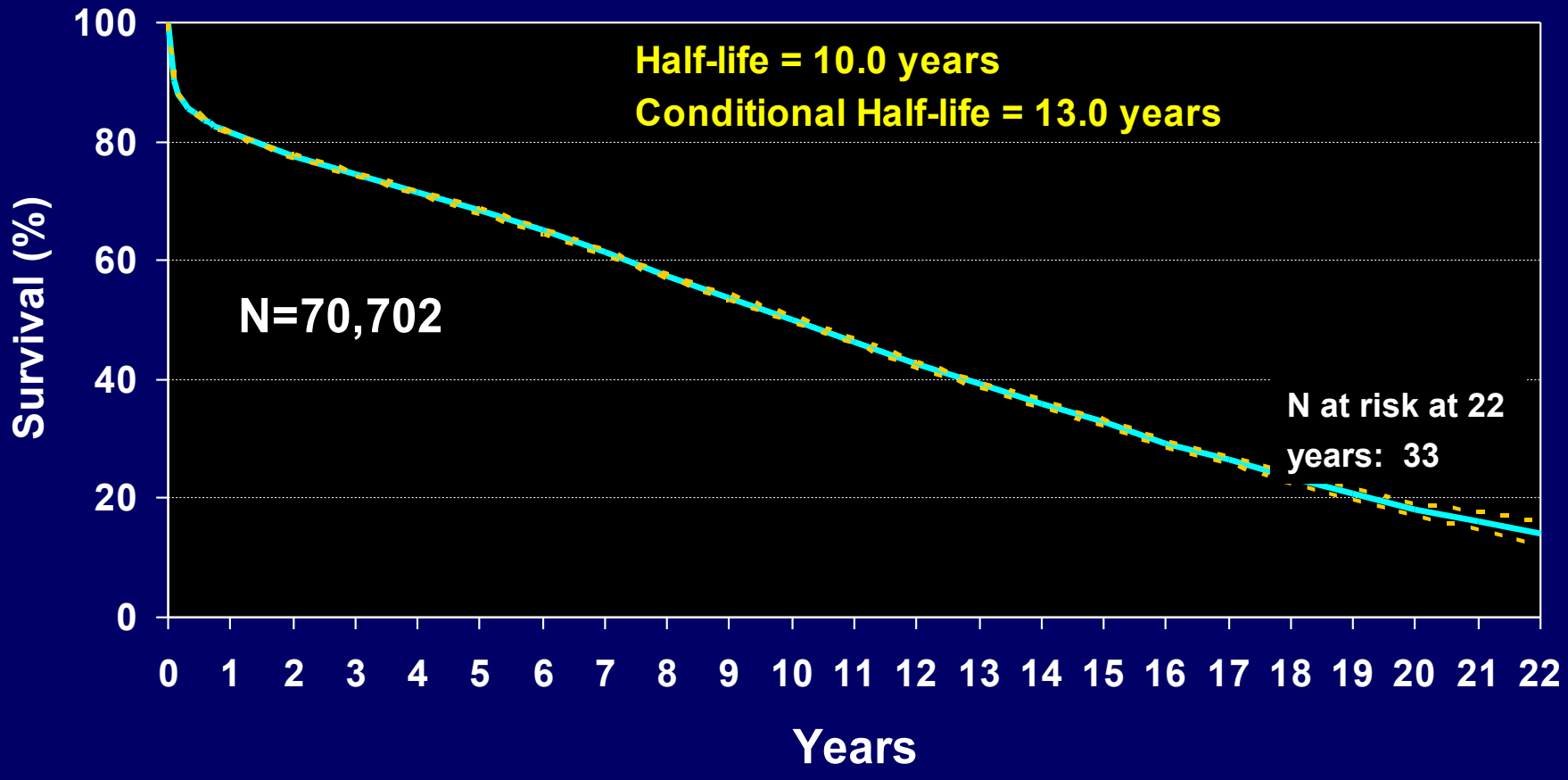
IMMUNOSUPPRESSIVE THERAPY AFTER HEART TRANSPLANTATION

YEDAEL HAR-ZAHAV MD

HEART TRANSPLANTATION

Kaplan-Meier Survival (1/1982-6/2005)



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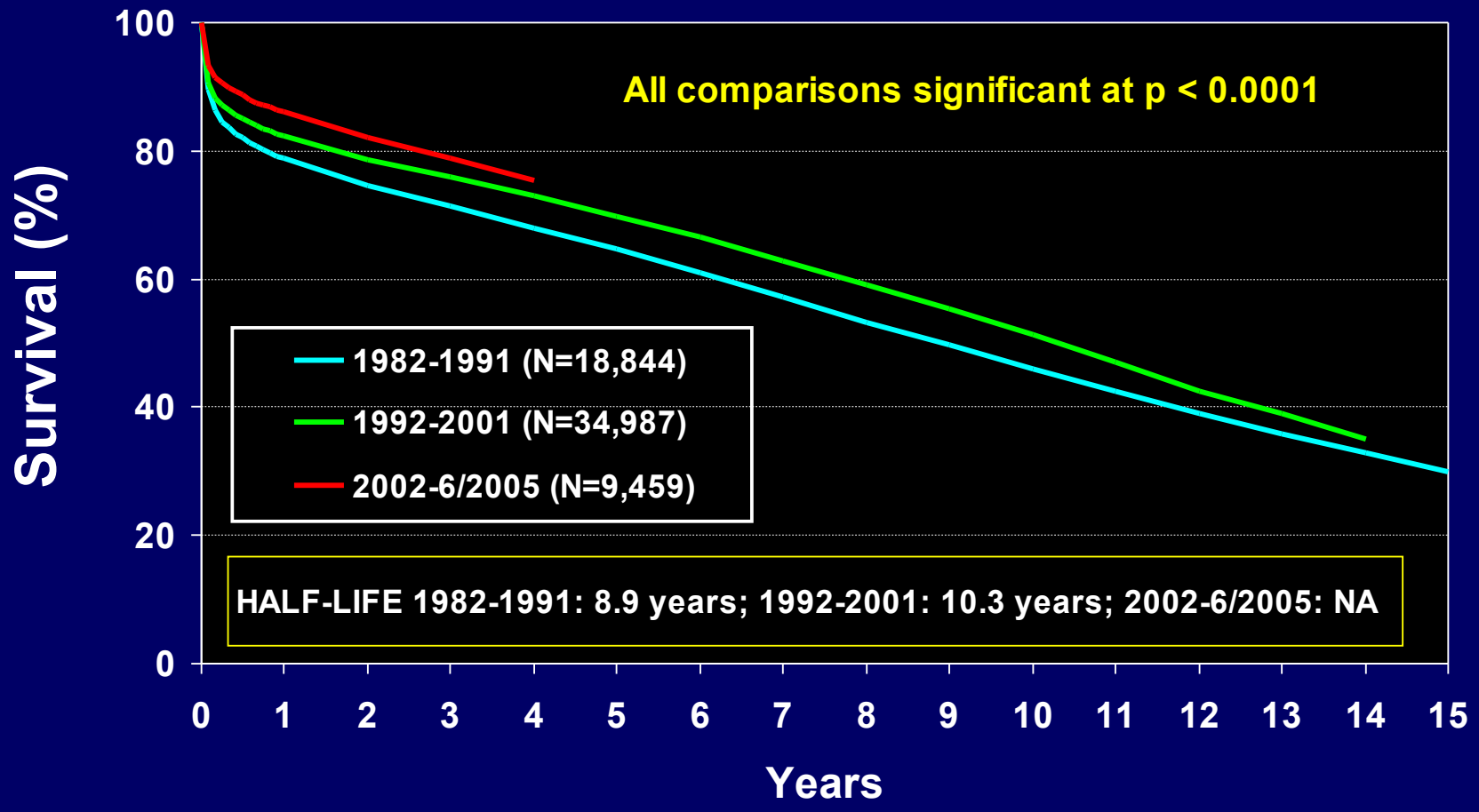
ADULT HEART TRANSPLANTATION

Kaplan-Meier Survival by Era ((Transplants: 1/1982 – 6/2005



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ADULT HEART TRANSPLANT RECIPIENTS:

Cause of Death (Deaths: January 1982 – June 2006)

CAUSE OF DEATH	Days 0-30 (N = 3,006)	– Days 31 Year 1 (N = 2,722)	– Year 1< Years 3 (N = 2,135)	– Years 3< Years 5 (N = 1,857)	– Years 5< Years 10 (N = 4,054)	Years 10< (N = 2,107)
CARDIAC ALLOGRAFT VASCULOPATHY	(1.7%) 52	(4.7%) 127	(14.0%) 298	(16.1%) 299	(14.3%) 581	(14.7%) 309
ACUTE REJECTION	(6.4%) 193	(12.4%) 338	(10.3%) 220	(4.4%) 82	(1.7%) 69	(1.2%) 26
LYMPHOMA	(0.1%) 2	(2.0%) 54	(4.0%) 85	(5.2%) 96	(4.8%) 195	(3.5%) 73
MALIGNANCY, OTHER	(0.0%) 1	(2.1%) 57	(10.2%) 218	(18.3%) 340	(18.5%) 749	(18.6%) 392
CMV	(0.1%) 4	(1.2%) 34	(0.7%) 16	(0.2%) 3	(0.1%) 5	(0.0%) 1
INFECTION, NON-CMV	(13.1%) 393	(32.9%) 896	(12.9%) 276	(9.7%) 180	(10.9%) 442	(10.1%) 213
PRIMARY FAILURE	(26.7%) 804	(7.2%) 196	(6.3%) 134	(4.4%) 81	(4.6%) 186	(2.0%) 43
GRAFT FAILURE	(15.1%) 453	(11.2%) 304	(17.1%) 365	(16.0%) 298	(14.3%) 579	(14.7%) 310
TECHNICAL	(7.8%) 233	(1.0%) 28	(0.8%) 17	(0.9%) 17	(0.9%) 36	(0.9%) 20
OTHER	(5.4%) 162	(6.4%) 175	(8.8%) 187	(7.9%) 147	(8.4%) 339	(8.3%) 175
MULTIPLE ORGAN FAILURE	(11.8%) 356	(9.8%) 268	(5.5%) 117	(5.5%) 102	(7.6%) 309	(9.0%) 190
RENAL FAILURE	(0.7%) 20	(0.9%) 25	(1.7%) 36	(3.5%) 65	(5.6%) 225	(8.2%) 173
PULMONARY	(4.4%) 133	(4.0%) 108	(4.5%) 96	(4.6%) 85	(4.2%) 172	(4.7%) 99
CEREBROVASCULAR	(6.7%) 200	(4.1%) 112	(3.3%) 70	(3.3%) 62	(4.1%) 167	(3.9%) 83

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ADULT HEART TRANSPLANT RECIPIENTS:
Cause of Death from Leading Causes by Era

((Deaths: January 1992 - June 2006

CAUSE OF DEATH	DATE OF DEATH	Days 0-30 (N = 3,005)	– Days 31 Year 1 (N = 2,722)	– Year 1< Years 3 (N = 2,135)	– Years 3< Years 5 (N = 1,857)	Years – 5< 10 Years (N = 4,054)	Years 10< (N = 2,107)
ACUTE REJECTION	1992-1997	(7.1%) 122	(14.3%) 231	(9.3%) 113	(4.4%) 41	(1.1%) 16	(1.1%) 16
	1998-6/2006	(5.5%) 71	(9.7%) 107	(11.7%) 107	(4.4%) 41	(2.0%) 53	(2.0%) 53
CARDIAC ALLOGRAFT VASCULOPATHY	1992-1997	(1.9%) 32	(5.1%) 83	(15.1%) 184	(20.1%) 189	(18.3%) 262	(18.3%) 262
	1998-6/2006	(1.6%) 20	(4.0%) 44	(12.4%) 114	(12.0%) 110	(12.2%) 319	(12.2%) 319
GRAFT FAILURE	1992-1997	(15.0%) 258	(11.0%) 179	(16.4%) 200	(12.7%) 119	(12.1%) 174	(12.1%) 174
	1998-6/2006	(15.2%) 195	(11.4%) 125	(18.0%) 165	(18.8%) 179	(15.5%) 405	(15.5%) 405
MALIGNANCY, OTHER	1992-1997	(0.1%) 1	(2.5%) 40	(9.7%) 118	(18.8%) 177	(17.9%) 257	(17.9%) 257
	1998-6/2006	(0.0%) 0	(1.5%) 17	(10.9%) 100	(17.8%) 163	(18.8%) 492	(18.8%) 492
PRIMARY FAILURE	1992-1997	(29.5%) 508	(10.4%) 168	(8.6%) 105	(5.2%) 49	(6.9%) 99	(6.9%) 99
	1998-6/2006	(23.1%) 296	(2.5%) 28	(3.2%) 29	(3.5%) 32	(3.3%) 87	(3.3%) 87

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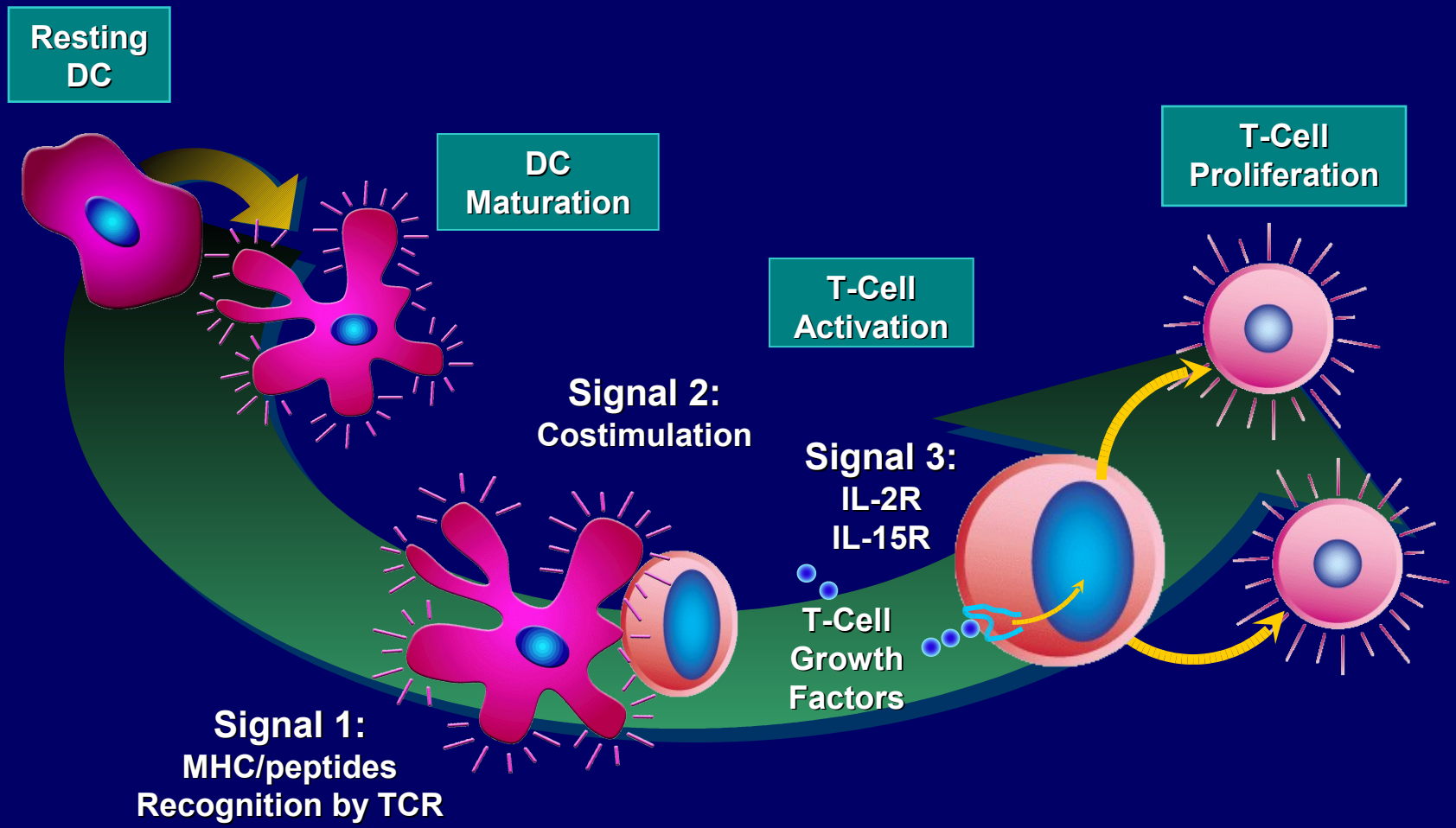
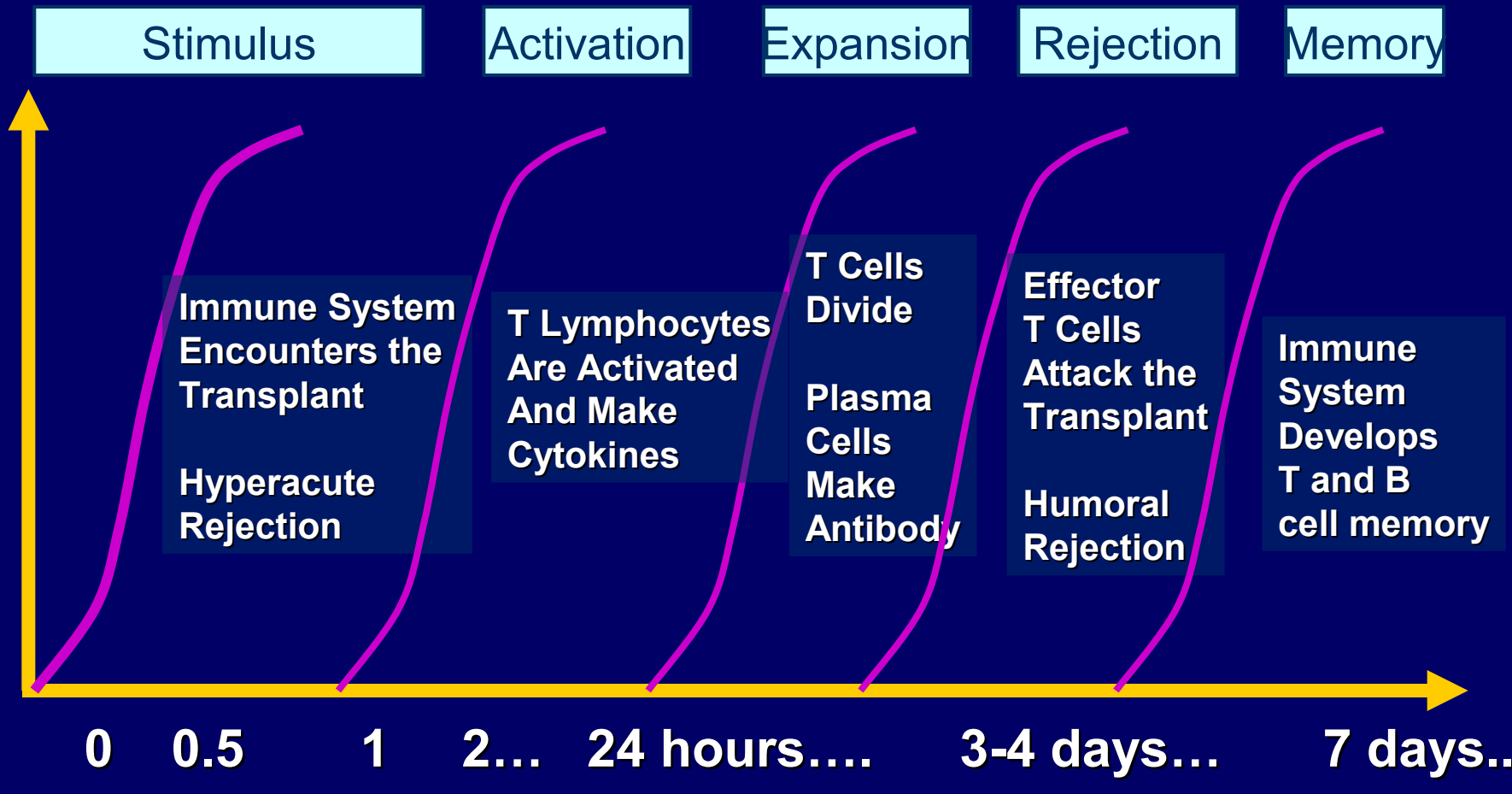
Immunobiology of Rejection



Adapted with permission from Professor Dr. Walter Land and M. Schneeberger, University of Munich, Germany.

Events Following T Cell Activation



Acute Rj Symptomes

עייפות

ירידת ל"ד (20 ממ"כ)

בצקת , JVP

Gallop S3

תפליט פריקרדיאלי

עליית חום

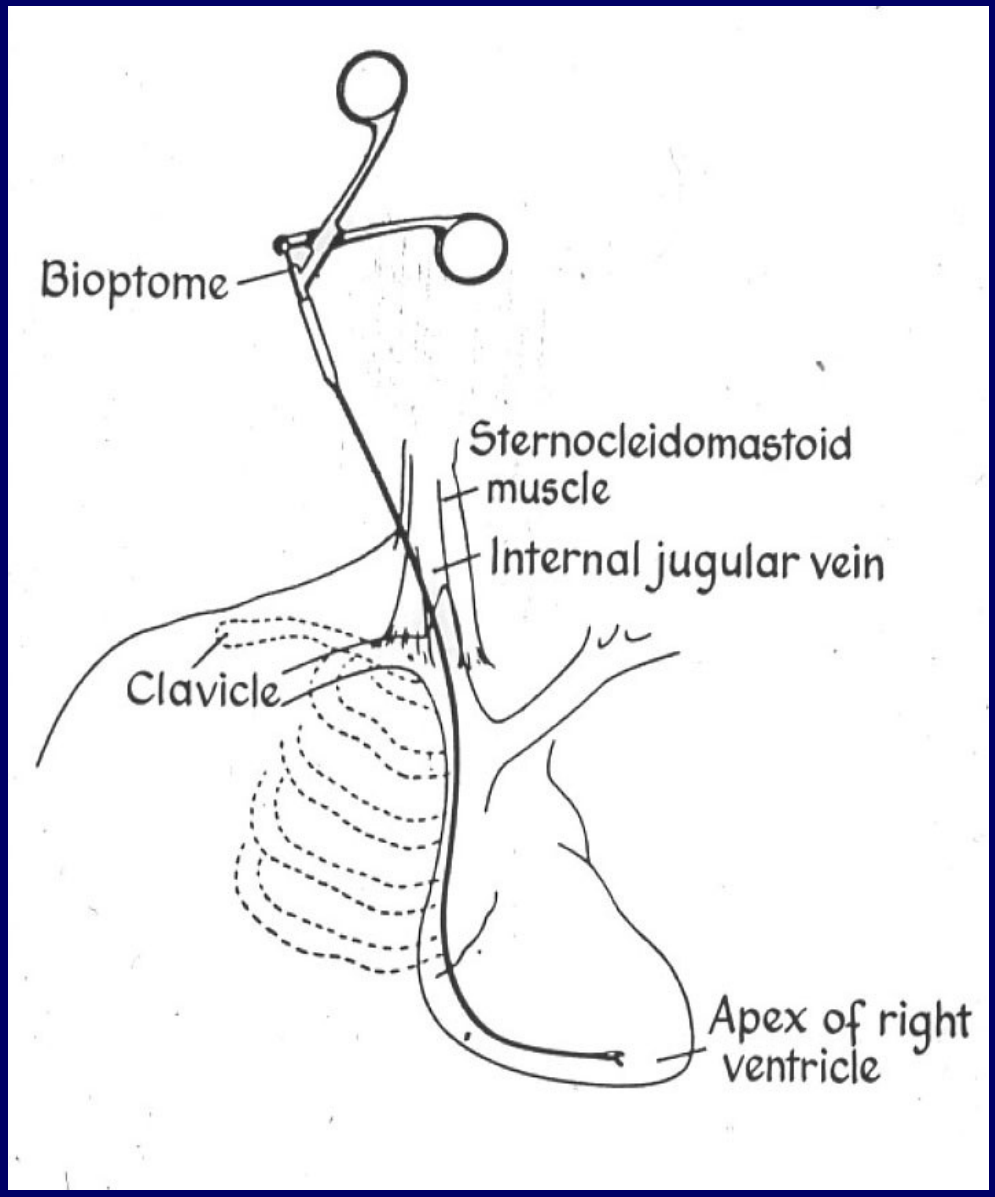
אריטמיה (על-חדרית , חדרית)

הפרעות הולכה

סימני אס"ק לב

Acute Rj - Echo

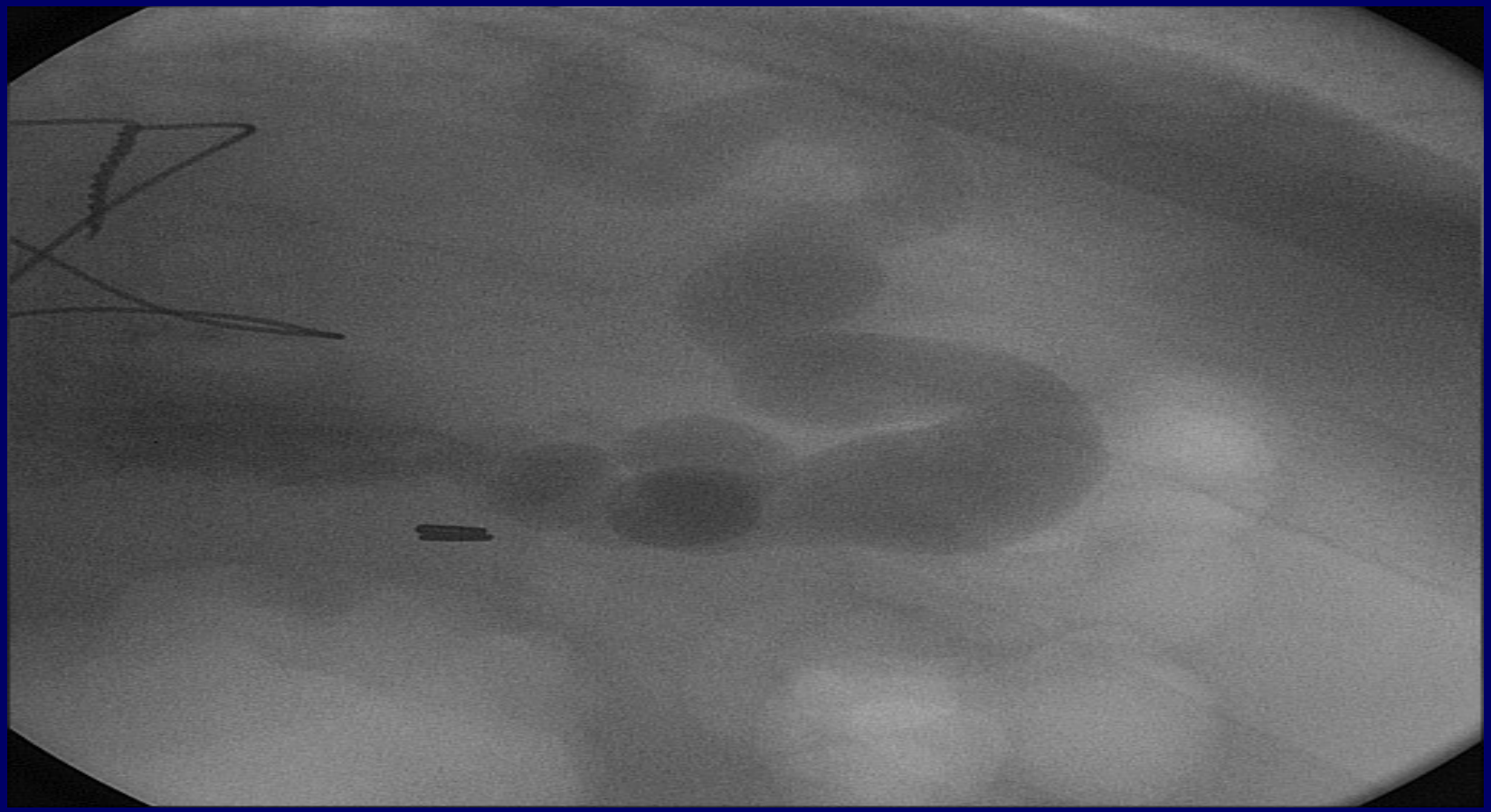
- Diastolic Dysfunction
- Systolic Dysfunction
- Wall Thickening


Bioptome
Sternocleidomastoid muscle
Internal jugular vein
Clavicle
Apex of right ventricle

Biopsy - Complications

- Perforation
- Tamponade
- Arrythmia
- TR
- Coronary-RV-Fistula

CORONARY FISTULA



FISTULA RCA--RV

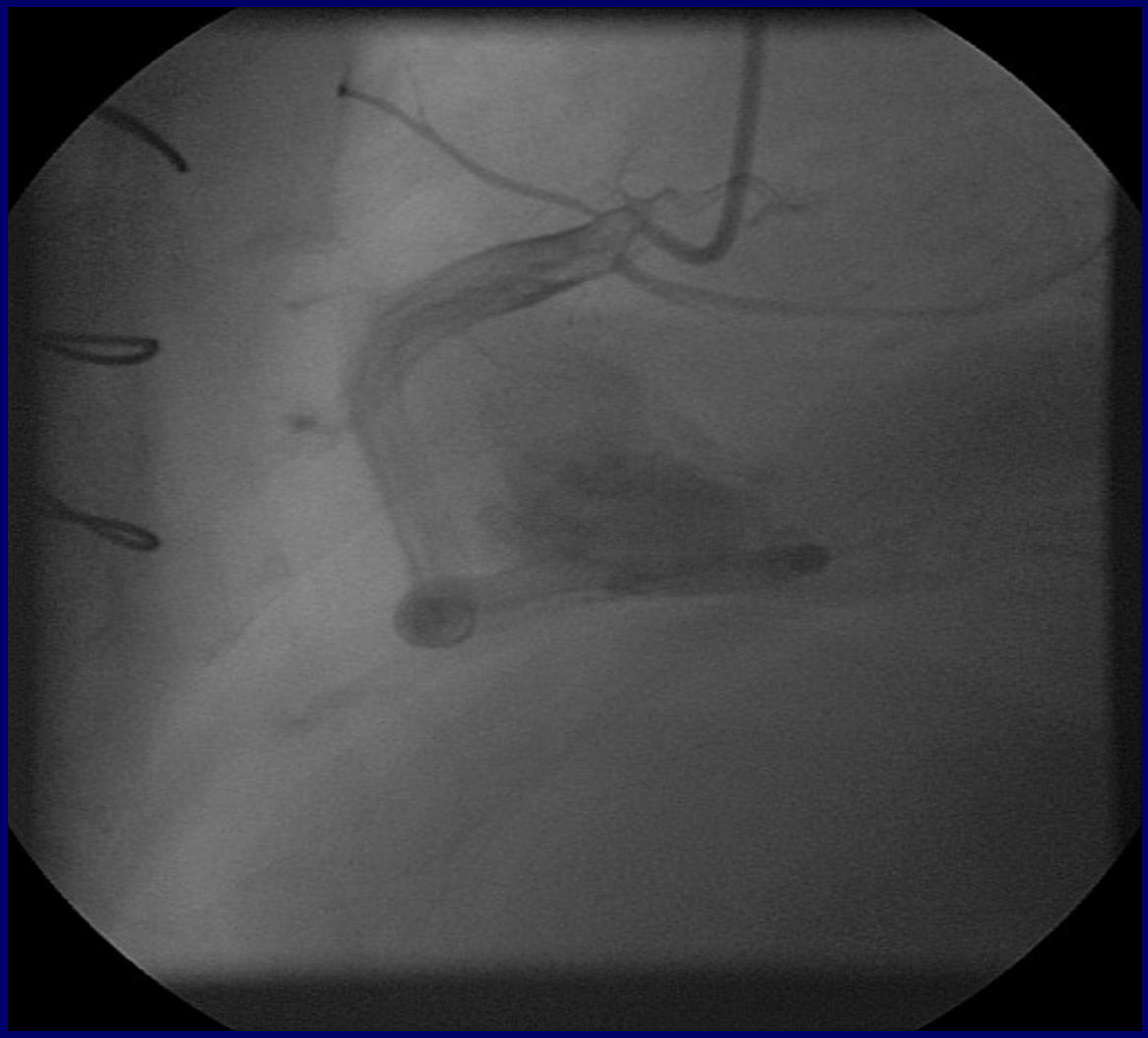


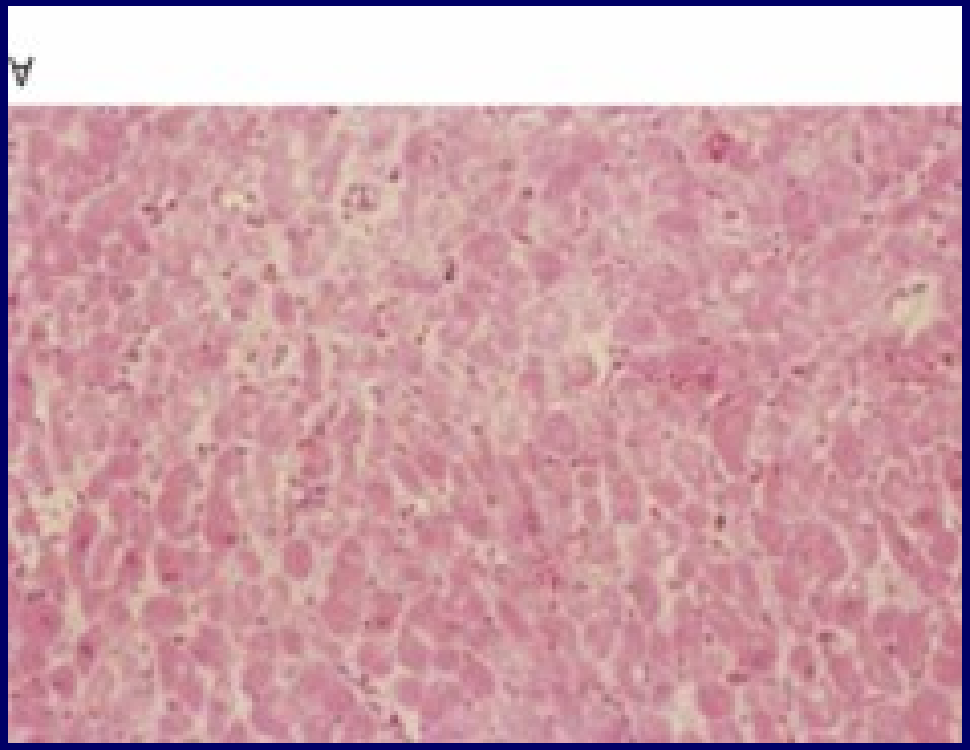
Table 1. ISHLT Standardized Cardiac Biopsy Grading: Acute Cellular Rejection[b]

2004		1990	
Grade 0 R[a]	No rejection	Grade 0	No rejection
Grade 1 R, mild	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage	Grade 1, mild A—Focal	Focal perivascular and/or interstitial infiltrate without myocyte damage
		B—Diffuse	Diffuse infiltrate without myocyte damage
		Grade 2 moderate (focal)	One focus of infiltrate with associated myocyte damage
Grade 2 R, moderate	Two or more foci of infiltrate with associated myocyte damage	Grade 3, moderate A—Focal	Multifocal infiltrate with myocyte damage
Grade 3 R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage ± vasculitis	B—Diffuse	Diffuse infiltrate with myocyte damage
		Grade 4, severe	Diffuse, polymorphous infiltrate with extensive myocyte damage ± edema, ± hemorrhage + vasculitis

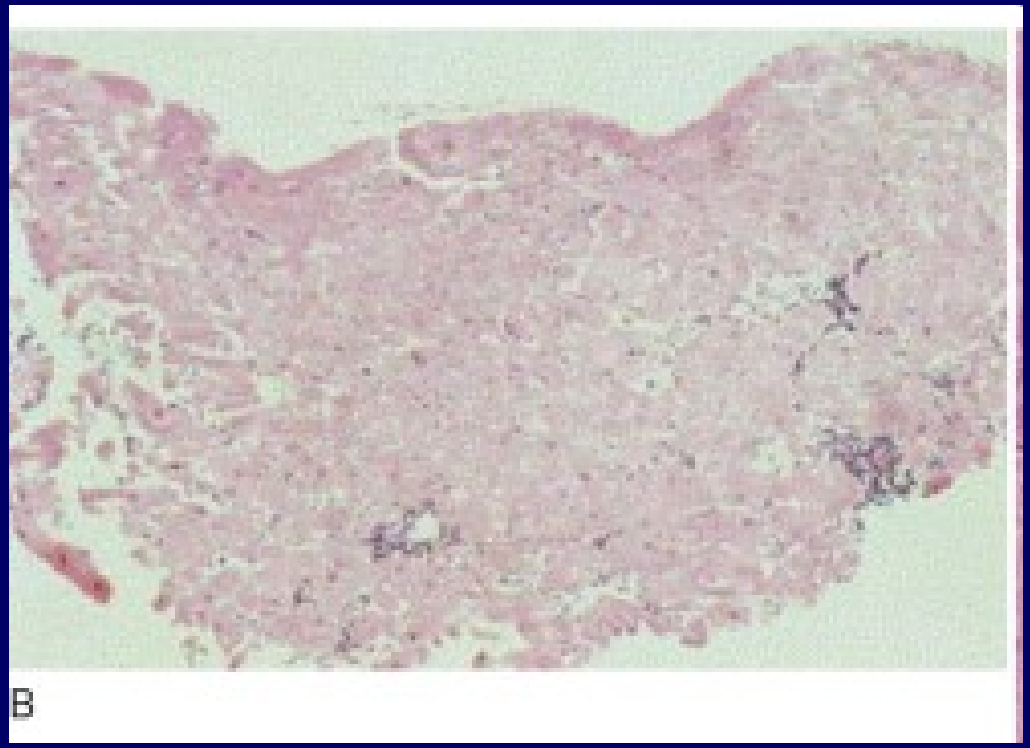
[a]Where "R" denotes revised grade to avoid confusion with 1990 scheme.

[b]The presence or absence of acute antibody-mediated rejection (AMR) may be recorded as AMR 0 or AMR 1, as required (see Table 3).

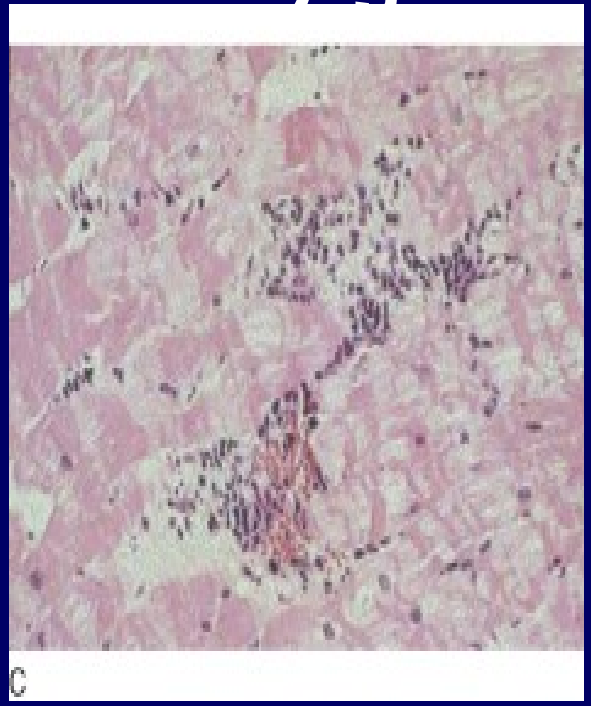
Grade 0 R—normal endomyocardial biopsy showing no evidence of cellular infiltration



Grade 1 R—low-power view of endomyocardial , biopsy showing three focal perivascular infiltrates without myocyte damage ,previously grade 1A

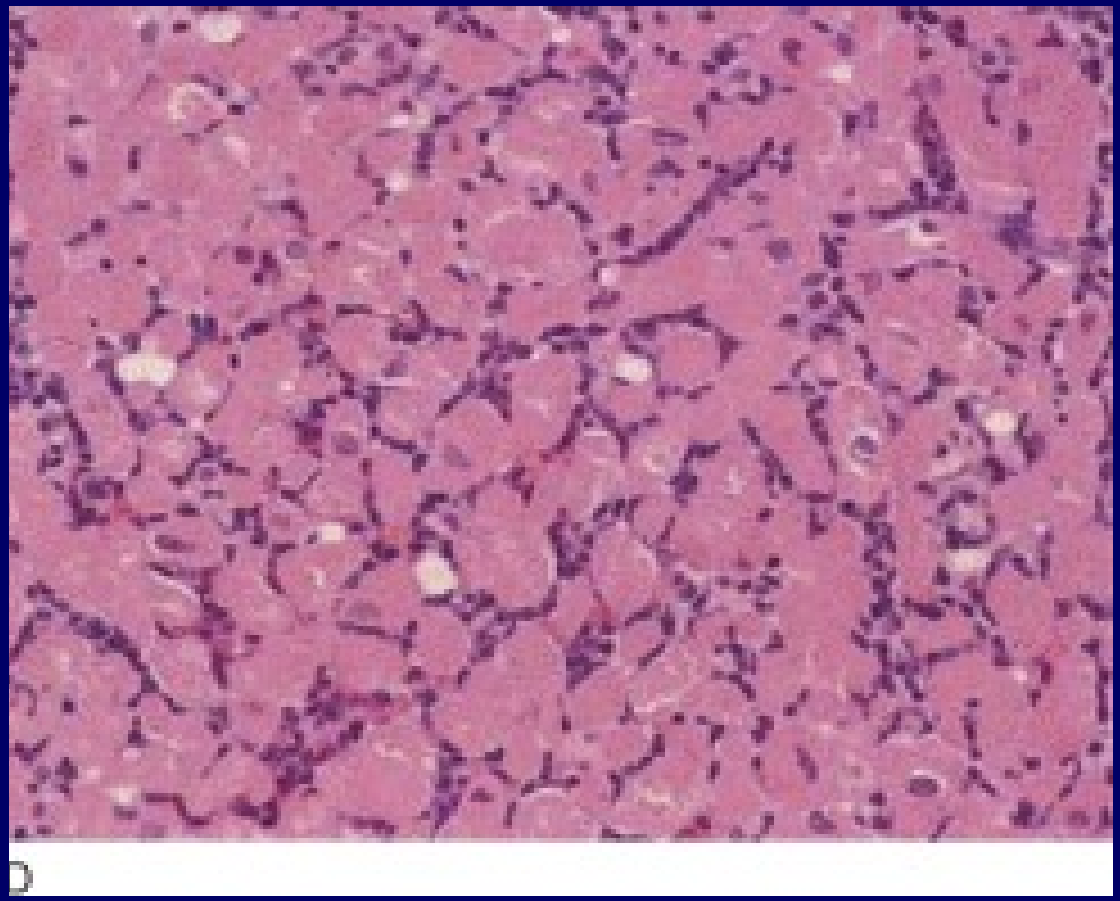


- **Grade 1 R—both perivascular and interstitial infiltrates are present but without definite evidence of myocyte damage (previously grade 1A**

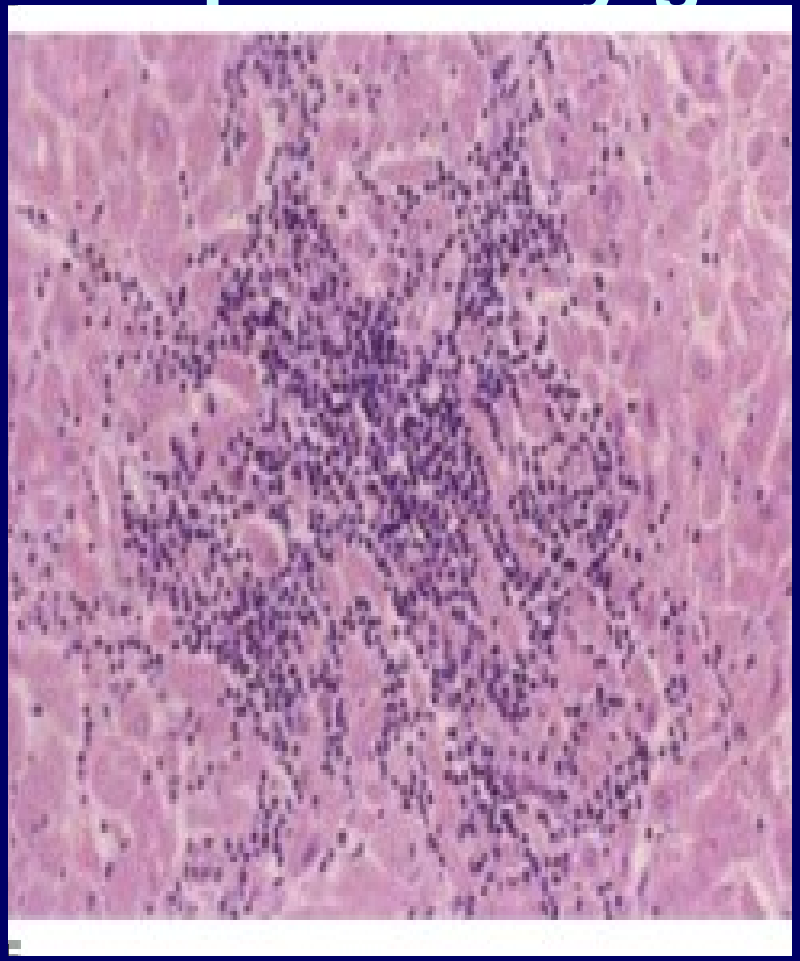


Grade 1 R—diffuse mononuclear cell infiltrate with an interstitial pattern of lymphocytes between and around myocytes without associated myocyte damage

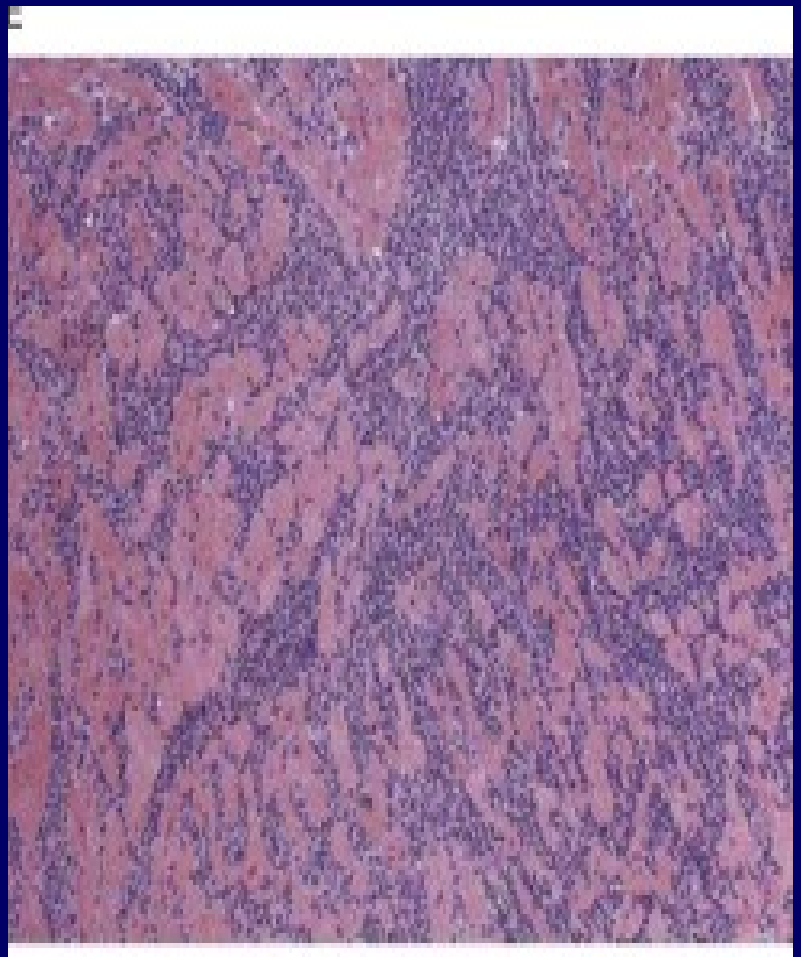
((previously grade 1B

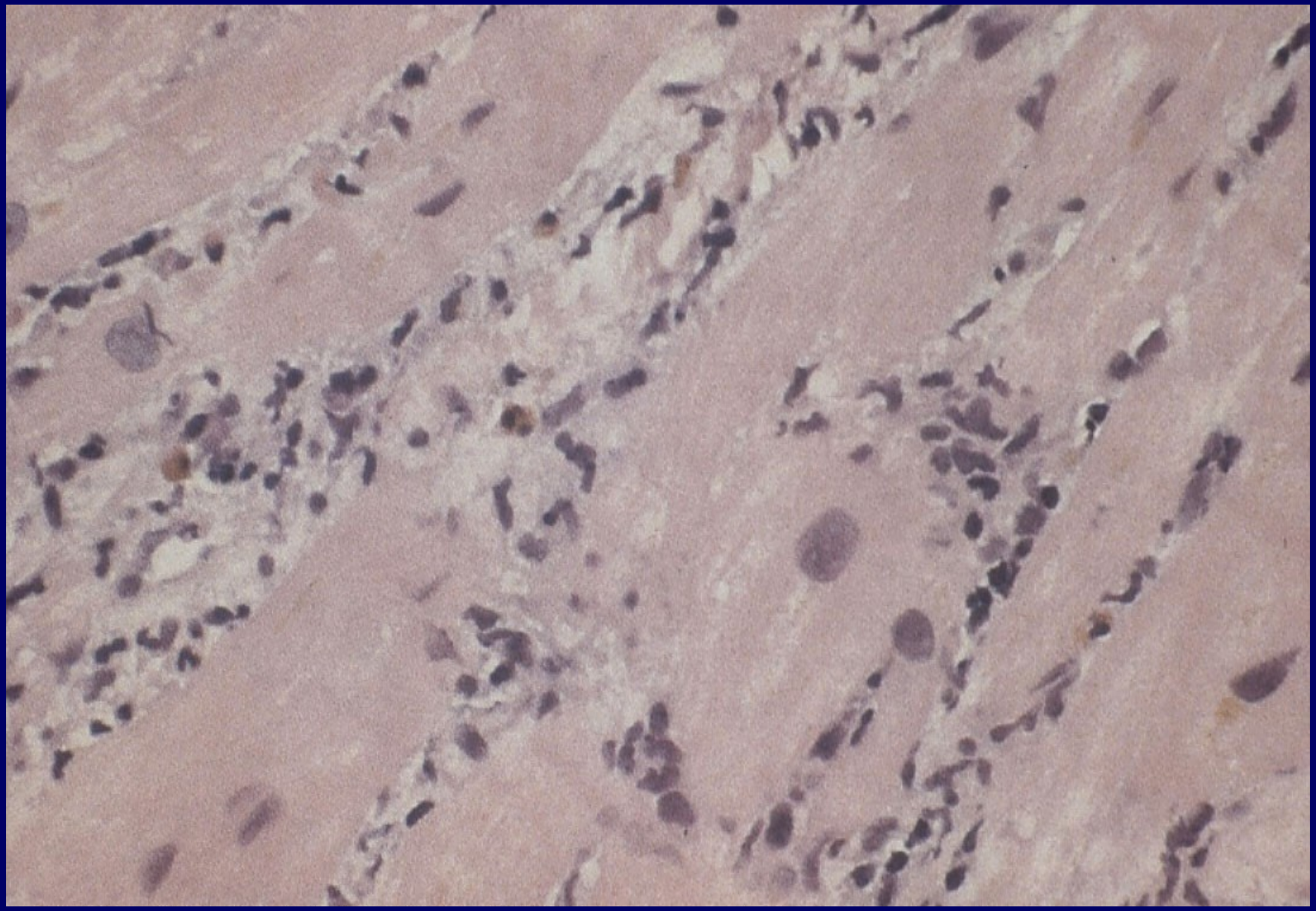


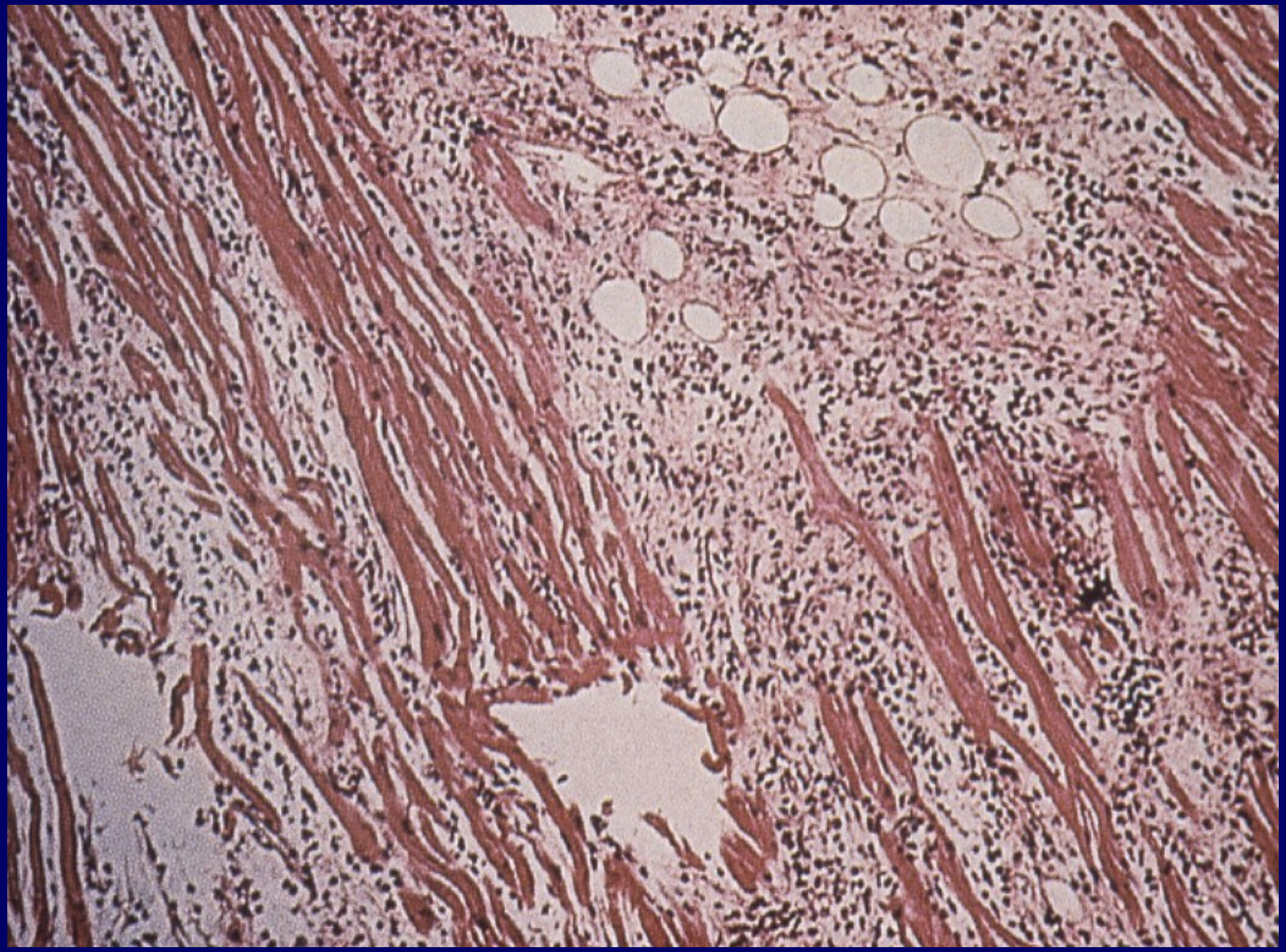
Grade 2 R—damaging infiltrate with , myocyte damage and architectural distortion previously grade 3A



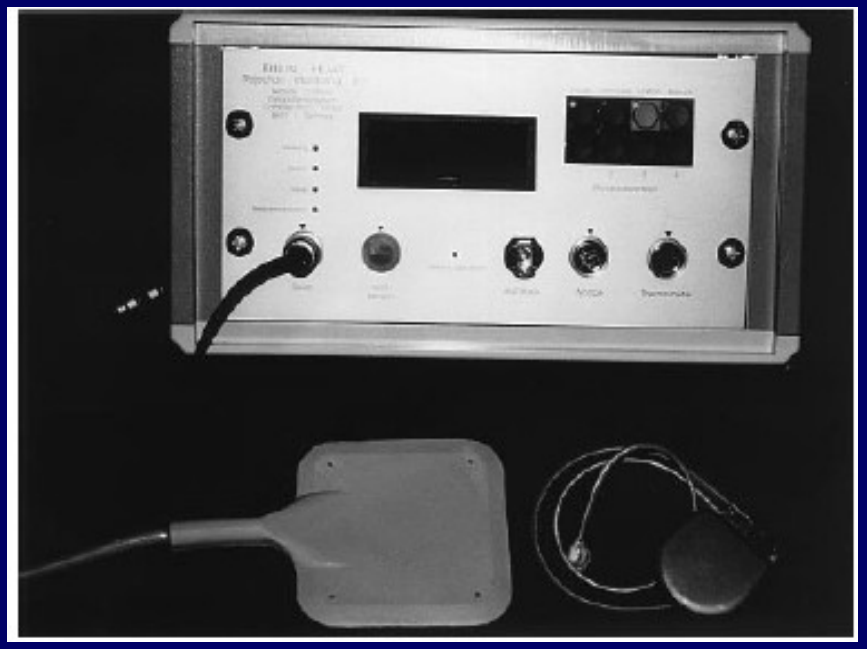
Grade 3 R—diffuse damaging infiltrates with encroachment of , myocytes and disruption of normal architecture (previously grade 3B

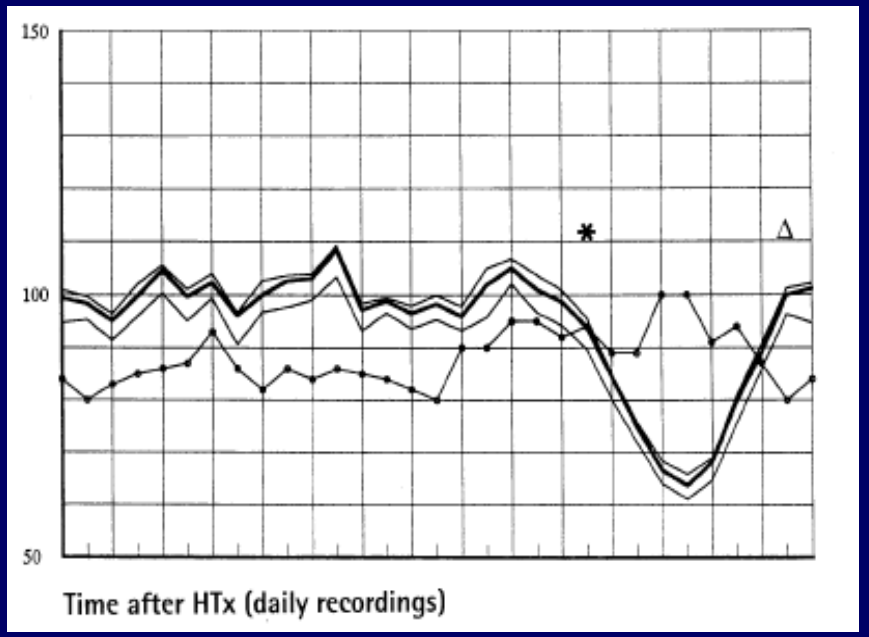






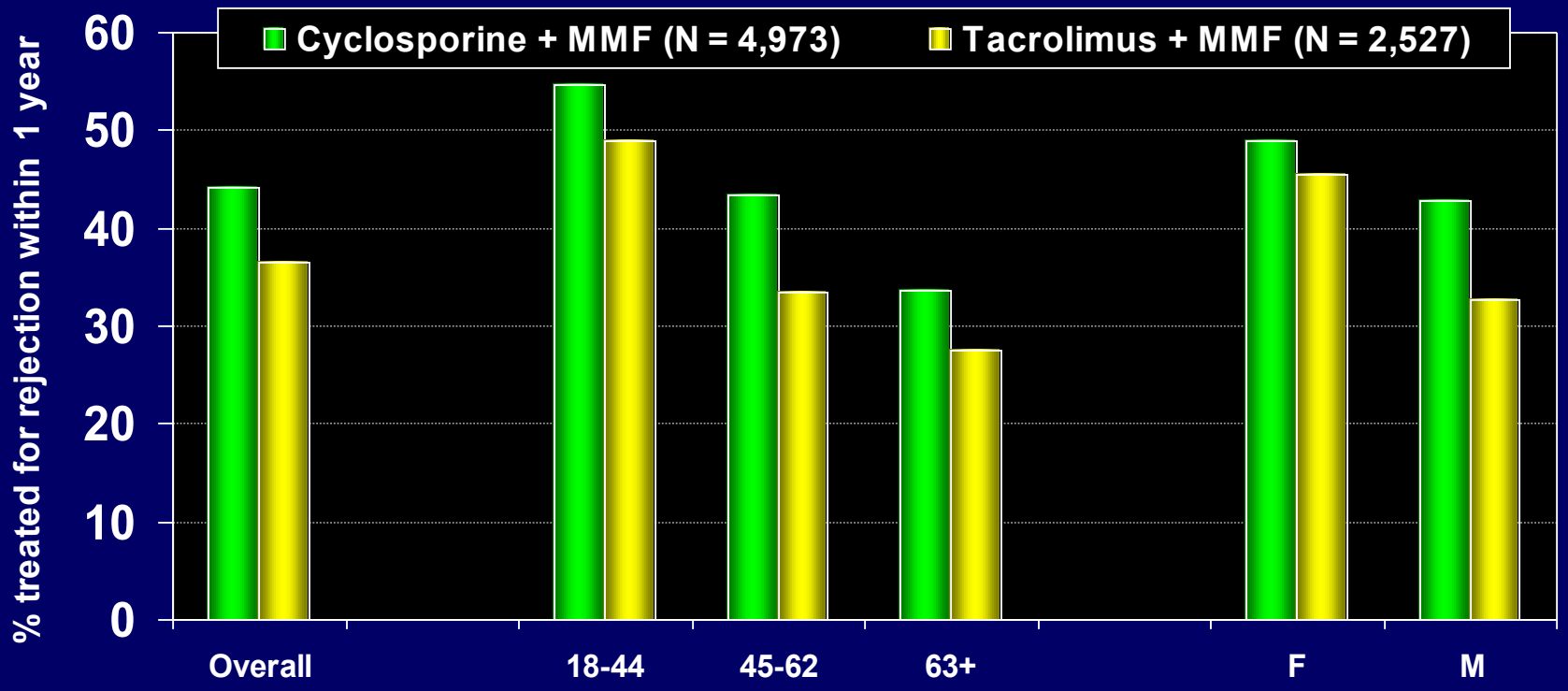
IMEG





PERCENTAGE OF ADULT HEART TRANSPLANT RECIPIENTS TREATED FOR REJECTION IN 1ST YEAR

(Stratified by Maintenance Immunosuppression (Transplants: January 1, 2000 - June 30, 2005



Overall: p<0.0001

18-44: p<0.0001

Male: p<0.0001

NOTE: There were 1,119 patients with cyclosporine+AZA and 138 with tacrolimus+AZA. These groups were excluded due to small numbers.

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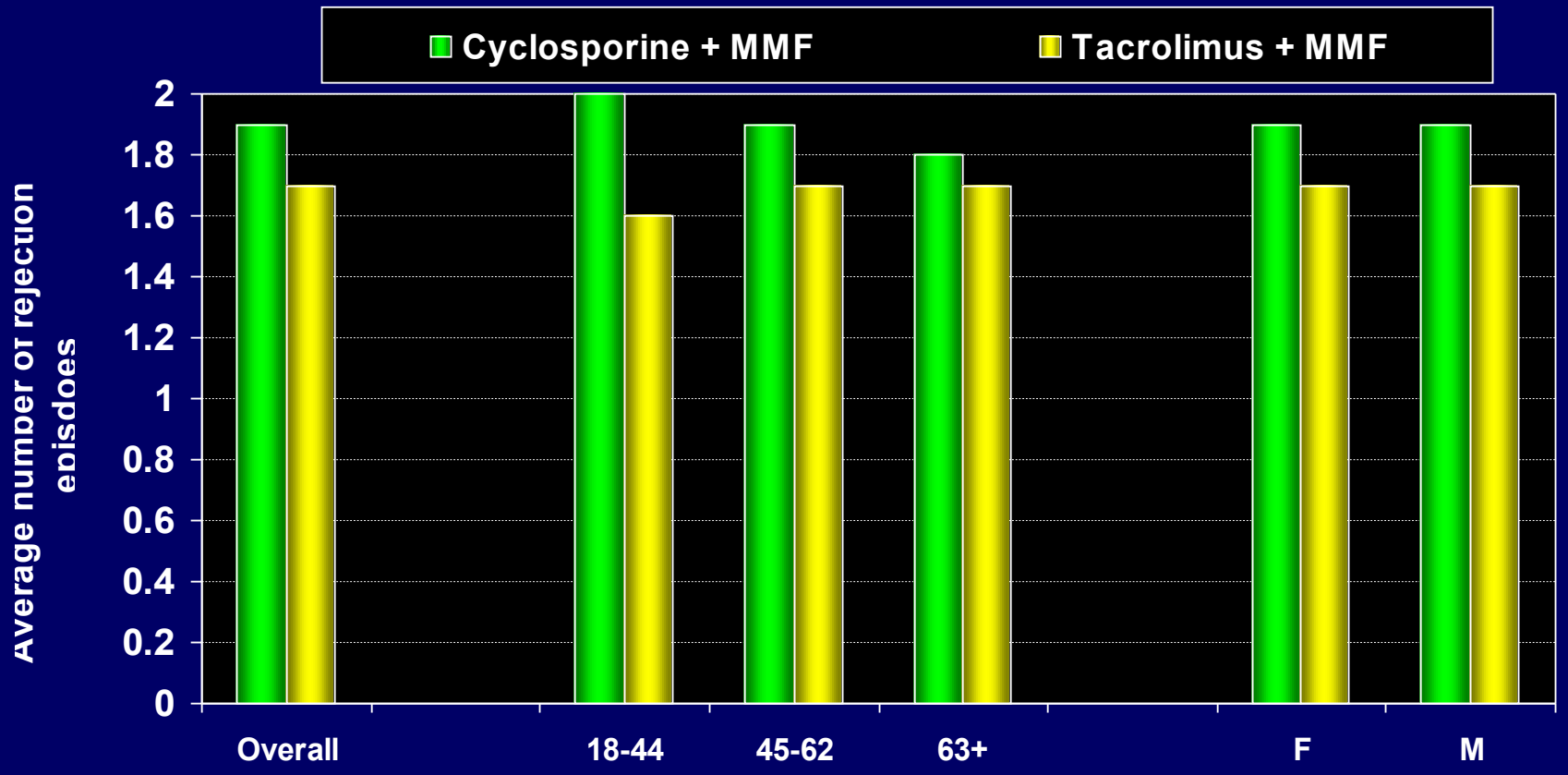
NUMBER OF REJECTION EPISODES FOR ADULT HEART TRANSPLANT RECIPIENTS TREATED FOR REJECTION IN 1ST YEAR

(Stratified by Maintenance Immunosuppression (Transplants: January 1, 2000 - June 30, 2005



Overall: p=0.0378
18-44: p=0.049

NOTE: Cyclosporine+AZA and tacrolimus+AZA were excluded due to small numbers.

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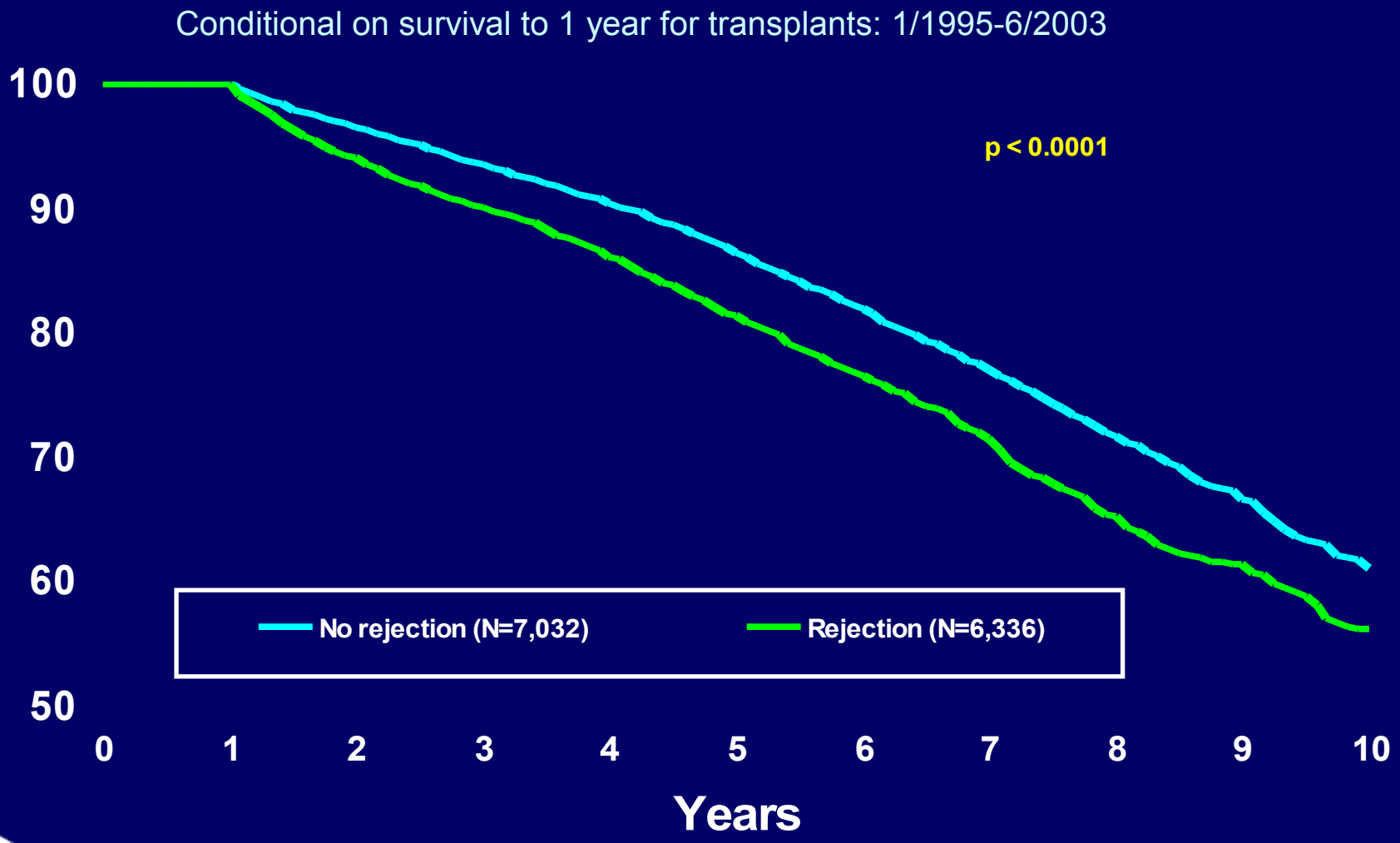
ADULT HEART TRANSPLANTATION

Kaplan-Meier Survival Stratified by Rejection Within 1st Year



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2006

J Heart Lung Transplant 2006;25:869-79

General Mechanisms of Action of Immunosuppressive Drugs

Small Molecules

- CsA, tacrolimus (FK506)
  - Inhibition of calcineurin phosphatase
- Mycophenolate mofetil (MMF)
  - Inhibition of inosine monophosphate dehydrogenase (IMPDH)
- Sirolimus
  - Inhibition of mTOR1 and 2
- Steroids
  - Pleiotropic effects including blocking activation of nuclear factor-kappa B (NF-κB)

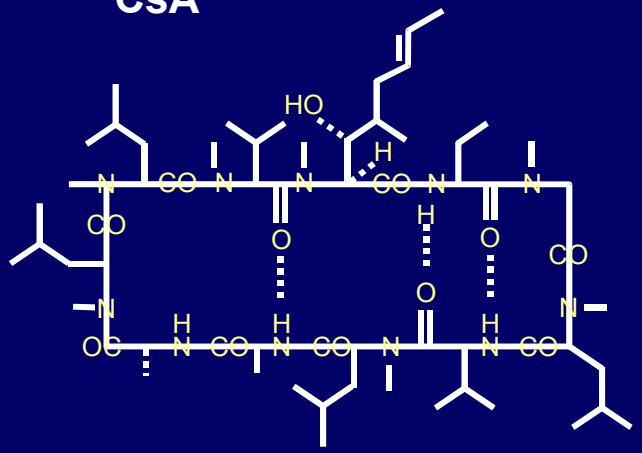
Available immunosuppressive agents

	Calcineurin inhibitors	Inosine monophosphate dehydrogenase (IMPDH) Inhibitors	Proliferation signal inhibitors	Antibody
Novartis	Ciclosporin (Neoral)	Enteric-coated mycophenolate sodium (*myfortic*)	Everolimus (Certican)	Basiliximab (Simulect)
Astellas	Tacrolimus (Prograf)			
Roche		Mycophenolate (Cellcept)		
Wyeth			Sirolimus (Rapamune)	
Other	Generic ciclosporin	Azathioprine (Imuran)		Thymoglobulin Anti-thymocyte globulin (ATGAM) OKT3

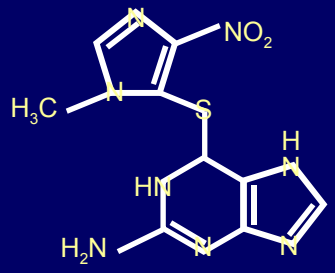
Danovitch GM. *Handbook of Kidney Transplantation 4th Edition*, Lippincott Williams & Wilkins 2005

Structures of Small Molecule Immunosuppressive Drugs

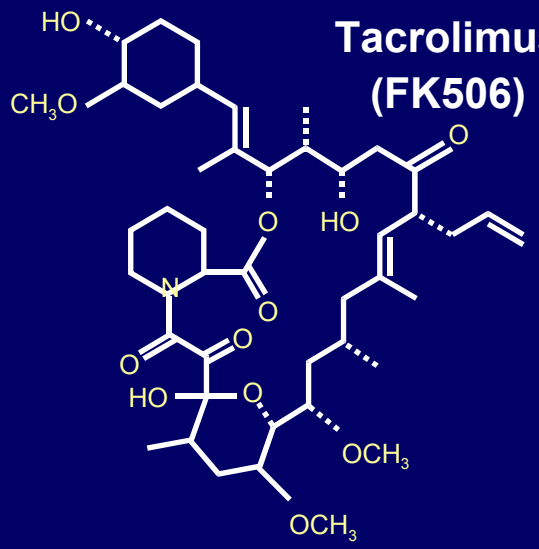
CsA

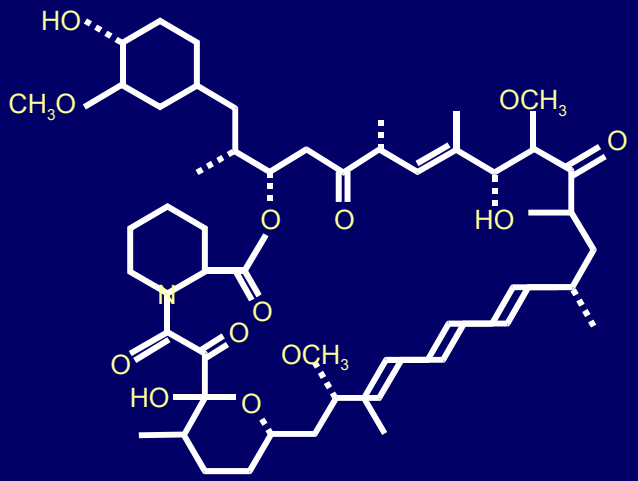


AZA

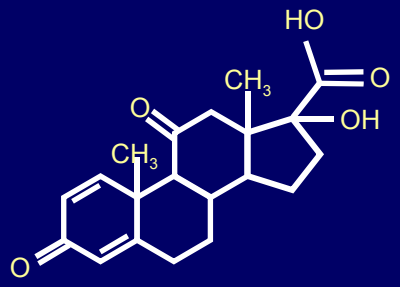


Tacrolimus (FK506)





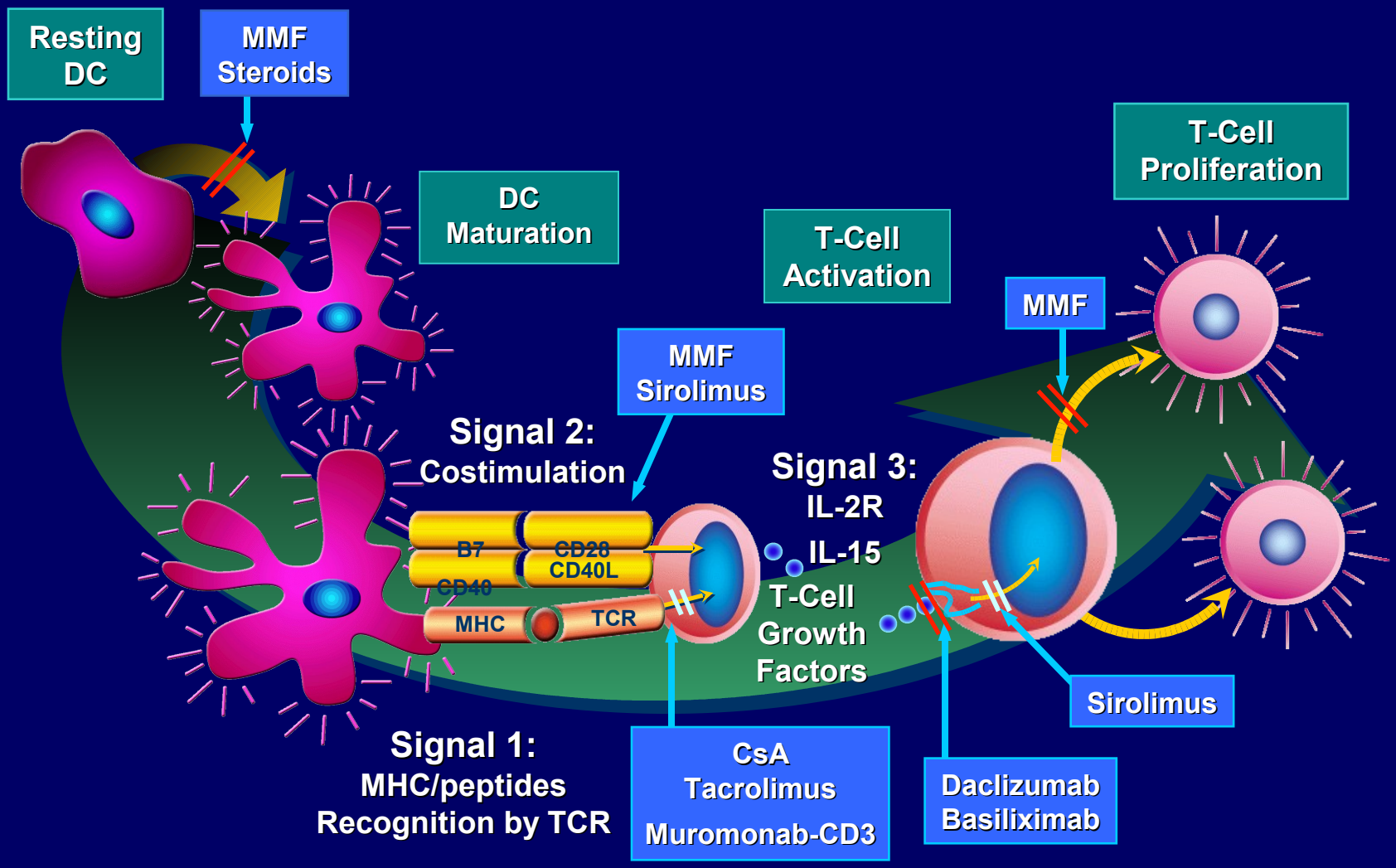
Sirolimus



Prednisone

Mycophenolic Acid Morpholinoethyl Ester (MMF)

Mechanisms of Action



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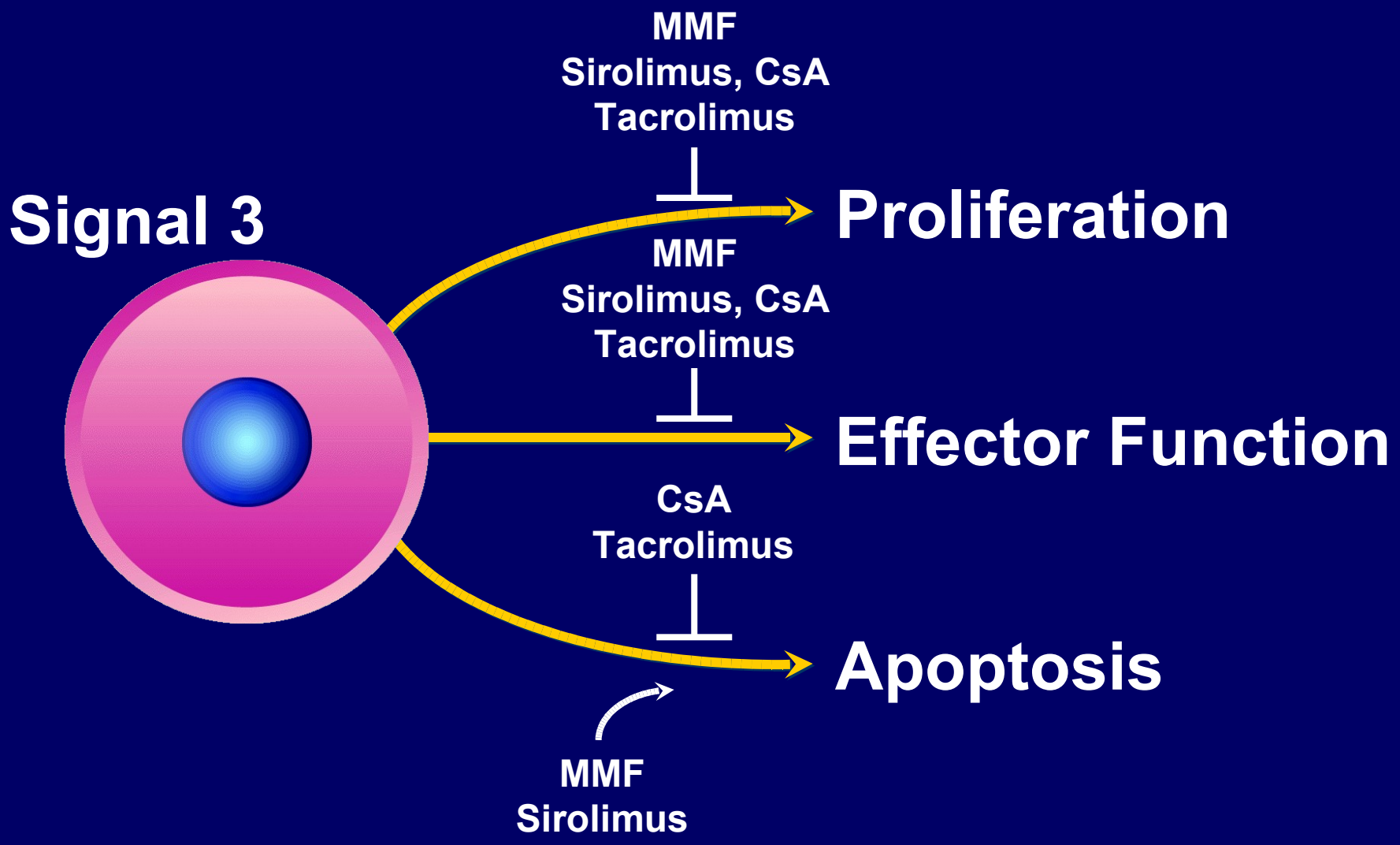
Composite Downstream Effects of Immunosuppressants



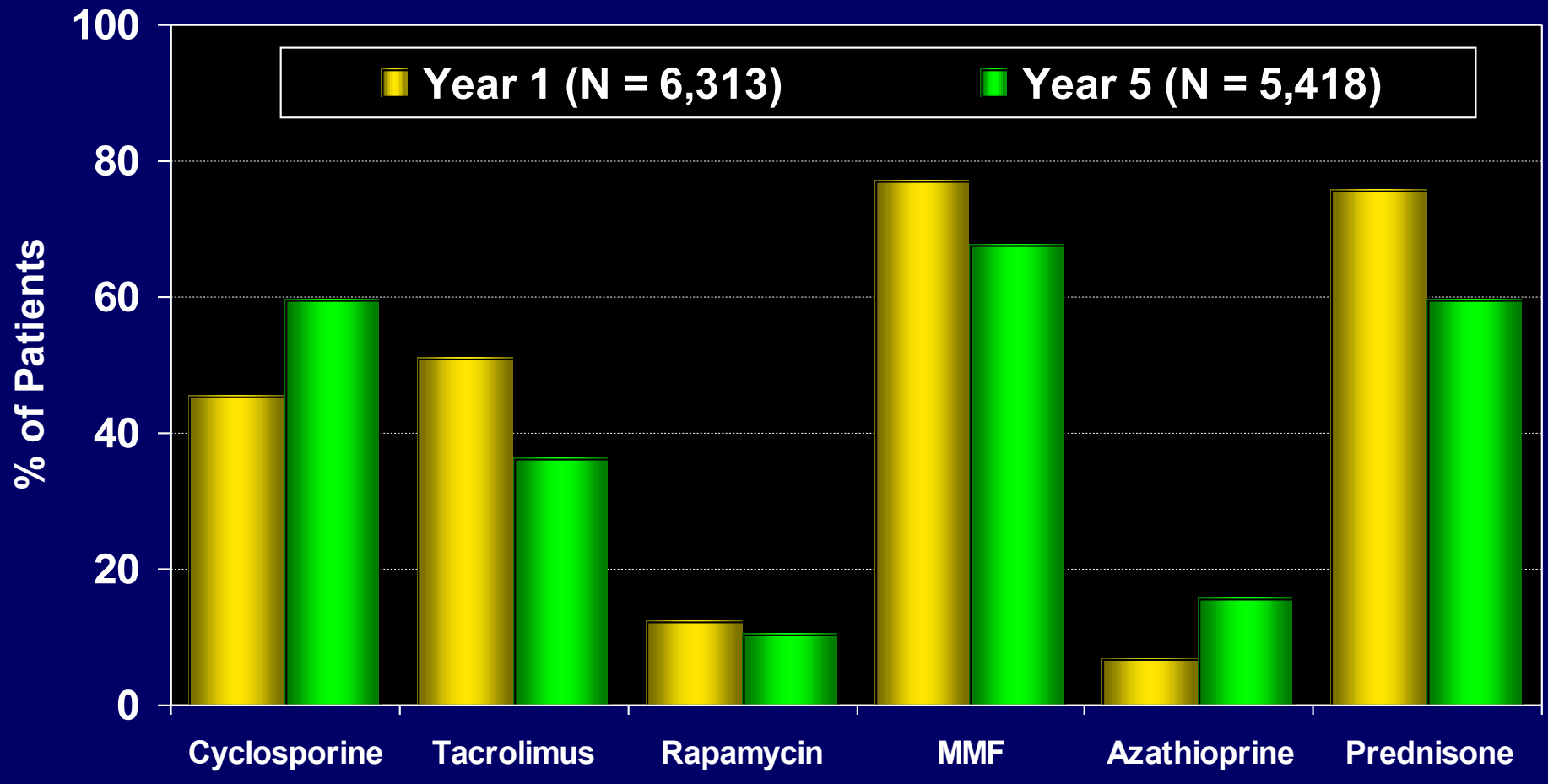
Downstream Effects

	CsA	Tacrolimus	MMF	Sirolimus
T-cell proliferation	↓	↓	↓	↓
T-cell effector functions	↓	↓	↓	↓
Cytokine expression	↓	↓	–	–
Cytokine effects	–	–	↓	↓
Apoptosis of activated T cells	↓	↓	↑	↑
TGF-β induction	↑	↑	–	↑

ADULT HEART RECIPIENTS

Maintenance Immunosuppression at Time of Follow-up

((Follow-ups: January 2003 - June 2006



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

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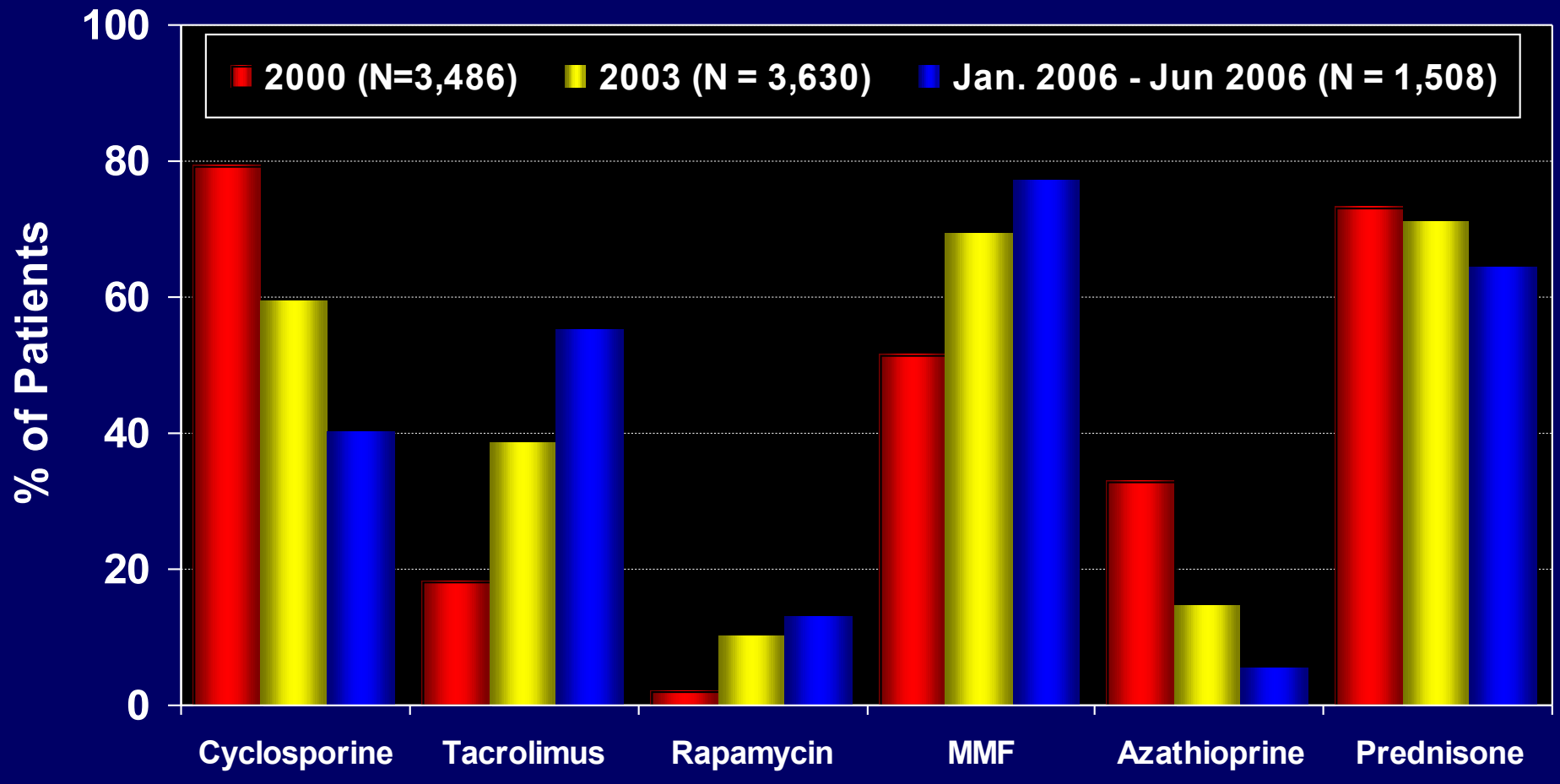
ADULT HEART RECIPIENTS

Maintenance Immunosuppression at Time of 1 Year Follow-up



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NOTE: Different patients are analyzed in each time frame.

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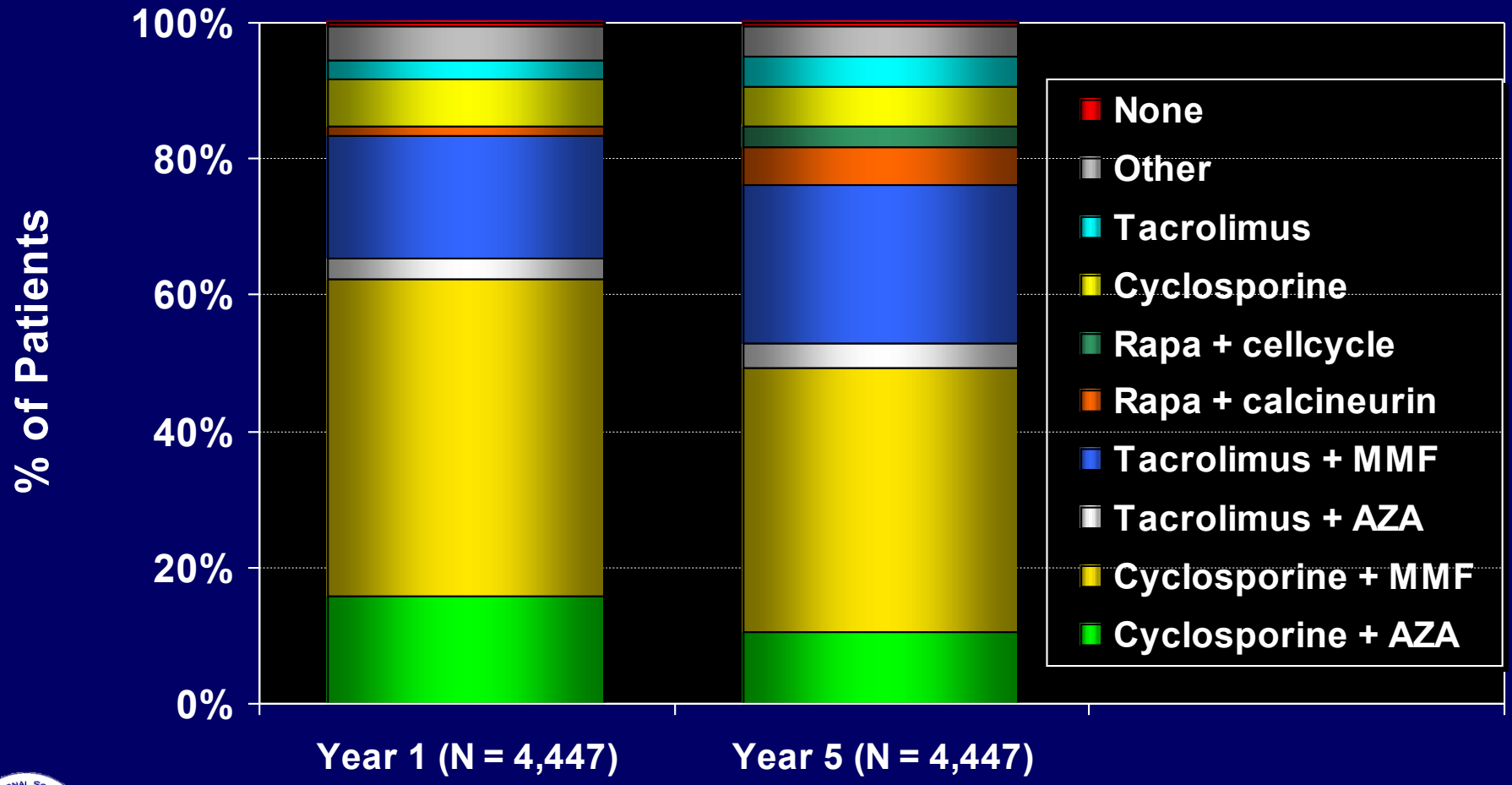
??Why Poly-Drug Use

1) Side effects of one drug can be avoided / decreased!!

2) Drug-Combinations may have positive effects/Synergism

ADULT HEART RECIPIENTS

Maintenance Immunosuppression Drug Combinations at Time of Follow-up
For the Same Patients
((Follow-ups: January 1999 - June 2006



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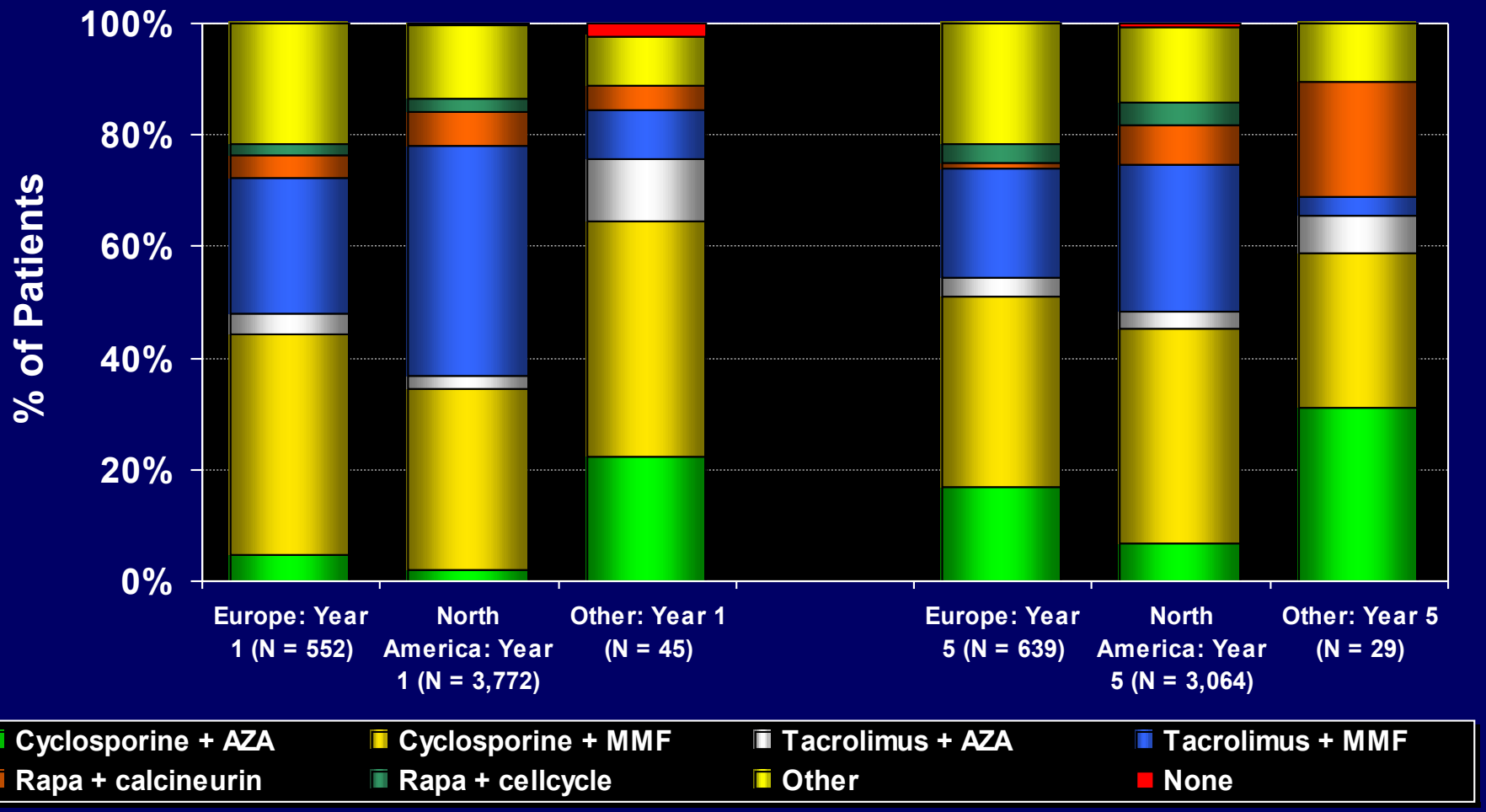
ADULT HEART RECIPIENTS

Maintenance Immunosuppression Drug Combinations at Time of Follow-up

((Follow-ups: January 2004 - June 2006



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NOTES: Different patients are analyzed in Year 1 and Year 5.

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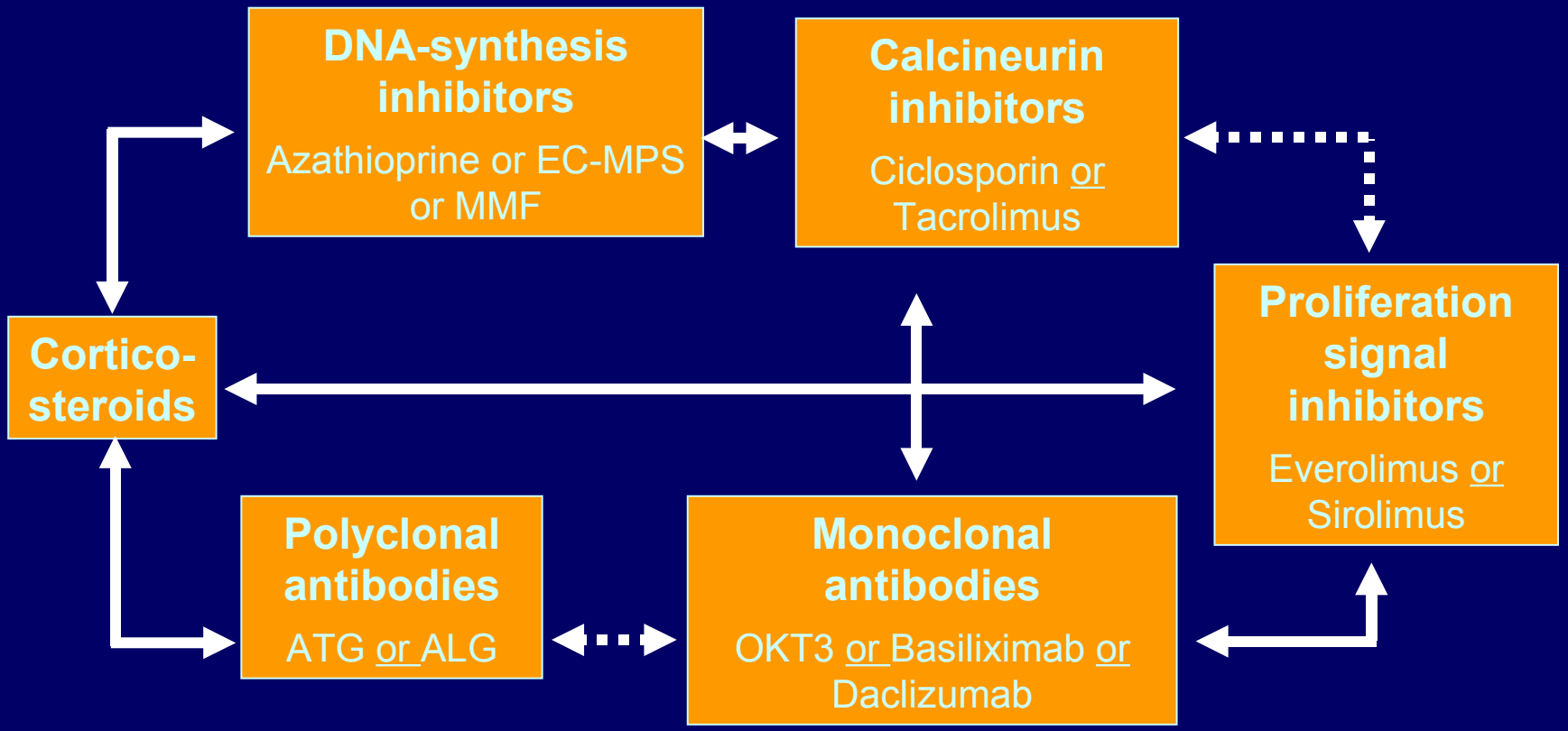
Combinations of immunosuppressants

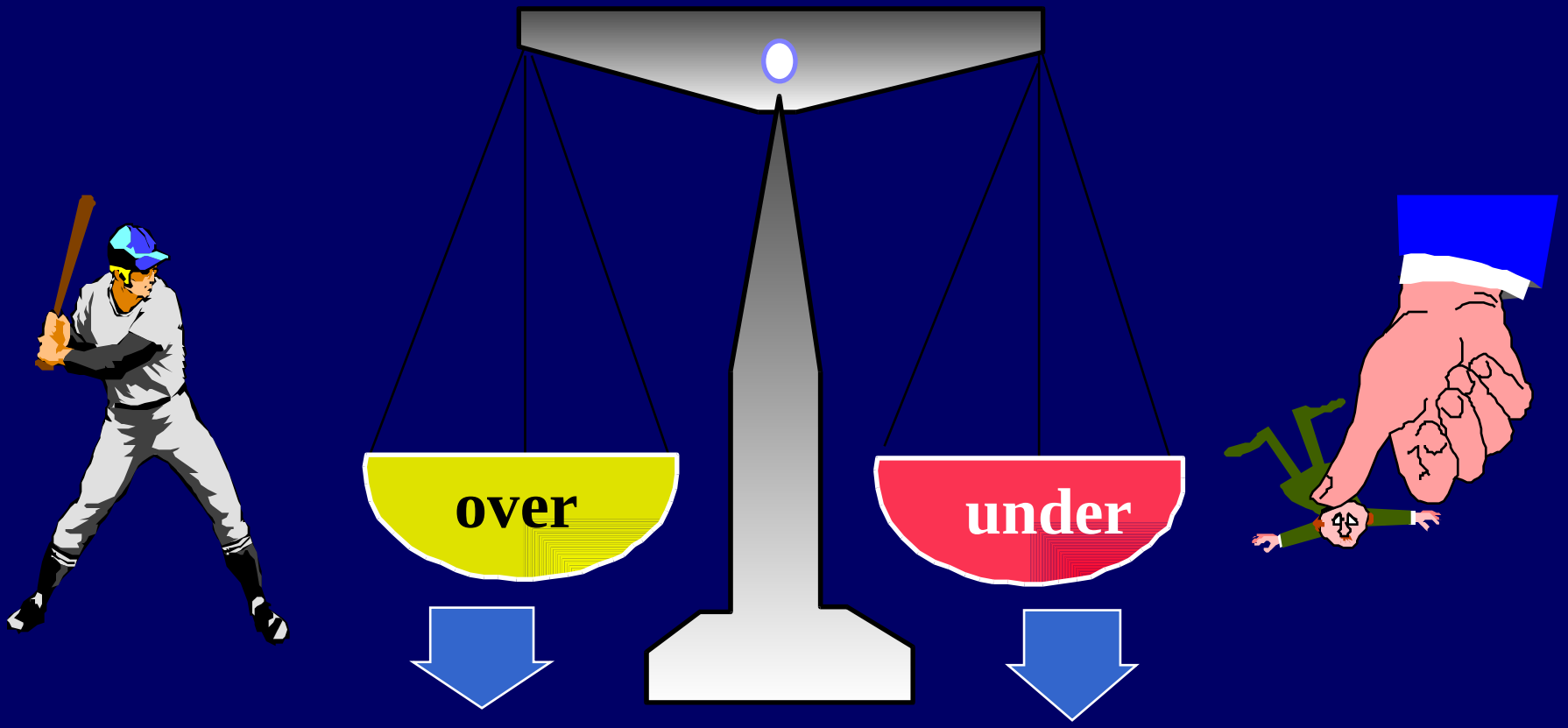


Combination possible: Synergistically effective

Combination possible: Everolimus + CsA + corticosteroids (CsA dose reduction 1 month post-transplant); Sirolimus + CsA + corticosteroids (CsA withdrawal 3 months post-transplant

Vitko S *et al. Am J Transplant* 2004; 4: 626–635; Mulay AV *et al. Am J Transplant* 2005; 5: 1748–56; Certican® (everolimus) Prescribing Information, December 2003; Rapamune® (sirolimus) Prescribing Information, October 2006.

Balance of Immunosuppression



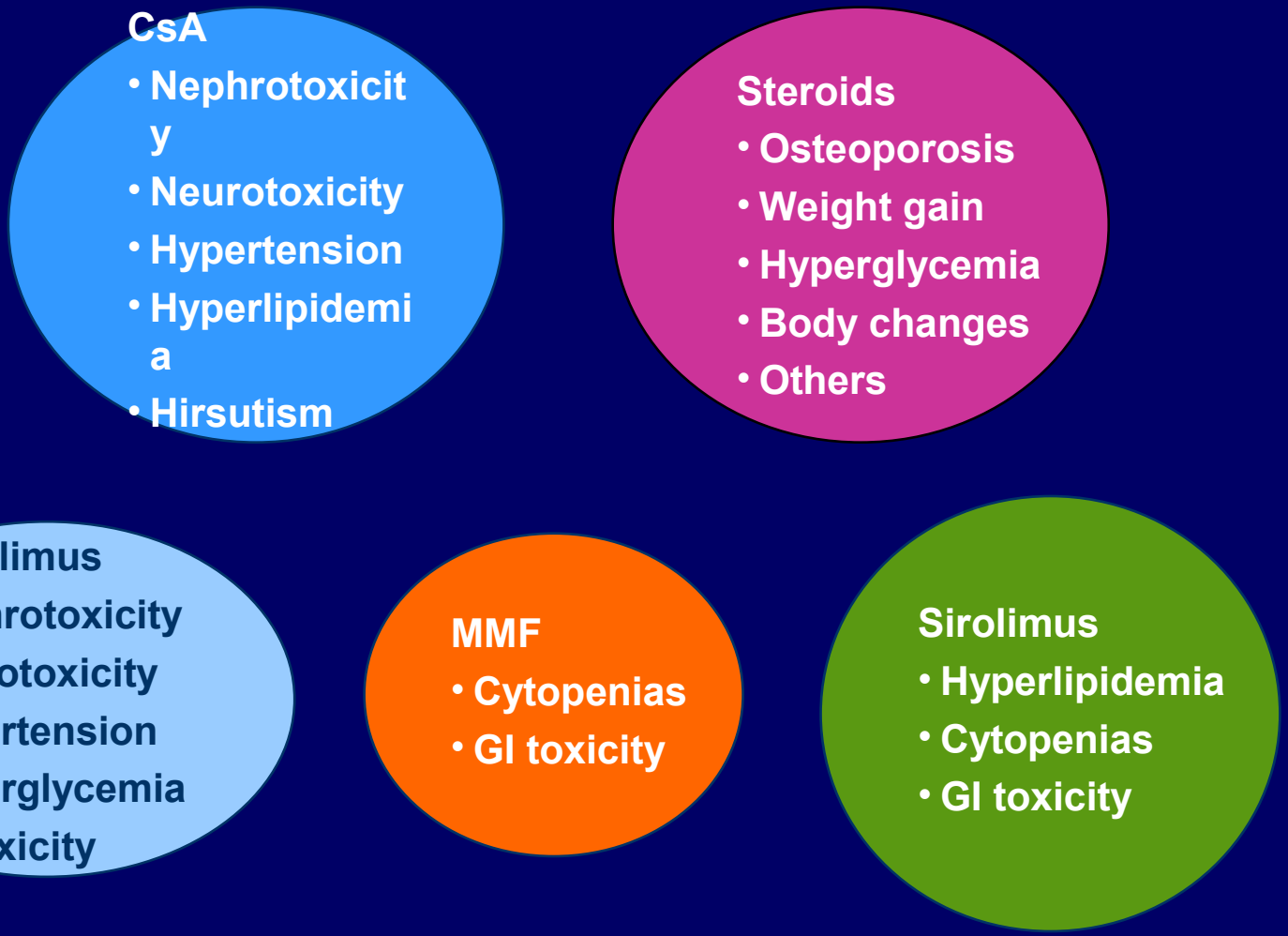
Infections (viral)
Lymphomas (PTLD)

Acute Rejection
chronic rejection (CAD, BOS)

Major side effects

	CsA	Tac	Aza	MMF	Rapa	steroids
nephrotocixity	+++	+++			!!!	
neurotoxicity	+	++				
gastrointestinal				++	+	+
Diabetes		++				+
hyperlipidemia	++	+			+++	++
Bone marrow			+++	+	++	
hypertensive	+++	++				+
hirsutism	++					
gingivahyperplasia	++					
hepatotoxicity	+	+	++			

Immunosuppressive Drug Toxicities



Safety of Immunosuppressants: Drug Interactions With CYP450

- Commonly encountered drugs that may affect CYP450
  - Azole antifungals: fluconazole, clotrimazole
  - Macrolide antibacterials: erythromycin, clarithromycin
  - Calcium channel blockers: nifedipine, verapamil
  - Anticonvulsants: phenobarbital, carbamazepine

Mignat C. *Drug Saf.* 1997;16:267-278.

Interactions Between Immunosuppressants

	Interaction With	Result
CsA	**Sirolimus**	**Increased bioavailability**
CsA	**MMF**	**Decreased MPA bioavailability**
Tacrolimus	**MMF**	**Increased MPA bioavailability**
Sirolimus	**MMF**	**?**
Sirolimus	**Tacrolimus**	**?**

Mignat C. *Drug Saf*. 1997;16:267-278.
Dominguez J. *Transplantation*. 2000;70:1244-1247.
van Gelder T et al. *Ther Drug Monit*. 2001;23:119-128.

Immunosuppressive Management Vienna

	week1	weeks 2-4	months2-6	>6 months
ATG (Thymoglobuline) 1-2.0mg/kg 3-7 days				
Cyclosporine	delay until days 2-7	target level: 200-250 ng/ml	target level: 150-200 ng/ml	target level: 100-150 ng/ml
Tacrolimus	delay until days 2-7	target level: 12-15 ng/ml	target level: 10-15 ng/ml	target level: 5-10 ng/ml
Mycophenolate-Mofetil	2x500mg	2x1000mg	EC-MPS	2x720mg
Sirolimus				target level: 5-10 ng/ml
Everolimus1.5mg/d	start day 3	target level: 3-8 ng/ml		
Steroids	500mg iv intra OP 3x125mg iv over first 24 h The pause until day 7	0.2mg/kg/d	0.15.0.2mg/kg/d	0.1mg/kg/d

Utility of the Cylex Assay in Cardiac Transplant Recipients

Sachin Gupta, MD,[a] Joshua D. Mitchell, MD,[b] David W. Markham, MD,[a] Pradeep P. A. Mammen, MD,[a] Parag C. Patel, MD,[a] Patricia A. Kaiser, RN,[c] Peter Stastny, MD,[d] W. Steves Ring, MD,[b] J. Michael DiMaio, MD,[b] and Mark H. Drazner, MD, MSc[a]

Background: Although the Cylex immune assay has been proposed as a means of tailoring immunosuppression after organ transplantation, there are limited data regarding its utility in cardiac transplant recipients. Therefore, we sought to determine the utility of the Cylex assay in assessing the risk of infection or rejection in cardiac transplant recipients.

Methods: This study is a retrospective review of the clinical course of all adult cardiac transplant recipients who underwent a Cylex assay at UT Southwestern Medical Center between January 2004 and September 2007.

Results: One hundred eleven patients were free of significant rejection or infection at the time of the first Cylex assay. Most patients (92%) were >1 year post-transplant. Over the next 157 ± 41 (mean ± SD) days, 2 patients had 3 episodes of rejection requiring therapy and 7 patients had 8 infections requiring therapy. The Cylex responses ranged from 17 to 894 ng/ml. No correlation was observed between the baseline Cylex response and subsequent risk of either infection or rejection within 6 months. Lower white blood cell count and African American ethnicity were correlated with a lower Cylex response.

Conclusions: In this study, the Cylex assay had limited utility as an adjunct to routine clinical evaluation in assessing risk of infection or rejection in cardiac transplant recipients. J Heart Lung Transplant 2008; 27:817–22.

MMF After Cardiac Transplantation

Study Design

- Twenty-eight centers in Australia, Europe, and North America
- Three year, double blind, active control
- Randomized prior to transplantation

Patients

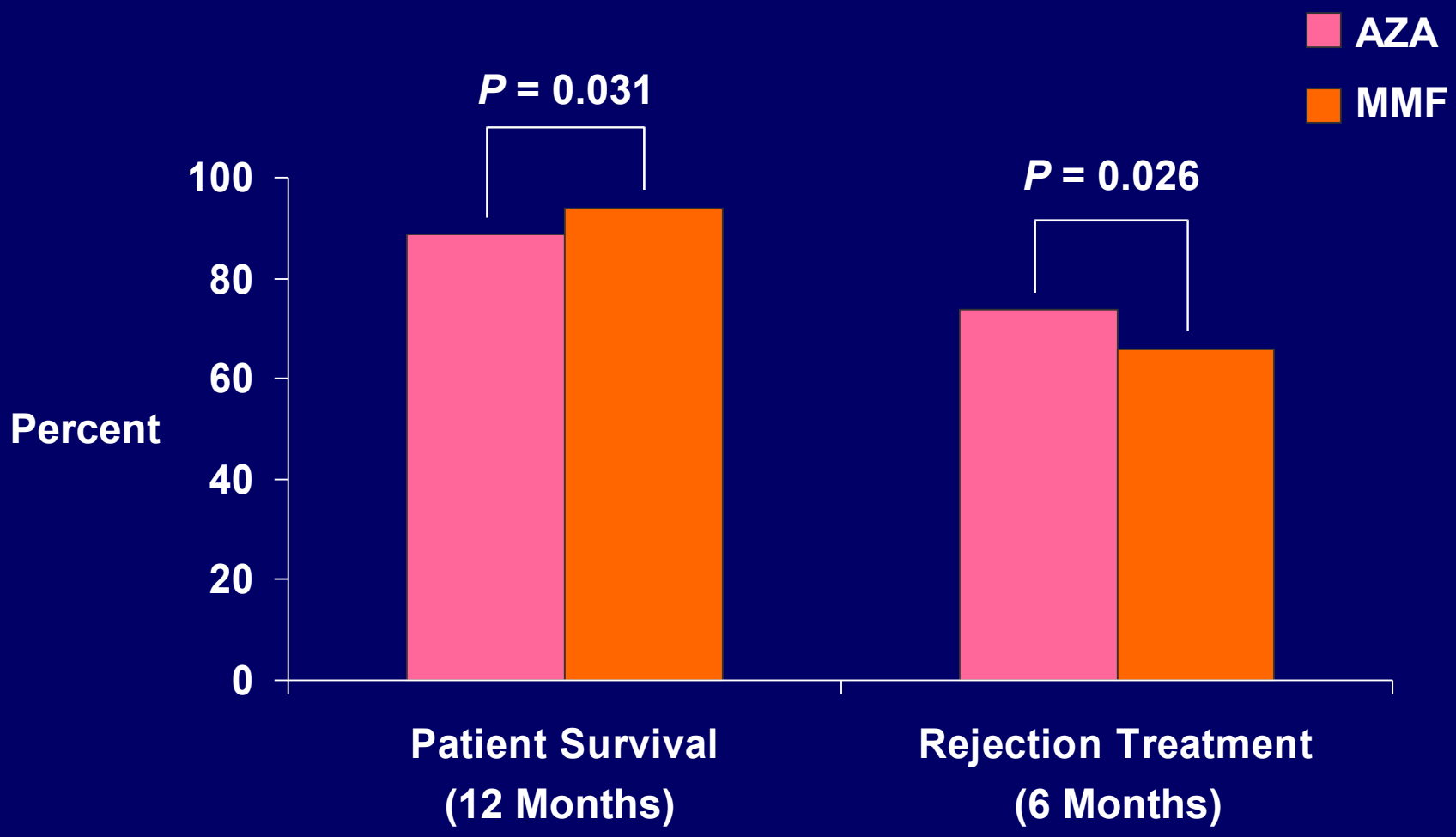
- First cardiac transplant recipients enrolled between February 1994 and July 1995 (N = 650)
- Eleven percent of patients withdrew before receiving study drug
- Rejection and survival data obtained for 6 and 12 months, respectively

Immunosuppression

- MMF (n = 289) or AZA (n = 289)
- CsA and steroids
- ± antibody induction

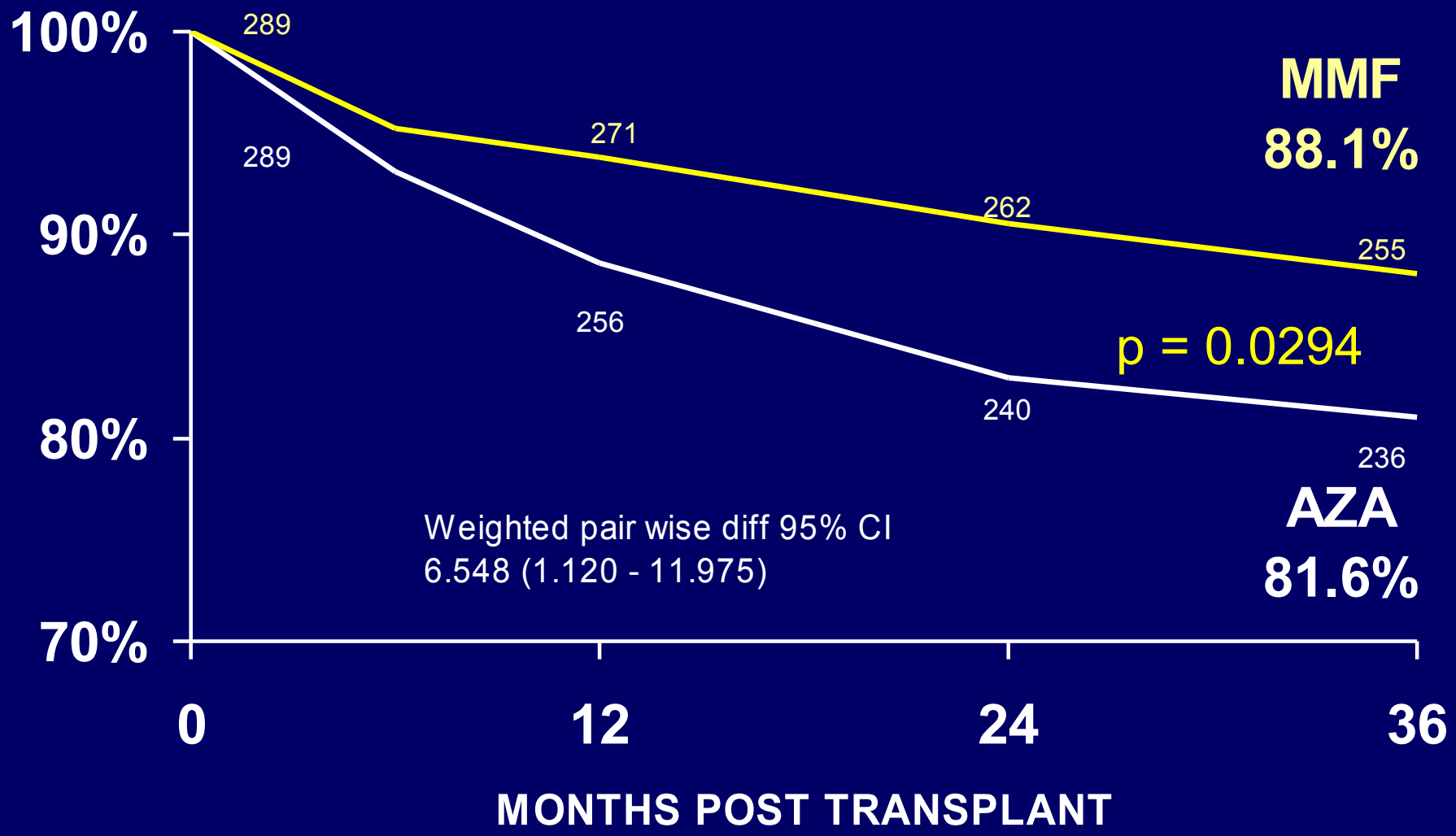
Kobashigawa J et al. *Transplantation.* 1998;66:507-515.

MMF After Cardiac Transplantation



Kobashigawa J et al. *Transplantation.* 1998;66:507-515.

MMF-pivotal trial
Survival



Kobashigawa et al, TX 1998

Late Conversion From MMF to AZA After Cardiac Transplantation

Study Design

- Open-label, nonrandomized

Patients

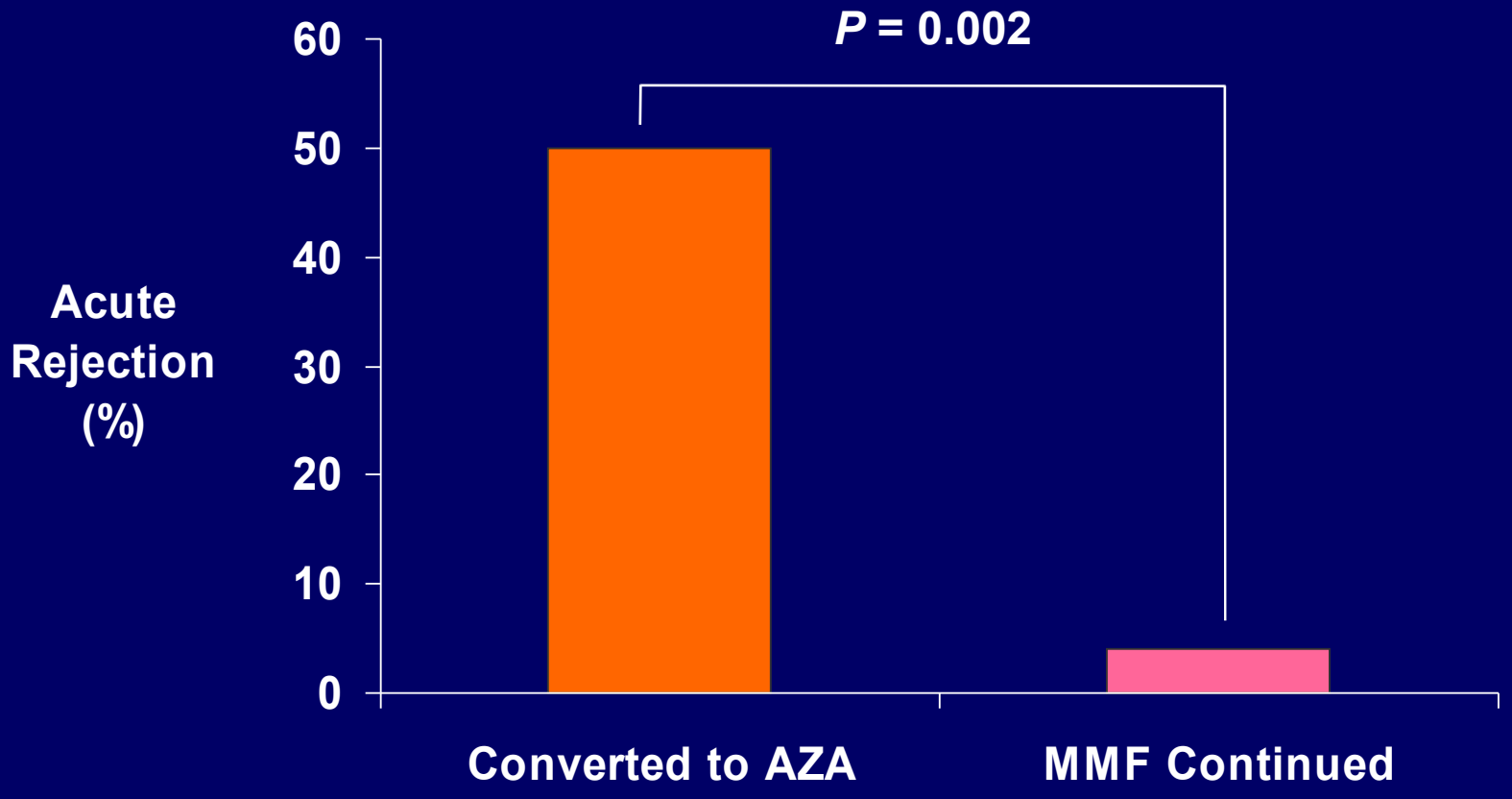
- Stable heart transplant patients on long-term MMF therapy (N = 43)

Immunosuppression

- Patients continued on MMF therapy (n = 23)
- Patients were converted to AZA after an average of 41 months on MMF (n = 20)

Taylor DO et al. *Clin Transplant.* 1999;13:296-299.

Late Conversion From MMF to AZA After Cardiac Transplantation



Taylor DO et al. *Clin Transplant.* 1999;13:296-299.

Tacrolimus vs CsA in Cardiac Transplantation

Study Design

- Retrospective
- Joint ISHLT/UNOS Thoracic Registry data analyzed for effects of tacrolimus vs CsA in patients discharged on one of these two agents

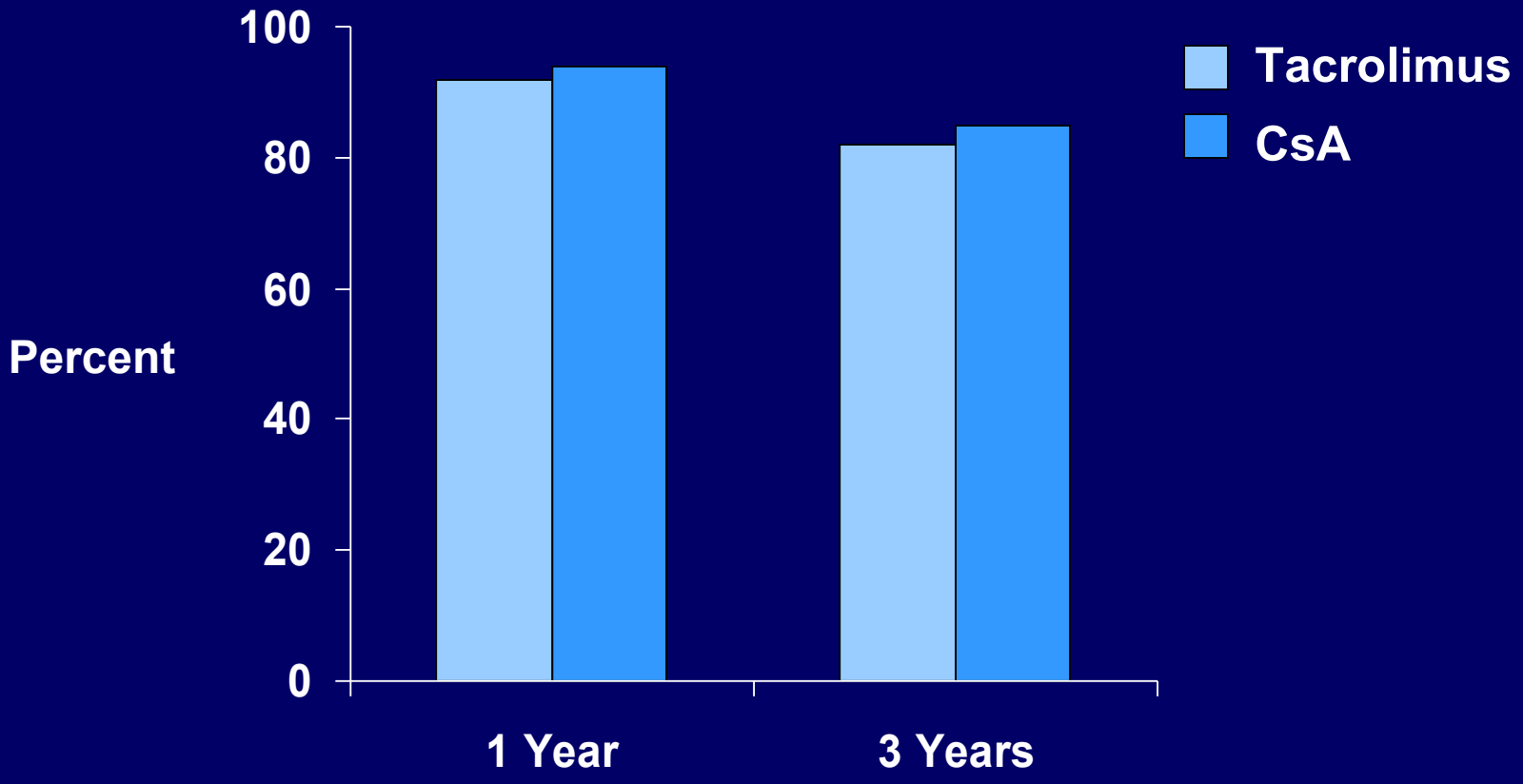
Patients

- Cardiac transplant patients receiving CsA at time of discharge (n = 7,247 transplanted from 1994 to 1998)
- Cardiac transplant patients receiving tacrolimus at time of discharge (n = 396 transplanted from 1994 to 1998)

Hosenpud JD, Bennett LE. *J Heart Lung Transplant.* 2001;20:161-162.

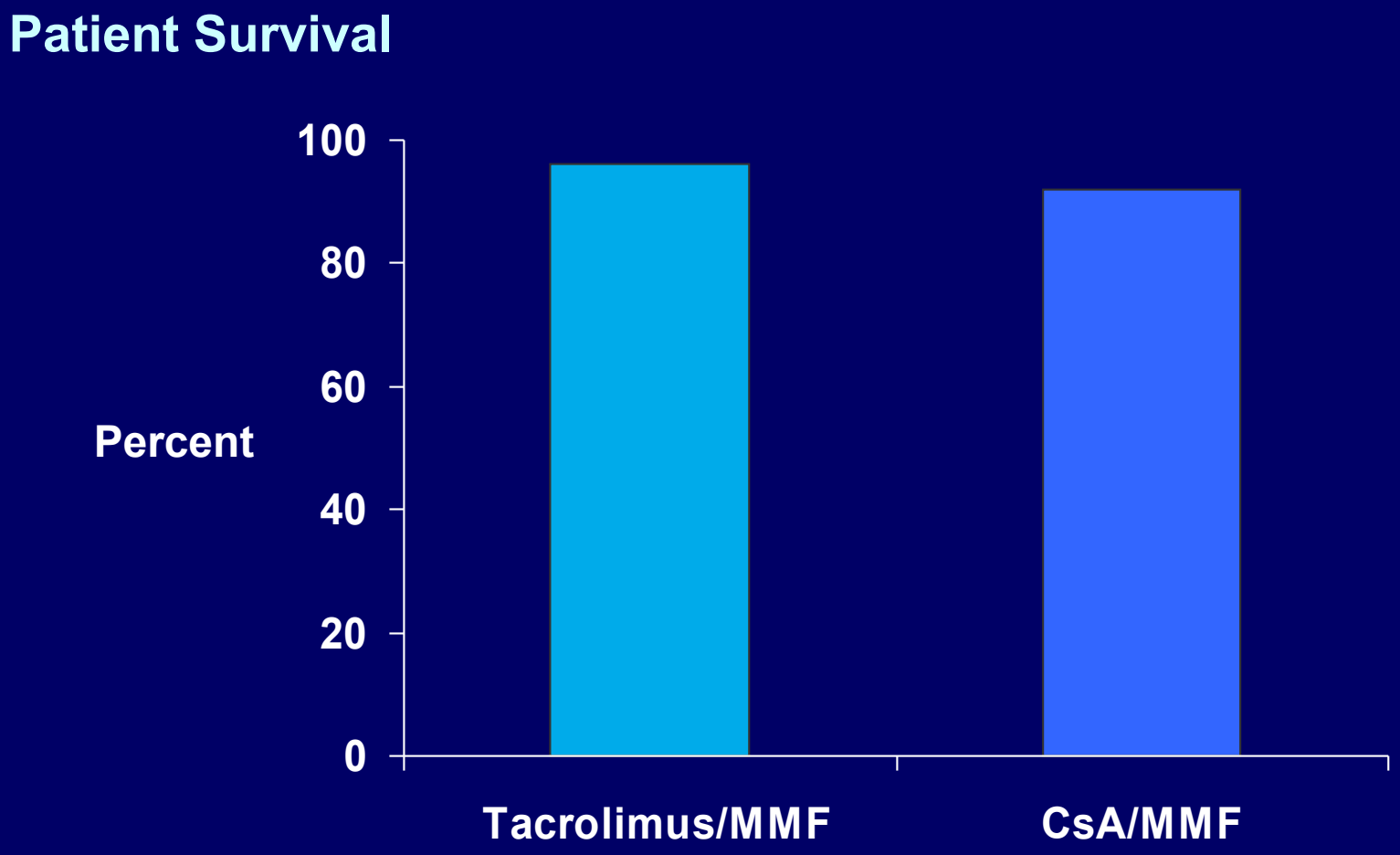
Tacrolimus vs CsA in Cardiac Transplantation

Patient Survival



Hosenpud JD, Bennett LE. *J Heart Lung Transplant.* 2001;20:161-162.

Tacrolimus/MMF vs CsA/MMF in Cardiac Transplantation



Groetzner J et al. *J Heart Lung Transplant.* 2001;20:191.

- Superior prevention of acute rejection by TAC vs CSA in heart transplant recipients – a large European trial

- Grimm M . Am.J.Transpl. 2006 Jun;6(6): 1243-5

During antibody induction, pts. were randomized (1:1)

TAC+AZA+ST n=157 pt.

CSA+AZA+ST n=157 pt.

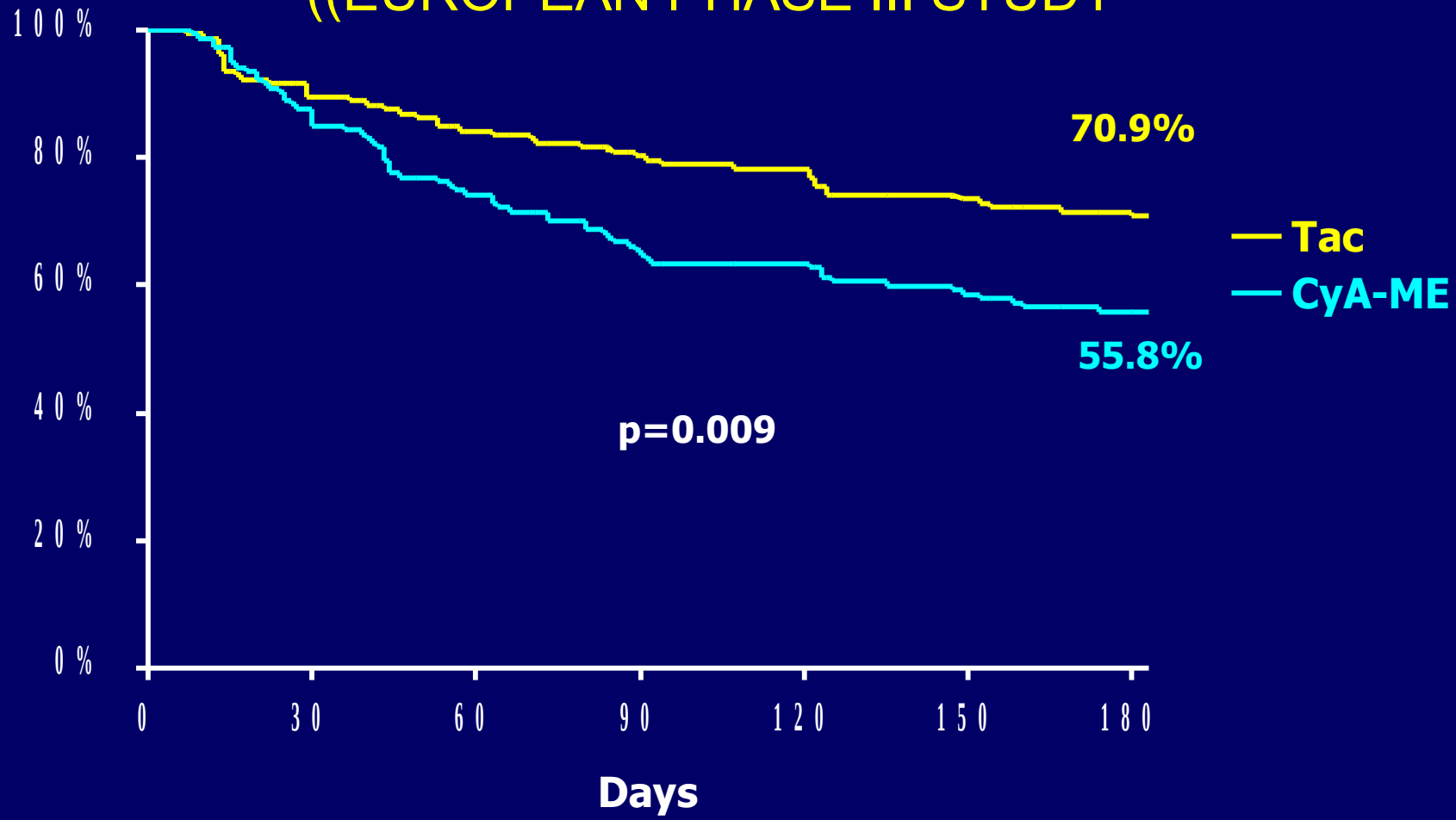
Episodes of acute rejection were assessed by protocol biopsies

(Local and blinded central evaluation)

	TAC	CSA
• Patient / graft survival (18 m)	92.9%	89.8% n=NS
• Incidence of first biopsy proven • Acute rejection grade =/ 1B (6 m)	54%	66.4% **P=0.029**
• Incidence of first biopsy proven • Acute rejection grade =/ 3A (6 m)	28%	42% **P=0.013**

TAC vs. CsA
Freedom from AR at Month 6

((EUROPEAN PHASE III STUDY



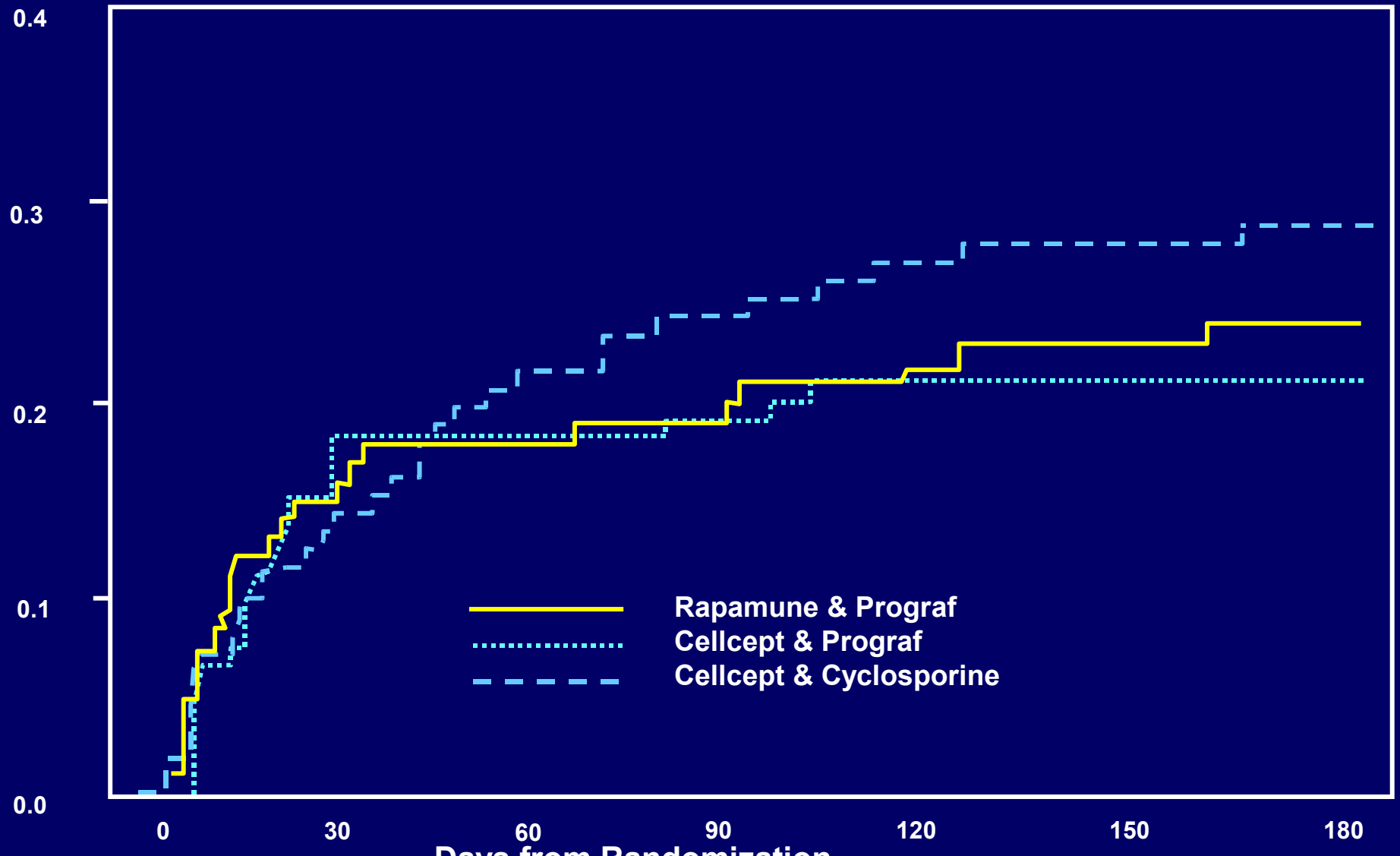
Grimm et al. AJT 2006

Generalized Wilcoxon test

	TAC	CSA	P
• New onset diabetes	20.3%	10.5%	0.05
• Post Tx hypertension	65.6%	77.7%	0.05
• Dyslipidemia (6 months)	28.7%	40.1%	0.05
• Infections		similar	
• Renal function (18 months)		similar	

arm Trial Tac-Srl/Tac-MMF/Csa-MMF 3

Probability of Rejection ≥ Grade 3A



Kobashigawa et al, AJT 2006

Tacrolimus or Cyclosporine :which is the better partner for MMF in heart transplant recipients?

Meiser BM et.al.

Transplantation .2004 Aug 27;78(4):591-8

SINGLE-CENTER SUDY

Randomized ,prospective,open-label,controlled

60 PT.

MMF+TAC +ST n=30

MMF+CSA +ST n=30

:Target blood trough levels

- TAC -10-15 ng/ml
- CSA -100-300 ng/ml
- MMF – 1.5-4.0 microg/ml

Baseline characteristics were well balanced

- All pt. were successfully withdrawn from corticosteroid within 6 months

Freedom from acute Rj.-significantly (higher in TAC group (p=0.0001

- Incidence of ARE per 100 pt. days
- TAC+MMF 0.03
- CSA+MMF 0.15
- P=0.00007

Overall pt. survival during follow-up was similar

93% vs.90%

- To achieve the targeted MMF blood levels a significantly lower dose of MMF was required for TAC vs. CSA

- GRAFG VASCULAR DISEASE

- TAC+MMF 1.85 +/- 3.18
- CSA+MMF 3.95+/- 4.8
- P=0.08

Influence of immunosuppression regimen on heart transplantation survival

- Aguero j et.al.
- Transplant Proc . 2006 Oct. ;38(8) :2550-2

Comparing long –term survival in HT Pt depending on the immunosuppression regimen

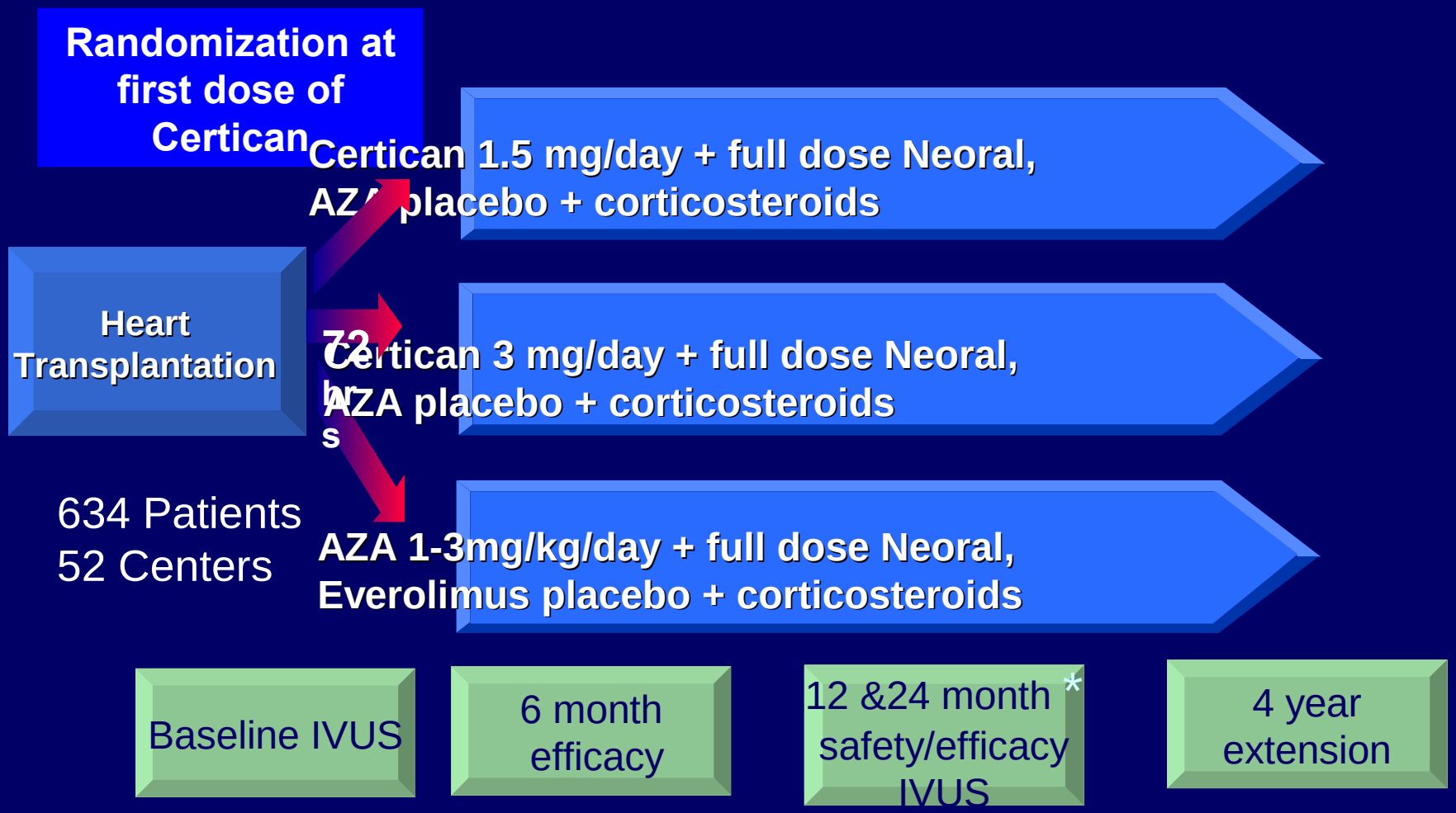
- 317 consecutive HT pt.
- Excluded : pediatric cases
- Combined transplantation
- Retransplantation
- Immunosuppressive regimens with fewer than 10 y

- The survival by groups at the end of follow-up
- OKT3 7 days +CSA +MMF +ST 75.8%
- OKT3 7 days +CSA +AZA +ST 51.2%
- OKT3 10days +CSA +MMF +ST 63.6%
- OKT3 10 days +CSA +AZA +ST 25.3%
- IL-2 antagonist +CSA +MMF +ST 91.2%
- IL-2 antagonist +TAC+MMF +ST 84.6%

Conclusions

- Association between the immunosuppressive regimen and long-term survival
- The best result were obtained with an induction based on IL-2 antagonist
- The maintenance combination we regard as “optimal” based on a combination of CSA, MMF and ST

RAD B253: Study Design



SAMPLE SIZE:

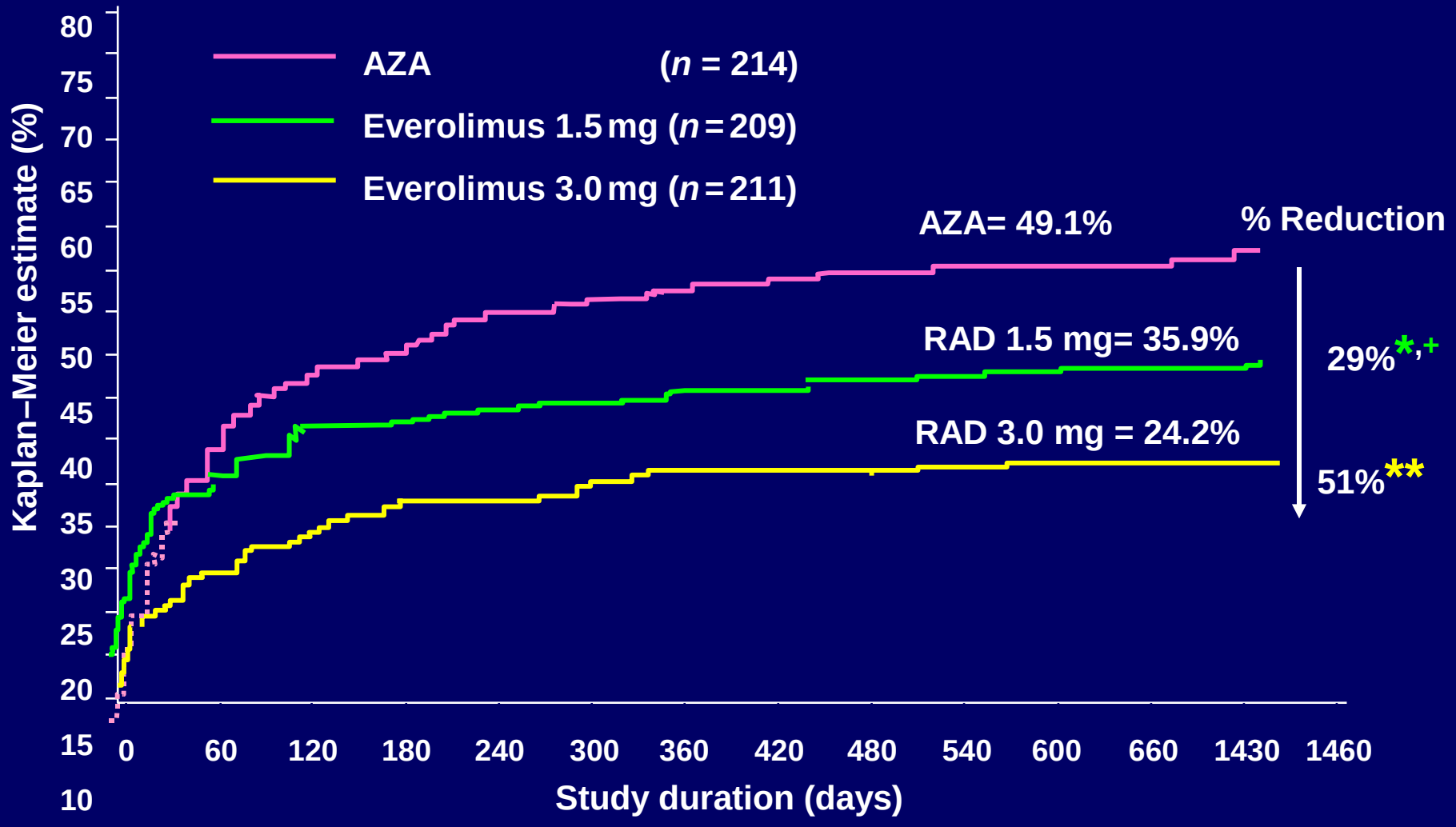
Primary efficacy failure: AZA 45%, Everolimus 30%

210 per treatment arm (two-sided alpha at 2.5%, power 80%)

***Study unblinded at 12 months**

Everolimus Pivotal Trial

Cumulative ISHLT AR Grade ≥ 3A – M 48



*p = 0.006 vs AZA; **p < 0.001 vs AZA; +p = 0.005 vs everolimus 3 mg

Eisen et al, NEJM 2003

Everolimus

Why?

- Synergistic with CNIs (low rates of acute rejection)
- Non-nephrotoxic
- May be CNI and steroid-sparing
- Possibly anti-atherogenic
- Possibly anti-neoplastic

Why not?

- Synergistic with CNIs (enhanced nephrotoxicity)
- Side effects:
  - Hyperlipidemia
  - Bone marrow suppression
  - Impaired wound healing?

Everolimus adverse events profile

Body system	Adverse reaction
Infections and infestations	Viral, bacterial and fungal infections, sepsis
Blood and lymphatic system disorders	Leucopenia, thrombocytopenia, anaemia, coagulopathy
Metabolic and nutrition disorders	Hypercholesterolemia, hyperlipidemia,hypertriglyceridemia
Gastrointestinal disorders	Abdominal pain, diarrhea, nausea, vomiting
Skin and subcutaneous tissue disorders	Acne, surgical wound complication

Patient groups

Pre-Transplant

- Pediatrics
- Old patients (>60,65a)
- Diabetes
- Renal Insufficiency
- Pre-sensitized (PRA's)
- Assist device
- Re-TX

Post-Transplant

- Rejection
- Infection (CMV)
- Diabetes
- Renal Insufficiency
- Hyperlipidemia
- Hypertension
- Vasculopathy
- Cancer

Pediatrics vs. old Patients

Pediatrics

- More rejections
- Growth
- Side effects
- Compliance
- Tac (no hirsutism)
- MMF
- Long term: use Rapa (low CNI or MMF)

Old patients (>60-65)

- Less rejections
- More Infections (CMV)
- Osteoporosis
- Diabetes
- Low CNI
- Lower MMF
- Long term: Rapa mono?

Wean steroids!!

New Era in Immunsuppression

IS scheme for all patients

Individualised Immunsuppression

high → low

preTX rejection markers high (PRA‘s, posXM)

Early rejection

recurrent rejection

Early development of graft vasculopathy or BOS

Late Retransplantation

old Patients

Diabetics

Skin-tumors

Infections

cancer

Side effects

Combination of drugs depending on risk factors

Summary

- Immunosuppression gets more and more complicated
- Trials do not show everything
- IS-therapy will be dynamic not static
- Individualise according to patients needs

Guidelines for the future

- Never change a winning team
- If real problems occurs react quickly
- Life style changes can help too
- Play safe (if you switch)

Trouble makers

(Late Acute Rejection (LAR

Late Rejection pitfalls/troubleshooting

- Reason #1: incompliance
- Reason #2: diarrhea (more than 3 days!!!)
- Mostly low Csa/Tac levels!
- Almost always hemodynamic compromise!!!
- Biopsy!
- Start therapy before diagnosis: 500mg Urbason
- After biopsy result > 0 two more doses!!
- heart failure therapy (inotropic support)
- Often vascular component--> ATG!!

Re-Transplantation

- Low number
- Chronic immunosuppression
- Lower risk for acute rejection?
- Higher risk for vasculopathy??
- Early CNI weaning (renal function side effects)
- Introduce rapa and/or MMF

Long-term Complications

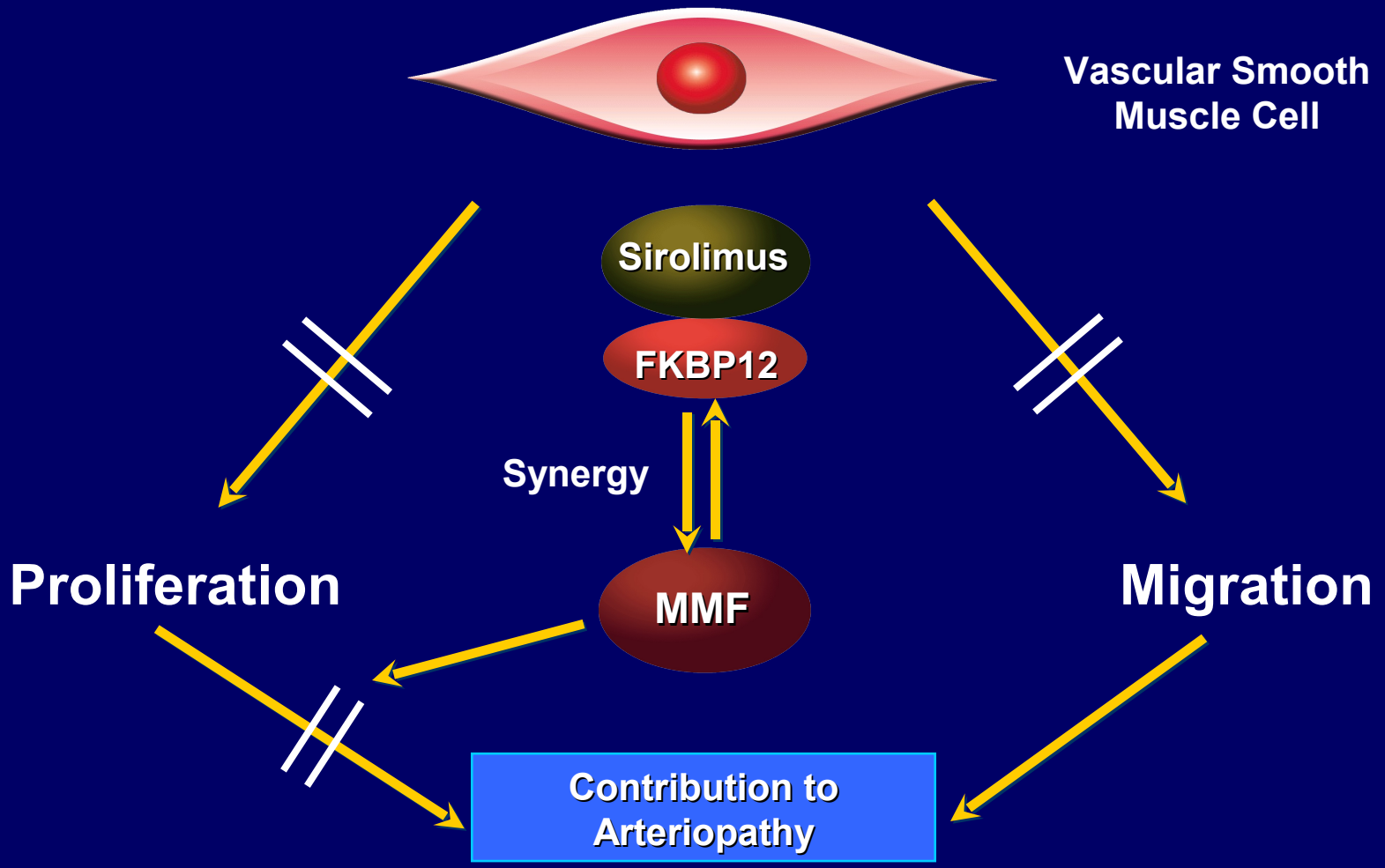
Vaculopathy

- No influence of CNI
- Rapamycin (Srl/Evl) show better protection
- Therapy? (rapastat, Mancini)
- Steroid weaning?

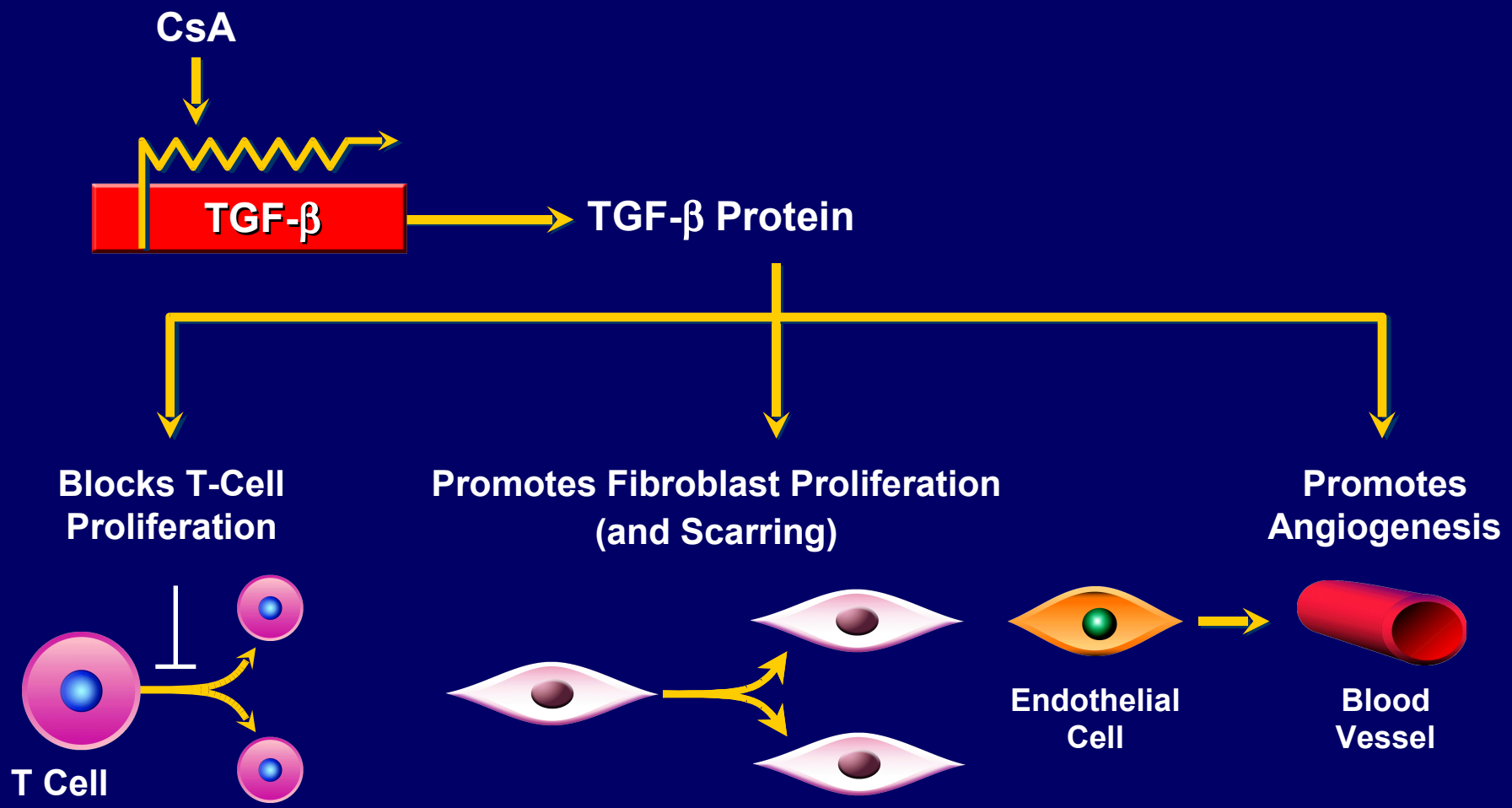
Cancer

- Cumulative level of immunosuppression
- Aza potential cancerogen
- Less cancer with MMF
- Rapa possible antineoplastic

Effects of Sirolimus and MMF on Vascular Smooth Muscle Cell Proliferation and Migration

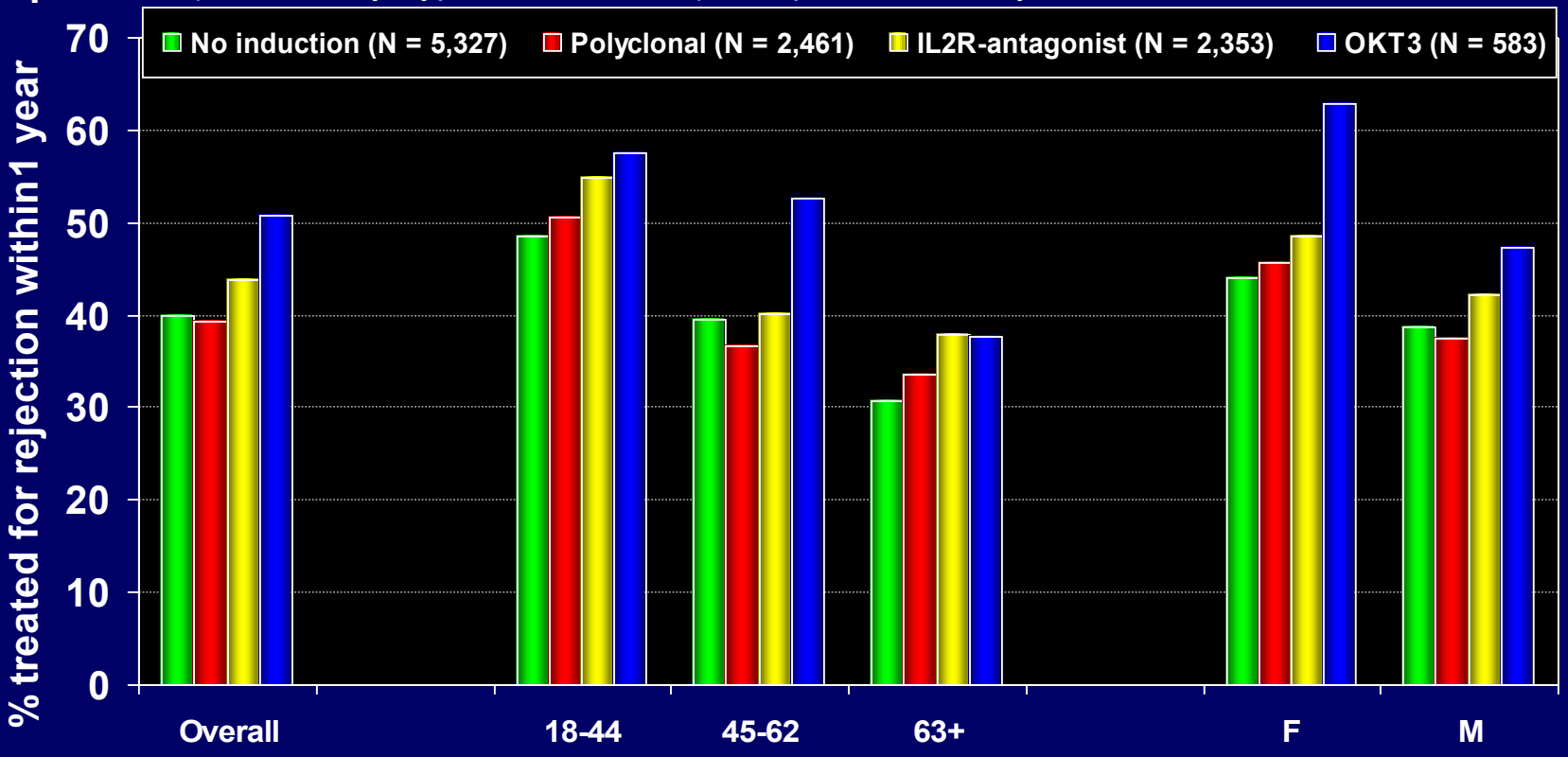


TGF-β Mediates Important CsA Effects



PERCENTAGE OF ADULT HEART TRANSPLANT RECIPIENTS TREATED FOR REJECTION IN 1ST YEAR

(Stratified by Type of Induction (Transplants: January 1, 2000 - June 30, 2005



Overall: no induct vs. OKT3 (p<0.0001); poly vs. OKT3 (p<0.0001); poly vs. IL2 (p=0.026); IL2 vs. OKT3 (p=0.013)
45-62: All comparisons with OKT3 (p=0.0005 or less).
No other comparisons within age groups were statistically significant at 0.05.
For females: no induction vs. OKT3 (p = 0.0006); polyclonal vs. OKT3 (p = 0.004); IL2R vs. OKT3 (p = 0.0157)
For males: no induction vs. OKT3 (p = 0.0038); polyclonal vs. OKT3 (p = 0.0386); IL2R vs. OKT3 (p = 0.002)

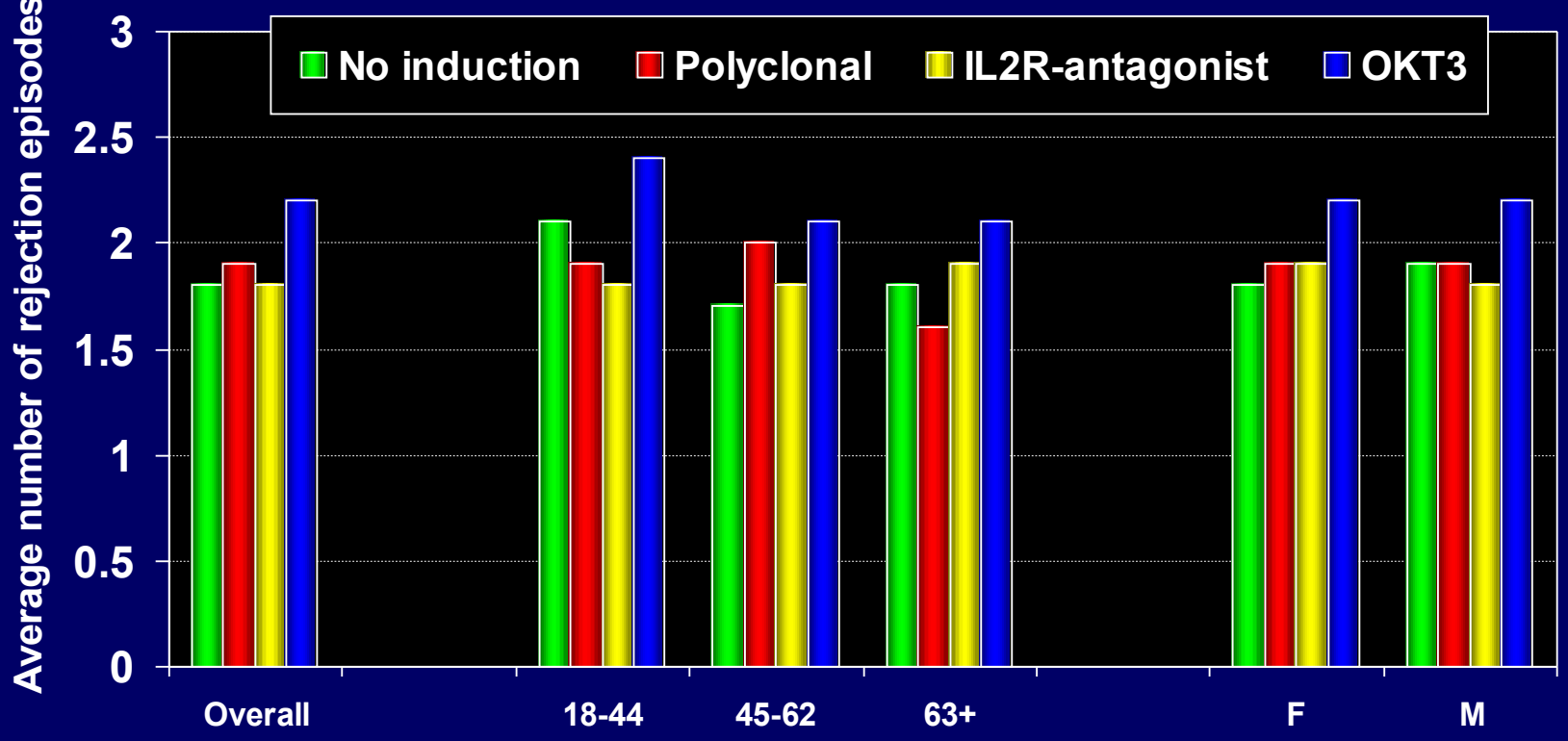
ISHLT

2007

J Heart Lung Transplant 2007;26: 769-781

NUMBER OF REJECTION EPISODES FOR ADULT HEART TRANSPLANT RECIPIENTS TREATED FOR REJECTION IN 1ST YEAR

(Stratified by Type of Induction (Transplants: January 1, 2000 - June 30, 2005



Overall: no induction vs. OKT3 (p = 0.0017); polyclonal vs. OKT3 (p=0.0065); IL2 vs. OKT3 (p=0.0003).

18-44: no induction vs. IL2 (p = 0.037).

45-62: no induction vs. OKT3 (p = 0.0025); IL2 vs. OKT3 (p = 0.0034).

63+: polyclonal vs. OKT3 (p = 0.0228).

For females: no induction vs. OKT3 (p = 0.0078); IL2 vs. OKT3 (p = 0.0466).

For males: no induction vs. OKT3 (p =0.040); polyclonal vs. OKT3 (p=0.045); IL2 vs. OKT3 (p = 0.0022).

ISHLT 2007

J Heart Lung Transplant 2007;26: 769-781

- Randomized trial of TAC monotherapy : TAC in combination, compared to TAC alone (TICTAC Study)

- Baran DA JHLT 2007 (oct) ;26(10):992-7

- Prospective, Randomized, 2 center study

- April 2004 to Sept 2005

- TAC combination vs TAC monotherapy

- 58 pts.
- All received TAC +MMF +ST for 14 days
- MMF maintained vs. MMF discontinued
- (ST were rapidly withdrawn in both groups between 8-12 weeks)

Mean 6 month ISHLT biopsy score :

- Monotherapy : 0.44+/- 0.04
- Combined : 0.60+/- 0.05
- p=0.013

Freedom from rejection(2R or higher at 6 ,12 m)

- Monotherapy : 93.3%
- Combined : 92.9%

Conclusions :

- TAC monotherapy appears to be safe and efficacious in heart transplant recipients.

- It is not associated with excess rejection in the first year post transplantation

Efficacy of Immunosuppressants in Cardiac Transplantation

Induction Therapy With Rabbit ATG After Cardiac Transplantation

Study Design

- Single center, European, retrospective

Patients

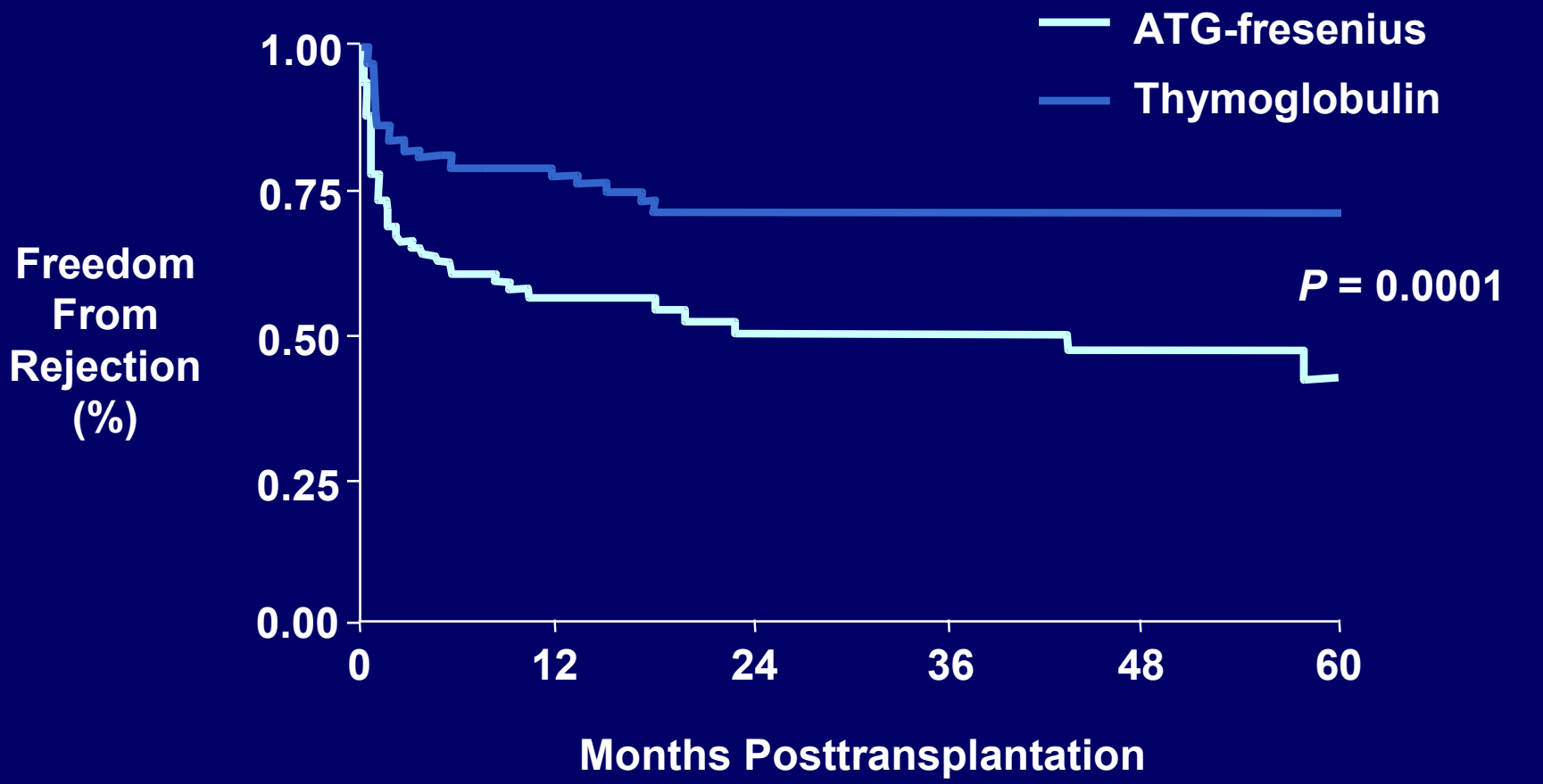
- Cardiac transplant recipients from March 1984 to December 1996 (N = 519)
- Five-year follow-up

Immunosuppression

- ATG-fresenius (n = 156) or thymoglobulin (n = 363)
- CsA, AZA, and steroids

Zuckerman AO et al. *Transplantation.* 2000;69:1890-1898.

Induction Therapy With Rabbit ATG After Cardiac Transplantation



Zuckerman AO et al. *Transplantation.* 2000;69:1890-1898.

Daclizumab for Cardiac Transplantation

Study Design

- Single center, randomized

Patients

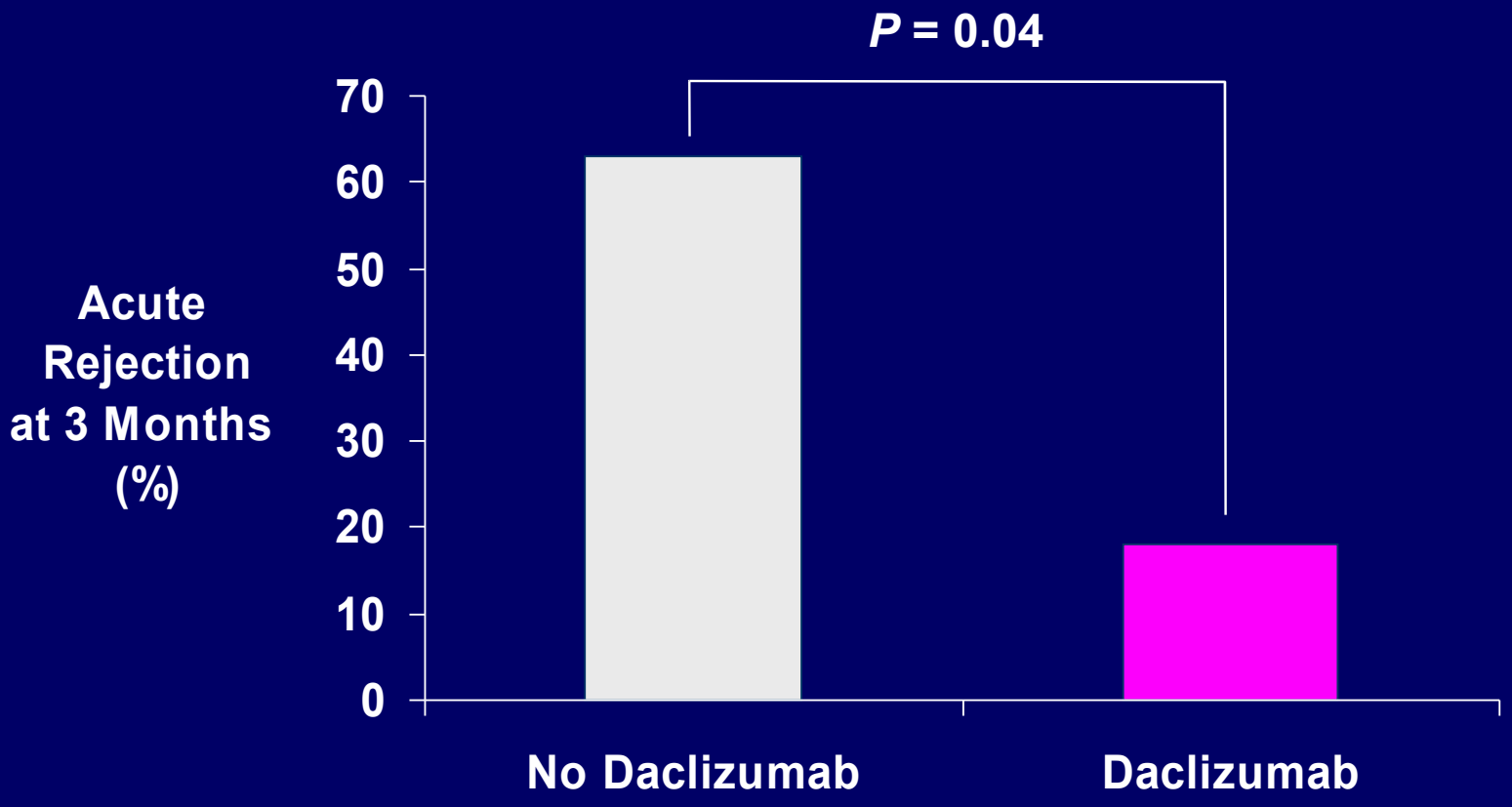
- Nonsensitized cardiac transplant recipients from January to December 1998 (N = 55)
- Follow-up 502 ± 117 vs 454 ± 76 days for no daclizumab vs daclizumab groups
- January to December 1998

Immunosuppression

- Induction therapy with daclizumab (n = 28) for 3 months
- 1.0 mg/kg body weight IV within 24 hours posttransplantation and every two weeks thereafter (5 total doses) or no induction (n = 27)
- CsA, MMF, and steroids

Benjamin MX, et al. *N Engl J Med.* 2000;342:613-619.

Daclizumab for Cardiac Transplantation

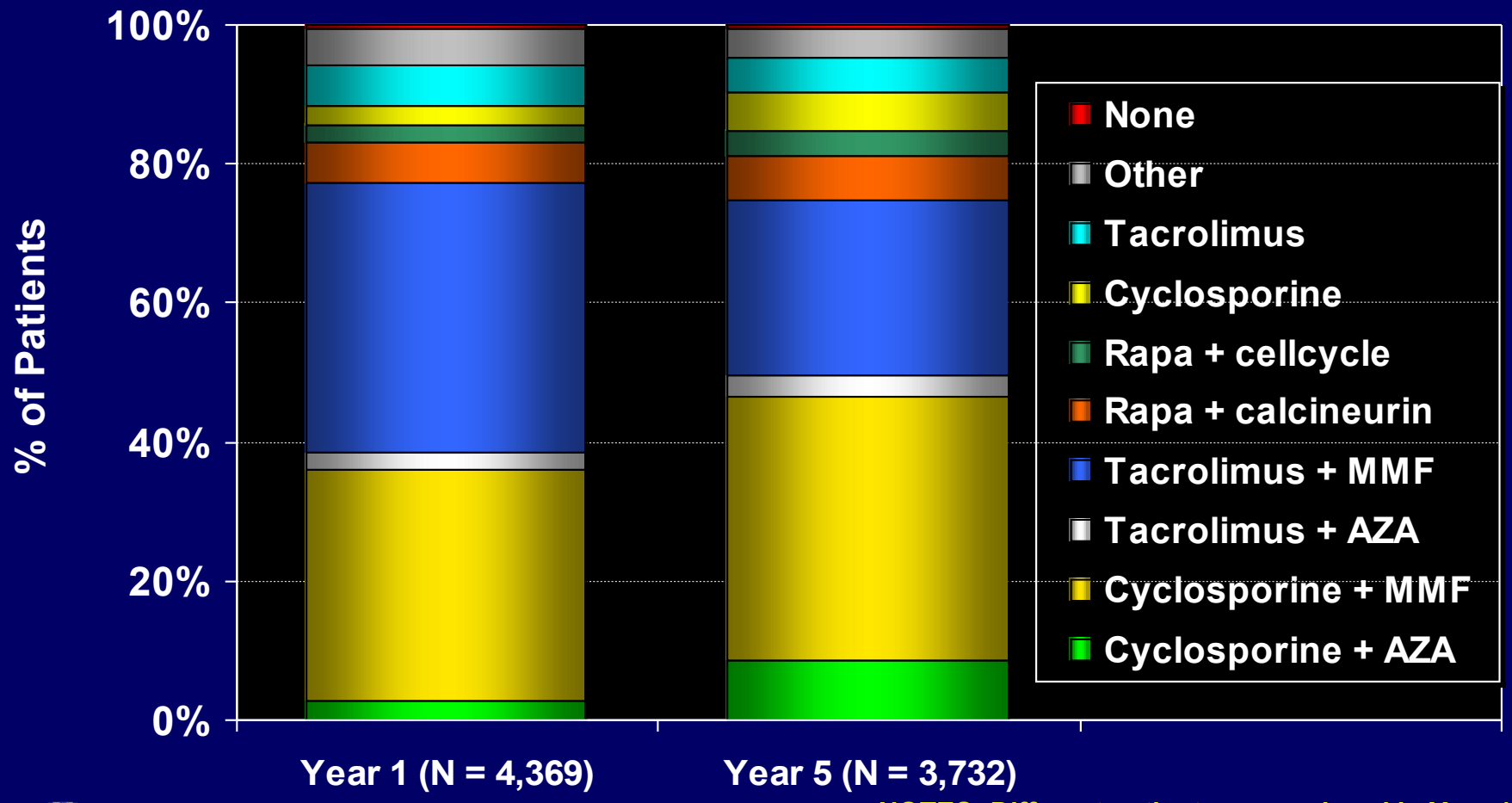


Beniaminovitz A et al. *N Engl J Med.* 2000;342:613-619.

ADULT HEART RECIPIENTS

Maintenance Immunosuppression Drug Combinations at Time of Follow-up

((Follow-ups: January 2004 - June 2006



ISHLT

2007

J Heart Lung Transplant 2007;26: 769-781

NOTES: Different patients are analyzed in Year 1 and Year 5. In the Year 1 cohort 73.9% of patients were on prednisone; in the Year 5 cohort 56.8% of patients were on prednisone.

Safety of Immunosuppressants: Drug Interactions With CYP450

	Interaction With	Result
CsA	P450 Inhibitors	Increased bioavailability
Tacrolimus	P450 Inhibitors	Increased bioavailability
Sirolimus	P450 Inhibitors (?)	Decreased metabolism (?)

Mignat C. *Drug Saf.* 1997;16:267-278.
Spicer ST et al. *Br J Clin Pharmacol*. 1997;43:194-196.
Vella JP, Sayegh MH. *Am J Kidney Dis.* 1998;31:320-323.
Islam SI et al. *Ther Drug Monit.* 1996;18:624-626.