Immunologic Risk Factors:
Approach to the Sensitized Patient

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RESOLVING THE ORGAN SHORTAGE

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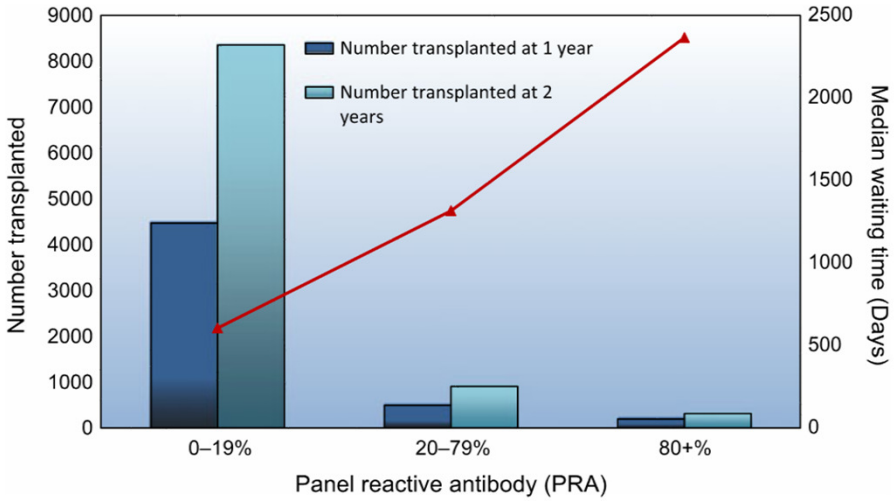
Conflict of Interest Disclosure

- Alexion Pharmaceuticals – Research Grant
- I will discuss off-label use of the following drugs:
  - Rituximab, bortezomib, IVIG, eculizumab

The Challenge of the Sensitized Patient..

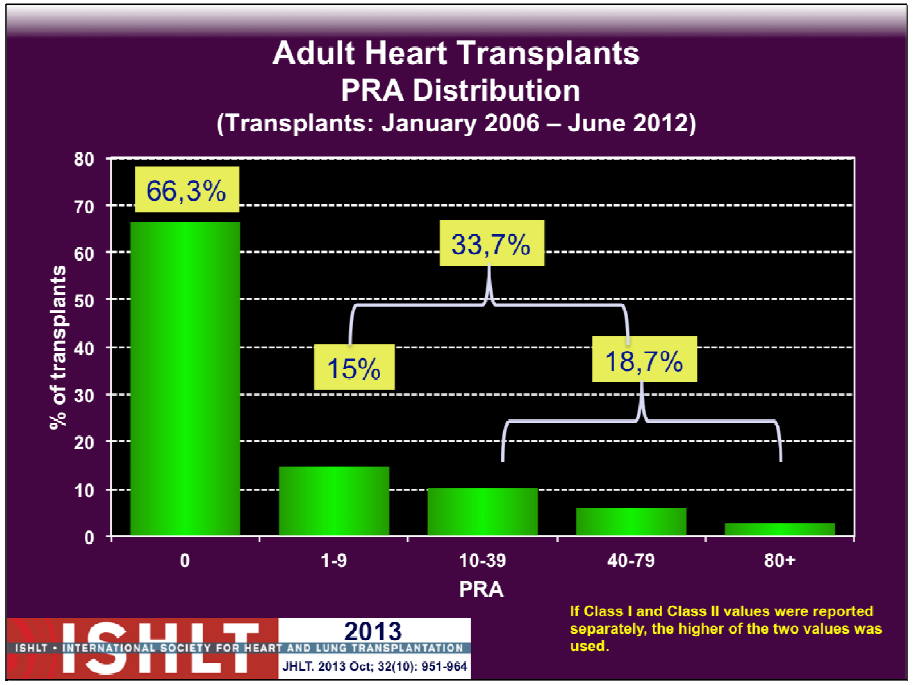
- Pre-transplant
  - Limited donor pool
  - Prolonged (prohibitive) time on wait-list
  - Increased wait-list mortality

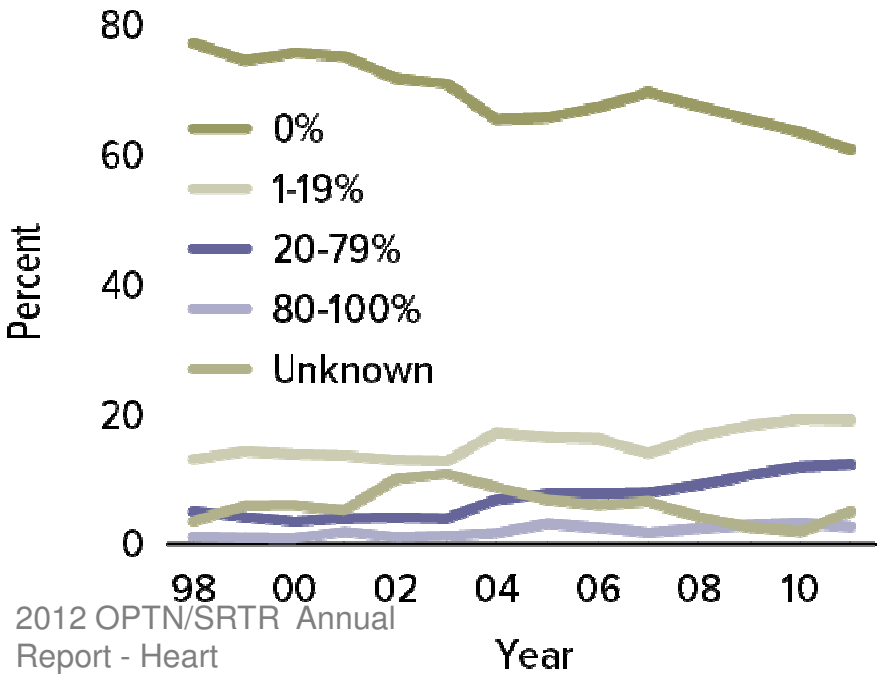


2013 OPTN/SRTR Annual Report (All Organs)

- …And yet the sensitized patient does not qualify for priority on the current (or proposed!) donor heart allocation scheme

Sensitization – an emerging problem

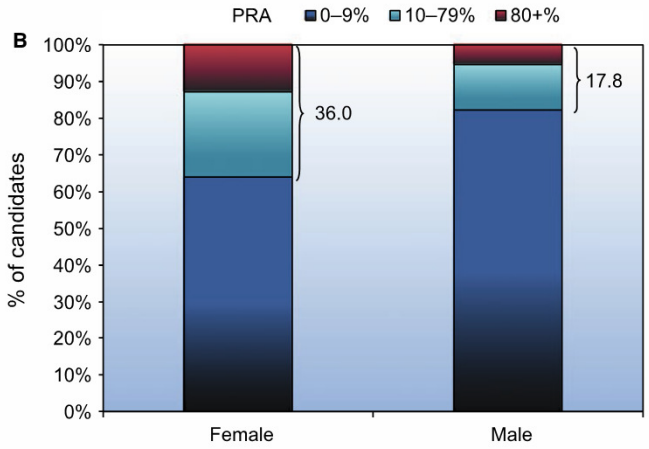


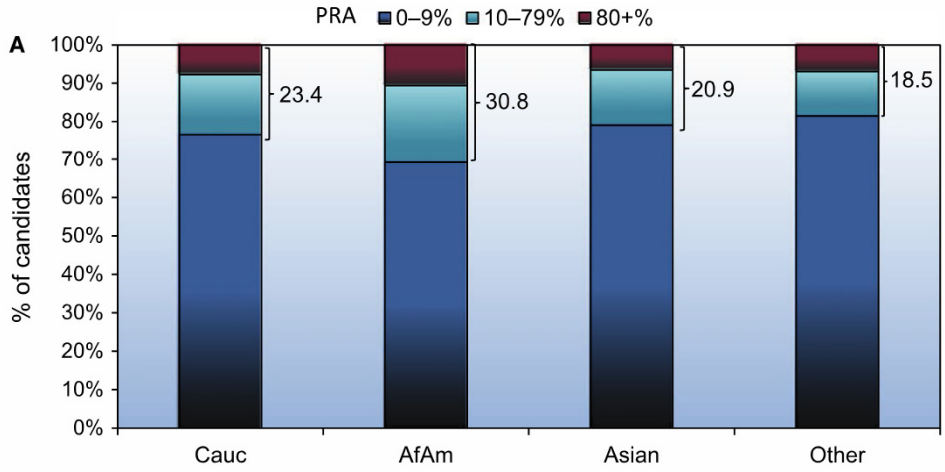


2012 OPTN/SRTR Annual Report - Heart

Risk Factors for Sensitization

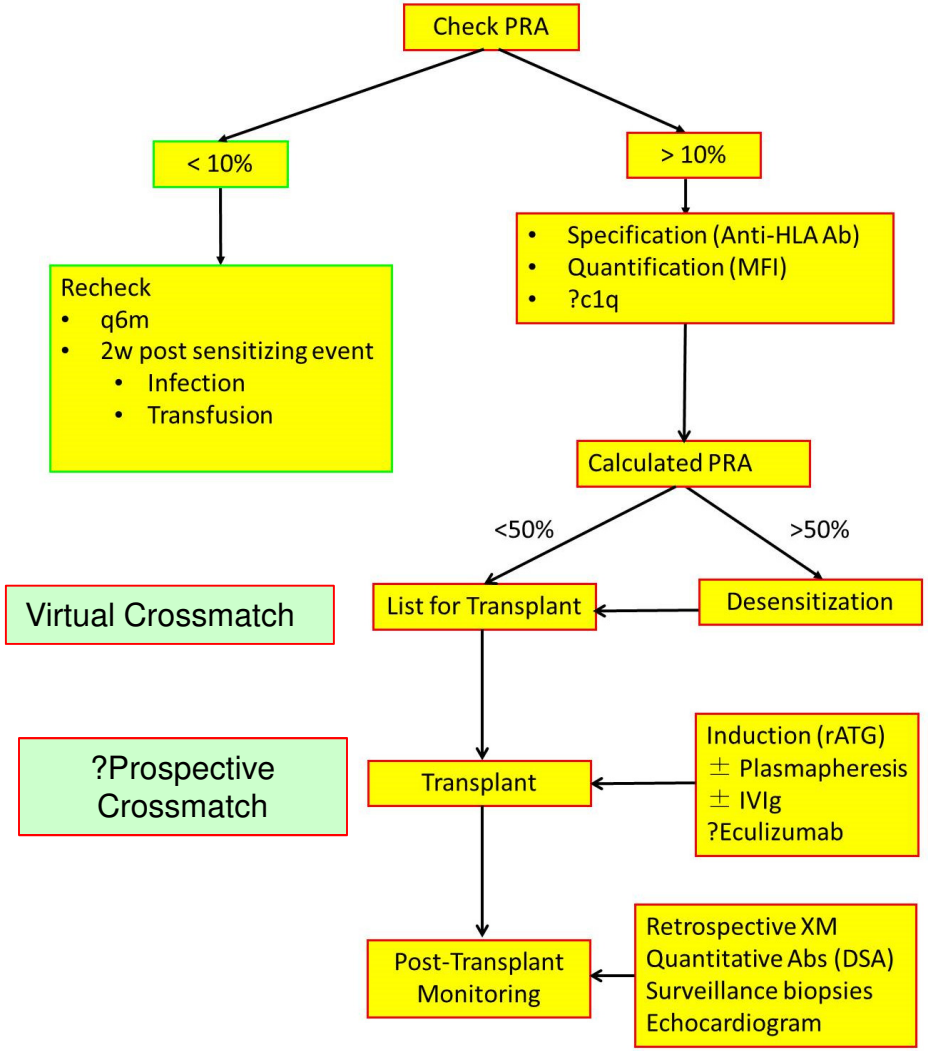
- Blood transfusion
- Infection
- Prior transplant
- Gender
- Race
- Prior cardiac surgery with homograft
- Ventricular Assist Devices





2004 OPTN/SRTR Annual Report

Pre-transplant Protocol: Management of Sensitized Patients – Heart



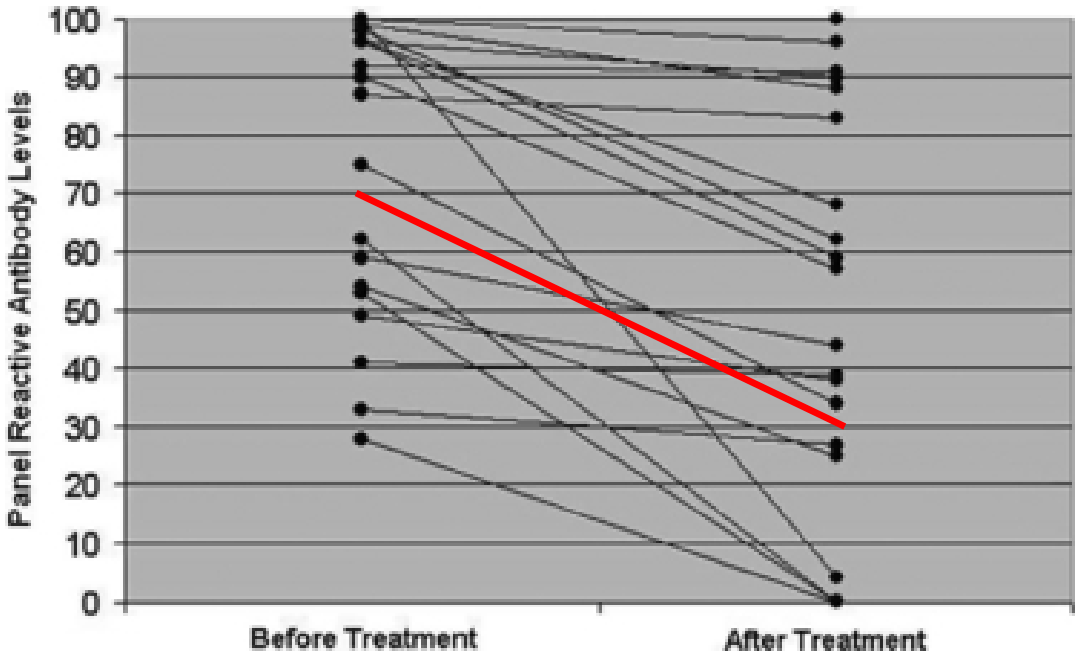
Patel and Kobashigawa
Future Cardiol. 2012
Jul;8(4):623-35

Desensitization Therapies

Combined Strategies

Approaches	Therapies
Antibody removal	Therapeutic Plasma Exchange, Immunoadsorption
To alter antibody production B cell modulation Plasma cell depletion	Rituximab, Bortezomib
Immunomodulation (Ab inactivation)	IVIG
Suppression of the T-cell response	Steroids, cytolytic therapy, MMF, CNI
Complement blockade	Eculizumab

Desensitization in Heart Transplantation



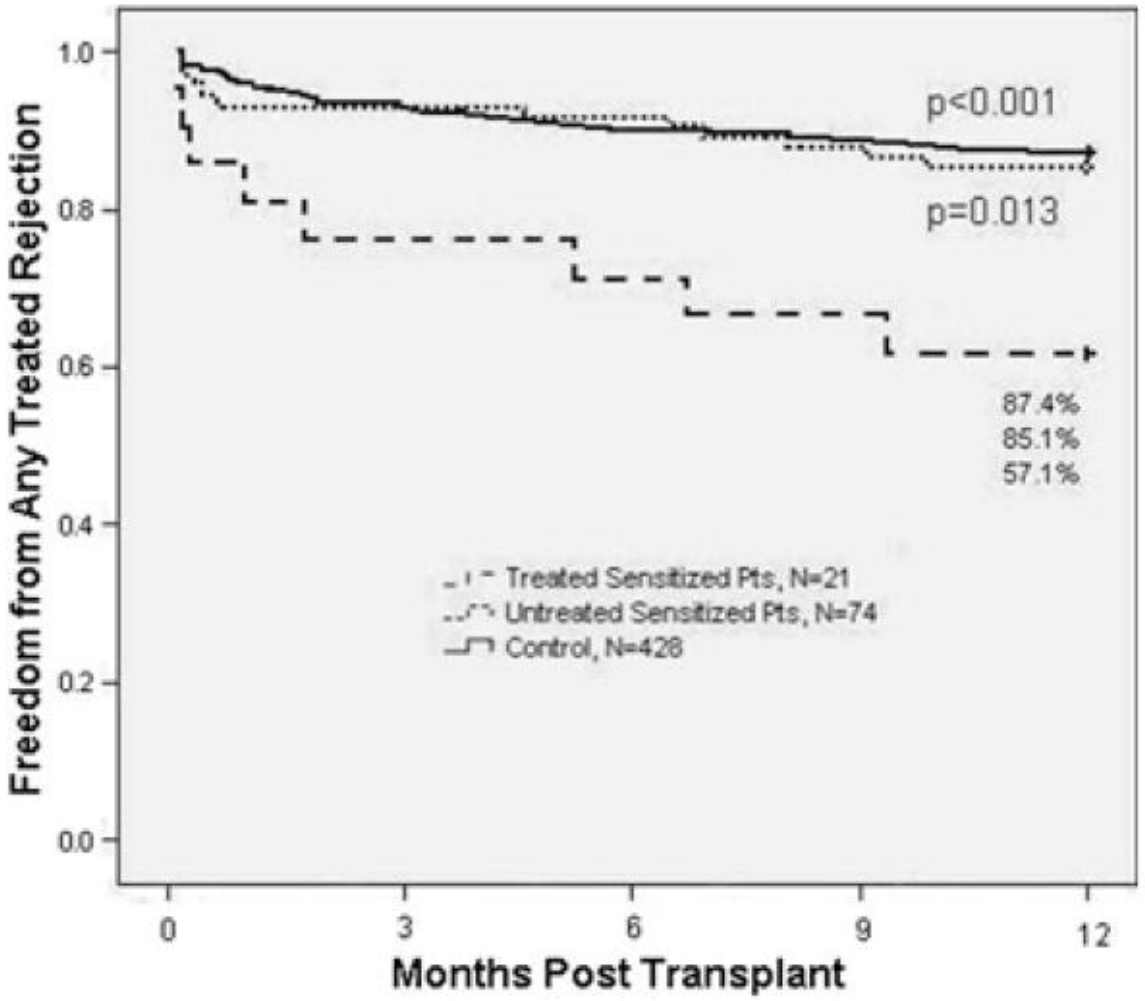
N=21

Individual reductions in mean PRA levels of treated sensitized heart transplant candidates.

Treatments: plasma exchange, IVIg, rituximab

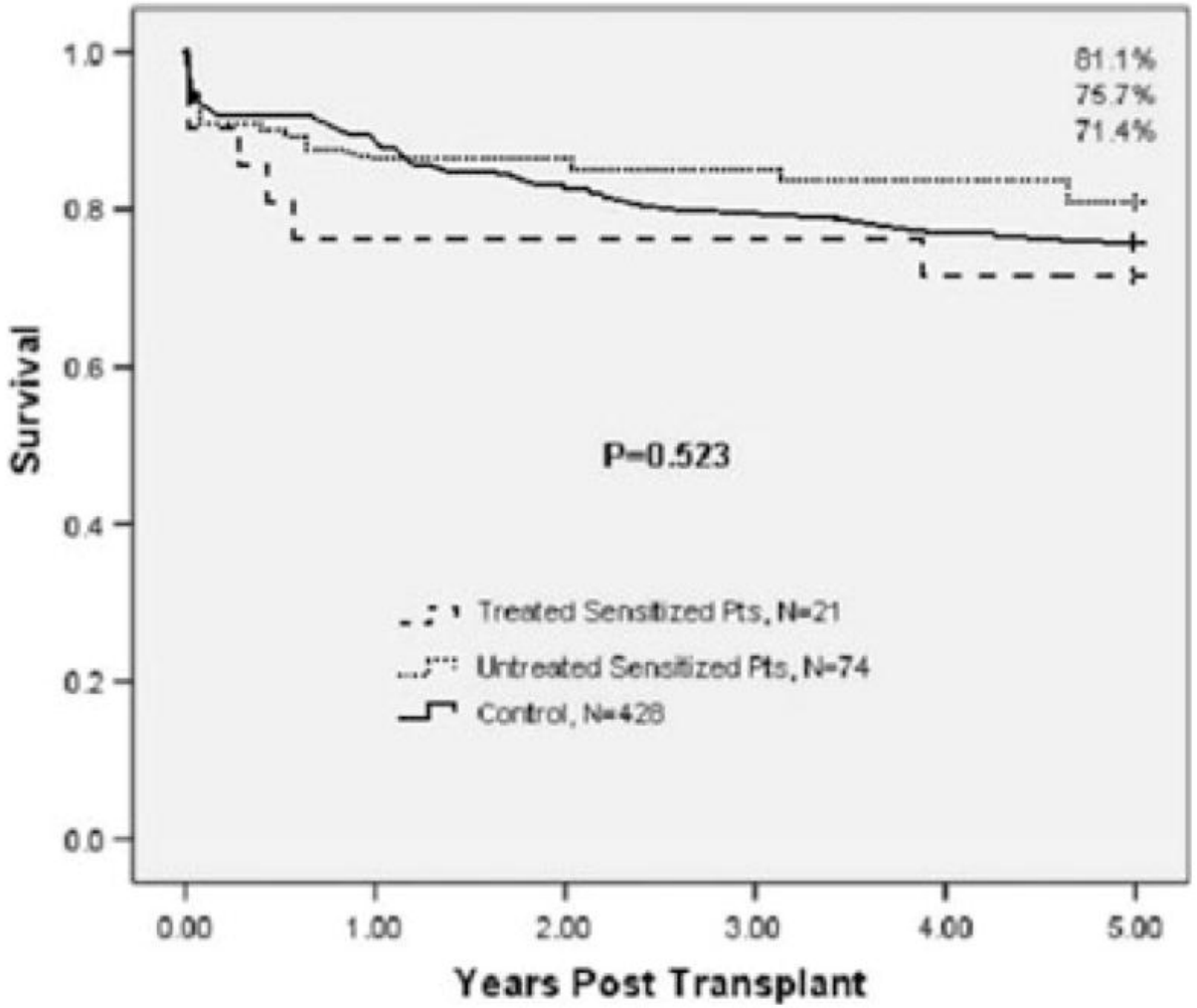
Kobashigawa, Patel et al: Clin Transplant. 2011 Jan;25(1):E61-7.

1-year Freedom From Any Treated Rejection



Kobashigawa, Patel et al: Clin Transplant. 2011 Jan;25(1):E61-7.

5-year Survival



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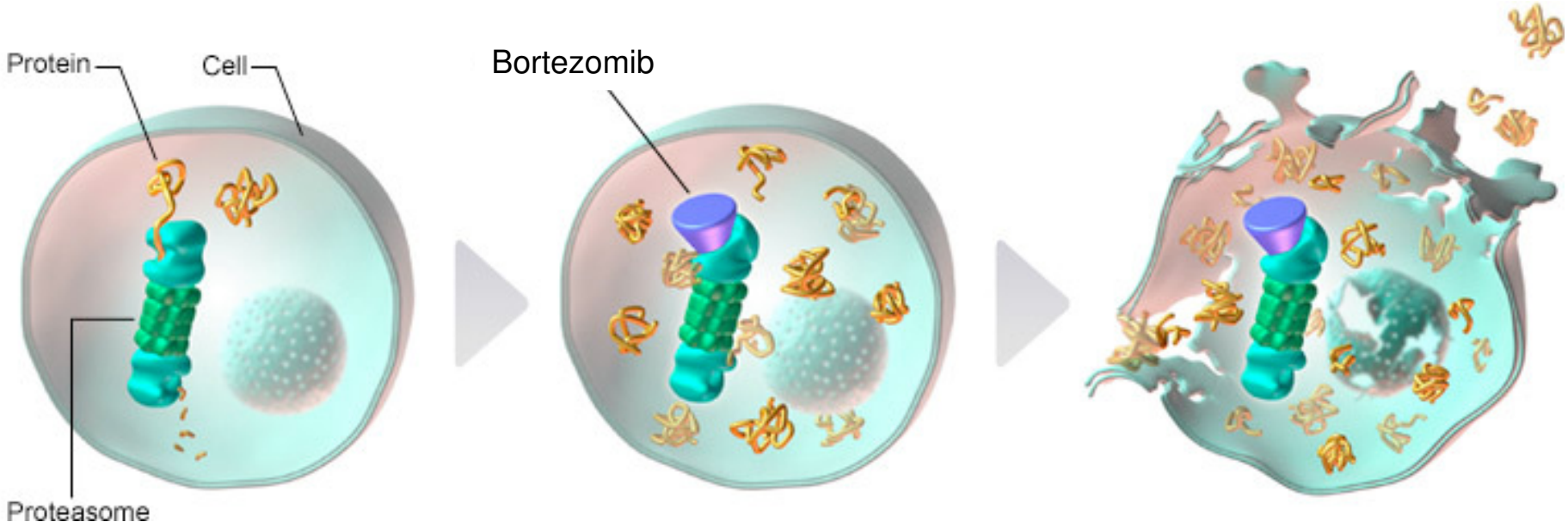
Bortezomib

Proteasome inhibitor active against plasma cells

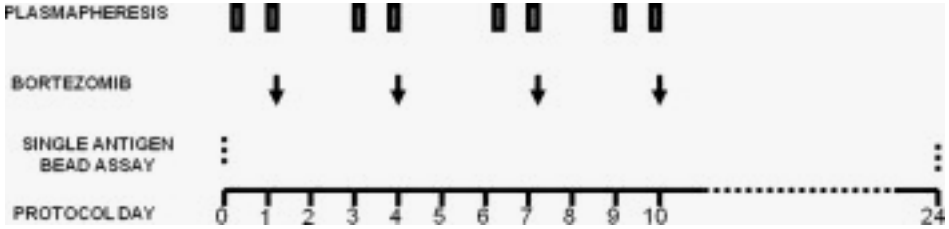


Normal breakdown of proteins

Bortezomib blocks the proteasome, causing an imbalance of proteins in the cells

Protein imbalance can lead to cell death

Refractory Antibodies in Heart Transplantation:



cPRA ≥ 50% after IV Ig/ritux protocol

Days 1, 4, 7, 10

plasma exchange

Bortezomib 1.3 mg/m²

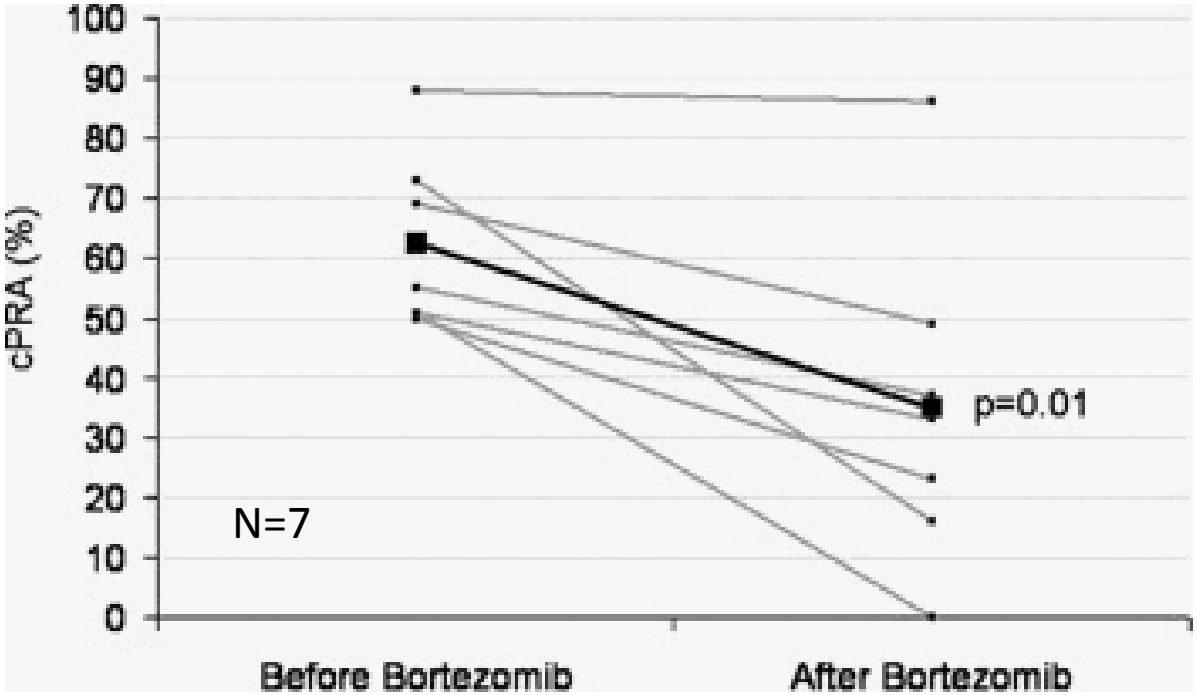
Day 24

Check PRA

Repeat 2-wk cycle if cPRA ≥ 50%

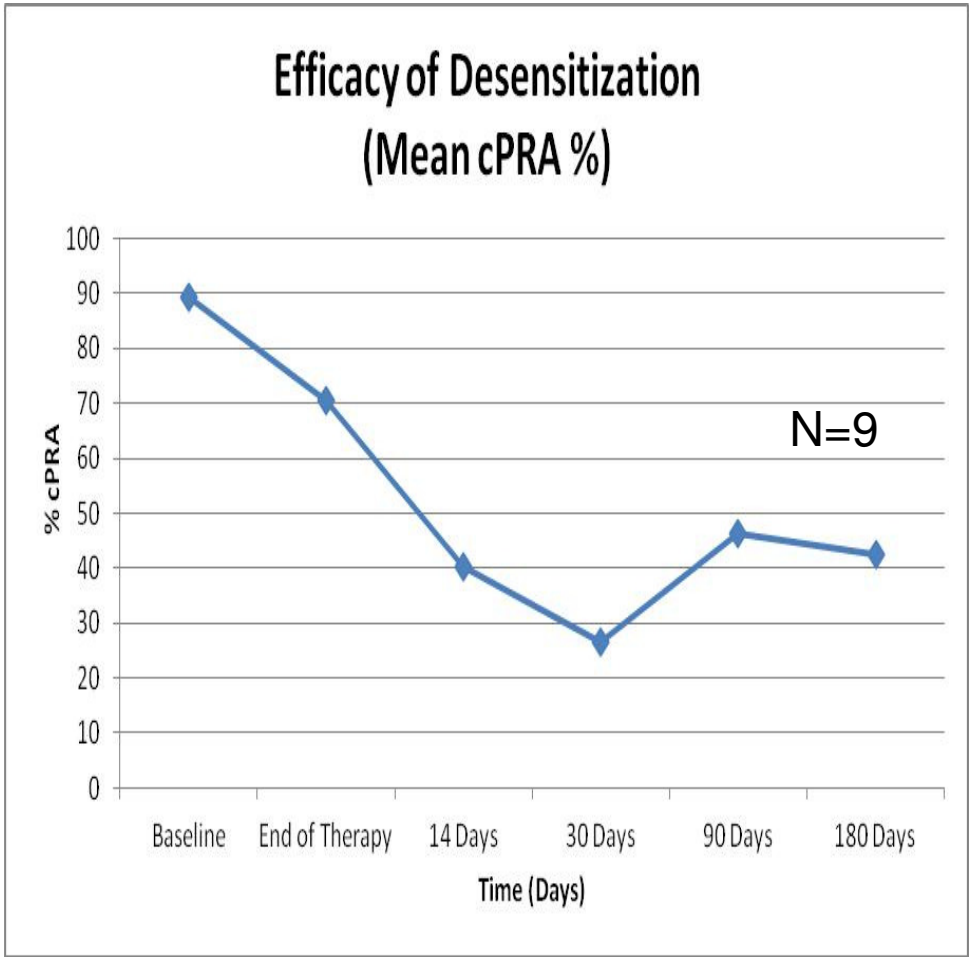
Patel JK et al: J Heart Lung Transplant. 2011 Dec;30(12):1320-6

Desensitization with Plasma Exchange and Bortezomib for Refractory Antibodies:



Patel JK et al: J Heart Lung Transplant. 2011 Dec;30(12):1320-6

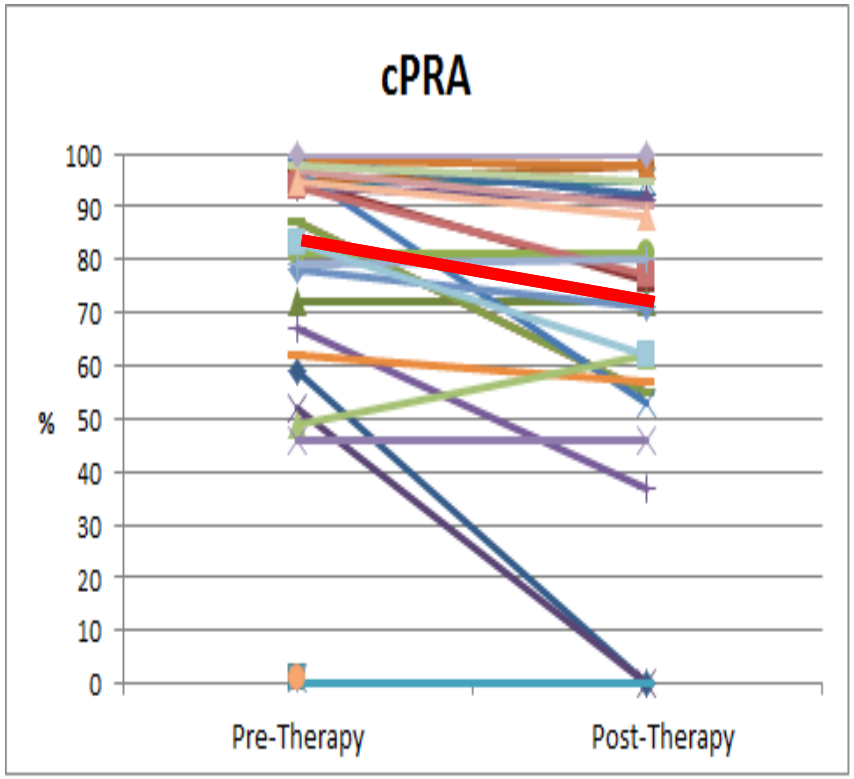
Late Response to Desensitization Therapy



Kobashigawa et al ATC 2012

Desensitization for Heart Transplantation with Plasma Exchange and Bortezomib

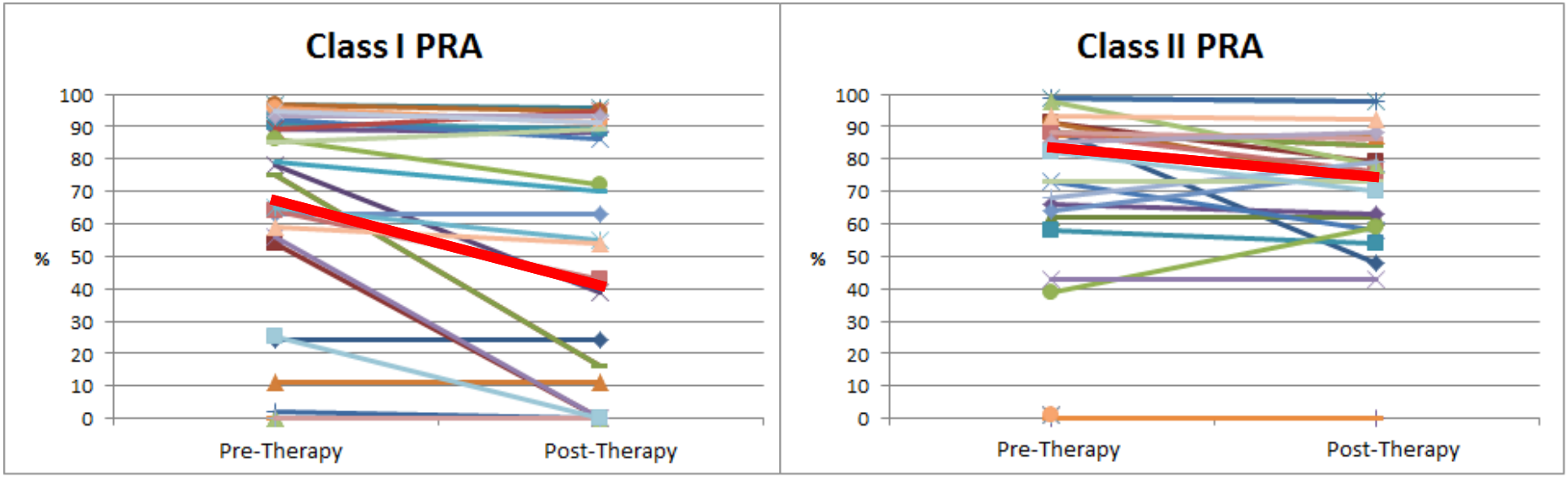
- 29 patients treated with plasma exchange and bortezomib
- 7 patients received prior therapies
  - Plasmapheresis
  - IVIg
  - Rituximab
- Overall modest decrease in cPRA
  - Mean cPRA 82% ➔71%
- Bimodal response
  - 8/29 patients >15% drop in cPRA
  - For these patients:
    - Mean cPRA 79%➔45%



N=29

Patel J et al. ISHLT 2015

Desensitization for Heart Transplantation with Plasma Exchange and Bortezomib



N=29

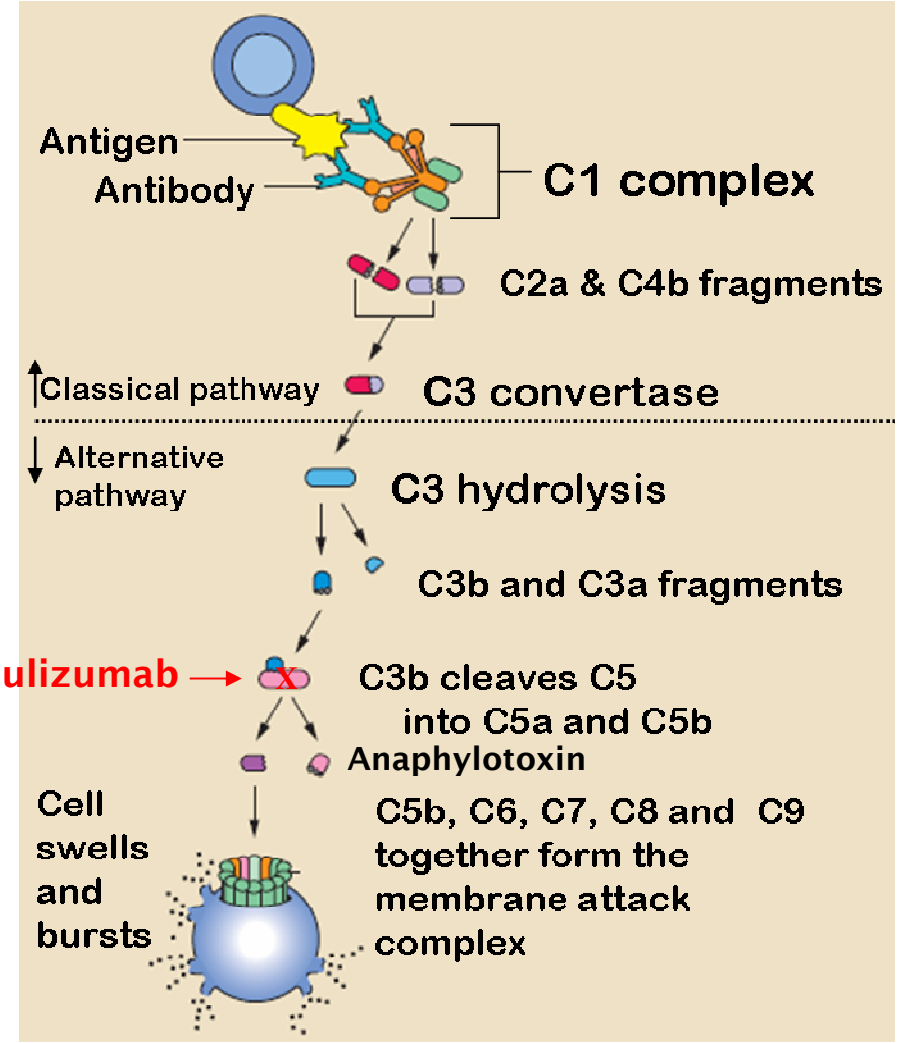
Patel J et al. ISHLT 2015

Desensitization for Heart Transplantation with Plasmapheresis and Bortezomib

- All 29 patients successfully transplanted
- 1 death at 20 months at retransplant
- 10/29 (34%) treated for rejection
  - 3 patients ≥ ACR 2R
  - 3 patients ≥ AMR 2
  - 1 patient Biopsy Negative Rejection
  - 3 patients Mixed Rejection

Patel J et al. ISHLT 2015

Eculizumab



Eculizumab In Highly Sensitized Patients After Heart Transplantation -DUET Pilot Study

clinicaltrials.gov NCT02013037

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Pilot Study of Eculizumab in Highly Sensitized Patients Undergoing Heart Transplant

- Pilot study using eculizumab immediately after heart transplant for the highly sensitized patient (PRA>70%).
- Study endpoints:
  - Assess efficacy to prevent symptomatic AMR or ACR.
  - IVUS to assess efficacy to prevent cardiac allograft vasculopathy (CAV).
- Eculizumab Protocol:
  - Eculizumab
    - Day 0: 1200 mg
    - Day 1,7,14,21: 900 mg
    - Day 28,42,56: 1200 mg
  - Thymoglobulin 1.5 mg/kg x 5days followed by IVIg 1 gm/kg x 2days

Patel/Kobashigawa – Cedars-Sinai DUET Study

Demographics (N=10)

Mean recipient Age, Year ± SD	50.6 ± 12.9
Mean Donor Age, Years ± SD	31.3 ± 12.8
BMI, Mean ± SD	24.6 ± 3.4
Female (%)	80.0%
Previous Pregnancy in Females (%)	100.0%
Ischemic Time, Mean Mins ± SD	126.5 ± 55.6
Primary Reason for Tx, Underlying Diagnosis of CAD (%)	40.0%
Status 1 at Transplant (%)	100.0%
CMV Mismatch (%)	20.0%
Diabetes Mellitus (%)	30.0%
Treated Hypertension (%)	60.0%
Prior Blood Transfusion (%)	70.0%
Pre-Transplant cPRA, Mean ± SD	93.7 ± 8.6
Pre-Transplant Creatinine Mean ± SD	1.5 ± 0.6
Insertion of MCS Device	50.0%

Prior Desensitization Therapies

Therapy	N=10
Bortezomib + Plasmapheresis	70.0% (7/10)
Bortezomib + Plasmapheresis + IVIG	10.0% (1/10)
IVIG + Plasmapheresis	10.0% (1/10)
None	10.0% (1/10)

Prospective Donor-Specific Crossmatch Results at Transplant

Crossmatch Type	Results, N=10
T-Flow Cytometry Crossmatch	117 ± 145 MCS
B-Flow Cytometry Crossmatch	220 ± 96 MCS
T-Cell Complement-Dependent Cytotoxicity Crossmatch	All negative
B-Cell Complement-Dependent Cytotoxicity Crossmatch	All negative

Positive T-Flow >50 MCS Positive B-Flow >100 MCS

Preliminary Outcomes

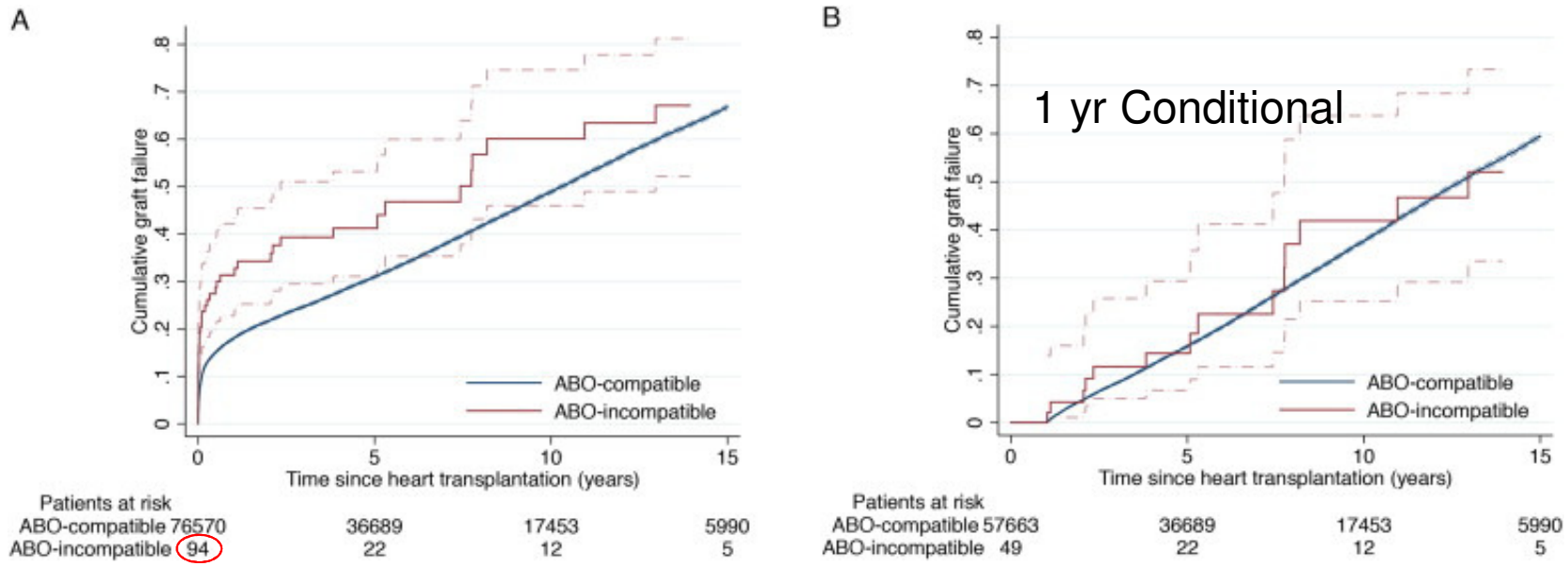
Endpoints	N=10
% of Patients with DSA at 1 Month Post-Transplant	80.0%
1-Year Freedom from Treated Infection	90.0%
1-Year Actuarial Survival	90.0%
1-Year Actuarial Freedom from Cellular Rejection (ISHLT ≥2R)	100.0%
1-Year Actuarial Freedom from Antibody-Mediated Rejection (AMR ≥2)	77.8%
1-Year Actuarial Freedom from Any Treated Rejection	80%
Average 6-Month Left Ventricular Ejection Fraction (%)*	65.0 ± 2.6

* No patient with reduced LVEF

ABO Incompatible (ABOi) Transplantation

- Well established in pediatric solid organ transplantation including hearts
- In adults, experience is greatest in living donor kidney transplantation (LDKT)
- In Japan constitutes 14% of kidney transplants and 30% of LDKT
- May lower incidence of AMR due to early antibody depletion
- Potential to significantly expand the donor pool – approx. 35% of donors ABOi.

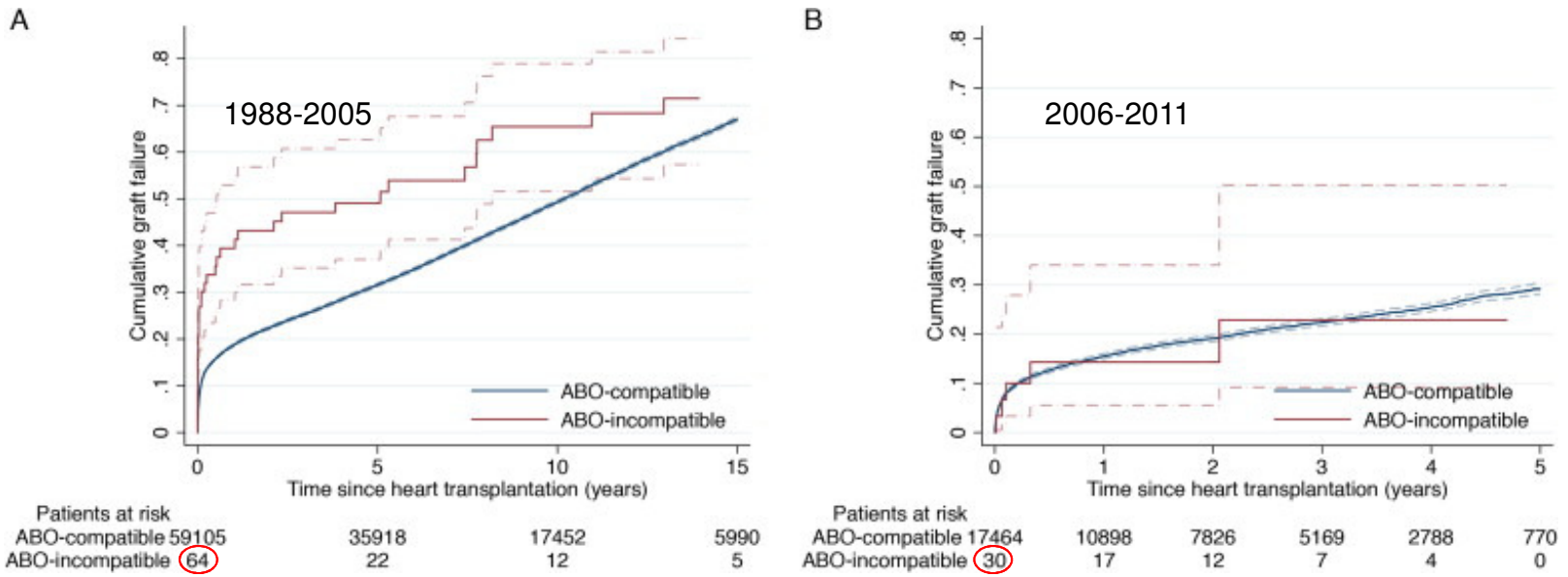
Outcomes after ABO-incompatible heart transplantation in adults: A registry study Cumulative death or retransplantation



Cumulative death or retransplantation of ABO-incompatible and ABO-compatible heart transplants for the entire study period (A) and for grafts surviving the first year (B).

Bergenfeldt H et al, JHLT Volume 34, Issue 7, 2015, 892–898

Outcomes after ABO-incompatible heart transplantation in adults: A registry study death or retransplantation by era



Overall incidence of death or retransplantation for ABO-incompatible and ABO-compatible heart transplants during the periods 1988-2005 (A) and 2006-2011 (B).

Bergenfeldt H et al, JHLT Volume 34, Issue 7, 2015, 892–898

Summary

- Number of sensitized patients awaiting heart transplant continues to increase
- Sensitized patients spend a longer time on the wait-list, have increase wait-list mortality
- There are no randomized trials of desensitization in solid organ transplantation
- Efficacy of treatment varies widely – **Not All Sensitized Patients Are Equal**
- Combination therapies appear to be more effective
- Patients transplanted following desensitization appear to have acceptable survival although allograft rejection rates remain high
- There is a suggestion that even if therapies are ineffective at significantly reducing alloantibody burden, there may be sufficient **immunomodulation** to permit transplantation with acceptable outcomes
- Adult ABOi heart transplantation is an emerging area with promise of acceptable long-term outcomes
- The proposed US Heart Allocation Scheme will not allow priority for sensitized patients, unlike the Canadian scheme or new US Kidney Transplant Allocation Scheme