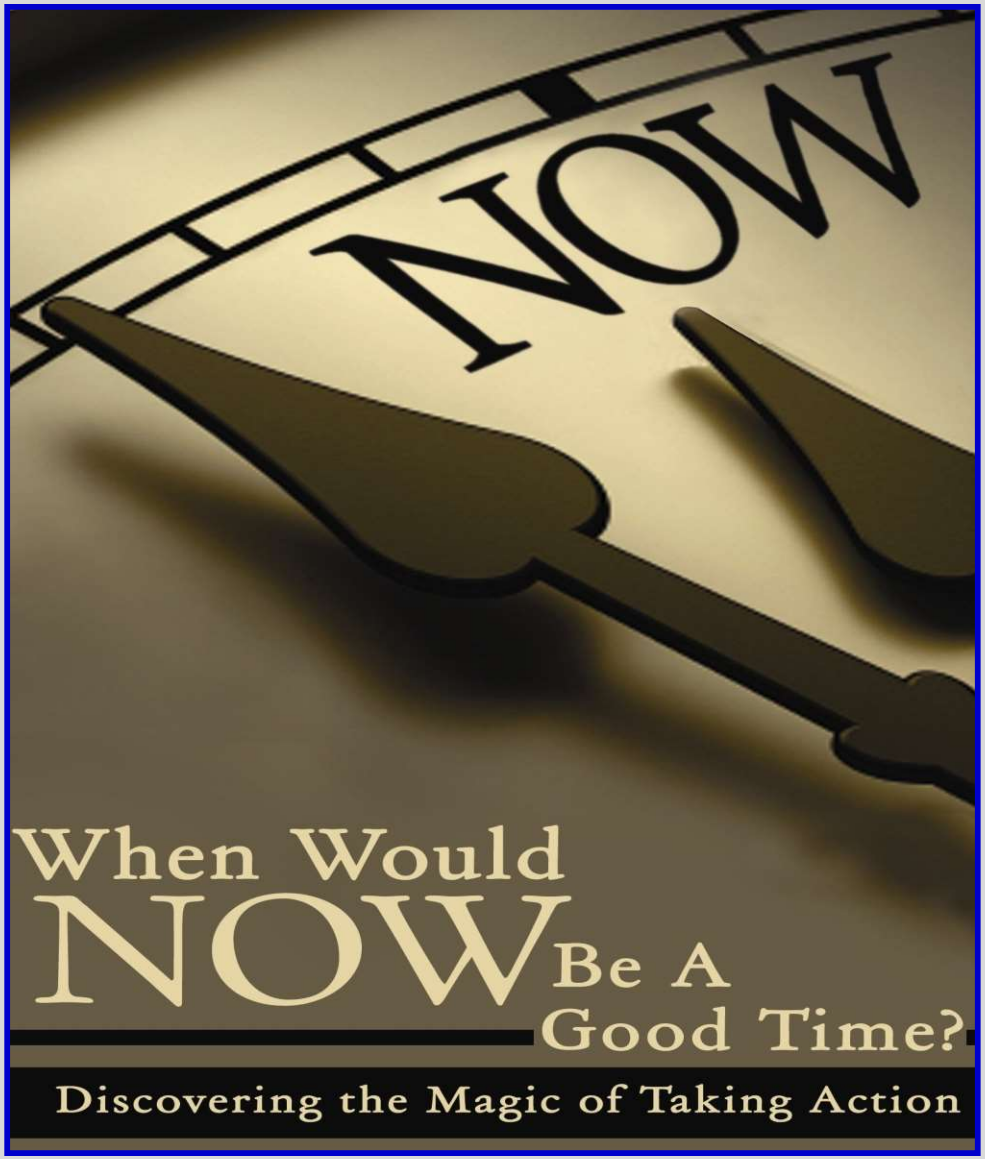
# Advances in Heart Failure Therapeutics



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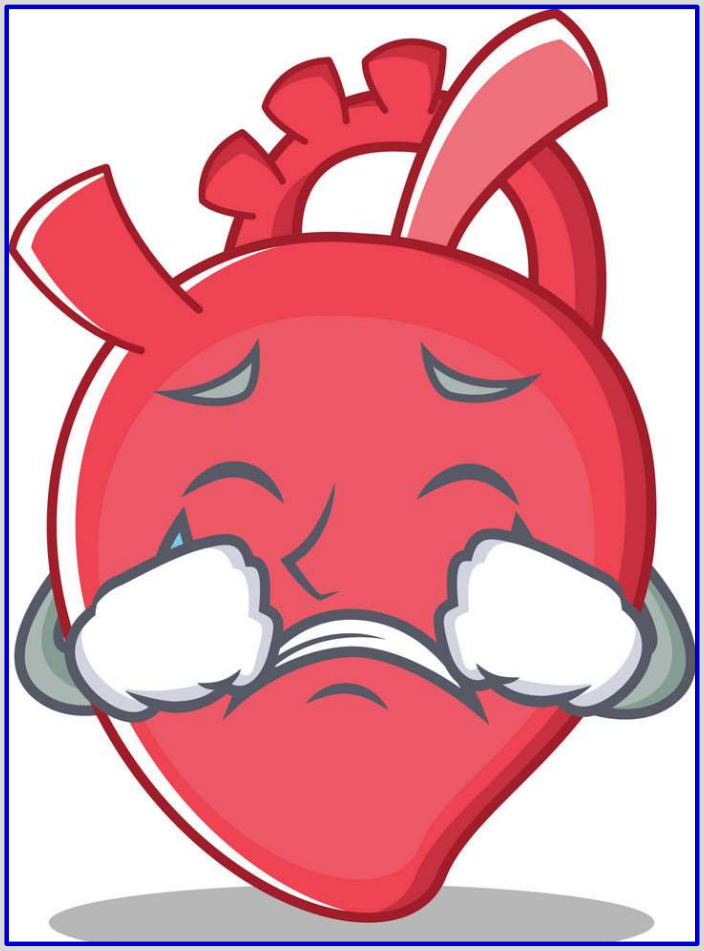
**Norton Thoracic Institute/St Joseph Hospital and Medical Center**


**No Financial Disclosure**

- Definition of Advanced Heart Failure
- Diagnostics
- Inotropic Approach
- Temporary Circulatory Support Devices
- Durable Circulatory Support Devices
- Heart Transplantation



# Introduction

- *Burden:*
  - Heart failure (HF) affects nearly 6.2 million Americans
  - Hospitalizations annually: 1 million (primary diagnosis)/2 million (secondary diagnosis)
  - By 2030, more than 8 million people in the United States (1 in every 33) will have HF

- *Mortality/Morbidity*
  - Inpatient mortality ranges from 4% to 12% and may increase to 20% to 25% in high-risk subgroups
  - Readmissions and events are common, and the age adjusted risk for all-cause mortality is tripled compared with non–HF patients

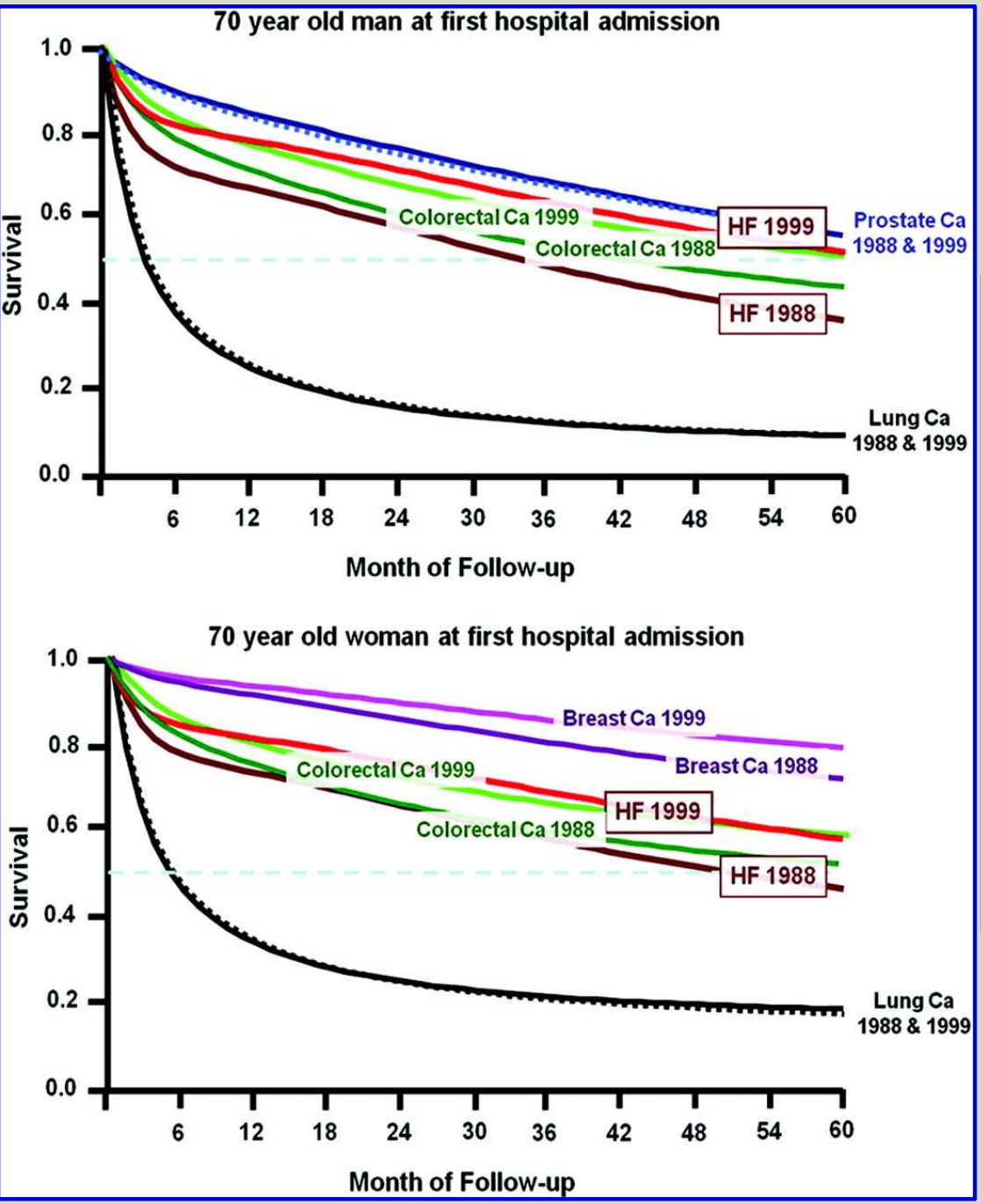
*Circulation. 2013;127:e6–245*
*JACC. 2019,74 (15):1966–2011*

- The stages are progressive and inviolate; once a patient moves to a higher stage, regression to an earlier stage of HF is not usually observed

- Progression in HF stages is associated with reduced 5-year survival

- 5-year mortality data, survival for stages:
  - A: 97 %
  - B: 96 %
  - C: 75 %
  - ***D: 20 %***

*Circulation. 2007;115:1563–70*


70 year old man at first hospital admission
Survival
1.0
0.8
0.6
0.4
0.2
0.0
Colorectal Ca 1999
Colorectal Ca 1988
HF 1999
HF 1988
Prostate Ca
1988 & 1999
Lung Ca
1988 & 1999
6
12
18
24
30
36
42
48
54
60
Month of Follow-up
70 year old woman at first hospital admission
Survival
1.0
0.8
0.6
0.4
0.2
0.0
Breast Ca 1999
Breast Ca 1988
Colorectal Ca 1999
Colorectal Ca 1988
HF 1999
HF 1988
Lung Ca
1988 & 1999
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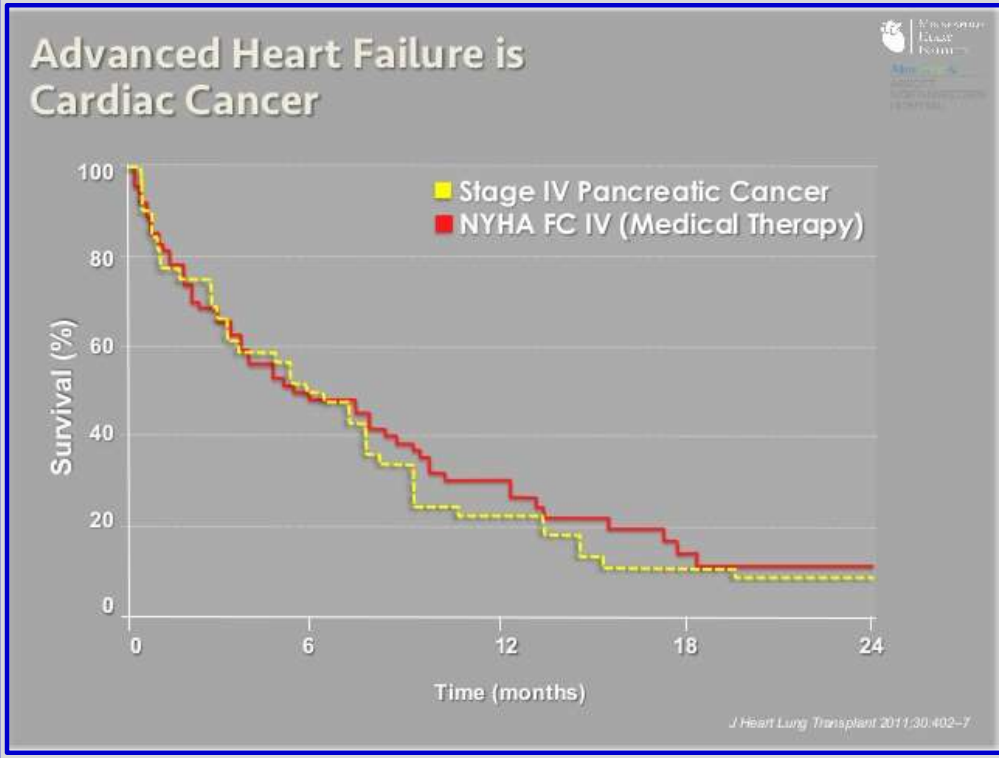
12
18
24
30
36
42
48
54
60
Month of Follow-up


Advanced Heart Failure is
Cardiac Cancer
Survival (%)
100
80
60
40
20
0
Stage IV Pancreatic Cancer
NYHA FC IV (Medical Therapy)
0
6
12
18
24
Time (months)
J Heart Lung Transplant 2011;30:402–7

# Definition of Advanced Heart Failure

# ACCF/AHA Stages of HF

| Stage | Definition |
|---|---|
| A | At high risk for HF but without structural heart disease or symptoms of HF |
| B | Structural heart disease but without signs or symptoms of HF |
| C | Structural heart disease with prior or current symptoms of HF |
| D | Refractory HF requiring specialized interventions |

*Circulation. 2009;119:e391–479*

# Clinical Events: Advanced HF

- Repeated (≥ 2) hospitalizations or ER visits for HF in the last one year

- Persistent dyspnea/fatigue with:
  - Dressing/bathing requiring rest
  - Walking 1 block on level ground

- Wt loss without other causes (eg cardiac cachexia)

*Congest Heart Fail. 2008;14:316–21*

# Clinical Findings: Advanced HF

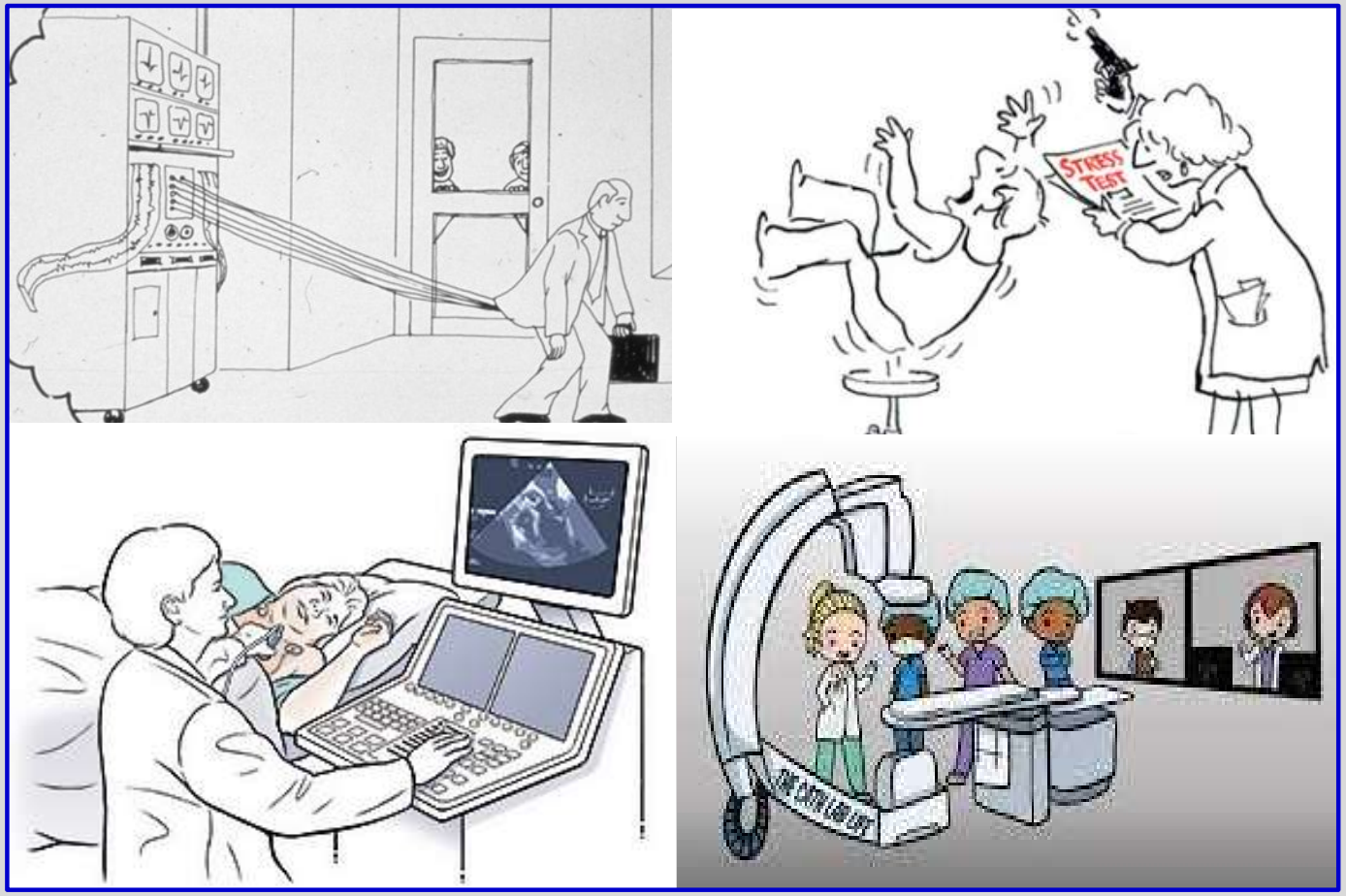
- Progressive deterioration in renal function
- Frequent systolic blood pressure < 90 mmHg
- Frequent ICD shocks
- Progressive decline in serum sodium (<133 mEq/L)

*Congest Heart Fail. 2008;14:316–21*

# Clinical Findings: Advanced HF

- Intolerance to ACE-I due to hypotension and/or worsening renal functions
- Intolerance to BB due to worsening HF or hypotension
- Recent need to escalate diuretics to maintain volume status (often reaching furosemide equivalent dose > 160 mg/day and or supplemental metolazone)

*Congest Heart Fail. 2008;14:316–21*




# Diagnostic Tools

# Echocardiography

- Transthoracic Echocardiogram: Gold standard Initial Diagnostic tool
- Transesophageal Echocardiogram: Special conditions needing evaluation of Valvular Disease
- Defines the LV and RV systolic and diastolic function along with size
- Hence key to screen and serially follow the cardiomyopathy
- Sonar technology and Bernoulli's principle (modified)

# Cardio-Pulmonary Exercise Test

- Significance: peak VO2 ≤ 14 ml/kg/min [peak VO2 > 14 ml/kg/min had 6% 1-year mortality]

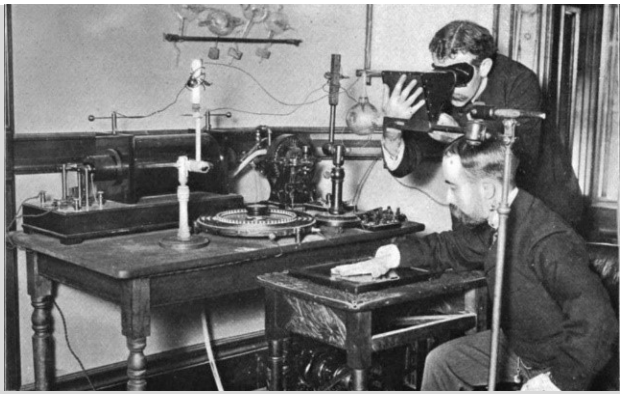
- peak VO2 and VE/VCO2 slope:
  - incremental prognostic value beyond relevant clinical covariates for the composite of all-cause death, LVAD implantation or heart transplant, and for incident HF hospitalization

*Circulation 1991;83:778–86*
*JACC HF 2016;4:607–16*
*J Am Heart Assoc.2017;6*

# Cardiac Catheterization

- Left Heart Cath/Coronary Angiogram
- Right Heart Cath
- Continuous Hemodynamics via Pulmonary Artery Catheter

# Left Heart Catheterization



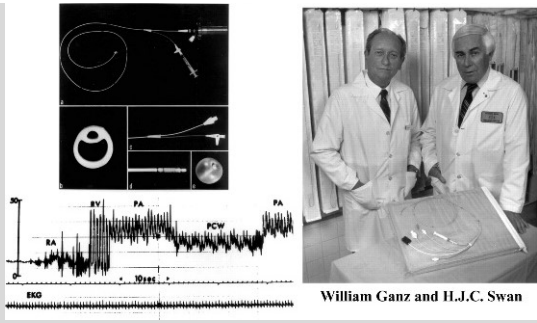
- Assessment of post pulmonary cardiac hemodynamics
- Assessment of Coronary Anatomy
- Based on X-ray technology

# Right Heart Catheterization

- Assessment of:
  - Pressures:
    - PCWPm: a surrogate of LVEDp
    - PA Pressure: a surrogate of lung/pulmonary strain
    - RA Pressure: surrogate of RV stain and Volume Status
  - Flows: Cardiac Output
  - Shunt Runs

- Ohm's Law (V = IR)

# Continuous PA Cath Monitoring




- Cardiogenic Shock: prognostication and management
- Pulmonary HTN
- Temporary Mechanical Circulatory Support device management
- VAD/Heart Transplant Work up/Management

*Circulation. 2009;119:147–152*
*Curr Treat Options Cardio Med. 2021;23,29*

# A word or two on CCO swan guided therapy

- *SUPPORT/ESCAPE/PAC-Man/Cochrane Database Syst Rev trials*:
  - Recommended against routine use in heart failure hospitalizations
  - However they excluded cardiogenic shock patients

- *2019 Study:*
  - Mortality for CS patients with PA catheter was 29.7% compared with 38.1% in those without it

*JAMA. 1996;276(11):889–97*
*JAMA. 2005;294(13):1625–33*
*Lancet. 2005;366(9484):472–7*
*Cochrane Database Syst Rev. 2013;2:CD003408*
*Curr Treat Options Cardio Med. 2021;23,29*

# Cardiogenic Shock Working Group

- PA catheter Hemo before MCS device initiation:
  - survival from CS across all SCAI CS stages and having no PA catheter assessment was associated with higher in-hospital mortality than complete PA catheter assessment

*JACC: Heart Failure. 2020;8(11):903–13*
*Curr Treat Options Cardio Med. 2021;23,29*

# 2013 ISHLT Guidelines

- After MCS if persistent or recurrent HF symptoms to evaluate for evidence of RV failure or device malfunction (I, B)
- After MCS placement when evaluating for myocardial recovery before pump explantation (IIa, C)
- At regular intervals in patients being evaluated for or listed for heart transplant for evaluation of irreversible pulmonary hypertension (I, A)

*JHLT. 2013;32(2):157–87*

# SCAI/HFSA clinical expert consensus

- Diagnosis of cardiogenic shock
- Continuous hemodynamic monitoring with a PA catheter in patients with MCS
- To guide weaning of MCS
- To assess candidacy for and transition to advanced heart failure therapies (VAD/HTx)

*Catheter Cardiovasc Interv. 2017;89(7):E233–47*


# Advanced HF Therapies

- Bridge Therapy
  - Inotrope therapy
  - Temporary Mechanical Circulatory Support Devices

- Definitive Therapy
  - Ventricular Assist Device
  - Heart Transplant
  - Palliative Therapy


# Inotrope Therapy

- Intravenous continuous infusion of inotropes
  - Milrinone
  - Dobutamine

- Best used as a "bridge" while patients undergoing evaluation for more definitive therapies

- Additional ICU Inotrope Therapies
  - Epinephrine
  - Norepinephrine

*Circulation: Heart Failure. 2015;8:880–886*
*Chest. 1997;112(5):1298-1303*

- Reduces hospital admissions
- Length of stay
- Cost of care
- Improves functional class in patients with advanced (NYHA class IV) heart failure

- Now more and more patients are utilizing Intravenous continuous infusion as part of *Palliation* at home

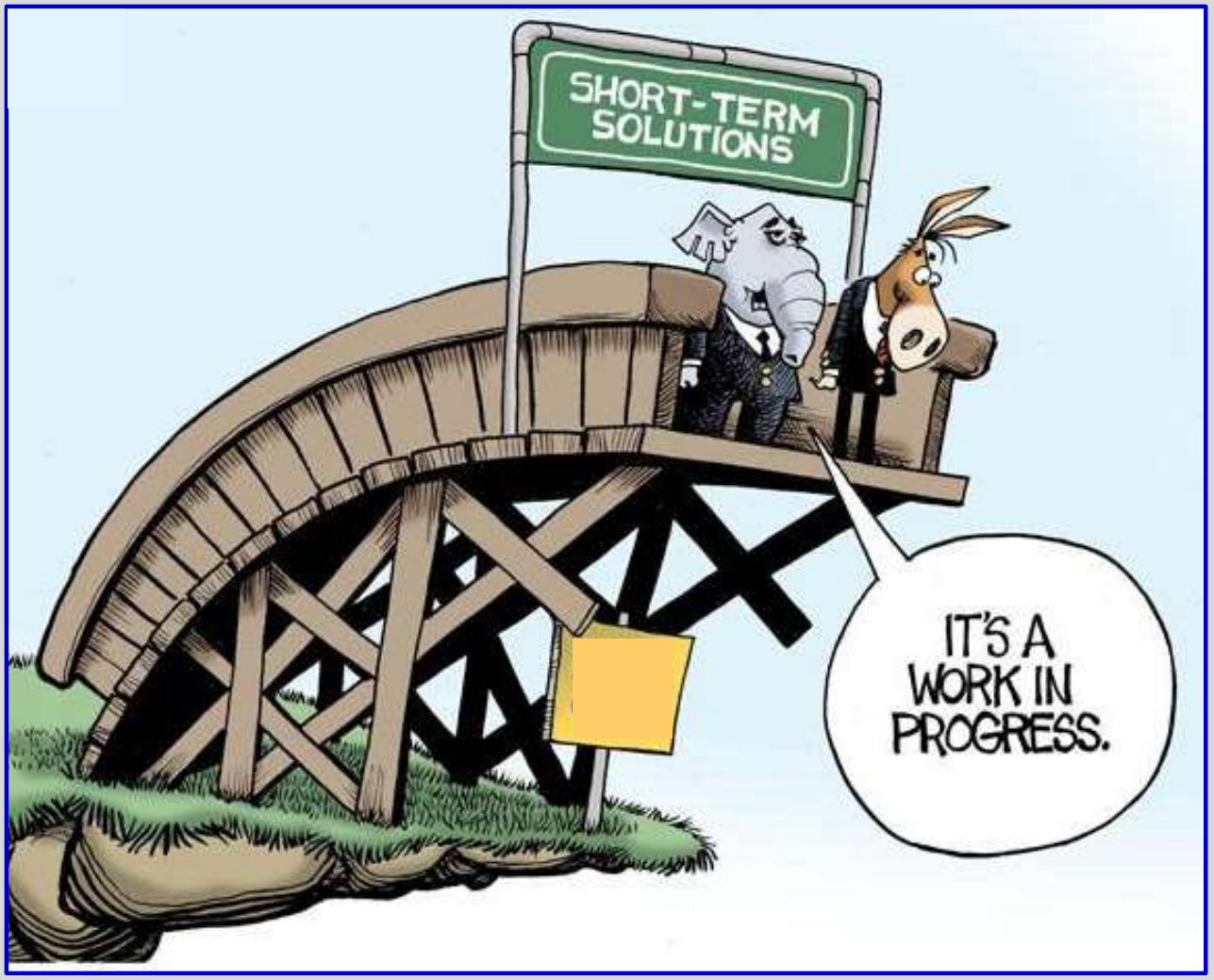
- Made Possible by our understanding of titrations of Inotropes

*Journal of Pain and Symptom Management. 2018;55(1):159-163*
*Circulation: Heart Failure. 2015;8:880–886*

# Levosimendan

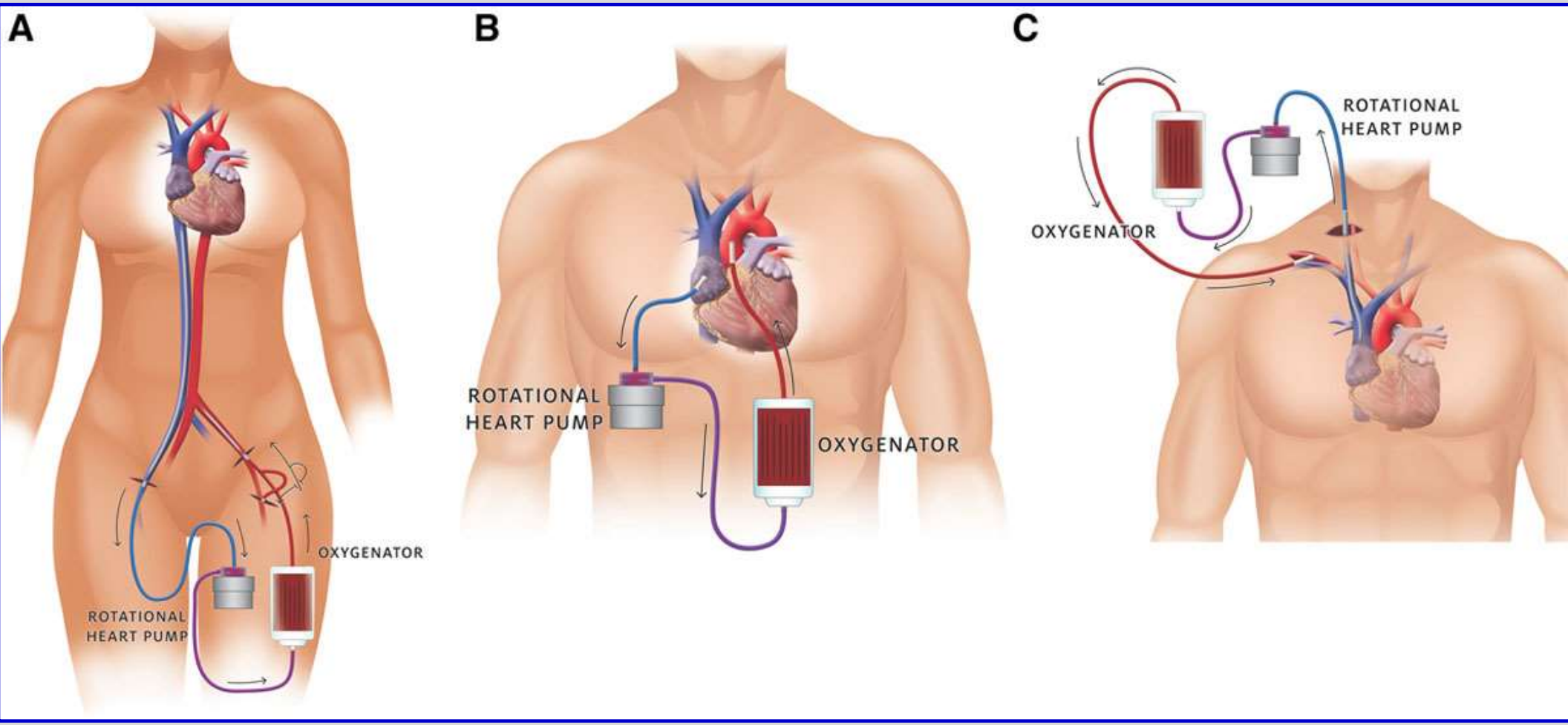
- SURVIVE Trial
  - Compared to dobutamine
- LEVO-CTS
  - Used on CABG patients
- Both have been associated with increased mortality
- AFib/Hypokalemia/Headache

*JAMA. 2007;297:1883-1891*
*ACC.2017:NEJM 2017*




# Temporary Mechanical Circulatory Support Devices

# Veno-Arterial ECMO




*Circulation: Heart Failure. 2018;11:e004905*

# Veno-Arterial ECMO

- Initial Introduction: 1972
- US FDA: Approves use up to 6 hours
- Bridge Therapy:
  - To Recovery
  - To Definitive Therapy
  - To Decision
- Due to concerns for increasing LV end-diastolic pressures, unloading is recommended
- All patients are recommended to have continuous PAC monitoring

*Circulation: Heart Failure. 2018;11:e004905*

# Veno-Arterial ECMO

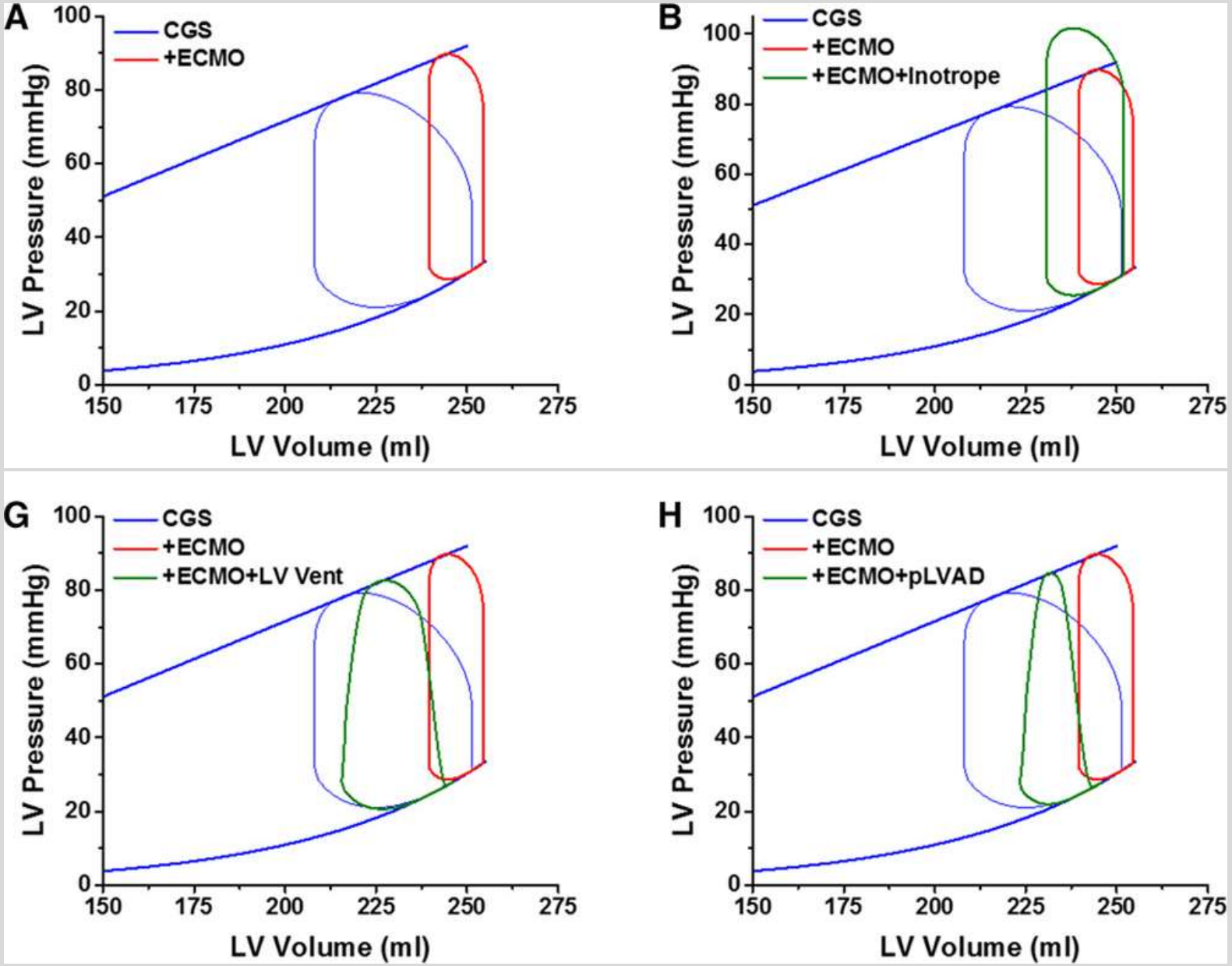
- Survival to hospital discharge:
  - 29% (extracorporeal cardiopulmonary resuscitation)
  - 41% (refractory cardiogenic shock)

- Non-post-cardiotomy Data (n=55 with 36 ± 20.9 month follow up):
  - Complications: Bleeding (38.2%)
  - Bridge to LVAD (47.3%)
  - Survival to death (months): 26 ± 5.3

- Adult ECLS Registry Report (33,115 patients):
  - Cardiac Survival: 59%
  - Survival to DC/transfer: 44%

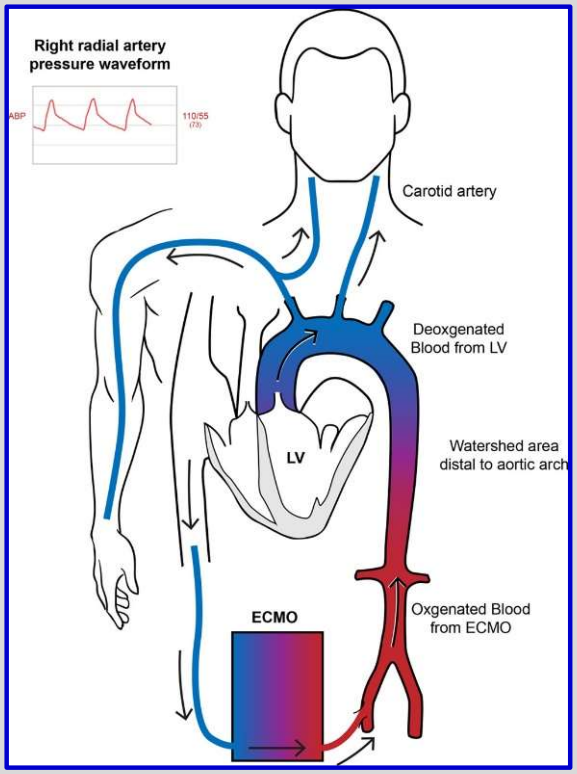
*Circulation: Heart Failure. 2018;11:e004905*
*Medicina Kaunas. 2022 Mar 15;58(3):427*
*ECLS Registry Report. International Summary, October 2021*

# Veno-Arterial ECMO: LV Unloading




*Circulation: Heart Failure. 2018;11:e004905*
*J Card Surg. 2011; 26:666–668*

- North-South Syndrome (Harlequin/Watershed Region)
- Limb Ischemia (12% to 22%)
- Anticoagulation Related Coagulopathy
- Device related Coagulopathy



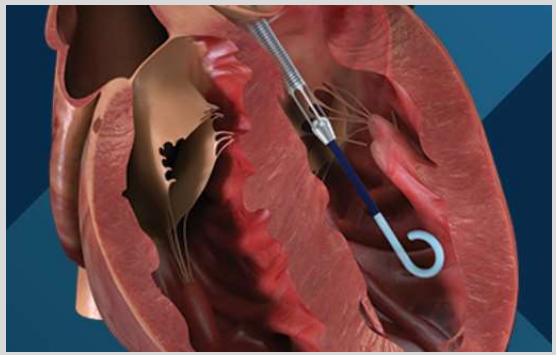

- SAVE Score can be helpful but limited due to baseline data drive

*Circulation. 2014; 130:864–865*
*Int J Cardiol. 2015; 187:164–165*
*Eur Heart J. 2015;36(33):2246-56*

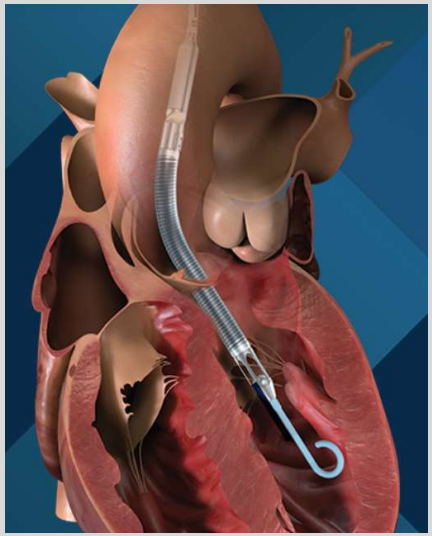
# Impella® Heart Pump

## Impella

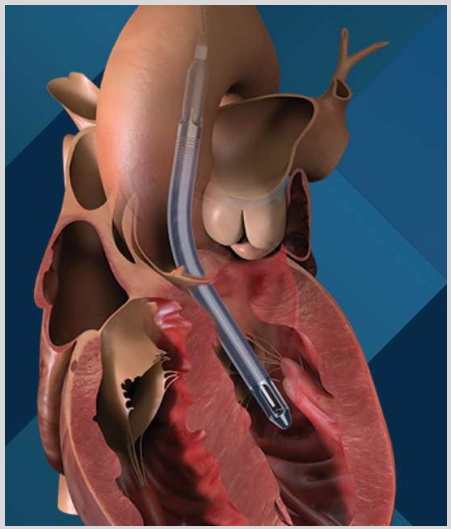
- Impella 2.5
- Impella CP



- Impella 5.0



- Impella 5.5



## Impella 2.5 and CP

- PROTECT II Study:
  - 2.5 vs IABP: 3 v/d or LM with low LVEF (~25%)
  - Slight non-significant benefit (30 and 90 day outcomes)
  - MACE: reduced with 2.5

## Impella 5.0 and 5.5

- RECOVER I:
  - 75 % survived at one year *-- > 64% (later 100 pt study)*
  - 93 % recovered native heart function

- 55 pt study:
  - 84 % survived
  - 76 % recovered native heart function

*Circulation. 2012;126:1717–1727*
*J Thorac Cardiovasc Surg. 2013;145(2):548-554*
*Ann Thorac Surg. 2020;109(5):1370-1377*
*ASAIO Journal. 2020;66(7):746-752*

## Impella Connect®

- Secure, cloud-based, remote monitoring of Impella® status for better patient outcomes


## SmartAssist® Technology

Optical Sensor and Advanced Metrics

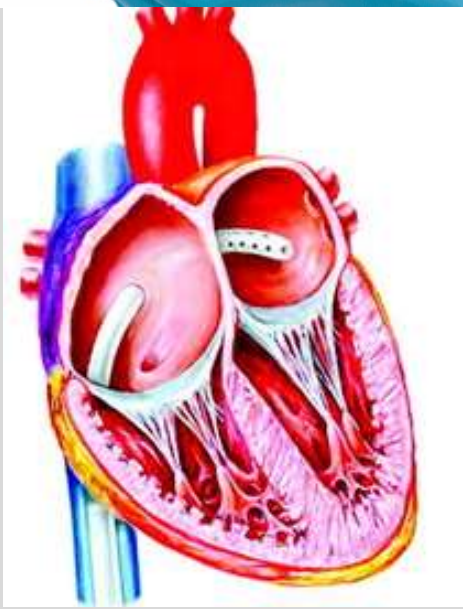
- Pump re-positioning without image guidance
- Better, faster resolution of suction alarms
- Earlier identification of right heart failure
- Assist in hemodynamic assessment and successful weaning guidance

*FDA Approved, PMA Supplement, 2018*

# TandemHeart®

## Centrifugal System

- Magnitude of hemodynamic benefit is good, but it may worsen ischemia in shock
- Afterload: increased



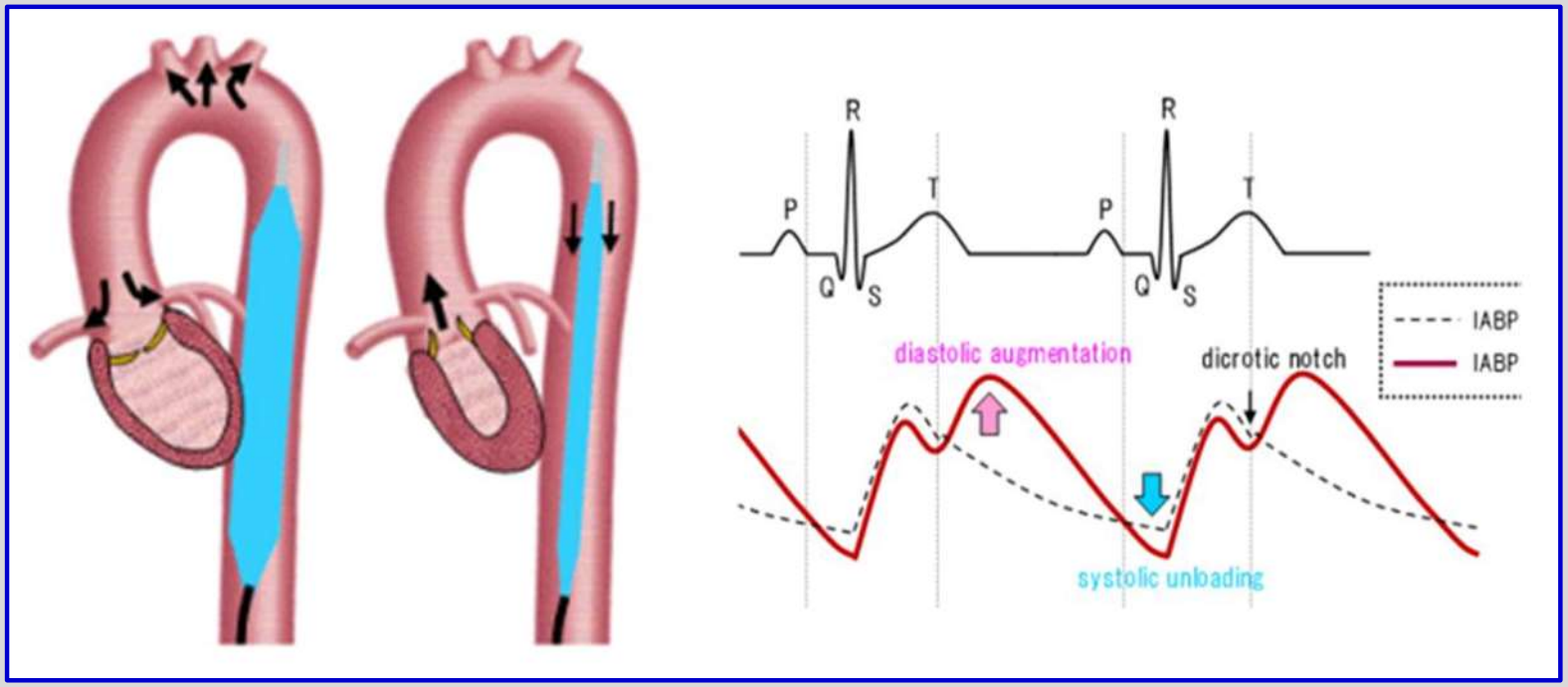
- Bridge to LVAD: 44%
- Recovery: 20%
- Death: 36%
- Complication: ~ 50%



*JACC Intv. 2016;9(22):2292–2303*
*Circulation. 2011;123:533–543*
*ASAIO J. 2011;57(4):254-61*

# Intra Aortic Balloon Pump

- SHOCK Trial
- Currently most useful in ACS/Acute Proximal CAD with active angina -- > Cardiogenic Shock




*Circ Cardiovasc Interv. 2017;10:e00433*

*http://www.eonet.ne.jp/~hidarite/ce/sinpai06.html*

- Afterload: Reduced
- LV stroke volume: Slight increase
- Coronary perfusion: Slight increase
- 
- LV preload: Slightly reduced
- PCWP: Slightly reduced
- Peripheral tissue perfusion: No significant increase

*European Heart Journal. 2014;35:156–67*

| | IABP (Ascending Ao) | Impella 2.5 (LV/LVOT) | Impella 5.0 (LV/LVOT) | TandemHeart (LA to Systemic Artery) | ECMO (Femoral Artery and Vein) |
|---|---|---|---|---|---|
| Primary hemodynamic effect(s) | LV volume or pressure unloading | LV volume or pressure unloading | LV volume or pressure unloading | LV volume unloading | Biventricular pressure and volume unloading |
| TPR | Decreased | Decreased | Decreased | Mildly increased | Highly increased |
| Bridge to recovery | Yes | Yes | Yes | Yes | No* |
| Hemodynamic support | Low | Moderate | High | High | High |
| Pump mechanism | Pneumatic | Axial flow | Axial flow | Centrifugal | Centrifugal |
| Cannula size | 7.9 Fr | 13 Fr | 22 Fr | 21 Fr inflow; 15–17 Fr outflow | 18–21 Fr inflow;15–22 Fr outflow |
| Implantation time | Very low | Low | Moderate | High | Moderate |
| Risk of limb ischemia | Very low | Low | Low | High | High |
| Anticoagulation | Very low | Very low | Very low | High | High |
| Hemolysis | Very low | Low | Low | Low | Low |
| Postimplantation management complexity | Very low | Moderate | Moderate | High | Very high |

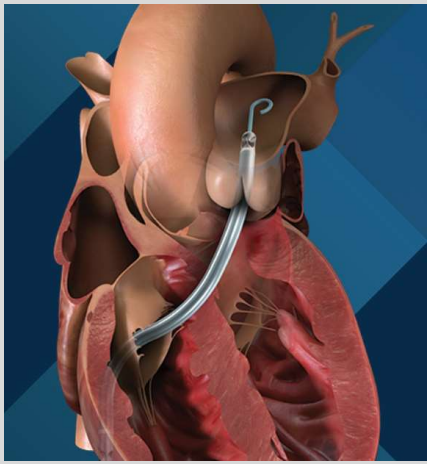
*Circ Cardiovasc Interv. 2017;10:e00433*

# Augmentation of Cardiac Output

- IABP: 0.5 L/min
- Impella 2.5: 2.5 L/min
- TandomHeart: 3.5 L/min
- Impella CP: 3.7 L/min
- Impella 5.5: 5.5 L/min

*Circulation. 2011;123:533–543*

# Right Sided Support Devices



## Impella RP

- Recover Right Study:
  - 12 after cardiotomy/MI
  - 18 after LVAD implantation
  - 30 day survival 73.3% (All 30 patients alive at 180 days)

- RVF in Acute PE
  - Initial data was promising but not in real-world experience (worst outcome in post ACS-MI)

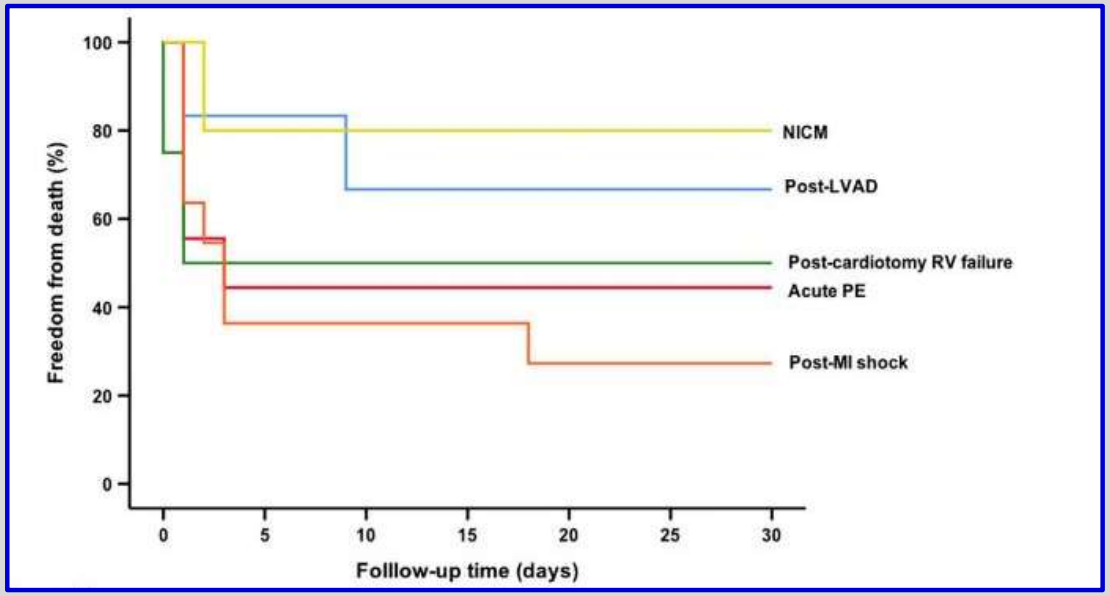
- Pig Study:
  - Norepi + Mil resulted in better cerebral perfusion

*JHLT. 2015;34(12):1549-60*
*J Artif Organs. 2020;23(2):105-112*
*J Cardiovasc Transl Res. 2021;14(6):1021-1029*

# Right Sided Support Devices

## Impella RP

- Real-world experience (worst outcome in post ACS-MI)




- FDA Post-Approval Study:
  - 30-day survival: 28.6 % (in patients who did not meet premarket clinical study enrollment criteria)

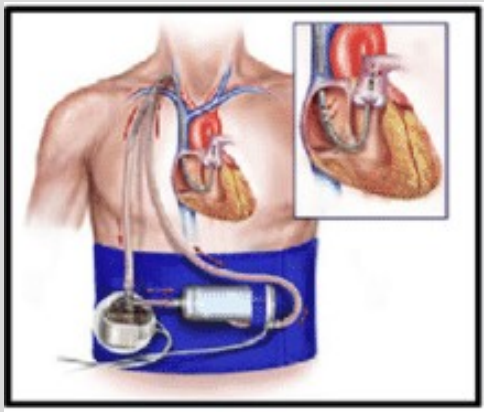
*Catheter Cardiovasc Interv. 2021;97(1):E161-E167*

*https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=615919&c_id=4556*

# Right Sided Support Devices

## Protek Duo

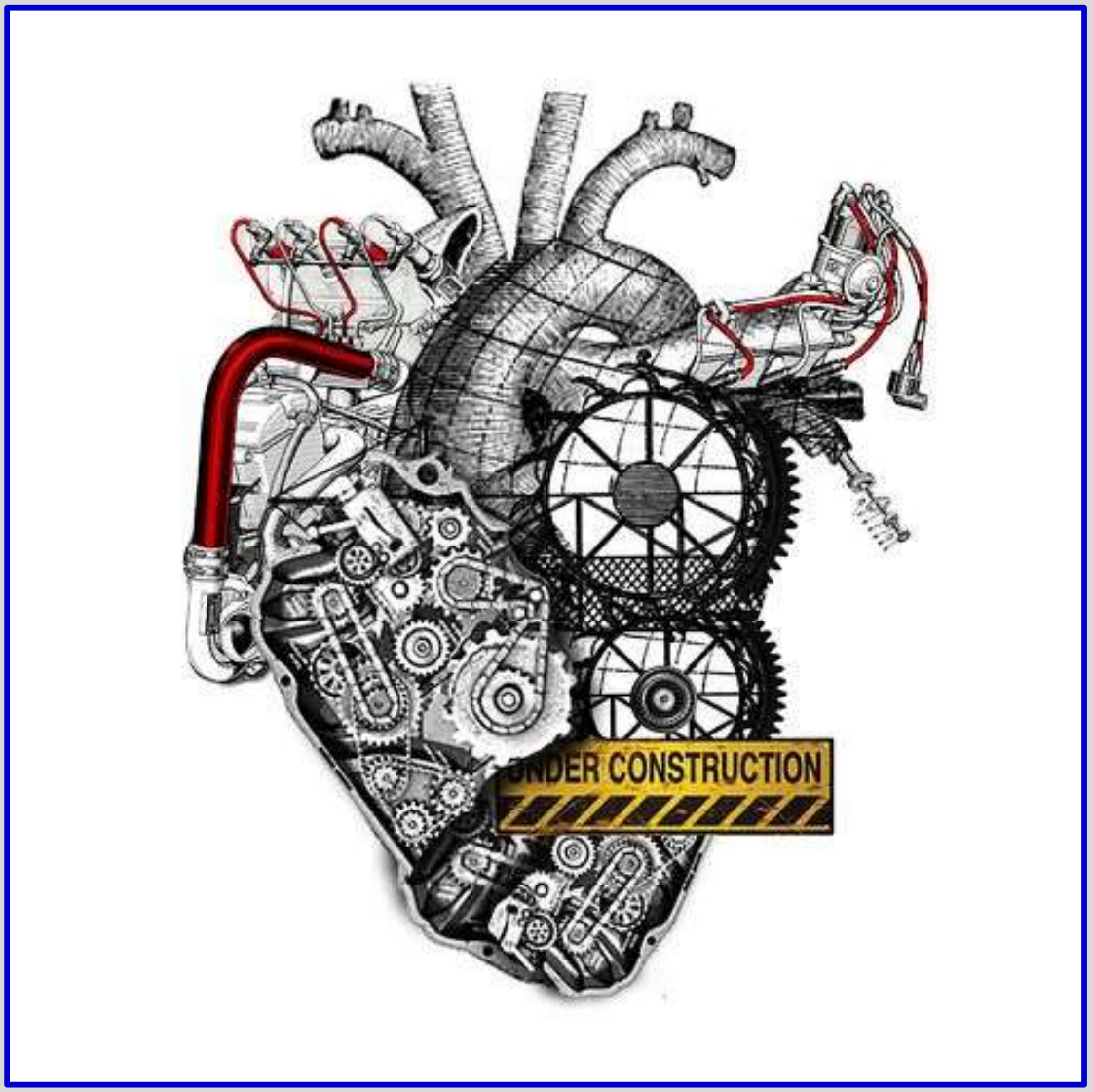
- 23% successful wean without additional support
- 41% did not survive



Protek Oxy-RVAD

- Current studies based on Post-Surgical Acute RVF
  - Post LVAD
  - Post OHTx (Acute/Hyperacute Rejections)

*ASAIO. 2018;64(4):570-572*
*J Card Surg. 2021;36(10):3884-3888*




# Ventricular Assist Devices

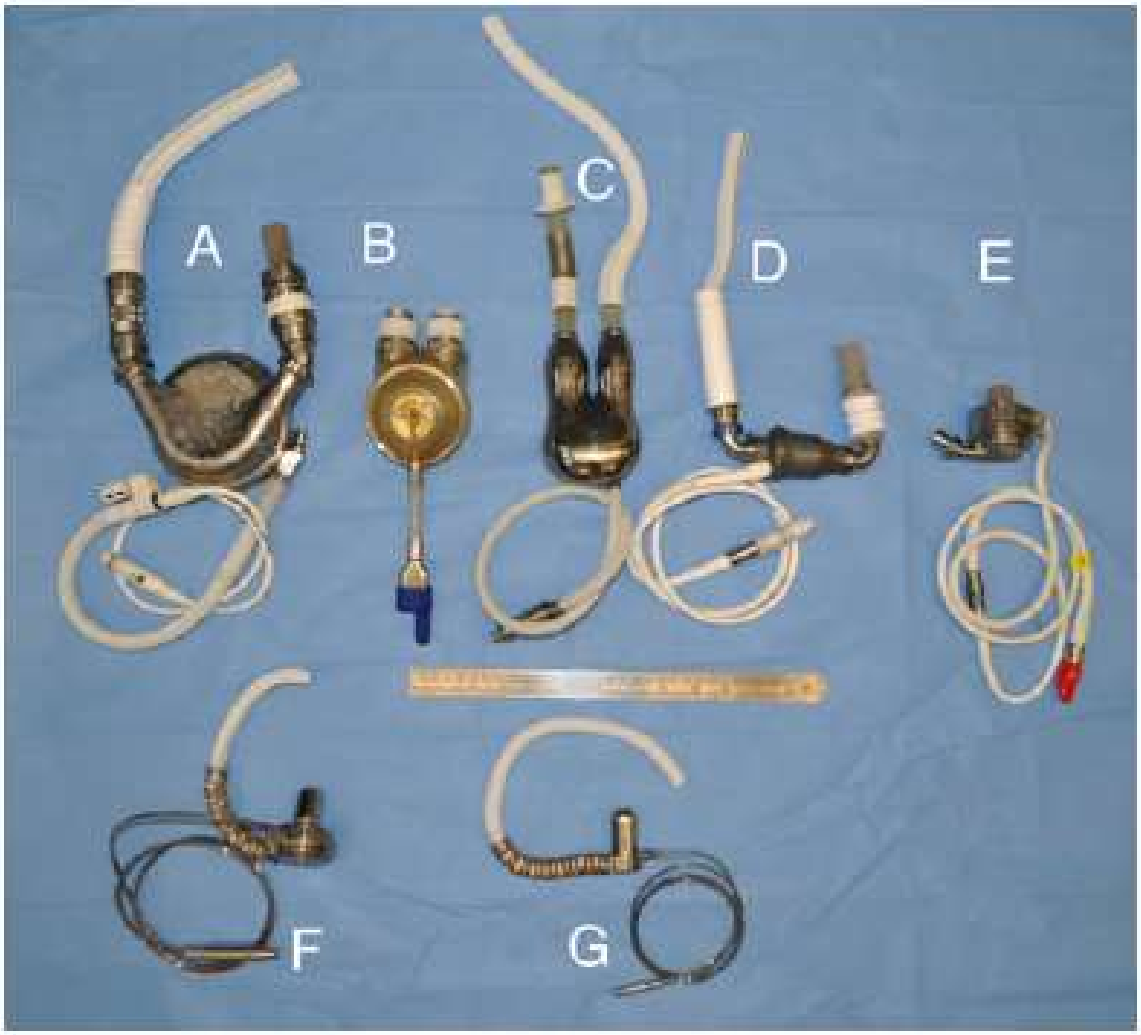
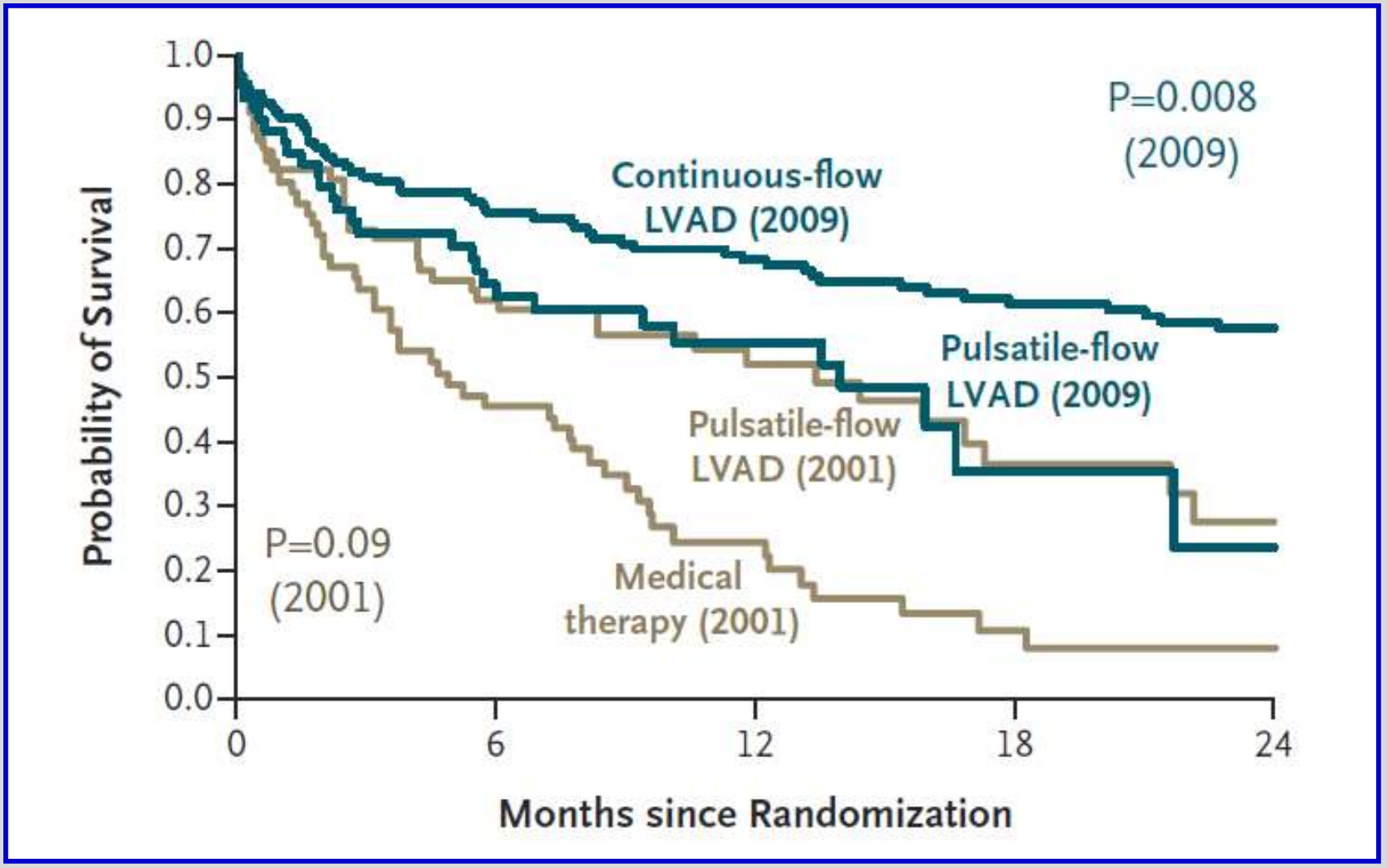


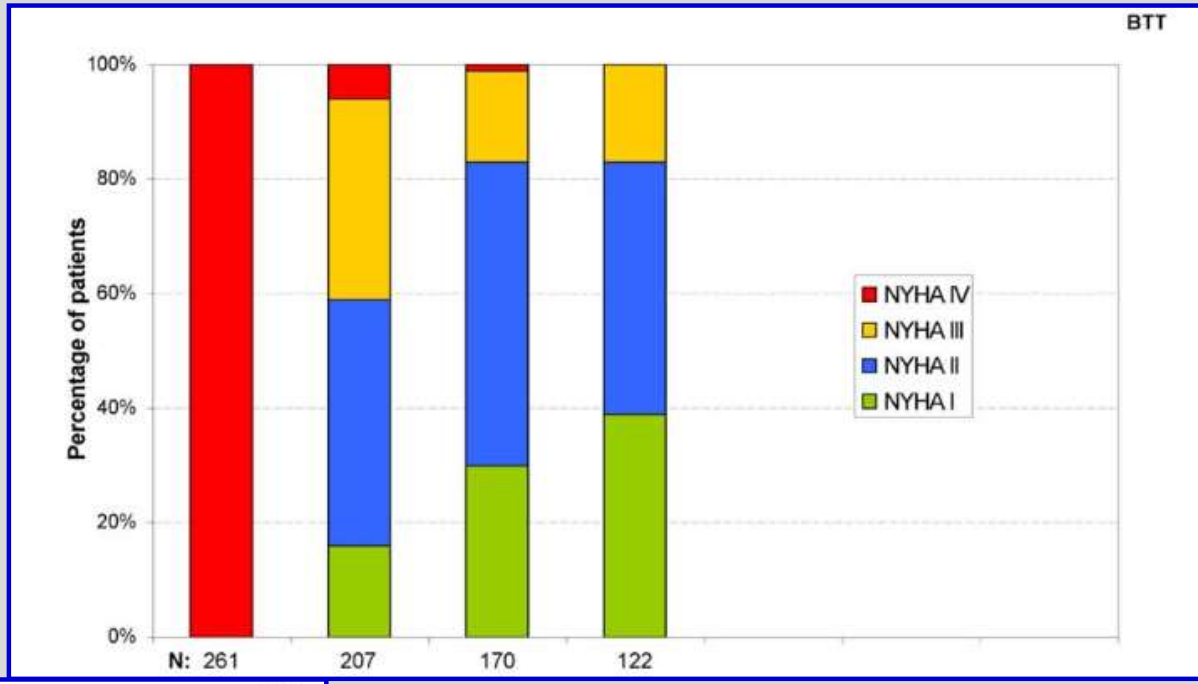

**Figure 1** The progression of miniaturization of left ventricular assist devices. Adapted from Giridharan *et al.* and reproduced with permission from John Wiley and Sons.[11] (*A*) HeartMate XVE, (*B*) Thoratec PVAD, (*C*) Thoratec IVAD, (*D*) HeartMate II, (*E*) HeartMate III, (*F*) HeartWare HVAD, and (*G*) HeartWare MVAD.

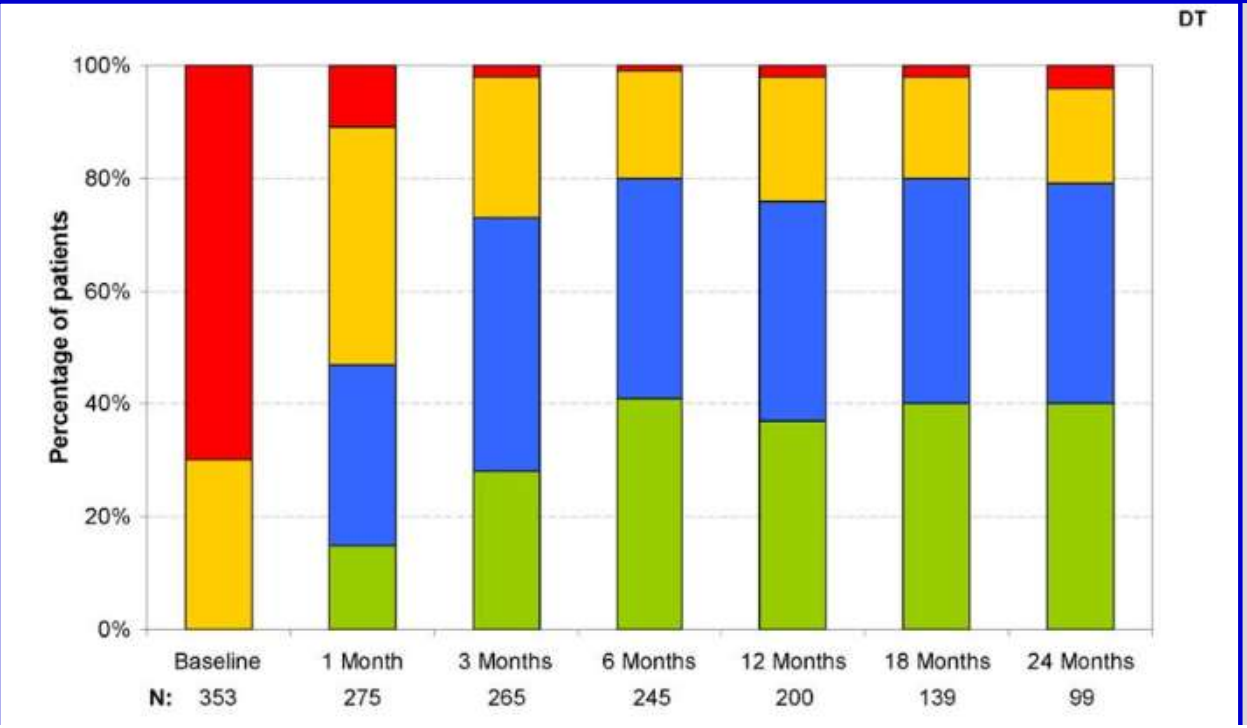
# VAD: Survival




*NEJM 2009; 361:2241-2251*

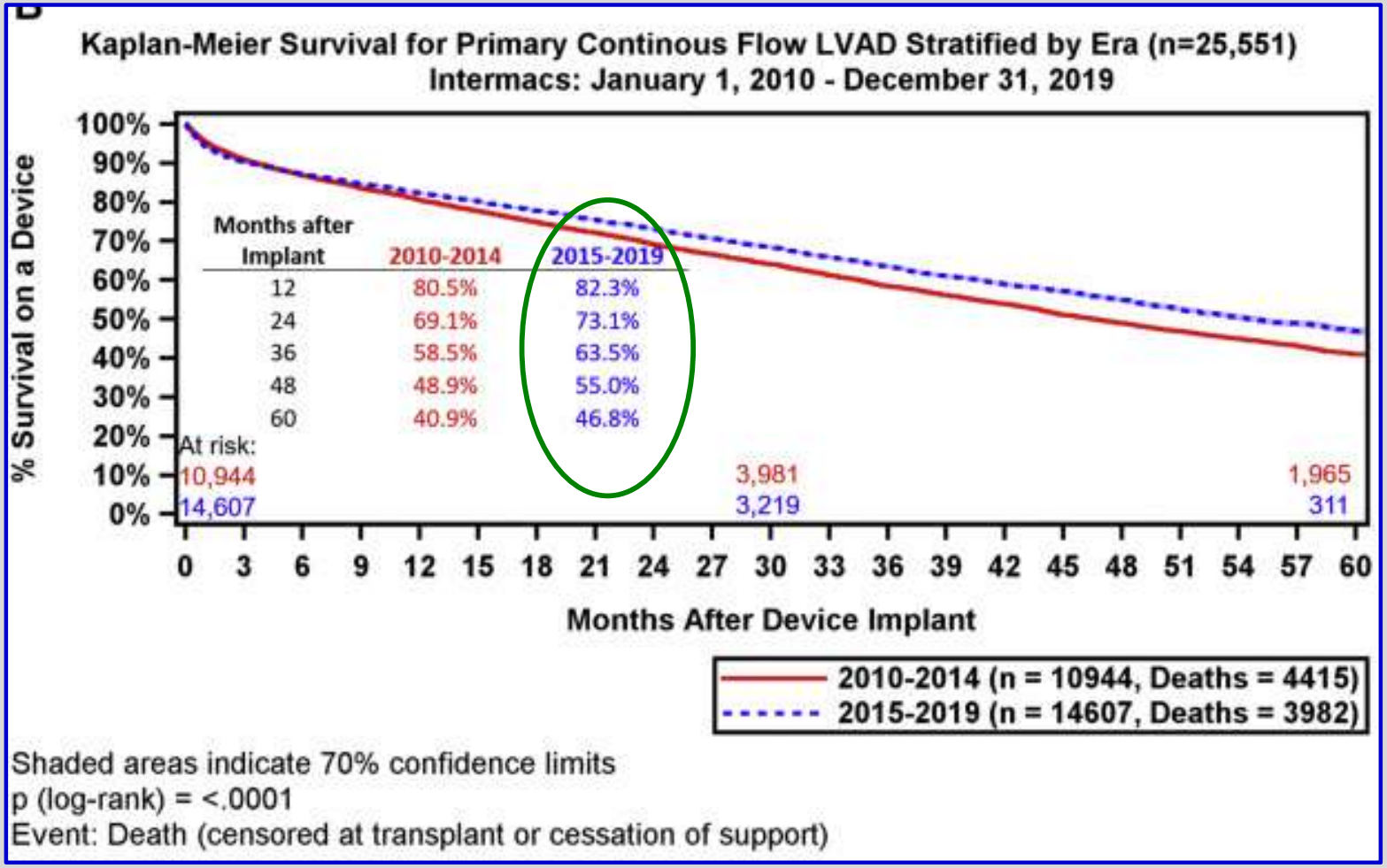
# Functional Status



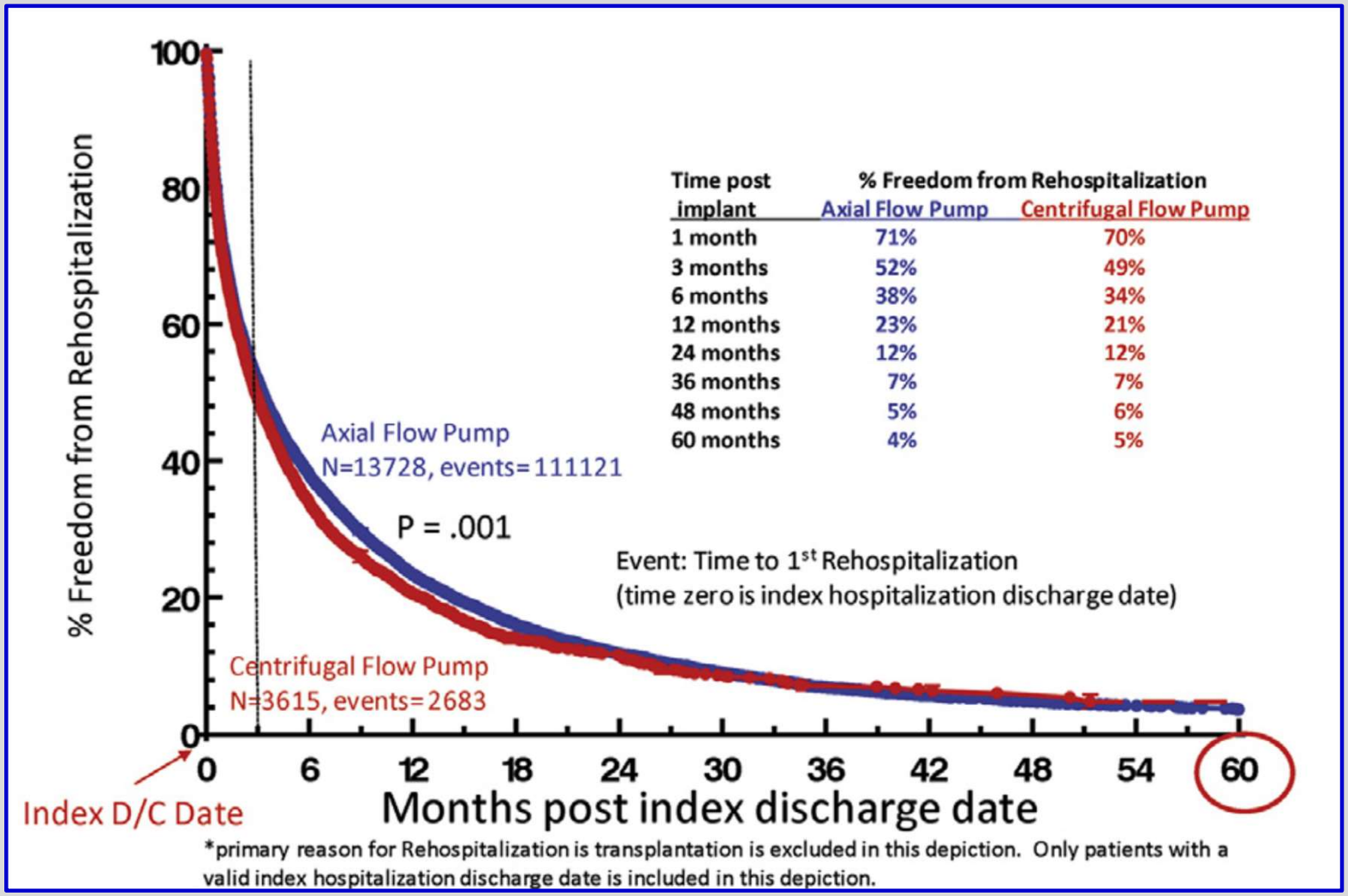

*NEJM 2009;361:2241-51*

# VAD: Survival




*Ann Thorac Surg 2021;111:778-92*

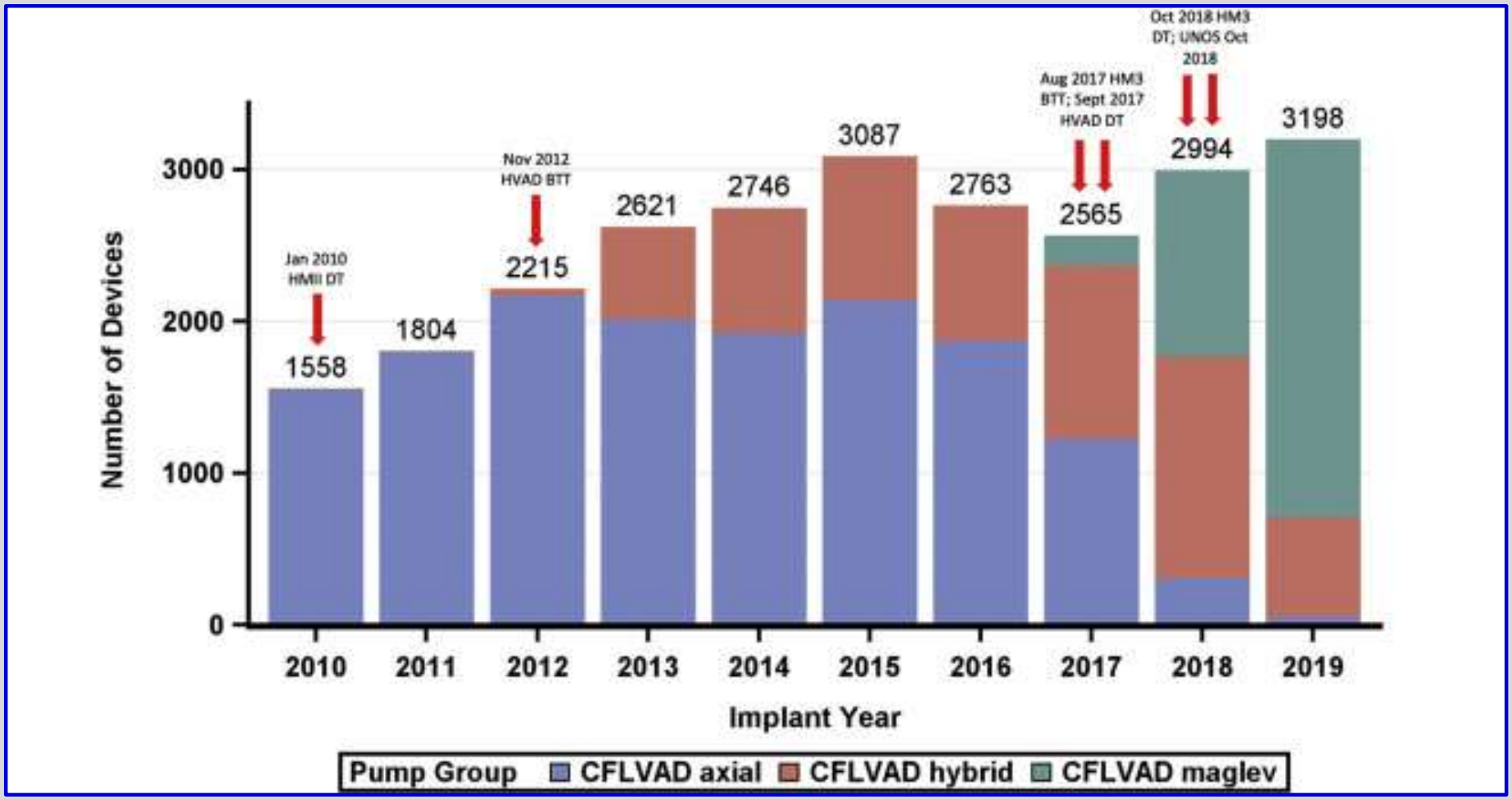
# VAD: Freedom from Rehospitalization




| Time post implant | % Freedom from Rehospitalization | |
|---|---|---|
| | Axial Flow Pump | Centrifugal Flow Pump |
| 1 month | 71% | 70% |
| 3 months | 52% | 49% |
| 6 months | 38% | 34% |
| 12 months | 23% | 21% |
| 24 months | 12% | 12% |
| 36 months | 7% | 7% |
| 48 months | 5% | 6% |
| 60 months | 4% | 5% |

*primary reason for Rehospitalization is transplantation is excluded in this depiction. Only patients with a valid index hospitalization discharge date is included in this depiction.

*JHLT 2019;38:114–126*



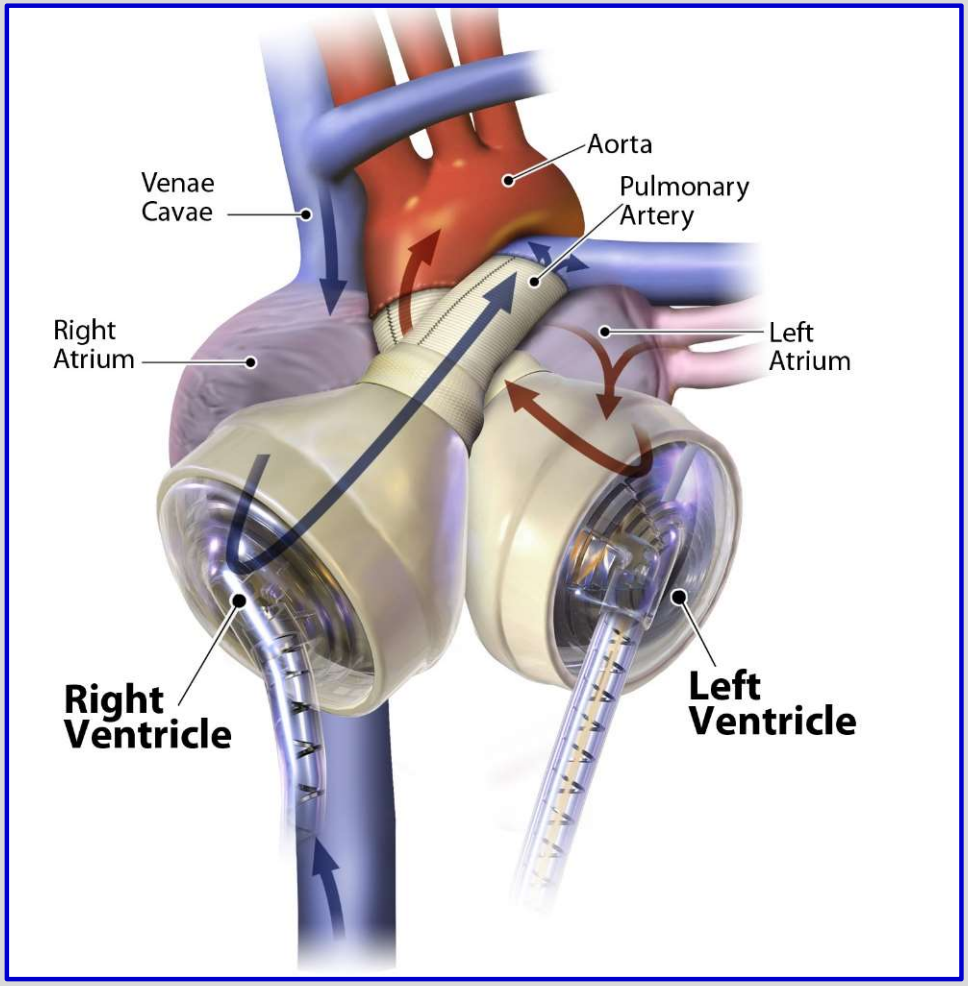

*Ann Thorac Surg 2021;111:778-92*

# VAD: AE CnF LVAD

| Adverse Event (percentage) | Early (≤ 90 days) | Late |
|---|---|---|
| Rehospitalization | 37.0 | 65.9 |
| Major Bleeding | 22.4 | 22.7 |
| GIB | 11.7 | 16.5 |
| CVA | 6.3 | 10.4 |
| Device Malfunction | 2.5 | 8.0 |
| Pump Thrombus | 3.6 | 8.8 |
| Infection | 23.2 | 31.9 |

*Ann Thorac Surg 2021;111:778-92*

# Total Artificial Heart




*Circulation: Heart Failure. 2018;11:e004905*

- Bridge to Heart Transplant
- FDA approval: Oct 15, 2004

  - Two Sizes: 70cc [9.5 L/min] and 50cc [7.5 L/min]

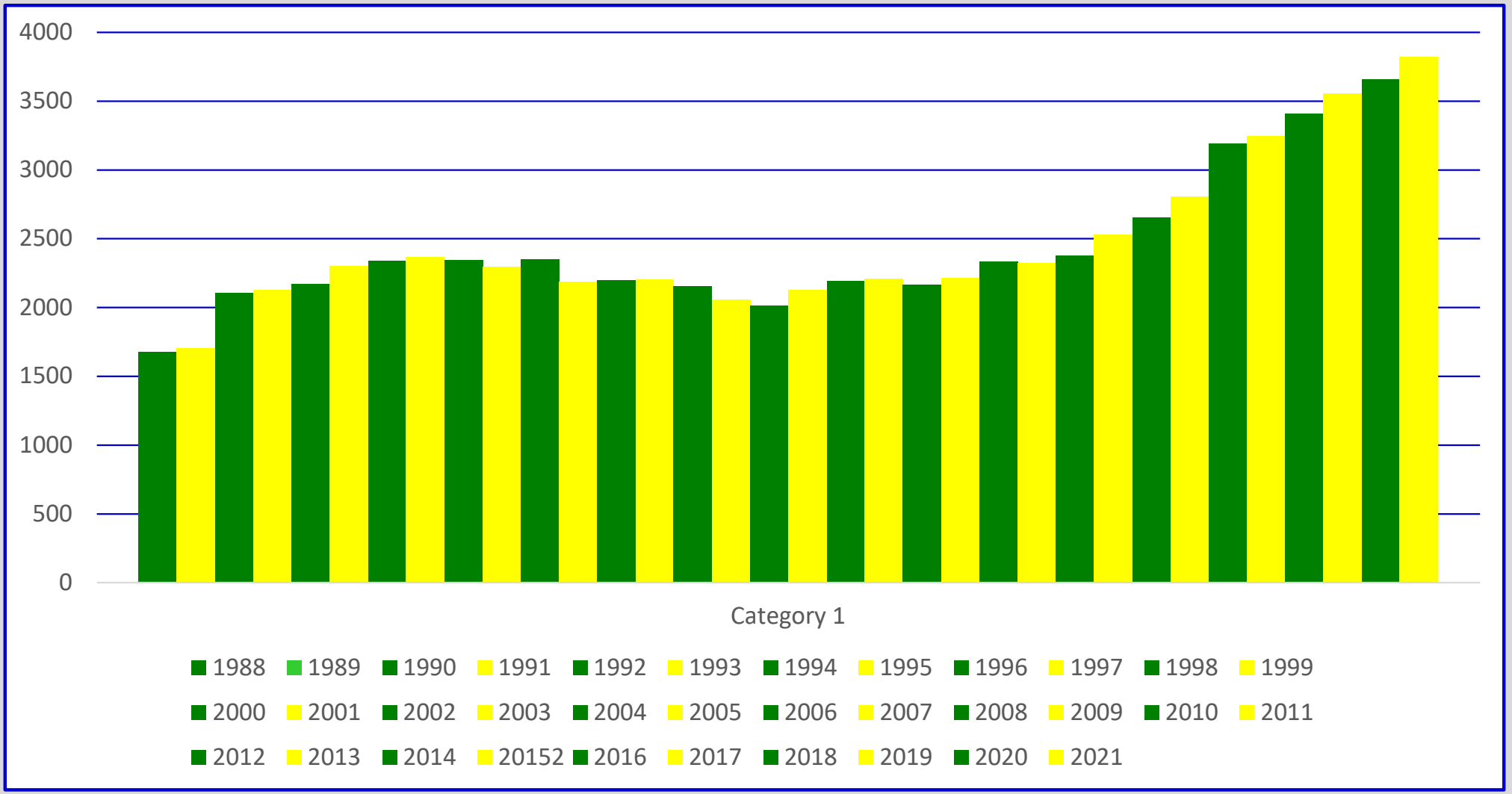
  - Companion 2(C2) Driver
  - Freedom Driver: 13.5 pounds

  - Trial: Destination Therapy


*NEJM. 2004;351:859–67*

# Heart Transplantation

# U.S. Transplants Performed : January 1, 1988 - February 28, 2022




*Based on OPTN data as of March 31, 2022*

# Donor and Recipient Characteristics

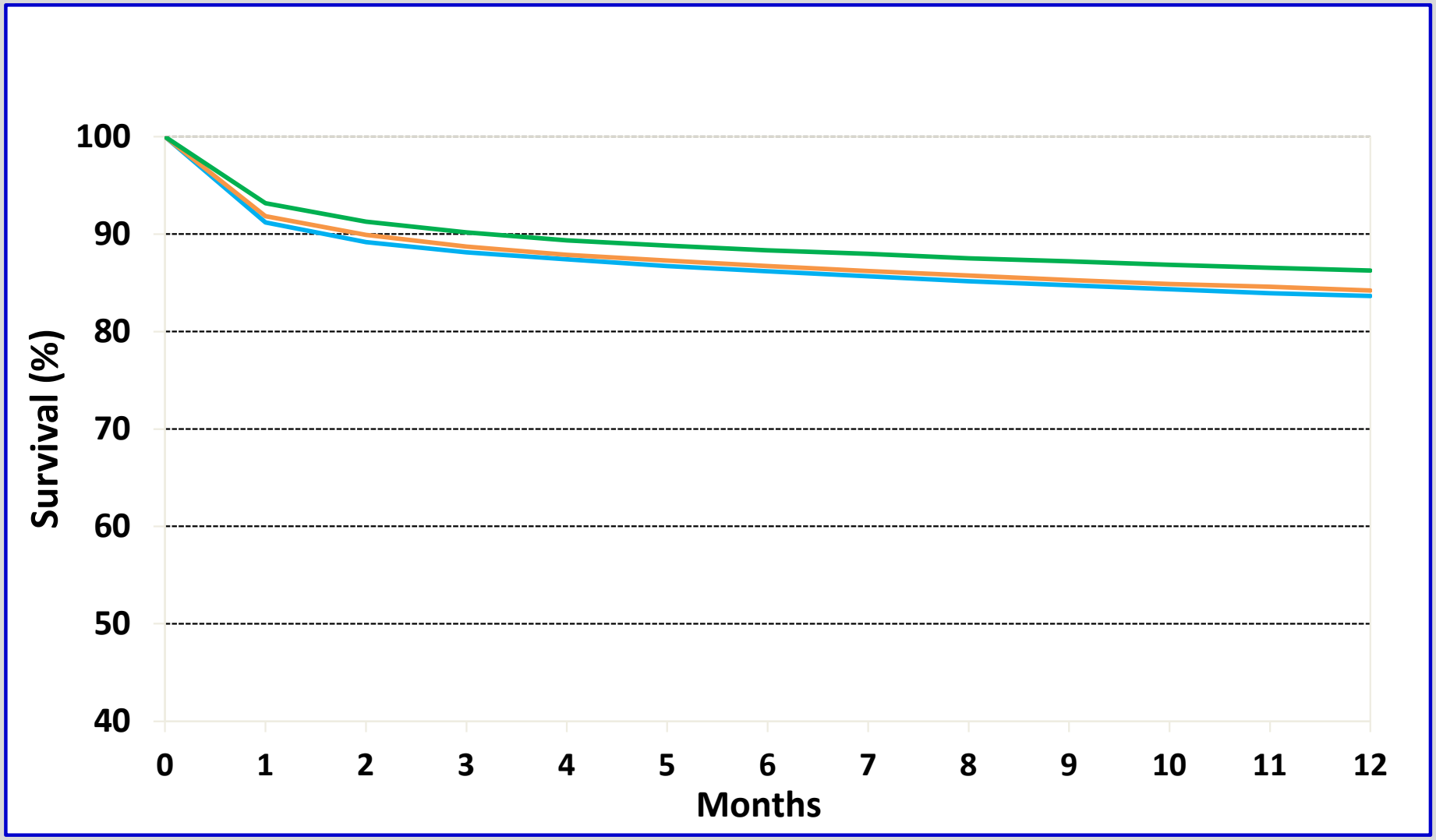
| | 1992-2003 (N = 48,388) | 2004-2008 (N = 17,666) | 2009-6/2015 (N = 24,474) | p-value |
|---|---|---|---|---|
| Pre-operative support (multiple items may be reported) | | | | |
| Hospitalized at time of transplant | 59.0% | 46.4% | 44.1% | <0.0001 |
| On IV inotropes | 54.6%[1] | 44.6% | 39.4% | <0.0001 |
| Ventilator | 3.3% | 3.0% | 2.1% | <0.0001 |
| IABP | 6.4% | 7.0% | 6.4% | 0.1497 |
| ***Mechanical circulatory support*** | 22.2%[2] | 26.0% | **44.7%** | <0.0001 |
| ***LVAD*** | 20.1%[2] | 22.2% | **38.1%** | <0.0001 |
| RVAD | - | 4.4%[3] | 3.2% | <0.0001 |
| TAH | 0.5%[2] | 0.5% | 1.4% | <0.0001 |
| ECMO | 0.3%[4] | 0.9% | 1.3% | <0.0001 |

[1] **Based on 4/1994-2003 transplants.**
[2] **Based on 11/1999-2003 transplants.**
[3] **Based on 2005-2008 transplants.**
[4] **Based on 5/1995-2008 transplants.**

*JHLT 2016; 35(10): 1149-1205*

# Kaplan-Meier Survival within 12 months by Era

## Transplants: January 2000 – June 2017

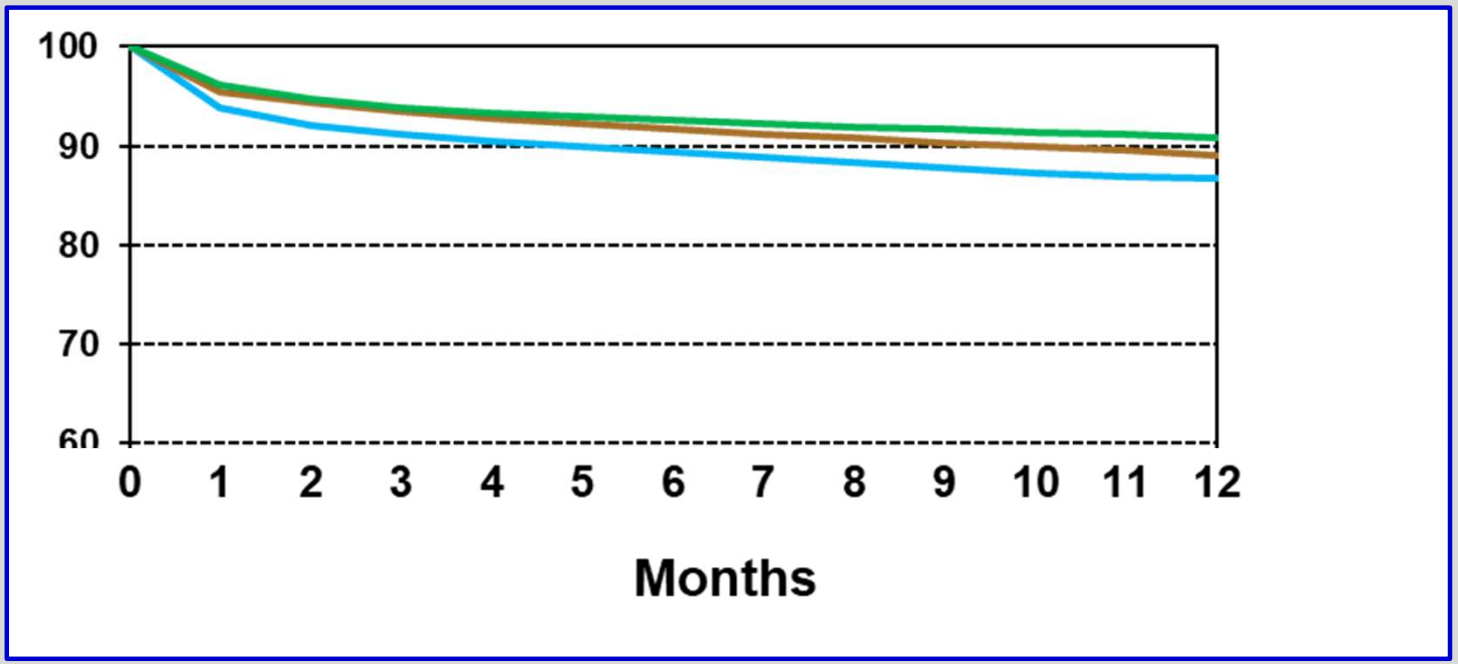



2000-2005 (N=21,600)
2006-2011 (N=22,422)
2012-2017 (N=23,202)

*JHLT 2021;40(10);1023-1072*

# Kaplan-Meier Survival within 12 months in North America

## Transplants: January 2000 – June 2017

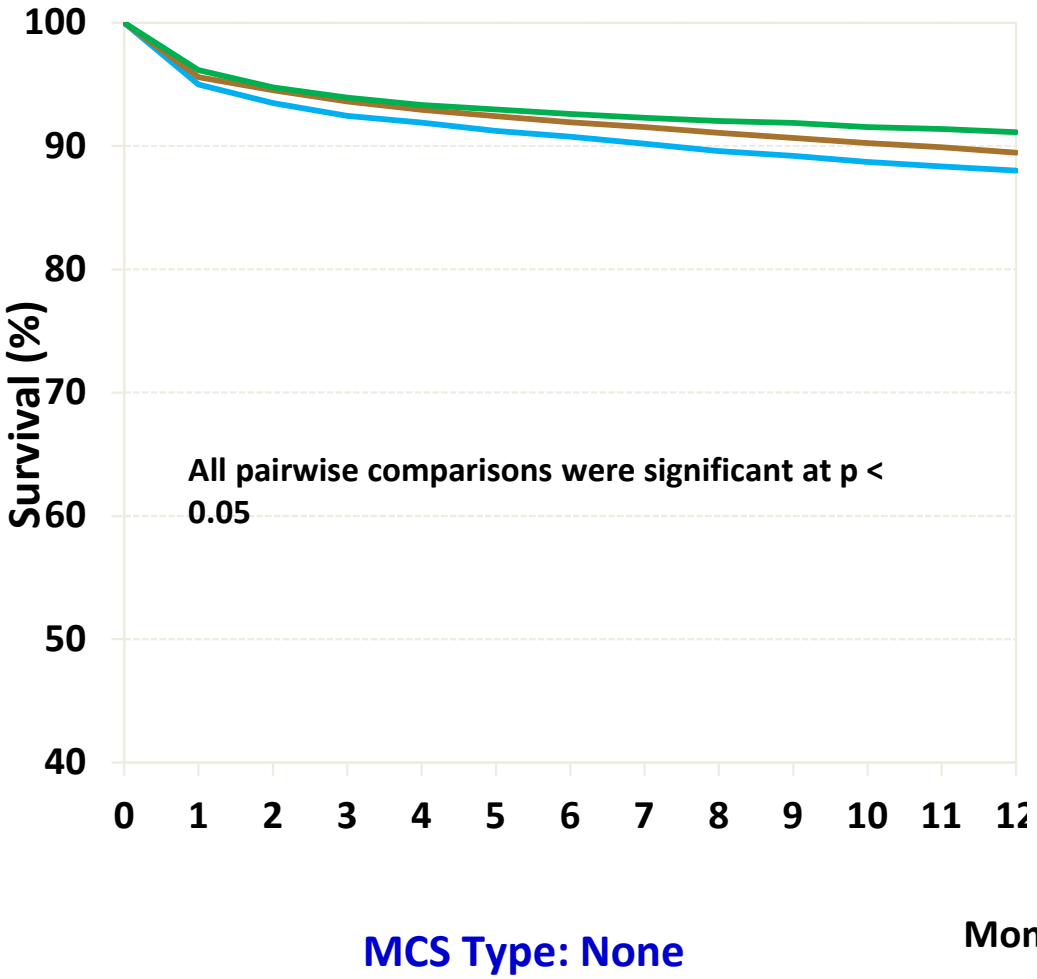


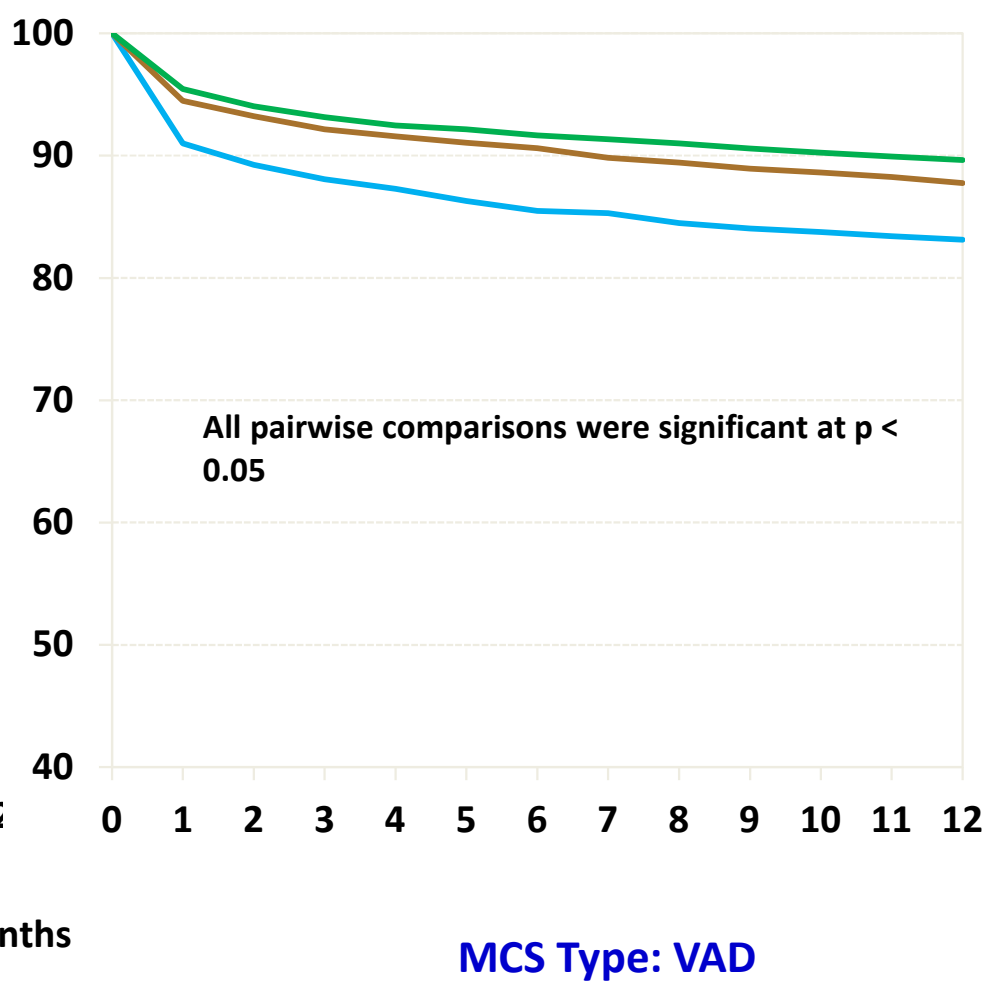

2000-2005
2006-2011
2012-2017

*JHLT 2021;40(10);1023-1072*

# Kaplan-Meier Survival within 12 months by Recipient MCS and Era

## Transplants: January 2000 – June 2017




2000-2005 (N=21,600)

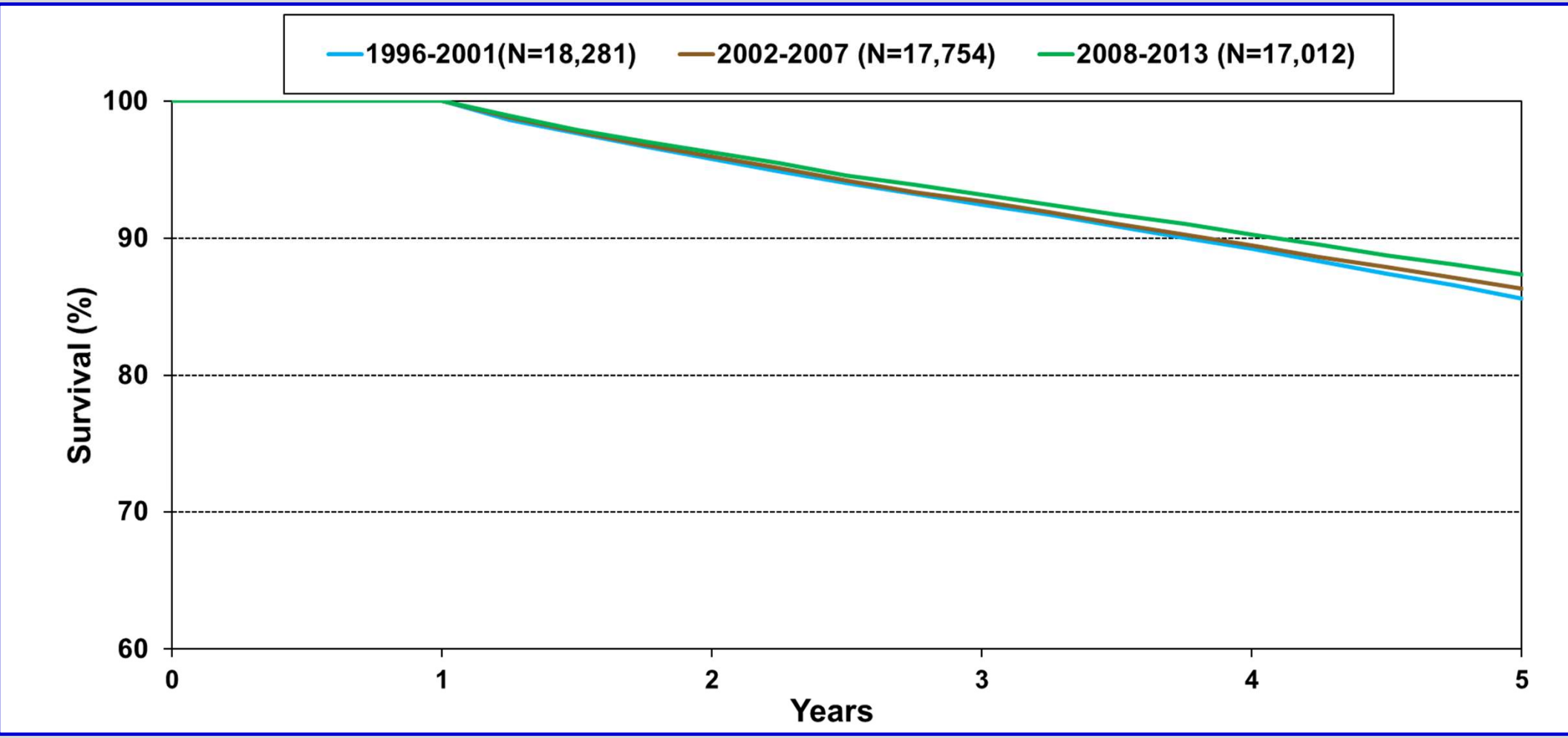
2006-2011 (N=22,422)

2012-2017 (N=23,202)

*JHLT 2021;40(10);1023-1072*

# Kaplan-Meier Survival within 5 years by Era

## Transplants: January 1996 – June 2013




*JHLT 2021;40(10);1023-1072*


# Candidacy for Advanced Heart Failure Therapy

# Contraindications for Advanced Therapy

- Systemic Illness with life expectancy < 2 years
- Severe lung disease
- Severe diabetes with end organ damage (≥ Stage IV CKD)
- Severe peripheral vascular disease
- Severe liver disease (cirrhosis)
- Active mental illness/lack of psychosocial support

# Transplant Specific Evaluation Concerns

- Pulmonary hypertension problematic
  - Cannot have irreversible pulmonary hypertension
- Age cutoffs more strict
  - Generally must be < 70
- Obesity (BMI > 35 - 38)
- Underlying infection
- Uncontrolled Diabetes with end-organ failure

# LVAD Specific Evaluation Concerns

- Right ventricular dysfunction
  - VAD can contribute to RV failure
- Significant renal disease
  - Practically difficult to dialyze patients with VAD
- Immuno-compromised patient
  - Risk of driveline infection is high
- Patients at high risk for bleeding
  - VAD increases risk of bleeding

# Advanced HF Referral Process

- Referral Coordinator
  - Ms Ebony
  - Call MD directly anytime
- Our Team will start the coordinated transfer of care within 24 hours
  - Following records:
    - Patient Information/Face Sheet/Last office visit note/TTE report (+/- images)/Heart Cath report (+/- images)/Previous Surgical reports/Latest Labs

# Advanced Heart Failure Team

## Cardiovascular Surgery

- Kevin Brady, MD
- Ken Ashton, MD
- Linda McLaughlin, NP

## Cardiovascular Medicine

- Raj Vijayakrishnan, MD
- Andrew Boshara, MD
- Linda Staley, NP
- Kelly Wesselhoff, NP
- Cathy Garcia, NP
- Cameron Scott, RN

## Administration

- Brady Krushelniski (VP)
- Ms Ebony (Coordinator)

## Multidisciplinary Team Members

- Intensivists
- Palliative Care
- VAD specific Quality team members
- Perfusion Services
- 4T-ICU and 7T-Intermediate Care Nurse Managers
- Pharmacy
- Dietary
- Physical / Occupational Therapy
- Social Work
- Psychiatry/Psychology

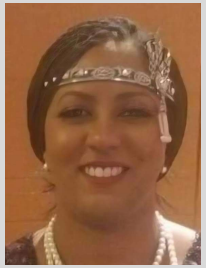
## Support Departments

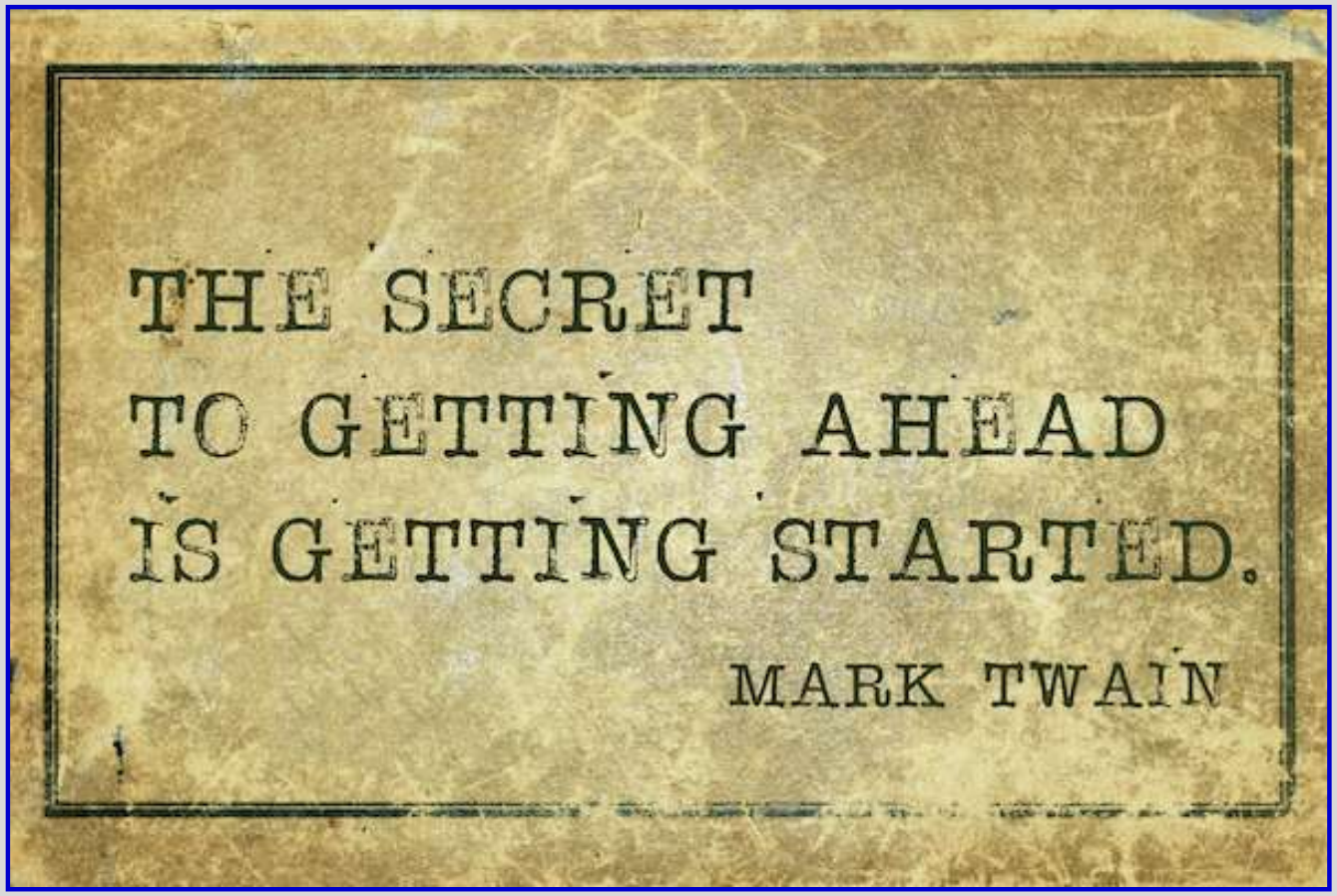
- Cardiopulmonary/Diagnostics
- Cardiac Catheterization Lab
- Operating Room
- PACU
- Hospital and NTI Quality Departments
- Hospital Chief Medical Officer

# SJHMC Team


Center for Advanced Heart Failure
at Norton Thoracic Institute







THE SECRET
TO GETTING AHEAD
IS GETTING STARTED.
MARK TWAIN

# Thank You