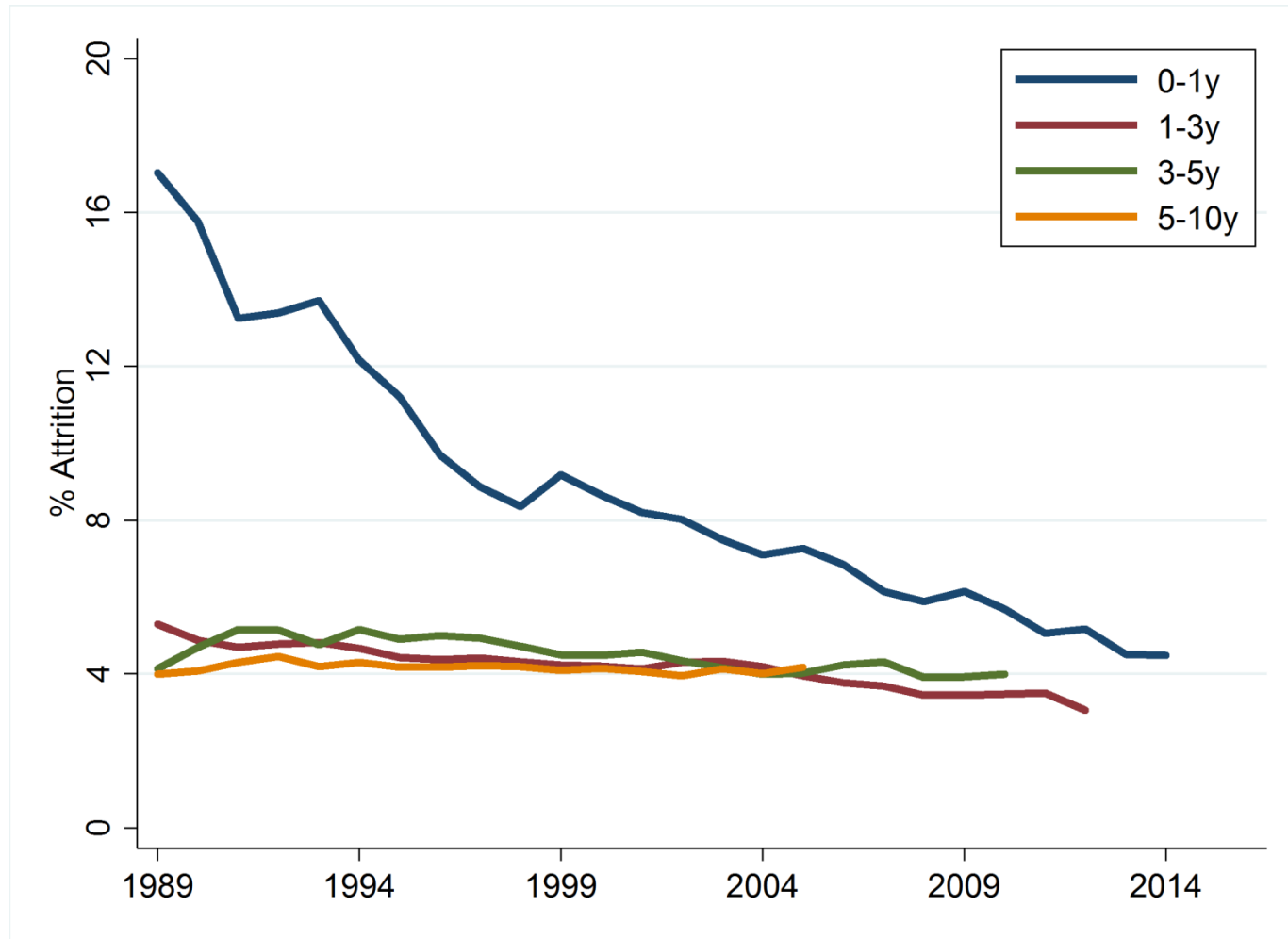
- Desensitization protocols available (AB0i & HLAi)
- dnHLA and non-HLA DSAs: poor predictors of outcomes but important
- Better 'Kidney Swap' (KPD)

List of References

1. Reindl-Schweighofer R, Heinzl A, Signorini L, et al. Mechanisms underlying human genetic diversity: consequence for anti-graft antibody responses *Transplant Int* 2017
2. Wekerle T, Segev D, Lechler R, et al. Strategies for long-term preservation of kidney graft function. *Lancet* 2017; 389: 2152-2162.
3. Klintmalm GB, Kaplan B. The Kidney Allocation System Claims Equity; It Is Time to Review Utility and Fairness. *Am J Transplant* 2017.
4. Heidt S, Witvliet MD, Haasnoot GW, et al. The 25th anniversary of the Eurotransplant Acceptable Mismatch program for highly sensitized patients. *Transpl Immunol* 2015; 33: 51-57.
5. Asensio E, Lopez-Hoyos M, Romon I, et al. Assessment of Spanish Panel Reactive Antibody Calculator and Potential Usefulness. *Front Immunol* 2017; 8: 540.
6. Eskandari FA. Et al *JASN* 2017. (pending)
7. Kiberd BA, Miller A, Martin S, et al. De Novo Donor-Specific Human Leukocyte Antigen Antibody Screening in Kidney Transplant Recipients After the First Year Posttransplantation: A Medical Decision Analysis. *Am J Transplant* 2016; 16: 3212-3219.
8. Axelrod D, Segev DL, Xiao H, et al. Economic Impacts of ABO-Incompatible Live Donor Kidney Transplantation: A National Study of Medicare-Insured Recipients. *Am J Transplant* 2016; 16: 1465-1473.
9. Held PJ, McCormick F. ABO-Incompatible Kidney Transplants: Twice as Expensive, Half as Good. *Am J Transplant* 2016; 16: 1343-1344.
10. Orandi BJ, Luo X, Massie AB, et al. Survival Benefit with Kidney Transplants from HLA-Incompatible Live Donors. *N Engl J Med* 2016; 374: 940-950.
11. Redfield RR, Scalea JR, Zens TJ, et al. The mode of sensitization and its influence on allograft outcomes in highly sensitized kidney transplant recipients. *Nephrol Dial Transplant* 2016; 31: 1746-1753.
12. Bohmig GA, Fronek J, Slavcev A, et al. Czech-Austrian kidney paired donation: first European cross-border living donor kidney exchange. *Transpl Int* 2017; 30: 638-639.
13. Cantwell L, Woodroffe C, Holdsworth R, et al. Four years of experience with the Australian kidney paired donation programme. *Nephrology (Carlton)* 2015; 20: 124-131.

Strategies to improve Long Term Outcomes

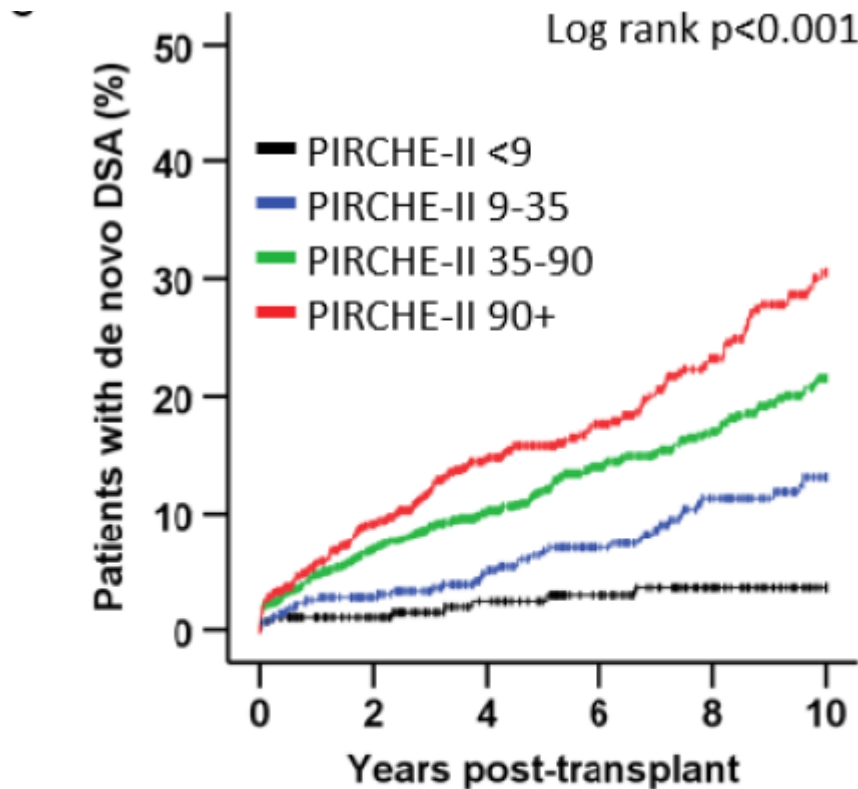
State of the Art – Long-Term Outcomes



Wekerle T et al. *The Lancet* 2017 May 27;389(10084):2152-2162

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HLA-Epitope Matching

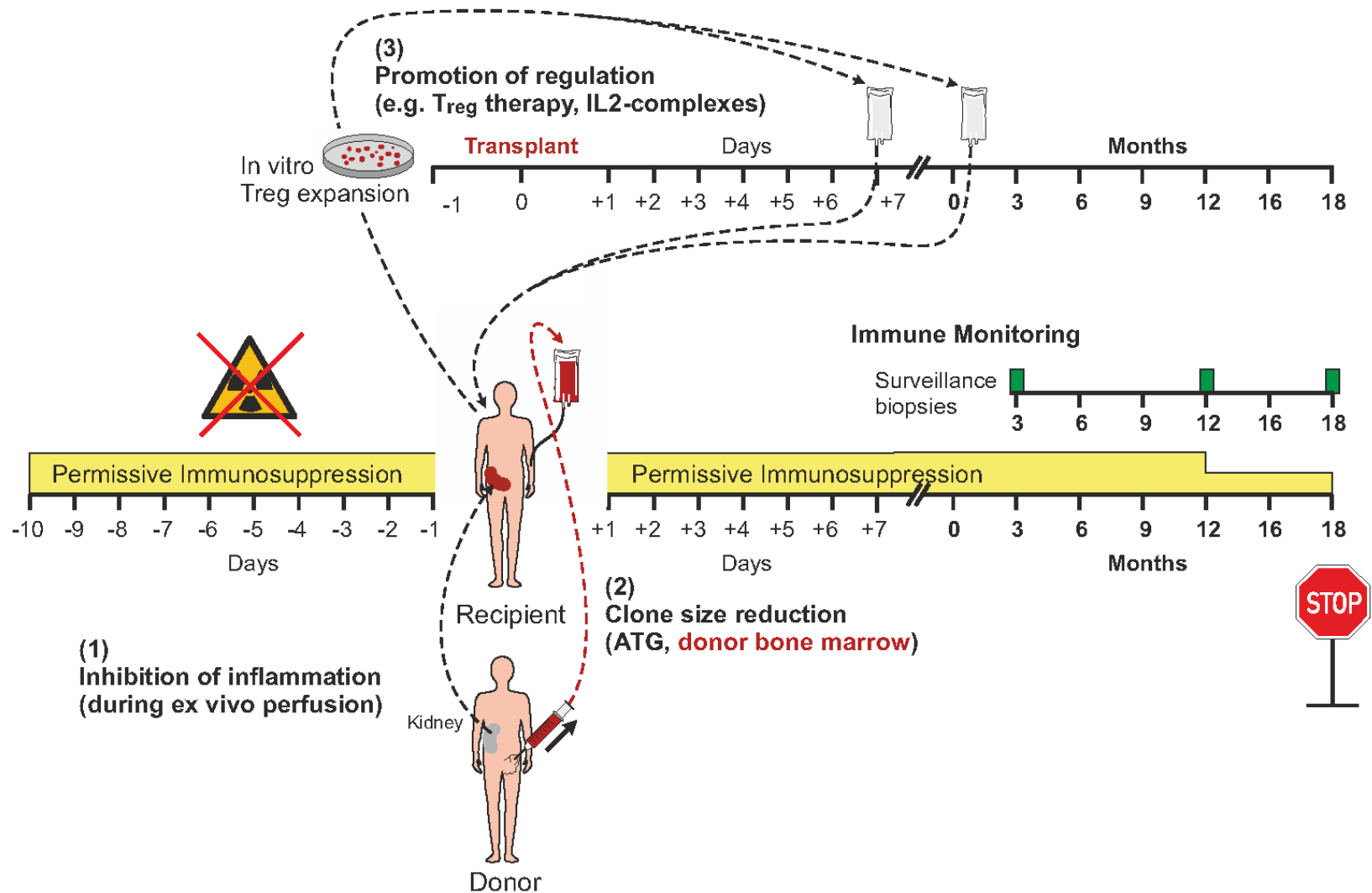


Number at risk

Years post-transplant	0	2	4	6	8	10
PIRCHE <9	285	246	203	168	126	87
PIRCHE 9-35	446	378	311	245	182	131
PIRCHE 35-90	1222	984	763	578	451	301
PIRCHE 90+	834	630	463	346	240	143

Lachmann N et al. *AJT* 2017 Jun 14. [Epub ahead of print]

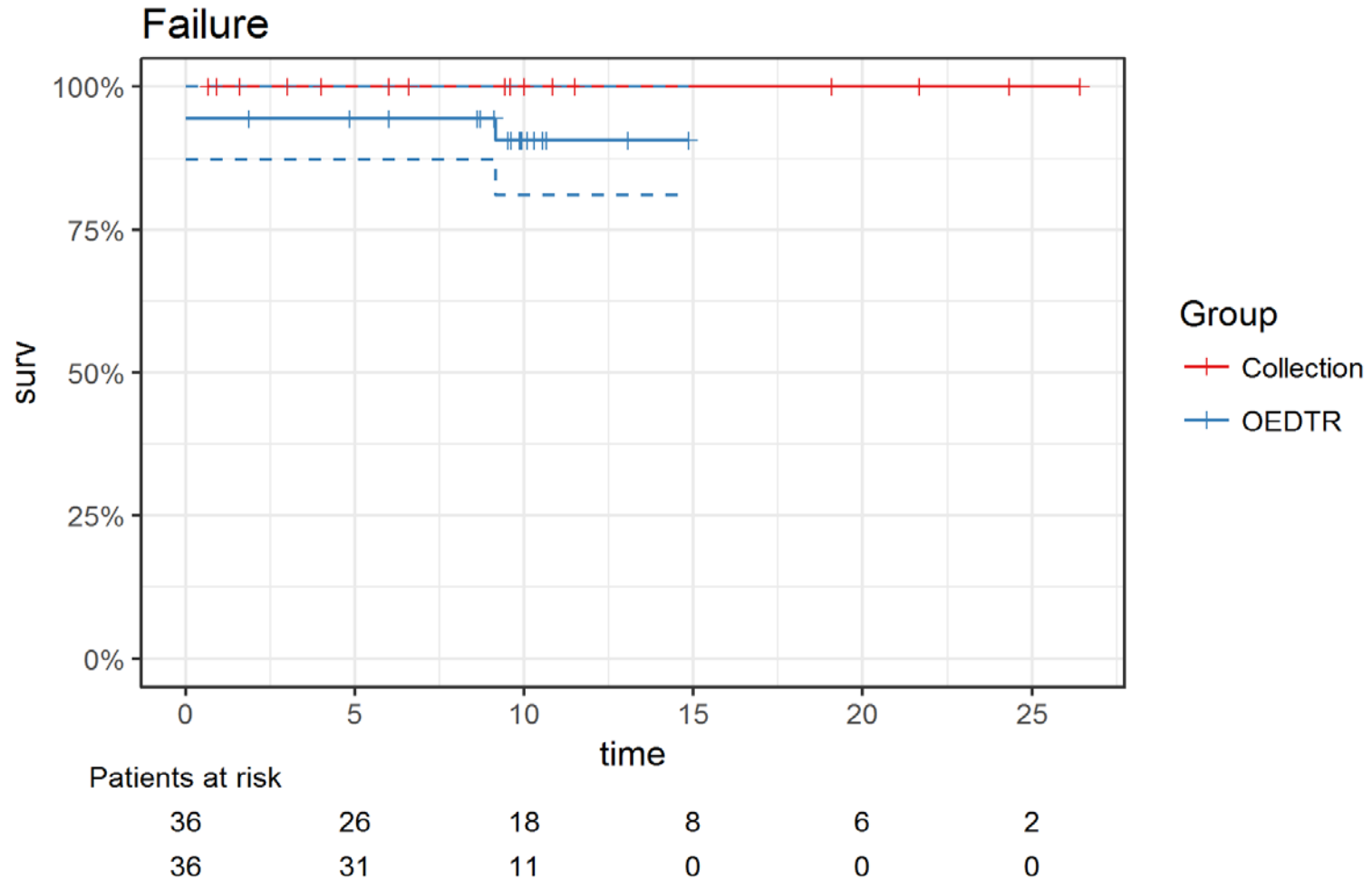
State of the Art – Long-Term Outcomes



Wekerle T et al. The Lancet 2017 May 27;389(10084):2152-2162

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State of the Art – Long-Term Outcomes BMT & KTX



Eder M et al. 2017 (pending)

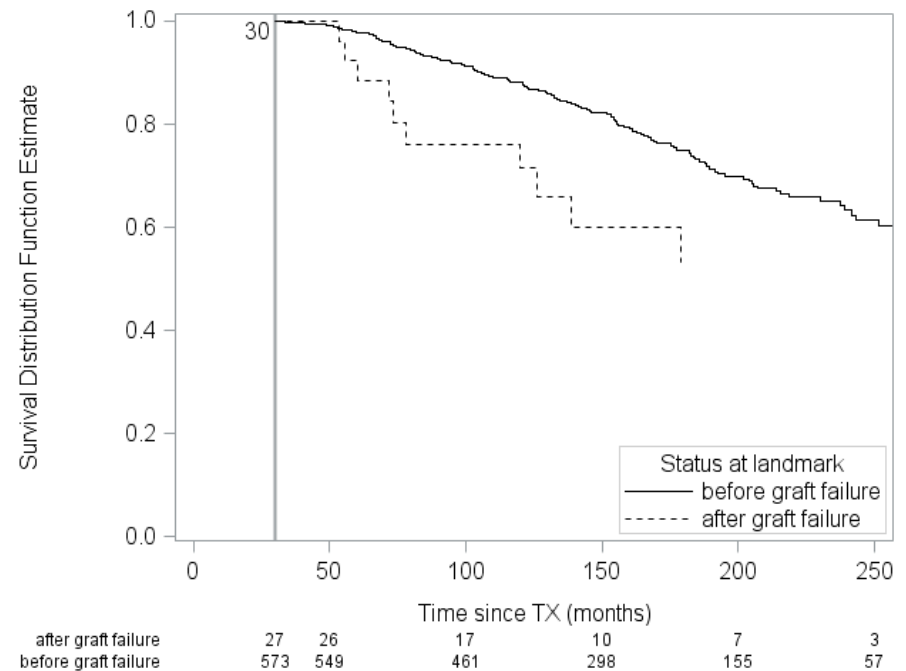
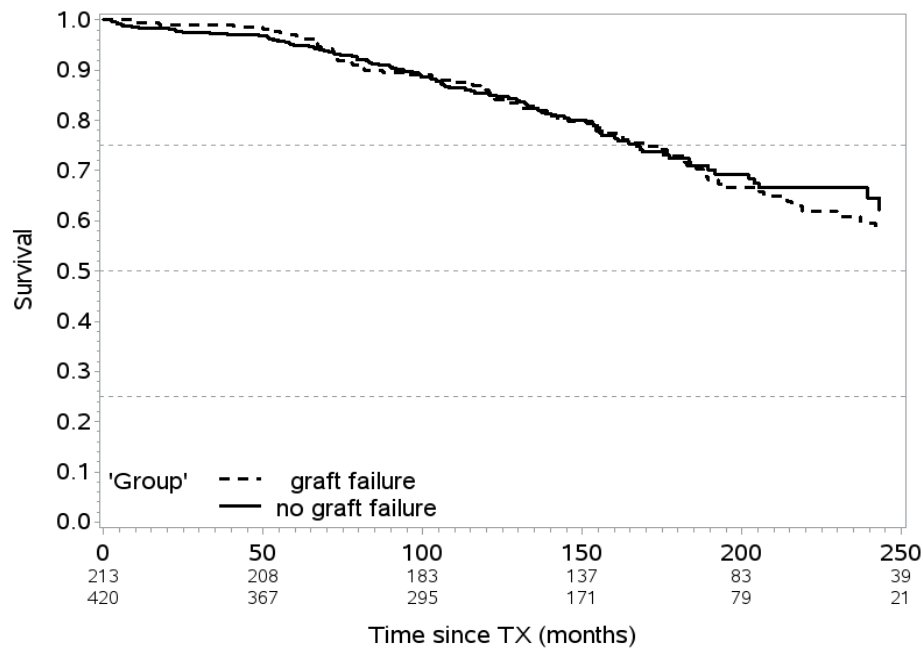
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Take-Home Message

- The Transplant field has fast advanced and results are excellent
- Better Histocompatibility matching (Epitopes)
- Improving adherence
- Future outlook: Tolerance via mixed chimerism of non-toxic regimens

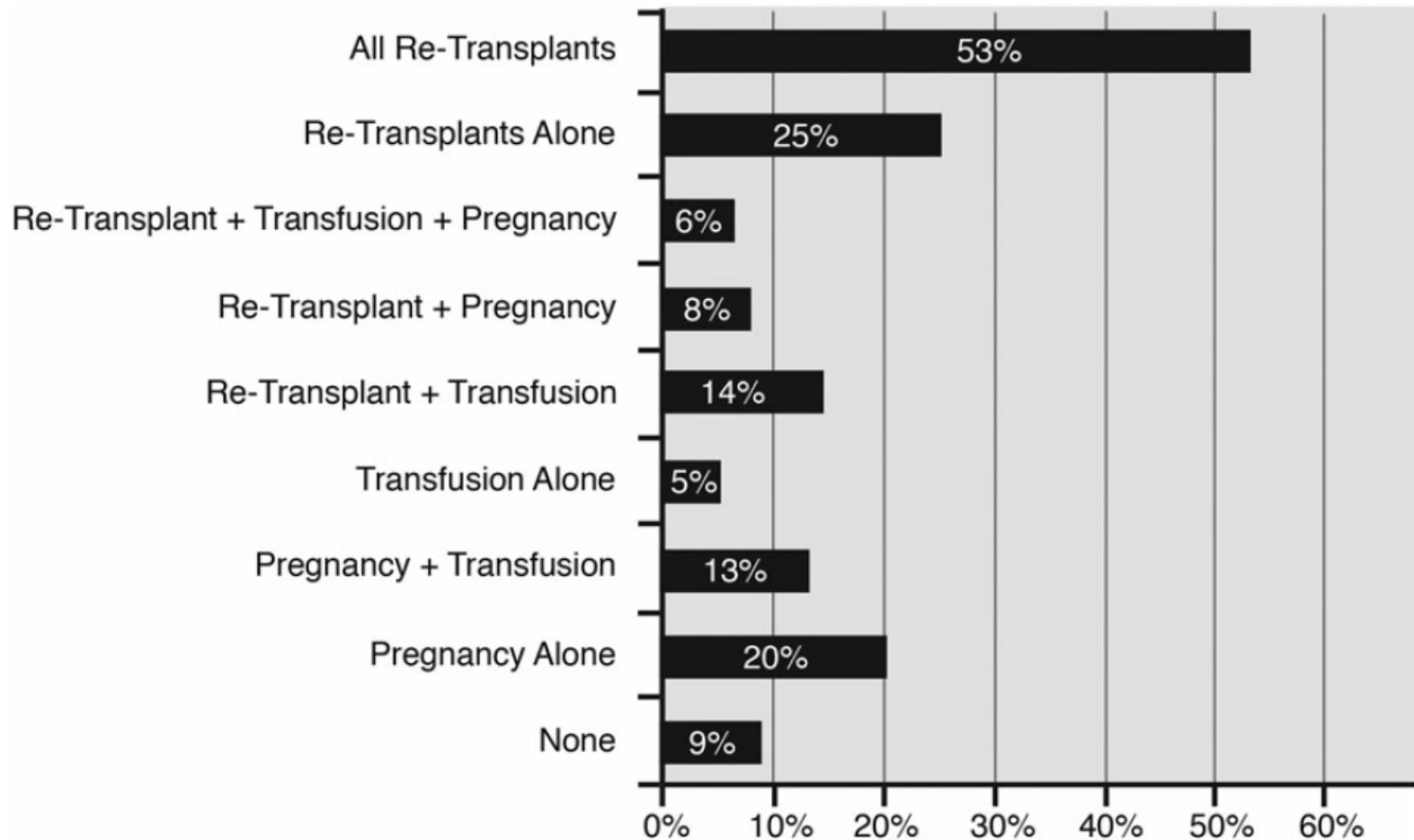
Transplant vs HD?

Beware of the immortal time bias!



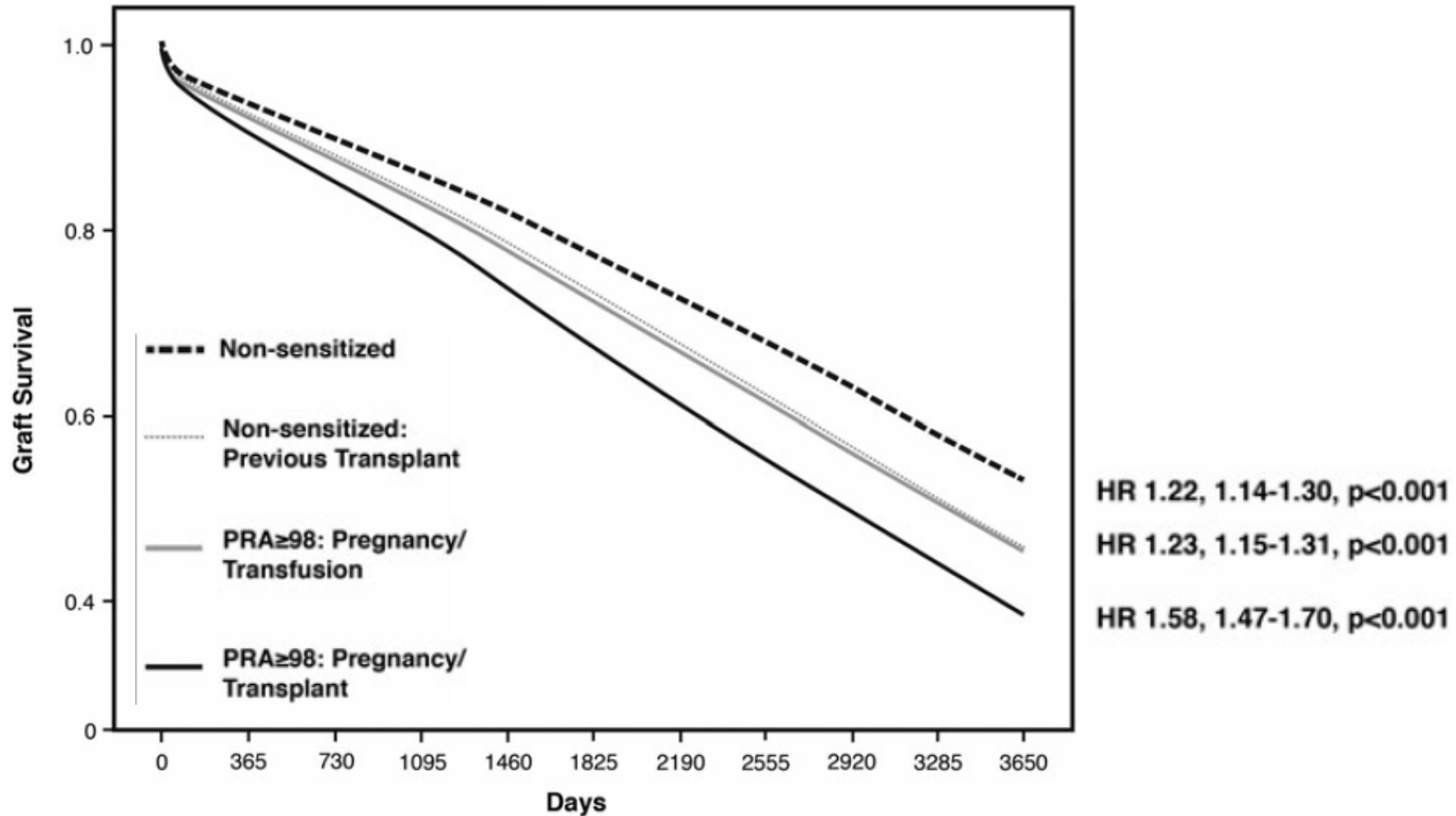
Gleiss A et al. Transplant Int 2017 (in press)

Cause of sensitization cPRA>98% in UNOS



Redfield RR et al. NDT 2016 Oct;31(10):1746-53.

Mode of sensitization & outcomes



Redfield RR et al. *NDT* 2016 Oct;31(10):1746-53.

List of References

1. Wekerle T, Segev D, Lechler R, et al. Strategies for long-term preservation of kidney graft function. *Lancet* 2017; 389: 2152-2162.
2. Lachmann N, Niemann M, Reinke P, et al. Donor-Recipient Matching Based on Predicted Indirectly Recognizable HLA Epitopes Independently Predicts the Incidence of De Novo Donor-Specific HLA Antibodies Following Renal Transplantation. *Am J Transplant* 2017.
3. Eder M et al. 2017 (pending)
4. Gleiss A et al. *Transplant Int* 2017 (in press)
5. Redfield RR et al. *NDT* 2016 Oct;31(10):1746-53.