Donor specific alloantibodies in the setting of kidney transplantation

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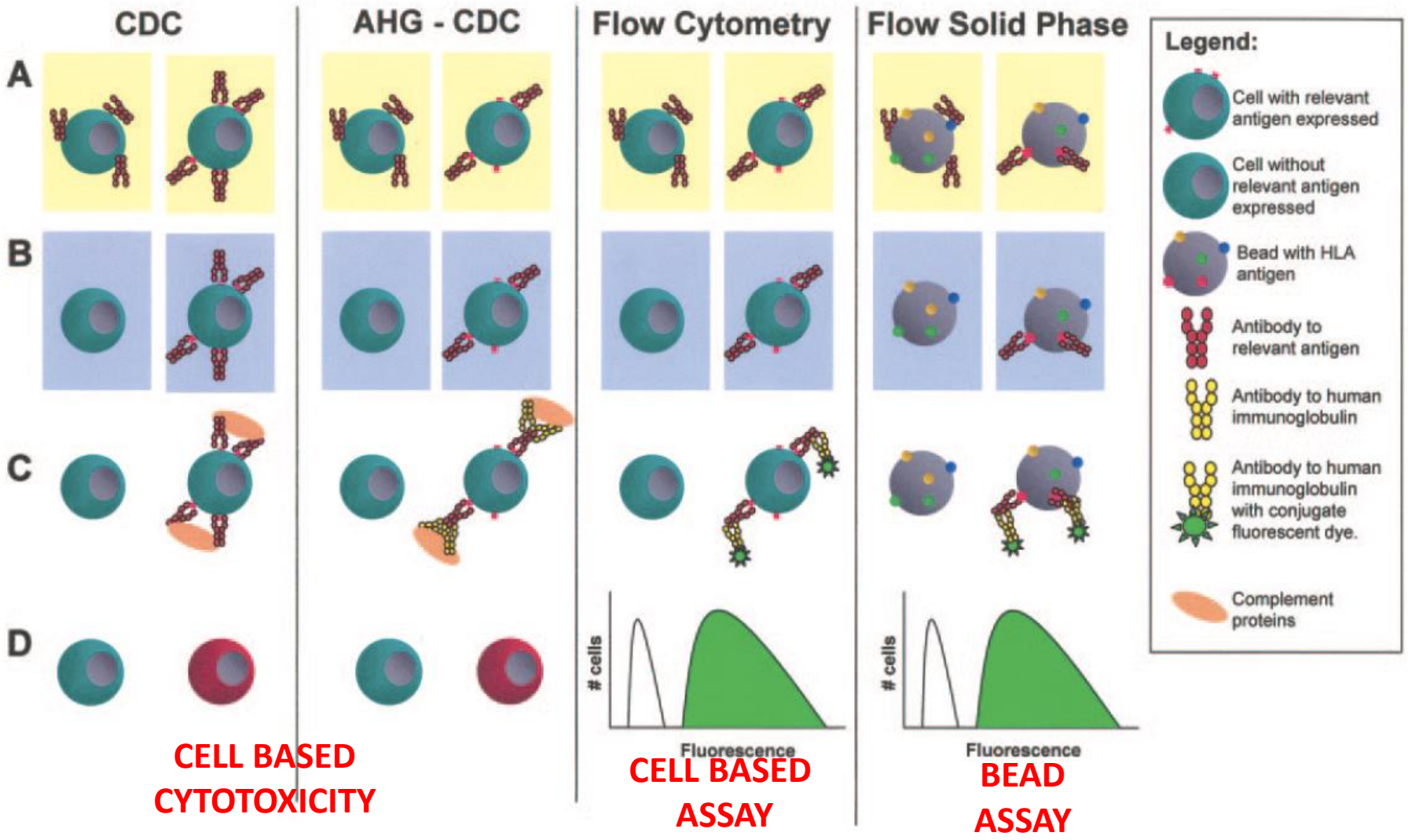
Tehran, July 19th 2018

Crossmatch, PRA and HLA antibodies

Complement dependent cytotoxicity **FACS** **Luminex/ELISA**



CELL BASED CYTOTOXICITY

CELL BASED ASSAY

BEAD ASSAY

Tinckam KJ and Chandraker A. CJASN 1: 404, 2006

Donor-specific alloantibodies (DSA)

- *How do we detect them?*

  - By microlymphocytotoxicity : detect DSAs that do bind and activate complement : low sensitivity and high specificity (PRA)

  - By Elisa : specific and a bit more sensitive (PRA)

  - By Luminex (single bead): very sensitive but less specific. Detect DSAs that DO and DO NOT bind the complement (PRA useless)

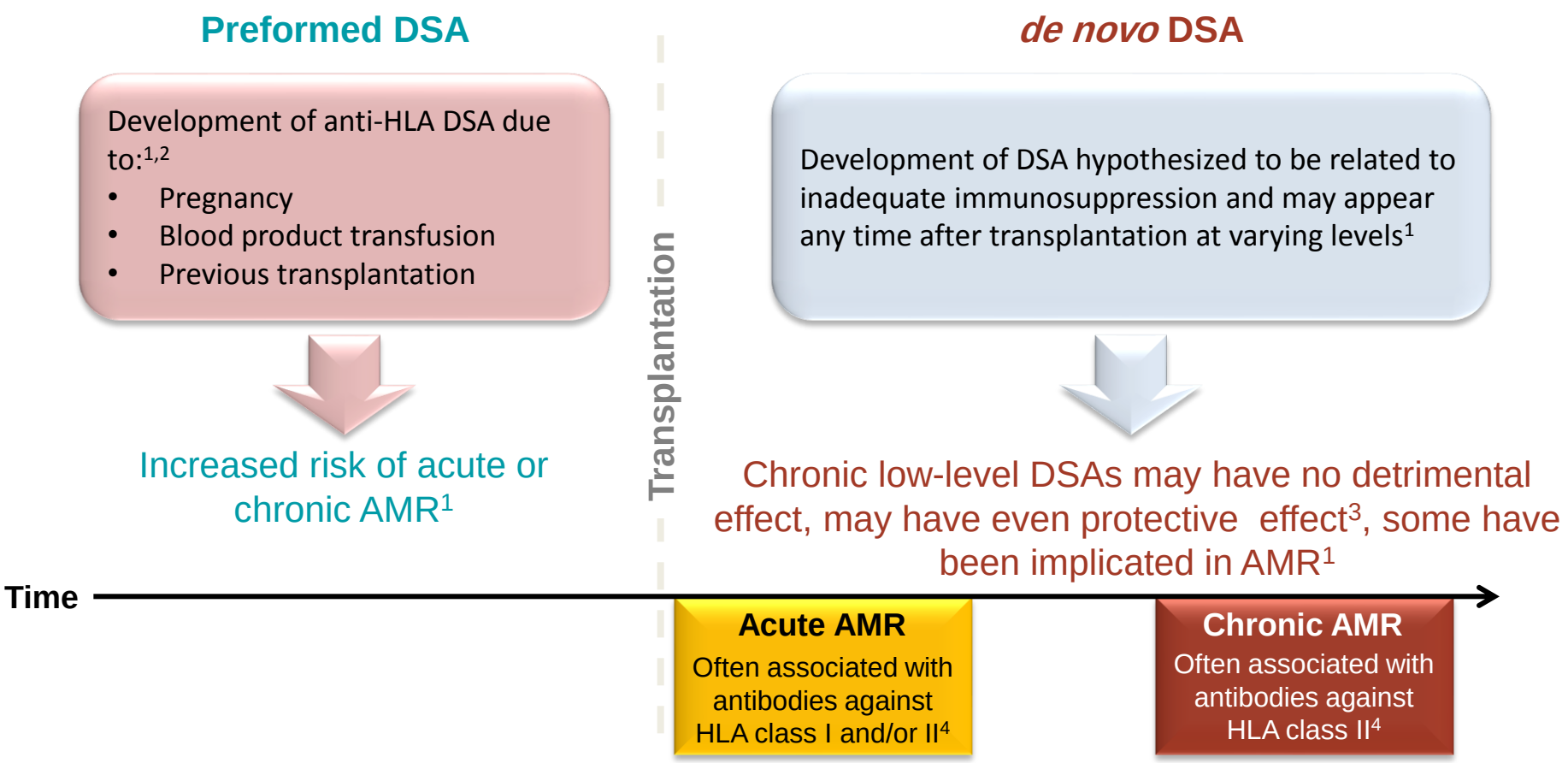
    - ✓ Those DSAs that bind complement result in a positive CDC cross-match. In this setting kidney transplantation is contraindicated

    - ✓ Those DSAs that do not bind complement allow kidney transplantation; however their strength might increase posttransplant and thereafter result in acute antibody-mediated rejection, which sometimes has the feature of thrombotic microangiopathy.

DSA

- Donor-specific alloantibodies (detected by Luminex®)
  - Preformed
  - *De novo* synthesis after KTx
    - Antibody-mediated rejection – AMR- (acute or chronic)
  - Different types of DSA :
    - those who bind C1q (+) ***or*** C3d (+) (bad guys)
      and those who don't bind C1q (-) ***or*** C3d (-): bystanders?
    - Those with high MFI (> 6000) vs. those with low MFI
  - May result in poor allograft outcome: this is recognized in kindey, liver, heart transplant recipients.
  - Very few drugs are able to decrease DSA

DSA can be preformed or arise *de novo* at anytime after Tx



AMR, antibody-mediated rejection; DSA, donor-specific antibody; HLA, human leukocyte antigen.

1. Loupy A, et al. Nat Rev Nephrol. 2012;8:348–357;
2. Nankivell BJ, et al. N Engl J Med. 2010;363:145114–62;
3. Turgeon NA, et al. Transplant Rev. 2009;23:25–33;
4. Colvin RB. J Am Soc Nephrol. 2007;18:1046–1056.

DSA

- When donor-specific alloantibodies (detected by Luminex®) are present what can we do?

  - It is better to prevent than to cure

cPRA vs. DSA

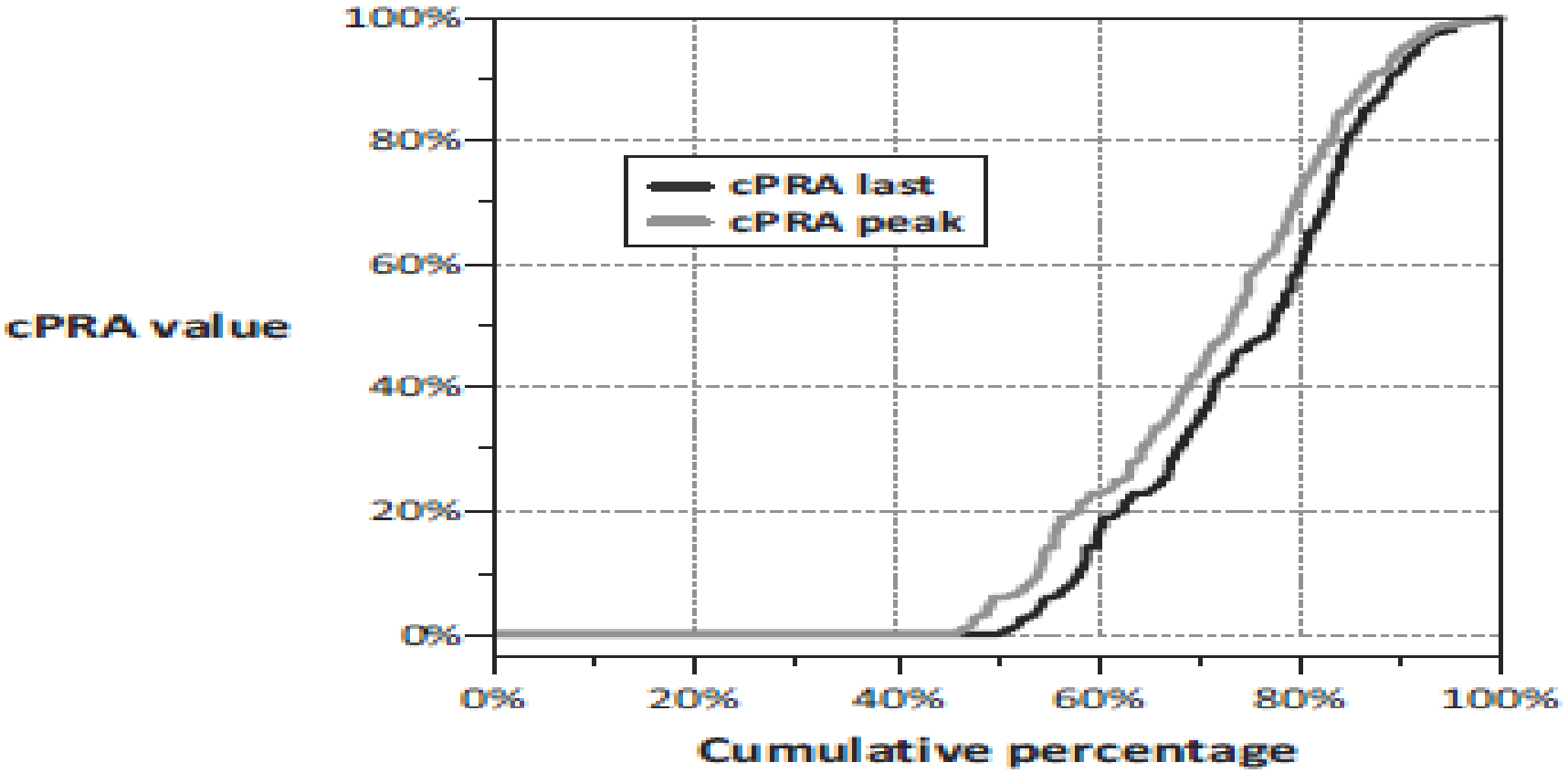
Donor Specificity but Not Broadness of Sensitization Is Associated With Antibody-Mediated Rejection and Graft Loss in Renal Allograft Recipients (1)

- Single center study (Basel, Switzerland); 527 KTx patients
- calculated PRA (c PRA) at pretransplant:
  - cPRA 0% (n=250) ; cPRA 1-50% (n=124) ; 51-100% (n=43) and DSA (n=105)
- In the absence of DSA = standard risk → IS = basiliximab, Tac, MPA and steroids (for 3 months posttransplant)
- In the presence of DSA: ATG induction + IVIg (2 g/kg) + Tac +MPA + steroids
- Surveillance kidney biopsies = M3 and M6
- Median follow-up = 5.7 years

Wehmeier C. et al. AJT 2017; 17: 2092–2102

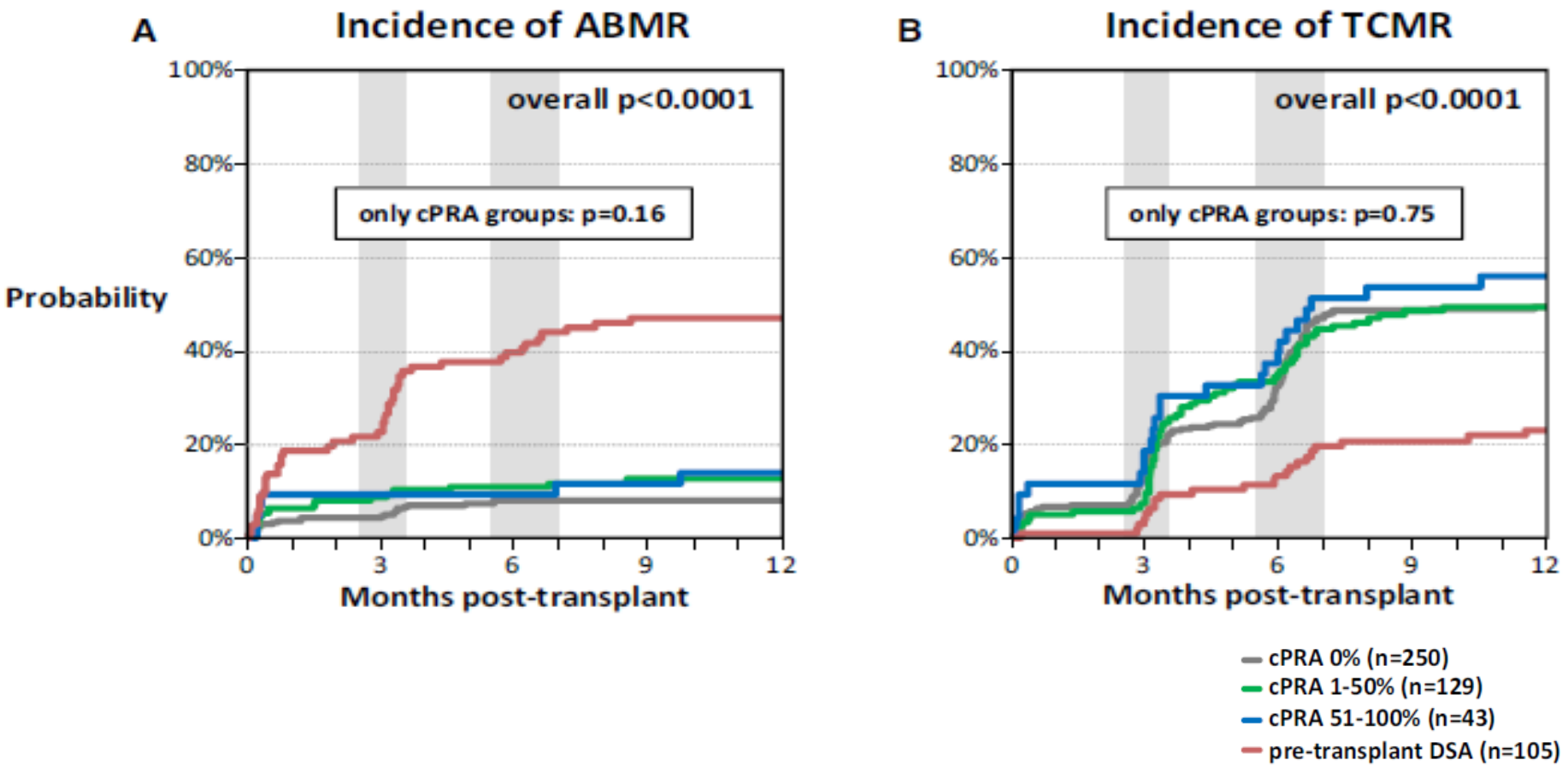
Donor Specificity but Not Broadness of Sensitization Is Associated With Antibody-Mediated Rejection and Graft Loss in Renal Allograft Recipients (2)

Distribution of calculated population-reactive antibody values among the 527 patients.



Wehmeier C. et al. AJT 2017; 17: 2092–2102

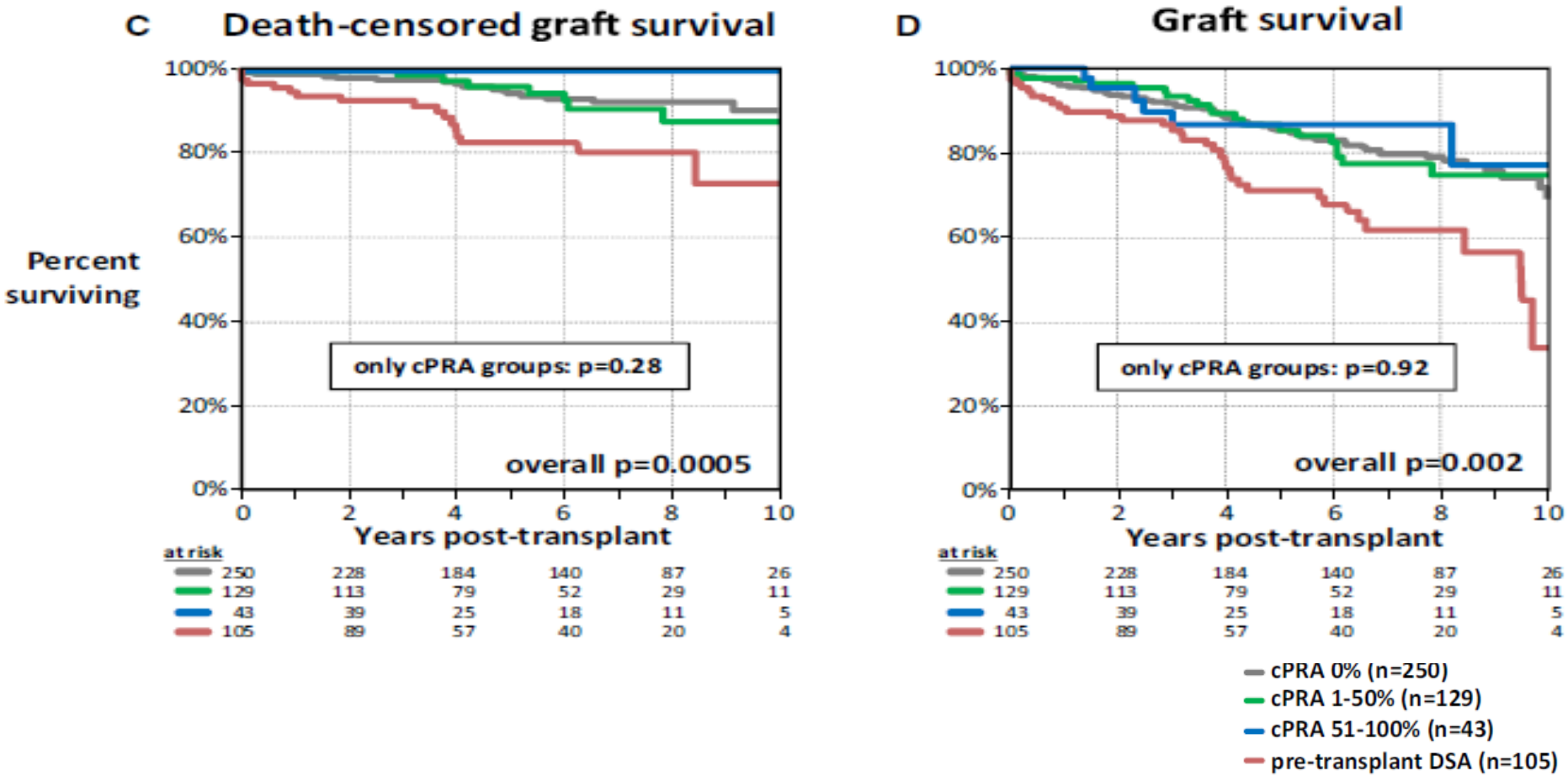
Donor Specificity but Not Broadness of Sensitization Is Associated With Antibody-Mediated Rejection and Graft Loss in Renal Allograft Recipients (3)



Major outcomes among the cPRA and the DSA groups. **(A)** Incidence of ABMR; **(B)** incidence of TCMR; antibody; DSA, donor-specific antibody; ABMR, antibody-mediated rejection; TCMR, T cell–mediated rejection.

Wehmeier C. et al., AJT 2017;17:2092-2102.

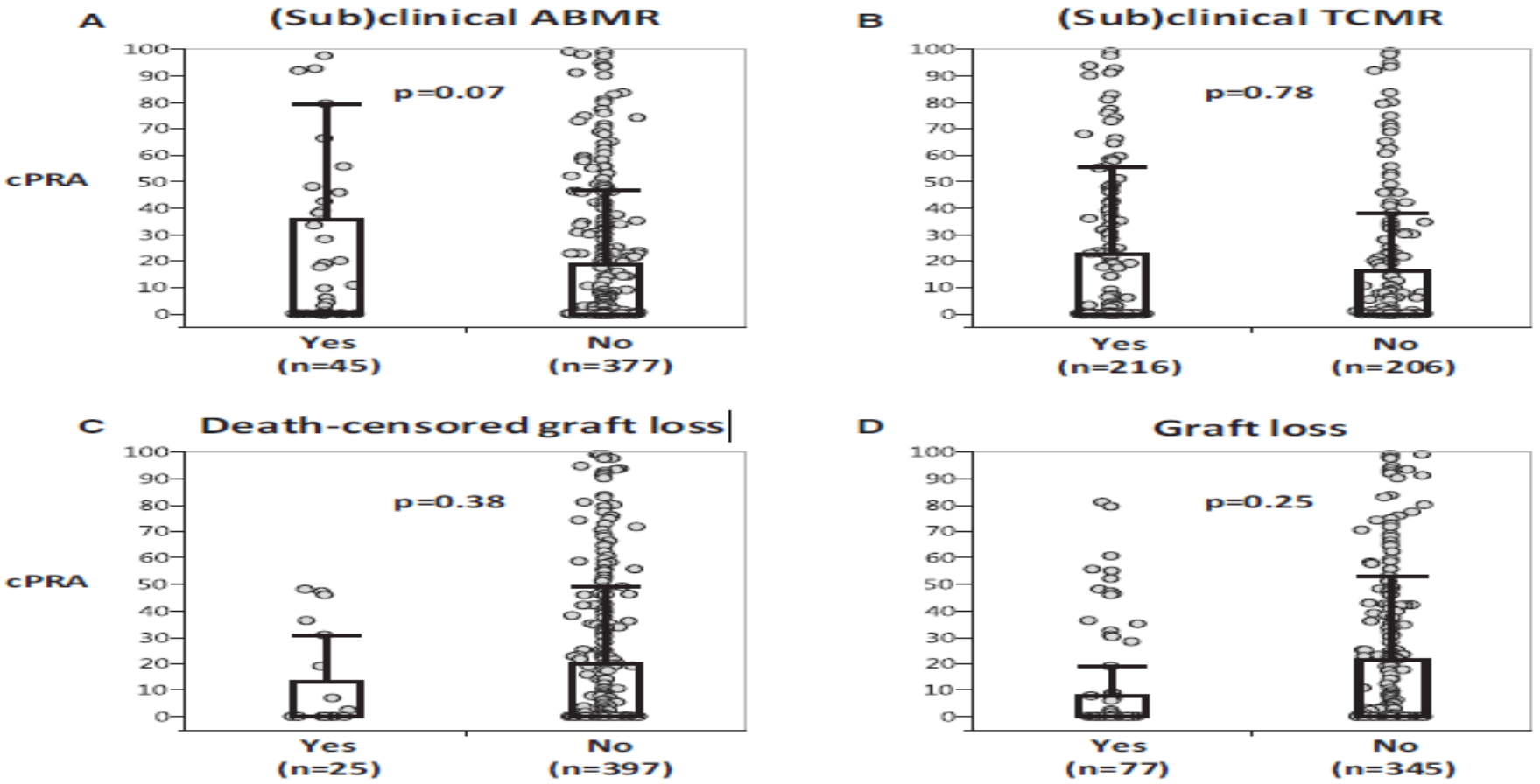
Donor Specificity but Not Broadness of Sensitization Is Associated With Antibody-Mediated Rejection and Graft Loss in Renal Allograft Recipients (4)



Major outcomes among the cPRA and the DSA groups. **(C)** death-censored graft survival; **(D)** graft survival. The gray shades in (A) and (B) represent the time frames, in which surveillance biopsies were performed. Borderline changes were included in the calculation of the incidence of TCMR. cPRA, calculated population-reactive antibody; DSA, donor-specific antibody; ABMR, antibody-mediated rejection; TCMR, T cell–mediated rejection

Wehmeier C. et al., AJT 2017;17:2092-2102.

Donor Specificity but Not Broadness of Sensitization Is Associated With Antibody-Mediated Rejection and Graft Loss in Renal Allograft Recipients (5)



Correlation of cPRA values with outcomes in patients without DSA (n = 422). (A) cPRA and presence/absence of (sub)clinical ABMR; (B) cPRA and presence/absence of (sub)clinical TCMR; (C) cPRA and occurrence of death-censored graft loss; (D) cPRA and occurrence of graft loss. cPRA, calculated population-reactive antibody; DSA, donor-specific antibody; ABMR, antibodymediated rejection; TCMR, T cell–mediated rejection.

Wehmeier C. et al., AJT 2017;17:2092-2102.

de novo DSA

Incidence and impact of DSA occurrence after 1st kidney transplantation (1)

- Single center study (Greenville, NC) including 189 consecutive, non-sensitized, non-HLA identical recipients of a 1st kidney transplantation between 1999 and 2006

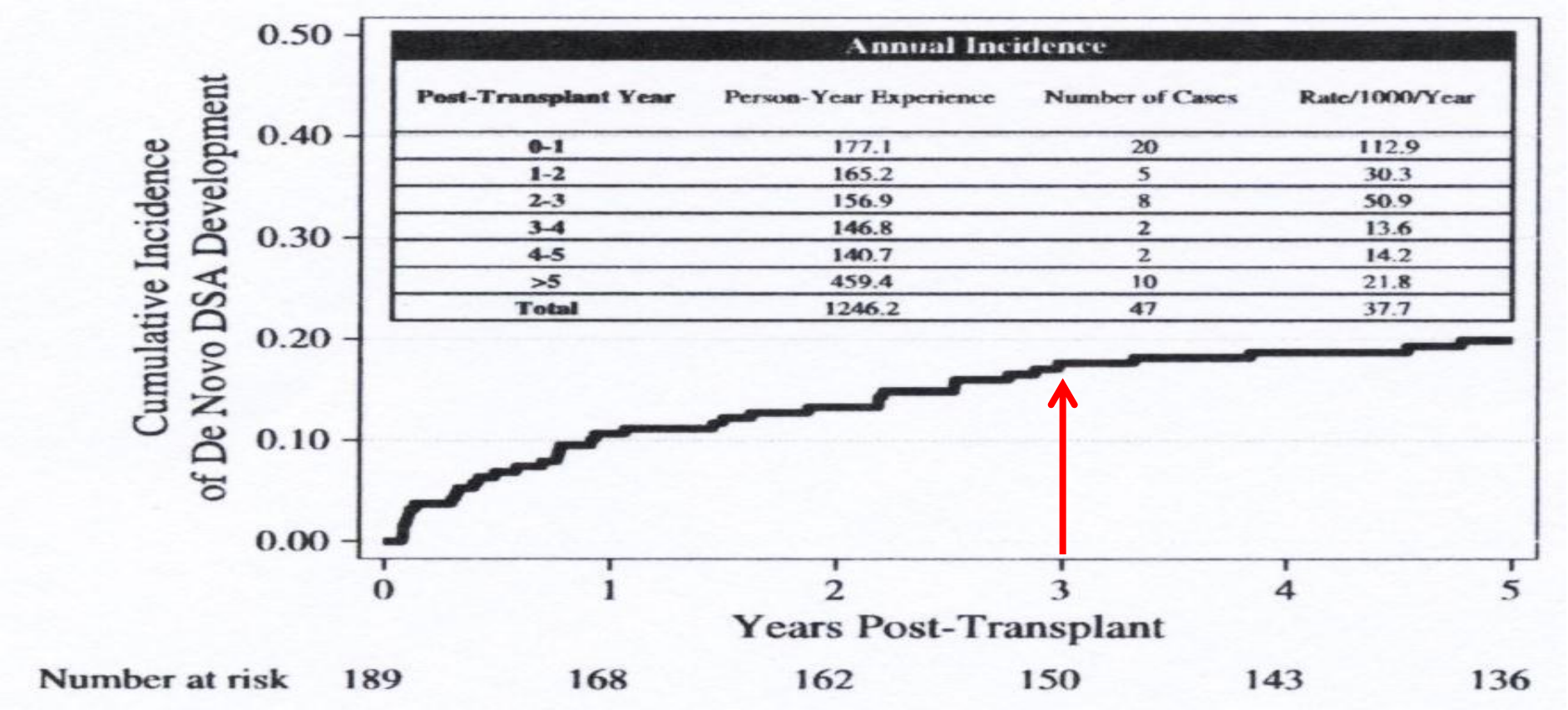
  - CNI + MPA + steroids + induction therapy (mainly daclizumab)

  - DSA assessment : M1, M3, M6, M9, M12, and then yearly

- Within a median follow-up of 92 months ***de novo*** **DSA developed in 25% of patients**

Everly MJ et al. Transplantation 2013 :95(3):410-7

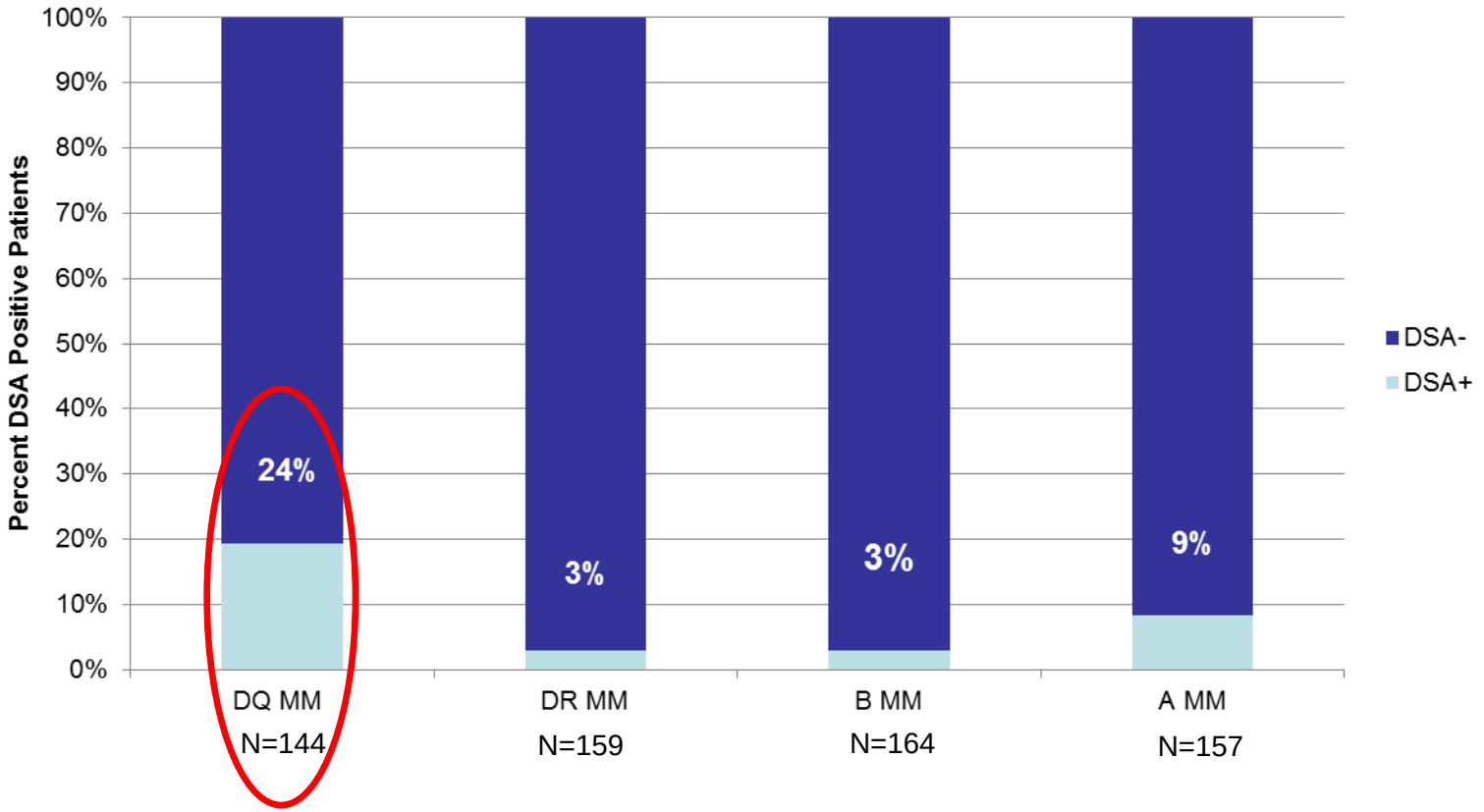
Cumulative incidence of *de novo* anti-HLA DSA



Probability of DSA development based on the year after transplantation. The highest rate of development was in the first year after transplantation.

Everly MJ et al. Transplantation 2013 :95(3):410-7

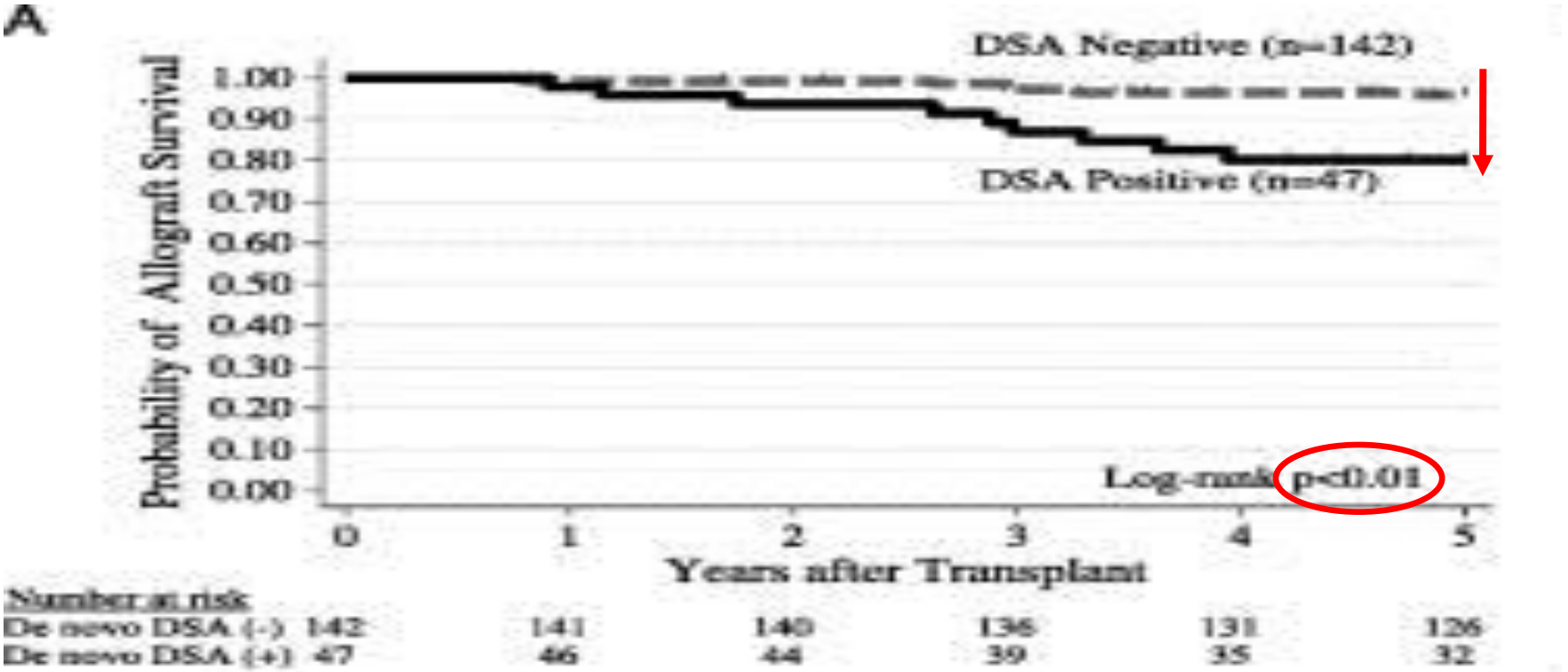
Incidence and impact of DSA occurrence after 1st kidney transplantation (1)



Number of DSAs relative to the number of mismatches for each HLA loci, indicating that **DQ DSA may be more immunogenic**.

Everly MJ et al. Transplantation 2013 :95(3):410-7

Incidence and impact of DSA occurrence after 1st kidney transplantation (2)

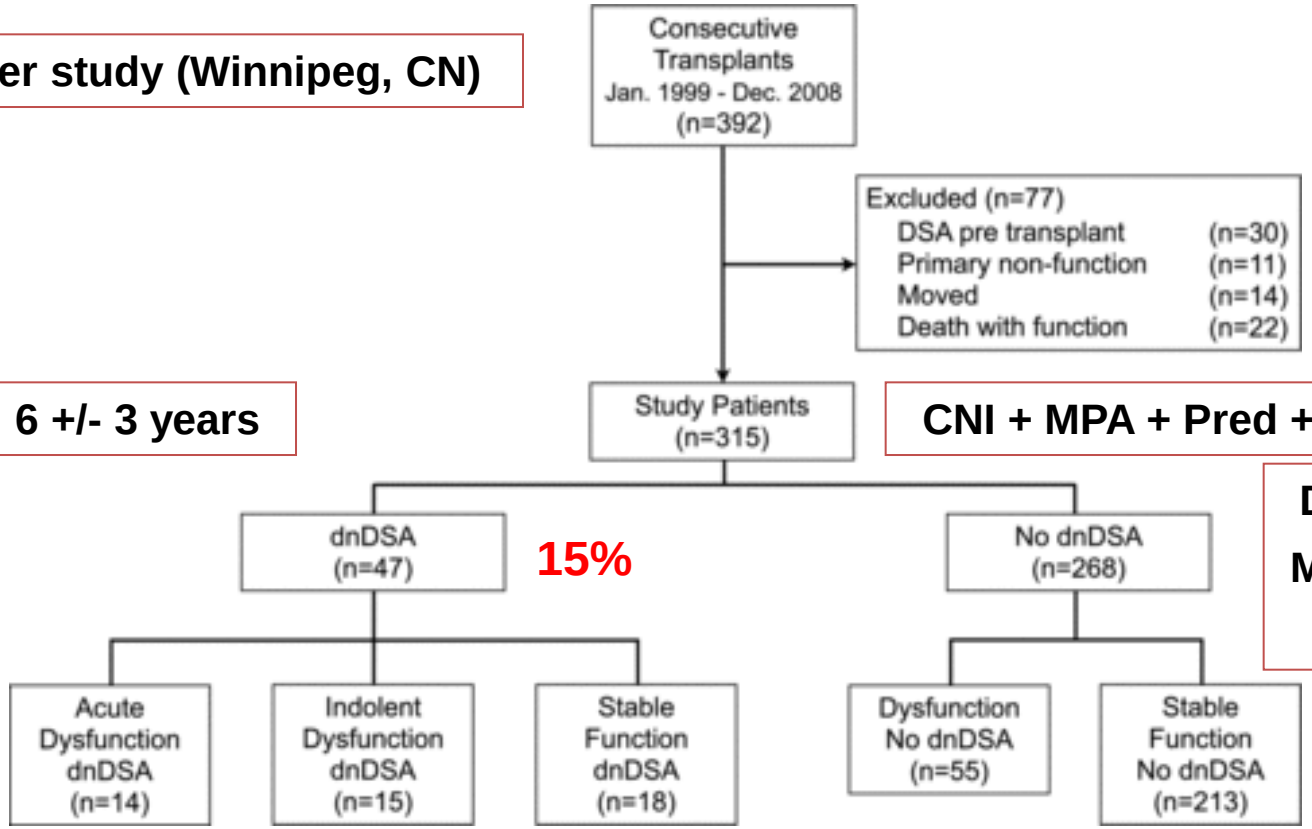


A : **actual 5-year death-censored graft survival** from the time of transplantation showing that *de novo* DSA-positive patients are at a higher risk of failure than DSA-negative patients.

Everly MJ et al. Transplantation 2013 :95(3):410-7

De novo DSA after KTx and outcome (1)

Single center study (Winnipeg, CN)



Follow-up: 6 +/- 3 years

CNI + MPA + Pred +/- induction

DSA testing: M0,1,2,3,6,12, then yearly

Wiebe C et al. AJT 2012 :12(5):1157-67

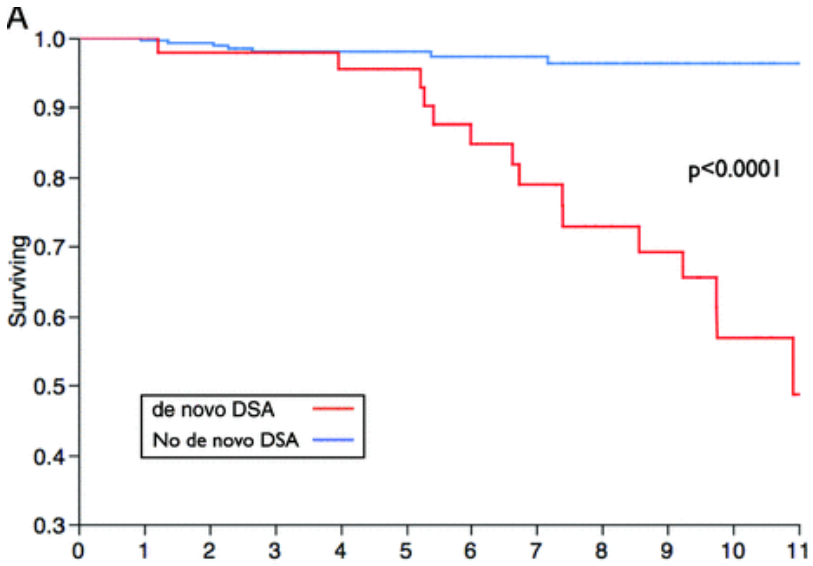
De novo DSA after KTx and outcome (2)

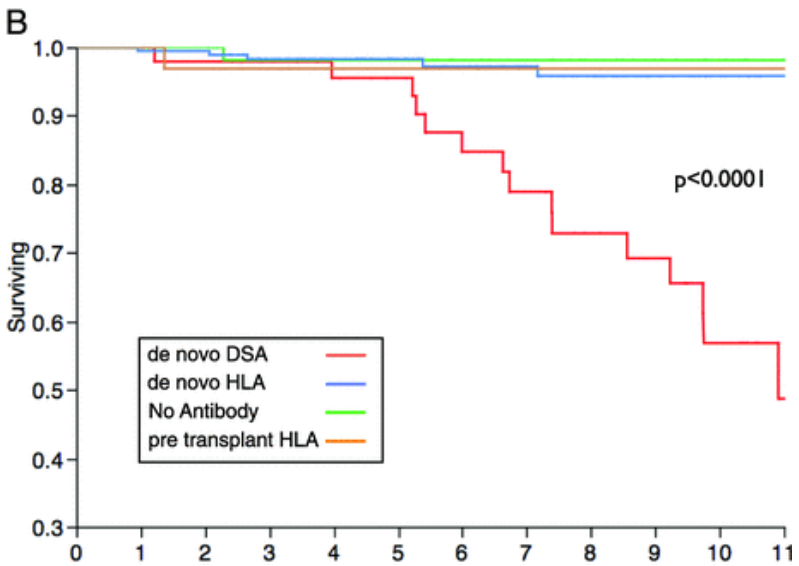
- Clinical presentation and treatment adherence in patients developing DSA

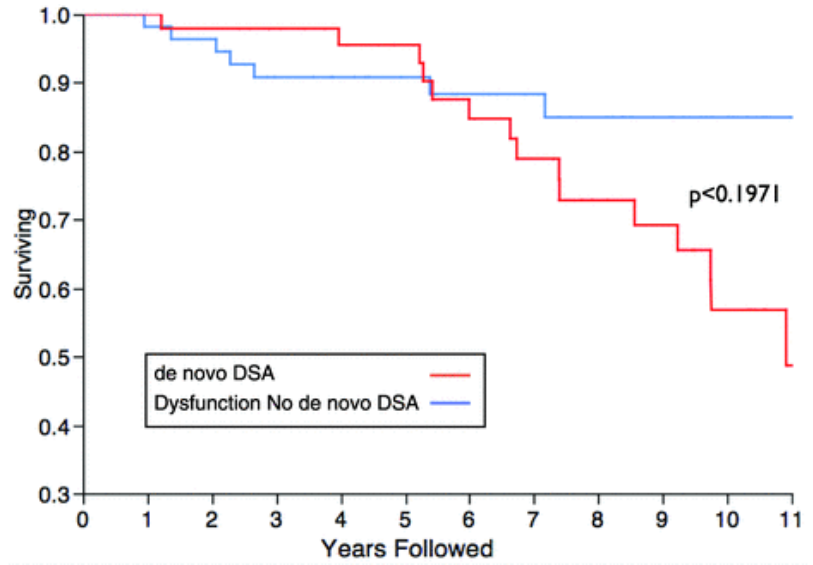
Presentation	Total	Compliant	Non compliant
Acute increase in SCr	14	0	14
Proteinuria and/or creeping SCr	17	12	5
Asymptomatic	15	15	0

Wiebe C et al. AJT 2012 :12(5):1157-67

De novo DSA after KTx and outcome: graft survival (3)







Kaplan–Meier estimates of graft survival. (A) The graft survival of patients with *de novo* donor-specific antibodies (dnDSA) versus those without. (B) The graft survival of pretransplant human leukocyte antibodies (HLA) antibodies, posttransplant *de novo* HLA antibodies, or no antibodies compared to patients with dnDSA. (C) The graft survival of those with dnDSA compared to those with dysfunction from other causes.

Wiebe C et al. AJT 2012 :12(5):1157-67

Complement-binding anti-HLA antibodies and kidney-allograft survival (1)

- Retrospective study performed in 2 kidney transplant centers in Paris (Necker and Saint-Louis) between 2005 and 2011

- 1016 KTx with various IS (based on CNIs)

  - 855 patients have had protocol kidney biopsies at 1 year (no previous AR); 171 patients have had KTx biopsy for AR

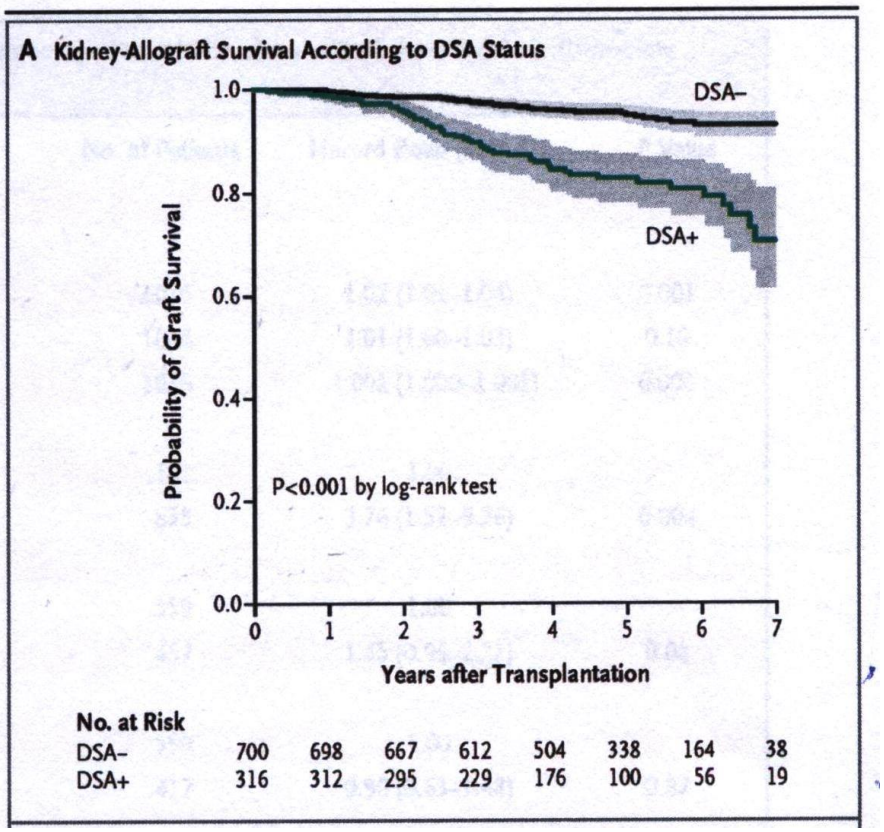
  - After transplantation 3 populations:

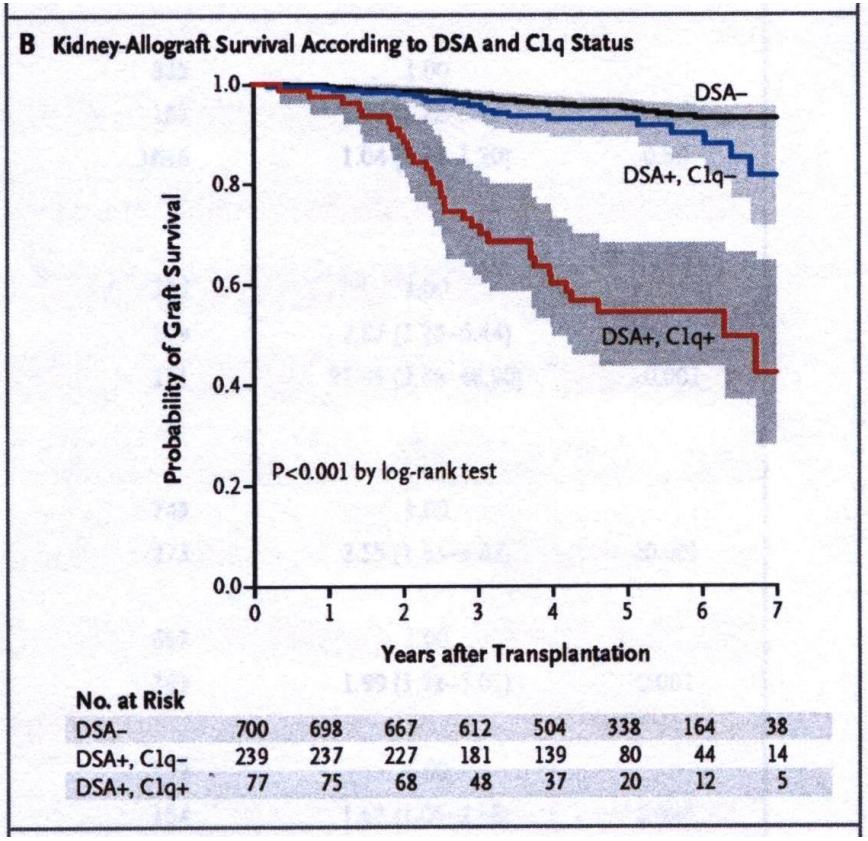
    - ✓ 700 patients without DSA
    - ✓ 239 patients with non-complement binding DSA
    - ✓ 77 patients with complement binding DSA

Loupy A et al. NEJM 2013;369:1215-1226

Complement-binding anti-HLA antibodies and kidney-allograft survival (2)

Kaplan-Meier curves for kidney-graft survival according to donor-specific anti-HLA antibody status after transplantation





Loupy A et al. NEJM 2013;369:1215-1226

Complement-binding anti-HLA antibodies and kidney-allograft survival (3)

Clinical, functional, histologic and immunologic factors associated with kidney-graft loss (multivariate analysis)*

Variable	No. of Patients	No. of Events	Hazard Ratio (95% CI)	P Value
Estimated GFR at 1 yr				
≥60 ml/min/1.73 m²	313	7	1.00	
≥30 and <60 ml/min/1.73 m²	579	36	2.45 (1.09–5.53)	
<30 ml/min/1.73 m²	111	42	12.49 (5.56–28.06)	<0.001
Interstitial fibrosis and tubular atrophy†				
Low score: 0 or 1	738	45	1.00	
High score: 2 or 3	265	40	2.22 (1.41–3.49)	0.005
Glomerular and peritubular inflammation and transplant glomerulopathy				
No	809	42	1.00	
Yes	194	43	2.26 (1.31–3.89)	0.003
C1q-binding donor-specific anti-HLA antibodies after transplantation				
No	928	52	1.00	
Yes	75	33	4.78 (2.69–8.49)	<0.001

* Risk factors were identified with the use of backward elimination, with a P value of 0.05 or lower for retention in the model.
† Banff scores range from 0 to 3, with higher scores indicating more severe abnormality.

Loupy A et al. NEJM 2013;369:1215-1226

Consensus for clinical management of DSA

	screening*** *de novo* DSA	protocol biopsy	immunological risk
DSA (-)*	3-12 month	*de novo* DSA+	low
DSA current (-) DSA historical (+)	<1 month	*de novo* DSA+	intermediate
DSA (+)**	<3 month	<3 month	high/very high

*in case of PRA0% (CDC) and DSA- allocation XM not mandatory.
Cave: actual XM- is still mandatory
**even in case of desensitization therapy
***at leat 1x / in given period

Tait BD et al, Transplantation 2013, 95, 19-47

Preformed DSA vs. de novo DSA

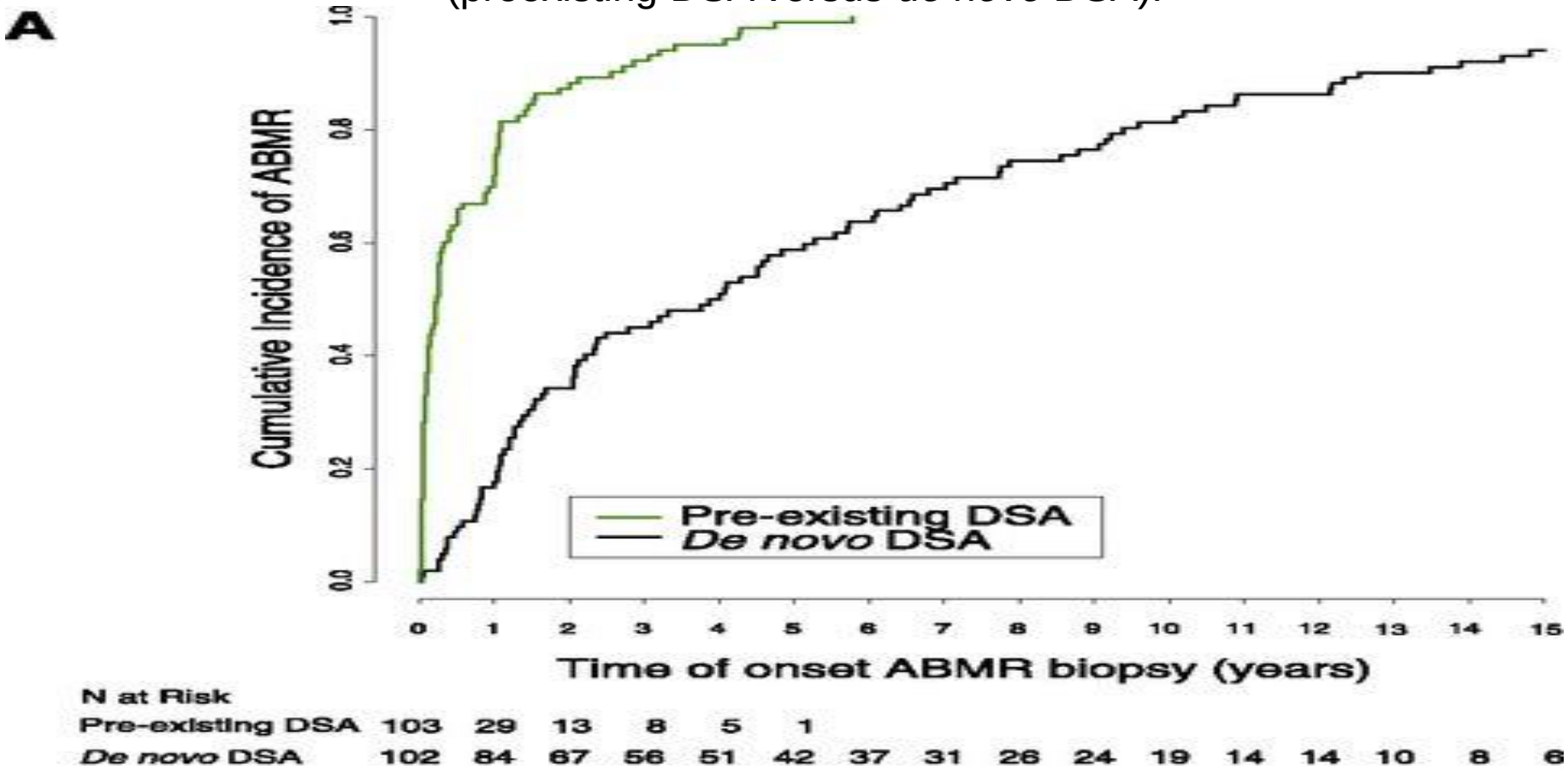
Antibody-Mediated Rejection Due to Preexisting versus *de novo* Donor-Specific Antibodies in Kidney Allograft Recipients (1)

- Multicenter-retrospective study (Paris and North America)
  - 771 kidney biopsies for cause
    - 205 had ABMR of which 103 (50.2%) had pre-existing DSA and 102 (49.8%) had *de novo* DSA
    - Histopathology; immunohistochemistry; gene allograft expression

Aubert O, et al. JASN 2017 ;28:1912-1923

Antibody-Mediated Rejection Due to Preexisting versus *de novo* Donor-Specific Antibodies in Kidney Allograft Recipients (2)

(A) Cumulative incidence of **onset ABMR** according to the DSA characteristics (preexisting DSA versus *de novo* DSA).



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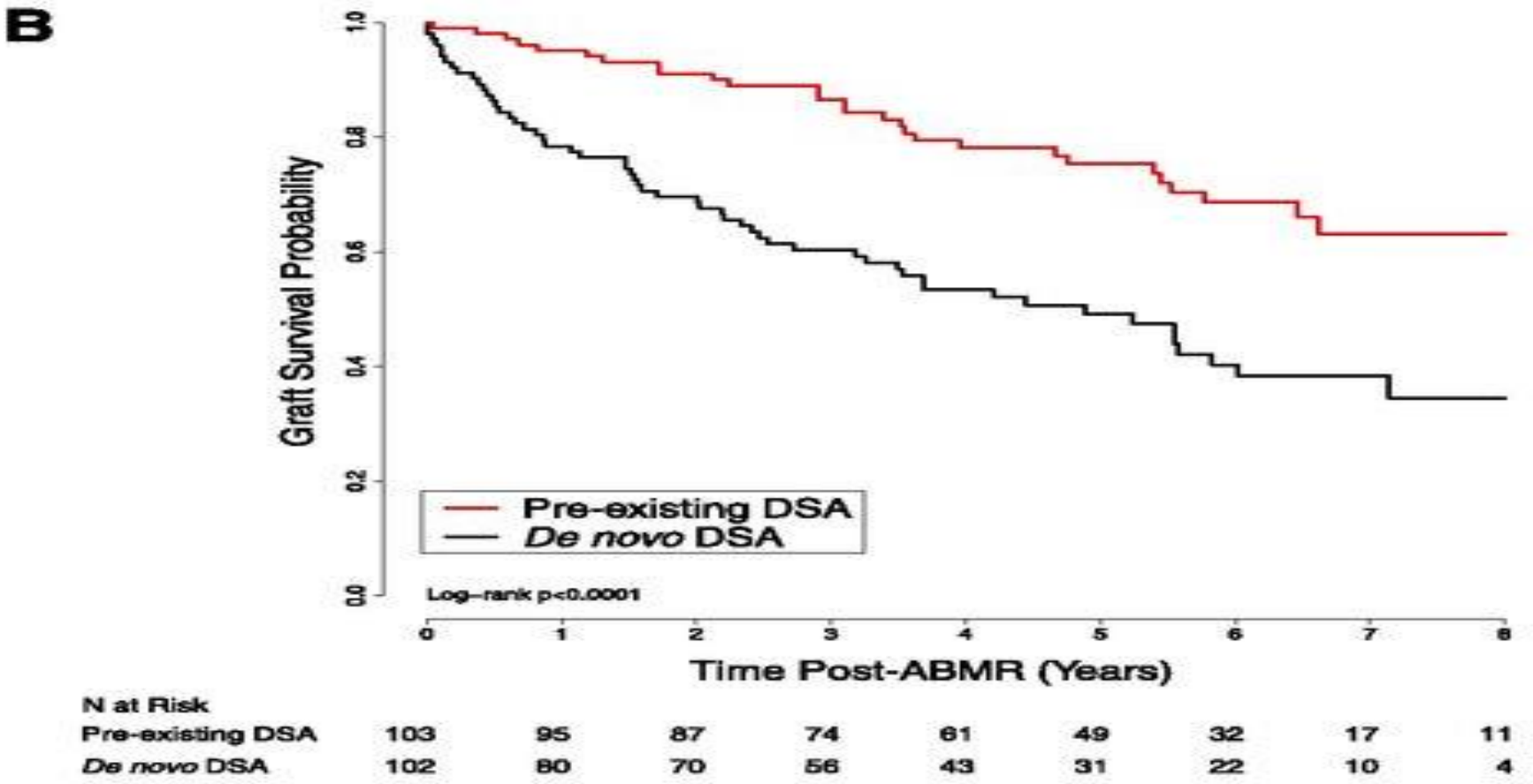
Antibody-Mediated Rejection Due to Preexisting versus *de novo* Donor-Specific Antibodies in Kidney Allograft Recipients (3)

(B) Probability of **graft survival** on the basis of DSA characteristics.



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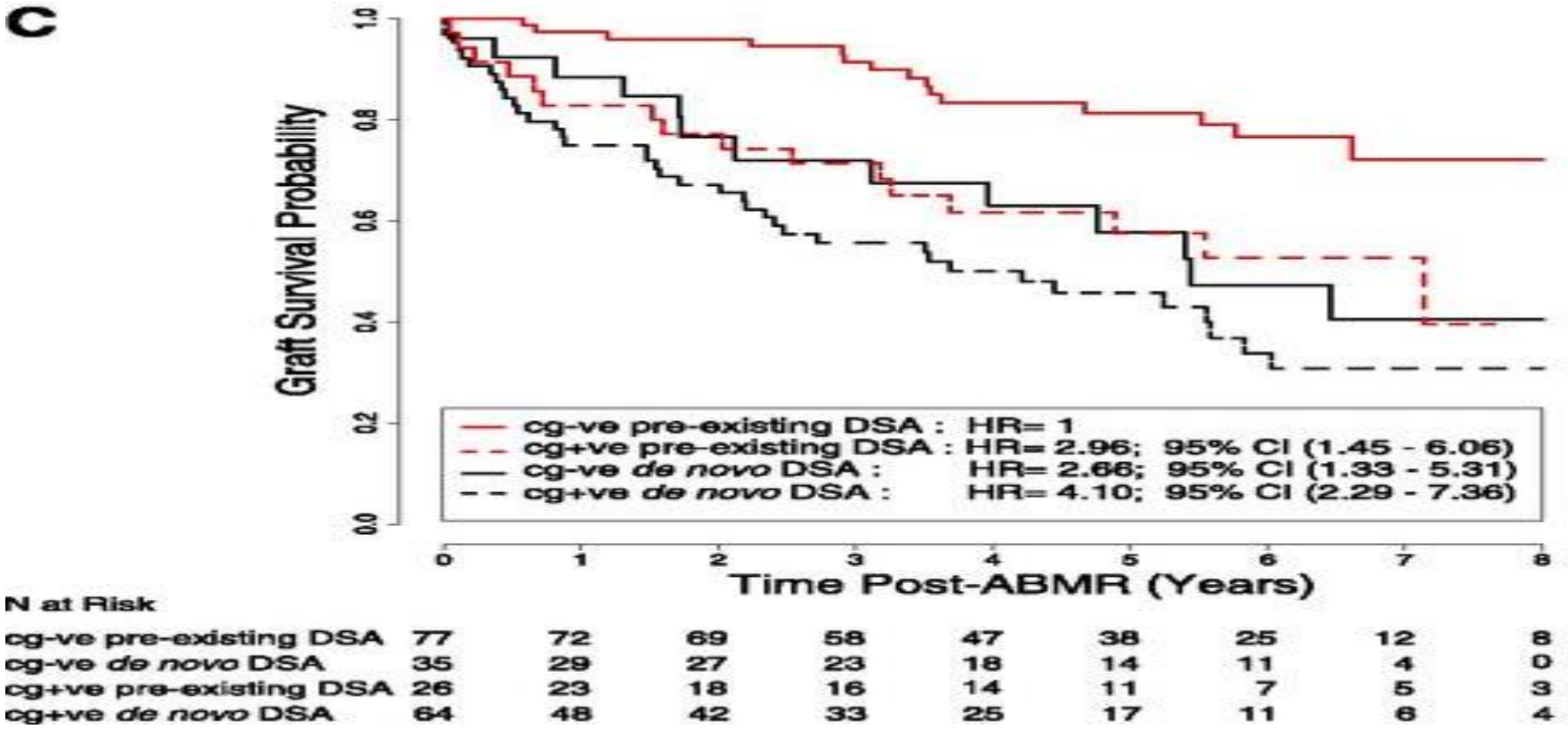
Antibody-Mediated Rejection Due to Preexisting versus *de novo* Donor-Specific Antibodies in Kidney Allograft Recipients (4)

(C) Probability of graft survival according to the DSA characteristics and the presence or absence of cg lesions. cg+ve, cg-positive; cg-ve, cg-negative.



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Antibody-Mediated Rejection Due to Preexisting versus *de novo* Donor-Specific Antibodies in Kidney Allograft Recipients (5)

Histology, DSA, and renal function at the time of ABMR-proven biopsy

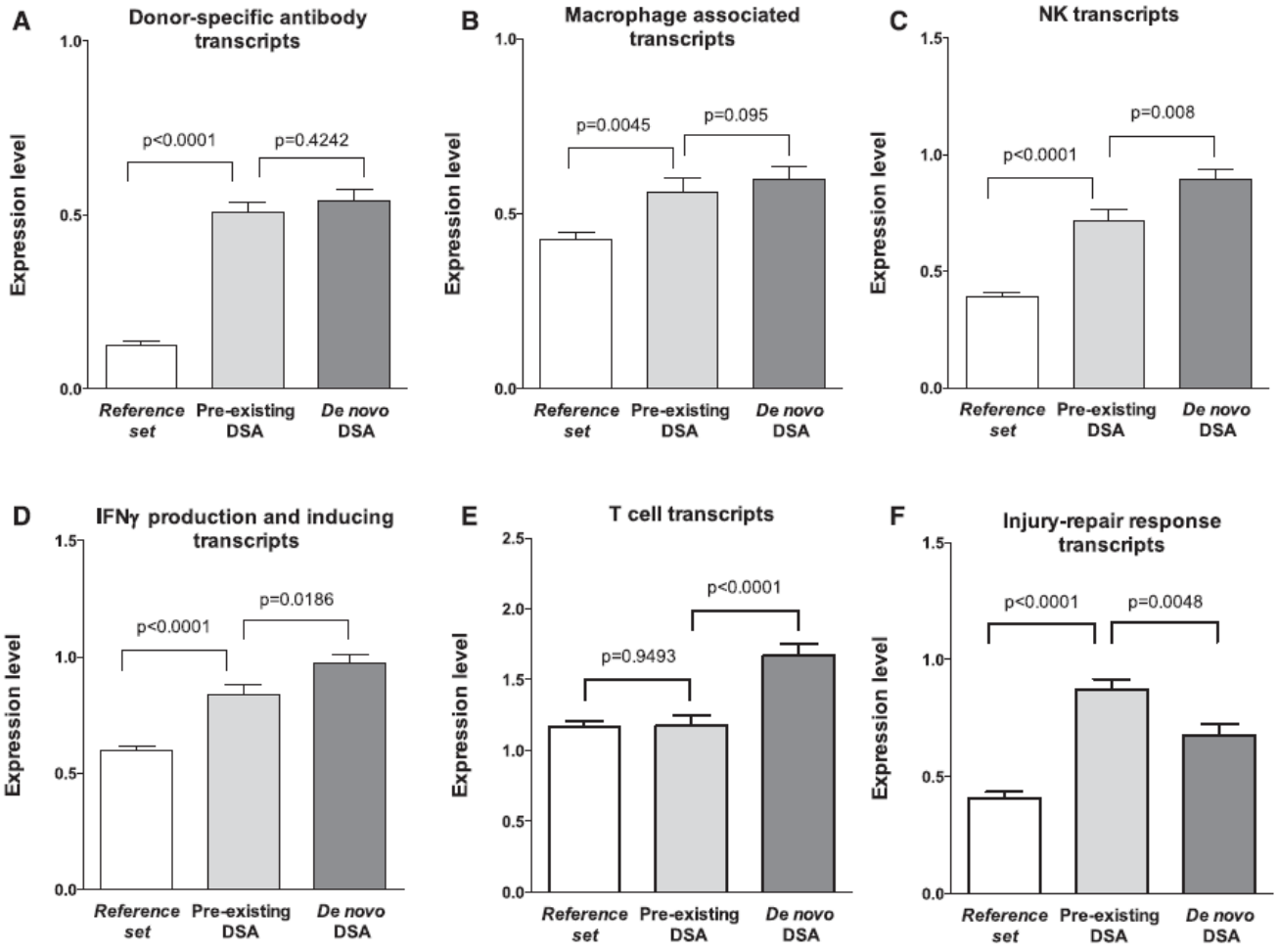
Parameters	Preexisting Anti-HLA DSA ABMR (*n*=103)	*De Novo* Anti-HLA DSA ABMR (*n*=102)	*P* Value
Histology			
g (0–3), mean (SD)	1.71 (1.02)	1.06 (0.91)	<0.001
ptc (0–3), mean (SD)	1.76 (0.98)	1.66 (1.00)	0.47
C4d positive, *n* (%)	53 (51.46)	39 (42.39)	0.13
cg (0–3), mean (SD)	0.48 (0.94)	1.28 (1.15)	<0.001
i (0–3), mean (SD)	0.61 (0.92)	1.23 (1.01)	<0.001
t (0–3), mean (SD)	0.59 (0.90)	1.01 (1.11)	0.003
v (0–3), mean (SD)	0.32 (0.65)	0.22 (0.60)	0.29
ci (0–3), mean (SD)	0.96 (1.04)	1.60 (0.92)	<0.001
ct (0–3), mean (SD)	0.99 (0.99)	1.60 (0.91)	<0.001
cv (0–3), mean (SD)	1.26 (1.00)	1.44 (0.98)	0.2
ah (0–3), mean (SD)	0.97 (0.92)	1.53 (1.05)	<0.001
Immunology at the time of the ABMR biopsy			
Anti-HLA DSA class 1, *n* (%)	40 (38.83)	26 (25.49)	
Anti-HLA DSA class 2, *n* (%)	63 (61.17)	76 (74.51)	0.02
Anti-HLA DSA MFI, median [IQR]	2561 [1252–6937]	7295 [1948–11,814]	<0.001
Renal function			
eGFR, ml/min per 1.73 m^2, mean (SD)	39.00±18.26	41.65±21.19	0.34
Proteinuria, g/g creatinine, mean (SD)	0.51±1.05	1.51±2.51	<0.001

g, glomerulitis; ptc, peritubular capillaritis; cg, transplant glomerulopathy; i, interstitial inflammation; t, tubulitis; v, endarteritis; ci, interstitial fibrosis; ct, tubular atrophy; cv, arteriosclerosis; ah, arteriolar hyaline thickening; MFI, mean fluorescence intensity.

Aubert T. et al, JASN 2017;28:1912–1923

Antibody-Mediated Rejection Due to Preexisting versus *de novo* Donor-Specific Antibodies in Kidney Allograft Recipients (6)

Molecular biopsy scores according to DSA characteristics.



Data are on the basis of **666 kidney allograft biopsies assessed for intragraft gene expression of the PBTs** ([A] endothelialDSA-selective transcripts, [B]macrophage-inducible transcripts, [C] natural killer cell [NK] transcripts, [D] IFNg production and inducing transcripts, [E] T cell transcripts, [F] injury–repair response transcripts) according to circulating anti-HLA DSA and ABMR status (reference set without ABMR, preexisting DSA ABMR, and de novo DSA ABMR).

Aubert T. et al, JASN 2017;28:1912–1923

Antibody-Mediated Rejection Due to Preexisting versus *de novo* Donor-Specific Antibodies in Kidney Allograft Recipients (7)

Factors associated with kidney allograft loss in the multivariate analysis

Factors		No. of patients	No. of events	HR	95% CI	*P* Value	Internal Validation HR 95% CI Bootstrap BCA
GFR, ml/min per 1.73 m^2	≥60	29	8	1	—		—
	30–60	105	37	1.30	(0.60 to 2.82)		
	<30	60	32	3.27	(1.48 to 7.23)	<0.001	(1.31 to 3.21)
Proteinuria, g/g creatinine	<0.30	96	22	1	—		—
	≥0.30	98	55	2.44	(1.47 to 4.09)	<0.001	(1.53 to 4.31)
DSA characteristic	Preexisting DSA	101	28	1	—		—
	De novo DSA	93	49	1.82	(1.07 to 3.08)	0.03	(1.01 to 3.28)
Transplant glomerulopathy (cg) score	Low score: 0	109	29	1	—		—
	High score ≥1	85	48	2.25	(1.34 to 3.79)	0.002	(1.19 to 3.81)

The final multivariate Cox model was obtained by entering the risk factors from the univariate model that achieved $P \leq 0.10$ as the thresholds in a single multivariate proportional hazards model. The final multivariate model was adjusted for the following parameters: recipient's sex, donor's sex, DD, GFR, proteinuria, DSA characteristics, interstitial fibrosis and tubular atrophy, C4d deposition, transplant glomerulopathy, hyalinosis, solumedrol, and plasmapheresis. BCA, Bias-corrected and accelerated bootstrap; —, no 95% CI.

Aubert T. et al, JASN 2017;28:1912–1923

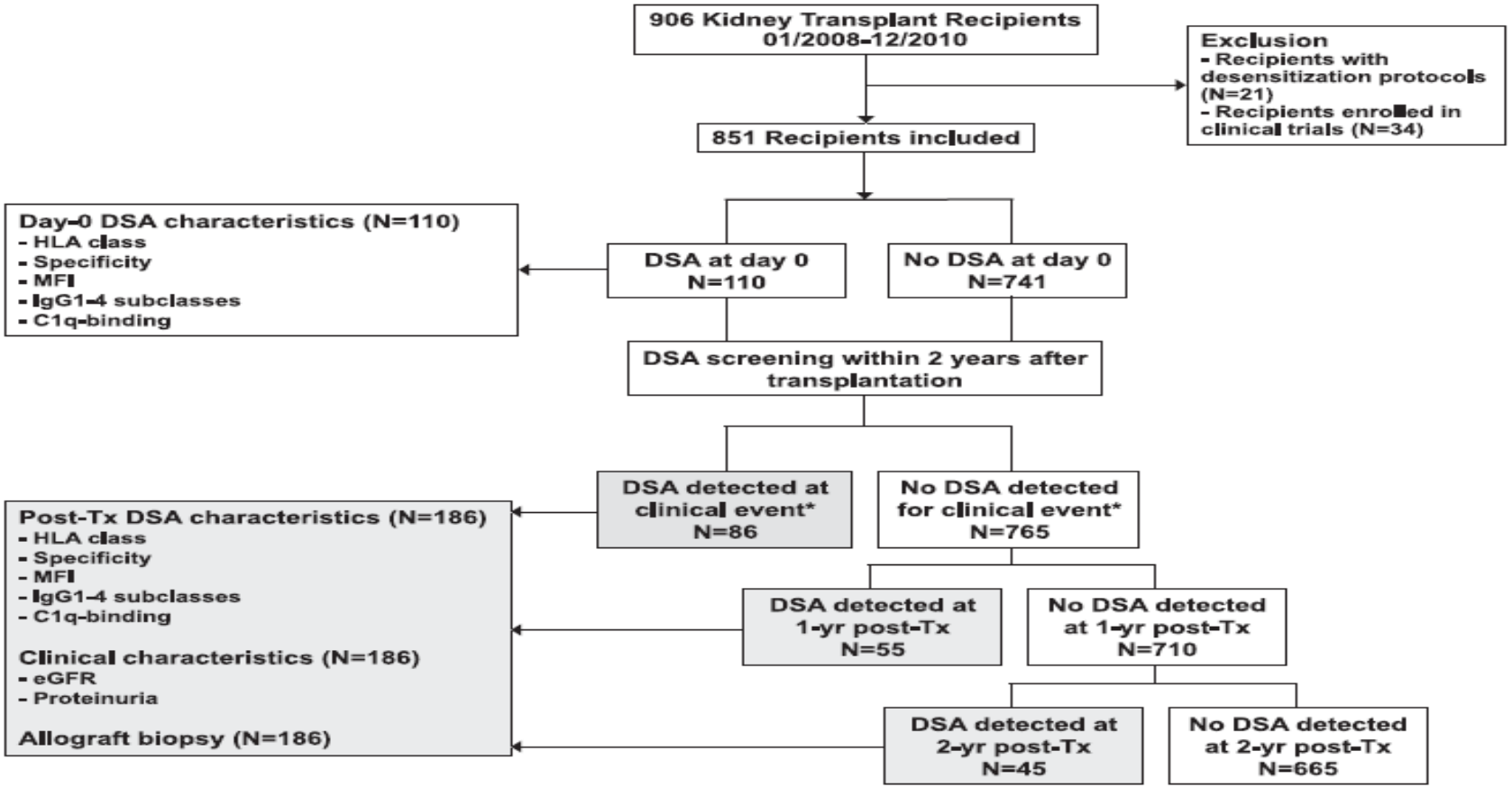
Value of Donor–Specific Anti–HLA Antibody Monitoring and Characterization for Risk Stratification of Kidney Allograft Loss (1)

- Value of systematic monitoring of DSA with extensive characterization (C1q binding / IgG subclasses) to predict kidney allograft loss
  - 851 KTx (2008-2010 in Paris)
    - DSA screening at transplant ; Y1 ; Y2
    - Protocol biopsies

Viglietti D, et al. JASN 2017; 28:702–715

Value of Donor–Specific Anti–HLA Antibody Monitoring and Characterization for Risk Stratification of Kidney Allograft Loss (2)

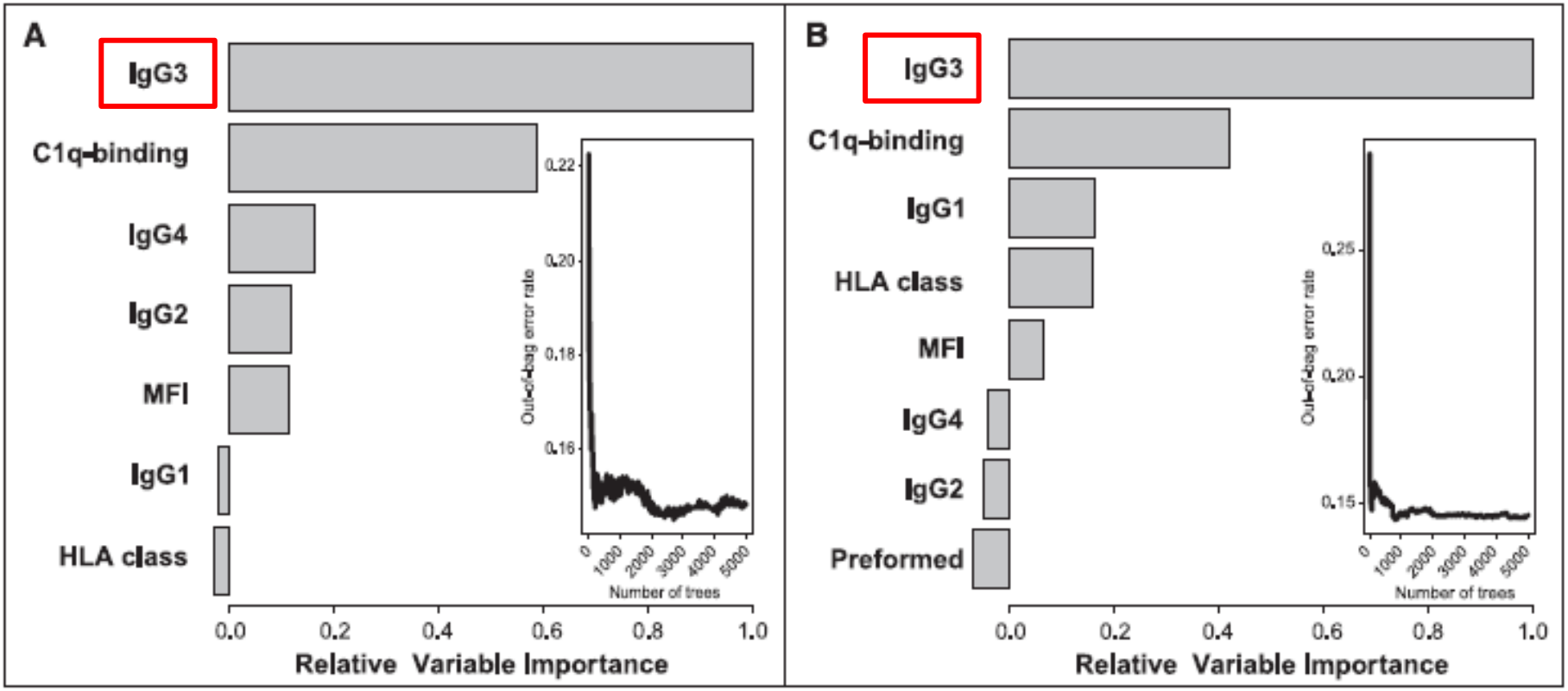
Prospective post-transplant anti-HLA DSA screening using single-antigen Luminex technique identified 110/851 (12.9%) patients with circulating anti–HLA DSA at the time of transplantation and 186/851 (21.9%) patients with circulating anti-HLA DSA after transplantation.



Viglietti D, et al. JASN 2017; 28:702–715

Value of Donor–Specific Anti–HLA Antibody Monitoring and Characterization for Risk Stratification of Kidney Allograft Loss (3)

Hierarchical ranking of anti–HLA iDSA characteristics on the basis of their ability **to classify patients according to their risk of allograft loss** using random survival forest modeling. **(A)** At the time of transplantation (n=110). **(B)** Post-transplantation (n=186).



Viglietti D, et al. JASN 2017; 28:702–715

Value of Donor–Specific Anti–HLA Antibody Monitoring and Characterization for Risk Stratification of Kidney Allograft Loss (4)

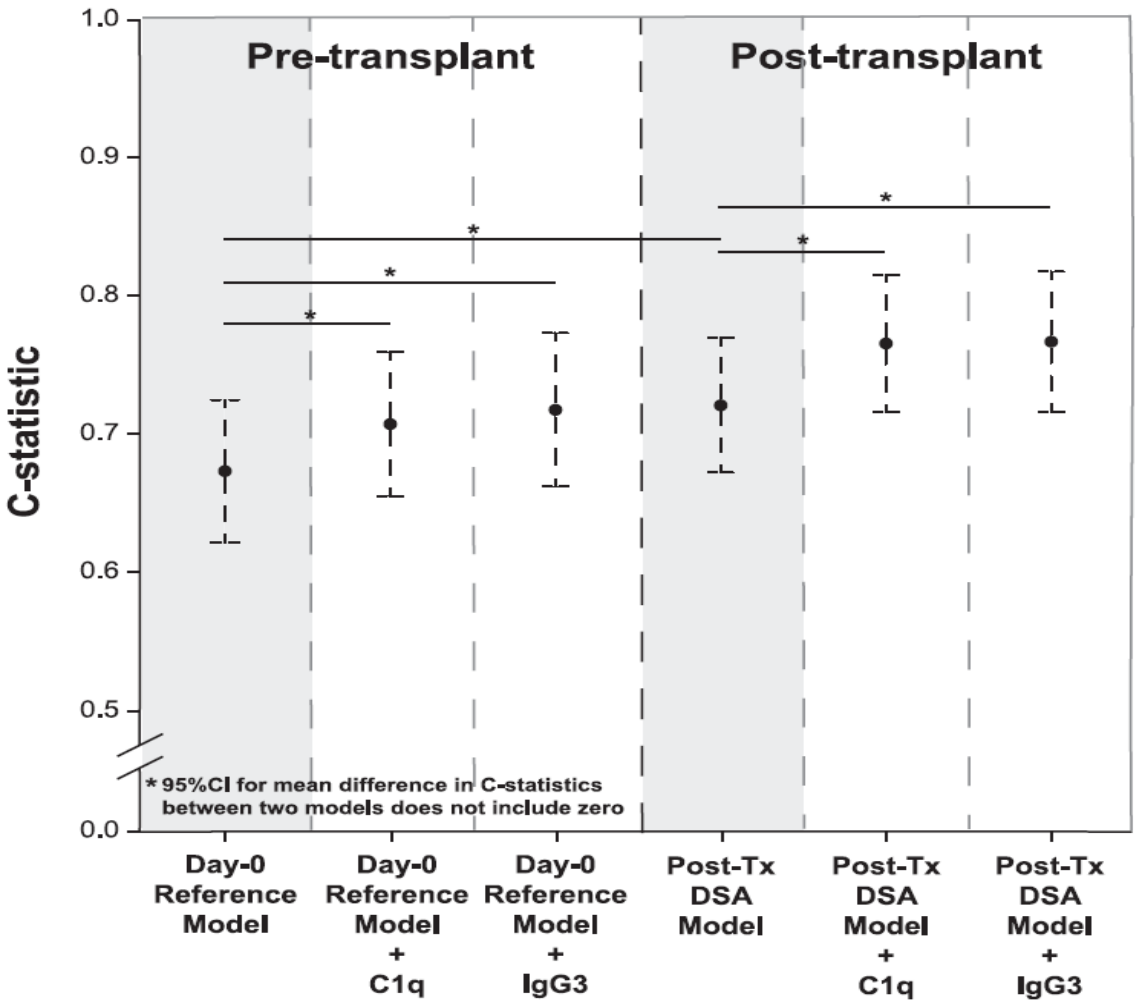
Performance of anti-HLA DSA, IgG3–positive anti–HLA iDSA, and C1q binding anti–HLA iDSA to predict clinical and subclinical ABMR in an unselected population of kidney transplant recipients (n=851)

Measures of Diagnostic Accuracy	Day 0 DSA, %	Day 0 IgG3 DSA, %	Day 0 C1q DSA, %	Post-Transplant DSA, %	Post-Transplant IgG3 DSA, %	Post-Transplant C1q DSA, %
Clinical ABMR						
Sensitivity	55.4	33.8	32.3	100	58.5	52.3
Specificity	91.0	98.9	98.2	84.6	99.5	97.1
PPV	32.7	71.0	60.0	34.9	90.5	59.6
NPV	96.1	94.8	94.6	100	96.7	96.1
Subclinical ABMR						
Sensitivity	49.3	4.5	11.9	100	4.5	29.9
Specificity	90.2	96.4	96.6	84.8	95.0	95.3
PPV	30.0	9.7	22.9	35.5	7.1	35.1
NPV	95.4	92.2	92.8	100	92.1	94.1

PPV, positive predictive value; NPV, negative predictive value.

Viglietti D, et al. JASN 2017; 28:702–715

Value of Donor–Specific Anti–HLA Antibody Monitoring and Characterization for Risk Stratification of Kidney Allograft Loss (5)



Predictive value for allograft loss of a strategy on the basis of a systematic monitoring of anti-HLA DSAs and integration of anti–HLA DSA characteristics in an unselected population of kidney transplant recipients (n=851). Predictive value for allograft loss was assessed by Cox model Harrell c statistics in the overall study population (n=851). Day 0 anti–HLA DSA characteristics (IgG3 positivity and C1q binding) were added to the day 0 reference model, which was on the basis of a conventional strategy. Post–transplant anti–HLA DSA characteristics (IgG3 positivity and C1q binding) were added to the post–Tx DSA model. In the day 0 reference model and the post–Tx DSA model, anti-HLA DSAs were detected using the single–antigen Luminex technique. **A c statistic of 0.5 indicated that the model is no better than chance at predicting membership in a group, and a value of one indicates that the model perfectly identifies those within a group and those not in a group.**

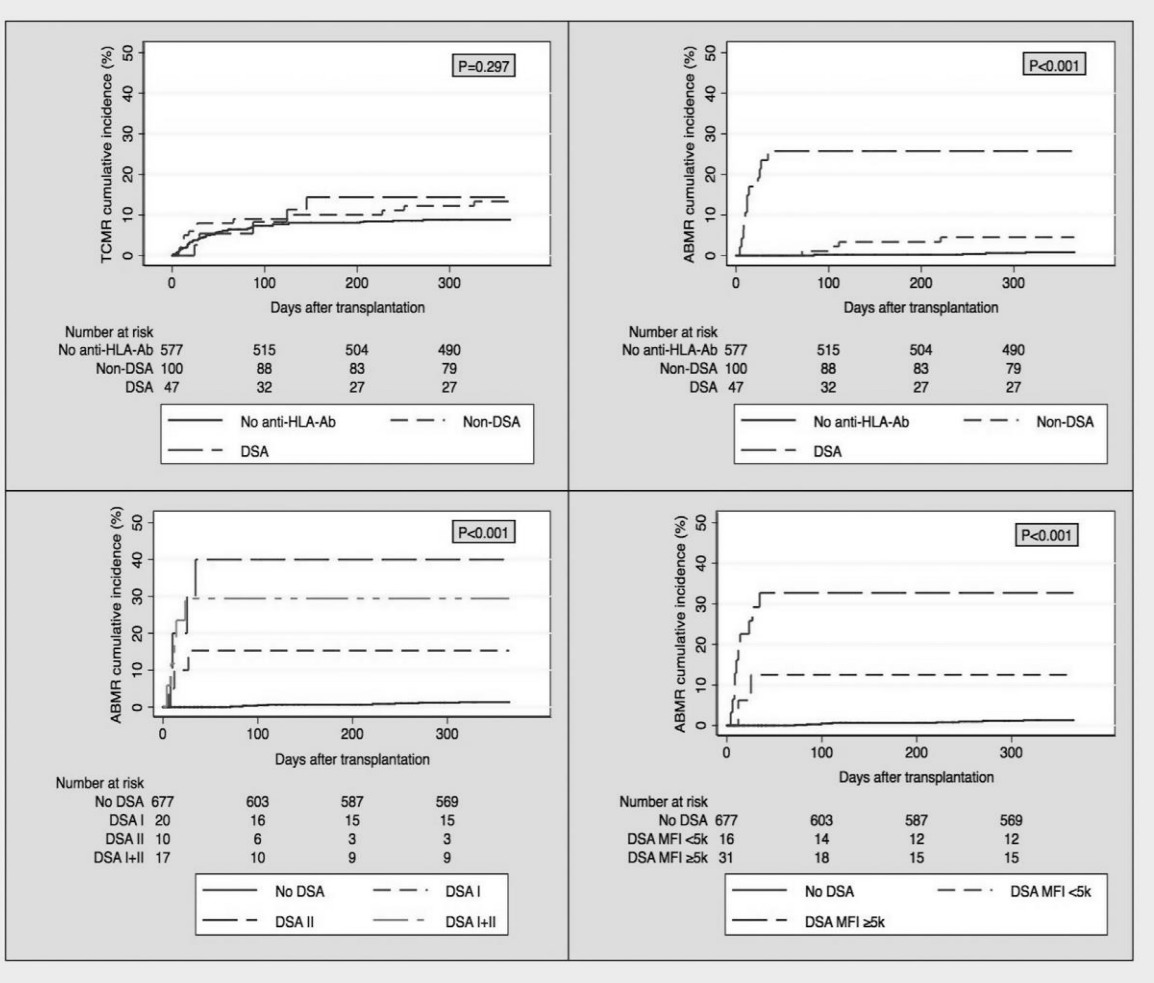
Viglietti D, et al. JASN 2017; 28:702–715

Impact on mid-term kidney graft outcomes of pre-transplant anti-HLA antibodies detected by solid-phase assays: Do donor-specific antibodies tell the whole Story? (1)

- Single –center study on 724 KTx
  - Evaluation of the impact of pretransplant anti-HLA alloantibodies (donor-specific = DSA, and non-donor specific - NDSA -) on allograft failure
  - Negative impact of pretransplant DSA and NDSA except in those having had ATG induction

Malheiro J, et al. Human Immunol. 2017:78 526–533

Impact on mid-term kidney graft outcomes of pre-transplant anti-HLA antibodies detected by solid-phase assays: Do donor-specific antibodies tell the whole Story? (2)



Acute rejection cumulative incidence 1-year after transplantation**. Top left: TCMR incidence by anti-HLA antibodies status** (No anti-HLA antibodies 8.7%, Non-DSA 13.0%, DSA 10.6%); No anti-HLA antibodies vs. Non-DSA P = 0.166, No anti-HLA antibodies vs. DSA P = 0.373, Non-DSA vs. DSA P = 0.991. **Top right: ABMR incidence by anti-HLA antibodies status** (No anti-HLA antibodies 0.7%, Non-DSA 4.0%, DSA 25.5%); No anti-HLA antibodies vs. Non-DSA P = 0.004, No anti-HLA antibodies vs. DSA P < 0.001, Non-
DSA vs. DSA P < 0.001. Bottom left: ABMR incidence by DSA presence and class (No DSA 1.2%, DSA I 15.0%, DSA II 40.0%, DSA I + II 29.4%); No DSA vs. DSA I P < 0.001, No DSA vs.DSA II P < 0.001, No DSA vs. DSA I + II P < 0.001, DSA I vs. DSA II P = 0.146, DSA I vs. DSA I + II P = 0.288, DSA II vs. DSA I + II P = 0.665. **Bottom right: ABMR incidence by DSA presence and MFI** (No DSA 1.2%, DSA MFI < 5 k 12.5%, DSA MFI 5 k 32.3%); No DSA vs. DSA MFI < 5 k P < 0.001, No DSA vs. DSA 5 k P < 0.001, DSA MFI < 5 k vs. DSA MFI 5 k P = 0.134. (P-values for overall comparisons are presented in the graphs).

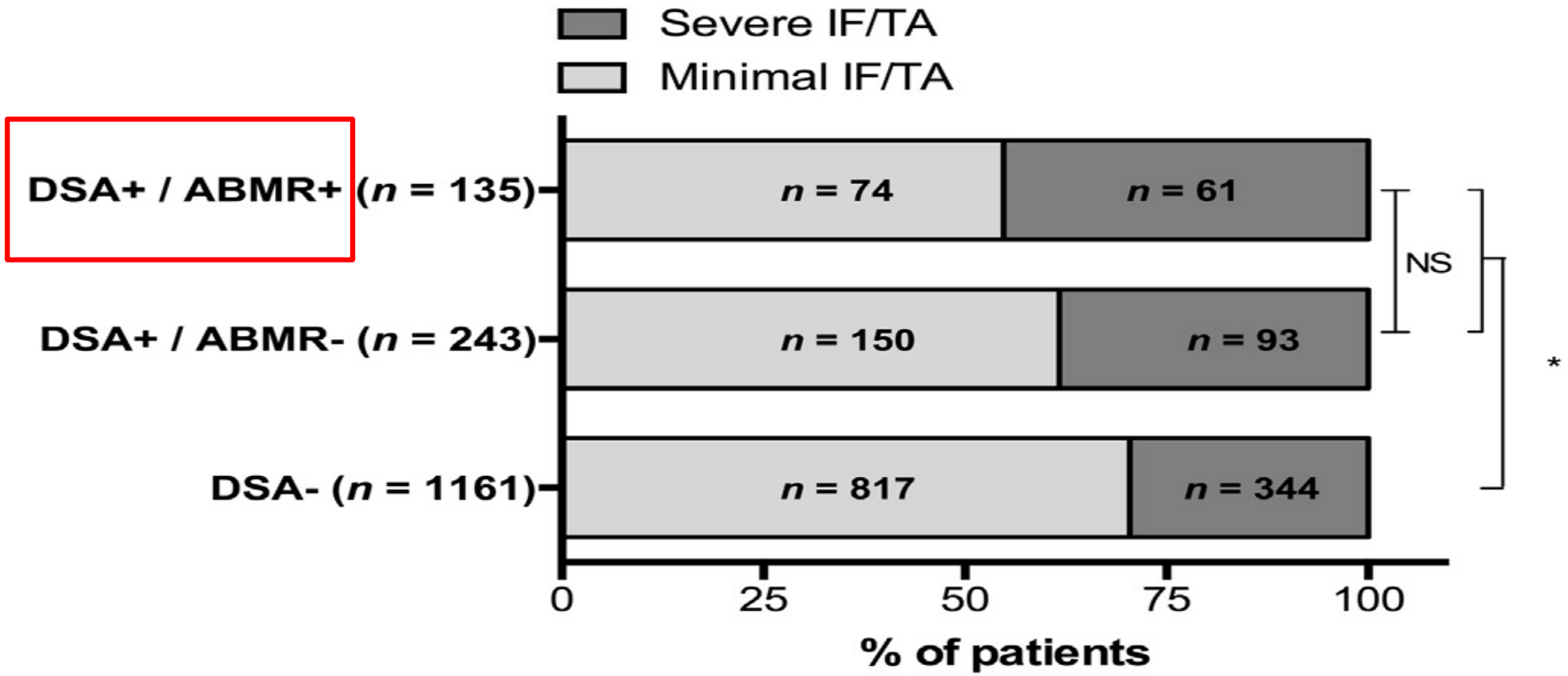
Malheiro J, et al. Human Immunol. 2017:78 526–533

Circulating donor-specific anti-HLA antibodies are a major factor in premature and accelerated allograft fibrosis (1)

- Two-center study (Paris) including 1539 *de novo* KTx patients that have had 1-year protocol kidney biopsy
  - Assessment of interstitial fibrosis/tubular atrophy (IF/TA) and correlation with DSA
  - 498 (32%) patients had severe IF/TA (>=2)
  - Significant correlation between IF/TA and DSA even after excluding patients with AMBR.

Gosset C, et al. Kidney Int. 2017; 92: 729–742

Circulating donor-specific anti-HLA antibodies are a major factor in premature and accelerated allograft fibrosis (2)



Distribution of patients according to anti-human leukocyte antigen donor-specific antibody (anti-HLA-DSA) status, the occurrence of antibody-mediated rejection (ABMR) within the first year posttransplantation, and the severity of interstitial fibrosis/tubular atrophy (IF/TA) at 1 year posttransplantation.
*P < 0.001. NS, nonsignificant.

Gosset C, et al. Kidney Int. 2017; 92: 729–742

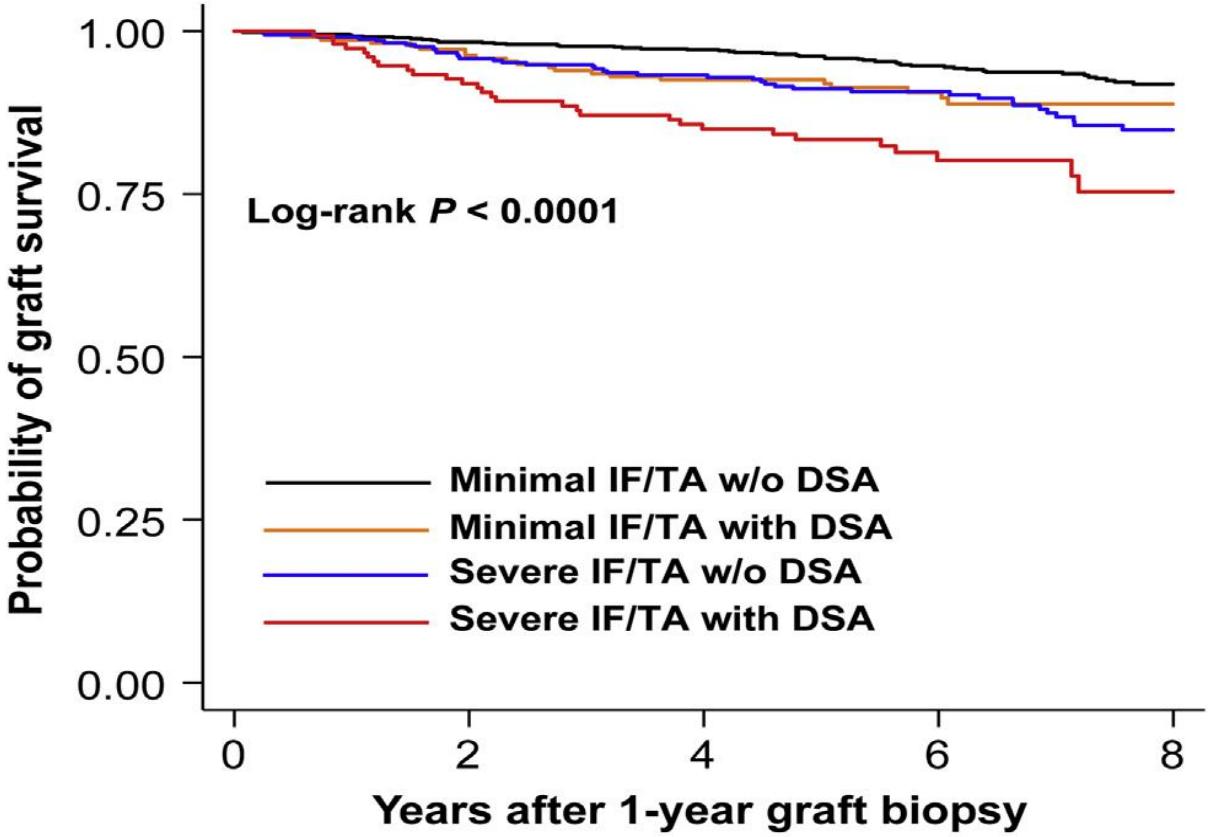
Circulating donor-specific anti-HLA antibodies are a major factor in premature and accelerated allograft fibrosis (3)

Population-attributable fractions for modifiable risk factors of severe IF/TA at 1 year posttransplantation

	PAF, %	95% CI
Anti-HLA-DSAs	10.5	4.8–16.0
TCMR	9.4	6.3–12.3
CNI toxicity	8.0	1.5–14.0
ATN	6.4	2.0–10.7
Pyelonephritis	4.7	0.2–9.0
BKVAN	3.7	2.5–4.8

Gosset C, et al. Kidney Int. 2017; 92: 729–742

Circulating donor-specific anti-HLA antibodies are a major factor in premature and accelerated allograft fibrosis (4)



Number at risk					
Minimal IF/TA w/o DSA	817	766	718	515	271
Minimal IF/TA with DSA	224	209	191	104	23
Severe IF/TA w/o DSA	344	314	280	188	95
Severe IF/TA with DSA	154	134	119	66	16

Kaplan-Meier estimates for **death-censored kidney allograft survival according to 1-year** posttransplantation interstitial fibrosis and tubular atrophy (IF/TA) severity and antihuman leukocyte antigen donor-specific antibody (DSA) status (n =1539)

Gosset C, et al. Kidney Int. 2017; 92: 729–742

A patient

- 32 y old young man
- IgA nephropathy; grafted in 2010
- No antibodies at transplantation
- Maintenance IS: Tac (trough levels: 4-6ng/mL +MMF)
- Particularities: very unstable trough levels needing multiple adjustments

HLA Ab at 6 y post tx

Dépistage des anticorps anti-HLA de classe I et II

Technique Luminex, Kit LM-HLA Class I/II DeLuxe Screening (Immucor) *Ant*

Référence du kit : 3002066-LMX

Dépistage luminex classe I	**négatif**	nég
Dépistage luminex classe II	**positif**	nég

Le sérum de votre patient est mis en sérothèque.

Identification des antigènes HLA de classe II en haute définition

Technique Luminex, Kit LSA Class II (Immucor)

Référence du kit: 08304C-SA2

HLA II interdits (BCM 1500-10000)	**DQ7 DQ8 DQ9**
HLA II interdits (BCM < 1500)	**DR11**
BCM (MFI) le plus élevé du HD2	2120

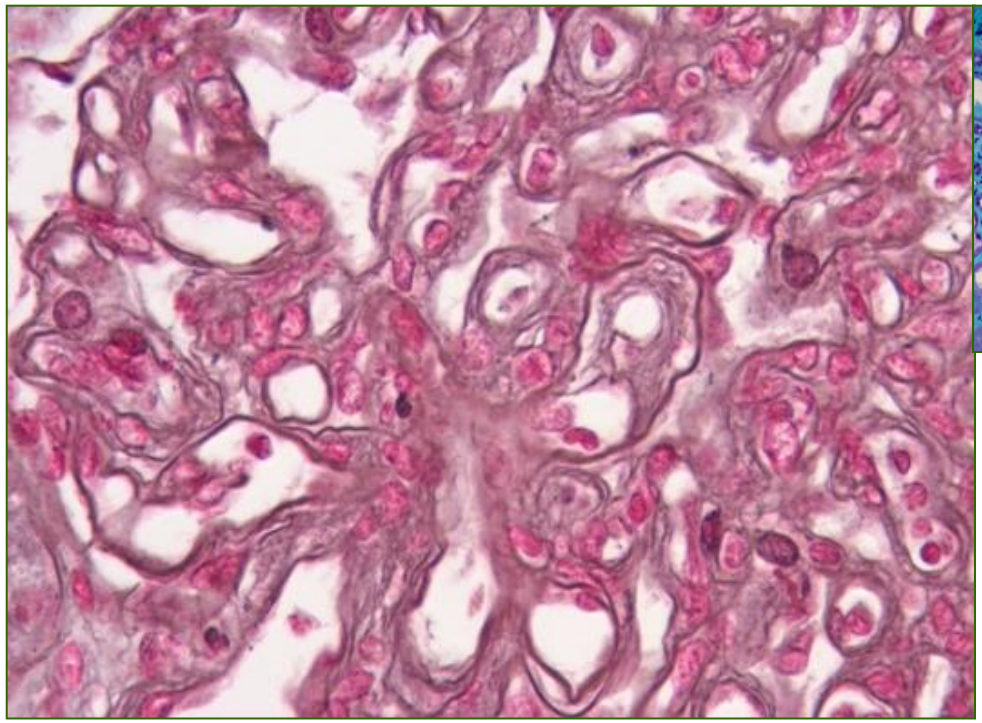
GREFFE 1 le 07/03/10 A1 A2 B7 B8 DR11 DR15 DQ6 DQ7

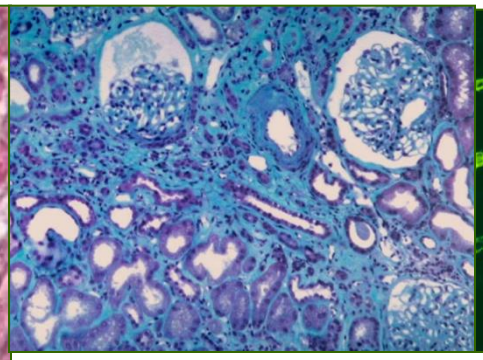
AG mismatch A1 B7 B8 DR11 DQ7

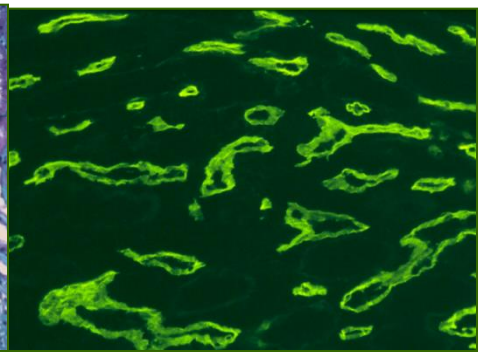
Commentaires : Bilan annuel post greffe : apparition de DSA DQ7 et DR11 en limite de positivité

Active chronic humoral rejection *(category 2)*

❑ **Histological lesions :**



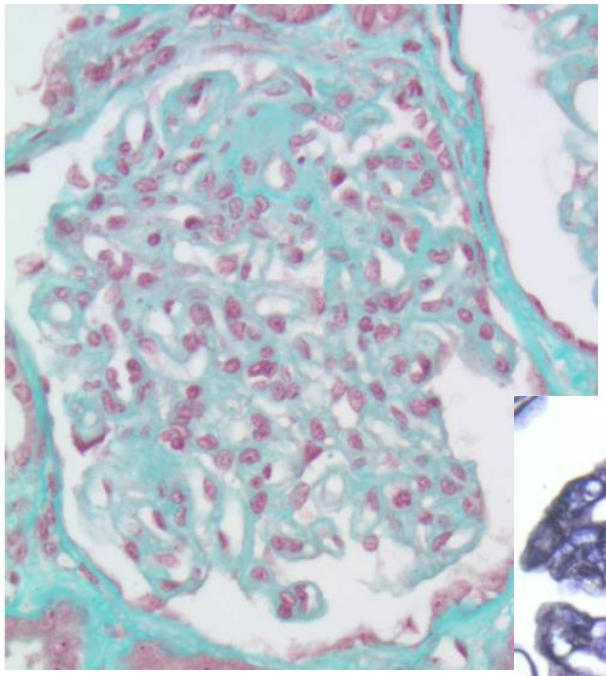


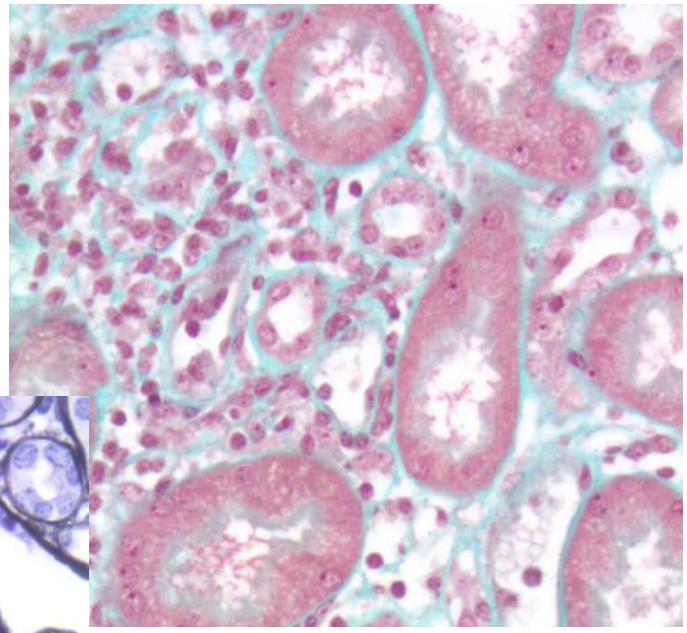


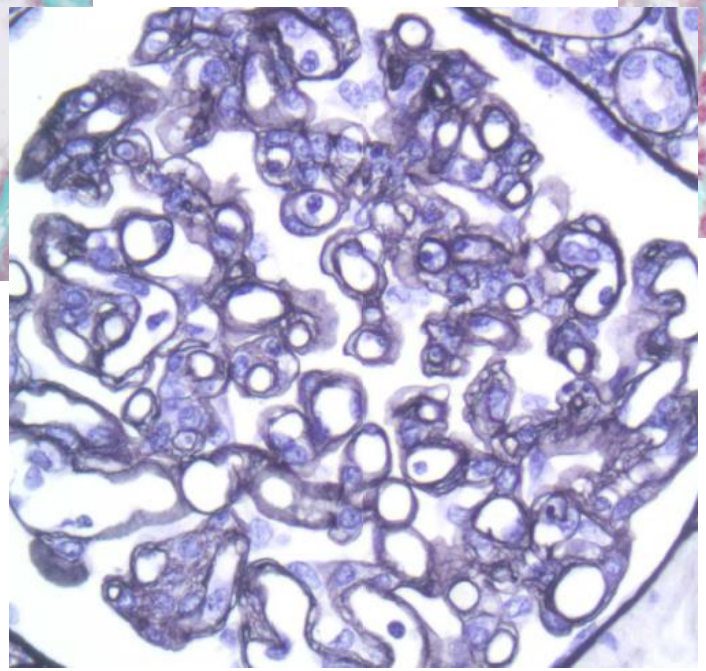
❑ **diffuse C4d+** (>50% of PTC)

❑ **circulating DSA+**
« suspicion de RHCA »
en l'absence d'anticorps anti-donneur circulants

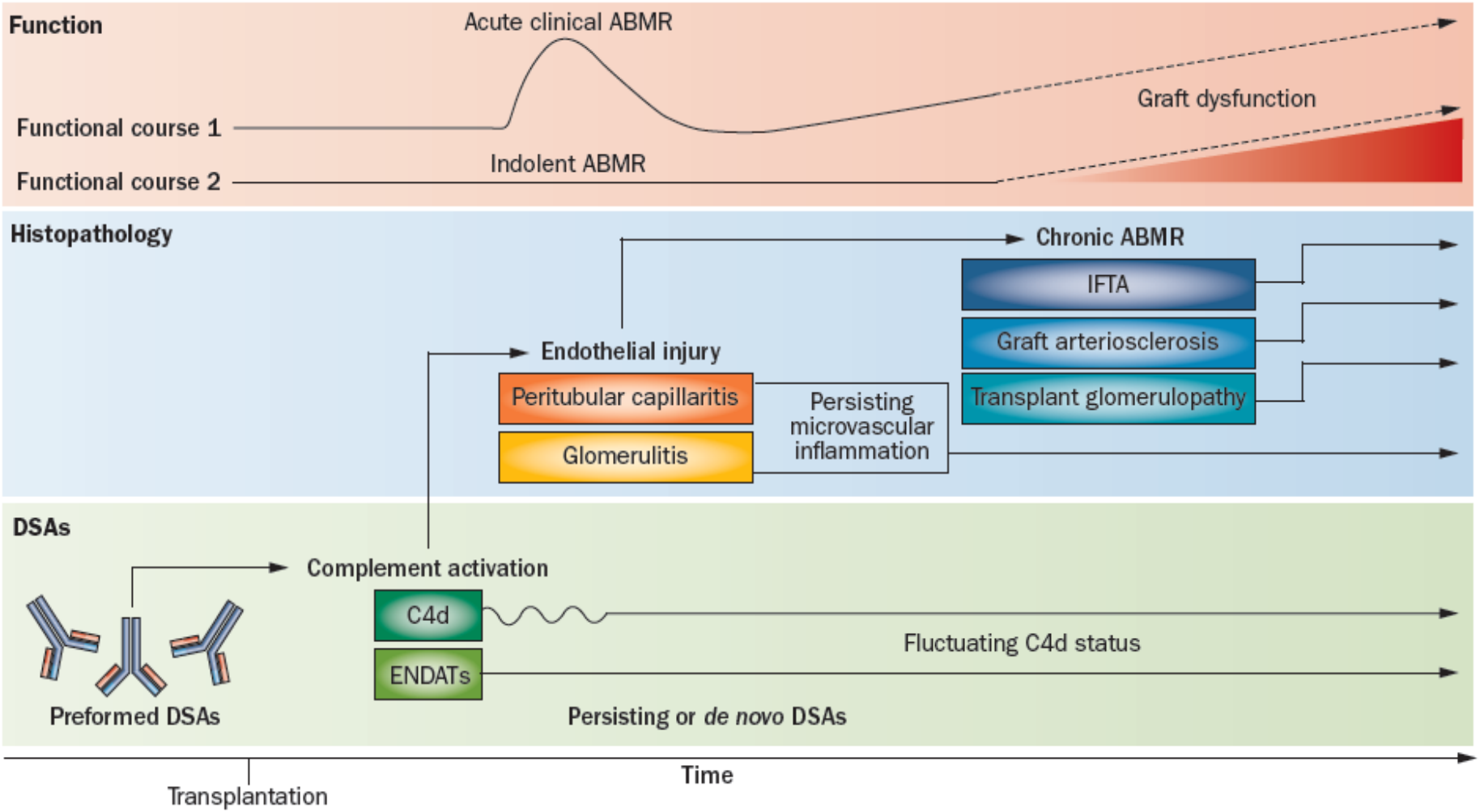
Chronic antibody-mediated rejection (CAMR)







DSA and the kidney graft: time lapse



ENDATs: endothelial-associated transcripts
IF/TA: interstitial fibrosis/tubular atrophy

Loupy et al. Nat Rev Nephrol 2012

Typical presentation

1. « Creeping » microalbuminuria
2. Followed by « creeping serum creatinine »

Treatment is not codified and very little conclusive data are available

Treatment

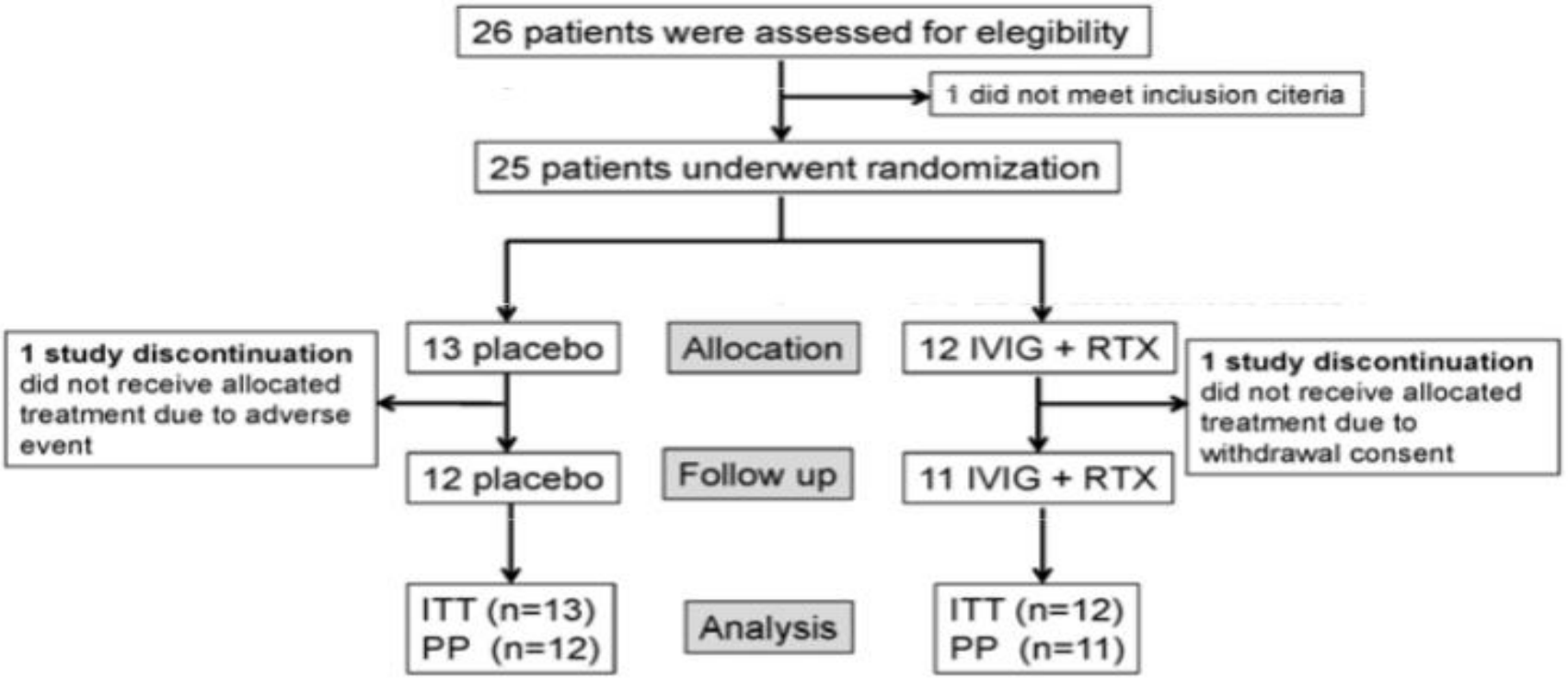
- Prevention of donor-specific alloantibodies formation:
  - Optimal immunosuppression
- When donor-specific alloantibodies are present:
  - Assess allograft DSA-related lesions
  - Optimize immunosuppression
  - Bortezomib (vs. placebo) is of no value (Eskandary et al. JASN 2017)
  - IVIg?
  - Rituximab? Rituximab + IVIg?
  - Anti-IL6 (R) antibodies, e.g. tocilizumab? Clazaclizumab?

Treatment of chronic antibody mediated rejection with intravenous immunoglobulins and rituximab: a multicenter, prospective, randomized, double blind clinical trial (1)

- Multicenter, prospective, randomized, double blind clinical trial : 2012 – 2015
- 25 adult patients with biopsy-proven chronic ABMR (cg score > 0) with or without C4d deposition in peritubular capillaries and the presence of anti-HLA DSA
- Stable eGFR (and > 20 mL/min)
- Randomization 1:1 placebo vs. IVIg (0.5g/kg; Privigen®) every 3 weeks up to 4 infusions plus one single dose of Rituximab (375 mg/m²) 1 week after the last IVIg infusion

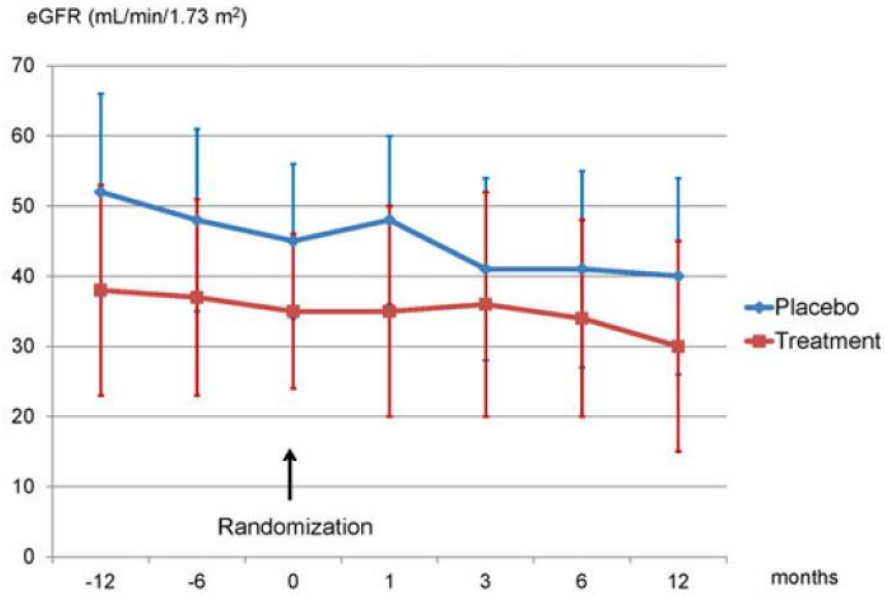
Moreso F. et al., AJT 2017 Sep 26. doi: 10.1111/ajt.14520.

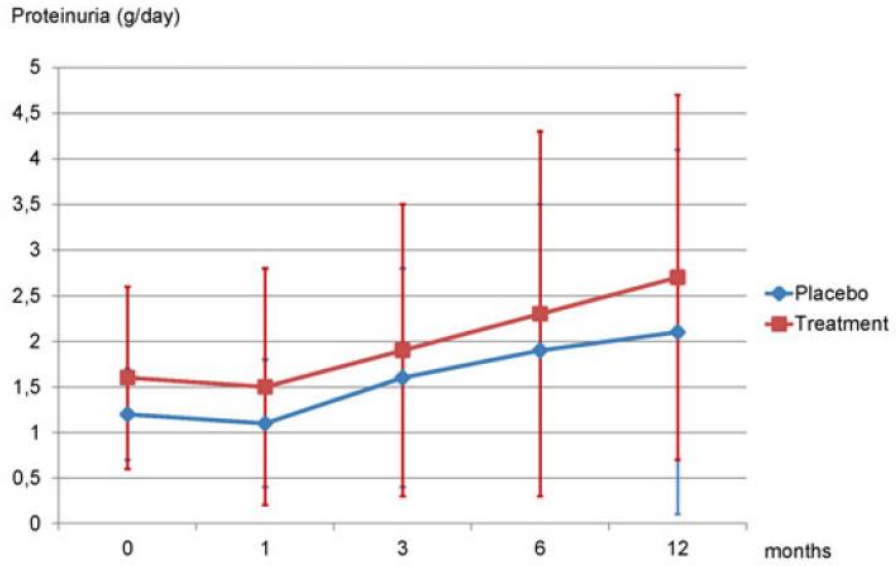
Treatment of chronic antibody mediated rejection with intravenous immunoglobulins and rituximab: a multicenter, prospective, randomized, double blind clinical trial (2)



Moreso F. et al., AJT 2017 Sep 26. doi: 10.1111/ajt.14520.

Treatment of chronic antibody mediated rejection with intravenous immunoglobulins and rituximab: a multicenter, prospective, randomized, double blind clinical trial (3)





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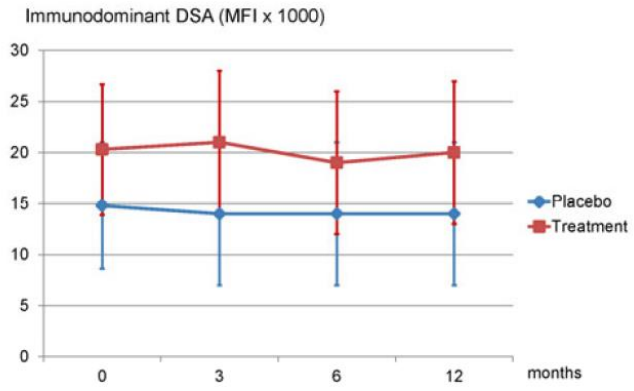
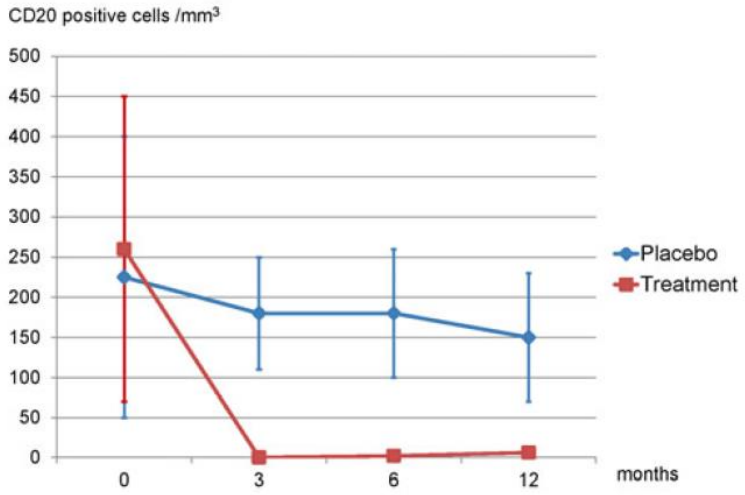
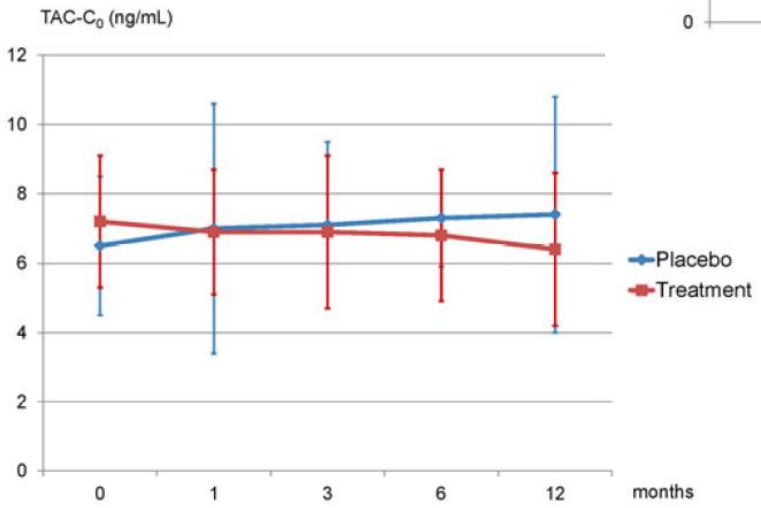






Moreso F. et al., AJT 2017 Sep 26. doi: 10.1111/ajt.14520.

Assessment of Tocilizumab (Anti–Interleukin-6 Receptor Monoclonal) as a Potential Treatment for ronic Antibody-Mediated Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Allograft Recipients (1)

- 36 kidney transplant patients with chronic ABMR plus DSA and transplant glomerulopathy that failed standard of care therapy ,i.e. IVIg plus rituximab with or without plasma exchanges.

  → Tocilizumab : 8 mg/kg monthly for 6-25 months plus Tac / MPA/ Steroids

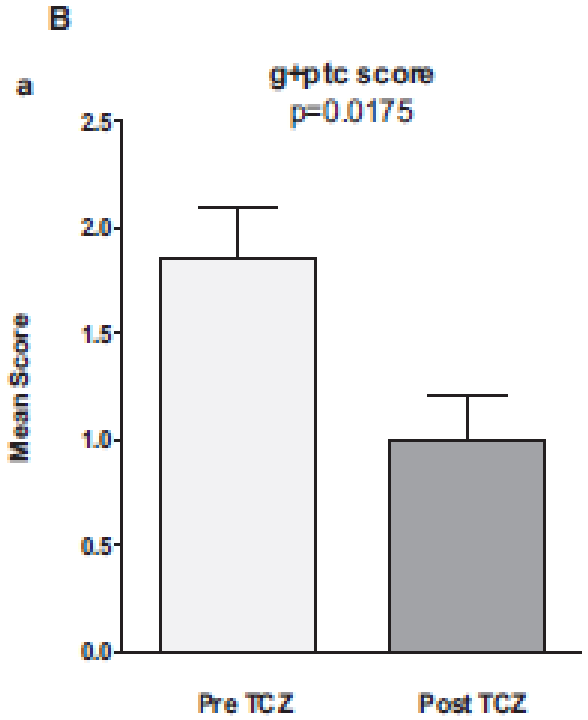
  → Treatment failure if no improvement in eGFR and reduction in DSA levels 3 months after standard of care had started

  → 91% patient survival and 80% survival at 6 years

Choi J. et al., AJT 2017;17:2381–2389.

Assessment of Tocilizumab (Anti–Interleukin-6 Receptor Monoclonal) as a Potential Treatment for ronic Antibody-Mediated Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Allograft Recipients (2)

Index and 1 year post–tocilizumab allograft biopsies



(B) This figure shows kidney allograft biopsy phenotypes before and after tocilizumab treatment (N = 9). Allograft biopsy specimens were obtained 1 year after tocilizumab treatment and compared with pretocilizumab chronic active antibody-mediated rejection biopsy specimens in nine patients. Significant reductions in g plus ptc scores and C4d deposition were seen with tocilizumab treatment. Other parameters were stable. TG, transplant glomerulopathy; IF/TA, Interstitial fibrosis/tubular atrophy.

Choi J. et al., AJT 2017;17:2381–2389.

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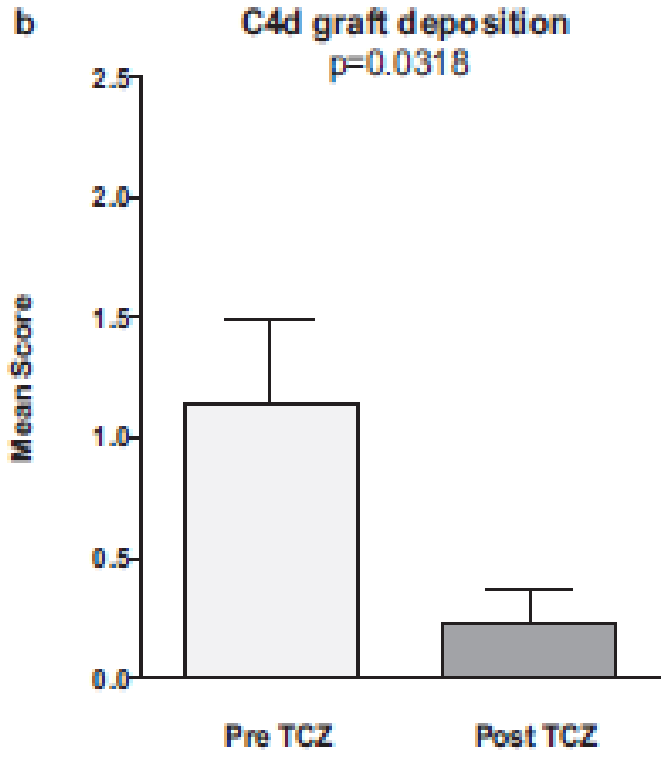

Choi J. et al., AJT 2017;17:2381–2389.

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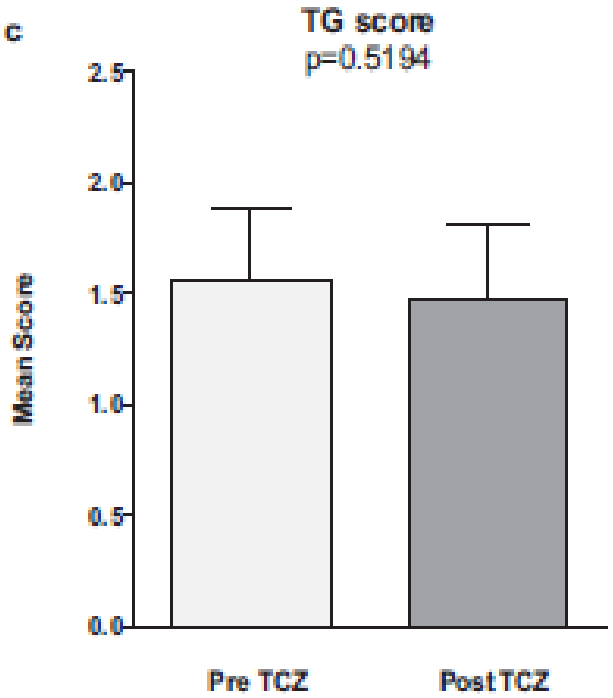
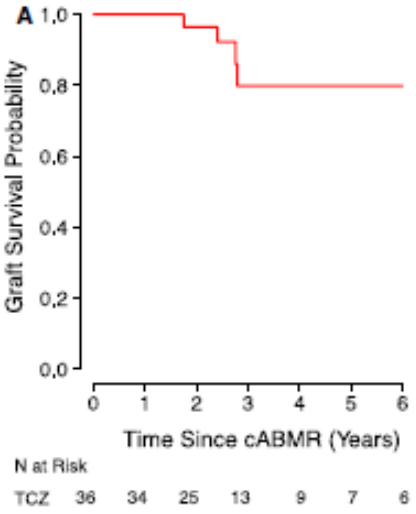


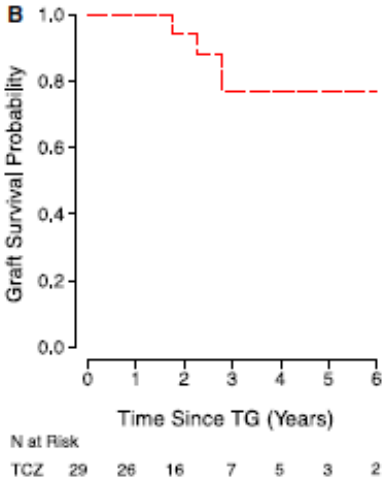
Choi J. et al., AJT 2017;17:2381–2389.

Assessment of Tocilizumab (Anti–Interleukin-6 Receptor Monoclonal) as a Potential Treatment for ronic Antibody-Mediated Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Allograft Recipients (5)

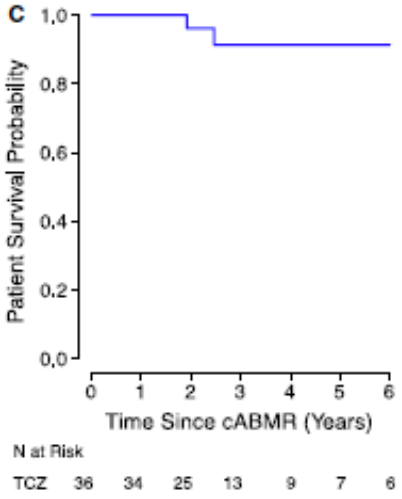
Kaplan–Meier curves of kidney allograft and patient survival after treatment with tocilizumab for chronic active antibody-mediated rejection (cAMR).



(A**) Kidney allograft survival** by treatment for all tocilizumab-treated cAMR patients.



(B) **Graft survival** for all tocilizumab-treated patients with transplant glomerulopathy.

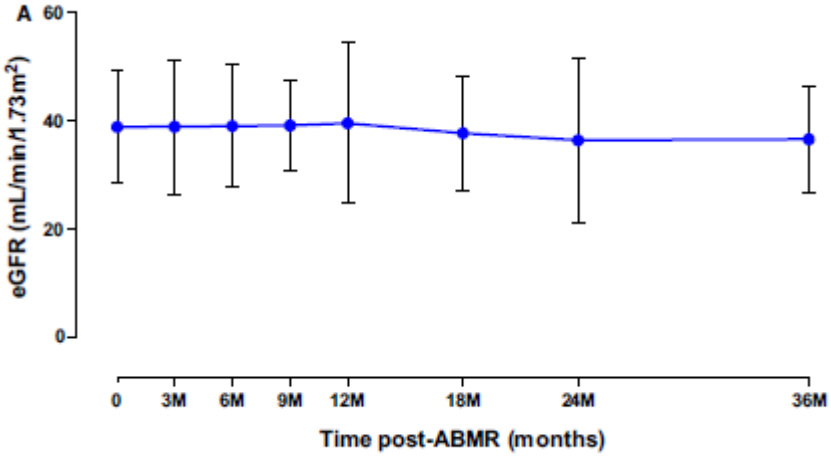


(C**) Patient survival** of cAMR patients treated with tocilizumab. Overall, tocilizumab was associated with good graft and patient survival.

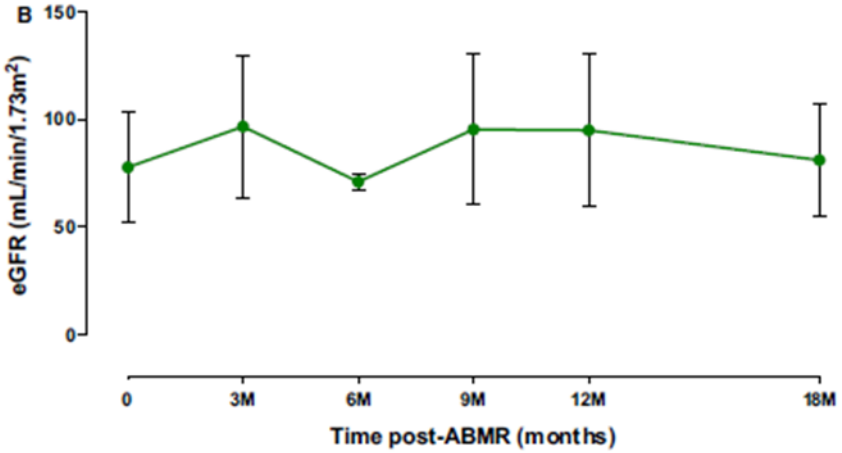
Choi J. et al., AJT 2017;17:2381–2389.

Assessment of Tocilizumab (Anti–Interleukin-6 Receptor Monoclonal) as a Potential Treatment for ronic Antibody-Mediated Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Allograft Recipients (6)

Estimated glomerular filtration rates post–tocilizumab treatment.



(A) Mean estimated glomerular filtration rate (eGFR) value of tocilizumab-treated **adult chronic active antibody-mediated rejection** (cAMR) patients (N = 32, >18 yrs old). eGFR values were maintained during the course of tocilizumab treatment after cAMR biopsy (36 months). eGFR values were calculated by using the Modification of Diet in Renal Disease equation for all adult patients.

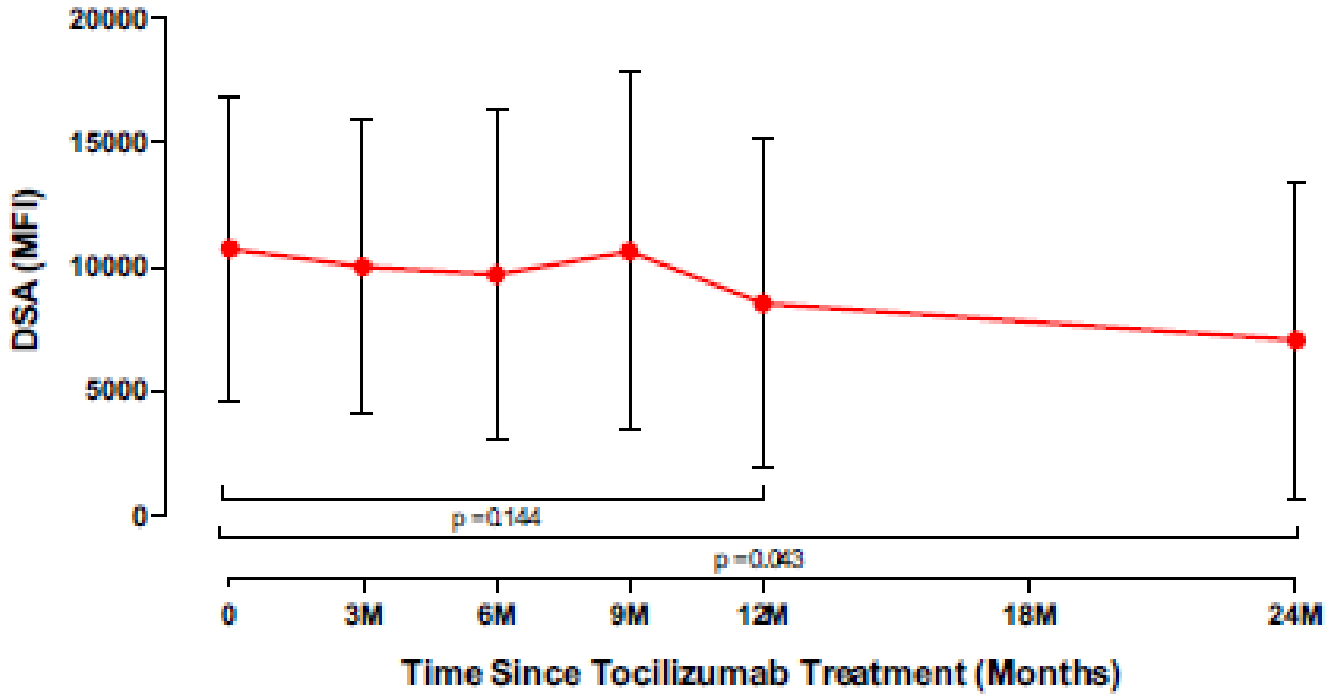


(B) Mean eGFR of tocilizumab-treated **pediatric patients** (N = 4, 6–17 yrs old) is shown. eGFR values were maintained during the course of tocilizumab treatment after cAMR biopsy. eGFR values were calculated by using the Schwartz formula for pediatric patients

Choi J. et al., AJT 2017;17:2381–2389.

Assessment of Tocilizumab (Anti–Interleukin-6 Receptor Monoclonal) as a Potential Treatment for ronic Antibody-Mediated Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Allograft Recipients (7)

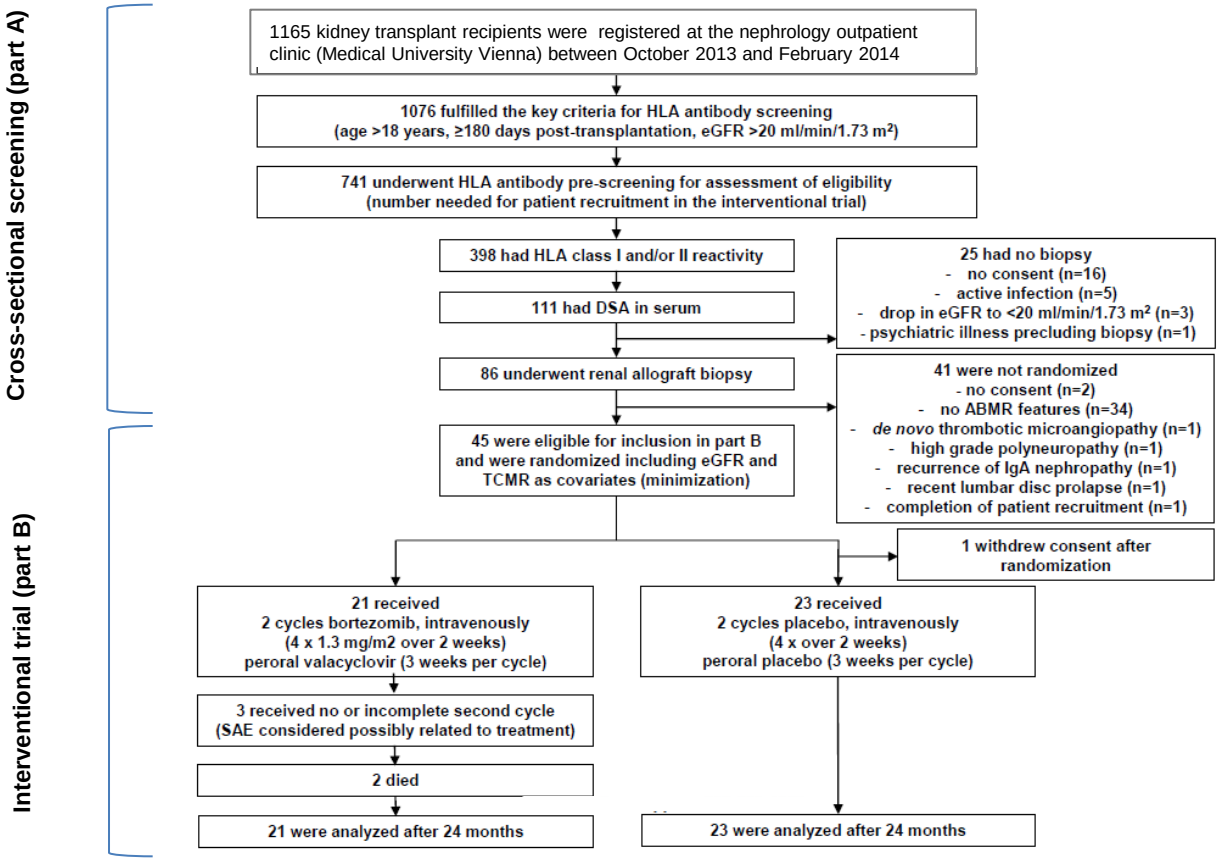
Mean immunodominant donor-specific antibody (iDSA) values for tocilizumab-treated patients



This figure shows the mean iDSA in mean fluorescence intensity (MFI) values up to 24 months post initiation of tocilizumab therapy. Significant reductions were seen beginning at 24 months (p = 0.043).

Choi J. et al., AJT 2017;17:2381–2389.

A Randomized Trial of Bortezomib in Late Antibody-Mediated Rejection (BORTEJECT) (3)



Study flow chart. Cross-sectional ABMR screening of 741 prevalent kidney transplant recipients (part A of the study) identified 45 subjects eligible for inclusion in the interventional part of the trial (part B). One recipient withdrew consent shortly after randomization and did not receive trial treatment. Twenty-three patients received placebo and 21 bortezomib. Two patients died during follow-up, and the other 42 recipients completed the study. DSA, donor-specific antibody; SAE, severe adverse event; TCMR, T cell-mediated rejection.

Eskandery F. et al. JASN 2017

A Randomized Trial of Bortezomib in Late Antibody-Mediated Rejection (BORTEJECT) (1)

Renal function, urinary protein excretion and survival rates in relation to trial treatment

Parameter	Bortezomib (n=21)	n assessed	Placebo (n=23)	n assessed	*p* Value
eGFR (ml/min/1.73 m^2), median (IQR)[a]					
Study inclusion	49 (34-65)	21	53 (31-91)	23	
3 months	55 (34-61)	19	70 (26-87)	23	0.29
6 months	56 (29-78)	21	59 (26-75)	23	0.92
12 months	43 (25-69)	20	53 (23-81)	23	0.66
18 months	35 (27-63)	20	53 (21-67)	23	0.94
24 months	46 (27-61)	18	51 (21-69)	22	0.82
mGFR (ml/min/1.73 m^2), median (IQR) at 24 months[a]					
Study inclusion	36 (29-46)	21	48 (30-67)	23	
24 months	33 (28-39)	17	42 (23-49)	22	0.31
Urinary protein/creatinine ratio (mg/g), median (IQR)[a]					
Study inclusion	289 (113-857)	20	130 (64-672)	20	
3 months	374 (88-827)	19	142 (0-573)	23	0.18
6 months	379 (115-1350)	21	140 (50-654)	22	0.11
12 months	208 (100-1427)	21	194 (82-959)	23	0.73
18 months	238 (127-904)	20	242 (60-673)	23	0.53
24 months	304 (146-682)	18	376 (33-1049)	21	0.54
Overall graft survival					
12 months	100	21	100	23	0.12
24 months	81	21	96	23	
Death-censored graft survival					
12 months	100	21	100	23	0.23
24 months	85	21	96	23	
Patient survival, %					
12 months	100	21	100	23	0.13
24 months	90	21	100	23	

eGFR, estimated glomerular filtration rate; IQR, interquartile range; mGFR, measured glomerular filtration rate.

[a]GFR and urinary protein/creatinine ratio were not recorded for patients on dialysis, or if laboratory data were not available for a given study visit.

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Parameter	Bortezomib (n=21)	n assessed	Placebo (n=23)	n assessed	*p* Value
24-month follow-up biopsy, n (%)[a]	16 (76)		22 (96)		
Morphological ABMR lesions and scores[b]					
Glomerulitis (g score ≥1), n (%)	10 (62.5)	16	15 (68.2)	22	0.74
g score, median (IQR)	2 (0-3)	16	1 (0-3)	22	0.69
Peritubular capillaritis (ptc score ≥1), n (%)	10 (62.5)	16	13 (59.1)	22	>0.99
ptc score, median (IQR)	1 (0-2)	16	1 (0-2)	22	0.76
Microcirculation inflammation (g+ptc) score, median (IQR)	4 (0-5)	16	2 (1-5)	22	0.87
Transplant glomerulopathy (cg score ≥1), n (%)	11 (68.8)	16	14 (63.6)	22	>0.99
cg score, median (IQR)	1 (0-2)	16	2 (0-3)	22	0.69
C4d in PTC (C4d score ≥1), n (%)	5 (31.3)	16	8 (36.4)	22	>0.99
C4d score, median (IQR)	0 (0-2)	16	0 (0-2)	22	>0.99
High-grade MLPTC, n (%)[c]	5 (35.7)	14	12 (54.5)	22	0.32
Interstitial fibrosis (ci score ≥1), n (%)	15 (93.8)	16	17 (77.3)	22	0.37
ci score, median (IQR)	1 (1-2)	16	2 (1-3)	22	0.47
Tubular atrophy (ct score ≥1), n (%)	13 (81.3)	16	17 (77.3)	22	>0.99
ct score, median (IQR)	1 (1-2)	16	1 (1-2)	22	0.73
Vascular fibrous intimal thickening (cv score ≥1), n (%)[d]	11 (84.6)	13	13 (68.4)	19	0.42
cv score, median (IQR)	2 (1-2)	13	1 (0-2)	19	0.34
Molecular classifiers[e]					
ABMR score, median (IQR)	0.77 (0.41-0.90)	16	0.58 (0.24-0.89)	21	0.62
TCMR score, median (IQR)	0.01 (0.01-0.02)	16	0.01 (0.01-0.03)	21	0.60
all Rejection score, median (IQR)	0.76 (0.41-0.88)	16	0.57 (0.26-0.86)	21	0.53
Atrophy/Fibrosis score, median (IQR)	0.58 (0.28-0.73)	16	0.46 (0.26-0.77)	21	0.87
Banff 2013 rejection types and categories					
ABMR, n (%)[f]	12 (75.0)	16	19 (86.4)	22	0.43
Acute/active ABMR, n (%)	0 (0)	16	1 (4.5)	22	>0.99
Chronic/active ABMR, n (%)	12 (75.0)	16	16 (72.7)	22	>0.99
Chronic/inactive ABMR, n (%)	0 (0)	16	2 (9.1)	22	0.50
C4d-positive ABMR, n (%)	4 (25.0)	16	8 (36.4)	22	0.50
Banff borderline lesion, n (%)	1 (6.3)	16	1 (4.5)	22	>0.99

ABMR, antibody-mediated rejection; DSA, donor-specific antibody; IQR, interquartile range; MLPTC, multilayering of peritubular capillary basement membranes.

[a]Six study subjects were not subjected to follow-up biopsies (death or return to dialysis: n=4; contraindication because of dual platelet aggregation inhibition: n=1; lack of consent: n=1).

[b]Morphological ABMR-typical lesions were scored according to the Banff 2013 classification of renal pathology [3].

[c]For two patients in the bortezomib group, no biopsy material was preserved for electron microscopy.

[d]Vascular fibrous intimal thickening was not recorded for three biopsies in the bortezomib group and three in the placebo group (biopsy material inadequate for complete lesion scoring).

[e]For one patient in the placebo group, no biopsy material was preserved for gene array analysis.

[f]Seven of the 38 follow-up biopsies (bortezomib: n=4; placebo: n=3) did not fulfill the Banff 2013 criteria of ABMR, even though five biopsies were associated with detectable DSA (MFI_max between 1069 and 14321). None of the biopsies showed ptc, cg or high grade MLPTC. One biopsy showed mild g (score 1). One biopsy stained C4d positive (c4d score 3), however, without any signs of microcirculation inflammation/injury. This and another biopsy had a molecular ABMR score above the threshold of 0.20 (0.39 and 0.21, respectively).

Morphological and molecular results of 24-month follow-up biopsies in relation to trial treatment

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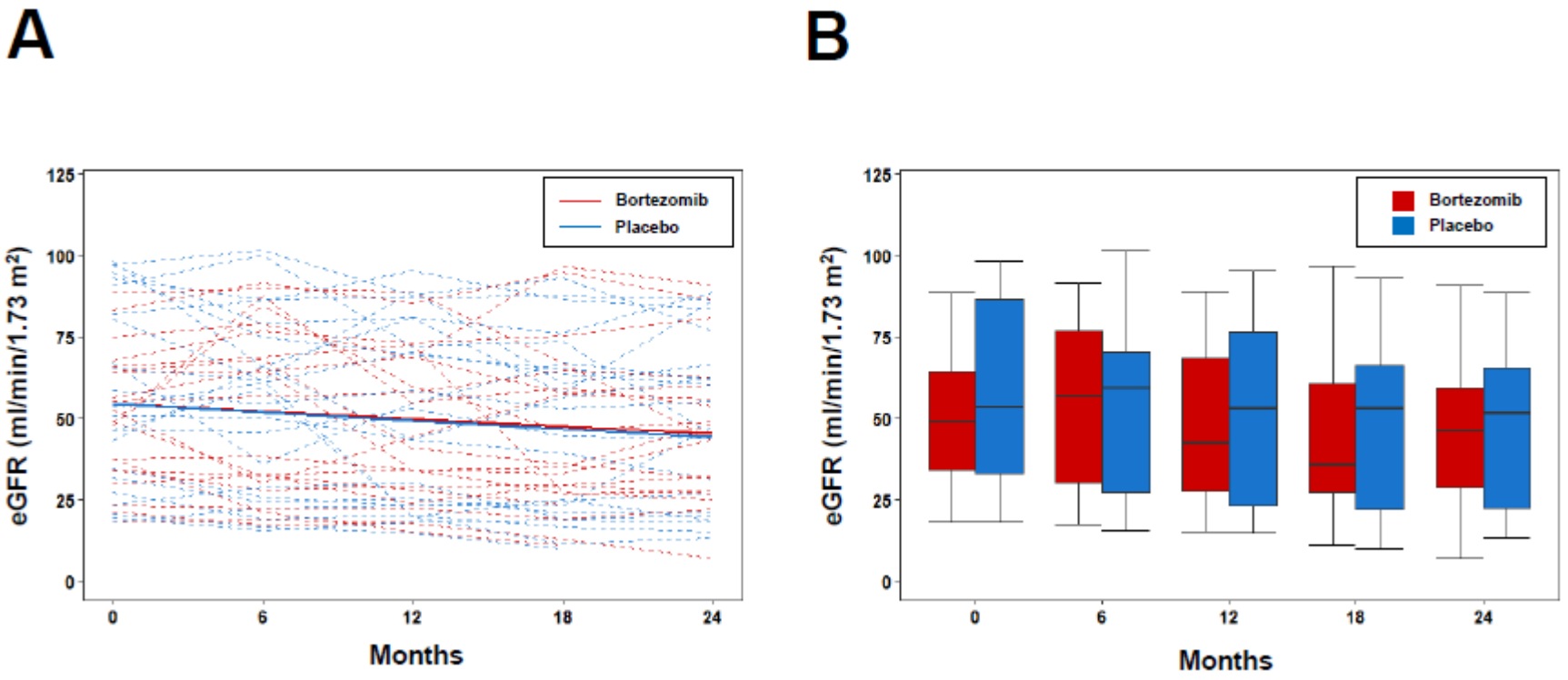

Kidney allograft function in relation to trial medication. (A) Individual Egfr course (dashed lines) and estimated mean eGFR (solid lines) computed from the mixed model for the primary analysis, and (B) comparison between bortezomib and placebo for median levels of eGFR. Analyses are based on serial eGFR measurements at 0, 6, 12, 18 and 24 months (for patient death or return to dialysis no data were imputed). Box plots indicate the median, interquartile range, and the minimum and maximum of the measures.

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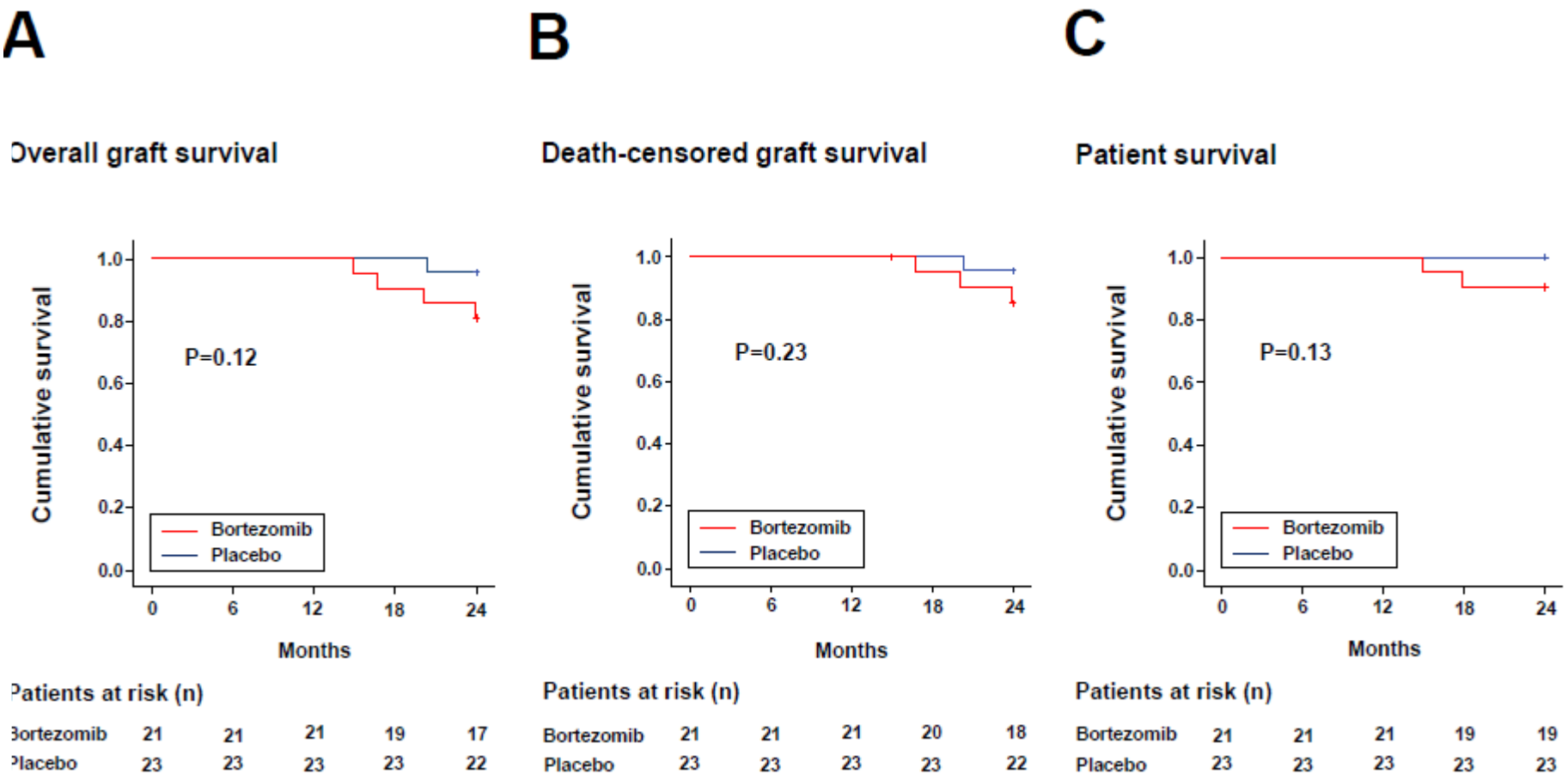

Kaplan Meier transplant and patient survival. Overall graft survival (Panel A), death-censored graft survival (Panel B), and patient survival (Panel C) are shown in relation to treatment allocation. The Mantel Cox log-rank test was used to compare survival rates between groups.

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It is *better* to prevent!

FUTURE?

Future

- Monoclonal anti-IL-6 (or anti-IL-6 receptor) antibodies, i.e. Tocilizumab or Clazaclizumab
- Imlifidase (formely IdeS)
- Complement inhibitors?
-

Conclusion

- Donor-specific alloantibodies have a negative impact upon allograft survival, especially when formed after transplantation
- Donor-specific alloantibodies formation result mostly from underimmunosuppression, e.g. non-compliance; low CNI levels
- Donor-specific alloantibodies result in (sub)acute antibody mediated rejection as well as in chronic antibody-mediated rejection
- As of now, we still do not have efficient treatment for established DSAs.


Thank you for your attention