UHN Ajmera Transplant Centre

Donor Specific Antibodies

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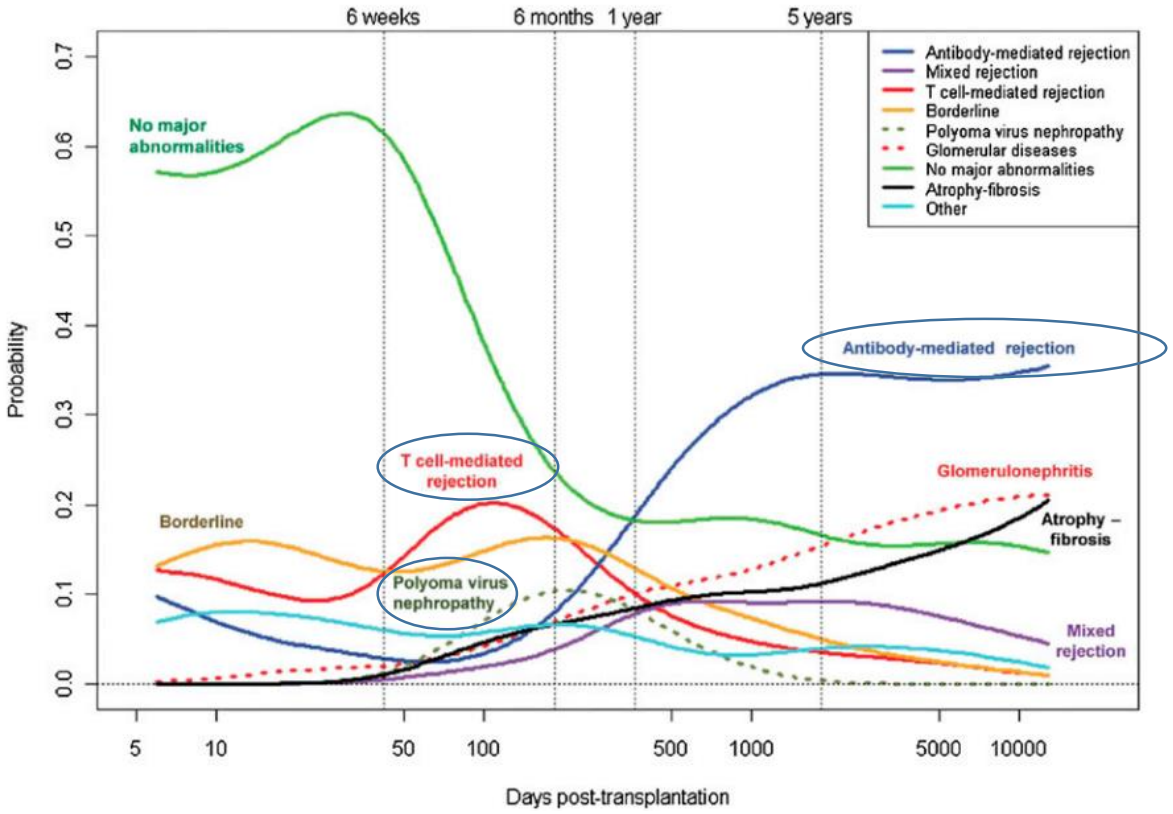
Disclosures/Acknowledgments

- I have no conflicts relevant to this talk
- My talk will focus on clinical approaches to donor specific HLA antibodies
- My thanks to Peter Nickerson and Kathryn Tinckam for helpful conversations and slides

Summary

- Why do we lose allografts?
- Types of DSA
- Impact of Pre transplant DSA
- Clinical approaches to pre transplant DSA
- De Novo DSA
- Approach to DSA monitoring
- Prediction of likelihood de novo DSA will form
- How can we use risk predictors in post transplant management?
- Conclusions

Why do we lose allografts?



Sellares et al. *AJT* 2012

Types of DSA

- Preformed DSA

  -Present at time of transplant or within 2 weeks to 3 mo post transplant

  -Issue of memory cells (consider past and current DSA)

- De Novo DSA

  -Develop post transplant

- Both associated with ABMR (and T Cell) and reduced graft survival

Detection of DSA

- DSA can change with time and exposure, especially in highly sensitized. Thus requires serial monitoring while patients are on transplant list and stat cross match before transplant in highly sensitized

- Standardization between labs has been an issue
- It is of critical importance in organ sharing between regions e.g. in Kidney Paired Donation
- In Canada our national HLA group spent much time to be sure that Flow Cross Match and Virtual Cross Match results would be the same regardless of lab

Pre Transplant DSA

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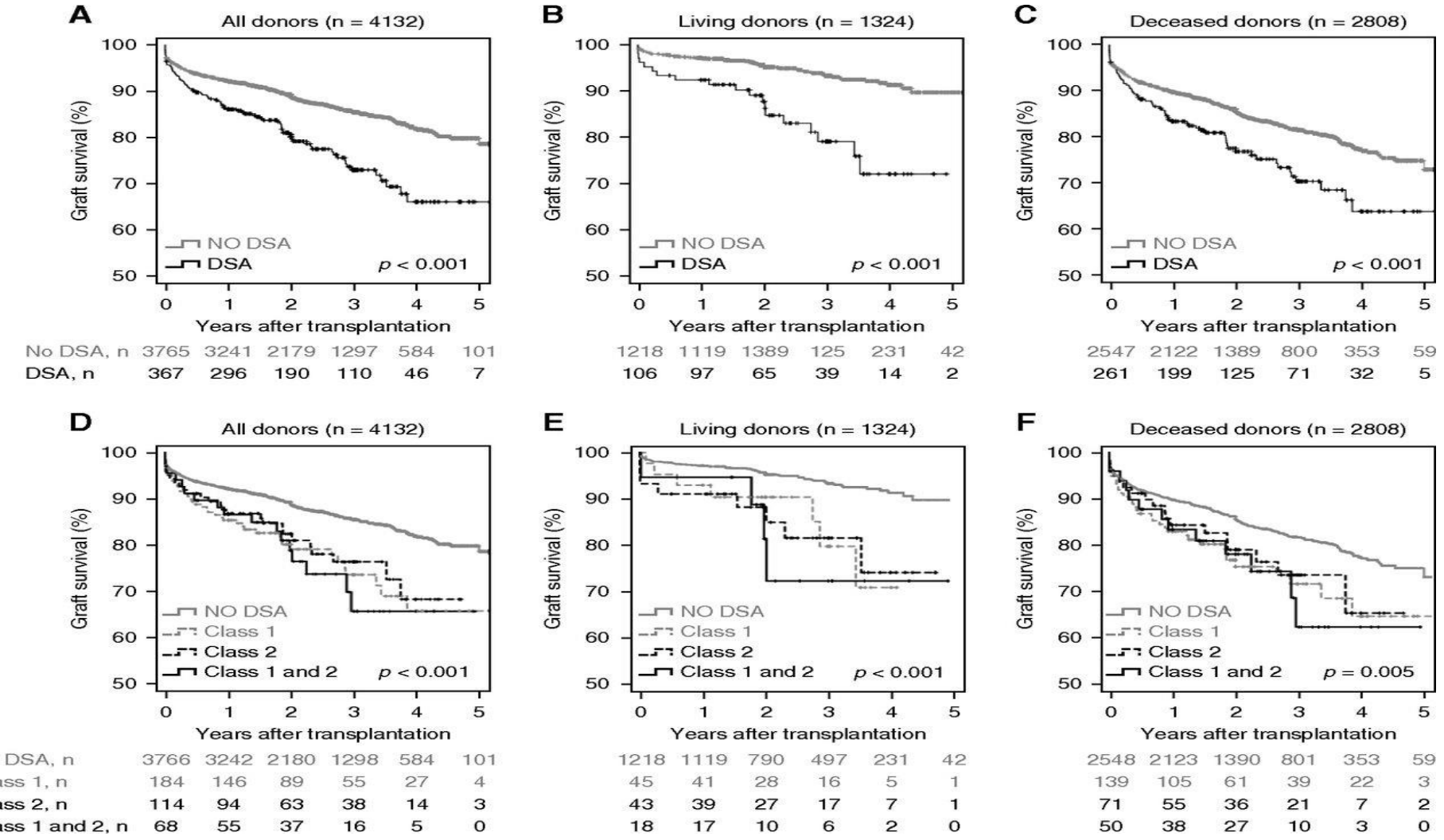
Graft Survival Preformed DSA vs No DSA

Ziemann et al Clin J Am Soc Neph, 2019



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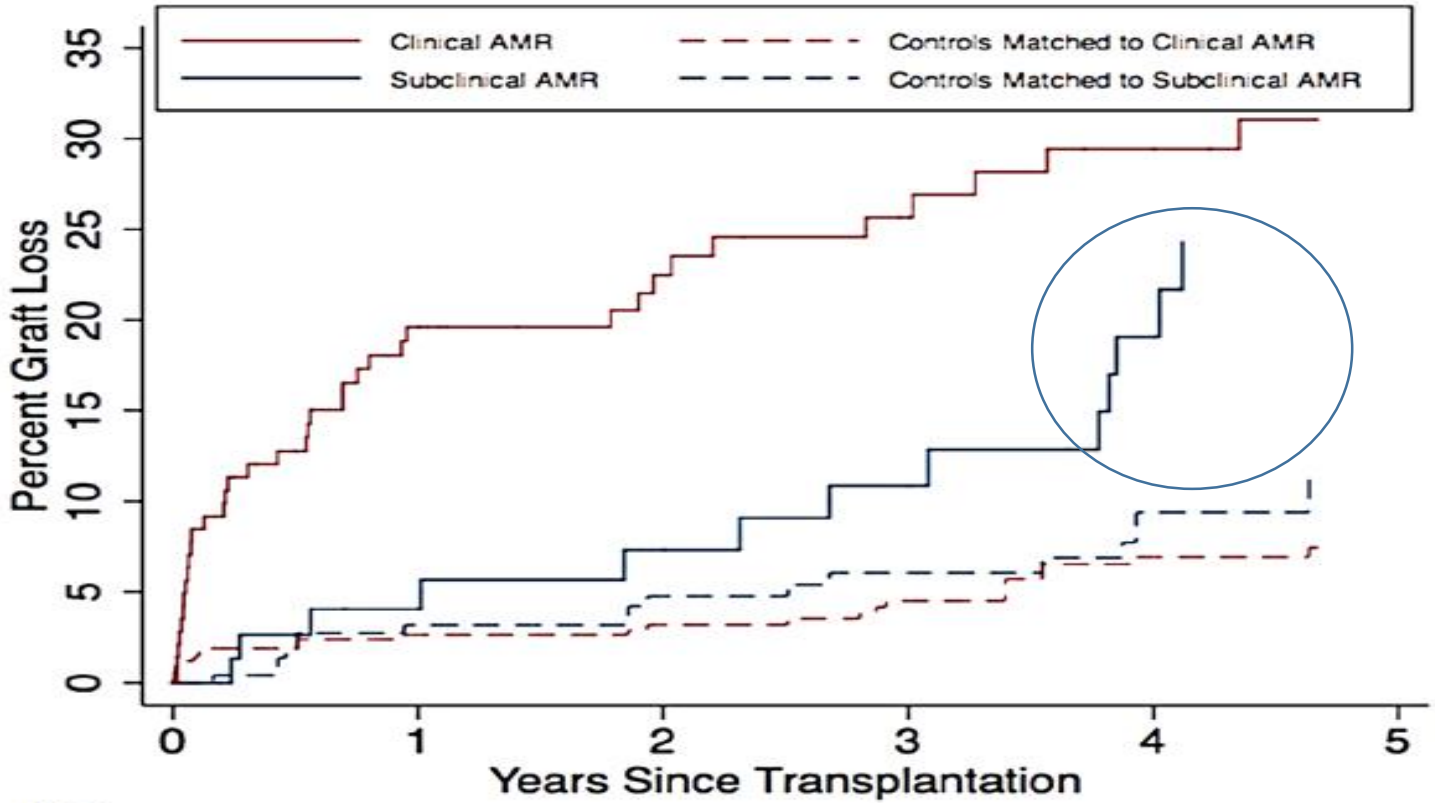
Antibody Mediated Rejection Within 1 Year Post Transplant and Outcome

Orandi et al AJT, 2015



Number at risk

Clinical AMR	142	104	82	68	55	42
Controls Matched to Clinical AMR	426	396	337	289	229	184
Subclinical AMR	77	66	57	50	39	29
Controls Matched to Subclinical AMR	231	209	181	143	108	80

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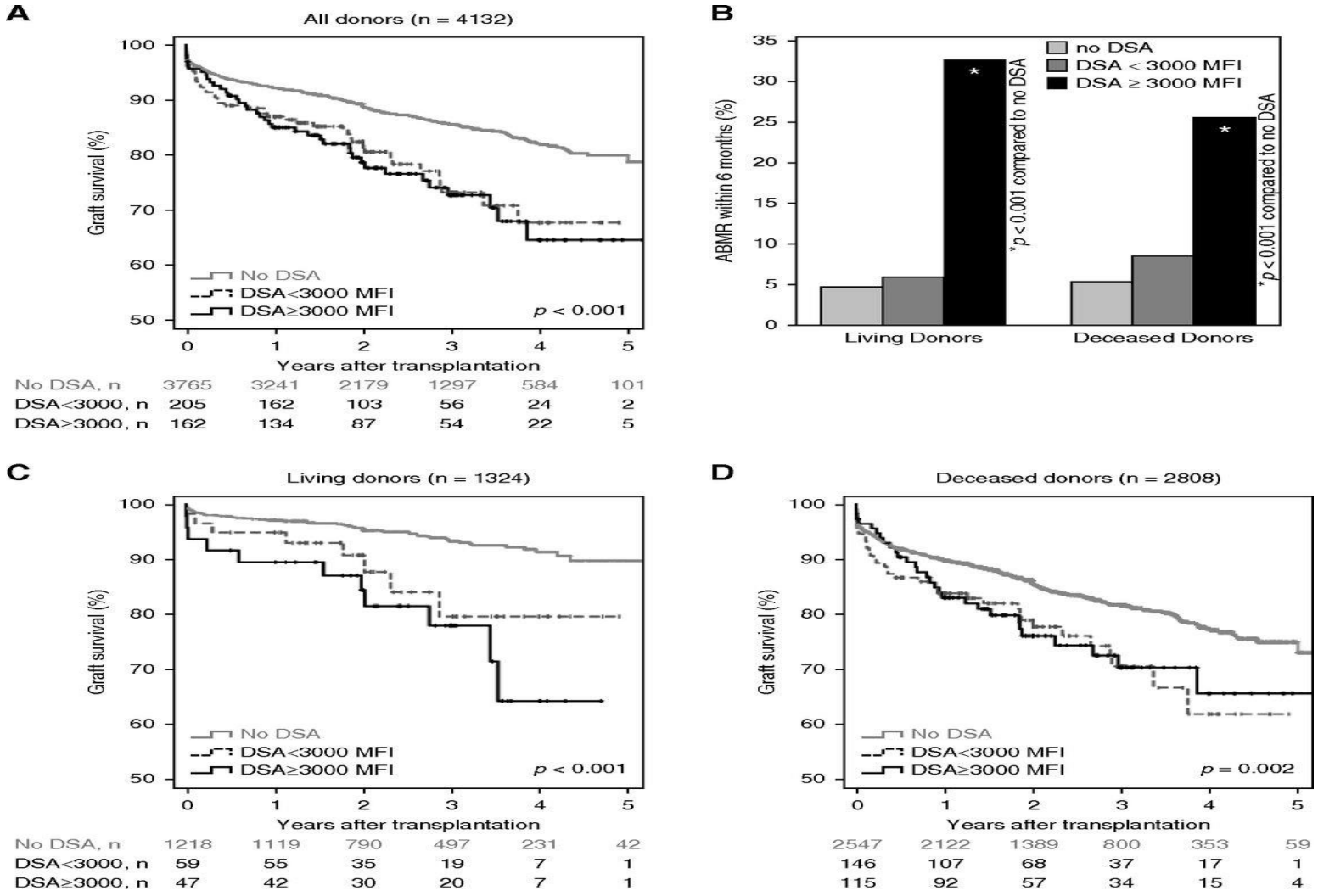
Strength of Preformed DSA and Graft Survival

Ziemann et al Clin J Am Soc Neph, 2019



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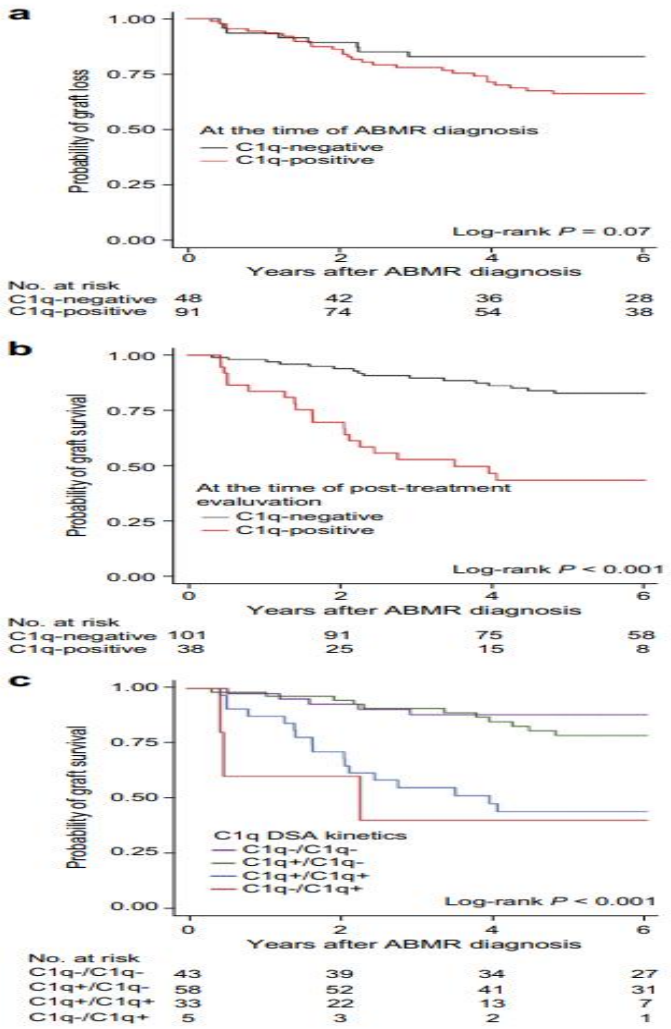
C1q Fixing DSA and AMR Outcome

Viglietti et al Kidney Int, 2018



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Impact of Repeat Mismatch and DSA on Death Censored Graft Survival and AMR

Lucisano et al Am J Transplant, 2020

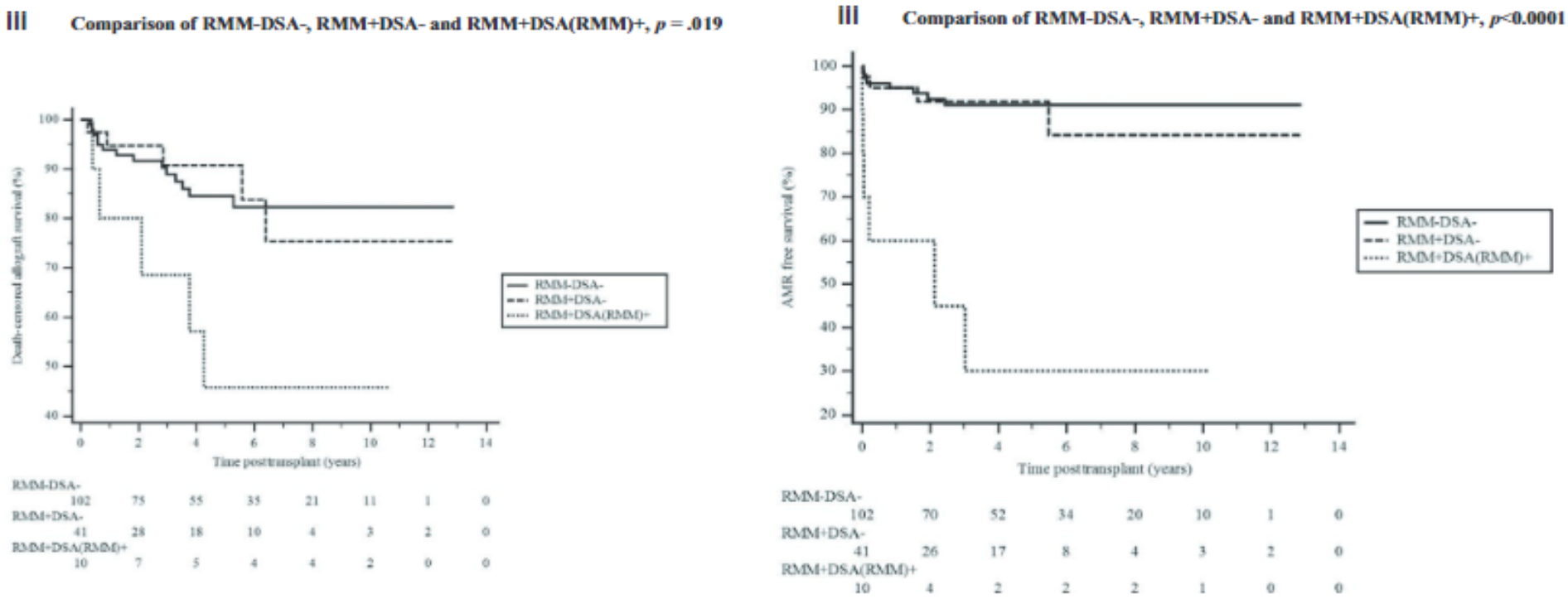


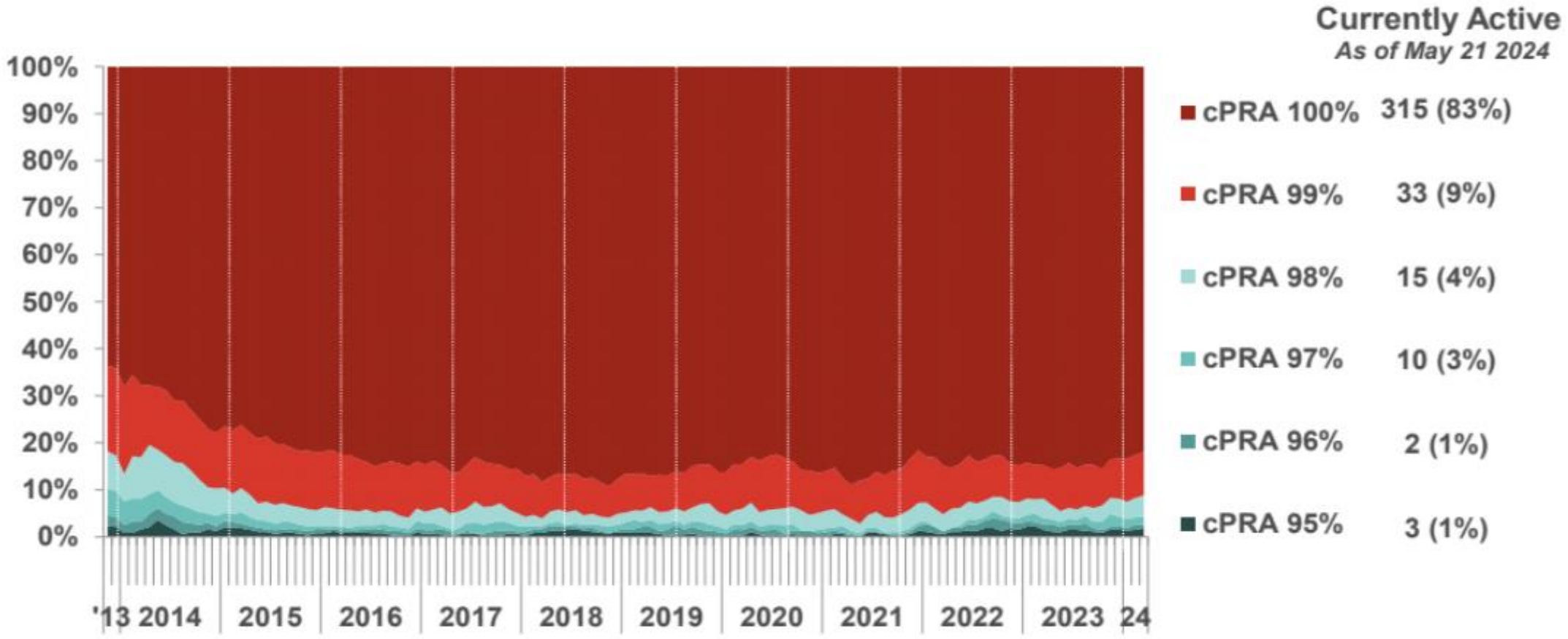
FIGURE 2 Allograft outcomes by RMM and DSA status: A, Death-censored allograft survival: (i) comparison of RMM- and RMM+ patients, *P* = .44 (logrank); (ii) comparison of preformed DSA− and DSA+ patients, *P* = .02; (iii) comparison of RMM+ DSA(RMM)+ vs RMM-DSA−, *P* = .006 and RMM+ DSA−, *P* = .03. B, AMR free survival by RMM and preformed DSA status: (i) comparison of RMM- and RMM+ patients, *P* = .07 (logrank); (ii) comparison of preformed DSA− and DSA+ patients, *P* = .0001; (iii) comparison of RMM+ DSA(RMM)+ vs RMM−DSA−, *P* < .0001 and RMM+ DSA−, *P* = .0001

Management of Pre Transplant DSA

- Ideal strategy is to avoid transplanting across DSA
- If living donor available, Kidney Paired Donation works well and has become primary option
- Requires large donor and recipient pool and standardization of antibody detection between labs
- In Canada we have done well over 1000 KPD transplants. The US has done much larger numbers

4.3 HSP Registry is dominated by candidates who are extremely difficult to match

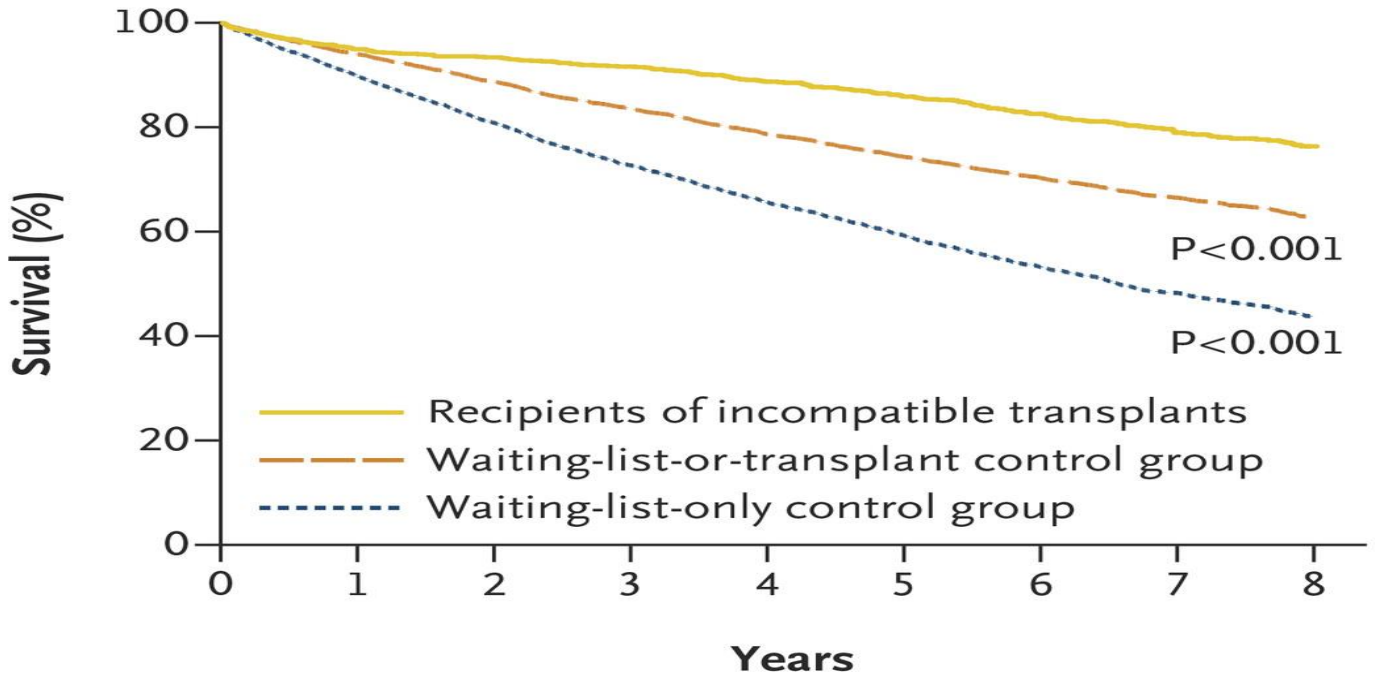
Active HSP candidates over time by cPRA



Canadian Blood Services

Survival in Living Donor Incompatible Transplantation vs Remaining on the List

Segev et al NEJM, 2016



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

Other Strategies

- Can combine with KPD and classical desensitization if suitable living donor available. Best if only low level DSAs with negative Flow X match

- Most current deceased donor allocation strategies give priority to high PRA with negative cross match
- National Highly Sensitized Registries can improve access further
- Exclude low level DSAs or previous DSAs, especially if Flow Cross Match negative, to reduce PRA (Living and Deceased Donors)

- Imlifidase may offer future opportunities for living and deceased donor transplants, but very expensive, and await long term outcomes in larger numbers of patients

De Novo DSA

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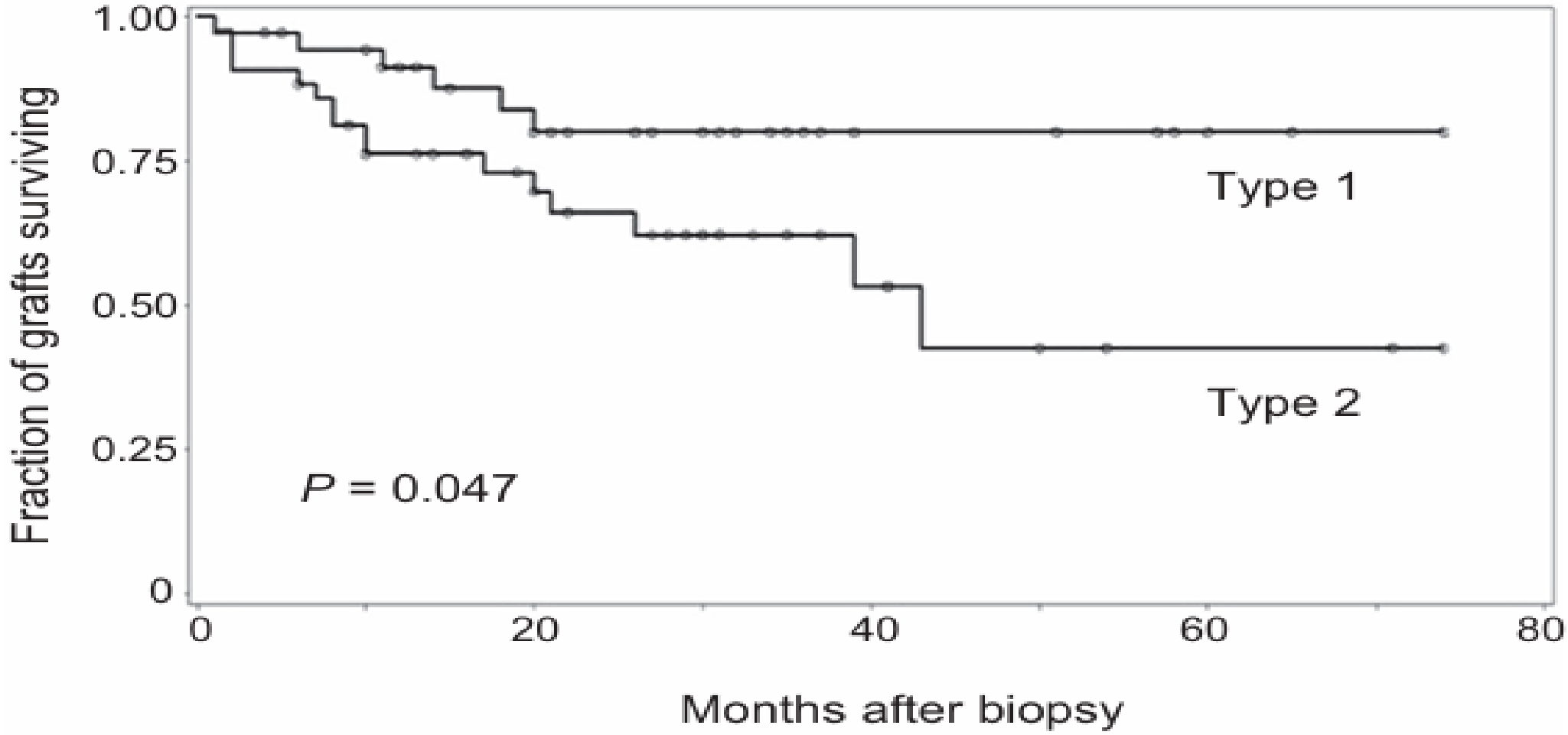
Graft Survival in Type 1 (preformed DSA) vs Type 2 (De Novo DSA)

Haas et al Kidney Int, 2017



Approaches to De Novo DSA

- Biopsy if positive even in stable patients - Protocol biopsy in presence of DSA associated with 40% biopsy proven subclinical antibody mediated rejection (Bertrand et al Transplantation, 2020)
- Higher rejection risk for Class 2 vs Class 1 DSA
- Consider optimizing immunosuppression and IVIg as limited other options
- However there are tools to predict likelihood of de novo DSA
- Identification of de novo DSA risk and occurrence can impact decisions about immunosuppression dosing

Should DSA be Routinely Tested in Low Risk Patients

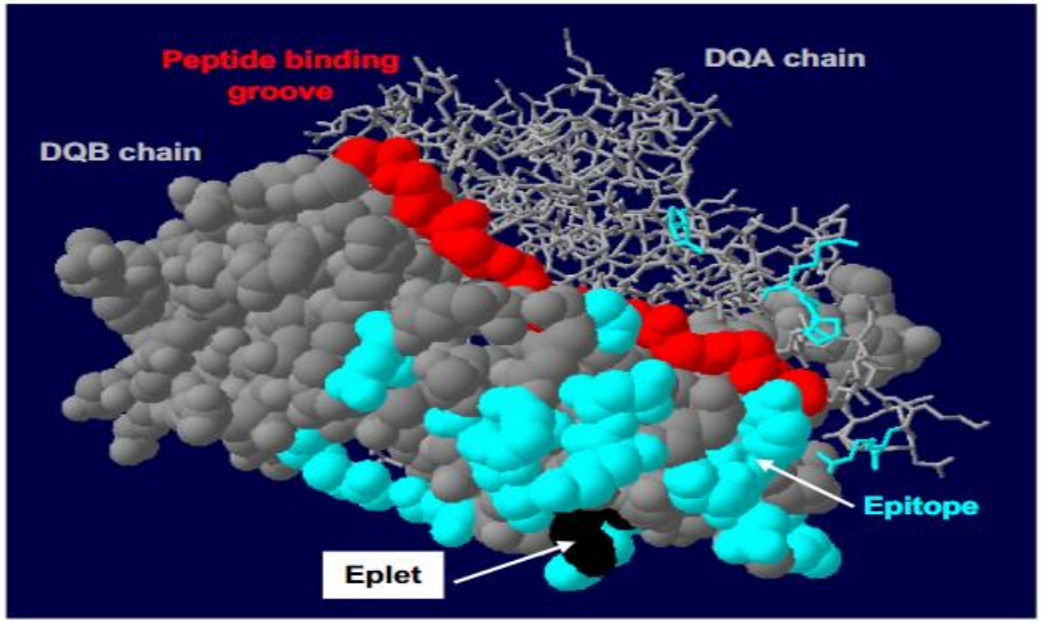
Salhi et al Kidney Int Reports, 2024

- Tested 1072 stable pt over 8 yr
- 7.2% had DSA
- 56% of those with positive DSA had changes of antibody mediated rejection on biopsy
- 46% detected within first year
- In 95% of DSA pos pt an immunizing event identified

- Conclude that routine testing of stable patients after 1 year has limited clinical impact
- Not universal agreement (van den Broek et al, Transplant Int, 2023)

Antigens, Epitopes and Eplets

- Antibody binds to epitope. Eplet is a made up term that represents the individual binding site that gives specificity
- Depending on specific Ag mismatch, there may be few or many eplet mismatches



McCaughan and Tinckam Transplant Int 2018

HLAMatchmaker:

A molecularly based algorithm for histocompatibility determination

- Eplet matching for HLA-DR, HLA-DQ, and HLA-DP

Requires High Resolution, Allele level HLA Typing

Patient HLA	Donor HLA	mmEp	Mismatched Donor Eplets
DRB1*1101	DRB1*0405	11	, ,12VKH,14HEH, , ,32FYH,34HQ, , ,57SA, ,67LR,71QRA, , , ,96YL,98EN, ,120N, , , ,180LT, ,
DRB1*1302	DRB1*1119	1	, , , , , , , , , , , ,67IR, , , , , , , , , , , , ,
DRB3*0101	DRB3*0202	-	, ,
DRB3*0202	DRB4*0101	19	4Q,18L,12AKC,14CEH,16HLW,26WN,32IYN, ,41YNL,48YQ, , ,67LR,71RRA, ,81YV,85VV,96QM,98KN,
DQB1*0301	DQB1*0301	-	, ,
DQB1*0301	DQB1*0302	7	,14GM, ,26L, ,45GV,46GVY, , ,57PA, , , , , , , , , , , , ,167RG, ,185I, ,
DQA1*0103	DQA1*0302	13	, , ,25YS,34HE,41ER, ,47EQL,48LF,50LF,52FRR,56RR, , , ,75IVR,80IRS, , , , , ,160DD, ,175E,187T
DQA1*0505	DQA1*0505	-	, ,
DPB1*0301	DPB1*0201	-	, , , , , , , , , , , , ,
DPB1*0201	DPB1*2301	3	, , , , , ,55AA,56AE, , , , , ,
DPA1*0103	DPA1*0103	-	, , , , , , ,
DPA1*0103	DPA1*0103	-	, , , , , , ,

National Institute of Allergy and Infectious Diseases

Duquesnoy and Askar, Human Immunology (2007) 68:12-25

HLA DR or DQ Eplet vs Whole Antigen Mismatch and DSA

Wiebe et al JASN, 2017

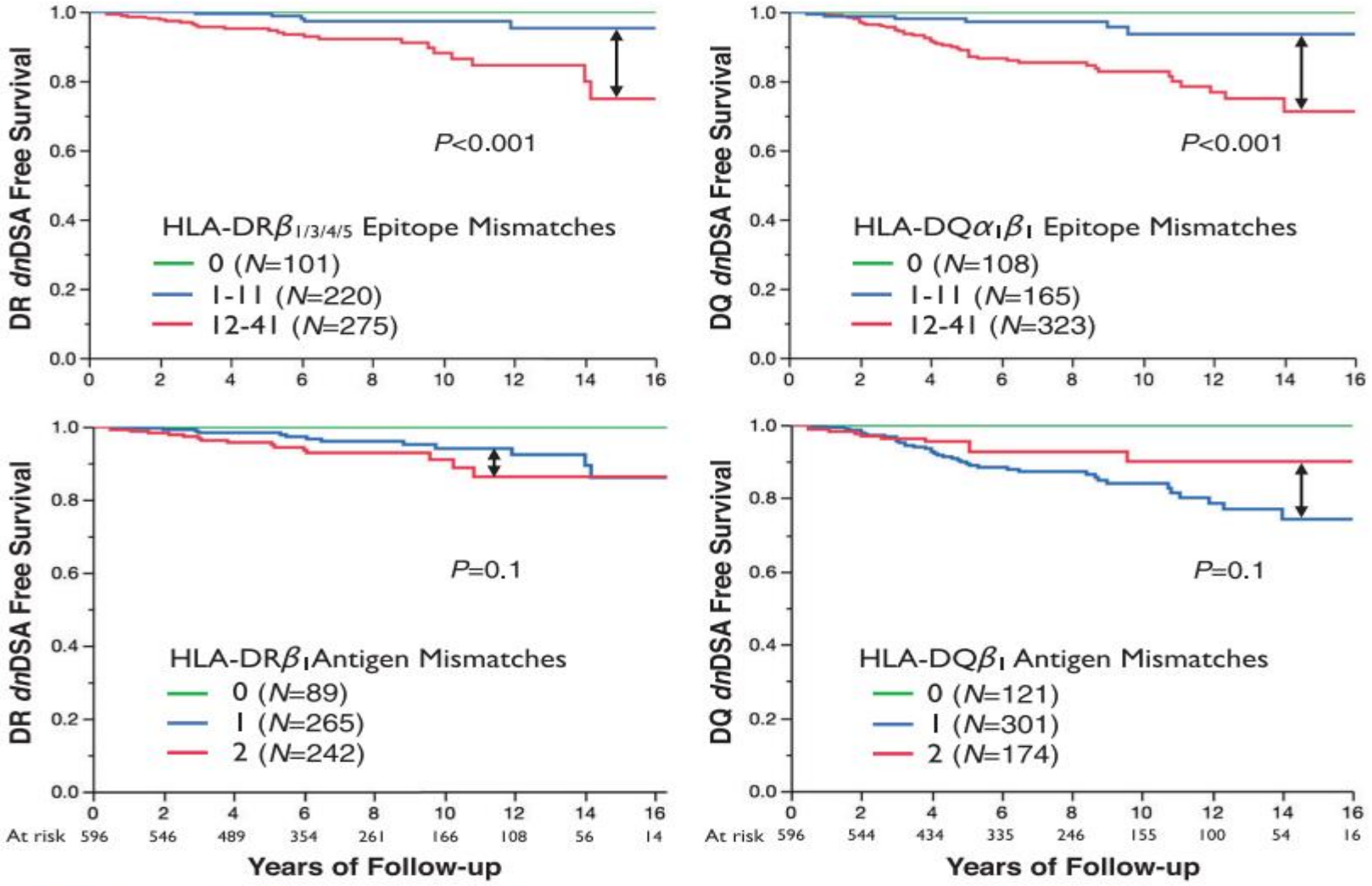


Figure 3. HLA-DR or -DQ eplet mismatch thresholds outperformed traditional whole-antigen HLA-DR or -DQ mismatch (zero, one, or two mismatches) to predict Class II *dn*DSA-free survival post-transplant. HLA locus specific Kaplan-Meier *dn*DSA free survival curves shown stratified by eplet mismatch (top) or whole-antigen mismatch (bottom).

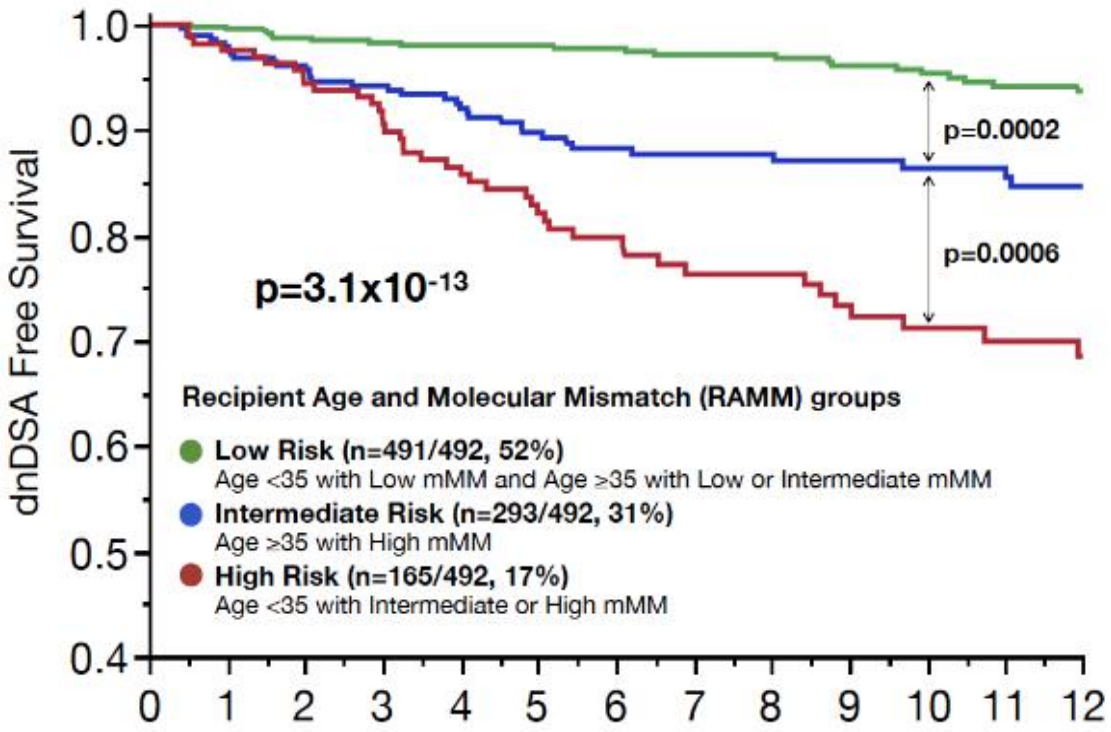
Independent Correlates of *de novo* DSA

Total Cohort	DR *dn*DSA *n*=596, 29 Events		DQ *dn*DSA *n*=596, 51 Events	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Recipient age at transplant, yr	0.97 (0.95 to 0.99)	0.02	0.97 (0.95 to 0.98)	0.002
Nonadherence	3.07 (1.40 to 6.52)	<0.01	3.11 (1.71 to 5.58)	<0.001
Cyclosporin versus tacrolimus	2.14 (0.93 to 4.70)	0.07	1.97 (1.06 to 3.52)	0.03
HLA-DR$\beta_{1/3/4/5}$ eplet mismatch/ten mismatches	2.79 (1.84 to 4.27)	<0.001		
HLA-DQα_1/β_1 eplet mismatch/ten mismatches			2.00 (1.52 to 2.67)	<0.001

Wiebe et al., JASN (2017) 28:3353-3362

Hard Coded Variables at Transplant that are Prognostic of de novo DSA Risk

RAMM Score (Recipient Age & HLA-DR|DQ molecular mismatch)



n=102 dnDSA events	HR	95% CI	p value
Donor Sex (male versus female)	0.81	0.5-1.2	0.3374
Donor age (per year)	0.99	0.9-1.1	0.696
Deceased versus Living Donor	1.60	0.8-3.0	0.153
Previous transplant	1.83	0.7-5.0	0.239
Panel reactive antibody	1.0	1.0-1.0	0.366
Recipent Sex (male versus female)	1.35	0.9-2.1	0.176
Caucasian ethnicity versus other	1.50	0.9-2.4	0.085
Cold Ischemic Time (hours)	1.00	0.9-1.1	0.913
Delayed graft function	0.84	0.5-1.5	0.571
Tacrolimus versus Other (Cyclosporin/Sirolimus)	**0.37**	**0.2-0.6**	**<0.001**
Induction versus none	0.74	0.5-1.2	0.185
RAMM (recipient age and molecule mismatch) category			
Intermediate versus Low	**2.48**	**1.5-4.2**	**<0.001**
High versus Low	**6.36**	**3.7-10.8**	**<0.001**

Wiebe et al., AJT (2023) 23:1882-1892

Hard Coded Variables at Transplant that are Prognostic of de novo DSA Risk

RAMM Score modulated by level of immunosuppression

Immunosuppression Level is a RISK MODIFIER

Primary Alloimmune Risk
RAMM Score
- **Recipient Age**
- **HLA DR|DQ molecular MM**

High Risk (17%)

Intermediate (31%)

Low Risk (52%)

Transplant

de novo DSA	Lowest recorded FK levels (ng/ml)		
Time Post-Transplant	De novo DSA*	Control†	p value
Months 12-24	3.4±1.5	5.0±1.4	0.0003
Months 24-36	3.4±1.5	5.2±1.4	0.0001
Months 36-48	2.7±1.6	5.0±1.6	0.0008
Months 48-60	3.6±1.7	5.0±1.3	0.0620
Months 60-72	2.0±1.9	4.9±1.5	0.0007

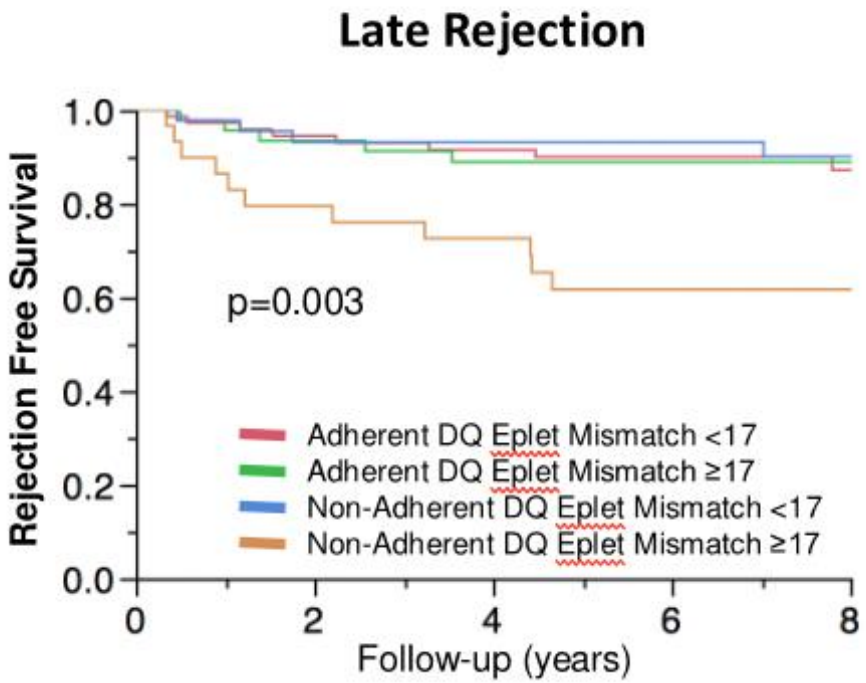
Subset Analysis: Mycophenolate dose lower in **de novo DSA** 194 ± 338 mg/d vs **Control** 690 ± 399 mg/d **p=0.0008**

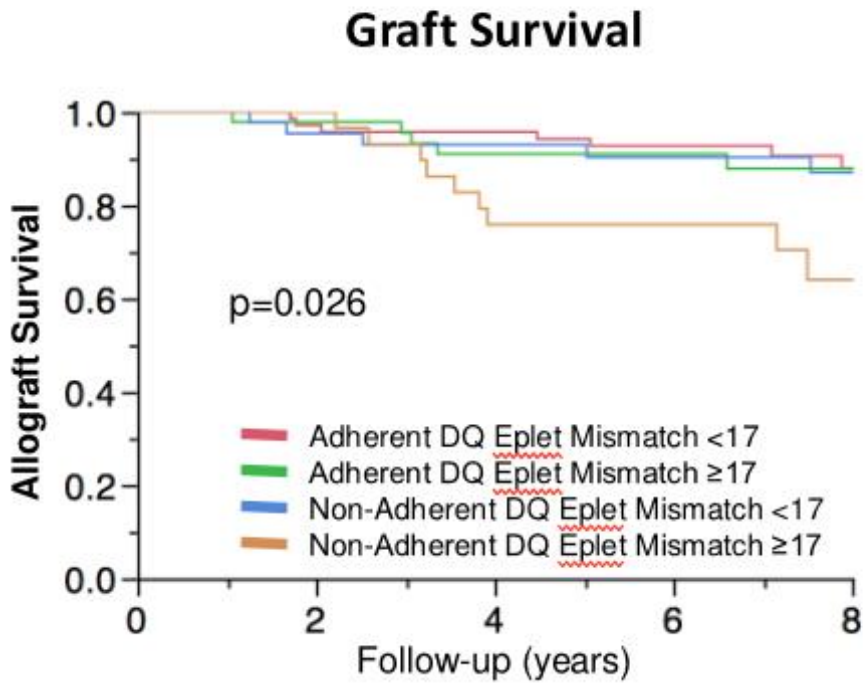
Wiebe et al., AJT (2023) 23:1882-1892

HLA-DR|DQ Molecular Mismatch Score

Predictive Biomarker for Immunosuppressive Minimization (Minnesota Cohort)

Synergy of Non-Adherence and DQ Eplet MM Load





Wiebe et al., AJT (2015) 15:2197-2202

How Can We Use This Information?

- To decide on immunosuppression induction
- To consider if reducing immunosuppression
- To decide about DSA monitoring

An Approach to DSA Monitoring Based on Risk

Wiebe et al AJT, 2023

- Testing all patients after 1 year expensive and low yield
- Can define high vs lower risk categories based on
  - -Age <35
  - -High DR/DQ Molecular mismatch
  - -CSA vs tacrolimus immunosuppression
  - -Tac level < 5 ng/ml
  - -Poor adherence
- This would be group to focus DSA testing on

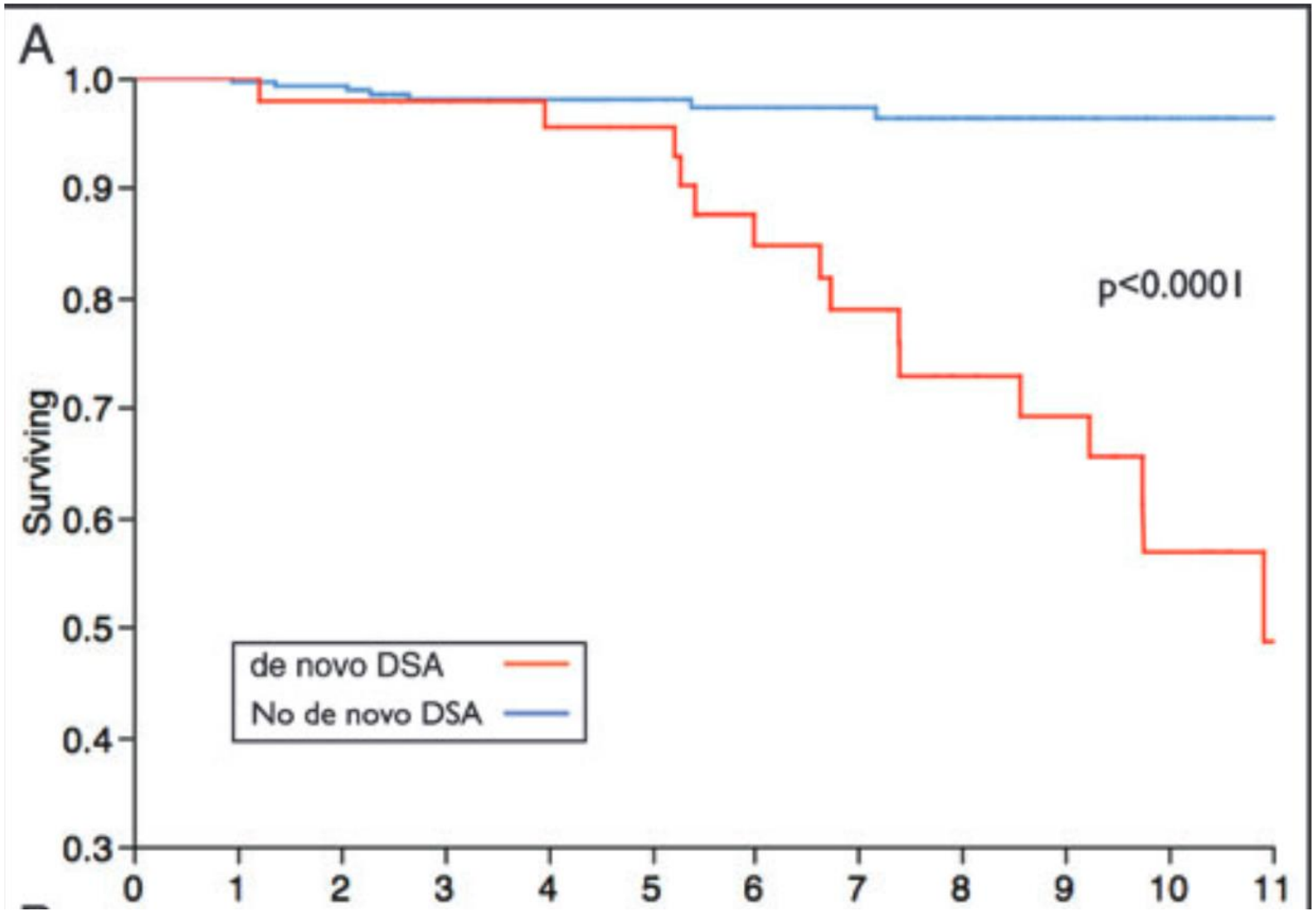
Conclusions

- Pre transplant and de novo DSA are important predictors of graft loss
- Newer approaches to Pre formed DSA have improved transplantation access and outcomes in most highly sensitized patients
- We still need better ways to reduce preformed DSA for the very highly sensitized to improve access

- Newer approaches may allow better prediction of the likelihood de novo DSA will form
- They offer the opportunity to tailor immunosuppression and monitoring to risk
- We need better treatments to remove de novo DSA and treat antibody mediated rejection

Graft Survival With and Without De Novo DSA

Wiebe et al AJT, 2012



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Not all eplet mismatches are made equal

- Class II > Class I
- DQ > DR

- Only a subset of eplet mismatches (A*11, A2, DQ6, DQA5) were linked to antibody formation in a pediatric US cohort (Charnaya O, Pediatr Nephrol 2021)

- Certain epitope specificities at DR and DQ had higher odds (1.6-4.7) of dnDSA in a Canadian single-centre cohort, often in setting of nonadherence (Wiebe C, AJT 2013)