Chronic Renal Allograft Dysfunction

An unsolved problem

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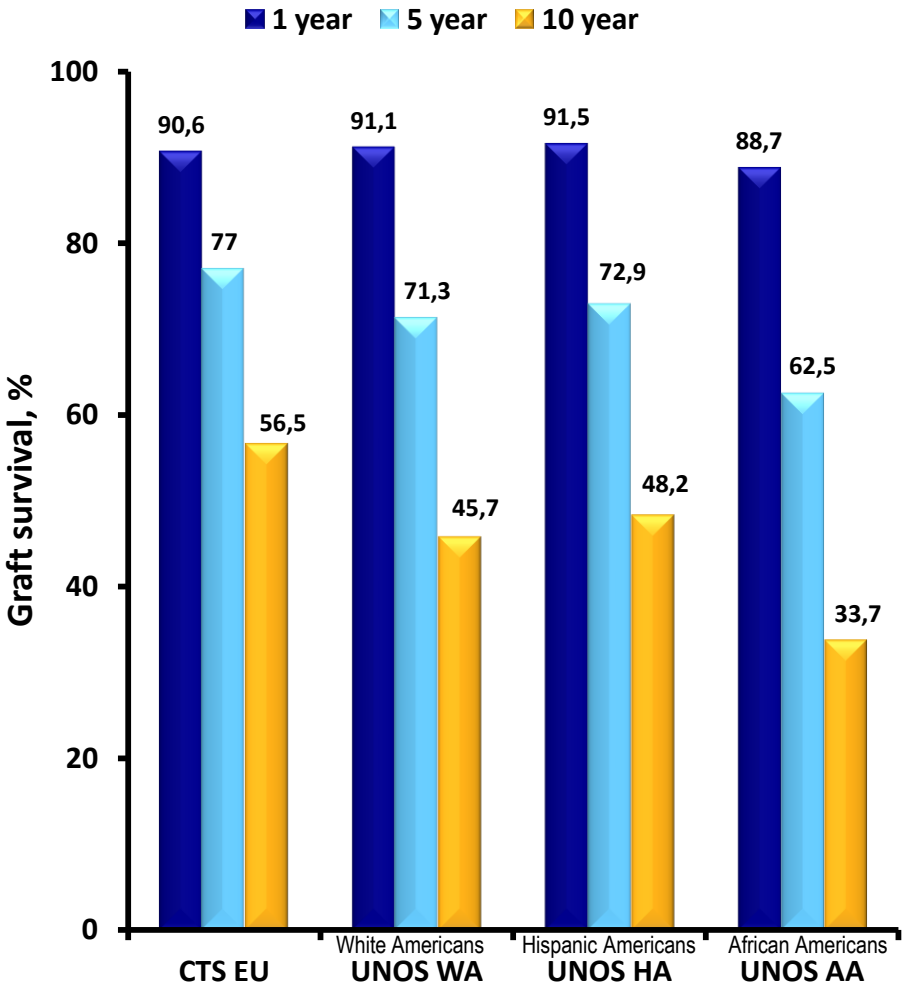
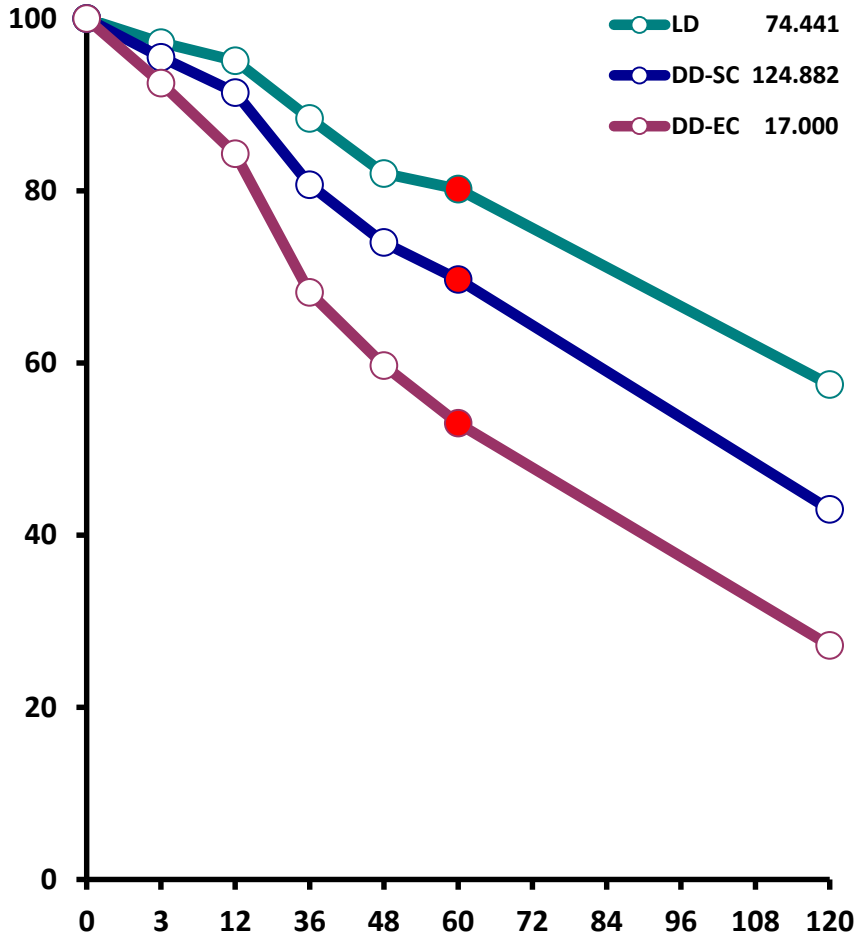
Catalan Transplantation Society, Barcelona March 18th, 2015

LUMC

Kidney Transplantation

Long-term outcomes remain poor and inadequate



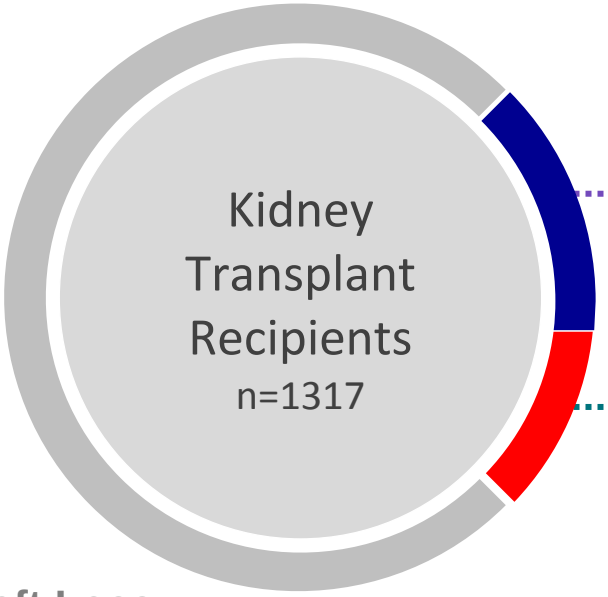


Gondos A, et al. *Transplantation* 2013;95:267–74.

US OPTN / SRTR: Annual Report 2007

Graft Loss

Death with function dominated by Cardiovascular Disease



75%
No Graft Loss

14.5%
Graft Failure
incl. PNF

10.5%
Death with Graft Function

- **28.2%** Cardiovascular
- **15.2%** Infections
- **13.8%** Malignancies
- 11.6% Other
- 31.2% Unknown

Mean follow-up: 50.3 ± 32.6 months

El-Zoghby ZM, et al. *Am J Transplant.* 2009;9:527–535.

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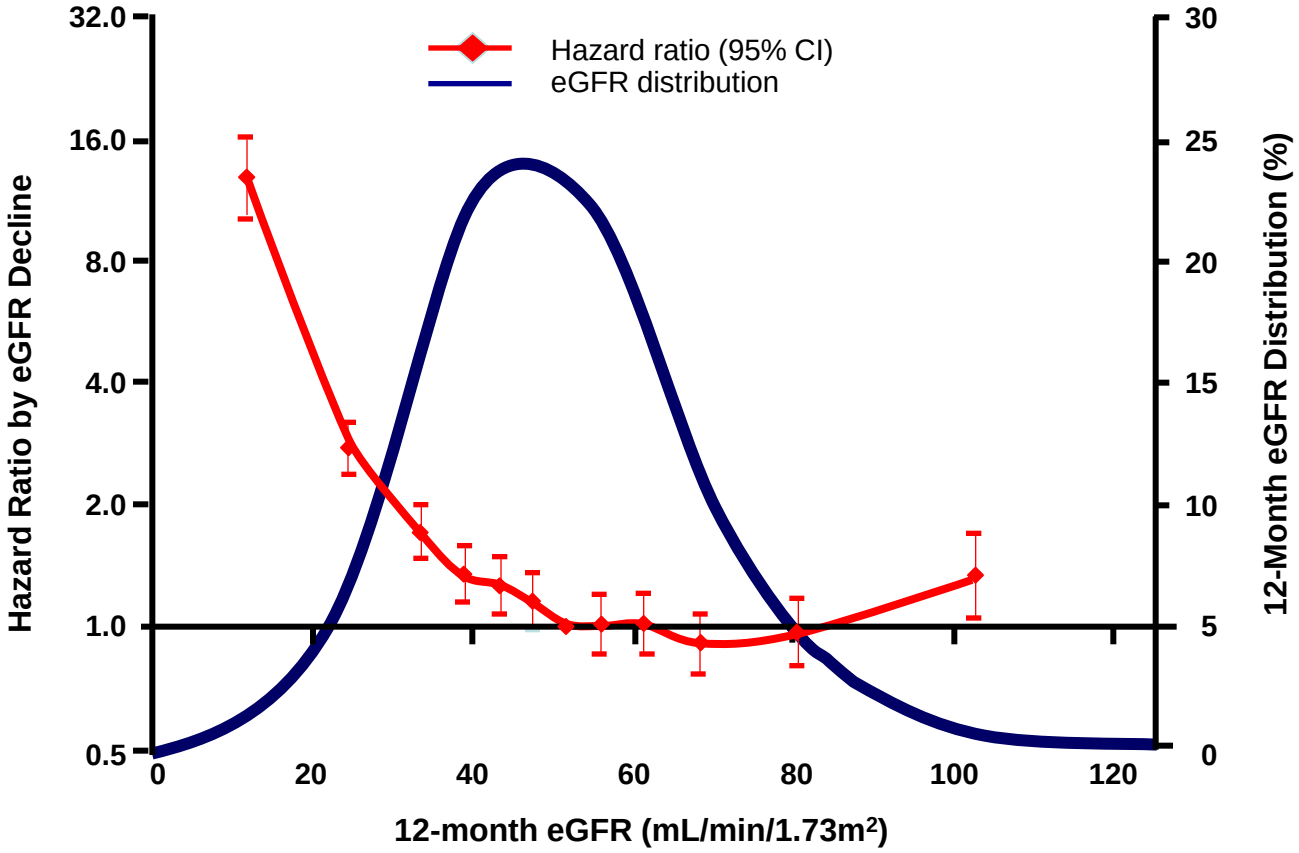
Robust association between GFR and CV-mortality

One-year eGFR <50 mL/min/1.73m^2 is associated with inferior outcome

Relationship between eGFR and graft failure over 10-years follow-up

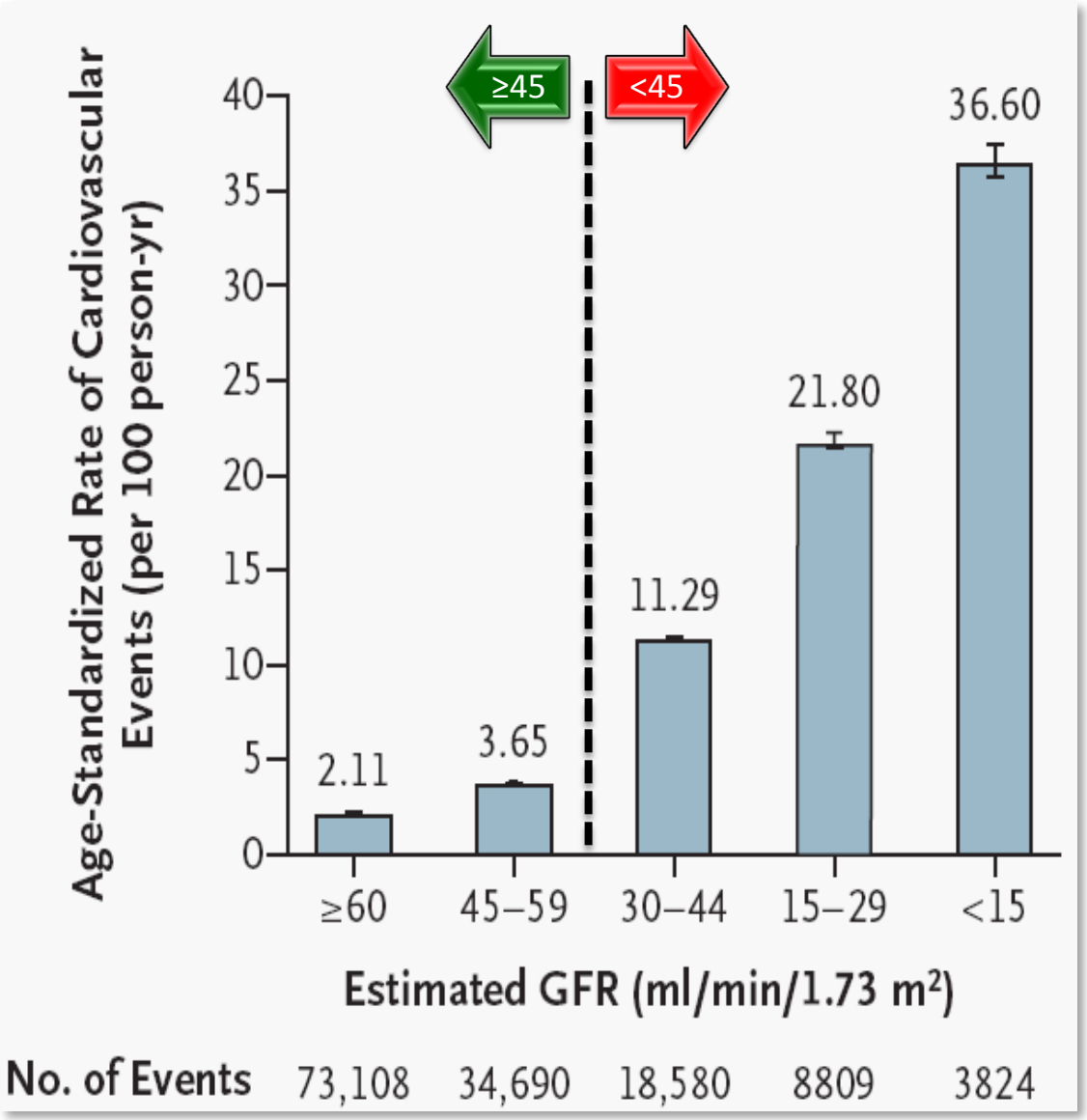
(Cox proportional hazard adjusted for multiple covariates)



Kasiske B, *et al. Am J Kidney Dis* 2011;57:466–75

GFR a robust risk factor for cardiovascular mortality

Standardized Cardiovascular Event Rate (GP mean follow-up 2.8 years)

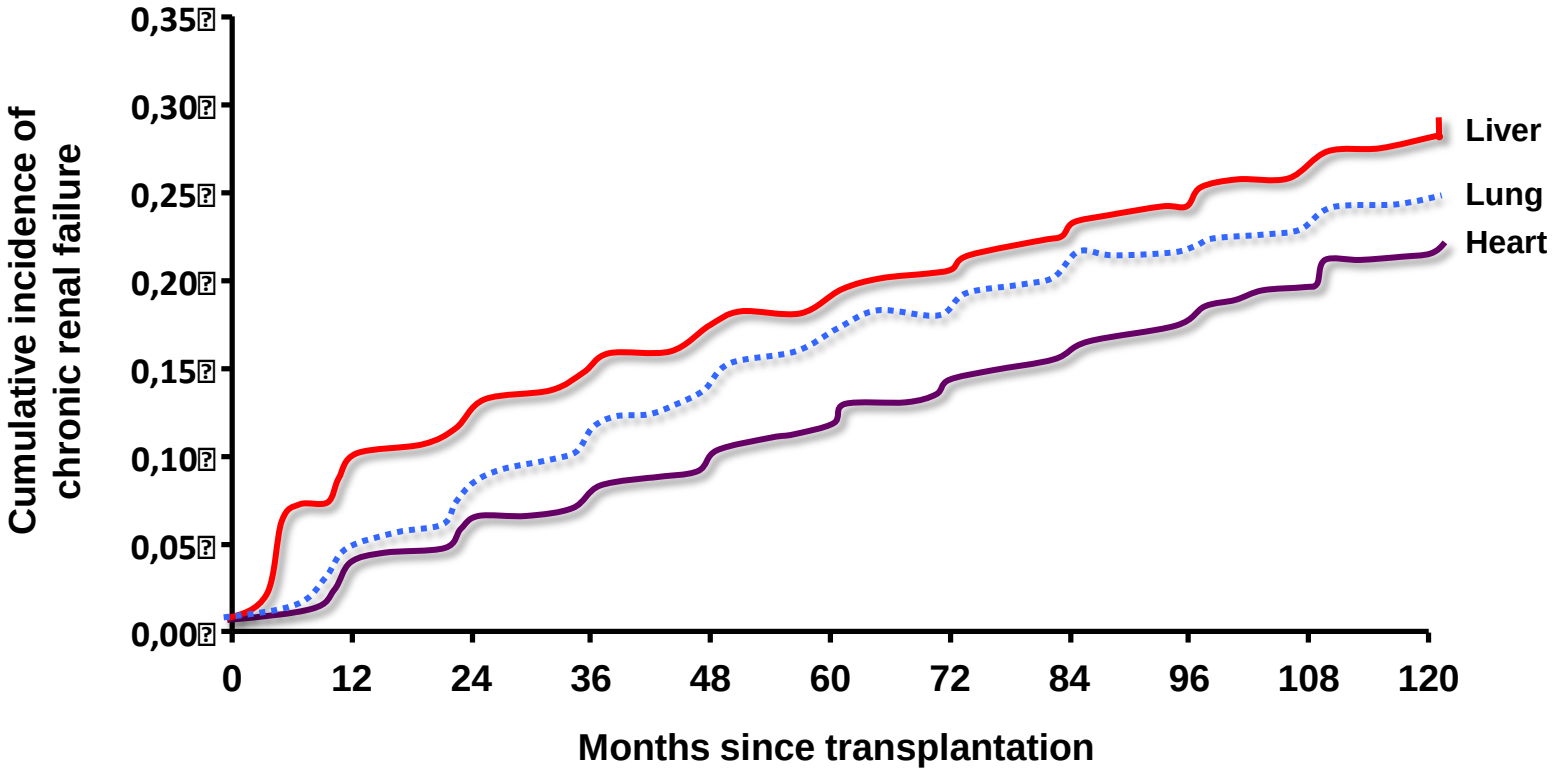


Go AS et al, N Eng J Med 2004, 351:1296-1305

LUMC

Non-Renal Solid Organ Transplant recipients

High risk of renal failure



No. at risk

Liver	36,849	28,495	24,041	19,508	15,724	12,564	9,844	7,345	5,292	3,614	2,261
Lung	7,643	5,633	4,316	3,184	2,327	1,629	1,136	745	468	258	133
Heart	24,024	19,885	17,238	14,687	12,341	10,022	7,997	6,104	4,526	3,096	1,991

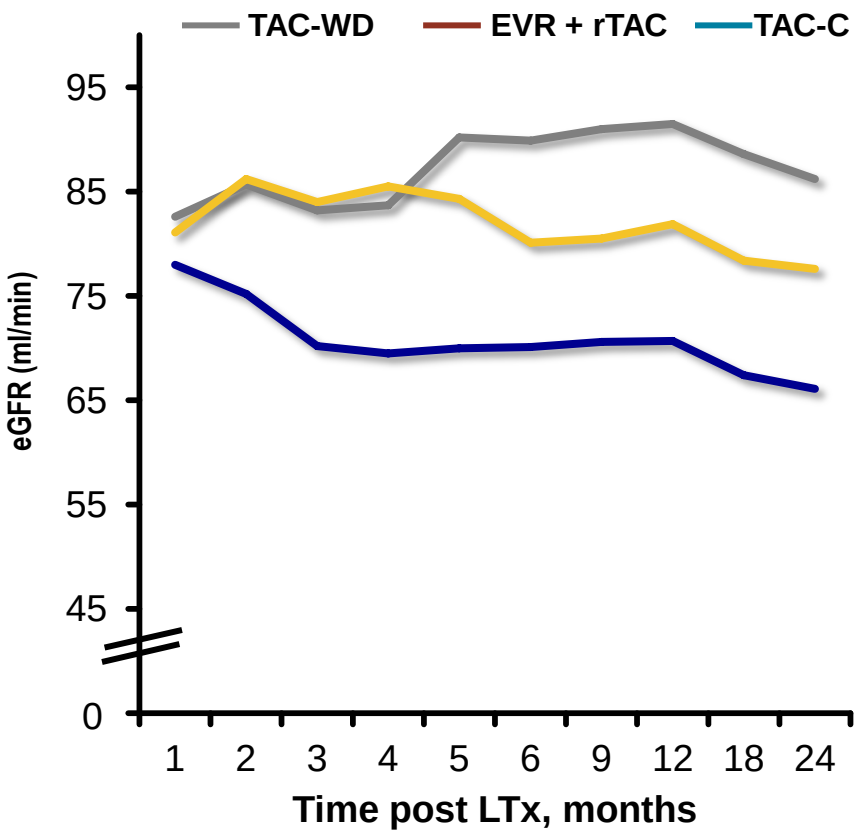
From: Ojo AO, et al. *N Engl J Med*. 2003;349:931–940.

Early CNI-reduction in Liver Transplant recipients

Impressive improvement in native renal function

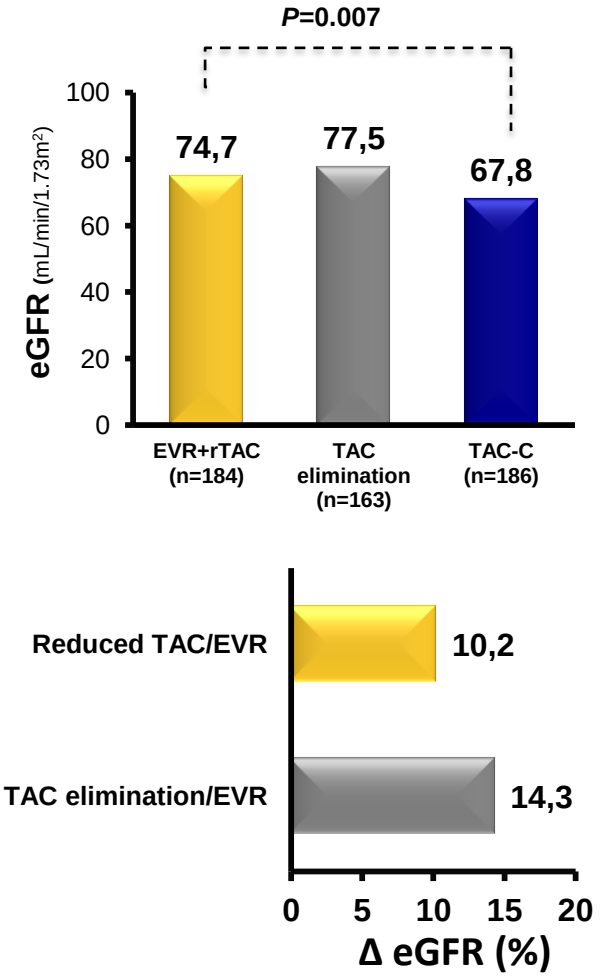
Evolution of Renal Fuction over time

(On-Treatment population)



Renal endpoints at 24-months

(ITT population)

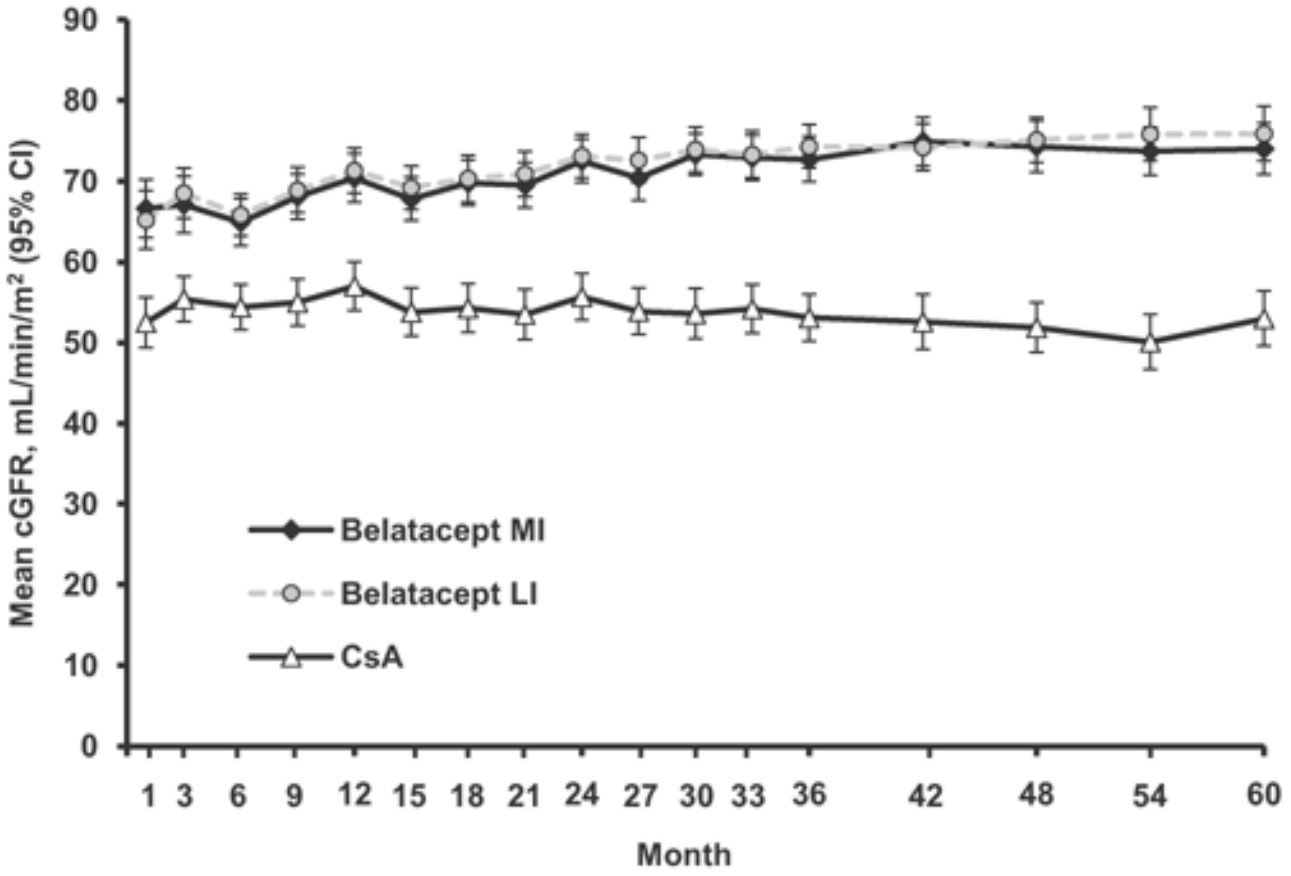


Saliba F. Presented at the AASLD, 2012; Boston

Saliba F, et al. *Am J Transplant.* 2013;3:1734–45.

BENEFIT: long-term extension study

Belatacept vs. CNI: Renal Function at 5 Years



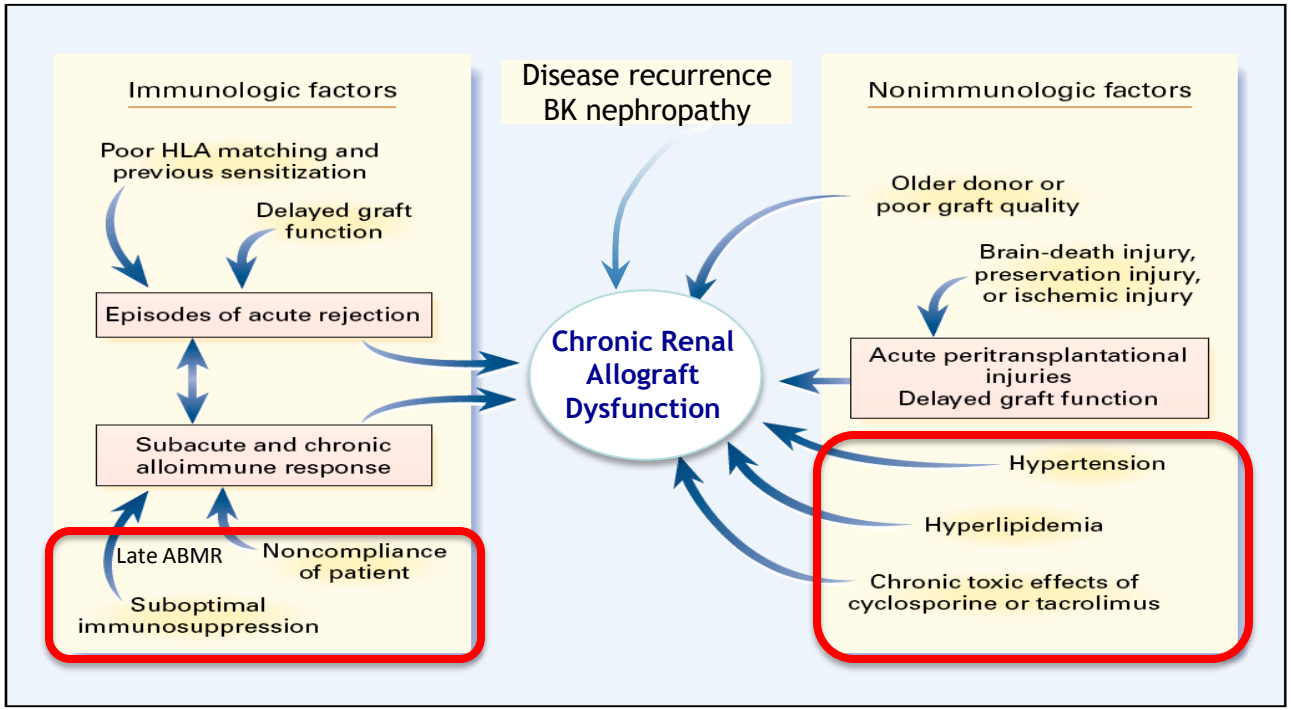
Patients with measurements

MI:	152	150	140	149	153	146	144	145	152	143	148	149	150	140	136	133	132
LI:	162	159	157	150	162	152	157	149	162	153	153	155	153	151	141	140	139
CsA:	134	132	126	123	129	127	122	122	129	125	125	123	129	113	107	102	98

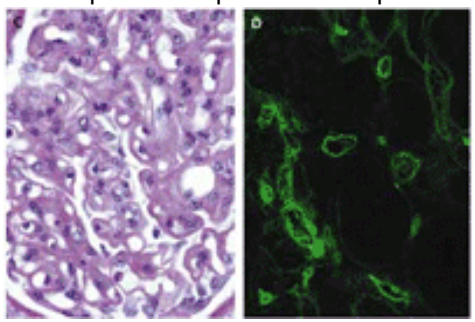
Rostaing L et al., Am J Transplant 2013;13: 2875-83

Chronic Renal Allograft Dysfunction

Immunosuppression: Too much or not enough?

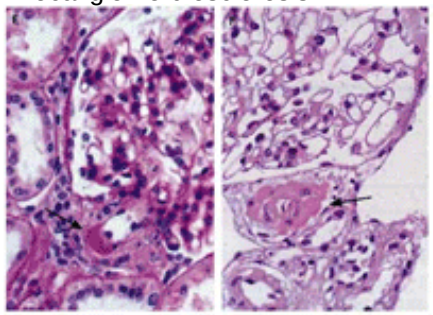


Late cellular and/or humoral rejection
Transplant glomerulitis/-opathy
C4d deposition in peritubular capillaries



IF/TA

CNI-induced nephrotoxicity
Hyalinosis of arterioles
Focal glomerulosclerosis

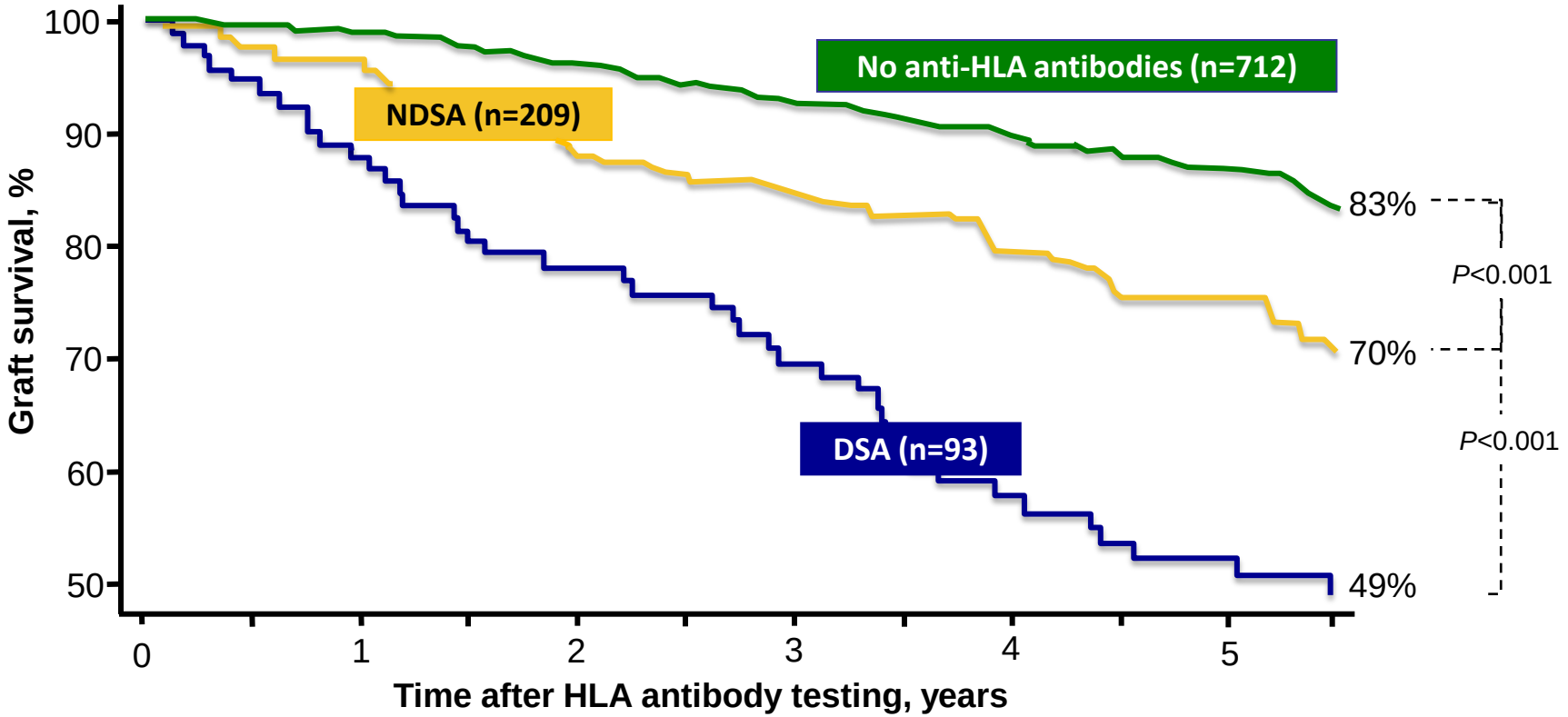


Modified from: Pascual M, et al. *N Engl J Med.* 2002;346:580–590 and Colvin RB. *N Engl J Med*. 2003; 349: 2288–9220..

Anti-HLA Abs detected after transplantation

Inferior long-term renal allograft outcome

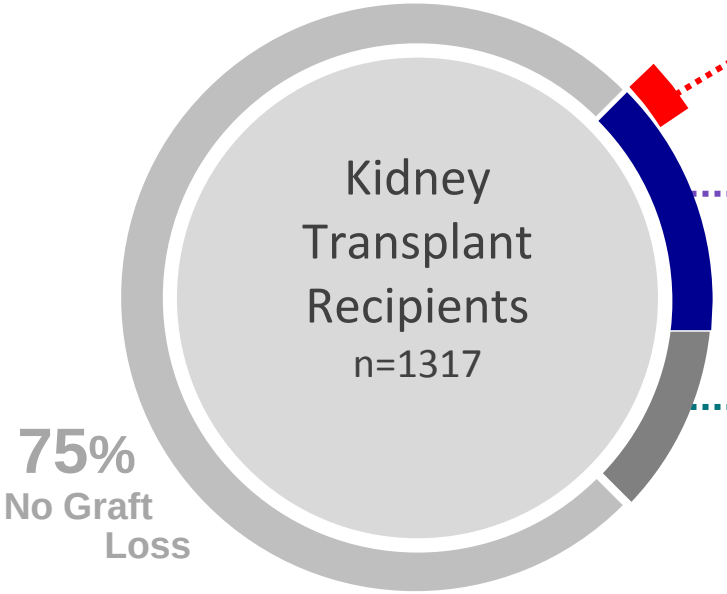
Kidney allograft survival according to HLA-Abs status (N=1014)



Lachmann N, et al. *Transplantation.* 2009:1505–1513.

Antibody-Mediated Rejection

Represents a small but definite component of renal transplant failure



75%
No Graft Loss

2% ABMR

14.5%
Graft Failure
incl. PNF

10.5%
Death with Graft Function

4.6%	Unknown
11.7%	Acute rejection
16.3%	Medical
30.7%	IF/TA
36.6%	Glomerular

~15% Recurrent Disease
~15% Transplant Glomerulopathy

Evidence from Histology:
Chronic tissue injury (any 2 of below):
- Arterial intimal fibrosis w/o elastosis
- Duplication of the GBM
- Multi-laminated PTC basement membrane
- IF/TA

Evidence from Tissue staining:
Ab action/deposition (e.g. Cd4 in PTC)

Evidence from Serology:
Anti-HLA or other anti-donor antibody

Mean follow-up: 50.3 ± 32.6 months

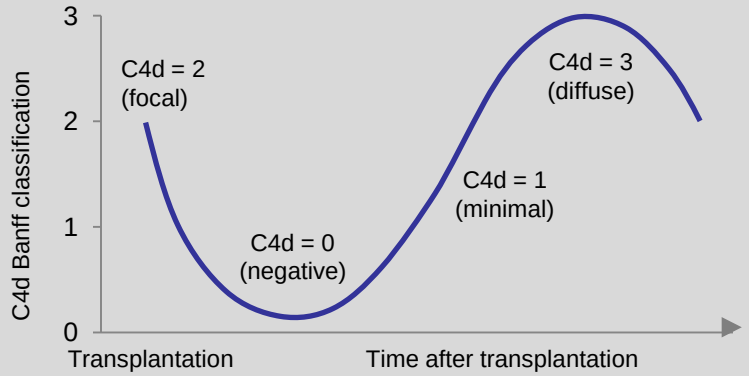
El-Zoghby ZM, et al. *Am J Transplant.* 2009;9:527–535.

LUMC

C4d-staining for the diagnosis of ABMR

Neither completely specific nor sensitive enough[1,2]

Fluctuations in C4d-status in a DSA-positive patient in the first post-transplant year[2]



- Progression to TGP in DSA-positive patients with micro-vascular inflammation, but w/o C4d deposition[3]
- High endothelial cell-specific gene expression leading to ABMR in renal transplant biopsy samples with DSA but w/o C4d[4]
- Positive C4d occurs with recurrent glomerular diseases (LN; ICX-GN)[4]

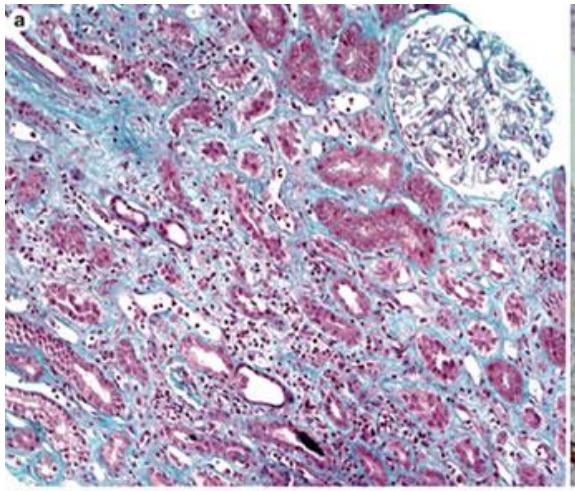
1. Colvin RB. *J Am Soc Nephrol*. 2007;18:1046–56; 2. Loupy A, *et al. Nat Rev Nephrol.* 2012;8:348–57; 3. Loupy A, *et al. Am J Transplant*. 2011;11:56–65; 4. Sis B, *et al. Am J Transplant*. 2009;9:2312–23

LUMC

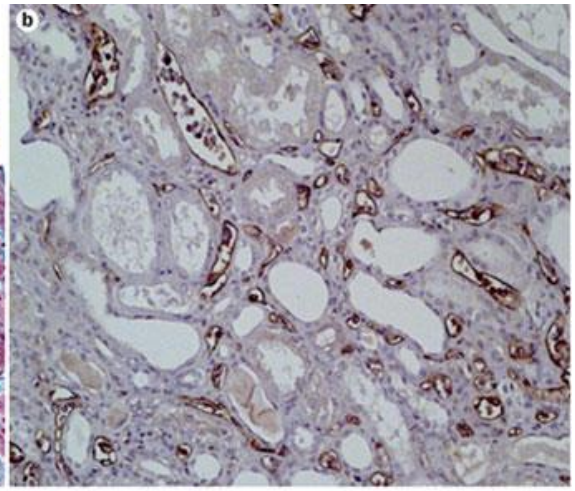
De novo donor-specific HLA-antibodies

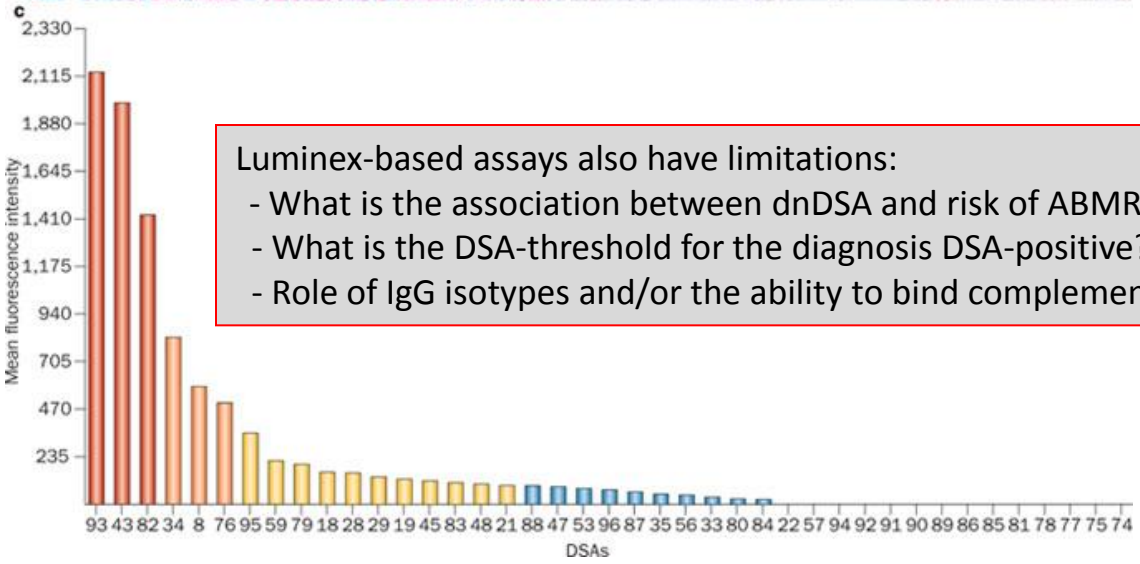
Evidence derived from Histology, C4d-staining and Serology

Microvascular inflammation



C4d-positive PTC staining





Luminex-based assays also have limitations:

- What is the association between dnDSA and risk of ABMR ?
- What is the DSA-threshold for the diagnosis DSA-positive?
- Role of IgG isotypes and/or the ability to bind complement?

Loupy A, *et al. Nat Rev Nephrol.* 2012;8:348–57; Mengel M, et al. *Am J Transplant*. 2012;12:563–70.

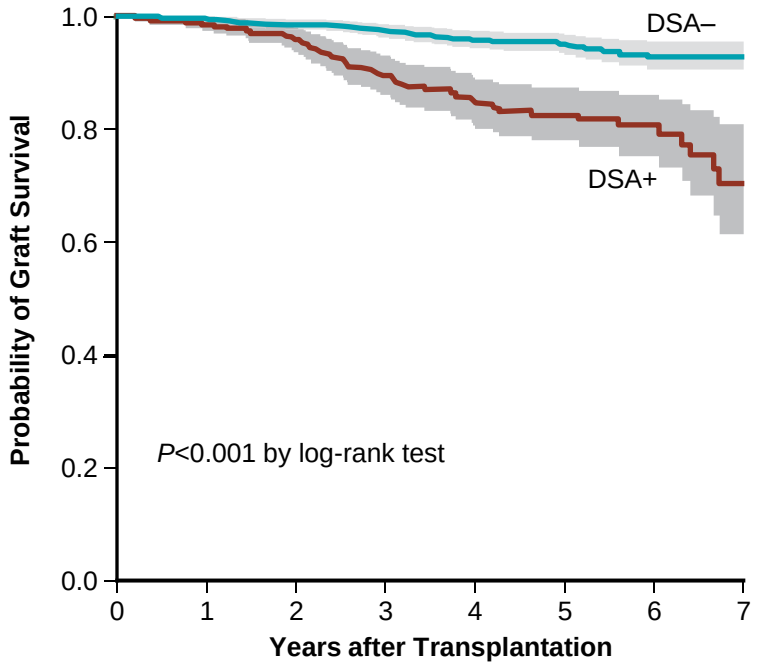
LUMC

Donor-specific anti-HLA Abs after transplantation

Complement fixing or non-complement fixing antibodies

Consecutive patients, population-based study (N=1016)[1]

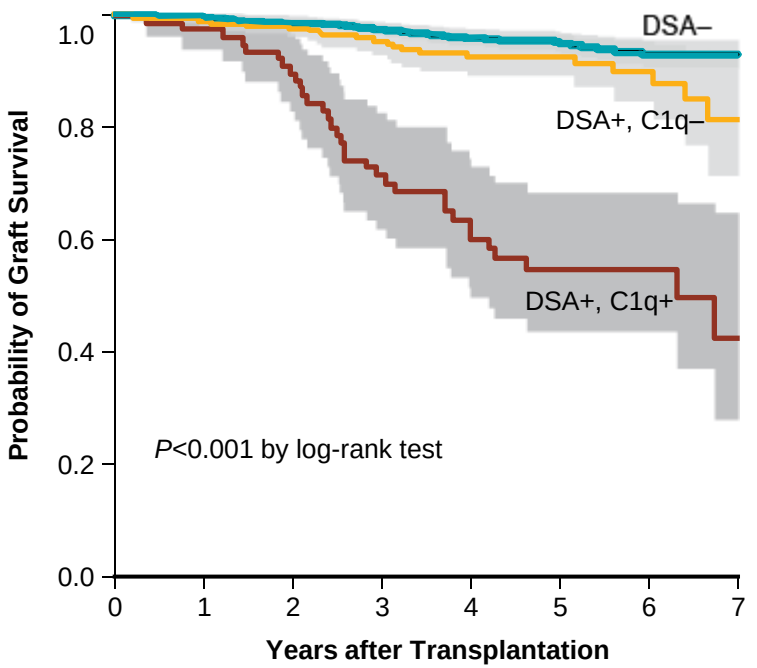
Allograft survival and DSA-status



No. at Risk

DSA-	700	698	667	612	504	338	164	38
DSA+	316	312	295	229	176	100	56	19

Allograft survival DSA+C1q-status



No. at Risk

DSA-	700	698	667	612	504	338	164	38
DSA+/C1q-	239	237	227	181	139	80	44	14
DSA+/C1q+	77	75	68	48	37	20	12	5

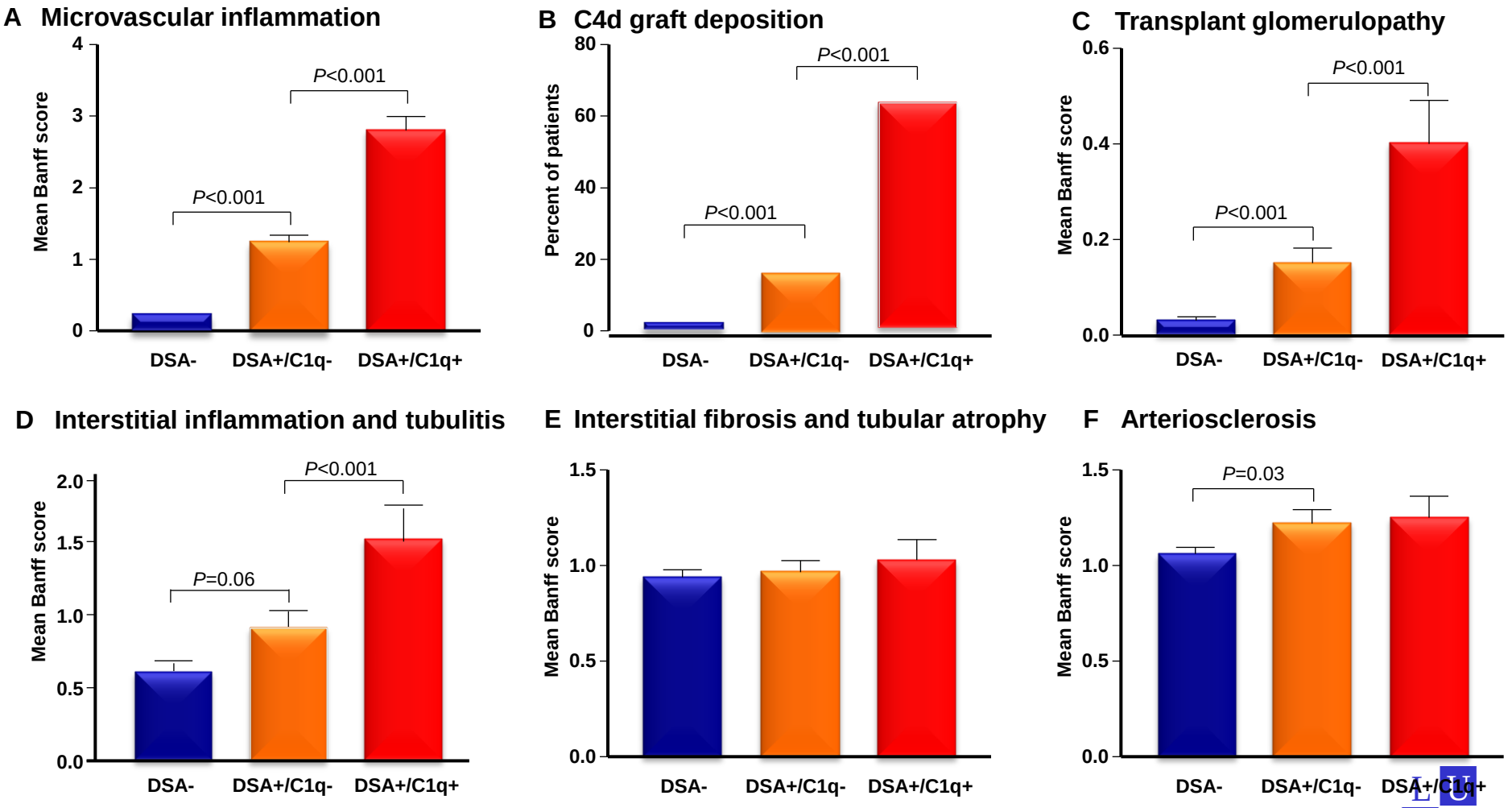
The distribution of graft-injury phenotypes and rates of allograft survival were similar across all classes.
Both class I and class II of donor-specific anti-HLA antibodies after transplantation were harmful[2]

1. Loupy A, et al. *N Engl J Med.* 2013;369:1215–1226; 2. Lefaucheur C, et al. *N Engl J Med.* 2014;370:85–86.

Complement-binding DSAs

Association with Tissue damage/Inflammation

Graft histopathology (N=1016) according to HLA-DSA status

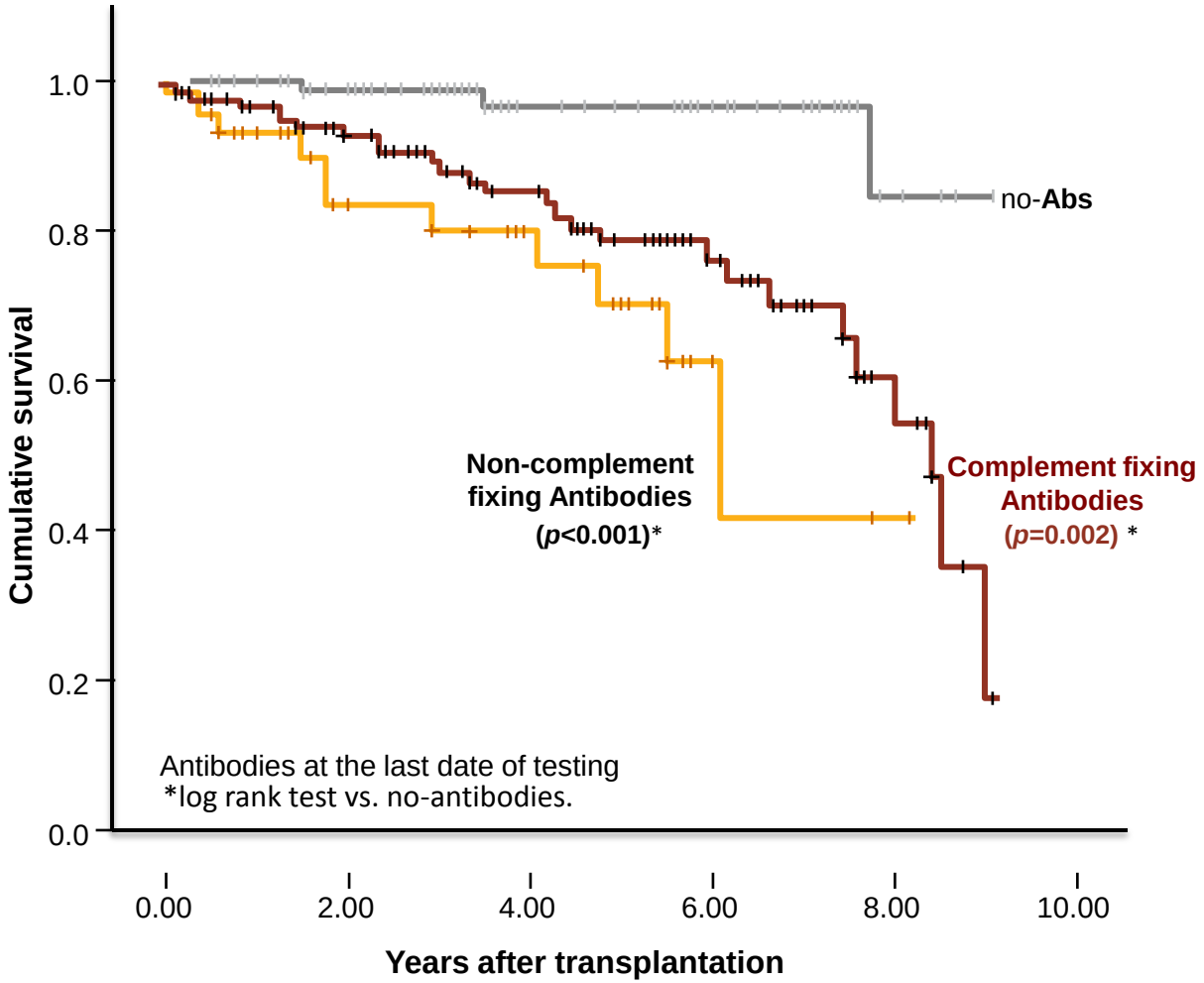


Data based on 1016 kidney-allograft biopsies performed in the first year after transplantation. (845 at 1-year and 171 during acute rejection in the first year).
Loupy A, et al. *N Engl J Med*. 2013;369:1215–1226.

Antibodies not binding complement

Equally associated with inferior graft survival

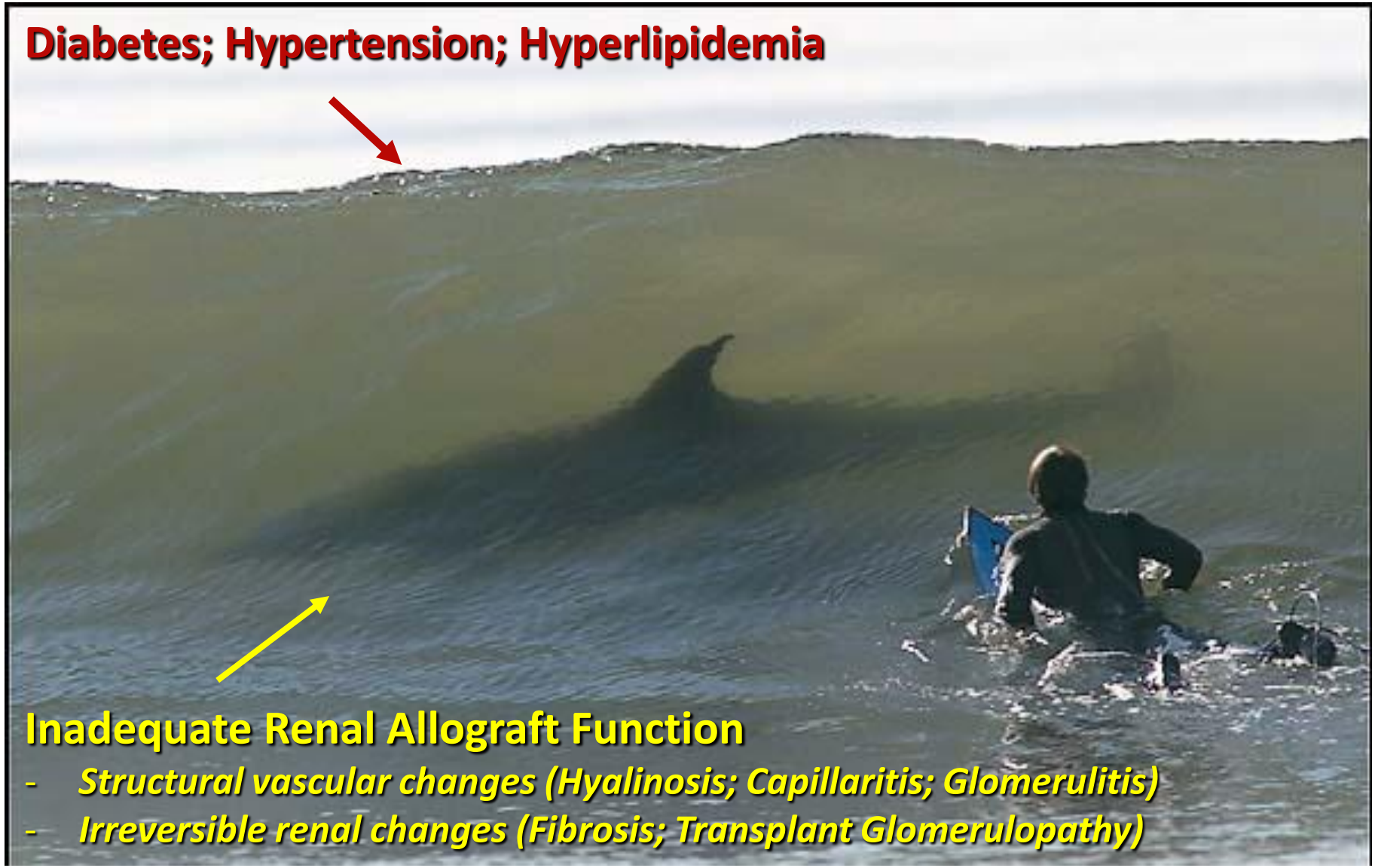
Graft survival in RTRs tested for anti-HLA immunoglobulin subclasses (n=274; 2008)



Arnold ML et al. *Transplant Int* 2014;27:253-61.

Clinical Immunosuppression

Long-term outcome after kidney transplantation



1: Reduced exposure to CNIs in RTRs

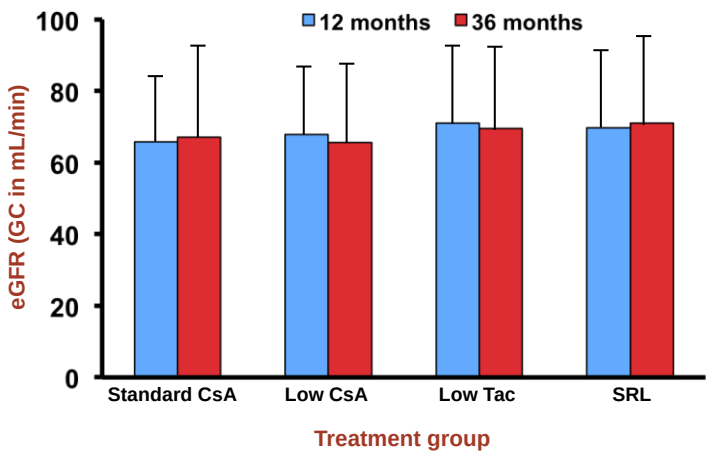
Lower rejection rates do not translate in better long-term outcome parameters

Regimen tested	n	eGFR (C-G) mL/min	BPAR %	1-Yr GS %
Standard-dose CsA (150–300 ng/mL first 3 months & 100–200 ng/mL thereafter)	390	57.1±25.1	30.1	91.9
Low-dose CsA (50–100 ng/mL)	399	59.4±25.1	27.2	94.3
Low-dose TAC (3–7 ng/mL)	**401**	**65.4±27.0**	**15.4**	**96.4**
Low-dose sirolimus	399	56.7±26.9	40.2	91.7

Ekberg, et al. *N Eng J Med.* 2007;357:2562–75.

ELITE–SYMPHONY
Comparable eGFR results at 3-years

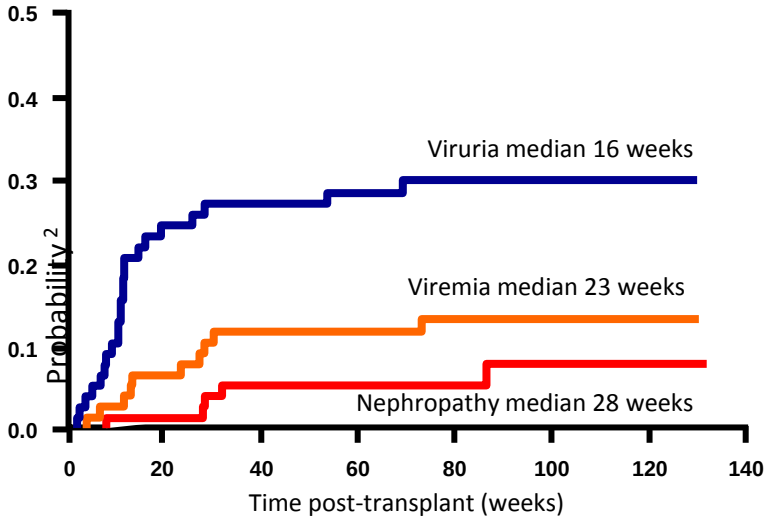
SYMPHONY trial: 12-month and 36-month eGFR[a]

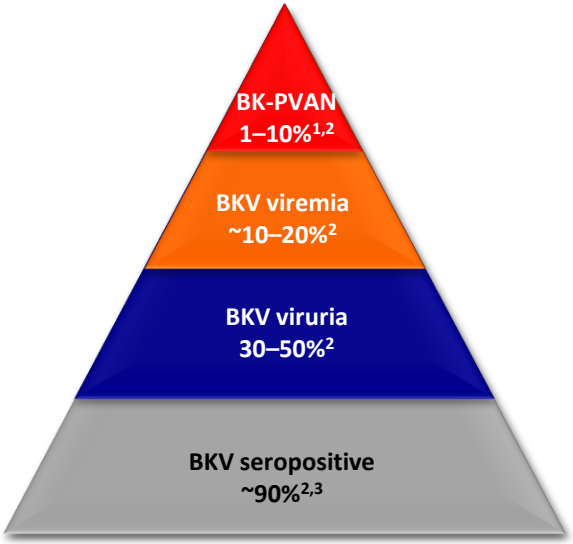


Ekberg H *et al. Am J Transpl* 2009;9:1876–85

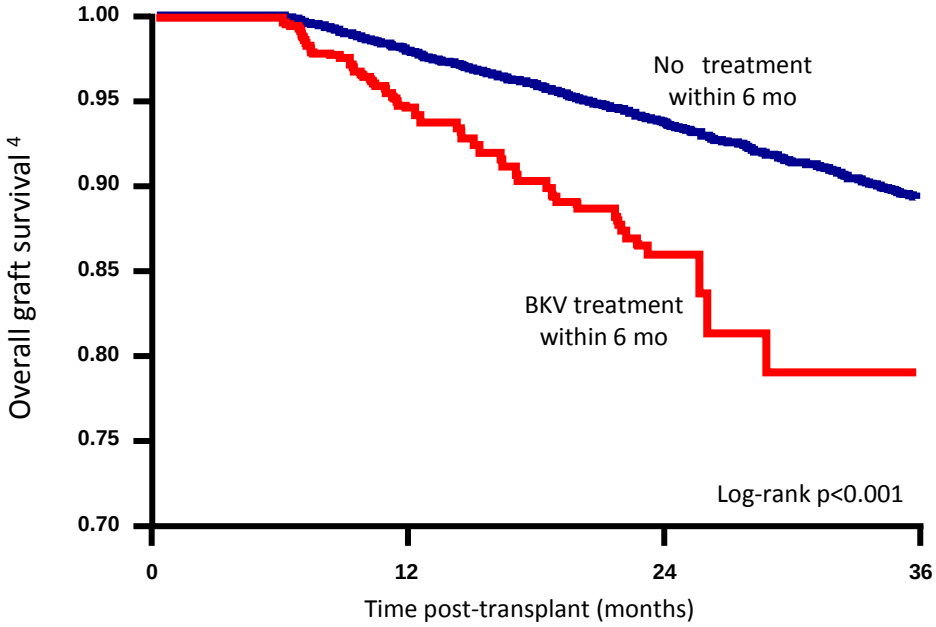
Low acute rejection rate vs. excess BKV replication

Common in RTRs and associated with graft loss





Retrospective analysis of 34,937 RTRs (SRTR: 2004–2006)
Significant difference in overall graft survival at 3 years



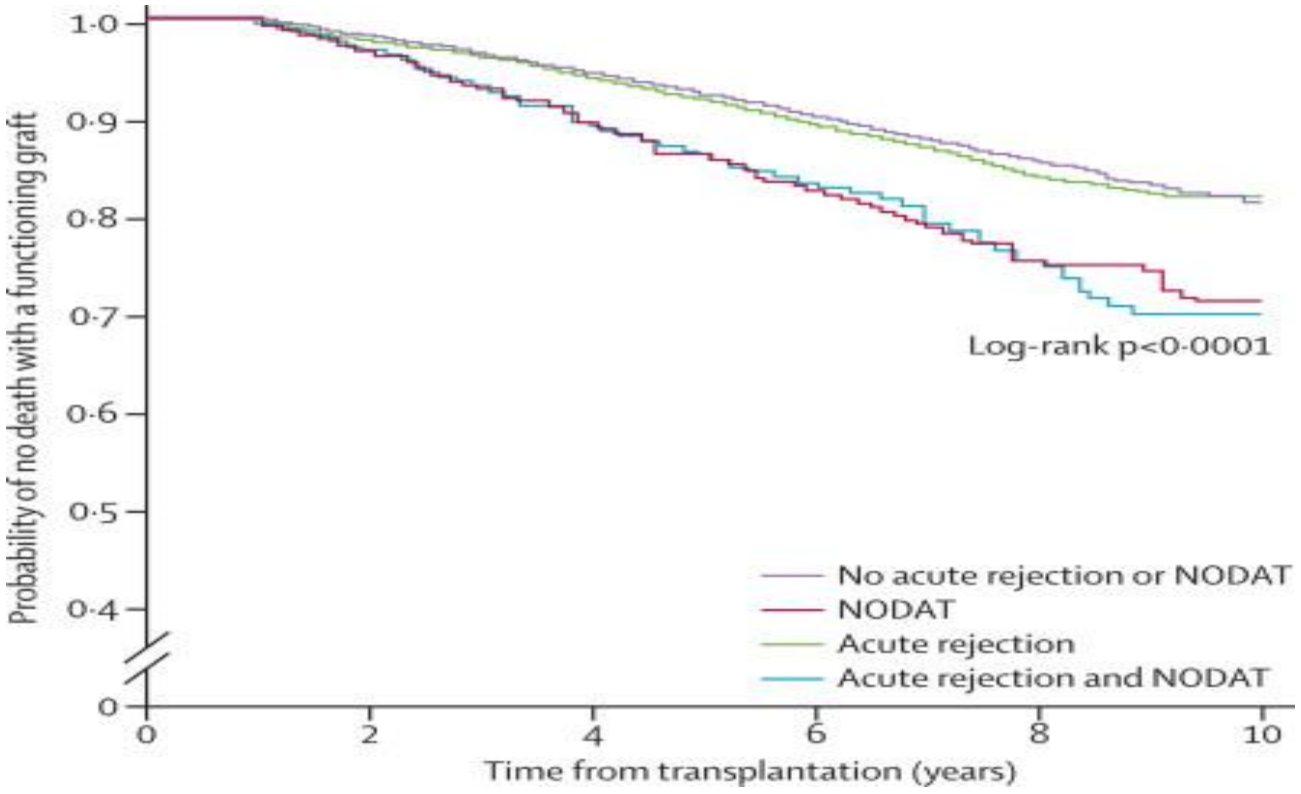
1. Egli A et al. J Infect Dis 2009;199:837–46; 2. Hirsch HH et al. N Engl J Med 2002;347:488–96;
3. Nickeleit V et al. N Engl J Med 2000;342:1309–15; 4. Schold JD et al. Transpl Int 2009;22:626–34

LUMC

2: Prolonged CNi/CS vs. New-onset Diabetes

Dominant impact on patient survival beyond the first Year

After the first year, a history of acute rejection had no effect on outcome.



Cole EH. et al. Clin *J Am Soc Nephrol.* 2008;3:814-–21.

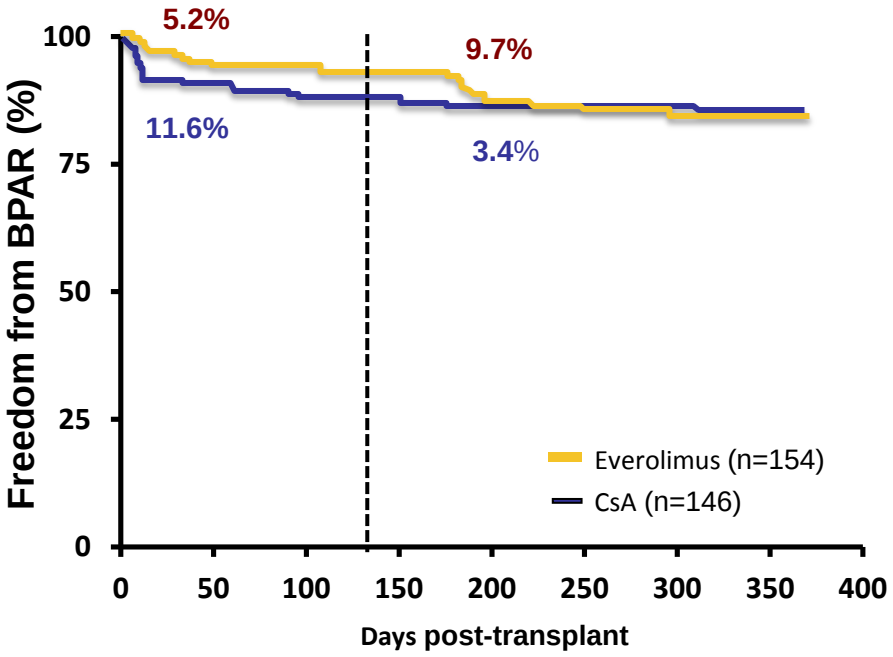
Empiric dose reduction/drug withdrawal

CNi- and/or CS-elimination with mTORis

ZEUS trial

CNi-elimination with EVR at 4.5 months

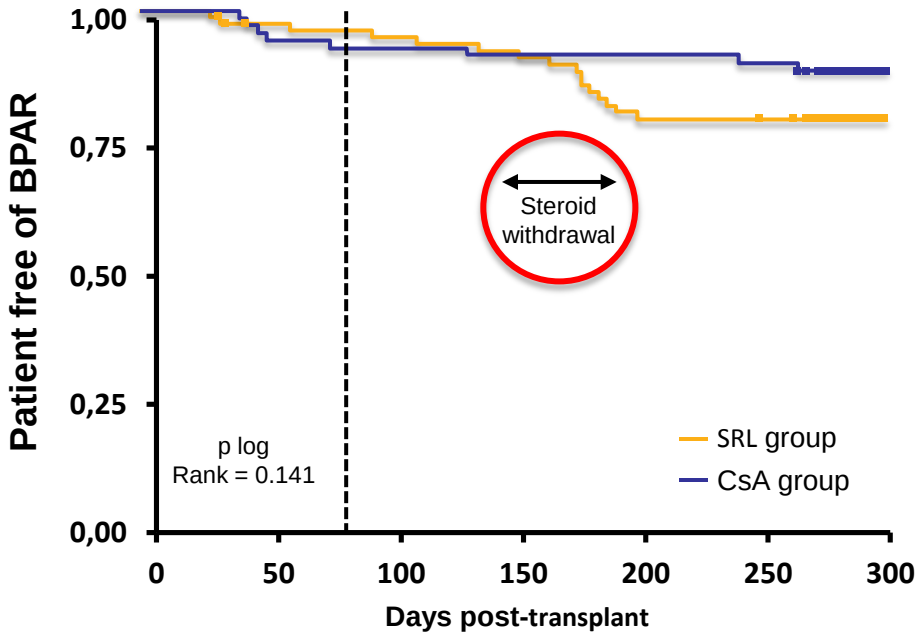
Intention-to-treat population



CONCEPT trial

CNi-elimination with SRL at 3-months

Intention-to-treat population



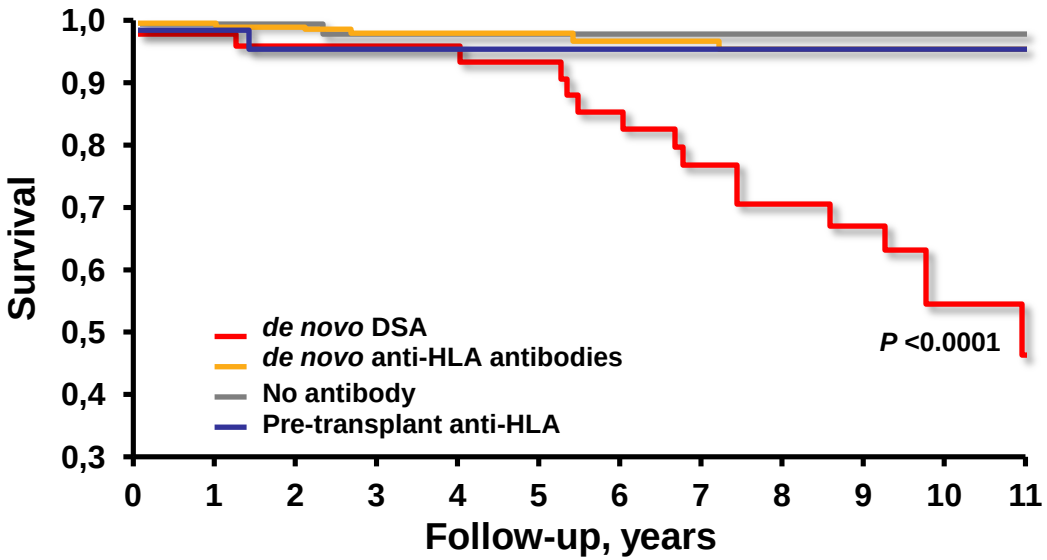
Adapted from Budde K *et al.* Lancet 2011;377:837-47

Lebranchu Y, et al. *Am J Transplant*. 2011;11:1665–75.

3: Risk for *de novo* DSA and ABMR

1. Incompatibility for HLA class-II antigens

Median 10-year graft survival for the 15% of patients with *de novo* DSA was 40% lower than those w/o DSA (59% vs 96%, *P*<0.0001)



Independent predictors for de novo DSA formation:

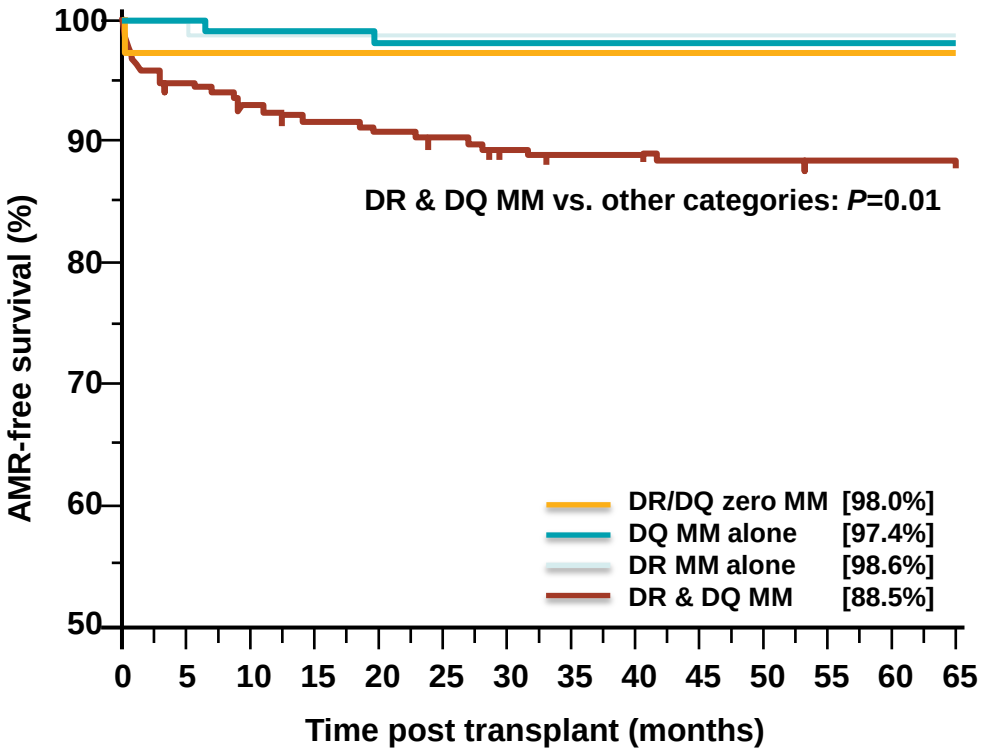
1) **HLA-DR mismatch**
2) **Non-adherence (pediatric recipients)**
3) **History of rejection or protocol biopsy with SCR between month 0-6**

Wiebe C, et al. *Am J Transplant.* 2012;12:1157–67

Most dnDSA are HLA-DQ specific

Linkage disequilibrium between HLA-DR and -DQ

AMR-free survival by DR & DQ matching



DQ & DR mismatch and corresponding DSA

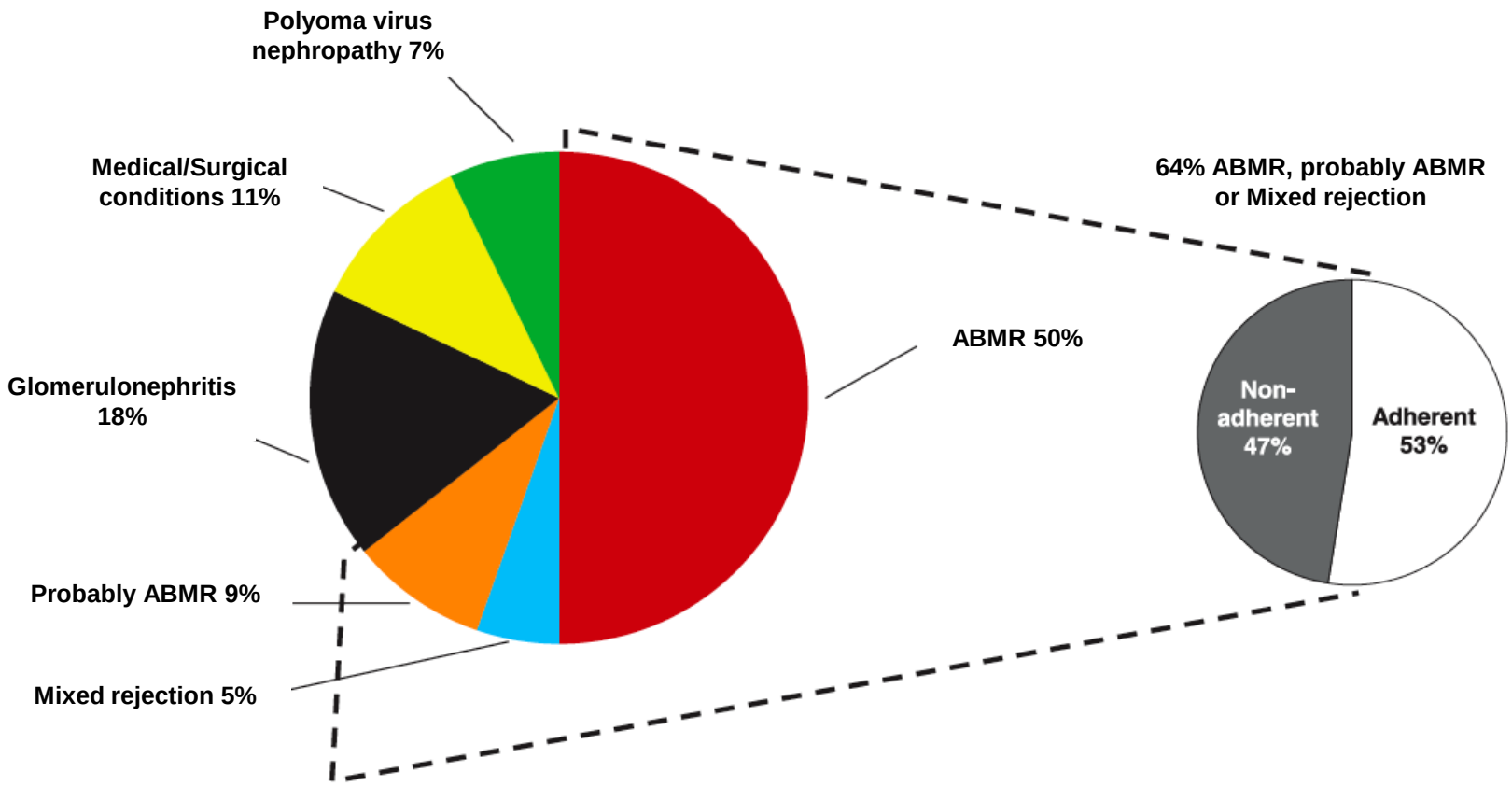
	Mismatch (n)	Patients (n, %)	Corresponding DSAs (n, %)
DR	0-DR	146 (28.9)	0
	1-DR	263 (52.1)	20 (7.6)
	2-DR	96 (19.0)	9 (9.4)
DQ	0-DQ	184 (36.4)	0
	1-DQ	250 (49.5)	35 (14.0)
	2-DQ	71 (14.1)	15 (21.1)
DR =0	DQ 0	108 (21.4)	0
	DQ ≥1	38 (7.5)	2 (5.3)
DR ≥1	DQ 0	75 (14.9)	2 (2.7)
	DQ ≥1	284 (56.2)	60 (21.1)

Willicombe M, et al. *Transplantation*. 2012;94:172–77.

Risk for Antibody-mediated Rejection

2. Non-adherence

For-cause biopsies (n=315) between 2004-2008 with documented failure (n=56) in 3 N-A Centers



Sellares J, et al. *Am J Transplant.* 2012;12:388–399.

DSA occur with all types of immunosuppressive regimen

3. Inadequate Overall Immunosuppression

Immunosuppression	N	DSA posttransplantation	
CsA 43% (n=129)*; Tac 35% (n=106)* w/AZA 16% (n=50)*; w/MMF 34% (n=102)*	1014	29.8% (n=302): de novo HLA antibodies 9.2% (n= 93): de novo DSA	Lachmann N, et al. *Transplantation 2009;* 87:1505–13
CNI (CsA or Tac) Prednisone MMF	203	26.6% (n=54) de novo DSA - 16.6% (n=34) *de novo* DQ-DSA - 9,8% (n=20) *de novo* DQ-DSA + other DSA	Freitas MA, et al. *Transplantation.* 2013;95:1113–19;
MMF (2 g/d); Prednisone Tac (8–10 ng/mL: first 3 mo; 6–8 thereafter CsA (C2: 800–1200 ng/mL first 3 mo; 600–800 thereafter	1016	31.1% (n=316) de novo DSA at 4.8 yrs. (0.2-7) 7.6% (n= 77) C1q+	Loupy A, et al. *N Engl J Med.* 2013;369:1215–26;
CsA (n=129); Tac (n=57)	189	25% (n=47) *de novo* DSA within 10 years	Everly MJ, et al. *Transplantation.* 2013;95:410–17
MMF/MPA + CsA + Pred MMF/MPA + Tac + Pred Aza + CsA + Pred CsA/Tac + Sir + Pred	78	16% de novo DSA within first year 19% de novo DSA within first year 5% de novo DSA within first year 3% de novo DSA within first year	Banasik M, et al. *Transplant Proc.* 2013;45:1449–52;
CsA/Tac MMF/MZR/AZA/EVR	320	13.3% (n=39) *de novo* HLA antibody	Ashimine S, et al. *Kidney Int.* 2014;85:425–30;
Tac+MMF+glucocorticoids: (n=48) CsA+MMF+glucocorticoids: (n=4) EVR+CsA+glucocorticoids: (n=3)	55	10% de novo DSA at 1 year 28% *de novo* DSA at 3 years	Libri I, et al. *Am J Transplant.* 2013;13:3215–3222
Belatacept, more intensive + MMF (n=219) Belatacept, less intensive + MMF (n=226) CsA + MMF (n=221)	66	6% de novo DSA by year 3 5% de novo DSA by year 3 11% de novo DSA by year 3	Vincenti F, et al. *Am J Transplant.* 2012;12:210–217.

*Data reflects proportion and numbers of patients with HLA antibodies post-transplantation.

LUMC

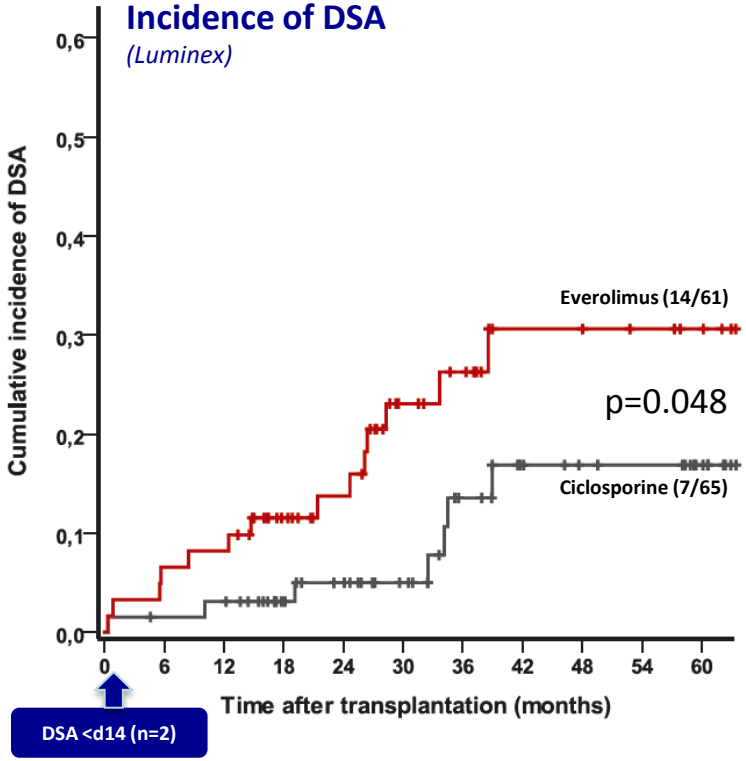
Inadequate control over immune reactivity

CNi-elimination (mo 4.5) followed by Steroid-withdrawal in 60%

Retrospective single-center analysis, pooled data from participation in two (comparable) trials

Incidence of DSA

(Luminex)

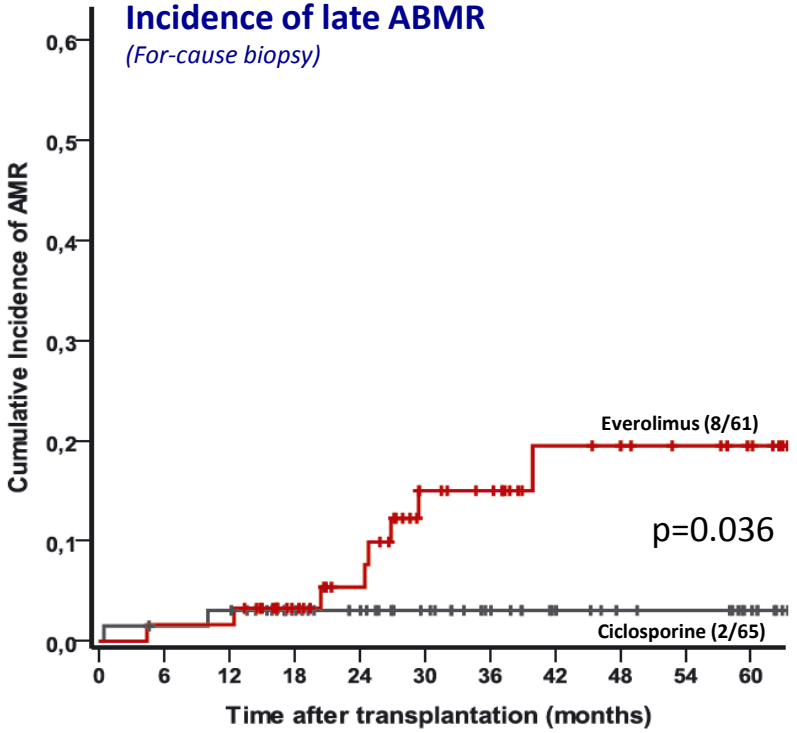


Independent risk factors:

Everolimus (=CNi/CS stop) arm	*2.67 (1.07-6.66)*
Living donor	*2.39 (1.01-5.66)*
HLA-mismatch ≥4	*3.26 (1.37-7.75)*

Incidence of late ABMR

(For-cause biopsy)



Independent risk factors:

Everolimus (=CNi/CS stop) arm	*5.35 (1.11-25.70)*
Living donor	*5.78 (1.44-23.16)*
HLA-mismatch ≥4	*5.10 (1.39-18.72)*
Treated AR first year	*10.22 (2.56-40.87)*

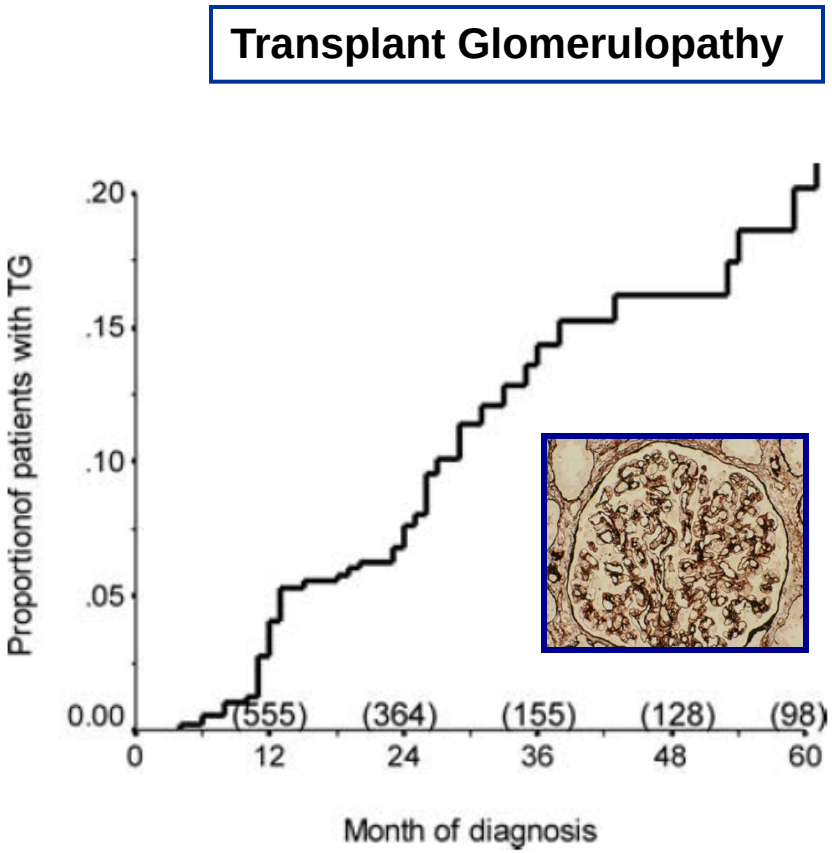
LUMC

Liefeldt L, *et al. Am J Transplant.* 2012;12:1192-8.

4: Transplant Glomerulopathy

Antibodies against non-HLA antigens

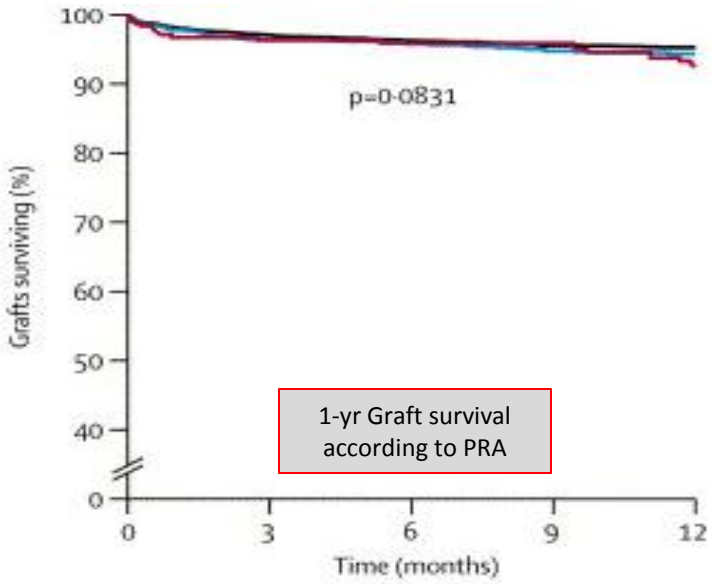
Variable	No TG	TG	p-Value
Number of patients	527	55	
Recipient age (years)	51 ± 14	46 ± 17	0.02 [1]
Diabetes (%)	34.9	30.9	NS[2]
Dialysis pretransplant (%)	55	62	NS[2]
PRA peak (%)	2.4 ± 12.7	6.5 ± 19.6	0.004[3]
Donor age (years)	42 ± 13	40 ± 12	NS[1]
Donor type (%)			NS[2]
Living related	50	43	
Living unrelated	27	29	
Deceased	23	28	
First transplant (%)	68	52	0.03[2]
Hepatitis C antibodies (%)	1.7	7.3	0.007[2]
Acute rejection (AR)	75 (14.2%)	18 (32.7%)	<0.0001[2]
AR type (%)			
Borderline	9.9	16.4	<0.0001[2]
Cell mediated	3.8	10.9	
Antibody mediated	0.6	5.5	
Follow-up months	41 ± 16.5	43 ± 15.7	NS[3]



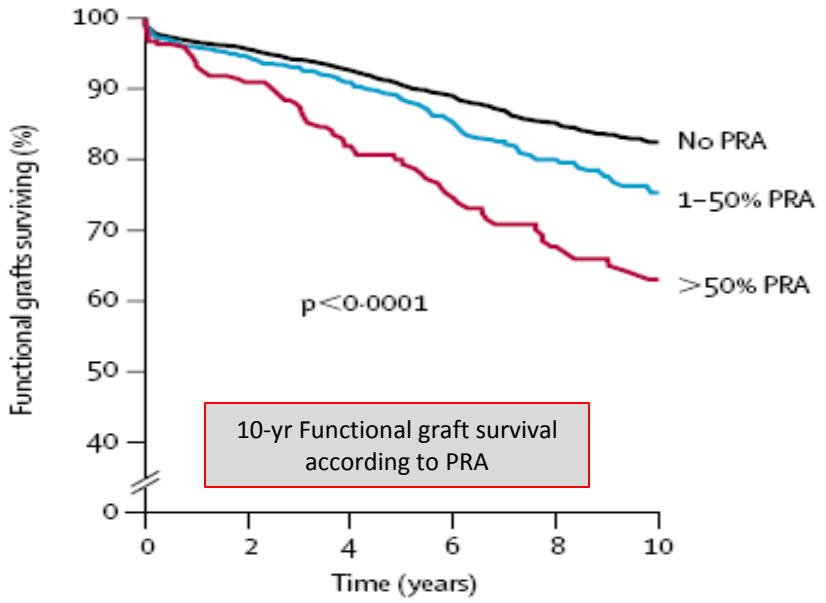
Gloor et al., Am J Transpl, 2007;7:2124

HLA-identical Kidney Transplant Recipients (siblings)

Impact of pre-transplant %-PRA (HLA & non-HLA antigens)



1-yr Graft survival according to PRA



10-yr Functional graft survival according to PRA

Number of transplants					
No PRA	3001	2914	2864	2774	2765
1–50% PRA	803	774	766	744	741
>50% PRA	244	235	229	223	215

3001	2495	1929	1418	989	687
803	647	514	362	249	158
244	192	149	111	84	65

Characteristic	Preformed PRA			p
	None (n=3001)	1–50% (n=803)	>50% (n=244)	
Proportion female	1014 (34%)	361 (45%)	154 (63%)	<0·0001
Proportion with retransplant	159 (5%)	112 (14%)	97 (40%)	<0·0001
Mean (SE) pretransplant blood transfusions	3·47 (0·15)	6·01 (0·43)	10·7 (1·12)	<0·0001

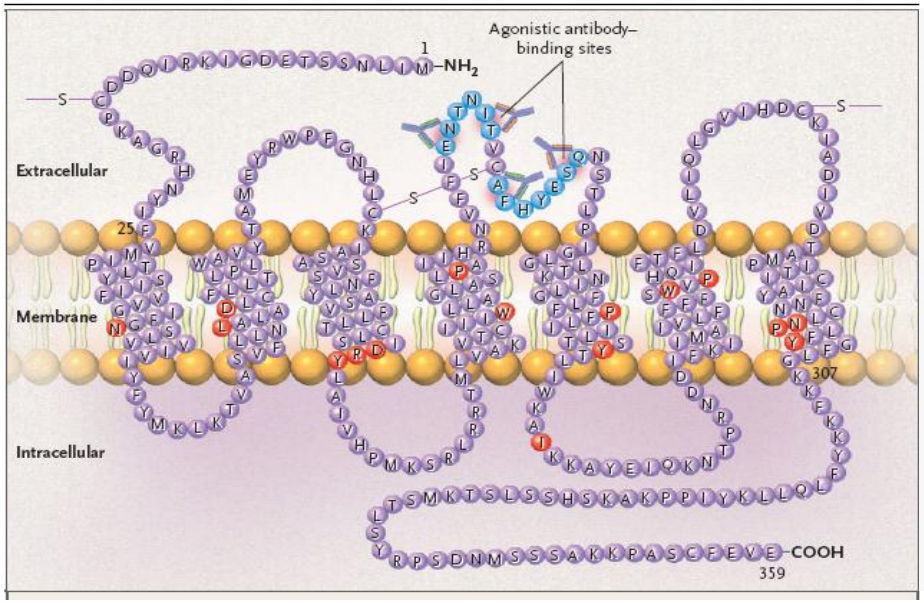
Table: Association of preformed PRA with various characteristics of patients

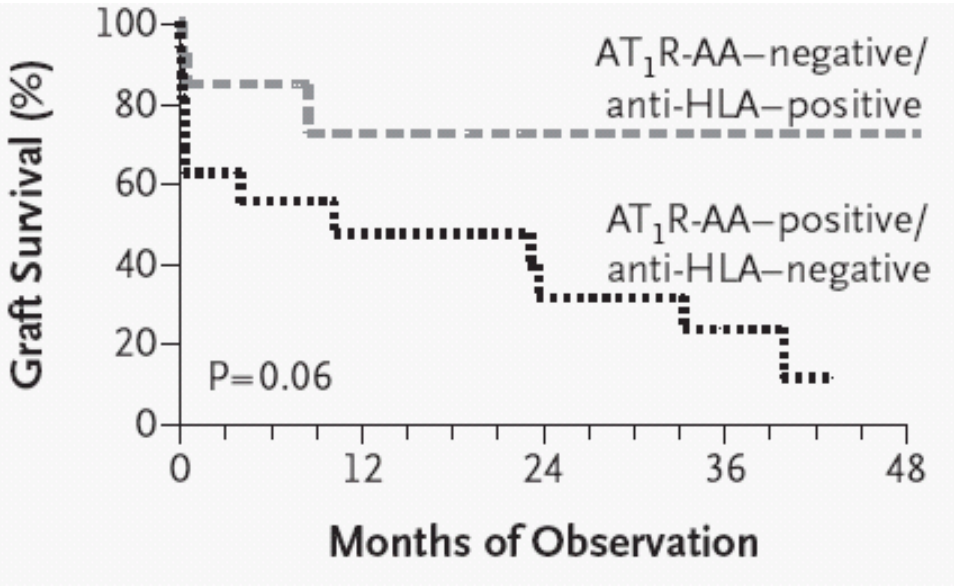
Opelz et al., Lancet 2005, 365:1570-6

Agonistic antibodies against the AT1-R

Refractory vascular rejection in RTRs (n=33)

Angiotensin II Type 1–Receptor Activating Antibodies in Renal-Allograft Rejection





Dragun D et al N Eng J Med 2005

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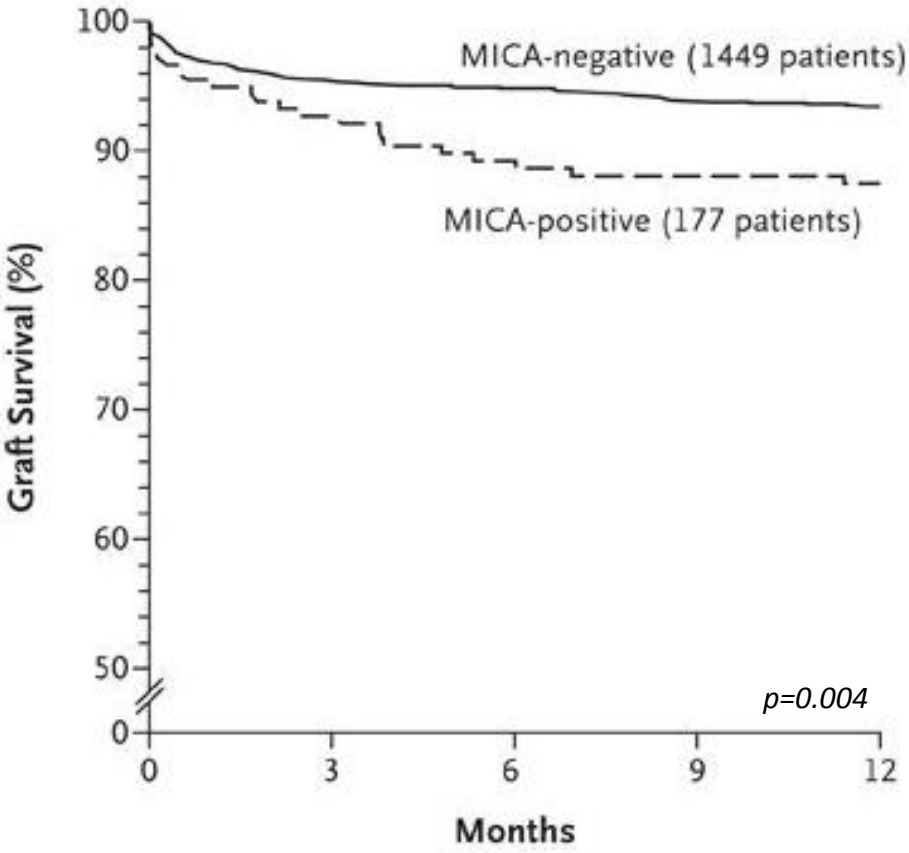
Pretransplant MHC class I–related chain A antibodies

Early kidney graft loss and Tissue expression

Pre-transplant antibodies against MICA
non HLA-sensitized RTRs

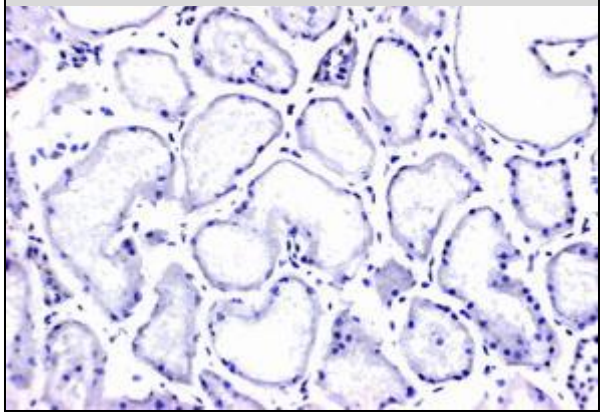


First graft/well matched/low-risk/non-sensitized

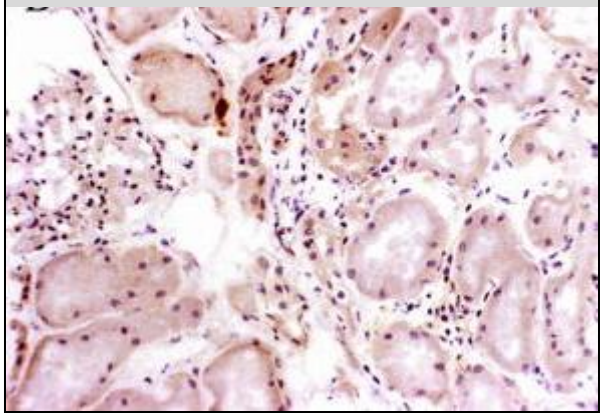
Zou Y et al. N Engl J Med 2007;357:1293-1300.

Sequential kidney biopsies pre-implantation
and at day-7 stained with MICB antibody

(A) Very low levels of tubular MICB expression on the renal tubules in the donor kidney biopsy



(B) Up-regulated MICB expression 7 days post-transplant in proximal and distal tubular cytoplasm



Quiroga I et al. Transplantation 2006;81:1196-1203

LUMC

Chronic Renal Allograft Dysfunction

- Inadequate renal (allograft) function is a robust independent risk factor for excess cardiovascular mortality, especially with concomitant diabetes.
- ABMR is a relative small component of overall graft loss[1], but a definite cause of premature graft failure[2]
- De *novo* DSA have been documented in RTRs while treated according to all major immunosuppressive maintenance regimen[7,8]. Major risk factors include
  - Incompatibility for HLA-class II, and/or
  - Non-adherence, and/or
  - Inadequate overall immunosuppression
- Clinical immunosuppression is further challenged by:
  - Low acute rejection rates vs. excess BKV-replication
  - Prolonged CNi- and CS-use vs. unfavourable CV risk profile (GFR/DM/HT)
  - Inappropriate (empiric) dose reduction(s) and chronic/late (humoral) rejection

1. El-Zoghby ZM, et al. *Am J Transplant.* 2009;9:527–35. 2. Sellares J, et al. *Am J Transplant.* 2012;12:388–399. 3. Djamali A, et al. *Am J Transplant* 2014;14:255-71; 4. Loupy A, et al. *Nat Rev Nephrol*. 2012;8:348–57; 5. Freitas MC, et al. *Transplantation* 2013;95:1113–19; 6. Loupy A, et al. *N Engl J Med.* 2013;369:1215–26; 7. Vincenti F, et al. *Am J Transplant*. 2012 ;12:210-7; 8. Ashimine S, et al. *Kidney Int*. 2013

LUMC