

***ABO incompatible kidney
transplantation:
desensitization protocols and results***

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Inadequacy between demande and supply

- Deceased donors :
 - Marginal donors (ECDs)
 - Donors after cardiac death
 - Maastricht 3 donors
- Living donors:
 - Public awareness campaigns
 - Swap programs (chains)
 - Pair exchange
 - **ABO incompatible and/or HLA incompatible KTx**

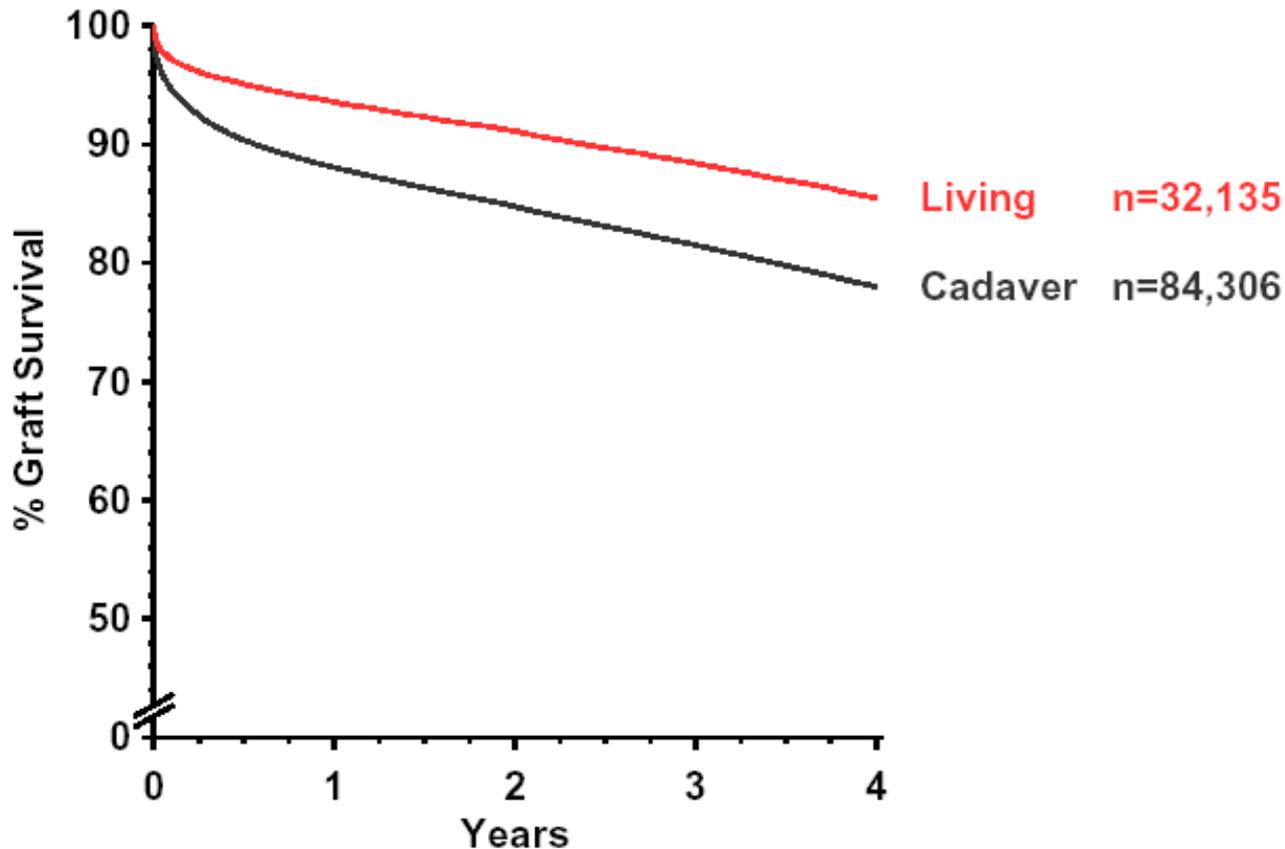
ABOi and/or HLAi KTx

- Immunological barriers :
 - ABOi : isoagglutinins
 - HLAi: anti-HLA alloantibody(ies) directed against the donor (DSA), that might bind or not complement (C1q, C3d)
- If kidney transplantation is attempted in these settings :
 - Possibility of hyperacute rejection
 - Possibility of vascular/humoral rejection within the posttransplant days
 - PREVENTION = Desensitization, i.e. to remove by apheresis before transplant the deleterious antibodies and to prevent their re-synthesis.

Rationale for ABOi and/or HLAi KTx

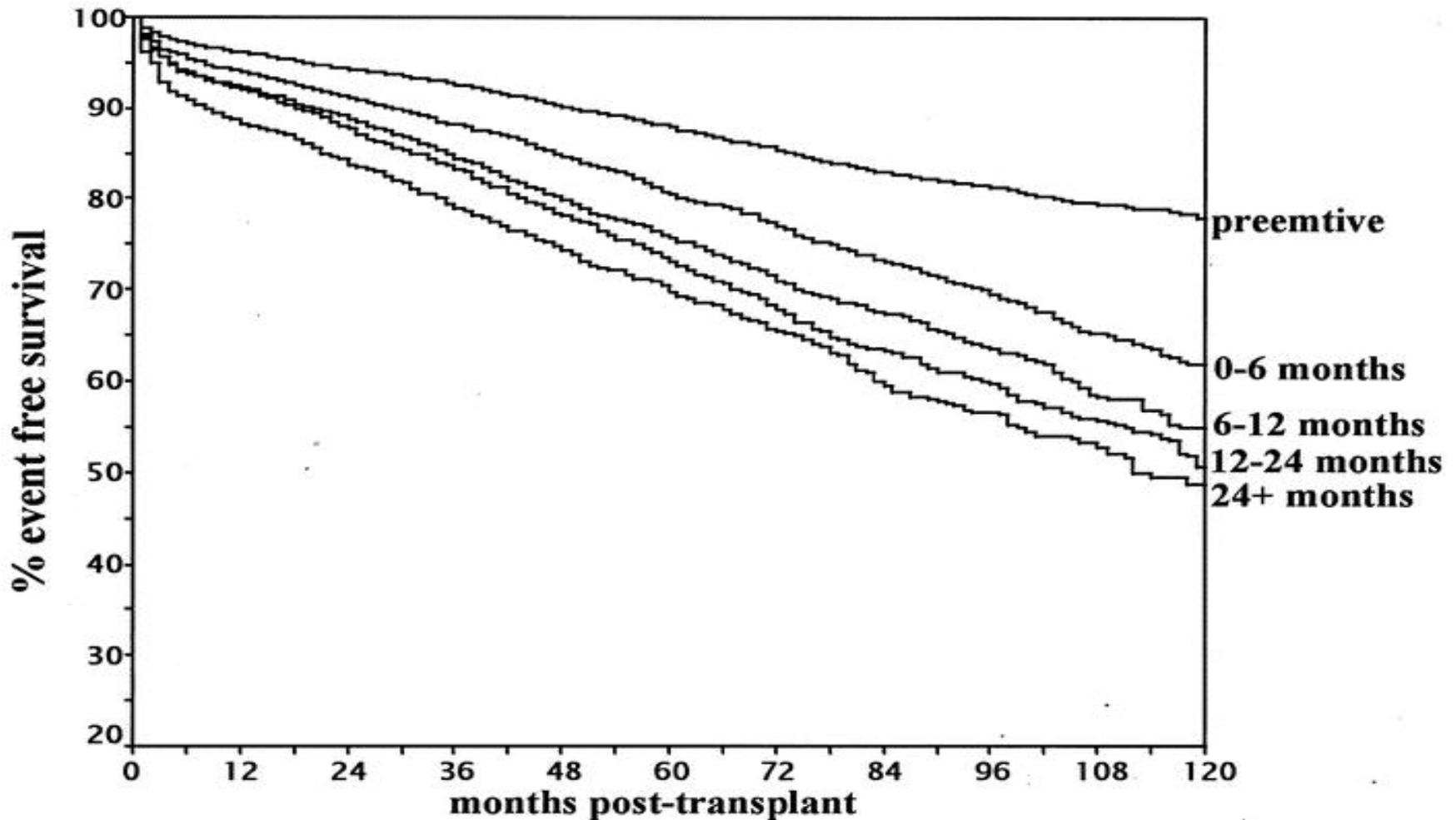
- Living donor (better results in the long-term than with deceased donors)
- Possibility of pre-emptive KTx (better results in the long-term)

Outcomes of KTx with regards to the donor type: Kidney transplants 1997-2005



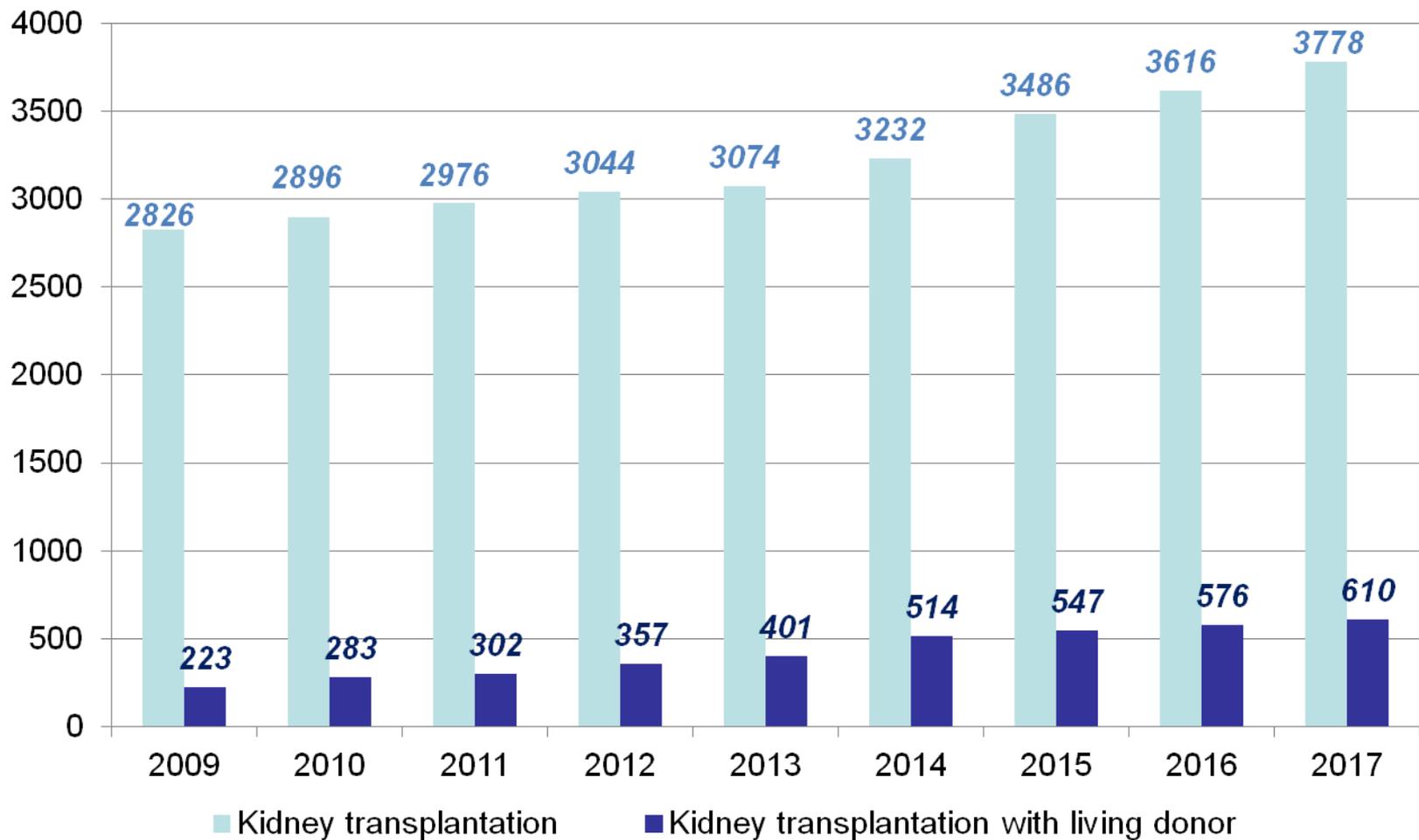
Results of kidney transplantation: Influence by the time on dialysis

Unadjusted graft survival in 21,836 recipients of living transplants by length of dialysis treatment before transplant.

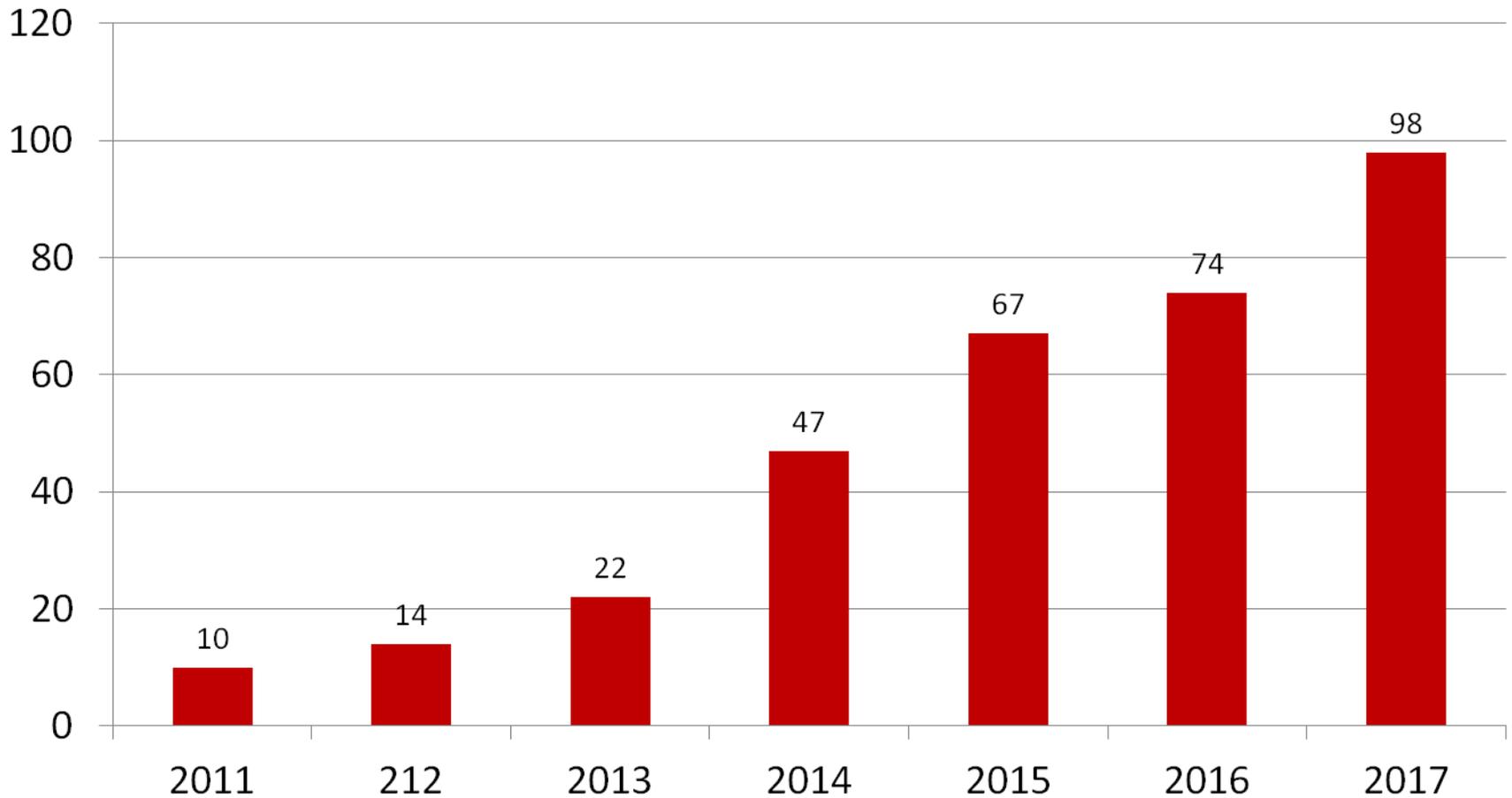


***ABO incompatible kidney
transplantation***

Kidney Transplantation in France (deceased vs. living donors)

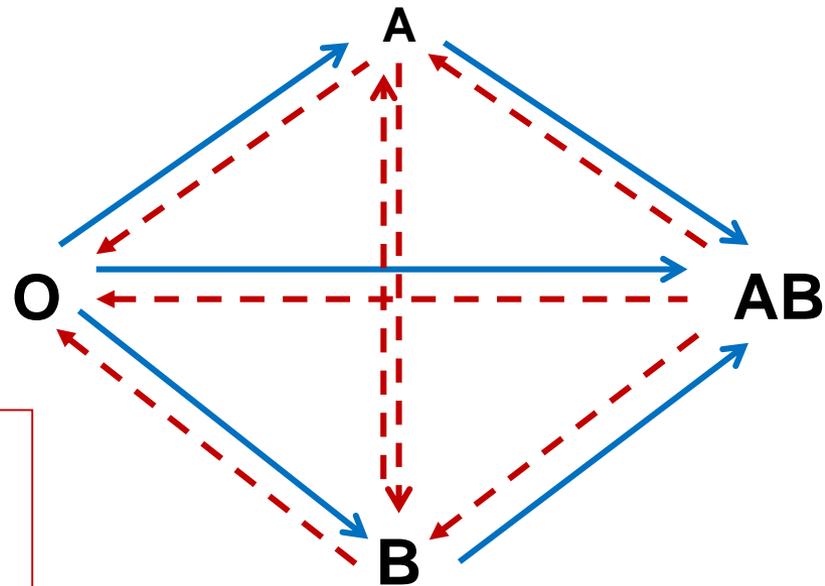


ABO incompatible kidney transplantation in France since 2011



When are we facing ABO incompatible KTx?

Isoagglutinins
anti-B



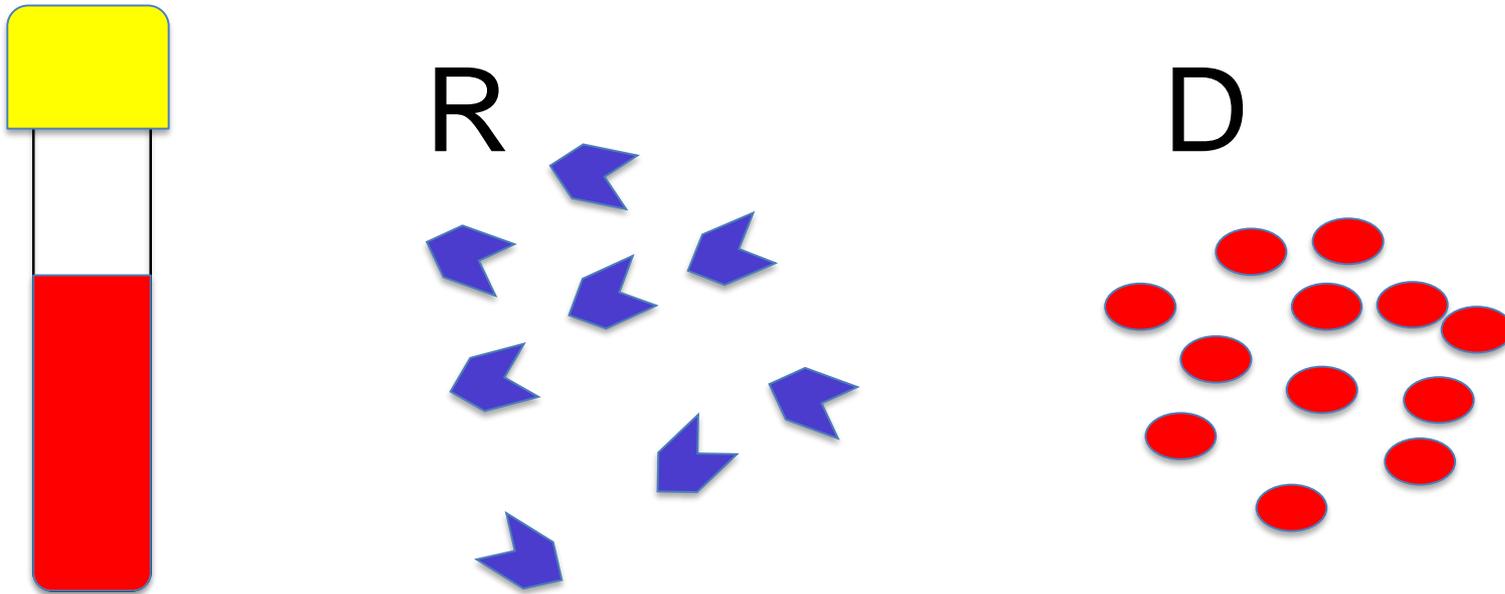
Isoagglutinins
Anti-A
Anti-B

No natural (IgM)
isoagglutinins

Isoagglutinins
anti-A

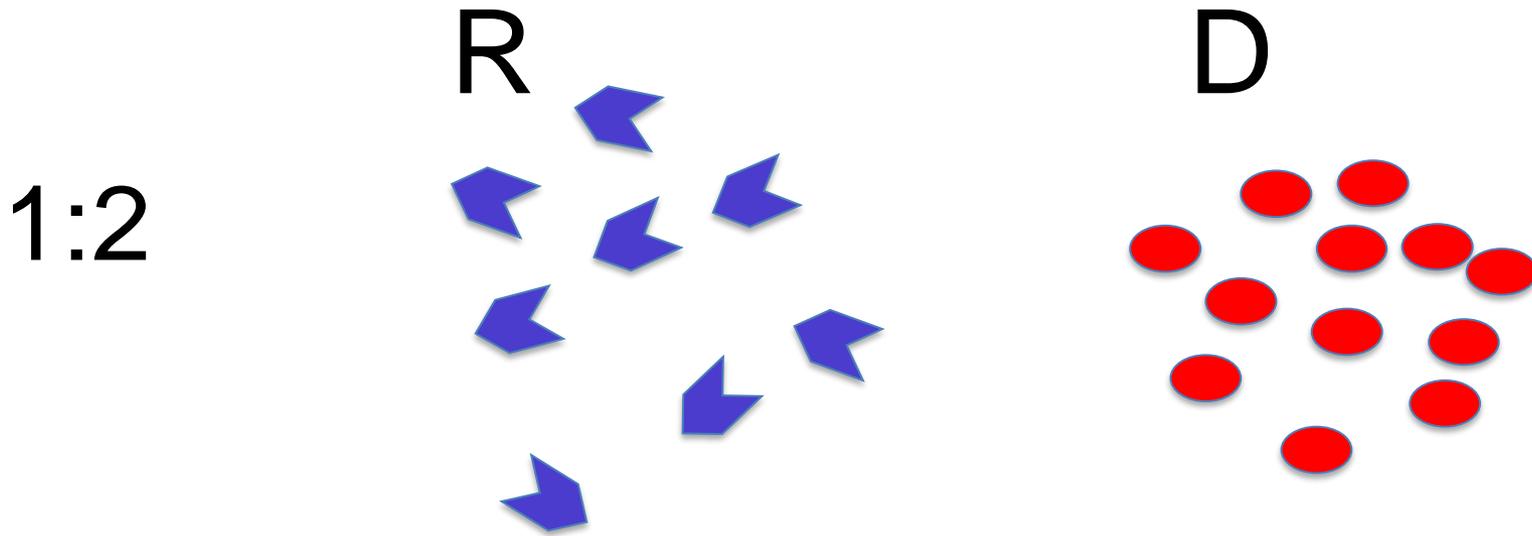
Isoagglutinins may result in acute vascular / humoral rejection

Isoagglutinin titration (antiA or anti-B) by hemagglutination (1)



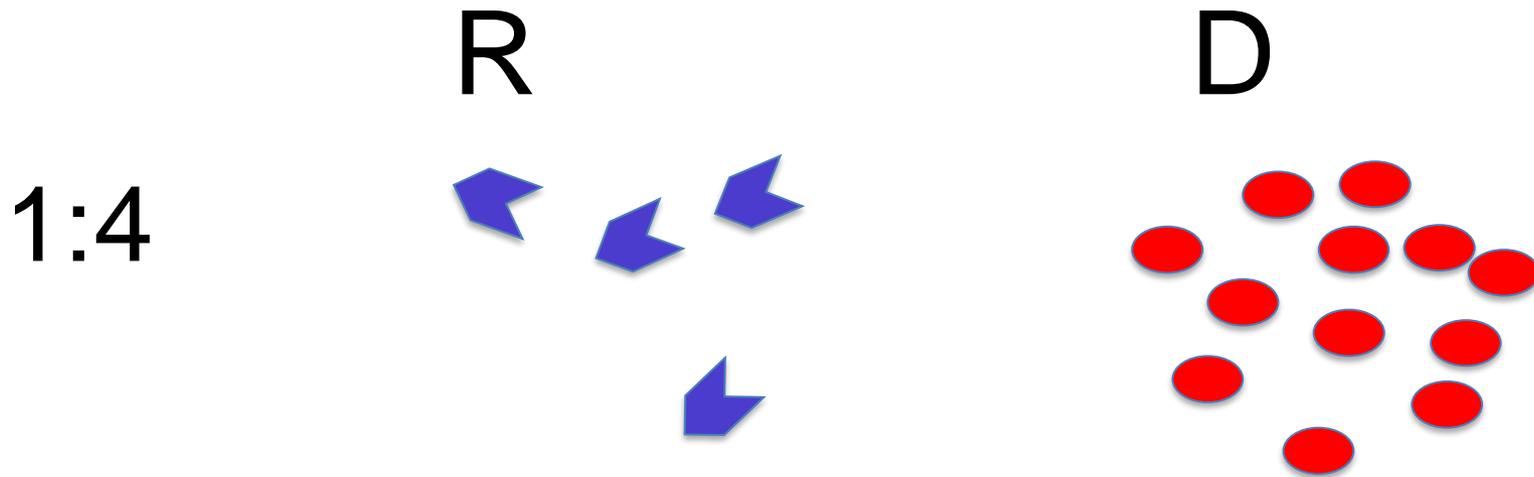
The ultimate dilution of patient's serum that does not result in red blood cell agglutination defines the **isoagglutinin titer**

Isoagglutinin titration (antiA or anti-B) by hemagglutination (2)



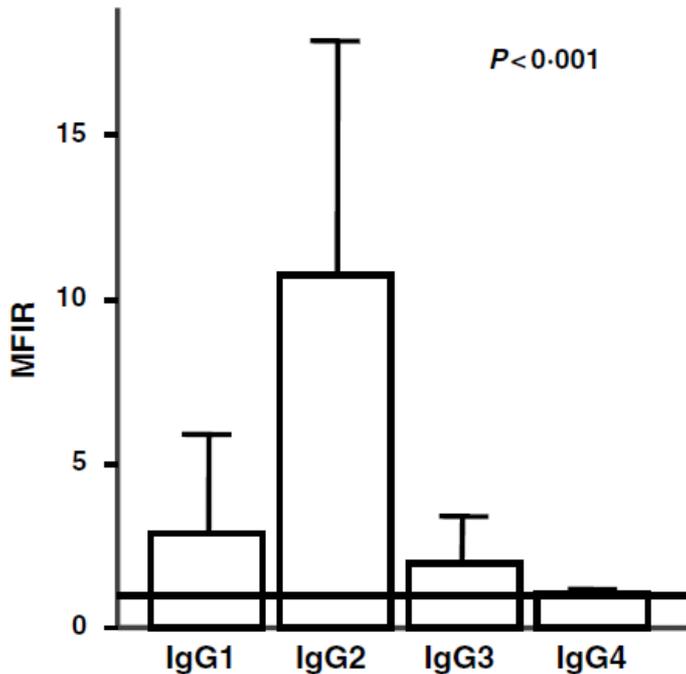
The ultimate dilution of patient's serum that does not result in red blood cell agglutination defines the **isoagglutinin titer**

Isoagglutinin titration (antiA or anti-B) by hemagglutination (3)

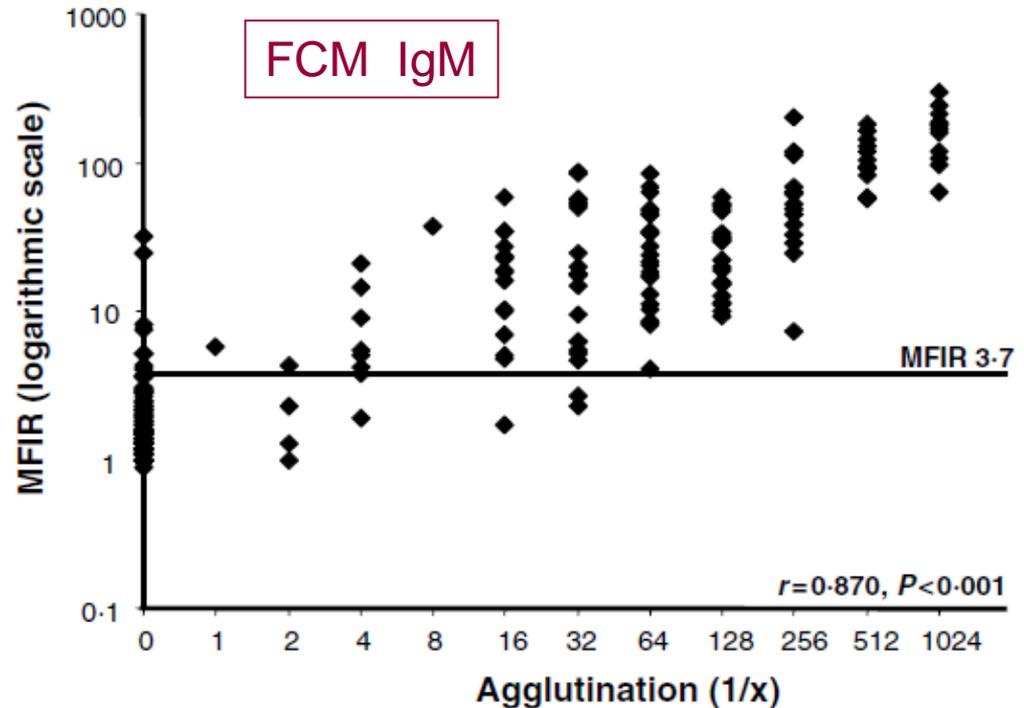


The ultimate dilution of patient's serum that does not result in red blood cell agglutination defines the **isoagglutinin titer**

How do we assess isoagglutinins?



Blood O type donors : n=15
 Anti-A/B
 All have IgG2
 <50% have IgG1 or IgG3
 None have IgG4



$r=0.78$ for IgG
 Similar for IgG and IgM
 Positivity threshold for FCM = 3.7 (IgM)
 2 (IgG)

4% of FCM +/agglutination -
 6% of FCM -/ agglutination +

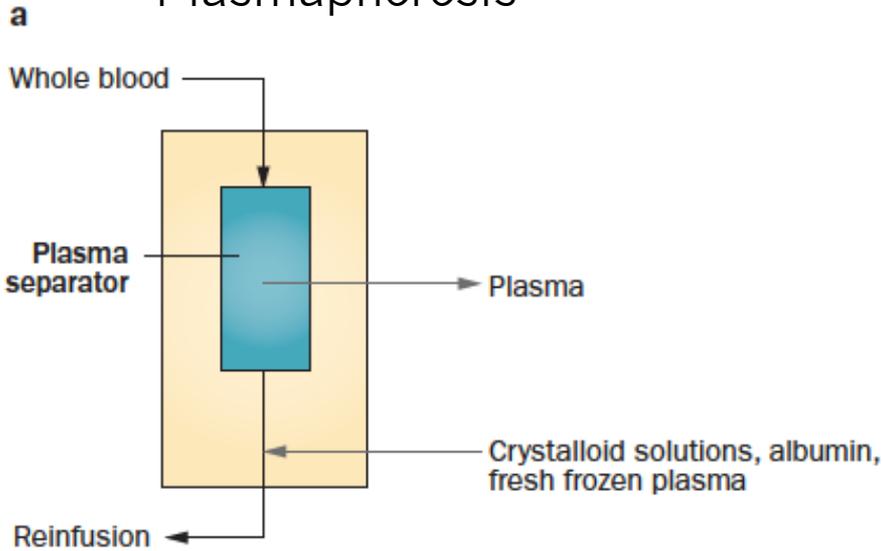
How can we get rid of isoagglutinins?

- ➔ *By desensitization that includes :*
- *Plasmapheresis*
 - *Immunosuppression*

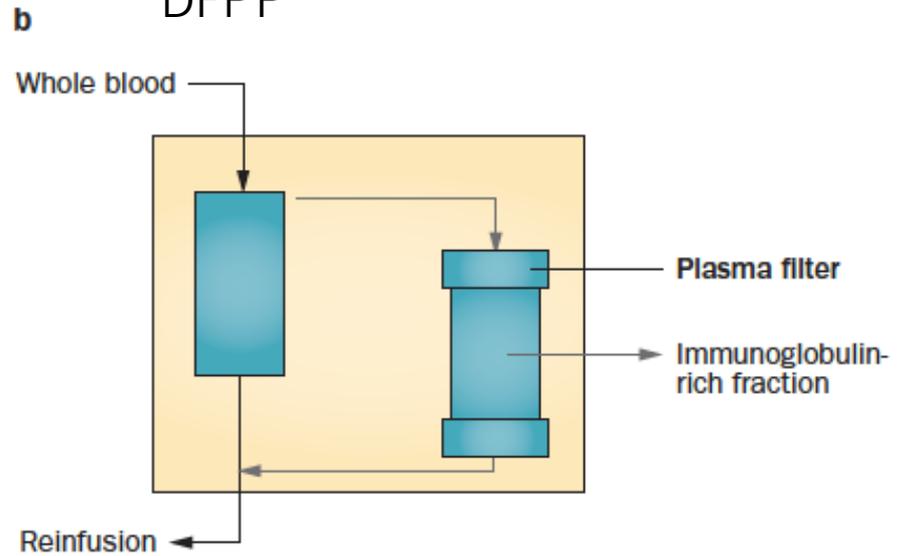
Isoagglutinin removals

- Apheresis :
 - Plasmapheresis (PP): not expensive; partly efficient (only 4L of plasma can be treated per session)
 - Double filtration plasmapheresis (DFPP) : more efficient than PP but removes a lot of clotting factors such as fibrinogen.
 - Specific immunoadsorption (IA), i.e. anti-A or anti-B columns: single use columns are very expensive (4000 euros) but within a single session 15 to 25L of plasma can be treated) without any rebound. And it is sufficient to reduce isoagglutinin titers to the desirable levels,

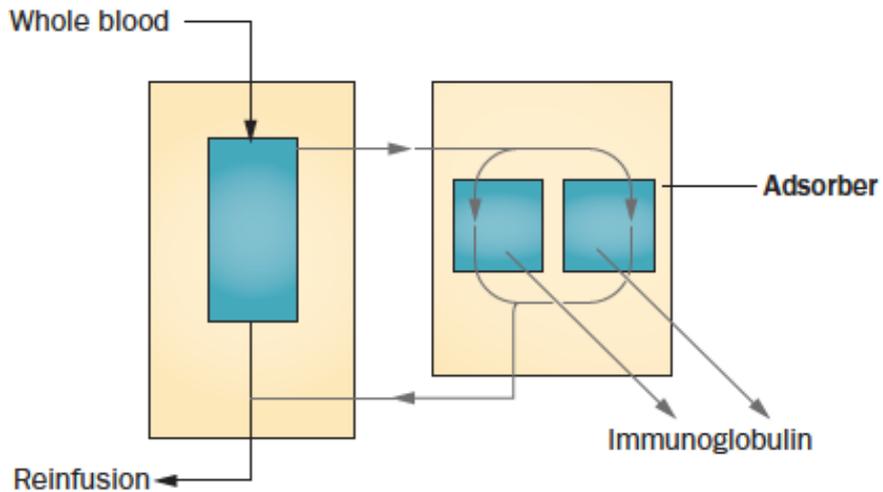
Plasmapheresis



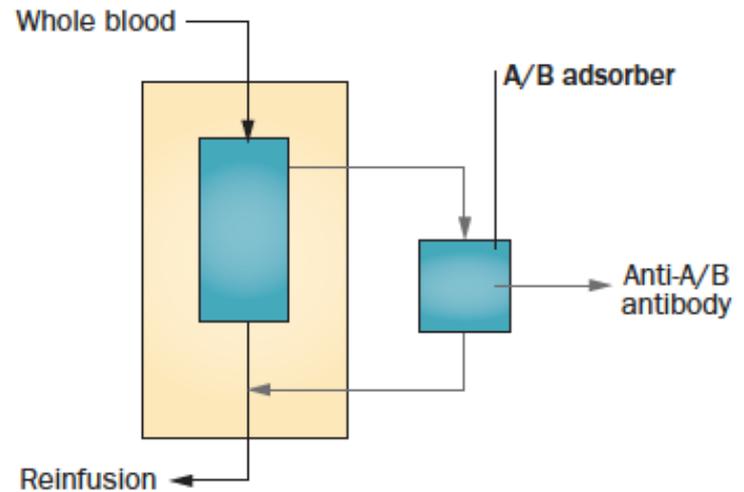
DFPP



Non-specific Immunoabsorption



Specific Immunoabsorption



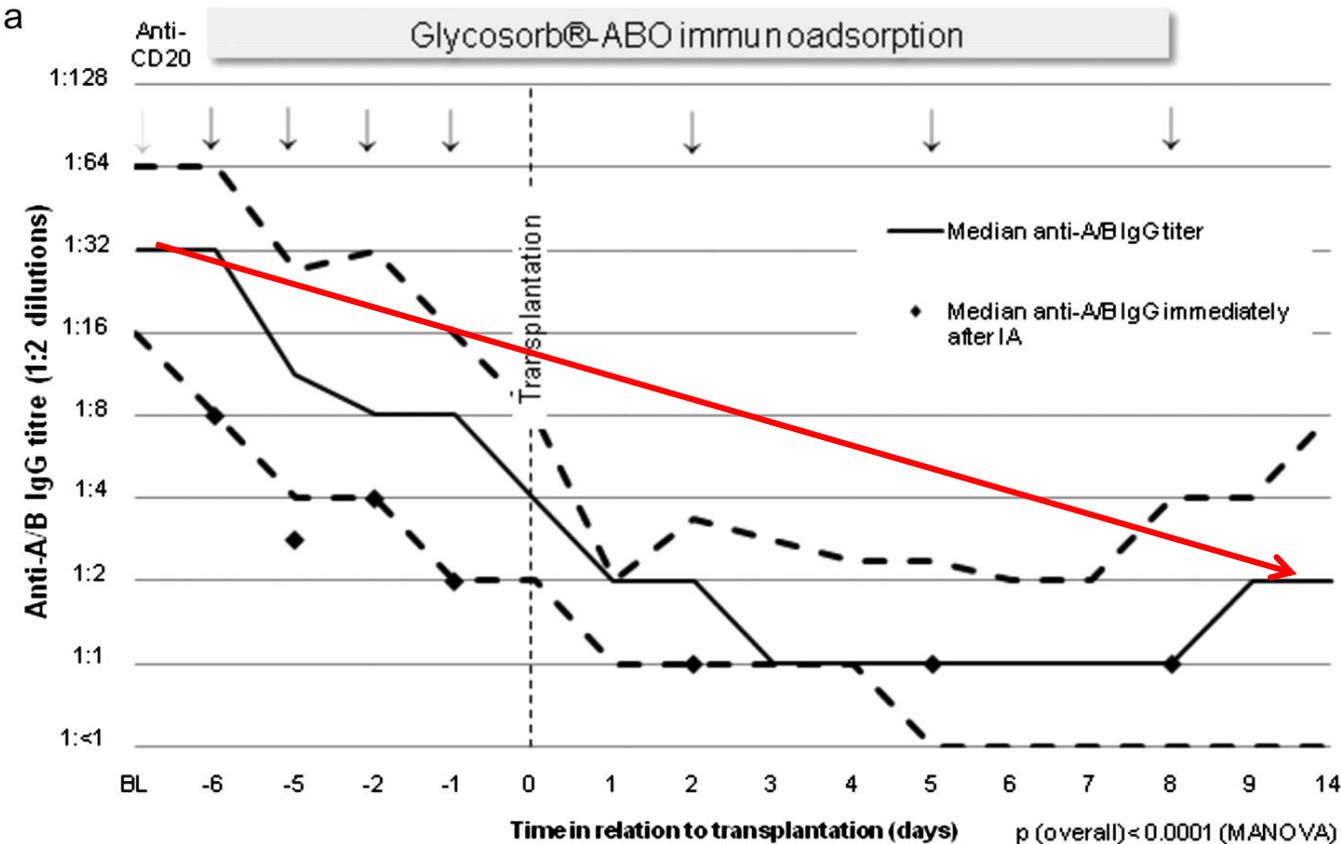
Inhibition of isoagglutinin resynthesis

- Rituximab : when and which dose ?
 - Between 30 to a few days pretransplant (it replaced splenectomy)
 - At least 200 mg/patient
 - Always mandatory?
- Other immunosuppressants : started as of 10-13 days pretransplant
 - Tacrolimus
 - Mycophenolic acid
 - Steroids

Isoagglutinins

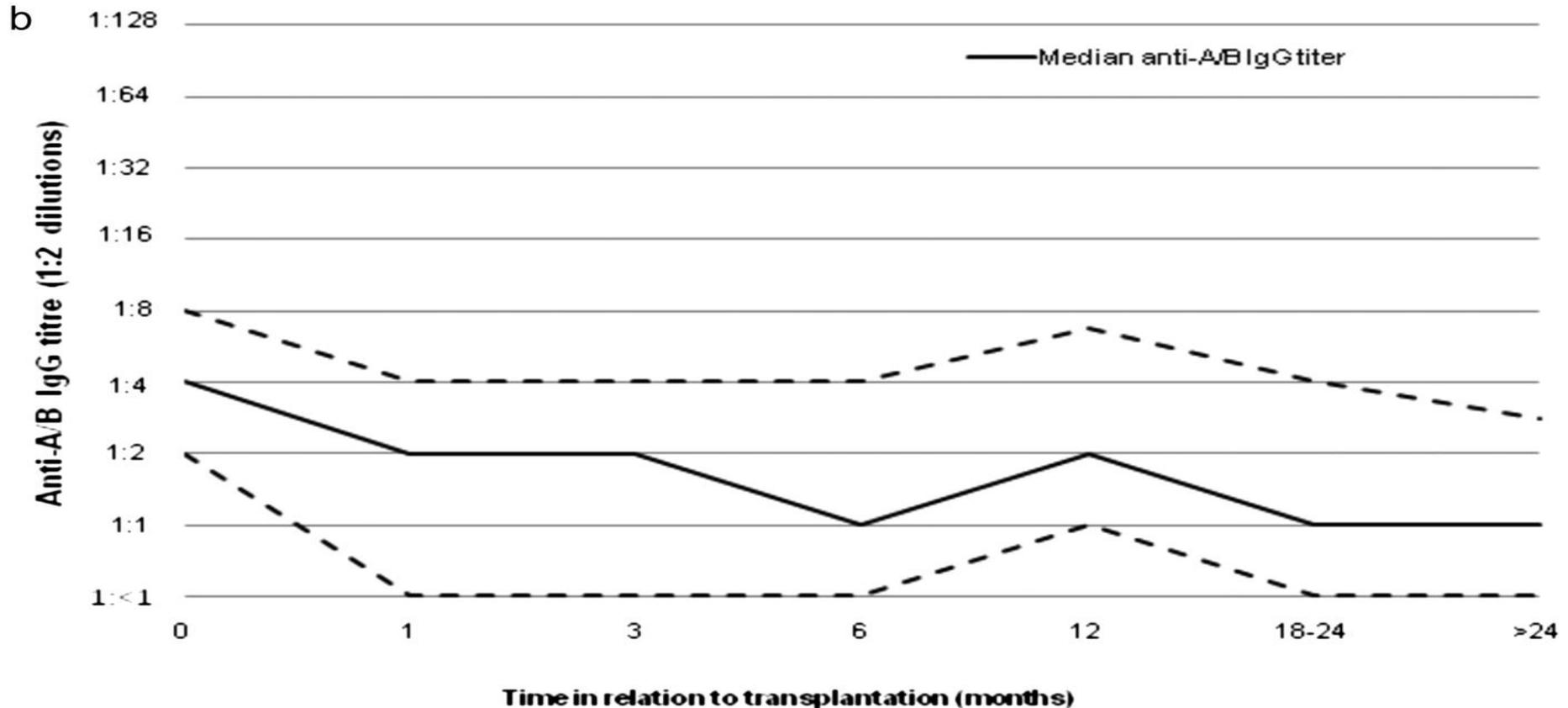
- Some rebounds after the first apheresis sessions at pretransplant
 - This can be overcome by long-lasting apheresis sessions
- Isoagglutinin titers at transplant day should be $< 1/16$
- No rebound at posttransplant: no need to perform isoagglutinin titration at posttransplant except if clinically indicated (delayed graft function; suspicion of antibody-mediated acute rejection)

Median changes in anti-A/B IgG titre before ABOi kidney transplantation and during the first two postoperative weeks (n=43) after Immunoadsorption + Rituximab



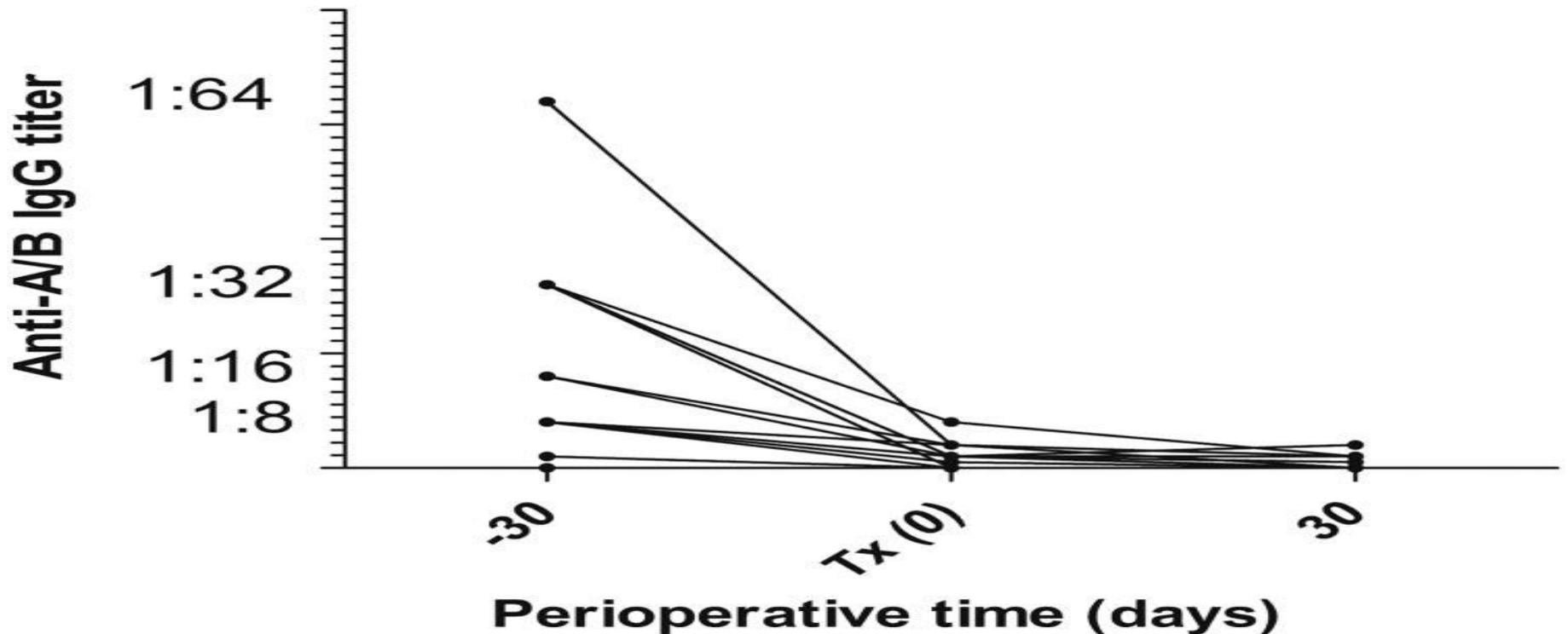
The area within the broken lines represents the IQR. Light gray arrow represents single-dose anti-CD20 monoclonal antibody (rituximab). Black arrows represent Glycosorb®-ABO IAs and the black diamonds represent the anti-A/B IgG titre *in vivo* immediately after completed IA. BL, baseline, i.e. at referral; IA, Glycosorb®-ABO IA.

Median changes in anti-A/B IgG titre in the long-term following ABOi kidney transplantation (n=41)



The area within the broken lines represents the IQR. (P = not significant).

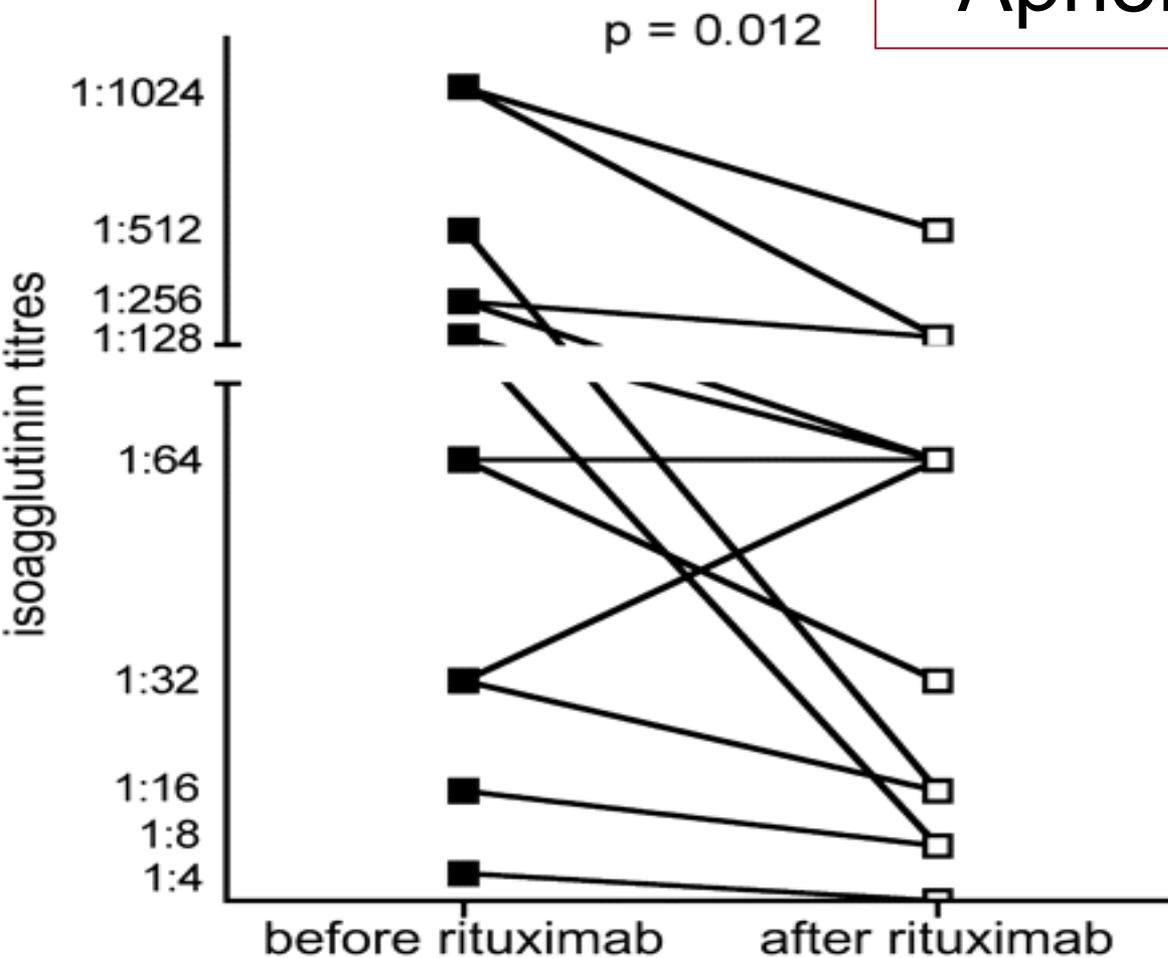
Isoagglutinin titres before and after treatment with rituximab and specific IA



Anti-A/B IgG titers on day -30, the day of transplantation (0), and at postoperative day 30 in a cohort of 19 consecutive recipients of ABO-incompatible kidney transplantation.

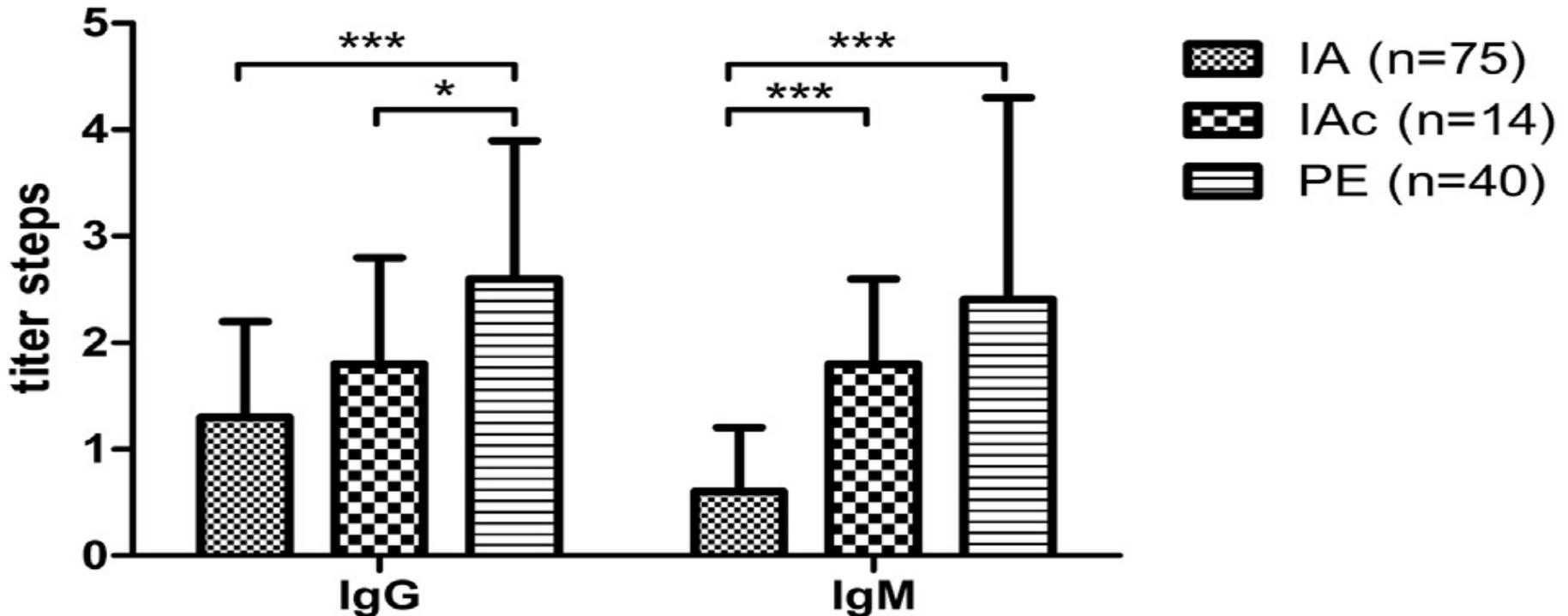
Isoagglutinin titres before and after treatment with rituximab (without PP or IA)

Apheresis is **NEEDED**



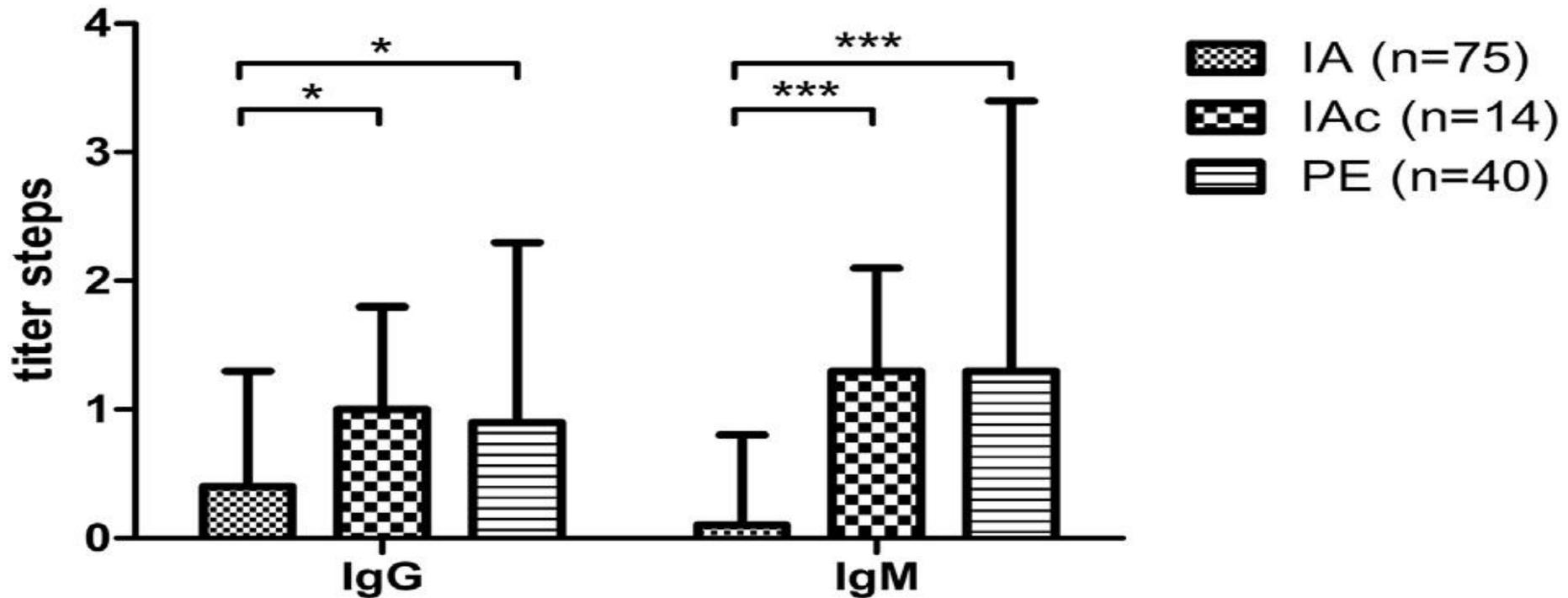
The median anti-donor IgG Isoagglutinin titres significantly decreased after rituximab treatment in the ABOi group ($P = 0.0012$).

Comparing the efficacy of three techniques to reduce isoagglutinin titers in ABO incompatible kidney transplant recipients (1)



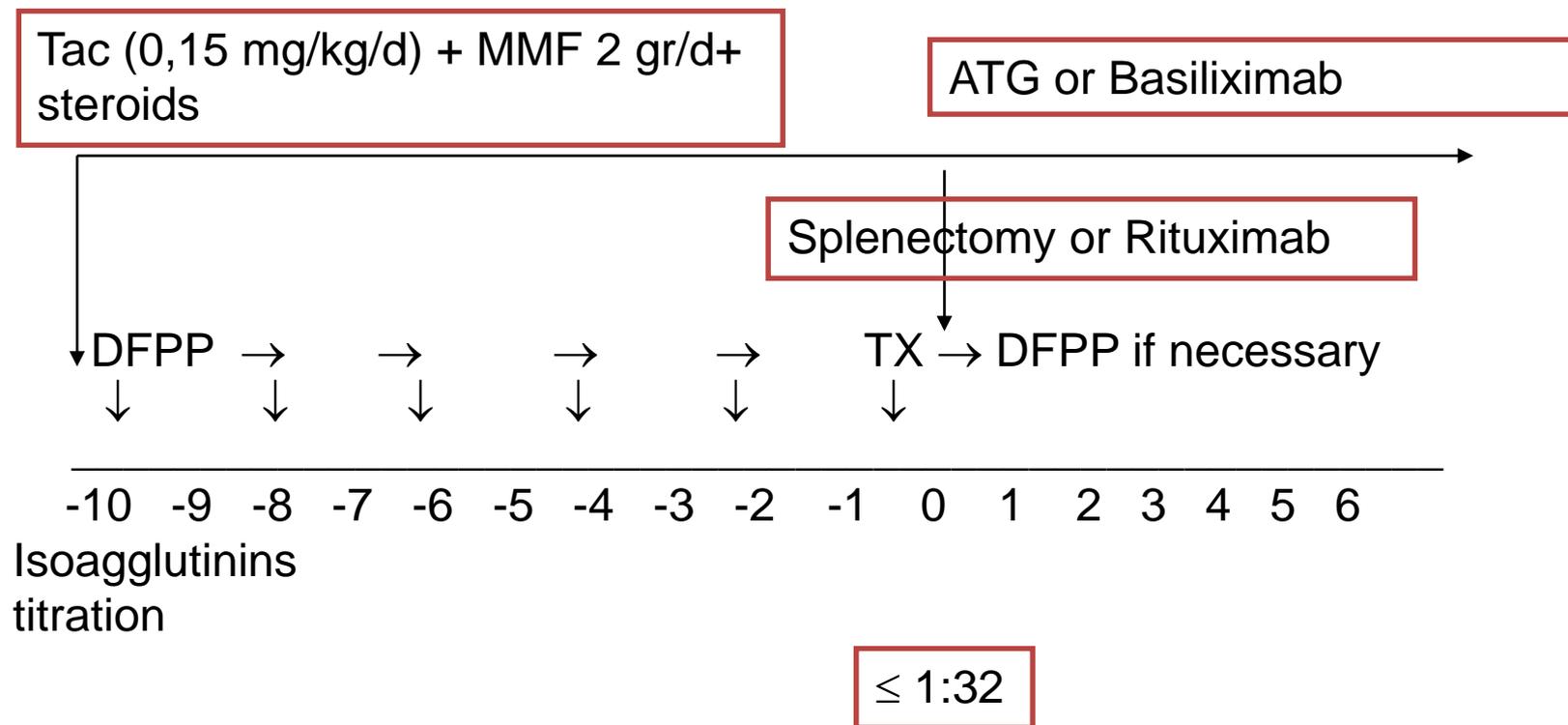
Total titer reduction per treatment. Total titer reductions are shown as changes in titer steps by comparing pre to post treatment titer values. Level of significance is marked with * for $p < 0.05$ and *** for $p < 0.001$.

Comparing the efficacy of three techniques to reduce isoagglutinin titers in ABO incompatible kidney transplant recipients (2)



Net titer reduction per treatment. Net titer reductions were calculated by comparing the pretreatment titer with the titer ascertained right before the next scheduled session. Level of significance is marked with * for $p < 0.05$ and *** for $p < 0.001$.

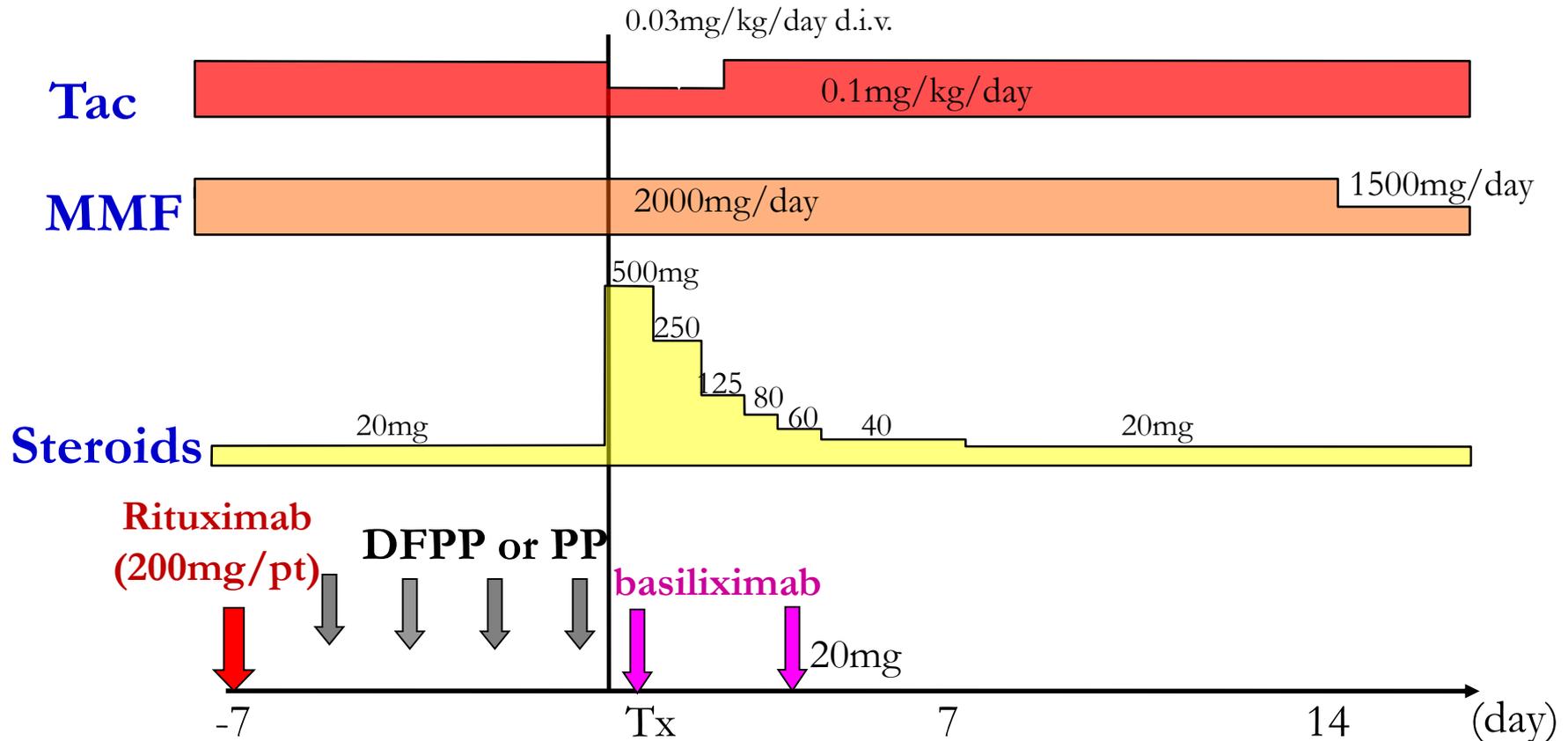
ABOi kidney transplantation: the japanese protocol



DFPP: double filtration plasmapheresis
ATG: antithymocyte globulins

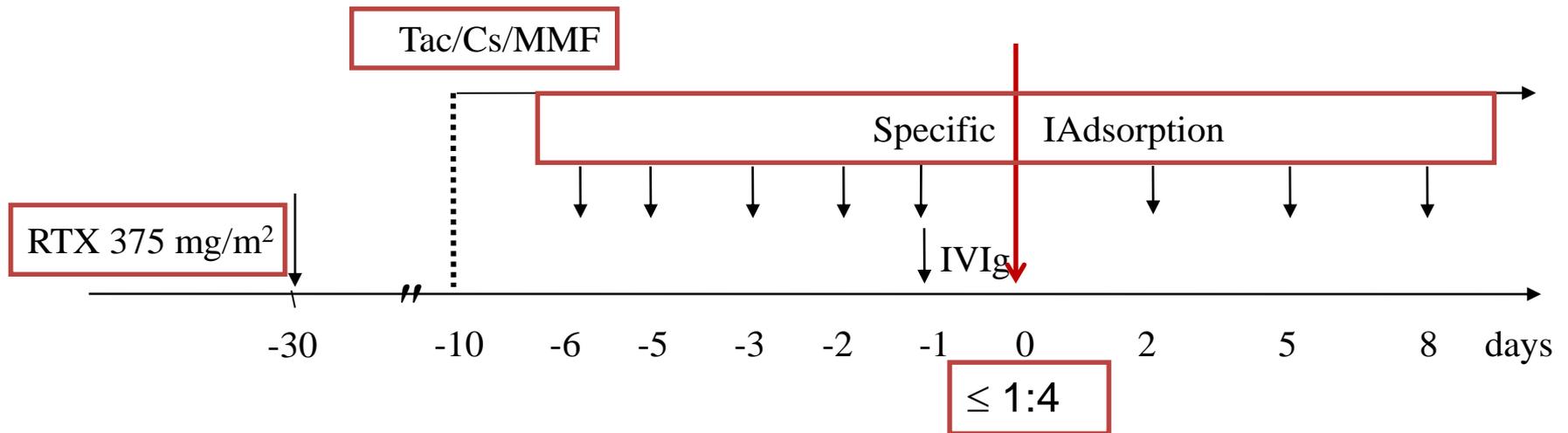
Immunosuppressive regimen in ABO-incompatible living kidney transplantation at TWMU (Japan)

With or w/o splenectomy



Tac: tacrolimus, MMF: mycophenolate mofetil.

Tyden protocol (Sweden)

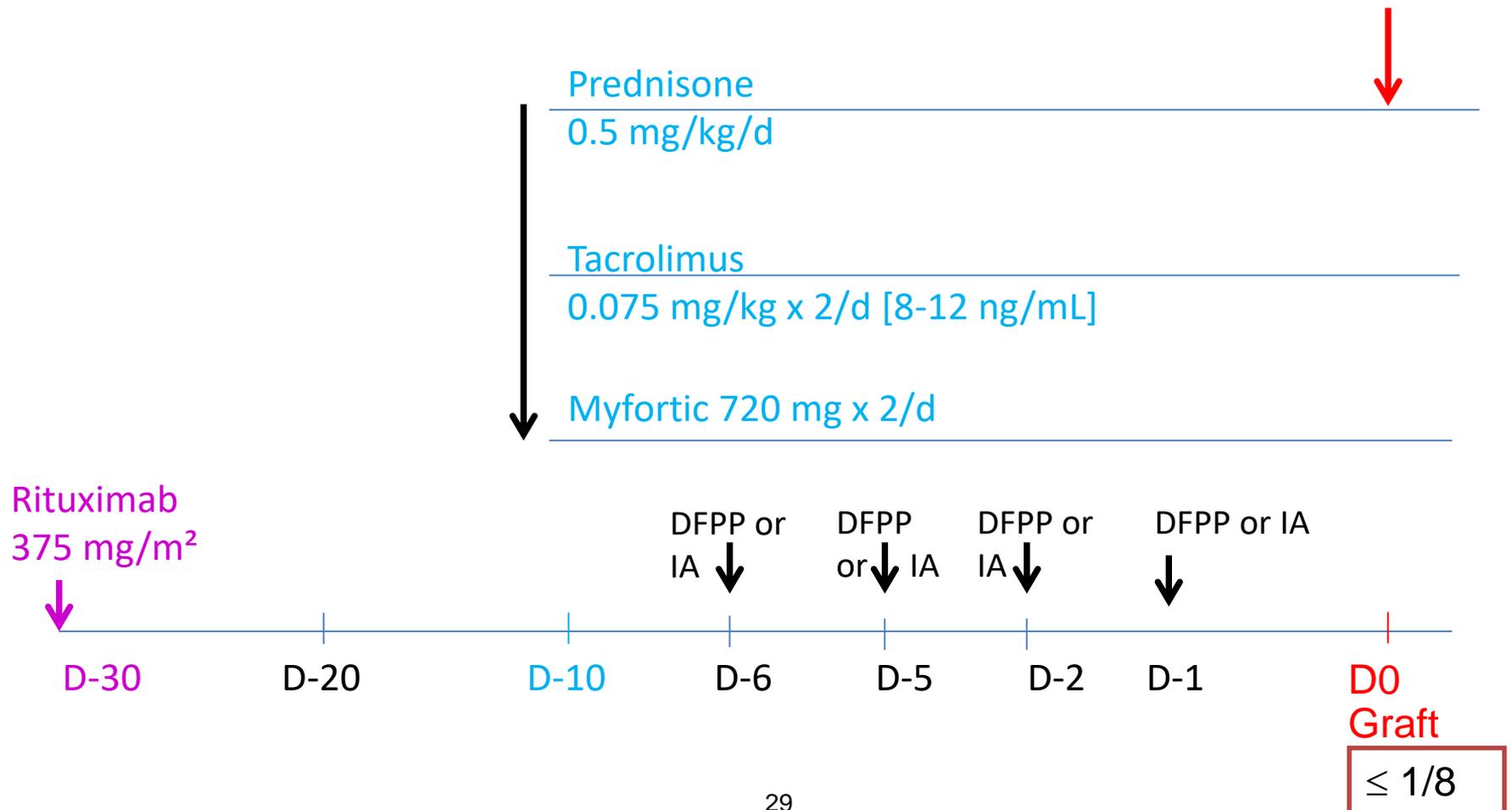


pre-KTx : A/B titer:

post KTx : if \nearrow A/B titers and/or \nearrow creatinine \rightarrow Immunoadsorption

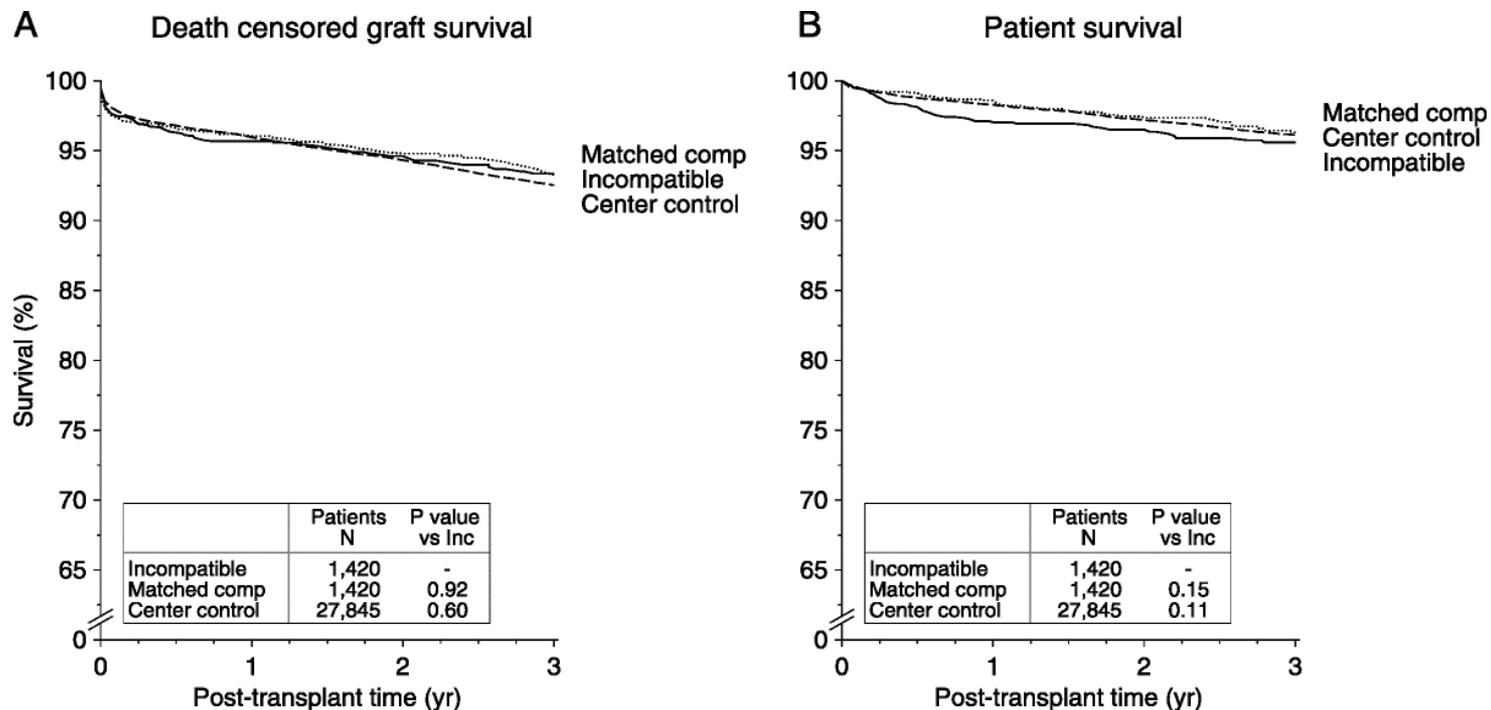
ABOi KTx in Grenoble: adapted from Tyden's protocol (1)

Basiliximab 20 mg D0 and D4



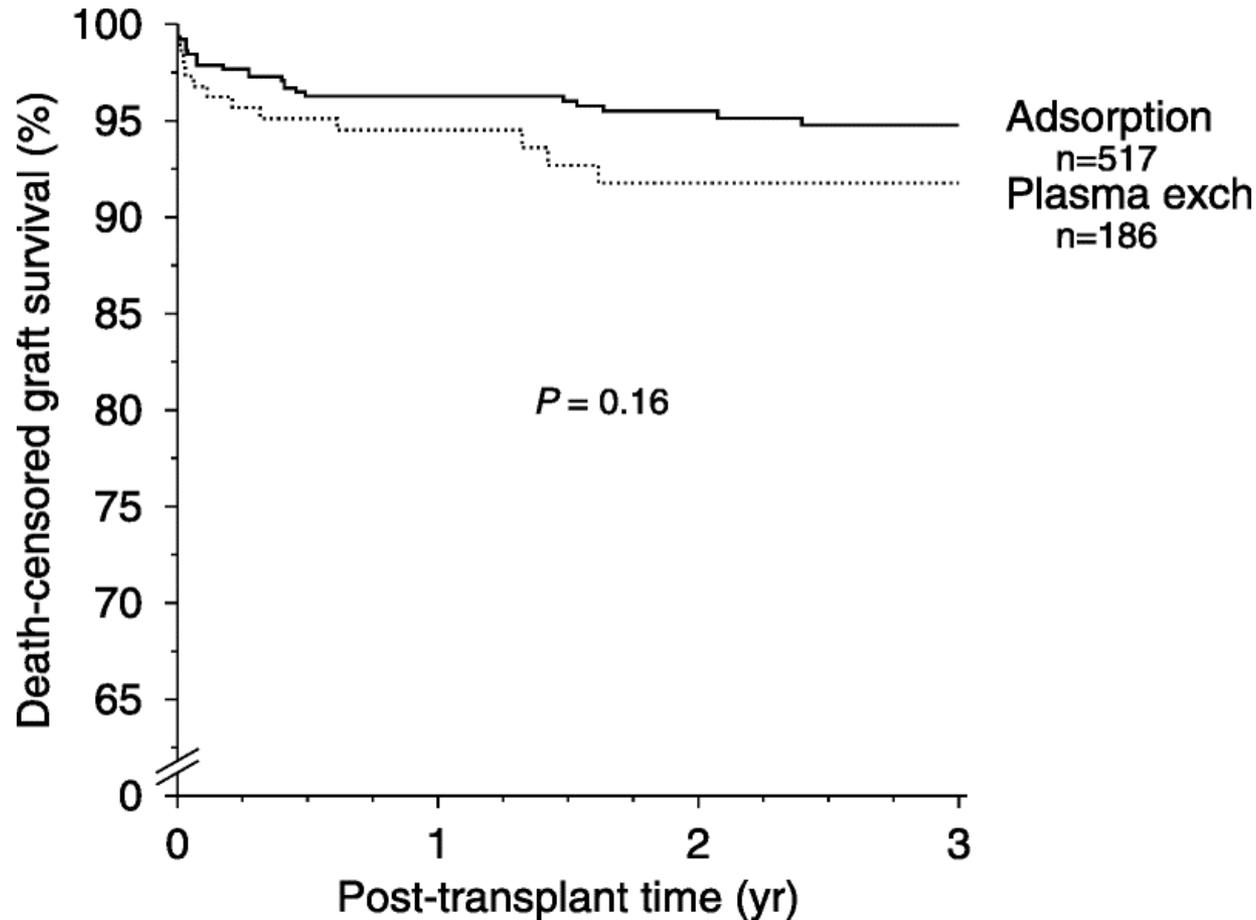
RESULTS

Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction : results from 101 centers (1)



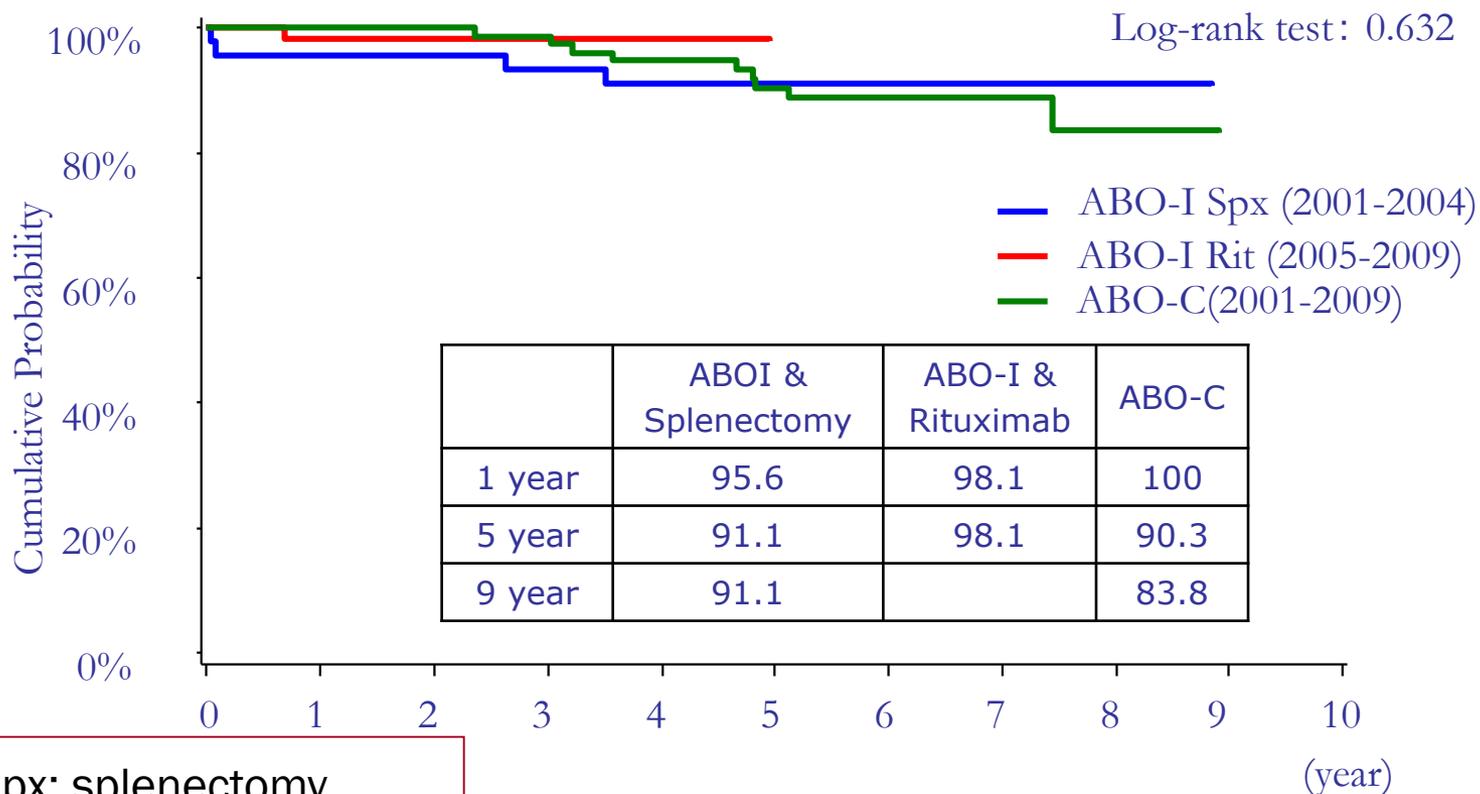
Cumulative incidence of (A) death-censored graft survival and (B) patient death in living-donor recipients of an ABO-incompatible graft, matched controls receiving an ABO-compatible graft, or all ABO-compatible transplants from centers that performed at least five ABO-incompatible grafts during the study period ('center control' group) (Kaplan-Meier estimates). P values according to the log-rank test.

Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction : results from 101 centers (2)



Cumulative incidence of death-censored graft survival in living-donor recipients of an ABO-incompatible graft according to whether ABO antibody reduction was performed by adsorption columns or plasma exchange (Kaplan-Meier estimates). P values according to the log-rank test.

ABOi KTx vs. ABOc KTx : graft survival

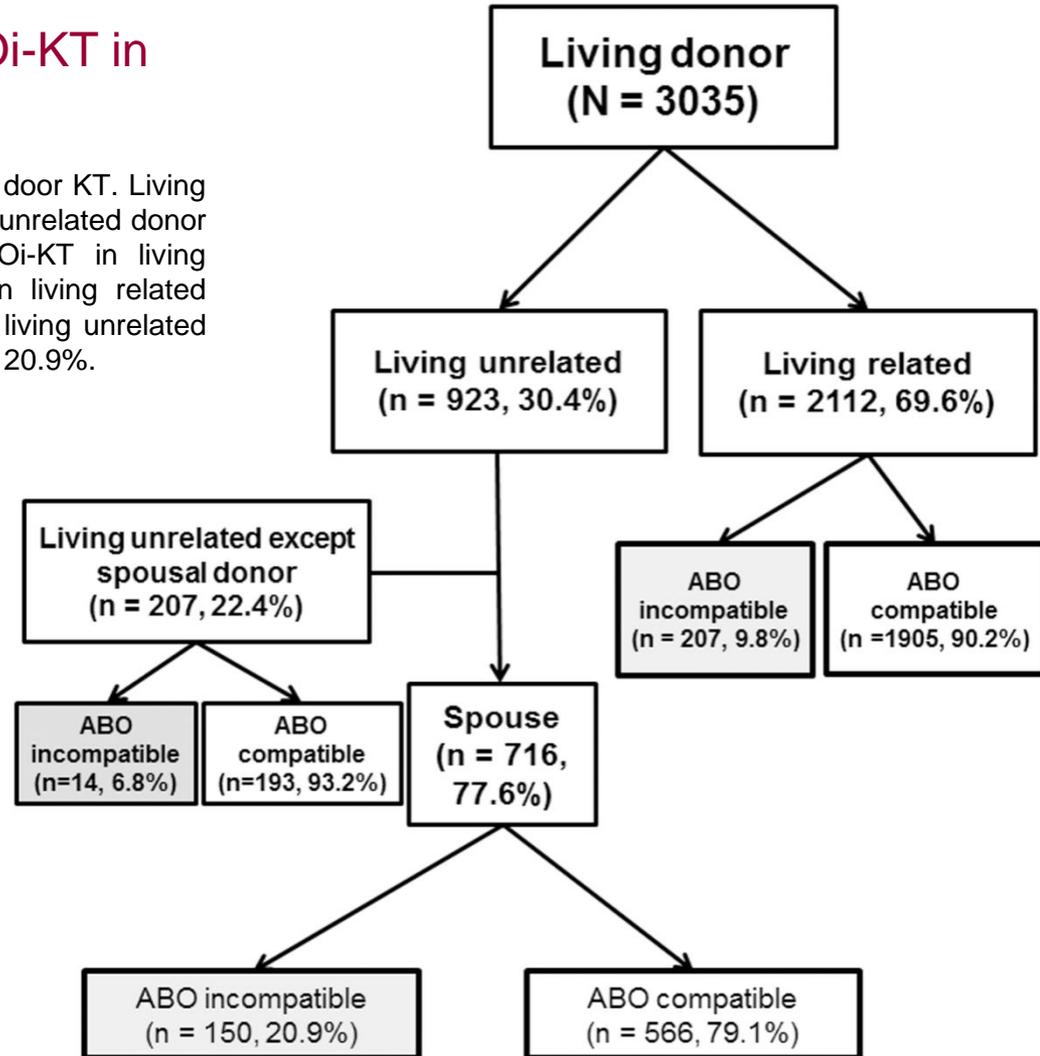


ABO-I Spx: splenectomy
 ABO-I Rit: Rituximab injection
 ABO-C: ABO-Compatible

Impact of ABO incompatible kidney transplantation on living donor transplantation (1)

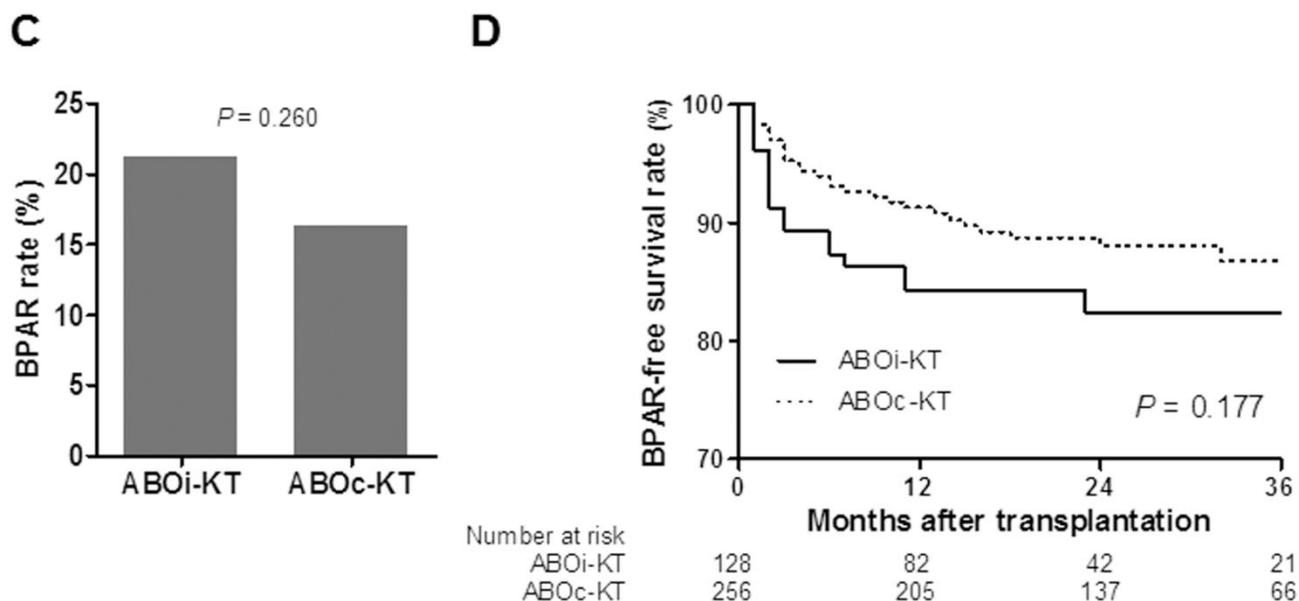
Number and proportion of ABOi-KT in living donor KT.

Total 371 ABOi-KT was performed in 3045 living donor KT. Living related donor KT was 55.4% (n = 207) and living unrelated donor KT was 45.6% (n = 164). Proportion of ABOi-KT in living unrelated donor KT was two times higher than living related donor KT. Spouse was a major donor source of living unrelated donor (77.6%), and its proportion of ABOi-KT was 20.9%.



Impact of ABO incompatible kidney transplantation on living donor transplantation (2)

Comparisons of the BPAR between ABOi-KT and ABOc-KT from spousal donors.

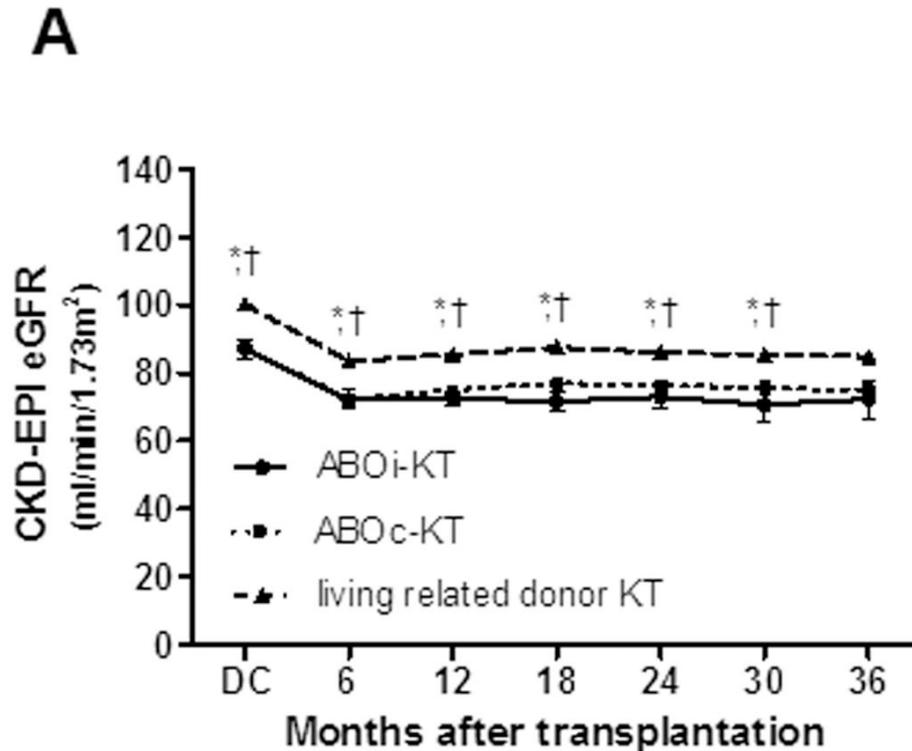


(C) Incidence of BPAR after the propensity score-matching analysis. (D) BPAR-free survival rate after the propensity score-matching analysis.

Note that BPAR or BPAR-free graft survival rate were not significantly different between ABOi-KT and ABOc-KT from spousal donors *, $P < 0.05$ for ABOi-KT from spousal donor vs. living related donor KT; ², $P < 0.05$ for ABOc-KT from spousal donor vs. living related donor KT; ³, $P < 0.05$ for ABOi-KT vs. ABOc-KT from spousal donor. BPAR, biopsy-proven acute rejection; ABOi, ABO incompatible; KT, kidney transplantation; ABOc, ABO compatible.

Impact of ABO incompatible kidney transplantation on living donor transplantation (3)

Comparison of allograft function.

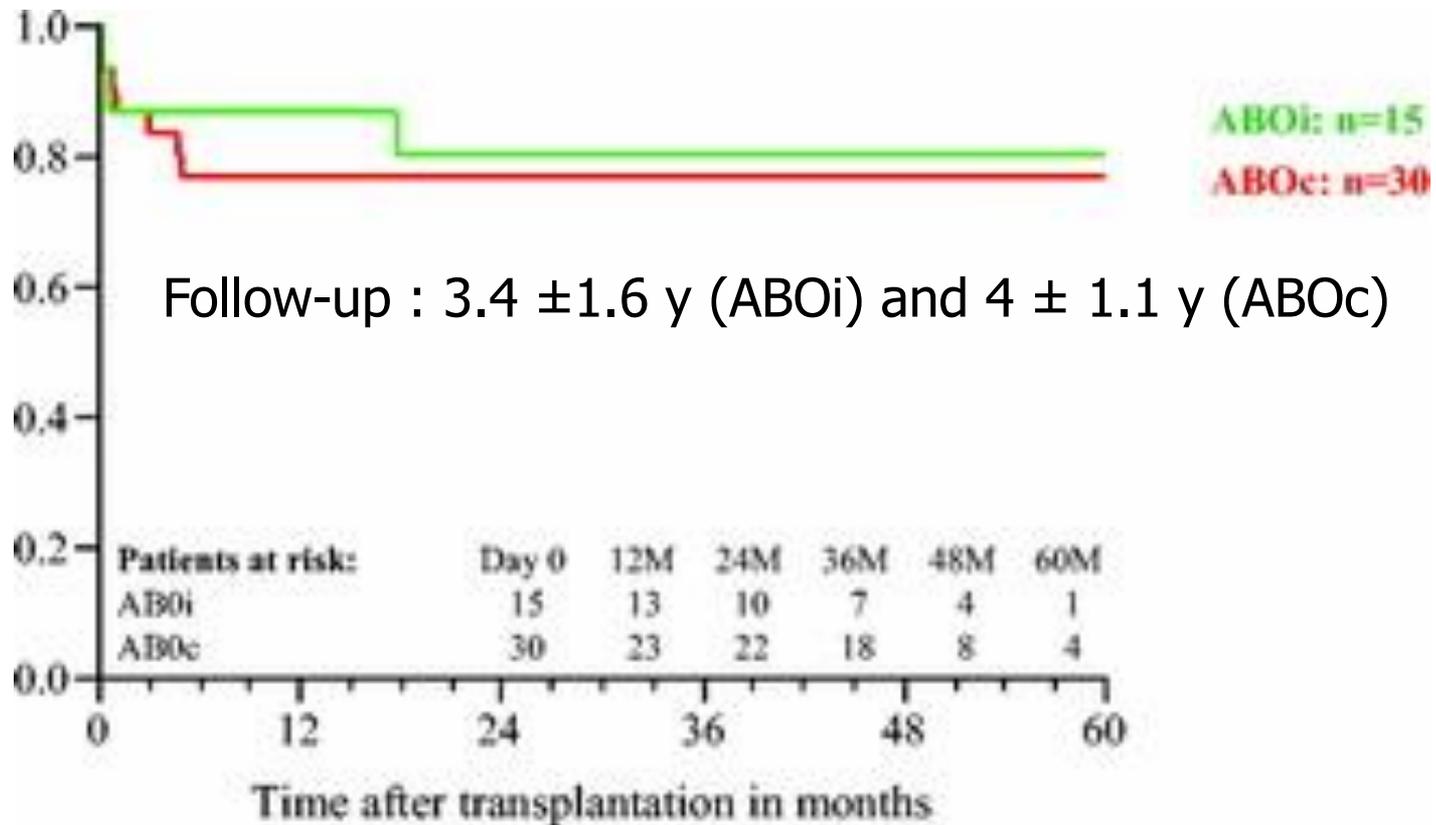


(A) Comparison of eGFR among spousal donor KT and living related donor KT.

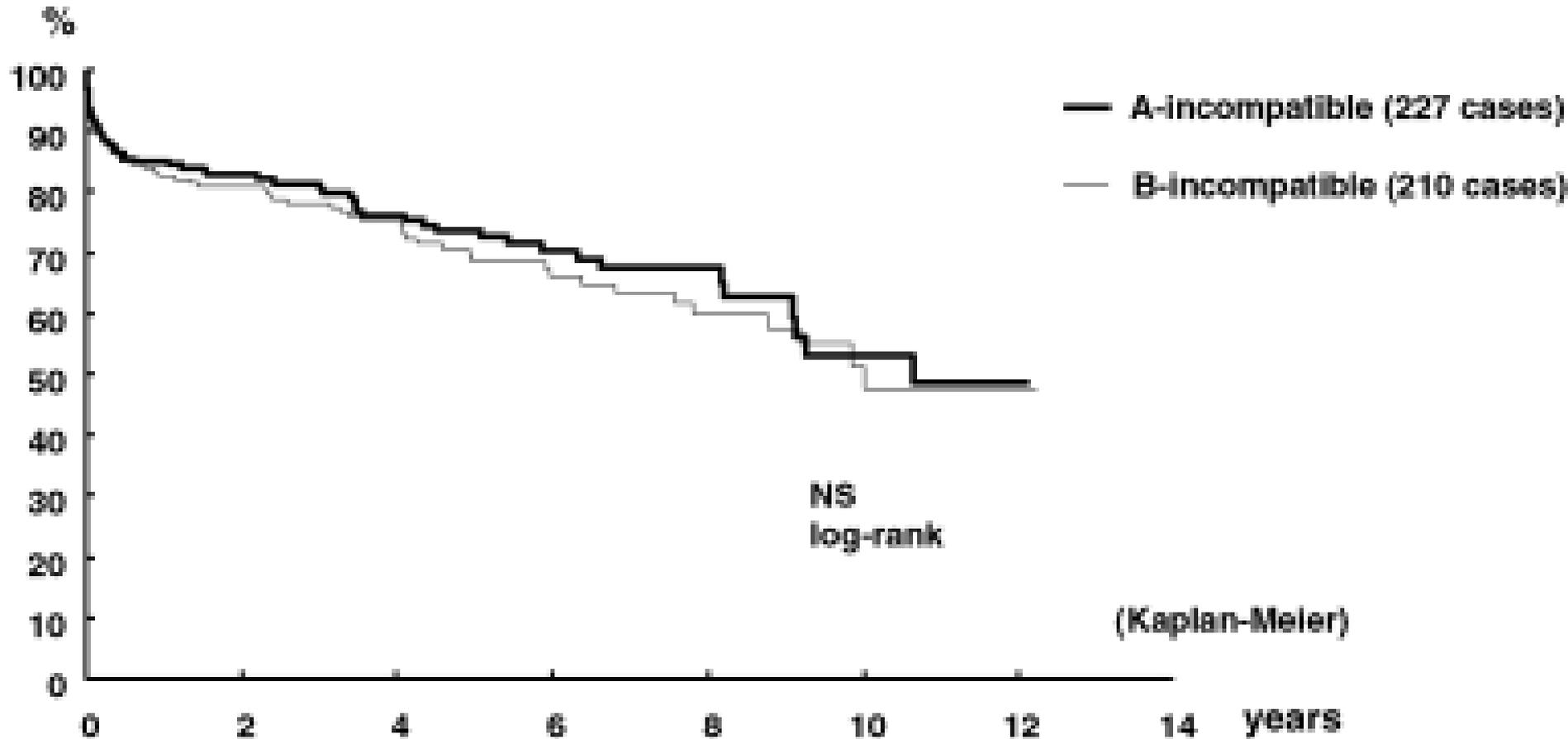
Comparison of eGFR of the male-to-female patients in the spousal donor KT and living related donor KT. *, $P < 0.05$ for ABOi-KT from spousal donor vs. living related donor KT; ², $P < 0.05$ for ABOc-KT from spousal donor vs. living related donor KT; ³, $P < 0.05$ for male-to-female vs. female-to-male; §, $P < 0.05$ for husband-to-wife vs. wife-to-husband. eGFR, estimated glomerular filtration rate; ABOi, ABO incompatible; KT, kidney transplantation; ABOc, ABO compatible;

Yu JH, et al. PLoS One. 2017 Mar 21;12(3):e0173878

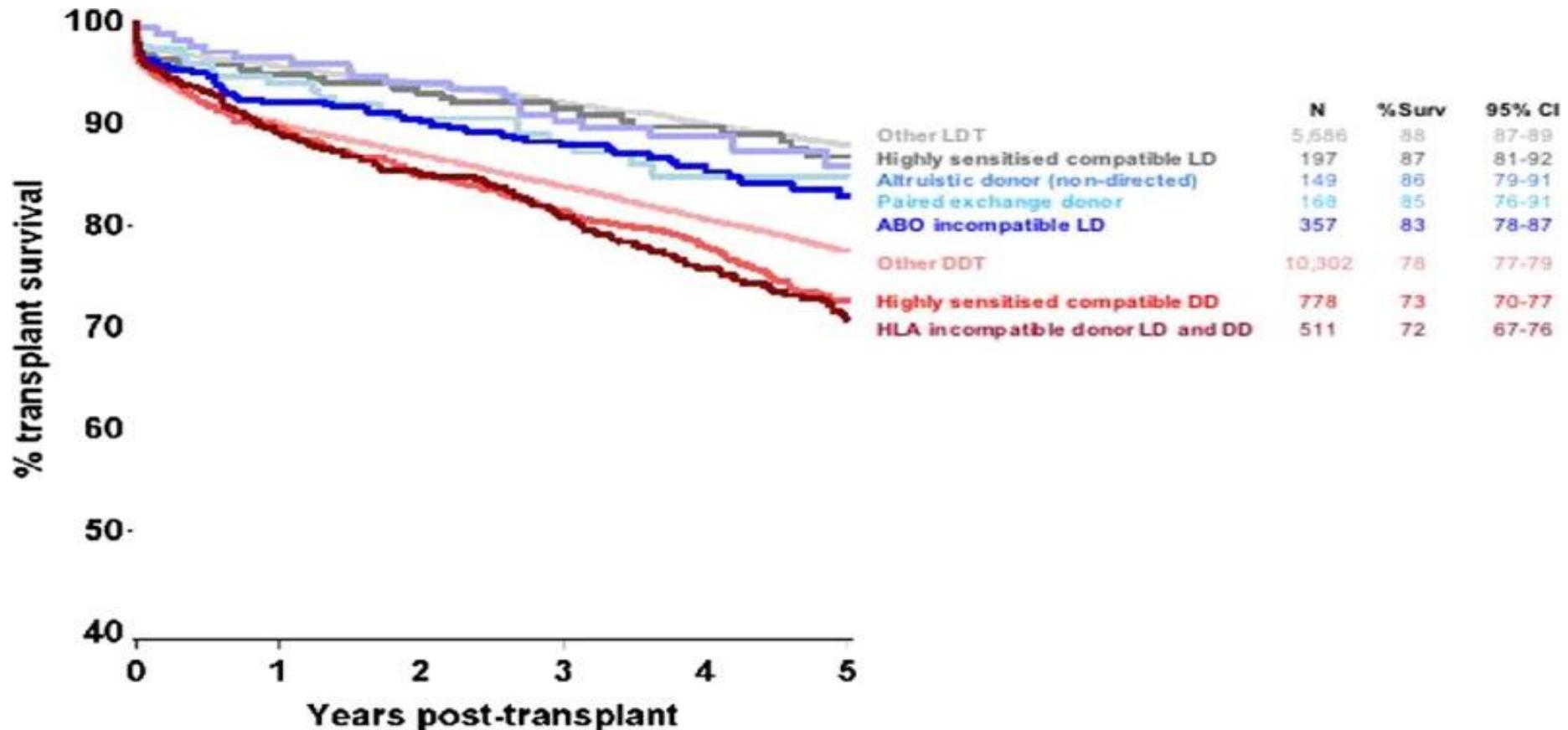
ABOi KT_x vs. ABOc KT_x : Tyden protocol (Sweden)



Graft survival rates for A-incompatible transplantation and B-incompatible transplantation



The UK National Registry of ABO and HLA Antibody Incompatible Renal Transplantation: Pretransplant Factors Associated With Outcome in 879 Transplants

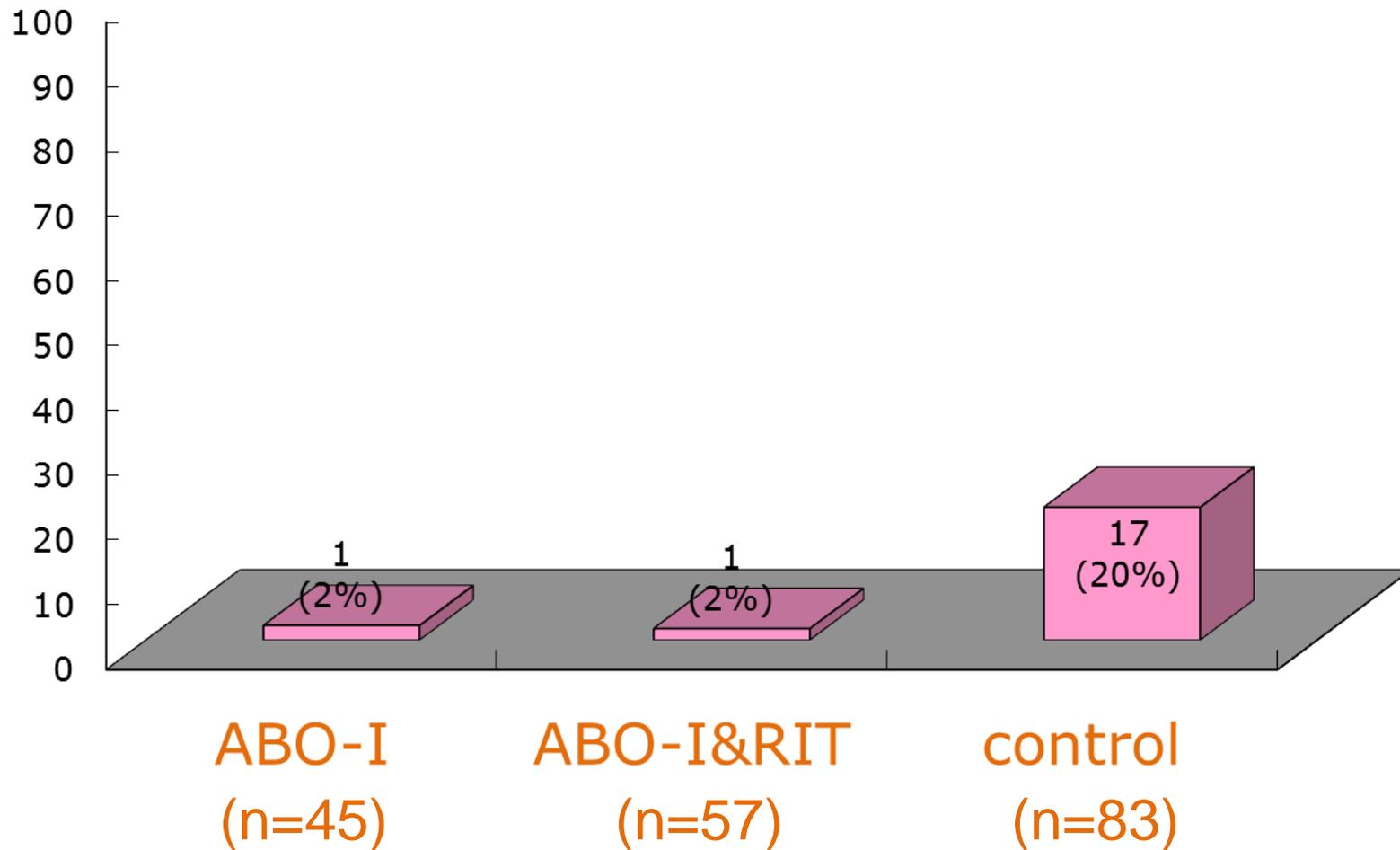


Five-year transplant survival for all kidney only transplants in the United Kingdom between January 1, 2005, and December 31, 2012.

Rejection

- Cellular rejection occurs in 10 to 15% of cases : they are mostly steroid-sensitive
- Isoagglutinin-mediated humoral rejection occurs in 5-15% of cases, always before postop day 21 (thereafter there is accommodation) :
 - Symptoms : mild fever; sudden oligoanuria; rise in serum creatinine
 - Kidney biopsy : interstitial haemorrhage; diffuse C4 d(+)
 - Treatment (urgent): plasmapheresis + rituximab
 - ✓ In most of the cases: recovery; otherwise eculizumab therapy or splenectomy

ABOi KTx: Incidence of *de novo* anti-HLA antibodies

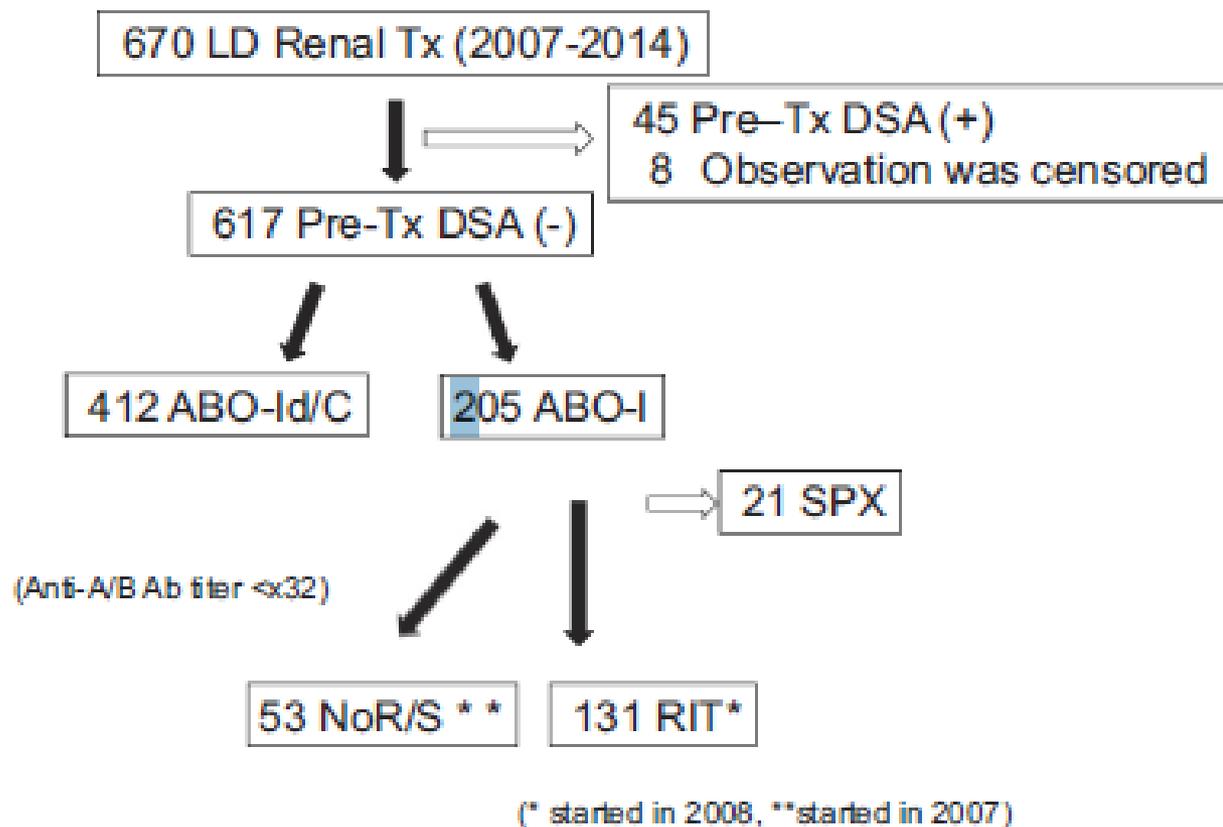


***Desensitization when
isoagglutinin titers are low***

Favorable results in ABO-incompatible renal transplantation without B cell-targeted therapy: Advantages and disadvantages of rituximab pretreatment (1)

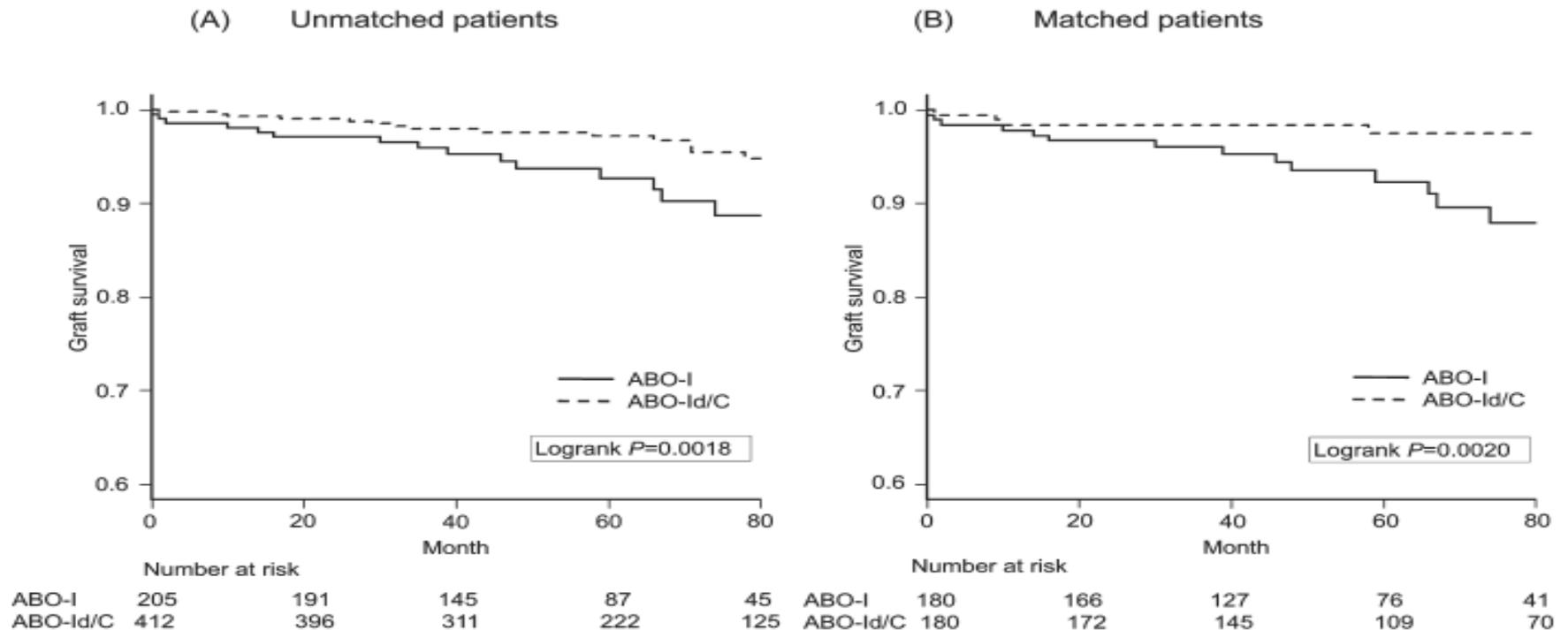
- Single center study (Nagoya)
- ABOi ; patients ; desensitization with splenectomy or rituximab (x2) or nothing if titers < 1/32
 - in addition to MMF (as of D-14) and DFPP (at least 4 sessions)
- Induction therapy with basiliximab

Favorable results in ABO-incompatible renal transplantation without B cell-targeted therapy: Advantages and disadvantages of rituximab pretreatment (2)



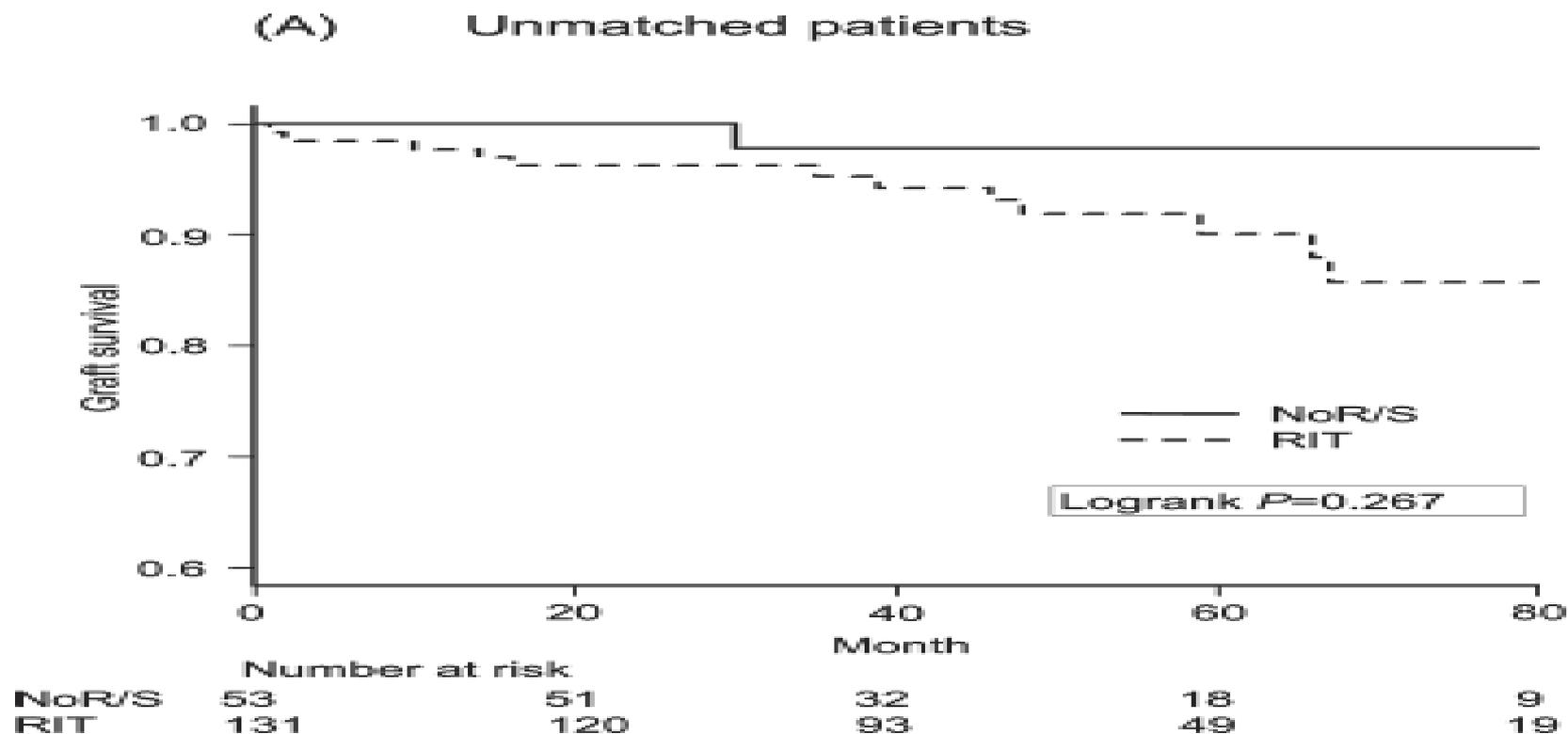
Retrospective cohort study of 617 consecutive renal transplantations without pretransplant donor-specific antibody (DSA). Six hundred and seventy living donor renal transplantations were performed between 2007 and 2014. After the exclusion of 45 cases with pretransplant DSA and 8 that could not be followed up, 617 cases were included for this retrospective cohort study. Rituximab pretreatment was started in 2008, and ABO-incompatible renal transplantation with neither rituximab nor splenectomy pretreatment protocols were started in 2007. NoR/S, ABO-incompatible renal transplantation treated with neither rituximab nor splenectomy due to low anti-A/B antibody titers [$\leq x32$]

Favorable results in ABO-incompatible renal transplantation without B cell-targeted therapy: Advantages and disadvantages of rituximab pretreatment (3)



Graft survival in ABO-Id/ C and ABO-I. **(A) Kaplan-Meier curves for overall graft survival of unmatched patients in the ABO-Id/ C (n = 412) or ABO-I (n = 205) groups ($P = .0018$).** The 5-year overall graft survival rates in the ABO-Id/ C and ABO-I groups were 97.2% and 92.8%, respectively. **(B) Kaplan-Meier curves for overall graft survival of the propensity score-matched ABO-Id/ C (n = 180) and ABO-I (n = 180) groups ($P = .002$).** The estimated 5-year overall graft survival rates were 97.5% and 92.3%, respectively. (ABO-Id/ C, ABO-identical/ Compatible renal transplantation; ABO-I, ABO-incompatible renal transplantation) Okada M, et al. Clinical Transplantation. 2017;31:e13071.

Favorable results in ABO-incompatible renal transplantation without B cell-targeted therapy: Advantages and disadvantages of rituximab pretreatment (4)

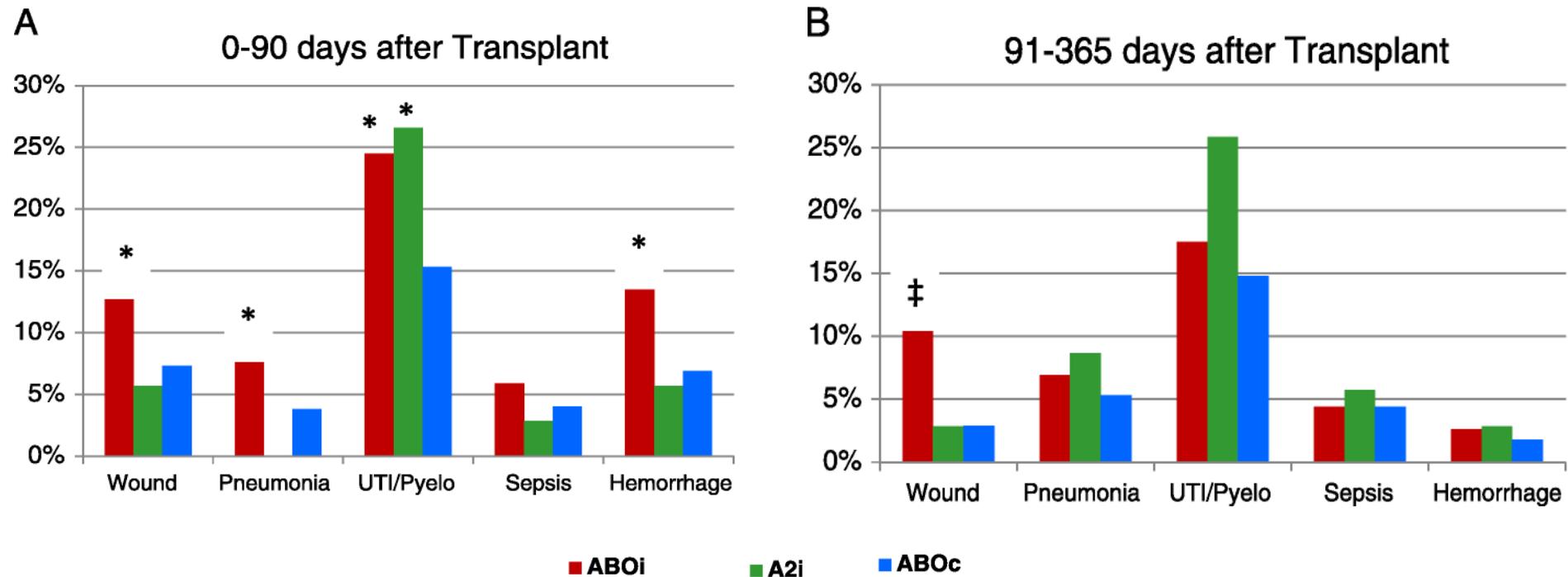


Graft survival in NoR/S and RIT. (A) Kaplan-Meier curves for overall graft survival of unmatched patients in the NoR/S (n = 53) and RIT (n = 131, $P = .267$) groups. The 5-year overall graft survival rates in the NoR/S and RIT groups were 97.7% and 90.1%, respectively.

Okada M, et al. *Clinical Transplantation*. 2017;31:e13071.

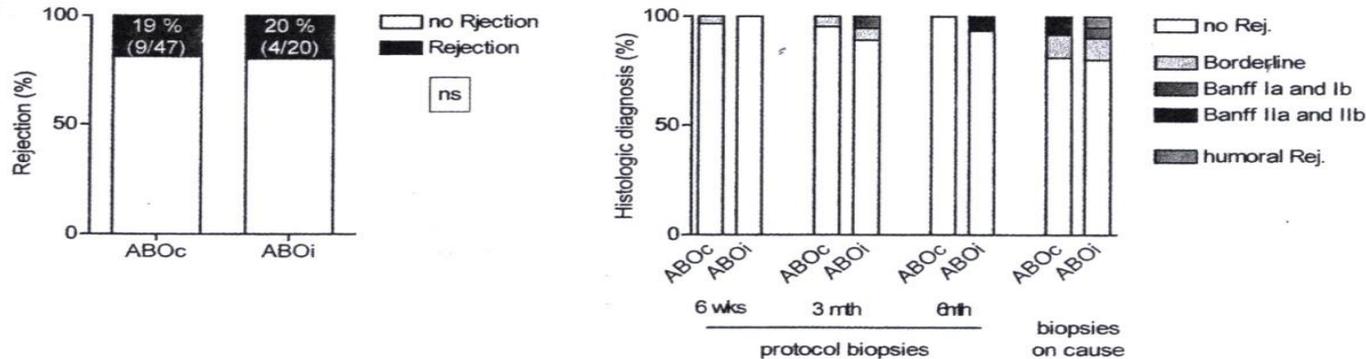
Surgical Complications

Early clinical complications after ABO-incompatible live-donor kidney transplantation : a national study of medicare-insured recipients

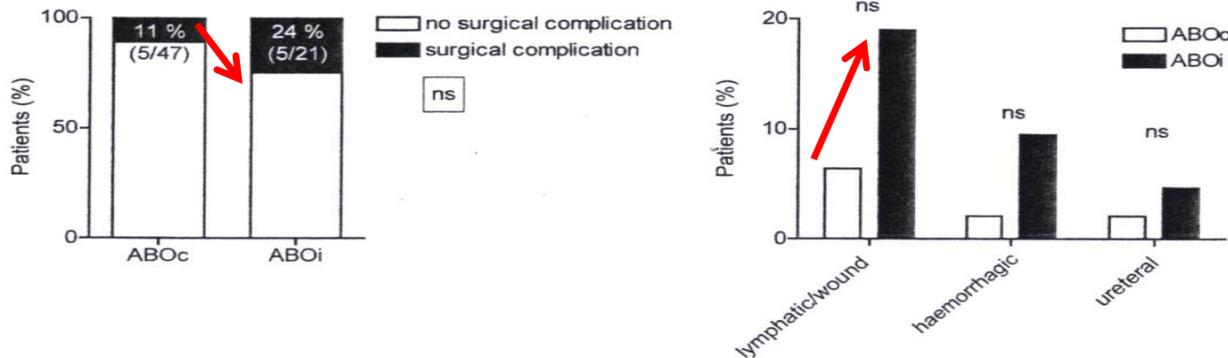


Kaplan-Meier estimates of infectious complications and hemorrhage frequencies over periods of 0 to 90 days and 91 to 365 days, according to blood type compatibility. ABOi, ABO incompatible; A2i, A2 incompatible; ABOc, ABO compatible. P values versus ABOc, *0.0001 to <0.05, ‡<0.0001.

ABO-i vs. ABO-c kidney transplantation: acute rejection and surgical complications

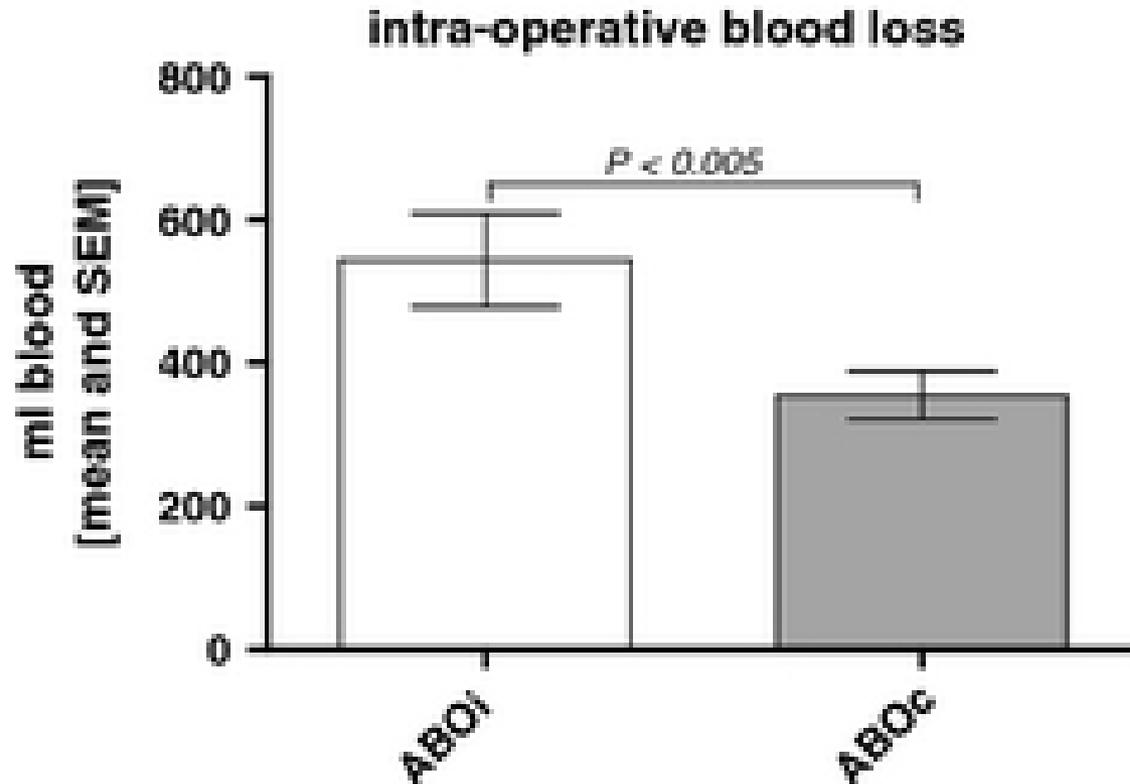


Number of rejections in ABOi and ABOc recipients. The number of patient experiencing one or more rejections (including borderline cases with impaired renal graft function) diagnosed in any of the three protocol biopsies or biopsies on cause did not differ between ABOi and ABOc recipients, while the number of subclinical rejections showed a higher tendency in ABOi recipients (non-significant).



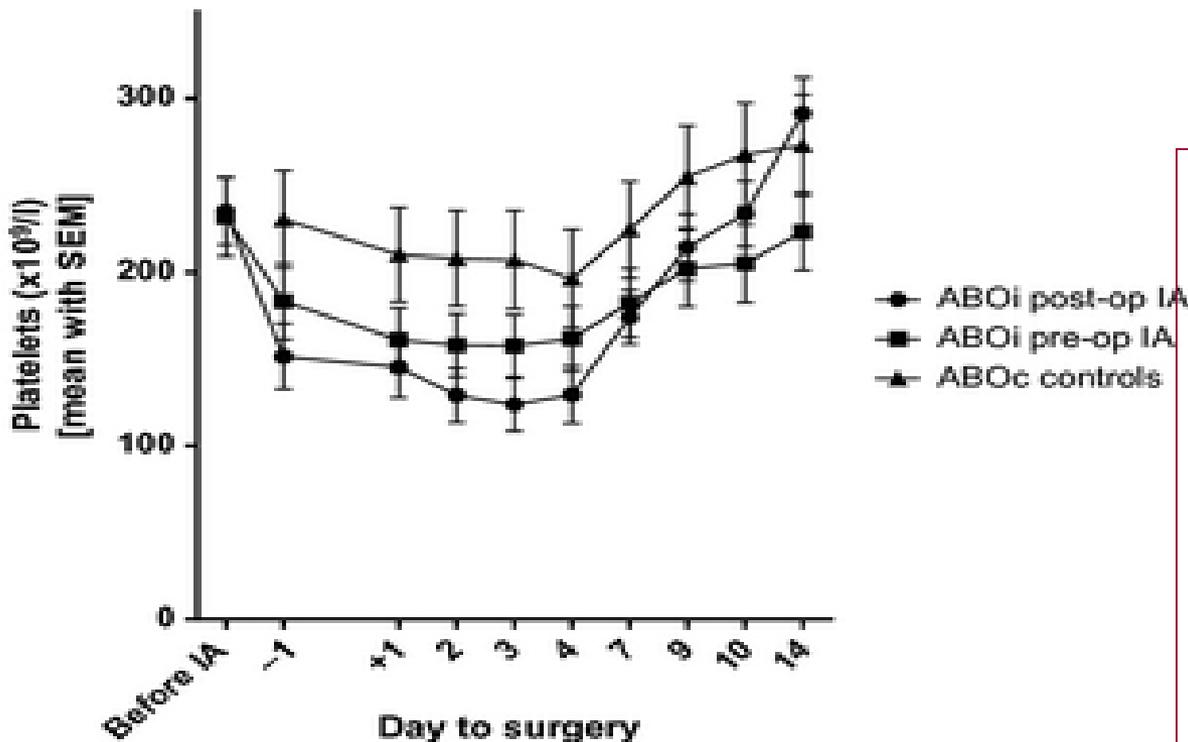
Incidence of SCs in ABOi and ABOc recipients. The number of patient experiencing one or more SC was higher in ABOi transplant recipients as compared to ABOc recipients (non-significant).

ABO-incompatible kidney transplant recipients have a higher bleeding risk after antigen-specific immunoadsorption (1)



Intra-operative blood loss. ABOi patients (n=63) lost more blood intra-operatively than controls (ABOc; n=130) (536 ± 66 vs. 364 ± 34 ml, mean and SEM, $P < 0.005$).

ABO-incompatible kidney transplant recipients have a higher bleeding risk after antigen-specific immunoadsorption (2)



Platelet count in ABO-incompatible patients and their ABO-compatible controls. Platelet count before start of the immunoadsorption (IA) (mean 233 x 10⁹/l) was comparable to controls (230 x 10⁹/l) 1 day pre-operatively (*P* > 0.1). Platelet count fell by 28% 1 day pre-operatively in ABO-incompatible patients (169 x 10⁹/l, *P* < 0.0001). Platelets in ABO-incompatible patients remained lower up to day 10 compared with controls (all *P* ≤ 0.001). In the group of ABOi patients with postoperative IA (first 30 patients), platelet count was higher after 2 weeks than without postoperative IA (292 vs. 223 x 10⁹/l; *P* = 0.02). Platelet count after postoperative IA was even higher at day 14 than before IA (292 vs. 235 x 10⁹/l; *P* = 0.02).

- ABOi post-op PP ABO-incompatible kidney transplantation with pre- and post-operative plasmapheresis
- ABOi pre-op PP ABO-incompatible kidney transplantation with only pre-operative plasmapheresis
- ABOc controls ABO-compatible controls

Hemorrhagic complications and requirements in blood transfusions (Toulouse experience).

	ABOi patients (n=44)	ABOc patients (n=44)	p-value
Overall bleeding complications (n, %)	20 (40.4)	8 (18.2)	0.006
Renal-artery anastomosis leakage (n; %)	2 (4.5)	0	NS
Intraoperative bleeding (n; %)	12 (27.3)	2 (4.5)	0.0004
Large wound hematomas (n; %)	16 (36.3)	6 (13.6)	0.013
Gross hematuria after postoperative D5 (n; %)	3 (6.8)	2 (4.5)	NS
Number of patients requiring red-blood cell transfusions (BT) between D0 and D10 (n; %)	35 (79.5)	12 (27.3)	0.00002
Intraoperative BT (n; %)	14 (31.8)	3 (6.8)	0.006
D0 BT excluding intraoperative (n; %)	12 (27.3)	3 (6.8)	0.023
D1 BT (n; %)	10 (22.7)	4 (9.1)	NS
Number of BTs/patient	3.5 ± 3.4	0.8 ± 1.9	0.00002

Abbreviations: D, day; BT, blood transfusion, i.e., red blood-cell packs; Hb, hemoglobin

Risk factors for perioperative bleeding (Toulouse experience)

	ABOi patients (n=44)	ABOc patients (n=44)	p-value
D0 (pre-op) fibrinogen (g/L)	1.88 ± 0.62	3.65 ± 1.62	0.0006
D0 platelets (pre-op/mm ³)	146,520 ± 35,880	195,610 ± 50,940	0.00001
D0 (pre-op) prothrombin time (%)	83.8 ± 12.1	89.8 ± 9.5	0.012
D0 (pre-op) activated cephalin time(s)	27.1 ± 4.1	29.5 ± 4	0.005
D0 Hb (pre-op) (g/dL)	10.1 ± 1.2	10.9 ± 1.5	0.006

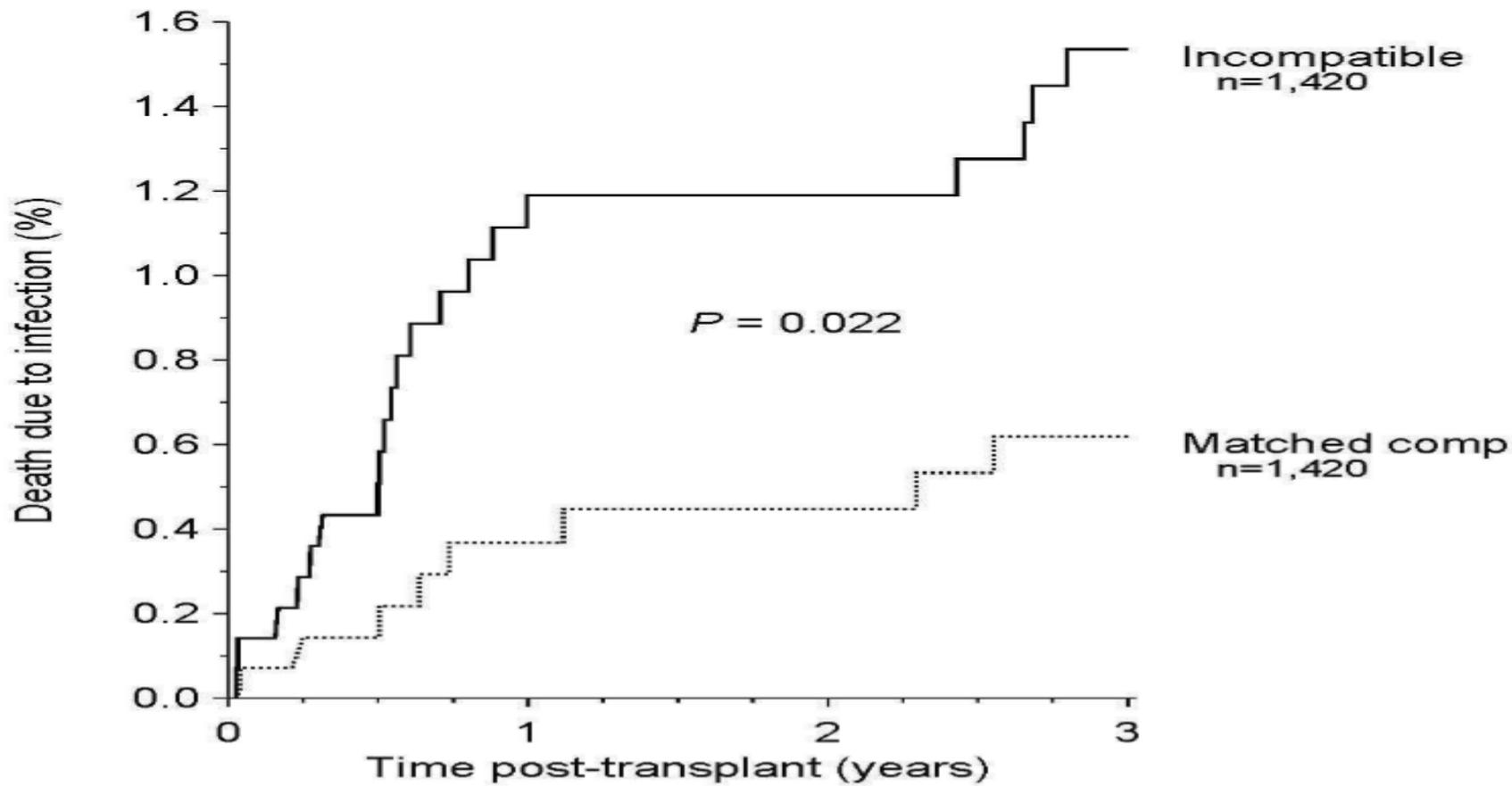
Abbreviations: D, day; BT, blood transfusion, i.e, red blood-cell packs; Hb, hemoglobin

Postoperative surgical complications (Toulouse experience)

	ABOi patients (n=44)	ABOc patients (n=44)	p-value
Renal artery thrombosis (n)	0	0	NS
Renal venous thrombosis (n)	1	0	NS
Renal artery stenosis (n; %)	4 (9.1)	6 (13.6)	NS
Urinary leakage (n; %)	0	2 (4.5)	NS
Lymphoceles (n; %)	8 (18.2)	7 (16)	NS
Wound dehiscence (n (%)) and requiring surgery (n)	5 (11.3); 3	2 (4.5); 1	NS
Peritoneal breach (n; %)	1 (2.3)	0	NS

Infectious Complications

Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction : results from 101 centers



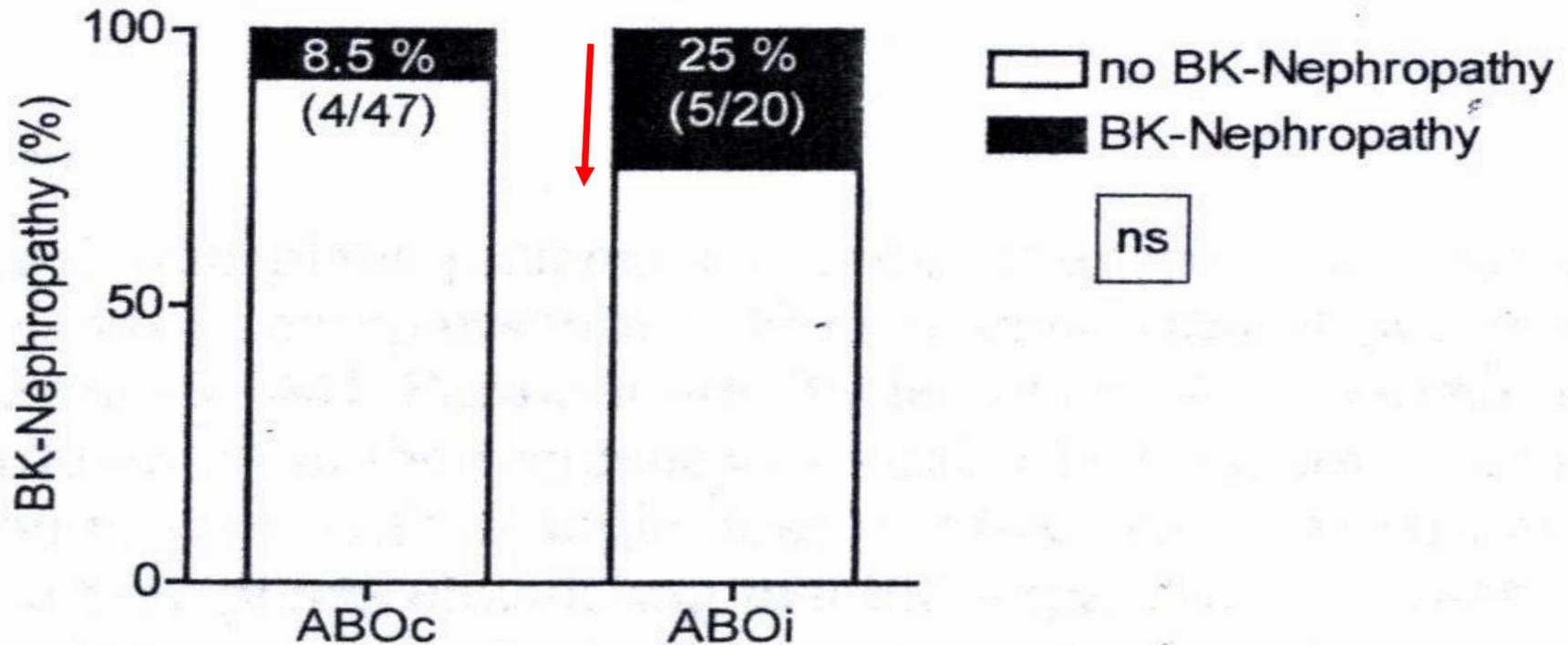
Infectious complications after ABO-i kidney transplantation (1)

Binary logistic regression analysis for pooled infectious complications^a

Variables	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
ABO-status	0.283	0.095–0.842	0.02*	0.319	0.102–0.995	<0.05*
Previous Tx	1.065	0.232–4.888	0.9			
SCs	0.222	0.065–0.756	0.02*	0.475	0.078–2.873	0.4
Rejections (overall)	0.204	0.055–0.757	0.02*	0.232	0.060–0.898	0.03*
Rejections (clinical)	0.393	0.055–2.230	0.3			
Rejections (subclinical)	n.s.					

^aAll variables were included as categorical variables (yes/no). Abbreviations: CI = confidence interval; HR = hazard ratio; n.s. = non-significant; PRA = preformed antibodies.

Infectious complications after ABO-i kidney transplantation (2)



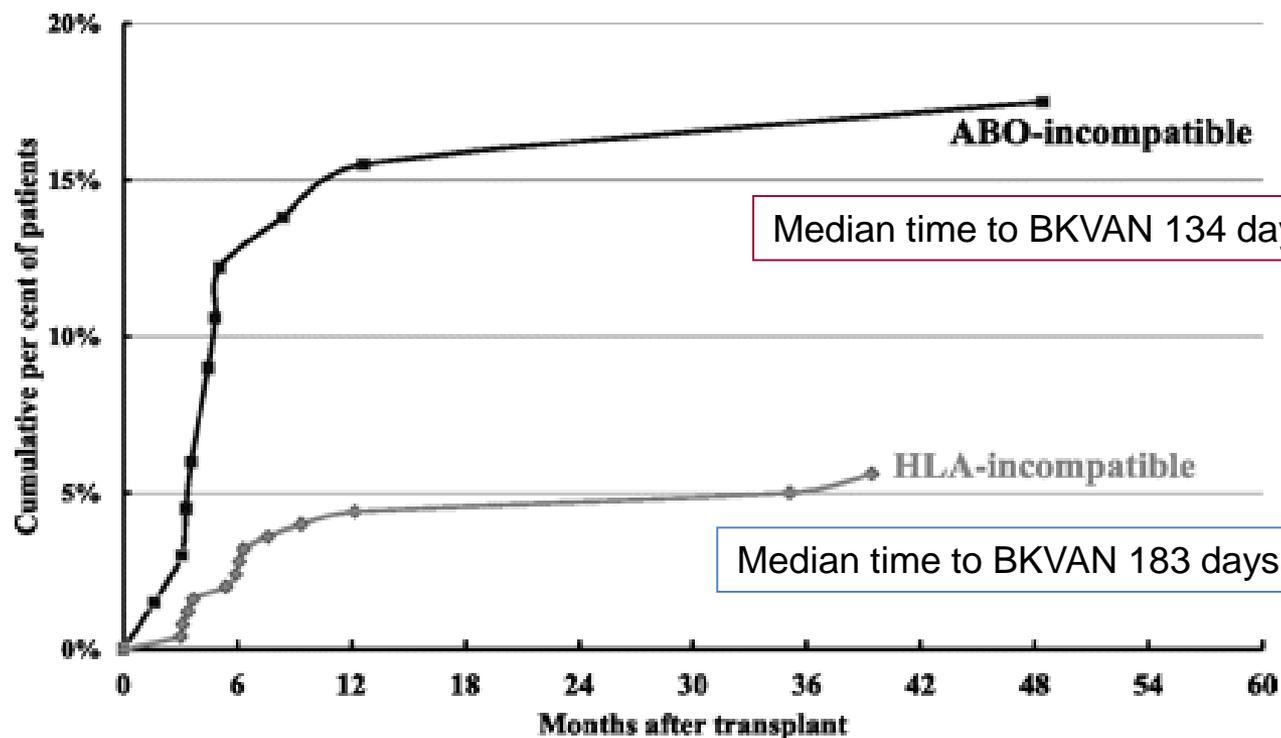
Incidence of BK nephropathy in ABOi and ABOc recipients. The number of patients with a biopsy-proven BK nephropathy was higher in the ABOi group as compared to the ABOc group.

BKV infection after ABO-i or HLA-i kidney transplantation (1)

- Retrospective analysis from 1998 to 2010 (62 ABO-incompatible and 221 HLA-incompatible kidney transplantation). Focus on patients in whom BKVAN was diagnosed by biopsy (per protocol or for cause).
- Risk for BKVAN was greater among ABO-i than HLA-i patients (17.7% versus 5.9%; $P=0.008$).
 - Of BKVAN cases, 42% were subclinical, diagnosed by protocol biopsy.
 - ABO-i and age were independent predictors for BKVAN on logistic regression.
 - C4d deposition without histologic features of glomerulitis and capillaritis (graft accommodation-like phenotype) on 1-year biopsies of ABO-incompatible patients with and without BKVAN was 40% and 75.8%, respectively ($P=0.04$).
 - Death-censored graft survival (91%) and serum creatinine level among surviving kidneys (1.8 mg/dL) were identical in ABO- and HLA-incompatible patients with BKVAN (median, 1399 and 1017 days after transplantation, respectively).

Incidence and outcomes of BK virus allograft nephropathy among ABO-and HLA-Incompatible kidney transplant recipients (2)

Overall 3% of BKVAN between 1997 to 2008



Incidence of BK virus allograft nephropathy in incompatible kidney transplant recipients (diagnosed by protocol and for-cause biopsies). Cumulative incidence was 17.7% for ABO-incompatible kidney recipients and 5.9% for HLA-incompatible kidney recipients; the difference was statistically significant ($P=0.008$).

Incidence and outcomes of BK virus allograft nephropathy among ABO-and HLA-Incompatible kidney transplant recipients (3)

Independent predictors for development of **BK nephropathy** by multivariable logistic regression analysis

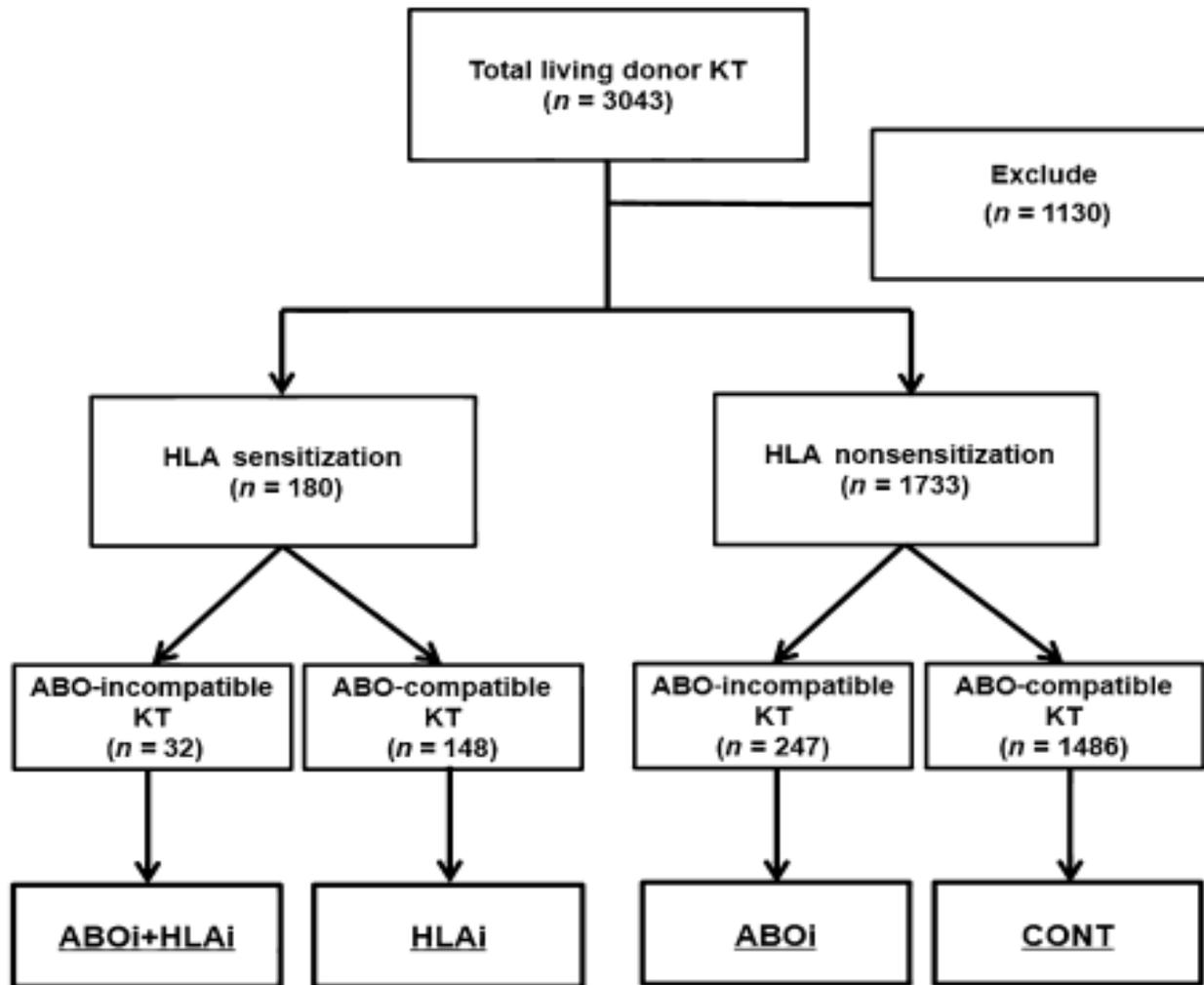
Variable	Odds Ratio	<i>P</i> Value
ABO incompatibility	2.32	0.04
Age (median \geq 46 yr)	3.27	0.01

***ABO incompatible + HLA
incompatible kidney
transplantation***

Clinical outcomes of ABO- and HLA-incompatible kidney transplantation: a nationwide cohort study (1)

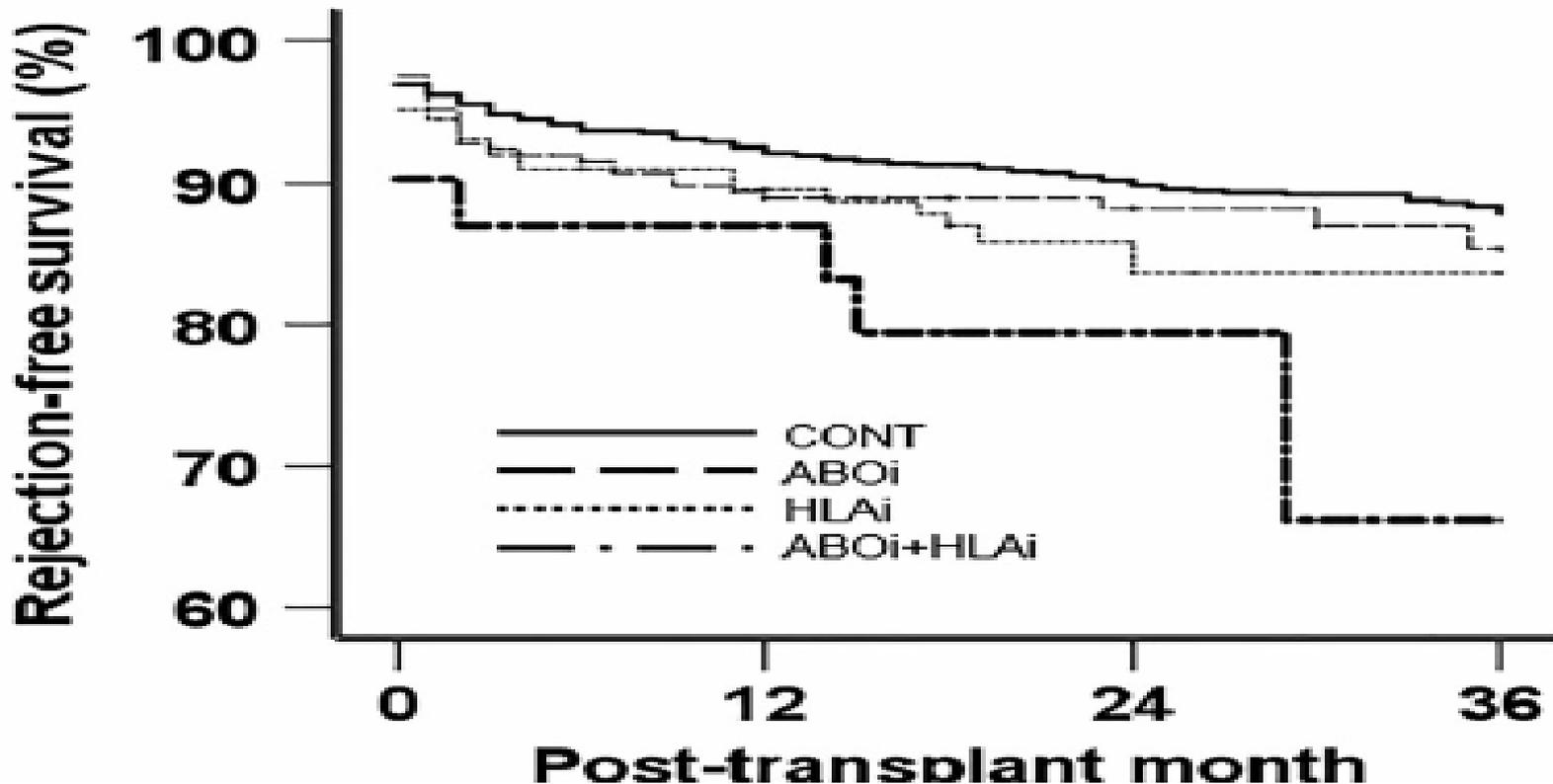
- Desensitization protocol :
 - PP or DFPP
 - 1 rituximab infusion 2 to 4 weeks pretransplant (100 to 375 mg/m²)

Clinical outcomes of ABO- and HLA-incompatible kidney transplantation: a nationwide cohort study (2)



Distribution of the patient population according to ABO or HLA incompatibility. Of the 1922 KTR patients included in this study, 279 were ABO-incompatible KT, and another 1685 cases were ABO-compatible. Among the ABO-incompatible patients, those who were positive for PRA and cross-matched or positive for HLA-DSA were placed in the ABOi + HLAI group (n = 31), with the remainder categorized as ABOi (n = 248). Similarly, among the 1685 ABO-compatible patients, those who were positive for PRA and cross-matched or positive for HLA-DSA were placed in HLAI (n = 144), with the remaining patients placed in CONT (n = 1541).

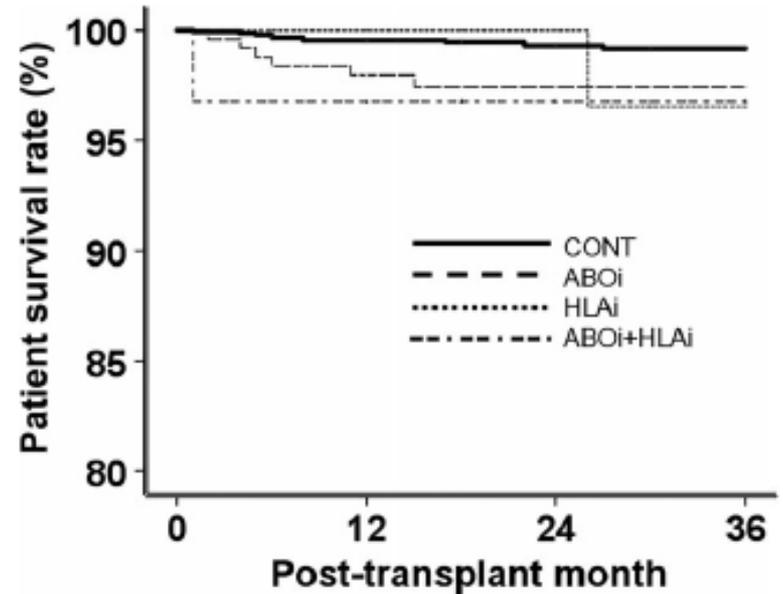
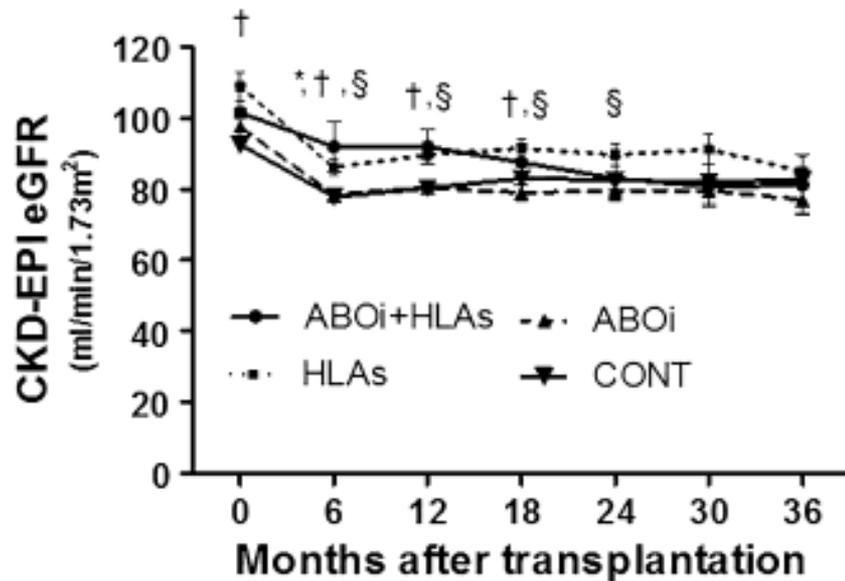
Clinical outcomes of ABO- and HLA-incompatible kidney transplantation: a nationwide cohort study (3)



Comparison of the **incidence of biopsy-proven acute rejection** across the four groups.

(c) the overall BPAR-free survival rate was significantly lower in HLAi ($P = 0.045$) and ABOi + HLAi ($P = 0.018$) compared with CONT group. ABOi, ABO-incompatible; HLA, human leucocyte antibody; HLAi, positive for PRA and cross-matched or positive for HLA-DSA; HLA-DSA, donor-specific anti-HLA antibody; CONT, control group.

Clinical outcomes of ABO- and HLA-incompatible kidney transplantation: a nationwide cohort study (4)



Comparison of the changes in renal allograft function.

During the 18 months post-transplant, both the HLAI and ABOi + HLAI groups demonstrated higher graft function compared with CONT. However, note that these differences dissipated at 30 months following KT.

*P < 0.05 versus ABOi + HLAI, †P < 0.05 versus

HLAI,

‡P < 0.05 versus ABOi, §P < 0.05 versus CONT. -71-

Comparison of the patient survival rates across the four groups. Note that mortality rates were reduced in ABOi (P = 0.004) and ABOi + HLAI (P = 0.005) relative to CONT.

Clinical outcomes of ABO- and HLA-incompatible kidney transplantation: a nationwide cohort study (5)

Univariate and multivariable binary logistic analysis for biopsy-proven acute rejection.

	Crude models			Adjusted model		
	OR	95% CI	P	OR	95% CI	P
ABOi	0.82	0.56–1.20	0.29	0.85	0.52–1.39	0.52
HLAi	1.94	1.29–2.92	0.002	1.99	1.20–3.29	0.007

ABOi, ABO-incompatible; HLA, human leucocyte antibody; HLAi, positive for PRA and cross-match, or positive for HLA-DSA; MN, mismatch number.

Adjusted model: multivariable model including living unrelated donor (versus living related donor) [19], HLA MN [20], re-transplant [20].

Univariate and multivariable Cox proportional hazards analysis for graft failure.

	Crude models			Adjusted model		
	HR	95% CI	P	HR	95% CI	P
ABOi	0.84	0.25–2.87	0.78	0.87	0.25–2.96	0.82
HLAi	0.04	0–39.42	0.37	0.01	0–25.72	0.93

ABOi, ABO-incompatible; DM, diabetes mellitus; HLA, human leucocyte antibody; HLAi, positive for PRA and cross-match, or positive for HLA-DSA.

Adjusted model: multivariable model including living unrelated donor (versus living related donor) [19], donor age [21], DM [22].

Clinical outcomes of ABO- and HLA-incompatible kidney transplantation: a nationwide cohort study (6)

Univariate and multivariable Cox proportional hazards analysis for **patient death**.

	Crude models			Adjusted model		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
ABOi	3.65	1.45–9.19	0.006	1.36	0.28–6.60	0.70
HLAi	1.89	0.55–6.44	0.31	0.96	0.15–6.22	0.96
DSZ	3.79	1.57–9.18	0.001	3.40	1.41–8.25	0.002

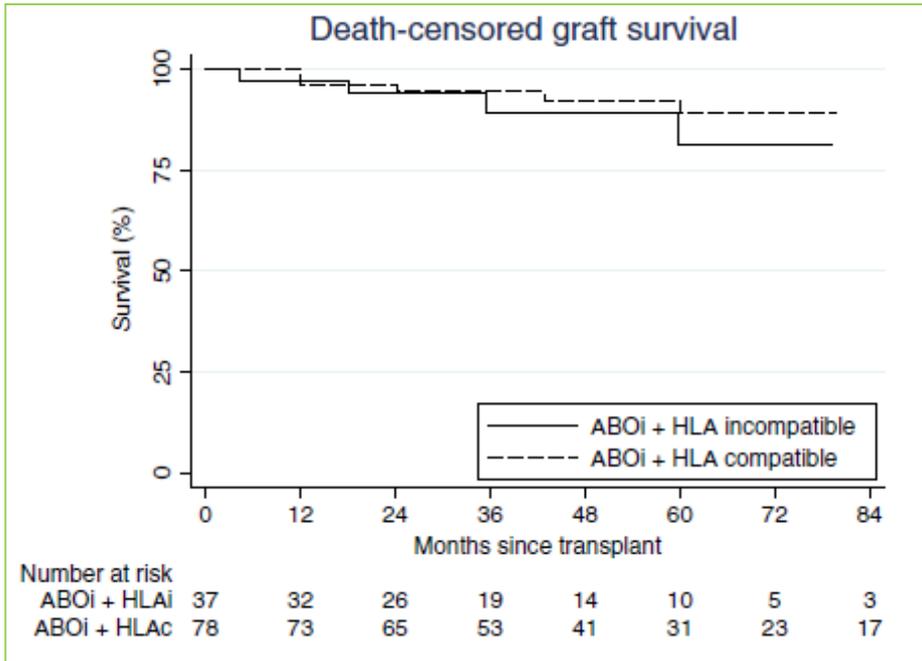
ABOi, ABO-incompatible; DM, diabetes mellitus; DSZ; desensitization using plasmapheresis and rituximab; HLA, human leucocyte antibody; HLAi, positive for PRA and cross-match, or positive for HLA-DSA.

Adjusted model: multivariable model including DM [22], recipient age [22], duration of dialysis [23].

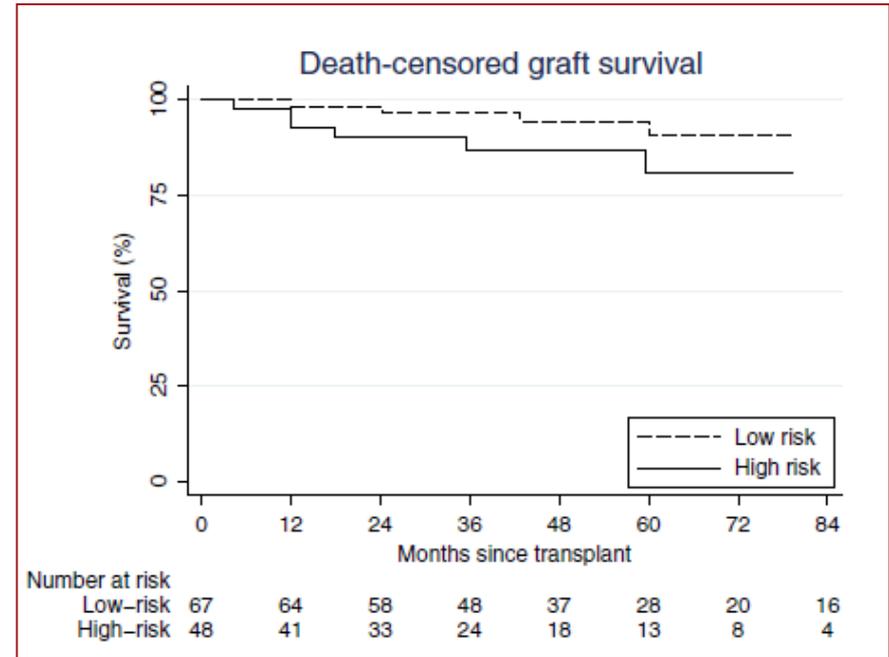
Outcomes and risk stratification for late antibody-mediated rejection in recipients of ABO-incompatible kidney transplants: a retrospective study (1)

- 115 living donor AOBi KTx; single center study (Johns Hopkins Hospital)
- Desensitization :pre- and post-op PP+ low dose of IVIg
- Transplantation when isoagglutinin titers $\leq 1/16$
- Some patients :
 - Received rituximab 375 mg/m² at D-1
 - Had splenectomy
- ⇒ 32% were HLA incompatible

Outcomes and risk stratification for late antibody-mediated rejection in recipients of ABO-incompatible kidney transplants: a retrospective study (2)

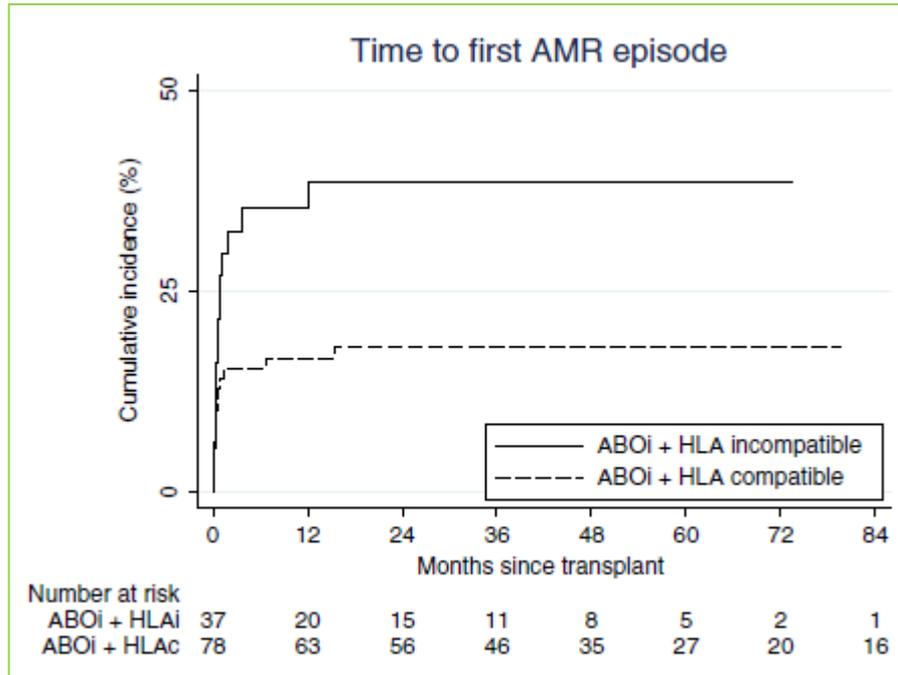


Renal allograft survival. Kaplan–Meier estimates of deathcensored graft survival stratified by the presence of concomitant human leukocyte antigen incompatible (HLAi). Seventy-eight patients were ABO incompatible (ABOi) alone, and 37 patients were both ABOi/HLAi with their donors. Twenty-three patients were transplanted via kidney-paired donation.

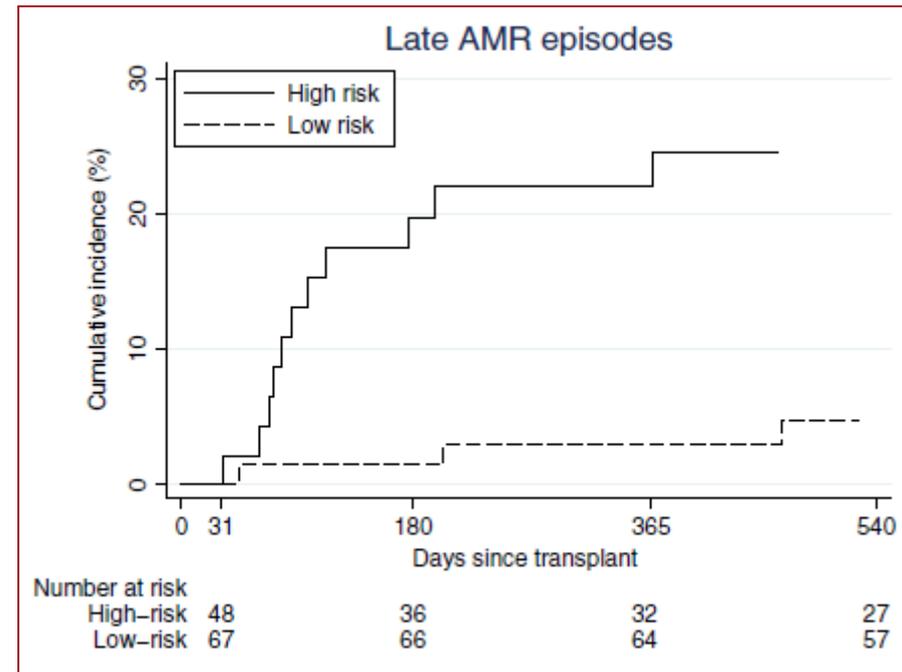


Renal allograft survival. Kaplan–Meier estimates of **death censored graft survival** stratified by high-risk [presence of early antibody-mediated rejection (AMR) and human leukocyte antigen incompatible (HLAi)] and low-risk groups [no early antibody-mediated rejection (AMR) and ABO incompatible (ABOi) alone].

Outcomes and risk stratification for late antibody-mediated rejection in recipients of ABO-incompatible kidney transplants: a retrospective study (3)



Timing of antibody-mediated rejection episodes. Time in months versus cumulative incidence of first antibody-mediated rejection (AMR) episode in ABO incompatible (ABOi) recipients stratified by the concomitant presence of human leukocyte antigen incompatible (HLAi). Seventy-eight patients were ABO incompatible only, and 37 patients were both ABOi/HLAi with their donors.



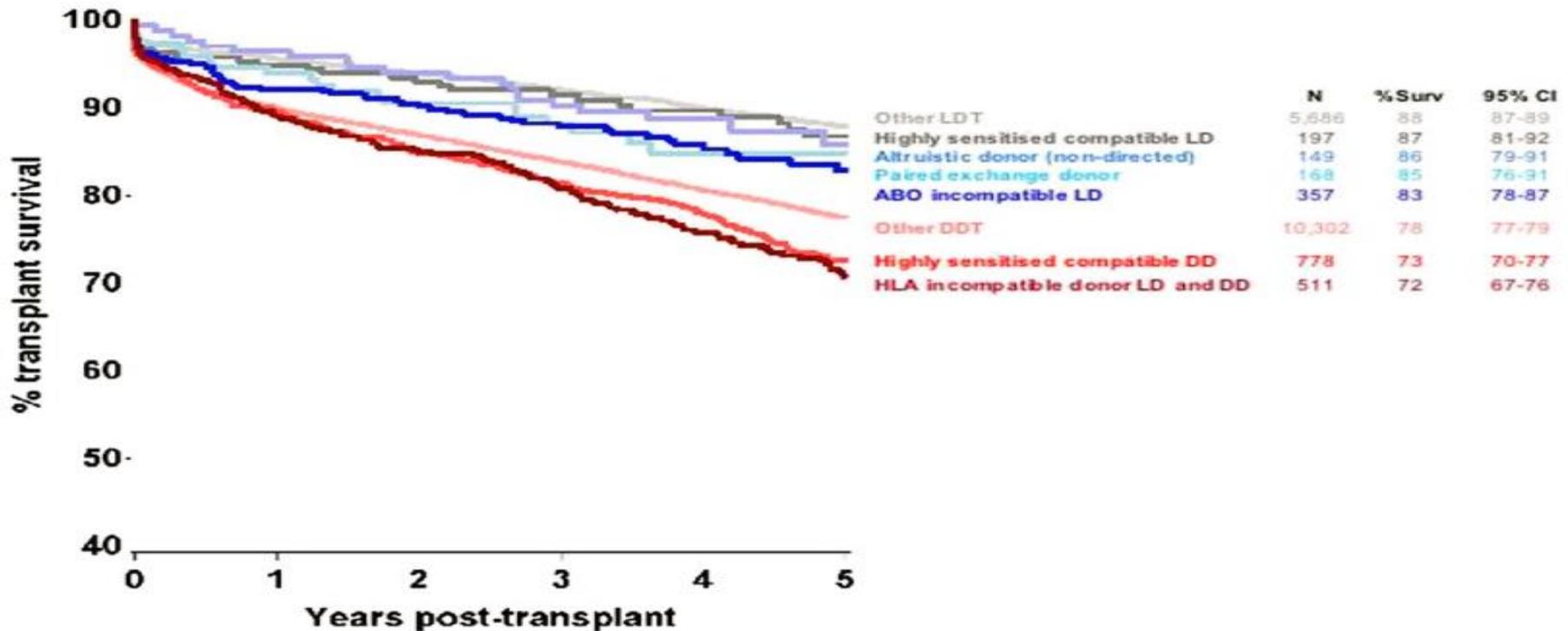
Timing of late antibody-mediated rejection episodes. Time in months versus cumulative incidence of late antibody-mediated rejection (AMR) episodes in ABO incompatible (ABOi) recipients stratified by high-risk [presence of early antibody-mediated rejection (AMR) and human leukocyte antigen incompatible (HLAi)] and low-risk groups (no early AMR and ABOi alone).

The UK National Registry of ABO and HLA Antibody Incompatible Renal Transplantation: Pretransplant Factors Associated With Outcome in 879 Transplants (1)

- UK transplant registry (2001-2012)
- ABOi and / or HLAi live-kidney transplant recipients

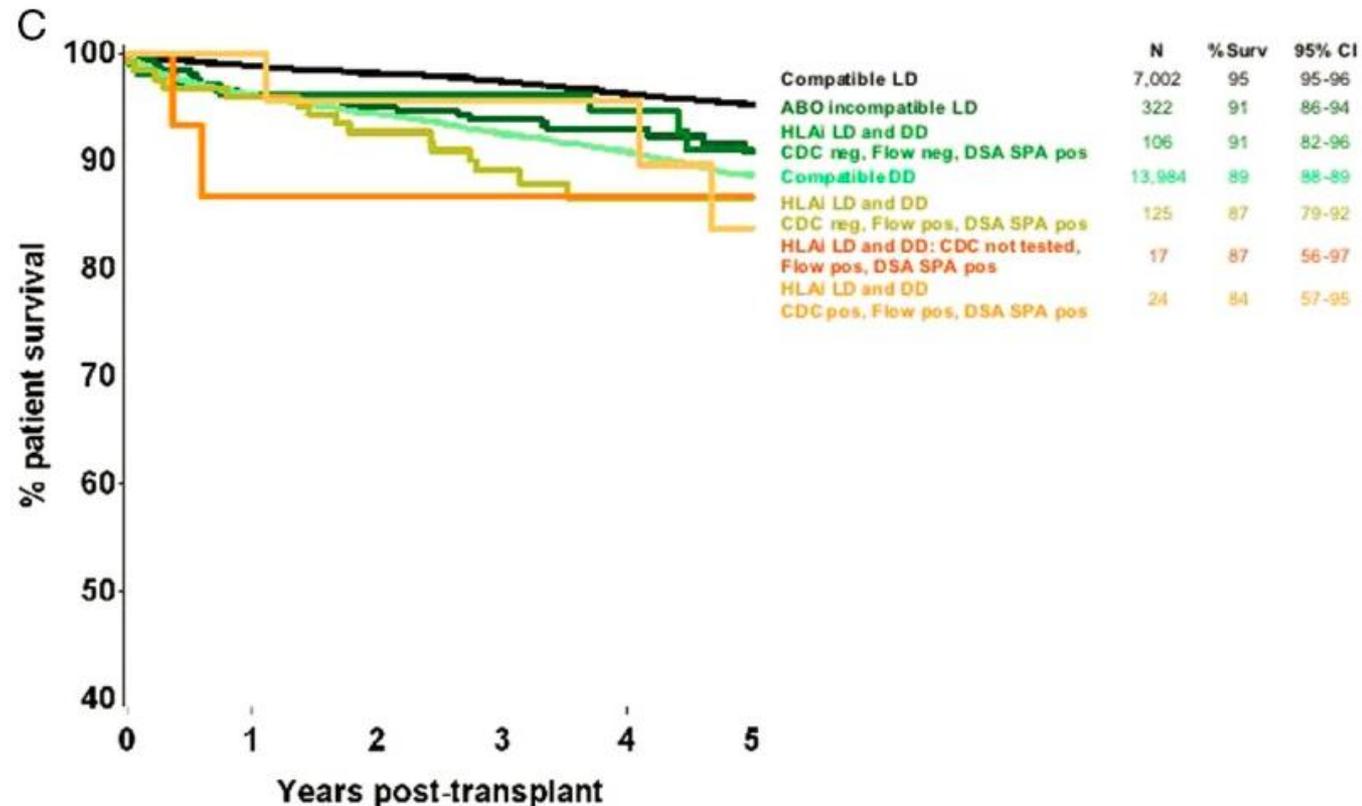
The UK National Registry of ABO and HLA Antibody Incompatible Renal Transplantation: Pretransplant Factors Associated With Outcome in 879 Transplants (2)

Five-year transplant survival for all kidney only transplants in the United Kingdom between January 1, 2005, and December 31, 2012.



The UK National Registry of ABO and HLA Antibody Incompatible Renal Transplantation: Pretransplant Factors Associated With Outcome in 879 Transplants (3)

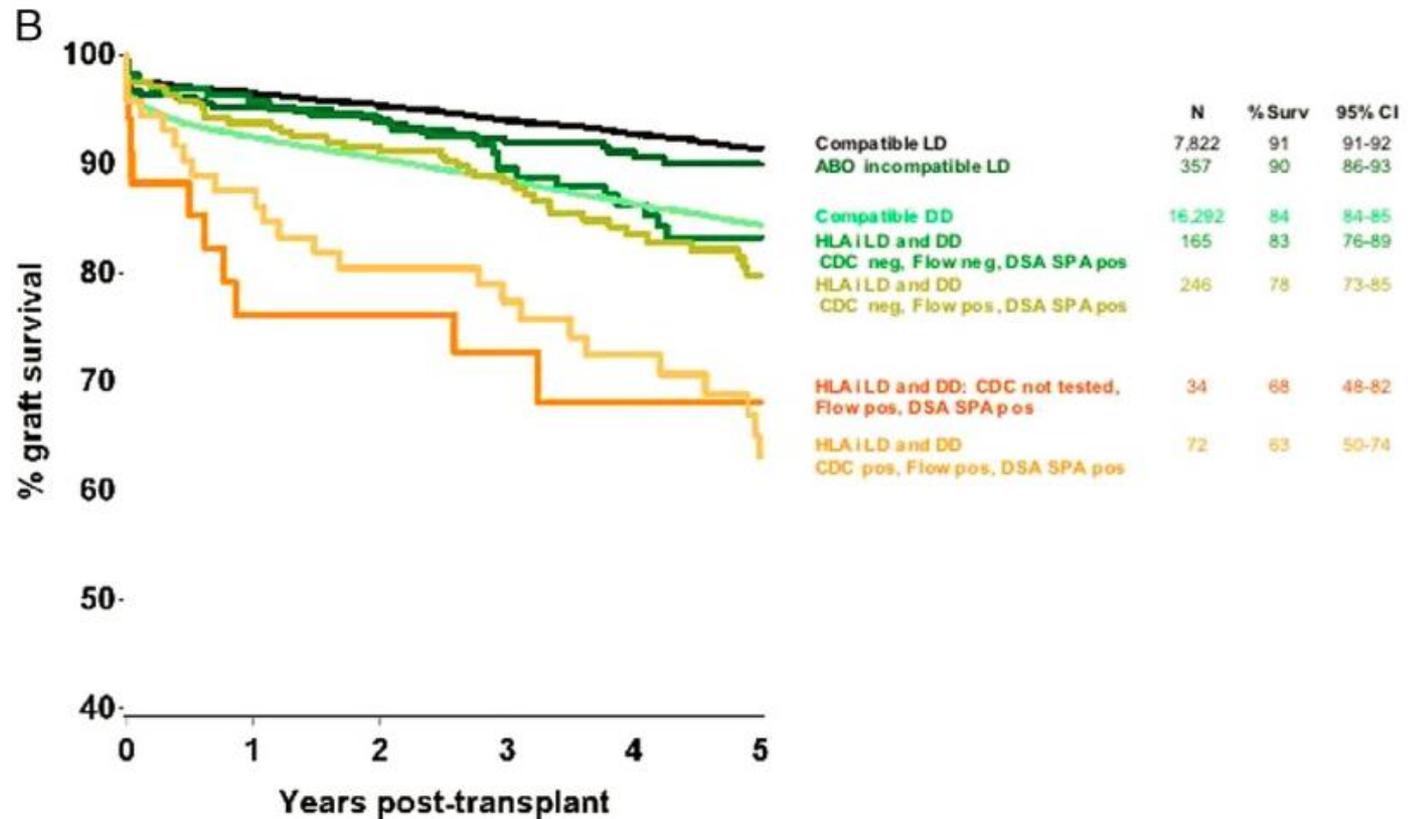
Five-year transplant survival for all kidney only transplants in the United Kingdom between January 1, 2005, and December 31, 2012.



C, patient survival. Levels of antibody reported pretreatment. flow, flow cytometric crossmatch; NT, not tested. Five HLAi transplants which had an unknown pretreatment antibody level group have been excluded from this figure.

The UK National Registry of ABO and HLA Antibody Incompatible Renal Transplantation: Pretransplant Factors Associated With Outcome in 879 Transplants (4)

Five-year transplant survival for all kidney only transplants in the United Kingdom between January 1, 2005, and December 31, 2012.



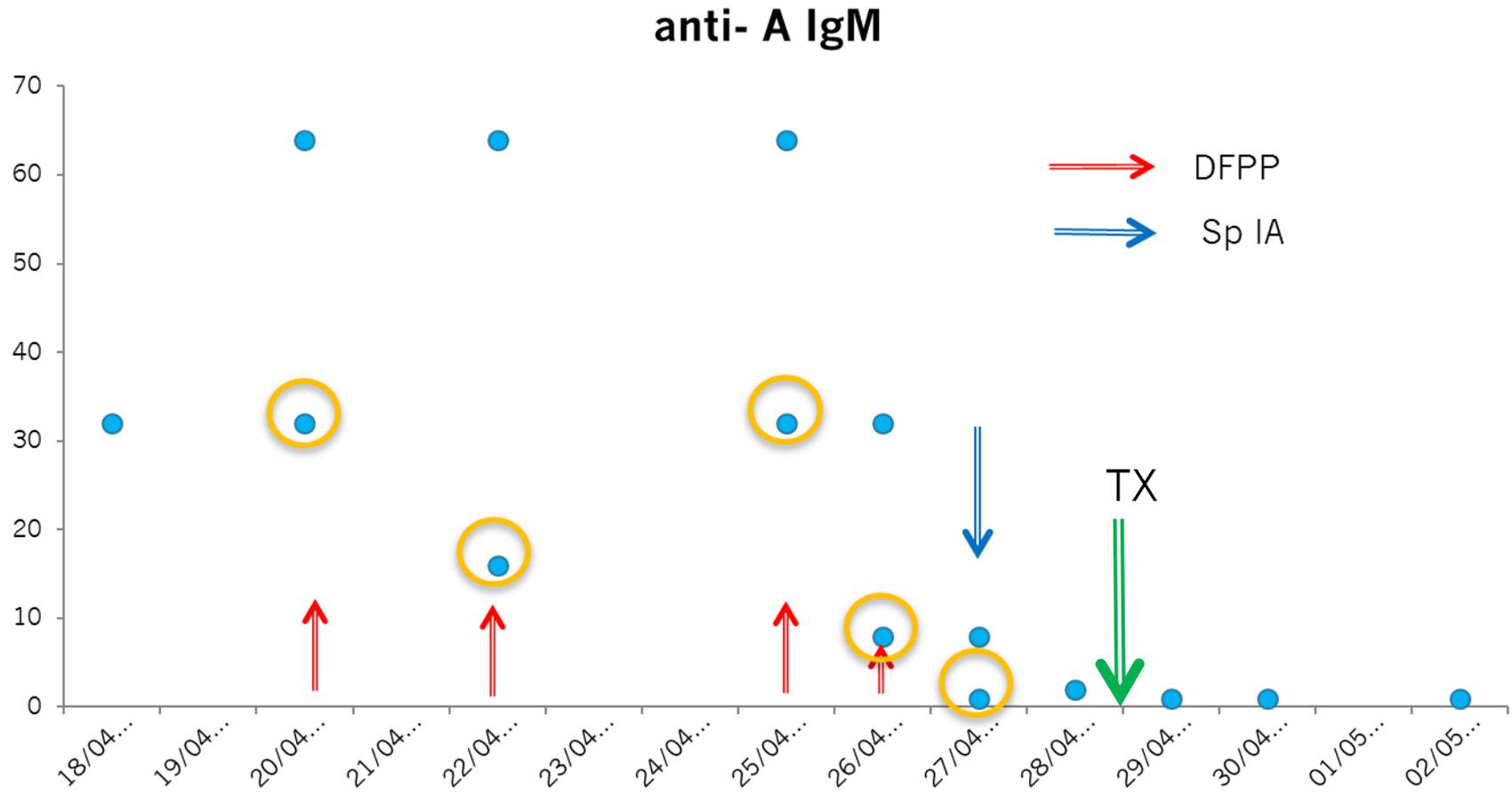
B, graft survival

NT, not tested. Five HLAi transplants which had an unknown pretreatment antibody level group have been excluded from this figure.

A typical example of desensitization

- D: 56 y spouse group A
- R: 62 y old M; hypertension leading to kidney failure. Group 0
- Pre-emptive transplantation
- Immunosuppression:
 - Rituximab M -1
 - Basiliximab + Tac + MMF + steroids
- Pre-rituximab Ab titer: IgM 1:128; IgG 1:256
- Apheresis: 4 DFPP and 1 specific IA
- Plasma: 2 units pre-tx
- Complications: cerebral ischemic attack at day 15.
- Latest creatinine (1 year later): 145 $\mu\text{mol/l}$ Ptu: 0,3g/l

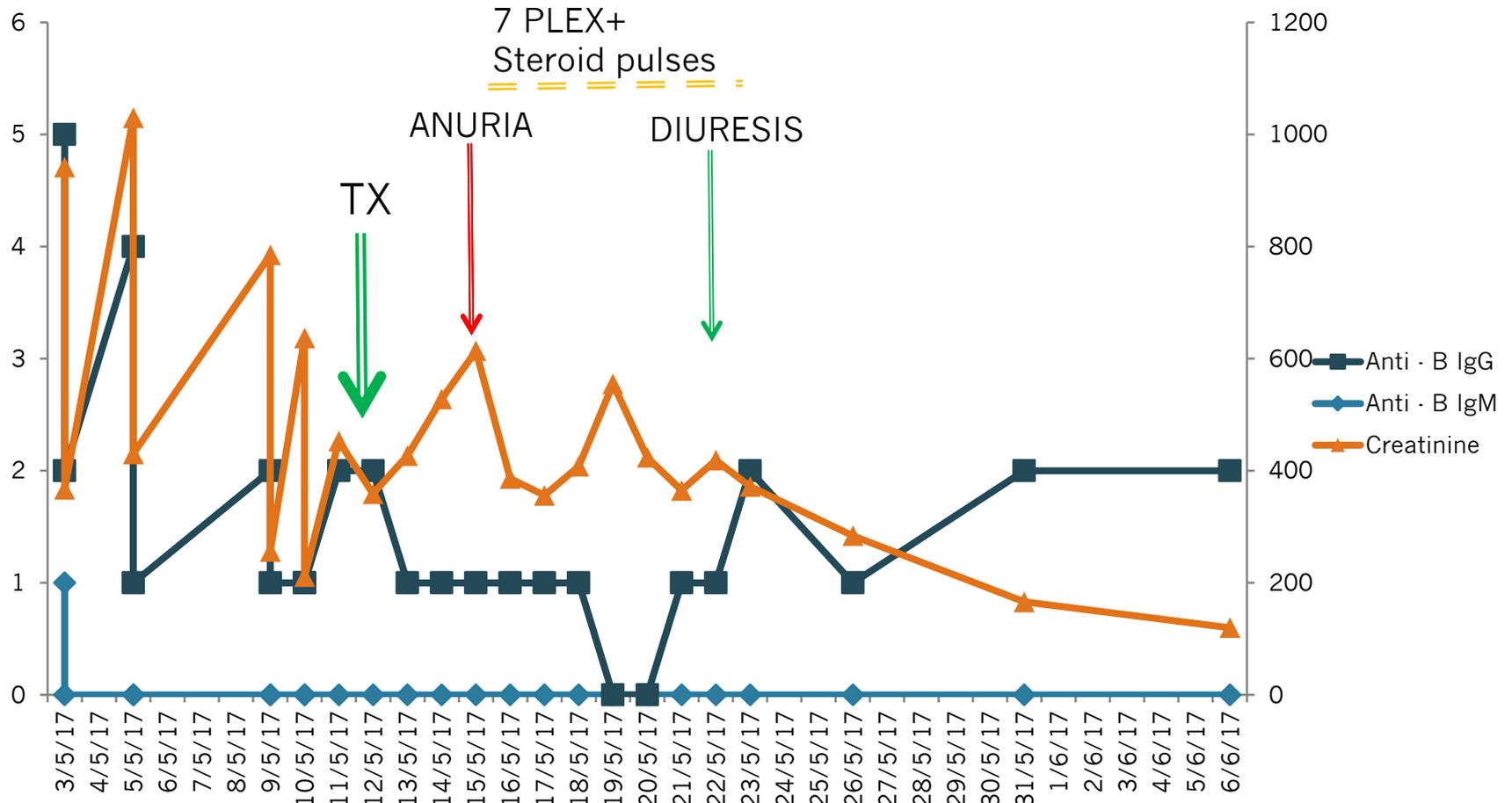
A typical example of desensitization



Rejection or no rejection?

- D 58y-old spouse; groupe B
- R: 76 year-old M; group A
- Kidney failure cause unknown; on dialysis since 7 years.
- Immunosuppression:
 - Rituximab M -1
 - Basiliximab + Tac + MMF + steroids
- Pre-rituximab Ab titer: IgM 1:1; IgG 1:4
- Apheresis: 4 PE (last with plasma substitution)
- Complications: anuria at day 3.
- Latest creatinine (1 month later): 130 $\mu\text{mol/l}$; Ptu: 0,2g/l

Rejection or no rejection ! – ABOi LD



Biopsy: interstitial oedema, no tubulitis, no peritubular capillaritis, C4d neg

CONCLUSIONS

- ABO incompatible kidney transplantation (KTx) results in the longterm in comparable results to those obtained with ABO compatible KTx, thanks to accomodation
- Humoral rejection mediated by isoagglutinins occurs mostly within the first 4 weeks posttransplantation
- ABOi + HLAi KTx have poorer outcome / ABOi KTx
- Desensitization protocols are easy to implement and are not too expensive
- ABO incompatible KTx is thus a good alternative to ABO compatible when no compatible donor is available.

Thank you for your attention

