

# The Natural History Of Pre-Existing Donor Specific Antibody And Amnestic Responses After Heart Transplantation

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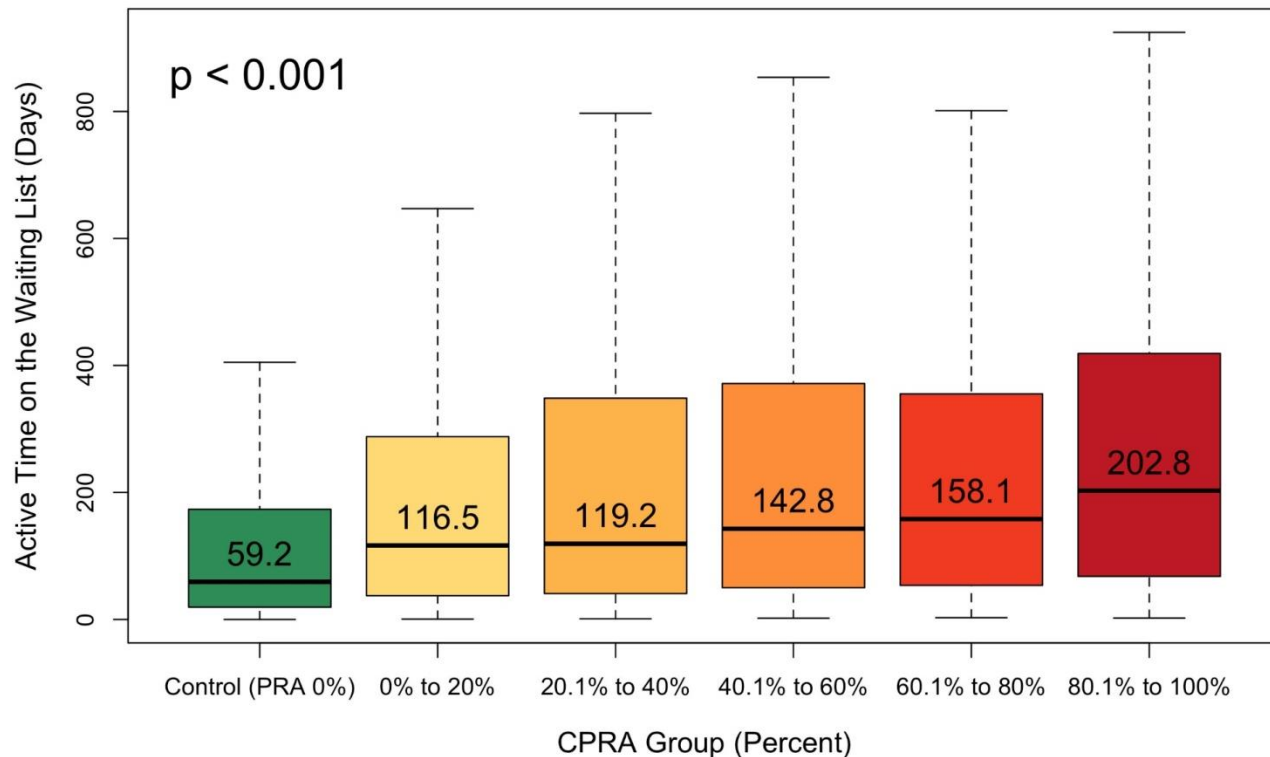
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# Disclosures

- I will not discuss off label use and/or investigational use of drugs/devices in my presentation.
- I have received research grants and/or serve on the advisory board/speaker bureau for Alexion Pharmaceuticals, Pfizer, Alnylam Pharmaceuticals, Mallinckrodt Pharmaceuticals, Therakos, Akcea, and Astra Zeneca

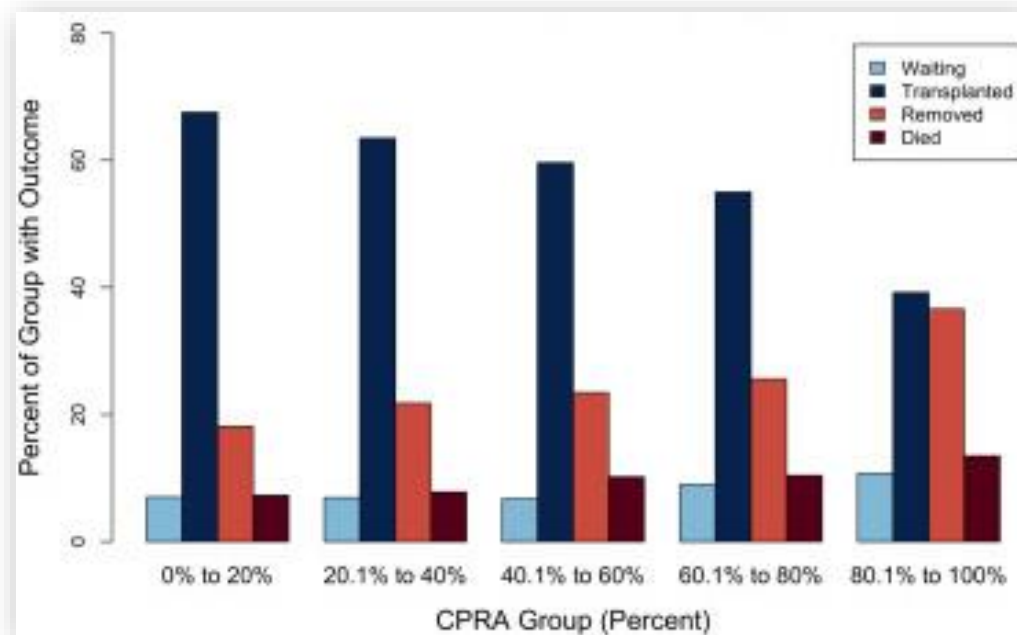
# Sensitization Limits the Suitable Donor Pool..

## Waiting Time by cPRA Group in Candidates Undergoing Heart Transplant

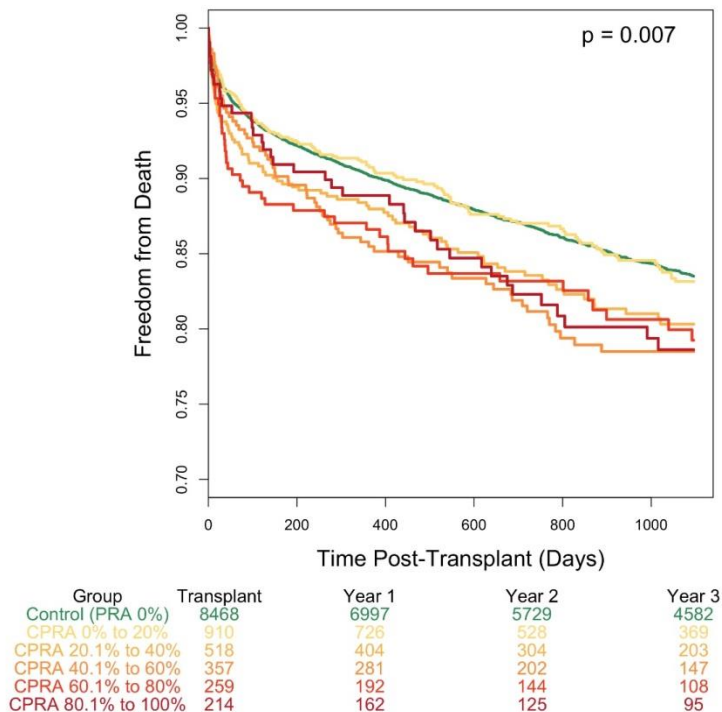


N=3855  
UNOS Registry

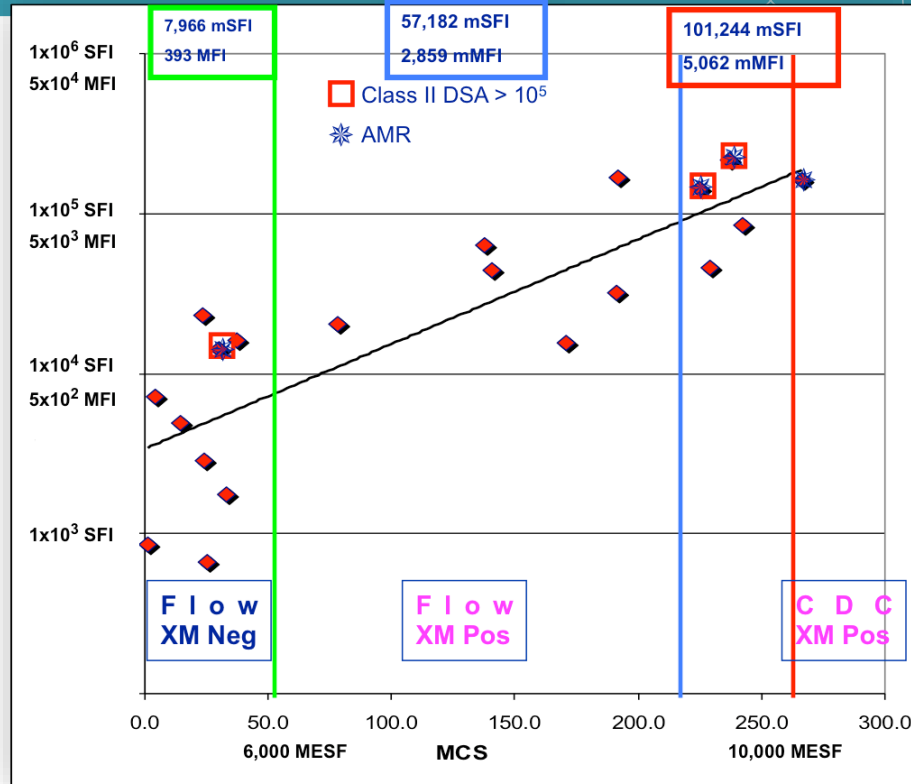
# Outcomes on the Heart Transplant Waiting List by cPRA Group



# Post-Transplant Mortality According to Pre-Transplant cPRA



# Determination of Acceptable Pretransplant Class I DSA Levels in Desensitized Renal Transplant Recipients



# Virtual Crossmatch

## Purpose

Avoid donors with HLA for which the recipient has strong anti-HLA Ab

Prevent hyperacute rejection

## Advantages

Does not require donor cells + recipient serum

No geographic constraints

## Process

Step 1: define cytotoxic HLA Ab by MFI threshold

Step 2: avoid donors with these HLA

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- PANEL REACTIVE ANTIBODY SCREEN
-   ANTIBODY CLASS II % PRA  75
-   ANTIBODY CLASS I  % PRA  78

-   SINGLE ANTIGEN ID CLASS I

-                                     MFI
-   B78: 6829
-   B51: 6537
-   B37: 5717
-   B75: 3996
-   B35: 3190
-   B53: 2748
-   B76: 2521
-   B52: 2455
-   A66: 2397
-   A26: 2164
-   A25: 2125

-   SINGLE ANTIGEN ID CLASS II

-                                     MFI
-   DR7: 14135
-   DQ7: 7789
-   DQ9: 6256
-   DQ8: 4472
-   DR12: 4403
-   DR103: 4111
-   DR53: 3268
```

# Purpose

- Sensitized patients have prolonged wait times for heart transplant and often low-level donor specific antibodies (DSA) will be crossed when accepting a donor heart.
- The purpose of this study was to determine if positive low-level DSA at the time of transplant increase in strength post transplant and impact outcomes after heart transplantation.



# Methods

- Between 2010 and 2018, we assessed 72 heart transplant patients in whom low-level DSA were crossed.
- Patients were compared to a contemporaneous control group (n=583) conditional to 1-year survival without DSA at transplant.

# Methods

- DSA strength, as measured by mean fluorescence intensity (MFI) was assessed at 1, 3, 6, 12 months post transplant.
- Other outcomes assessed at 1-year included:
  - Freedom from cardiac allograft vasculopathy (CAV, stenosis  $\geq 30\%$  by angiography)
  - Freedom from graft dysfunction (LVEF  $\leq 40\%$ )
  - Freedom from rejection (acute cellular rejection (ACR), antibody-mediated rejection (AMR), any treated rejection (ATR))

# Demographics

| Demographics                                                                          | Crossed Low-level DSA<br>(n=72) | Control: No DSA<br>(n=583) | P-Value          |
|---------------------------------------------------------------------------------------|---------------------------------|----------------------------|------------------|
| Mean Recipient Age, Years $\pm$ SD                                                    | 52.7 $\pm$ 12.3                 | 56.2 $\pm$ 12.7            | <b>0.025</b>     |
| Mean Donor Age, Years $\pm$ SD                                                        | 34.8 $\pm$ 13.2                 | 35.3 $\pm$ 12.7            | 0.749            |
| Body Mass Index, Mean $\pm$ SD                                                        | 24.7 $\pm$ 4.3                  | 25.2 $\pm$ 4.7             | 0.403            |
| Female (%)                                                                            | 60.8%                           | 25.2%                      | <b>&lt;0.001</b> |
| Previous Pregnancy in Females (%)                                                     | 91.1%                           | 65.8%                      | <b>0.001</b>     |
| Ischemic Time, Mean Mins $\pm$ SD                                                     | 187.4 $\pm$ 61.3                | 170.1 $\pm$ 50.7           | <b>0.008</b>     |
| Primary Reason for Transplant, Underlying<br>Diagnosis of Coronary Artery Disease (%) | 31.1%                           | 31.5%                      | 1.000            |
| Status 1 at Transplant (%)                                                            | 66.7%                           | 74.0%                      | 0.392            |

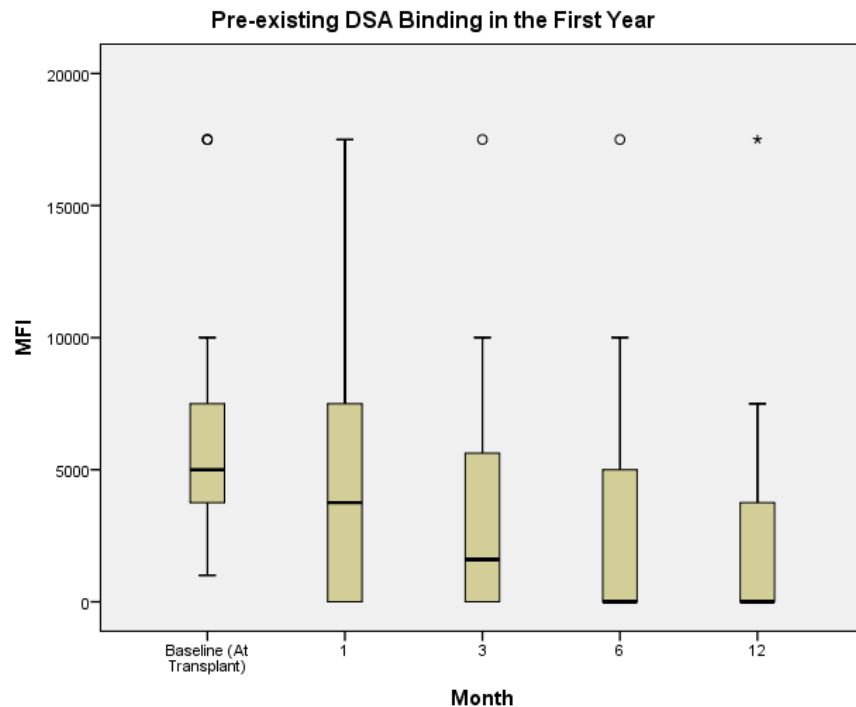
# Demographics

| Demographics                                           | Crossed Low-level DSA<br>(n=72) | Control: No DSA<br>(n=583) | P-Value          |
|--------------------------------------------------------|---------------------------------|----------------------------|------------------|
| Cytomegalovirus Mismatch (%)                           | 21.1%                           | 23.3%                      | 0.766            |
| Diabetes Mellitus (%)                                  | 37.8%                           | 31.6%                      | 0.293            |
| Treated Hypertension (%)                               | 59.5%                           | 51.9%                      | 0.266            |
| Insertion of Mechanical Circulatory Support Device (%) | 27.0%                           | 28.6%                      | 0.891            |
| Prior Blood Transfusion (%)                            | 45.6%                           | 37.0%                      | 0.187            |
| Pre-Transplant PRA $\geq$ 10% (%)                      | 89.0%                           | 23.0%                      | <b>&lt;0.001</b> |
| Pre-Transplant Creatinine, Mean $\pm$ SD               | 1.5 $\pm$ 1.0                   | 1.6 $\pm$ 1.2              | 0.610            |

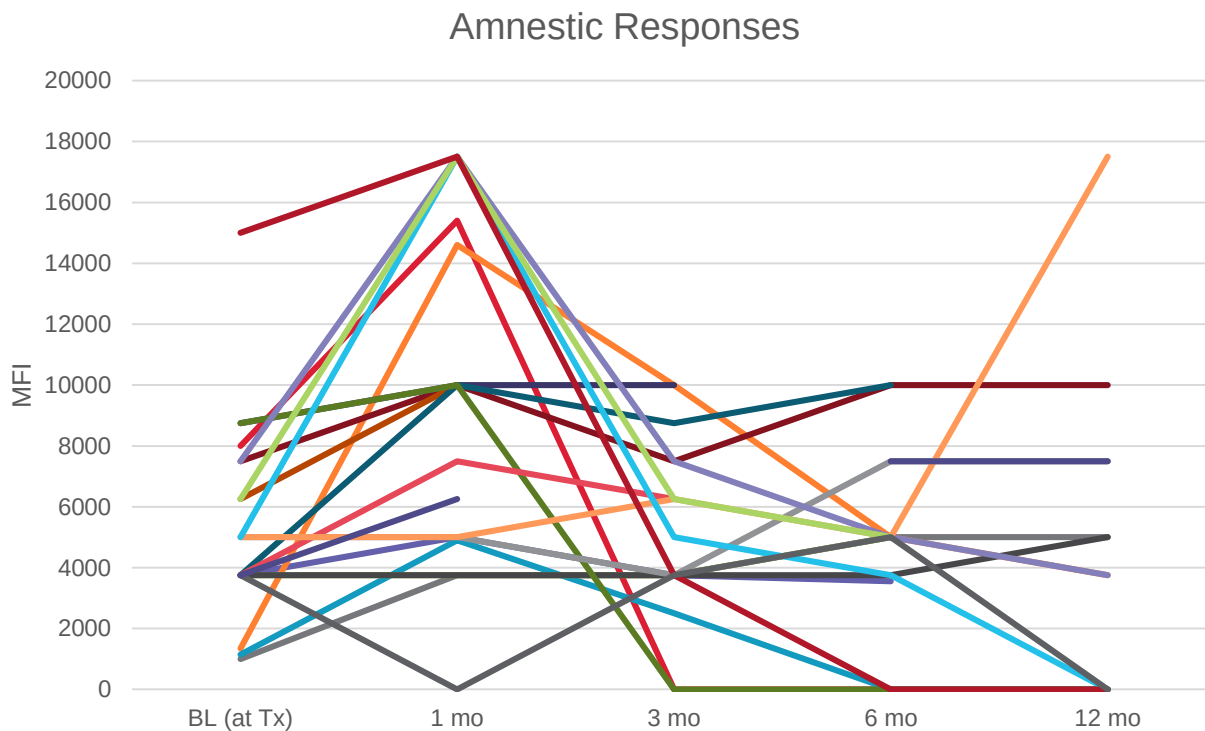
## Results: DSA Binding

| Endpoints                              | Crossed Low-level DSA<br>(n=72) |
|----------------------------------------|---------------------------------|
| MFI at Baseline, Mean $\pm$ SD         | 6187 $\pm$ 3511                 |
| MFI at 1 Month, Mean $\pm$ SD          | 4823 $\pm$ 4984                 |
| MFI at 3 Months, Mean $\pm$ SD         | 3118 $\pm$ 3816                 |
| MFI at 6 Months, Mean $\pm$ SD         | 2515 $\pm$ 3572                 |
| MFI at 12 Months, Mean $\pm$ SD        | 1890 $\pm$ 3443                 |
| Amnestic Response within 1-Year, n (%) | 23 (31.9%)                      |

# Results: DSA Binding



# Results: Amnestic Responses



## Results: Clinical Outcomes

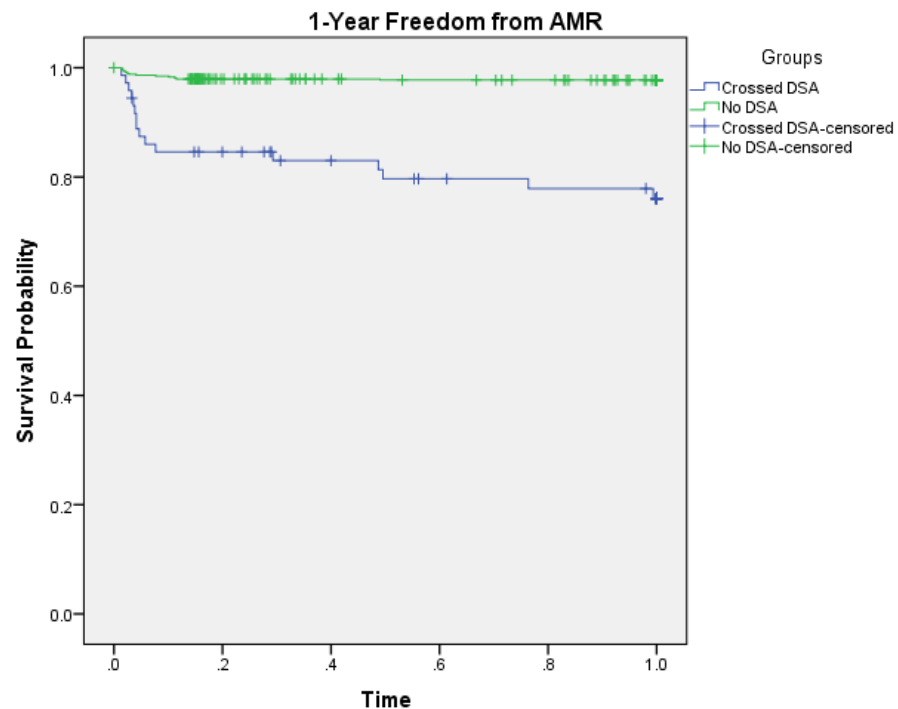
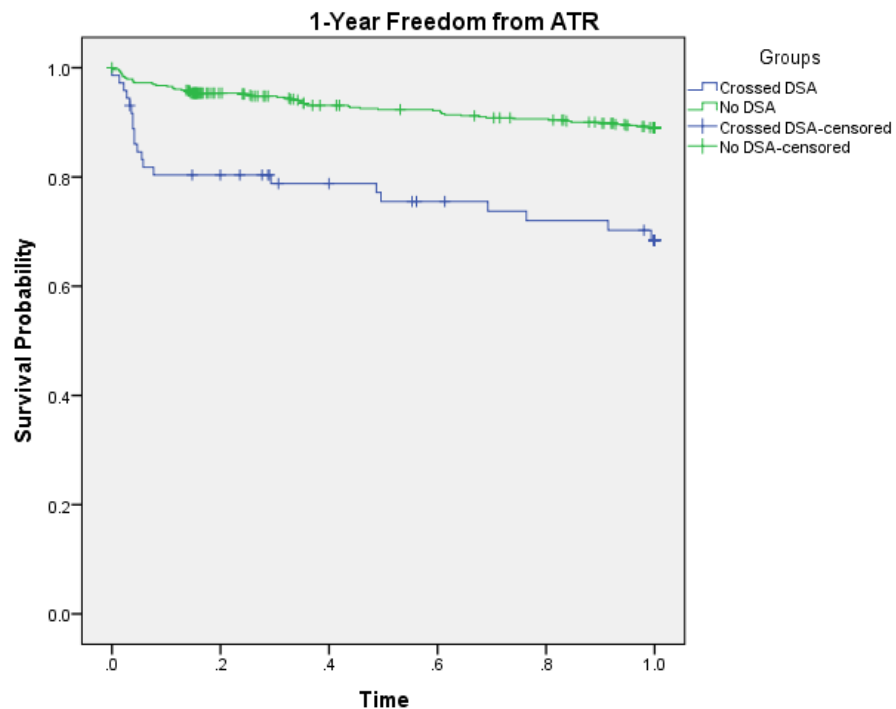
| Endpoints                                                  | Crossed Low-level DSA<br>(n=72) | Control: No DSA<br>(n=583) | P-Value |
|------------------------------------------------------------|---------------------------------|----------------------------|---------|
| 1-Year Freedom from CAV                                    | 94.4%                           | 94.3%                      | 0.991   |
| 1-Year Freedom from Graft Dysfunction<br>(LVEF $\leq$ 40%) | 90.3%                           | 93.5%                      | 0.294   |



# Results: Rejection Outcomes

| Endpoints               | Crossed Low-level DSA<br>(n=72) | Control: No DSA<br>(n=583) | P-Value |
|-------------------------|---------------------------------|----------------------------|---------|
| 1-Year Freedom from ATR | 70.8%                           | 89.7%                      | <0.001  |
| 1-Year Freedom from ACR | 90.3%                           | 94.7%                      | 0.099   |
| 1-Year Freedom from AMR | 77.8%                           | 97.8%                      | <0.001  |

# Results: Kaplan Meier Curves For Rejection



# Results Summary

- Approximately one third of patients with pre-existing DSA at transplant demonstrated an increase in DSA strength.
- Patients with pre-existing DSA had decreased freedom from ATR and AMR but no differences in freedom from CAV, graft dysfunction, or ACR compared to the control group.

# Conclusion

- Crossing low-level DSA may increase the risk of AMR, but there is no difference in clinically important sequelae such as CAV or graft dysfunction.
- Thus, accepting low-level DSA at the time of transplant appears feasible and could broaden the donor pool.