ALLOGRAFT VASCULOPATHY AFTER HEART TRANSPLANTAION

YEDAEL HAR-ZAHAV MD

POST-HEART TRANSPLANT MORBIDITY FOR ADULTS

Cumulative Prevalence in Survivors at 1 Year Post-Transplant

((Follow-ups: April 1994 – December 1997 and January 2002 - June 2006

Outcome	Follow-ups: April 1994-December 1997 Within 1 Year	Total N with known response	Follow-ups: January 2002 – June 2006 Within 1 Year	Total N with known response
Hypertension	68.9%	(N = 6,425)	74.4%	(N = 7,099)
Renal Dysfunction	20.4%	(N = 6,378)	30.4%	(N = 7.247)
Abnormal Creatinine < 2.5 mg/dl	*11.3%*		*22.4%*	
Creatinine > 2.5 mg/dl	*8.1%*		*5.9%*	
Chronic Dialysis	*1.0%*		*1.6%*	
Renal Transplant	*0.1%*		*0.4%*	
Hyperlipidemia	33.3%	(N = 6,816)	67.8%	(N = 7,640)
Diabetes	20.9%	(N = 6,433)	31.5%	(N = 7,199)
Cardiac Allograft Vasculopathy	7.9%	(N = 5,847)	7.1%	(N = 6,556)

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POST-HEART TRANSPLANT MORBIDITY FOR ADULTS

Cumulative Prevalence in Survivors at 5 and 10 Years Post-Transplant (Follow-ups:

(April 1994 - June 2006

Outcome	Within 5 Years	Total N with known response	Within 10 Years	Total N with known response
Hypertension	93.8%	(N = 8,266)	98.5%	(N = 1,586)
Renal Dysfunction	32.6%	(N = 8,859)	38.7%	(N = 1,829)
Abnormal Creatinine < 2.5 mg/dl	*21.2%*		*24.4%*	
Creatinine > 2.5 mg/dl	*8.4%*		*8.2%*	
Chronic Dialysis	*2.5%*		*4.9%*	
Renal Transplant	*0.5%*		*1.2%*	
Hyperlipidemia	87.1%	(N = 9,237)	93.3%	(N = 1,890)
Diabetes	34.8%	(N = 8,219)	36.7%	(N = 1,601)
Cardiac Allograft Vasculopathy	31.5%	(N = 5,944)	52.7%	(N = 896)

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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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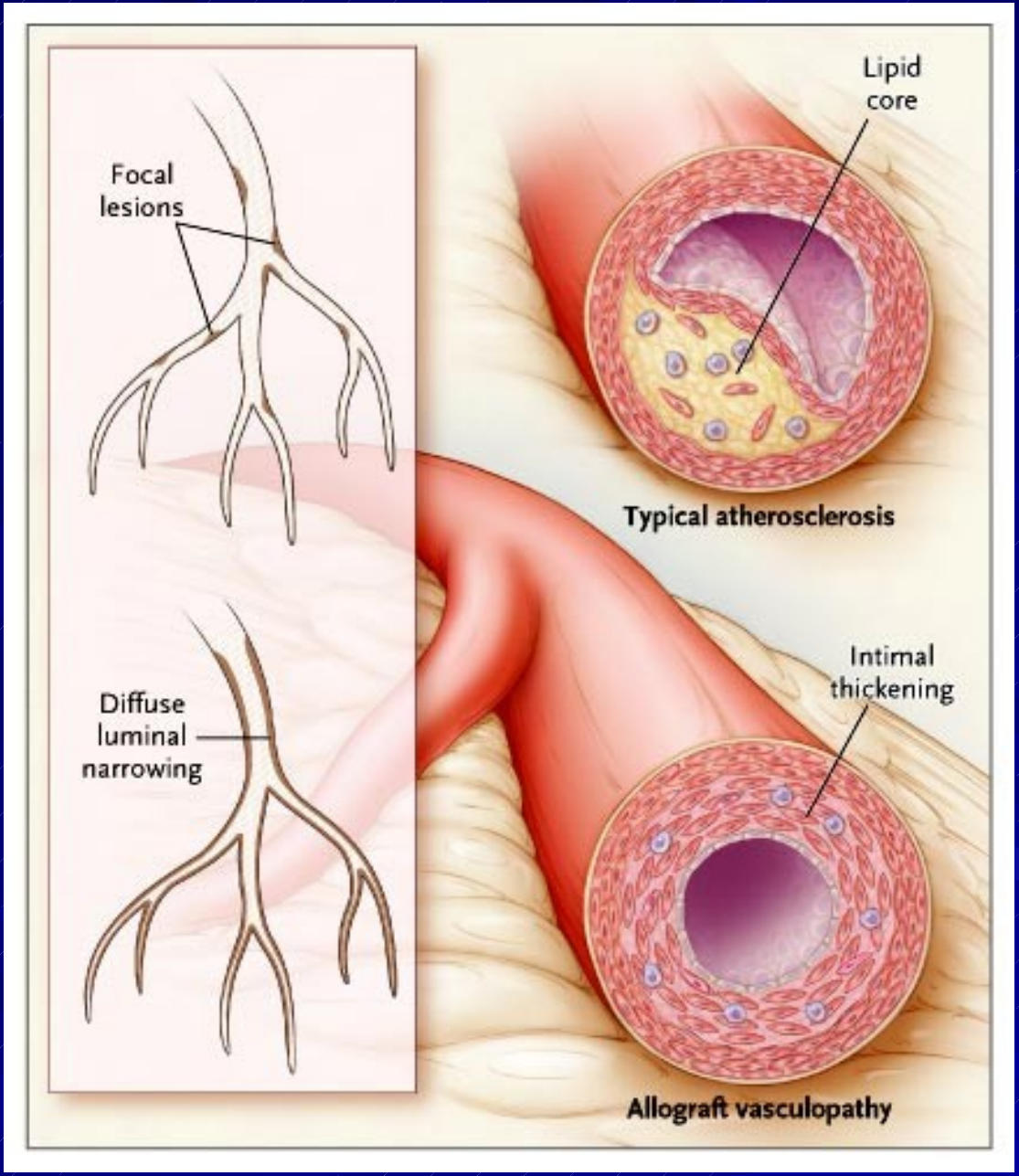
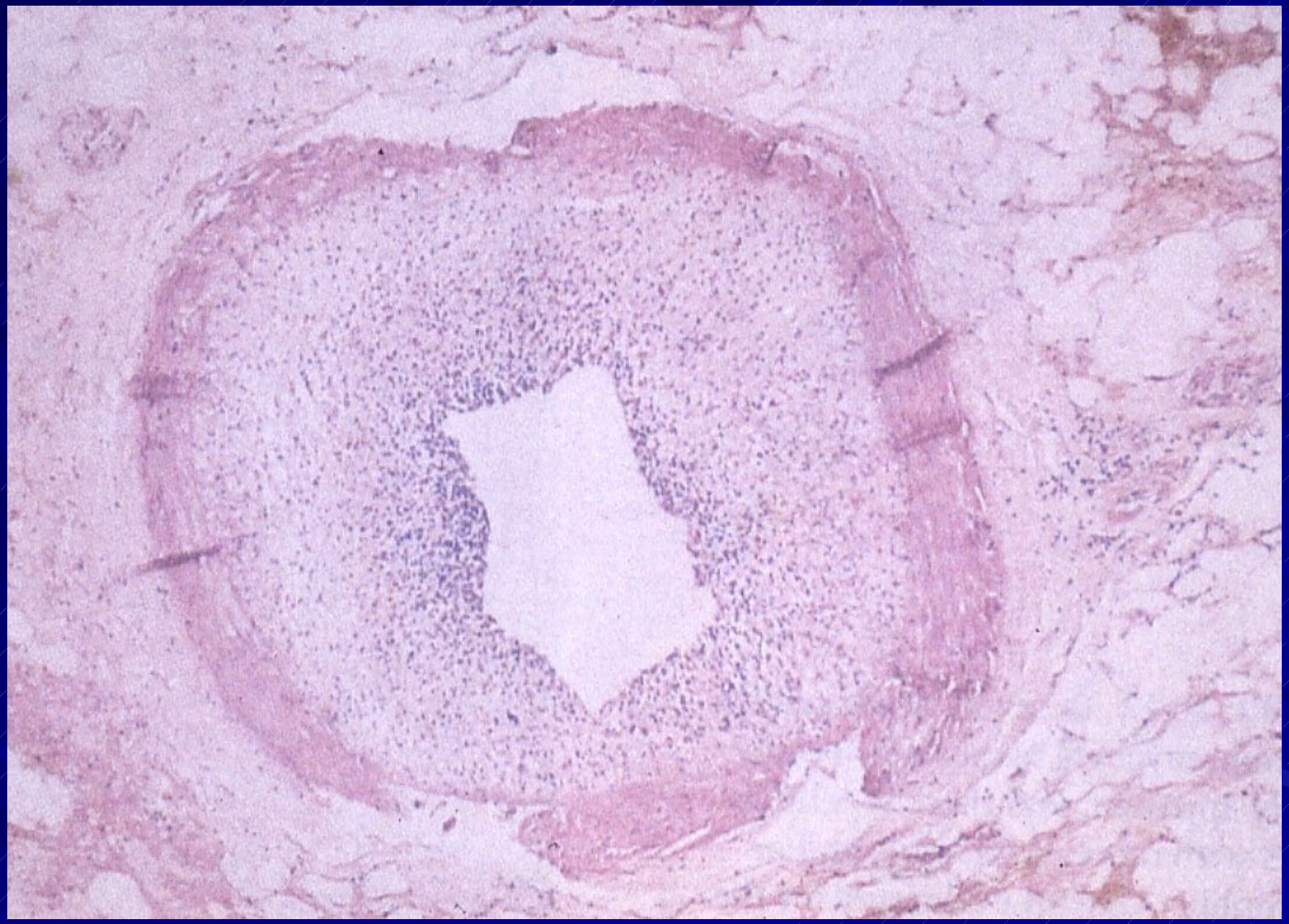
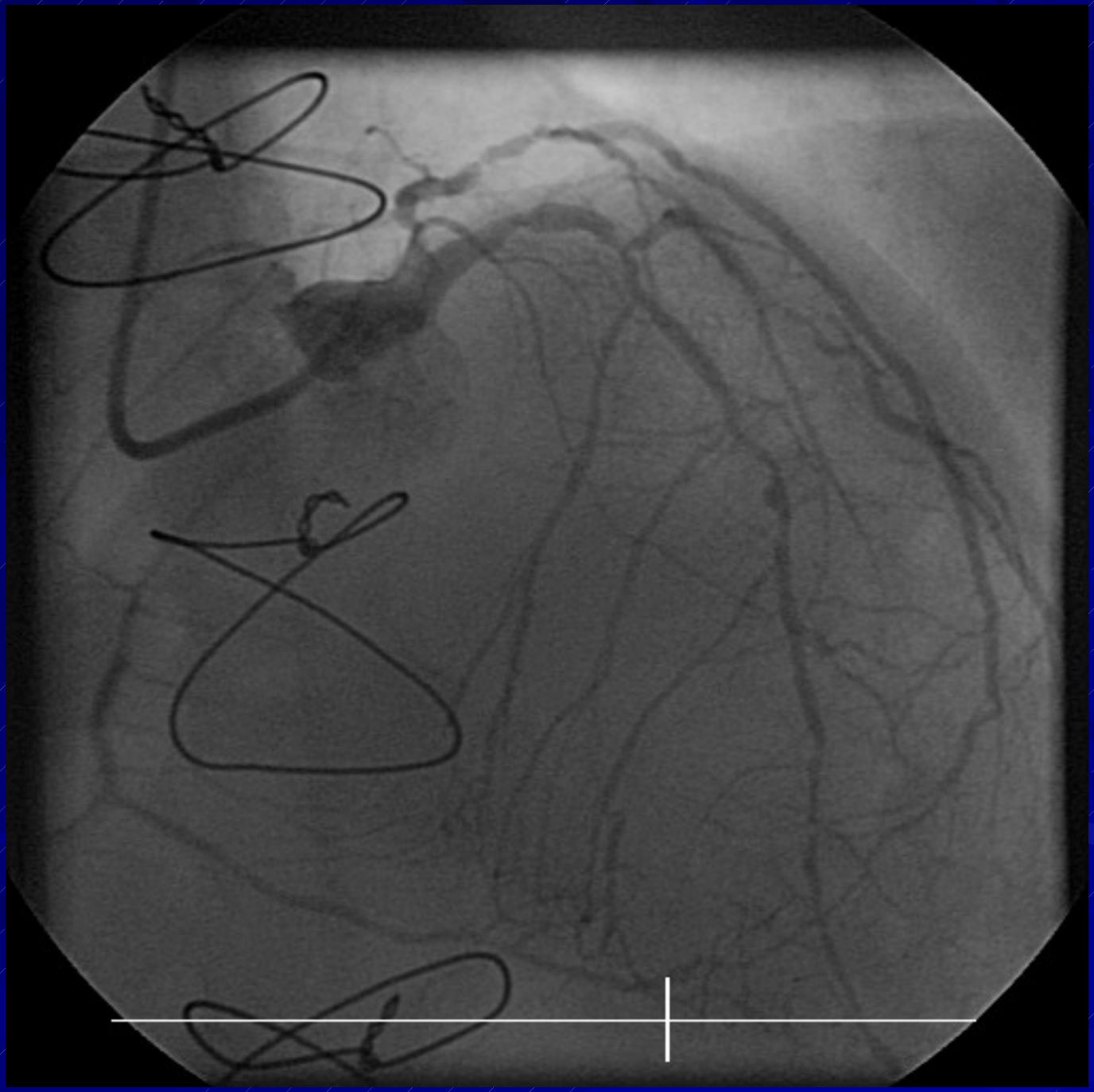
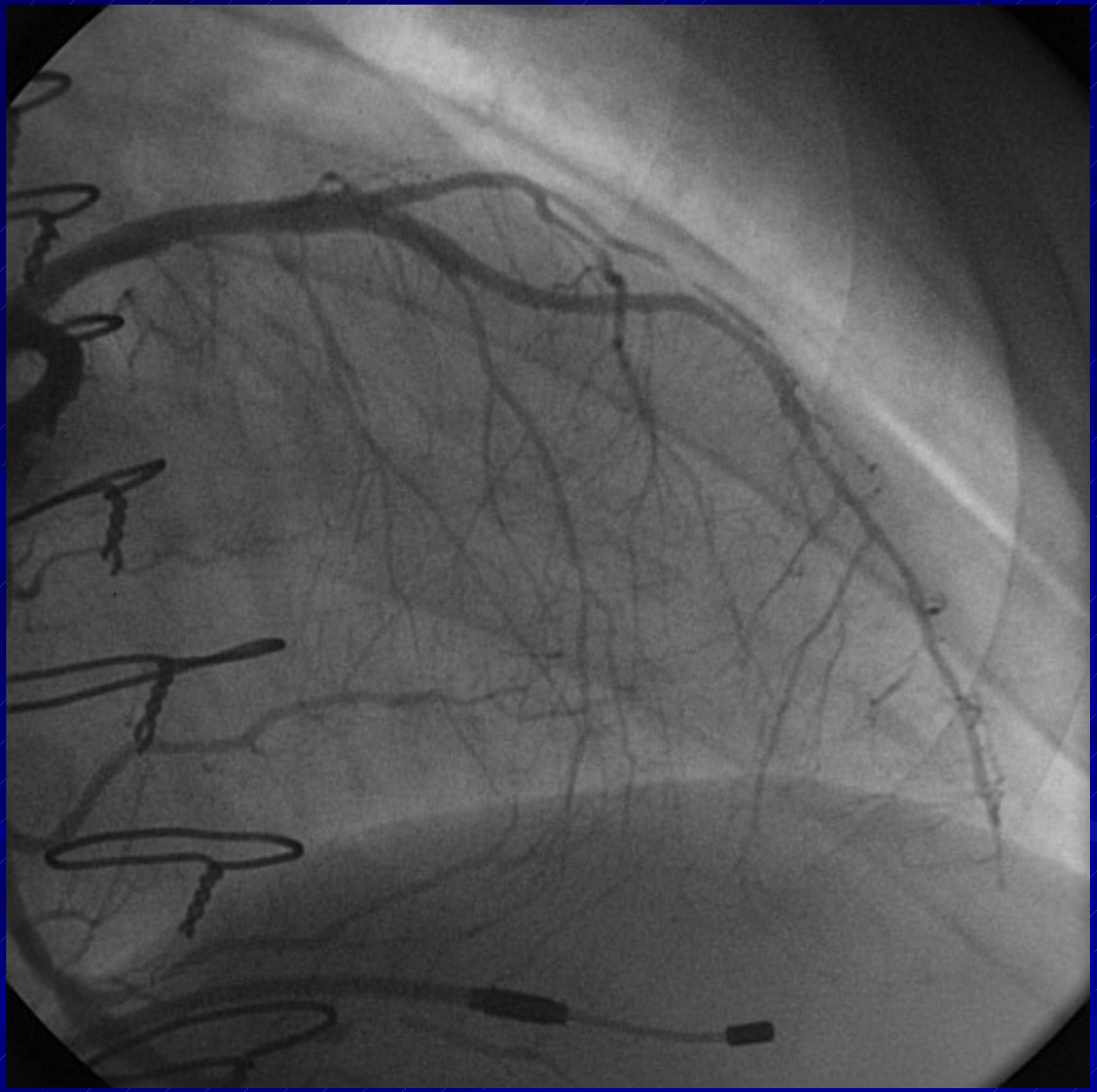
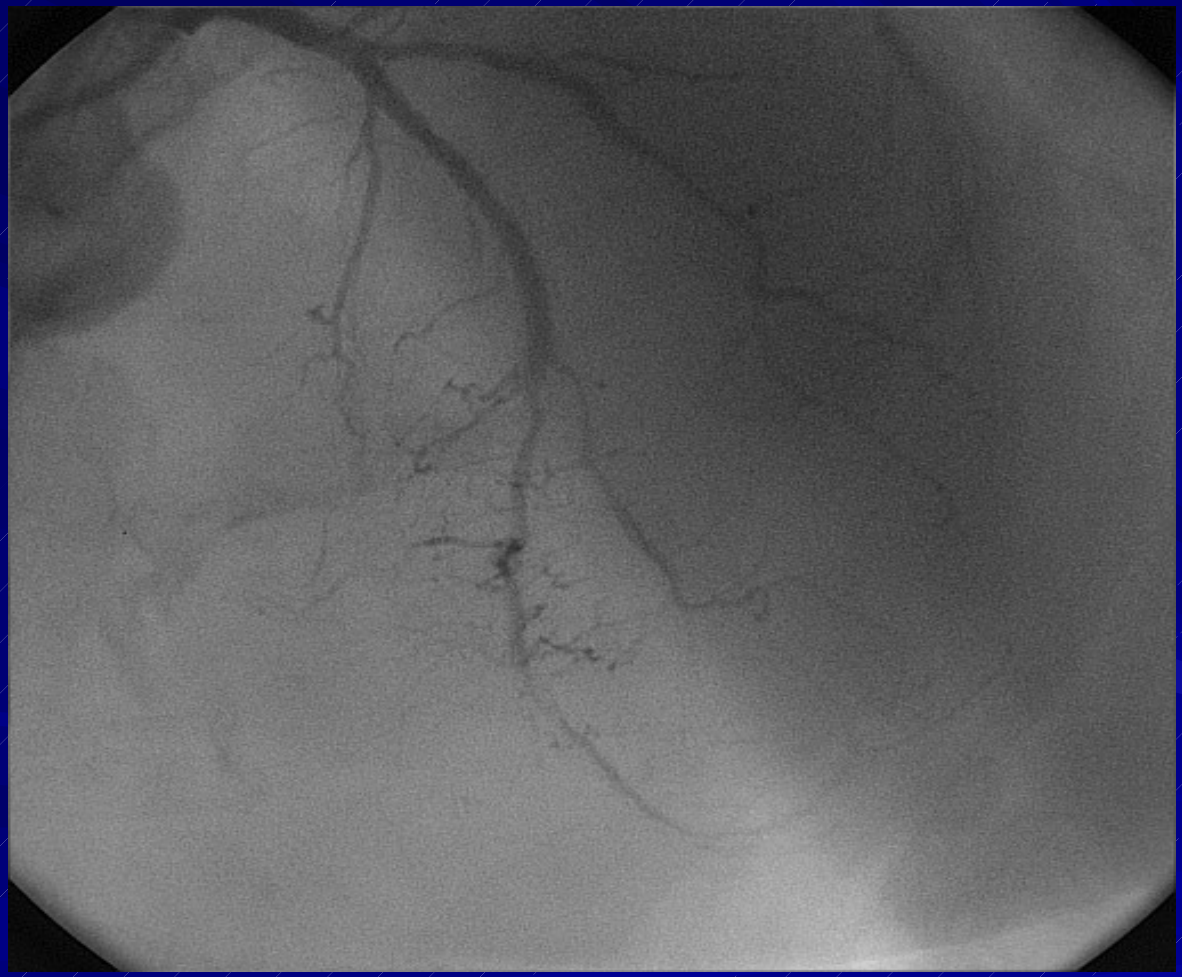

Lipid core
Focal lesions
Typical atherosclerosis
Intimal thickening
Diffuse luminal narrowing
Allograft vasculopathy



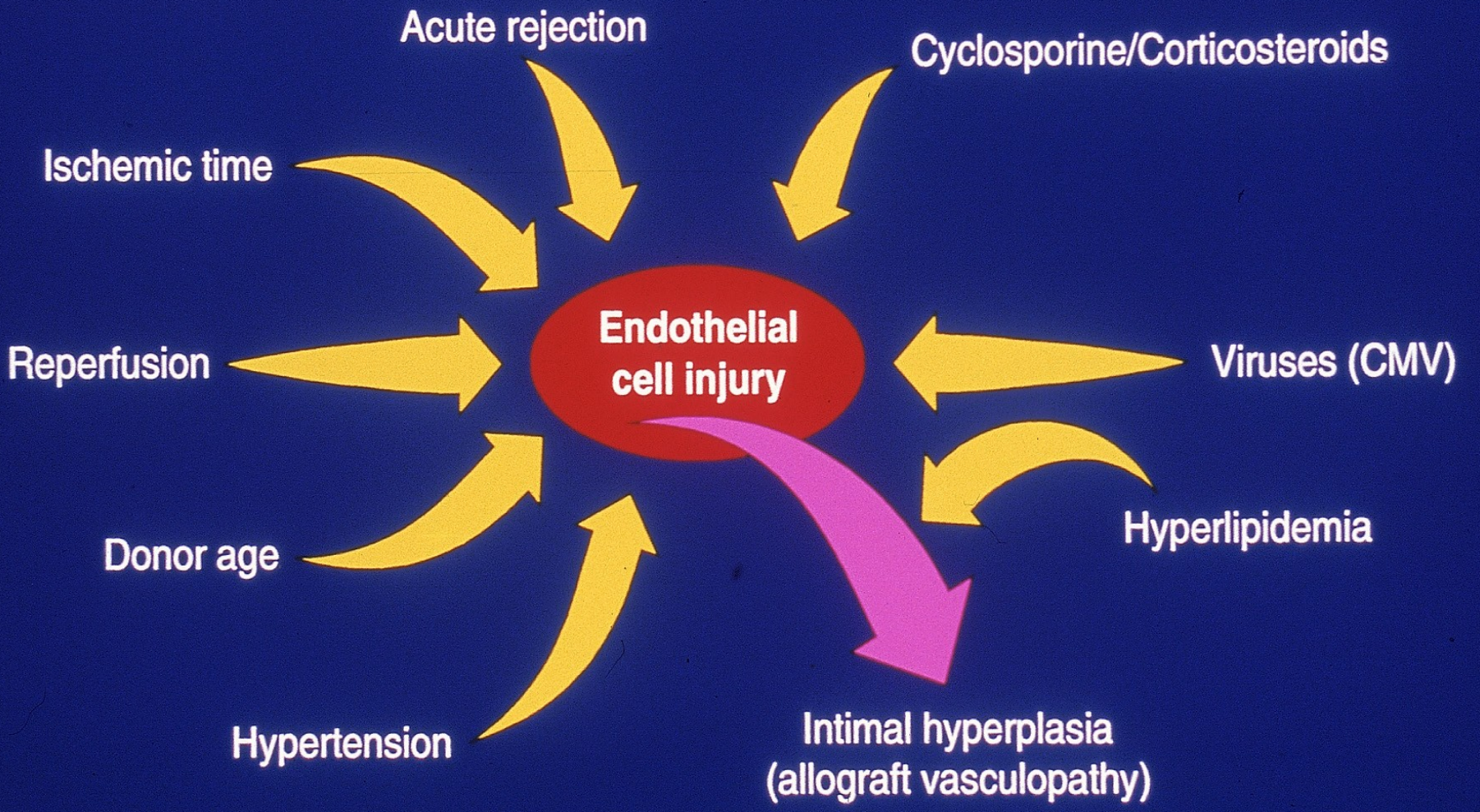




DIFFUSE DISEASE CAD



Proposed Mechanisms in the Development of Allograft Vasculopathy



Cellular consequences of vascular injury

INJURY

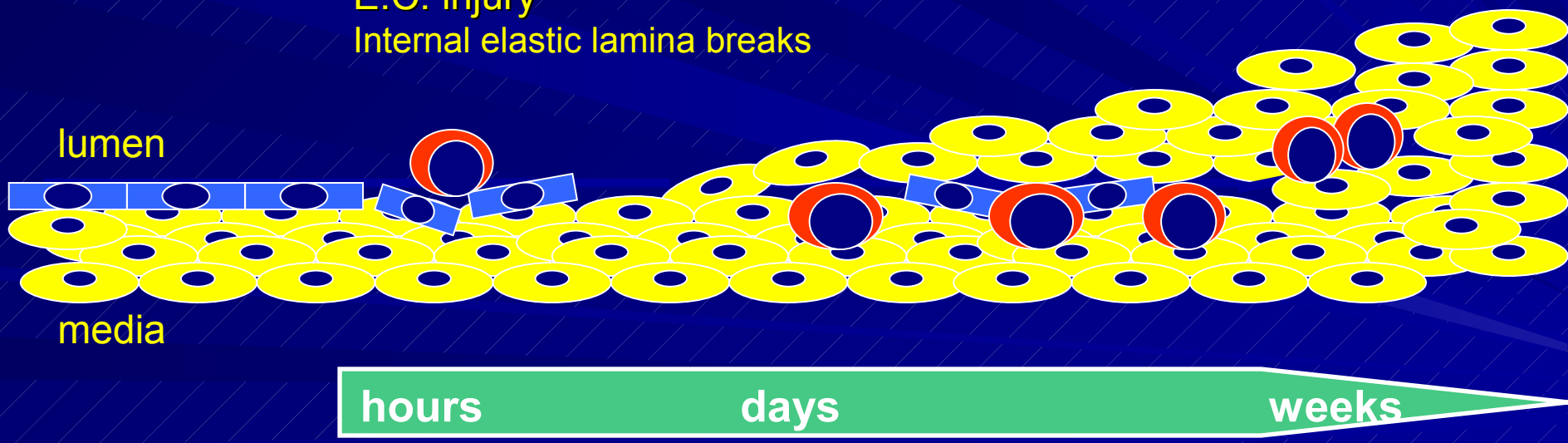
platelet adhesion
leukocyte infiltration

cytokines
growth factors
chemoattractants

neointimal hyperplasia

VSMC autocrine activation:
migration
proliferation
matrix deposition

E.C. injury
Internal elastic lamina breaks



CORONARY DISEASE

Incidence: 20-50% at 5 years

Incidental finding at autopsy

Incidental finding at coronary angiography

Arrhythmias

Myocardial infarction

Sudden death

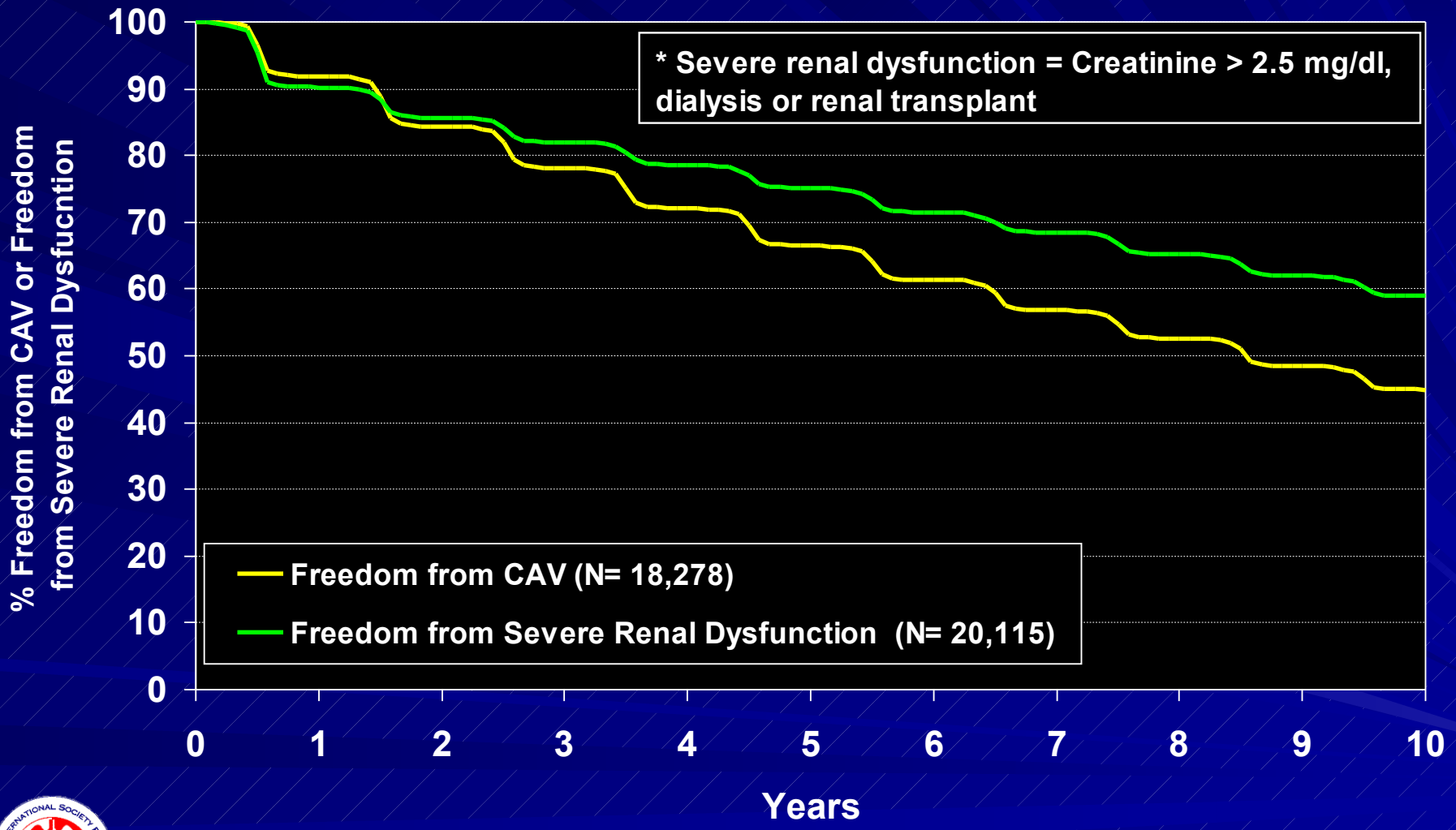
CHF

(LV dysfunctuon (Echo

(ANGINAL PAIN- Rare (less than 40%

FREEDOM FROM CARDIAC ALLOGRAFT VASCULOPATHY AND FREEDOM FROM SEVERE RENAL DYSFUNCTION*

(For Adult Heart Recipients (Follow-ups: April 1994-June 2006



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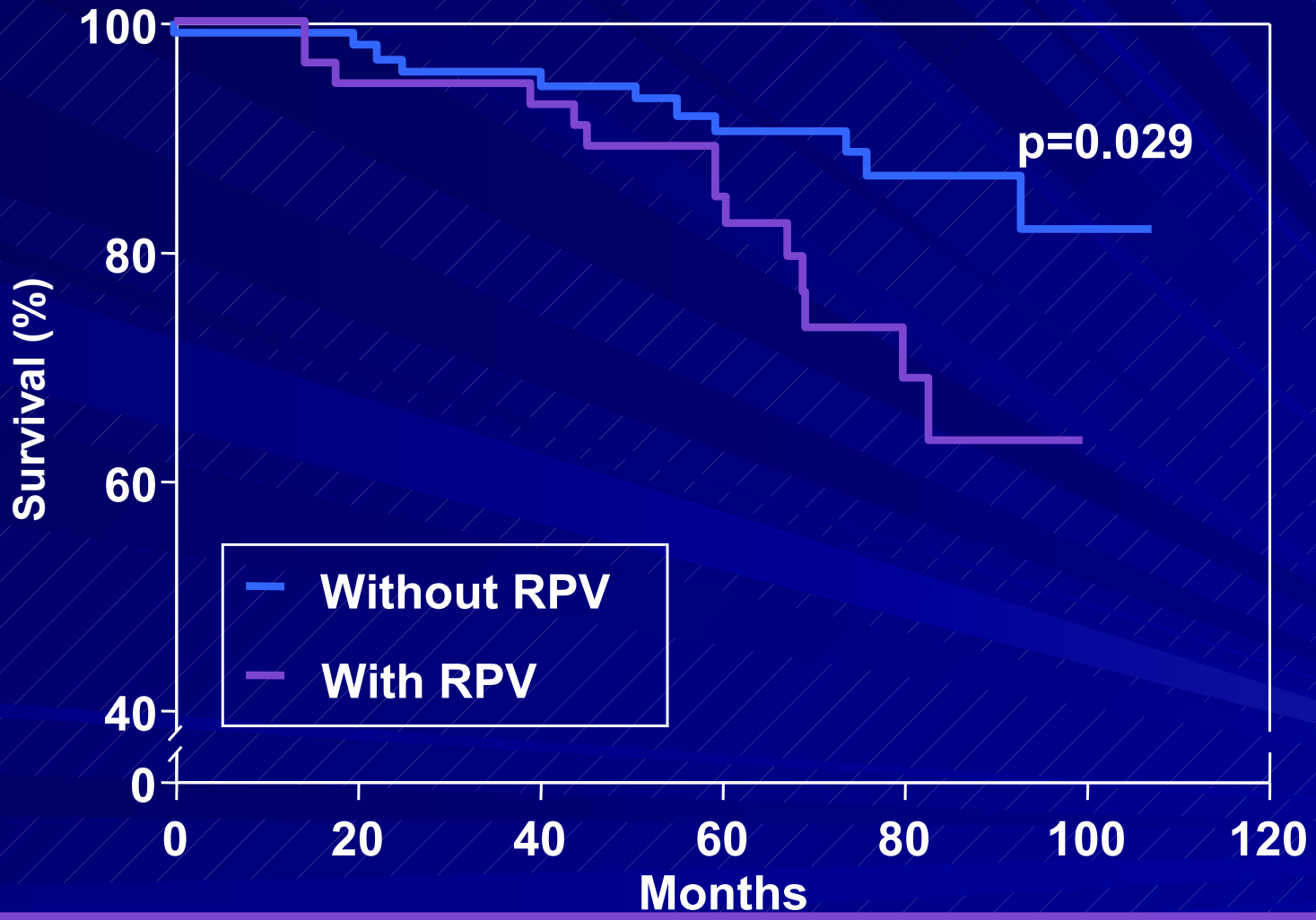
NATURAL HISTORY OF CARDIAC ALLOGRAFT VASCULOPATHY

- **Survival at three years after diagnosis is made is 60-80%.**
- **Patients with severe disease (≥ 40% stenosis) in three vessels have 6 % three year survival while those with single vessel disease have a 22% three year survival.**
- **Death usually due to sudden cardiac death, MI or CHF. Ischemic events usually silent.**

Rapidly Progressive Vasculopathy

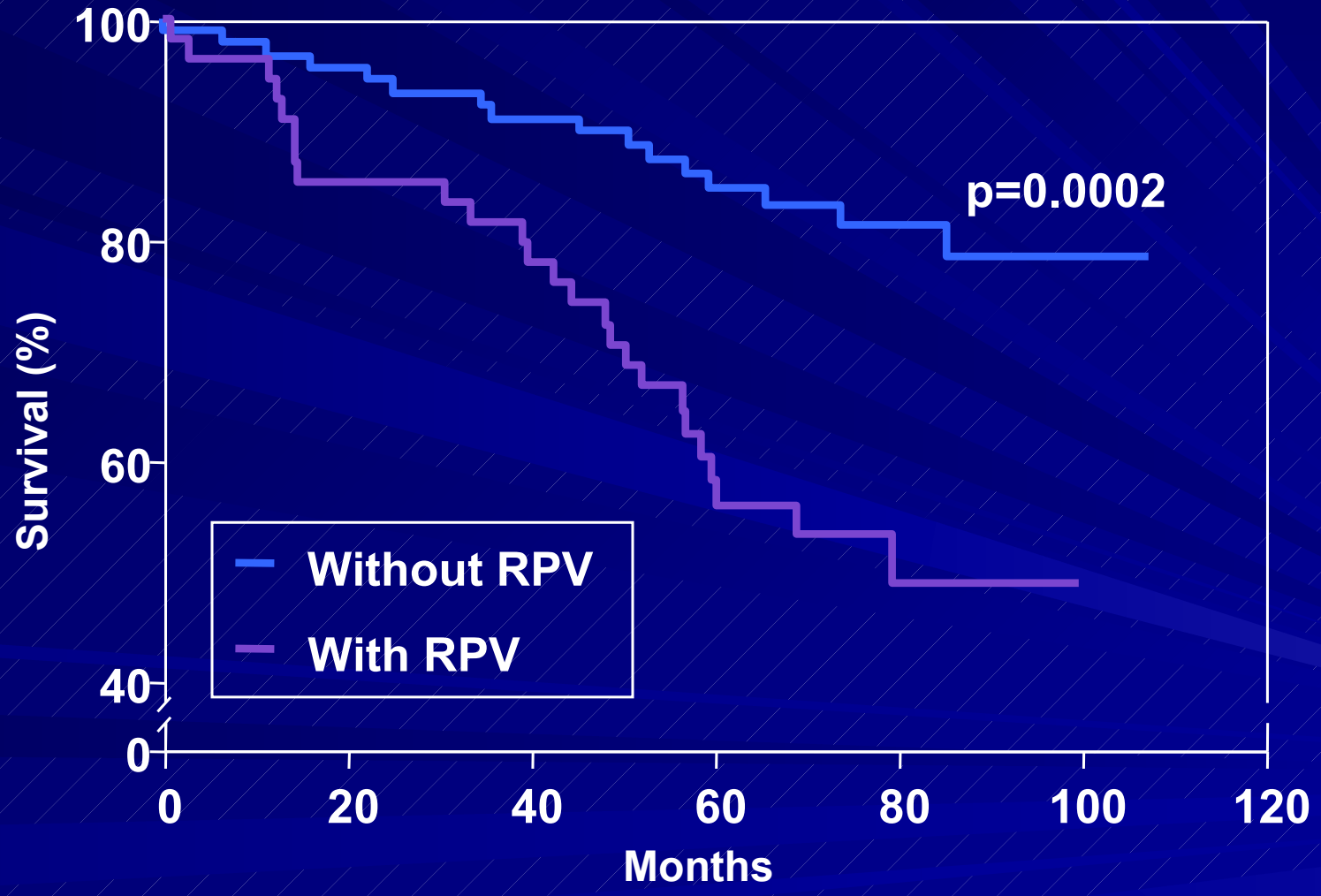
All Cause Mortality

Tuzcu et al. CCF Transplant Program Unpublished Data



De Novo Lesion: **Intimal thickness ≥ 0.5 mm at 1 yr. follow-up in an area which was < 0.5 mm at baseline**

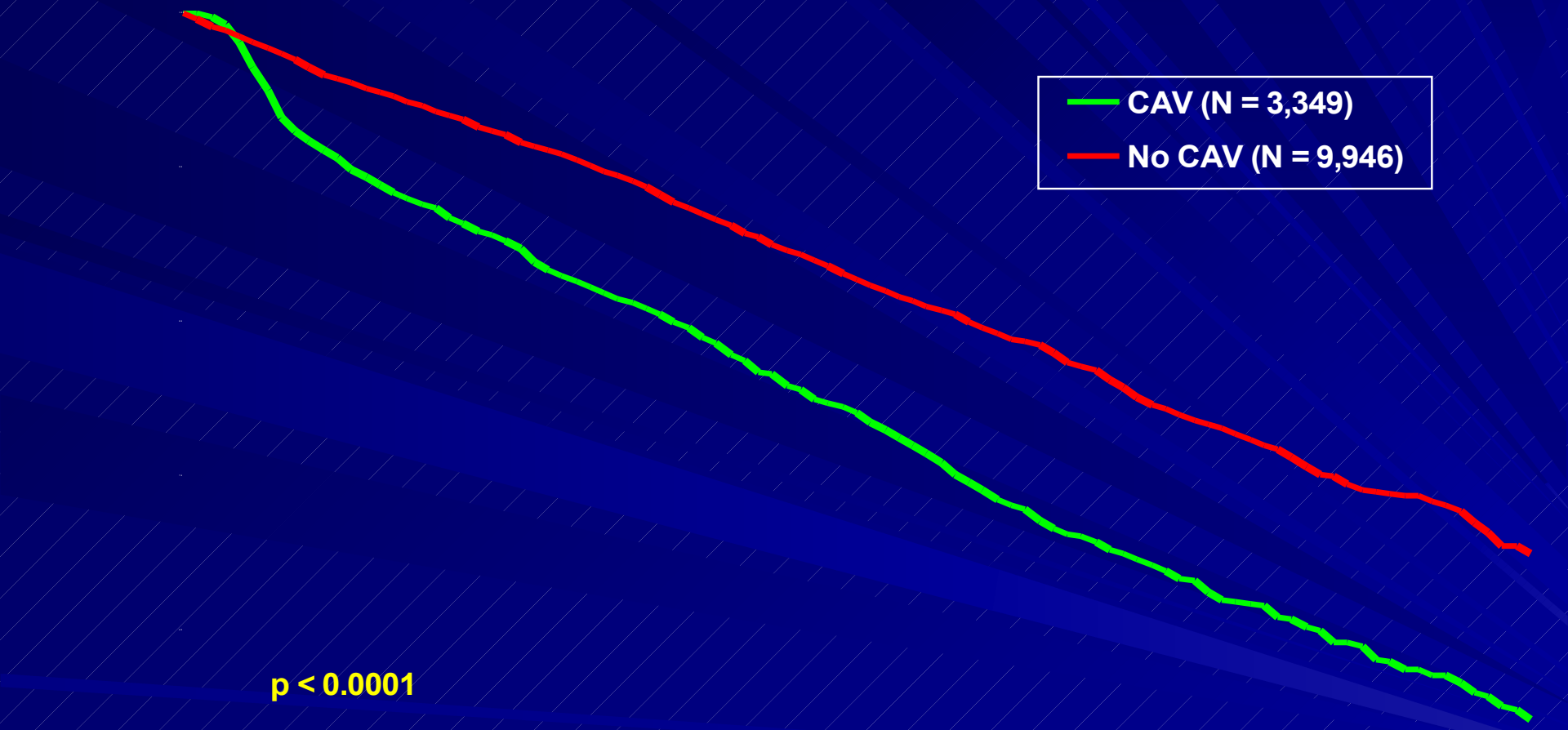
Rapidly Progressive Vasculopathy
Death and Myocardial Infarction



Tuzcu et al. CCF Transplant Program Unpublished Data

PATIENT SURVIVAL AFTER REPORT OF CAV AND PATIENT SURVIVAL IN PATIENTS WITHOUT CAV*

((Transplants: April 1994-June 2003



Time after Report of CAV (Years)

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*** Patients without CAV conditioned on survival to median time of CAV development (562 days)**

J Heart Lung Transplant 2006;25:869-79

Coronary disease

Diffuse and concentric---CAV

Focal---Donor disease

Focal—atherosclerotic

IVUS

Intimal thickening-25% at 1 year

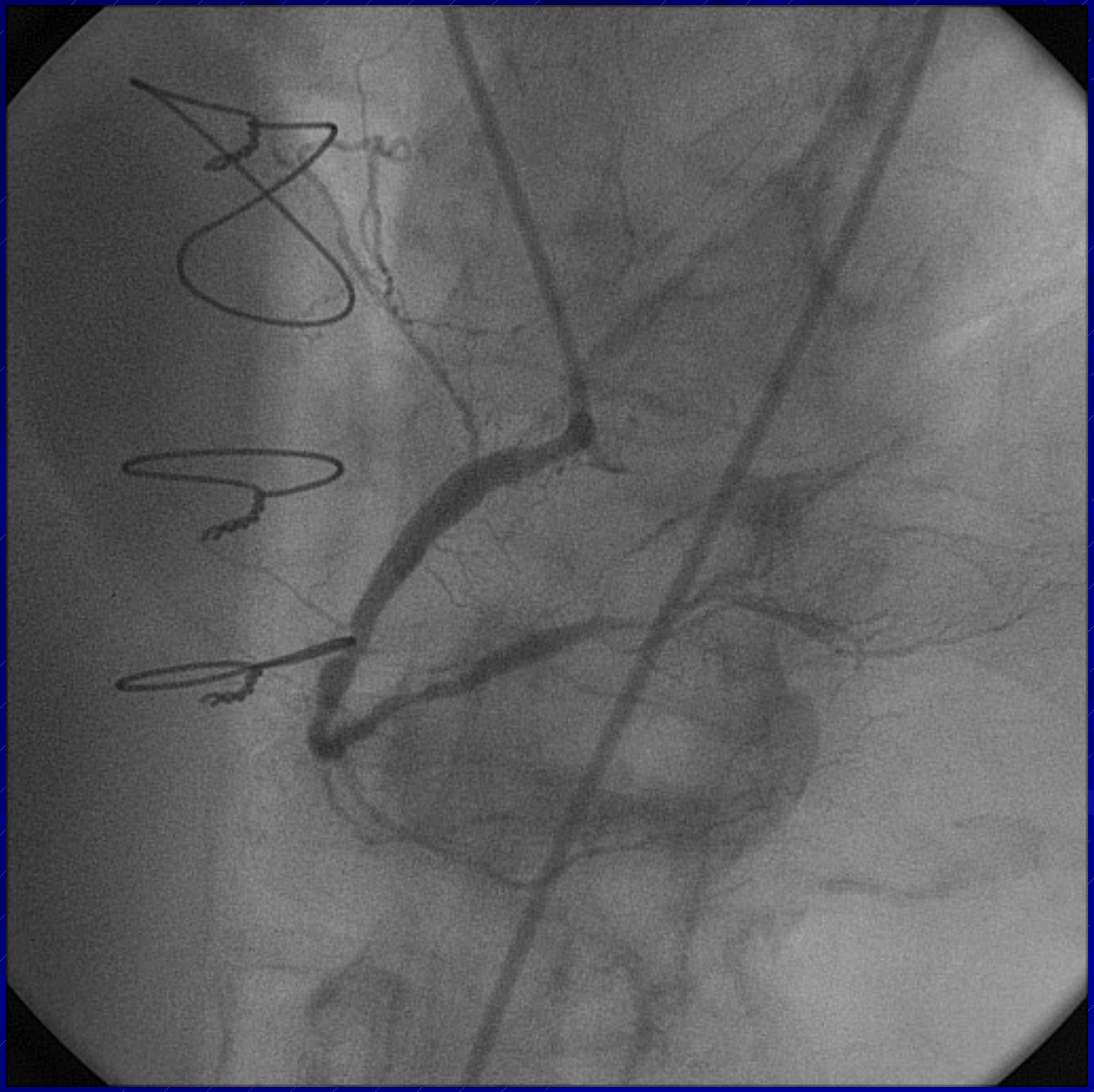
80% at 5 years

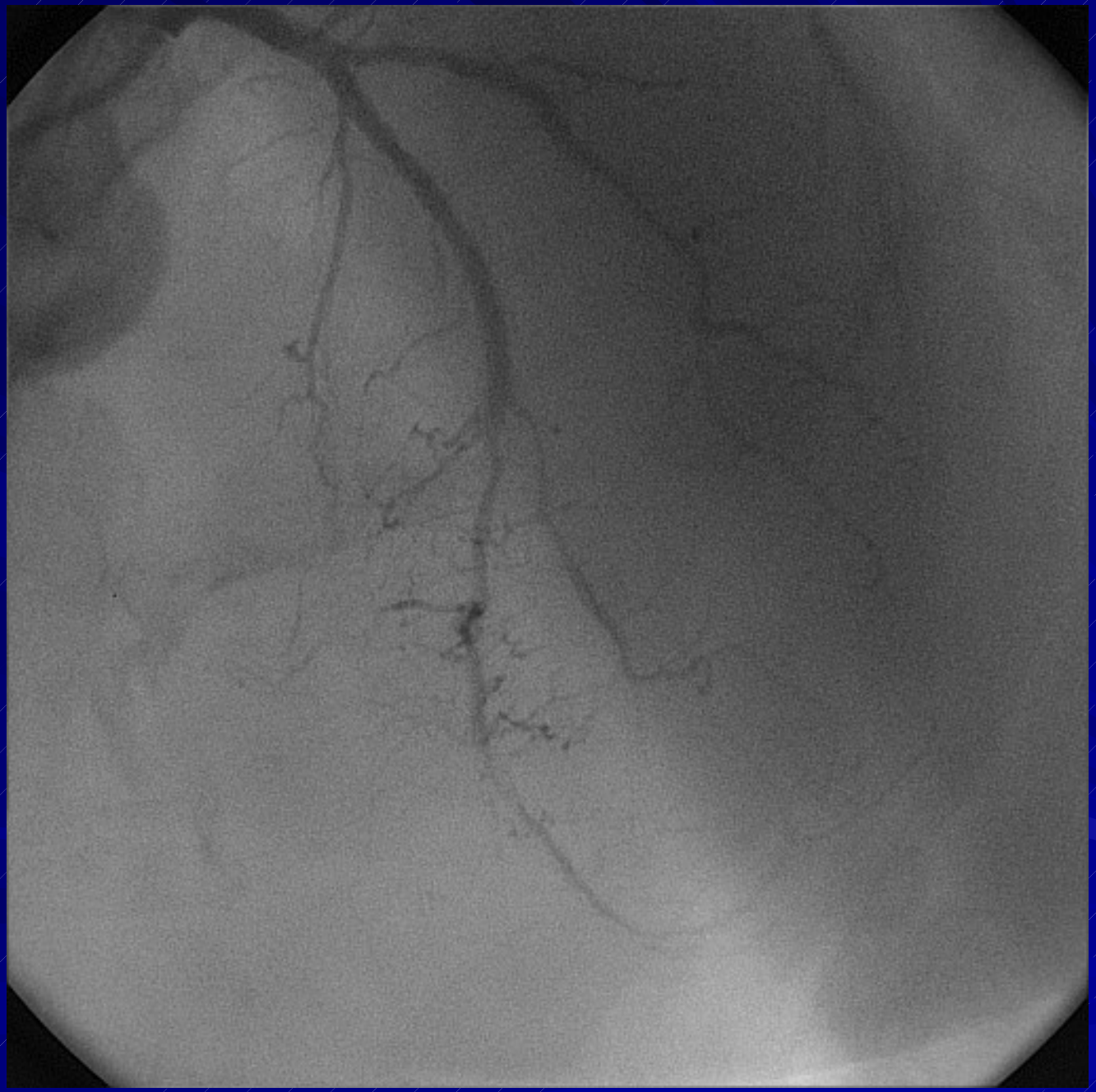
(Stanford University)

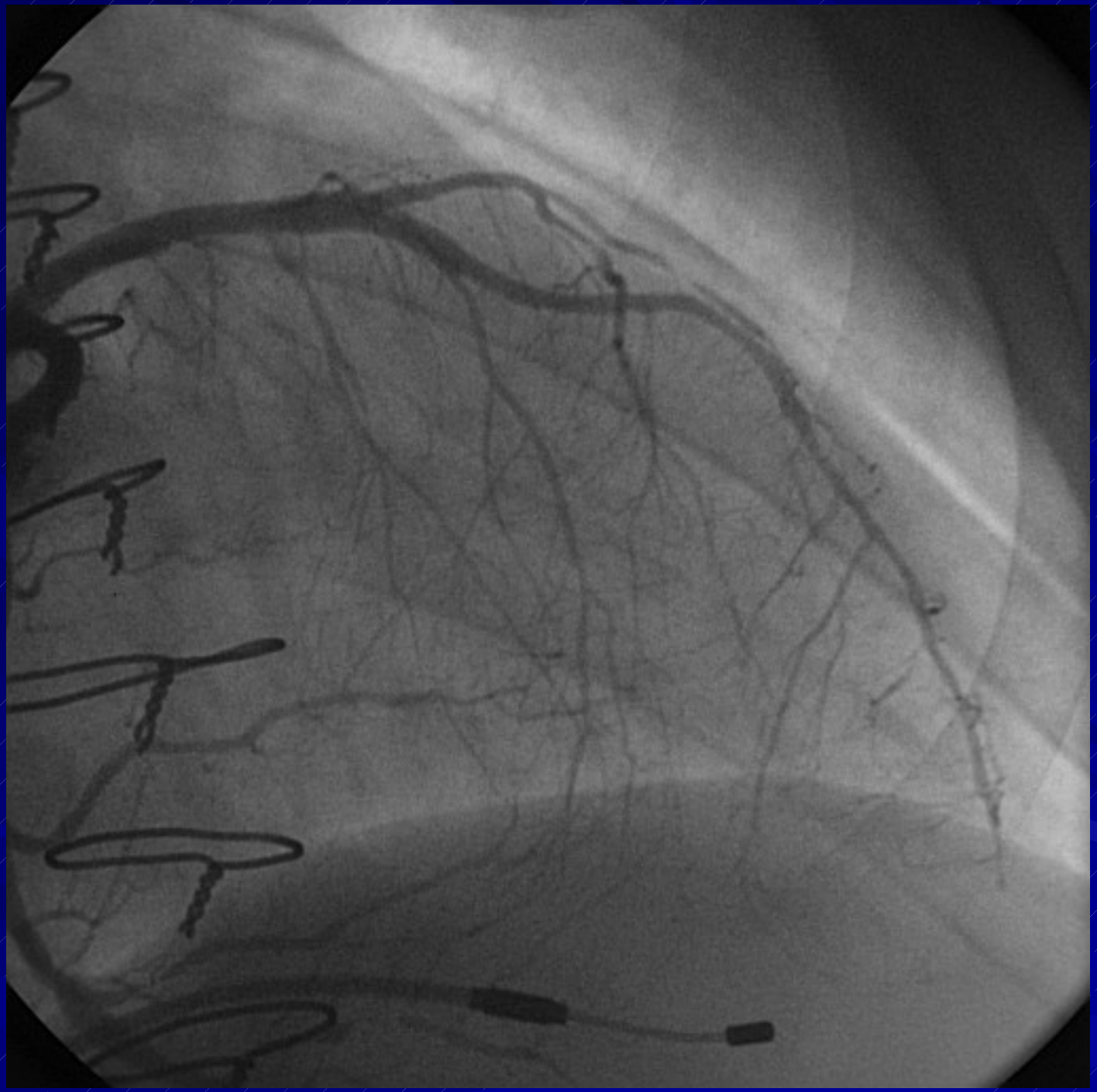
Calcification--< 10%-at 5 years

25% and 50% at 10 and 15 years

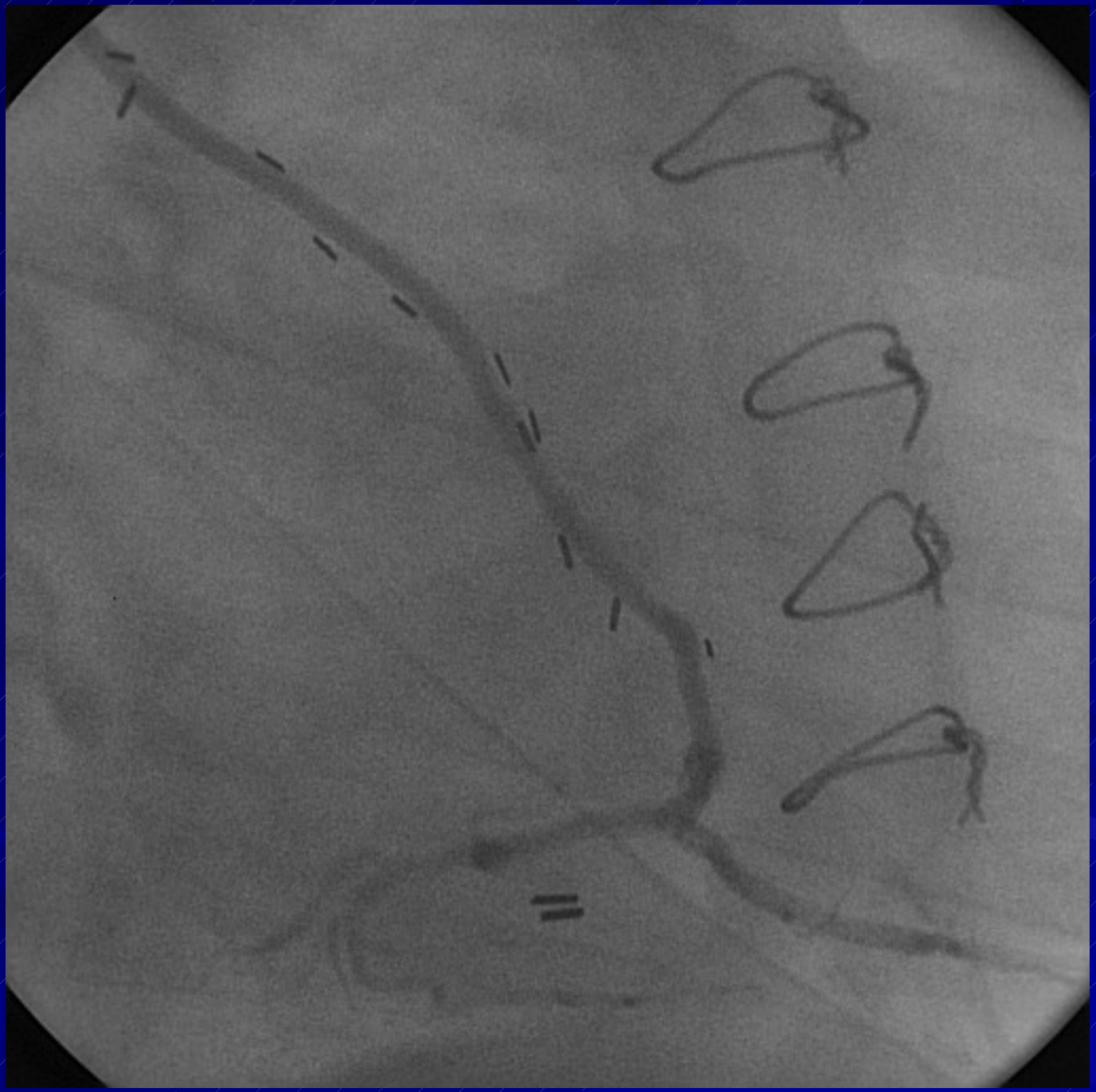
- ALLOGRAFT VASCULOPATHY



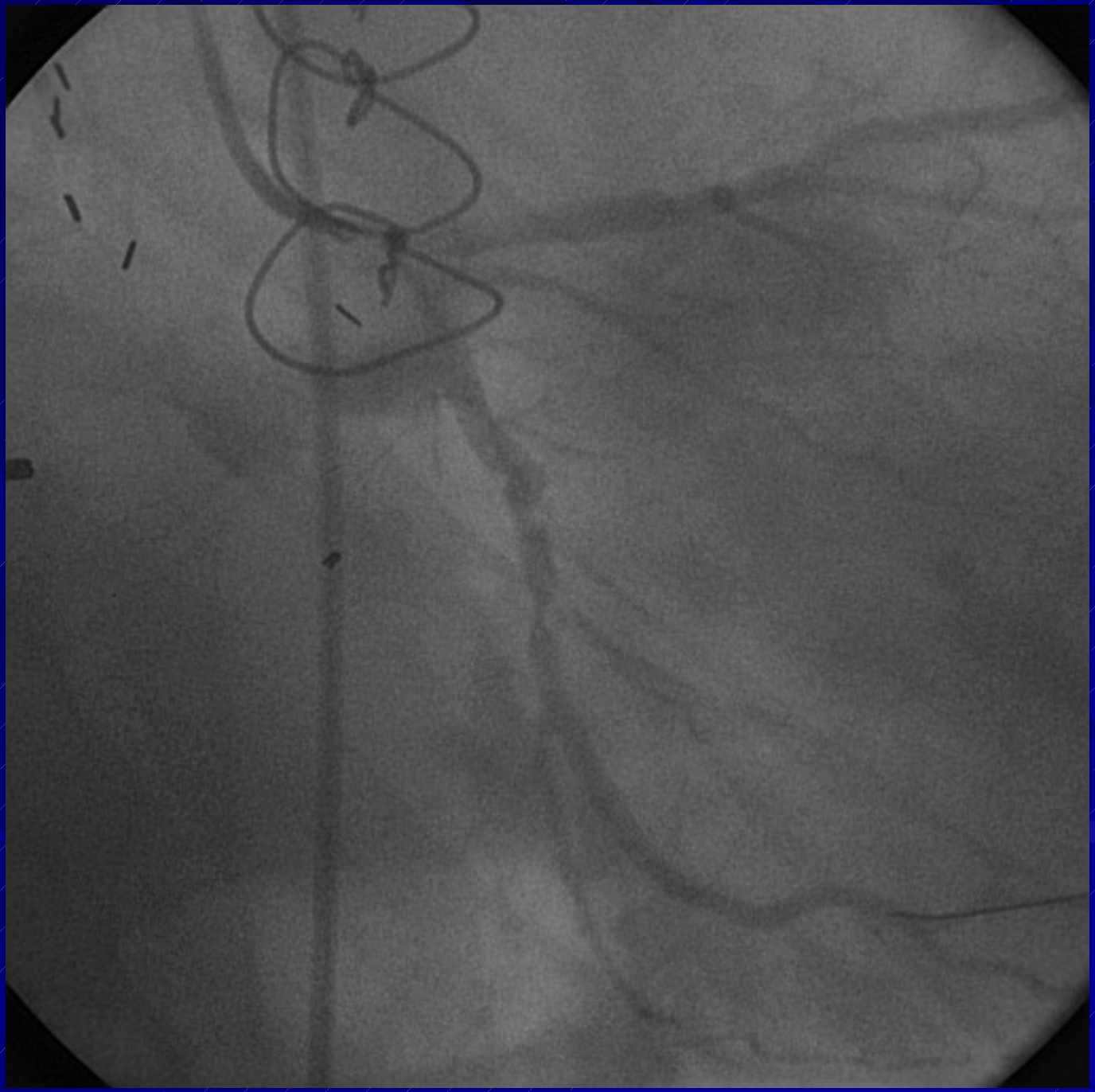


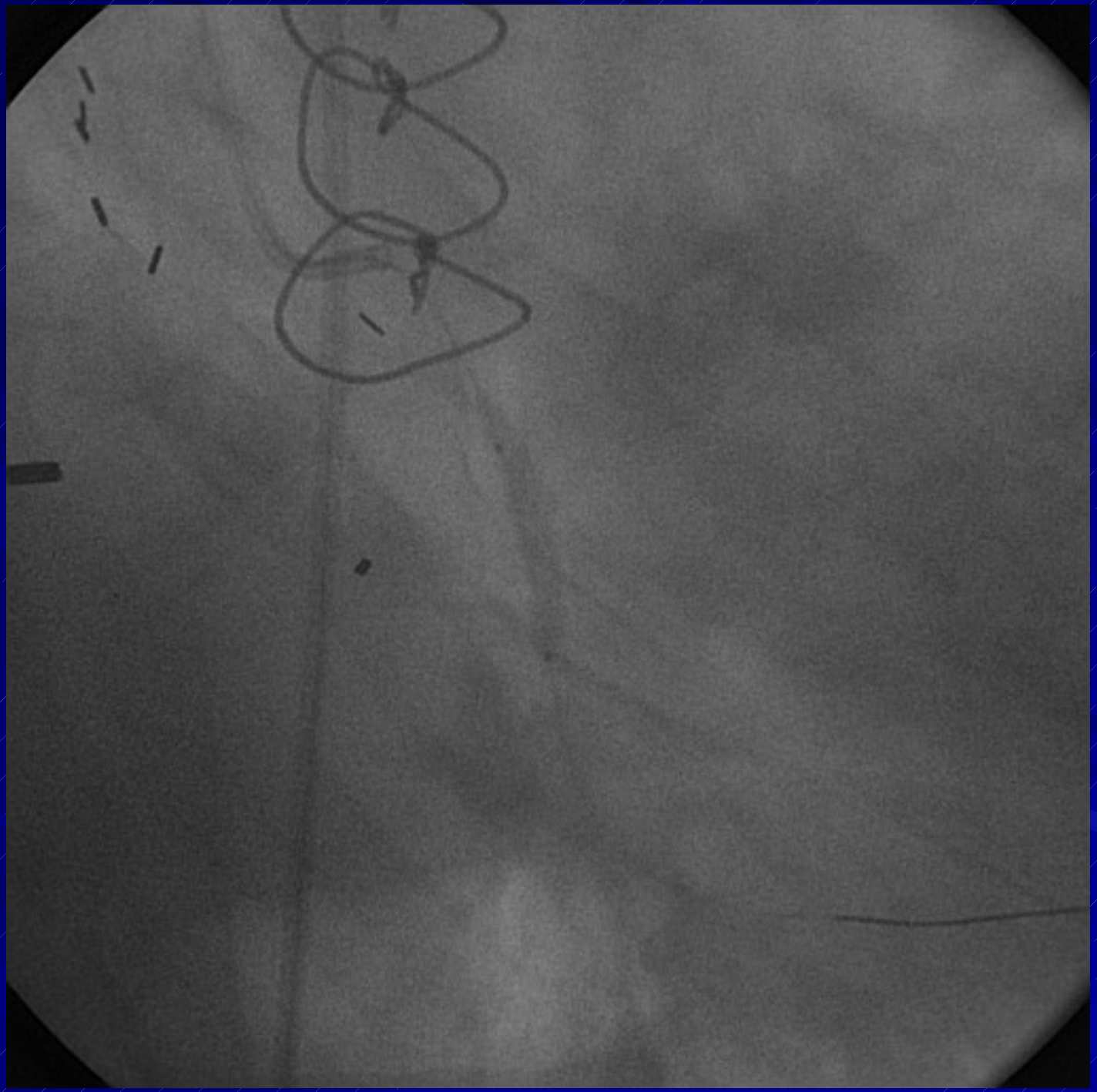


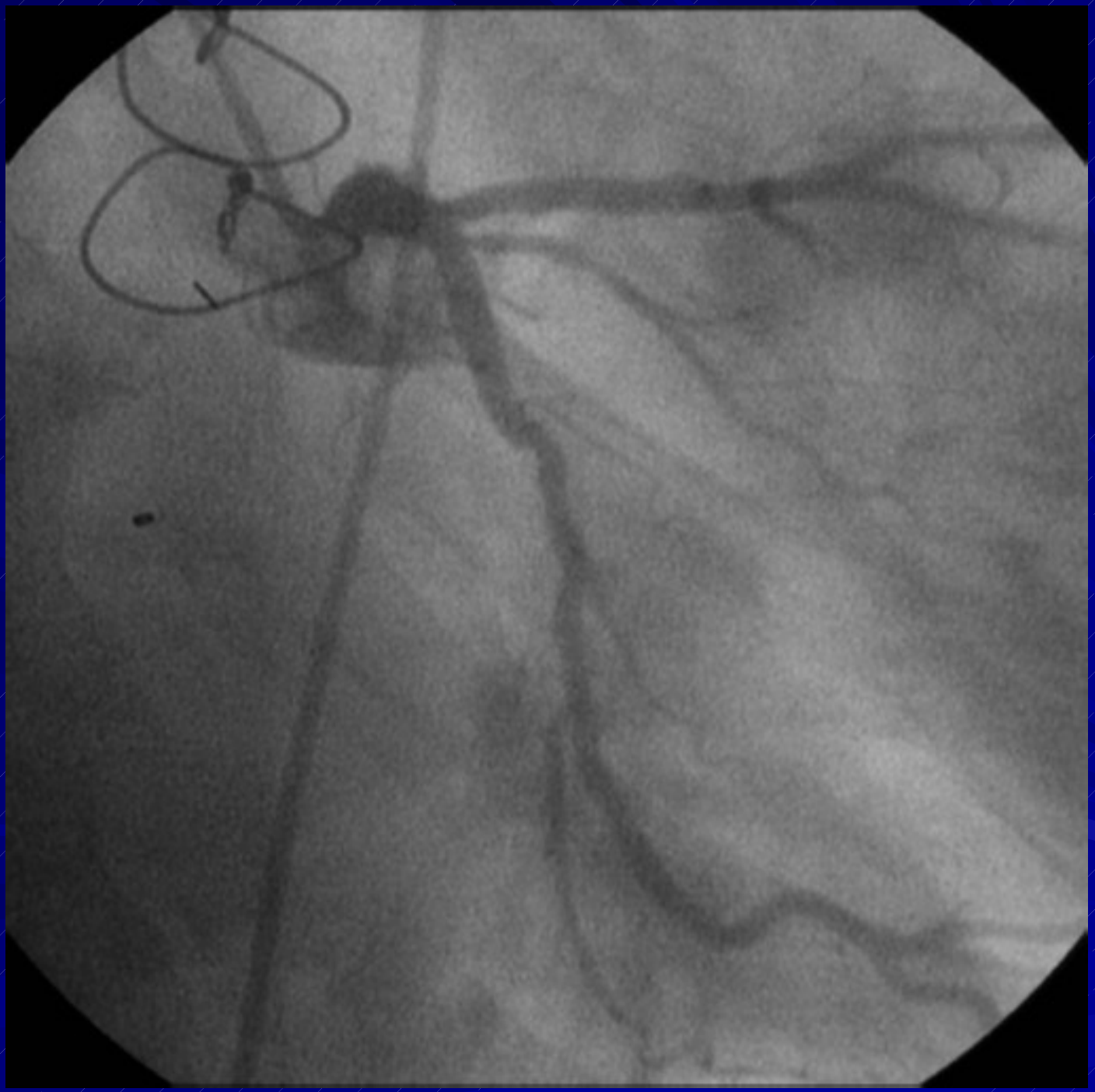
- DONOR DISEASE



- DONOR DISEASE
- שנה לאחר השתלת לב
- בזמן ההשתלה הושק מעקף עורקי לעורק הימני

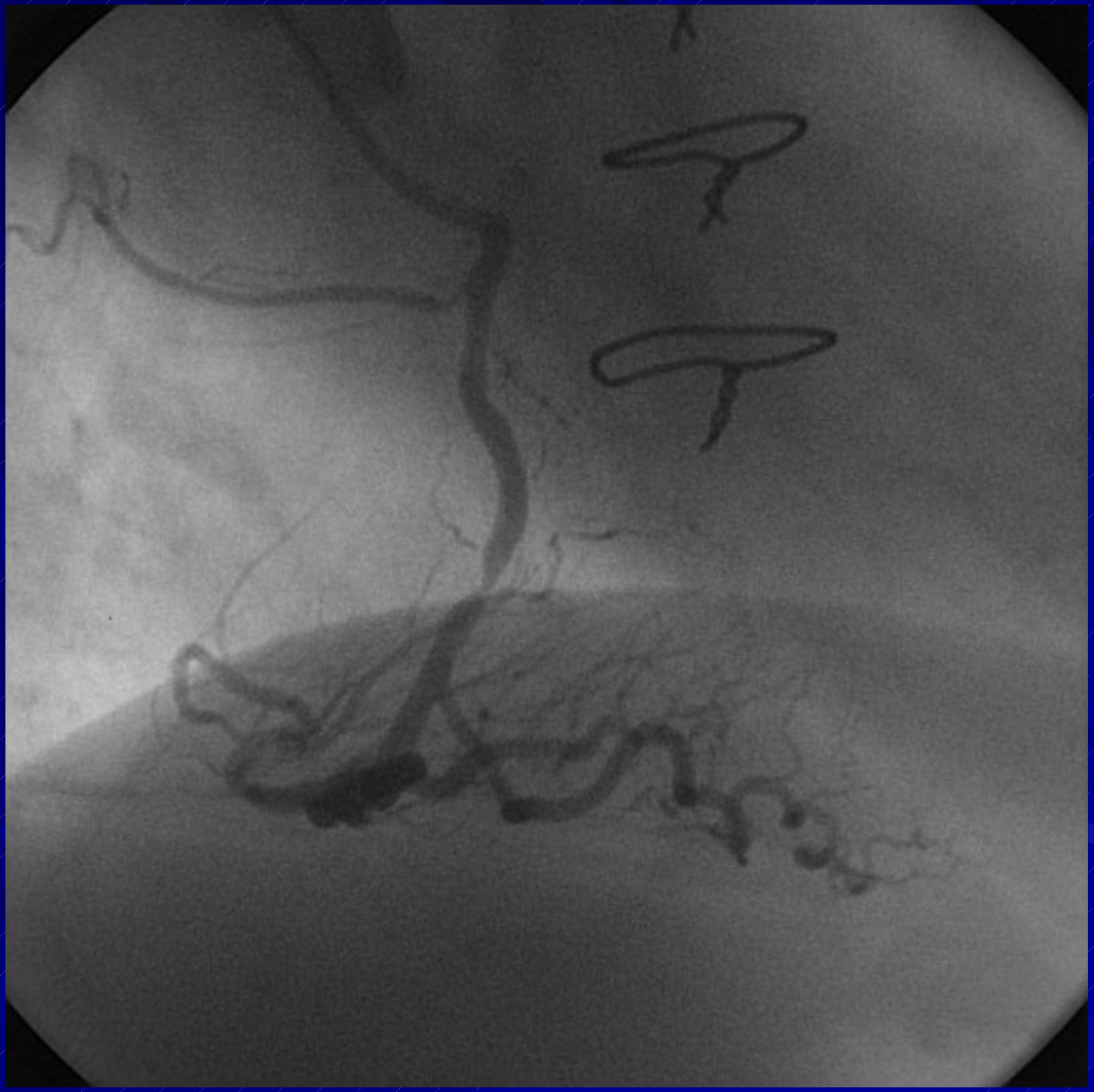


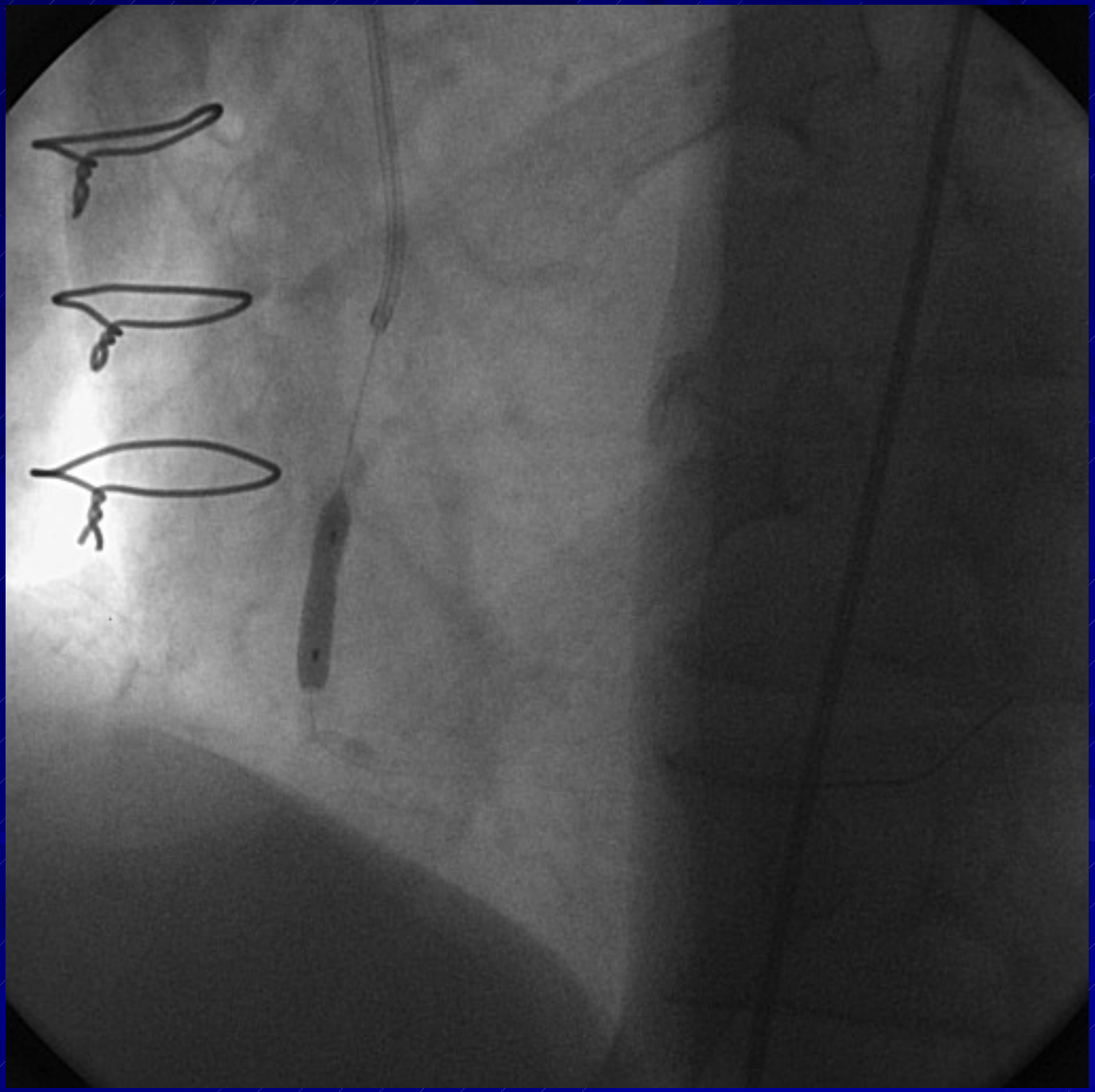


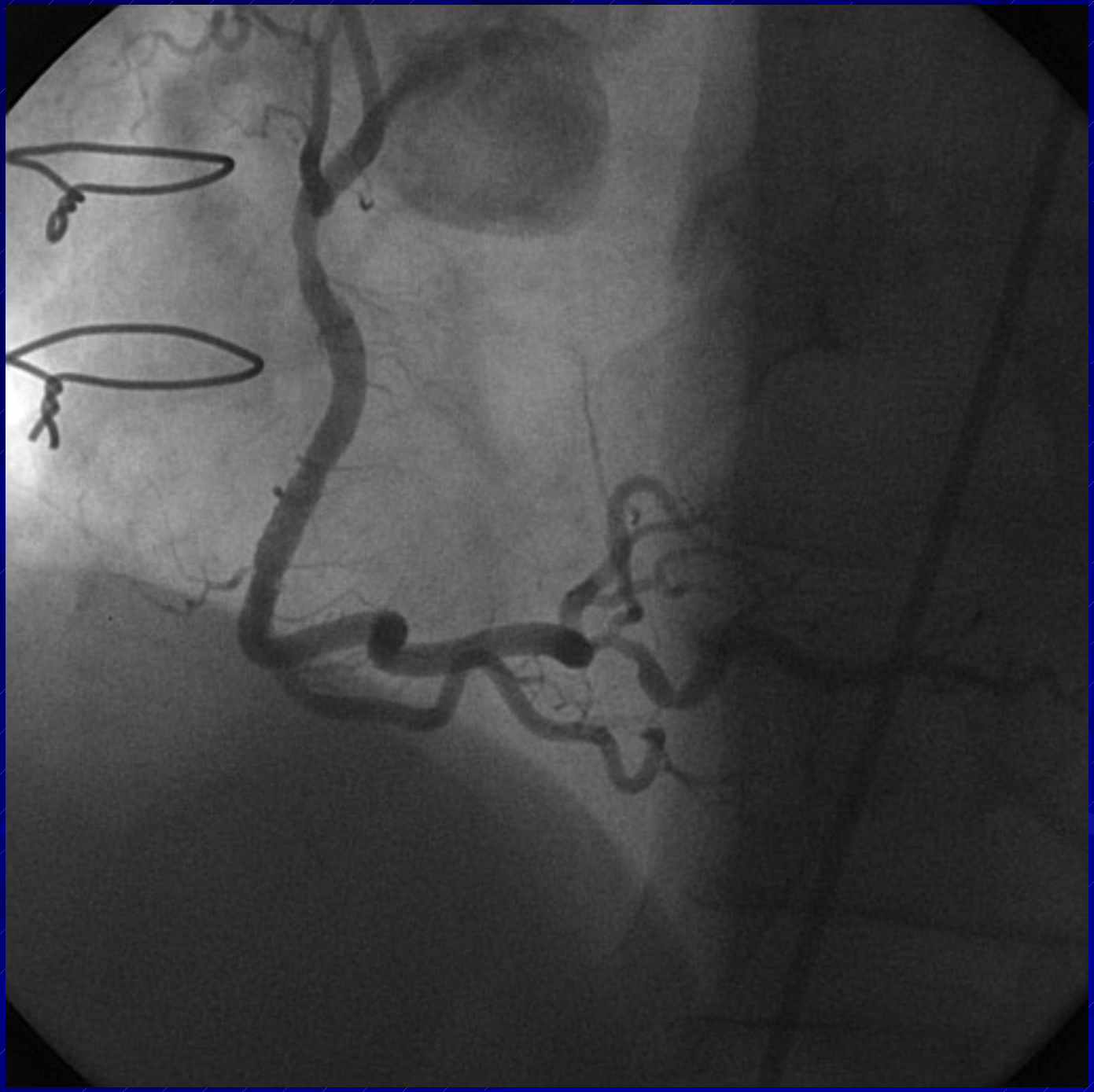


- DONOR DISEASE

חודשיים לאחר השתלת לב

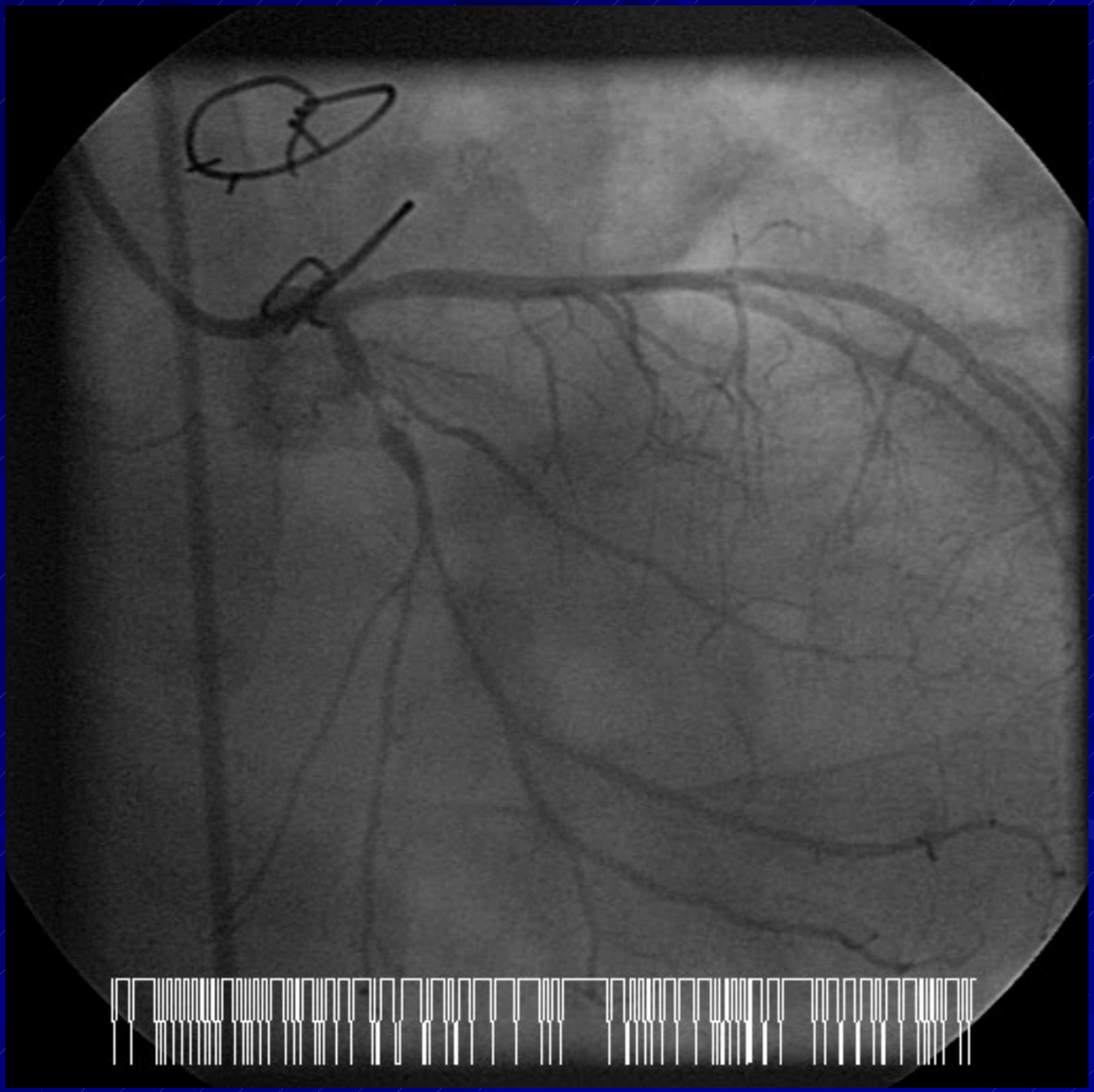


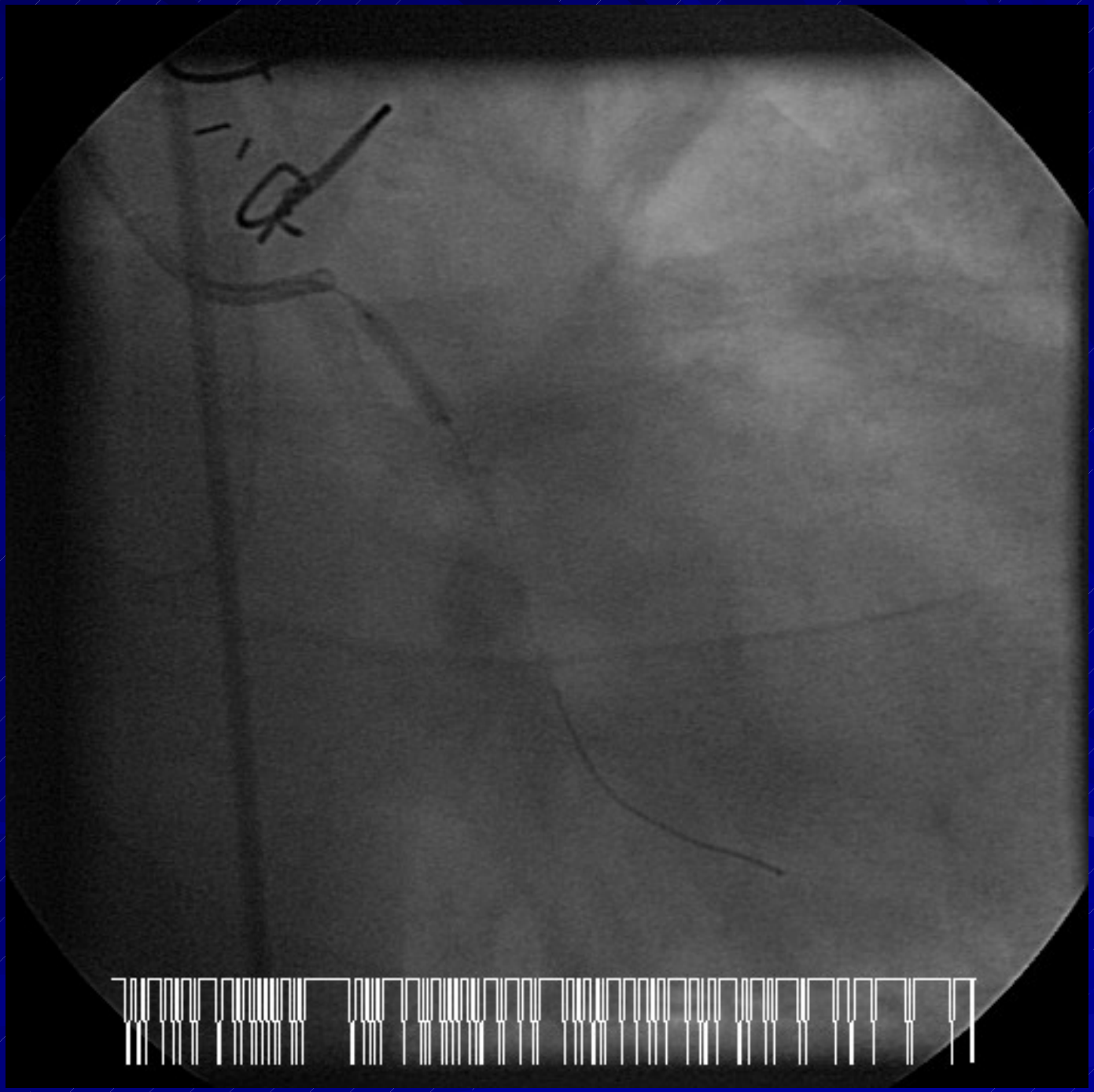


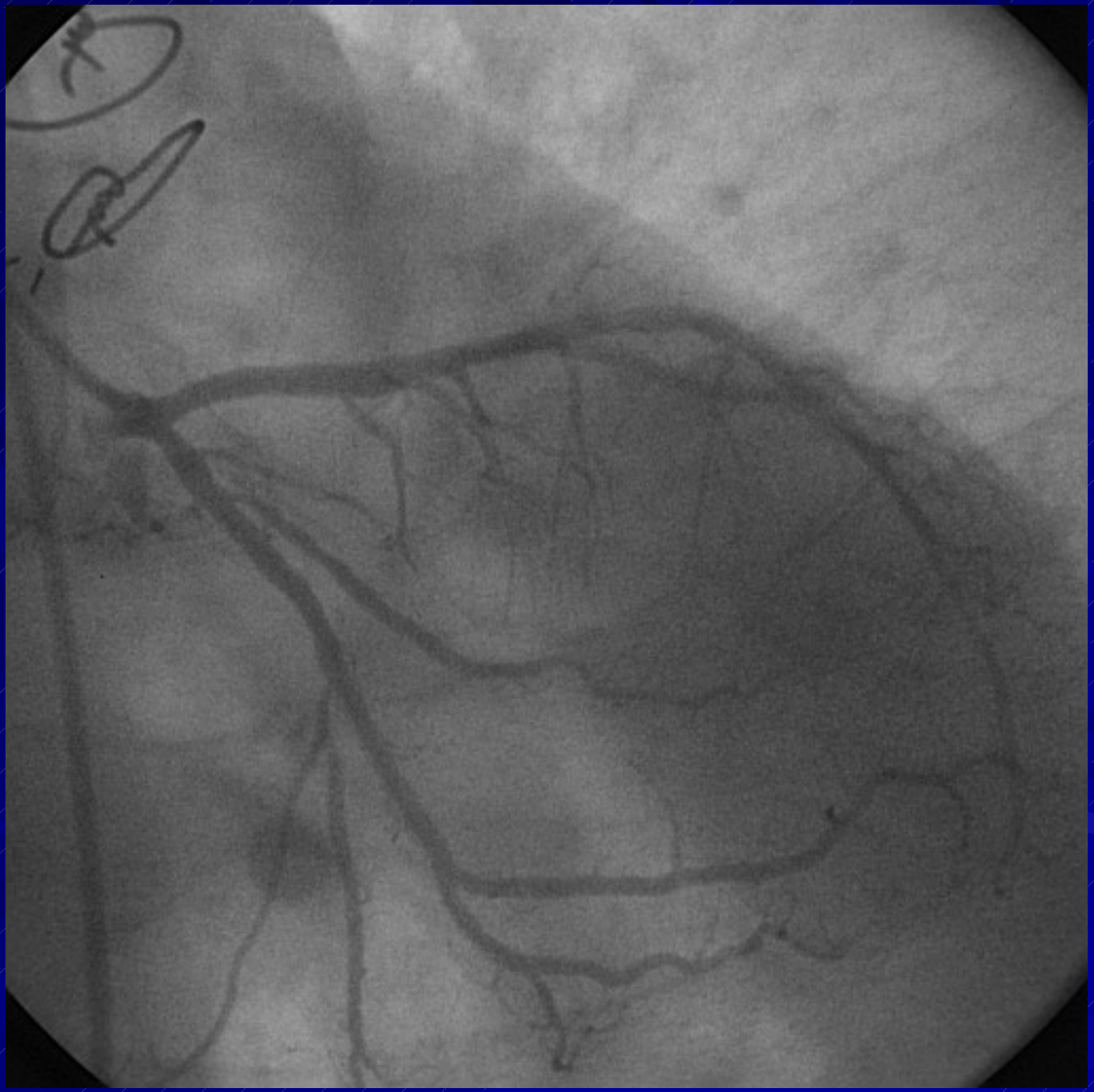


ATHEROSCLEROSIS

צנתורים קודמים ללא היצרויות

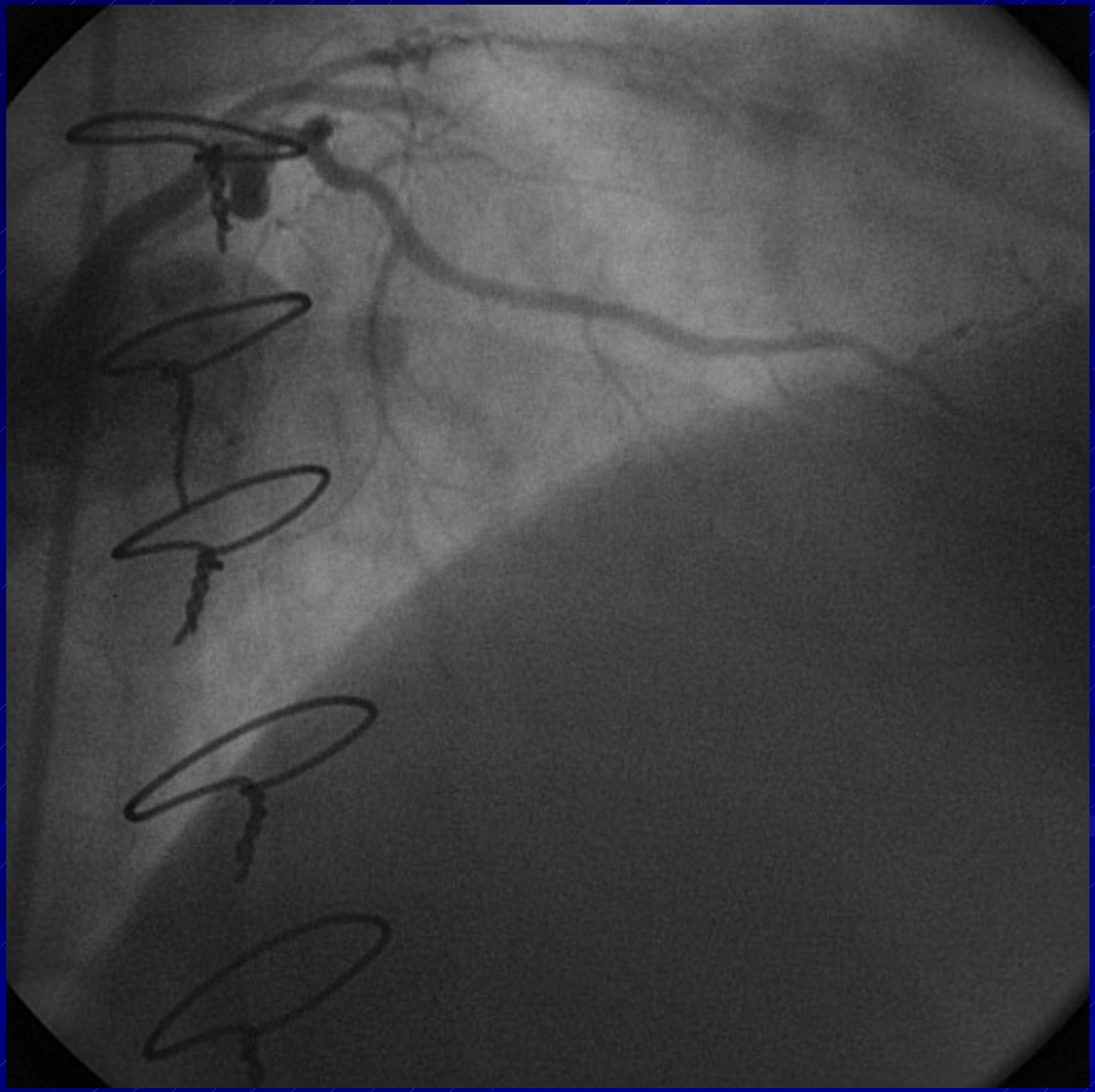


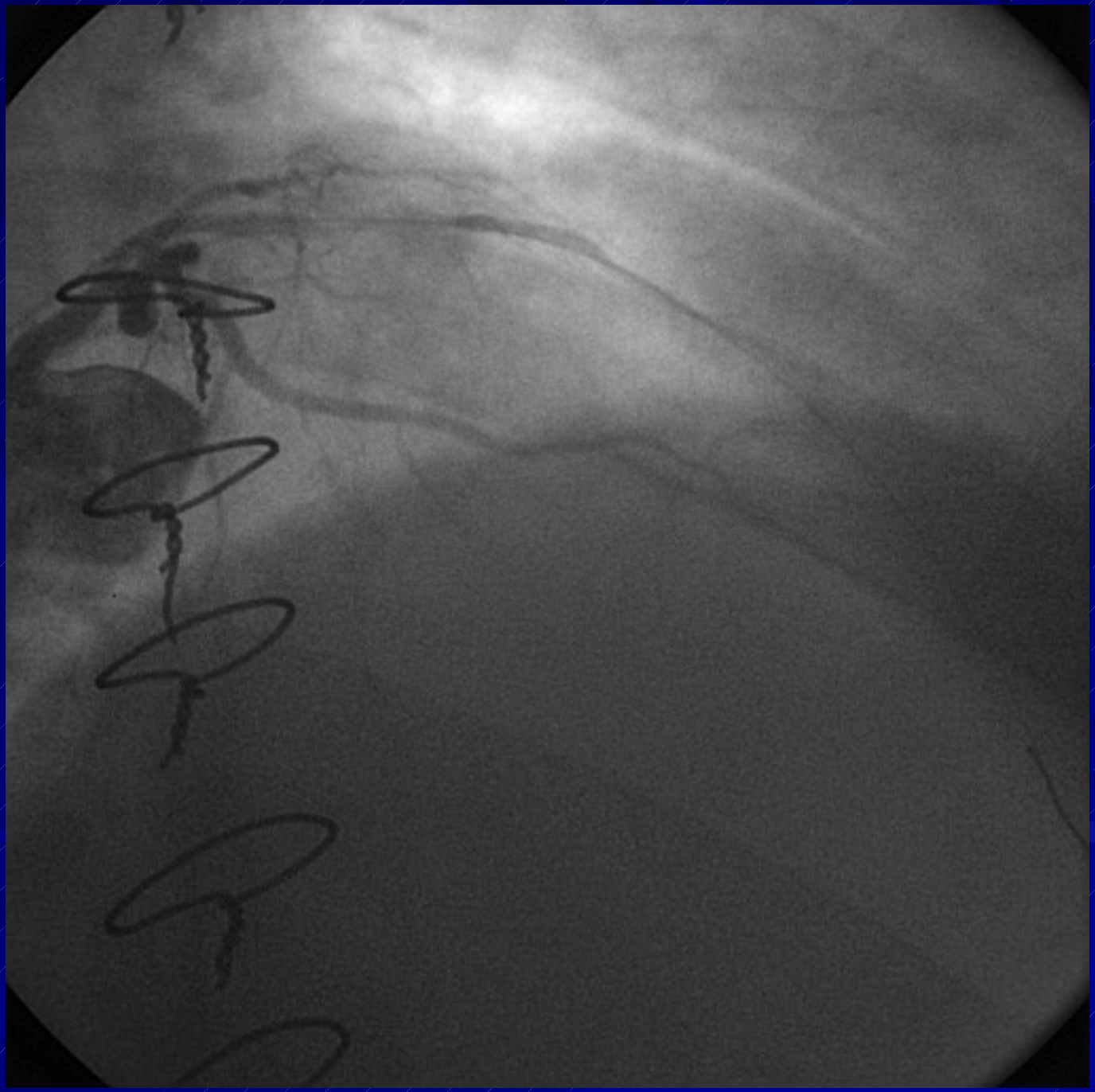


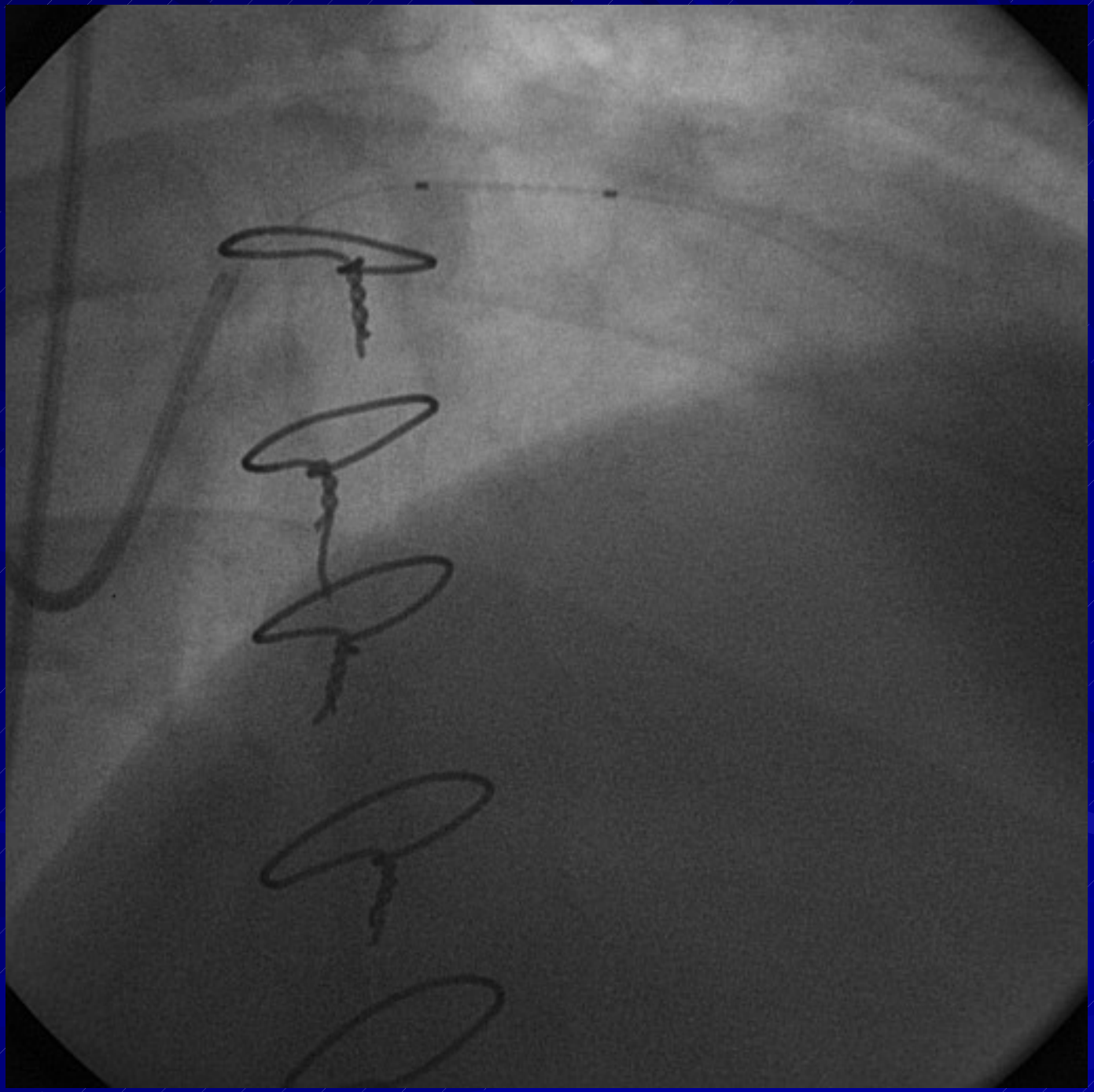


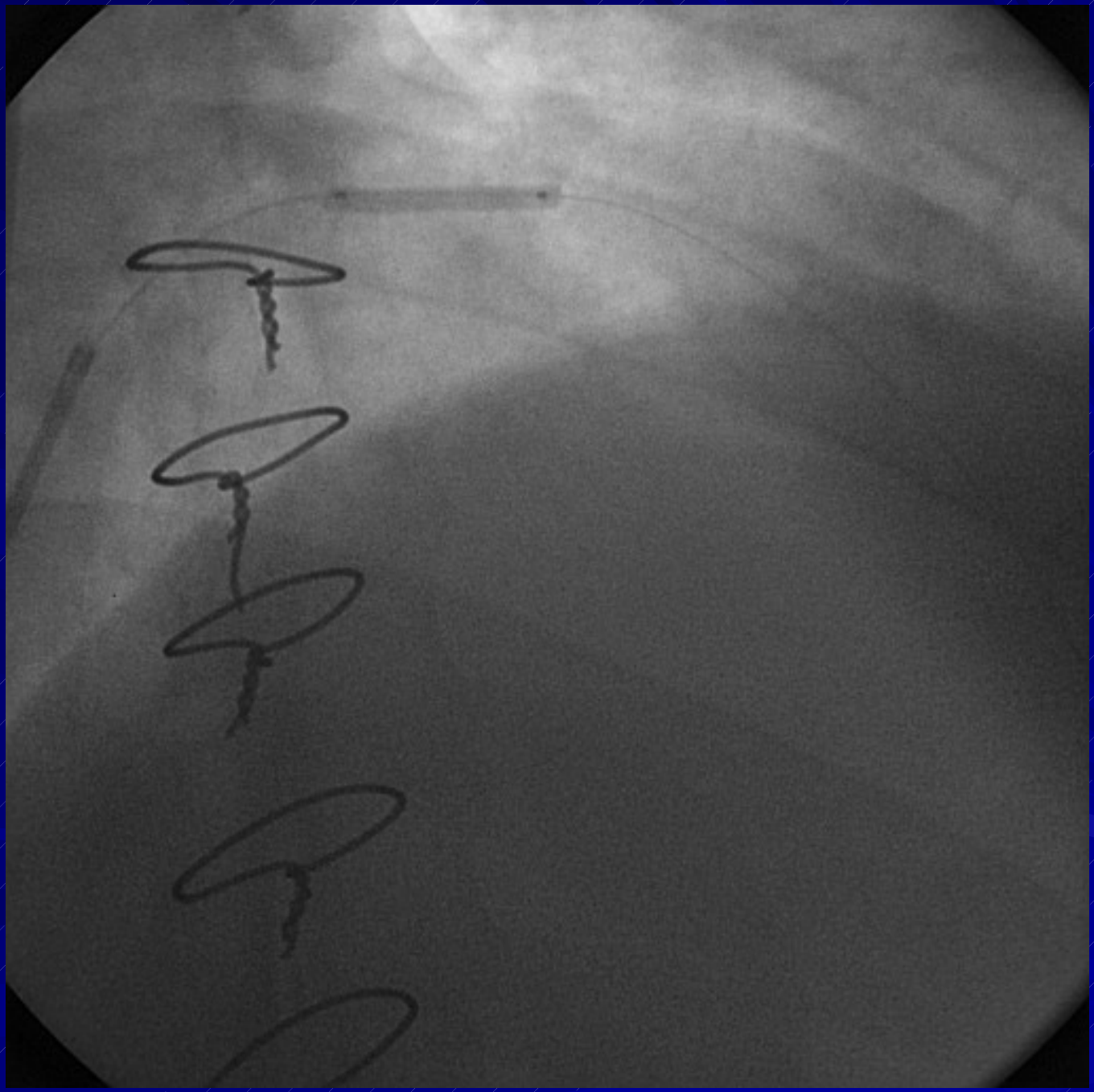
- ATHEROSCLEROSIS

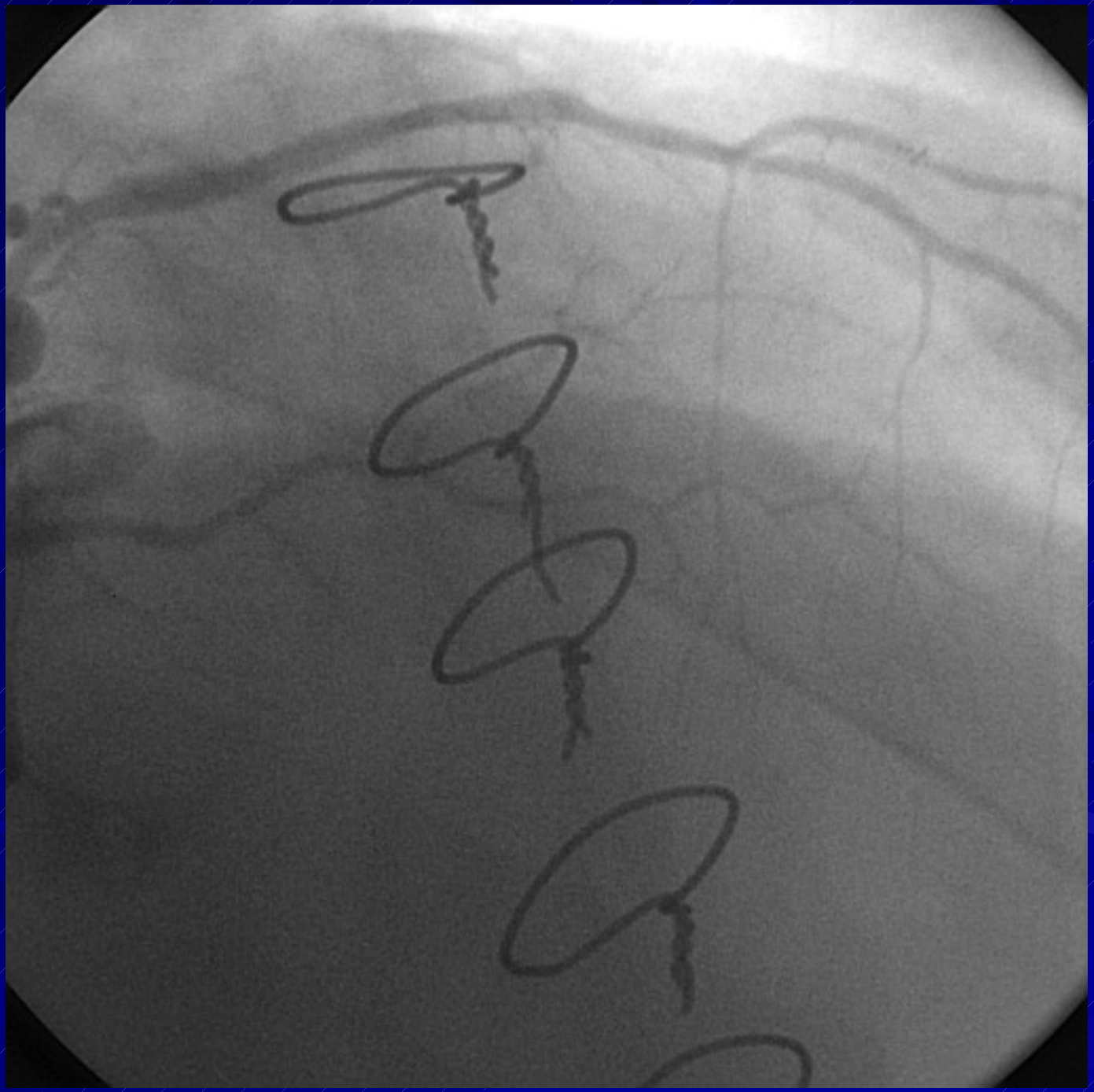
Acute MI





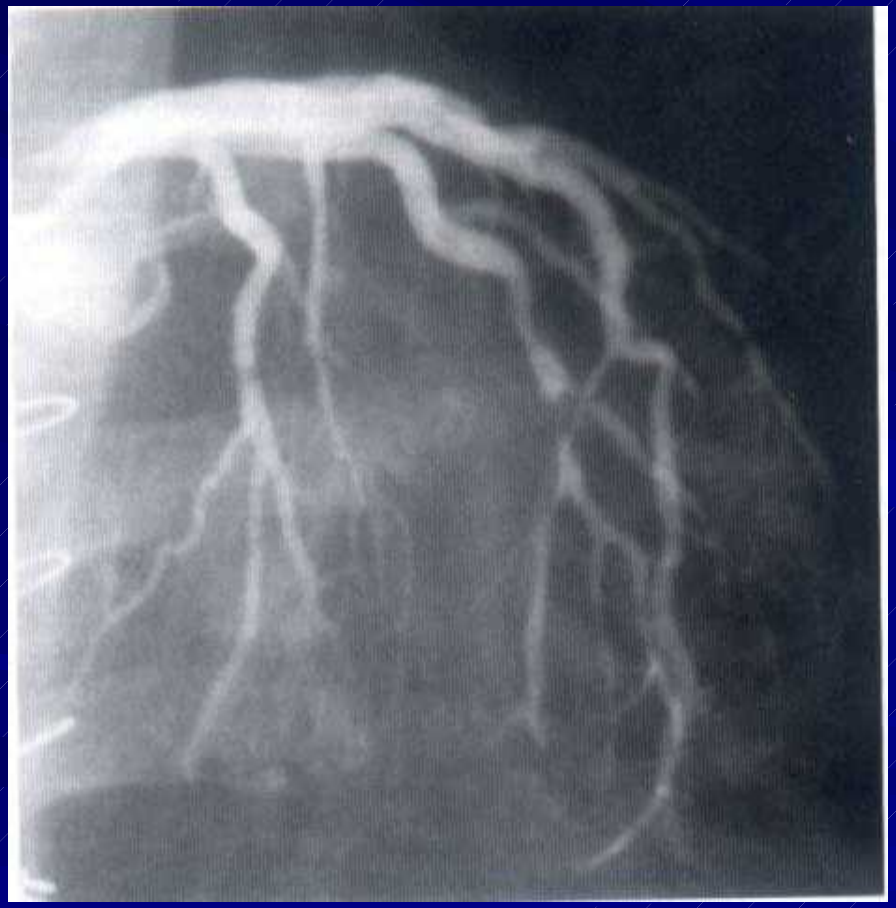




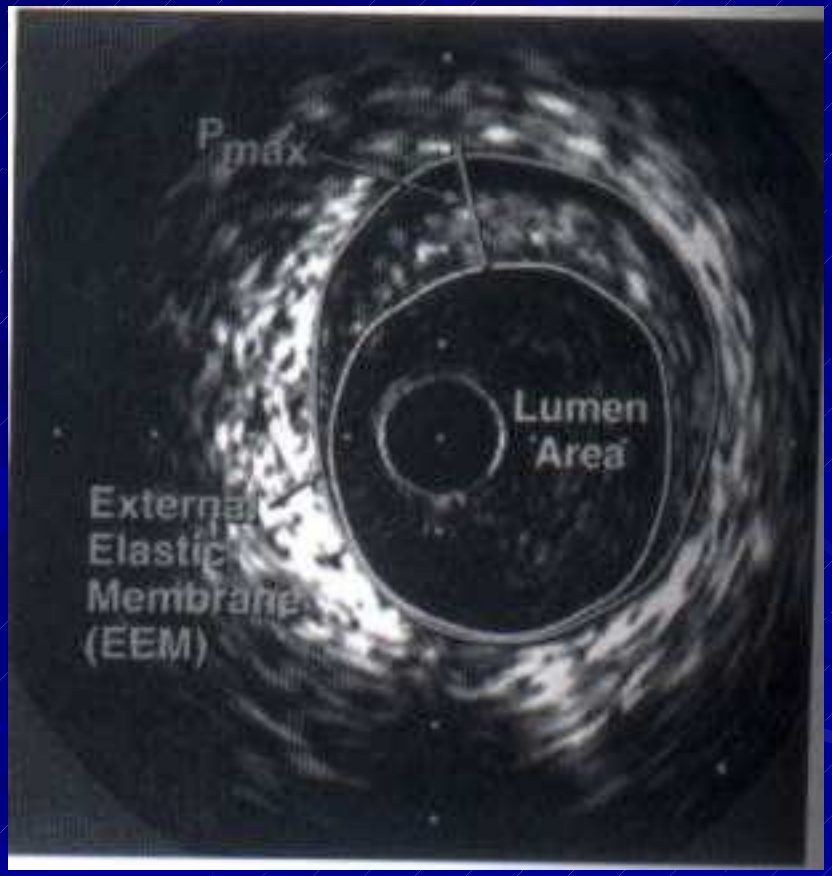


Graftsclerosis

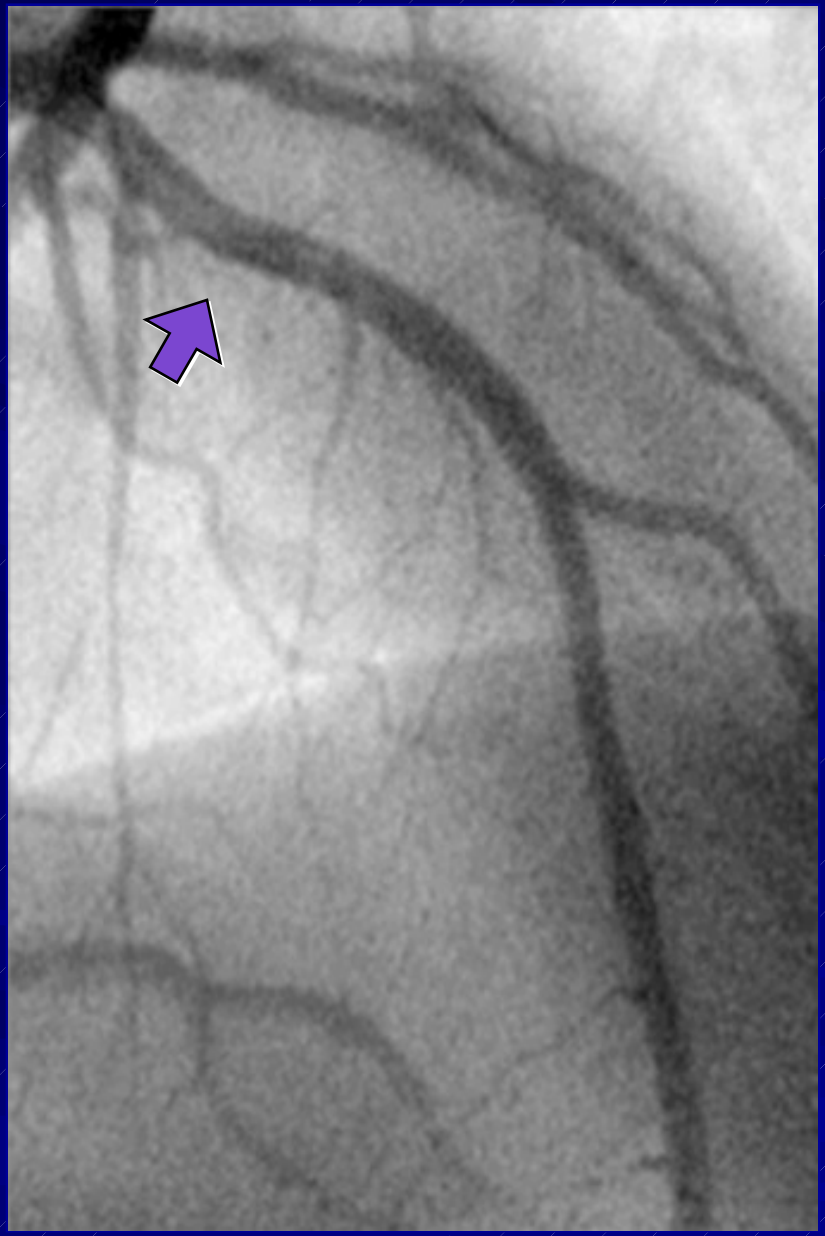
Angiography

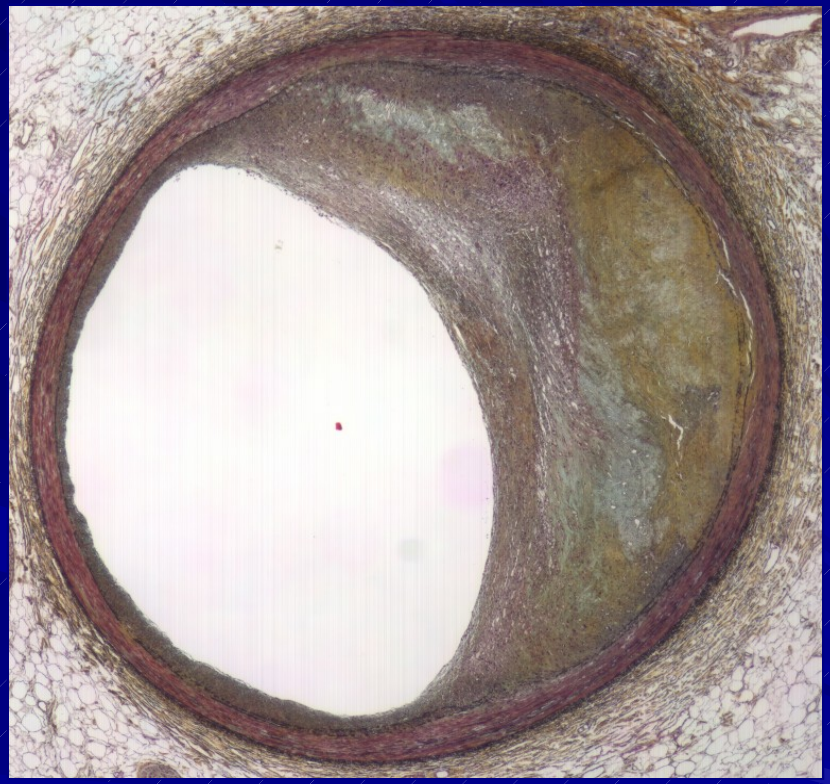


IVUS

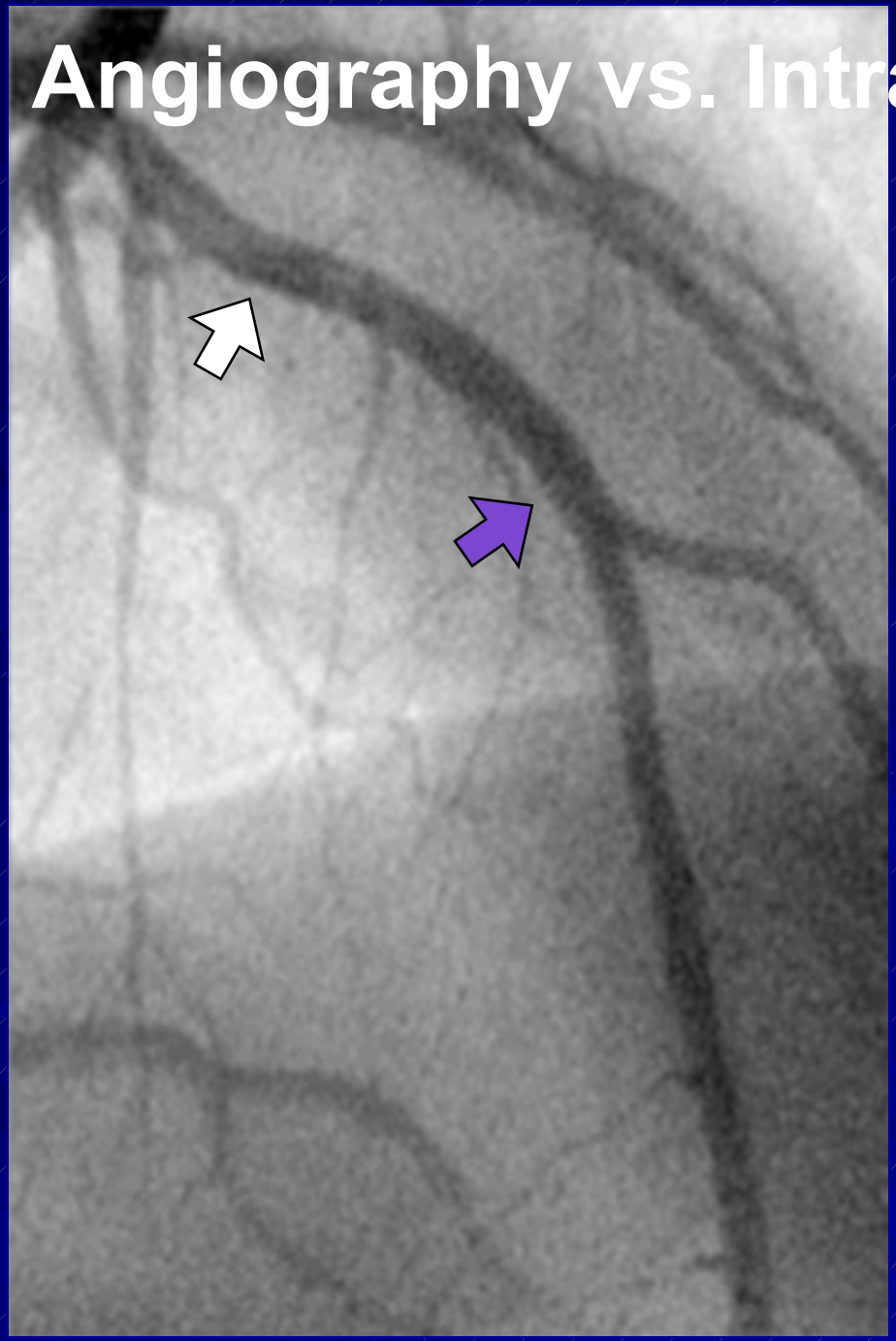


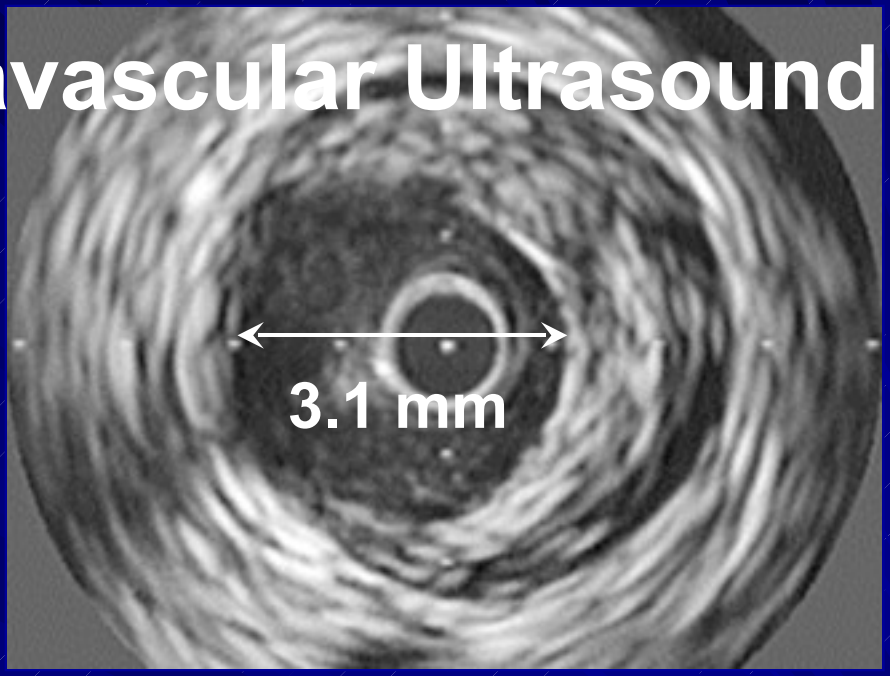
Angiography vs. Histology

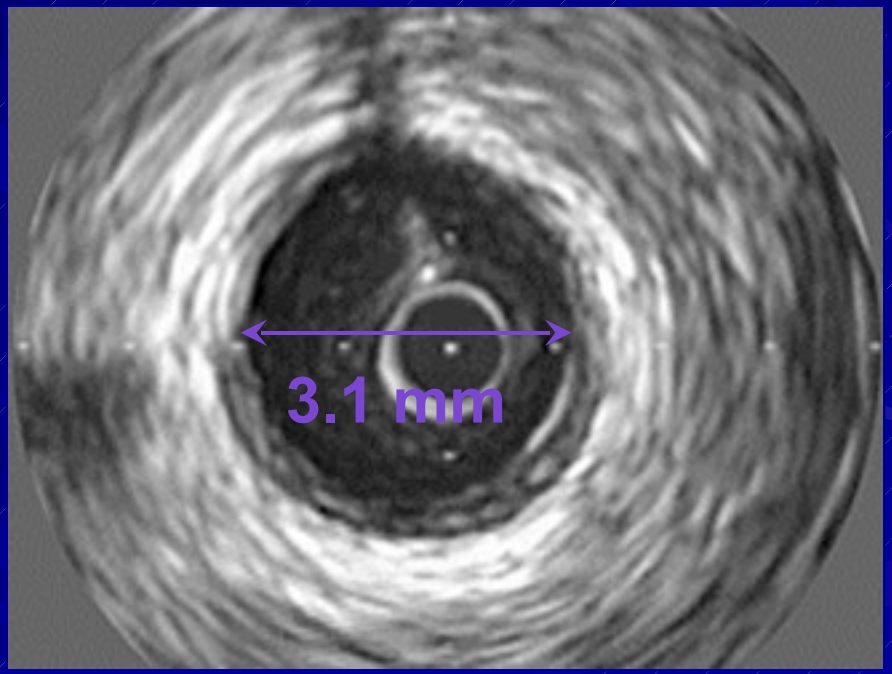




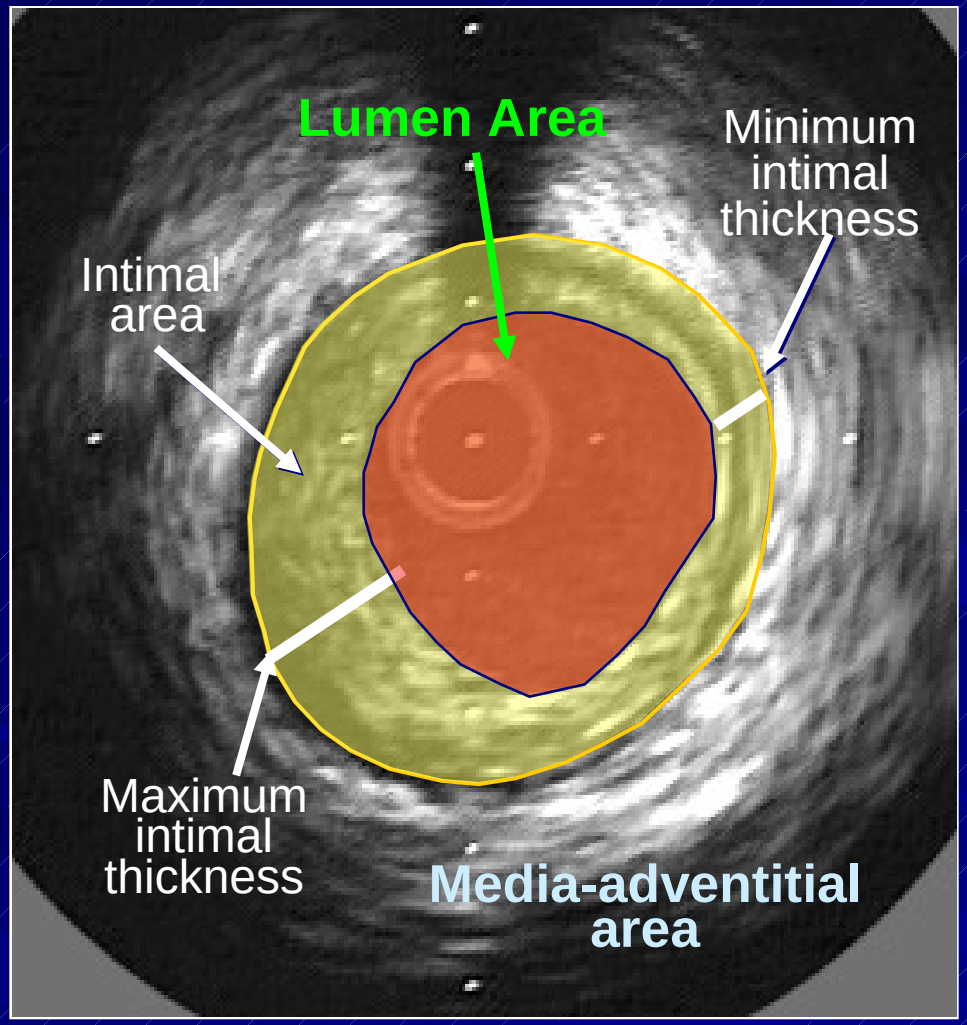
Angiography vs. Intravascular Ultrasound







IVUS population core laboratory measurements



Lumen

Cross sectional area (mm^2)

Maximum diameter (mm)

Minimum diameter (mm)

Intimal thickness

Intimal area (mm^2)

Maximum intimal thickness (mm)

Minimum intimal thickness (mm)

Media-adventitia

Cross sectional area (mm^2)

Maximum diameter (mm)

Minimum diameter (mm)

- The first year IVUS results render the greatest amount of intimal thickening compared to the other early years after transplant

Kobashigawa J . JHLT 2000 19; 546-550

- First year IVUS measurements, including the change from baseline to 1 year maximal intimal thickness (MIT) , have been reported to be a surrogate marker for long-term outcome after heart transplantation.

Mehra MR JHLT 1995;14:632-649

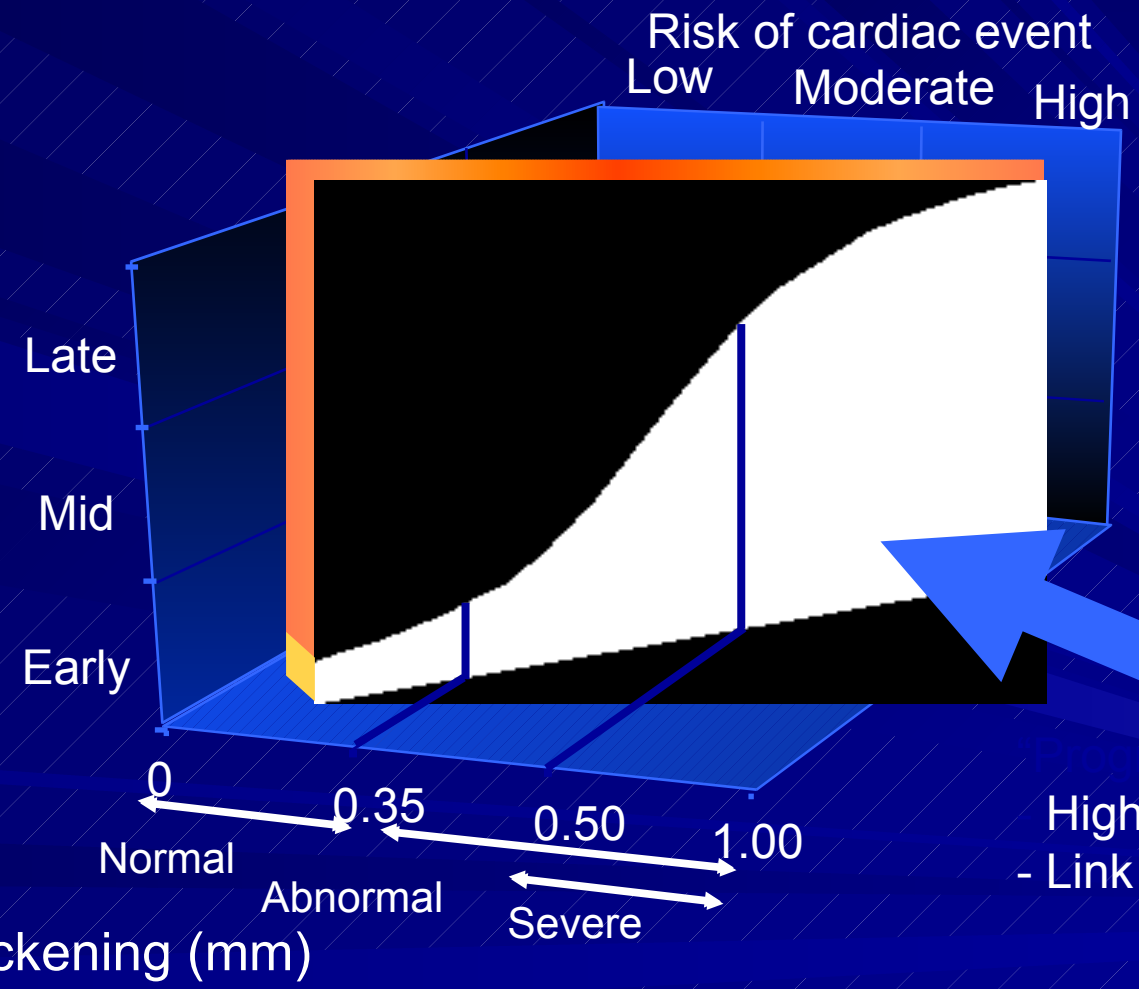
Rickenbacher PR circulation 1995;92:3445-3452

Kapadia SR Curr.Opin Cardio 1999;14:140-150

- This IVUS measurement most likely represents a heightened immune response of recipient to the donor heart , which can lead to cardiac allograft vasculopathy (CAV) and subsequent poor outcome

Kobashigawa ja JHLT 2003;22: 711-714

Maximal Intimal Thickening Predicts (Cardiac Events (IVUS



High plaque burden
- Link with cardiac events

Mehra M et al. *J Heart Lung Transplant* 1995; 14:S207-11; Kobashigawa JA et al. *J Am Coll Cardiol* 2005; 45:1532-7; Tuzcu EM et al. *J Am Coll Cardiol* 2005; 45:1538-42.

- Multicenter IVUS validation study among heart transplant recipients . Outcome after 5 years

Kobashigawa JA

J.Am.Coll.Cardio 2005;45:1532-1537

- 125 PT.
- 5 centers
- Transplanted prior to 1997
- 5 year clinical data follow-up

IVUS tapes (at baseline and 1 year) were reanalyzed

At core IVUS laboratory (UCLA)

- Pt. with MIT more then 0.5 mm (in any site) compared to those with MIT less then 0.5 mm

- Incidence of death or graft loss :

- 20.8% vs 5.9%

P=0.007

- Non fatal major adverse cardiac events

- 45.8% vs 16.8%

P=0.003

- Findings of newly occurring angiographic luminal irregularities

- 65.2% vs 32.6%

P=0.004

Cardiac Allograft Vasculopathy Treatment Approach

- Modification of risk factors
- Medical therapies/strategies
- Revascularization
- Retransplantation

Therapeutic Modalities to Treat Cardiac Allograft Vasculopathy

- Antiproliferative agents:
  - **Sirolimus/everolimus, mycophenolate**
  - **Low-MW heparin**
- Antimetabolites:
  - **Methotrexate**
- Antithrombotic agents:
  - **Hirulog**
  - **AT III**
- Monoclonal antibodies:
  - **Growth factors**
  - **Adhesion molecules**
  - **Cytokines**

Antihypertensive agents:

- Calcium channel blockers
- ACE inhibitors

New immunosuppressive therapies:

- Use of photopheresis

Lipid-lowering agents:

- HMG-CoA reductase inhibitors

Anti-oxidants:

- Vitamins C and E

MW, molecular weight; AT III, antithrombin III; ACE, angiotensin-converting enzyme;HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A

Year Results of Statin Trials-8

	Pravastatin		N=97	Simvastatin		N=72
	Pravastatin N=47		Control N=50	Simvastatin N=35		Control N=37
Chol / LDL mg/dl	*183±9		205±20	* 116±18		156±24
% Survival	* 67%		47%	* 89%		60%
% CAV	* 47%		72%	* 24%		55%
1st yr IVUS	50% reduction			50% reduction		
% Rejection Mortality	4%		10%	3%		14%

Kobashigawa, unpublished data

Wenke, Circ 2003;107:93-97

***p<0.05**

Graft Vasculopathy

- 1,3,5,7,10 a coronary angiogram + IVUS
- Changes in IVUS:
  - Aggressive treatment of risk factors
  - No influence of CNI (studies underway)
  - Rapamycin (SrI/EvI) shows better protection
  - Rapamycin Therapy? (rapastat, Mancini)
  - Steroid weaning?
- Late changes in angiogram
  - Aggressive treatment of risk factors
  - PTCA + stenting (drug eluting)
  - ACBP only selective cases
  - Retransplantation only young healthy patients

- Use of Rapamycin slows progression of cardiac transplantation vasculopathy

- Mancini D , Circulation 2003; 108: 48-53

- Single center, open –label , randomized
- Pt. with severe CAV
- Defined as :
- Epicardial stenosis 50%
- MIT 0.5 mm
- Severe diffuse vessel tapering

- 46 pt.

- Sirolimus
- n=22

continued treatment

n=24

- Primary endpoint :
- Death
- Need for angioplasty
- Need for CABG
- MI

- Sirolimus 13.6%
- Current immunosuppression 58.3%
- P 0.001

Therapy of Vasculopathy

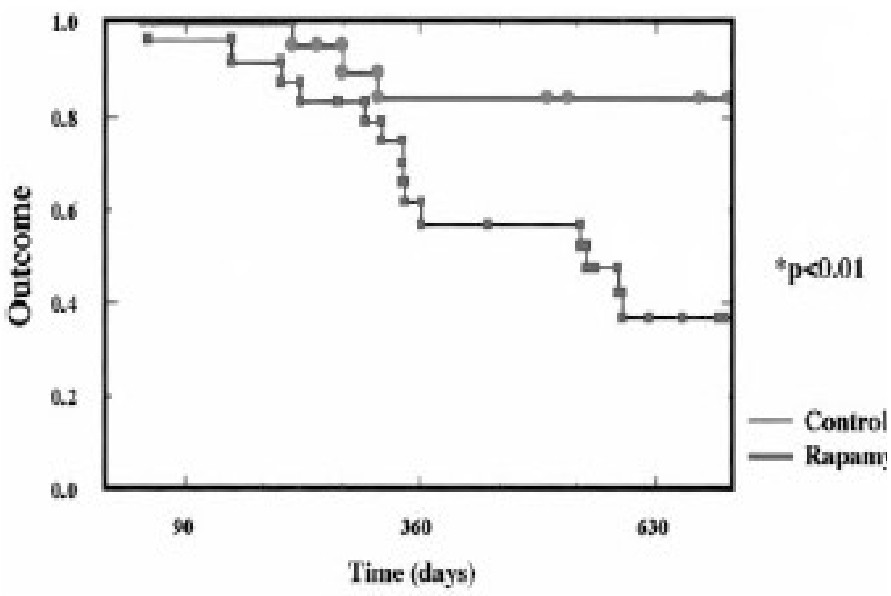


Figure 3. Time to primary end point (death, angioplasty, myocardial infarction, or >25% increase in catheterization score) i the control and rapamycin groups.

TABLE 3. Study End Points	N=24 Control	N=22 Rapamycin
Primary end points		
Death	4	1
PTCA	5	1
CABG	1	0
Myocardial infarction	7	1
>25% increase in catheterization score	8	2
Total	25	5
Secondary end points		
Cardiac hospitalizations	20	5
Congestive heart failure	14	5
Chest pain	6	
Relist for transplantation	5	2
Total	25	7

Mancini et al Circulation 03

Everolimus – Proliferation Signal Inhibitor

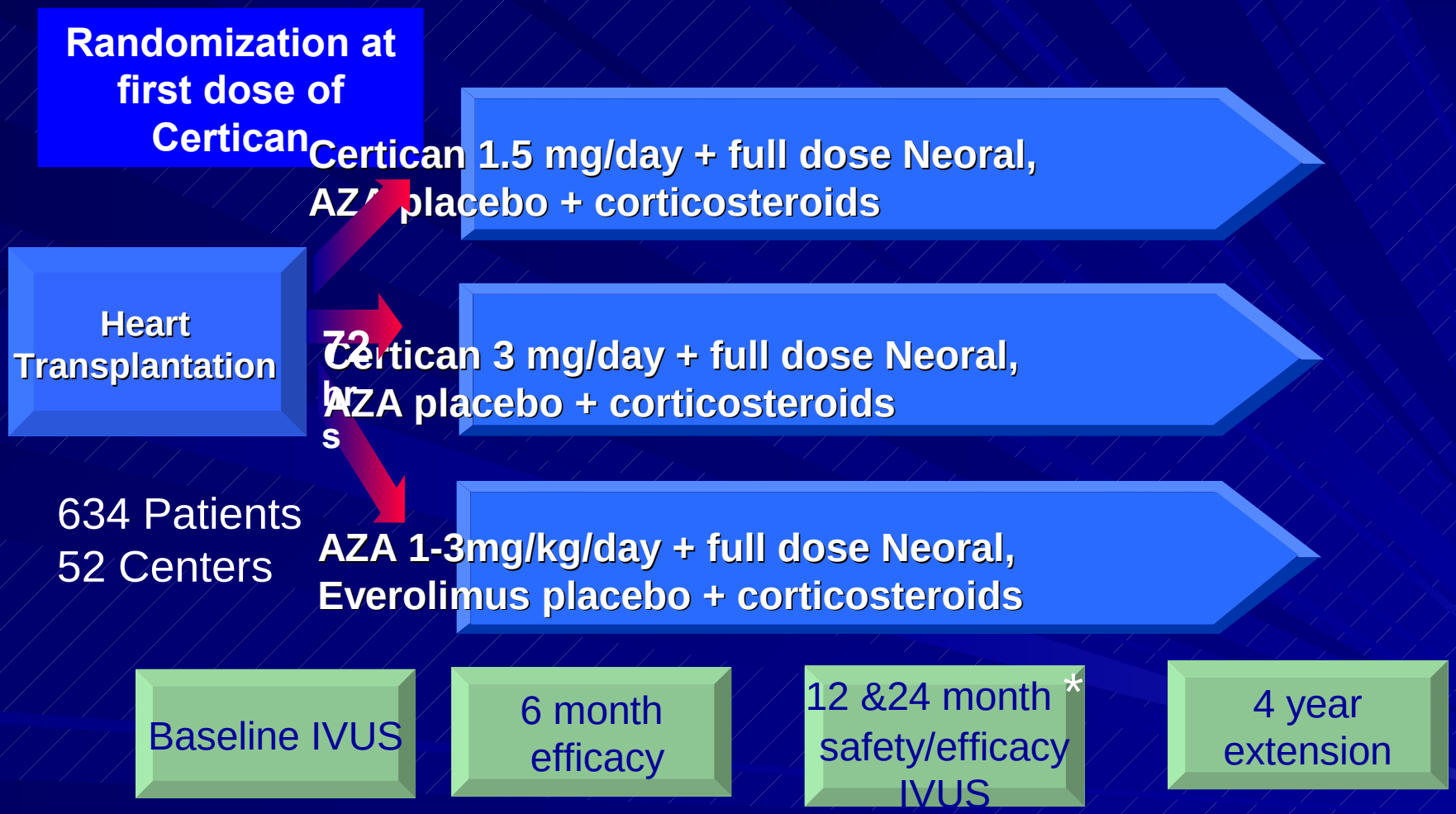
"Dual-action" drug class

- **IMMUNOSUPPRESSIVE:** Acts synergistically with cyclosporine (CsA) to prevent rejection and prolong allograft survival
- **ANTI-PROLIFERATIVE:** Inhibits growth-factor-driven vascular smooth muscle cell proliferation

ACUTE REJECTION

VASCULAR REMODELING

RAD B253: Study Design

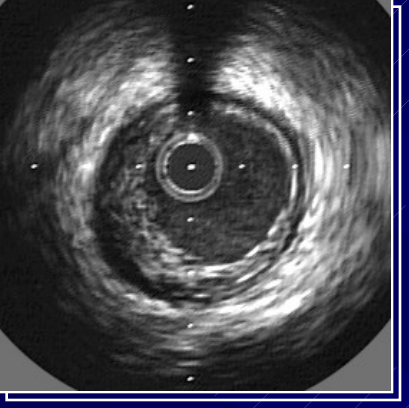


SAMPLE SIZE:

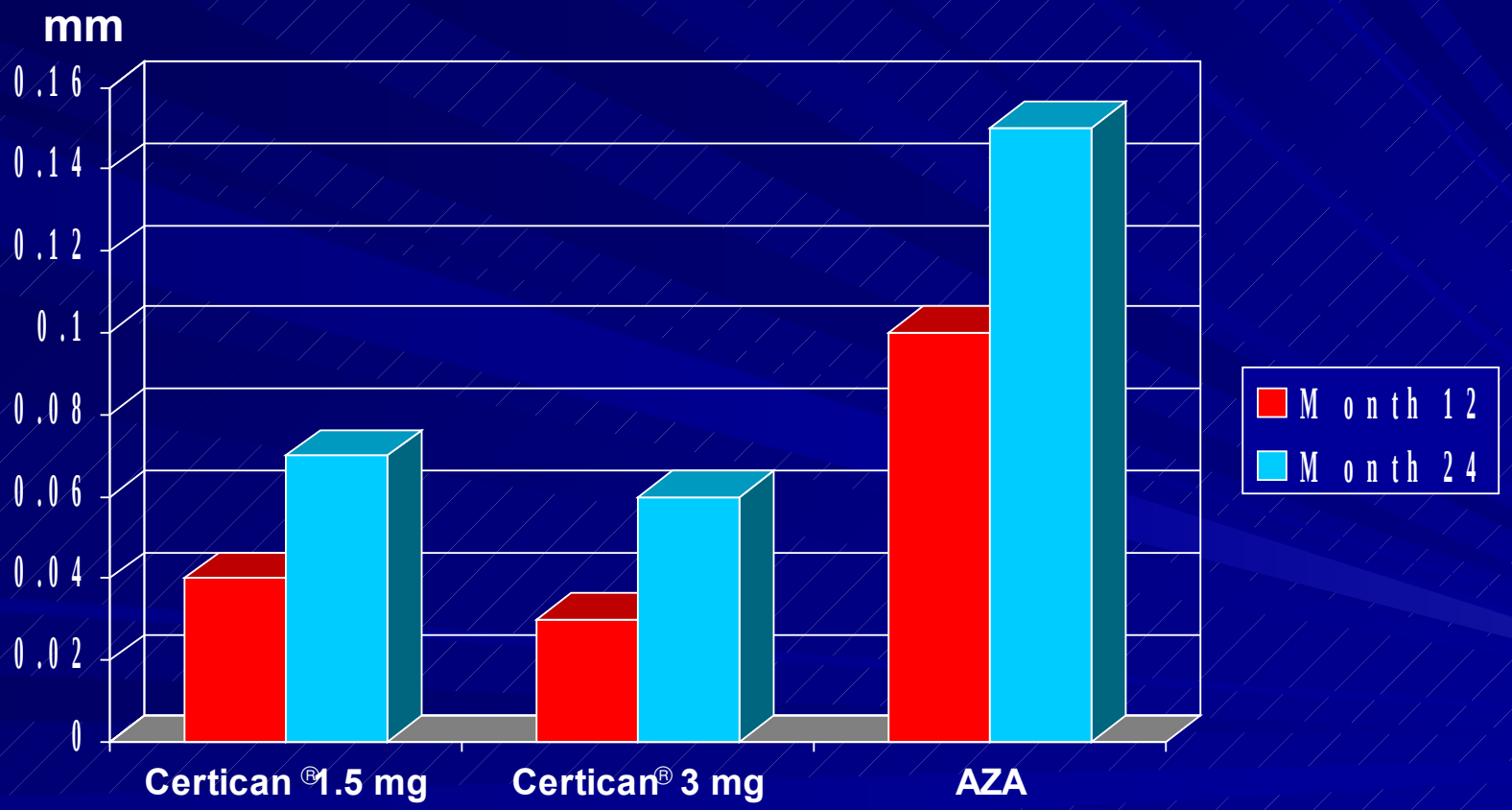
Primary efficacy failure: AZA 45%, Everolimus 30%

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

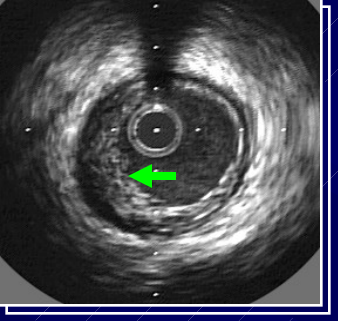
***Study unblinded at 12 months**



Change in MIT (IVUS) at 12 and 24 month



Month 12 and 24: p<0.05 Certican® 1.5mg vs AZA, p<0.01 Certican® 3 mg vs AZA



IVUS Parameters: Transplant Vasculopathy((24mo

AZA (*n*(=60/214	Certican® 3.0 mg (*n*=44/211)	Certican® 1.5 mg (*n*=45/209)	IVUS measurement: Change from baseline
0.15	0.06**	0.07*	Max. intimal thickness ((MIT) (mm
1.52	0.83**	0.79**	Intimal area (mm^2)
20.25	12.54**	13.21*	Intimal volume (mm^3)
58.3	45.5	33.3*	Incidence vasculopathy (%) (MIT increase ≥0.5 (mm

*$p < 0.05$ vs AZA; **$p < 0.01$ vs AZA

- Everolimus for the prevention of allograft rejection and vasculopathy in cardiac transplant recipients

Eissen HJ

N.Engl.J.Med 2003;349:847-858

- Randomized, Double-blind
- Follow-up 1 year
- Everolimus +CSA+ST vs AZA+CSA +ST
- In Everolimus group :
- Fewer incidences of biopsy proven acute rejection
- Less pt. with MIT =0.5 mm (from baselin to 1 year)

Randomized active controlled trial of MMF in transplant recipient

- Transplantation 1998; 66:507-515
- Kobashigawa J

- Large scale ,Randomized ,Double-blind
- Active controlled

heart transplant pt. 650
28 centers

- Received MMF or AZA in addition to CSA+ST

- 72 pt. did not receive any study drug
- (unable to take oral study medication within 5 days of transplantation)

- The treated population did not differ from the enrolled population with respect to baseline
- Characteristics and demographics

MMF GROUP

- Significant reduction in treated rejection episodes at 1 year
- Significant reduction in mortality at 1 year

Baseline and 1 year IVUS

- (morphometric analysis)
- 196 Pt.
- 102 MMF 94 AZA

No significant differences in the result between the two study groups

- First year IVUS data (baseline to 1 year) can be analyzed using :

- Site to site analysis

or

- By morphometric analysis

(average of 10 sites, without matching sites)

Since intimal thickness is heterogeneous with most sites having little or no intimal thickening , morphometric analysis will not be sensitive to detect changes at any one particular site, as it averages data from multiple (usually 10) sites.

- The IVUS data from the randomized multicenter MMF trial was restudied using matched site to site analysis

- MMF reduces intimal thickness by IVUS after heart transplantation : Renalysis of the Multicenter Trial

Kobashigawa ja

Am.J. of Transplantation 2006; 6:993-997

Conclusion

- MMF-treated heart transplant patients compared to AZA-treated patients ,both concurrently on CSA and corticosteroids , in this study have significantly less progression of first year intimal thickening.

- This multicenter study suggests that progression of intimal thickening more then 0.5 mm in the first year after transplantation appears to be a surrogate marker for subsequent mortality, nonfatal major adverse cardiac events and the development of angiographic CAV through 5 years after HT

- The exact mechanism for MMF's beneficial effect in decreasing the development of CAV may be due to the anti proliferative effect of MMF to suppress both T and B lymphocyte function and to control arterial smooth muscle cell migration and proliferation

- Gregory CR Transplantation 1994;59:655-661
- Kobashigawa JA Cur.Opin.Cardio 1998;13:117-121

- MMF has been reported to reduce B lymphocyte responses as patient treated with this agent developed lower antivimentin antibody titers ,and this was correlated with the lower incidence of CAV by IVUS .

Rose ML JHLT 2002;21:282-285

- MMF has been reported to reduce the B lymphocyte count, downregulate activation markers on B lymphocytes ,and decrease activation of T lymphocytes and HLA-DR expressing natural killer cells

Weigel G JHLT 2002;21:1074-1079

- MMF has been reported to decrease systemic inflammatory activity in heart transplant patients as indicated by reduced levels of high – sensitive C-reactive protein

Pethig K JHLT 2004;23:61-65

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Lipid-lowering agents:

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Anti-oxidants:

- Vitamins C and E

MW, molecular weight; AT III, antithrombin III; ACE, angiotensin-converting enzyme;HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A

- Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years
- A randomized clinical trial

- Keogh A , Circulation 2004;110:2694-2700

- Sirolimus+CSA+ST vs AZA+CSA+ST
- (2 different dosages)
- 2 years follow-up
- MIT : sirolimus 0.5 mm
  aza 0.9 mm
- P=0.865

Prognostic importance of intimal thickness as measured by IVUS after cardiac transplantation

Rickenbacher PR

Circ. 1995;92:3445-3452

1 pt.

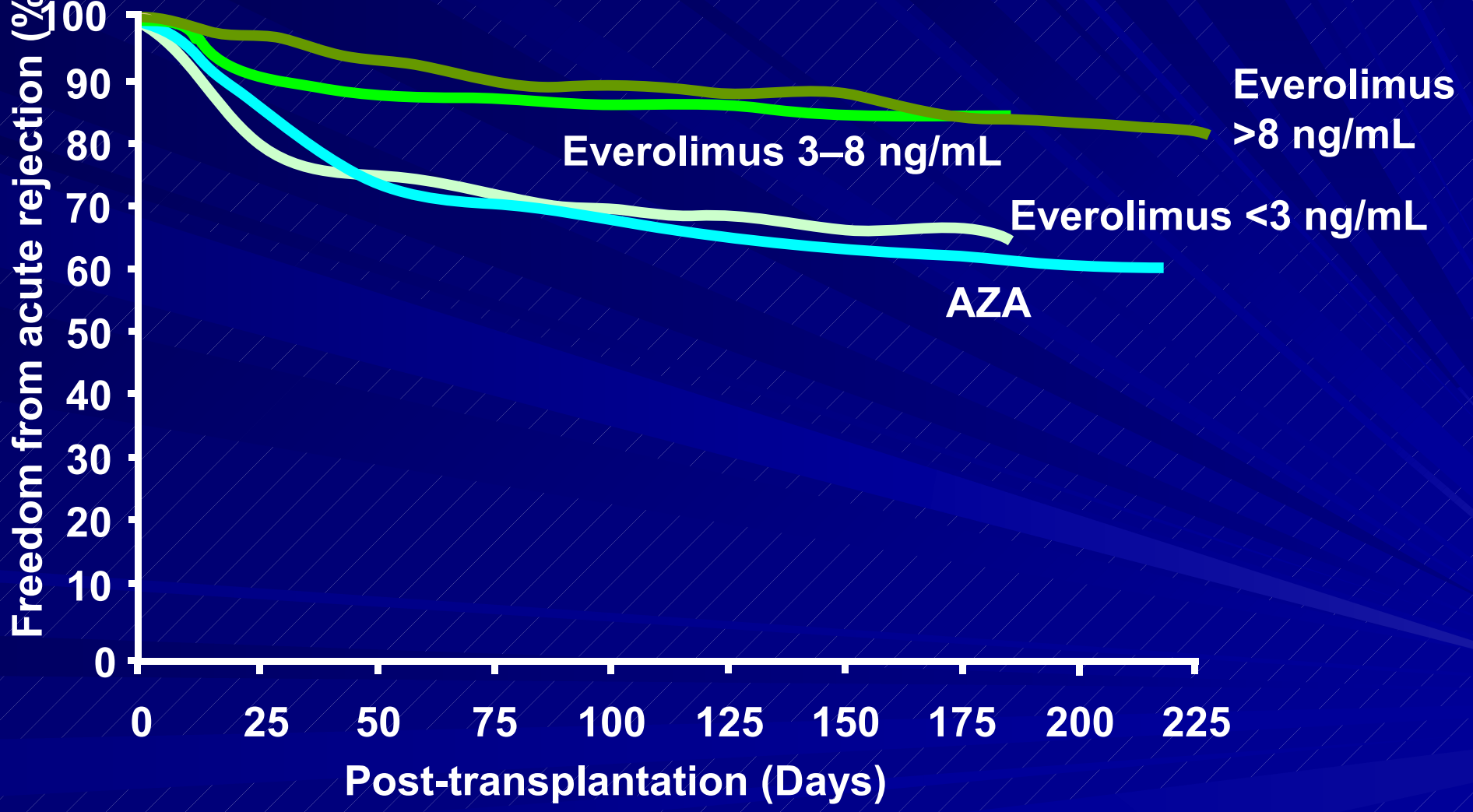
Mean intimal thickening - 0.3

- IVUS follow-up 48 months
- 4 year overall survival 73% vs 96%

  p=0.005
- 4 year cardiac survival 79% vs 96%

  p=0.005

Efficacy improves with trough l(evels >3 ng/mL (Study 253



Major side effects

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

Presence of severe intimal thickening by IVUS predicts cardiac events in cardiac allograft vasculopathy

- Mehra HR, JHLT 1995;14:632-649

Presence of severe intimal thickening by IVUS predicts cardiac events in cardiac allograft vasculopathy

74 HT pt. with severe intimal thickening (0.5 mm)

4 years follow-up

- Death
- MI
- Retransplantation

Impact of IVUS in understanding transplant coronary artery disease

- Kapadia SR, Opin Cardio 1999;14: 140-150

- 100 PT.
- 43 months of follow-up
- Pt. with 1 year rapidly progressive intimal thickening
- 0.5 mm
- DEATH, MI , CHF 25% VS 11%

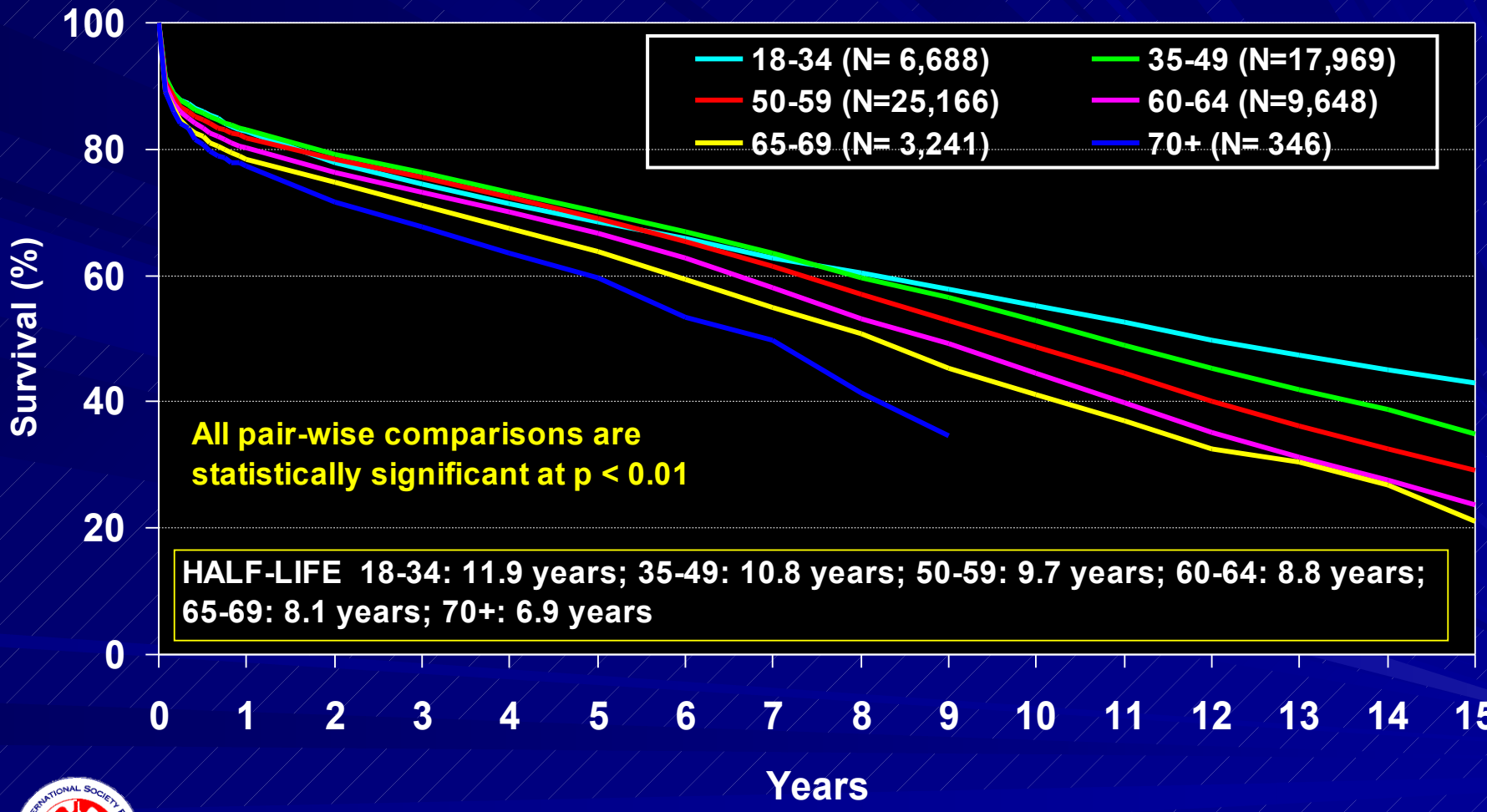
??Why Poly-Drug Use

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

2) Drug-Combinations may have positive effects/Synergism

ADULT HEART TRANSPLANTATION

Kaplan-Meier Survival by Age Group ((Transplants: 1/1982-6/2005



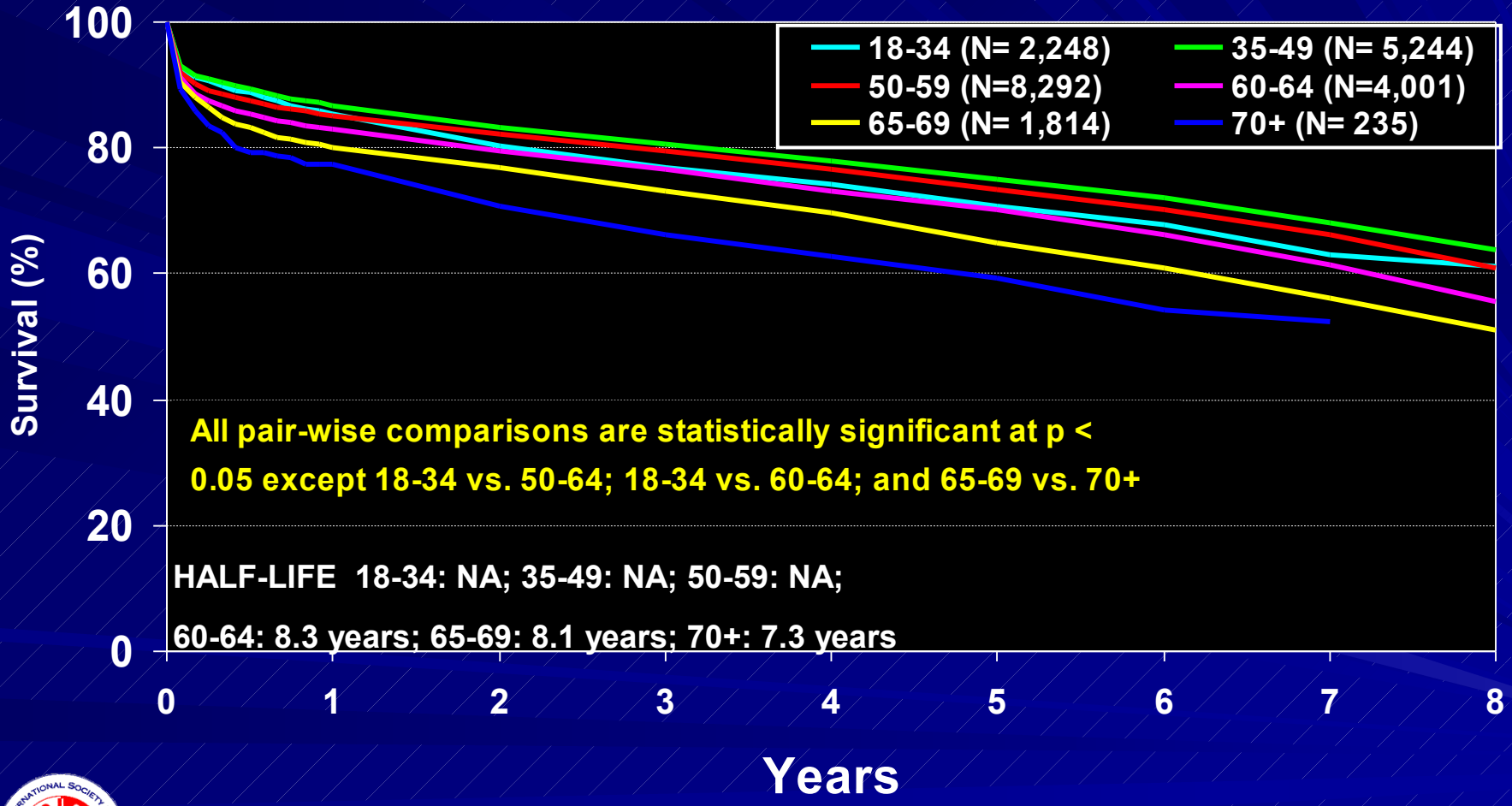
ISHLT

2007

J Heart Lung Transplant 2007;26: 769-781

ADULT HEART TRANSPLANTATION

Kaplan-Meier Survival by Age Group ((Transplants: 1/1998-6/2005



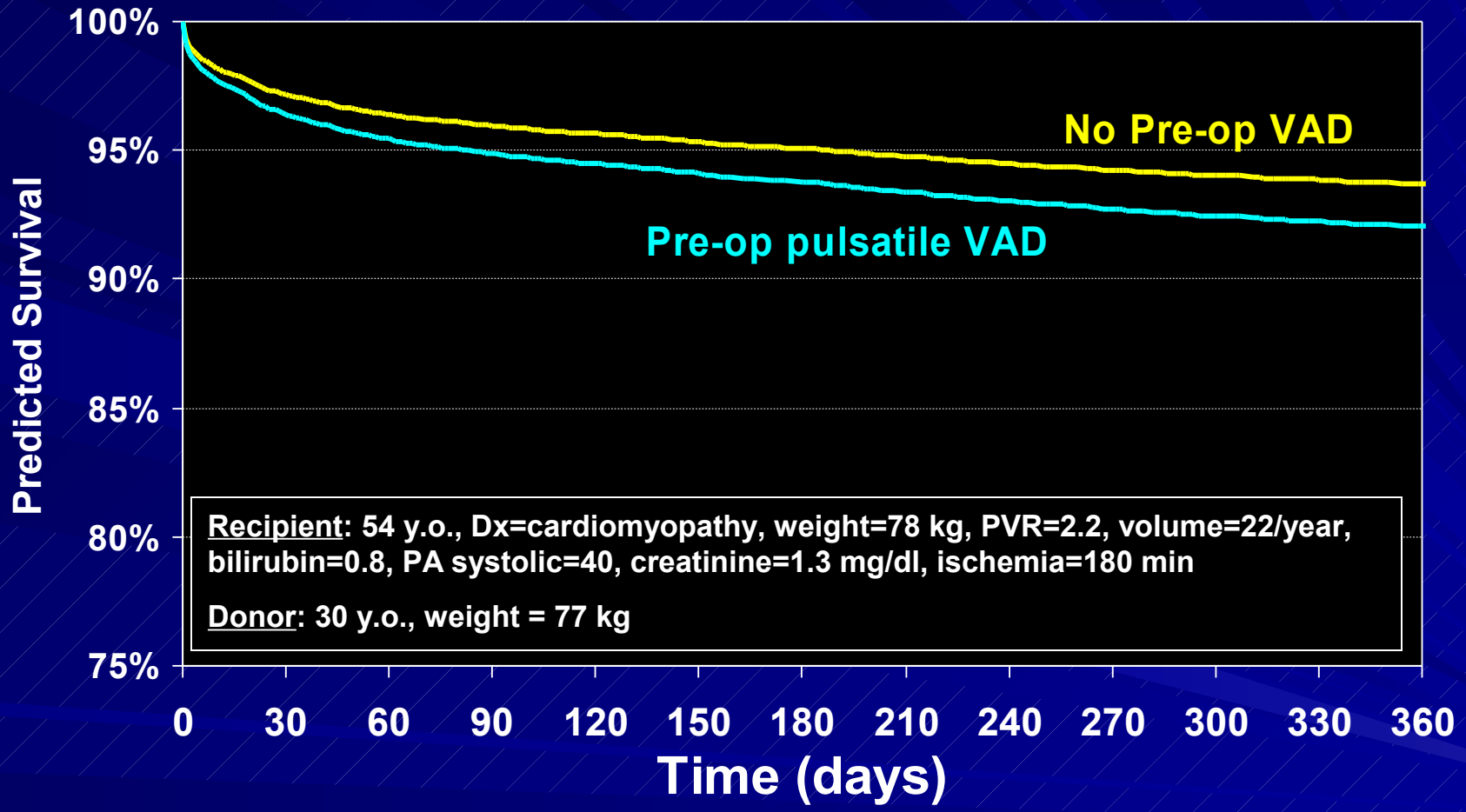
ISHLT

2007

J Heart Lung Transplant 2007;26: 769-781

ADULT HEART TRANSPLANTS

1-Year Predicted Survival Model (Transplants: 1/2002-6/2005)
Impact of Pre-Transplant VAD



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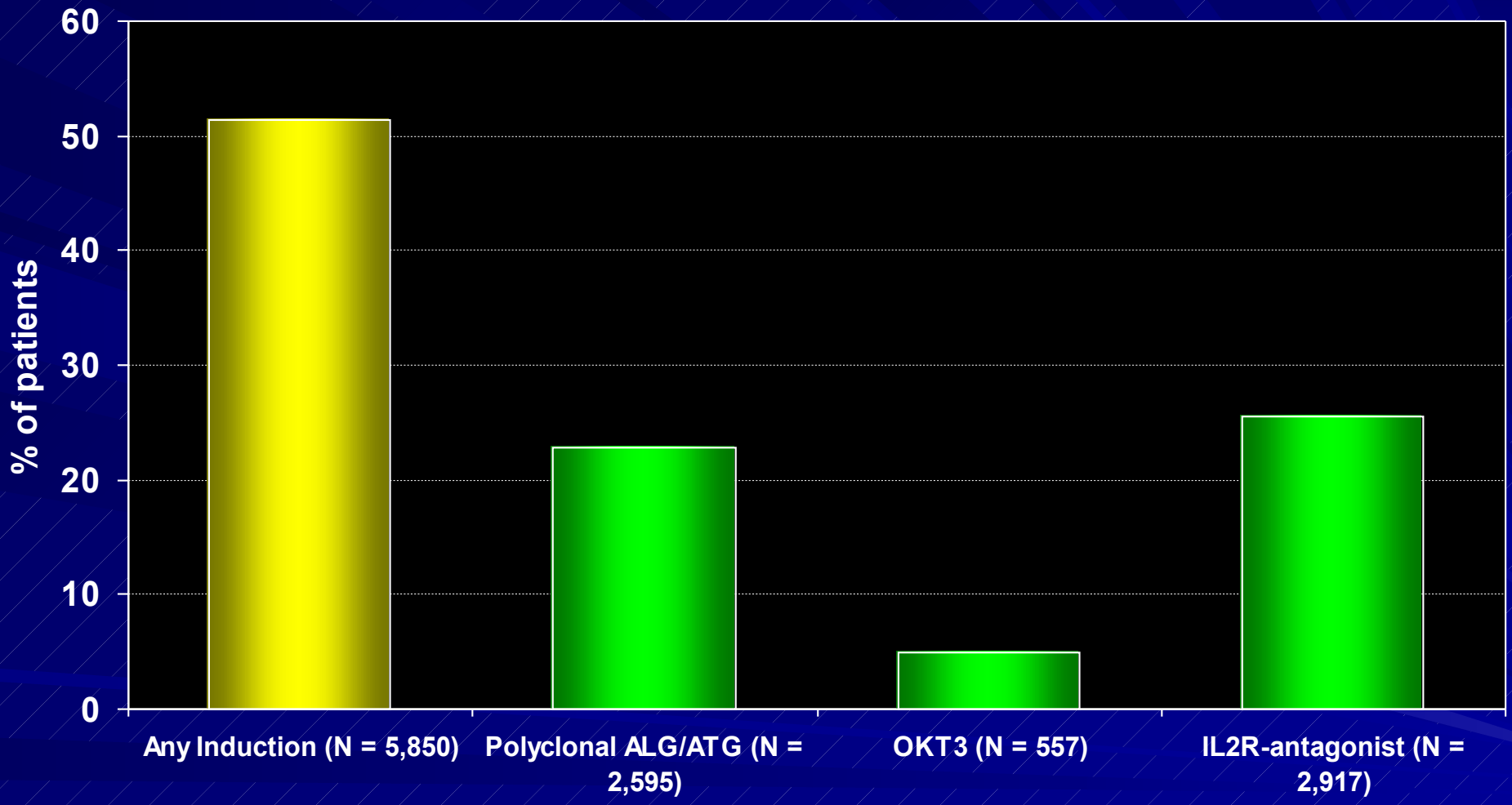
2007

J Heart Lung Transplant 2007;26: 769-781

ADULT HEART RECIPIENTS

(Induction Immunosuppression (Transplants: January 2001 – June 2006



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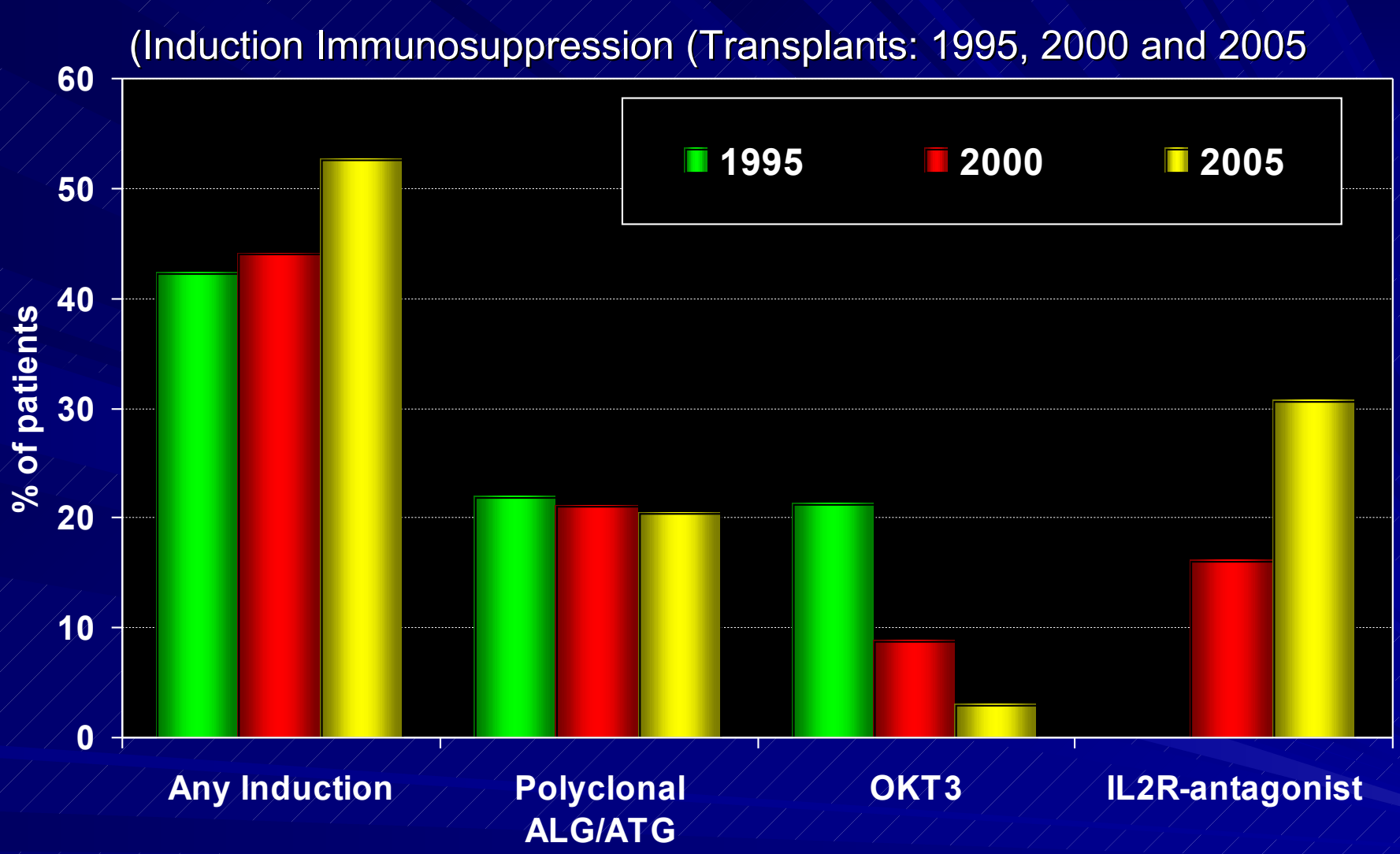
2007

J Heart Lung Transplant 2007;26: 769-781

ADULT HEART RECIPIENTS



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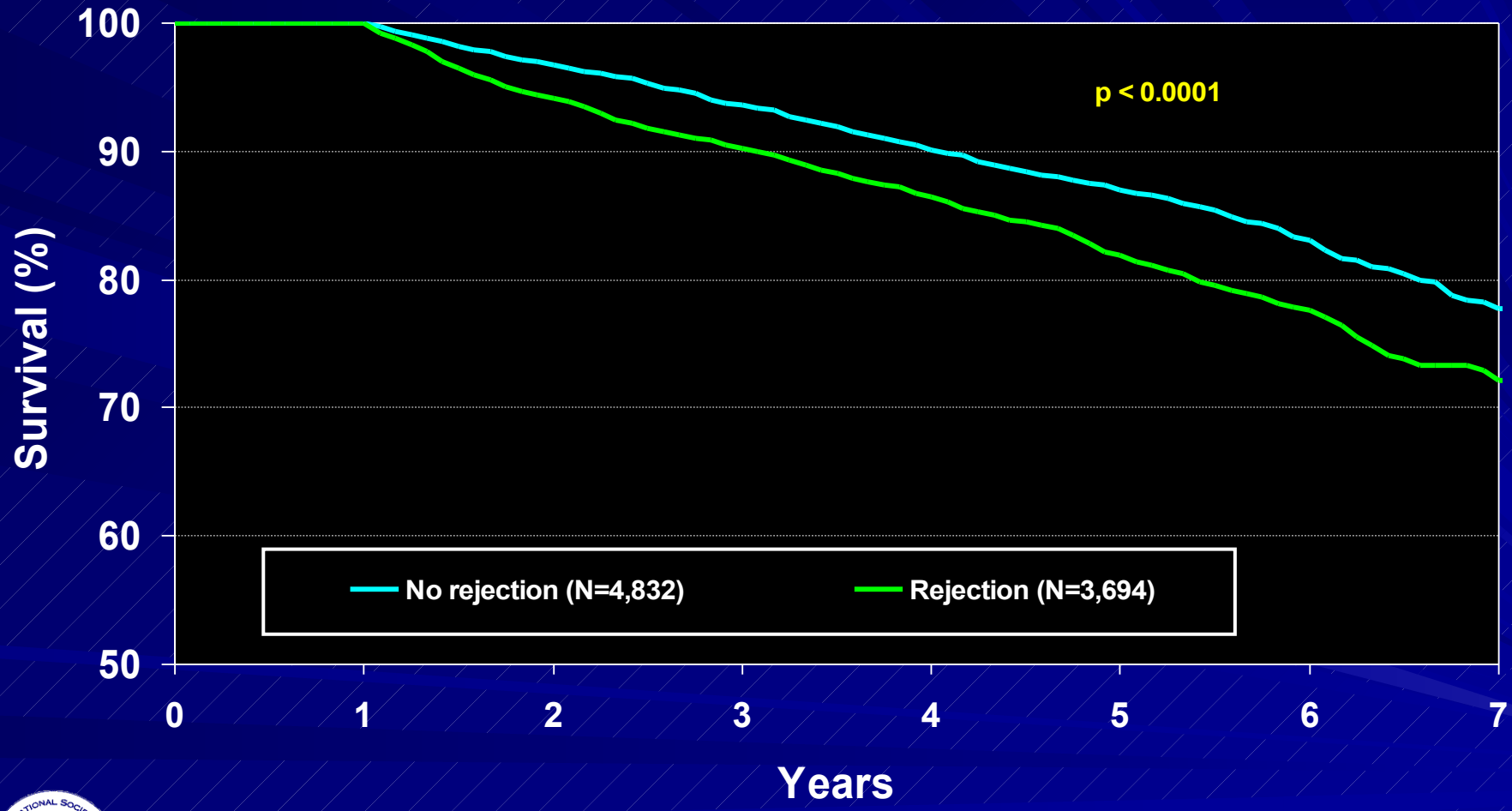
J Heart Lung Transplant 2007;26: 769-781

ADULT HEART TRANSPLANTATION

Kaplan-Meier Survival Stratified by Rejection Within 1st Year

Conditional on survival to 1 year for transplants: 1/1999-6/2004



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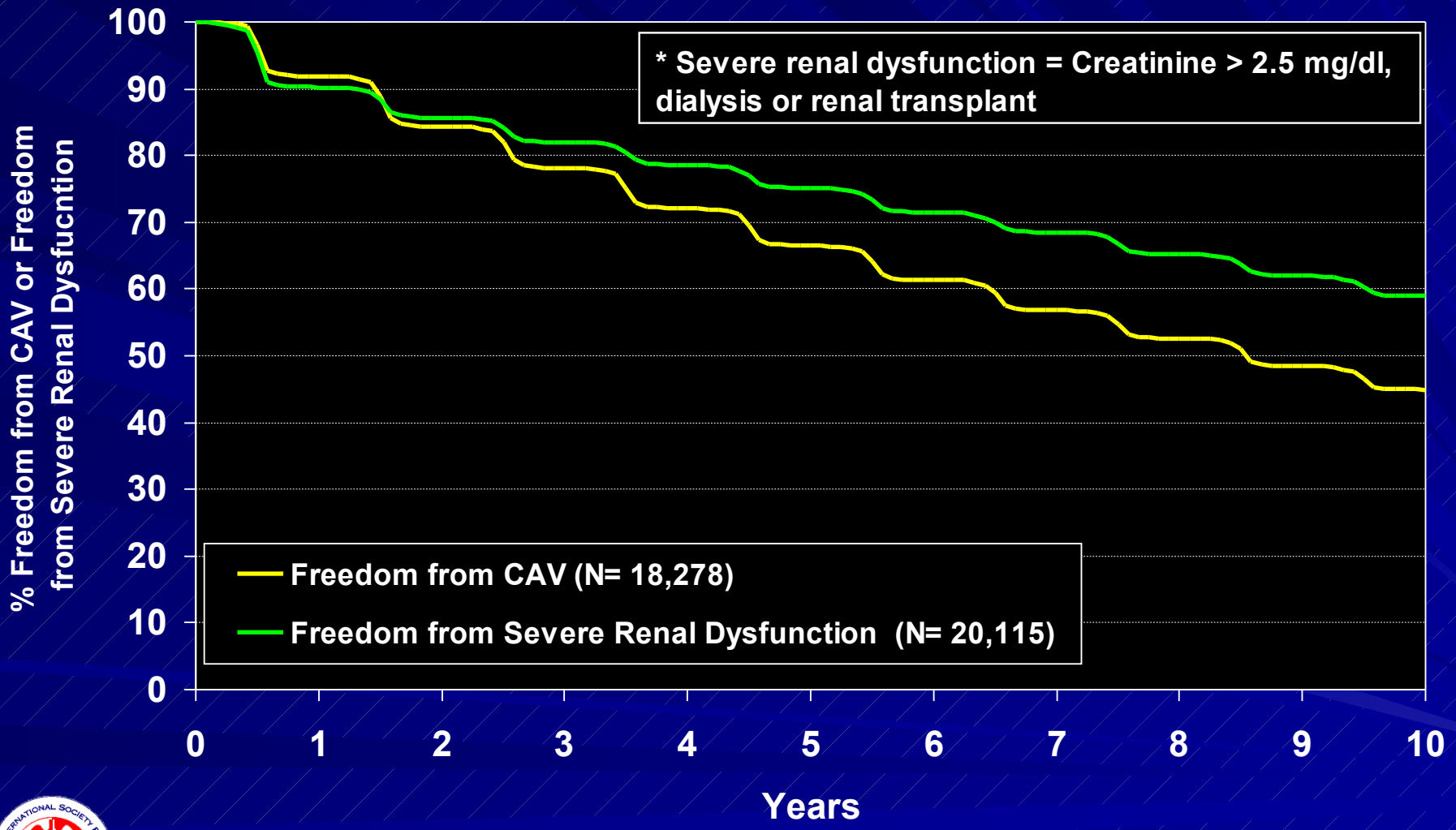
2007

J Heart Lung Transplant 2007;26: 769-781

FREEDOM FROM CARDIAC ALLOGRAFT VASCULOPATHY AND FREEDOM FROM SEVERE RENAL DYSFUNCTION*

(For Adult Heart Recipients (Follow-ups: April 1994-June 2006



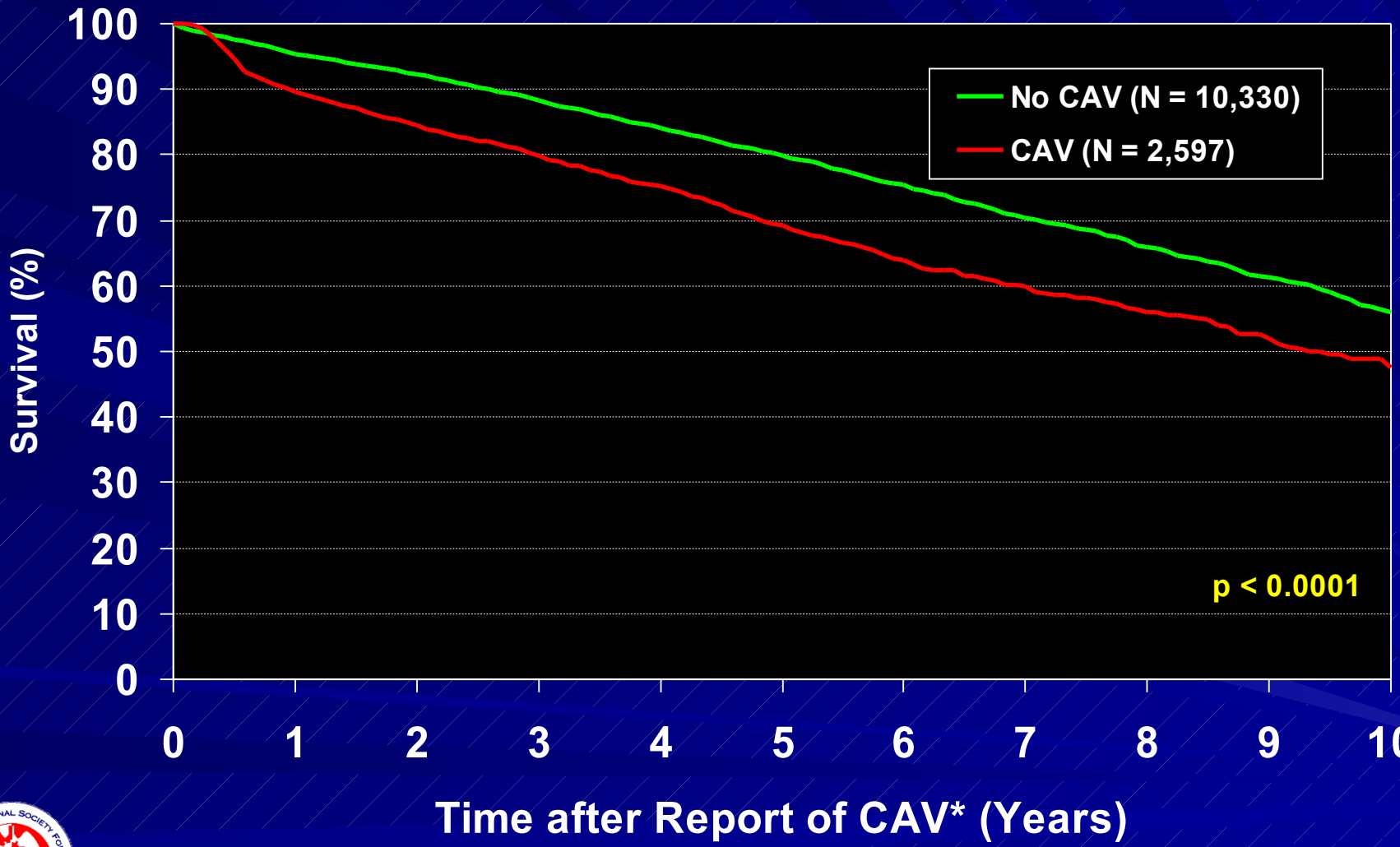
ISHLT

2007

J Heart Lung Transplant 2007;26: 769-781

PATIENT SURVIVAL AFTER REPORT OF CAV AND PATIENT SURVIVAL IN PATIENTS WITHOUT CAV*

((Transplants: April 1994-June 2004



ISHLT

2007

* Patients without CAV conditioned on survival to median time of CAV development (514 days)

J Heart Lung Transplant 2007;26: 769-781

MALIGNANCY POST-HEART TRANSPLANTATION FOR ADULTS

Cumulative Prevalence in Survivors ((Follow-ups: April 1994 - June 2006

Malignancy/Type		Year-1 Survivors	Year-5 Survivors	Year-10 Survivors
No Malignancy		(97.1%) 20441	(84.9%) 7780	(68.1%) 1264
(Malignancy (all types combined		(2.9%) 612	(15.1%) 1389	(31.9%) 592
Malignancy Type	*Skin*	*282*	*937*	*360*
	Lymph	*142*	*127*	*38*
	Other	*132*	*359*	*108*
	Type Not Reported	*56*	*39*	*126*

"Other" includes: prostate (11, 34, 17), adenocarcinoma (7, 4, 2), lung (5, 4, 1), bladder (4, 5, 4), sarcoma (3, 3, 1), breast (2, 8, 3), cervical (2, 4, 0), colon (2, 3, 1), and renal (2, 7, 2). Numbers in parentheses are those reported within 1 year, 5 years and 10 years, respectively.

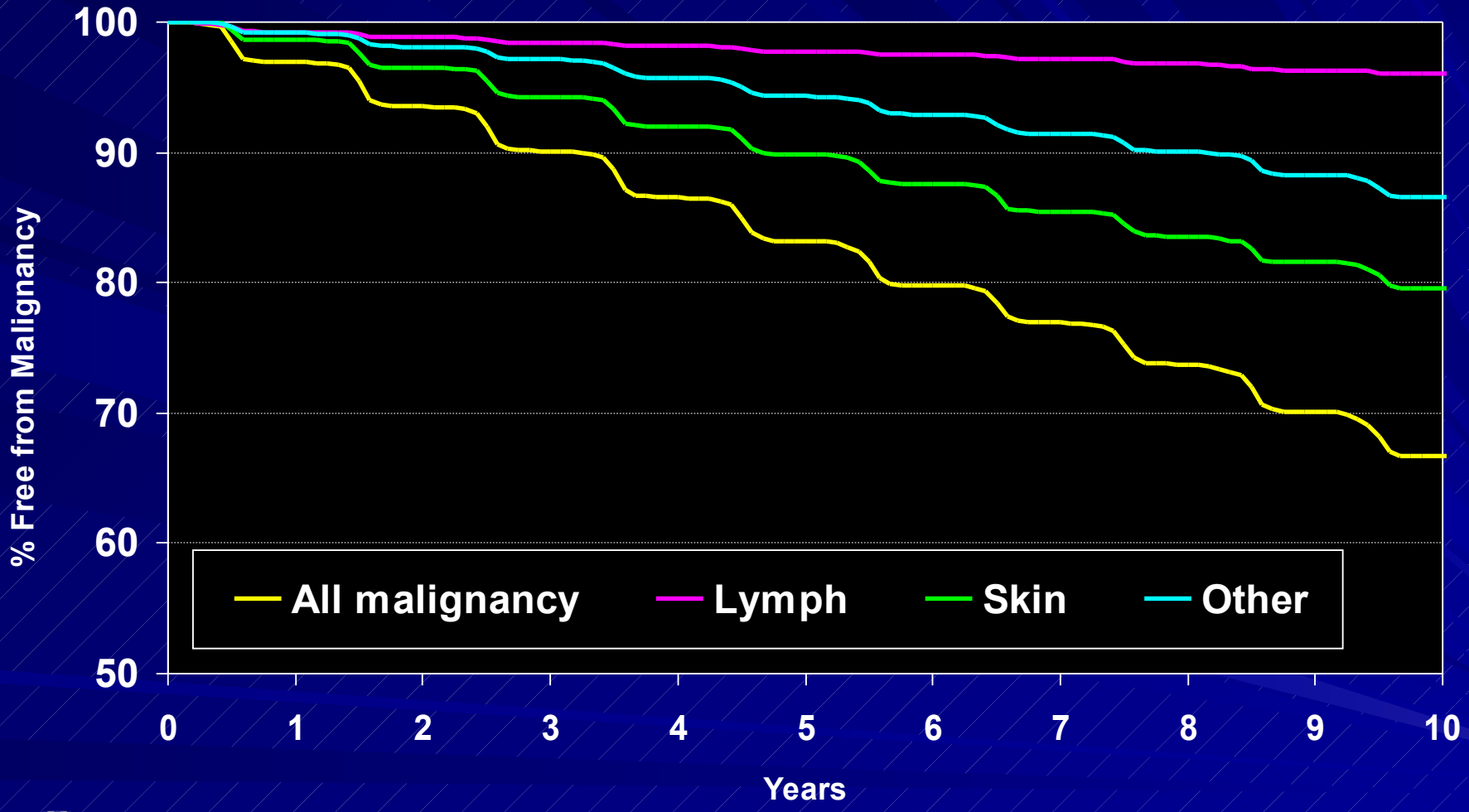
ISHLT

2007

J Heart Lung Transplant 2007;26: 769-781

FREEDOM FROM MALIGNANCY

(For Adult Heart Recipients (Follow-ups: April 1994 - June 2006

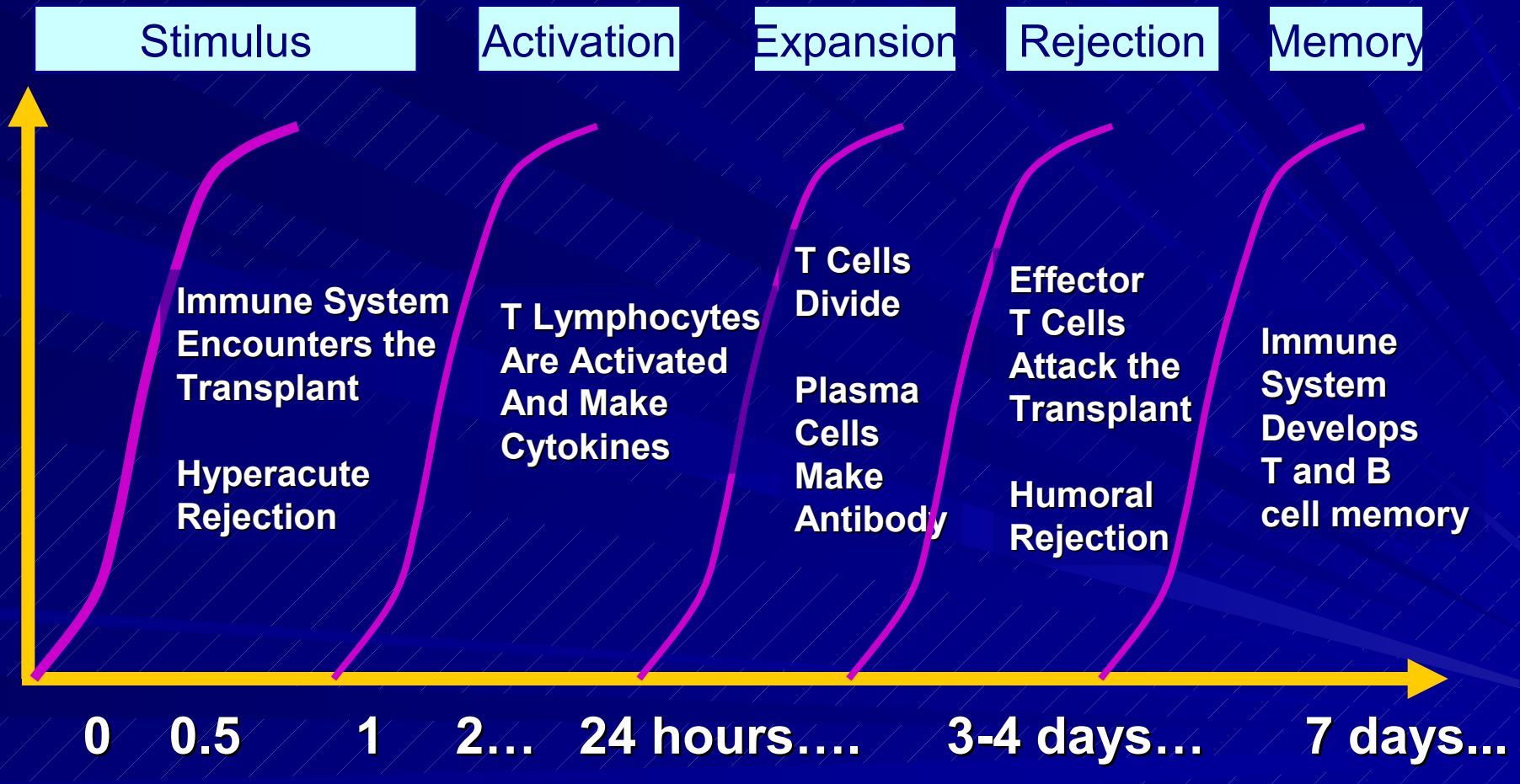


ISHLT

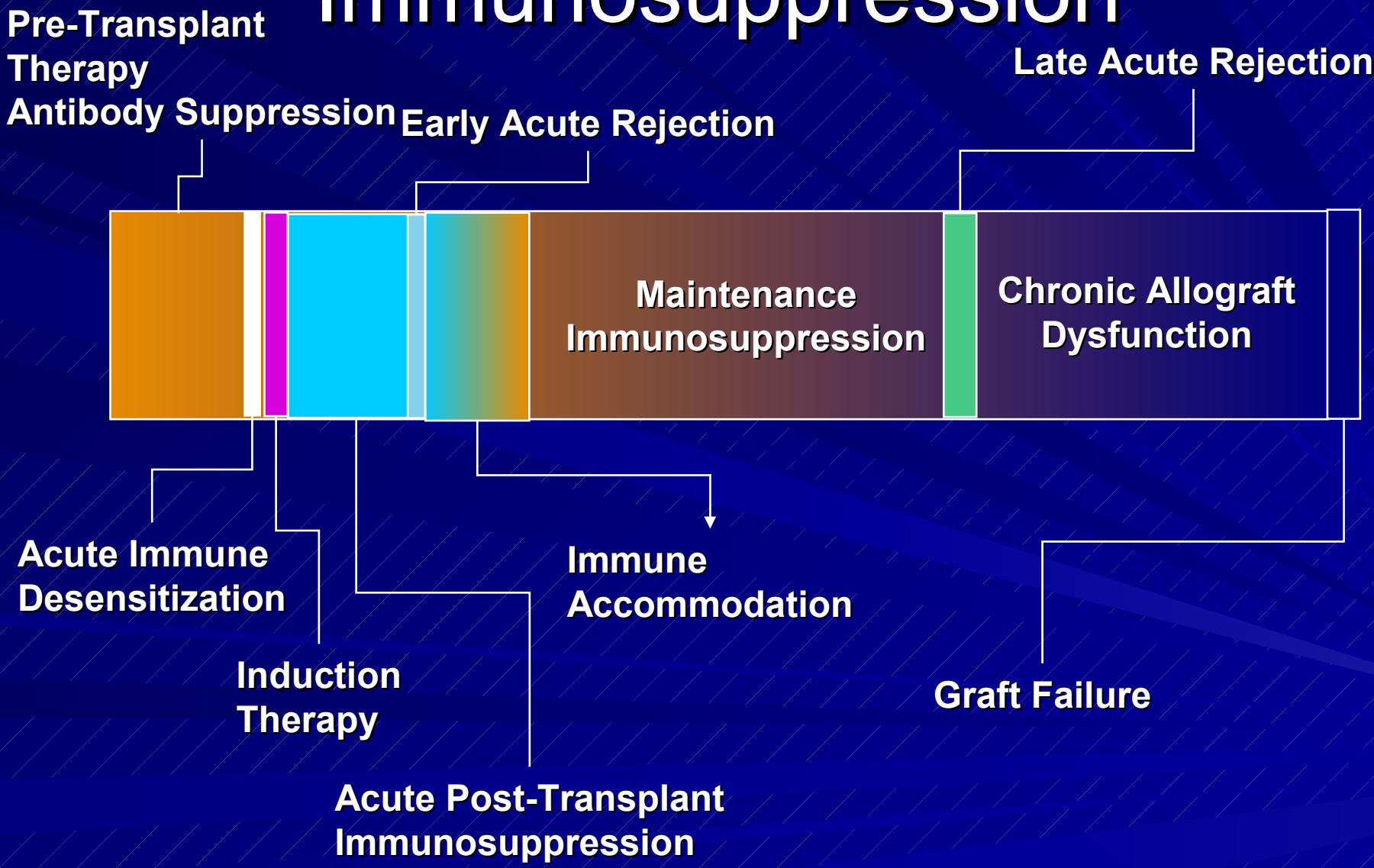
2007

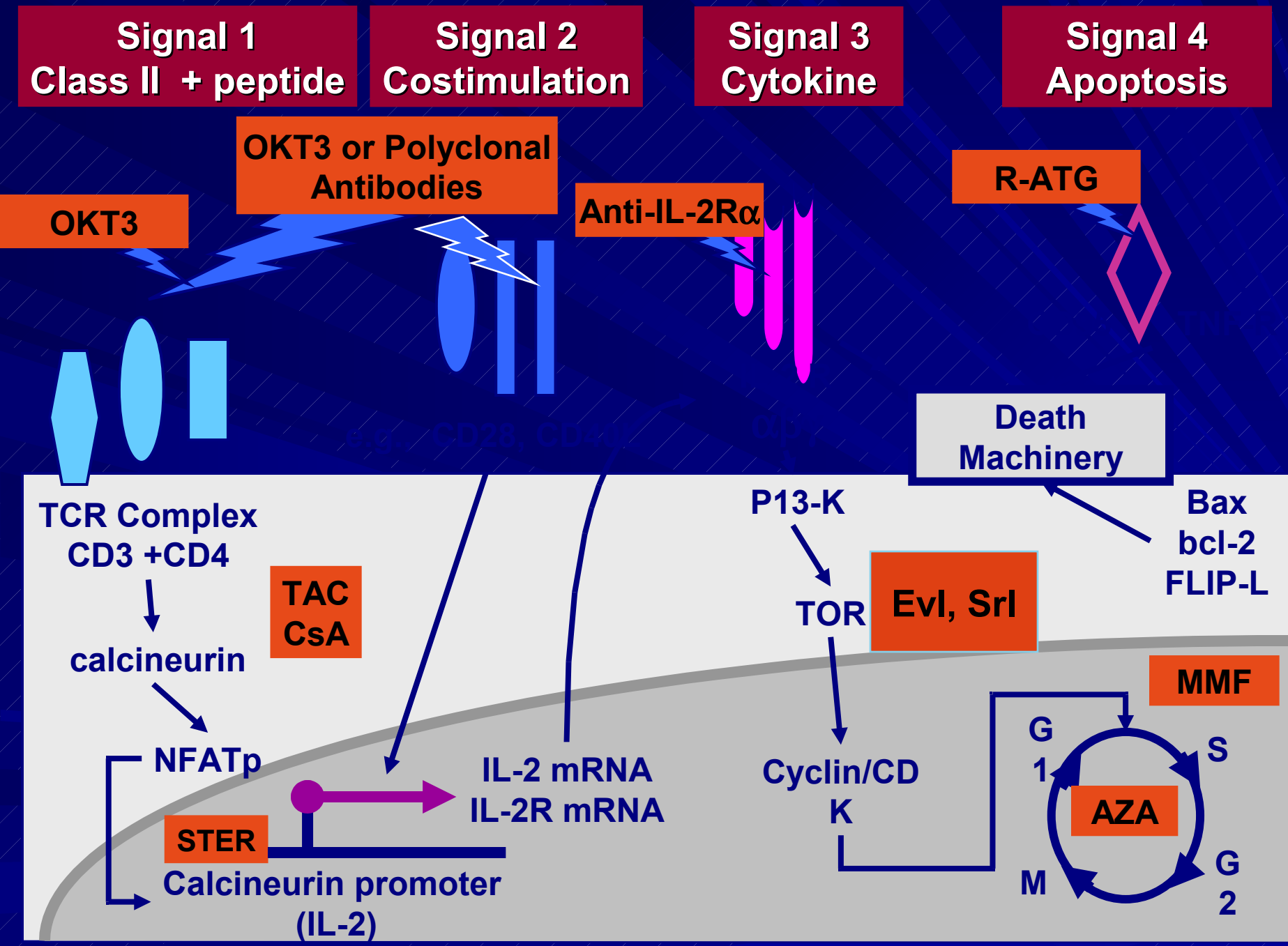
J Heart Lung Transplant 2007;26: 769-781

Events Following T Cell Activation



The Phases of Immunosuppression



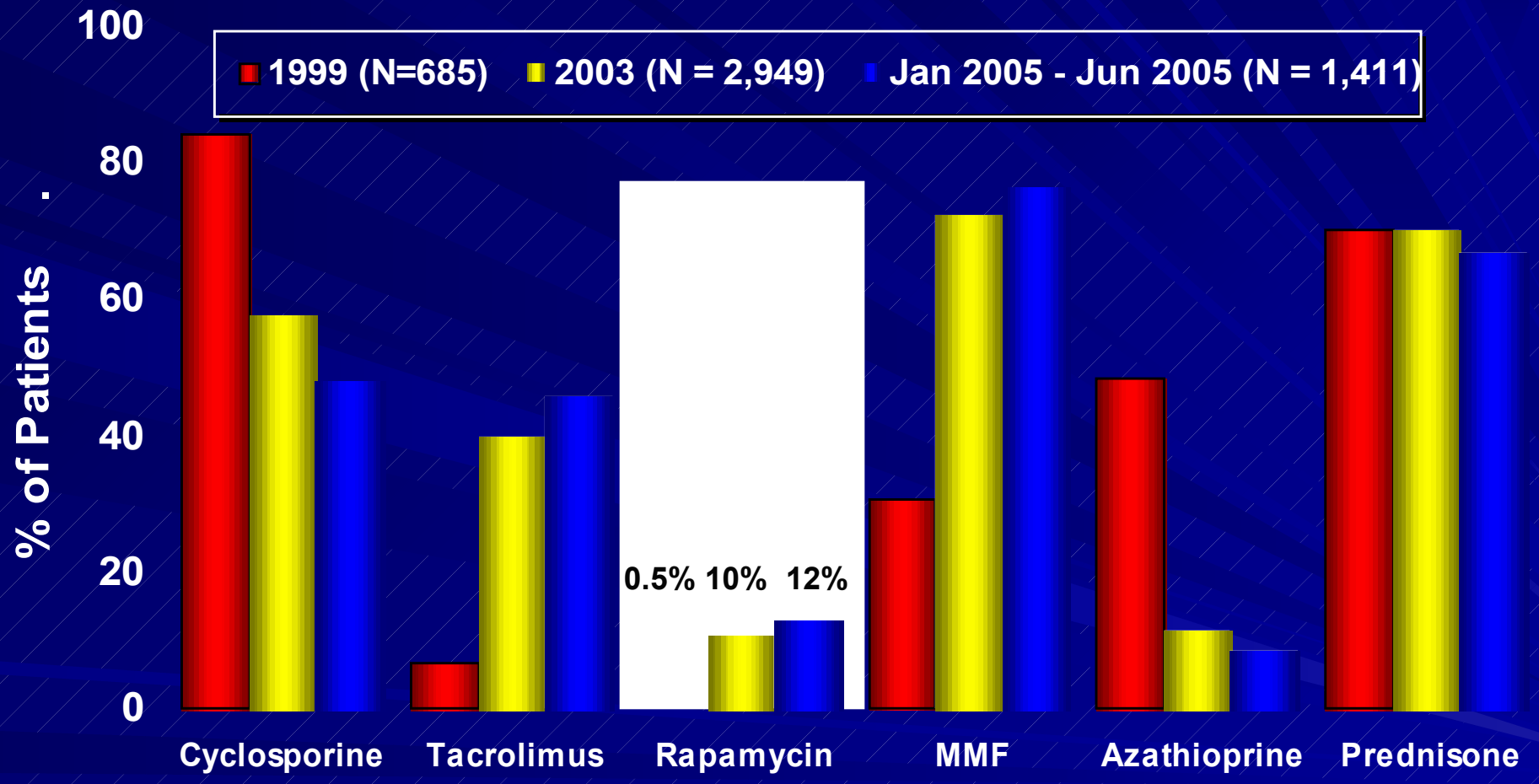

Signal 1
Class II + peptide
Signal 2
Costimulation
Signal 3
Cytokine
Signal 4
Apoptosis
OKT3 or Polyclonal Antibodies
OKT3
Anti-IL-2Rα
R-ATG
Death Machinery
TCR Complex
CD3 +CD4
calcineurin
TAC
CsA
P13-K
TOR
Evl, Srl
Bax
bcl-2
FLIP-L
MMF
NFATp
IL-2 mRNA
IL-2R mRNA
Cyclin/CD
K
G
1
S
AZA
M
G
2
STER
Calcineurin promoter
(IL-2)

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

ADULT HEART RECIPIENTS

Maintenance Immunosuppression at Time of 1 Year Follow-up



NOTE: Different patients are analyzed in each time frame.

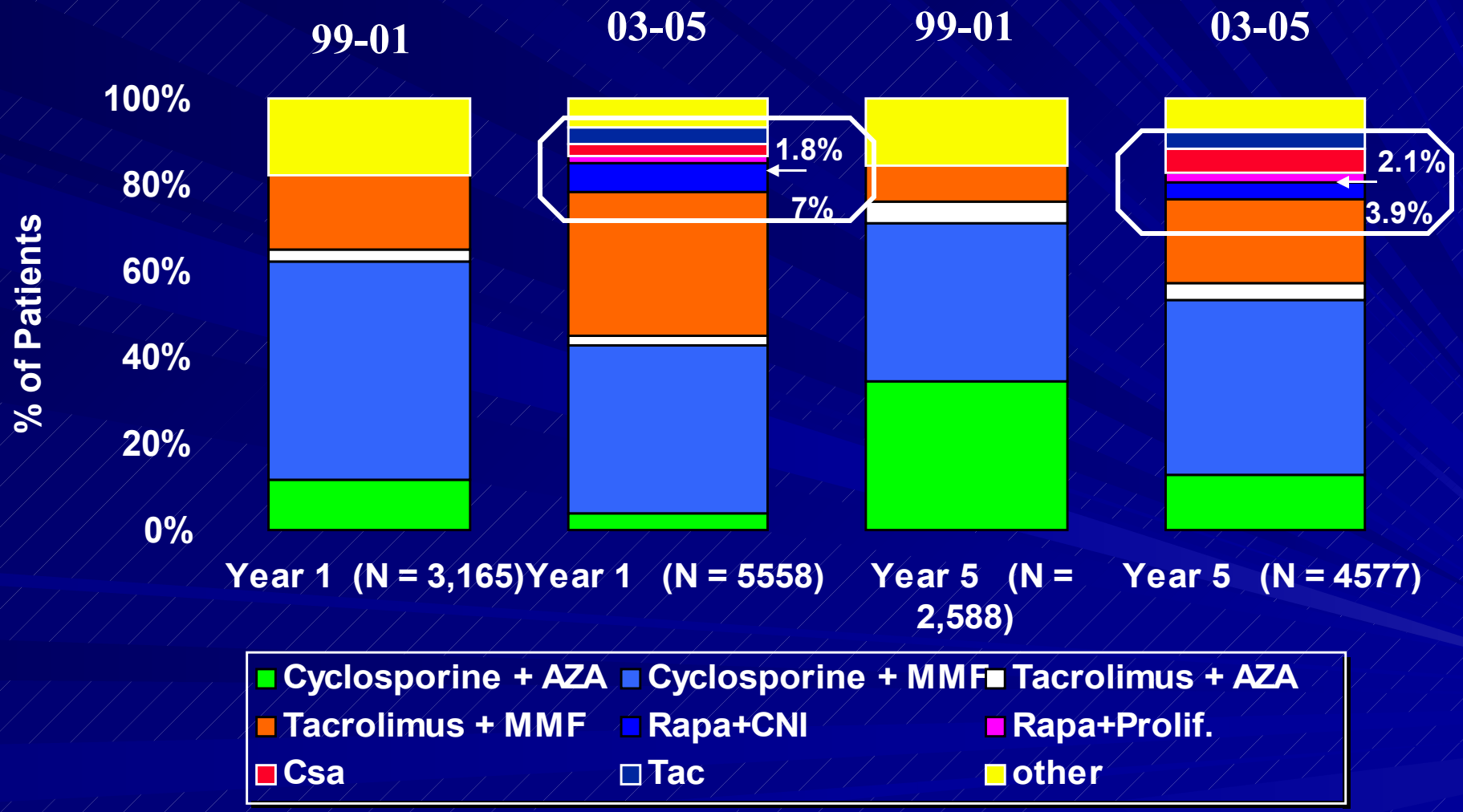
ISHLT

2006

J Heart Lung Transplant 2006;25:869-79

Maintenance Immunosuppression different time periods

at Time of Follow-up



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

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

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)

Cellular consequences of vascular injury

INJURY

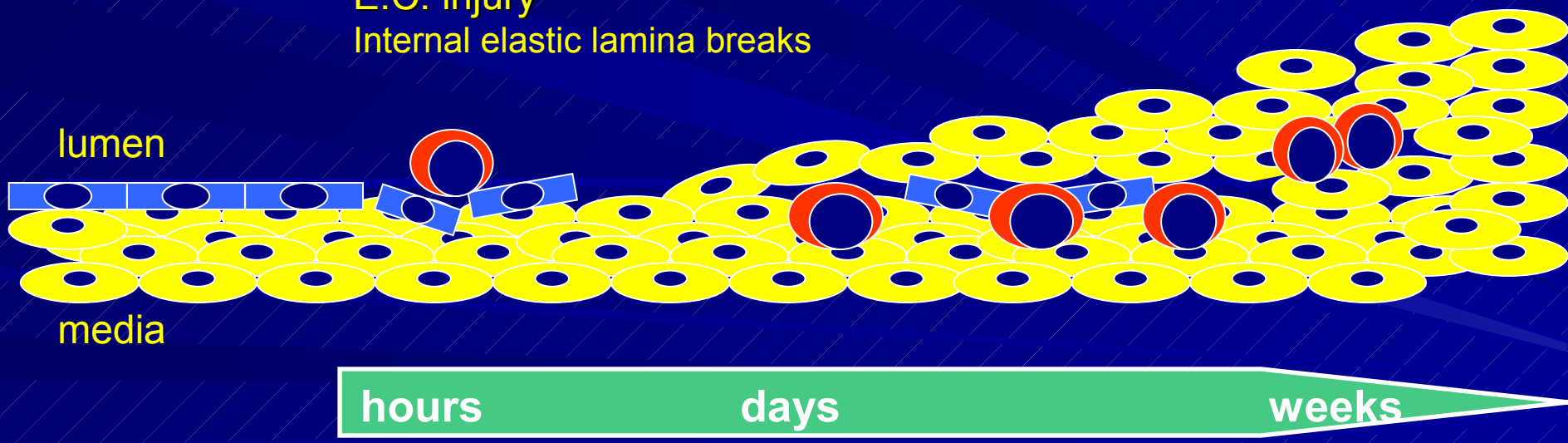
platelet adhesion
leukocyte infiltration

cytokines
growth factors
chemoattractants

neointimal hyperplasia

VSMC autocrine activation:
migration
proliferation
matrix deposition

E.C. injury
Internal elastic lamina breaks



Therapeutic Modalities to Treat Cardiac Allograft Vasculopathy

:Antiproliferative agents

Sirolimus/everolimus, mycophenolate

Low-MW heparin

:Antimetabolites

Methotrexate

:Antithrombotic agents

Hirulog

AT III

:Monoclonal antibodies

Growth factors

Adhesion molecules

Cytokines

- **Antihypertensive agents:**
  - Calcium channel blockers
  - ACE inhibitors
- **New immunosuppressive therapies:**
  - Use of photopheresis
- **Lipid-lowering agents:**
  - HMG-CoA reductase inhibitors
- **Anti-oxidants:**
  - Vitamins C and E

MW, molecular weight; AT III, antithrombin III; ACE, angiotensin-converting enzyme;HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A

Everolimus – Proliferation Signal Inhibitor

"Dual-action" drug class

IMMUNOSUPPRESSIVE: Acts synergistically with cyclosporine (CsA) to prevent rejection and prolong allograft survival

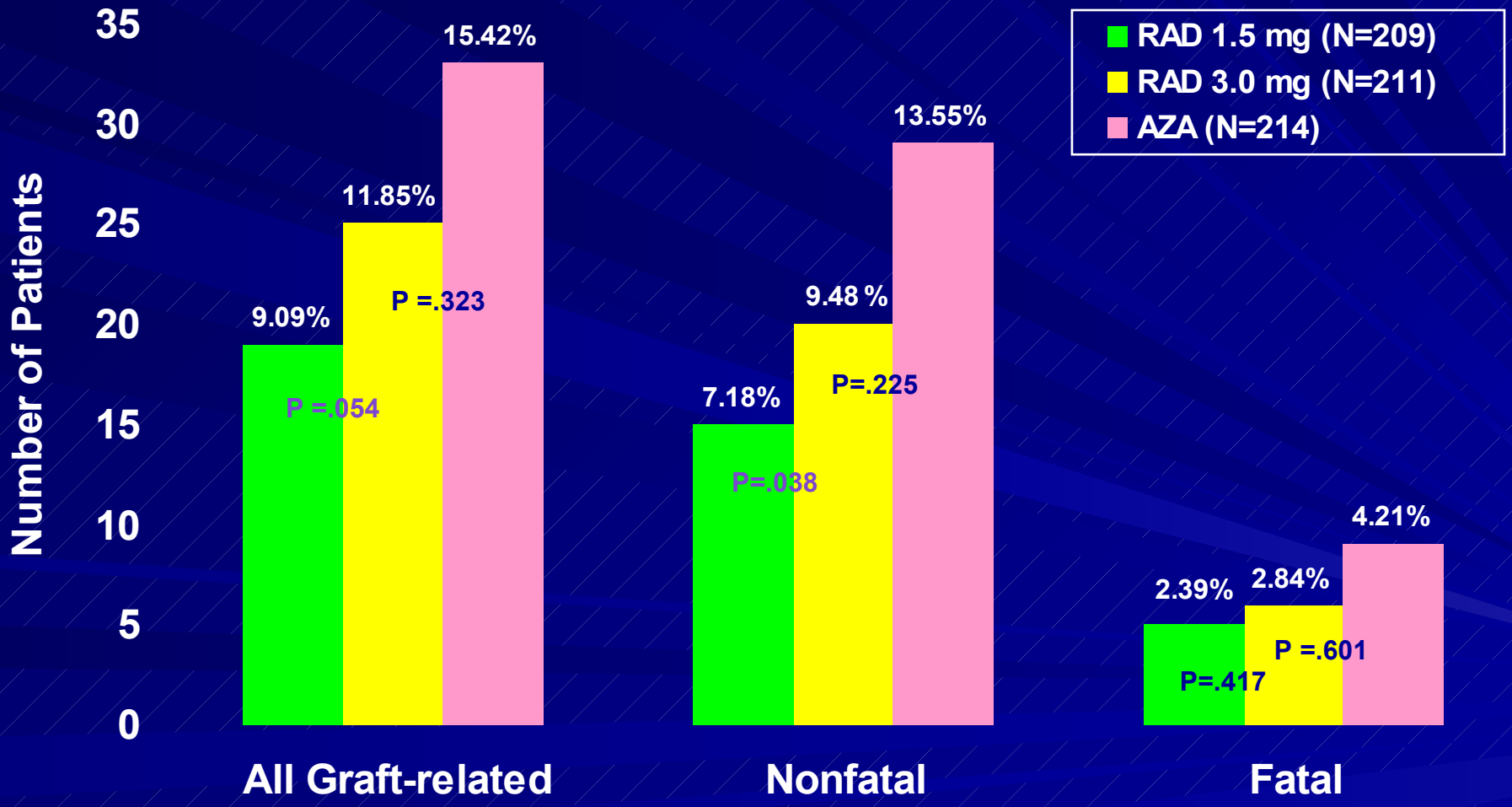
ANTI-PROLIFERATIVE: Inhibits growth-factor-driven vascular smooth muscle cell proliferation

ACUTE REJECTION

VASCULAR REMODELING

All graft-related MACE – M1- 48

(MCI, CHF, PCI, CABG, ICD, VF/VT, SCD)



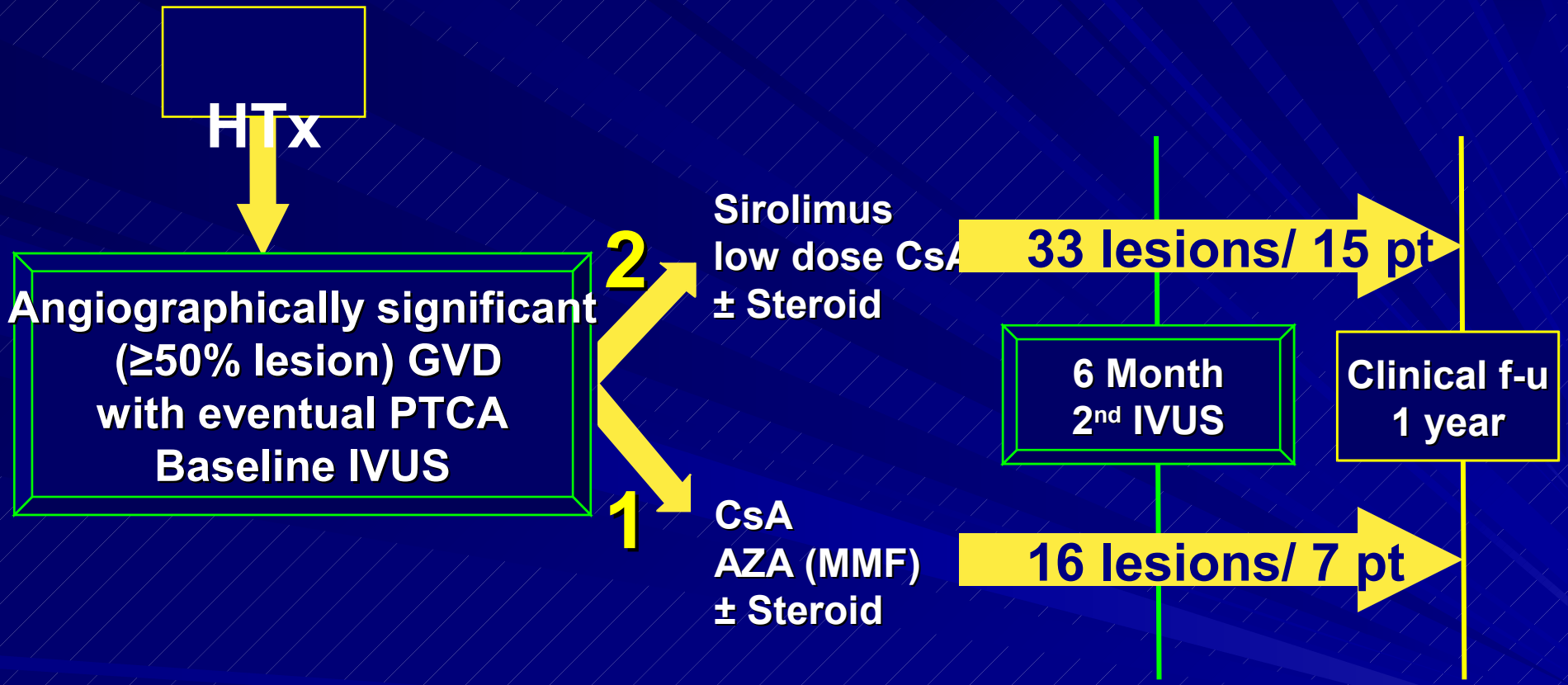
RAPASTAT: evaluation of the role of oral sirolimus in the treatment of established graft vessel disease. A prospective, randomized intravascular ultrasound study.

J. Segovia, L. Alonso-Pulpón, P. Ortiz, J. Jiménez-Mazuecos, F. Alfonso, J. Escaned, R.A. Hernández Antolín,C. Macaya.

Clínica Puerta de Hierro / Hosp. Univ. San Carlos, Madrid, Spain.

ISHLT meeting , San Francisco 2004

Study design: prospective, randomized, preliminary study

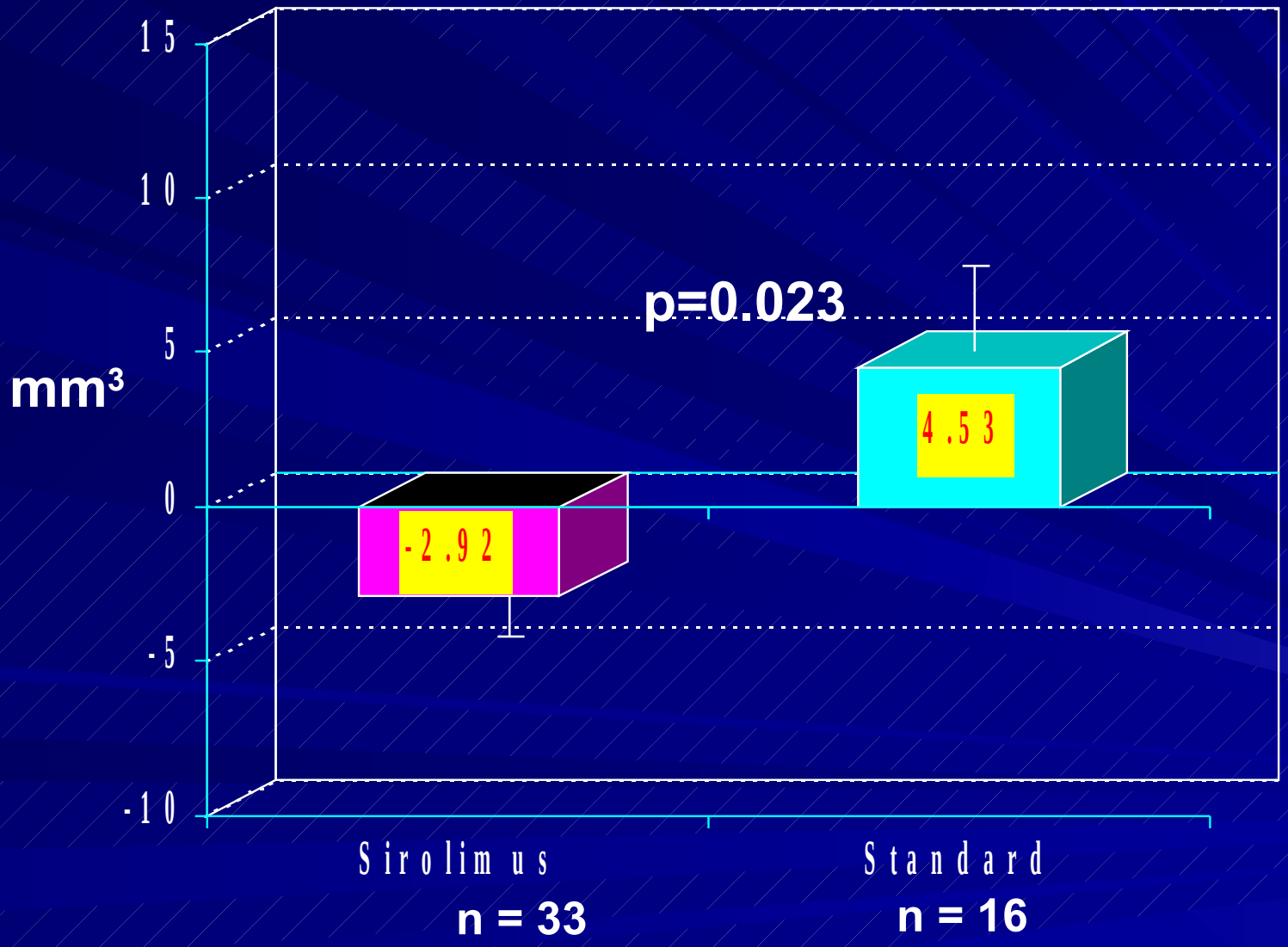


Blind analysis of paired coronary segments after 2nd IVUS

IVUS lesion characteristics

	Sirolimus (n=33)	Standard ((n=16
Time 1st – 2nd IVUS (mo)	6.6 ± 1.9	6.6 ± 1.1
No. lesions / patient	2.5 ± 2.53 ± 1.4	0.8
Average lesion length (mm)	10.1 ± 1.3	9.8 ± 1.7
located in LAD / CX / RCA %	50 / 49 / 39 / 12	31 /19
hypoecog. / fibrotic / calcified %	24 / 49 / 27	p = NS

Primary endpoint: change in intimal volume



Graft Vasculopathy

- a coronary angiogram + IVUS 1,3,5,7,10
- :Changes in IVUS
  - Aggressive treatment of risk factors –
  - (No influence of CNI (studies underway –
  - Rapamycin (SrI/EvI) shows better protection –
  - (Rapamycin Therapy? (rapastat, Mancini –
  - ?Steroid weaning –
- Late changes in angiogram
  - Aggressive treatment of risk factors –
  - (PTCA + stenting (drug eluting –
  - ACBP only selective cases –
  - Retransplantation only young healthy patients –

Everolimus

Why?

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

Why not?

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

Infections

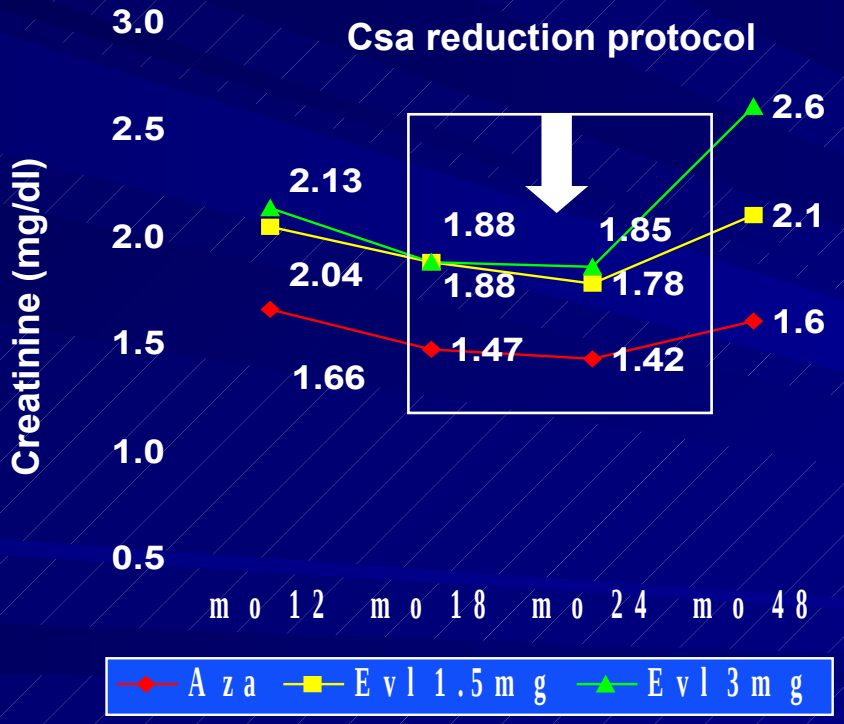
12 months - RADB253

AZA ((n=214	Everolimus 3.0 mg (n=211)	Everolimus 1.5 mg (n=209)	
22.0%	8.1%*	8.1%*	CMV
10.3%	5.7%	8.1%	Herpes simplex
4.7%	5.7%	2.9%	Herpes zoster
24.8%	37.9*	33.0%*	Bacterial
8.9%	11.4%	7.7%	Fungal
0.5%	2.4%	1.9%	*Aspergillus*
7.4%	8.5%	4.7%	*Candida*

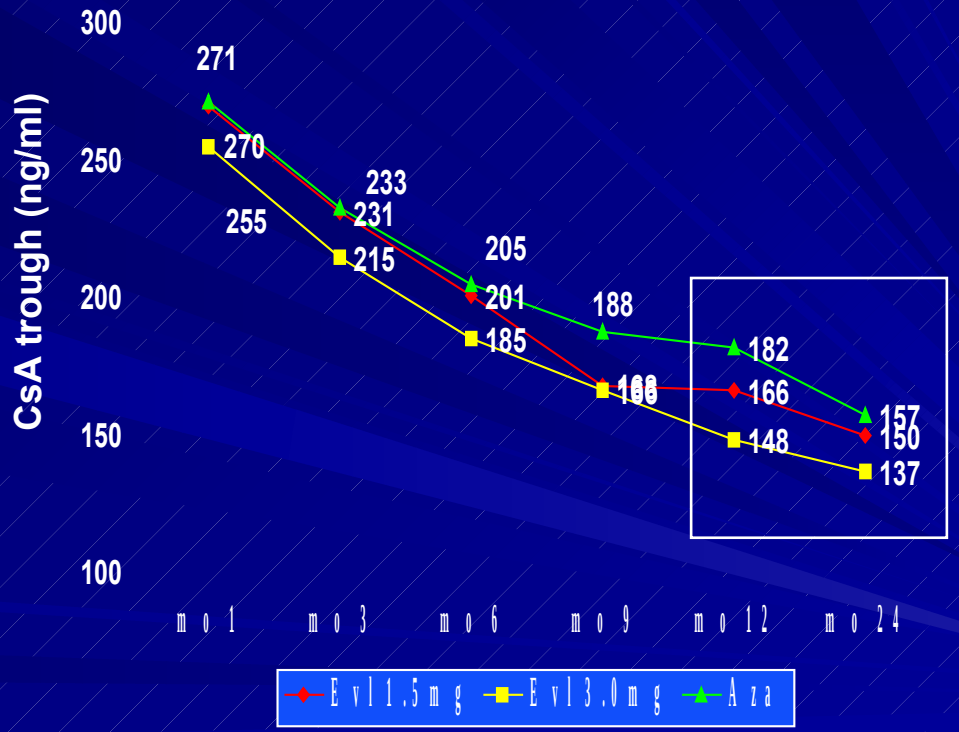
*p<0.05 vs AZA

Caution: Renal Function with *Full-dose CNI

Mean creatinine (48 months)

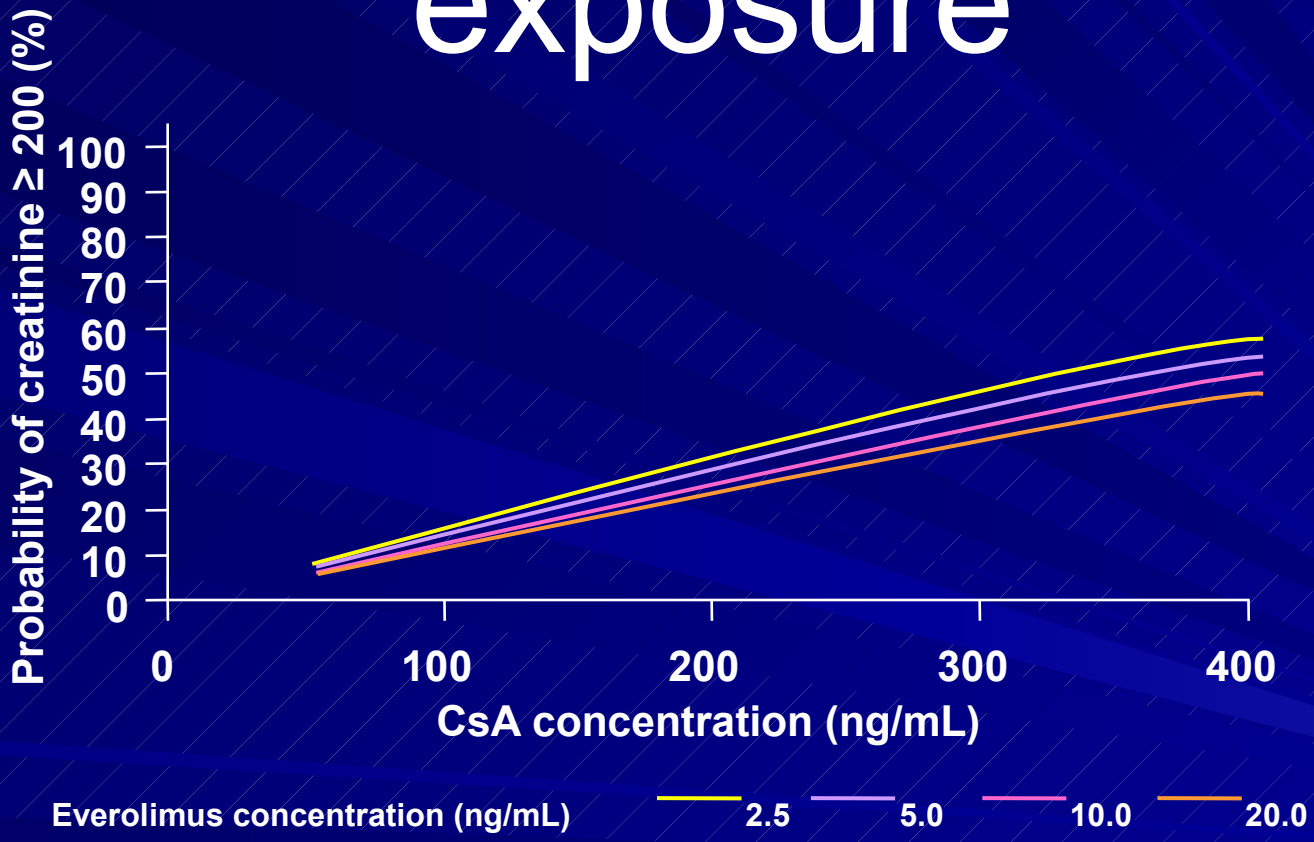


CsA trough levels (24 months)



*CNI = CsA microemulsion

Renal function decreases with increasing CsA exposure



Probability of creatinine ≥200 µmol/L (Day 30–225) as a function of simultaneous everolimus and CsA trough levels (Study B253)

Adverse Events

- Triglycerides higher in everolimus groups
- LDL, HDL similar
- Platelets lower in everolimus groups
- Wound healing complications similar

Sirolimus trial

Keough et al Circulation 04

TABLE 3. Investigator-Reported Treatment-Emergent Adverse Events, n (%)

	Sirolimus 3 mg (n=34)	Sirolimus 5 mg (n=58)	Azathioprine (n=44)	P*
More common on azathioprine				
Arrhythmia	0 (0)	0 (0)	3 (7.0)	0.047
Atrial fibrillation	7 (20.6)	2 (3.5)	11 (25.6)	0.002
Nausea	5 (14.7)	22 (38.6)	16 (37.2)	0.034
More common on sirolimus				
Anemia	18 (52.9)	45 (78.9)	23 (53.5)	0.008
Thrombocytopenia	14 (41.2)	28 (49.1)	10 (23.3)	0.028
Diarrhea	11 (32.4)	28 (49.1)	8 (18.6)	0.006
Hyperlipemia	18 (52.9)	10 (17.5)	2 (4.7)	<0.001
Epistaxis	4 (11.8)	19 (33.3)	1 (2.3)	<0.001
Mouth ulceration	7 (20.6)	12 (21.1)	0 (0)	0.001
Pericardial effusion	8 (23.5)	13 (22.8)	3 (7.0)	0.063
Pleural effusion	13 (38.2)	26 (45.6)	14 (32.6)	0.544
Peripheral edema	26 (76.5)	47 (82.5)	33 (76.7)	0.765
Abnormal healing	5 (14.7)	1 (1.8)	2 (4.7)	0.045
Renal function abnormal	29 (85.3)	41 (71.9)	25 (58.1)	0.035

*Fisher exact test vs azathioprine.

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

Wound healing complications with *de novo* sirolimus versus MMF-based regimen in cardiac transplant recipients

Starting dose: 1–3 mg/day, no loading dose, target level: 5–10 ng/mL

Complication	Sirolimus ((n=48	MMF ((n=46	p value
All wound complications	(52.0%) 25	(28.2%) 13	0.019
Deep wound complication			0.012
– Sterile dehiscence	(6.3%) 3	0	
– Sternal osteomyelitis	(2.1%) 1	0	
– Mediastinitis/deep organ infection	(27.0%) 13	(13.0%) 6	

Kuppahally et al. *Am J Transplant* 2006

Wound healing complications

((B253

Event	RAD 1.5mg N=209	RAD 3.0mg N=211	AZA N=214	P-value
Pat with sternal wound infection	(8.6%)18	(8.5%) 18	(5.1%)11	.n.s
Wound complication ((not LVAD site	(1.9%) 4	(1.9%) 4	(1.4%) 3	.n.s
Oozing/serous drainge ((sternal site	(2.9%) 6	(6.6%) 14	11 (5.1%)	.n.s
Wound dehiscence				
at sternal site-	(1.45) 3	(2.4%) 5	(0.9%) 2	.n.s
with infection --	(0.55) 1	(0.5%) 1	(0.55) 1	.n.s
wthout infection--	(1.0%) 2	(1.9%) 4	(0.5%) 1	.n.s
other-	(0.5%) 1	0	0	n.s
Lymphocele	(4.8%) 10	(4.3%) 9	(0.9%) 2	0.065
groin-	(2.4%) 5	(3.3%) 7	(0.5%) 1	.n.s
other-	(2.4%) 5	(1.0%) 2	(0.5%) 1	.n.s

Patients with pericardial effusion and/or pleural effusion ((B253

Event	Everolimus 1.5 mg/day ((n = 209	Everolimus 3.0 mg/day ((n = 211	Aza ((n = 214	Significance
Pericardial/pleural effusion				
Pleural effusion	(15.3%) 32	(15.1%) 32	(14.5%) 31	.n.s
Mild pericardial effusion no non drug therapy/) (no hospitalization	(5.7%) 12	(4.7%) 10	(5.6%) 12	
Moderate pericardial effusion (non drug (therapy	(8.1%) 17	(6.6%) 14	(7.9%) 17	.n.s
Severe pericardial effusion (non drug (therapy/hospitalization	(10.0%) 21	(11.8%) 25	(3.3%) 7	$p < 0.01$
Cardiac tamponade	(2.4%) 5	(4.3%) 9	(1.4%) 3	$p < 0.07$ *vs* everolimus 3.0 mg/day

Drug Interactions I

- Csa, Tac, Rapa metabolized in liver by Cytochrome p450 pathway
- Interactions either increase or decrease !blood levels
- Increase: Ketokonazol, Itraconazol (2-10x) Erythromycin, diltiazem
- ,Decrease: Antikonvulsiva
- Nephrotoxicity: ,AmphoB,Aminoglykoside
- Always check if drug interactions are

Drug Interactions II

Take home message

INHIBITORS AND INDUCERS OF CYP3A

Choose alternative agents or temporarily stop everolimus and switch to MPA if these agents must be used

USE CAUTION AN THERAPEUTIC DRUG MONITORING OF EVEROLIMUS

Moderate inhibitors → increase everolimus blood levels

Moderate inducers → decrease everolimus blood levels

Everolimus in special populations

Black patients	May require higher starting dose of everolimus (e.g. 3 mg/day) due to 20% higher clearance[1]
Renal impairment	No dose adjustment required
Mild-to-moderate hepatic impairment	Titrate dose as necessary
Paediatrics	Currently insufficient clinical evidence
Pts > 65 years	**No pharmacokinetic difference**

1. Kovarik JM et al. Clin Pharmacol Ther 2001; 70: 247–54

Remaining Questions

- Primary therapy
  - everolimus seems better than AZA –
  - Impact vs. MMF –
  - potential for graft CAD not clear (strong evidence to support –
    (everolimus
- (Everolimus very potent (rejection, infection
- Target levels need to be measured
  - frequency of monitoring: early vs late phase post-transplant –
- Drug interactions
  - ?CsA, FK506, MMF: which drug combination is best –
  - azoles, statins: what interacts with CsA most likely interacts –
    !with everolimus

Safety Endpoints 24months

	AZA	Certican® 3.0 mg	Certican® mg 1.5
PTLD	(3 (1.4%	4 (1.9%)	3 (1.4%)
Skin	(6 (2.8%	5 (2.4%)	10 (4.8%)
Other	(8 (3.7%	5 (2.4%)	5 (2.4%)

P value = NS

Safety Endpoints

Serum lipids at Month 24

AZA	Certican® 3.0 mg	Certican® 1.5 mg	
(108 (32	116 (48)	119 (45)	LDL-cholesterol mg/dL (SD)
(46 (22	42 (16)	46 (18)	HDL-cholesterol mg/dL (SD)
(203 (91	283 (127)*	274 (195)*	Triglycerides mg/dL (SD)

Certican® 1.5 mg: 90.4%Patients treated with statins:

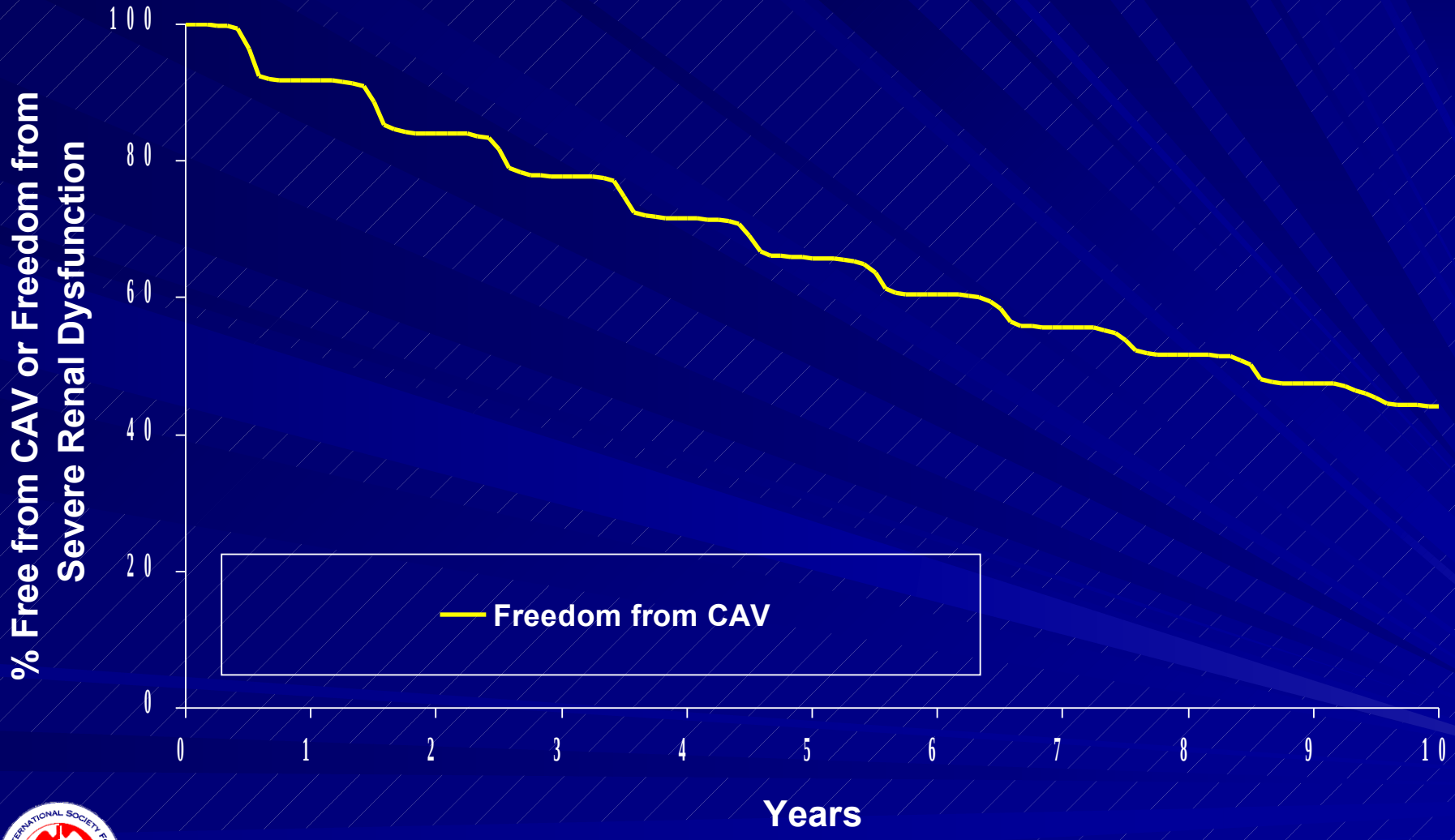
Certican® 3 mg: 91.5%

AZA: 90.2%

*$p < 0.05$ vs AZA;

FREEDOM FROM CARDIAC ALLOGRAFT VASCULOPATHY AND FREEDOM FROM SEVERE RENAL DYSFUNCTION*

(For Adult Heart Recipients (Follow-ups: April 1994-June 2005



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2006

J Heart Lung Transplant 2006;25:869-79