Higher Risk of Kidney Graft Failure in patients with AT1R Antibodies

Angiotensin II Type 1 Receptor

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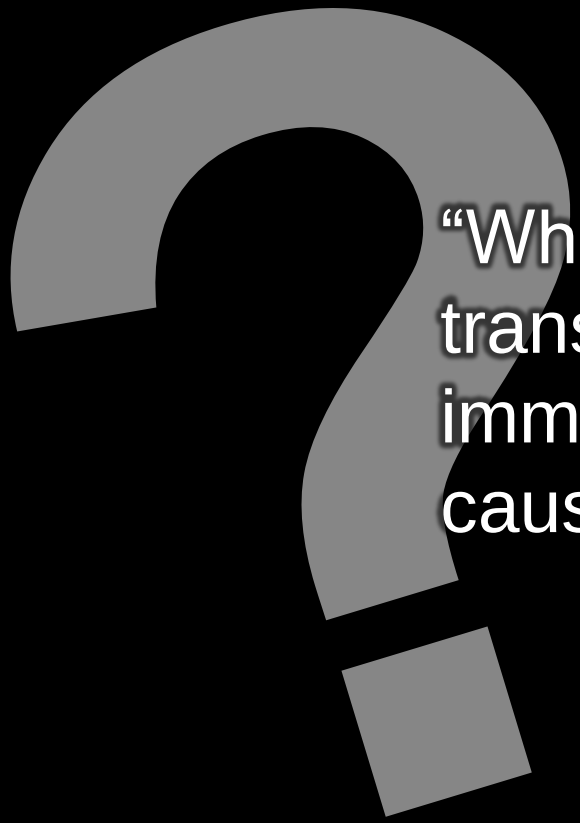
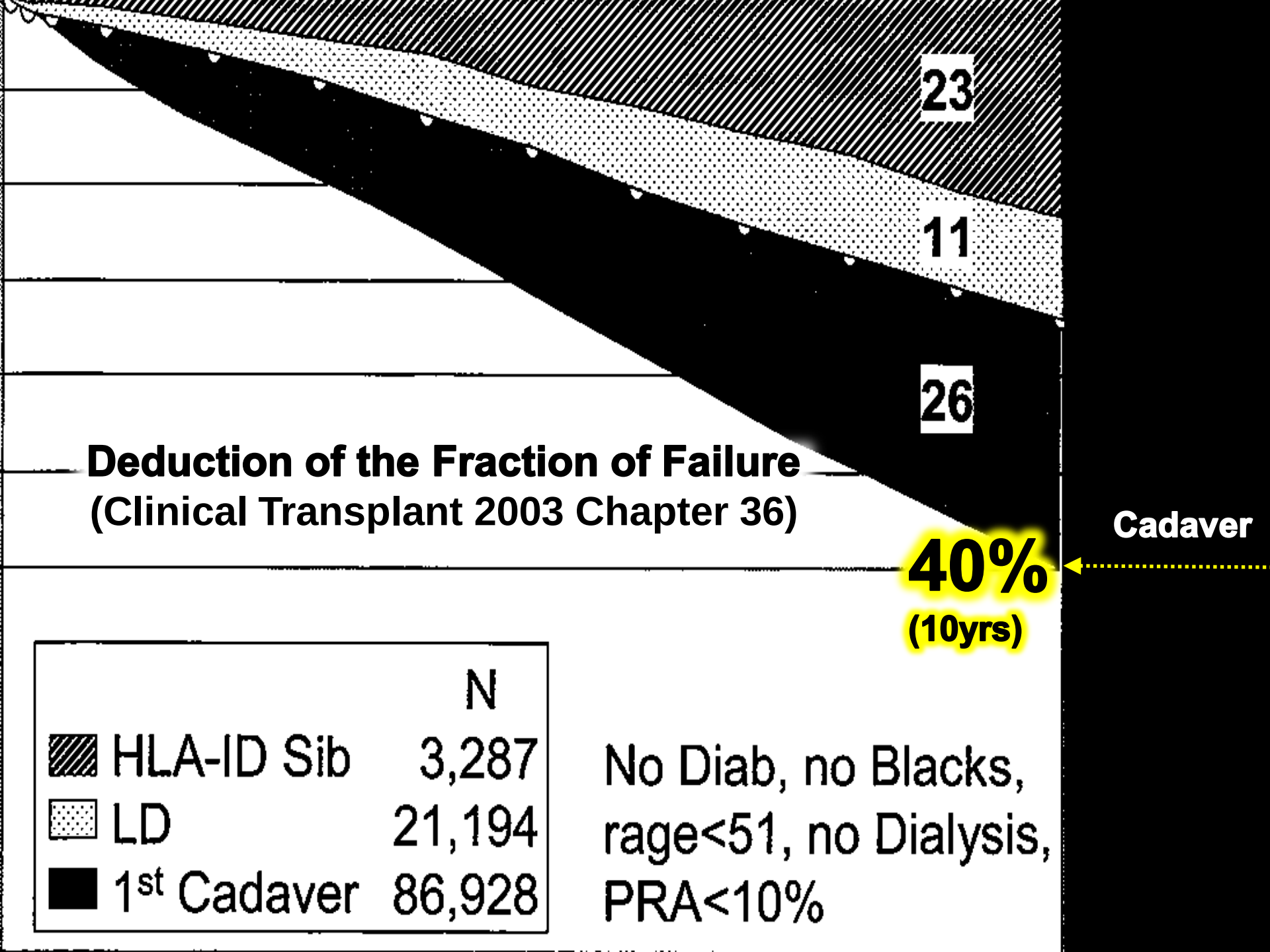
TFL

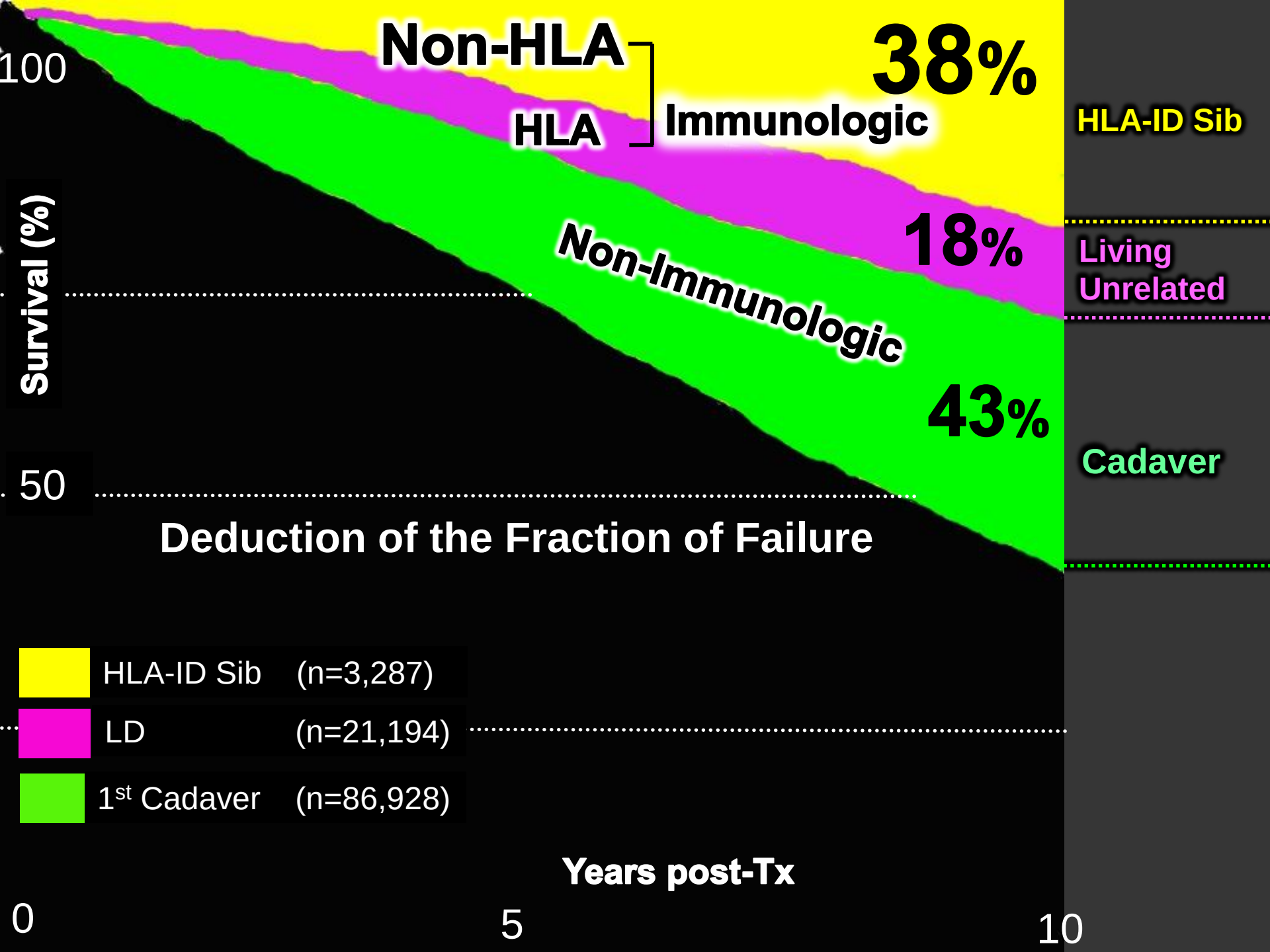
Deduction of the Fraction of Failure
(Clinical Transplant 2003 Chapter 36)
Dr. Terasaki



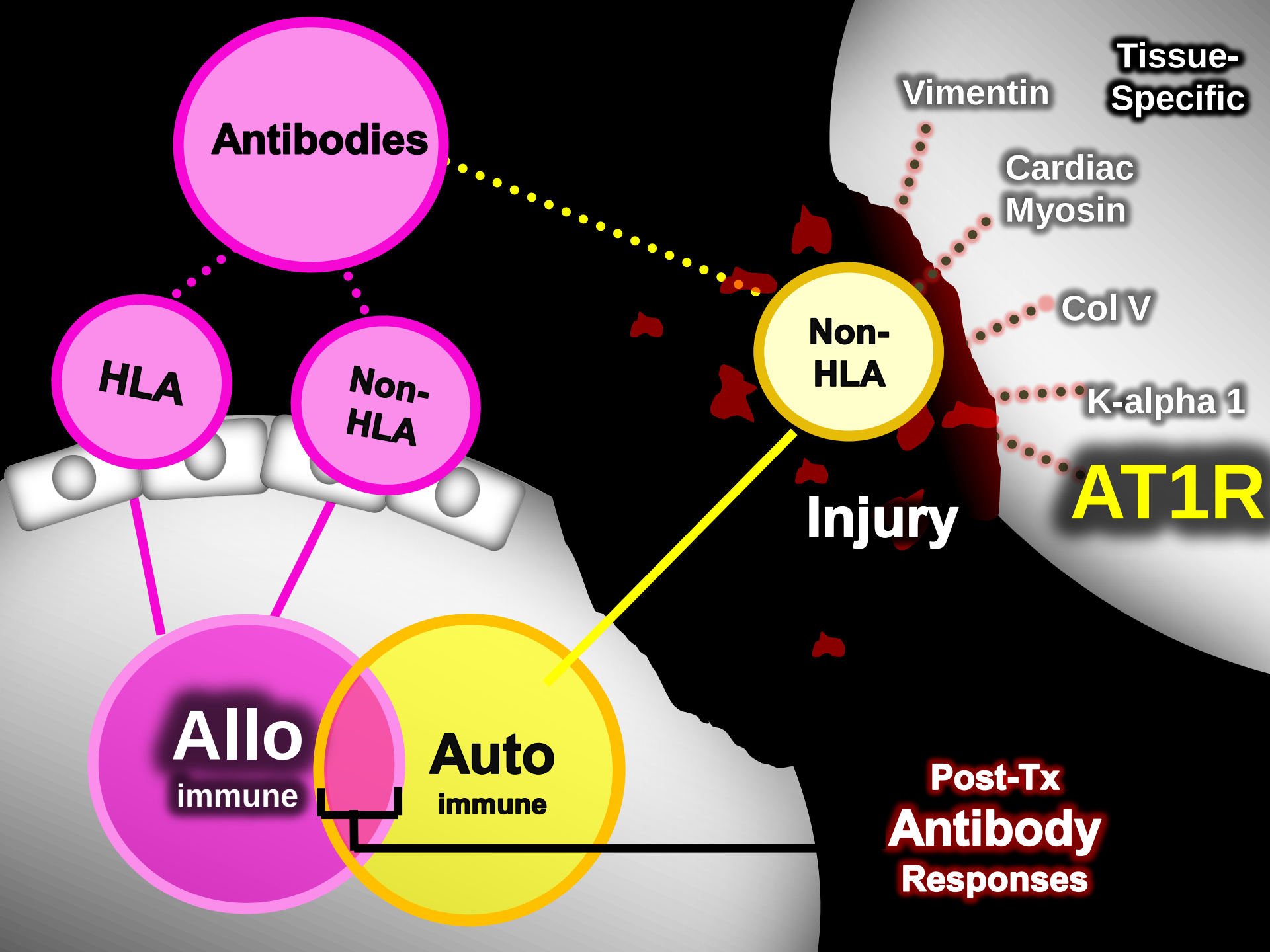
“What fraction of cadaver donor transplants fails as a result of immunologic and non-immunologic causes? “

Much higher percentage of failures is attributable to immunologic response to non-HLA factors.


23
11
26
Deduction of the Fraction of Failure
(Clinical Transplant 2003 Chapter 36)
Cadaver
40%
(10yrs)
N
HLA-ID Sib 3,287
LD 21,194
1st Cadaver 86,928
No Diab, no Blacks,
rage<51, no Dialysis,
PRA<10%


Non-HLA
HLA
Immunologic
38%
18%
Non-Immunologic
43%
HLA-ID Sib
Living Unrelated
Cadaver
100
50
Survival (%)
Deduction of the Fraction of Failure
HLA-ID Sib (n=3,287)
LD (n=21,194)
1st Cadaver (n=86,928)
Years post-Tx
0
5
10

It is increasing recognized that immune responses to both HLA and non-HLA targets act together in the pathogenesis of graft rejection.


Antibodies
HLA
Non-HLA
Non-HLA
Injury
Tissue-Specific
Vimentin
Cardiac Myosin
Col V
K-alpha 1
AT1R
Allo immune
Auto immune
Post-Tx Antibody Responses

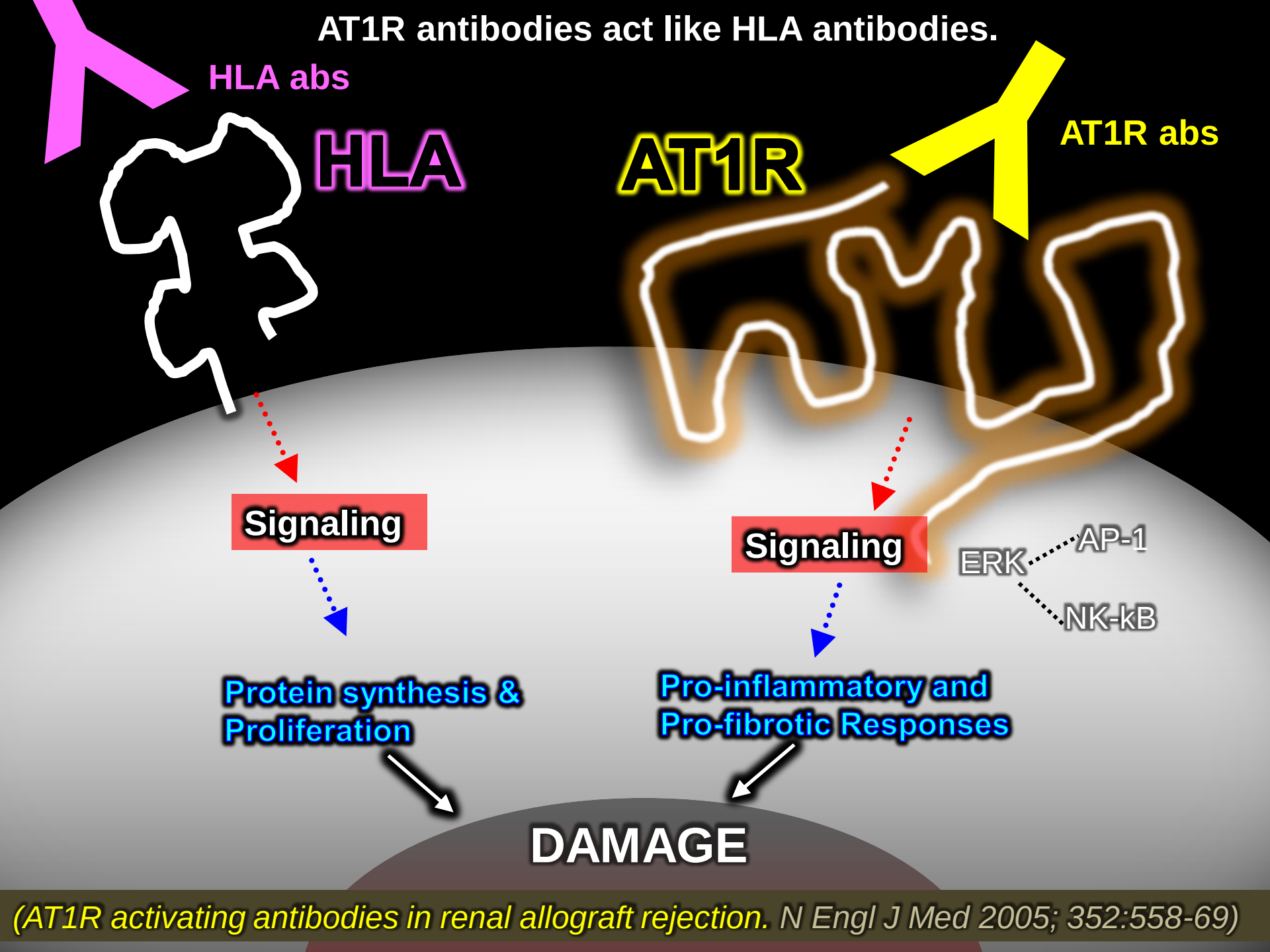
(among many non-HLA targets)

Antibodies against AT1R are unique because…

1

AT1R antibodies act like HLA antibodies.

(Signal transduction that causes direct injury)

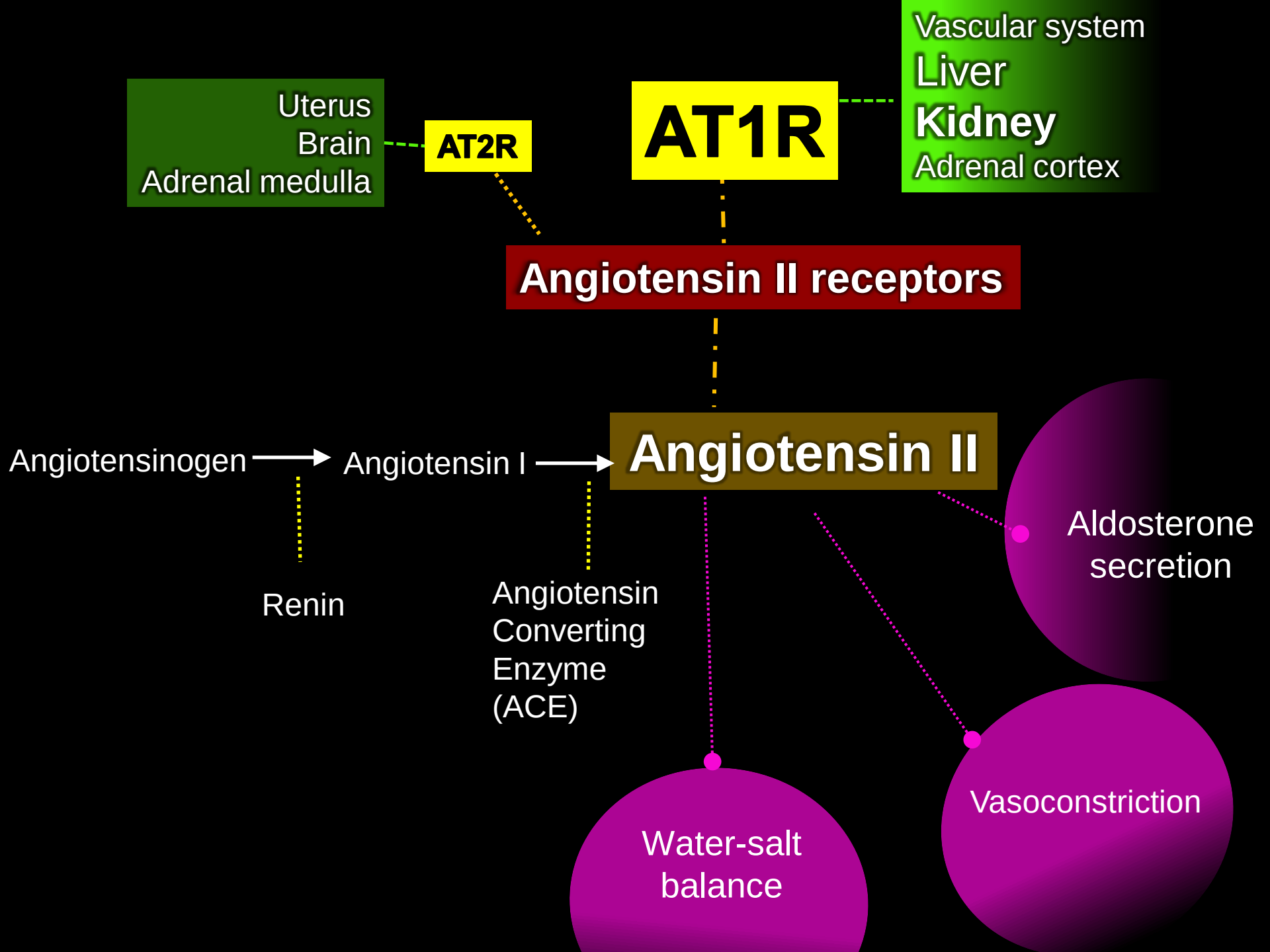


(AT1R activating antibodies in renal allograft rejection. N Engl J Med 2005; 352:558-69)

2

AT1R antibody acts like a ligand.

AT1R: the main mediator of Angiotensin II (ligand)


Uterus
Brain
Adrenal medulla
AT2R
AT1R
Vascular system
Liver
Kidney
Adrenal cortex
Angiotensin II receptors
Angiotensinogen
Angiotensin I
Angiotensin II
Renin
Angiotensin Converting Enzyme (ACE)
Aldosterone secretion
Water-salt balance
Vasoconstriction

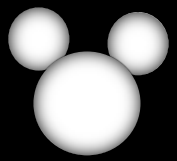
Mimic Effect of AT1R antibodies

AT1R abs

Aldosterone secretion

Vasoconstriction

Water-salt balance

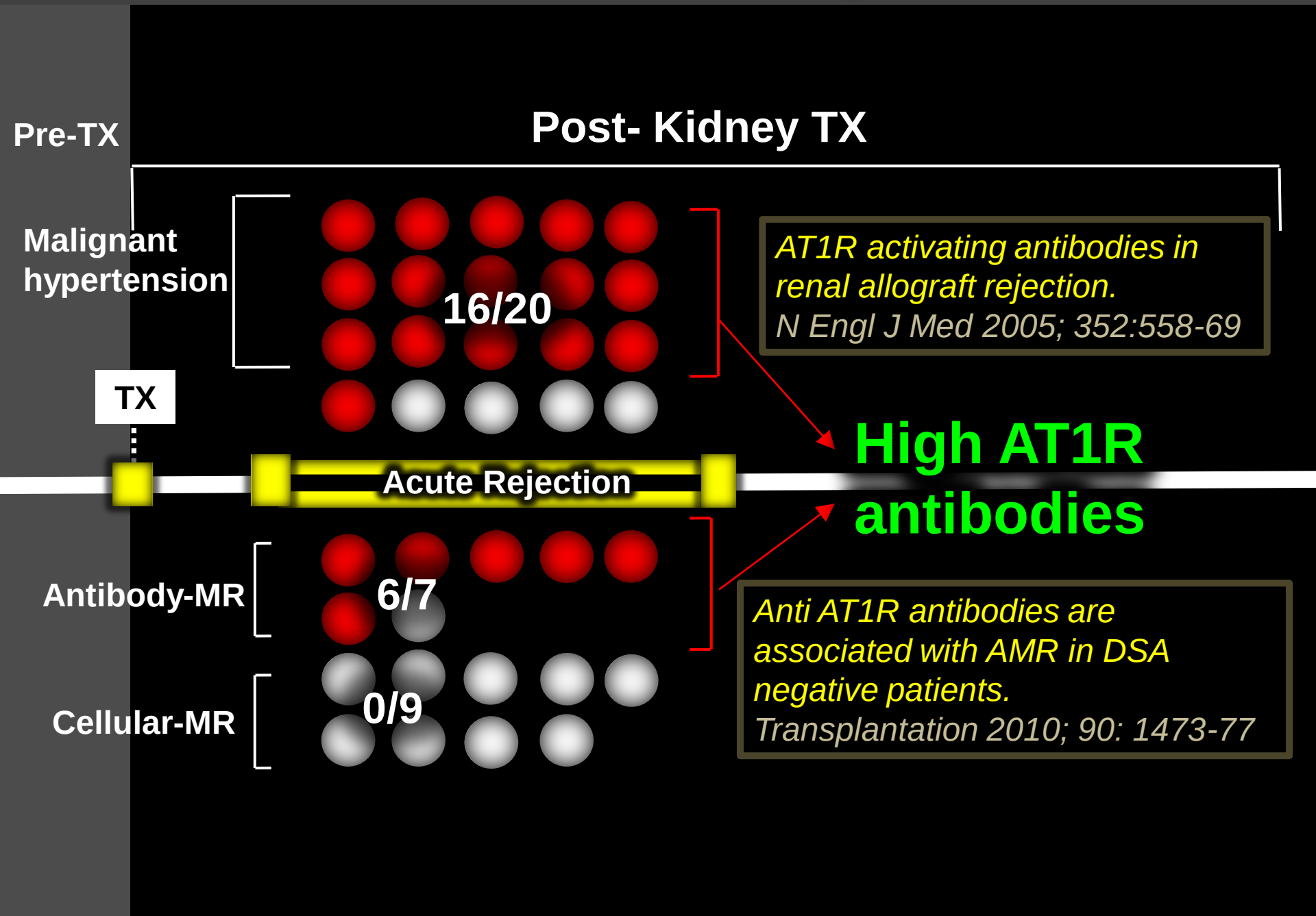


Rat + Y = Anti-AT1R

Acute Vascular Rejection

(N Engl J Med 2005; 352:558-69)

AT1R antibodies in Transplantation



What is the impact of post-Tx AT1R antibodies on Graft Failure?

(graft outcome)

Study Protocol

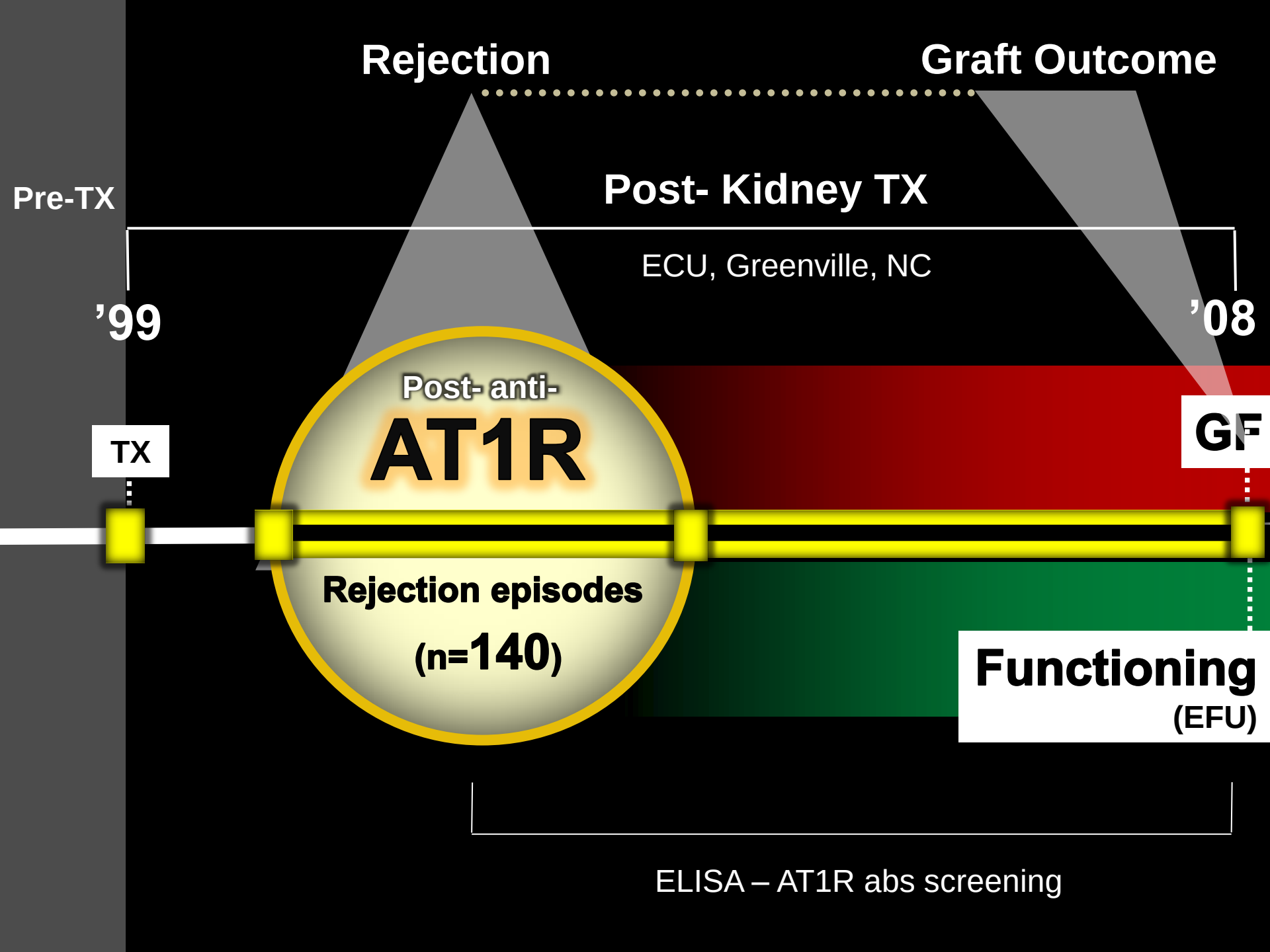
Study Protocol

- The study enrolled a total of 140 patients who received kidney transplants between 1999 and 2008 at EUC, Pitt county Memorial Hospital, Greenville, NC.

- All the patients had rejection episodes (at least one) with or without graft failure as the result.

- The serum samples at the time of or during rejection were screened for the presence of AT1R antibodies with ELISA using a plate coated with the extracts from Chinese hamster ovary cells over-expressing the human AT1R.

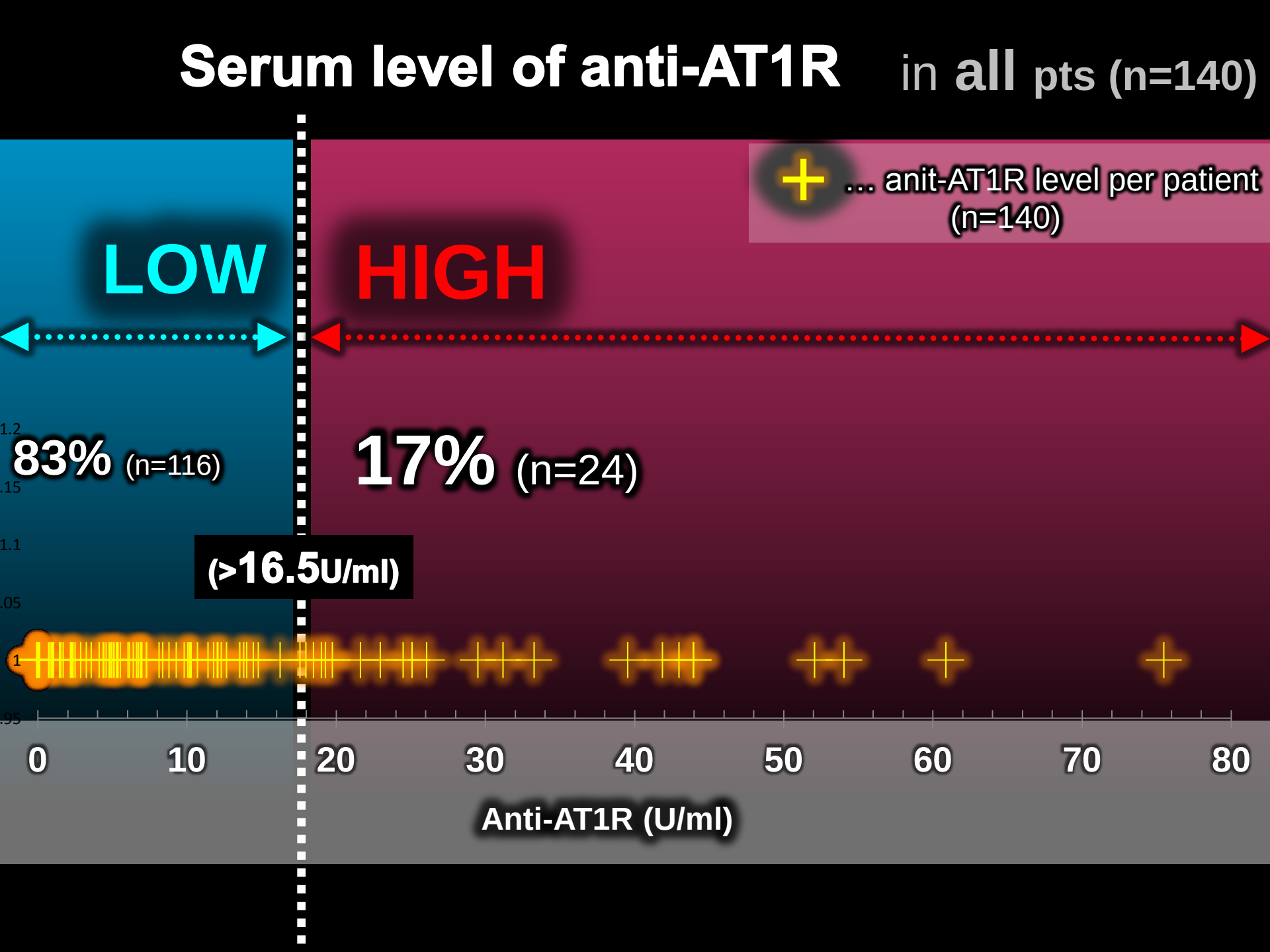
- All the patients were previously screened for the presence of HLA-DSA.


Rejection
Graft Outcome
Pre-TX
Post- Kidney TX
ECU, Greenville, NC
’99
’08
Post- anti-
AT1R
TX
GF
Rejection episodes
(n=140)
Functioning
(EFU)
ELISA – AT1R abs screening

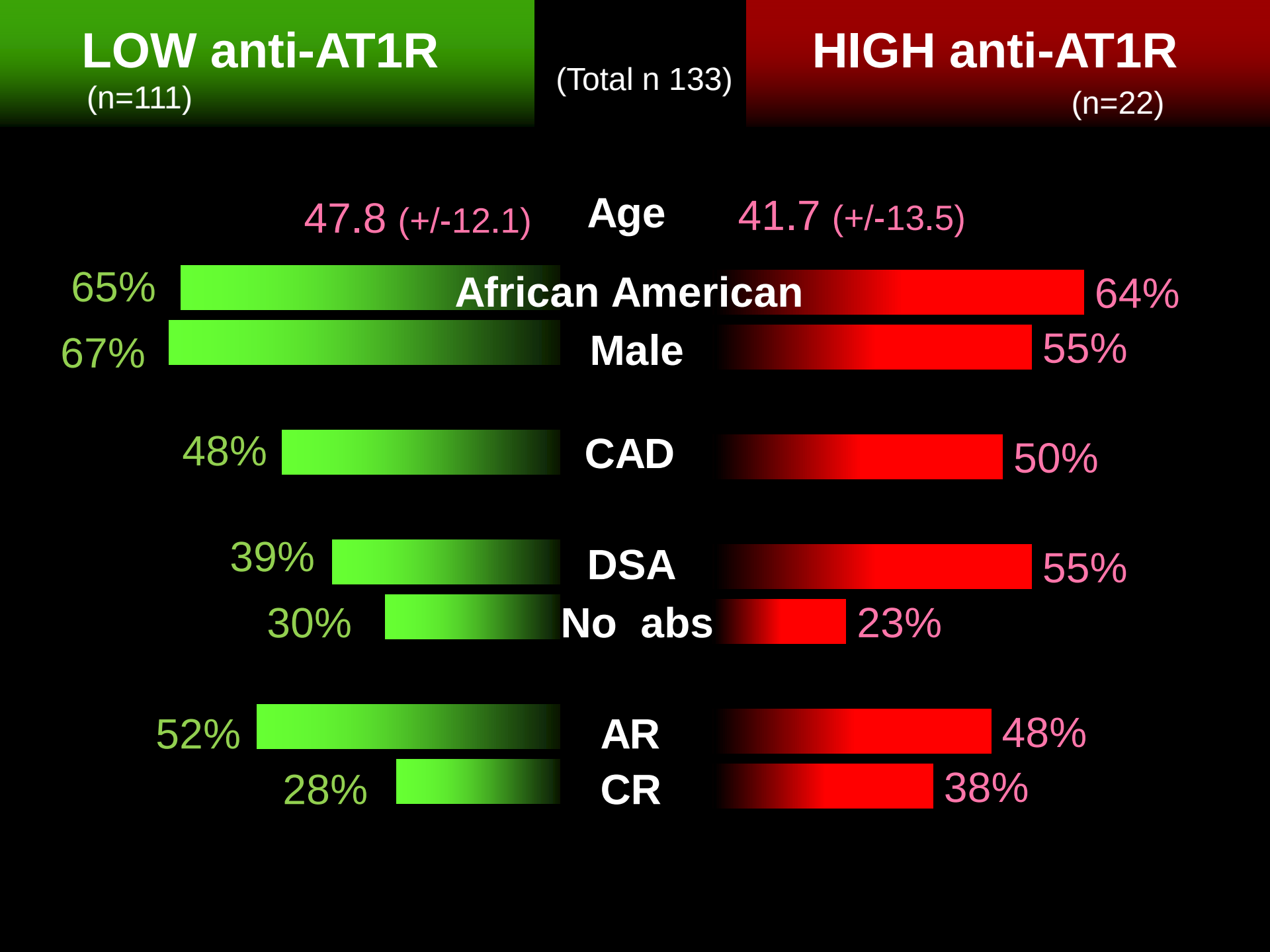
Results

anti AT1R Level & %

in **all** pts (n=140)

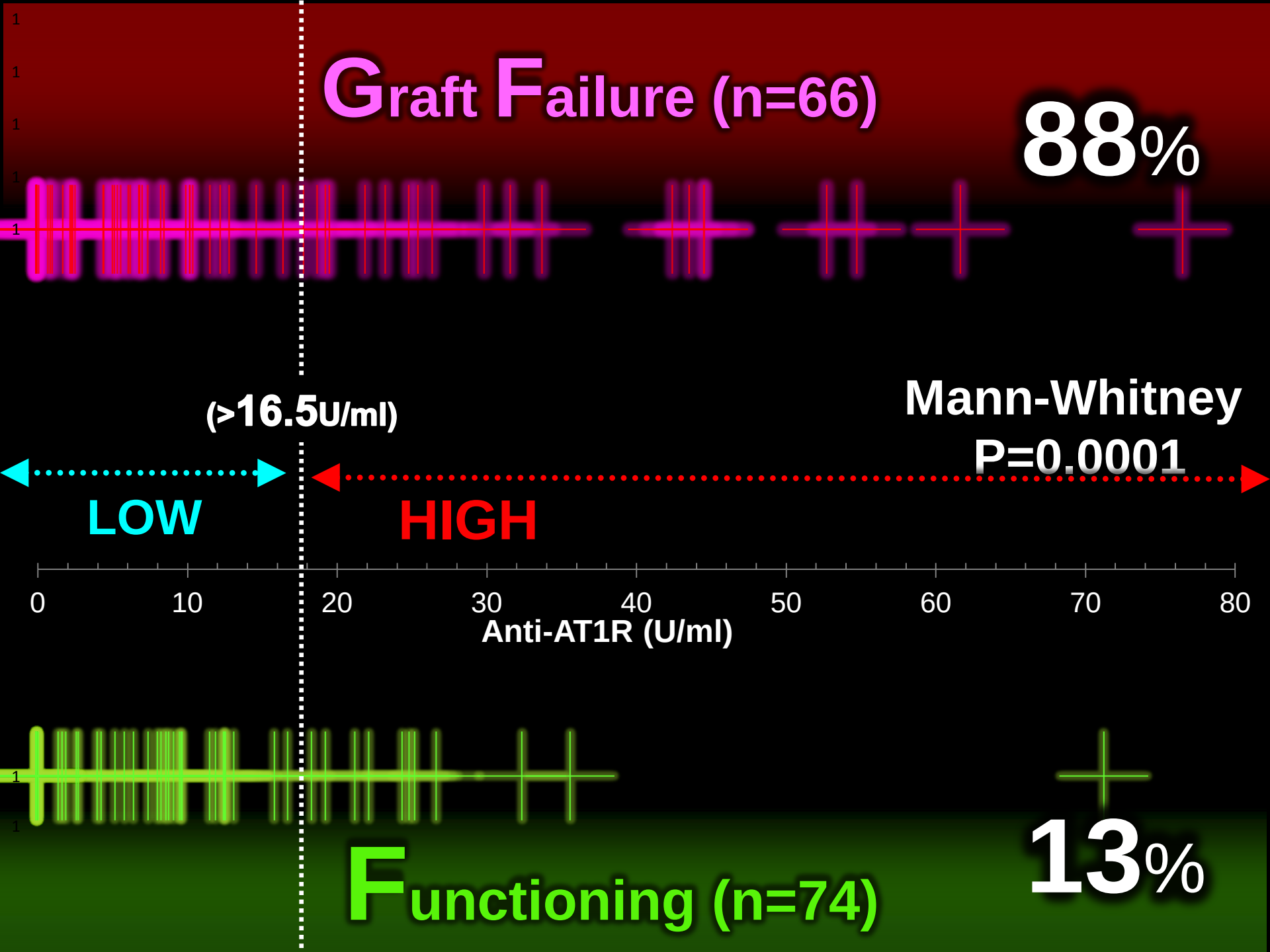

Serum level of anti-AT1R in all pts (n=140)
… anit-AT1R level per patient (n=140)
LOW
HIGH
83% (n=116)
17% (n=24)
(>16.5U/ml)
1.2
.15
1.1
.05
1
.95
0
10
20
30
40
50
60
70
80
Anti-AT1R (U/ml)

Patient Characteristics by anti-AT1R levels


LOW anti-AT1R
(n=111)
(Total n 133)
HIGH anti-AT1R
(n=22)
47.8 (+/-12.1)
Age
41.7 (+/-13.5)
65%
African American
64%
67%
Male
55%
48%
CAD
50%
39%
DSA
55%
30%
No abs
23%
52%
AR
48%
28%
CR
38%

anti AT1R Level & %

Graft Failure vs. Functioning


Graft Failure (n=66)
88%
(>16.5U/ml)
Mann-Whitney
P=0.0001
LOW
HIGH
0
10
20
30
40
50
60
70
80
Anti-AT1R (U/ml)
Functioning (n=74)
13%

- The overall AT1R level was significantly higher in graft failure group compared with functioning group with Mann-Whitney P value .0001.

- At the 16.5 U/ml cut-off, 88% of the patients were positive to AT1R antibodies whereas only 13% was positive in the functioning patients.

How do AT1R antibodies (with or without HLA-DSA) have the impact on

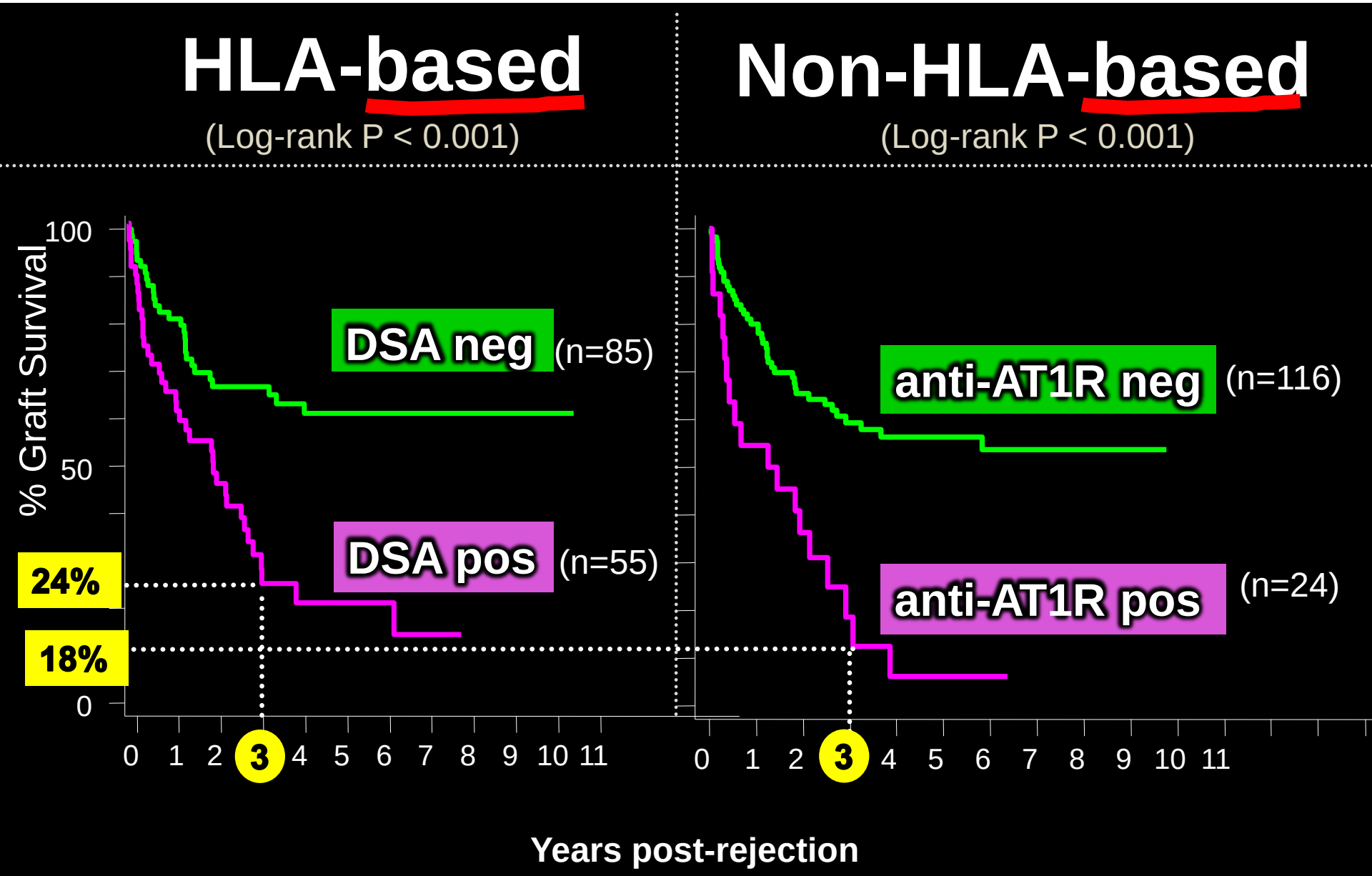
Graft Survival ?

Graft Survival

by HLA vs. non-HLA

(AT1R)

% Graft survival by



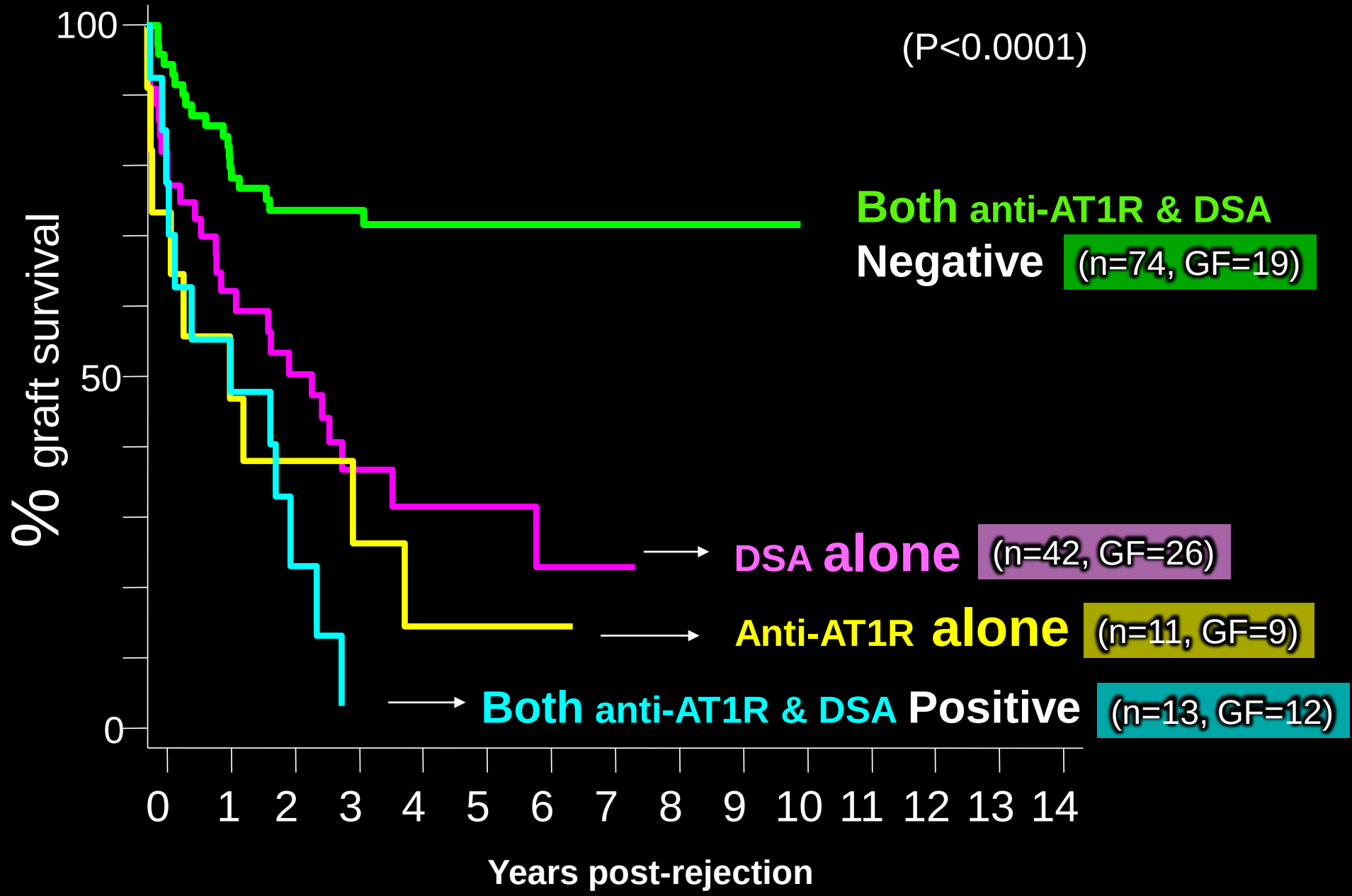
Survival

in the presence of (or absence of)

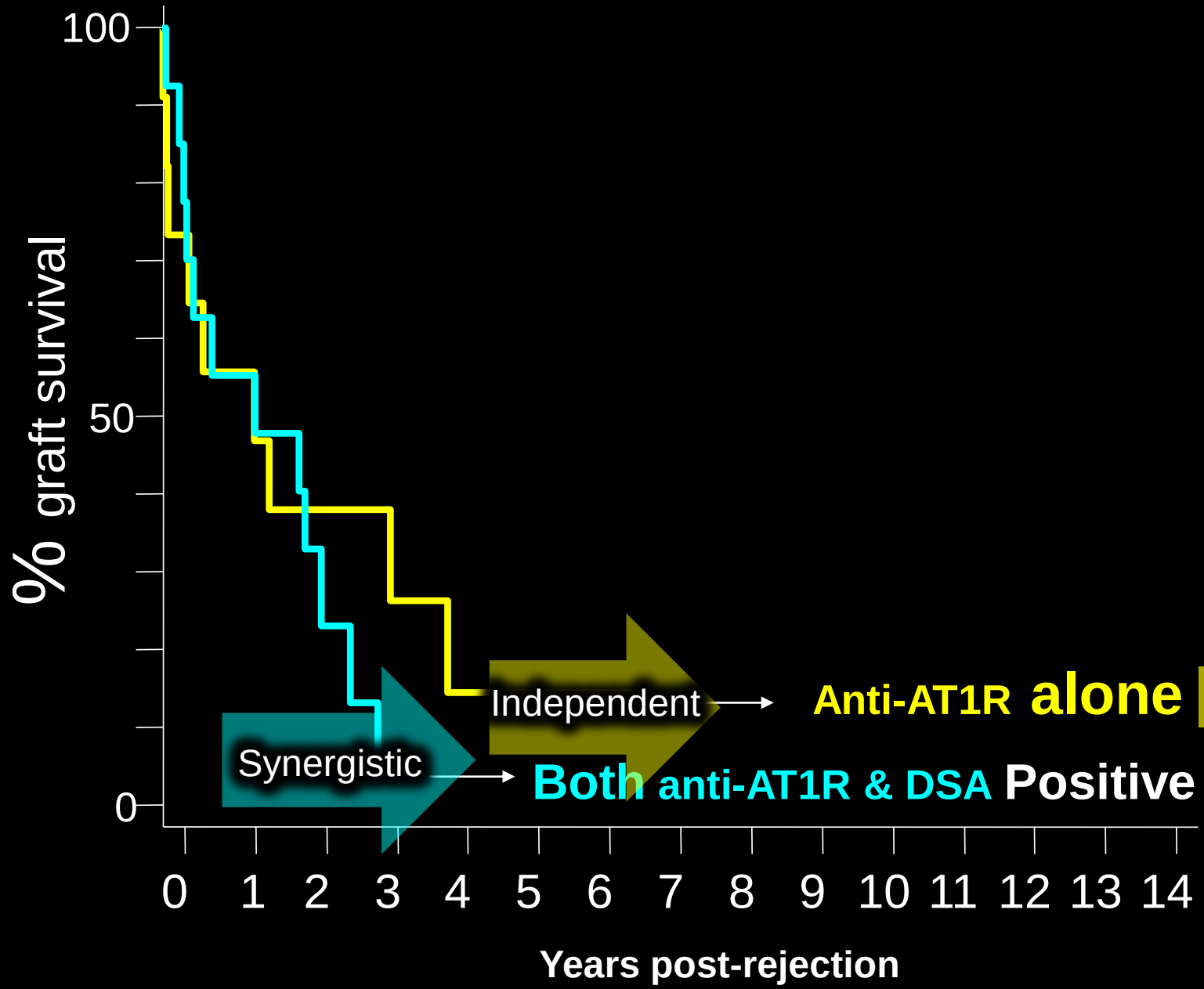
both DSA & AT1R antibodies ?

- **Both anti-AT1R & DSA Negative**
- **Both anti-AT1R & DSA Positive**
- **Anti-AT1R alone**
- **DSA alone**

Comparison between anti-AT1R vs. HLA-DSA in graft survival



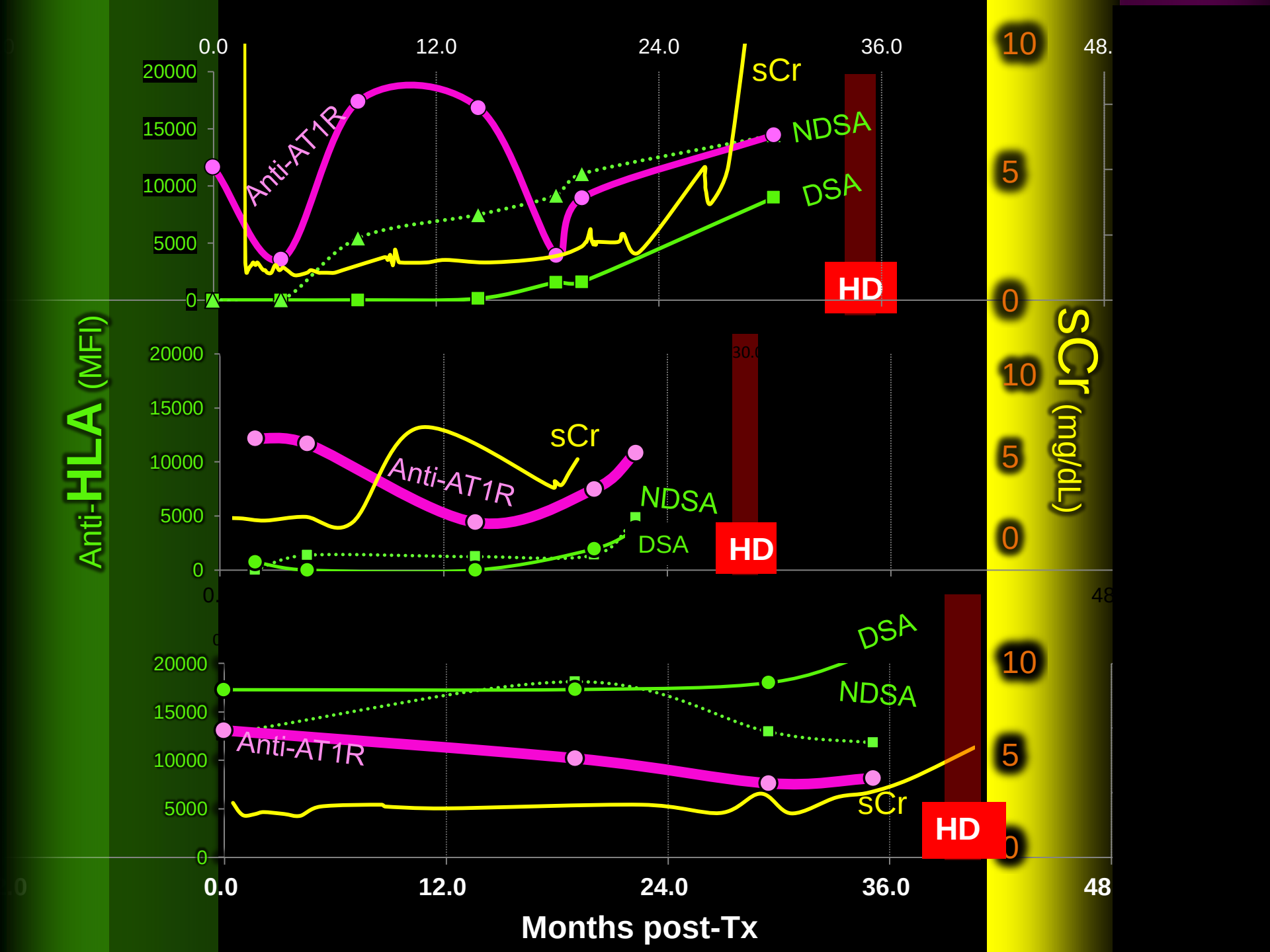
Comparison between anti-AT1R vs. HLA-DSA in graft survival



Synergistic & Independent
effect of AT1R antibodies

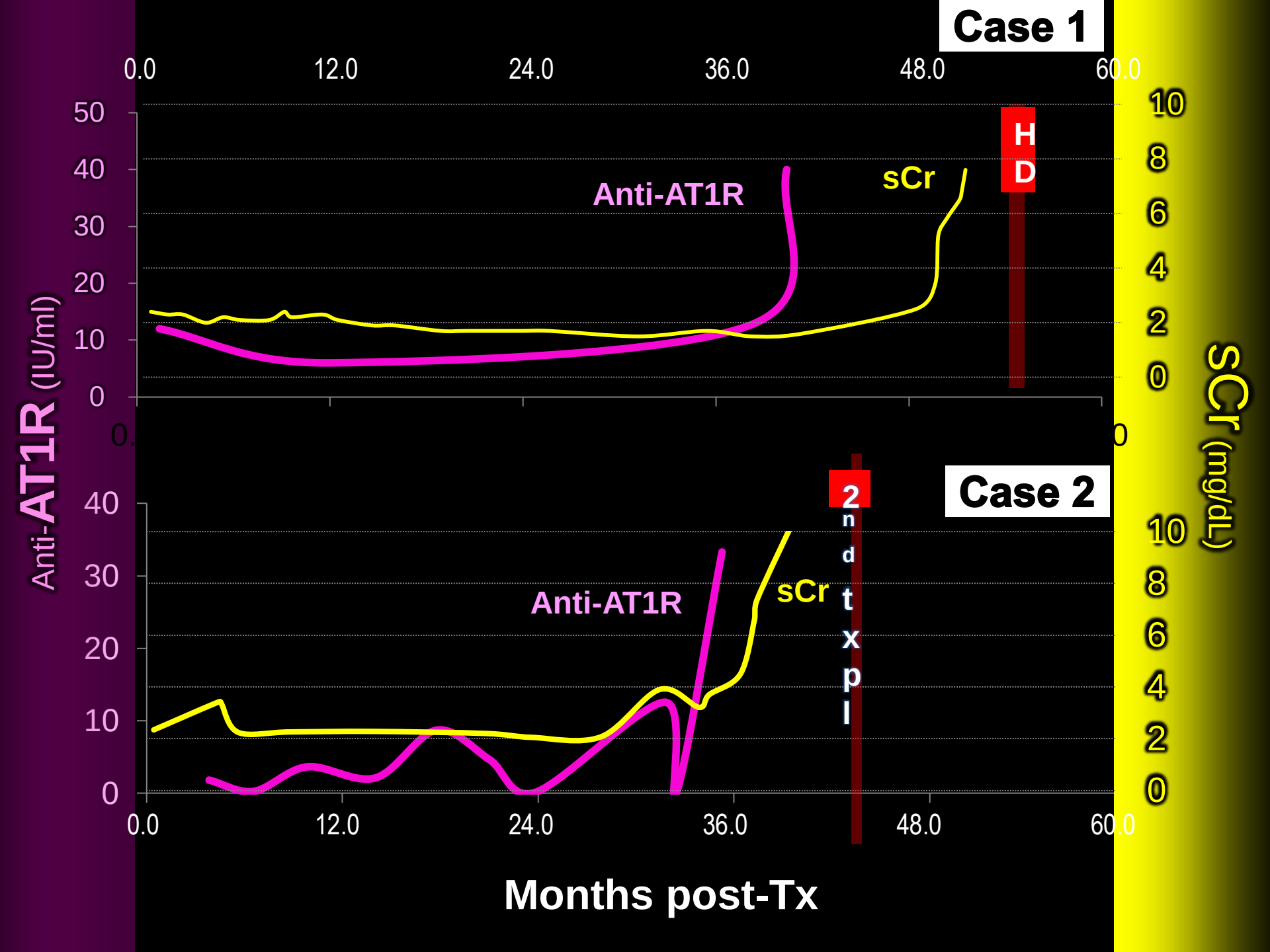
“Synergistic”

Both increasing **anti-AT1R** & **DSA**
followed by graft failure.

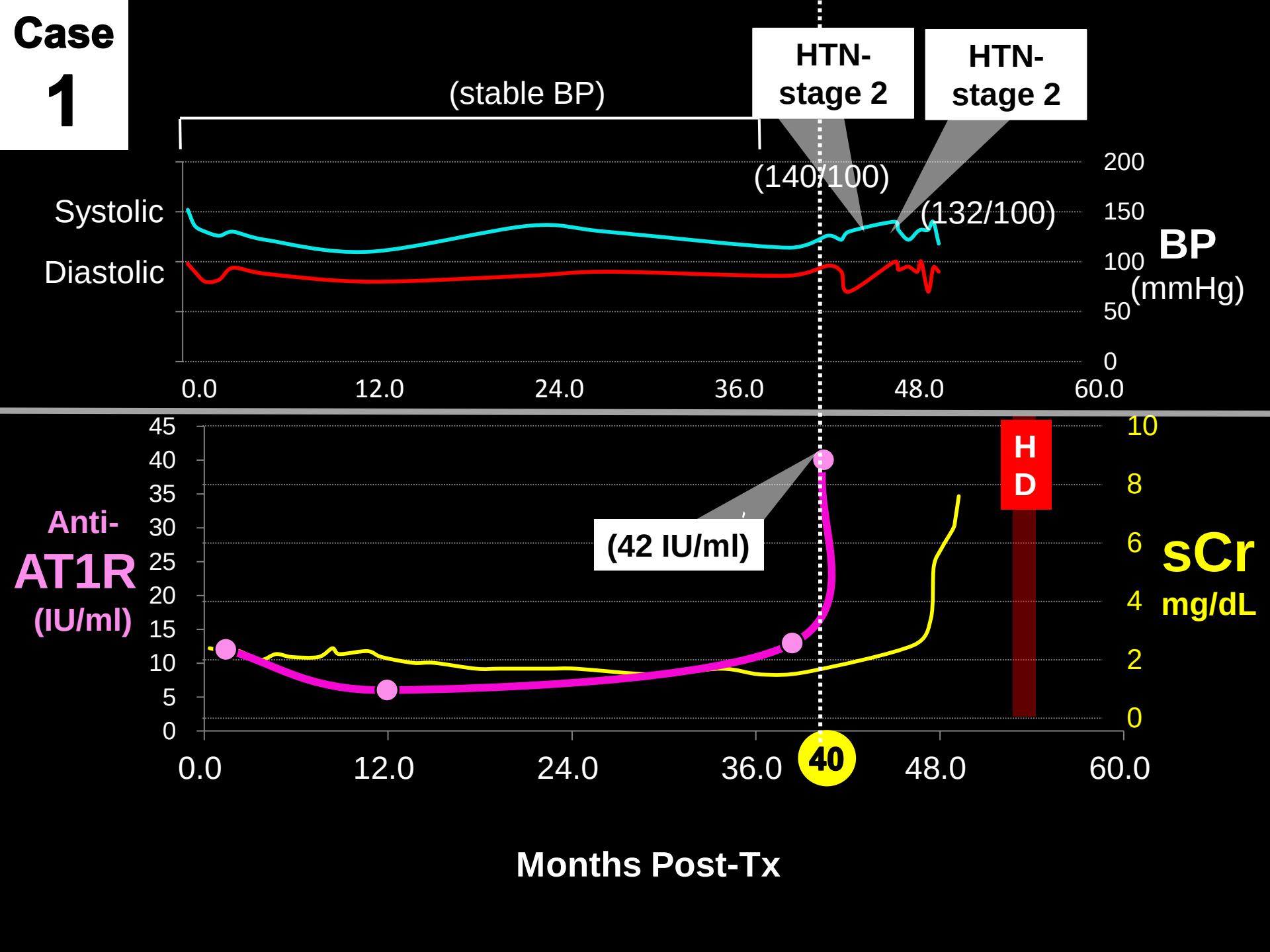

Anti-HLA (MFI)
sCr (mg/dL)
Months post-Tx
0.0
12.0
24.0
36.0
48
20000
15000
10000
5000
0
10
5
0
Anti-AT1R
sCr
NDSA
DSA
HD

“Independent”

Increasing anti-AT1R alone
in the absence of HLA antibodies


Case 1
0.0
12.0
24.0
36.0
48.0
60.0
50
40
30
20
10
0
Anti-AT1R
sCr
H
D
10
8
6
4
2
0
Anti-AT1R (IU/ml)
SCr (mg/dL)
Case 2
2nd txpl
Anti-AT1R
sCr
Months post-Tx

The above cases
with Blood Pressure levels

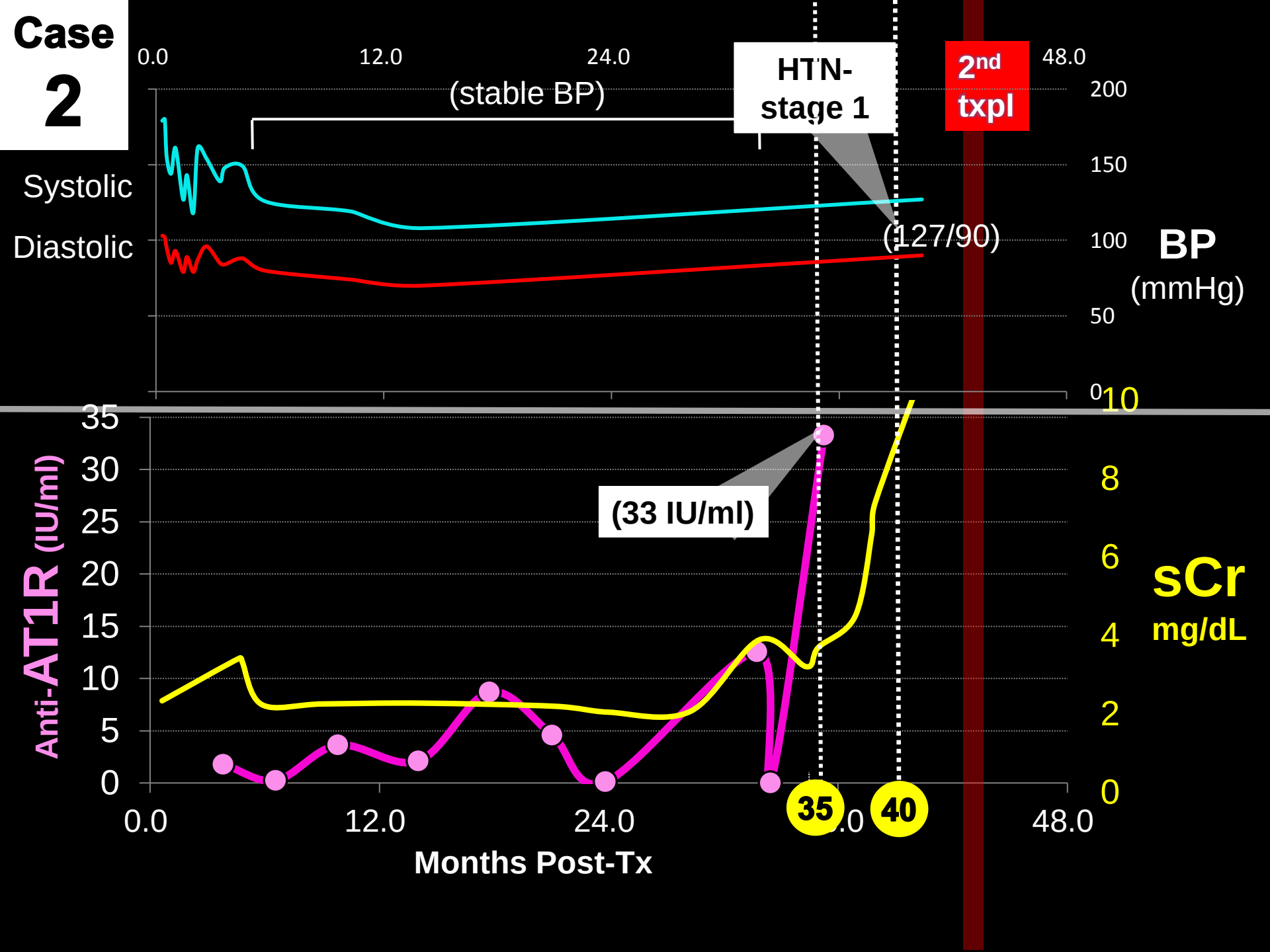

Case 1
(stable BP)
HTN-stage 2
HTN-stage 2
(140/100)
(132/100)
Systolic
Diastolic
200
150
100
50
0
BP (mmHg)
0.0
12.0
24.0
36.0
48.0
60.0
Anti-AT1R (IU/ml)
45
40
35
30
25
20
15
10
5
0
(42 IU/ml)
HD
10
8
6
4
2
0
sCr mg/dL
0.0
12.0
24.0
36.0
40
48.0
60.0
Months Post-Tx

Case 1

The patient anti-AT1R level was stable during the first 36 post-Tx months, and the BP was controlled at pre-HTN level.

However, within a couple of months, the level was dramatically increased despite the stable sCr level.
And the highest anti-AT1R 42U/ml was finally reached at 40 post Tx month.

After this time period, (the patient BP had been HTN-stage 1, and finally) in 8 months after the highest anti-AT1R record, there were two records of HTN stage2 before the patient returned to hemodialysis.


Case 2
0.0
12.0
24.0
48.0
(stable BP)
HTN-stage 1
2nd txpl
Systolic
Diastolic
(127/90)
200
150
100
50
0
BP (mmHg)
10
8
6
4
2
0
sCr mg/dL
35
30
25
20
15
10
5
0
Anti-AT1R (IU/ml)
(33 IU/ml)
35
40
Months Post-Tx

Case 2

This patient maintained relatively lower anti-AT1R levels during the first 3 post-Tx years.

The hypertension admitted at the time of Tx was controlled to the normal level at least during two years.

For the last three months before GF (in 3 years of post-Tx), anti-AT1R level suddenly jumped up from undetectable level to very high level (33U/ml) .

After about 5 months, the BP returned from normal level to HTN stage 1 and the patient was referred back to the 2nd txpl.

Is **AT1R antibody**
an independent predictor
of poor graft survival?

	Variable	Hazard Ratio	P	95% CI
Univariable	Recipient Male	0.70	0.16	0.43 - 1.15
	Non-black	1.53	0.13	0.88 - 2.66
	Deceased Donor	1.47	0.12	0.91 - 2.40
	Age	0.99	0.41	0.97 - 1.01
	Total HLA mismatch	1.05	0.43	0.93 - 1.19
	Biopsy-proven Acute Rejection	0.62	0.05	0.38 - 1.01
	Biopsy-proven Chronic Rejection	1.05	0.87	0.62 - 1.78
	High anti-AT1R alone	2.31	0.02	1.14 - 4.67
	DSA alone	1.88	0.01	1.15 - 3.10
	Both anti-AT1R and DSA	2.95	0.00	1.56 - 5.57
	Pre-Tx antibodies	1.13	0.69	0.62 - 2.08
Multivariable	Both anti-AT1R and DSA	5.81	0.00	2.7 - 12.5
	High anti-AT1R alone	4.95	0.00	2.2 - 11.1
	DSA alone	4.00	0.00	2.2 - 7.4
	Biopsy-proven Acute Rejection	0.54	0.02	0.3 - 0.9

Multivariable Analysis

- The presence of both anti-AT1R and DSA was an independent predictor of poor graft survival as well as anti-AT1R alone and DSA-alone.

- The patients with both DSA & AT1R antibodies and the patients with AT1R antibodies alone were 5 to 5.8 times more likely to lose their graft than those who don’t.

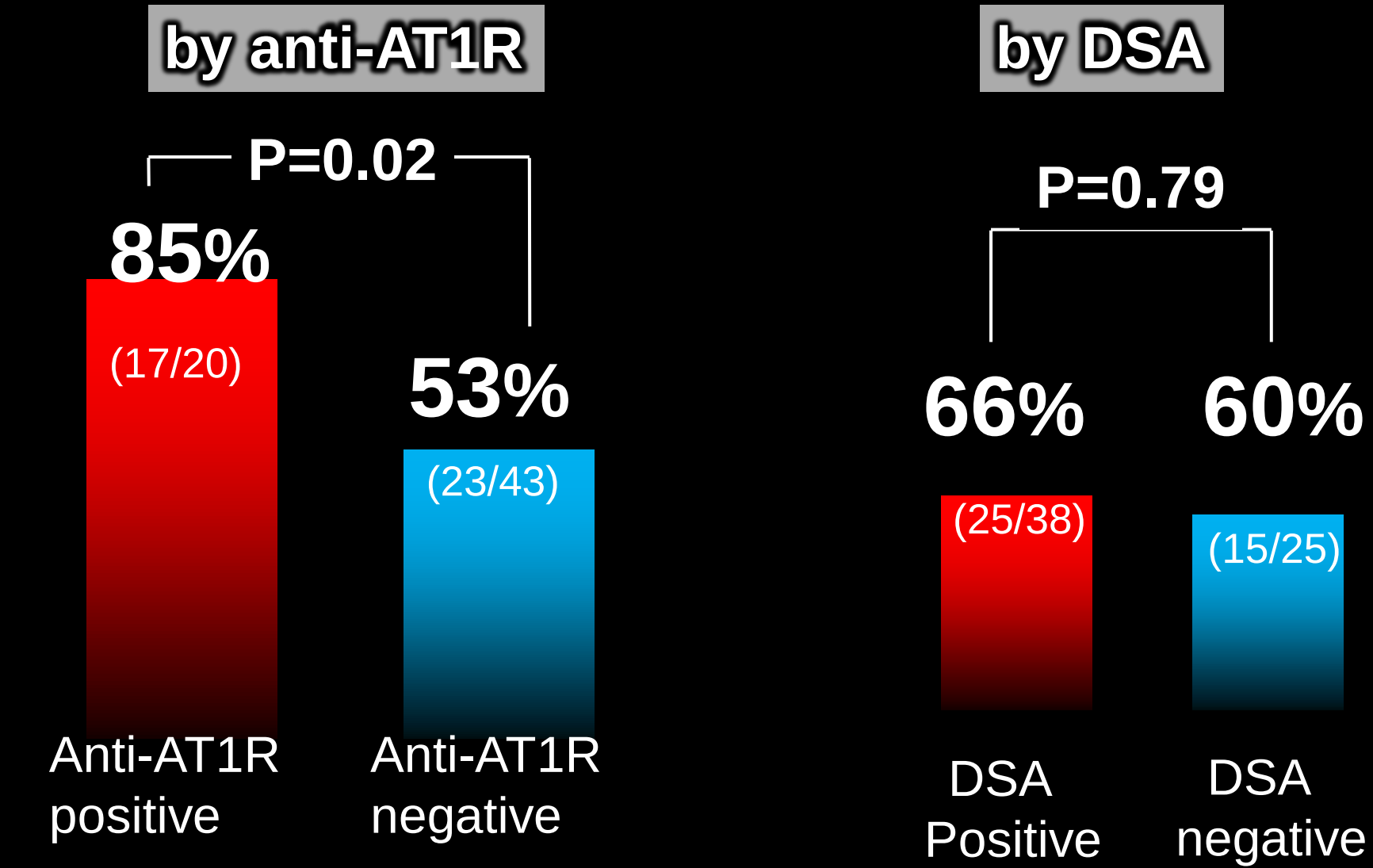
High AT1R antibodies:

Are they “**agonistic**” antibodies?

(receptor-activating)

% Hypertension of failed patients

(last BP: Systolic ≥140 or Diastolic ≥ 90)



Summary

1 Stratification

88% of the patients with **high AT1R antibodies** failed.

Agonistic
(85% hypertension)

32%
Anti-AT1R
HIGH

39%
DSA
alone

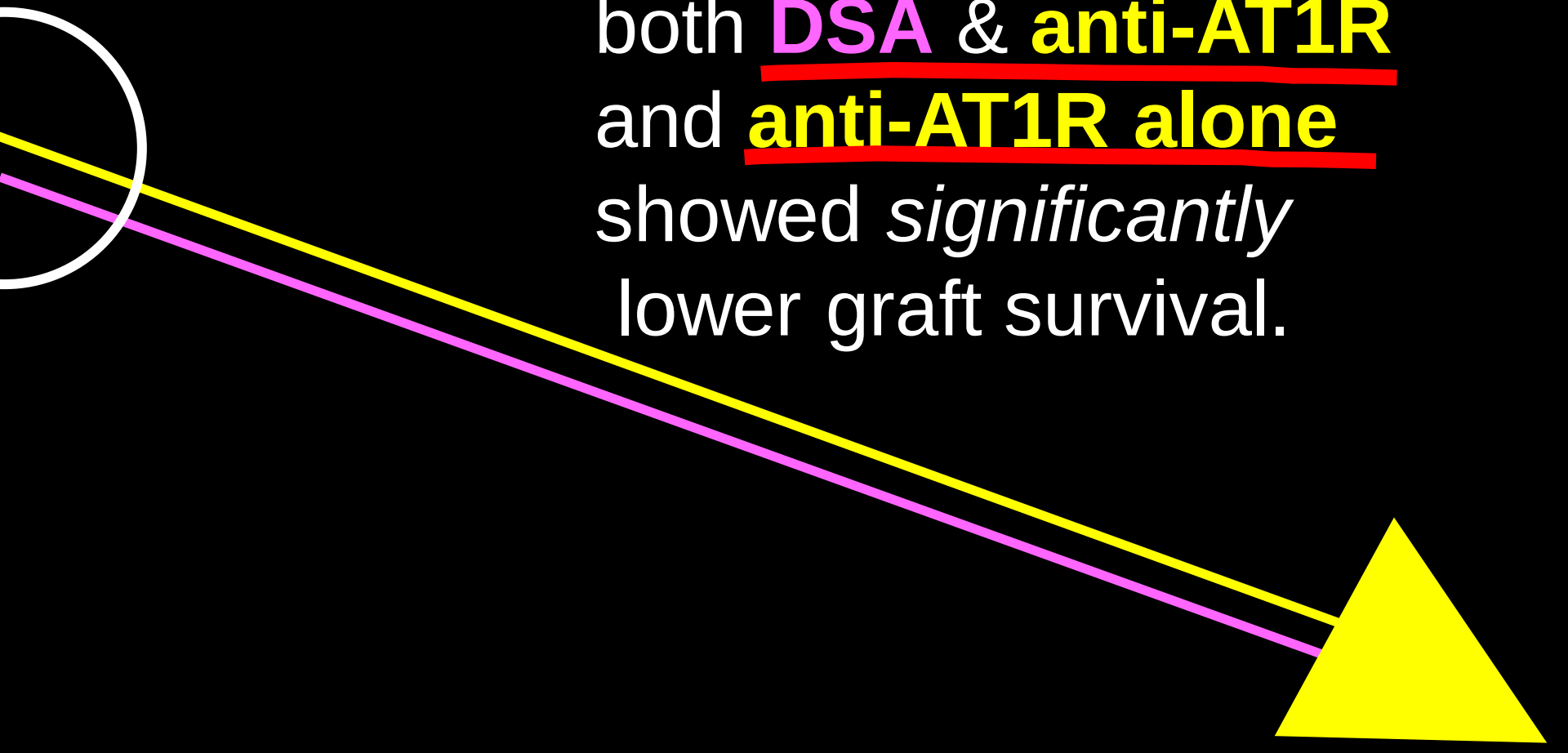
29%
Both neg

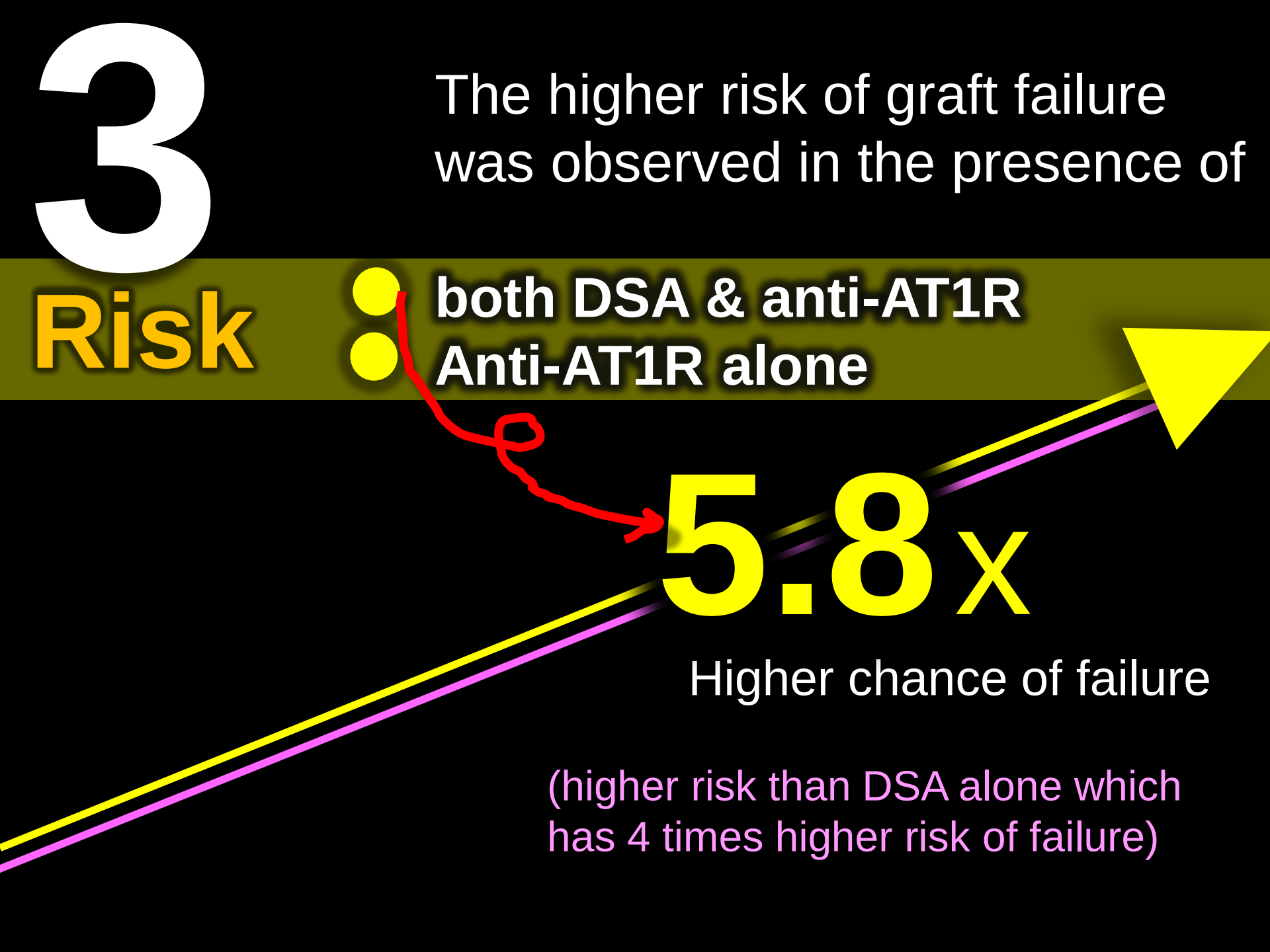
Total Failures

2

Survival

The presence of both **DSA** & **anti-AT1R** and **anti-AT1R alone** showed *significantly* lower graft survival.




3
Risk
The higher risk of graft failure was observed in the presence of
both DSA & anti-AT1R
Anti-AT1R alone
5.8x
Higher chance of failure
(higher risk than DSA alone which has 4 times higher risk of failure)

Conclusions

Stronger Risk Factor:

Non-HLA

AT1R antibodies

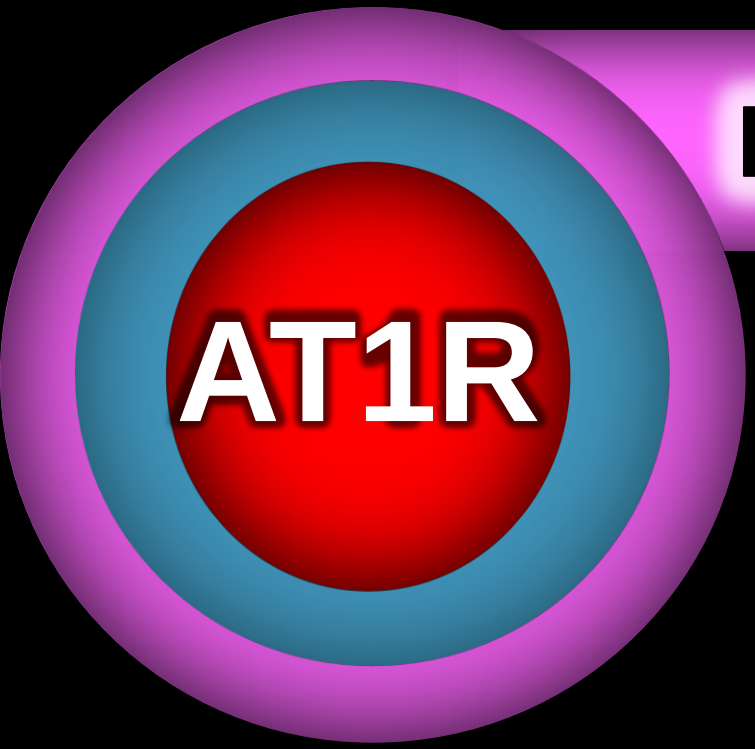
can ALSO lower graft survival.

Improved antibody-monitoring

Monitoring non-HLA

AT1R antibodies

(as well as HLA antibodies)



Better therapeutic target

Removal of **AT1R antibodies**

&

Blockage of AT1 receptors

Questions & Comments? : mtaniguchi@onelambda.com