Advanced Heart Failure Therapies 2017: Diuretics to LVAD and Everything in Between

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Outline

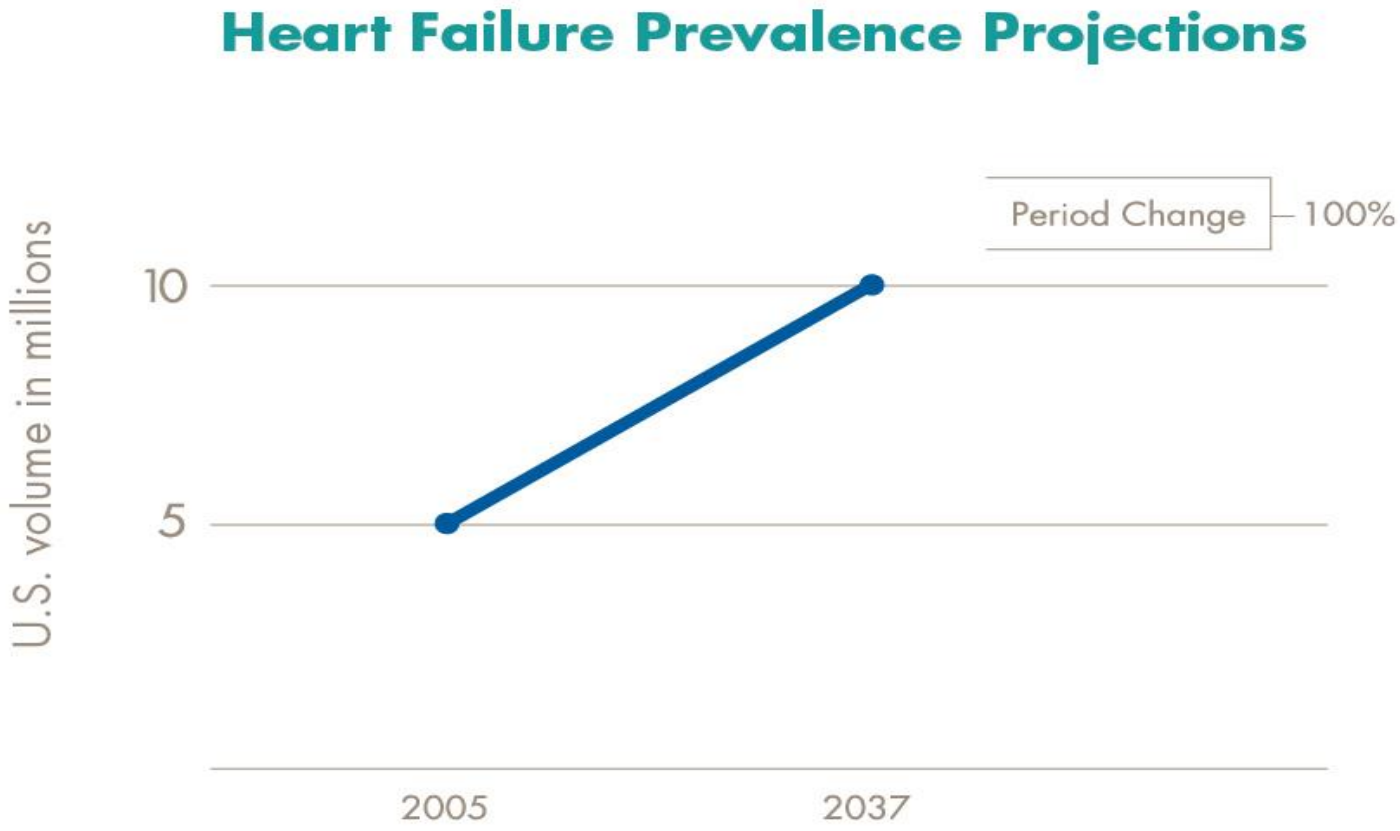
- Definition and Prevalence of Heart Failure
- Progression of Disease
- HF Risk Stratification
- Advanced Therapies
  - Inotrope
  - LVAD
  - Transplant

Heart Failure Prevalence

- Heart failure affects over 5.3M patients in the United States [1]
- 300,000-800,000 Americans have advanced heart failure, defined as patients with left ventricular systolic dysfunction experiencing symptoms limiting daily activity with poor exercise capacity, despite maximal therapy [2]
- It is difficult to determine when stable Class III will progress to advanced staged heart failure, Class IV [3]
- Over 280,000 patients die of heart failure each year [1]

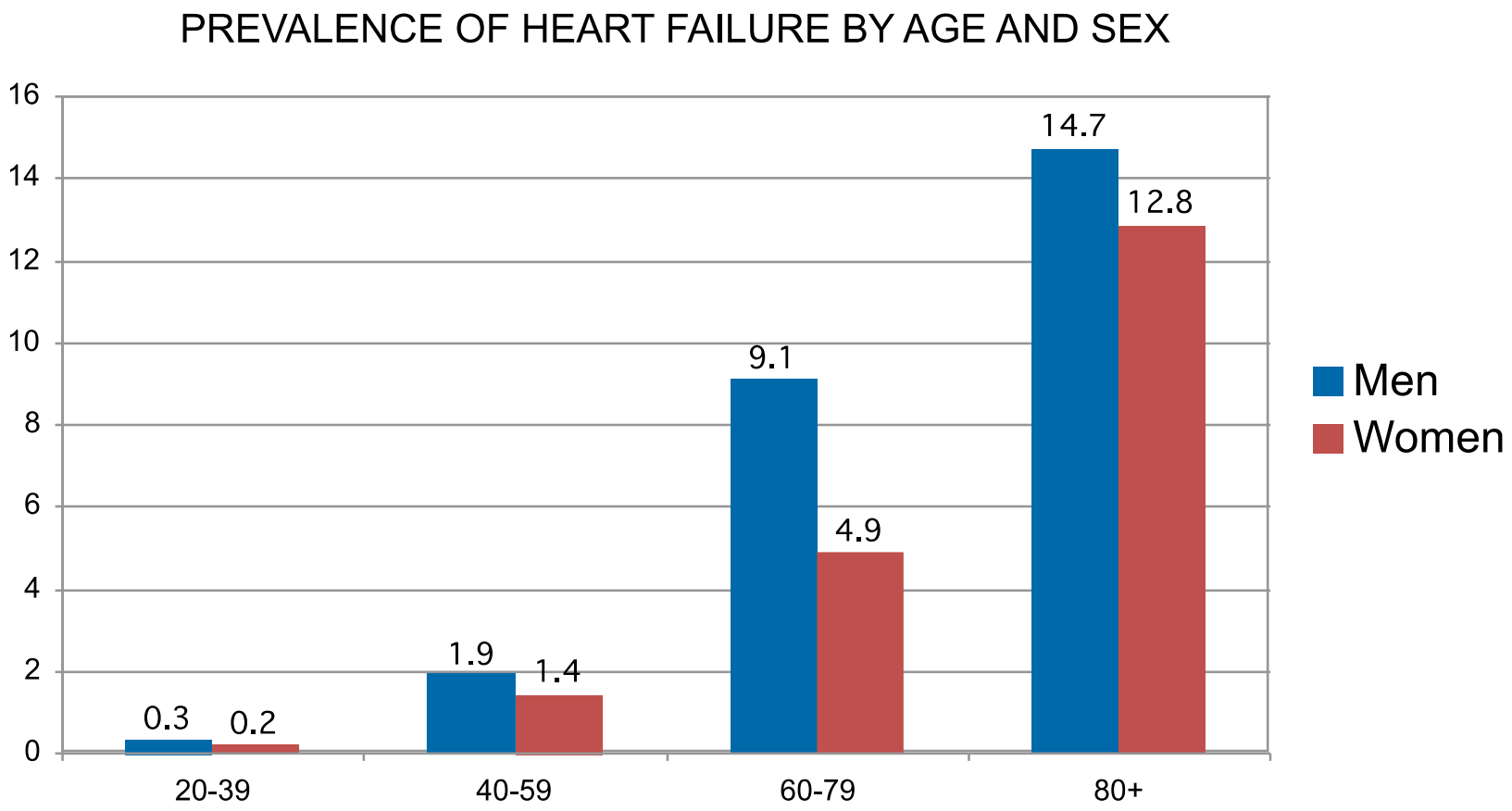
1 Lloyd-Jones D, Adams R, Carnethon M, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics 2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2009;119(3):480-6.
2 Adams KF, Zannad F. Clinical definition and epidemiology of advanced heart failure. *Am Heart J* 1998;135:S204-S215.
3 Russell SD, Miller LW, Pagani FD. Advanced heart failure: a call to action. Congest Heart Fail. 2008; 14: 316-321.

Heart Failure Expected to Become More Common as Population Ages



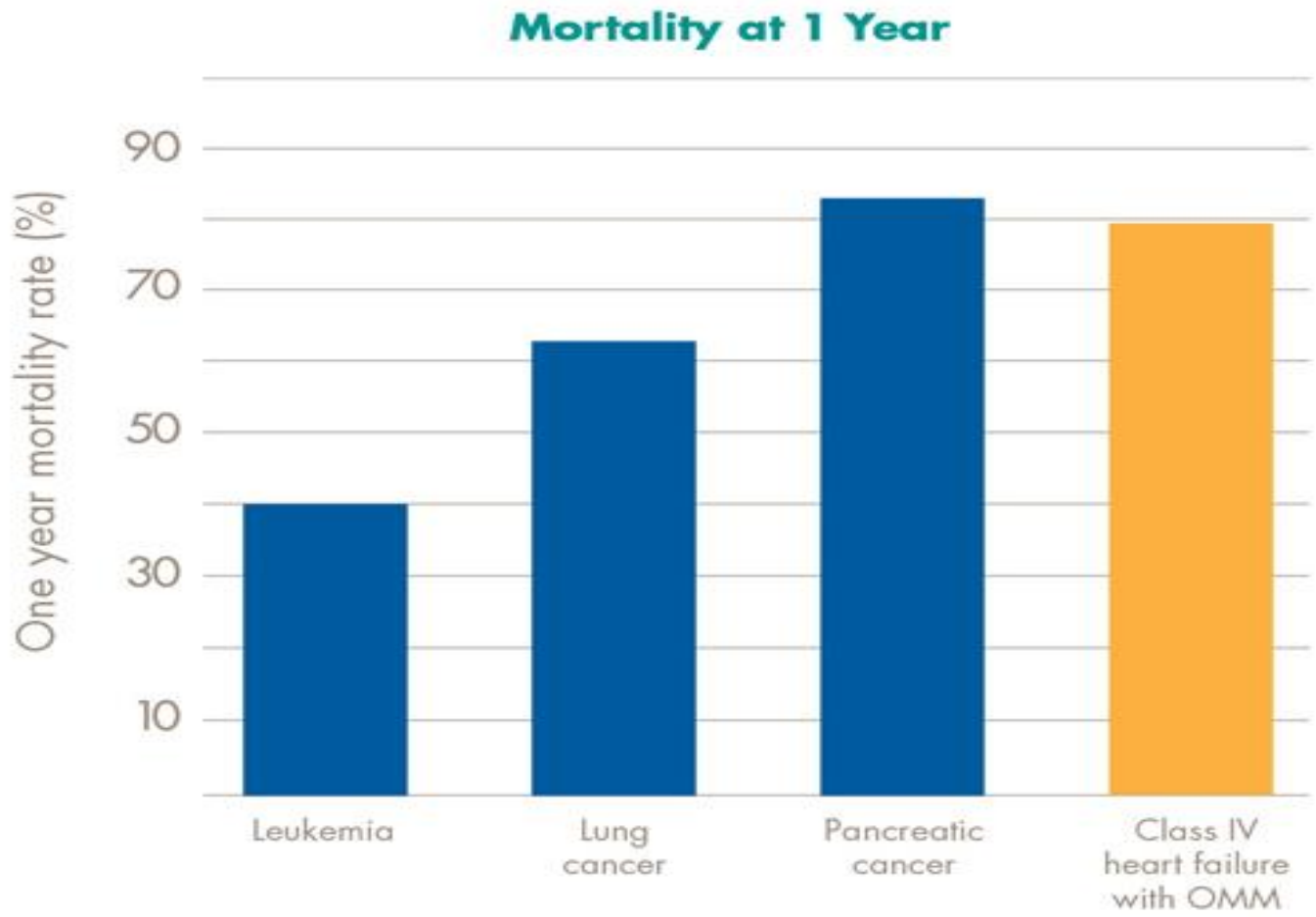
Outlook for Heart Failure: Five-year Technology and Business Assessment. The Advisory Board; 2007.

Heart Failure Prevalence Increases with Age



Heart Failure Statistics. American Heart Association Web site. http://www.americanheart.org/presenter.jhtml?identifier=1200026. Accessed January 12, 2010.

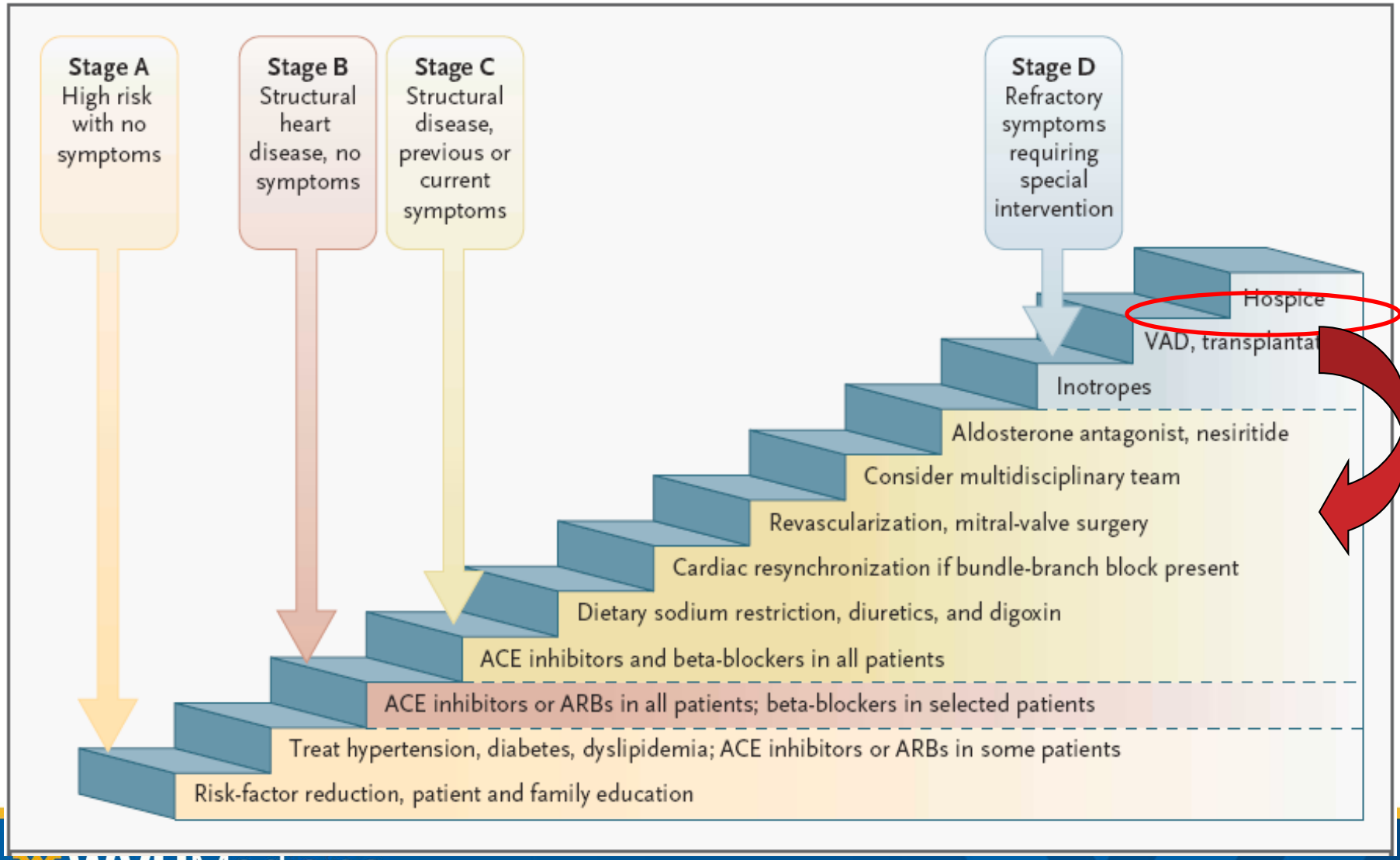
Projected Mortality for Advanced Heart Failure Exceeds Other Terminal Diseases



Data on file, Thoratec Corporation.
Rose EA, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. *N Engl J Med.* 2001 Nov 15;345(20):1435-43.

How do we define End Stage Heart Failure?

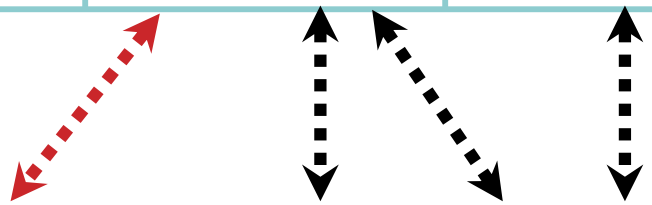
ACC/AHA Staging of Heart Failure



Jessup M, Brozena S. *N Engl J Med* 2003;348:2007-18.

Classification of HF: Comparison Between ACC/AHA HF Stage and NYHA Functional Class

ACC/AHA HF Stage	A	B	C	D
	High risk of developing HF	Structural heart disease but without symptoms of HF	Structural heart disease with HF symptoms, either *prior* or *current*	Refractory HF requiring specialized interventions



NYHA Functional Class	I	II–III	IV
	Asymptomatic HF No symptoms	Mild and Moderate HF Symptoms upon mild to moderate exertion	Severe HF Symptoms at rest

ELSEVIER

European Journal of Heart Failure 9 (2007) 684–694

The European Journal of Heart Failure

www.elsevier.com/locate/ejheart

Review

Advanced chronic heart failure: A position statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology

Marco Metra [a,*], Piotr Ponikowski [b], Kenneth Dickstein [c], John J.V. McMurray [d], Antonello Gavazzi [e], Claes-Hakan Bergh [f], Alan G. Fraser [g], Tiny Jaarsma [h], Antonis Pitsis [i], Paul Mohacsi [j], Michael Böhm [k], Stefan Anker [l,m], Henry Dargie [n], Dirk Brutsaert [o], Michel Komajda [p]
on behalf of the Heart Failure Association of the European Society of Cardiology

HFA/ESC: Advanced Heart Failure

1. Severe symptoms of HF with dyspnoea and/or fatigue at rest or with minimal exertion (NYHA functional class III or IV)
2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral oedema) and/or of reduced cardiac output at rest (peripheral hypoperfusion)
3. Objective evidence of severe cardiac dysfunction, shown by at least one of the following:
    a) A low LVEF (<30%),
    b) A severe abnormality of cardiac function on Doppler-echocardiography with a pseudonormal or restrictive mitral inflow pattern [5];
    c) High LV filling pressures (mean PCWP>16 mm Hg, and/or mean RAP>12 mm Hg by pulmonary artery catheterisation) [6],
    d) High BNP or NT-ProBNP plasma levels, in the absence of non-cardiac causes.

HFA/ESC: Advanced Heart Failure

4. Severe impairment of functional capacity shown by one of the following:
    a) Inability to exercise,
    b) 6-MWT distance <300 m [7] or less in females and/or patients aged ≥ 75 years [8]
    c) peak VO_2 <12 to 14 ml/kg/min [9,10]
5. History of ≥ 1 HF hospitalisation in the past 6 months
6. Presence of all the previous features despite "attempts to optimise" therapy including diuretics, inhibitors of the renin–angiotensin–aldosterone system, and beta-blockers, unless these are poorly tolerated or contraindicated, and CRT, when indicated.

HF RISK STRATIFICATION

Characteristics of who dies with heart failure and a low EF

- All patients seen in HF clinic between 1/1/2000 and 10/20/2003 who subsequently died
- 160 pts
- 80 died as outpatients
- 21% died suddenly

J Cardiac Failure 2006;12:47

Death with HF

	All deaths (n=160)	Outpt deaths (n=80)	Inpt deaths (n=80)
Medications			
ACE-I (%)	55	58	53
ACE intolerant (%)	35	34	36
ARB (%)	7	5	9
Loop diuretic (%)	91	90	92
Spironolactone (%)	32	30	34
Beta-blocker (%)	38	34	43
Laboratories			
Na (mmol/L)	135	135	134
BUN (mg/dL)	62	52	69
Cr (mg/dL)	2.2	2.1	2.4
Hospitalized - past 6 mos (%)			
0	26	26	27
1	32	38	27
2+	42	37	46

Teuteberg et al. J Card Fail 2006;12:47

Death with HF

Characteristic	All deaths (n=160)	Outpt deaths (n=80)	Inpt deaths (n=80)
CHF clinic (mos)	24.7	23.1	26.6
CHF duration (yrs)	5.0	4.6	5.4
Age (yrs)	59.9	57.9	61.1
Male (%)	74	75	74
NYHA III (%)	14	13	14
NYHA IV (%)	79	74	83
ICD (%)	37	30	46
CRT (%)	5	7	5
EF (%)	20	22	19

Deaths from 1/1/00-10/20/03

Teuteberg et al. J Card Fail 2006;12:47

Worrisome signals

- Symptoms
  - Refractory
  - At rest
- Recurrent admissions
- Medications
  - Intolerance or lower doses
    - ACE-I/ARBs
    - Beta blockers
  - Increasing diuretic doses
- Hypotension
- Laboratory
  - Renal insufficiency
  - Hepatic dysfunction
  - Hyponatremia
- Pulmonary Hypertension
- RV dysfunction
- Unresponsiveness to CRT
- Inotropes

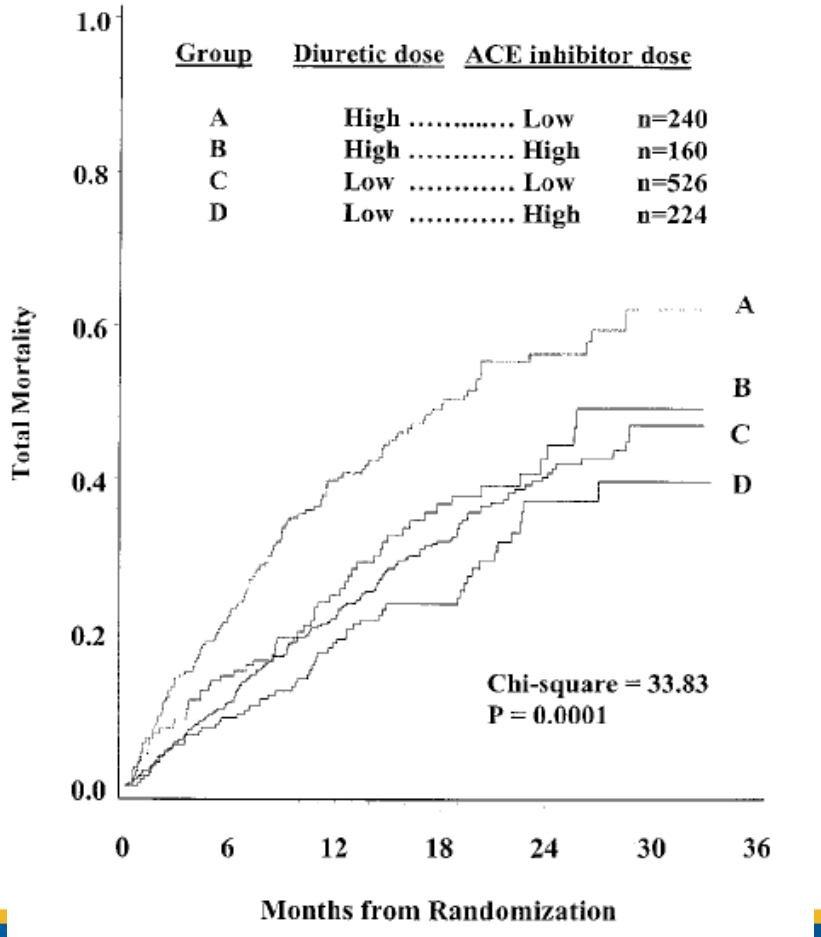
Inpatient risk studies

Author	n	Risk Factors	Survival (%) 1 year
Chin	257	BP < 100, DM, non sinus rhythm	
Alla	301	HR >100, Na < 134, Cr > 2.0, Age > 70, prior hosp	57.6
Cowie	220	Age, crackles, low BP, elevated Cr	62
Jong	38,702	Male, age, malignancy, renal, dementia, cerebrovasc dz, rheum, PVD, or pulmonary, ischemic etiology, DM	66.9
Bouvy	152	DM, Cr, NYHA III/IV, low BMI, low BP, edema	
Lee	4031	Age, low BP, high RR, high BUN, low Na	69.5
Kittleson	259	No ACE, low BP, low Na, Cr	
Felker	949	Age, low BP, NYHA IV, high BUN, low Na	
Fonarow	37,772	BUN > 43, SBP < 115, Cr > 2.75	
Rector	769	Age, low BP, low Hgb, low Na, high BUN	50
Rohde	779	SBP < 124, Cr > 1.4, BUN > 37, Na < 136, age > 70	

Outpatient Risk Studies

Study	n	Markers
Mahon	585	CrCl, 6MW < 262, low EF, recent admit, diuretic dose
Eshaghian	1354	Low EF, low Na, low Hg, high BUN/Cr, diuretic dose
Greenberg	4280	NYHA III/IV, HF admit, angina
Levy	1125	Diuretic dose, low BP, % lymph, Hgb < 16, ischemic CM, EF, low cholesterol, high uric acid/allopurinol, Na < 138, NYHA, age, male sex
Teuteberg	160	High BUN/Cr, low Na, low Hct, recent admit, no ACE/BB

Diuretic Doses



Diuretic

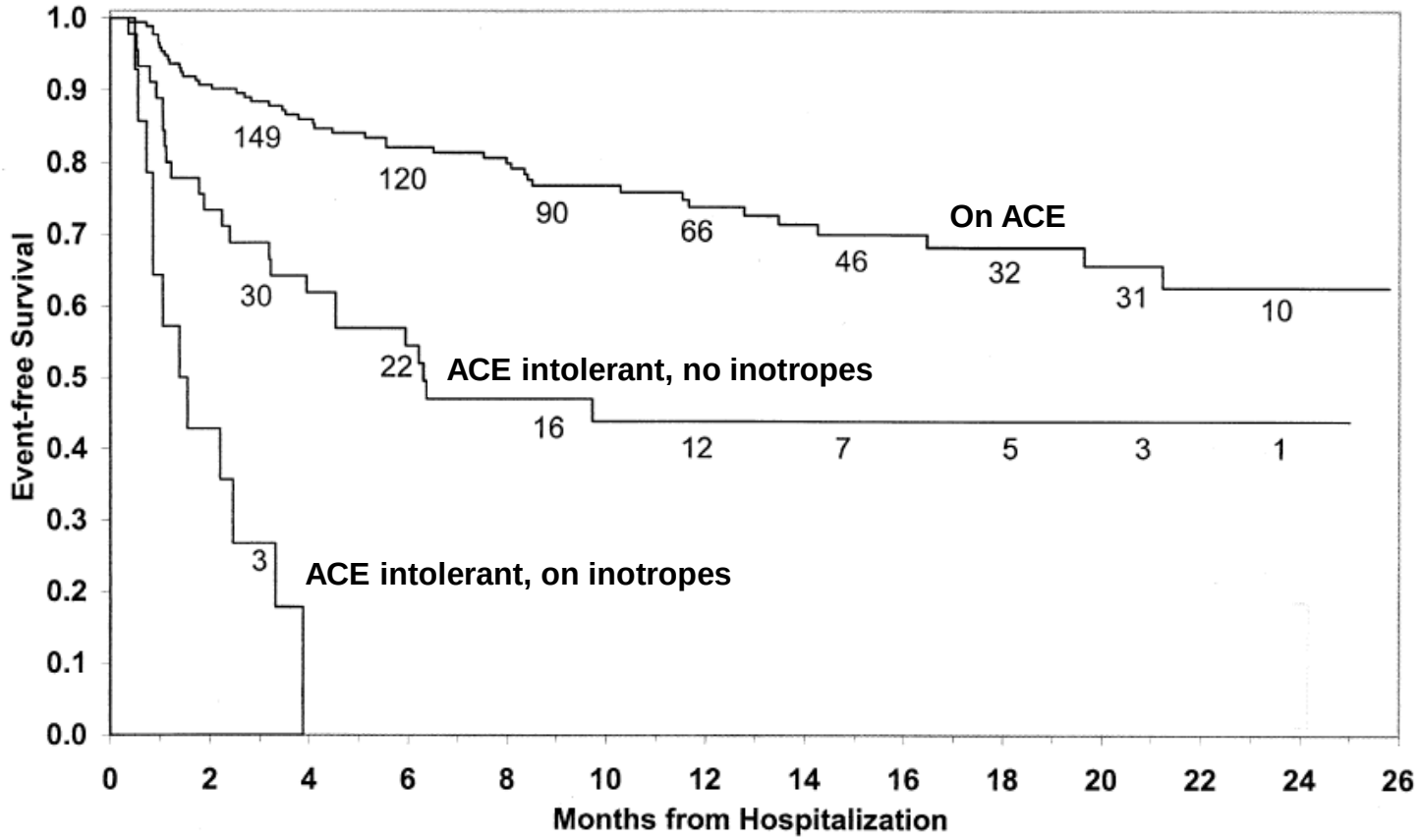
- High
  - Lasix > 80 mg/d
  - Bumex > 2 mg/d

ACE inhibitor

- High
  - Captopril > 75 mg/d
  - Enalapril > 10 mg/d
  - Lisinopril > 10 mg/d

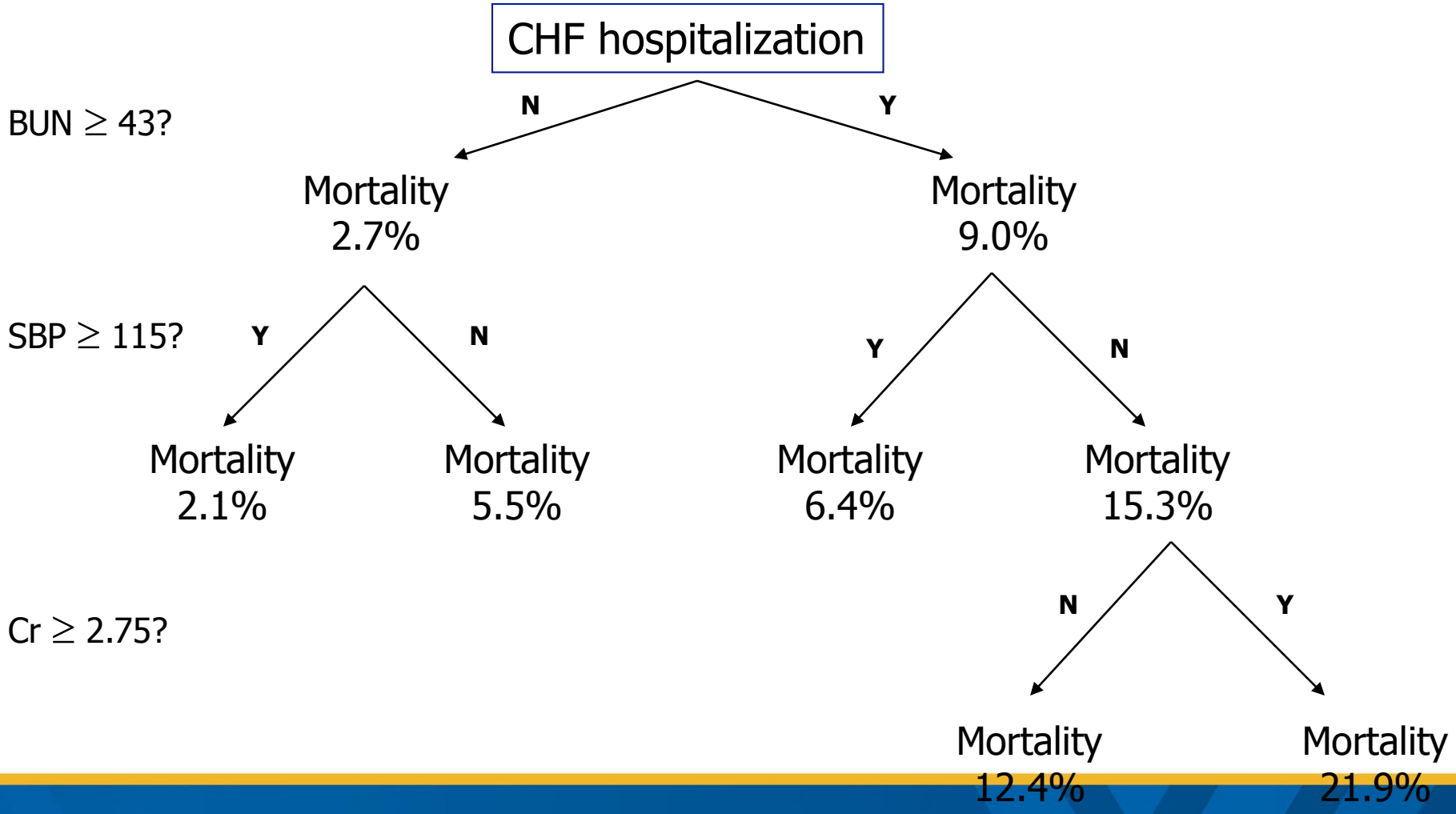
Neuberg et al. Am Heart J 2002;144:31-8.

Intolerance of ACE



KIttleson et al. J Am Coll Cardiol 2003;41:2029-35.

Renal function – ADHERE registry



Fonarow et al. JAMA 2005;293:572-80.

Advanced Therapies

- Define and explain advanced therapies including:
  - Inotrope
  - LVAD
  - Transplant
- Who is a candidate for advanced therapies
- What is the right time for advanced therapies

Inotrope Therapy

- What is the indication
- What is the outcome
- Long term risk vs Short term gain
- Monitoring Parameters
- Palliative care

Pharmacotherapy

Vasodilators
- Nitroglycerin
- Nesiritide
- Nitroprusside

Inotropes
- dobutamine
- milrinone
- isoproterenol

Vasopressors
- dopamine
- norepinephrine
- phenylephrine
- epinephrine
- vasopressin

Inotropes

- Dobutamine
- Milrinone
- Isoproterenol
- *Dopamine*
- *Norepinephrine*
- *Epinephrine*

Receptor Pharmacology

	α_1	α_2	β_1	β_2	DA
Dobutamine					
2-10 mcg/kg/min	+	0	++++	++	0
10-20 mcg/kg/min	++	0	++++	+++	0
Milrinone					
0.25-1 mcg/kg/min	0	0	++++ - ”like”	+++- “like”	0
Isoproterenol					
1-10 mcg/min	0	0	++++	++++	0

Hemodynamic Comparison

	HR	MAP	CI	SVR	PCWP
Dobutamine	↔ ↑	↓ ↑	↑	↔ ↓	↔ ↓
Milrinone	↔ ↑	↔ ↓	↑	↓	↓
Isoproterenol	↑	↔ ↓	↑	↓	↓

Dobutamine

- ↑ myocardial contractility and vasodilation
- Initial agent of choice for cardiogenic shock in pts w/ systolic BP > 80 mm Hg

Dobutamine

- Short half-life
- Greater ↑ CO & less arrhythmogenic than dopamine
- May exacerbate hypotension and tachydysrhythmias

Milrinone

- Phosphodiesterase inhibitor (↑ contractility and vasodilation)
- Reserved when other agents ineffective for cardiogenic shock
- Usually given without bolus

Milrinone

- Longer half-life
- May exacerbate hypotension and tachydysrhythmias
- Renal elimination
- Consider if patient on beta-blocker therapy

Milrinone: OPTIME-CHF trial

- Purpose
  - evaluate short-term use of milrinone and placebo on hospitalizations for cardiovascular (CV) events
- Design
  - prospective, randomized, double-blind, PC
- Study subjects (n = 949)
  - LVEF < 40%, inotrope/ vasopressor not essential

The OPTIME-CHF Investigators. JAMA 2002;287:1541-47.

Milrinone: OPTIME-CHF trial

- Outcomes
  - primary: total number of days hospitalized for CV causes within 60 days of randomization
  - milrinone vs. placebo: mean 12.3 d vs. 12.5 d
  - treatment failure at 48 hrs due to adverse events significantly higher with milrinone vs. placebo

The OPTIME-CHF Investigators. JAMA 2002;287:1541-47.

Utility of Inotropic Therapy

- Continuous support for acute HF
  - palliation of symptoms
  - bridge to transplantation or VAD
  - allow hospital discharge

- Intermittent infusion therapy for chronic HF
  - +/- clinical benefits
  - long-term therapy associated with significant increase in mortality

Uretsky et al. Circulation 1990;82:774-80. Cohn JN et al. N Engl J Med 1998;339:1810-6. Cowley AJ et al. Br Heart J 1994;72:226-30. Feldman AM, et al. N Engl J Med 1993;329:149-55. Hampton JR, et al. Lancet 1997;349:971-7. Lubsen J, et al. Heart 1996;76:223-31. Packer M, et al. N Engl J Med 1991;325:1468-75. Elis A, et al. Clin Pharmacol Ther 1998;63:682-5.

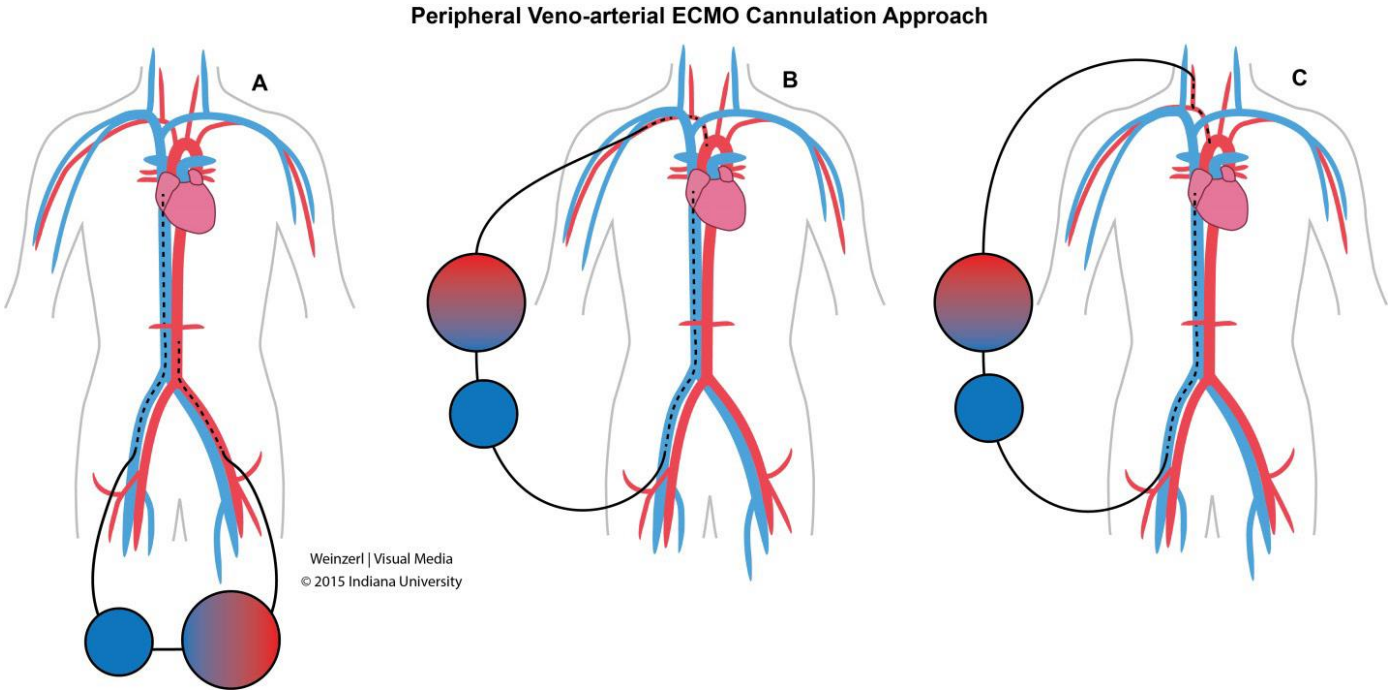
Adverse Effects/ Monitoring of Inotropes & Vasopressors

- Arrhythmogenic
- Hypotension (dobutamine, milrinone)
- PICC line/Hickman Catheter site infection
  - Redness/irritation
  - Drainage
  - Fevers/Chills/Sweats
- Worsening Heart Failure
  - Fatigue
  - Dyspnea
  - Increased Tachycardia

ExtraCorporeal Membrane Oxygenation

- A form of extracorporeal life support where an external artificial circuit carries venous blood from the patient to a gas exchange device (oxygenator) where blood becomes enriched with oxygen and has carbon dioxide removed.
- The blood is then returned to the patient via a central vein or an artery.

ECMO


Peripheral Veno-arterial ECMO Cannulation Approach
A
B
C
Weinzerl | Visual Media
© 2015 Indiana University

Ventricular Assist Device (VAD)

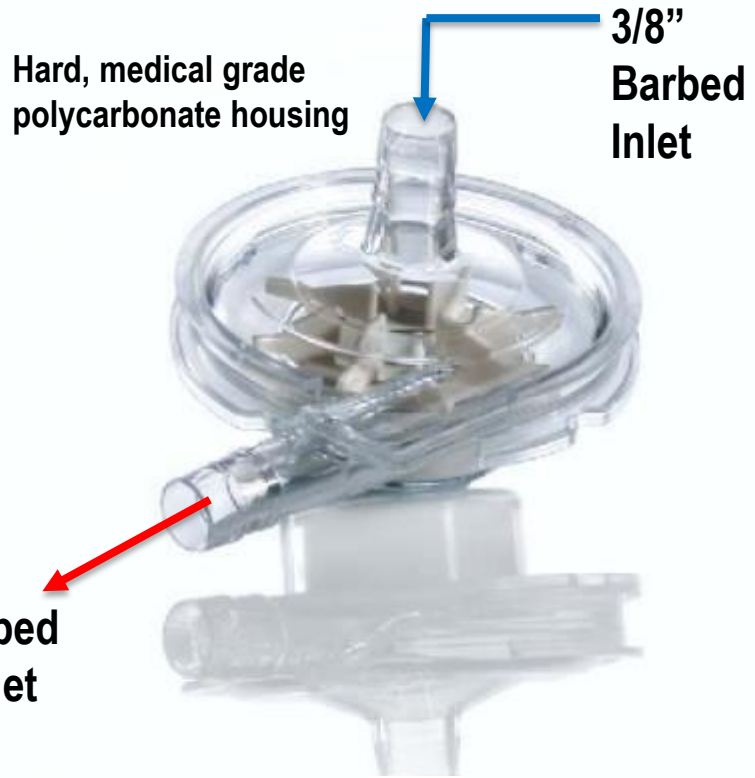
- Right and Left Ventricular Assist Devices
- Temporary RVAD and LVAD
- Durable LVAD
- Preoperative risks
- Long term data

CENTRIMAG BLOOD PUMP SYSTEM: OVERVIEW

BLOOD PUMP

Specifications:

- **Centrifugal Pump**
- **Priming Volume:** 31mL
- **Typical Patient Speed:** 3000-4000 rpm
  - Max Speed Capability: 5500 rpm
- **Max Pump Flow:** 10 LPM
- **Max Pressure:** 600 mmHg
- **No bearings or seals**



CentriMag VAS Patient & Device Management Guidelines
©2016 Thoratec Switzerland GmbH- Document No. PL-0156, Rev. 01 (Nov 2016) pg 8

Thoratec CentriMag ® Blood Pump IFU, pgs 2, 4, and 6
© 2013 Thoratec Switzerland GmbH – Document No. PL-0070, Rev 04 (Jan 2013)

CENTRIMAG 2ND GENERATION SYSTEM: OVERVIEW

2ND GENERATION SYSTEM: REQUIRED THORATEC EQUIPMENT

Blood Pump

- 31 mL
- Disposable
- Centrifugal
- Fully Magnetically Levitated

Motor

- Each pump requires a separate motor

Primary Console

- Each primary console operates one CMag pump

Optional

Monitor

- **Optional** component
- CMag values can be viewed and adjusted in one location

Thoratec CentriMag Blood Pump IFU pgs, 2, 4, and 6

2nd Generation CentriMag System Operating Manual (US) pg 10-14, 31

ST. JUDE MEDICAL

ST. JUDE MEDICAL

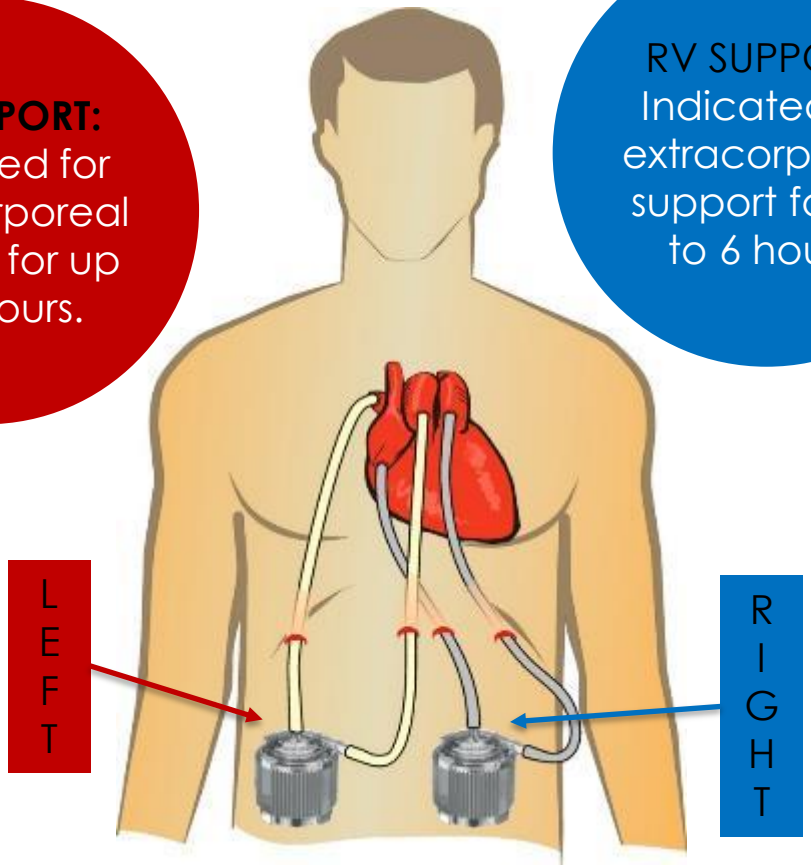
CentriMag Blood Pump System: System Overview

The Patient View*

LV SUPPORT: Indicated for extracorporeal support for up to 6 hours.

RV SUPPORT: Indicated for extracorporeal support for up to 6 hours.

RVAD: HDE for use as a temporary RVAD for patients in cardiogenic shock due to acute right heart failure for up to 30 days.+



* For illustrative purposes only.

\+ For details see page 6 of this presentation and PL-0085

Thoratec CentriMag ® Blood Pump IFU © 2013 Thoratec Switzerland GmbH – Document No. PL-0070, Rev 04 (Jan 2013) pg 2-3

CentriMag® RVAS (Blood Pump) IFU ©2015. Thoratec Switzerland GmbH – Doc No PL-0085, Rev. 09; DCO No. 15-032, pg 3

Ventricular Assist Device Innovation

- Pulsatile Flow
- Valves
- Mechanical bearings

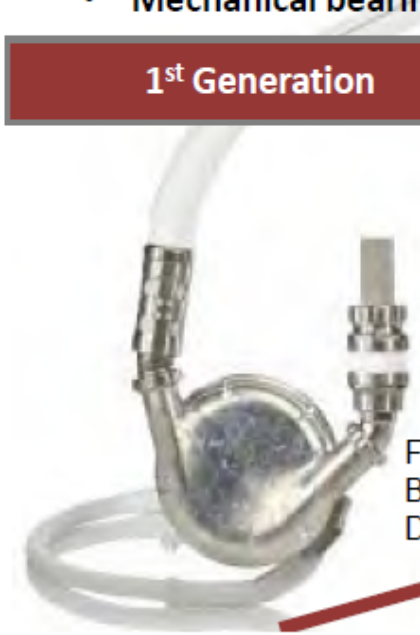
1st Generation

- Continuous Flow
- Axial Design
- Bearing with mechanical pivot

2nd Generation

- Continuous Flow
- Centrifugal Design
- Noncontact bearing design

3rd Generation



FDA Approved
BTT 1998
DT 2002

Bearings

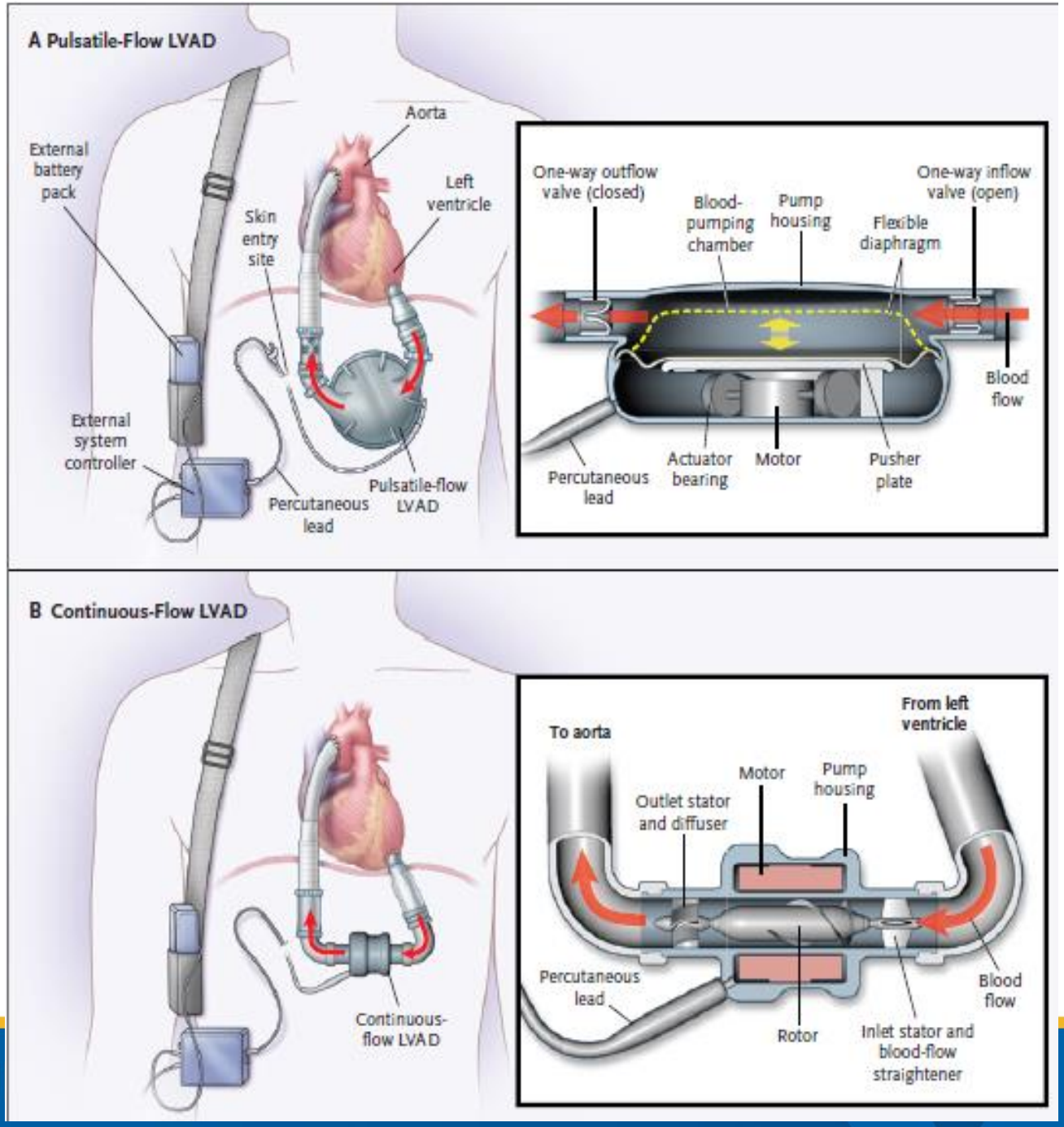
FDA Approved
BTT 2008
DT 2010

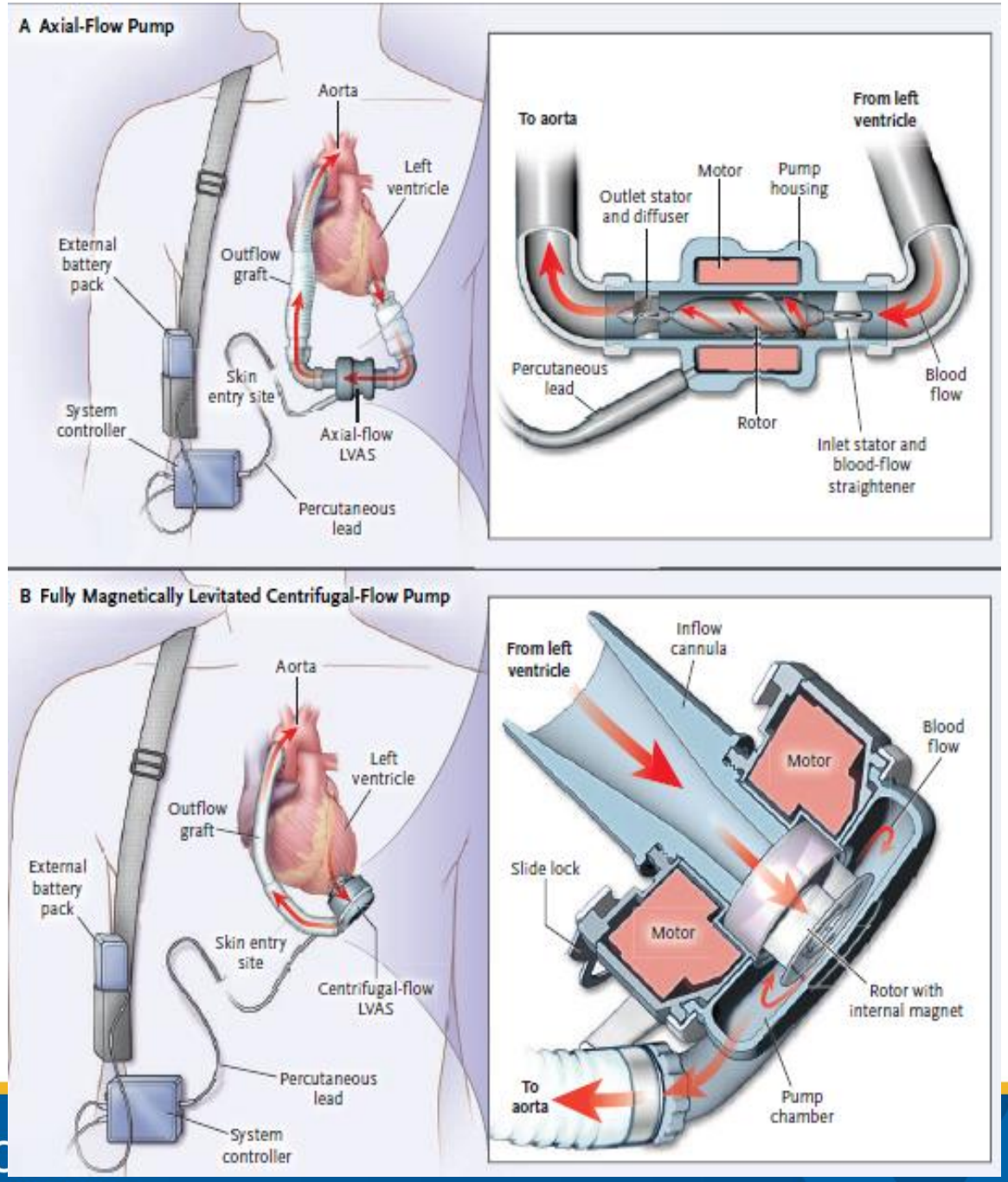
Bearings with stator

FDA Approved
BTT 2012
DT Investigational

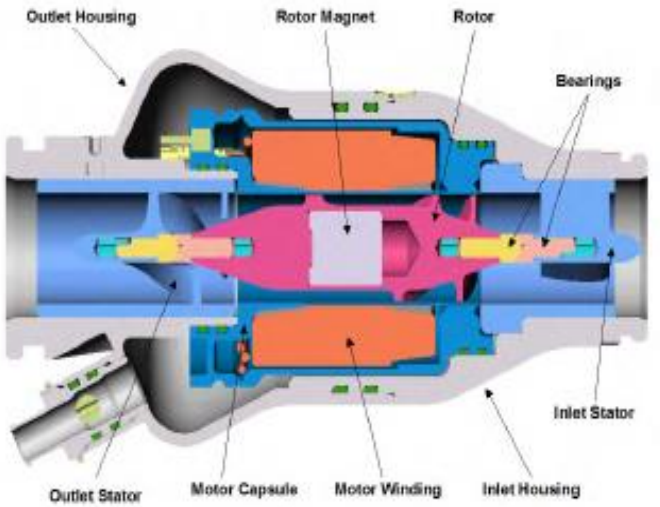
Bearingless with magnetic and hydrodynamic levitation

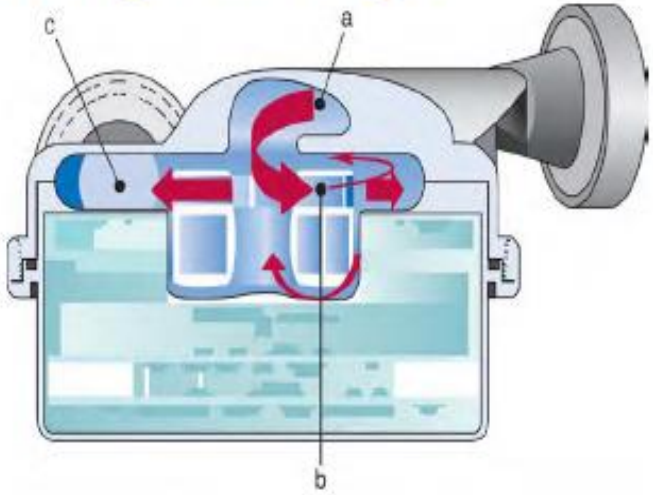
- **Minaturization**
- **Durability**


A Pulsatile-Flow LVAD
Aorta
External battery pack
Left ventricle
Skin entry site
External system controller
Percutaneous lead
Pulsatile-flow LVAD
One-way outflow valve (closed)
Blood-pumping chamber
Pump housing
Flexible diaphragm
One-way inflow valve (open)
Blood flow
Percutaneous lead
Actuator bearing
Motor
Pusher plate
B Continuous-Flow LVAD
Continuous-flow LVAD
To aorta
From left ventricle
Motor
Pump housing
Outlet stator and diffuser
Percutaneous lead
Blood flow
Rotor
Inlet stator and blood-flow straightener


A Axial-Flow Pump
Aorta
Left ventricle
External battery pack
Outflow graft
Skin entry site
System controller
Axial-flow LVAS
Percutaneous lead
To aorta
From left ventricle
Motor
Pump housing
Outlet stator and diffuser
Percutaneous lead
Rotor
Blood flow
Inlet stator and blood-flow straightener
B Fully Magnetically Levitated Centrifugal-Flow Pump
Aorta
Left ventricle
Outflow graft
External battery pack
Skin entry site
Centrifugal-flow LVAS
Percutaneous lead
System controller
From left ventricle
Inflow cannula
Blood flow
Motor
Slide lock
Motor
Rotor with internal magnet
To aorta
Pump chamber

Continuous Flow Rotary Pumps
Axial versus Centrifugal Design





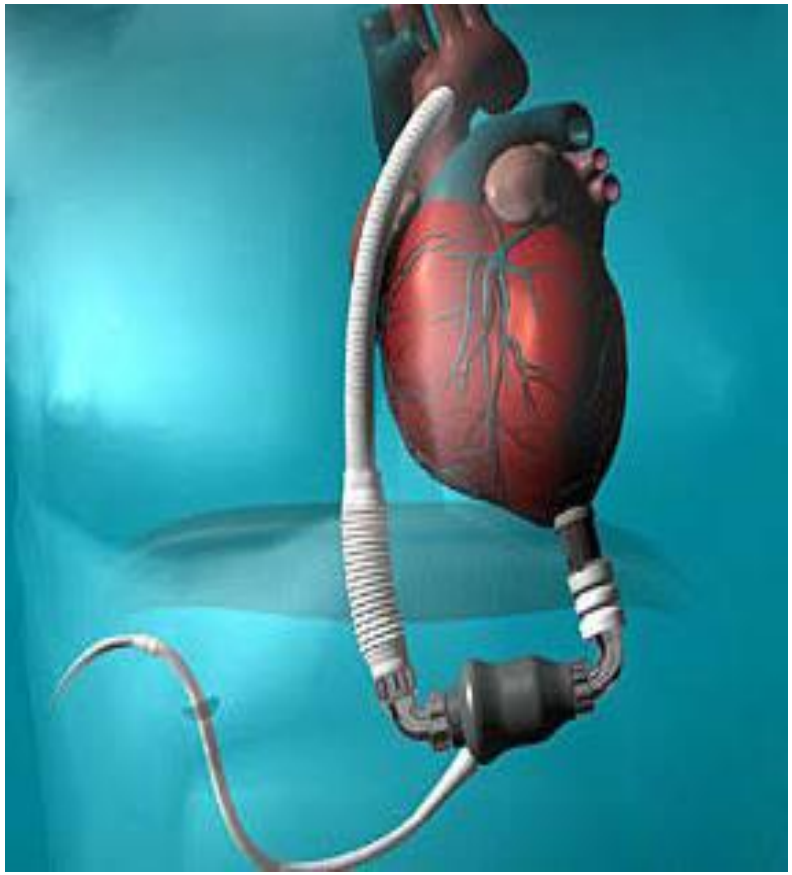
Axial Flow Pump

- Flow along the axis of symmetry
- Mechanical pivot – 2nd Generation pumps

Centrifugal Flow Pump

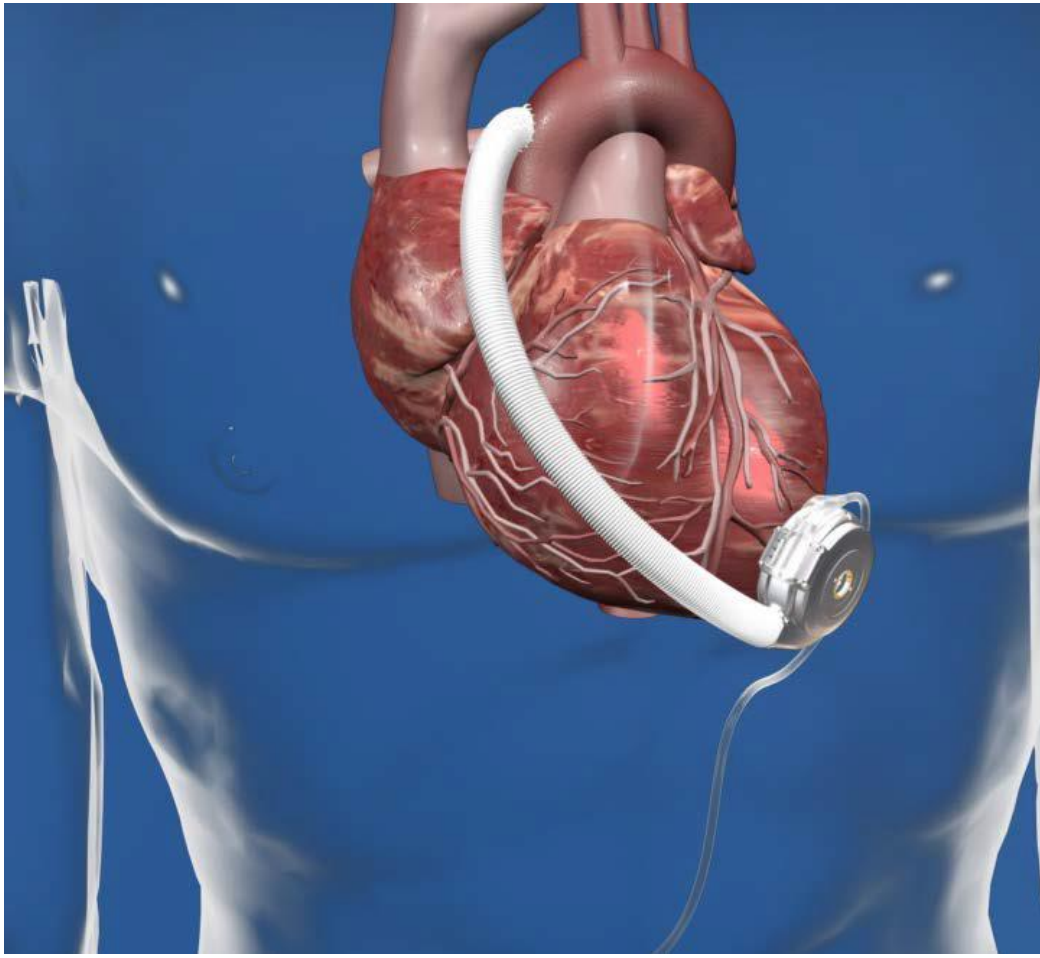
- Blood enters near to the rotating axis and flows radially outward
- Impeller suspended by hydrodynamic or magnetic forces – 3rd Generation pumps

HM2



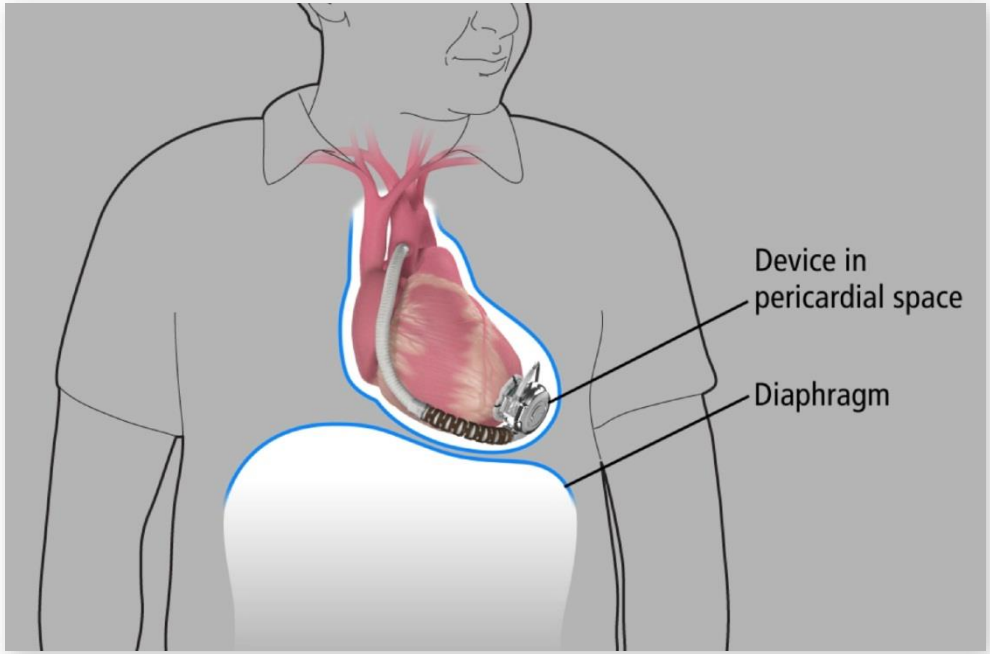
Continuous flow axial pump
•Sub-diaphragmatic placement
•FDA approved for BTT in 2008, DT in 2010

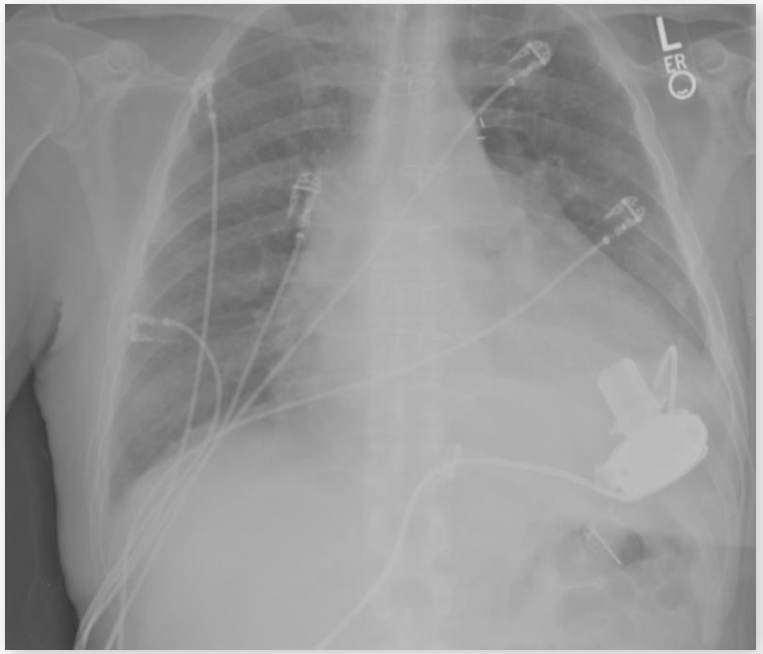
HVAD



Continuous flow centrifugal HVAD® Pump
•Pericardial placement
•FDA approved for BTT in 2012

Pericardial Placement





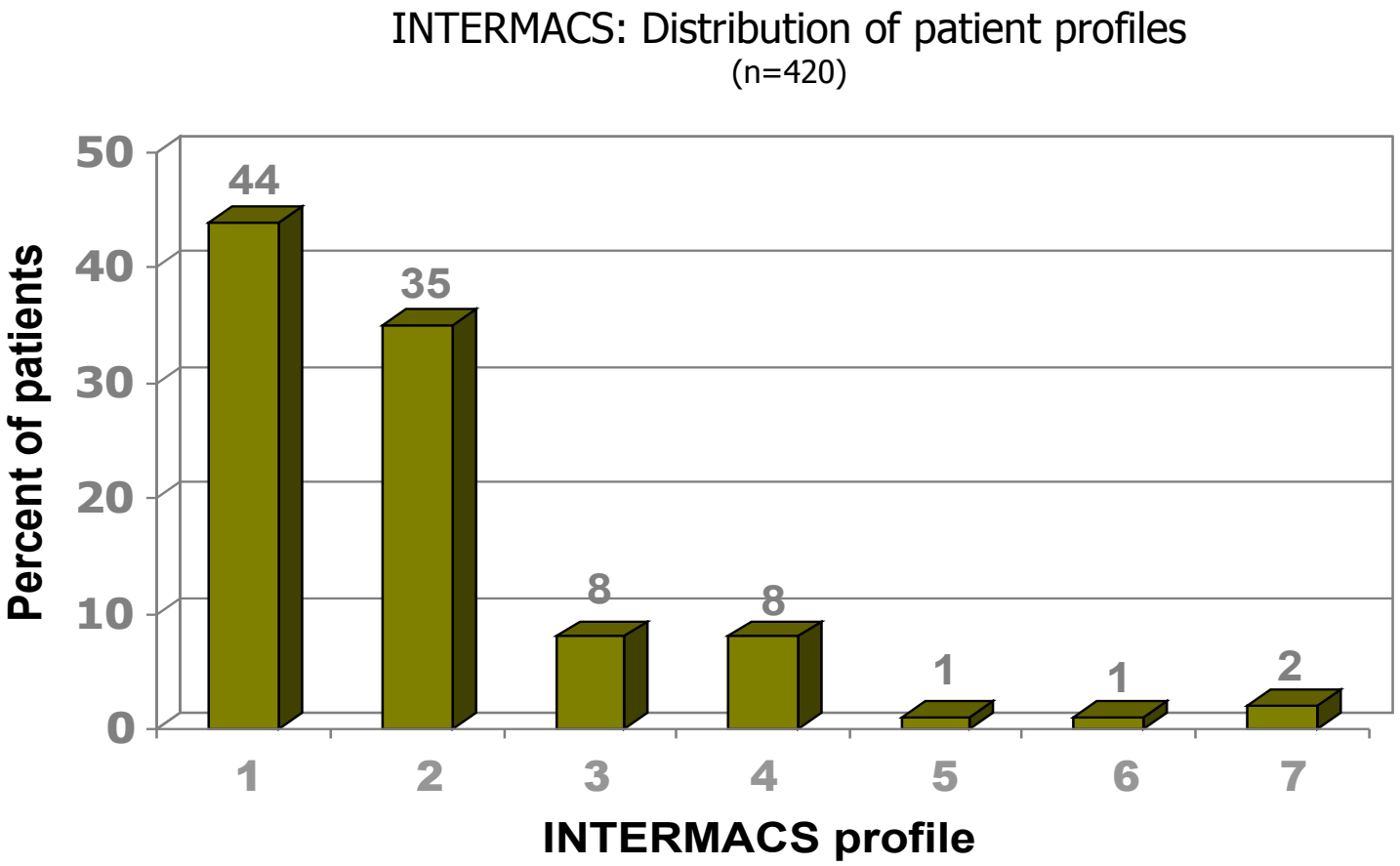
Risk Factors Associated with Poor Outcomes

- Chronic RV dysfunction
  - Moderate to severe chronic malnutrition, cardiac cachexia
  - Moderate to severe liver disease
  - Moderate to severe renal dysfunction
- Extreme obesity
- Severe chronic obstructive pulmonary disease
- History of noncompliance

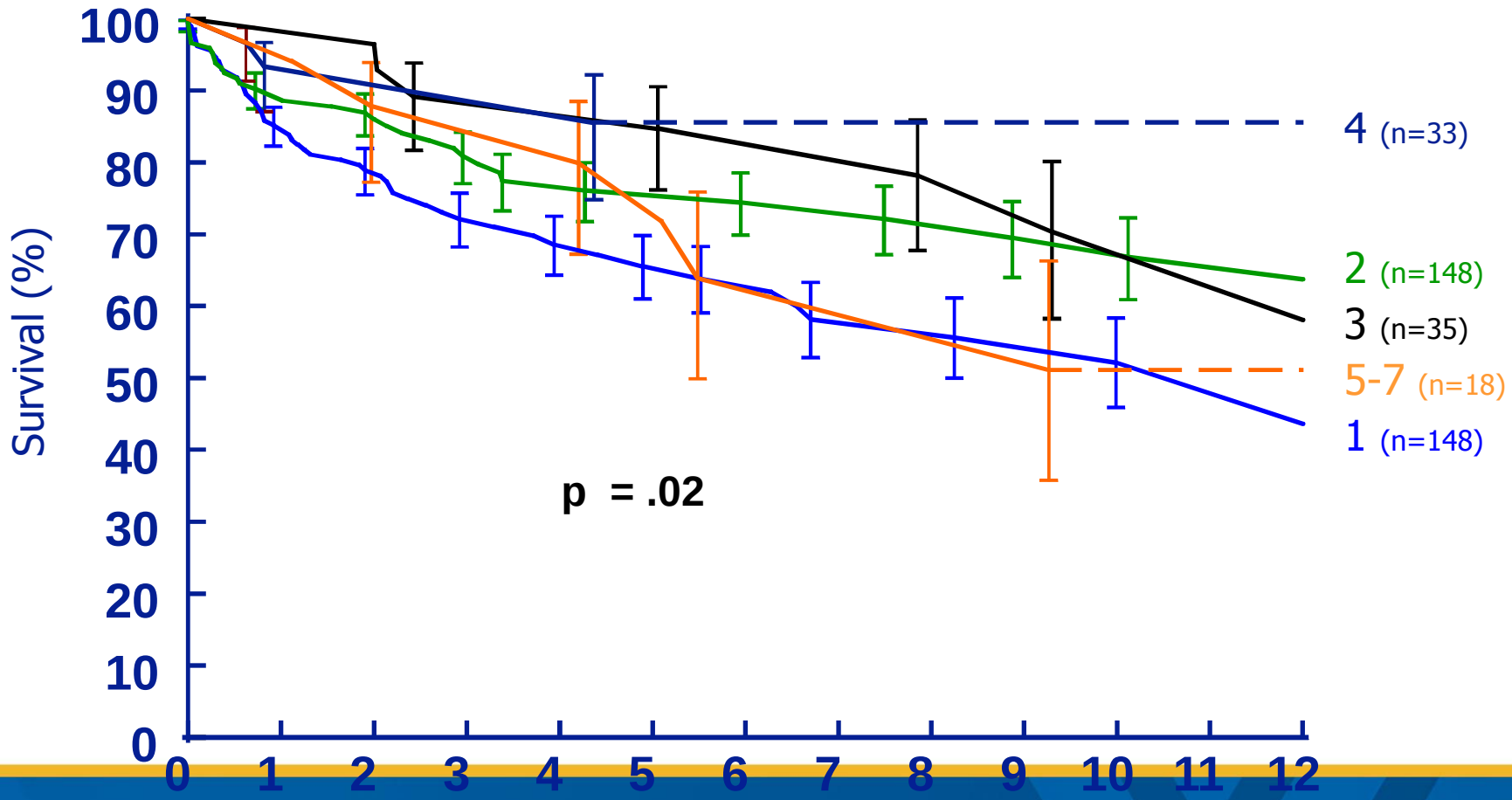
INTERMACS

1. Critical cardiogenic shock
2. Progressive decline, on inotropes
3. Stable, but inotrope dependent
4. Recurrent advanced HF
5. Exertion intolerant
6. Exertion limited
7. Advanced NYHA III

Patient selection

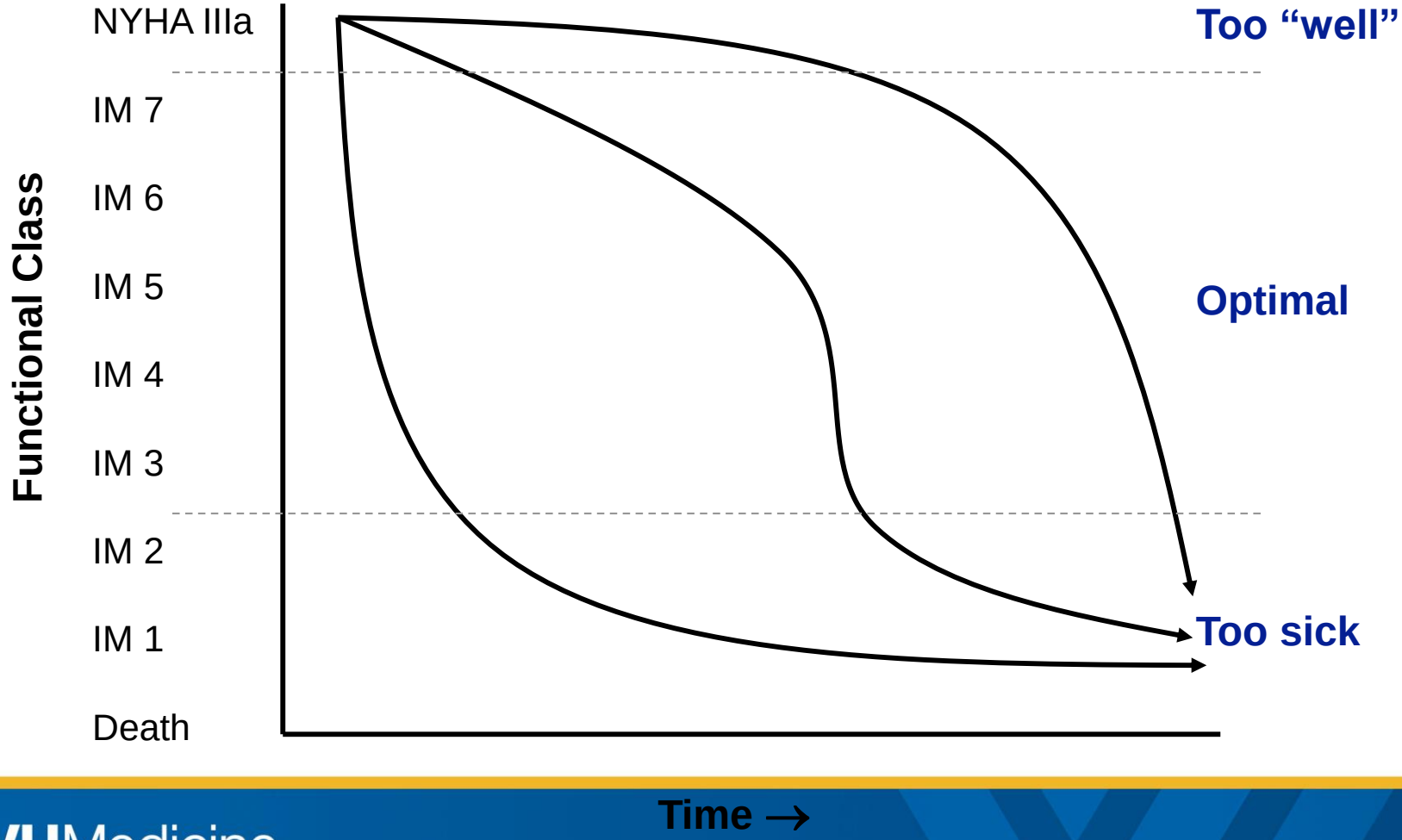


Survival by INTERMACS



Pagani et al. ISHLT 4/2

Timing of MCS



GOALS OF LVAD THERAPY

Achieve satisfactory hemodynamic support

- CI > 2.2, improved end organ perfusion, renal/liver function
- No signs/symptoms of HF

Optimally decompress the LV

- Need to achieve balance so that patient does not have persistent HF/PH but LV doesn't risk suction from over-decompression and small LV size

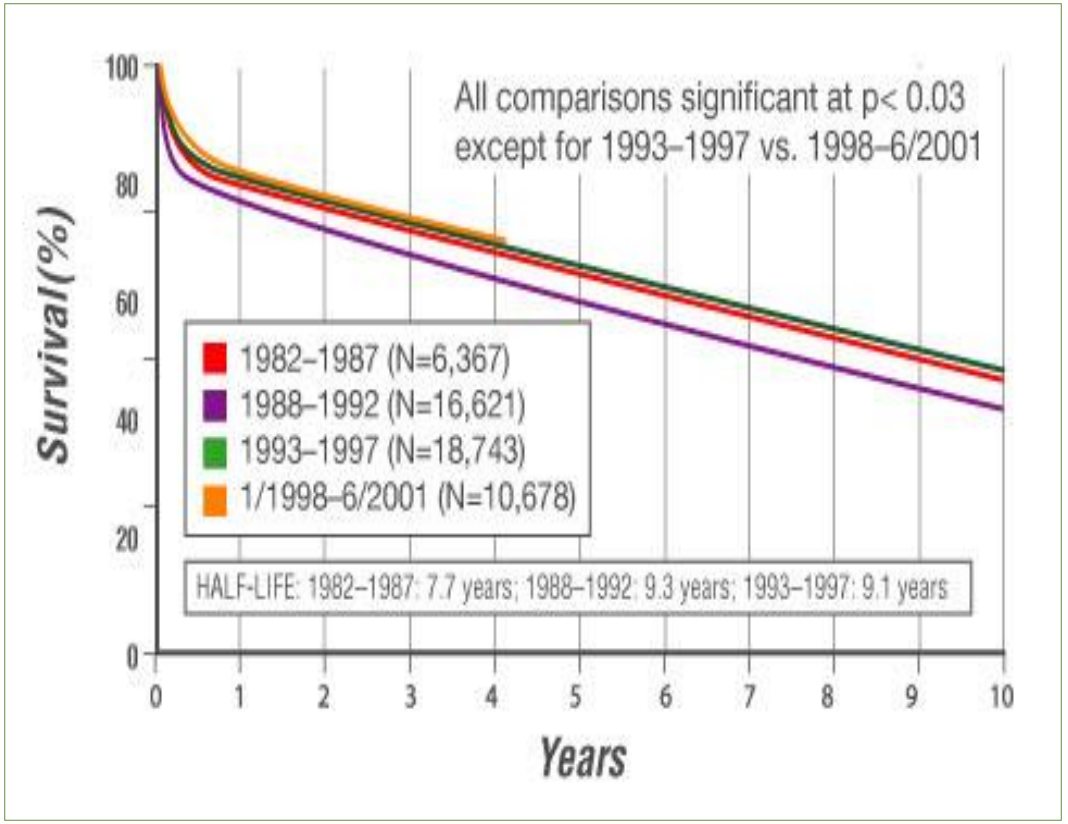
Achieve better survival outcomes

Greater scrutiny on QOL outcomes > survival as population of LVAD candidates expands and technology proves durable

CARDIAC TRANSPLANT

Cardiac Transplantation

- **Remains the most effective Tx for end-stage heart disease, although donor shortage limits its use**
- **Approximately 2,000 hearts are available each year**
- **1-year survival: 86%**
- **5-year survival: 71%**
- **10-year survival: 46%**



Vitali E, Colombo T, et al. Surgical therapy in advanced heart failure. *Am J Cardiol* 2003;91(suppl):88F-94F
Taylor et al. *J Heart Lung Transplant* 2003;22:616.
American Heart Association. Heart Disease and Stroke Statistics-2009 Update.

QUESTIONS?