# End-Stage Heart Failure Care: Advances in Technology and Patient Survival

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***Advanced Heart Failure, Transplant, & Mechanical Circulatory Support Program***

St.Vincent HEART CENTER OF INDIANA

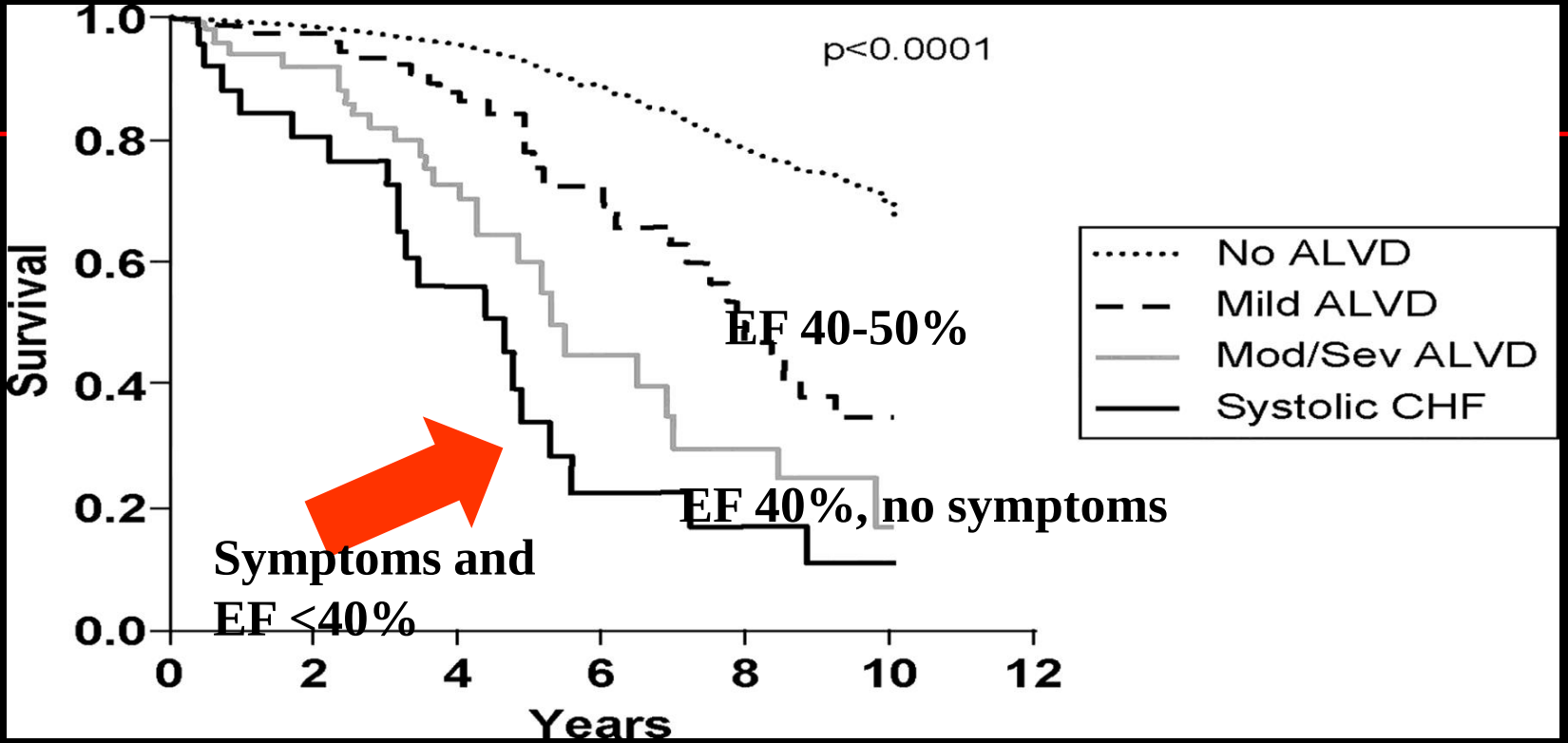
Disclosures: Educational Consultant to Novartis

# Heart Failure Statistics


- **5.8 million** Americans carry the diagnosis of heart failure

American Heart Association. Heart Disease and Stroke Statistics – 2013 update. Circulation;e6-245

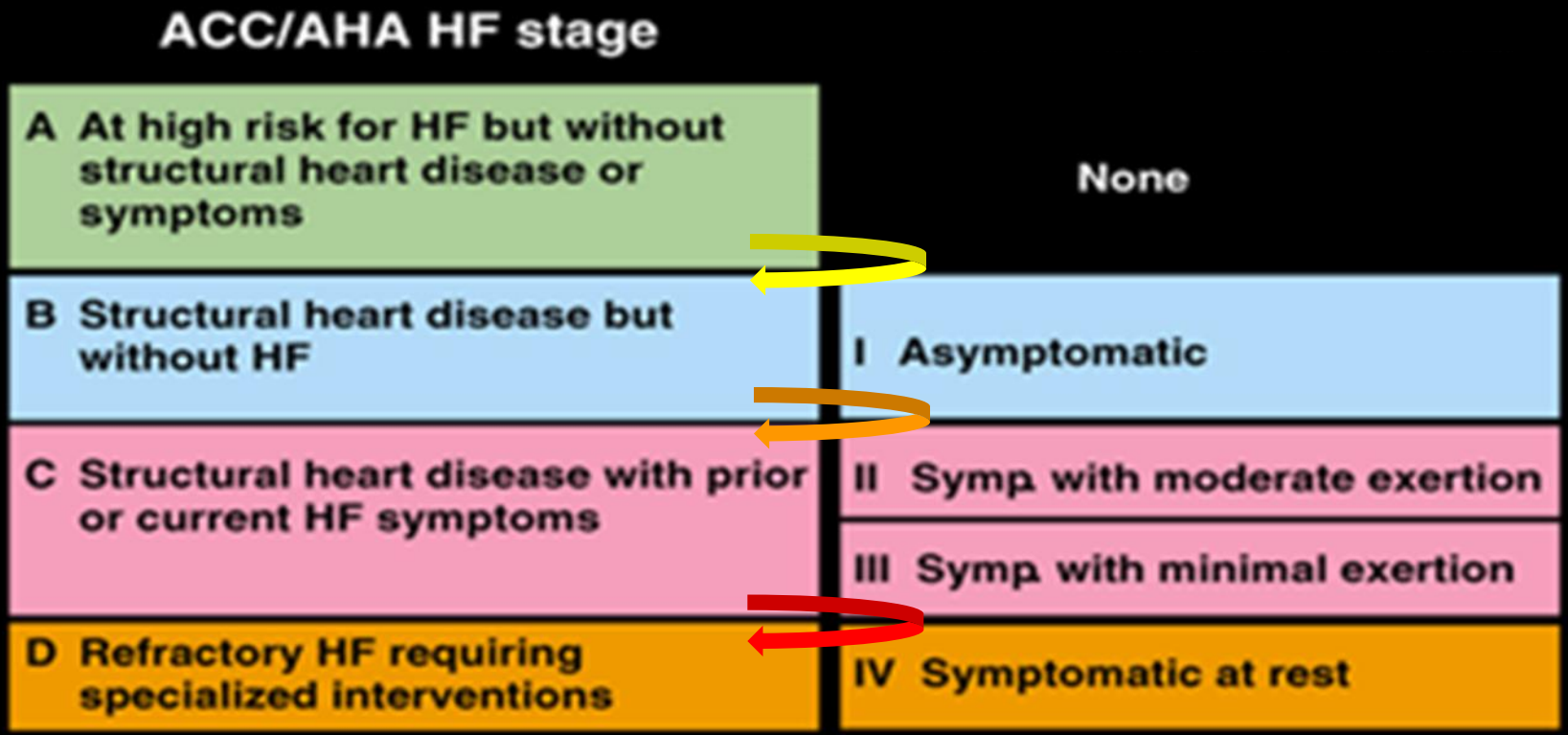
American Heart Association®




Goldberg L R , and Jessup M Circulation 2006;113:2851-2860

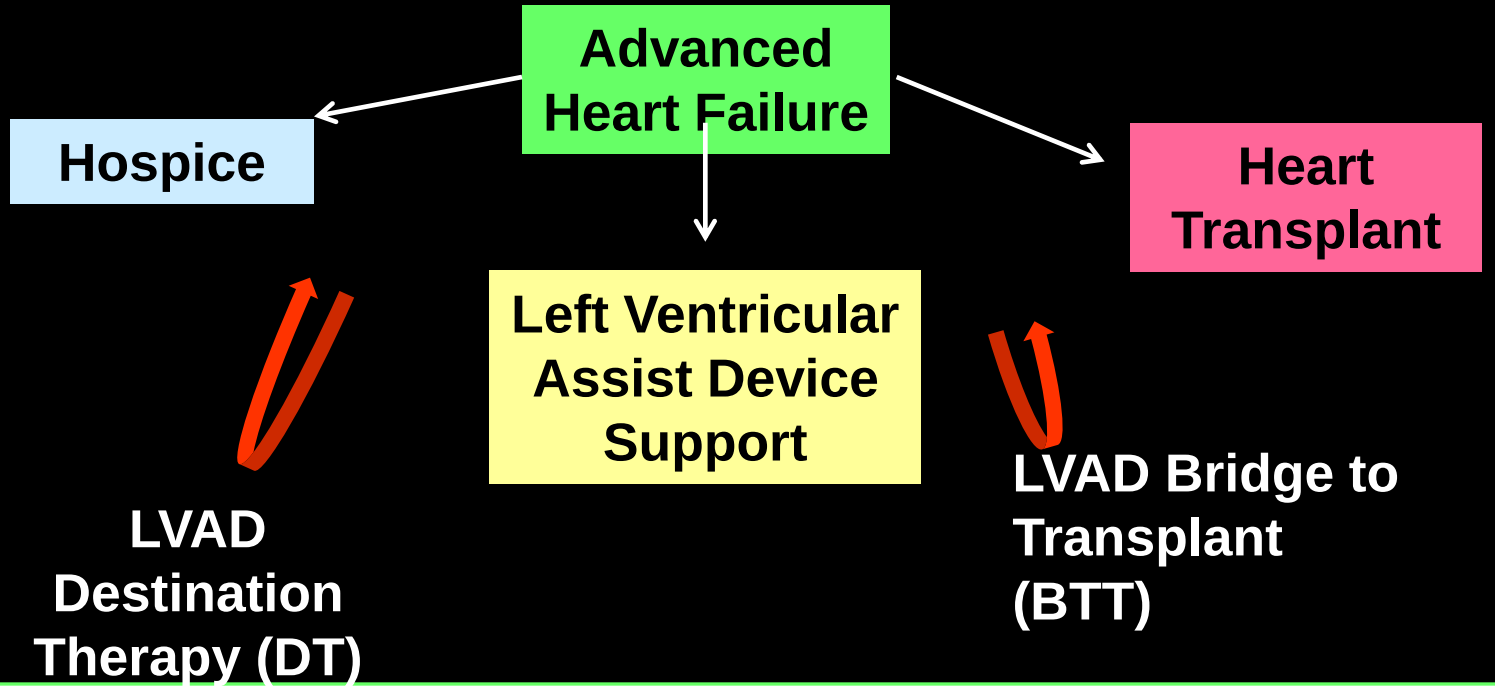
American Heart Association
Learn and Live

# Classification of HF: ACC/AHA stage vs NYHA class




There are about 250,300,000 individuals

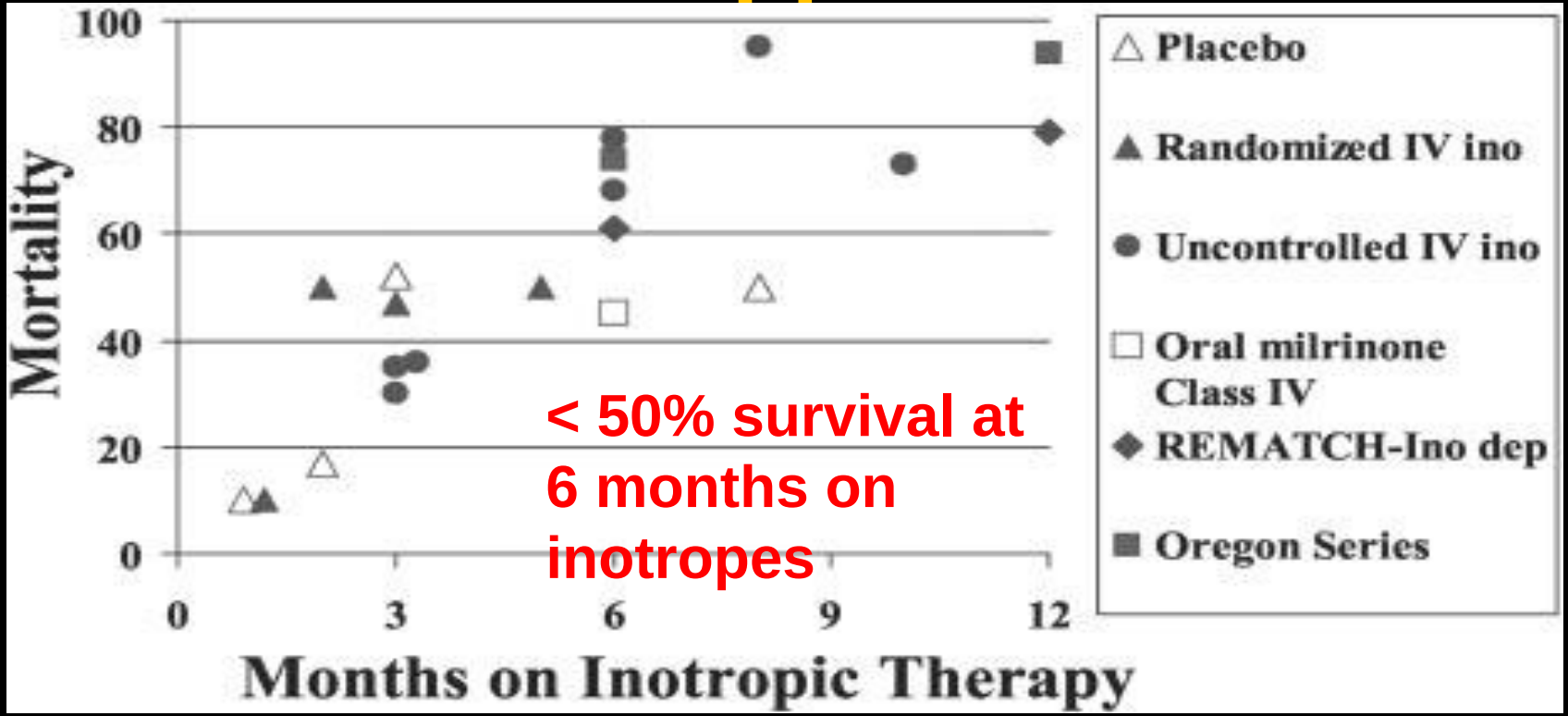
# Management Pathways



# Home Inotrope

- Palliative Care- comfort

# Mortality on Chronic Inotrope Support




Stevenson, Circulation 2003;108:492-97.

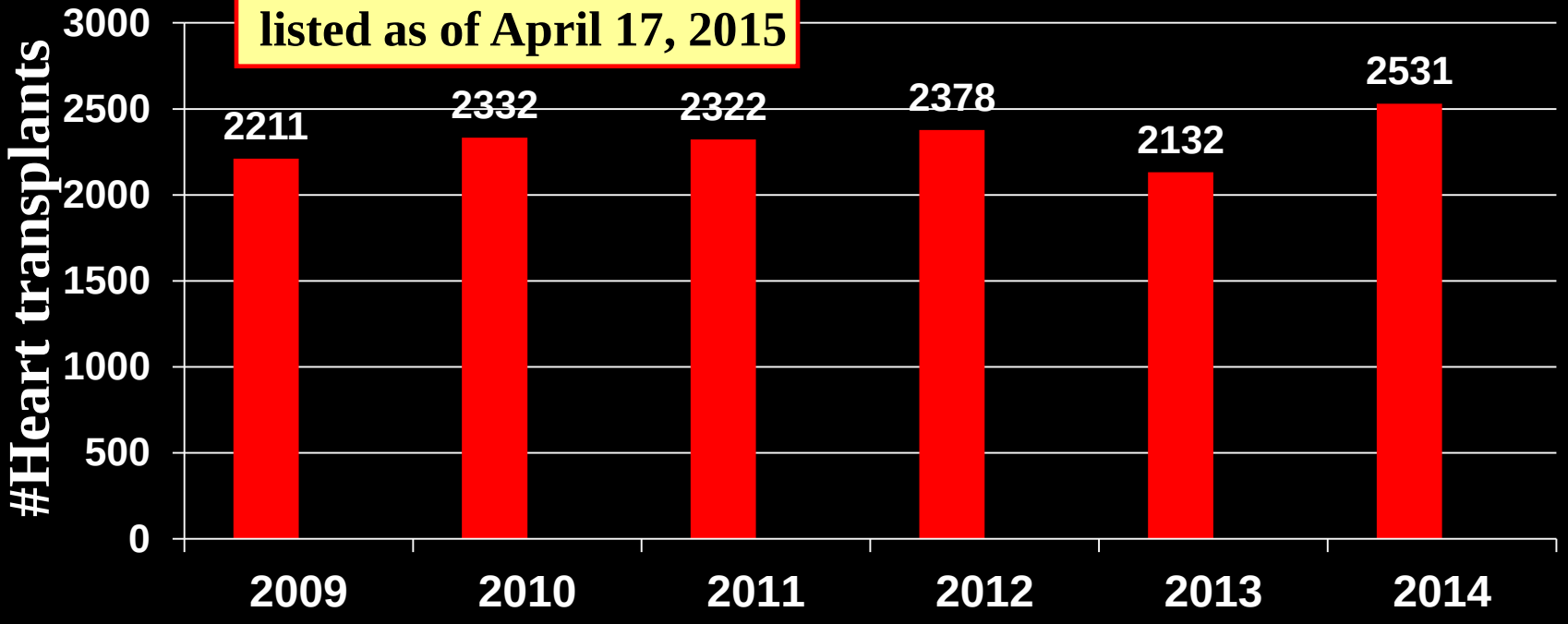
# Heart Transplant

- For the “select few”
- Match based on:
  - Blood type
  - Body size
  - Donor/recipient sex
  - Antibodies
  - Distance from transplant center: <4 hours “igloo cooler time” (ischemic time)

# US Donor Shortage

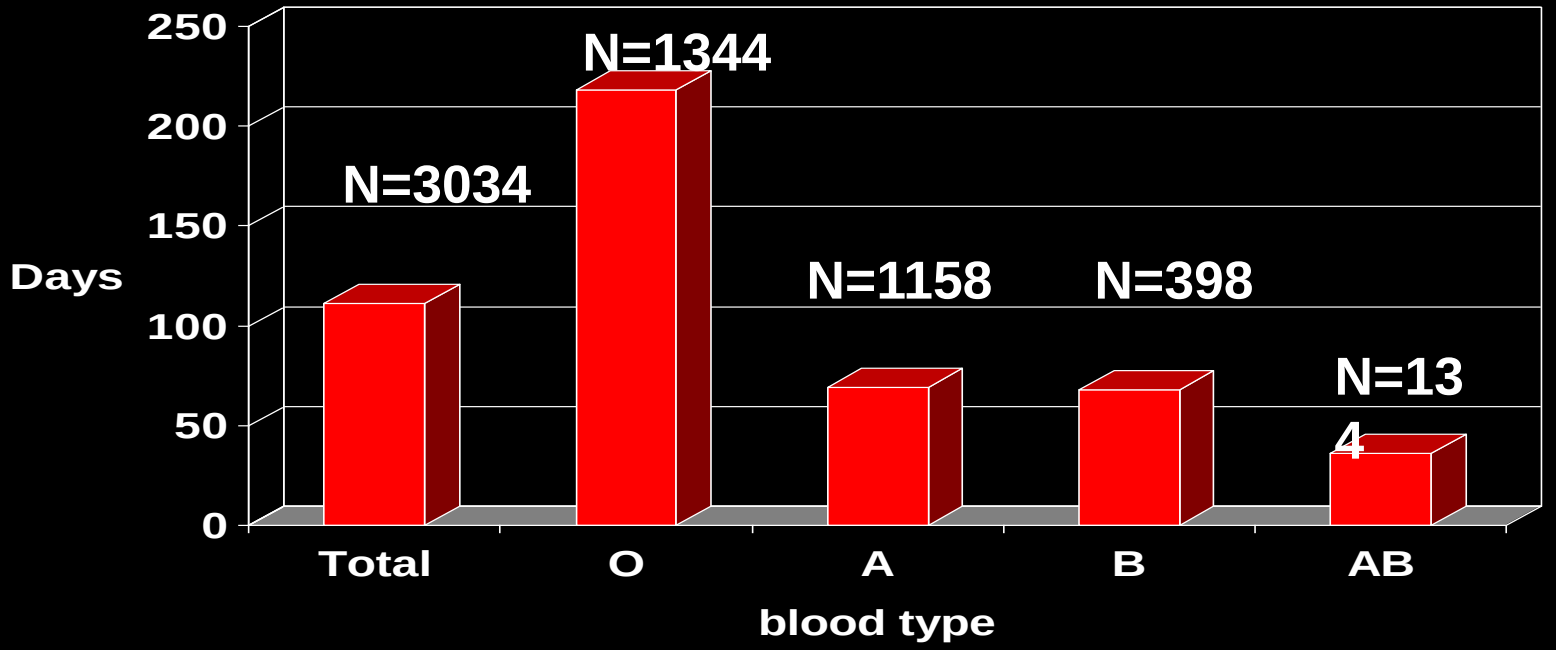
**4155 patients in US**

**listed as of April 17, 2015**




Source: Organ Procurement and Transplantation Network,
http://www.optn.org/latestData/rptData.asp

# Wait time for Listed Patients




OPTN data 2006. http://www.optn.org/AR2007/1503_abo_hr.htm

# Transplant Listing Candidacy

## CONSIDERATIONS:

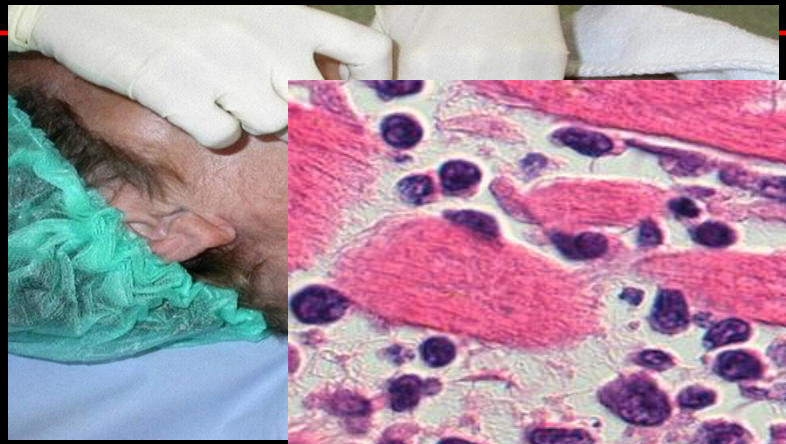
- Age: <70 years; not absolute
- Cancer free >5 years
- Obesity: BMI ≤35 kg/$m^2$
- Severity of other medical comorbidities
  - Renal Function (Cr <1.8 mg/dL) or dual organ transplant….
  - Cirrhosis (cardiac or otherwise)
  - Functional status
  - Nutritional status
  - Diabetes control (HgA1C <7.5)
  - COPD

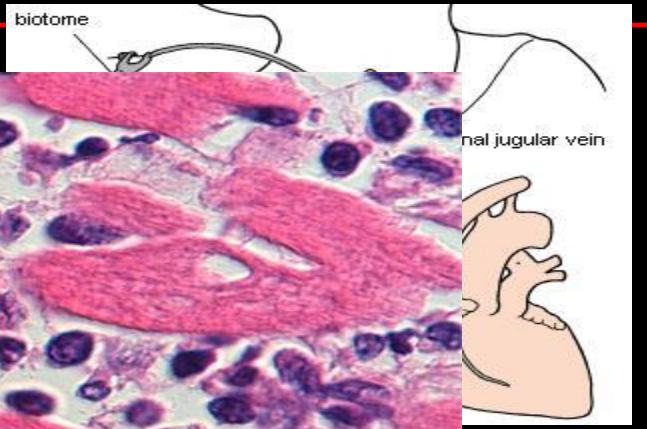
# Transplant Listing Candidacy

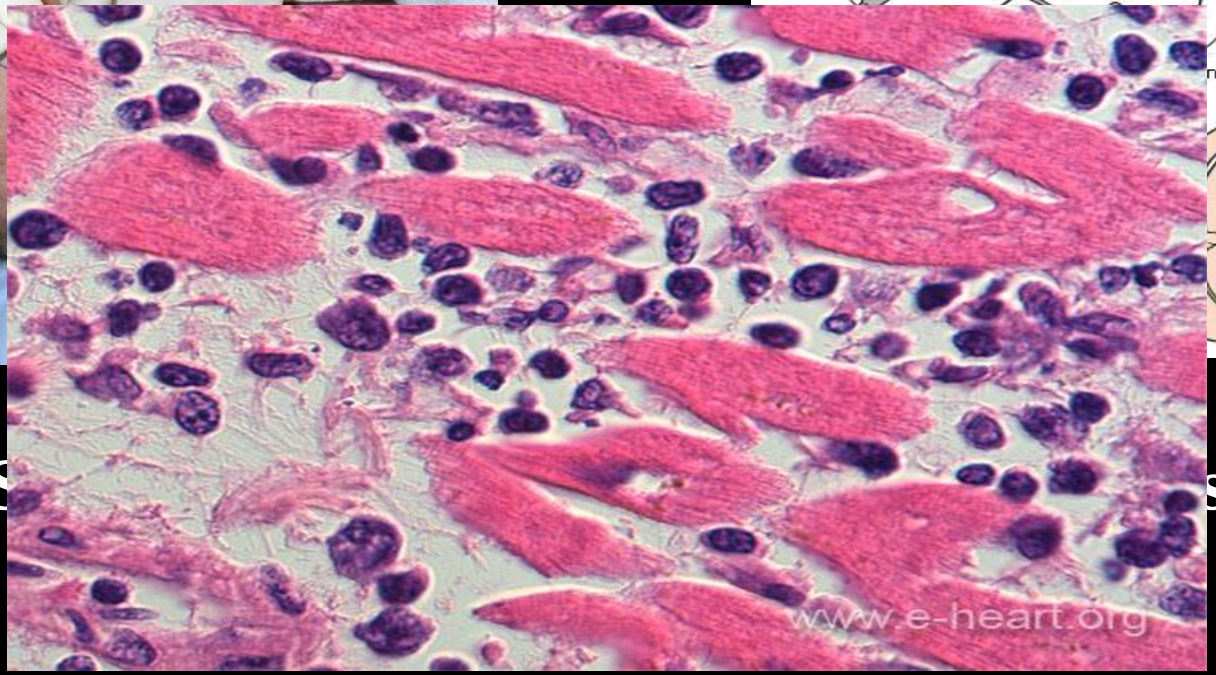
- Social:
  - and
- $
- A

**HIGHLY Selected Patients**

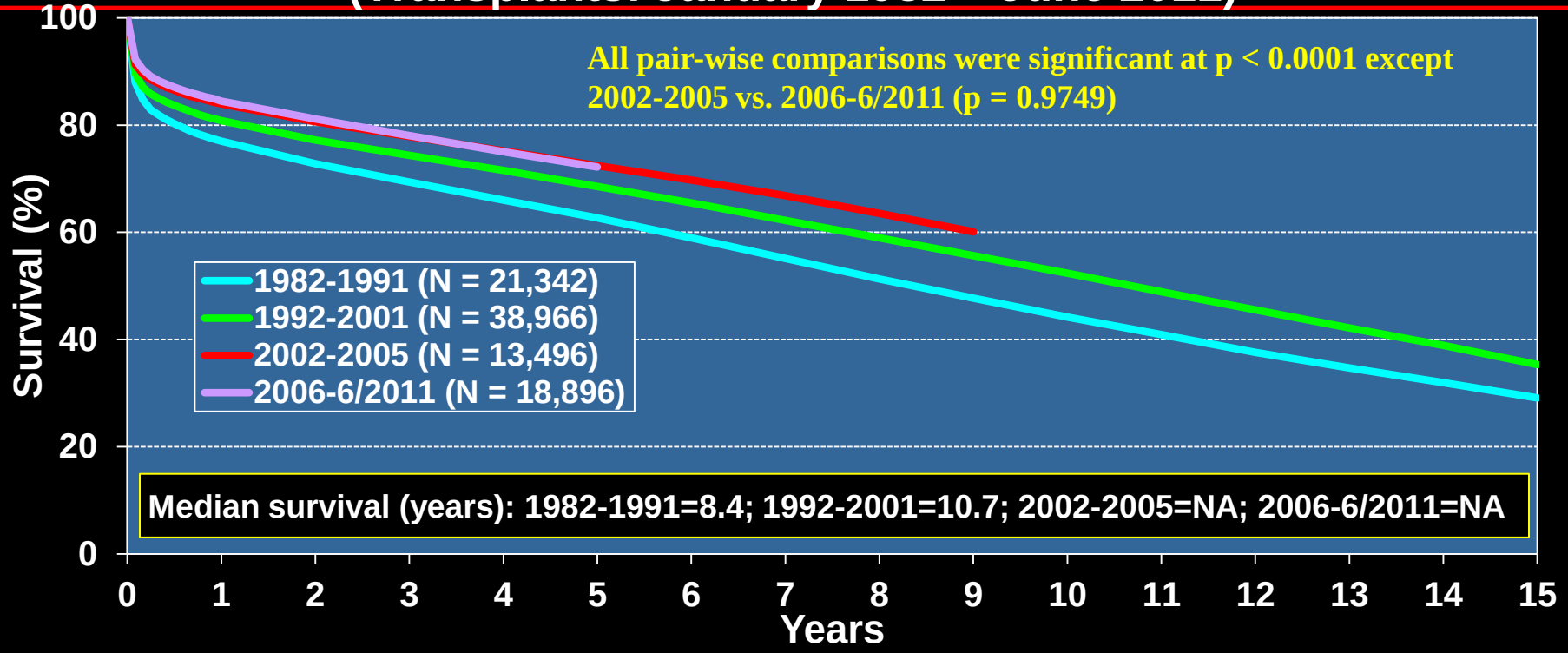
# Post Transplant





# Adult Heart Transplants
# Kaplan-Meier Survival by Era
## (Transplants: January 1982 – June 2011)

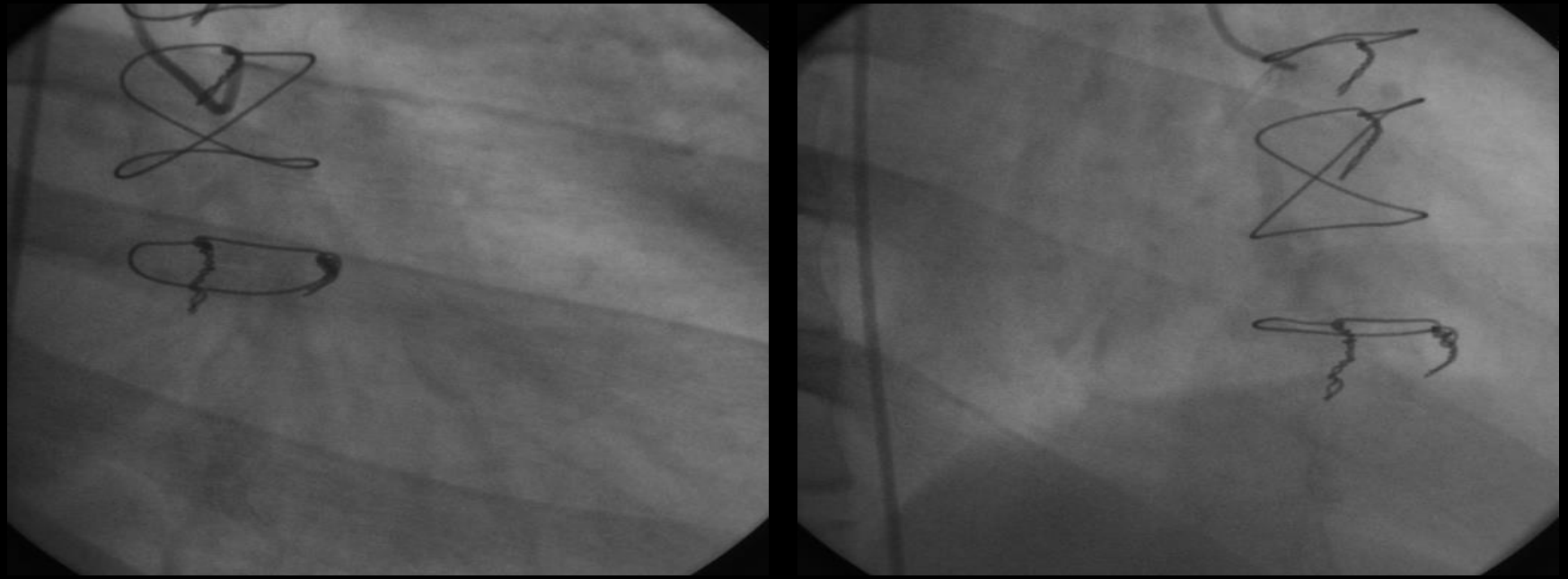



ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
2013
JHLT. 2013 Oct; 32(10): 951-964

# What do TXPs die of?

- **30 days:**
  - Graft failure 40% of deaths
  - Multisystem organ failure (14%)
  - Infections (13%)
- **30-365 days:**
  - Infections (36%)
  - Graft failure (18%)
  - Acute rejection (12%)
- **5 years:**
  - Graft failure due to txp CAD (30%)
  - Malignancy (22%)
  - Infections (10%)

# Chronic Vascular Rejection: Coronary Vasculopathy



**Antibody mediated rejection of recipient Ab against donor vessels**

# Left Ventricular Assist Device Support (LVAD) of the Failing Heart

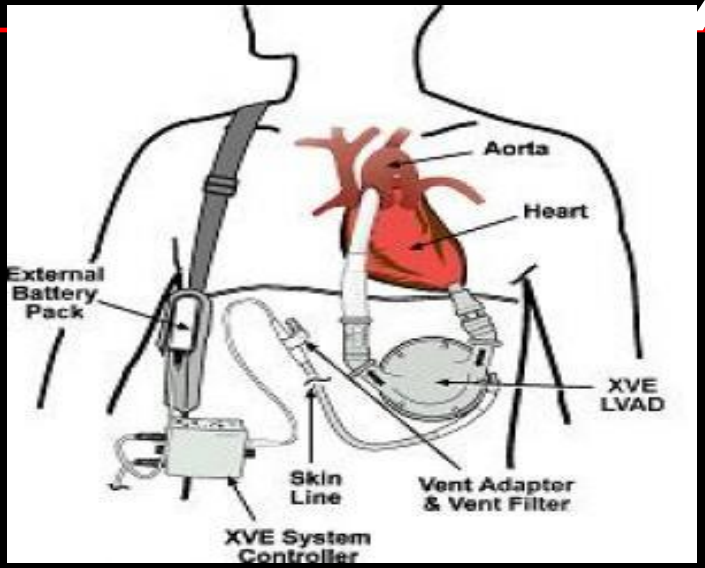

"Bionic Bride" on Today Show Dec 2010


*Grey's Anatomy*- ABC 2006

# What is an LVAD

- An LVAD is a heart pump that is surgically implanted.
- Takes over function of the LEFT side of the heart, restoring normal blood flow to organs in pts with severe CHF
- Uses:
  - As a “Bridge” to get patients to transplant
  - Destination Therapy: aka permanent therapy- for those who are not transplant candidates

# First Generation: HeartMate XVE

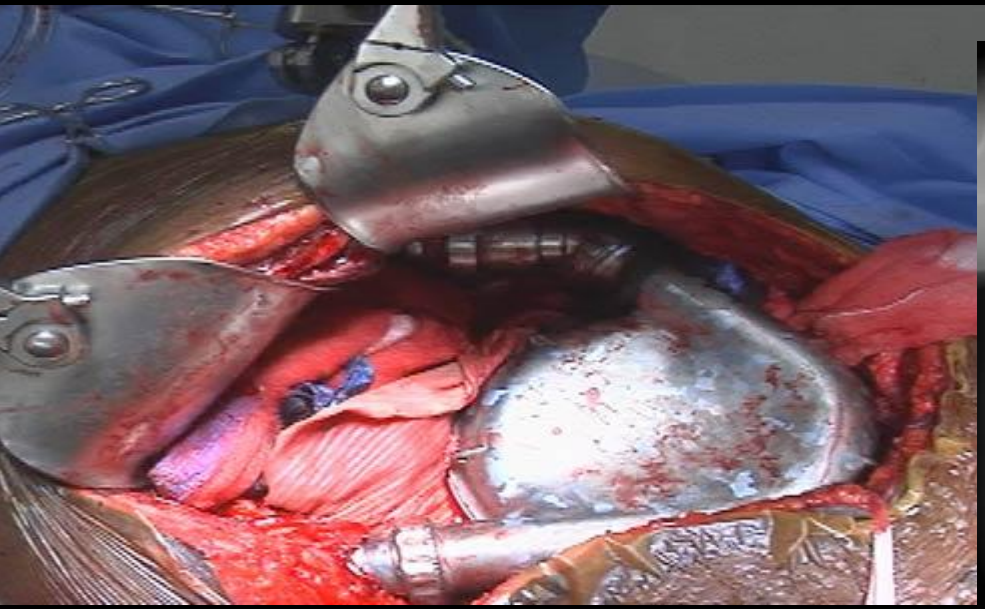


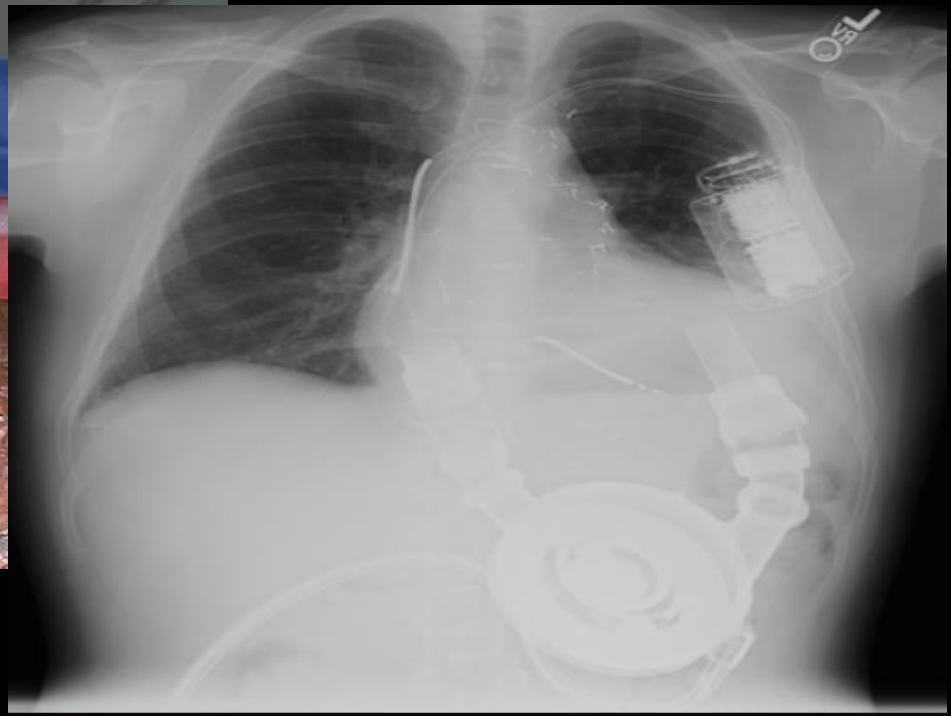

**Heart Mate XVE***

- Weighs 4 pds
- 4 inches in Diameter
- Pulsatile pneumatically driven blood flow up to 7 L/min

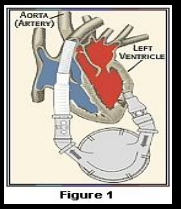
**Thoratec Corp, Pleasanton, California**

# HeartMate XVE:

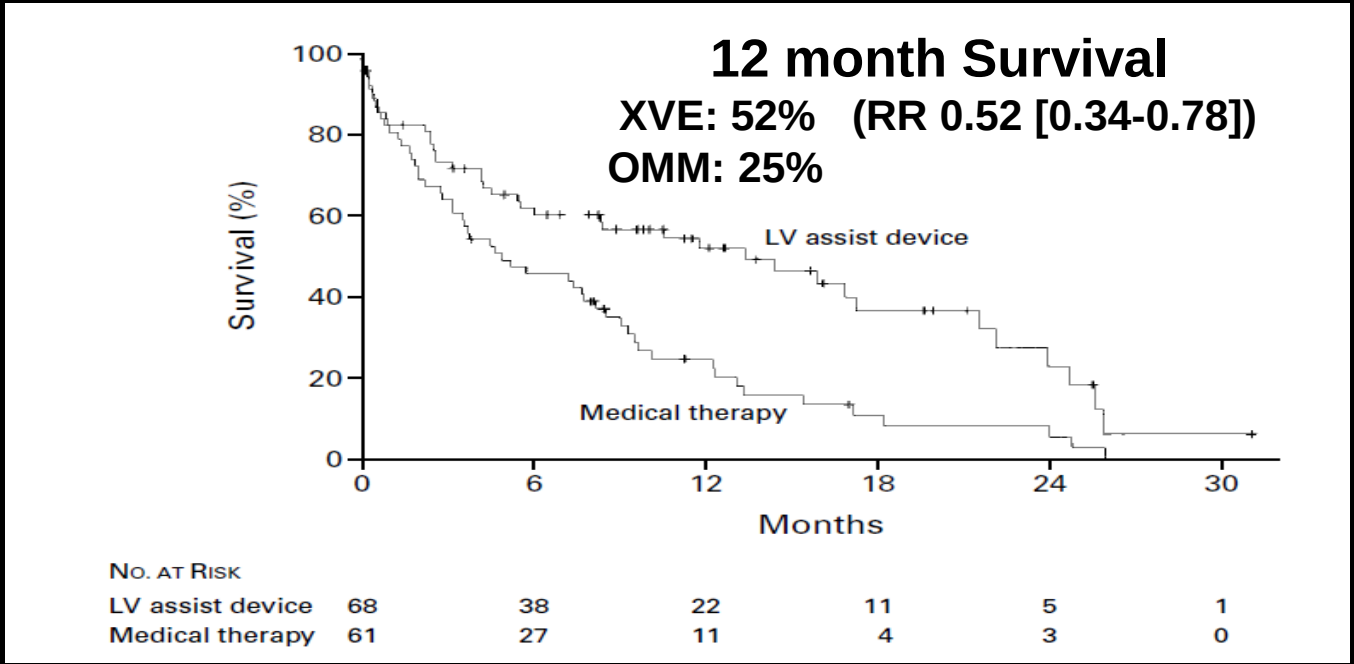




# REMATCH




- N=129 pts randomized to HeartMate XVE LVAD vs. OMM
- 100% class IV
- None eligible for transplant
- Mean age 67 years
- ~70% on inotropes




*OMM=optimal medical management

Rose et al. N Engl J Med 2001;345:1435

# REMATCH Mortality

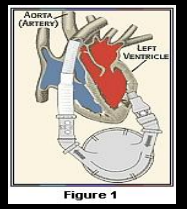


Figure 1

-Adverse event risk 2.4 [1.9-3.0] for LVAD patients

-28% infection risk by 3 months

-35% risk of LVAD failure by 24 months

**TABLE 2. CAUSES OF DEATH.***

| CAUSE OF DEATH | MEDICAL-THERAPY GROUP N=61 | LVAD GROUP N=68 | TOTAL |
|---|---|---|---|
| | no. of patients | | |
| Left ventricular dysfunction | 50 | 1 | 51 |
| Sepsis | 1 | 17 | 18 |
| Failure of LVAD | 0 | 7 | 7 |
| Miscellaneous noncardiovascular causes | 0 | 5 | 5 |
| Cerebrovascular disease | 0 | 4 | 4 |
| Miscellaneous cardiovascular causes | 1 | 2 | 3 |
| Pulmonary embolism | 0 | 2 | 2 |
| Acute myocardial infarction | 1 | 0 | 1 |
| Cardiac procedure | 1 | 0 | 1 |
| Perioperative bleeding | 0 | 1 | 1 |
| Unknown | 0 | 2 | 2 |
| Total | 54 | 41 | 95 |

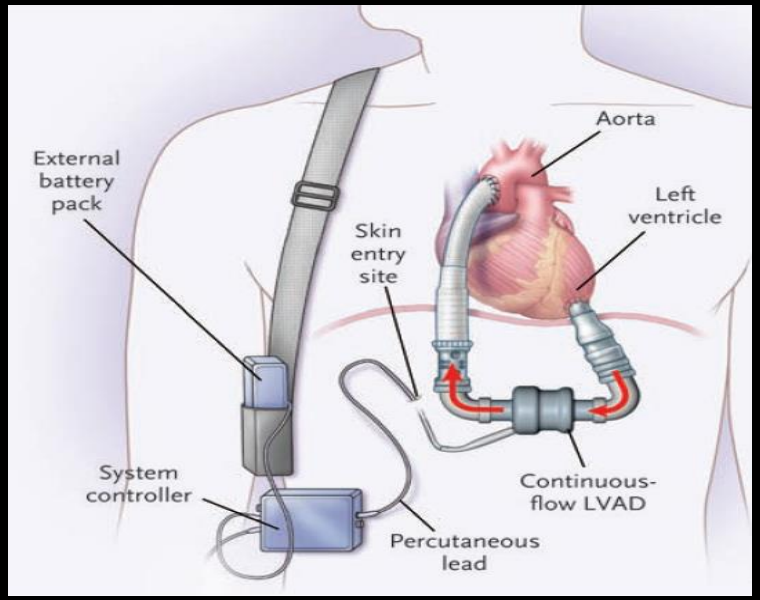
*LVAD denotes left ventricular assist device.

Rose et al. N Engl J Med 2001

Is this an uphill battle worth conquering?

# Continuous Flow LVADs

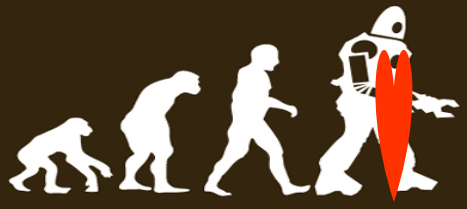
## HeartMate II LVAD




- >20,000 implants to date world wide
- FDA approved for BTT and DT

## HeartWare LVAD

- >7,000 implants world wide
- FDA approved for transplant eligible



# LVAD Evolution

Continuous Flow Technolog

Continuous Flow Technology

Axial Design

2nd Generation

Centrifugal Design

3rd Generation

Pulsatile Technology

1st Generation

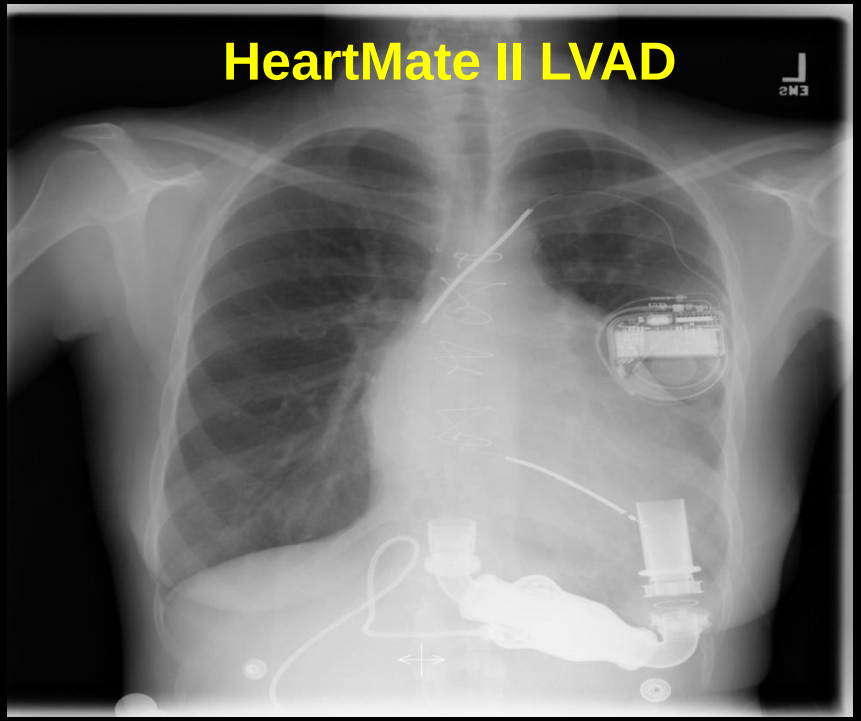
FDA Approved
BTT 1998
DT 2002

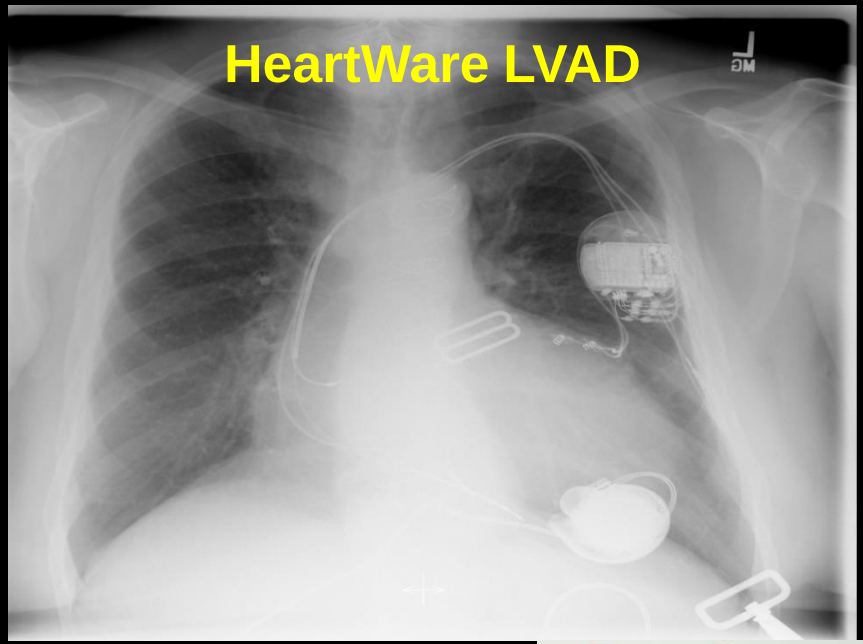
Bearings

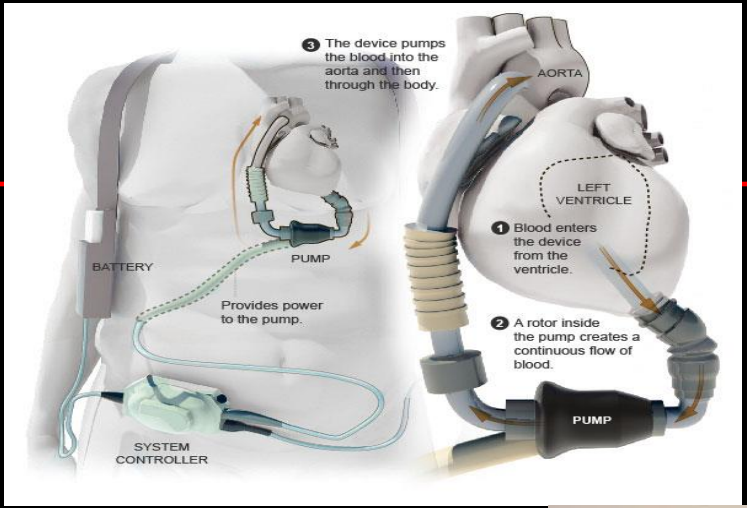
FDA
BTT
DT 2010

Bearings with

# LVADs

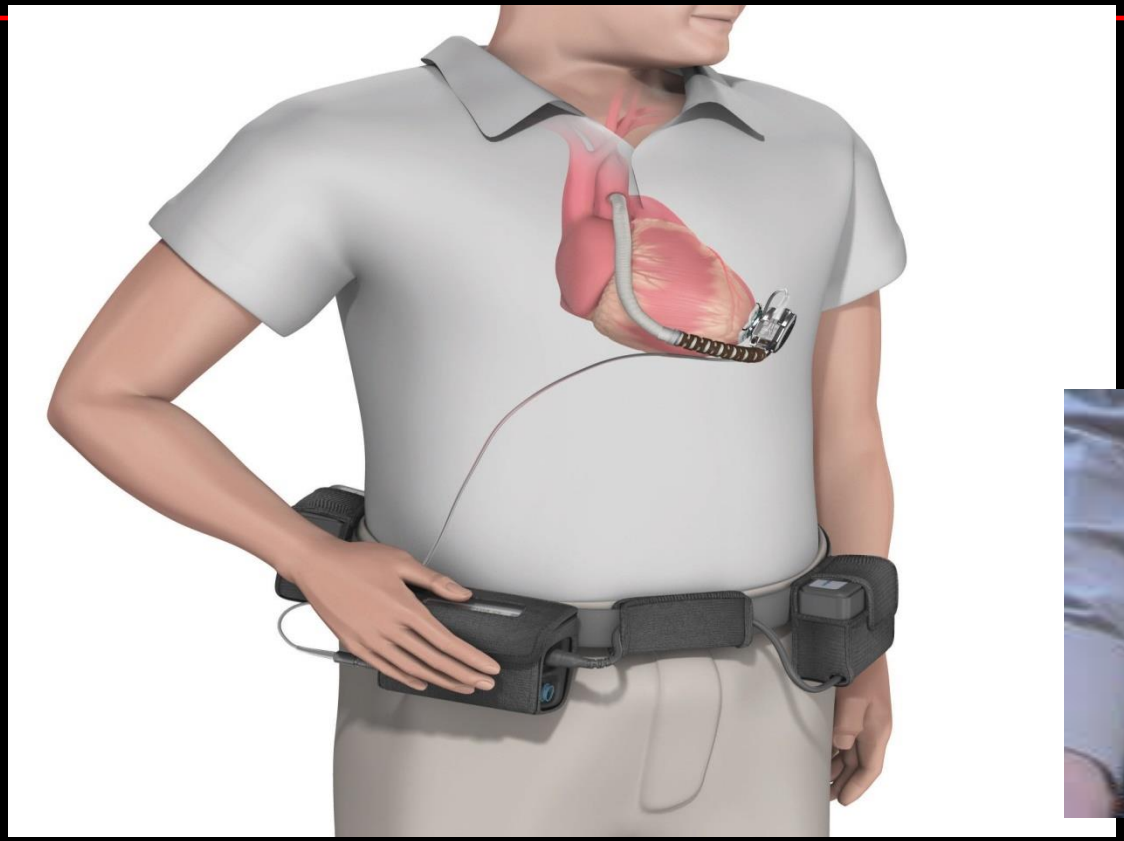



**Batteries and charger**

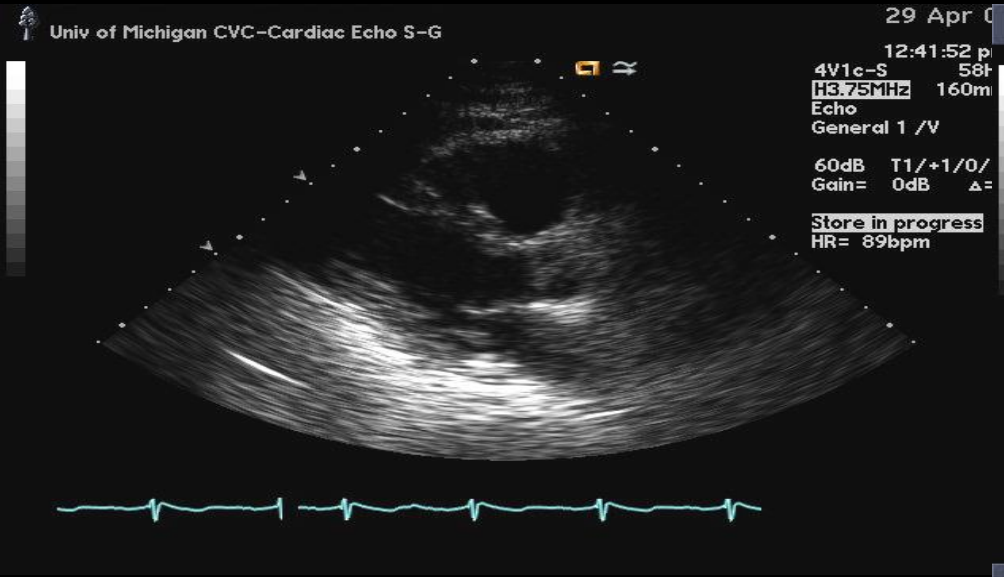
# LVAD

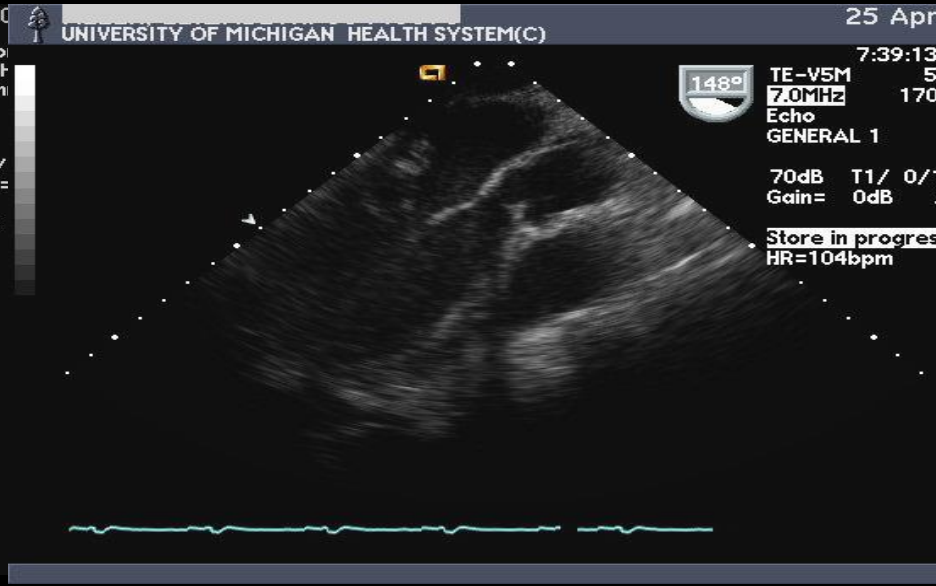


- Batteries last 4-20 hours
- No swimming

# Patients have no pulse!

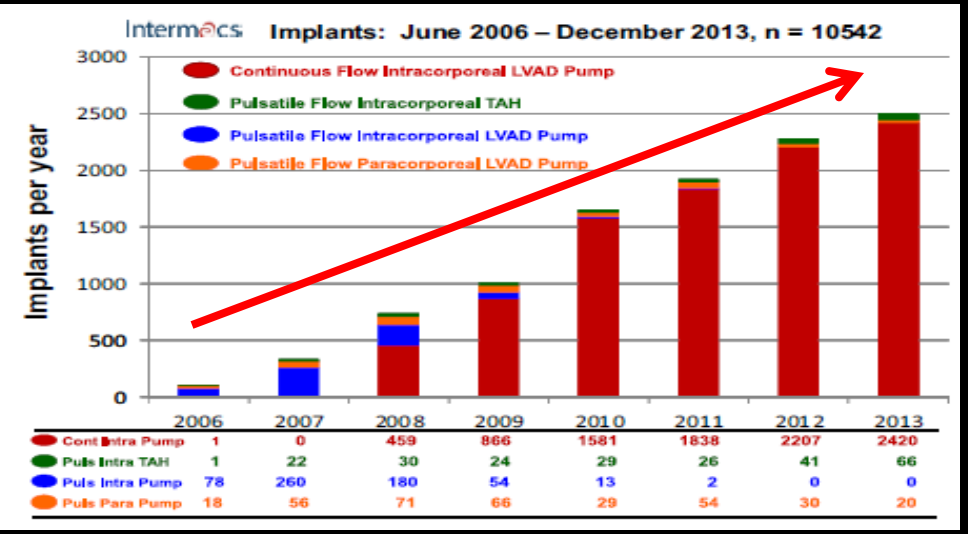
**AoV often NEVER opens**



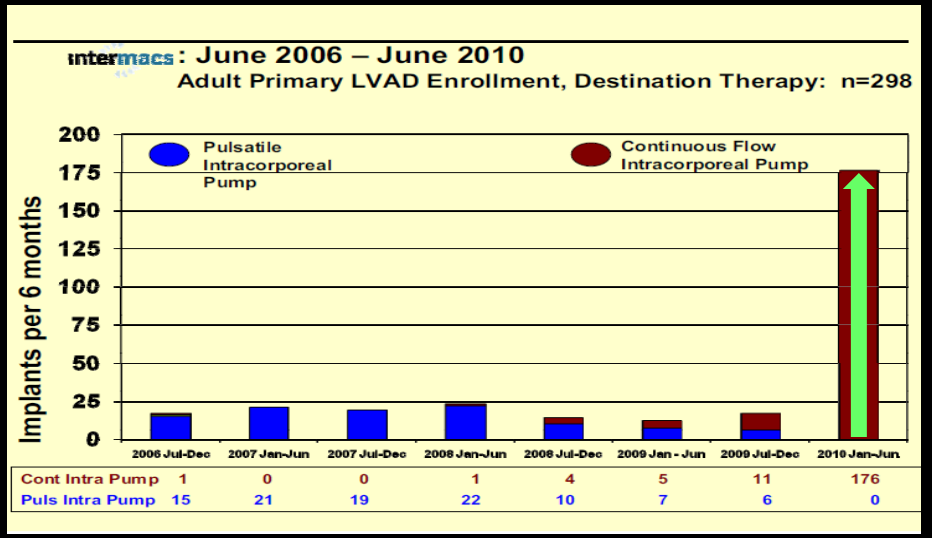



# Rise in LVAD Utilization

## INTERMACS LVAD Implants




## LVADS for Destination Therapy




**>10,000 FDA approved LVAD implants to date in US**

Kirklin J. et al. *J Heart Lung Transplant* 2014;33:555-64.

# Why LVADs have increased in use?

- Organ donor shortage with rising HF prevalence
  - Improved survival on the transplant waiting list
  - >70% of StVs transplant patients had an LVAD in to get them to transplant
- In selected patients (elderly, high risk transplants), LVAD is preferable to transplant to better utilize “limited resource” of donor organs
  - Destination Therapy

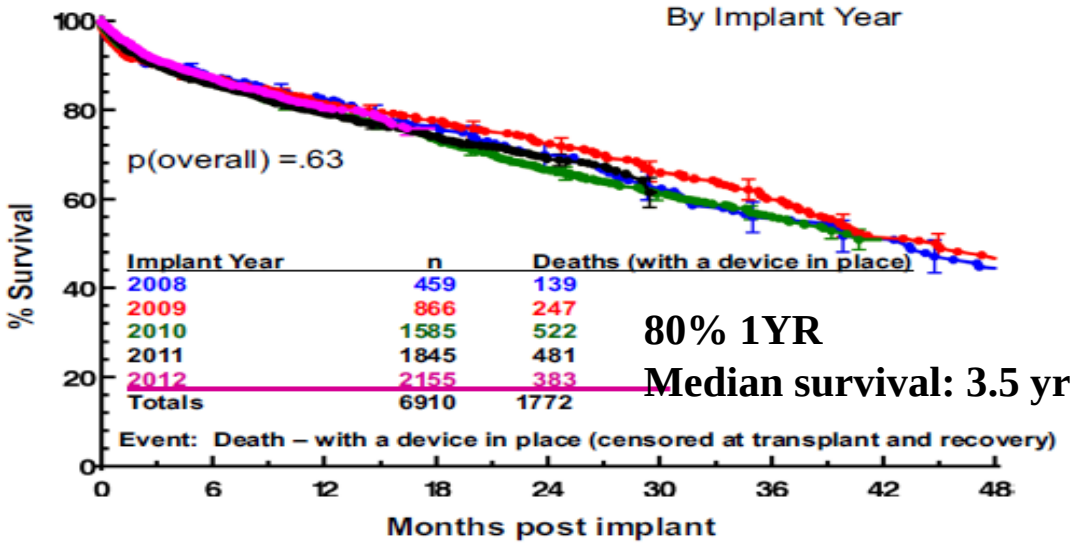
# LVAD mortality risk

| | n | Operative Survival | 6 Mo | 1 Y |
|---|---|---|---|---|
| **REMATCH** (NEJM 2001;345) | 68 XVE<br>61 OMM | 88% | 61% XVE<br>52% OMM | 52% XVE<br>25% OMM |
| **HMII-DT** (NEJM 2009;361) | 134 HMII<br>66 XVE | 93% HMII<br>89% XVE | 78% HMII<br>64% XVE | 68% HMII<br>55% XVE |
| **HMII-BTT** (NEJM 2007;357) | 133 | 89% | 75% | 68% |
| **HMII-BTT PIVOTAL** (JACC 2009;54:312) | 281 | 92% | 82% | 73% |
| **INTERMACS-HMII BTT** (JACC 2011;57(19): 1890) | 169 | 96% | 91% | 85% |
| **ADVANCE- HeartWare BTT** (Circ 2012;125:1) | 140 HW<br>[illegible] | 99%<br>[illegible] | 94%<br>[illegible] | 86%<br>85% |

MORTALITY

BTT=bridge to transplant, DT= destination therapy

# Contemporary Survival Estimates After HMII Implant




**80% 1YR**

**Median survival: 3.5 yr**

**Figure 2** Actuarial survival after implantation of HeartMate II left ventricular assist device, stratified by year of implant. The error bars represent ± 1 standard error.

Kirklin et al. J Heart Lung Transplant 2014;33;12-22.

# LVAD: Gains in Quality of Life

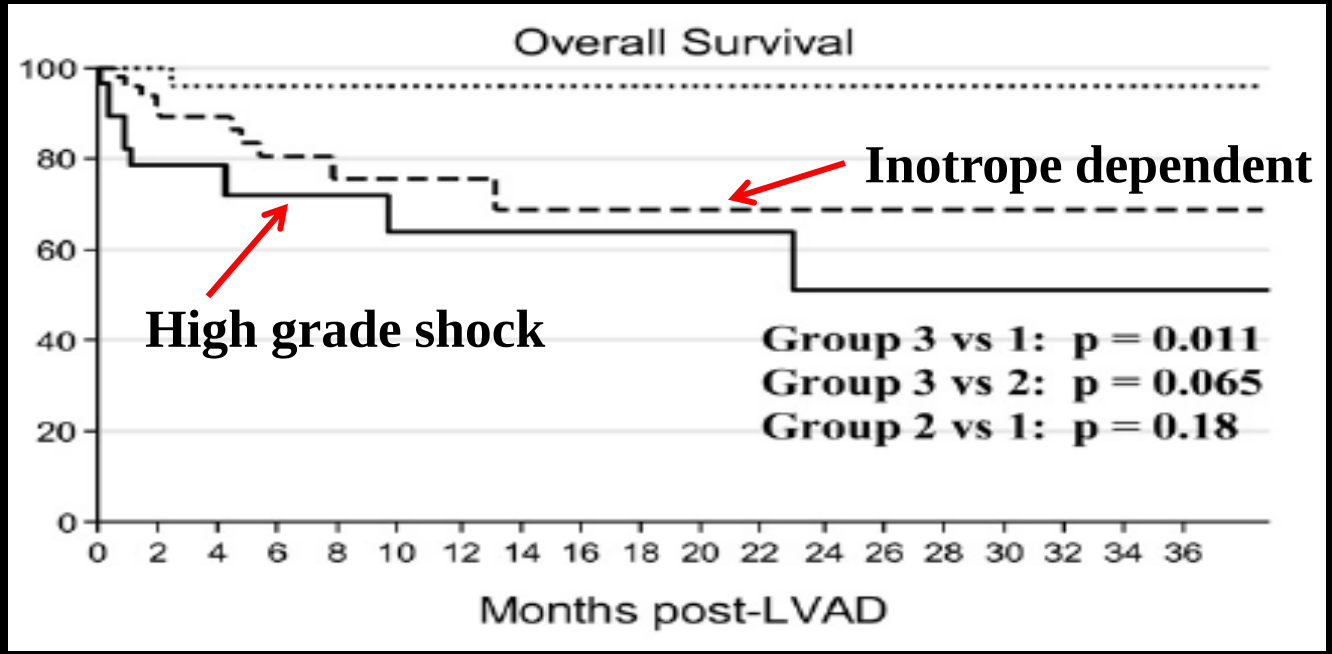
**Table 4** Functional Status, Quality of Life, and End-Organ Function for Patients With Pai

| Parameter | Baseline | 6 Months |
|---|---|---|
| Blood chemistry | | |
| Serum sodium (mmol/l) | 134.1 ± 5.0 | 139.3 ± 3.1 |
| Blood urea nitrogen (mg/dl) | 28.0 ± 15.2 | 20.3 ± 9.0 |
| Serum creatinine (mg/dl) | 1.4 ± 0.5 | 1.3 ± 0.7 |
| ALT (IU/l)† | 108 ± 327 | 28 ± 15 |
| AST (IU/l)† | 93 ± 295 | 34 ± 16 |
| Total bilirubin (mg/dl) | 1.3 ± 0.9 | 0.8 ± 0.4 |
| INR | 1.3 ± 0.5 | 2.1 ± 0.9 |
| Functional status | | |
| NYHA functional class | 3.9 ± 0.3 | 1.8 ± 0.7 |
| Class I or II (%) | 0 | 83 |
| 6-min walk distance (m) | | |
| Patients able to walk at baseline | 201 ± 140 | 368 ± 125 |
| Unable to walk at baseline | 0 ± 0 | 326 ± 232 |
| Percent of patients able to walk | 13 | 89§ |
| Quality of life | | |
| MLWHF‖ | 69.4 ± 23.3 | 40.7 ± 24.6 |
| KCCQ¶ | 35.8 ± 21.4 | 62.5 ± 22.6 |

Pagani et al. JACC 2009;54;312

# **EARLY** referral is key to survival post VAD or Transplant

# Worst Survival in Shock



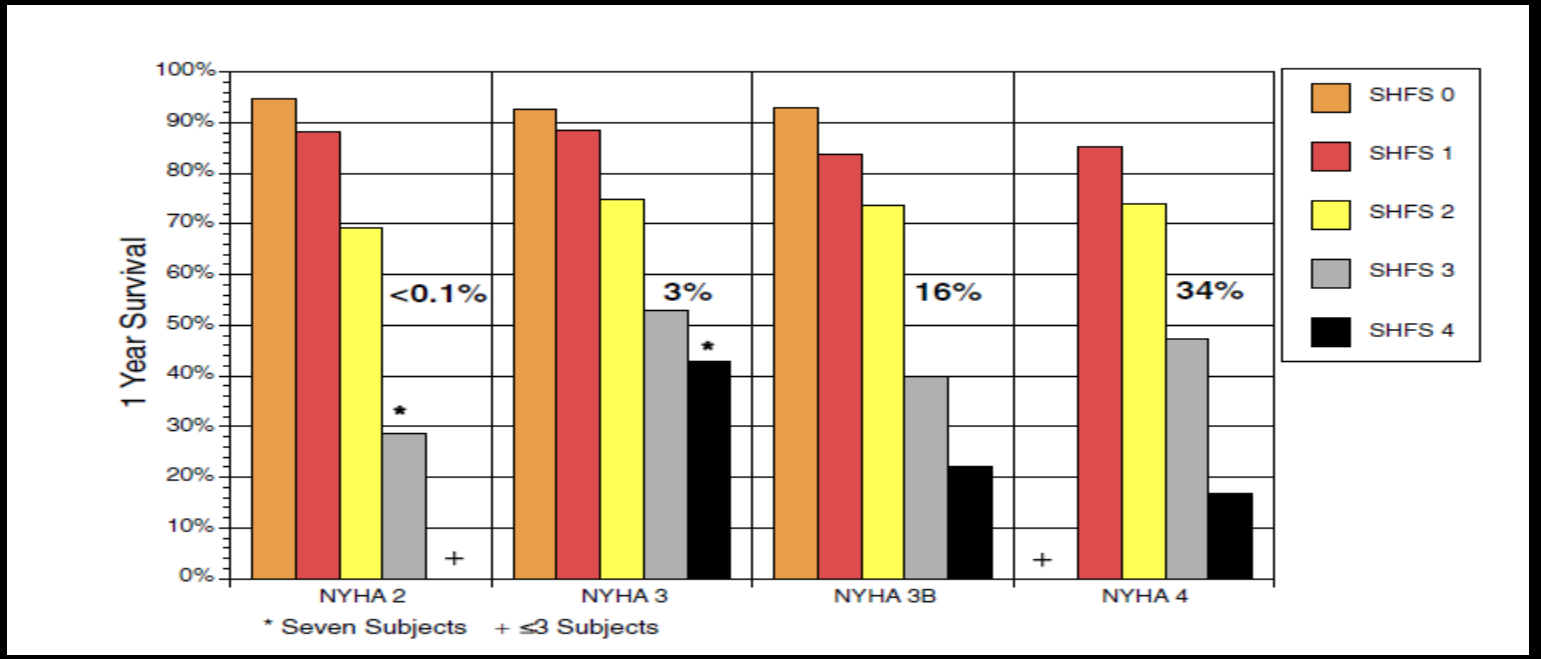

Boyle et al J Heart Lung Transplant 2011;30:402-7.

# Seattle Heart Failure Model
## Outpatient Risk Assessment

- **Derivation of the SHFM**:
  - demographic, lab and clinical data of 1125 patients enrolled into the PRAISE (EF <30%, NYHA III-IV) study
  - hazard ratios for certain meds and devices obtained from previously published literature.
- Validated in 5 different cohorts of patients enrolled into other trials.

http://depts.washington.edu/shfm/ Levy et al. Circulation. 2006;113:1424-33.

# SHFM and NYHA Class




**Score of ≥3 has >50% 1Y mortality**

Levy et al J Heart Lung Transplant 2009;28:231-36

# Inpatient HF Risk Studies

| Author | n | Markers | 1 year surv (%) |
|---|---|---|---|
| Chin | 257 | BP < 100, DM, non sinus rhythm | N/A |
| Alla | 301 | HR >100, Na < 134, Creat > 2.0, Age > 70, prior hosp | 57.6 |
| Cowie | 220 | Age, crackles, low BP, high Creat | 62 |
| Jong | 38,702 | Male, Age, malig, renal, dementia, cerebrovasc, rheum, periph vasc or pulm dis, ischemic etiology, DM | 66.9 |
| Bouvy | 152 | DM, high Creat, NYHA III/IV, low BMI, low BP, edema | N/A |
| Lee | 4031 | Age, low BP, high RR, high BUN, low Na | 69.5 |
| Kittleson | 259 | No ACE, low BP, low Na, high Creat | N/A |
| Felker | 949 | Age, low BP, NYHA IV, high BUN, low Na | N/A |
| Fonarow | 37,772 | BUN > 43, SBP < 115, Creat > 2.75 | N/A |
| Rector | 769 | Age, low BP, low Hgb, low Na, high BUN | 50% (high risk) |
| Rohde | 779 | Cancer, SBP < 124, Creat > 1.4, BUN > 37, Na < 136, Age > 70 | N/A |

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|---|---|---|
| Mahon | 585 | Low CrCl, 6 MW < 262 m, low EF, recent hosp., diuretic |
| Eshaghian | 1354 | Low EF, low Na, low Hgb, high BUN, high Cr, diuretic dose |
| Greenberg | 4280 | NYHA III/IV, HF hosp, angina |
| Levy | 1125 | Diuretic dose, low BP, % lymph, Hgb < 16, ischemic etiol, EF, low chol, high uric acid/allopurinol, Na <138, NYHA, age, male sex |
| Teuteberg | 160 | High BUN, high Cr, low Na, low Hct, recent hosp, no ACE/BB |
| Lund | 10062 | SBP <90, no ACE/BB, Hg <12, Cr >1.8 |

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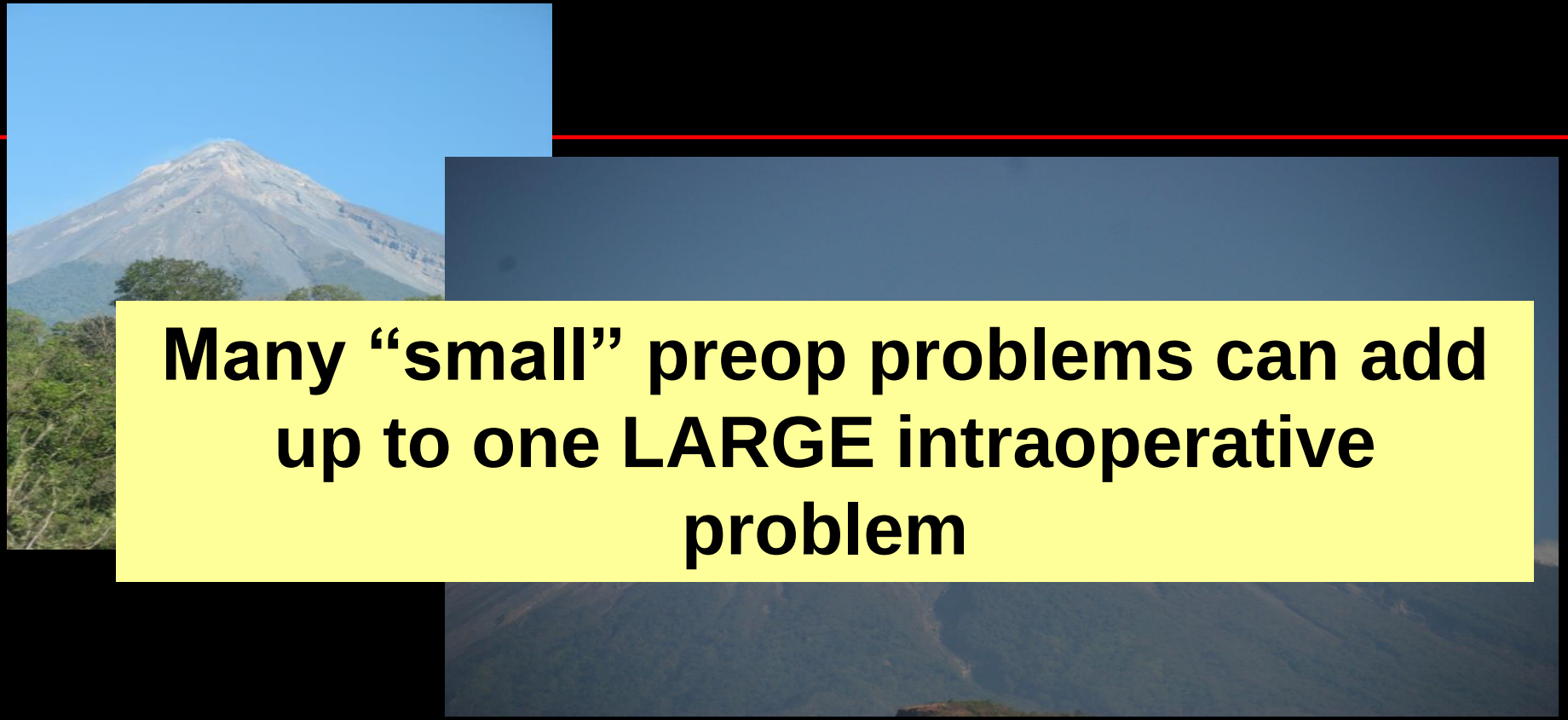
“My patient’s Seattle HF Model is high risk with an unacceptable survival…..”

- **What is their anticipated LVAD Survival?**



**Many “small” preop problems can add up to one LARGE intraoperative problem**

# Criteria for VAD

FDA approved for :

- LVEF <25%
- Failed OMM for 45 of last 60 dys or dependent on IABP or inotropes
- NYHA Class IV
- BTT: requires pt meet institutional listing requirements for transplant

Different from transplant:

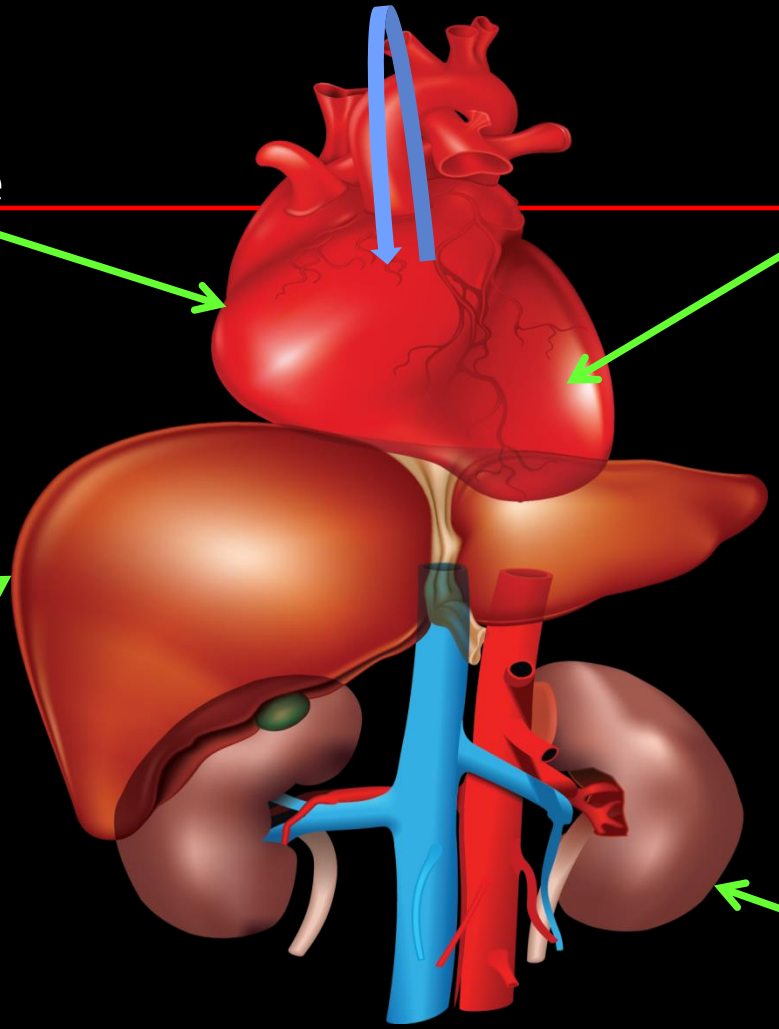
- BMI- no cut off
- Age- no strict cut off
- Tobacco- ok
- Drugs/ETOH- center dependent
- Recent cancer- center dependent
- BSA >1.5
- Less strict comorbidity limits

## Off load RV:

- Inotropes/nipride
- Diuretics
- RV-Tandem, IABP
- Goal CVP <13, PAS <55

## Address hepatic dysfunction:

-congestion
-ischemia
-Vit K def



## End-organ perfusion and pre-emptive RV protection:

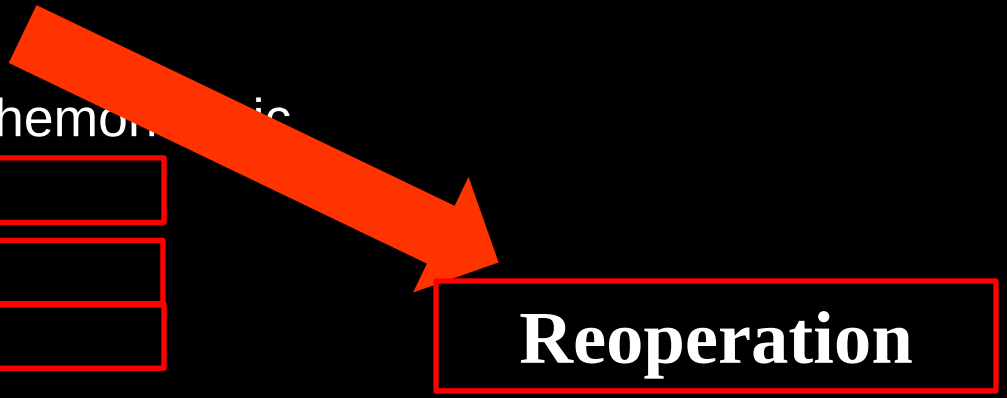
- Inotropes
- Diuretics: goal WP <25
- Tandem/IABP or Impella

## Address uremia

- CVVHD
- Inotropes

# Long Term Mortality Contributors

- VAD Related Factors:
  - Thrombosis
  - Stroke- ischemic or hemor[illegible]ic
  - Aortic Insufficiency
  - Infection/Sepsis
  - Device malfunction
  - Bleeding
- NonVAD Factors:
  - Right Ventricular Failure
  - Preop comorbidities



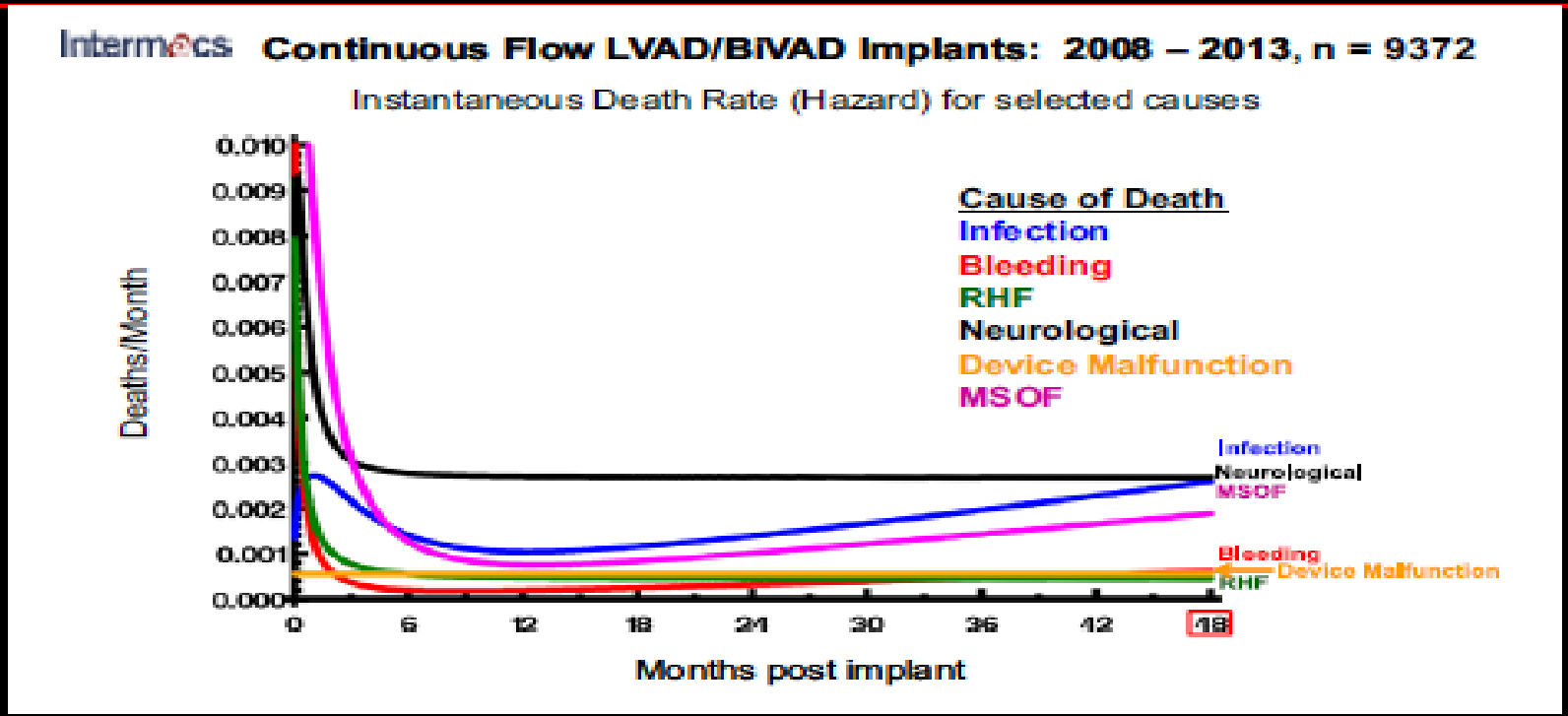
# AE for HMII-VAD by Device Indication

| Post-FDA BTT (n=169) | n (event rate) | Post-FDA DT (n=247) | n (event rate) |
|---|---|---|---|
| Bleeding | 75 (1.44) | Bleeding | 133 ( 0.84) |
| Infection | 78 (1.00) | Infection | 186 (0.99) |
| Stroke<br>Hemorrhagic<br>Ischemic | 11 (0.08)<br>2 (0.01)<br>8 (0.06) | Stroke<br>Hemorrhagic<br>Ischemic | 29 (0.08)<br>19 (0.03)<br>10 (0.05) |
| Rt Heart Failure | 26 (0.18) | Rt Heart Failure | 44 (0.18) |
| Renal Failure | 17 (0.13) | Renal Failure | 44 (0.15) |
| Pump XC | 2 (0.01) | Pump XC | 9.9 (0.03) |

Starling et al. JACC 2011;57:1890-9

Uriel, JACC 2014;63:1751-7

# Causes of Death after VAD




Kirklin J. Heart Lung Transplant 2014;33:555-64

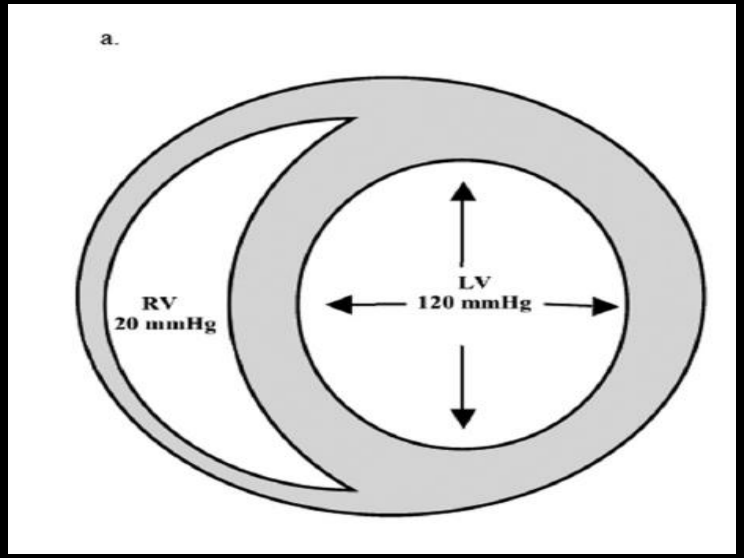
# Right-sided Circulatory Failure

- Post-LVAD RV failure affects 17-30% of LVAD patients:
  - 19-43% post-LVAD mortality[1-3]
- RV failure leads to:
  - Prolonged hospital stays, postop multisystem organ dysfunction, delayed rehabilitation, increased transfusion requirements, reduced bridge to transplant success[2,3]
- RV failure can result from:
  - Pre-existing RV dysfunction, increased pulmonary vasoreactivity from CPB and transfusions, increased RV filling pressures post LVAD, geometric RV changes with LV offloading.


1. Dang. J Heart Lung Transplant 2006;25:1-6
2. Matthews. JACC 2008;51:2163-72
3. Kavarana. Ann Thorac Surg. 2002;73(3):745-750

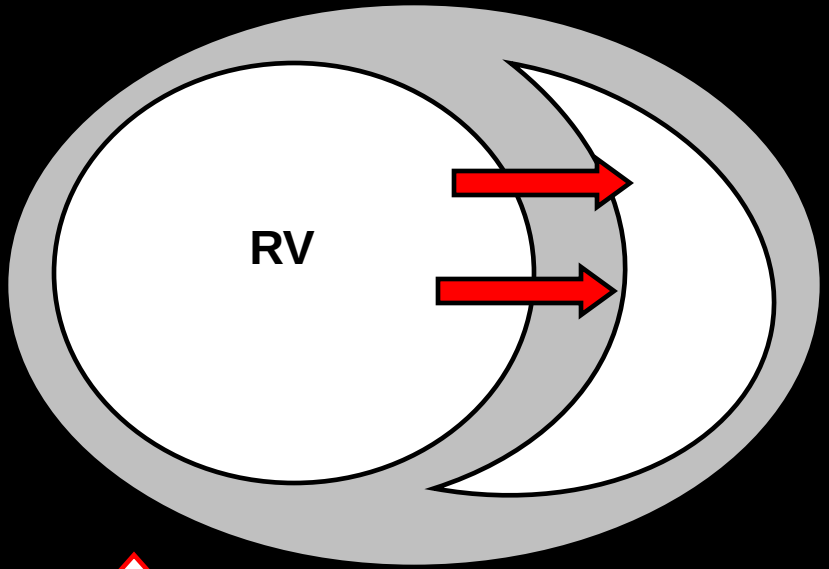
# RV Failure after LVAD

Normal RV/LV geometry

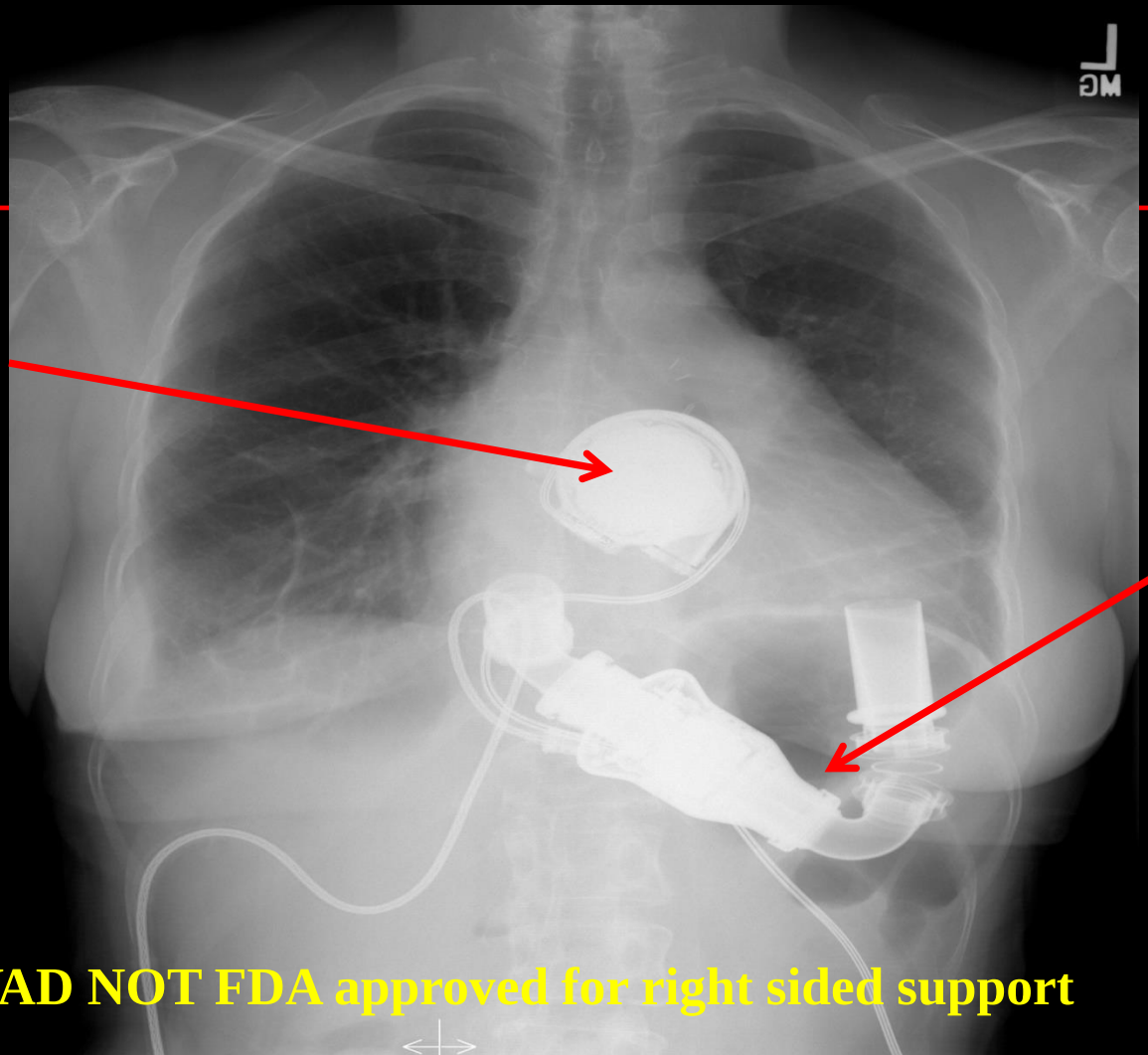



**Wall stress= RVSP*radius/(2*thickness)**

RVF after LVAD therapy

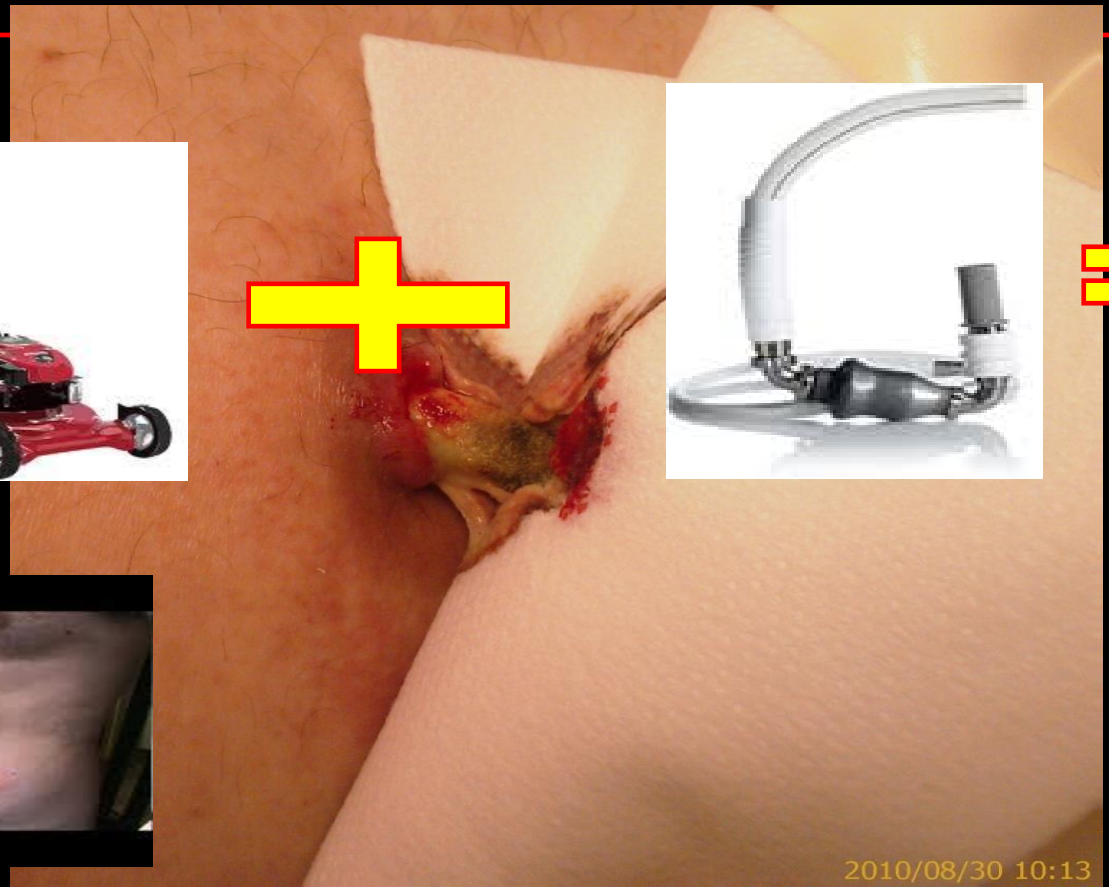



RV Preload, TR, Wall RV dilation with high wall stress



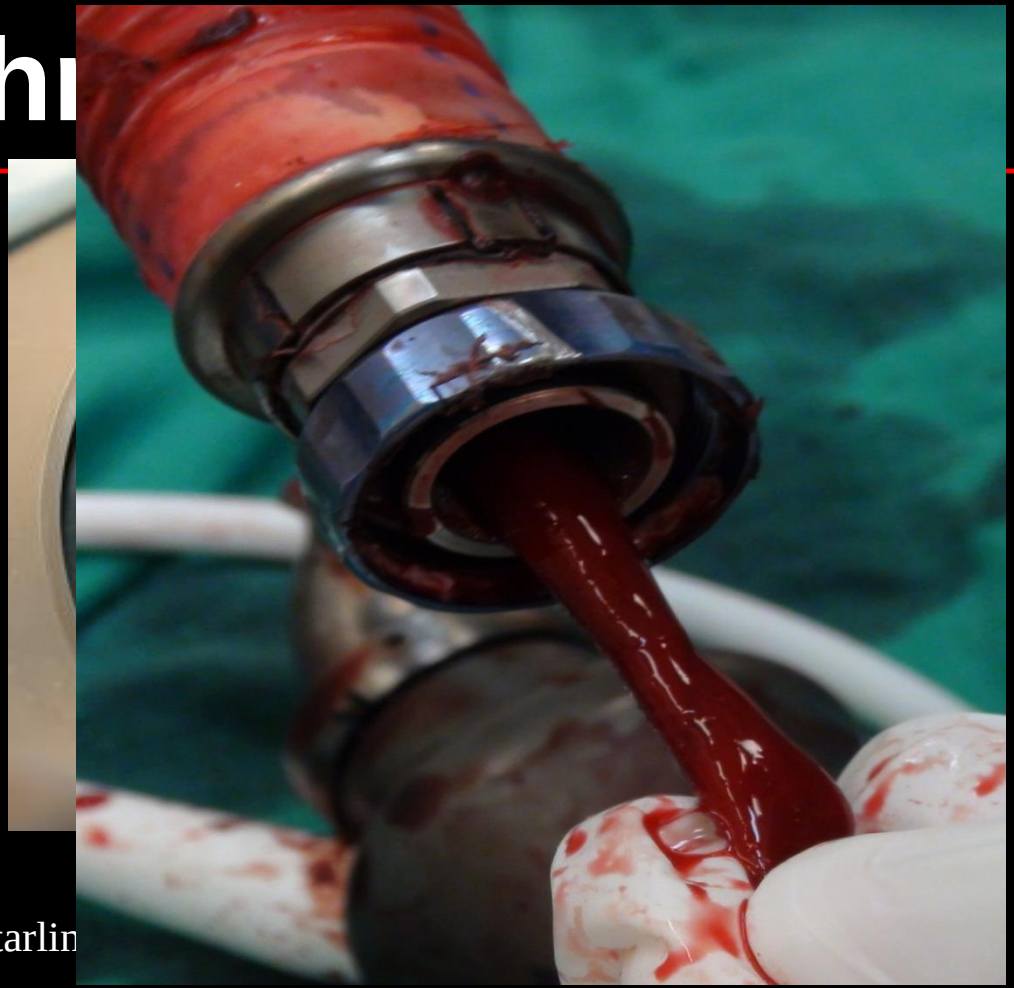

**Heartware VAD NOT FDA approved for right sided support**

# VAD-Related Infection



# VAD Th

- Multifactorial in etiology
- Cumulative Incidence of 5-11% at 1 YR[1-3]
- High rate of pump exchange and ↑mortality




1. Kirklin et al. JHLT 2014;33;12-22. 2. Starlin
3. Cowger et al. JHLT 2014;33:35-43.

# VAD thrombosis, hemolysis, and Events

- n= 182 at the University of Michigan
  - 37% had evidence of hemolysis (LDH ≥600

| | Freedom from Embolism | Freedom From Pump XC for Thrombosis | Survival |
|---|---|---|---|
| **LDH ≥600** (n=64) | 86±4.5% (HR=3.6 [1.6-8.0]) | 82±4.7% (HR 139 [1.8,1800]) | 79±5.1% (HR death 3.7 [1.7-7.9]) |
| **LDH <600** (n=118) | 99±1.0% | 100% | 70±8.0% |

Cowger et al. JHLT 2014;33:35-43

# PostVAD Complications: GI bleed and CVA

## GI Bleeding

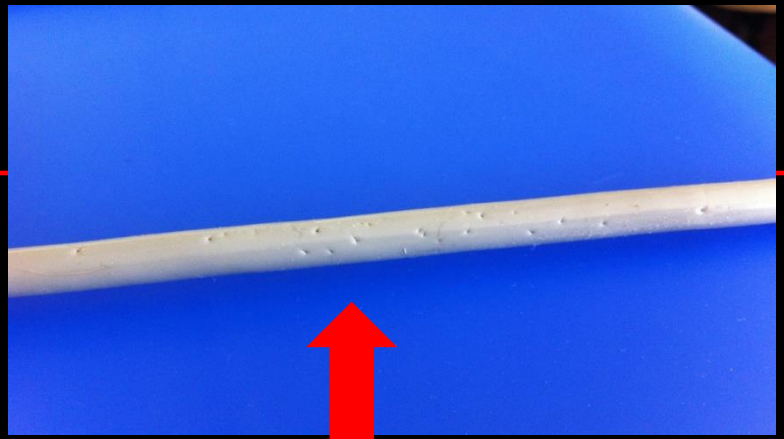
- 19-22%[1-2]
- #1 cause: Acquired vWF deficiency with recurrent AVM related GI bleeding
- 25% GI location not found
- 35% recurrent
- Exacerbated by antiplatelet and anticoagulation needs

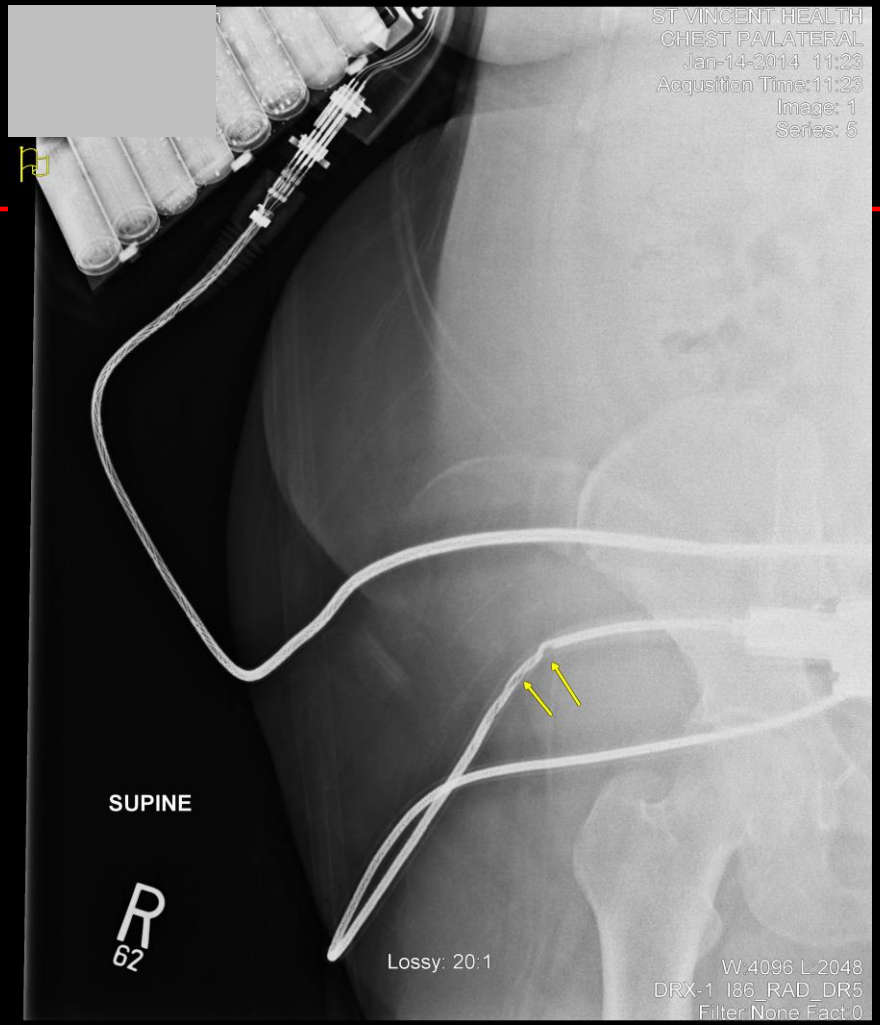
## CVA

- Hemorrhagic stroke, 8% cumulative incidence (0.05 events ppy)
  - Possible AVM related
- Ischemic stroke, 6% cumulative incidence (0.04 events ppy)

1. Aggarwal Ann Thorac Surg 2012;93:1534-40
2. Demirozu JHLT 2011;30:849-53

Boyle JACC 2014;63:880

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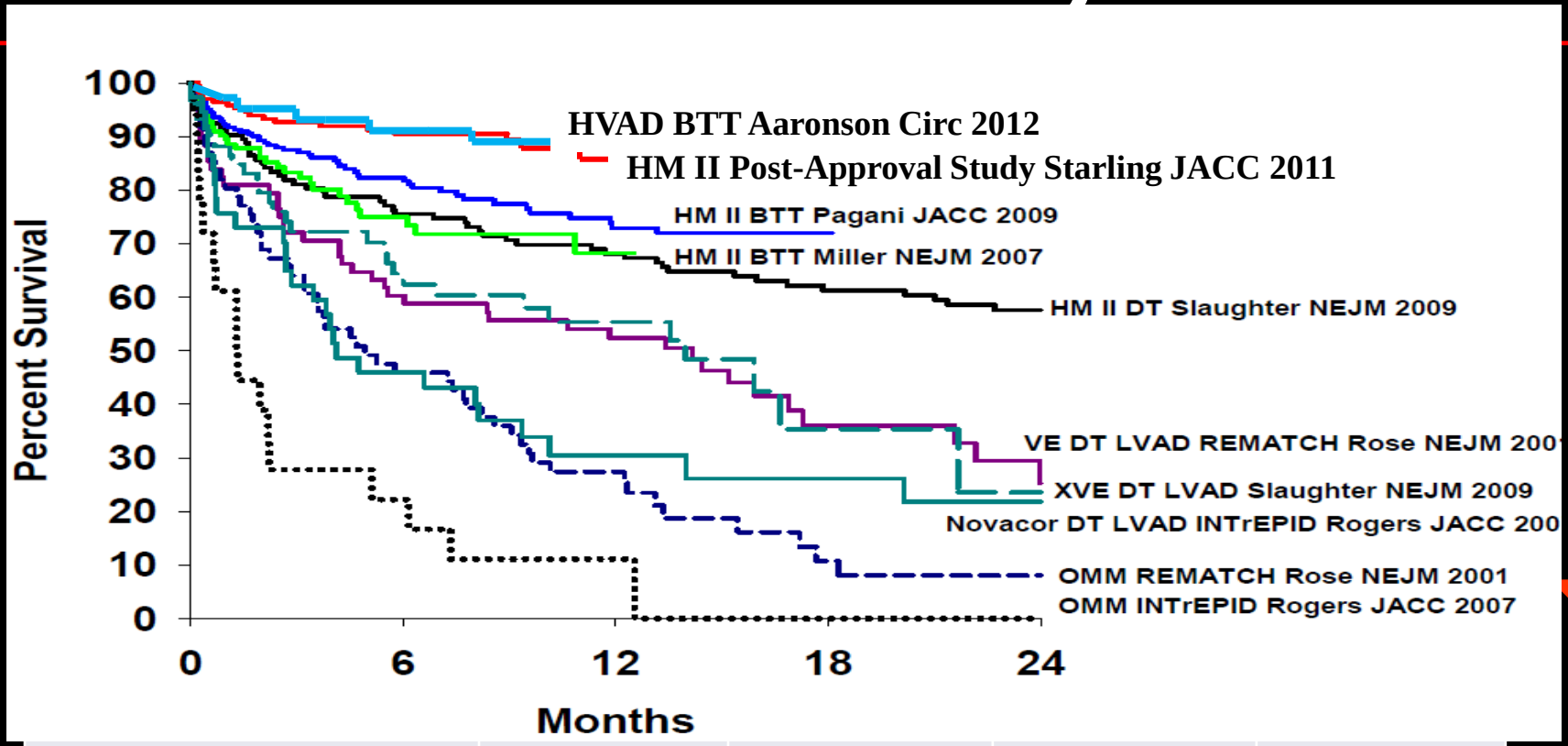
# Success Achieved with VAD Support

# LVAD mortality risk




| | | | | |
|---|---|---|---|---|
| BTT (Circ 2012;125:2191) | 490 Other | 97% | 92% | 85% |

BTT=bridge to transplant, DT= destination therapy

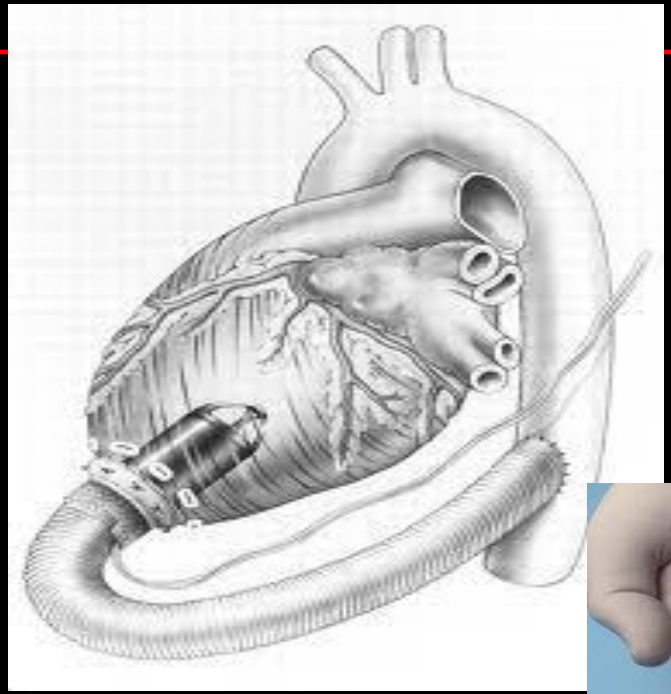
# Pending Clinical Trial

- Thoratec HeartMate III


- HeartWare mVAD

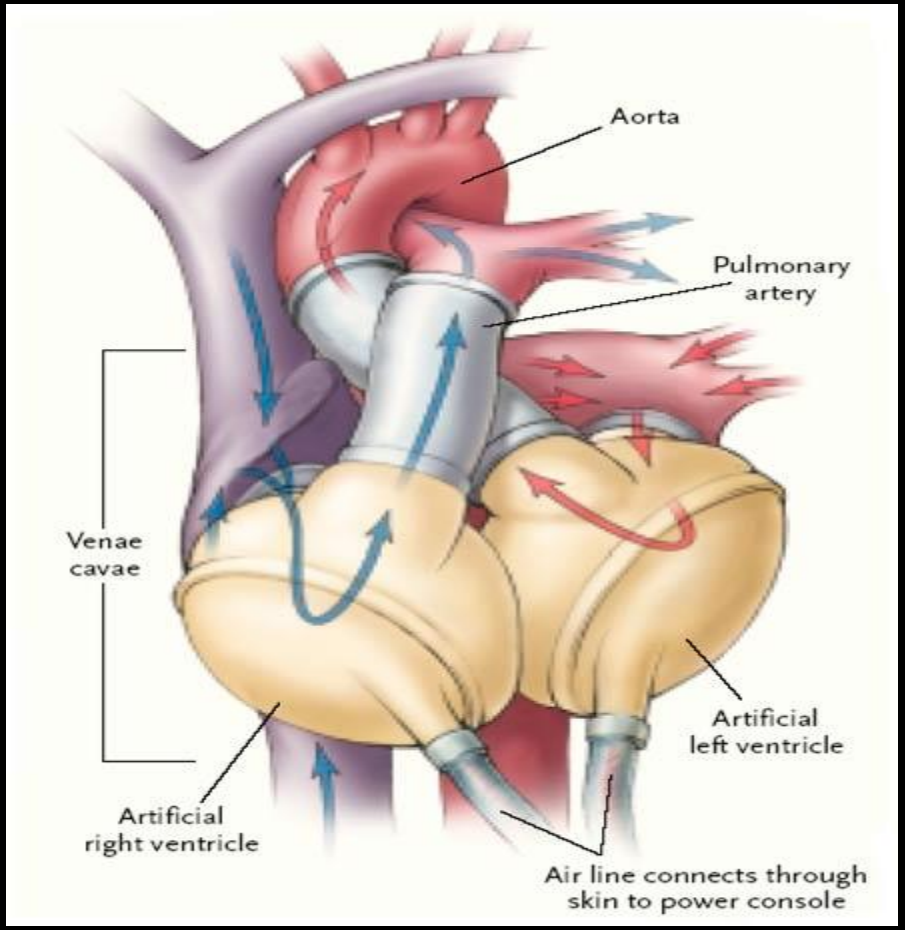
**Still in Clinical Trial- not FDA approved**

# Jarvik 2000



**Still in Clinical Trial- not FDA approved**

## Jarvik 7 Total Artifical Heart, Syncardia




**Takes over for BOTH sides of the heart- heart is removed**

Under trial for DT; FDA approved for BTT

# Summary: When to Refer

**Inpatients:**

- End organ dysfunction:
- ↑ALT, ↑ Bili, ↑Cr, ↑INR off warfarin
- Need for ventilator or balloon pump support
- Need for:
  - ≥ inotropes
  - Vasopressor
- Low EF and poor surgical candidate: LVEF ≤25% with CAD, dilated LV (LViDd >65 mm), RV dysfunction, or pulmonary HTN

# Summary: When to Refer

Outpatients:

- ≥2 admissions for CHF in a year and LVEF <25%
- Abnormal labs: ↑Cr ↓NA
- Inability to titrate CHF Meds due to hypotension
- Escalating diuretic needs (>80 mg lasix QD) or need for primer
- >1 ICD discharge for VT in a year


If I only had
an LVAD…

# VAD Criteria

- Dilated cardiomyopathy (LVEF ≤25%)
- NYHA class IIIb-IV symptoms
- Failure of OMM
- Absence of
  - RV failure
  - Severe renal failure
  - Cirrhosis
- Adequate Social support
- No fixed BMI limit or substance use policy

# Multivariable Predictors* of Death after LVAD Implant

**HMRS = 0.0275*Age-0.723*Albumin + 0.74*Creatinine + 1.136*INR + 0.87*Center-Volume (≥15)**

**Table 3** Multivariable Predictors of 90-Day Mortality in Derivation Cohort and Formula for Calculating HMRS

| Parameter | Estimate | SE | OR (95% CI) | p Value |
|---|---|---|---|---|
| Age (per 10 yrs) | 0.274 | 0.12 | 1.32 (1.05–1.65) | 0.018 |
| Albumin (per g/dl) | −0.723 | 0.23 | 0.49 (0.31–0.76) | 0.002 |
| Creatinine (per mg/dl) | 0.740 | 0.22 | 2.10 (1.37–3.21) | <0.001 |
| INR (per unit) | 1.136 | 0.32 | 3.11 (1.66–5.84) | <0.001 |
| Center volume <15 | 0.807 | 0.34 | 2.24 (1.15–4.37) | 0.018 |

Cowger *JACC 2013;61:313-21*

# Preop HMII Risk Correlates

## Frailty[3]

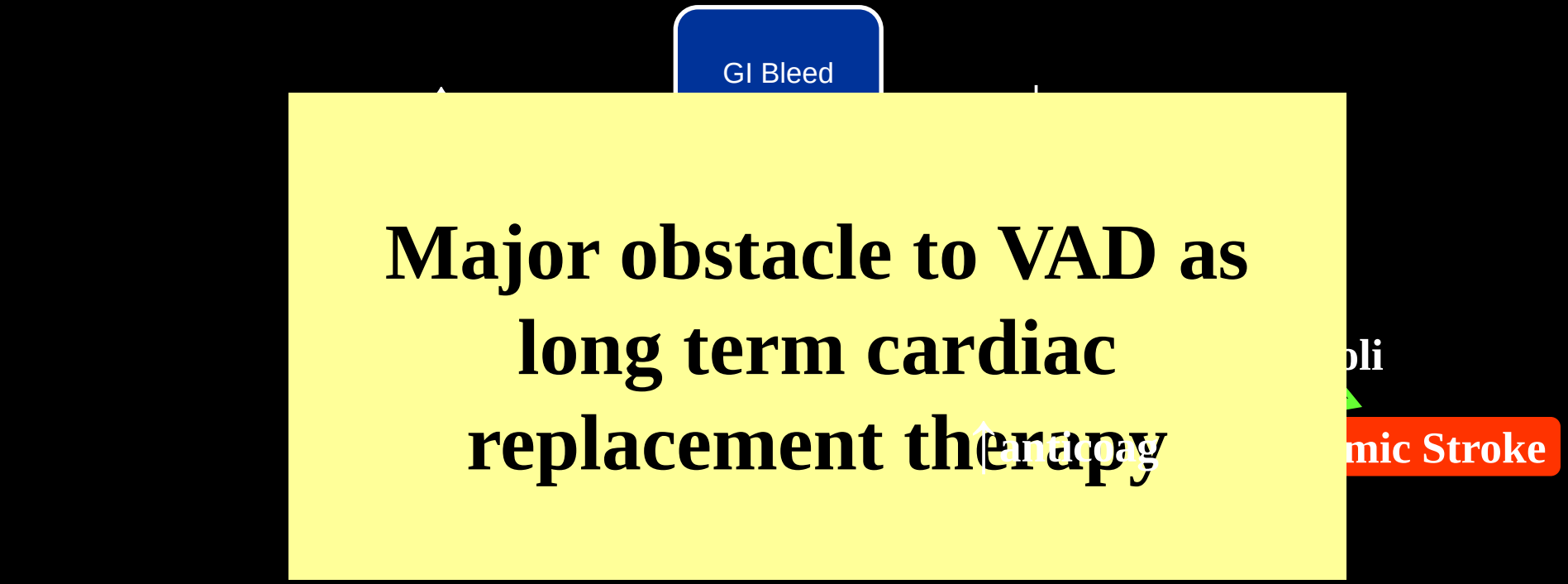
| HMR | le[1,3] |
| --- | --- |
| Age | reopMCS |
| Albumin | emale Sex |
| Center V | nation Therapy |

**HMRS = (0.0274 x [ ... 36 x [INR]) + (0.807 x [center volu ...**

**MELD = 9.57($\log_e$ ...**

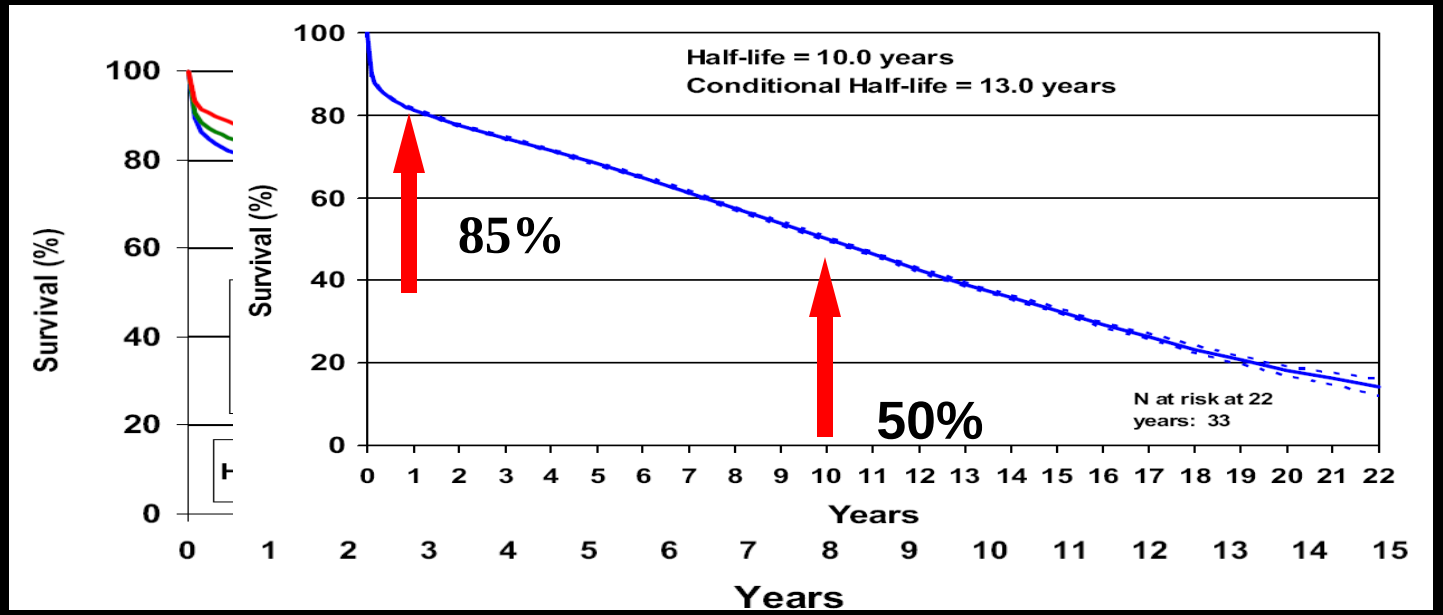

1. Cowger et al J ...
2. Cowger Matthews Circ 2010;121:214-20.

# Vicious Interdependent Cycle



# Survival Post-Transplant

## Internationally:




Taylor. J Heart Lung Transplant 2007;26:769-781

Special thanks to Jennifer Cowger, MD, for assistance with these slides.

Thank you very much!