Defining and Prioritizing Highly Sensitized Candidates

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CEOT
CUTTING EDGE OF TRANSPLANTATION
RESOLVING THE ORGAN SHORTAGE
PRACTICE | POLICY | POLITICS
FEBRUARY 25-27, 2016 • PHOENIX, ARIZONA

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Conflict of Interest Disclosure

- I have no relevant financial relationships to disclose

Sensitization - The Problem

1. Increasing numbers of sensitized patients – overall 6-9% of HTx candidates
    - Ventricular assist devices – 35-66% of BTT
    - Congenital heart disease – prior blood transfusions, homografts

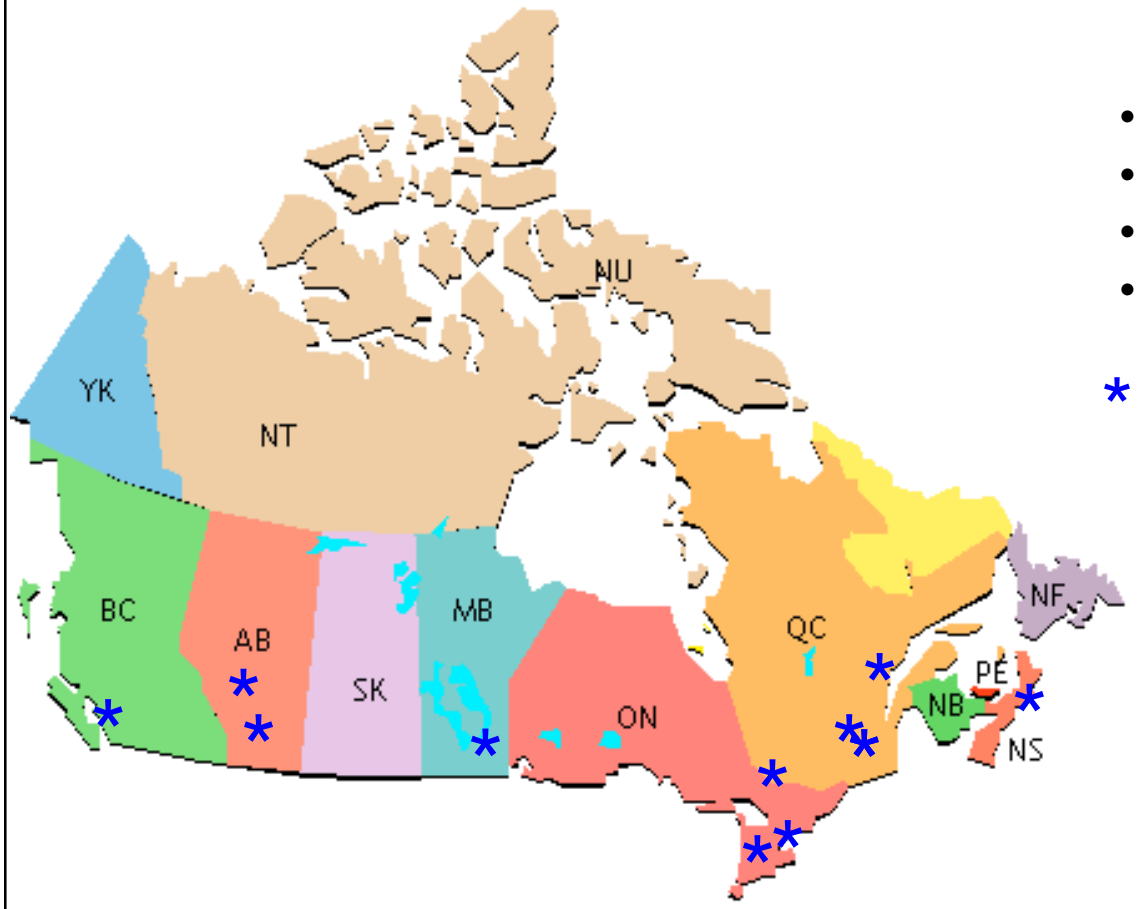
2. Presently Inferior outcomes post transplant
    - Longer waiting times to transplant
    - Increased risk of CMR and antibody mediated rejection
    - Increased cardiac allograft vasculopathy
    - Increased mortality

3. No clear evidenced based approach, currently non-standardized management

www.ishlt.org accessed November 2015; Askar et al, JHLT. 2013;32:1241–1248 Patel et al Ann Thorac Surg 2009;88:814

Canadian Cardiac TRANSPLANT NETWORK

Highly Sensitized Patients in Cardiac Transplantation: Outcomes from the Canadian Prioritized Sharing Program



- 35.6 million population
- ~ 10 million km^2 area
- Pop. density of 3.5/mi^2
- 7600 km from east to west

* Cardiac transplant programs

Disadvantage: geographic distances

Advantage: small, collaborative cardiac transplant community

Overarching Goals – National 4S, Established 2010

- High Priority – equivalent to 1A status UNOS
- Provide access to organs equitably for all candidates while maintaining tolerable outcomes
- Virtual XM – single centre with good results to date
  - Nationally allocation for highly sensitized patients to increase likelihood of transplanting these pts
    - For those with no reasonable chance of local VCM (-)
- Not intended for desensitization/transplant protocols
- Review after one year to determine
  - Waiting times for sensitized patients
  - Movement of hearts between regions
  - Time spent in process

Canadian Heart Listing Status Criteria

Status 4
- Mechanically ventilated patient on high-dose single or multiple inotropes ± mechanical support excluding VAD.
- Patient with VAD malfunction or complication.
- Patient should be reconfirmed every 7 days as a Status 4 by a qualified physician, if still medically appropriate.

Status 4S
- *High PRA >80%.

Status 3.5
- High-dose or multiple inotropes in hospital, and patients not candidates for VAD therapy or no VAD available.
- Acute refractory ventricular arrhythmias.

Status 3
- VAD not meeting Status 4 criteria.
- Patients on inotropes in hospital, not meeting above criteria.
- Heart/Lung recipient candidates.
- Cyanotic congenital heart disease with resting saturation <65%.
- Congenital heart disease – arterial-shunt-dependent.
- Adult-sized complex congenital heart disease with increasing dysrhythmic or systemic ventricular decline.

Status 2
- In-hospital patient, or patient on outpatient inotropic therapy not meeting the above criteria.
- Adult with cyanotic CHD: resting 0_2 saturation 65–75% or prolonged desaturation to less than 60% with modest activity (i.e. walking).
- Adult with Fontan palliation with protein-losing enteropathy or plastic bronchitis.
- Patients listed for multiple organ transplantation (other than heart-lung).

Status 1
- All other out-of-hospital patients.

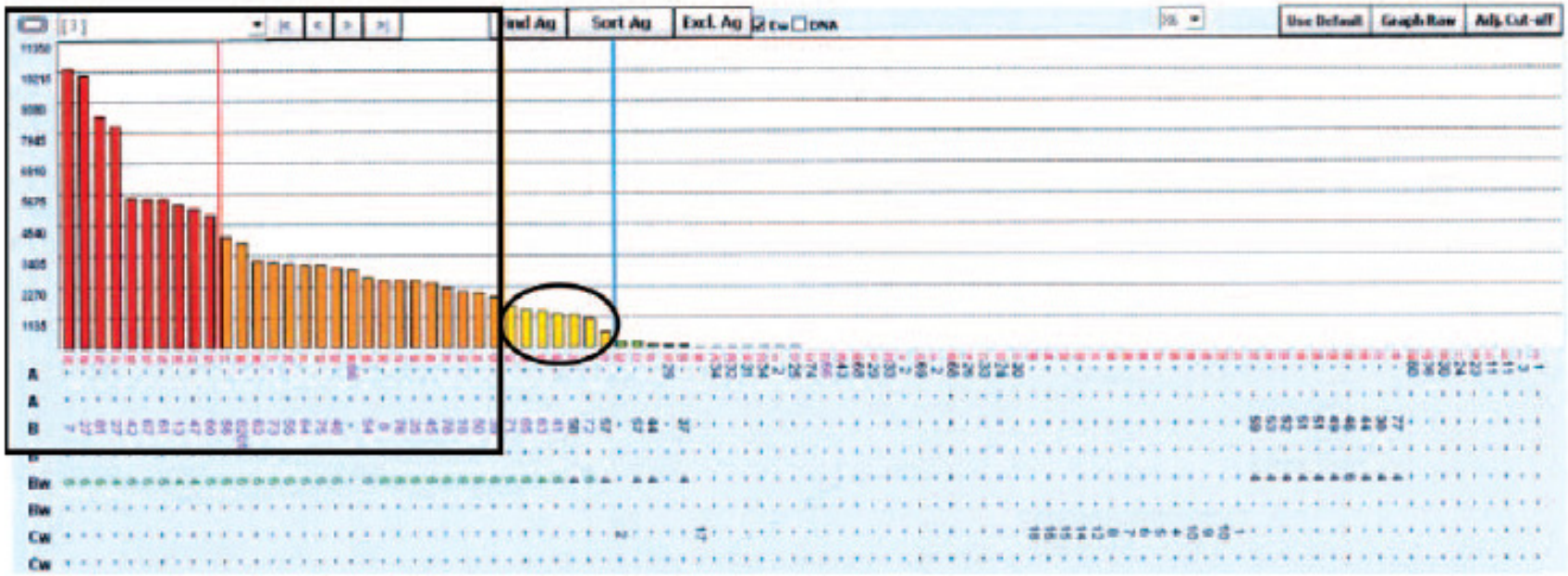
*Prior to October 2011, 4S included patients with PRA >20% with 3 prior positive crossmatches

Virtual Crossmatch

Step 1: PRA (+) → Identify specific HLA antibodies to quantify chances of negative CM

Step 2: Potential Donor Identified — ***Await Donor HLA Type***

Ross et al. J Heart Lung Transplant 2010;29:728-30



Unacceptable antigens entered for this patient:

A66	B7,8,13,14,18,27,35,39,42,45,47,48,50
	54,55,56,60,61,62,64,67,73,75
	76,78,81,82
Watch	B71,65,63,41,72,58

SA bead Luminex profile: At this centre antigens with MFI > 2000 are "unacceptable" (boxed); antigens with MFI 1000 - 2000 are "watch" (oval)

Bingaman et al, Transplantation 2008;86: 1864–1868

Virtual Crossmatch

Step 1: PRA (+) → Identify specific HLA antibodies to quantify chances of negative CM

Step 2: Potential Donor Identified — ***Await Donor HLA Type***

Step 3: Crossmatch

- VXM – National Optimized Sharing Algorithm
- Prospective CM (limited to local donors)

Step 4: Crossmatch Results:

Negative XM (real time or virtual)	Positive XM (real time or virtual)
↓	↓
Proceed with transplant	**No Transplant → Proceed with allocation according to established guidelines**

Ross et al. J Heart Lung Transplant 2010;29:728-30

Aims and Methods

Aim: To assess status 4S patients

1. Waiting times for heart transplantation
2. Patient and allograft outcomes

Retrospective multicentre analysis

- Jan 2010 – Jun 2011
- Status 4S, N = 27
  - 9 transplanted
  - 5 deaths (3 cardiac, 2 neurologic post LVAD) and 1 on hold
  - 12 active on list (16% of 75 total patients listed)

Patient Demographics

	ALL (n = 27)*	ACTIVE ON LIST (n = 12)	TRANSPLANTED (n = 9)
Age in years, mean (SD)	45 (13)	42 (14)	49 (13)
Female (%)	15 (56)	6 (50)	6 (67)
Diagnosis (%)			
Ischemic cardiomyopathy	3 (11)	0 (0)	3 (33)
Idiopathic cardiomyopathy	8 (30)	6 (50)	1 (11)
Congenital heart disease	5 (19)	1 (8)	3 (33)
Other†	11 (41)	5 (50)	2 (22)
Status 4S listing indication (%)‡			
cPRA >80%	20 (74)	8 (67)	6 (67)
cPRA >20% and ≥3 positive VXM	7 (26)	4 (33)	3 (33)
cPRA prior to 4S, mean % (SD)			
Peak HLA class I cPRA	63 (37)	74 (29)	68 (32)
Peak HLA class II cPRA	50 (40)	29 (37)	24 (37)
LVAD (%)	14 (52)	7 (58)	5 (56)
Desensitization (%)§	4 (15)	0 (0)	3 (33)

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	ALL (n = 27)*	ACTIVE ON LIST (n = 12)	TRANSPLANTED (n = 9)
Total days on waiting list, median (range)	382 (9 – 2437)	387 (9 -2437)	499 (68 – 2360)
Blood group O	414 (77 – 2437)	396 (141 – 2437)	830 (188 – 2360)
Blood group A	163 (9 – 362)	139 (9 – 360)	184
Blood group B	574	574	-
Blood group AB	55 (42 – 68)	-	68
Days on 4S waiting list, median (range)	134 (2 – 532)	219 (9 – 532)	67 (2 – 188)
Blood group O	151 (50 – 532)	276 (139 – 532)	79 (13 – 188)
Blood group A	50 (2 – 360)	50 (9 – 360)	2
Blood group B	241	241	-
Blood group AB	23 (6 – 40)	-	6

Chih et al, JHLT 2012 Jul;31(7):780-2

Canadian Cardiac TRANSPLANT NETWORK

4S Transplanted (N = 9, 33%)

- 6 from non-local donor
  - Distance 1050 km (352 – 2218)
  - Ischaemic time 338 min (241 – 397) vs. 168 min (105 – 180) for local donor
- VXM
  - 6 negative VXM and negative CDCXM/FCXM
  - 3 positive VXM and 2 negative CDCXM/FCXM
- Immunosuppression: induction and steroids, MMF, TAC
- Average f/u 340 ± 90 days
  - All alive
  - Rejection: ISHLT 2R 78% (pulse steroid), AMR in 2
  - Allograft function: LVEF>55% in 71% (6 month TTE available in 78%)

Chih et al, JHLT 2012 Jul;31(7):780-2

Canadian Cardiac TRANSPLANT NETWORK

Limitations

1. Small patient numbers
2. Lack of an appropriate control group (historical and non-sensitized)
3. Unclear direct impact of 4S

Conclusions

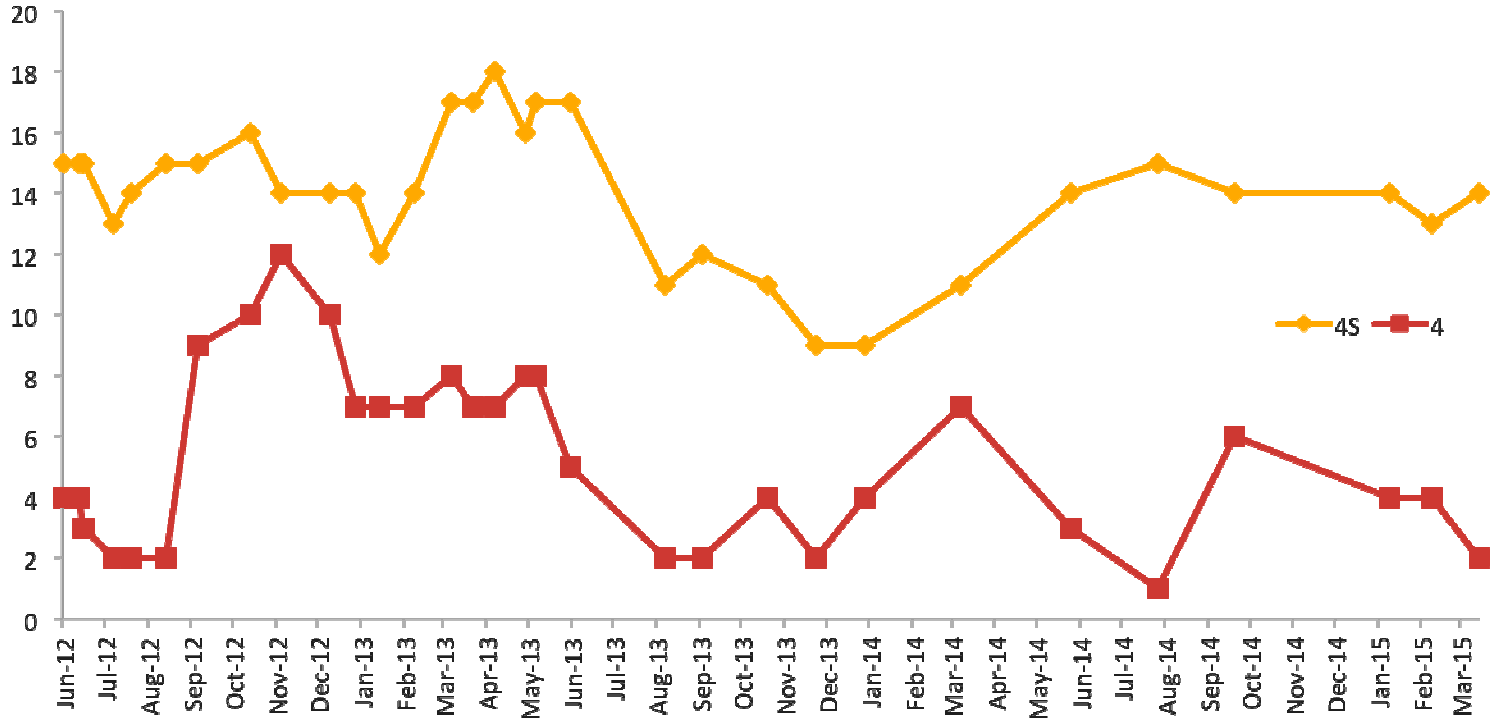
1. Satisfactory short term outcomes
2. Long waiting times and significant mortality for sensitized patients
3. High rate of rejection
4. Ongoing evaluation required

Adapted Current Approach to Status 4S Listing
1. Qualification for 4S status based on cumulative cPRA ≥80%.
2. I **cPRA including ALL loci (including DQA and DP)** ude an organ offer.
3. If a program plans to cross a VXM, the patient cannot be listed status 4S.

Chih et al, JHLT 2012 Jul;31(7):780-2

Heart Listing for 4 and 4S Patients
Date Range: June, 2012 – April 7, 2015

PRA methods – 2008-2011 standardized across various Canadian laboratories – aligned practices for calling 'antibody'
National alignment with proficiency testing in 2013, 2015



Source: National Organ Waitlist 2015-04-07

2015 4S Update

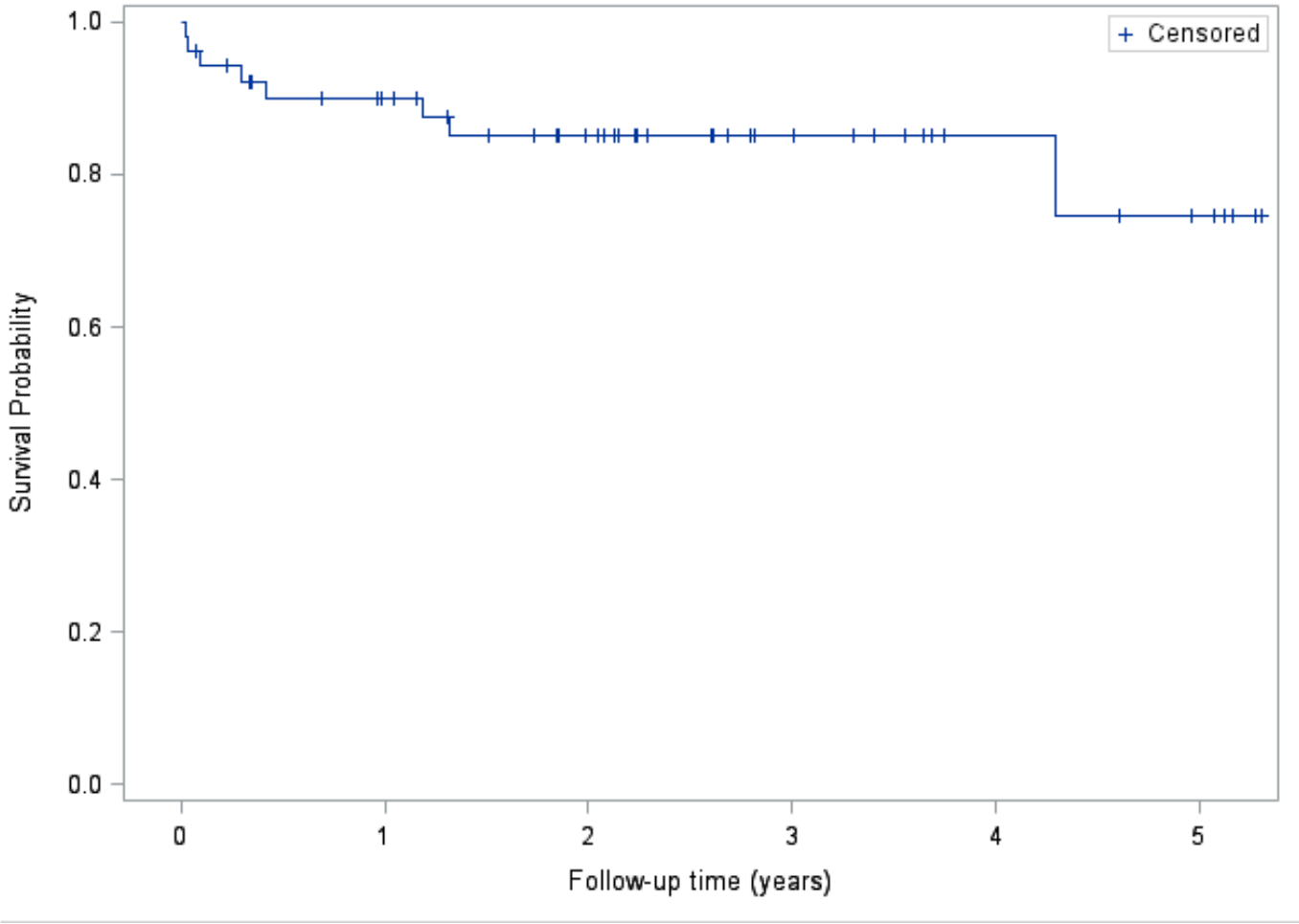
- 96 patients were listed status 4S from January 2010 to September 2015.
  - 52 were transplanted as Status 4S,
  - 7 were transplanted as a different status,
  - 5 de-listed,
  - 4 died waiting and 28 remain active.
- Of 52 transplants,
  - Mean age was 47 years; 46% male
  - 44% had dilated cardiomyopathy
  - Blood group O - 42%
  - 53% had a VAD as BTT
  - All patients received induction
  - Maintenance immunosuppression was standard and included tacrolimus and MMF, in addition to prednisone.

2015 4S Update

- Mean follow up - 28 months (1 week – 5.3 years),
  - 9 patients died (17%)
  - Primary graft failure/AMR accounted for 1/3 of deaths.
- Kaplan Meier 1-year survival - 88%
- AMR occurrence
  - Pathologic AMR - 12 patients (23%)
  - Clinical AMR - 3 patients in the first year post-transplant (5.8%)
  - Only clinical AMR was treated
- 17% of patients developed de novo DSA and demonstrated no correlation to AMR (clinical or pathologic).
- 33% of patients had at least 1 - 2R cellular rejection in the first year and 15.4% of patients had CAV 1 at follow up

2015 4S Update

Kaplan Meier Survival



Clarke et al, ISHLT 2016 on behalf of CCTN

Limitations of Current Antibody Evaluation

- ‘Biologically speaking, antibody strength refers to the intensity of affinity and avidity for a particular antigen–antibody complex’.
  - kinetics of antigen–antibody binding, or more accurately, antigen–antibody dissociation
- MFI challenges
  - Not transferable between centres
  - Not strictly quantitative
  - neat MFI values do not always accurately depict antibody strength
- ‘prozone’ effect - interference with binding of the secondary detection reagent, giving false-negative results
  - EDTA treatment (6%) does not always remove all inhibitory factors
- C1q assay limited by low sensitivity and inability to detect the presence of weak antibodies
- Titration studies - costly

Tambur et al, Am J Transplant 2015; XX: 1–10
Konvalinka/Tinckam JASN 2015;26:

Question?

- For the sensitized HT candidate…. to achieve access/optimal outcomes post heart transplant a virtual crossmatch strategy is more effective than desensitization

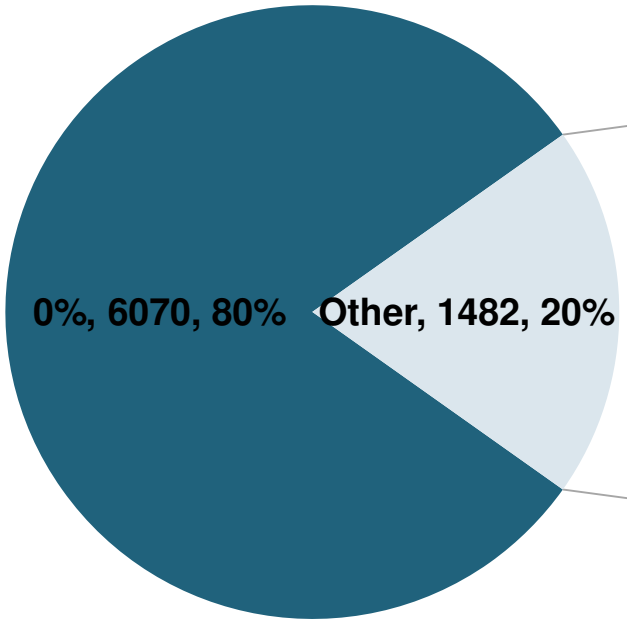
Answer: …….we don't know

CPRA distribution: Adult WL candidates (N=7,552)

Candidates ever waiting 1/1/11-6/30/13; limited to candidates at heart programs with any UAs

Barriers:
25% of programs don't submit data
Unclear if 0% PRA represents truly unsensitized or not reported
CPRA based upon renal calculator
No standardization on testing methodology
No standardization of minimum threshold to define a "significant" antibody

OPTN | UNOS



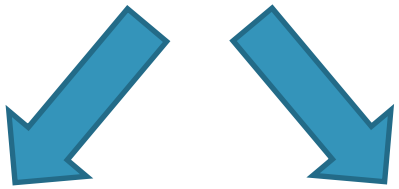
PRA (%)	N	%
1-10	275	4
11-20	175	2
21-30	199	3
31-40	99	1
41-50	106	2
51-60	106	1
61-70	103	1
71-80	92	1
81-90	110	2
91-100	217	3

https://www.transplantpro.org/news/education/heart-allocation-system-webinar/

For consideration at the time of assessment of any patient with a positive PRA: A pragmatic approach

Assess risk of dying waiting – combination of:

- ❖likelihood of achieving HTx (odds of - VXM); and
- ❖stability on VAD or on list



Low Risk – proceed with VXM approach

- High likelihood of (–) VXM
- Priority listing 4S status (cPRA > 80 but < 95) common size and blood type)
- Stable on VAD/list

High Risk – consider desensitization

- cPRA > 95%;
- multiple (+) CM
- Unstable on list (VAD ineligible)
- VAD complications

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