



Should red cells be matched for transfusions to patients listed for renal transplantation?

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# Should red cells be matched for transfusions to patients listed for renal transplantation?

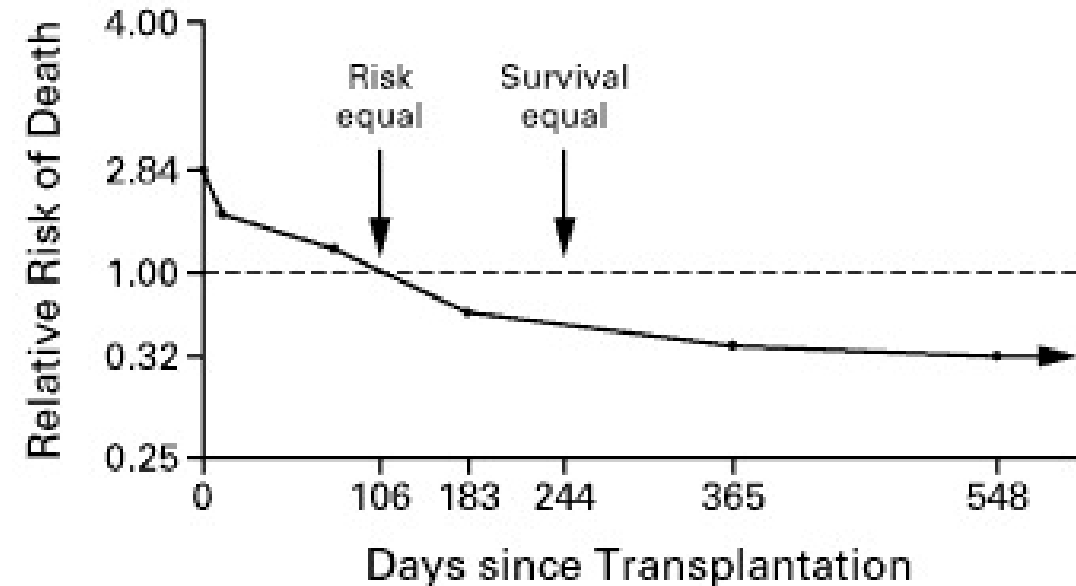
## Aims:

1. Evidence that HLA sensitisation causes inferior patient and renal transplant outcomes (both pre and post transplantation)
2. Evidence that blood transfusions cause HLA sensitisation (both pre and post transplantation)

## Why renal transplantation?

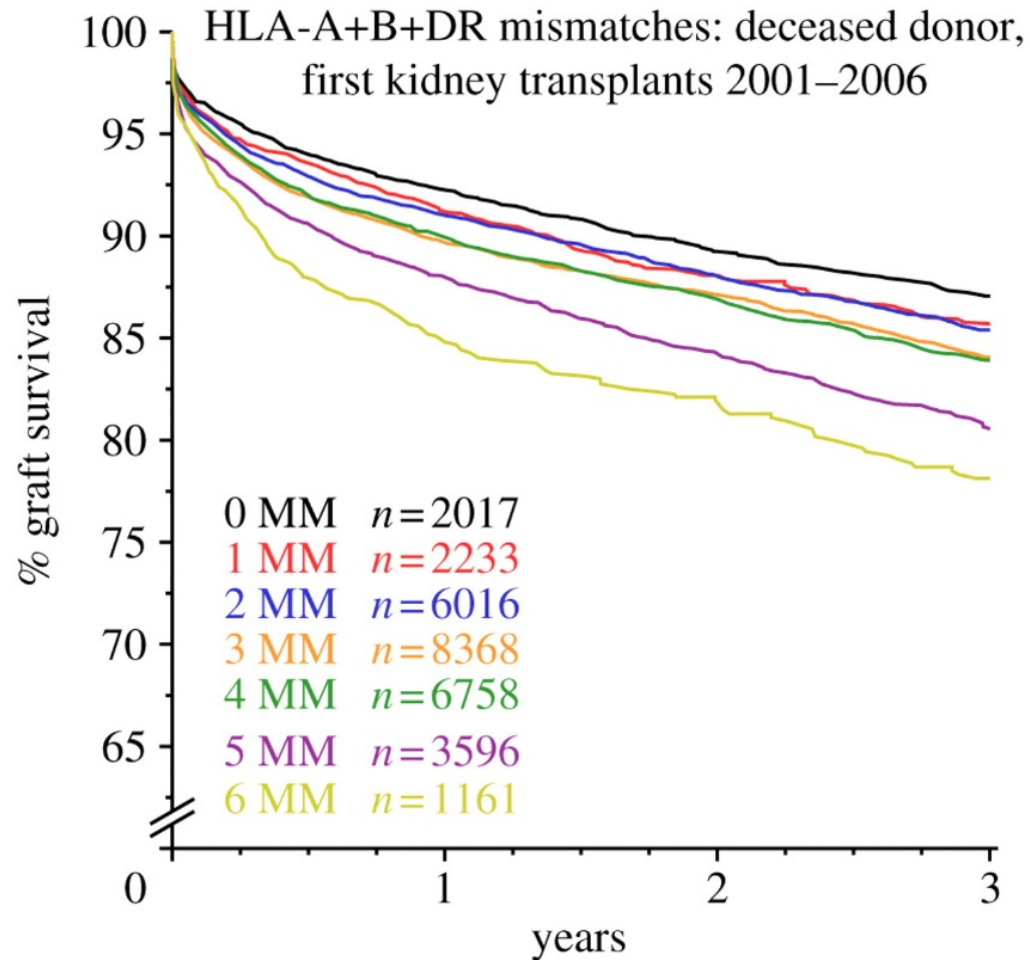
Transplantation is the treatment of choice for patients with ESRD, offering:

1. Improved prognosis
2. Improved quality of life
3. Cost advantage



Wolfe RA et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. NEJM 1999; 341: 1725

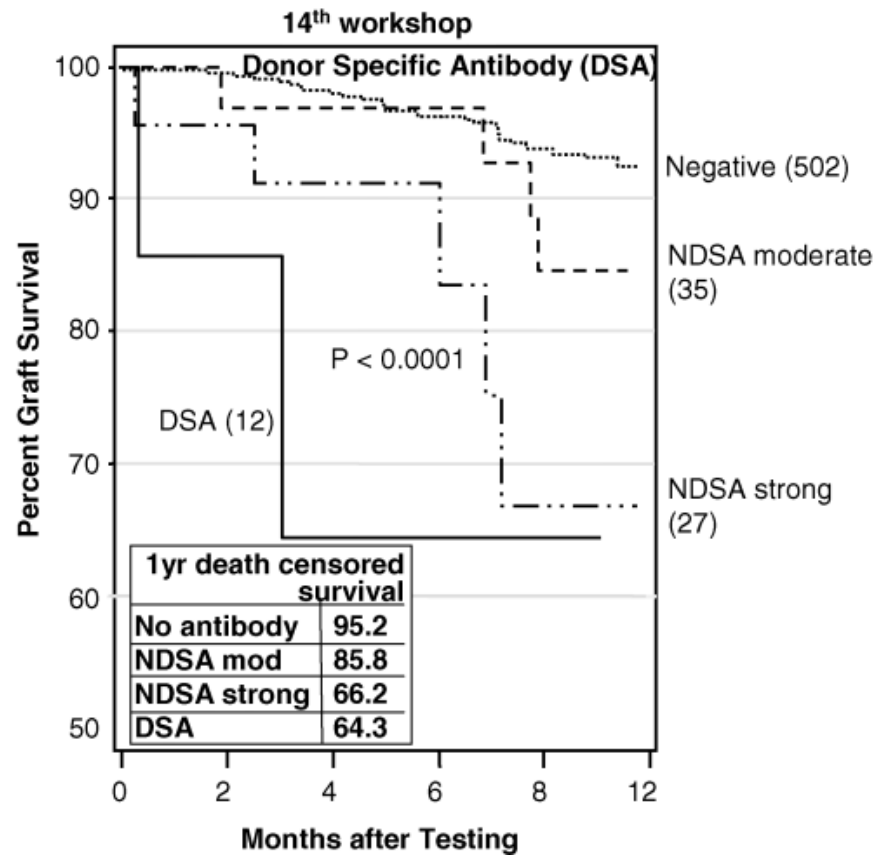
# Histocompatibility and Immunogenetics



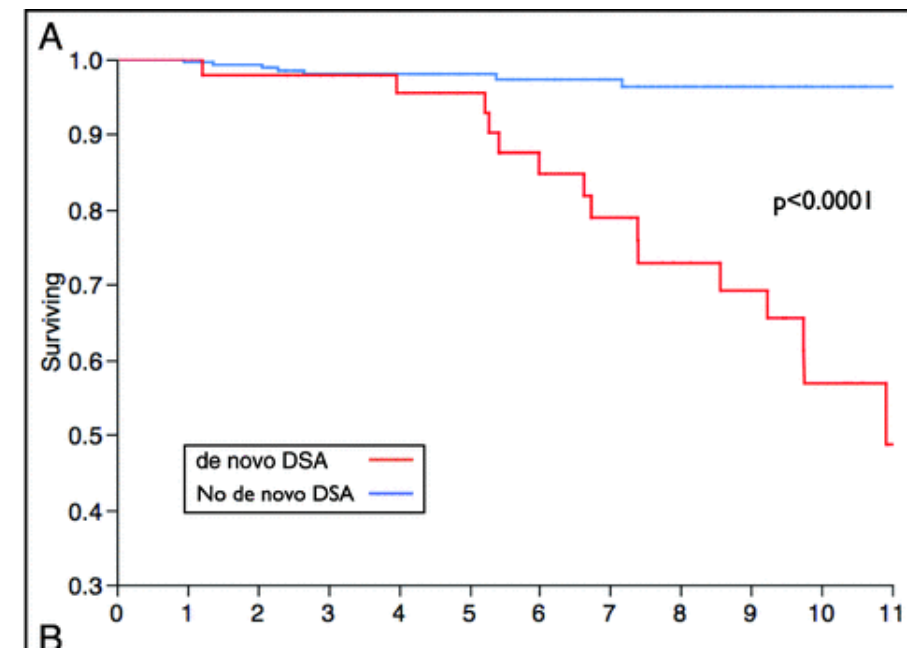
Influence of HLA mismatches on the outcome of  
deceased donor kidney transplants

Taylor C J et al. Phil. Trans. R. Soc. B 2011;366:2312-2322

# De novo HLA and DSA antibodies post transplant

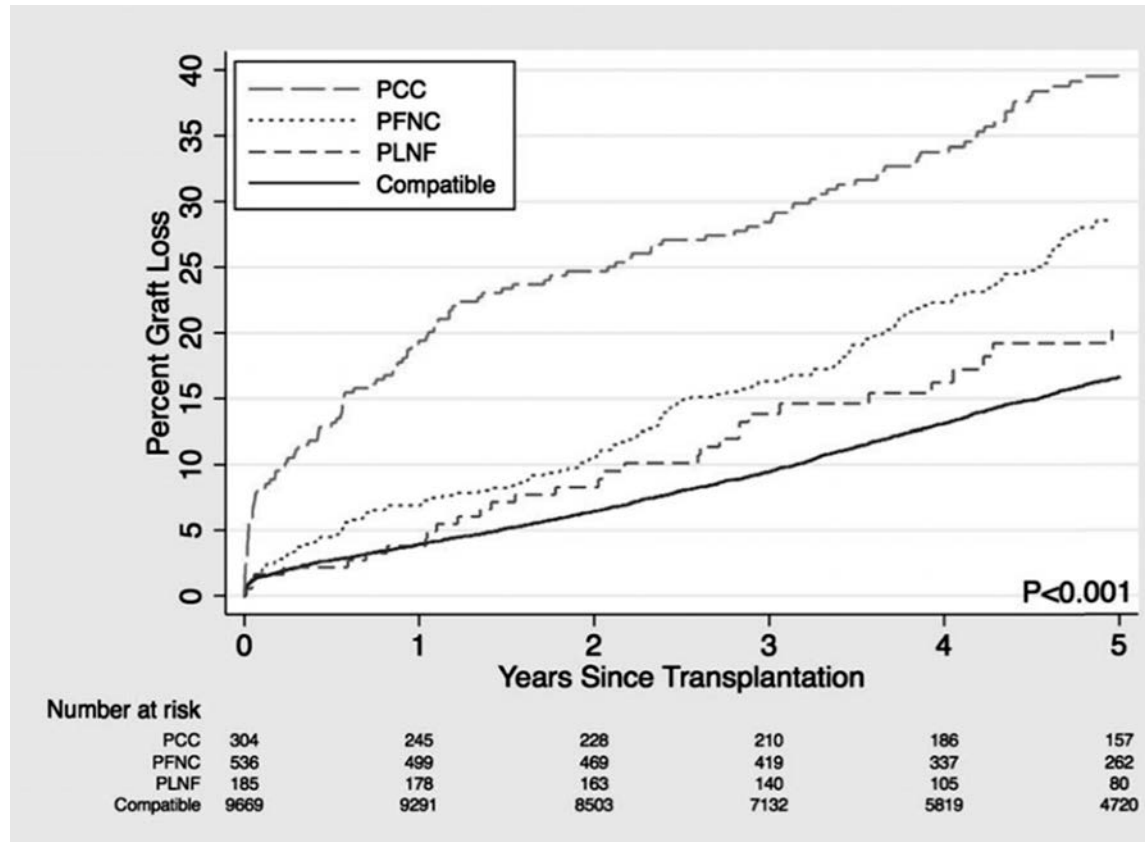


Teraskai PI. Four-year Follow-up of a Prospective Trial of HLA and MICA Antibodies on Kidney Graft Survival. *AJT* 2007; 7: 408



Wiebe c et al. Evolution and Clinical Pathologic Correlations of *De Novo* Donor-Specific HLA Antibody Post Kidney Transplant. *AJT* 2012 12:1157

## HLAi transplantation is associated with poor allograft outcomes

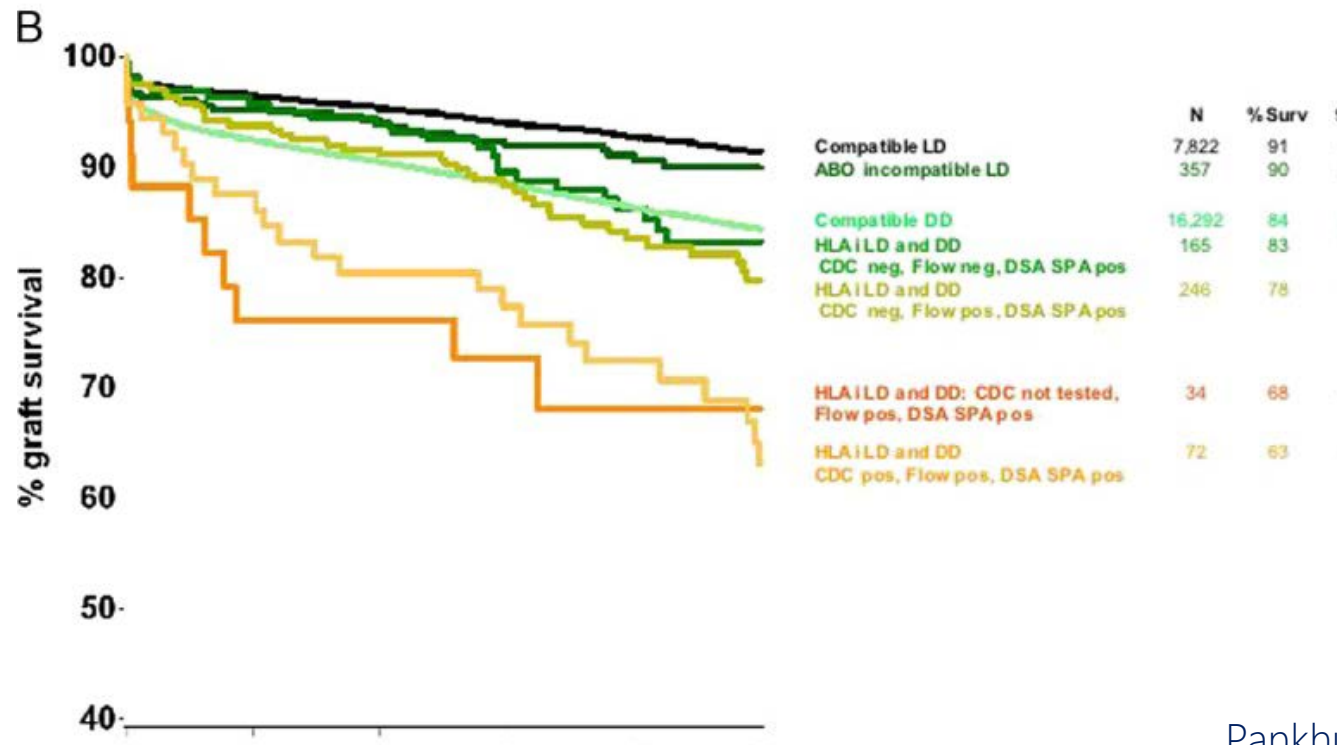


Multicentre US Study  
22 centres performing HLAi LD transplants  
10694 LD HLAc transplants  
1025 [9.6%] HLAi transplants

HLA+, DSAb- = HLA compatible  
HLA+, DSAb+ but FXM- and CDC- = PLNF  
HLA+, DSAb+, FXM+ and CDC- = PFNC  
HLA+, DSAb+, FXM+ and CDC+ = PCC

Orandi BJ et al. Quantifying the risk of incompatible kidney transplantation: a multicentre study. AJT 2014; 7: 1573

## HLAi transplantation is associated with poor allograft outcomes



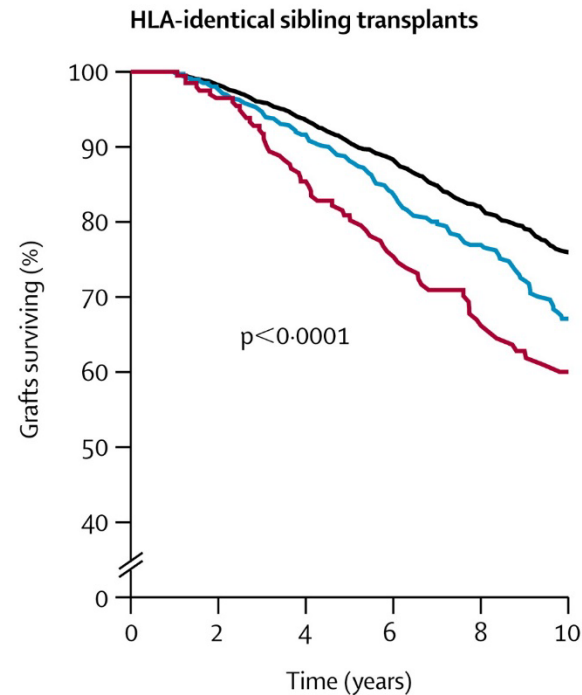
UK AIT Registry

517 HLAi transplants

7822 HLAc LD transplants

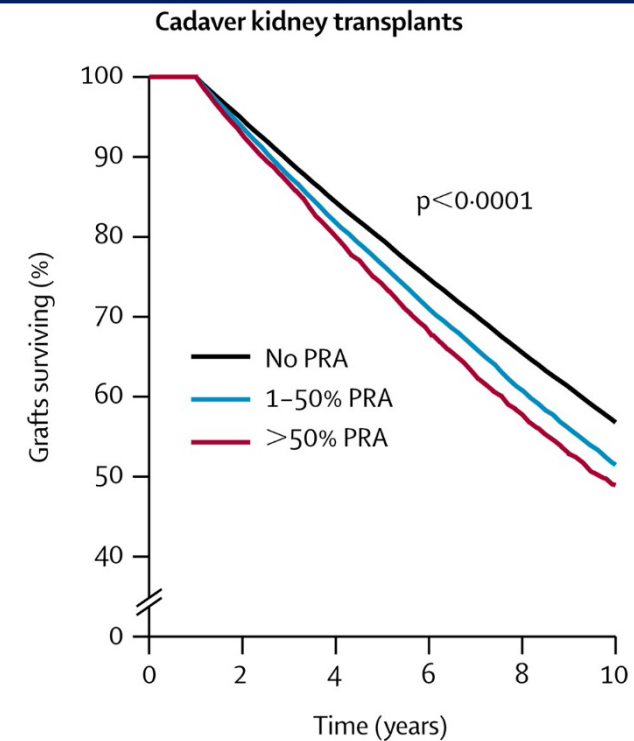
Pankhurst L et al. The UK National Registry of ABO and HLA Antibody Incompatible Renal Transplantation: Pretransplant Factors Associated With Outcome in 879 Transplants. Transplantation Direct 2017.

# Impact of sensitisation on allograft survival



**Number of transplants**

No PRA	2539	2495	1929	1418	989	687
1-50% PRA	664	647	514	362	249	158
>50% PRA	199	192	149	111	84	65



**Number of transplants**

No PRA	88389	83720	62516	44887	30819	20674
1-50% PRA	26676	25005	18402	12842	8590	5586
>50% PRA	5075	4712	3582	2579	1817	1242

Opelz G et al. Non-HLA transplantation immunity revealed by lymphocytotoxic antibodies. Lancet 2005; 365 (9470): 1570

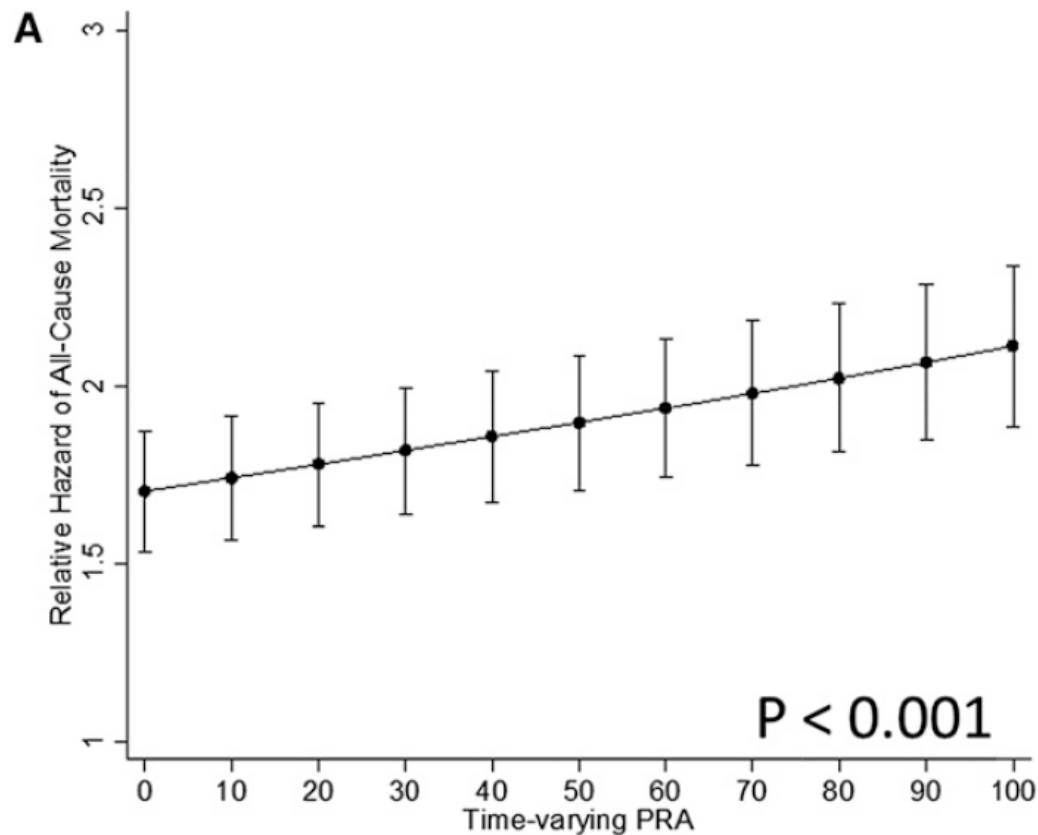


## Median wait time to transplant in the UK by sensitisation

Level of sensitisation	Patients registered	Waiting time (days)	
		N	95% CI
0-9	6,731	1,063	(1,039–1,087)
10-29	308	1,148	(1,014–1,282)
30-84	1,297	1,475	(1,400–1,550)
85+	718	2,218	(1,958–2,478)
Total	9,054	1,160	(1,136–1,184)

Median waiting time to kidney only transplant in the UK by sensitisation at registration, for patients registered 1st January 2006 to 31st December 2009. UK Renal Registry 2013

# HLA sensitisation is an independent predictor of mortality in wait-listed patients

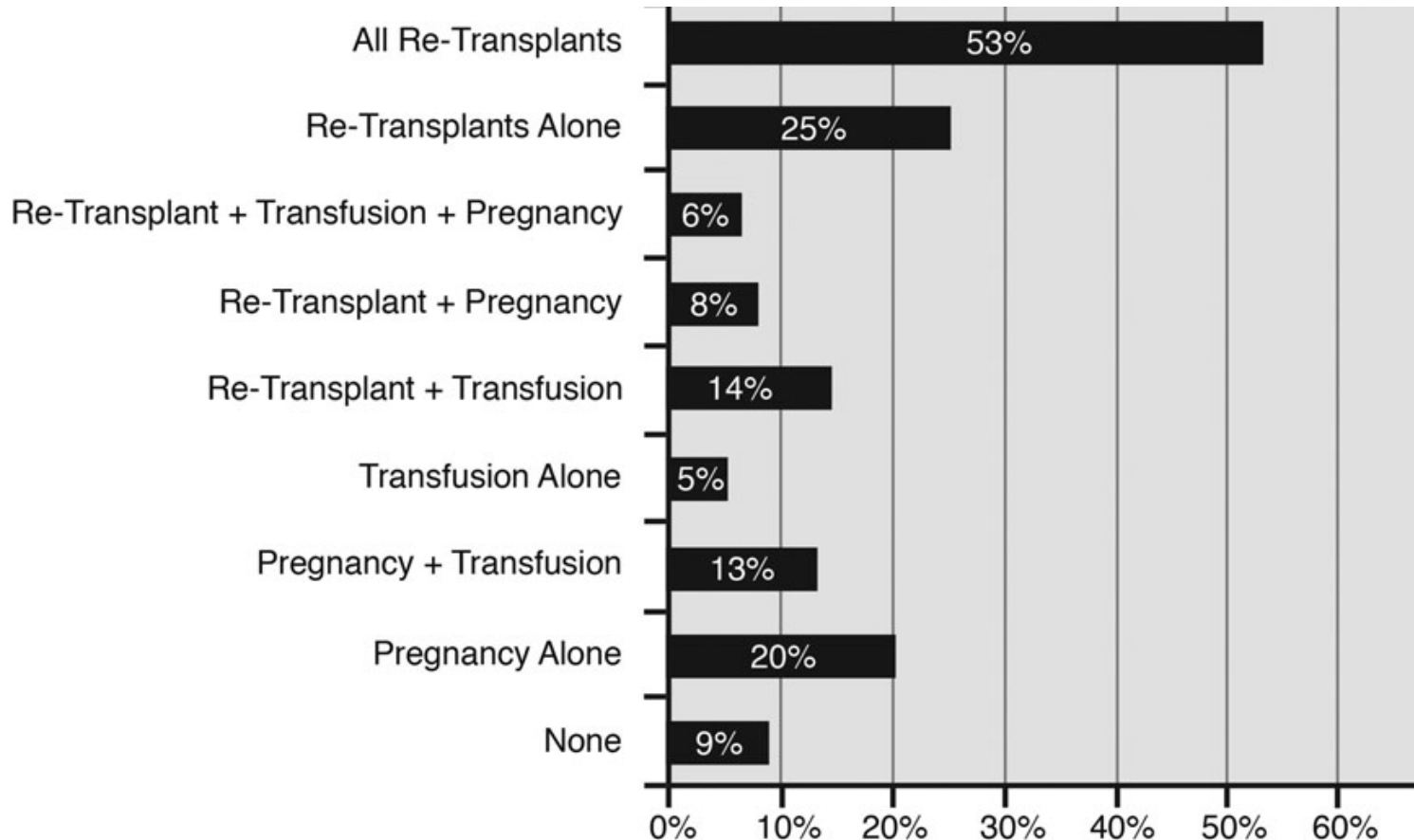


Retrospective cohort study in first-time adult kidney transplant candidates (N=161,308) using data from the Scientific Registry of Transplant Recipients.

All cause mortality increased with sensitisation

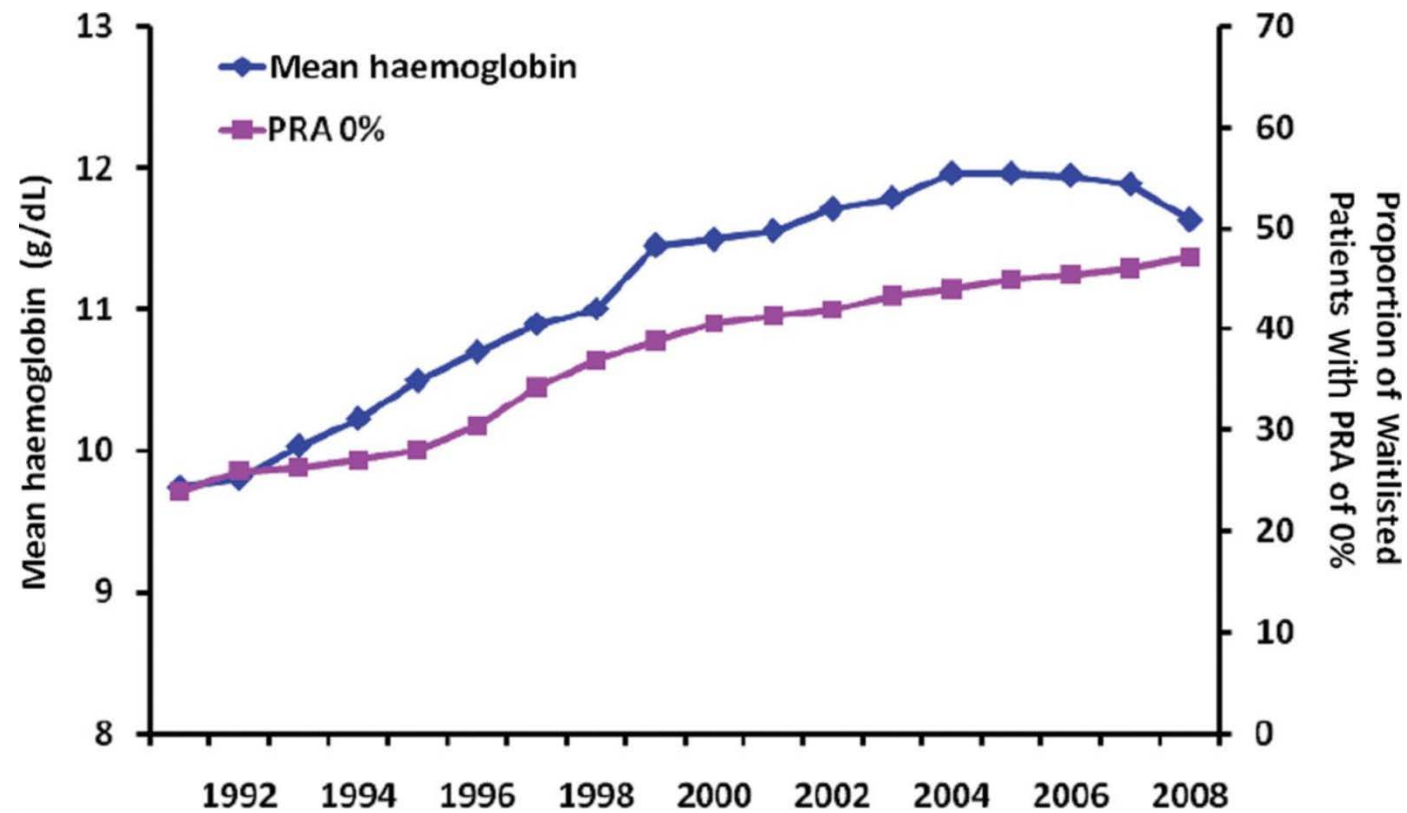
Sapir-Pichhadze et al. Immune sensitisation and mortality in wait-listed kidney transplant candidates. JASN 2015

## Causes of sensitisation in 'highly sensitised' patients awaiting renal transplantation



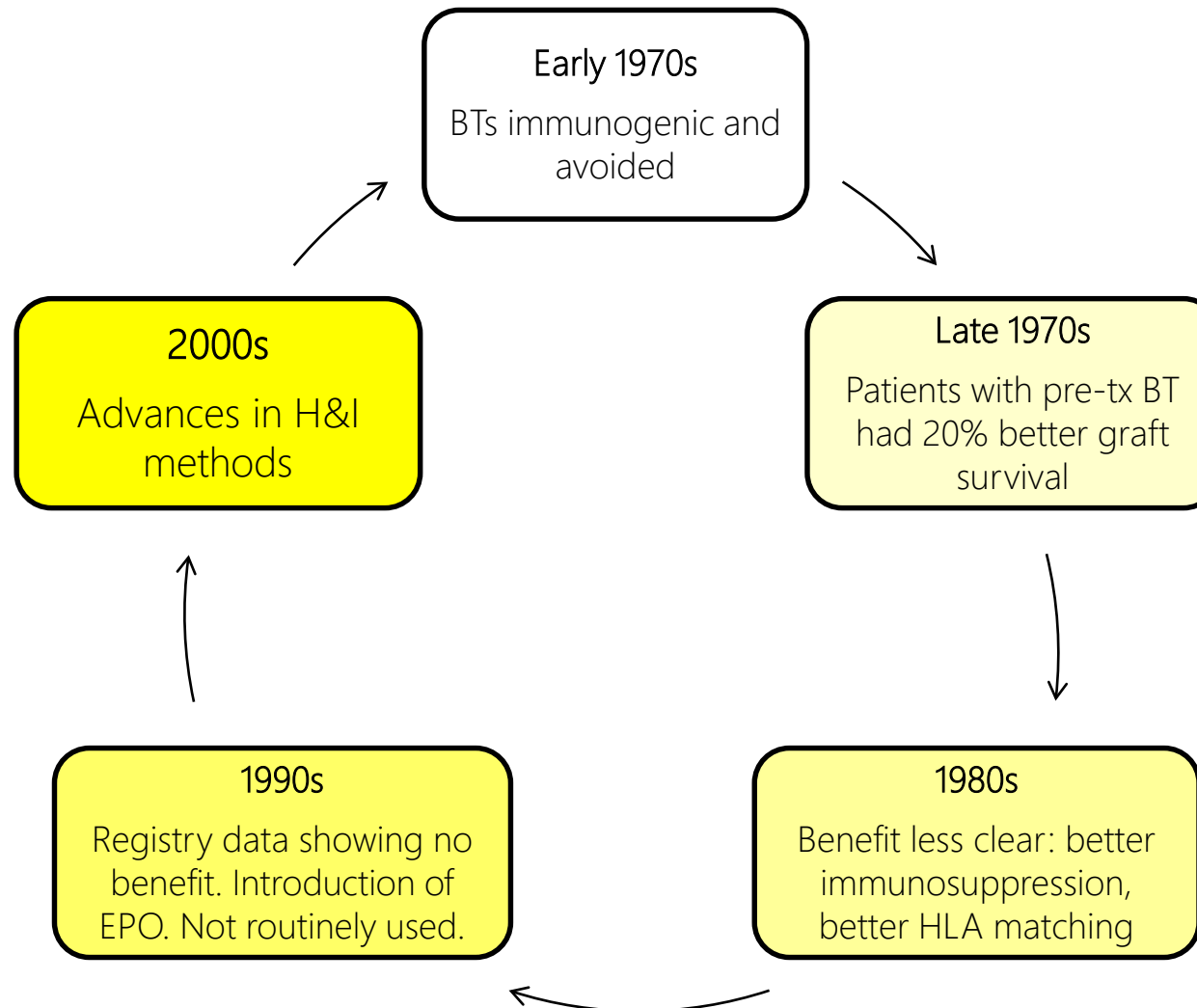
UNOS dataset 1997-2014  
7145 patients  
PRA > 98%

Redfield RR et al. The mode of sensitisation and its influence on allograft outcomes in highly sensitised kidney transplant recipients. Nephrol Dial Transplant, 2016 31: 1746



How important is transfusion avoidance in 2013?  
Nephrol Dial Transplant. 2013;28(5):1092-1099  
Macdougall IC

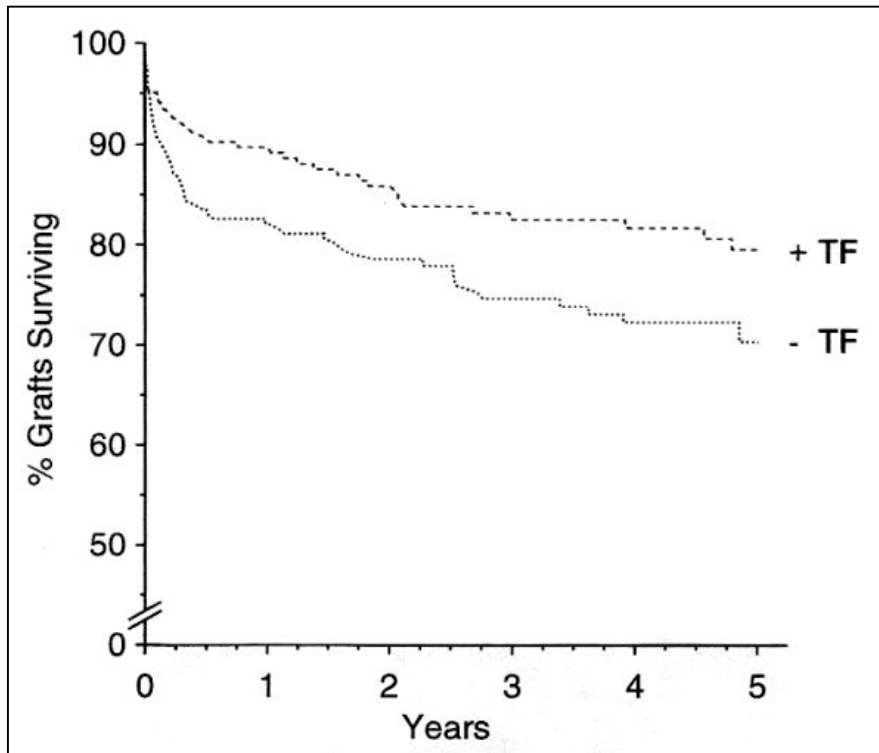
# History of blood transfusions as a 'sensitising' event



Opelz G. Lancet 1974  
Opelz G. NEJM 1978  
Obrador G. CJANS 2013  
Deierhoi M. Transplantation 1992

## Historic 'sensitising' practices

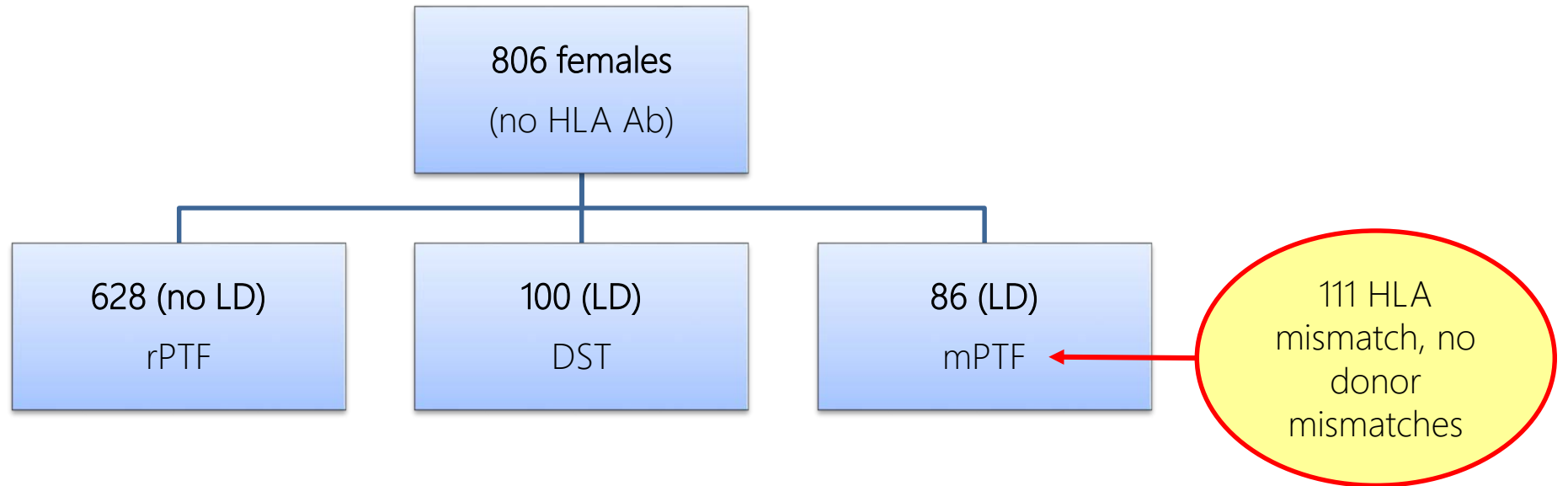
Improved renal allograft outcomes were seen in transplant recipients receiving RBC transfusion (random or donor specific pre-transplantation) prior to the CNl era.



Despite favourable results of this RCT, no consensus favoured transfusion over sensitisation risk.

**Prospective evaluation of pretransplant blood transfusions in cadaver kidney recipients.** Opelz et al. Transplantation 1997

GS of DDTx in patients with transfusion [205] pre-transplant, compared with those without [218],  $p=0.025$



165/806 (20.1%) developed CDC+ HLA Abs

Of 100 patients who received a DST: 25 developed HLA Abs/CDC+ XM which precluded transplantation

Only 1/86 of the LD who received a mPTF did.

**Patients with mPTF had significantly lower risk of sensitisation than those with rPTF or DST**

## Evidence that blood HLA mismatch increases risk of sensitisation

Magee BA et al. Effects of HLA-Matched Blood Transfusion for Patients awaiting Renal Transplantation. Transplantation 2012; 94: 1111

PRA <sup>a</sup> levels	No change	Change from negative to positive	>20% increase in peak levels
HLA selected units	37/37 (100%)	0/37 (0%)	0/37 (0%)
Random units	24/31 (77.4%)	3/31 (9.7%)	4/31 (12.9%)
<sup>a</sup> Panel reactive antibody.			

Compared sensitization in Class I HLA matched blood versus random blood. Only 33 (27.5% of total blood given was HLA Class I Matched)



## HLA expression on RBC

Class I HLA molecules on human erythrocytes: Quantitation and transfusion effects. *Everett et al.* Transplantation 1987.

Radiolabeling techniques and scatchard analysis show that erythrocytes contain 100-2000 class I molecules.

1 lymphocyte has  $\sim 10^5$  HLA class I molecules/cell

Platelets have a similar concentration

So despite the low level expression of HLA class I molecules, given the large number of RBC in a unit of blood....blood transfusions can represent a significant sensitising event.

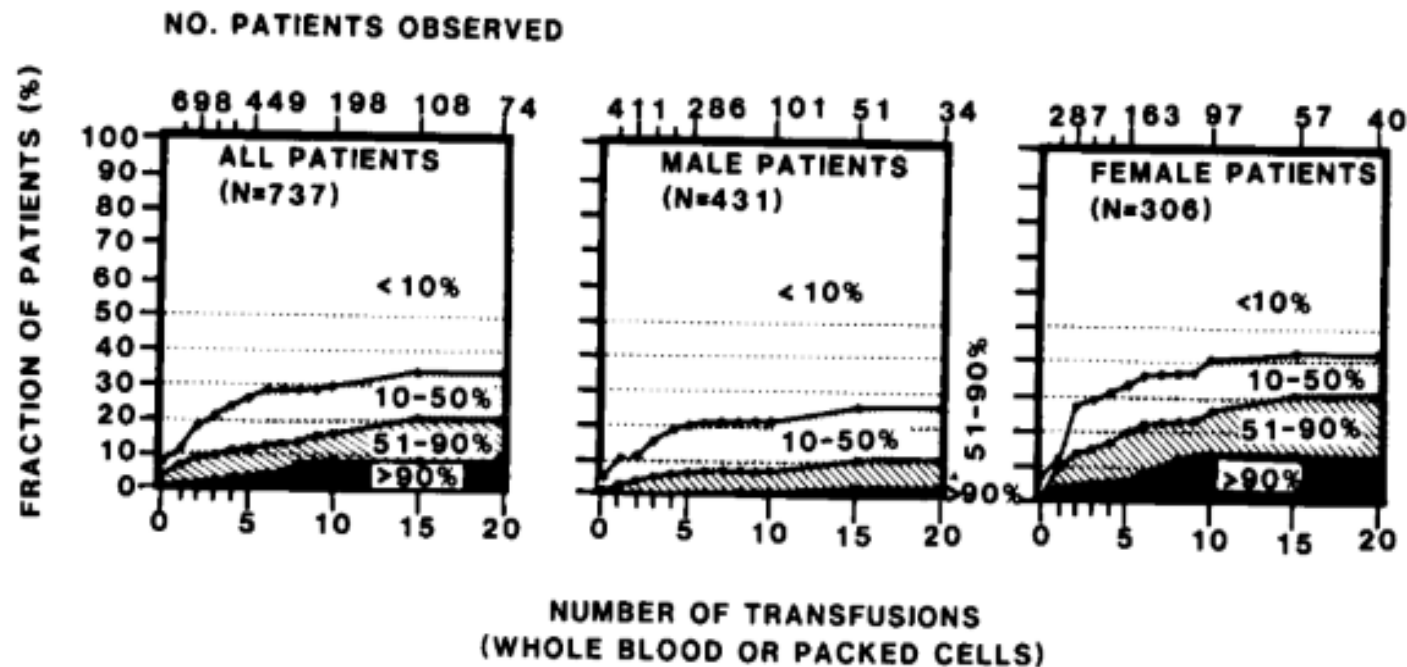
## Impact of leukodepletion and washed RBC

Karpinski M et al. Leukocyte reduction of red blood cell transfusions does not decrease allosensitisation rates in potential transplant recipients. JASN 2004; 15: 818-824

	Transfusion-Associated Allosensitization		<i>P</i>
	Pre-leukoreduction	Leukoreduction	
All patients ( <i>n</i> = 112)	16/60 (27%)	17/52 (33%)	NS
High risk ( <i>n</i> = 52) (previous pregnancy, Tx, $\geq$ 5 tf)	12/23 (52%)	16/29 (55%)	NS
Low risk ( <i>n</i> = 44) (no previous pregnancy, Tx, or tf)	3/31 (10%)	1/13 (8%)	NS
<sup>a</sup> Tx, transplant; tf, transfusion.			

Aston A et al. Washing red cells after leucodepletion does not decrease human leukocyte antigen sensitisation risk in patients with chronic kidney disease. Pediatr Nephrol 2014; 29: 2005-2011

## Inequality in sensitisation risk



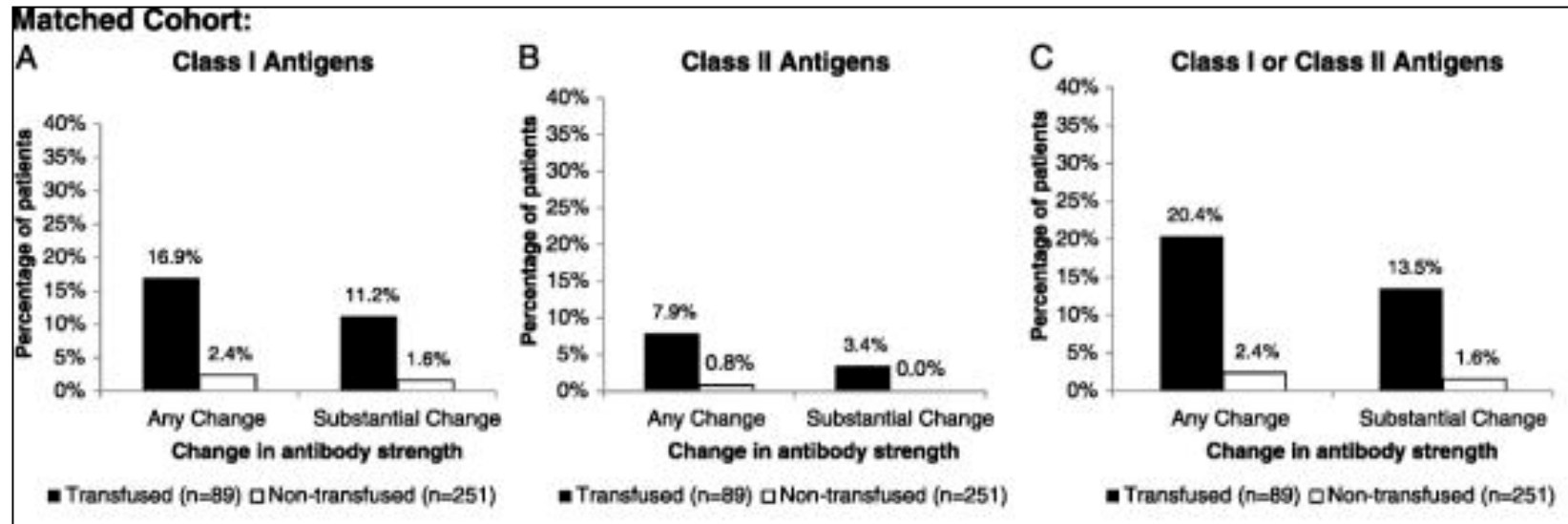
Opelz et al. Lymphocytotoxic antibody responses to transfusions in potential kidney transplant patients. Transplantation. 1981; 32:177

28% incidence of HLA antibodies in patients who had transfusions, with greater risk amongst multiparous females.

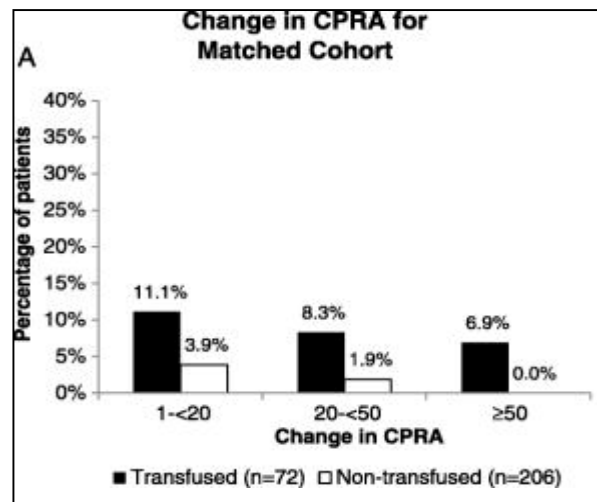
Males could have >20 transfusions and still not develop high reactivity (PRA>90%)

Transfusions are poorly immunogenic in naïve recipients.

# RBC transfusions increase level and breadth of HLA sensitisation



Leffell M et al. Red Blood Cell Transfusions and the Risk of Allosensitization in Patients Awaiting Primary Kidney Transplantation. *Transplantation*. 97(5):525-533, March 15, 2014.



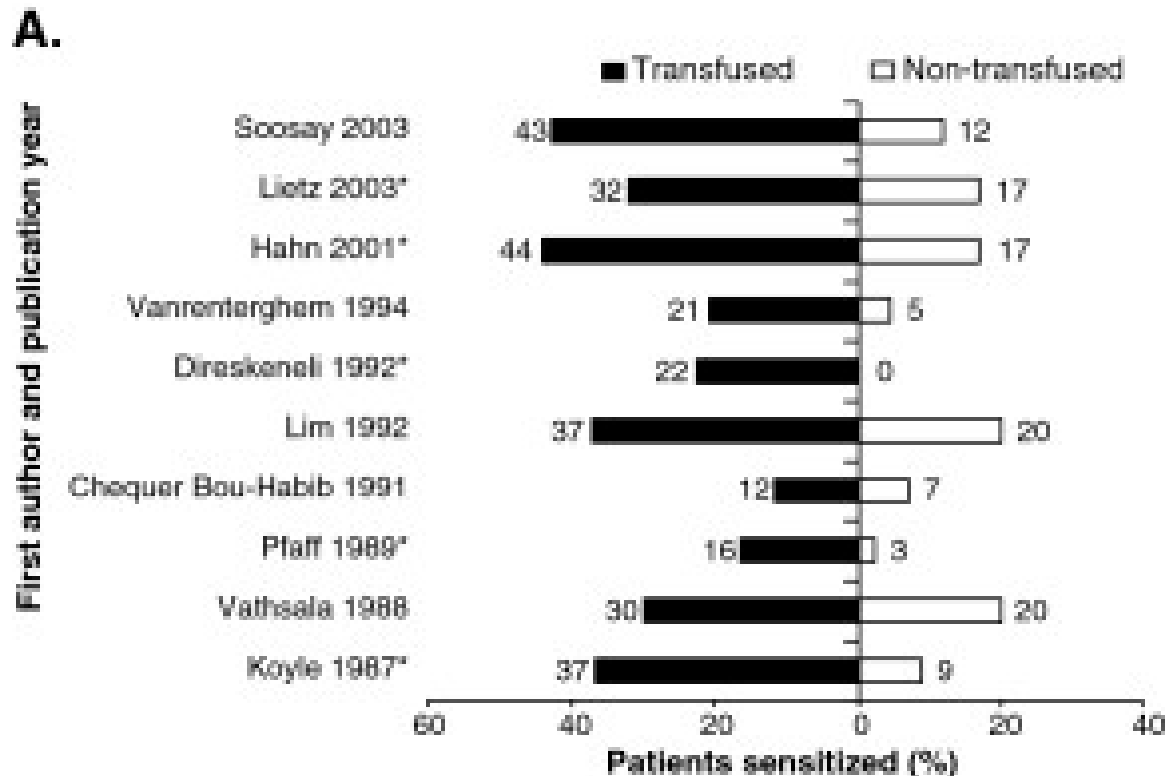
1342 patients on the wait-list 2004-2010  
(Transfusion data from medicare claims)

Sensitisation was more common in female and black patients

20% of transfused patients, and only 2% of non-transfused patients exhibited an antibody response.

10-fold increase risk of broad sensitisation and 32-point increase in PRA.

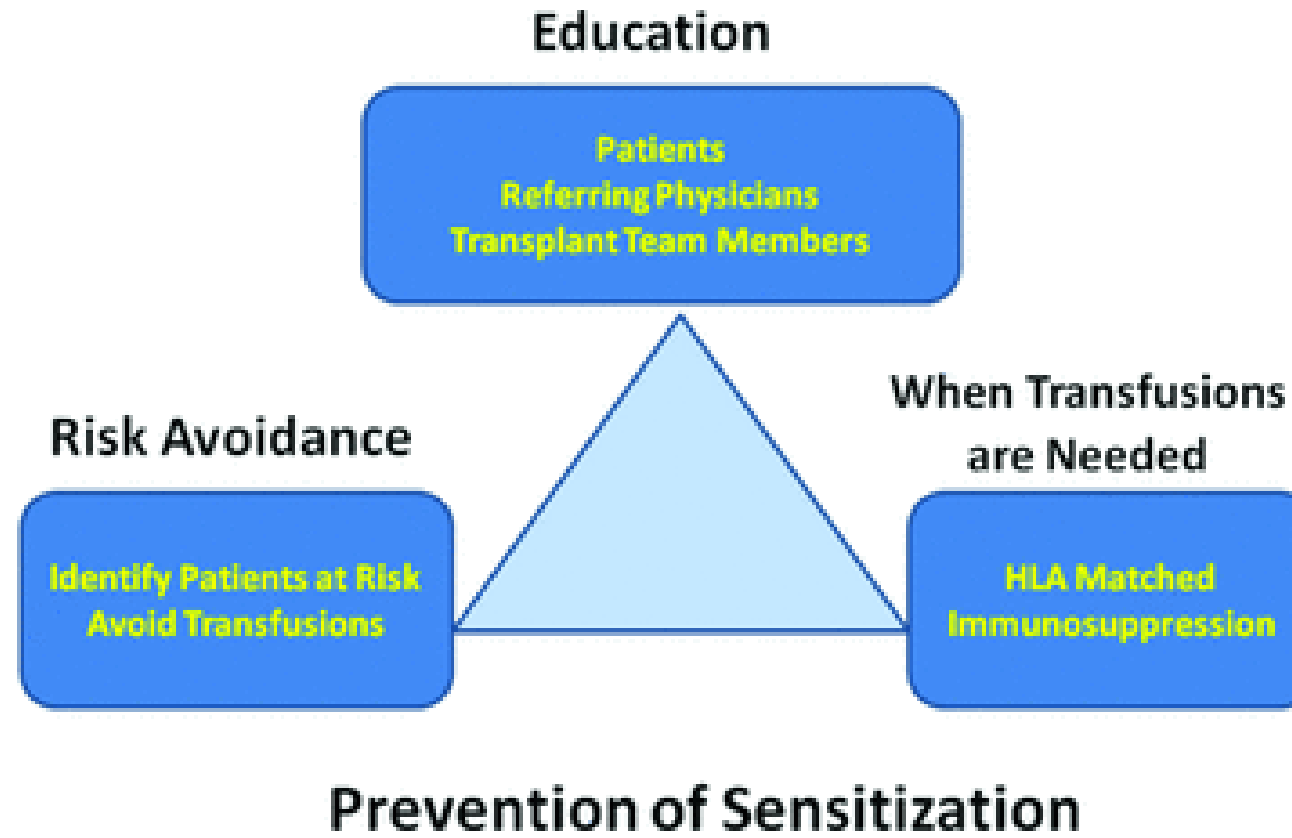
# Sensitisation and blood transfusions



Sample Size (N)	Prior Transplant (%)	Prior Pregnancy (%)	Method of Sensitization Measurement	Definition of Sensitization	Data Collection Period
244	NR	NR	CDC <sup>1</sup>	PRA ≥ 10%	Jan 1996 – Dec 1996
502	None	NR	CDC	PRA > 20%	Jan 1990 – July 1998
177	NR	NR	CDC	PRA ≥ 10%	NR
171	None	NR	CDC <sup>1</sup>	PRA > 10%	Dec 1986 – Sep 1993
111	11%	31%	CDC	PRA > 20%	NR
3790	NR	NR	CDC <sup>1</sup>	PRA > 10%	1985 – 1990
135	NR	NR	FCXM	MPC shift ≥ 9 of T-cells peak	Dec 1982 – Dec 1989
797	None	24%	Mixed	PRA > 10%	Jul 1980 – Jun 1987
69	NR	NR	CDC	PRA > 5%	Jul 1970 – Oct 1987
135	NR	NR	CDC <sup>1</sup>	PRA > 25%	Nov 1983 – Mar 1986

Scornik JC et al. An update on the impact of pre-transplant transfusions and allosensitisation on time to renal transplant and on allograft survival. BMC Nephrology 2013; 14:217

# Measures to prevent sensitisation when patients need RBC in transplant patients



## Evidence that immunosuppression may reduce risk of sensitisation

1. **Scornick JC et al.** Effects of blood transfusions given after renal transplantation. Transplantation 2009; 87: 1381.  
Incidence of post-transplant HLA Abs similar in the transfused [14/83 (17%)], compared with the non-transfused [17/116 (15%)],  $p=0.67$ . Maintenance immunosuppression: CNI, MMF, steroids
2. **Cheigh JS.** Minimal sensitization and excellent renal allograft outcome following donor-specific blood transfusion with a short course of cyclosporine. Transplantation 1991; 51:378.  
Incidence of de novo HLA Abs was 4/75 (4%) of patients who received DST from their one-haplotype kidney donor under the cover of CSA, compared with 3/30 (10%) of patients who did not have CA cover

# Post-transplant RBC transfusions are associated with alloimmune response

Parameter	Total population, n = 390	Transfusion group, n = 250	Non-transfusion group, n = 140	p-value
De novo anti-HLA antibodies	34 (8.7%)	32 (12.8%)	2 (1.4%)	<0.0001
De novo DSAs	19 (4.9%)	18 (7.2%)	1 (0.7%)	<0.0001
De novo anti-class I DSAs	8 (2.1%)	8 (3.2%)	0	<0.0001
De novo anti-class II DSAs	19 (4.9%)	18 (7.2%)	1 (0.7%)	0.06
AMRs	17 (4.4%)	15 (6%)	2 (1.4%)	0.04

Ferrandiz I et al. Impact of early blood transfusion after kidney transplantation on the incidence of donor specific anti-HLA Antibodies. AJT 2016; 16: 2661



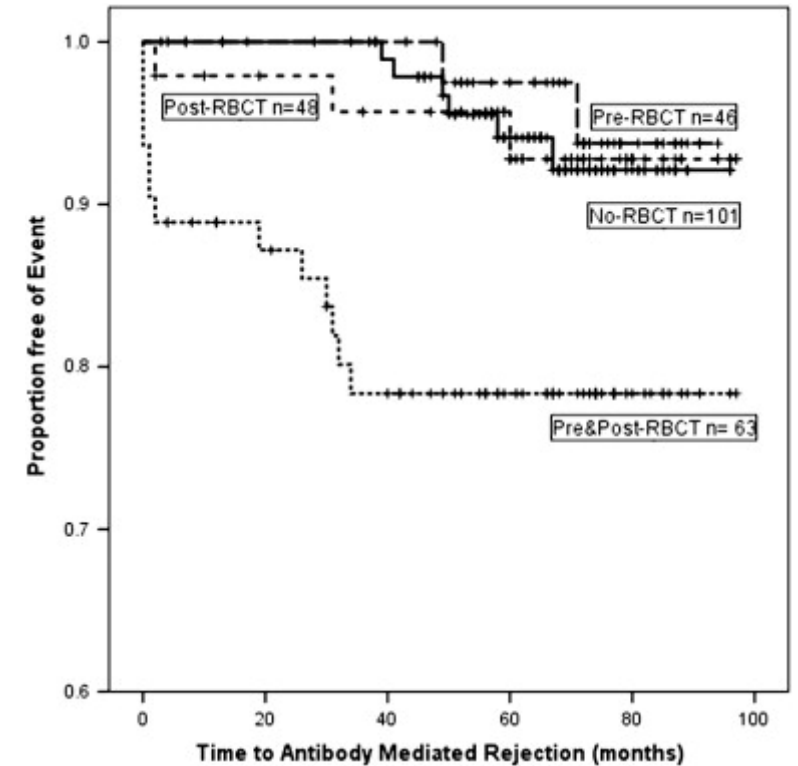
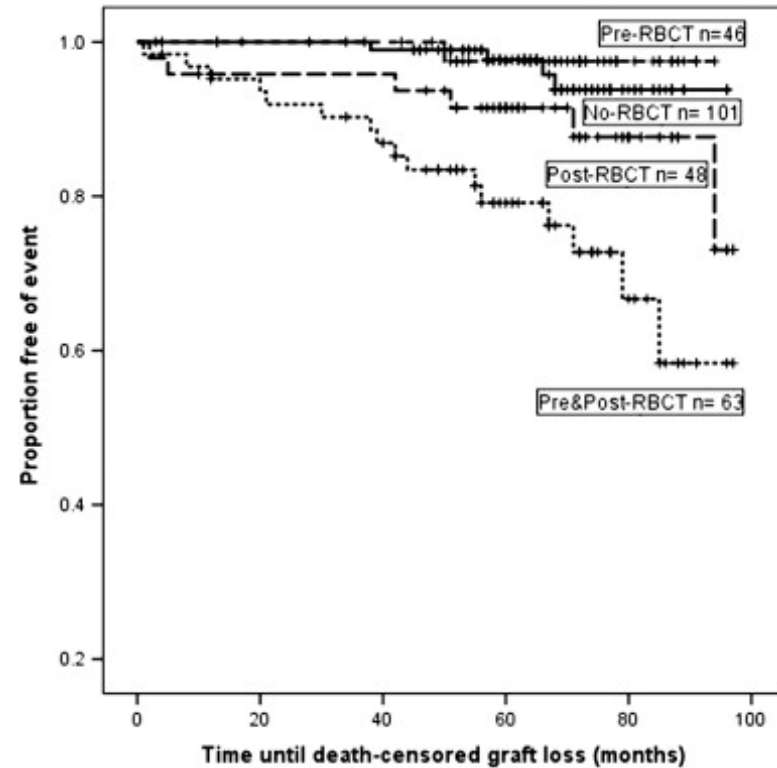
## Effect of blood transfusion after transplantation

258 patients from 3 centres

Patients with pre and post RBC transfusion:

At risk of AMR (HR 13.9)

At risk of graft loss (HR 7.1)



Fidler S et al. Peri-operatively third party blood transfusion I renal transplantation and the risk of AMR and graft loss. Human Immunology 2013

## Preliminary data

Retrospective study demonstrated that blood transfusions were a risk factor for de novo DSA development.

Hypothesis: patients are more likely to develop a DSA post transfusion if the HLA antigens of the blood and transplant donor are shared.

HLA typing was performed in blood donors (299), who donated blood to:  
54 transplant recipients who developed de novo DSA post transfusion  
47 transplant patients who remained DSA negative post transfusions

Preliminary findings:

De novo DSA group received a higher mean number of transfusions [231 versus 68]

In the dnDSA group [n=54], 90/231 [39%] of transfusions resulted in a TSA which was of the same specificity as the DSA [TSA=DSA], this occurred in 31 patients.

Patients with de novo DSA were more likely to develop AMR and graft loss.

## Conclusions

- Renal patients on the transplant wait list who are HLA sensitised:
  1. Have a longer wait-time to transplantation
  2. Higher risk of death
  3. Worse transplant outcomes, if they receive a transplant.
- Blood transfusions are a cause of HLA sensitisation
- Avoidance of transfusions for all potential transplant recipients is crucial
- HLA matched or selected blood may reduce sensitisation and improve outcomes, in those patients (transplant or wait-listed) in whom transfusion cannot be avoided

THANK YOU!

