Cardiac transplantation

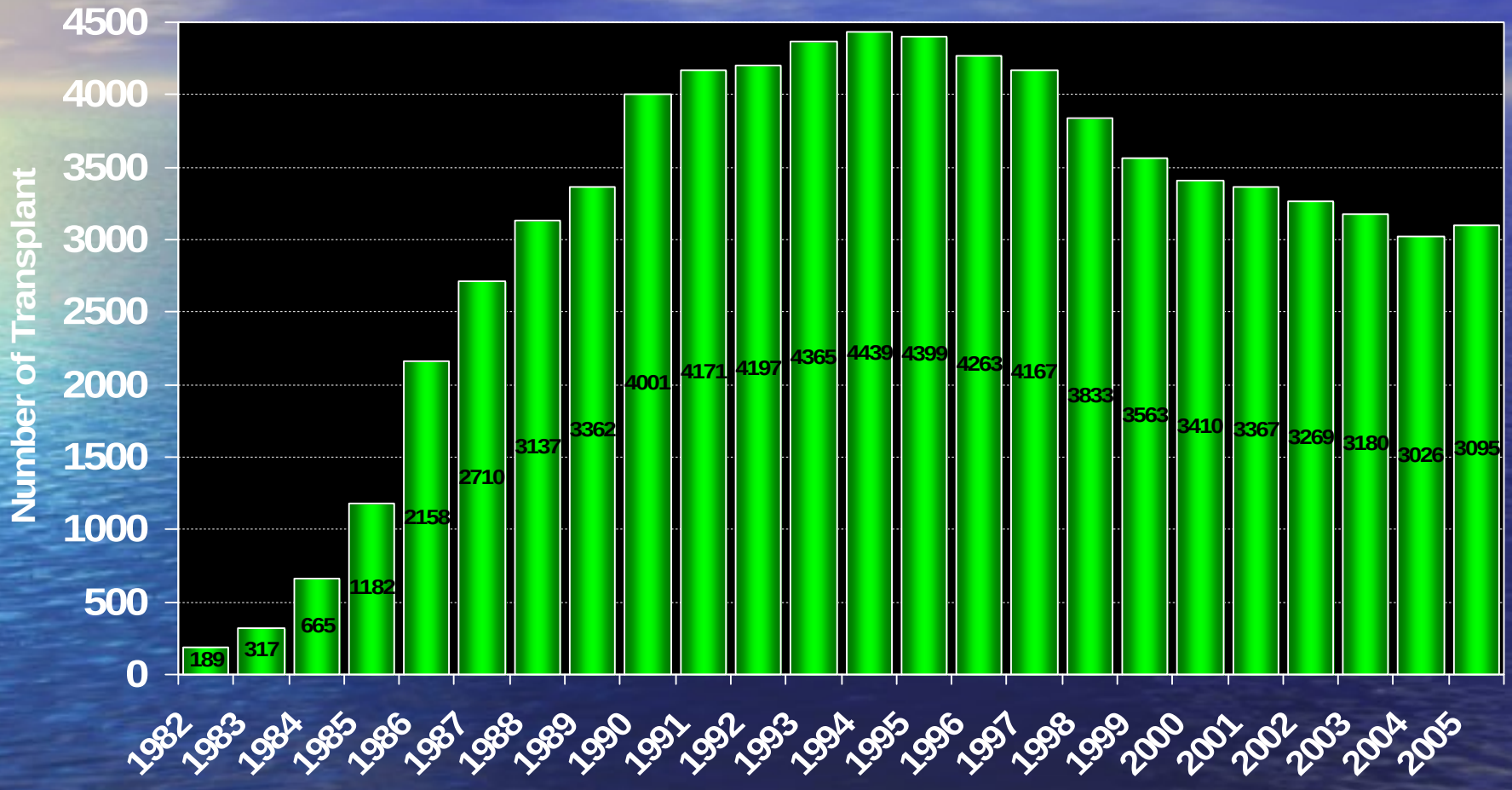
Sotiris Papaspyros

- Indications/contraindications
- Overview of surgery
- Overview of immunosuppression
- Prognosis

Background

- 1905 – Alexis Carrel transplanted puppie's heart into the neck of a dog.
- 1960 - Surgical technique was reported (Norman Shumway)
- 1967 – first successful human heart transplant by Christian Barnard
- 1970 - Recipient selection criteria standardized
- 1973 - Surveillance endocardial biopsy (Philip Caves)
- 1977 - Distant donor heart procurement
- 1981 – Cyclosporine introduced in post op management

NUMBER OF HEART TRANSPLANTS REPORTED BY YEAR



NOTE: This figure includes only the heart transplants that are reported to the ISHLT Transplant Registry. As such, this should not be construed as evidence that the number of hearts transplanted worldwide has declined in recent years.

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- Definition

  - Cardiac transplantation is the procedure by which the failing heart is replaced with another heart from a suitable donor.

- General indication

The procedure is generally reserved for patients with:

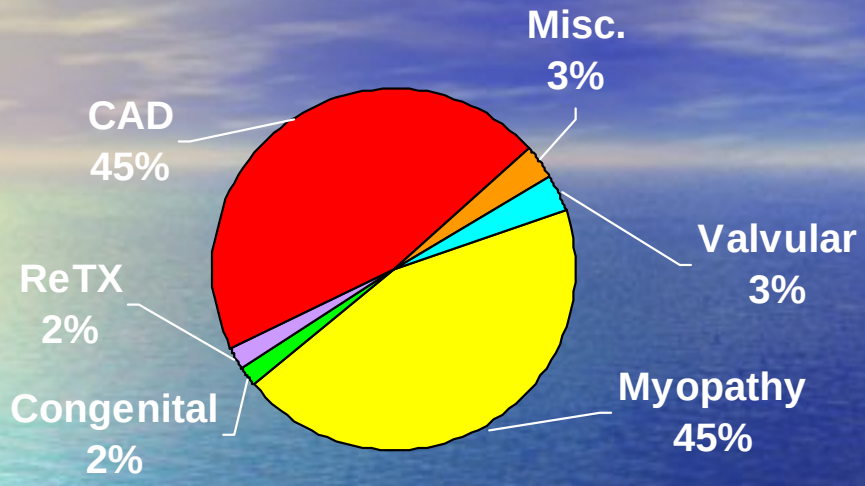
- end-stage congestive heart failure with a
- prognosis of less than a year to live without the transplant
- not candidates for conventional medical therapy or have not been helped by conventional medical therapy.

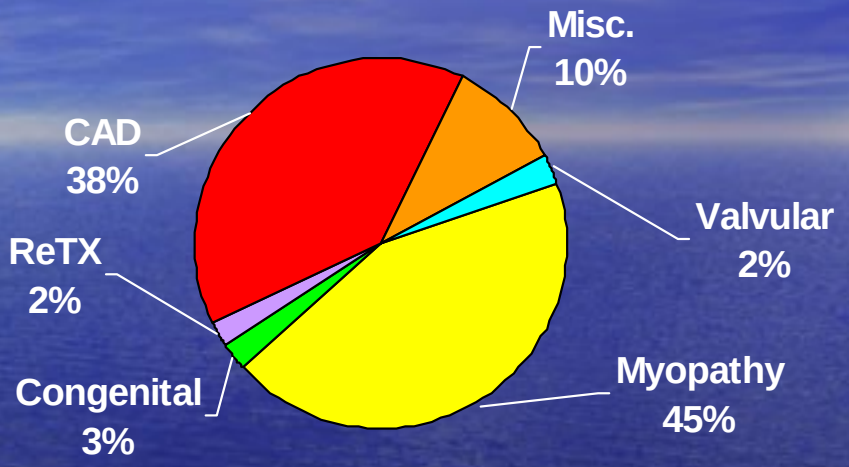
- **Clinical picture of recipient**
  - Candidates for cardiac transplantation generally present with New York Heart Association (NYHA) class III or IV symptoms.
  - Ejection fractions of less than 25%.
  - Attempts are made to stabilize the cardiac condition while the evaluation process is undertaken.
    - The interim therapy can include oral agents as well as inotropic support.
    - Mechanical support with the intra-aortic balloon pump or
    - implantable assist devices may be appropriate in some patients as a bridge to transplantation.

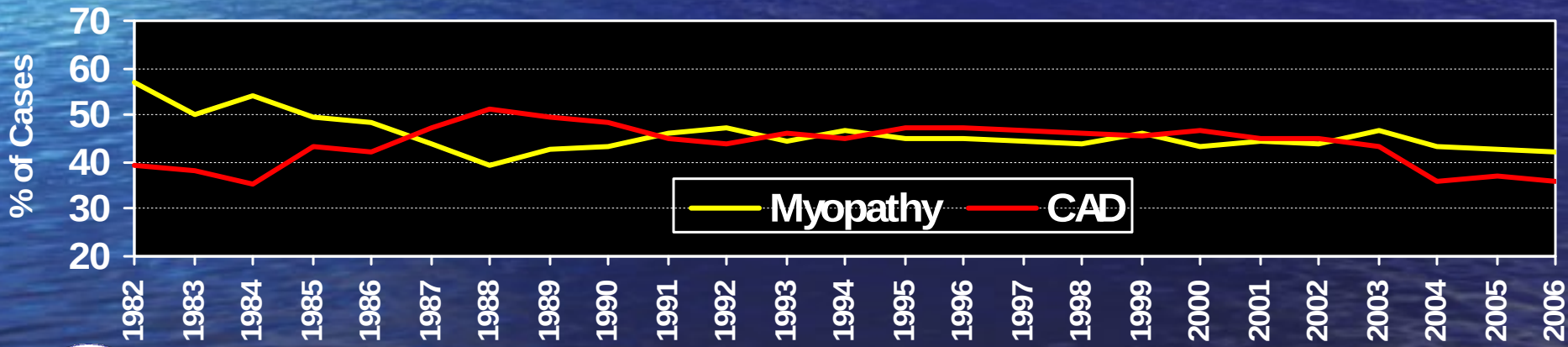
Aetiology

- Idiopathic dilated cardiomyopathy - 54%
- Ischemic cardiomyopathy - 45%
- Congenital heart disease for which no conventional therapy exists or has failed - 1%

DIAGNOSIS IN ADULT HEART TRANSPLANTS







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Specific indications/criteria

- Dilated cardiomyopathy
- Ischaemic cardiomyopathy
- Congenital heart disease for which no conventional therapy exists or that conventional therapy has failed
- EF < 25%
- Intractable angina or malignant cardiac arrhythmias for which conventional therapy has been exhausted
- PVR < 2 Wood units
- Age < 65 years
- Ability to comply with medical follow-up care

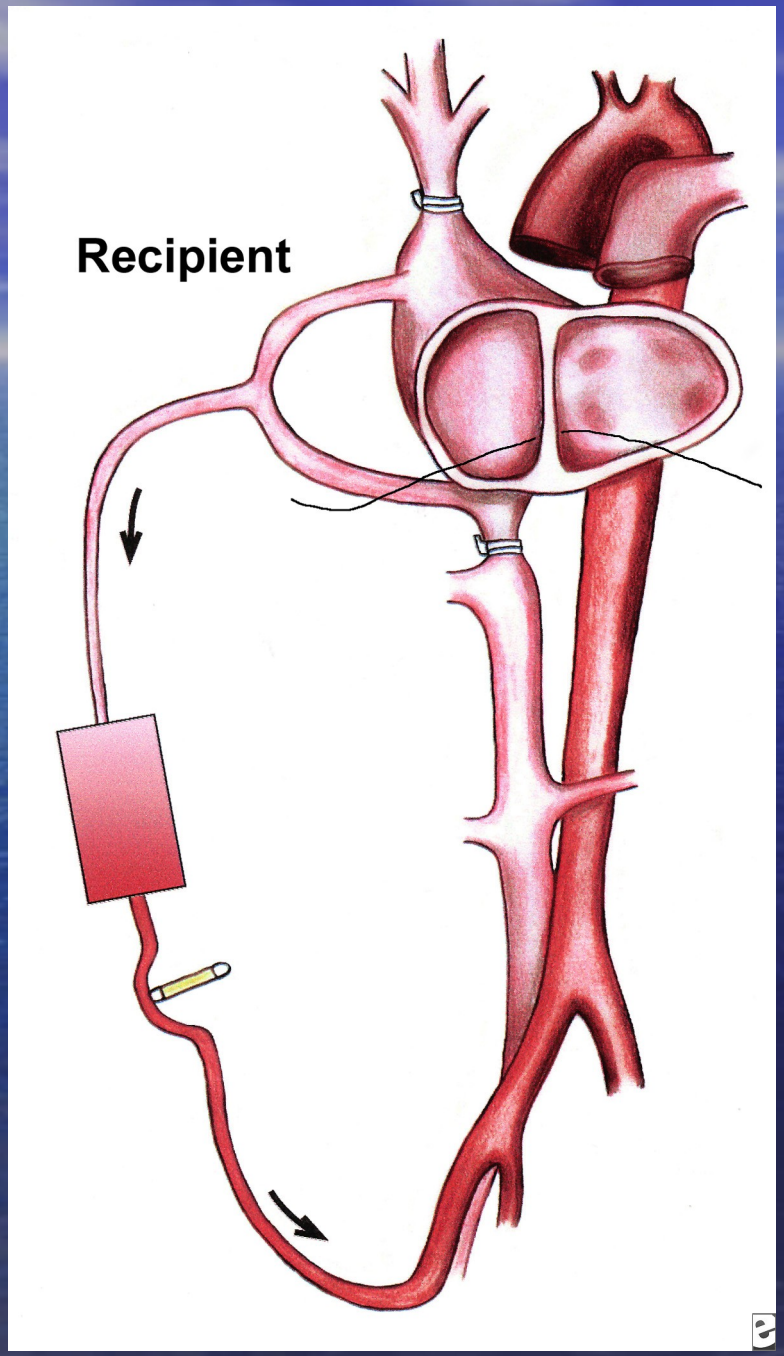
Contraindications

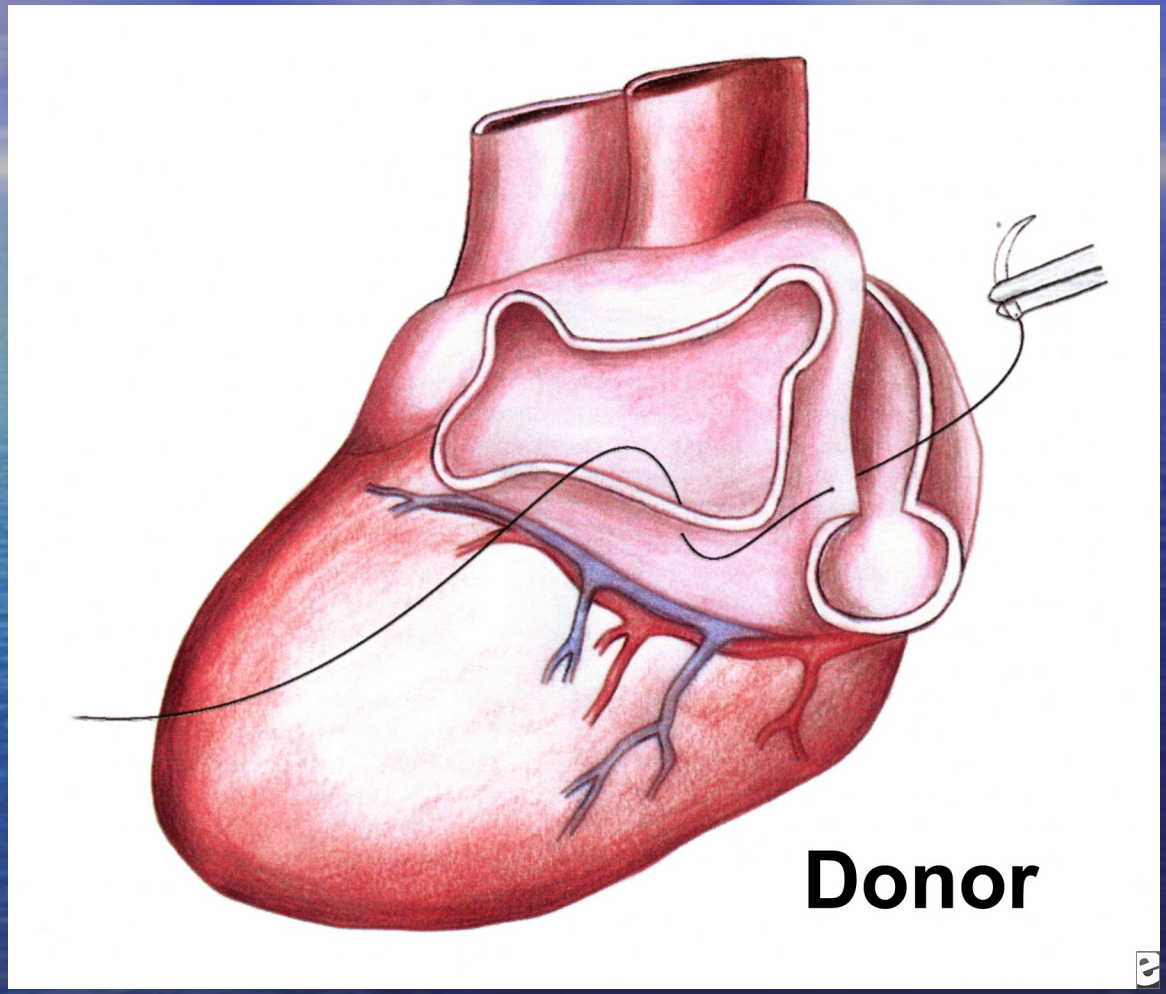
- Age (>65 y): This is a relative issue; patients who are older than 65 years are evaluated on an individual basis.
- Fixed PVR > 4 Wood units
- Active systemic infection
- Active systemic disease such as collagen vascular disease or sickle cell disease
- Active malignancy: Patients with malignancies who have demonstrated a 3- to 5-year disease-free interval may be considered, depending upon the tumor type and the evaluating program.
- An ongoing history of substance abuse (eg, alcohol, drugs, tobacco)
- Psychosocial instability
- Inability to comply with medical follow-up care

Operation overview

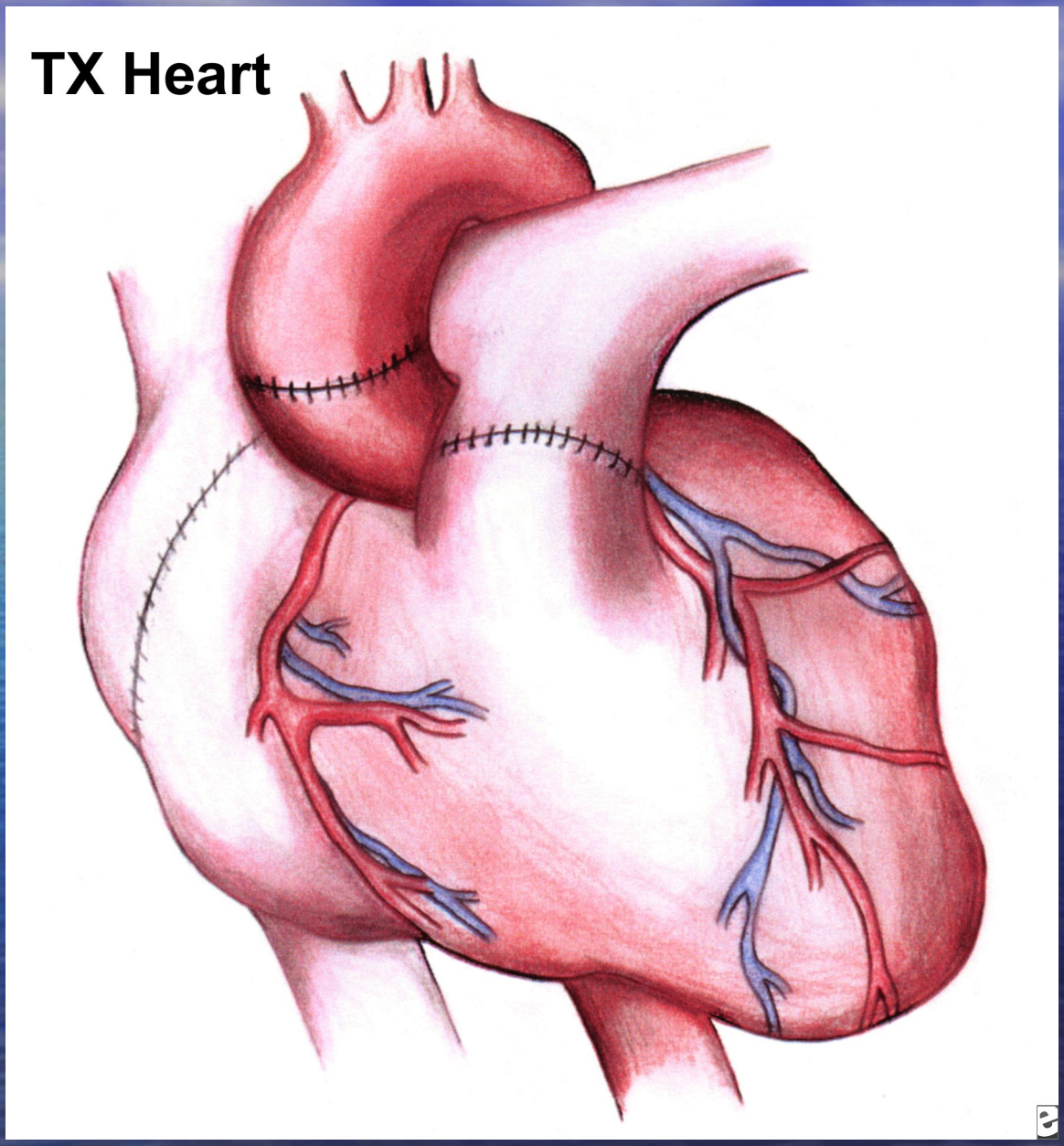
- Ventricles are excised, leaving the great vessels, right atrium, and left atrium of the recipient. (Shamway-Lower)
- The donor heart is then sewn to these areas.
- The bi-atrial anastomosis method is simpler and saves perhaps 10-15 minutes of ischemic time.
- A recent trend has been to revert to bicaval anastomoses rather than right atrial anastomoses in an attempt to decrease the incidence of postoperative tricuspid insufficiency.
- The donor heart can be better preserved by continuous cold retrograde blood cardioplegia through the coronary sinus. Of course, topical cooling of the graft continues to be the primary means of graft preservation.

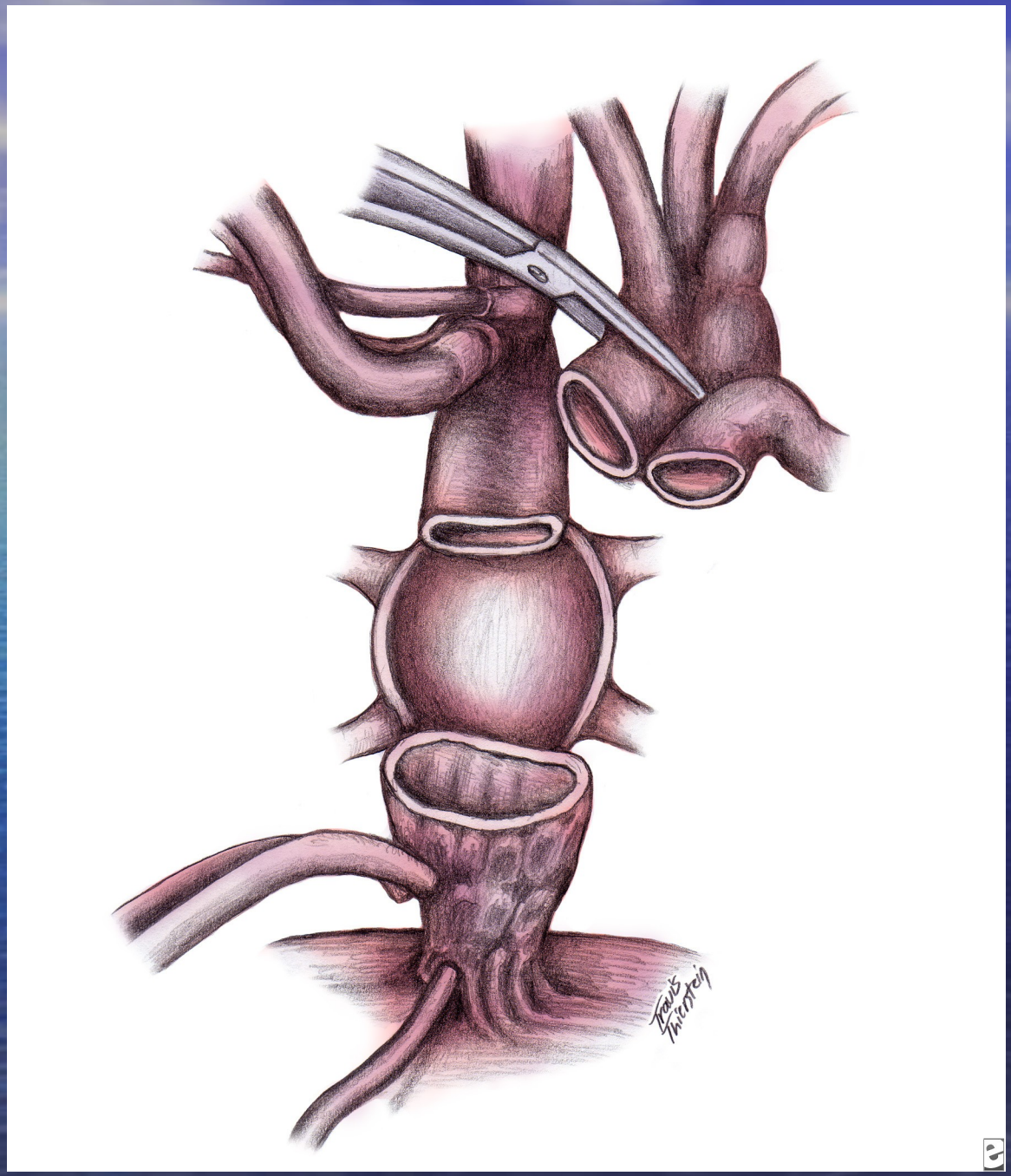
- A cardiac allograft can be sewn in a heterotopic or orthotopic position.
- The incidence of tricuspid regurgitation is reported to be as high as 47-98% following heart transplantation (Chan, 2001). Some centers have now begun to prophylactically perform tricuspid annuloplasty on donor grafts before performing the transplantation


Recipient

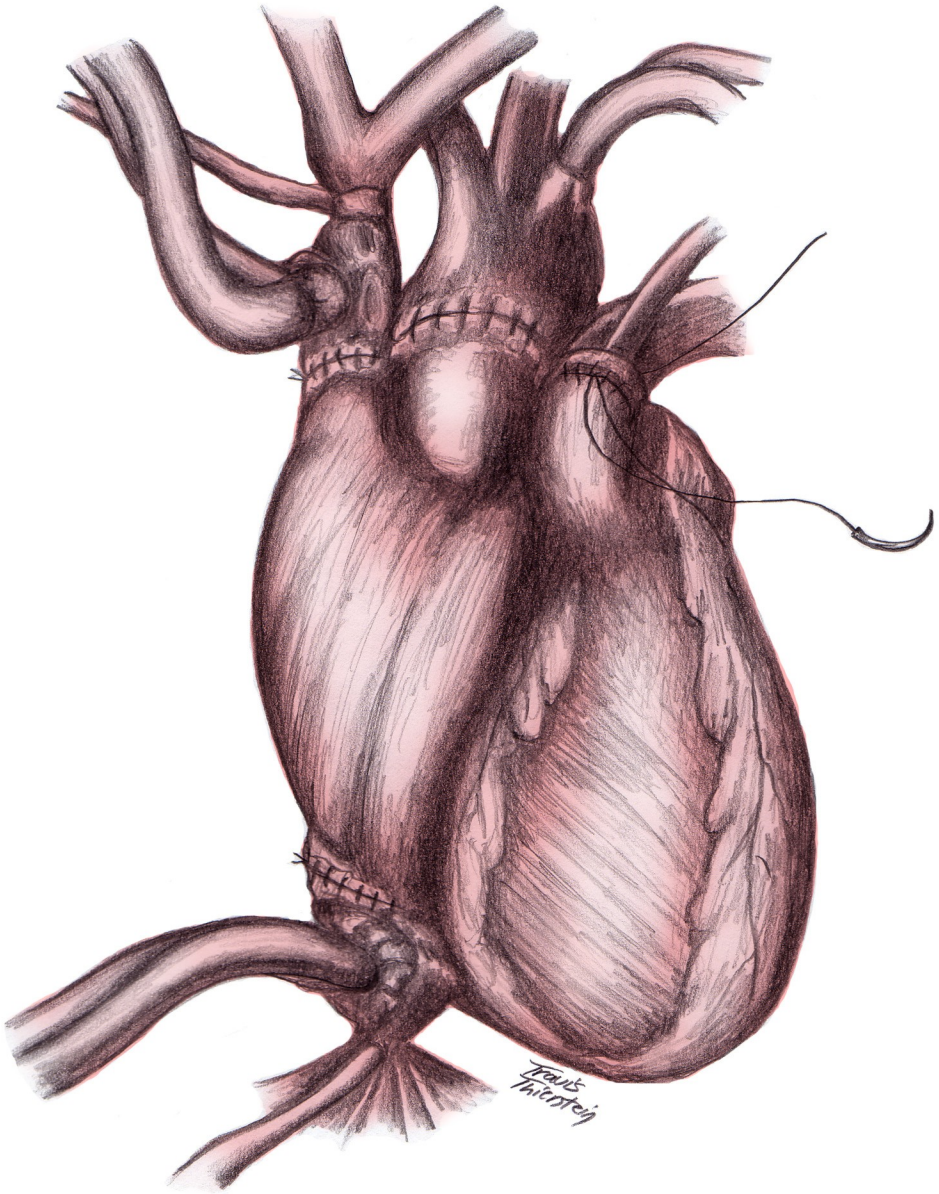

Donor

TX Heart





Completed bicaval transplant technique



Postoperative details

- Pressor agents while the donor heart regains energy stores.
- Initially extremely dependent on circulating calcium ions.
- Immunosuppression is started soon after surgery. Several regimens can be used, including pretransplantation induction therapy or simply postoperative maintenance therapy. The choice of regimen is dependent upon the training and experience of the transplant center.
- Once stabilized, the patient is rapidly weaned from the ventilator and the pressors. The posttransplant hospital stay can be as short as 5 days, depending upon the condition of the recipient prior to surgery.

Follow-up

- Endomyocardial biopsies are performed to assess for allograft rejection. Every week for the first month, with the frequency decreasing over time.
- Regulation of immunosuppression is being adjusted during first month.(regular follow-up).
- The frequency of visits gradually diminishes until the patient is generally seen on an annual basis.
- Certain centers perform coronary angiography annually after transplantation to monitor the patient for the development of allograft vascular disease.

Complications

- Bleeding from the suture lines. This is a rare occurrence but may require reexploration in the early postoperative period.
- Hyperacute rejection can occur immediately after blood flow is restored to the allograft and up to 1 week after surgery despite therapeutic immunosuppression.
- Infection is the primary concern in transplant patients. Preventive measures should be instituted. Bacterial or fungal . Prophylaxis for *Pneumocystis carinii* is universally administered, as is therapy for CMV infection.
- Psychiatric disturbances from steroid therapy can occur in the immediate posttransplant period.
- Cardiac rejection is to be expected and should be detected by endomyocardial biopsy. The process can be treated with steroid therapy alone, polyclonal antibody therapy, or monoclonal antibody therapy.
- Allograft vascular disease is the main cause of late graft failure and death. The coronary arteries develop a progressive concentric myointimal hyperplasia.Can develop as early as 3 months after transplantation. The cause of the process is unclear. However, CMV infection and recurrent rejection episodes are thought to be associated with the cause. The only available therapy is retransplantation. The process can sometimes be treated by stenting of the diseased vessels.

Unique features

- Denervated heart – hence dependant on its own intrinsic rhythm
- Resting cardiac output is normal in most patients and responds appropriately to exercise
- Arterial hypertension is present in most patients (side effect of cyclosporine)
- Left ventricular end diastolic pressure is elevated
- LV mass is increased

Unique features

- The RV is easily damaged and may initially function as a passive conduit until recovery occurs (RA and RV dilated for first week)
- Right-sided function is directly dependent upon the ischemic time incurred prior to re-implantation and the adequacy of preservation.
- Pre op pulmonary hypertension also affects RV function
- Ventricular arrhythmias are similar to normal hearts

Immunosupression

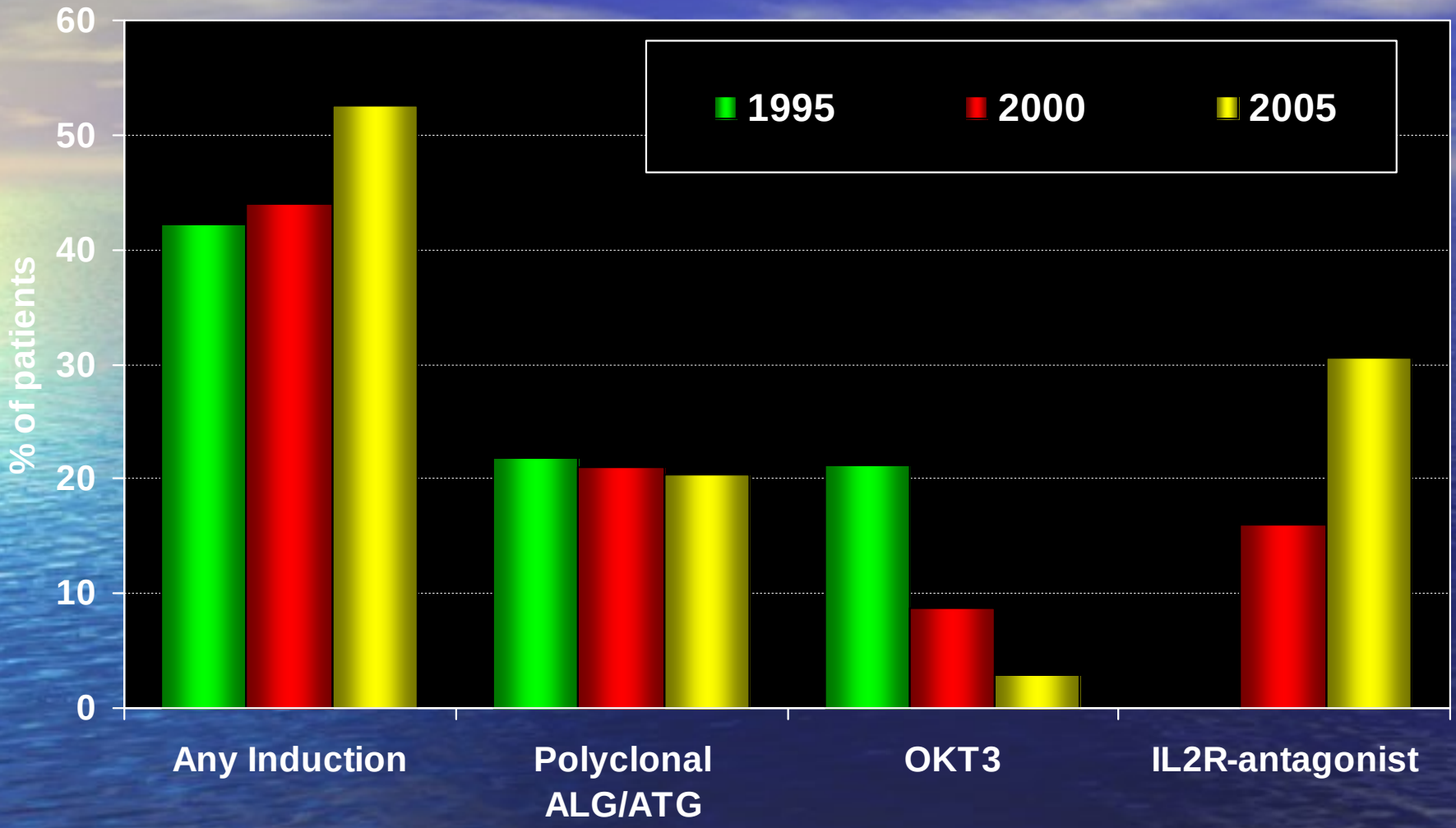
- Tissue compatibility for transplantation has traditionally required only HLA-A, HLA-B, and HLA-DR typing
- Current data support the conclusion that HLA matching confers an important benefit after heart transplantation, and probably after heart-lung and lung transplantation
- Heart and lung allografts tolerate only 4 to 6 hours of ischemic time

Immunosuppressive drugs

- **Corticosteroids**
- **Cytokine Synthesis Inhibitors.(Cyclosporin (CsA) inhibits the gene activation necessary for IL-2 production).Tacrolimus.**
- **Inhibitors of DNA Synthesis.AZA, MMF.**
- **IL-2 Signal Transduction Inhibitor.Rapamycin.**
- **Receptor Antagonists and Monoclonal Antibodies.Polyclonal anti-T-cell preparations(ATG).**

ADULT HEART RECIPIENTS

Induction Immunosuppression (Transplants: 1995, 2000 and 2005)



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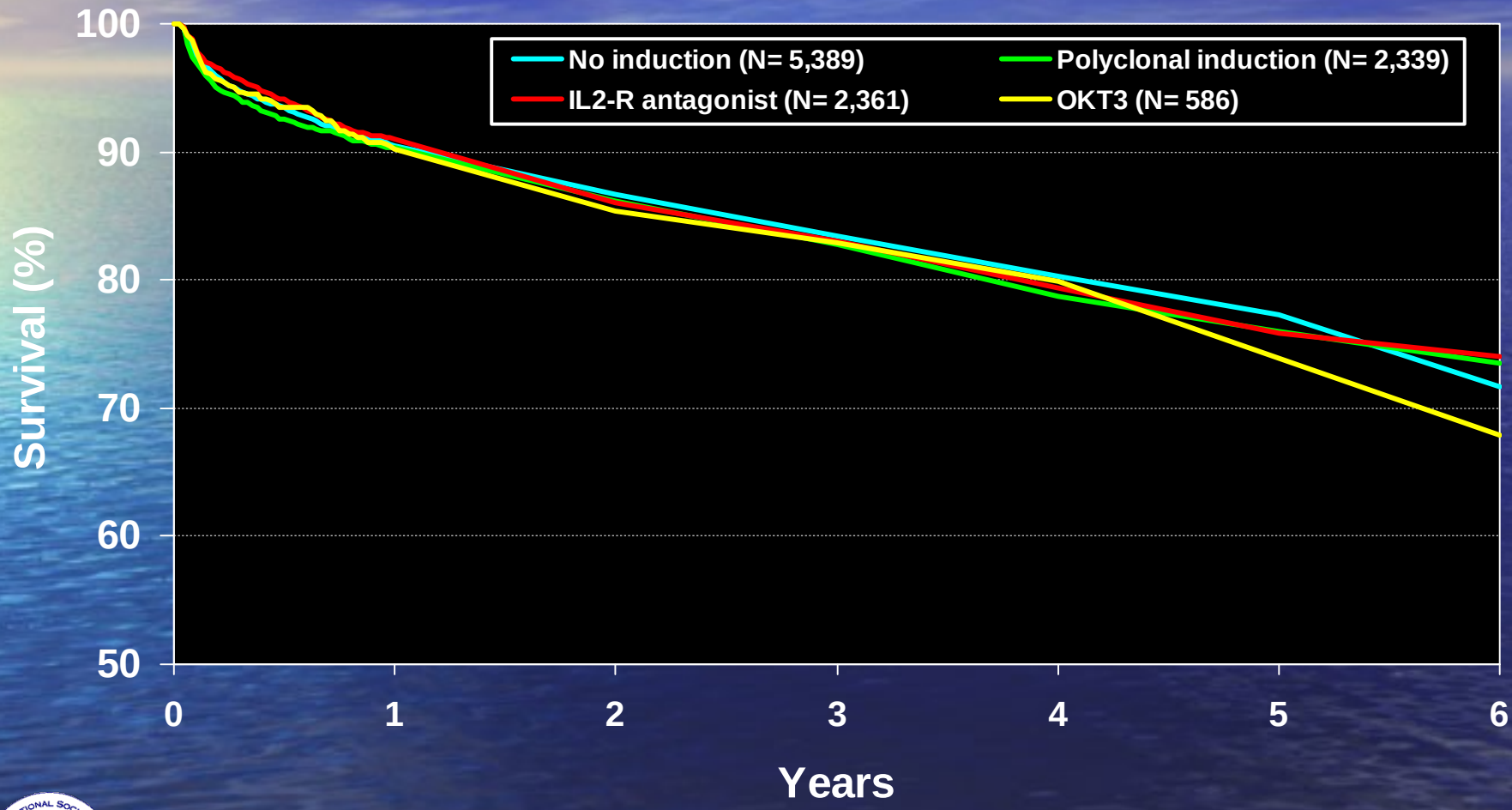
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ADULT HEART TRANSPLANTATION

Kaplan-Meier Survival by Induction Type

(Transplants: 1/2000-6/2005, conditional on survival to 14 days)



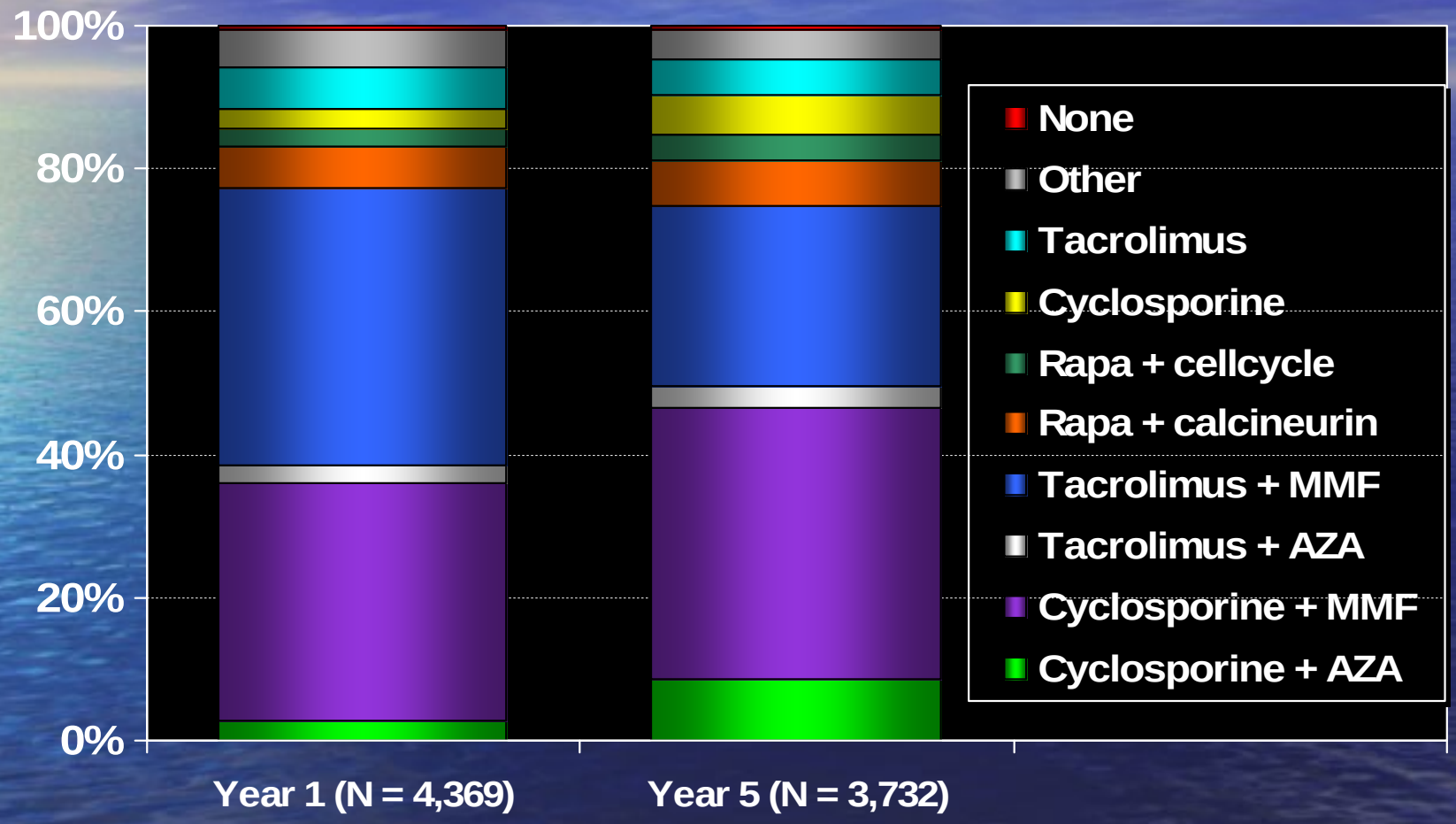
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ADULT HEART RECIPIENTS

Maintenance Immunosuppression Drug Combinations at Time of Follow-up
(Follow-ups: January 2004 - June 2006)



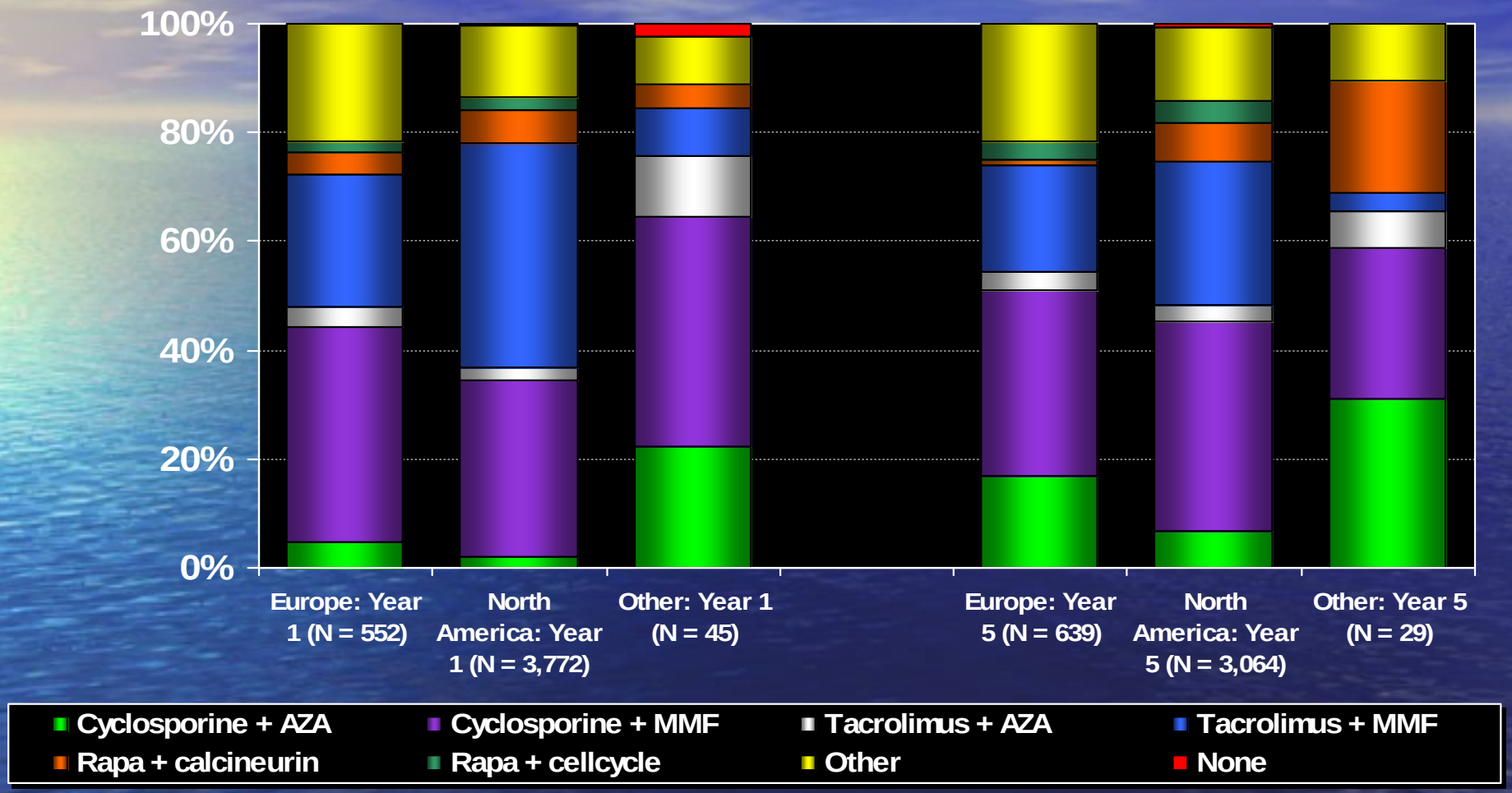
NOTES: Different patients are analyzed in Year 1 and Year 5. In the Year 1 cohort 73.9% of patients were on prednisone; in the Year 5 cohort 56.8% of patients were on prednisone.

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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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Rejection

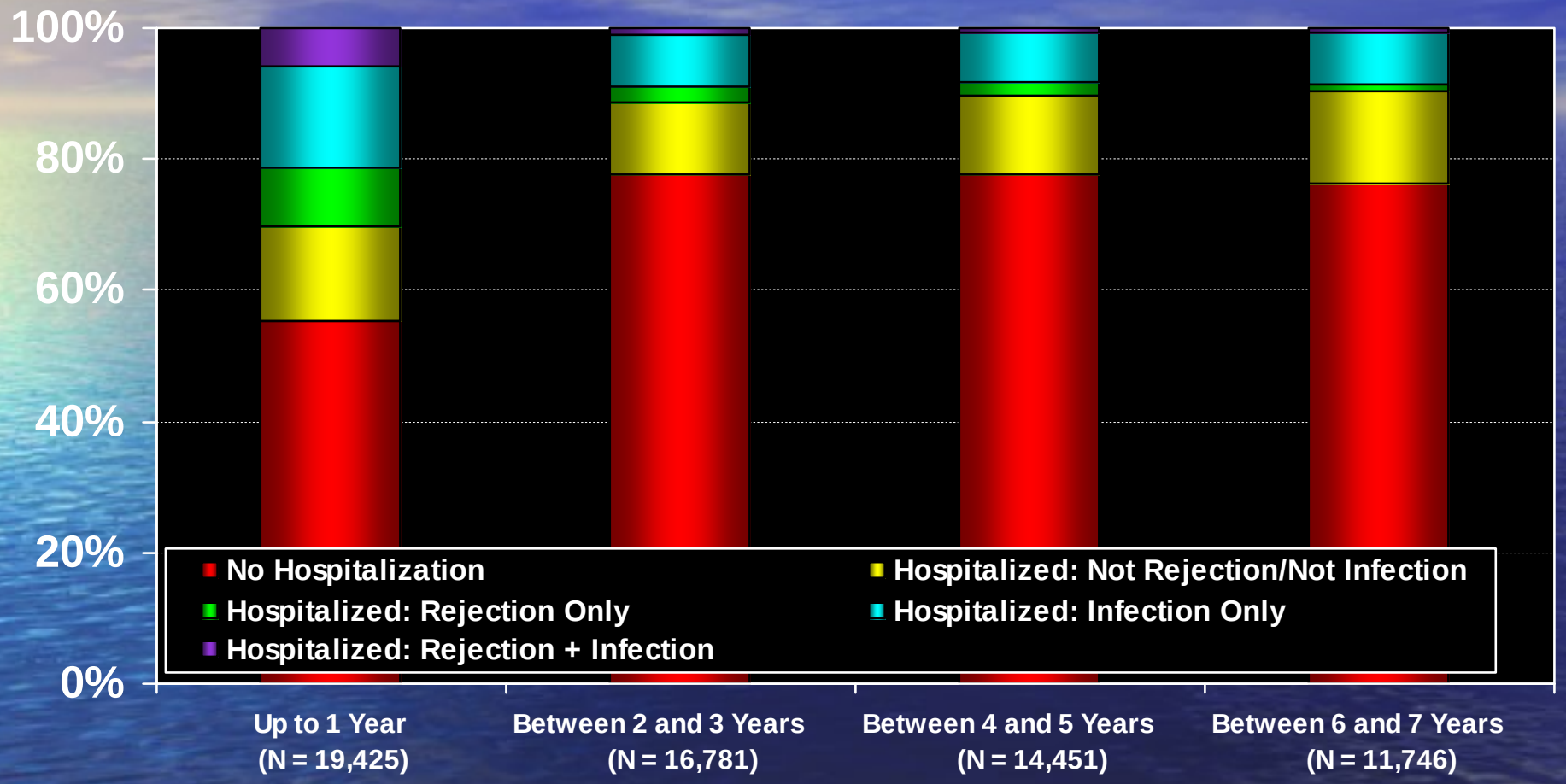
- Cellular and humoral
- Cellular rejection is the classic form of rejection and is characterized by perivascular infiltration of lymphocytes with subsequent myocyte damage and necrosis if left untreated.

Pathophysiology

- Humoral rejection is much more difficult to characterize and diagnose.
- Humoral rejection is thought to be a generalized antibody response initiated by several unknown factors.
- The antibody deposition into the myocardium results in global cardiac dysfunction.
- This diagnosis is generally made on the basis of clinical suspicion and exclusion because endomyocardial biopsy is of little value.

ADULT HEART RECIPIENTS

Rehospitalization Post-transplant of Surviving Recipients (Follow-ups: 1995 - June 2006)



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Coronary artery disease

- Coronary artery disease can occur starting very early after transplantation
- No angina – denervated heart
- Ventricular arrhythmias, cardiac failure, silent infarctions, sudden death may be the only manifestation
- Lesions are of 2 types –

  type A – discrete stenosis of proximal arteries

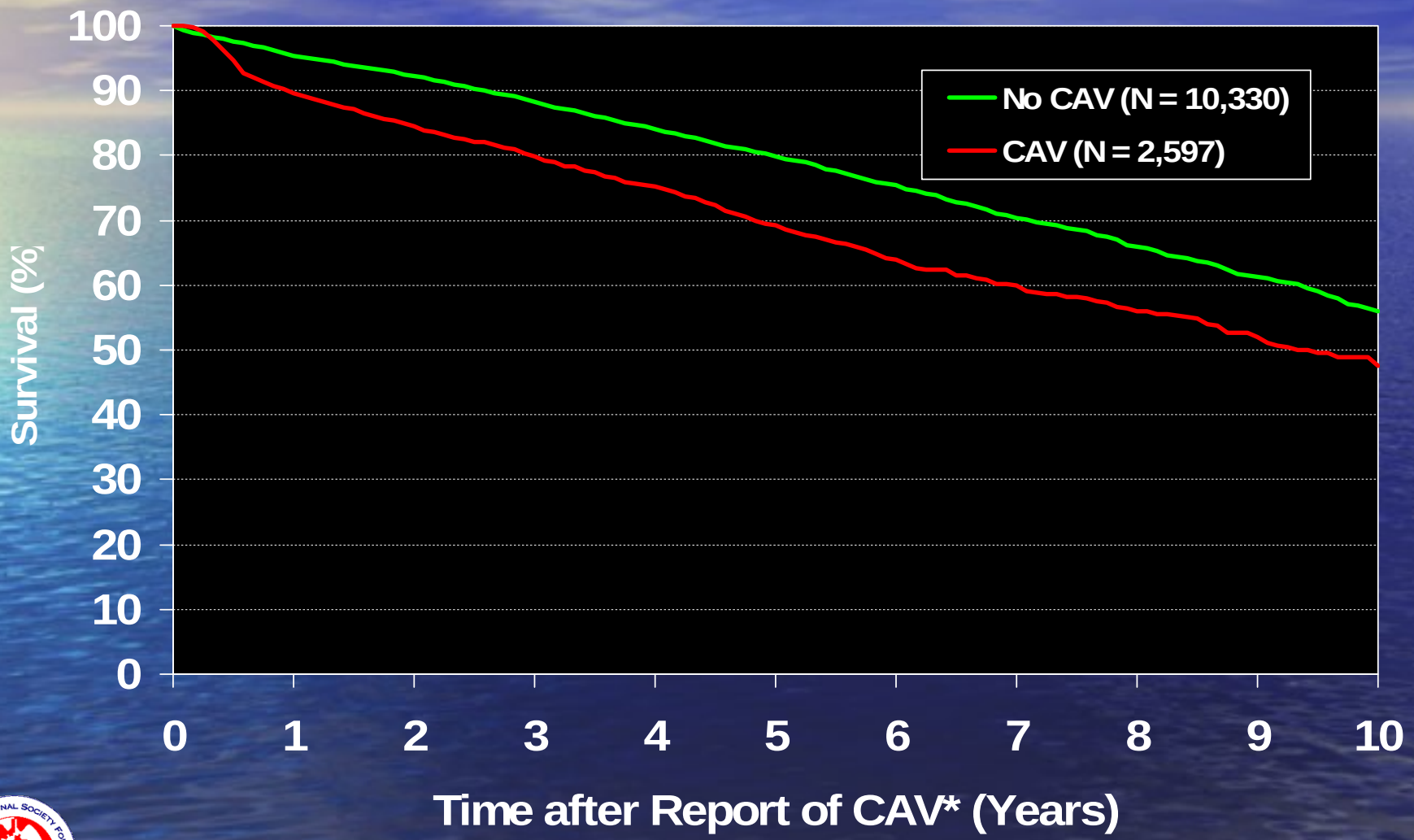
  type B – long tubular constrictions in distal arteries

CAD II

- Can take 3m to several years to develop
- Reason – not clear – CMV infection, Chronic rejection, Lymphocyte derived growth factor are all implicated.
- Treatment is retransplantation

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

(Transplants: April 1994-June 2004)

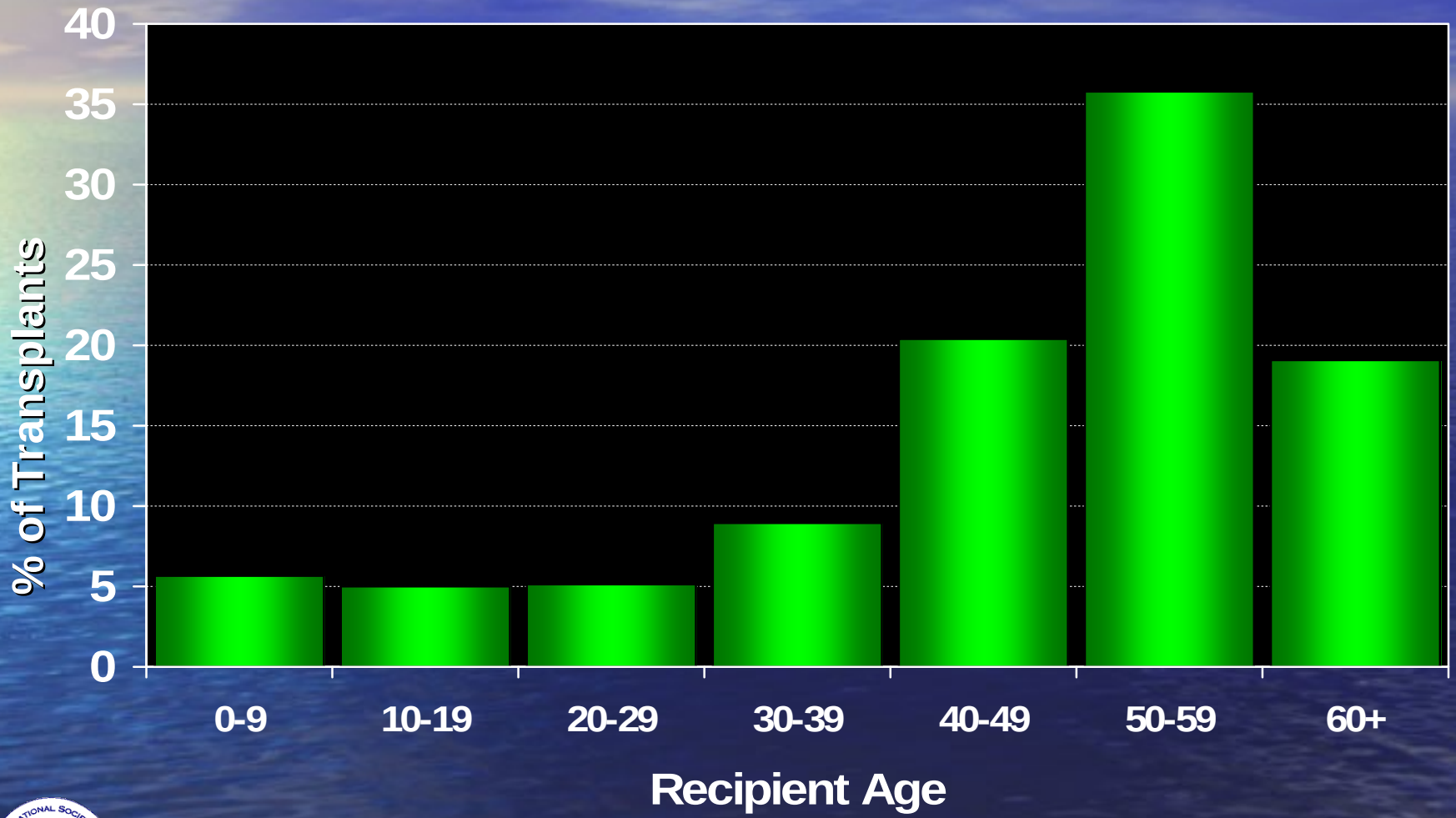


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* Patients without CAV conditioned on survival to median time of CAV development (514 days)

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AGE DISTRIBUTION OF HEART RECIPIENTS (1/1982-6/2006)



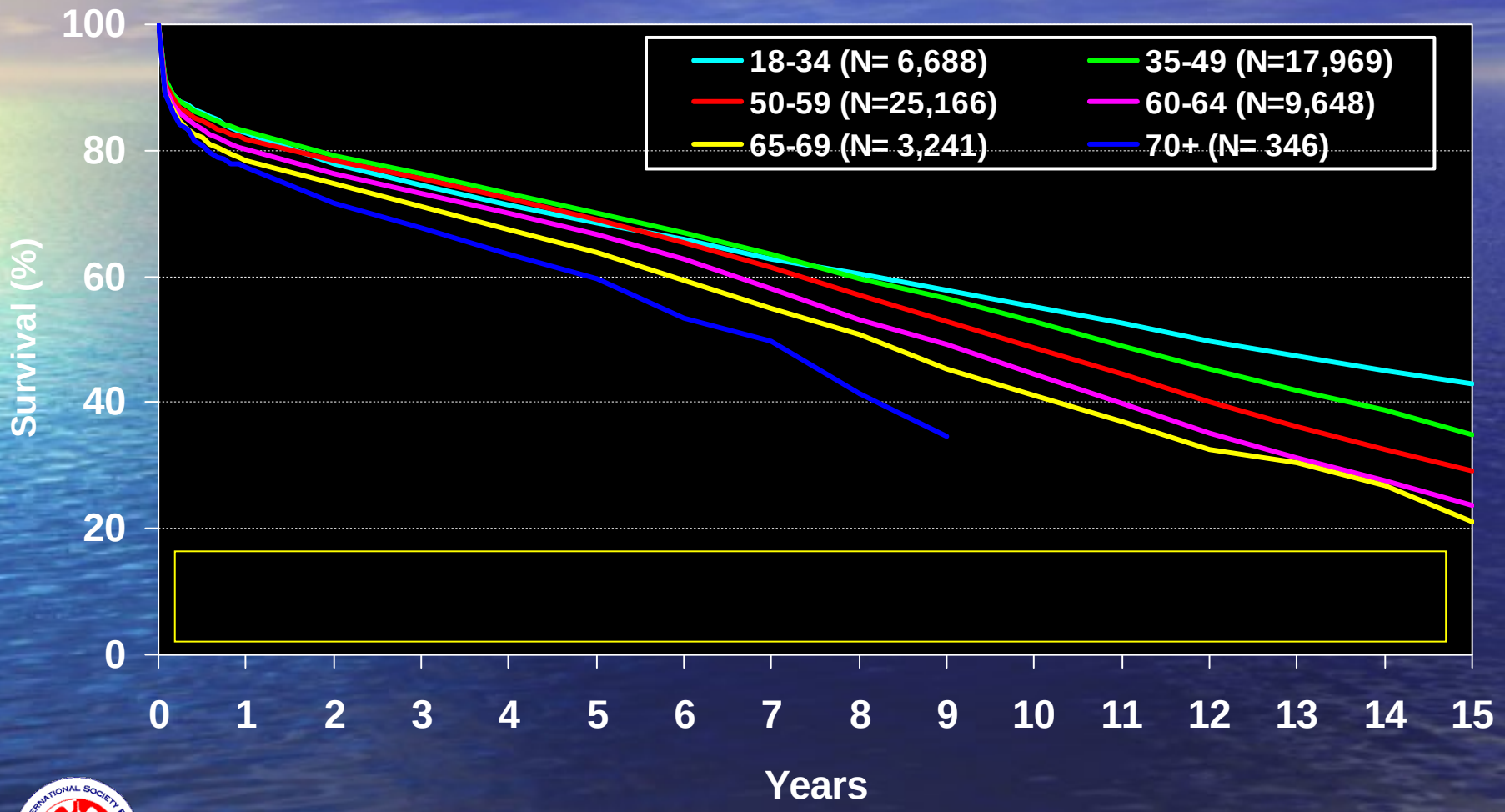
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ADULT HEART TRANSPLANTATION

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



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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)



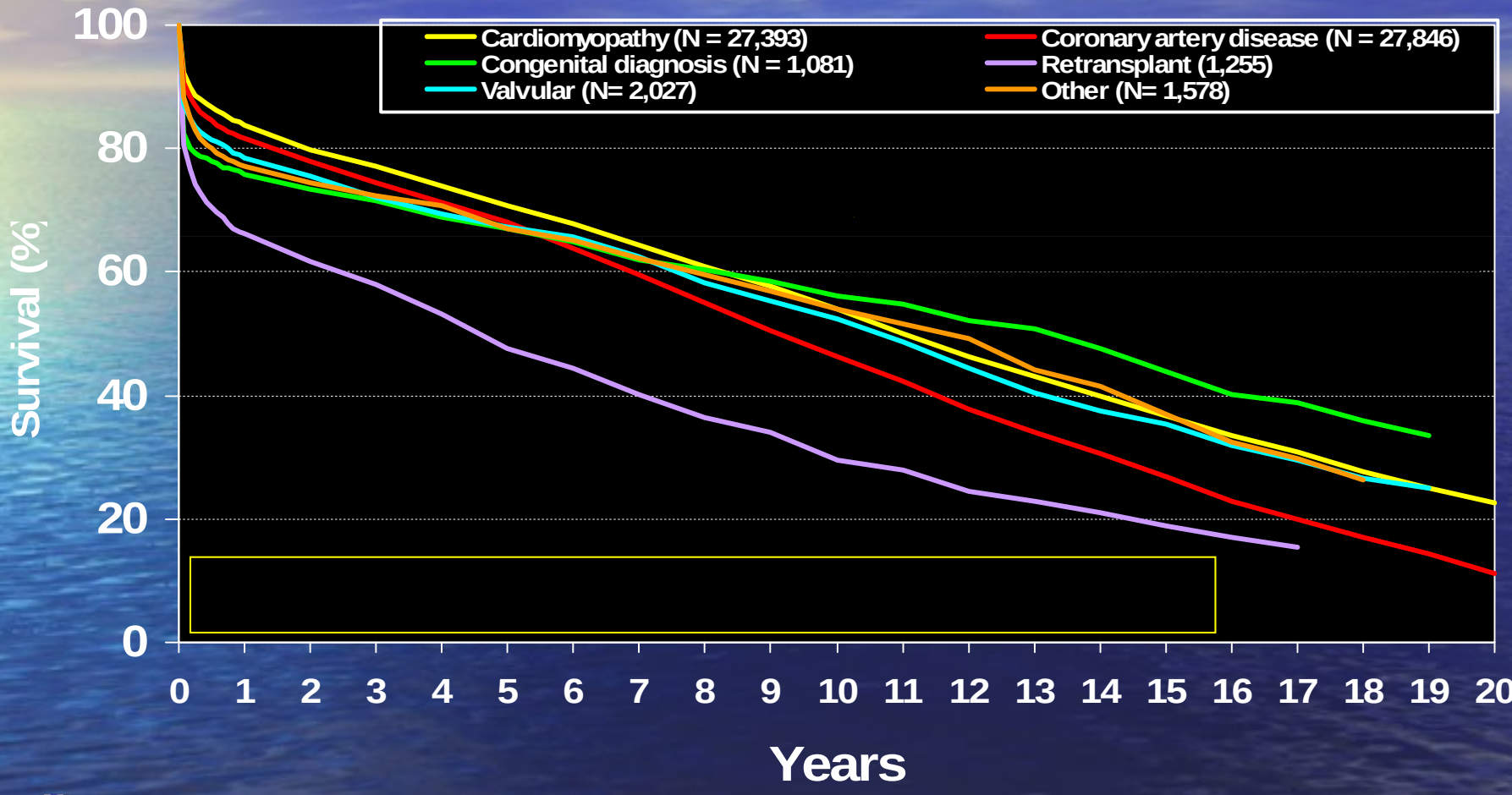
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ADULT HEART TRANSPLANTATION

Kaplan-Meier Survival by Diagnosis (Transplants: 1/1982-6/2005)

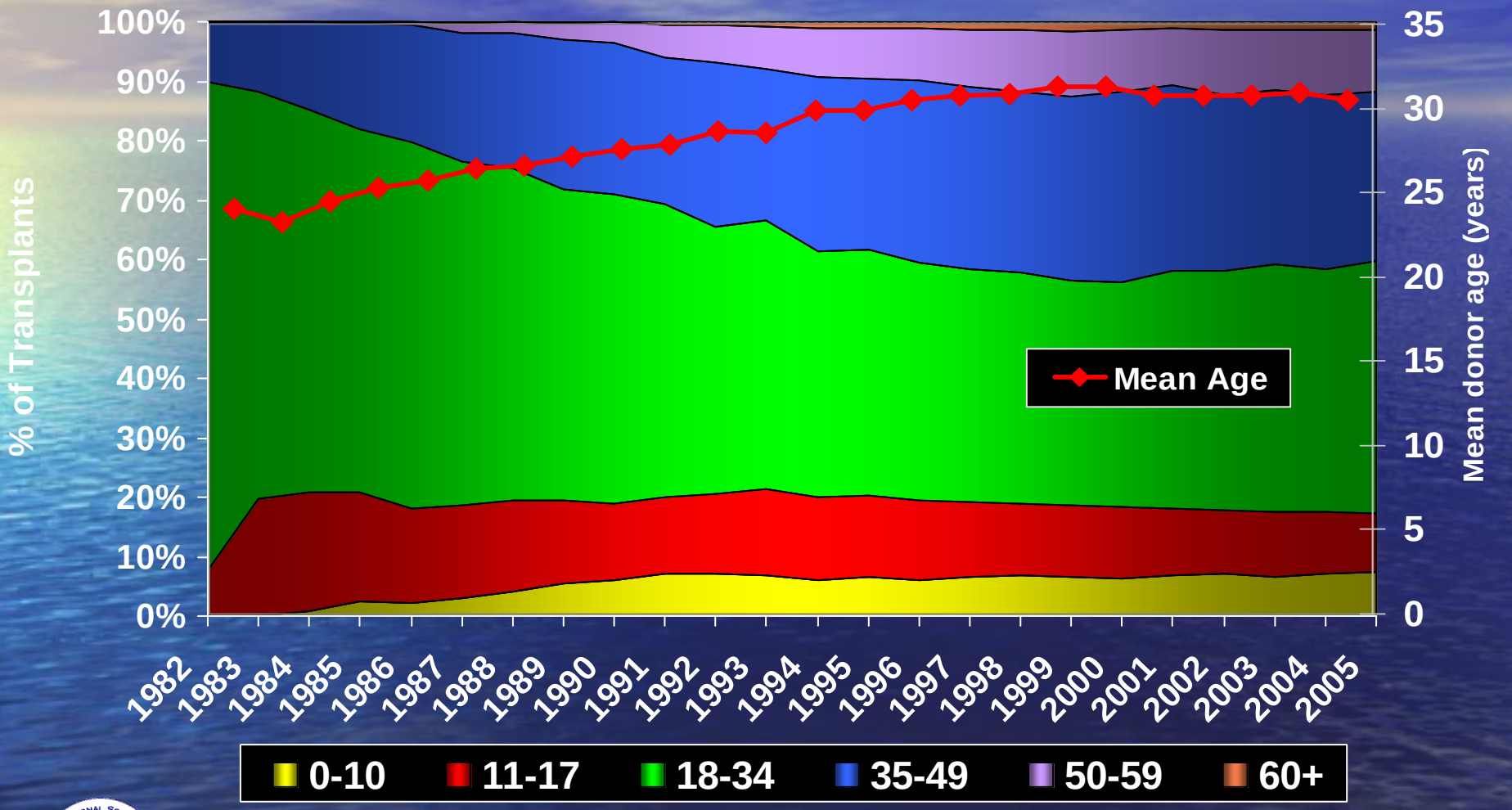


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HEART TRANSPLANTS:
Donor Age by Year of Transplant

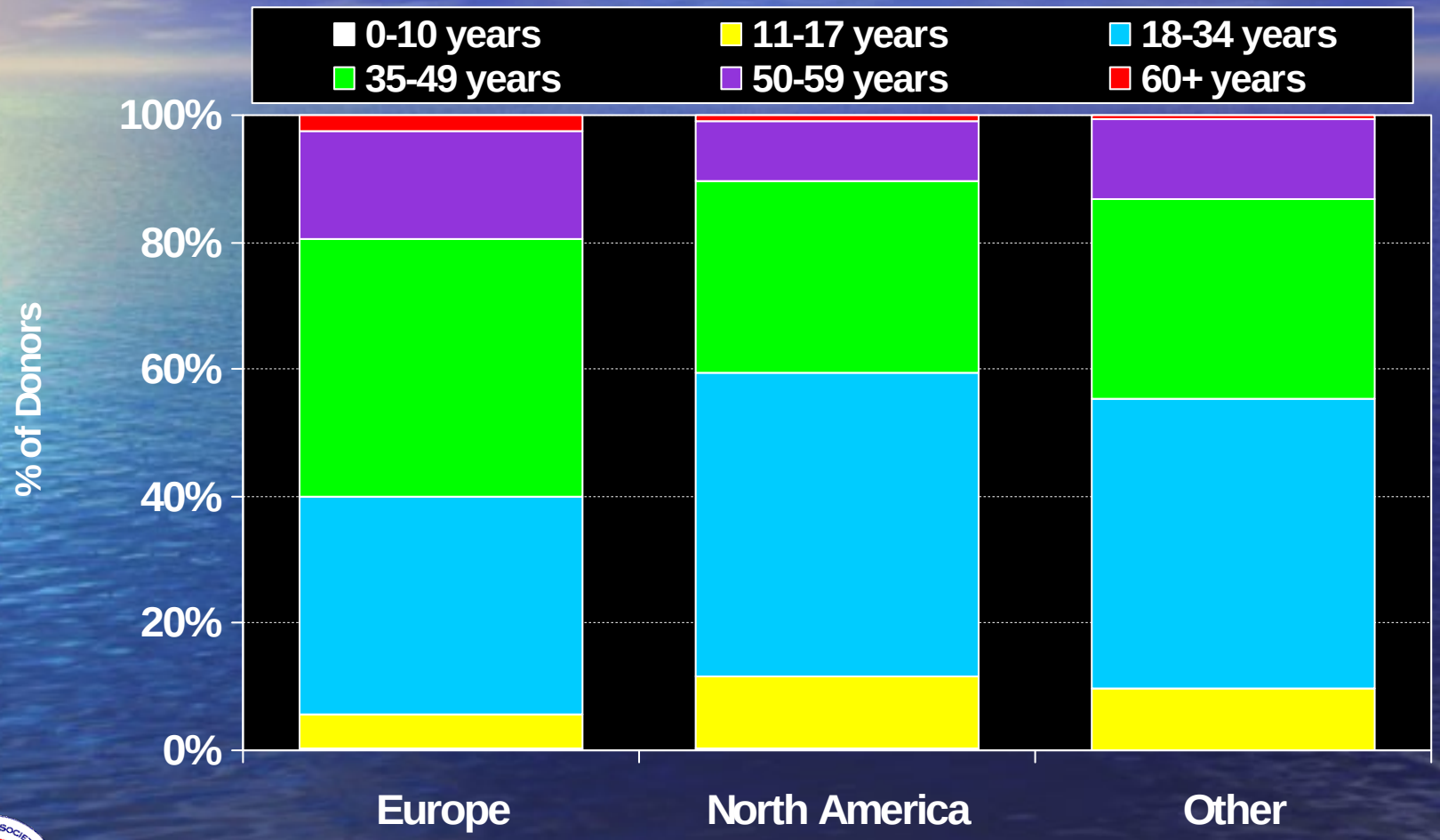


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ADULT HEART TRANSPLANTS:
DONOR AGE DISTRIBUTION BY LOCATION
Transplants between January 2000 and June 2006

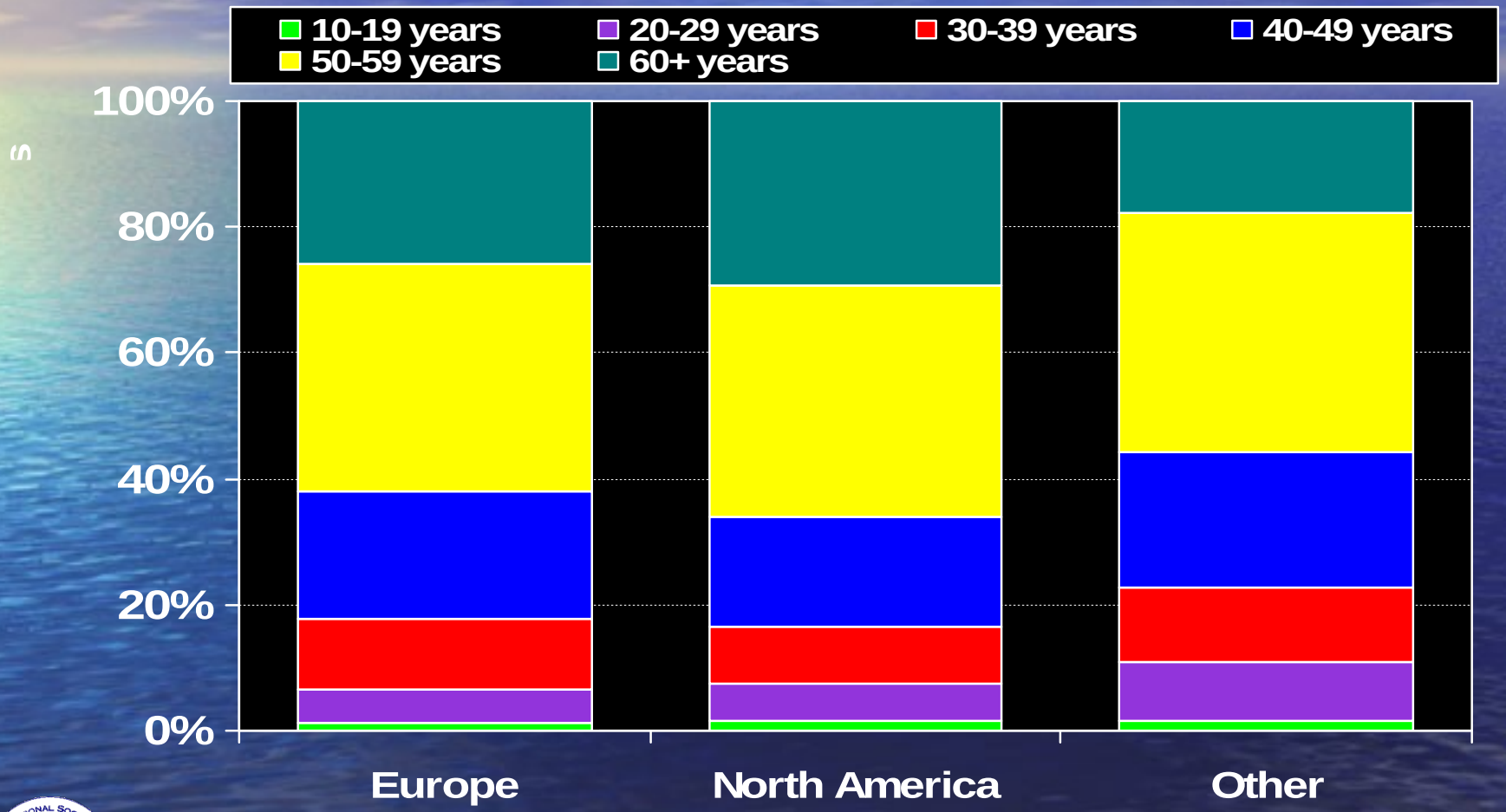


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ADULT HEART TRANSPLANTS:
RECIPIENT AGE DISTRIBUTION BY LOCATION
Transplants between January 2000 and June 2006



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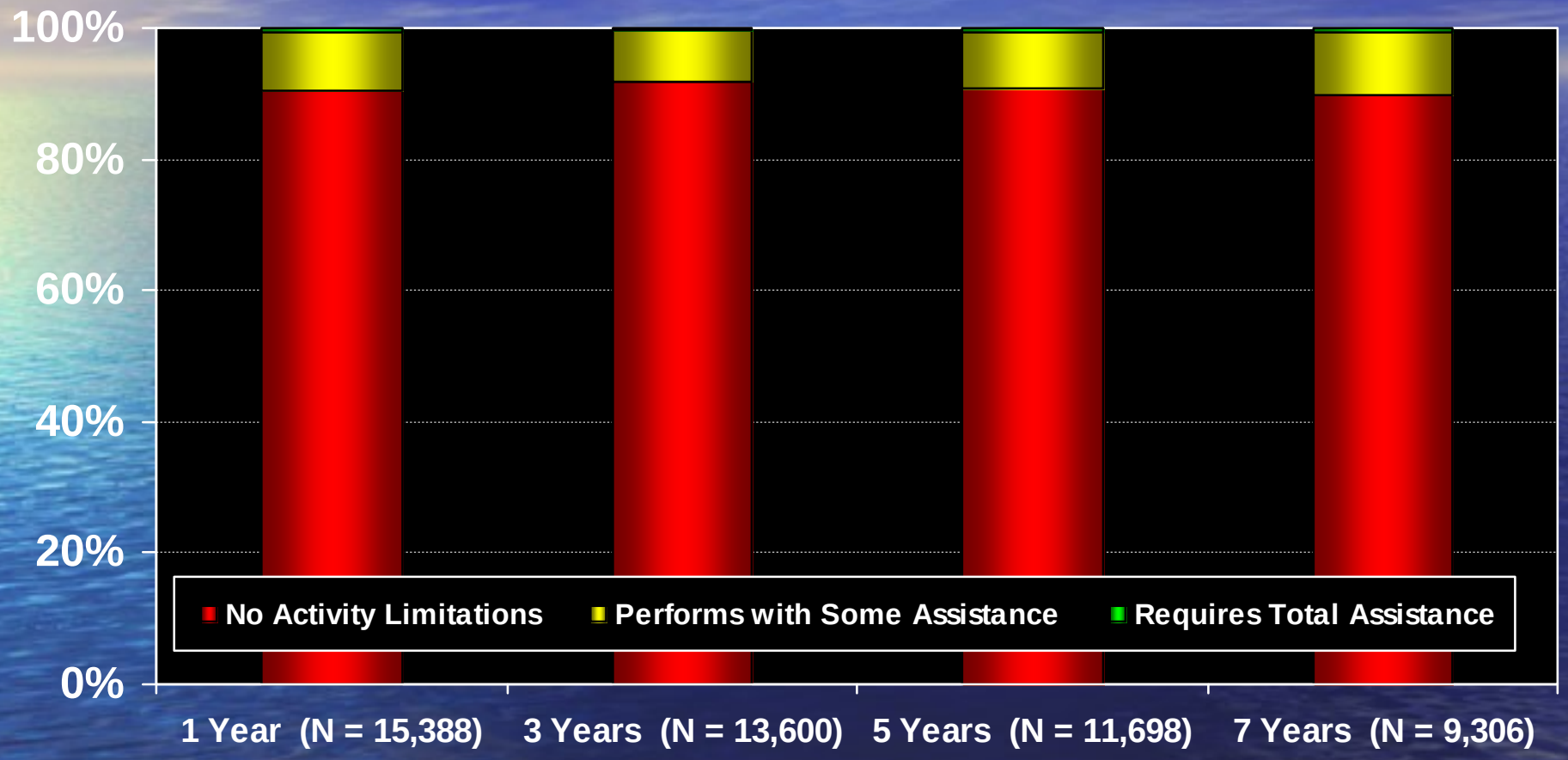
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ADULT HEART RECIPIENTS

Functional Status of Surviving Recipients

(Follow-ups: 1995 - June 2006)



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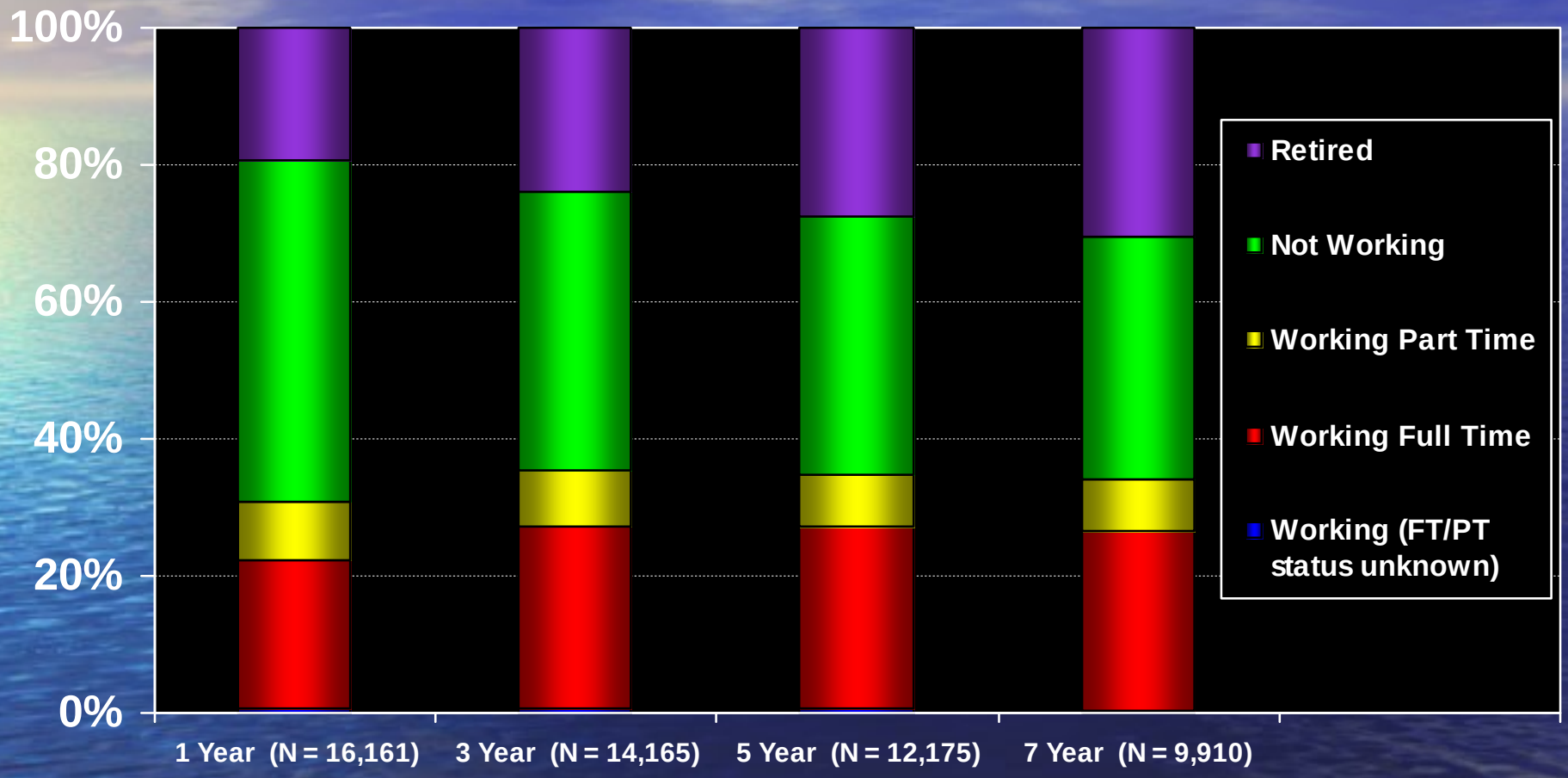
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ADULT HEART RECIPIENTS

Employment Status of Surviving Recipients

(Follow-ups: 1995 - June 2006)



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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		Follow-ups: January 2002 – June 2006	
	Within 1 Year	Total N with known response	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)

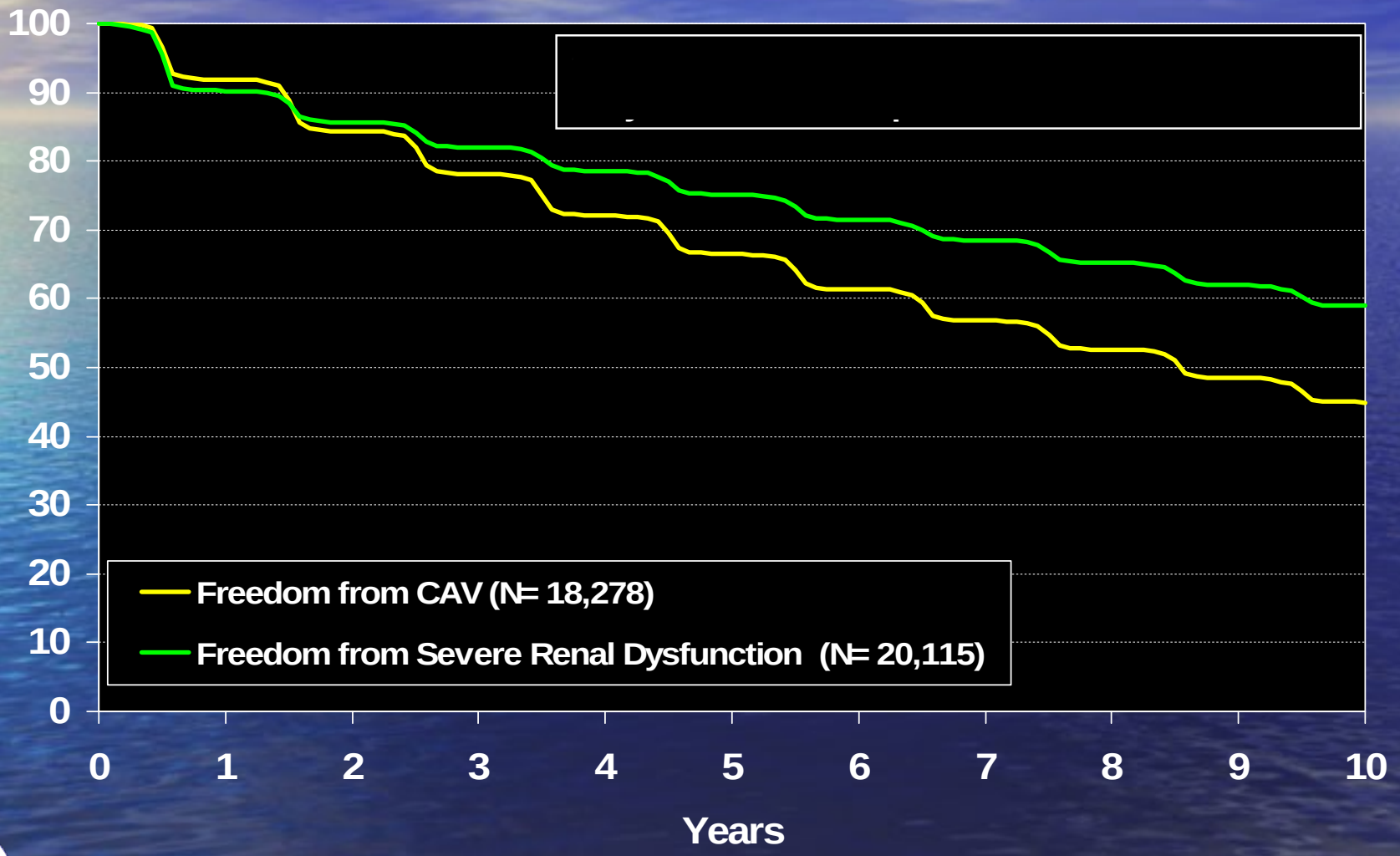
Outcome	Within 5 Years	Total N with known response	Within 10 Years	Total N with known response
Hypertension	**93.8%**	**(N = 8,266)**	**98.5%**	**(N = 1,586)**
Renal Dysfunction	**32.6%**	**(N = 8,859)**	**38.7%**	**(N = 1,829)**
Abnormal Creatinine < 2.5 mg/dl	***21.2%***		***24.4%***	
Creatinine > 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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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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MALIGNANCY POST-HEART TRANSPLANTATION FOR ADULTS
Cumulative Prevalence in Survivors (Follow-ups: April 1994 - June 2006)

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

"Other" includes: prostate (11, 24, 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.



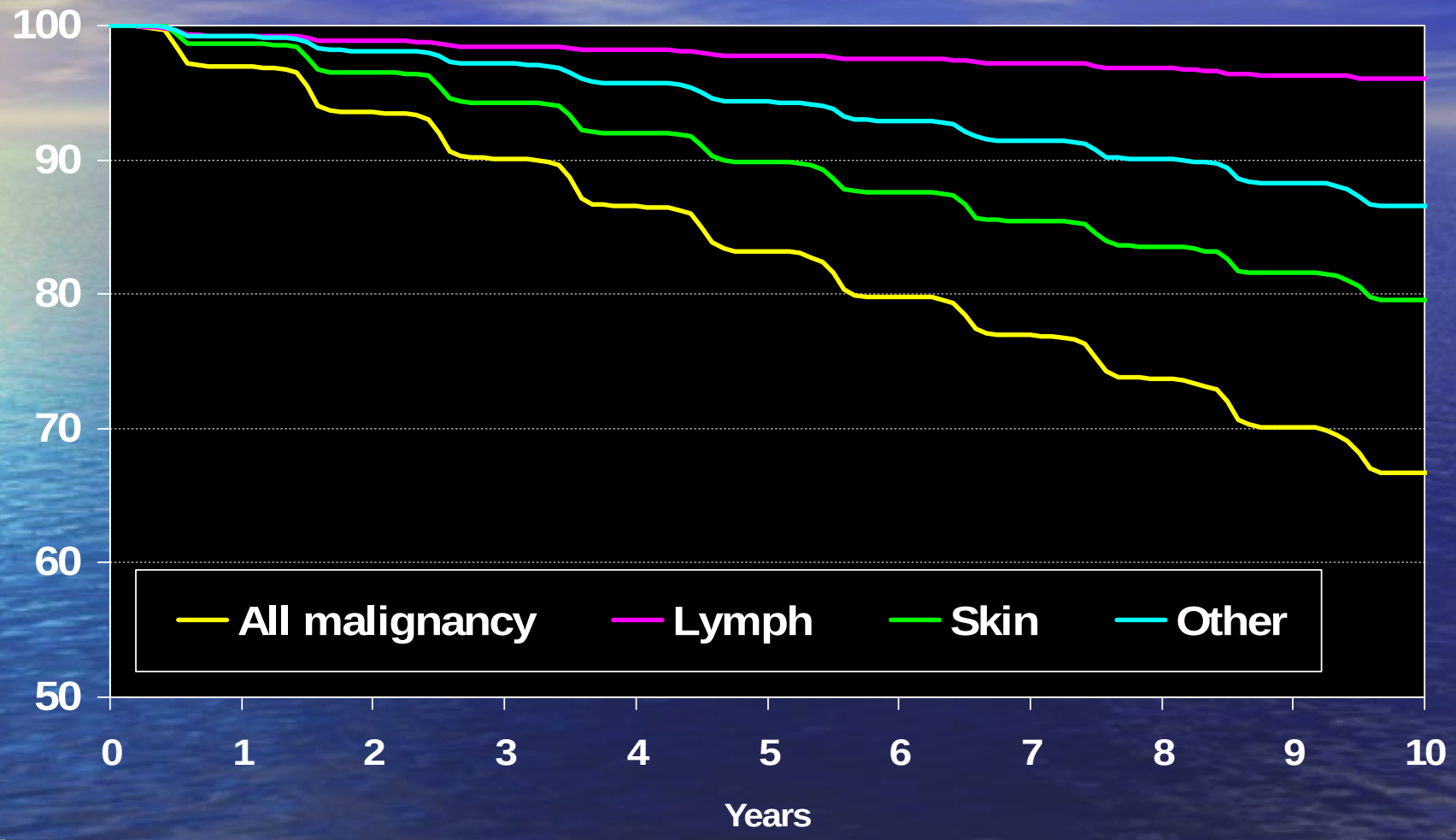
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FREEDOM FROM MALIGNANCY

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



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ADULT HEART TRANSPLANT RECIPIENTS:
Cause of Death (Deaths: January 1992 - June 2006)

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

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J Heart Lung Transplant 2007;26: 769-781