Meds to Machines

Evolving Heart Failure Management

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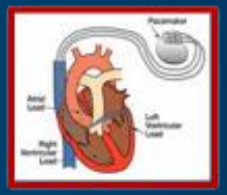
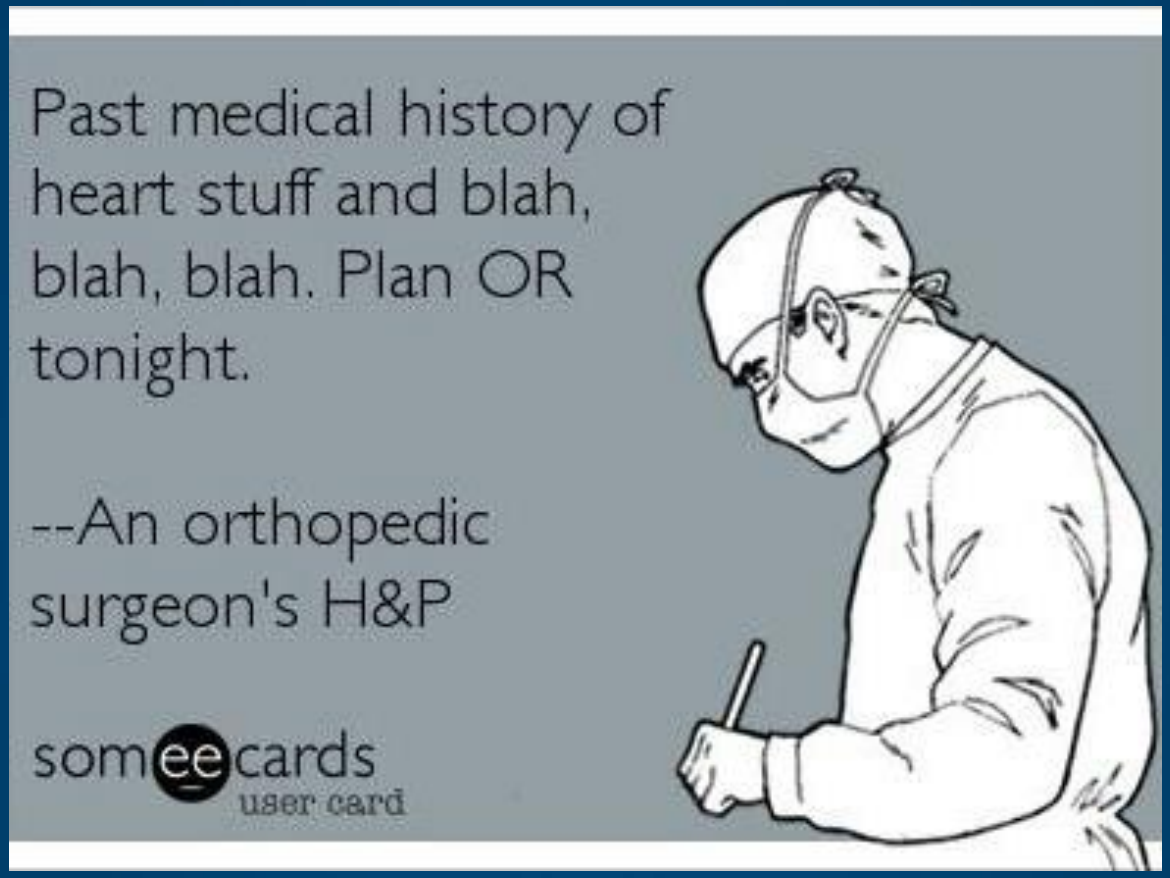
UNIVERSITY HEALTH NETWORK

Medicines to Machines (Devices)





How do you make treatment of heart failure appeal to a surgical audience?

Heart Failure – A Growing Global Concern

Prevalence and Incidence

- Overall 2.1% prevalence: 5.1M heart failure patients in 2010[1]
- 825,000 people ≥ 45 years of age are newly diagnosed each year with HF[1]
- 15M heart failure patients in the ESC 51-member countries[2]
  - Overall 2-3% prevalence[2]

Mortality

– For AHA/ACC stage C/D patients diagnosed with HF:
  - 30% will die in the first year.[3-5]
  - 60% will die within 5 years.[5]

HF prevalence in the US is projected to increase 46% from 2012 to 2030, resulting in > 8M people ≥ 18 years of age with HF.[6]

1. AHA 2014 Statistics at a Glance, 2014
2. The European Society of Cardiology, ESC HF Guideline, 2008
3. Curtis et al, Arch Intern Med, 2008.
4. Roger et al. JAMA, 2004.
5. Cowie et al, EHJ, 2002.
6. Heidenreich PA et al. Circ Heart Failure 2013.

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

ACC/AHA HF Stage[1]	NYHA Functional Class[2]
A At high risk for heart failure but without structural heart disease or symptoms of heart failure (eg, patients with hypertension or coronary artery disease)	None
B Structural heart disease but without symptoms of heart failure	I Asymptomatic
C Structural heart disease with prior or current symptoms of heart failure	II Symptomatic with moderate exertion
	III Symptomatic with minimal exertion
D Refractory heart failure requiring specialized interventions	IV Symptomatic at rest

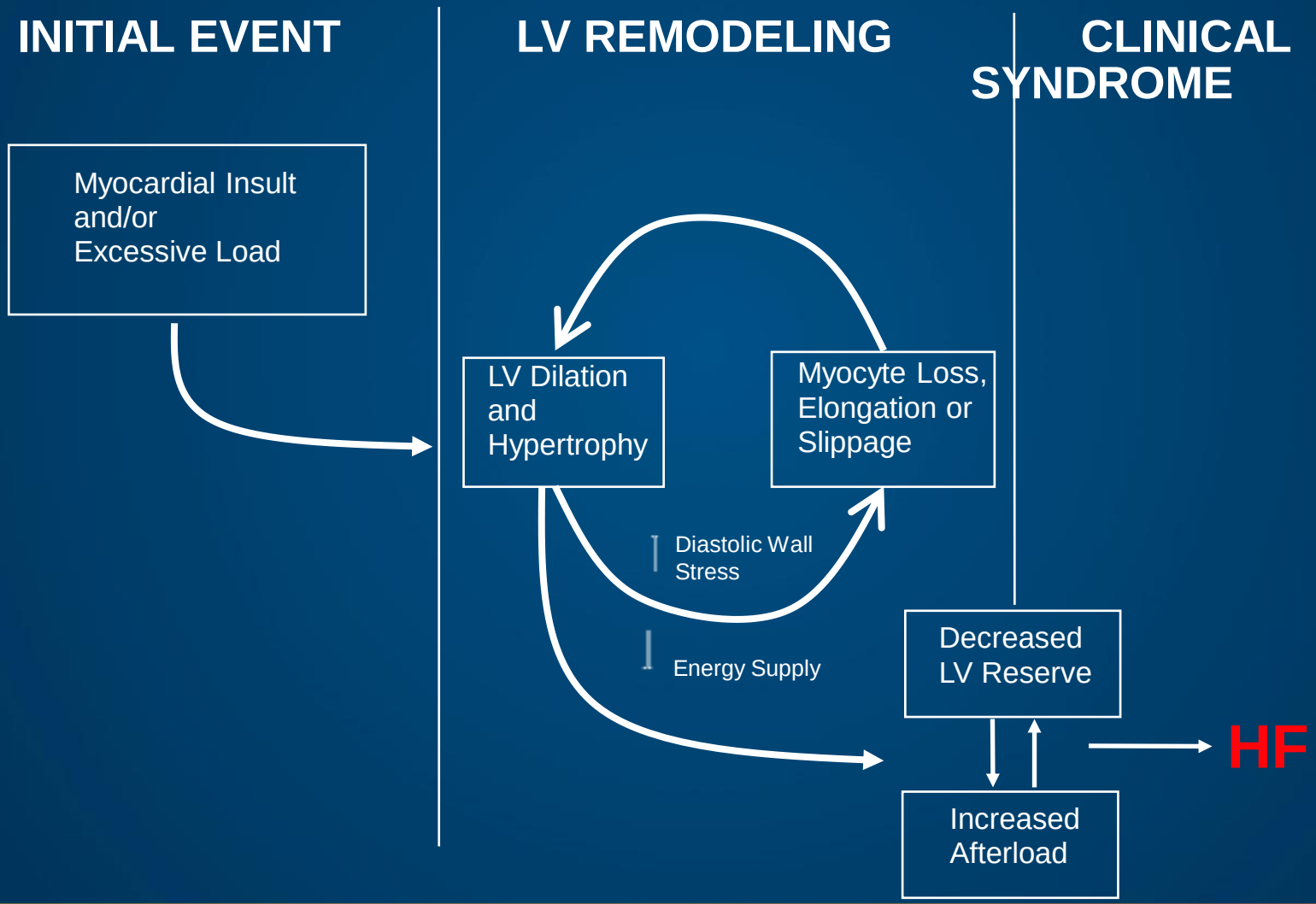
[1]Hunt SA, et al. *J Am Coll Cardiol.* 2001;38:2101–2113.
[2]New York Heart Association/Little Brown and Company, 1964.

Adapted from: Farrell MH, et al. *JAMA.* 2002;287:890–897.

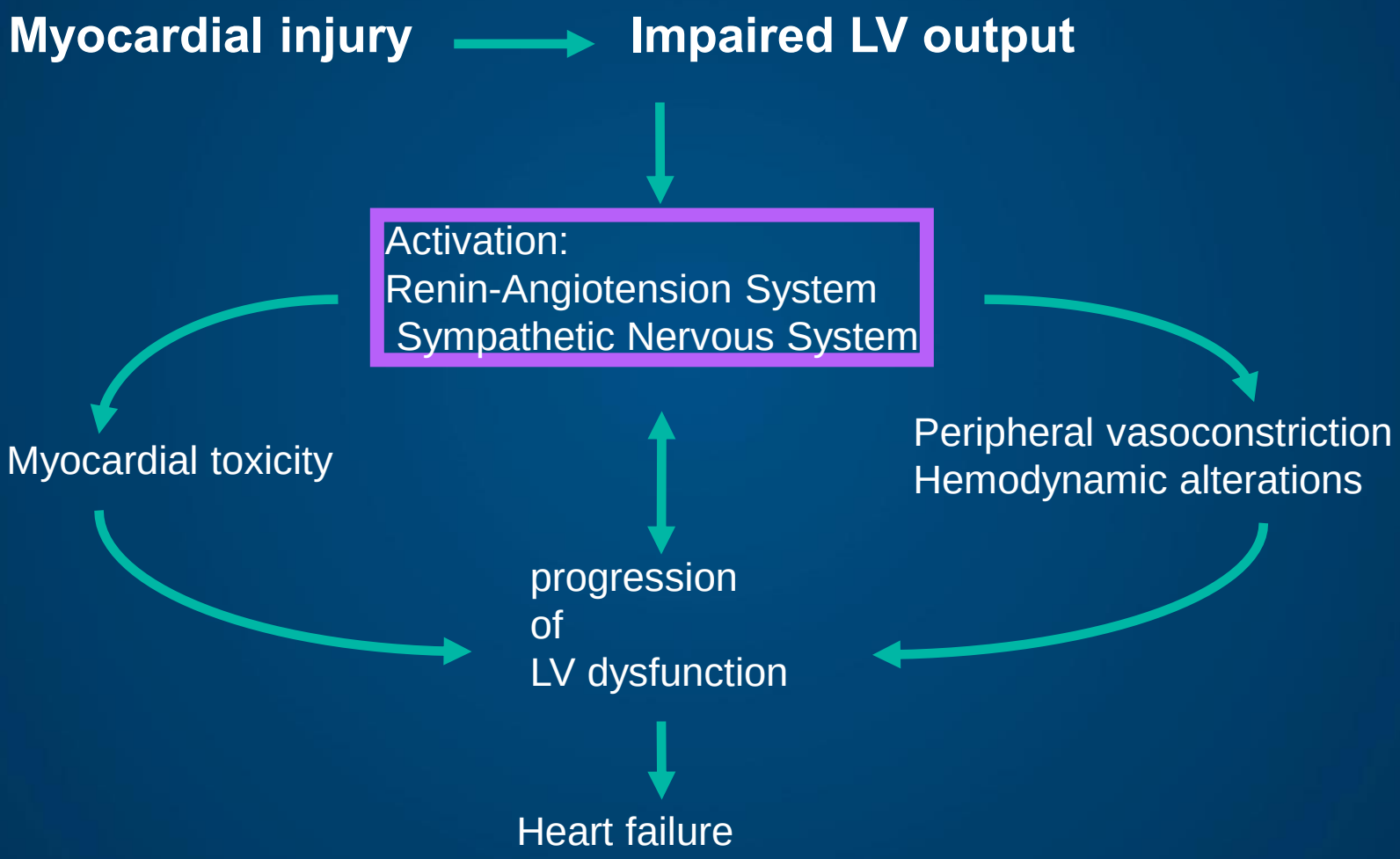
Annual Mortality

- NYHA 1 : 5%
- NYHA 2: 3-25%
- NYHA 3: 10-45%
- NYHA 4: 50-77%

Evolution of Congestive Heart Failure



Neurohormonal Activation in Heart Failure



Principles of HF management

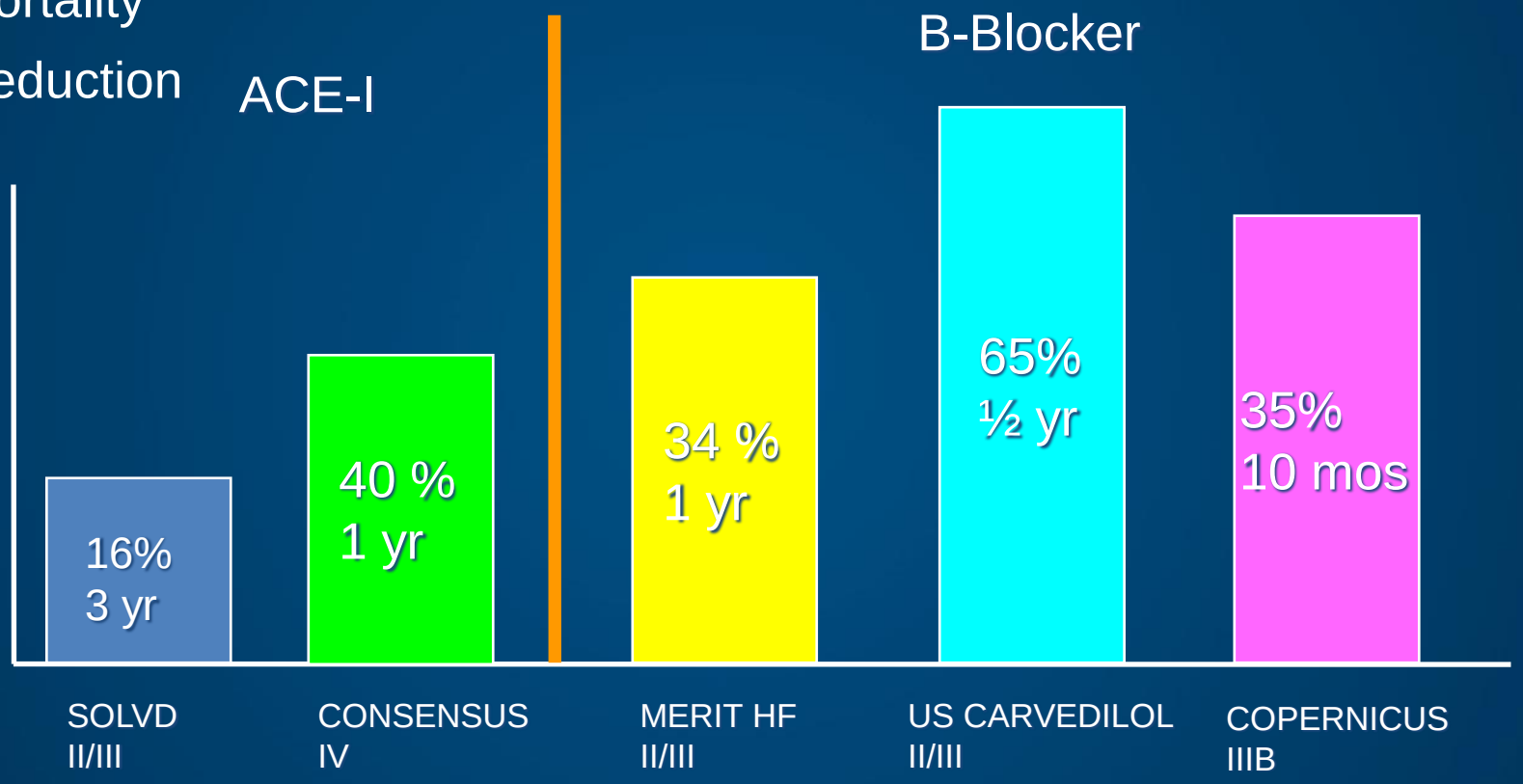
- Reduce excess myocardial oxygen demand
  - Reduce mechanical stress on the heart
    - Decrease afterload
    - Decrease preload
- Increase myocardial contractility
- Reduce Neurohumoral cardiac toxicity
  - Sympathetic blockade
  - Renin-angiotensin blockade

So How Has Treatment Progressed?

- *Consensus 1987*: Enalapril vs Placebo in class lV CHF- 40% all cause mortality reduction at 6 mo
- *V-Heft 1986* (1st major randomized trial of HF powered to assess mortality): Isosorbide dinitrate and hydralazine in CHF EF< 45%- there was a 22% relative risk reduction of mortality (but of borderline significance)- FDA chose to not initially approve for HF but later approved for self described African Americans based on A-Heft trial. V-heFT-2 demonstrated superiority of enalapril over ISDN/ hydralazine- so only used when can not tolerate AceI
- *U.S. Carvedilol Heart Failure Trial 1996*: Pts with EF < 35%, 65% reduction in RR of death. 1st trial to demonstrate a mortality benefit with beta blockers in treatment of HF. Later trials (CIBIS (bisoprolol), COPERNICUS (carvedilol), MERIT HF (metoprolol XL) firmly established beta blockers (in addition to ACE-I) as cornerstone of heart failure therapy
- *RALES 1999*: Spironolactone vs placebo: Active NYHA III and IV, Hx of NYHA lV pts. 30% reduction in all cause mortality. NNT to prevent one death with 2 years of therapy was 9. Performed before widespread use of beta blockers. Eplerenone was added based on EMPHASIS-HF NYHA II

Reduction in Mortality with ACE-I & ®-Blocker therapy

- Mortality
- Reduction

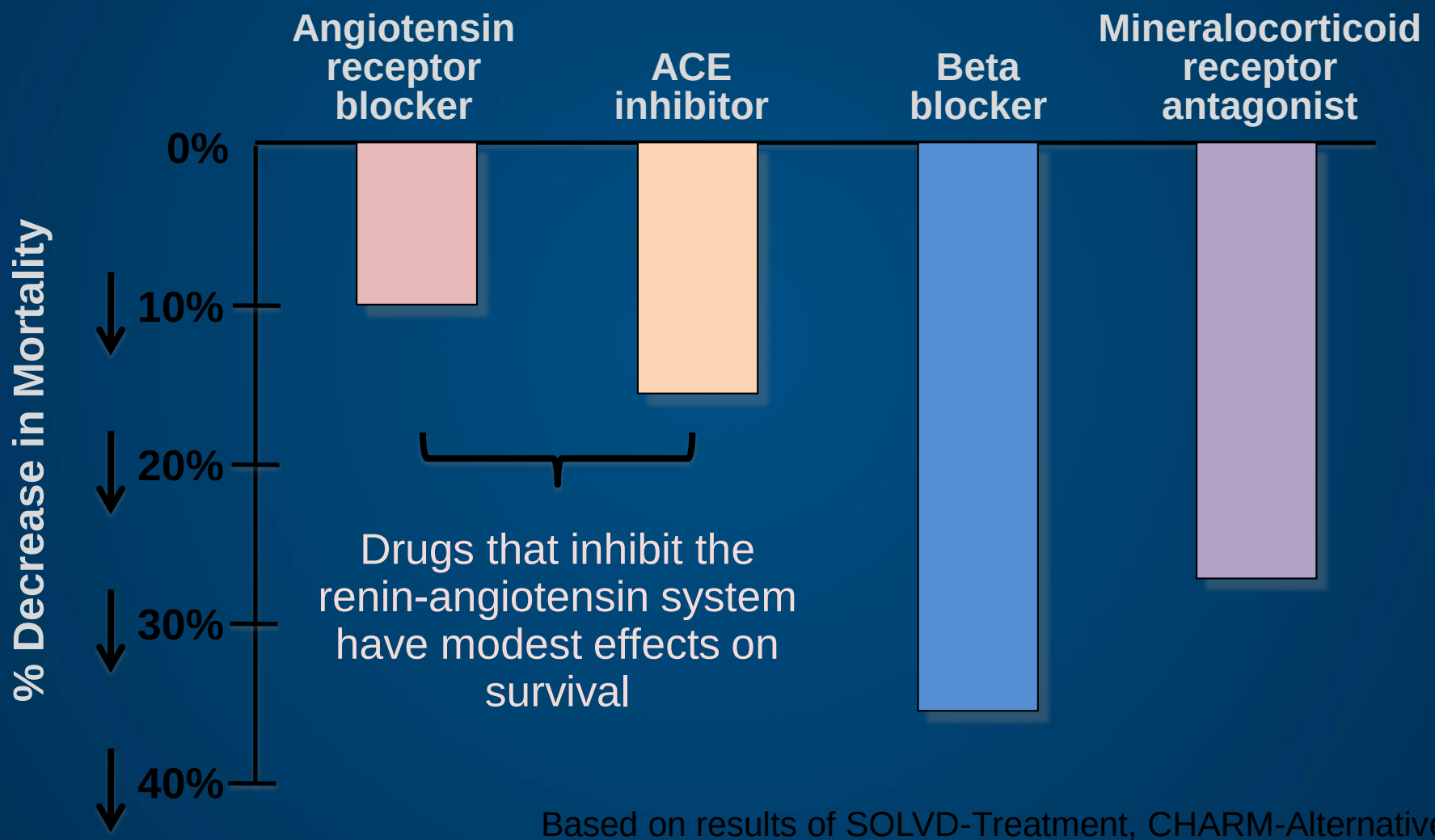


Bloodletting

"it is the least equivocal of remedies: its good effects, when properly administered, are, in most cases, so immediate and striking...In short, bloodletting is a remedy which, when judiciously employed, it is hardly possible to estimate too highly."

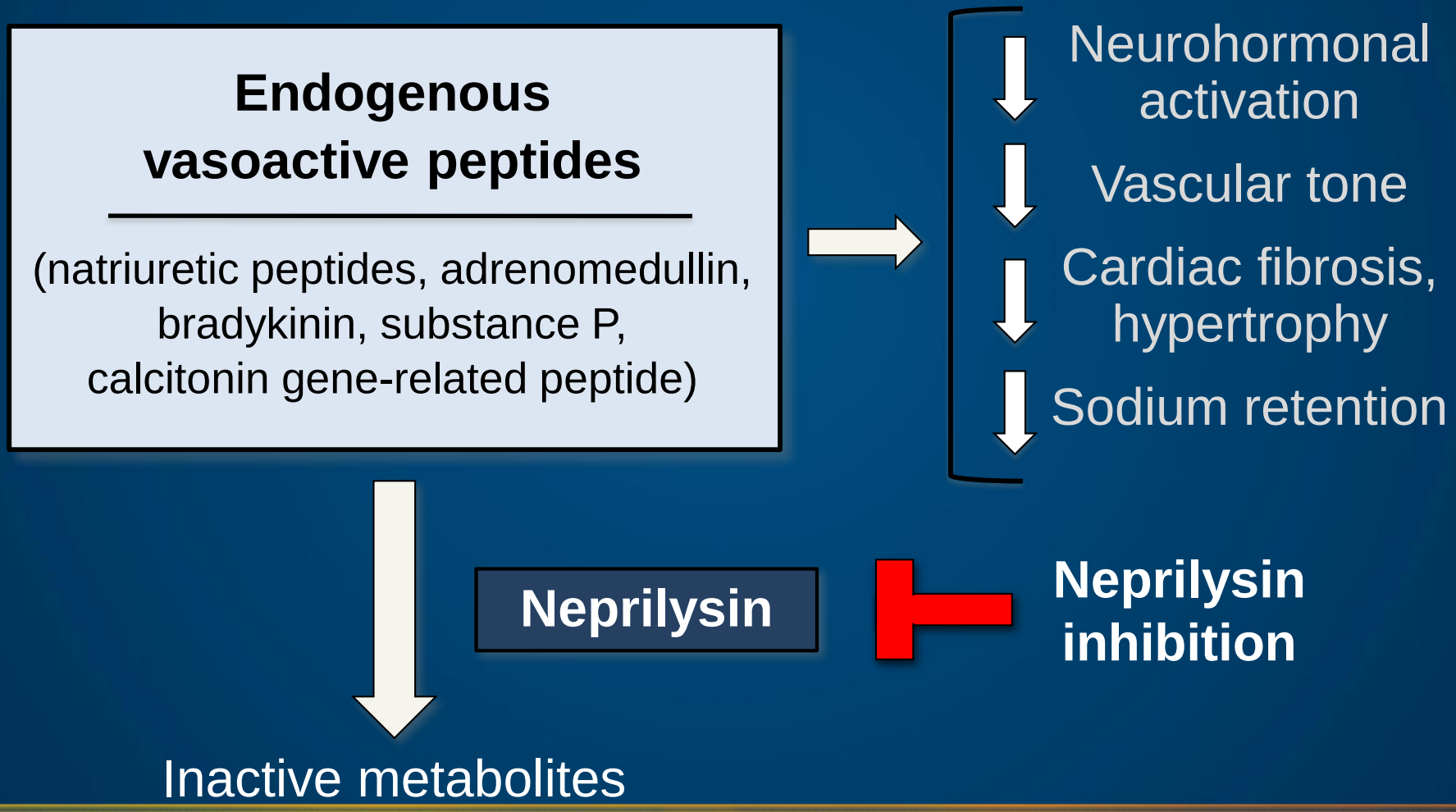
Ventura HO, Mehra MR Bloodletting as a cure of dropsy: Heart failure down the ages. J Card Fail 2005;11: 247-252

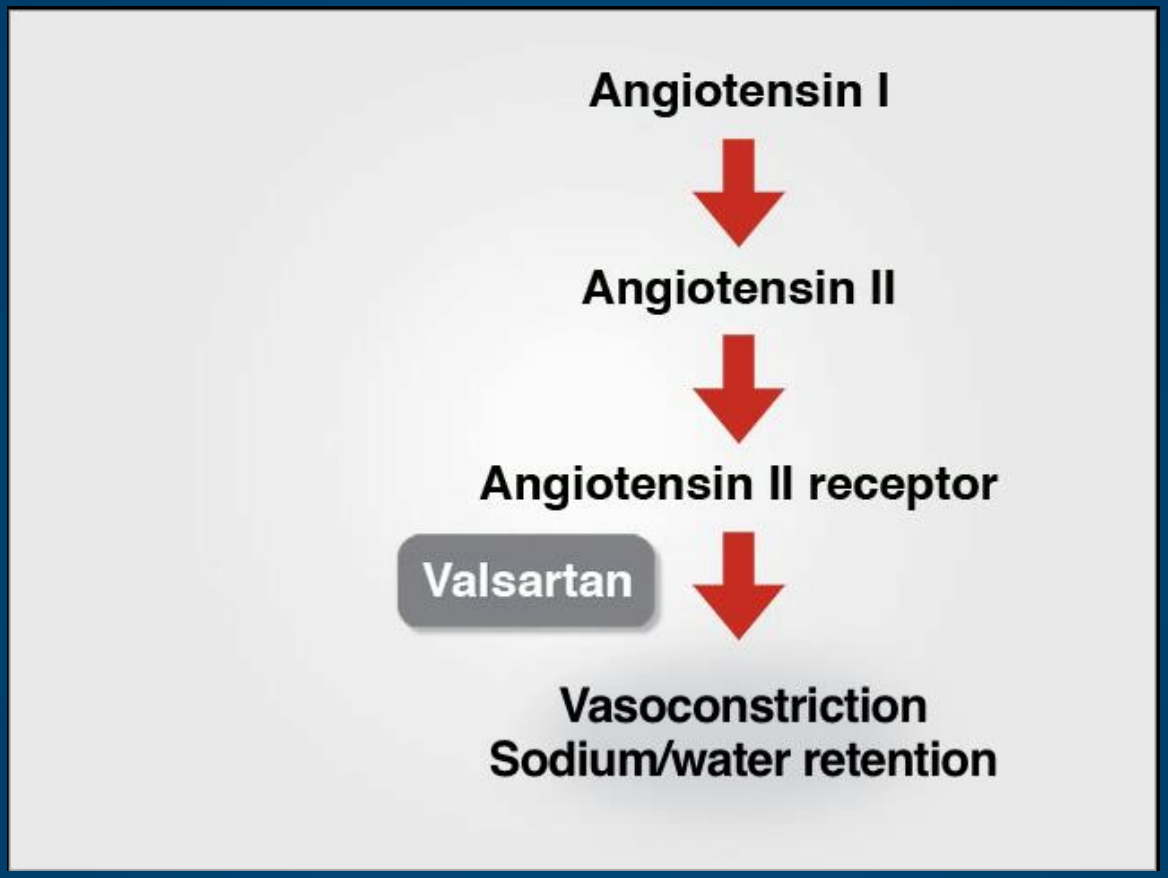
Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction



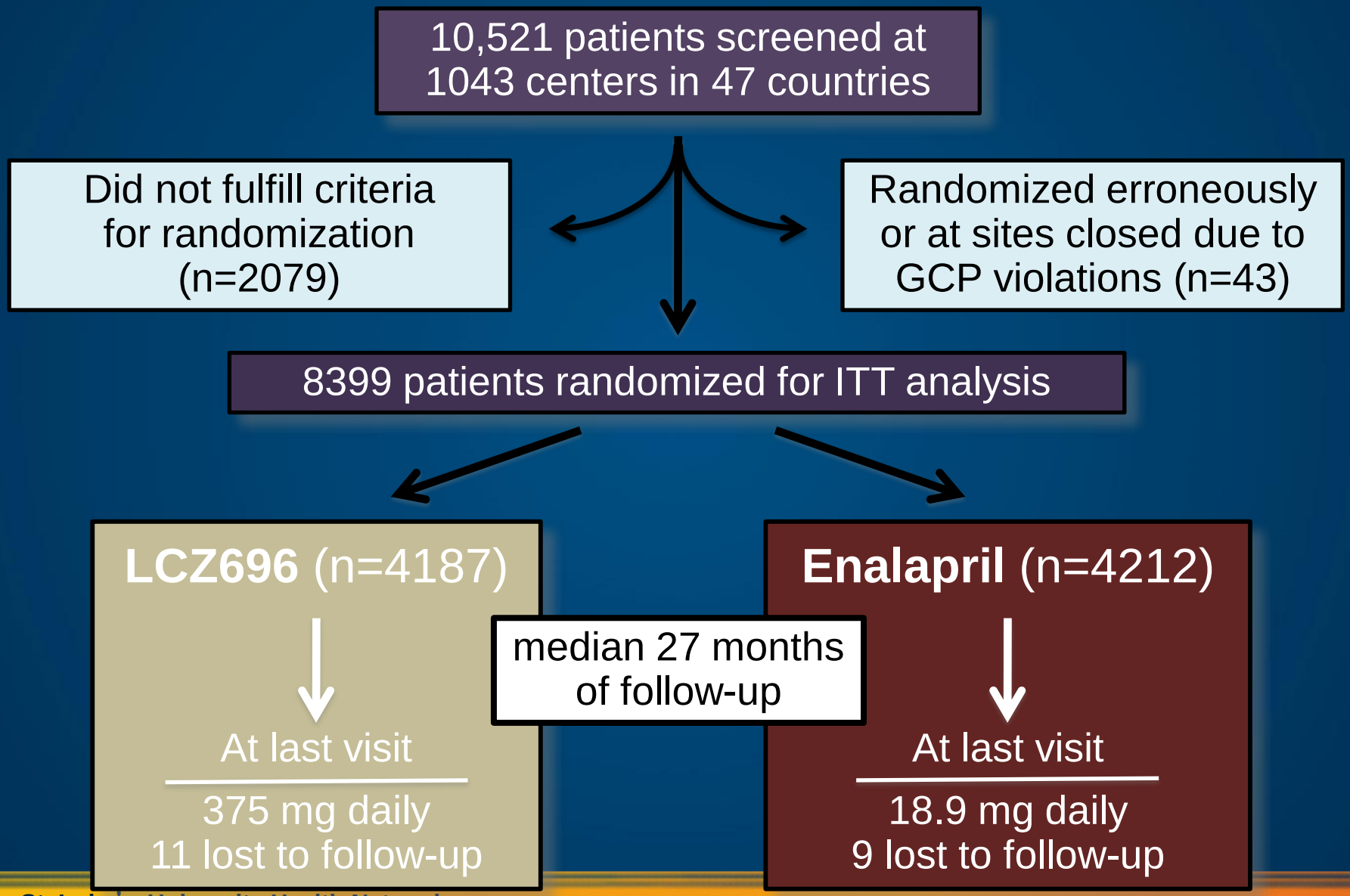
Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure

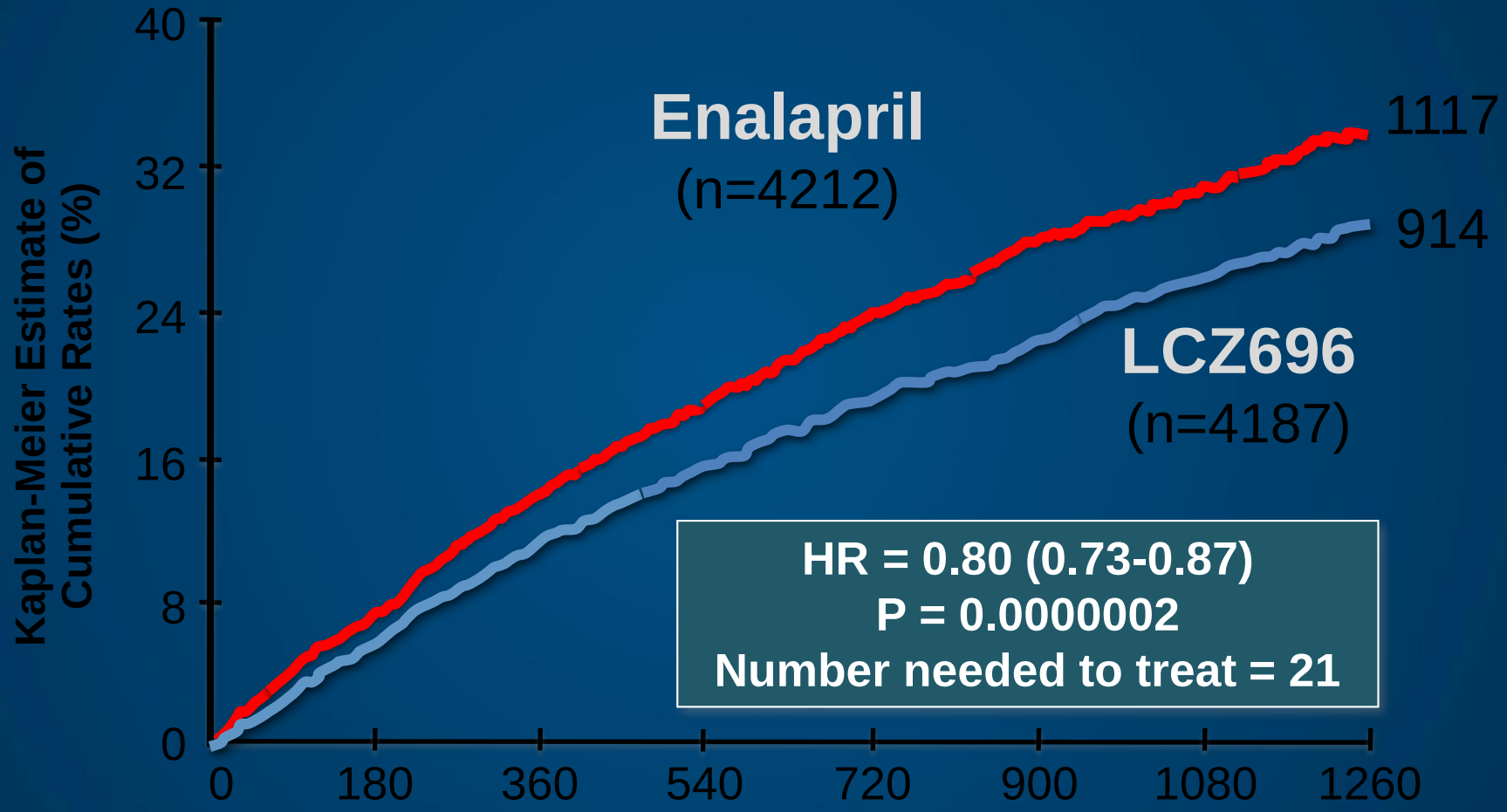



Angiotensin I
Angiotensin II
Angiotensin II receptor
Valsartan
Vasoconstriction
Sodium/water retention

PARADIGM-HF: Patient Disposition



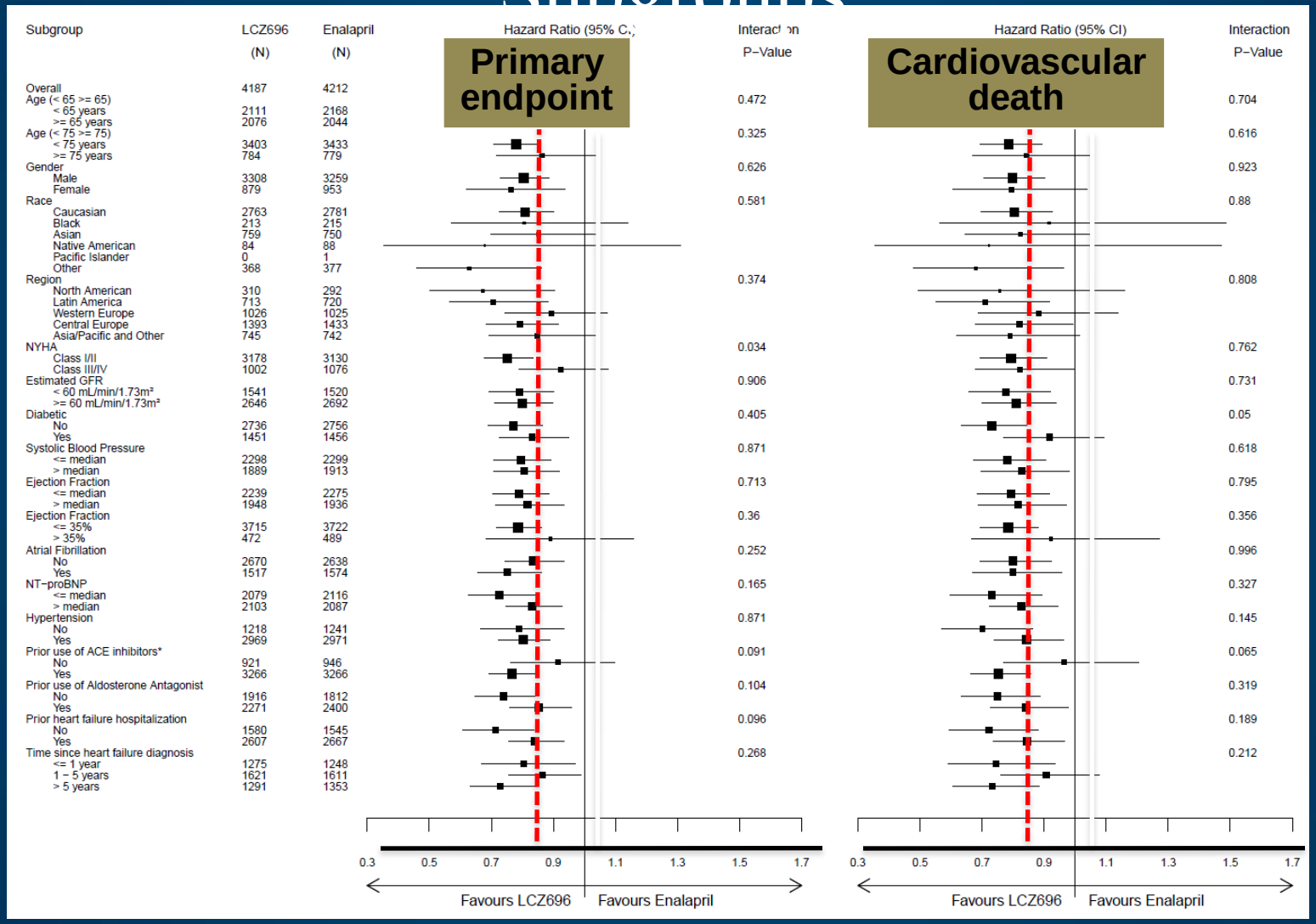
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)



Patients at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

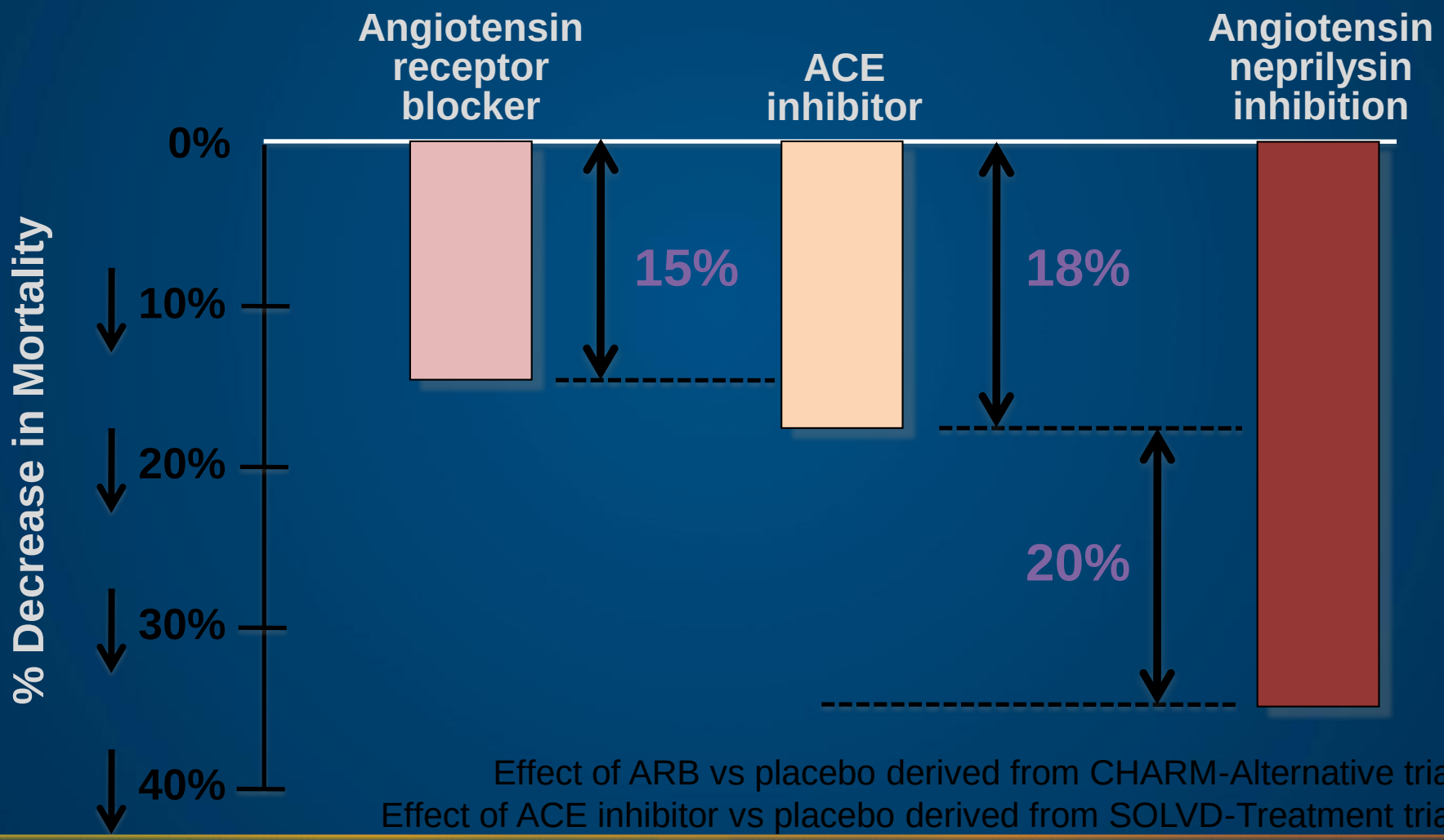
LCZ696 vs Enalapril on Primary Endpoint and on Cardiovascular Death, by Subgroups



Subgroup	LCZ696 (N)	Enalapril (N)	Interaction P-Value
Overall	4187	4212	
Age (< 65 >= 65)			0.472
< 65 years	2111	2168	
>= 65 years	2076	2044	
Age (< 75 >= 75)			0.325
< 75 years	3403	3433	
>= 75 years	784	779	
Gender			0.626
Male	3308	3259	
Female	879	953	
Race			0.581
Caucasian	2763	2781	
Black	213	215	
Asian	759	750	
Native American	84	88	
Pacific Islander	0	1	
Other	368	377	
Region			0.374
North American	310	292	
Latin America	713	720	
Western Europe	1026	1025	
Central Europe	1393	1433	
Asia/Pacific and Other	745	742	
NYHA			0.034
Class I/II	3178	3130	
Class III/IV	1002	1076	
Estimated GFR			0.906
< 60 mL/min/1.73m²	1541	1520	
>= 60 mL/min/1.73m²	2646	2692	
Diabetic			0.405
No	2736	2756	
Yes	1451	1456	
Systolic Blood Pressure			0.871
<= median	2298	2299	
> median	1889	1913	
Ejection Fraction			0.713
<= median	2239	2275	
> median	1948	1936	
Ejection Fraction			0.36
<= 35%	3715	3722	
> 35%	472	489	
Atrial Fibrillation			0.252
No	2670	2638	
Yes	1517	1574	
NT-proBNP			0.165
<= median	2079	2116	
> median	2103	2087	
Hypertension			0.871
No	1218	1241	
Yes	2969	2971	
Prior use of ACE inhibitors*			0.091
No	921	946	
Yes	3266	3266	
Prior use of Aldosterone Antagonist			0.104
No	1916	1812	
Yes	2271	2400	
Prior heart failure hospitalization			0.096
No	1580	1545	
Yes	2607	2667	
Time since heart failure diagnosis			0.268
<= 1 year	1275	1248	
1 – 5 years	1621	1611	
> 5 years	1291	1353	

Subgroup	Interaction P-Value
Overall	
Age (< 65 >= 65)	0.704
< 65 years	
>= 65 years	
Age (< 75 >= 75)	0.616
< 75 years	
>= 75 years	
Gender	0.923
Male	
Female	
Race	0.88
Caucasian	
Black	
Asian	
Native American	
Pacific Islander	
Other	
Region	0.808
North American	
Latin America	
Western Europe	
Central Europe	
Asia/Pacific and Other	
NYHA	0.762
Class I/II	
Class III/IV	
Estimated GFR	0.731
< 60 mL/min/1.73m²	
>= 60 mL/min/1.73m²	
Diabetic	0.05
No	
Yes	
Systolic Blood Pressure	0.618
<= median	
> median	
Ejection Fraction	0.795
<= median	
> median	
Ejection Fraction	0.356
<= 35%	
> 35%	
Atrial Fibrillation	0.996
No	
Yes	
NT-proBNP	0.327
<= median	
> median	
Hypertension	0.145
No	
Yes	
Prior use of ACE inhibitors*	0.065
No	
Yes	
Prior use of Aldosterone Antagonist	0.319
No	
Yes	
Prior heart failure hospitalization	0.189
No	
Yes	
Time since heart failure diagnosis	0.212
<= 1 year	
1 – 5 years	
> 5 years	

Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System



Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial

Primary objective

To evaluate whether the I_f inhibitor ivabradine improves cardiovascular outcomes in patients with

1. Moderate to severe chronic heart failure
2. Left ventricular ejection fraction ≤35%
3. Heart rate ≥70 bpm in sinus rhythm
4. Best recommended therapy

OVERVIEW OF SHIFT

SHI_fT (**S**ystolic **H**eart failure treatment with the I_f inhibitor ivabradine **T**rial) is the first study to assess whether heart rate reduction by direct sinus node inhibition can decrease cardiovascular outcomes in patients with chronic heart failure and left ventricular systolic dysfunction.[1]

6505 patients randomized

37 countries

Main results presented in Stockholm ESC Congress 2010

Ancillary studies and additional analysis

February 2012

European Medicines Agency granted the indication of ivabradine in chronic heart failure

[symptomatic patients (NYHA II–IV) in sinus rhythm with heart rate ≥75 bpm][2]

May 2012

ESC guidelines for the diagnosis and management of heart failure included ivabradine in the algorithm for the treatment of chronic heart failure

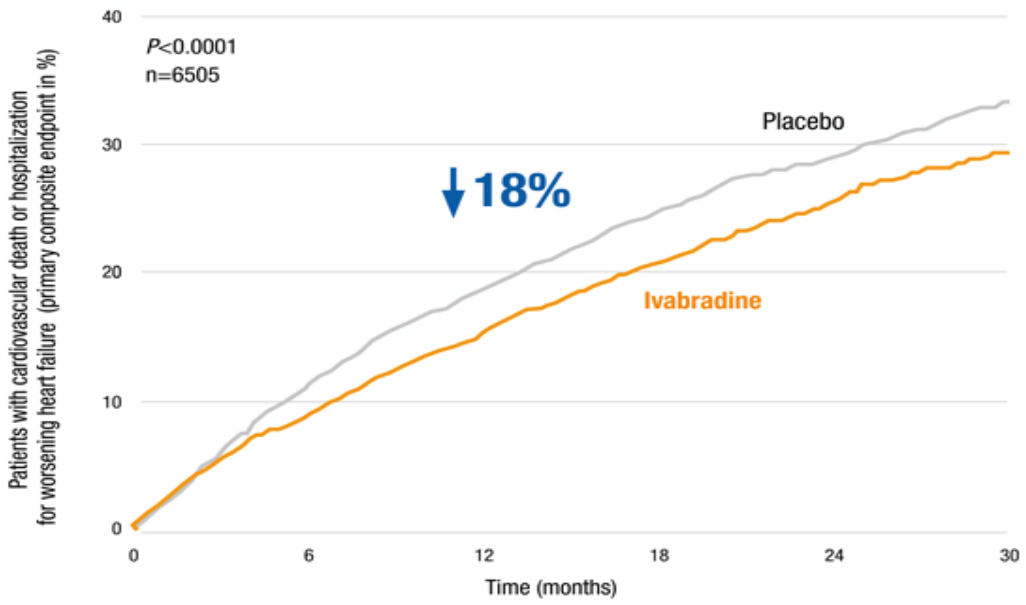
[symptomatic patients (NYHA II–IV) in sinus rhythm with heart rate ≥70 bpm][3]

Ivabradine is the first innovative drug after more than a decade to improve the prognosis, to reduce hospitalizations, and to improve the quality of life of heart failure patients.

PRIMARY END POINT

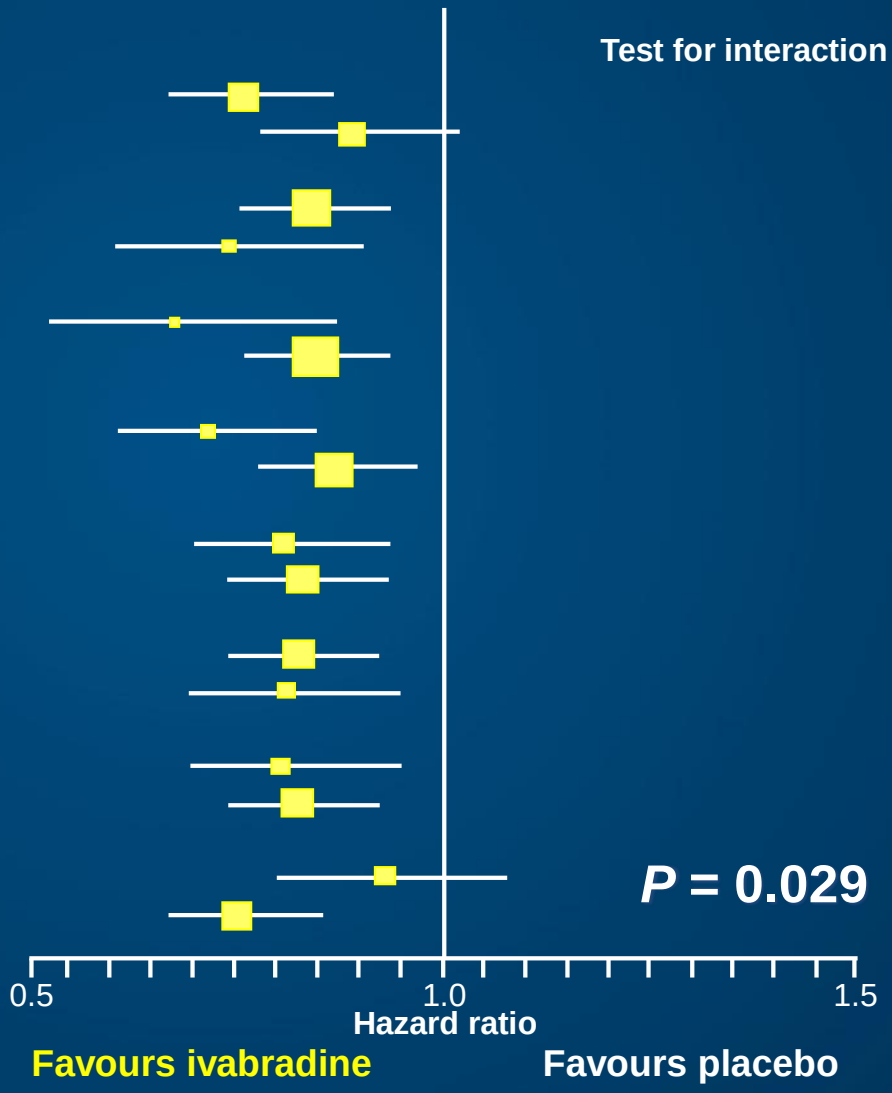
18% P<0.0001 **REDUCTION of cardiovascular death or hospitalization for worsening heart failure**

26 **NNT at 1 year to avoid one primary end point**



Ivabradine or placebo on top of guideline-recommended therapy including ACE inhibitor, β-blocker, mineralocorticoid receptor antagonist.

Effect of ivabradine in prespecified subgroups



Swedberg K, et al. *Lancet*. 2010;376(9744):875-885

Treatment discontinuation

	Patients with an adverse event, leading to withdrawal		
	Ivabradine N=3232, **n** (%)	Placebo N=3260, **n** (%)	*p* value
All adverse events	467 (14%)	416 (13%)	0.051
Symptomatic bradycardia	20 (1%)	5 (<1%)	0.002
Asymptomatic bradycardia	28 (1%)	5 (<1%)	<0.0001
Atrial fibrillation	135 (4%)	113 (3%)	0.137
Phosphenes	7 (<1%)	3 (<1%)	0.224
Blurred vision	1 (<1%)	1 (<1%)	1.000

Conclusion

Ivabradine significantly reduces major risks associated with heart failure:

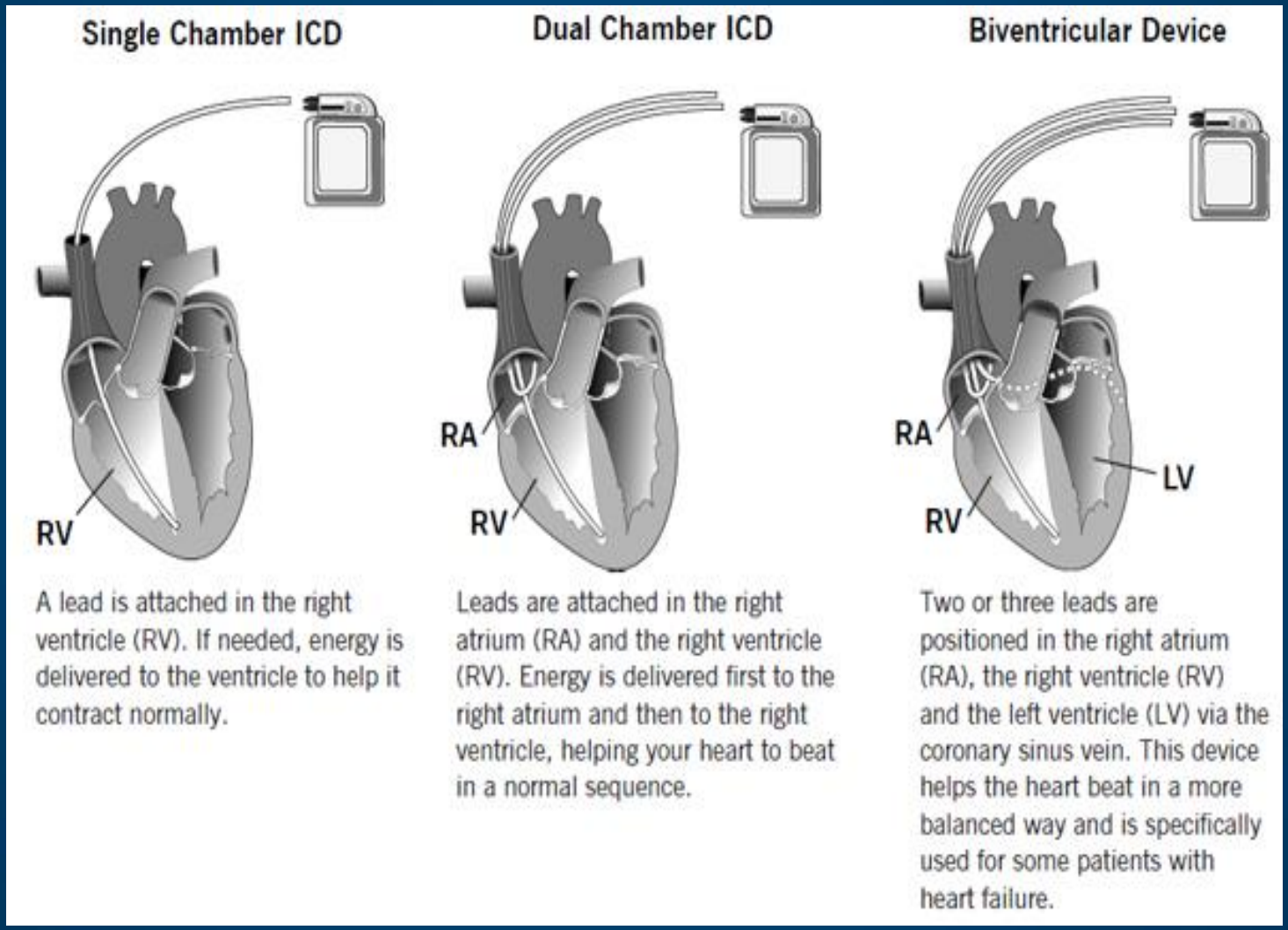
- 18% reduction in CV death or hospital admission for worsening HF
- 26% reduction in death from heart failure
- 26% reduction in hospital admission for worsening heart failure

Benefits are apparent early, are consistent in predefined subgroups, and have been demonstrated on top of recommended therapy

Treatment is well tolerated

Swedberg K, et al. Lancet. 2010;376(9744):875-885.

The ERA of ‘Machines’



Major Implantable Cardioverter-Defibrillator Trials for Prevention of Sudden Cardiac Death

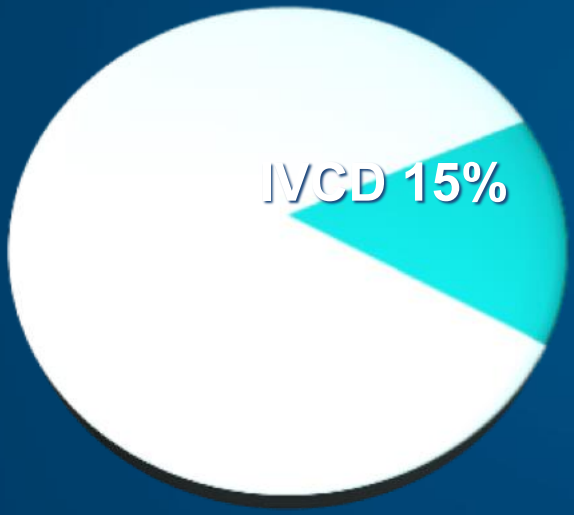
Trial	Year	Patients (n)	Inclusion Criterion: LVEF	Additional Study Features	Hazard Ratio*	95% CI	p
MADIT I	1996	196	≤ 35%	NSVT and EP+	0.46	(0.26-0.82)	p=0.009
MADIT II	2002	1232	≤ 30%	Prior MI	0.69	(0.51-0.93)	p=0.016
CABG-Patch	1997	900	< 36%	+SAECG and CABG	1.07	(0.81-1.42)	p=0.64
DEFINITE	2004	485	< 36%	NICM, PVCs or NSVT	0.65	(0.40-1.06)	p=0.08
DINAMIT	2004	674	≤ 35%	6-40 days post-MI and Impaired HRV	1.08	(0.76-1.55)	p=0.66
SCD-HeFT	2006	1676	≤ 35%	Prior MI or NICM	0.77	(0.62-0.96)	p=0.007
AVID	1997	1016	≤ 40%	Prior cardiac Arrest, or Unstable VT	0.62	(0.43-0.82)	p<0.02
CASH†	2000	191	Mean ≤ 45% ±18 at baseline	Prior cardiac arrest	0.766	‡	1-sided p=0.081
CIDS	2000	659	≤ 35%	Prior cardiac Arrest, Unstable VT, or Syncope	0.82	(0.60-1.1)	NS

* Hazard ratios for death from any cause in the ICD group compared with the non-ICD group. †Includes only ICD and amiodarone patients from CASH. ‡CI Upper Bound 1.112. CI indicates Confidence Interval, EP+ = positive electrophysiologic study, HRV = heart rate variability, LVEF = left ventricular ejection fraction, MI = myocardial infarction, NICM = nonischemic cardiomyopathy, NS = Not statistically significant, NSVT = nonsustained ventricular tachycardia, PVCs = premature ventricular contractions, SAECG = signal-averaged electrocardiogram, VT = ventricular tachycardia.

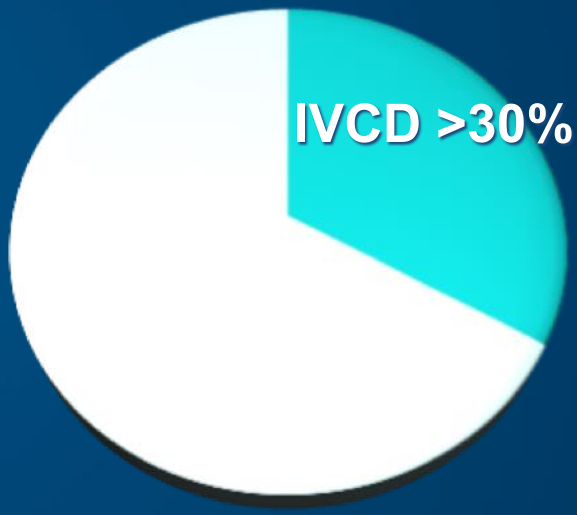
Epstein A, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. J Am Coll Cardiol 2008; 51:e1–62. Table 5.

Prevalence of Inter- or Intraventricular Conduction Delay

General HF Population[1,2]



Moderate to Severe HF Population[3,4,5]

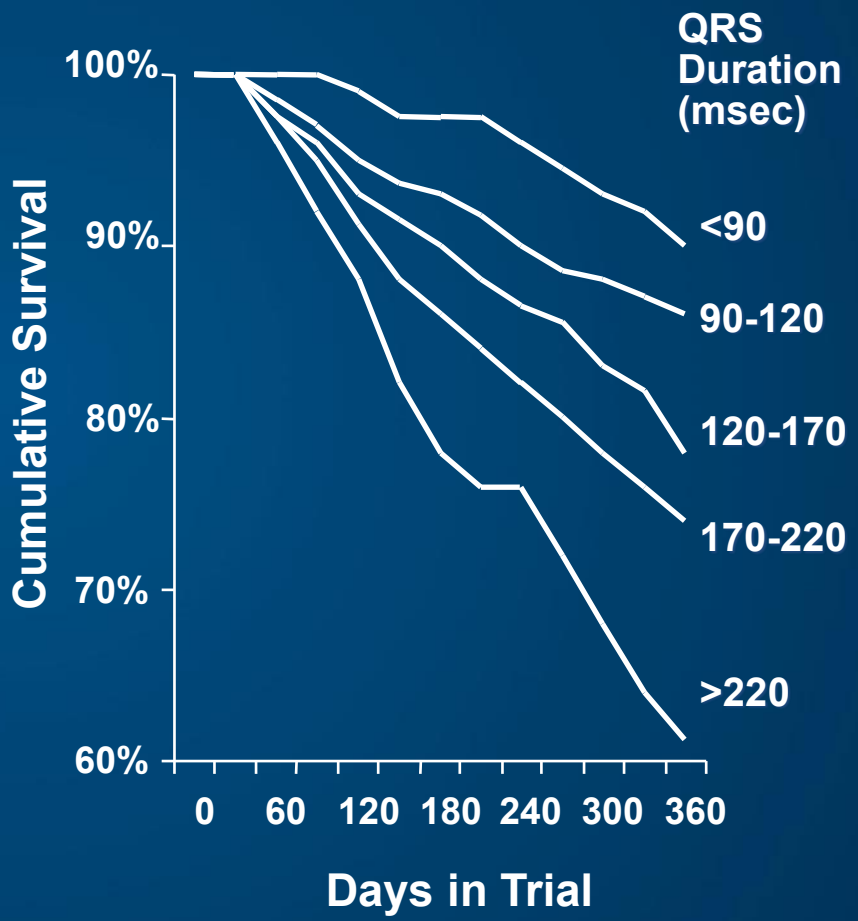


[1] Havranek E, Masoudi F, Westfall K, et al. Am Heart J 2002;143:412-417
[2] Shenkman H, McKinnon J, Khandelwal A, et al. Circulation 2000;102(18 Suppl II): abstract 2293
[3] Schoeller R, Andersen D, Buttner P, et al. Am J Cardiol. 1993;71:720-726
[4] Aaronson K, Schwartz J, Chen T, et al. Circulation 1997;95:2660-2667
[5] Farwell D, Patel N, Hall A, et al. Eur Heart J 2000;21:1246-1250

Wide QRS – Proportional Mortality Increase

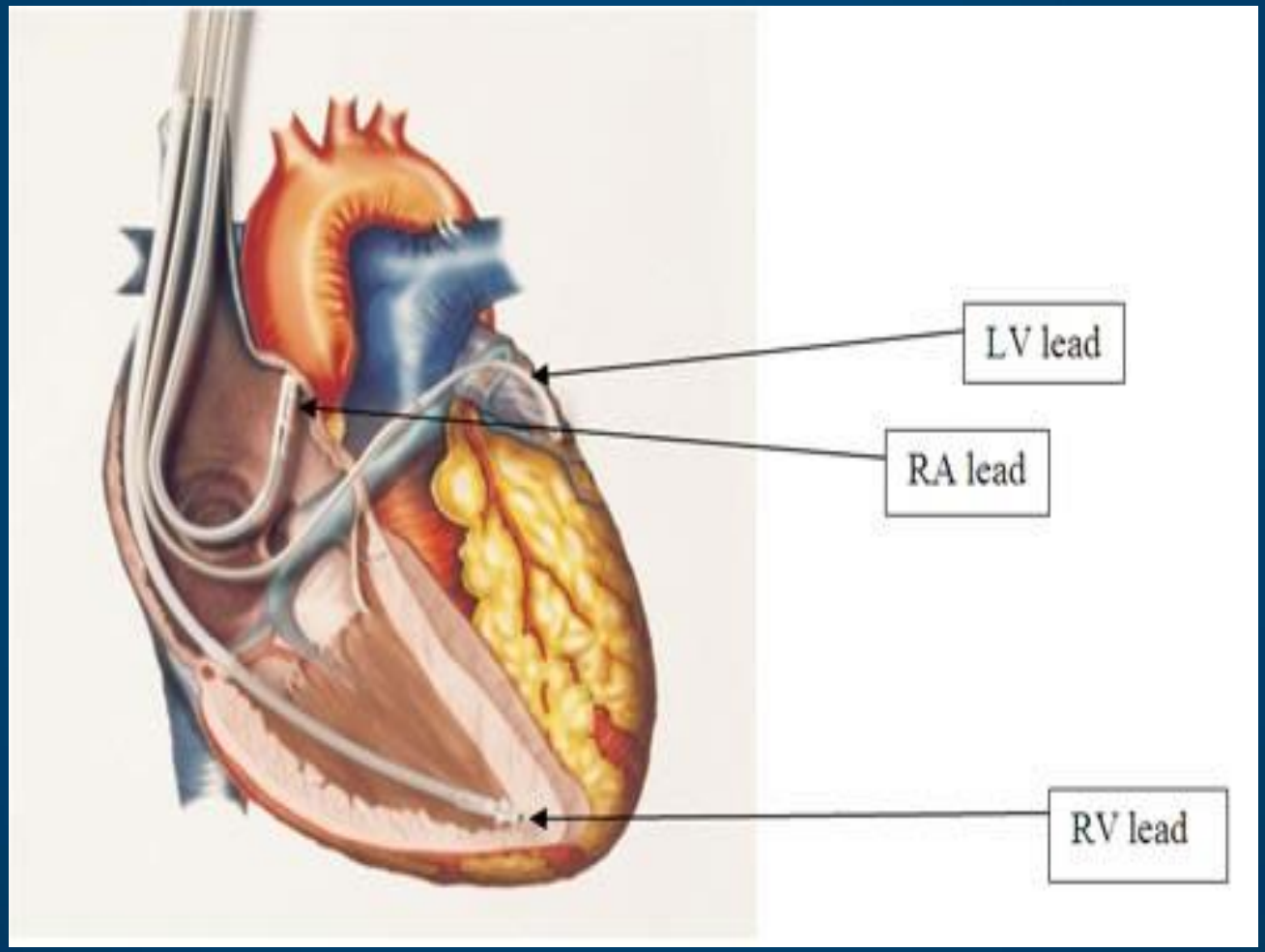
Vesnarinone Study[1] (VEST study analysis)

- NYHA Class II-IV patients
- 3,654 ECGs digitally scanned
- Age, creatinine, LVEF, heart rate, and QRS duration found to be independent predictors of mortality
- Relative risk of widest QRS group 5x greater than narrowest

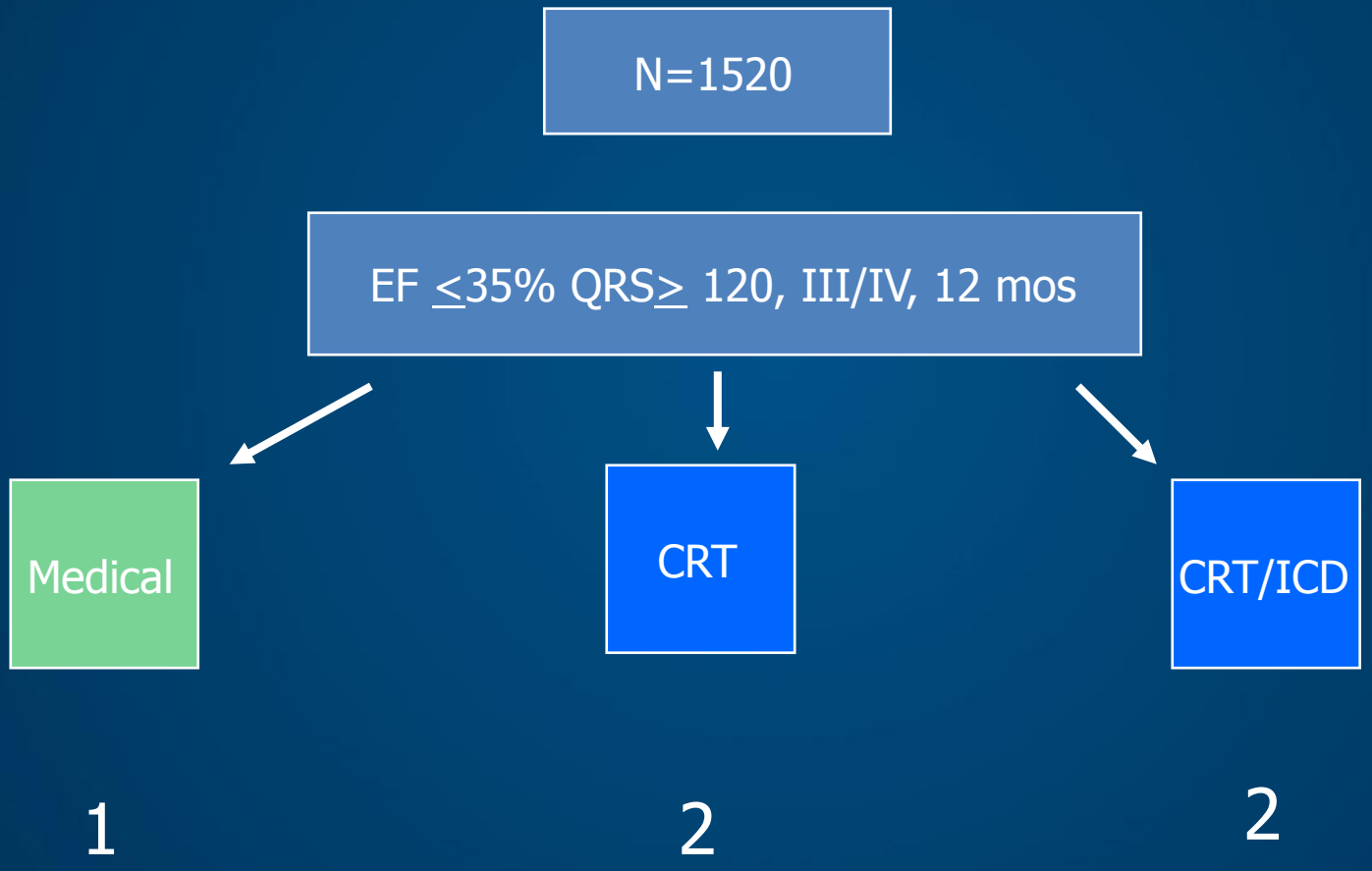


[1] Gottipaty V, Krelis S, Lu F, et al. *JACC* 1999;33(2) :145 [Abstr847-4].

Resynchronization Therapy



COMPANION Trial



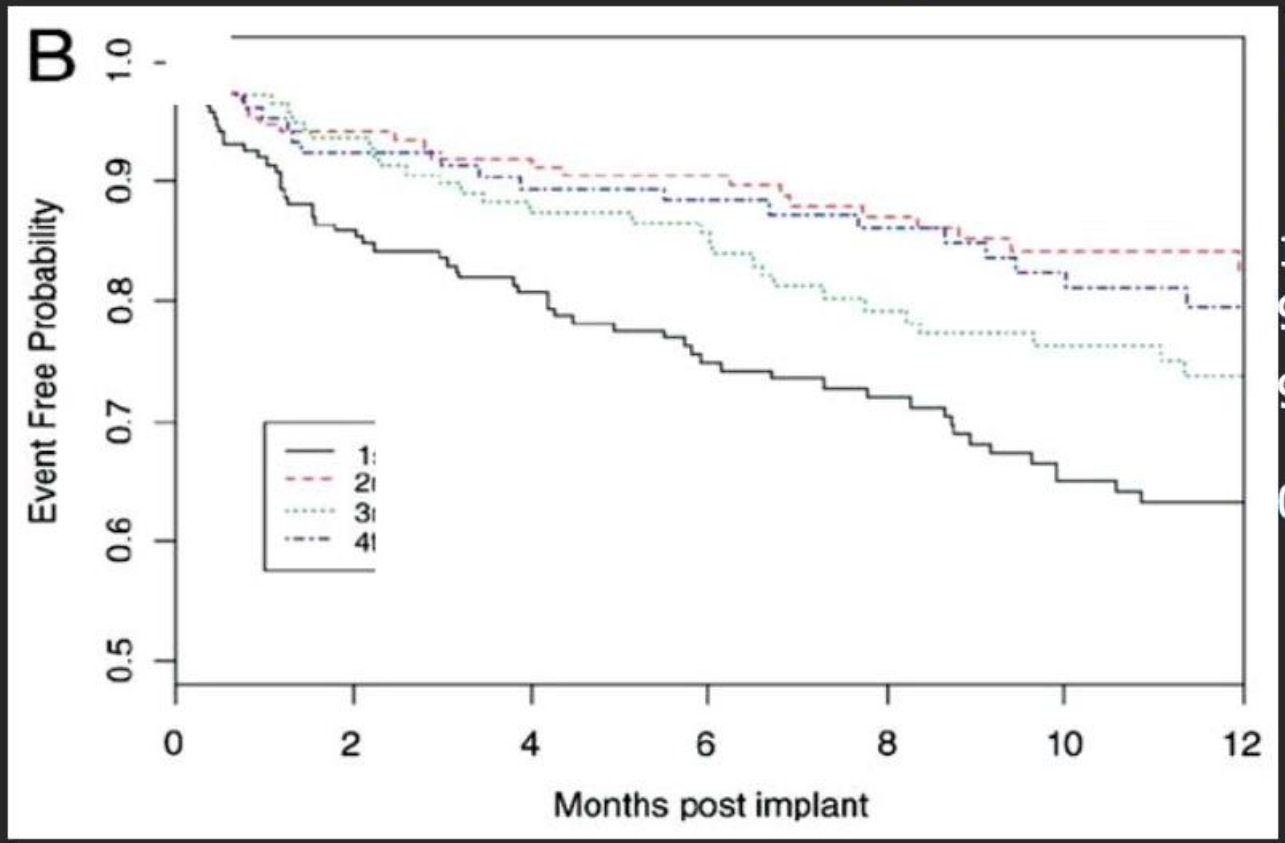
COMPANION Trial Results

	Medical	CRT	CRT/ICD
Any d/hosp	68%	56%*	56%*
Annual Mort	**19%**	**15%**	**12%***
Risk of death			36% decr*
CV d/hosp	60%	45%*	44%*
HF d/hosp	45%	31%*	29%*
Other benefits @ 3 & 6 mos		NYHA, 6 min walk, QOL *	

Feldman et al. J Am Coll Cardiol, 2005; 46:2311-2321

How Much CRT Pacing is Really Needed?

Pts. with AT (n=617) HF hospitalization/mortality



BiVpacing

100%

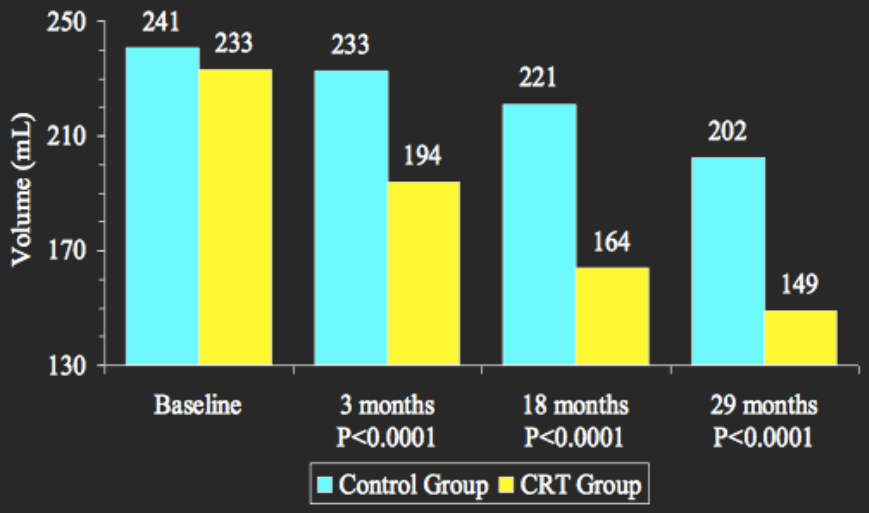
98-99%

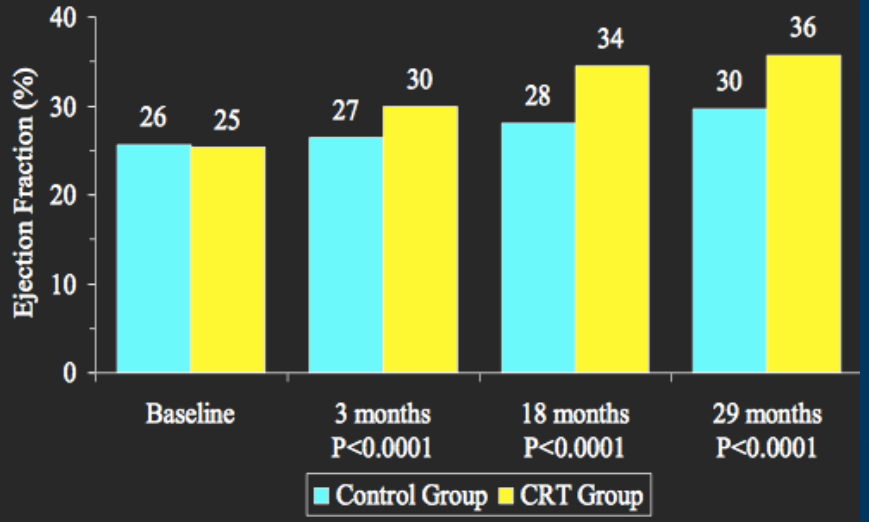
93-97%

0-92%

Koplan et al., JACC 2009

Care-HF: Changes in LVES volume & LVEF





LV End-Systolic Volumes

LV ejection Fraction

Issues in patient selection for CRT- beyond QRS duration

Conventional echocardiographic measures may predict unfavourable response after CRT:

- EF extremely low (< 15-18%);
- EDV > 250 ml **[Gasparini et al, AHA 2003]**;
- End-diastolic wall thickness (EDWT) < 6 mm

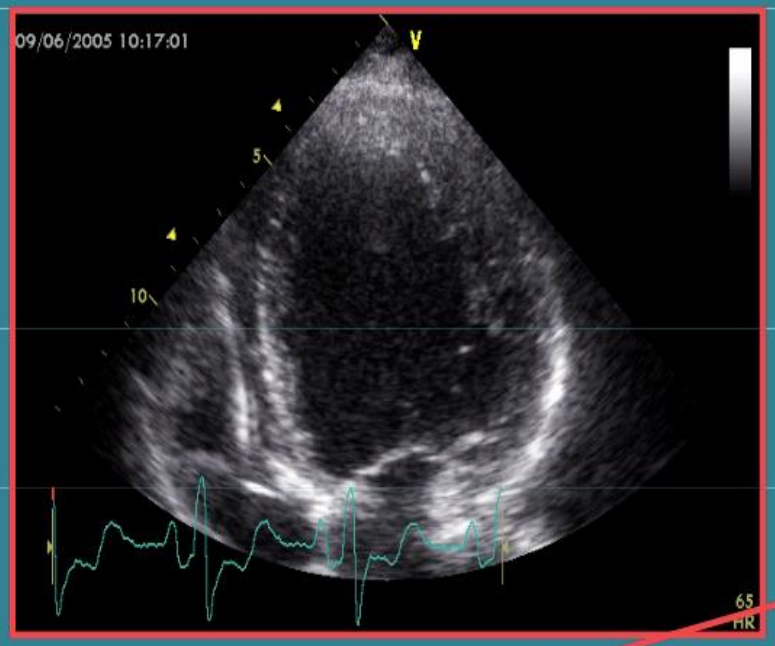
[Cwajg et al, *JACC* 2000]

Moderate as opposed to severe LV dilatation and dysfunction may influence CRT response favourably…

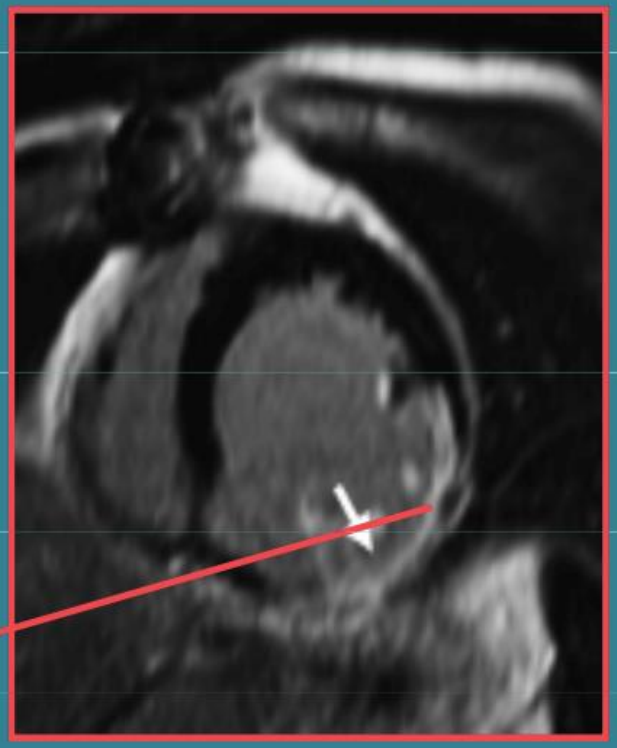
[Auricchio et al, JACC 2002, Gasparini et al, PACE 2007]

Benefit with Ischemic Cardiomyopathy?

Viable myocardium

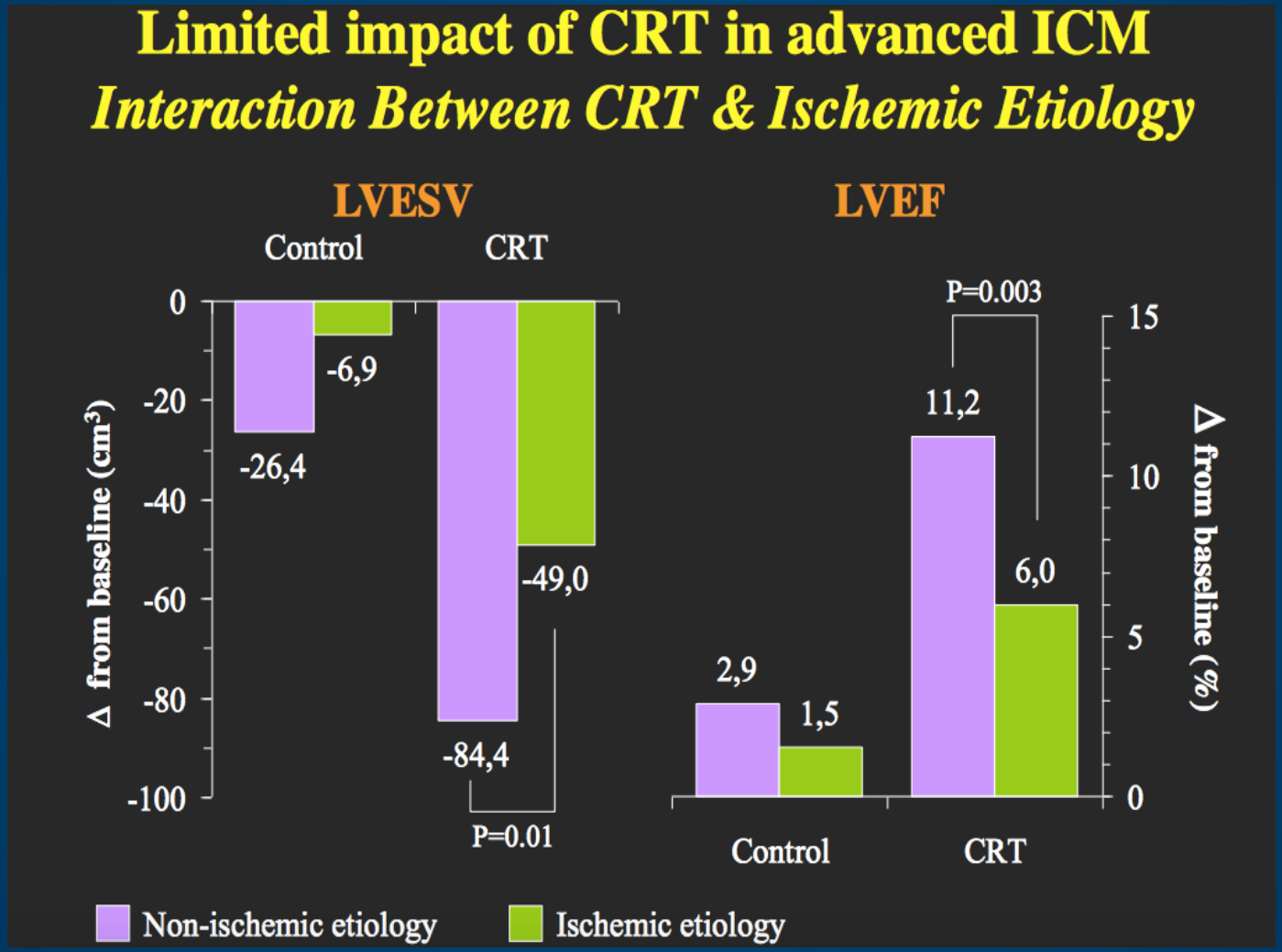


Non-viable myocardium



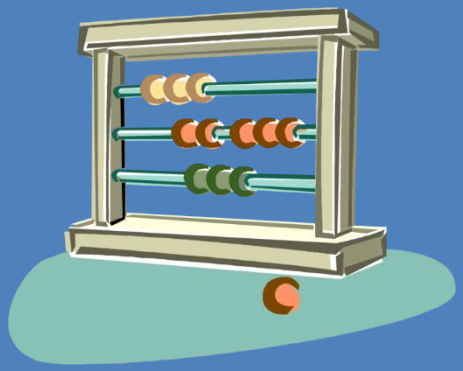
Important SCAR BURDEN→ unlikely to benefit from CRT

Ischemic vs Non-ischemic



Heart Transplant as Solution?

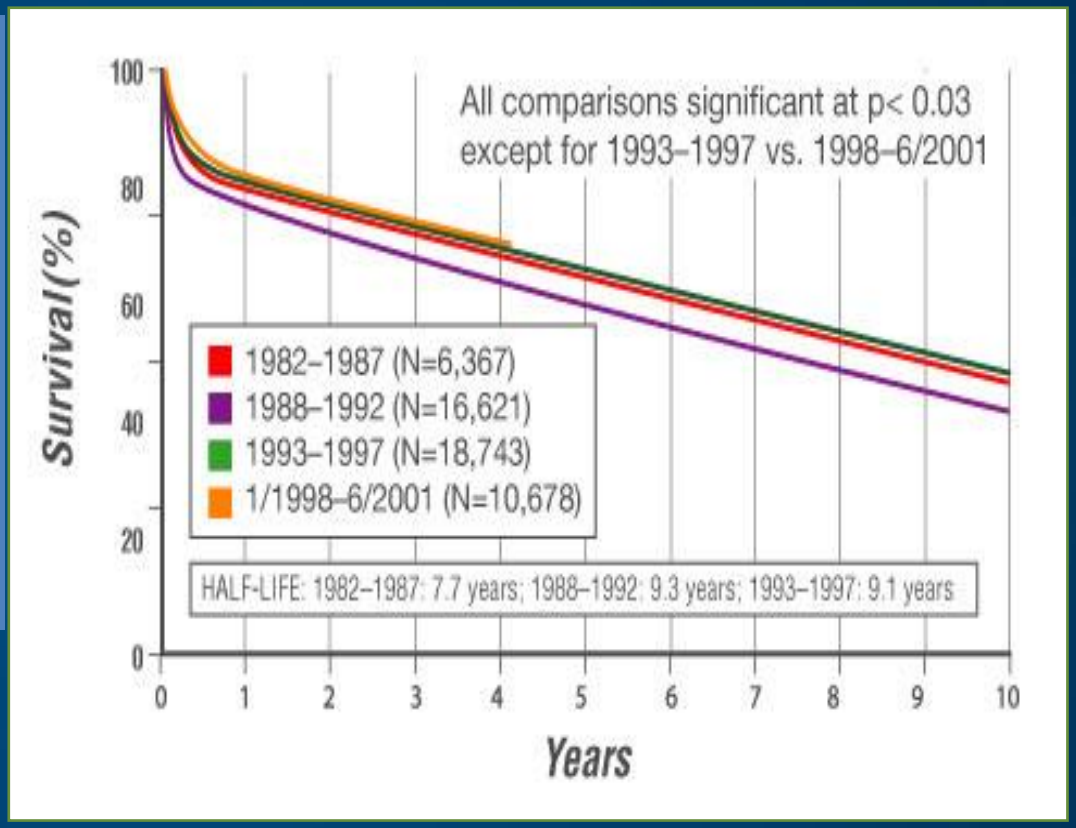
- Approximately, 2200 hearts are donated each year and it is on the decline.



- **NOW LET'S COMPARE:**
- 300,000 Class IV Heart Failure Patients
- vs.
- 2,200-2500 Heart Donations

Cardiac Transplantation

- Remains the most effective Tx for end-stage heart disease, although donor shortage limits its use
- 1-year survival: 86% (2002)
- 5-year survival: 71%
- 10-year survival: 46%

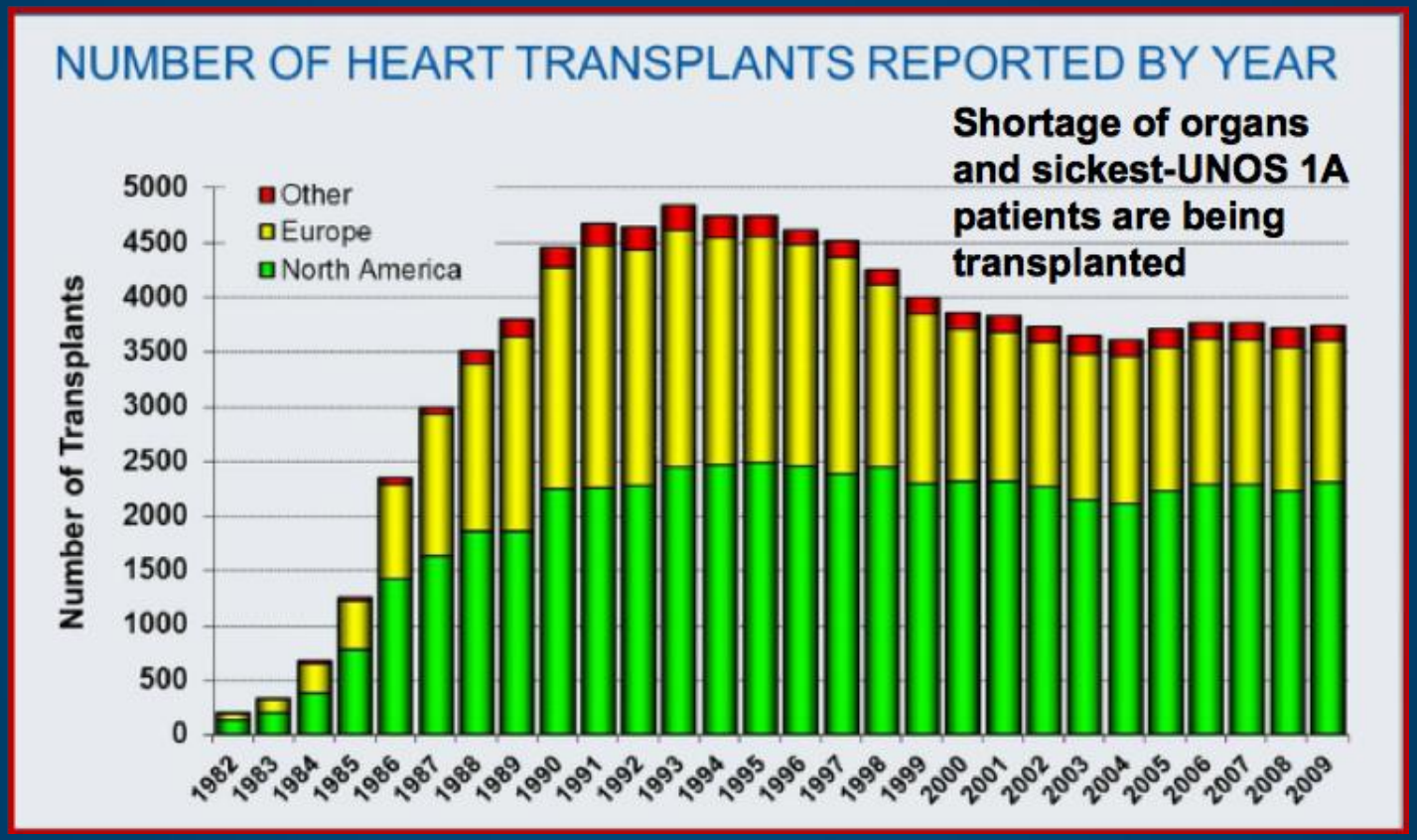


Vitali E, Colombo T, et al. Surgical therapy in advanced heart failure. *Am J Cardiol* 2003;91(suppl):88F-94F

Taylor et al. *J Heart Lung Transplant* 2003;22:616.

American Heart Association. Heart Disease and Stroke Statistics-2009 Update.

Heart Failure



UNOS Classification- Given Limited Supply – imperative to UNOS 1A and 1B

TABLE I. UNOS Definition of Status 1A for Candidates on Waiting List*

A candidate listed as Status 1A is admitted to the listing transplantation center hospital (with the exception for 1A[b] candidates) and has at least one of the following devices or therapies in place:

a) Mechanical circulatory support for acute hemodynamic decompensation that includes at least one of the following:

i) left and/or right ventricular assist device-implanted candidates listed under this criterion may be listed for 30 days at any point after implantation as Status 1A once the treating physician determines that they are clinically stable. Admittance to the listing transplantation center hospital is not required.

ii) total artificial heart;

iii) intra-aortic balloon pump; or

iv) extracorporeal membrane oxygenator (ECMO).

Qualification for Status 1A under criterion 1A(a)(ii), (iii) or (iv) is valid for 14 days and must be recertified by an attending physician every 14 days from the date of the candidate's initial listing as Status 1A in order to extend the Status 1A listing.

b) Mechanical circulatory support with objective medical evidence of significant device-related complications such as thromboembolism, device infection, mechanical failure, or life-threatening ventricular arrhythmias.

*Adapted from the United Network for Organ Sharing's Organ Procurement & Transplantation Network policies: 3.7 Organ Distribution; Allocation of Thoracic Organs

UNOS Classification

- **Status 1B**- Dependent on intravenous medications or a mechanical-assist device – in the hospital or at home.
- **Status 2:** Stable on oral medications and able to wait at home.
- **Status 7 or inactive list:** Inactive due to a change in condition – patients do not lose time they have already accrued.

Wait Times for Cardiac Transplant

- Factors affecting wait time include blood type (O- longest, AB shortest), weight (> 90 KG), height (> 180 cm), region, and PRA > 10%
- **Panel Reactive Antibody (PRA)** is an immunolgical lab test performed on patients awaiting organ transplantation. The PRA score is expressed as a percentage between 0% and 99%. It represents the proportion of the population to which the person being tested will react via pre-existing antibodies. These antibodies target HLA, a protein found on most cells of the body. HLA antigens vary by demographics so PRA test will differ from country to country. Individuals with a high PRA are often termed "sensitized", which indicates that they have been exposed to "foreign" (or "non-self") proteins in the past and have developed antibodies to them
- Donor hearts are provided to patients based on the donor's blood type and body weight, the recipient's severity of illness, and geographic location. These data are contained in the UNOS computer database.

Heart Failure

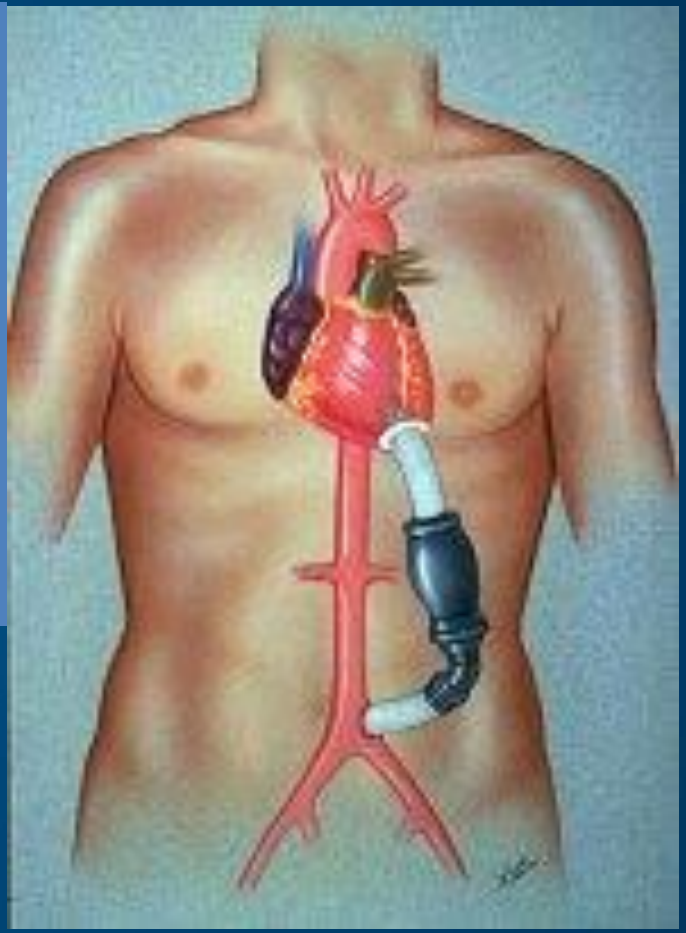
- ***Best estimates are that 250,000 patients have advanced heart failure, but only 1% will receive a transplant.***

- ***VADs can help bridge this gap between supply and demand.***

- ***As time spent on the waiting list increases, more patients are receiving a VAD to bridge the time from listing to identification of a suitable donor.***

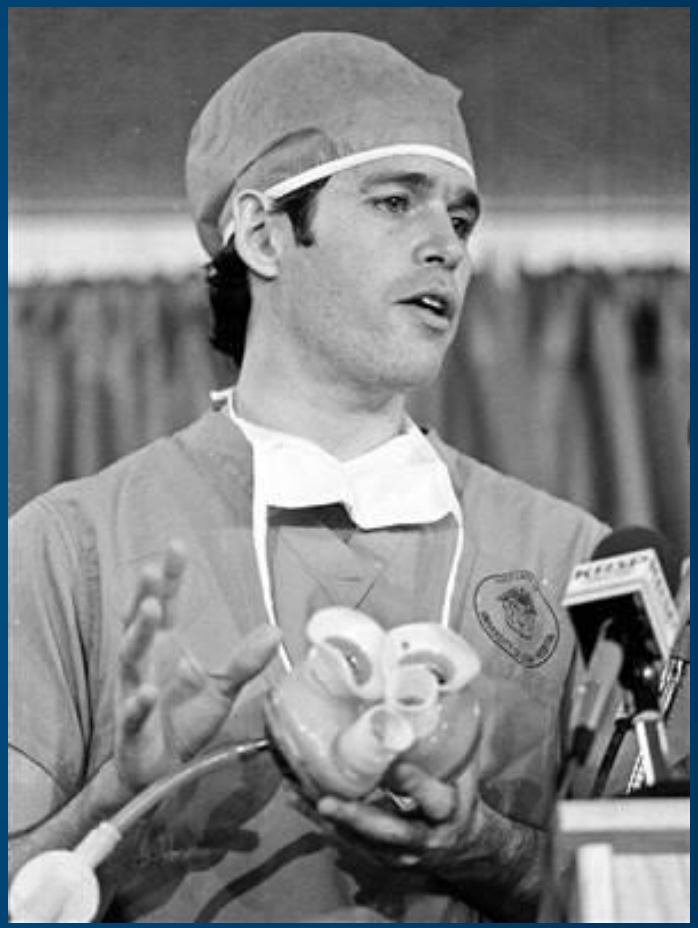
1978 Dr. John Norman & Dr. Denton Cooley

- First use of an LVAD as a bridge to transplant in a 21 year old post MVR/AVR. Patient received a heart transplant 5 days later.
- The pumps was interposed between the apex of the left ventricle and the infrarenal abdominal aorta (ALVAD).

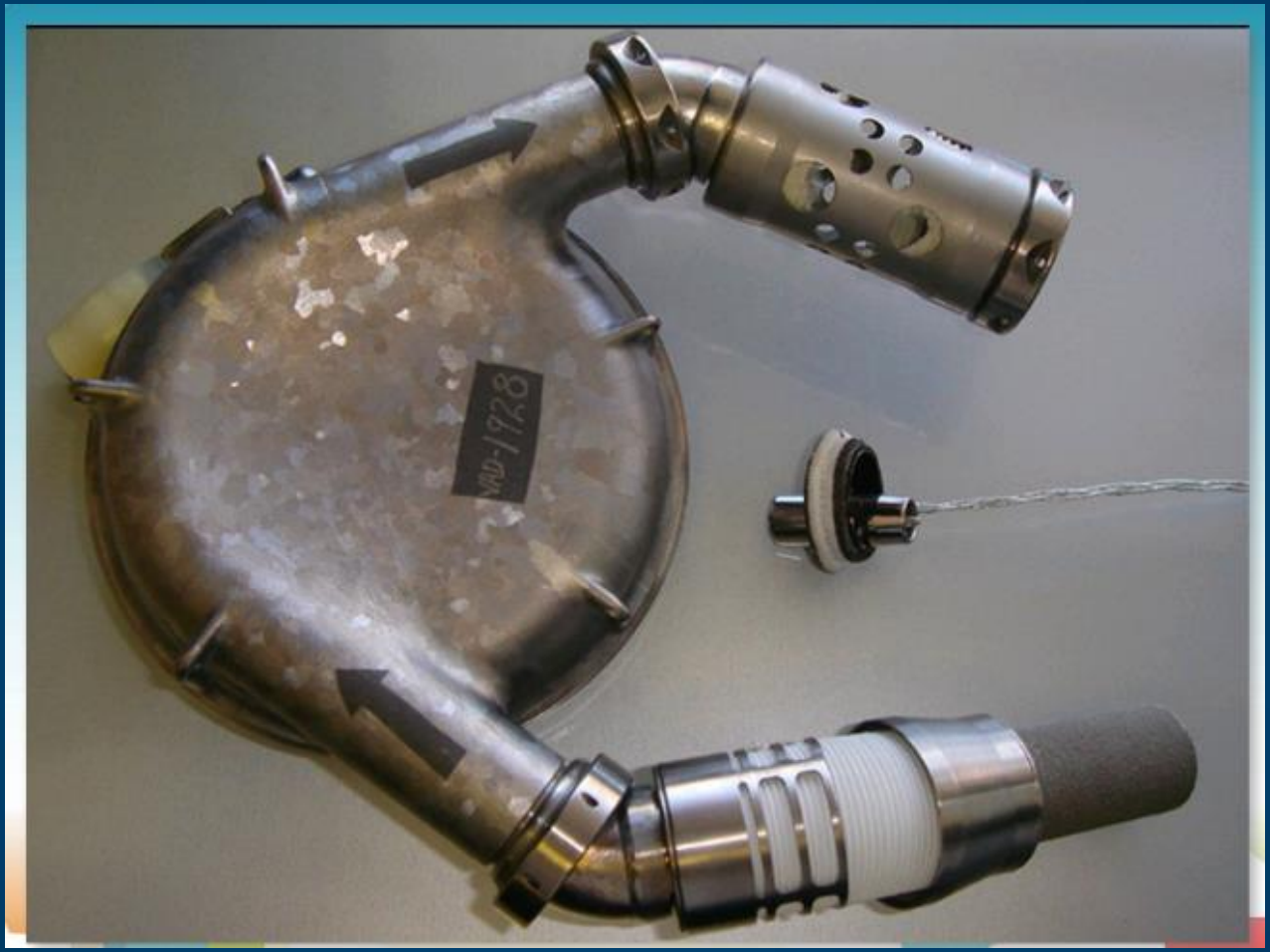


1982 Barney Clark

- Dr. William DeVries implanted the Jarvik 7 in Barney Clark for destination therapy. He lived for 112 days



Heartmate XVE



HeartMate XVE and HeartMate II® Comparison

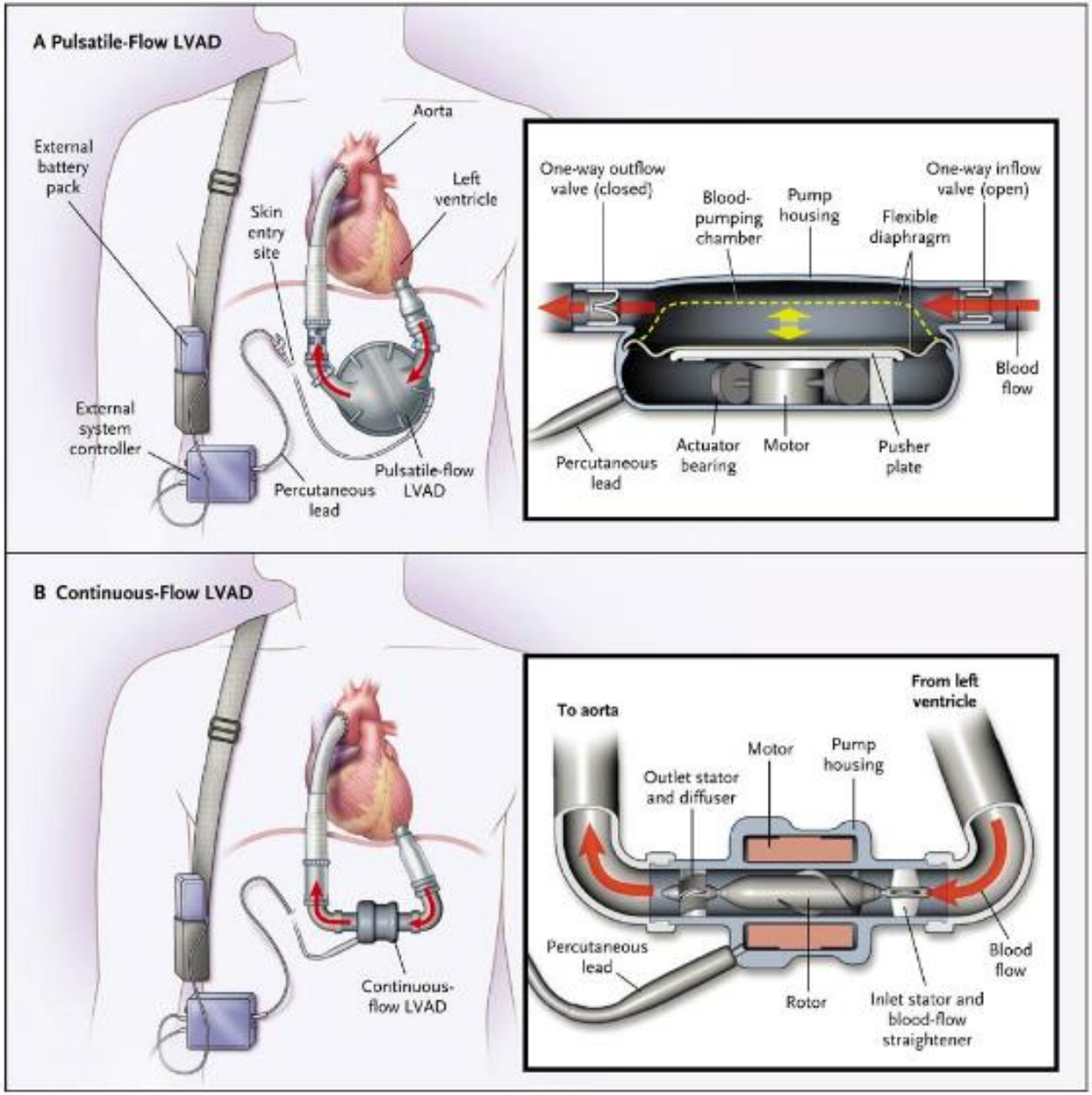
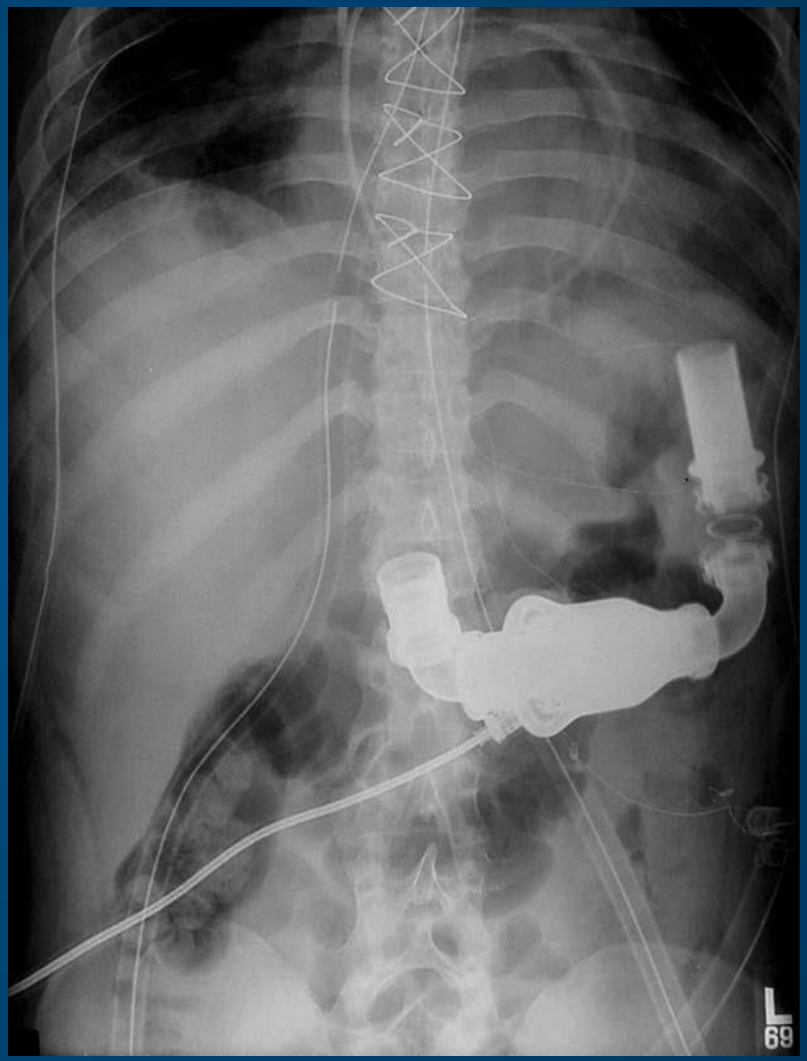


Figure 1. Pulsatile-Flow (Panel A) and Continuous-Flow (Panel B) Left Ventricular Assist Devices (LVADs).

2003 First HeartMate II US implant

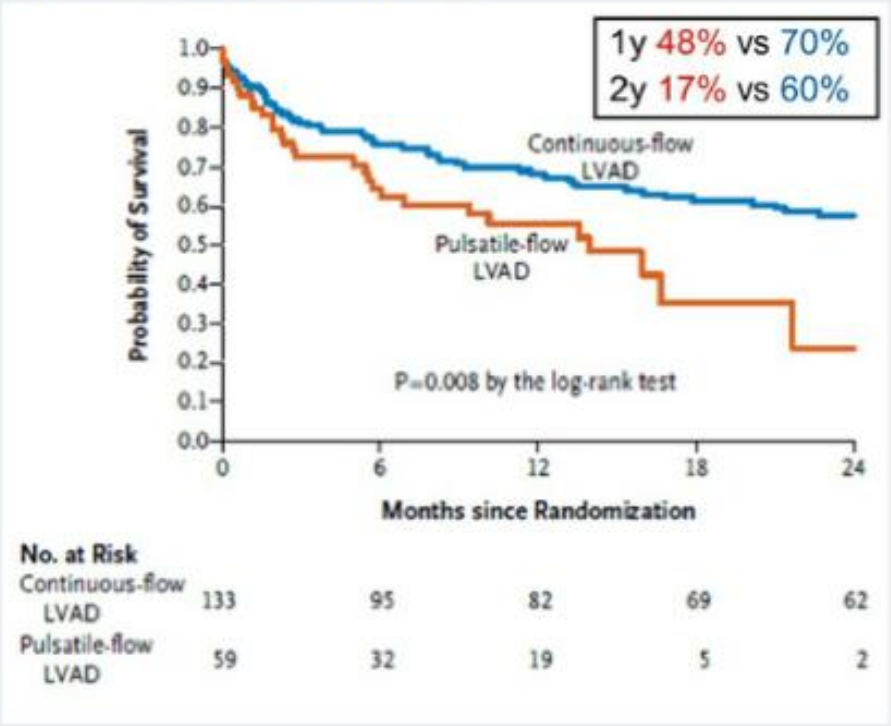
- Dr. O.H. Frazier, Texas Heart Institute implanted 1st US HMII in November 2003
- Pt was a 18 y/o Male, Non-Ischemic Cardiomyopathy



Heart Failure

Heartmate II vs. Heartmate I - Survival

(US – RCT – Chronic Implants)



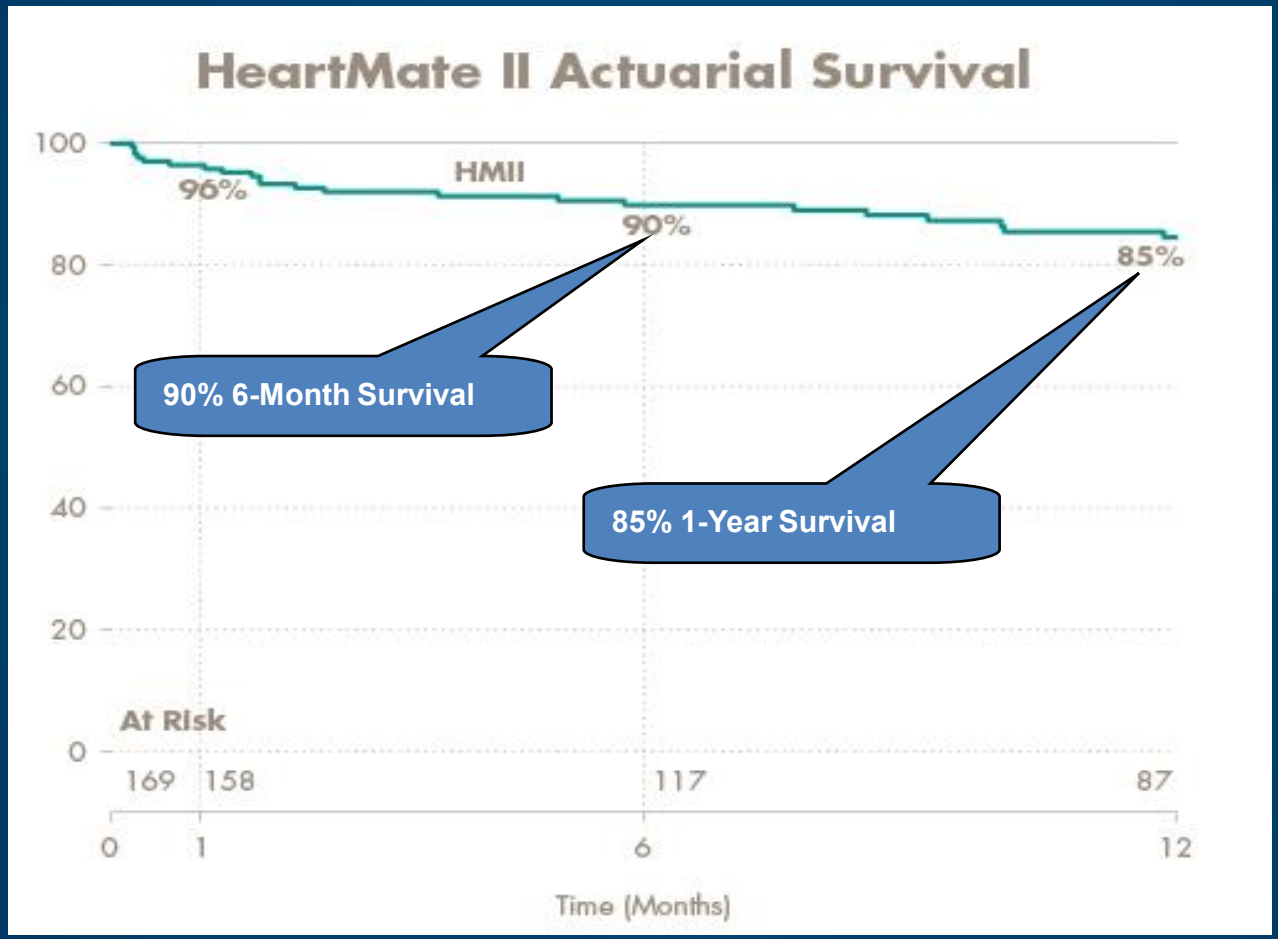
UniversitätsSpital Zürich

Slaughter NEJM 2010

Continuous flow pumps do better than pulsatile flow pumps

BTT Actuarial Survival

Post Approval Study



Starling, Naka, Boyle JACC, in press 2010

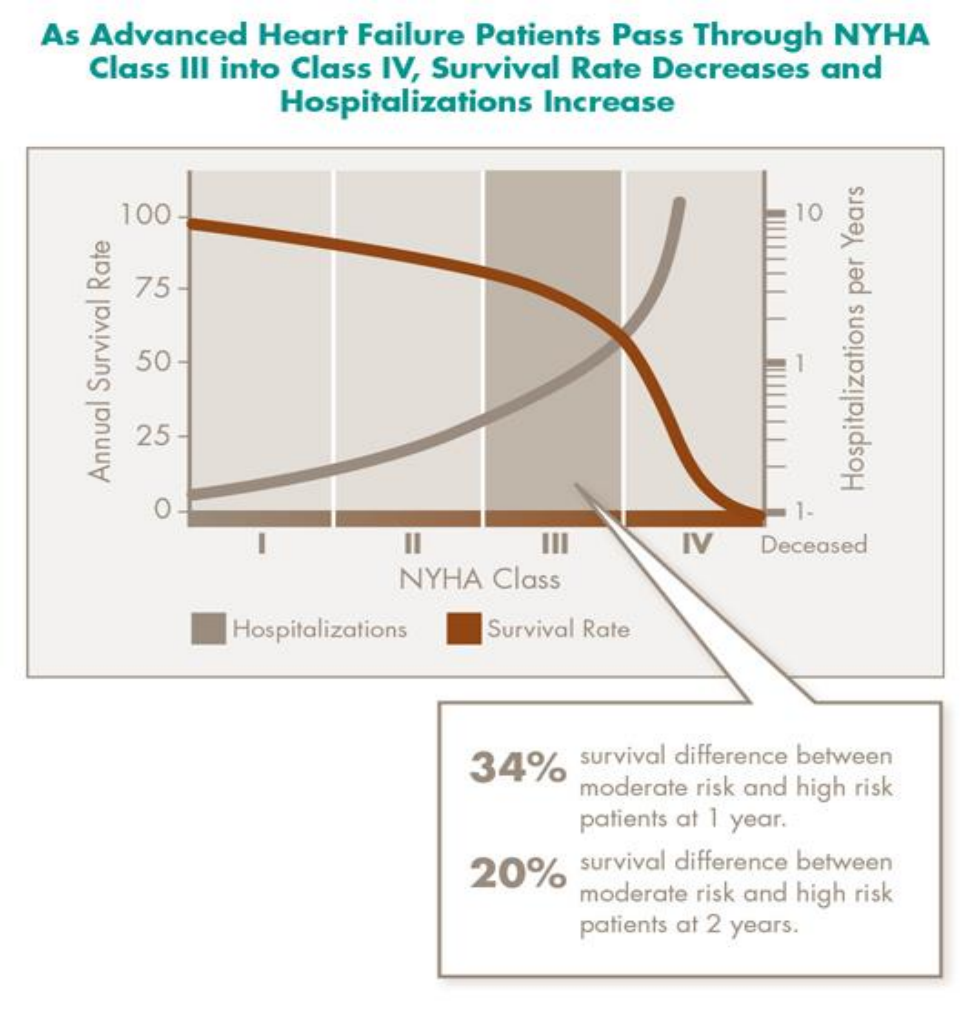
HeartMate II Indications for Use

- Bridge to Transplantation
  - Non-reversible left heart failure
  - Imminent risk of death
  - Candidate for cardiac transplantation
- Destination Therapy
  - NYHA Class IIIB or IV heart failure
  - Optimal medical therapy 45 of last 60 days
  - Not candidate for cardiac transplantation

FDA/CMS Criteria for Destination Therapy

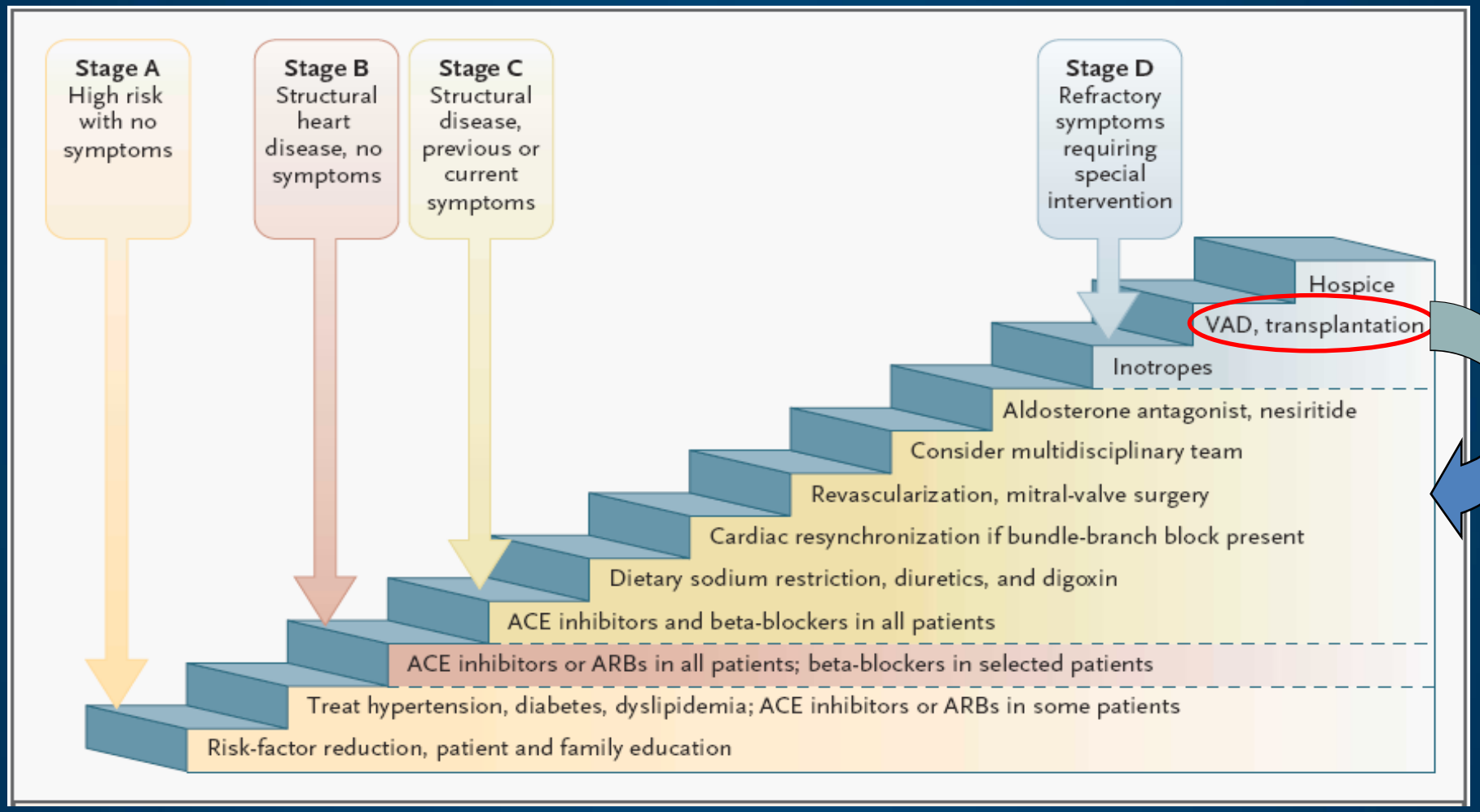
- Not a candidate for heart transplant
- NYHA class IV end-stage LV failure
- Life expectancy < 2 years
- Symptoms failed to respond despite optimal medical management for ε 45 days
- LVEF < 25%
- Peak VO2 < 12 ml/kg/min or inotrope dependence
- BSA ε 1.5 m2

Early Evaluation is Critical



Bristow MK. Management of heart failure. In: Braunwauld E, ed. *Heart Disease: a Textbook of Cardiovascular Medicine.* Vol 1. 6th ed. Philadelphia: W.B. Saunders Company, 2001:635-651

When Should the MCS Discussion Begin?

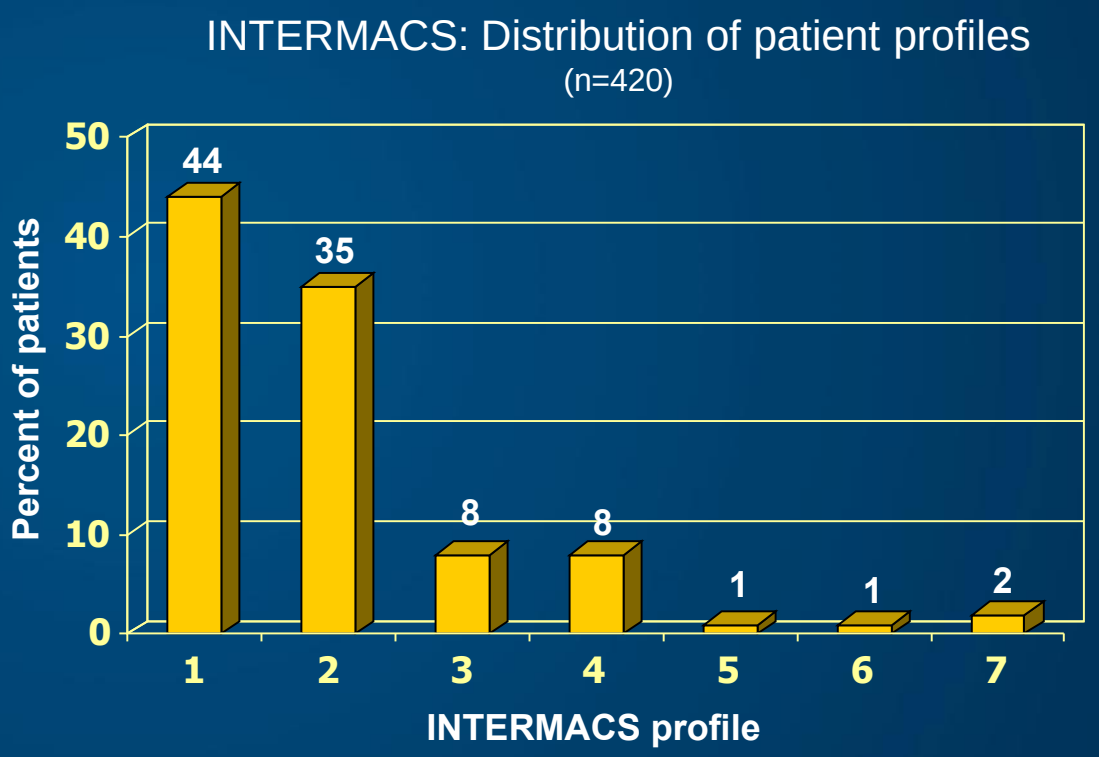


Jessup M, Brozena S. N Engl J Med 2003;348:2007-18.

Patient selection

INTERMACS Profile

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



Pagani et al. ISHLT 4/2008.

Economic Risks of HF Readmissions in the US

Medicare's Hospital Readmissions Reduction program penalizes hospitals that have above average all-cause readmissions within 30 days following HF discharge.

22.7%

national average 30-day readmissions rate[1,2]

Percent withholding of all inpatient Medicare payments will increase to up to 3% by 2015 and beyond.[3]

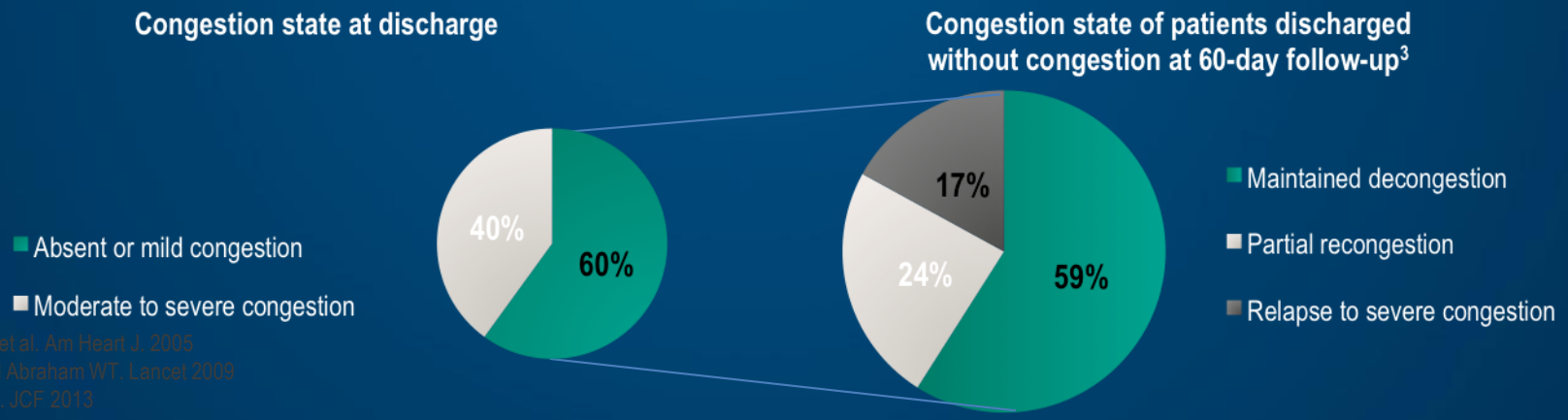
Fiscal Year	2013	2014	2015+
% payment withholding	up to 1%	up to 2%	up to 3%

1. Dharmarajan K, et al. JAMA. 2013;309(4):355-363.
2. Linden A, Adler-Milstein J. *Health Care Finance Rev*. 2008;29(3):1-11.
3. CMS Hospitals Readmissions Reductions Program of the Patient Protection and Affordable Care Act (PPACA). 2010.

Current HF Management Is Inadequate For Identifying and Managing Congestion Leading to Decompensation

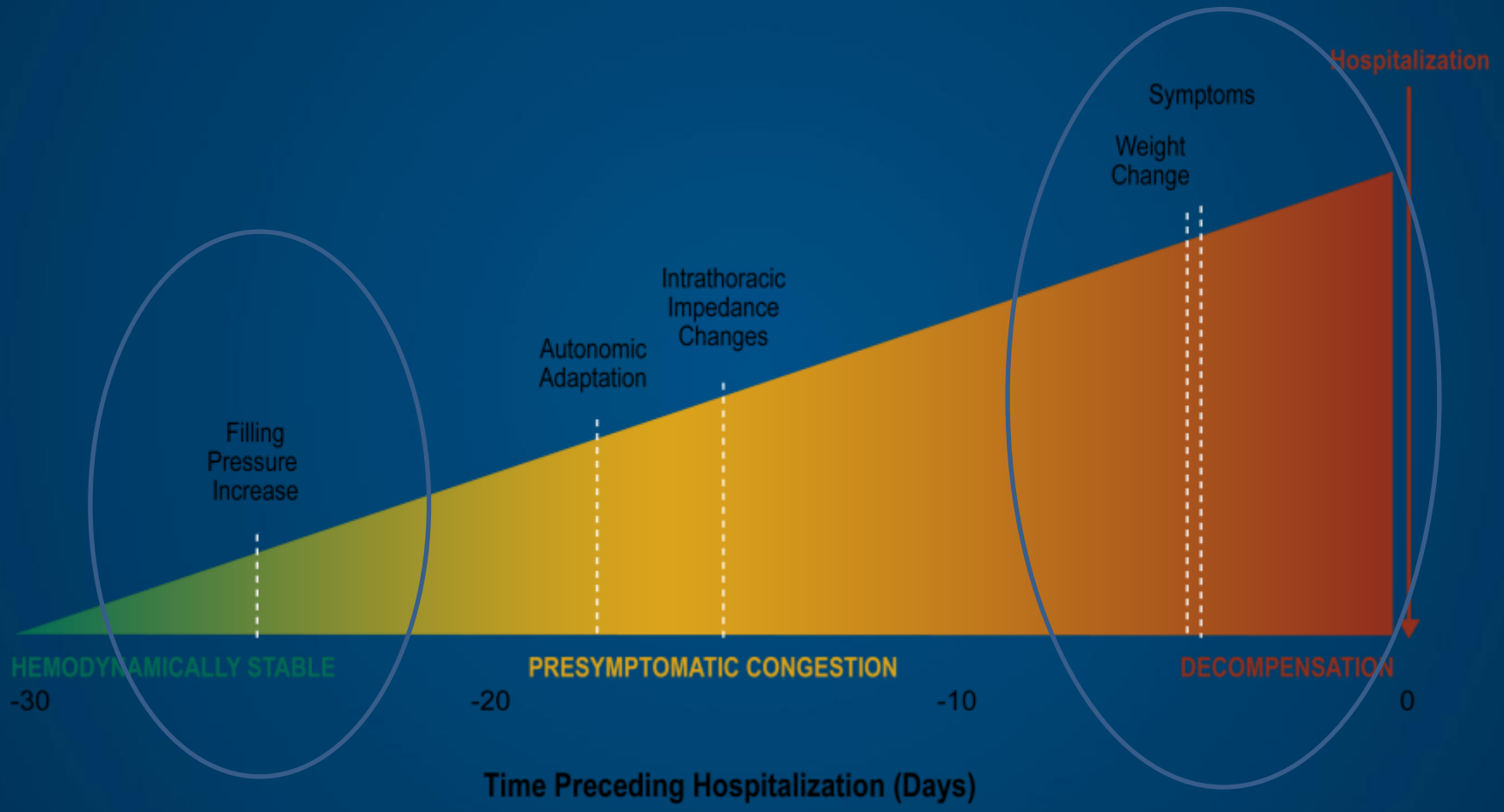
Identifying congestion early will lead to early treatment, prevent hospitalizations and slow the progression of HF.

- 90% of HF hospitalizations present with symptoms of pulmonary congestion.[1,2]
- Post-hoc analysis of 463 acute decompensated HF patients from DOSE-HF and CARRESS-HF trials showed:
  - 40% of patients are discharged with moderate to severe congestion.[3]
  - Of patients decongested at discharge, 41% had severe or partial re-congestion by 60 days.[3]



1. Adams KF, et al. Am Heart J. 2005
2. Krum H and Abraham WT. Lancet 2009
3. Lala A, et al. JCF 2013

Physiologic Markers of Acute Decompensation



Graph adapted from Adamson PB, et al. Curr Heart Fail Reports, 2009.

Clinical Examination has Limited Reliability in Assessing Filling Pressures

Data from clinical evaluations has poor sensitivity and predictive value in determining hemodynamic profile

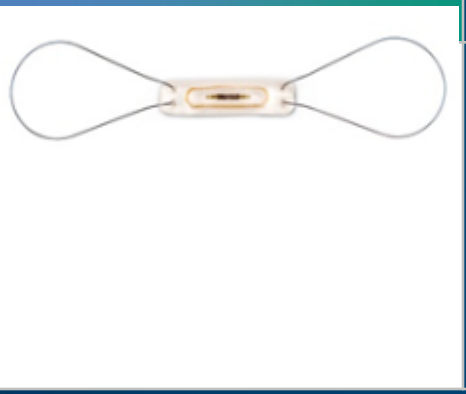
Capomolla, 2005. N = 366

Variable	Estimate of	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
JVP	RAP	48	78	60	69
Edema		10	94	55	60
Pulse Press	Cardiac Index	27	69	52	44
S3	PCWP	36	81	69	54
Dyspnea		50	73	67	57
Rales		13	90	60	48

Table adapted from Capomolla S, et al. Eur J Heart Failure, 2005.

CardioMEMS™ HF System

Pulmonary Artery Pressure Sensor

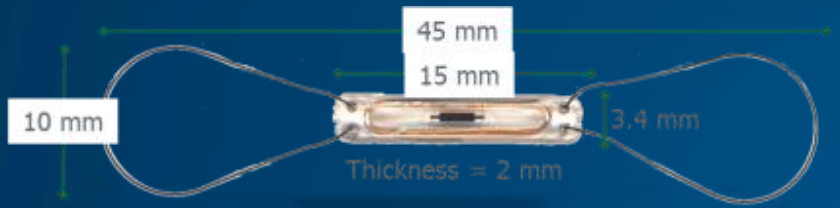


Patient Electronics System

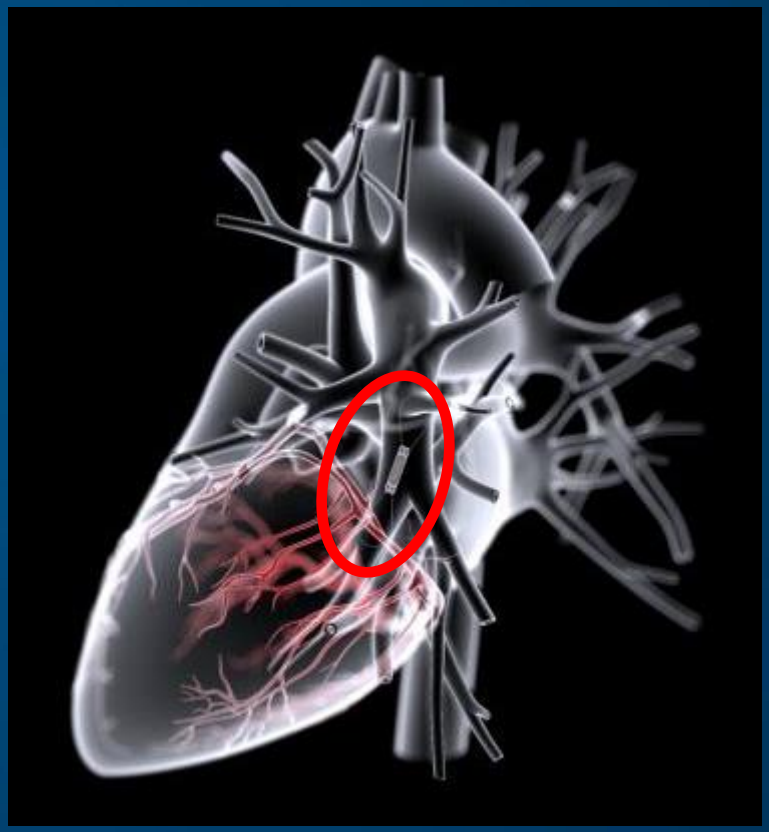
CardioMEMS™ HF System Website

CardioMEMS™ HF System

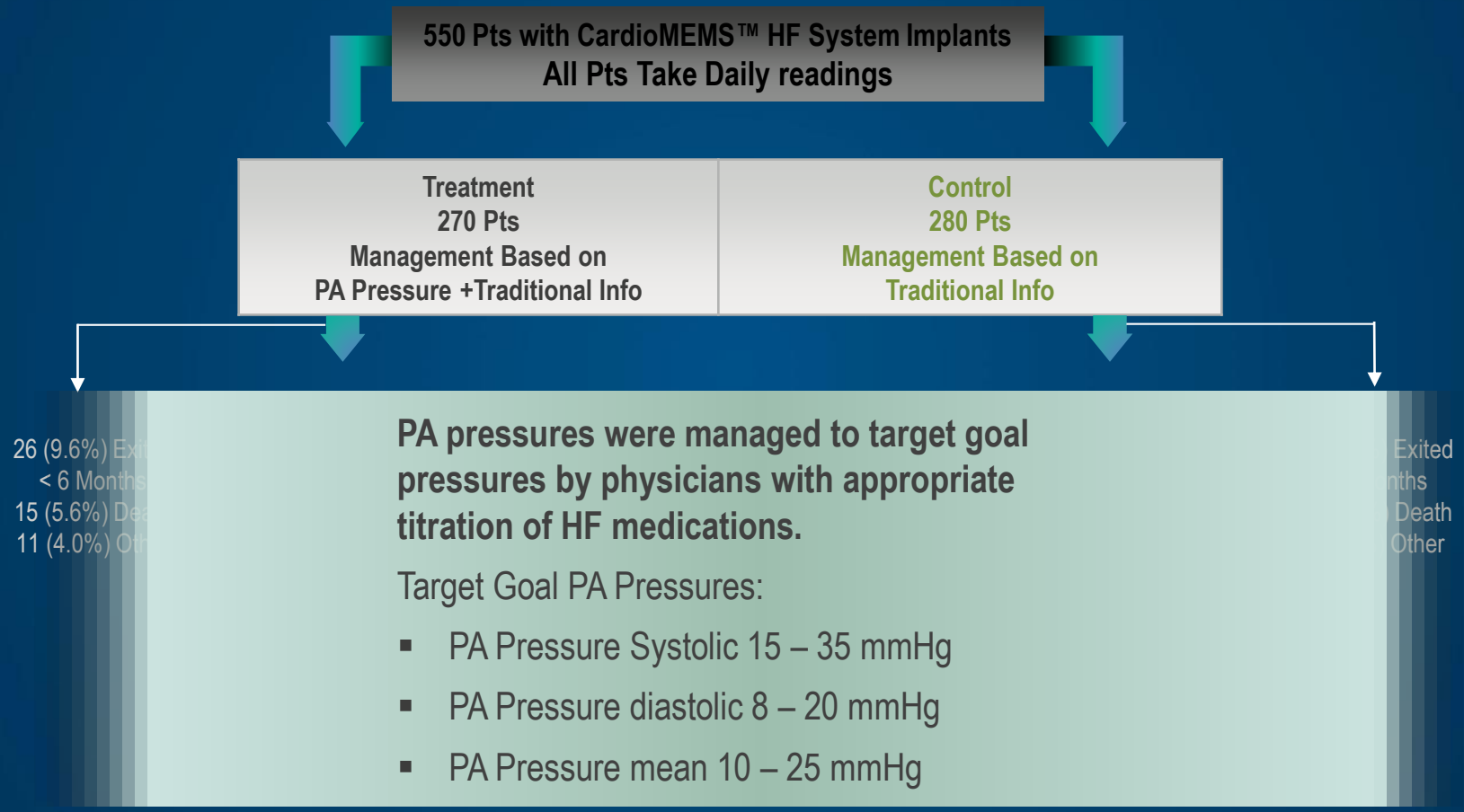
The pulmonary artery pressure sensor is implanted via a right heart catheterization procedure via femoral vein approach.



Target location for pulmonary artery pressure sensor



CHAMPION Clinical Trial: Managing to Target PA Pressures



Abraham WT, et al. Lancet, 2011.

GUIDELINES FOR MANAGING TRENDS OF AMBULATORY PA PRESSURES*

LOW PA PRESSURES (HYPO-VOLEMIC)
PA pressure trending below the hemodynamic range

Has poor perfusion in the absence of signs and symptoms of congestion

If on thiazide and loop diuretic, lower or D/C the thiazide diuretic
- if only on loop diuretic, lower the dose or discontinue
- consider liberalization of oral fluid or salt restriction

Lower or hold vasodilators
- if postural hypotension present

Re-evaluate PA pressures
- 2-3 days per week until PA pressures stabilize

Lower or hold ACE/ARB dose
- if worsening renal function is present with hypotension

If patient has signs of poor perfusion (cold), consider other interventions such as: admission for monitoring and adjustment of medical management; IV therapeutic agents, IV diuretics, IV fluid repletion; invasive hemodynamic monitoring to evaluate CO.

NORMAL PA PRESSURES (OPTI-VOLEMIC)
PA pressure trending within the hemodynamic range

Has minimal symptoms or minimal evidence of poor perfusion

No medication changes based on hemodynamic information

Continue ACC/AHA Guidelines recommended therapies

Evaluate PA pressures weekly

ELEVATED PA PRESSURES (HYPER-VOLEMIC)
PA pressure trending above the hemodynamic range

Add or increase diuretic
- add/increase loop diuretic
- change loop diuretic
- add thiazide diuretic
- IV loop diuretic

Add or increase vasodilators
- add/increase nitrate

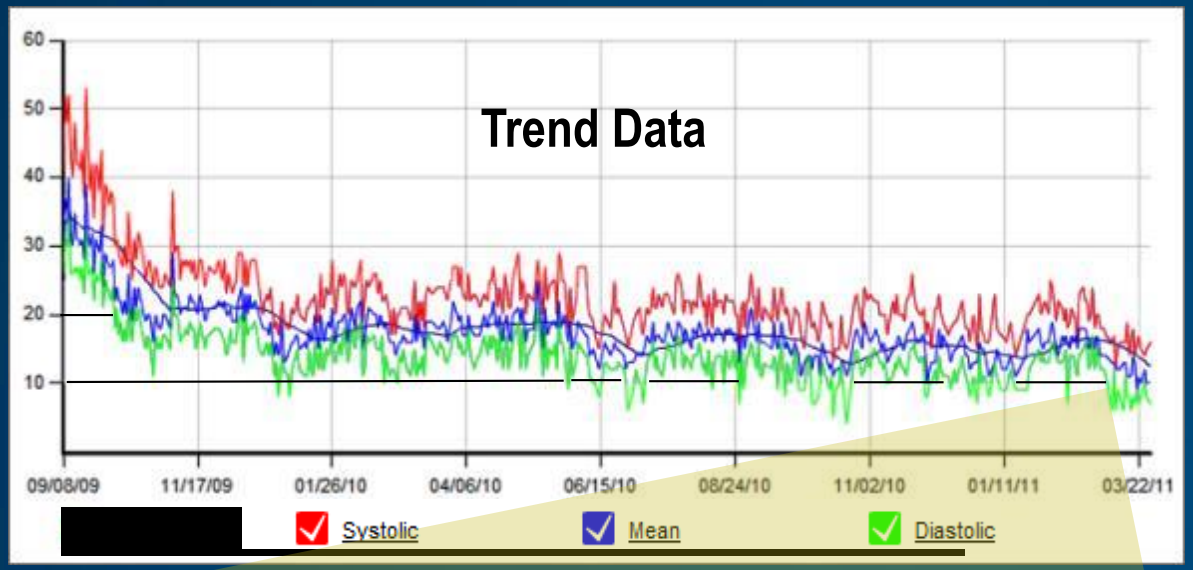
Re-evaluate PA pressures
- 2-3 days per week until PA pressures stabilize

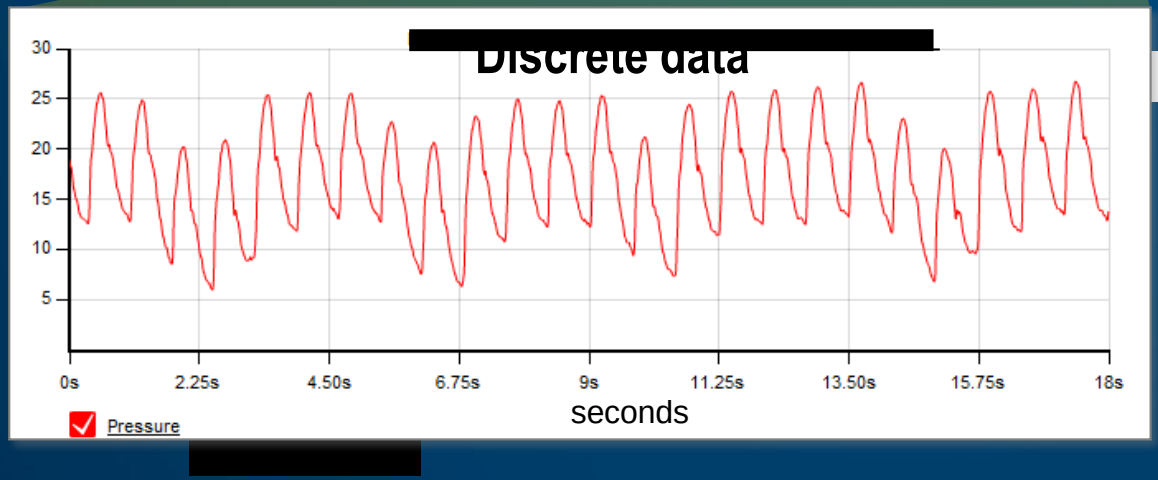
Evaluate other etiologies
- if PA pressures remain elevated consider dietary indiscretion, sleep apnea, etc.

If patient has signs of poor perfusion (cold), consider other interventions such as: admission for monitoring and adjustment of medical management; IV therapeutic agents, IV diuretics, IV fluid repletion; invasive hemodynamic monitoring to evaluate CO.

*These guidelines were included in the protocol for the CHAMPION clinical trial. For additional information, please refer to the CardioMEMS HF System User's Manual.

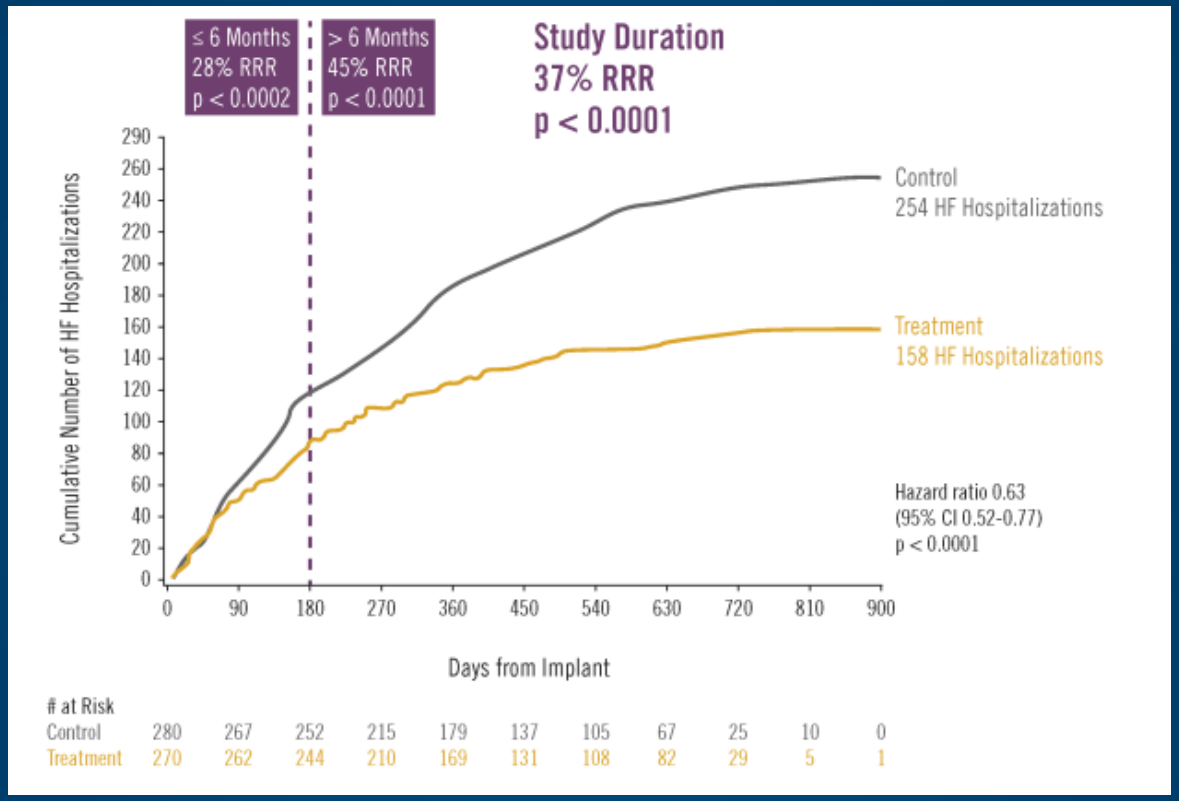
Pulmonary Artery Pressure Database





Reading	
Systolic:	24
Mean:	19
Diastolic:	16
Heart Rate:	81

CHAMPION Clinical Trial: PA Pressure-guided Therapy Reduces HF Hospitalizations



Patients managed with PA pressure data had **significantly fewer HF hospitalizations** as compared to the control group.

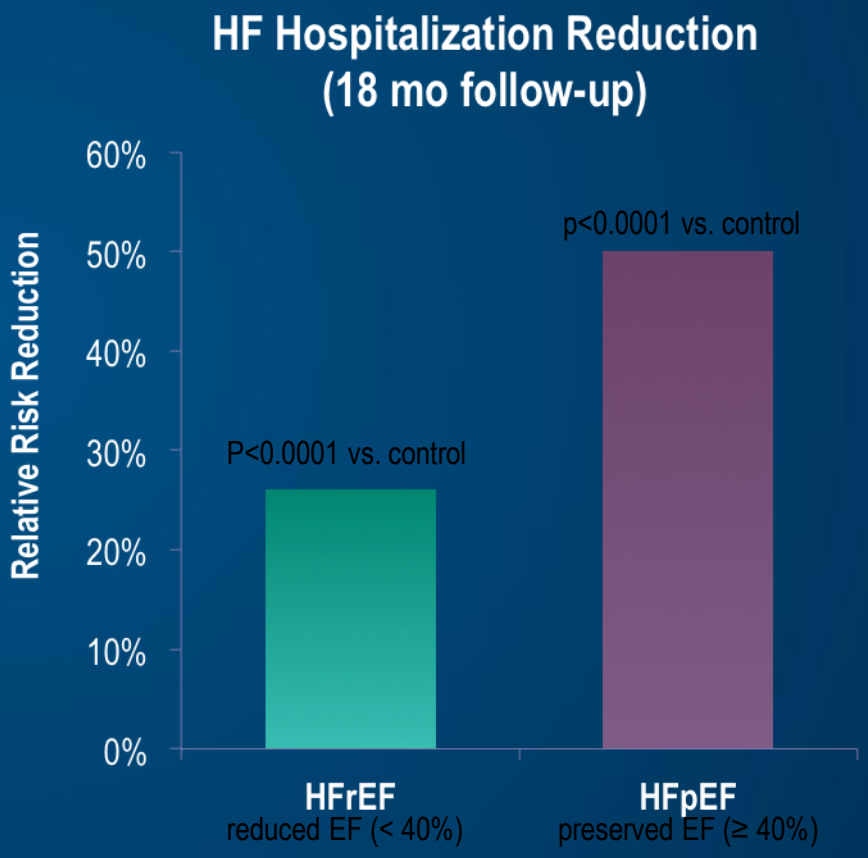
Abraham WT, et al. Lancet, 2011.

CHAMPION Clinical Trial: The Number Needed to Treat (NNT) to Prevent One HF-related Hospitalization is Lower vs. Other Therapies

Intervention	Trial	Mean Duration of Randomized Follow-Up	Annualized Reduction in HF Hospitalization Rates	NNT per year to Prevent 1 HF Hospitalization
Beta-blocker	COPERNICUS	10 months	33%	7
Aldosterone antagonist	RALES	24 months	36%	7
CRT	CARE-HF	29 months	52%	7
Beta-blocker	MERIT-HF	12 months	29%	15
ACE inhibitor	SOLVD	41 months	30%	15
Aldosterone antagonist	EMPHASIS-HF	21 months	38%	16
Digoxin	DIG	37 months	24%	17
Angiotensin receptor blocker	Val-HeFT	23 months	23%	18
Angiotensin receptor blocker	CHARM	40 months	27%	19
PA pressure monitoring	**CHAMPION**	**17 months**	**33%**	**4**

CHAMPION Clinical Trial: PA Pressure-Guided Therapy Improves Outcomes in Patients with Preserved Ejection Fraction

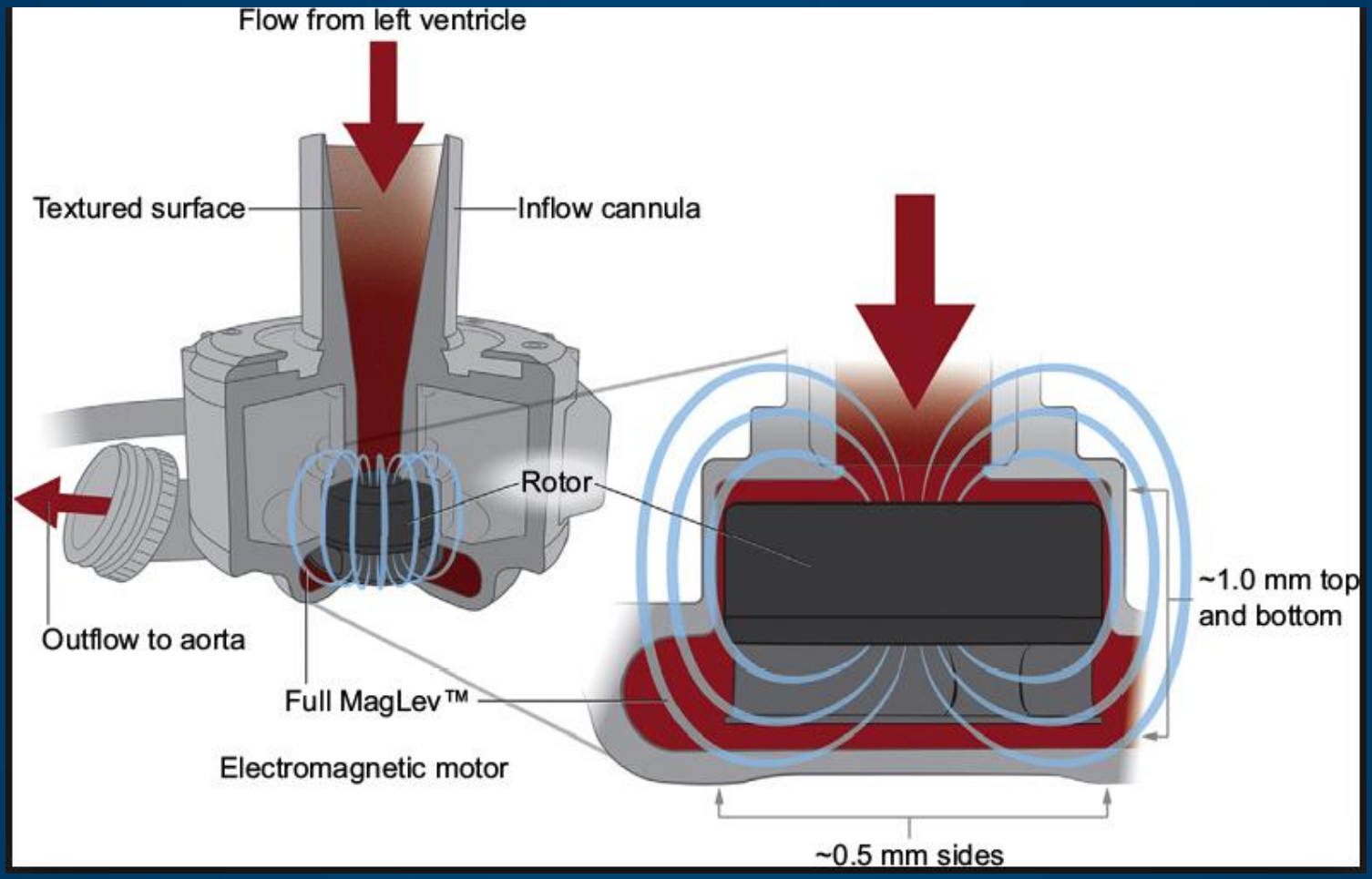
- Preserved Ejection Fraction Heart Failure (HFpEF) or diastolic HF patients represent ~50% of all HF patients
- Pulmonary artery pressure-guided therapy significantly reduced HF hospitalizations in HFpEF patients in the treatment group by 46% at 6 months (p<0.0001) and by 50% at 18 months (p<0.0001)
- The effect in HFpEF patients is even more dramatic than HFrEF or systolic patients with an estimated NNT = 2

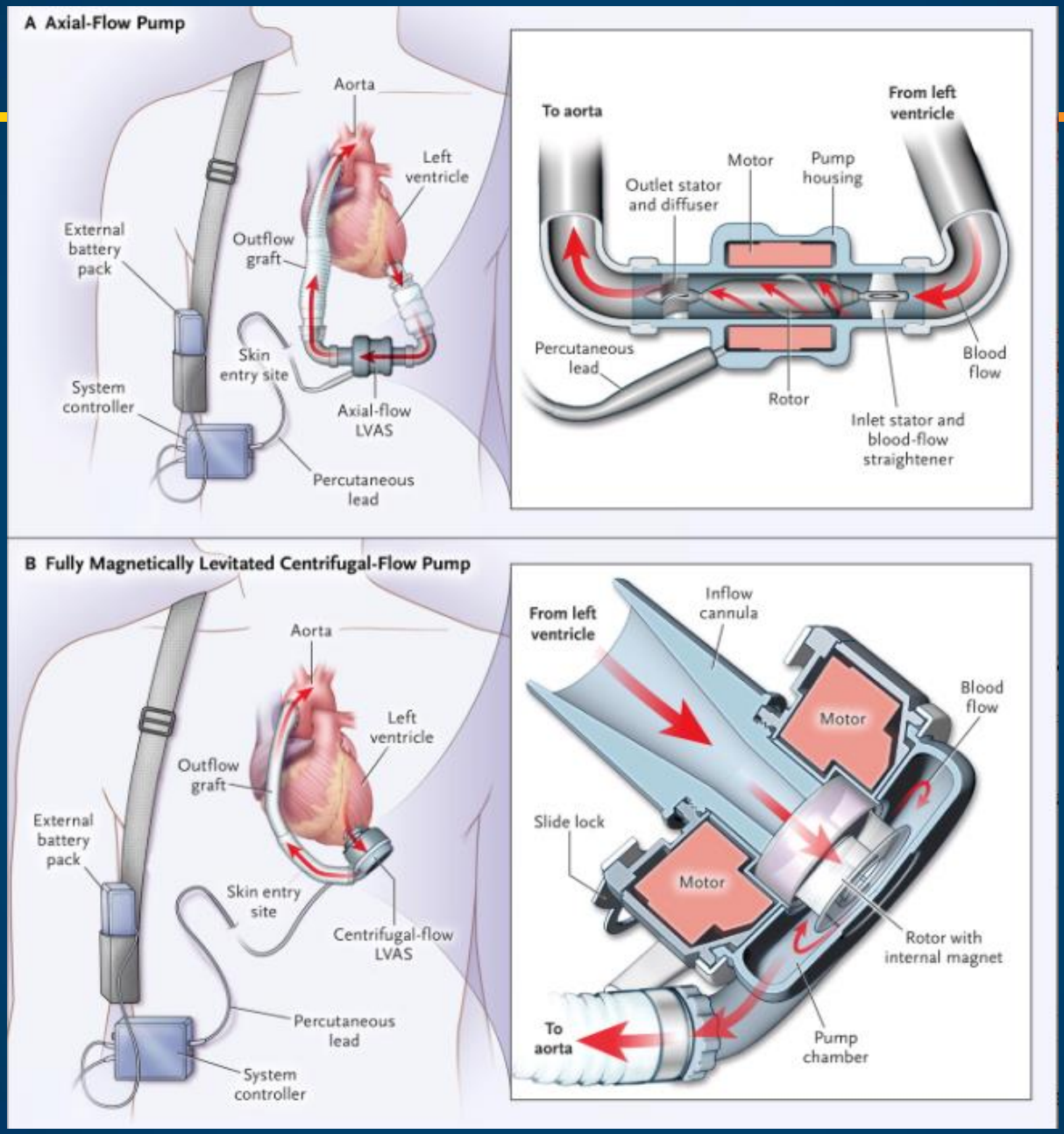


Adamson PB,, et al.. Circ Heart Fail. 2014.

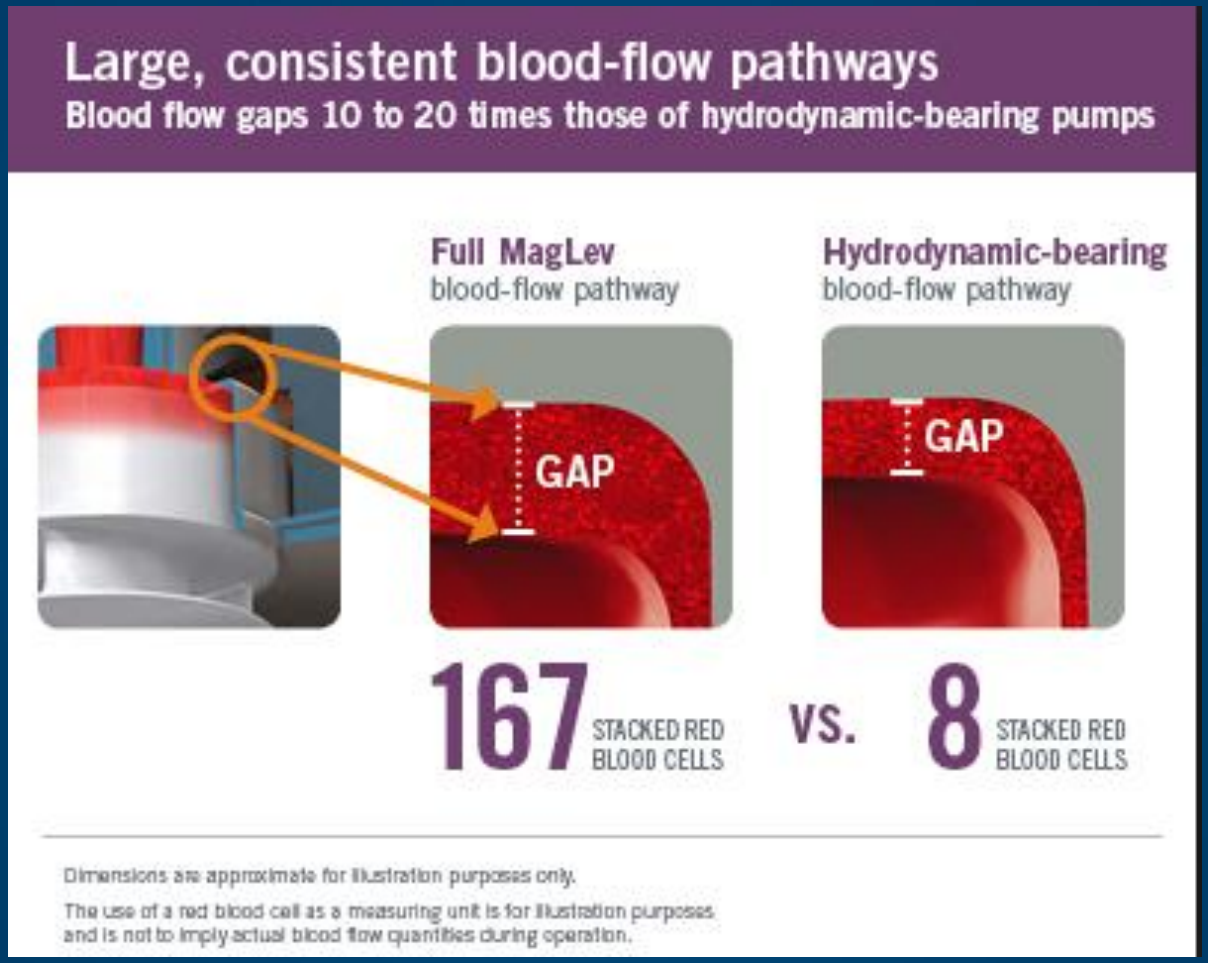
HeartMate 3

Fully Magnetically Levitated

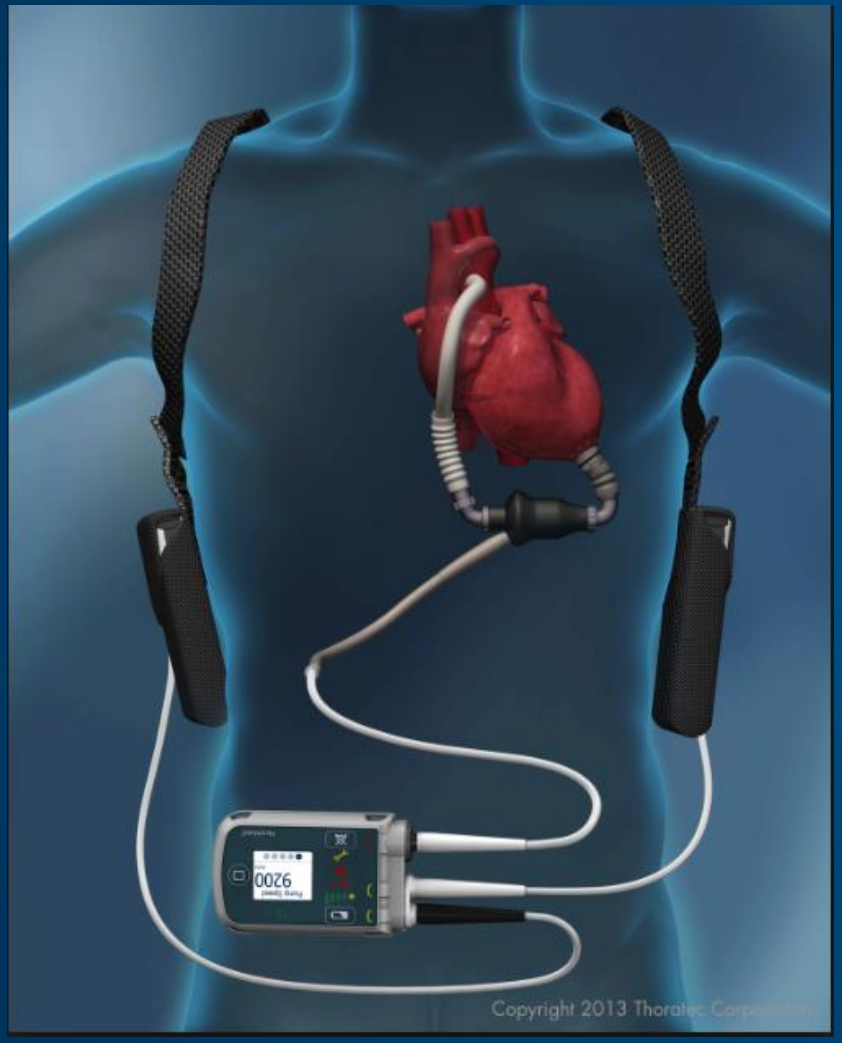


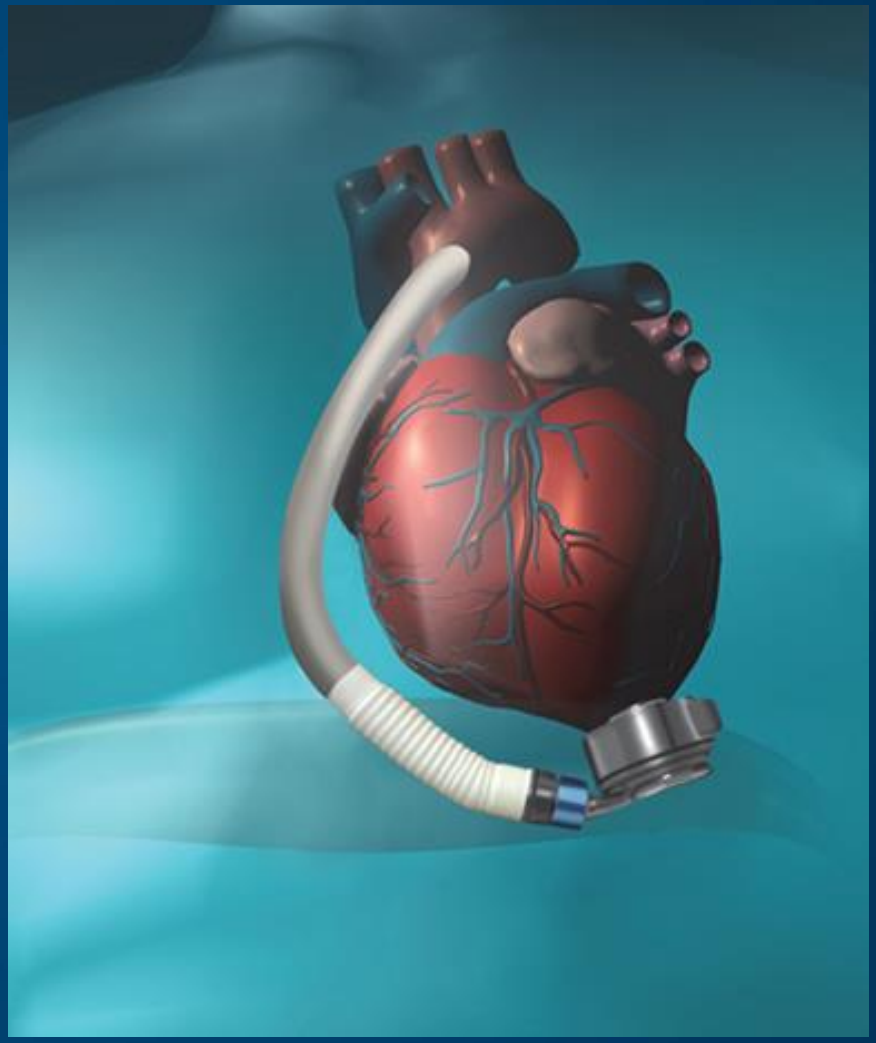

A Axial-Flow Pump
Aorta
Left ventricle
External battery pack
Outflow graft
Skin entry site
System controller
Axial-flow LVAS
Percutaneous lead
To aorta
From left ventricle
Motor
Pump housing
Outlet stator and diffuser
Percutaneous lead
Blood flow
Rotor
Inlet stator and blood-flow straightener
B Fully 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

Less Shear Stress



HeartMate 2 and HeartMate3





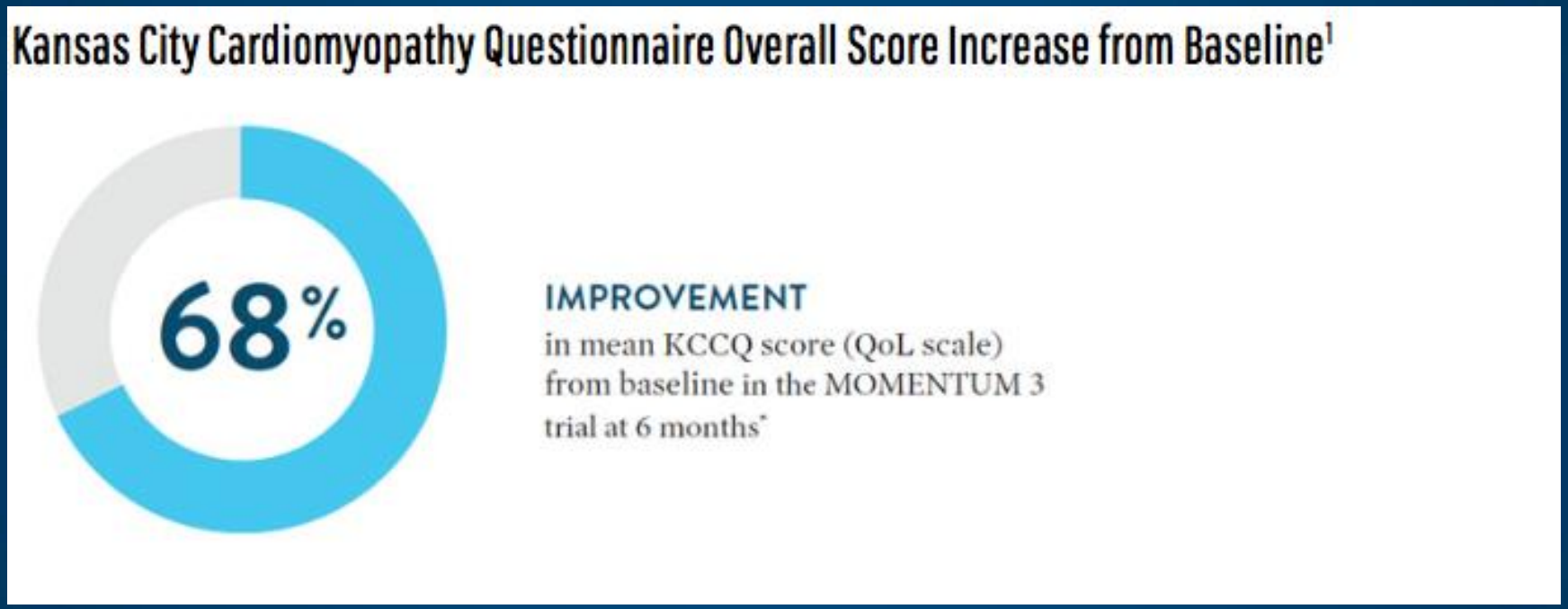
77%

PATIENTS IMPROVED

to NYHA Class I or II from NYHA Class III or IV
(n = 127) at 6 months ($p < 0.0001$ compared to baseline)

83% of patients increased their average 6-minute walk distance.[1]

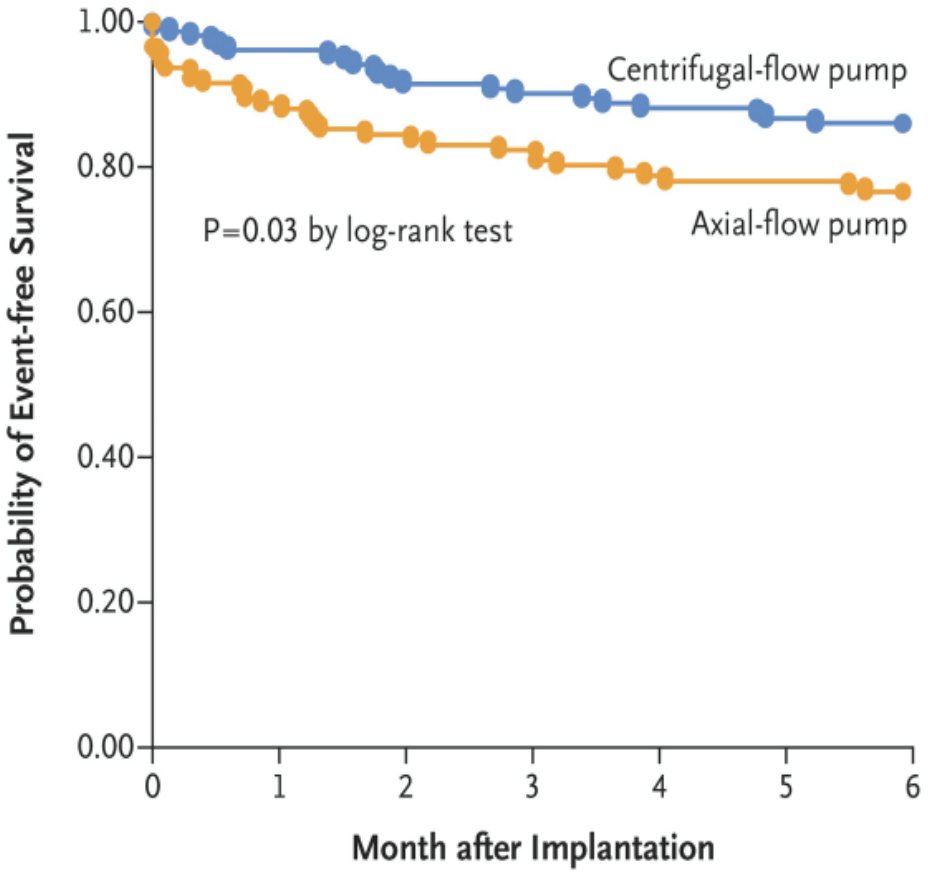
Quality, not just Quantity



Adverse events through six months for patients implanted with the HeartMate 3™ LVAD (n = 151).[1]

Adverse Events	Number of Patients	Percentage of Patients	Number of Events
Device thrombosis	0	0%	0
Hemolysis not associated with pump thrombosis	1	0.7%	1
GI bleeding	24	15.9%	47
Stroke**	12	7.9%	12
Ischemic	8	5.3%	8
Hemorrhagic	4	2.6%	4
Bleeding requiring surgery	15	9.9%	15
Device malfunction requiring reoperation	1	0.7%	1
Driveline infection***	18	11.9%	21
RVAD usage	4	2.6%	4

Outcomes



No. at Risk							
Centrifugal-flow pump	152	146	138	135	130	128	127
Axial-flow pump	142	125	119	116	110	106	103