MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

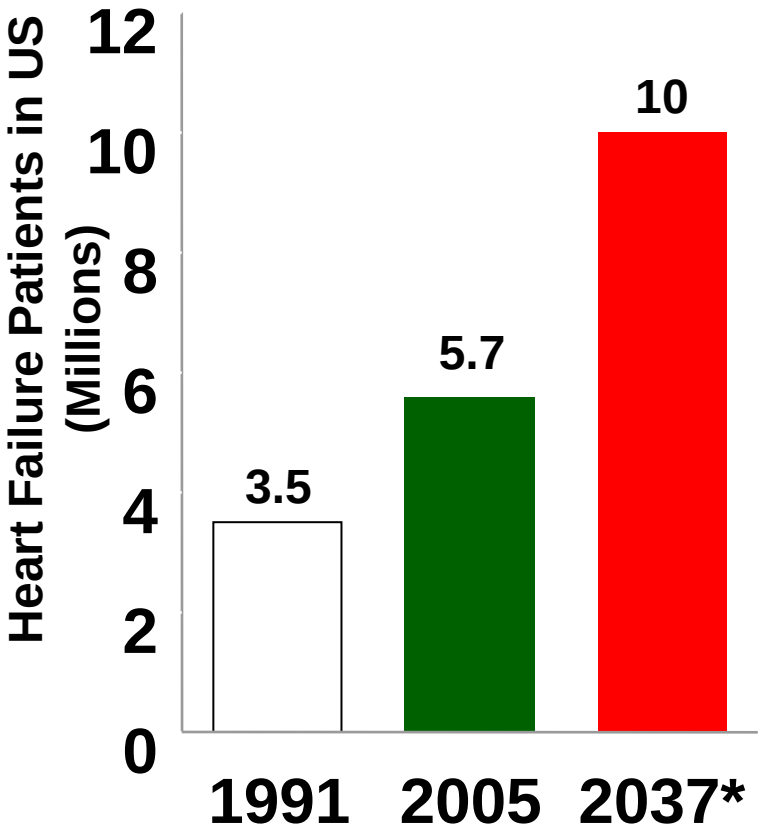
Contemporary Management of Heart Failure

Greg Lewis, MD

Section Head, Heart Failure
Medical Director, Cardiac Transplantation
Director, Cardiopulmonary Exercise Testing Laboratory
glewis@partners.org

A Teaching Affiliate of Harvard Medical School

2017 Heart Failure Epidemiology



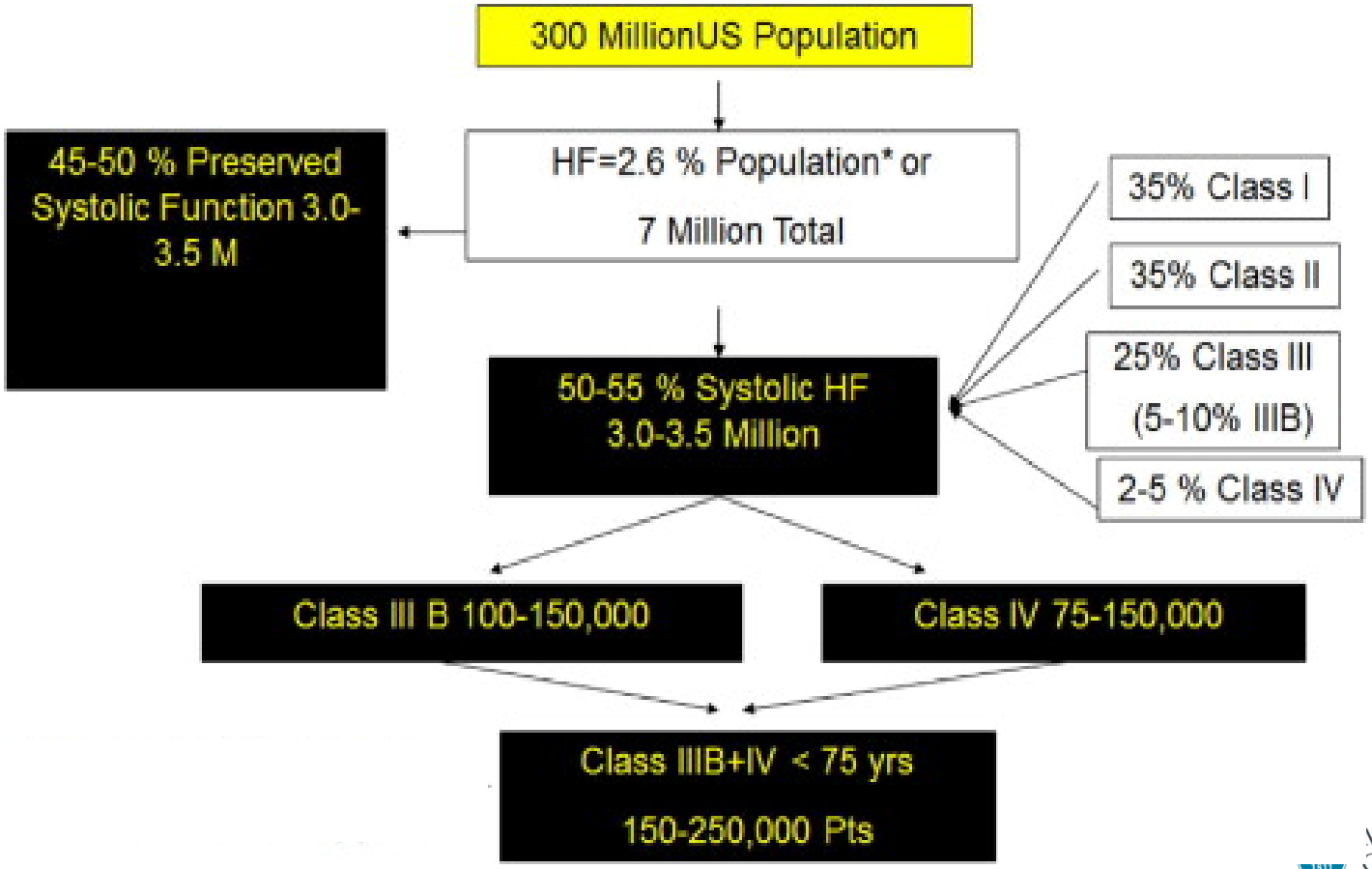
- At age 40, lifetime risk of developing HF is 20%, >900,000 new cases per year
- **>1 million annual hospitalizations**
  -Case fatality following HF hospitalization
    - 10% at 30 days
    - 22% at 1 year
- >1.7 million office visits
  - (1.7:1 ratio vs. 7:1 ratio for CHD)
- Cost: 2012: $21 billion
  2030: $70 billion ($244/US citizen)

American Heart Association 2017 Heart and Stroke Statistical Update
Mozaffarian et al, Circulation 2017

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

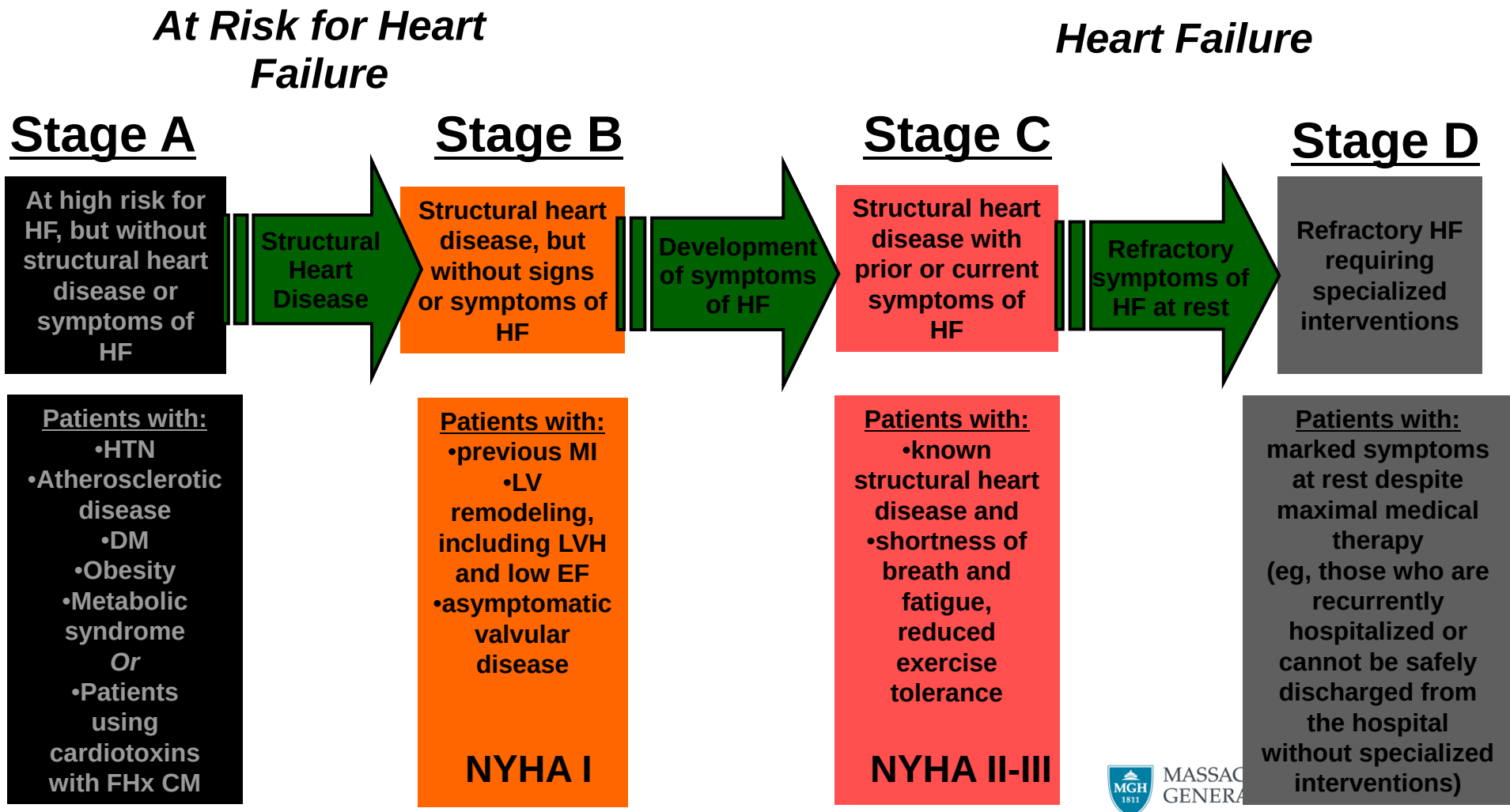
2017 Heart Failure Epidemiology: The Disease Spectrum

Heart Failure Prevalence



MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

ACC/AHA Staging of Heart Failure Patients



DM=diabetes mellitus; HTN=hypertension; LV=left ventricular; FHx= family history; CM=cardiomyopathy

Hunt SA et al. *Circulation.* 2005;112:1825–1852.

Does My Patient Have Heart Failure?
Definition of Heart Failure

- Heart Failure Definition: Clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood
  - Framingham Criteria: 2 MAJOR or 1 MAJOR + 2 MINOR

MAJOR CRITERIA

Paroxysmal nocturnal dyspnea
Radiographic cardiomegaly
Acute pulmonary edema
Weight loss > 4.5kg in 5 days with Rx
Neck vein distention
Rales
S3 Gallup
Increased CVP (>16)
Hepatojugular reflux

MINOR CRITERIA*

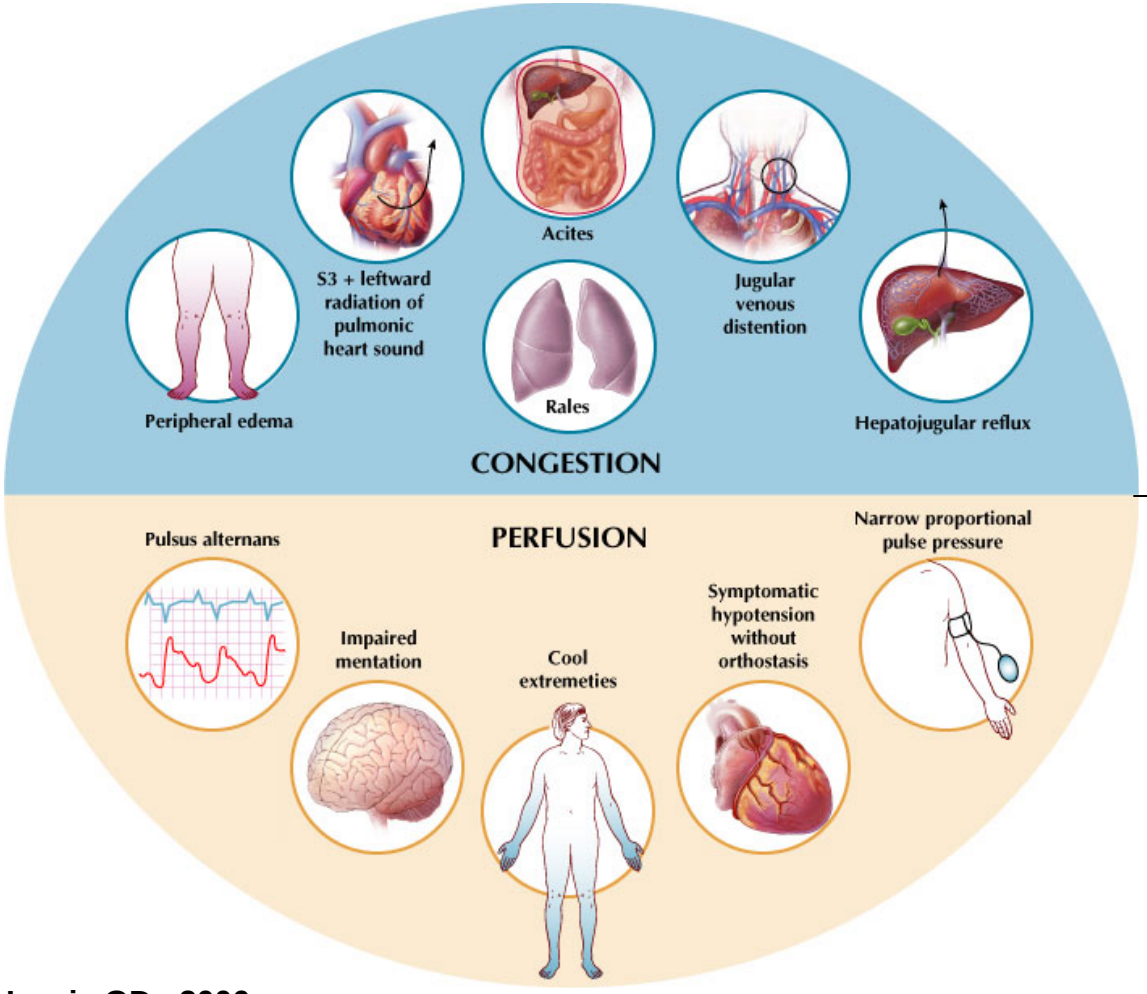
Bilateral ankle edema
Heart rate > 120
Hepatomegaly
Nocturnal cough
Dyspnea on ordinary exertion
Pleural effusion
Reduced vital capacity by 1/3

* Minor criteria only acceptable if not attributable to another medical condition

-HF is not a numeric value retrievable in EPIC
-HF patients are cared for by a wide variety of providers

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Bedside Evaluation: Physical Exam Signs of Heart Failure and Heart Failure Severity



Lewis GD. 2006

S3: relation to ↑ LVEDP, ↓ EF
- -40% sensitive
- -90% specific[1]

JVD: manipulate bed angle

Rales: Only present in 2/3 HF presentations[2]

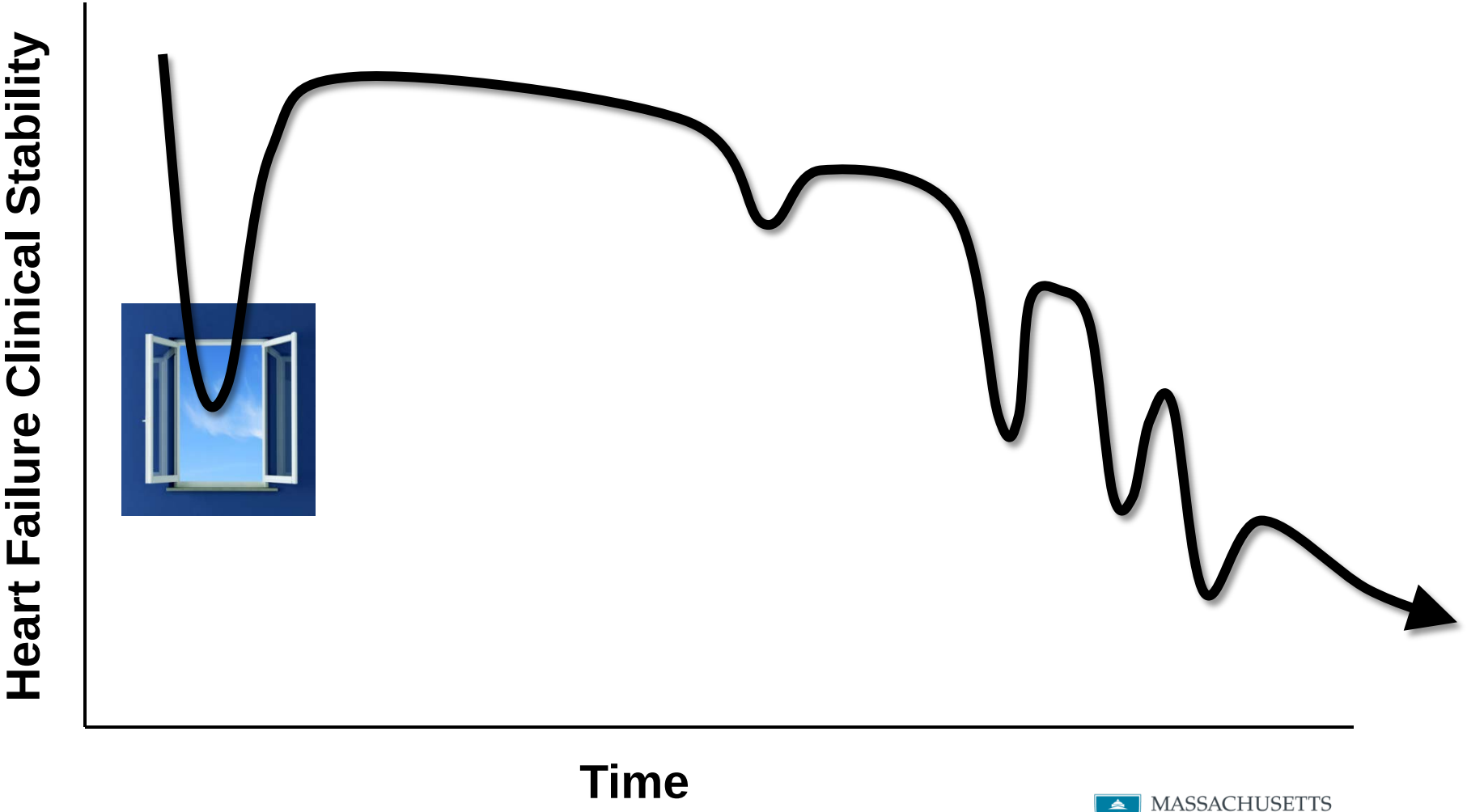
Proportional Pulse Pressure
SBP-DBP/SBP < 25%→
CI < 2.2 $L \cdot min^{-1} \cdot m^2$

Warm vs. cool and wet "cold" patients, 2x mortality[3]

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

1. Marcus GM JAMA 2005. 2. ADHERE Registry, 2005 3. Nohria A J Card Fail. 2000

Heart Failure Characteristic Patient Course



Adapted From Gheorghiade M Am Journal of Cardiology 2005

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

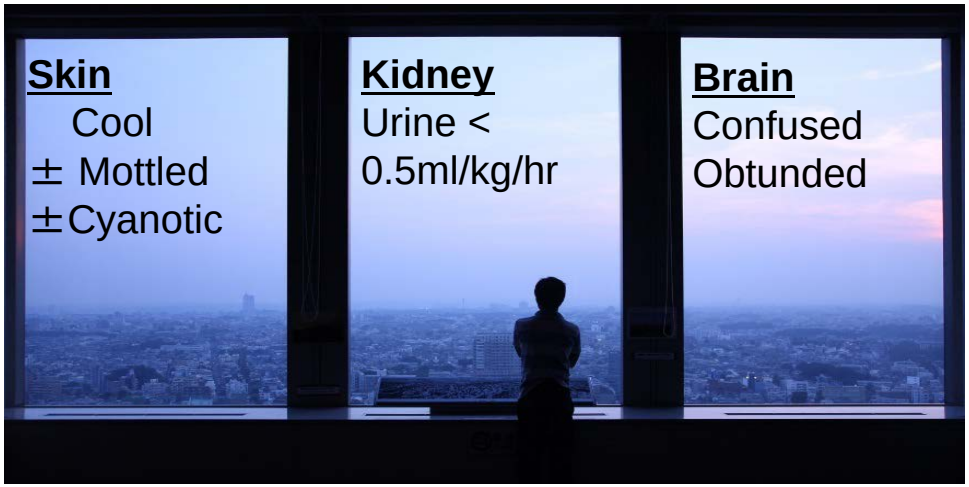
Identify the “Trigger”/Precipitant for ADHF

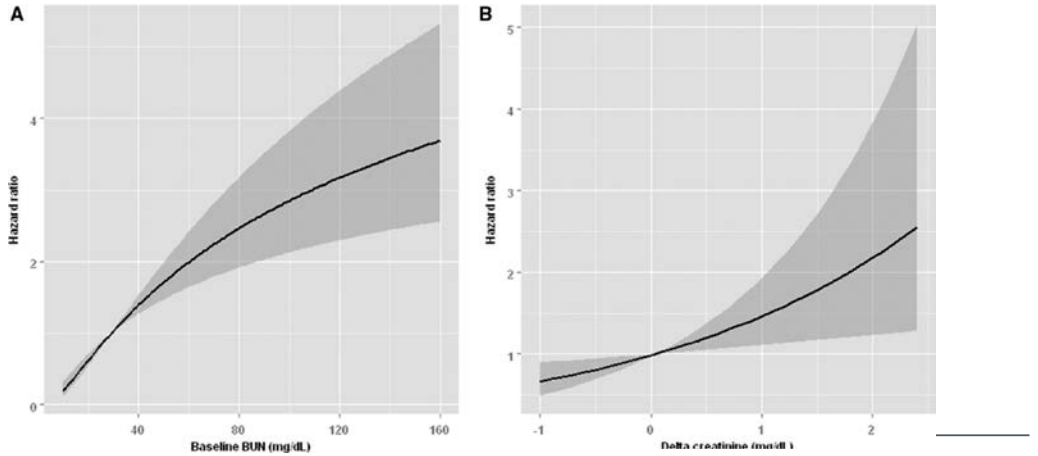
Precipitating Factors	
Adherence to care	-Dietary indiscretion -Nonadherence to medications
Drug Exposures	βB, CCB, NSAIDs, TZDs chemo (anthracyclines, trastuzumab)
Direct cardiac insults	-Ischemia -Valve disease (i.e. rupture chordae) -Arrhythmia -Takatsubo CM -Cardiotoxins (EtOH) -RV pacing
Extra-cardiac insults	-Hypertension (RAS, OSA) -Renal failure (AKI, CKD progression) -Anemia -Thyroid dysfunction -Systemic Infection -Extreme emotional distress

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Predictors of Survival with ADHF and Clues to the Presence of Impending Cardiogenic Shock

N=1960 ADHF PROTECT Trial





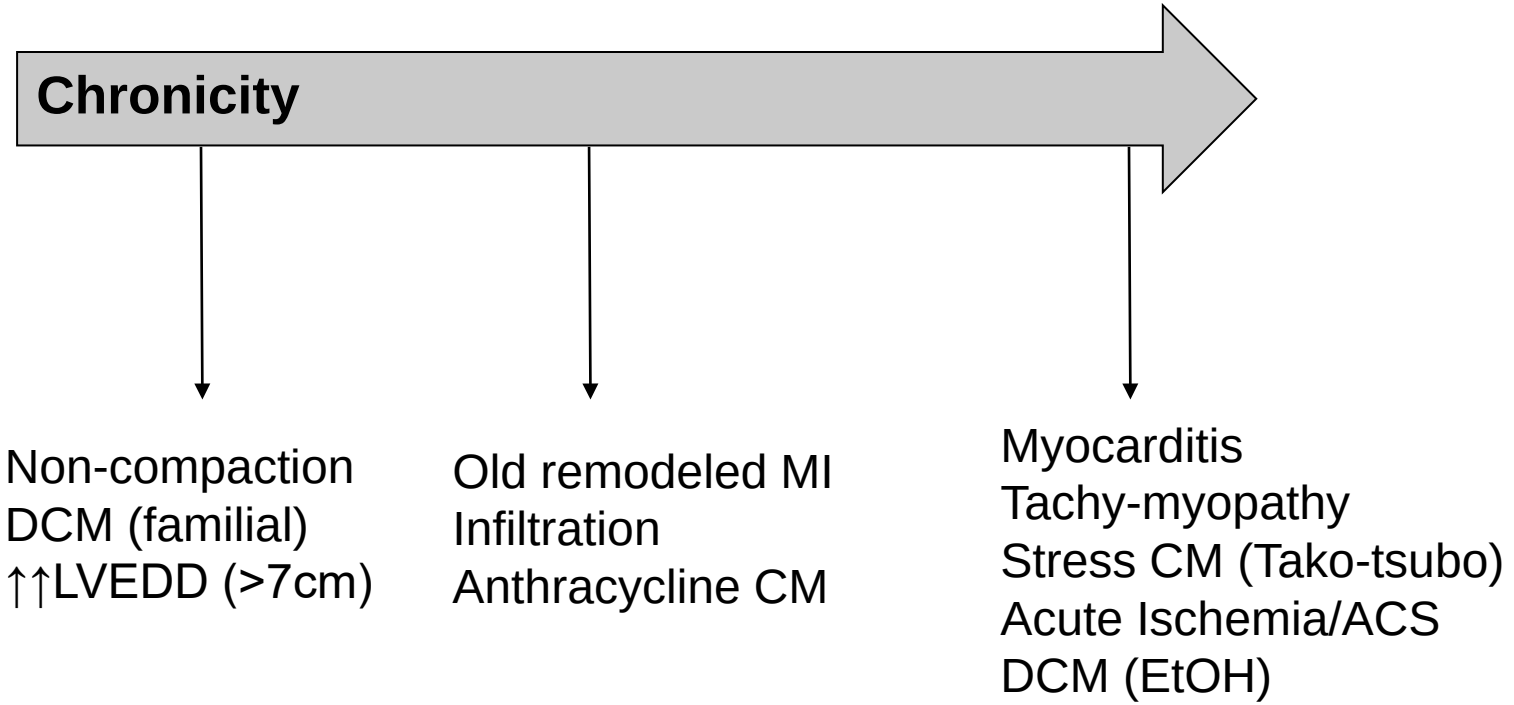
Michael M. Givertz et al. Circ Heart Fail. 2014;7:59-67

Myocardial Substrate Considerations

Reversibility tends to be inversely related to

-Chronicity

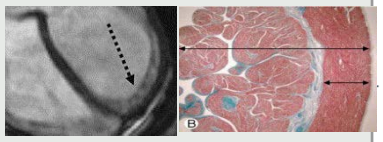
-LV size (much more important than LVEF!)



MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

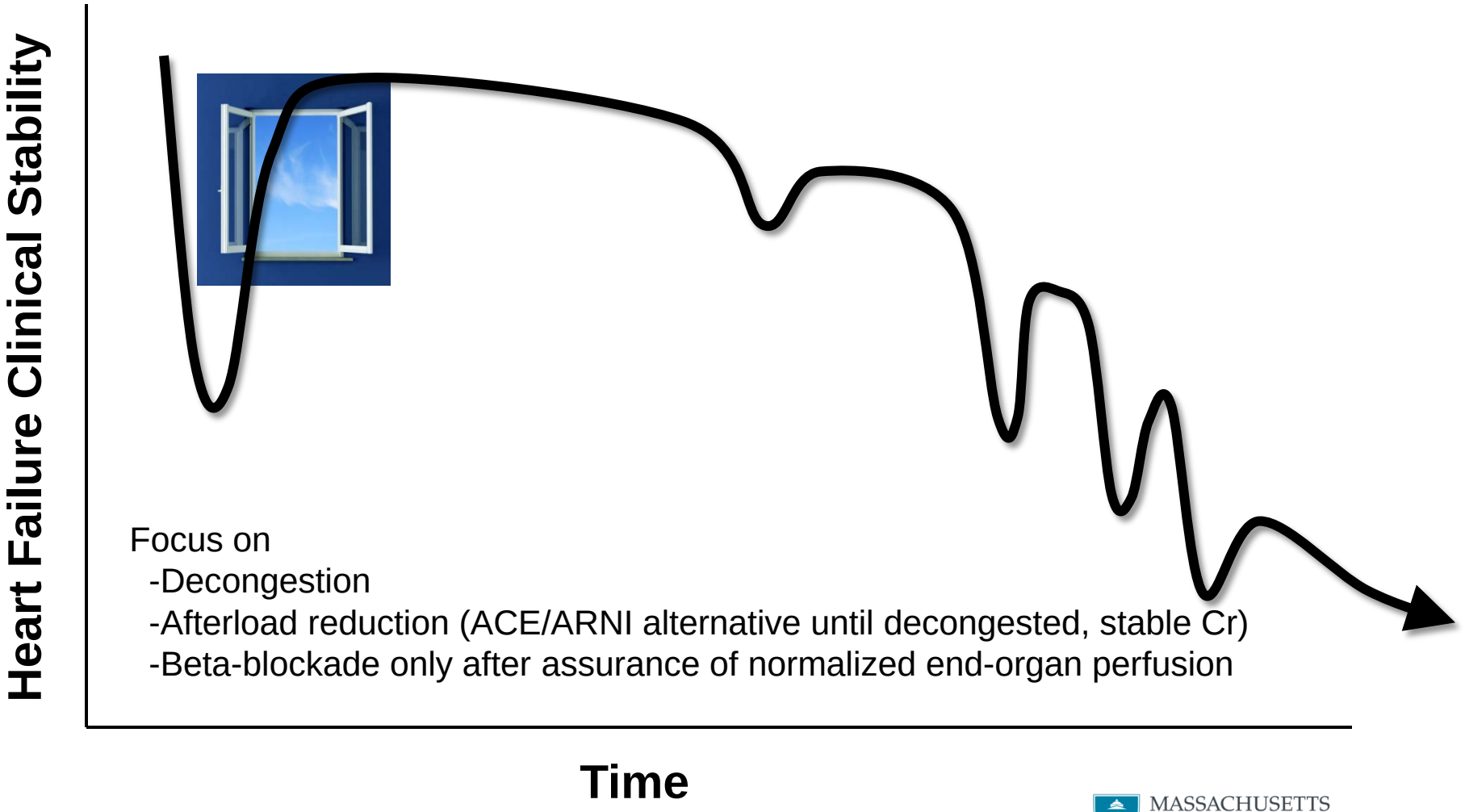
Newly Diagnosed Heart Failure: Specific Etiologic Considerations that Impact Management

Etiology	ECG Pattern	Imaging Pattern
Ischemia/Infarction	Qw, ST segment deviation	TTE: regional WMA, ± thinning/aneurysm, infarct Cor angio/CTA: obstructive CAD MRI: subendocardial or transmural LGE
Infiltrative	Low limb lead voltage, heart block, pseudoMI	TTE: LVH, "starry sky," ↑ biatrial size → amyloid MRI: Inapprop nulling of myocardium + diffuse LGE → amyloid; patchy LV + RV LGE → sarcoidosis; ↓ T2 star → iron overload
Idiopathic DCM	Low limb lead volts, precordial LVH, BBB	TTE: 4 chamber dilation, diffuse hypokinesis MRI : mid-myocardial LGE
Tachy-myopathy	Persistent SVT	TTE: diffuse hypokinesis MRI: absent LGE in early stage
Myo(peri)-carditis	Pseudo-ischemia/MI Pericard: diffuse concave STE w/ ST:T ratio >0.24 in V6	TTE: typically global HK MRI: mid-myocardial + epicardial LGE, ↑ T2 (edema)
LV non-compaction	Non-specific	TTE: heavily trabeculated LV MRI: >2:1 non-compacted/compacted



APPROACH TO CHRONIC MANAGEMENT OF LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

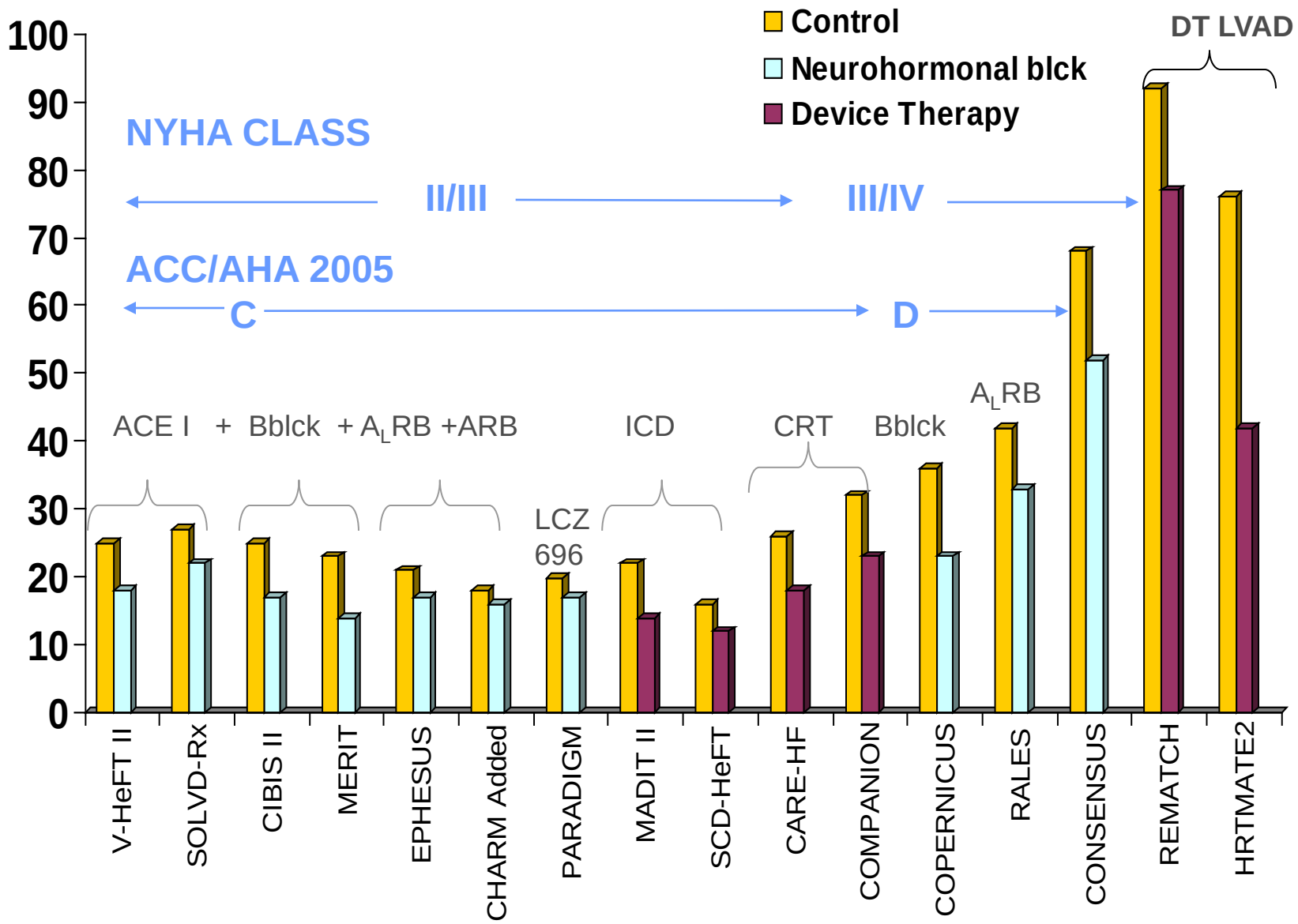
Post-Acute Decompensation Management



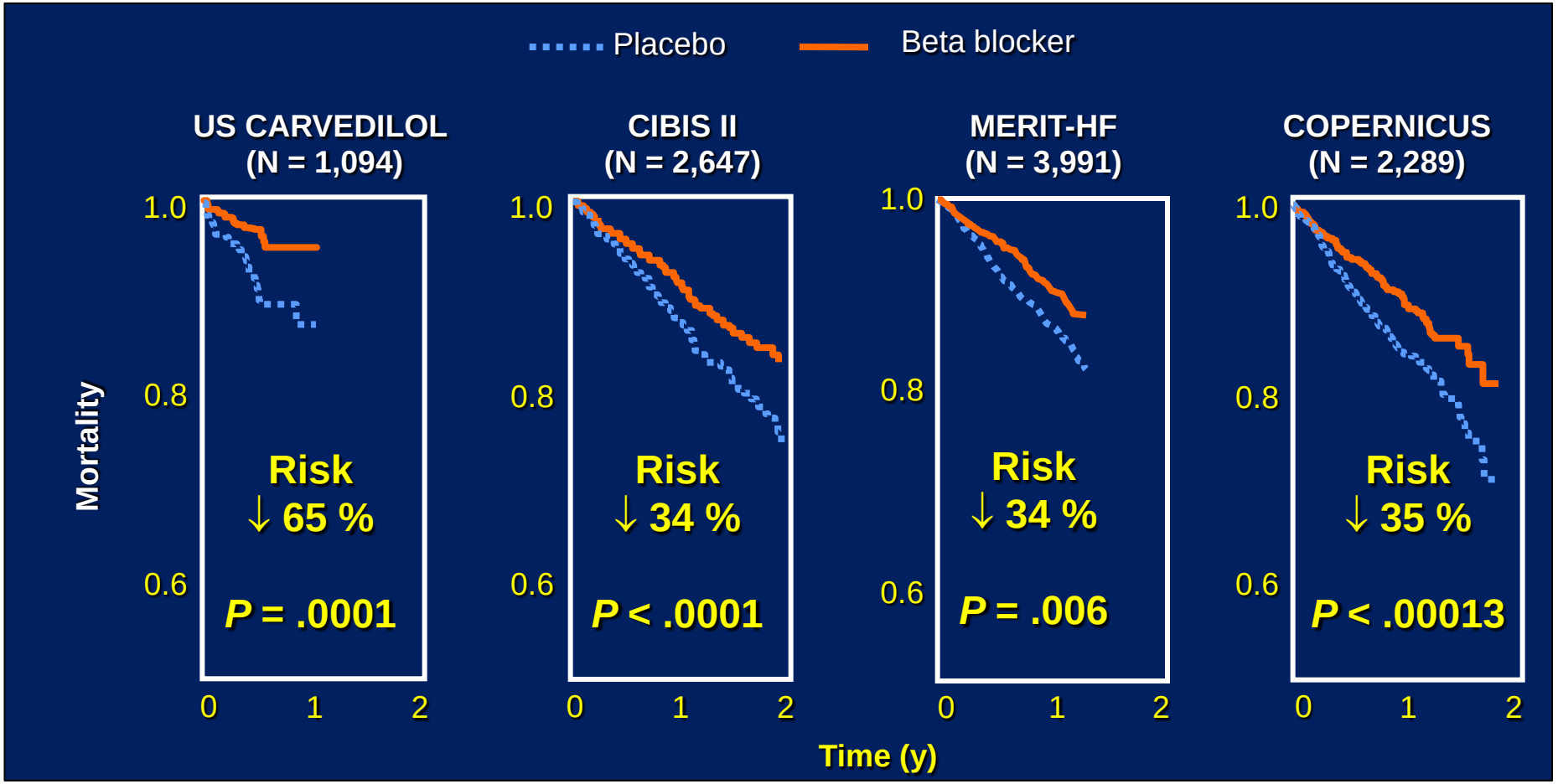
Adapted From Gheorghiade M Am Journal of Cardiology 2005

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

2 Year Mortality in Systolic Heart Failure Trials



Beta Blockers with Proven Mortality Benefit in HF



CIBIS = Cardiac Insufficiency Bisoprolol Study; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival Trial.

Colucci WS et al. *Circulation.* 1996;94:2800–2806. CIBIS II. *Lancet.* 1999;353:9–13.
Hjalmarson A et al. *JAMA*. 2000;283:1295–1302. Packer M et al. *Circulation*. 2002;106:2194–2199.

Evidence based use of Beta-blockers

Dose Escalation Strategy

Beta-blocker	Starting Dose	Target Dose	Reference Trial
Metoprolol XL	12.5mg qd	200mg qd	MERIT-HF 1999, Class II-III
Bisoprolol	1.25mg qd	10mg qd	CIBIS II 1999, Class II-III
Carvedilol	3.125mg bid	25-50mg bid	Packer meta anal 1996, Class I-III COPERNICUS, 2002, Class IV

Comparative Studies: Coreg > Metoprolol Tartrate (COMET)
Coreg vs. Toprol XL unknown

Evidence based use of Beta Blockers Based on ACC/AHA Classification

ACC/AHA Guidelines All stable patients with current or previous symptoms of HF and reduced LVEF Class I, Evidence A

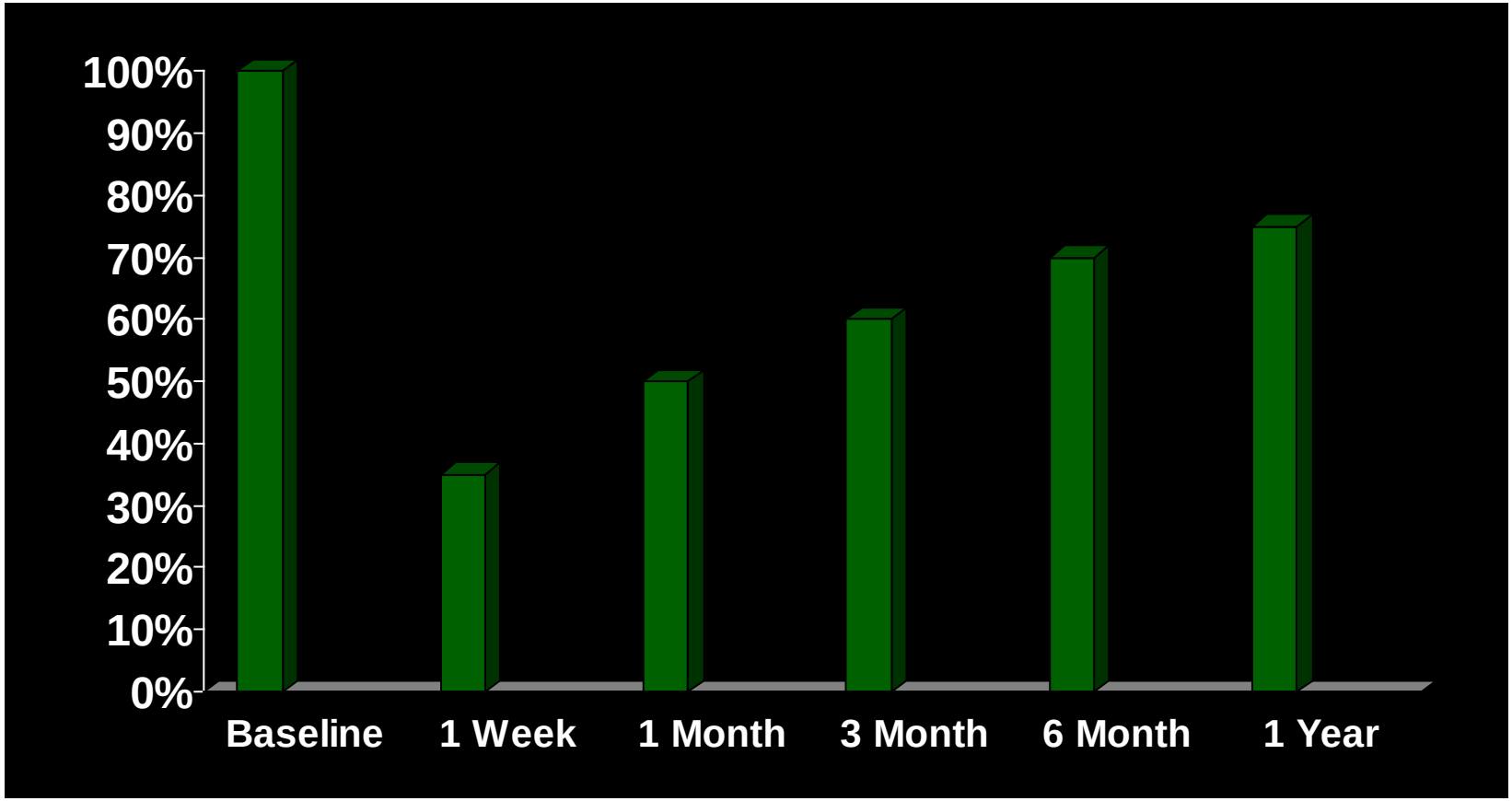
Coreg > Metoprolol Tartrate (COMET)
Coreg vs. Toprol XL unknown
- **-Significant blood pressure rese→ coreg**
- **-Marginal blood pressure, concern about non-selective bblck→ metoprolol xl**

Evidence Based use of ACE I Dose titration strategy

ACE I	Initial Dose	Target Dose	Reference Trial
Captopril	6.25mg tid	50mg tid	**SAVE**
Enalapril	2.5mg bid	10mg bid	**CONSENSUS** **V-HeFT II**
Lisinopril	2.5-5mg qd	20-40mg qd	**ATLAS**
Ramipril	1.25-2.5mg qd	10mg qd	**AIRE**

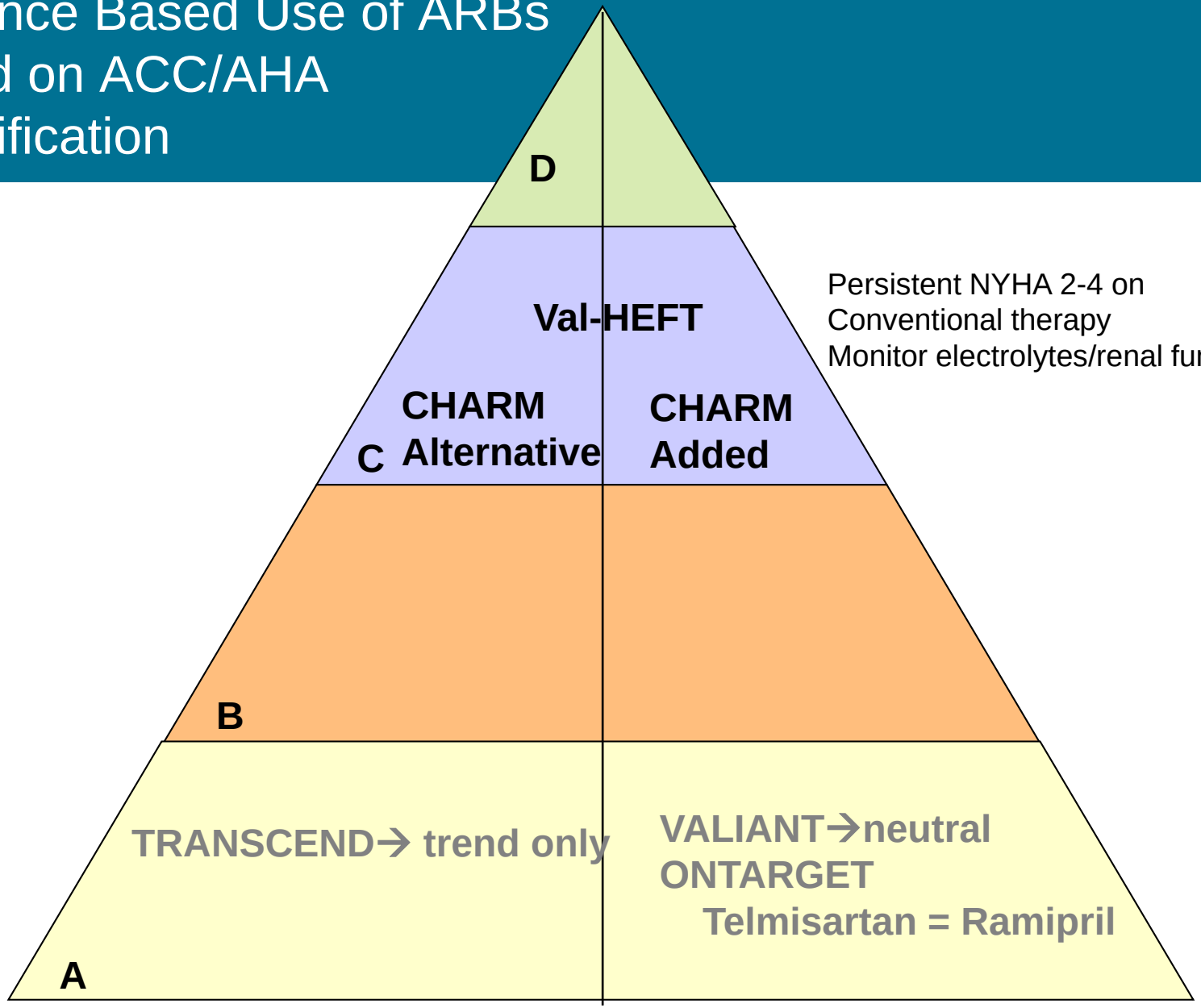
CHANGE IN ANGIOTENSIN II DURING LONG-TERM ACE INHIBITOR TREATMENT

Plasma Angiotensin II



Blollasz et al. J Cardiovasc Pharm, 1982

Evidence Based Use of ARBs Based on ACC/AHA Classification



Persistent NYHA 2-4 on Conventional therapy
Monitor electrolytes/renal function

Angiotensin Receptor Blockers

DRUG	BIOAVAILABILITY	HALF LIFE	DAILY DOSE Goal (mg)
Losartan	33%	6-9 hours	50-100
Candesartan	15%	9 hours	16-24
Valsartan	25%	6 hours	160-320
Telmisartan	50%	24 hours	40-80

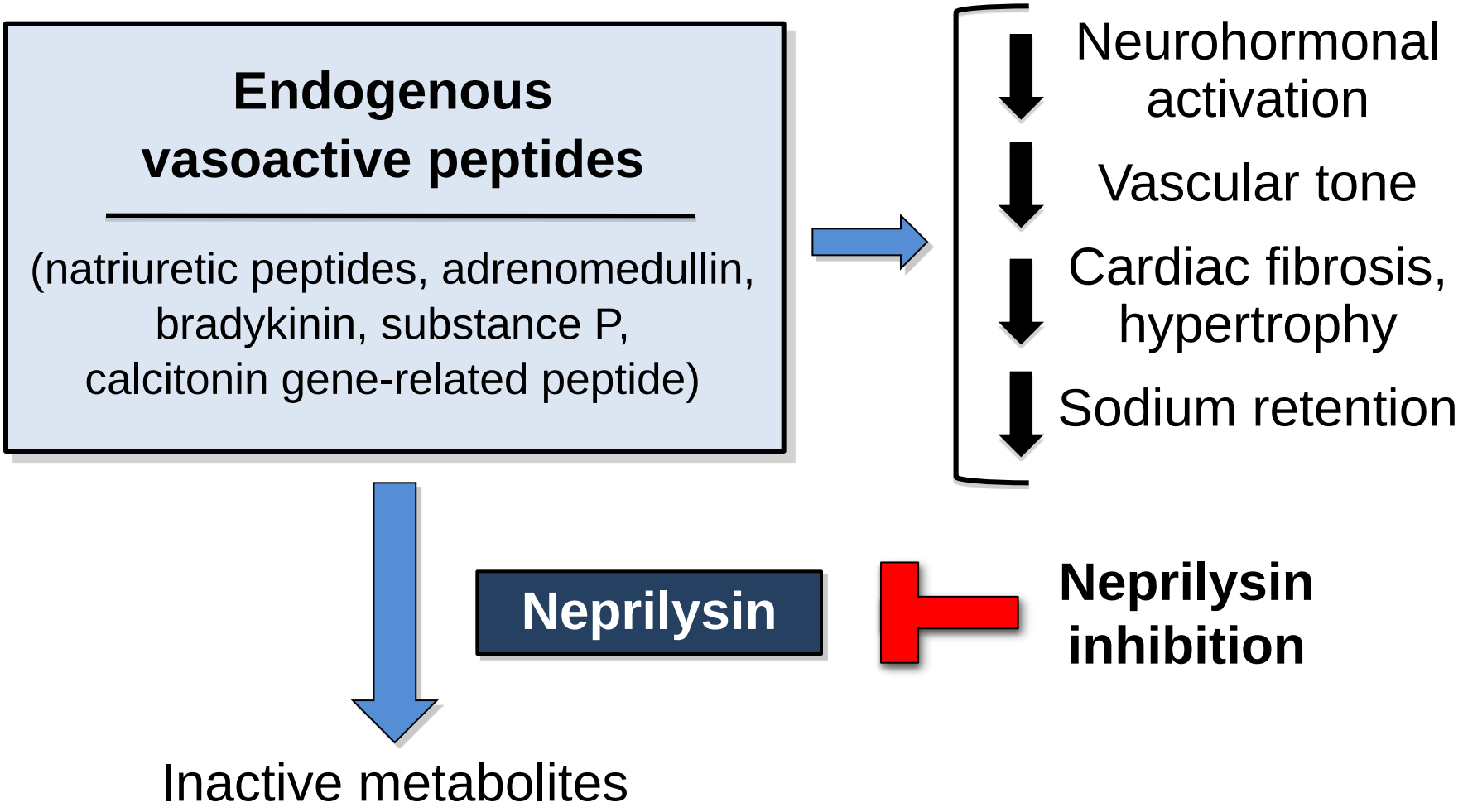
Angiotensin Receptor Blockers in the Treatment of Heart Failure

- ARBs are better tolerated than ACE inhibitors
- ARBs are comparable to ACE I for first line therapy in HF (ELITE I, II)
- ARBs should be substituted for ACE I in bradykinin-mediated ACE I intolerance (CHARM Alternative)

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Evidence for use of Angiotensin Receptor-Neprilysin Inhibition in Systolic HF

Neprilysin Inhibition: Potentiates Actions of Endogenous Vasoactive Peptides that Counter Maladaptive Mechanisms in HF



LCZ 696 (Sacubitril/Valsartan) vs. Enalapril: PARADIGM Trial

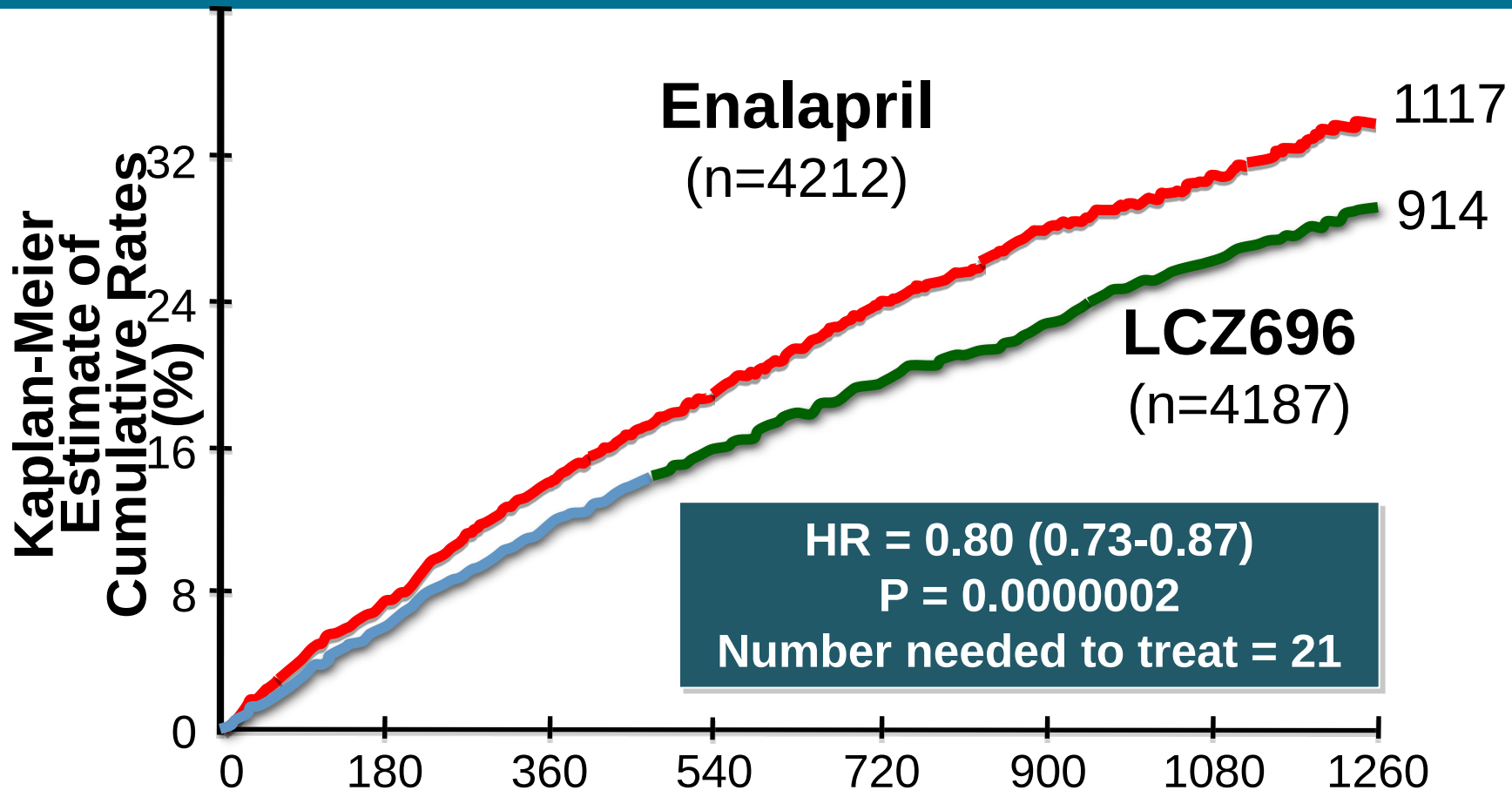
NYHA class II-IV heart failure

- LV ejection fraction ≤ 40% changed to < 35%
- BNP ≥ 150 (or NT-proBNP ≥ 600), but one-third lower if hospitalized for heart failure within 12 months
- Any use of ACE inhibitor or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for at least 4 weeks
- Guideline-recommended use of beta-blockers and mineralocorticoid receptor antagonists
- Systolic BP ≥ 95 mm Hg, eGFR ≥ 30 ml/min/1.73 m^2 and serum K ≤ 5.4 mEq/L at randomization

PARADIGM: Baseline Characteristics

	LCZ696 (n=4187)	Enalapril (n=4212)
Age (years)	63.8 ± 11.5	63.8 ± 11.3
Women (%)	21.0%	22.6%
Ischemic cardiomyopathy (%)	59.9%	60.1%
LV ejection fraction (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class II / III (%)	71.6% / 23.1%	69.4% / 24.9%
Systolic blood pressure (mm Hg)	122 ± 15	121 ± 15
Heart rate (beats/min)	72 ± 12	73 ± 12
N-terminal pro-BNP (pg/ml)	1631 (885-3154)	1594 (886-3305)
B-type natriuretic peptide (pg/ml)	255 (155-474)	251 (153-465)
History of diabetes	35%	35%
Digitalis	29.3%	31.2%
Beta-adrenergic blockers	93.1%	92.9%
Mineralocorticoid antagonists	54.2%	57.0%
ICD and/or CRT	16.5%	16.3%

LCZ 696 (Sacubitril/Valsartan) vs. Enalapril: PARADIGM Trial



Patients at Risk

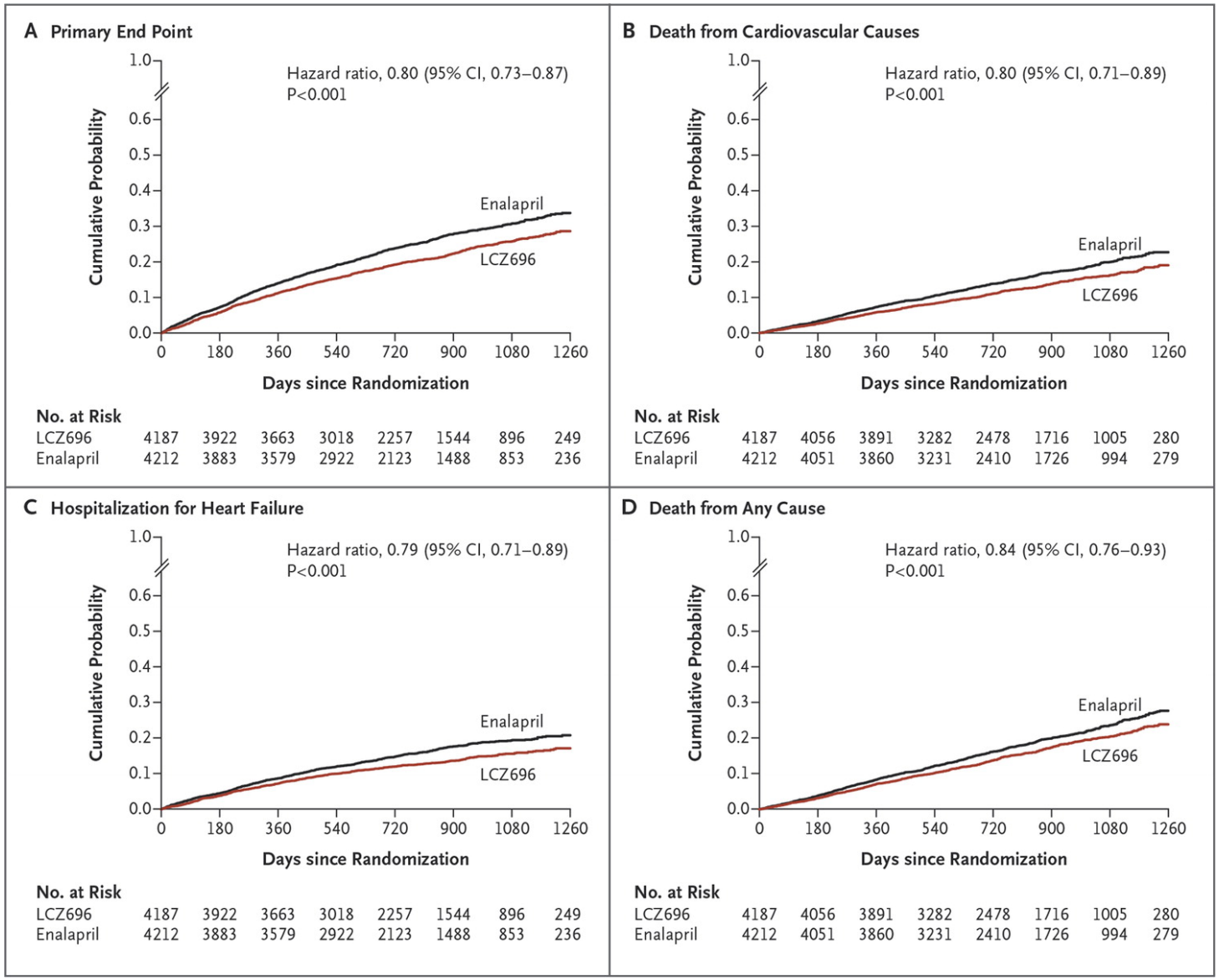
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

LCZ 696 (Sacubitril/Valsartan) vs. Enalapril: PARADIGM Trial

Patient Population

Tolerated run-in Phase (12% dropout)

Enalapril ≥ 10mg



McMurray NEJM 2014

LCZ 696 (Sacubitril/Valsartan) vs. Enalapril: PARADIGM Trial

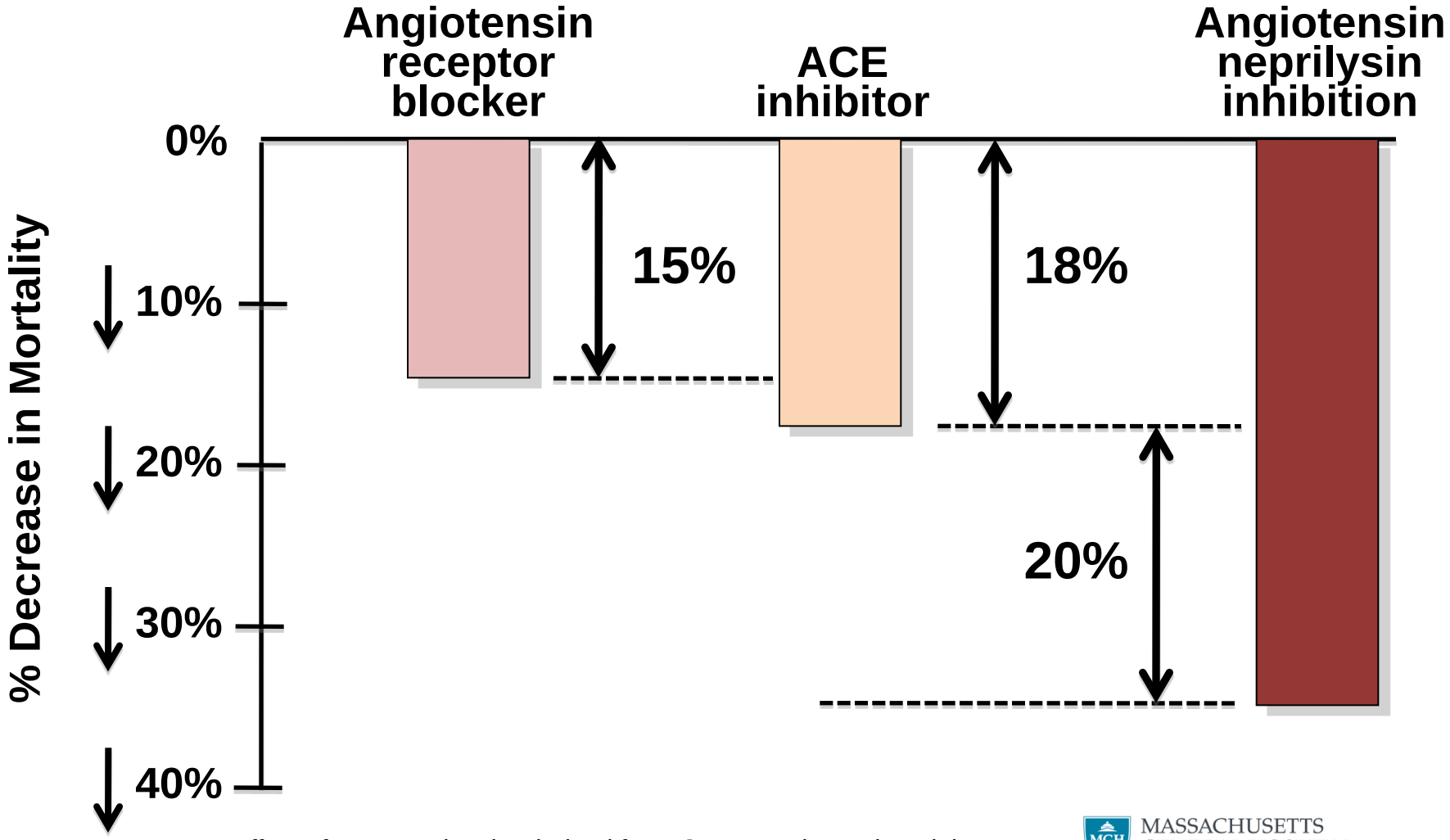
Table 3. Adverse Events during Randomized Treatment.*

Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema†			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

* Shown are results of the analyses of prespecified safety events at any time after randomization. The numbers of patients who permanently discontinued a study drug were as follows: for hypotension, 36 (0.9%) in the LCZ696 group and 29 (0.7%) in the enalapril group (P=0.38); for renal impairment, 29 (0.7%) and 59 (1.4%), respectively (P=0.002); and for hyperkalemia, 11 (0.3%) and 15 (0.4%), respectively (P=0.56).

† Angioedema was adjudicated in a blinded fashion by an expert committee.

LCZ 696 (Sacubitril/Valsartan) vs. Enalapril: PARADIGM Trial



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

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

2016 ACC/AHA/HFSA Heart Failure Guidelines

- **<u>Class I:</u> In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.**
  - A 36 hour ACE I washout is required
  - Avoid in patients with a history of angioedema
  - Start slowly (24/26mg combination bid for enalapril or lisinopril <10 mg/d)
  - Not yet studied in hospitalized HF patients
    - *PIONEER Trial (enrolling)*
  - Not yet studied in NYHA Class IIIb and IV Patients
    - *LIFE Trial (enrolling)*
  - *Obtain prior authorization prior to cessation of ACE/ARB*

Yancy C. et al. Circulation, 2016

Aldo-Receptor Blocker Trials

RALES

1663 pts, NYHA III-IV, LVEF < 35%

Rx with loop diuretics (100%) with omission of KCl unless K<3.5

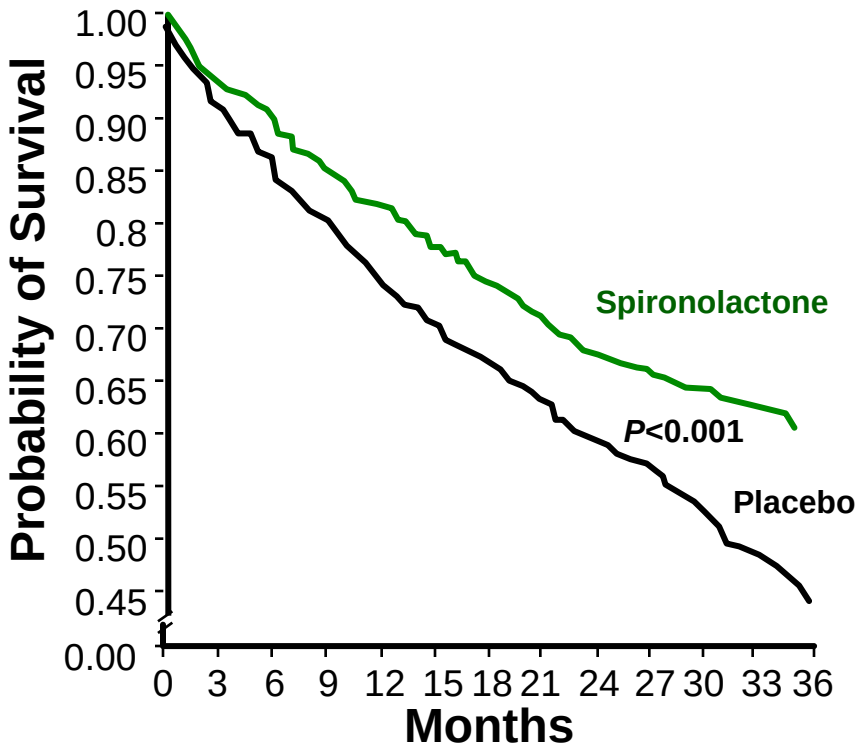
Average dose: **26 mg/d**

EPHESUS

6634 pts, 3-14 days post-MI, Evident HF, LVEF < 40%

16 month follow-up

Target dose: **50 mg/d**



-15% reduction in all-cause mortality (p=0.008);

-13% reduction in combined end-point of CV death or hospitalization (p=0.002)

Exclusion Criteria:

Cr > 2.5, K > 5.0

Use of K-sparing diuretics

Trial Designs:

Frequent electrolyte monitoring

Pitt et al. *N Engl J Med.* 1999;341(10):709-717.

Pitt et al. *N Engl J Med.* 2003; 348:1309-1321

Aldo-Receptor Blocker Trials

EMPHASIS

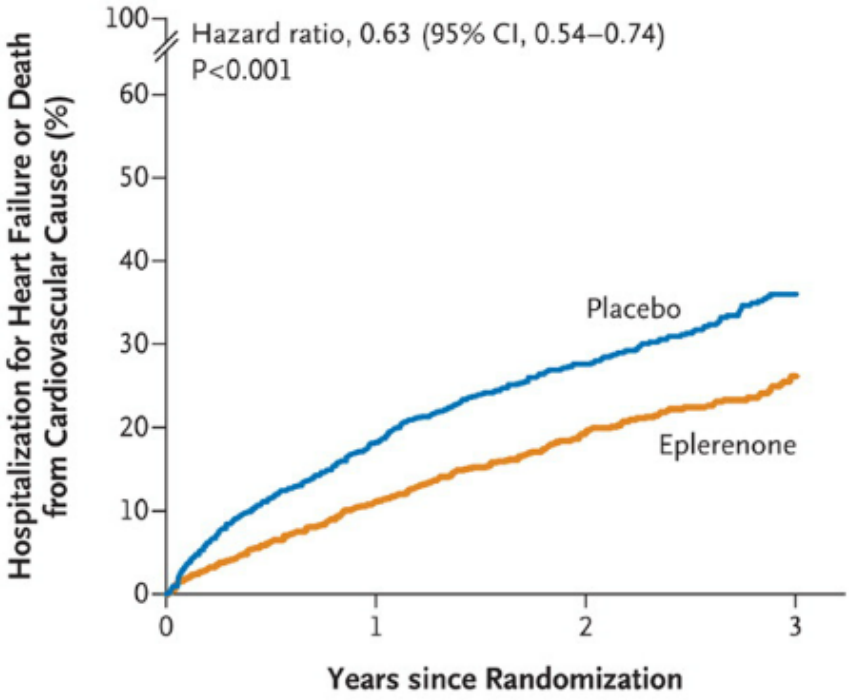
2737 pts, NYHA II, LVEF < 35%

Rx with ACE/ARB, BBlck, Hosp within 6mo

Excl: K>5.0, GFR<30

Average dose: **40 mg/d**

Placebo-corrected fall in SBP: 2mmHg
K>5.5 in 11.8% vs. 7.2%



Take home points

-Potent anti-remodeling and ↓ mortality at a minimal blood pressure cost

-With use in NYHA II patients who are not on loop diuretics monitor K levels very closely

SHIFT: Heart Rate Modulation Ivabradine

Selective inhibitor of Na/K channel in the sinus node
N=6505, LVEF<0.35, HR>70, HF hospitalization in last yr

Outcomes in SHIFT	Ivabradine, n=3241	Placebo, n=3264	HR (95% CI)	p
CV death or HF hospitalization	24	29	0.82 (0.75-0.90)	<0.0001
Death from heart failure	3	5	0.74 (0.58-0.94)	0.014
HF hospitalization	16	21	0.74 (0.66-0.83)	<0.0001
CV death, HF hospitalization, or admission for nonfatal MI	25	30	0.82 (0.74-0.89)	<0.0001

90% bblck use, comparable to Registry use but < clinical trial goals
Greatest benefit with highest HR.

Swedberg K, Lancet 2010

2016 ACC/AHA/HFSA Guidelines

Class IIa: Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest

Yancy C. et al. Circulation, 2016

Digoxin (≤0.125mg/d)

Evidence:

DIG: Neutral mortality, decreased HF hospitalizations, levels < 1 ng/ml preferable

RADIANCE: Withdrawal of digoxin → 5X RR of HF hospitalization, decr LVEF

Positives:

Adjunctive rate control in HF with AF

Reduces HF hospitalizations

Positive inotrope without harm

Negatives:

Narrow therapeutic index

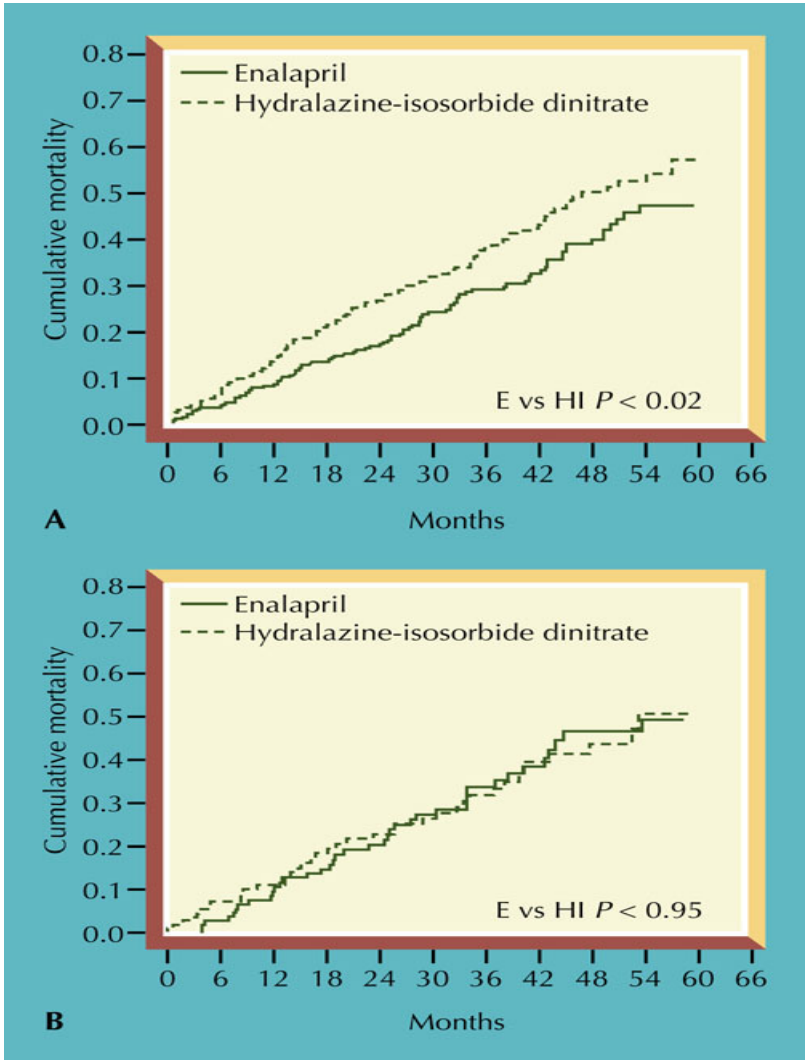
Unknown outcomes with BBlck

Polypharmacy w/o incr survival

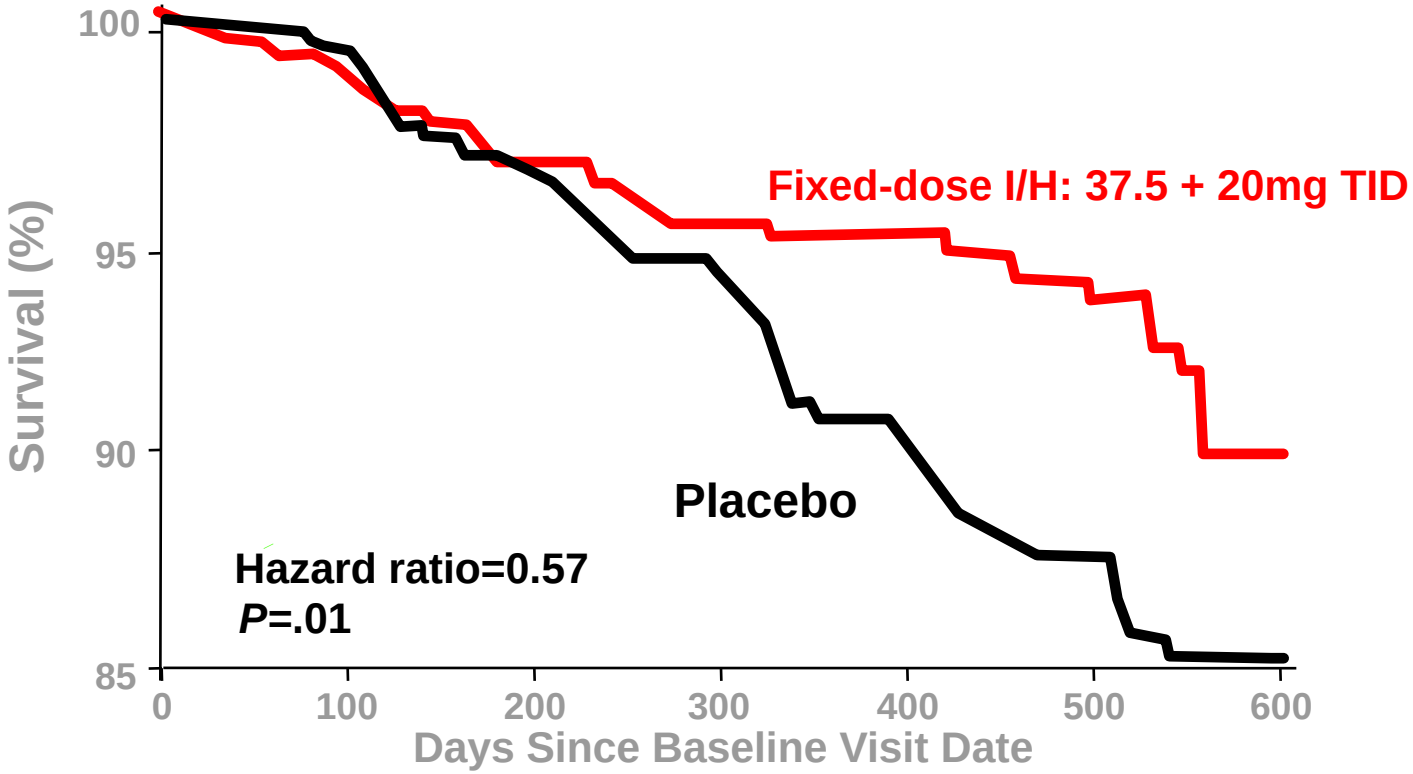
Emerging Targets and Treatments: HFrEF

Isordil + Hydralazine: A fortuitous combination in HF

VHEFT 2, White vs. Black Patients



A-HeFT: Results Isosorbide/Hydralazine Confers a 43% Relative Risk Reduction for Mortality in NYHA III-IV patients self-identified as black

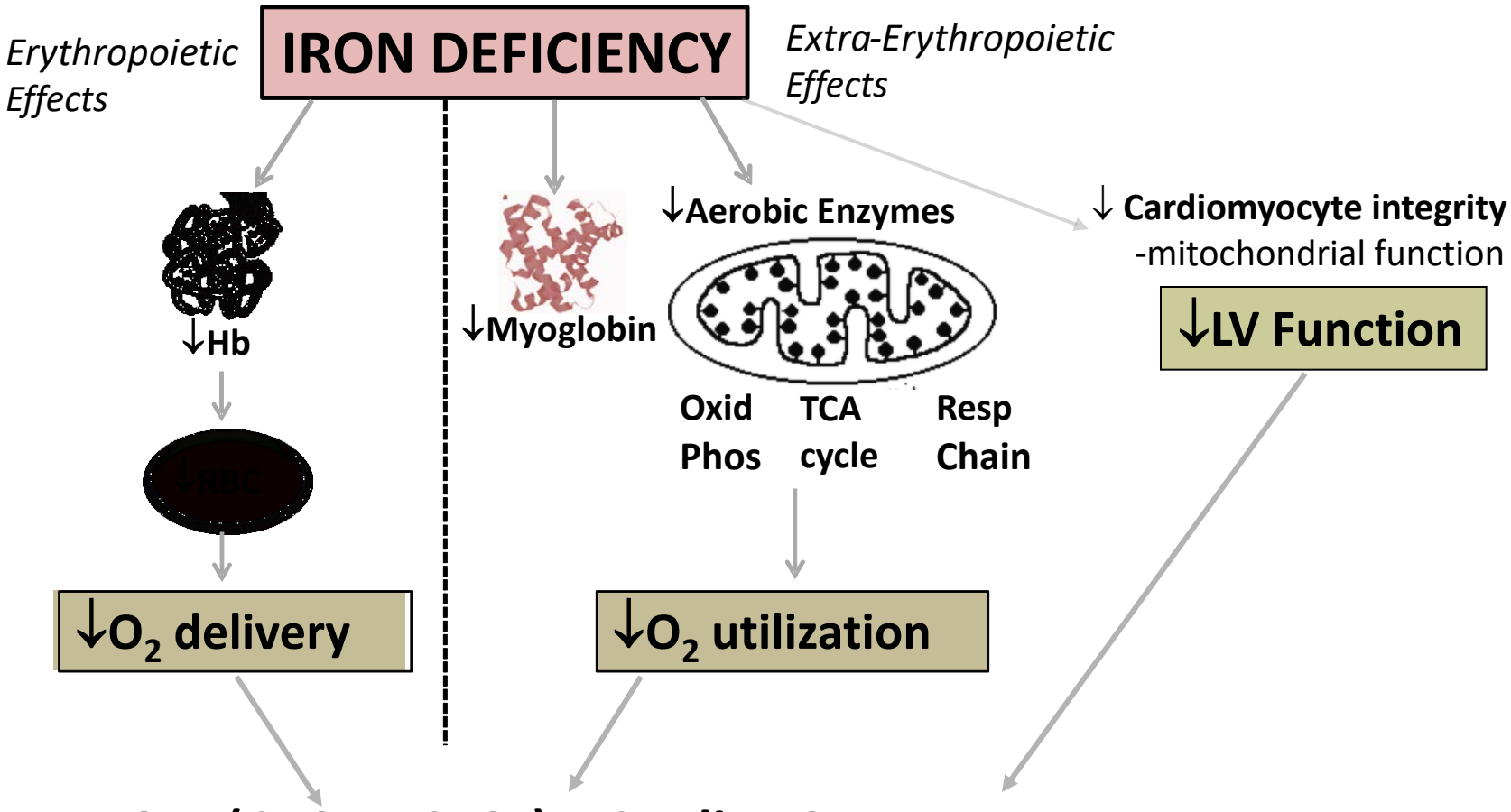


Fixed-dose I/H	518	463	407	359	313	251	13
Placebo	532	466	401	340	285	232	24

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Taylor AL et al NEJM 2005

The Influence of Iron on Functional Capacity in Heart Failure



$$VO_2 = (CaO_2 - CvO_2) \times \text{Cardiac Output}$$

Gold Standard Objective Measurement of Functional Capacity

Anker SD et al. EJHF 2009
Dong Clin Sci. 2005. Tobolli JACC 2008
Petering LH, Ann Nutr Metab 1990

Background and Rationale: Prevalence of Iron Deficiency in HFrEF

-**Iron (Fe) Deficiency is common in HFrEF**

Incidence

-70%: ↓ bone marrow iron[1]

-35-61%: ↓ ferritin, T-sat [2,3]

-25-42%: without anemia[3]

International Pooled Analysis (Klip I et al, AHJ 2013)

1506 patients with LVSD (Ferritin < 100 ug/L or 100-299 ug/L with Tsat < 20%)

50% had iron deficiency

Fe deficiency (but not anemia) independently predicted mortality (HR=1.42 1.14-1.77, P=0.002)

-No consensus guidelines on when, how, and whether to treat Fe Def in HF

-Oral Fe is inexpensive and readily available without reliance on industry support

-Oral iron repletion in HF has not been investigated

1. Nanas, JN JACC 2006
2. Grzeslo, A Eur Heart J 2007
3. Klip IT, AHJ 2013
4. Anker S, NEJM 2009

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

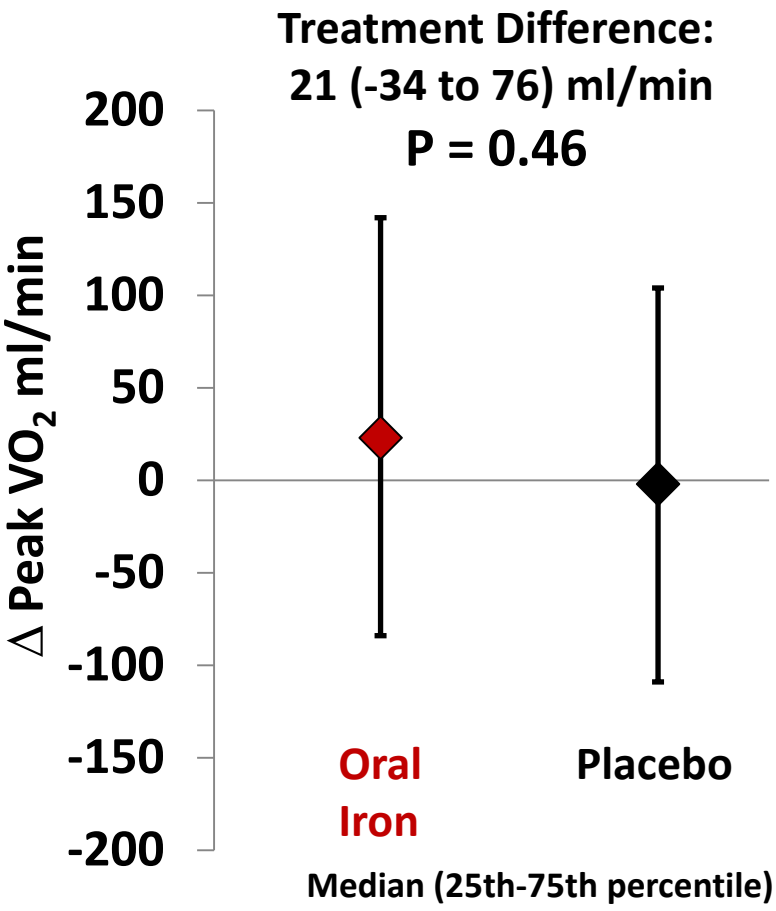
IV Iron Repletion Trials in HFrEF

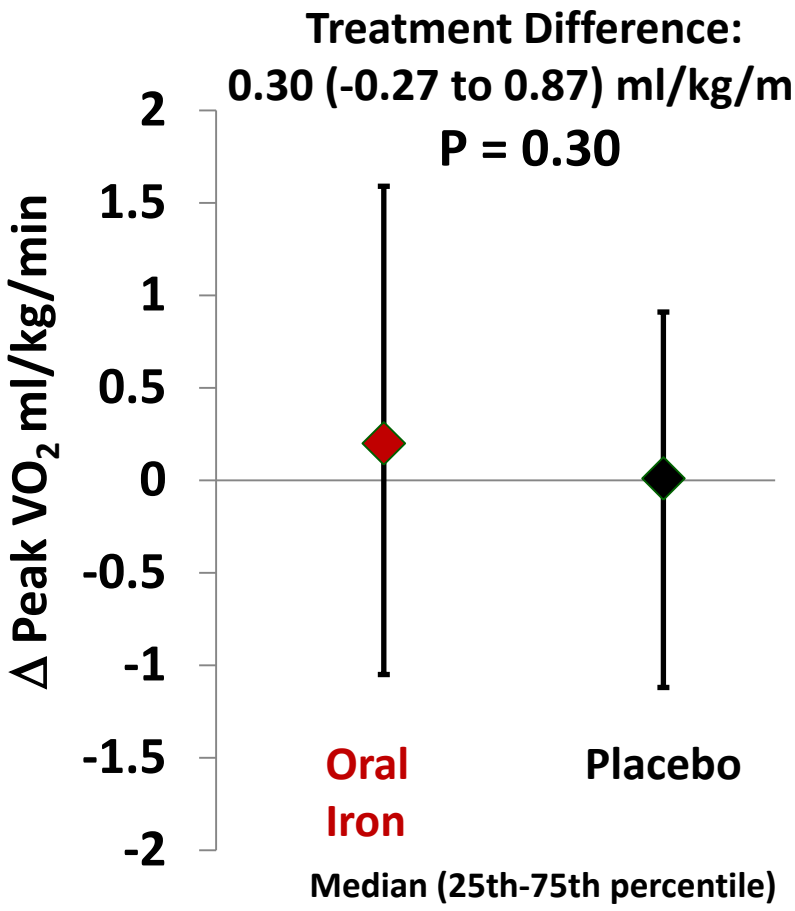
Drug	Authors/ Journal	N	Subjects Studied	Fe-Def Definition	Time	Primary Endpoint	Findings
IV Iron Sucrose	Tobilli *JACC 2007*	40	NYHA 3-4 LVEF<0.35	Ferritin<100 ng/ml and/or Tsat<20%	5 wks	Δ Global Assessment score	↑ PGAS, ↑ 6MWT ↑ NT-BNP, ↑LVEF
IV Iron Sucrose	Okonko *JACC 2008*	35	NYHA 2-3 LVEF<0.35	Ferritin<100 ng/ml or 100-300 with Tsat<20%	16 wks	Δ peak VO_2	↑ PGAS, ↑ NYHA ↑ Peak VO2 α Δ Tsat
IV Iron Carboxy maltose	Anker *NEJM 2009*	459	NYHA 2-3 LVEF<0.4 Hb 9.5-13.5	Ferritin<100 ng/ml or 100-300 with Tsat<20%	24 wks	Δ Global Assessment Score	↑ PGAS, ↓NYHA ↑ 6MWD Similar benefit Hb<>12
IV Iron Carboxy maltose	Ponikowski *EHJ 2014*	304	NYHA 2-3 LVEF<0.45 Hb <15	Ferritin<100 ng/ml or 100-300 with Tsat<20%	52 wks	Δ 6MWD	↑ PGAS, ↓NYHA Similar benefit Hb<>12 ↓ HF hospitalizations

Challenges and Unanswered Questions:

1. No consensus guidelines on when, whether, and how to treat Fe deficiency in HF
2. IV Fe is expensive ($4,000/dose) and requires repeated IV infusions (5+ in trials)
   -IV Rx studies: Blinded + unblinded study staff, 6% injection site reactions
3. The efficacy of oral iron repletion in HF is unknown despite its low cost and availability

What About Oral Iron Repletion in HF?





High dose oral iron minimally repleted iron stores and did not improve peak VO_2 in patients with iron deficiency and HFrEF

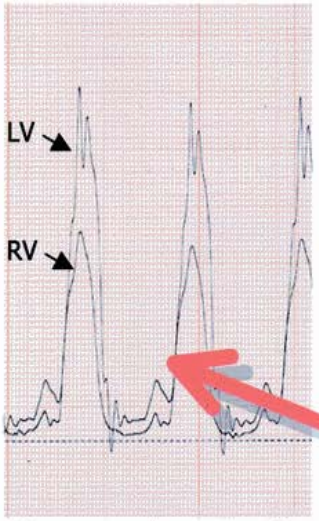
Lewis GD, JAMA 2017

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Iron Deficiency in Heart Failure

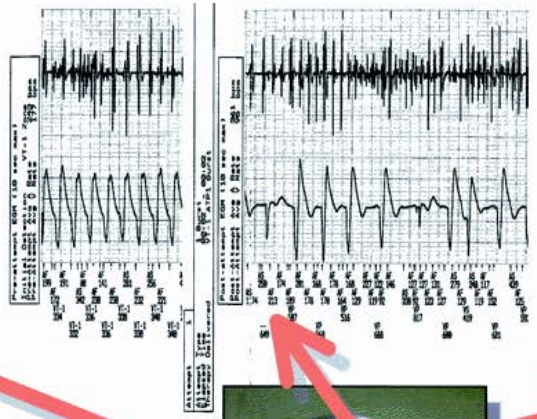
IIb Guideline:

In patients with NYHA class II and III HF and iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation is <20%), intravenous iron replacement might be reasonable to improve functional status and QoL

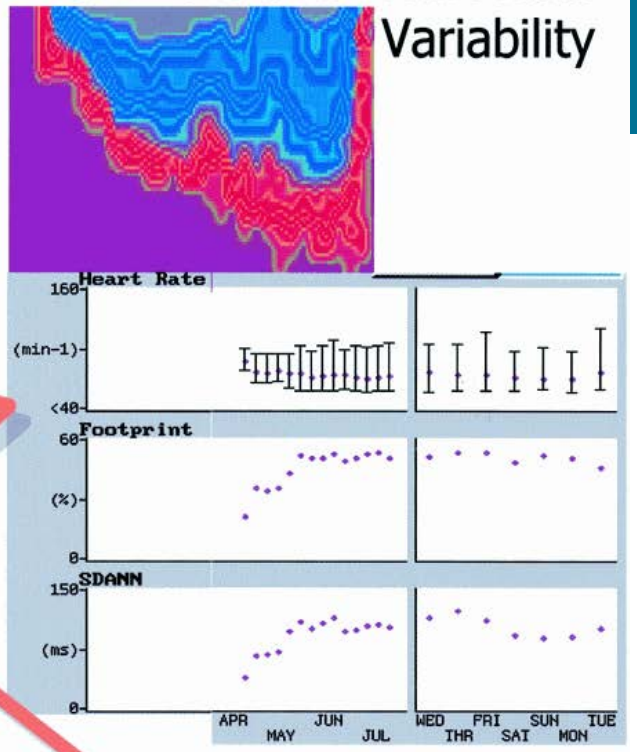


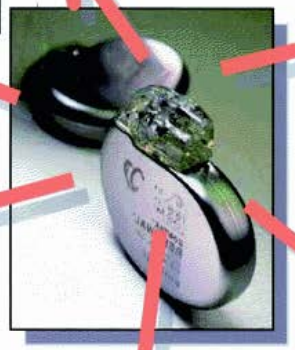
Hemodynamics

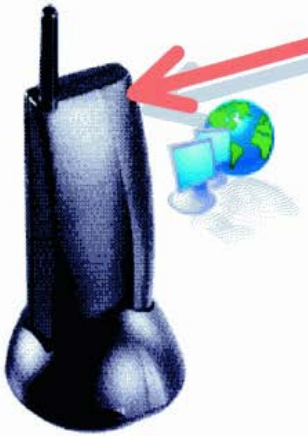
IECGs



Heart Rate and Heart Rate Variability

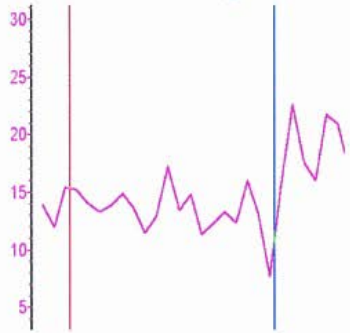




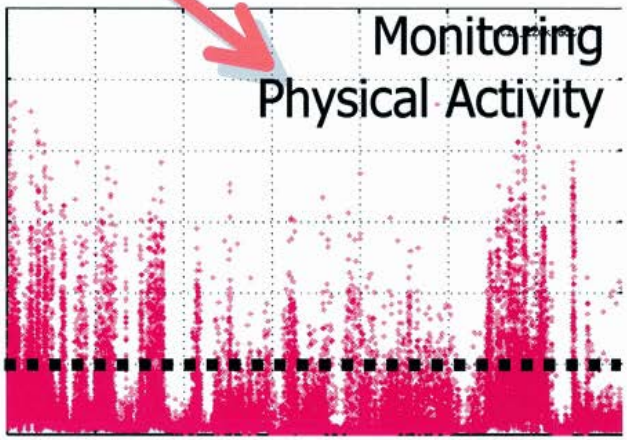


Internet-based Monitoring

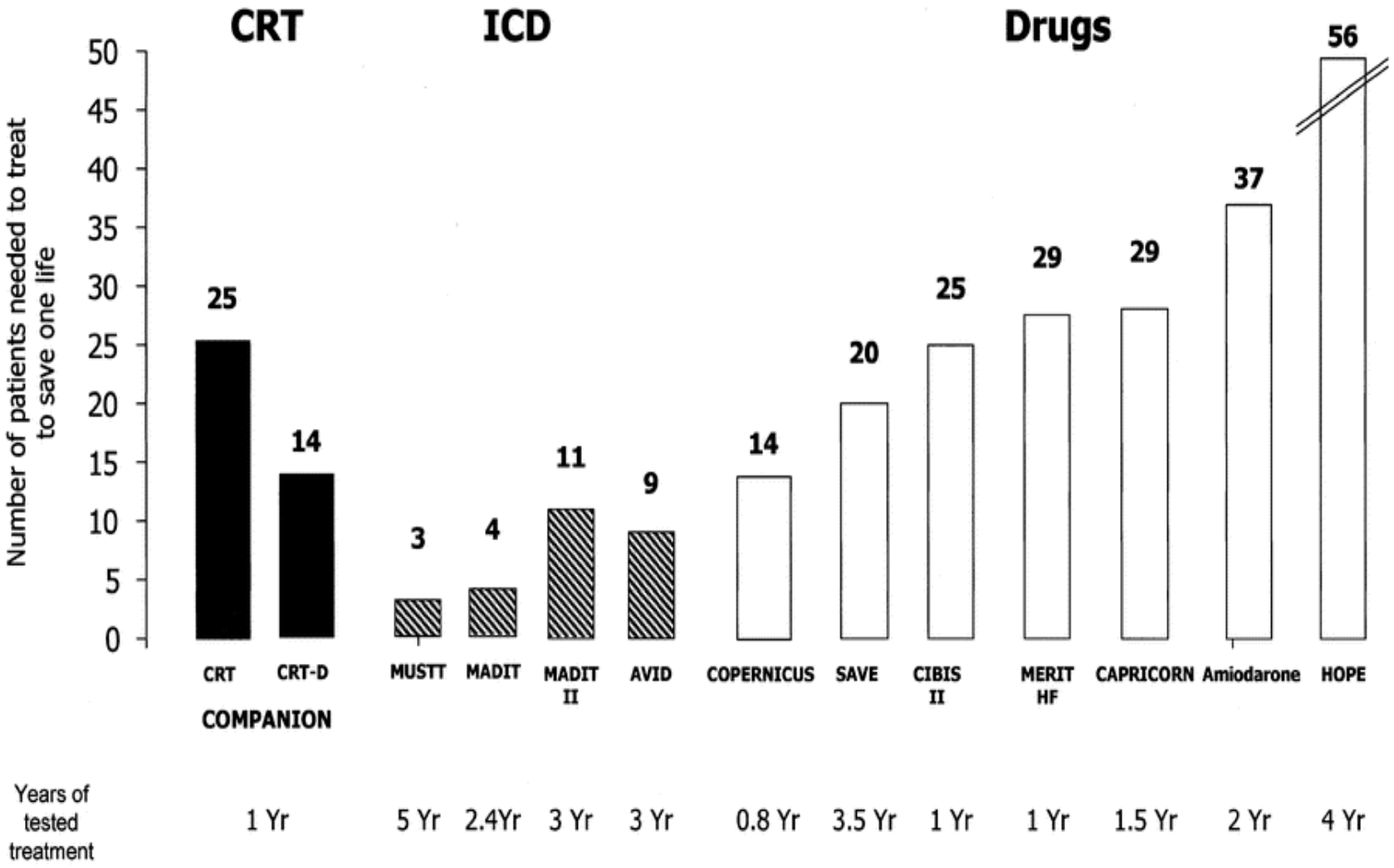
Respiration



Monitoring Physical Activity



$$\text{NNTx years} = \frac{100}{(\%\text{Mortality in Control Group} - \%\text{Mortality in Treatment Group})}$$



Indications for ICD in HF in 2017

Ischemic Cardiomyopathy

LVEF < 30% (MADIT II)

LVEF < 35% with NYHA Class II-III HF (SCD-HeFT)

LVEF < 40% with +EPS MADIT I, MUST

Non-ischemic Cardiomyopathy

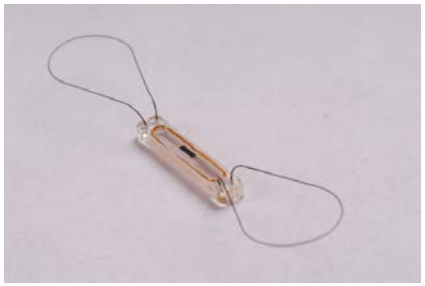
LVEF < 35% with Class II-III HF (SCD-HeFT, DEFINITE vs. DANISH)

-Excluding patients with Class D (NYHA IV) HF unless Bi-V PPM as well
-Excluding patients with concomitant diseases that will shorten life expectancy
->40 days s/p myocardial infarction (DINAMIT)
-At least 3 months of standard HF pharmacotherapy with persistent LVSD

The Pulmonary Artery Pressure Measurement System*

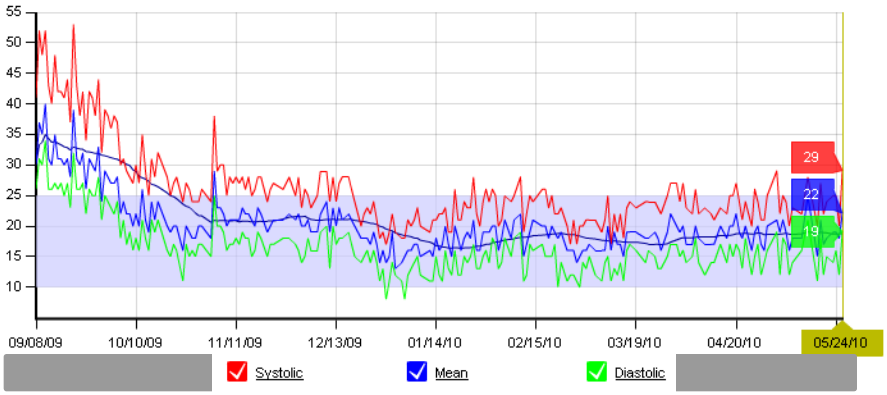
Catheter-based delivery system

MEMS-based pressure sensor



Home electronics

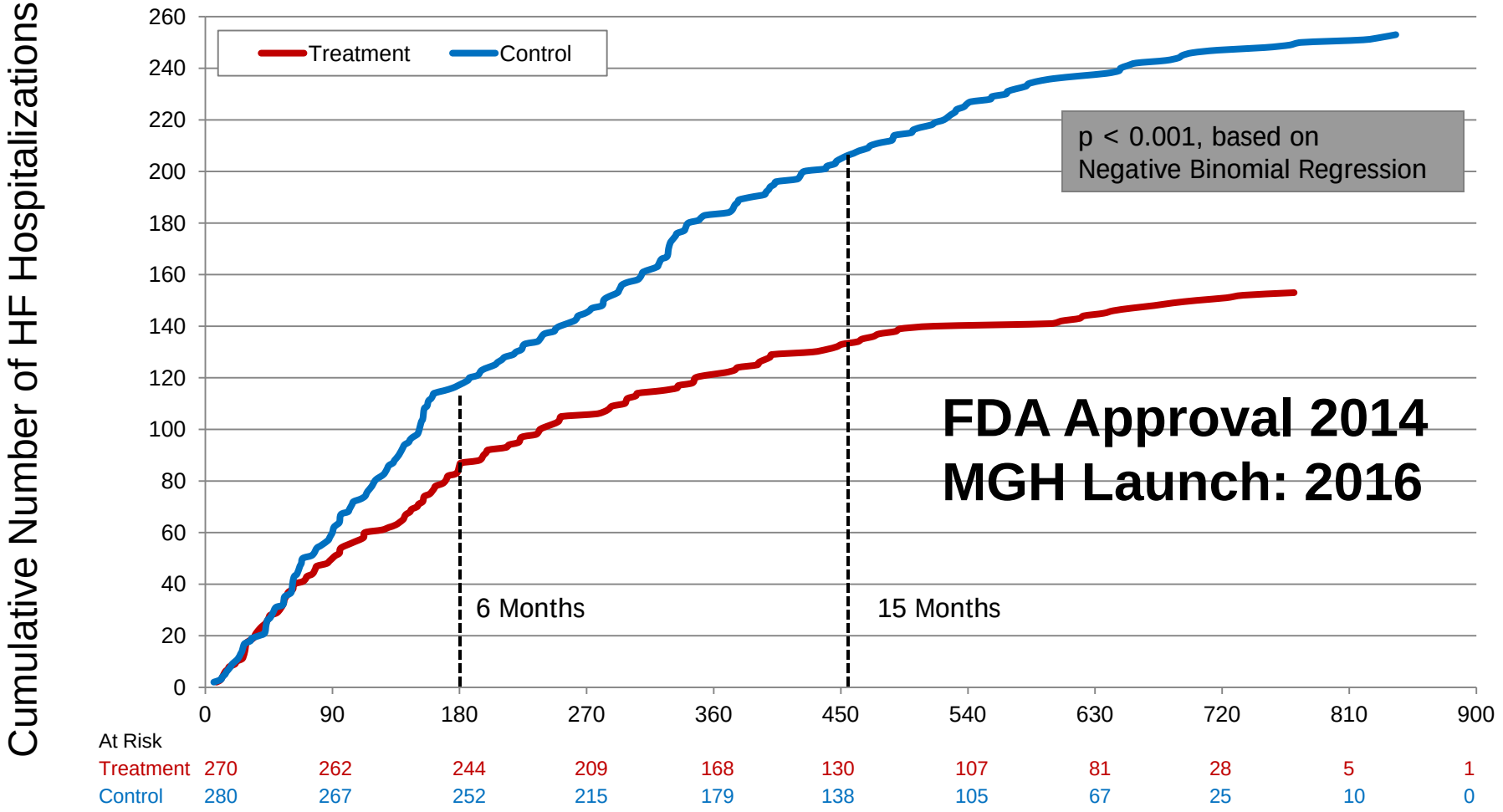
PA Measurement database



*CardioMEMS Inc., Atlanta, Georgia, USA

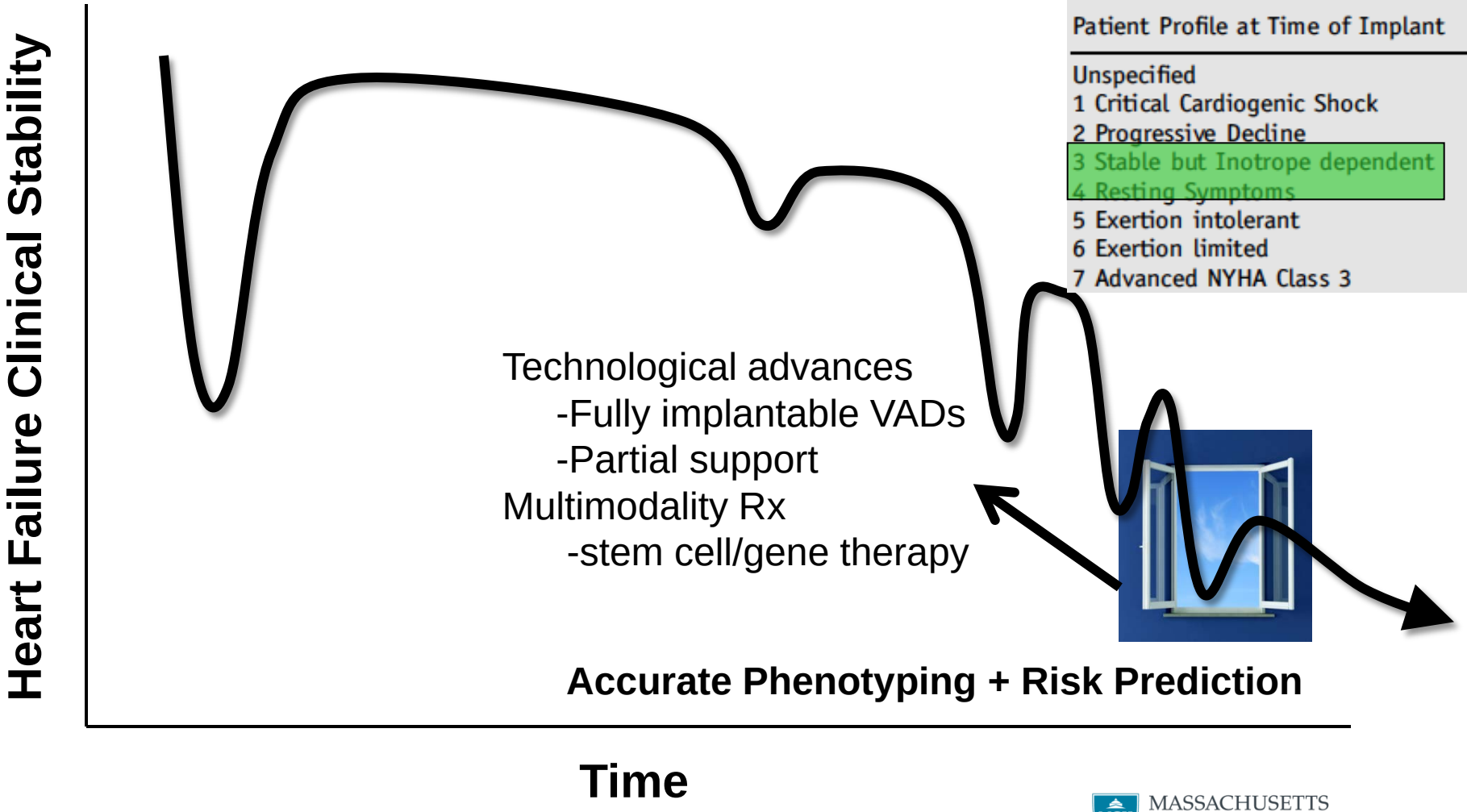
MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Cumulative HF Hospitalizations Over Entire Randomized Follow-Up Period



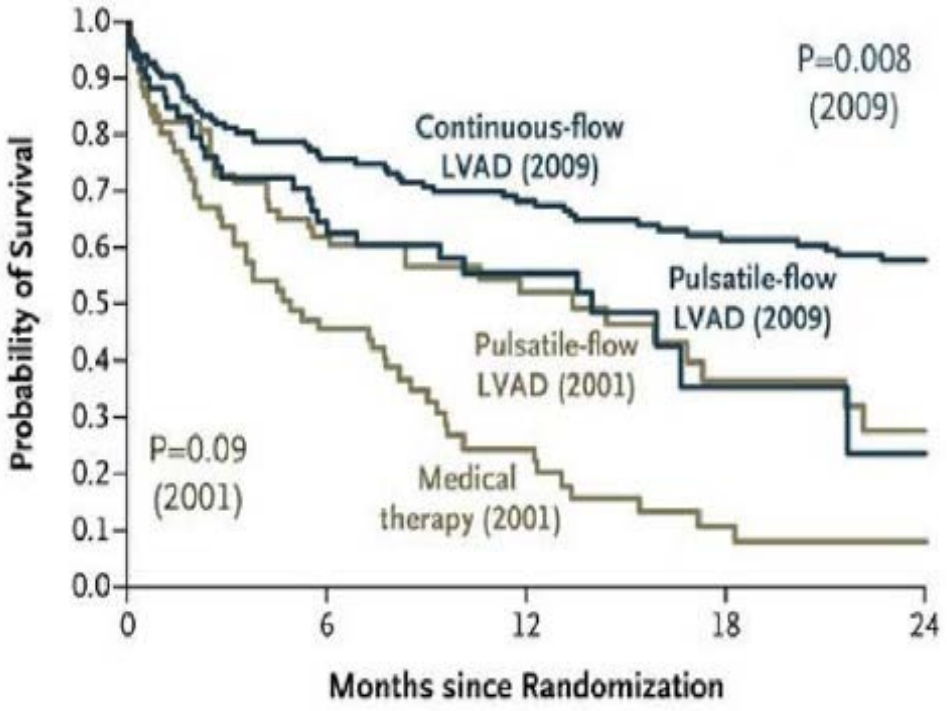
GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

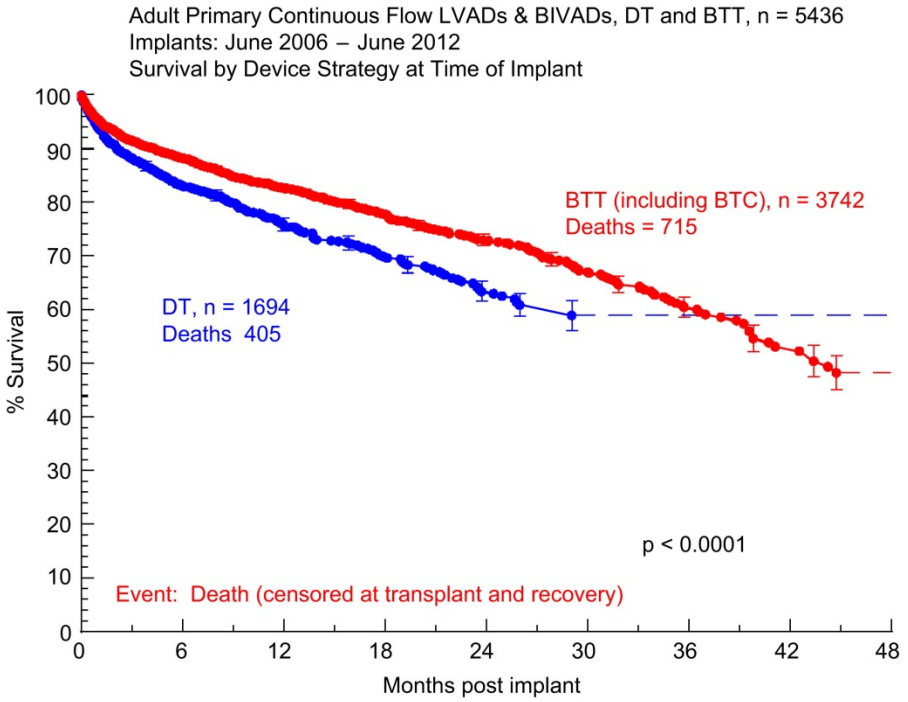
Sick Enough or Too Sick to Consider a Left Ventricular Assist Device?



MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

The Evidence: Survival in VAD Trials





HM2 LVAD: ~60% 24 mo survival
vs
IV inotropes: ~50% 6 mo survival

"The rise of the machines"
…..J Fang, 2009

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

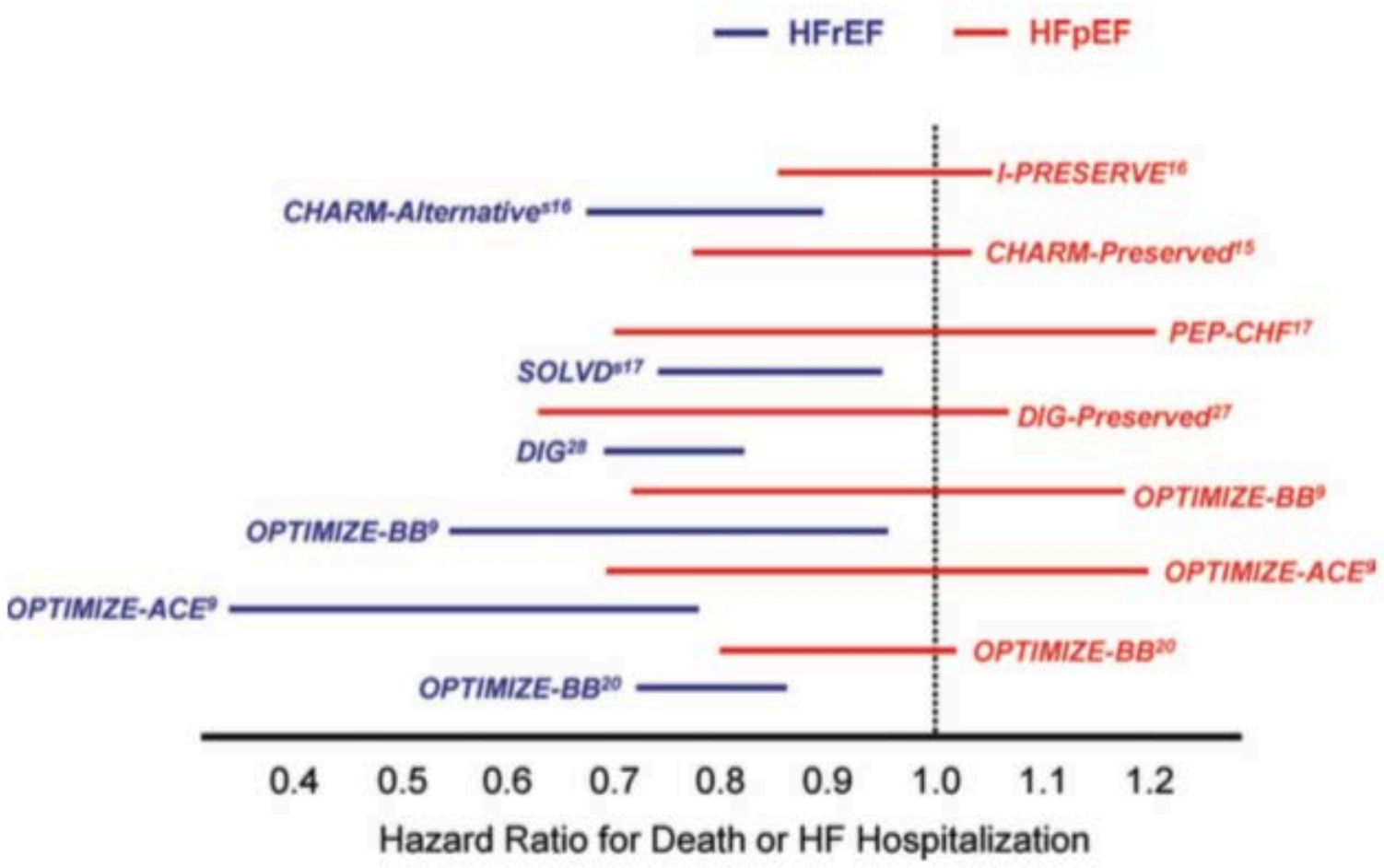
DIASTOLIC HEART FAILURE
PREVALENCE AND NATURAL HISTORY

- Approximately 40% of all cases of heart failure occur in patients with normal or near normal LVEF >45%
- Disease prevalence varies widely by age
  - <15% for middle-aged patients
  - >50% for elderly patients
- Annual mortality ranges from 1.3% to 17.5%; 2 largest retrospective series report rates of 8%-9%

Hogg et el, JACC 2004; Bursi et al, JAMA 2006; Owan et al, NEJM 2006; Bhatia et al, NEJM 2006; Klapholz et al JACC 2004

Current Pharmacologic Treatments for HPpEF that Improve 2 year Survival

HFpEF vs. HFrEF Comparative Results with Neurohormonal Blockade



Borlaug BA et al, Circulation, 2011

Trials of Therapeutic Interventions that Improve 2-year Mortality in HFpEF

Trial	Drug	N	Result
PEP CHF	ACE I (Perindopril)	850	HR 0.92, p=0.55
SENIORS	Bblck (Nebivolol)	752	HR 0.71-1.08, all p=0.21
CHARM Added	ARB (candasartan)	700	HR 0.89, p=0.12
I-Preserve	ARB (irbesartan)	4128	HR 0.99
TOPCAT	MRA (spironolactone)	3450	HR 0.89, p=0.12
RELAX	PDE 5I (sildenafil)	220	pkVO2 -0.2ml/kg, p=0.9
NEAT	Nitrates (isosorbide)	100	↓ Actigraphy levels
PARAGON-HF	LCZ 696	4300	Enrollment→2019

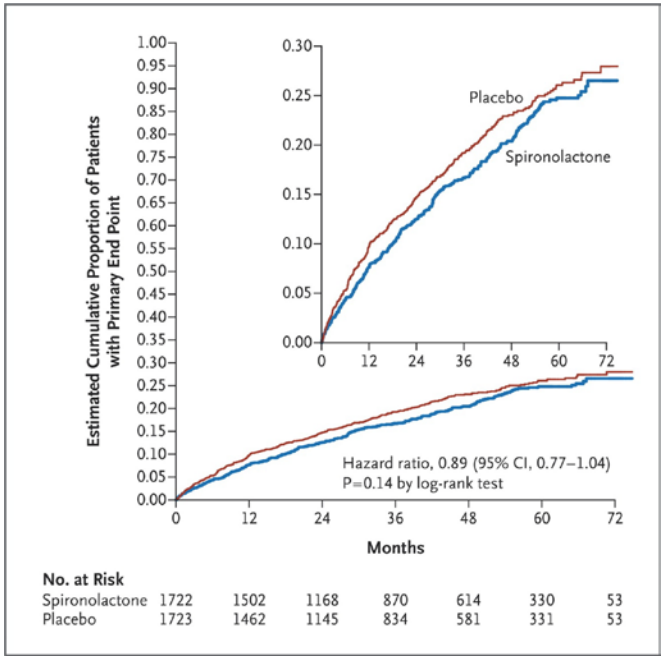
Patients: Symptomatic, LVEF>0.45, ±structural hrt disease (LAE, LVH)

Definition of HFpEF

HFpEF Definitions	ACC/AHA	ESC	HFSA	TOPCAT	RELAX	PARAGON-HF	FHS
Author	*Yancy C, Circ, 2013*	*McMurray JJV, EHJ, 2012*	*Lindenfeld J, JCF, 2010*	*Pitt B, NEJM, 2014*	*Redfield MM, JAMA, 2013*	*clinicaltrials.gov*	*Lam, Circ HF 2010*
Symptoms	x (for stage C)	x	x	x	x	x	xx
Signs		x	x	x	x		x
LVEF	>=50%	normal/mildly depressed	>=50%	>=45%	>=50%	>=45%	>=50%
structural heart disease		LVH, LAE, or DD and not dilated	cLVH, LAE echo or cath evidence of DD			LAE or LVH	
HF admission				x	x		
CV admission			x				
Exclude	nonardiac causes		nonmyocardial disease				
BNP/NT-proBNP		alternative to echo: >=100/>=300 (acute) or >=35/>=125 (non-acute)		alternative to HF admission: >=100/>=360	NT-proBNP >=400 or elevated filling pressures at time of NT-proBNP<400		

HFpEF Trials: TOPCAT

- **Treatment Of Preserved Cardiac function heart failure with an Aldosterone anaTagonist**
- NHLBI sponsored trial; n=4500 patients randomized to an aldosterone antagonist versus placebo, LVEF > 45%; age > 50 years; controlled blood pressure; K^+ < 5.0 mEq/L
- Endpoints: CV mortality, aborted sudden cardiac death, or hospitalization



MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Next Steps in HF Treatments

There is an unmet need to apply heart failure physiologic subphenotyping in order to improve targeted approaches to interventions…..

Candidate Subphenotypes

Obesity with normal cardiometabolic capacity

Isolated/Predominant LV dysfunction

Abnormal peripheral function: impaired oxygen utilzation

Chronotropic incompetence

Right Ventricular - Pulmonary Vascular Dysfunction

ACC/AHA GUIDELINES ON PAHRMACOLOGICAL TREATMENT OF DIASTOLIC HEART FAILURE

Recommendation	Class	Level of Evidence
Treat hypertension in a in accordance with guidelines	I	A
Control ventricular rate in atrial fibrillation	I	C
Diuretics to control congestion	I	C
Beta-blockers, ACE-I, ARBs *or* calcium channel blockers may ↓Sx	IIa	C
Digitalis may reduce symptoms	IIb	C

Hunt S, et al. *Circulation* 2005; 112:1837

MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

THANK YOU

END

MASSACHUSETTS
GENERAL HOSPITAL
INSTITUTE FOR HEART,
VASCULAR AND STROKE CARE