Heart Transplantation current and future

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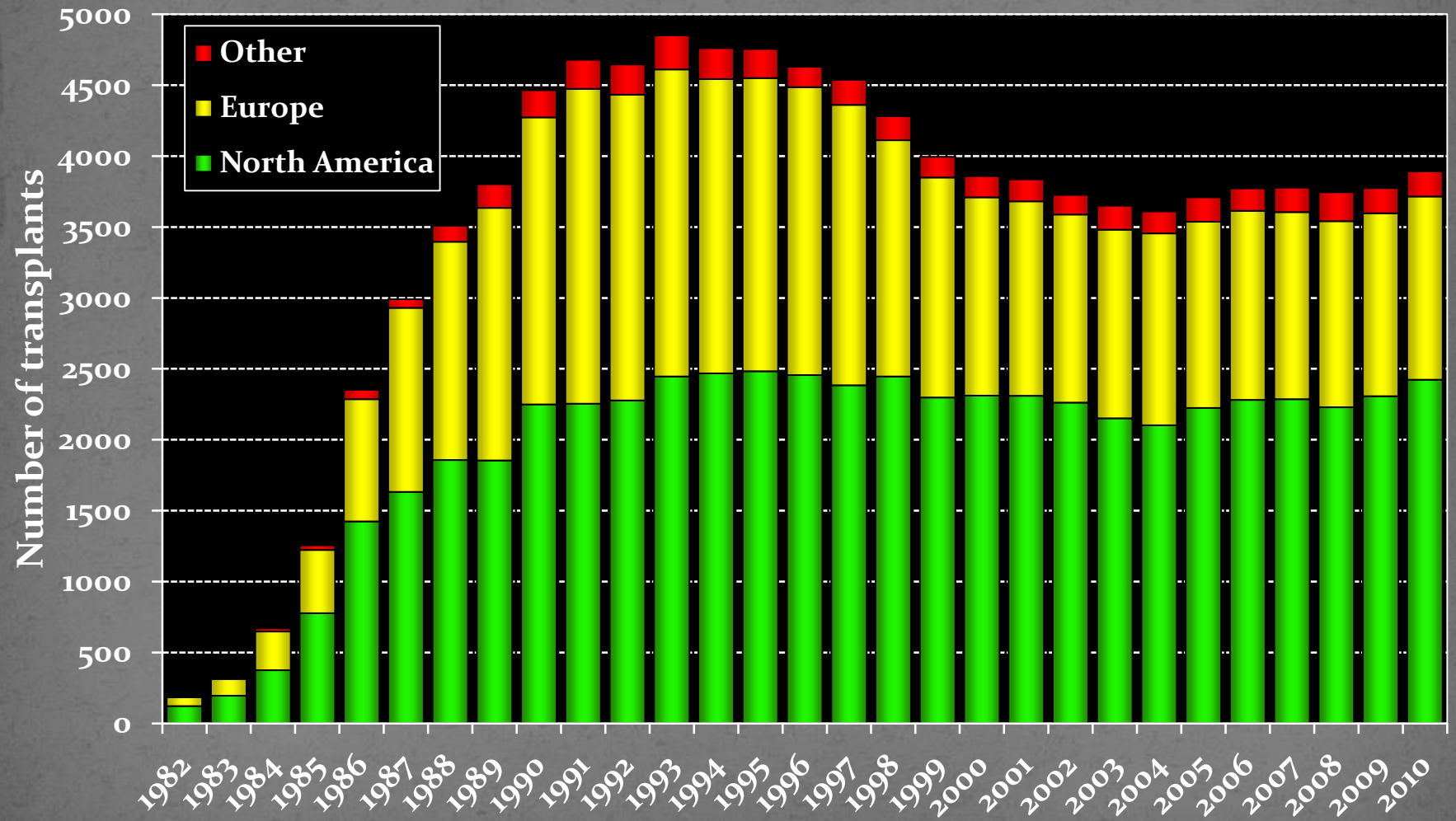
김 재 증

Current Status

Number of Heart Transplants



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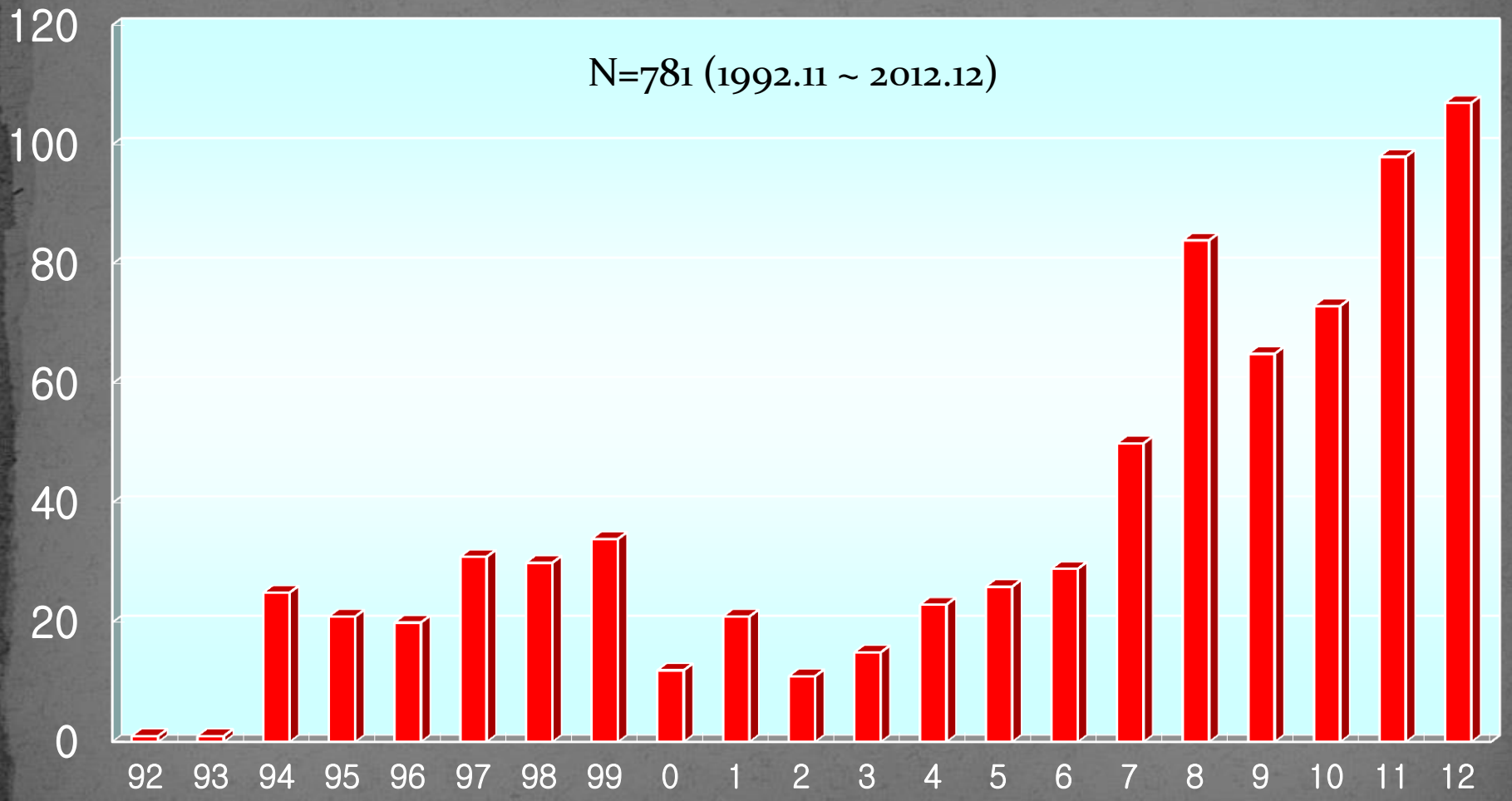
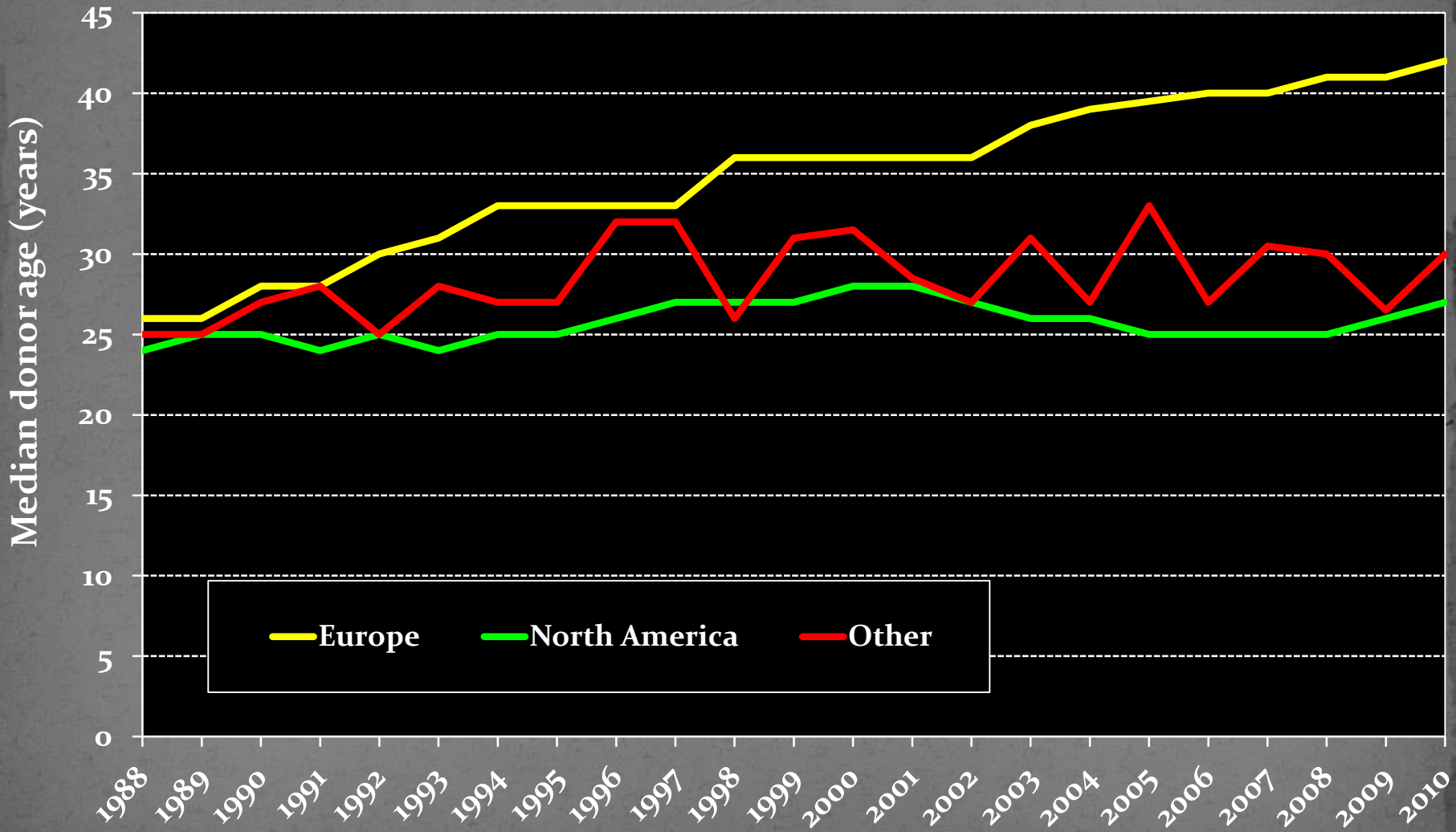
Heart Transplants in Korea



Adult Heart Transplants ; Median Donor Age by Location



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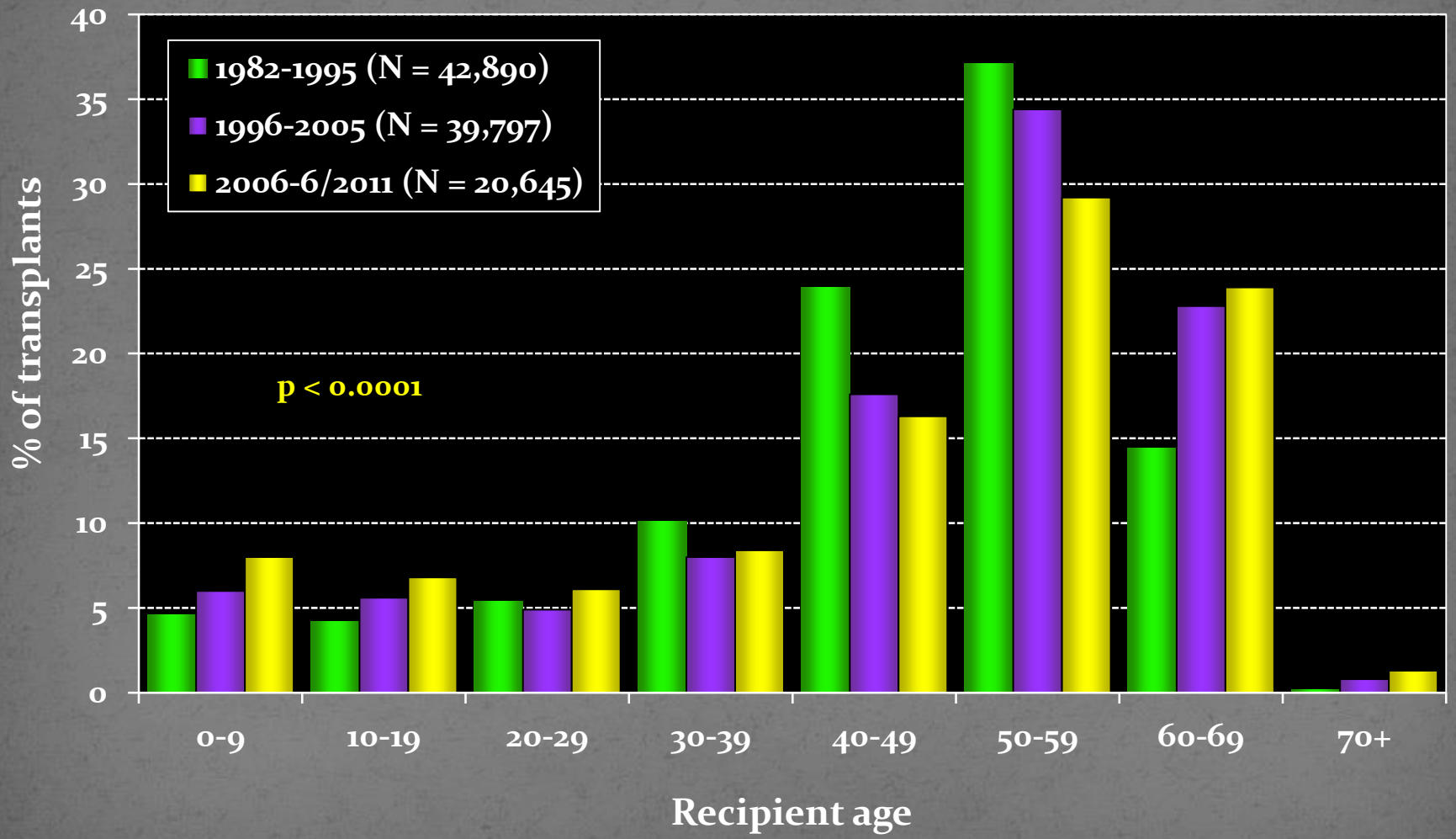
Recipients Age by Era



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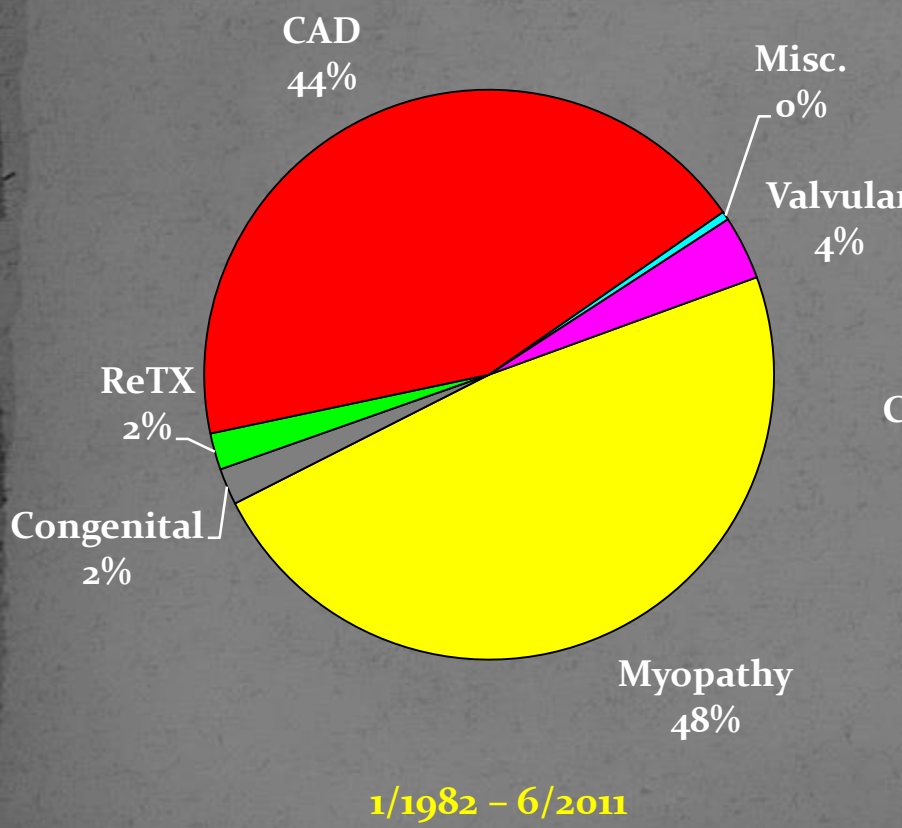
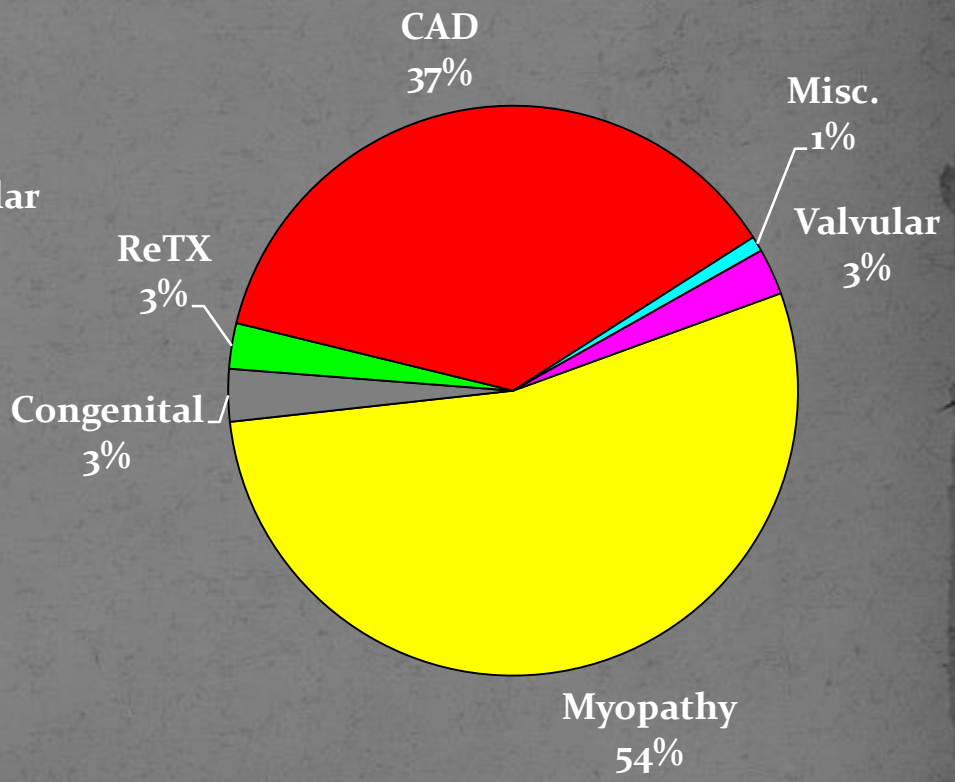
Diagnosis in Adult Heart Transplants



1/1982 – 6/2011



1/2006 – 6/2011

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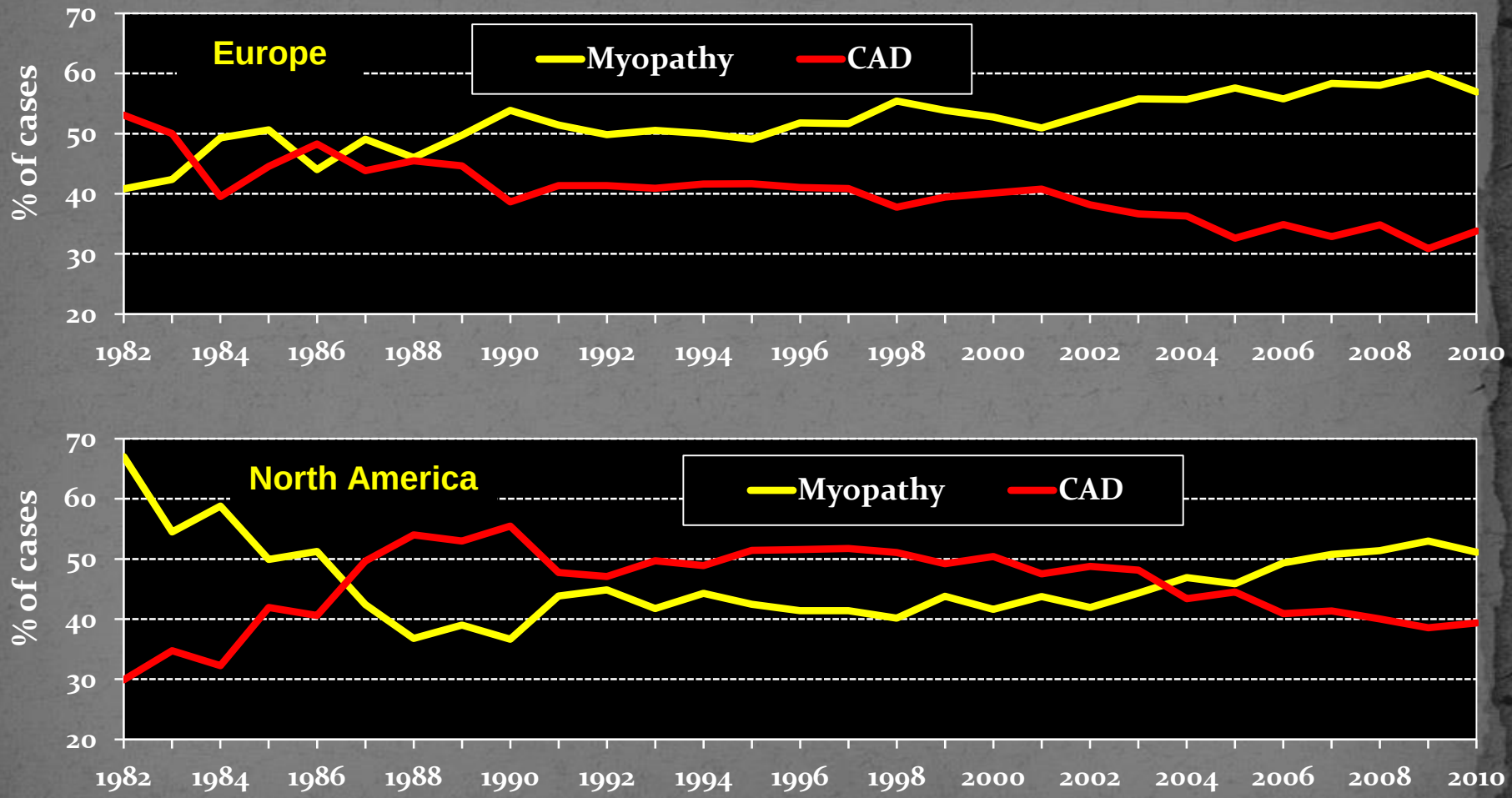
Adult heart Transplants

Diagnosis: Cardiomyopathy vs. CAD



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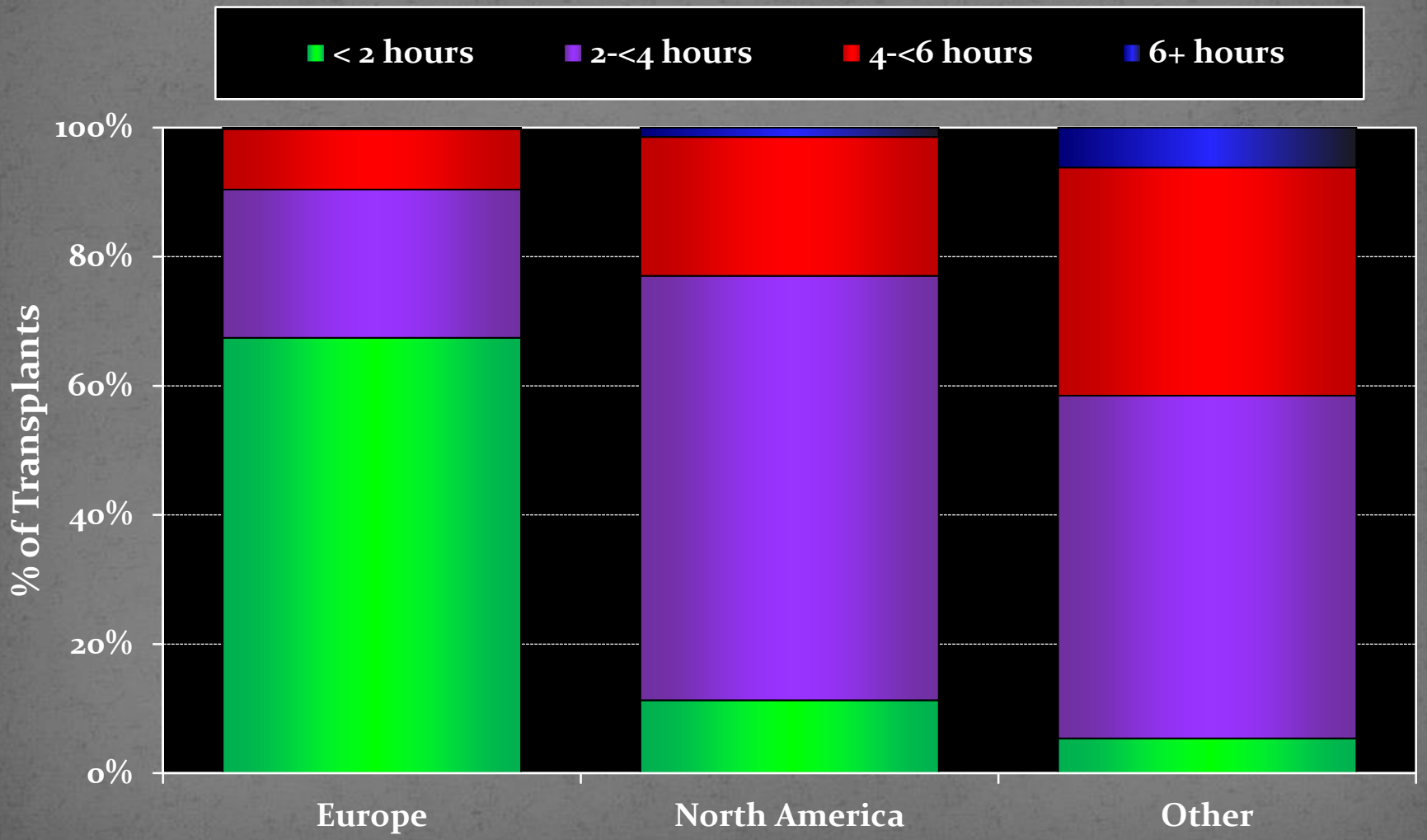
Adult Heart Transplants
Ischemic time Distribution



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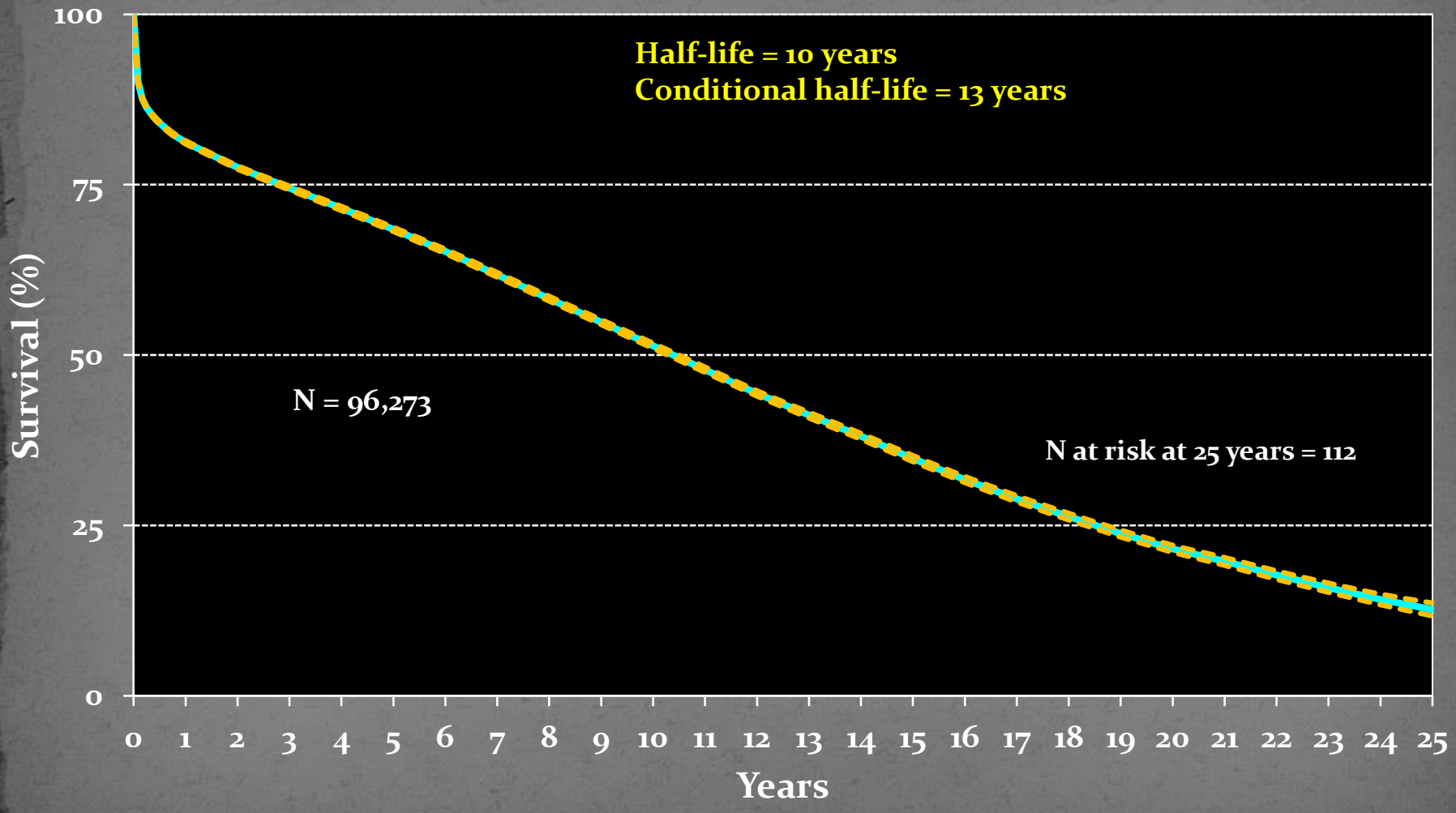
Heart Transplants Survival
(Transplants: January 1982 - June 2010)



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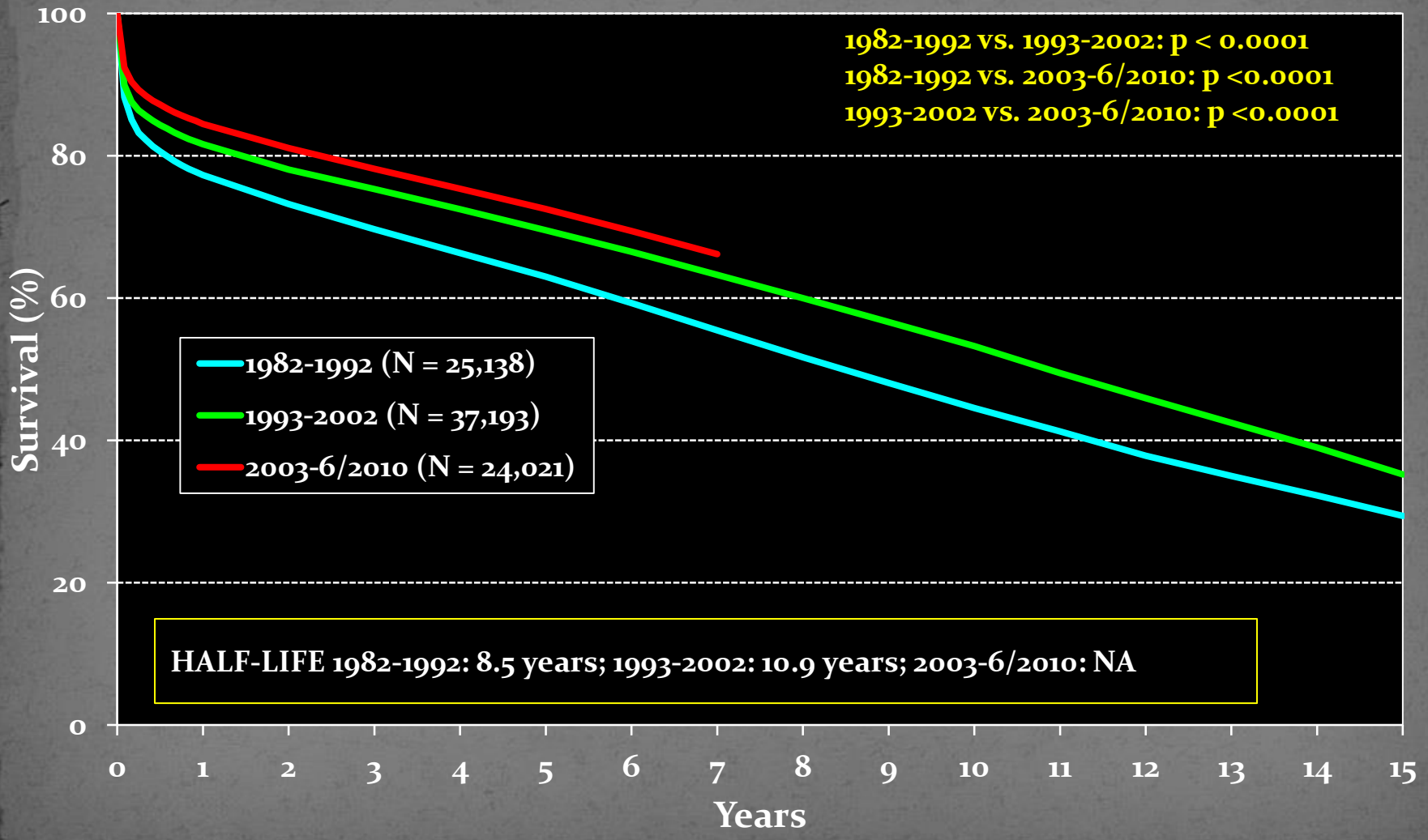
Heart Transplants Survival by Era
(Transplants: January 1982 - June 2010)



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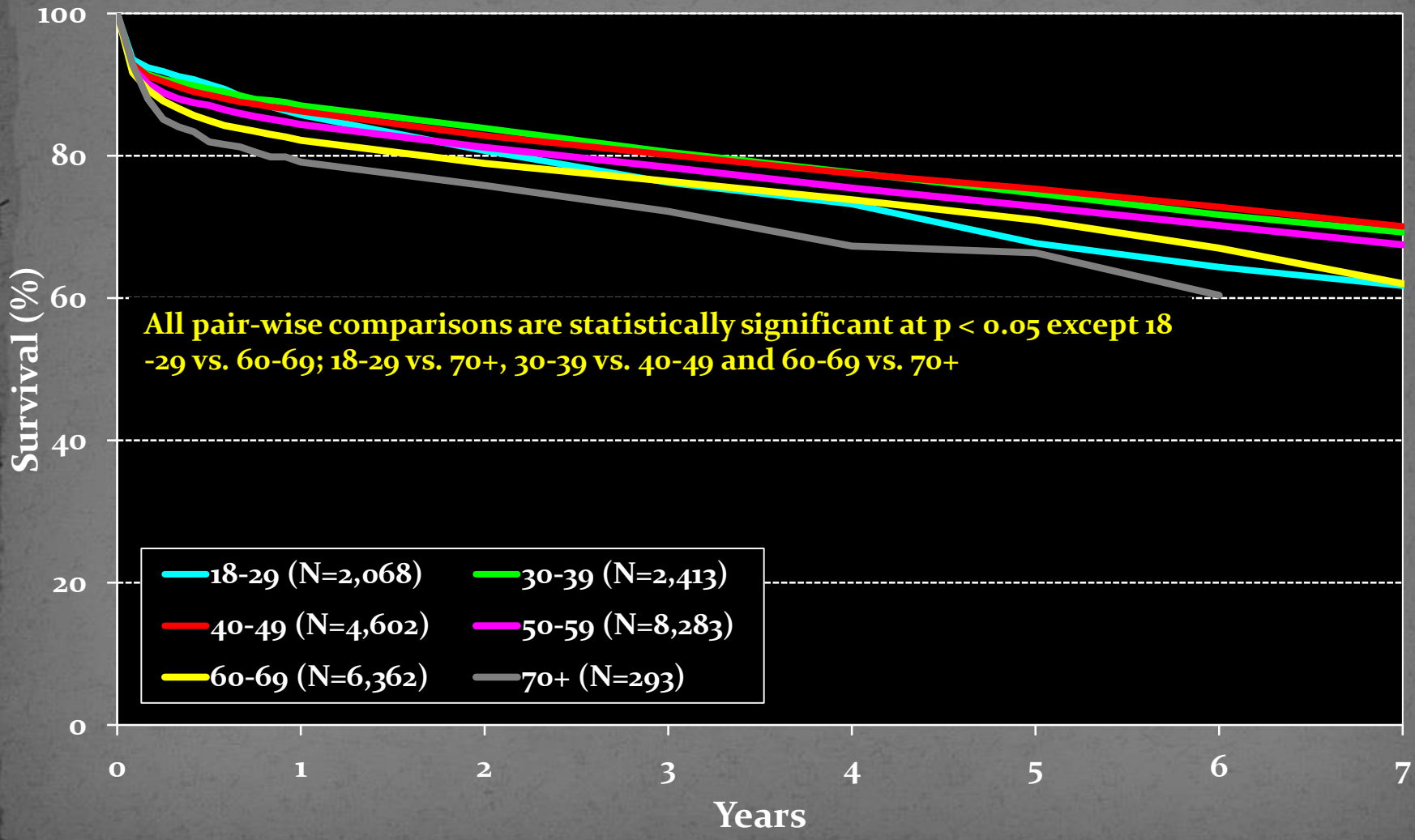
Heart Transplants Survival by Age

(Transplants: January 1982 - June 2010)



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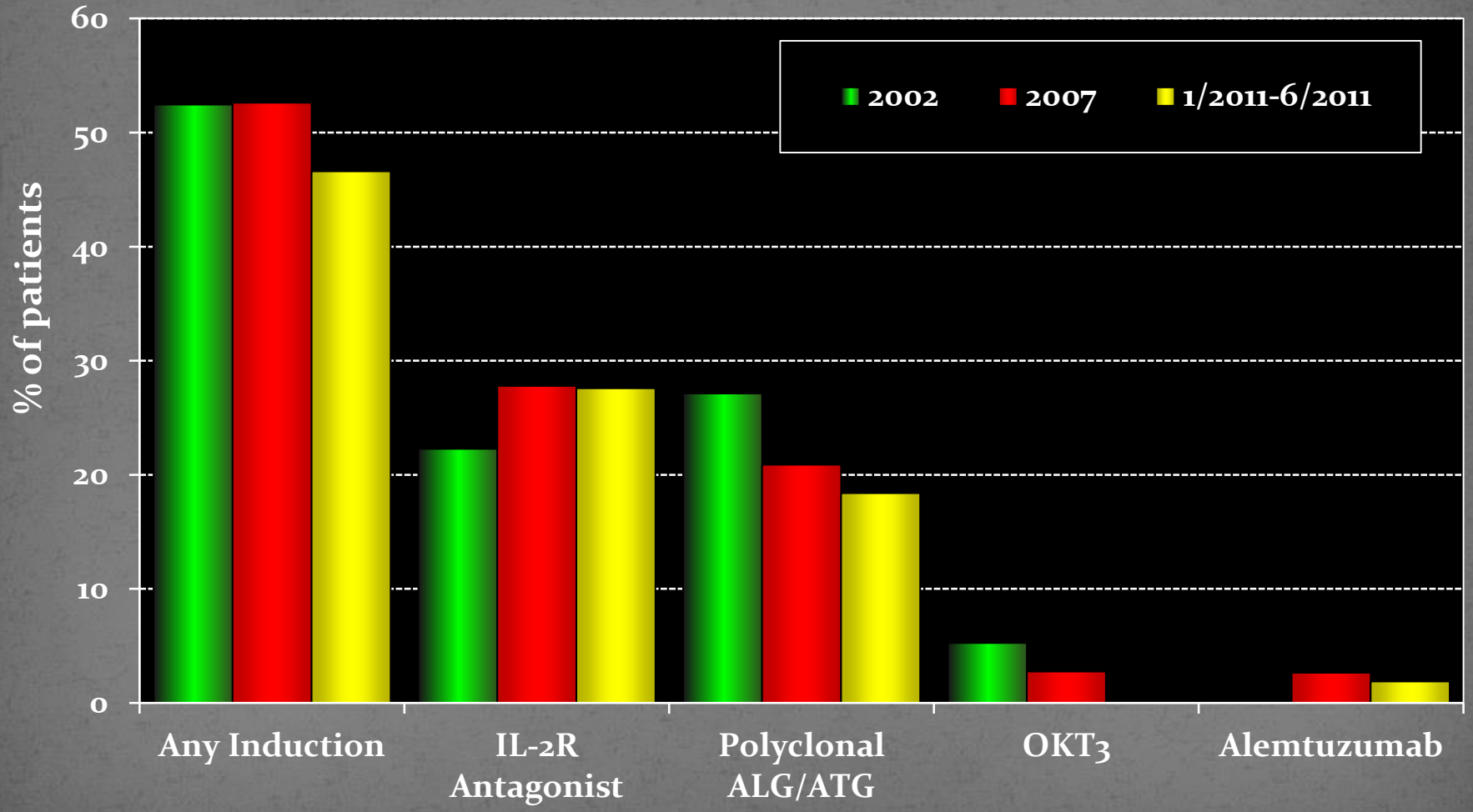
Adult Heart Recipients
Induction Immunosuppression



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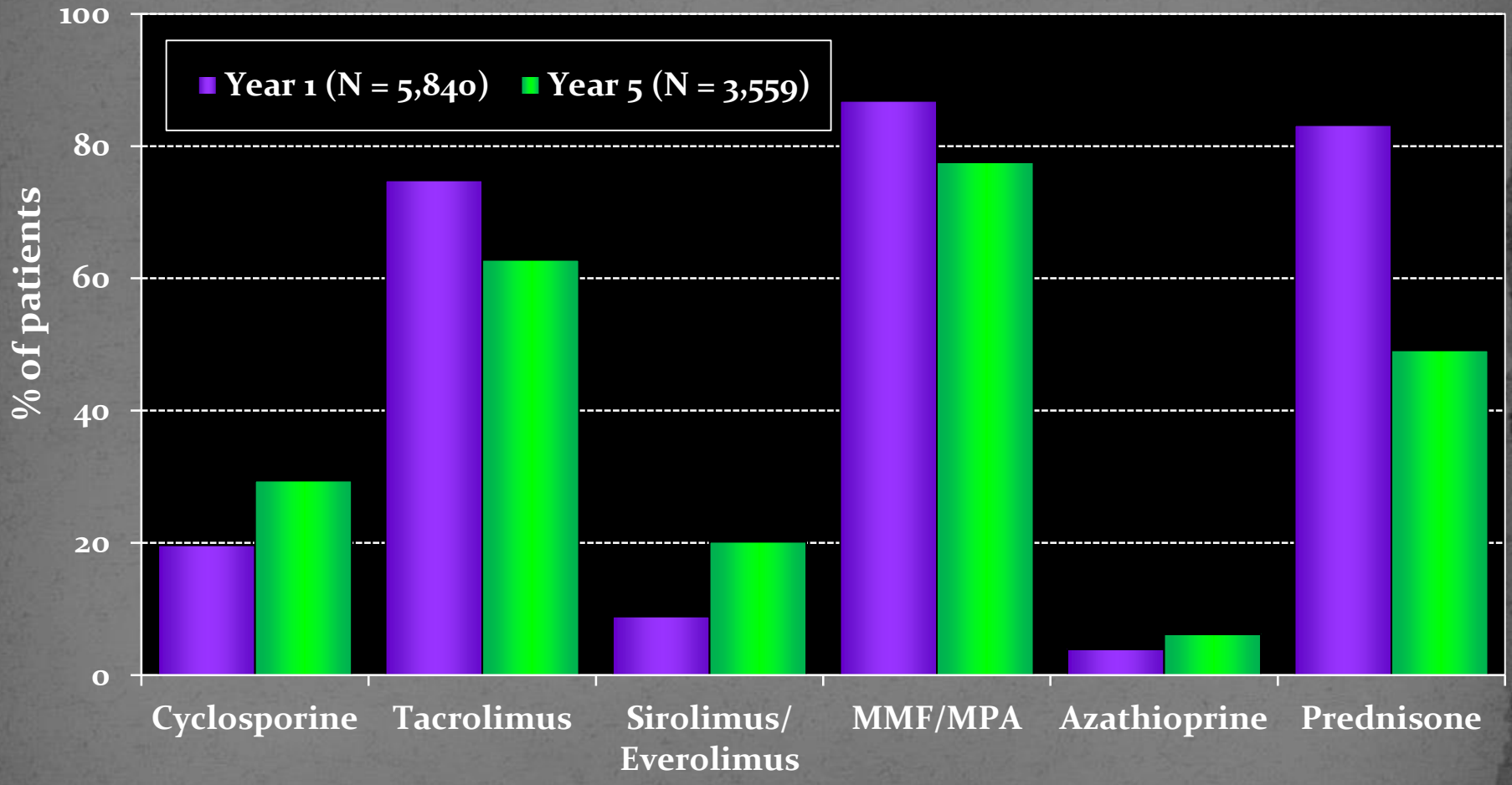
Maintenance Immunosuppression

at Time of Follow-up (January 2008 – June 2011)



NOTE: Different patients are analyzed in Year 1 and Year 5

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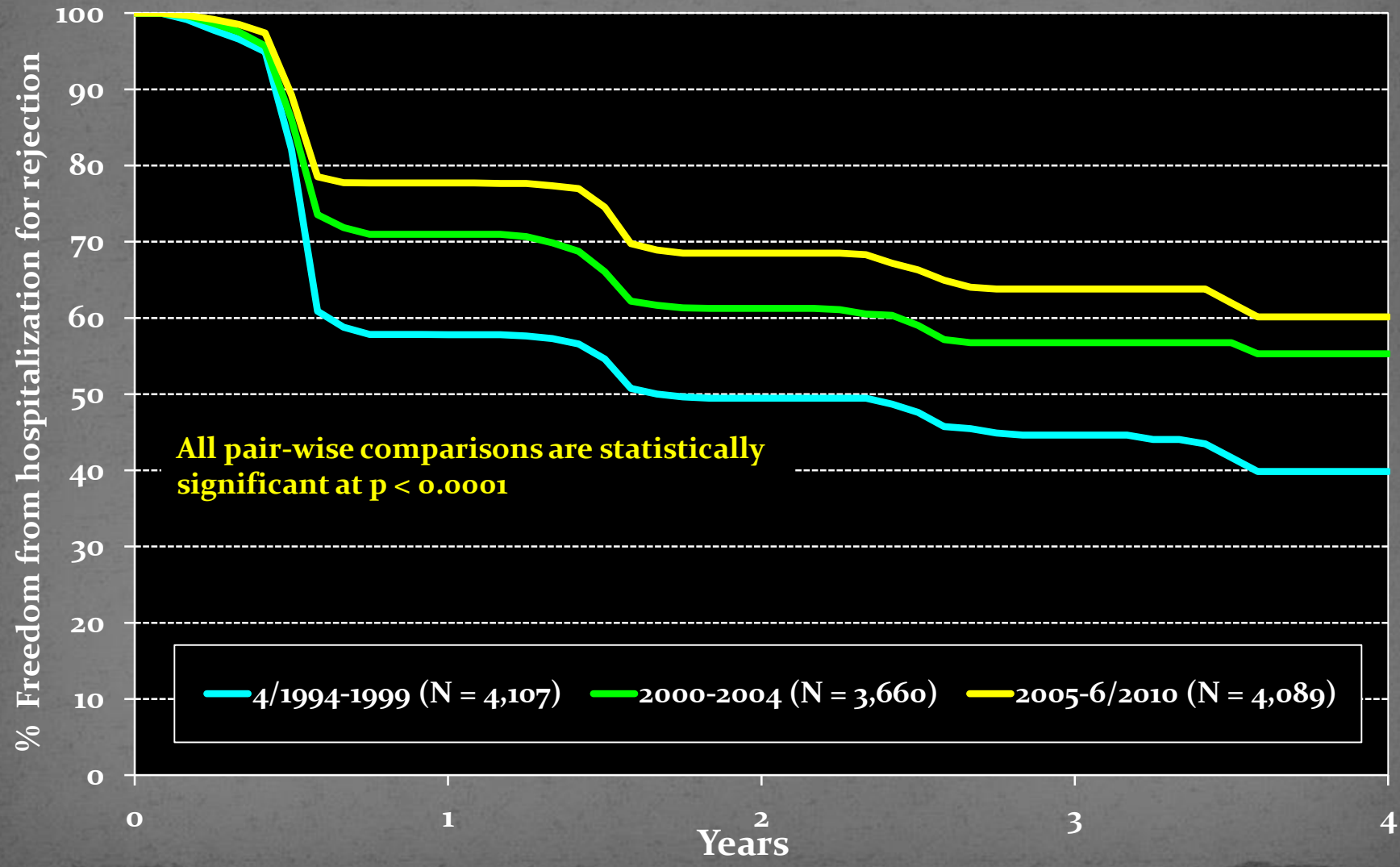
Freedom from Hospitalization for Rejection For Adult Heart Recipients



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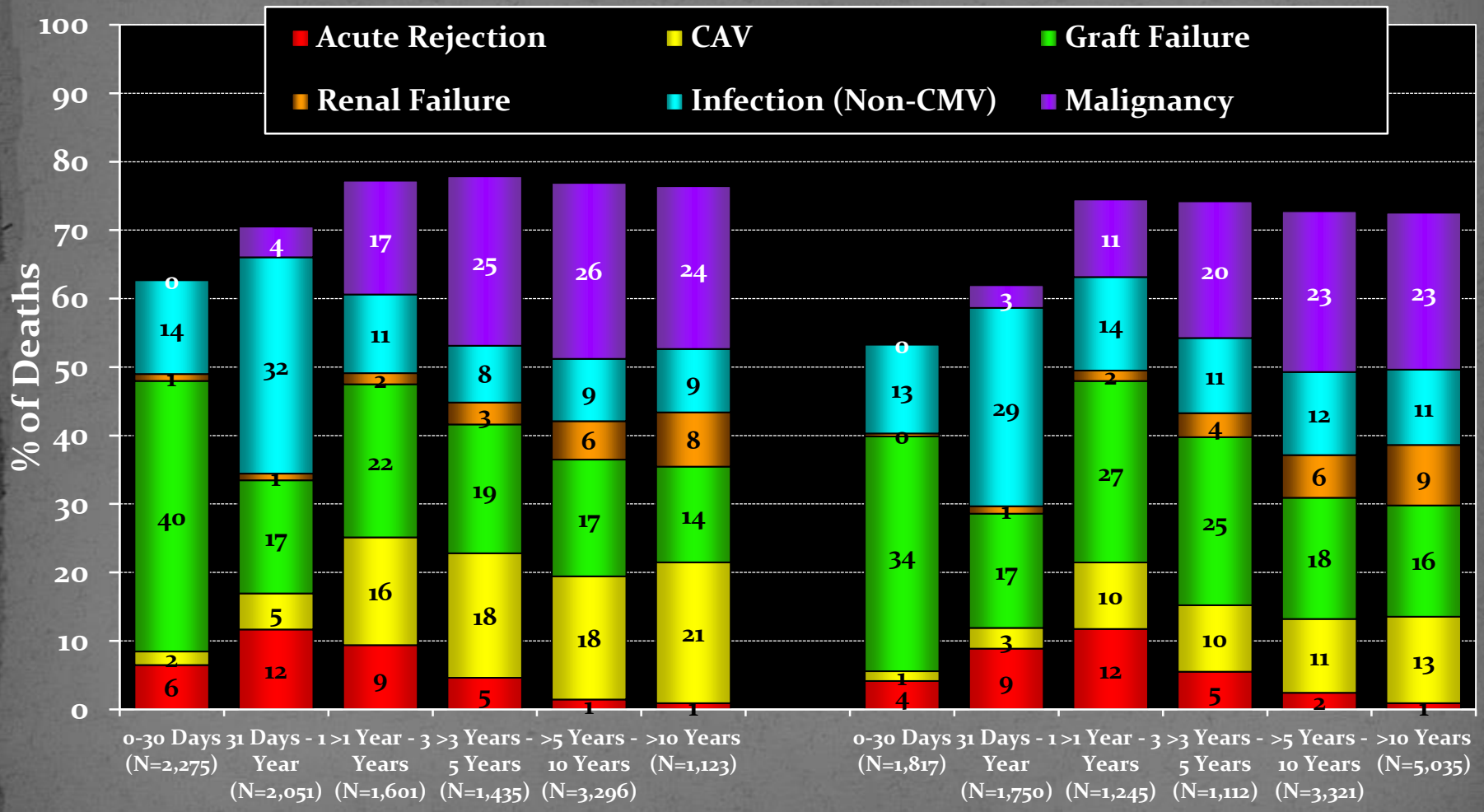
Adult Heart Recipients

Cause of Death



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Post-heart Transplant Morbidity for Adults
(Follow-ups: January 1995 – June 2011)

Outcome	Within 1 Year	Total N with known response	Within 5 Years	Total N with known response	Within 10 Years	Total N with known response
Hypertension*	72.8%	(N = 25,542)	92.6%	(N = 11,853)	–	
Renal Dysfunction	26.7%	(N = 27,478)	53.0%	(N = 13,481)	68.2%	(N = 4,339)
Abnormal Creatinine < 2.5 mg/dl	*18.3%*		*33.2%*		*37.5%*	
Creatinine > 2.5 mg/dl	*6.6%*		*15.8%*		*21.1%*	
Chronic Dialysis	*1.5%*		*2.9%*		*6.1%*	
Renal Transplant	*0.3%*		*1.2%*		*3.6%*	
Hyperlipidemia*	60.2%	(N = 26,810)	88.0%	(N = 13,191)	–	
Diabetes*	26.5%	(N = 27,474)	38.0%	(N = 13,306)	–	
Cardiac Allograft Vasculopathy	7.9%	(N = 24,790)	30.4%	(N = 9,819)	49.7%	(N = 2,482)

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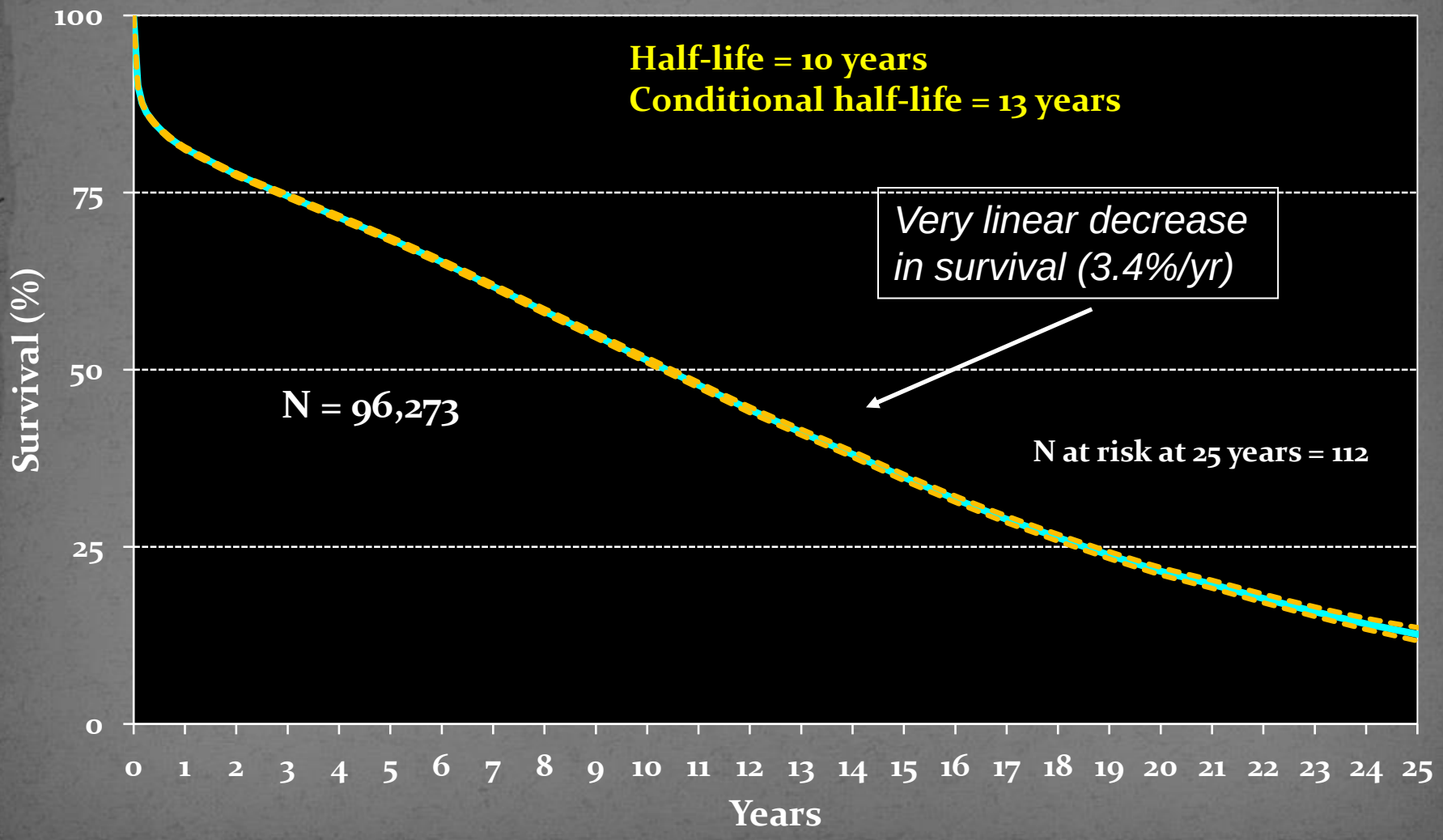
The Future

Improving outcomes

Donor Shortage

Heart Transplants
(Transplants: January 1982 - June 2010)



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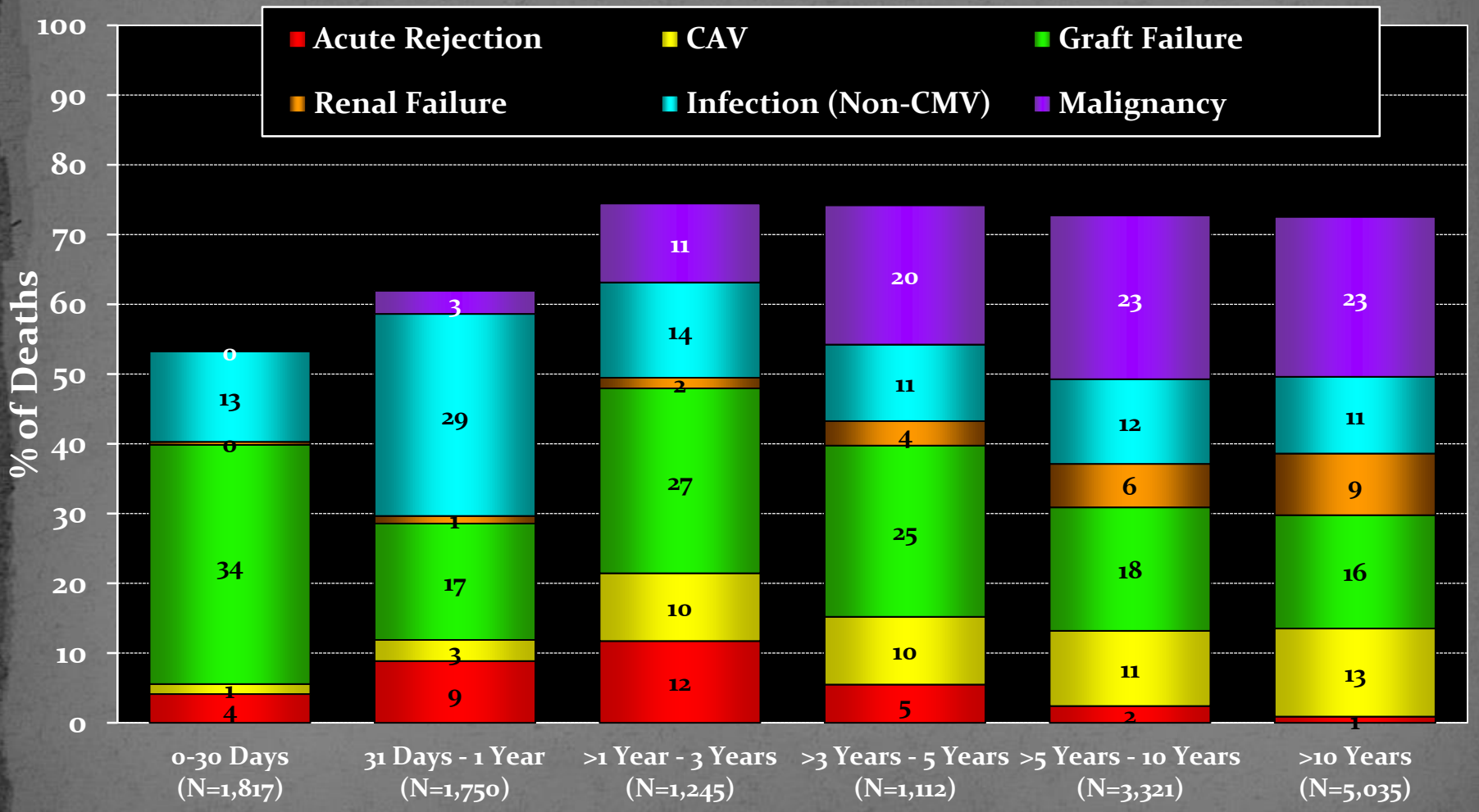
Adult Heart Recipients
Cause of Death (January 2002 - June 2011)



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Improving Outcomes

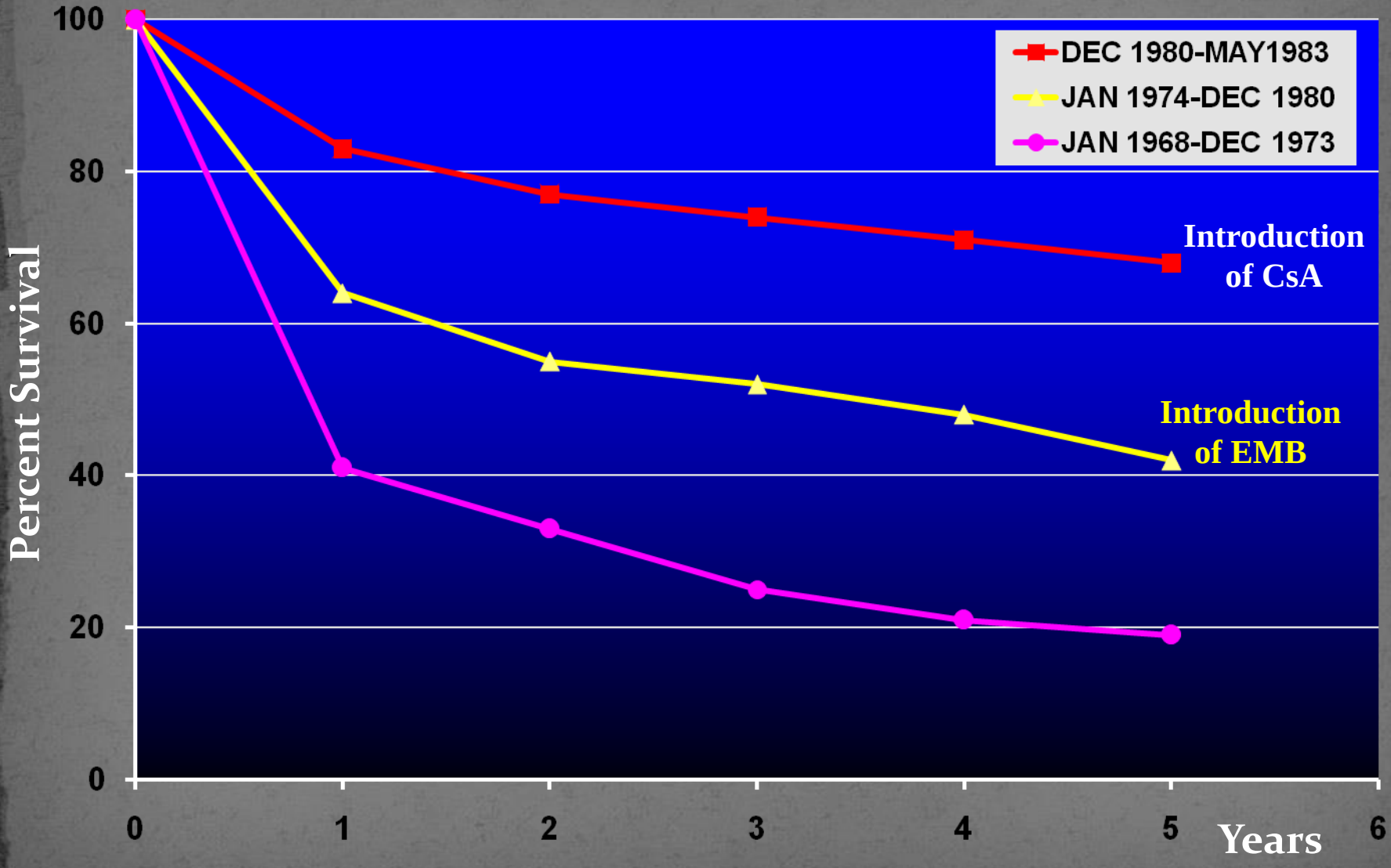
Hurdles to be overcome

- Acute rejection
- Cardiac Allograft Vasculopathy (chronic rejection)
- Malignancy

Acute Rejection

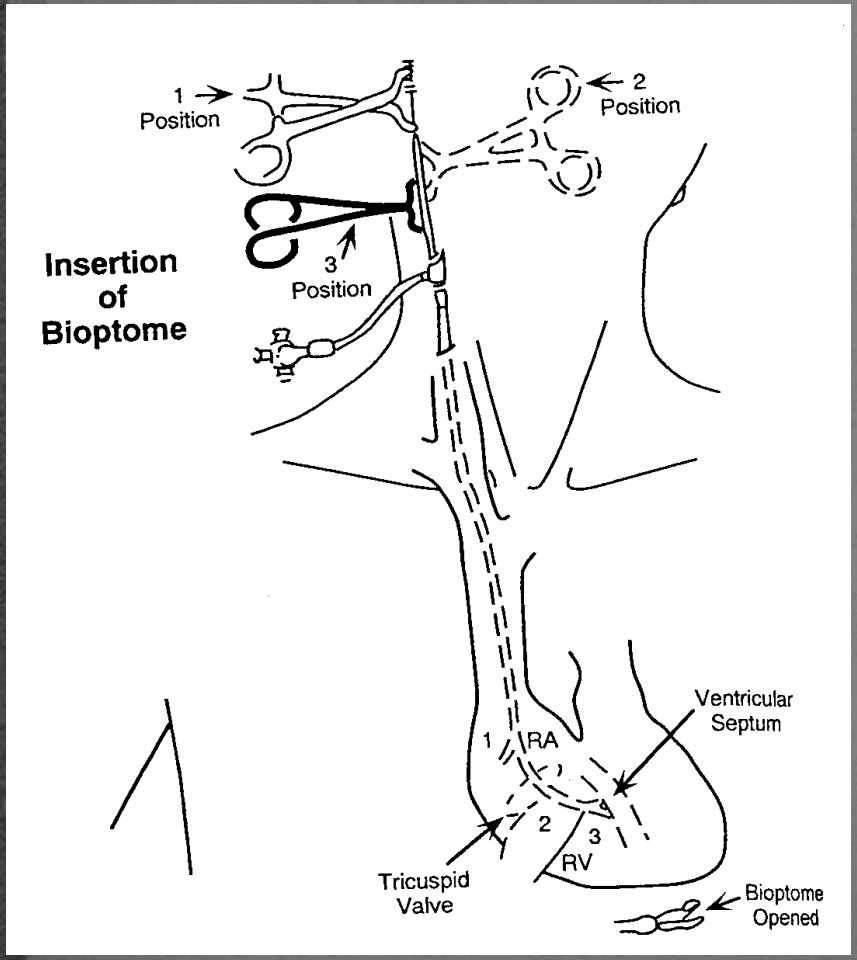
- Noninvasive diagnosis
- Effective immunosuppression

Breakthrough of Heart TPL



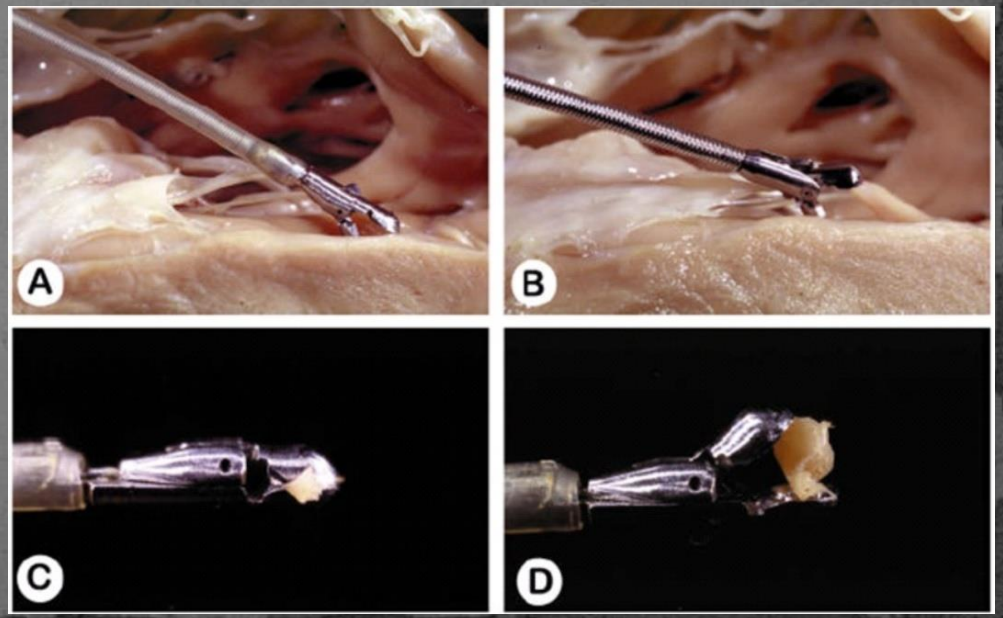
Oyer PE et al. Transplant Proc 15(suppl I):2546-2552, 1983

Endomyocardial Biopsy



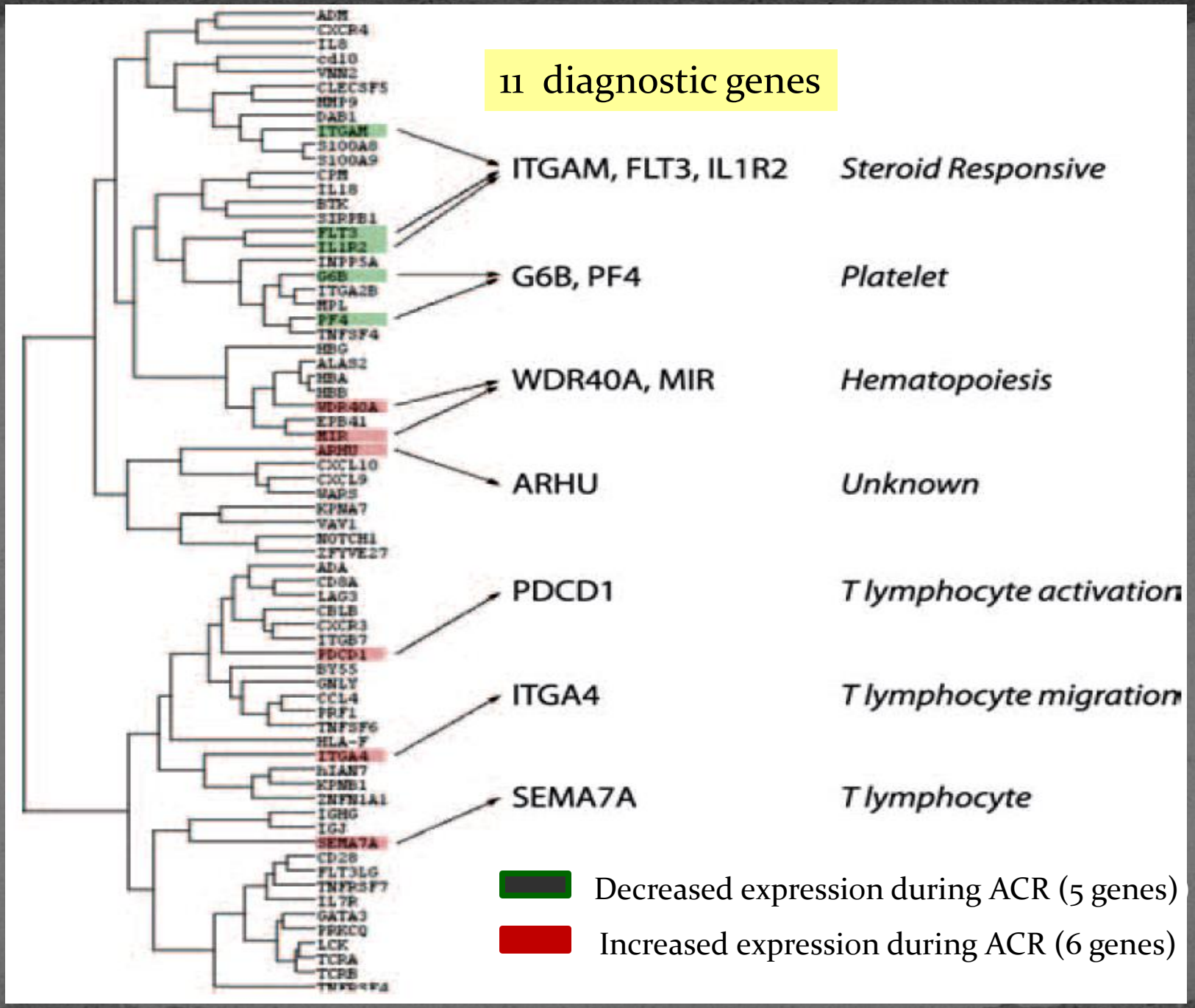
- Biopsy at blind site and small pieces
  - Adequate number !
- Invasive procedure
  - Biopsy related complication in 3.3%
  - TR is related to Repeated biopsy
    - moderate to severe in as many as one-third

Chan MC et al. J Heart Lung Transplant. 2001;20(7):709



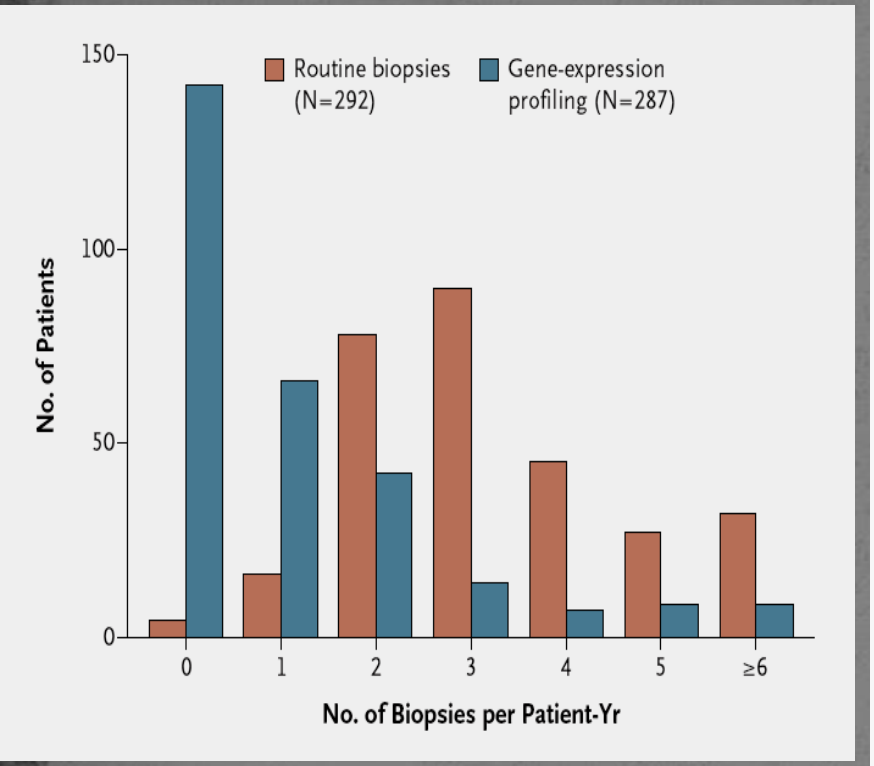
Noninvasive Diagnosis

- Molecular techniques
- Noninvasive imaging study
- Using biomarker

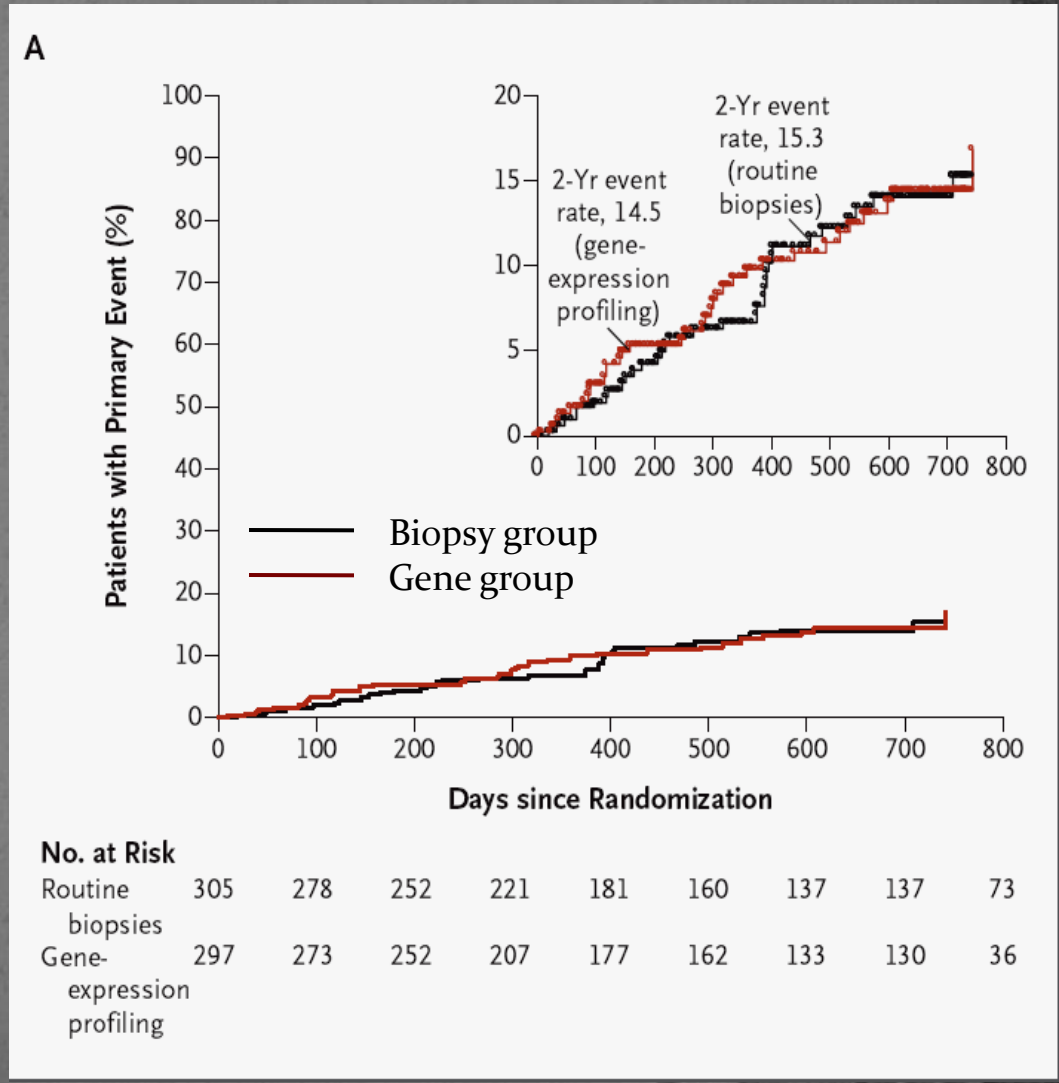


Deng MC, et al. Am J Transplant 2006;6:150-60

IMAGE (Invasive Monitoring Attenuation through Gene Expression) trial



409 biopsies in gene group
1249 biopsies in biopsy group

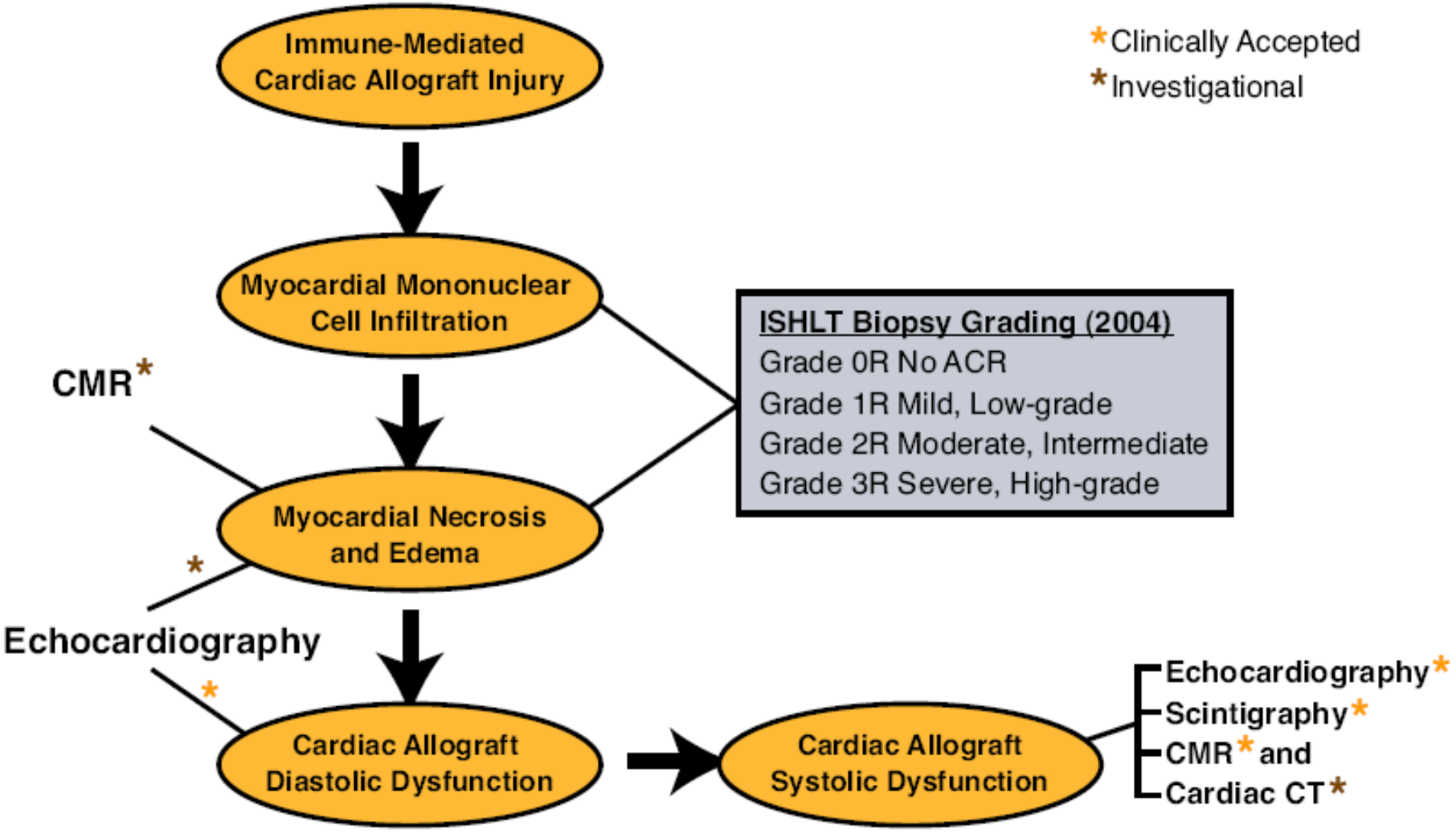


No. at Risk

Routine biopsies	305	278	252	221	181	160	137	137	73
Gene-expression profiling	297	273	252	207	177	162	133	130	36

Pham MX, et al. NEJM 2010;362:1890-900.

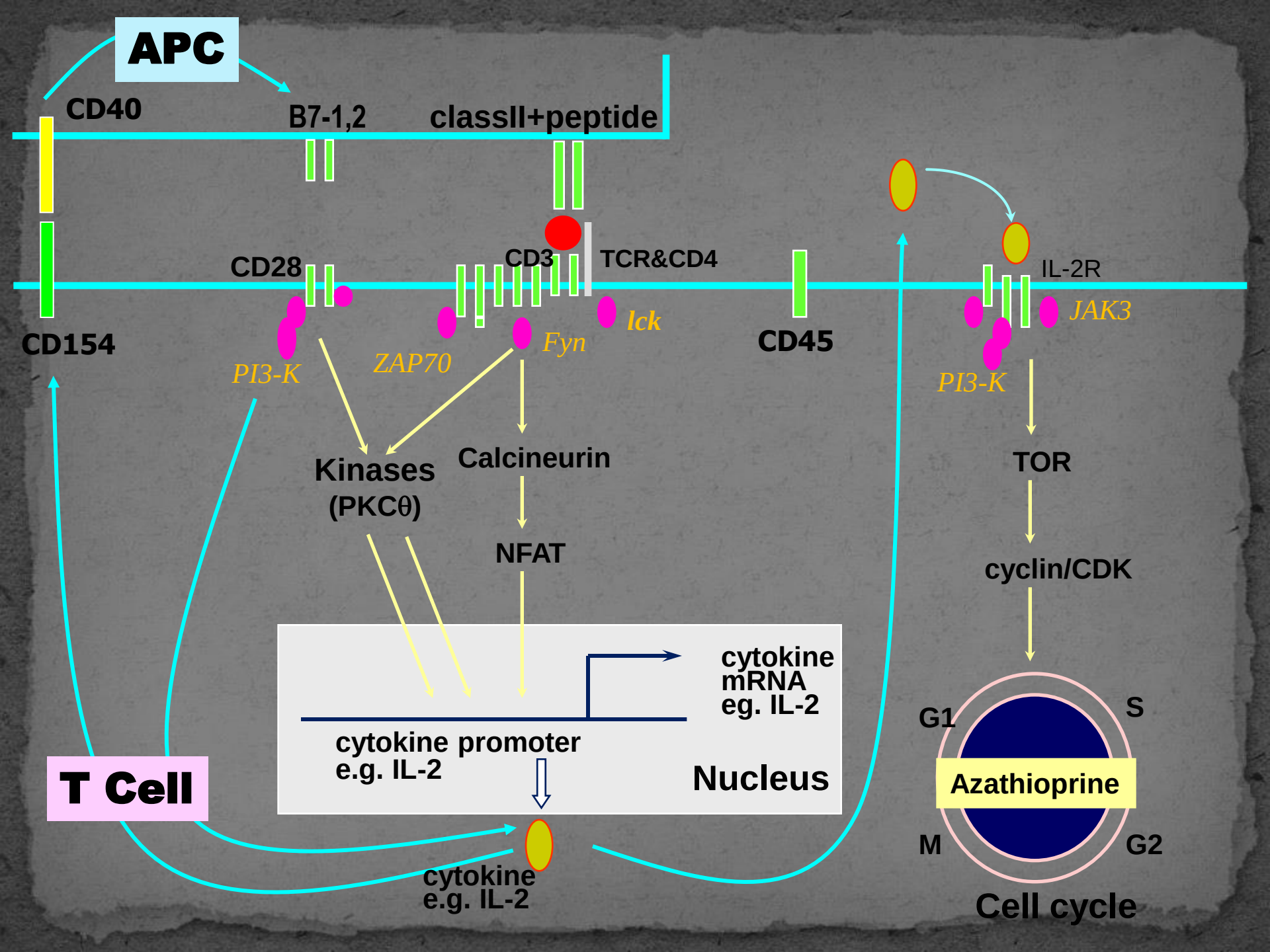
Noninvasive Imaging Techniques to Detect Acute Cellular Rejection (ACR)

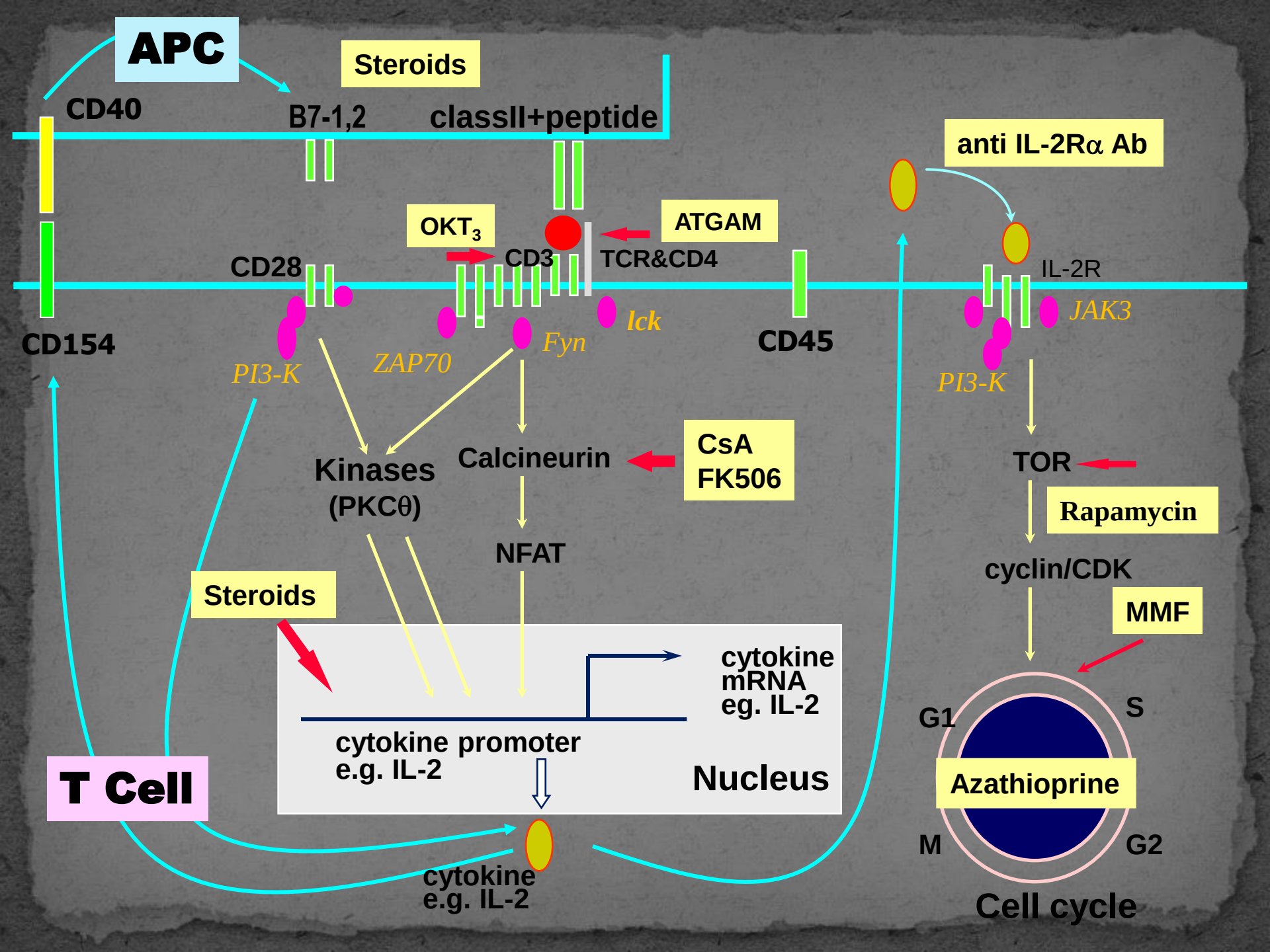


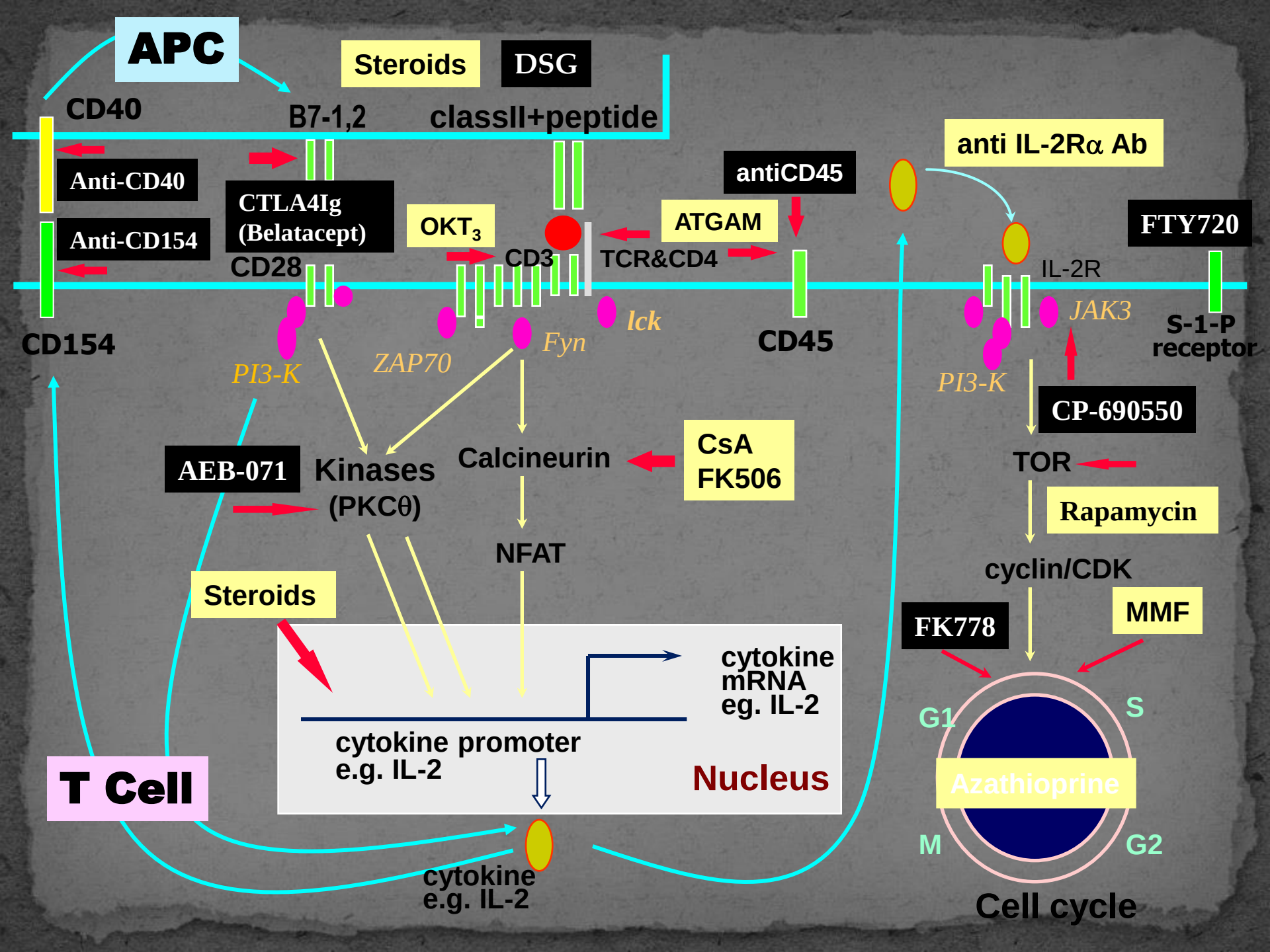
Estep JD, et al. JACC Cardiovasc Imaging 2009;2:1126-40.

Future Immunosuppression

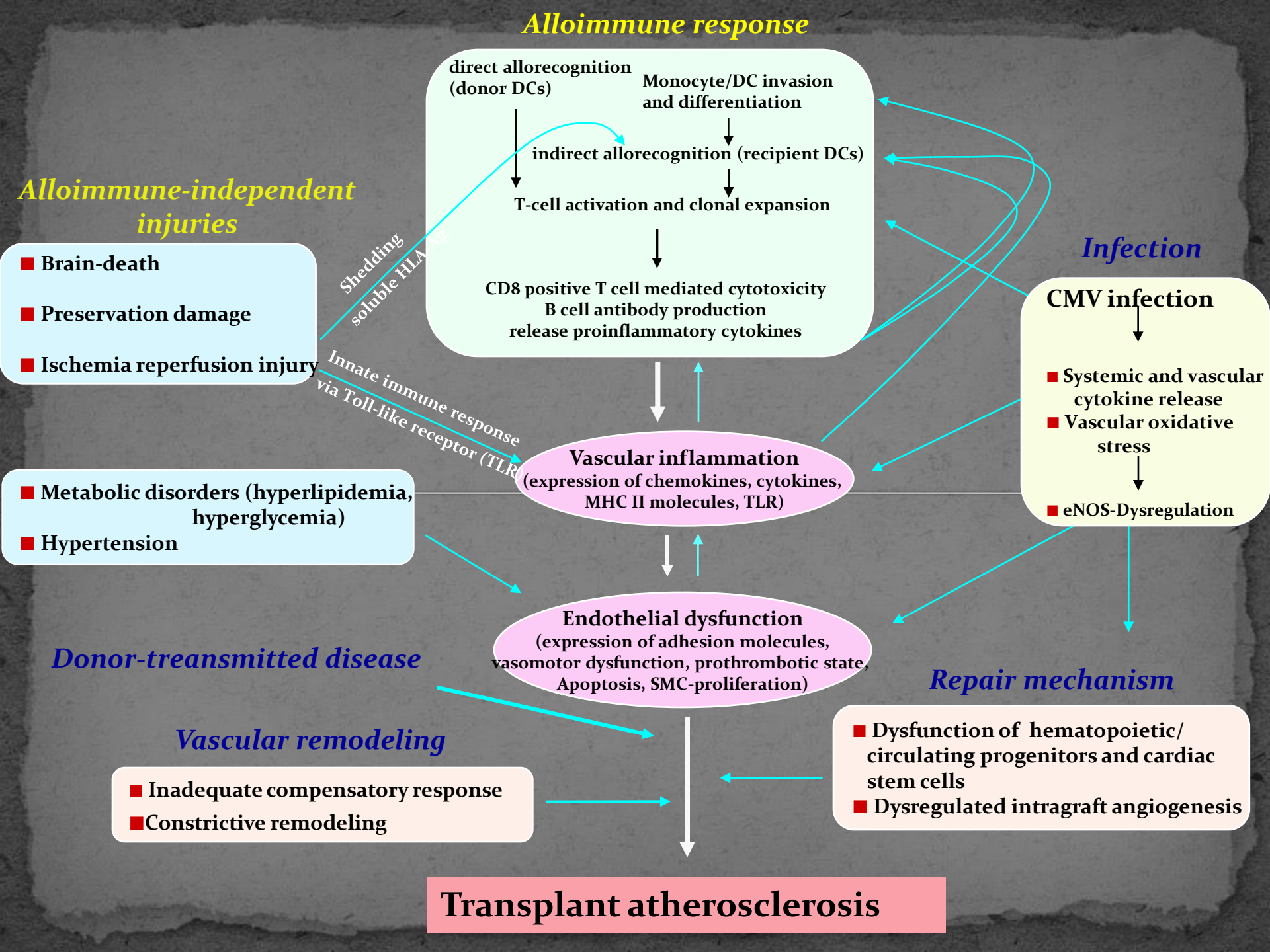
- More specific to graft
  - Less generalized immunosuppression
  - Less infection
- Less systemic side effects
  - Less CV and metabolic side effects
- Favorable nonimmune effects
  - Less cardiac allograft vasculopathy
  - Less malignancy


APC
CD40
B7-1,2
classII+peptide
CD28
CD3
TCR&CD4
IL-2R
CD154
lck
CD45
JAK3
PI3-K
ZAP70
Fyn
PI3-K
Kinases
(PKCθ)
Calcineurin
TOR
NFAT
cyclin/CDK
cytokine
mRNA
eg. IL-2
cytokine promoter
e.g. IL-2
Nucleus
T Cell
G1
S
Azathioprine
M
G2
cytokine
e.g. IL-2
Cell cycle

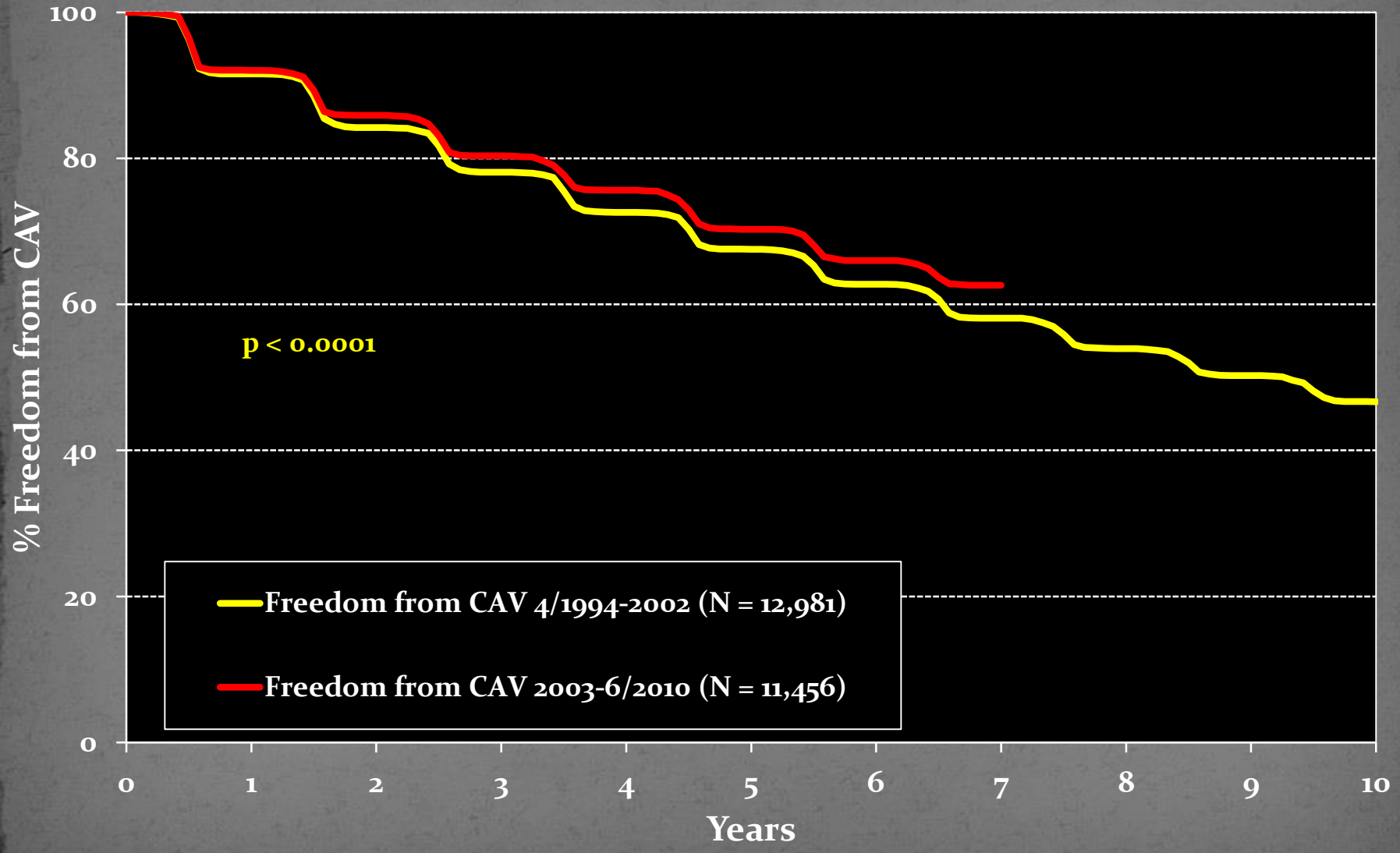

APC
Steroids
CD40
B7-1,2
classII+peptide
anti IL-2Rα Ab
OKT3
ATGAM
CD28
CD3
TCR&CD4
IL-2R
CD154
lck
CD45
JAK3
PI3-K
ZAP70
Fyn
PI3-K
Kinases
(PKCθ)
Calcineurin
CsA
FK506
TOR
Rapamycin
NFAT
cyclin/CDK
Steroids
MMF
cytokine
mRNA
eg. IL-2
cytokine promoter
e.g. IL-2
Nucleus
T Cell
G1
S
Azathioprine
M
G2
cytokine
e.g. IL-2
Cell cycle


APC
Steroids
DSG
CD40
B7-1,2
classII+peptide
anti IL-2Rα Ab
Anti-CD40
CTLA4Ig
(Belatacept)
antiCD45
FTY720
Anti-CD154
OKT3
ATGAM
CD28
CD3
TCR&CD4
IL-2R
CD154
lck
CD45
JAK3
S-1-P
receptor
PI3-K
ZAP70
Fyn
PI3-K
CP-690550
AEB-071
Kinases
(PKCθ)
Calcineurin
CsA
FK506
TOR
Rapamycin
NFAT
cyclin/CDK
Steroids
FK778
MMF
cytokine
mRNA
eg. IL-2
cytokine promoter
e.g. IL-2
Nucleus
T Cell
G1
S
Azathioprine
M
G2
cytokine
e.g. IL-2
Cell cycle

CAV and Chronic Rejection


Alloimmune response
direct allorecognition (donor DCs)
Monocyte/DC invasion and differentiation
indirect allorecognition (recipient DCs)
T-cell activation and clonal expansion
CD8 positive T cell mediated cytotoxicity
B cell antibody production
release proinflammatory cytokines
Alloimmune-independent injuries
Brain-death
Preservation damage
Ischemia reperfusion injury
Shedding soluble HLA Ag
Innate immune response via Toll-like receptor (TLR)
Infection
CMV infection
Systemic and vascular cytokine release
Vascular oxidative stress
eNOS-Dysregulation
Metabolic disorders (hyperlipidemia, hyperglycemia)
Hypertension
Vascular inflammation
(expression of chemokines, cytokines, MHC II molecules, TLR)
Endothelial dysfunction
(expression of adhesion molecules, vasomotor dysfunction, prothrombotic state, Apoptosis, SMC-proliferation)
Donor-treansmitted disease
Repair mechanism
Dysfunction of hematopoietic/ circulating progenitors and cardiac stem cells
Dysregulated intragraft angiogenesis
Vascular remodeling
Inadequate compensatory response
Constrictive remodeling
Transplant atherosclerosis

Freedom from Cardiac Allograft Vasculopathy For Adult Heart Recipients



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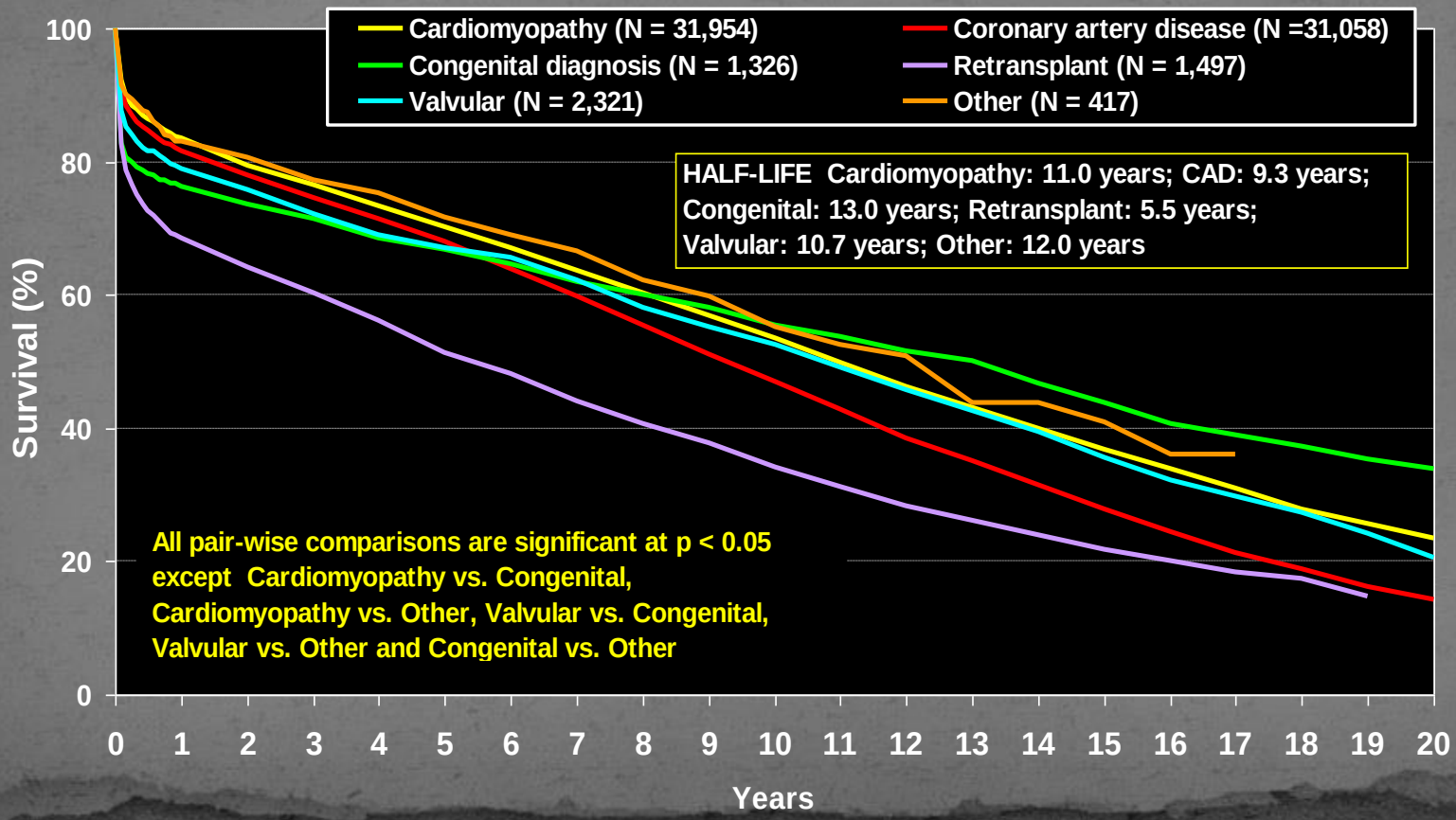
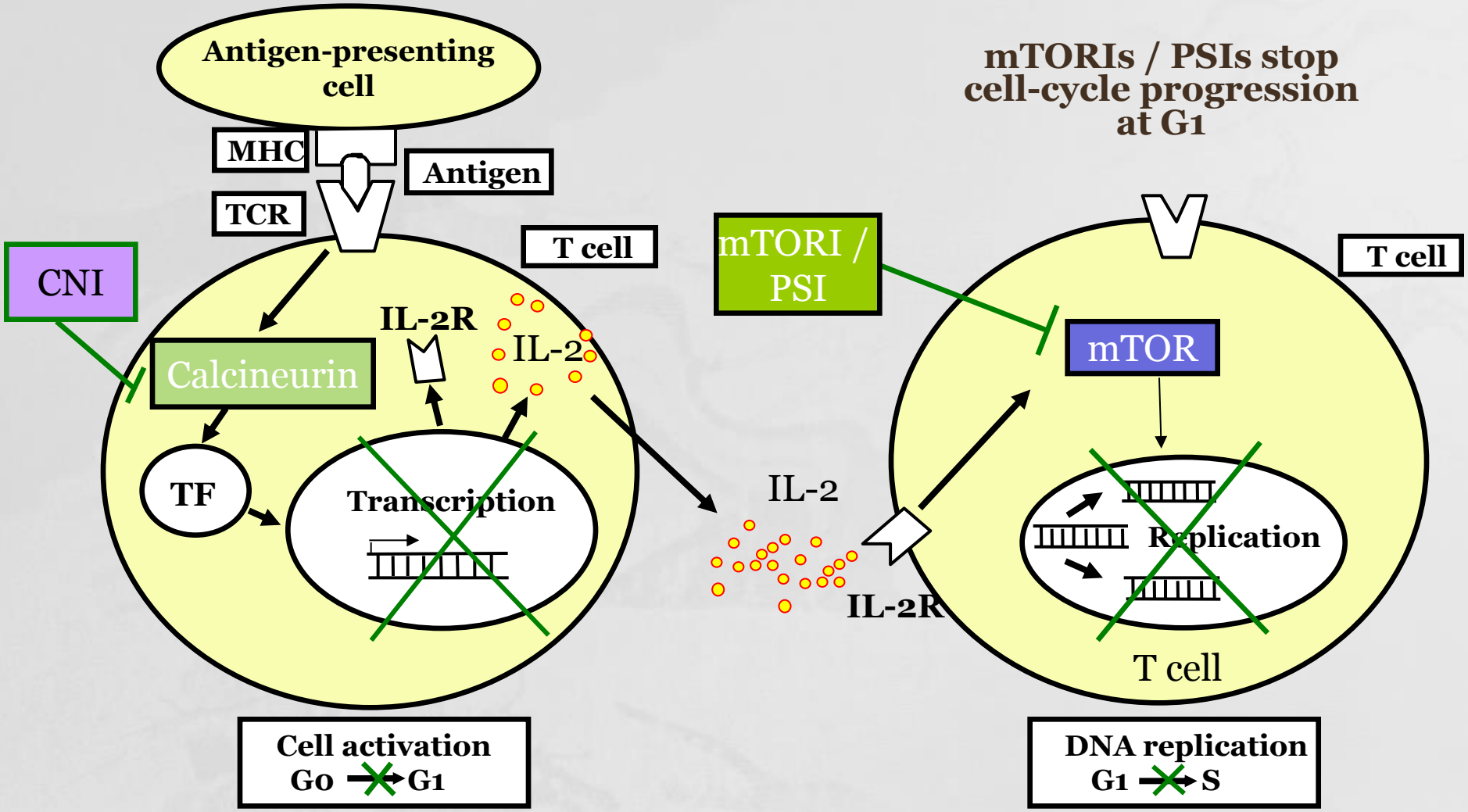
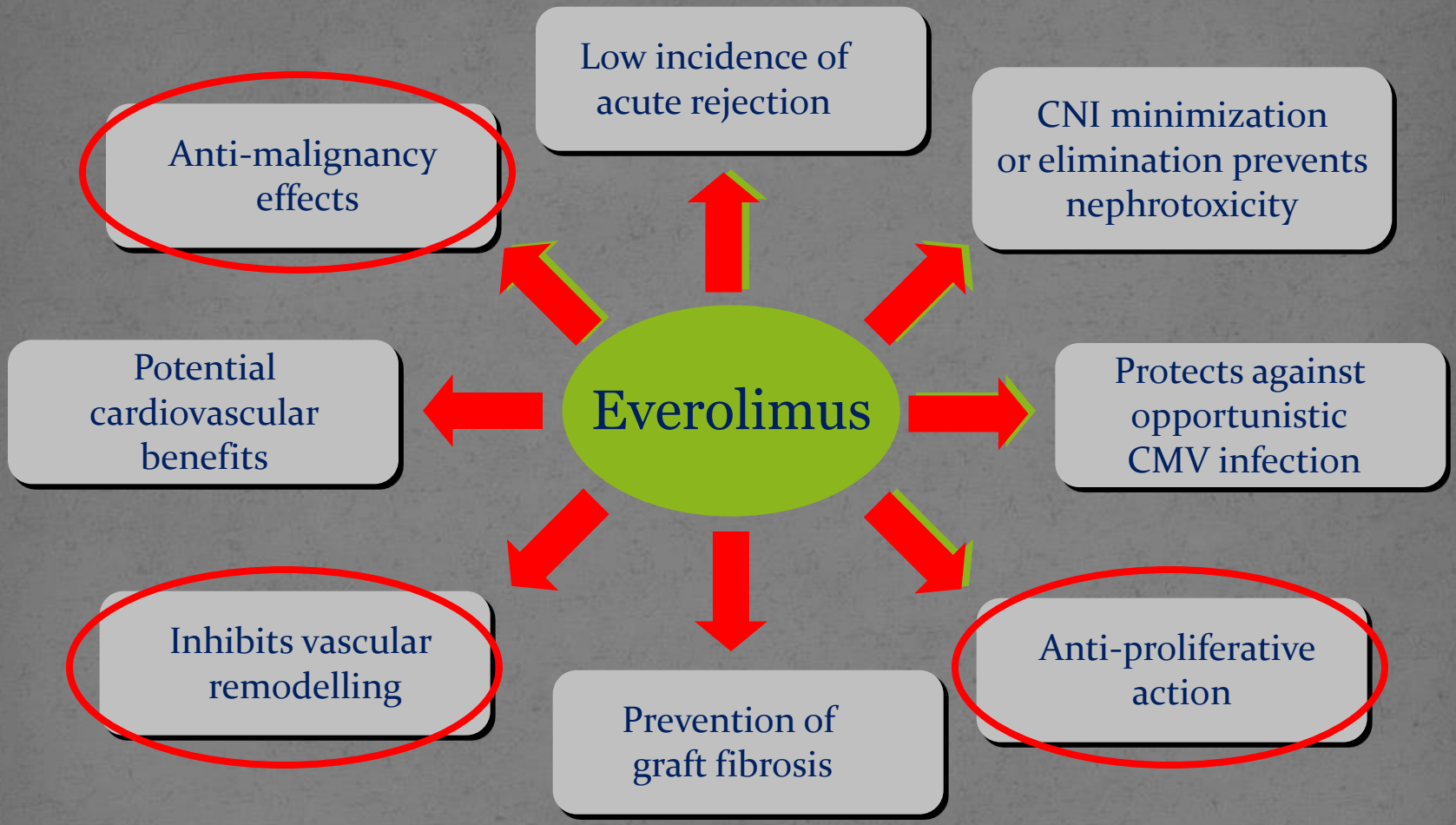
Prevention and Treatment of CAV

- Retransplantation
  - The only definitive treatment for CAV
  - Lower survival than the primary transplantation





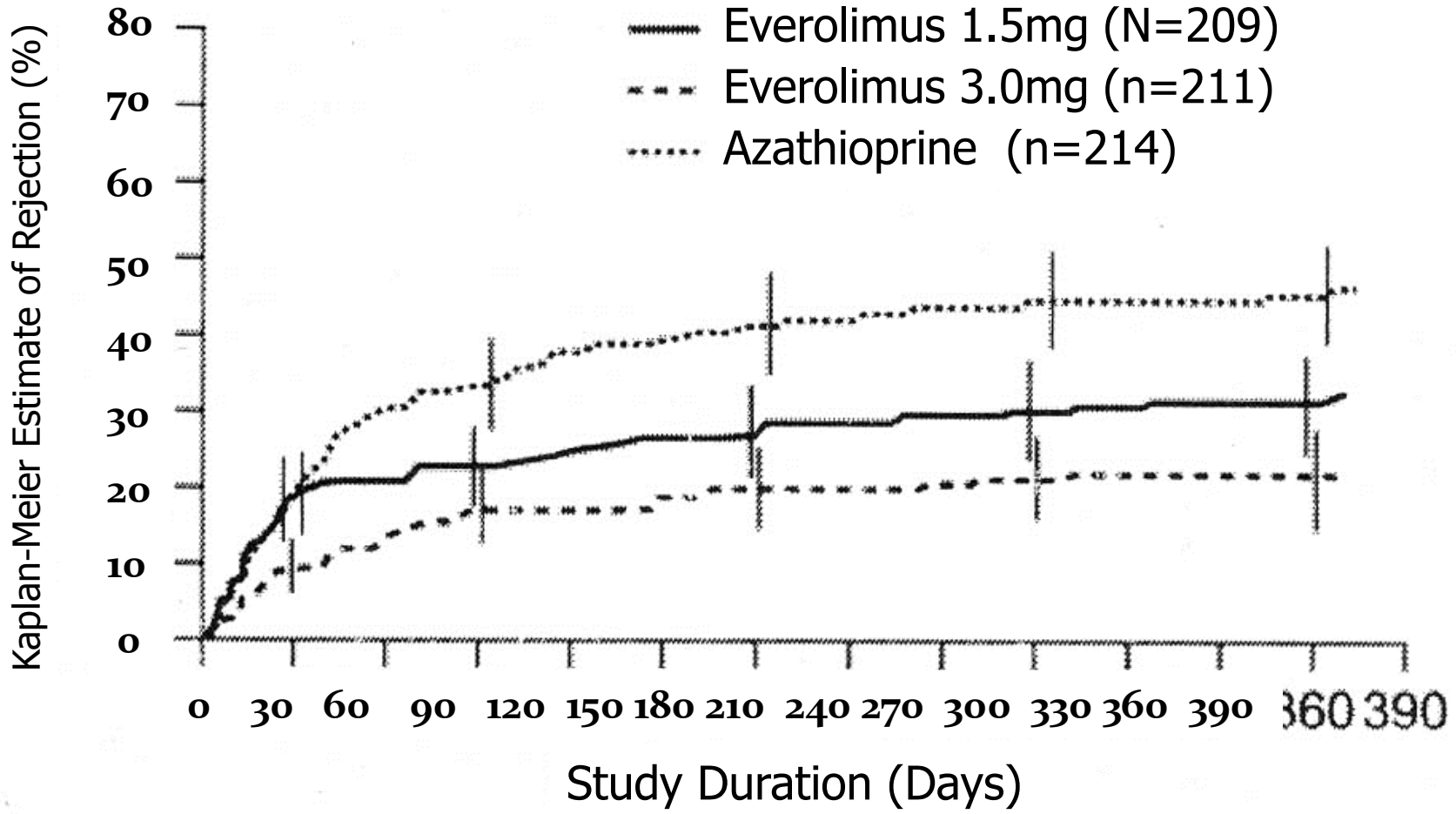
mTORI, mammalian target of rapamycin inhibitor; PSI, proliferation signal inhibitor; MHC, major histocompatibility complex; TCR, T cell antigen receptor; CNI, calcineurin inhibitor; IL-2R, interleukin-2 receptor; TF, transcription factor; mTOR, mammalian target of rapamycin



CNI, calcineurin inhibitor; CMV, cytomegalovirus

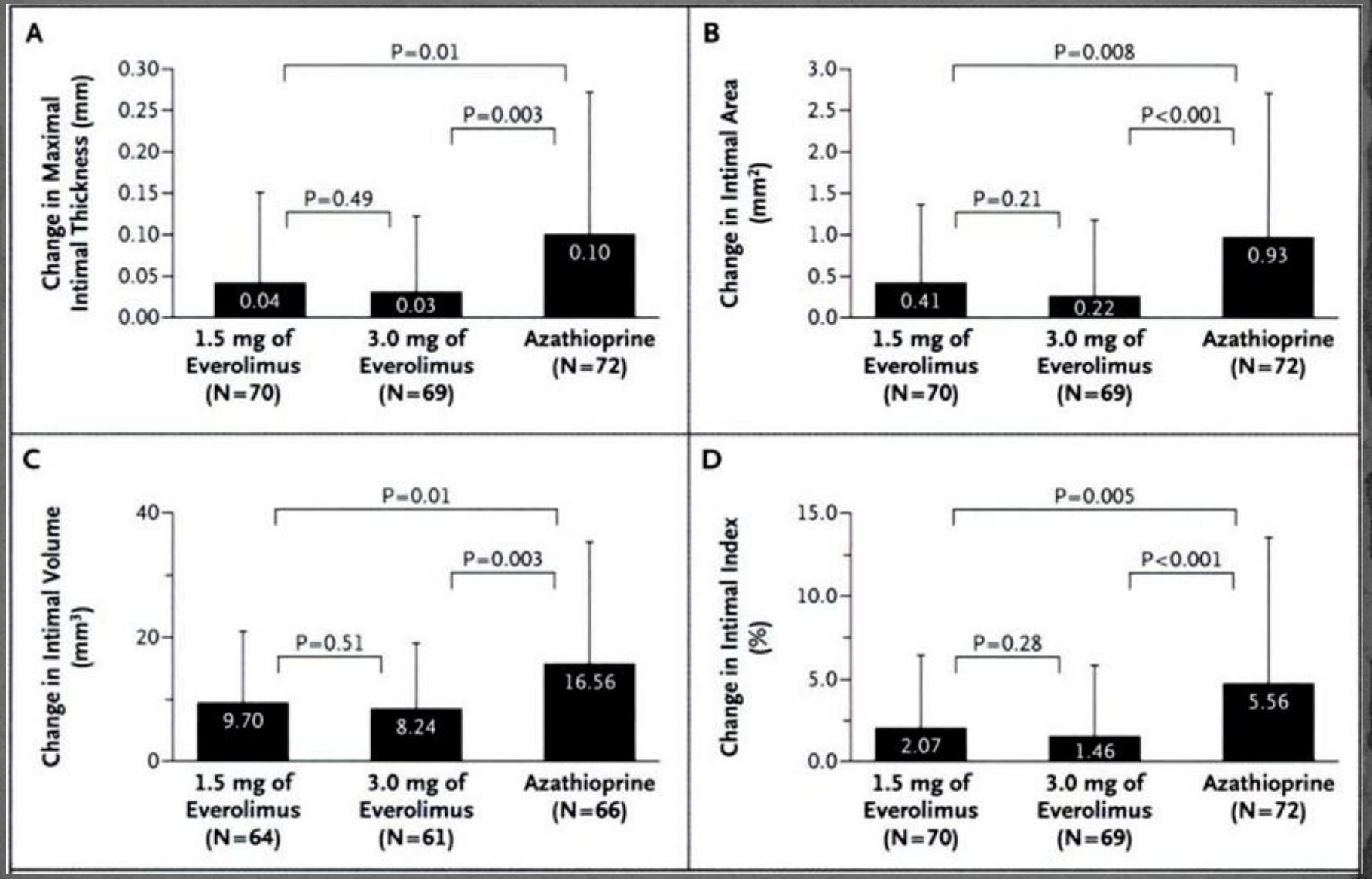
Everolimus vs Azathioprine

In Heart transplantation



N Engl J Med. 2003;349:847

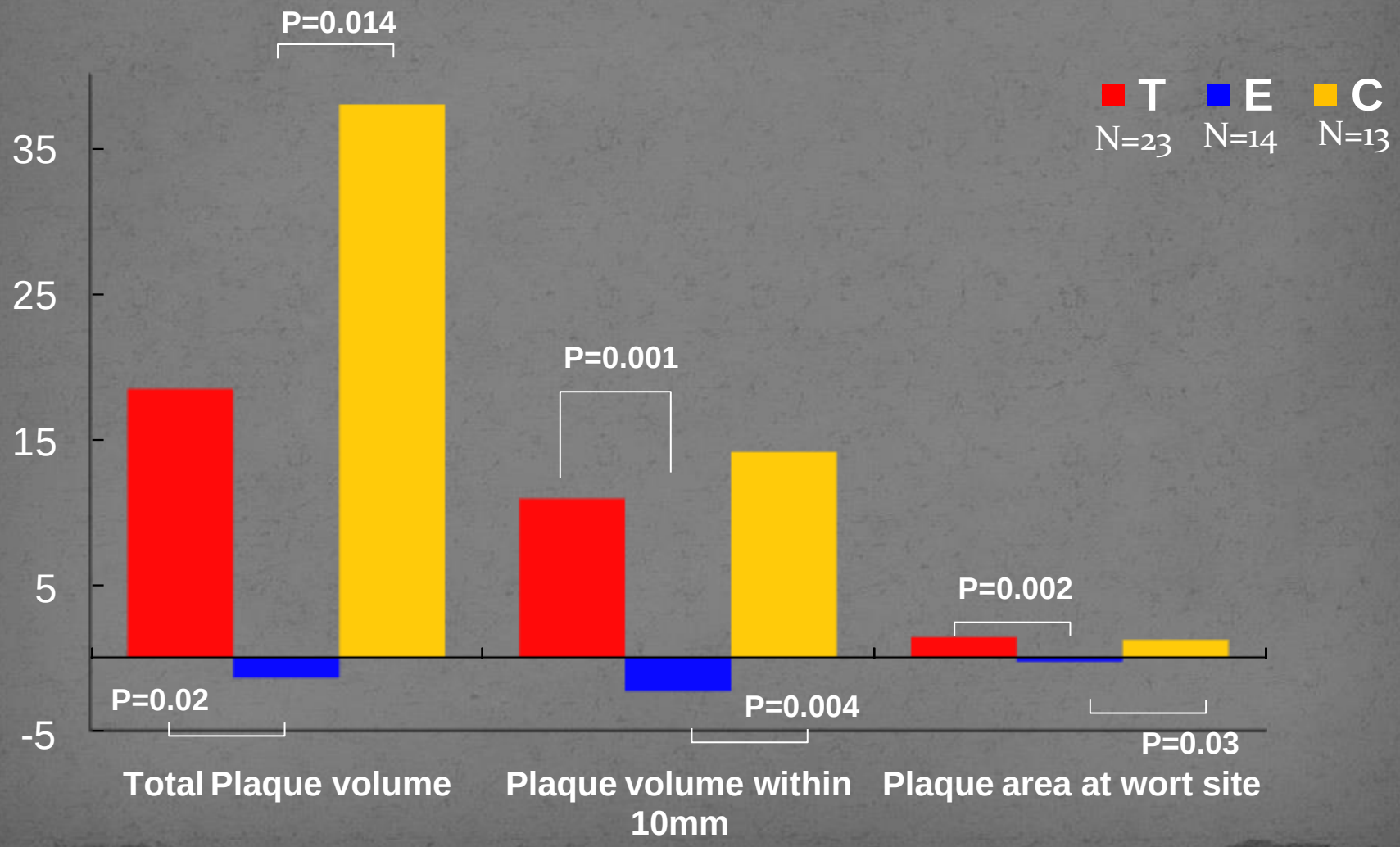
Everolimus vs Azathioprine



N Engl J Med. 2003;349:847

Results- IVUS data

Changes of plaques during the 1st year



Prevention and Treatment of CAV

Emerging new strategies

- Inhibition of growth factors, cytokines, and circulating antibodies
- Cell therapy
  - Hematopoietic and vascular progenitors for angiogenesis
- Tolerance induction

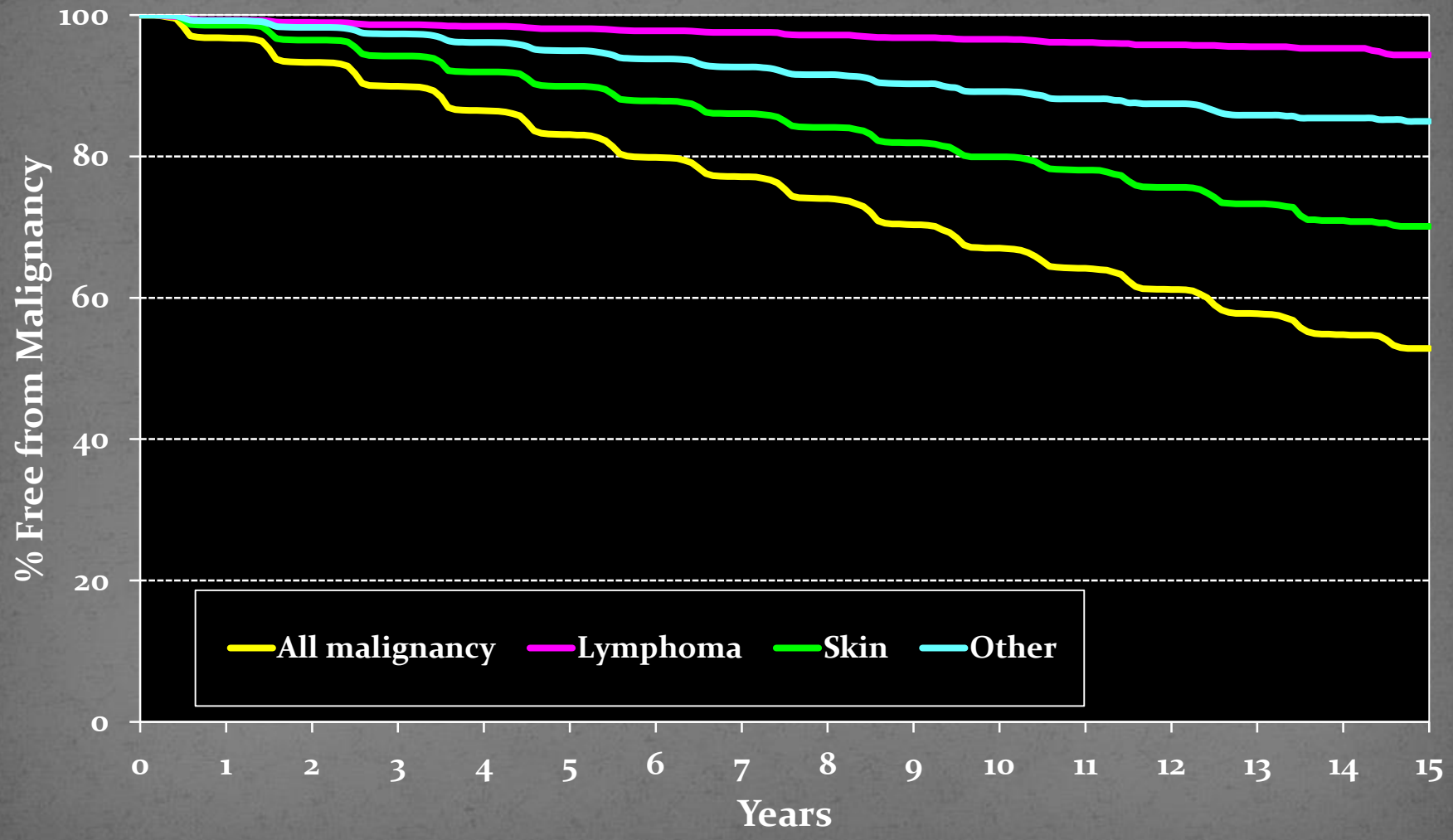
Malignancies

Malignancies after Heart TPL

- Etiology
  - Suppressed tumor surveillance system
    - ➔Cytolytic drugs ; increased PTLD
  - Smoking
  - Virus ; EB virus – PTLD, HHV8 – Kaposis' sarcoma
- Types
  - High incidence
    - ➔Skin cancer, PTLD(lymphoma), anal cancer
  - Other cancers common to usual person
    - ➔Breast cancer, lung cancer, prostate cancer etc
    - ➔nearly same incidence

Freedom from Malignancy

For Adult Heart Recipients (April 1994 – June 2011)



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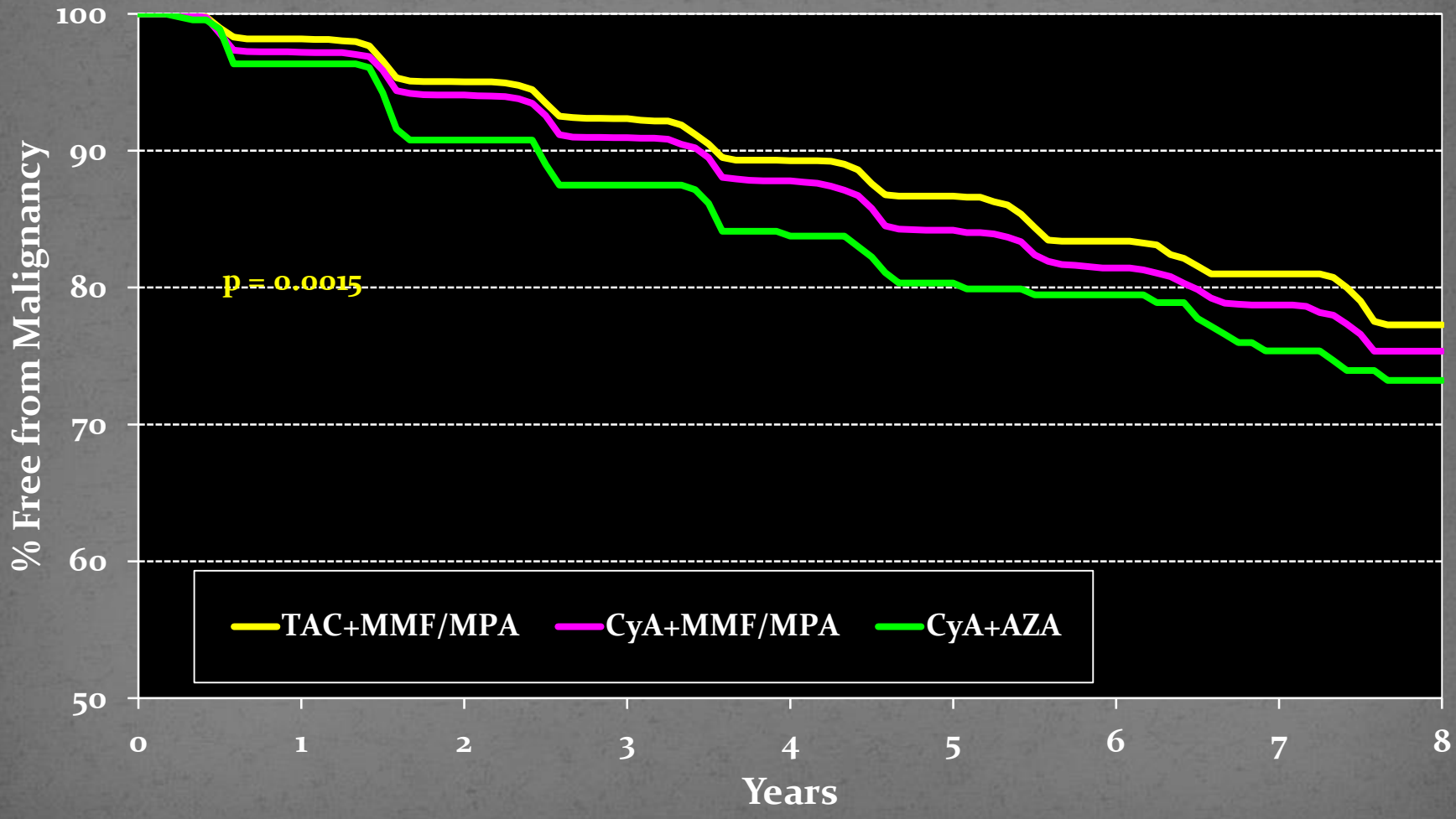
Freedom from Malignancy

by Maintenance Immunosuppression (January 2001 - June 2010)



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Improving Outcomes

- Acute rejection
- Cardiac Allograft Vasculopathy (chronic rejection)
- Malignancy

Induction of Immune Tolerance

Immune tolerance

Central tolerance

- Combined bone marrow transplantation
- Thymic injection of donor cells

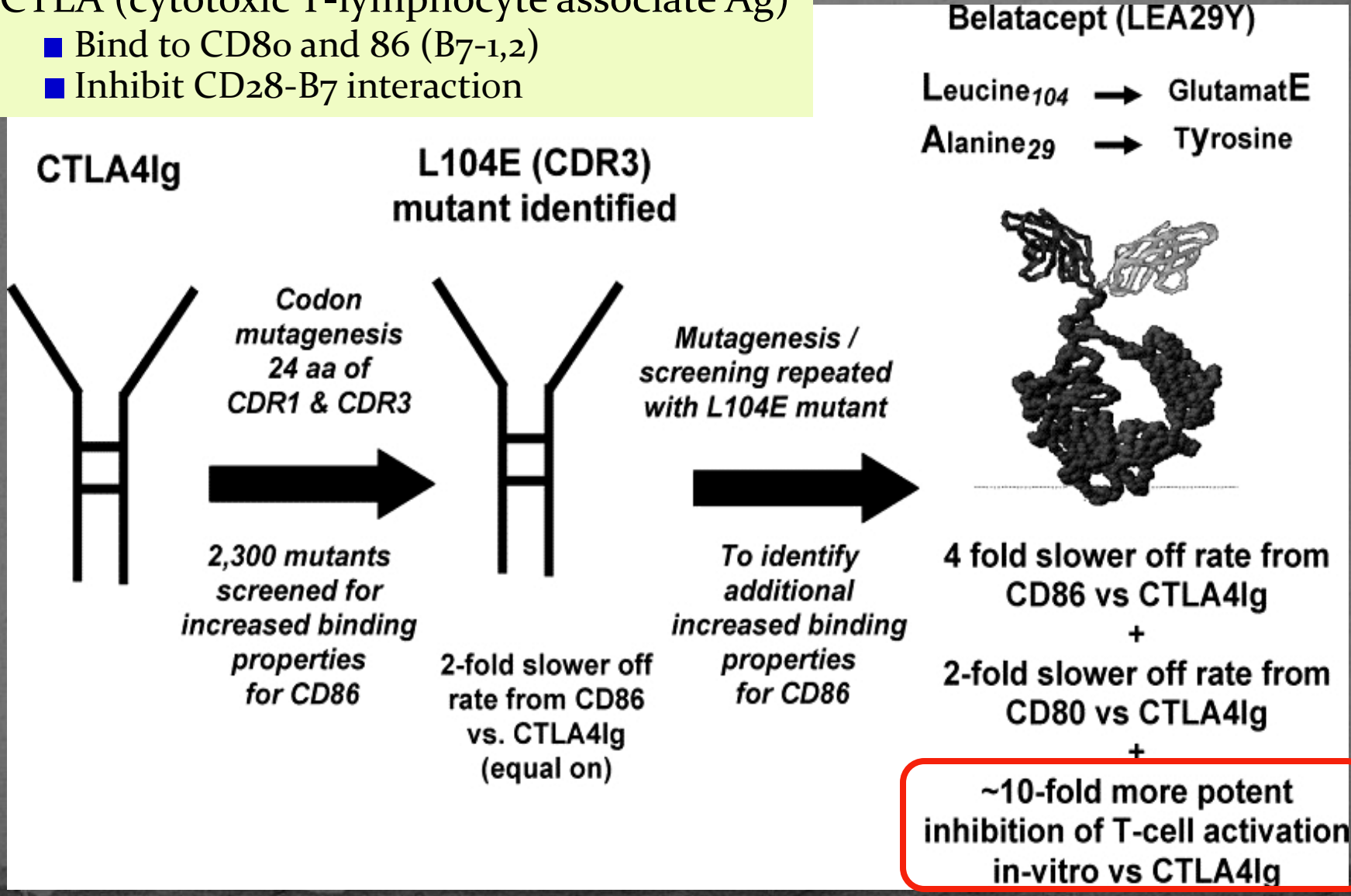
Peripheral tolerance

- Anergy
- AICD (activation-induced cell death)

- Modulation of T-cell costimulation pathways
- Induction of regulatory T-cell ($CD4^+CD25^+$) and anergic $CD4^+$ T cell
- Manipulation of dendritic cell
  - ➔ Silencing NF-kB protein RelB
  - ➔ Induction of alloAg presenting plasmacytoid DCs

Development of Belatacept

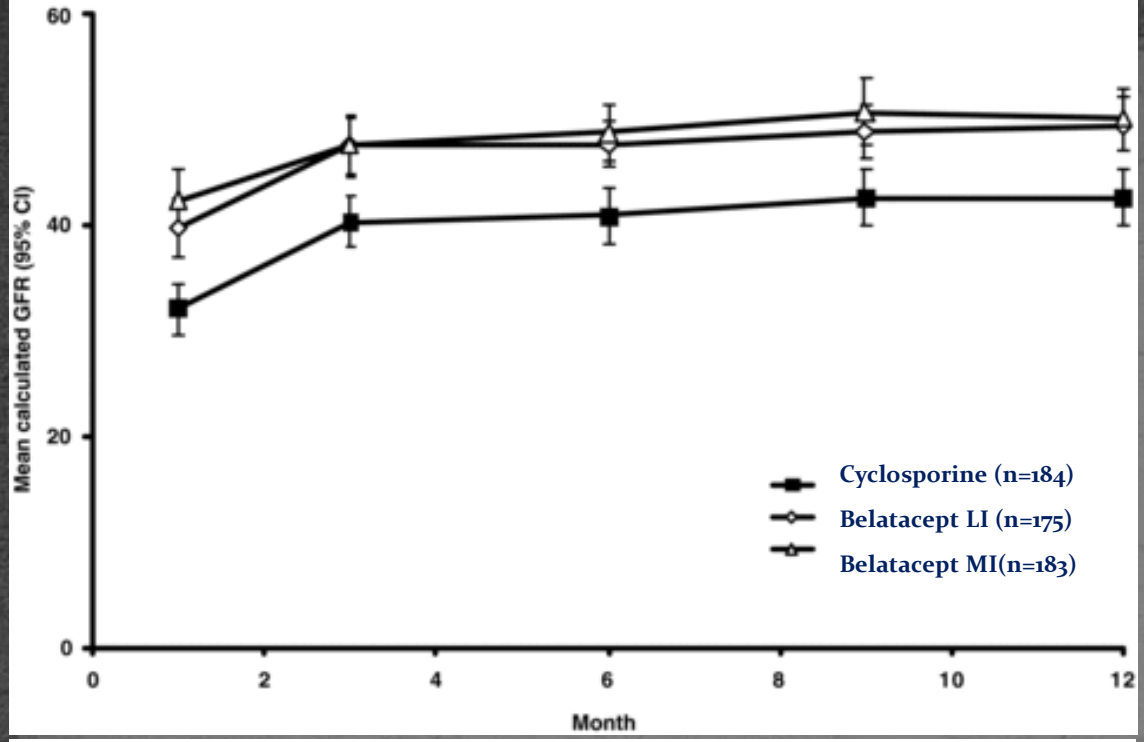
- CTLA (cytotoxic T-lymphocyte associate Ag)
  - Bind to CD80 and 86 (B7-1,2)
  - Inhibit CD28-B7 interaction

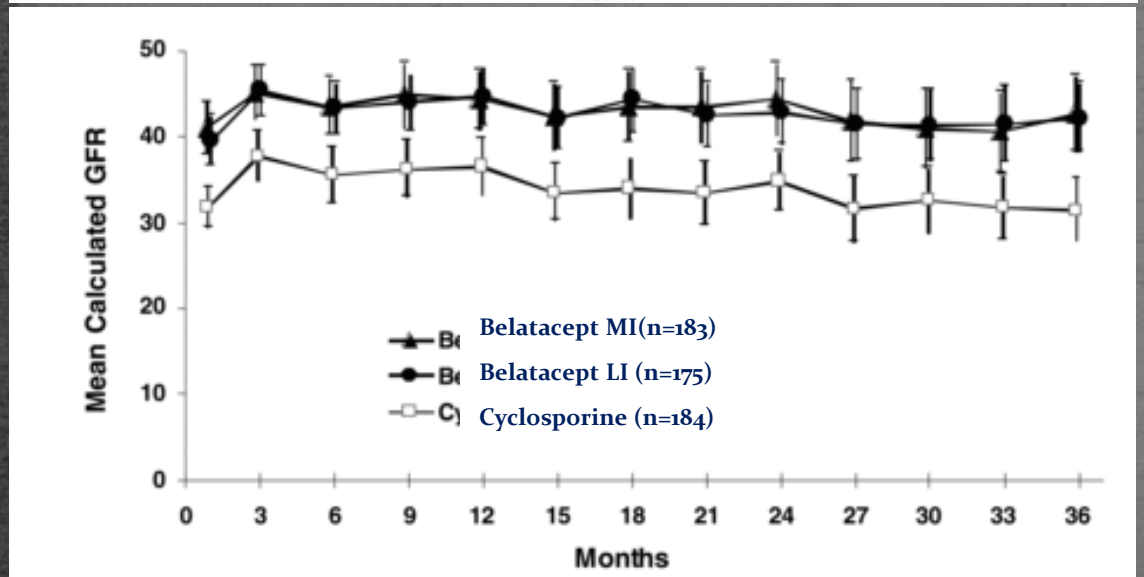


Belatacept *(LEA29Y)*

- Belatacept
  - A second-generation of CTLA4Ig
  - Belatacept-based vs Cyclosporine-based
    - In phase II; same acute rejection in KT but lower chronic rejection and higher GFR
    - Phase III trial 
  - Belatacept with mTOR inhibitor regimen
    - Evaluation of the effectiveness of immune tolerance in progress
  - Belatacept with Efalizumab (anti-LFA-1)
    - Possible combination for tolerance induction

A Phase III Study of Belatacept Versus Cyclosporine in Kidney Transplants from Extended Criteria Donors (BENEFIT-EXT Study)





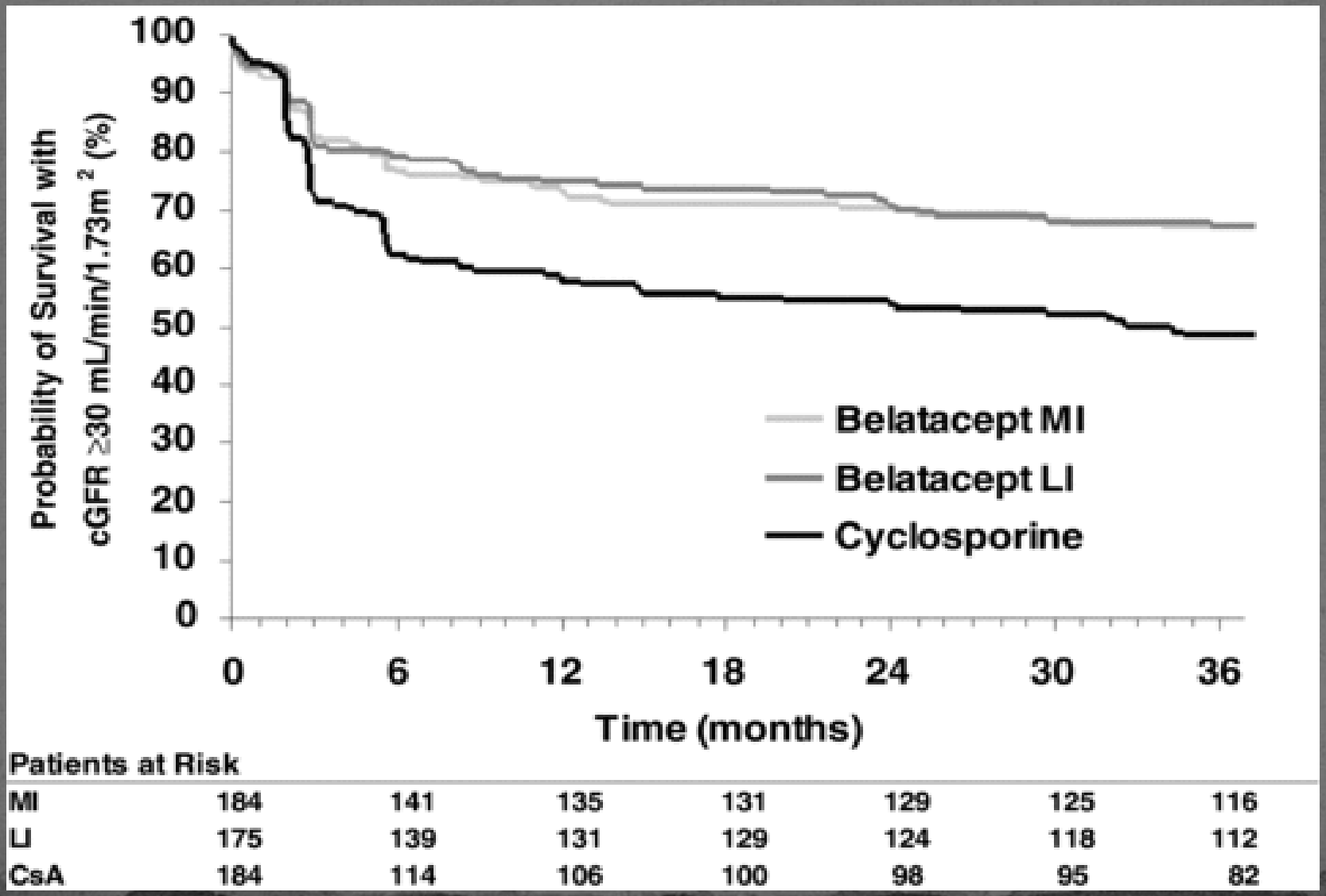
Patients with Measurements

Bela MI	182	177	161	153	165	145	143	140	152	129	136	139	152
Bela LI	173	168	152	149	157	140	142	144	158	139	140	132	154
CsA	184	172	153	147	159	139	140	137	154	126	132	133	143

In Belatacept group

- Similar acute rejection
- Similar overall infection and malignancy
- Favorable CV and metabolic complications
- More PTLD and tuberculosis

BENEFIT-EXT Study

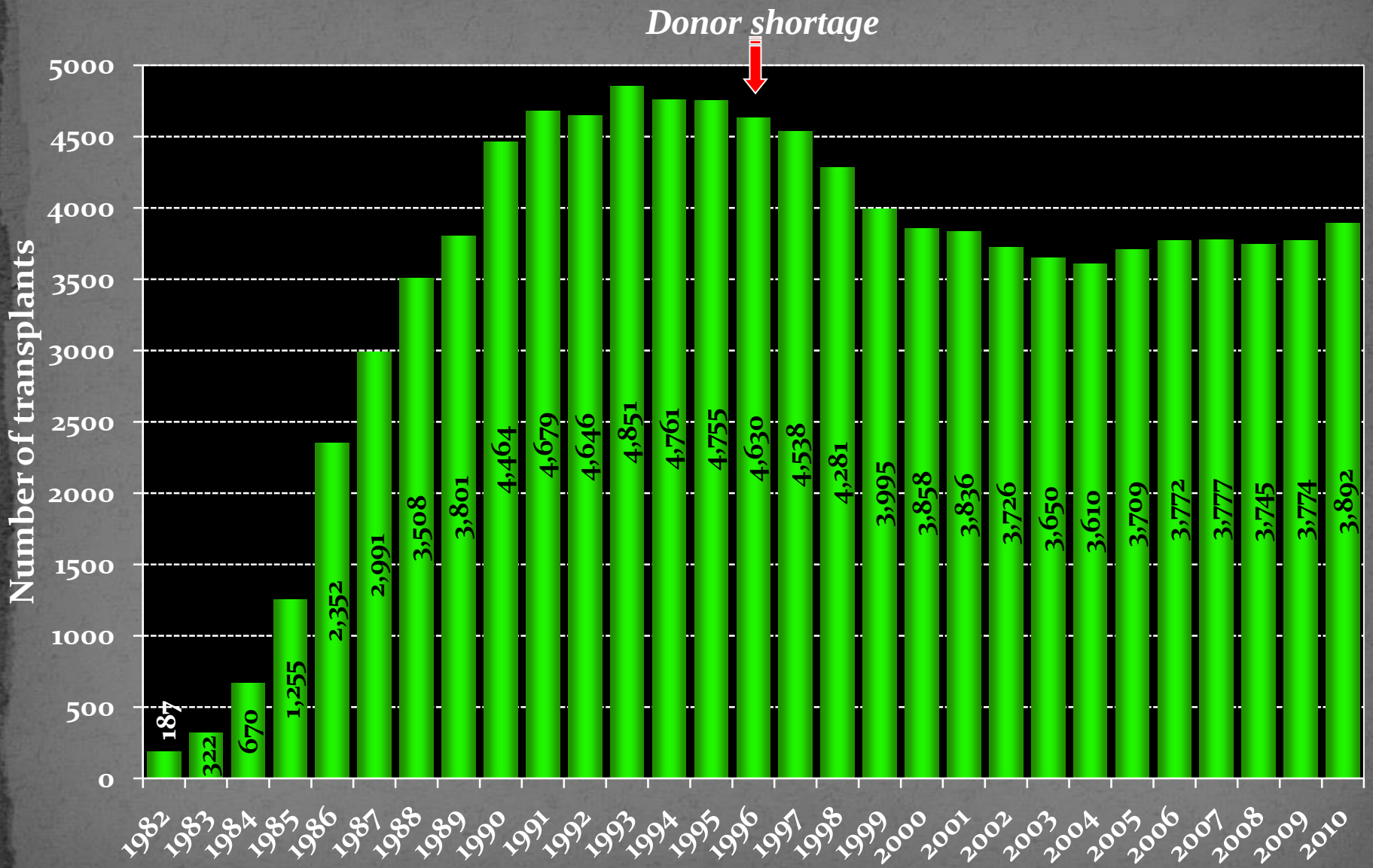


Patients at Risk

MI	184	141	135	131	129	125	116
LI	175	139	131	129	124	118	112
CsA	184	114	106	100	98	95	82

Donor Shortage

Number of Heart Transplants



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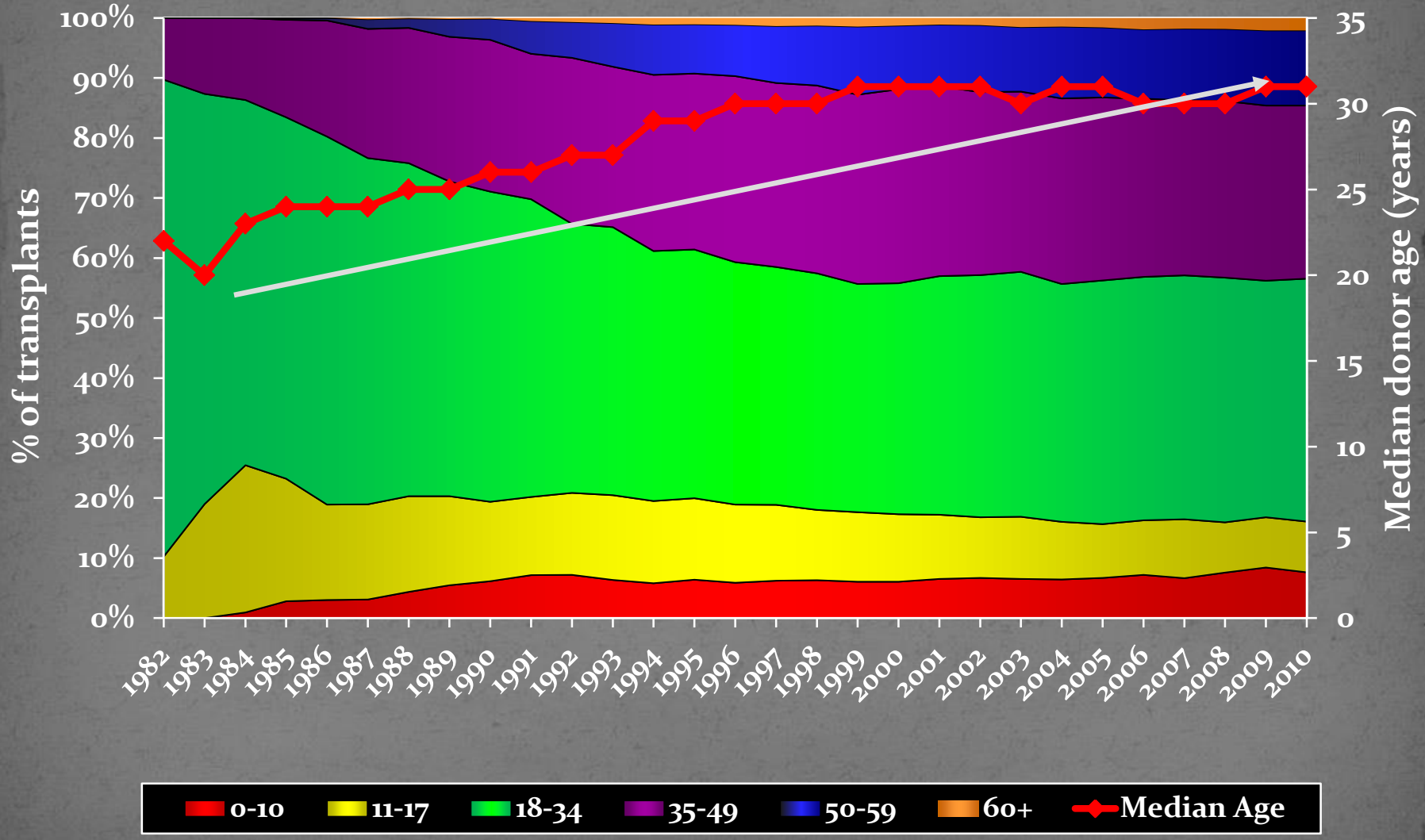
Adult Heart Transplants; Donor Age



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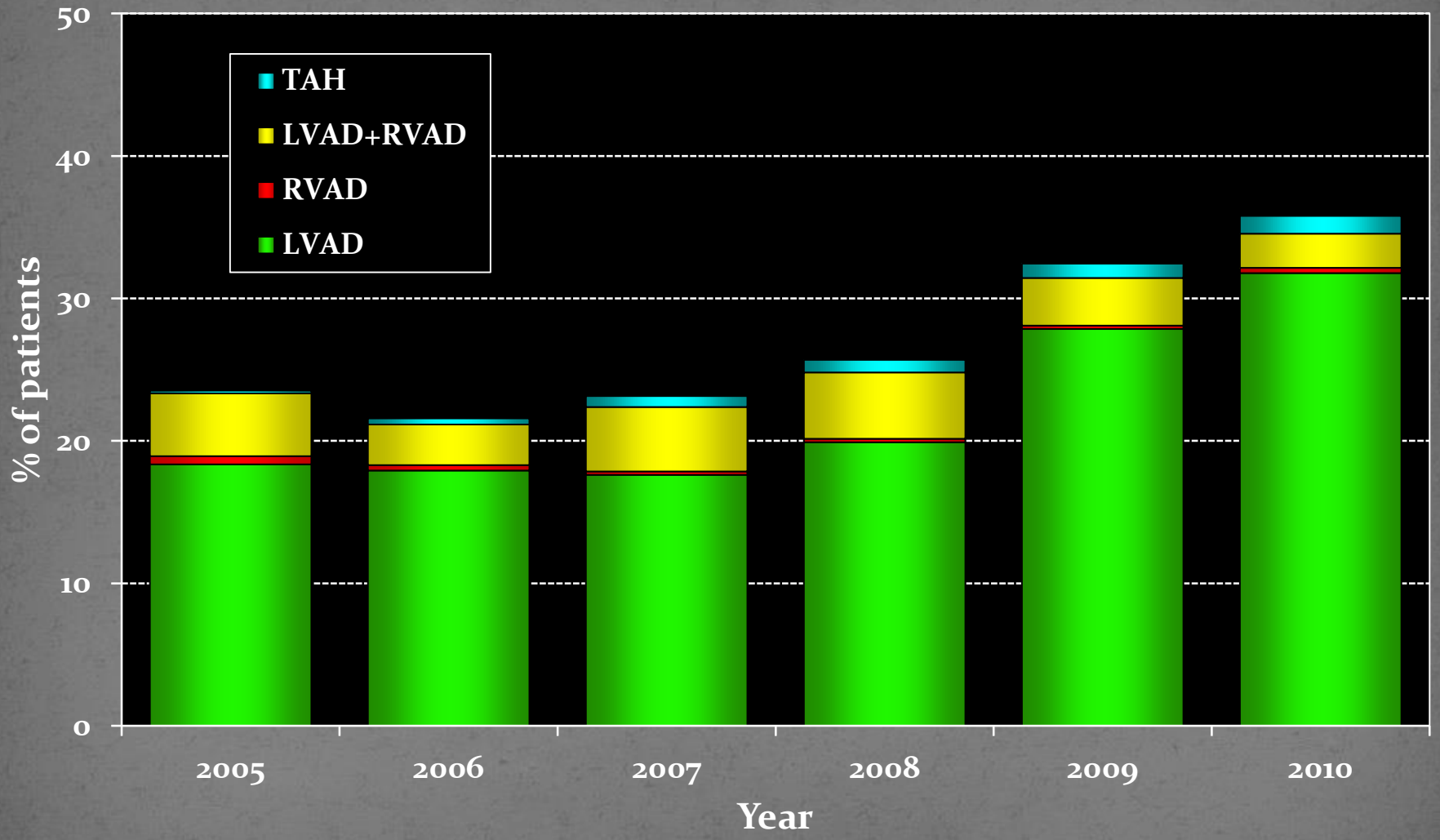
% of Patients Bridged with MCS



J Heart Lung Transplant. 2012 Oct; 31(10): 1045-1095


XENOTRANSPLANTATION
The Future for Donor Shortage

Index of Dissimilarity

Species	*Index of dissimilarity*
Hominoidea(humans and apes)	
Homo sapiens (human)	1.0
Gorilla gorilla (gorilla)	1.09
Pan troglodytes (chimpanzee)	1.14
Pongo pygmaeus (orang-utan)	1.22
Hylobates lar (gibbon)	1.28
Cercopithecoidea (Old World monkeys)	2.23 - 2.26
Ceboidea (New World monkeys)	2.7 - 5.0
Non-primates	
Bos taurus (bull)	32
Sus scroga (pig)	> 35

Anti α-Gal Natural Abs

- Preformed xenoreactive natural antibodies to Pig heart
- >80% of complement-fixing xenoreactive natural Abs
- Human, Apes(higher primates), Old world monkey
  - ➔ cannot produce Gal α 1-3Gal due to absence of α1,3-galactosyl transferase
  - ➔ instead use α 1-2 fucosyl transferase to form H substance
- Appears after birth due to exposure to environment bacteria
- Loss of the galactosyl transferase and formation of anti α-gal Abs give survival advantage (protection from environmental pathogen)

Free tissue xenograft → **Biological hurdle**
Neovascularization
Support by host GFs
Foreign microenvironment
→ **Cellular rejection**
Humoral rejection

Discordant organ xenograft → **Hyperacute rejection** → **Acute vascular rejection** → **Elicited cellular/ humoral rejection** → **Chronic rejection**

Concordant organ xenograft → **Acute vascular rejection** → **Elicited cellular/ humoral rejection** → **Chronic rejection**

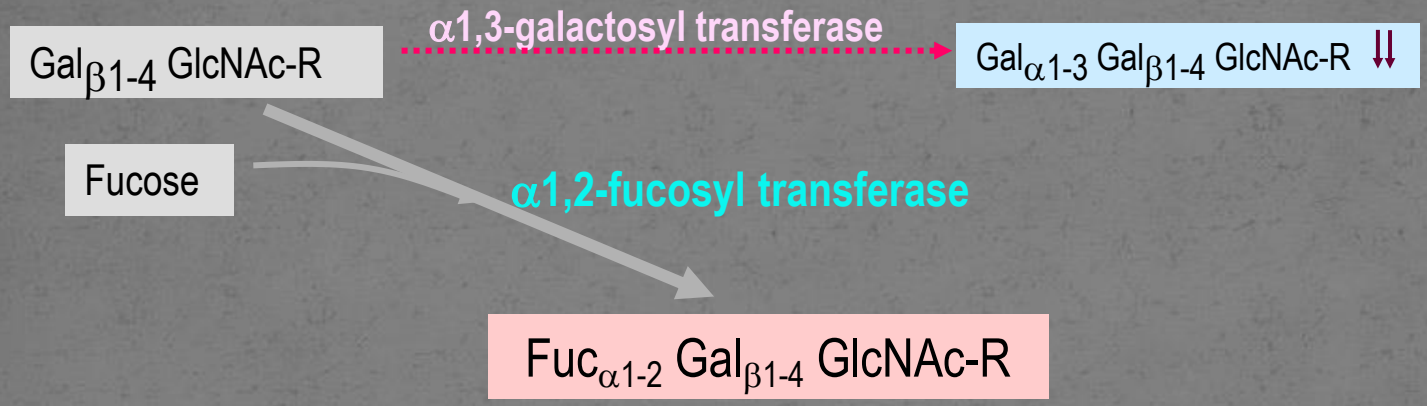
Escape Hyperacute Rejection

- Removing preformed antibodies
  - Only transient effect and often marked rebound
  - Depletion of the B-1 population of B cells entirely
- Expression of human complement regulatory proteins
  - hDAF gene, hMCP gene, hCD59 gene
- Removing the α-gal determinant
  - Expression of α-1,2 fucosyl transferase
  - With a galactosidase for complete suppression of α-gal
  - Elimination of α-1,3 galactosyl transferase

Escape Hyperacute Rejection

Recent advance

- Expression of α-1,2 fucosyl transferase



- Elimination of α-1,3 galactosyl transferase
  - α-1,3 galactosyl transferase knock out animal

Physiological Barriers

- Perhaps the most important potential barrier
  - Primate surviving with pig kidney ; marked anemia
  - Human recipient with baboon liver ; lower levels of serum uric acid and cholesterol
  - Lack of appropriate stem cell growth factors in some species
  - For metabolically more complex organ (liver) , significant deficiencies may exist
- But for heart
  - If appropriate size, may function adequately
- ***Consider species-specific life span***

Hurdles to be Overcome

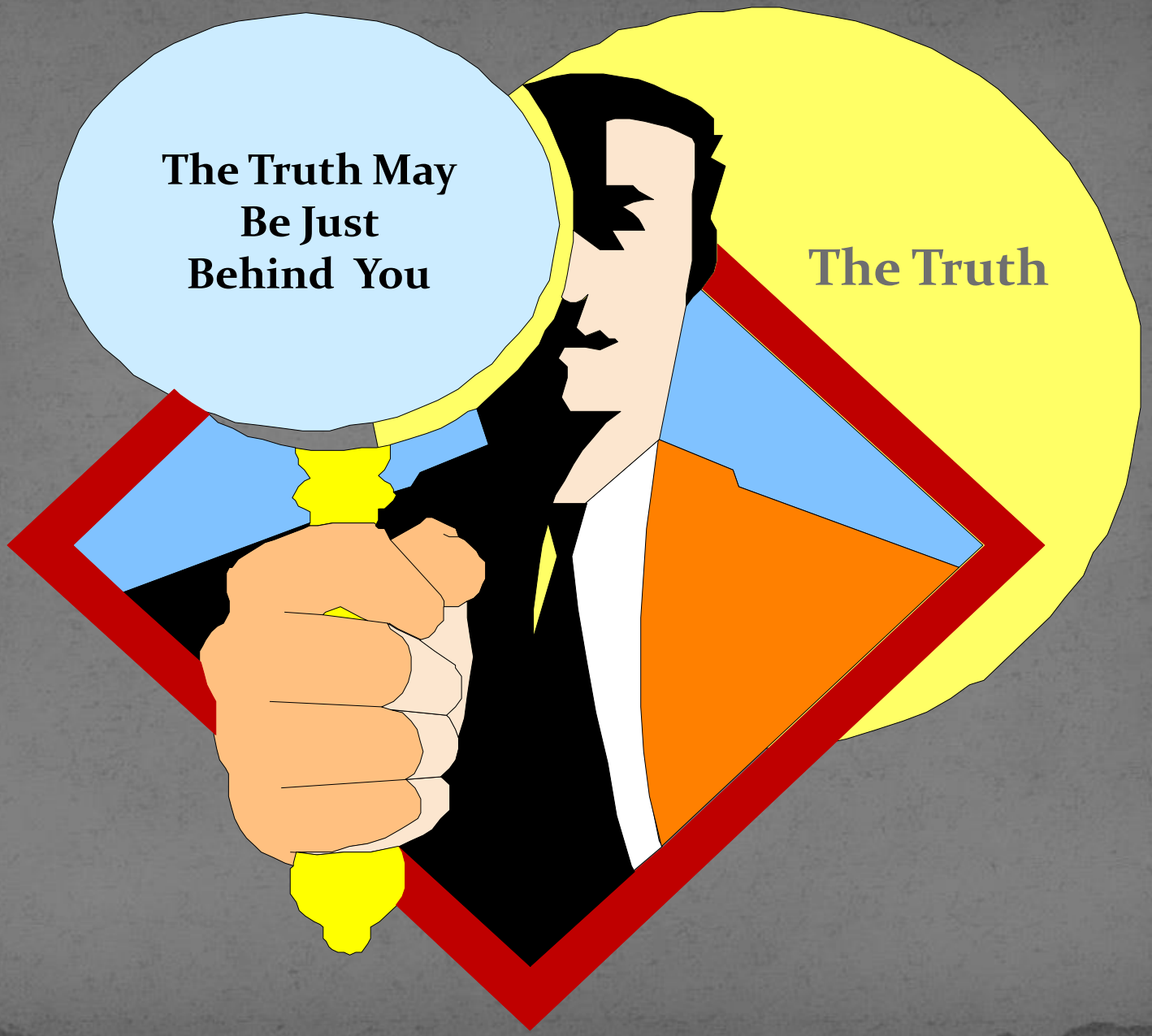
- Acute/delayed vascular rejection
- Acute cellular rejection
- Chronic rejection
- Physiologic barrier

The Future

Immune Tolerance

Xenotransplantation

Can We ?


The Truth May
Be Just
Behind You
The Truth


HEART TRANSPLANTATION
The Rising Sun