Harefield Hospital

NHS
Guy's and St Thomas'
NHS Foundation Trust

Living in the fast lane, HLA style

Andy Morley-Smith

Transplant Cardiologist

Disclaimers:

I am a cardiologist

I work with an amazing tissue typing team who know much more than me

Outline

- Context of heart transplantation in the UK
- Why are we so cautious about HLA mismatch?
- Are these patients truly “not transplantable”?
- Harefield experience

Putting heart transplantation in context

HIDDEN IN PLAIN SIGHT

Recognise the symptoms of heart failure:

FIGHTING FOR BREATH
FATIGUED
FLUID RETENTION

IF YOU HAVE THESE SYMPTOMS,
PLEASE SEE YOUR GP AND ASK
IF IT COULD BE HEART FAILURE

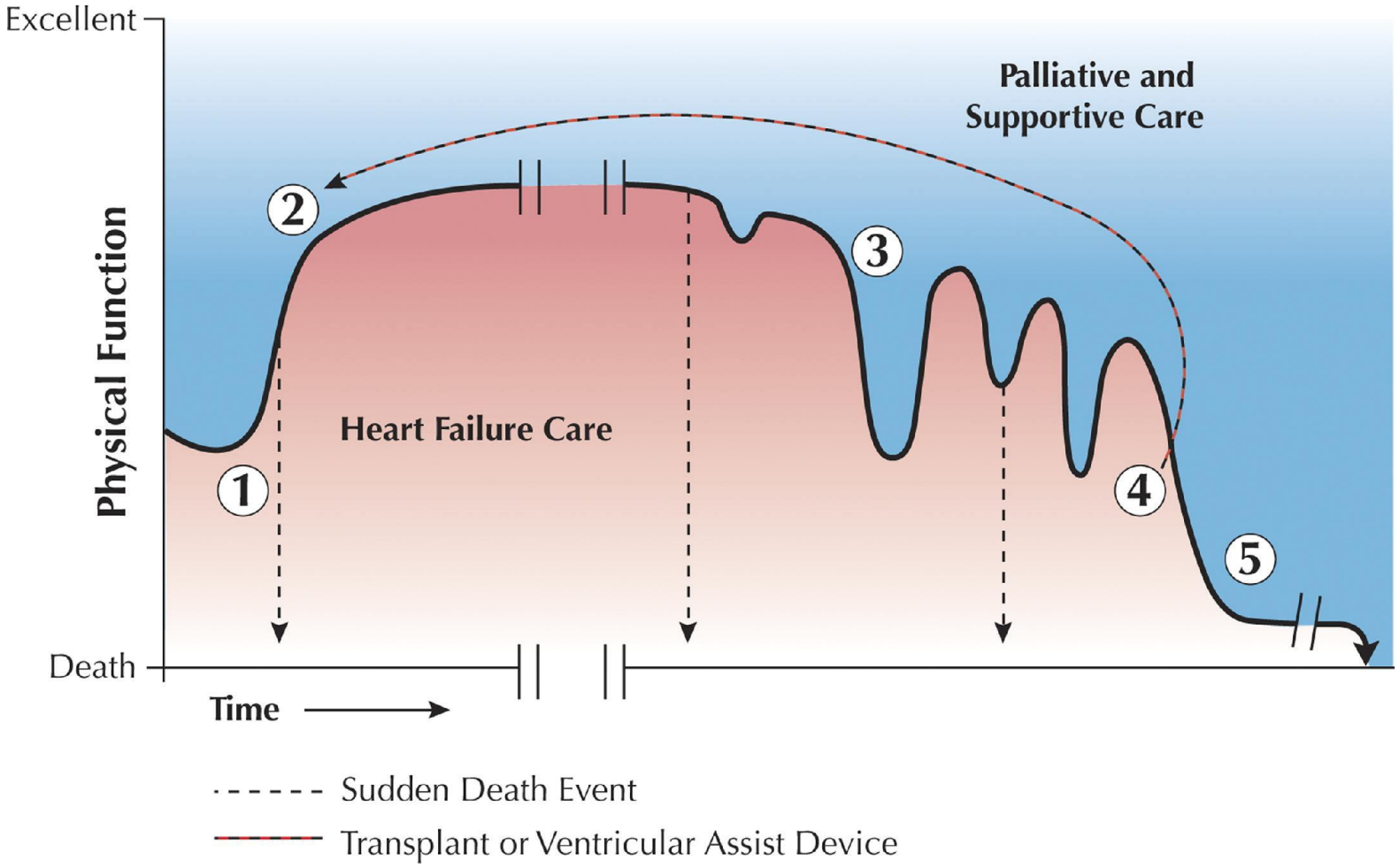
HEART FAILURE IS TREATABLE

BRITISH SOCIETY FOR HEART FAILURE

www.bsh.org.uk

25 IN 25

When is it “advanced”?



Goodlin SJ. JACC 2009

When is it “advanced”?

Table 3 Updated HFA-ESC criteria for defining advanced heart failure

All the following criteria must be present despite optimal guideline-directed treatment:

1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV].
2. Severe cardiac dysfunction defined by a reduced LVEF ≤30%, isolated RV failure (e.g. ARVC) or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF.[9]
3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months.
4. Severe impairment of exercise capacity with inability to exercise or low 6MWTD (<300 m) or pVO_2 (<12–14 mL/kg/min), estimated to be of cardiac origin.

In addition to the above, extra-cardiac organ dysfunction due to heart failure (e.g. cardiac cachexia, liver, or kidney dysfunction) or type 2 pulmonary hypertension may be present, but are not required.

Criteria 1 and 4 can be met in patients who have cardiac dysfunction (as described in criterion #2), but who also have substantial limitation due to other conditions (e.g. severe pulmonary disease, non-cardiac cirrhosis, or most commonly by renal disease with mixed aetiology). These patients still have limited quality of life and survival due to advanced disease and warrant the same intensity of evaluation as someone in whom the only disease is cardiac, but the therapeutic options for these patients are usually more limited.

Pagnesi et al EJHF 2022

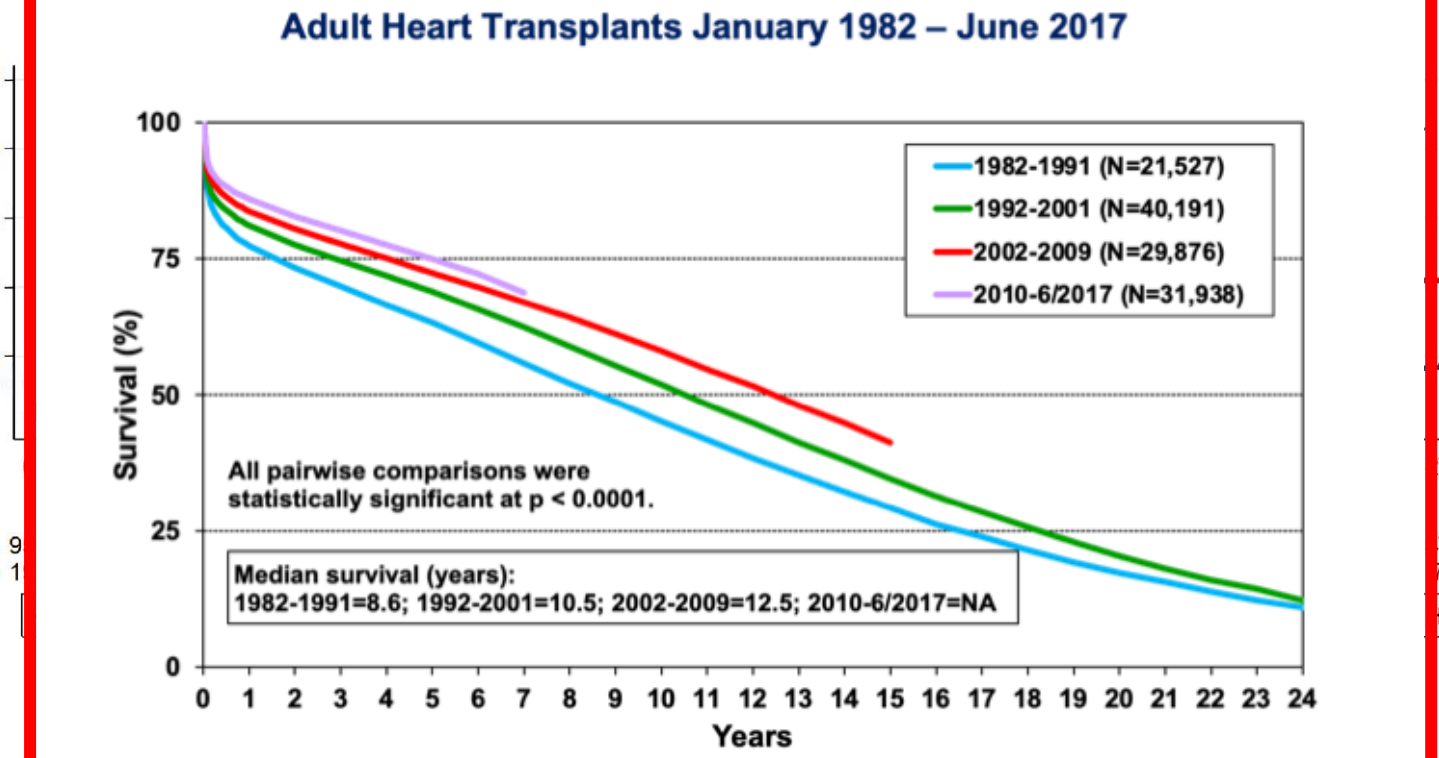
54% survival at 1 year

Table 3 Updated HFA-ESC criteria for defining advanced heart failure

All the following criteria must be present despite optimal guideline-directed treatment:

1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV].
2. Severe cardiac dysfunction defined by a reduced LVEF ≤30%, isolated RV failure (e.g. ARVC) or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF.[9]
3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months.
4. Severe impairment of exercise capacity with inability to exercise or low 6MWTD (<300 m) or pVO_2 (<12–14 mL/kg/min), estimated to be of cardiac origin.

➔ 85-90% survival at 1 year



ISHLT Registry. JHLT 2019

A

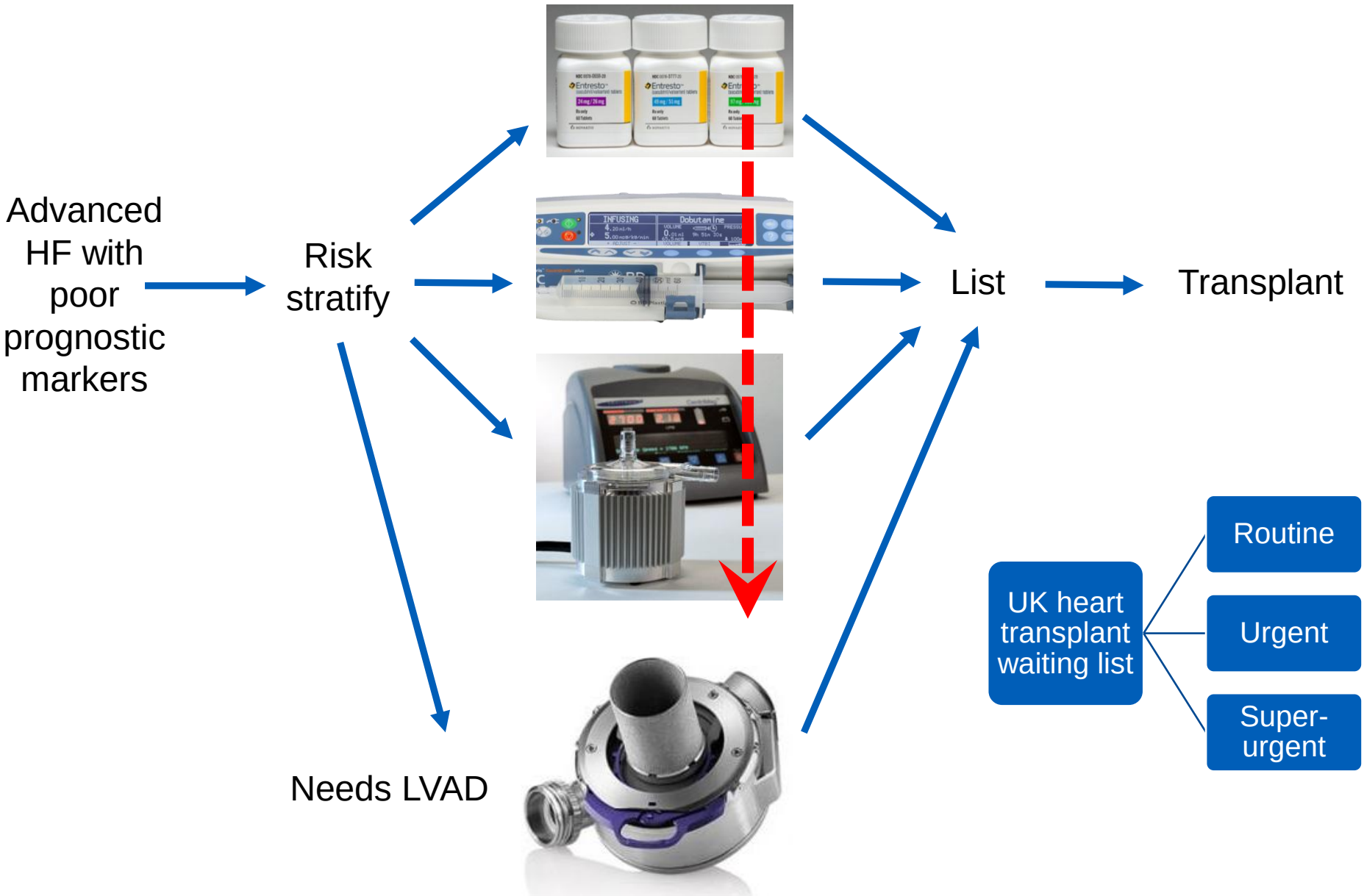
Event rate (%) 20 40 60 80 100

Number at risk
No HFA-ESC criteria 9
HFA-ESC criteria 1

70 365
75 281
71 52
HFA-ESC criteria

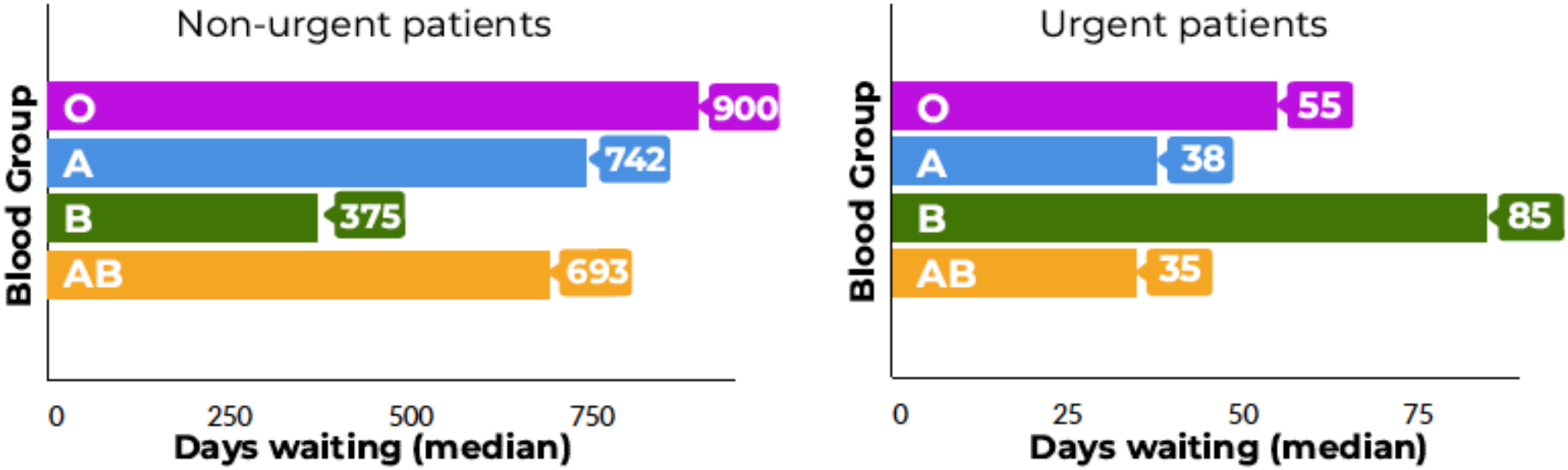
HF 2022

Routes through the service

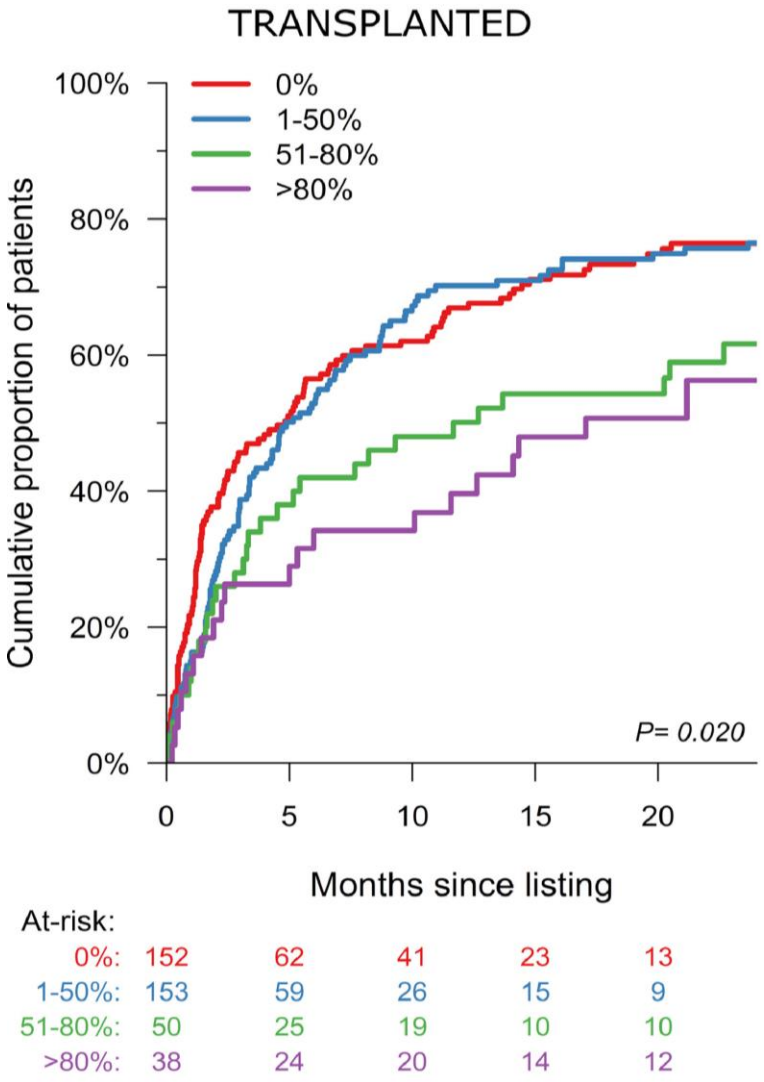


NHS
Blood and Transplant

National waiting time by blood group



Sensitised patients wait longer



Aleksova et al. JHLT 2019

Two sick patients

48M previous endocarditis with emergency mechanical MVR in 2008

Progressive heart failure and presents in extremis

Blood group O

Highly HLA sensitised with total cRF 99% from previous blood transfusion

27F dilated cardiomyopathy presenting post-partum

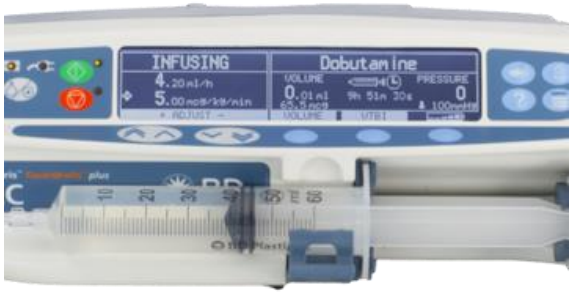
Too sick to transplant – emergency LVAD

But now 6 years on LVAD with pump infection, brain haemorrhage

Blood group A

Highly HLA sensitised with total cRF 99% from pregnancy/blood transfusion

Both will die soon without a heart transplant – how to get them there…



…or are they “not transplantable” due to HLA sensitisation

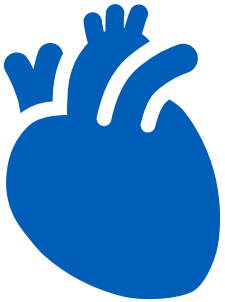
Why are we so cautious about HLA mismatch?

We rely on virtual crossmatch

Donor HLA profile → Virtual crossmatch ← Recipient HLA profile

↓

Decision to proceed



↓

Transplantation

↓

Cell based crossmatch

↙ ↘

Severe early graft dysfunction

Cause

- Donor factors eg existing heart problem, catecholamine syndrome after brain injury
- Preservation eg prolonged ischaemic time
- Immune injury eg rejection

Support circulatory function until heart recovers

- ECMO +/- BIVAD

Majority wean MCS in a few days

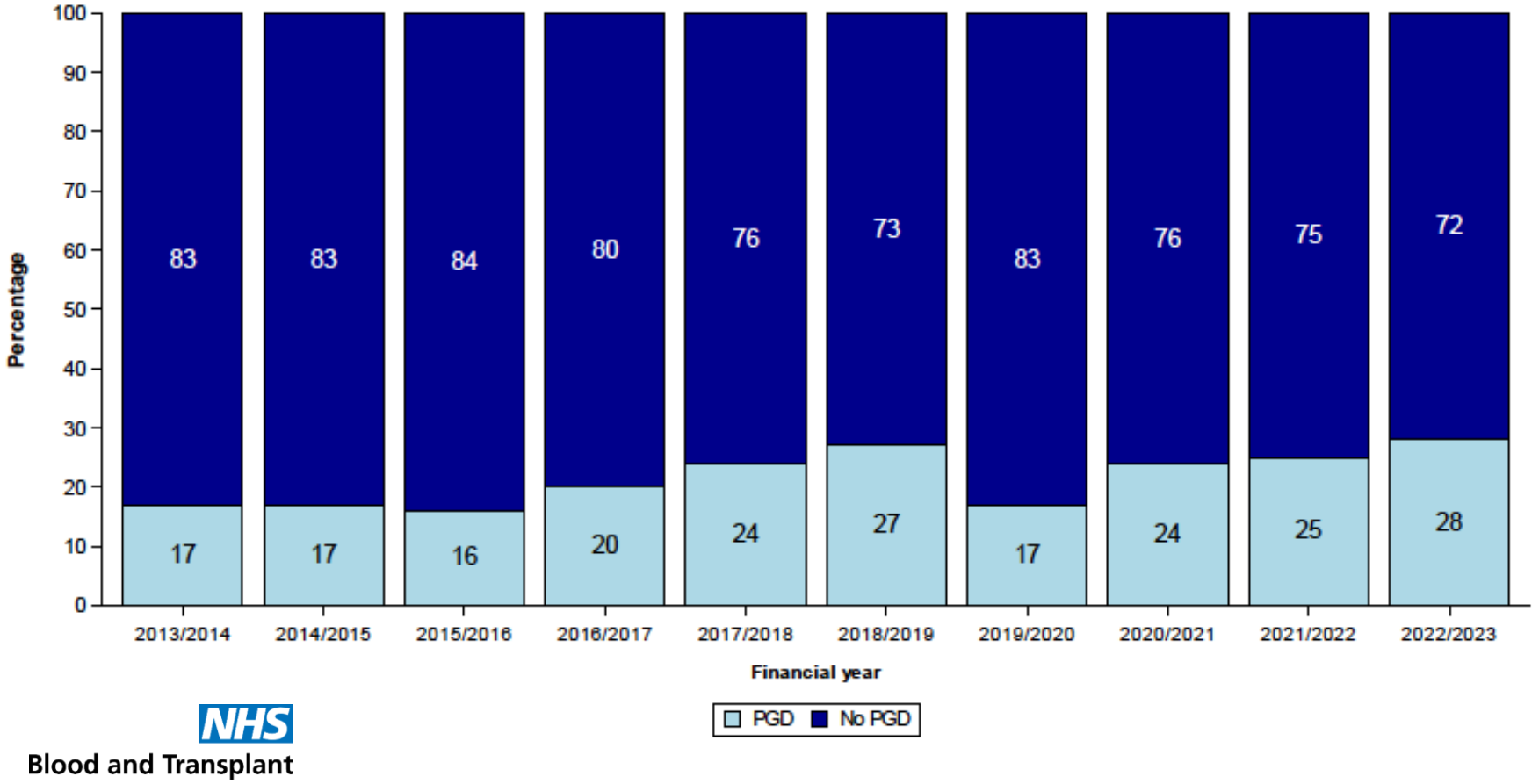
- MCS "rests" the heart – median 5 days in last UK report

If not consider redo transplantation – but…

- High risk, rarely done, need to be highly selective
- Immune risks during acute rejection

Severe early graft dysfunction

Figure 7.1b Proportion of transplants requiring short-term support for (severe) PGD, out of total number of adult heart transplant by financial year, 1 April 2013 to 31 March 2023



NHS Blood and Transplant

Annual Report on Heart Transplantation 2022/23, NHS Blood and Transplant

Cautious approach because…

We rely on virtual XM pre-transplant

Goal is negative retrospective direct XM

Absence of prospective direct XM requires caution

Risks of EGD: increases mortality, redo rare

Long term risks: AMR, CAV, reduced longevity?

Ethical: donor numbers, utility in allocation

But – are we getting “false positive” virtual XM

Two sick patients

48M previous endocarditis with emergency mechanical MVR in 2008

Progressive heart failure and presents in extremis

Blood group O

Highly HLA sensitised with total cRF 99% from previous blood transfusion

27F dilated cardiomyopathy presenting post-partum

Too sick to transplant – emergency LVAD

But now 6 years on with pump infection, brain haemorrhage

Blood group A

Highly HLA sensitised with total cRF 99% from pregnancy/blood transfusion

Are these patients truly “not transplantable”?

Estimating alloimmune risk

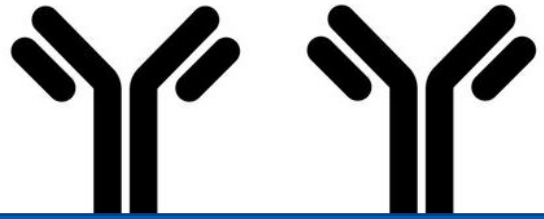
Memory

Functional significance

Clinical outcome

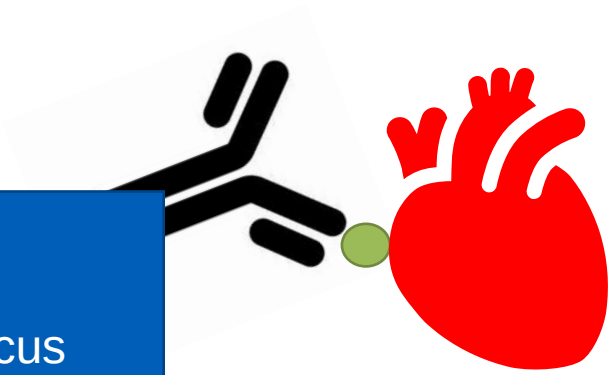
No good laboratory assays

Inference from
- Nature of sensitisation
- Persistence of antibodies



Detect with luminex assay
- More than just presence/ absence – which class/focus
- MFI gives semi-quantitative estimate
- High sensitivity, cross-reactivity

Functional assessment
- Dilution studies – 1:8
- C1q binding assays – are they going to bind complement
- Cell-based crossmatch – but retrospective



Clinical AMR

Accept no Luminex mismatch

- Most conservative
- Misses safely transplantable donors

Set MFI threshold

- What is meaningful threshold?

Combined estimate of risk

- MFI and functional assessment

Accept no Luminex mismatch

- Most conservative
- Misses safely transplantable donors

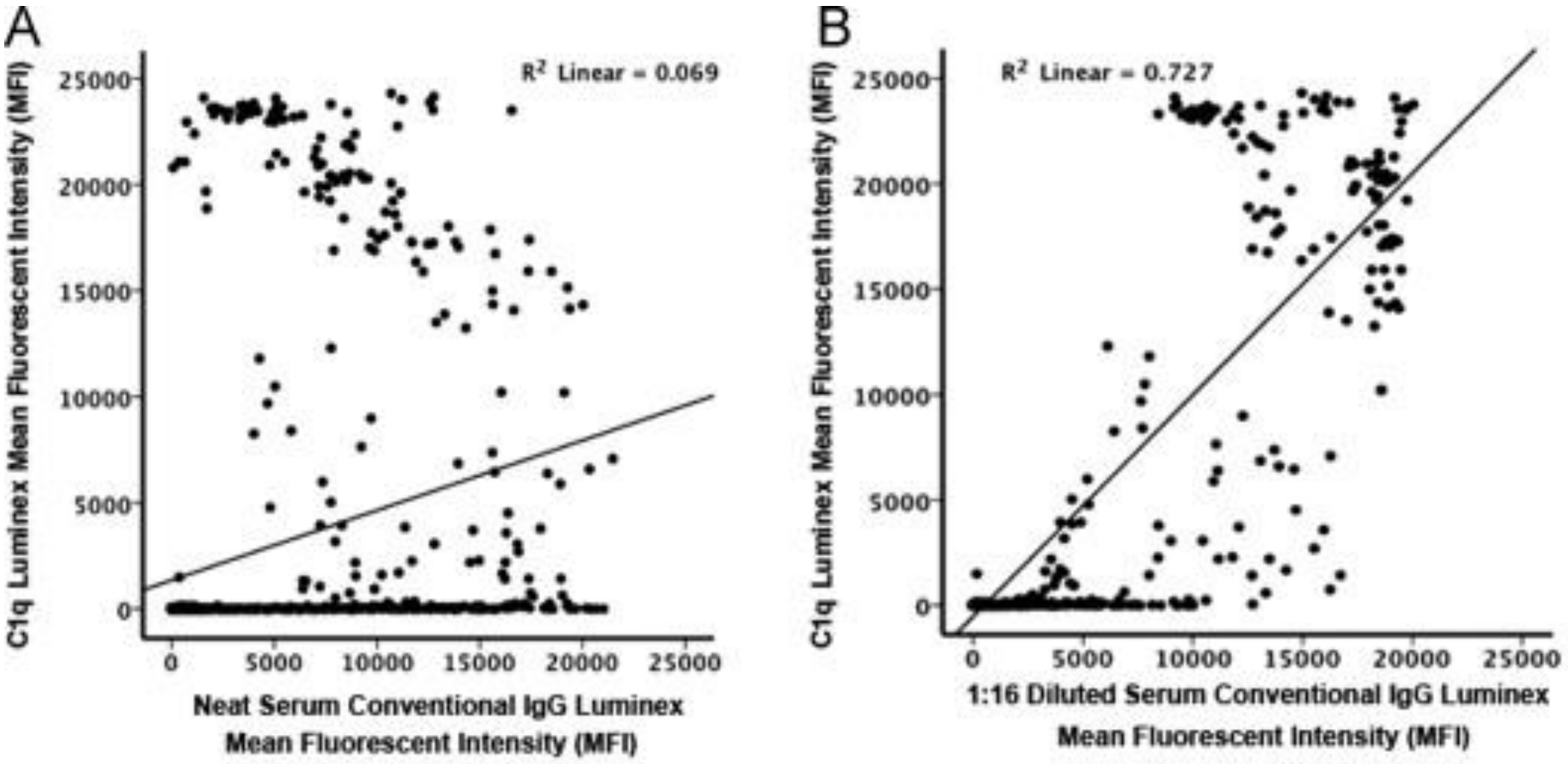
Set MFI threshold

- What is meaningful threshold?

Combined estimate of risk

- MFI and functional assessment

MFI alone is a poor marker



Zeevi et al JHLT 2013

Accept no Luminex mismatch

- Most conservative
- Misses safely transplantable donors

Set MFI threshold

- What is meaningful threshold?

Combined estimate of risk

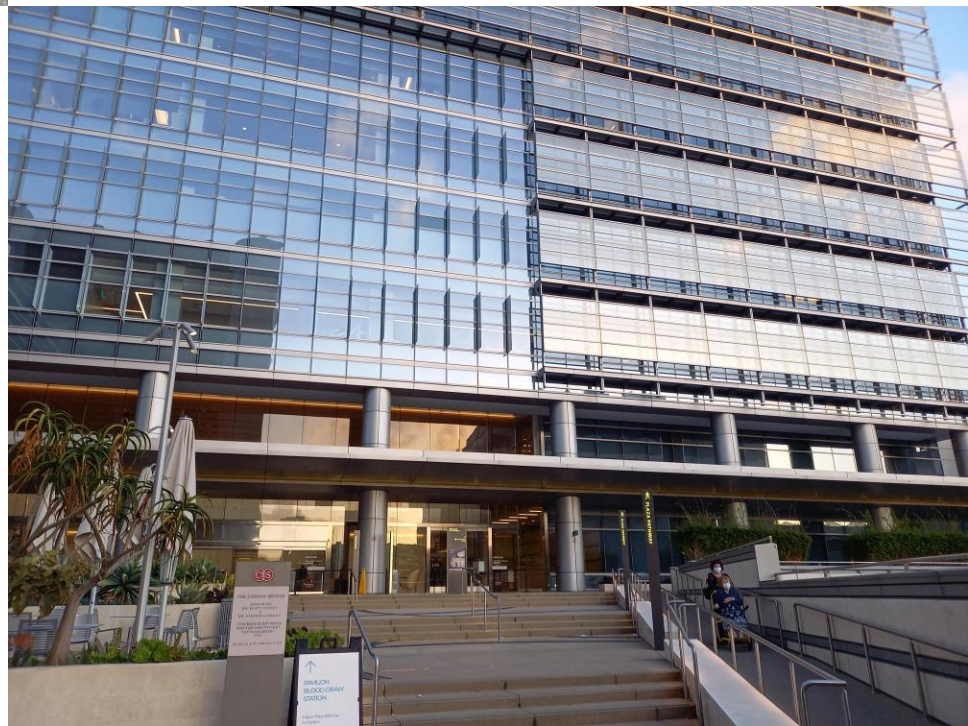
- MFI and functional assessment
- Are they pathogenic alloantibodies

What have we done at Harefield

Harefield experience

- Collaboration with Cedars Sinai initiated by Mark Peterzan in late 2022
- Starting from a highly conservative base and tentatively challenged our assumptions

The Pavilion



Harefield experience

- Collaboration with Cedars Sinai initiated by Mark Peterzan in late 2022
- Starting from a highly conservative base and tentatively challenged our assumptions

- **Now transplanted 8 patients against pre-identified HLA mismatch**
- **7 alive (thriving!) at median 440 days (range 27-720)**
- **1 died POD 355 – likely acute rejection**

Harefield approach

- Proper history of sensitising events
- If cRF > 75%, functional test with dilution studies
- Define “relevant” antibodies as
  - MFI > 5,000
  - Detectable after 1:8 dilution
  - *(Binding on C1q assay)*
- MDT evaluation of risk
- Consider peri-transplant enhanced immunosuppression
- Enhanced DSA +/- biopsy monitoring

	Sensitising event	BG Ht /cm	Peak cRF	HLA workup	MDT acceptable VX mismatch	Wait /days	Induction	Flow XM	Severe GD	Biopsy AMR	DSA	POD
34 F	Pregnancy	O 151	95	Undil MFI >5000 72%	Tx against cumulative MFI<5000	U 93	rATG	Neg	No	No	No	720
62 M	None identified	A 177	67	Undil all <5000, HLA neg on 1:8	Tx against cumulative MFI<5000	U 30	rATG	Neg	No	No	No	486
16 M	Transfusion	O 170	72	Undil MFI >5000 0%	Tx against cumulative MFI<5000	SU 22	rATG	Neg	Yes	No	No	Died POD 355
48 M	Transfusion	O 182	99	Undil class I 0% and 1:8 class II 0%	Tx against all specificites MFI <10,000	U-SU 155	rATG	Neg	No	No	Yes	452
27 F	Pregnancy, LVAD, transfusion	A 163	99	Gradual wane Several persist in 5000-1000 on 1:8	Tx against all specificities <5000	U 293	rATG	Neg	No	Yes	Yes	450
41 M	None identified	O 158	69	Peak MFI >10,000 but HLA negative on 1:8 dilution	Tx against all specificities <10000	U 315	rATG	Neg	No	No	Yes	431
42 F	Pregnancy, transfusion	A 165	57	All specificities <5000 1:8 cRF 0%	Tx against cumulative MFI<5000	R 715	rATG	Neg	No	No	Yes	271
22 M	Transplant, transfusion	O 179	97	Reduced after IA for AMR. cRF 0 on 1:8.	A2 unacceptable	U-SU 146	rATG	Neg	No	No	No	27

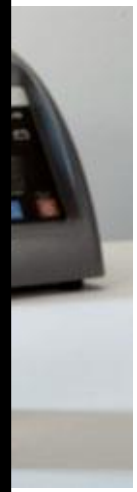
48M pre
emerge
2008

Progres
present

Blood g

Highly H
cRF 99
transfus

	Undiluted	1:8 dilution
Total cRF	**99%**	**Negative**
Total Class I cRF	0%	0%
Class I cRF > 2,000mfi	0%	
Class I cRf > 5,000mfi	0%	
Class I cRF > 10,000mfi	0%	
Class I < 2,000mfi		
Class I 2,000- 5,000mfi		
Class I > 5,000mfi		
Class I > 10,000mfi		
Total Class II cRF	99%	0%
Class II cRF > 2,000mfi	99%	
Class II cRf > 5,000mfi	84%	
Class II cRF > 10,000mfi	0%	
Class II < 2,000mfi		
Class II 2,000- 5,000mfi	DQ7, DQA1*05,*06, DP15	
Class II > 5,000mfi	DP2,4,18,23,28	
Class II > 10,000mfi		



Are we really in the fast lane?

- I would wager that:
  - Some colleagues in kidney programmes will think we're pedestrian
  - Some colleagues in other heart centres think we're reckless

What we haven't done

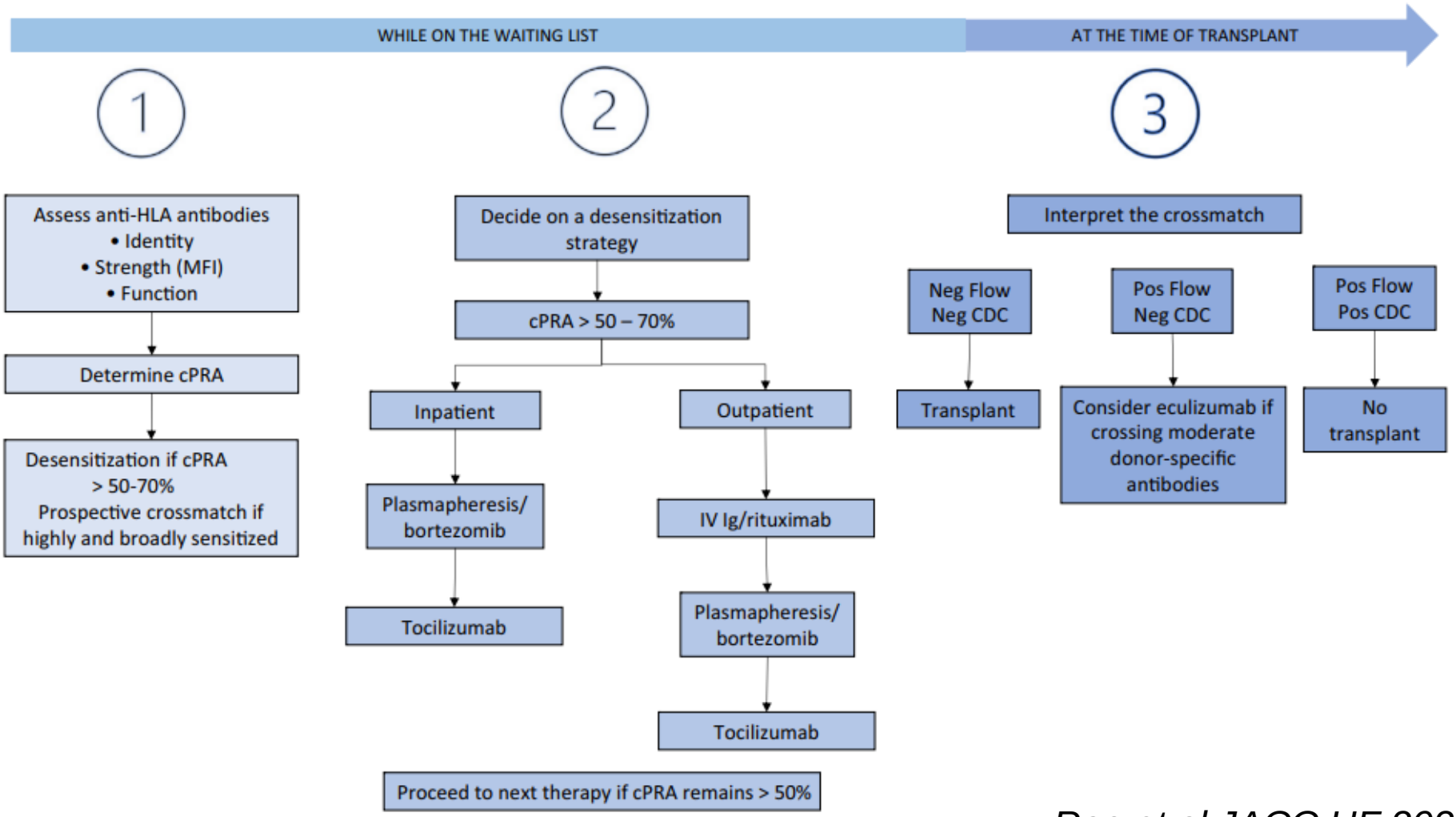
- Successfully transplanted after pre-transplant desensitisation
- Taken on higher risk HLA mismatches with an expectation of early AMR

Summary points

- Finding opportunities to safely expand access for sensitised heart recipients
- Basic functional testing allows teams to safely discount some HLA antibodies and increase likelihood of donor matching
- Balanced against enhanced early and late risks, and importance of using donor organs wisely

How to Approach HLA Sensitization in Heart Transplant Candidates

Roopa A. Rao, MBBS,[a] Evan P. Kransdorf, MD, PhD,[b] Jignesh K. Patel, MD, PhD,[b] Jon A. Kobashigawa, MD, PhD,[b] Michelle M. Kittleson, MD, PhD[b]



Rao et al JACC HF 2023