



Heart Failure: The Clinician's Perspective

Ileana L. Piña, MD, MPH

Professor of Medicine, Epidemiology and Population Health

Albert Einstein College of Medicine

Associate Chief of Cardiology for Academic Affairs

Director, Cardiology, Einstein Campus

Montefiore-Einstein Medical Center

Bronx, NY



Disclosures

- Advisory Board: Relypsa, modest
- Speakers Bureau: None
- FDA Senior Staff Fellow
- Medscape: Heart Failure editor/blog
- *Today my comments are purely my own and speak as a clinician with over 20 years of HF/Transplant/LVAD experience.*

Today: The Clinician's Perspective

- 1. standalone, meaningful primary health outcomes in research studies of heart failure treatment technologies:
 - *Heart failure hospitalization;*
 - *Heart failure hospitalization or heart failure hospitalization equivalent events (i.e., outpatient IV therapy for heart failure);*
 - *Total Hospitalizations?*
- The appropriate length of follow-up post-heart failure intervention for assessing this outcome;
- Assessing the merits of composite outcomes in research studies of HF treatment technologies with the combination of mortality, HF hospitalization, or HF hospitalization equivalents.

Today: The Clinician's Perspective

- How confident are you that surrogate and intermediate endpoints are predictive of standalone, meaningful primary health outcomes (e.g., reduction in mitral regurgitation, cardiac remodeling, ejection fraction, or biomarkers) in clinical research studies of heart failure treatment technologies for:
 - *Heart failure with preserved ejection fraction;*
 - *Heart failure secondary to mitral regurgitation where the focus of therapy is mitral valve repair/ replacement;*
 - *Heart failure with reduced ejection fraction (e.g., cardiac remodeling, ejection fraction)?*
- **Discussion:**
- the specific surrogate or intermediate endpoints and associated disease or therapy which you believe are sufficiently predictive of meaningful health outcomes.
- Please discuss how these intermediate and surrogate endpoints meaningfully contribute towards the evidence base for HF treatment technologies.
- Important factors to consider when assessing the utility of surrogate and intermediate endpoints.

Today: The Clinician's Perspective

- The focus of the meeting is on clinical research studies of medical devices for treating patients with:
- 1) Heart failure with preserved ejection fraction; (**HFPeF**)
- 2) Heart failure secondary to mitral regurgitation where the focus of therapy is mitral valve repair/ replacement; **MR**
- 3) Heart failure with reduced ejection fraction (e.g., cardiac remodeling, ejection fraction). (**HFReF**)
- There will also be discussion around outcomes of interest and appropriate follow-up duration in studies of technologies designed for diagnosis of **ADHF**

HFReF clinical goals

- **When are my patients the happiest?**

- When they feel better
 - Independence
 - Self care
 - More function ADL's
 - Better appetite
- Out of the hospital
 - Stretch out their visits
 - No arrhythmias, especially AFib
- When they are told they don't need an ICD because their LV is better
- Their heart has improved
- When I simplify their med regimen
 - Limit diuretics
- When they meet their life milestones
- Health status including QOL

- **When am I the happiest?**

- See reverse remodeling
 - Equates to lower mortality
 - No need for ICD
 - Less MR
- Keep them out of the hospital
 - Last hospitalization
 - No arrhythmias
- When I can medicate them to my standards
 - Keep them euvolemic
 - When adherent to meds
 - Limit diuretics
 - Minimize side effects
- When I hear how much they can do—walk as much as they want
- Loosing weight (not muscle mass)
- Increased activity levels
- Na and K are stable
- Stretch out their visits

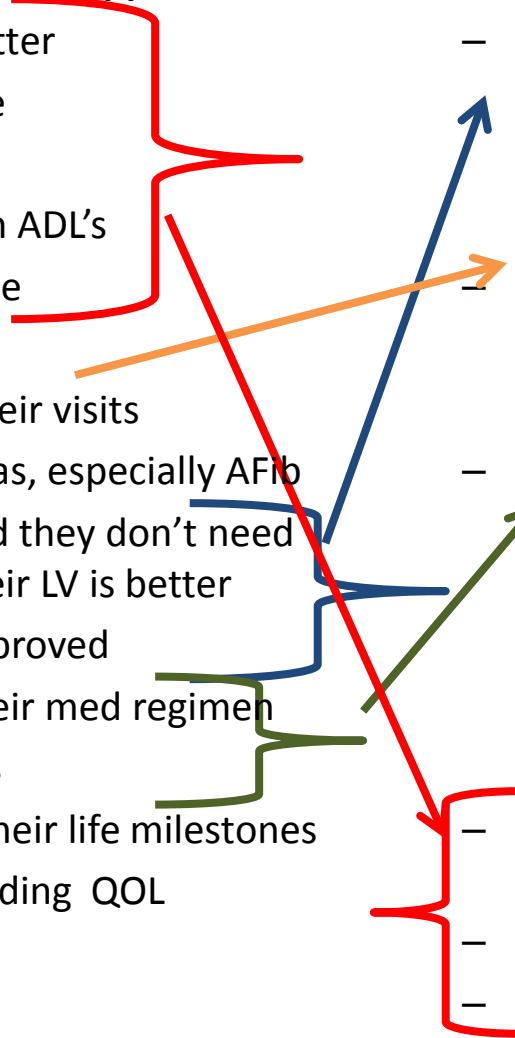
HFReF clinical goals often match

- **When are my patients the happiest?**

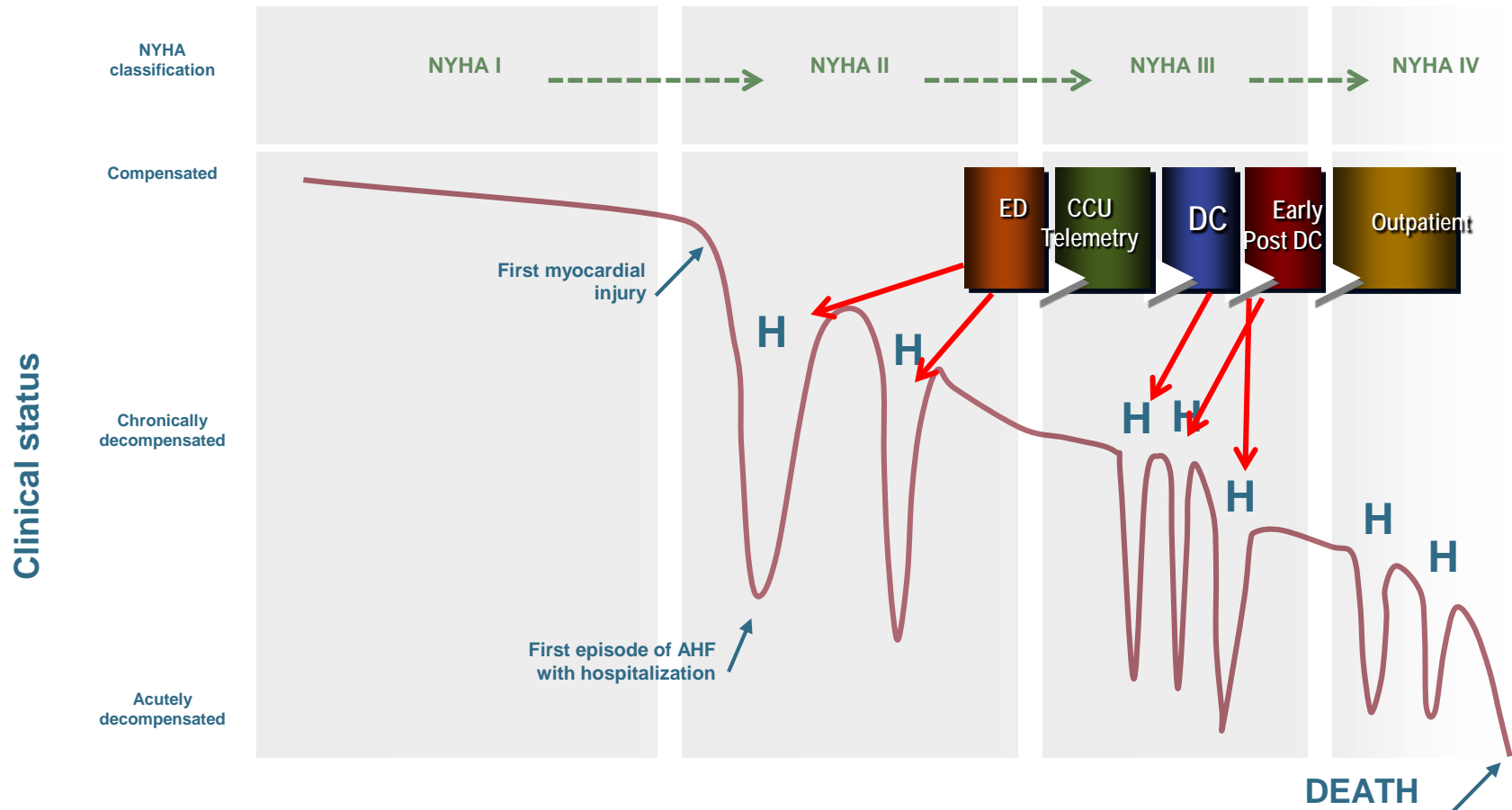
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Continuity of the syndrome forgotten



“Failure” of Usual Care in Heart Failure

- Failure to prescribe evidence-based medications
- Failure to discontinue medication that may exacerbate HF
- Failure to titrate medications to target doses
- Failure to adhere to prescribed medications
- Failure to adequately address comorbidities
- Failure to consider device therapies
- Failure to provide adequate dietary counseling
- Failure to comply with dietary regimen
- Failure to seek early care with escalating symptoms
- Failure of adequate discharge planning
- Failure of adequate follow-up
- Failure of adequate monitoring
- Failure of patient social support systems
- Failure to address patient and care-giver needs

Hospitalizations: An important outcome for HFReF at a minimum, 30, 60 and 90 days

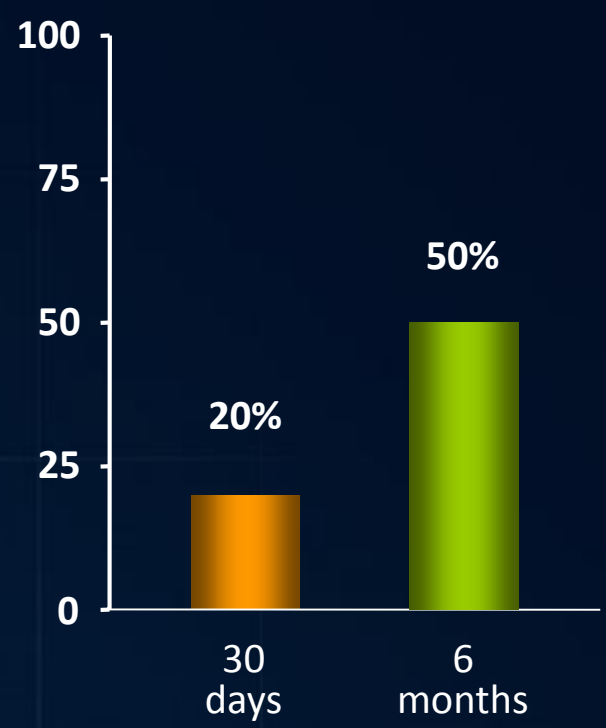
The Why's

- Why do I believe in reducing hospitalizations (all kinds)
 - Increased mortality
 - The revolving door
 - Good drugs removed and Good drugs not given
 - Bad drugs given
 - Loss of function in bed
 - Poor physical therapy or rehab
 - No consistent pattern of care determined by attending (often not even Cardiology)
 - LOS usually not sufficient to reverse the storm and adequately decongest. Pressure to discharge
-
- Hospitalizations (all cause) should be an **OUTCOME**
 - HF Hospitalizations should be an **OUTCOME**
 - Hospitalization equivalents (ED visit, unscheduled HF office visit) should be an **OUTCOME**

Outcomes in Patients Hospitalized with HF

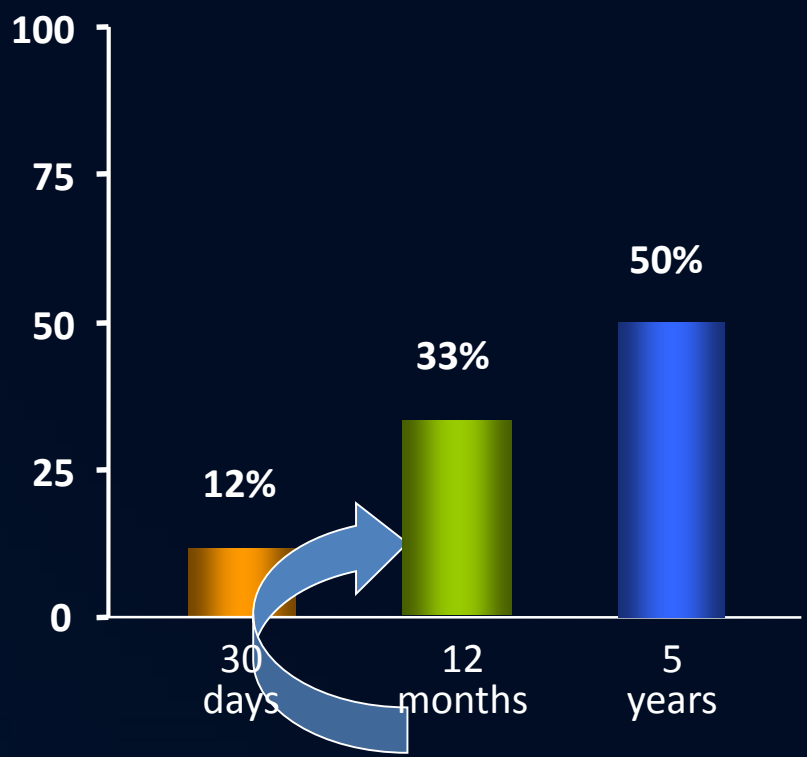


Hospital Readmissions



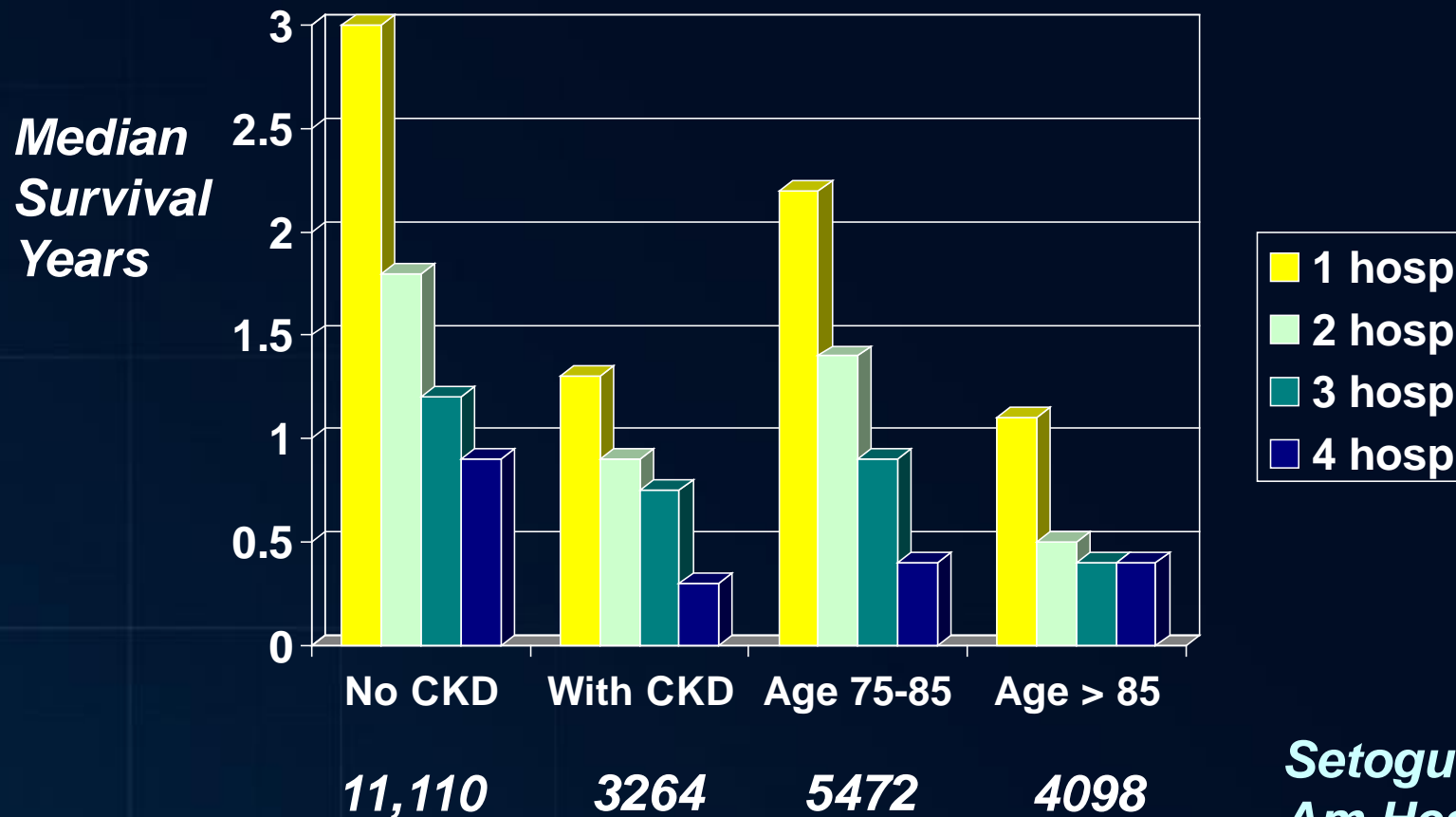
Median hospital LOS: 6 days

Mortality



Annual mortality rate
NYHA class III HF: 12% [COPERNICUS DATA]
NYHA class II HF: 7% [SCD-HeFT DATA]

Survival After HF Hospitalizations



*Setoguchi et al
Am Heart J 2007*

Typical List of Meds: BB Clinic



Date: 5/18/15
 ✓ HF BIC MAP # 2102 PM 40+ F
 DOB: 12/24/24; Phone: (718) 559-3224
 (301) 112-44475 → HF Homecare?
 Hosp: 3/2-3/2/15 → HF Discharge; PCT: Sophia, MD; Cardiac Dr. Richard, MD
 **HF Medications
 KFLA, Labwork, 4/24/2015; PFT; Hgb 4/6/15
 **ALL: 10/20/15
 PMH: CHD, HLD, DM, FLD, C/P, Anemia, COPD (2005), Laceration, Urt, Allergies, HF, Fall Risk, Hypertension
 Lab: 4/6/15
 E: 5.4
 BUN/Cr: 18/0.7
 GFR: 54 (ml/min)
 CCI:
 Hgb/Hct: 12.0/37.3 (4/6/15)
 AUC: 7.1 (4/6/15)
 LBN: 29 (4/6/15)
 ProBNP: 34, 205 (4/6/15)
 EF: 50 % (5/1/15) - 60% (normal), 40% (low)
 VLDL: 20.1 (4/6/15) - 110 (low), 150 (normal)
 BP: 140/75 NR: 58 - 110/60
 BG:
 Mag = 1.4 (4/6/15)
 Phos = 3.1
 ① Diltiazem 100mg QD
 ② Hydralazine 100mg TID
 ③ Torsemide 40mg BID (D/C Furosemide)
 ④ Labwork
 First Aid Pharmacy
 (718) 893-5700

What am I confident of?



- GDMT
- Reverse remodeling should mean improvement in outcomes
- Exercise therapy can improve health outcomes, safe
- Capturing health status clinically
- Other prognostic factors, e.g., serum sodium, Pro BNP, VO2

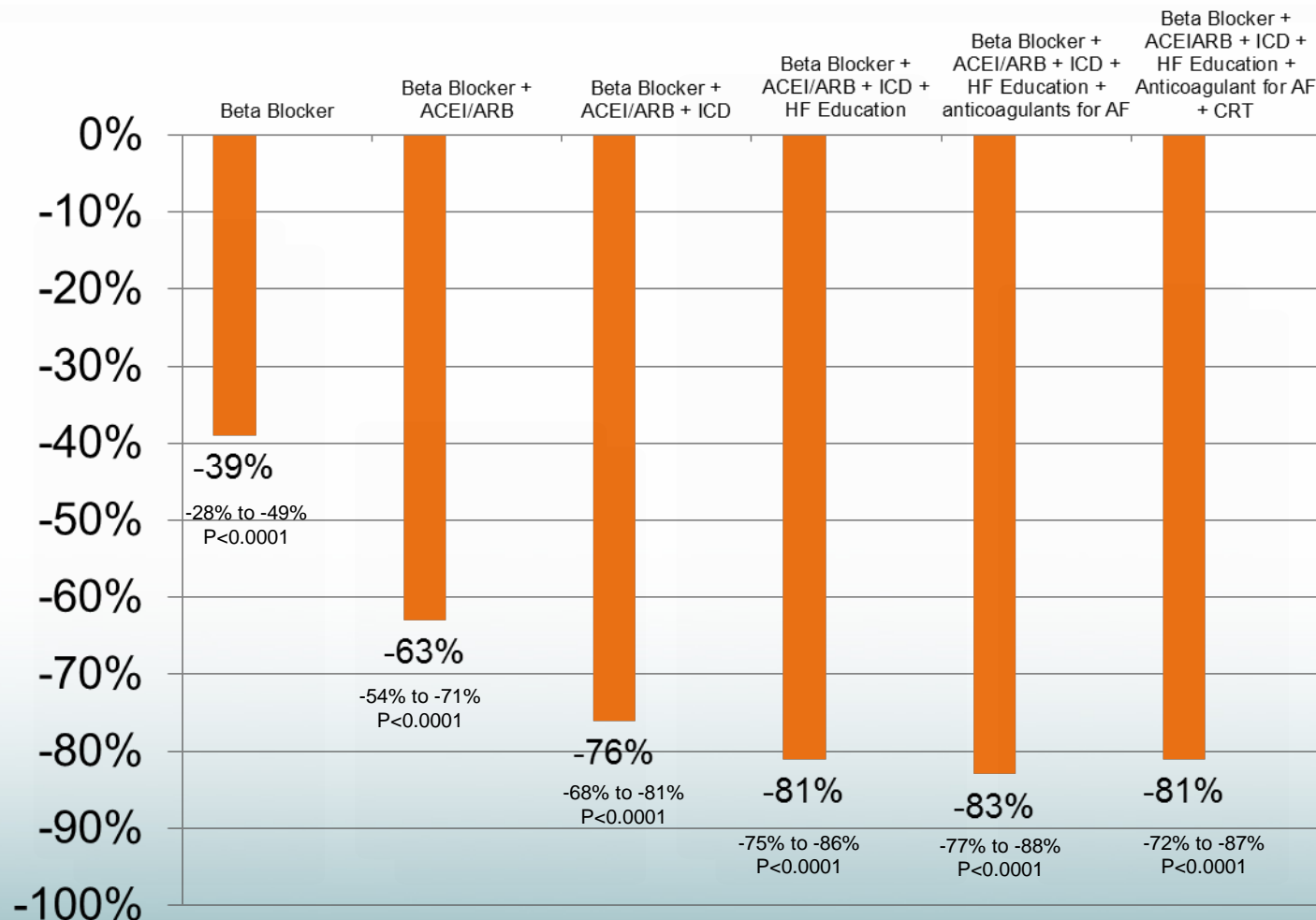


Why do I insist on GDMT?


- It works!
 - Consistent
 - Gradual
 - Know pharmacology
 - Confident with dosing
 - Follow biomarkers
- The inability to medicate (by experts) = **Outcome**
- Not a checkbox without doses or reasons
- Can it be done?

Incremental Benefits with HF Therapies

(Cumulative % Reduction in Odds of Death at 24 Months)

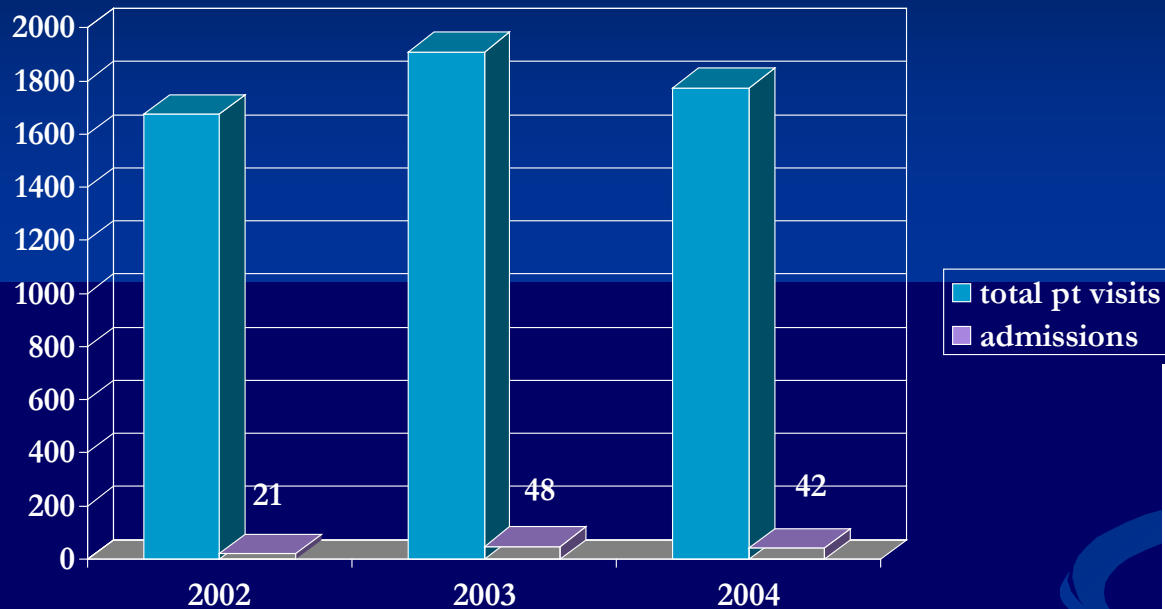


Reverse Remodeling?

- Remodeling is an adverse myocardial process
- Advanced remodeling  worse outcomes
- Remodeling involves not only myocytes
- Surrogates of remodeling or its true reversal:
 - LVEDV, LVEDVi
 - LVESV, LVESVi
 - Mass
 - EF
 - Reduction or resolution of MR
- Remodeling is a time related process
- Reverse remodeling is a time related process
- May serve as a response to specific therapies
- Reverse remodeling should be linked to favorable outcomes: Causal relationship
- Should reverse remodeling be an outcome: YES

Heart Failure Clinic Stats CWRU

2002-2004



Age	59 ± 16
Gender	49% women
Etiology	41% ICM
Wt	175 lbs
B/P	133/70
HR	78
NYHA	2.4 ± 0.8

Beta blocker use in CASE HF clinic

	<i>Improved LVEF</i>	<i>Non-Improved</i>	<i>P value</i>
	N=37	N=48	
<i>Female (%)</i>	40	48	0.79
<i>Caucasian (%)</i>	47	44	0.98
<i>Nonischemic (%)</i>	77	58	0.25
<i>Initial LVEDD (mmHg)</i>	6.4	6.3	0.94
<i>ACEI Use (%)</i>	95	83	0.28
<i>Mean Dose of ACEI (mg/day)</i>	36	35	0.78
<i>β-B-Blocker Use (%)</i>	81	77	0.9
<i>Initial Pulmonary Artery Systolic Pressure (mmHg)</i>	37	45	0.13
<i>Initial Peak Oxygen Uptake (ml/kg/min)</i>	13.8	13.6	0.89
<i>Cardiac Index (L/min/m²)</i>	2.3	2.5	0.57
<i>Initial NYHA Class</i>	2.4	2.5	0.15

Beta blocker use in CASE HF clinic

Figure 2: Changes in LVEF

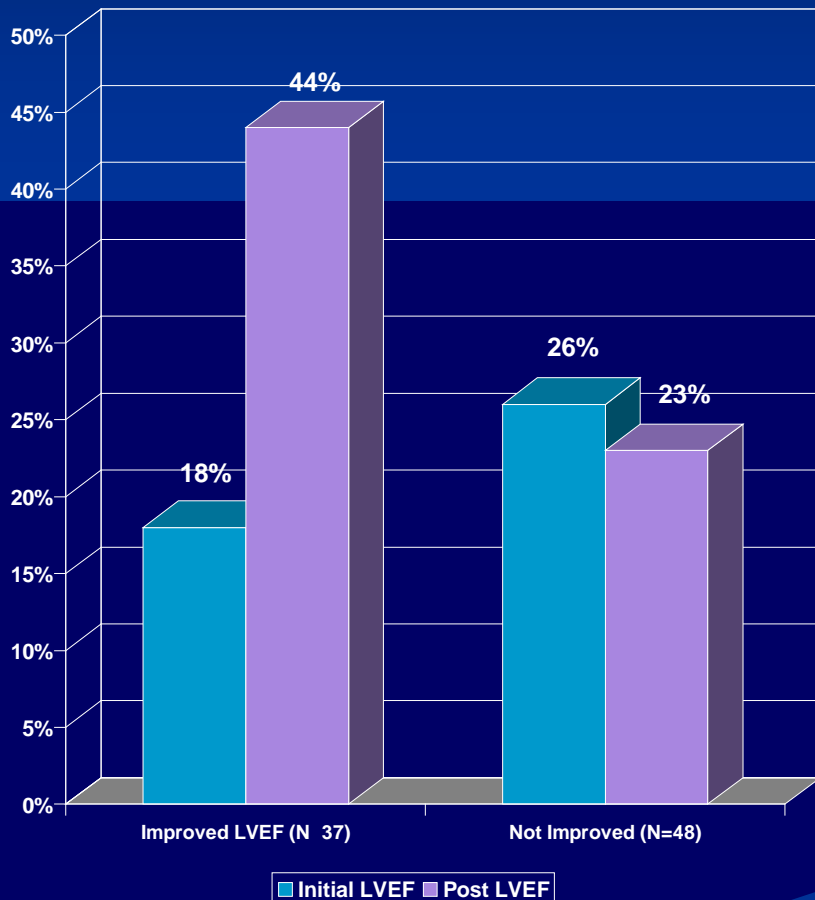
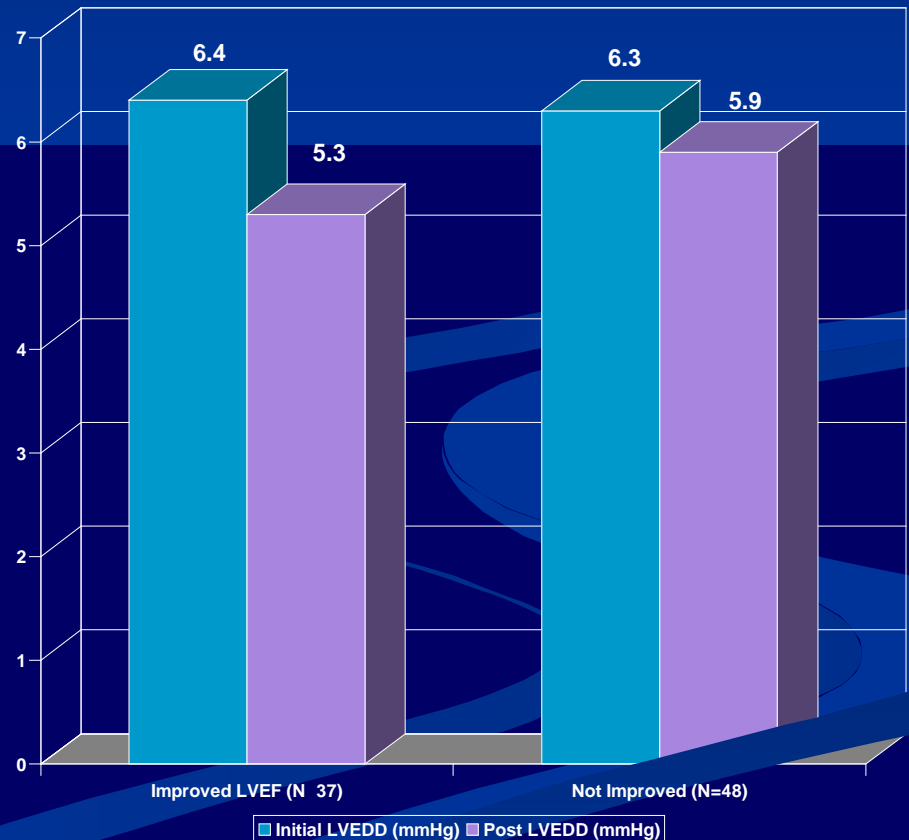
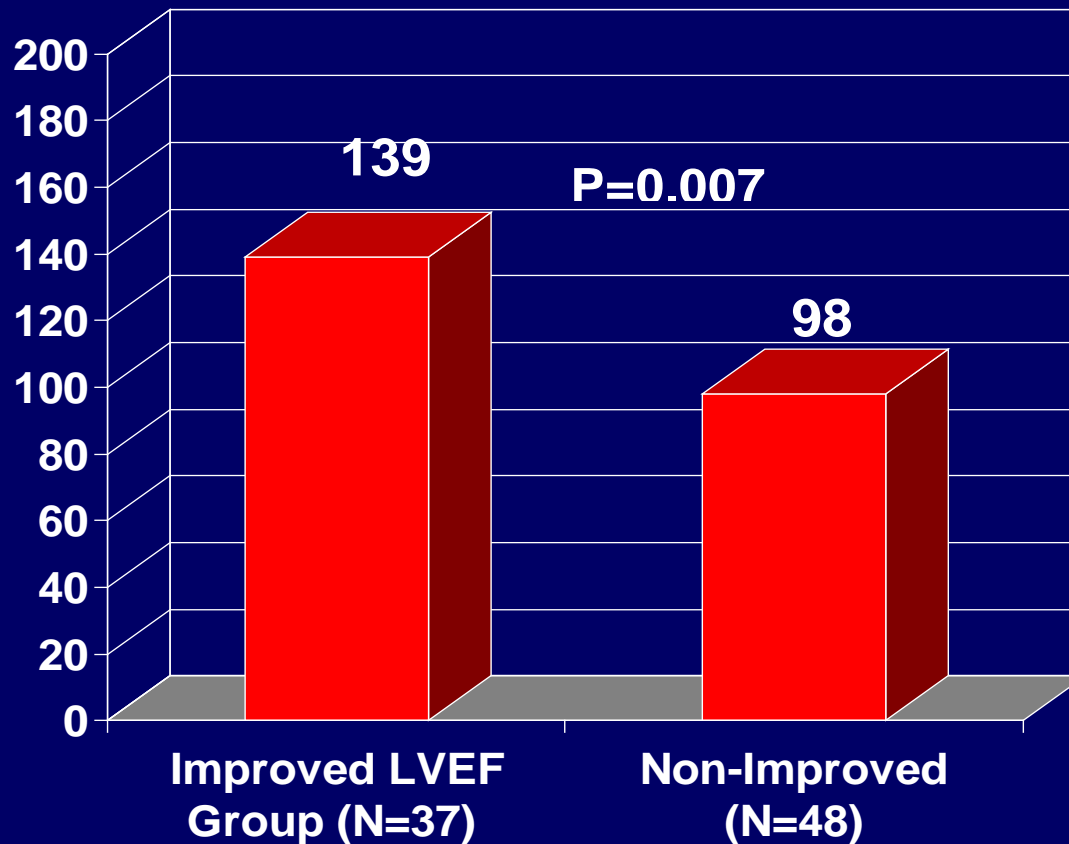


Figure 3: Changes in LVEDD

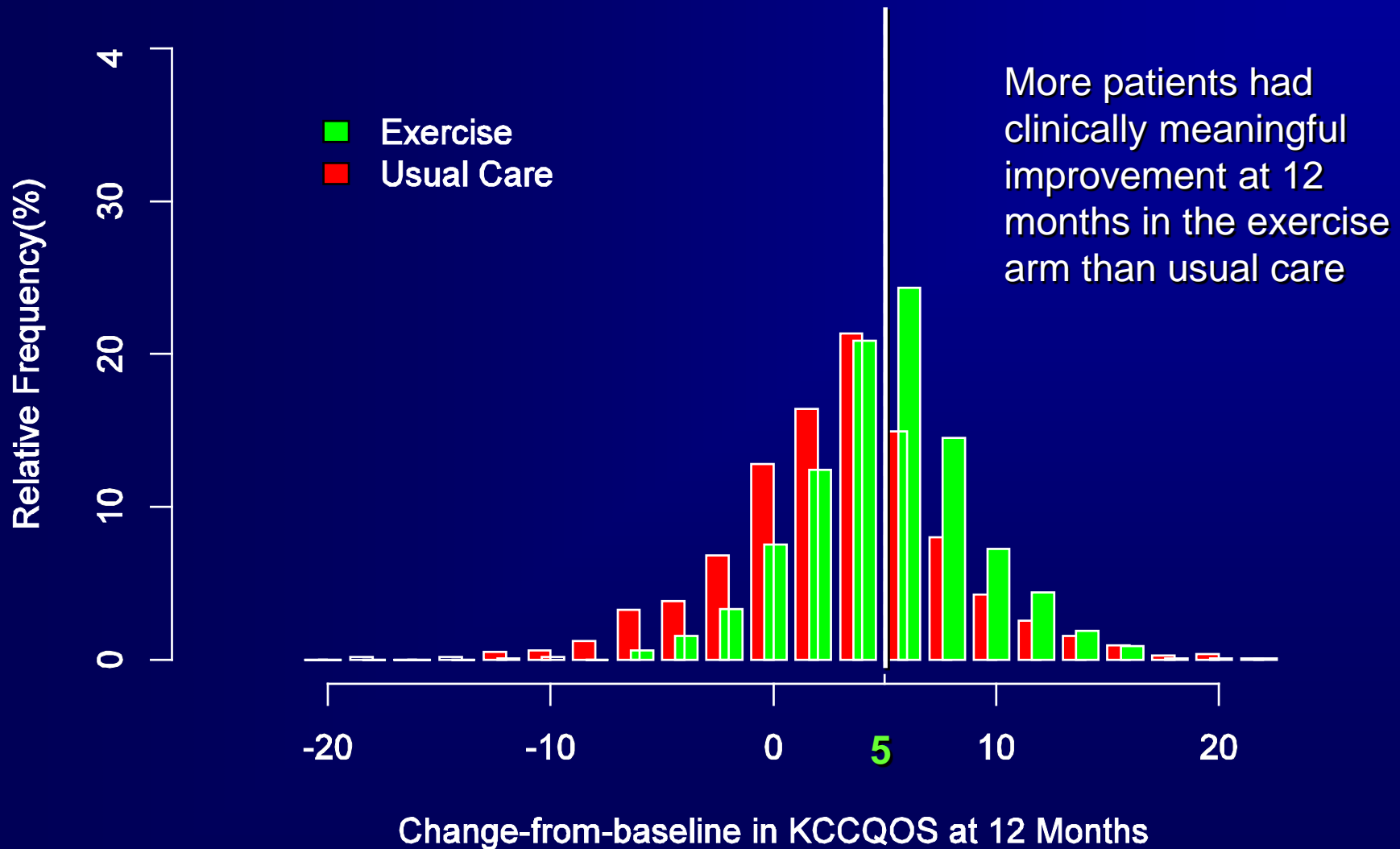


Beta blocker use in CASE HF clinic

Figure 1: Differences in Beta Blocker Doses in Metoprolol Equivalent Doses in mg/day



Predicted Change in KCCQ at 12 Months



Results

Demographics

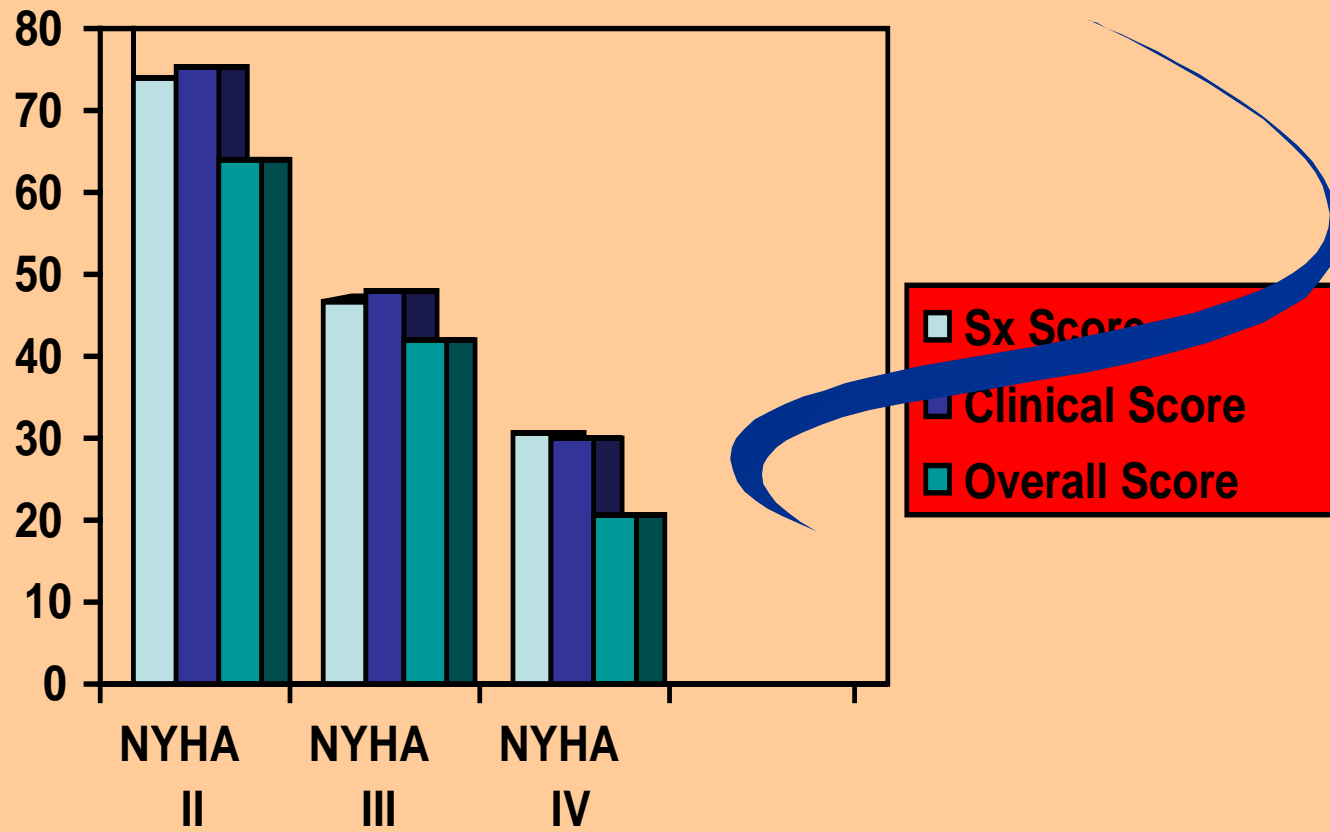
Number of Patients	86
Age	51 \pm 8 years
Men	49
Women	37
Caucasian	40
African-American	31
Hispanic	1
EF (%)	19.8 \pm 8.1%

Results

NYHA	Physical Limitation	Total Symptom	Self-Efficacy	QoL	Social Limitation	Overall Summary	Clinical Summary	EF (%)	VO ₂ ml/min/kg
2.00	76.23	74.62	61.62	50.08	55.15	64.23	75.62	21.54	16.31
3.00	48.94	47.00	73.71	36.12	37.00	42.35	48.24	19.29	13.59
4.00	29.25	31.00	34.50	10.25	16.00	21.75	30.50	18.33	13.26
Total	57.06	55.68	64.47	38.41	41.47	48.29	56.62	20.09	14.56

Results are in mean values

Kansas City Cardiomyopathy Questionnaire at CASE



Brown Bag Clinic: Montefiore

Parameter (n=32)	Mean \pm Std Dev
Age (years)	61 \pm 14
Gender (% women)	25%
HF-PEF (n)	8
EF (%)	72 \pm 8
Pro BNP	1382.5 \pm 159 pg/ml
HF-REF (n)	24
EF (%)	30 \pm 6
Pro BNP	7008 \pm 7905 pg/ml
KCCQ overall Score	52.14 \pm 20.46

HFPeF



Why Do HFPEF Patients Decompensate?

- Excess salt
- Inadequate diuretic Rx
- Worsening hypertension
- Medications: NSAIDs, thiazolidinediones, ?CCBs, ?alpha-blockers
- Atrial fibrillation
- Worsening renal function
- Myocardial ischemia
- Anemia
- Iatrogenic volume overload

Can absence of any of these be Outcomes? E.g., Afib, renal function

Treatment of HF_pEF

Recommendations	COR	LOE
Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines	I	B
Diuretics should be used for relief of symptoms due to volume overload	I	C
Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT	IIa	C
Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF	IIa	C
Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF	IIa	C
ARBs might be considered to decrease hospitalizations in HFpEF	IIb	B
Nutritional supplementation is not recommended in HFpEF	III: No Benefit	C



*Helping Cardiovascular Professionals
Learn. Advance. Heal.*



Echocardiographic parameters in select HFpEF trials.

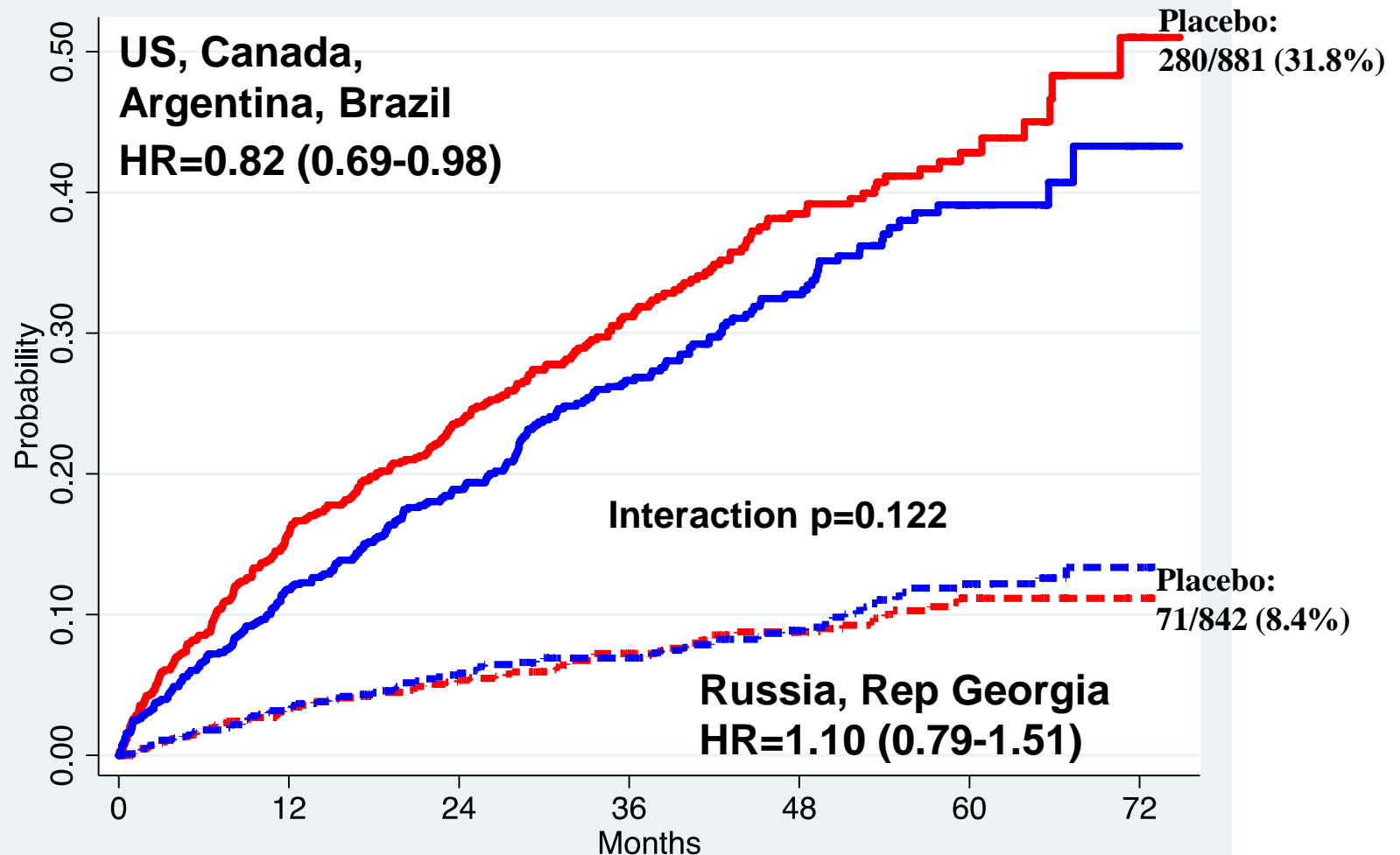
Anderson and Vasan. Heart Fail Clin. 2014 July ; 10(3)

Table 2	TOPCAT(62)	PARAMOUNT(63)	RELAX(20)	I-PRESERVE(17,64)	CHARMES(65,66)	Aldo-DHF(6)	PEP-CHF(18)
N	935	292	216	745	312	422	850
Definition of diastolic heart failure	LVEF \geq 45%, HF hospitalization, or BNP \geq 100 or NT-proBNP \geq 360 pg/mL	LVEF \geq 45%, NT-pro-BNP $>$ 400 pg/mL	LVEF \geq 50%, NT-pro-BNP $>$ 400, pVO2 $<$ 60% of predicted	LVEF \geq 45%, recent HF hospitalization or other objective signs of HF	LVEF $>$ 40%	LVEF \geq 50%, echocardiographic diastolic dysfunction or AF pVO2 \leq 25	LVEF $>$ 40%, HF by clinical criteria
Age (years)	70 \pm 10	71 \pm 9	69 (62–77)	72 \pm 7	66 \pm 11	67 \pm 8	75 (72–79)
Women	49%	56%	48%	62%	34%	52%	56%
<i>LV structure</i>							
EDD (cm)	4.80 \pm 0.58	4.64 \pm 0.48	4.6 (4.3–5.1)	4.8 \pm 0.6	5.4 \pm 0.7	4.65 \pm 0.62	4.6 (4.2–5.1)
EDVi (mL/m2)	49.9 \pm 15.5	61.4 \pm 15.4	NA	49 \pm 14	NA	NA	NA
MWT (cm)	1.18 \pm 0.20	0.91 \pm 0.16	NA	0.93 \pm 0.15	NA	NA	1.3 (1.2–1.5)
LVMi (g/m2)	111 \pm 31	79.1 \pm 22.2	78 (62–94)	NA	117 \pm 42	109 \pm 28	NA
RWT	0.49 \pm 0.10	0.38 \pm 0.08	NA	0.40 \pm 0.08	NA	NA	NA
<i>LV geometry</i>							
Normal	14%	72%	NA	46%	NA	NA	NA
Concentric remodeling	34%	14%	NA	25%	NA	NA	NA
Concentric hypertrophy	43%	7%	NA	29%	NA	NA	NA
Eccentric hypertrophy	9%	7%	NA	0%	NA	NA	NA
<i>LV systolic function</i>							
EF (%)	59.6 \pm 8.0	57.7 \pm 7.9	60 (56–65)	64 \pm 9	50 (18–65)	67 \pm 8	65 (56–66)
<i>LV diastolic function</i>							
LAVi (mL/m2)	29.8 \pm 12.5	35.9 \pm 13.5	44 (36–59)	NA	41.3 \pm 14.7	28.0 \pm 8.4	NA
LA diameter (cm)	4.3 \pm 0.6	3.7 \pm 0.5	NA	NA	NA	NA	4.5 (4.1–4.8)
E/A ratio	1.2 \pm 0.7	1.1 \pm 0.62	1.5 (1.0–2.1)	1.05 \pm 0.74	1.1 \pm 0.7	0.91 \pm 0.33	0.7 (0.6–0.9)
TDI E– septal (cm/s)	6.1 \pm 2.2	5.8 \pm 2.0	6 (5–8)	7.2 \pm 2.9	NA	5.9 \pm 1.3	NA
TDI E– lateral (cm/s)	8.2 \pm 3.2	7.5 \pm 2.8	NA	9.1 \pm 3.4	NA	NA	NA
E/E– ratio (septal)	15.6 \pm 6.8	15.9 \pm 7.3	16 (11–24)	NA	NA	12.8 \pm 4.0	NA

Incident Atrial fibrillation: A growing problem and concern

- **Often coexists with HFpEF presentation**
- **May be the causation of decompensation**
- **Meta-analysis of > 54,000 patients,**
- **A significantly higher risk of death in AF patients with HFrEF compared to those with HFpEF.**
 - **There was a crude mortality rate of 24% *versus* 18% respectively, over 2 years.**
 - **no significant difference in incident stroke or heart failure hospitalization between the two groups.**

Exploratory (post-hoc): Placebo vs. Spiro by region



Exercise Training in Older Patients With Heart Failure and Preserved Ejection Fraction

A Randomized, Controlled, Single-Blind Trial

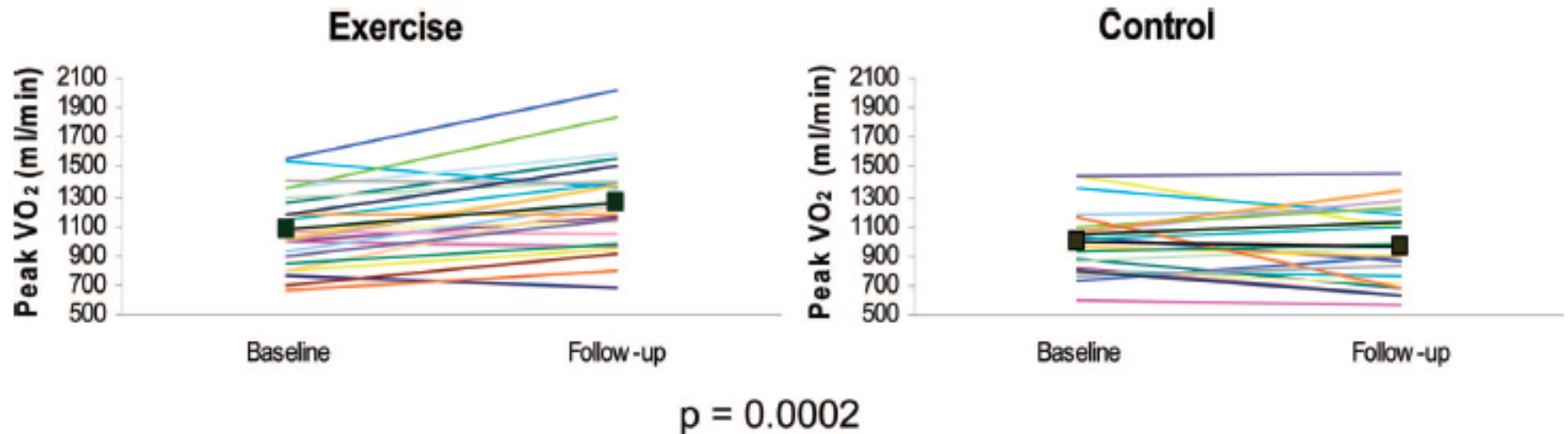


Figure. Individual and mean (■) responses of peak exercise $\dot{V}O_2$ following 16 weeks of supervised exercise training. Results are displayed in raw, nonindexed peak $\dot{V}O_2$, as this is uninfluenced by weight.

Kitzman et al. Circ Heart Fail. 2010;3:659-667.

HFPeF: Key points

- HFPeF is common, especially among the elderly and in women.
- With an increasing prevalence of HTN, obesity, Afib, and diabetes, and the growing elderly segment of the general population, the prevalence of HFPEF is projected to increase.
- HFPEF = diagnostic challenge and studies differ widely in their reported incidence and mortality rates associated with this condition.
- There is agreement that between a third and one half of HF patients in the community have HFPEF.
- Prognosis is overall poor. Patients with HFPEF have substantial comorbidity, high rates of repeated hospitalizations, and a high mortality.
- Is the mortality often not related to the HFPEF but to the comorbidities?
- Are there different groups within the phenotypes?
- **OUTCOME:**
 - **Reduction in all cause hospitalization**
 - **Improvement in objective function: ability to rehab**
 - **Improvement in symptoms (well captured)**
 - **Absence of a fib**

In Devices for HF (HFReF or HFPeF)

**Benefit
(outcome)**



Risk

What do I expect from a device vs. drug in HF?

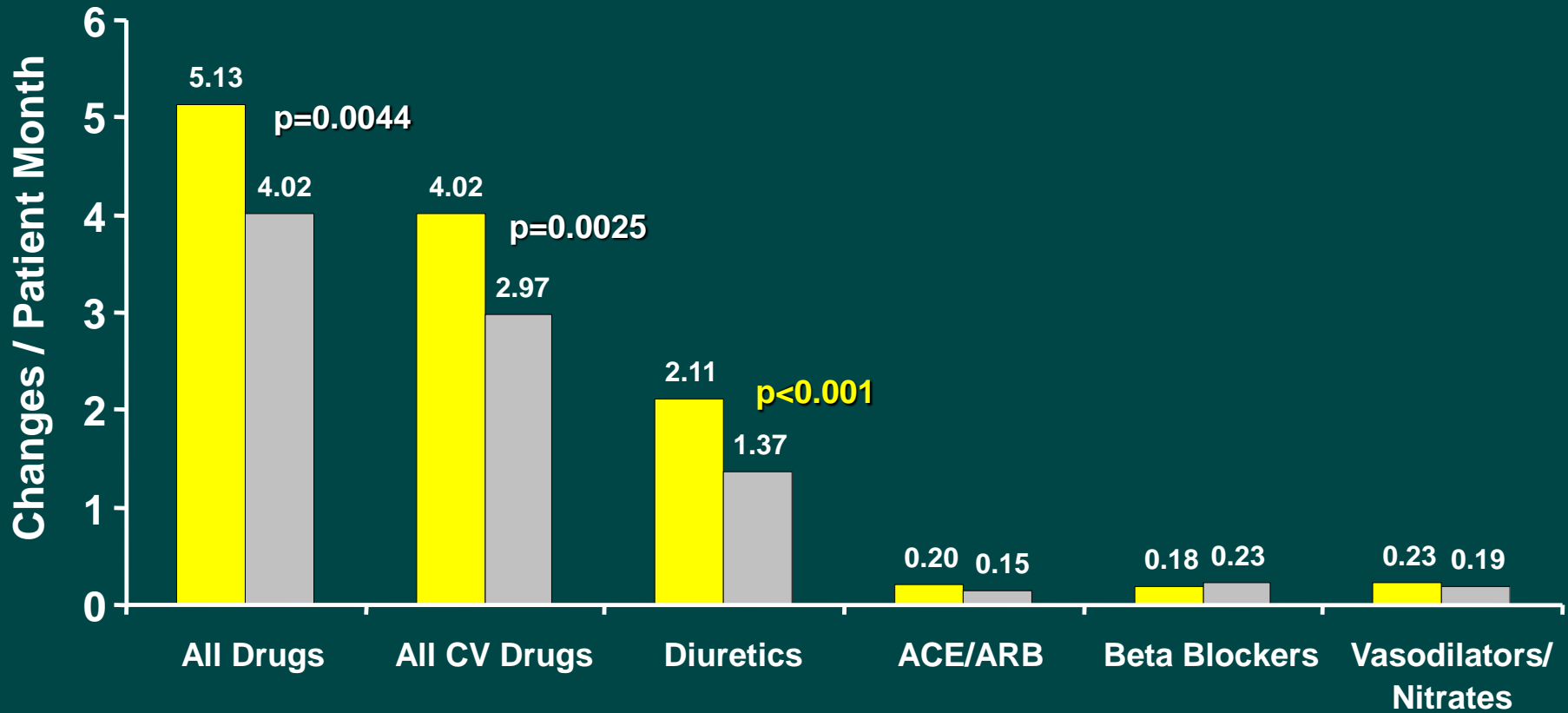
	drug	device
Mechanism of action		
Biological plausibility	+	+++
Improves blood flow	+	++
Improves physiologic parameters	++	+++
Does not worsen others	++	+++
Long term mortality protection	+++	+
Lower hospitalizations (all)	+++	+++
Allows maintenance or uptitration		+++
GDMT		
How long?	Life of pt	min 12 mos.

Types of Devices

- High risk
 - Full or partial support
- Purely monitoring—allowing provider to manage physiologic parameters
 - What does management of physiologic parameters achieve? Symptoms, survival, hospitalizations, biomarkers?
 - Who responds to changes?
 - Is it the monitor or the system of deployment
 - “allowed” to change Rx

Medication Change Analysis

■ CHRONICLE ■ CONTROL



Types of monitoring devices

- Endpoints will vary
 - Implantable: Risk vs benefit. Risk of implanting
 - Non-implantable
- Combined Endpoints: Can include death
 - Functional improvement (CPX, 6 min walk)
 - Reduction in hospitalizations (sometimes challenging)
 - Health Status
 - Should time to or ability to GDMT be an endpoint?
 - All in the same direction, not different

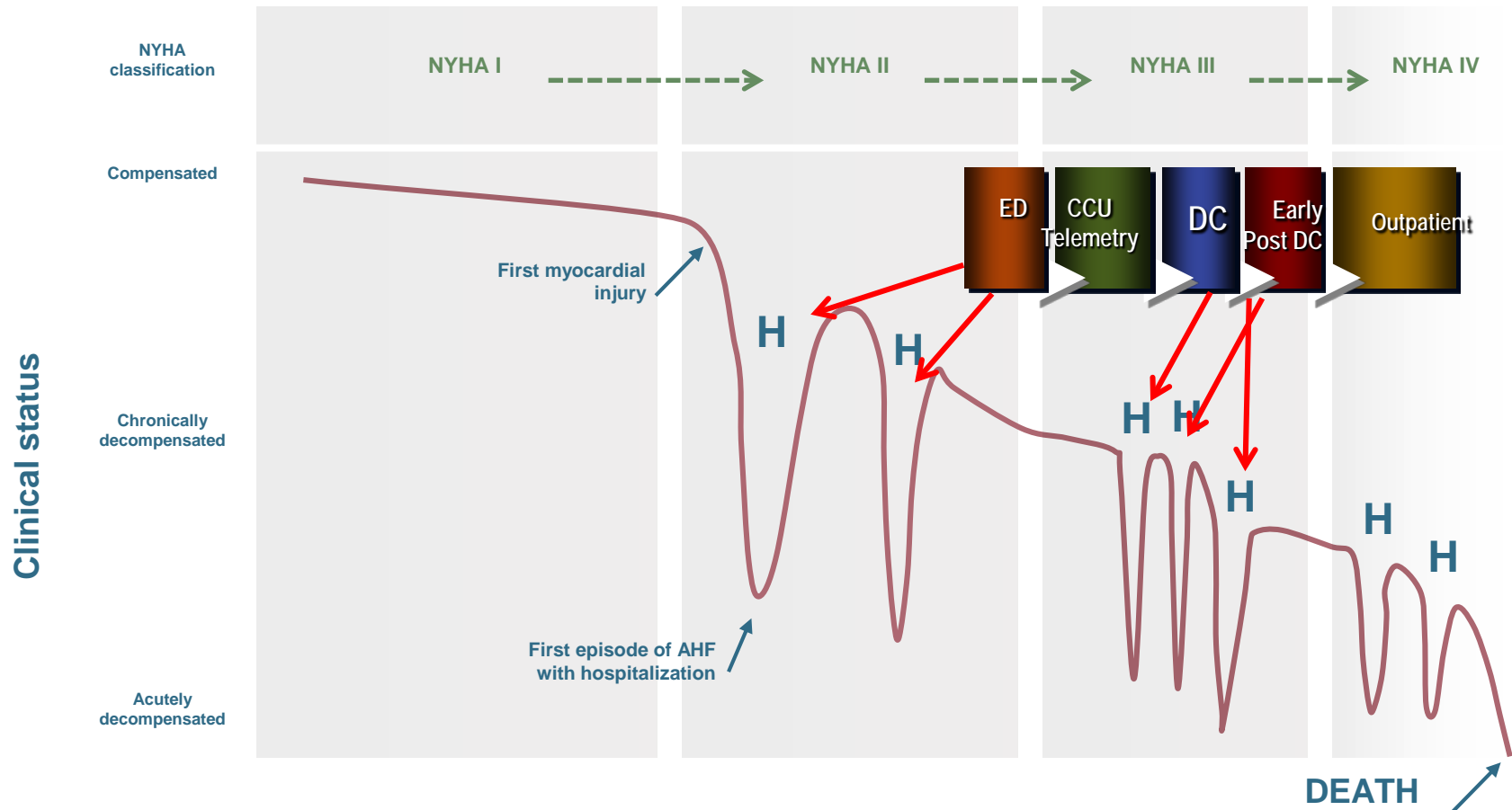


Considerations for device endpoints: implanted or non-implanted

- Who monitors the monitor?
 - PCP, EP, HF Specialist?
- How often to obtain signal?
- Will signal diminish with time?
 - Reliability
- Is it volume, or compliance?
 - Beyond diuretic treatment
- Patient alarms and acceptance
- Availability of web-based approach
- For monitoring systems to be useful, they must be used the right way by the right people

What is ADHF?
A semicolon in the total sentence...

Continuity of the syndrome forgotten



The Progression of Symptoms in ADHF

S
Y
M
P
T
O
M
S

E
V
E
N
T
S

ORTHOPNEA

FATIGUE

DYSPNEA

EDEMA

Systemic congestion
(JVD, edema)

↑ RV + RA pressure

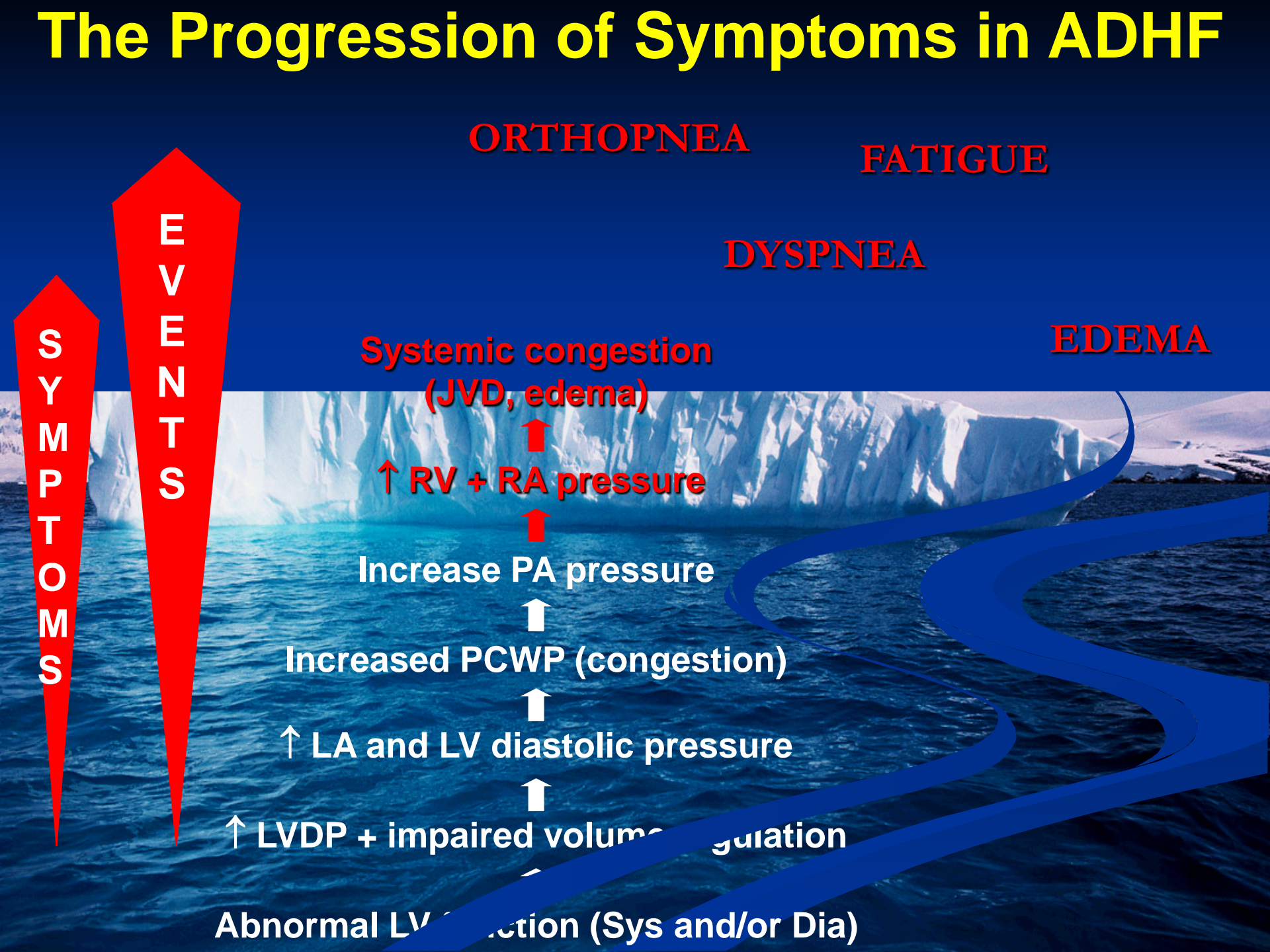
Increase PA pressure

Increased PCWP (congestion)

↑ LA and LV diastolic pressure

↑ LVDP + impaired volume regulation

Abnormal LV function (Sys and/or Dia)



Most Heart Failure Hospitalizations are due to Worsening Chronic Heart Failure

- ~70% Worsening chronic HF
 - Associated with reduced or preserved left ventricular systolic function (LVEF)
- ~25% de novo HF
 - After a large MI; sudden increase in blood pressure superimposed on a noncompliant LV
- ~5% Advanced HF
 - Refractory to therapy; with severe LV systolic dysfunction, associated with a worsening low-output state

Clinical Trials of ADHF

Therapy	Study	Physiologic Target	Sx or outcome	mortality
Diuretic	DOSED	Hi vs. low continuous	Modest	NA
AVP blockers	EVEREST	AVP receptor	Neutral on dyspnea	No benefit
UF	UNLOAD CARESS	Volume	Relief of dyspnea	No benefit; renal fct worse
Seralaxin	RELAX-AHF	Vasodilation in ADHF	Modest dyspnea relief	No benefit in hospitalizations RELAX II almost complete
Nesiritide	ASCEND-HF	Vasodilation	Modest Sx relief	No benefit
Levosimendan	SURVIVE REVIVE II	Ca++ sensitization	Modest Sx relief	Possible harm
Ularitide	TRUE-AHF	Mortality In-hospital worsening	Lower ProBNP less hospital events. No reduction in hospitalizations	No benefit on mortality but lowered BNP

Do we need to change our “injury” theory?

- The “neurohormonal storm” not addressed with diuretics or vasodilators
- No guide after the early intervention
- Is it time for devices to treat or to prevent?
 - Safe if implanted
 - Durable (do not lose signal)
 - Cost effective
 - Who monitors the monitor?
 - Patient or providers?
 - How to respond to signals? Best drug, dose?

Transition from IVAM to Chronic Oral Heart Failure Therapy

Beyond the
First 48 hrs:
Then what?

A
Transition
Ignored

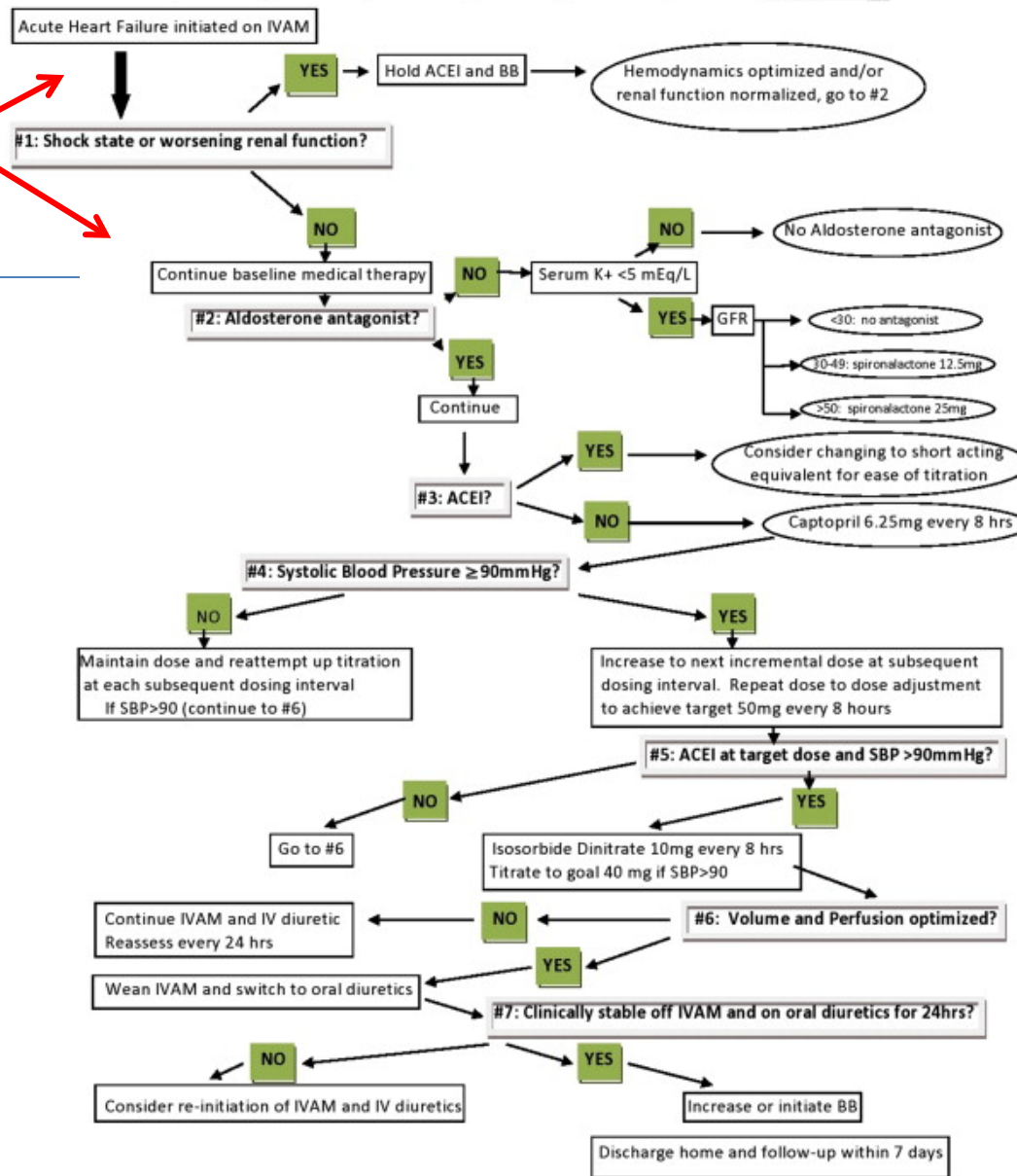
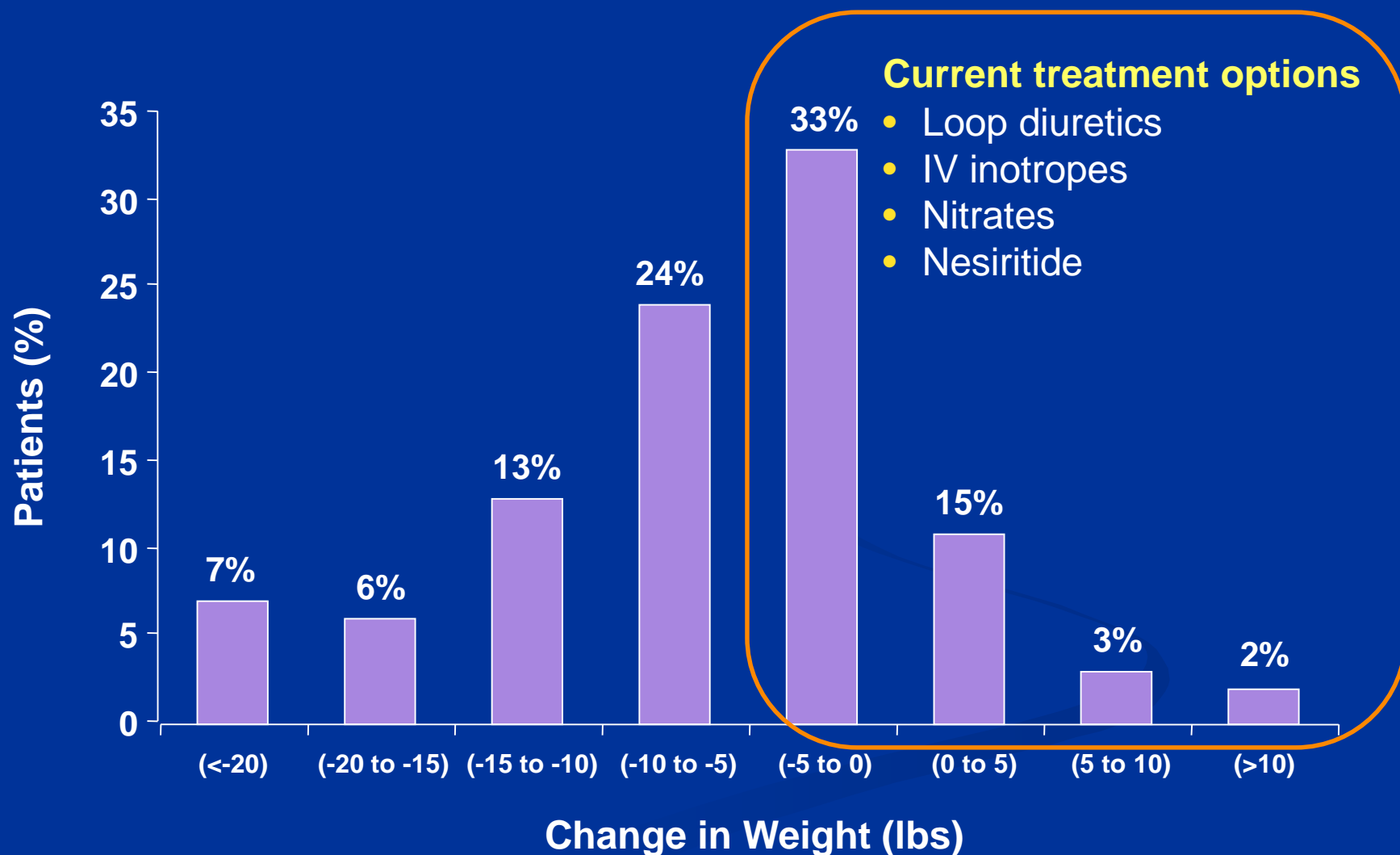


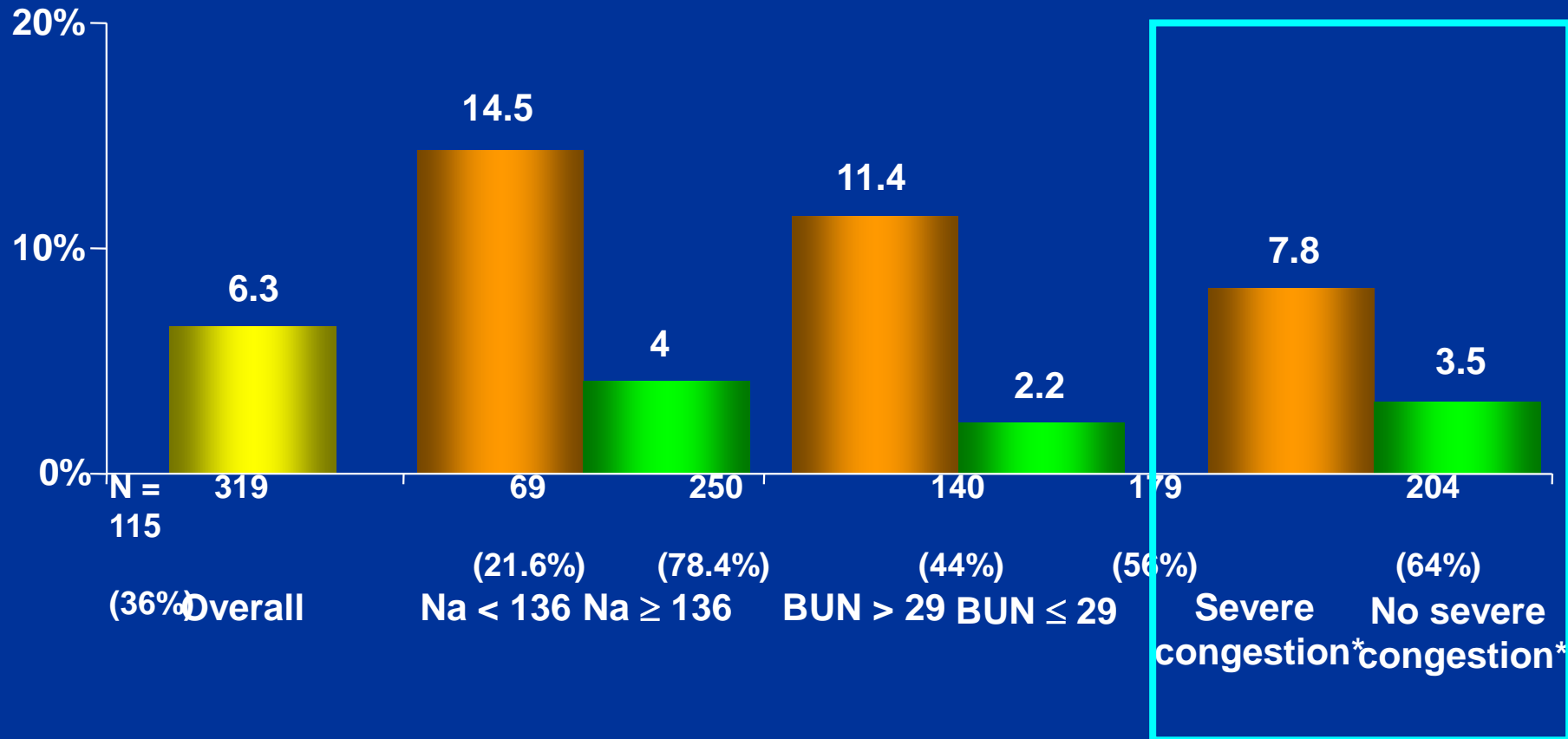
Figure 1. Suggested algorithm for continuation and initiation of long-term therapy during an admission for ADHF in which the patient is receiving IVAM. There are 7 cardinal points for decision making.

More than 50% of Patients Have Little or No Weight Loss During Hospitalization



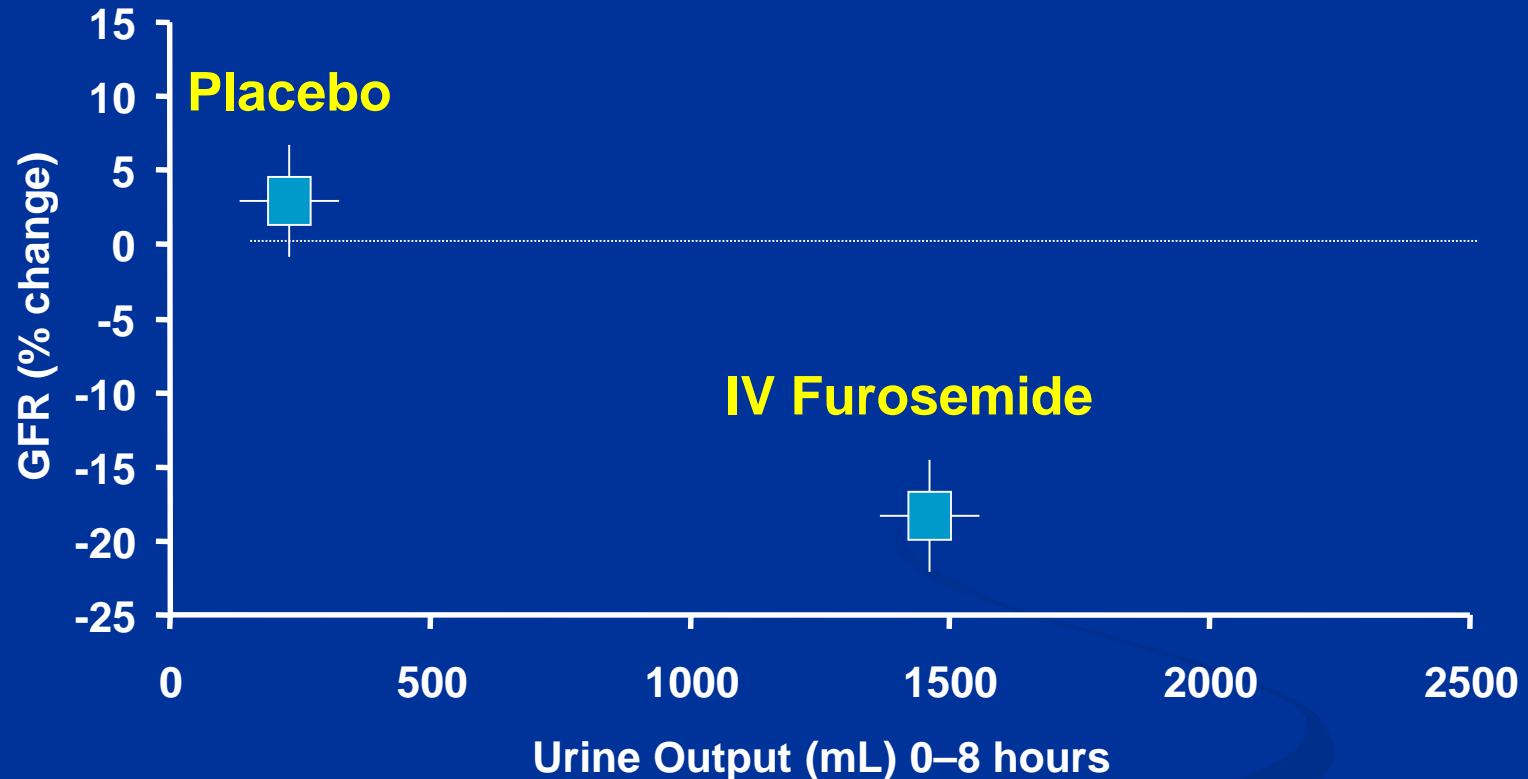
Congestion After Initial In-Hospital Therapy Is Associated with Higher 60-day Mortality

60-Day All-cause Mortality



* Edema, dyspnea, and JVD at baseline.
Gheorghiade M et al. *JAMA*. 2004.

Furosemide Monotherapy Causes a Significant Decline in Renal Function

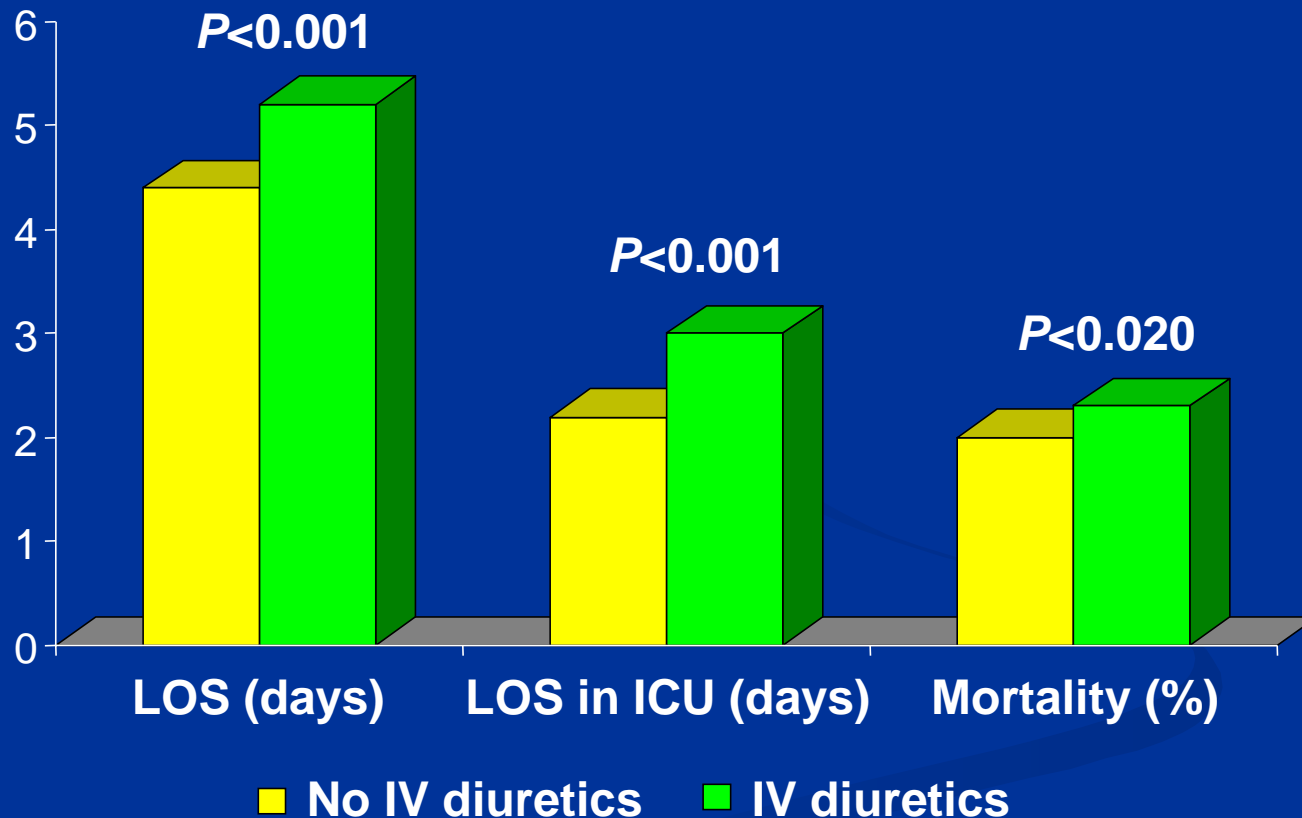


Change in GFR after furosemide 80 mg IV
Class III HF, n = 16, age 61, LVEF 0.28, CAD 63%

Gottlieb SS et al. *Circulation*. 2002;105:1348

Impact of IV Diuretics on Patients Hospitalized With ADHF

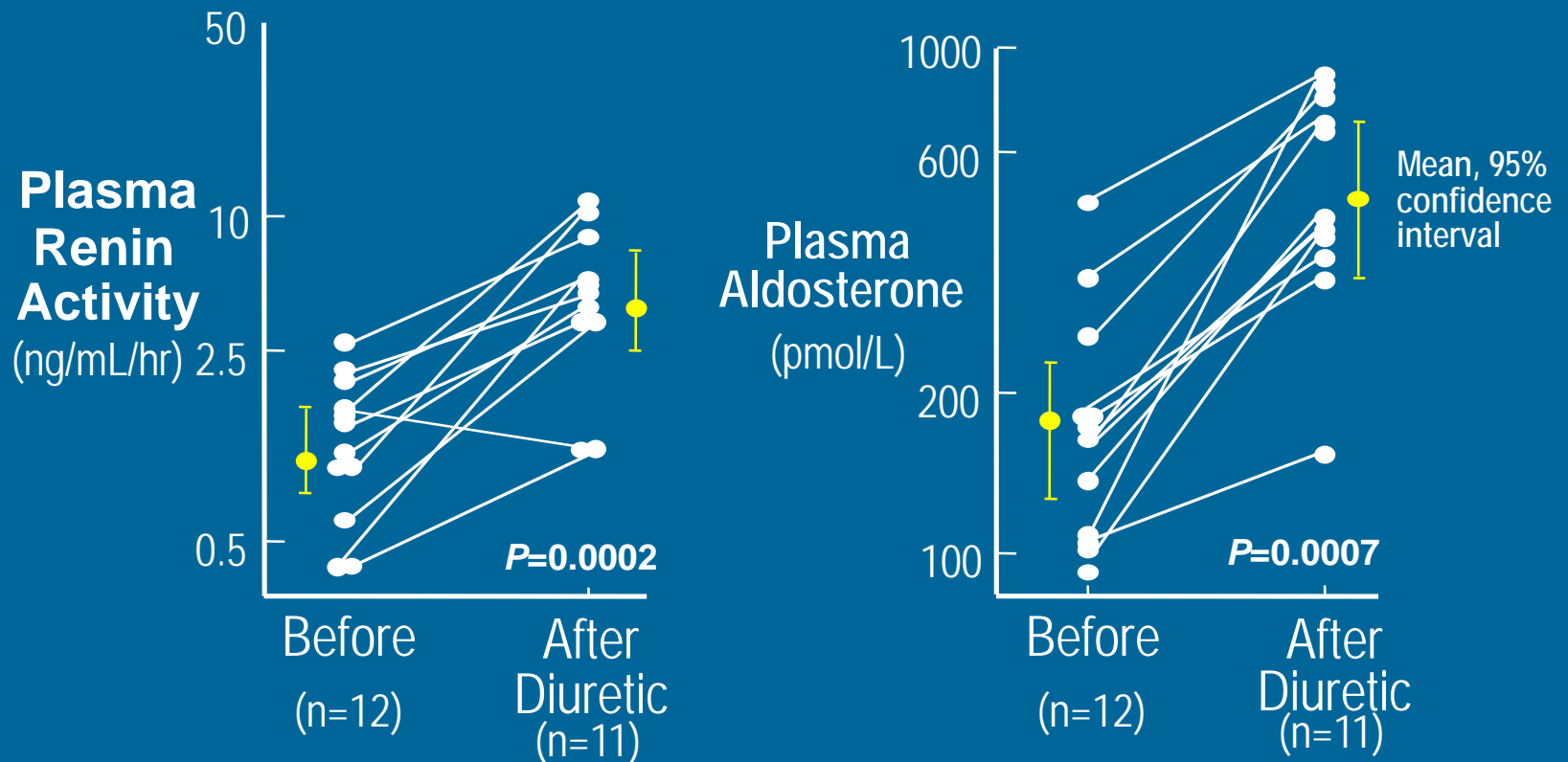
ADHERE: All Enrolled Discharges (n = 56,484) October 2001 to October 2003



Risk-adjusted data from ADHERE.

Emerman CL et al. *J Card Fail.* 2004;10:S116

Diuretics Activate Neurohormonal Systems in HF



Background:

Limitations of diuretic therapy

- Deleterious acute hemodynamic effects
- Activation of neurohormonal axes
- Decline in renal function
- Tubuloglomerular feedback mechanisms
- High doses associated with worse outcomes

Acute Therapy = Acute Endpoints (24 hrs. → Until Discharge)

- Clinically important symptoms and/or signs
- Hemodynamics (BNP, NT-pro BNP? as surrogate)
- Myocardial injury (Tn? as surrogate)
- Renal function (BUN, BUN/Cr),
- Normalizing serum sodium, hemoglobin?

Long-term Safety Endpoints

- Readmissions
- Mortality
- Acute surrogate endpoints predicting long-term safety (Tn, BNP/NT-pro BNP, viability/remodeling assessment) should not worsen

If we want to predict, prevent and treat the ADHF syndrome, we need to think differently.

- If a device can do this, how to respond in a physiologic way, with consistency of treatment and resume GDMT or not stop GDMT.
- Diuretics are only a part of the answer.
- Clinicians MUST be convinced and have self efficacy to respond physiologically to signals

Tools for Smoothing HF Transitions

- Better communication to ambulatory MD
 - Discharge summaries, EMR exchanges, etc.
- Triage follow-up to match need
 - *Minimizing “Door to clinic times”*
- Better patient education tools
 - Informing patients, family about disease and treatment
- Tools to increase medication adherence
 - Pill boxes
- Disease and risk management programs
 - Web-based, patient empowering

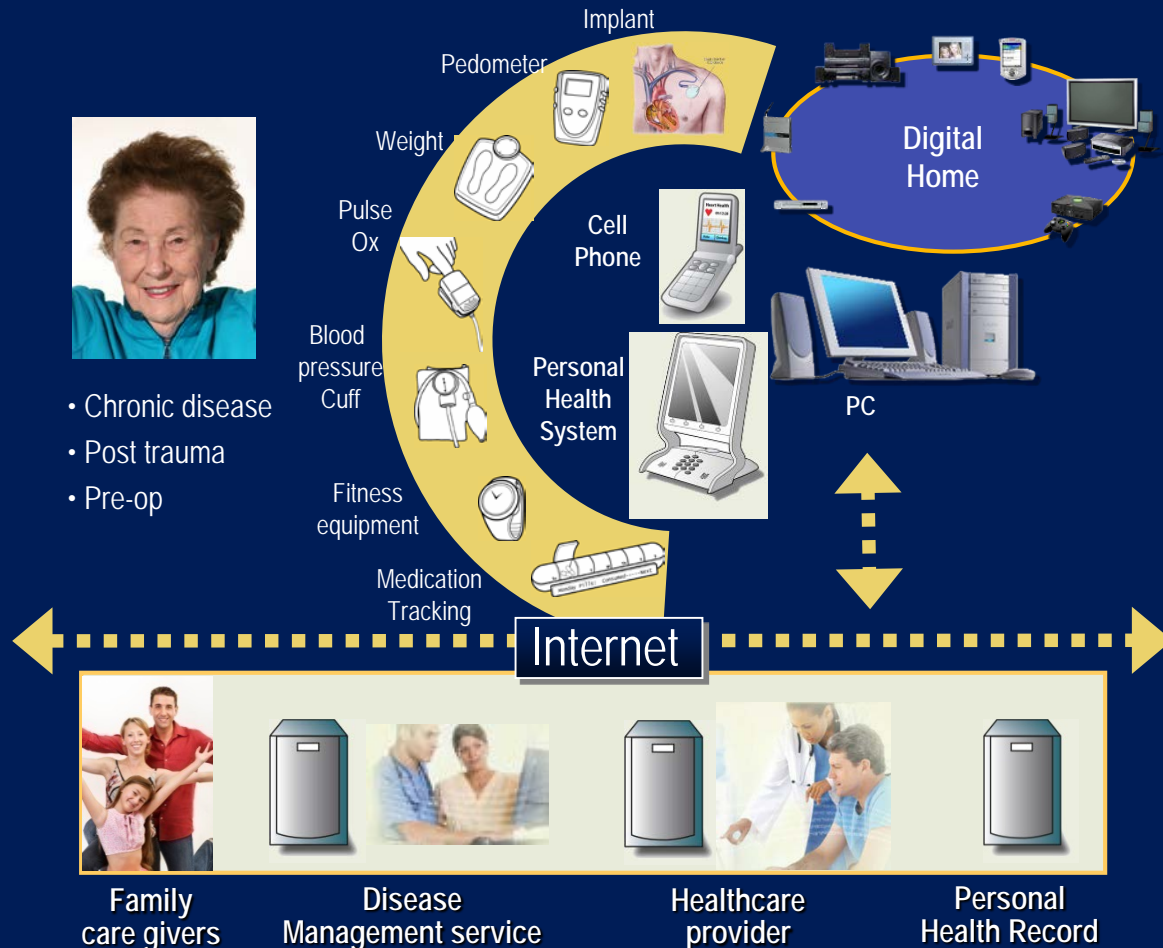
Over Time, Improving Transitions Is Key

Can Devices Help?

- Random control trials with best results include comprehensive, seamless care – from inpatient to ambulatory care
- Assuring patient and caregiver understanding of discharge instructions
- Appropriate case management to assure resources necessary for self-care
- **Devices to help for transitions and maintenance: scales, implanted, non-implanted, EMR, web-based**

Disease Management

860 Million Chronic Disease Patients World Wide



Disease Management

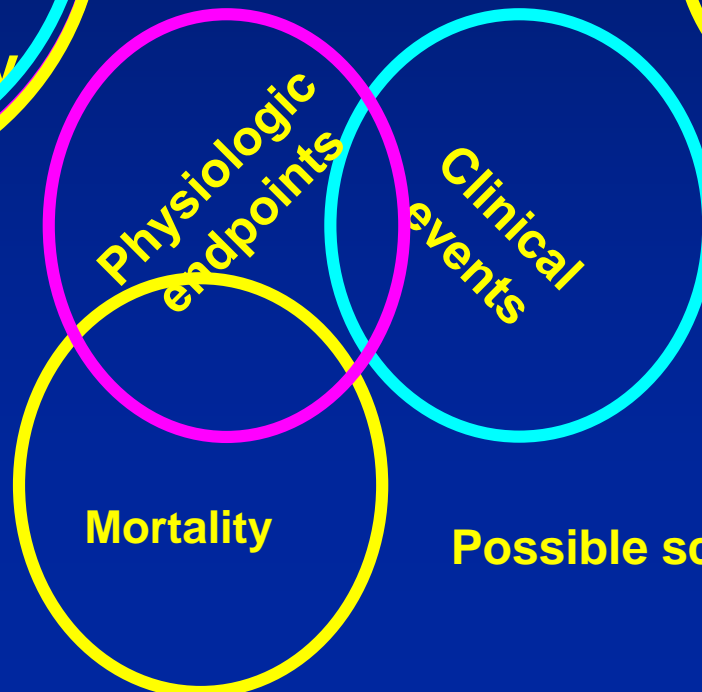
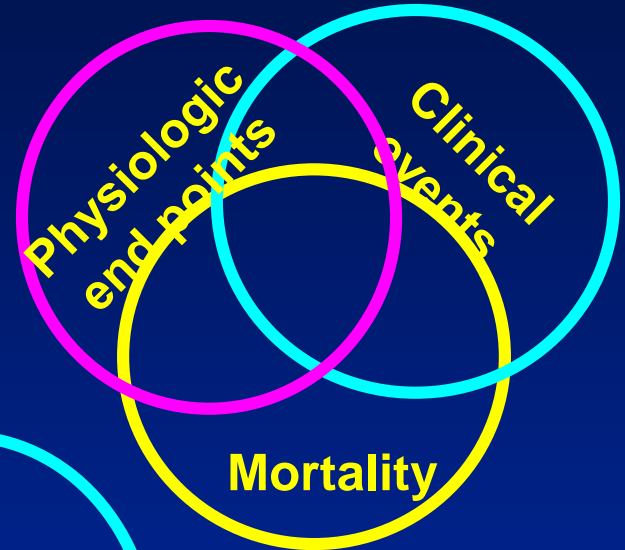
- Vital sign monitoring (RPM)
- Medication reminders and compliance
- Utilize home network to locate devices in logical places:
 - Scale in bathroom
 - Pill minder in kitchen
 - BP cuff in living room
- Trend analysis and alerts
- Email, chat, video
- Appointment scheduling

Endpoints

Ideal occurrence



“Real World”



Possible scenario

Adverse Events

- **Direct Risks of Device Implantation vs. not device or vs. drug therapy**
 - Bleeding
 - Perforation e.g., coronary sinus
 - Induction of arrhythmias
 - Tamponade
 - Infection
 - Limb ischemia

“I’d rather live a shorter time
and enjoy it than live five
extra years and constantly
feel miserable.”



"I've had these delusions for quite some time now that quality, not cost, should drive patient care."